THE APPLICATION OF SYSTEMS THEORY IN BIOLOGY. AN INTRODUCTION*

A. A. VERVEEN

Starting point: the basic model

If we look around us at what is going on and observe it carefully, we can make the following statements about what we see:

Organisms (plants and animals, including man) are in constant interaction with their environment. (1)

The environment is not static; it changes constantly. (2)

Organisms react to these changes in their environment, and in their turn they influence the environment by their activities. (3)

In these three sentences something essential about the functioning of living organisms is expressed in words. And this is done in such a way that, taken together, these sentences form a *verbal model.* Two 'things' are mentioned, things we can only name by indicating them here: the things we call organisms and also the things we call environment. To be able to make this model, we had to make agreements (albeit unspoken) about the names, and if we are to avoid confusion we must hold to these agreements. The six words with which the first sentence begins form a reminder of the agreement about indication. This is the basic or fundamental agreement we must maintain in proceeding with the analysis. We can now make an agreement about the concept 'environment' by saying that we shall call the collection of all the things (living and non-living) outside an organism its environment.

We can understand a verbal model by reading or hearing it. But this takes time and, in addition, we must also be able to remember exactly what we have just read or heard. It is much easier to grasp a model by looking at it. For this purpose we use drawings or photographs comparable to the comic strips and photographs in newspapers. But if these graphic representations are to be understood, agreements must first be made about the mode of representation.

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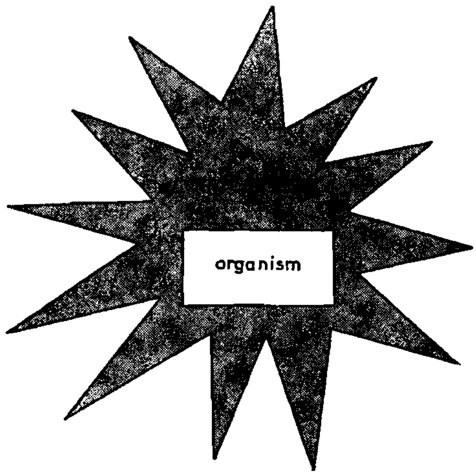
Consequently, I propose to make an agreement with you as reader that in this paper and for its duration, a thing will be represented by a rectangle. Furthermore, the name of the thing will be written in this rectangle. One such thing is an arbitrarily chosen organism:

The environment is contained in this representation, because everything inside the rectangle belongs to the organism. Everything outside it does not belong to the organism and therefore, according to the agreement, represents the environment.

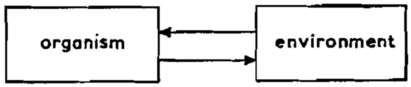


But because the environment too forms a 'thing', i.e. the entirety of all the things that do not belong to the organism, we can also represent the environment by a rectangle. Now the rest of the sheet of paper no longer functions as the symbolic representation of the environment:

This configuration represents only part of what we can observe about organisms and of what is described in sentences (1), (2), and (3). A change in the environment will exert an influence on the organism – for instance, if the light fades it will become dormant – and, conversely, the organism influences its environment: it takes up certain things from the environment – it eats – and after some time it expels things – it excretes (solids, fluids, and gases). As a result, the environment too is changed.

We shall now agree to use an arrow to represent the effect of a change in the environment on the organism:

The reciprocal situation, i.e. the influence of the organism on its surroundings causing a change in its environment, will likewise be symbolized by an arrow:



Now the graphic model is rounded, both literally and figuratively. Why this is so will be explained in the next paragraph.

How the basic model works

Since an arrow represents an event, i.e. 'something' flows from one thing to another, the concept 'change' is automatically included in this diagram. Similarly, the 'constancy' of this relationship is also included in the permanent nature of the drawing. This drawing is consequently more than a deliberately constructed collection of symbols; because (with due observance of the agreements about rectangles and arrows) it may be said to function, it is a model. By comparing this graphic model with the verbal model formed by sentences (1), (2), and (3), you will be able, perhaps after a little practice, to see that both models describe the same event.

This drawn model is highly generalized, it does not refer to a particular organism or one particular species and it also does not say anything about particular changes and interactions. But although it does not do this, it nevertheless in essence tells more than it seems to. Despite the fact that it looks so simple, it has predictive power. For if we allow this model to function in our mind, by regarding it with observance of the agreements we have made a sequence of changes follows, such as:

The environment changes;
this change affects the organism;
the organism changes;
this change affects the environment;
the environment changes;
this change affects the organism;
and so on.

Thus, this model predicts the possibility of the occurrence of a circular course, a cyclic process which starts with a change in either the environment or the organism. If, keeping this result in mind, we look at real organisms, we see that such processes do indeed occur. To give an example:

X comes to work in a state of irritation. His colleagues (*X*'s environment) notice this and become fidgety, which makes *X* even more irritable. This goes on until *X* can no longer stand it. He gets up and leaves, banging the door after him.

Here we have a cyclic process ending in a small explosion.

The *form* of the cyclic process in this example (the explosive course) is not included in our graphic model, but the cyclic process as such is present in it. This is even directly visible: the graph contains a loop. As a result, this model has more force than the verbal model in which the words and sentences follow each other, neatly arranged on the basis of the pertinent rules. The verbal model is limited by this linguistic structure, which obscures it and makes it more difficult to think through. The graphic model makes the consideration independent of the time required to read the verbal model and of the structure of our sentences, and this makes the structure easier to distinguish and the processes easier to follow.

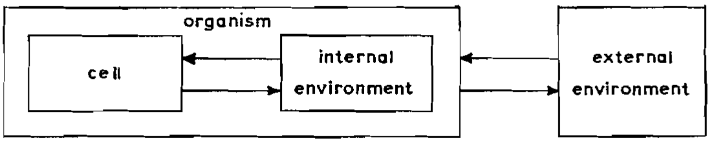
The word 'process' has meanwhile crept into these considerations, indicating something which takes place in time, something that happens. Such a process can be indicated, but the one to whom it is indicated must expend time to follow and comprehend it. A thing can simply be indicated.

