BIOLOGICAL SYSTEMS THEORY: AN INTRODUCTION

General definitions and mathematical modelling

Dourado, António, Full Professor
CISUC - Center for Informatics and Systems of the University of Coimbra
Department of Informatics Engineering
Pólo II- University of Coimbra
3030-290 Coimbra Portugal
dourado@dei.uc.pt, http://www.dei.uc.pt/~dourado

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António Dourado, Full Professor
CISUC - Center for Informatics and Systems of the University of Coimbra
Department of Informatics Engineering
Pólo II- University of Coimbra
3030-290 Coimbra Portugal
dourado@dei.uc.pt, http://www.dei.uc.pt/~dourado

Abstract
An overview of systems theory is proposed with application to biological systems, particularly in medical context. The main general properties are discussed and the more representative techniques for mathematical modelling of these systems are introduced, covering the main used paradigms: transfer function (continuous and discrete), state equations (continuous and discrete), artificial neural networks, and fuzzy systems. Oscillations and chaotic behaviour of nonlinear systems are introduced. The main purpose is to stress the importance of mathematical modelling and to give an overview of the most used techniques.

1. General definitions and properties of systems [1][2]

Biological Systems are systems, in the normal sense. If they have some special characteristics, the general properties of systems are also applied to them. Let us review the basic definitions of general systems theory.

Systems and Relations

A **system** is a representation of a situation. It is an assembly of elements interrelated by a relation R in an **organized whole**. The behavior of one element in the relation R is different from its behavior in another relation S.

Element is the representation of some phenomena of the natural or social world. It has some significant attributes that may change in time through its own behavior.

There exists a **relationship** between the elements E1 and E2 if the behavior of either is influenced or controlled by the other. The relationship or **communication** between the elements may be flows of materials, information, or energy.

Attribute: any characteristic quality or property of an element (color, size, strength, weight, shape, taste, etc.) or of a relationship (intensity, speed, throughput rate, etc.). In the study of systems the changes in the attributes are of prime importance.

Feedback: exists when the influence of an initial element impacts on other elements, but through a series of relationships the effect of its initial influence feeds back to the initial element.

Example: the dynamics of predator-prey pair. Let us assume that due to an increase in vegetation the population of a small herbivore explodes. This enables the population of a carnivore species that eat this herbivore to explode. Consequently the herbivore population decreases. The increase in the herbivore population feeds back on itself through its relationship with the carnivore population.

Environment (of a system), closed and open systems

A system and the relationships between its elements, including feedback, can be distinguished from its **environment,** with which the system shares only **input** and **output** relationships. Defining a **boundary** around the system makes the demarcation between the system and its environment. This distinction is absolute in the theoretical construct of a **closed system** where no relationships are found or made between elements of the system and things external to it. For example physical chemistry treats the reactions, their rates, and the chemical equilibrium established in a closed vessel where reactants are brought together. The laws of thermodynamics apply only to closed systems.

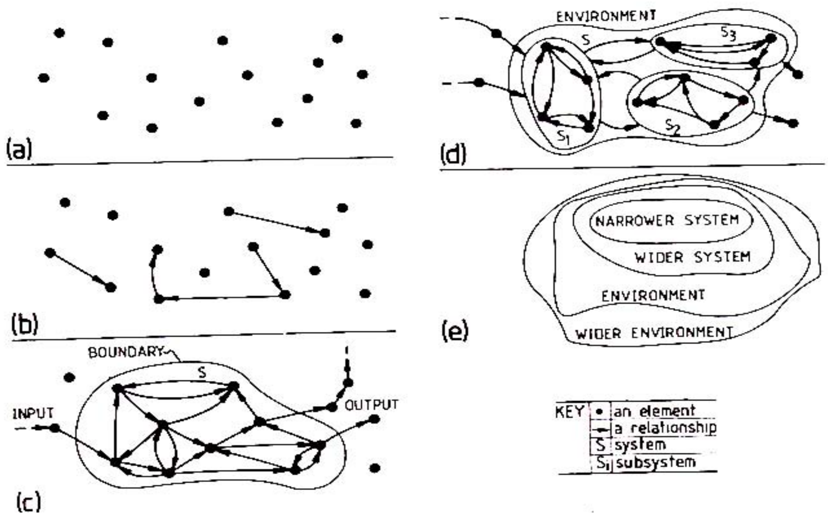


Figure 1. Definition of system. a) a set of elements without relationships is not a system; b) a set of elements with few relationships is not a system; c) a system (with many relationships between elements, its boundary, its input and its output: d) S is a system, S_1, S_2 and S_3 are subsystems; e) system and environment.(From [1]).

An **open system** exchanges material, information and/or energy with its environment across a boundary. Boundary identification is usually not evident. An open system maintains itself in continuous inflow and outflow, a building up and breaking down of components, never being, as long as it is alive, in a state of chemical or thermodynamical equilibrium, but is maintained in a so-called steady-state. This is the essence of metabolism in living cells. At instant t the state of an organism has some value $x(t)$ and at a later instant $t+dt$, the state remains more or less the same, but in the meanwhile the organism exchanges materials, information and energy with its environment in order to survive. At instant $t+dt$ the identity of the organism may appear to be unchanged (it is in a steady-state), but the actual materials that make up the organism at time t will be partially or totally replaced at time $t + dt$.

Open systems verify the **principle of equifinality:** the same final state may be reached from different initial conditions and in different ways. In this sense it can be said that the steady state has a value equifinal or independent of the initial conditions.

We can talk about a **wider environment** whose component parts are able to change the environment (of our system of concern) and by this way influence indirectly the system.

A system has some very important elemental attributes called **state variables** (volumes of water in a series of reservoirs, population sizes of interdependent species, inventories in a warehouse, speed in cars, temperatures in bodies, etc.) that compose the **state vector** x (1)

$$x = \begin{bmatrix} x_1 \\ x_2 \\ . \\ . \\ x_n \end{bmatrix} \tag{1}$$

where each component of the vector represents one of the system states. The state is the synthesis of the system history: it results from all the previous evolution of the system.
When the state of the system changes, its successive values create the **state trajectory** that may be anywhere in the attainable multidimensional **state space** of the system. A system is **deterministic** if the future values of its state variables can be uniquely determined. If this is not the case, the system is **indeterminate** or **probabilistic**.

Homeostasis is the dynamic equilibrium between a system and its environment, with fluxes in and out .For the thermoregulation in warmblooded animals, cooling of the blood stimulates certain centers in the brain which “turn on” some heat-producing mechanisms of the body, and the body temperature is monitored back to the brain such that temperature is maintained at a constant level. Similar homeostatic mechanisms exist in the body for maintaining the constancy of a great number of physicochemical variables. Many feedback systems comparable to the servomechanisms in mechanics and technology exist in the

animal and human body for the regulation of a multiplicity of actions. Homeostasis works to maintain a certain order within the system.

Entropy and homeostasis are concepts closely related in opposite sense. The first refers to the tendency of things to move toward great disorder, or disorganization, rather than maintaining order as homeostasis works to. Entropy, like a force working against homeostasis, emphasizes the importance for an open system to import energy, information and materials, which will be used to compensate the tendency towards disorganization.

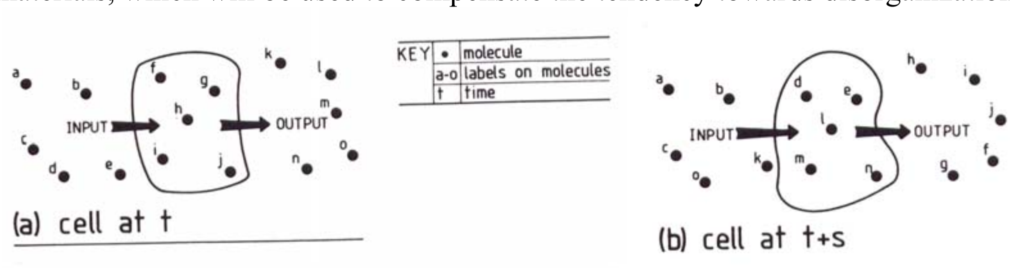


Figure 2. Illustration of homeostasis. Between instants t and t+s the living cell replaces its constituents and maintains itself in a steady state. (From [1]).

Entropy is a process that carries out the "irreversible" law of degradation of energy and matter. An open system imports negative entropy. Living systems, maintaining themselves in a steady state, importing negative entropy, avoid the increase in entropy (see eq.3), and may even develop themselves towards states of increased order and organization.

In a closed system, entropy always increases according to the Clausius equation (2) (http://www-groups.dcs.st-and.ac.uk/~history/Mathematicians/Clausius.html)

$$dS \geq 0 \tag{2}$$

In an open system, in contrast, the total change of entropy can be written according to Prigogine equation (3) (http://nobelprize.org/chemistry/laureates/1977/prigogine-autobio.html#10 http://www.fortunecity.com/emachines/e11/86/entropy.html)

$$dS = d_eS + d_iS \tag{3}$$

where d_eS denotes the change of entropy by import, and d_iS the production of entropy due to irreversible processes in the system, such as chemical reaction, diffusion, heat transport, etc. The term d_{is} is always positive, according to the second law of thermodynamics; d_eS, the entropy transport from outside, may be positive or negative; it is negative when matter is imported as potential carrier of free energy or "negative entropy". The second principle of thermodynamics states that entropy must increase to a maximum and eventually the process comes to a stop at a state of equilibrium. Entropy is a measure of probability (of the states) and so a closed system tends to a state of most probable distribution, which is the tendency to maximum disorder.

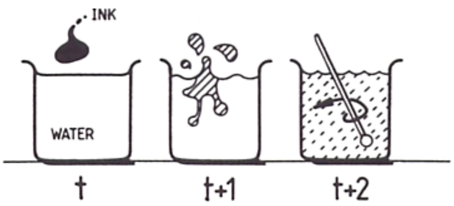


Figure 3. Illustration of the concept of entropy. The ink will dissipate in the vessel, increasing the disorder.(From [1]).

By the notion of entropy machines, organisms, organizations, societies, etc., will rapidly deteriorate into disorder and will collapse. But animate things can **self-organize** themselves using imported materials and energy (that may for example be serviced to them by human beings). These are **negentropic** or homeostatic activities. That is the reason why they do not collapse.

The way in which the elements of a system can be related to each other define the **structure** of the system, Structure provides the supporting framework in which the processes occur in the system.

The **behavior** of the system is the perception of its evolution from sequential observations at successive time instants t_1, t_2, … The behavior is **goal-seeking** if it can be appreciated in the light of a particular purpose.

Adaptation occurs to deal with **environment change** and is necessary to survival in such circumstances. It is a type of goal-seeking behavior. Darwinian evolution of life forms is a theory of adaptation. If the environment is mainly constant, adaptation is not critical. **Environmental disturbances** are changes (in the environment) that may throw the system out of balance. They may have acute or chronic impact on the functioning of the system. Acute impact requires short-term adaptive behavior of the system and this means that a system must rapidly employ **regulation** or **control** procedures to regain balance. If the changes are chronic, long-term regulation and control mechanisms will be required to maintain the systems integrity. Thus a system needs a variety of short and long-term control mechanisms designed to cope with a range of environment changes This is the so called **law of requisite variety.** Frequently we have **piecemeal** thinking by seeing only parts and neglecting to deal with the whole. As a consequence we have **counterintuitive behavior** manifested in the fact that outcomes of our actions rarely occur as we expect. It is mainly caused by our neglect or sub estimation of the nature of complexity of phenomena. That brings the need for systems thinking, for methodologies and models to deal with complexity. Without this formal thinking we see only parts, the extremes, the simple explanations or simple solutions.

Adaptation, regulation and control bring us to **cybernetics.** Cybernetics is the science of control and communication in animals and machines. It describes natural laws that govern communication and control of dynamic situations.

A traditional way of describing a system is by a black box and its transfer function. The TF lumps the whole systems generative mechanism (those mechanisms that generate behavior). The TF describes the action on an input that produces an output. If control is needed, then by feedback the output of the TF is brought back into its input where the difference between the desired and actual states of the system is determined. This information can be acted upon by the control element of the TF to achieve the desired goals. Homeostasis can be achieved by monitoring and controlling system states, choosing critical variables which must remain within vital limits. If we wish to move a system to a new steady state, then the new desired state is compared to the actual state and control action is applied to bring about desired changes. These sorts of control require either negative or positive feedback.

Negative feedback helps to achieve defined objectives as set in control parameters. Control parameters may be man-made or may occur naturally. If a system moves out of its steady state, then either control action is taken or natural feedback occurs to reverse this. The previous predator-pray model is dominated by negative feedback. As soon as the population of herbivores increases, the population of carnivores increases, which feeds back and controls the population of herbivores, stabilizing it and bringing it back towards earlier values. The increase in herbivores population will also lead to increased grazing, which will cut back on the expansion of vegetation. As the carnivores impact on the population of herbivores, the vegetation has the opportunity to expand again and so the cycle continues. Negative feedback ensures an overall stabilizing effect on the related species of vegetation, herbivore, and carnivore.

Feedback exists in human body in very complex loops, as illustrated in Figure 4.

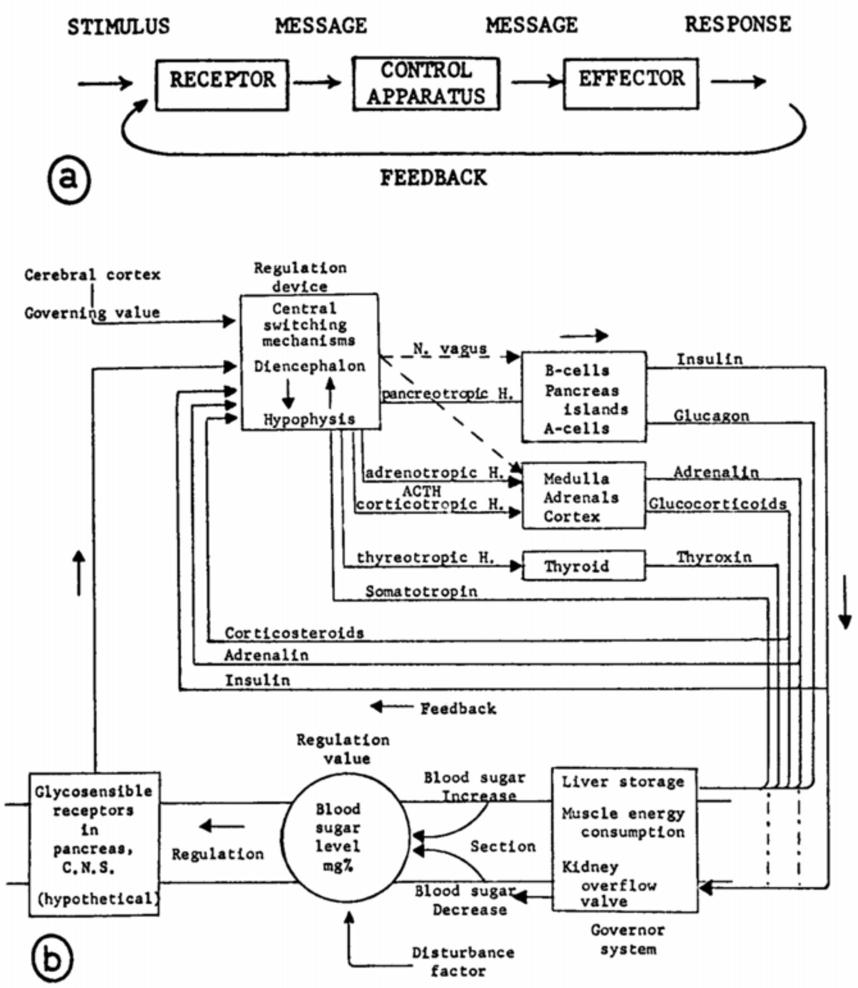


Figure 4. Complex feedback system: the homeostatic regulation of the blood sugar level. (From [2]).

