TIMELINE

Self-organization in cell biology: a brief history

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Abstract | Over the past two decades, molecular and cell biologists have made important progress in characterizing the components and compartments of the cell. New visualization methods have also revealed cellular dynamics. This has raised complex issues about the organization principles that underlie the emergence of coherent dynamical cell shapes and functions. Self-organization concepts that were first developed in chemistry and physics and then applied to various morphogenetic problems in biology over the past century are now beginning to be applied to the organization of the living cell.

One of the most fundamental problems in biology concerns the origin of forms and their associated functions. This has been a long-lasting question in developmental biology, but similar questions must also be addressed at the cellular level. Since the discovery of the structure of DNA, the genome has often been thought of as the overriding architect: a given combination of genes that determines the phenotype through a linear chain of causal events. The problem is that embryogenesis and dynamic cell forms and functions emerge from multiple molecular interactions and interconnected regulatory feedback loops[1–4]. Moreover, many parameters, such as physical constraints and collective behaviours, are not under the direct control of the genome. Therefore, we cannot hope to explain cell morphogenesis, for example, by invoking simple linear chains of causal events that link genes to phenotypes[5–7].

It seems that the philosopher Kant was the first to define life as a "self-organized, self-reproducing" process (TIMELINE). Through pure reasoning, he defined life as the emergence of functions by self-organization. He said that in an organism, every part owes its existence and origin to that of the other parts, with the functions that are attributed to a complete living organ or organism emerging from the properties of the parts and of the whole. He defined this complex state of living matter as a self-organized end[8–10]. This led him to question the validity of using the causality principle of classical physics to explain life, and to suggest that a new kind of science would be required to study how purpose and means are intricately connected[8].

The new science he was talking about did emerge much later, from observations and studies made by chemists and physicists who discovered new, more complex forms of causality than what Kant had foreseen[11,12]. Ironically, although Kant attempted to characterize life as a self-organization process in opposition to non-living matter, the first well-defined concepts and observations of self-organized processes came from theoretical considerations by Lotka[13,14], from chemistry by Bray[15] and from the Belousov–Zhabotinsky reaction[16–19] (TIMELINE). Chemical oscillations emerged from reaction–diffusion processes that were formalized in mathematical terms by Kolmogorov *et al.*[20] in the 1930s and by Turing in the 1950s, who predicted that steady-state spatial patterns could also arise from such processes in living systems[21]. The full formalization of the nature of self-organization processes came from the work of Prigogine on instabilities and the emergence of organization in 'dissipative systems' in the 1960s[22–24], and from Haken who worked on similar issues under the name of synergetics[11] (TIMELINE).

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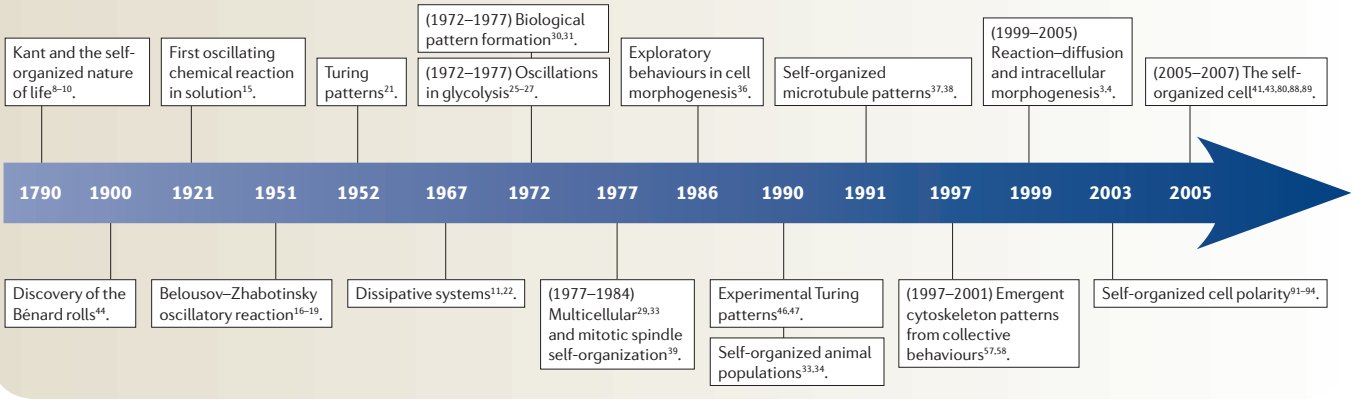
It was clear from the outset that the emergence of dynamical organization observed in physical and chemical systems should be of importance to biology, and scientists who are interested in the periodic manifestations of life and developmental biology have been actively working in this field[19,25–29]. From a more general point of view, Kauffman built on the ideas of Prigogine and Haken in an attempt to explain the origin of order in biology[30–32]. Self-organization was also invoked to explain the formation of regular patterns in the fur of animals and the collective behaviour of organisms in ant colonies, termite nest building, schools of fish and flocks of birds[33,34]. The importance of self-organization processes in molecular cell biology began to be recognized in the 1980s and 1990s[1,35–40], but only really started to gain momentum recently[6,41–43] (TIMELINE).

