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Review

Multi-scale Chimerism: An experimental window on the algorithms of anatomical control

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ABSTRACT

Despite the immense progress in genetics and cell biology, major knowledge gaps remain with respect to prediction and control of the global morphologies that will result from the cooperation of cells with known genomes. The understanding of cooperativity, competition, and synergy across diverse biological scales has been obscured by a focus on standard model systems that exhibit invariant species-specific anatomies. Morphogenesis of chimeric biological material is an especially instructive window on the control of biological growth and form because it emphasizes the need for prediction without reliance on familiar, standard outcomes. Here, we review an important and fascinating body of data from experiments utilizing DNA transfer, cell transplantation, organ grafting, and parabiosis. We suggest that these are all instances (at different levels of organization) of one general phenomenon: chimerism. Multi-scale chimeras are a powerful conceptual and experimental tool with which to probe the mapping between properties of components and large-scale anatomy: the laws of morphogenesis. The existing data and future advances in this field will impact not only the understanding of cooperation and the evolution of body forms, but also the design of strategies for system-level outcomes in regenerative medicine and swarm robotics.

1. Introduction

The need to predict and control large-scale structure of various complex systems given knowledge of their sub-components is a central problem spanning numerous disciplines (Anderson, 1972). Developmental biology is a paradigmatic example, since complex anatomy emerges from the parallel activity of numerous complex subunits which have distinct form and function at many scales and levels of organization (Furusawa and Kaneko, 1998; Varenne et al., 2015). Modular decomposition and recombination is a key strategy in engineering; here, we review a body of experimental data that are invaluable fodder for the search for the meso-scale laws of morphogenesis.

Genomics has made great strides in identifying information encoding the cellular hardware of cells, but it is still not possible to say much about the overall shape of an organism or of its organs from knowing its genomic sequence or the properties of its cells (other than by comparison with molecular data from an organism whose anatomy we already know). Thus, an exciting frontier of research involves understanding the mapping between the properties of subunits to body-scale anatomy in a way that enables prediction and control of system-level outcomes. This is important not only for evolutionary developmental biology, but also for solving the inverse problem: how to set or re-set the properties of low-level subunits (e.g., by editing genomic sequence in cells) to achieve a desired system-level outcome (e.g., by inducing growth of a correct human limb or produce a bespoke synthetic living machine with any specific morphology (Kamm et al., 2018; Lobo et al., 2014)). Transformative progress in regenerative medicine and synthetic bioengineering depends on being able to determine what cell- and molecular-level stimuli would induce desired large-scale changes in organ or whole body structure. The major opportunity to improve fundamental understanding and bioengineering capabilities is the discovery of rules determining large-scale structure and function given knowledge of the components and their microenvironmental boundary conditions. Understanding the reliable emergence of specific forms from competent subunits such as cells will require frameworks describing what will happen in systems consisting of components that on their own lead to distinct emergent outcomes.

Most work in molecular development takes place in standard model systems in their normal environment and configuration, such as zebrafish or mouse, in which a genome reliably gives rise to (and is widely

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thought to explain) a species-specific morphology. This can occur even despite drastic perturbations. For example, embryos can recover from removal of large amounts of body mass (Cooke, 1979, 1981), and tails transplanted onto flanks of salamanders remodel into limbs (Farinella-Ferruzza, 1956a). Regenerative animals, such as axolotls, repair after amputation damage of limbs and eyes - the cells rapidly proliferate and migrate, stopping when the precisely correct structure of the target morphology is complete (Maden, 2008). Tadpoles with abnormal faces rearrange their craniofacial tissues until a correct frog face is made (Vandenberg et al., 2012). Such observations suggest that default anatomical outcomes are extremely robust (reviewed in (Pezzulo and Levin, 2016)). However, robustness is only one side of the coin with respect to the deep questions of the emergence of large-scale anatomy from cellular components (Levin et al., 2018); the other important aspect is plasticity and ability to produce coherent outcomes in novel circumstances, which haven't been previously "tested" in the course of evolution.

Experiments in synthetic bioengineering of wild-type cells are beginning to reveal novel functional forms that can emerge from cellular activity without genomic editing (reviewed in (Ebrahimkhani and Levin, 2021; Kamm et al., 2018)). Moreover, techniques such as specific and brief perturbation of bioelectrical circuits (Durant et al., 2017) can create permanently altered morphologies such as lines of 2-headed flatworms that regenerate to the new body-plan in future rounds of amputation (without any further manipulation or transgenes). Such deviations from genomic-default outcomes underscore the need to understand how form and function are controlled in novel settings, when the starting state and microenvironmental signals are altered. Pushing outside the standard events of single-genome embryogenesis in its typical milieu offers the opportunity to understand the algorithms that guide the changes and stabilization of form (Couzin, 2009; Goldenfeld and Woese, 2011).

How exactly do cellular collectives determine what shapes they will make, and when morphogenesis and active remodeling will stop? The considerable knowledge and capability gap between relying on a familiar anatomy vs. being able to understand the rules and predicting its emergence ab initio is clearly illustrated by the following thought experiment (Fig. 1). Normally, the fragments of round-headed planarian species regenerate flatworms with round heads and stop when they are complete, while fragments of triangle-headed planarian species likewise keep growing and remodeling until flatworms with the normal triangular heads result. What will happen if the neoblasts of one species are mixed into the body of the other – what head shape will result? Will one type be dominant? Will an intermediate shape stabilize? Or will remodeling never cease because neither set of neoblasts is satisfied with the head shape? Despite the numerous high-resolution studies of molecular pathways guiding stem cell differentiation, the field has no models that make a prediction about this scenario. This is because we still lack a formalism for quantitatively modeling the process by which cellular collectives recognize deviations from normal and make the "stop" decision when the error between current morphology and target morphology is small enough (Harris, 2018; Pezzulo and Levin, 2015). A

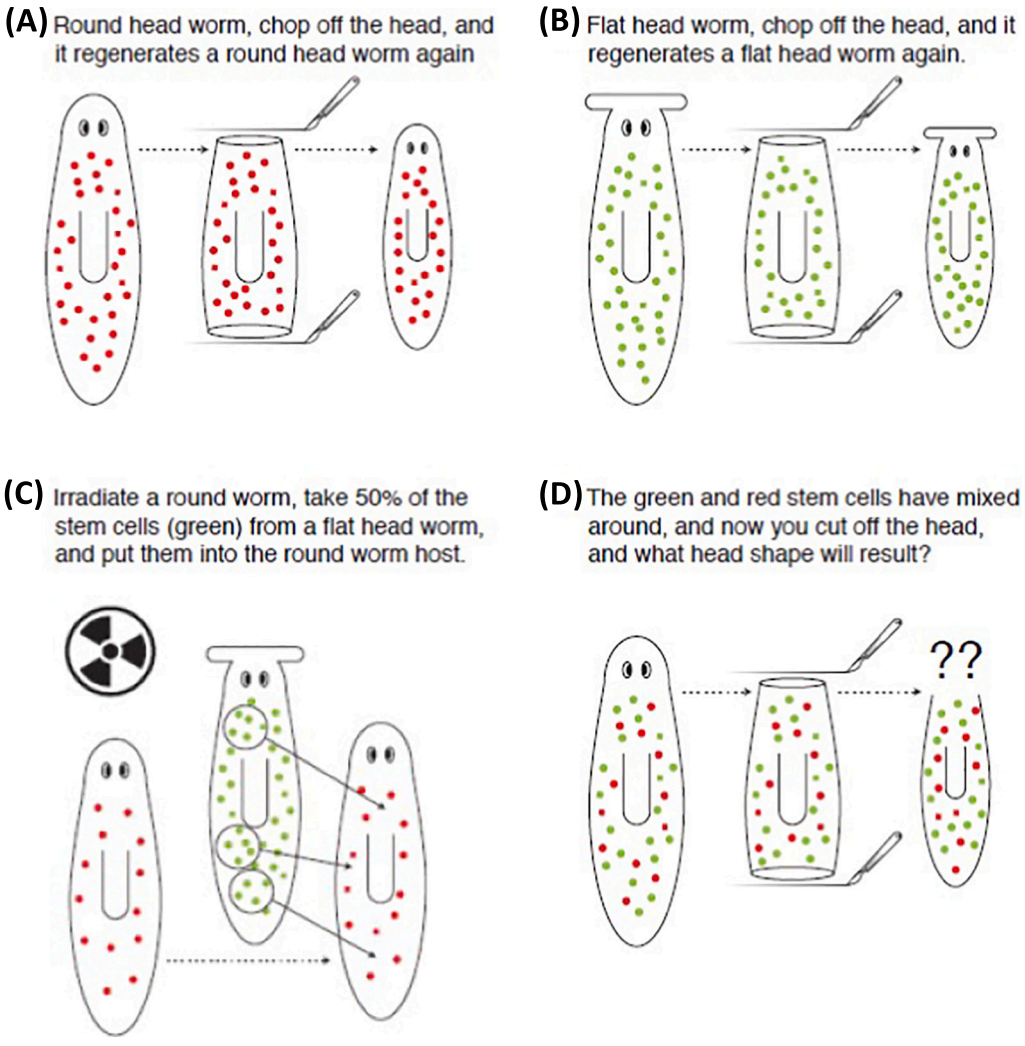

Fig. 1. What determines the anatomical setpoint of regenerative homeostasis? Planarian flatworms regenerate after amputation using a resident population of stem cells. This process reliably stops when the correct species-specific head shape is restored. The following thought experiment illustrates the profound knowledge gap in our understanding of the rules of morphogenesis despite ample information about genes required for neoblast differentiation. (**A**) Fragments from a round-head species result in a round-headed regenerate; (**B**) Fragments from a flat-head species result in flat-headed regenerates. (**C**) A chimera can be produced by irradiating one species (removing half of the stem cells) and receiving injections of donor neoblasts from a flat-head species. (**D**) When neoblasts from diverse species combine in the same body, and the head is amputated, what head shape will the regenerative process construct? Despite genomic and molecular-biological information on regeneration in multiple species, the field as yet has no models which make a prediction. This illustrates the importance of chimeras in identifying gaps in our understanding of the rules of emergent processes such as anatomical homeostasis and collective decision-making by cell groups.

critical aspect of this problem is that the remodeling and stop decisions are made based on large-scale anatomical criteria (length of limbs, distribution of craniofacial components, etc.) - at levels of organization higher than genomes or cells; thus, these are in effect actions of a swarm agent, consisting of numerous parts that work together toward a large-scale stable outcome. In addition to understanding the emergence of shape and anatomical homeostasis toward specific anatomies, such recombination experiments highlight important commonalities between morphogenesis and parallel problems in swarm cognition and group decision-making (Couzin, 2007; Pezzulo and Levin, 2015; Sole et al., 2016).

The ubiquitous reliability of stereotypical, default embryogenesis emphasizes a view of hardwired species-specific information within genomes and suggests that predictive control of form and function should be within reach. It tends to obscure surprising, novel phenomena and the deep opportunities for improved rational control, which are only observed when biological systems are confronted with truly novel circumstances or configurations (Ebrahimkhani and Levin, 2021; Kriegman et al., 2021). Here, we survey natural and experimental recombinations of living components (chimeras) at different levels of organization, as a powerful tool for driving a deeper understanding of interoperability, cooperativity, emergence, and control of collective behavior in morphogenesis. We review fascinating examples of transfer of material and information between diverse biological sources, highlighting the central concept of *chimerism* which can occur at the molecular, cellular, tissue, organ, and even organism and population scales (Box 1).

Many of these experiments were conducted at times when modern molecular biology, mathematical tools of emergence and complexity science, and computer modeling platforms, necessary for conclusive interpretations of the experimental outcomes, were still missing. Their value lies not in offering a complete answer but in showing what is possible; unconventional assays demonstrating interoperability and viability suggest new approaches for developmental biology and bioengineering and reveal new scenarios where our ability to predict outcomes is lacking. We hope to reinvigorate interest in chimerism so that modern approaches can be brought to bear to develop our understanding of the mapping of the properties of subunits toward large-scale outcomes. Furthermore, we discuss a number of chimeric systems that demonstrate functional rather than morphological chimerism. We propose a kind of symmetry that links many diverse biological phenomena, suggesting chimerism as an invariant that ties together a number of disparate approaches at different levels of organization that are not often discussed together in terms of their deep commonalities. This leads to new perspectives on classic problems such as cancer, aging, and genetic heterogeneity as instances of a more general phenomenon - chimerism. Finally, we discuss examples of chimeric techniques as a bridge between biology and related concepts in robotics and cognitive science: taking chimerism as a fundamental linking concept allows interesting new bridges to be forged between open problems in biology and other fields. We conclude with the implications of these data for biology, medicine and engineering, and suggestions for future work in this emerging interdisciplinary field.

