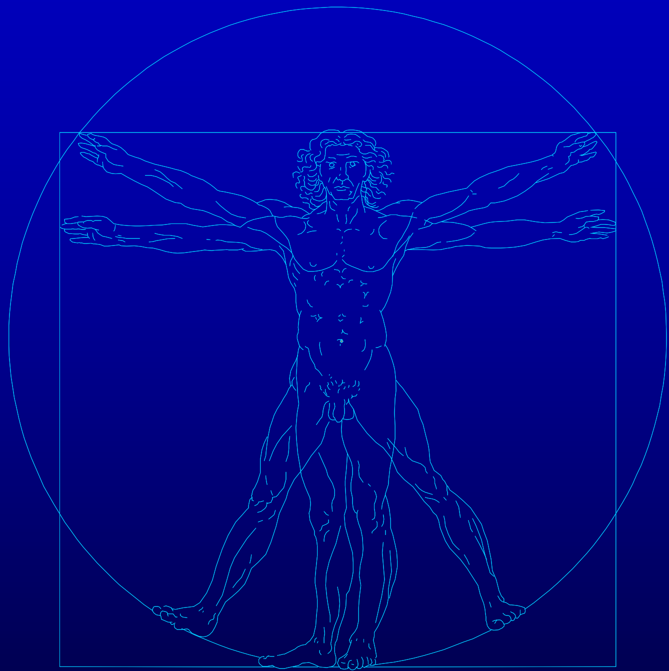
1.3. The feed-back

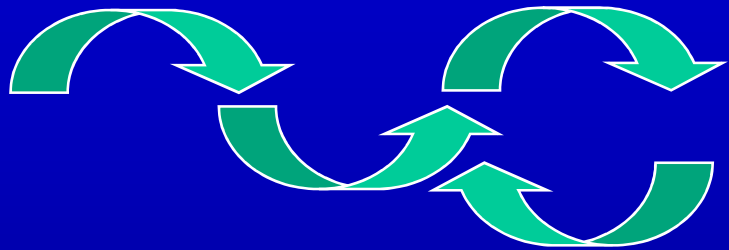


(action-reaction principle)

1.3. Models of feed-back

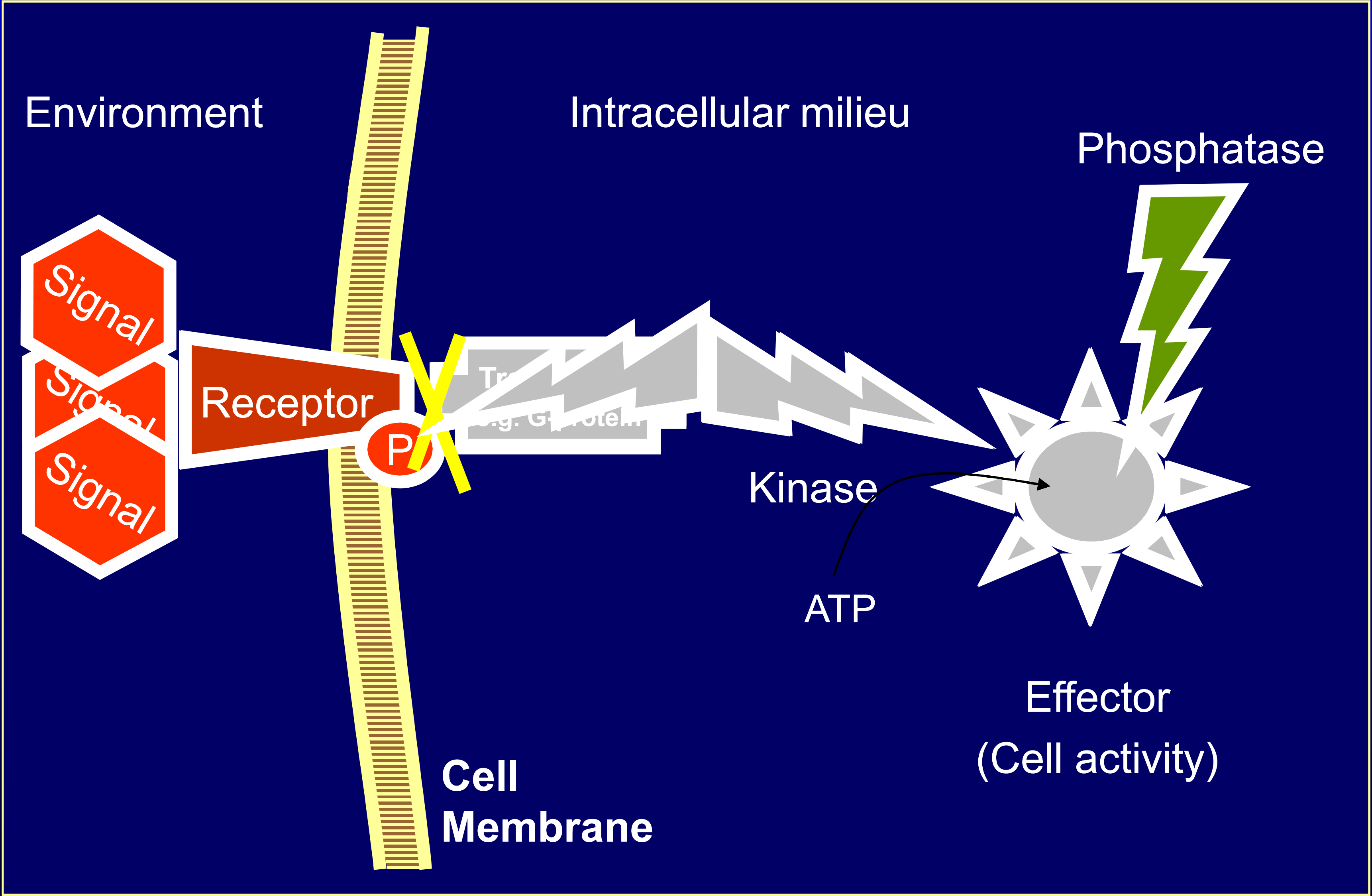
-The action-reaction principle and homeostasis

-Mathematical model of a dynamic system



THE FEED-BACK
(ACTION-REACTION PRINCIPLE, COMPENSATION RULE)
IS THE ESSENTIAL
BUILDING BLOCK
OF EVERY HOMEODYNAMIC SYSTEM

(mechanical, chemical, psychological, etc.)