In the following article, I do not deal with developmental biology issues but specifically focus on how self-organization principles and mechanisms (BOX 1) can help to understand subcellular and whole-cell morphogenesis. I first summarize the essence of the theory of self-organization in physico-chemical systems in simple terms. I then show how this concretely applies to some examples of cell organization and function.

Self-organization concepts

The initial definition of self-organization by Kant as a characteristic of living systems implied the existence of a loop between organization and function. A simpler definition used by modern scientists is that dynamic organization emerges from the collective behaviour of 'agents', the individual properties of which cannot account for the properties of the final dynamic pattern. This definition is more general and has the

Timeline | **Key events in the application of self-organization concepts in cell biology**



advantage of being applicable to systems that do not necessarily acquire a function, even though they become dynamically organized. The understanding of the emergence of function can be studied separately. The other advantage of this definition is that it establishes how self-organized dynamical systems should be studied: the goal of the science of self-organization is to identify the principles and mechanisms by which an ensemble of agents in interaction evolves towards a particular dynamical temporal or spatial pattern.

Origins in thermodynamics. At first sight, the spontaneous emergence of order in the universe contradicts the second law of thermodynamics: a thermodynamically closed system settles in the most disordered state (that is, the state with the highest entropy, when molecules occupy all of the space randomly; FIG. 1a). Ordered states can and do emerge at thermodynamic equilibrium (for example, crystals, lipid bilayers, molecular complex formation), but they are static.

In a thermodynamically open system that receives energy from the outside, the energy that flows through it can be used to decrease its entropy (that is, generate order). Molecules can suddenly organize themselves in dynamic patterns. Bénard rolls[44,45] (longitudinal cylinders of liquid molecules that form precise and stable dynamic patterns) represent such an example and were called 'dissipative structures' by Prigogine[22] (FIG. 1b).

Collective behaviour and the Bénard rolls. Bénard rolls form when a liquid is heated from below, which generates a temperature gradient. Molecules at the bottom of the container are more agitated than at the top, creating a lighter layer of liquid than that at the top. Roll formation results from local instabilities that lead the system to break its symmetry when molecules start to behave collectively. This happens at different critical temperatures for different fluids, but always occurs when all of the parameters balance each other so that they satisfy a universal number, called the Rayleigh number, which equals 1708 under specific conditions[33].

The system can generate rolls that, at a given position in the container, move clockwise or counter-clockwise with alternate orientation. When the temperature is raised to the critical value, the system bifurcates between two alternative steady states (FIG. 1b). The bifurcation is based on local fluctuations that occur at the critical temperature and is almost irreversible. This comes from the fact that the molecules in the liquid begin to behave collectively, all moving up together on one side of the roll and downwards on the other (FIG. 1b). A long-range correlation has been established between the molecules of the system: the whole pattern of rolls in the container emerges from the collective properties of the molecules in the fluid and the geometry of the container, and cannot be predicted from the properties of any of its parts.

Box 1 | **Self-organization concepts and mechanisms**

Self-organization occurs when elements interact dynamically with each other to generate a system that acquires emergent properties that cannot be directly predicted from the individual properties of the elements. This only happens when the system dissipates energy.

Principles	Mechanisms	Examples in the cell
Thermodynamics: non-equilibrium thermodynamics.	Thermal, chemical or other energy dissipation that is associated with dynamic pattern formation.	ATP consumption coupled to dynamic pattern formation.
Symmetry breaking: occurs when a system switches from one symmetry level to another.	Gravity, temperature or chemical gradients, local fluctuations.	Intrinsic asymmetry of agents, nonlinear reactions, stereospecific localization of enzymes, pre-existing structures.
Emergence: a new property that arises from the collective behaviour of agents.	Collective effects and reactions that lead to systems properties.	Cytoskeleton behaviour, enzymatic oscillators, functional networks.
Robustness: the system evolves towards a steady state that constrains its agents to remain within this steady state.	Feedback loops, physical or collective constraints.	Reaction networks with two-state systems, such as kinase–phosphatase or small G-protein systems, combined with feedback loops. Physical, chemical and collective constraints.
Bifurcation: the system moves from one steady state to another when a specific parameter varies around a critical value.	Local instabilities at critical parameter values, nonlinearities.	Toggle switches between network states, switches between collective dynamics states.