2. Molecular chimeras

The ways in which system-level properties of living things are determined by the nature of their molecular constituents are illuminated by the results of recombination at the level of genetic material (Fig. 2A). The first experiments of this kind were natural ones: modern phylogenetic studies show that over billions of years of evolution, genetic material has been exchanged between unicellular prokaryotic organisms such as bacteria, archaea, and protozoa as well as multicellular eukaryotes (originated by the fusion of eubacteria and archaea) such as plants and animals. Thus, all life on the molecular level is profoundly/fundamentally chimeric, causing the “tree of life” metaphor to be replaced by the more accurate “web of life” (Doolittle, 2008).

The process by which distantly related species exchange genetic

Box 1
Definitions of terms used in literature on chimerism at multiple scales.

- Chimera - uni- or multicellular organism, consisting of molecular, cellular or tissue components from at least two different individuals of the same or distinct species.
- Mosaic - An organism developed from a single fertilized egg which at some point acquires cells with at least two different genotypes. This can happen through somatic mutations or Horizontal Gene Transfer (HGT), e.g. via viral infections.
- Homoplastic transplantation - transplantation of organic material such as germ layers, tissues or organs between two individuals of the same species resulting in chimeras.
- Heteroplastic transplantation - transplantation of organic material such as germ layers, tissues or organs between individuals of closely related species resulting in chimeras.
- Xenoplastic transplantation - transplantation of organic material such as germ layers, tissues or organs between individuals of distantly related species resulting in chimeras.
- Homochronic transplantation - transplantation of organic material such as germ layers, tissues or organs between individuals at the same developmental stage.
- Heterochronic transplantation - transplantation of organic material such as germ layers, tissues, or organs between individuals at different developmental stages
- Heteromorphosis/heteromorphic - organ or tissue that differs from its normal morphology as a result of disturbed embryonic development, regeneration or transplantation.
- Homeosis/homeotic mutation - morphological transformation of an organ into another one induced by mutations in homeotic genes or by transplantation into another organ field.
- Temporal (or phylogenetic) chimera: An organism that develops an ancestral or atavistic trait which has been lost but reactivated by mutation or artificially induced means. Organisms with atavistic traits can be regarded as a form of temporal (or phylogenetic) chimera, resulting in the combination of the current with the ancestral morphology.
- Spatial chimera: Foreign material or information molecules sourced not from another species but from a different region of the body.
- Parabiosis: The surgical unification of two organisms resulting in a shared physiological system. The organisms can belong to the same or different species. The unification of two organisms of different age is referred to as heterochronic parabiosis. The term parabiosis was originally used to describe populations of different species such as ants sharing a nest.
- Cell-autonomous vs. non-autonomous: Cell-autonomous traits are those in which the cellular phenotype is a function of that cell's genome; non-cell-autonomous effects are changes in cell behavior triggered by events in other cells and propagating laterally.

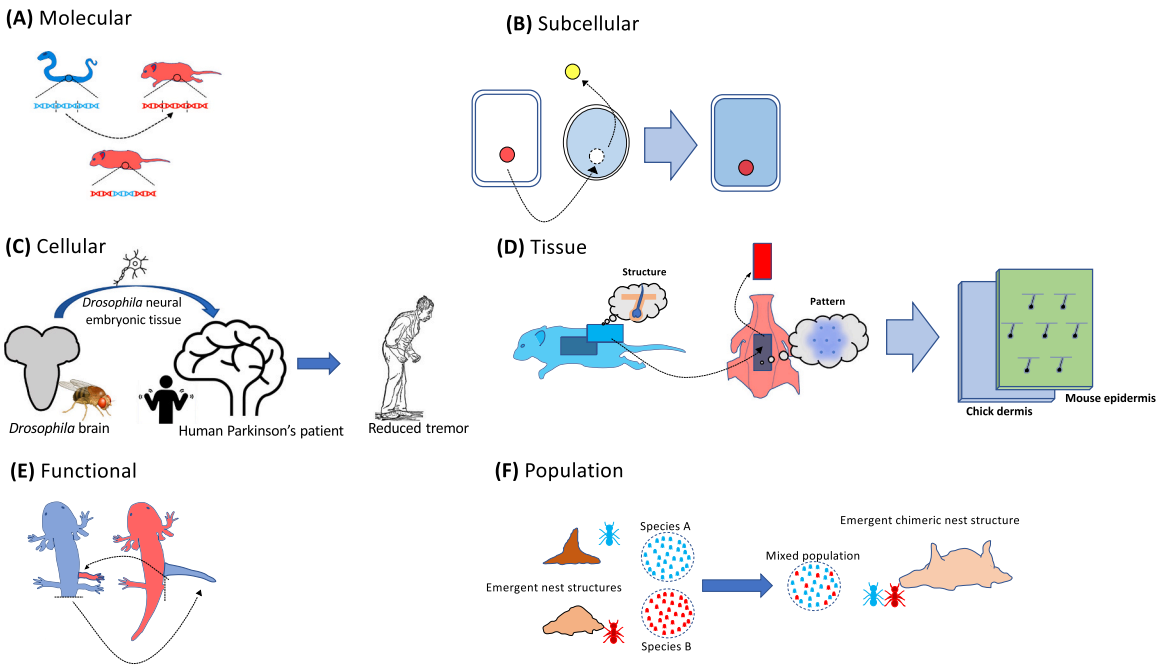

Fig. 2. Chimeras at different scales: subcellular, molecular, cellular, tissue, organ, and population.
Illustrations of chimeras created at different scales of organization. (**A**) Chimerism at the molecular level results from the transfer of genetic material from one organism into another, for example by creating transgenic mice exchanging the mouse limb enhancer element with the snake limb enhancer resulting in the loss of limbs. (**B**) At the subcellular level chimeras can be generated via transplanting the nucleus from one species into to the enucleated egg of another species. Subcellular chimeras can also be created by introducing any sort of functional cellular component such as cytoplasm or cell organelles. (**C**) Cellular chimeras can be made by introducing xenogenic cells into a new host organism. (**D**) Tissue level chimerism can be achieved for example by dermo-epidermal recombination, resulting in altered cutaneous structures. (**E**) Organ level functional chimeras are generated by the transplantation of entire functional units such as organs like liver and brain or appendages. (**F**) Population chimeras result from the mixing of different species in colonies, such as ant populations with distinct nest morphologies creating a new, emergent, chimeric nest structure.

material is referred to as horizontal gene transfer (HGT), and is mainly driven by conjugation between bacteria and across kingdoms from prokaryotes to eucaryotes (even between bacteria and mammalian cells) via a cellular bridge (McKay, 2002; Waters, 2001), viruses (viral infections), and events of endosymbiosis. For example, sequencing of the *Vibrio cholerae* genome, which consists of two circular chromosomes, indicates that the smaller chromosome carries a relatively high number of genes that do not seem to have originated in *Vibrio* itself. The smaller chromosome was likely taken up by *Vibrio's* ancestor via horizontal gene transfer, presumably providing *Vibrio* with an evolutionary advantage by carrying genes involved in energy metabolism and DNA repair; this thereby created a unicellular chimera carrying two chromosomes of distinct origin which together regulate the cell's biochemical processes (Heidelberg et al., 2000).

HGT, even between distantly related species, plays a critical role in evolving novel traits (Boto, 2014), and has been proposed to be a key driving force in speciation events. For instance, animals such as the ascidian Tunicates, which belong to the urochordates, are among the few metazoans that can produce cellulose via a cellulose synthase-like gene, most likely acquired via HGT from Actinobacteria. This enables Tunicates to synthesize cellulose and integrate it into an extracellular matrix external to the epidermis, serving as a protective layer (Hirose et al., 2011; Matthysse et al., 2004; Sasakura et al., 2016). Genes transferred between bacteria and animals provide especially interesting examples of molecular components that can be exploited in different ways by systems with radically different architectures (Dunning Hotopp, 2011).

The classic form of multicellular molecular chimeras results from combining gametes belonging to different species. Cross-breeding of animals and plants has been observed and performed by humans in agricultural practices for several millennia (e.g., mules). It is estimated that around 10% of animals and 25% of plants hybridize naturally with at least one other species; this process is believed to play an important role in speciation (Mallet, 2005, 2007). The increased fitness of some interspecies hybrids has led to the concept of hybrid vigor (Arnold and Hodges, 1995; Baranwal et al., 2012). It is hypothesized that hybrids are able to combine the main advantages of sexual reproduction (genetic diversity) and clonal reproduction (increased levels of regenerative capabilities) (Bullini, 1994). Consistent with this, the unisexual *Ambystoma* indeed possess an elevated capacity to regenerate lost body parts in comparison to their diploid sexual relatives (Saccucci et al., 2016).

Such assays emphasize our lack of fundamental knowledge via the difficulty of quantitatively predicting in advance the structural features of the hybrid (and deriving those predictions from anatomical properties of the parents). The unisexual all-female salamanders of the genus *Ambystoma*, believed to be the result of a natural hybridization event some 3.9 million years ago, reproduce via a process called kleptogenesis (Bogart et al., 2009). Despite their unisexual mode of reproduction, females need sperm to induce development of their oocytes and therefore have to "steal" the sperm from males of other bi-sexual salamander species. Individuals have been found with several levels of ploidy ranging from diploid to pentaploid integrating genomes from at least five distinct species due to their ability to switch sperm donor species, resulting in more than 20 different nuclear genomic combinations (Bogart et al., 2009). The morphology of the animals is determined by the number and origin of the inherited chromosome sets, resulting in differences in overall size and allometric proportions between body and appendages as well as color patterning.

Remarkably, while amphibians with different ploidies have very different sizes of certain cells, the animals' overall size remains normal and morphogenetic process adjusts to correctly sized kidney tubules (Fankhauser, 1945a, 1945b). This includes using cell:cell interactions between ~8 cells (normal ploidy and small cells) to make tubules, vs. using cytoskeletal control to force one cell to bend around itself leaving

the correctly-sized lumen in the middle, when cells are made to be very large. The ability of cell collectives to maintain the same large-scale target morphology despite radical changes in cell-level properties points to fascinating opportunities for future work to identify how diverse lower-level molecular mechanisms are activated in a context-sensitive manner to fulfill higher-level structural specifications. This degree of plasticity has not been achieved in robotics, where the structure and function of artificial machines is extremely sensitive to precise scale parameters of all of their parts. It also raises interesting questions about aspects of evolution that select for plasticity and adaptability to new conditions (such as changes in cell size) vs. short-term optimization of mechanisms to work with a specific extant cell size.

Interestingly, even commonplace sexual reproduction can be seen as a form of chimerism, in which DNA from two different morphotypes of a given species (male and female anatomical forms, which can be quite different) co-exist in the same zygote and drive subsequent morphogenesis. Paternal and maternal imprinting of DNA from parents ensure that many kinds of zygotes are in fact significantly chimeric with respect to genetic information. This is clearly seen when contrasted with the baseline, more "genetically pure" case of parthenogenetic animals. For example, invertebrates such as females of Daphnia (Decaestecker et al., 2009) and nematodes (Triantaphyllou and Hirschmann, 1964), as well as some vertebrates (e.g. fish (Chapman et al., 2008), amphibians and reptiles (Booth and Schuett, 2016) and others) can produce truly isogenic offspring in specific circumstances. In comparison, the introduction of a male, with a different genome, and the integration of sex chromosome signals in the embryo to give rise to one of two possible (male or female) body forms, is a kind of chimerism. The difficulties in rationally predicting specific aspects of morphology from those of two parents (e.g., facial features for humans, or plant morphologies) represent a ubiquitous form of the inverse problem of emergent morphogenesis, which has been realized by farmers and animal breeders since long before formal biological science.

Horizontal gene transfer has been performed experimentally, creating a chimeric chromosome by combining two genomes in one cell. Using the newly developed megacloning technique, it was possible to clone and insert the entire 3.5-megabase genome of the bacterium *Synechocystis* into the 4.2-megabase *Bacillus subtilis* resulting in a chimeric 7.7-megabase genome. The chimera exhibited no obvious phenotypic differences compared to the host organism, but it is not known whether other important differences (e.g., in response to novel situations, evolvability, or robustness) may remain to be discovered (Itaya et al., 2005). It was shown, via a newly developed technique called genome transplantation, that it is possible to replace the entire *Mycoplasma capricolum* genome with the genome of *Mycoplasma mycoides*. The successful replacement of the genomes was confirmed via genotype (PCR) and phenotype analysis (proteomic) (Lartigue et al., 2007). In the laboratory setting, moving genes from one organism to another is a very common method used to probe the contributions of DNA information to form and function, although extensive study in novel environments will be necessary to determine what aspects are and are not converted by this procedure, given that important information also exists in cytoskeletal and other cellular components (Fields and Levin, 2017).

