Self-organization: the fundament of cell biology

Roland Wedlich-Söldner and Timo Betz

Excellence cluster Cells in Motion (CiM), Westfalische Wilhelms-Universität Münster, 48149 Münster, Germany

Self-organization refers to the emergence of an overall order in time and space of a given system that results from the collective interactions of its individual components. This concept has been widely recognized as a core principle in pattern formation for multi-component systems of the physical, chemical and biological world. It can be distinguished from self-assembly by the constant input of energy required to maintain order—and self-organization therefore typically occurs in non-equilibrium or dissipative systems. Cells, with their constant energy consumption and myriads of local interactions between distinct proteins, lipids, carbohydrates and nucleic acids, represent the perfect playground for self-organization. It therefore comes as no surprise that many properties and features of self-organized systems, such as spontaneous formation of patterns, nonlinear coupling of reactions, bi-stable switches, waves and oscillations, are found in all aspects of modern cell biology. Ultimately, self-organization lies at the heart of the robustness and adaptability found in cellular and organismal organization, and hence constitutes a fundamental basis for natural selection and evolution.

In the new millennium, cell biology has been greatly influenced by a renewed emergence of systems biology in its various manifestations. New directions of research have been largely driven by two lines of systems approaches. On the one hand, various ‘omics’ techniques have led to the assembly of extensive inventories of genes, expression profiles, proteins and protein modifications, as well as genetic and protein interactions. However, it has also become obvious that linear chains of causality and simple inventories of components are not sufficient to explain the dynamic spatial and temporal patterns typical for the complex interactions that control individual cells, let alone whole organisms. On the other hand, mesoscale systems biology, as eloquently described by Marc Kirschner more than a decade ago [1], relies on a combination of quantitative cellular perturbation and visualization approaches and the application of theoretical concepts from physics, mathematics and information theory to biological systems. This aspect of systems biology has been greatly fuelled by revolutionizing developments in fluorescence microscopy and has enabled us to obtain a conceptual understanding of many non-intuitive behaviours that are inherent to cellular physiology. One of the overarching themes that has emerged from the many detailed studies in mesoscale systems biology over the past decades is that nearly all cellular and subcellular structures, patterns and behaviours rely to some extent on self-organization.

Self-organization refers to the emergence of an overall order in time and space of a given system that results from the collective interactions of its individual components. This concept has been widely recognized as a core principle in pattern formation for multi-component systems of the physical, chemical and biological world. It can be distinguished from self-assembly by the constant input of energy required to maintain order—and self-organization therefore typically occurs in non-equilibrium or dissipative systems. Cells, with their constant energy consumption and myriads of local interactions between distinct proteins, lipids, carbohydrates and nucleic acids, represent the perfect...
playground for self-organization. It therefore comes as no surprise that many properties and features of self-organized systems, such as spontaneous formation of patterns, non-linear coupling of reactions, bi-stable switches, waves and oscillations, are found in all aspects of modern cell biology. Ultimately, self-organization lies at the heart of the robustness and adaptability found in cellular and organismal organization, and hence constitutes a fundamental basis for natural selection and evolution.

The concept of self-organization and its manifold implementations in biological systems were beautifully summarized a decade ago in a seminal review by Karsenti [2]. Now, after ten additional years of systematically inventorying cellular constituents by various omics approaches and the rapid development of microscopy techniques, cell biology and systems biology are at a stage where fundamental principles such as self-organization can be quantitatively characterized. Such conceptual understanding can then be applied to engineered or synthetic systems with the potential to generate a multitude of novel and precisely controlled cellular behaviours. The currently ongoing integration of systems and synthetic biology is bound to shape our future understanding of cell organization—and ultimately of the principles of life. This theme issue on self-organization in cell biology aims to summarize current approaches and identify future challenges in the study and application of self-organization in natural and synthetic biological systems.

