CHAPTER 1

FROM NATURE TO NATURAL COMPUTING

"... science has often made progress by studying simple abstractions when more realistic models are too complicated and confusing."
(I. Stewart, Does God Play Dice, Penguin Books, 1997, p. 65)

"Often the most profound insights in science come when we develop a method for probing a new regime of Nature."
(M. Nielsen and I. Chuang, Quantum Computation and Quantum Information, Cambridge University Press, 2000, p. 3)

1.1 INTRODUCTION

During the early days of humanity natural resources were used to provide shelter and food. We soon learned to modify and manage nature so as to breed crops and animals, build artifacts, control fire, etc. We then started to observe and study biological, chemical, and physical phenomena and patterns in order to better understand and explain how nature works. As examples, by learning about the physical laws of motion and gravity it became possible to design aircrafts; and by understanding some basic principles of life it is now possible to manage nature in various levels, from the creation of transgenic food to the control of diseases.

With the advent of computers, the way human beings interact with nature changed drastically. Nature is now being used as a source of inspiration or metaphor for the development of new techniques for solving complex problems in various domains, from engineering to biology; computers can simulate and emulate biological life and processes; and new material and means with which to compute are currently being investigated. *Natural computing* is the terminology introduced to encompass these three types of approaches, named, respectively: 1) *computing inspired by nature*; 2) *the simulation and emulation of natural phenomena in computers*; and 3) *computing with natural materials*. This book provides an introduction to the broad field of natural computing. It constitutes a textbook-style treatment of the central ideas of natural computing, integrated with a number of exercises, pseudocode, theoretical and philosophical discussions, and references to the relevant literature in which to gather further information, support, selected websites, and algorithms involving the topics covered here. This introductory chapter provides some motivations to study natural computing, challenges the student with some sample ideas, discusses its philosophy and when natural computing approaches are necessary, provides a taxonomy and makes a brief overview of the three branches of the proposed taxonomy for natural computing.

1.1.1. Motivation

Why should we study natural computing and why should research in this broad area be supported? There are many reasons for doing so; from the engineering of new computational tools for solving complex problems whose solutions are so far unavailable or unsatisfactory; to the design of systems presenting nature-like patterns, behaviors and even the design of new forms of life; and finally to the possibility of developing and using new technologies for computing (new computing paradigms). Although still very young in most of its forms, the many products of natural computing are already available in various forms nowadays, in washing machines, trains, toys, air conditioning devices, motion pictures, inside computers as virtual life, and so forth. Some of these applications will be reviewed throughout this book with varying levels of details.

Natural phenomena (e.g., processes, substances, organisms, etc.) have long inspired and motivated people to mimic, design, and build novel systems and artifacts. For many centuries, the observation of the natural world has allowed people to devise theories about how nature works. For example, physics is abounded with laws describing electromagnetism (Maxwell's equations), thermodynamics (first law: conservation, second law: entropy, and third law: absolute zero), motion (Newton's laws), and so forth. Artifacts, such as sonar echolocation, chemical substances used for pharmaceutical purposes, infrared imaging systems, airplanes, submarines, etc., were all developed by taking inspiration from nature, from animals (bats, birds, etc.) to chemical substances.

Natural computing is the computational version of this process of extracting ideas from nature to develop 'artificial' (computational) systems, or using natural media (e.g., molecules) to perform computation. The word artificial here means only that the systems developed are human-made instead of made by nature. While not the rule, in some cases, the products of natural computing may turn out to be so life-like that it becomes difficult to tell them apart from natural phenomena. Natural computing can be divided into three main branches (Figure 1.1) (de Castro and Von Zuben, 2004; de Castro, 2005):

1) *Computing inspired by nature*: it makes use of nature as inspiration for the development of problem solving techniques. The main idea of this branch is to develop computational tools (algorithms) by taking inspiration from nature for the solution of complex problems.

2) *The simulation and emulation of nature by means of computing*: it is basically a synthetic process aimed at creating patterns, forms, behaviors, and organisms that (do not necessarily) resemble 'life-as-we-know-it'. Its products can be used to mimic various natural phenomena, thus increasing our understanding of nature and insights about computer models.

3) *Computing with natural materials*: it corresponds to the use of natural materials to perform computation, thus constituting a true novel computing paradigm that comes to substitute or supplement the current silicon-based computers.

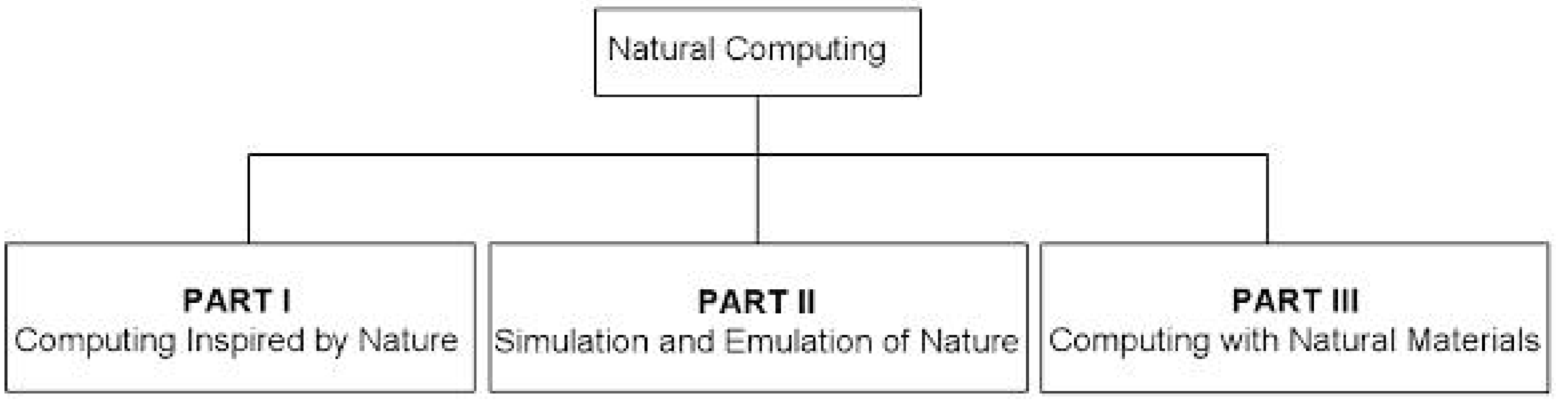
Natural Computing
PART I
Computing Inspired by Nature
PART II
Simulation and Emulation of Nature
PART III
Computing with Natural Materials

Figure 1.1: The three main branches of natural computing and their order of appearance in the book.

Therefore, natural computing can be defined as the field of research that, based on or inspired by nature, allows the development of new computational tools (in software, hardware or 'wetware') for problem solving, leads to the synthesis of natural patterns, behaviors, and organisms, and may result in the design of novel computing systems that use natural media to compute.

Natural computing is thus a field of research that testimonies against the specialization of disciplines in science. It shows, with its three main areas of investigation - *computing inspired by nature*, *the simulation and emulation of nature by means of computing*, and *computing with natural materials* - that knowledge from various fields of research are necessary for a better understanding of life, for the study and simulation of natural systems and processes, and for the proposal of novel computing paradigms. Physicists, chemists, engineers, biologists, computer scientists, among others, all have to act together or at least share ideas and knowledge in order to make natural computing feasible.

It is also important to appreciate that the development and advancement of natural computing leads to great benefits to the natural sciences, like biology, as well. Many computational tools developed using ideas from nature and the biological sciences are applied to create models and solve problems within the biosciences. This application domain is becoming even more important over the last few years with the emergence of new fields of investigation like computational biology and bioinformatics (Attwood and Parry-Smith, 1999; Baldi and Brunak, 2001; Waterman, 1995). Natural computing has also proven to be useful for a better understanding of nature and life processes through the development of highly abstract models of nature. Sometimes natural computing techniques can be directly aimed at being theoretical models of nature, providing novel insights into how nature works.

1.2 A SMALL SAMPLE OF IDEAS

The history of science is marked by several periods of almost stagnation, intertwined with times of major breakthroughs. The discoveries of Galileo, Newtonian mechanics, Darwin's theory of evolution, Mendel's genetics, the development of quantum physics, and the design of computers are just a small sample of the scientific revolutions over the past centuries. We are in the midst of another technological revolution - the *natural computing age*; a time when the interaction and the similarity between computing and nature is becoming each day greater. The transformation may be revolutionary for all those involved in the development of natural computing devices, but, if they do their job well, it will not necessarily make much difference for the end users. We may notice our spreadsheets recalculating faster, our grammar checker finally working, several complex problems being solved, robots talking naturally to humans, cars driving themselves, new forms of life, and patterns emerging in a computer screen in front of us, computers based on biomolecules, etc. But we will all be dealing with the end results of natural computing, not with the process itself. However, will ordinary people and end-users get a chance to experiment and play with natural computing? In fact, we can get our hands dirty already. And we will start doing this just by testing our ability to look at nature and computing in different ways.

Below are discussions about some natural phenomena and processes involving natural means: 1) clustering of dead bodies in ant colonies; 2) bird flocking; and 3) manipulating DNA strands. All of them have already served as inspiration or media for the development of natural computing techniques and will be presented here as a first challenge and motivation for the study of natural computing. Read the descriptions provided and try to answer the following questions.

To clean up their nests, some ant species group together corpses of ants or parts of dead bodies, as illustrated in Figure 1.2. The basic mechanism behind this type of clustering or grouping phenomenon is an attraction between dead items mediated by the ants. Small clusters of items grow by attracting more workers to deposit more dead bodies. This grouping phenomenon can be modeled using two simple rules:

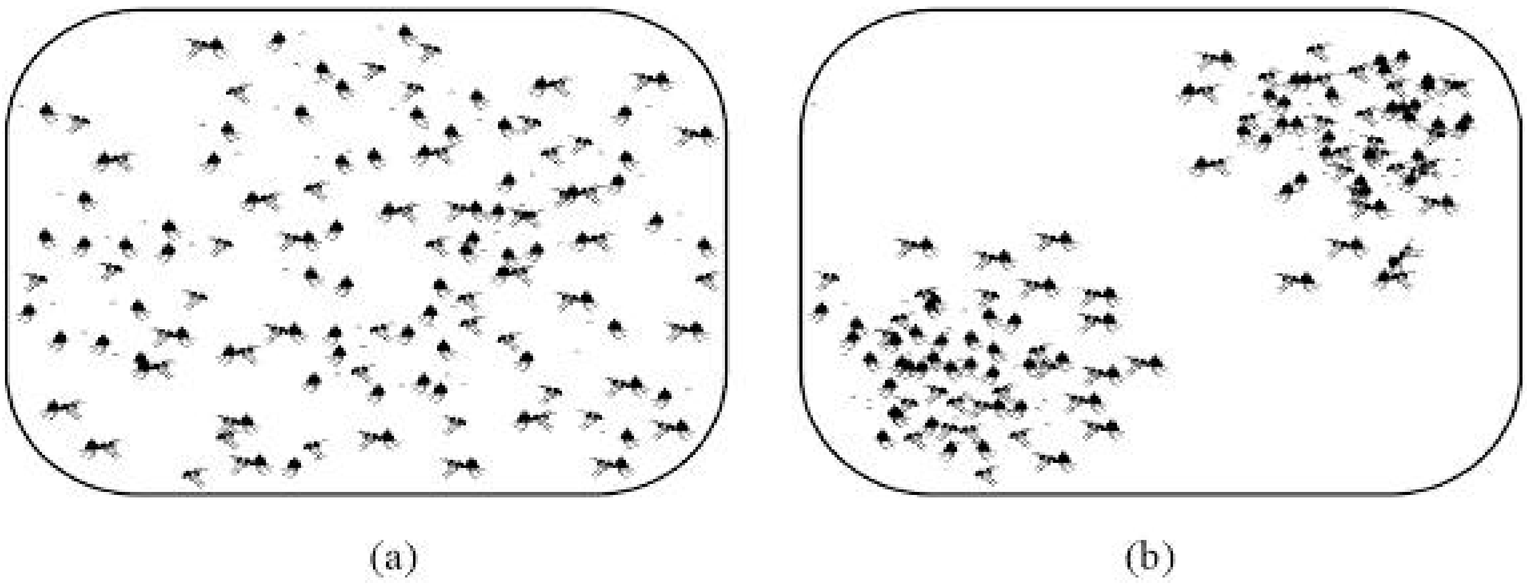
(a) (b)

Figure 1.2: Clustering of dead bodies in an ant colony. (a) Initial distribution of ants. (b) Clustered bodies.

Pick up rule: if an ant finds a dead body, it picks it up and wanders around the arena until it finds another dead body. The probability or likelihood that an ant picks up a dead body is inversely proportional to the number of items in that portion of the arena; that is, the more dead bodies around, the smaller the probability it is picked up, and vice-versa.

Dropping rule: while wandering around, the loaded ant eventually finds more dead bodies in its way. The more dead bodies are found in a given region of the arena, the higher the probability the ant drops the dead body it is carrying at that location of the arena, and vice-versa.

As a result of these very simple behavioral rules, all dead items will eventually be brought together into a single group, depending on the initial configuration of the arena and how the rules are set up.

Question 1: what kind of problem could be solved inspired by this simple model of a natural phenomenon?

Question 2: how would you use these ideas to develop a computing tool (e.g., an algorithm) for solving the problem you specified above? ■

Figure 1.3 illustrates a bird flock. When we see birds flocking in the sky, it is most natural to assume that the birds 'follow a leader'; in this picture, the one in front of the flock. However, it is now believed (and there are some good evidences to support it) that the birds in a flock do not follow any leader.

There is no 'global rule' that can be defined so as to simulate a bird flock. It is possible, however, to generate scripts for each bird in a simulated flock so as to create a more realistic group behavior (for example, in a computer simulation). Another approach, one that is currently used in many motion pictures, is based on the derivation of generic behavioral rules for individual birds. The specification of some simple individual rules allows realistic simulation of birds flocking. The resultant flock is a result of many birds following the same simple rules.

Question 1: describe (some of) these behavioral rules that, when applied to each bird in the flock, result in an emergent group behavior that is not specifically defined by the individual rules. It means that such rules, together with the interactions among individual birds, result in a global behavior that cannot often be predicted by simply looking at the rules.

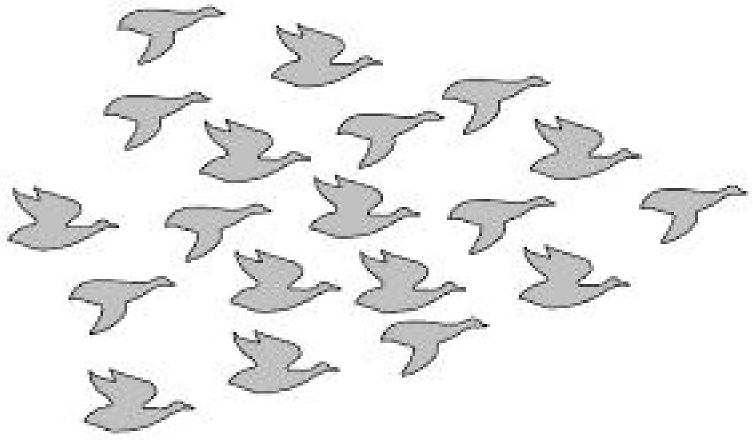

Figure 1.3: Illustration of a flock of birds.

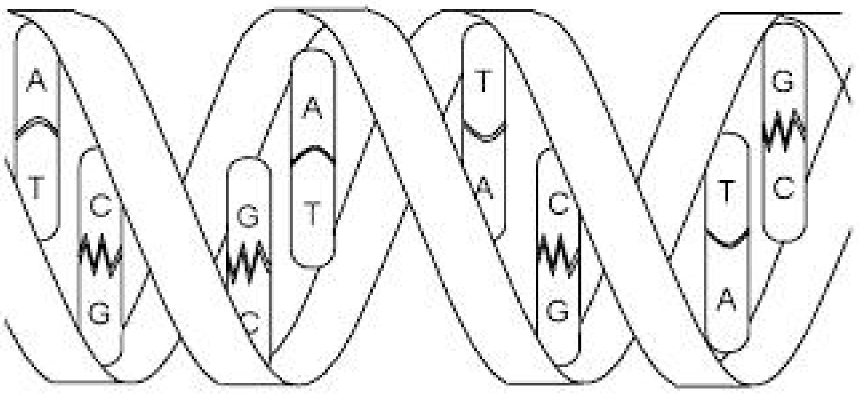

Figure 1.4: Double strand of DNA.

Question 2: can you extend these rules to herds of land animals and schools of fish? That is, is there a significant qualitative difference between these various types of group behavior? ■

Figure 1.4 depicts a double strand of DNA. The DNA molecules contain the genetic information of all living beings on earth. It is known that this genetic information, together with the environmental influences, determines the phenotype (expressed physical characteristics) of an individual.

Roughly, DNA molecules are composed of four bases which bind to each other exclusively in a complementary fashion: A binds with T, and C binds with G. Genetic engineering techniques can nowadays be used to artificially manipulate DNA so as to alter the genetic information encoded in these molecules. For instance, DNA molecules can be *denatured* (separated into single strands), *annealed* (single strands can be 'glued' together to form double strands of DNA), *shortened* (reduced in length), *cut* (separated in two), *multiplied* (copied), *modified* (e.g., new sequences inserted), etc.

Question 1: if the information that encodes an organism is contained in DNA molecules and these can be manipulated, then life can be seen as information processing. Based on your knowledge of how standard computers (PCs) work, propose a new model of computer based on DNA strands and suggest a number of DNA manipulation techniques that can be used to compute with molecules.

Question 2: what would be the advantages and disadvantages of your proposed DNA computer over the standard computers? ■

If you have not tried to answer these questions yet, please take your time. They may give you some flavor of what researchers on some branches of natural computing do. If you want to check possible answers to these questions, please refer to Chapters 5, 8, and 9 respectively

. . .

So, how did you get on?

If your answers were too different from the ones presented in this volume, do not worry; they may constitute a potentially new algorithm or computing paradigm!

1.3 THE PHILOSOPHY OF NATURAL COMPUTING

One important question this book tries to answer is how researchers discover the laws and mechanisms that are so effective in uncovering how nature functions and how these can be used within and for computing. A natural result of this line of investigation is the proposal of novel ways of computing, solving real-world problems, and synthesizing nature. Scientific explanations have been dominated by the formulation of principles and rules governing systems' behaviors. Researchers usually assume that natural systems and processes are governed by finite sets of rules. The search for these basic rules or fundamental laws is one of the central issues covered in this book. It is not easy to find such rules or laws, but enormous progress has been made. Some examples were provided in Section 1.2.

Most of the computational approaches natural computing deals with are based on highly simplified versions of the mechanisms and processes present in the corresponding natural phenomena. The reasons for such simplifications and abstractions are manifold. First of all, most simplifications are necessary to make the computation with a large number of entities tractable. Also, it can be advantageous to highlight the minimal features necessary to enable some particular aspects of a system to be reproduced and to observe some emergent properties. A common question that may arise is: "if it is possible to do something using simple techniques, why use more complicated ones?"

This book focuses on the extraction of ideas and design aspects of natural computing, in particular the teaching of modeling, how to make useful abstractions, and how to develop and use computer tools or algorithms based on nature. In contrast to some books on the technological and advanced aspects of specific topics, this text outlines the relations of theoretical concepts or particular technological solutions inspired by nature. It is therefore important to learn how to create and understand abstractions, thus making a suitable simplification of a system without abolishing the important features that are to be reproduced.

Which level is most appropriate for the investigation and abstraction depends on the scientific question asked, what type of problem one wants to solve, or the life phenomenon to be synthesized. As will be further discussed, simple behavioral rules for some insects are sufficient for the development of computational tools for solving combinatorial problems and coordinate collective robotic systems. These are also useful for the development of computer simulations of biological systems in artificial life, and the creation of abstract models of evolution, and the nervous and immune systems, all aimed at solving complex problems in various domains.

Natural computing usually integrates experimental and theoretical biology, physics and chemistry, empirical observations from nature and several other sciences, facts and processes from different levels of investigation into nature so as to design new problem solving techniques, new forms of mimicking natural phenomena, and new ways of computing, as summarized in Figure 1.5.

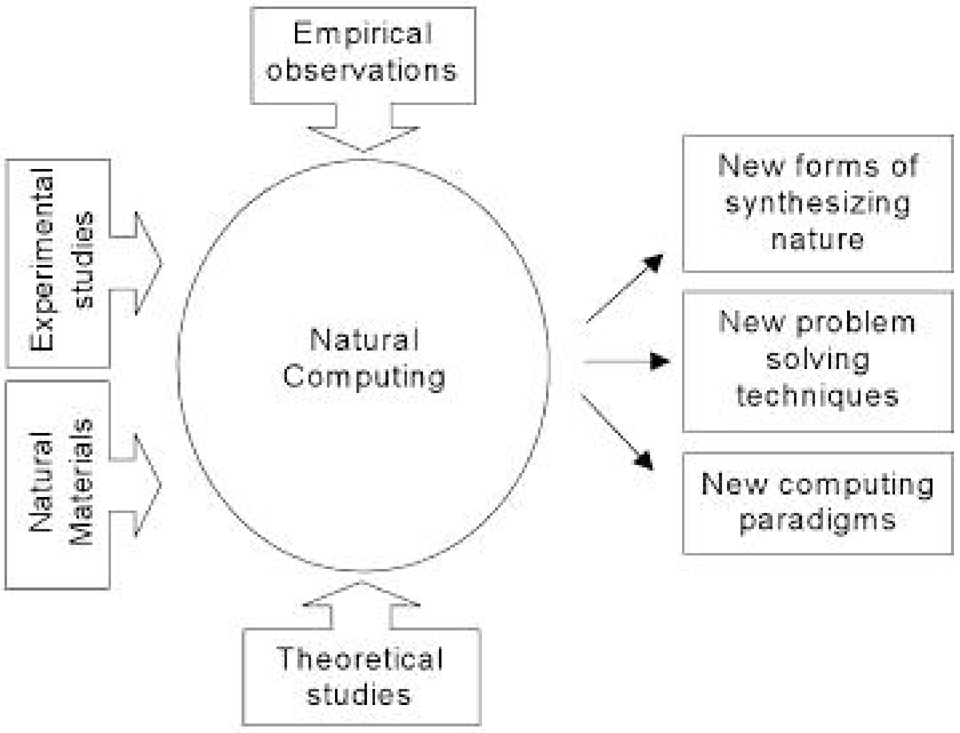

Figure 1.5: Many fields of investigation have to be integrated for the study and development of natural computing. As outcomes, new ways of computing, new problem solving techniques, and possible forms of synthesizing nature result.

1.4 THE THREE BRANCHES: A BRIEF OVERVIEW

This section provides a very brief overview of the three branches of natural computing and their main approaches. The bibliography cited is basically composed of references from pioneer works and books where further and didactic information can be found on all topics discussed. Instead of trying to cover the areas reviewed in detail, general comments about most natural computing tools, algorithms, techniques and their potential application areas are provided, together with a discussion of how the resultant computational tools or systems relate (interact) with nature and the natural sciences. The reader will be pointed to the chapters that deal specifically with each of the approaches discussed.

1.4.1. Computing Inspired by Nature

The main motivation for this part of the book is that nature has greatly enriched computing. More importantly, nature has been very successful in solving highly complex problems. In a very low level, there is an urge for survival in living organisms: they have to search for food, hide from predators and weather conditions, they need to mate, organize their homes, etc. All this requires complex strategies and structures not usually directly modeled or understood. But, for instance, viewing a colony of ants foraging for food as an 'intelligent behavior' is not always very intuitive for us, used to attribute 'intelligent behaviors' to 'intelligent beings'. What if I tell you that the way ants forage for food has inspired algorithms to solve routing problems in communication networks? Can you imagine how this is done?

Among all natural computing approaches, computational algorithms and systems inspired by nature are the oldest and most popular ones. They arose with two main objectives in mind. First, researchers were interested in the modeling of natural phenomena and their simulation in computers. The common goal in this direction is to devise theoretical models, which can be implemented in computers, faithful enough to the natural mechanisms investigated so as to reproduce qualitatively or quantitatively some of their functioning. Theoretical models are supposed to provide a deeper insight and better understanding of the natural phenomena being modeled, to aid in the critical analysis and design of experiments, and to facilitate the recovery of results from laboratory experimentation or empirical observations. There is a vast number of theoretical models available in the literature concerning all natural sciences, including biology, ethology, ecology, pharmacology, nutrition and health care, medicine, geophysics, and so forth.

However, the focus of computing inspired by nature, under the umbrella of natural computing, is most often on problem solving instead of on theoretical modeling, and this leads to the second objective of computing based on nature. The second objective, thus, involves the study of natural phenomena, processes and even theoretical models for the development of computational systems and algorithms capable of solving complex problems. The motivation, in this case, is to provide (alternative) solution techniques to problems that could not be (satisfactorily) resolved by other more traditional techniques, such as linear, nonlinear, and dynamic programming. In such cases, the computational techniques developed can also be termed *bio-inspired computing* or *biologically motivated computing* (Mange and Tomassini, 1998; de Castro and Von Zuben, 2004), or *computing with biological metaphors* (Paton, 1994).

As computing inspired by nature is mostly aimed at solving problems, almost all approaches are not concerned with the creation of accurate or theoretical models of the natural phenomena being modeled. In many situations highly abstract models, sometimes called metaphors (Paton, 1992), are proposed mimicking particular features and mechanisms from biology. What usually happens is that a natural phenomenon, or a theoretical model of it, gives rise to one particular computational tool and this is then algorithmically or mathematically improved to the extent that, in the end, it bears a far resemblance with the natural phenomenon that originally motivated the approach. Well-known examples of these can be found in the fields of artificial neural networks and evolutionary algorithms, which will be briefly discussed in the following.

A landmark work in the branch of bio-inspired computing was the paper by McCulloch and Pitts (1943), which introduced the first mathematical model of a neuron. This neuronal model, also known as artificial neuron, gave rise to a field of investigation of its own, the so-called *artificial neural networks* (Fausett, 1994; Bishop, 1996; Haykin, 1999; Kohonen, 2000). Artificial neural networks, to be discussed in Chapter 4, can be defined as information processing systems designed with inspiration taken from the nervous system, in most cases the human brain, and with particular emphasis on problem solving. There are several types of artificial neural networks (ANNs) and learning algorithms used to set up (train) these networks. ANNs are distinct from what is currently known as *computational neuroscience* (O'Reilly and Munakata, 2000; Dayan and Abbot, 2001; Trappenberg, 2002), which is mainly concerned with the development of biologically-based computational models of the nervous system.

Another computing approach motivated by biology arose in the mid 1960's with the works of I. Rechenberg (1973), H. P. Schwefel (1965), L. Fogel, A. Owens and M. Walsh (Fogel et al., 1966), and J. Holland (1975). These works gave rise to the field of *evolutionary computing* (Chapter 3), which uses ideas from evolutionary biology to develop *evolutionary algorithms* for search and optimization (Bäck et al., 2000a,b; Fogel, 1998; Michalewicz, 1996). Most evolutionary algorithms are rooted on the neo-Darwinian theory of evolution, which proposes that a population of individuals capable of reproducing and subject to genetic variation followed by natural selection result in new populations of individuals increasingly more fit to their environment. These simple three processes, when implemented in computers, result in evolutionary algorithms (EAs). The main types of EAs are the *genetic algorithms* (Mitchell, 1998; Goldberg, 1989), *evolution strategies* (Schwefel, 1995; Beyer, 2001), *evolutionary programming* (Fogel, 1999), *genetic programming* (Koza, 1992, 1994; Bahnzaf et al., 1997), and *classifier systems* (Booker et al., 1989; Holmes et al., 2002).

The term *swarm intelligence* (Chapter 5) was coined in the late 1980's to refer to cellular robotic systems in which a collection of simple agents in an environment interact based on local rules (Beni, 1988; Beni and Wang, 1989). Nowadays, the term is being used to describe any attempt to design algorithms or problem-solving devices inspired by the collective behavior of social organisms, from insect colonies to human societies. Swarm intelligence has two main frontlines: algorithms based on the collective behavior of social insects (Bonabeau et al., 1999), and algorithms based on cultures or sociocognition (Reynolds, 1994; Kennedy et al., 2001). In the first case, the collective behavior of ants and other insects has led to the development of algorithms for solving combinatorial optimization, clustering problems, and the design of autonomous robotic systems. Algorithms based on cultures and sociocognition demonstrated effectiveness in performing search and optimization on continuous and discrete spaces.

Artificial immune systems (AIS) or *immunocomputing* (Chapter 6), borrow ideas from the immune system and its corresponding models to design computational systems for solving complex problems (Dasgupta, 1999; de Castro and Timmis, 2002; Timmis et al., 2003). This is also a young field of research that emerged around the mid 1980's. Its application areas range from biology to robotics. Similarly to ANNs, EAs and swarm intelligence, different phenomena, processes, theories and models resulted in different types of immune algorithms, from evolutionary-like algorithms to network-like systems. Several other (emerging) types of algorithms inspired by nature can be found in the literature. For instance, it is possible to list the *simulated annealing* algorithm, the systems based on *growth* and *development*, and the *cells and tissues* models (Kirkpatrick et al., 1983; Aarts and Korst, 1989; Paton et al., 2004; Kumar and Bentley, 2003; Glover and Kochenberger, 2003; de Castro and Von Zuben, 2004).

Figure 1.6 summarizes the main components of computing inspired by nature to be discussed in this book and the respective chapters.

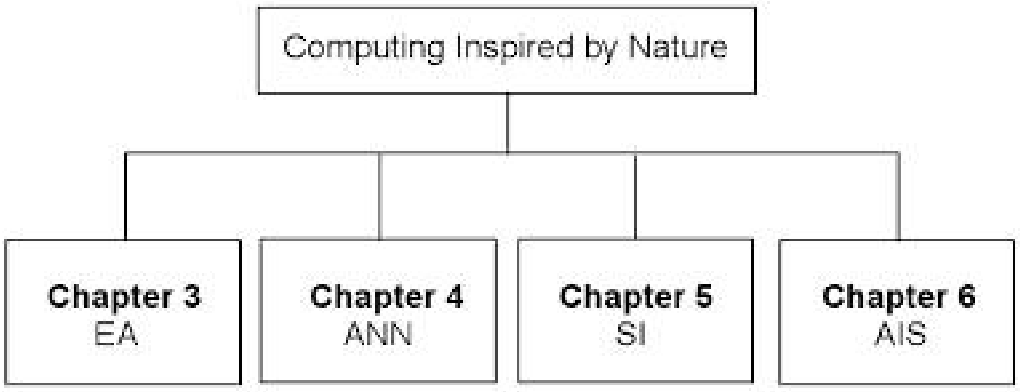

Figure 1.6: The main components of computing inspired by nature to be discussed in this book: ANN: artificial neural networks (neurocomputing); EA: evolutionary algorithms (evolutionary computing); SI: swarm intelligence; AIS: artificial immune systems (immunocomputing).

1.4.2. The Simulation and Emulation of Nature in Computers

While biologically inspired computing is basically aimed at solving complex problems, the second branch of natural computing provides new tools for the synthesis and study of natural phenomena that can be used to test biological theories usually not passive of testing via the traditional experimental and analytic techniques. It is in most cases a synthetic approach aimed at synthesizing natural phenomena or known patterns and behaviors. There is also a complementary relationship between biological theory and the synthetic processes of the simulation and emulation of nature by computers. Theoretical studies suggest how the synthesis can be achieved, while the application of the theory in the synthesis may be a test for the theory. There are basically two main approaches to the simulation and emulation of nature in computers: by using *artificial life* techniques or by using tools for studying the *fractal geometry of nature* (Figure 1.7).

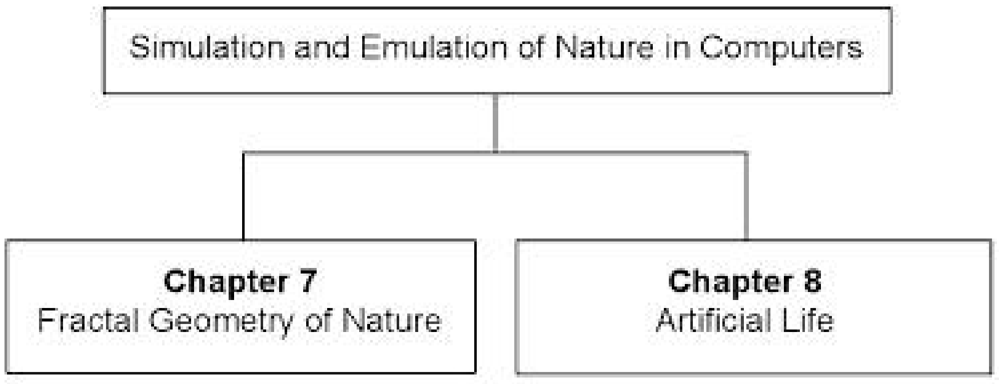
Simulation and Emulation of Nature in Computers
Chapter 7
Fractal Geometry of Nature
Chapter 8
Artificial Life

Figure 1.7: The two main approaches for the simulation and emulation of nature in computers and the chapters in which they are going to be presented.

Recent advances in computer graphics have made it possible to visualize mathematical models of natural structures and processes with unprecedented realism. The resulting images, animations, and interactive systems are useful as scientific, research, and educational tools in computer science, engineering, biosciences, and many other domains. One major breakthrough in the modeling and synthesis of natural patterns and structures is the recognition that nature is fractal in the sense that it can be successfully emulated by *fractal geometry* (Mandelbrot, 1983; Peitgen et al., 1992; Flake, 2000; Lesmoir-Gordon et al., 2000). In a simplified form, *fractal geometry* (Chapter 7) is the geometry of nature, with all its irregular, fragmented, and complex structures. In general, fractals are characterized by infinite details, infinite length, self-similarity, *fractal dimensions*, and the absence of smoothness or derivative. Nature provides many examples of fractals, for instance, ferns, coastlines, mountains, cauliflowers and broccoli, and many other plants and trees are fractals. Moreover, organisms are fractals; our lungs, our circulatory system, our brains, our kidneys, and many other body systems and organs are fractal.

There are a number of techniques for modeling fractal patterns and structures, such as *cellular automata* (Ilachinski, 2001; Wolfram, 1994), *L-systems* or *Lindenmayer systems* (Lindenmayer, 1968; Prusinkiewicz and Lindenmayer, 1990), *iterated function systems* (Hutchinson, 1981; Barnsley and Demko, 1985; Barnsley, 1988), *particle systems* (Reeves, 1983), *Brownian motion* (Fournier et al., 1982; Voss, 1985), and others. Their applications include computer-assisted landscape design, the study of developmental and growth processes, and the modeling and synthesis (and corresponding analysis) of an innumerable amount of natural patterns and phenomena. But the scope and importance of fractals and fractal geometry go far beyond these. Forest fires have fractal boundaries; deposits built up in electro-plating processes and the spreading of some liquids in viscous fluids have fractal patterns; complex protein surfaces fold up and wrinkle around toward three-dimensional space in a fractal dimension; antibodies bind to antigens through complementary fractal dimensions of their surfaces; fractals have been used to model the dynamics of the AIDS virus; cancer cells can be identified based on their fractal dimension; and the list goes on.

Artificial life (ALife) will be discussed in Chapter 8. It corresponds to a research field that complements traditional biological sciences concerned with the analysis of living organisms by trying to synthesize life-like behaviors and creatures in computers and other artificial media (Langton, 1988; Adami, 1998; Levy, 1992). Differently from nature-inspired computing, approaches in the ALife field are usually not concerned with solving any particular problem. ALife has, as major goals, to increase the understanding of nature (life-as-it-is), enhance our insight into artificial models and possibly new forms of life (life-as-it-could-be), and to develop new technologies such as software evolution, sophisticated robots, ecological monitoring tools, educational systems, computer graphics, etc.

ALife systems have, thus, been designed to simulate and emulate behaviors or organisms in order to allow the study or simulation of natural phenomena or processes. In most cases it emphasizes the understanding of nature, and applications as a problem solver are left in second plan. For instance, ALife systems have been created to study traffic jams (Resnick, 1994); the behavior of synthetic biological systems (Ray, 1994); the evolution of organisms in virtual environments (Komosinski and Ulatowski, 1999); the simulation of collective behaviors (Reynolds, 1987); the study and characterization of computer viruses (Spafford, 1991); and others. Its major ambition is to build living systems out of non-living parts; that is, to accomplish what is known as 'strong ALife' (Sober, 1996; Rennard, 2004).

1.4.3. Computing with Natural Materials

Computing with natural materials is concerned with new computing methods based on other natural material than silicon. These methods result in a non-standard computation that overcomes some of the limitations of standard, sequential John von Neumann computers. As any mathematical operation can be broken down into bits, and any logical function can be built using an AND and a NOT gate, any computable 'thing' can be worked out by appropriately wired AND and NOT gates. This independence of a specific representation makes it possible to use new concepts for the computational process based on natural materials, such as, chemical reactions, DNA molecules, and quantum mechanical devices.

The history of computer technology has involved a sequence of changes from one type of realization to another; from gears to relays to valves to transistors to integrated circuits. Nowadays, a single silicon chip can contain millions of logic gates. This miniaturization of the most basic information processing elements is inevitably going to reach a state where logic gates will be so small so as to be made of atoms. In 1965 G. Moore (1965) observed that there is an exponential growth in the number of transistors that can be placed in an integrated circuit. According to what is now known as the "Moore's law", there is a doubling of transistors in a chip every couple of years. If this scale remains valid, by the end of this decade, silicon-based computers will have reached their limits in terms of processing power. One question that remains thus, is "What other materials or media can be used to perform computation in place of silicon?". Put in another form, after certain level of miniaturization of the computing devices, the standard physical laws will be no longer applicable, because quantum effects will begin to take place. Under this perspective, the question that arises refers to "How should we compute under quantum effects?".

Computing with natural materials is the approach that promises to bring a major change in the current computing technology in order to answer the questions above. Motivated by the need to identify alternative media for computing, researchers are now trying to design new computers based on molecules, such as membranes, DNA and RNA, or quantum theory. These ideas resulted in what is now known as *molecular computing* (Păun et al., 1998; Gramß et al., 2001; Calude and Păun, 2001; Păun and Cutkosky, 2002; Sienko et al., 2003) and *quantum computing* or *quantum computation* (Hirvensalo, 2000; Nielsen and Chuang, 2000; Pittenger, 2000), respectively. Figure 1.8 summarizes the main components of computing with natural materials.

Molecular computing is based upon the use of biological molecules (biomolecules) to store information together with genetic engineering (biomolecular) techniques to manipulate these molecules so as to perform computation. It constitutes a powerful combination between computer science and molecular biology. The field can be said to have emerged due to the work of L. Adleman who, in 1994, solved an NP-complete problem using DNA molecules and biomolecular techniques for manipulating DNA (Adleman, 1994). Since then, much has happened: several other 'molecular solutions' to complex problems have been proposed and molecular computers have been shown to perform universal computation. The main advantages of molecular computing are its high speed, energy efficiency, and economical information storage. An overall, striking observation about molecular computing is that, at least theoretically, there seem to be many diverse ways of constructing molecular-based universal computers. There are, of course, the possibility of errors and difficulties in implementing real molecular computers. When compared with the currently known silicon-based computers, molecular computers offer some unique features, such as the use of molecules as data structures and the possibility of performing massively parallel computations. In Chapter 9, this book reviews one particular molecular computing approach, namely, *DNA computing*.

When the atomic scale of logic gates is reached, the rules that will prevail are those of *quantum mechanics*, which are quite different from the classical rules that determine the properties of conventional logic gates. Thus, if computers are to become even smaller in the (not so far) future, quantum technology must complement or supplement the current technology. *Quantum computation* and *quantum information*, introduced in Chapter 10, is the study of the information processing tasks that can be accomplished using quantum mechanical systems (Nielsen and Chuang, 2000). In quantum computers information is stored at the microphysical level where quantum mechanisms prevail.

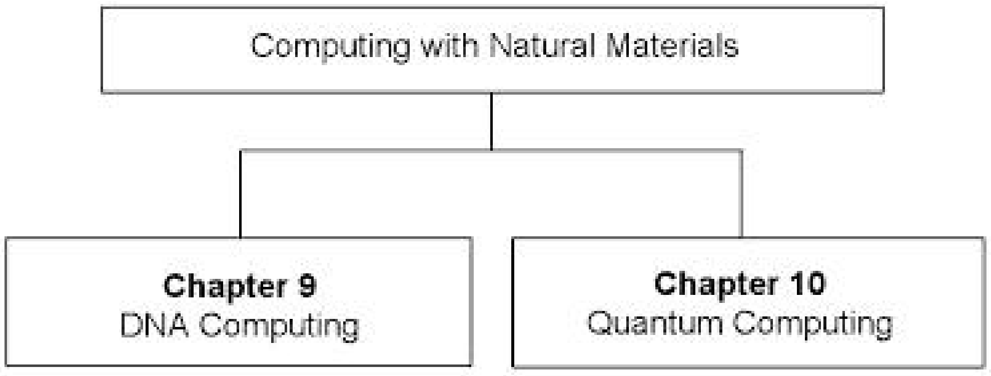

Figure 1.8: The two main branches of computing with natural materials or media.

In such cases, a bit could represent both zero and one simultaneously, and measurements and manipulations of these quantum bits are modeled as matrix operations. The seminal paper by R. Feynman (1982) introduced a computer capable of simulating quantum physics. A little later on, D. Deutsch (1984) published a paper where he demonstrated the universal computing capability of such quantum computers. Another seminal work that served to boost the field was the paper by P. Shor (1994) introducing the first quantum algorithm capable of performing efficient factorization, something that only a quantum computer could do. What is important to remark about quantum computing, though, is that it can provide entirely novel types of computation with qualitatively new algorithms based on quantum mechanics; quantum technology thus offers much more than simply adding the capability of processing more bits using the current silicon-based computers. Therefore, quantum computing aims at nontraditional hardware that would allow quantum effects to take place.

1.5 WHEN TO USE NATURAL COMPUTING APPROACHES

While studying this book, the reader will be faced with a diverse range of problems to be solved, phenomena to be synthesized and questions to be answered. In all cases, one or more of the natural computing approaches briefly reviewed above will be used to solve the problem, synthesize the phenomenon or answer the question. However, it is important to acknowledge that natural computing is not the only field of investigation that provides solutions to these, nor is it always the most suitable and efficient approach. To clarify when natural computing should be used, let us present some examples and arguments in each of the three branches. Let us assume that you have just finished your undergraduation course and now have an engineering or science degree in hand. In your first interview for a job in a major company, you are posed with three problems and given some time to provide solutions to them.

Problem 1: the company is expanding rapidly and now wants to build a new factory in a country so far unattended. The site where the factory is to be built has already been chosen as long as the cities to be attended by this factory. Figure 1.9 depicts the scenario. The problem is: given all the cities in the map find the smallest route from the factory to all cities passing by each city exactly once and returning to the departure city (factory). This problem is well-known from the literature and is termed *traveling salesman problem* (TSP).

Such problems have several practical applications, from fast food delivery to printed circuit board design. Although this problem may be simple to state it is hard to solve, mainly when the number of cities involved is large. For example, if there is one factory plus three other cities, then there are 6 possible routes; if there is one factory plus four other cities, then there are 24 possible routes; if there is one factory plus five other cities, then there are 120 possible routes; and so on. This corresponds to a factorial growth in the number of possible routes in relation to the number of cities to be attended.

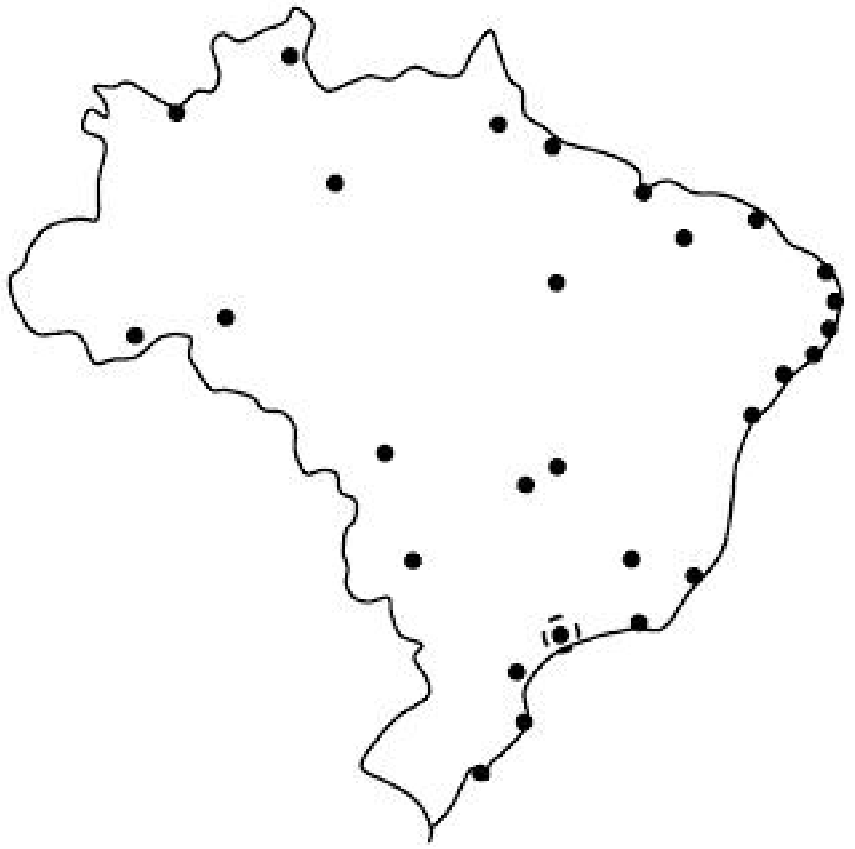

Figure 1.9: Map of the new country to be attended by the company. The city where the factory is going to be built is detached together with the 27 cities to be attended.

The most straightforward solution you could provide to this problem is to suggest the testing of all possible routes and the choice of the smallest one; an approach we usually call 'brute force' or 'exhaustive search'. Although simple, this approach is only efficient for a small number of cities. Assuming your computer is capable of analyzing 100 routes per second, it would take much less than a second to solve a three cities instance of this problem and a bit more than a second to solve a five cities instance of the problem. For the problem presented, however, the scenario is much different: there are 27! possible routes, and this corresponds to approximately 1.1×10^{28} possible routes to be tested. In your computer, the exhaustive search approach would take, approximately, 3.0×10^{23} hours, or 1.3×10^{22} days, or 3.5×10^{19} years of processing time to provide a solution. ■

Problem 2: the expansion plans of the company include the development of motion picture animations. The first animation to be designed involves a herd of zebras running away from a few hungry lions. Your task is to propose a means of realistically and effectively simulating the collective behavior of the zebras.

