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Review

Self-organized collective cell behaviors as design principles for synthetic developmental biology

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ABSTRACT

Over the past two decades, molecular cell biology has graduated from a mostly analytic science to one with substantial synthetic capability. This success is built on a deep understanding of the structure and function of biomolecules and molecular mechanisms. For synthetic biology to achieve similar success at the scale of tissues and organs, an equally deep understanding of the principles of development is required. Here, we review some of the central concepts and recent progress in tissue patterning, morphogenesis and collective cell migration and discuss their value for synthetic developmental biology, emphasizing in particular the power of (guided) self-organization and the role of theoretical advances in making developmental insights applicable in synthesis.

1. Introduction

Multicellular biological systems are extraordinary "machines" that possess capabilities such as self-assembly, growth and replication, adaptability, and self-repair – all of which are rarely found in machines constructed by humans today. Synthetic developmental biology in its applied science sense, i.e. the use of developmental mechanisms and principles for engineering and design purposes, thus harbors enormous potential for technological progress across domains, from medicine and agriculture to manufacturing and robotics.

Synthetic biology can be approached from two complementary perspectives (Fig. 1). One is to take inspiration from the design principles and techniques of classical engineering and seek to implement them in a biological context (Fig. 1A). The development of modular DNA parts libraries and the invention of technologies such as cell and matrix printing exemplify this strategy [1,2]. The other approach is to learn from design principles found in nature itself, for example in embryonic development, and utilize them to engineer and control biological systems (Fig. 1B). The generation of organoids by exposing cells to culture regimes that trigger their innate potential to self-organize represents a major stepping stone in this regard [3,4]. The long-term ambition for this strategy is to enable the first-principle design of novel multicellular systems that perform biological functions according to human specification, making full use of the aforementioned extraordinary capabilities that such systems exhibit in nature. However, whilst both traditional bioengineering and organoid culture have made rapid progress in recent years, this ambition remains far from fully realized.

In this review, we therefore discuss emerging concepts of developmental self-organization that can serve as design principles for multicellular bioengineering. Using selected examples from patterning, morphogenesis and migration, we highlight key principles underlying collective cell behaviors and show how recent advances bring them closer to synthetic utilization. We close by arguing that analysis and synthesis should advance together, as they complement and accelerate each other.

2. Self-organized pattern formation

In animal development, cells use a rich repertoire of molecular communication tools to generate diverse and robust patterns from simple and uniform initial conditions. Diffusible, substrate-bound and cell surface-bound signaling molecules broadcast information about a cell's internal state and relative position to different recipients. Cells reading these signals via ligand-specific receptors then update their state through computations performed by signaling cascades and gene regulatory networks, which may in turn trigger new signals to be sent. The resulting dynamical system can generate spatial and temporal patterns across the tissue.

From a synthetic perspective, it is of note that the same molecular communication tools can mediate the formation of many different

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patterns given minor changes in parameters or boundary conditions, which reveals the versatility of dynamical systems as tools for pattern generation [5]. Furthermore, the final configuration of a pattern is rarely completely hard-coded, but rather adaptive to the context within which it is formed. For instance, patterns generated in animal development often scale with tissue size [6–8] and the configuration of tubular networks is optimized for their function [9,10]. Thus, whilst most human-built machines rely on narrowly defined instruction sets and require a specific permissive environment to function, biological systems pattern themselves adaptively to perform their functions appropriately in a given context.

A deep understanding of how self-organized pattern formation achieves its versatility, adaptability and robustness is crucial if we are to harness these useful properties in synthetic applications.

2.1. Instability and symmetry breaking

The elementary case of pattern formation is symmetry breaking, in which an initially uniform cell or tissue adopts a non-uniform configuration along a given axis in space. Symmetry breaking is of fundamental importance in biological systems across scales, including in asymmetric stem cell division [11], establishment of migratory cell polarity [12], and generation of left-right body axis asymmetry [13].

Symmetry can be broken when a system adopts an unstable or metastable state that, once tipped out of balance, will resolve into two stable states that are spatially partitioned (Fig. 2A). One fundamental signaling motif that can implement this behavior combines short-range self-activation and mutual inhibition with long-range self-inhibition [14]. If both components are matched in their strength, they will each restrict the other's self-amplification sufficiently to maintain a precarious balance. Once this unstable state is disturbed, self-activation and mutual inhibition locally push for irreversible commitment to one of two states, whereas global self-inhibition ensures that both states can claim a spatially segregated domain.

With such a system in place, cells and tissues can rely either on random fluctuations or on pre-existing environmental or molecular asymmetries to topple the unstable state and thereby break symmetry. For example, the amplification of stochastic fluctuations has been proposed as a mechanism for neuronal polarization [15,16] and for lineage specification in mouse blastocysts and haematopoietic progenitor cells [17,18]. In other cases, some intrinsic or pre-specified asymmetry is exploited (see also Section 2.3). For instance, the presence of a tissue-scale gradient, even if weak or noisy, can bias self-organized cellular symmetry breaking to occur along a pre-determined angle [14]. Alternatively, molecular asymmetries such as the chirality of macro-molecular complexes can be amplified to act as a cue at the cell or organ level, including in left-right body axis asymmetry [13,19,20]. Finally, even basic geometric necessities can serve as cues: during the 8-cell stage of mouse development, cells polarize such that their apical domain faces the outside rather than cell-cell contacts, exploiting an asymmetry inherent in any bounded cluster of cells [21].

Despite its apparent simplicity, symmetry breaking is often the first step on the way from a uniform initial condition to a sophisticated pattern, as exemplified in the use of artificial symmetry breaking for morphogenetic engineering of bacterial colonies [22]. Broadly usable synthetic circuits for robust, inducible and controllable symmetry breaking would thus be an important addition to existing toolboxes for synthetic development.

2.2. Complex patterns from simple motifs

Unstable states that collapse into spatially partitioned domains are not just the basis of symmetry breaking but form a general design principle of self-organized pattern formation.