The contributions are organized into three sections, dealing with self-organization on the molecular level, in whole cells and with the physical and evolutionary implications of self-organization. Importantly, this separation between sections is by definition very soft, as the emergence of properties from self-organized circuits often occurs by bridging different scales and levels of complexity.

When focusing on the quantitative descriptions of self-organization in biological systems, it is essential to review the underlying physical and mathematical concepts of phase transitions and reaction–diffusion systems. This is provided in the review by Saha & Galic [3], describing the physics of phase transitions by a classical statistical mechanics approach. Here, an important point for biological systems is to extend this classical description to dynamic systems, which in turn requires consideration of phase transitions in dissipative systems. Overall, phase transitions in membranes and also in the cytoplasm are a rich research field, which is also discussed on the cellular level in the contributions by Sych et al. [4] and by Wheeler & Hyman [5]. Besides introducing phase transitions, the review by Saha and Galic [3] provides a brief discussion of reaction–diffusion systems. Since Turing’s seminal work [6], reaction–diffusion systems are recognized as a fundamental description for pattern formation and self-organization in biology. To exemplify the depth of such systems, Saha and Galic [3] provide not only an analytical description but also examples of one- and two-component systems and discuss the biological perspective of reaction–diffusion systems.

One of the best understood examples for self-organization in biology on the molecular level is the Min protein system, represented by three subsequent papers in this issue. Min proteins shuttle back and forth from a cytoplasmic to a membrane-bound state, a dynamic process that is self-organized into oscillations that define the position for cell division in bacteria. Schwille and co-workers [7] introduce the Min system from the experimental point of view, where the common approach of reverse engineering the complex biological situation is a prime example using genetic tools to obtain fundamental insights into the functional dependencies of the different players. Literally following Richard Feynman: ‘What I cannot create, I do not understand’ (a phrase found written on his blackboard at the time of his death in 1988; from a photo in the Caltech archives), modern reconstitution approaches allow us to engineer the Min system in vitro, where many characteristics of the bacterial system can be reproduced and studied in outstanding detail. However, according to Schwille and co-workers [7], for real breakthroughs in the investigation of complex living situations, a well balanced synthesis of both the reverse and the forward engineering approaches should be pursued. Besides these experimental insights, the Min system is also attractive for detailed theoretical approaches, as reviewed by Wettmann and Kruse [8]. The most popular approach to model the dynamics of Min protein self-organization is based on reaction–diffusion systems, which have been successfully used to develop analytical as well as stochastic simulations to reproduce typical experimental observations like standing and travelling waves but also rotating spirals. A key element of these theories is the concept of cooperativity, which is mathematically reflected in nonlinear terms. Currently, further advances in our understanding of the Min system would require more experimental details, such as precise rate constants, better knowledge of the molecular details underlying the cooperativity required for the theoretical approaches and further advances in the reconstituted systems to even better reflect the in vivo situation. A different approach on the theoretical description of the Min system is put forward by Frey and co-workers [9], who explain that the often-used activator–inhibitor approach, which leads to substrate depletion, is not the only way to describe reaction–diffusion systems. Instead, combining diffusion processes with general reactions that only reflect a change in conformational state of the proteins might be more appropriate for the Min system. In this view, the key process for the observed dynamics is a directed transport, which can indeed be achieved by simple diffusion along defined cytosolic gradients. Hence, patterns are not necessarily due to protein production and degradation, but simply reflect different possible states of a protein, such as membrane-bound or cytosolic. As examples, the self-organized systems of Min proteins, Cdc42 and PAR proteins are discussed without using the classical activator–inhibitor methodology, but by demonstrating the efficiency of simple cycling between different states. This rather generic approach highlights the benefits of a new and fresh look on seemingly well described systems to overcome current limitations.

