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Review

Self-organization versus Watchmaker: stochastic dynamics of cellular organization

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Abstract

The cell, as a molecular system, is often interpreted in terms of complex clockworks, and the design charts of mechanical and electrical engineering are assumed to provide adequate approximations for the description of cellular organization. However, a growing body of experimental evidence obtained through the observation and analysis of real-time dynamics of fluorescently labeled molecules inside living cells is increasingly inconsistent with the classico-mechanistic perception of the cell. An overview of recent studies favors an emerging alternative image of the cell as a dynamic integrated system of interconnected and interdependent metastable molecular organizations realized through stochasticity and self-organization.

Keywords: cellular organization; determinism; molecular machines; moonlighting proteins; self-organization; stochasticity.

Introduction

Most of our visual knowledge about sub-cellular architecture originated from the images representing snapshots of fixed, desiccated and stained biological structures collected by conventional electron and light microscopy. As the mind of the biological researcher often tends to comprehend novel phenomena in familiar terms and concepts pertaining to our human-scale physical reality, which is fairly well described by classical mechanics, the interpretation of these images naturally led to the perception of sub-cellular organization in terms of clockworks and molecular machines. In addition, macromolecular complexes, such as the cytoskeleton, chromatin, transcriptional apparatus, splicing and translation machineries, DNA replication and repair systems etc., have traditionally been studied in a reductionist manner, in other words: (i) separated from each other and (ii) by means of the isolation and characterization of their individual components. Combined with the habitual mechanistic interpretation of biochemical and imaging data, the reductionist agenda resulted over time in a clockwork image of the cell. The organization of the cell is generally perceived to be different from clockwork only in terms of quantity, but not quality, and the design charts of cars, aircrafts and computers are routinely used today to illustrate the complexity of cellular organization and to point out the smart ways in which the cell exploits the advanced design principles of modern mechanical and electrical engineering.

However, the introduction and ingenious use of novel technology and methods, in particular fluorescence-based *in vivo* imaging techniques such as fluorescence recovery after photobleaching (FRAP), fluorescence loss in photobleaching (FLIP), fluorescence resonance energy transfer (FRET), etc., are leading to the rapid accumulation of experimental data inconsistent with a clockwork perception of cellular organization (Misteli, 2001a,b). Instead they favor a new image of the cell as a dynamic integrated system of interlinked and interdependent metastable molecular organizations (Kurakin, 2004). This new image of the cell is poorly compatible with conventional assumptions of the mechanistic paradigm, such as determinism, linear causation, ideas of design and externally imposed purpose, and calls for active exploration of alternative interpretational frameworks. Self-organization was recently suggested as a general principle underlying cellular organization and function (Misteli, 2001a). The present article, which reviews *in vitro* and *in vivo* studies addressing the molecular dynamics of different cellular compartments and functional systems, strongly supports this earlier suggestion and indicates that self-organization, as a concept of emergence, and stochasticity, as a general principle of adaptation and plasticity, may provide a conceptual framework for an alternative interpretation of the cell.

Self-organization and self-assembly: the cytoskeleton

The cytoskeleton is composed of actin filaments, microtubules and intermediate filaments. It underlies the structural integrity, spatial organization and morphological appearance of the cell, and orchestrates cellular directional movements and interactions with other cells and the substratum. It was appreciated early on that actin filaments and microtubules, polymers of the evolutionarily conserved protein monomers, actin and tubulin, are highly dynamic, self-organizing macromolecular structures (Alberts et al., 1994). In contrast to protein assemblies representing near-equilibrium molecular complexes, such as bacteriophage particles, actin filaments and microtubules are steady-state structures maintained in far-from-equilibrium conditions by a constant flow of energy and matter passing through them (Figure 1A).