Cross-species transfer of DNA was used as a tool for understanding the evolution of morphogenetic control mechanisms. For example, Pax-6 is a highly conserved master control gene for metazoan eye morphogenesis with homologous genes found in insects and vertebrates, including mice and humans. Its loss-of-function mutations lead to reduced or completely lost eye structures. Although mammals and insects diverged more than 500 million years ago, mouse Pax-6 can still induce eye formation in *Drosophila* with structural morphology typical for the host (Gehring and Ikeo, 1999; Halder et al., 1995), illustrating the versatile context-sensitive nature of morphogenetic modules, whose internal component mechanisms can change during evolution while maintaining a conserved trigger.

Using the molecular chimerism approach, it was even possible to show how enhancer elements shape social hierarchies in mammals. PAS1 (placental-accelerated sequence), which is not highly conserved within placental and non-placental clades, acts as an enhancer for the transcription factor Lhx2, a gene involved in brain development and social stratification in mice. While male PAS1-deletion mice cannot establish proper social hierarchies, transgenic knock-in mice carrying ortholog sequences of PAS1 from non-amniotic (wallaby and chicken) animals showed different levels of social dominance depending on their genotype, without compromising other aspects of development and behavior (Wang et al., 2020). These examples illustrate how creation of animals with chimeric genetic information can reveal important genotype:phenotype relationships spanning morphology and behavior.

On the level of the gene, chimeric fusion genes (CFG), formed by a process called exon shuffling (Gilbert, 1978), results in the merging of two individual genes; this has been proposed to significantly contribute to the evolution of new genes coding for proteins with novel structures and functions (Jones and Begun, 2005). For example, synthetic fusion genes have been generated to study the function of homeotic genes and their role in establishing the body plan. In *Drosophila*, mutations in homeotic genes lead to the transformation and replacement of one body structure with another (McGinnis et al., 1984). Expression of the master control gene Antennapedia (Antp) specifies the second thoracic segment, and ectopic overexpression of Antp leads to the homeotic transformation of antennae into second legs (Schneuwly et al., 1987). This was achieved by creating an artificial fusion protein Antp fused to the inducible heat-shock promotor hsp70, which was introduced into the germline via P-element mediated germline transformation (Gibson and Gehring, 1988; Schneuwly et al., 1987). This illustrates the notion of a spatial chimera, where the foreign material or information molecules were sourced not from another species but from a different region of the body. On the level of chromosomes, genetic expression chimeras can occur naturally in female mammals, by sex-chromosome inactivation which is the transcriptional silencing of one of the two copies of the X chromosomes resulting in cellular mosaicism. In calico cats, for instance, this results in a patched color pattern of the fur (Gartler and Goldman, 2001; Panning, 2008), illustrating a natural and ubiquitous chimerism.

2.1. Cancer – a pathological example of somatic chimerism

Mutations are often found in tumors, which exhibit increased genomic instability (Negrini et al., 2010), elevated mutation rates, and epigenetic changes (Chen et al., 1998). The stochastic nature of mutations results in the development of intra- and intertumor heterogeneity with altered levels of gene expression (Burrell et al., 2013; Swanton, 2012). Due to these changes to the host genome, cancer results in high levels of molecular chimerism even within a single solid tumor. Affected cells lose their ability to properly cooperate with their environment, and de-couple from the information processing of cellular collectives that normally keep cells working toward large-scale morphogenetic goals (Chernet and Levin, 2013; Moore et al., 2017). In a sense, cancer cells free themselves by gaining autonomy from the constraints of their collective and regressing to the transcriptional and behavioral properties of unicellular ancestors (Levin, 2019b, 2021; Zhou et al., 2018). Waddington (1935) and Needham (1936) described this process as a "morphological escape" from the controlling influence of the individuation field of the host organism (Needham, 1936; Seilern-Aspang and Kratochwil, 1962; Waddington, 1935). This newly acquired individuality can reach an extent where cancer cells can even leave their hosts, as occurs in the case of facial tumor disease, a transmissible cancer affecting populations of Tasmanian devils with a mortality rate of almost 100%. Since the disease is spread as an allograft through biting during social interactions, it is able to continue to exist even though its original host has ceased to exist long before (Patton et al., 2020), using parasitic chimerism as a strategy to perpetuate the cellular lineage.

3. Subcellular and organelle chimeras

At the next level of organization above the molecular, we consider mixing of larger subcellular components, such as in "cybrids", or fusions between cells and cytoplasts (Bacman et al., 2020; Narbonne and Gurdon, 2012; Narbonne et al., 2012; Narbonne et al., 2011) to examine the roles of nuclei and mitochondria (Fig. 2B). The chimeric approach was used initially to address the question formulated by Boveri in 1889 (Boveri, 1889; Boveri, 1893; Hadorn, 1937): are species-specific traits determined by the nucleus or the cytoplasm?

To study the interplay between, and the respective roles of, the nucleus and the cytoplasm, amoebae, which are relatively large uninucleated eukaryotic cells without a rigid shape, were used (Lorch and Danielli, 1953b). Enucleation, the removal of the nucleus, results in disturbed movement and digestion. Remarkably, enucleated amoebae can survive up to 20 days and even show periods of apparently normal movement for several days (Lorch and Danielli, 1953a). Similarly, fragments of human somatic cells can also live without a nucleus for some time, exhibiting behavior (such as galvanotaxis) that is different from that of their nucleated counterparts (Sun et al., 2013). Enucleated cells can be reactivated via homo- or heterologous nuclear transfer facilitating studies of organelle-level chimerism. After heterotransfer of the nucleus, the host cell's cytoplasm mainly determines cell shape during movement (which is species-specific), locomotion pattern, and the transplanted nucleus's size, according to the host's specific nucleus size (Lorch and Danielli, 1953a; Lorch and Danielli, 1953b).

A truly outstanding model system in probing the contributions to large-scale shape of the nucleus and the cytoplasm in morphogenesis is the unicellular giant *Acetabularia.* This organism possess a complex morphology and the ability to live, grow, and regenerate without a nucleus for up to two months (Hämmerling, 1932). Grafting experiments have shown that when the nucleus-containing rhizoid is amputated (Fig. 3), followed by a cap amputation a few days later, the cap can regenerate even without a nucleus (Hämmerling, 1943b). Interspecific grafting of *Acetabularia crenulate* rhizoid onto the stalk of *A. mediterranea* with a developed cap blastema results in a cap of intermediate morphological phenotype, meaning that the shape of the cap will be a hybrid combination of the two species. Future work must address the mechanisms by which morphogenetic substances (e.g., mRNAs) from the original nucleus mix with newly synthesized morphogens from the transplanted nucleus, and ways in which non-chemical morphogenetic field information can combine (Briere and Goodwin, 1990; Chaplain and Sleeman, 1990; Goodwin and Pateromichelakis, 1979). If the cap is subsequently amputated a second time, the second regenerated cap develops the morphology specific for *A. crenulata* (Hämmerling, 1932; Hämmerling, 1934, 1943a, 1943b; Hämmerling, 1953; Maschlanka, 1943; Werz and Hämmerling, 1961). This experiment illustrates that by mixing subcellular components, which are located in different parts of the cell, it is not only possible to transform one species into another, but also to create hybrids occupying regions of morphospace in between the two original phenotypes and identifies large-scale features that can be blended.

Nuclear transfer experiments have been conducted in higher organisms as well. For instance, transfer of somatic endodermal nuclei into enucleated axolotl eggs was used to test whether somatic nuclei undergo genetic changes during embryonic development and whether they are able to keep their ability to induce normal development after nuclear transfer. It was shown that most nuclei, regardless of their origin, are able to induce cleavage, but usually do not develop beyond the blastula or gastrula stages. These limitations suggest a search for the limits of interoperability, to determine what exactly goes wrong in these cases that prevents the system from maintaining life (even if not correct morphology). Nuclear transfer between amphibians, even if they are distantly related, such as Urodeles and Anurans, will result in normally cleaved blastula (Gurdon, 1986). Heterotypic transplantations of nuclei between two subspecies of *Xenopus laevis* have been shown to develop viable adult frogs with phenotypes characteristic of the nuclei donor. Although rare, some individuals showed an intermediate phenotype for some traits (Gurdon, 1961), suggesting that models of consequences of chimeric experiments need to include a stochastic component.

Another example of the contribution of the cytoplasm to traits was provided using the technique of egg constriction. Hadorn fertilized *palmatus* eggs with *cristatus* sperm resulting in haploid hybrid merogones (with genetic contribution only from the sperm). Since these embryos

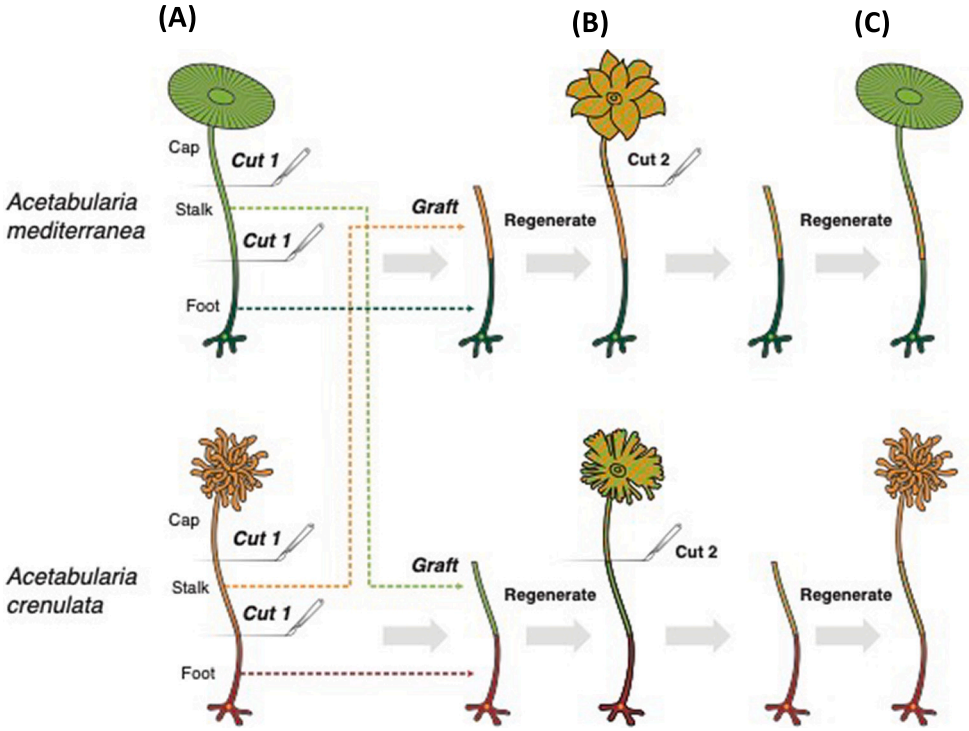

Fig. 3. Subcellular chimeras in algal grafts. *Acetabularia* are giant unicellular algae with one nucleus located in the foot. The figure illustrates several amputation and transplantation experiments that were performed using different species of *Acetabularia* with distinct cap shapes (**A**). Amputation of the cap (cut 1) and subsequent grafting of the stalk onto the nucleus containing foot from *A. mediterranea* to *A. crenulata* and vice versa will result in the regeneration of a cap with a chimeric morphology between the two species (**B**). A second amputation of the cap (cut 2) will result in the regeneration of a cap with a morphology according to species specific morphology of the nucleus carrying foot (**C**).

don't live long enough to develop species-specific traits that would distinguish them, Hadorn transplanted presumptive skin ectoderm at early gastrula stage from the merogones onto wild type hosts (alpine newt), which allowed for the subsequent development beyond metamorphosis into adult stage. The skin of the haploid merogon resembled the morphology of the egg/cytoplasm-donating species (bumpy) in contrast to the sperm-donating species whose skin was smooth (Chen; Hadorn, 1936, 1937). However, cross-genus nuclear transplantation of the common carp nucleus into the enucleated goldfish egg resulted in quantities of vertebrae more similar to that of goldfish (28–30) than the carp (32–36), proving that the cytoplasm can contribute to developmental outcomes (Sun et al., 2005; Sun and Zhu, 2014).