Feedback loops and spatio-temporal patterns. In the example of Bénard rolls, order emerges from collective physical interactions. In Belousov–Zhabotinsky reactions and Turing patterns, order emerges from the nonlinear kinetic properties of chemical reactions: that is, from a combination of diffusion and feedback loops in the reaction system. Turing[21] showed that a system of reactants that are initially homogeneously distributed in a solution can generate products that segregate in spatial patterns if certain conditions are met. The product of a reaction should act as a short-range positive activator of its own production while activating the production of an inhibitor that diffuses much faster[46,47]. This forms a local positive feedback loop and a long-range negative feedback loop. The symmetry of the solution is broken by diffusion-driven instabilities that get amplified by the feedback loops. Waves or steady-state patterns can emerge[48,49]. Again, the system can bifurcate between different states. In biology, such reaction–diffusion processes have obvious morphogenetic potential[50,51]. The problem is to identify them and understand how biological molecules interact to form the appropriate reaction networks. Biologists have been trying to find reaction–diffusion mechanisms that fit the Turing model exactly, especially in developmental biology[29,28]. Because biological molecules are complex, various types of reaction–diffusion processes that involve enzymatic reactions may occur — these might have powerful morphogenetic properties without having the exact characteristics of the Turing equations[3,4]. In addition, combinations of positive and negative feedback loops or other properties, such as ultrasensitivity and cooperativity, provide powerful sources of nonlinearities that can lead to the building of enzymatic oscillators or steady-state patterns[27,52]. Therefore, when trying to understand the self-organization properties of cells or embryos, it is more important to simply treat them as nonlinear dynamical systems than to try to find exactly what Turing had predicted.

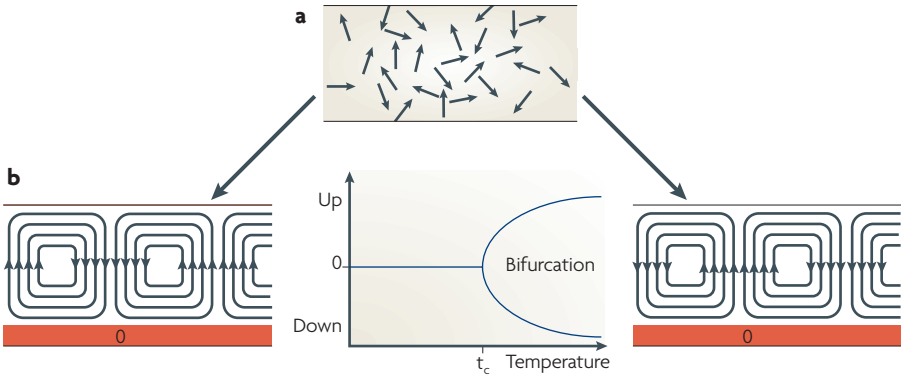


Figure 1 | **Bénard rolls. a** | In a liquid layer, molecules are agitated by thermal motion. **b** | The molecules in the liquid layer are heated from below (red zone) and self-organize into rolls (drawn in cross-section) when the temperature reaches a critical value (t_c). At this value, the molecules start to move collectively either up or down at point 0, which determines the alternative orientation of the rotation of the rolls throughout the layer. The orientation of the rotation choice is unpredictable and determined by local fluctuations at t_c.

Self-organization and the cell

A large part of cell organization depends on self-assembly processes that do not involve energy dissipation (thermodynamic equilibrium). But in the living cell, self-organization processes also occur through the dissipation of ATP or GTP. In fact, the dynamic order of the cell results from a combination of complex stereospecific interactions (deterministic self-assembly) and extremely varied dynamical interactions between molecules that require energy dissipation (self-organization). Here, I give some recent examples in which the problem of cellular self-organization has been addressed — from well-studied systems to more complex and less understood ones.

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Patterns and oscillators from collective behaviours. In 1990, Tabony and Job[37] published a paper in which they showed that pure microtubule solutions self-organized into stripes when they were incubated for several hours at 33°C, and noticed the analogy with patterns formed in the Belousov–Zhabotinsky reaction. Computer simulations suggest that the patterns may arise through a reaction–diffusion mechanism[53]. However, different interpretations of these observations have been proposed and have suggested that, instead, the patterns arise through collective effects that result from dynamic instability coupled to microtubule buckling[54]. In fact, the stripes are apparently made of aligned microtubules and, interestingly, the patterns formed are affected by boundary conditions[55]. These properties may contribute to complex patterns that are formed *in vivo*[56], but microtubule pattern formation in cells often requires both the regulation of microtubule dynamics and the contribution of motors.