Positive feedback helps to achieve contained contraction or replication and growth or leads to uncontained and unstable contraction or growth. Positive feedback may be desirable but can lead to structural changes and even to structural collapse [1].

Example: When one person runs, she needs to increase oxygen intake and lung ventilation by increasing respiration rate. Positive feedback loops in the body temporarily dominate, bringing about a desirable increase in respiration that enables the running to happen. In healthy people, however, the limits of human capability are dictated by negative loops, so that we can only run until certain limit, which prevents us from burning out. If the negative loops are broken, leading to an undesirable domination by positive ones, as happens when athletes take certain types of drugs, superhuman achievements can be realised, but sometimes tragic cases arrive where biological processes of athletes were unable to cope with uncontrolled demands leading to collapse and death, as the history tells us about.

A control system must have adequate variety. **Variety** can be measured as the number of possible distinguished states of a system, of an environment, of the control element of a system. The variety of the controller must be greater than or equal to the variety of the controlled system or of the environment to be dealt with, in order to guarantee that the system remains under control. This is the **law of requisite variety** of Ashby.

Hierarchy and Emergence

Metasystem (or supersystem) is one system that is placed above a system in a hierarchy of monitoring and control. It is for example the control system of the system of interest. In a human being one metasystem is the conscious brain, in an army is the command center, in a family with young children it is usually the parents.

Hierarchical organization is a logical representation of phenomena as systems and subsystems. Each level in the **hierarchical** structure is represented by a system. By employing systemic reductionism, we reduce the breath of analysis from systems to subsystems characterizing what we find as systems in their own right. By this way, one increases the **level of resolution** of analysis, seeing systems in a greater detail. By reversing the direction, we decrease the level of resolution and see systems in less detail. Choosing an appropriate level of resolution to study a system in a fundamental task, particularly in problem solving because it defines to some extend the issues that will be dealt with. The level of resolution that we choose to work on is termed the **system-in-focus**. To be an effective system scientist we must at the same time be both a **holist**, looking at the system as a whole, and a **reductionist**, understanding the system in more detailed forms.

Ascending hierarchical organizations reveal an important phenomenon: **the whole is greater than the sum of its parts**, a phrase that has been the systems hymn for many years. This means that systems have **emergent properties.** Cells form into distinct wholes (organs) like liver, pancreas, lung, heart, eye, nose, neural network, knee joint, skull, etc. each with its own function or role to play and each having different properties from the cellular parts. Together the organs form a whole with different emergent properties. They are organized through communication and control in a hierarchy of bodily parts that give rise to an observing, listening, feeling, tasting, walking, thinking, …, emotional person. A human being is not an aggregate of bodily parts. Nor is a business an aggregate of management functions, nor a society an aggregate of social groups. In each case, things come together to form wholes whose properties are different from the parts. Emergence offers insights into many phenomena across many disciplines. Laws can be used to define physical phenomena like action-reaction. But can laws define the emergence of a human being from parts of which we are comprised? The difficulty is that emergence is not a law (it cannot be derived from the laws governing the sub-systems). Nor is a belief in mystical interpretation. It is nothing more or less than a characterization of phenomena that otherwise leave us without an explanation. Emergence is a characterization.

The emergence of each society can be characterized by its culture. Cultures become distinct wholes when placed against others, when we contrast norms, roles, values and beliefs. Adding other components to this type of wholes, like national governments and

international organizations, emerges an international system. The international dimension points to other emergence (studied by international relations).

Synergy is a term also used to describe the emergence of unexpected and interesting properties, used often in management and organizations theory, to explain the benefit of group work: synergy in a group leads to greater creativity in strategic thinking and problem solving.

Autopoesis means self-producing systems. A cell produces its own components that in turn produce it. Living systems can be thought of as autopoietic since they are organized to enable their processes to produce components that are necessary for the continuation of these processes.

Along the history **several systems metaphors** were born.
The **machine metaphor** describes closed system with set goals to be achieved in a rigid hierarchy of control.
The **organic metaphor** describes complex network of elements and relationships with a transformation effected by feedback control..
The **brain metaphor** allows emotions.
The Culture metaphor includes the network of values, beliefs, and norms.
Finally the **political metaphor** allows networks of interacting interests that people pursue and may achieve.

According to Bertalanffy[2], the hierarchical organization of systems can be as in Table 1.

Level	Description and examples
Symbolic systems	Language, logic, mathematics, science, morals, etc.
Socio-cultural systems	Populations of organisms (humans included); symbolic-determined communities (cultures) in man only
Man	Symbolism; past and future, self and world, self-awareness, etc., as consequences: communication by language.
Animals	Increasing importance of traffic in information (evolution of receptors, nervous systems); learning; beginning of consciousness.
Lower organisms	“Plant-like” organisms: increasing differentiation in systems (“division of labor” in the organism); distinction of reproduction and functional individual (“germ track and soma”).
Open systems	Flame, cells, tissues, organs and organisms in general
Control mechanisms	Thermostat, servo-mechanisms, homeostatic mechanism in organisms

Table 1: Main levels in the Hierarchy of systems (adapted from [2]).

2. Mathematical Modelling of Biological Systems

A model is consider here as a tool for systems representation in an abstract sense, allowing the simulation and the prediction of the future behavior of the system. As these operations are carried out nowadays by computers, a model must be reducible to a computer program, i.e., must be computable. Actually there are several approaches for obtaining computable models of systems. These approaches are based on:

- Fundamental knowledge (physical-chemical, etc.) about the process and the properties of the system; models assume the form of differential or integral equations (the integral-differential paradigm).

- Experimental data processing through data mining in order to extract formal relations and knowledge from empirical (experimental) data; models assume the form of artificial neural networks (the data paradigm).

- Human expert knowledge expressed in verbal, qualitative terms; models assume the form of fuzzy systems (the qualitative paradigm).

Let us briefly look in more detail to each one of the forms.

2.1.The integral-differential paradigm. Transfer function and state equations.

Example 1.

Let us consider the population of a living species. At instant t, the population has y(t) individuals. If BR is the birth rate, number of births per unit population per unit time, and DR is the death rate, number of deaths per unit population per unit time, then the change in population Δy at during a small interval of time Δt, is (in the hypothesis that the population can grow infinitively) (4)

Variation in population= number of births – number of deaths

$$\Delta y = (BR - DR) y \Delta t$$

or, manipulating this expression

$$\frac{\Delta y}{\Delta t} = (BR - DR)y$$

$$\frac{dy}{dt} = \dot{y} = \lim_{\Delta t \to 0} \frac{\Delta y}{\Delta t} = (BR - DR)y \tag{4}$$

The model of the population dynamics is described by a fist order linear differential equation. Solving it, one obtains

$$\int_0^T \frac{dy}{y} = \int_0^T (BR - BR)d\xi \Rightarrow \ln y(T) - \ln y(0) = (BR - DR)T$$

$$\Rightarrow \ln \frac{y(T)}{y(0)} = (BR - DR)T \Rightarrow e^{\ln \frac{y(T)}{y(o)}} = e^{(BR-DR)T} \Rightarrow \frac{y(T)}{y(0)} = e^{(BR-DR)T} \Rightarrow$$
$$y(T) = y(0)e^{(BR-DR)T}$$

or more generally (5).

$$y(t) = y(0)e^{(BR-DR)t} \tag{5}$$

This is the known exponential law for the growth of an unconstrained population system (for ex. bacteria, mice, predators). It is an autonomous system (there is no input to the system). It starts the evolution from an initial condition (the initial population).

Example 1. Model of finite constrained population dynamics.

Let us consider a simple discrete model of population dynamics. If M is the maximum admissible value of the population, the increase in the population y takes the form [8],

$$\Delta y = R * y * \left(1 - \frac{y}{M}\right)\Delta t$$

where R is the growth rate (resulting from the birth and death rates).

The differential equation takes the form (6)

$$\frac{\Delta y}{\Delta t} = R * y * \left(1 - \frac{y}{M}\right) = R * y - R * \frac{y^2}{M}$$
$$\dot{y} = R * y - R * \frac{y^2}{M} \tag{6}$$

a first order nonlinear differential equation.

Example 2. Van der Pol dynamics.

Several natural phenomena show oscillations that can be described by the Van der Pol oscillator modelled by the equation of an autonomous system

$$\ddot{x} - \varepsilon(a^2 - x^2)\dot{x} + \omega^2 x = 0 \tag{7}$$

ε, *a*, ω are parameters determining the waveshape, amplitude and frequency of the nonlinear oscillator. It, or modifications of it, have been used to model electrical heart beat by Van der Pol itself in 1929, gut rhythms [9], the whole small intestine, biological and circadian rhythms [10], heartbeat [11], etc..

Example 3. Consider the mercury thermometer at a temperature of zero and immersed in water at the temperature t_i at instant t=0. The glass walls of the thermometer have a thermal resistance of R. Its equations are as following:

$\Delta Q = \dfrac{(\theta_i - \theta_m(t))}{R}\Delta\text{t}$, heat through the glass wall

$\Delta\text{Q}=\text{C}(\theta_m(t)-\theta_i) = \text{C}\Delta\theta_m(t)$, heat increase of mercury, C is its thermal capacity

$\dfrac{(\theta_i - \theta_m(t))}{R}\Delta t = \text{C}\Delta\theta_m(t)$, thermal equality (heat equilibrium)

or

$$RC\frac{\Delta\theta_m(t)}{\Delta t} + \theta_m(t) = \theta_i,$$

or

$$\lim_{\Delta t \to 0} RC\frac{\Delta\theta_m(t)}{\Delta t} + \theta_m(t) = RC\frac{d\theta_m(t)}{dt} + \theta_m(t) = \theta_i$$

or

$$RC\dot{\theta}_m(t) + \theta_m(t) = \theta_i$$

Finally

$$\dot{\theta}_m(t) + \frac{1}{RC}\theta_m(t) = \frac{\theta_i}{RC} \tag{8}$$

This is a first order linear ordinary differential equation. Solving it, given the input temperature, we obtain the expression for the mercury temperature (8)

$$\theta_m(t) = \theta_i(1 - e^{-\frac{t}{RC}}) = \theta_i(1 - e^{-\frac{t}{\tau}}) \tag{9}$$

Its graphical representation is given in figure

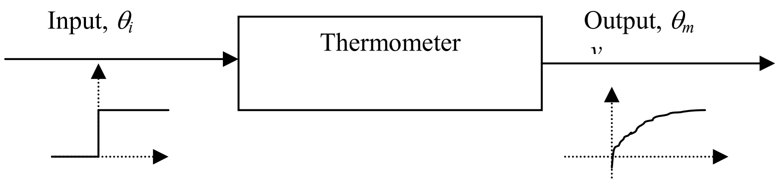


Figure 5. Step response of a second order system.

This simple case puts in evidence the important notion of time constant and speed of dynamic evolution. The time constant is the time interval needed for the output to reach

63% of its final value, after the application of a step at the input. The final value of the thermometer temperature is equal to the input temperature, using the same scale in both.
If a different scale was used for the input temperature, such that one degree in input scale corresponds to five degrees in output scale, then the differential equation would have the form (10)

$$\dot{\theta}_m(t) + \frac{1}{RC}\theta_m(t) = \frac{5\theta_i}{RC} \tag{10}$$

whose solution would be (11)

$$\theta_m(t) = \theta_i(1 - e^{-\frac{t}{RC}}) = 5 \cdot \theta_i(1 - e^{-\frac{t}{\tau}}) \tag{11}$$

The final value of the output would be (making t infinite) (12)

$$\theta_m = 5 \cdot \theta_i \tag{12}$$

The step, a signal of constant value started at some defined instant and going to infinity, is very useful in studying system properties. The resulting output illustrates some essential characteristics of the system dynamics.

Continuous Transfer Function of non-autonomous system

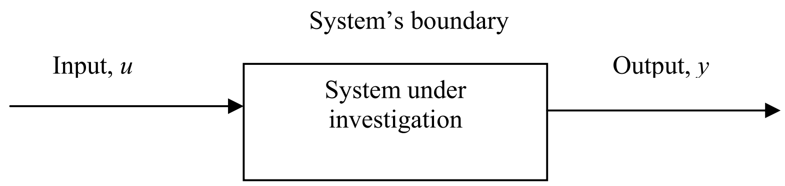


Figure 6. Block representation of a system.

A non-autonomous system has some input u from its environment, like the thermometer in the previous example and produces some output y to the environment. To model it in the integral-differential paradigm one obtains in general a differential equation, in the linear case in the form

$$\frac{d^n y}{dt^n} + a_{n-1}\frac{d^{n-1}y}{dt^{n-1}} + \ldots + a_1\frac{dy}{dt} + a_0 y = b_{n-1}\frac{d^{n-1}u}{dt^{n-1}} + b_{n-2}\frac{d^{n-2}u}{du^{n-1}} + \ldots + b_1\frac{du}{dt} + b_0 u \tag{13}$$

To solve this differential equation of order n some operator must be used. The most common is the Laplace Transform, using the complex variable s equivalent (to some extend) to the derivative operator

$$sy = \frac{dy}{dt} = \dot{y}, \quad s^2 y = \frac{d^2 y}{dt^2}, \ \ldots, \quad s^n y = \frac{d^n y}{dt^n} \tag{14}$$

Applying to the equation one obtains after some manipulations

$$(s^n + a_{n-1}s_{n-1} + \ldots + a_2 s^2 + a_1 s + a_0)y = (b_{n-1}s^{n-1} + \ldots + b_2 s^2 + b_1 s + b_0)u \tag{15}$$

or

$$\frac{y}{u} = \frac{b_{n-1}s^{n-1} + \ldots + b_2 s^2 + b_1 s + b_0}{s^n + a_{n-1}s^{n-1} + \ldots + a_2 s^2 + a_1 s + a_0} \tag{16}$$

One obtains a function that "transfers" the input *u* to the output *y*, and is called transfer function, one of the most used representations of linear systems. In block diagram it is as in figure 7.

