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## Self-organization vs Watchmaker: stochastic gene expression and cell differentiation

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**Abstract** Cell differentiation and organism development are traditionally described in deterministic terms of program and design, echoing a conventional clockwork perception of the cell on another scale. However, the current experimental reality of stochastic gene expression and cell plasticity is poorly consistent with the ideas of design, purpose and determinism, suggesting that the habit of classico-mechanistic interpretation of life phenomena may handicap our ability to adequately comprehend and model biological systems. An alternative conceptualization of cell differentiation and development is proposed where the developing organism is viewed as a dynamic self-organizing system of adaptive interacting agents. This alternative interpretation appears to be more consistent with the probabilistic nature of gene expression and the phenomena of cell plasticity, and is coterminous with the novel emerging image of the cell as a self-organizing molecular system. I suggest that stochasticity, as a principle of differentiation and adaptation, and self-organization, as a concept of emergence, have the potential to provide an interpretational framework that unites phenomena across different scales of biological organization, from molecules to societies.

**Keywords** Stochasticity · Self-organization · Gene expression · Cell differentiation · Cell plasticity

### Introduction

Physical reality at the human scale is relatively well approximated by the concepts and models of classical

mechanics. The mind of a modern biological observer subconsciously tends to comprehend molecular and cellular phenomena in concepts of our scale, physical reality of classico-mechanistic objects and processes. This conceptualization manifests itself in an all-pervasive vocabulary of “locks”, “keys”, “machineries”, “power strokes”, “rheostats”, etc. that populate the literature, discussions and presentations in the field. It tacitly involves and assumes as valid all the familiar logical implications, consequences and interrelations between the concepts used as metaphors. However, recent advances in technology and methods are leading to the accumulation of experimental evidence inconsistent with a classico-mechanistic perception of biological phenomena, thus suggesting the inadequacy of a clockwork interpretation of life systems. The inherent stochasticity underlying behaviors and responses of isogenic macromolecules (Xie and Lu 1999), cells (Hume 2000; Blake et al. 2003) and organisms (Herndon et al. 2002), as well as the emergent properties and non-linear behavior of their organizations, defies expectations and assumptions of purpose, design, determinism, linear causality and reductionism, which characterize the Newtonian paradigm (Kurakin 2004).

The aim of this article is to illustrate that the subconscious adherence to a mechanistic world perception may handicap our ability to adequately comprehend and model biological phenomena, for it tends to blind the biological observer from potentially more fruitful alternative interpretational frameworks. Specifically, it is pointed out that the conceptualization of cell differentiation and development as a process of self-organization appears to be significantly more compatible with the current experimental reality of stochastic gene expression and cell plasticity than the conventional notions of a differentiation program and organism design. Stochasticity as a general principle and self-organization as a concept may constitute a part of an emerging interpretational framework that has the potential to conceptually unify phenomena across different scales of biological organization, from molecules to societies.

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## Stochastic gene expression