The first proposal you may come out with is to write a *script* for each zebra; that is, a computer program that fully describes the action of the zebras in the field. This, of course, would seem easier than writing a single script to coordinate the whole herd. Again, though simple, this approach has some drawbacks when the number of zebras involved is large and when more realistic scenarios are to be created. First, as the script is static, in the sense that the behaviors modeled do not change over time, the resultant collective behavior is the same every time the simulation is run. Second, the number of scripts to be written grows with the size of the herd and the complexity of the scripts grows in a

3. What is the Occam's Razor (also spelled Ockham's Razor)? What is its relationship with the approach usually adopted in natural computing (Section 1.3)?
4. Name some limitations of the current silicon-based computing paradigm.
5. Name one natural phenomenon, process, or system that is a potential candidate to become a new natural computing technique. Include the biological and theoretical background, and the utility of the approach proposed.

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also provide a better understanding of what is meant by and what is behind of many of the phenomena, processes, and systems studied in natural computing. Finally, this chapter makes use of the many concepts reviewed to start our discussion of nature, which led to the development of natural computing. Several natural systems and processes are used to illustrate the meaning of the concepts investigated here. Most of these examples from nature will be returned to in later chapters.

2.1.1. Natural Phenomena, Models, and Metaphors

All the approaches discussed in this volume are rooted on and sometimes enhanced by their natural plausibility and inspiration. The focus is on how nature has offered inspiration and motivation for their development. However, all these approaches are very appealing to us mainly for computational reasons, and they also may help us study and understand the world we inhabit, and even to create new worlds, new forms of life, and new computing paradigms. They hold out the hope of offering computationally sufficient accurate mechanistic accounts of the natural phenomena they model, mimic, or study, almost always with a view of computing, understanding, and problem solving. They have also radically altered the way we think of and see nature; the computational beauty and usefulness of nature.

Modeling is an integral part of many scientific disciplines and lies behind great human achievements and developments. Most often, the more complex a system, the more simplifications are embodied in its models. The term *model* can be found in many different contexts and disciplines meaning a variety of different things. Trappenberg (2002) has defined "models [as] abstractions of real world systems or implementations of a hypothesis in order to investigate particular questions or to demonstrate particular features of a system or a hypothesis." (Trappenberg, 2002; p. 7) It corresponds to a (schematic) description of a system, theory, or phenomenon, which accounts for its known or inferred properties and that may be used for further study of its characteristics. Put in a different form, models can be used to represent some aspect of the world, some aspect of theories about the world, or both simultaneously. The representative usefulness of a model lies in its ability to teach us something about the phenomenon it represents. They mediate between the real world and the theories and suppositions about that world (Peck, 2004).

The critical steps in constructing a model are the selection of salient features and laws governing the behavior of the phenomena under investigation. These steps are guided by *metaphor* and knowledge transfer (Holland, 1998). However, for purely practical reasons, many details are usually discarded. In the particular case of natural computing, models are most often simple enough to understand, but rich enough to provide (*emergent*) behaviors that are surprising, interesting, useful, and significant. If all goes well, what may commonly be the case, the result may allow for the prediction and even reproduction of behaviors observed in nature, and the achievement of satisfactory performances when a given function is required from the model.

The word *metaphor* comes from the Greek for 'transference'. It corresponds to the use of language that assigns one thing to designate another, in order to characterize the latter in terms of the former. Metaphors have traditionally been viewed as implicit comparisons. According to this view, metaphors of the form *X is a Y* can be understood as *X is like Y*. Although metaphors can suggest a comparison, they are primarily attributive assertions, not merely comparisons (Wilson and Keil, 1997; p. 535-537). For example, to name a computational tool developed with inspiration in the human brain an 'artificial neural network' or a 'neurocomputing device' corresponds to attributing salient properties of the human brain to the artificial neural network or neurocomputing device. The first part of this book, dedicated to computing inspired by nature, is sometimes referred to as *computing with biological metaphors* (Paton, 1994) or *biologically inspired computing* (de Castro and Von Zuben, 2004).

The use of metaphors from nature as a means or inspiration to develop computational tools for problem solving can also be exemplified by the development of 'artificial immune systems' for computer protection against viruses. One might intuitively argue: "if the human immune system is capable of protecting us against viruses and bacteria, why can't I look into its basic functioning and try to extract some of these ideas and mechanisms to engineer a computer immune system?" Actually, this type of metaphor has already been extracted, not only by academic research institutions, but also by leading companies in the computing area, such as IBM (Chapter 6). There is, however, an important difference between a metaphor and a model. While models are more concerned with quantitatively reproducing some phenomena, metaphors are usually high-levels abstractions and inspirations taken from a system or process in order to develop another. Most metaphors are basically concerned with the extraction or reproduction of qualitative features.

A simple formula, a computer simulation, a physical system; all can be models of a given phenomenon or process. What is particularly important, though, is to bear in mind what are the purposes of the model being created. In theoretical biology and experimental studies, models may serve many purposes:

- Through modeling and identification it is possible to provide a deeper and more quantitative description of the system being modeled and its corresponding experimental results.
- Models can aid in the critical analysis of hypotheses and in the understanding of the underlying natural mechanisms.
- Models can assist in the prediction of behaviors and design of experiments.
- Models may be used to simulate and stimulate new and more satisfactory approaches to natural systems, such as the behavior of insect societies and immune systems.
- Models may allow the recovery of information from experimental results.

An *experiment* can be considered as a procedure performed in a controlled environment for the purpose of gathering observations, data, or facts, demonstrating known facts or theories, or testing hypotheses or theories. Most biological experiments are usually made *in vivo*, within a living organism (e.g., rats and mice), or *in vitro*, in an artificial environment outside the living organism (e.g., a test tube).

There is a significant conceptual difference between experiment, simulation, realization, and emulation. In contrast to experiments, *simulations* and *realizations* are different categories of models (Pattee, 1988). Simulations are metaphorical models that 'stand for' something else, and may cover different levels of fidelity or abstraction. They can be performed by physical modeling, by writing a special-purpose computer program, or by using a more general simulation package that is usually still aimed at a particular kind of simulation. They can be used, for instance, to explore theories about how the real-world functions based on a controlled medium (e.g., a computer). As an example, the simulation of a car accident can be performed by specifying the place and conditions in which the car was driven and then using a given medium (e.g., the computer) to run the simulation. Computer simulation is pervasive in natural computing. It has been used to design problem-solving techniques that mimic the behavior of several biological phenomena (Chapter 3 to Chapter 6), it has served to drive synthetic environments and virtual worlds (Chapter 7 and Chapter 8), and it has been used to simulate DNA computers (Chapter 9).

The *realization* of a system or organism corresponds to a literal, material model that implements certain functions of the original; it is a substantive functional device. Roughly speaking, a realization is evaluated primarily by how well it can function as an implementation of a design specification, and not in relation to the goodness of the measurements (mappings) they perform. A system or function is used to realize another when one performs in exactly the same way as another (Pattee, 1988; Mehler, 2003). To *emulate* a system is to imitate or reproduce its functions using another system or medium. The emulating system has to perform the same functions of the emulated system in the way the latter does. A typical example in computer science is the emulation of one computer by (a program running on) another computer. You may emulate a system as a replacement for the system, whereas you may simulate a system if the goal is, for instance, simply to analyze or study it.

Natural computing approaches are aimed at simulating, emulating, and sometimes realizing natural phenomena, organisms, and processes with distinct goals. The metaphorical representation of simulations makes them suitable for designing problem solving techniques and mimics of nature. Realizations of nature, on the contrary, would be the primary target of the so-called strong artificial life (Chapter 8). It is also important to acknowledge that, as most natural computing approaches to be studied here usually have not the same goals as models, they have the advantages of being explicit about the assumptions and relevant processes incorporated, allowing for a closer control of the variables involved, and providing frameworks to explain a wide range of phenomena.

Due mainly to these differences in goals and levels of details incorporated, most of the highly simplified models discussed in this volume are usually treated as metaphors, simulations, or simple abstractions of natural phenomena or processes. In addition, natural computing techniques are usually based upon a different modeling approach. The theoretical models used in biological sciences are based, in most cases, on ordinary differential equations (ODE) or Monte Carlo simulations. For example, when theoretical biologists want to create a model of an army ant, they use some rule of thumb such as "the more pheromone (a chemical released by ants) an ant detects, the faster it runs". This rule would be translated into an equation of the type $dx/dt = kP$, where dx/dt is the speed (distance change, dx, divided by time change, dt) of the ant, k is a constant of proportionality, and P is the pheromone level. This simple formula captures the essence of ant movement as described.

Despite the differences in approach, level of details, and accuracy, it is undeniable, and this will become clearer throughout the text, that the inspiration from nature and the relationship with it is the core of natural computing. Metaphors are important approaches not only for the creation of useful and interesting tools, but they may also aid the design of more accurate models and a better understanding of nature. Thus, it is not surprising that many researchers in natural computing call their products models instead of metaphors.

2.1.2. From Nature to Computing and Back Again

In most cases, the first step toward developing a natural computing system is to look at nature or theoretical models of natural phenomena in order to have some insights into how nature is, works, and how it behaves. In other cases, it might happen that you have a given problem at hand, and you know some sort of natural system solves a similar problem. A good example is the immune system metaphor for computer security mentioned above. Another classical example is the neural network metaphor: if there are brains that allow us to reason, think, process visual information, memorize, etc., why can I not look into this system and try to find its basic functioning mechanisms in order to develop an (intelligent) 'artificial brain'?

The problem with the extraction of metaphors and inspiration from nature is that it is usually very difficult to understand how nature works. In the particular case of the brain, though some basic signal transmission processes might be already known (and many other facts as well), it is still out of human reach to fully uncover its mysteries, mainly some cognitive abilities such as hate and love. The use of technological means (e.g., computers) to simulate, emulate or reproduce natural phenomena may also not be the most suitable approach. Would computers, such as the ones we have nowadays, be suitable to build an 'artificial brain' or an 'artificial organism'? Can we simulate 'wetware' with the current 'hardware'? Furthermore, even if we do know how some natural processes work, would it still be suitable to simply reproduce them the way they are? For example, we know that most birds are capable of flying by flapping wings, however airplanes fly using propellers or turbines. Why do airplanes not fly by flapping wings?

Last, but not least, sometimes looking at nature or theoretical studies may not be sufficient to give us the necessary insight into what could be done in computing and engineering with these phenomena. We have already seen, in Chapter 1, that the clustering of dead bodies in ants may result in computer algorithms for solving clustering problems, and that simple behavioral rules applied to many virtual birds result in flock-like group behaviors. What if I tell you that the behavior of ants foraging for food resulted in powerful algorithms for solving combinatorial optimization problems? Also, what if I tell you that the behavior of ant prey retrieval has led to approaches for collective robotics? Can you have an idea of how these are accomplished without looking at the answers in Chapter 5?

Due to all these aspects, designing novel natural computing systems may not be a straightforward process. But this book is not about how to design new natural computing devices, though some insights about it will certainly be gained. Instead, it focuses on how the main natural computing systems available nowadays were motivated, emerged, and can be understood and designed. Designing natural computing systems is basically an engineering task; that is, physical, mechanical, structural, and behavioral properties of nature are made useful to us in computational terms. They can become new problem-solving techniques, new forms of (studying) nature, or new forms of computing. Each part of natural computing, and its many branches, is rooted in some specific feature(s):

- Evolutionary algorithms were inspired by evolutionary biology.
- Artificial neural networks were inspired by the functioning of the nervous system.
- Swarm systems are based on social organisms (from insects to humans).
- Artificial immune systems extract ideas from the vertebrate immune system.
- Fractal geometry creates life-like patterns using systems of interactive functions, L-systems, and many other techniques.
- Artificial life is based on the study of life on Earth to simulate life on computers and sometimes develop synthetic forms of life.
- DNA computing is based on the mechanisms used to process DNA strands in order to provide a new computing paradigm.
- Quantum computing is rooted on quantum physics to develop another new computing paradigm.

Although it is generally difficult to provide a single engineering framework to natural computing, some of its many branches allow the specification of major structures and common design procedures that can be used as frameworks to the design of specific natural computing techniques. For instance, evolutionary algorithms can be designed by specifying a representation for candidate solutions to a problem, some general-purpose operators that manipulate the candidate solutions, and an evaluation function that quantifies the goodness or quality of each candidate solution (Chapter 3). In artificial life, however, it is much harder to provide such a framework. It will be seen that most artificial life (ALife) approaches reviewed here are based on the specification of usually simple sets of rules describing the behavior of individual agents. The remaining of the ALife project will involve the modeling of the agents, environment, etc., which are not part of the scope of this book.

2.2 GENERAL CONCEPTS

2.2.1. Individuals, Entities, and Agents

There is a body of literature about *agents* and agent-based systems. One of the main themes of this book is collectivity; populations of individuals, insect societies, flocks of bird, schools of fish, herds of land animals, repertoires of immune cells and molecules, networks of neurons, and DNA strands. What all these systems have in common is the presence of a number of individual *entities* or *components*. When we model or study these systems, the *individuals* may go by the generic name of *agents*. However, the words individuals, entities, components, and agents are sometimes used interchangeably and with no distinction throughout the text.

The term agent is currently used to mean anything between a mere subroutine of a computer program and an intelligent organism, such as a human being. Intuitively, for something to be considered an agent, it must present some degree of autonomy or identity; that is, it must, in some sense, be distinguishable from its environment by some kind of spatial, temporal, or functional boundary. Traditionally, agent-based models are drawn on examples of biological phenomena and processes, such as social insects and immune systems (Rocha, 1999). These systems are formed by distributed collections of interacting elements (agents) that work under no central control. From simple agents, who interact locally following simple rules of behavior and responding to environmental stimuli, it is possible to observe a synergistic behavior that leads to higher-level behaviors that are much more intricate than those of individuals.

Agent-based research has a variety of definitions of what is an agent, each hoping to explain one particular use of the word. These definitions range from the simplest to the lengthiest ones. Here are some examples:

> "An agent is anything that can be viewed as perceiving its environment through sensors and acting upon that environment through effectors." (Russell and Norvig, 1995)
>
> "Perhaps the most general way in which the term agent is used is to denote a hardware or (more usually) software-based computer system that enjoys the following properties: autonomy, social ability, reactivity, and pro-activeness." (Wooldridge and Jennings, 1995) [Summarized definition, for the full version please consult the cited reference]
>
> "An autonomous agent is a system situated within and part of an environment that senses that environment and acts on it, over time, in pursuit of its own agenda and also so as to effect what it senses in the future." (Franklin and Graesser, 1997)

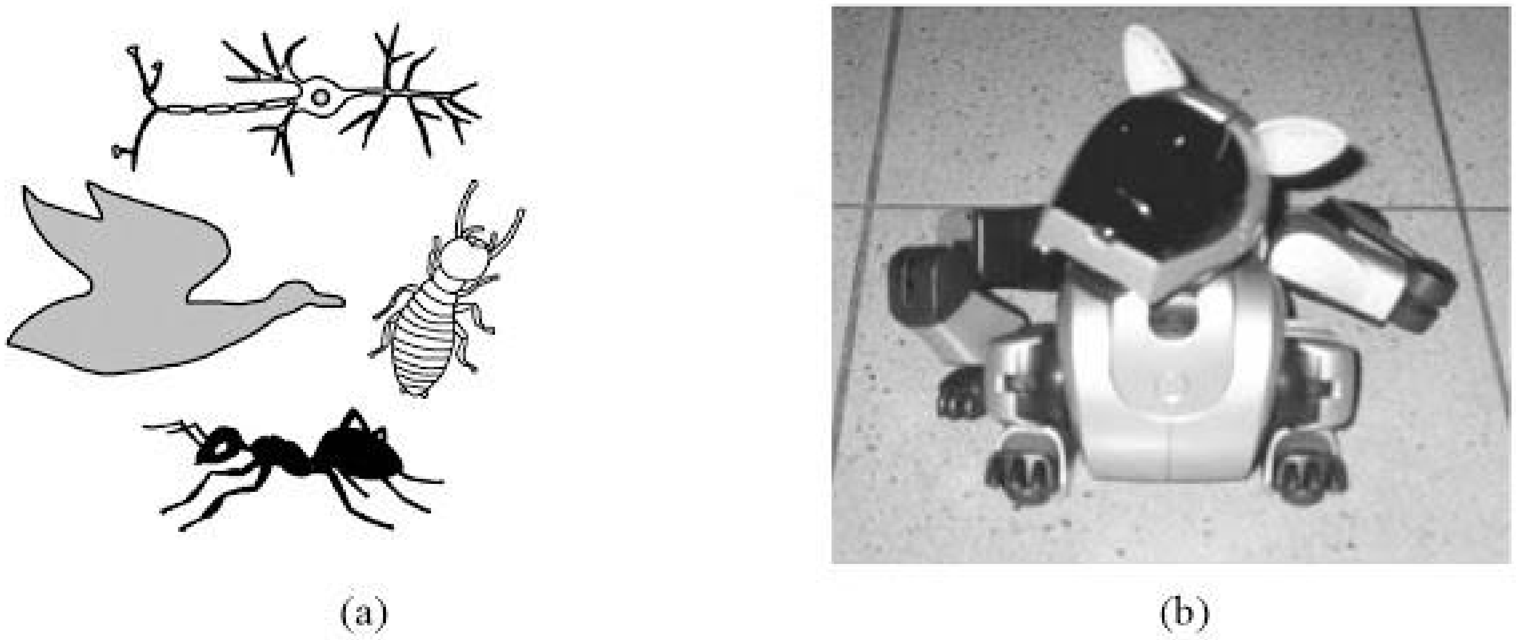


Figure 2.1: Examples of agents. (a) Pictorial representation of biological agents (bird, neuron, termite, and ant). (b) Physical agent (the AIBO ERS-210 robot by Sony®).

Therefore, an agent can be understood as an entity endowed with a (partial) representation of the environment, capable of acting upon itself and the environment, and also capable of communicating with other agents. Its behavior is a consequence of its observations, knowledge, and its interactions with other agents and the environment. Agents can be of many types, including biological (e.g., ants, termites, neurons, immune cells, birds, etc.), physical (e.g., robots), and virtual agents (e.g., a computer algorithm, Tamagotchi, etc.), as illustrated in Figure 2.1.

2.2.2. Parallelism and Distributivity

There are several well-known examples involving the capability of processing more than one thing at the same time. In the natural world, *parallel processing* is evident in insect societies, brain processing, immune functioning, the evolution of species, and so forth. All these examples will be studied in this book.

In order for evolution to occur, there must be a number of individuals in a population competing for limited resources. These individuals suffer genetic variation and those more fit (adapted) to the environment have higher probabilities of survival and reproduction. All the individuals in the population play important roles in exploring the environment and sometimes exchanging (genetic) information, thus producing progenies more adapted to the life in a spatial location.

In insect societies, in particular in ant colonies, a colony of ants has individuals assigned to various tasks, such as harvesting food, cleaning the nest, and caring for the queen. Termites, bees, and wasps also perform similar tasks in a distributed way; there are individuals allocated for different tasks. All insects in a colony work in parallel in a given task, but they may switch tasks when needed. For instance, some worker ants may be recruited for battle when the nest is being invaded.

In immune systems, a large variety and number of cells are involved in an immune response. When a virus infects a cell, some specialized immune cells, named T-cells, recognize fragments of this virus presented by a molecular complex of another specialized antigen presenting cell. This recognition triggers the action of many other immune cells to the site of infection. In addition, several other cells are performing the same and other processes, all at once in a distributed and parallel form.

In the human nervous system, a huge number of neurons are involved in processing information at each time instant. Talking while driving, watching TV while studying, hearing a name while having a conversation with someone in the middle of a party (a phenomenon called the 'cocktail party effect'), all these are just samples of a kind of parallel processing. Who does not know about the joke of not being able to walk while chewing gum? The vast number of neurons we have endow us with this capability of processing multiple information from multiple sensors at the same time.

What is surprising about each of the individual processes from the examples above is that they are all a product of a large number of elements and processes occurring in parallel. At the lowest level of analysis, evolution requires a large number of individuals to allow for a genetic variety and diversity that ultimately result in a higher adaptability; insect colonies are composed of thousands, sometimes millions, of insects that work in concert to maintain life in the colony; immune systems are composed of approximately 10^{12} lymphocytes (a special type of immune cell); and the human brain contains around 10^{11} nervous cells. Each of these individual agents contributes its little bit to the overall global effect of evolution, maintenance of life in the colony (insects), and the body (immune systems), and thought processes and cognition (nervous system).

From a biological and computational perspective, all the end results discussed are going to be emergent properties of the parallel and distributed operations of individual entities. All these systems can be termed *parallel-distributed systems* (PDS). Rumelhart and collaborators (Rumelhart et al., 1986; McClelland et al., 1986) have coined the term *parallel distributed processing* (PDP) to describe parallel-distributed systems composed of processing elements, in particular neurons. They used this terminology to refer to highly abstract models of neural function, currently known as *artificial neural networks* (ANN). These will be discussed in more detail in Chapter 4 under the heading of Neurocomputing. PDP networks are thus a particular case of parallel-distributed systems.

2.2.3. Interactivity

A remarkable feature of natural systems is that individual agents are capable of interacting with one another or the environment. Individual organisms interact with one another in variety of forms: reproductively, symbiotically, competitively, in a predator-prey situation, parasitically, via channels of communication, and so on. At a macro level, an important outcome of these interactions is a struggle for limited resources and life. Individuals more adapted to the (local) environment tend to survive and mate thus producing more progenies and propagating their genetic material. Genetic variation together with the selection of the fittest individuals leads to the creation of increasingly fitter species. Besides, interactivity allows for the emergence of self-organized patterns.

Interactivity is an important mean nature has to generate and maintain life. Complex systems, organisms, and behaviors emerge from interacting components. For instance, take the case of genes, known to be the basic functional elements of life. Researchers have created genetically modified organisms in which a single gene has been deleted or blocked, a process known as *knockout*. In some situations, these researchers have been surprised to find that some other gene(s) can take over its whole function or at least part of it. Similar cases are constantly being reported in the news where people with damaged brains, from accidents for example, are capable of recovering some of their lost functions after often long periods of treatment and recovery. It is observed, in most of these cases, that other portions of the brain assume the functions previously performed by the damaged areas. Interactions, thus, are not only necessary for the complexity, diversity, and maintenance of life, but it also leads to emergent phenomena and behaviors that cannot be predicted by simply looking at discrete components.

In all the main systems studied in this book, several types of interactions can be observed. For instance, immune cells and molecules communicate with one another and foreign agents through chemical messengers and physical contact; insects may also communicate with one another via chemical cues, dancing (e.g., bees dance to indicate where there is food to the other bees in the nest) or physical contact (e.g., antennation); and neurons are known to be connected with one another via small portions of its axons known as synapses. All these communication and contact means allow for the interaction of individual agents in the many systems. The interactions between individuals can be basically of two types: direct and indirect. One important example of direct interaction, namely *connectivity*, and one important example of indirect interaction, namely *stigmergy*, will be discussed in the next two sections. Other important examples of direct interaction are reproduction and molecular signaling, and these will be specifically discussed in the next few chapters.

Connectivity

Connectionist systems employ a type of representation whereby information is encoded throughout the nodes and connections of a network of basic elements, also called units. Their content and representational function is often revealed only through the analysis of the activity patterns of the internal units of the system. Although the term *connectionism* appeared in the mid 1980s to denote network models of cognition based on the spreading activation of numerous simple units (cf. Rumelhart et al., 1986; McClelland et al., 1986), it can refer to any approach based on interconnected elements. These systems are sometimes referred to as *networks*.

The peculiarity of connectionist systems is due to several factors. The connections establish specific pathways of interaction between units; two units can only interact if they have a connection linking them. The connection is also in most cases an active element of interaction, i.e., it not only specifies who interacts with whom, but it also quantifies the degree of this interaction by weighting the signal being transmitted. The direct interaction via connections also results in a structured pattern for the system that may, for instance, reflect the structural organization of the environment in which the network is embedded. Networks are also very successful examples of parallel-distributed processors, for instance, neural networks and immune networks. These two types of networks will be fully explored in this book in Chapter 4 and Chapter 6, respectively.

Stigmergy

Grassé (1959) introduced the concept of *stigmergy* as a means to refer to how the members of a termite colony of the genus *Macrotermes* coordinate nest building. He realized how individual termites could act independently on a structure without direct communication or interactions. This process was termed *indirect social interactions* to describe the same mechanism of indirect communication among bees in a bee colony (Michener, 1974).

The concept of stigmergy provides a general mechanism that relates individual and colony-level behaviors: individual behaviors modify the environment, which in turn modifies the behavior of other individuals. The environment thus mediates the communication of individuals, i.e., there is an indirect communication, instead of direct, by means such as antennation, trophalaxis (food or liquid exchange), mandibular contact, visual contact, and so on (Bonabeau et al., 1999). Self-organization is thus made possible due to the intensity of the stigmergic interactions among termites that can adopt a continuum of interactions.

Grassé (1959) gave the original example to illustrate stigmergy involving nest building in termite colonies (Figure 2.2). He observed that termite workers are stimulated to act during nest building according to the configuration of the construction and of other workers. Termite workers use soil pellets, which they impregnate with a chemical substance known as *pheromone*, to build pillars. Initially, termites deposit pellets in a random fashion until one of the deposits reaches a critical size. Then, if the group of builders is large enough and the pillars start to emerge, a coordination phase begins. The accumulation of pellets reinforces the attractivity of deposits due to the diffusing pheromone emitted by the pellets. Therefore, the presence of an initial deposit of soil pellets stimulates workers to accumulate more pellets through a *positive feedback* or self-reinforcing mechanism (Dorigo et al., 2000).

It is possible to extend the idea of stigmergy to other domains (Holland and Melhuish, 1999). It can be seen as an even more impressive and general account of how the interaction of simple entities, such as ants or termites, can produce a wide range of highly organized and coordinated behaviors and behavioral outcomes, simply acting and exploiting the influence of the environment. By exploiting the stigmergic approach to coordination, researchers have been able to design a number of successful algorithms and systems that can be applied to several domains, such as discrete optimization, clustering, and robotics.

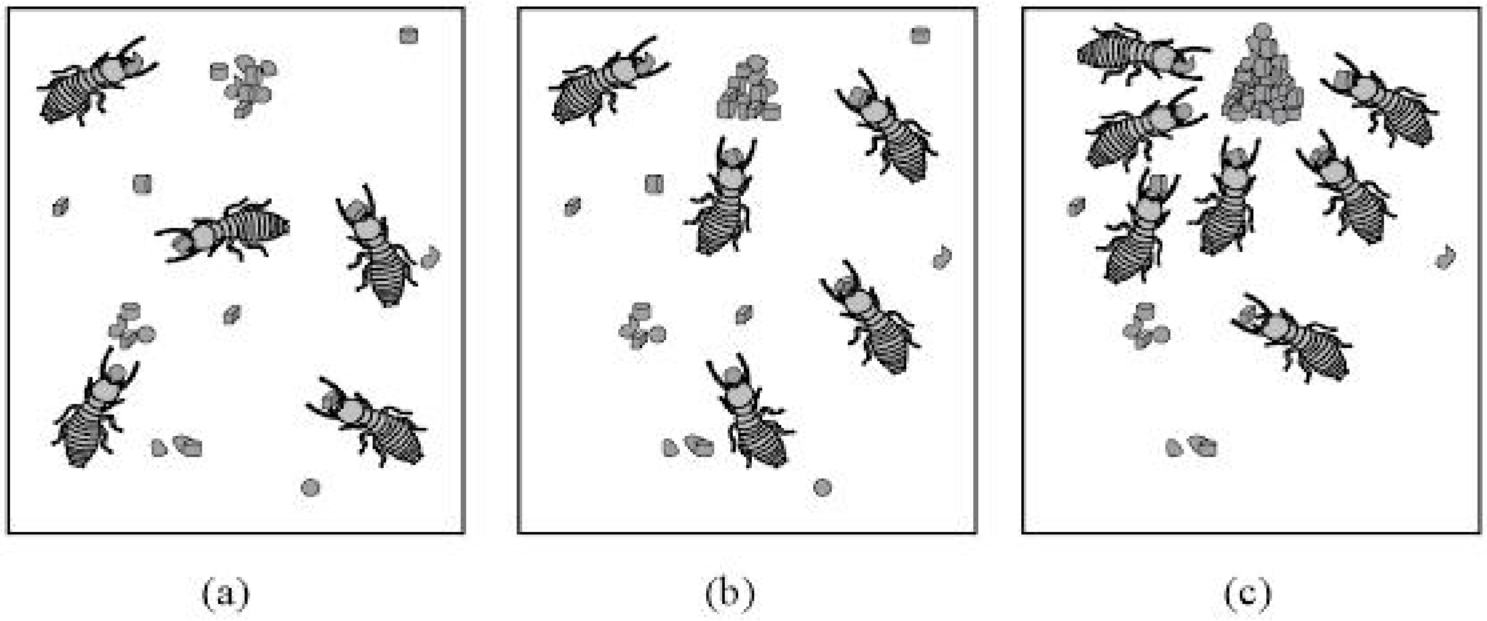


Figure 2.2: Termite mound building. (a) Pellets are initially deposited randomly in space. If the group of builders is large enough and pillars start to emerge (b), then a coordinated building phase starts (c).

Chapter 5 reviews some of these applications focusing on those systems inspired by the behavior of ants. Chapter 8 also provides some examples of stigmergic interactions such as the wasp nest building behavior.

2.2.4. Adaptation

Adaptation can be defined as the ability of a system to adjust its response to stimuli depending upon the environment. Something, such as an organism, a device, or a mechanism, that is changed (or changes) so as to become more suitable to a new or a special application or situation, becomes more adapted to the new application or situation. The use of the word adaptation is, in many cases, related with *evolution* (cf. Wilson and Keil, 1999; p. 3–4). However, many other important concepts in natural computing, such as learning and self-organization, can also be viewed as types of, or resulting from, adaptation mechanisms.

Learning

Learning may be viewed as corresponding to the act, process, or experience of gaining knowledge, comprehension, skill, or mastery, through experience, study, or interactions. Learning systems are those able to change their behavior based on examples in order to solve information-processing demands. An important virtue of adaptation in learning is the possibility of solving information processing tasks and the ability to cope with changing (dynamic) environments.

A consideration of what it takes to learn reveals an important dependence on gradedness (the passing through successive stages of changes) and other aspects of natural mechanisms (O'Reilly and Munakata, 2000). Learning, or more generally adapting, can be viewed as a synonym for *changing* with the end result of knowledge (memory) acquisition. When a system learns it changes its pattern of behavior (or another specific feature), such as the way information is processed.

It is much easier to learn if the system responds to these changes in a graded, proportional manner, instead of radically altering the way it behaves.

These graded changes allow the system to try out a number of different patterns of behavior, and get some kind of graded proportional indication of how these changes are affecting the system's interaction with the environment. By exploring several little changes, the system can evaluate and strengthen those that improve performance, while abandoning or weakening those that do not. There are, however, other types of learning procedures in nature that are more discrete than the graded one just described. For instance, it is believed that there are some specialized areas in the brain particularly good at 'memorizing' discrete facts or events.

In contrast to some beliefs, learning does not depend purely on consciousness and also does not require a brain. Insect societies learn how to forage for food, and our immune systems learn how to fight against disease-causing agents - a principle explored in the vaccination procedures. Even evolution can be viewed as resulting in learning, though evolutionary systems are more appropriately characterized as adaptive systems in the context of natural computing.

Neurocomputing models, and others based on computational neuroscience, provide useful accounts of many forms of learning, such as graded learning and memorization. Chapter 4 reviews some of the standard and most widely spread neurocomputing techniques, and provides a discussion about the main learning paradigms in this field, namely *supervised*, *unsupervised*, and *reinforcement learning*.

Evolution

In its simplest form, the *theory of evolution* is just the idea that life has changed over time, with younger forms descending from older ones. This idea existed well before the time of Charles Darwin, but he and his successors developed it to explain both the diversity of life and the adaptation of living things to their environment (Wilson and Keil, 1999; p. 290–292).

In contrast to learning, evolution requires some specific processes to occur. First, evolution involves an individual or a population of individuals that reproduce and suffer genetic variation followed by natural selection. Without any one of these characteristics, there is no evolution. Therefore, there cannot be evolution if there is a single individual, unless this individual is capable of asexually reproducing. Also, some variation has to occur during reproduction so that the progeny brings some 'novelty' that allows it to become more adapted to the environment. Finally, natural selection is responsible for the maintenance of the genetic material responsible for the fittest individuals to the environment; these will have survival and reproductive advantages over the others, less fit individuals. The outcome of evolution, like the outcome of learning, is a better adaptability to life and the environment.

Both, the evolved genetic configuration of organisms together with their learning capabilities make important contributions to their adaptability to the environment. But perhaps only in the context of learning the genetic encoding can be fully understood, much as the role of DNA itself in shaping the phenotype must be understood in the context of emergent developmental processes.

2.2.5. Feedback

Essentially, *feedback* occurs when the response to a stimulus has an effect of some kind on the original stimulus. It can be understood as the return of a portion of the output of a process or system to the input, especially when used to maintain performance or to control a system or process. The nature of the response determines how the feedback is labeled: *negative feedback* is when the response diminishes the original stimulus (they go in the opposite direction); and *positive feedback* is when the response enhances the original stimulus (they go in the same direction). An important feature of most natural systems described in this text is that they rely extensively on *feedback*, both for growth and self-regulation.

Take the case of the human brain as an example of extensive feedback loops and their importance. The brain can be viewed as a massive network of neurons interconnected via tiny gaps known as synapses. Any brain activity, such as thinking of a word or recognizing a face, triggers a vast array of neural circuitry. Each new brain activity triggers a new array, and an unimaginably large number of possible neuronal circuits go unrealized during the lifetime of an individual. Beneath all that apparent diversity, certain circuits repeat themselves over and over again. All these feedback and reverberating loops are believed to be necessary for learning, and are consequences of the high interconnectivity of the brain.

Positive Feedback

Positive feedback is a sort of self-reinforcing (growth) process in which the more an event occurs, the more it tends to occur. Take the case of the immune system as an example. When a bacterium invades our organism, it starts reproducing and causing damage to our cells. One way the immune systems find to cope with these reproducing agents is by reproducing the immune cells capable of recognizing these agents. And the more cells are generated, the more cells can be generated. Furthermore, the immune cells and molecules release chemicals that stimulate other immune cells and molecules to fight against the disease-causing agent. Therefore, the response of some immune cells provides some sort of *positive feedback* to other immune cells reproduce and join the pool of cells involved in this immune response.

The termite mound building behavior discussed previously is another example of a positive feedback mechanism. The more soil pellets are deposited in a given portion of the space, the more pellets tend to be deposited in that portion because there is more pheromone attracting the termites (Figure 2.3). But these self-reinforcing (positive feedback) processes have to be regulated by *negative feedback* processes, otherwise the systems would go unstable or the resources would be depleted.

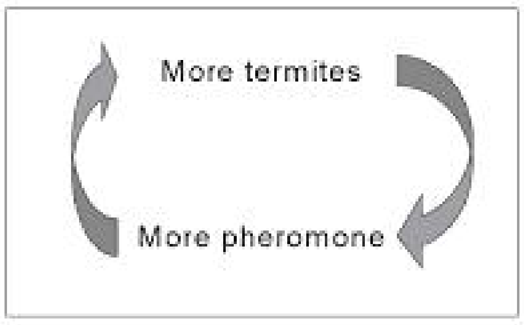


Figure 2.3: Example of positive feedback.

There are several other examples of positive feedback in nature:

- *Human breeding*: the more humans reproduce, the more humans exist to reproduce.
- *Feeding the baby*: a baby begins to suckle her mother's nipple and a few drops of milk are released, stimulating the production and release of more milk.
- *Avalanche*: an avalanche starts at rest and, when disturbed, accelerates quickly towards its end point at the base of a slope.
- *Autocatalysis*: autocatalysis occurs in some digestive enzymes such as pepsin. Pepsin is a protein-digesting enzyme that works in the stomach. However, the stomach does not secrete pepsin; it secretes an inactive form, called pepsinogen. When one pepsinogen molecule becomes activated, it helps to activate other pepsinogens nearby, which in turn can activate others. In this way, the number of active pepsin molecules can increase rapidly by using positive feedback.
- *Giving birth*: while giving birth, the more uterine contractions a mother has, the more it is stimulated to have, until the child is born.
- *Scratching an itch*: scratching an itch makes it more infected and damaged, and thus more itchy.
- *Ripening fruits*: a ripening apple releases the volatile plant hormone ethylene, which accelerates the ripening of unripe fruit in its vicinity; so nearby fruits also ripen, releasing more ethylene. All the fruits become quickly ripe.

Negative Feedback

Negative feedback by contrast, plays the role of regulating positive feedback so as to maintain a(n) (dynamic) equilibrium of the medium. It refers to change in the opposite direction to the original stimulus. The thermostat is one of the most classic examples of negative feedback. It takes the reading of a room's temperature, measures that reading according to a desired setting, and then adjusts its state accordingly. If the room's temperature is too low, more hot air is allowed to flow into the room; else if the temperature is too high, then more cold air flows into the room (Figure 2.4).

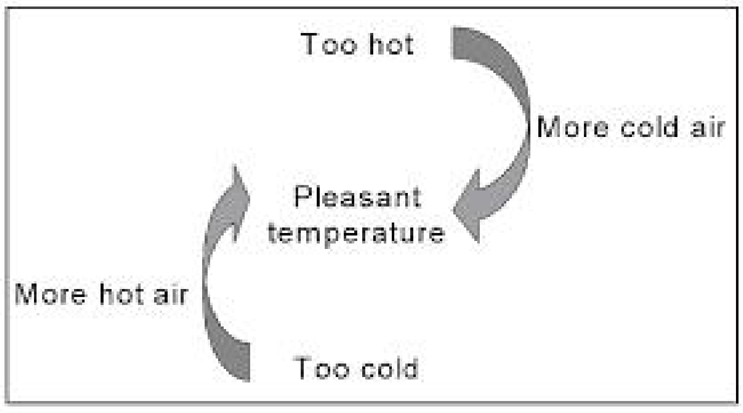


Figure 2.4: Example of negative feedback.

Negative feedback is at the heart of every stable, self-regulating system. If a company raises prices too high, people stop buying, and soon the company cuts the price to increase sales. In the immune system example given above, after the infection is successfully eliminated, specific immune cells are stimulated to release other chemical substances that suppress the replication of immune cells, thus ceasing the immune response. Without this negative feedback mechanism, death by uncontrolled cell reproduction would be inevitable. And without the positive feedback, death from infection would be inevitable.

There are also plenty of examples of negative feedback in nature:

- *Ecosystems*: in an ecosystem composed of, say rabbits and grass, when there is plenty of grass to feed the rabbits, they tend to reproduce with greater rates. But as there are more rabbits in the environment, the more grass will be eaten, and the less grass will be left as food; the amount of grass provides a feedback to the rabbits birth rate.
- *Homeostasis*: blood glucose concentrations rise after eating a meal rich in sugar. The hormone insulin is released and it speeds up the transport of glucose out of the blood and into selected tissues, decreasing blood glucose concentrations.
- *Metabolism*: exercise creates metabolic heat that raises the body temperature. Cooling mechanisms such as vasodilatation (flushed skin) and sweating begin, decreasing the body temperature.
- *Climate theory*: the curvature of the earth helps making it so that continental glaciers expanding equator ward experience strong sunlight and tend to melt. Another example is the tendency for continental glaciers to make cold, high-pressure regions, which do not favor further snowfall.

2.2.6. Self-Organization

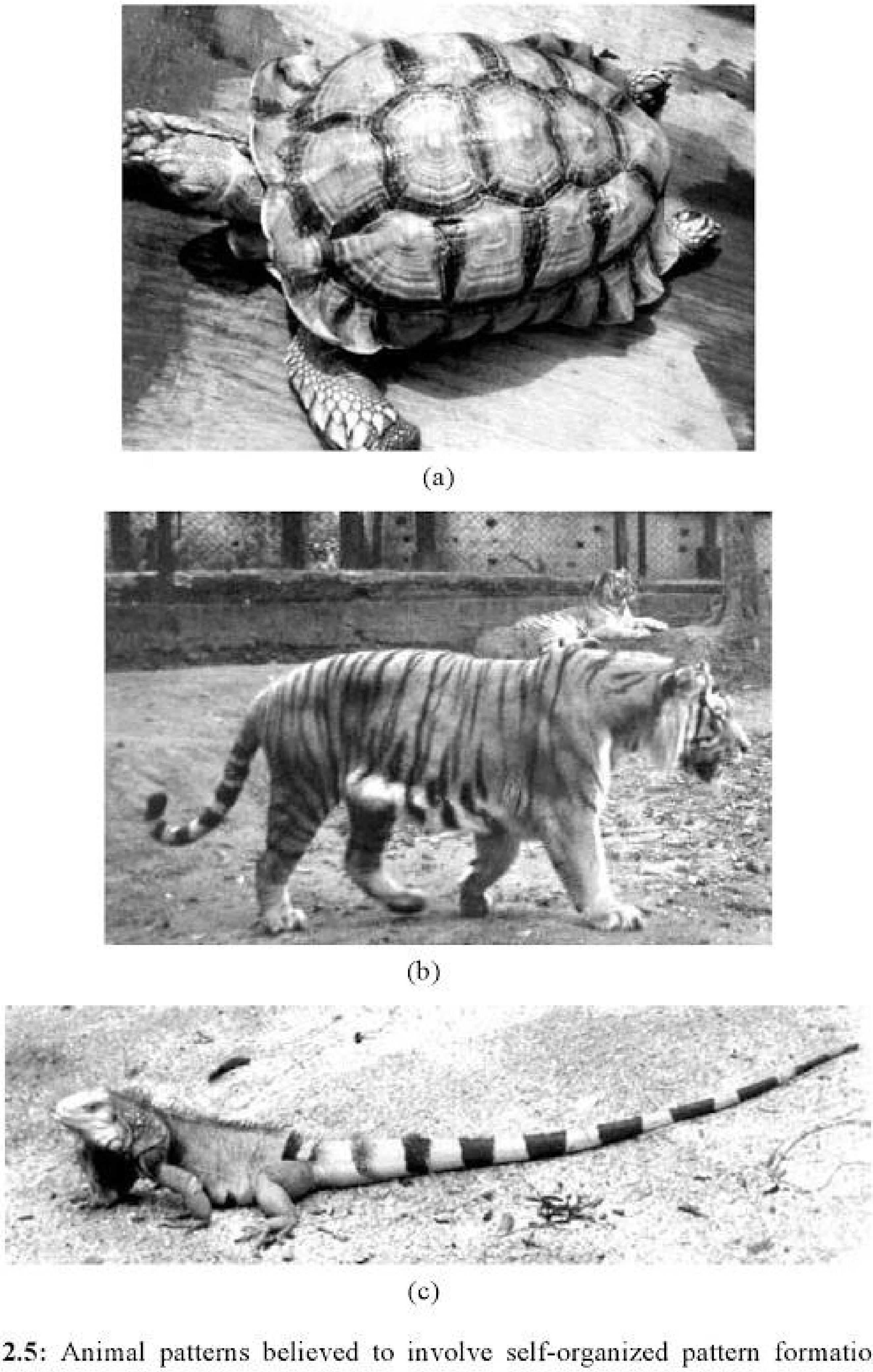
An important question in biology, physics, and chemistry is "Where does order come from?" The world abounds with systems, organisms, and phenomena that maintain a high internal energy and organization in seeming defiance of the laws of physics (Decker, 2000). Water particles suspended in air form clouds; a social insect grows from a single celled zygote into a complex multicellular organism and then participates in a structured social organization; birds gather together in a coordinated flock; and so forth. What is so fascinating is that the organization seems to emerge spontaneously from disordered conditions, and it does not appear to be driven solely by known physical laws or global rules. Somehow, the order arises from the multitude of interactions among the simple parts. Self-organization may also go by the name 'emergent structuring', 'self-assembly', 'autocatalysis', and 'autopoiesis', though most of these concepts have some slight differences to the self-organization concept provided here (see Project 3).

Self-organization refers to a broad range of pattern-formation processes in both physical and biological systems, such as sand grains assembling into rippled dunes, chemical reactants forming swirling spirals, cells making up highly structured tissues, and fishes joining together in schools. A basic feature of these diverse systems is the means by which they acquire their order and structure. In self-organizing systems, pattern formation occurs through interactions internal to the system, without intervention by external directing influences. As used here, a *pattern* corresponds to a particular, organized arrangement of objects in space or time. Examples of biological behavioral patterns include a school of fish, a raiding column of army ants, the synchronous flashing of fireflies, and the complex architecture of a termite mound (Camazine et al., 2001). But self-organization does not only affect behavioral patterns, it is also believed to play a role in the definition of patterns, such as shapes, and the coating of several animals (see Figure 2.5). In these cases, it is believed that not only the genetic code of these animals determine their physical expressed characteristics, some self-organized processes may also be involved.

The concept of self-organization can also be conveyed through counterexamples. A system can form a precise pattern receiving instructions from outside, such as a blueprint, recipe, orders, or signals. For instance, the soldiers marching form a neat organized process that is not self-organized. Their sequence of steps, direction of movement, velocity, etc., are all dictated by specific instructions. In such cases, the process is organized but not self-organized. It is less obvious, however, to understand how a definite pattern can be produced in the absence of such instructions.

The self-organized pattern formation in social systems is one of the main themes of this book, and will become clearer and more exemplified along the chapters. It will be seen that many social insects, such as ants, termites, and bees, are capable of building extremely complex nests without following any blueprint, recipe, leader, or template. It is interesting to note that, although all of them have a queen (the queen ant, the queen termite, and the queen bee), queens are basically involved in reproduction, mainly when the colony size is very large.

There is even an interesting historical fact about the queen bee. Until the late 19^{th} century, in a time when men were considered superior to women, queen bees were called kings, because people could not accept that anything so well organized could be run by females. Although females could actually run the colony, it is now known that, in most cases, the main role of the queens is to lay eggs. Even more surprising, such complex patterns of behavior, architecture designs, and foraging and hunting strategies, do not require any global control or rule whatsoever; they are amazing self-organized undertakings.



(a)

(b)

(c)

Figure 2.5: Animal patterns believed to involve self-organized pattern formation. (a) Polygonal shapes on the shell of a turtle. (b) Stripes coating the tiger skin. (c) Stripes in the iguana's tail.