Indeed, the motif of symmetry breaking described above is in some sense simply a special case of reaction-diffusion based patterning systems, famously first described by Turing [23] and much elaborated by Gierer and Meinhardt [24,25]. In its simplest form, a Turing instability emerges from the coupling of a short-range activator and a long-range inhibitor (Fig. 2C). In such systems, fluctuations or external inputs that lead to a small local increase in activator will be amplified into a high-activator domain. This domain simultaneously limits its own spatial expansion by virtue of a faster-traveling inhibitor and thus ensures the emergence of patterns of alternating high-activator and low-activator domains.

Strikingly, this principle is so simple that it can be implemented by a chemical reaction in a dish [26], yet it is capable of generating countless different patterns, including dots and stripes of various forms and wavelengths, depending on parameter values and initial/boundary conditions [5]. Turing systems have therefore been used to explain numerous biological phenomena, such as the patterning of hair and feather follicles [27,28], tooth cusp development [29], lung and kidney branching [30,31], as well as subcellular patterning [32]. In combination with other dynamical processes, such as the growth of a tissue over time, the versatility of the Turing mechanism expands further [33,34], as seen for instance in sea shell patterns [35] and mammalian palate development [36].

Despite the obvious power of Turing systems as pattern generators, it is not an easy task to design a synthetic Turing system that forms a predefined pattern of interest, with the first success in eukaryotic cells

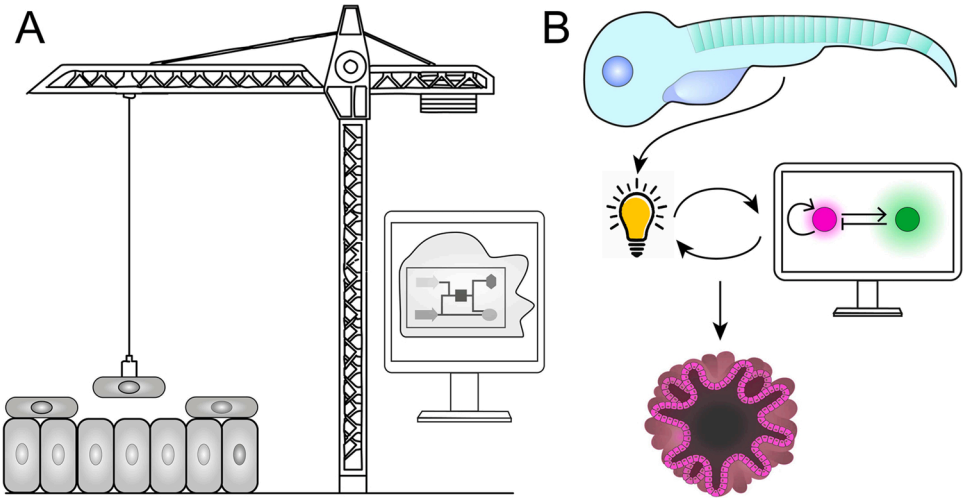

Fig. 1. Two conceptual viewpoints on synthetic biology, (A) Applying technologies and design principles inspired by classical engineering and computer science to biological components such as cells and gene regulatory elements. (B) Taking inspiration from natural systems such as embryos to gain an understanding of the underlying self-organization principles, which can then be utilized to assemble and control synthetic systems. Note that appropriate theoretical models and computational tools are key facilitators for both strategies. Furthermore, the two perspectives are complementary, with the bio-inspired approach in particular benefitting greatly from tools developed with the engineering approach.