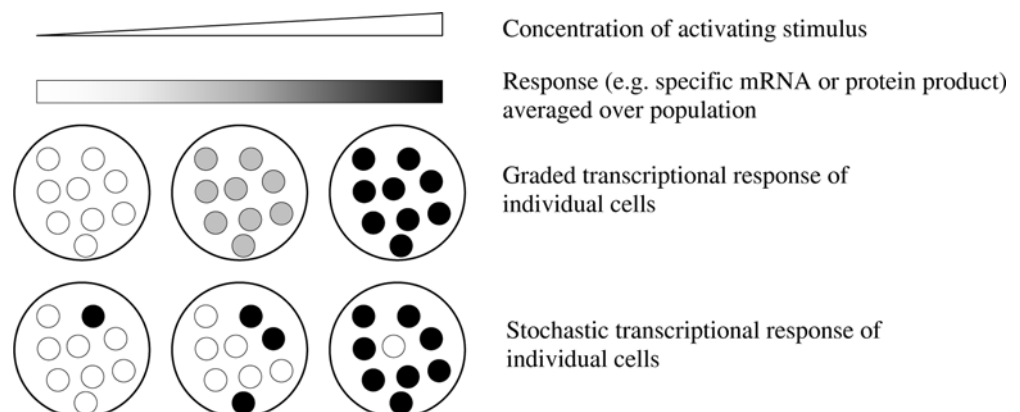
The mechanistic interpretational paradigm residing in and governing the sub-consciousness of a researcher leaves him/her no alternatives but to treat the cell as clockwork with all the ensuing panoply of logical inferences and assumptions. For instance, cells in a typical cell culture experiment are usually assumed to be identical like clockworks of a certain type. The same assumption is held for distinct cell lineages in the context of the organism. As a logical consequence, measurements of inducible gene expression, performed on “homogeneous” cell populations rather than on individual cells, led to a “rheostat” or “graded” model of regulation of gene expression, since in many cases a linear dependence was observed between the concentration of an external activating stimulus and the corresponding gene expression measured as total specific protein or mRNA product averaged over a large cell population. Within the framework of graded response, the appearance of an activating stimulus and an increase in its concentration are assumed to cause a corresponding and proportional rise in the rate of expression of a responsive gene gradually from zero to its maximum in every cell of a population (Kringstein et al. 1998; Biggar and Crabtree 2001; Fig. 1). Relatively recently the methods and technology were introduced and became readily available, which allowed researchers to analyze gene expression and other parameters in cell populations routinely on a cell-by-cell basis. As a result, the stochastic model of gene expression is becoming widely accepted. According to this model, each individual cell in a cell population has a certain and distinct probability to respond to a given concentration of an activating stimulus by the transcription of a responsive gene within a given time window. This probability may vary widely among individual cells even within isogenic populations and the ensuing gene expression follows an all-or-none response pattern. The responsive gene is either maximally expressed within a certain time window in a given cell or not expressed at all (Fig. 1).

As the concentration of an activating stimulus increases in the culture medium, the total specific mRNA or protein product of a responsive gene rises proportionally. However, the same overall increase of the product may result

either from a gradual increase of transcriptional rate from zero to its maximum in each cell of the population (graded response), or from the recruitment of increasing numbers of cells that switch from silence to maximum expression of the responsive gene once the concentration of the activating stimulus exceeds their individual response thresholds (stochastic response).

Quantitative experiments performed in different model systems, including animals, cultured cells and purified DNA templates, indicate that the increase in concentration of an activating stimulus usually results in the recruitment of increasing numbers of cells or templates in a given population that switch from silence to expression of the stimulus-responsive gene. At the same time the level of expression in the recruited cells remains largely unaffected by changes in concentration of the activating stimulus (Weintraub 1988; Fiering et al. 1990; Ko et al. 1990; Ross et al. 1994; White et al. 1995; Femino et al. 1998; Newlands et al. 1998; Takasuka et al. 1998). Transcription is proposed to be a stochastically determined event that occurs in short pulses. The number of active templates in a population defines its overall transcriptional output at any given time. The probability of a particular template to be active within a certain time window, rather than the rate of transcription from this template, is subject to regulation (Ross et al. 1994; Hume 2000). Transcriptional regulatory elements such as enhancers and activators, according to the probabilistic model of gene expression, simply increase the likelihood that their cognate promoters will be transcriptionally active within a certain time window, but do not affect the rate of transcription per se (Walters et al. 1995; Hume 2000). In a number of studies, it was suggested that transcriptional activators might act by modifying the probability of successful formation of pre-initiation complexes (Walters et al. 1995; Ho et al. 1996; Sandaltzopoulos and Becker 1998; Fiering et al. 2000; Blake et al. 2003). The specific molecular mechanisms that account for a binary response in inducible gene expression were proposed as well. As an example, Rossi et al. (2000) argued that the competition of transcriptional factors with opposing functions, such as repressors and activators, for the same target promoter might be necessary and sufficient for the establishment of an all-or-none transcriptional switch.

