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HYPOTHESIS

Exploring the interdependence between self-organization and functional morphology in cellular systems

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ABSTRACT

All living matter is subject to continuous adaptation and functional optimization via natural selection. Consequentially, structures with close morphological resemblance repeatedly appear across the phylogenetic tree. How these designs emerge at the cellular level is not fully understood. Here, we explore core concepts of functional morphology and discuss its cause and consequences, with a specific focus on emerging properties of self-organizing systems as the potential driving force. We conclude with open questions and limitations that are present when studying shape–function interdependence in single cells and cellular ensembles.

KEY WORDS: Functional morphology, Self-organization, Emergence, Cell shape, Cell function, Evolutionary fitness

Introduction

All objects obey the same physical laws. It is thus not surprising that for a given problem similar geometrical solutions can be observed in living and man-made structures. For instance, microvilli in the gut (Kamisaka and Rønnestad, 2011) and a terry towel both take advantage of small finger-like protrusions to augment absorption (Fig. 1A). Similarly, gills from mushrooms (Hosen et al., 2018) and fish (Ong et al., 2007) carry a close resemblance to radiator gills (Fig. 1B). Strikingly, similarities extend beyond the superficial to the mechanistic level. For example, structures exposed to similar mechanical stressors yield similar enforcement structures. This can not only be observed at the subcellular level, as illustrated with actin filaments forming a filopodium (Fig. 1C), but also in multicellular structures such as the calcaneum (Fig. 1D). How have such convergent solutions evolved across scales? And even more intriguing, can similar morphologies be traced back to the same basic design principles? In this Hypothesis, we explore whether functional morphology is an emerging property of self-organization. To that end, we revisit the mechanisms that lead to self-organization and cell shape changes, before using the example of arborization to discuss how interfaces with the environment are optimized in single and multicellular systems. We conclude by exploring the limitations of the hypothesis and highlighting open questions and future challenges.

Hypothesis

Before presenting the hypothesis, we need to briefly introduce some core terms. We begin with the term 'functional morphology'. In mathematics, a function defines a relationship between individual variables, while the term functional refers to the ability to perform a particular function. Morphology, on the other hand, describes the form or structure of an item. Consistently, functional morphology explores the interdependence of a particular task or activity (i.e. functional) in relation to a specific shape (i.e. morphology). Historically, phenomena in live matter attributed to functional morphology have already been anecdotally observed by Aristotle. However, the term functional morphology officially appears in anatomy textbooks only in the 18th century (Ashley-Ross and Gillis, 2002). In these early studies, Cuvier adopted teleological explanations of anatomical shapes described in ancient times (Steadman, 1979). Qualitative description of anatomical structures were, for the first time, explained by the function that had to be accomplished. Since Cuvier's work, it took another century until the concept of functional morphology entered mainstream science. Here, in particular, the seminal work of D'Arcy Thompson from 1917 '*On growth and form*' should be mentioned for its attempt to explore natural geometries in pure mathematical terms (Thompson, 1992). Since then, the interrelationship between shape and function has been the subject of intense research, and its role has been discussed for fundamental cellular mechanisms, such as division (Minc and Piel, 2012), polarity (Etienne-Manneville, 2004), migration (Zhong and Ji, 2013) and communication (Song et al., 2019).

A second term that requires a detailed introduction is 'self-organization'. Self-organization is frequently used to describe spontaneous formation of spatial and temporal patterns, some of which are influenced by the shape of the cell (Haupt and Minc, 2018). Shape dependent self-organization, for instance, was shown for cytoskeletal orientation and positioning of subcellular structures (Minc et al., 2011). Yet another hallmark of self-organizing systems is 'emergence'. Here, the interaction of components at the micro-scale leads to a qualitatively new property at the macro-scale. An emergent property is therefore not the sum of the properties of all components, but radically novel. Intriguingly, emergent properties can serve as new building blocks for even more intricate emergent properties at the next higher level. Over time, such a bottom-up approach can yield hierarchical multilevel systems of surprising complexity and stability (Fig. 2A). An elegant example for such a multilevel system is awareness, which is an emergent property of neuronal circuits. Circuits, in turn, consist of individual neurons that take advantage of emerging subcellular properties based on self-organizing systems (e.g. dendrite branching).

