# Chapter 2. Mathematical Modeling and Computer Simulation

Once upon a time, man started to use models in his practical activity. Modeling continues to play a very important role in studying natural phenomena and processes as well as helping to create modern engineering systems. Additionally, modeling is used in biology and medicine to find the mechanisms of function and malfunction concerning the organs of living organisms at both the micro and macro level.

Generally, a model has been defined [1] as the reconstruction of something found or created in the real world, a simplified representation of a more complex form, process, or idea, which may enhance **understanding** and facilitate **prediction**. The object of the model is called the **original**, or **prototype system**.

The model and the original may have the same physical nature; such models are called **physical models**. Correct physical models must satisfy the criteria of similarity, which include not only the conditions of geometrical similarity but also similarity of other characteristics (for example: temperature, strength of electromagnetic field, etc.). Physical models have been widely used in engineering and biomedicine. Examples include the testing of various civil constructions for seismic stability, testing the aero-dynamic characteristics of new aircraft and rockets in wind tunnels, and experimental studies on animals (organ, tissue, and cell) considered as a prototypes for human beings.

However, in scientific research this type of modeling studies is complemented with another modeling approach, which is based on the development of mathematical descriptions of the behavior of the prototype system under investigation. These descriptions are called mathematical models. The results are expected to be obtained by using existing mathematical methods (which give the solution in closed form mostly for very simplified cases) or by computer simulation using powerful serial or parallel supercomputers.

In this chapter we present definitions and terminology, classification of mathematical models, general assumptions accepted in mathematical modeling, and some considerations about mathematical models of direct analogy (see also Appendix) and computer simulations.

## 2.1. Mathematical modeling

The place of mathematical modeling among the other methods of scientific investigation [2] is shown schematically in Fig. 1.



Fig. 1 Schematic representation of different modeling approaches

Mathematical models represent a mathematical description of the original, based on known general laws of nature (First Principles) and experimental data. The wellknown fact that the systems of different physical natures have the same mathematical descriptions led to a special type of mathematical models: models of direct analogy. The tremendous advancements in computer hardware and software stimulated the wide use of mathematical models, especially because most of the new problems, particularly in physiology, are nonlinear and, thus, their solutions cannot be obtained analytically in closed form.

Mathematical modeling facilitates the solution of three major problems for a prototype system: analysis, synthesis and control. The characteristic of these problems (see [3]) is given in Fig. 2 and Table 1.



Fig. 2 The cause-and-effect relation between excitation, E, and, response, R as they relate to the system S

Problems can be classified according to which two of the items E, S, R are given and which is to be found. E represents excitations, S the system, and R the system's responses.

Type of Problem	Given	To find
Analysis (direct)	E, S	R
Synthesis (design identification)	E, R	S
Instrumentation (control)	S, R	Е

Table 1. General classification of the problems

The analysis problem is sometimes referred to as the direct problem, whereas the synthesis and control problems are termed as inverse problems. A direct problem generally has a unique solution. For example, if the Noble mathematical model of Purkinje fiber [4] is used, we obtain only one action potential shape in response to a specified stimulus for given cell parameters. In contrast, the inverse problem always gives an infinite number of solutions. To find a single solution additional conditions and constraints must be specified separately. An example of this is found in the modeling of  $Ca^{2+}$  induced  $Ca^{2+}$  release mechanisms from the cardiac cell sarcoplasmic reticulum (SR).

The spectrum of mathematical models can be constructed based on our prior knowledge of the prototype system (see Fig. 3 taken from [3] and reflecting the situation in the year 1980). The darker the color, the more restricted our knowledge about the system, and the more qualitative the simulation results. As our knowledge of prototype systems progresses, some parts of this spectrum became brighter and the possibility of obtaining quantitative results increases.