Considerations such as those given here concerning the difference in power between graphic and verbal models also apply to mathematical models. With due observance of the agreements made regarding the mathematical symbols, changes in time can be represented easily and precisely and be perceivable at a glance. It is impossible to represent such changes in time solely by the use of words (try to describe verbally the path in space and time of a stone thrown away or of a car when you brake suddenly). In fact, the use of diagrams and symbols as done here is already mathematics.

Systems

The graphic model we have discussed consists of two rectangles – the things – and two arrows – the relationships (changes, their direction and their effect). In our consideration the model functions because it represents processes, effects of one of the things on the other, or the reverse, or a cyclic process. We call a functioning whole of this kind, which consists of things that are interrelated with each other, a system.

Up to this point we have considered organisms and their environment, for which we made a general model. In the same way we can consider groups of organisms, their interactions, and the relationships with their environment of such groups (a herd, a colony, a society or state). Closer study also reveals sub-systems in organisms, for instance the living cells. These parts of organisms are in constant interaction with surrounding cells and with the intercellular fluid. In 1859, Claude Bernard gave this extracellular fluid the paradoxical name *milieu interne* (internal environment). A very good name, which gives the localization of the fluid exactly: in the organism, around the cells. To distinguish the environment outside the organism from the internal environment, Bernard called the former the *milieu extérieur*, the external environment. A graphic representation of this complex system would look like this:



In this representation the relationships between the innermost and outermost systems are not indicated. As a result, the whole does not function, and this graphic representation therefore constitutes a scheme and not a model.

Complex systems and their investigation

Organisms are things which are in constant interaction with their environment and which show a relatively high degree of stability in the constantly changing environment. They not only reproduce, grow, and develop (as a result of which a species shows a high degree of stability) but also react to changes in the environment: they avoid or compensate for disturbing influences, they defend themselves, and they repair themselves (and possibly each other). To do all these things they take from their environment both nourishment (nutrients and energy) and information about the state of the environment. They affect their environment in ways that we call purposeful and goal-directed.

Things that behave as just described, we call living. And the sciences that are concerned with these living things and combinations of them, we call the life sciences. Taken in this sense, the term life sciences covers all research on organisms and on organizations composed of organisms, a field which embraces at one extreme the biological sciences (the study of plants and animals) and at the other extreme the social sciences (the study of the structure and functioning of large organizations formed by people).

The complex structure and activity of organisms and their relationships with comparable organisms as a result of which they form part of still more complex organizations, distinguish them from the normal research subjects in classical physics and chemistry and make them correspond with the automatons, computers, factories, and man-machine systems in the technical sciences.

Within these sciences the systematic investigation of constructed systems led to the origination of systems theory (as well as to parallel developments in the biological and economic sciences). The use and development of this approach pushed the life sciences ahead of the classical physical and chemical approaches (which are incorporated into the life sciences).

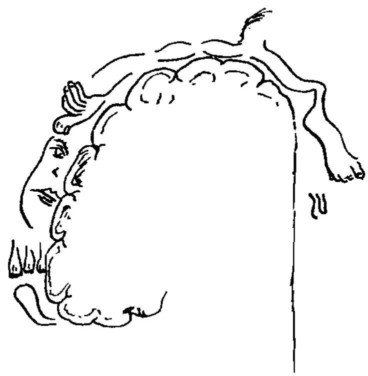
The life science that is concerned with the functioning of living organisms is called physiology. Within this field of research, sub-sciences have formed that are concerned with certain sub-systems, for example molecular genetics (the study of the structure and function of the molecules responsible for the transmission of hereditary characteristics and which control the development of the organism), biochemistry (which is mainly concerned with the chemical subsystems of organisms), biophysics (the study of the physical characteristics of relatively simple sub-systems), and cell biology (in which the cells themselves are the object of study). At present, physiology is restricted mainly to the study of complex sub-systems in organisms, which is an extremely large and largely untouched field. The terms control and regulation occur frequently in articles and books on physiological subjects, and there is increasing contact with other sciences concerned with control, regulation, communication, and computation, that is, with the technical sciences and psychology – and in the future, according to expectation, with the social sciences.

To illustrate the importance of the systems approach, in the second part (homeostasis, etc.) I shall work out a very simple regulatory system on the basis of systems providing for the constant temperature and composition of the internal environment. As you will see, even this simple approach provides a great deal of insight into the functioning of this type of system as well as into the disease processes that can occur in such systems. But this approach is not only important for physiology; it has equal value for other systems (among them social systems) – as the physiologist Cannon pointed out as early as 1932.

All living things function by model formation

You have now seen how a biological model originates, as it were, 'spontaneously' (and this is in no sense limited to biological models). Every description that is involved in the interaction with the described system is in essence a model of that system. Such a description of something – whether that something is a biological sub-system or a relationship between nations – opens the interaction of the describer with that something. If this does not occur, the description is invalid and must be rejected. In this description the power to act is contained, a power which can vary from being able to count, on the one hand, to the governing, even the control, of entire nations on the other. In the last case the model of the situation to be controlled cannot be completely verbalized – we then often speak of an intuitive or ingenious approach – and is therefore itself incomplete, so that it ultimately fails. This is certainly the case for the excessively simplified model formation involved in control by dictatorships.

What is this mysterious power the model possesses? Physiology can begin to answer this question. How does the brain 'know', for instance, that the foot is touched? Because a signal is sent from the foot to the brain? It is, but that is not enough. The brain appears to work with a functional model of the surface of the body.