Is there any connection between these terms? Functional morphology can be observed at various time and length scales. The same is also true for self-organization. This raises the interesting question as to whether the functionally optimized morphology of single cells might represent an emerging property of self-organizing systems. How could this work? Let's imagine the fitness of an organism as a 3D landscape, with local optima represented as hills (Wright, 1932). Changes at the genome level owing to mutations might influence the phenotype. Should these changes yield an increase in fitness, the system may evolve through natural selection

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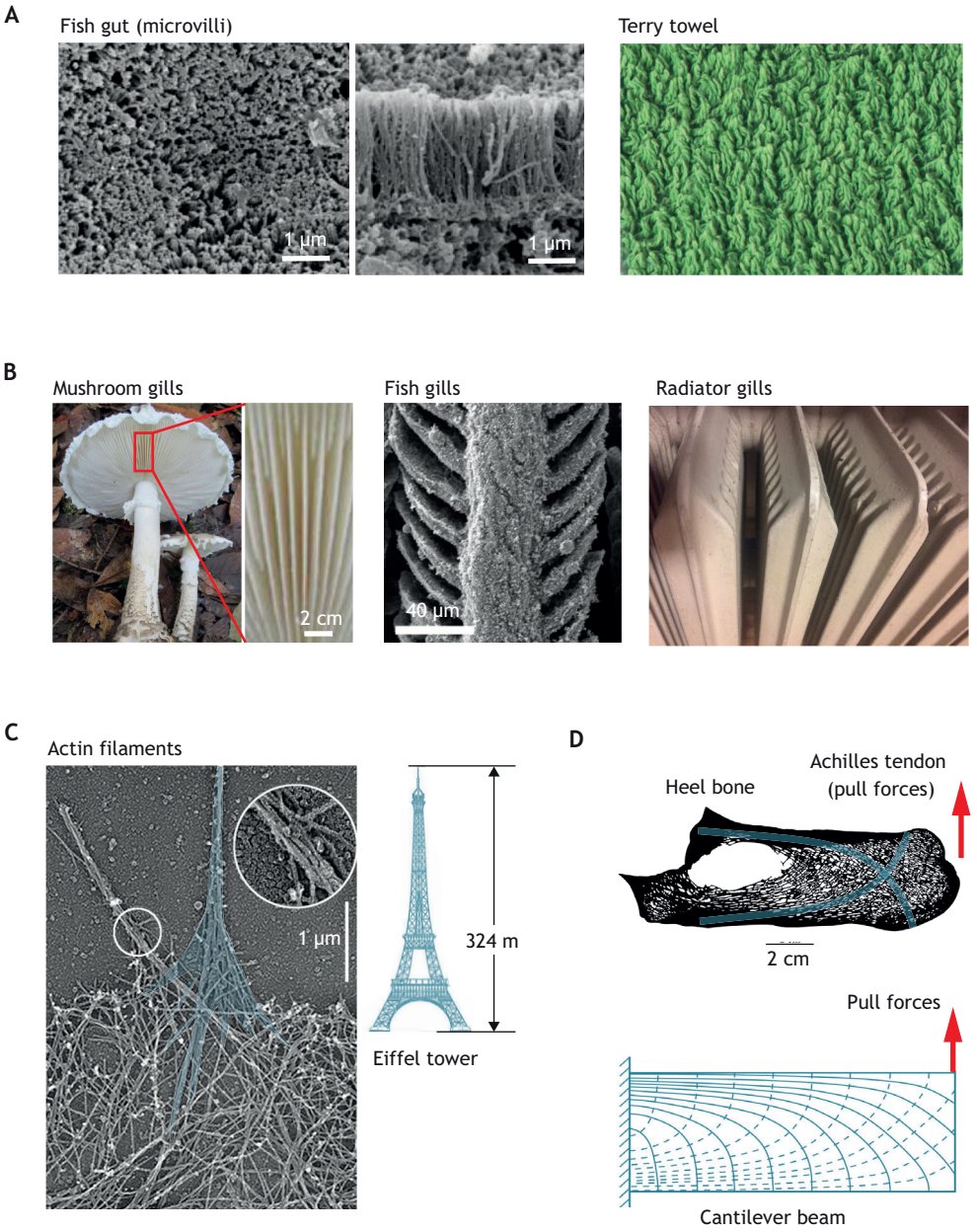

Fig. 1. Morphological similarities between cellular and artificial structures. (A) Finger-like protrusions increase uptake area. Left, gut lumen of Atlantic cod larva at 54 days post hatching taken by scanning electron microscopy (SEM) showing microvilli for increased nutrient uptake; adapted from Kamisaka and Rønnestad, 2011, where it was published under a CC-BY-NC-2.0 license. Right, terry towel showing an increase in surface for efficient fluid absorption; adapted from Chiesa, 2006; https://commons.wikimedia.org/wiki/File:Tessuto_a_spugna_grande.jpg, where it was published under a CC-BY-3.0 license. (B) Lamellar structures increase exchange area. Left, basidiomata of mushroom *A. griseoverrucosa* form lamella to augment spore production; adapted from Hosen et al., 2018, where it was published under a CC-BY-4.0 license. Middle, scanning electron micrographs of *Kryptolebias marmoratus* gills showing lamella for improved oxygen uptake; adapted with permission from Ong et al., 2007. Right, radiator containing lamellae to increase area for heat exchange. (C) Platinum replica EM image of filopodium showing a tight bundle of actin filaments rooted in the surrounding actin meshwork for stability. Note similarities to the Eiffel tower; adapted with permission from Biyasheva et al., 2004; image of the Eiffel tower was from Kuxu76, 2006; https://commons.wikimedia.org/wiki/File:Dimensions_tour_Eiffel.JPG, where it was published under a CC-BY-3.0 license. (D) Sagittal section through the heel bone of a cow (top) and the principal stress trajectories in a cantilever beam (bottom). Note that the trabeculae in the calcaneum (heel bone) closely follow the beam stress lines; adapted from Bishop et al., 2018, where it was published under a CC-BY-4.0 license.