**Fig. 1** Graded and stochastic transcriptional responses. Adopted from Kringstein et al. (1998)



The conventional notion of a deterministic linear pathway underlying induction of a set of genes in response to serum stimulation was recently challenged by elegant single-cell expression profiling experiments of high spatial and temporal resolution, which revealed stochastic activation of responsive genes (Levsky et al. 2002). Analysis of transcription in single cells indicated that both alleles of imprinted genes were expressed randomly, but with different probabilities (Jouvenot et al. 1999). The phenomena of monoallelic gene expression (Serizawa et al. 2003), haploinsufficiency (Cook et al. 1998) and phenotypic heterogeneity in isogenic cell populations (Blake et al. 2003) were explained by the inherently stochastic nature of gene expression.

Quantitative analysis of transcriptionally active sites within nuclei of individual cells suggested that only an insignificant fraction, approximately 6–8%, of protein-encoding genes may be expressed in each cell at any given time (Iborra et al. 1996; Grande et al. 1997). It is tempting to speculate that due to the inherently stochastic nature of gene expression, while each cell in a population expresses a small fraction of a genome, a large enough population may express all or almost all genes within a certain time window. The cell population, therefore, represents a large “receptive field” for any possible environmental challenge as opposed to the narrow “receptive fields” of individual cells. This view is supported by recent statistical analysis and modeling of the large-scale gene expression data (Kuznetsov et al. 2002) and by the experimental observation of promiscuous gene expression in differentiated cell populations (Chelly et al. 1989).

Stochasticity is becoming de facto a paradigmatic property of gene expression as indicated by the fact that, along with demonstrations of its ubiquitous occurrence populating the literature, an increasing number of theoretical models is being put forward for explanation and modeling of stochasticity in gene expression (Cook et al. 1998; Thattai and van Oudenaarden 2001; Sasai and Wolynes 2003). Importantly, the apparently graded response does not contradict and can be easily explained within the framework of the probabilistic model (Hume 2000), while the reverse situation seems implausible. Nevertheless, the acceptance of the stochastic model de jure is resisted by the conventional wisdom, for its implications are poorly consistent with other widely used mechanistic conceptions, such as deterministic programs of cell differentiation and organism development.

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### **Cell differentiation and development: conventional views and experimental reality**

The mechanistic paradigm, which brought to life the rheostat model of transcriptional regulation, implies that the specific pattern of gene expression in an individual cell is instructed to this cell by extracellular clues from the environment. Which, in its turn, implies the pre-existence of specified schemes for cell fate determination and organism development. Indeed, cell differentiation is

presented today in textbooks as a unidirectional hierarchically structured program, where a molecular signal triggers the sequential expression and silencing of defined sets of specific genes in a cascade fashion driving the cell to lineage commitment and differentiation. A sub-conscious mechanistic mindset makes us see the cell itself as a gear inside the clockwork of a larger scale system, the organism. The specific expression profile of each cell in a mature organism is therefore pre-determined, according to the mechanistic intuition, to fit the specifications of respective gear in the context of organism design.

The design perspective on the cell and on organism development, though undoubtedly appropriate in the past as part of a self-consistent conceptual framework used for comprehension and modeling of biological phenomena, is today becoming increasingly at odds with the experimental reality of stochastic gene expression, transdifferentiation and genome plasticity.

Nuclear transfer experiments demonstrate that nuclei from differentiated somatic cells are re-programmed by the oocyte environment to drive normal embryonic development (Tian 2004). The same is true for nuclei derived from cancer cells (Li et al. 2003). In heterokaryons, created between cells of different types, the donor nucleus displays changes in gene expression reflecting the characteristics of the host cell (Theise and Wilmut 2003). These observations suggest that differentiation is a largely reversible state, which is dynamically maintained through the interaction of the genome with its immediate microenvironment. It is worth pointing out that the term “re-programming” itself can be considered as an ad hoc assumption devised by our sub-consciousness to make the mentioned phenomena consistent with the conventional notion of a differentiation program. Instead of postulating a re-programming event and its causative agents for each distinct microenvironment, it appears more reasonable to re-conceptualize the behavior of the genome in terms of a self-organizing molecular system coupled and responding to environmental changes, discarding the assumptions of an externally imposed program, purpose and design altogether (see below).