Environment
Intracellular milieu
Phosphatase
Signal
Signal
Receptor
P
Kinase
ATP
Effector
(Cell activity)
Cell
Membrane

C.F.S. Hahnemann, Organon, par. 63

“Every agent that acts upon the vitality, every medicine, deranges more or less the vital force, and causes a certain alteration in the health of the individual for a longer or a shorter period. This is termed primary action.
To its action our vital force endeavours to oppose its own energy. This resistant action is a property, is indeed an automatic action of our life-preserving power, which goes by the name of secondary action or counteraction”

HOME

1.
LIFE FORCE
1.1.
Homeodynamics
1.2.
Communication
1.3.
Feed-back
1.4.
Chaos
1.5.
Networks

2.
PATHOLOGY
2.1.
The puzzle
2.2.
Acute diseases
2.3.
Chronicization

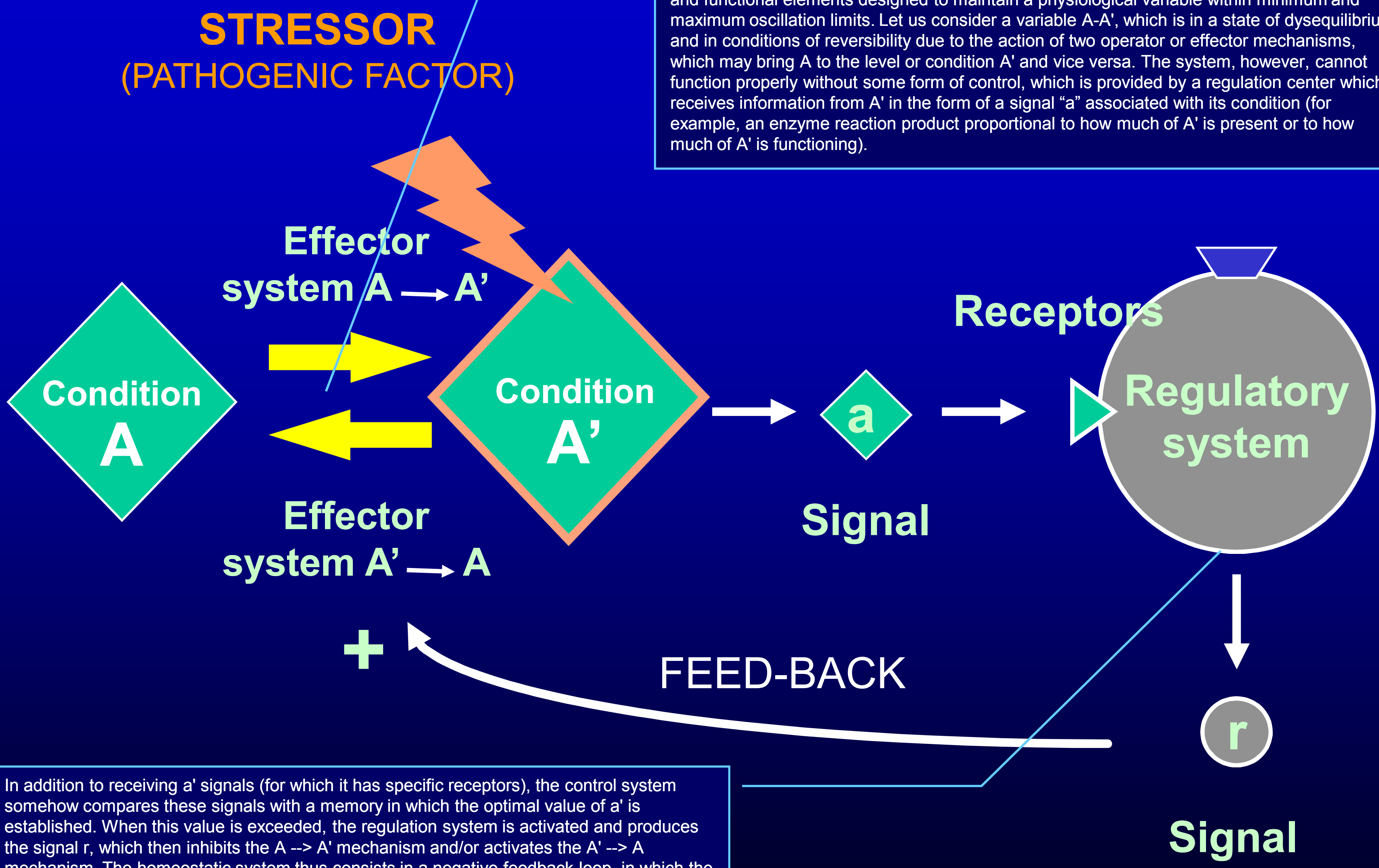
3.
REGULATIVE
INTERVENTIONS
3.1
History
3.2.
The "simile"
3.3.
The doses
3.4
Integrated
medicine

C.F.S. Hahnemann, Organon, par. 65

"Excessive vivacity follows the use of strong coffee (primary action), but sluggishness and drowsiness remain for a long time afterwards (reaction, secondary action).
After the profound stupefied sleep caused by opium (primary action), the following night will be all the more sleepless (reaction, secondary action).
After the constipation produced by opium (primary action), diarrhea ensues (secondary action); and after purgation with medicines that irritate the bowels, constipation of several days' duration ensues (secondary action).
And in like manner it always happens, after the primary action of a medicine that produces in large doses a great change in the health of a healthy person, that its exact opposite, when, as has been observed, there is actually such a thing, is produced in the secondary action by our Vital Force "

MODEL OF A SIMPLE HOMEODYNAMIC SYSTEM

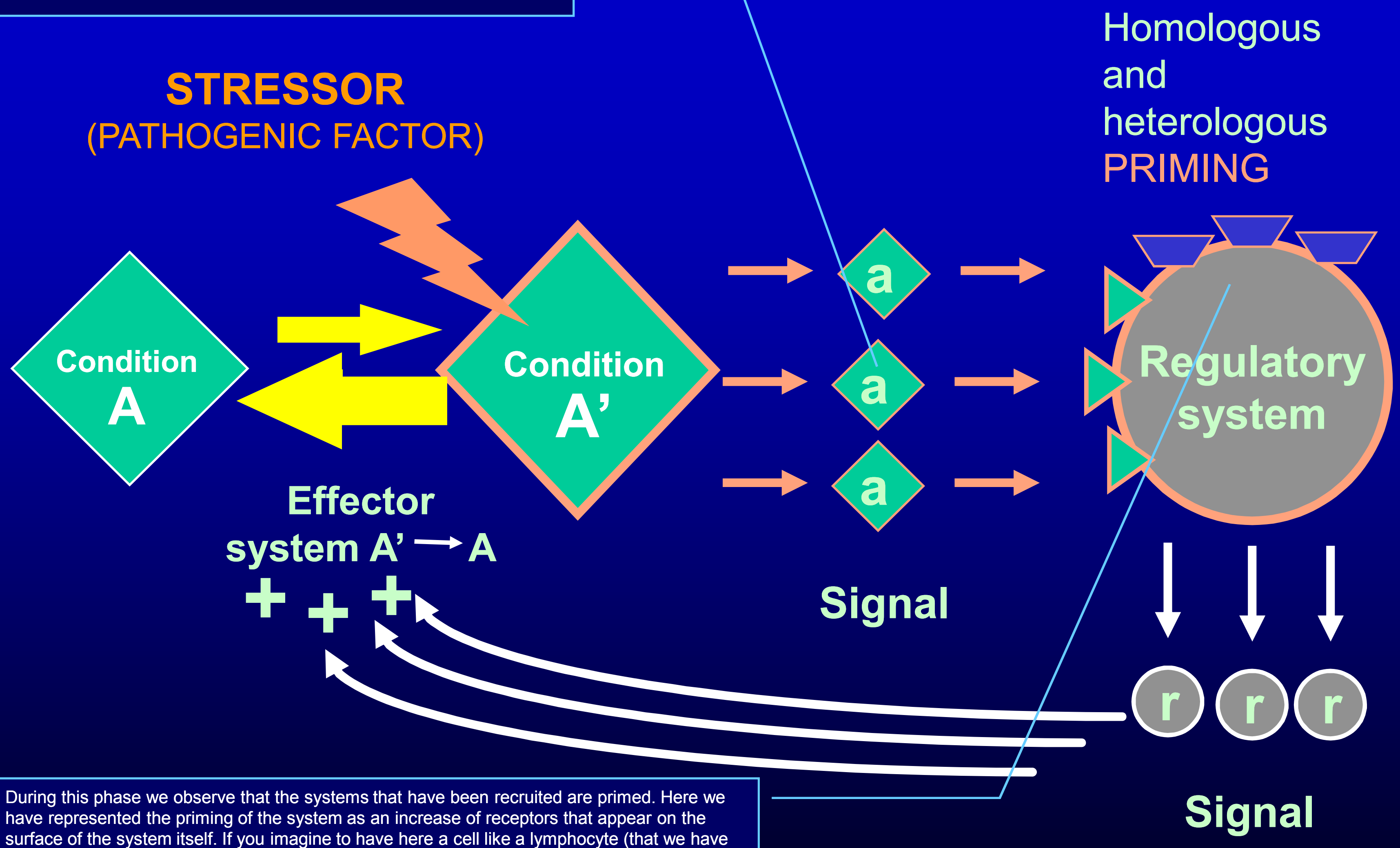
A homeostatic system, in its essential make-up, consists in a set of anatomical, biochemical, and functional elements designed to maintain a physiological variable within minimum and maximum oscillation limits. Let us consider a variable A-A', which is in a state of dysequilibrium and in conditions of reversibility due to the action of two operator or effector mechanisms, which may bring A to the level or condition A' and vice versa. The system, however, cannot function properly without some form of control, which is provided by a regulation center which receives information from A' in the form of a signal “a” associated with its condition (for example, an enzyme reaction product proportional to how much of A' is present or to how much of A' is functioning).