In 1991, Verde and colleagues showed that randomly nucleated microtubules in frog egg extracts organized themselves with the minus-end motor dynein to form steady-state asters[38]. This was further developed *in vitro*[57] and then *in silico*[58]. Computer simulation analyses showed that various patterns can emerge from interactions between similar components as a function of their physical properties, complexity and concentration[58,59]. Asters, vortices, antiparallel microtubule bundles and spindle networks were observed (FIG. 2a). In these systems, symmetry breaking comes from the asymmetric shape of the parts: the tubulin molecule is asymmetric[60] and the motors move towards one microtubule end or the other[61]. Therefore, the system has a built-in symmetry-breaking mechanism (FIG. 2a). Self-organization comes from the collective behaviour of the motors and microtubules, with the energy being dissipated by the motors as they move along microtubules.

Recently, these observations have been extended to the acto-myosin system[62]. Just as for microtubules, myosin II crosslinks actin filaments and the system self-organizes into various patterns including rings. Physicists call these systems active gels (as opposed to gels that are made of polymers that do not contain motors) and have developed a theory that predicts the behaviour of these active gels[63]. For an example of structures that are generated by self-assembly at thermodynamic equilibrium, see the study by Haviv *et al.*[64], who obtained self-assembled actin stars that formed in a passive gel of actin and actin regulators.