Some of the most remarkable examples of inter-species subcellular chimerism crosses Kingdoms. Across phyla from protists to multicellular live forms, organisms have used the strategy of symbiogenesis or endosymbiosis for acquiring new biochemical capabilities by taking up parts or entire organisms and integrating them into their own bodies (Margulis, 2004; Nowack and Melkonian, 2010; O'Malley, 2015). Two strategies to achieve this, used by animals and plants, are termed kleptoplasty (the "stealing" of organelles from another organism) (Krause, 2015; Van Steenkiste et al., 2019) and karyoklepty (the stealing of another species' nucleus) (Johnson et al., 2007; Onuma and Horiguchi, 2015). A remarkable example of kleptoplasty resulting from animal-plant chimerism is found in the sea slug *Elysia chlorotica*. These slugs have the ability to perform photosynthesis, which is most unusual in animals. They accomplish this by taking up chloroplasts from their algal food, storing them in their bodies as so-called kleptoplasts, and using the products of the resulting photosynthesis as an energy source (Rumpho et al., 2011). Since chloroplasts have lost many of their genes necessary for photosynthesis via HGT to their original algal hosts' nucleus, it is surprising that even when the slugs do not consume any algae, photosynthesis is maintained for months. It has been shown that genes coding for proteins necessary for photosynthesis have been horizontally transferred to the slug genome (Rumpho et al., 2011; Rumpho et al., 2008). It is striking that *E. chlorotica* even developed the morphology of a leaf.

Because chloroplasts have transferred a significant part of their genome into the nucleus of their hosts, they depend on the external supply of gene products from the host environment in order to stay functional. *Myrionecta rubra*, a marine photosynthetic ciliate, preys on the cryptomonad *Geminigera cryophila* and steals its chloroplasts. To avoid a rapid decline in photosynthetic activity of the chloroplasts, it also commits kleptoplasty by accumulating the foreign nuclei in its body. Even though the captured nuclei can no longer divide they stay transcriptionally active in the host's cytoplasm, supplying the chloroplasts with the necessary gene products for photosynthesis (Johnson et al., 2007; Onuma and Horiguchi, 2015).

Chimerism between plants and animals has even been found in vertebrates. The spotted salamander *Ambystoma maculatum* embryo develops in an egg capsule inhabited by the unicellular green algae *Oophila amblystomatis*. Living in ectosymbiotic mutualism, the embryo supplies the algae with nitrogenous waste products. In return, the embryo profits from elevated oxygen levels resulting in decreased embryonic mortality (Gilbert, 1944). Recently it was discovered that this relationship is even closer, with algal cells using oviductal transmission to invade the embryonic cells and promote the transfer of photosynthate from the symbiont to the host. Taken together, subcellular chimera experiments suggest that subcellular components such as nuclei and organelles even of evolutionary distant origin are able to function in a foreign cytoplasm, and emphasize the role of the cytoplasm with respect to guiding morphogenetic outcomes.

In addition to spatial structure, chimeras can also be used to test temporal properties of morphogenesis. Transplanting nuclei from Tilapia to enucleated eggs of Loach resulted in a developmental rate similar to Loach, which is much faster than Tilapia egg development. Furthermore, larvae with transplanted nuclei show no development of external gills and oral barb rudiments, while Loach larva at a similar developmental stage possesses these traits (Yan et al., 2004), revealing that morphogenesis results from the interplay of genetic and epigenetic factors carried by the cytoplasm.

4. Cellular chimeras

Another kind of chimera is formed by combining cells of diverse origins and properties (Fig. 2**C**). These chimeras have been especially useful in studying cell-extrinsic vs. cell-intrinsic (cell-autonomous vs. non-autonomous) regulatory mechanisms of development.

For example, in addition to its role in eye morphogenesis, Pax-6 is involved in the development of the brain. Intrinsic Pax-6 expression is required by thalamic progenitor cells for normal development of thalamic neurons (Clegg et al., 2015). Homozygous mouse Pax6-null mutants show mispatterning of thalamic progenitors and fail to develop proper axonal projections to the cortex, resulting in neonatal death. To overcome this obstacle, aggregation chimeras have been created consisting of Pax-$6^{-/-}$ and wild type (WT) Pax-$6^{+/+}$ cells. The WT cells prevented early death and allowed Pax-$6^{-/-}$ cells to develop projections to the cortex, showing that despite cell-intrinsic lack of Pax-6 expression, those cells still have the ability to make regular axonal projections (Clegg et al., 2015; Swanson and Goldowitz, 2011; Yeung et al., 2016).

The range of compatible cell complements is wider than might be expected, and numerous variations of xenoplastic transplantation experiments involving distantly related taxa have been conducted for studying neural cell differentiation. For example, adult rat hippocampal progenitor cells were transplanted into embryonic zebrafish (Sandquist et al., 2018) and *Drosophila* nerve cells were transplanted into amphibians (Korochkin et al., 1991; Saveliev et al., 1989; Saveliev et al., 1990); and even into human Parkinson patients, resulting in reduced tremor for some patients (Saveliev et al., 1997). The transplanted neurons integrated and differentiated, forming various neural structures and establishing axonal connections with recipient neural cells and in some cases resulting in altered behavior reflecting the behavior of the donor (Alexandrova and Polezhaev, 1984; Andres and Rossler, 1977; Giersberg, 1935). The relevance of this work is not its degree of therapeutic efficacy, but rather to reveal the great degree of interoperability of biological systems across taxa, which enables future work to study emergent properties of neural circuits composed of very diverse components.

Interestingly, xenogenic influences were observed regarding developmental timing, inducing accelerated development in amphibians (Korochkin et al., 1991), as well as in human-mouse pluripotent stem cell co-cultures in a dose-dependent manner (Brown et al., 2020). The underlying mechanisms regulating developmental rate are an intense subject of current study (Ebisuya and Briscoe, 2018), revealing both intrinsic and extrinsic controls. Furthermore, the xenoplastic transplantation of cells between cold- and warm-blooded animals reveals that many cells can have a broader range of temperatures where they can remain viable.

Some of the most informative examples of cell-level chimeras were constructed to study skin patterning (Chen and Chuong, 2012). To study how genotypic and phenotypic properties of embryonic skin cells relate to their morphogenetic patterns, Garber used aggregates consisting of mixed cell suspensions of skin cells obtained from chicken and mouse embryos at different ages, looking at the formation of feathers using chick cells and hair formation using mouse cells (Garber et al., 1968). Aggregates were transplanted on the chorioallantois of chicken embryos to ensure further morphogenesis. While aggregates consisting of cells from one species developed the corresponding histological structures such as feathers (chicken) or hair (mouse), mixed aggregates showed three types of developmental outcomes depending on the age of the embryonic cells used. In aggregates of skin cells from older 14–15-day-old mouse embryos and younger 8-day-old chicken embryos, mouse cells suppressed feather formation, and only hair formed.

Morphogenesis resulted in developing histological structures characteristic of both species such as hair and feathers when 13-day old mouse skin cells and 8-day-old chicken embryos were used. Cells from one species contributed to the morphogenesis of histological structures of the other species. Mouse cells were found to contribute to the formation of feathers, which was surprising to the authors since the formation of feathers is not part of the endogenous morphogenetic repertoire of mammalian cells. The authors concluded that "These mouse skin cells function in a manner which either is not explicitly programmed in their genome or is present but never expressed in the usual course of development." (Garber et al., 1968; Garber and Moscona, 1964)

Interspecies chimeras have also been used as a tool for cell complementation studies by knocking out a specific host cell line and thereby creating an open niche for xenogenic donor cells to occupy. For example, a mouse-human chimeric platform was used to test human neural crest cells (hNCCs) derived from pluripotent cells for their ability to integrate into the mouse organism and contribute to coat pigmentation. Using a mutant mouse line lacking melanoblasts to avoid competition with host NCCs, pluripotent human NCCs were injected in utero into mouse embryos. Human NCCs were able to complement missing melanoblasts resulting in chimeric mice with pigmented hair. In this regard, NCCs are particularly interesting, showing that human NCCs can detect and interpret the host environment's xenogenic cues crucial for proper NCC migration and functional integration into the host embryo (Cohen et al., 2016).

Chimeras between cells with different internal clocks have illuminated the embryogenesis of nervous systems, somitogenesis, stem cell differentiation, and other developmental processes in which timekeeping is an essential aspect of morphogenesis (Ebisuya and Briscoe, 2018). Heteroplastic transplantation of blastomeres between zebrafish as donor and medaka as host at the blastula stage was used to create interspecies chimeras addressing the problem of developmental timing and intrinsic vs. extrinsic factors of development in the context of retinal neurogenesis. The grafting resulted in the growth of an ectopic retina, which followed the zebrafish donor cells' species-specific developmental timing. The transplant was able to use the cues of its surrounding host environment for navigating axonal outgrowth. Furthermore, the zebrafish retina had the potency to induce lens formation by the host tissue, resulting in chimeric eyes (Fuhrmann et al., 2020).

5. Tissue-level chimeras

The next level of organization to consider exists at the level of tissues. Work on tissue chimeras, especially in plants, has a long and rich history with early references on plant grafting in the Hebrew bible and in Chinese literature more than 2000 years ago (Mudge et al., 2009). The oldest evidence on plant grafting was found in Sumerian cuneiform fragments from Mesopotamia, where the technique was probably discovered 3800 years ago (Harris et al., 2002; Mudge et al., 2009); it is thought that Sumerians may have grafted salt intolerant grape shoots onto salt-tolerant wild grape rootstocks to increase crop yield.

Grafting in plants does occur quite frequently and naturally, when shoots or roots of the same or different plants grow in close proximity which can result in the fusion of the two structures (Mudge et al., 2009). Three different graft combinations can occur: i. self-grafts, where structures of the same plant fuse, ii. intraspecific grafts between structures of two different plants of the same species, and iii. Interspecific grafts between different plant species (Bormann and Graham, 1966). The cells of the grafts develop apoplastic and symplastic connections via plasmodesmata resulting in a graft interface allowing for the exchange of cytoplasmic content (Coetzee and Fineran, 1989; Tiedemann, 1989). In 1972 it was concluded that natural root grafting facilitates cooperativity between trees allowing the exchange/transfer of nutrients such as carbohydrates, water and minerals to neighboring trees in need (and thereby increasing resilience) (Eis, 1972). In his book "The Variation of Animals and Plants under Domestication" Darwin coined the terms "graft hybrids" and "graft hybridization" claiming that grafted parts exchange properties that are heritable, resulting in plants different from the donors (Darwin, 1897; Wu et al., 2013b). Even though Darwin's ideas were met with skepticism at the time, recent advances shed light on the underlying mechanisms for exchanging and modifying genetic material between grafted plants. Research indicates that the transfer of RNA and DNA fragments, of entire plastid genomes, or alterations in DNA methylation, all can induce heritable changes in graft hybrids (Liu et al., 2010; Stegemann and Bock, 2009; Thyssen et al., 2012; Wu et al., 2013a). Also, chimerism at the tissue level can automatically induce subcellular chimerism, as tissue grafting can lead entire mitochondria to be transferred horizontally via tunneling nanotubes, extracellular vesicles, and cellular fusion (Torralba et al., 2016).

The literature on animal tissue chimeras is extensive, with the earliest and most famous experiments conducted by Hans Spemann and Hilde Mangold on the transplantation of organisers and various other tissue types, studying their inductive capabilities and potencies using frogs and salamanders as model systems (Mangold, 1929; Spemann, 1921, 1924; Spemann and Mangold, 1924; Spemann and Schotté, 1932). Using *Triton taeniatus* embryos at early gastrula stages, Spemann tested the developmental potencies of the ectoderm. Through the homeoplastic exchange of the presumptive epidermis and presumptive neural plate, he showed that the transplanted parts were able to develop according to their new positions (Spemann, 1918). The same was true for heteroplastic transplantations between *Triton taeniatus* and *cristatus* (Spemann, 1921),where differences in both species' pigmentation allowed for later developmental analysis of the transplanted tissue (Harrison, 1898, 1903). Spemann and Mangold have also shown that heteroplastic transplantation of a fragment of the blastopore lip (organizer) behaves very differently. Instead of integrating with the surrounding tissue, it keeps its identity and induces a secondary embryo with a neural tube, notochord, and somites formed by the host tissue (Spemann, 1918; Spemann and Mangold, 1924). Xenoplastic transplantation of fish organizer from *Danio rerio* into amphibian Triturus can induce neural plate formation of the proper host size even though the grafted organizer size is significantly smaller than the host organizer (Oppenheimer, 1936). Approaches like this are essential to our understanding of how borders are set up for specific structures during morphogenesis, and of the information signals which bind neighboring cells into working toward one or another component of the overall target morphology.

Mangold used xenoplastic transplantations to study the development of the balancer, using *Triton*, which develops adhesive threads during early larval stages, and Axolotl, which do not develop these structures. Transplantation of Axolotl neural plate tissue into the flank or blastocoel of *Triton* embryos at the neurula stage induced ectopic adhesive threads; in contrast, transplantation of *Triton* neural plate into Axolotl neurula would not induce any adhesive thread development, illustrating a technique for determining which tissues are responsible for specific anatomical features.

