# Physiological Systems Modeling, Simulation, and Control

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# Handbook of Research on Biomedical Engineering Education and Advanced Bioengineering Learning:

## 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.

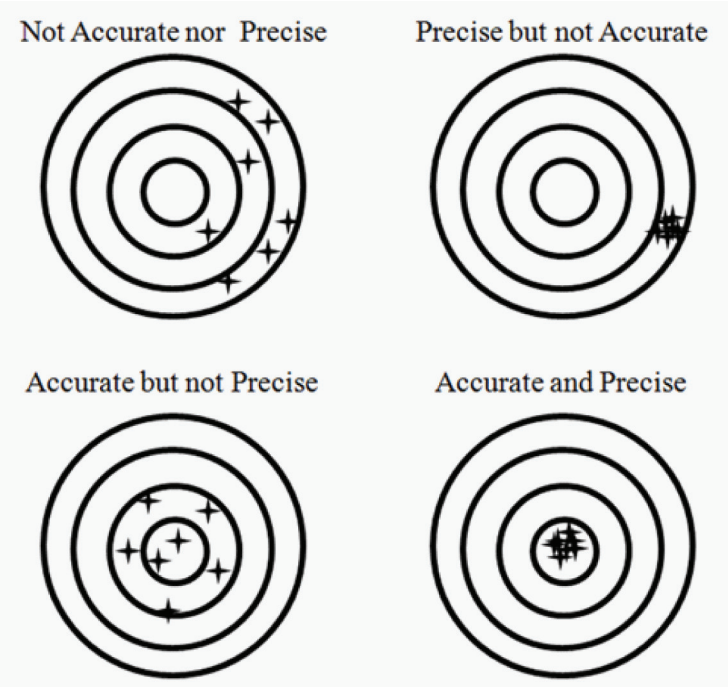
Various factors complicate the choice of biological input and output (I/O) measurands. First, most of the parameters that are measured in practice are quite small as compared with non-medical parameters in most industries. For example, most voltages are in the micro-volt range, and the signals are in 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*



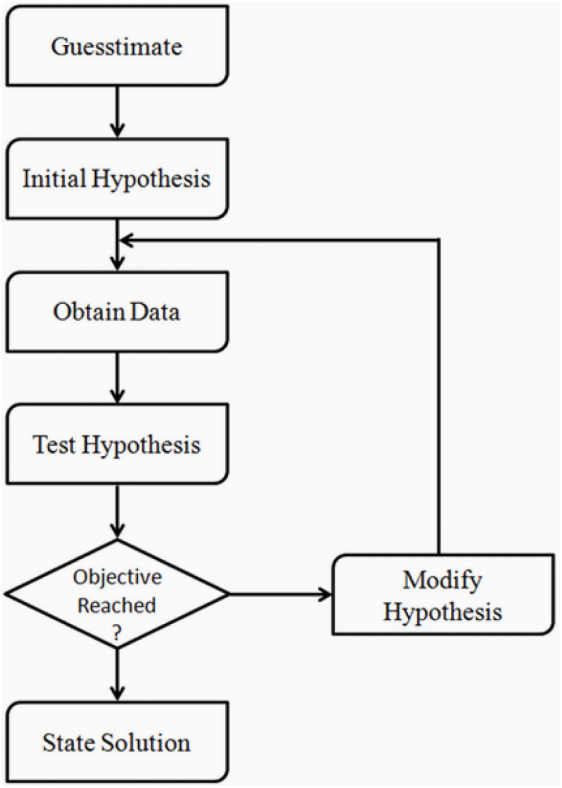
refining the model using new data continues until a satisfactory model is obtained. Typically, a quantitative criterion is used to test the goodness of fit between the model and the data. One of the characteristics of a good model is how well it predicts the future performance of the physiological system.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

*Figure 2. Model refinement graph*




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.

## 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 20$^{th}$ 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).

