Homeostasis and Stability

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Abstract

Homeostasis is known as a key concept in biology and well-documented on various levels of biological organization. Moreover, homeostasis appears to be strongly related to the stability of biological systems. Stability, on the other hand, is one of the basic concepts in dynamical systems theory. The aim of this paper is to link these two fundamental concepts. A simple model is proposed representing a cell or an organism as a selectively open self-regulating unit in a fluctuating environment. The idea is that the system can maintain itself simlutaneously open und homostatic by appropiatly adjusting its sensitivity to external signals. The particular term *adibatic stability* is introduced and discussed. For a large class of dynamical systems, it is shown that adiabatic stability implies homeostasis. A simple condition is given under which a system is adiabatically stable. It follows that a given system is adiabatically stable with respect to only a certain class of environmental perturbations characterized by their strength and rapidity. In particular, as a consequence of its internal adaptive behaviour, a system can be destabilized by sufficiently weak and rapidly fluctuating perturbations.

1 Introduction

Biological systems like organisms and cells exhibit a high but limited stability against a wide but restricted class of environmental perturbations. This might be regarded as a rather trivial observation and *So what?* may be one of most probable replies to it, but another one could be: *What is meant by saying: a biological system is stable?*, to which a heuristic answer could be of the type: *It is stable if it survives*, suggesting that stability of a biological system concerns its maintenance. Of course, the next question then is: *Who maintaines?* and especially: *What is maintained?* Intuitively, the answer to the first question will be: *A biological system maintaines itself.* And consequently, the answer to the second question should be: *It maintaines the conditions under which it is maintained* which immediately leads to the questions *What are the conditions to be maintained? And how are these conditions maintained?* Our claim is that, certainly among others, homeostasis is a condition which has to be maintained for survial. Homeostasis hereby is understood in the sense that there exist certain internal variables which are kept in given narrow bounds for almost all of the time. Various examples of internal variables are known exhibiting homeostatic behaviour, including the concentration of anorganic phosphat [Caverzasio & Bonjour, 1992] and strongly related to this, the concentration of free calcium in the cytosol of a cell [Carafoli,1987] [Dawson, 1990], [Cheek, 1991] as well as the intracellular pH [Lubman & Crandall, 1992], the amount of iron bounded to ferritin and transferrin [Morris *et al., 1992*] and the ATP-saturation of a cell [Lehninger, 1975]. Nowadays cell biology has eluminated the complexity of processes involved in intra-systemic regulation. Stated this way, homeostasis is a systemic property but since a long-lasting violation of homeostasis is known to be lethal for the system, homeostasis also represents a condition for the survival of the system. In this sense, the last of the above questions can be reformulated as: *How is homeostasis achieved?*.

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Homeostasis as a concept being strongly related to the stability of an organisms is, of course, an old one and was already clearly described by W. B. CANNON in a series of papers [Cannon, 1925] [Cannon, 1926] in which he refers to even older statements by Ch. Richet and C. Bernard. The aim of this paper is to revisite homeostasis as a basic concept and discuss its relation to stability in terms of dynamical systems theory. We investigate a model in which a cell, as well an organ or an organism, is represented as a self-regulating unit similar to that of a homeostat proposed by R. W. Ashby [Ashby, 1952]. A similar abstract model is discussed, for example, in [Adolph, 1964]. In order to show that this kind of scheme can be found to be realized analogously on different levels of biological organization, we refer to three very well-known examples: an unicellular organism, namely *Dictyostelium*, a single cell in a multi-cellular context: a *neuron*, and a multi-cellular complex: the so-called *light-reflex arc*. A simple formal model is proposed in order to represent the time evolution of such self-regulating systems. We then introduce a particular notation of stability, which we call *adiabatical stability* and give a simple condition under which the corresponding dynamical system is adiabatically stable. It will be shown that adiabatical stability implies homeostasis.

2 The main question

In an abstract sense, organisms as well as cells can be regarded as compact units surrounded by a connected, semi-permeable boundary which admits selective interaction with the environment. The property of being selectively open is due to the fact that interaction is performed by specialized subsystems, receptors and effectors, which are capable of receiving or producing only specific classes of signals. So, cells and organisms can be regarded as open systems in a thermodynamical sense for which an *internal state* can be defined evolving non-autonomously in time. CANNON describes this scenario as follows: *The highly developed living being is an open system having many relations to its surroundings ... . Changes in the surroundings excite reactions in this system, or affect it directly, so that internal disturbances of the system are produced. Such disturbances are normally kept within narrow limits, because automatic adjustments within the system are brought into action, and thereby wide oscillations are prevented and the internal conditions are held fairly constant.* So, there exist processes mapping selected external signals on to changes of the internal state of the system, which in turn alter the activation of other processes functioning in order to reduce internal disturbances. The requirement of a biological system to be homeostatic means that the time-evolution of its internal state is restricted to a small, bounded region of the state-space for almost all of the time. Therefore the question arises how the internal state of the system can be kept within a given region while the system is permanently perturbed by its environment, or:

How can a biological system achieve its property of being simultaneously open and homeostatic in a fluctuating environment?

3 The general scheme

According to the general view already taken by Cannon, we will now proceed by presenting a general self-regulating scheme, which is supposed to be realized analogously on different levels of biological systems organization.

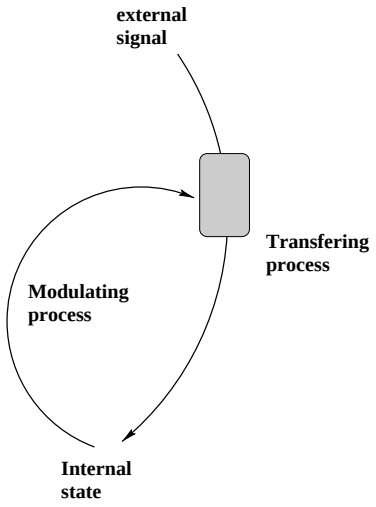
The construction of the general scheme is due to the following three steps:

1.) The first step consists in defining the INTERNAL VARIABLE of the system under consideration. Thereby, an internal variable is a quantity or a set of quantities, which can be determined completely by an intracellular measurement, at least in principle. Examples for internal variables are the activity of certain gens or enzymes, the cytosolic concentration of calcium or second-messengers like cAMP, as well as the ATP-saturation of a cell. Notice that according to the definition, a membran potential is not an internal variable of a cell.