Characteristics of Self-Organization

Self-organization refers to spontaneous ordering tendencies sometimes observed in certain classes of complex systems, both natural and artificial. Most self-organized systems present a number of features:

- *Collectivity and interactivity*: self-organizing systems (SOS) are usually composed of a large number of elements that interact with one another and the environment.
- *Dynamics*: the multiplicity of interactions that characterize self-organizing systems emphasize that they are dynamic and require continual interactions of lower-level components to produce and maintain structure.
- *Emergent patterns*: SOS usually exhibit what appears to be spontaneous order; the overall state of a self-organized system is an emergent property.
- *Nonlinearities*: an underlying concept in self-organization is nonlinearity. The interactions of components result in qualitatively new properties that cannot be understood as the simple addition of the individual contributions.
- *Complexity*: most self-organizing systems are complex. The very concepts of complexity and emergence are embodied in SOS. However, it is more accurate to say that complex systems can be self-organizing systems.
- *Rule-based*: most SOS are rule-based, mainly biological self-organizing systems. Examples of rules governing natural self-organized systems were already reviewed, such as the ones that result in dead body clustering in ant colonies. Further examples will be given in the following chapters.
- *Feedback loops*: positive and negative feedback contribute to the formation of self-organized processes by amplifying and regulating fluctuations in the system.

Alternatives to Self-Organization

Self-organization is not the only means responsible for the many patterns we see in nature. Furthermore, even those patterns that arise through self-organization may involve other mechanisms, such as the genetic encoding and physical constraints (laws). Camazine et al. (2001) provide four alternatives to self-organization:

- *Following a leader*: a well-informed leader can direct the activity of the group, providing each group member with detailed instructions about what to do. For example, a captain in a battle field gives order to each soldier relating to where to attack, etc.

- *Building a blueprint*: a blueprint is a compact representation of the spatial or temporal relationships of the parts of a pattern. For instance, each musician of an orchestra receives a musical score that fully specifies the pattern of notes within the composition and the tonal and temporal relationships among them.
- *Following a recipe*: each member of the group may have a recipe, i.e., a sequential set of instructions that precisely specify the spatial and temporal actions of the individual's contribution to the whole pattern. For example, you tell someone how to get to your place by specifying the precise sequence of streets he/she must follow. A blueprint is different from a recipe because it does not specify how something is done, only what is to be done.
- *Templates*: a template is a full-size guide or mold that specifies the final pattern and strongly steers the pattern formation process. For example, a company that makes car parts uses a template in which raw material is poured in order to make the desired parts; each part has its own template.

2.2.7. Complexity, Emergence, and Reductionism

Complexity and emergence are some of the most difficult terms to conceptualize in this chapter. Viewpoints and definitions of complexity (complex systems) and emergence vary among researchers and disciplines. This section discusses only some of the many perspectives; further and more complete studies can be found, for instance, in (Emmeche, 1997; Baas and Emmeche, 1997), the special issue on Complex Systems of the Science magazine (Science, 1999), on the Santa Fe volumes on Artificial Life and Complex Systems (e.g., Cowan et al., 1994; Morowitz and Singer, 1995), and on the Artificial Life and Complex Systems journals (see Appendix C).

Complexity

To start the discussion, let us present a very simplistic idea that fits into the context of natural computing: a *complex system* is a system featuring a large number of interacting components whose aggregate activity is nonlinear (not derivable by summing the behavior of individual components) and typically exhibit self-organization (Morowitz and Singer, 1995; Holland, 1995; Gallagher and Appenzeller, 1999; Rocha, 1999). Consider the case of an organism; say the human body. Can you fully uncover how it works by looking at its major systems and organs? The answer is no. Take an even more reductionist approach, and try to understand the organism by analyzing all its cells and molecules. Can you understand it now? Not still. Some limitations of this more traditional *reductionist* way of thinking will be discussed later. What is important here is the fact that for complex systems we are unable to understand/explain their behavior by examining its component parts alone.

The studies on *complexity* suggest that not only the internal organization (e.g., the genetic code of a biological organism) of a system is sufficient for its full understanding, but also how the system itself and its component parts interact with one another and the environment. The internal microstructure, self-organizing capabilities, and natural selection are part of the most important aspects necessary for a better understanding of complex systems.

Perhaps the most remarkable contribution of complexity to science was the perception that many natural phenomena and processes can be explained and sometimes reproduced by following some basic and simple rules. For instance, the most striking aspects of physics are the simplicity of its laws. Maxwell's equations, Schrödinger's equations, and Hamiltonian mechanics can each be expressed in a few lines. Many ideas that form the foundations of nature are also very simple indeed: nature is lawful, and some basic laws hold everywhere. Nature can produce complex structures even in simple situations and can obey simple laws even in complex situations (Goldenfeld and Kadanoff, 1999).

The five basic forms of investigating complex systems have already been discussed (Section 2.1.1), namely, experimentation, simulation, theoretical modeling, emulation, and realization. Experiments are necessary for raising a range of information about how the natural organisms and processes behave. Simulations are often used to check the understanding, validate experimental results, or simulate a particular system or process. Theoretical models are useful for the understanding, complementation, prediction, critical analysis, and quantitative and qualitative description of natural phenomena. Finally, realizations and emulations are fundamental for the possibility of creating and studying (new) life-like patterns and forms of life.

In order to explore the complexity inherent in nature, one must focus on the right level of description. In natural computing, higher-levels of description are usually adopted. Most systems developed are highly abstract models or metaphors of their biological counterparts. The inclusion of too many processes, details, and parameters, can obscure the desired qualitative understanding and can also make the creation of computational systems based on nature unfeasible. For instance, the 'artificial' neural networks are based upon very simple mathematical models of neural units structured in a network-like architecture and subjected to an iterative procedure of adaptation (learning). Despite all this simplicity, the approaches to be presented still capture some important features borrowed from nature that allow them to perform tasks and solve problems that, in most cases, could not be solved satisfactorily with the previously existing approaches.

In *Hidden Order*, J. Holland (1995) starts with a discussion of how natural (biological and social) systems are formed and self-sustained. Among the several instances discussed, there is the case of the immune system with its numerous cells, molecules and organs. Other examples range from the New York City to the central nervous system. These systems are termed *complex adaptive systems* (CAS), in which the (complex) behavior of the whole is more than a simple sum of individual behaviors. One of the main questions involved in complex adaptive systems is that of how a decentralized system - with no central planning or control - is self-organized.

Despite the differences among all complex adaptive systems and organizations, in most cases, the persistence of the system relies on some main aspects: 1) *interactions*, 2) *diversity*, and 3) *adaptation*. Adaptability allows a system or organism to become better fit to the environment or to learn to accomplish a given task. Adaptability also has to do with the system's capability of processing information (or computing); another important feature of a complex adaptive system. The major task of surviving involves the gathering of information from the environment, its processing and responding accordingly. It is clear, thus, that computing or processing information does not require a brain; ants, immune systems, evolutionary processes, flocks of birds, schools of fish, and many other complex adaptive systems present the natural capability of processing information.

According to Holland, the choice of the name *complex adaptive systems* is more than a terminology "It signals our intuition that general principles rule CAS behavior, principles that point to ways of solving attendant problems." (Holland, 1995; p. 4). This turns back to the idea that there are general rules or principles governing natural systems. The question, thus, can be summarized as how to extract these general principles. This is also one of the main aims of this book and will be illustrated and more clearly identified in all chapters.

Emergence

Important questions about complex adaptive systems rely upon the understanding of *emergent* properties. At a very low level, how do living systems result from the laws of physics and chemistry? That is, how do the genes specify the unfolding processes of biochemical reactions and interactions that result in the development of an organism? Are the genes the necessary and sufficient ingredients to development? At higher levels, how insect societies are organized? How do brains process information? How does the immune system cope with disease-causing agents? Why does a flock of bird present such a coordinated behavior? None of these questions can be answered without having in mind the concept of *emergence*; that is to say, the properties of the whole are not possessed by, nor are they directly derivable from, any of the parts - a water particle is not a cloud, and a neuron is not conscious.

All the systems and processes discussed above present behaviors by drawing upon populations of relatively 'unintelligent' individual agents, rather than a single, 'intelligent' agent. They are *bottom-up* systems, not *top-down*. They are complex adaptive systems that display emergent behaviors. Emergence is a concept tightly linked with complex systems. In these systems, agents residing on one scale or level start producing behaviors that lie scale(s) above them: social insects create colonies; social animals create flocks, herds, and schools; immune cells and molecules compose the immune system; neurons form brains, and so forth. The movement from low-level rules to higher-level sophistication is what we call emergence (Johnson, 2002).

One important feature most emergent systems and processes discussed in this book share is that they are rule-governed. Remember, nature is lawful! It means

and the environment in multiple ways, following local rules and unaware of any higher-level instructions. Nevertheless, the behavior of such a system can only be considered emergent if discernible macro-behaviors are observed. For instance, these lower-level rules may result in the appearance of traffic jams and a higher flux of cars on the high-speed lane than on the lower speed ones. All these are emergent phenomena that were not programmed in the local rules applied to the cars. They simply emerged as outcomes of the lower-level interactions, even though some of them could be predicted.

Several features and behaviors of natural systems are not so obviously emergent; only a detailed analysis of complex interactions at the organism level can show that they are genuinely new features that only appear at the higher levels. However, emergent behaviors of natural systems can be observed through the creation of models. Even highly abstract and simplified models, such as the ones that will be reviewed here, allow us to simulate, emulate, observe, and study several emergent behaviors of natural complex adaptive systems. In particular, DNA strands, chromosomes, ant colonies, neurons, immune systems, flocks of birds, and schools of fish, will all be seen to present a large variety of emergent properties.

Reductionism

The classical *vitalist* doctrines of the 18th century are based on the idea that all life phenomena are animated by immaterial life spirits. These life spirits determine the various life phenomena, but are themselves unexplainable and indescribable from a physical perspective. By contrast, the *reductionist* position, also in the 18th century, insisted that a large part, if not all, of the life phenomena can be reduced to physics and chemistry (Emmeche et al., 1997).

For long, scientists have been excited about the belief that natural systems could be understood by reductionism; that is, by seeking out their most fundamental constituents. Physicists search for the basic particles and forces, chemists seek to understand chemical bonds, and biologists scrutinize DNA sequences and molecular structures in an effort to understand organisms and life. These reductionist approaches suggest that questions in physical chemistry can be answered based on atomic physics, questions in cell biology can be answered based on how biomolecules work, and organisms can be understood in terms of how their cellular and molecular systems work (Gallagher and Appenzeller, 1999; Williams, 1997).

However, apart from a few radicals, the reductionists do not claim that the higher psychological functions can be reduced to physics and chemistry. As an outcome of the scientific development in many areas, such as cytology, neuroanatomy, immunology, and neurophisiology, it became very difficult to maintain the more classical positions (Emmeche et al., 1997).

Advances in science and technology have led to transformations in the vitalists' and reductionists' positions as well. After a number of scientific discoveries in the early 19th century, the vitalists gradually limited their viewpoints to a narrower field. They now insisted that only the higher psychological functions were

image
not
available

To make the distinction even clearer, consider the case of building a sand castle. A bottom-up approach is the one in which you keep pouring sand and molding it, and a top-down approach is the one in which you initially pour a lot of sand, making a big mountain of sand, and then you start molding the castle from the mountain of sand.

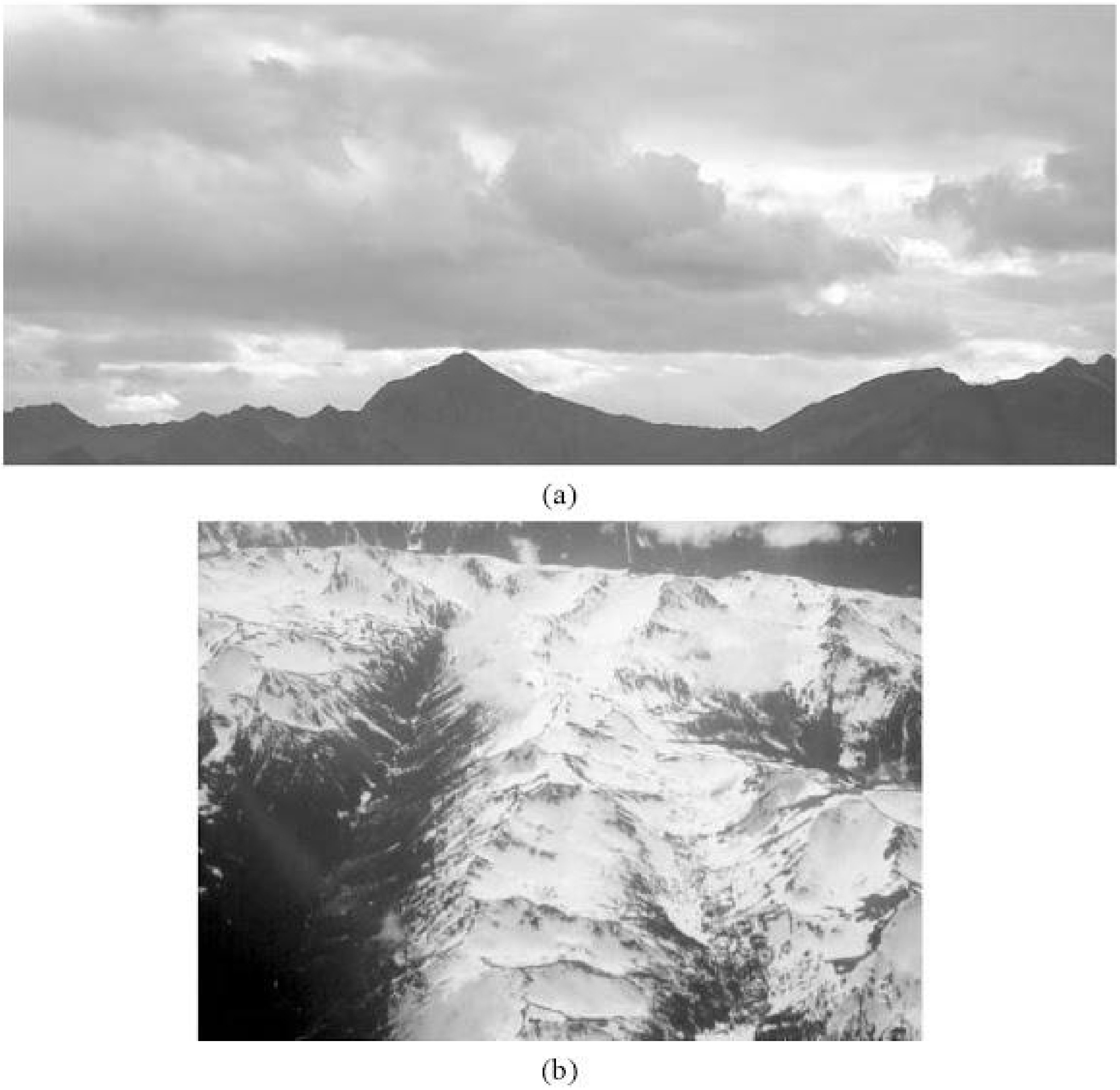
2.2.9. Determinism, Chaos, and Fractals

One of the classical positions in the theory of science is that scientific theories are capable of providing deterministic relations between the elements being investigated. A *deterministic system* can have its time evolution predicted precisely; all events are inevitable consequences of antecedent sufficient causes. The main characteristic of this type of deterministic system is *predictability*. When it is possible to predict the development or time evolution of a system from some predefined conditions there is a deterministic relation between the elements that constitute the system. This classical perspective demands the capacity of predicting the time evolution of a system, thus precluding the appearance of new and emergent phenomena.

One of the most interesting and exciting results of recent scientific development, mainly in physics, is the remodeling of the relation between determinism and prediction. It is now evident that there are many systems that can be described adequately as being strictly deterministic but that still remain unpredictable. The impossibility of predicting the properties arising within many systems considered totally deterministic is the consequence of the well-known Poincaré's treatment of the three-body problem and the Hadamard's investigation of the sensitivity to initial states - insights from the latter half of the 19th century that have recently given rise to the *chaos theory*. Several processes in physics and biology are deterministic but unpredictable. Thus, one of the very important theoretical consequences of chaos theory is the divorce between determinism and predictability.

Before chaos theory, scientists (mainly physicists) were suffering from a great ignorance about disorder in the atmosphere, in the turbulent sea, in the fluctuations of wildlife populations, in the oscillations of the heart and the brain. The irregular side of nature, the discontinuous and erratic side, has been a puzzle to science. The insights from chaos theory led directly into the natural world - the shapes of clouds, the paths of lightening, the microscope intertwining of blood vessels, the galactic clustering of stars, the coast lines. Chaos has created special techniques of using computers and special kinds of graphic images, pictures that capture fantastic and delicate structures underlying complexity. The new science has spawned its own language, such as the word *fractals*.

The word fractal comes to stand for a way of describing, calculating, and thinking about shapes that are irregular and fragmented, jagged and broken-up - shapes like the crystalline curves of snowflakes, coast shores, mountains, clouds, and even the discontinuous dusts of galaxies (see Figure 2.6). A fractal curve implies an organizing structure that lies hidden among the hideous complication of such shapes.



(a)

(b)

Figure 2.6: Examples of the fractal geometry of nature. (a) Clouds. (b) Top of mountains in Alaska.

Fractals - the term used to describe the shape of chaos - seem to be everywhere: a rising column of cigarette smoke breaks into swirls; a flag snaps back and forth in the wind; a dripping faucet goes from a steady pattern to a chaotic one; and so forth (Gleick, 1997; Stewart, 1997).

Chaos theory is often cited as an explanation for the difficulty in predicting weather and other complex phenomena. Roughly, it shows that small changes in local conditions can cause major perturbations in global, long-term behavior in a wide range of 'well-behaved' systems, such as the weather. Therefore, chaos embodies three important principles: sensitivity to initial conditions, cause and effect are not proportional, and nonlinearities. This book talks very little about chaos; however Chapter 7 describes the Fractal Geometry of Nature as the main branch of the study of biology by means of computers aimed at creating life-like shapes or geometrical patterns.

2.3 SUMMARY

This chapter started with a discussion of what are models, metaphors, experiments, simulations, emulations, and realizations. These concepts are important for they allow us to distinguish natural computing techniques from theoretical models, computer simulations from realizations, and so on. Some comments about the difficulty in creating a general framework to design natural computing systems were also made. However, it was argued that each approach, with the exception of some topics in the second part of this book, do have specific frameworks for their design. Also, it was emphasized that this is a book about how existing techniques can be understood, reproduced, and applied to particular domains, not a book about how to engineer new techniques. Of course, from reading this text the reader will certainly get the feeling of natural computing and will then find it much easier to go for his/her own personal explorations and design of novel natural computing approaches.

If the contents of this chapter were to be summarized in a single word, this word would be *complexity* or *complex system*. Complexity encompasses almost all the terminology discussed here. It may involve a large number of interacting individuals presenting or resulting in emergent phenomena, self-organizing processes, chaos, positive and negative feedback, adaptability, and parallelism. Although this book is not about the *theory of complex systems*, it provides design techniques, pseudocode, and applications for a number of complex systems related with nature.

2.4 EXERCISES

2.4.1. Questions

1. Provide alternative definitions for all the concepts described in Section 2.2.
2. List ten journals that can be used as sources of information about natural systems and processes that could be useful for natural computing and explain your choice.
3. Name two connectionist systems in nature in addition to the nervous system and the immune network. Explain.
4. Section 2.2.5 presented the concepts of positive and negative feedback. In Section 2.2.3, the presence of an initial deposit of soil pellets was demonstrated to stimulate worker termites to accumulate more pellets through a positive feedback mechanism. It is intuitive to think that if no negative feedback mechanism existed in this process, the process could go uncontrolled. Name three negative feedback mechanisms involved in the termite mound building process.
5. Name a natural system or process that involves both, positive and negative feedback, and describe how these are observed.

Physiological Systems Modeling, Simulation, and Control

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Interdisciplinary Concepts

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Chapter 17
Physiological Systems Modeling, Simulation, and Control

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ABSTRACT

Physiological systems modeling, simulation, and control is a research area integrating science and engineering and contributes to a continuous refinement of knowledge on how the body works. The roots of modeling a body area date back thousands of years, yet it was not until the 1950s that the tree of knowledge started to be fed with data-driven hypotheses and interventions. This chapter tries to organize disparate information of the most important modeling, simulation, and control perspectives into a coherent set of views currently applied to modern biological and medical research. It is addressed to researchers on human system physiological modeling, working both in academia and in industry to address current and future research goals.

17.1. CHAPTER OBJECTIVES

It is Zeus anathema on physiological models to agonize between the Scylla of simulating a biological system and the Charybdis of controlling such systems. This chapter aims to serve as an introduction to and overview of the interdisciplinary field of modeling, simulation, and control of physiological systems. Research and applications in the area extend from cells to organs and systems, and include linear and nonlinear approaches having time-varying or time-constant variables. Although it is not possible to cover all of the physiological modeling domains in the subsequent pages, we have made an effort to present and briefly discuss the major fields of activity in which models of biological systems are engaged. We first provide an introduction to important concepts and then we illustrate these ideas with examples acquired from physiological systems. We focus on techniques in modeling that motivate the inclusion of control mechanisms into physiological systems and

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models. In parallel, we provide methodological approaches and we discuss their advantages and limitations in order to motivate the reader to have a hands-on experience on the main modeling aspects covered.

17.2. INTRODUCTION

How does an organ work? What is really happening inside a diseased organ? How can we monitor and supervise a drug molecule to help an organ work in a healthy manner? What is a healthy manner of living for a cell, organ or body anyways? The motivation of modeling is convoluted with our distinctive characteristic of wondering. Models in physiology are mainly used for insight, description, and control. We want to know, and sometimes we need to learn, how the components of a system and their interconnections generate the overall operating characteristics of that system. We also seek to capture the characteristics of a physiological system response accurately and concisely.

In practice, the physiological modeling road does not resemble the directional straightness of a roman road. Biological signals are typically amplitude limited and distorted by colored (i.e., non-white) noise. Signal recordings have limited length and are generally nonstationary; whereas, the underlying system is either unknown or very complex to describe. But we still need models, since they can verify our designs before the prototype stage; and, even if they are not exactly accurate, they can help us gain a basic understanding of the underlying system. Models of physiological systems often aid in the specification of design criteria for the design of procedures aimed at alleviating pathological conditions. Models also summarize the physiological behavior of a system concisely, making them an appropriate testing bed for a plethora of scientific hypotheses being stated. This has also been proven useful in the design of medical devices. In a clinical setting, models can make predictions before any intervention or after failures (lesions). Models can also be used to evaluate the functional limits of an operation, be it biological or that of an instrument interrelated with a biological system. They can also explore linear behavior at selected operating points. Lastly, physiological models provide the means (simulations) to truly explore the non-linear nature of the biological physics.

17.3. COMPREHENSIVE DEFINITION OF PHYSIOLOGICAL SYSTEMS MODELING, SIMULATION, AND CONTROL

In order to start thinking about modeling a system, let us begin with the parable of a Saturday theater that is crammed to suffocation by all kinds of spectators. By the end of the theatrical play, each of the spectators is asked to talk about his/her experience. One person, sitting in the last rows of the theater finds that the stage design was ingenious. Another, having the opportunity to sit in the first row of the theater is amazed by the expressiveness of the actors. A third, positioned in a corner of the theater shows a tendency to talk only for specific scenes of the play; the ones performed near his/her side. Each person, inside the theater, gives a different description of the same object; yet none keeps the ultimate truth in his/her hands.

Before projecting our parable to modeling, three aspects need to be further discussed. First, in the real world, we cannot go into the mind of the director. We do not know the script or even the number of the actors in the play; and what is more, there is no unbiased observer that holds an unconditional truth. Second, all spectators formed a personal opinion based on a hypothesis of the play that was consistent with the data they collected. This activity, which seems easy and natural to humans, is called *abduction*. Third, abduction is not an infallible way for discovering truth. This chapter describes most of the basic tools that can be used to create a quantitative formula of the description abducted from observations on physiological systems.

In essence, each spectator created a model (a descriptive version) of a system (the play). Let us introduce some main terminology at this point. A *system* may be considered to be any collection of interconnected processes and/or objects. A *model* is a representation that approximates the behavior of an actual system. This representation is descriptive in a certain level of detail, for that system. By using a set of simplifying assumptions, the system is conceptually reduced to that of a mathematical model. Therefore, the results of each model have significant limitations and are valid only in the regimes of the real world where the assumptions are valid. A model is always connected to an experiment from which we obtain data. To optimize the experiment, we need to have access to the data related to important variables of the model. Consequently, designing and executing an experiment is a crucial step in modeling that usually involves a careful and usually time-consuming selection of the model's variables. Next, we will discuss the two most important classes of variables for any modeled system: the input and the output.

The *input* of a system is the information or signals that flow into a system, and which can normally be manipulated independently. The *output* of the system is the information or signals that flow out of a system, and result from the operation of the system on the input. Both the input and the output can be material flows, voltages, temperatures, pressures, or any other biological signal. The information that is getting into the system or out of it is depicted by a physical quantity, property or condition that is being measured (i.e., the biological signal), usually called a *measurand*. In terms of a physiological system, there are various measurand accessibility sites, namely a) internal to the body (e.g., blood pressure), b) external to the body (e.g., electrocardiogram potential), c) emanating from the body (e.g., infrared radiation), or d) extracted tissue (e.g., blood or biopsy). Most medically important measurands can be grouped into five categories: i) biopotential (e.g., electromyography - EMG, electrocardiography - ECG), ii) pressure flow displacement (e.g., velocity, acceleration, force), iii) impedance, iv) temperature, and v) chemical concentration.

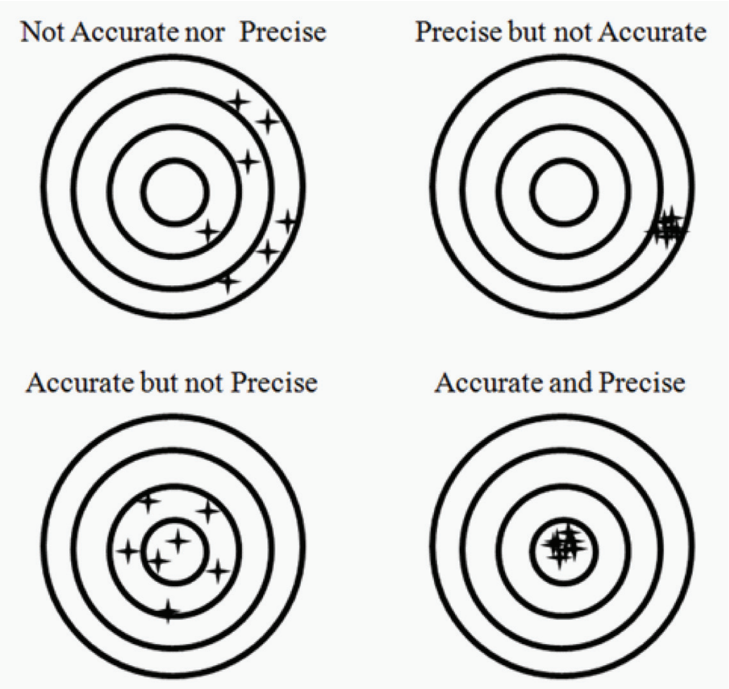
Various factors complicate the choice of biological input and output (I/O) measurands. First, most of the parameters that are measured in practice are quite small as compared with non-medical parameters in most industries. For example, most voltages are in the micro-volt range, and the signals are in the audio-frequency range or below. Many crucial I/O variables in living systems are also inaccessible because the proper measurand transducer interface cannot be achieved without compromising the system (e.g., cardiac output). Patient's comfort is another parameter selection factor that is also related to the level of invasiveness and the safety of the patient in general. Compatibility with existing equipment and the cost of the experiment also affect decisions on the level of abduction used to define a physiological model. Thus, there are times that a model is forced to be designed with less details as compared to what was the initial target.

Desired inputs are the physiological signals (i.e., the measurands) that the model is designed to process. In practice, they are subjected to two unwanted artifacts; namely, *interfering* and *modifying inputs*. Interfering inputs relate to how things are measured. They are quantities that inadvertently affect the data as a consequence of the principles used to acquire and process the desired inputs. Modifying inputs relate to how the experiment is physically built or laid out. They are undesired quantities that indirectly affect the input by altering the performance of the measurement itself. They can influence both the desired and the interfering inputs. Some undesirable quantities can act as both a modifying input and an interfering input.

A model needs to be tested on some quantitative measures that describe the goodness of fit between the simulated and the true data. The *accuracy* of a single model is the difference between the true value and the predicted value. The difference is sometimes divided by the true value of the quantity measured; this ratio is often expressed as a percent. However, the true value of the reference is seldom available. The *precision* of a measurement system, also known as reproducibility or repeatability, expresses the closeness of the system's output in several measurement experiments made in the same way. Typically, this value is determined by statistical analysis of repeated measurements. It is related to the number of significant figures to which a measurement can be made (e.g., an output variable of 2.434 V is more precise than 2.43 V). High precision does not imply high accuracy because precision makes no comparison to the true value. Figure 1 illustrates the difference between accuracy and precision.

Physiological modeling is initiated by experimental observations of a phenomenon that lead to a guesstimate or a verbal description of the observed system. An initial hypothesis is formed followed by a mathematical or computational model that describes our understanding of the phenomenon. The accuracy of the model is tested by acquiring some more data and testing (simulating) the model against the new data. If the model performs adequately, the model is ready to serve its purpose (e.g., to replace a module of a control system). If the model's accuracy does not meet performance specifications, then we need to refine the model. Additional experiments are carried out to acquire even more data and use them to update our model. Usually, some of the variables in the model are observable and some are not. Hence, the new experiments aim to provide the data that are needed in order to increase our understanding of the physiological system. The new data include information about previously unobservable variables. The process of

Figure 1. Accuracy vs. precision of a model's output



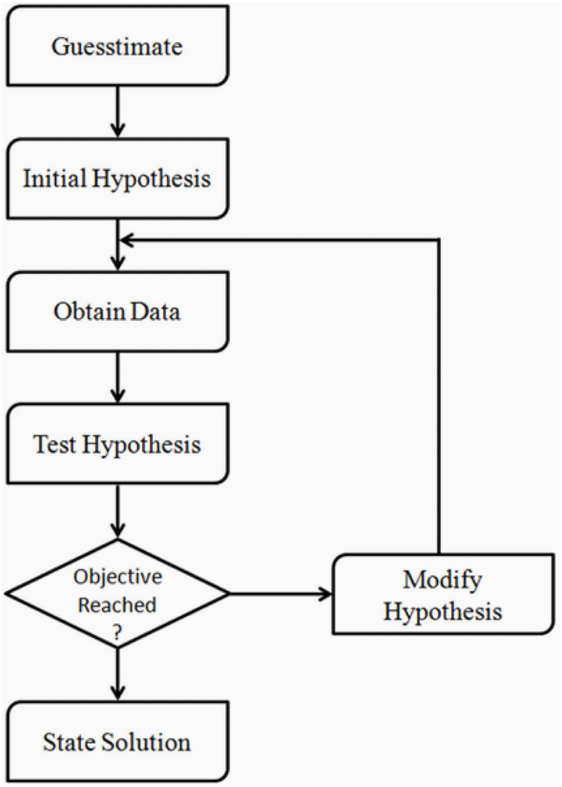
refining the model using new data continues until a satisfactory model is obtained. Typically, a quantitative criterion is used to test the goodness of fit between the model and the data. One of the characteristics of a good model is how well it predicts the future performance of the physiological system. The process is illustrated in Figure 2.

Instead of a concluding remark, two important modeling principles are underlined: i) The starting point for successful physiological modeling is always a simple model that gains a basic understanding of the underlying system. If that model partially succeeds in capturing the known or anticipated behavior, then the subsequent job is to refine it. ii) An otherwise hidden structure of a biological process can become clearer if the process is successfully modeled with adequate mathematical and statistical concepts. A deep knowledge of the modeled structure, and of the way its mathematical representation responds to change, allows the formulation of hypotheses and the testing of theories that are usually not evident from the phenomenological descriptions of the system. Engineers and scientists aiming to model very complex behaviors, such as biomedical phenomena, should not escape the memory of these hallmark principles.

17.3.1. Diagnostic and Therapeutic Challenges

The results of medical or biological models serve three different purposes: i) *to understand*; to have a deep, profound knowledge of a real physiological system, ii) *to predict*; to know the future of such a system that is currently unknown, and iii) *to control*; to constrain or manipulate a system to function inside desirable working conditions. In analogy to the above purposes, physiological models can contribute in i) *diagnosis* if they acquire information for presentation to the human senses (i.e., extend the human senses), ii) *therapy* if they are used to control a physiological process that has gone awry due to disease, trauma or some other intervention, and iii) *assist* if they are used to substitute a diminished or lost function (e.g., robotic systems that help the paretic side of a patient after a stroke, for example see (Krebs & Hogan, 2006), or cardiac pacemaker able to predict and control rhythmic heart beats). Usually, these models have life-supporting or life-sustaining applications.

Figure 2. Model refinement graph



17.4. HISTORICAL BACKGROUND AND LITERATURE OVERVIEW

17.4.1. History of Modeling

The process of modeling a physiological system has a long history interconnected with the history of medicine. It was first introduced as a vague concept with rather philosophical roots; and, after centuries, it acquired its scientific entity and a proper name. Modeling of the living world, the *universe*, has its origins in the sixth century BC among the Ionian Greeks of Asia Minor. At that time, it was mainly occupied with speculation about the cause of the universe, and was associated with the name of *Thales of Miletus*, whose chief successors (also sixth-century BC Milesians) were *Anaximander* and *Anaximenes*. The material principle of the universe was modeled as a single uncreated and imperishable substance that underwent various modifications to produce the plethora of phenomena in the universe. Thales thought that this substance was water; Anaximander defined it as something indeterminate, without specific qualities, and Anaximenes believed it was the air. Around 500 BC, *Alcmaeon of Croton*, a Greek writer and philosopher, localized the brain as the center of understanding reality and introduced brain pathways by using the term channels (*poroi* – πόροι) that connected the brain to the sensory organs. By using a political metaphor, he was also the first to relate health with balance. He defined a healthy body as the result of equality (*isonomia* – ισονομία) of opposing powers (e.g., hot vs. cold) which make up the body. *Empedocles* (490 BC - 430 BC), a Greek philosopher that lived in Sicily, was the advocate of the segregation of the matter to four basic elements: water, earth, air, and fire. He was the first to consider an interconnection among the various compartments of his model of the human body. In addition to the four elements (which he called roots), he used the words love (*philotis* – φιλότις) to model the attraction of different forms of matter, and strife (*neikos* - νείκος) to account for their separation. He considered love and strife to be distinct substances in equilibrium, with the four elements in solution with them.

Interrupting centuries of superposition and mythology that entwined the understanding of the real world and the treatment of diseases, *Hippocrates* (ca. 460 BC - ca. 370 BC) combined the sixth century BC philosophical trend of Asia Minor with Alcmaeon's percepts and Empedocles' concepts about the equilibrium to develop the *humoral theory* for human physiology (Longriff, 1989). According to this theory, human beings are modeled to consist of a soul and a body, which contain four humors: blood, phlegm, black and yellow bile; humors that correspond to the four organs of the body: the heart, the brain, the liver and the spleen. These four humors were believed to be in continuous motion through the circulation. The equilibrium and the harmony of the four humors (*eucrasia* in Greek terminology) were identified with health. Their disequilibrium and disharmony (*dyscrasia* in Greek terminology) produces what is known as disease (Marketos, 1997).

For six consecutive centuries, the Hippocratic view of humorism that regarded the disease as a dynamic process, withstood the pressure of the Atomists' view of the body as an interconnection of indivisible particles in which the disease remained a static phenomenon. Around 150 AD, *Galenos*' understanding of anatomy and medicine, principally influenced by theory of humorism, reestablished the Hippocratic ideas of the unity of the organism in which the interaction with the environment (homeostatis) is crucial for survivor. His theories dominated and influenced Western medical science for nearly two millennia. Galenos' theory of the physiology of the circulatory system endured until 1628, when *William Harvey* published his treatise entitled *De motu cordis*, in which he established a model of blood circulation with the heart acting as a pump (Furley & Wilkie, 1984). *Stephen Hales*, nearly a century later, introduced arterial elasticity and postulated its buffering effect on the pulsatile nature of blood flow (Hales, 1733). He modeled the depulsing effect with the fire engines of his day, in which a chamber with an air-filled dome, "*inverted globe*", acted to cushion the bolus from the inlet water pump so that "*a more nearly equal spout*" flowed out of the nozzle. His analogy became the basis of the first modern cardiovascular models. In 1897, *Stewart* first measured cardiac output in intact animals (Stewart, 1897), more or less affirming Harvey's calculations. *Krogh* and *Erlang*, in 1919, presented what is believed to be the first paper on mathematical modeling in biomedical science (Krogh, 1919). About ten years later, *Wiggers* used Fourier analysis to describe intraventricular pressure waveforms (Wiggers, 1928).

In 1952, *Alan Lloyd Hodgkin* and *Andrew Huxley* initiated the sub-cellular and cellular modeling. They presented a set of nonlinear ordinary differential equations that approximates the electrical characteristics of excitable cells such as neurons and cardiac myocytes. Their model explains the ionic mechanisms underlying the initiation and propagation of action potentials in the squid giant axon (Hodgkin & Huxley, 1952). For their work, they received the 1963 Nobel Prize in Physiology or Medicine, and the Hodgkin-Huxley model became the "*paradigm*" physiological model of nerve excitation. A few years later, *Noble* presented the first cardiac Purkinje fiber cell model (Noble, 1960). These two works set the foundations for the development of the current, quantitative approach to computational modeling of biological systems, which is thoroughly based on experimental data, and aims to make experimentally verifiable predictions. Together with the first physiological models, the methodology to acquire them began to develop as well. The iterative process in model building was first introduced by *Popper*, who pointed out that no model should be considered perfect. In fact, he proposed that models must exhibit "*falsifiability*" (Popper, 1959).

During the last 50 years, fuelled both by advancements of digital computers, programming languages, and simulation software and by the increasing demand in quantitative assessment of element interrelations in physiological systems, computational modeling of physiological processes and systems witnessed a remarkable development. Now attention is shifting toward integrative computational modeling in biomedical research to link the magnificent body of new knowledge to an understanding of how intact organisms function. Multidisciplinary scientific research spotlights the characteristics of various physiological systems. Complex, nonlinear, nonhomogeneous, discontinuous, anisotropic, multilayered, multidimensional, etc. systems needed the development of analogous models that described them.

17.4.2. Evolution of Computer Power and Relation with Advancements in Physiological Systems Modeling

In the second half of the 20th century, biological models, used to describe and classify the normal and abnormal physiological conditions, pushed the researchers to descend the modeling ladder: from the organismal level down to the sub-cellular and even nuclear (gene) level. But before the use of digital computers, mathematical models of biomedical systems were either oversimplified or involved a great deal of hand calculation as described in the Hodgkin-Huxley investigations published in 1952. Since the 1980's, the progressive introduction of the digital computer, programming languages, and simulation software to every lab space in laboratories across the world enormously shrank the time required to acquire data from simulation experiments. In fact, since the 1990's, digital computer environment became the working place for any scientist; and, the terms modeling and simulation have almost become synonymous. In addition, the internet boom at the start of the new millennium was the major contributor to the international partnership among scientists, and allowed for time and resource consuming modeling projects to become feasible since simulations could run on multiple processing sites spread throughout the world. This has allowed the development of much more realistic or homeomorphic models that include as much knowledge as possible about the structure and interrelationships of the physiological system without any overriding concern about the number of calculations.

The development of information-gathering technologies and the introduction of modeling methodologies that incorporate large-scale data have facilitated a dramatic increase in the degree of quantification applied to modern physiological research. In the past few years, computational modeling and analysis played a critical role in decoding complex systems descriptions from large sets of noisy and sometimes redundant data, and in developing an engineering understanding of physiological systems. In November 2010, the search-term "*modelling OR modeling*" yielded over 111,000 entries in PubMed, with more than 58,000 since the year 2006. Thus, almost half of the papers appeared in the last four years, as compared to the rest of the papers published in the preceding six decades. These developments show that the distance between theory (models) and experiment (simulations) is rapidly diminishing.

The start of the 21st century has found researchers working behind their computers climbing the simulation ladder, and composing low level information to gradually form a first-principles physiological knowledge from the low scale of the nucleus of a cell all the way to the level of a complex organism. Various international cooperation projects on healthcare information systems, based on grid capabilities and biomedical informatics, among European Union (EU), North and Latin America, and North Africa countries, aim to create a common health information infrastructure in Western countries and extend it to other regions. In EU, various FP6 initiatives such as SHARE (http://www.eu-share.org), ImmunoGrid (http://www.immunogrid.org), SeaLife (http://www.biotec.tu-dresden.de/sealife), and ACGT (http://www.eu-acgt.org) have concluded successfully, and other FP7 initiatives, such as Sim-e-child (http://www.sim-e-child.org) and ActioGrid (http://www.action-grid.eu) have begun. At the planet level, HealthGrid initiative (http://initiative.healthgrid.org), supported by the HealthGrid Association, was created to promote deployment of grid technologies in health.

Though models can continue to be made more complex, it is important to evaluate the value added with each stage of complexity – the model should be made as simple as possible to explain the data, but not so simple that it becomes meaningless. On the other hand, a model that is made too complex is also of little use. Such models fail to generalize well either due to a lack of computing resources (such as time and processing power), or because they are gradually becoming sluggish in keeping pace with the new knowledge that is constantly being added to the description of physiological systems. Models, currently developing, constitute a pivotal point in solving the many open questions of human systems' dynamics, and the information processing from singe cells. The present and forthcoming advances in biology and systems modeling are expected not only to further increase the huge amount of information coming from physiological studies, but also to represent an opportunity to help improve the well-being or quick healing of individuals facing health issues.

17.4.3. Presentation of Current Projects: The Physiome Project, The Virtual Physiological Human-VPH

Whereas the *reductionist* approach in the last century focused on studies of isolated systems aiming for the finest possible molecular and cellular events, *integration* is becoming the most popular scientific term today. The remarkable achievement of completion of the first draft of the human genome sequence demonstrates the power of integration of the interdisciplinary scientific power. Following the contemporary trend, currently developed models aim not only to explicitly understand the physiological entity under study, but also to relate the subsystems' interconnections to the systemic behavior. Scientists trawl for relations in a large area extending from molecules, genes, proteins, cells, organs, and systems up to whole organisms. Interrelationships among biological systems span more than one descriptive level, at all space and time scales. The aggregation of various modeling levels is achieved by identifying appropriate variables that can be omitted, averaged, or approximated. In that sense, a newly developed model should be placed with respect to a modeling hierarchy at all scales so that parameters in one model are the output of models at a finer spatial or temporal scale.

The elucidation of such multilevel models relies on acquiring detailed structural and functional information. For instance, research on Parkinson's disease is based on data ranging from the properties of membrane ion channels using patch clamp techniques, to neuronal *in vivo* characteristics available by means of multiple microelectrodes, populations of neurons using stereo-electroencephalography or electro-corticography, up to extended brain activities with high density electroencephalography and magneto-encephalography.

Nevertheless, the knowledge gathered is hampered by the system's intrinsic complexity and by the fact that biological mechanisms are still poorly understood. That is why model design, experimental investigations and observational tools have to be wisely chosen to represent consistently the true system. Scientists in medicine, biology, physics, chemistry, applied mathematics, and computer and engineering science are needed to collaborate. Database management, recognition and fusion of multidimensional signals and sensing devices are to provide the means to modeling and control studies.

Over the past decade, several model integration initiatives have been launched that aim to create reliable biological and physiological models, including projects like E-cell, Virtual Cell, the Virtual Physiological Human, and the Physiome Projects. These projects attempt to formulate a comprehensive framework for modeling the human body using computational methods to provide answers to basic questions, and better care for human beings. The collaborative research initiatives consist of scientifically independent projects on integrative systems physiology and biology undertaken by individual laboratories mainly in Western countries. Financial support is provided mainly from national and international health research agencies.

The main scope of those projects is to gather interdisciplinary modeling work, information processing methodologies and relevant software tools, data banks, etc., and make them approachable to research groups across the globe. However, most of the projects have just begun and have not achieved great depth yet, for many theoretical and technological issues have to be addressed. The challenge for the projects is to link these two developments for an individual – to use complementary data together with computational modeling tailored to the anatomy, physiology and genetics of that individual, for diagnosis or treatment.

The Physiome Project represents current quantitative attempts in this direction that establish top-down paths to meet up with the sub-cellular information and, so, introduce models traveling the whole way from genes to health. Its concept was first presented in a report from the Commission on Bioengineering in Physiology to the International Union of Physiological Sciences (IUPS) Council at the 32nd World Congress in Glasgow, in 1993. The name of the project comes from "*physio-*" (*φύσις*- life) and "*-ome*" (as a whole), and is intended to provide a "*quantitative description of physiological dynamics and functional behaviour of the intact organism*". A synthesium on the Physiome Project was held at the 34th World Congress of IUPS in Christchurch, New Zealand, in August 2001, and the Physiome Project was designated as a major focus for IUPS for the subsequent decades. The main projects of the Physiome include models of the brain and the central nervous system, the cardiovascular, the respiratory, the urinary, the musculo-skeletal, the alimentary, the reproductive, the endocrine, the haemolymphoid, and the integumental systems. To illustrate the international collaboration, more than 16 research laboratories from five countries (Australia, USA, United Kingdom, Israel, and

Switzerland) are currently working only on cardio-models.

Virtual Physiological Human is a European Union initiative which started in 2007. Its main targets are the creation of several patient-specific computer models that will be used for personalized and predictive healthcare; as well as, the creation of ICT-based tools for modeling and simulation of human physiology and disease-related processes. The Physiome and the Virtual Physiological Human projects seek to understand and describe the human organism, its physiology and pathophysiology, and to use this understanding to improve human health. While it will be a very long time before a surgery will be executed or a drug's effects will be tested on a virtual patient, that day is closer than ever. But we need to recognize the potential of such international efforts. The most daunting challenge for the future remains the integration of this incredible wealth of information to increase our awareness of how biological systems are structured at all levels, and how this structure drives the function of a healthy or diseased entity.

17.5. LEVELS OF MODELING: FROM CELLULAR TO ORGAN AND SYSTEMS MODELING

The breadth and depth of the experimental data currently obtained across laboratories all over the world has allowed the design of sub-cellular to whole organ models. For the reasons discussed in Section 17.4.2, a rapid expansion of detailed experimental data, mainly occurred in the last decade of the previous millennium, had created the area to develop the "*theoretical biology*" (Noble, 2002). The term "*Systems Biology*" represents a novel, quantitative approach to biological research that encompasses physiological functioning as well. Biology and physiology are merged together using a combination of experimental data and a quantitative theoretical description of the interactions between system components across multiple spatial and temporal scales. Modeling at the sub-cellular level has advanced to an impressive level in most biological tissues, partially guided by direct knowledge transfer from cardiac to other cell models (Youm *et al.*, 2006).

Models are formulated in the cellular, intercellular, tissue, organ, and organism levels. At the organ and organism level, complexity of computational (and experimental) models increases rapidly. In order to handle this problem, the multitude of interacting processes and components must be assessed for inclusion into, or elimination from, mathematical representation of biological behavior. Different researchers have taken different approaches, but applied (i.e., experimentally testable) work seems to follow the pattern that, once the research question has been determined experimentally, the mathematical models are developed to maximally reproduce relevant behavior with minimal complexity. This process of selection and reduction is, of course, difficult and usually requires a continuous iteration between experimental and theoretical model application. In order to formulate a model description, two main pathways exist. The first pathway leads to a mathematical model via a physical description of the system. The second pathway is based on the system identification using observations. These pathways will be further discussed in the next Section.