In addition to receiving a' signals (for which it has specific receptors), the control system somehow compares these signals with a memory in which the optimal value of a' is established. When this value is exceeded, the regulation system is activated and produces the signal r, which then inhibits the A --> A' mechanism and/or activates the A' --> A mechanism. The homeostatic system thus consists in a negative feedback loop, in which the information on the result of a transformation or an activity oscillation is fed back in revised and corrected form to the entry point of the cycle.

MODEL OF A SIMPLE HOMEODYNAMIC SYSTEM

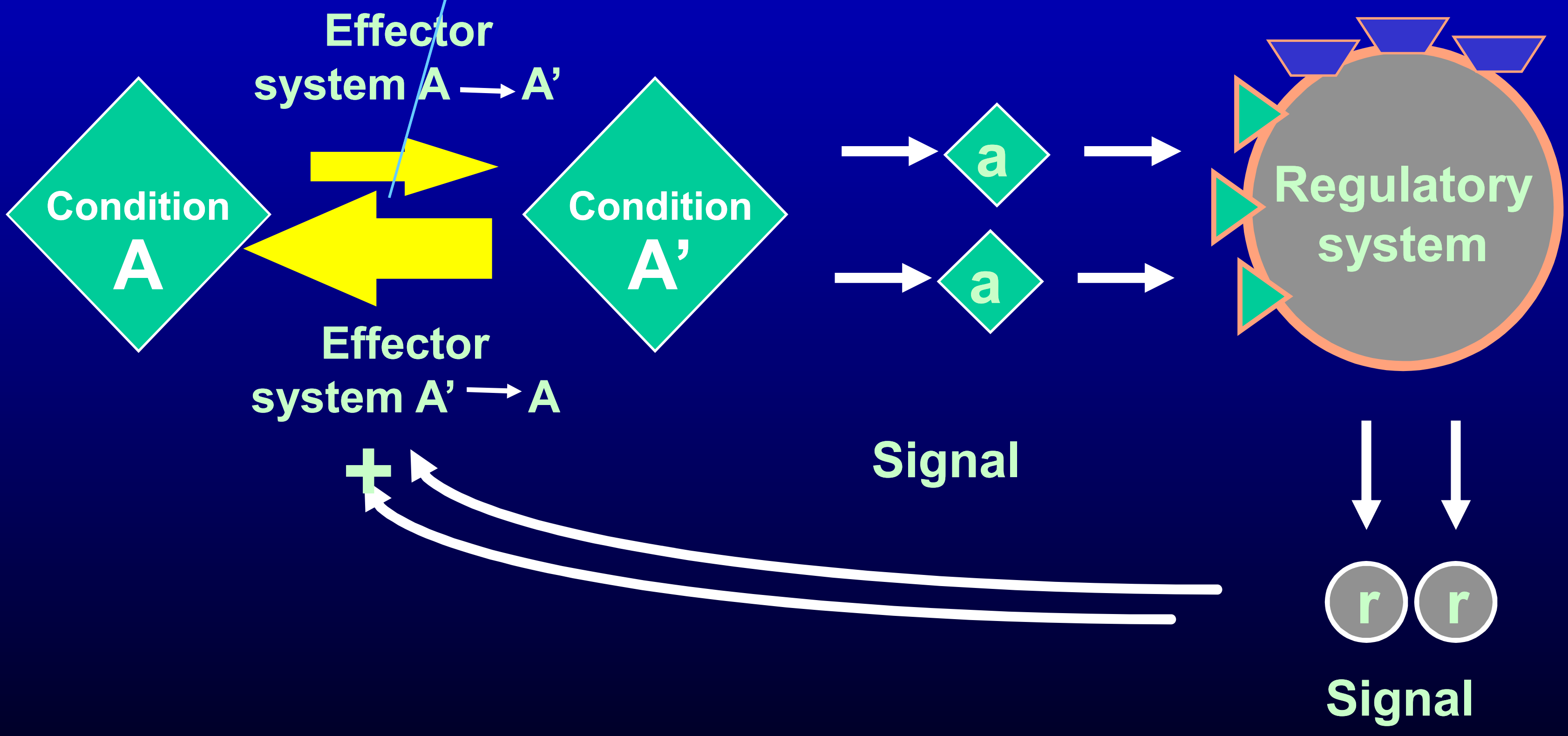
CONDITION A’ PRODUCES MORE SIGNALS (a), WHICH ACTIVATE THE REGULATORY SYSTEM



During this phase we observe that the systems that have been recruited are primed. Here we have represented the priming of the system as an increase of receptors that appear on the surface of the system itself. If you imagine to have here a cell like a lymphocyte (that we have seen as an essential part of immune homeostasis), when a lymphocyte is stimulated by a cytokine or by a specific antigen, it is primed, it is activated and express on its plasmamembrane an increased number of receptors for many compounds.