2.) Then collect all downstream paths of the signal transducing network emerging from receptors and converging on the internal variables chosen. This subnetwork has the property of transfering externally induced

activities of the receptors onto changes of the internal variables and, therefore, will be called the SIGNAL-TRANSFERING NETWORK. Notice that this network is only defined with respect to the internal variables chosen before.

3.) Finally consider all parts of the remaining internal network emerging from the internal variables chosen and functioning by modulating the signal transfering paths. This subnetwork is called the TRANSFER-MODULATING NETWORK. According to its definition, the modulating network emerges from the internal variable in the sense that it maps changes in the internal variables onto changes in the signal-transducing properties of the transfering system. We define the modulatory state of the system as being the state of the modulating network representing the activity of its components with respect to the components of the transfering network. If the modulating components were enzymes exclusively, the modulatory state of this network would be defined as the tupel of activities of all of these enzymes.



The self-regulating loop:
Cyclical coupling of transfering and modulating processes.

In summary: the self-regulating loop can be regarded as consisting of two cyclically coupled processes: The *signal-transfering process* maps external signals onto changes of the internal state, whereas the *transfer-modulating process* alters the transducing properties of the transfering process by activating or inhibiting its components, depending on the internal state of the cell.

Let us illustrate the above procedure by means of three well-known examples. To avoid misunderstandings, the schemata to be presented now are not intended to mimice any specific mechanistic realization of signal transfering and transfer modulating processes in a cell or an organism, but are intended to show that the interplay between these processes can be found to be realized in concrete examples taken from different levels of biological organization.

Activation/desensizitation dynamics in *Dictyostelium*
[Devreotes, 1989][Insall & Borleis & Devreotes, 1996]

We first choose the internal variable to be the concentration of $cAMP$ and define the amount of external $cAMP$ as the external signal. As well known, Dictyostelium possesses receptors which can be activated by $cAMP$ and subsequently activate the $cAMP-$synthetizing enzyme $adenylate-cyclase$ by a cascade of intra-cellular events, such that an activation of cAMP-receptors by the external signal cAMP is transduced intracellulary, resulting in an increase of internal cAMP. Therefore, the signal-transfering system includes the entire molecular cascade which is emerging from cAMP-receptors down to the adenylate-cyclase, in the simpliest case. The transfer modulating system then includes all cellular components affecting cAMP-receptors and adenylate-cyclase molecules, in particular. If we had included the cytosolic calcium concentration as another internal variable, the transfering as well as the modulating system would have been consisting of additional elements, of course.

The glutamat-sensitive neuron ([Mayer, 1994]).

As the internal variable, we define the cytosolic calcium concentration. For simplicity, we will restrict ourself to the situation that this neuron possesses only NMDA-receptors and, moreover, will assume that the potential-dependent Mg-block of the NMDA-receptors is removed. When the population of receptor-channels becomes activated by binding of glutamat-molecules, the

cytosolic calcium concentration will be increased locally due to the influx of calcium ions according to the enhanced permeability of the calcium-channel population. In this particular situation, the signal transfering system corresponds to the population of NMDA receptor-channels. Variations in the cytosolic calcium concentration produce modulatory effects at receptors by various mechanisms, for example: By allosteric inhibition dependent on the calcium-concentration, the opening probability of the channels is decreased, whereas the sensitivity of the receptors is increased by the action of the calcium-dependent CaM-Kinases II, which is activated at sufficiently high local concentrations of free calcium ions. So, the modulating network includes calcium itself as well as the enyzme CaM-Kinase II, both inducing changes in the transfering pathway according to changes in the internal state. Of course, compared to the well-known complexity of the glutamate action in neurons, the above situation is an oversimplification, but by filling in other glutamat-triggered mechanisms, including the ionotropic AMPA-receptor-channel pathway as well as the metabotropic pathway, the activation/modulation scheme remains unchanged, in principle.

The light-reflex arc

Eyes are the receptors of the visual system in man, whose sensitivity to light are known to be controlled by several mechanisms. We focus here on the reflex-arc by which the pupil is adjusted to light such that its width is decreased due to a large amount of light playing on the retina, and *vice versa*. This reflex arc is very well understood and described elsewhere, so that we can restrict ourselves to a very brief sketch. The afferent fibres emerging from the retina are known to end in the nuclei of the pretectal region of the central nervous system from where parasympathetic efferents for pupillo-contriction and sympathetic efferents for pupillo-dilatation emerge. The width of the pupil, therefore, is controlled by two antagonistically acting efferent paths emerging from the same central region. By defining the activity of the pretectal region as the internal state of this reflex system, the signal-transfering system consists of the eye and the afferent fibres mentioned, whereas the modulating system includes the corresponding sympathetic and parasympathetic paths antagonistically innervating the muscles of the pupil.

4 Definition of the formal model

Our method for treating the above questions concerning the conditions under which homeostasis is achieved is mathematical in the sense that we propose a formal model which is abstracted from the level of concrete biological examples in order to translate the above questions into mathematical terms and subsequently analyse the mathematical problem by methods developed in the context of dynamical systems theory. Therefore, a short remark concerning this strategy seems to be appropiate. In contrast to physical theories, there is no canonical way for constructing models from so called *first principles* in biology. Being dogmatic, one would therefore claim that results about mathematical models in biology belong to the field of applied mathematics, whereby their relations to biology remain unclarifed. Moreover, compared to the overwhemling diversity and complexity of biological systems, formal models, even when intended to described only particular aspects, are so simple compared to the observed complexity of a concrete biological object that a defence against the reproach of over-simplification is at least difficult. But, more pragmatic, results concerning a mathematical model can be regarded as being related to the concrete biological system by analogy [Tyson & Kagan, 1988]. There are indeed various examples for formal models which are successfull in the sense that their analogy to the biological object or problem under consideration is rather strong. One of these examples certainly is the Hodgin-Huxley model of electrical conductance in nerve cells which, although not derivable from physical principles in a strict sense [?], is quit successful in providing a basis for describing and predicting many of interesting phenomena concerning signal transduction in neuronal systems. Turings treatment of morphogenesis [Turing, 1952] by reaction-diffusion systems, although widely abstracted from biology but brilliantly argued, was a landmark for further theoretical as well as experimental approaches towards a better understanding of pattern formation in biological systems. Evolutionary game theory seems to provide an appropriate mathematical framework for investigating the cooperative and competetive effects in the evolution of interacting genotyps and opens the possibility for further discussions of the concept of Darwinian evolution itself [?] and may contain the logical

as well as formal power for further developing the theory.