Starting from the sub-cellular and cellular levels, Hodgkin & Huxley introduced the "*paradigm*" physiological model of nerve excitation (Hodgkin & Huxley, 1952). Eight years later, Denis Noble presented the first cardiac cell model (Noble, 1960). These two works were the cornerstones for the development of the current, computational approach to modeling of living cells. As we ascend the spatial biological ladder, we need to integrate the cell functioning to a more complicated level of structure that resembles that of a tissue. Numerous mathematical and computational descriptions of cellular and inter-cellular effects use the work of Beeler & Reuter (1977) for models of the electrical activity propagation in the intracellular and extracellular spaces. At the organ and organism level, complexity of computational (and experimental) models increases rapidly, and scientists usually simplify their models in order to gain insight into the underlying physiological system that is being examined. The work from researchers at the University of California, San Diego, CA, USA is a good example of how advanced the field of system modeling has become in this regard. Bigg is a freely available model of the first complete computer model of human metabolism that helps researchers uncover new drug pathways, and understand the molecular basis of cancer and other diseases (Schellenberger *et al.*, 2010).

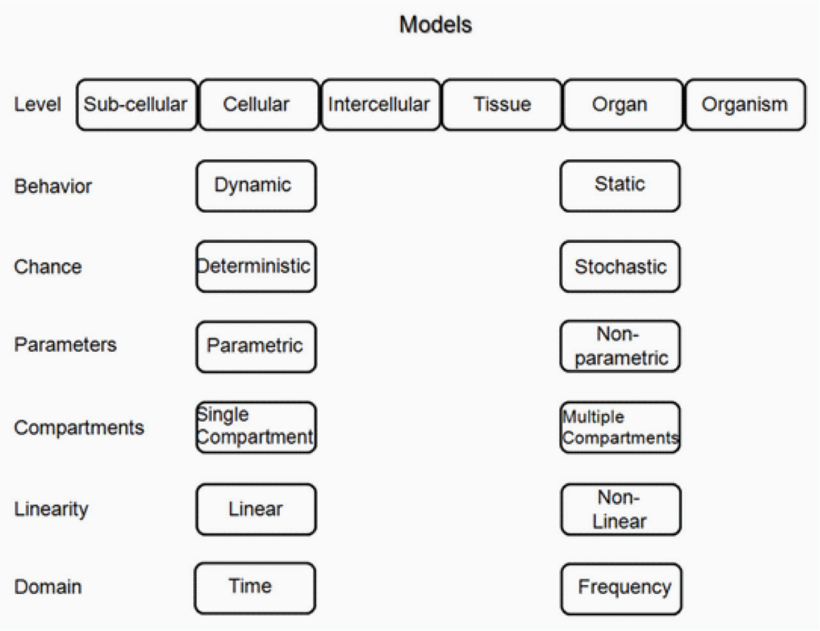
17.6. CLASSIFICATION OF MODELS

We can now begin to get to the heart of the matter, by describing and classifying models. This section will deal with models of physiological systems and their behavior; either dynamic or static. A *dynamic model* is characterized by a number of variables whose values change with time, even in the absence of external inputs. These variables fully describe the systemic behavior at any given time and are known as *state variables*. On the other hand, a *static model* has direct instantaneous links between all variables. A very broad categorization, which is nonetheless quite useful for creating more finely structured hypotheses, considers *randomness*, *a priori knowledge of the model's structure* and the *domain of description*. A major target in modeling a physiological system is to identify these properties through the use of appropriate computational tools.

17.6.1. Deterministic and Stochastic Models

In a *deterministic system*, we always have an exact relationship between measurable and derived variables. Given a clear knowledge of the initial conditions and the system dynamics, the future behavior of a deterministic system has no uncer-

Figure 3. Classification of models



tainty for all time. Most physiological systems are studied as deterministic and the unavoidable uncertainty is introduced into the model as a separate random process superimposed into the variables of the system. What makes a deterministic system so desirable is that, given sufficient knowledge about the dynamics and the values of the state variables at a given time (the state of the system at that time), the future course of the system can be predicted with some degree of accuracy.

On the other hand, the outcome of a *stochastic model* is governed by some degree of chance. Even if complete information on the dynamics and the initial states of such a model is given, the future course of the system is impossible to be fully predicted. Rather, the model's output can be described in terms of its statistics; that is, the likelihood of its state variable having particular values. A basic modeling question in many experimental situations is whether the system used to provide the acquired data is to be modeled as deterministic or stochastic. In practice, the acquired data set is the result of a mix of deterministic and stochastic processes. In fact, such a concern is further complicated; we can always construct a deterministic system that will generate the specific data of any given finite data set, even if our data set is acquired from a highly stochastic process. A golden rule for these kinds of situations is this: *We always seek to model a process with the maximum possible simplicity*.

17.6.2. Parametric and Nonparametric Models

For a better description and analysis of any system, we need to introduce the subtle distinction between *variables* and *parameters*. A parameter is a constant; it is a term in an equation that is fixed. On the contrary, a variable changes with time to reflect the dynamics of the system.

A *parametric model* is a bottoms-up representation of a process based on physical principles and *a-priori* knowledge of constitutive laws governing the sub-processes. These laws, together with physical constraints, are used to integrate the models of subsystems into an overall mathematical model of the system. If one has valid representations from basic science, then equations can be postulated to represent the system under study in either continuous time or discrete time (events). In which case, the variables are related by equations containing parameters which define system behavior. In the case of static systems, the relations are simple algebraic equations independent of time. For dynamic systems (linear or non-linear), the equations include functions of time and require knowledge of past values for variables. In addition, the system under study may have lumped variables, or require distributed parameters over a domain of interest (e.g., temperature in space). The latter is usually described with partial differential (or difference) equations or finite elements.

A *nonparametric model* provides a method to estimate a system's output representing the actual relationship between the input and the output, without making restrictive assumptions about the variables of the system or its statistic properties. Such models can provide accurate methods of data analysis, because they make minimal assumptions about the data-generating process. In the nonparametric black box approach, a mathematical model is formulated on the basis of the input output characteristic of the system without consideration of the internal functioning of the system. Linear nonparametric models consist of data tables representing the impulse response, step response, and frequency response of the system. Because nonparametric models are not represented by a compact mathematical formula with adjustable parameters, such models do not impose a specific mathematical structure on the system.

Now a question arises on the selection criteria between those two types of models. The modeling choice depends mainly on the nature of the system, on the type of behavior that is expected, and on the intended use of the model. Nonparametric models serve well as preliminary models that are used to analyze system characteristics. For example, estimating the transient response provides insight into the rise time and settling time of the system response. Similarly, estimating frequency response might indicate the order of the system, locations of resonances and notches, crossover frequencies, and the bandwidth of the system. In some cases, a specific mathematical form is preferable because the estimated parameters have a physical interpretation. However, when estimates of dynamic characteristics are only required, nonparametric models are usually used.

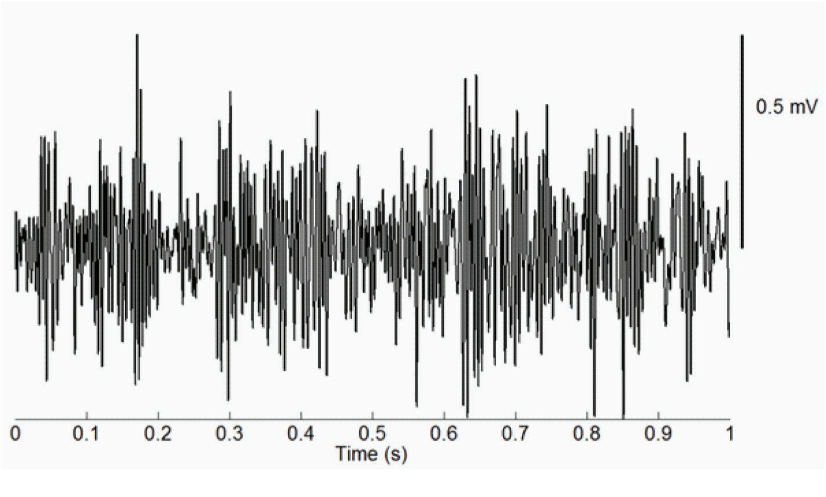
17.6.3. Applied Examples

Example 17.1: A simple example of a dynamic system is that of a bicycle ride. The state variables of the model include the bicycle's speed and the feet pressure on the pedals. The variables are related in a direct but potentially complicated manner. A simple model would just consider speed to be proportional to pedal pressure. A more realistic model would include time delays resulting from the chain dynamics and neural lag. An even more extensive model would also include chain dynamics explicitly, as well as air pressure against the running bicycle. Knowing which variables are important to include in the model is one of the keys to successful modeling, and this is, in many cases, more an art than a science.

Example 17.2: Another example, aimed to distinguish between parameters and state variables is given below. In the case of modeling the heart rhythm during a specific short-term physical activity, the subject should not eat during the exercise, and the exercise should take place in a limited amount of time so that circadian fluctuations do not have a significant effect on the experiment. Hence, food and the time of the day are considered as fixed parameters (i.e., they are constant). On the contrary, if we want to model the heart rhythm over the day, then the time of day and food absorption become state variables.

Example 17.3: Any signal that is recorded from the brain, either inside (e.g., local field potentials - LFP) or outside of the scalp (e.g., electroencephalograph - EEG)), is a highly stochastic signal. The LFP is an

Figure 4. A local field potential (LFP) recorded inside the subthalamic nucleus of a Parkinson's disease patient. The signal is highly stochastic since it is produced by a stochastic system. The LFPs are dominated by the more sustained currents in the tissue, typical of the somato-dendritic currents.



electrophysiological signal, dominated by slow varying potentials, typical of a neuron's somato-dendritic processes within a volume of tissue. The electrical potential is usually recorded with a very small electrode embedded within neuronal tissue, typically in the brain of an anesthetized animal or patient (*in vivo*) or within a thin slice of brain tissue maintained in a solution (*in vitro*). A typical LFP signal, acquired from the subthalamic nucleus of a Parkinson's disease patient, is shown in Figure 4.

17.7. COMPARTMENTAL MODELING

Compartmental modeling is mainly used to describe systems that include transfer of solutes across compartments, such as the respiratory and circulatory systems. It is based on metabolism of tracer-labeled compound studies that started in the 1920s. Compartmental models are linear, nonlinear, continuous or discrete models of systems that are divided into homogenous well-mixed components, called *compartments*. A compartment is a well-delineated biotic or abiotic entity. The models may have constant or even time-varying parameters. The internal behavior of the system is characterized by the movement of materials between two neighboring compartments. Two of the main difficulties of compartment modeling are the determination of the exact number of compartments to be used in the model, and the accessibility of some of the compartment's data. Lumped compartmental variables are mainly substances (solutes) that are either exogenous (e.g., a drug) or endogenous (e.g., insulin). Blood and chemical species (such as hormones) distribution to various organs, cellular dynamics, temperature distribution, etc. are just few examples in which compartmental models are used in studies involving pharmacokinetics, chemical reaction engineering, fluid transport etc.

Compartmental modeling is also a significant approach of modeling neural systems. Various platforms have been developed to provide the tools for a detailed realistic simulation of a real neuron, or even a large network of neurons based on a "*building block*" approach. In such systems, simulations are constructed from modules that receive inputs, perform calculations on them, and then generate outputs. GEneral NEural SImulation System (GENESIS) is a general purpose object-oriented software platform developed by James Bower and David Beeman (Bower & Beeman, 1998) to support the biologically realistic simulation of neural systems. This object-oriented environment enables the modification of existing simulations for new purposes. GENESIS, and its version for parallel and networked computers (PGENESIS), was the first broad scale modeling system in computational biology to encourage modelers to develop and share model features and components. It supports the simulation of neural systems, ranging from subcellular components and biochemical reactions to complex models of single neurons, simulations of large networks, and systems-level models.

An alternative to the GENESIS simulation environment is NEURON (http://www.neuron.yale.edu), which is widely used by experimental and theoretical neuroscientists. It was primarily developed by Michael Hines, John W. Moore, and Ted Carnevale at Yale University, New Haven, CT, USA and Duke University, Durham, NC, USA (Hines & Carnevale, 1997). Both platforms implement a built in "*scalability*" in models. This is a major advantage compared to other custom made codes needed to be written for a specific simulation (e.g., in a MATLAB & Simulink environment), but it comes with the expense of a need to invest the time required to understand the analysis and graphic tools provided by platforms such as GENESIS and NEURON.

17.7.1. Detailed Compartmental Models

In order to describe the transfer of a solute by diffusion between two compartments, the following assumptions are needed:

1. All compartments have constant volumes.
2. The solutes, upon entering a compartment, are dispersed homogenously in the entire compartment.
3. The rate of solute depletion from a compartment is analogous to the concentration of the solute in the same compartment.

If the aforementioned assumptions are met, the time course of a solute transfer across two compartments can be examined. Using a law of diffusion derived by Adolph Fick in the year 1855, we can model the diffusion coefficient, D of a solute, transferred between two compartments, that has quantity, q, and concentration, c, using a membrane with surface area, A, and thickness dx, as follows,

$$\frac{dq}{dt} = -DA\frac{dc}{dx} \tag{17.1}$$

The transfer rate, *R,* of the diffusion is defined as

$$R = \frac{DA}{dx} \tag{17.2}$$

For a thorough review and an analytical approach of two-compartment models, please see (Enderle, 2005). The simplification of compartment models is allowed by the fact that the distribution inside a compartment is not included. The basic assumption of a solute homogeneously mixed inside a compartment, results in knowing everything about a system's behavior, when the inflow and outflow for each compartment are identified.

17.7.2. Modified Compartmental Models

The compartment analysis presented in Section 17.7.1 is not adequate to fully describe systems in which the transfer rates are not constant, but depend, for example, on the concentration of a solute in a single compartment. But even in those systems, we can apply a *modified compartment analysis* to cope with the nonlinearities present. As the model becomes more and more complex, an analytical solution is not feasible; yet, simulations of such models can give us an approximation of the solution.

One of the earliest modeling attempts that aimed at analyzing smallpox morbidity and mortality dates back to 1766 when the Dutch-Switch mathematician, Daniel Bernoulli, tried to analyze it as a statistical problem to demonstrate the efficacy of vaccination. The next infectious disease modeling attempt belongs to Hammer and Soper who created a model of measles spreading, in 1906. Their model contained separate compartments for susceptibles, infectives, and recovered, taking into consideration the births, the infection rate, etc. Twenty years later, Kermack and McKendrick (in the continuous time), and Reed and Frost (in the discrete time) presented extensions for the model of Hammer and Soper.

For both the *Kermack-McKendrick* and *Reed-Frost* models, any given person is related to a certain time period. The *latent period* is the time elapsed between contact and the actual discharge of the infectious agent. The *infectious period* is the time during which the contagious agent is spread to others. The *immune period* is the time during which a person has temporal or permanent immunity and can no longer transmit the agent. The *incubation period* is the time elapsed between contact and the observation of symptoms. The *symptomatic period* is the time interval in which the person overtly displays signs of the illness; see (Enderle, 2005) for an illustration of these periods.

If we consider a population of size, *n*, with *x* susceptibles, *y* infectives, and *z* immunes, so that *n* = *S* + *C* + *R*, the assumptions for a Kermack-McKendrick continuous time modeling approach are the existence of: i) a uniform mixing among the population, ii) a zero latent period, iii) a closed and isolated population, iv) a negative exponential distribution for the infectious period, v) an infectious rate, *b*, and vi) a removal rate, *g*. The course of an infectious epidemic in a closed and isolated population is a function of the number of susceptibles and the infectious rate between susceptibles and infectives. In Figure 5 (upper panel), the Kermack-McKendrick model is shown. Arrows indicate a nonnegative transfer of individuals from one state to another, dependent on the infective rate *b* (infectives) and the removal rate *g*. The Kermack-McKendrick model describes the transfer of *S* susceptibles, *C* infectives, and *R* immunes at time *t* from state to state. With *b* as the infective rate, the differential equations that describe the model are:

$$\begin{aligned} \frac{dS}{dt} &= -bSC \\ \frac{dC}{dt} &= bSC - gC \\ \frac{dR}{dt} &= gC \end{aligned} \qquad (17.3)$$

Equation 17.3 can be solved analytically using a Taylor series expansion; see (Enderle, 2005).

The Reed-Frost model is a deterministic discrete time model; this makes it more practical in being used with true data which is usually sampled versions of continuous data. The assumptions for a Reed-Frost discrete time modeling approach are as follows: i) the existence of a uniform mixing among the population; ii) the existence of a zero latent period (although the model can extend easily to a nonzero latent period having a well defined distribution); iii) the existence of a closed population at steady state; iv) susceptible individuals can develop the infection only once and then become permanently immune; v) since the person can be infected at any instant during the time period, the average latent period is one-half of the time period, where the length of the time period represents the period of infectivity; and, vi) each individual has a fixed probability of coming into adequate contact *p* with any other specified individual within one time period.

The structure of the Reed-Frost model is shown in Figure 5 (bottom panel). Note that the probability of adequate contact *p* can be thought of as

$$p = \frac{\bar{n}}{N} \qquad (17.4)$$

where, $\bar{n}$ is the average number of adequate contacts.

As before, the Reed-Frost model describes the transfer of *S* susceptibles, *C* infectives, and *R* immunes, but now the transfer is measured with respect to the next discrete time (state), *k+1*. After adequate contact with an infective in a given time period, a susceptible will develop the infection and be infectious to others only during the subsequent time period, after which one becomes immune. If the infective rate is (1 - $q^{C(k)}$), the model can be described by the nonlinear difference equations

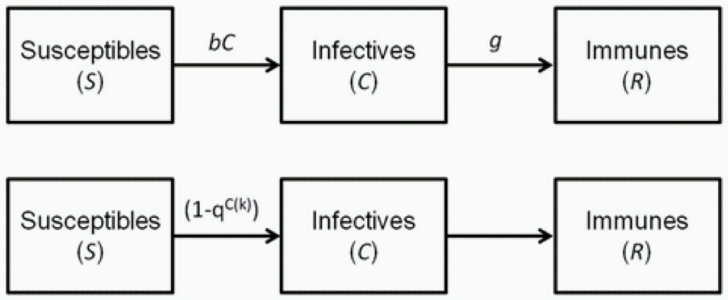
$$\begin{aligned} C(k+1) &= S(k)(1-q^{C(k)}) \\ S(k+1) &= S(k) - C(k+1) \\ R(k+1) &= R(k) + C(k) \end{aligned} \qquad (17.5)$$

The time period T is understood to be the length of time an individual is infectious, so that the removal rate is equal to one.

17.7.3. Expansion to Multi-Compartmental Models

It should be clear by now that real biological models incorporate more than the limited number of compartments already described in previous sections. A single compartment model can be

Figure 5. Modified compartmental models. The Kermack-McKendrick (upper panel) and the Reed-Frost (bottom panel) models are shown.



divided to multiple compartments if we choose to include more details on it such as cell volume, interstitial volume, or plasma volume. But even these volumes can be further compartmentalized. For instance, the interstitial volume can be defined with compartments including the GI tract, mouth, liver, kidneys, and other unidentified compartments. Each of these compartments has its own transfer rate for moving the solute from one compartment to another. In general, concern about how the solute moves from and into a compartment is not a focus, but only the amount of solute that is transferred. The concepts described in the previous section can be applied to a model with any number of compartments. Each compartment is characterized by a conservation of mass differential equation that describes the rate of change of solute. Thus, for the case of N compartments, there are N equations of the general form

$$\frac{dq_i}{dt} = Input - Output \tag{17.6}$$

where, q_i is the quantity of solute in compartment *i*. For a linear system, the transfer rates are constants.

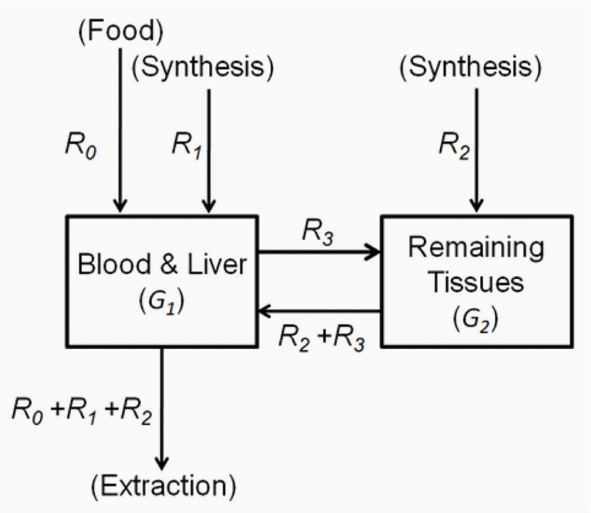
Physiologically based pharmacokinetic (PBPK) modeling is a multi-compartmental modeling technique used in pharmaceutical research and drug development, and in health risk assessment for cosmetics or general chemicals. Compartments correspond to *a-priori* defined organs or tissues, and their interconnections correspond to blood or lymph flows. This modeling approach aims to balance between complexity and simplicity to predict the absorption, distribution, metabolism and excretion (ADME) of synthetic or natural chemical substances in humans and animal models. PBPK models may have purely predictive uses, but other uses, such as statistical inference, have been made possible by the development of various statistical tools. A system of differential equations for concentration or quantity of substance on each compartment is usually written, and its parameters represent blood flows, pulmonary ventilation rate, organ volumes, etc. PBPK models are also used for inter-species transpositions or extrapolation from one mode of administration to another (e.g., males to females, adults to infants, inhalation to oral) to asses toxicity risk and therapeutic drug development.

17.7.4. Applied Example

Example 17.4: Let us consider a two compartment model, shown in Figure 6, in analogy to the one presented by Goodman and Noble (1968). According to that model, the rate of cholesterol turnover has been described as conforming to a two-compartmental system consisting of one pool that turns over rapidly and a second pool with a low turnover rate. Cholesterol is inserted into the blood plasma of all animals by two sources, namely the food and synthesis from simpler substances within the body. Cholesterol is recycled. It is excreted by the liver via the bile into the digestive tract. This system can be described using a two-compartment model, where some of the tissue (primarily the liver, which is the main organ playing a role in the dynamics of the cholesterol levels) and the blood exchange cholesterol with the blood. We assume that the exchange of cholesterol between the liver and the blood is happening in a high, almost instantaneous speed; that is why we model the blood-liver system as a single compartment. The rest of the exchange – between blood and liver and the rest of the tissues, lumped together in a second compartment – is happening at a much slower speed. Hence, the first compartment represents the amount of cholesterol in the blood and liver, and the second represents the amount of cholesterol in all the rest of the body. If we inject a small amount of C^{14} into the blood stream, we can estimate the amount of radioactive cholesterol in the two compartments, Q_1 and Q_2 respectively. We assume that the concentration of radioactive cholesterol-C^{14} in the first compartment is $C_1(t)=Q_1(t)/G_1$, and the concentration of radioactive cholesterol in the second compartment is $C_2(t)=Q_2(t)/G_2$. Let us first consider the blood-liver compartment. The cholesterol that is inserted via food and from biosynthesis is not radioactive. Hence, the only inflow of cholesterol-C^{14} into the first compartment arrives from the second compartment. Now, let us consider the second compartment. The total inflow of cholesterol into the second compartment is R_2+R_3 and the amount of the cholesterol-C^{14} is $C_2(t)=Q_2(t)/G_2$. This means that the amount of cholesterol-C^{14} that flows into the first compartment is $(R_2+R_3)Q_2(t)/G_2$, and the amount of cholesterol-C^{14} that flows out of the first compartment and into the second compartment is $R_3Q_1(t)/G_1$. The amount of cholesterol-C^{14} that is extracted to the environment is given by $(R_0+R_1+R_2)Q_1(t)/G_1$. From these relations, we can write down the differential equations that govern the system as follows,

$$\begin{aligned} Q_1'(t) &= \frac{R_2+R_3}{G_2}Q_2(t) - \frac{R_0+R_1+R_2+R_3}{G_1}Q_1(t) \\ Q_2'(t) &= \frac{R_3}{G_1}Q_1(t) - \frac{R_2+R_3}{G_2}Q_2(t) \end{aligned} \qquad (17.7)$$

Figure 6. Compartmental model of cholesterol concentration in the body



17.8. LINEAR MODELING OF PHYSIOLOGICAL SYSTEMS

Linear systems are highly popular among the physiological models since they are simple to implement and provide extremely powerful tools for their analysis. In contrast, methods available for the study of nonlinear systems are much more limited. In fact, almost all physiological systems are nonlinear; however, many of these systems can be modeled as linear systems in a limited range of operation.

Let us introduce a short description of the terminology in the field. If the operation that transforms the input into the output varies with time, the system is *time varying*; whereas, if the operation remains constant, the system is *time invariant*. Two attributes of linear time-invariant (LTI) systems form the basis for almost all analytical techniques applied to these systems:

1. Response obeys the principle of superposition.
2. Response can be expressed as the convolution of the input with the unit impulse response of the system.

The concepts of superposition, convolution, and impulse response will now be defined shortly. The *principle of superposition* states that if the system has an input that can be expressed as a sum of signals, then the response of the system can be expressed as the same sum of the individual responses to the respective signals. Superposition can be expressed mathematically as follows:

$$f(a_1x_1 + a_2x_2) = a_1f(x_1) + a_2f(x_2) \qquad (17.8)$$

where, x_1 and x_2 are two inputs, $f(x_1)$, $f(x_2)$ are the respective outputs of a system, $f$and a_1, a_2 are two scalars. Superposition applies if and only if a system is linear. The effects of performing any linear operation on the input of a linear system (e.g., integration, differentiation, Fourier transformation, etc.) will affect a change on the output in exactly the same way as if the transformation were applied to it directly. That is, if f and g are two linear operators, then$f(g(x))=g(f(x))$.Thus, for example, the response of a linear system to a step input can be computed by integrating its impulse response, since a step is the integral of an impulse.

Under the same test conditions, a system that is *time-invariant* will respond identically to a specific stimulus irrespective of when it is introduced. That is, except for the time shifts between responses, all responses are identical. Just as not all systems are linear, not all linear systems are time-invariant. Mathematically, time invariance can be expressed as follows:

$$y(t) = f(x(t)) \Rightarrow y(t-\tau) = f(x(t-\tau)) \qquad (17.9)$$

where, τ is a time constant. A system that satisfies both of these properties is naturally called a linear time-invariant (LTI) system.

Testing a system for linearity may be done using the principle of superposition. An easy way to implement such tests is to apply the same input at different amplitudes. If the system is linear, the output will have the same shape and the output amplitude will scale with the input amplitude. It is also useful to remember that the response of a linear system to a sinusoidal input will be a sinusoid at the same frequency. Thus, if the output has components at frequencies not in the input, it must be nonlinear.

Many systems behave linearly over a restricted range of inputs. For example, a rectifier is linear as long as the input remains either positive or negative. Almost any system will become nonlinear if the input is large enough. Conversely, most nonlinear systems can be described by a linear approximation if the input amplitude is small enough. Thus, it is important to determine not only whether a system is linear, but over what range of values does it behave linearly. Thus, it is important to determine the linear range of a system.

In some cases, a system may have more than one linear range and display different behaviors in each range (e.g., a full wave rectifier). Note that the linear range is a property of the amplitude of the input – not its frequency content. That being said, the linear range may vary with frequency for some types of nonlinear systems.

An approach that is frequently useful in dealing with nonlinear systems is to transform either the input or the output in order to make the resulting input-output relation more linear. For example, logarithmic transformations are useful in linearizing systems in which there is a power relation between input and output.

17.8.1. Time-Domain and Frequency-Domain Models

If a system is known to be linear, it is always guaranteed that an adequate model of the system can be determined. This consists of determining the system's response to a set of basis functions (for example impulses or sinusoids of different frequencies). Once these responses are known, the response to an arbitrary input may be determined as follows:

1. Decompose the arbitrary input into a linear combination of basis functions (e.g., Fourier analysis decomposes the signal into a linear combination of sinusoids).
2. Determine the response to each component using the principle of proportionality.
3. Sum the resulting components to determine the overall response by relying on the principle of superposition.

If the basis functions are a series of impulses, then the analysis results in *time domain models*. On the other hand, if the basis functions are sinusoids, then the analysis results in *frequency domain models*.

One way to characterize the dynamic behavior of a linear system is in terms of its response to an impulse. The impulse response function (IRF) can be used as a representation of a linear system because it can be used to predict the response of the system to any input. To visualize how this works, consider the input to the system to be a series of impulses of different amplitudes. The response of the system to any one impulse is simply the IRF multiplied by the amplitude of the input impulse, and delayed by the time at which the input impulse occurs. Now, because a linear system obeys the superposition principle, the overall output is simply the sum of the responses to all the input impulses. The convolution integral is the mathematical statement of this procedure.

A system's IRF can have both positive time values, representing system memory, and negative time values, representing system anticipation. The response, *y(t)*, of such a two-sided IRF, *h(t)*, to an input, *x(t)*, is given by the convolution integral

$$y(t) = \int_{-\infty}^{\infty} h(\tau)x(t-\tau)d\tau \tag{17.10}$$

If, as is usually the case, $\int_{-\infty}^{\infty} h^2(\tau)d\tau < \infty$, then the system has finite memory and $h(t) \cong 0$ when $\tau < T_1$ and $\tau > T_2$ for some value of T_1 and T_2. Under these conditions, Equation 17.10 may be simplified to

$$y(t) = \int_{T_1}^{T_2} h(\tau)x(t-\tau)d\tau \tag{17.11}$$

In *causal* (physically realizable or non-anticipatory) systems there is no anticipatory component to the response; e.g., *h*(*τ*)=0 for τ<0 so that T1_0. The IRF is then o*ne-sided* and the convolution integral further simplifies to

$$y(t) = \int_{0}^{T_2} h(\tau)x(t-\tau)d\tau \tag{17.12}$$

A linear system can be represented by either a parametric or non-parametric IRF. A parametric IRF is in the form of an equation. The structure of the equation defines the class of systems it represents, and the parameters of the equation determine how the behavior differs from that of the other members of the same class. In contrast, a non-parametric IRF consists of the sampled values of the response, and is stored as a real vector in the time domain. In short, the parametric form can be represented by an equation, and the non-parametric form can be represented by a curve.

It is normally assumed that physical systems are causal and do not anticipate. Consequently, the usual IRF identification procedures employed in engineering determine only the positive or memory part of the IRF. There are a number of areas of research, particularly those involving the life sciences, where it is important to determine both the positive and negative parts of an IRF. Two-sided IRFs will be important in situations involving actual prediction. Living systems frequently demonstrate predictive behavior. For example, the frequency response of the visual pursuit system is wider for predictable stimuli than for random stimuli. Effective prediction can occur when the input is unknown but structured (e.g., periodic), or when preview of the input is possible. Under such conditions, a negative portion of the IRF may well occur. A pure delay of τ, either preceding or following a linear dynamic system, moves the IRF τ to the right. Thus, whether or not a system contains a pure delay may often be determined from the IRF. If the input to the system is measured after a delay of τ, then the IRF is shifted to the left with the result that negative time values may occur, necessitating the use of two-sided IRF identification techniques. Once the delay has been determined from the identified IRF, the input can simply be shifted with respect to the output to eliminate the delay. There are many situations where the input to a system is related to its output by feedback. Attempting to identify the system under such conditions can lead to incorrect estimates of the system's dynamics. However, the presence of a feedback relation can be detected as an anticipatory component of the IRF, relating the input to the output. Hence, computing the two-sided IRF provides a means of testing for a feedback relation between two signals.

Now, we will deal with an alternative approach in which linear dynamics are characterized in terms of the response to sinusoidal stimuli of different frequencies. The response of a linear system to a sinusoidal stimulus will be a sinusoid of the same frequency but of different amplitude and phase. The frequency response of a linear system describes the relative magnitudes of the input and output sinusoids (gain), and the phase difference as a function of frequency.

The frequency response of a linear system may be used to determine the response of the system to an arbitrary input as follows:

1. Decompose the input signal into a sum of sinusoids using Fourier analysis.
2. Multiply each sinusoid by the gain of the system at the appropriate frequency, and shift it by the corresponding phase.
3. Sum the scaled and phase-shifted sinusoids to reconstruct the overall response.

The response of a linear system to an arbitrary input may be computed from its impulse response using the convolution integral defined in Equation 17.10. The Laplace transform of this relation gives $Y(s)$=$H(s)X(s)$; where, $H(s)$ is the Laplace transform of the impulse response, $Y(s)$, $X(s)$ are the Laplace transforms of the output and the input, respectively, and s is a complex variable defined as $s = \sigma + j\omega$, σ being a damping factor and ωbeing a frequency term. The transfer function of the system can then be written as

$$H(s) = \frac{Y(s)}{X(s)} \tag{17.13}$$

The transfer function of any linear, time-invariant, constant-parameter system without delays may be written as the ratio of two polynomials:

$$H(s) = K\frac{(s - z_1)...(s - z_m)}{(s - p_1)...(s - p_m)} \tag{17.14}$$

where, the zeros (z_i) and poles (p_i) of the polynomials may be real, zero, or complex (if complex they come as conjugate pairs). To determine the frequency response of a system with transfer function $H(s)$, apply a sine wave stimulus:

$$x(t) = A\sin(\omega t) \tag{17.15}$$

which has the Laplace transform $X(s) = \mathrm{A}\frac{\omega}{s^2 + \omega^2}$. The response in the Laplace domain will be

$$Y(s) = AK\frac{s}{(s^2 + \omega^2)}\frac{(s - z_1)...(s - z_m)}{(s - p_1)...(s - p_n)} \tag{17.16}$$

Expanding the right hand side of Equation (17.16) using partial fractions gives

$$Y(s) = \frac{c_1}{s + j\omega} + \frac{c_2}{s - j\omega} + \frac{c_3}{s - p_1} + \frac{c_4}{s - p_2} + ... \tag{17.17}$$

Taking the inverse transform gives the solution

$$y(t) = c_1 e^{-j\omega t} + c_2 e^{j\omega t} + c_3 e^{p_1 t} + c_4 e^{p_2 t} + ... \tag{17.18}$$

All p_i, i=1,…,n must be less than zero for the system to be stable, so the steady state response is

$$y_{ss}(t) = c_1 e^{-j\omega t} + c_2 e^{j\omega t} \tag{17.19}$$

Standard partial fraction techniques then give

$$c_1 = \frac{AH(-j\omega)}{2}, c_2 = \frac{AH(j\omega)}{2} \tag{17.20}$$

so that

$$y_{ss}(t) = A\left|H(j\omega)\right|\cos\left(\omega t + \phi\left\langle H(j\omega)\right\rangle\right) \tag{17.21}$$

where, $|H(j\omega)|$ denotes the magnitude of $H(j\omega)$, and $\phi\left\langle H(j\omega)\right\rangle$ is its phase.

Thus, the steady state sinusoidal response of a linear system can be operationally determined from its transfer function by letting $s=j\omega$, and then evaluating the magnitude and phase of the resulting complex number as a function of frequency. Conversely, the frequency response of a system can often be used to determine the underlying transfer function.

Sinusoidal inputs provide a convenient, straightforward means of determining the frequency response of a system. The procedure is as follows:

1. Apply a sinusoidal stimulus at frequency ω to the system, wait for the response to reach steady state, and record the resulting sinusoidal response.
2. Compute the ratio of the response amplitude to the input amplitude, and use it as a measure of the system gain at frequency ω.
3. Compute the phase shift of the output with respect to the input, and use it as a measure of the system phase shift at ω.
4. Repeat steps i-iii at frequencies over the range for which the system responds.
5. Draw or fit a smooth curve through the resulting points.

Advantages of sinusoidal testing include:

1. The gain of the recording system can be adjusted at each frequency (either manually

or automatically) to use the full dynamic range and minimize the effects of noise.

2. The amplitudes of the input sinusoids can be adjusted until the output amplitude reaches some desired value.
3. In the presence of noise and nonlinearities, only the amplitude and phase of the sinusoidal component at the input frequency need be measured.

Sinusoidal testing is very effective, when practical, but does have a number of limitations:

1. The approach requires the application of pure sinusoids of a single frequency. This is often difficult technically. Furthermore, in the life sciences, particularly in behavioral studies, it is often desirable to avoid predictable, periodic stimuli.
2. The procedure is time consuming. Each stimulus frequency must be applied separately and the response recorded only after the transient response has decayed. If the system's time constant is long, this may require many cycles at each frequency. The time taken to do sinusoidal testing is particularly important in the study of physiological systems where experimental time is always limited. In addition, living systems are frequently time varying so it is important to obtain an identification in as short a time as possible.
3. Only a limited number of frequencies can be tested. If too few frequencies are tested, sharp changes in the frequency response, e.g. resonances, may be missed.

17.8.2. Stochastic Testing

Consider a constant parameter, linear system described by the one-sided, impulse response *h(τ)* with the corresponding frequency response function *H*(*jω*). Assume that the system is subjected to a stationary, random input x(*t) w*hich generates the stationary random process y(*t) a*s output. Then,

$$y(t) = \int_0^t h(\tau)x(t-\tau)d\tau \tag{17.22}$$

The autocorrelation function of the output is given by

$$R_{yy}(\tau) = \mathrm{E}\left[y(t)y(t-\tau)\right] \tag{17.23}$$

which has the expected value

$$\int_0^t \int_0^t h(v)h(\mu)R_{xx}(t-\mu+v)dvd\mu \tag{17.24}$$

where, R_{xx} is the autocorrelation of the input. Thus, the output autocorrelation function is defined by the system's impulse response and the autocorrelation function of the input. The cross-correlation function R_{xy} between the input *x(t)* and the output *y(t)* may be derived from the relation

$$\mathrm{E}\left[x(t)y(t+\tau)\right] = \mathrm{E}\left[\int_0^\infty (h(v)x(\tau)x(t+\tau-v)dv\right] \tag{17.25}$$

which has the expected value

$$R_{xy}(\tau) = \int_0^\infty h(v)R_{xx}(\tau - v)dv \tag{17.26}$$

Thus, the cross-correlation between the input and output is simply the convolution of the input auto-correlation function, with the Fourier that is transforming these relations, yields the frequency domain expressions:

$$S_{yy}(j\omega) = \left|H(j\omega)\right|^2 S_{xx}(j\omega) \tag{17.27}$$

and

$$S_{xy}(j\omega) = H(j\omega)S_{xx}(j\omega) \qquad (17.28)$$

where, S_{xx}*(jω)*and S_{yy}*(jω)* are the input and the output power spectra, and S_{xy}*(jω) i*s the input-output cross spectrum. The gain portion of the system frequency response may be estimated from the input and output power spectra as

$$\left|H(j\omega)\right|^2 = \frac{S_{yy}(j\omega)}{S_{xx}(j\omega)} \qquad (17.29)$$

However, this estimate gives no information about the phase. Moreover, it will be biased if there is noise at either the input or the output. A better approach is to determine the system frequency response function from the input power spectrum and the input-output cross spectrum by using Equation 17.26 to get the relation:

$$H(j\omega) = \frac{S_{xy}(j\omega)}{S_{xx}(j\omega)} \qquad (17.30)$$

$S_{xy}$is a complex number, so the frequency response has both a magnitude (or gain) and a phase characteristic. Moreover, because of the averaging involved in computing the cross-spectrum, the estimate will not be biased as a result of output noise. However, if there is much output noise, then long data records and, hence, much averaging may be needed to reduce the random error. Furthermore, noise at the input will still result in biased results.

The coherence squared function between the input $x(t)$ and the output $y(t)$ of a system is a real-valued function defined by:

$$\gamma^2_{xy}(j\omega) = \frac{\left|S_{xy}(j\omega)\right|^2}{S_{xx}(j\omega)S_{yy}(j\omega)} \qquad (17.31)$$

The coherence-squared function will have values in the range 0 to 1, and is analogous to the variance accounted for as a function of frequency (i.e., the square of the correlation coefficient function which arises in linear regression). For a constant parameter linear system with no noise, the coherence-squared will identically equal to 1. If the input and output are completely unrelated, the coherence-squared function will have a value of 0. If the coherence-squared function is greater than zero but less than one, three possibilities exist:

1. Extraneous noise is present in the measurements.
2. The system is not linear.
3. *y(t)* is an output due to an input *x(t)* as well as to other inputs.

The coherence-squared can be interpreted as the fraction of the output variance that is linearly related to the input at each frequency.

Note that the coherence function is usually estimated from spectral estimates obtained by averaging a number of segments of the original data. The bias error associated with coherence estimates varies with the number of segments and the expected value of the coherence; the error decreases as either or both increase. Estimates of the coherence function may be in serious error if the number of segments is small and/or if the value of the coherence function is low. Indeed, the worst case occurs if only one segment is used to estimate the coherence function, since the coherence estimate will always be equal to one for this case.

The procedure for doing frequency analysis of a system using a stochastic input is:

1. Apply a stochastic input having power over the range of frequencies where the system is expected to respond.
2. Record the input and resulting output.

3. Compute the input spectrum, the output spectrum, and the input-output cross spectrum.
4. Evaluate the gain, phase and coherence using Equations 17.29 through 17.31.

Note that since the stochastic input has power over a wide range of frequencies, the stochastic technique can be thought of as testing a large number of frequencies simultaneously. Consequently, it takes much less time than pure sinusoidal testing. Furthermore, the coherence provides a quantitative measure of how well the resulting linear model describes the system. If the coherence function is less than one, it is useful to determine whether this is due to additive noise or due to nonlinearities. One way to investigate this is to increase the amplitude of the input signal; if the problem is noise, then the coherence function should increase since the output signal-to-noise ratio (SNR) should increase. Conversely, if the problem is nonlinearity, then the coherence function will stay the same or will decrease. Another possibility is to repeat the experiment a number of times with the same input, and average the input and output signals before doing the analysis. If noise is the problem, then the coherence of the average signals will be greater than that of the individual trials. If the problem is nonlinearity, then the results will not change.

17.8.3. Applied Examples

Example 17.5: A method to model a dynamic linear physical system uses simple basic electrical components, namely a resistor (R), an inductor (L), a capacitor (C), and sources of potential (V) and current (I). Such method allows for a more natural modeling approach, since the system has a direct correspondence to its graphic representation that is more comprehensible than differential equations. In this example, we will introduce the basic elements of an electrical model of a system and the procedure to get the differential equation from the graphic description, which is based on the Kirchhoff's circuit laws.

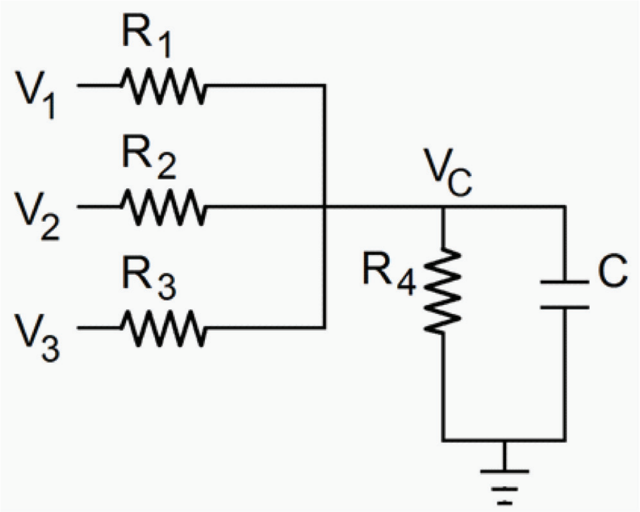
Let us consider the simplest dynamic linear model ("*leaky integrator*") of a nerve cell, depicted in Figure 7. The resistors R_1, R_2, R_3 represent the neuron's dendrites and the respective voltages V_1, V_2, V_3 are generated by the synapses from other neurons. The respective currents, I_1, I_2, I_3 are integrated in the capacitor C that models the cell body membrane capacity. The presence of the membrane resistance, R_4 denotes that the integrator is "*leaky*". The differential equation of this model can be written as follows:

1. We regard all the currents to have a direction towards out of the point, V_C.
2. Kirchhoff's current law says that the sum of all currents in a single node is equal to zero, $I_{R_1} + I_{R_2} + I_{R_3} + I_{R_4} + I_C = 0$
3. We replace the currents by their voltage values as follows:
$$\frac{V_C - V_1}{R_1} + \frac{V_C - V_2}{R_2} + \frac{V_C - V_3}{R_3} + \frac{V_C}{R_4} + C\frac{dV_C}{dt} = 0$$
4. We can write the same equation in a simplified form,
$$\left(\frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} + \frac{1}{R_4}\right)V_C - \left(\frac{V_1}{R_1} + \frac{V_2}{R_2} + \frac{V_3}{R_3}\right) + C\frac{dV_C}{dt} = 0$$

This is a standard form for a first order differential equation that can be solved analytically or numerically, or even be transformed to the Laplace domain for further analysis.

Example 17.6: A class of simple, yet accurate models, estimated from microelectrode recordings, can predict spike generation of single and multiple subthalamic nucleus (STN) neurons of Parkinson's disease (PD) patients. The most characteristic attribute of an STN neural recording is the presence of bursting/quietness segments. It has been

Figure 7. Associative linear neural network

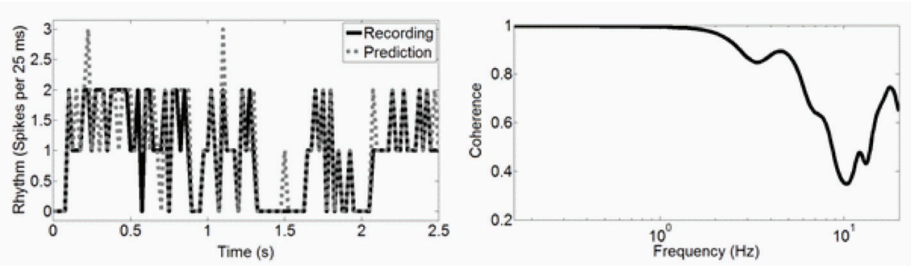


suggested that the STN sends the bursting pulse of spikes as a braking signal to reset the major basal ganglia output nuclei. This mechanism does not work right in abnormal situations, such as the PD. To be able to have a quantitative validation of the prediction of the model, the coherence between the predicted spike rhythm and the recorded one is estimated. In Figure 8, the two rhythms, calculated in 50 ms bin, and their coherence are shown. The coherence is 1 in low frequencies and drops after 2 Hz (3 dB point is calculated at 2.4 Hz). This depicts that the model predicts the ups and downs of the rhythm accurately; whereas, it misses one or two spikes (per 50 ms bin), explaining the small jittering observed in the exact spike prediction.