towards a local optimum (Fig. 2B). Yet, such an unbiased exploration of the landscape through natural selection is incremental, which limits transition between local optima (Fig. 2C, gray arrow). This is relevant, as it reduces the ability of the system to explore the full phenotype space. How may self-organization affect the evolvability of a system? In a self-organizing system, small changes to components at the micro-level (i.e. gene mutations) can yield fundamentally different outcomes at the macro level (e.g. pattern or morphology). Using the analogy of the fitness landscape, such a phase transition at the macro-scale is reminiscent of discontinuous jump to a completely different spot in the phenotype space. Hence, the shape of the landscape will decide whether a self-organizing system will be selected through evolution or not (Fig. 2C, red dashed line). A self-organizing system, however, not only yields discontinuous steps but also precludes an unbiased exploration of the newly found local optimum. Such a system thus remains at the 'apparent optimal' spot with limited possibilities to reach perfection (i.e. the tip of local optimum).

Pattern formation in cells and cellular ensembles

Cellular pattern can be induced by various mechanisms, not all of which are based on self-organization. In the following section, we will revisit some of the most prominent examples. Note that the definition of self-organization varies across scientific fields (reviewed in Bensaude-Vincent, 2009). Here, we will adhere to the physico-chemical definitions of Ilya Prigogine (Glansdorff and Progogine, 1971).

Self-assembly refers to a dynamic process, where order emerges as a closed system reaches a state of minimum free energy. As such, a self-assembling system is autonomous (i.e. lacks external control), spontaneous and not adaptable. An excellent example of self-assembly are lipids, which spontaneously form membranes and micelles. From a thermodynamic perspective, spontaneous self-assembly of lipids into membranes yields an increase in enthalpy (caused by the ever-changing hydrogen bonds between individual water atoms), which in turn reduces the total free energy of the system. Other examples of self-assembly in biological processes include

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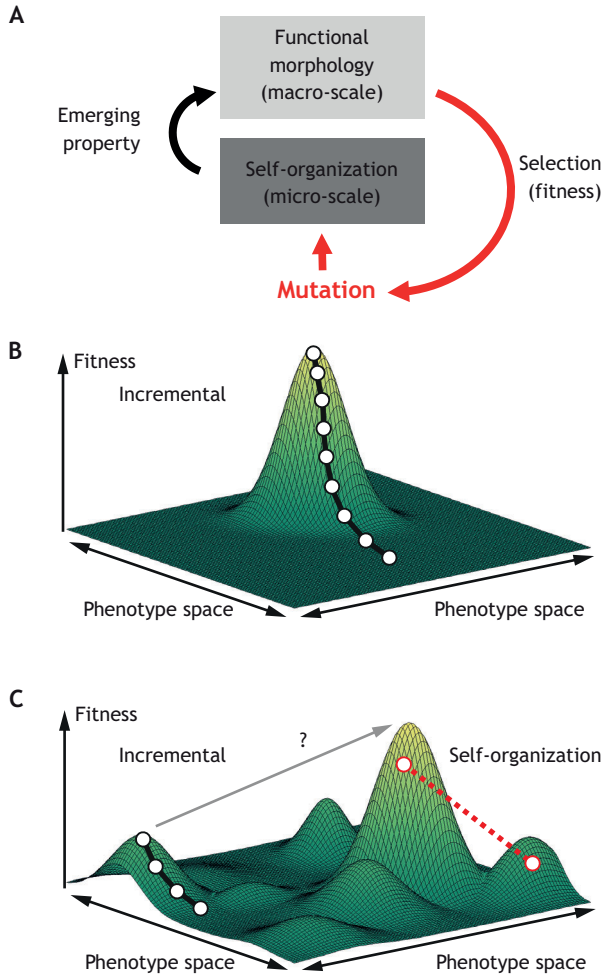

Fig. 2. Fitness landscape of self-organizing systems. (A) Self-organization at the microscopic scale yields radically new emerging properties at the macroscopic scale (black). We hypothesize that functional cell morphology is an emerging property of such self-organization on the subcellular level. Stochastic mutations on the micro scale (in red) lead to changes in diffusion and/or reaction rates of molecules that form the self-organizing system, ultimately altering its emerging properties. The resulting shape changes then influence overall cell performance. Over time, improved functional cellular morphologies can arise by natural selection. (B) Evolutionary landscape showing one optimum. Here, random mutations yield a suitable strategy to continuously increase evolutionary fitness of the system. (C) Evolutionary landscape with multiple optima. Here, random mutations will allow reaching the peak of a local maximum, but preclude departure thereof (gray). In contrast, self-organizing systems allow abrupt transition (red). The beneficial position in the fitness landscape will be selected. Note that no subsequent increase in evolutionary fitness can be achieved in a self-organizing system.

protein folding and virus assembly (Wood, 1980). Minimizing the free energy further yields phase separation, if interaction energies (i.e. repulsion and attraction) between molecules (e.g. lipid–lipid and lipid–protein) dominate the entropy contribution (Veatch and Keller, 2002; John and Bär, 2005). The resulting inhomogeneity in molecule localization in membranes or the cytosol have been described to mediate cellular function (Hyman et al., 2014).