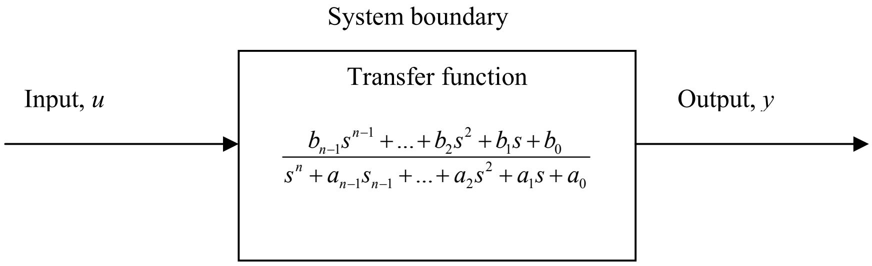


Figure 7. Transfer function.

Transfer function is very useful and allows the study of key properties of the system: order, stability, dynamics, time and frequency response, etc. Furthermore, it allows the synthesis of adequate controllers.

Time response

Let us apply this to the differential equation of the thermometer for the case of different scales

$$\begin{gathered}\dot{\theta}_m(t) + \frac{1}{RC}\theta_m(t) = \frac{5\theta_i}{RC} \\ s\theta_m + \frac{1}{RC}\theta_m(t) = \frac{5}{RC}\theta_i \Leftrightarrow \theta_m(s + \frac{1}{RC}) = \frac{5}{RC}\theta_i \Rightarrow \\ \Rightarrow \frac{\theta_m}{\theta_i} = \frac{\frac{5}{RC}}{s + \frac{1}{RC}} = \frac{5}{RCs + 1} = \frac{5}{\tau s + 1}\end{gathered} \tag{17}$$

This is the transfer function of a first order system. Is evidences the relation between the coefficients of the transfer function and some key properties of the system:

- the time constant: the coefficient of s in the denominator when the denominator independent term is 1.
- the system gain : the relation of the output and the input in long term, that is 5 . This is the constant term (independent of s) in the numerator when the denominator is written in this way.

The order of the system is the degree of the denominator polynomial.

First (18), second (19) and third (20) order systems are illustrated by Figure 8.

$$G_1(s) = \frac{1}{s+1} \tag{18}$$

$$G_2(s) = \frac{1}{s^2+2s+1} = \frac{1}{(s+1)(s+1)} \tag{19}$$

$$G_3(s) = \frac{1}{s^3+3s^2+3s+1} = \frac{1}{(s+1)(s+1)(s+1)} \tag{20}$$

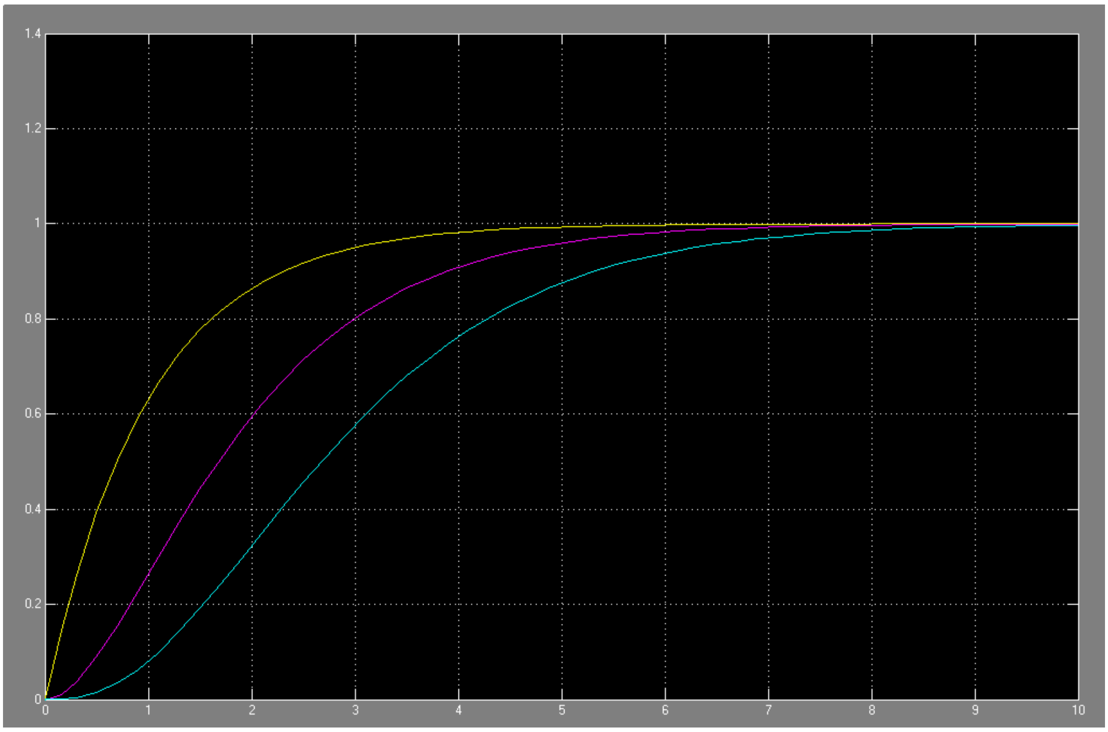


Figure 8. Time (step) response of first, second and third order systems. As the order increases, the response takes more time (more inertia).

Second order system systems are very representative, since they have enough degrees of freedom to approximate many practical cases. The time response may have different shapes, according to the values of its poles.

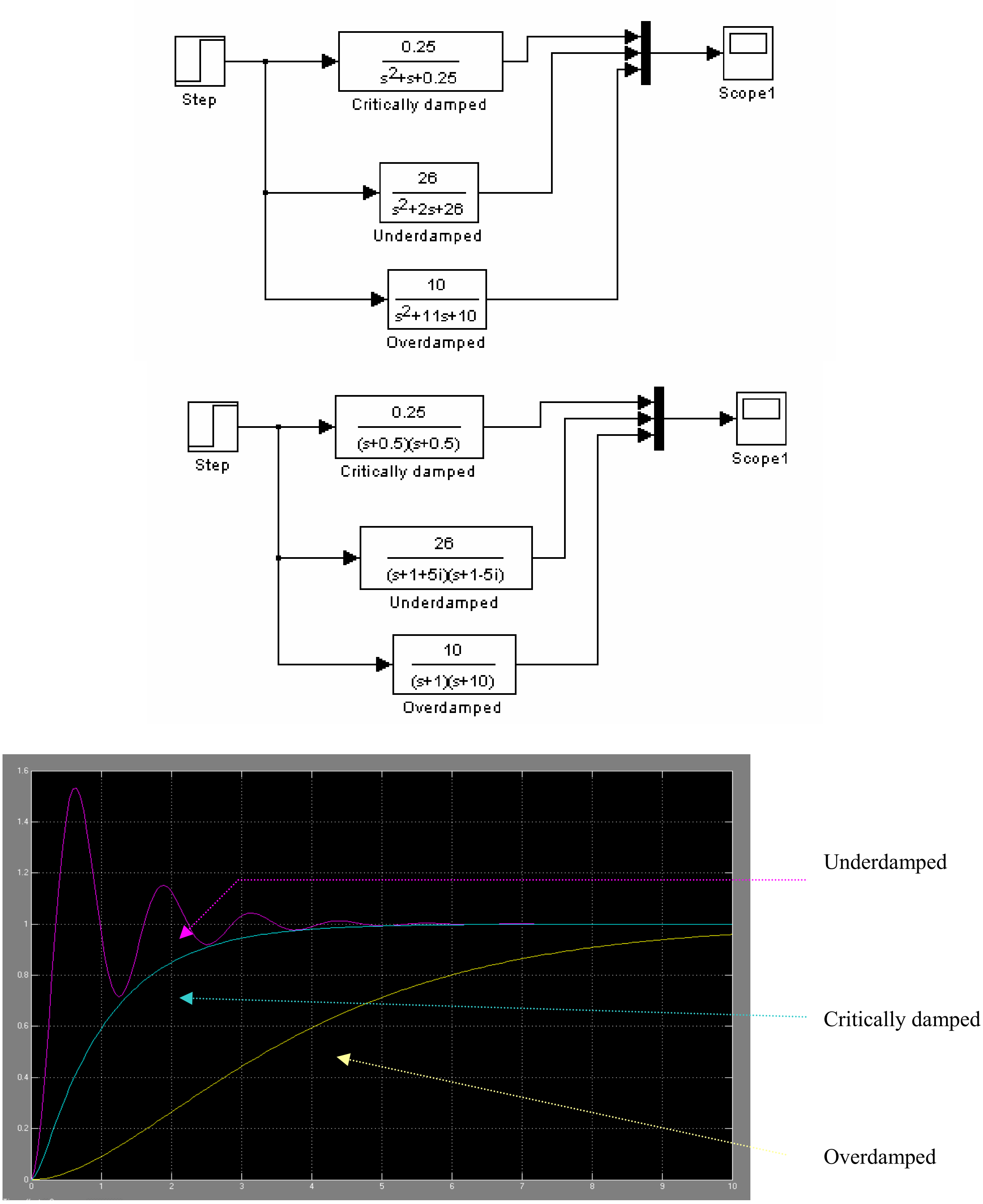


Figure 9. Time response of second order systems. The systems are presented in the block diagrams (from Simulink, Mathworks [13]).

Frequency response

Figure [10] illustrates a very common health problem: insufficient hearing. When you have this problem your doctor measures your frequency response and probably will say that you "lost high frequencies", that happens as we get old.

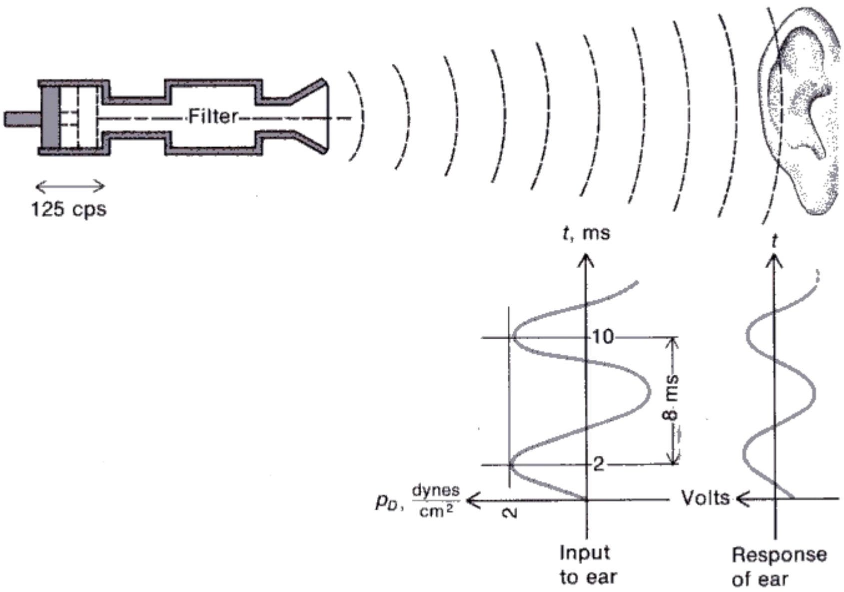
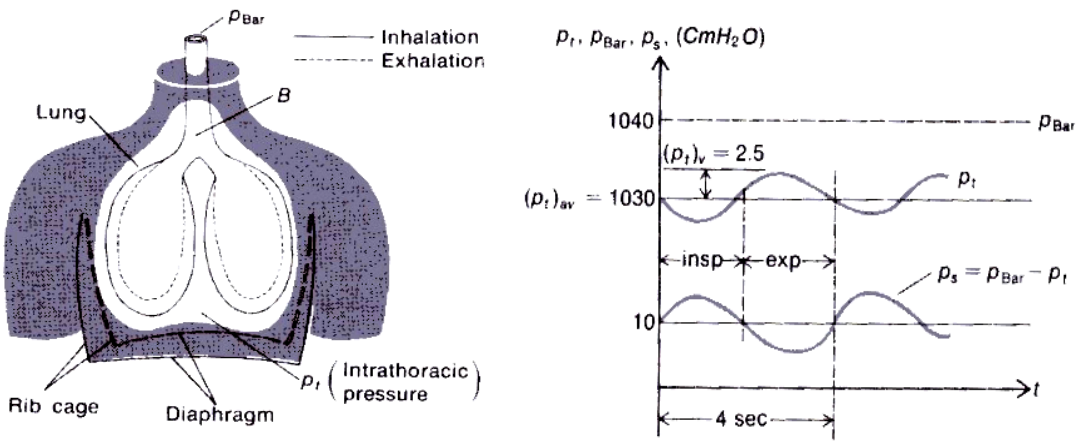


Figure 10. Frequency response of the ear. The heard amplitude of the signal is a fraction of the signal that excited the ear, and this fraction depends on the frequency of excitation. Before 20 cps (cycles per second) or after 20 000 cps, it is null. From [6].

Another situation where periodical signals are important is illustrated by figure [11].



a) b)

Figure 11. Respiratory system with its periodical signals. (From [6]). a) Schematic of respiratory system; b) plot of intrapleural or intrathoracic pressure.

Frequency response is an important characteristic of systems. It can be obtained from the transfer function. For this purpose we replace the complex operator s by the complex frequency $j\omega$. We can then study the system behavior: given a permanent sinusoidal input of a certain frequency with a certain amplitude, which is the amplitude of the output, after the transient state is over? Which is the phase difference between the input and the output?

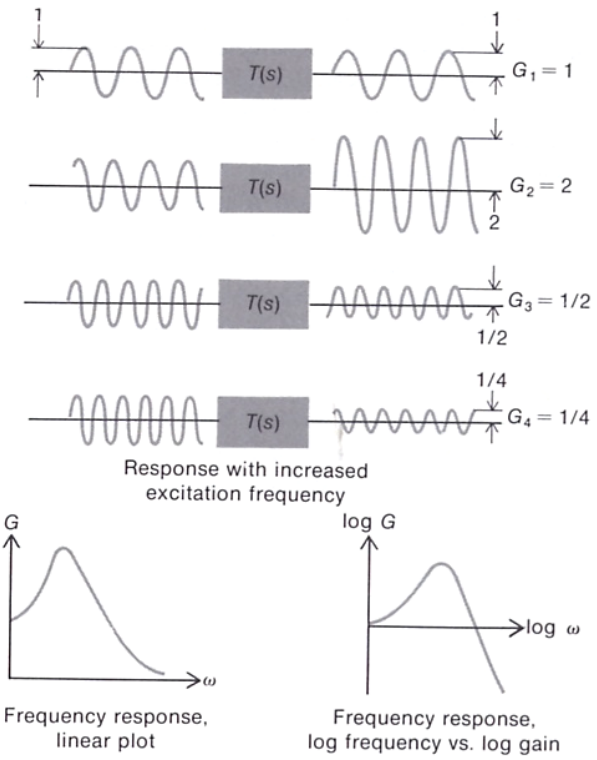


Figure 12. Frequency response in amplitude. Some frequencies are damped, some are amplified. The curve of gain G is more frequently represented in a log-log scale by practical reasons (the Bode plot).(From [6]).