The most important body surfaces (i.e. of the hands, the face – particularly the lips and the area around them – and the feet) occupy a large place in this model, the remaining surfaces a smaller one. Our muscles are functionally represented in the same way, again according to their importance for the organism. We find this kind of representation in our cerebellum too, and in other neutral structures. Thus, to return to our example, if the foot is stimulated because someone steps on it, the signals sent to the brain will activate the cells that represent the foot in the region that models the body-surface area of the foot. In another part of the brain (the 'visual brain') we find cells whose activity signals a straight line; these cells represent this kind of line, other cells parallel lines or an angle between two lines. There are probably – still unidentified – cells that become activated when a letter or some other pattern is seen. All these activities represent certain processes, and through their representation form a model for the process in question, one which is used in further activity. This is not a trivial matter. Where in nature – things not formed by our hands – do we find straight lines, parallel lines, and angles between two straight lines? Can we work and live just because we analyse and rework everything by means of the formation of often abstract but effective models?

The word table forms a model for a table, and evokes a table in your mind as well as mine. You 'see' a table before you, your model 'table' is activated. Is this pure hocus pocus or have we stumbled over an essential aspect of our existence? To my way of thinking, it is related to the old question about 'reality'. What is reality? That which is effective, no more and no less. Take telepathy. Even though telepathy has long attracted attention, the man has not yet been born who, feeling sick, would think of getting in touch with his doctor by telepathy. No, he uses a messenger or he reaches for the telephone, because that is effective. Only in unverifiable matters in which the telephone or direct transport does not help would he possibly – and that would depend on his sense of reality, his is-it-effective? sense – resort to telepathy. This is a kind of model that is apparently ineffective: a fiction. Only that which can be 'modelled' is effective, and we can work and live only because we make models, not only in theory or daily practice (although we are rarely conscious of doing so) but also because of the processes in us which work on the basis of model formation. Our brains – and those of animals – continually form models of, and in interaction with, their environment, and anything which is not effective is discarded. We do this consciously too, and then we call it science or technology or statecraft, or any name your interests or professional field would lead you to apply. When processes are guided, the one who does the guiding forms a model of the process, tests it, and is then compelled to include it in the interaction with that process. If this is not done, there can be no interaction. For living systems, processes and models of processes are both indispensable aspects of what takes place, and both are equally real when used together and equally fictive when separated. In short, the making of models is an essential characteristic of living organisms. Recently, this has been derived rigorously by Conant and Ross Ashby: every good regulator of a system must contain a model of that system. Our brain (and thus we ourselves) *must* function by the formation of models on pain of death.

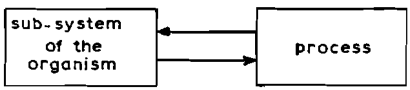
Homeostasis

In the second half of the last century Claude Bernard discovered that the cells of our body are laved by a fluid. He called this fluid the *internal* environment. In the following the term blood will often be used to denote this fluid, although it is not entirely correct to do so. From this fluid the cells take the substances they require to function, and to it they return their products and wastes. Claude Bernard also discovered that the characteristics of this fluid – its temperature and composition – are kept constant within narrow limits. The body temperature of warm-blooded organisms varies little, despite wide fluctuations in the temperature of the external environment. And regardless of the variation in the amount of nutrients taken from the food or of the substances produced by the cells, the concentration of salts and other chemical substances in the blood shows little variation. How is this possible?

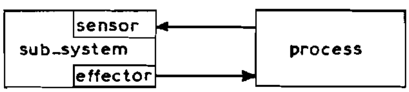
As early as the eighteenth century, Seguin and Lavoisier came to the conclusion that regulatory systems must be present in organisms to preserve 'the balance of the animal economy'. But it was not until the beginning of this century, after the First World War, that the physiologist Cannon introduced the concept of the regulatory system in a form that could be used for the description of systems providing for the constant composition of the internal environment, which is a necessary prerequisite for the ability of organisms to function. For this regulation he introduced the term homeostasis. Following Cannon, we shall call regulatory systems that keep a given state as constant as possible, homeostatic systems. In the field of physiology it was only after the Second World War, that the possibility of quantitative computation, based on methods known for control engineering, became more widely known. This was the result of the publication in 1948 by Wiener, a mathematician, of a book entitled 'Cybernetics, or Control and Communication in the Animal and the Machine', in which he showed that this application greatly increases our understanding of the processes occurring in the human body.

Homeostatic systems

When a certain state such as the body temperature or the level of a substance in our blood is kept constant in spite of loads and disturbances, it is evident that this state of the process in question is controlled by something. By a system in close interaction with this process. The general interaction model developed before can therefore be applied here in this way:



But this must now be worked out further. Since the state of the process is kept roughly constant despite disturbances, the organism must possess organs with which the process requiring control can be observed continuously. These organs we call sensors (literally: feelers) or, in technology, transducers.



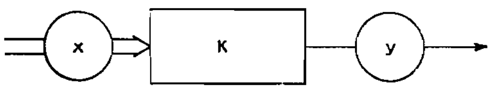
Thus, there are sensors that constantly take (measure) and transmit the body temperature, and others that continuously register the concentration of a given substance in the blood and transmit the data they obtain. In other words, a sensor is a coding apparatus. A temperature sensor (in our jargon a thermoreceptor) takes the temperature (x) of the process, and according to whether the temperature (the input x of the sensor) is higher or lower (in which case x is larger or smaller, respectively) the sensor will report this change to the organs that will process this information. The quantity reported, the output y of the sensor, is a measure for the input quantity x, and differs in nature from x (hence the term transducer). For a temperature sensor, x is the temperature of the process and y is an electrical signal.