In the following, a simple formal model is proposed representing typical features of the abovementioned scheme. It is intended only as an illustrative example belonging to a much wider class of formal models for which the following consideration remain true (see *Appendix*).

4.1 Modelling a fluctuating environment

The idea is to represent a fluctuating environment of a given biological system as a sequence of external signals $\omega(t)$. So, for *Dictyostelium* let $\omega(t)$ denote the amount of external cAMP at time t, for the *glutamat neuron* $\omega(t)$ represents the amount of glutamat and for the light-reflex arc, $\omega(t)$ is the intensity of light on the retina. Notice that in each of these cases, $\omega(t)$ is a non-negative, real number. It seems to be quite reasonable to assume, that fluctuations of an environment are neither arbitrary high, nor arbitrary fast. Therefore, let $J \subset \mathbb{R}^{\geq 0}$ be a bounded real intervall and define

$$\Omega_J := \left\{\omega = (\omega(t))_{t\in\mathbb{N}_0} : \omega(t) \in J\right\}$$

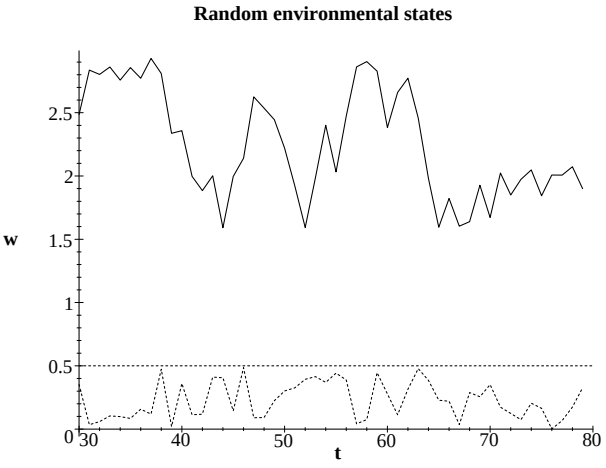
as the set of all signal-sequences taking their values in the bounded range J for all of the time. Requiering that the rapidity of environmental fluctuations should be bounded from above, means that the distance between two successive signals should be bounded by a certain non-negative real number, which we will denote by θ. Formally, by

$$\mathcal{T} \; : \; \left\{ \begin{array}{l} \Omega_J \rightarrow \mathbb{R}^{\geq 0}, \\ \omega \; \mapsto \limsup_{t\in\mathbb{N}_0} \left\{|\omega(t+1) - \omega(t)|\right\}, \end{array} \right.$$

a non-negative number $\mathcal{T}(\omega)$ is assigned to a given sequence ω which can be regarded as a measure for the fastest dynamical component of the environmental sequence ω. Obviously, $\mathcal{T}(\omega) = 0$, if ω is the constant sequence. Moreover, if ω, ν are two sequences in Ω_J with $\mathcal{T}(\omega) < \mathcal{T}(\nu)$, we call ω *slower* than ν. We can then characterize an environment fluctuating in the range of J not faster than θ by the set of sequences

$$\Omega_{J,\theta} := \left\{\omega \in \Omega_J \; : \; \mathcal{T}(\omega) = \theta\right\}. \qquad (1)$$

In the following picture, a sequence of randomly chosen signals is shown fluctuating not faster than $\frac{1}{2}$. Observe that the horicontal dashed line indicates the value $\theta = \frac{1}{2}$, and the line beneath represents the distances between two successive signals, that is $|\omega(t+1) - \omega(t)|$. Appearantly, the distances remain bounded by $\frac{1}{2}$.



4.2 The formal model

We are now in the position to formulate the dynamics of the system, or a *cell* for short, subject to an environment $\Omega_{J,\theta}$. We assign two real-valued variabels to a cell which are the internal variable p and the modulatory variable r. Further, we assume that variations of the internal state are caused by externally signals mediated by the signal-transfering systems on the one hand and by internal, autonomous processes on the other. The net effect of autonomous processes is summarized by the mapping $p \mapsto a\,p$, where $a \in \mathbb{R}^{\geq 0}$ and $\mapsto$ means: *changes to*. Notice that $a > 1$ ($a < 1$) corresponds to an autonomous increase (decrease) of the internal state. In order to describe externally induced perturbations of the internal state, let f be a real-valued function of r such that $f(r)$ represents the sensitivity of signal-transfering of the cell with respect to a signal when its modulatory state is r. Then the

internal effect induced by an external signal $\omega(t)$ is supposed to be $f(r)\omega(t)$. Alltogether, in our caricature the time evolution of the internal variable of a cell, which is in the state $(p,\ r)^T$ and subject to an external signal $\omega(t)$, is given by $p \longmapsto a\,p + f(r)\,\omega(t)$. The dynamics of the modulatory variable r is defined by $r \longmapsto r + \tau(1-p)\,r$, where the real-valued parameter τ is regarded as a time-scale of the modulatory process and, hence, is assumed to be non-negative. Notice that for $\tau = 0$, the modulatory state r remains constant whatever p is, otherwise, r changes according to $\tau(1-p)\,r$. So, the absolute value of r is increased if $p < 1$, whereas for $p < 1$ it is decreased. Further notice that the modulatory state remains unchanged if $p = 1$. So, in this model, we assume that there exists a certain value of the internal state, for which the state of the modulatory systems remains unchanged.

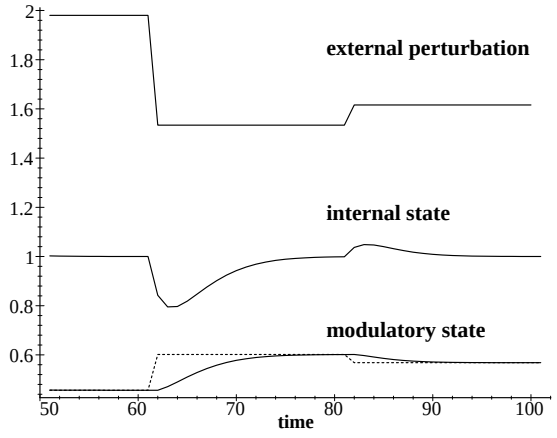
Let us briefly consider the dynamics defined by the mapping[1] $F_{\omega(t)} : \mathbb{R}^2 \to \mathbb{R}^2$,

$$F_{\omega(t)} \ : \ \begin{pmatrix} p \\ r \end{pmatrix} \longmapsto \begin{pmatrix} a\,p \ + \ f(r)\,\omega(t) \\ r \ + \ \tau\,(1-p)\,r \end{pmatrix} \qquad (2)$$

with real-valued non-negative parameters a and τ and $f : \mathbb{R} \to \mathbb{R}$, with $f(0) = 0$, a smooth and strictly monotonous function.[2] By denoting the state of the cell by $x := (p, r)^T$, we call $x(t) := F^t_\omega(x_0)$ the state of the cell at time t and the sequence $\big(x(t), t \in \mathbb{N}_0\big)$ the (state-) trajectory of the cell emerging from the initial state x_0.