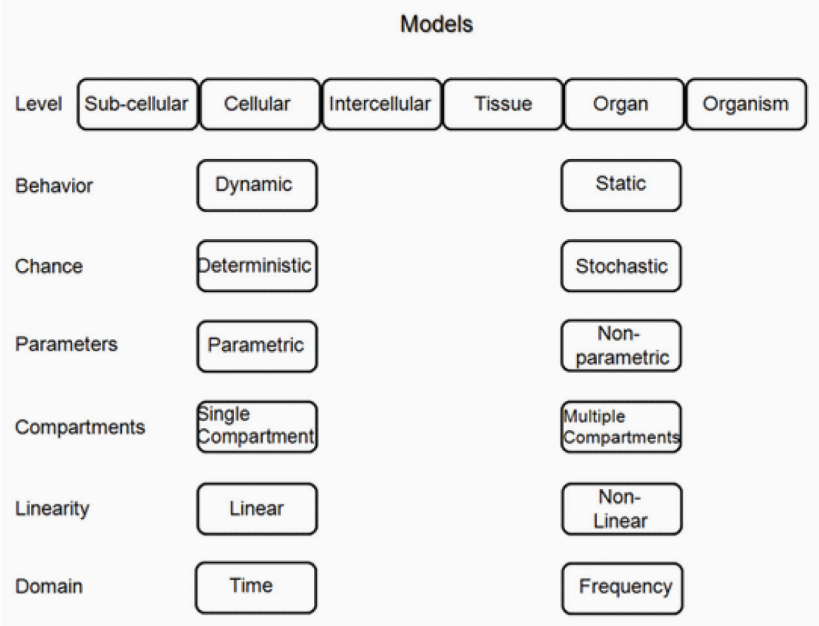
## 17.6. CLASSIFICATION OF MODELS

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.

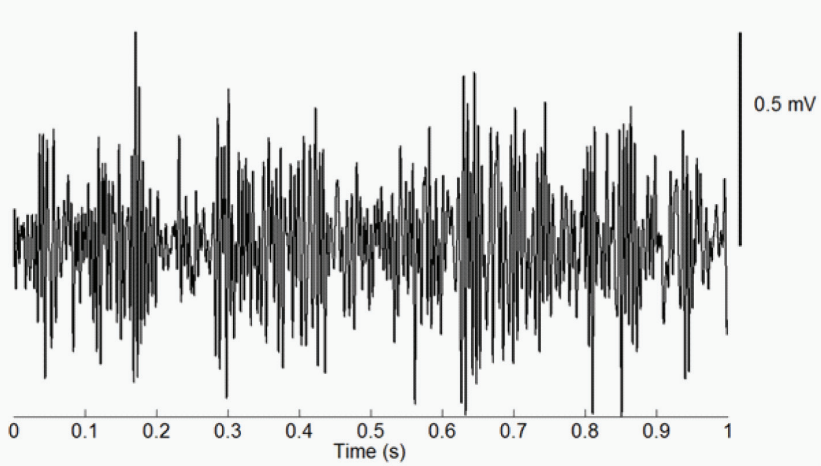
### 17.6.3. Applied Examples

**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:

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

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

$$p = \frac{\bar{n}}{N} \tag{17.4}$$

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

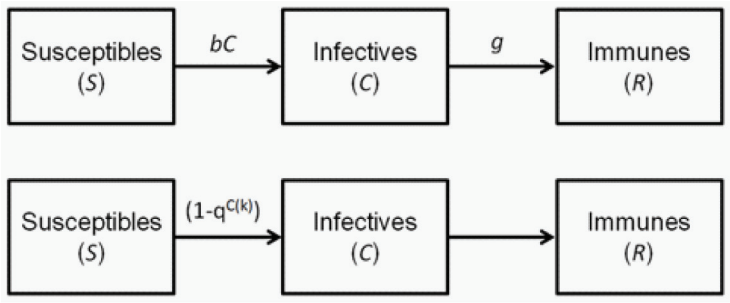
$$\begin{aligned} C(k+1) &= S(k)(1 - q^{C(k)}) \\ S(k+1) &= S(k) - C(k+1) \\ R(k+1) &= R(k) + C(k) \end{aligned} \tag{17.5}$$

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.