These different energetic structures of the process and of the signals (e.g. heat *versus* electricity) will be indicated in this paper by the use of double and single arrows, respectively. The amplitudes will be indicated by means of algebraic symbols in circles. For our sensor, thus, we have:

For other organs the output signal can also occur and be transmitted in chemical form. We then speak of chemical signals, chemical messengers, or hormones. Here too, the *amplitude* of the output signal y tells something about the measured quantity x. We can formulate this more strictly by saying that the value y of the signal at the output is a function of the state of x at the input of the organ. This relationship can be described mathematically. To keep it as simple as possible, we shall use the simplest mathematical function applicable to this case. We assume, therefore, that the output is proportional to the input:

$$y = Kx$$

in which K is a constant, the proportionality constant. K may have the value of, for instance, $\frac{1}{2}$ or 1 or 9.4. Thus, it is a question here of simple multiplication. This constant K is called the transfer factor of the sensor. And in the graphic representation we write K in the rectangle representing the sensor:



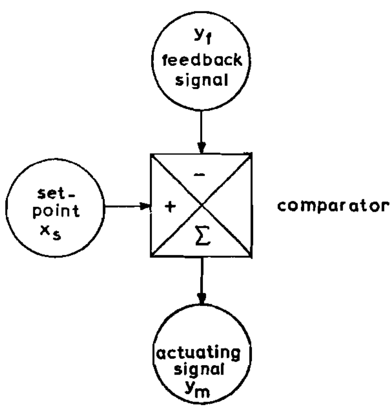
Which we again read as $y = Kx$; or put into words: for this sensor the output y is equal to K times the input x.

Effectors

The organism must also possess organs by which it controls the state of the processes that are regulated. We call these organs the *effectors* (literally: do-ers) or, in technology, actuators. When, for instance, the body temperature is in danger of dropping due to some disturbance, the organs producing heat receive orders (the input signals for these effectors) to increase heat production (the output variable), as a result of which the body temperature rises. Here again we see a difference in the form of energy at the input and output, for example an electrical input signal and heat as the output variable. The size of the output is again a function of the value of the input signal. In its simplest form this relationship too can be described by a multiplication, the constant (K_2) now being greater than 1. The signal itself does not require much energy, but considerable energy is produced at the output. For this power amplification a considerable source of external power must be available to the effector. We shall now indicate the transfer factor for the sensor by the index 1, giving K_1.

The comparator

How are the signals from the sensor processed and how is the effector controlled? The information from the sensor is sent via a channel or transmitter (the thin arrow) to a comparator. This apparatus compares this quantity with a quantity representing the desired state of the process. And since the comparison of two processes means that the difference between them is estimated, an apparatus that performs a simple calculation, i.e. a subtraction, will suffice. In engineering this kind of apparatus, the comparator, is symbolized by a circle, often with a cross in it. Because this would be confusing due to the agreements made for the duration of this paper, we shall use a square containing a cross. The comparator has two inputs, one for the feedback signal y_f (the f indicating feedback) from the sensor of the process and one for the quantity symbolizing the amplitude of the desired state, the reference input. For homeostatic systems that attempt to maintain a constant value for the controlled quantity of the process, we call this reference value the set-point x_s (with the s of set-point).

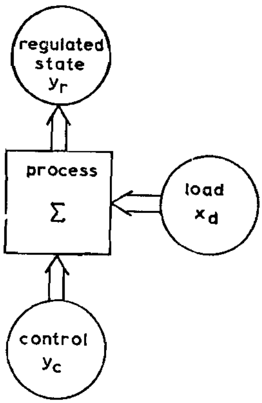


The actuating or error signal at the output y_a (a for actuating) is equal to the difference between the set-pcint value x_s and the feedback quantity y_f of the process (this is indicated in the graphs by the use of the sign $\sum$ and the + and − signs). Written as an equation, this configuration reads:

$$y_a = x_s - y_f.$$

The process

Finally, the process itself. Like all processes, it is exposed to the influence of the environment, which disturbs it or makes demands on it (x_d, with the d for disturbance). The lower external temperature and its fluctuations influence the body temperature, and the effects of these influences must be corrected, which is done by the heat supply y_c (the c for control) from the effector.



The regulated state y_r (the r for regulation) is equal to the sum of the load x_d and the actuation y_c:

$$y_r = x_d + y_c.$$

It is this quantity y_r which is registered and transmitted by the sensor.

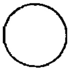
This notation can now be used to describe the functions of the sensor and the effector as:

$$y_t = K_1 \cdot y_r \quad \text{and} \quad y_c = K_2 \cdot y_a.$$

List of agreements

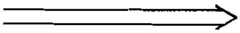
Now that all the parts of the system have been discussed, it will be useful to tabulate the agreements we have made. This will serve to refresh our memory before we approach the complete system.

apparatus, organ



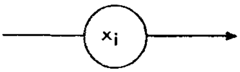
quantity

organ with input and output

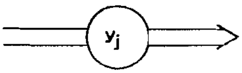


energy flow

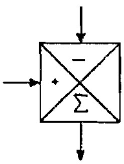
signal flow (which occurs over transmitters)



signal flow with indication of value and function (index)



energy flow with indicated value and function (index)



comparator (two inputs, one output), the output signal being equal to the difference between the two input signals

$\sum$ = summation sign

x = independent variable

y = dependent variable

K = a constant

x_s = set-point

x_d = disturbance or load

y_r = regulated state

y_f = feedback signal

y_a = actuating signal

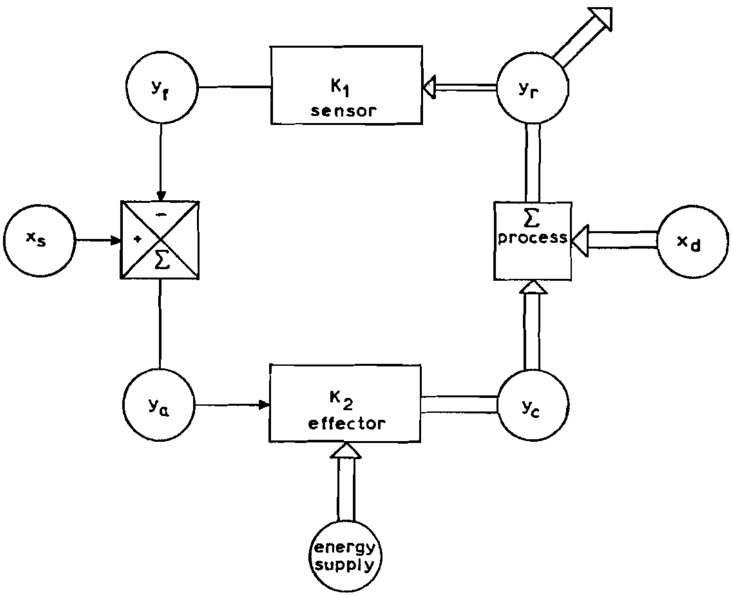
y_c = control variable

K_1 = constant of sensor (feedback transfer factor)