In order to illustrate the dynamics defined by $F_{\omega(t)}$, assume for the moment that $a \approx 1$, $\tau \approx 1$ and f is increasing with $f(0) = 0$ and a constant external signal $\omega(t) = w$. let the cell be in the state $(p, r)^T$, where $r > 0$ and $p > 1$. Then $f(r)\,\omega(t) > 0$ and p increases. Since p is already larger than 1, r is decreased to a value $r' < r$. Since f was assumed to be increasing, the sensitivity also decreases from $f(r)$ to $f(r')$. As long as r remains positive, the internal state will increase but if p is large enough then r becomes negative, so that the corresponding term $f(r)\ w$ is less than 0 and p decreases. Therefore, we can recognize two features: 1.) the cell desensitizes its transfering system when its internal state is to high, otherwise the sensitization is increased, 2.) under suitable conditions, the value of the internal state will be kept around the value 1. The following pictures shows this kind of internal adaptive behaviour of the cell subject to an environment whose time course is shown by the above line. The curve fluctuating around 1 indeed represents the fluctuation of the internal state, whereas the solid line at the bottom indicates the time course of the modulatory state, or similarily, the sensitivity of the system. The meaning of the dashed line will be discussed later.

Fig A



Obviously, the system answers to weaker signals with sensibilization and de-sensibilizes itself against stronger ones in order to keep its internal state around the given value 1.

The cell maintaines its internal state around the value 1 by modulating its sensibility according to the environmental perturbation.

[1] The model is attended to be as simple as possible. In fact, it can be regarded as a special member of a more general class of open systems constituted by cyclically coupling two subsystems corresponding to the internal and the modutating systems mentioned above. We do not consider the general case here.

[2] A formal denition of the dynamical systems corresponding to $F_{\omega(t)}$ will be given in the *Appendix*.

5 Adiabatic stability and homeostasis

The following considerations are intended to motivate our particular notation of stability. First notice that for each signal $\omega(t)$, the mapping $F_{\omega(t)}$ has two stationary states, one of which is $(0,0)^T$, the other is

$$\zeta_{\omega(t)} := \begin{pmatrix} 1 \\ \rho(\,\omega(t)\,) \end{pmatrix}, \qquad (3)$$

where

$$\rho(\omega(t)) := \begin{cases} f^{-1}\left(\frac{1-a}{\omega(t)}\right) & : \quad \frac{1-a}{\omega(t)} \in f[\mathbb{R}] \\ \infty & : \quad \text{else} \end{cases}$$

is the stationary modulatory state which is associated to a given signal $\omega(t)$. Notice that $\zeta_{\omega(t)}$ varies with the external perturbation $\omega(t)$ as indicated in the above picture in which the dashed line represents the time-course of $\rho(\omega(t))$ for the signal sequence shown.

In the following, we will focuss only on the non-trivial fixed points $\zeta_{\omega(t)}$, since we are interested in the conditions under which the internal variable is kept around the given value 1. According to above, to each signal sequence $\omega \in \Omega_{J,\theta}$ there corresponds a sequence of points $\zeta_\omega = \left(\zeta_{w(t)} | t \in \mathbb{N}_0\right)$ in the state-space of the cell, which will be called the *trajectory of virtual fixed points associated with the signal-sequence* ω, or the *virtual trajectory* for short. Roughly speaking, the virtual trajectory is a kind of an internal representation of the environment fluctuating. If for all $t \in \mathbb{N}$ the virtual fixed points $\zeta_{\omega(t)}$ were attracting strongly enough, the state trajectory of the cell would follow the corresponding virtual trajectory ζ_ω in the sense that the state of the system $x(t)$ will remain in some finite neighbourhood of $\zeta_{w(t)}$, provided that the signal-sequence ω variies slowly enough. So, the intuitive picture is that the cell evolves in time like being coupled to an other system which moves along the trajectory ζ_ω. Being suggestiv, we will call the later system the associated *virtual system.*

The following section is devoted to a more general treatment of the stability of such systems, since, as will be shown, homeostasis is strongly related to this kind of stbaility. The numerical examples given are done due to the dynamical system defined by (2).

5.1 Adiabatic stability

This considerations suggest the following idea of stability: we will regard the cell as stable if it "follows" its virtual system at least for almost all of the time.

Definition 1 *Let a sequence of virtual fixed points* $\zeta = \zeta_\omega$, $\omega \in \Omega_{J,\theta}$ *be given and*

$$L_\omega := \limsup_{t \in \mathbb{N}_0} \left\{ \, |\zeta_{\omega(t+1)} - \zeta_{\omega(t)}| \, \right\} < \infty \, .$$

Then the dynamical system defined by (2) is called ADIABATICALLY STABLE *with respect to* ω *if for a given* $\epsilon > 0$, *there exists a* $\delta = \delta(\epsilon, L_\omega)$ *such that for all* x *with* $\left| \, x - \zeta_{\omega(t)} \, \right| < \delta$

$$\left| \, F_{\omega(t)}(x) \; - \zeta_{\omega(t+1)} \; \right| < \epsilon$$

for all but finitely many $t \in \mathbb{N}$.

Anticipating the follwing considerations, we will call ϵ the *homeostatic range*. Notice that *adiabatic stability* is strongly related to *synchronicity*, since the above definition can be reformulated as: A cell subject to a perturbation ω is adiabatically stable if it is synchronized to the corresponding virtual system in a master-slave fashion [Tresser & Worfolk, 1995].

