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# Stability/Flexibility: the tightly coupled homeostasis generator is at the same time the driver of change

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**Abstract**
There is "no Flexibility without Stability and no Stability without Flexibility": this is a crucial feature common to any system interacting with its environment. This tight link between two apparently opposite features is at the basis of the time-honoured concept of homeostasis (the tendency of any adaptive system to go back to its "comfort zone" contrasting the incoming perturbations) and is widely recognized since long time. On the contrary, the fact that the escape from a stable attractor state is a consequence of the same homeostasis mechanisms is often overlooked. In this brief note, we will try to give a proof-of-concept of the relation existing between stability/flexibility based homeostasis and the state changes at all the levels of biological organization. The ubiquity of the same principles across very different systems is a signature of a new attitude to look at scientific enterprise from a network-based viewpoint.

**Key words**
- biological regulation
- systems biology
- physiology, philosophy of science
- statistical mechanics

## INTRODUCTION

In the half of XIX century [1], the French physiologist Claude Bernard stated the first (and probably most important) principle of experimental medicine: organism survival is made possible by the existence of control processes contrasting ever-changing (but relatively small) perturbations and so keeping, on the long run, a substantially invariant internal environment (*milieu interieur*) [2]. The name for this continuous "going back" to a global condition favourable to life is homeostasis (keeping the system in the same state). Since Bernard's times, homeostasis became a fundamental principle of physiology [3], holding at any organization layer from biomolecules to ecological systems [4].

Homeostasis implies the need of a certain degree of flexibility to maintain the global stability of systems embedded into a largely unpredictable ever-changing environment: this is why the two (apparently) opposite flexibility and stability terms constitute, in the case of complex systems, an inseparable couple. In the case of biology, the "agents of stability" often coincide with the "agents of change": the same molecular players assuring the stability-by-flexibility homeostasis can push the system toward a different state.

In the following, we will present this mechanism in action in the cell-fate determination with reference to both similar cases at different levels of biological organization and to the Self-Organized-Criticality (SOC) physical model giving a theoretical explanation to the consilience existing between homeostasis and the (apparently) opposite transition behaviour.

## SELF-ORGANIZED CRITICALITY: LIVING ON THE EDGE OF CHAOS

In biological systems, the mechanisms involved in maintaining homeostasis by an increase in flexibility mirroring the ability to cope with external perturbations and those responsible for massive changes are the same [5, 6]. The statistical mechanics model of Self-Organized Complexity (SOC) [6] gives a vivid explanation of such behaviour.

The model of "self-organized complexity" (or "self-organized criticality" when the focus is on the peculiar situation of having an attractor state located in a critical position on the edge of chaos) or SOC (both interpretations give rise to the same acronym) was developed by Per Bak *et al.* [7]. The idea of SOC stems from the so-called sandpile model: think of pouring sand very slowly onto a flat, circular surface, at first, the grains stay close to where they land and soon start to accumulate creating a pile. Adding sand, the grains slide down, causing small avalanches that keep invariant the slope of the pile but, as we add more sand, the slope of the pile steepens, and the average size of avalanches increases. The pile stops growing when the amount of sand added balances the amount of sand falling off. The pile keeps

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invariant its shape and this state can be considered an "attractor" (stable state) of the dynamics. At odds with classical attractors that are static (e.g., think of a marble rolling down along the walls of a cup, until it reaches the minimum energy state correspondent to the bottom of the cup) or follow a regular orbit (think of a pendulum), the SOC equilibrium state is dynamic. The pile undergoes continuous local destruction/reconstruction events. At equilibrium, the added sand counterbalances avalanches, while the height and shape of the pile remain the same [7].

Occasionally, an added grain initiates a domino effect in which small (homeostatic) avalanches sum-up invading the core of the pile (normally unaffected by perturbations that are confined in the periphery of the system) dramatically altering its height and shape (critical avalanches) [7].

This behaviour is at the basis of an apparent conundrum of many complex systems: the attractor (stable) states of the dynamics are kept stable by a relentless adjustment to relatively small perturbations (added grains) that could foster its state transition (disruption of the sandpile).