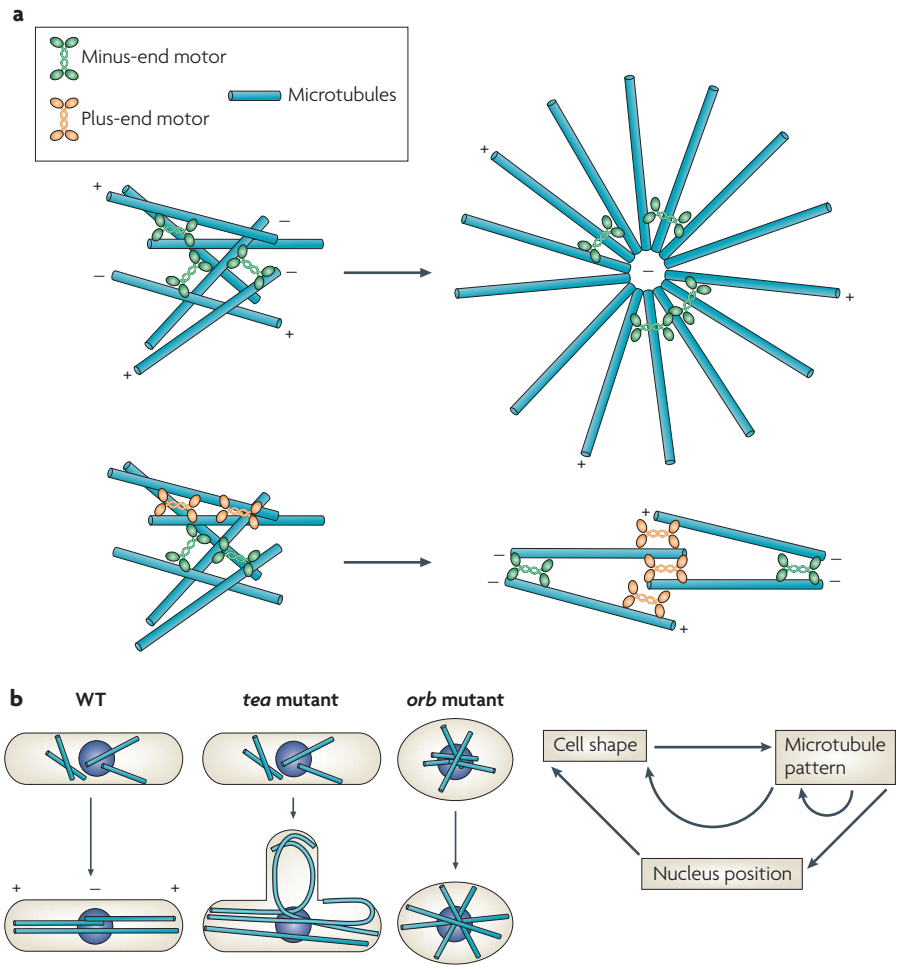

Figure 2 | **Examples of self-organized microtubule patterns and cell shapes. a** | Self-organization of mixtures of microtubules and motors. A minus-end motor can, under certain conditions, crosslink microtubules and focus the minus ends to form asters (top). A mixture of minus-end and plus-end motors can form various patterns. An antiparallel pattern with overlapping plus ends[59] is shown (bottom). **b** | Self-organization of microtubule patterns and cell shape in *Schizosaccharomyces pombe*. The elongated shape of *S. pombe* forces microtubules to align because microtubules depolymerize when they reach the tips of the cells. Motors (together with crosslinking molecules) force microtubules to form antiparallel bundles with the minus ends at the cell centre[87]. In tip-elongation-aberrant (*tea*) mutants, microtubules keep growing when they reach the cell tips. Because tip-promoting factors move towards microtubule plus ends and because, in this case, microtubules curl along cell edges, additional growth tips can form, thereby generating T-shaped cells[84]. Cells that are mutated in the Ser–Thr protein kinase Orb6 (*orb* mutants) have a round shape and microtubules cannot organize into long bundles[83]. This shows that self-organization of microtubules and the cell cortex feed back on each other to generate a self-organized dynamic cell shape. The circularity of this process is shown on the right of the figure.

An important aspect of self-organization in living systems concerns the formation of oscillators. They arise from the collective behaviour of cytoskeletal systems or from enzymatic networks (see below). Kruse and Jülicher have reviewed this field recently[42], and the first theoretical treatment of the emergence of spontaneous oscillations of collective molecular motors was published in 1997 (REF. 65). The principle is relatively simple: a collection of motors can lose its grip on the filaments in a cooperative manner before rebinding, which leads to dynamic instability of the force–velocity relationship and collective periodic binding and unbinding. This demonstrates how nonlinear collective effects can lead to periodic temporal patterns (for many other examples, see REF. 42).

Patterns and oscillators from enzymatic feedback loops. Substantial work on oscillators has already been mentioned above, but relatively little has been said about pattern formation inside cells. Here, I take the cell cycle in eukaryotes as an example because it is probably the best-characterized system. (Further examples in biology in general and in cells more specifically can be found in REFS 27, 29, 42, 66.)

In eukaryotic cells, an oscillator coordinates DNA replication with chromosome segregation. The cyclin-dependent kinase (CDK) oscillator[67,68] (FIG. 3a) self-organizes through the permanent synthesis of one protein, cyclin, which triggers intertwined positive and negative feedback loops[68–74]. The CDK oscillator is a truly self-organized temporal pattern because it is entirely autonomous. The principle of its mechanism is analogous to a Belousov–Zhabotinsky reaction, except that it is built of much more complex molecules. It has two stable states — bifurcation between the two states is triggered when cyclin reaches a threshold concentration and when it is degraded. It works because there is a long time-delay built into the negative feedback loop that leads to cyclin degradation[72].

The function of this oscillator is to change abruptly the cytoplasmic state of the cell. When CDK1 is inactive, a nucleus assembles and DNA replicates, and when it is active, a mitotic spindle assembles. In both cytoplasmic states, chromatin breaks the spatial symmetry of the cytoplasm by the local accumulation of regulatory factors (through stereospecific targeting) that set off a series of (enzymatic) reaction–diffusion processes, which leads to the emergence of a nucleus in interphase and a spindle in metaphase[3,75] (FIG. 3b). Therefore, this reaction–diffusion process contributes to the formation of spatial patterns inside the cytoplasm. The whole cell cycle in eukaryotes can be seen as being based on the principle of self-organization by reaction–diffusion, both temporally and spatially. I say reaction–diffusion, although it is important to realize that none of these processes are true Turing patterns. Indeed, the symmetry is not broken by spontaneous instabilities, but rather by deterministic effects (cyclin synthesis for the oscillator, and stereospecific targeting of a small G-protein exchange factor to chromatin for nuclear and spindle assembly).

The emergence of functions. Above, I have described purified cytoskeletal molecules that can self-organize into patterns as a result of their collective behaviour. In isolation, these patterns have no function because they have nothing to act on. In the cell, however, this might be different. During mitosis, for example, chromosomes induce the assembly of a spindle that acts on the chromosomes