MODEL OF A SIMPLE HOMEODYNAMIC SYSTEM

IF THE STRESSOR IS REMOVED, THE EQUILIBRIUM IS RESTORED



MODEL OF A SIMPLE HOMEODYNAMIC SYSTEM

Examples of priming:

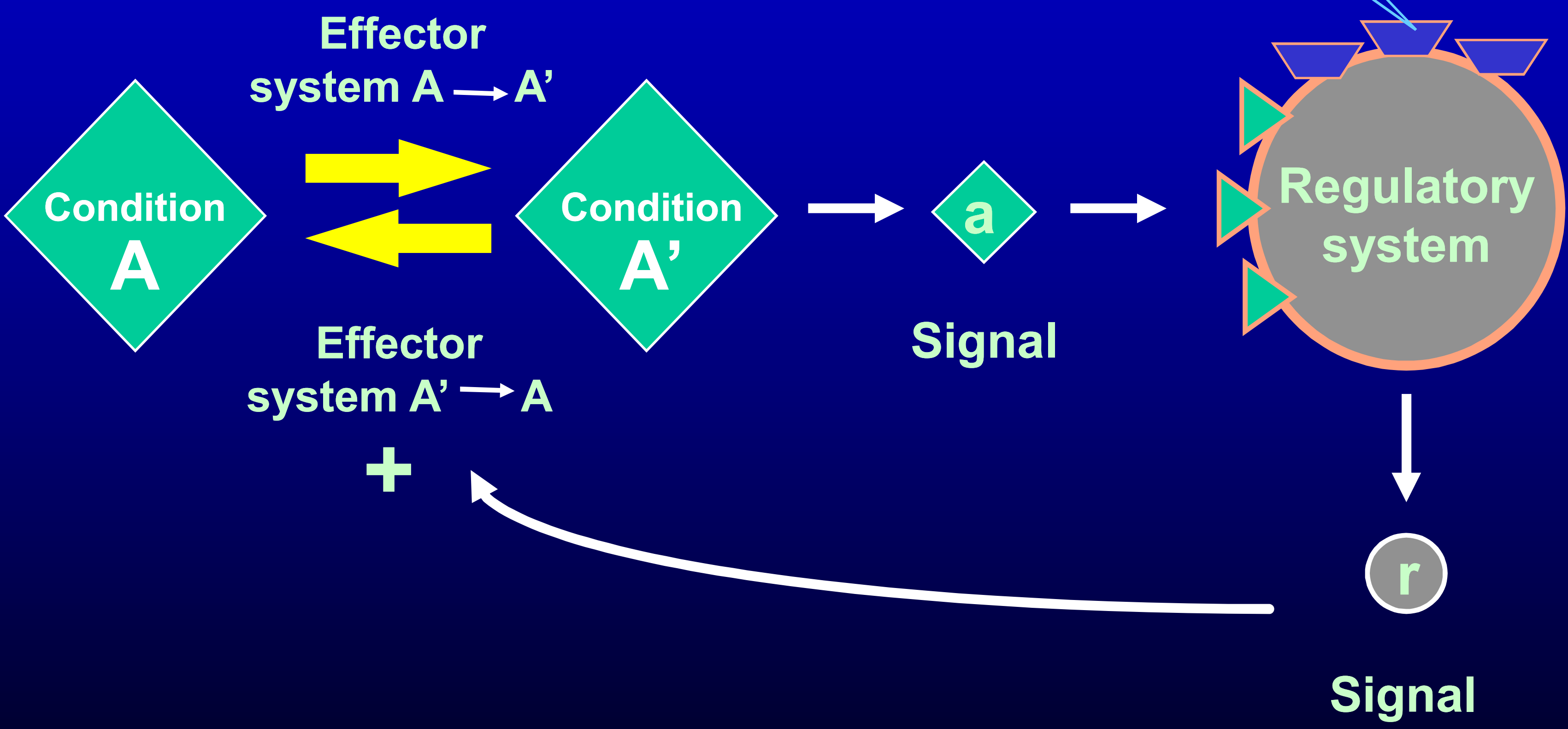
Cellular models (e.g. leukocytes: increase of sensitivity or of response to a second stimulus after the challenge with a first stimulus)

Tissues (e.g. bronchial reactivity in asthmatics)

Organs (e.g. liver induction of detoxifying enzymes after ingestion of alcohol of drugs, heart with hypertrophy after repeated exercise)

General systems (e.g. immune hypersensitivity after challenge with antigens)

Homologous and heterologous PRIMING



THE ESSENTIAL CONSTITUENTS OF HOMEOSTATIC BIOLOGICAL SYSTEMS

- *Anatomical or biochemical structures* with adjustable and reversible effector functions. To mention only a few examples, these structures are represented at cell level by enzymes, membranes, contractile proteins, and at body level by the endocrine glands, vessel walls, the cell mass of a certain tissue, etc.
- *Signal molecules* which enable nearby and remote structures to communicate, such as neurotransmitters, hormones, local chemical mediators, cytokines, physiological inhibitors, and antagonists. A particular complexity feature of the signal molecules is that their message is never wholly specific: the same molecules can be used to communicate between different systems. The same molecules can be produced by many different types of cells. The same molecules can bind to different receptors present on cells in different tissues and organs. There is thus a substantial degree of *redundancy* of biological information, which enables the system to enjoy a considerable measure of flexibility and plasticity, but at the same makes it difficult to achieve any kind of rigid schematization of the events following the production of a certain mediator in given pathophysiological conditions.
- *Receptors* for signal molecules or for other types of messengers, endowed with specific affinity and capable of transmitting the signal to other elements of the regulation system. There are membrane receptors, intracellular receptors, and even intranuclear receptors. It should be noted that the receptors are highly *plastic*: the cells are capable of increasing (hypersensitivity, priming) or decreasing (desensitization, tolerance, adaptation, down-regulation) the number of receptors according to their needs, as well as of regulating their activity by modifying the affinity for the signal molecule. On occasion, the cells present more than one receptor for the same molecule, but with different affinities and different intracellular effects.
- *Transduction systems*: coupling of receptor activation and production of signals or activation of effector mechanisms; variations of intracellular *second messengers*, covalent and noncovalent modifications of membrane lipids and proteins, and the opening of ion channels. The multiform characteristics of the transduction systems are too vast a topic to be dealt with here. What is beyond doubt, however, is that the level of responsiveness of a certain (control or effector) system is also controlled by such systems in the cell, that they are also modified in the course of disease, and that they are susceptible to pharmacological modulation.
- *Elements responsible for storage of information* for a given time period: when a system undergoes a change, this may be rapidly and wholly reversible (e.g. the contraction of a muscle), but it may also be a phenomenon which leaves a more or less permanent trace. Usually, though not always, the longer-lasting changes are those which in some way involve the genetic code of the cells.


Relax…
Music: Misterioso March by Kevin MacLeod (incompetech.com)

1.3. Models of feed-back

-The action-reaction principle and homeostasis

-Mathematical model of a dynamic system

"DYNAMIC SYSTEM"