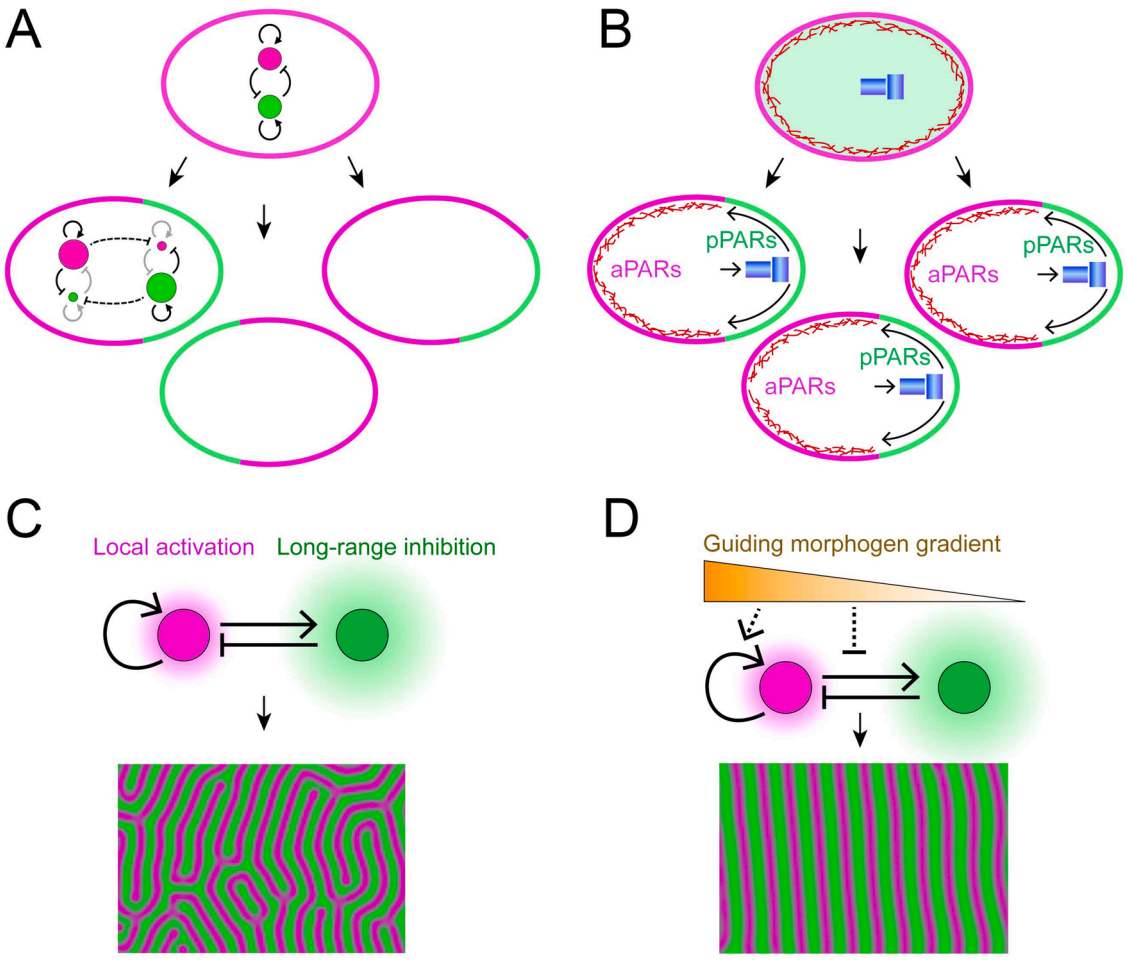

Fig. 2. Pattern formation and guided self-organization, (A) The simplest pattern is polarity, which is established by breaking symmetry. Self-organized symmetry breaking relies on motifs with a mutually balanced uniform state that can destabilize into two dominant states that each cannot take over the entire domain due to long-range self-repression. In the absence of external cues, such systems can spontaneously polarize in a random direction, represented by the three different outcomes. (B) Under guided self-organization, the system is tuned such that spontaneous symmetry breaking does not occur. The addition of a cue then triggers symmetry breaking in a given direction. The example shown here is symmetry breaking of anterior/posterior PAR proteins (aPARs/pPARs) in the *C. elegans* zygote [51], where the centrosome (blue) acts as the cue by inducing actin (red) cortical flow and by locally stabilizing pPARs. (C) This simple reaction-diffusion system, where the inhibitor (green) diffuses more readily than the activator (pink), can generate a near-endless variety of patterns. However, the exact configuration of these patterns is not very robust. (D) A guidance cue, such as a pre-established morphogen gradient (orange), can be super-imposed onto such systems to robustly produce an optimized pattern. The example shown here is a much-simplified version of the system described in [52].

having been achieved only recently [37]. One major obstacle is that the feedback-driven dynamics of Turing systems are hard to grasp through human intuition. Thus, progress in this direction heavily depends on theoretical and computational advances. For example, it has long been thought that the extracellular signaling molecules mediating a Turing system must have differential diffusivity. However, a high-throughput computational study by Marcon and colleagues revealed that this requirement is readily overcome if the extracellular signals are allowed to interact with immobile, cell-autonomous components [38]. In subsequent theoretical work from the same lab, it was further shown that several important properties of Turing systems can be inferred from a motif's topology alone [39].

These and related theoretical advances [40–42] are valuable to synthetic biology in multiple ways. When engineering synthetic signaling molecules and receptors [43,44], they can be used to predict which properties are most important to gain control over. At the systems level, they provide abstractions that increase intuition and facilitate the design of synthetic patterning systems [45].

2.3. *Guided self-organization*

Beyond motif topology and kinetic parameters, the outcome of self-organized patterning is heavily influenced by a system's initial conditions and boundaries. This is a double-edged sword for synthetic biology. On the one hand, context-dependence can confer adaptability to a system, allowing it to generate patterns that are optimized for a given environment. On the other hand, it introduces fragility, making a system sensitive to noise and prone to yield non-reproducible outcomes [40,46]. Intriguingly, evolution has evidently found a way of resolving this issue in natural embryonic development; despite its reliance on self-organization, development is surprisingly robust to various sources of variation and generally produces stereotypical outcomes within a fairly narrow range of variation [47–49]. One possible explanation for this discrepancy comes in the form of *guided self-organization*, which posits that a self-organizing system can be guided into reproducible behavior by external cues and boundary conditions [50].

This idea was lucidly worked out in a recent study on self-organized symmetry breaking during polarity establishment in the *C. elegans* zygote [51] (Fig. 2B). Combining experiments and theory, the authors analyzed the interplay of the relevant self-organization system

(involving PAR protein interactions and actomyosin cortical flow) with two pre-determined polarity cues provided by the centrosome. They found that an increase in feedback strength in the self-organized system makes symmetry breaking independent from the centrosomal cues and thus random, whereas a decrease prevents symmetry breaking altogether. Between these two extremes, there is a large domain in parameter space where the self-organization system alone remains in its homogeneous meta-stable state, but in the presence of the cue is pushed to resolve into two domains. Under these conditions, which apply in the unperturbed embryo, self-organization and pre-established cues robustly cooperate to break symmetry in a reproducible fashion.

This general principle applies not just to symmetry breaking but may in fact be at the heart of many developmental systems that undergo robust self-organization. An example involving a Turing instability is found in the stripe-forming system that patterns digits in the developing vertebrate limb [52,53] (Fig. 2D). Here, a three-component reaction-diffusion system featuring Wnt, Sox9 and Bmp implements a stripe-generating Turing motif. However, when simulated on the shape of a growing limb bud, there is no parameter combination under which this system on its own robustly produces the nicely arrayed periodic stripe pattern required for proper digit formation. It is only under the guidance of pre-patterned morphogen signaling from Hoxd3 and Fgf, which locally modulate the parameters of the Turing model, that robust self-organization of the experimentally observed digit pattern becomes possible.

One can envision a future in which synthetic developmental biologists will design biological patterns by choosing (or constructing) a Turing-like pattern generation motif and coupling it to additional cues that can be sculpted to guide the self-organization process to a desirable outcome. However, this will require not only knowledge of the relevant molecular components and pathways, but also strong theoretical models that allow us to understand and predict the dynamics of such systems.