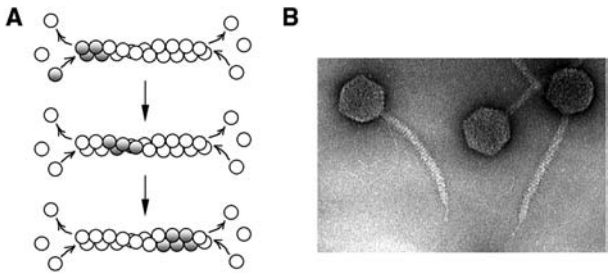

Figure 1 Steady-state self-organization and self-assembly. (A) Schematics of an actin filament, which is a dynamic polymer that constantly exchanges subunits with a free pool of monomers in the cytoplasm and requires ATP hydrolysis for its maintenance. Matter and energy continuously flow through the self-organized steady-state molecular organization. The filament structure may respond dynamically and rapidly by extending or shrinking if the rates of monomer association and/or dissociation are affected by the environment. (B) Phage λ particles as an example of dead-end static self-assembly. Following the assembly, phage particles are stable as molecular structures over a wide range of environmental conditions and do not appear to require energy and matter to maintain the structure. The electron micrograph of negatively stained phages was kindly provided by Dr. R. Inman, University of Wisconsin, Madison, USA.

It is useful to stress the differences between the steady-state dynamics of self-organization and dead-end self-assembly. Consider a phage particle (Figure 1B). It can assemble itself *in vitro* from purified components. Once assembled it is extremely stable, does not seem to require energy and matter for maintenance and is insensitive to a wide range of environmental conditions. The phage particle is an example of a self-assembled static structure. Following the assembly, interactions of the phage with the environment are absent or minimized and in this sense it does not perceive or is not 'aware' of the environment. On the contrary, as a rule, steady-state self-organized structures are dynamic organizations that are highly sensitive to changes in their microenvironment. Actin filaments and microtubules, for example, are sensitive to concentrations of their monomers, ATP and GTP, ionic strength, pH, and the presence or absence of activities that affect association and/or dissociation rates of monomers, etc. In a certain sense, steady-state structures are 'aware' of their environment and normally respond to environmental changes by changes in their morphology and functional characteristics.

Elegant experiments with purified tubulin, molecular motors, ATP and GTP have revealed that even simple molecular mixtures *in vitro* can give rise to a rich variety of different macromolecular structures resembling those that are observed in live cells, such as meshworks, vortices and asters (Nedelec et al., 1997; Surrey et al., 2001). Three observations are especially relevant to the discussion: (i) the structures formed in these studies represented true self-organized steady-state molecular organizations feeding on a flow of energy and matter; (ii) the emergence of a particular structure was dependent on the biophysical properties of the components mixed and their relative concentrations; and (iii) a model that faithfully reproduced the experimentally observed structures in computer simulations assumed stochastic interactions underlying the self-organization of macromolecular complexes composed of tubulin and motor molecules. One of the implications of these *in vitro* experiments is that a significant part of the dynamic complexity and variety of cytoskeletal structures observed in living cells can be controlled by the differential spatio-temporal distribution of a limited number of interacting molecular components. Or, putting aside externally imposed purpose and control, cytoskeletal structures might simply be reflections of the differential spatio-temporal distribution of their basic constituents within the context of a specific microenvironment (Niethammer et al., 2004).

A growing body of experimental data obtained *in vitro* and in studies carried out in living cells strongly suggests that both the spatial organization and directional movement of the cell are mediated by metastable dynamic macromolecular cytoskeletal structures (Misteli, 2001a; Destaing et al., 2003; Nedelec et al., 2003; Niethammer et al., 2004). In light of these data, it seems more appropriate to consider the cytoskeletal structures as self-organized molecular fluxes dynamically responding to changes in their microenvironment, rather than as deterministic static constructions that are assembled and disassembled according to a pre-conceived design.

Nuclear organization

The nucleus contains multiple morphologically and functionally distinct compartments, such as nucleoli, Cajal bodies, perinuclear compartments (PNC), promyelocytic leukemia (PML) bodies, splicing compartments, etc. (Spector, 2003). In contrast to the typical cytoplasmic compartments, their sub-nuclear counterparts are not delineated by membranes, although they are readily visualized under the microscope and some of them have been isolated and studied biochemically. How these sub-nuclear compartments are formed and maintained has remained unclear. Recently, quantitative analysis of the real-time movement of fluorescently tagged molecules in living cells dethroned several mechanistic conceptions and assumptions pertaining to the structural and functional organization of the nucleus, and brought about a new image of the sub-nuclear compartments as steady-state molecular organizations that are formed through stochastic molecular interactions and are maintained by a balance between the influx and efflux of their resident proteins (Misteli, 2001b; Hager et al., 2002; Vermeulen and Houtsmuller, 2002; Janicki and Spector, 2003).