The following considerations are intended to motivate rather than to prove our main result concerning adiabatical stability. [3] Let $\epsilon > 0$ be given and assume that the cell is in a state $x(t-1)$ at time $t-1$ which is sufficiently close to the point $\zeta_{\omega(t-1)}$. Moreover, let $\omega(t)$ be a signal at time t. Then according to (2), the state of the cell at time t is $x(t) = F_{\omega(t)}\, x(t-1)$. Our aim is to find a simple condition in order to guarantee that the distance between $x(t)$ and $\zeta_{\omega(t)}$ is less than a given number ϵ. Therefore, it is necessary that the mapping $F_{\omega(t)}$ is (locally) contracting strongly enough, [4] that is:

[3] A more precise formulation as well as the proof of the main result will be given in the *appendix*.

[4] Let $w \in J$ and F_w defined by (2). Then the mapping F_w is called LOCALLY CONTRACTING in ζ_w if there exists real numbers $0 < h_w \leq \infty$ and $0 \leq S_w < 1$ such that

$$\left| F_w(x) - \zeta_w \right| \; \leq \; S_w \, \left| x - \zeta_w \right|$$

for all $|x - \zeta_w| < h_w$, where h_w is the maximal radius of a ball centered at ζ_w which is contracted by the mapping F_w. Since one can not expect the fixed points ζ_w to be *globally attractive*, h_w will be finite, in general.

$F_w(x)$ acts on a neighbourhood of $\zeta_{\omega(t)}$ by contracting it due to a non-negative factor $S_{\omega(t)}$ less than 1. Obviously, the contraction must be stronger, the larger the distance between $\zeta_{\omega(t)}$ and $\zeta_{\omega(t+1)}$ is and, furthermore, the smaller the homeostatic range ϵ is. In order to formulate our main result, let a signal sequence $\omega = \big(\omega(t)\big)$ be given and

$$S_\omega := \limsup_{\omega(t)\in\omega} S_{\omega(t)} \ , \tag{4}$$

which is a measure for the *weakest* contraction of the family of mappings $\big\{F_{\omega(t)} \,|\, \omega(t) \in \omega\big\}$ along the virtual trajectory.

Main Result *Let $\omega \in \Omega_{J,\theta}$ be a signal sequence, L_ω defined as above and $\epsilon > 0$ sufficiently small. If*

$$0 \le S_\omega < 1 - \frac{L_\omega}{\epsilon} \ , \tag{5}$$

then the trajectory of the cell keeps following the virtual trajectory in a distance not exceeding the given value ϵ, at least for almost of the time.

Since L_ω is a measure for the largest variations along the virtual trajectory, the condition $L_\omega < \epsilon$ in (4) means that subsequent virtual fixed points have to stay in a distance less than ϵ from each other for almost all of the time. Since the virtual fixed points vary continously with the values of the signal sequence, this implies that subsequent signals $\omega(t-1)$ and $\omega(t)$ also are not allowed to differ too much, that is: θ has to be small enough. In other words, the environmental fluctuations have to be slow enough. This is the reason for calling this kind of stability *adiabatical*.

Observe that the above definition and the statement, as well as its proof do not refer to our particular model explicitly. Moreover, if the sequence of virtual fixed points is the constant sequence, one recovers the usual definition of stability [Katok & Hasselblatt, 1995]: In this case $L_\omega = 0$, and the stability conditions (5) reduces to $0 \le S_\omega < 1$. For our particular example, $0 \le S_\omega < 1$ for arbitray $w \ge w$, if $0 < a$, $\tau < 1$, as is proven in the appendix.

5.2 Adiabatical stability and homeostasis

This section is intended to show that adiabatic stability implies homeostasis. Therefore, let us first recall that homeostasis was characterized heuristically as follows:

A system is called HOMEOSTATIC*, if its internal state is kept within certain narrow bounds for almost all of the time.*

From the definition of adiabatical stability, it follows immediately:

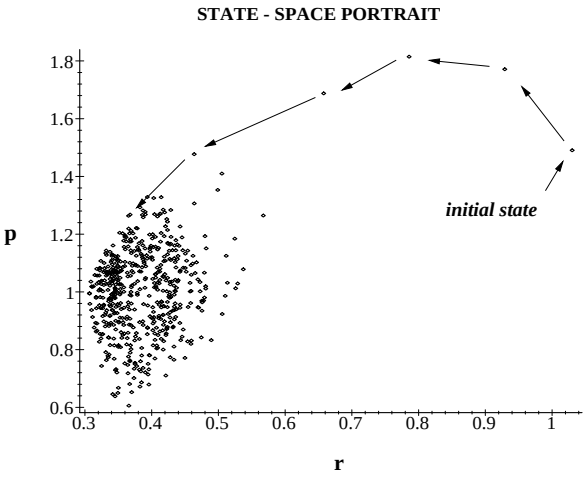
If a cell is adiabatically stable, then it is homeostatic.

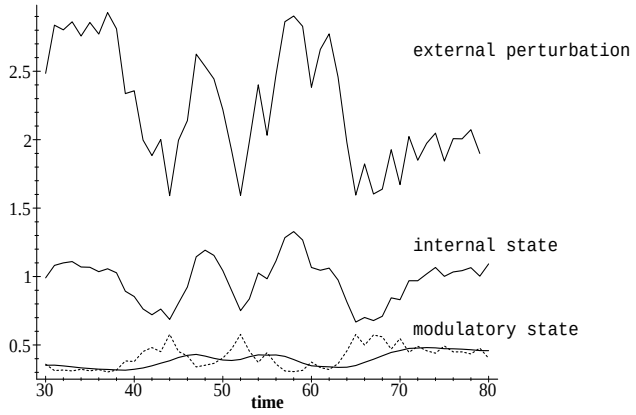
The argument is as follows: Consider a cell and let a sequence ω of external signals be given such that the conditions sufficient for the cell to be adiabatically stable with respect to ω are fullfilled. Then the corresponding trajectory of virtual fixed points $\zeta_{\omega(t)} = \big(1, \rho(\omega(t))\big)^T$ is contained in the set $\{1\} \times \mathbb{R}$. According to its adiabatical stability, the state trajectory of the cell will follow the virtual trajectory in a distance not exceeding the given range ϵ, that is: $|x(t) - \zeta_{\omega(t)}| < \epsilon$ for almost all of the time. Since $x(t) = \big(p(t), r(t)\big)^T$, this in particular means: $1-\epsilon < p(t) < 1+\epsilon$, in other words: the internal state is kept in the intervall $(1-\epsilon,\ 1+\epsilon)$ for almost all of the time. Moreover, it follows from the proof in the appendix that a trajectory staring in a distance not too far from the strip $(1-\epsilon,\ 1+\epsilon) \times \mathbb{R}$, will enter this strip after a finite number of steps and will remain in there.