Fig. 3 Motivations for modeling [3] showing the shift from quantitative models (light end of the spectrum) to qualitative models (dark end)

#### 2.1.1. Deductive, inductive and combined mathematical models

In cases when there is enough knowledge and insight about the system, the deductive approach is used for model formulation. Deduction derives knowledge from known principles in order to apply to them to unknown ones; it is reasoning from the general to the specific. The deductive models are derived analytically (from first principles), and experimental data is used to fill in certain gaps and for validation. The alternative to deduction is induction. Generally, induction starts with specific information in order to infer something more general. An induction approach in biomedicine is fully based on experimental observations and has led to the development of numerous phenomenological models (e.g. Wiener and Rosenbluth [5], Krinski [6], Moe [7] models of the cardiac cell). In most practical modeling situations of the heart processes, both deductive and inductive approaches are required. The gate variable equations introduced by Hodjkin-Huxley [8], derived from the cell-clamp experiments, are an example of an inductive approach, whereas the application of Kirchoff's law to the current balance through the cell membrane is an indicator of the deductive approach used in formulating the action potential models for nerve and heart cells.

Using induction, we must accept the possibility that the model might not be unique and its predictions will be less reliable than when the model is purely deductive. Consequently, such a model will have less **predictive validity**; defined as the ability of the model to predict the behavior of the original system under conditions (inputs) which are different from that used when the model was originally formulated. Most of the mathematical models in biology are semiphenomenological. This means that part of the model derives from first principles (the laws of conservation of matter and energy) and the rest represent the appropriate mathematical interpretation of experimental findings.

#### 2.1.2. General assumptions used in mathematical modeling

Some simplified assumptions of general character are used in formulation of mathematical models. These assumptions relate to the general properties of the original system or phenomena under investigation:

- 1. *Separability* makes it possible to divide the entire system into subsystems and study them independently (with the possibility of ignoring some interactions). For example, typically AP models do not include cardiac cell metabolic processes. Practically, they remain unchanged during the time course of many cardiac cycles (changing over different time scales).
- 2. *Selectivity* makes it possible to select some restricted number of stimuli, which affect the system. The excitable membrane, for example, can be excited by current stimulus, changing the concentration of chemical substances inside the cell and changing the cell temperature.
- 3. *Causality* makes it possible to find cause and reason relationships. It is not enough to observe that variable 'y' always appears after variable 'x'. There is a possibility that they both are the result of the common reason-variable 'u'.

## 2.1.3. Mathematical Models of direct analogy

Let us consider, as examples, the mathematical models of two prototype systems with different physical natures. The first is an electrical lumped R, L, C circuit and the second is a mechanical mass, spring system with damping. Both are shown in Fig. 4.

The electrical circuit serves here as a mathematical model of direct analogy for mechanical systems and vice versa. With the development of powerful computers the role of direct analogy models becomes negligibly small. Nevertheless, historically, the FitzHugh-Nagumo simplified AP model, which is still widely used today [4], was derived for nerve cell study as a direct analogy for the Van der Pol equation of relaxation oscillation (see Chapter 5).



Fig. 4 Schematic diagram of electrical and mechanical oscillators.

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We will assume that the capacitor was initially charged to the voltage  $U_c(0) = U_{co}$  and mass m was initially displaced (from the equilibrium position x = 0) by the value  $x(0) = x_0$  and released with  $(dx / dt)_{t=0} = 0$ . We also suppose that these perturbations are small enough to consider that the parameters of the systems remain constant.

Kirhoff's law for electrical circuits and Newton's law for mechanical systems give respectively:

a. Balance of voltages in an electrical circuit:

$$U_{L} + U_{R} + U_{C} = 0; \text{ where: } U_{L} = L\frac{di}{dt}; \qquad U_{R} = iR; \qquad i = C\frac{dU_{C}}{dt}$$
  
Thus,  
$$\frac{d^{2}U_{C}}{dt^{2}} + \frac{R}{L}\frac{dU_{C}}{dt} + \frac{1}{LC}U_{C} = 0 \qquad (1)$$

b. Balance of forces in a mechanical system:

$$F_a + F_d + F_s = 0$$
, where:  $F_a = m \frac{d^2 x}{dt^2}$ ;  $F_d = k_d \frac{dx}{dt}$ ;  $F_s = k_s x$ ;

So,  

$$\frac{d^2x}{dt^2} + \frac{k_d}{m}\frac{dx}{dt} + \frac{k_s}{m}x = 0$$
(2)

The coefficients:  $R/L = 2\alpha_e$  in (1) and  $k_d/m = 2\alpha_m$  in (2) are the damping ratios; coefficients  $1/LC = (\omega_0^2)_e$  and  $k_s / m = (\omega_0^2)_m$  represent the squares of natural angular frequencies for systems (1) and (2) respectively.