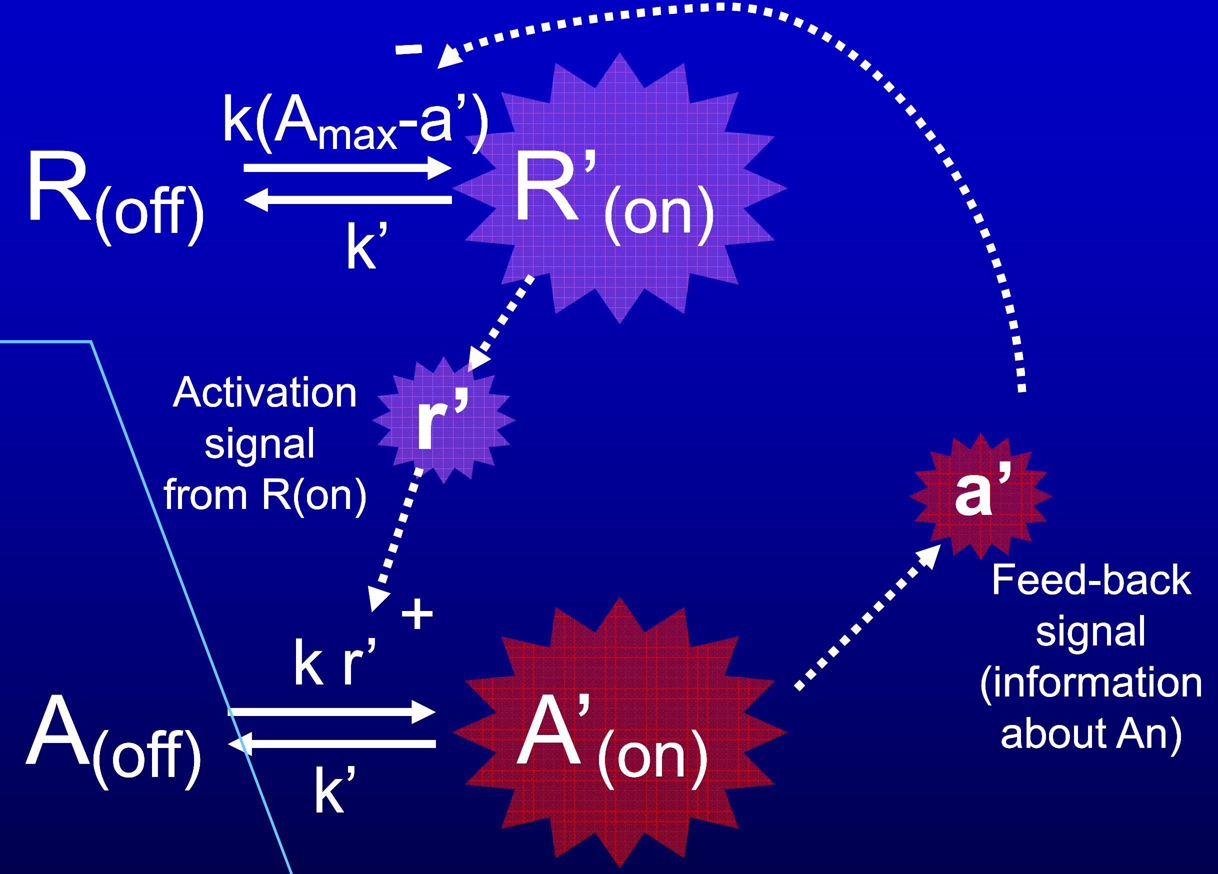
A dynamic system finds itself in different states in different times

The dynamic system is described by two fundamental components:
- its STATE in the phase-space (structure and position)
- its DYNAMIC (the law of evolution, i.e. the rules of the change of the system from time=0 to time>0).

MATHEMATICAL MODEL OF A SIMPLE FEED-BACK

REGULATORY SYSTEM

DYNAMIC VARIABLE



An+1 is the value of the next cycle n+1 which can be calculated on the basis of the value resulting from the previous cycle (An) added to the growth due to the cycle itself, which is equal to An multiplied by a coefficient of growth k and by a factor given by the difference between the maximum allowed (Amax) and An. An equation similar to this was described in 1845 by the mathematician B.F. Verhulst to analyze population trends

Verhulst iterative function

$$A_{n+1} = A_n + A_n\,k\,(A_{max} - An)$$

MATHEMATICAL MODEL OF A SIMPLE FEED-BACK

- The contribution made by the physico-mathematical approach to the problem of complexity is much greater than might be imagined: while it is true to say that a living system with its thousands of subcomponents will never resemble a chemical system with two or only a very few components and can never be described by a mathematical formula, on the other hand it is also true that the study of the complexity of “simple” systems may enable us to discover “basic rules” of behavior which are repeated in substantially identical forms in systems with a different evolutionary status.
- It has been suggested that a complex, nonlinear feedback system is something like “*a universal formula for life*” (Cramer, 1993), because it summarizes, admittedly in a very general way, most of the processes of life.

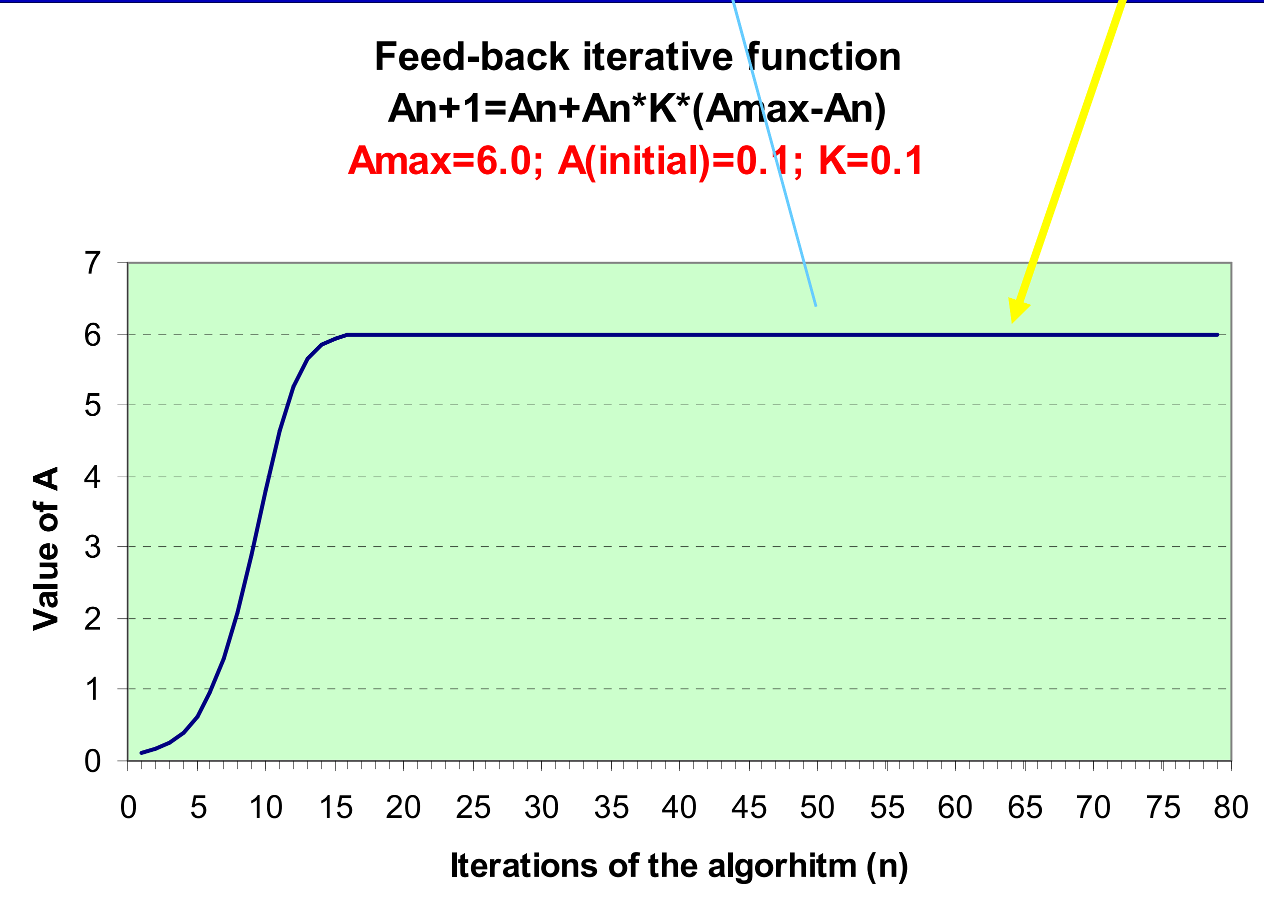
MATHEMATICAL MODEL OF A SIMPLE FEED-BACK

- The mathematical formulation of feed-back essentially describes the dynamics of a mechanism operating in living beings.
- As we have seen, living systems, in fact, are regulated by reaction and counteraction cycles which constitute the so-called *homeostasis*.
- These cycles are nothing more or less than the repetition of the same operation (by analogy with mathematical iteration) in which the result of the previous cycle serves as the basis of the next one.
- For example, at the end of the systole-diastole cycle the heart reverts to the end-diastolic condition; at the end of a mitotic cycle the condition of the two daughter cells becomes in turn the starting condition for a new mitosis.
- Thus, every rhythmic modification of the organism hinges upon the previous state and occurs according to fixed rules (in the analogy we have adopted, the rule is the mathematical formula).