This is the reason for calling ϵ the *homeostatic range*. Notice that the above statement is not restricted to our particular model. In fact, the crucial property used is that the stationary value of the internal state is independent of the external environment ω. (see *Appendix*)

The following pictures illustrate this kind of internal adaptive behaviour again descrtibed by (2). In the first picture, the state trajectory of a cell is shown starting at about $(1, 1.4)$ thereby being subject to the random environmental perturbations as already shown in Figure **2** . Notice that the system remains in a small region of its state space after having entered it after only about 8 steps. The second picture shows the time evolution of the random external signal sequence, the internal state

and the modulatory state, as well as of the virtual fixed points, again indicated by the dashed line.





6 Discussion

Recall our initial statement concerning the high but limited stability of biological systems against a wide but finite range of environmental perturbations. This section is intended to further discuss this observation my means of the particular model defined by (2). In particular, we are going to discuss the question how fast an environment is allowed to fluctuate in a given range such that a given cell is adiabatically stable with respect to it.

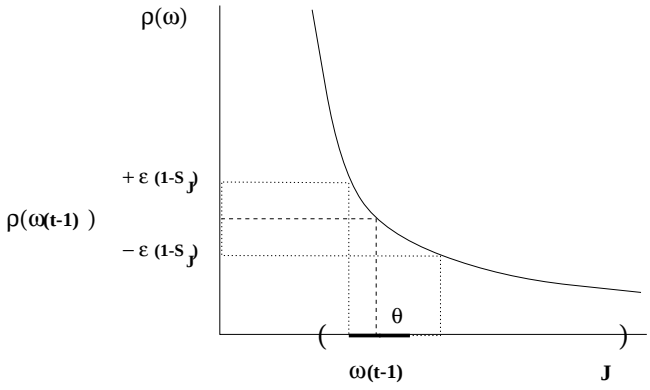
Consider a cell represented by the mapping $F_{\omega(t)}$ defined in (2) subject to perturbations in a given (bounded) range J.[5] Then to the interval J, there is associated a number $S_J := \sup_{w \in J} S_w$. We assume that the parameters a, τ were chosen such that S_J is less than 1. This can be done according to the results in Section B of the Appendix. Notice that $S_\omega \leq S_J < 1$ for all $\omega \in \Omega_J$. But, according to the stability condition (5), $S_\omega < 1$ is necessary but not sufficient for gurantee-ing adiabatical stability. Therefore, the question arises how fast environmental sequences $\omega \in \Omega_J$ are allowed to fluctuate such that the system is adiabatically stable with respect to them. In other words, we are asking how large the time-scale parameter θ of thye environmental perturbations can be chosen depending on the perturbation range J and the parameters of the mapping F.

Let the homeostatic range $\epsilon > 0$ be given and $\omega = (\omega(t),\, t \in \mathbb{N}_0)$ a signal sequence in Ω_J. Then condition (5) is equivalent to that for almost all of the time, the following inequality must hold:

$$\Big|\rho\big(\,\omega(t)\,\big) - \rho\big(\,\omega(t-1)\,\big)\Big| \;<\; \epsilon(1 - S_J)$$

Notice that the right-hand side is already determined by the assumptions and choises made. This inequality obviously imposes restrictions on the the distance between two subsequent signals. We will discuss this restriction by means of the following picture without refering to any explicit calculations.

[5] Recall that an environment fluctuating in the range J is represented by a sequence $\omega \in \Omega_J$.



Suppose that at time $t-1$ the signal $\omega(t-1) \in J$ is applied to the cell. In order to fullfill the above condition, the subsequent signal $\omega(t)$ must be located in the range around $\omega(t-1)$ as indicated. Notice that θ is the radius of the largest ball centered at $\omega(t-1)$ and completely contained in the marked range. Obviously, θ is larger the larger $\omega(t-1)$ is, whereas it is smaller the smaller $\omega(t-1)$ is. Moreover, the higher the perturbation level is, the more rapid are the fluctuations allowed to be, whereas adiabatical stability with respect to weak perturbations is achieved only if the fluctuations are sufficiently slow. Moreover, weak but rapidly fluctuating perturbations tend to destabilize the system.

The reason for this seeming paradox property of the system is its adaptive behaviour. According to it, a cell answers to a strong external signal by decreasing its sensitivity, such that the effective input is decreased. In particular, the effective input can be made arbitrally small by decreasing $|r|$ to 0. The next perturbation will then again cause only a weak effective input, since the sensitivity is already small. On the other hand, if a perturbation is weak, the cell reacts by increasing its sensitivity to this input and therefore by internally amplifying the signal. But then, the next signal also is amplifyed by the signal-transfering system, such that the effective input induced by this signal can be very large which might cause the variables of the cell to leave the attracting region, which is finite, in general. Therefore, the difference between two weak signals must be small enough. Hence, it is the adaptive behaviour of the cell that makes it sensitive to the rapidity of weak fluctuations.

It is important to notice that the above statement does not mean that a cell is stable against single arbitrary strong perturbations. The crucial point, again, is that the virtual fixed points ζ_w, in general, are not globally stable, that is: there exists only a finite attracting region around each fixed point. Hence, a single sufficiently strong perturbation may cause the cell state to leave this bassin and therefore destabilize a cell. However, by adjusting its sensitization on a sufficiently low level, a cell can stabilize itself against perturbation on a high level.

In summary, these considerations demonstrate that an adaptively behaviouring system is adiabatically stable only with respect to a restricted class of environmental perturbations. This refers directly to our initial statement that a biological system exhibits a limited stability against a restricted class of environmental perturbations.