In a second set of experiments, he showed that the epidermis is responsible for the development of the balancer. Transplantation of presumptive epidermis from Triton embryos into the future face area of the Axolotl embryos resulted in the formation of adhesive threads. Conversely, the transplantation of Axolotl presumptive epidermis results only in the development of structures that are familiar to the Axolotl epidermis, such as eye lenses and gills (Mangold, 1931). These experiments illustrate the interplay between a tissue with an inductive capacity and the induced tissue itself, which needs to possess the potency to develop a given structure under the influence of the inducer.

Along similar lines, Sengel and Dhouailly performed a series of dermo-epidermal recombination experiments between reptiles, birds, and mammals, studying the development of the corresponding cutaneous structures of scales, feathers, and hair (Fig. 2**D**). Dermo-epidermal recombination through xenoplastic grafting of the epidermis between different species has shown that the induction and development of cutaneous structures such as scales, feathers, and hair are a two-step

process. In the first step, the dermis exerts a non-class specific induction signal inducing the differentiation of epidermal placodes (precursor of the specific structure such as scale, hair), which means that, e.g., mouse dermis can induce the development of feather formation and, conversely, chicken dermis can induce the formation of hair papillae. A second dermal induction is required for proper development, which is class-specific and cannot be transmitted across species. As a result, the development of cutaneous structures in recombinants gets arrested at an early stage (Dhouailly, 1975; Sengel, 2003; Sengel and Dhouailly, 1977).

An example of developmental control via tissue-level chimerism is observed with respect to intercalary growth. In amphibian, insect, and crustacean limbs, rotation of grafted tissue induces the growth of ectopic structures at the boundary (French, 1980; Meinhardt, 1983; Mittenthal and Nuelle, 1988; Muneoka and Murad, 1987). This is due to discontinuities in the axial coordinates of tissue: sites at which neighboring cells possess non-adjacent positional information will undergo significant morphogenetic activity to resolve the discrepancy and fill in (intercalate) the missing positional values via growth and remodeling. Such experiments in vertebrate limbs and planaria (Agata et al., 2003; Saito et al., 2003)) reveal that informational chimerism (with respect to positional information) is detected by tissue and used as an input to morphogenetic decision-making to coordinate growth and repair. Remarkably, the same phenomenon is observed in single cells (such as ciliates, (Nelsen and Frankel, 1989; Shi et al., 1991)), suggesting that this design principle is re-used at different levels of organization, from subcellular to tissue-level positional information (Agata et al., 2003; Saito et al., 2003). Another example of tissue-level chimerism exerting effects on patterning concerns malignant neoplasms (disordered growth), in the absence of DNA damage or oncogenic mutations, induced by the in vivo juxtaposition of tissues that are not normally adjacent, such as testis and spleen or ovary and spleen (Biskind and Biskind, 1945; Biskind and Biskind, 1944).

6. Organ-level chimeras: from structure to function

Transplantation can be used to create chimeric bodies consisting of a mix of organs of diverse origins, which is especially helpful to understand not only the structural but also the functional aspects of the part/whole relationship (Fig. 2**E**). For example, transplantation of the eye cup has been used to study induction, as transplantation of additional eye cups can induce ectopic lenses (Twitty and Elliott, 1934). This reveals the modularity of development and highlights the control points that can be used in the context of a wild-type genome to modulate anatomy. Trying to understand the underlying mechanisms of organ scaling and organ intrinsic and extrinsic factors involved in size regulation, classical workers used the technique of grafting entire functional units such as limbs, eyes (Harrison, 1929; Twitty and Elliott, 1934), heart (Copenhaver, 1927, 1930, 1939), and spinal cord between the two salamander species *Ambystoma tigrinum* (larger and faster-growing) and *Ambystoma punctatum* (smaller and slower growing). In his classic paper "Some unexpected results of the heteroplastic transplantation of limbs", Harrison observed that forelimbs from *A. tigrinum* transplanted onto the forelimb position of *A. punctatum* after a short period of slow growth not only catch up and grow to the size specific for the donor but significantly exceed it in size. On the other hand, transplantation of *A. punctatum* forelimbs onto *A. tigrinum* results in even smaller limbs than the original donor limb size (Harrison, 1924). These experiments showed that both limbs are able to grow and develop in the new host environment and suggest that limb size is regulated by a combination of organ-intrinsic properties and extrinsic factors. One possibility is that *A. tigrinum* limbs on *A. punctatum* bodies have a competitive advantage (or higher sensitivity) for those external resources such as nutrients and growth factors (growth hormones) provided by the host body (such competition within the body is reviewed in (Gawne et al., 2020)).

Transplantation of eyes between the two species results in eyes very similar to the size of the donor species, showing little effect of the new environment on eye growth (Twitty and Schwind, 1931). Chimeric composite eyes generated by exchanging the lens of one species for the other's lens revealed a coordinative organ internal scaling relationship where lens size regulates the size of the developing retina (Harrison, 1929). From a functional perspective, this makes sense since the eye's proper function strongly depends on the internal proportions of the lens and retina. On the other hand, transplantation of the heart and spinal cord resulted first in the transplanted organs' growth according to their intrinsic genetic program, showing adaptation to the new host environment (Copenhaver, 1939). Again, from a functional perspective, it is essential that vital organs such as the heart have the proper size in relation to the body, and recent molecular experiments have shown bioelectric properties (Beane et al., 2013; Daane et al., 2018; Lanni et al., 2019; Perathoner et al., 2014) and biochemical signals (Vollmer et al., 2017a; Yamamoto and Mak, 2017) to be mechanisms by which organ primordia coordinate size control. Different organs can have different mechanisms of size regulation. An example of organ intrinsic size regulation was demonstrated by the transplantation of multiple fetal thymus glands into a developing mouse embryo resulting in glands of regular size (Metcalf, 1963). On the other hand, transplantation of multiple fetal spleens shows a coordinated growth of all spleens resulting in smaller individual organs but with total mass similar to one normal spleen (Metcalf, 1963; Vollmer et al., 2017b).

Another rather spectacular finding by Farinella-Ferruzza resulted from xenoplastic transplantation of the tail bud from Axolotl (urodele) onto Anuran embryos during the neural stage. The transplanted tail bud first develops into an anatomically normal and functional tail. When the tail bud is transplanted into the host's limb field, it transforms during metamorphosis into a limb with a variable number of digits (Farinella-Ferruzza, 1950; Farinella-Ferruzza, 1956b). Holtfreter performed a similar set of experiments and found that tail blastema transplanted at heterotopic sites into the limb field can transform into limb or gill-like structures influenced by the morphogenetic field of the host (Holtfreter, 1955). These are intriguing experiments showing that remodeling and morphogenetic change can be induced not only by wounding, but also by deviations from correct global form (an appendage being in the wrong place), since the tips of the transplanted tails had no trauma and were locally in a correct environment but nevertheless transformed. Such data reveal global error-correcting homeostatic loops (Friston et al., 2015; Kuchling et al., 2020; Pezzulo and Levin, 2015, 2016). The classical papers showed that grafts sometimes induced the growth of supernumerary limbs, which could fuse with the induced tail and form a limb-tail chimera, suggesting fascinating questions around how large-scale anatomical target morphologies (the arrangement that, once achieved, causes further growth and remodeling to cease) are encoded and detected by mixed cell populations.

One of the most important aspects of organ-level chimerism is the opportunity to study robustness of function. Transplantation of supernumerary eyes at ectopic positions has shown that eyes can adapt to their new position and alien host environments. Axonal projections can still be formed and do not depend on following typical pathways for growing to their proper target structures in the brain (Constantine-Paton and Law, 1978; Harris, 1980; Hibbard, 1959; Sharma and Hollyfield, 1980). In *Xenopus* embryos, it has been shown that heteroplastically transplanted eye primordia onto ectopic positions along the body, including the tail, not only develop into anatomically functional eyes but develop optic nerve connections to the posterior spinal cord. Behavioral analysis (instrumental training with color cues) confirmed that the tadpoles could perform well in visual tasks despite having no primary eyes, and that the brain could readily learn to interpret visual information generated at ectopic positions without the need for lengthy evolutionary adjustments to the new bodyplan layout (Blackiston and Levin, 2013).

Sensory organs, such as eyes, play a significant role in peripheral information processing. To test whether an increase in the sensory

capacity could increase the learning rate in animals, removal of naturally occurring eyes and/or transplantations of ectopic eyes onto salamander larvae were performed (Schneider and Pietsch, 1968). Using a light-dependent behavioral avoidance assay, acquisition rates were tested in normal salamanders with two eyes, one eye, Triclops with three eyes (two natural eyes plus an additional eye), and Cyclops with the two normal eyes removed and one grafted eye. Information processing and learning rates were measured. Surprisingly, Cyclops animals learned at a much higher rate (Schneider and Pietsch, 1968), suggesting that there must be other benefits of having two eyes that balance this effect in terms of evolutionary fitness.

Whole and partial brain transplantations have been used to study some basic principles of behavior (Balaban, 1990; Balaban et al., 1988; Gahr, 2003) and brain development (Balaban et al., 1988; Le Douarin et al., 1997; Long et al., 2001; Streit and Stern, 2014). Chick-quail brain chimeras have been produced by transplanting quail mesencephalic and diencephalic primordium to the chicken brain at the 8- to 15 somite stage for studying crowing behavior. The transplantation resulted in chimeras producing segmented crowing sounds uncharacteristic for chicken, with a temporal pattern specific for quail (Balaban et al., 1988), suggesting that different aspects of behavior have distinct degrees of modularity or localizability. Moreover, beyond inborn instinctual behaviors, the same assays can be used to test the dynamics and localization of learned information - testing the possibility of memory transfer between organisms (Pietsch, 1981; Pietsch and Schneider, 1969). For instance, reports have been published on brain transplantation between salamander larvae and frog tadpoles looking for changes in feeding behavior (Balaban, 2003; Pietsch, 1972; Pietsch, 1981; Pietsch and Schneider, 1969), with transfer of behavioral patterns and memory (measured as improved performance on specific tasks) being reported.

If we are committed to the idea that memory resides in the brain, then it is inevitable that an appropriate transfer of the memory medium should also transfer the memory. However, the amphibian memory transfer experiments have been inconclusive, and much more can be done to address this question, as it bears directly on the nature of memories, their encoding/decoding by an organism, and the mechanisms of cohesion of neural tissues into a single cognitive Subject as owner of experience and memory (Ameriks, 1976; Wilson and Arch, 1972). Attempts to show this have been made in a variety of animal model systems (Holt and Bentz, 1983b; Miller and Holt, 1977b; Reinis, 1968; Setlow, 1997). Modern experiments on chimeric memory content have successfully focused on injection of RNA extracted from the central nervous system of trained donors into naïve animals as demonstrated in the marine mollusk *Aplysia* (Bédécarrats et al., 2018), or injection of brain and liver RNA extracts and brain tissue homogenate in rats (Holt and Bentz, 1983a; Miller and Holt, 1977a; Whiddon et al., 1976). Thus future experiments in chimeric memories within one functional organism could involve mixtures of cellular, molecular, or tissue-level information.

7. Parabiosis

Even larger-scale organism-level chimeras can be made via parabiosis - an old technique first performed in 1864 using mice, where two whole bodies are surgically connected resulting in the development of a shared circulatory system (Bert, 1864). Such experiments have been used to study the determination of embryonic left-right asymmetry in amphibia (von Kraft, 1999) and birds (Levin, 1998, 1999, 2001; Levin et al., 1997), where the spillover of lateralization molecules such as Sonic hedgehog and Nodal from one side of one body affects the LR identity of the adjacent side of the second body. This revealed much about the signaling range, timing, and nature of the large-scale asymmetry signals, especially since the geometry and relative ages of the two embryos were controlled during the grafting, showing how specific factors such as *Sonic hedgehog* and *Nodal* can cross between embryos and impact the acquisition of identity information by half of the body based on information obtained from the grafted adjacent body.

Punctatum tigrinum whole-body chimeras have been created by uniting the larvae's anterior and posterior portions, resulting in viable graft hybrids with each half and its appendages showing scaling relationships according to the donor species (Burns and Burns, 1929; Church, 1956). Heterochronic parabiosis, which is the surgical fusion of two organisms of different age, e.g. an adult and a juvenile, have been used to study the process of aging, showing that a supply of "young blood" or blood serum can counteract the effects of aging at the molecular, structural and functional level (Villeda et al., 2014). This phenomenon has been shown to be induced by the transfer of factors such as GDF11 (Katsimpardi et al., 2014) and hormones like oxytocin (Elabd et al., 2014), resulting in the rejuvenation of aged stem cells and thereby increased levels of regenerative potential (Conboy et al., 2005). It is not yet known whether young blood can counteract the age-related development of cancer.