Stability, in a continuously varying environment, asks for a relentless oscillation of the system between disruption and rebuilding: the small avalanches make it possible to integrate incoming grains in the sandpile keeping the system in a dynamically stable mode. The variability of periphery elements (involved in homeostatic avalanches) prevents the incoming perturbations to affect the core of the system but at the cost of keeping the system in a critical state prone to disruptive changes. Biological systems live at the "edge-of-chaos" [8].

## GENE EXPRESSION: A TRANSIENT STATE CHANGE PROMOTES A LONG-TERM JUMP TO A DIFFERENT ATTRACTOR

In the case of genome expression, the peripheral elements are genes endowed with an elevated spontaneous temporal variability. These genes (partially) escape the strong correlation among different gene expression coming from the need of a tissue-specific mutual balance of different gene expression levels. Formally these constraints correspond to a first principal component (PC1) getting rid of the great part (around 90%) of between genes variability in time, while periphery elements in charge of the continuous adaptation to environmental vagaries are more influences by the second component (PC2) of gene expression variability [5]. The minor axis of variation (PC2, second component, orthogonal to PC1 by construction) depicts the amount of discrepancy of single gene expressions from their average, tissue-specific expression level. The administration of a differentiation stimulus to a breast cancer derived cell culture [5] provokes, after 15-20 minutes, a transient state change increasing by one order of magnitude the variance explained by PC2 and causing a drop of the between expression profiles Pearson r [5]. After approximately five minutes, this perturbation is dissipated, but the changes initiated by this transient modification will provoke a dramatic phenotypic transition of the cells after 3 hours [5].

It is worth noting that the genes with higher values of PC2, despite the different amount of total variability explained by this component, are the same in both transition and "business-as-usual" (homeostasis) conditions. This is both consistent with SOC model and with the identity of the agents (genes) promoting stability and driving state changes [5]. This result suggests the presence of a fluid-like part of the system (peripheral high variability genes) staying side-by-side with a crystal-like core (low variability genes), as we will discuss in the next section.

## PROTEINS STRUCTURED AND FLEXIBLE PHASES: NATIVELY UNFOLDED REGIONS AS ENTROPIC RESERVOIRS

Critical equilibrium states are present in many biological systems, and protein science is the most convenient viewpoint for appreciating their structural counterpart [9]. Over the last two decades [10], the discovery that almost all the eukaryotic proteins have intrinsically disordered patches, drastically changed the canonical paradigm of a well-defined quasi-crystalline 3D structure (native structure) as the necessary prerequisite of protein function.

Proteins live in a microenvironment continuously perturbing their native structure, the entity of these perturbations (mainly due to thermal agitation) are of the same order of magnitude of intermolecular forces responsible for protein 3D configuration. This makes necessary to dissipate the "extra energy" coming from thermal noise to keep the structural core invariant (homeostasis). This is the role played by more flexible (disordered, fluid-like phase) protein domains [10]. At the same time, a given protein, in order to carry out its physiological role, is strictly dependent from the generation of a complex network of interaction with other protein molecules implying the mutual recognition of different protein systems. These interactions are crucial for the metabolic and signalling needs of the cell and involve "disordered" (highly flexible) domains that recognize (and mutually arrange with) fluid-like unfolded tracts of protein specific partners. This "fluid-like" phase of proteins ("entropic reservoir" [9]) correspond to highly flexible (natively unfolded) regions of the molecule that both dissipate thermal noise (homeostasis) and drive structural transition necessary to both allosteric behaviour and protein-protein interactions and re-shaping (attractor change). These drastic structural changes happen, thanks to the "invasion" of the protein (rigid) core by a wave of coordinated motion generated by a SOC-like mechanism coming from fluid-like phase. The presence of partially (or total) natively unfolded proteins, allows the cell to display a huge repertoire of biochemical patterns without the need of inflating the number of different protein species.