K_2 = constant of effector (forward transfer factor)

The primitive homeostatic system

So far, we have only included a few things: elements or organs which summate quantities (the comparator: a subtraction; and the process: a simple addition), organs which multiply quantities (sensor and effector), and transmitters for the signals. We have not taken into account delays in the transmitters via which the messages are sent (from sensor to comparator and from there to the effector) or the time required for an effector to reach a desired level of activity or for the process to reach the intended state. We shall leave these factors out of consideration to avoid complicating our model, although the result will be a primitive model. This is not objectionable, however, because the model can always be adjusted. If we now combine the parts we have discussed, we obtain the graphical model:



This system has a circular structure, a so-called closed loop. The *forward path* runs from the comparator over the effector – which must draw on a supply to deliver the required energy – to the process. The state of the process is reported to the comparator over the *feedback path* via the sensor. This is why this system is called a feedback control system. And because comparison is performed here (note the minus sign), the system is said to be a *negative feedback system.*

There are two independent variables, which are the inputs to the system: the reference value (set-point) x_s and the load or disturbance x_d. The system output is the controlled or regulated state y_r. We can now calculate the value of the (desired) regulated state y_r by letting the model function, and we can begin at any arbitrary point in the loop.

sensor:	$y_f = K_1 y_r$
comparator:	$y_a = x_s - y_f$
together:	$y_a = x_s - K_1 y_r$
effector:	$y_c = K_2 y_a$
together:	$y_c = K_2 x_s - K_1 K_2 y_r$
process:	$y_r = y_c + x_d$
together:	$y_r = K_2 x_s - K_1 K_2 y_r + x_d$
thus:	$y_r(1+K_1 K_2) = K_2 x_s + x_d$
and therefore:	$y_r = \dfrac{K_2}{1+K_1 K_2} x_s + \dfrac{1}{1+K_1 K_2} x_d$

This equation, which describes the regulated state y_r as a function of the set-point x_s and the load x_d, forms *the mathematical model* of our primitive homeostatic system. You can now make your own test to see whether you have understood the foregoing, by performing the calculation of y_r starting at another point in the loop.

Next, we shall take a more detailed look at the behaviour of this kind of system on the basis of our graphic and mathematical models. For the reader who is not accustomed to handling equations I wish to stress again that no operations more complicated than multiplication, division, addition, and subtraction are involved. But since these operations are included in the reasoning, it may seem more difficult at first sight than it really is. The main difficulty lies in the circular structure of these systems, because the classical cause-and-effect relationship no longer holds (it applies only to open systems, i.e. without loops) and is only clarified by performing the calculation through the whole system, as has just been done.

Reference input and desired output

It might be thought that the set-point x_s, the reference input, would be numerically equal to the state aimed at for the process in this system. This is not the case unless $K_1 = 1$. The true reference variable X_s, which is the desired output of the system, is that value of y_r for which $y_f = x_s$. Then, $y_a = 0$ and no correction need be applied. Because now $y_f = K_1 X_s$, then $x_s = K_1 y_r$, and it follows from this that X_s can be derived by solving y_r and taking it equal to X_s:

$$X_s = \frac{x_s}{K_1}.$$

Thus, the desired output X_s (the true set-point) is equal to the reference input

x_s (the given set-point) divided by the feedback transfer factor of the sensor K_1.

If, in the equation for the entire system, we now write $x_s = K_1 X_s$ and take $K = K_1 K_2$ (the loop gain, which we shall henceforth call the gain of the system), the mathematical model becomes clearer:

$$y_r = \frac{K}{1+K} X_s + \frac{1}{1+K} x_d .$$

On the basis of the graphic model and of the mathematical model derived from it, the characteristics of this system can now be derived and discussed. The first thing we see is that with this system the regulated state y_r of the process (the line $y_{r,\,\mathrm{controlled}}$ in the graph) gives a good approximation of the desired output X_1 ($K/(1+K)$ is only slightly smaller than 1 for larger values of K) and that the disturbance x_d is strongly suppressed by the factor $1+K$. Because y_r is proportional to X_s and to x_d, this type of system is called a *proportional control system* (there are other types of control systems as well).

It is evident from all this that a model constructed with elements that are also present in the organism (sensors, effectors, comparators, and transmitters) does indeed have a regulatory effect. The system provides for homeostasis, i.e. the approximate constancy of the state of a given process. This model, however, represents the simplest homeostatic system conceivable, and as such it is found to be too simple when certain homeostatic systems are investigated; nevertheless, for a description that is only intended as a first approximation it should be able to tell us a great deal about this type of system and even have predictive value.