The solutions of (1) and (2) depend on the ratio  $\alpha_e / (\omega_0)_e$  and  $\alpha_m / (\omega_0)_m$  correspondingly.

For initial conditions:

 $U_c(0) = U_{C0}$ ,  $(dU_c/dt)_{t=0} = 0$  and  $x(0) = x_0 (dx/dt)_{t=0} = 0$  and when parameters are such that  $\alpha_e < (\omega_0)_e$  and  $\alpha_m < (\omega_0)_m$  we get:

$$U_c = U_{c_0} e^{-\alpha} e^t \cos \omega_e t ; \qquad x = x_0 e^{-\alpha} m^t \cos \omega_m t$$
(3)

Here,  $\omega_e = \sqrt{(\omega_0)_e^2 - \alpha_e^2}$  and  $\omega_m = \sqrt{(\omega_0)_m^2 - \alpha_m^2}$ 

If  $\alpha_e = \alpha_m$  and  $\omega_{0e} = \omega_{0m}$ , then  $U_c(t) / U_{c0} = x(t) / x_0(t)$  and we can study the behavior of a mechanical system using an electrical circuit where it is easier to perform the measurements and change the system parameters.

Using this example it is possible to notice that both systems, when using the appropriate initial conditions, are mathematically described by the same differential equation:

$$\frac{d^2u}{dt^2} + 2\alpha \frac{du}{dt} + \omega_0^2 u = 0 \tag{4}$$

with appropriate initial conditions.

This equation represents the mathematical model for second order linear dynamic systems, independently of the physical nature of state variable u. In Table 2 we demonstrate the predictive ability of this model.

Table 2 The predicted behavior of a linear oscillator based on the mathematical model of direct analogy

	α > 0	α < 0	$\alpha = 0$
$\alpha^2 < \omega^2$	Sinusoidal oscillations with decreasing amplitude	Sinusoidal oscillations with increasing amplitude	sinusoidal oscillations with
$\alpha^2 > \omega^2$	Aperiodic process with decreasing amplitude	Aperiodic with increasing amplitude	constant amplitude

#### 2.1.4. Relaxation oscillations

Van Der Pol [10] discovered relaxation oscillations when he investigated the problem of stabilization of the amplitude of a carrier signal generated to broadcast radio translations. For this purpose he proposed the introduction of nonlinear positive damping proportional to the square of oscillation amplitude in addition to negative damping ( $\alpha$ <0) in the second order oscillator equation (4). The equation (4) with this modification attains the form:

$$\frac{d^2u}{dt^2} + 2\alpha(1 - \beta u^2)\frac{du}{dt} + \omega_0^2 u = 0$$
(5)

Here  $\beta$  is a coefficient usually chosen equal to one.

This is the Van Der Pol equation. Its solution for  $\alpha^2 < \omega_0^2$  and  $\alpha < 0$  is shown in Fig.5. Each time the amplitude *u* becomes more or less than unity the sign of the damping ratio changes respectively stabilizing the amplitude of oscillation.



Fig. 5 The solution of Van Der Pol equation for  $\mathcal{E} = \frac{\alpha}{\omega_0} = 0.1$ 

The relaxation oscillations were discovered as a solution of equation (5) for  $\alpha < 0$  and when  $\alpha^2 >> \omega_0^2$  (see Fig. 6)



Fig. 6 Relaxation oscillations,  $\mathcal{E} = \frac{\alpha}{\omega_0} = 10$ .  $T_{rel} = \frac{|\alpha|}{\omega^2} = RC$  approximately gives the period

of the relaxation oscillations.