Defying the previously widely held notion of the nucleus as a viscous gel-like environment, the mobility of non-physiological solutes in the nucleoplasm was shown to be only approximately four-fold lower than in aqueous solutions (Fushimi and Verkman, 1991; Seksek et al., 1997). Fluorescently tagged dextran microinjections revealed that the nuclear space inaccessible to injected molecules constituted less than 15% of the total nuclear space, thus challenging the presumed 'crowdedness' of the nucleoplasm (Seksek et al., 1997; Misteli, 2001b). Energy-independent random diffusion appears to be an efficient enough process to account alone for rapid translocations of proteins, RNAs and their complexes inside the nucleus (Houtsmuller et al., 1999; Pederson, 2000;

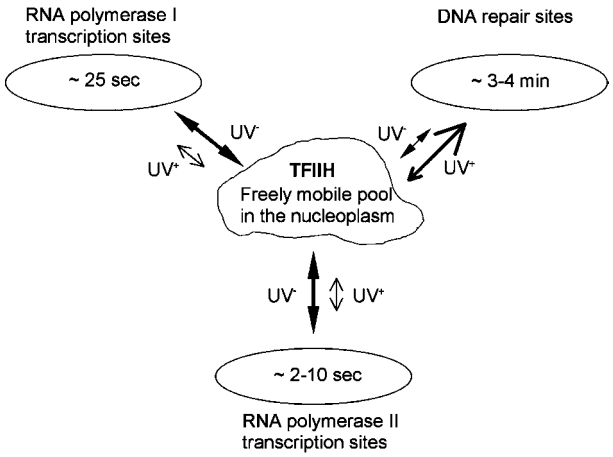

Figure 2 Schematics of the nuclear dynamics of TFIIH factor molecules.
The evidence and the model presented in Hoogstraten et al. (2002) suggest that TFIIH molecules are constantly and stochastically exchanged between the four pools indicated. The average residence times of TFIIH molecules within functional pools appears to be defined by transient association events and the activity of the TFIIH factor within the corresponding complexes. Note that the induction of DNA damage (UV^+) results in the dynamic and reversible shift of TFIIH activity to DNA repair sites. This shift is proportional to the DNA damage load and lasts until the damage has been repaired. The dynamic behavior of TFIIH is an illustration of how moonlighting activities may potentially integrate and coordinate diverse cellular functions into one dynamic and adaptive molecular system (see discussion in the text).

Phair and Misteli, 2000). Kinetic modeling of data, which were obtained in photobleaching experiments carried out in living cells, allowed the authors (Phair and Misteli, 2000) to estimate that approximately 10 000 molecules of the pre-mRNA splicing factor SF2/ASF and approx. 12 000 molecules of the RNA processing protein fibrillarin were leaving their respective compartments in a single nucleus every second. The residence times (t_{res}) of these proteins within splicing compartments and nucleoli were estimated to be less than 50 s for SF2/ASF and less than 40 s for fibrillarin. The transcription/repair factor TFIIH was shown to exist in a rapid and stochastic exchange between four pools within the same nucleus: RNA polymerase I (RNAPI) transcription sites, RNA polymerase II (RNAPII) transcription sites, DNA repair sites and a freely mobile unbound pool of TFIIH in the nucleoplasm (Figure 2). It was suggested that translocation between these pools is an energy-independent diffusion-driven stochastic process. The residence times of TFIIH molecules engaged in functional pools were estimated to be approx. 25 s, 6 s and 4 min for RNAPI, RNAPII and DNA repair sites, respectively (Hoogstraten et al., 2002).