In contrast to self-assembly, self-organization is a spontaneous process, which leads to the formation of ordered structures in open systems (i.e. far off thermodynamic equilibrium). As a cell is an open system, various self-organizing structures exist. Possibly the most famous example for self-organization are reaction–diffusion systems, first introduced by Alan Turing almost 70 years ago (Turing, 1953). Here, two diffusive agents, an inhibitor and an activator, mutually affect the activity of each other. Pending well-adjusted reaction and diffusion rates, this minimal system is capable of forming long-lived spatial and temporal patterns, without the need of any external signaling cues. Representative of a self-organizing system, these spontaneously forming patterns are autonomous, robust and can yield multiple stable final states (i.e. phase transitions). Strikingly, reaction–diffusion systems reminiscent of those initially proposed by Turing were subsequently confirmed in living systems (Jacobo and Hudspeth, 2014). An alternative system cells employ for self-organization is based on stigmergy (Holland and Melhuish, 1999). In this scenario, the assumption is that only limited amounts of an agent are available. As the agent forms a positive-feedback loop to trigger its own enrichment, it is depleted elsewhere. Hence, initial stochastic fluctuations in this system yield patterning through indirect environment coordination (Holland and Melhuish, 1999). Like Turing-type systems, patterning based on stigmergy has been reported in biological structures as diverse as bacterial biofilms (Gloag et al., 2013) and morphogenic membrane systems (Gavriljuk et al., 2018 preprint).

Similar to what is seen in single cells, various strategies exist for pattern formation in multicellular ensembles (reviewed in Isaeva, 2012). For instance, spontaneous pattern formation can be achieved by differential cell adhesion (Steinberg, 1970). Here, cells rearrange themselves to minimize their total adhesive free energy (Steinberg, 1970). Analogous to self-assembly, a mixed cell population approaches a final equilibrium configuration where cohesive cells are enveloped by less cohesive ones. Self-organizing multicellular patterns can emerge upon lateral inhibition (Collier et al., 1996). By employing a feedback loop, where a cell of a particular fate inhibits its neighbors, random stochastic fluctuations yield fine-grained spatial patterns in a tissue of initially equal cells. Possibly the best known example of lateral inhibition is Delta–Notch signaling, where a cell that is inhibited (i.e. activation of Notch) loses the ability to inhibit (i.e. produce active Delta) its neighbors to form pattern in multicellular systems such as the bristles on the *Drosophila* notum (Cohen et al., 2010).

Collectively, these systems imprint various types of spatial and temporal patterns. The examples mentioned in this section are representative of a larger, intensely studied group of strategies employed by cells for pattern formation (Mori et al., 2008). We refer readers interested in learning more on this exciting topic to previous reviews (Hyman et al., 2014; Saha and Galic, 2018).

Mechanical forces in space and time

How are patterns translated into shape changes? To convey mechanical forces, cells rely on polymers composed of repetitive protein structures. Possibly the best studied polymers are semi-flexible actin filaments, with a persistence length of ∼10 µm. Within cells, these relatively soft actin filaments are entangled and cross-linked by actin-binding proteins, forming a viscoelastic cortical meshwork (Pullarkat et al., 2007). In its most simple form, such a viscoelastic system can be described by a ‘Maxwell body’ that is composed of a dashpot and a spring connected in series. Here, the force at the spring scales linearly with the displacement, while the forces at the dashpot scale with the displacement velocity. Hence, a sudden extension of such a system will initially be absorbed predominantly by the spring component (i.e. be elastic and reversible), whereas a slow extension will be mainly absorbed by the dashpot (i.e. be viscous and irreversible). Strikingly, actin filaments are actively patterned by self-organizing systems. How exactly is this achieved? Reaction–diffusion systems, for instance,

yield symmetry-breaking and spatial patterning of GTPase activity (Goryachev and Pokhilko, 2008). Since GTPases regulate actin polymerization dynamics, this yields a subcellular organization of actin filaments without the need for external stimulation (i.e. bottom up). Spontaneous symmetry breaking can also occur through biased GTPase delivery (Wedlich-Soldner et al., 2003). Once patterned, cortical actin provides crucial protrusive and contractile forces in cells (Chugh and Paluch, 2018; Sedzinski et al., 2011). Notably, local changes in actin-based forces can then lead to plasma membrane deformations, which are detected by curvature-sensitive molecules, such as members of the BAR domain family (Galic et al., 2012). As some of these curvature-sensing molecules alter actin polymerization rates, this by itself can create local self-organizing circuits that are suitable for either enhancing (Begemann et al., 2019) or inhibiting (Galic et al., 2014) the initial actin-based forces responsible for sustained cell-shape changes.