17.9. NONLINEAR MODELING OF PHYSIOLOGICAL CONTROL SYSTEMS

Any system which violates the principle of superposition is non-linear. Many physical and virtually all biological systems are nonlinear. In this case, it is impossible to provide a general system description that can be used for any input, and applied at

Figure 8. Coherence estimate between the predicted and the observed spiking rhythm. The prediction is done using a model that accepts the local field potentials as its input.



any time. Instead, functional series are typically used. A *functional* is a function whose argument is a function and whose value is a number. For instance, the convolution integral evaluated at a given time is a functional.

17.9.1. Volterra Series

An example of a functional series to describe a non-linear system is the Volterra series. Volterra showed that if a system is time invariant, has finite memory, and is analytic (differentiable), then the relation between input $x(t)$ and output $y(t)$ can be expressed as the infinite sum

$$\begin{aligned} y(t) = k_0 &+ \int_0^\infty k_1(\tau)x(t-\tau)d\tau \\ &+ \int_0^\infty \int_0^\infty k_2(\tau_1,\tau_2)x(t-\tau_1)x(t-\tau_2)d\tau_1 d\tau_2 \\ &+ \int_0^\infty \int_0^\infty \int_0^\infty k_3(\tau_1,\tau_2,\tau_3)x(t-\tau_1)x(t-\tau_2)x(t-\tau_3)d\tau_1 d\tau_2 d\tau_3 \\ &+ \ldots \end{aligned} \tag{17.32}$$

where, k_0, $k_1(\tau)$, $k_2(\tau_1,\tau_2)$, $k_3(\tau_1,\tau_2,\tau_3)$, ... are the kernels of the system, and are symmetric functions of their arguments. The zero-eth order kernel k_0, a constant, can be assumed to be zero without loss of generality by assuming $y(t) = 0$ when $x(t) = 0$ (in other words, we remove the non-zero bias). The nth order kernel describes the pattern of interaction between n pieces of the past stimulus and its contribution to the total response. However, there are other contributions due to nth order interactions also present in all other terms with kernels of order greater than n. That is the response to nth-order interactions is defined by all kernels of order n or greater; it is not isolated in the nth component. For example, the first-order term in the series is exactly the same as the convolution integral in a linear system, where the first kernel then represents the impulse response. However, note that in a non-linear system, the above series defines the impulse response (1st order effect) to depend on all kernels

$$\begin{aligned} y(t) = k_0 &+ \int_0^\infty k_1(\tau)\delta(t-\tau)d\tau \\ &+ \int_0^\infty \int_0^\infty k_2(\tau_1,\tau_2)\delta(t-\tau_1)\delta(t-\tau_2)d\tau_1 d\tau_2 \\ &+ \int_0^\infty \int_0^\infty \int_0^\infty k_3(\tau_1,\tau_2,\tau_3)\delta(t-\tau_1)\delta(t-\tau_2)\delta(t-\tau_3)d\tau_1 d\tau_2 d\tau_3 \\ &+ \ldots \end{aligned} \tag{17.33}$$

or equivalently,

$$y(t) = k_0 + k_1(t) + k_2(t,t) + k_3(t,t,t) + \ldots k_n(t,\ldots,t) + \ldots \tag{17.34}$$

Hence, the use of impulses to isolate kernels of different order is not practical here. Another problem is that full description of a non-linear system with Volterra series, theoretically, has an infinite number of terms. Because the importance of each functional depends on the form of the non-linearity, and because the terms in this series are not orthogonal to each other, then

1. One cannot know *a priori* when or where to truncate the series (small kernels can be followed by an important large kernel at higher dimensions).
2. Adding terms changes all the previously evaluated kernels and they must be recomputed.

17.9.2. Wiener Series

To address the above issues, Wiener proposed a special form for a functional series description of a non-linear system. Assuming white Gaussian noise as the input, the G_i functionals in the series are designed to be orthogonal with respect to each other and with respect to white noise input functionals of lower order. As a result, the importance of Wiener functionals in the series usually decrease in magnitude with kernel order, and adding terms does not affect already computed functionals. Furthermore, the mean squared error associated with truncation of the series is lowest for Wiener descriptions, when compared to other series truncated at the same order (like Volterra).

Starting with the general Volterra series form, Wiener proposed

$$y(t) = \sum_{m=0}^{\infty} G_m \left[h_m(\tau_1, \tau_2, ... \tau_m); x(t'), t' \le t \right] \tag{17.35}$$

where, G_m are now orthogonal functions, $x(t)$ is a Gaussian white-noise signal with zero mean, and h_m is the set of Wiener kernels. Each h_m is a symmetrical function with respect to its arguments. The first four Wiener kernels are defined by the following functionals:

$$\begin{aligned}
G_0\left[h_0; x(t)\right] &= h_0 \\
G_1\left[h_1; x(t)\right] &= \int_0^\infty h_1(\tau)x(t-\tau)d\tau \\
G_2\left[h_2; x(t)\right] &= \int_0^\infty \int_0^\infty h_2(\tau_1,\tau_2)x(t-\tau_1)x(t-\tau_2)d\tau_1 d\tau_2 - P\int_0^\infty h_2(\tau_1,\tau_2)d\tau_1 \\
G_3\left[h_3; x(t)\right] &= \int_0^\infty \int_0^\infty \int_0^\infty h_3(\tau_1,\tau_2,\tau_3)x(t-\tau_1)x(t-\tau_2)x(t-\tau_3)d\tau_1 d\tau_2 d\tau_3 \\
&\quad -3P\int_0^\infty \int_0^\infty h_3(\tau_1,\tau_2,\tau_2)x(t-\tau_1)d\tau_1 d\tau_2
\end{aligned} \tag{17.36}$$

where, $x(t)$ is Gaussian white noise of zero mean and power density spectrum $\varphi_{xx}(f)=P$ (or otherwise, autocorrelation $\varphi_{xx}(\tau) = P\delta(\tau)$. The functionals have been selected to be orthogonal to each other so that

$$E\left\{ G_i\left[h_i; x(t)\right] G_j\left[h_j; x(t)\right] \right\} = 0 \text{ for all } i \neq j \tag{17.37}$$

Furthermore, Wiener constructed the functionals so that a given G_k is orthogonal to all homogenous functionals of $x(t)$ whose order is less than k, when x is white noise. For example, if $x(t-\tau)$ is an homogenous functional of order 1, then $E\left\{ G_k[h_k; x(t)](t-\tau) \right\} = 0$, for $k>1$. The kernels in a Volterra series {k} can be related to those in a Wiener series {h} according to even or odd terms:

$$\begin{aligned}
h_{2n}(\sigma_1,...,\sigma_{2n}) &= \sum_{m=n}^{\infty} \frac{2m!\,P^{m-n}}{2n!(m-n)!2^{m-n}} \times \\
&\quad \times \int_0^\infty ... \int_0^\infty k_{2m}(\tau_1,\tau_1,...,\tau_{m-n},\sigma_1,...,\sigma_{2n})d\tau_1 ... d\tau_{m-n} \\
h_{2n+1}(\sigma_1,...,\sigma_{2n+1}) &= \sum_{m=n}^{\infty} \frac{(2m+1)!\,P^{m-n}}{(2n+1)!(m-n)!2^{m-n}} \times \\
&\quad \times \int_0^\infty ... \int_0^\infty k_{2m+1}(\tau_1,\tau_1,...,\tau_{m-n},\sigma_1,...,\sigma_{2n+1})d\tau_1 ... d\tau_{m-n}
\end{aligned} \tag{17.38}$$

This makes it clear that Wiener kernels, in contrast to Volterra kernels, are polynomial functions of P, the power of this noisy stimulus. Also, a given Wiener kernel is a function of higher order Volterra kernels.

17.9.3 Applied Example

Example 17.7: A special class of Volterra-Wiener non-linear models is the block oriented non-linear models in which a linear time invariant (LTI) dynamic block is preceded and/or followed by a static non-linearity. When the linear dynamic block is preceded by a static input non-linearity, the model is referred to as a Hammerstein model; and, when the linear dynamic block is followed by a static output non-linearity, the model is referred to as a Wiener model. Both are a special case of the situation in which the linear dynamic block is sandwiched between two static non-linear blocks, a Hammerstein-Wiener (H-W) model.

Briefly, in state space, an H-W model is represented by

$$\begin{aligned}
&v\left(k \mid k\right) = f\left(u(k \mid k)\right) \\
&LTI = \begin{cases} x(k+1 \mid k) = Ax(k \mid k) + Bv(k \mid k) \\ \quad w(k \mid k) = Cx(k \mid k) + Dv(k \mid k) \end{cases} \\
&y(k \mid k) = h\left(w(k \mid k)\right)
\end{aligned} \tag{17.39}$$

where, $u \in \Re$ is the physical input to the plant, which is passed through the non-linear mapping $f(u)$ to give the input $v \in \Re$ of the linear dynamic block. A, B, C, and D are the system matrices (of conformal dimensions) of the linear dynamic block, $x(k+1|k) \in \Re$ is the state at time k+1 calculated at time k, $w \in \Re$ is the output of the linear block which is passed through the non-linear mapping $h(w)$ to give the output $y \in \Re$ of the plant. The static non-linear functions $f(u)$ and $h(w)$ are assumed to be invertible. The H-W model can be used to investigate whether it is possible to infer STN spike trains using only the underlying local field potentials (LFPs) from intranuclear recordings, acquired intraoperatively during deep brain stimulation procedure. The model regards the LFPs to be the input, and the presence of the spikes to be the output of a Hammerstein-Wiener model and predicts, at least partially, that STN spikes can indeed be inferred from intranuclear LFPs, at least with moderate success. Such a model can be seen in Figure 9.

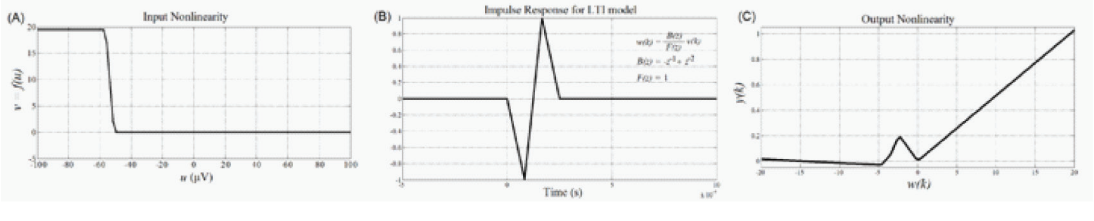
17.10. IDENTIFICATION OF PHYSIOLOGICAL CONTROL SYSTEMS

The system identification approach to constructing a mathematical model of a physiological system is much different than what has been presented until now. The modeler's task is first to select a general form, or structure, for the mathematical model, and then estimate the parameter values. Often, a variety of model structures are evaluated, and the most successful one is retained. In this section, we will first describe the estimation problem in general, and then concentrate on the pragmatic guidelines to select a model.

The general problem of parameter estimation is formalized as follows: Let the model's general mathematical structure be represented by an operator, **M**. Let the model depend on a set of parameters, ordered in a vector, θ. Then, for a specific parameter vector, θ_0, the $y(t,\theta_0)$=**M**(θ_0, $u(t)$) is a static input/output function or a transfer function in the Laplace domain, where u is the input and y is the output. Now, if the model structure, **M**, and the parameter vector, θ_0, *exactly* represent the physical system, the objective of system identification is then to find a suitable model structure, **M**, and corresponding parameter vector, θ, given measurements of input and output. The identified model will have a parameter vector, $\widehat{\theta}_0$, and generate $\hat{y}(t) = M\left(\hat{\theta}_0, u(t)\right)$, where $\hat{y}(t)$ is an estimate of the system output, y(t). The system identification problem is then to choose the model structure model, **M**, and find the corresponding parameter vector, $\widehat{\theta}_0$, that produces the model output that best predicts the measured system output.

In the remaining parts of this section, the identification steps that are usually involved for discrete models are presented. The process requires four steps, which are often applied iteratively:

Figure 9. A Hammerstein-Wiener cascade model is able to predict the spikes from the recorded local field potentials (Michmizos & Nikita, 2010).



1. Postulate a model form (structure) and select the appropriate identification tool.
2. Postulate a model order and imbed data in a set of equations for the identification.
3. Compare predictions to real observations in the data set used for identification (i.e., find residuals and their statistics), and estimate confidence in parameter estimates; then, correct model form or order as needed and repeat steps i-ii.
4. Validate the selected model by examining predictions in new data sets in the same experiment or in completely novel experimental protocols. If several model forms perform equivalently in step ii, they may not do so here when tested on new data.

First, a model order is selected, by fixing the model type and polynomial orders. The properties of the residual noise, $r = y - \hat{y}$, y being the real output and $\hat{y}$ being the predicted output, for the data set can be examined. For standard regression, if the residual is white with approximately Gaussian distribution, its variance can be used to set confidence intervals on the parameters and decide if any of them are superfluous. If the noise sequence is not white, or diverges greatly from the normal distribution, then it could be assumed that we have either the wrong model form or the wrong order in the current form.

Pragmatic guidelines to select model structures at this stage are:

1. **Residual is nearly white, Gaussian and zero-mean:** The t-statistics should be used in order to define confidence intervals on all the estimated parameters, or to examine those provided by the applied estimation function. If all are significantly different from zero at the desired confidence level, then the current model is a valid possibility, provided the quality of fit is satisfactory (e.g., the %Variance of Accounted for (VAF) is high enough). If some parameters have confidence levels which include zero, then an attempt should be made by the investigator to fit another model with those parameters removed (if one is manipulating his/her own regressor matrix); otherwise, a fit with a supplied algorithm setting a lower order is to be attempted. Once an order for the current model form is decided, the final parameter estimates must then come from a final fit with that selected order.
2. **Residual is not white and not zero-mean:** Assuming the underlying noise statistics are indeed Gaussian, this means that either the wrong model form (schematic or hypothetical relationship) is attained, or an insufficient number of parameters exist. The investigator should then increase the order and try again. Subsequently, the investiagator is to examine the current residuals for deterministic trends (like ramps or sinusoids), and adjust the model form accordingly.
3. **Residual is not Gaussian but is zero-mean and white:** This may happen if the underlying noise properties are actually themselves not Gaussian, or the wrong model order exists. Whatever the reason, one cannot rely on the usual t-statistics for the confidence intervals of estimated parameters – these could lead to erroneous selection of model order and/or pertinent parameters. In this case, it is often recommended to resort to *'Monte Carlo'* or *'Bootstrap'* methods. These approaches are computationally demanding, but they generate pseudo statistics on parameter estimates from which more accurate confidence intervals can be determined, regardless of the form of each parameter's probability distribution (e.g., limits for 95% of area under curve). Monte Carlo relies on repeating the estimation routine many times, using many experimental protocols, or dividing a large data set into multiple sets – but, it may not always be

feasible to have long experimental protocols. Bootstrap instead uses a single data set and generates multiple sets for parameter estimation by for example: A) iteratively using each estimate to generate a new shuffled noise sequence (the investigator is to use $r = y - \hat{y}$ as defined previously, shuffle randomly, and add back onto $\hat{y}$ for a 'new' data set), creating new virtual noisy data sets-, or B) selecting a subset of data randomly from the original set to generate estimates with each. This is repeated as many times as necessary to obtain smooth parameter histograms; and, does not lengthen experimental data acquisition. However, there are differences between approaches A and B. In particular, method B means that each estimation run will have fewer data observations than that of the original experimental data length; in method A, the number of observations entering the estimation step is always the same total as the whole data segment.

Finally, validation of the selected model should include a demonstration that the predictors perform well on new data not used in the original fitting procedure. This can be data reserved from the original experiment, or a totally new data stream from a different protocol. The best models will fit well the data used in the identification, and will also duplicate well other data sets. This last cross-validation step is the final test which can tell the best models from those specific to a special condition. Hence, this is an important step in justifying the final choice of a model form and order.

17.10.1 Applied Example

Example 17.8: Next, we will present a simple parameter estimation problem for a linear model, in order to illustrate the theory previously discussed. Let us model an unknown physiological system with a linear model $y = \sum_i w_i u_i$. Please note that the real system may or may not be linear, and that the data we acquire from the experiments are usually noisy. But if we insist on finding the optimal linear model according the least square criterion, we have to find an optimum matrix notation, W^T for which $y{=}W^TU$, U being the input matrix. According to the least square criterion, we have to calculate $W{=}\Phi^{-1}P$, whereby $P = E\ [Y{\cdot}U]$ and $\Phi = E\ [U{\cdot}U^T]$, and where E stands for expectation and U^T is the transpose input matrix. For further information on the origin and proof pertaining to the above discussion, the reader is to refer to a textbook on linear parameter estimation, e.g., (Ljung, 1999).

Assume that we have a static system with two inputs and one output, $y{=}w_{1.}u_1{+}\ w_{2.}u_2$. To estimate the model's parameters, we conduct an experiment measuring the inputs and the output four times, as shown in Table 1.

We now calculate the estimation of P as follows:

$$P = E\left[Y \cdot U\right] = E\begin{bmatrix} y \cdot u_1 \\ y \cdot u_2 \end{bmatrix} = \frac{1}{4}\begin{bmatrix} 5.1 - 1.1 - 0.8 + 4.7 \\ 5.1 + 1.1 + 0.8 + 4.7 \end{bmatrix} = \begin{bmatrix} 1.975 \\ 2.925 \end{bmatrix}$$

Next, we calculate the estimation of Φ as follows:

$$\Phi = E\left[U \cdot U^T\right] = E\begin{bmatrix} u_1 \cdot u_1 & u_1 \cdot u_2 \\ u_2 \cdot u_1 & u_2 \cdot u_2 \end{bmatrix} = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$$

Now, we can calculate the optimal parameters $W^T{=}(\Phi^{-1}{\cdot}P)^T{=}[1.975,\ 2.925]$.

We can see that the model's outputs for the four experimental measurements in Table 2.

Table 1. System's inputs and outputs.

u_1	u_2	y
-1	-1	-5.1
-1	1	1.1
1	-1	-0.8
1	1	4.7

As one can see, the model outputs are very similar to the data we acquired. However, in a real experiment, it is highly expected to have more noise than the one we had here. Hence, more experiments should be conducted to gather more data and have a good estimation of the model's parameters.

17.11. ARTIFICIAL NEURAL NETWORKS FOR PHYSIOLOGICAL SYSTEMS CONTROL

Artificial neural network models represent a black box type of model. These models are used in situations where the precise functioning of the system is not understood or easily implemented, and only the sample input-output data are known. This section will provide a brief description of the basic principles of neural network control systems and their use in control of physiological systems. Neural networks have been used for more than two decades in solving engineering problems, especially in pattern recognition and pattern classification applications. Neural networks are also used in modeling problems that are difficult to solve. For instance, controlling a nonlinear system has always been an advanced modeling task that most of the times led to an insufficient solution. The introduction of the neural networks to the field of physiological systems control resulted in a new area of research for both the neural network and systems control scientific communities.

Table 2. Model's outputs.

u_1	u_2	$\hat{y}$
-1	-1	-4.90
-1	1	0.95
1	-1	-0.95
1	1	4.90

17.11.1. Basic Principles

The term neural network was traditionally used to refer to a network or circuit of biological neurons. The usage of the term has changed to refer to artificial neural networks, which are composed of artificial neurons or nodes. Various neural network algorithms currently exist, but they all share common characteristics that include a set of inputs and outputs, the distributed processing of the information, and their adaptive parameterization. The structure of a neural network resembles the structure of the nervous system. The input information inserted into such a network is collectively processed by a group of distinct units (in analogy to the neurons). Each processing unit interacts with the information given locally, and then sends an output to other units or the environment (output information). The significance of a certain connection (synapse) between two units is determined by a value of strength (synaptic weight). These values modify the input-output behavior of the entire neural network, and are adjusted according to a learning algorithm. In order to design a neural network, one has to consider the internal characteristics, the architecture, and the number of the processing units, as well as the learning algorithm.

The architecture of the neural network is not the only analogy between the artificial and the biological systems. The internal characteristics of the processing unit mimic the ones of a neuron. A neuron receives chemical messages (inputs) from other neurons that are transformed to dendritic potential, which is then added up in the neuron's soma to fire an action potential (output). In general, the decision upon firing an action potential relies on a nonlinear function of a weighted summation of the neuron's inputs. The most common equation used to model the decision is the sigmoid curve produced by the mathematical function having an "*S* " shape, as shown in Figure 10. The general equation for a sigmoid function is

$$Y = \frac{1}{(1+e^{-mx})} \tag{17.40}$$

where, *x* is the input (the weighted summation of the artificial neuron), and *m* is a constant that regulates the slope of the sigmoidal output function. For *m* = 1, the function is named logistic function and is related to population growth studies. Sometimes, a constant is added to the term *–mx,* and is called the bias of the sigmoid function. The inputs of an artificial neuron, u_i, are related to their weighted summation by the equation

$$x = \sum_{i=1}^{n} w_i u_i \tag{17.41}$$

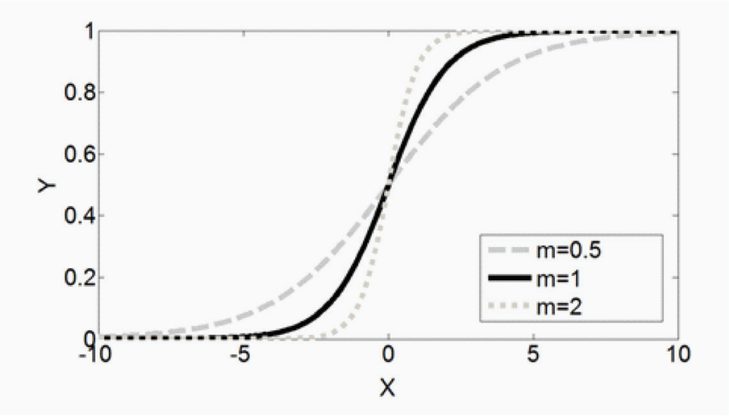
where, *n* is the number of neurons that give their outputs to the neuron, and w_i is the synaptic weight from presynaptic neuron *i* to the postsynaptic neuron. Equations 17.40 and 17.41 denote that the output of an artificial neuron depends on its inputs only and does not depend on time; hence, the output is a static nonlinear function of the weighted summation of the inputs.

The most common architecture used in neural networks is a structure that uses three layers of processing units. The first layer, the input layer, processes the input information and sends its output to a second layer, called the hidden layer that sends the processed information to the last layer, the output layer. A neural network is called *feedforward network* if all its processing units receive inputs from the units of previous layers. Defining the number of the processing units on each layer is more of an art than a science.

A general learning algorithm, used to train a neural network, is a function of: i) the learning rate, η; ii) the activation of the presynaptic unit, a_i, and that of the postsynaptic unit, a_j; and, iii) a training (error in supervised learning techniques) signal, e_{ij}

$$\Delta w_{ij} = f(\eta, a_i, a_j, e_{ij}) \tag{17.42}$$

Figure 10. Sigmoid function for various values of m



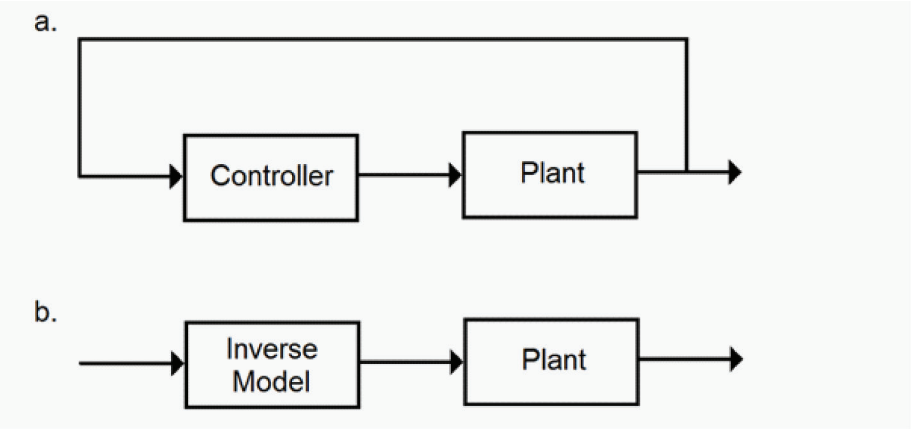
Not all learning algorithms, used in practice, include all those parameters. For instance, a Hebbian learning algorithm changes the weights, w_{ij}, in proportion to the product of the presynaptic activation, a_i, and the postsynaptic activation, a_j. Another class of learning algorithms that is heavily used is the one that uses gradient descent techniques to adjust the synaptic weights, w_{ij}. An example is the error back-propagation algorithm that uses an error gradient descent technique. This technique passes the output error to previous layers of a neural network in order to estimate the input signal for any given neuron. These techniques are also classified as supervised learning techniques since they use a specification of the true output in order to estimate the output error of the network prediction. Other learning algorithms, such as reinforcement learning, are used when the true output of the network is not directly accessible.

The motivation behind the utilization of neural networks to control a system is usually our need to model a nonlinear process or the requirement for the control system to adapt. In a control system, the neural network mimics the behavior of one or more of the system's components so well that it can even replace them. In supervised control systems, shown in Figure 11a, a neural network may replace the controller of the system in situations where the true controller is not time or cost efficient. The neural network is trained using learning data acquired from the system's output. Alternatively, computer simulations of the true system can be used. The training (error) signal, e_{ij}, is usually the difference between the output of the original controller and the output of the network. After the network is adequately trained, it can replace the controller entirely. In direct inverse control systems, shown in Figure 11b, the neural network is used to estimate an inverse model of the system to be controlled. The network learns to map the output of the system to its input. Direct inverse control systems are common among physiological control systems.

17.11.2. Applied Examples

Example 17.9: We will now use the basic notions described in previous section to construct a basic model for associative memory, which stands as well, as the most likely model for cognitive memories. It is based on the observation that human beings retrieve information best when it is linked to other related information. That "*linkage*" between already known and new information is mathematically described by the weight (strength) of the connections between processing units of a neural network. The architecture, illustrated

Figure 11. Single modules of controlling structures can be replaced from neural networks models



in Figure 12, is the most general static linear neural network since the addition of neuron layers does not change the capability of the structure.

In this example, the input can be inferred as a set of characteristics of an object (e.g., a set of measurements that describe features of a tumor in a CT image, such as tumor diameter, number of tumors found, level of seriousness with respect to location, etc.) and the output can be inferred as a decision (e.g., the degree of malignancy, the prognosis of the disease, etc.) For convenience reasons, we select the inputs and the outputs of the neural network to be binary {-1, 1}. Let us assume that a learning set of two inputs-output is given to train the neural network. Let the first input be $u^1 = [1,1,-1,-1]$ and let the second input be $u^2 = [-1,-1,1,1]$. The respective outputs are $y^1 = [1]$ and $y^2 = [-1]$. According to Hebb's rule, the weights represent the correlation between the input and the output

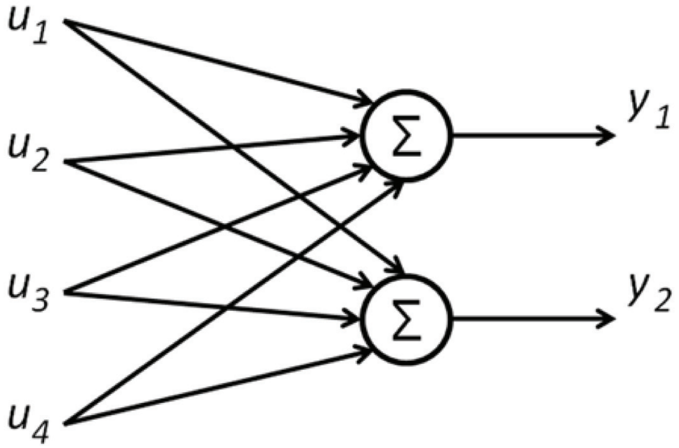
$$w_i = \varepsilon \sum_{\lambda=1}^{L} x_i^{\lambda} y_i^{\lambda}$$

where, e is a constant called the learning rate, usually taken to be the reciprocal of the number of training vectors (usually referred to as the learning examples) presented. In this case, the weights of the neuron will be

$$W = \left\{ \varepsilon \sum_{i=1}^{L} u \right\} = \frac{1}{4} \begin{vmatrix} 1\times 1+(-1)\times(-1) \\ 1\times 1+(-1)\times(-1) \\ (-1)\times 1+1\times(-1) \\ (-1)\times 1+1\times(-1) \end{vmatrix} = \begin{vmatrix} 1/2 \\ 1/2 \\ -1/2 \\ -1/2 \end{vmatrix}$$

Now, we question ourselves about what will be the result, *y*, if a new, unseen before, input is introduced into the neural network. Let us take for example, the input $u = [1,1,1,-1]$. For this vector, the output is calculated as $y = \sum_i w_i u_i = 1/2 + 1/2 - 1/2 + 1/2 = 1$. As one can see, the result of what we acquire when u^1 is the input of the neural network, which is what we really wanted, since the new item is closer to the first learning example (only one bit needs to be inversed to have an identical input, compared to three bits in the second learning example).

Figure 12. Associative linear neural network



However, the associative memory has many disadvantages. A major drawback is that the stored data should be binary orthogonal vectors. Another one is that there are a lot of intra-neuron connections. Other nonlinear associative memories exist; however, they are not as simple as the example given and they are beyond the scope of this chapter.

Example 17.10: Figure 13 presents a personalized insulin infusion advisory system (IIAS) which serves as a control algorithm towards the development of a closed-loop artificial pancreas using the subcutaneous (SC) route (Mougiakakou *et al.*, 2010). The IIAS is able to provide real time estimations of the appropriate insulin infusion rate for type 1 diabetes mellitus (T1DM) patients using continuous glucose monitors and insulin pumps. It is based on Nonlinear Model Predictive Control (NMPC) and comprises of two modules: i) a personalized glucose-insulin metabolism model, based on the combined use of a Compartmental Model (CM) and a Recurrent Neural Network (RNN), and ii) an NMPC strategy. For the *in silico* evaluation of the IIAS, a Mathematical Model (MM) of a patient with T1DM has been used. Each of the aforementioned modules is briefly described in the following.

Personalized glucose-insulin metabolism model: The model, which is based on the combined use of a CM and an RNN, is able to provide glucose predictions (Zarkogianni *et al.*, 2007; Mougiakakou *et al.*, 2008). More specifically, information regarding meal intake is fed to the CM, which simulates the glucose absorption into the blood from the gut. CM's output along with the SC insulin intake and previous SC glucose measurement are applied to the RNN, which models the patient's glucose kinetics and predicts subsequent glucose levels. The CM for glucose absorption into the blood from the gut is linear and consists of one compartment, while the gastric emptying rate is given by trapezoidal or triangular function. The used RNN is a fully connected multilayered perceptron NN with two recurrent loops, the initial weights of which are set to unity. The RNN is trained using the Real Time Recurrent Learning (RTRL) algorithm (Williams & Zipser, 1989), which is a sequential, error-correction learning based algorithm and allows the RNN to update the weights, while operating, as long as the RNN is provided with the correct glucose level value. The teacher-force version of the RTRL has been applied, according to which the RNN replaces the previous glucose level prediction with the corresponding glucose level value, when available, in order to perform future predictions.

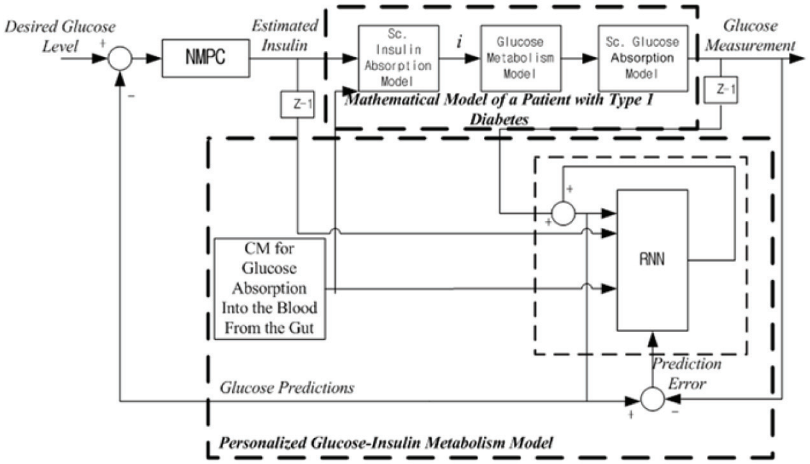
NMPC: The NMPC uses the personalized glucose-insulin metabolism model, which provides estimates of the future glucose levels. The NMPC is based on an optimizer, which computes at each sample time future control movements based on the minimization of an appropriate cost function. Particularly, at each sample time: i) future outputs are generated by the personalized glucose-insulin metabolism model; ii) a cost function of the future control movements is minimized, providing a set of future control signals; and, iii) only the first element of the suggested control sequence is applied to the system. The cost function encompasses the differences between the glucose predictions and the desired glucose level.

MM of a patient with T1DM: The MM of a Type 1 diabetes patient consists of the following CMs: i) an SC insulin absorption model, ii) a glucose metabolism model, iii) a SC glucose absorption model, and iv) a model for the glucose absorption into the blood from the gut.

17.12. MODELING CHAOS IN PHYSIOLOGY

Reductionists' approach treated the body as a machine in which the relationships among the subsystems were governed by deterministic laws.

Figure 13. A multicompartmental model of artificial pancreas that is based on neural networks


Desired Glucose Level
+
-
NMPC
Estimated Insulin
Z-1
Sc. Insulin Absorption Model
i
Glucose Metabolism Model
Sc. Glucose Absorption Model
Glucose Measurement
Z-1
Mathematical Model of a Patient with Type 1 Diabetes
CM for Glucose Absorption Into the Blood From the Gut
+
+
RNN
Prediction Error
Glucose Predictions
+
-
Personalized Glucose-Insulin Metabolism Model

Current research has proven that for a liveable system to maintain its *milieu intérieur*, the internal environment, a plethora of interrelated feedback loops are miraculously put in place and in balance. On the other hand, the phenomenological functions of a biological subsystem, especially the ones observed macroscopically, seem aperiodic and unpredictable in nature. The biological signals are so variable that they appear as random or noisy. To illustrate this "*stochastic determinism*", we consider a large cruising boat, full of passengers. Any one of the passengers (processes) is free to wonder around the boat (system), whereas the boat itself has a determinate route, regardless of the random movements of its passengers. The paradigm illustrates that we are incredibly ordered on several levels, but irregularly so. The human body is not a deterministic machine, but an amazingly complex chaotic system.

Chaos *(χάος)* is an ancient Greek word given to someone to show that he was preponderant of all the others. Similarly, in science, *chaos* describes a deterministic system that is extremely complicated for its observer to be fully understood. From the point of view of an observer with limited capabilities on data selection and information understanding, a chaotic system is an inherently unpredictable system due to its extraordinary sensitivity to its internal conditions. For instance, in order to predict accurately the electrical activity in a certain area of the brain, one has to have a complete and precise description of everything that would have an effect on that particular brain area. It is logical to assume that for a human observer, the factors contributing to the area's activity are infinite. What is more, each one of these factors plays a role in creating the area's activity. That explains why an activity recorded from the brain of an individual never looks the same, even if the subject repeatedly executes the same function. Another characteristic of such systems is the presence of order under the absence of periodicity. The output of a chaotic system, although follows a general pattern (called *strange attractor),* it is random and never repeats itself. Another characteristic aspect is the ability of these systems to fall into the chaotic behavior and come out of it, depending on the situation. When the system instability becomes large enough, the system splits and returns to order (the analysis of such behaviors is called bifurcation analysis).

A chaotic system, although deterministic in its structure, appears to be extremely variable. The structure of a chaotic system is not required to be complex. In fact, simple nonlinear deterministic systems can exhibit chaotic behavior. For example, chaotic solutions to cellular membrane equations have been found (Chay, 1985).

The heart is one of the prime chaotic physiological systems (Biktashev & Holden, 1998; Belair & Glass, 2003). A physician may judge upon the healthy behavior of the heart by its periodic beats. However, our hearts almost never beat the same way twice. A more thorough study reveals a varying interval between beats. More than one reason exists for this variability. The natural pacemaker of the heart, named the sinoatrial node (SA node) and found in the right atrium of the heart, is a group of cells that generates the normal sinus rhythm. Stimulation of the parasympathetic fibers that reach the SA node causes a decrease in the beat rate. On the other hand, stimulation of sympathetic fibers that reach the SA node causes an increase in the SA node rate, and a subsequent increase of both the heart rate and the force of the heart contraction. The existence of the two antagonistic systems (sympathetic and parasympathetic) creates the diversity observed in the temporal distance between two subsequent beats. In addition, a third system, the respiratory system, further increases the heart rhythm variability since the beating of the heart increases with increased inspiration.

However, the best place for someone to search for chaotic behavior is the human brain. The fundamental reductionist approach, proposed in 1891 by H. Waldeyer-Hartz, regarded the brain functions to be fully modeled in the level of discrete individual neurons. The *neuron doctrine*, as this fundamental idea was named, is strongly opposed by modern chaos theory. The brain possesses a large number of feedbacks that give rise to internal uncertainties amplified over time, making long term predictions of brain activity impossible (Skarda & Freeman, 1990).

A question arises on whether the chaotic behavior observed in physiological systems is happening by accident or on purpose. It seems that there are several deterministic reasons for the existence of randomness in the biological systems. Take for example the heart we discussed previously. There is more than one good implication of the variations observed in heart rhythm. By varying its rhythm, the heart relaxes for different time periods per beat; this limits its fatigue. Also, a chaotic system shows better adaptation capabilities. The heart is able to compensate for varying blood demands. From a person dreaming of playing a soccer game to someone actually running in a soccer field for 90 minutes, it is the variance in beat rhythm and intensity that makes the heart effective at any of the conditions met in an unknown external environment. When the body's demands for blood increase, the heart is able to pick up the slack without the shock of a quick tempo change (Ward, 2001). In the brain, chaos is related to the ability to learn. A never seen before stimulus in the brain, moves the underlying subsystems to an unpatterned chaotic state. This chaos results in the ignition of a new network assembly that is specifically associated to the new stimuli. A chaotic system is also able to reach new solutions. Such a system is able to learn from its mistakes and create new pathways to deal with old problems. Thus, what was regarded as randomness in the brain, started to be proved as an essential part of normal brain function.

Although the first and most general single word definition of health was "*balance*", it seems that "*out of balance*" situations inside the body are also connected to health. If we introduce to a linear system an input that is slightly out of its typical input range, the system's output will most probably be derailed. A nonlinear system, even if it sees at its input a "*bizarre*" nudge, it will most probably return to its starting point. Let us look to what is happening in a diseased body. Take for example Parkinson's disease and the basal ganglia system that controls motion. The amount of chaos in the Parkinsonian brain actually decreases as the loss of dopamine (a neurotransmitter used in synapses) forces neurons in the basal ganglia system to fire in synchrony. This synchrony is present in recordings and results in a beta band peak, observed in the local field potentials. The peak is considered to emerge as the projection of widespread synchronized beta band oscillations of the underlying neuronal elements (Boraud *et al.*, 2005; Brown & Williams, 2005). From Parkinson's disease to seizures, disease is recognized as an acute attack of order against chaos. Physicians have begun to classify a new order of "*dynamical diseases*" caused by abnormally periodic order. Epileptic seizures, Parkinson's disease, heart attack, and infant apnoea are just a few such dynamic disorders. Even aging itself is related to a loss of deterministic variability (Kaplan *et al.*, 1991; Kim & Stringer, 1992). In fact, neurosurgeons are creating chaos in the brain as a form of treatment of symptoms. Take, for example, the Deep Brain Stimulation procedure used in Parkinsonian patients. A stimulation lead is inserted into the brain to deliver an electrical impulse and return the brain to its previous chaotic state. It has recently been found that the stimulation of the STN results in the loss of beta synchronization in the neurons inside the nucleus (Bronte-Stewart *et al.*, 2009). This is not the only application of chaos in medicine. The opportunities are as infinite as the dynamic systems themselves.

17.13. THE FUTURE OF PHYSIOLOGICAL SYSTEMS MODELING, SIMULATION, AND CONTROL

Physiological modeling is increasingly providing a sophisticated set of tools for processing measurement inputs into clinically relevant outputs. Based on a physical and biological understanding of the underlying processes, models have the short-term potential to be used to extract information that is not directly available from the data itself, and, thus, aid clinical diagnosis. However, various challenges remain to be met in order to reach a level of modeling that would take full control of a physiological system. Substituting a physiological system has significant potential to become feasible, and indeed some preliminary studies have shown significant improvement in body-prosthetics that are controlled by models (see for example Song *et al.*, 2007; Lebedev & Nicolelis, 2006). To successfully implement this combined approach, it is essential that the mathematical models are sophisticated enough to capture the key physiological features of the system. This is a computational challenge in its own right; our body has anisotropic and multi-scale properties that must be realized in mathematical models and solved on real time simulations. In addition, the personalized physiological properties of each data set should be reflected to a change of parameters in the mathematical models; and, accordingly, the physiological models must be customized through inputting patient-specific structural and functional information. Within initiatives such as the Physiome and Virtual Physiologic Human projects, the need to have universal simulation platforms, software languages, and in general the necessity to speak the same "*modeling language*" became apparent. It is also important to speak specifically for the brain. For the first time in history of mankind, the human brain initiated a discussion with itself. In this endeavor, it is extremely important to mention the requirement to develop more advanced statistical techniques applied specifically to brain modeling. The long-term aim should be the embracement of the power of modeling and the integration of simulations with clinically, scientifically, and economically effective data acquiring techniques in order to achieve the goal of personalized treatment. Physiological models that are able to combine patient specific data with the personal opinion of a physician can become a pivotal point in the healthcare system in terms of both prognosis and diagnosis. This will further increase the opinion of the society that science comes not only from but also for the human kind.

17.14. PROFESSIONAL SOCIETIES AND ORGANIZATIONS

Engineering in Medicine and Biology Society (EMBS)
www.embs.org
NSR Physiome Project, National Simulation Resource, Department of Bioengineering, University of Washington, Seattle, WA, USA
http://www.physiome.org/
Virtual Physiological Human Network of Excellence
http://www.vph-noe.eu/

17.15. CHAPTER SUMMARY

In this chapter, a variety of techniques to model physiological systems and study their underlying functions are described. The potential and limitations of the presented methodologies are discussed and supported with appropriate examples. Compartmental analysis describes a biological system with a finite number of compartments. Almost all biological systems are inherently nonlinear, and a purely linear model is, thus, partially satisfactory. However, linear models show important advantages due to their simplicity. Other approaches, such as nonlinear models and neural networks, may lack the theoretical foundation upon which linear modeling of physiological systems is based, but promising theoretical developments have attested the importance of these techniques for successful simulation and control of biological processes.

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Bio-inspired computation

Biologically inspired computing (also bio-inspired computing) is a field of study that loosely knits together subfields related to the topics of connectionism, social behavior and emergence. It is often closely related to the field of artificial intelligence, as many of its pursuits can be linked to machine learning. It relies heavily on the fields of biology, computer science and mathematics. Biologically inspired computing is a major subset of natural computation. The field of biocomputation has a twofold definition: the use of biology or biological processes as metaphor, inspiration, or enabler in developing new computing technologies and new areas of computer science; and conversely, the use of information science concepts and tools to explore biology from a different theoretical perspective. In addition to its potential applications, such as DNA computation, nanofabrication, storage devices, sensing, and health care, biocomputation also has implications for basic scientific research. It can provide biologists, for example, with an IT-oriented paradigm for looking at how cells compute or process information, or help computer scientists construct algorithms based on natural systems, such as evolutionary and genetic algorithms. Biocomputing has the potential to be a very powerful tool.

The domain of bio-inspired computing is gradually getting prominence in the current times. As organizations and societies are gearing towards a digital era, there has been an explosion of data. This explosion of data is making it more and more challenging to extract meaningful information and gather knowledge by using standard algorithms, due to the increasing complexity of analysis. Finding the best solution increasingly becomes very difficult to identify, if not impossible, due to the very large and dynamic scope of solutions and complexity of computations. Often, the optimal solution for such a NP hard problem is a point in the n-dimensional hyperspace and identifying the solution is computationally very expensive or even not feasible in limited time. Therefore intelligent approaches are needed to identify suitable working solutions.

In this context, intelligent meta-heuristics algorithms can learn and provide a suitable working solution to very complex problems. Within meta-heuristics, bio-inspired computing is gradually gaining prominence since these algorithms are intelligent, can learn and adapt like biological organisms. These algorithms are drawing attention from the scientific community due to the increasing complexity of the problems, increasing range of potential solutions in multi-dimensional hyper-planes, dynamic nature of the problems and constraints, and challenges of incomplete, probabilistic and imperfect information for decision making. However, the fast developments in this domain is increasingly getting difficult to track, due to different algorithms which are being introduced very frequently. However, no study has attempted to identify these algorithms exhaustively, explore and compare their potential scope across different problem contexts.

In fact very few researchers are often familiar with the developments in the domain, where more and more new algorithms are gaining acceptance and prominence. Therefore, with limited visibility across algorithms, new researchers working in this domain tend to focus on very limited and popular approaches, and therefore often “force-fit” algorithms rather than exploring the most suitable one, based on the problem statement, due to limited awareness. To address this gap, we review some of the popularly used bio-inspired algorithms as well as introduce the newly developed algorithms which have a huge potential for applications. Further to that, we also explore the potential scope of applications of the algorithms in specific domains, based on published scientific literature. While twelve of the slightly popular algorithms have been discussed, the scope of future research in other bioinspired algorithms has been discussed. However, in depth discussion about the implementation (e.g. pseudocode, etc) and enhancements in each algorithm is beyond the scope of the current article. Further, specific detailed citations of each application could not be provided, but we attempt to generalize whenever possible based on other focused reviews.

I-485/H-400 *Biologically-inspired computing*, Lecture Notes
Spring 2015, Indiana University, By Luis M. Rocha

1. What is Life?

> "*What was life? No one knew. It was undoubtedly aware of itself, so soon as it was life; but it did not know what it was*". Thomas Mann [1924]

Threshold of Complexity

> "*Seeking a connecting link, they had condescended to the preposterous assumption of structureless living matter, unorganized organisms, which darted together of themselves in the albumen solution, like crystals in their mother-liquor; yet organic differentiation still remained at once condition and expression of all life. One could point to no form of life that did not owe its existence to procreation by parents*". Thomas Mann [1924].