The architecture of sub-nuclear compartments appears to be tightly coupled to their function. Inhibition of ribosomal gene transcription results in disassembly of the nucleolus (Oakes et al., 1993). Conversely, the addition of extrachromosomal ribosomal genes leads to the appearance of micronucleoli (Karpen et al., 1988; Oakes et al., 1998). Expression of the Cajal body resident p80-coilin protein in p80-knockout cells is sufficient to regenerate Cajal bodies (Tucker et al., 2001). Blocking splicing factor efflux from splicing compartments leads to their enlargement and reshaping (Misteli, 2001a). Nuclear subcompartments are naturally lost and re-assembled during the course of each cell division (Dundr et al., 2000; Olson et al., 2000). This architecture-function coupling suggests that sub-nuclear compartments do not exist as pre-assembled parts of the 'clockwork' mechanism of the cell, but rather are self-organized in response to functional need(s) of the cell, dynamically maintained as steady-state organizations while performing their function(s), and dissolved when the function(s) is no longer required.

Not readily explainable within the clockwork paradigm, the experimental data recently collected are consistent with and support the image of sub-nuclear compartments as self-organized dynamic macromolecular organizations that exchange their components incessantly. The specific interactions and activity of proteins within the steady-state macromolecular complexes appear to be the defining factor of their apparent mobility and transient immobilization events (Misteli, 2001b; Hoogstraten et al., 2002).

Sub-cellular self-organization

In addition to the commonly recognized dynamic and steady-state character of the endocytic and exocytic molecular organization, the Golgi complex is an example of an intracellular compartment delineated by membranes that displays clear hallmarks of self-organization (Misteli, 2001a). The tracking of fluorescently labeled proteins in living cells unexpectedly revealed the highly dynamic nature of the Golgi complex, identifying it as a steady-state organelle with continuous and rapid exchange of lipid membranes and proteins between the Golgi compartments, the secretory pathway and the endoplasmic reticulum (ER; Lippincott-Schwartz et al., 2000). The morphology of the Golgi complex is dependent on its functional status and can be modified by manipulating the influx and efflux of material passing through the compartment. Inhibition of traffic from the ER leads to dispersion of the Golgi complex into small vesicles (Zaal et al., 1999), while blocking vesicle transport from the *trans*-Golgi network results in enlargement of the latter (Griffiths et al., 1989). It is speculated that in a cell entering mitosis the continuous shedding of budding vesicles concomitant with blocking of their fusion results in disintegration of the Golgi complex (Warren, 1993; Lowe et al., 1998). Reassembly of the Golgi in the telophase is thought to occur by self-sorting and fusion of the dispersed vesicles through specific protein-protein interactions. Reassembly of the Golgi complex from mitotic Golgi fragments can be achieved in a cell-free system, indicating the self-organizing character of this organelle (Rabouille et al., 1995a,b).

Gene expression, DNA repair and specialized molecular 'machines'

Gene expression is a complex set of coupled molecular processes, such as chromatin remodeling, transcription,

RNA processing, RNA transport and translation. These basic biological processes are presumably carried out by specialized, pre-designed and often pre-assembled macromolecular complexes and 'machines' (Alberts et al., 1994). Quite unexpectedly, measurements of the mobility of protein components of various macromolecular complexes in living cells revealed a highly dynamic and inherently stochastic molecular behavior underlying the formation and maintenance of these complexes and 'machines'.

The residence times of chromatin-binding structural proteins such as histone H1 and high mobility group (HMG) proteins, previously believed to be stably associated with their binding sites on chromatin, were found to be unexpectedly short, of the order of 1 or 2 minutes for H1 molecules and of seconds for HMG molecules (Lever et al., 2000; Misteli et al., 2000; Phair and Misteli, 2000). Although the binding sites on chromatin remain occupied by the respective proteins, the occupancy is characterized by rapid exchange rates and short residence times (Misteli, 2001b). Similar observations were made for heterochromatin (Cheutin et al., 2004). Recently reported real-time integrative visualization of gene expression, in which the dynamics of a specific chromatin region and its RNA and protein products were followed simultaneously in living cells, revealed dynamic histone exchange as one of the mechanisms by which the transition of chromatin from a heterochromatic to a euchromatic state occurs upon gene induction (Janicki et al., 2004). In summary, experimental evidence indicates that chromatin is not a near-equilibrium structure of a mechanistic type, but a steady-state dynamic metastable molecular organization.