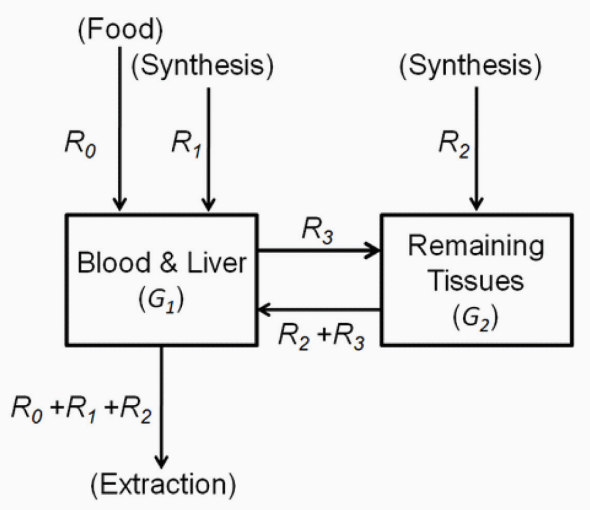
## 17.7.4. Applied Example

**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,

$$Q_1'(t) = \frac{R_2 + R_3}{G_2} Q_2(t) - \frac{R_0 + R_1 + R_2 + R_3}{G_1} Q_1(t)$$
$$Q_2'(t) = \frac{R_3}{G_1} Q_1(t) - \frac{R_2 + R_3}{G_2} Q_2(t) \tag{17.7}$$

*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, $\tau$ 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

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

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

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

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

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

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 $\tau$, either preceding or following a linear dynamic system, moves the IRF $\tau$ 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 $\tau$, 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

$$y(t) = c_1e^{-j\omega t} + c_2e^{j\omega t} + c_3e^{p_1 t} + c_4e^{p_2 t} + ... \tag{17.18}$$

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

$$y_{ss}(t) = c_1e^{-j\omega t} + c_2e^{j\omega t} \tag{17.19}$$

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 $\omega$ 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 $\omega$.
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 $\omega$.
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 $h(\tau)$ with the corresponding frequency response function $H(j\omega)$. 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

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

where, $S_{xx}(j\omega)$ and $S_{yy}(j\omega)$ are the input and the output power spectra, and $S_{xy}(j\omega)$ is the input-output cross spectrum. The gain portion of the system frequency response may be estimated from the input and output power spectra as

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

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:

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

$S_{xy}$ 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:

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

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.

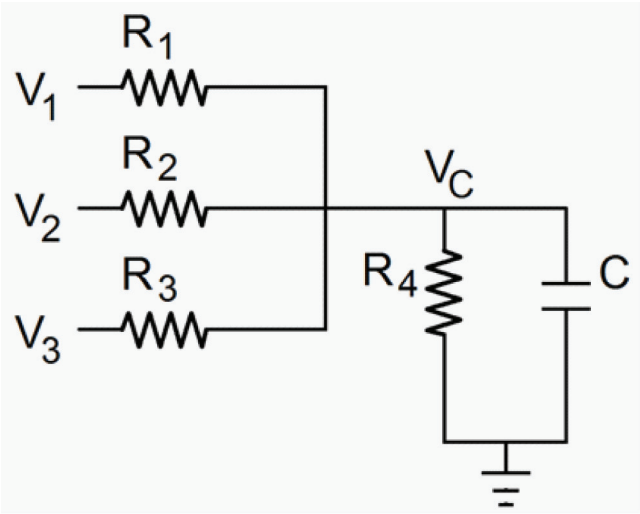
Let us consider the simplest dynamic linear model ("*leaky integrator*") of a nerve cell, depicted in Figure 7. The resistors $R_1$, $R_2$, $R_3$ represent the neuron's dendrites and the respective voltages $V_1$, $V_2$, $V_3$ are generated by the synapses from other neurons. The respective currents, $I_1$, $I_2$, $I_3$ 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*