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A Supplement to 5.1

We start by defining the dynamical system under consideration in general terms:

Definition 2 *Let $X \subseteq \mathbb{R}^{2n}$, $n \geq 1$, denote the set of local states $x = (p,r)^T$ and $\omega \in \Omega_{J,\theta}$ a sequence of environmental perturbations. Further, for each $\omega(t) \in \omega$ let $F_{\omega(t)} : X \to X$ be a continuous mapping having a fixed point*

$$\zeta_{\omega(t)} := \begin{pmatrix} P \\ R(\omega(t)) \end{pmatrix} .$$

Finally define the dynamical system F_ω by:

$$F_\omega^0 := x\ , \tag{6}$$
$$F_\omega^{t+1}(x) := F_{\omega(t)} \circ F_\omega^t(x)\ . \tag{7}$$

Corollary 1 *The dynamical system defined above is homeostatic if it is adiabatically stable.*

The convers is, of course, not true. The proof is completly analogous to the argument in 5.2. Notice that the mapping $F_{\omega(t)}$ defined by (2) belongs to this class of dynamical systems. We now state the Theorem corresponding tothe main result in 5.1.

Let a sequence $\omega = (\omega(t)) \in \Omega_{J,\theta}$ be given and denote the corresponding virtual trajectory by $\zeta_\omega = (\zeta_{w(t)},\ t \in \mathbb{N}_0)$. Furthermore, assume that $F_{\omega(t)}$ is locally contracting for all but finitely many t with contraction radius $h_{\omega(t)} > 0$ and Lipschitz constant $0 \leq S_{\omega(t)} < 1$, i.e.:

$$\left| F_{\omega(t)}(x) - \zeta_{\omega(t)} \right| \ \leq\ S_{\omega(t)} \left| x - \zeta_{\omega(t)} \right|$$

for all $|x - \zeta_{\omega(t)}| < h_{\omega(t)}$, where $h_{\omega(t)}$ is the maximal radius of a ball centered at $\zeta_{\omega(t)}$ which is contracted by $F_{\omega(t)}$. Then set

$$h := \liminf_{t\in\mathbb{N}_0} h_{\omega(t)} \qquad \text{and} \qquad S_\omega := \limsup_{t\in\mathbb{N}_0} S_{\omega(t)}\ .$$

Theorem 1 *Let $\omega \in \Omega_{J,\theta}$ and h, S_ω and L_ω defined as above, furthermore, let $0 < \epsilon < h$ be given. If for all but finitely many $t \in \mathbb{N}_0$ the mapping $F_{\omega(t)}$ is contracting in a $h-$neighbourhood of $\zeta_{\omega(t)}$ with*

$$0 \leq S_\omega < 1 - \frac{L_\omega}{\epsilon}\ , \tag{8}$$

then $\limsup_{t\in\mathbb{N}} \left| F_\omega^t(x) - \zeta_{w_{t+1}} \right| < \epsilon$ for all $|x - \zeta_{\omega(t)}| < h$.

Proof: Because of the contraction property of the mapping $F_{\omega(t)}$, we get

$$\begin{aligned} \left| F_{\omega(t)}(x) \ -\ \zeta_{\omega(t+1)} \right| &\leq \\ &\leq \left| F_{\omega(t)}(x) - \zeta_{\omega(t)} \right| + \left| \zeta_{\omega(t)} - \zeta_{\omega(t+1)} \right| \\ &\leq S_\omega \left| x - \zeta_{\omega(t)} \right| + \left| \zeta_{\omega(t)} - \zeta_{\omega(t+1)} \right| \end{aligned}$$

Then for $x \in \mathcal{B}_d(\zeta_{\omega(t)})$, $0 < d \leq \epsilon$, it follows

$$\begin{aligned} \limsup_{t\in\mathbb{N}} \left| F_\omega^t(x) \ -\ \zeta_{w_{t+1}} \right| &< \left(1 - \frac{L_\omega}{\epsilon}\right) d + L_\omega \\ &\leq \left(1 - \frac{L_\omega}{\epsilon}\right) \epsilon + L_\omega = \epsilon\ . \end{aligned}$$

We are now going to show that, given a $\epsilon \leq D < h$, the annulus $\overline{\mathcal{B}_D(\zeta_{\omega(t)})} \setminus \mathcal{B}_\epsilon(\zeta_{\omega(t)}) \supset \mathcal{B}_h(\zeta_{\omega(t)})$ is contracted by $F_{\omega(t)}$. For a $x \in \mathcal{B}_D(\zeta_{\zeta_{\omega(t)}}) \setminus \mathcal{B}_\epsilon(\zeta_{\zeta_{\omega(t)}})$, we have $\epsilon \leq |x - \zeta_{\omega(t)}| \leq D < h$ and therefore

$$\begin{aligned} \limsup_{t\in\mathbb{N}} \left| F_{\omega(t)}(x) \ -\ \zeta_{w_{t+1}} \right| &< \left(1 - \frac{L_\omega}{\epsilon}\right) D + L_\omega \\ &= D - L_\omega \left(\frac{D}{\epsilon} - 1\right)\ . \end{aligned}$$

Since $D > \epsilon$ and $0 \leq L_\omega < \epsilon$, it follows $L_\omega \left(\frac{D}{\epsilon} - 1\right) < D - \epsilon > 0$ and $\limsup_{t\in\mathbb{N}} \left| F_{\omega(t)}(x) - \zeta_{w_{t+1}} \right| < D$ for $\epsilon \leq |x - \zeta_{\omega(t)}| \leq D < h$. It remains to be shown that points x in a sufficiently small but finite neighbourhood of the $\epsilon-$ball around $\zeta_{\omega(t)}$ are mapped into the $\epsilon-$ball around $\zeta_{\omega(t+1)}$. Hence, let $0 \leq \epsilon' \leq \frac{\epsilon\, L_\omega}{\epsilon - L_{J,\omega}} < h$ and choose x such that $|x - \zeta_{\omega(t)}| = \epsilon + \epsilon'$. Then:

$$\begin{aligned} \limsup_{t\in\mathbb{N}} \left| F_\omega^t(x) \ -\ \zeta_{w_{t+1}} \right| &< \left(1 - \frac{L_\omega}{\epsilon}\right) (\epsilon + \epsilon') \\ &< \epsilon \left(1 - \frac{L_\omega}{\epsilon}\right) \left(1 + \frac{L_\omega}{\epsilon - L_\omega}\right) = \epsilon\ , \end{aligned}$$

what completes the proof.

$\triangle$.