SIMULATIONS OF THE HOMEODYNAMIC FUNCTION

The additive growth (or decline) of each cycle depends on the result of the preceding cycle and is limited by the fact that there is a maximum achievable value: in fact, with the increase in the An trend the number to be subtracted from the maximum achievable value increases and the multiplication factor (Amax-An) decreases. Consequently, it is only logical that An+1 tends to increase at the beginning, but then the increase progressively declines until a plateau is reached where no further increase takes place. The formula, then, describes a fairly simple mathematical feedback.

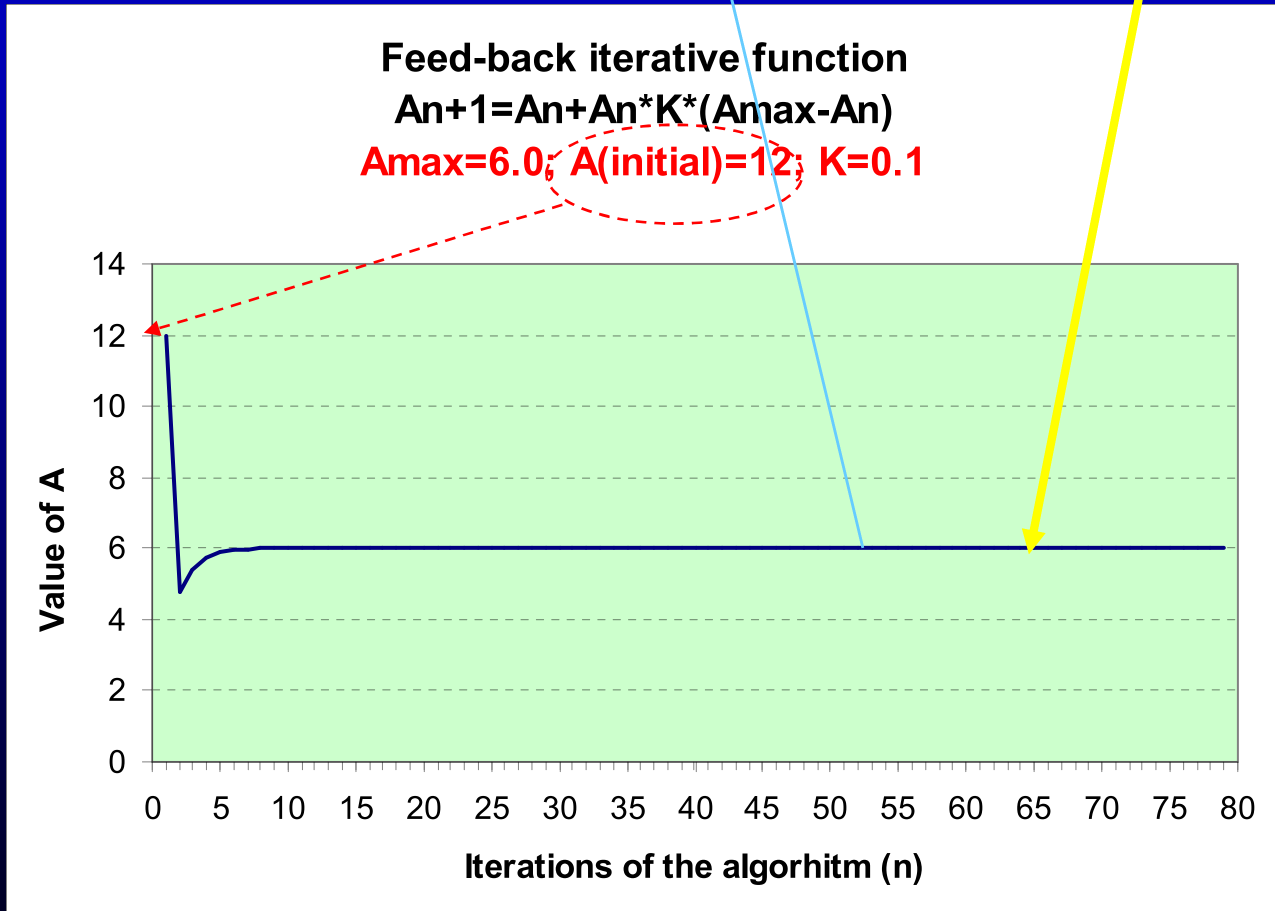
"Homeostasis" (point attractor)



SIMULATIONS OF THE HOMEODYNAMIC FUNCTION

The formula, then, describes a fairly simple mathematical feedback.