An interesting phenomenon related to frequency behavior is the resonance. Some systems have the property that for some frequency they oscillate very strongly in the output, sometimes so much that they collapse (as happens with some singers whose voices have a frequency able to excite glasses until they brake).

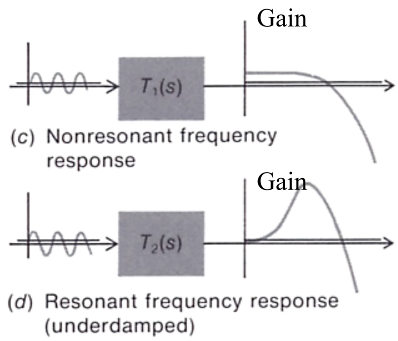


Figure 13. Gain curves for nonresonant and resonant responses. IN this case some frequencies are strongly amplified (from [6]).

Second order underdamped systems are resonant systems.

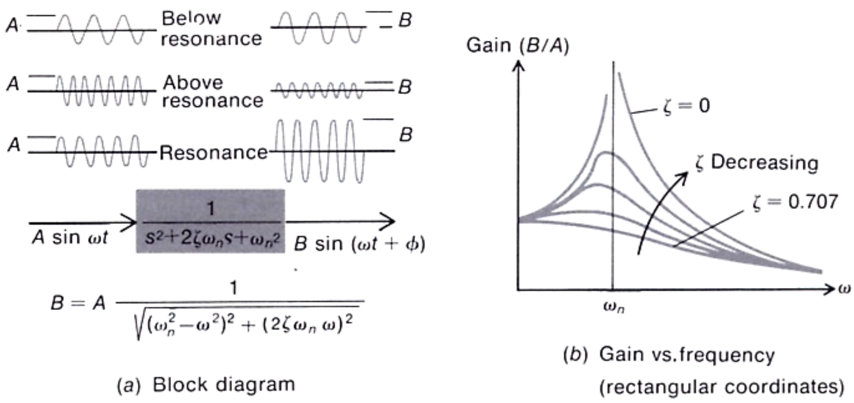


Figure 14. Second order underdamped systems are resonant (from [6]).

The frequency response is computed replacing s in the transfer function by the complex frequency $j\omega$. Then from (16) one obtains (21)

$$\frac{y}{u}(jw) = \frac{b_{n-1}(j\omega)^{n-1} + \ldots + b_2(j\omega)^2 + b_1(j\omega) + b_0}{(j\omega)^n + a_{n-1}(j\omega)^{n-1} + \ldots + a_2(j\omega)^2 + a_1(j\omega) + a_0} \tag{21}$$

For example for the system given by the transfer function (22),

$$G(s) = \frac{100}{s^2 + 0,2s + 100} \tag{22}$$

the Bode plot (magnitude) given in figure 15 . For the frequency 10 cps (10 Hz), the magnitude is 34 db, which means 50.12. If the system is excited with a frequency of 10 cps, the output amplitude will be 50.12 times the input amplitude!

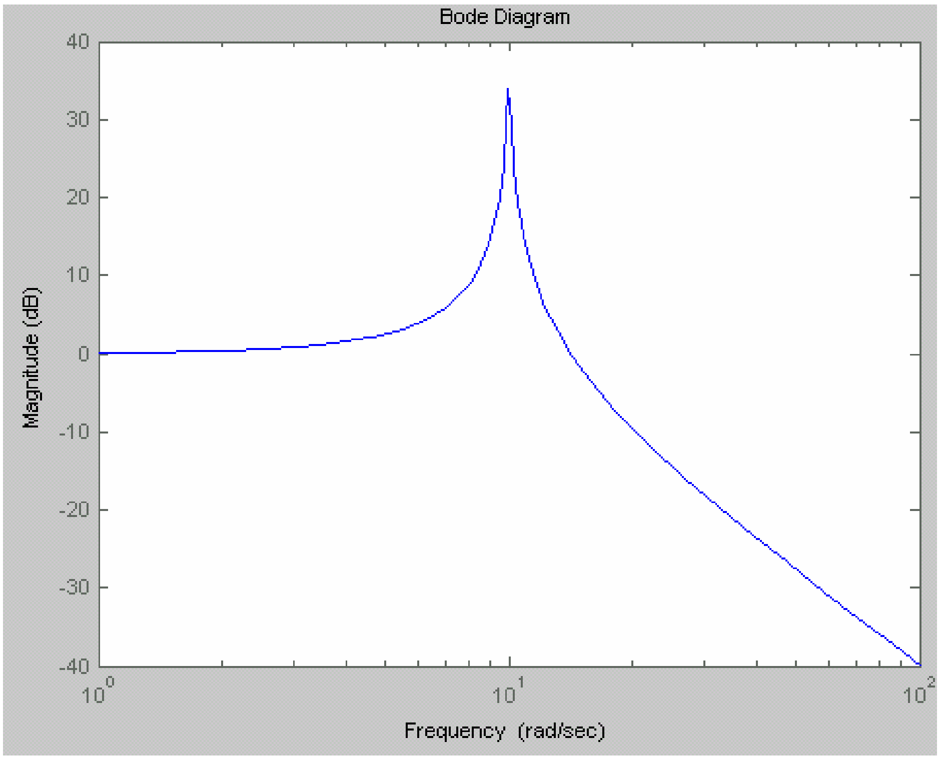


Figure 15. Amplitude (Bode) frequency response of system given by (22), a resonant one.

Representation by difference equations

The representation in the integral-differential paradigm can be made in the discrete time domain, where time is considered only in some instants, for example every second, every minute, etc. This is convenient for simulation in digital computers and for systems that are inherently discrete.

The derivative can be approximated by a difference between two consecutive time instants separated by T, the discretization interval:

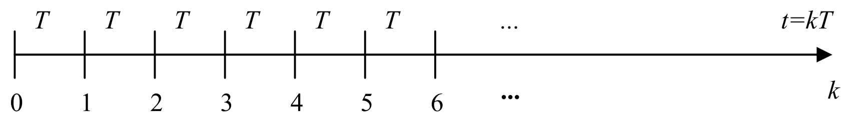


Figure 16. The discretization of the time axis.

$$\frac{dx}{dt}(kT) = \overset{\bullet}{x} = \frac{x((k+1)T) - x(kT)}{T}$$

$$\begin{aligned}\frac{d^2x}{dt^2}(kT) = \overset{\bullet\bullet}{x} &= \frac{\overset{\bullet}{x}((k+1)T) - \overset{\bullet}{x}(kT)}{T} = \\ &= \frac{\dfrac{x((k+2)T) - x((k+1))T}{T} - \dfrac{x((k+1)T) - (xkT)}{T}}{T} = \\ &= \frac{x((k+2)T - 2x((k+1)T + x(kT)}{T^2}\end{aligned} \tag{23}$$

Making this approximation in the differential equation (7) one obtains, after some manipulation (24),

$$\begin{aligned} y(k+n) + c_{n-1}y(k+n-1) + c_{n-2}y(k+n-2) + \ldots + c_1 y(k+1) + c_0 y(k) = \\ = d_{n-1}u(k+n-1) + d_{n-2}u(k+n-2) + \ldots + d_1 u(k+1) + d_0 u(k)\end{aligned} \tag{24}$$

A linear forward difference equation of order *n*. The constants c_i and d_i depend on the constants a_i and b_i and on the discretization interval T.
If we subtract *n* **to** each and every index, we obtain (25)

$$\begin{aligned} y(k) + c_{n-1}y(k-1) + c_{n-2}y(k-2) + \ldots + c_1 y(k-n+1) + c_0 y(k-n) = \\ = d_{n-1}u(k-1) + d_{n-2}u(k-2) + \ldots + d_1 u(k-n+1) + d_0 u(k-n)\end{aligned}$$

or,

$$\begin{aligned} y(k) = -c_{n-1}y(k-1) - c_{n-2}y(k-2) - \ldots - c_1 y(k-n+1) - c_0 y(k-n) + \\ + d_{n-1}u(k-1) + d_{n-2}u(k-2) + \ldots + d_1 u(k-n+1) + d_0 u(k-n)\end{aligned} \tag{25}$$

a linear backward difference equation of order *n*. This equation evidences the characteristics of memory in a dynamical system: the output at instant *k* depends on what happened at a certain number of past instants. This number is *n*, the order of the system. For a linear system, the elements of memory are linearly combined. For a general nonlinear system the combination of the memory elements is nonlinear (26)

$$y(k) = f(y(k-1), y(k-2), \ldots, y(k-n), u(k-1), u(k-2), \ldots, u(k-n)) \tag{26}$$

Example. Discrete model of constrained population dynamics

Consider again the equation (6)

$$\frac{\Delta y}{\Delta t} = R * y * \left(1 - \frac{y}{M}\right) = R * y - R * \frac{y^2}{M}$$

$$\dot{y} = R * y - R * \frac{y^2}{M}$$

applying the previous discretization, one obtains (27).

$$\begin{gathered} y_{k+1} = y_k + (R * y_k - R * \frac{{y_k}^2}{M})T \\ \frac{y_{k+1}}{M} = \frac{y_k}{M} + R * \frac{y_k}{M} T - R * \left(\frac{y_k}{M}\right)^2 T \end{gathered} \tag{27}$$

If the population is normalized with respect to *M*, then this equation becomes (28).

$$\begin{gathered} y_{k+1} = y_k + R * y_k T - R * {y_k}^2 T \\ y_{k+1} = y_k + R * y_k (1 - y_k) T \end{gathered} \tag{28}$$

For R=0.1 one obtains the evolution, starting from y(0)=0.1, illustrated in Figure 17.

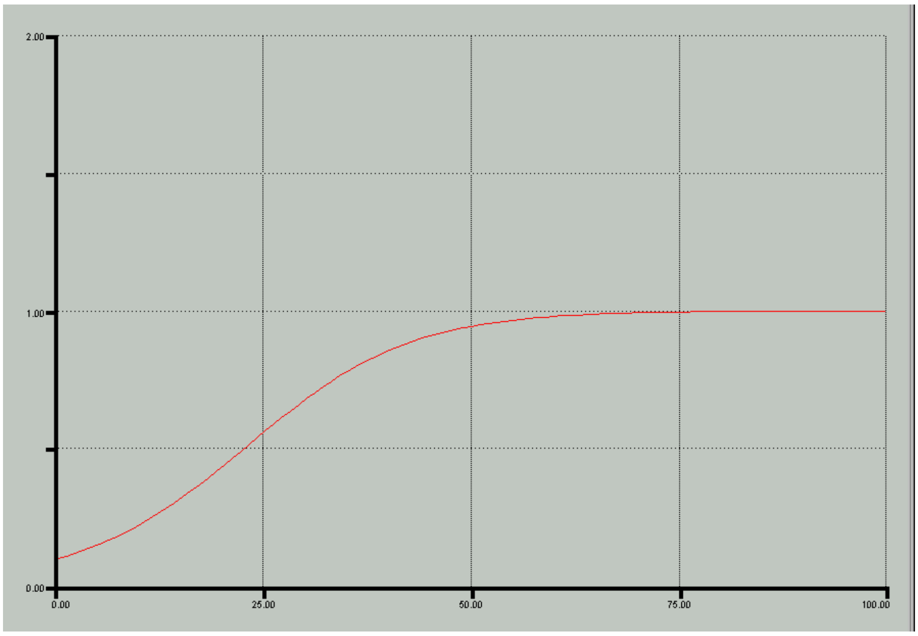


Figure 17. Evolution of the constrained population, by years. This curve was obtained with the software StellaII, accompanying the book [8].

Oscillations and chaotic behavior of discrete nonlinear systems

In equation (28) for R=2.1, the population evolution is given in Figure 18.

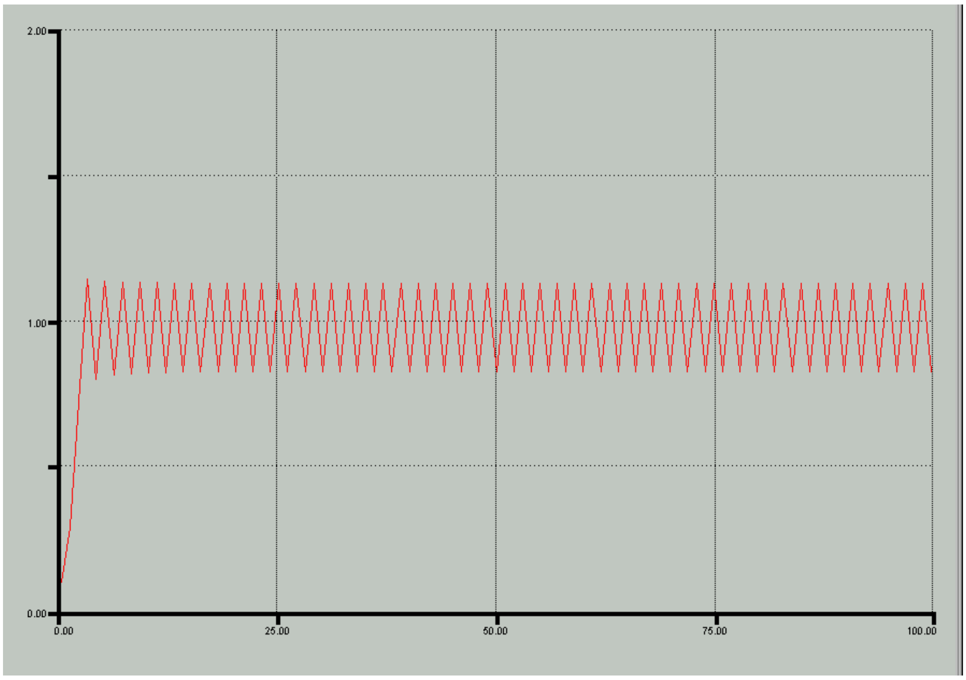


Figure 18. Population evolution by eq. (17) with R= 2.1. See the oscillating behavior.