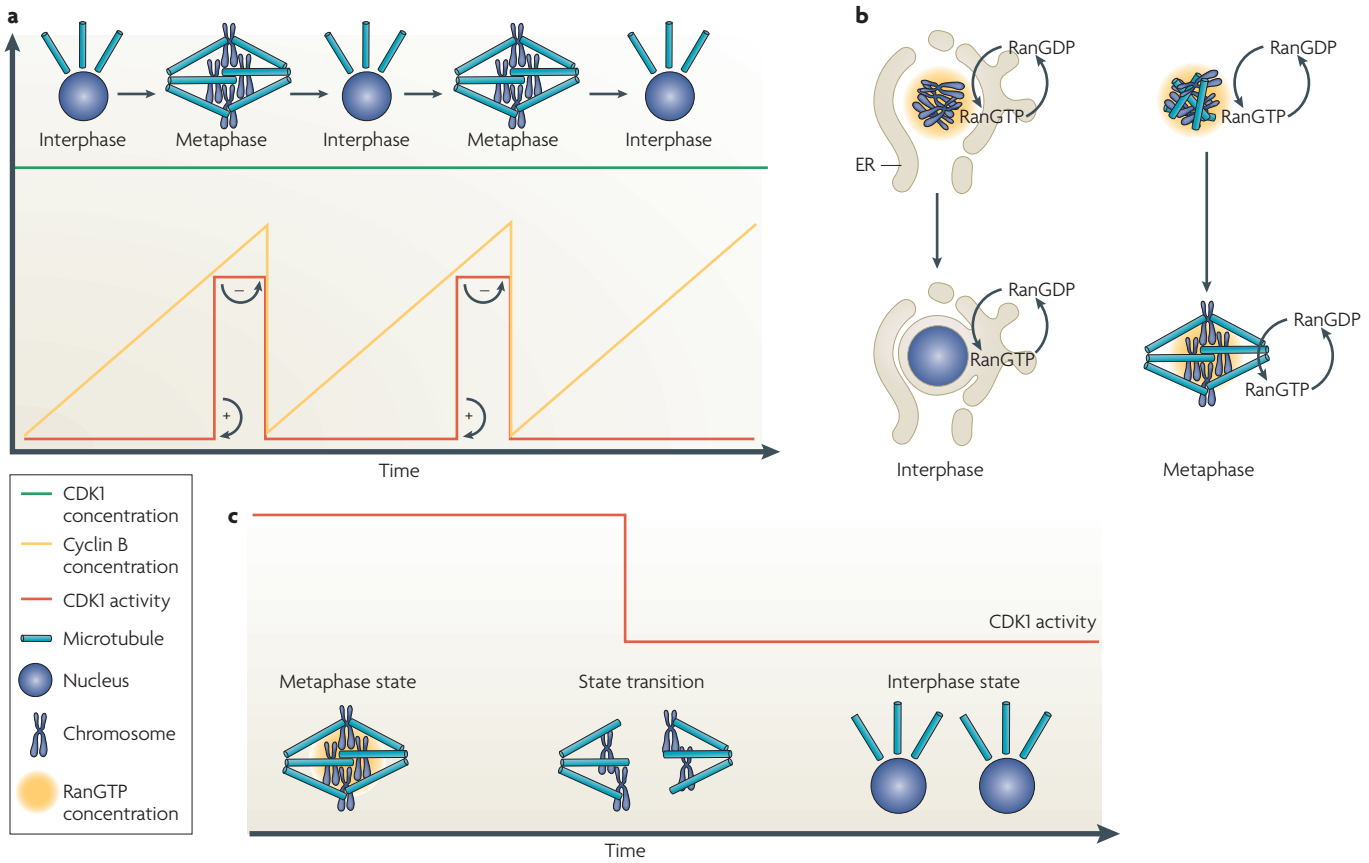

Figure 3 | **Examples of self-organized cell-cycle processes. a** | In eukaryotes, the timing of the cell cycle is determined by an oscillator that is driven by the accumulation of cyclin B, which binds to cyclin-dependent kinase-1 (CDK1). When the concentration of the cyclin B–CDK1 complex reaches a threshold, it triggers a positive feedback loop that leads to the abrupt activation of CDK1. When CDK1 activity reaches a threshold level, it triggers the delayed degradation of cyclin B (negative feedback), which results in the onset of anaphase. **b** | Chromatin generates a gradient of RanGTP that, through a series of complex reactions, triggers nuclear assembly in interphase and spindle assembly in metaphase. The local production of RanGTP is determined by a reaction–diffusion mechanism. **c** | The transition between metaphase and interphase corresponds to a bifurcation between two steady states; that is, nuclear components are in two discrete dynamic interaction states that respond to the presence of DNA by self-organizing into either a nucleus or a spindle. When CDK1 is inactivated at the end of metaphase, the cytoplasm moves through a transient state. This is when chromosomes are segregated. ER, endoplasmic reticulum.

themselves. Therefore, the chromosomes trigger the self-organization of a pattern (the spindle) that acquires the function of segregating them[76]. This is exactly the loop between organization and function that Kant was looking for and there is nothing mysterious about it — so, we can now understand the structure of this logic because we understand many of the underlying mechanisms.