> "*Nothing in biology makes sense without evolution*". Theodosius Dobzhansky [1973]

Biologically-inspired computing is an interdisciplinary field that formalizes processes observed in living systems to design computational methods for solving complex problems, or simply to endow artificial systems with more natural traits. But to draw more than superficial inspiration from Biology we need to understand and discuss the concept of *life*. It should be noted that for the most part of the history of humanity, the question of what *life* is was not an important issue. Before the study of mechanics became important, everything was thought to be alive: the stars, the skies, the rivers and mountains, etc. There was no non-life, so the concept was of no importance. It was only when people started to see the World as determined by the laws of mechanics that the question arose. If all matter follows simple physical laws, then what is indeed the difference between life and non-life, between biology and physics? Let us then start with a current dictionary definition:

> "life adj.— n.1. the general condition that distinguishes organisms from inorganic objects and dead organisms, being manifested by growth through metabolism, a means of reproduction, and internal regulation in response to the environment. 2. the animate existence or period of animate existence of an individual. 3. a corresponding state, existence, or principle of existence conceived of as belonging to the soul. 4. the general or universal condition of human existence. 5. any specified period of animate existence. 6. the period of existence, activity, or effectiveness of something inanimate, as a machine, lease, or play. 7. animation; liveliness; spirit: The party was full of life. 8. the force that makes or keeps something alive; the vivifying or quickening principle." [Random House Webster's Dictionary]

The definitions above fall into three main categories: (1) life as an organization distinct from inorganic matter (with an associated list of properties), (2) life as a certain kind of *animated behavior*, and (3) life as a special, incommensurable, quality—*vitalism*. Throughout this course we will see that all principles, and indeed all controversies, associated with the study of life fall into one of these categories or the differences among them. The third category has been discarded as a viable scientific explanation, because for science nothing is in principle incommensurable. The question of whether life is organized according to a special design, intelligent or mysterious, pertains to metaphysics. If the agent of design cannot be observed with physical means, then it is by definition beyond the scope of science as it cannot be measured, and any theories derived from such a concept cannot tested.

While metaphysical dispositions do not pertain to science, many scientists have observed that a naive mechanistic decomposition of life may also fail to explain it. The traditional scientific approach has lead the study of living systems into a reductionist search for answers in the nitty-gritty of the biochemistry of living organisms. This alternative sees life as nothing more than the complicated physics of a collection of moving bodies. However, the question remains unanswered since there are many ways to obtain some complicated dynamics, but of all of these, which ones can be classified as *alive*? What *kind of complexity* are we looking for? No one disputes that life is some sort of complex material arrangement, but when do we reach a necessary *threshold of complexity* after which matter is said to be living? Is it a discrete step, or is life a fuzzy concept? To understand it without meaningless reduction, must we synthesize organizations with the same threshold of complexity (first category above), or is it enough to simulate its animated behavior (second category above)?

Information Organizes and Breeds Life

"*Life is a dynamic state of matter organized by information*". Manfred Eigen [1992]

"*Life is a complex system for information storage and processing*". Minoru Kanehisa [2000]

Traditionally life has been identified with material organizations which observe certain lists of properties, e.g. *metabolism*, *adaptability*, *self-maintenance* (autonomy), *self-repair*, *growth*, *replication*, *evolution*, etc. Most living organisms follow these lists, however, there are other material systems which obey only a subset of these rules, e.g. viruses, candle flames, the Earth, certain robots, etc. This often leads to the view that life is at best a fuzzy concept and at worst something we are, subjectively, trained to recognize—life is what we can eat—and is thus not an objective distinction. The modern-day molecular biology view of life, on the other hand, tends to see life as a material organization that if not completely defined by *genomic information*, is at least fully controlled by it. Thus, when Craig Venter's team [Gibson et al, 2010] recently produced a bacteria with a "*prosthetic genome*" [a termed coined by Mark Bedau, see *Nature* | Opinion, 2010] copied from another bacteria but synthesized in the lab, the momentous synthetic biology feat was announced as the creation of the first synthetic or artificial life form.

The artificial life field, whose members tend to follow the fuzzy list of properties conception of life, does not typically recognize Venter's bacteria with a prosthetic genome as a bona fide synthesis of artificial life, since it relies on the pre-existence of a working, naturally-obtained cell to implant a prosthetic genome into. Even most molecular biologists will agree that we are nowhere near <u>understanding</u>, let alone synthesizing an artificial cell from scratch [e.g. George Church, see *Nature* | Opinion, 2010]. Nonetheless, Venter's achievement begs at least the question of what is it about life's *design principle* that makes it easier to synthesize a working prosthetic genome than a working "prosthetic proteome or metabolome"? It also makes us think about what does "understanding life" mean for biology, biomedical technology, artificial life, and informatics? Why is *genetic information* so important and how does it relate to *information technology*?

Life requires the ability to both categorize and control events in its environment in order to survive. In other words, organisms pursue (or even decide upon) different actions according to *information* they perceive in an environment. Furthermore, living organisms reproduce and develop from genetic *information*. More specifically, genetic information is <u>*transmitted*</u> "vertically" (inherited) in phylogeny and cell reproduction, and <u>*expressed*</u> "horizontally" within a cell in ontogeny for the functioning of living organisms as they interact and react with their environments—we are now sure that genetic information can also be transmitted horizontally between organisms and play an important role in evolution [Goldenfeld & Woese 2007; Riley, 2013]. Indeed, the difference between living and non-living organizations seems to stand on the ability of the former to use *relevant* information for their own functioning. It is this "relevant" which gives life an extra attribute to simple mechanistic interactions. When an organization is able to recognize and act on aspects of its environment which are important *to its own* survival, we say that the mechanisms by which the organization recognizes and acts are *functional* in reference to the organization itself (*self-reference*). Physics is not concerned with function. A physical or chemical description of DNA is certainly possible, but will tell us nothing as to the function of a DNA molecule as a gene containing relevant information for a particular organism. Only in *reference* to an organism does a piece of DNA *function* as a gene (e.g. an enzyme with some effect in an environment).

Thus it is remarkable that in Venter's experiment, a cell with a synthesized prosthetic genome from a similar but distinct organism, was able to reproduce over and over resulting in a cell with a different phenotype from the original, implanted cell—in effect, a cell *re-programmed* by a synthesized genome. Is life then a type of computer that can be reprogrammed? This also leads us to question how general-purpose can such genomic re-programming be? Will it be restricted to very narrow classes of similar organisms, or will it ever be possible to re-program any prokaryotic or eukaryotic cell ?

Emergence and Explanation

> "*First, nothing in biology contradicts the laws of physics and chemistry; any adequate biology must be consonant with the 'basic' sciences. Second, the principles of physics and chemistry are not sufficient to explain complex biological objects because new properties emerge as a result of organization and interaction. These properties can only be understood by the direct study of the whole, living systems in their normal state. Third, the insufficiency of physics and chemistry to encompass life records no mystical addition, no contradiction to the basic sciences, but only reflects the hierarchy of natural objects and the principle of emergent properties at higher levels of organization*". Stephen Jay Gould [1984].

This issue could be rephrased in terms of the notion of *emergence*. Whatever (macro-level) organization exists after the complexity threshold for life is passed, we may say that it is emergent because its attributes cannot be completely explained by the (micro-) physical level. In particular, function, control, and categorization cannot be explained by the mechanics and dynamics of the components of life alone. Notice, however, that emergence does not imply vitalism or dualism. When we say that certain characteristics of life cannot be explained by physics alone, we mean that they must be explained by different, additional models—namely, *informational*, *historical* and *functional* descriptions. In other words, though biological function, control, and categorization cannot be explained by physics alone, organisms, like anything else, must nonetheless follow physical laws. But information is contextual, and therefore requires more than universal models: it requires contingent, context-specific descriptions. In particular, the *origin of life*, is a problem of emergence of information from a physical milieu under specific constraints [Eigen, 1992]. This is the crux of complex systems: the interplay between micro- and macro-level descriptions determines their behavior, and both levels (emergence) are required to understand complexity.

The definition of emergence as an epistemological, explanatory requirement, is related to the notion of *emergence-relative-to-a-model* [Rosen, 1985; Cariani, 1989] or *intensional emergence* [Salthe 1991]. It refers to the impossibility of epistemological reduction of the properties of a system to its components [Clark, 1996]. As an example, we can think of phase transitions such as that of water in its transition from liquid to gas. Water and its properties cannot be rephrased it terms of the properties of hydrogen and oxygen, it needs a qualitatively different model. Another example of complementary models of the same material systems is the wave-particle duality of light.

Physicists *understand* the laws of nature (as best they can), but it takes engineers to *control* nature. The very best physicists are the very best engineers, but those are exceedingly rare (e.g. Von Neumann). The goal of complex systems is to understand *organized complexity* (life, society, cognition) in the same way physicists understand nature [Weaver, 1948]. Biology, as a discipline, has not entirely "made up its mind" if it wants to understand life as a physicist or control it as an engineer. Due to its focus on the micro-level of life, its biochemistry, molecular biology follows essentially a (reverse-) engineering, black-box methodology (knockouts, controls, etc.). This leads to a bit of a schizophrenic agenda: focusing exclusively on micro-level experiments in order to *suggest* macro-level understandings. If the goal is control of biology, say for biomedical advances, then we really need to focus on biotechnology engineering. If the goal is understanding, then we need to focus more on macro-level organized complexity. Ideally, a healthy life sciences program would tie the need to understand with the need to control better—like physicists and engineers do.

This is where complex systems, artificial life, and bio-inspired computing can contribute to a wider arena of the life sciences; they can be used as laboratories for experimenting with theories of organized complexity, and thus enrich our understanding of life. Artificial life concerns both the simulation and realization of life in some artificial environment, usually the computer. At least regarding the second of its goals, artificial life aims to understand the fundamental micro/macro-level interaction that leads to organized complexity. Bio-inspired computing, as a more pragmatic endeavor, does not need to concern itself with synthesizing actual life, but only with drawing analogies from life (real and artificial). Nonetheless, if the main motivation of bio-inspired computing is that life with its designs has already solved versions of many complex engineering problems we are interested in, then a thorough and accurate understanding of the essential characteristics of life is inescapable. Moreover, by abstracting context-specific principles of life to make them relevant in other settings, provides a useful laboratory to experiment with theoretical biology.

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2. The logical Mechanisms of Life

> "The designs found in nature are nothing short of brilliant, but the process of design that generates them is utterly lacking in intelligence of its own". Daniel Dennett, NY Times 2005

Life-As-It-Could-Be: but, what is *non*-life-as-it-could-be?

> "Artificial Life [AL] is the study of man-made systems that exhibit behaviors characteristic of natural living systems. It complements the traditional biological sciences concerned with the *analysis* of living organisms by attempting to *synthesize* life-like behaviors within computers and other artificial media. By extending the empirical foundation upon which biology is based *beyond* the carbon-chain life that has evolved on Earth, Artificial Life can contribute to theoretical biology by locating *life-as-we-know-it* within the larger picture of *life-as-it-could-be.* [...] [AL] views life as a property of the *organization* of matter, rather than a property of the matter which is so organized. Whereas biology has largely concerned itself with the material basis of life, Artificial Life is concerned with the formal basis of life. [... It] starts at the bottom, viewing an organism as a large population of *simple* machines, and works upwards *synthetically* from there — constructing large aggregates of simple, rule-governed objects which interact with one another nonlinearly in the support of life-like, global dynamics. The 'key' concept in AL is *emergent behavior*." [Langton, 1989, pp 1-2]

> "Artificial Life is concerned with tuning the behaviors of such low-level machines that the behavior that emerges at the global level is essentially the same as some behavior exhibited by a natural living system. [...] Artificial Life is concerned with generating lifelike behavior." [Langton, 1989, pp 4 and 5]

The previous quotes indicate the goals of Artificial Life according to Chris Langton: the search for complex, artificial, systems which instantiate some kind of lifelike *organization*. The field is interested in both synthesizing an actual artificial living organization, as well as simulating lifelike behavior. The first goal is more ambitious and related to the first definition of life introduced in lecture one, while the second goal is related to the second definition. The methodology to reach either of these goals is also in line with the notion of emergence mentioned in lecture one: from the non-linear interaction of simple, mechanistic, components, we wish to observe the emergence of complicated, life-like, unpredictable, behavior. Natural living organisms are likewise composed of non-living components. As pointed out in lecture one, the origin problem in biology is precisely the emergence of life from non-living components. The material components follow, and are completely described, by physical laws, however, a mechanistic explanation of the overall living system is incomplete. Similarly, in Artificial Life, we have formal components obeying a particular set of axioms, and from their interaction, global behavior emerges which is not completely explained by the local formal rules. Clearly, the formal rules play the role of an artificial matter and the global behavior, if recognized as life-like, plays the role of an artificial biology.

> "Of course, the principle assumption made in Artificial Life is that the 'logical form' of an organism can be separated from its material basis of construction, and that 'aliveness' will be found to be a property of the former, not of the latter." [Langton, 1989, page 11]

The idea is that if we are able to find the basic design principles of living organization, then the material substrate used to realize life is irrelevant. By investigating these basic principles we start studying not only biological, carbon-based, life — life-as-we-know-it — but really the universal rules of life, or life-as-it-could-be. Moreover, from a better understanding of the design principles of life, we can use them to solve engineering problems similar to those that living organisms face [Segel and Cohen, 2001; DeCastro and Von

Zuben, 2005]. Several problems have been raised regarding this separation of matter from form, or the search for a universality without matter [Cariani, 1992; Moreno et al, 1994], which will not be discussed here. What needs to be made more explicit is the relationship between the two distinct goals of AL.

Looking at emergent behavior, obtained from formal complex systems, in search of *interesting* behavior leads to a certain circularity. If AL is concerned with finding life-like behavior in artificial, universal, systems, we are ultimately binding life-as-could-be to the behavior of life-as-we-know-it by virtue of some subjective resemblance. This can hardly be accepted as the search for universal principles.

> "They say, 'Look, isn't this reminiscent of a biological or a physical phenomenon!' They jump in right away as if it's a decent model for the phenomenon, and usually of course it's just got some accidental features that make it look like something." [Jack Cowan as quoted in *Scientific American*, June 1995 issue, "From Complexity to Perplexity", by J. Horgan, page 104]

> "Artificial Life — and the entire field of complexity—seems to be based on a seductive syllogism: There are simple sets of mathematical rules that when followed by a computer give rise to extremely complicated patterns. The world also contains many extremely complicated patterns. Conclusion: Simple rules underlie many extremely complicated phenomena in the world. With the help of powerful computers, scientists can root those rules out." [J. Horgan, *Scientific American*, June 1995 issue, "From Complexity to Perplexity", page 107]

> "Artificial Life is basically a fact-free science". [John Maynard Smith as quoted in *Scientific American*, June 1995 issue, "From Complexity to Perplexity", by J. Horgan, page 107]

The problem is that Artificial Life must be compared to something, otherwise it becomes a factless manipulation of computer rules with subjective resemblances to real life. Again, we are faced with many possible types of emergent complex behaviors, this time formal, but what kinds of behaviors can be classified as "life-as-could-be"? What is the formal *threshold of complexity* needed? In the natural world we are able to distinguish life from non-life, biology from physics due to the known signatures of bio-chemistry. In the logical realm, we likewise need a formal criteria to distinguish logical life from logical non-life, artificial life from artificial physics.

> "Artificial Life must be compared with a real or an artificial nonliving world. Life in an artificial world requires exploring what we mean by an alternative physical or mathematical reality." [Pattee, 1995]

The two goals of AL are usually described as *hard* and *soft AL* respectively. The first concerns the synthesis of artificial life from computational or material (e.g. embodied robotics) components. The second is interested in producing life-like behavior and is essentially metaphorical. To be accepted as a scientific field, Alife cannot settle for subjective rules of what constitutes living behavior. Indeed, whether we want to synthesize life or merely simulate a particular behavior of living organisms, we need investigate the rules that allow us to distinguish life from non-life . Only by establishing an artificial physics, from which an artificial biology can emerge, and a *theory*, or set of rules, distinguishing the two, can we aim at a proper science based on fact. In other words, the methodology of Artificial Life requires existing theories of life to be compared against; it can also contribute to the meta-methodology of Biology by allowing us to test and improve its theories beyond the unavoidable material constraints, such as the incomplete fossil record or measurement of cellular activity. Naturally, the requirements for hard AL are much stricter, as we are not merely interested in behaviors that can be compared to real biological systems with looser or stricter rules, but the actual realization of an artificial organization that must be agreed to be living against some theory. Soft AL, may restrict itself to particular behavioral traits which need only to be simulated to a satisfactory degree.

Simulations, Realizations, Systemhood, Thinghood, and Theories of Life

> "Boids are *not* birds; they are not even remotely like birds; they have no cohesive physical structure, but rather exist as information structures — processes — within a computer. But — and this is the critical 'but'— at the level of behaviors, *flocking Boids and flocking birds are two instances of the same phenomenon*: flocking. [...] The 'artificial' in Artificial Life refers to the component parts, not the emergent processes. If the component parts are implemented correctly, the processes they support are genuine — every bit as genuine as the natural processes they imitate. [...] Artificial Life will therefore be genuine life —it will simply be made of different stuff than the life that has evolved on Earth." [Langton, 1989, pp. 32-33]

> "Simulations and realizations belong to different categories of modeling. Simulations are metaphorical models that symbolically 'stand for' something else. Realizations are literal, material models that implement functions. Therefore, accuracy in a simulation need have no relation to quality of function in a realization. Secondly, the criteria for good simulations and realizations of a system depend on our theory of the system. The criteria for good theories depend on more than mimicry, e.g., Turing Tests." [Pattee, 1989, page 63]

As Pattee points out, the bottom line is that a simulation, no matter how good it is, is not a realization. Nonetheless, it may still be possible to obtain artificial living organisms (realizations) if, from an artificial environment, we are able to generate, in a bottom-up manner, organizations which conform to some theory of life we wish to test. Howard Pattee [1989] has proposed that if emergent artificial organisms are able to perform measurements, or in other words, categorize their (artificial) environment, then they may be considered realizations. Some claim that computational environments do not allow for this creative form of emergence [see Cariani, 1992; Moreno, et all, 1994]. In any case, whatever artificial environment we may use, computational or material, we need a theory allowing us to distinguish life from non-life.

Related to this issue, and in the context of complex systems science, is the search of those properties of the world which can be abstracted from their specific material substrate: systemhood from thinghood. Systems science is concerned with the study of *systemhood* properties, but there may be systems from which systemhood cannot be completely abstracted from *thinghood*. Life is sometimes proposed as one of those systems [see Rosen, 1986, 1991; Moreno et al, 1994; Pattee, 1995]. The difficulty for systems science, or complexity theory, lies precisely in the choice of the appropriate level of abstraction. If we abstract enough, most things will look alike, leading to a theory of factless, reminiscent analogies, exposed by Cowan and Maynard-Smith above. If, on the other hand, we abstract too little, all fields of inquiry tend to fall into increasingly specific niches, accumulating much data and knowledge about (context-specific) components without much *understanding* of, or ability to *control*, the (general) macro-level organization. In the context of life, we do not want to be tied uniquely to carbon-based life, or *life-as-we-know-it*, but we also do not want *life-as-could-be* to be anything at all. The challenge lies precisely on finding the right amounts of systemhood and thinghood, as well as the interactions between the two, necessary for a good theory of life, real or artificial.

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3. Formalizing and Modeling the World

"*When you can measure what you are speaking of and express it in numbers you know that on which you are discoursing. But if you cannot measure it and express it in numbers. your knowledge is of a very meagre and unsatisfactory kind.*". (Lord Kelvin)

The Nature of Information and Information Processes in Nature[1]

The word **information** derives from the Latin *informare* (*in* + *formare*), meaning to give form, shape, or character to. Etymologically, it is therefore understood to be the formative principle of something, or to imbue with some specific character or quality. However, for hundreds of years, the word information is used to signify knowledge and aspects of cognition such as meaning, instruction, communication, representation, signs, symbols, etc. This can be clearly appreciated in the *Oxford English Dictionary*, which defines information as "the action of informing; formation or molding of the mind or character, training, instruction, teaching; communication of instructive knowledge".

When we look at the world and study reality, we see order and structure everywhere. There is nothing that escapes description or explanation, even in the natural sciences where phenomena appear sometimes catastrophic, chaotic and stochastic. A good example of order and information are our roads. Information can be delivered by signs. Drivers know that signs are not distant things, but they are *about* distant things in the road. What signs deliver are not things but a sense or knowledge of things – a message. For information to work that way, there have to be signs. These are special objects whose function is to be *about* other objects. The function of signs is reference rather than presence. Thus a system of signs is crucial for information to exist and be useful in a world, particularly for the world of drivers!

The central structure of information is therefore a relation among signs, objects or things, and agents capable of understanding (or decoding) the signs. An AGENT is *informed* by a SIGN about some THING. There are many names for the three parts of this relation. The AGENT can be thought of as the recipient of information, the listener, reader, interpretant, spectator, investigator, computer, cell, etc. The SIGN has been called the signal, symbol, vehicle, or messenger. And the about-some-THING is the message, the meaning, the content, the news, the intelligence, or the information.

The SIGN-THING-AGENT relation is often understood as a sign-system, and the discipline that studies sign systems is known as *Semiotics*. In addition to the triad of a sign-system, a complete understanding of information requires the definition of the relevant context: an AGENT is informed by a SIGN about some THING in a certain CONTEXT. Indeed, (Peircean) semiotics emphasizes the *pragmatics* of sign-systems, in addition to the more well-known dimensions of *syntax* and *semantics*. Therefore, a complete (semiotic) understanding of information studies these three dimensions of sign-systems:

1. ***Semantics***: the content or meaning of the SIGN of a THING for an AGENT; it studies all aspects of the relation between signs and objects for an agent, in other words, the study of meaning.
2. ***Syntax***: the characteristics of signs and symbols devoid of meaning; it studies all aspects of the relation among signs such as their rules of operation, production, storage, and manipulation.
3. ***Pragmatics***: the context of signs and repercussions of sign-systems in an environment; it studies

[1] This subsection is an excerpt of [Rocha and Schnell, 2005]

how context influences the interpretation of signs and how well a signs-system represents some aspect of the environment.

Signs carry information content to be delivered to agents. However, it is also useful to understand that some signs are more easily used as referents than others. In the beginning of the 20th century, Charles Sanders Peirce defined a typology of signs:

1. ***Icons*** are direct representations of objects. They are similar to the thing they represent. Examples are pictorial road signs, scale models, and of course the icons on your computer. A footprint on the sand is an icon of a foot.
2. ***Indice***s are indirect representations of objects, but necessarily related. Smoke is an index of fire, the bell is an index of the tolling stroke, and a footprint is an index of a person.
3. ***Symbols*** are *arbitrary* representations of objects, which require exclusively a social convention to be understood. A road sign with a red circle and a white background denotes something which is illegal because we have agreed on its arbitrary meaning. To emphasize the conventional aspect of the semantics of symbols, consider the example of variations in road signs: in the US yellow diamond signs denote cautionary warnings, whereas in Europe a red triangle over a white background is used for the same purpose. We can see that convention establishes a code, agreed by a group of agents, for understanding (decoding) the information contained in symbols. For instance, smoke is an index of fire, but if we agree on an appropriate code (e.g. Morse code) we can use smoke signals to communicate symbolically.

Clearly, signs may have iconic, symbolic and indexical elements. Our alphabet is completely symbolic, as the sound assigned to each letter is purely conventional. But other writing systems such as Egyptian or Mayan hieroglyphs, and some Chinese characters use a combination of phonetic symbols with icons and indices. Our road signs are also a good example of signs with symbolic (numbers, letters and conventional shapes), iconic (representations of people and animals) and indexical (crossing out bars) elements.

Finally, it is important to note that due to the arbitrary nature of convention, symbols can be manipulated without reference to content (syntactically). This feature of symbols is what enables computers to operate. As an example of symbol manipulation without recourse to content, let us re-arrange the letters of a word, say "deal": dale, adel, dela, lead, adle, etc. We can produce all possible permutations (4! = 4×3×2×1 = 24) of the word whether they have meaning or not. After manipulation, we can choose which ones have meaning (in some language), but that process is now a semantic one, whereas symbol manipulation is purely syntactic. All signs rely on a certain amount of convention, as all signs have a pragmatic (social) dimension, but symbols are the only signs which require exclusively a social convention, or code, to be understood.

We are used to think of information as pertaining purely to the human realm. In particular, the use of symbolic information, as in our writing system, is thought of as technology used exclusively by humans. Symbols, we have learned, rely on a code, or convention, between symbols and meanings. Such a conventional relation usually specifies rules created by a human community. But it can have a more general definition:

> "A code can be defined as a set of rules that establish *a correspondence between two independent worlds*". The Morse code, for example, connects certain combinations of dots and dashes with the letters of the alphabet. The Highway Code is a liaison between illustrated signals and driving behaviours. A language makes words stand for real objects of the physical World." [Barbieri, 2003, page 94]

We can thus think of a code as a process that implements correspondence rules between two independent worlds (or classes of objects), by ascribing meaning to arbitrary symbols. Therefore, meaning is not a characteristic of the individual symbols but a convention of the collection of producers and recipients of the encoded information.

Interestingly, we can see such processes in Nature, where the producers and recipients are not human. The prime example is the genetic code, which establishes a correspondence between DNA (the symbolic genes which store information) and proteins, the stuff life on Earth is built of. With very small variations, the genetic code is the same for all life forms. In this sense, we can think of the genetic system and cellular reproduction as a symbolic code whose convention is "accepted" by the collection of all life forms.

Other codes exist in Nature, such as signal transduction from the surface of cells to the genetic system, neural information processing, antigen recognition by antibodies in the immune system, etc. We can also think of animal communication mechanisms, such as the ant pheromone trails, bird signals, etc. Unlike the genetic system, however, most information processes in nature are of an analog rather than digital nature. Throughout this course we will discuss several of these natural codes.

Formalizing Knowledge: Uncovering the Design Principles of Nature[2]

Once we create symbols, we can also hypothesize relationships among the symbols which we can later check for consistency with what we really observe in the World. By creating relationships among the symbols of things we observe in the World, we are in effect formalizing our knowledge of the World. By formalizing we mean the creation of *rules*, such as verbal arguments and mathematical equations, which define how our symbols relate to one another. In a formalism, the rules that manipulate symbols are independent of their meaning in the sense that they can be calculated mechanically without worrying what symbols stand for.

It is interesting to note that the ability to abstract characteristics of the world from the world itself took thousands of years to be fully established. Even the concept of number, at first was not dissociated from the items being counted. Indeed, several languages (e.g. Japanese) retain vestiges of this process, as different objects are counted with different variations of names for numbers. Physics was the first science to construct precise formal rules of the things in the world. Aristotle (484-322 BC) was the first to relate symbols more explicitly to the external world and to successively clarify the nature of the symbol-world (symbol-matter) relation. "In his Physics he proposed that the two main factors which determine an object's speed are its weight and the density of the medium through which it travels. More importantly, he recognized that there could be mathematical rules which could describe the relation between an object's weight, the medium's density and the consequent rate of fall." [Cariani, 1989, page 52] The rules he proposed to describe this relations were:

> 1. *For freely falling or freely rising bodies: speed is proportional to the density of the medium.*
> 2. *In forced motion: speed is directly proportional to the force applied and inversely proportional to the mass of the body moved*

This was the first time that the relationships between observable quantities were hypothesized and used in calculations. Such a formalization of rules as a hypothesis to be tested is what a model is all about. Knowledge is built upon models such as this that sustain our observations of the World.

[2] This subsection is an excerpt of [Rocha and Schnell, 2005b]

> “While these quantities were expressed in terms of numbers, they were still generally regarded as inherent properties of the objects themselves. It was not until Galileo took the interrelationships of the signs themselves as the objects of study that we even see the beginnings of what was to be progressive dissociation of the symbols from the objects represented. Galileo's insight was that the symbols themselves and their interrelations could be studied mathematically quite apart from the relations in the objects that they represented. This process of abstraction was further extended by Newton, who saw that symbols arising from observation […] are distinct from those involved in representing the physical laws which govern the subsequent motion”. [Cariani, 1989, page 52]

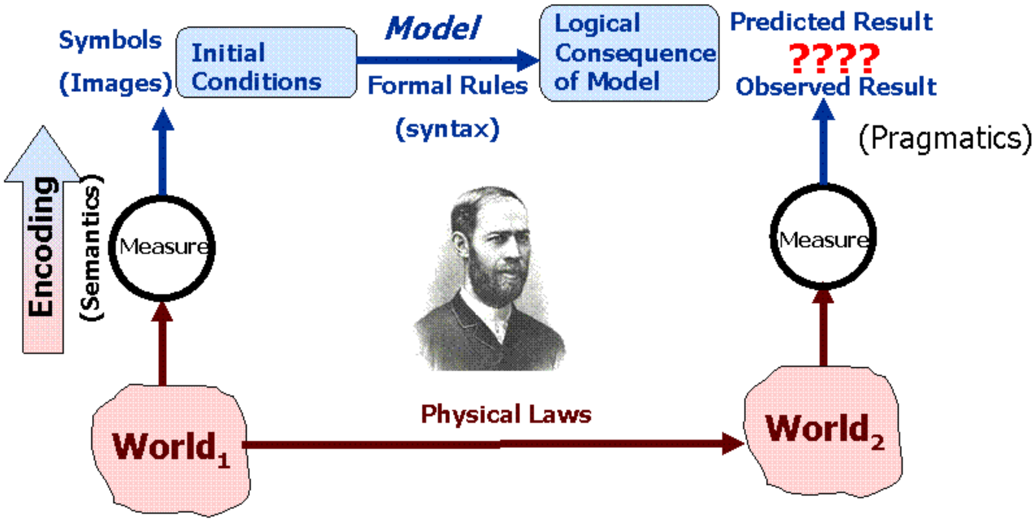

Figure 1: The Modeling Relation between knowledge and reality according to Hertz (adapted from Cariani, 1989)

“In 1894 Heinrich Hertz published *his Principles of Mechanics* which attempted […] to purge mechanics of metaphysical, mystical, undefined, unmeasured entities such as force and to base the theory explicitly on measurable quantities. Hertz wanted to be as clear, rigorous, and concise as possible, so that implicit, and perhaps unnecessary, concepts could be eliminated from physical theories, [which he thought should be based solely on measurable quantities].” [Cariani, 1989, page 54]. Since the results of measurements are symbols, physical theory should be about building relationships among observationally-derived symbols, that is, it should be about building formal *models*, which Hertz called "images”:

> “The most direct and in a sense the most important, problem which our conscious knowledge of nature should enable us to solve is the anticipation of future events, so that we may arrange our present affairs in accordance with such anticipation. As a basis for the solution of this problem we always make use of our knowledge of events which have already occurred, obtained by chance observation or by prearranged experiment. In endeavoring thus to draw inferences as to the future from the past, we always adopt the following process. We form for ourselves images or symbols of external objects; and the form which we give them is such that the necessary consequents of the images in thought are always the images of the necessary consequents in nature of the things pictured. In order that this requirement may be satisfied, there must be a certain conformity between nature and our thought. Experience teaches us that the requirement can be satisfied, and hence that such a conformity does in fact exist. When from our accumulated experiences we have succeeded in deducing images of the desired nature, we can then in a short time develop by means of them, as by

> means of models, the consequences in the external world which only arise in a comparatively long time, or as a result of our own interposition. We are thus enabled to be in advance of the facts, and to decide as to present affairs in accordance with the insight so obtained. The images which we here speak are of our conceptions of things. With the things themselves they are in conformity in *one* important respect, namely, in satisfying the above mentioned requirement. For our purpose it is not necessary that they should be in conformity with the things in any other respect whatever. As a matter of fact, we do not know, nor do we have any means of knowing, whether our conceptions of things are in conformity with them in any other than the *one* fundamental respect. [Hertz, 1894 pp. 1-2]"

A model is any complete and consistent set of verbal arguments, mathematical equations or computational rules which is thought to correspond to some other entity, its prototype. The prototype can be a physical, biological, social psychological or other conceptual entity.

The etymological roots of the word model lead us to the Latin word "modulus", which refers to the act of molding, and the Latin word "modus" (a measure) which implies a change of scale in the representation of an entity. The idea of a change of scale, can be interpreted in different ways. As the prototype of a physical, social or natural object, a model represents a change on the scale of abstraction: certain particularities have been removed and simplifications are made to derive a model.

In the natural sciences, models are used as tools for dealing with reality. They are caricatures of the real system specifically build to answer questions about it. By capturing a small number of key elements and leaving out numerous details, models help us to gain a better understanding of reality and the design principles it entails.

Computational Models[3]

> "Insofar as the propositions of mathematics are certain they do not refer to reality; and insofar as they refer to reality, they are not certain". Albert Einstein

Computation is the ultimate abstraction of a formal mathematical system, or an axiomatic system. It is defined by the purely syntactic process of mapping symbols to symbols. Such mapping is the basis of the concept of mathematical function, and it is all that computers do. This abstraction requires that all the procedures to manipulate symbols are defined by unambiguous rules that do not depend on physical implementation, space, time, energy considerations or semantic interpretations given to symbols by observers. Formal computation is, by definition, implementation-independent.

Modeling, however, is not entirely a formal process. The Hertzian modeling paradigm clearly relates formal, computational models to *measurements* of reality against which they must be validated. The measuring process transforms a physical interaction into a symbol – via a measuring device. The measuring process cannot be formalized as it ultimately depends on interacting with a specific (not implementation-independent) portion of reality. We can simulate a measurement process, but for that simulation to be a model we will need in turn to relate it to reality via another measurement. This important aspect of modeling is often forgotten in Artificial Life, when the results of simulations are interpreted without access to real world measurements.

[3] This section is indebted to many writings of Howard Pattee, including lecture notes and personal communications.

Likewise, a computer is a physical device that implements a particular abstract computational model as precisely as possible. Modern day computers are so successful because they can implement general-purpose computations almost independently of their specific physics. We do not have to worry about the specific physical architecture of the device as we compute, even though small errors in our computations do occur due to the physical elements of the computing device.

In summary, a computation is a process of rewriting symbol strings in a formal system according to a program of rules. The following characteristics are important: (1) Operations and states are syntactic. (2) Symbols follow syntactical rules. (3) Rate of computation is irrelevant. (4)Program determines result, not speed of machine (Physical implementation is irrelevant).

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4. Self-Organization and Emergent Complex Behavior

Self-organization is usually understood as the process by which systems of many components tend to reach a particular state, a set of cycling states, or a small volume of their state space (attractor basins), with no external interference. This *attractor behavior* is often recognized at a different level of observation as the spontaneous formation of well-organized structures, patterns, or behaviors, from random initial conditions (emergent behavior). The systems used to study this behavior are referred to as dynamical systems or *state-determined systems*, since every trajectory is perfectly determined by its initial state. Dynamical systems are traditionally studied by continuous variables and sets of discrete-time difference equations (such as the logistic map) or continuous-time differential equations (such as models of the motion of bodies under gravitational forces). However, self-organization is more easily studied computationally with *discrete dynamical systems* (DDS) such as Boolean networks or cellular automata.

The state-determined transition rules of DDS are interpreted as the laws of some physical system [Langton, 1986] where the state of each component depends on the states of its neighbor (or related) components at the previous time instance. DDS possess a large number of components or variables, and thus very large state spaces. However, when started with random initial conditions (note: not from special initial conditions) they tend to converge, or self-organize, into small sets of attractor states in this space. Attractors may be chaotic in which case the emergent behavior is sensitive to initial conditions. But even chaotic attractors tend to be restricted to small volumes of their state-space (e.g. chaotic in a subset of dimensions of the state-space), therefore we still consider the convergence of a dynamical system into a chaotic basin of attraction to be a form of self-organization.

Since material systems are accurately modeled by dynamical systems, it follows from the observed attractor behavior [Wuensche and Lesser, 1992] of these systems that there is a propensity for matter to self-organize (e.g., [Kauffmann, 1992]). In this sense, matter is described by the (micro-level) dynamics of state transitions and the observed (emergent or macro-level) attractor behavior of self-organization. In general, attractors manifest or *emerge* as global patterns that involve many of components of the dynamical system, and are not easily describable in terms of their state-determined transition rules. For instance, the simple transition rules of the automata in Conway's *Game of Life* cannot describe what the emergent patterns of "blinkers" and "gliders" are. These emergent patterns pertain to a different, complementary level of observation of the same system [Pattee, 1978]. The process of self-organization is often interpreted as the *evolution* of order from random initial conditions. However, notice that this evolution is limited to the specific attractor landscape of a given dynamical system. Unless its parameters are changed (structural perturbation), no dynamical system can escape its own attractor landscape. This limitation will become more apparent when we approach the problem of self-replication.

Life on the Edge of Chaos?

Another interesting aspect of the behavior of dynamical systems concerns the concept of *bifurcation* or *phase transition*. When the parameters of a dynamic system are changed gradually its trajectories and attractors typically change gradually, however, for certain parameter values sudden changes in the dynamic behavior can occur. It is at this critical point that complicated spatio-temporal organization may occur (e.g. from a steady-state to a limit cycle attractor). Close to bifurcations the system also becomes increasingly more sensitive to parameter and initial condition changes. It is often proposed that bifurcations offer a selection mechanism [Prigogine, 1985], as a dynamical system may respond very differently to very small changes in their parameters.

However, if the parameter space is divided by many bifurcations, the system becomes increasingly sensitive to initial conditions and small parameter changes; in this sense its behavior becomes chaotic. It has been argued that the most useful behavior lies instead in between full order and chaos. Langton [1990, 1992] has shown (for one-dimensional cellular automata) that it is in this range of behavior that dynamical systems can carry the most complicated "computations". Computation here is used in a loose sense—not as the rate-independent, symbolic manipulation of Turing-machines—meaning that information exchange between elements of these systems is maximized in this range. In other words, Langton showed that the highest correlation among the automata in a cellular lattice occur at this stage.

Kauffman [1993,] likewise hypothesized that "living systems exist in the [ordered] regime near the edge of chaos, and natural selection achieves and sustains such a poised state". This hypothesis is based on Packard's [1988] work showing that when natural selection algorithms are applied to dynamical systems, with the goal of achieving higher discriminative power, the parameters are changed generally to lead these systems into this transitional area between order and chaos. This idea is very intuitive, since chaotic dynamical systems are too sensitive to parameter changes, that is, a single perturbation or mutation (structural perturbation) leads the system into another completely different behavior (sensitive to damage). By contrast, ordered systems are more resilient to damage, and a small parameter change will usually result in a small behavior change which is ideal for smooth adaptation. However, even though very ordered systems can adapt by accumulation of useful successful variations (because damage does not propagate widely), they may not be able 'step out' of their particular organization in the presence of novel demands in their environment.

It is here that systems at the edge of chaos were thought to enter the scene; they are not as sensitive to damage as chaotic systems, but still they are more sensitive than fully ordered systems. Thus, most mutations cause only minor structural changes and can accumulate, while a few others may cause major changes in the dynamics enabling a few dramatic changes in behavior. These characteristics of simultaneous mutation buffering (to small changes) and dramatic alteration of behavior (in response to larger changes) is ideal for evolvability [Conrad, 1983, 1990]. However, many of the real gene networks that have been successfully modeled with dynamical systems (e.g. the network of segment polarity genes in Drosophila melanogaster [Albert and Othmer, 2003]), exist in a very ordered regime, being very robust to structural changes [Chaves, Albert and Sontag, 2005; Willadsen&Wiles, 2007; kauffman et al, 2003]. Still, other genetic regulatory network models do operate close to criticality [Balleza et al, 2008]. It appears that evolution favors ordered, very robust regimes of self-organization in gene networks – at least the ones involved in very conserved regulatory pathways – though there is also evidence of near-critical regimes for increased evolvability.

Complex Self-organization

We have studied several computational systems said to be self-organizing in the sense described above. The discrete logistic equation observes several ranges of ordered behavior according to its parameter r. For $r \leq 3$, the system converges to a single point steady state (independently of its initial value). For $3 \leq r \leq 4$ the system enters a series of bifurcations, meaning that it changes its attractor behavior, first from a steady-state into a two-state limit cycle, and then progressively doubling the number of states in an attractor limit cycle as r increases. Close to $r = 4$, the limit cycle becomes chaotic. That is, in the chaotic range, the slightest change in the initial value, will lead to a completely different trajectory (though similarly chaotic). The system goes from being independent to strongly dependent of initial conditions, though, in each range, the attractor behavior of the equation is the same for random initial conditions. Thus, we can see the logistic equation as self-organizing.

But there is another aspect of the logistic equation that should be understood. In all of its ranges of behavior, from full order to full chaos, the system is (fairly) reversible. That is, I can always obtain a specific initial condition which caused some behavior, by formally running the system backwards. This means the system is deterministic in both temporal directions. Formally, this means the state transition function is invertible. (This is actually only true, if we decide to work on the lower half of its state space, since the logistic equation is a quadratic function, it has always two possible solutions for the previous value of the current state, these values are symmetric about the middle point of its state space). Some, resist calling this kind of reversible systems self-organizing because they are not sufficiently complex. They reason that if a system is self-organizing, when ran backwards it should be self-*dis*organizing, that is, it should lead to random initial conditions, or to an incomplete knowledge of possible initial states. Indeed, *complexity* is typically equated with the inability to describe the behavior of a system from the behavior of its components or predecessors. This way, we ought to reserve the term self-organization to those irreversible systems whose behaviors must be evaluated statistically. The logistic map shows "hints" of this backwards self-disorganization, but we can still work out effectively its backwards trajectory to an initial condition by restricting the quadratic solutions to half of its state space.

Random Boolean Networks are much more complicated than this. They are completely deterministic since a certain state will always lead to the same next state (state-determinacy), however, we cannot usually know exactly what the predecessor of a current state was. Systems like this are usually studied with statistical tools. Even though the rules that dictate the next state of its components are simple and deterministic, the overall behavior of the system is generally too complicated to predict and statistical analysis has to be performed. For instance, Kauffman has shown that when *K*=2 (number of inputs to each node), his networks will have on average $\sqrt{N}$ basins of attraction with a length of$\sqrt{N}$ states; if the output of one node is switched to the other boolean value (perturbation), the trajectory returns to that cycle 85% of the time, while on the remaining 15% of the time it will "jump" into a different basin of attraction. *Cellular automata* (CA) fall into this same category of deterministic, irreversible, self-organization.

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5. Reality is Stranger than Fiction

Updated from a presentation in the "Biocomplexity" discussion section at the 9th *European Conference on Artificial Life*, September 12, 2007 in Lisbon, Portugal

What can Artificial Life do about Advances in Biology?

> "By extending the empirical foundation upon which biology is based *beyond* the carbon-chain life that has evolved on Earth, Artificial Life can contribute to theoretical biology by locating *life-as-we-know-it* within the larger picture of *life-as-it-could-be".* [Langton, 1998, page 1]

From Langton's original artificial life manifesto, the field was largely expected to free us from the confines of "life-as-we-know-it" and its specific biochemistry. The idea of "life-as-it-could-be" gave us a scientific methodology to consider and study the general principles of life at large. The main assumption of the field was that instead of focusing on the carbon-based, living organization, life could be better explained by synthesizing its "logical forms" from simple machines [Langton, 1989, page 11]—where, "fictional" machines substituted real biochemistry. The expectation was that this "out-of-the-box", synthetic methodology would gain us a wider scientific understanding of life. We would be able to entertain alternative scenarios for life, challenge the dogmas of biology, and ultimately discover the design principles of life.

Interestingly, during the 20 years since the first artificial life workshop, biology witnessed tremendous advances in our understanding of life. True, biology operates at a completely different scale of funding and in a much larger community base than artificial life (the impact factors of key journals in both fields differ by an order of magnitude). But, still, it is from biology, not artificial life, that the strangest and most exciting discoveries and design principles of life arise today. Consider looking at the [September 6, 2007] number of *Nature*, with the quite apropos editorial title "Life as We Know it" [Vol. 449, 1], arguing for a comparative genomics approach, with articles, for instance, moving towards evolutionary principles of gene duplication [Wapinski et al, 2007]. Publications in the [September 2007 issue of] *PLoS. Biol.*, also presented new evidence towards updating or discovering general principles of life: for instance, Venter's sequencing of his diploid genome, which updates our expectations of differences in chromosome pairs [Levy et al, 2007]), and the Ahituv et al [2007] study that challenges the idea that utraconserved DNA (across species) must be functional. Since then, many advances, often enabled by big data approaches of computational biology, keep being discovered; for instance, from large-scale comparative genomics, it has been found that retroviral genomic sequences account for 6 to 14% of host genomes—~8% of human DNA is from endogenous retroviruses, which comprises more DNA than the human proteome [Weiss & Stoye, 2013].

It is good to notice that this sort of work is not so much an exception, but has been a signature of research in the biosciences in the last couple of decades. Consider cases such as the discovery of DNA transfer from bacteria to the fly [Dunning Hotopp, 2007], extra-genomic inheritance in *Arabidopsis* [Lolle et al, 2005], or the profound importance of non-coding RNA in life which is a major player in, among other features, patterning [Martello et al, 2007] , essential gene regulation [Mattick, 2005], development [Mattick, 2007], epigenetic neural development and modulation [Mehler & Mattick, 2007; Mattick & Mehler, 2008], eukariotic complexity [Taft et al, 2007], etc. Moreover, advances such as these do not seem to be mere epiphenomena of a specific life form. Indeed, they point at important organization principles—as those that artificial life was supposed to provide. When we discover that non-transcribed RNA is involved in extra-genomic inheritance or that most of the evolutionary innovation responsible for differences between marsupials and placental mammals occurs in non-protein coding DNA [Mikkelsen et al, 2007], some fundamental principles of the living organization are to be re-thought: the simple, generalized genotype-phenotype mappings on which most of artificial life is based on, are just not enough to capture the principles of life as we know it. More intricate genomic structure, and its principles, need to be modeled and theories need to be built to understand life.

One could go on and on about many other advances in biology. We can also point to themes at the forefront of (bio)complexity theory that go largely overlooked in artificial life—though not completely (i.e. [Calabretta et al, 2000; Hintze & Adami, 2007]). Perhaps the key topic in complexity theory today is that of modularity in evolution [Schlosser & Wagner, 2004] and in networks [Newman, 2006; Guimerà et al 2007]. Nonetheless, looking at the papers accepted for the main sections of the latest Alife and ECAL conferences, it is easy to see that most papers, not only do not discover or even address such issues, but largely trade in biological and computational concepts that have not changed much since the field's inception (see list of top themes and terms in appendix). Is artificial life trapped in the (evolutionary) biology of twenty years ago? Why is reality stranger and more surprising than fiction?

Clearly, there has been very widely successful artificial life research. First and foremost, artificial life has been most successful as a means to study animal behavior, learning and cognition. Certainly, evolutionary robotics and embodied cognition have had an impact in cognitive science. But is artificial life simply a better way to do artificial intelligence? Moreover, one could argue that given the embodied nature of evolutionary robotics, it would seem that it is bound to some kind of material reality, rather than synthesized by constituent "logical forms" as Langton initially suggested.

But what to do about the organization of life itself? Surely the idea of explaining the living organization was behind the origin of the field. For the purposes of this discussion, we must question ourselves why artificial life does not produce more and surprising results about the living organization? Certainly, there is sound research in the field with impact outside of it [e.g. Adami, 2006; Hintze & Adami, 2007]. But even the most successful research in artificial life rarely goes beyond showing that artificial organisms can observe the same behaviors as their real counterparts (i.e. selective pressures, epistasis, etc.). A problem for the field is that as biotechnology gains more and more control of cellular processes, it is reasonable to ask what can one do with artificial organisms that one cannot do with real bacteria? For instance, recent studies of the evolutionary speed towards beneficial mutations were quite effectively done with E-coli [Perfeito et al, 2007], pointing to a much larger rate of beneficial mutations in bacteria than previously thought, and shedding new light on the general principal of clonal interference.