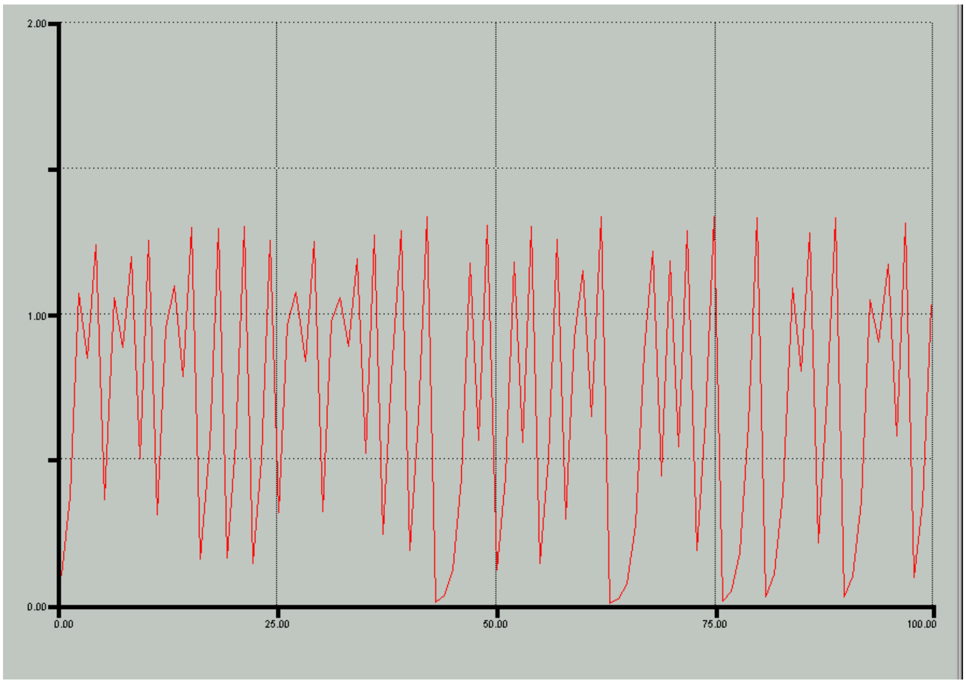


Figure 18. Population evolution by eq.(17) with R= 3.0. See the chaotic behavior.

If the initial population is slightly changed, for 0.11, the obtained chaotic path is quite different, shown in the figure in blue.

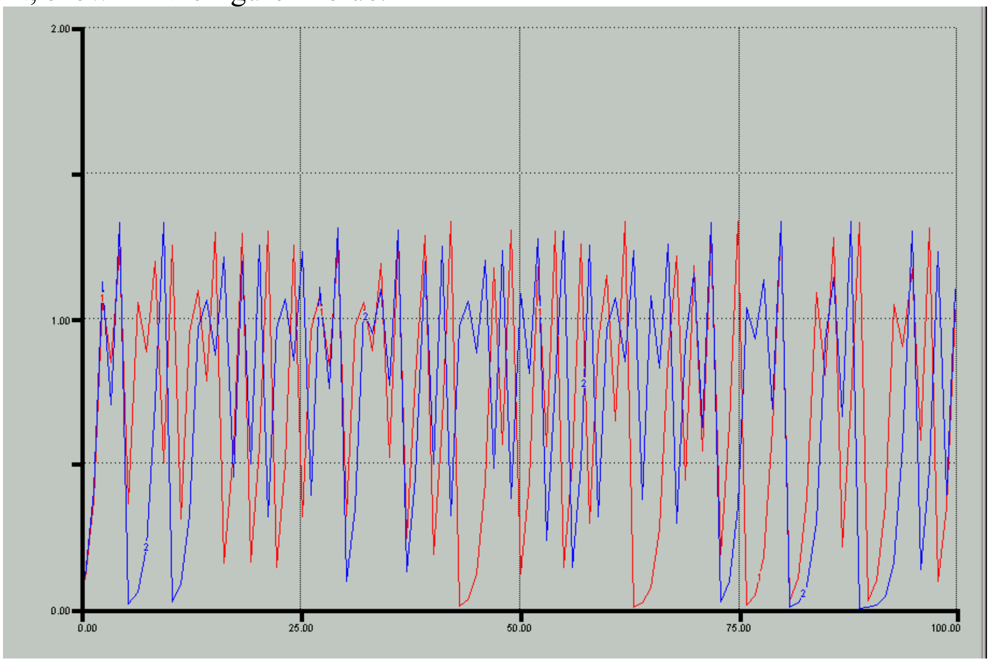


Figure 19. Population evolution by eq. (17) with R= 3.0 . In read, initial population of 0.10. In blue an initial population of 0.11. Both produce chaotic behavior, but with very different trajectories.

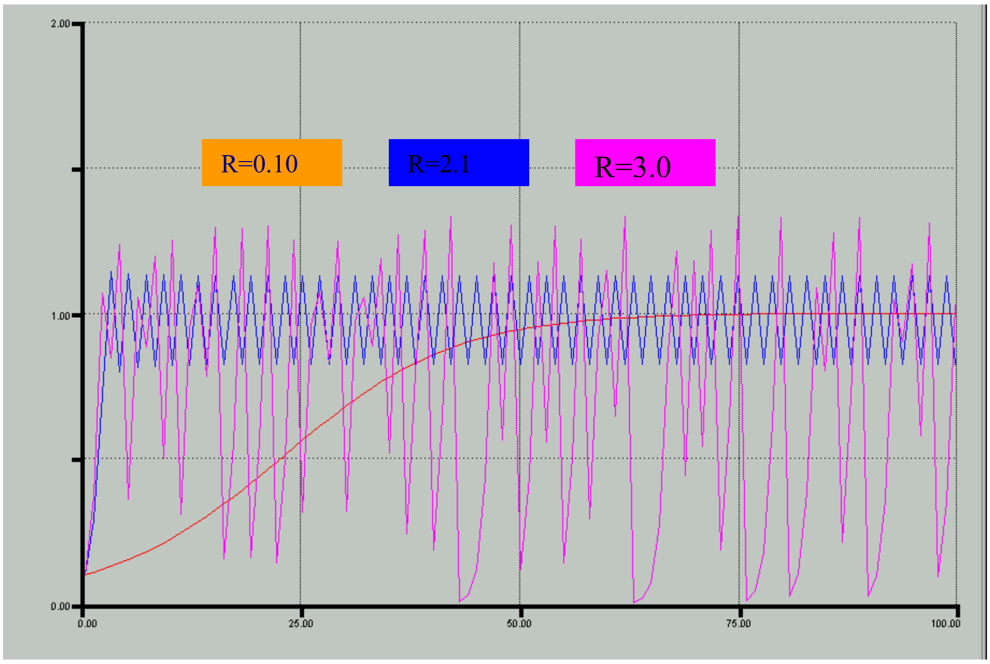


Figure 20. Superposition of Figures 17 (R=0.10), 18 (R=2.10) and 19 (R=3.0). Nonlinear systems may be very sensitive to small variations in its parameters.

Heart beat and brain wave variations show chaotic behaviour [8].

State-equations

A linear equation of order *n* (like the one previous) may be reduced to a set of *n* first order linear differential equations in the form (29)

$$\begin{aligned}
\dot{x}_1 &= a_{11}x_1 + a_{12}x_2 + \ldots + a_{1n}x_n + b_1u \\
\dot{x}_2 &= a_{21}x_1 + a_{22}x_2 + \ldots + a_{2n}x_n + b_2u \\
&\ldots \qquad \ldots \qquad \ldots \\
\dot{x}_n &= a_{n1}x_1 + a_{n2}x_2 + \ldots + a_{nn}x_n + b_nu
\end{aligned} \tag{29}$$

$$y = c_1x_1 + c_2x_2 + \ldots + c_nx_n$$

The output *y* of the system is a linear combination of the state variables. In matrix notation we have

$$\begin{aligned}
\dot{x} &= Ax + Bu \\
y &= Cx
\end{aligned} \tag{30}$$

This is the state equation, where the state vector *x* is composed by the *n* state variables representing internal attributes of the system.

Example 3. Ackerman et al (1969) (in [13]) model of glucose metabolism

$$\frac{dg}{dt} = -m_1g - m_2h + J(t)$$

$$\frac{dh}{dt} = -m_3h + m_4g + K(t)$$

g : deviation of glucose level from its fasting value (31)
h : deviation of insulin level from its fasting value
J : experimental rate of infusion of glucose
K : experimental rate of infusion of insuline
m_1, m_2, m_3, m_4, are constants characteristic of each individual subject.

This model is composed by two linear ordinary differential equations, interacting between each other. Matrices A and B are easily identified

$$A = \begin{bmatrix} -m_1 & -m_2 \\ -m_3 & -m_4 \end{bmatrix} \qquad B = \begin{bmatrix} J \\ K \end{bmatrix} \tag{32}$$

Linear state equations have nice properties. The matrix A contains important properties describing the dynamics of the system. The general solution of the state equation is

$$x(t) = x(0)e^{At} + \int_o^t e^{A(t-\xi)} Bu(\xi)d\xi \tag{33}$$

This expresses the fact that the state trajectory results from the initial state through the composition of exponentials of the eigenvalues of the *A* matrix plus a part dependent of the input and on the *B* matrix.

It all the eigenvalues have negative real parts, the contribution of the initial state vanishes and the system is stable. In by contrary one of the eigenvalues has positive real part, then the state tends to infinity and the system is unstable. If there is one eigenvalues with zero real part (with all the others negative) then the system remains inside a limited zone in the state space or goes to infinity, depending on the input. If there are two or more eigenvalues with zero real part, the system is unstable.

In general, an autonomous system may be represented by a set of first order nonlinear equations of the form

$$\begin{aligned} \frac{dx_1}{dt} &= f_1(x_1, x_2, ..., x_n) \\ \frac{dx_2}{dt} &= f_2(x_1, x_2, ..., x_n) \\ \\ \frac{dx_3}{dt} &= f_3(x_1, x_2, ..., x_n) \end{aligned} \tag{34}$$

where x_i is the value of some attribute of the system (usually measured). The change in any attribute is therefore a function of all attributes, and reversell y, a change in one attribute entails change of all other attributes and of the system as a whole.

Example 4. (from [14). A mathematical model of chronic renal disease, in terms of sclerosis index *s*, the glomerular diameter *g* ,has the form of two coupled nonlinear ordinary differential equations (35)

$$\frac{ds}{dt} = s(1 - \frac{s}{s_{\max}})$$

$$\frac{dg}{dt} = g(1 - \frac{g}{g_{\max}}) - \frac{2sg}{s_{\max}} \tag{35}$$

$s_{\max}$ represents the completely sclerosed situation

$g_{\max}$ represents the maximum value of *g*

There is a condition of stationary state, characterized by the disappearance of the changes (of the derivatives)

$$f_1 = f_2 = ... = f_3 = 0 \tag{36}$$

One obtains then a set of *n* algebraic equation for *n* unknowns, and solving them, if there is a solution, one obtains the values

$$\begin{aligned} x_1 &= x_1^* \\ x_2 &= x_2^* \\ &... \\ x_n &= x_n^* \end{aligned} \tag{37}$$

These values are constant, since the changes in the system disappeared. In general, there will be a number of stationary states, some stable, some unstable.

We may introduce new variables representing the distance to a steady state,

$$\Delta x_i = x_i - x_i^*, \quad i = 1, 2, .., n \tag{38}$$

and develop the Taylor series of the nonlinear functions f_i around that steady-state. If we consider only the first term of the Taylor series (the linear one), then a linear state space equation is obtained, to which the former properties can be applied. The origin in this linear state space represents in fact the steady state in the original nonlinear state space. The steady state may then be a node, stable or unstable, a loop, stable or unstable, or a cycle. For a second order system a detailed analysis is made by Bertalanffy, p. 58-9.

Discrete state-equations

In the equation

$$\dot{x} = Ax + Bu$$

the derivative can be approached by the difference, just as in (23), discretizing the time by constant intervals T.

$$\begin{aligned}
&\dot{x}(t) = Ax(t) + Bu(t) \\
&t = kT \\
&\frac{x(k+1) - x(k)}{T} = Ax(k) + Bu(k) \\
&x(k+1) = x(k) + ATx(k) + BTu(k) \\
&x(k+1) = (I + AT)x(k) + BTu(k) \\
&x_d(k+1) = A_d x(k) + B_d u(k)
\end{aligned} \tag{39}$$

Similarly, the output equation may be discretized

$$\begin{aligned}
&y(t) = Cx(t) \\
&y(kT) = C_d x(kT)
\end{aligned}$$

or simplifying the notation (40)

$$y(k) = C_d x(k)$$

This is a discrete linear state equation. The relations between the matrices of the continuous and discrete representations are (41).

$$\begin{aligned}
&A_d = I + AT \quad \text{(approximation)} \\
&B_d = TB \qquad \text{(approximation)} \\
&C_d = C \quad \text{(exact)}
\end{aligned} \tag{41}$$

The approximations result from the approximation of the derivative. In fact the exact relations for A and B are a bit more complex. In fact it can be shown that the exact expression for A is (32)

$$A_d = I + AT + \frac{1}{2!}A^2T^2 + \frac{1}{3!}A^3T^3 + \ldots + \frac{1}{k!}A^kT^K + \ldots = e^{AT} \tag{42}$$

However if A^2 and higher powers are small, compared to A, the approximation in (31) is enough. For linear systems there is also a known transformation between transfer functions and state equations, in continuous and discrete cases. There are software packages, for example Matlab and Control Systems Toolboxes, which implement these transformations quite easily.

Phase plots

For the simple constrained population model seen previously, let us make a small change: consider the population change at instant k dependent on the population of instant k-1 , that is instead of (28) we have (43) ,

$$y_{k+1} = y_k + R * y_{k-1}(1 - y_{k-1})T \tag{43}$$

A state equation with two state variables x_1 and x_2 may be obtained by the following procedure

$$\begin{aligned} x_1(k+1) &= x_2(k) \\ x_2(k+1) &= x_2(k) + R * x_1(k)(1 - x_1(k)) \\ y(k) &= x_2(k) \end{aligned} \tag{44}$$

The second state variable represents the population and the first one the population delayed one interval T.

If the trajectory in the state space is represented in a plane, called the phase-plane, the following figures are obtained.