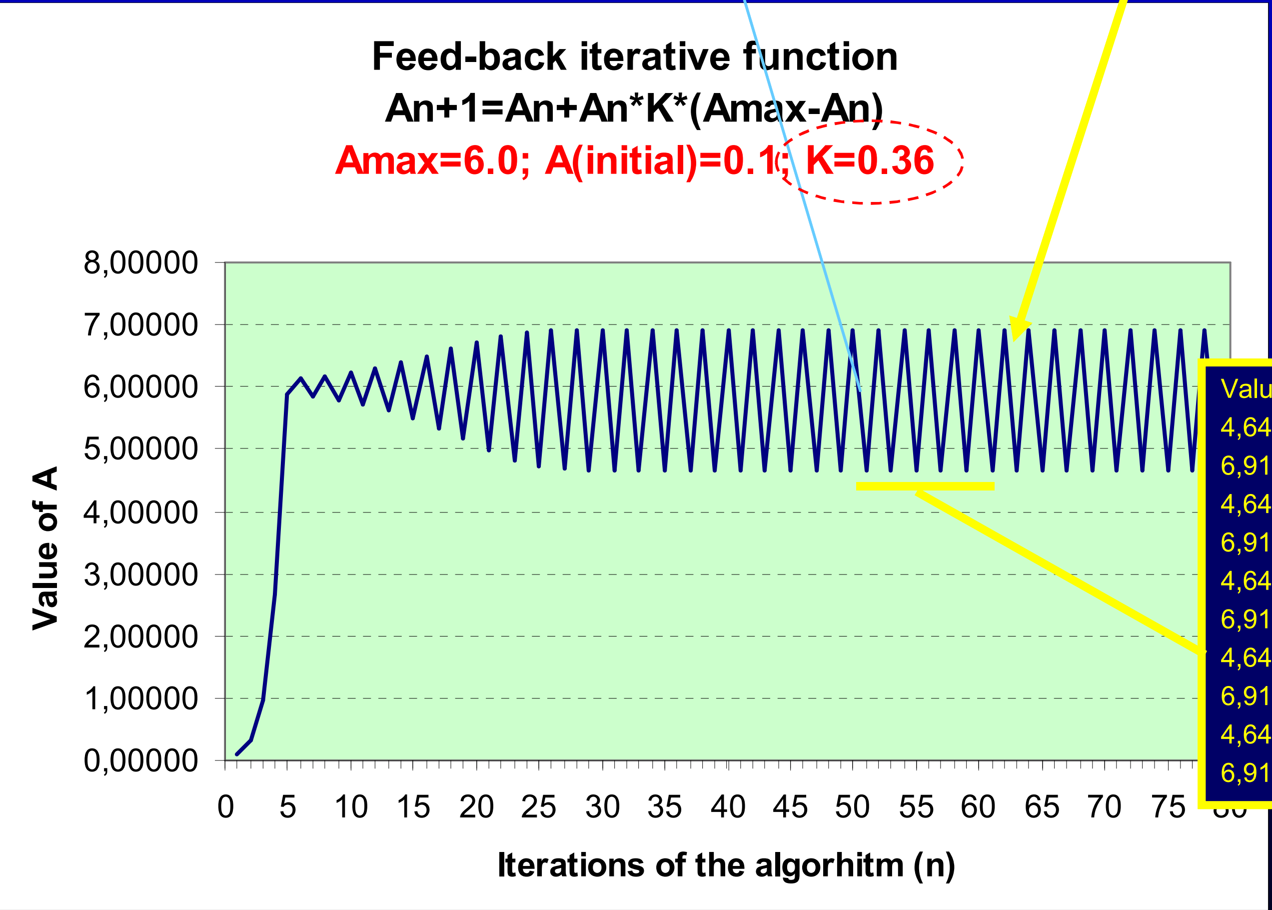
"Homeostasis" (point attractor)



SIMULATIONS OF THE HOMEODYNAMIC FUNCTION

The formula, then, describes a fairly simple mathematical feedback. In actual fact, however, it "conceals" a very substantial measure of complexity: the results the iterative calculation allows are very different depending upon what value is assumed for the coefficient k and depending upon the initial value you start out with.

"Homeodynamics" (periodic attractor)

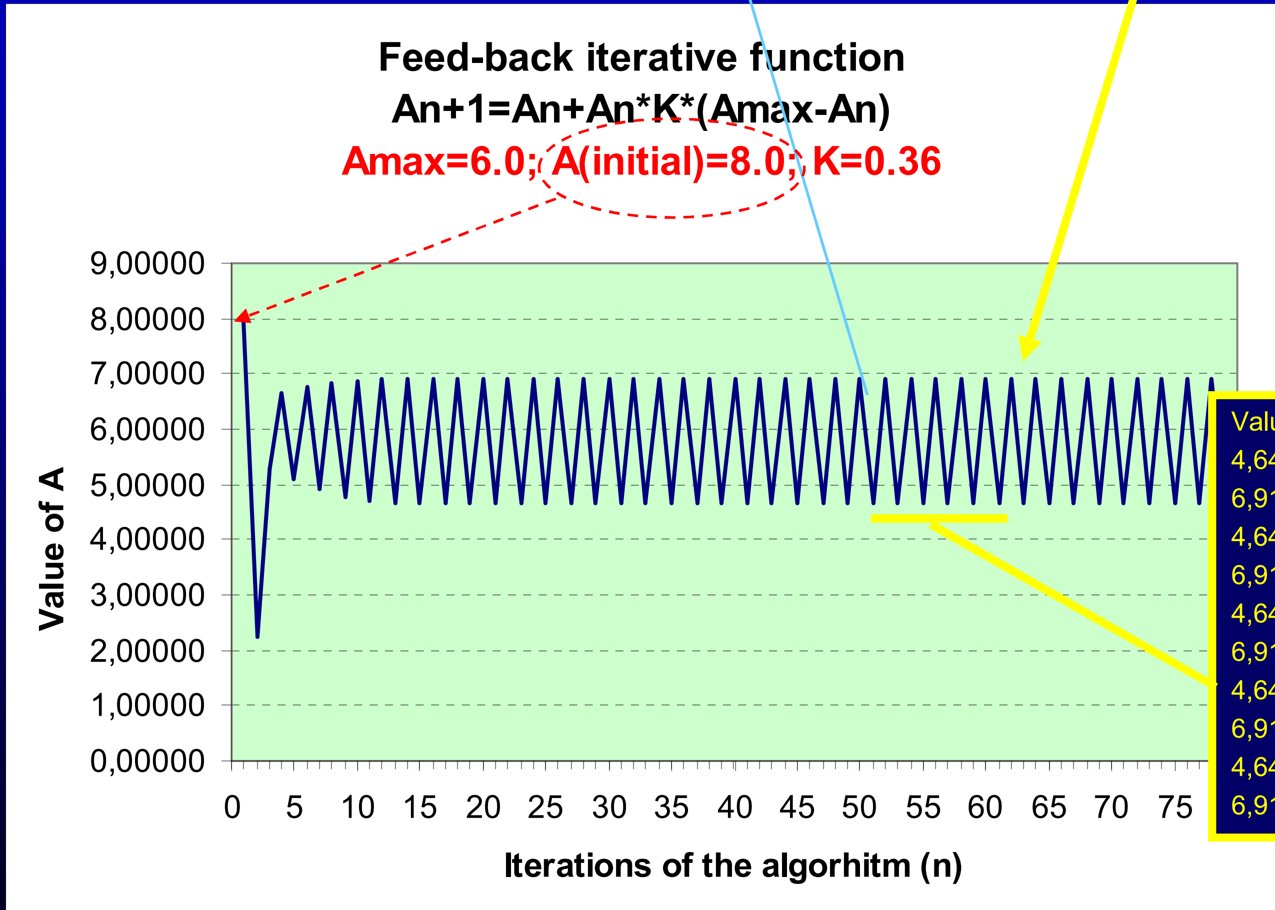


Values from 50 to 59:
4,64466
6,91089
4,64466
6,91089
4,64466
6,91089
4,64466
6,91089
4,64466
6,91089

SIMULATIONS OF THE HOMEODYNAMIC FUNCTION

The formula, then, describes a fairly simple mathematical feedback. Even in this case, changing the initial value from 0.1 to 8.0 does not affect the final trajectory.