While Frey and co-workers [9] discuss a general approach to understanding reaction–diffusion systems, Yang & Wu [10] focus on oscillatory waves observed at the cell cortex. Their review provides a thorough discussion of the different protein networks that are known to result in cortex waves such as positive and negative feedbacks between GTPases and the emerging awareness of possible interaction between membrane curvature and actin polymerization. From a biological point of view, the key question that remains is assigning a functional role to such oscillations and cortical waves. Currently discussed functions range from a relevance in information storage and frequency-dependent signalling to
more complex scenarios involving information transfer within networks, up to the control of cell size via a connection between length-scales and oscillation frequencies. However, the possibility that oscillations are pure side effects of complexity, without a general biological function should not be fully ignored in the effort to understand cortical waves and oscillations.

Complementary to the experimental discussion of cortical waves by Yang and Wu [10], the article by Gov [11] provides a detailed theoretical description connecting curvature sensing/inducing proteins to membrane shape via active forces that deform and move the membrane. The generic approach of this model is based on a free energy minimization, thus ignoring hydrodynamic coupling that typically leads to long-range interactions. The theory developed here couples the mechanical effect of any force on the membrane to the expected dynamical changes of curvature, which result in a recruitment of curvature-sensitive proteins. Positive or negative feedback can then be included if these curvature-sensitive proteins can influence the initial, force-generating processes. These ideas can be illustrated in detail on different experimentally observed membrane curvatures and protein characteristics. The well described patterns are indeed predicted by the model, as demonstrated by the self-organization of structures like membrane protrusions, membrane retractions and tube formation. Besides such membrane shapes, even protein oscillations and waves are correctly predicted by the model.

The previously introduced contributions to this issue all focus on self-organization at the molecular level. However, many processes of self-organization happen at the cellular level. For example, the organization of the plasma membrane is well known to be heavily dependent on the formation of local domains that are defined by different membrane phases. Roemer and co-workers [4] discuss the current knowledge of such membrane phase transitions and their importance for membrane homeostasis, with a focus on lectin-induced transitions of glycosphingolipids. Here, the lectin confines such lipids to nanometre-sized areas with characteristics similar to lipid rafts. Depending on the details, the lipids and the lectins and even membrane curvature can be induced, thus supporting or even triggering endocytosis.

But it is not only at the level of the membrane where phase transitions have been shown to be of key importance for cellular organization. In their review article, Wheeler & Hyman [5] discuss the properties of non-membrane bound liquid organelles that emerge as liquid droplet-like condensations of proteins. The condensation of these droplets is driven by scaffold proteins typically falling in two classes: proteins with low complexity domains and proteins made up of multiple copies of interaction domains. Understanding the emergent properties and critical transitions of such condensates allows us to infer the status of the proteins involved. It is possible to determine characteristics and regulation of relative solubility, phosphorylation or SUMOylation. A key feature of such condensates is the connection between physical phase transitions and biological function, up to direct effects of signalling. Currently, these intracellular protein condensates are studied in great detail, but still little is known about fundamental processes such as condensate nucleation, control of condensate dynamics, condensate mixing and nested compartments.

Another example of such direct connection between physics and biology can be found in the crosstalk between physical forces and biochemical signalling, as described in the paper by Weiner and co-workers [12]. They review the self-organization of actin polymerization and acto-myosin contractility in the context of migration, where membrane tension is an important player. Similar to the contributions by Gov [11] and Yang & Wu [10], introduced above, the relation between forces and membrane deformation is discussed, although here the focus lies in the direct link to cell polarity and cell migration. The known connection between actin polymerization and acto-myosin contractility is the starting point to discuss the regulation of experimentally observed contractile pulses. The two main candidates to model such dynamics are a biochemical pacemaker and a biomechanical, feedback-driven self-organization. The investigation of the interlink between membrane tension and signalling events that are triggered by rapid tension variations favours the interpretation that intracellular waves of actin polymerization and contractility are indeed self-organized by biomechanical feedback mechanisms.