B Asymptotical stability of ζ_w

In this section, conditions are considered under which the fixed point $\zeta_{\omega(t)}$ of the mapping

$$F_w\ :\ \begin{pmatrix} p \\ r \end{pmatrix} \longmapsto \begin{pmatrix} ap + f(r)\, w \\ r + \tau(1-p)r \end{pmatrix}$$

is asymptotically stable. Let $w \in J$ and ζ_w the corresponding non-trivial fixed point. Linearizing F_w in ζ_w gives the following linear mapping

$$\varphi_w\ :\ \begin{pmatrix} p \\ r \end{pmatrix} \longmapsto \begin{pmatrix} a \cdot p + b(w)\, r \\ r - p \end{pmatrix}$$

where $b(w) = \tau\, w\, \rho(w)\, f' \circ \rho(w)$.

Lemma 1 *Let $\sigma(\varphi_w)$ denote the spectral radius of φ_w. Then $\sigma(\varphi_w) < 1$ if and only if*

$$0 < a < 1, \quad (9)$$

$$0 < b(w) < 1 - a \quad (10)$$

Notice that for $f(r) := c\,r$, $b(w) = \tau(1-a)$ is independent of w. For $f(r) := c_1\, arctan(c_2\, r)$,

$$b(w) = \begin{cases} \frac{1}{2}\tau\, c_1\, w\, \sin\left(2\,\frac{1-a}{c_1\, w}\right) & : \quad w > \frac{2}{\pi}\frac{1-a}{c_1} \\ \infty & : \quad else \end{cases}$$

More generally:

Lemma 2 *Assume $0 < a < 1$, $0 < \tau < 1$ and f smooth, monoton increasing and concave with $f(0) = 0$. Then $0 < b(w) < 1 - a$ for all $w \geq 0$.*

Proof: First rewrite the function b by defining $\phi(w) := -w\frac{\rho'(w)}{\rho(w)}$ so that $b(w) = \tau\frac{1-a}{\phi(w)}$. Since f is strictly increasing with $f(0) = 0$, w and $\rho(w)$ are of equal sign whereas $\rho(w)$ and $\rho'(w)$ have opposite sign. Therefore $\phi(w(\kappa)) > 0$. Moreover, since $f'' < 0$, it follows: $\phi(w) \geq 1$, so that $0 < b(w) < 1 - a$ for all $w \geq 0$. $\triangle$

Let the assumptions of Lemma 3 be fullfilled, then the spectralradius of the linearized mapping is less than one and with respect to the Euclidean norm $\|\varphi_w\| = \sigma(\varphi_w) < 1$. Moreover, the mappings F_w and φ_w are conjugated to each other in a sufficiently small neighbourhood of ζ_w, and $S_w = \|\varphi_w\| < 1$.

References

[Adolph, 1964] Adolph, E.F.(1964). Perspectives of adaptation: some general properties. In: *Handbook of Physiology*:Section 4, Adaptation to the Environment, American Physiological Socienty, Washington, 1964.

[Ashby, 1952] Ashby, W. R. (1952): *An Introduction to Cybernetics*. John Wiley, New York.

[Belousov,1985] Belousov, B. P. In Oscillations and Travelling waves in Chemical Systems, ed. by R. J. Field, M. Burger (Wiley-Interscience, 1985) 65

[Cannon, 1925] Cannon, W.B...(1925). Organization for Physiological Homeostasis. In: *Homeostasis:* Origins of the concept, Benchmark Papers in Human Physiology (1973) (L.L. Langley, ed.). Dowden. Hutchingson & Ross.

[Cannon, 1926] Cannon, W.B.(1926) Physiological Regulation of Normal States: Some Tentative Postulates Concerning Biological Homeostasis. In: *Homeostasis:* Origins of the concept, Benchmark Papers in Human Physiology, (1973)(L.L. Langley ed.). Dowden. Hutchingson & Ross.

[Carafoli,1987] E. Carafoli (1987): Intracellular Calcium Homeostasis. *Ann. Rev. Biochem* **56**, pp. 395-433.

[Cheek, 1991] Cheek, T.R. (1991) Calcium regulation and homeostasis. *Curr. Op. Cell Biology* **3**, pp. 199-205 .

[Caverzasio & Bonjour, 1992] Caverzasio, J., Bonjour, J.P. (1992) IGF-1 and phosphat homeostasis during growth. *Nephrology* **13**(3), pp. 109-113.

[Dawson, 1990] Dawson, A.P. (1990) Regulation of intracellular Ca^{2+}. *Essays in Biochemistry* **25**, pp. 1-37 .

[Devreotes, 1989] Devreotes P.N. (1989) Dictyostelium discoideum: a model system for cell-cell interactions in development. *Science* **245**, pp. 1054-1058.

[Insall & Borleis & Devreotes, 1996] Insall, R.H., Borleis L., Devreotes P.N. (1996) The aimless RasGEF is required for processing of chemotactic signals through G-protein-coupled receptors in Dictyostelium. *Current Biology* **6**(6), pp. 719-729.

[Katok & Hasselblatt, 1995] x Katok, A., Hasselblatt, B. (1995) Introduction to the modern theory of dynamical systems, *Encyclopedia of mathematics and its applications*; **54**(Cambridge University Press) Braunschweig, [u.a.], Vieweg.

[Lehninger, 1975] LEHNINGER, A.L. (1975): BIOCHEMISTRY. Worth Publishers, Inc., New York

[Lubman & Crandall, 1992] LUBMAN, R.L., CRANDALL, E.D. (1992): Regulation of intracellular pH in alveolar epithelial cells. *Am. J. Physiol* **262**(1 Pt 1), pp. L1-14.

[Mayer, 1994] MAYER, M.L. (ED.) (1994): Glutamate Receptors and Transporters. Seminars in The Neurosciences **6**(2).

[Morris *et al., 1992*] MORRIS, C.M., CANDY J.M., KEITH A.B., OAKLEY A.E., TAYLOR G.A., PULLEN R.G., BLOXHAM C.A., GOCHT A., EDWARDSON J.A. (1992) Brain iron homeostasis. *J. Inorgan Biochem* **47**(3-4), pp. 257-65.

[Tresser & Worfolk, 1995] TRESSER, CH., WORFOLK, P.A. (1995) Master-slave synchronozation from the point of view of global dynamics. *Chaos* **5**(4). pp. 693-699.

[Turing, 1952] TURING, A.M. (1952). The chemical basis of morphogenesis. *Phil. Trans. R. Soc.*, **237**, pp. 37-72.

[Tyson & Kagan, 1988] TYSON, J.J., KAGAN, M.L. (1988). In *From chemical to biological organization* (M.Markus, S.C. Müller, G.Nicolis, eds.) (Springer-Verlag) 14