3. Self-assembling into functional structures

To construct a functional organ from a group of naïve cells, it is not sufficient to merely pattern different domains in terms of signaling, polarity or gene expression. Cells and tissues must also undergo morphogenesis, meaning they must adopt a spatial configuration and shape appropriate for their function. This inherently physical task is accomplished by tissue-scale transformation events such as bending, compaction or convergent extension, which emerge from concerted mechanical actions of cells, such as protrusion and contraction. Traditionally, these cellular behaviors were thought to be downstream of biochemical tissue patterning and thus in some sense "hard-coded" by the patterning mechanisms discussed in Section 2. However, it is now more widely appreciated that morphogenesis is in many cases a self-organized process in which physical mechanisms serve as pattern generators and which can dynamically adapt to different mechanical and biochemical contexts. Recent years have also seen a groundswell of evidence for mechanisms that allow morphogenetic events to feed back into biochemical patterning and genetic regulation.

3.1. Cell sorting in aggregates

Since tissues and organs are constructed from cells, physical phenomena characteristic of cellular soft matter are inherently present and can be exploited as a platform to implement morphogenetic self-organization. Already in the mid-20th century, experiments with heterotypic cell mixtures revealed that cellular aggregates can undergo spontaneous re-organization, including homotypic sorting akin to phase separation (Fig. 3A) [54–56]. Early models put forward to explain this phenomenon focused on cell-cell adhesion, either in the form of selective adhesion among homotypic cells [56,57] or based simply on absolute differences in adhesion strength, a well-known model termed the *Differential Adhesion Hypothesis* (DAH) [58,59].

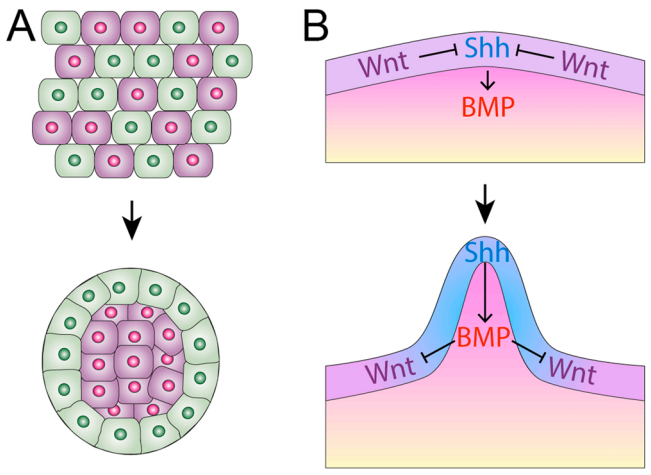

Fig. 3. Self-assembly and feedback from morphology to patterning, (A) An aggregate containing two types of cells that differ in their adhesive or mechanical properties (green and purple) will naturally sort out as it relaxes toward mechanical equilibrium. In the case shown here, the purple cells might be more contractile and thus end up occupying the inside of the forming spheroid, as the softer green cells offer less mechanical opposition to the stretching necessary to envelop their stiffer neighbors. (B) Morphology can feed back onto biochemical patterning systems, for instance by shaping the environment in which signals diffuse. Illustrated here is the feedback from intestinal villus formation onto stem cell specification signals found in [76]. The forming villus alters the morphogenetic field such that diffusible signals (Shh and BMP) are locally concentrated, which acts as a guidance cue for their feedback-based patterning mechanism.

Although it was pointed out early on that cell mechanics may also play a role in cell sorting [60], it took several decades until computer simulations confirmed the importance of differential contractile forces at cell-cell interfaces [61,62]. This directly led to the development of a general theory of cellular rearrangements, named the *Differential Interfacial Tension Hypothesis* (DITH) [63]. Under this model, adhesion forces at a cell-cell interface favor an enlargement of the interface area (releasing binding energy), but are opposed by interfacial contraction forces, mediated for instance by cortical actomyosin, which seek to reduce the interface area (driving cells toward their minimum surface shape, the sphere). These two opposing forces combined form an effective interfacial tension, which acts on junctions to cause shape changes and cellular reorganization that ultimately tends toward the aggregate's minimum energy configuration. In groups of cells with differential adhesion and/or differential contractility, this can give rise to cell sorting and morphogenesis [63].

The principle expressed in the DITH has since been found to explain developmental phenomena far beyond the sorting of aggregates in culture, including the tension-based sorting of mouse blastula cells into an inner cell mass and a surrounding ectodermal layer [64] and the robustness of stripe patterning among neural progenitors in the zebrafish spinal cord based on an adhesion code [65]. However, work on sorting at embryonic boundaries in *Drosophila* [66], *Xenopus* [67] and zebrafish [68] has led to the proposal of yet another model of sorting-based tissue self-organization, termed *High Heterotypic Interfacial Tension* (HIT) [67]. In this model, tension is specifically increased at heterotypic cell-cell contacts by local activation of actomyosin contractility. This minimizes heterotypic contact areas and induces sorting and straightening of the segregated tissue boundary. Interestingly, the HIT mechanism also seems to generalize to epithelial cell sheets, where it can drive cell extrusion, cyst formation or boundary straightening depending on the relative size of the interacting heterotypic cell populations [69].

The DITH, extended with HIT where applicable, provides an intuitive and quantitative theoretical framework that is broadly applicable and

can readily be simulated using a range of computational techniques, from Cellular Potts [70] and Finite Element [71] models to mesh-based surface-tracking [64]. It is therefore a morphogenetic principle that is ideally positioned for application in synthetic developmental biology. Indeed, Cachat and colleagues used a Cadherin-based adhesion code to generate patterned 2D and 3D structures of mammalian cells in culture [72]. Since then, adhesion-based cell sorting has been incorporated into toolboxes for multicellular engineering of bacterial and mammalian cells [73,74]. The coming years will no doubt see an evolution of these tools toward an integrated computational and experimental toolkit for programmable multicellular assembly through adhesion and tension modulation.