## PSYCHOTHERAPY: THE ALTERNATION OF FLUID AND STRUCTURED PHASES ALONG THERAPY PROCESSES

A recent study by De Felice *et al*. [11] compares "good outcome" and "poor outcome" psychotherapy processes; the authors observed that "good outcome" therapies alternate phases of high and low "flexibility" (entity of changes in correlation structure among the items of a psychological multi-item scale). There are significant differences in trajectories of stability and flexibility over time between therapeutic processes leading to a stable restoring of a healthy behaviour from not efficient therapies. The trajectories of good-outcome cases are characterized by cycles of stability (among items invariant correlation) and flexibility (rapidly changing correlation structure), while such cycles are relatively rare in the poor-outcome cases [11]. This behaviour is formally equivalent to order-disorder transitions of protein molecules. In the case of proteins, disordered phases mirror the need of "opening" (so making the system prone to change) a previously structured compact phase to make the molecule to reach a different configuration after the binding to a partner. Thus, it is not by chance that psychotherapy refers to the flexible phases as "openness" and ordered phases as "re-integration" (creation of a new configuration): successful psychotherapy relies on the alternation of these two phases to foster the reach of a new cognitive/motional configuration of patient system of thoughts and feelings.

Psychotherapy is a learning process, in which the attainment of constructive (re-integration) phases needs the disruption of a previous "unhealthy" cognitive "attractor". A good therapist should be able to recognize these phases during the therapeutic processes and consequently trying to canalize the therapy toward the desired goal (or, at least, to monitor the relative progress of the cure) of a global stabilization of the patient toward a "healthy" attractor state. It is worth noting this process can be fruitfully described in terms of a SOC-like mechanism [12].

## CONCLUSIONS

At the end of this brief note, we must answer a very important question: "Are the evident phenomenological similarities among the very different fields of investigation rapidly discussed in this review only the consequence of a mainly didactical metaphor or there is something more?".

To answer this question, two important papers appeared in the year 2000 in the same journal issue and having as first author the 1998 Nobel laureate for physics, Robert Laughlin [13, 14]. These two papers deal with the failure of a "Theory of Everything" at the basis of all the aspects of the natural world (an old dream of physics resembling the natural human attitude toward a substantial unity of the world around us) and the consequent need to approach the mesoscopic realm of emergent phenomena by a different attitude.

The authors state [13] "We call this physics of the next century the study of complex adaptive matter. For better or worse we are now witnessing a transition from the science of the past, so intimately linked to reductionism, to the study of complex adaptive matter, firmly based in experiment, with its hope for providing a jumping-off point for new discoveries, new concepts, and new wisdom". They affirm this view is not only confined to a specific scale, but could foster a new definition of what is fundamental, shifting from quantum mechanics to organization principles [14]: "In any event, the applicability of the science of mesoscale organization that we believe can be developed will not be limited to the world between angstroms and centimeters. Organization following similar principles may well be manifested in astrophysics. As we have noted, complex structures already have been proposed for the exotic matter expected in neutron stars, while ideas developed to explain mescoscopic organization on Earth may be useful in explaining the origin of large-scale structure in the Universe".

The authors refer to principles instead of laws, so marking the passage from a top-down approach to emerging (and thus mainly statistical) properties derived from the observation of structure and state changes at different levels of organization. This new attitude is made still more evident (and directly operational) by Donald Mickulecki [15] that demonstrates the existence of two kinds of "laws" named constitutive and relational "(…) constitutive laws for the network elements and the network topology. The use of constitutive laws for the network elements is the way the physical character of each network element is represented abstractly. It is a common feature of the material world. The topology or connected pattern of these elements in a network is an independent reality about the system. The same topology can be realized for an infinite variety of collections of network elements". The author demonstrates how many properties of natural phenomena are only dependent on the wiring structure of the set of correlations among their parts (network topology) with no relation with the intrinsic nature of the nodes of the network.

The search of "unification" of different natural phenomena passes from the recognition that "anything in the world is made by the same fundamental matter" to the acceptance of the fact that "anything in the world can be represented by a set of parts each other interacting".

This network-centric perspective (together with the emphasis on representation that allows putting together very diverse science fields without looking for an impossible to achieve reduction to a shared fundamental organization layer) allows for a direct empirical, largely data-driven, translation of empirical findings into a physically motivated frame. This opens the way to a directly operational common language to describe (and explain) natural phenomena independently of the degree of knowledge of the underlying microscopic laws. This is decidedly much more than a successful metaphor and opens the way to a re-integration of scientific culture after a too long fragmentation period.

### *Conflict of interest statement*

No conflict of interest is declared by the Authors regarding this paper.

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