Such feedbacks are not only important at the cell cortex, but also for the organization of acto-myosin fibres, as extensively discussed by Bershadsky and co-workers [13]. Focusing on the assembly of acto-myosin and the importance of forces for this assembly, this review gives a detailed overview of the bundle organization. After discussing muscle sarcomere organization, which is highly stable with turnover times longer than one hour, the difference from myosin II-containing stress fibres in non-muscle cells becomes evident as these are highly dynamic, with turnover times faster than one minute. Such fast turnover times are surprising since stress fibres need to support stresses over longer timescales. Although we know that in non-muscle cells fibres are assembled with the help of the formin-like protein Fmn14, Cofilin and α-actinin-4, the details of fibre assembly remain unknown. A possible model proposed by Dasbiswas et al. [13] suggests an analogy to myofiber formation by explaining the self-organization in non-muscle cells with an interaction between myosin-generated force dipoles and the intervening actin meshwork that effectively provides the elastic scaffold supporting mini-filament alignment.

With all studies in cell biology, regardless of the scale and complexity of the system, there is a general conundrum: when introducing long-term or large-scale changes with classical perturbation approaches, the self-organized circuits in cells and tissues often adapt and can shift to a new steady state. While this new state is functionally linked to the original perturbation, it can encompass a multitude of hidden adaptations that can interfere with a correct interpretation of phenotypes. In this issue, Isogai and Danuser therefore suggest supplementing perturbations with correlative analyses of fluctuations in unperturbed systems [14]. They illustrate this approach using the succession and cooperation of different actin nucleators during the formation of cellular protrusions and cell adhesion structures. They also provide a general discussion of the advantages and limitations of fluctuation analysis.

In many of the examples discussed so far, physical constraints determine the precise outcome of self-organized systems. When considering shape determination of multicellular organisms and also of simpler systems such as fungi or slime moulds, physics often plays a more direct
morphogenetic role. In her contribution, Karen Alim considers the role of fluid flow for shaping the network architecture of the slime mould *Plasmodium polycephalum* [15]. In this organism, cytoskeleton-mediated contractions create flow patterns in the cytoplasm that exhibit long-range oscillations and can support very fast cell growth with up to 400 μm s⁻¹. The underlying feedback loops between fluid flow, cell shape and cytoskeletal functions provide a powerful example for a self-organized circuit that could be applied to novel applications in synthetic systems.

Like all aspects of biology, self-organization processes in cells are subjected to natural selection and evolution. Hallatschek and co-workers [16] focus on the interplay between pattern formation in microbial cell populations and genetic variability, or drift, in these populations. They discuss several examples of growth patterns in fungal or bacterial communities (colonies and biofilms). They demonstrate how stochastic effects on the single cell level (steric hindrance or growth speed) coupled to simple growth patterns can affect genetic drift on the population level. This in turn feeds back on growth patterns, leading to dramatic effects such as ‘fingering’ (protruding region of faster growth). They conclude that spatio-temporal patterns have to be considered when studying genetic drift and propose to study the feedback between pattern formation and evolutionary dynamics. This extension of the systems biology approach from the cellular to the population scale could ultimately allow the prediction and potential control of evolutionary processes.

In the final contribution of the theme issue, Alon and co-workers [17] study the distribution of genetic polymorphisms (differences) when organisms evolve under multiple tasks that require phenotypic trade-offs. They show that multi-task selection creates polymorphisms that align with the so-called ‘Pareto front’. This polytope line connects the vertices that describe the optimal phenotypes for individual tasks and delineates the region of ‘optimal’ compromise between different tasks. Combining theory and simulations, they demonstrate that polymorphisms that become prevalent in a population under multi-task selection have pleiotropic phenotypic effects that align with the Pareto front. This special structure allows mating to produce offspring that stand a good chance of being optimal multi-taskers.

**Data accessibility.** This article has no additional data.

**Competing interests.** We declare we have no competing interests.

**Funding.** We are grateful for funding from the German research foundation (EXC1003-CiM to R.W.-S. and T.B., SFB944 and WE22750/4-1 to R.W.-S.), and an ERC consolidator grant PolarizeMe to T.B.

### References