A natural form of parabiosis referred to as sexual parasitism is found in some anglerfish species. The males of some anglerfish can be significantly smaller than the females and fuse permanently to the female body, developing a shared circulatory system and becoming dependent on blood-transported nutrients by the host female. In return the males supply the female with sperm, turning the female into a self-fertilizing hermaphrodite (Pietsch, 2005). Taken together, the work on fusions of entire bodies presents new perspectives on the mechanisms, and the functional consequences, of boundaries on the border between the self and the outside world. It enables the study of homeostatic and other physiological systems when the scale of a single body is radically expanded (being the complementary technique to the study of ex-vivo organ culture which fragments whole bodies into autonomous subunits).

8. Population-level chimeras

Populations can be regarded as a very high scale of biological organization (Fig. 2**E**). Living in groups, organisms often show collective behaviors resulting in synchronized movement and migration patterns as observed in fish schools and animal flocks (Couzin and Krause, 2003), the formation of the migrating slug in *Dictyostelium* (Hashimura et al., 2019), dynamics of cancer cells (Deisboeck and Couzin, 2009), and even bacteria in biofilms (Gloag et al., 2013; Ishikawa et al., 2020). The spatio-temporal structures formed by organismal groups are studied by the field of collective intelligence (Couzin, 2007; Heylighen, 2013), which illustrates at this larger scale important invariants between the computations of patterning agents in morphospace and those of behavioral systems in functional space (Fields and Levin, 2020; Pezzulo and Levin, 2015).

Eusocial insects such as ants and termites are known for their ability to collectively build nests and mounds resulting in structures which can be several meters high (Korb, 2003), with complex architecture and functionality maintaining homeostasis (Turner, 2009a). The architecture of the mound depends on the species and the environmental conditions (Ocko et al., 2019). The mound structure itself is involved in maintaining homeostasis between the termites and its own structure, regulating temperature, carbon dioxide concentrations and air humidity at constant levels (also referred to as extended or embodied physiology) (Turner, 2005). Furthermore, it shows characteristics of a living organism, such as growth, development and regeneration mediated by feedback loops between the mound and the termites (Ocko et al., 2019; Turner, 2009b).

These structures can be understood as a form of an extended phenotype or body (Turner, 2004). As an analog to cells which use themselves as building blocks to build the body of a multicellular organism through the process of morphogenesis, termites build the structure of their mounds using soil as material. Since no single termite is thought to have an internal representation of the actual mound structure, the collective must rely upon simple genetically encoded behavioral rules that use local information (such as pheromones) to

successfully build the mound (Ocko et al., 2019) – a classic example of emergent complexity arising from parallel execution of local rules by active agents. Such animals also utilize an indirect form of communication via deposited chemical signals, known as stigmergy (Theraulaz and Bonabeau, 1999). This enables the collective intelligence of the hive to coordinate the building of complex mound structures, using the environment as an informational scratchpad – the memory medium of the collective intelligence of the group (Heylighen, 2016a, 2016b; Khuong et al., 2016a; Khuong et al., 2016b). The multi-scale nature of this process is revealed by the same design principle exploited in bacteria to coordinate colony structure and function (Gloag et al., 2016), and by cells in the body using extracellular matrix information to coordinate somatic morphogenesis (Yan and Lin, 2009).

Since the mound architecture emerges from non-linear collective behavior based on local information and local interactions, it presents us (as does morphogenesis) with the inverse problem of trying to predict its shape from known behaviors of individual ants. Parallel to the problem of inferring interventions in regenerative medicine, one could ask which ant behaviors need to be changed to alter mound structure toward a specific shape, and whether this is most efficiently done by manipulating the genes of the ants or by specific stimuli during the construction process. Much could be learned by introducing into the collective biological or engineered individuals whose behavior differs from that of others.

It is unfortunately very difficult to perform such "population-level" chimeric grafting experiments, as olfaction-based cues are used to implement aggressive self vs. not-self distinctions inhibiting the cooperation of individuals from different populations and species (much as immune incompatibilities hamper certain kinds of somatic chimerism experiments). Nevertheless, some experiments have worked around this problem to a degree, by amputating a portion of the antenna, the anatomical structure where smell is located (Fielde, 1903). A different method is to raise larvae of different species together, which accustoms them to the odor of individuals from different colonies (Fielde, 1903), and perhaps future work using transgenic ants or use of psychoactive compounds could overcome this resistance to chimerism at the colony level.

An exemption to this behavior occurring in nature are slave-making ants that capture the brood of other (usually closely related) species and integrate them into their own work force (Breed et al., 2012; Topoff and Zimmerli, 1991). To our knowledge there are no reports on how this affects the nest architecture, but it has been shown in laboratory settings that ants of different worker types with different sizes (small and big ants) of the same species (and colony) create different nest architectures. A mixture of small and big ants (Fig. 4) results in the emergence of a new nest structure with an increased number of branches and an architecture that can't be predicted by the sum of nest morphologies created by the two different ant worker types (Kwapich et al., 2018). This and previous studies reveal that ants might use their body length as a template for construction (Khuong et al., 2016b; Kwapich et al., 2018), showing how chimeric experiments can shed light on the computational properties (such as measurement and decision-making mechanisms) of collectives (whether made of cells or whole organisms).

The relationship between solving problems in 3-dimensional space

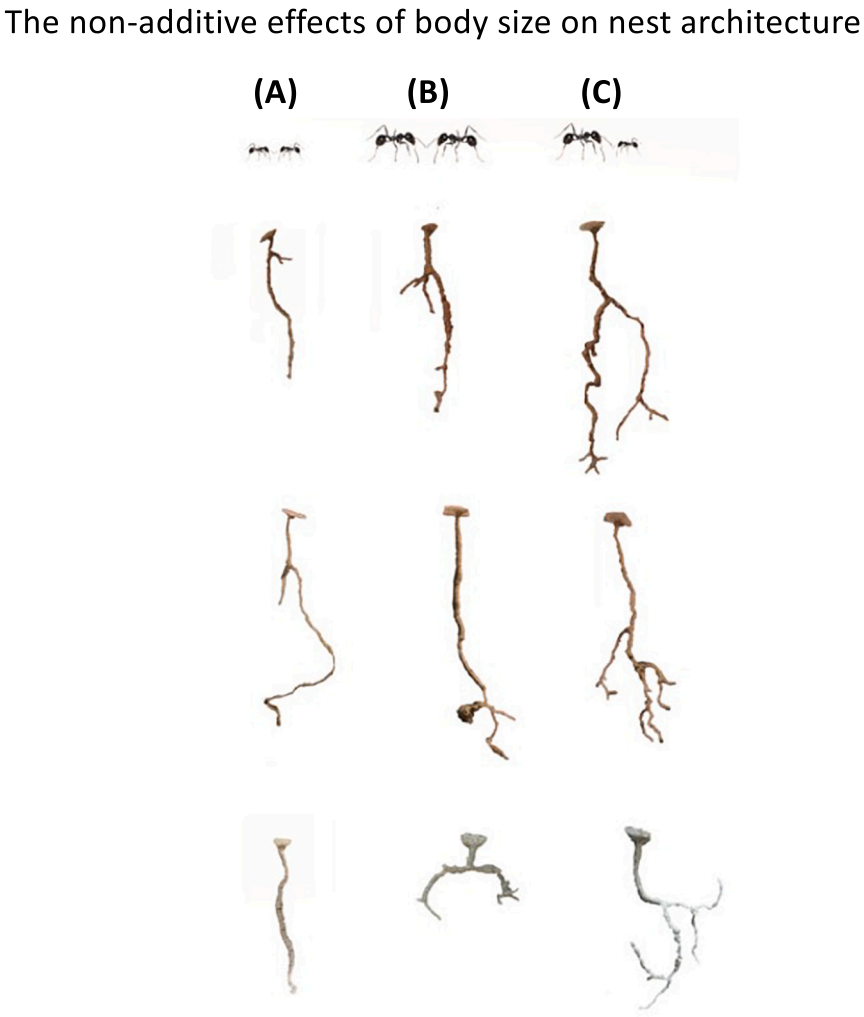

Fig. 4. The non-additive effects of body size on nest architecture.
Illustration of nest structures built by worker ants of the same colony with different body sizes. (**A**) small workers, (**B**) big workers. (**C**) A mixed group of small and big sized workers results in a nest architecture that can't be predicted by the contribution of single sized workers (A,B), showing a greater complexity, with more excavated sand and longer nests.

(such as behavior or mound construction) and in anatomical morphospace (building or repairing specific body structures) is seen in forms such as slime molds: for example, *Physarum polycephalum* explores and navigates the world via outgrowth and die-back – for this animal, active morphogenesis *is* its behavior (Beekman and Latty, 2015; Murugan et al., 2021). And this fascinating transitional case of problem-solving in very different spaces can also be analyzed by chimerism. Different species of cellular slime molds are able to form chimeras, under some circumstances resulting in chimeric fruiting bodies. In each case the number of cells is dominated by one species determining the morphology of the fruiting body (Jack et al., 2008). One paper reports the emergence of a chimeric phenotype (Raper and Thom, 1941). For mixed bacteria that are involved in biofilm formation, it has been shown that it is possible to generate chimeric biofilms with new fractal or flowerlike biofilm morphologies unlike the inherent morphology of either contributing species (Xiong et al., 2020). Many opportunities exist to use microbes to understand the emergence of colony-level form driven by metabolic, game-theoretic, evolutionary, and biophysical phenomena (Ben Jacob et al., 1992; Ben-Jacob, 1998, 2003, 2009; Ben-Jacob et al., 2006; Jacob et al., 2004; Norris et al., 2011).

Population level chimeras can even span across several taxa as is the case for lichen, a composite organism arising from the symbiotic relationship of fungi with algal and/or cyanobacterial photobionts living as extracellular endosymbionts surrounded by fungal filaments. Interestingly, lichen possess a high level of morphological diversity; at the same time, morphologically similar phenotypes can arise from unrelated fungal taxa with various combinations of photobionts (Honegger, 1991). This provides exciting opportunities to understand cooperation and competition.

In recent years, synthetic robotic swarms emerged as a new tool for studying the inverse problem: the difficulty of inferring what changes need to be made to the functional properties of individual agents in order to make desired changes to the structure or function of the system-level collective. Individual robots equipped with sensors for distance measurements and programmed with a simple set of behavioral rules are able to form complex structures as a swarm based on local interactions (Korb, 2014; Rubenstein et al., 2014; Werfel et al., 2014). Swarm robotics is a medium in which conceptual aspects of chimerism, and the development of strategies for predicting stable goal states of swarm dynamics, can be studied (Barca and Sekercioglu, 2013; Brambilla et al., 2013; Gomes et al., 2013; Trianni and Campo, 2015). In addition to physical robots, simulations including cellular automata and neural network components, with many surprising and emergent features, are powerful tools with which to understand how large-scale control and global properties arise from the interactions of diverse subunits (Mordvintsev et al., 2020; Wang-Chak Chan, 2018). In this way, Artificial Life research is poised to help biologists develop computational and conceptual tools to understand complexity.

9. Conclusion

> "At first they led a somewhat wretched existence and lived without rule after the manner of beasts. … Oannes … had the whole body of a fish, but above his fish's head he had another head which was that of a man, and human feet emerged from beneath his fish's tail. … He taught them the use of letters, sciences and arts of all kinds. He taught them to construct cities, to found temples, to compile laws, and explained to them the principles of geometrical knowledge."
>
> -From Ancient Fragments, by I.P. Cory.

The significance of chimeras for driving increases in knowledge has been known long before the common era. One of the oldest known mentions of a mythological chimera is the Sumerian amphibious half-man half-fish hybrid god called Oannes (Uanna in Sumerian) from the 4th century BCE. Oannes taught humanity the arts and sciences, how to read and write, how to build cities and how to create a functioning society. In short, he was believed to have brought humankind all the emergent properties of culture and civilization. It is an intriguing thought that this pre-scientific civilization was already using the idea of chimerism to understand the emergent properties of human culture. Today, centuries later, we are again using the concept of chimerism in an attempt to understand the emergent properties of life.