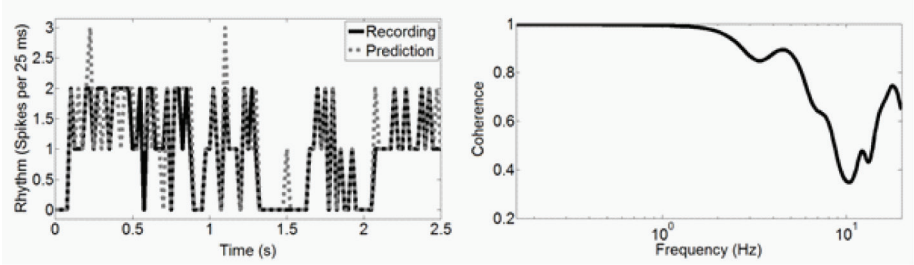



suggested that the STN sends the bursting pulse of spikes as a braking signal to reset the major basal ganglia output nuclei. This mechanism does not work right in abnormal situations, such as the PD. To be able to have a quantitative validation of the prediction of the model, the coherence between the 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 $n^{th}$ 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 $n^{th}$ order interactions also present in all other terms with kernels of order greater than n. That is the response to $n^{th}$-order interactions is defined by all kernels of order n or greater; it is not isolated in the $n^{th}$ 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 ($1^{st}$ 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

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

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.

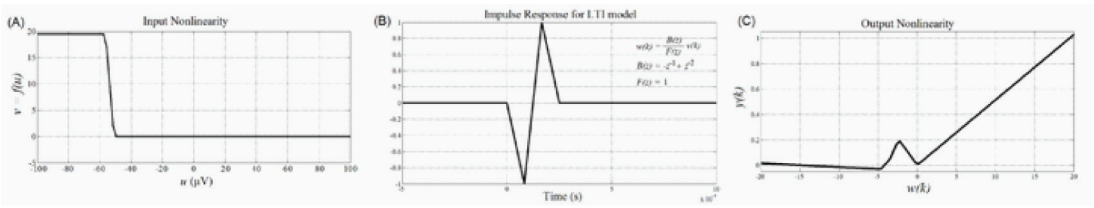
## 17.10. IDENTIFICATION OF PHYSIOLOGICAL CONTROL SYSTEMS

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, $\theta$. Then, for a specific parameter vector, $\theta_0$, the $y(t,\theta_0)=\mathbf{M}(\theta_0, u(t))$ 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, $\theta_0$, *exactly* represent the physical system, the objective of system identification is then to find a suitable model structure, **M**, and corresponding parameter vector, $\theta$, given measurements of input and output. The identified model will have a parameter vector, $\hat{\theta}_0$, 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, $\hat{\theta}_0$, 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 $\Phi$ 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

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

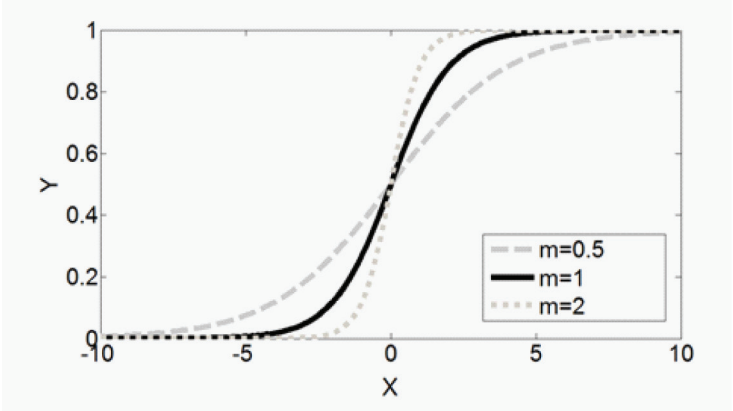
where, $n$ is the number of neurons that give their outputs to the neuron, and $w_i$ is the synaptic weight from presynaptic neuron $i$ to the postsynaptic neuron. Equations 17.40 and 17.41 denote that the output of an artificial neuron depends on its inputs only and does not depend on time; hence, the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