The point of this short statement is to discuss at this conference [ECAL 2007], how biocomplexity is dealt within artificial life, twenty years after the field's inception. Certainly the community can think of a variety of responses to this lack of new principles of life coming out of research in artificial life—even in theoretical biology. One concept that I venture may need updating in artificial life is its view of the genotype/phenotype relationship. Langton proposed that we generalize this relationship, but this meant that research in the field largely regarded the two as indistinguishable. While this move at fist glance seems appropriate to deal with the complexity of genomic-proteomic interaction, it prevents us from studying the specific roles each plays in the living organization. Genotype and phenotype are intertwined in a complex manner, but each operates under different principles that are often overlooked in artificial life. Thus, artificial life rarely approaches issues of genomic structure and regulation, or the co-existence of DNA and RNA as different types of informational carriers. This could well be because artificial life models seem to trade most often on the concept of Mendelian gene than on the molecular biology gene. In other words, artificial life models tend to regard genes solely as mechanisms of generational (vertical) inheritance, rather than as (informational) mechanisms of ontogenetic (horizontal) development, regulation, maintenance, phenotypic plasticity, and response to environmental change. This way, most artificial life models do not test, or even deal with, possible genomic structure architectures and their impact on development and evolution. This is a big shortcoming in the field since, as we have seen in the last two decades, the molecular biology gene and the genomic structure it implies are behind many essential principles of life—from hypersomatic mutation in vertebrate immunity to speciation.

Additionally, it is most often the case that artificial organisms in artificial life models are designed with many top-down features, rather than emerging out of artificial biochemical machines. For instance, typically the genes of artificial organisms encode pre-defined computer operations. Not only is the encoding pre-defined, but the function of individual genes is also pre-programmed, rather than emergent from some artificial chemistry—what is typically emergent is the behavior of a collection of such "atomic" genes and genotypes.

It is interesting to note that when biologists were looking for the location of genetic information for inheritance, they naturally assumed that it would reside in proteins. They knew of DNA chemically, but its sheer inertness deemed it unfit for the job. It took some time to realize that relative inertness was really the point--- from Griffith's experiment in 1928 to Avery's in 1944, the implications of which were only fully accepted much later , probably costing Avery a deserved Nobel [Judson, 2003]. This episode illustrates how reality very often surprises the best scientific expectations of the day—a big problem for Artificial Life, as long as it defines itself as the study of life-as-it-could-be, since it implies a science built on what scientists *think* life is and not on what experiments show it is. For instance, the biochemical difference between highly inert memory molecules and highly reactive, functional ones, while often overlooked in artificial life as a design principle, is ultimately the hallmark of life [Rocha and Hordijk, 2005; Brenner, 2012]. Indeed, Venter's achievement in successfully replicating a living cell with a "*prosthetic genome*" until the original organism's phenotype is fully re-programmed (see chapter 1), should lead Artificial Life scientists to ponder at least the question of what is it about life's *design principle* that makes it easier to synthesize a working prosthetic genome than a working "prosthetic" proteome or metabolome? Perhaps, Langton's view of artificial life being built-up from simple machines, may have clouded the fact that life as we know it is made of biochemical constituents with very different chemical and functional roles: chiefly, DNA (long-term, random-access memory), RNA (short-term memory and symbol processing) and proteins (functional machines). Perhaps more attention should be directed to the "logical forms" of these lower level, structural constituents that produce life, before we can tackle "life-as-it-could-be".

ACKNOWLEDGMENTS

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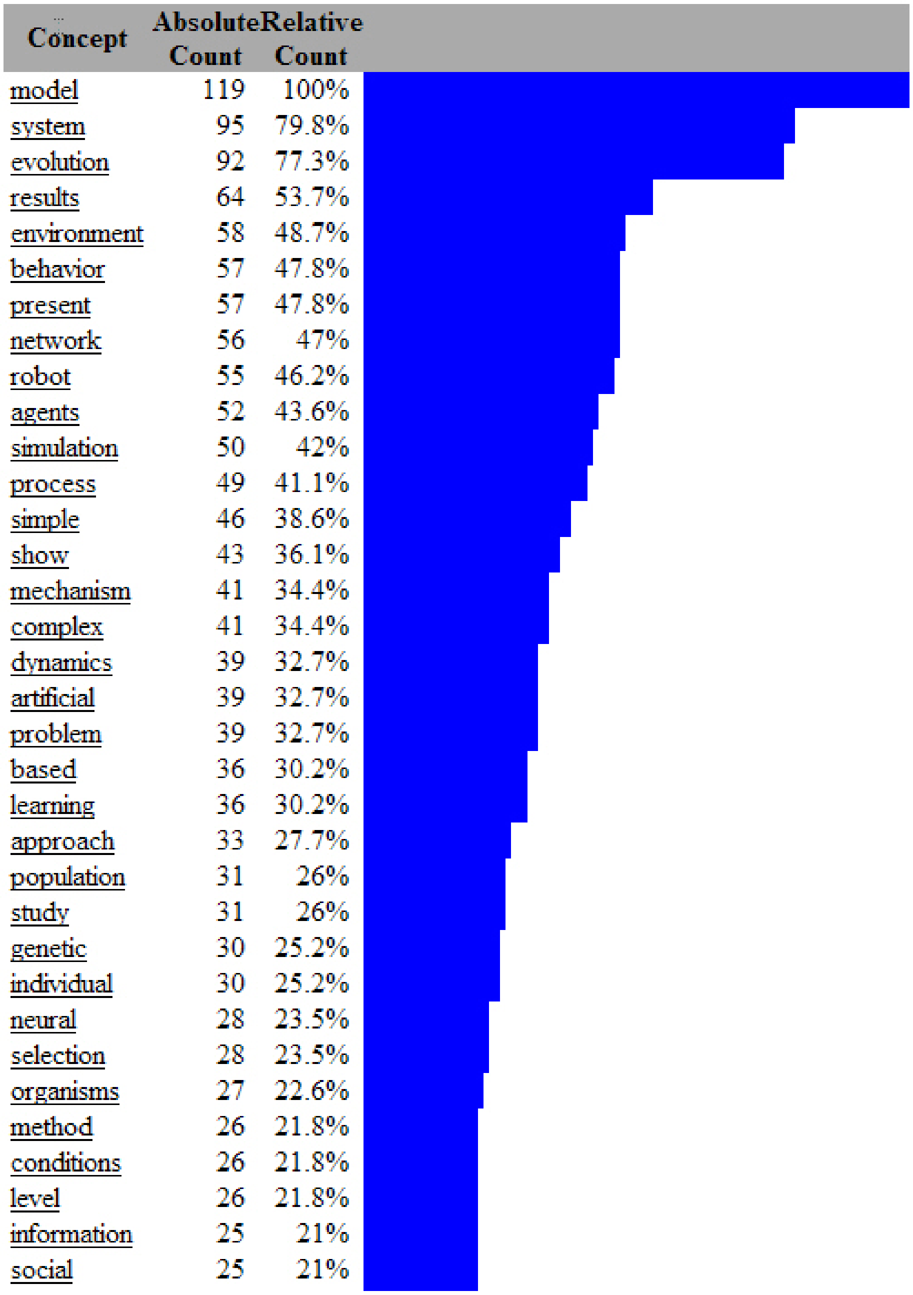
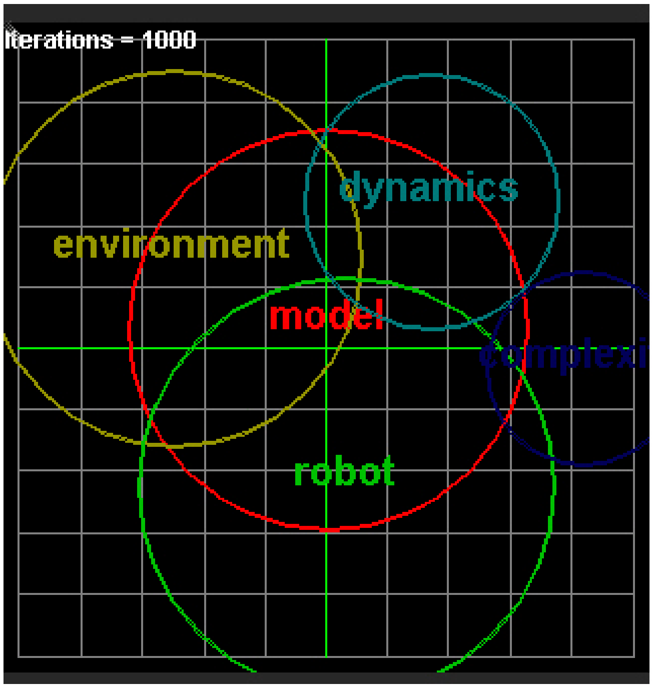
APPENDIX:

Top themes extracted from all abstracts accepted to ECAL 2007, produced the Leximancer (courtesy of Janet Wiles)



Concept	Absolute Count	Relative Count
model	119	100%
system	95	79.8%
evolution	92	77.3%
results	64	53.7%
environment	58	48.7%
behavior	57	47.8%
present	57	47.8%
network	56	47%
robot	55	46.2%
agents	52	43.6%
simulation	50	42%
process	49	41.1%
simple	46	38.6%
show	43	36.1%
mechanism	41	34.4%
complex	41	34.4%
dynamics	39	32.7%
artificial	39	32.7%
problem	39	32.7%
based	36	30.2%
learning	36	30.2%
approach	33	27.7%
population	31	26%
study	31	26%
genetic	30	25.2%
individual	30	25.2%
neural	28	23.5%
selection	28	23.5%
organisms	27	22.6%
method	26	21.8%
conditions	26	21.8%
level	26	21.8%
information	25	21%
social	25	21%

Top Themes produced from Leximancer set at 65% coverage themes (courtesy of Janet Wiles)



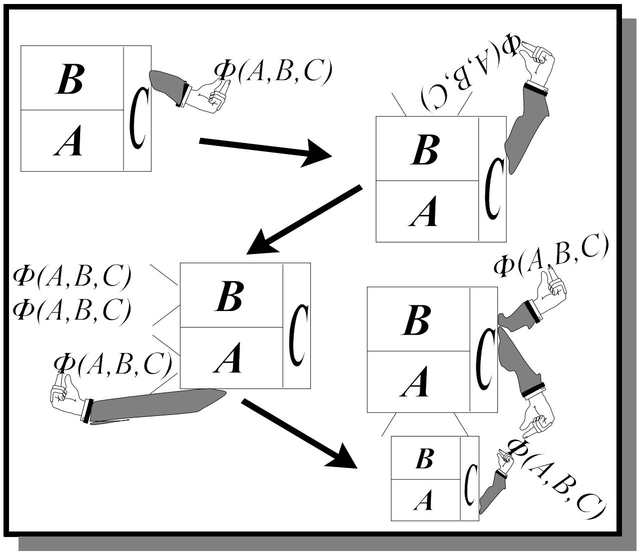
Top co-occurring (stemmed) word pairs in abstracts

neural--network
chang--environ
artifici--life
simul--result
autonom--robot
evolutionari--algorithm
evolutionari--robot
comput--simul
genet--algorithm
robot--mobil
cellular--automata
interact--between
artifici--chemistri
agent--adapt
pressur--select
neural--control

6. Von Neumann and Natural Selection

> “Turing invented the stored-program computer, and von Neumann showed that the description is separate from the universal constructor. This is not trivial. Physicist Erwin Schrödinger confused the program and the constructor in his 1944 book What is Life?, in which he saw chromosomes as “architect's plan and builder's craft in one”. This is wrong. The code script contains only a description of the executive function, not the function itself.” [Brenner, 2012]

6.1 Von Neumann’s Self-Reproduction Scheme



Von Neumann thought of his logical model of self-reproduction as an answer to the observation that, unlike machines, biological organisms have the ability to self-replicate while seemingly increasing their complexity without limit. Mechanical artefacts are instead produced via more complicated factories (as opposed to self-production) and can only degenerate in their complexity. He was searching for a complexity threshold beyond which systems may self-reproduce (with no outside control) while possibly increasing their complexity.

Von Neumann concluded that this threshold entails a memory-stored description Φ(*X*) that can be interpreted by a universal constructor automaton *A* to produce any automaton *X*; if a description of *A*, Φ(*A*), is fed to *A* itself, then a new copy of *A* is obtained. However, to avoid a logical paradox of self-reference, the description, which cannot describe itself, must be both copied (uninterpreted role) and translated (interpreted role) into the described automaton. This way, in addition to the universal constructor, an automaton *B* capable of copying any description, Φ(*X*), is included in the self-replication scheme. A third automaton *C* is also included to perform all the manipulation of descriptions necessary—a sort of operating system. To sum it up, the self-replicating system contains the set of automata (*A* + *B* + *C*) and a description Φ(*A* + *B* + *C*); the description is fed to B which copies it three times (assuming destruction of the original); one of these copies is then fed to *A* which produces another automaton (*A* + *B* + *C*); the second copy is then handled separately to the new automaton which together with this description is also able to self-reproduce; the third copy is kept so that the self-reproducing capability may be maintained (it is also assumed that *A* destroys utilized descriptions). Notice that the description, or program, is used in two different ways: it is both *translated* and *copied*. In the first role, it controls the construction of an automaton by causing a sequence of activities (*active* role of description). In the second role, it is simply copied (*passive* role of description). In other words, the *interpreted* description controls construction, and the *uninterpreted* description is copied separately, passing along its stored information (memory) to the next generation. This parallels the horizontal and vertical transmission of genetic information in biological organisms, which is all the more remarkable since Von Neumann proposed this scheme before the structure of the DNA molecule was uncovered by Watson and Crick[1953]—though after the Avery-MacLeod-McCarty [1944] experiment which identified DNA has the carrier of genetic information.

> "The concept of the gene as a symbolic representation of the organism–a code script–is a fundamental feature of the living world and must form the kernel of biological theory." [Brenner, 2012]

The notion of description-based self-reproduction implies a language. A description must be cast on some *symbol system* while it must also be implemented by some physical or a logical structure. When *A* interprets a description to construct some automaton, a *semantic* code is utilized to map instructions into construction commands to be performed. When *B* copies a description, only its *syntactic* aspects are replicated. Now, the language of this semantic code presupposes a set of primitives (e.g. parts and processes) for which the instructions are said to "stand for". Descriptions are not universal insofar as they refer to these building blocks which cannot be changed without altering the significance of the descriptions. The building blocks ultimately produce the dynamics, behavior, and/or functionality of the overall system, and may be material or computational. In Biology, we can think of the genetic code as instantiating such a language. Genes are descriptions that encode specific parts: amino acids chains. In a computational setting, parts are typically logical operations, but they can also be, for example, the building blocks of neural networks coded by genetic algorithms and L-Systems. Von Neumann [1966] (posthumously aided by Arthur Burks) produced a specification of a universal constructor using a 29-state cellular automaton. Implementations of this automaton appeared only fairly recently [e.g. Pesavento, 1995, see Sipper, 1998]

6.2 Open-ended evolution and natural selection

> "Biologists ask only three questions of a living organism: how does it work? How is it built? And how did it get that way? They are problems embodied in the classical fields of physiology, embryology and evolution. And at the core of everything are the tapes containing the descriptions to build these special Turing machines." [Brenner, 2012]

Perhaps the most important consequence of *separate* descriptions in Von Neumann's self-reproduction scheme (and Turing's Tape) is its opening the possibility for open-ended evolution [Rocha, 1998; McMullin, 2000]. As Von Neumann [1966] discussed, if the description of the self-reproducing automata is changed (mutated), in a way as to not affect the basic functioning of $(A + B + C)$ then, the new automaton $(A + B + C)$` will be slightly different from its parent. Von Neumann used a new automaton *D* to be included in the self-replicating organism, whose function does not disturb the basic performance of $(A + B + C)$; if there is a mutation in the *D* part of the description, say *D*`, then the system $(A + B + C + D) + \Phi(A + B + C + D$`$)$ will produce $(A + B + C + D$`$) + \Phi(A + B + C + D$`$)$. Von Neumann [1966, page 86] further proposed that non-trivial self-reproduction should include this "ability to undergo inheritable mutations as well as the ability to make another organism like the original", to distinguish it from "naive" self-reproduction like growing crystals.

Notice that changes in $(A + B + C + D)$ are not heritable, only changes in the description, $\Phi(A + B + C + D)$, are inherited by the automaton's offspring and are thus relevant for evolution. This ability to transmit mutations (vertically) is precisely at the core of the principle of natural selection of modern Darwinism. Through variation (mutation) populations of different organisms are produced; the statistical bias these mutations impose on reproduction rates of organisms will create survival differentials (fitness) on the population which define natural selection. In principle, if the language of description is rich enough, an endless variety of organisms can be evolved: *open-ended evolution*.

The evolvability of a self-reproducing system is dependent on the parts used by the semantic code. If the parts are very simple, then the descriptions will have to be very complicated, whereas if the parts possess rich dynamic properties, the descriptions can be simpler since they will take for granted a lot of the dynamics that otherwise would have to be specified. In the genetic system, genes do not have to specify the functional characteristics of the proteins produced, but simply the string of amino acids that will produce that functionality "for free" [Moreno et al, 1994]. Furthermore, there is a trade-off between programmability and evolvability [Conrad, 1983, 1990] which grants some self-reproducing systems no evolutionary potential whatsoever. When descriptions require high programmability they will be very sensitive to damage. Low programmability grants self-reproducing systems the ability to change without destroying their own organization, though it also reduces the space of possible evolvable configurations [Rocha, 2001].

Turing and Von Neumann were the first to correctly formalize the required inheritance mechanism behind neo-Darwinian evolution by Natural Selection. This understanding of the most fundamental design principle of life, puts Turing and Von Neumann on the Parthenon of great thinkers in Biology, alongside Darwin and Mendel. The dovetailing of computational thinking and biology, inherent in the cybernetics movement of Turing, Von Neumann, Shannon, Wiener and others, emphasizes how (material) control of symbolic information is the hallmark of both computation and biocomplexity.

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7. Modeling Evolution: Evolutionary Computation

> "How does evolution produce increasingly fit organisms in environments which are highly uncertain for individual organisms? How does an organism use its experience to modify its behavior in beneficial ways (i.e. how does it learn or 'adapt under sensory guidance')? How can computers be programmed so that problem-solving capabilities are built up by specifying '*what* is to be done' rather than '*how* to do it'?" [Holland, 1975, page 1]

These were some of the questions concerning John Holland when he thought of Genetic Algorithms (GA's) in the 1960's. All these questions were shown to be reducible to a problem of optimizing multi-parameter functions. Nature's "problem" is to create organisms that reproduce more (are more fit) in a particular environment: the environment-organism coupling dictates the selective pressures, and the solutions to these pressures are organisms themselves. In the language of optimization, the solutions to a particular problem (say, an engineering problem), will be selected according to how well they solve that problem. GA's are inspired by natural selection as the solutions to our problem are not algebraically calculated, but rather found by a population of solution alternatives which is altered in each time step of the algorithm in order to increase the probability of having better solutions in the population. In other words, GA's, or other Evolutionary Strategies (ES) such as Evolutionary Programming (EP), explore the multi-parameter space of solution alternatives for a particular problem, by means of a population of encoded strings (standing for alternatives) which undergo variation (crossover and mutation) and are reproduced in a way as to lead the population to ever more promising regions of this search space (selection) [Goldeberg, 1989; Mitchell, 1999; De Jong, 2006].

7.1 Evolutionary Strategies and Self-Organization

The underlying idea of computational ES is the *separation* of solutions for a particular problem (e.g. a machine) from *descriptions* of those solutions (memory). GA's work on these descriptions and not on the solutions themselves, that is, variation is applied to descriptions, while the respective solutions are evaluated, and the whole (description-solution) selected according to this evaluation. Such machine/description separation follows von Neumann's self-reproducing scheme (see chapter 6) which is able to increase the complexity of the (organization of) machines described. Therefore, the form of organization evolved by GA's is not self-organizing in the sense of a boolean network or cellular automata (see chapter 4). Even though the solutions are obtained from the interaction of a population of elements, and in this sense following the general rules usually observed by computationally emergent systems (e.g. Langton [1988], Mitchell [1992]), they do not ***self***-organize since they rely on the *selective* pressures of some environment (in ES, defined by an explicit or implicit fitness function). The order so attained is not a result of the internal dynamics of a collection of interacting elements, but is instead dictated by the *external* selection criteria. In this sense, ES follow an organizing scheme that is driven by external selection of encoded symbolic descriptions (a "Turing tape"). It is perhaps useful to think that ES are modeling the most fundamental design principle of biological systems: natural selection. While self-organizing systems model the dynamical characteristics of matter, ES model the existence of, external, selective pressures on populations of symbolic descriptions of some system. While self-organization models material dynamics, ES models the selection of information about dynamics.

7.2 Development and morphogenesis: self-organization and selection come together

Since the original introduction of GA's, many subsequent developments had to do with the inclusion of a developmental stage, or intermediate layers between genotype and phenotype; in other words, the creation of some artificial morphogenesis or regulation. The idea has been to encode rules that will themselves self-organize to produce a phenotype, rather than the direct encoding of the phenotype itself, or the introduction of gene regulation . As discussed in class, these rules often use L-System grammars which dictate production system programs [Wilson, 1988] leading to some phenotype. The most important advantage of this intermediate stage, as explored by Kitano [1990], Gruau [1993], Belew [1992] and others, is the ability to code for much larger structures than a direct encoding allows. In practical terms, they have solved some of the scalability problems of encoding (e.g.) neural networks in GA's, by reducing the search space dramatically.

L-system grammars are higher-level descriptions of self-organizing developmental processes. However, these first approaches used solely context-free, state-determined, L-System grammars, compromising epistasis (or mutual, non-linear, influence of genetic descriptions amongst each other) in the simulation of self-organizing development. Dellaert and Beer [1994] and Kitano [1994], for instance, used Boolean networks to simulate genetic epistasis and self-organization. In other words, the GA encodes rules which construct Boolean networks whose nodes stand for aspects of the phenotypes we wish to evolve on some physical simulation. In Dellaert and Beer's model, the nodes stand for cell mitosis and other characteristics. This way, the solutions of the GA are self-organizing systems whose attractor behavior dictates pre-defined phenotypic traits.

These approaches in effect offer an emergent morphology, that is, they encode rules which will themselves self-organize into some phenotype (instead of strict programming of morphology). The indirect encoding further allows the search to occur in a reduced space, amplified through development. An interesting side effect has to do with the appearance of modularity traits on the evolved phenotypes [Wagner, 1995]. Subsequent developments paid even more attention to the contextual regulation that indirect encodings afford to the search [Rocha 1995, 1997]. More recently, given our expanded view of genomics, other intermediate layers between genotype and phenotype have been explored, such as transcription regulation [Reil, 1999; Hallinan & Wiles, 2004] and RNA Editing [Rocha et al, 2006]. The inclusion of more sophisticated regulation of genetic information prior to translation, while not necessarily including a self-organizing component, allows us to model a much more realistic genotype/phenotype/environment interaction. Instead of genotypes used exclusively for Mendelian inheritance (see chapter 5) of (directly encoded) phenotypic traits, ES with genotype regulation allow us to model the contextual, plastic development of phenotypes we have come to understand via modern Genomics—thus also learning additional design principles for bio-inspired computation [Huang et al, 2007].

The most important aspect of GA's with emergent morphologies is the utilization in the same model of an external selection engine (the GA) coupled to a particular self-organizing dynamics (e.g. Boolean networks) standing for some materiality. Such schemes bring together, computationally, the two most important aspects of evolutionary systems: self-organization and selection. These models belong to a category of self-organization referred to as *Selected Self-Organization* which is based on symbolic memory [Rocha, 1996, 1997, 1998]. Selected Self-Organization with distributed memory is also possible in autocatalytic structures, though its evolutionary potential is much smaller than the local memory kind [Rocha, 2001][Vasas, 2010]. The reason lies in Von Neumann's notion of self-reproduction (see chapter 6). The introduction of symbolic descriptions allows a much more sophisticated form of communication: structures are constructed from static descriptions and do not have to reproduce through some complicated, and limited process of self-inspection. In other words, separate descriptions can be used to reliably construct any kind of structure in an open-ended manner, while self-inspection relies on only those structures that happen to be able to make copies of themselves. As an example, a non-genetic protein-based life form, would have to rely only on those proteins that could make direct copies of themselves [Rocha, 2001].

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An Introduction to Evolutionary Computation

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Abstract

Researchers in many fields are faced with computational problems in which a great number of solutions are possible and finding an optimal or even a sufficiently good one is difficult. A variety of search techniques have been developed for exploring such problem spaces, and a promising approach has been the use of algorithms based upon the principles of natural evolution. This tutorial will introduce the basic principles underlying most evolutionary algorithms, as well as some of the key details of the four most popular methods: genetic algorithms, genetic programming, evolutionary strategies, and evolutionary programming. The aim of the tutorial is to introduce the participants to the jargon and principles of the field of evolutionary computation, and to encourage the participants to consider the potential of applying evolutionary optimization techniques in their own research.

1. Introduction

An important area in current research is the development and application of search techniques based upon the principles of natural evolution. Most readers, through the popular literature and typical Western educational experience, are probably aware of the basic concepts of evolution. In particular, the principle of the '*survival of the fittest*' proposed by Charles Darwin (1859) has especially captured the popular imagination. We shall use this as a starting point in introducing evolutionary computation.

The theory of natural selection proposes that the plants and animals that exist today are the result of millions of years of adaptation to the demands of the environment. At any given time, a number of different organisms may co-exist and compete for the same resources in an ecosystem. The organisms that are most capable of acquiring resources and successfully procreating are the ones whose descendants will tend to be numerous in the future. Organisms that are less capable, for whatever reason, will tend to have few or no descendants in the future. The former are said to be more *fit* than the latter, and the distinguishing characteristics that caused the former to be more fit are said to be *selected for* over the characteristics of the latter. Over time, the entire population of the ecosystem is said to *evolve* to contain organisms that, on average, are more fit than those of previous generations of the population because they exhibit more of those characteristics that tend to promote survival.

Evolutionary computation techniques abstract these evolutionary principles into algorithms that may be used to search for optimal solutions to a problem. In a search algorithm, a number of possible solutions to a problem are available and the task is to find the best solution possible in a fixed amount of time. For a search space with only a small number of possible solutions, all the solutions can be examined in a reasonable amount of time and the optimal one found. This *exhaustive search*, however, quickly becomes impractical as the search space grows in size. Traditional search algorithms randomly sample (e.g., *random walk*) or heuristically sample (e.g., *gradient descent*) the search space one solution at a time in the hopes of finding the optimal solution. The key aspect distinguishing an evolutionary search algorithm from such traditional algorithms is that it is *population-based*. Through the adaptation of successive generations of a large number of individuals, an evolutionary algorithm performs an efficient directed search. Evolutionary search is generally better than random search and is not susceptible to the hill-climbing behaviors of gradient-based search.

2. Basic Evolutionary Computation

In an evolutionary algorithm, a *representation scheme* is chosen by the researcher to define the set of solutions that form the search space for the algorithm. A number of individual solutions are created to form an *initial population*. The following steps are then repeated iteratively until a solution has been found which satisfies a pre-defined *termination criterion*. Each individual is evaluated using a *fitness function* that is specific to the problem being solved. Based upon their fitness values, a number of individuals are chosen to be *parents*. New individuals, or *offspring*, are produced from those parents using *reproduction operators*. The fitness values of those offspring are determined. Finally, survivors are selected from the old population and the offspring to form the new population of the next *generation*.

The mechanisms determining which and how many parents to select, how many offspring to create, and which individuals will survive into the next generation together represent a *selection method*. Many different selection methods have been proposed in the literature, and they vary in complexity. Typically, though, most selection methods ensure that the population of each generation is the same size.

The remainder of the paper presents the traditional definitions of the four most common evolutionary algorithms: genetic algorithms (Holland, 1975), genetic programming (Koza, 1992, 1994), evolutionary strategies (Rechenberg, 1973), and evolutionary programming (Fogel et al., 1966). The traditional differences between the approaches involve the nature of the representation schemes, the reproduction operators, and the selection methods.

3. Genetic Algorithms

The most popular technique in evolutionary computation research has been the *genetic algorithm*. In the traditional genetic algorithm, the representation used is a *fixed-length bit string*. Each position in the string is assumed to represent a particular feature of an individual, and the value stored in that position represents how that feature is expressed in the solution. Usually, the string is "evaluated as a collection of *structural* features of a solution that have little or no interactions" (Angeline, 1996, p. 4). The analogy may be drawn directly to genes in biological organisms. Each gene represents an entity that is structurally independent of other genes.

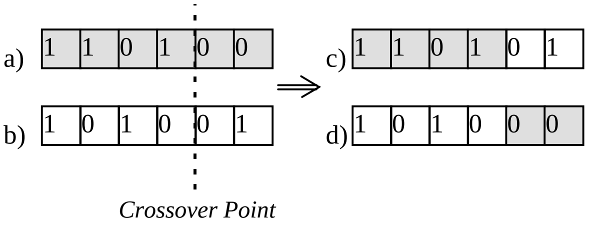


Figure 1: Bit-String Crossover of Parents a & b
to form Offspring c & d

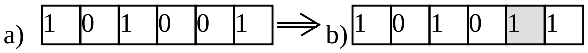


Figure 2: Bit-Flipping Mutation of Parent a
to form Offspring b

The main reproduction operator used is *bit-string crossover*, in which two strings are used as parents and new individuals are formed by swapping a sub-sequence between the two strings (see Figure 1). Another popular operator is *bit-flipping mutation*, in which a single bit in the string is flipped to form a new offspring string (see Figure 2). A variety of other operators have also been developed, but are used less frequently (e.g., *inversion*, in which a subsequence in the bit string is reversed). A primary distinction that may be made between the various operators is whether or not they introduce any new information into the population. Crossover, for example, does not while mutation does. All operators are also constrained to manipulate the string in a manner consistent with the structural interpretation of genes. For example, two genes at the same location on two strings may be swapped between parents, but not combined based on their values.

Traditionally, individuals are selected to be parents *probabilistically* based upon their fitness values, and the offspring that are created replace the parents. For example, if N parents are selected, then N offspring are generated which replace the parents in the next generation.

4. Genetic Programming

An increasingly popular technique is that of *genetic programming*. In a standard genetic program, the representation used is a variable-sized tree of functions and values. Each leaf in the tree is a label from an available set of value labels. Each internal node in the tree is label from an available set of function labels. The entire tree corresponds to a single function that may be evaluated. Typically, the tree is evaluated in a left-most depth-first manner. A leaf is evaluated as the corresponding value. A function is evaluated using as arguments the result of the evaluation of its children.

Genetic algorithms and genetic programming are similar in most other respects, except that the reproduction operators are tailored to a tree representation. The most commonly used operator is *subtree crossover*, in which an entire subtree is swapped between two parents (see Figure 3). In a standard genetic program, all values and functions are assumed to return the same type, although functions may vary in the number of arguments they take. This *closure* principle (Koza, 1994) allows any subtree to be considered structurally on par with any other subtree, and ensures that operators such as sub-tree crossover will always produce legal offspring.

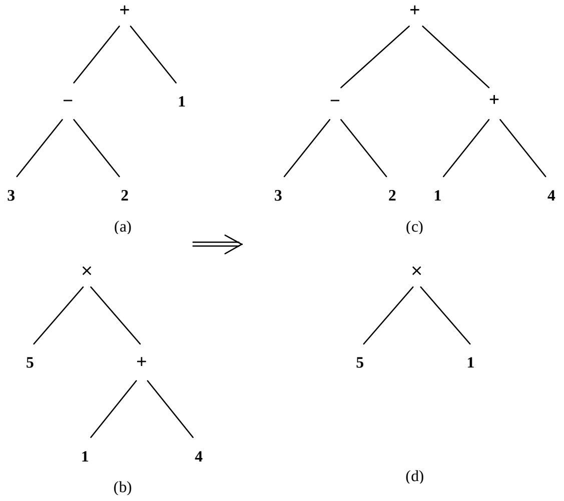
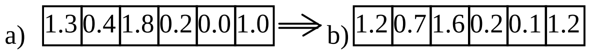


Figure 3: Subtree Crossover of Parents a & b
to form Offspring c & d

5. Evolutionary Strategies

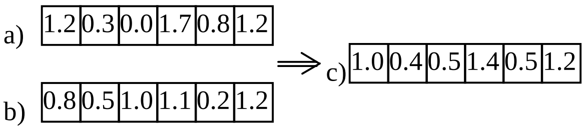
In evolutionary strategies, the representation used is a fixed-length real-valued vector. As with the bit-strings of genetic algorithms, each position in the vector corresponds to a feature of the individual. However, the features are considered to be behavioral rather than structural. "Consequently, arbitrary non-linear interactions between features during evaluation are expected which forces a more holistic approach to evolving solutions" (Angeline, 1996, p. 4).

The main reproduction operator in evolutionary strategies is *Gaussian mutation*, in which a random value from a Gaussian distribution is added to each element of an individual's vector to create a new offspring (see Figure 4). Another operator that is used is *intermediate recombination*, in which the vectors of two parents are averaged together, element by element, to form a new offspring (see Figure 5). The effects of these operators reflect the behavioral as opposed to structural interpretation of the representation since knowledge of the values of vector elements is used to derive new vector elements.



a) 1.3 0.4 1.8 0.2 0.0 1.0 ⟹ b) 1.2 0.7 1.6 0.2 0.1 1.2

Figure 4: Gaussian Mutation of Parent a to form Offspring b



a) 1.2 0.3 0.0 1.7 0.8 1.2

b) 0.8 0.5 1.0 1.1 0.2 1.2

⟹ c) 1.0 0.4 0.5 1.4 0.5 1.2

Figure 5: Intermediate Recombination of Parents a & b to form Offspring c

The selection of parents to form offspring is less constrained than it is in genetic algorithms and genetic programming. For instance, due to the nature of the representation, it is easy to average vectors from many individuals to form a single offspring. In a typical evolutionary strategy, N parents are selected uniformly randomly (i.e., not based upon fitness), more than N offspring are generated through the use of recombination, and then N survivors are selected deterministically. The survivors are chosen either from the best N offspring (i.e., no parents survive) or from the best N parents and offspring (Spears et al., 1993).

6. Evolutionary Programming

The representations used in evolutionary programming are typically tailored to the problem domain (Spears et al., 1993). One representation commonly used is a fixed-length real-valued vector.

The primary difference between evolutionary programming and the previous approaches is that no exchange of material between individuals in the population is made. Thus, only mutation operators are used. For real-valued vector representations, evolutionary programming is very similar to evolutionary strategies without recombination.

A typical selection method is to select all the individuals in the population to be the N parents, to mutate each parent to form N offspring, and to probabilistically select, based upon fitness, N survivors from the total 2N individuals to form the next generation.

7. Current Issues

In current research, the line distinguishing these different approaches has started to blur. Researchers in each technique have begun to examine more complex representation schemes and to apply a variety of selection methods. Many genetic algorithm researchers are examining the use variable-length representations and analyzing how such representations grow in size over the course of evolution (Wu & Lindsay, 1996). Many genetic algorithms now use selection methods, such as *elitist recombination*, in which parents compete with their offspring for survival into the next generation (Thierens, 1997). Some genetic programming researchers have begun to examine the effects of allowing multiple types of functions and values into the representation. The benefits of such strongly typed genetic programming are only beginning to be explored (Haynes et al., 1996).

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3.4 EVOLUTIONARY BIOLOGY

Evolutionary biology is a science concerned, among other things, with the study of the diversity of life, the differences and similarities among organisms, and the adaptive and non-adaptive characteristics of organisms. Its importance are manifold, from the health sciences to the understanding of how the living organisms adapt to the environment they inhabit. For instance, evolutionary biology helps in the understanding of disease epidemics, population dynamics, and the production of improved cultures. Over roughly the last 60 years, computer scientists and engineers realized that evolutionary biology has various interesting ideas for the development of theoretical models of evolution (some of them being rather abstract models) that can be useful to obtain solutions to complex real-world problems.

The word *evolution* is originated from the Latin *evolvere*, which means to unfold or unroll. Broadly speaking, evolution is a synonym for 'change'. But what type of change? We do not usually employ the word evolution to refer to the changes suffered by an individual during its lifetime. Instead, an evolving system corresponds to the one in which there is a descent of entities over time, one generation after the other, and in which characteristics of the entities differ across generations (Futuyma, 1998). Therefore, *evolution* can be broadly defined as *descent with modification* and often *with diversification*. Many systems can be classified as evolutionary: languages, cellular reproduction in immune systems, cuisines, automobiles, and so on.

Any evolutionary system presents a number of features:

- *Population(s)*: in all evolutionary systems there are populations, or groups, of entities, generally termed *individuals*.
- *Reproduction*: in order for evolution to occur, the individuals of the population(s) must reproduce either sexually or asexually.
- *Variation*: there is variation in one or more characteristics of the individuals of the population(s).
- *Hereditary similarity*: parent and offspring individuals present similar characteristics. Over the course of generations, there may be changes in the proportions of individuals with different characteristics within a population; a process called *descent with modification*.
- *Sorting of variations*: among the sorting processes, it can be emphasized *chance* (random variation in the survival or reproduction of different variants), and *natural selection* (consistent, non-random differences among variants in their rates of survival and reproduction).

Adaptation as a result of variation plus natural selection leads to improvement in the function of an organism and its many component parts. "Biological *or* organic evolution *is change in the properties of populations of organisms, or groups of such populations, over the course of generations*." (Futuyma, 1998; p. 4). Note that according to this definition of evolution, individual organisms do not evolve and the changes of a population of individuals that are assumed to be evolutionary are those resultant from inheritance, via the genetic material, from one generation to the other.

The history of evolutionary biology is marked by a number of hypotheses and theories about how life on earth appeared and evolved. The most influential theory to date is the one proposed by Charles Darwin and formalized in his book *On the Origins of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life* (Darwin, 1859). Historically, Alfred Wallace is also one of the proponents of the theory of evolution by means of natural selection, but it was Darwin's book, with its hundreds of instances and arguments supporting natural selection, the landmark for the theory of evolution.

Among the many preDarwinian hypotheses for the origin and development of beings, the one proposed by Jean Baptist Pierre Antoine de Monet, chevalier de Lamarck, was the most influential. According to Lamarck, every species originated individually by spontaneous generation. A 'nervous fluid' acts within each species, causing it to progress up the chain over time, along a single predetermined path that every species is destined to follow. No extinction has occurred: fossil species are still with us, but have been transformed. According to Lamarck, species also adapt to their environments, the more strongly exercised organs attract more of the nervous fluid, thus getting enlarged; conversely, the less used organs become smaller. These alterations, acquired during an individual's lifetime through its activities, are inherited. Like everyone at that time, Lamarck believed in the so-called *inheritance of acquired characteristics*.

The most famous example of Lamarck's theory is the giraffe: according to Lamarck, giraffes need long necks to reach the foliage above them; because they are constantly stretching upward, the necks grow longer; these longer necks are inherited; and over the course of generations the necks of giraffes get longer and longer. Note that the theory of inheritance of acquired characteristics is not Lamarck's original, but an already established supplement to his theory of 'organic progression' in which spontaneous generation and a chain of beings (progression from inanimate to barely animate forms of life, through plants and invertebrates, up to the higher forms) form the basis. Lamarck's theory may also be viewed as a *transformational theory*, in which change is programmed into every member of the species.

3.4.1. On the Theory of Evolution

Darwin's studies of the natural world showed a striking diversity of observations over the animal and vegetal kingdoms. His examples were very wide ranging, from domestic pigeons, dogs, and horses, to some rare plants. His research that resulted in the book *Origin of Species* took literally decades to be concluded and formalized.

In contrast to the Lamarckian theory, Darwin was certain that the direct effects of the conditions of life were unimportant for the variability of species.

> "Seedlings from the same fruit, and the young of the same litter, sometimes differ considerably from each other, though both the young and the

> parents … have apparently been exposed to exactly the same conditions of life; and this shows how unimportant the direct effects of the conditions of life are in comparison with the laws of reproduction, and of growth, and of inheritance; for had the action of the conditions been direct, if any of the young had varied, all would probably have varied in the same manner." (Darwin, 1859; p. 10)

Darwin starts his thesis of how species are formed free in nature by suggesting that the most abundant species (those that range widely over the world) are the most diffused and which often produce well-marked varieties of individuals over the generations. He describes some basic rules that promote improvements in organisms: reproduce, change and compete for survival.

Natural selection was the term used by Darwin to explain how new characters arising from variations are preserved. He starts thus paving the ground to his theory that slight differences in organisms accumulated over many successive generations might result in the appearance of completely new and more adapted species to their environment. As defended by himself

> "… as a general rule, I cannot doubt that the continued selection of slight variations … will produce races differing from each other …" (Darwin, 1859; p. 28) and "… I am convinced that the accumulative action of Selection, whether applied methodically and more quickly, or unconsciously and more slowly, but more efficiently, is by far the predominant Power." (Darwin, 1859; p. 35)

In summary, according to Darwin's theory, evolution is a result of a population of individuals that suffer:

- Reproduction with inheritance.
- Variation.
- Natural selection.

These very same processes constitute the core of all evolutionary algorithms. Before going into the details as to how reproduction and variation happen within individuals and species of individuals, some comments about why Darwin's theory was so revolutionary and 'dangerous' at that time (and, to some people, until nowadays) will be made.

3.4.2. Darwin's Dangerous Idea

Darwin's theory of evolution is controversial and has been refuted by many because it presents a sound argument for how a "Nonintelligent Artificer" could produce the wonderful forms and organisms we see in nature. To D. Dennett (1991), *Darwin's dangerous idea* is that evolution, thus life, can be explained as the product of an *algorithmic process*, not of a superior being (God) creating everything that might look wonderful to our eyes. But the reason there is a section on Dennett's book here is not to discuss particular beliefs. Instead, to discourse about some key interpretations of evolution, from a computational perspective, presented by D. Dennett in his book *Darwin's Dangerous Idea: Evo-*

lution and the Meanings of Life. These are not only interesting, but also useful for the understanding of why the theory of evolution is suitable for the comprehension and development of a class of search techniques known as evolutionary algorithms.

Dennett defines an algorithm as a certain sort of formal process that can be counted on (logically) to yield a certain sort of result whenever it is run or instantiated. He emphasizes that *evolution* can be understood and represented in an abstract and common terminology as an *algorithmic process*; it can be lifted out of its home base in biology. Evolutionary algorithms are thus those that embody the major processes involved in the theory of evolution: a population of individuals that *reproduce with inheritance*, and suffer *variation* and *natural selection*.

Dennett also discusses what can be the outcomes of evolution and its probable implications when viewed as an *engineering process*. He stresses the importance of genetic variation and selection, and quotes an interesting passage from M. Eigen (1992).

> "Selection is more like a particularly subtle demon that has operated on the different steps up to life, and operates today at the different levels of life, with a set of highly original tricks. Above all, it is highly active, driven by an internal feedback mechanism that searches in a very discriminating manner for the best route to optimal performance, not because it possesses an inherent drive towards any predestined goal, but simply by virtue of its inherent non-linear mechanism, which gives the appearance of goal-directedness." (Eigen, 1992; quoted by Dennett, 1991, p. 195)

Another important argument is that evolution requires *adaptation* (actually it can also be seen as adaptation plus selection, as discussed in the previous chapter). From an evolutionary perspective, adaptation is the reconstruction or prediction of evolutionary events by assuming that all characters are established by direct natural selection of the most adapted state, i.e. the state that is an 'optimum solution' to a 'problem' posed by the environment. Another definition is that under adaptation, organisms can be viewed as complex adaptive systems whose parts have (adaptive) functions subsidiary to the fitness-promoting function of the whole.

The key issue to be kept in mind here is that evolution can be viewed as an algorithmic process that allows - via reproduction with inheritance, variation and natural selection - the most adapted organisms to survive and be driven to a state of high adaptability (optimality) to their environment. These are the inspiring principles of evolutionary algorithms; the possibility of modeling evolution as a search process capable of producing individuals (candidate solutions to a problem) with increasingly better 'performances' in their environments.

3.4.3. Basic Principles of Genetics

The theory of evolution used in the development of most evolutionary algorithms is based on the three main aspects raised by Darwin as being responsible for the evolution of species: reproduction with inheritance, variation, and selection. However, the origins of heredity along with variations, which were some of the main ingredients for the natural selection theory, were unknown at that time. This section explores the genetic basis of reproduction and variation in order to provide the reader with the necessary biological background to develop and understand evolutionary algorithms, in particular *genetic algorithms*. The union of genetics with some notions of the selection mechanisms, together with Darwin's hypotheses led to what is currently known as neo-Darwinism.

Gregor Mendel's paper establishing the foundations of *genetics* (a missing bit for a broader understanding of the theory of evolution) was published only in 1865 (Mendel, 1865), but it was publicly ignored until about the 1900. He performed a series of careful breeding experiments with garden peas. In summary, Mendel selected strains of peas that differed in particular *traits* (characteristics). As these differences were clearly distinguishable, their *phenotypes* (measurable attributes, or observable physical or biochemical characteristics of an organism) were identified and scored. For instance, the pea seeds were either smooth or wrinkled, the pod shape was either inflated or constricted, and the seed color was either yellow or green. Then, Mendel methodically performed crosses among the many pea plants, counted the progeny, and interpreted the results. From this kind of data, Mendel concluded that phenotypic traits were controlled by *factors*, later called *Mendelian factors*, and now called *genes*. *Genotype* is the term currently used to describe the genetic makeup of a cell or organism, as distinguished from its physical or biochemical characteristics (the phenotype). Figure 3.4 summarizes the first experiment performed by Mendel.

The basic structural element of all organisms is the *cell*. Those organisms whose genetic material is located in the *nucleus* (a discrete structure within the cell that is bounded by a nuclear membrane) of the cells are named *eukaryotes*. *Prokaryotes* are the organisms that do not possess a nuclear membrane surrounding their genetic material. The description presented here focuses on eukaryotic organisms.