3.2. Tissues shaping signals shaping tissues

Embryonic development proceeds as finely interwoven steps of patterning and morphogenesis [75]. This implies the intriguing possibility of chemo-mechanical self-organization principles, which are based on the interplay of biochemical and mechanobiological mechanisms. Indeed, numerous examples of such interplay have already been discovered.

For one, morphogenesis can directly constrain or alter the pattern of extracellular signaling molecules (Fig. 3B). In studying intestinal villi formation, Shyer and colleagues found that buckling of the surface epithelium deforms the geometry of the morphogenetic field such that an Shh signal secreted by epithelial cells is concentrated at the tips of nascent villi [76]. This instructs local gene expression in the underlying mesenchyme, which in turn expresses high levels of BMP and thereby represses epithelial stem cell potential at villus tips through suppression of Wnt signaling. It is through this feedback system that intestinal stem cells are restricted to the crypts between villi during development. Notice that this is another example of guided self-organization: a mutual repression mechanism between epithelial Shh and Wnt (via mesenchymal BMP) endows the system with the capability of self-organized pattern formation, but in a geometrically flat tissue this feedback is sub-critical (cmp. Section 2.3). Local accumulation of Shh as a consequence of morphogenesis breaks this meta-stable state and guides the system into the proper pattern.

Cell collectives have multiple ways of implementing morphogenetic constraints that lead to local accumulation of signaling molecules. During sensory organ morphogenesis in the zebrafish lateral line, clusters of epithelial cells undergo apical constriction to form onion-shaped rosettes that harbor and support sensory hair cells. Durdu and colleagues have found that apical constriction in this case entails the formation of a small extracellular space, termed a microlumen, which is surrounded by the apical surfaces of the participating cells and sealed off from the environment by their tight junctions [77]. Apically secreted FGF is therefore accumulated into the microlumen and feeds back on the cells participating in lumen formation through FGF receptors on their apical surface. This mechanism ensures that all participating cells are exposed to the same levels of FGF signaling, whereas any cells not included in the process receive none, so the microlumen acts as a "private space" for rosette-forming cells to communicate. Recently, luminal signaling has also been implicated in mouse blastocyst development, both in a direct fashion [78] and indirectly as a means of robust morphogen gradient formation [79].

A very different but equally important way in which patterning and morphogenesis can interact is through cell contact signaling pathways such as Delta-Notch [80,81]. Morphogenetic movements can alter the neighborhood of cells or the area of cell-cell contacts and thereby modulate the levels of signaling by surface-bound ligands and receptors [82]. This effect is well-studied for the interplay of cell rearrangements with Notch lateral inhibition in inner ear development [83–85] and in leader cell selection during collective cell migration [86–88] (see also Section 4). Interestingly, there is a mechanical component to Notch activation by its ligand Delta [89,90], which opens up the possibility that it is not just contact area but also cellular mechanics that controls Notch activation [88,91].

Cell surface signaling via Delta-Notch has already inspired several seminal works in synthetic biology. Matsuda and colleagues have shown both synthetic signal propagation [92] and synthetic lateral inhibition [93] using a modified Notch IntraCellular Domain (NICD) and artificial gene regulatory circuits. Morsut and colleagues developed a platform for engineering heterologous synthetic Notch (synNotch) receptors with freely configurable inputs and outputs [94]. Specifically, the Notch extracellular domain can be swapped for essentially any recognition domain of choice, including single-chain antibodies, and can therefore be specified to bind and sense any endogenous or synthetic surface cue. The NICD, which upon ligand binding is cleaved and translocates into the nucleus to regulate gene expression, can be swapped for a transcriptional activator or repressor of choice. Among other applications, synNotch has been employed in combination with Cadherins to enable the programmable assembly of diverse multilayered cellular structures based on the interplay of cell sorting and cell contact signaling [74], a paradigmatic example of synthetic developmental biology.

3.3. Mechanics as signals

Morphogenetic forces can also feed into signaling cascades and gene regulatory networks in a more direct fashion, namely by means of mechanotransduction. Early work in *Drosophila* has shown that some cell fate decisions are sensitive to the application of mechanical stress and that this sensitivity requires the presence of specific gene products [95]. It is now clear that cells have a large catalogue of such mechanosensitive proteins at their disposal to sense their mechanical environment, including junctional proteins and ion channels [96–98]. These sensors interface with different parts of the cell's mechanical toolset, such as actin, adherens junctions and focal adhesions, and report strains and stresses applied to these structures by triggering biochemical signals such as protein phosphorylation and ion flux upon a mechanically induced conformational change. Evidence is also growing that macroscopic mechanical events such as stretching of the cell membrane or compression of the nucleus can more directly modulate signaling in a number of ways [99,100].

Intriguingly, these mechanosensory signals are rarely just linearly forwarded into gene expression regulation, but are integrated and processed by dedicated signaling networks. One of the most established examples of such a network is centered on the transcriptional co-factors YAP and TAZ, which receive inputs from several different mechanosensory pathways and integrate them with other inputs such as Hippo signaling [101]. All of these inputs ultimately regulate the nuclear-cytoplasmic shuttling of YAP/TAZ and its interactions with various TEAD-family transcription factors to control gene expression. Even mechanical deformation of the nucleus itself has recently been shown to directly regulate YAP/TAZ nuclear localization [102]. Thus, the nuclear/cytoplasmic ratio of YAP/TAZ reflects the mechanical state of cells, being for instance elevated in cells that stretch on a highly adhesive or very stiff substrate. Depending on context, this can induce proliferation, differentiation, stem cell self-renewal, or cell migration [101]. Intriguingly, the aforementioned Hippo pathway, which retains YAP/TAZ in the cytoplasm and triggers its degradation, receives its input at least in part from cell-cell adhesion sensors and polarity proteins [103] – important factors of self-organized morphogenesis, as discussed in previous sections. The YAP/TAZ signaling network may therefore constitute a general platform on which cells compute their morphogenetic state.