The same appears to be true for transcription and DNA repair machineries. The general assumption of stable initiation complexes existing under conditions of the primary activator competence was questioned by photobleaching experiments performed in living cells, which suggested that liganded steroid receptors such as the glucocorticoid receptor (GR) (Berk, 1999), the estrogen receptor (ER) (Stenoien et al., 2001b) and the androgen receptor (Farla et al., 2004), as well as co-activators such as GRIP-1 (Becker et al., 2002), CBP and SRC-1 (Stenoien et al., 2001a), are maintained in a rapid and dynamic exchange between their respective complexes and freely mobile pools. The Cockayne syndrome B protein (CSB) was recently reported as the first example of a transcriptional elongation factor that does not function as a stably associated component of the elongation complex, but is rapidly exchanged in a dynamic equilibrium between a mobile CSB pool and a transiently immobilized (t_{res} approx. 2–5 s) pool of CSB molecules associated with an elongating RNAPII (Van Den Boom et al., 2004). Two recent publications addressing the dynamics of RNAPI (Dundr et al., 2002) and RNAPII (Kimura et al., 2002) 'machines' and the recruitment of their components to functional complexes demonstrate that components of transcription complexes do not reside in pre-formed and stable holoenzymes, but associate transiently and dynamically through stochastic interactions into elongation-competent complexes. Kinetic modeling of experimental data has suggested that RNAPI assembly is a rather inefficient process that proceeds in a sequential manner via metastable intermediates. The stability of each intermediate appears to increase as more components are added to the metastable organization (Dundr et al., 2002). A dynamic steady-state organizational model was also proposed for different DNA repair 'machines'. In the case of double-strand break repair, it was shown that components of the repair system, such as Nbs1 and Mdc1/NFBD1, do not reside in preassembled holocomplexes in the absence of DNA damage, but rapidly localize to the induced DNA breaks where they form, together with other components, dynamic steady-state repair organizations. Each protein is only transiently engaged in the repair complexes, with average residence times of approximately 6.7 s for Mdc1 and 0.7 s for Nbs1 (Lukas et al., 2004). The same conclusions were reached for Rad 52 (t_{res} ca. 26 s; Essers et al., 2002) in the case of homologous recombination repair and for the core nucleotide exchange repair factors ERCC1/XPF (t_{res} ca. 4 min; Houtsmuller et al., 1999), XPA (t_{res} ca. 4–6 min; Rademakers et al., 2003) and TFIIH (t_{res} ca. 3–4 min; Hoogstraten et al., 2002). The efficient diffusion coefficients of the free fraction of repair factors in the nucleoplasm do not change after damage induction, thus indicating that self-organization of repair complexes takes place only at DNA lesion sites (Houtsmuller et al., 1999; Essers et al., 2002; Rademakers et al., 2003). Consistent with this conclusion, the fraction of transiently immobilized repair factors changes proportionally to the DNA damage load (Houtsmuller et al., 1999; Hoogstraten et al., 2002; Rademakers et al., 2003; Van Den Boom et al., 2004).

To summarize, the newly revealed and unexpected properties – such as steady-state character, transient self-organization on demand, stochastic dynamics and interconnectedness – that characterize cellular structures and molecular machines believed to exist as pre-assembled complexes designed for certain functions according to programs and blueprints, clearly suggest the inadequacy of expectations and assumptions based on the mechanistic intuition.

Flexibility, robustness and integration through moonlighting

It can be argued that stochastic self-organization is a highly inefficient and wasteful process. As an example, more than 90% of RNAPI subunits are not engaged at any given moment in elongation complexes, but are randomly tumbled around within the nucleoplasm as free unbound molecules. At the same time the assembly of RNA polymerase is incessantly attempted via unstable intermediates (Dundr et al., 2002). This apparent inefficiency, as judged from a mechanistic design perspective, is more than counterbalanced by the invaluable properties it may endow cellular systems. The conditions of natural existence require constant adaptation of cells to their changing and unpredictable environments. Therefore, it is highly advantageous for the cell to keep transcription, DNA repair and other systems flexible and ready to respond to any unforeseen stimuli, damages and/or