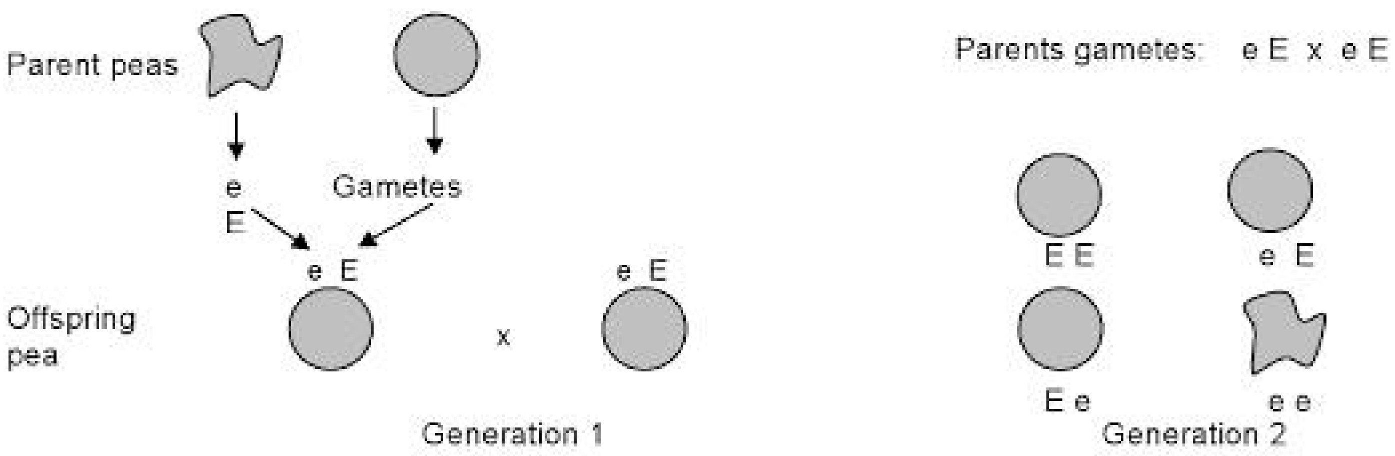


Figure 3.4: First experiment of Mendel. When crossing a normal pea with a wrinkled pea, a normal pea was generated (generation 1). By crossing two daughters from generation 1, three normal peas were generated plus one wrinkled pea. Thus, there is a recessive gene (e) that only manifests itself when there is no dominant gene together. Furthermore, there is a genetic inheritance from parents to offspring; those offspring that carry a factor that expresses a certain characteristic may have offspring with this characteristic.

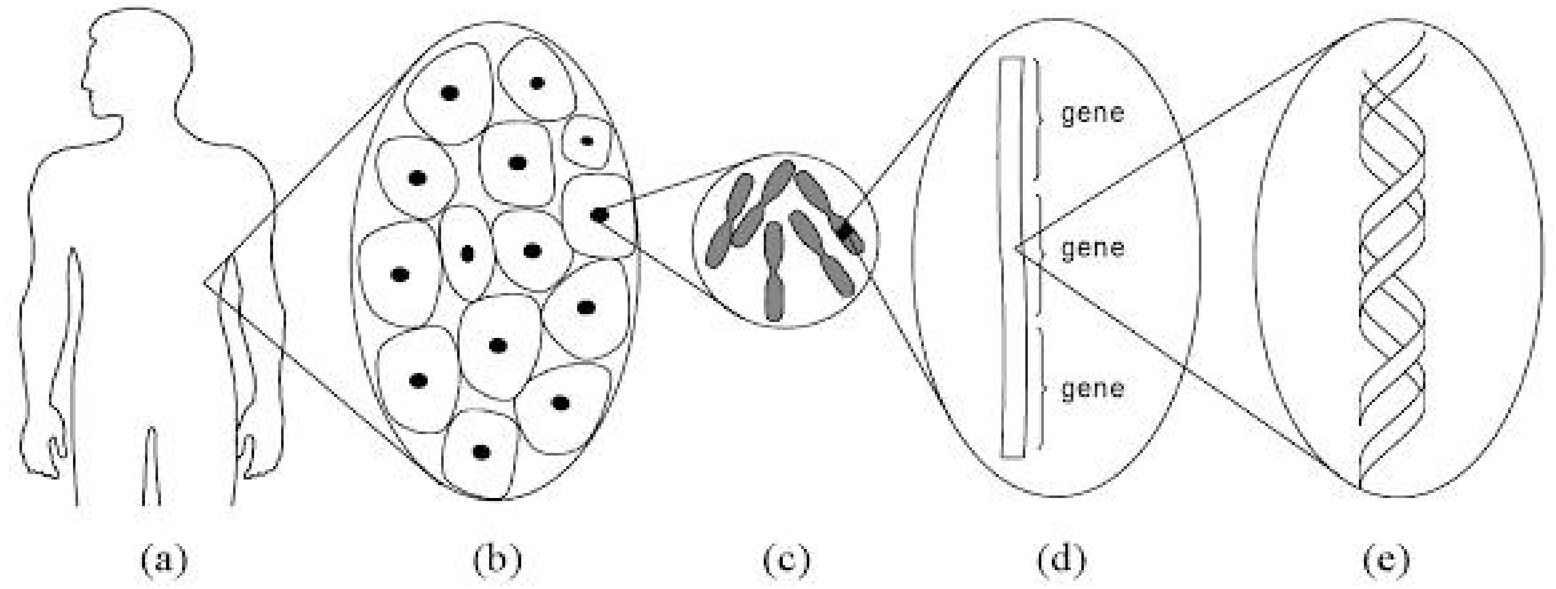


Figure 3.5: Enlargement of an organism to focus the genetic material. (a) Human organism. (b) Cells composing the organism. (c) Each cell nucleus contains chromosomes. (d) Each chromosome is composed of a long DNA segment, and the genes are the functional portions of DNA. (e) The double helix of DNA. (Modified with permission from [Griffiths et al., 1996], © W. H. Freeman and Company.)

In the cell nucleus, the genetic material is complexed with protein and is organized into a number of linear structures called *chromosomes*, which means, 'colored body', and is so named because these threadlike structures are visible under the light microscope only after they are stained with dyes. A *gene* is a segment of a helix molecule called *deoxyribonucleic acid*, or *DNA* for short. Each eukaryotic chromosome has a single molecule of DNA going from one end to the other. Each cell nucleus contains one or two sets of the basic DNA complement, called *genome*. The genome itself is made of one or more chromosomes. The *genes* are the functional regions of DNA. Figure 3.5 depicts a series of enlargements of an organism to focus on the genetic material.

It is now known that the DNA is the basis for all processes and structures of life. The DNA molecule has a structure that contributes to the two most fundamental properties of life: reproduction and development. DNA is a double helix structure with the inherent feature of being capable of replicating itself before the cell multiplication, allowing the chromosomes to duplicate into *chromatids*,

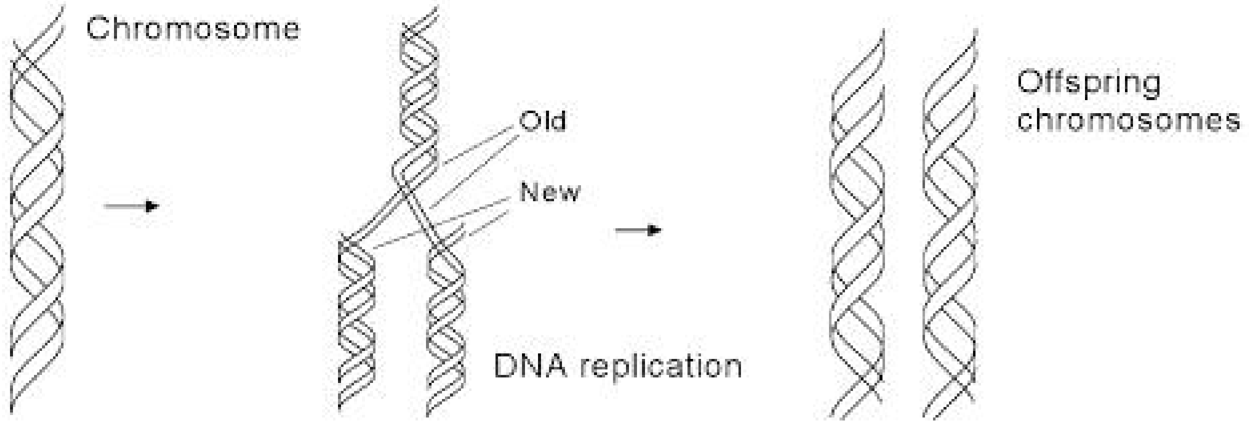


Figure 3.6: When new cells are formed, the DNA replication allows a chromosome to have a pair of offspring chromosomes and be passed onto the offspring cells.

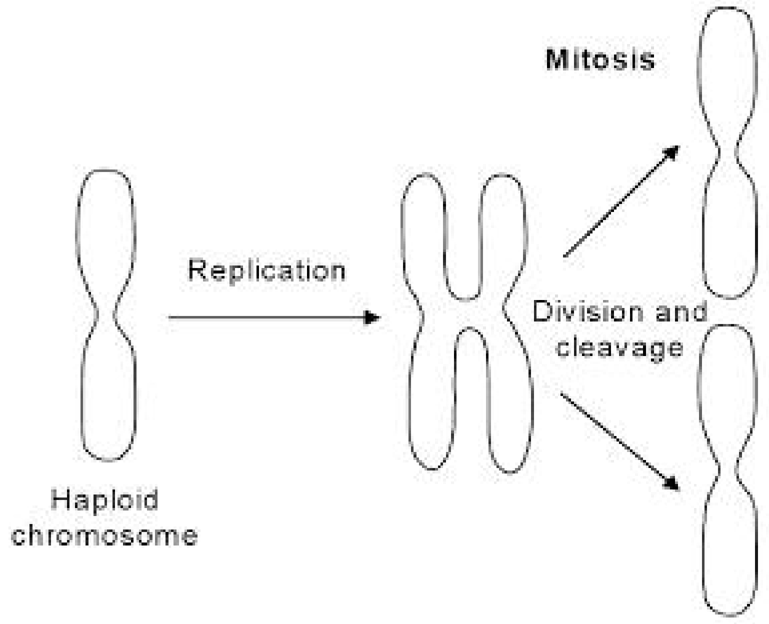


Figure 3.8: Asexual reproduction in haploids. The chromosome replicates itself, the cell nucleus is divided through a process named mitosis, and then the cell is divided into two identical progeny.

Sexual reproduction is the fusion of two *haploid gametes* (sex cells) to produce a single *diploid zygote* cell. An important aspect of sexual reproduction is that it involves *genetic recombination*; that is, it generates gene combinations in the offspring that are distinct from those in the parents. Sexually reproducing organisms have two sorts of cells: *somatic* (body) cells, and *germ* (sex) cells. All somatic cells reproduce by a process called *mitosis* that is a process of nuclear division followed by cell division. Figure 3.9 illustrates the process of sexual reproduction.

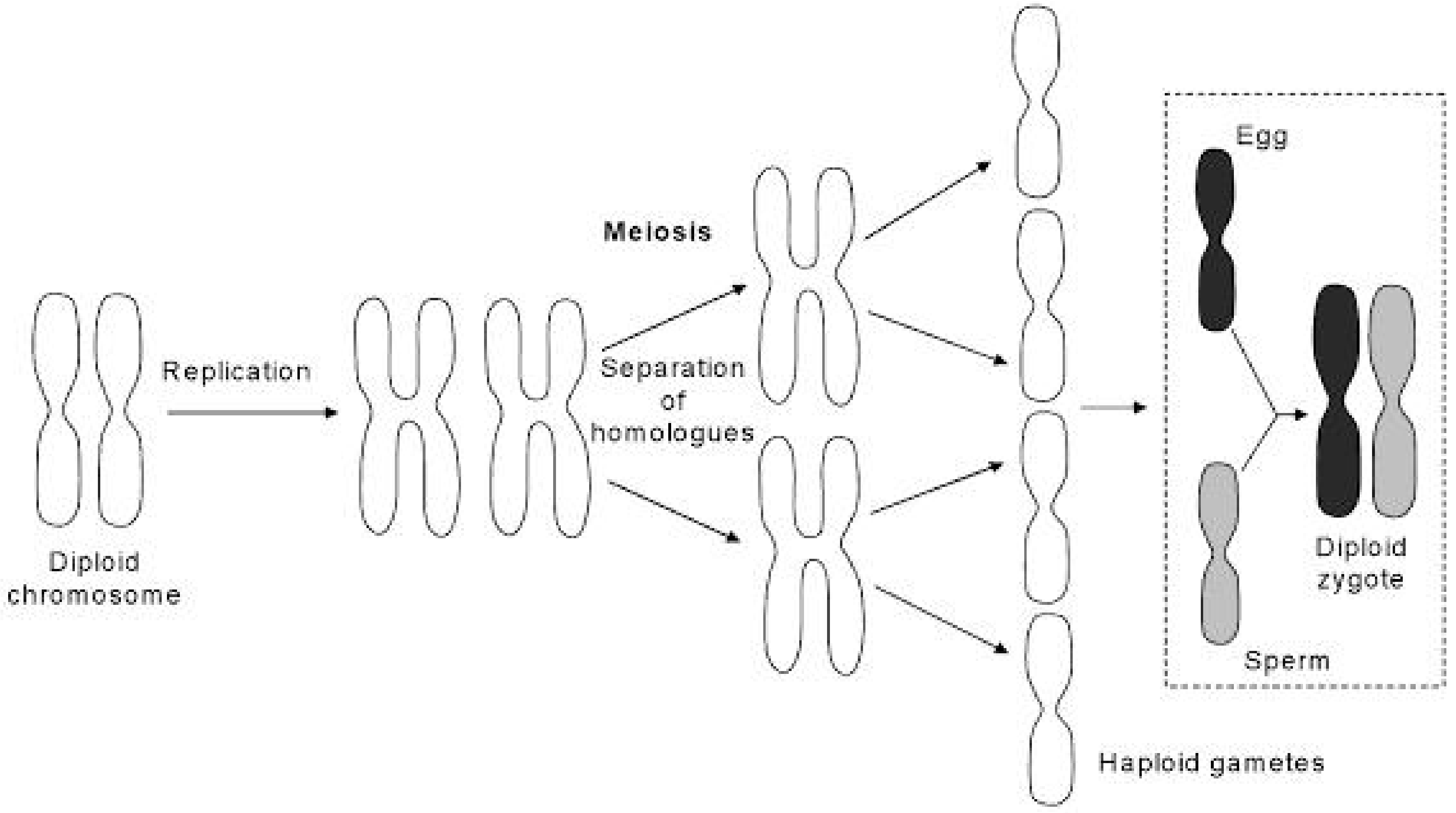


Figure 3.9: Sexual reproduction. A diploid chromosome replicates itself, then the homologues are separated generating haploid gametes. The gametes from each parent are fused to generate a diploid zygote.

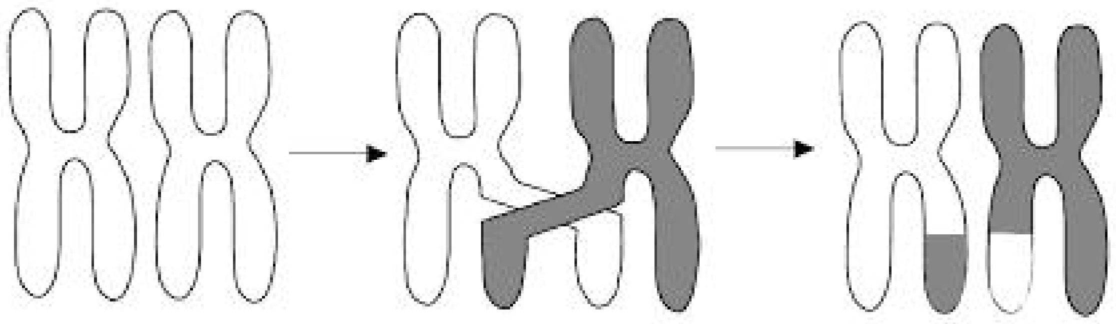


Figure 3.10: Crossing over between two loci in a cell undergoing the first meiotic division. Of the four chromatids, two will have new combinations and two will retain the parental combination of alleles.

In the classical view of the meiosis process in sexual reproduction, homologous chromosomes first undergo the formation of a very tight association of homologues, and then the reciprocal physical exchange of chromosome segments at corresponding positions along pairs of homologous chromosomes, a process termed *crossover* (Russel, 1996). Crossing-over is a mechanism that can give rise to *genetic recombination*, a process by which parents with different genetic characters give birth to progeny so that genes are associated in new combinations. Figure 3.10 depicts the crossing-over process.

The differences among organisms are outcomes of the evolutionary processes of *mutation* (a change or deviation in the genetic material), *recombination* or *crossover* (exchange of genetic material between *chromosomes*; see Figure 3.10), and *selection* (the favoring of particular combinations of genes in a given environment). With the exception of gametes, most cells of the same eukaryotic organism characteristically have the same number of chromosomes. Further, the organization and number of genes on the chromosomes of an organism are the same from cell to cell. These characteristics of chromosome number and gene organization are the same for all members of the same species. *Deviations* are known as *mutations*; these can arise spontaneously or be induced by chemical or radiation mutagens. Several types of mutation exist, for instance point mutation, deletion, translocation, and inversion. Point mutation, deletion and inversion are illustrated in Figure 3.11.

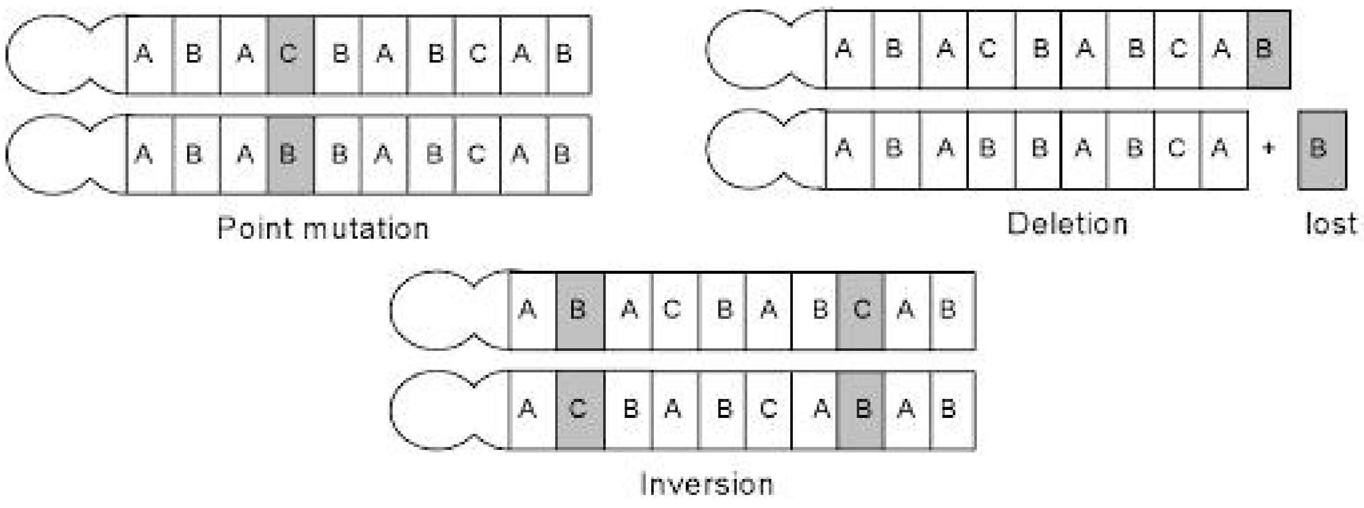


Figure 3.11: Some types of chromosomal mutation, namely, point mutation, deletion, and inversion.

3.4.4. Evolution as an Outcome of Genetic Variation Plus Selection

So far we have seen the two types of reproduction, sexual and asexual, and some of the main mechanisms that alter the genetic makeup of a population of individuals, emphasizing crossover and mutation. It still remains to discuss the process by which these altered individuals survive over the generations.

Populations of individuals change over time. The number of individuals may increase or decrease, depending on food resources, climate, weather, availability of breeding areas, predators, and so forth. At the genetic level, a population may change due to a number of factors, such as mutation and selection. These processes not only alter allele frequencies, but also result in changes in the adaptation and diversity of populations, thus leading to the evolution of a species (Gardner et al., 1991).

The viability and fertility of an individual are associated with *fitness*, a term that is used to describe the overall ability of an organism to survive and reproduce. In many populations, survival and reproductive ability are variable traits. Some individuals die before they have a chance to reproduce, whereas others leave many progeny. In a population of stable size, the average number of offspring produced by an individual is one.

Variation in fitness is partially explained by the underlying genetic differences of individuals. The crossing-over of parental genetic material and mutation can increase or decrease fitness, depending on their effects on the survival and reproductive capabilities of the individuals. Thus, genetic recombination and mutation can create phenotypes with different fitness values. Among these, the most fit will leave the largest number of offspring. This differential contribution of progeny implies that alleles associated with superior fitness will increase in frequency in the population. When this happens, the population is said to be undergoing *selection*.

As Darwin made a series of observations of domestic animals and plants, and also those existing free in nature, he used the term natural selection to describe the latter in contrast to men's selection capabilities of domestic breeds. To our purposes, the more general term *selection* is assumed in all cases, bearing in mind that selection under nature has been originally termed natural selection, and selection made by men has been sometimes termed artificial selection.

Under the evolutionary biology perspective, *adaptation* is the process by which traits evolve making organisms more suited to their immediate environment; these traits increase the organisms' chances of survival and reproduction. Adaptation is thus responsible for the many extraordinary traits seen in nature, such as eyes that allow us to see, and the sonar in bats that allow their guidance through the darkness. Note however, that, more accurately speaking, adaptation is a result of the action of both, variation and selection. Variation by itself does not result in adaptation; there must be a way (i.e., selection) of promoting the maintenance of those advantageous variations.

S. Wright (1968-1978) introduced the concept of *adaptive landscapes* or *fitness landscapes*, largely used in evolutionary biology. In his model, each population of a *species* (reproductively isolated group) is symbolized by a point on a *topographic map*, or *landscape*. The contours of the map represent different levels of adaptation to the environment (fitness). Populations at high levels (peaks) are more adapted to the environment, and populations at low levels (valleys) are less adapted. At any one time, the position of a population will depend on its genetic makeup. Populations with alleles that improve fitness will be at a higher peak than populations without these alleles. Consequently, as the genetic makeup of a population changes, so will its position on the adaptive landscape. Figure 3.12 depicts a landscape representing the different levels of adaptation of the populations in relation to the environment.

The adaptive (fitness) landscape corresponds to the response surface discussed in Section 3.2.1 in the context of problem solving via search in a search space. Note that, under the evolutionary perspective, the search performed is for individuals with increased survival and reproductive capabilities (fitness) in a given environment (fitness landscape).

A *niche* can thus be defined as the region consisting of the set of possible environments in which a species can persist; members of one species occupy the same ecological niche. In natural ecosystems, there are many different ways in which animals may survive (grazing, hunting, on water, etc.), and each survival strategy is called an ecological niche. However, it is generally recognized that the niche of a single species may vary widely over its geographical range. The other fundamental concept of niche was proposed by Elton (1927) "The niche of an animal means its place in the biotic environment, its relations to food and enemies;" where the term *biotic* refers to life, living organisms. Thus, niche in this case is being used to describe the role of an animal in its community (Krebs, 1994).

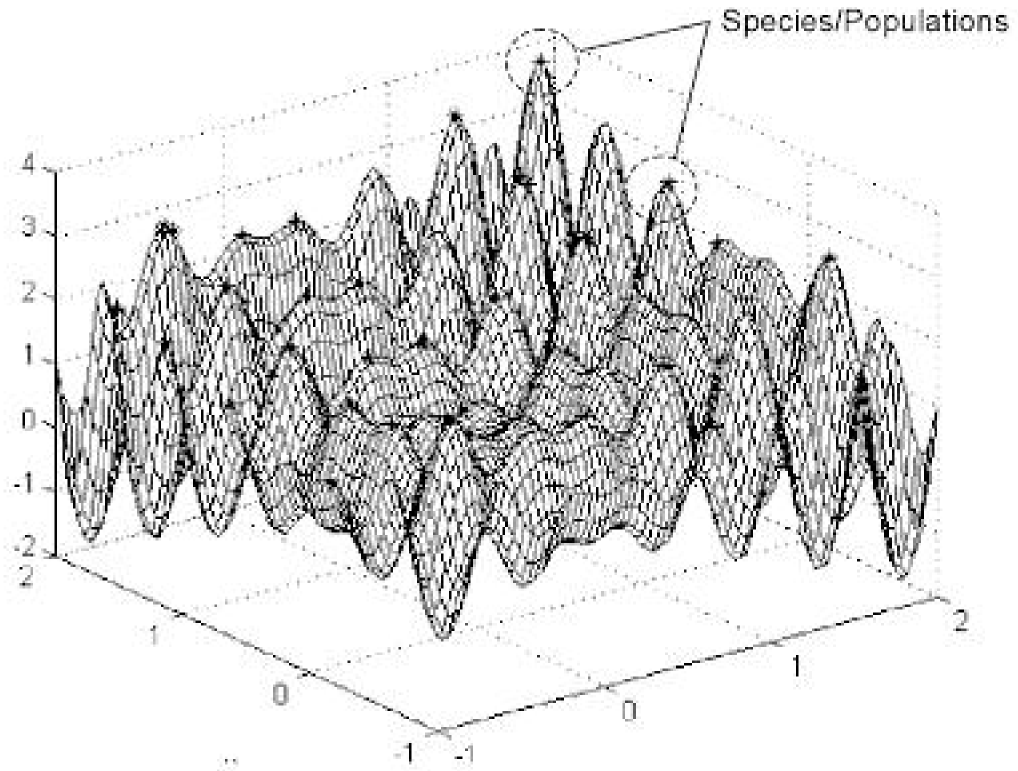


Figure 3.12: An example of an adaptive landscape. The topographic map (landscape or surface) corresponds to the different levels of adaptation of the populations (points in the landscape) to the environment. The populations or individuals at each peak are assumed to be reproductively isolated, i.e., they only breed with individuals in the same peak, thus forming species inhabiting distinct niches.

It has been discussed that evolution is an outcome of genetic variation plus selection. In order for continuing evolution to occur, there must be mechanisms that increase or create genetic variation and mechanisms that decrease it. We have also seen that recombination and mutation cause differences among (variations in) organisms. Other two important mechanisms of evolution are the so-called *genetic drift* (chance fluctuations that result in changes in allele frequencies) and *gene flow* (spread of genes among populations via *migration*). It is known that selection and genetic drift decrease variation, while mutation, recombination, and gene flow increase genetic variation (Colby, 1997).

Natural selection sifts through the genetic variations in the population, preserving the beneficial ones and eliminating the harmful ones. As it does this, selection tends to drive the population uphill in the adaptive or fitness landscape. By contrast, the random genetic drift will move the population in an unpredictable fashion. The effect of all these mechanisms (mutation, recombination, genetic drift, gene flow, plus selection) will bring the population to a state of 'genetic' equilibrium, corresponding to a point near or at a peak on the adaptive landscape. Actually, the population will hover around a peak because of fluctuations caused by genetic drift. Note also, that, under nature, the environment is constantly changing, hence the population is also adapting to the new landscape resultant from the new environment, in a never-ending process of variation and selection.

3.4.5. A Classic Example of Evolution

A classic example of evolution comes from species that live in disturbed habitats. In the particular example of the evolution of melanic (dark) forms of moths, human activity has altered the environment and there has been a corresponding change in the species that inhabit this environment. The peppered moth, *Biston betularia*, is found in wooded areas in Great Britain, where it exists in two color forms, light and dark; light being the typical phenotype of this species. The difference between the two forms is believed to involve a single gene. Since 1850, the frequency of the dark form has increased in certain areas in England, in particular in industrialized parts of the country. Around heavily industrialized cities, such as Manchester and Birmingham, the frequency of the dark form has increased drastically from 1 to 90% in less than 100 years. In other areas of England, where there is little industrial activity, the dark form has remained very rare (Gardner et al., 1991).

The rapid spread of the dark form in industrialized areas has been attributed to natural selection. Both, light and dark forms are active at night. During the day, the moths remain still, resting on tree trunks and other objects in the woodlands. Since birds may find the moths and eat them during their resting period, camouflage is their only defense against predation. On white or gray tree bark, the light moths are protectively colored, especially if the bark is overgrown with lichens. However, in industrialized areas most of the lichens have been killed by pollution and the tree bark is oftenest darkened by soot. Such conditions offer little or no cover for the light moths, but make ideal resting spots for the dark

Evolutionary Systems

All biological systems result from an evolutionary process. The sophistication, robustness, and adaptability of biological systems represent a powerful motivation for replicating the mechanisms of natural evolution in the attempt to generate software and hardware systems with characteristics comparable to those of biological systems. More than 40 years ago, computer scientists and engineers began developing algorithms inspired by natural evolution (Rechenberg 1965; Fogel et al. 1966; Holland 1975) to generate solutions to problems that were too difficult to tackle with other analytical methods. Evolutionary computation rapidly became a major field of machine learning and system optimization and, more recently, it spread into the area of hardware design by exploiting new technologies in reconfigurable electronic circuits, computer-assisted manufacturing, material production tech nologies, and robotics. Before delving into the features of natural and artificial evolution, we wish to emphasize that there is a major, and often neglected, difference between these two processes. Whereas natural evolution does not have a predefined goal and is essentially an open-ended adaptation process, artificial evolution is an optimization process that attempts to find solutions to predefined problems. Therefore, while in natural evolution the fitness of an individual is defined by its reproductive success (number of offspring), in artificial evolution the fitness of an individual is a function that measures how well that individual solves a predefined problem. The consequence of this difference is that artificial evolution, as it is formulated today, cannot possibly hope to match the diversity and creativity generated by natural evolution because, by definition, artificially evolved systems will all tend to satisfy the predefined problem.

1.1 Pillars of Evolutionary Theory

Biology is making continuous progress in the description of the components that make up living organisms and of the ways in which those components work together. However, the ultimate explanation is to be found in the theory of natural evolution. As Dobzhansky (1973) put it, "nothing in biology makes sense except in the light of evolution." A bewildering number of books and articles have been written on the theory of natural evolution, but its foundations are rather simple and elegant.

POPULATION

DIVERSITY

HEREDITY

The theory of natural evolution rests on four pillars: population, diversity, heredity, and selection. The premise for evolution is the existence of a *population*, which here we will loosely define as a pool of two or more individuals. In other words, we cannot speak of evolution of a single organism. *Diversity* means that the individuals of the population vary from one another to some extent. Individual diversity, both within and between species, has been observed and described for thousands of years. *Heredity* indicates that individual characters can be transmitted to offspring through reproduction. The notion that individual characters are hereditary was suggested in the

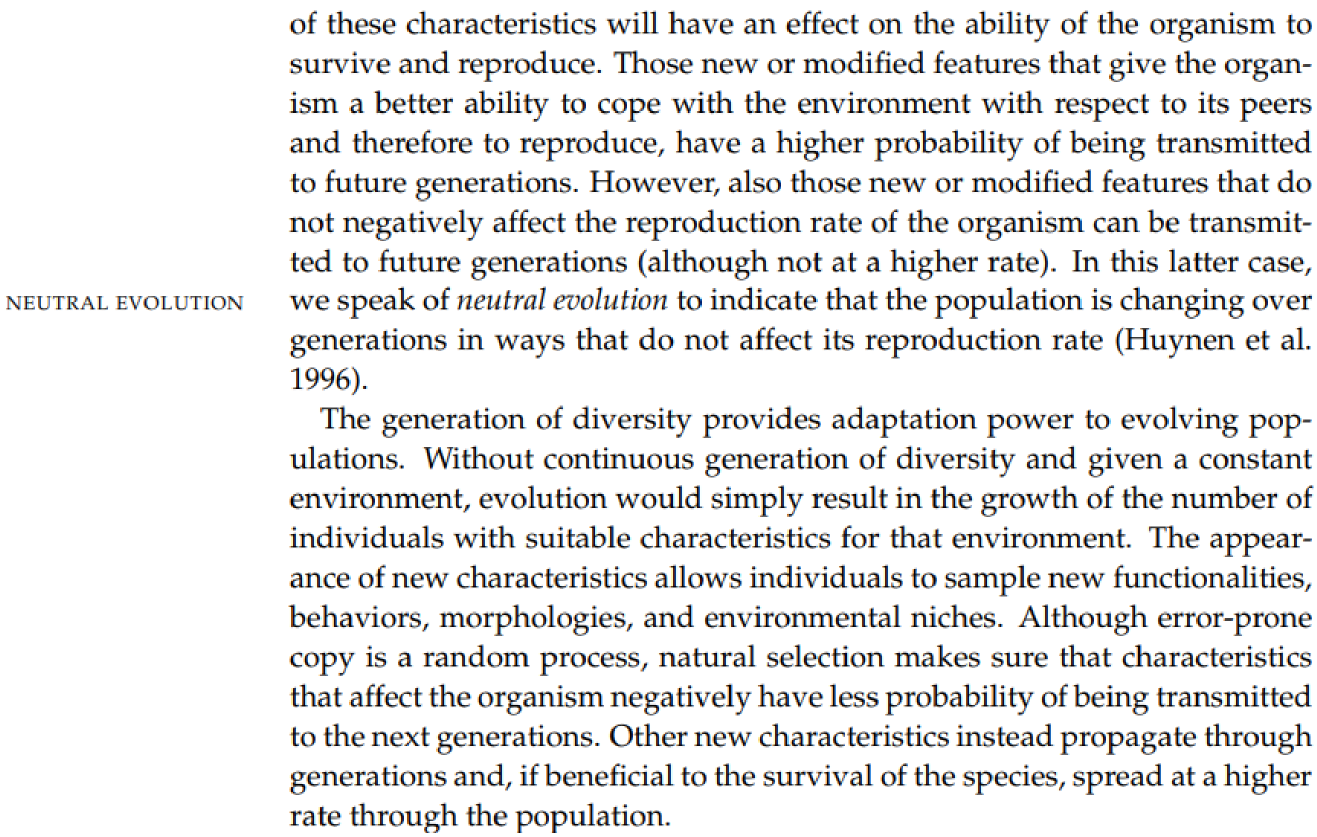
SELECTION

eighteenth century by Maupertuis (1753). *Selection* indicates that only part of the population is capable of reproducing and transmitting its characters to future generations. Natural selection, put forward by Darwin (1859) and Wallace (1870) in the nineteenth century, is based on the premise that individuals tend to make several offspring and that not all of them may reproduce. The selection of individuals that can reproduce is not completely random, but regulated by environmental constraints. For example, if an environment contains too many individuals for the available food , those individuals that are better or faster at gathering food will have a higher chance of survival and reproduction.

PROGRESS

Natural selection is the most debated, often misunderstood, and abused pillar of natural evolution. In the engineering community, it is commonly described as selection of the fittest; "fittest" is often associated with "best"; and selective reproduction of the best is often associated with progress. However, organisms are not always selected for how well they score individually. For example, some animal societies maintain a number of altruistic individuals that pay a cost in terms of reproduction for the good of their society. Furthermore, selective reproduction of the fittest does not necessarily imply progress in the two common meanings of the word. One meaning of progress is that new individuals are better than previous ones. However, natural selection has no comparative memory. The only way in which selection operates is here and now. Individuals are selected against the environment and/or their peers at a specific point in space and time. For example, prey at a given point in evolutionary time may be very good at escaping the current generation of coevolving predators they are confronted with, but may not be better than prey of previous generations when predators were different. In general, any change in the environment over time creates different selection conditions and therefore does not guarantee that recent generations are comparatively better than older generations selected in different environmental conditions. The other meaning of progress is that individuals tend to become better in the future. This notion of progress implies a final goal or optimal state of matter. However, natural evolution has no goal, no plan, and no end. In the best case, the combination of variety, heredity, and selection can increase *today* the rate of individuals whose parents had more suitable characteristics *yesterday*.

Where does population diversity come from? From an evolutionary perspective, generation of diversity takes place during reproduction. Offspring are copies of selected parents with small variations. This error-prone copy process can generate individuals with new or modified characteristics. Some



NEUTRAL EVOLUTION

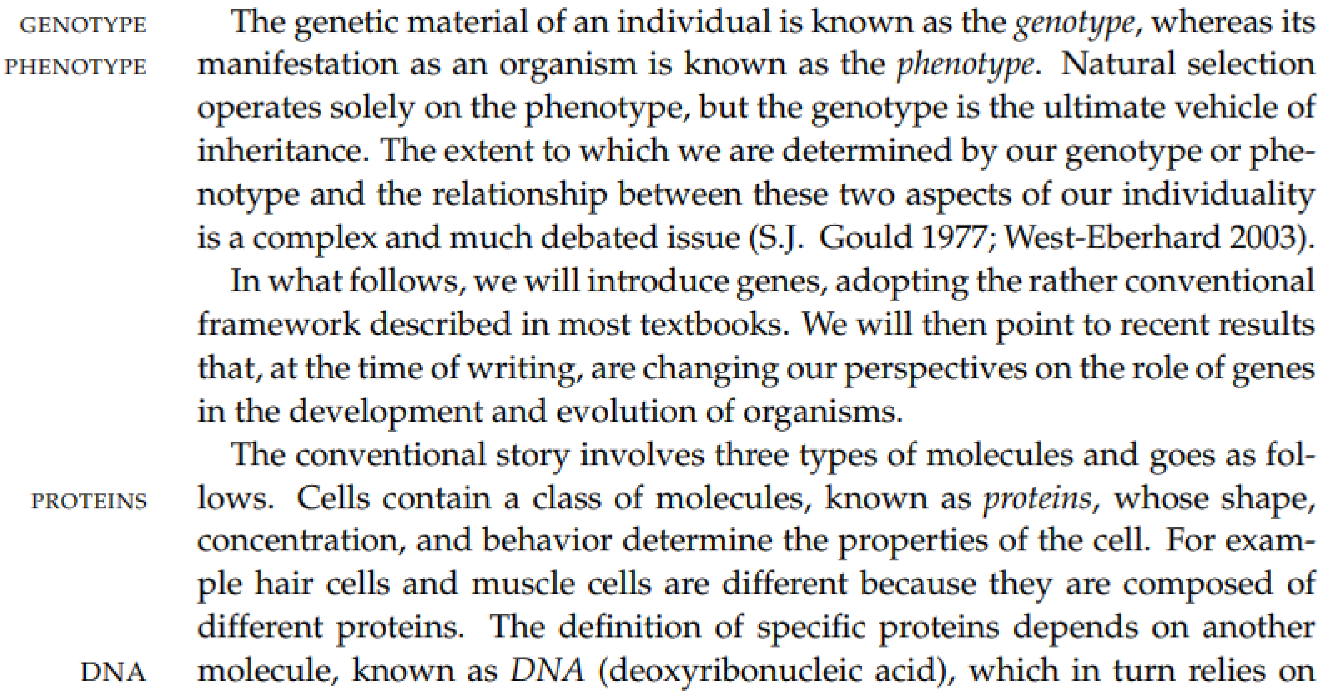
of these characteristics will have an effect on the ability of the organism to survive and reproduce. Those new or modified features that give the organism a better ability to cope with the environment with respect to its peers and therefore to reproduce, have a higher probability of being transmitted to future generations. However, also those new or modified features that do not negatively affect the reproduction rate of the organism can be transmitted to future generations (although not at a higher rate). In this latter case, we speak of *neutral evolution* to indicate that the population is changing over generations in ways that do not affect its reproduction rate (Huynen et al. 1996).

The generation of diversity provides adaptation power to evolving populations. Without continuous generation of diversity and given a constant environment, evolution would simply result in the growth of the number of individuals with suitable characteristics for that environment. The appearance of new characteristics allows individuals to sample new functionalities, behaviors, morphologies, and environmental niches. Although error-prone copy is a random process, natural selection makes sure that characteristics that affect the organism negatively have less probability of being transmitted to the next generations. Other new characteristics instead propagate through generations and, if beneficial to the survival of the species, spread at a higher rate through the population.

Again, evolutionary adaptation does not necessarily imply progress in the two meanings of the word described earlier. Natural evolution may simply increase diversity by continuously generating new organisms that occupy new environmental niches. Or, it may increase complexity by incrementally adding new features to previous ones, provided that previous features do not represent a cost for the organism, do not interact negatively with new features, or simply have a higher probability to be preserved than to be replaced by the error-prone copy mechanism. Considering the enormous explanatory power and relative simplicity of the basic tenets of evolutionary theory, we might expect to find in the literature a compact and universal model that formally describes the evolution of populations, something akin to the laws of thermodynamics or to Newton's laws of physics. In practice, the complexity of the factors that affect the mechanisms and dynamics of evolution has not yet been sufficiently understood to allow the development of a universal formalism. Nonetheless, several formal models have been developed to address specific issues, mainly in the field of population genetics. It is worth pointing out that the great majority of these formal models describe evolutionary phenomena in terms of their effect on the variation rate of the population size or of a given character of the evolving individuals. In other words, formal measures of evolution, if we may liberally call them so, describe frequencies of the occurrence of given characters, or of given types of organism, over generations. For example, these models predict that in a relatively stable environment the percentage of individuals with fitter characteristics will gradually grow until they dominate the population (Fisher 1930). These models do not address the notion of performance and progress in evolving populations, but only the change in proportion of organisms of a certain type.

The Genotype

So far, we have not yet explained how individual characters can be inherited and modified. In 1865 Mendel arrived at the conclusion that individuals reproduce by transmitting specific particles, now known as genetic material, to their own offspring. Recent progress in genetics (the discipline studying the structure and behavior of genes) and in functional genomics (the discipline studying the role of genes in organisms) has provided several clues to the molecular mechanisms and processes that support inheritance and variation. Although Darwin was probably not aware of Mendel’s conclusions when he formulated the theory of evolution, genetics has become an integral part of modern evolutionary theories.



GENOTYPE
PHENOTYPE

The genetic material of an individual is known as the *genotype*, whereas its manifestation as an organism is known as the *phenotype*. Natural selection operates solely on the phenotype, but the genotype is the ultimate vehicle of inheritance. The extent to which we are determined by our genotype or phenotype and the relationship between these two aspects of our individuality is a complex and much debated issue (S.J. Gould 1977; West-Eberhard 2003).

In what follows, we will introduce genes, adopting the rather conventional framework described in most textbooks. We will then point to recent results that, at the time of writing, are changing our perspectives on the role of genes in the development and evolution of organisms.

PROTEINS
DNA

The conventional story involves three types of molecules and goes as follows. Cells contain a class of molecules, known as *proteins*, whose shape, concentration, and behavior determine the properties of the cell. For example hair cells and muscle cells are different because they are composed of different proteins. The definition of specific proteins depends on another molecule, known as *DNA* (deoxyribonucleic acid), which in turn relies on

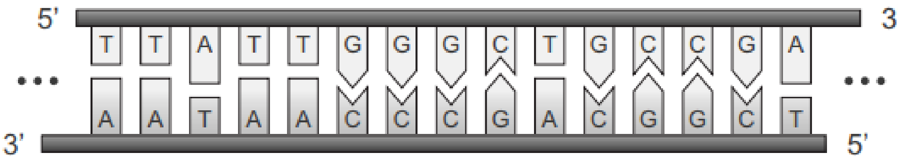


Figure 1.1 Structure of a piece of DNA molecule showing the two strands with matching nucleotides. The numbers 5 and 3 refer to the atomic structure of the molecule and affect the way in which the molecule sequence is translated into a protein. The order of translation always proceeds in the direction from 5′ to 3′.

proteins to become operative and on the mediation of a third type of molecule, known as *RNA* (ribonucleic acid), which is structurally similar to the DNA molecule.

RNA

The DNA is the genetic material that is transmitted over generations. It is often enclosed within the nucleus of the cell and all cells in the organism have the same genetic material. DNA molecules (figure 1.1) are long chains of complementary strands composed of four types of chemical units (*nucleotides* or bases): adenine (A), cytosine (C), guanine (G), and thymine (T). The two strands stick together because nucleotides can lock to each other: Adenine binds to thymine and cytosine binds to guanine. This specific binding means that the two DNA strands are perfectly complementary. If we find the sequence ACA on one strand, we know that the corresponding part of the complementary strand will display the sequence TGT (although some mismatch may occur very rarely).

NUCLEOTIDES

The genetic material is organized in several separated DNA molecules, called *chromosomes*. Furthermore, in several organisms chromosomes occur in pairs (also known as diploid organisms in contrast to haploid organisms). The two chromosomes in a pair are approximately homologous in the sense that corresponding areas produce proteins with a similar functionality in similar cells. The number of chromosome pairs and total length of the DNA molecules vary from species to species. For example, humans have 23 pairs of chromosomes totaling several hundreds of millions of nucleotides (International Human Genome Sequencing Consortium 2001). The redundant structure of the genetic material (two chromosomes, two strands) allows replication of DNA molecules during cell replication.

CHROMOSOMES

There are two types of cell replication: mitosis and meiosis (figure 1.2). *Mitosis* occurs during growth of the organism when a cell divides by producing a copy with the same number of chromosomes (23 times 2 in humans). During mitosis, the two strands of the 46 DNA molecules are separated and each

MITOSIS

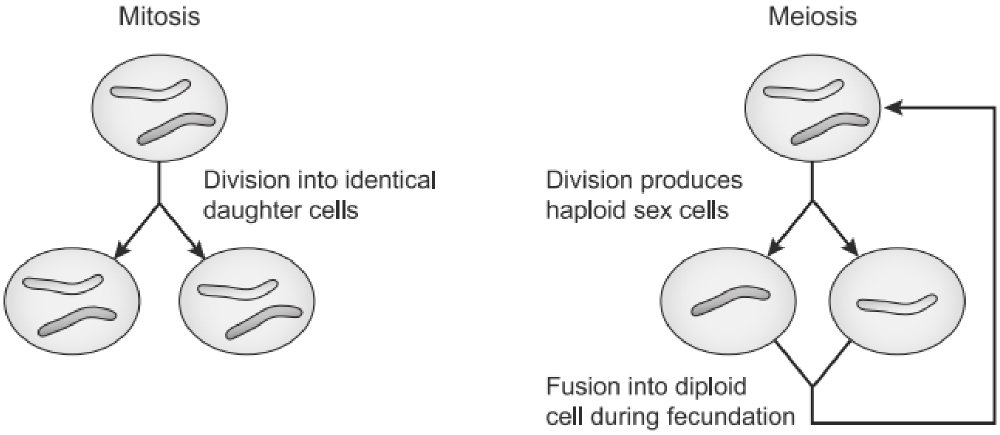

Mitosis
Division into identical daughter cells
Meiosis
Division produces haploid sex cells
Fusion into diploid cell during fecundation

Figure 1.2 Cell replication during mitosis and meiosis. For the sake of simplicity, only a pair of homologous chromosomes are shown.

MEIOSIS

strand goes to one cell. Each strand then rebuilds the missing strand by recruiting the complementary nucleotides. The process ends with two exact copies of the double-stranded DNA molecule, one for each cell. *Meiosis* occurs during the production of sex cells (sperm and eggs). Sex cells receive only one chromosome for each pair. In diploid organisms the pairs of chromosomes are recombined during fecundation of the egg cell (containing the set of chromosomes from the mother) by the sperm cell (containing the set of chromosomes from the father). Although the chromosomes from the mother and father sex cells are homologous, their sequences may be slightly different and produce different proteins for the same functionality. This may result in the expression of features that belong either to the mother or to the father.