"Homeodynamics" (periodic attractor)

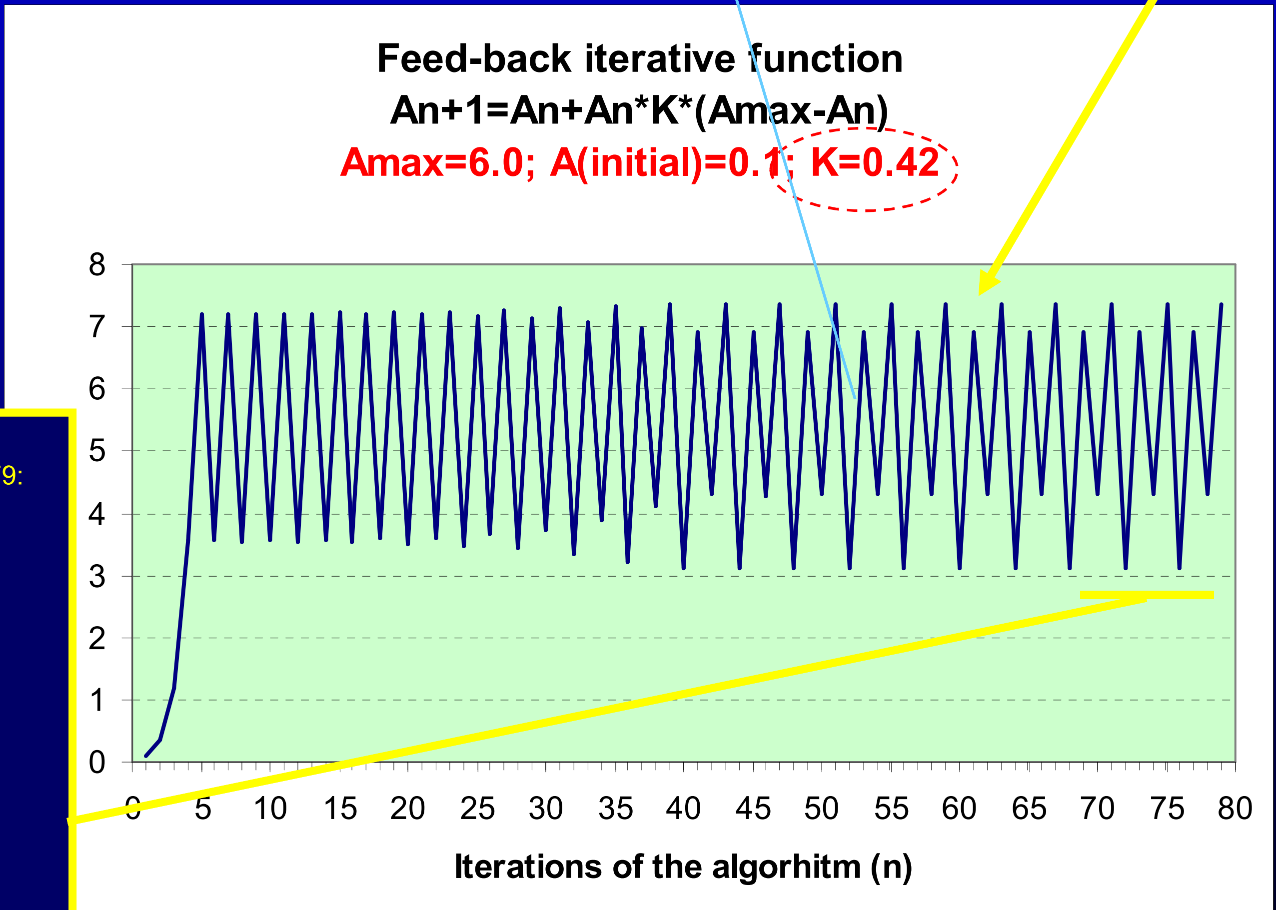


Values from 50 to 59:
4,64466
6,91089
4,64466
6,91089
4,64466
6,91089
4,64466
6,91089
4,64466
6,91089

SIMULATIONS OF THE HOMEODYNAMIC FUNCTION

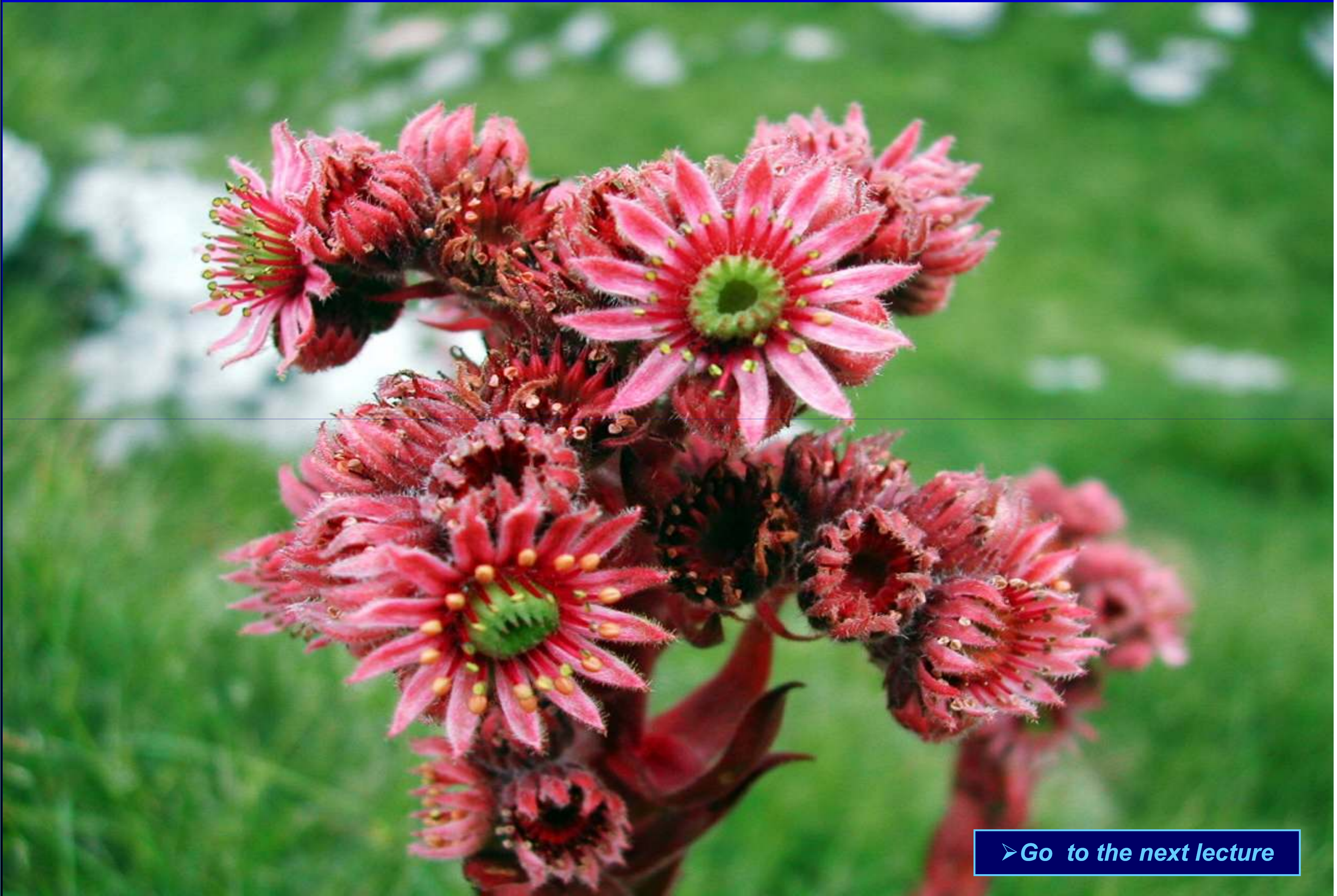
By increasing the value of K, that determines the rate of change at each iteration, we observe an increase of complexity of the trajectory of the function.

"Homeodynamics" (periodic attractor, with period of 4 values)



Values from 70 to 79:
6,900
4,291
7,370
3,126
6,900
4,291
7,370
3,126
6,900
4,291

1.3. THE FEED-BACK - END OF THE LECTURE



➢Go to the next lecture