All living things are deeply multi-scale, modular systems defined by the interactions of subunits within and across levels of organization. The science of complexity (Adami, 2002; Csete and Doyle, 2002) has given rise to a number of paradigms relevant to understanding collective dynamics, including cellular automata, dynamical systems theory, network theory, and deterministic chaos (Goodwin, 1994; Kauffman, 1993; Mitchell, 2009). However, the work of predicting system-level properties and multi-scale relationships from interaction rules of molecular components is just beginning; moreover, the general ability to infer low-level rules sufficient to drive desired high-order structures is an even more distant goal. Similarly, evolutionary game theory offers a rich set of formalisms for understanding the conditions under which subsystems with diverse origins and goals might cooperate or compete (Axelrod et al., 2006; Rainey and Monte, 2014; Szathmary and Maynard Smith, 1997). Despite the many studies highlighted above, which reveal aspects of control in specific chimeric cases, inferring general principles and design strategies for understanding chimeric configurations remains as a future goal. The hard work of predicting degree of cooperation from subsystem rules, inferring and rationally modifying the large-scale outcomes of such cooperation, and taming combinations of cooperation and competition (Gawne et al., 2020) in biomedical contexts and engineered systems has only begun. This presents an important future challenge and an exciting opportunity to develop the science of complexity and learn to understand, predict, and tame emergence and the scaling of properties. Moving beyond standard components to test the interactions and emergent higher-level dynamics of composite living systems is a powerful tool for reverse-engineering biology. This is especially true since artificially combining subunits that have not had eons of evolutionary selection to hone their interactions reveals aspects of plasticity, interoperability, and origins of novelty. Thus, the study of how molecules, cells, tissues, etc. act to create a specific anatomical outcome requires continuous cycles of inquiry in which understanding of subunits drives insight into larger scales of organization, while in turn questions at these higher levels suggest new experiments to reveal more about the capabilities of the subunits (Fig. 5A,B).

We suggest that numerous kinds of experiments, in contexts ranging from molecular biology to swarm ecology, are instances of one powerful, common approach: multi-scale chimerism, whether experimental or natural (Table 1). All of these examples have in common the ability to shed light on the key question for the 21st century: how higher-level properties emerge from the properties of individual components. Despite its long history we have very little ability to make predictions about morphological and functional outcomes of chimeric systems; therefore chimeras are a crucial complement to the study of pure systems, whose reliable morphogenesis and evolutionary history obscure fundamental questions. It is taken for granted that frog eggs make tadpoles, and Axolotl eggs make larval axolotl. But how are the setpoints for anatomical homeostasis in regulative development and regeneration set in the context of collectives containing a mix of genetic and cellular material from diverse species? What will frog embryo cells and Axolotl cells make when mixed together? Will the end product have legs (like Axolotls do, and *Xenopus* embryos do not)? And if so, will those legs contain *Xenopus* cells? How do genomes function in such novel environments? What new aspects of cooperation and competition are revealed (Gawne et al., 2020), when the normally tight linkage between genetic relatedness and somatic proximity is made to diverge? Few predictions on such questions can be made in advance, despite the growing deluge of genetic information and molecular pathway details.

The ability to mix diverse biological components into whole

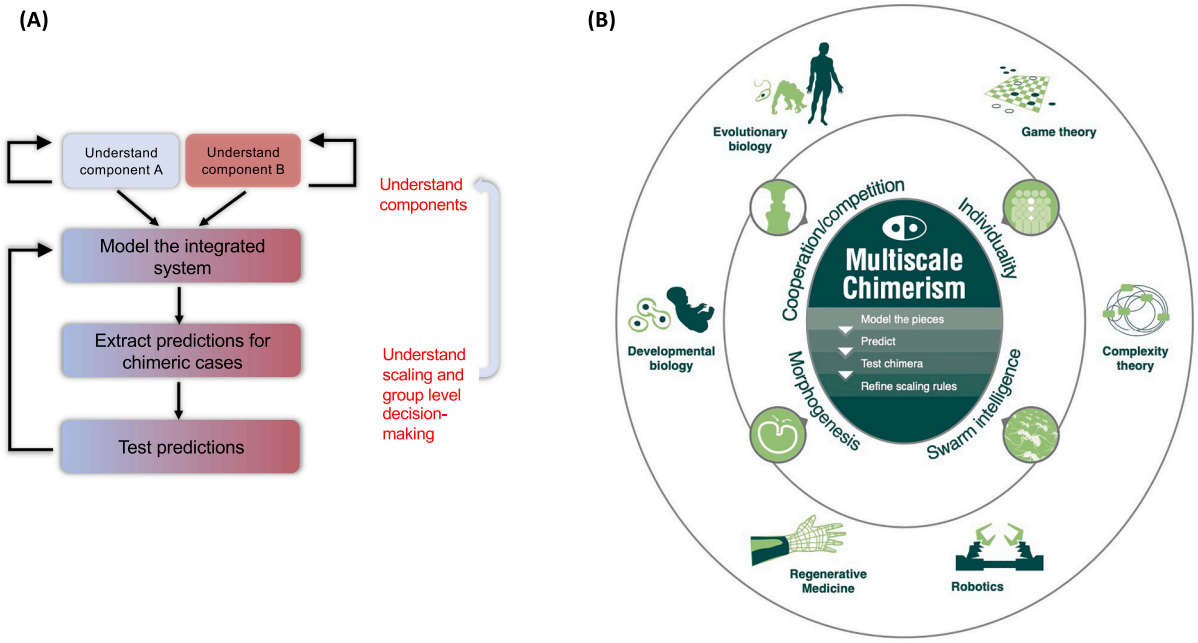

Fig. 5. Schematic of the study of multiscale chimerism. (**A**) Biological systems consist of multiple levels of active subunits. The grand challenge of complexity science is to predict the structure and function of complex living systems from properties of the subunits. This is a cyclical process of model-building and testing, comprising reductive analysis and synthesis of models with emergent behavior. Models of subcomponents, such as the physical and computational capabilities of cells, are refined by experiment. The rules governing their behavior are used to build multi-scale integrated models. The goal is to be able to use these insights to make successful predictions about novel combinations of diverse components - chimeras with unknown system-level behaviors. Understanding emergent outcomes in novel scenarios will be required to infer interventions and design principles for desired outcomes in regenerative medicine, synthetic bioengineering, and hybrid robotics. (**B**) Multi-scale chimerism is studied through a process of modeling, prediction, testing, and inference of scaling rules. Understanding the outcomes of diverse chimeras in biology has strong implications for fundamental questions of the origin and meaning of individuality, the forces balancing cooperation and competition among subunits at each level, morphogenetic setpoints, and collective decisions and problem-solving of swarm intelligences. Thus, impacts of chimeric research will extend not only to basic questions of evolutionary and developmental biology, but to related fields in which the whole-to-part relation is key, such as complexity and game theory, and practical applications in regenerative medicine and swarm robotics.

functional systems has several important consequences. First, it emphasizes fundamental knowledge gaps that are present, but not apparent, in work on pure, standard model systems and phylogenetic lineages. Second, it creates opportunities to improve our predictive understanding of morphogenetic scaling and collective decision-making. Third, it provides model systems different from existing organisms, enabling the study of novel forms outside specific contingencies of the biosphere's evolutionary history.

Thus, one of the most enticing aspects about chimerism is how it highlights what we do not know. In making explicit our lack of ability to predict the resulting morphology of chimeric forms, this work draws attention to our basic inability to predict anatomical forms from genetic or cell biological data even within one species. As with developmental biology, machine learning could be used to predict the outcomes of such experiments. However, the black box problem (interpreting successful AI systems via human-understandable rules, to gain insight in addition to performance) will loom large, as the difference between successful prediction of specific cases vs. deep understanding of the algorithms of life (Sero et al., 2019). These knowledge and capability gaps require not only more molecular detail or big data, but also the use of techniques from computational and cognitive sciences to understand the origin and encoding/decoding of target morphology information for anatomical homeostasis (Levin et al., 2018; Pezzulo and Levin, 2015, 2016), and to understand how collectives (molecular, cellular, and swarm) make system-level decisions (Friston et al., 2015; Heylighen, 2013; Kuchling et al., 2020; Sole et al., 2016). Experimental models for testing insights from these approaches are emerging in the field of synthetic bioengineering (Doursat and Sanchez, 2014; Doursat et al., 2013; Macia et al., 2017; Olle-Vila et al., 2016; Sole, 2016a, 2016b; Sole et al., 2016; Urrios et al., 2016).

While numerous facts about specific developmental processes can be discerned based on individual cases described above, there are a few general conclusions that are suggested by the body of work on chimerism. The first is that the many disparate types of recombination experiments, done by diverse communities (molecular geneticists, developmental biologists, behavioral scientists working on swarm intelligence, etc.) are in fact facets of one unified approach. Chimerism results from the powerful engineering strategy of modular reconstitution, which can be applied (in parallel) on multiple scales of organization, from molecules to whole communities. Second, this is not only a strategy for scientists to better reverse-engineer life, but is also a strategy used by evolution for fascinating and important augmentation of the basic (vertical) Darwinian cycle. Third, both the natural and bioengineering versions of chimerism work because of remarkable interoperability of living components at all scales. Recombining DNA, molecular circuits, organelles, cells, tissues, etc. results in coherent living organisms even when their sources are evolutionarily quite distant. This may suggest important revisions to notions of cooperativity based on genetic relatedness toward notions based on informational or computational compatibility. Together with the increasing appreciation of competition within bodies (Gawne et al., 2020), an emphasis on chimerism suggests a systems view of components that interact in highly diverse combinations across boundaries of standard model system bodies (Fields and Levin, 2017; Fields and Levin, 2018; Fields and Levin, 2020). Fourth, chimerism reveals life's plasticity and ability to produce adaptive structure and function in novel circumstances. Chimeras, consisting of components that have never lived together in evolutionary history, form viable new life forms even without a lengthy history of selection to lubricate their mutual interactions. This reveals and highlights the ease and speed with which biological novelty can be produced, and suggests that

Table 1
Summary of natural and experimental chimerism at different levels.

Scale	Process/mechanism	What has been transferred?	Organisms Donor → Host	Outcome	References
Molecular	Horizontal gene transfer (HGT)	Cellulose synthase-like gene	Actinobacteria → Tunicates (urochordates)	Metazoan with cellulose integrated into their extracellular matrix and epidermis. Illustrates the feasibility and interoperability of genes and their products even between distantly related species.	(Hirose et al., 2011; Matthysse et al., 2004; Sasakura et al., 2016)
	Genome transplantation	Transfer and replacement of entire genome	*M. mycoides* → *M. capricolum*	The process involves no recombination between the donor and recipient DNA and results in transforming the chimera from *M. capricolum* to *M. mycoides* with respect to single gene products and proteome analysis.	(Lartigue et al., 2007)
Subcellular and organelle	Symbiogenesis or endosymbiosis; Kleptoplasty	Chloroplast	Algae - → Sea slug (*Elysia chlorotica*)	Chimerism resulted in animal with the ability to perform photosynthesis. Genes involved in photosynthesis have been horizontally transferred to the *E. chlorotica* genome. The slug developed a morphology resembling a leaf.	(Rumpho et al., 2011) (Rumpho et al., 2008)
	Cross-genus nuclear transplantation	Nucleus	Common carp → Goldfish (enucleated egg)	Resulted in numbers of vertebrae more similar to that of goldfish than the carp proving that the cytoplasm can drive specific developmental outcomes.	(Sun et al., 2005; Sun and Zhu, 2014)
Cellular	Allograft through biting	Cancer cells	Tasmanian devil → Tasmanian devil	Parasitic chimerism can be a strategy to perpetuate the cellular lineage. Cancer cells free themselves by gaining autonomy from the constraints of their collective and regressing to the transcriptional and behavioral properties of unicellular ancestors. They then use the population of Tasmanian devil bodies as the environment through which they spread and evolve.	(Levin, 2019a; Levin, 2021; Patton et al., 2020; Zhou et al., 2018)
	Xenogenic transplantation	Nerve cells	Drosophila → Human Parkinson patients	Transplantation resulted in reduced tremor in Parkinson patients. The xenoplastic transplantation of cells between cold- and warm-blooded animals reveals surprisingly wide temperature tolerance and interoperability of neural tissue across distant genetics.	(Saveliev et al., 1997)
Tissue	- Self-graft - Intraspecific graft - Interspecific graft	Exchange of cytoplasmic content via plasmodesmata	Plant → Plant	Root grafting facilitates cooperativity between trees allowing the exchange/transfer of nutrients such as carbohydrates, water and minerals to neighboring trees in need and thereby increasing resilience. Viable bodies readily support diverse tissue types.	(Coetzee and Fineran, 1989) (Tiedemann, 1989)
	Xenogenic transplantation; Dermo-epidermal recombination	Epidermis, dermis	Grafts between reptiles, birds and mammals	The dermis is the carrier of special pattern, while the epidermis carries the potentiality to develop specific structures such as feathers, scales or hair.	(Dhouailly, 1975; Sengel and Dhouailly, 1977)
Organ	Xenoplastic transplantation	Tail bud	Axolotl → Frog (limb field)	Tail bud transplanted into the host's limb field transforms during metamorphosis into a limb with a variable number of digits Results reveal global error-correcting capacity which drives remodeling toward large-scale anatomical target morphology.	(Farinella-Ferruzza, 1950; Farinella-Ferruzza, 1956b; Holtfreter, 1955)
Organism (Parabiosis)	Sexual parasitism	Shared circulatory system (nutrients) Transfer of sperm	Some angler fish species Female → male	Permanent fusion of the male to the female turning the female into a self-fertilizing hermaphrodite and blurring the boundaries between distinct animal bodies.	(Pietsch, 2005)
	Heterochronic parabiosis	Blood, blood serum Shared circulatory system	Adult ↔ juvenile	Counteract the effects of aging at the molecular, structural and functional level, showing how specific organism components can contribute to a body-wide property such as age.	(Conboy et al., 2005; Villeda et al., 2014)
Population	Chimeric ant population Cleptobiosis	Brood of usually closely related ant species	Slave making ants → other ant species	Integration into host work force. It is not clear how that affects the nest morphology, but in laboratory settings it has been shown that of different worker types and sizes result in the emergence of new nest architectures that can't be predicted by the sum of nest morphologies created by the two different ant worker types.	(Breed et al., 2012; Topoff and Zimmerli, 1991) (Kwapich et al., 2018) 227
	Chimeric biofilm	Mixed bacteria	*E. coli* ↔ *A. baylyi*	Chimeric biofilms result in new fractal or flowerlike biofilm morphologies unlike the inherent morphology of either contributing species.	(Xiong et al., 2020)

components can be evolved individually and recombined later – a very powerful property that both engineers and evolution exploit for rapid development of complex systems.