Microtubules form stiff cylindrical structures with *in vitro* persistence lengths of the order of millimeters (Janson and Dogterom, 2004). This high flexural rigidity, which is ∼100 times higher than actin, allows individual microtubules to be subjected to relatively large forces without buckling or breaking. Similar to load-bearing manmade objects, this rigidity allows individual microtubules to serve as a principal delivery system for cargo (van Bergeijk et al., 2016), or to exert forces along a pre-determined axis (Singh et al., 2018). Microtubule-based forces (Gotlieb et al., 1981; Gundersen et al., 2004) are similarly subject to spatial and temporal patterning. Notably, *in vitro* studies have shown that microtubules self-organize into non-isotropic patterns, such as vortices or asters, upon changes in the relative concentration of motors and tubulin monomers (Misteli, 2001; Pinot et al., 2009). Furthermore, when coupled through a deformable membrane, mechanical forces exerted by growing microtubule ends yield patterning by capturing of neighboring microtubules (Gavriljuk et al., 2018 preprint). Strikingly, microtubules can also be patterned by reaction–diffusion systems (Nagashima et al., 2018). In *Arabidopsis*, for instance, ROP11-activated domains are formed by a reaction–diffusion mechanism that consists of the slowly diffusing guanine nucleotide exchange factor (GEF) ROPGEF4 and the highly diffusive GTPase-activating protein (GAP) ROPGAP3. In this system, local activation of ROP11 by ROPGEF triggers recruitment of the MIDD1–Kinesin13A complex to induce cortical microtubule disassembly. Ultimately, patterning of ROP11-activated domains, through the reaction–diffusion system and the resulting microtubule disassembly, mediates formation of pits that are critically involved in the cellular transport across the secondary cell wall (Nagashima et al., 2018).

By contrast, intermediate filaments (IFs) form flexible polymers with a persistence length of 0.2–1 µm. IFs self-assemble into stable biopolymers with random configurations, many of which show hardening upon exertion of strain (Goldman et al., 1996; Lowery et al., 2015; Biskou et al., 2019; Helfand et al., 2003). Considering that IFs readily interact with actin and MTs, this strain-dependent adaptive response of the cytoskeleton (i.e. IFs with actin and MTs) is of central importance to cells that are exposed to mechanical stress. While beyond the scope of this article, the diversity in material properties suggest a functional morphology at the level of individual protein polymers. We refer readers interested in learning more about cytoskeletal mechanics to previous reviews on this exciting topic (Huber et al., 2013; Bashirzadeh and Liu, 2019).

While incomplete, these few examples provide evidence for a rich repertoire of mechanisms for patterning cytoskeletal forces in space and time. Complementing cytoskeletal forces, modifications in lipid organization (Singer and Nicolson, 1972) or membrane tension (Diz-Muñoz et al., 2013) also influence cell shape, owing to rearrangements or changes in protein-membrane interactions (Hoffmann et al., 2009; Jiang and Sun, 2013; Liu et al., 2008; Ebrahimkutty and Galic, 2019), thus establishing a plethora of mechanisms used by cells to translate spatial patterning via self-organization into long-lived local and global shape changes.

Arborization – a case study

To further explore the intricate relationship between self-organization and functional morphology, we here use the example of arborized structures. On first sight, branching patterns appear complex. However, upon closer inspection we notice that such patterns frequently rely on self-repeating motifs. This observation has been formalized, among others, in the Lindenmayer system that uses strings of recurrent functions (Lindenmayer, 1968). Depending on segment lengths, and the nodes and angles between them, intricate branching structures with close resemblance to many plant forms can be achieved. Readers interested to learn more about this topic, should refer to excellent work published elsewhere (e.g. Prusinkiewicz and Lindenmayer, 1990).

Yet, what benefits does branching actually yield? Let us assume that absorption of a particular substance occurs with a particular rate at the surface of a cylinder. For a constant volume ($V = \pi r^{2}h$), the surface area ($A = 2\pi rh$; cylinder open on both sides) increases as the radius is reduced, whereby the surface-to-volume ratio is proportional to the radius^{-1}. Hence, thinning out the tubes allows increasing total absorption without the need to augment absorption rates or volume. In arborized structures, the size and distribution of such cylinders are spatially arranged to maximize resorption. Indeed, mathematical modelling indicates that the optimal geometrical solution (i.e. dendritic tree shape) relies on source distribution and resorption rates (Ochoa-Espinosa and Affolter, 2012; Hannezo et al., 2017; Hannezo and Simons, 2019). For instance, absorption of slowly diffusing objects requires a denser network than for fast diffusing material. Likewise, structures that absorb locally produced objects (i.e. regenerating resource) will substantially differ in geometry from systems that absorb items produced elsewhere (Brophy et al., 2018). As we will see in the following section, arborization frequently takes advantage of self-organizing systems to form rudimentary branching patterns that are then further fine-tuned in an adaptive fashion.