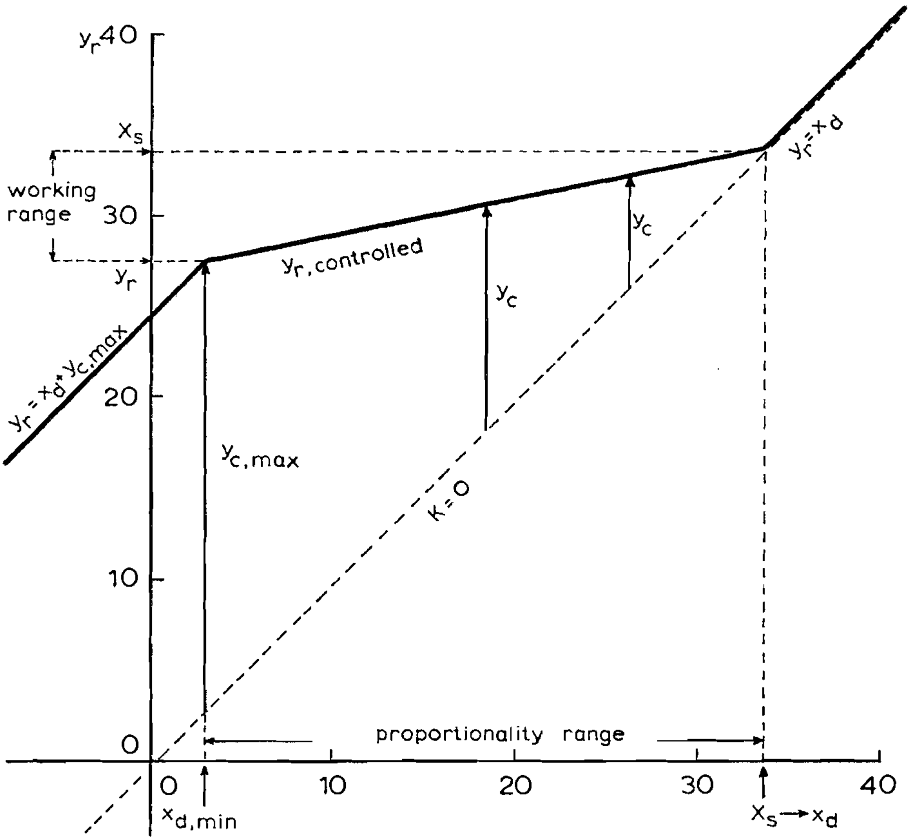
The activity of the effector

When we take a closer look at the graphic model, we notice that the effector can do only one thing. If we remember the situation for temperature regulation, for instance, we know that one type of effector can either heat, and only that, or cool, and only that. At external temperatures x_d from roughly 0 to 30 °C, the body temperature y_r of mammals is held at about 37 °C, so that the presence of a heat-producing effector is imperative. Under conditions of heavy work or high air temperatures, another effector is linked up (we sweat), so that the body can give off extra heat to the surroundings by means of the evaporation of water. For temperature regulation, therefore, the model must be expanded. You, reader, can do this yourself along the same lines, after having read the paper, by, for instance, activating the warming effector when y_a is larger than zero and by linking up the cooling effector when y_a is smaller than zero. The limitation to a single effector used here means that the system is either set to cope with loads x_d smaller than X_s (our example of the heat regulation with X_s

equal to about 37 °C) or to cope with loads x_d larger than X_s (for which, in our example, a cooling effector is required). We shall now examine the first of these situations.

The regulatory characteristic of the primitive system

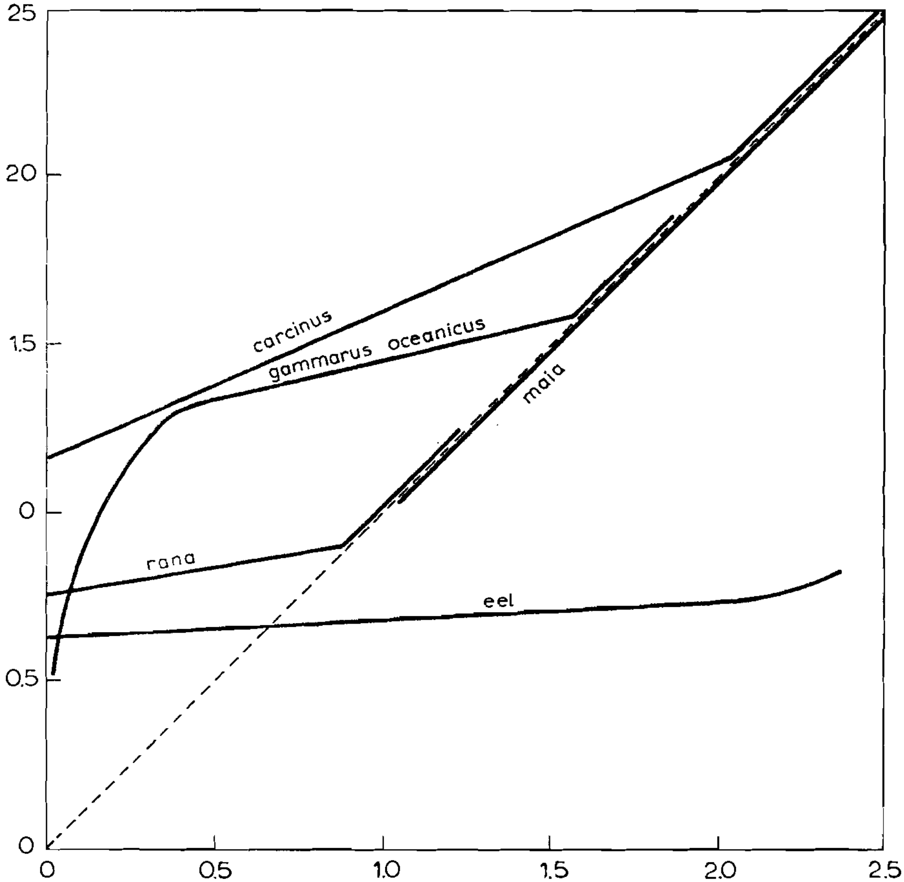
How does a proportional control system behave which regulates for loads x_d smaller than the desired output X_s? It does not work for loads larger than X_s and for such loads the state y_r of the process will be equal to state x_d of the environment. Then the body temperature y_r will be equal to the external temperature x_d, as can be the case for cold-blooded animals. The same occurs in warm-blooded animals when the effector is out of action, as a result of which $K = 0$ (hibernation, anaesthesia). It we represent this graphically by plotting the regulated state of the process y_r on the y axis and the load x_d on the x axis



Graph 1. The regulatory characteristic: graphical representation of the behaviour of the state y_r of a regulated process for various loads x_d of that process.