There are three interlocked, self-organized systems that constitute the whole cell cycle: the oscillator (temporal self-organization), the spindle and the nucleus (spatial self-organization), and each subsystem has its own specific function. However, it is interesting to note that chromosome segregation does not occur while the spindle is at steady state, but during anaphase; that is, while the cell bifurcates back towards interphase, when a new steady state is established and a nucleus has reassembled (FIG. 3c).

The functional organization of the nucleus in interphase is another interesting example of self-organization in which function and structure are interdependent, as described by Misteli, Glick and Cook[41,43,77–80], although the exact mechanisms involved are still under investigation.

Let's take just two more examples of the emergence of function by self-organization. We have seen above that actin and myosin can form self-organized contractile rings *in vitro*[62]. Again, these rings have no function. However, *in vivo*, similar rings self-organize, triggered by the small G protein RhoA that is locally activated at the plasma membrane at the mid-zone of the dividing cell. This contractile ring functions to cut the cell in two[81]. In fact, this system works exactly like chromosome-induced spindle assembly, both logically and mechanistically: the final function of the self-organized cytoskeletal structure is triggered by the cell domain on which it should act.

The second example concerns the spontaneous beating of axonemes that results from the self-organization of bending waves, which are generated by the collective effects of motor activity and bending elasticity of microtubules[42,82]. Axoneme beating (the function) emerges from the self-organization properties of the system, which itself results from the interaction between dynein and microtubules.

Self-organized cells. The loops that link self-organization and function are also found when we start to look at the self-organization of large systems such as whole cells. In *Schizosaccharomyces pombe*, for example, the self-organization of microtubule bundles is required to maintain the

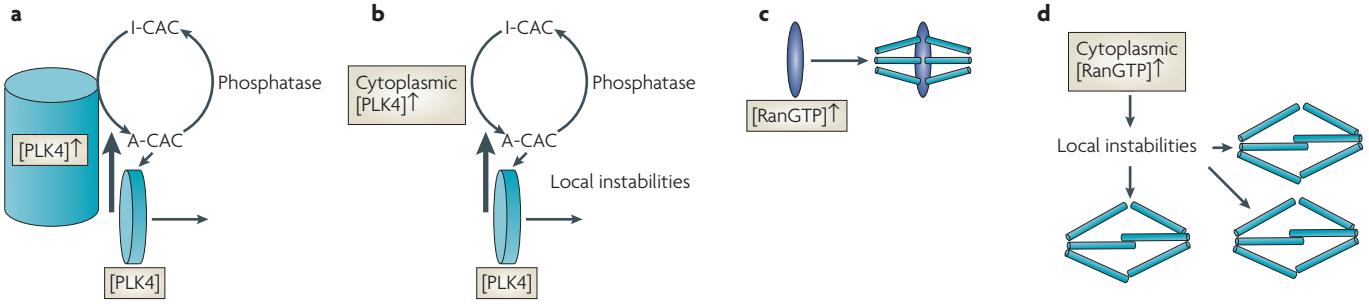

Figure 4 | **Self-organized versus templated pattern transmission.** **a** | A model of centriole duplication or spontaneous formation. The Polo-like kinase PLK4 is present in very low amounts in the cytoplasm but binds strongly to existing centrioles (turquoise) at the time of centriole duplication[102]. Because its substrate (centriole assembly complex; CAC) and the opposing phosphatase are in solution, inactive CAC (I-CAC) becomes phosphorylated and activated (A-CAC) just around centrioles, which leads to the assembly of new centrioles that bind more PLK4. This, in turn, leads to the autocatalytic assembly of a new centriole. **b** | In the absence of pre-existing centrioles, PLK4 needs to be present in high concentrations in the cytoplasm to counterbalance the phosphatase enzyme of CAC. In this case, local instabilities can lead to localized assembly of A-CAC that could trigger the autocatalytic assembly of centrioles. This is based on the same idea as that of Turing: a local positive feedback loop coupled to long-range inhibition (the phosphatase). **c** | The previous scenario is analogous to the mechanism of RanGTP-induced local spindle assembly in the presence of a localized GTP exchange factor on chromatin, or **d** | global spontaneous spindle assembly if RanGTP is overexpressed throughout the cytoplasm.

simple cylindrical morphology. But the reverse is also true: cell shape is important to determine the morphology of microtubule bundles that self-organize through dynamic instability, the action of motors and associated molecules, and interaction with the cell periphery[83–87]. Again, we find a loop between the whole and the parts[88,89] (FIG. 2b).