Strikingly, repetitive branching patterns can be found across scales. For multicellular systems, many excellent example of this concept have been described in plants (Kutschera, 1997). Reminiscent of a self-organizing system, some plants form a rudimentary pattern when grown in darkness (Low, 1971). However, the resulting emerging structures are by no means optimal. Considering the variability in the environmental parameters (e.g. localization of light source and spatial restrictions), achieving an optimal solution purely by self-organization is not possible. Here, fine-adjustments through a tunable adaptive system that works independently of the self-organizing pattern allow plants to reach their optimum. This adaptive component can be observed, for instance, in the final shape of the canopy that is adjusted to its specific environmental factors (Kutschera, 1997). Notably, arborized structures can be found in other multicellular ensembles (Metzger et al., 2008), such as the capillary system (Fig. 3A) and the lungs (Fig. 3B). As above, conceptual work on lung arborization suggests that self-organizing reaction–diffusion systems yield rudimentary branched structures (Menshykau et al., 2012), which are then further fine-tuned in an adaptive manner.

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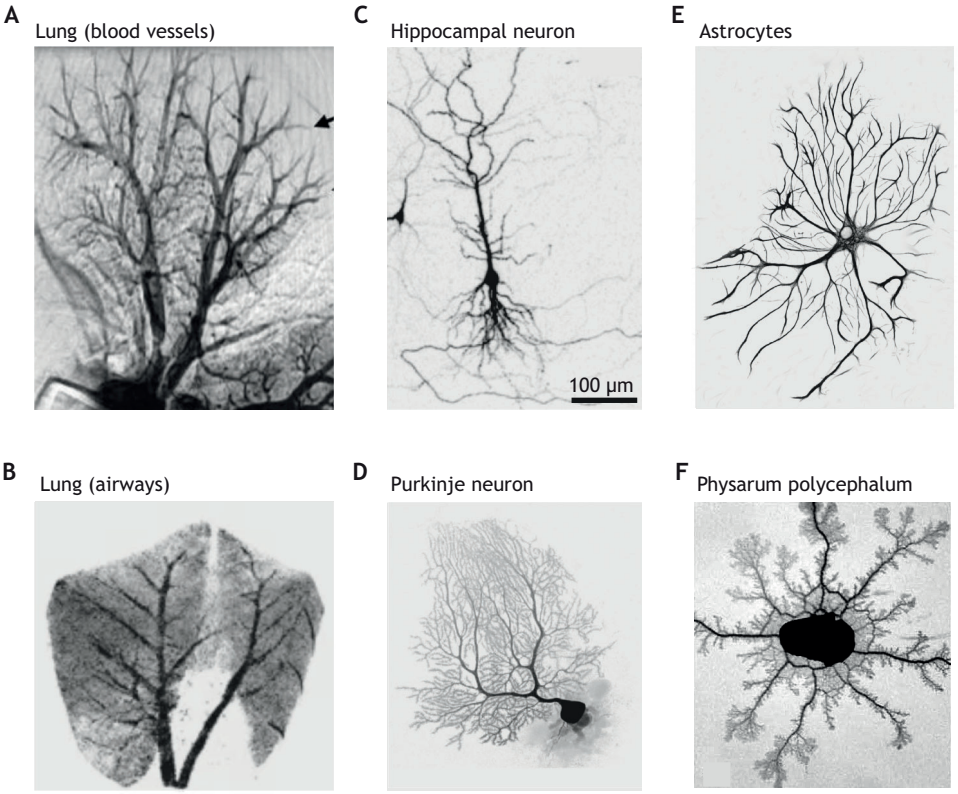

Fig. 3. Arborization in biological systems. (A) Human lung angiograph; adapted from Khoshgoo et al. (2017), where it was published under a CC-BY-4.0 license. (B) CT scan of mouse lung airways; adapted from Khoshgoo et al. (2017), where it was published under a CC-BY-4.0 license. (C) CA1 pyramidal neuron (adapted from Zha et al., 2009, Copyright 2009 Society for Neuroscience). (D) Purkinje cell from mouse cerebellum; adapted from Martone, 2002; https://commons.wikimedia.org/wiki/File:3_recon_512x512.jpg, where it was published under a CC-BY-3.0 license. (E) Astrocyte cell grown in culture; adapted from GerryShaw, 2013; https://commons.wikimedia.org/wiki/File:Astrocyte5.jpg, where it was published under a CC-BY-3.0 license. (F) The slime mold *Physarum polycephalum* extending from a colonized oat flake onto the agar substrate; adapted from Ricigliano et al. (2015), where it was published under a CC-BY-4.0 license.