The conventional notion of a cell differentiation program is being shattered by the failure to demonstrate the existence of mechanisms for irreversible gene restriction, and by multiple studies reporting such examples of unexpected cell plasticity as neuronal stem cells turning into hematopoietic cells (Bjornson et al. 1999), bone marrow cells engrafting as liver and neuronal cells (Alison et al. 2000; Brazelton et al. 2000; Lagasse et al. 2000) and hematopoietic stem cells differentiating into cells of endodermal and ectodermal lineages such as epithelial cells of the liver, lung, stomach, small and large intestine, and skin (Krause et al. 2001). The claims that the observed examples of transdifferentiation can be explained exclusively by cell-cell fusion events have been rebutted recently by the demonstration of genuine cell plasticity in two different experimental models (Harris et al. 2004; Wurmser et al. 2004). Having reviewed the evidence challenging the unidirectional and hierarchical lineage

commitment, Theise and Krause (2002) recently suggested that: (1) any cell with an intact genome can potentially become any other cell type under appropriate treatment of the cell and its microenvironment; (2) any attempt to isolate a cell from its natural context alters the cell at the time of characterization and introduces inherent uncertainty in respect to the cell's origin and fate; (3) the nature of cell differentiation and lineage commitment should be considered as probabilistic. Loeffler and Roeder (2002) advocate that "stemness" should be treated not as an inherent or pre-programmed property of stem cells, but as a concept pertaining to flexible and dynamic tissue self-organization based on stochastic switches in expression profiles of individual cells, which are driven by cell-cell and cell-environment interactions.

### **Cell differentiation and development: self-organization through stochasticity**

Let us try now to re-conceptualize cell differentiation and organism development within an alternative framework, as a process of self-organization, which does not require or invoke any specification or design. Experimental evidence indicates that any cell population is heterogeneous in at least two respects. First, genes are expressed stochastically though infrequently in the population, thus causing a spontaneous diversification drift even within isogenic cell populations (Ross et al. 1994; Kuznetsov et al. 2002). Second, each cell in the population has a different threshold or a different probability to respond by specific gene expression to a given activating stimulus at any given time (Hume 2000). It is reasonable to suggest that the appearance of an external activating cue selects a sub-population of cells that happens by chance to be most responsive to this particular stimulus in that specific moment. The recruited cells switch then to expression of the responsive gene. It can be hypothesized that the expression of the responsive gene leads to re-arrangements in the individual transcriptional networks of the recruited cells, shaping these networks toward more similar, yet distinct, patterns of gene expression. The gene expression profiles in the recruited cells become in part synchronized by the appearance and presence of the activating stimulus. The activating stimulus may provide a selective advantage to the recruited sub-population on a local scale, but at the same time the synchronization of the recruited cells should be consistent with, and most probably provides a selective advantage to the whole of which this recruited sub-population is a part. In the context of the organism, any recruited sub-population is always embedded into a larger matrix of cell-cell interactions. In the case of hematopoiesis, a considerable body of experimental evidence suggests that lineage commitment occurs probabilistically and that regulatory factors select sub-populations of cells in which the commitment has already occurred, rather than dictate cell fate to target cells (Ogawa 1993).

The inherent stochasticity underlying gene expression in individual cells and the intercellular interactions turn a

cell population into a whole that is more than a sum of its parts. This whole becomes sensitive and discriminative to a much wider variety of changes in its environment than individual cells. It might be expected that virtually any new lasting environmental change will bias the "chaos" of individual expression profiles by giving a selective advantage to certain profiles in the population. At the same time, indirectly, through cell-cell interactions, it will affect and shape the structure of the global transcriptional network of the population. As the spectrum of interdependent individual expression profiles of a cell population is molded and maintained through interactions with the environment, the population as a whole *reflects*, models or, in other words, becomes cognizant of its environment.