From the synthetic perspective, the sensitivity of cells and tissues to mechanical forces opens up new ways of controlling cellular behaviors through the application of mechanical stimuli or engineering of particular mechanical environments, an approach termed mechanogenetics [104]. The ingenious nature of biochemical mechanosensors such as mechanically gated ion channels can even inspire new artificial

mechanosensing technologies in non-living systems [105]. More broadly, although we have only just begun to explore the ways in which biochemistry and mechanobiology interact, these early forays hint at the existence of a deep connection between gene regulation and cellular morphodynamics that mediates a set of emergent principles of developmental patterning and morphogenesis. As our understanding of this connection grows, so too will our ability to design systems in which the right cells end up in the right place for optimal functionality.

4. Cells and tissues as moving materials

Morphogenetic self-organization in compact tissues can be achieved through relatively minor feats of cellular reorganization such as neighbor exchanges and local contraction. This belies the fact that individual cells are highly versatile agents capable of extensive remodeling of their structure and mechanics. A particularly striking behavior made possible by this versatility is cell migration, where cells actively crawl through their environment, either alone or as a collective, in some cases traveling across the length of an entire embryo [106,107]. Tissues can therefore behave as "moving materials" that dynamically change not only their shape but also their location.

This spectacular type of mechanical cell behavior gives rise to new modes of developmental self-organization. Migrating cell collectives can build organism-scale structures and patterns such as the vasculature and the arrays of mechanical sensory organs on the skin of aquatic vertebrates [108]. Cell migration can further act as a "smart delivery system", bringing cells that possess a particular developmental potential to regions of the embryo that need them, as is the case for primordial germ cells and the vertebrate neural crest [109,110]. Wound healing, another remarkable property of biological machines, is also mediated by collective cell migration [111].

4.1. Transitioning from stationary to motile

Embryonic groups of cells looking to move will rarely find an open road ahead of them. Instead, they must squeeze past other tissues and through meshworks of extracellular matrix. To make this possible, they rely on the ability of biological materials to change their mechanical properties essentially on demand. In particular, tissues can undergo a phase transition between a more solid and a more liquid state (Fig. 4A), where one primarily responds in an elastic and the other in a viscous fashion to external forces [112–114]. Taking on the properties of a viscous fluid enables motile cell collectives to more readily navigate the complex mechanical environment of a developing embryo [115,116].

Importing concepts from the physics of materials, particulates and colloidals has led to significant progress in establishing the biophysics of tissue phase transitions, which are now commonly referred to as *jamming* and *unjamming*. In essence, as cells become more crowded or less deformable, they increasingly block the motion of neighboring cells. If the agitation introduced into the system by cell motility is insufficient to relieve such blockages, they can propagate across the entire collective, jamming the tissue and halting motion [115]. Such jamming transitions have been identified both in non-confluent systems, where cell density and the cell-cell contact network are key control parameters [117,118], and in confluent systems, where cell deformability, adhesion and effective interfacial tension are key [112,119].

Numerous computational models have been used to quantitatively investigate both cases [112,120,121] and have led to the derivation of readily measurable order parameters such as a geometric shape index that allows the jamming state of a confluent tissue to be determined