(graph 1), we obtain the $K = 0$ line at a 45 degree angle through the origin: $y_r = x_d$ for all values of x_d. For the regulator under discussion, this occurs only when x_d is larger than X_s; in the graph this is shown by the drawn line for $K = 0$ at the upper right.

It is also evident from the equation for y_r that the true set-point X_s is not reached (except for $x_d = X_s$). The environmental temperature is usually lower than X_s, and therefore the body temperature will lie somewhat below this value. But the system keeps the body temperature within certain limits (the working range of the system). When these limits are exceeded, the process is seriously disturbed. This line for y_r as a function of x_d ($y_{r,\,\text{controlled}}$) does not run to the left indefinitely. In the Figure, arrows indicate the vertical distance between the



Graph 2. Regulatory characteristics of the salt-concentration regulation of several aquatic animals. The salt concentration y_r of the blood is plotted on the vertical ordinate and on the horizontal that of the surrounding water x_d (in freezing-points). Adapted after figs. 12, 13 and 21 in Prosser.

line $y_r = x_d$ (for $K = 0$) and the line $y_{r,\text{controlled}}$. This distance indicates the size of the control variable i.e. the production y_c of the regulator (as you can check by calculating y_c and comparing the result with the calculated difference between $y_{r,\text{controlled}}$ and $y_r = x_d$). This production increases with decreasing values ot x_d and will be maximal, which is indicated by $y_{c,\max}$, for a given value of x_d. When x_d shifts further to the left (i.e. the environmental temperature becomes still lower), the production y_c will not be able to increase any further and y_r (the body temperature) will drop according to the line $y_r = x_d + y_{c,\max}$.

When $x_d = X_s$, the state y_r of the process is equal to the true set-point X_s (this is the lowest point on the 45 degree line), as you can check by substituting $x_d = X_s$ for y_r in the equation.

For loads x_d smaller than X_s, the system will regulate and y_r will assume the values indicated by the equation derived above. For the regulation of our body temperature K is roughly equal to 9 and the resulting line is shown in the Figure, i.e. the thicker part of the line $y_{r,\text{controlled}}$.

Thus, the system has a regulatory effect for values of x_d lying between a low value of x_d ($x_{s,\min}$) determined by $y_{c,\max}$ and $x_d = X_s$. Within this proportionality range of the system, y_r does not vary greatly and lies between a minimal value ($y_{r,\min}$) determined by $y_{c,\max}$ and $y_r = X_s$, which is the working range of the system. Outside this range the system follows the state of the environment directly or at a given distance ($y_{c,\max}$).

Some homeostatic systems in organisms

If we now examine the behaviour of homeostatic systems in organisms on the basis of this prediction, we see that some systems do indeed behave in this way under varied loads: the already-mentioned thermostat (the system regulating the body temperature) and also the systems in aquatic animals regulating the salt level in the internal environment. In the second graph the salt concentrations of the blood are plotted vertically for various salt concentrations of the surrounding water (horizontally) for several animal species. Since negative concentrations do not occur in nature, the regulatory characteristics of these systems end at $x_d = 0$.

We see from the second graph that the spider crab *Maia* has no regulatory system for the salt levels in the blood. The crayfish-like species *Gammarus oceanicus* has a very narrow proportionality range, and therefore its effector works less satisfactorily in fresh water (the lefthand part of the line does not run parallel with the $K = 0$ line). The beach crab *Carcinus* has a wide proportionality range and can control the salt level in its blood in fresh, brackish, and salt water. Its gain K is not so large (about 3), and therefore its blood concentrations can vary rather widely (a large working range). The frog *Rana* does not regulate in salt water but otherwise keeps the salt levels within narrow limits (K about 5). The eel has a very large proportionality range, and its system has a gain K of 19. The line therefore is rather flat. Furthermore, this animal, which has the lowest set-point value X_s of all the species mentioned, also has effectors that can cope with loads x_d larger than X_s.

Diseases

On the basis of even this simple model, certain diseases can be predicted. We have already referred to overloading, and although the system itself is not directly affected under these conditions, the state of the process y_r lies outside the working range, which has consequences for the organism. We can see from the graph, for instance, that the effector of *Gammarus* does not work as well when there is an overload: the system breaks down.

The effector can show anomalies as a result of which its gain (K_2) decreases and, in the worst case, even becomes eliminated ($K_2 = 0$). In this case the gain K of the system is reduced. The set-point x_s does not change. From this point in the regulatory characteristic the line drops with a sharper slope to the left. Thus, for the same proportionality range the working range becomes larger and the state y_r of the process will vary more widely at variable loads.

There can also be a decrease in the maximal capacity $y_{c,\max}$ of the effector. This results in a reduction of the proportionality range. When in this case, the gain remains the same, the heavier loads that could originally be compensated for will now take effect, which means that the organism has become more vulnerable.

When K_2 becomes zero, the forward path is eliminated. The process is no longer regulated, and follows the environment (the $K = 0$ line).

Besides disturbances in the forward path there can also be anomalies in the feedback path. When the gain of the sensor, K_1, becomes smaller, the total gain K will also be reduced, as a result of which the regulated state y_r will again fluctuate more widely under variable loads but now the true set-point of the process (X_s) will also undergo changes (the given set-point x_s does not change). Because $X_s = x_s/K_1$, X_s will become larger and shift upward and to the right along the $K = 0$ line. For the temperature-regulating system an anomaly of this kind results in a higher body temperature. When the feedback path is completely eliminated ($K_1 = 0$), then $y_f = 0$, and $y_r = K_2 x_s$, thus becoming very large. The system no longer regulates but is forced far outside its working range, which will result in the destruction of the organism as well as in the exhaustion of the energy supply of the effector. In all likelihood, the condition known as brain fever – which is very difficult to treat and, fortunately, very rare – in which the body temperature is severely elevated and remains very high until no further heat can be produced, is the result of a pathological disturbance of the feedback path of the system responsible for the regulation of the body temperature.