Similarly, arborization can be observed in single cells. Neuronal cells, for instance, take advantage of a highly branched dendritic tree to collect information through their synapses. Depending on the distribution of incoming signals, dendritic shapes substantially differ among individual neuronal types – an observation that was first made by Ramon y Cajal over 100 years ago. For example, cortical pyramidal neurons that are implicated in cognition show relative small apical and basal dendrites (Fig. 3C), while cerebellar Purkinje cells that coordinate body motion form large dendritic arbors (Fig. 3D). *In silico*, reaction–diffusion systems have been shown to create branching patterns reminiscent of neuronal arbors (Sugimura et al., 2007). Consistent with this, *in vitro* experiments demonstrate that rudimentary neuronal arborization occurs in the absence of external signaling cues (Dotti et al., 1988; Witte et al., 2008; Banker and Cowan, 1977). Under physiological conditions, these basic patterns are then further fine-tuned by external signaling cues, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (Huang and Reichardt, 2001; Song et al., 2017; Leal et al., 2015). Note that neurons are not the sole example of branched single-cell structures (Cuntz et al., 2010). Arborized morphologies can also be found in other vertebrate cells, such as astrocytes (Fig. 3E), as well as in cells from other branches of the phylogenetic tree, such as the slime mold *Physarum polycephalum* that relies on branched structures for foraging (Fig. 3F).

Curiously, arborization can be even observed at the molecular level. Glycogen, starch and amylopectin all form multi-branched glucose chains with various branching patterns. As glucose can only be digested from the distal tips, this type of arborization improves its release velocity compared with that for linear glucose assemblies. Collectively, these few examples elucidate the repetitive use of branched structures to maximize transfer of a specific compound. Yet, despite the fact that many of these objects display repetitive (e.g. 11-order of branching in the human lungs) and self-similar (i.e. small pieces of the object look similar to the overall shape) structures, they are, in the mathematical sense, not fractal as they do not continue to branch infinitely. A term for this intricate convergence in design solutions observed across scales was elegantly coined by Louis Henry Sullivan, notably an architect and not a life scientist, stating that "form follows function" (Sullivan, 1896).

Limitations of the hypothesis

Many cell types assume their unique, final shape in the complete absence of external signaling cues. When cultured on a glass slide, for instance, primary neuronal cells spontaneously arborize (Fig. 4A), umbilical vein endothelial cells flatten out (Fig. 4B), and epithelial tracheal cells form bushels of cilia (Fig. 4C). Likewise, immortalized intestinal epithelial Caco-2 cells forms microvilli (Fig. 4D), while PC-12 cells form neurite-like arborized protrusions (Fig. 4E). This seemingly trivial observation is of high relevance, as it argues that the final (i.e. functional) morphology is to some extent based on spontaneous cell-intrinsic patterning (i.e. self-organization).

Yet, is self-organization per se necessarily beneficial? To answer this question, we simply have to reflect on its core features. A self-organizing system (1) allows spontaneous pattern formation, (2) yields phase transitions at the macro-scale upon small changes on the micro-level, yet (3) is limited in its adaptability. While such a system is well suited for initial formation of basic pattern, it may hinder top-down processes. One such example is the transplantation of cells from the dorsal lip of a newt embryo to another, which is sufficient to artificially induce gastrulation in the host embryo (Spemann and Mangold, 1924). This serial developmental process relies on external inputs, quality checkpoints and transcriptional cell fate changes, rather than on bottom up self-organizing mechanisms.

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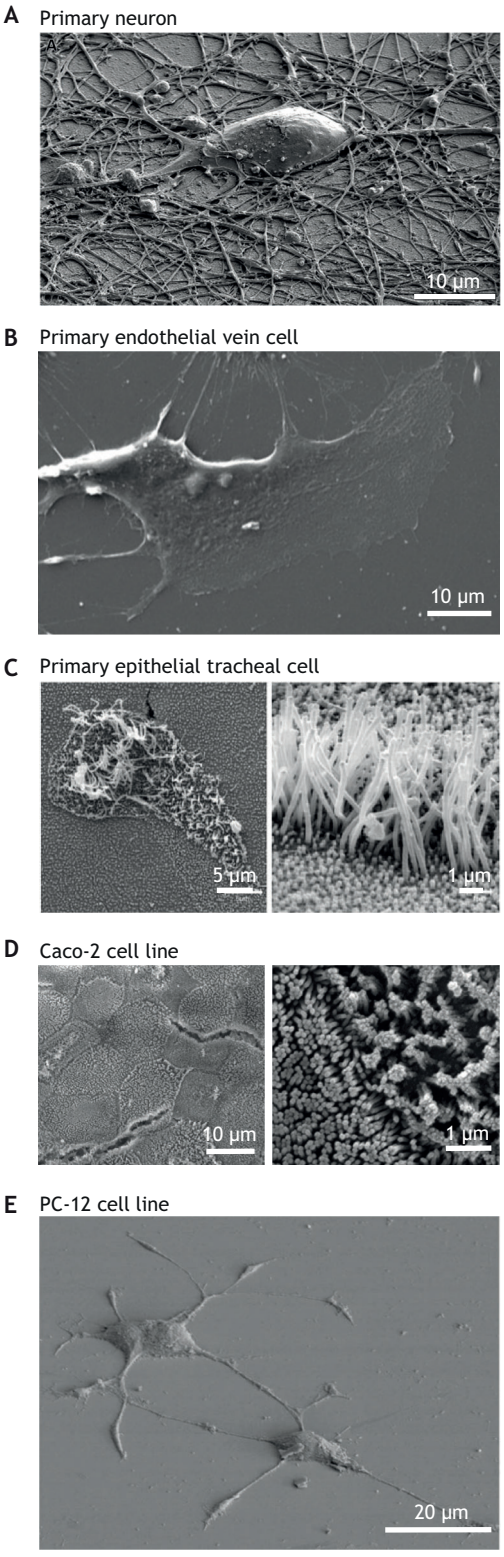