In this model, the cell population is presented as a self-organizing adaptive system of interacting adaptive agents. The system gradually emerges and evolves over time driven by interactions with the environment, through dynamics of specialization and cooperation of its agents. It becomes a whole, which possesses novel emergent properties that cannot be reduced to or inferred from the properties of individual isolated cells. There are two equally legitimate interdependent entities co-existing and co-evolving at different spatio-temporal scales, the cell and the organization of cells. Though individual expression profiles in a cell population are inherently stochastic, a certain combination of interdependent profiles is selected, awarded and dynamically maintained through the continuous interaction of the population with its environment, provided this combination ensures and serves prosperity of the organization and, as a consequence, prosperity of its individual components.

Consider together (1) the revolutionary changes in the current views on cell plasticity, (2) an inherently probabilistic nature of gene expression and (3) a fair argument presented by Roeder and Loeffler (2002) proposing to re-define "stemness" as a functional (virtual) rather than a physical cellular attribute and introducing the concept of within-tissue plasticity, and it becomes reasonable to suggest that in a mature steady-state cell organization, such as tissue, for example, the dynamically maintained system of interdependent expression profiles represents essentially a steady-state system of distinct and interacting virtual functions, analogous to the integrated system of interacting and interdependent functions that constitute a human business organization. And, like in a human business organization, where a certain function is largely dissociated from the physical identity of the person performing that function, distinct expression profiles maintained in the mature steady-state cell organization are not necessarily represented physically by the same cells all the time. The stochastic nature of gene expression, providing a possibility for probabilistic switches of individual cells between distinct expression profiles, allows a flow of physical cells through a virtual steady-state structure of organization with average residence times characteristic for each "occupation", probabilistic transitions of physical cells between different "occupa-

tions” within the organization, “lay-offs”, “filling in vacancies”, etc. Notice that this interpretation of cell differentiation and development is not only compatible with the established body of experimental knowledge, but at the same time seems to be significantly more consistent with the current experimental reality of stochasticity in gene expression and phenomena of genome plasticity in comparison to the deterministic notions of differentiation and development.

It should be pointed out that the conceptualization of differentiation and development outlined here as a process of self-organization, which includes such principles and mechanisms as the formation of metastable organizations of interacting cells through their specialization and cooperation, the advancement of the individual prosperity of the cell through the success of the organization of cells, and the dissociation of distinct expression profiles maintained within the steady-state cell organization from physical identities of the cell comprising this organization, is explicitly not only non-Newtonian but non-Darwinian as well, as it cannot be reduced to the variation-selection principle and individualistic adaptation to a changing microenvironment in terms of “survival of the fittest” (Kupiec 1997; Paldi 2003).

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### **Self-organization and stochasticity as a unifying conceptual framework**

It is important to notice that, as a consequence of the continuous advance in experimental technology and methods, the adequacy of the mechanistic interpretational framework is being challenged at virtually all levels of biological organization, suggesting a systemic crisis of the mechanistic paradigm in life sciences. At the same time, stochasticity and self-organization are emerging as part of an alternative framework promising to conceptually unify phenomena across different scales of biological organization. The following are illustrative examples, not meant to be exhaustive.

At the molecular scale, folding of a protein molecule is considered as a process of self-organization realized through stochastic molecular interactions (Vendruscolo et al. 2003).

At the sub-cellular scale, the experimental evidence of stochastic self-organization of macromolecular complexes mediating transcription (Dundr et al. 2002; Kimura et al. 2002), DNA repair (Essers et al. 2002; Hoogstraten et al. 2002) and chromatin organization/function (Misteli et al. 2000; Cheutin et al. 2004), as well as the stochastic self-organization of steady-state cytoskeleton structures (Nedelec et al. 2003), sub-cellular and sub-nuclear compartments (Misteli 2001) is leading to a new image of the cell that emerges as a dynamic system of interconnected and interdependent metastable molecular organizations realized through self-organization and stochasticity (Kurakin 2004). This new image of the cell is conceptually coterminous with the treatment of cell differentiation and organism development in terms of self-organization and

evolution of steady-state specialized and interdependent organizations of cells.