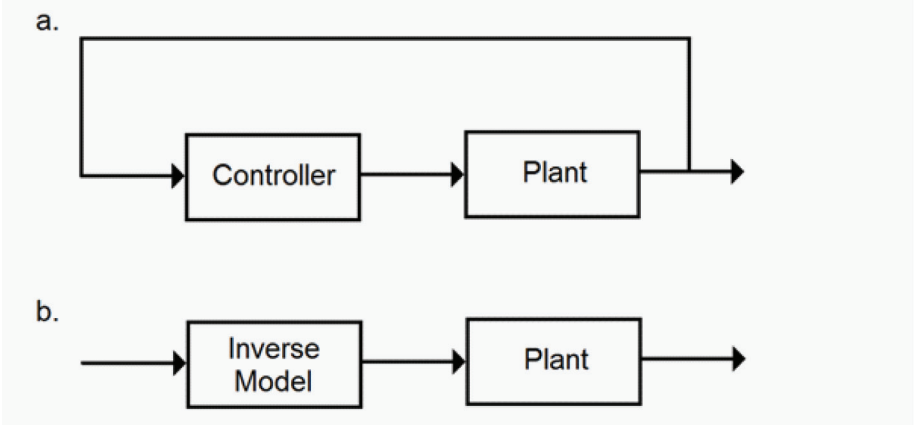
Not all learning algorithms, used in practice, include all those parameters. For instance, a Hebbian learning algorithm changes the weights, $w_{ij}$, in proportion to the product of the presynaptic activation, $a_i$, and the postsynaptic activation, $a_j$. Another class of learning algorithms that is 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

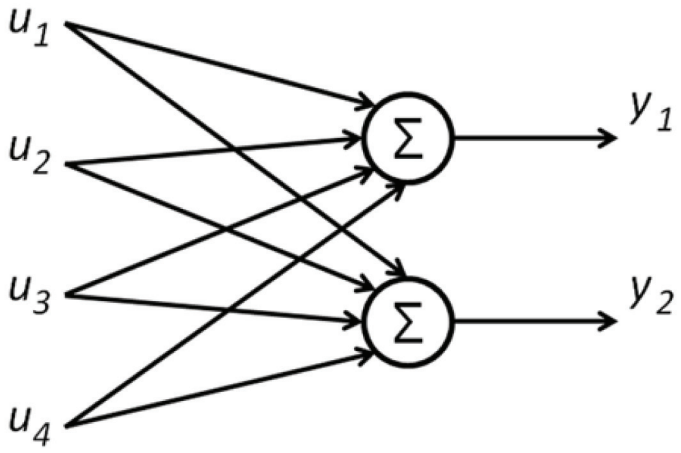
$$w_i = \varepsilon \sum_{\lambda=1}^{L} x_i^{\lambda} y_i^{\lambda}$$

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.

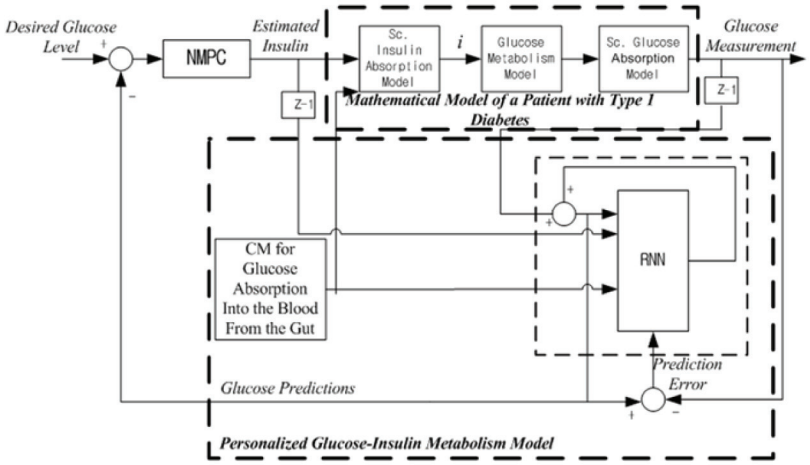
*NMPC*: The NMPC uses the personalized glucose-insulin metabolism model, which provides estimates of the future glucose levels. The NMPC is based on an optimizer, which computes at each sample time future control movements based on the minimization of an appropriate cost function. Particularly, at each 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*




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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