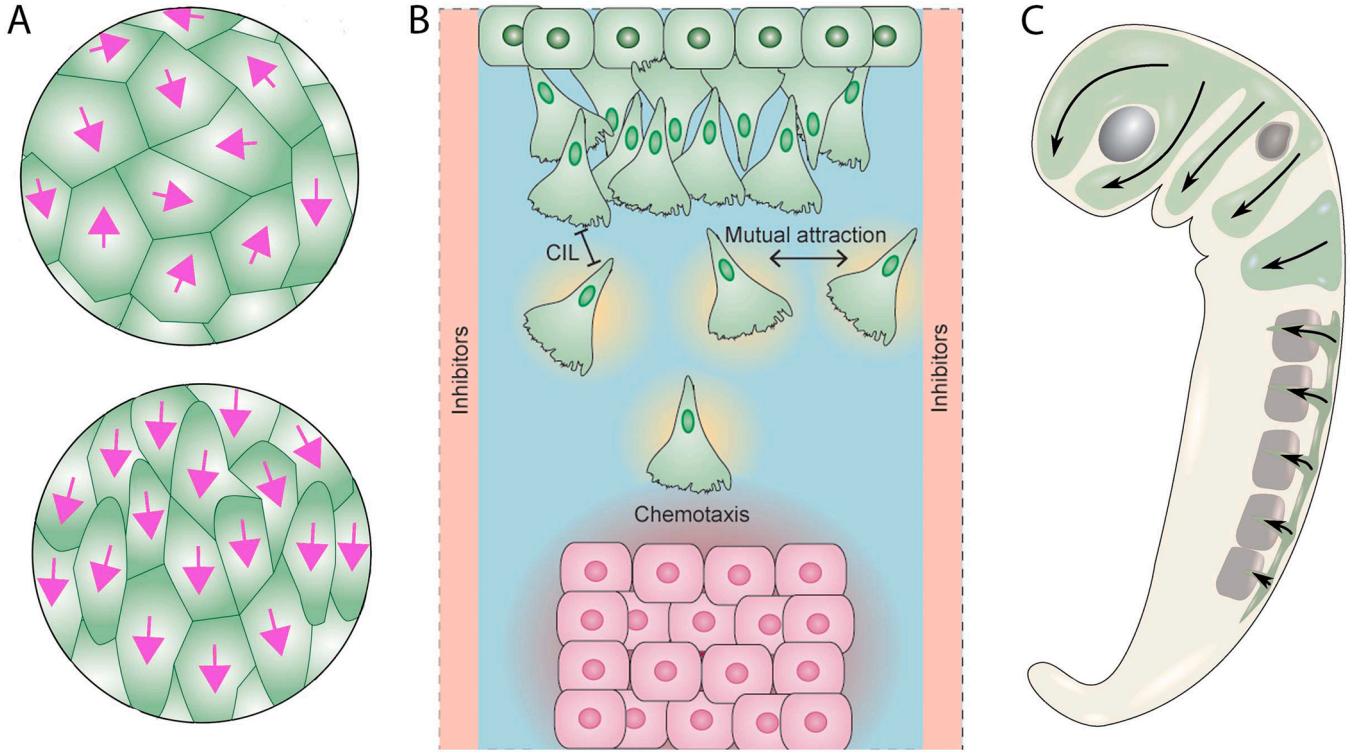

Fig. 4. The complex world of collective cell migration, (A) Tissues can transition between a jammed phase (top), where cells are rigid and randomly oriented (pink arrows) and thus block each other's movement, and an unjammed phase (bottom), where cells are flexible enough to avoid blockages and can align their orientations to undergo collective motion. (B) Collectively migrating cells (green) make their way as a swarm of interacting individuals. Density, speed and directionality of the swarm depend on attractive and repulsive interactions among the migrating cells and between them and the environment. (C) The versatility of swarm-like collective cell migration allows embryonic cell populations such as the Neural Crest (green) to migrate in streams across many different regions of the embryo, finding their way to target sites as different as the heart and mouth. How they adapt their migratory strategies to cope with different mechanical and biochemical environments is a subject under intense study.

from cell shape alone [119]. Recent work by Petridou and colleagues adds another important tool to characterize tissue state transitions: network analysis [117]. Analyzing the fluidization of the zebrafish blastoderm [122], they found that extracting the cell-cell contact network and measuring the size of its largest rigid cluster was sufficient to determine the phase of the tissue. This network-based framework represents another example of a highly simplified yet powerful abstraction over a widely important collective cell behavior. It could thus become a way for synthetic biologists to predict the mechanical phase of synthetic tissues and to manipulate it with the very same toolboxes that provide control over cell sorting (see Section 3.1) [72,74].

Intriguingly, there appears to be a connection between the mechanical phase transition of fluidization and a broader cellular state transition, the Epithelial to Mesenchymal Transition (EMT). When undergoing EMT, the cells of a stable epithelium alter their gene expression and cytoskeletal architecture, lose their tight connections and become more individual and dynamic [123]. This multi-modal change in cellular organization and its converse, MET, often coincide with tissue fluidization or solidification, respectively, and both the cellular and mechanical transitions are important in modifying the malleability and migratory capacity of tissues. However, it remains unclear if and how they are connected, as there are examples where they occur independently [124,125]. A better understanding of both transitions and their relationship, as well as the design of means to exploit such transitions in a synthetic context, are important open research goals.

4.2. Flowing together: collective cell migration

Once ready to move, cells individually employ (guided) symmetry breaking (see Section 2) to polarize into a protrusive and a retractive end. They then propel themselves forward by generating actin retrograde flow that is mechanically coupled to an external physical substrate, usually the surrounding extracellular matrix [106]. When moving collectively, migrating cells coordinate directionality, speed and density of the group through biochemical and biophysical interactions [126] (Fig. 4B).

An instructive example of such coordination is found in vertebrate Neural Crest Cells (NCCs), which originate from dorsal ectoderm during gastrulation and migrate through the embryo as a loose collective, ultimately reaching different target sites where they contribute to the formation of many different organs [109]. While migrating, NCCs mutually attract each other at mid range through chemokine signaling, but repel each other at short range via Contact Inhibition of Locomotion (CIL). This system of interactions leads to the emergence of coherent yet only loosely coupled streams of migrating cells with varying densities depending on additional internal and external factors [127].

Such loosely coupled collective movement, reminiscent of swarming behaviors exhibited by bird flocks and schools of fish, forms the basis of "swarm intelligence". Single cells or small subgroups of the collective retain the ability to sense and respond to local cues, but the resulting change in their behavior feeds forward to the rest of the collective and the overall state of the collective feeds back into the local response. Thus, swarms can perform local sensing and global decision making, which enables the emergence of complex, robust and adaptive collective behaviors without the need for a global blueprint [128].

What to a school of fish might be the detection of food or the sighting of a predator are to the neural crest the various attractive and repulsive cues that are distributed across the embryo in the form of diffusible chemokines and substrate-bound repellents (Fig. 4B) [127]. Mechanical cues also play a role, as we have recently shown that neural crest migration is triggered by substrate stiffening [129], guided by durotaxis [130] (see also Section 4.3), and regulated by the mechanically gated ion channel Piezo1 [131]. Collectively, these cues guide NCCs along their many paths through the embryo (Fig. 4C), ensuring an adaptive yet consistent developmental outcome – a principle similar to guided self-organization.

The highly adaptive nature of collectively moving cells and their receptiveness to numerous different cues make them challenging to study and manipulate, but could also form a powerful platform for synthetic applications. In particular, problems that require that generation of adaptive solutions rather than the manufacturing of a stereotypical product could harness the swarm intelligence of migrating cells. An example of this is vascularization, which is a major obstacle in bringing engineered tissues into clinical applications and therefore continues to be the subject of intense research, with numerous different strategies being explored for promoting and guiding the migration of endothelial cells and their progenitors [132].

4.3. Remodeling cues on the go

A swarm of cells is guided by cues in its environment, but these cues need not be static. Indeed, migrating cells themselves can shape their environment as they travel, altering the distribution of cues and thereby affecting the behavior of other motile cells.

Many migrating collectives use metalloproteinases to degrade their substrate or deposit new matrix as they migrate [133,134]. Even the purely mechanical interactions generated by cells pushing and pulling on their substrate can lead to lasting changes in the environment [135]. Such environmental modification enables a form of self-organization termed *stigmergy*, which is famously exemplified in the emergent behavior of ant colonies, where individual ants both follow and deposit pheromone cues [136]. Although the concept of stigmergic self-organization finds application from bacterial biofilms to human economies [137,138], its usefulness in cell and developmental biology remains largely unexplored. Toy models built through synthetic biology may provide an entry point for further exploration on this front.