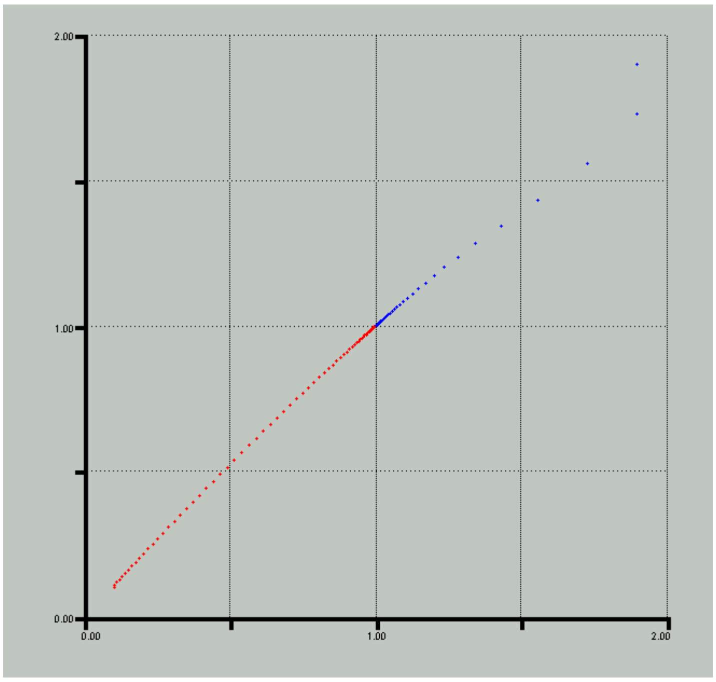


Figure 21. Phase plot of (44) with R=0.1, T=1.0. Starting from any position, the state trajectory converges towards the point (1,1) without overshoot

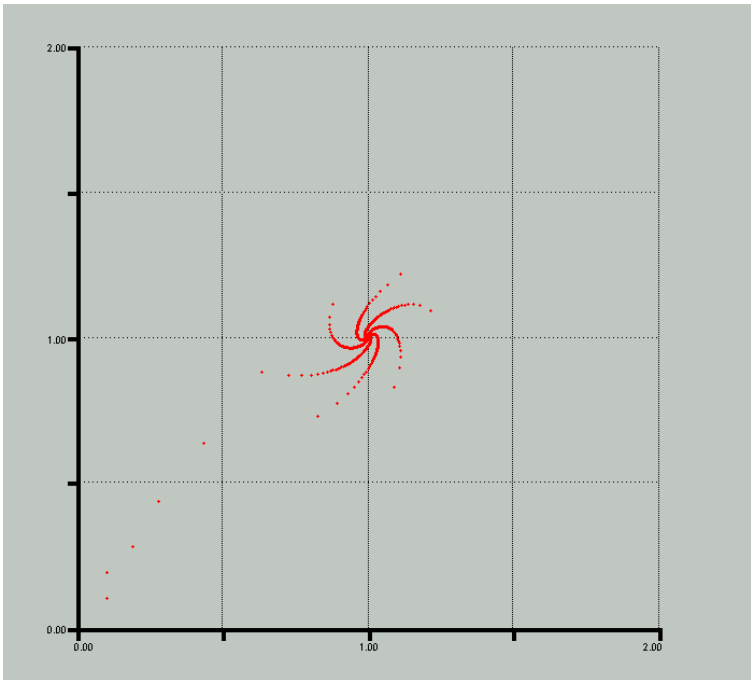


Figure 22. Phase plot of (44) with R=1.0, T=1.0. Starting from any position, the state trajectory converges towards the point (1,1) with overshoot.

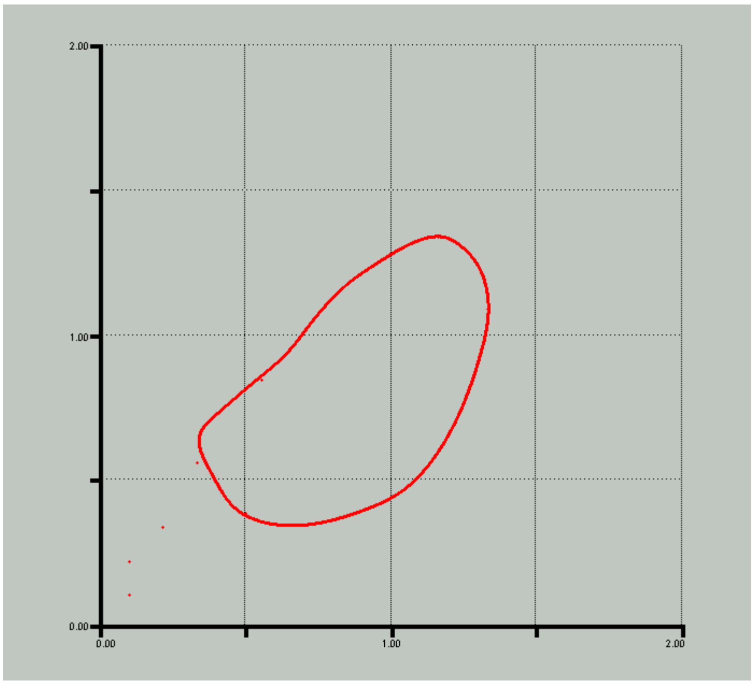


Figure 23. Phase plot of (44) with R=1.3, T=1.0. Starting from any position, the state trajectory does not converge. The system shows chaotic behaviour.

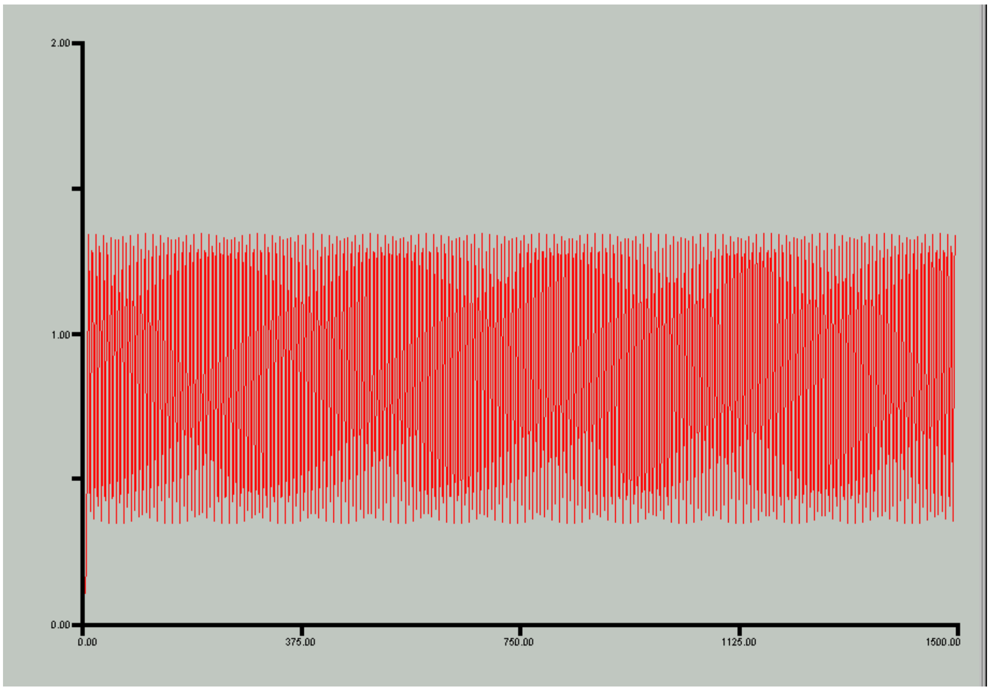


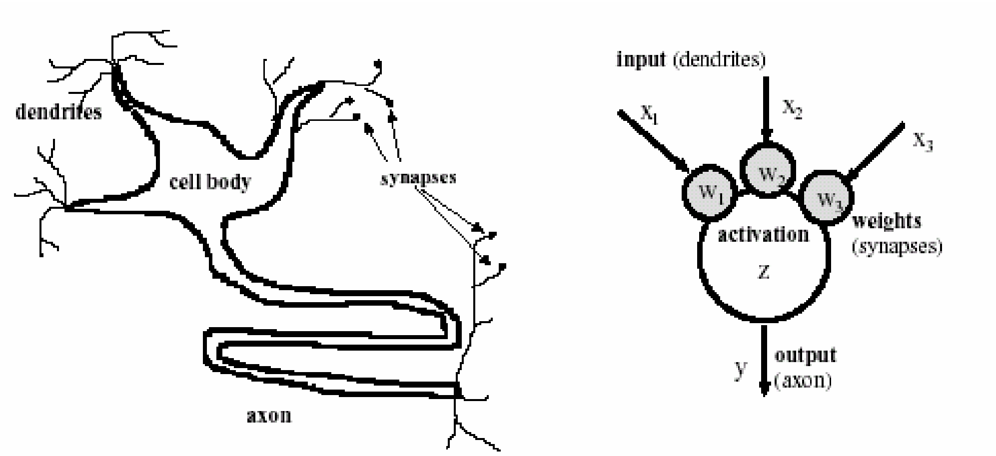
Figure 24. Evolution of the population with R=1.3, T=1.0.Ther is no repeated pattern (chaotic behaviour).

2.2.The data paradigm: artificial neural networks

The name of this representational and computational tool derives from its similarities with the natural neuron. The basic element of an artificial neural network is a single neuron that can be represented by the following figure. It is inspired by the natural neuron and its first use in academic community was in 1944 more or less at the same time of the birth of the digital computer. For a brief history of Artificial Neural Networks see [15].

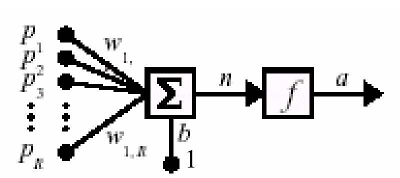
In the natural neuron it receives electrical impulses from its neighbours through the dendrites, these impulses are combined in the cell body that attains a certain activation degree and an electrical impulse is transmitted though the axon to a synapse of the following neuron.

In the artificial neuron, signals represented by numeric values are given to the input, weighted by the artificial synapses (called weights by this reason), are combined (usually summed) and the resulting signal is the argument of a certain function – the activation function - that produces as output a transformed signal.



a) natural b) artificial

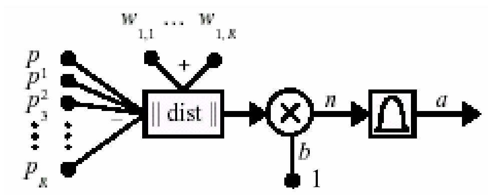
Figure 25. An artificial and a natural neuron [16]



a) Weighted sum

$$n = w_{11}p_1 + w_{12}p_2 + ... + w_{1R}p_R + b \quad \Leftrightarrow \quad n = \mathrm{W}p + b$$

$$a = f(\mathrm{W}p + b)$$



b) Radial distance

$$a = radbas(n) = radbas(\|w - p\| b) =$$

$$= radbas(\sqrt{(w_{11} - p_1)^2 + (w_2 - p_2)^2 + ... + (w_{1R} - p_R)^2})$$

Figure 26. Artificial Neuron. a) weighted sum neuron. b) radial distance neuron; the *radbas* function is illustrated in Figure 27. (From [21]).

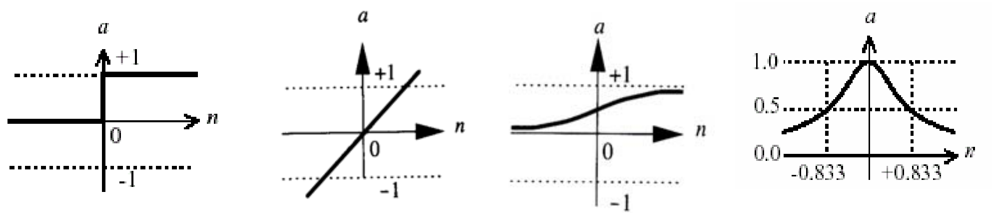
A single artificial neuron is a simple and powerful computational tool. The weighted sum n of several inputs is passed through an activation function f to produce the output a of the neuron (eq. 45).

$$n = w_{11}p_1 + w_{12}p_2 + ... + w_{1R}p_R + b \quad \Leftrightarrow \quad n = \mathrm{W}p + b$$
$$a = f(\mathrm{W}p + b) \tag{45}$$

The special output of constant value 1 is called the *bias* of the neuron, allowing a nonzero output for a zero input. It has the following degrees of freedom:

- The number of inputs
- The value of the weights
- The type and parameters of the activation function f
- The value of the constant bias.

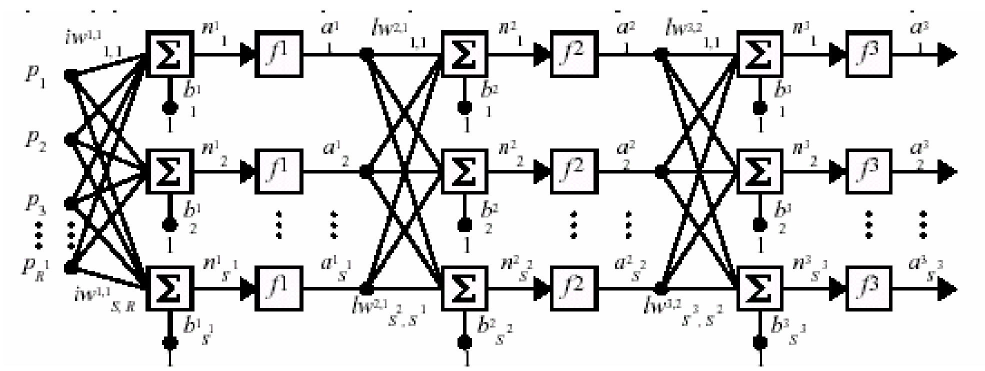
It is possible to use a multiplicity of activation functions. In Fig. 27 some of them are shown.



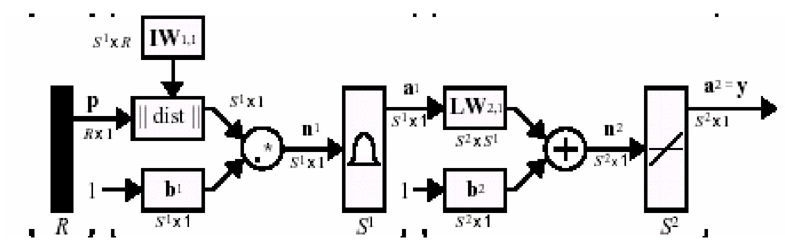
a) binary b) linear c) logistic d) radbas, radial based

Figure 27. Some types of activation functions [21].

A neuron can be combined (networked) in an arbitrary way in series and/or in parallel, giving place to structures that can model any non-linear relations between a set of inputs and a set of outputs, with or without feedback. Some of the most used structures are shown in figure 28: the Multi Layer Feedforward Neural Network (MLFNN), the Radial Basis Function Neural Network (RBFNN), and the Recurrent Neural Network (RNN) [20].



a) Multilayer feedforwared network



b) Radial Basis Function Network in matricial representation. The first layer is built with *radbas* neurons. The second layer is built with linear neurons.[21]

Figure 28: Neural networks. a) A MLFNN – Multi-Layer Feedforward Neural Network also known as perceptron (two layers in the case).b) RBF- Radial Basis Function ([21]).