At the scale of organizations of organisms, consider the response threshold models of division of labor in social insects (Beshers and Fewell 2001; Fewell 2003). These models assume that the individual insects in a swarm begin to perform a particular task only when a corresponding stimulus from their environment exceeds a certain value. The response threshold varies among members of the group, and individuals with the lowest response thresholds are recruited to the task first. By performing the task, the recruits diminish the stimulus, and thus reduce the probability that other individuals will be recruited to the same task. Because the individual insects in the swarm have different thresholds to distinct environmental stimuli, the ensuing division of labor occurs in a self-organized fashion, benefiting both the group as a whole and the individual members as its parts. The remarkable parallels of the response threshold models of division of labor in social insects with the conceptualization of the organism and the cell as self-organizing adaptive systems of interacting adaptive agents are evident and unlikely to be coincidental. Most probably they reflect common patterns in the dynamics and evolution of self-organizing complex systems.

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### **Self-organization and determinism**

The folding of a protein, organism development and the organization of a social swarm are faithfully reproduced in nature over and over again, giving sometimes the impression of a deterministic program in-built in the dynamics of self-organization. This impression may be misleading, for “determinism” of self-organization is probabilistic in its nature and is highly context-dependent, unlike the familiar mechanistic determinism, and therefore may be more appropriately called “developmental robustness” and treated in terms of probabilistic attractor states. The folding of a protein, organism development or the organization of a swarm can be seen then as the emergence of an organizational form and its evolution to a certain, but not necessary unique, attractor state, which is realized with high probability within a given environmental context. Though the evolutionary outcomes of the same process repeated over and over again are statistically similar, evolutionary trajectories are unique as a rule, due to stochasticity underlying self-organization. The trajectories therefore are not pre-determined and always have a potential to diverge and escape the usual attractor state. The evolution of the organizational form is driven both by the internal dynamics of the evolving organization and by the interactions with the environment. Neither the environment nor the internal dynamics of the system alone defines the evolutionary outcome or the final attractor state. How many attractor states are available for a given biological organization within a given environmental context and what parameters of the environment and the system are critical for evolution to and/or for transitions

between different attractor states are questions that remain to be answered.

Finally, it may be argued that any biological organization is a dynamic metastable part of one continuum of life, always influencing and being influenced both by the other parts and by the whole, while the reality of individual context-independent deterministic biosystems is simply an interpretational illusion of the reductionist observer.

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## Concluding remarks

The conceptualization of natural phenomena in terms of self-organization is becoming an increasingly popular interdisciplinary trend promising to connect traditionally isolated and seemingly unrelated research fields that study the emergence and evolution of different organizations at different scales. It is applied to the description of the dynamics of sub-cellular organization (Misteli 2001), the emergence of organization and division of labor in social insects (Fewell 2003), as well as to the evolution and dynamics of human business and social organizations (Morel and Ramanujam 1999), to give a few examples. It is worth noting that power-law scaling, an indicator of self-organized complexity, is shared by many biological, social and physical phenomena, but is not normally found in human-made systems, clockworks and artifacts built according to a pre-conceived design (Turcotte and Rundle 2002).

As examples of experimental evidence inconsistent with the conventional dogmas rooted in mechanistic interpretation of life systems continue to accumulate, stochasticity as a general principle of differentiation and adaptation, and self-organization as a concept of emergence appear to provide a foundation for an alternative conceptual framework that unites phenomena across different scales of biological organization, describing the cell as an evolving organization of molecules, the organism as an evolving organization of cells and the society as an evolving organization of individuals and their organizations.

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