Another important design principle arising from local guidance cue modification is the Self-Generated Gradient (SGG) [139]. By not only sensing an externally present diffusible attractor but also degrading it, a cluster of migrating cells can act as a sink and thereby locally generate a gradient across its length, even if the external cue was originally uniformly distributed. This is especially important for adaptive and long-range migration, where it would be challenging to generate a pre-patterned gradient across the entire migration path.

A well-studied example of SGG formation is found in the zebrafish posterior Lateral Line Primordium (pLLP), a group of cells that migrate along the flank of the developing embryo as a tightly connected collective [140]. Clever experimental perturbations revealed that the pLLP can perform a U-turn half-way along its path and migrate back the way it came, proofing that the guidance cue does not function as a global gradient [141]. Subsequent work by Donà and colleagues demonstrated that cells at the rear of the pLLP express a non-signaling decoy receptor that mediates binding, internalization and degradation of the chemokine [142]. The resulting SGG is necessary and sufficient to drive directed pLLP migration. Intriguingly, a follow-up study further showed that the pLLP dynamically upregulates expression of the decoy receptor in response to an exogenously induced chemokine flood [143]. This allows the tissue to generate a gradient and migrate persistently independent of absolute chemokine levels, thus bolstering the robustness of collective cell migration. Other systems that have been shown or suggested to use self-generated gradients include melanomas and social amoeba, as well as the vertebrate neural crest [144–146]. It is likely that they, too, make use of this principle to ensure robust long-range migration.

As implied in section 3.4, principles of biological self-organization that can be implemented using biochemical signals may have alternative implementations through mechanobiology. For self-generated gradients, our lab recently showed that this is indeed the case [130]. We showed that NCCs can undergo durotaxis, meaning they sense and follow stiffness gradients in the substrate upon which they migrate [147]. When asking whether a stiffness gradient exists along the path of

NCC migration in vivo, we found no global gradient but rather a dynamic local gradient that moves along with the neural crest. We determined that it is the interaction between the neural crest's leading edge and placodal cells that migrate ahead of it which leads to the local self-generation of a stiffness gradient, in turn further stimulating neural crest migration through durotaxis [130].

Such sophisticated self-guidance schemes – and the multi-facetted mechanisms of collective cell migration in general – may at present appear too complicated to be usefully implemented in a synthetic context. However, this also once appeared to be the case for many of the self-organization principles discussed above, yet it changed as appropriate abstractions led to substantial conceptual progress. We hope that such efforts will also bring about a strong theoretical framework of collective cell migration that enables us to harness the power of cellular swarm intelligence.

5. Analysis and synthesis advance together

Much attention is rightly being paid to the extensive molecular toolbox that nature and human ingenuity together have made available to us and that continues to grow at a rapid pace. However, equal attention should be given to the suite of systems design principles offered to us by nature, which is no less extensive. Indeed, the principles of self-organization and guidance discussed here are by necessity only a subset of those present in nature. Others include positional information [148], epithelial folding [149], cell competition [150], hydraulic fracturing [151], and many more. Taking advantage of these principles to engineer versatile, adaptive and robust systems that perform biological functions to human specification is among the principal aspirations of synthetic biology.

A major obstacle on this path comes from the limitations in our understanding of self-organization in nature. Decades of work have unearthed many of the molecular components and basic mechanisms of development, but models at the systems level are often qualitative or highly idiosyncratic to the specific species and process under study, offering little predictive capability and thus limited value for engineering and design. This is in part because the study of complex, nonlinear, out-of-equilibrium systems is inherently challenging. However, some of the works highlighted in this review show that it is possible to derive quantitative and general abstractions of such systems. Accomplishing this for as many of the key principles of biological self-organization as possible remains a central goal for cell and developmental biology.

Synthetic biology itself may play a crucial role in achieving this goal [152,153]. The analysis of self-organization in natural systems often relies on destructive perturbations to ascertain causality, which can be difficult to interpret due to the complexity of the feedbacks present. By contrast, the tools of synthetic biology allow the construction of biological toy models and the reconstitution of self-organizing systems in a simplified and more controllable context. This makes it possible to test the merit of theoretical generalizations empirically and to determine minimal models sufficient to explain a given phenomenon. For guided self-organization in particular, synthetic approaches promise the possibility of separating guidance from self-organization, which can lead to a better understanding of both. It is thus clear that there is considerable potential for synergy between synthetic and analytic developmental biology.

Another natural bridge between the two is formed by mathematical modeling and simulation. Good models are able to explain natural biological phenomena and simultaneously make valid predictions for the behavior of synthetic systems. They also foster better intuitions and facilitate the import of concepts from other fields, e.g. soft matter physics. Simulations can be used to test hypotheses and parameter optimization can assist in fine-tuning of synthetic designs. An open question in this context, which has begun to be explored [154,155], is to what extent machine learning might take over some of the design process.

It has become something of a tradition to end reviews on technological advances with a token cautionary note on potential ethical implications, which likely has little impact on readers. We follow this tradition here by pointing out that, as our capability to control and synthesize biological and bio-inspired systems grows, ethical questions on stem cell usage, human genetic manipulation, human enhancement, environmental impact, biosafety and biosecurity will need to be addressed [156,157]. In addition to these better-known issues, we also note the potential for military applications resulting from progress in synthetic biology. It is often forgotten that throughout human history any successful engineering paradigm has invariably been used to design weapons of war and terror. Indeed, one could argue that there is no stronger indicator for the success of a synthetic discipline than its adoption for military purposes. The same will be true of synthetic biology. Hence, researchers working in this field should be aware that they may directly or indirectly contribute to the development of weaponry that will harm or end the lives of many human individuals. As is customary for this type of warning, we offer no solutions here and ask only that this point be pondered gravely but briefly before readers return their attention to solving the outstanding questions of developmental self-organization and synthetic developmental biology.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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