Each structure has its own potentialities and is more adequate for certain types of applications. In general terms, ANN are used to find relations between two sets of data: an input set is given to the network and it is trained to reproduce the other set, the output set or to classify the input set among a finite number of classes. Training means to use its degrees of freedom to find the configuration that best fits to the situation (best according to some criteria). Figure 29 illustrates how this is done in the case of modelling biological systems.. The same input set is given to the system to be modelled and to the network. The output of the network is compared with the system output (the output set) and an error information is

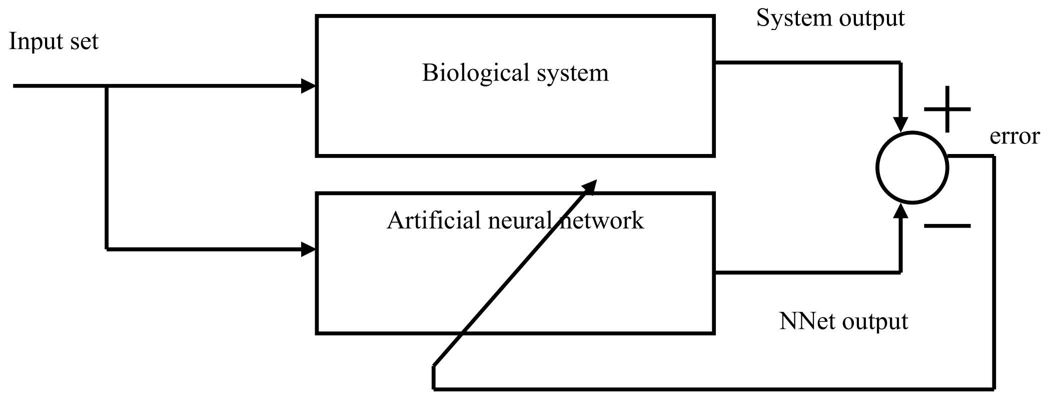


Figure 29. Training of the artificial neural network to model biological systems.

fed back to the network, where a training algorithm changes its degrees of freedom (usually the weights) until the error is minimized.

The MLFNN are RBFNN are appropriate for function approximation, like in modelling of biological systems. There is one weight for each input for each neuron, resulting in a high number of weights even for small networks. For a particular problem, the training of the network is just the procedure to find the best set of values of these weights such that the network is able to mimic the response to a certain history of inputs. After that training phase, the network is able to predict the future behaviour, or to give answers to new inputs. Of course the prediction capability of the network depends of many factors, namely the quantity and quality of inputs, the particular architectures, etc. To have a good set of examples is decisive for the "experience" of the neural network. For pattern recognition, some kinds of a single layer networks (Hebb, Widrow-Hoff, etc.[20]) can also be adequate.

Similarly, Doctors make decisions not based on a single symptom because of the complexity of the human body [16]; a doctor with more experience is more likely to make sound decisions that a newcomer because he learned from past mistakes and successes (it has more training data).

In medical decision problems, the medical symptoms, such as "stabing pain in head", are presented to the inputs (after being codified by a numerical value), as training examples.

For a set of past data, containing symptoms for which the correct diagnosis is known, the weights of the network are varied in a systematic way such that the output of the network produces the correct diagnosis (also codified by a numeric value), - “brain tumour”, “stress”, etc. The hidden layers are just used for the computation of the mapping between the inputs and the outputs.

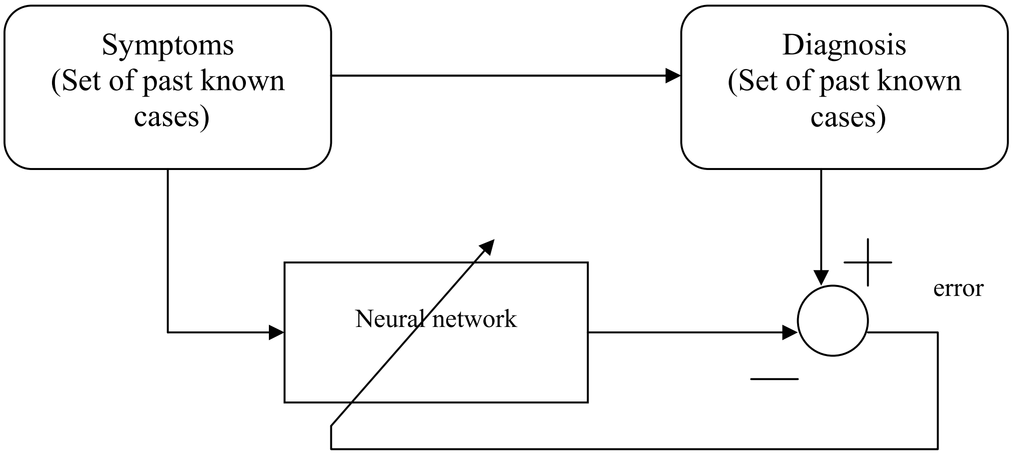


Figure 30. Training the artificial neural network for diagnosis tasks.

So the network is trained just like a doctor, being presented with a large number of known cases (training set) with known outcome. The most used algorithm for training the multilayer network, i.e., the adjustment of its weights, is the backpropagation algorithm, using the propagation of the information backwards. Basically it is a computational procedure that varies the weights in order to progressively reduce the distance between the correct answer and the network answer. The information is sent backwards because only at the end of the network (its output) can this distance be computed and the changes of the weights in the beginning of the network depend on that information.

If properly trained, the network can give answers to new unknown cases with some reliability. If the training is made constantly, as new cases happen, the networks becomes adaptive and with improved capabilities. For a good review see [23].

The total number in September 10th, 2003, of references in Pub Med under “artificial AND neural AND networks” was 2263. In the last then years the number is indicated in Table 2, ([22], in All fields). Under “neural AND networks” the total number was 8263 (most of these are related with artificial networks) and for the last 10 years the number of publications is shown in Table 3.

Year	Number of papers	Year	Number of papers
1994	125	1999	223
1995	144	2000	248
1996	167	2001	276
1997	201	2002	275
1998	232	2003	281

Table 2. Publications in Pub Med with “artificial AND neural AND networks”. The total number in September 10th, 2003, was 2263.

Year	Number of papers	Year	Number of papers
1994	424	1999	800
1995	500	2000	889
1996	628	2001	942
1997	637	2002	948
1998	727	2003	555

Table 3. Publications in Pub Med with “neural AND networks”. The total number, in September 10th 2003, was 8263.

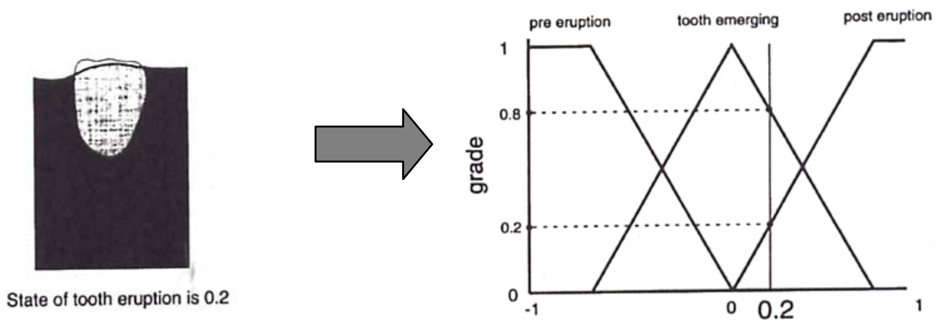
The main drawback of artificial neural networks is that they are “black boxes”: they do not give any understandable explanation for the relation between its inputs and its outputs. They just give numbers that cannot be interpreted in terms of a natural language. If the machine would become transparent, explaining the reasons for the diagnosis, then it would increase its importance and usability.

The Fuzzy systems allow making this evolution of the machine, because fuzzy logic is a way to compute with words.

2. 3. Fuzzy logic and fuzzy systems

Fuzzy logic was born in 1965 by the pioneer work of Lofti Zadeh [22], at MIT, USA, as a mathematical tool for dealing with uncertainty. In fuzzy logic statements are not “true” of “false” (as in the Aristotelian bi-valued logic), but they may have several degrees of truth and several degrees of false. Fuzzy sets do not have a well-defined frontier, but a imprecise (fuzzy) one. It is not only black and white but it has many levels of grey in-between. Consider for example the classification of teeth development in pre-eruption, emerging, post-eruption. Is there a well defined frontier between these phases? If a tooth has a state of eruption 0.2, which is its state? It is still emerging but it has already emerged! How can we represent that in the classical binary Aristotelic logic (true or false, 0 or 1, black or white)? Fuzzy sets are very convenient to represent the situation (Figure 31).

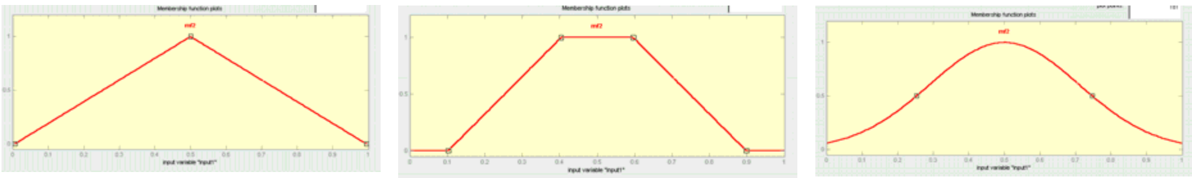
a)



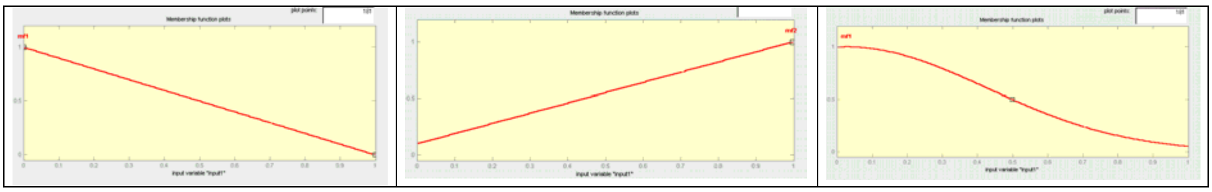
b)

Figure 31. Membership functions b) of teeth development phases. From [4]).

The membership functions, representing the membership degree may have several shapes (Fig. 32).



a) Symmetrical: triangular, trapezoidal, gaussian



b) Non symmetrical: triangular, triangular, gaussian.

Figure 32. Membership functions: a) symmetrical, b) non symmetrical.

For any variable (for example temperature) its universe of discourse is divided into several labels, each one corresponding to a fuzzy set ("very low", "low", "regular", "high", "very high", for example).

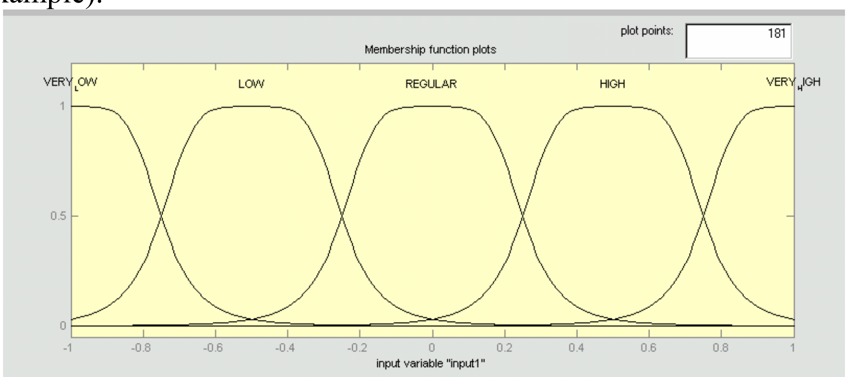


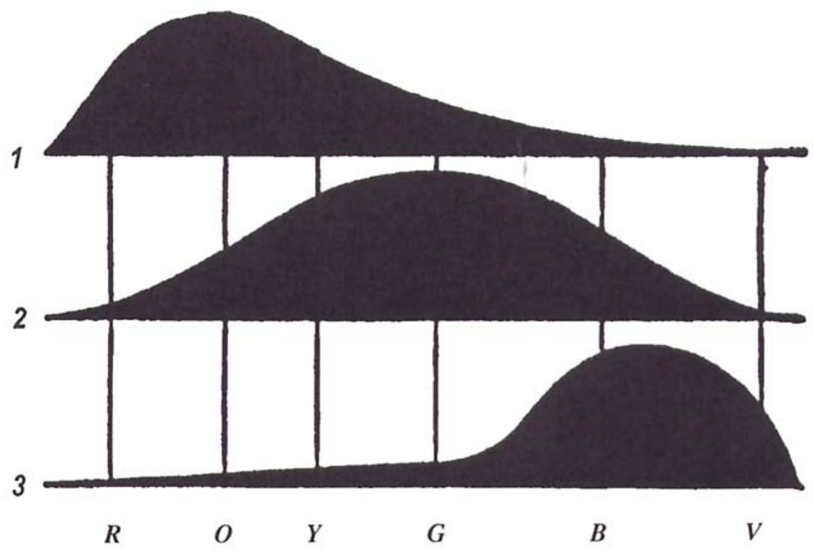
Figure 33. A universe of discourse (one variable) divided into 5 fuzzy sets. The first and last ones are non symmetrical.

The fuzzy sets must overlap and they must cover completely the universe of discourse (all the interval of possible temperatures, in the example and as illustrated by Figure 33).

Usually they must overlap in such a way that the sum of the membership degrees for any point is 1, and at most two sets are valid for that point.

Fuzzy logic is the logic of fuzzy sets. In fuzzy logic there are many levels of truth and of false, in the real interval [0,1]. A value in the universe of discourse belongs simultaneously to several fuzzy sets eventually with different membership values.

There are some characteristics of our brain that can be seen as fuzzy sets. For example the way our brain identifies colours. According to Sir Thomas Young (1802) theory [5] there are three principal colours, red, yellow and blue and three types of visual receptors.
The way these visual receptors vibrate with the colours wavelengths is illustrated in Fig. 34. Maximum excitation in each is produced by one wavelength; adjacent wavelengths produce progressively less activity in the particular receptor.
This seems to be the case of all sensorial systems: although we have many neurons, there aren't enough to function as crisp sets- for each neuron to have a specific function (e.g. to encode blue triangles) distinct and disjoint from that of every other neuron. There is too much information to be encoded. The sensitivity functions of all individual neurons in all sensory systems are bell-shaped, at a first approximation and have been referred to as "Neural Response Functions"(NRF) [5]. There are few neural resources to represent many stimuli. So the few neurons available must have fuzzy sets (NRF's) that are as broadly as possible to cover all stimuli.



(Red, Orange, Yellow, Green, Blue, Violet)

Figure 34. Illustration of the theory of Young. The curves show the amount of activity of each of the three visual receptors types by each wavelength (of the several colours). Maximum excitation in each is produced by one wavelength, and adjacent wavelengths produce progressively less activity.(From [5]).