Van Der Pol proposed using the sequentially connected relaxation oscillators as a model of the heart pacemaker system [10]. For this purpose each relaxation oscillation generator in the system is adjusted to the frequency of the corresponding pacemaker system node. The discovery of relaxation oscillations and the development of the phase-plan approach in the analysis of nonlinear dynamic systems facilitated the development of simplified nerve and heart cells models (see Chapter 5 for details)

### 2.1.5. Validation of mathematical models

Mathematical model validation involves the comparison of computer simulation results with those obtained on a real prototype of the simulated object, assuming the digital computer implementation introduces negligible additional errors. Model identification theory and methods have been developed for most linear and quasi-linear dynamical systems (in engineering and some in biology). These methods can be used to identify the parameters [11] and even structure of the model without and with the presence of noise [12]. One of the possible block diagrams of mathematical model validation and identification is presented in Fig. 7.



Fig. 7 Simplified block diagram for validation and identification of a mathematical model. E is a vector of chosen input excitation, R is the measured response, c is a vector of control parameters of the model, and {e} is a vector of mathematical model error.  $F\{e\}$  is a chosen error function (typically,  $F\{e\}=e^2$ ). Q[  $F\{e\}$ ] is a criterion of identification quality (typically mean square)

Unfortunately, most biological systems are significantly nonlinear dynamical systems (nerve, heart, vascular and skeletal muscle systems etc.), which cannot be reduced to linear or quasi-linear models without loss of their major functions. Moreover, for these systems even the most advanced experimental technology cannot provide the necessary data not only for full verification but also for formulation of some phenomenological part of the mathematical model (for example, there is no experimental data to formulate the mathematical model of spontaneous Ca release from SR). In these cases, some plausible hypothesis is usually formulated and the model predictions are considered correct until new contradictory experimental data is obtained. Similar situations have been encountered throughout the history of studying different natural phenomena.

### 2.2. Appendix: Lilly-Bonhoeffer Iron Wire Model

William Ostwald (1900) [13] was the first to notice that iron wire in nitric acid exhibits an electrochemical surface phenomenon quite similar to the action potential in nerves. Later the iron wire model was investigated experimentally by Lillie [14] and theoretically by Bonhoeffer [15]. The one-dimensional iron wire model is a mathematical model of direct analogy for nerve pulse propagation and is shown in Fig. 8.



Fig. 8. One-dimensional iron wire model.  $\varphi$  – *electrical potential* 

The iron wire, IW, is immersed in the vessel, V, filled with nitric acid of some concentration (electrolyte). The iron wire is covered with a thin film of iron oxide, shown by the dotted line in Fig. 8. After an application of a suprathreshold current stimuli, the difference of potential between the iron wire and electrolyte,  $\varphi$ , rises so that the thin film of iron oxide is destroyed at that place. Then, this potential accompanied by the destruction of the thin film begins to propagate toward the two ends of the wire, resembling the propagation of a nerve pulse along the nerve fiber.

The mathematical model can be derived from the current balance in the system:

$$C\frac{\partial\varphi}{\partial t} = i_f + i_a + i_{na} + i_{Iw} + i_{st} + \frac{1}{R}\frac{\partial^2\varphi}{\partial x^2}$$

Here:

arphi	the difference of potential between the iron wire and the electrolyte
C	capacitance of a double layer
T	time
$i_f$	thin film current $i_f = \begin{cases} (1-\alpha)k_2(\varphi) & \varphi \ge \varphi_{th} \\ \alpha k_2(\varphi) & \varphi < \varphi_{th} \end{cases}$
α	degree of activation $\frac{\partial \alpha}{\partial t} = -\frac{1}{Q}i_f$
Q	electrical charge per unit of film surface
$i_{IW}$	iron wire current $i_{IW} = k_1(\varphi)\alpha$
i <sub>na</sub>	nitric acid current; $i_{na} = [NA]k_3(\varphi)$
[NA]	the concentration of nitric acid near the surface of wire

$$\frac{\partial [NA]}{\partial t} = D \frac{\partial^2 [NA]}{\partial y^2}$$

I <sub>st</sub>	stimuli current
R	the longitudinal specific resistance of electrolyte
D	diffusion coefficient



Fig. 9 Shape of propagated potential

A grid of iron wires (see Fig. 10*a*) supports propagation of 2D waves. The first publication of this experimental system [16] exhibited both circular waves radiating from a point source of excitation and spiral waves rotating loosely about one endpoint of the wavefront (Fig. 10*b*). Figure 10a shows a 26×26 grid of iron wires (30cm × 30cm). Figure 10b shows pencil tracing at 1/8s intervals (left to right, then down arrow) taken from a photo of an iron wire grid when stimuli were introduced at  $S_1$ ,  $S_2$ ,  $S_3$ , and  $S_4$ . Spontaneous activity persisted for a while in the form of waves irregularly pivoting about moving points [16].