changes in extra- and/or intracellular milieu. Consider the transcriptional response as an example. It requires the combined activities of both common and stimulus-specific factors to initiate transcription from a wide variety of promoters in the genome. The same is true for the DNA repair system, which is poised to mend diverse DNA lesions. The constant stochastic shuffling of molecular components and the transient self-organization of specific complexes in response to an activating stimulus or a particular DNA lesion provide robust, just-in-time specific solutions, while continually maintaining system flexibility and responsiveness. In addition, the coupling and coordination of different processes, such as transcription and DNA damage repair, may occur automatically, since some of the participating molecules, such as TFIIH mentioned above (Figure 2) or the CBS protein functioning in both transcription and DNA repair (Van Den Boom et al., 2004), are shared by different functional systems. None of the most ingenious deterministic models of transcription or DNA repair 'machines' can outperform this solution under conditions of the inherent unpredictability of cell environment and fate.

To generalize, the phenomenon of stochastic self-organization, observed in a wide range of different processes studied in different model systems, suggests a new perception of the cell as a dynamic integrated system of interconnected and interdependent molecular organizations. Steady-state macromolecular organizations are realized through transient and specific molecular associations and coupled by fluxes of molecular components that are shared between different functional systems. When the organization of the cell is viewed from this perspective, the 'surprising' discovery of the so-called moonlighting proteins (Jeffery, 2003), i.e., proteins involved in two or more unrelated functions, seems more natural and even expected in hindsight. Consider examples of moonlighting proteins that may potentially couple and coordinate different cellular functions: the Clf1p splicing factor that participates in DNA replication (Zhu et al., 2002); proteosomal subunits that participate in transcription (Gonzalez et al., 2002); PutA proline dehydrogenase that acts as a transcription regulator (Ostrovsky de Spicer and Maloy, 1993); ribosomal proteins that function in DNA repair (Wool, 1996); the enzyme of phenylalanine metabolism, DcoH, that acts as a transcriptional regulator (Citron et al., 1992); and the glycolytic-pathway enzyme phosphoglucose isomerase that functions as a neuroleukin (Gurney et al., 1986), as an autocrine motility factor (Watanabe et al., 1996) and as a differentiation factor (Xu et al., 1996), etc.

Repercussions for research strategies

The mechanistic paradigm has a vested interest to interpret everything as structures, for it has little handle on processes. The term 'structure' carries a static undertone. A structure can often be isolated and studied separately. Frequently, its analysis can be legitimately further reduced to studies of separate and independent substructures. The term 'process' has more holistic connotations. It is difficult to imagine isolating a process without significantly affecting it. The experimental evidence reviewed suggests that much of what were believed to be cellular 'structures' appear under closer scrutiny as interlinked dynamic processes. The emerging image of the cell as a dynamic system of interconnected and interdependent molecular organizations, which are themselves maintained in a constant flux, underscores the limitations of reductionism as a basic strategy to study cellular processes. It is indicative that unexpected discoveries, which bring about a novel image of the cell, have originated mostly from studies carried out in living cells, where the dynamic behavior of cellular components was followed in their natural context, in real time, and with minimal external interference. Most probably, these discoveries would not have been made if researchers were following the routine strategy of fixing and isolating molecular complexes, characterizing individual components and publishing the inferred charts of pathways in accordance with the concepts and standards of mechanical and electrical engineering. It is therefore crucially important to complement the dominating reductionist strategies with studies of molecular components and their organizations in living systems and in the context of their natural environment, where the dynamic relationships are not disrupted by the fact of isolation.