In *S. pombe*, we really begin to understand how the nucleus, the microtubule system and cell shape form a circular integrated self-organized system in which none of the elements comes first (FIG. 2b). This is also a beautiful example of modular self-organization in which one versatile system (the microtubule system) interacts in various ways with other parts of the cell that are themselves self-organized, to form a whole. Chemotaxis and cell polarization are also interesting in this context. Cell polarization can occur in the absence of any cue through spontaneous symmetry breaking[90,91], involving instabilities in small G proteins, phosphorylation and cytoskeletal networks. This self-organized process can become functional for the cell by responding in a directional way to signalling gradients[90–95].

De novo *versus templated*. A discussion of self-organization brings us naturally to the old problem of templated versus *de novo* formation of organelles. It is clear that structural heredity exists: the structure and shape of membranes, the Golgi apparatus, centrioles and even whole cytoskeleton patterns pass from one generation to the next. But how are these structures transmitted? Does this occur through some sort of template that duplicates and on which new structures grow, or do these structures assemble periodically *de novo* through instability-driven self-organization by virtue of the physical properties of their components?

A good example is the centriole. There have been many discussions about the templated duplication of centrioles because of their beautiful geometry and the mechanism of duplication at an exact angle to each other[96–99]. However, centrioles do arise *de novo* in many cases[100], and the recent discovery of Polo-like kinase-4 (PLK4), which is essential for centriole duplication, indicates how this *de novo* formation may occur[101]. Indeed, overexpression of PLK4 triggers the formation of ectopic free centrioles, which suggests that under some conditions, pre-existing centrioles act as a concentration spot for PLK4 (that is, it binds to centrioles)[102]. If the opposing activity of a phosphatase is present throughout the cytoplasm, PLK4 may locally phosphorylate key substrates around pre-existing centrioles, leading to local self-organization of centriolar components through a reaction–diffusion mechanism (FIG. 4a). In the absence of pre-existing centrioles, an excess of PLK4 could phosphorylate the same substrate by opposing the phosphatase globally and, through local instabilities, trigger spatially restricted positive feedback loops that lead to local assembly of the nucleating agents that are required to initiate centriole self-organization (FIG. 4b). This would be similar in principle to chromatin-induced spindle self-organization[76] (FIG. 4c,d). Indeed, in this latter case, when chromosomes are present they also induce the self-organization of spindles around them. However, on overexpression of the signalling molecules that are normally activated by chromosomes, spindles self-organize randomly in the cytoplasm in the absence of chromosomes[103] (FIG. 4d).

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The case of the Golgi apparatus is also interesting. Again because of its unique structure, it has been proposed that the Golgi duplicates during cell division through a templated process[104]. However, further work suggested that, in fact, new Golgi buds out from the endoplasmic reticulum (ER) at sites that are apparently specified by the basal body[105,106], and it now seems possible that the Golgi apparatus self-organizes from the ER in response to its very function[41,107–109].

The essence of life and evolution

There is a tendency for engineers who enter the field of biology to speak of design. Design does not exist in living matter (unless we believe in creationism). Nobody ‘thought’ through the advantage of positive and negative feedback loops to build the cell-cycle oscillator in *Xenopus laevis*. It just springs from a mixture of gene products that interact dynamically with each other, as in Belousov–Zhabotinsky reactions.

Something incredibly important for the understanding of the origin of life and evolution is emerging here: self-organization principles tell us that if there is an ensemble of products that can interact dynamically to reach a functional steady state, they will do so robustly at least under certain conditions[31]. Suddenly, life becomes much less improbable, as Kauffman suggested[30].

The principles that are associated with self-organization processes tend to indicate that the driving force behind the diversity of life and its evolution is not mainly selection. Instead, it may derive largely from the intrinsic properties of living matter and the combination of various self-organized functional modules. The maximum diversity of life is probably represented by the parameter space within which dynamic interactions between the whole and the parts robustly produce a cell or an organism that can survive in a given environment. In a sense we are moving back to the views of D'Arcy Thompson, who thought that biologists overemphasize the role of evolution over that of physical laws in the origin of growth and form[5].

Conclusion

Studying self-organization processes in cell biology forces us to focus on principles and collective behaviours rather than on single molecules. This makes it necessary to use mathematics and physics as well as computer simulations to analyse the often counter-intuitive properties of dynamical systems. This also forces us to clarify the difference between principles and mechanisms (BOX 1).

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DATABASES

UniProtKB: http://beta.uniprot.org/uniprot
CDK1 | Orb6 | PLK4 | Ran | RhoA

FURTHER INFORMATION

Eric Karsenti's homepage:
http://www-db.embl.de/jss/EmblGroupsOrg/g_40.html
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