Fig. 4. Functional morphology in single-cell systems. (A) Scanning electron microscopy (SEM) image of primary hippocampal neuron 7 days after plating; adapted from Ojovan et al. (2014), where it was published under a CC-BY-3.0 license. (B) Scanning electron microscopy (SEM) image of human umbilical vein endothelial cells 4 days after plating; adapted from van den Beucken et al. (2007) with permission from Mary Ann Liebert Inc, New Rochelle, NY. (C) SEM images of epithelial tracheal cells. The formation of bushels of cilia can be seen at higher magnification; adapted from Stennert et al. (2008), where it was published under a CC-BY-NC-2.0 license. (D) SEM images of Caco-2 monoculture at two different magnifications; adapted from Cabellos et al., (2017), where it was published under a CC BY-NC-ND-4.0 license. (E) SEM of PC-12 cells forming neurite-like arborized protrusions; adapted from Pinkernelle et al. (2015), where it was published under a CC-BY-4.0 license.

Similar limitations also apply to simple systems with rapidly changing inputs. To accomplish their physiological role, motile cells sense and readily respond, in a receptor-dependent manner, to biochemical (Arrieumerlou and Meyer, 2005) and mechanical (del Rio et al., 2009) signaling cues from the environment. This relies on highly non-linear input–output relationships and noise suppression (reviewed in Ferrell and Ha, 2014; Devreotes and Janetopoulos, 2003). In such motile systems, self-organization would yield disadvantages.

On a conceptual level, we also can ask whether form necessarily needs to follow function as stated by Sullivan. Could in some cases physical restraints limit the architecture? To illustrate this point, let us assume that we try to build a simple three-dimensional object composed of only one (planar) unit. In its most simple form, only five objects can be formed: the tetrahedron, the cube, the octahedron, the dodecahedron and the icosahedron. To create more complex structures – for instance a cylindrical shape – requires more than one component. Hence, in cases where storage space is the limiting factor, for example the viral genome, function may indeed follow form.

And even more fundamentally, does form necessarily imply function? Neutral evolution theory postulates that the overwhelming majority of mutations on the molecular level do not harbor any large functional consequences for protein function (Wright, 1931; Kimura, 1968). Rather, selection of mutations is the consequence of random genetic drift in finite populations (Kimura, 1968). In theory, it is thus plausible that neutral mutations may yield functionally equal yet distinct cell shapes. In this case, entrenchment rather than natural selection would explain cell shape changes (i.e. non-functional morphology).

Conclusions and future directions

In this Hypothesis article, we explored the interdependence of self-organization and functional morphology. As specified above, many self-organizing systems are frequently used in cellular systems to induce functional morphology. This causal connection not only recapitulates the core hypothesis that functional morphology is an emerging property of self-organization, but also indicates how evolution may shape self-organizing systems over time (Fig. 2C, red dashed line). Elucidating the contribution of self-organizing systems for functional morphology will thus not only advance our understanding of fundamental physiological mechanisms, but may also open up new avenues to study pathophysiological conditions. One such example is the mechano-chemical feedback loop that forms at the leading edge of migratory cells (Begemann et al., 2019). Here, loss of the curvature-sensing domain that locally triggers formations of the self-organizing system yields profound changes in emerging properties such as the motion pattern of single motile cells (Begemann et al., 2019).

Seemingly, such a view is applicable across scales. For subcellular structures, the relationship between self-organization and functional morphology has already been investigated for mitochondria (Anesti and Scorrano, 2006), endoplasmic reticulum (Schwarz and Blower, 2016) and the Golgi (Makhoul et al., 2019). Similarly, self-organizing functional morphology also occurs in multicellular ensembles, such as the branching pattern in the lung

(Metzger et al., 2008). However, proper subcellular and tissue architecture critically relies on signaling cues from the environment (Turing, 1952; Wolpert, 1969; Kondo and Miura, 2010), stressing the importance of external control for the final design. Undoubtedly, more work will be needed to unequivocally answer the fundamental question of whether functional morphology can be considered an emerging property of self-organizing cellular systems across all scales.

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