Analysis of recently published studies addressing molecular dynamics in living cells reveals another clear and much-welcomed trend, the shift from qualitative description to quantitative analysis and experimentation coupled to computer-aided modeling. Computer modeling constrained by parameters measured in the experiment permits the extraction of quantitative estimates for other parameters that are difficult or impossible to obtain directly. Tuning of the adequacy of a model within experimental constraints leads to deep and often counterintuitive insights into the dynamics underlying cellular organization (Dundr et al., 2002). The benefits of this approach are immediately obvious, and the trend promises to deliver even more fruitful rewards in the future. It can be envisaged that the rapid accumulation of quantitative data on diffusion coefficients, binding kinetics, residence times, recruitment probabilities and other parameters obtained for different individual molecules and their complexes will soon provide a self-consistent quantitative framework and fertile ground for large-scale computer modeling and predictive simulation of spatio-temporal dynamics of specific processes, sub-compartments and eventually the cell as a whole. It should be pointed out that this new way of approaching the study of cellular processes may, and most probably will, diverge ideologically from the traditional strategy and goals. The self-educating loop, experiment – computer model – simulation – prediction – experiment – refined model – more accurate simulation – etc., does not necessary imply or claim the discovery of some pre-existing design or the 'ultimate equation' as its final goal. Instead, the development of an ever-evolving self-consistent system of coupled computer models, which would permit increasingly precise simulation and prediction of biological processes of ever-increasing scope and complexity, may become a less ambitious, but at the same time less illusory and more fruitful pursuit.

Concluding remarks

Studies of molecular dynamics in living cells suggest that sub-cellular and sub-nuclear compartments, as well as specialized macromolecular complexes mediating basic biological processes, are more adequately described as dynamic metastable organizations rather than as pre-designed molecular constructions of a mechanistic type. Stochastic self-organization is proposed as the mechanism of formation and maintenance of steady-state compartments and specialized molecular complexes, endowing cellular systems with such qualities as perception, adaptability and robustness. The morphological appearance of self-organized macromolecular organizations appears to be tightly coupled to their functional status. It should be pointed out that the new emerging image of the cell as a dynamic integrated system of interconnected and interdependent steady-state molecular organizations, which are sources of and, at the same time, subjects of change, adaptation and evolution, is more reminiscent of the evolving integrated system of human business and social organizations, and much less resembles the familiar images of clockworks and electric circuits designed for some purpose. It is most likely not coincidental that the topologies of both protein interaction and metabolic cellular networks obey a power-law scaling (Jeong et al., 2000, 2001). Power-law scaling is a symptom of self-organized complexity. It is shared by many biological, social and physical phenomena, but is not normally found in engineered constructions built according to a pre-conceived design (Turcotte and Rundle, 2002). It is therefore reasonable to suggest that the design charts of mechanical and electrical engineering that are frequently exploited for representation and conceptualization of cellular organization are hardly meaningful, if not outright misleading, and that the modeling and analysis of cell behavior in accordance with the new image of the cell may require the introduction, development and use of concepts, principles and descriptions that are qualitatively different from the mechanistic ones (Kurakin, 2004, 2005). As illustrated in the present review, self-organization, as a concept of emergence, and stochasticity, as a general principle of plasticity and adaptation, may constitute a part of an alternative conceptual framework, within which the cell is understood as a dynamic self-organizing system of molecular interactions.

On the term ‘stochasticity’

There is a certain degree of ambiguity in the literature as to use of the term ‘stochasticity’ with reference to molecular interactions. Some authors seem to reserve the term ‘stochastic’ to describe a situation in which one (or both) of the interacting partners is in such low abundance that local variation of its concentration makes occurrence of the interaction an inherently probabilistic event within a certain time window. However, the concept of self-organization through stochasticity implies a broader meaning of the term. When a system composed of multiple components, which interact in a stochastic and transient manner (molecules of water in the case of the Benard instability, for instance), is moved away from equilibrium and maintained in far-from-equilibrium conditions, it may spontaneously self-organize itself into ordered macrostructures through the coordinated activities of its microcomponents. Order comes out of chaos, but the order is a dynamic steady-state order. Chaos does not cease to be the chaos. The coordinated activities of the microcomponents represent a ‘biased chaos’, i.e., interactions between individual microcomponents always are and remain inherently stochastic, but become statistically biased when the macro-order is formed. What is ordered and dynamically maintained as a steady-state metastable structure is the organization of relationships between microcomponents, but not necessary the physical identities of the organized and interacting microcomponents, which are not preserved as a rule at the time scale of the organization. The term ‘stochasticity’ is used throughout the review in this last sense. The subject in itself deserves a separate discussion, which is unfortunately outside the space limitations of the present article.

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