This brain fever is very different from ordinary fever, for which it is now clear that in the brain the given set-point x_s is reset at a larger value. As a result, the regulatory characteristic shifts as a whole upward to the right, and the mean body temperature rises. This situation occurs, for instance, with an infection, and the elevated temperature (fever) contributes to a more effective defence against the infection. Salicylates depress the raised set-point and thus reduce the fever. From all this it will be clear to you that in this way an *effect* is suppressed but that the *cause* of the fever (the infection) has not been abolished; quite the contrary: the organism is now more vulnerable and cannot fight the infection as effectively. This 'treatment' eliminates the body's reaction to the infection (the raising of the set-point x_s).

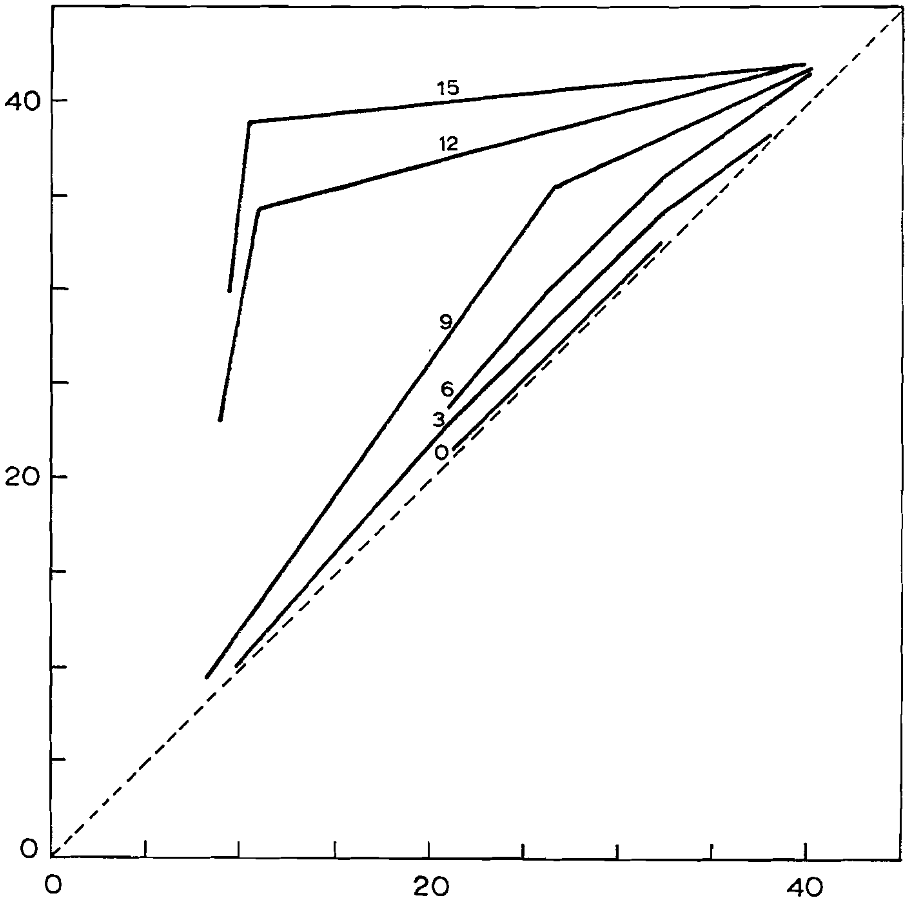
Lastly, changes can also occur in the comparator, for instance increased retardation in the system. One of the results of this delay is that the state of the process no longer remains stationary but begins to fluctuate widely. To understand this, the model would have to be extended to include delays and inertia, which would take us beyond the scope of this introductory paper.

Growth

In newborn animals and humans many of the homeostatic systems are not yet completely developed. Research on the physiology of growth, development, and aging is relatively new, but something can be said about them in this context on the basis of the regulatory characteristics determined by Kendeigh in young wrens. We can see from graph 3 that on the day of hatching, regulation of the body temperature does not occur. On the third day the first signs can be distinguished, and starting on the sixth day there is distinct regulation. The true set-point X_s is then set for 42 °C, but both the gain K and the range of regulation are still restricted. The maximum capacity of the effector remains constant over a wide range. On the succeeding days the gain and the range show a distinct increase, and at the end of two weeks the system functions at full strength with $K = 9$ and a proportionality range of 30 degrees Celsius. The working range then covers 3 degrees Celsius. From the curves for the ninth and subsequent days it is also evident that the maximal output $y_{c,\,max}$ of the effector drops when the body temperature decreases under an increasing load. This dependence would have to be included in a better model.

Concluding remarks

Closed-loop systems occur frequently in both organisms and technical systems.



Graph 3. Regulatory characteristics for the body temperature of a young bird. Horizontal ordinate: environmental temperature x_d in °Celsius; vertical ordinate: body temperature y_r in degrees Celsius. The age of the bird is indicated as number of days after hatching. Adapted after Kendeigh (fig. 95 in Prosser).

We are schooled to think exclusively in terms of open systems, in one-way cause-effect relationships. The activity of the circular structures encountered cannot be understood on that basis. At present, the term 'feedback' is often heard in public discussions; it is used as a kind of magic cure-all, without any notion whatsoever of its (often dangerous) implications. In this paper the structure and properties of the simplest feedback system possible are discussed. Without such a model it is quite impossible to understand the characteristics of organisms or of social group structures. For instance, the maintenance of constancy of the internal environment, or the capacity of the organism to move in its surroundings, or of an organization to work towards some goal. And only on the basis of models of this kind can phenomena such as fever, dysregulations, and the effects of overloads be understood and corrected. And this is even more critical for the time-dependent phenomena that are not treated here except the explosion mentioned in the beginning. This explains why such models are now included in the curricula of students in biology and medicine.

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