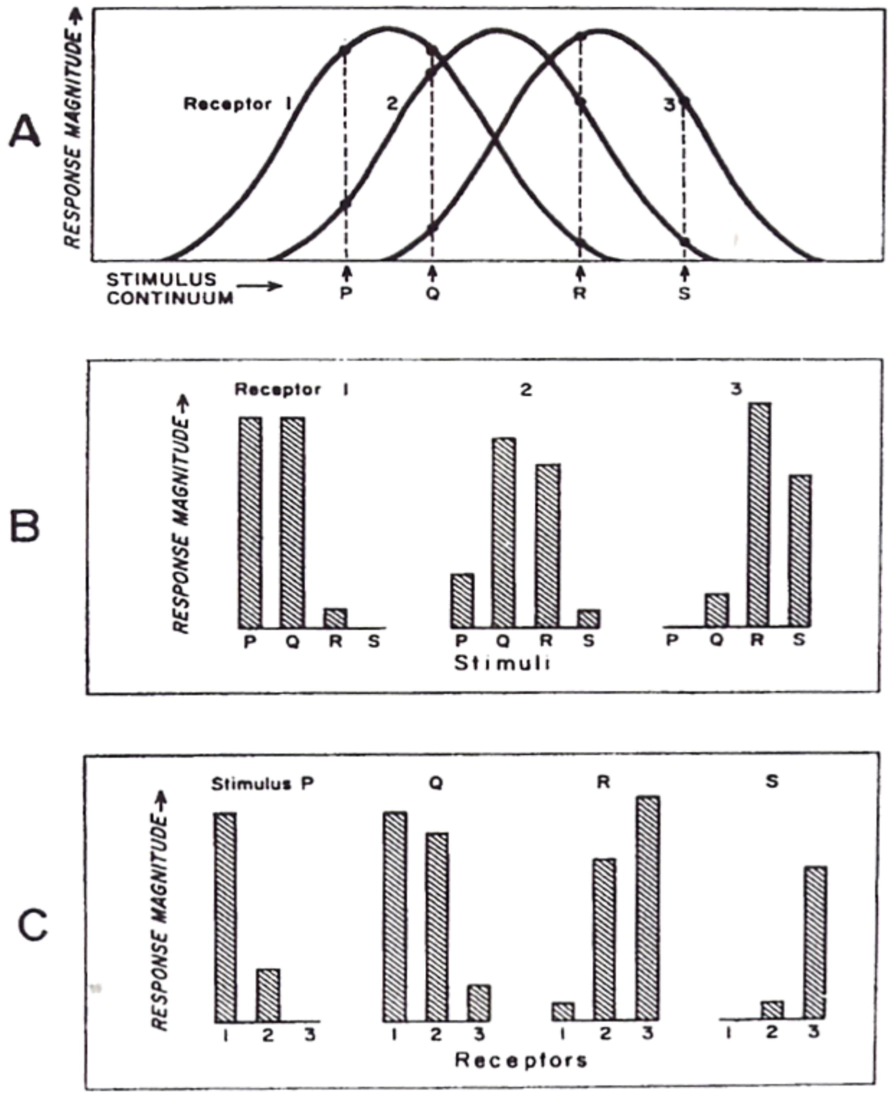


Figure 35 . Fuzzy sets and neural codes according to Young's theory. In A, three idealized receptor types (1,2,3) and 4 stimulus (P,Q,R,S). In B the magnitude of the response of each receptor to each stimulus. In C the neural codes for P, Q, R, S. Now the brain interprets these codes. From [5].

Fuzzy systems work in a similar way. Using fuzzy sets and fuzzy logic, fuzzy inference systems may be built enabling to compute a decision based on a set of rules. Fuzzy rule based systems perform a sequence of fuzzy logical operations: fuzzification, conjunction, inference, defuzzification [26].

Fuzzification is the operation of transforming a numeric value, issued from a measurement, into a membership degree of a fuzzy set. In the figure there are 2 measurements: Symptom1=-0.443 and Sympton2=0.193. All four rules have some degree of truth and some degree of false. All rules must be *fired.* To compute the firing intensity of one rule,

one may consider the weakest case in the antecedents, corresponding to the application of the minimum operator. Now we transport these values to the consequents. This is done by cutting the fuzzy set of the consequent at the height equal to the firing intensity of the antecedent The graph shows that (in blue, on the right): rule 3 is quite truth, rule 1 is about 0.3 truth, rules 2 and 4 are about 0.2 truth.

The final decision is the result of the balanced contribution of the four rules. The defuzzification is this balancing, in order to obtain a numerical value to be assigned to the decision.. If the four figures (of the consequents) are superposed, in geometrical terms the point of equilibrium is the center of mass. This is the most used defuzzification method and is used in the example.

The graphical construction is quite intuitive. Formally, there are some properties and operations of fuzzy logic supporting it. For example the cutting of the membership function on the consequent is made by a minimum operator:

Diagnosis = min (Symptom1, Symptom2)

The operator maximum performs the aggregation of outputs:

OutputFinal = max(diagnosis1, diagnosis2, diagnosis3, diagnosis4)

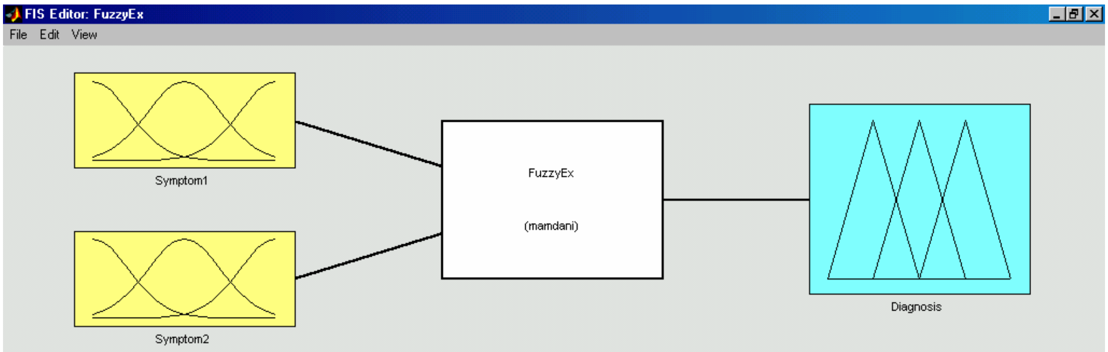


Figure 36. The fuzzy system

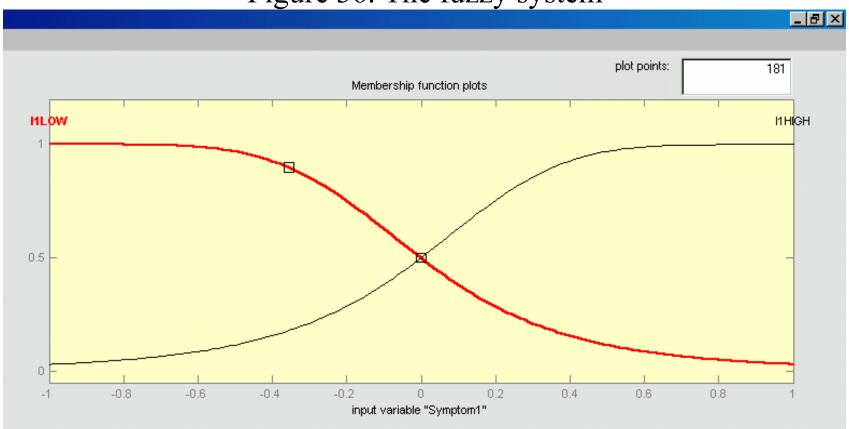


Figure 37. Membership functions for the example are similar for both inputs and output.

Rule 1: IF Symptom1 is LOW and Symptom2 is LOW THEN Diagnosis is LOW
Rule 2: IF Symptom1 is LOW and Symptom2 is HIGH THEN Diagnosis is HIGH
Rule 1: IF Symtom1 is HIGH and Symptom2 is LOW THEN Diagnosis is LOW
Rule 1: IF Symtom1 is HIGH and Symptom2 is HIGH THEN Diagnosis is HIGH

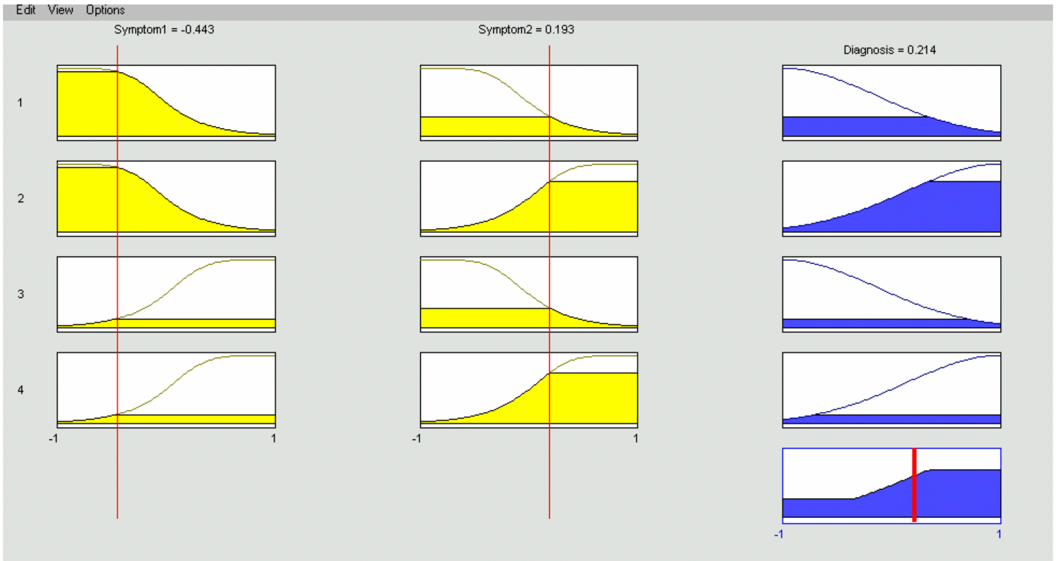


Figure 38. Firing the rule base: fuzzification, conjunction, inference, defuzzification.

Takagi-Sugeno fuzzy systems

Takagi-Sugeno-Kang fuzzy systems are based on rules that have a non-fuzzy consequent. They are in the form (for a similar example).

Rule 1: IF Symptom1 is LOW and Symptom2 is LOW THEN Diagnosis is 0
Rule 2: IF Symptom1 is LOW and Symptom2 is HIGH THEN Diagnosis is 1
Rule 1: IF Symtom1 is HIGH and Symptom2 is LOW THEN Diagnosis is 1
Rule 1: IF Symtom1 is HIGH and Symptom2 is HIGH THEN Diagnosis is 1

Figure 39 illustrates how it works.

Now for the same measurement values, it proceeds as follows:

Rule 1: firing strength: 0.15 output1 = 0
Rule 2: firing strength: 0.75 output2 = 1
Rule 3: firing strength: 0.15 output3 = 0
Rule 4: firing strength: 0.4 output4 = 1

The overall output is the sum of the individual outputs weighted by their degrees of truth, i.e, the firing strength of the respective rule, giving 0.8. It is in blue on the right of the Fig. 39.

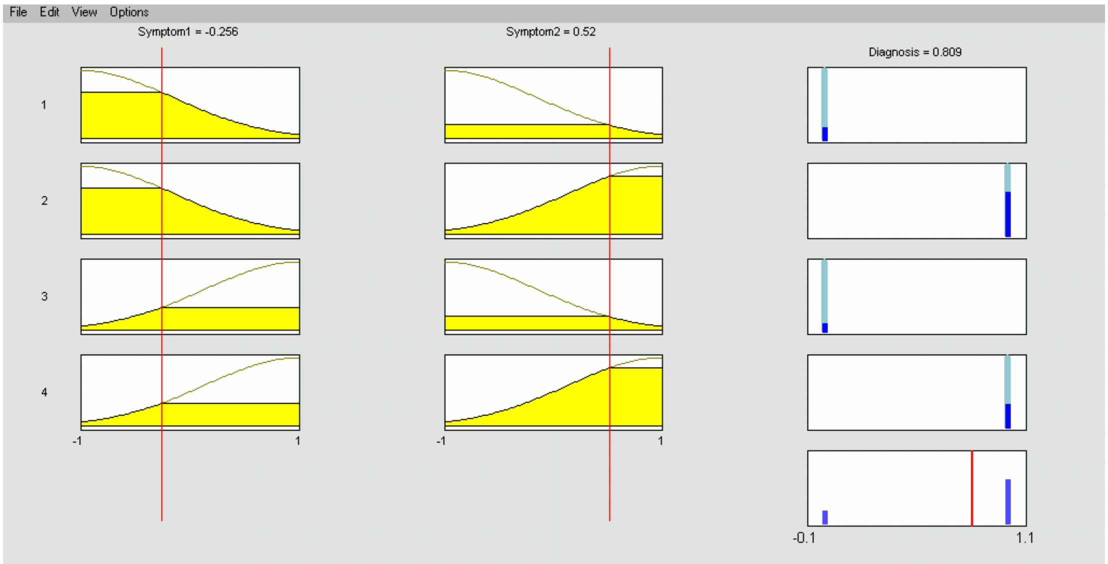


Figure 39. Firing the rule base in TSK model: fuzzyfication, conjunction, inference, defuzzification.

TSK fuzzy systems are simpler to compute that the previous ones called Mamdani fuzzy systems. They are particularly important in neuro-fuzzy system.

A fuzzy system is a set of fuzzy rules describing what is known about some problem. The development of the fuzzy system is basically the writing of the rules. How to obtain the rules?

Several approaches are used and will be studied during this course:

- Expert interviews (actual medical knowledge),
- Simulation using models of the processes (seldom possible),
- Rule extraction from data,

This last is becoming the most important. Machine (computer) learns from data. Two aspects must be analysed:

- The determination of an initial set of rules (the initial structure of the system)
- The update and optimisation of the rules as new data and knowledge becomes available.

For the determination of the initial set of rules, the most important technique is clustering.

The second operation, the optimisation of the fuzzy structure (i.e., the number of rules, the parameters of the membership function, etc) is actually carried out in the context of neuro-fuzzy systems

The first application of fuzzy logic to the medical field dates back to 1969, when Zadeh published a paper on the possibility to apply fuzzy sets in biology[17].

The number of papers published on fuzzy logic in medicine during the last 10 years, are given in table 1 (Pub Med [22] under "fuzzy, on September 10th 2003, All fields").

Year	Number of papers	Year	Number of papers
1994	72	1999	131
1995	107	2000	149
1996	98	2001	210
1997	127	2002	183
1998	133	2003	118

Table 4. Publications in Pub Med with "fuzzy" (all fields) in September 10th 2003. The total number was 1827.

The first applications were related to assessing of symptoms and the model of medical reasoning. For a more detailed historical perspective of the early stage see [18].

For the similarity between fuzzy reasoning and the physiology of the nervous system, see Erikson and Coll (1999)[19], where the dynamic model of sensory systems, by the neural response functions, for example for taste neurons, is made by a TSK fuzzy system.

Under "neuro-fuzzy", all fields, the number of publications in Pub Med on September 10th, 2003, was as indicated in Table 4.

Year	Number of papers	Year	Number of papers
1994	0	1999	6
1995	1	2000	4
1996	1	2001	10
1997	1	2002	10
1998	0	2003	5

Table 4. Publications in Pub Med with "neuro-fuzzy".

Conclusion

The application to biological and medical systems of the general systems theory and methodologies, including the modern techniques of computational intelligence (such as neural networks and fuzzy logic) is the subject of an intense activity in research community. It is expected that this will allow important progresses in decision support for all parts involved in the process and that advanced medical systems will embed many of these techniques. Biological systems (including medical) will probably be a field of convergence of modern digital technology and modern biology (see for. ex. [27]).

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