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Fig. 10. The 2D iron wire model. a: grid of iron wires. b: circular wave propagation.

A two dimensional closed surface (a ten-inch iron sphere) behaves in many ways like a human heart, even "fibrillating" when made too excitable or stimulated too frequently (see Smith and Guyton, [17]). This type of model was vigorously investigated for decades (see [18, 19] for a review). Fortunately for many in the West, this remarkable and thorough study published only in Japanese became known to English speakers thanks to a book published by the late outstanding scientist A. Winfree [20].

## 2.3. References

- 1. Bekey, G.A., Models and reality: some reflections on the art and science of simulation. Simulation, 1977. **29**: 161-164.
- Kogan, B.Y. and I.M. Tetelbaum, Modeling techniques in scientific research. Automation and Remote Control, 1979. 40: 917-924.
- 3. Karplus, W.J., The spectrum of mathematical models. Perspectives in Computing, 1983. 3: 4-13.
- 4. Noble, D., A modification of the Hodgkin-Huxley equations applicable to Purkinje fiber action and pace-maker potentials. J Physiol, 1962. **160**: 317-352.
- Wiener, N. and A. Rosenblueth, The mathematical formulation of the problem of conduction of impulses in a network of connected excitable elements, specifically in cardiac muscle. Arch. Inst. Cardiol. Mexico, 1946. 16: 205-265.
- 6. Krinsky, V.I., Fibrillation in excitable media. Problems in Cybernetics, 1968. 20: 59-80.

#### 2.3 References

- 7. Moe, G.K., W.C. Rheinboldt, and J.A. Abildskov, A computer model of atrial fibrillation. Am Heart J, 1964. 67: 200-220.
- Hodgkin, A.L. and A.F. Huxley, A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol, 1952. 117: 500-544.
- Moskalenko, A.V., A.V. Rusakov, and Y.E. Elkin, A new technique of ECG analysis and its application to evaluation of disorders during ventricular tachycardia. Chaos, Solitons & Fractals, 2008. 36: 66-72.
- 10. van der Pol, B. and J. van der Mark, The heartbeat considered as relaxation oscillations, and an electrical model of the heart. Archives Neerlandaises Physiologe De L'Homme et des Animaux, 1929. XIV: 418-443.
- 11. Rao, V.S.H. and N. Yadaiah, Parameter identification of dynamical systems. Chaos, Solitons & Fractals, 2005. 23: 1137-1151.
- 12. Tzypkin, Y.Z., Information Theory of Identification. 1995, Moscow: Nauka-Fizmatlit.
- 13. Ostwald, W., Periodische erscheinungen bei der auflosung des chrom in sauren. Zeit Phys Chem, 1900. **35**: 33-76 and 204-256.
- Lillie, R.S., The electrical activation of passive iron wires in nitric acid. J Gen Physiol, 1935. 19: 109-126.
- 15. Bonhoeffer, K.F., Modelle der nervenerregung. Naturwissenschaften, 1953. 40: 301-311.
- 16. Nagumo, J., R. Suzuki, and S. Sato. Electrochemical active network. in Notes of Professional Group on Nonlinear Theory of IECE. 1963. Japan.
- 17. Smith, E.E. and A.C. Guyton, An iron heart model for study of cardiac impulse transmission. Physiologist, 1961. 4: 112.
- 18. Suzuki, R., Electrochemical neuron model. Adv Biophys, 1976. 9: 115-156.
- MacGregor, R.J. and E.R. Lewis, Neural Modeling: Electrical Signal Processing in the Nervous System. 1977, New York: Plenum.
- 20. Winfree, A.T., The Geometry of Biological Time. 1980, New York: Springer-Verlag.