These features suggest new aspects of the evolution of bodies and the relationship between genomes and anatomies (Levin, 2020). They also have strong implications for synthetic bioengineering efforts to make novel living constructs (Kamm and Bashir, 2014; Kamm et al., 2018; Kriegman et al., 2020) that can contain DNA, cells, and tissues from numerous species, as well as inorganic components (passive nanomaterials and AI-bearing electronics in the context of brain-computer

interfaces (Chamola et al., 2020; Green and Kalaska, 2011)). The in silico evolution (Kriegman et al., 2020) and design (Kamm and Bashir, 2014; Kamm et al., 2018) of bioengineered organisms will shed much light on the plasticity of genomic exploitation of generic physics (Arias Del Angel et al., 2020; Newman, 2016) and cellular decision-making in novel contexts (Baluška and Levin, 2016). At the same time, chimeric assembloids (Panoutsopoulos, 2020; Sahu and Sharan, 2020; Vogt, 2021) will provide critical basic knowledge for biomedical efforts to control complex, system-level outcomes. Importantly, advances in this interdisciplinary area are as useful for basic biology and biomedicine as for robotics, which likewise struggles with developing strategies for the design and control of multi-scale robotic swarms (de Oca et al., 2010; Nishikawa et al., 2016; Patil, 2014; Slavkov et al., 2018). The possibility of chimeric forms with emergent new structures and functions will not only result in useful synthetic living machines and cybernetic organisms, but will also provide a near-infinite collection of "model systems" for exploring not only the results of Earth's specific evolutionary timeline, but Life as it Could Be (Langton, 1995).

Credit authorship contribution statement

Both authors wrote the manuscript.

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References

Adami, C., 2002. What is complexity? BioEssays 24, 1085–1094.
Agata, K., Tanaka, T., Kobayashi, C., Kato, K., Saitoh, Y., 2003. Intercalary regeneration in planarians. Dev. Dyn. 226, 308–316.
Alexandrova, M., Polezhaev, L., 1984. Xenografting of brainin frogs and the change in behavior of animals. Dokl. Akad. Nauk SSSR 274, 711–715.
Ameriks, K., 1976. Personal identity and memory transfer. South.J. Phil. 14, 385–391.
Anderson, P.W., 1972. More is different - broken symmetry and nature of hierarchical structure of science. Science 177, 393.
Andres, G., Rossler, E., 1977. Transplantation yon verhalten. Umschau 74, 144–174.
Arias Del Angel, J.A., Nanjundiah, V., Benítez, M., Newman, S.A., 2020. Interplay of mesoscale physics and agent-like behaviors in the parallel evolution of aggregative multicellularity. EvoDevo 11, 21.
Arnold, M.L., Hodges, S.A., 1995. Are natural hybrids fit or unfit relative to their parents? Trends Ecol. Evol. 10, 67–71.
Axelrod, R., Axelrod, D.E., Pienta, K.J., 2006. Evolution of cooperation among tumor cells. Proc. Natl. Acad. Sci. U. S. A. 103, 13474–13479.
Bacman, S.R., Nissanka, N., Moraes, C.T., 2020. Cybrid technology. Methods Cell Biol. 155, 415–439.
Balaban, E., 1990. Avian brain chimeras as a tool for studying species behavioral differences. In: The Avian Model in Developmental Biology: From Organism to Genes, pp. 105–118.
Balaban, E., 2003. Brain switching: studying evolutionary behavioral changes in the context of individual brain development. Int. J. Dev. Biol. 49, 117–124.
Balaban, E., Teillet, M.-A., Le Douarin, N., 1988. Application of the quail-chick chimera system to the study of brain development and behavior. Science 241, 1339–1342.
Baluška, F., Levin, M., 2016. On having no head: cognition throughout biological systems. Front. Psychol. 7, 902.
Baranwal, V.K., Mikkilineni, V., Zehr, U.B., Tyagi, A.K., Kapoor, S., 2012. Heterosis: emerging ideas about hybrid vigour. J. Exp. Bot. 63, 6309–6314.
Barca, J.C., Sekercioglu, Y.A., 2013. Swarm robotics reviewed. Robotica 31, 345–359.
Beane, W.S., Morokuma, J., Lemire, J.M., Levin, M., 2013. Bioelectric signaling regulates head and organ size during planarian regeneration. Development 140, 313–322.
Bédécarrats, A., Chen, S., Pearce, K., Cai, D., Glanzman, D.L., 2018. RNA from trained Aplysia can induce an epigenetic engram for long-term sensitization in untrained Aplysia. eNeuro 5.
Beekman, M., Latty, T., 2015. Brainless but multi-headed: decision making by the acellular slime mould Physarum polycephalum. J. Mol. Biol. 427, 3734–3743.
Ben Jacob, E., Shmueli, H., Shochet, O., Tenenbaum, A., 1992. Adaptive self-organization during growth of bacterial colonies. Phys.AStat.Mech.Appl. 187, 378–424.
Ben-Jacob, E., 1998. Bacterial wisdom, Godel's theorem and creative genomic webs. Phys.A 248, 57–76.
Ben-Jacob, E., 2003. Bacterial self-organization: co-enhancement of complexification and adaptability in a dynamic environment. Philos. Trans. A Math Phys. Eng. Sci. 361, 1283–1312.
Ben-Jacob, E., 2009. Learning from bacteria about natural information processing. Ann. N. Y. Acad. Sci. 1178, 78–90.
Ben-Jacob, E., Shapira, Y., Tauber, A.I., 2006. Seeking the foundations of cognition in bacteria: from Schrodinger's negative entropy to latent information. Phys.AStat. Mech.Appl. 359, 495–524.
Bert, P., 1864. Expériences et considérations sur la greffe animale.
Biskind, M.S., Biskind, G.S., 1944. Development of tumors in the rat ovary after transplantation into the spleen. Proc. Soc. Exp. Biol. Med. 55, 176–179.
Biskind, M.S., Biskind, G.R., 1945. Tumor of rat testis prodced by heterotransplantation of infantile testis to spleen of adult castrate. Proc. Soc. Exp. Biol. Med. 59, 4–8.
Blackiston, D.J., Levin, M., 2013. Ectopic eyes outside the head in Xenopus tadpoles provide sensory data for light-mediated learning. J. Exp. Biol. 216, 1031–1040.
Bogart, J., Bartoszek, J., Noble, D., Bi, K., 2009. Sex in unisexual salamanders: discovery of a new sperm donor with ancient affinities. Heredity 103, 483–493.
Booth, W., Schuett, G.W., 2016. The emerging phylogenetic pattern of parthenogenesis in snakes. Biol. J. Linn. Soc. 118, 172–186.
Bormann, F., Graham Jr., B., 1966. Natural root grafts. Bot. Rev. 32, 255–292.
Boto, L., 2014. Horizontal gene transfer in the acquisition of novel traits by metazoans. Proc. R. Soc. B Biol. Sci. 281, 20132450.
Boveri, T., 1889. Ein geschlechtlich erzeugter organismus ohne mutterliche eigenschaften. Sitz. Gesel. Morph. Physiol. Munchen 5, 73–83.
Boveri, T., 1893. An organism produced sexually without characteristics of the mother. Am. Nat. 27, 222–232.
Brambilla, M., Ferrante, E., Birattari, M., Dorigo, M., 2013. Swarm robotics: a review from the swarm engineering perspective. Swarm Intell. 7, 1–41.
Breed, M.D., Cook, C., Krasnec, M.O., 2012. Cleptobiosis in social insects. Psyche 2012.
Briere, C., Goodwin, B.C., 1990. Effects of calcium input/output on the stability of a system for calcium-regulated viscoelastic strain fields. J. Math. Biol. 28, 585–593.
Brown, J., Barry, C., Schmitz, M., Argus, C., Bolin, J., Schwartz, M., Van Aartsen, A., Steill, J., Swanson, S., Stewart, R., 2020. Interspecies Chimeric Conditions Affect the Developmental Rate of Human Pluripotent Stem Cells. bioRxiv..
Bullini, L., 1994. Origin and evolution of animal hybrid species. Trends Ecol. Evol. 9, 422–426.
Burns Jr., R.K., Burns, L.M., 1929. The growth of the whole organism and of the limbs in two species of Amblystoma united in parabiosis. J. Exp. Zool. 53, 455–477.
Burrell, R.A., McGranahan, N., Bartek, J., Swanton, C., 2013. The causes and consequences of genetic heterogeneity in cancer evolution. Nature 501, 338–345.
Chamola, V., Vineet, A., Nayyar, A., Hossain, E., 2020. Brain-computer interface-based humanoid control: a review. Sensors (Basel) 20.
Chaplain, M.A., Sleeman, B.D., 1990. An application of membrane theory to tip morphogenesis in Acetabularia. J. Theory Biol. 146, 177–200.
Chapman, D.D., Firchau, B., Shivji, M.S., 2008. Parthenogenesis in a large-bodied requiem shark, the blacktip Carcharhinus limbatus. J. Fish Biol. 73, 1473–1477.
Chen, n.d.Chen, P.S., Aus dem Forschungsgebiet der Entwicklungsphysiologie.
Chen, J., Chuong, C.M., 2012. Patterning skin by planar cell polarity: the multi-talented hair designer. Exp. Dermatol. 21, 81–85.
Chen, R.Z., Pettersson, U., Beard, C., Jackson-Grusby, L., Jaenisch, R., 1998. DNA hypomethylation leads to elevated mutation rates. Nature 395, 89–93.
Chernet, B., Levin, M., 2013. Endogenous voltage potentials and the microenvironment: bioelectric signals that reveal, induce and normalize cancer. J. Clin. Exp. Oncol. (Suppl. 1).
Church, G., 1956. The growth and morphology of amblystoma chimeras. J. Morphol. 98, 405–428.
Clegg, J.M., Li, Z., Molinek, M., Caballero, I.M., Manuel, M.N., Price, D.J., 2015. Pax6 is required intrinsically by thalamic progenitors for the normal molecular patterning of thalamic neurons but not the growth and guidance of their axons. Neural Dev. 10, 26.
Coetzee, J., Fineran, B., 1989. Translocation of lysine from the host Melicope simplex to the parasitic dwarf mistletoe Korthalsella lindsayi (Viscaceae). New Phytol. 112, 377–381.
Cohen, M.A., Wert, K.J., Goldmann, J., Markoulaki, S., Buganim, Y., Fu, D., Jaenisch, R., 2016. Human neural crest cells contribute to coat pigmentation in interspecies chimeras after in utero injection into mouse embryos. Proc. Natl. Acad. Sci. 113, 1570–1575.
Conboy, I.M., Conboy, M.J., Wagers, A.J., Girma, E.R., Weissman, I.L., Rando, T.A., 2005. Rejuvenation of aged progenitor cells by exposure to a young systemic environment. Nature 433, 760–764.
Constantine-Paton, M., Law, M.I., 1978. Eye-specific termination bands in tecta of three-eyed frogs. Science 202, 639–641.
Cooke, J., 1979. Cell number in relation to primary pattern formation in the embryo of Xenopus laevis. I: the cell cycle during new pattern formation in response to implanted organisers. J.Embryol.Exp.Morphol. 51, 165–182.
Cooke, J., 1981. Scale of body pattern adjusts to available cell number in amphibian embryos. Nature 290, 775–778.
Copenhaver, W., 1927. Results of heteroplastic transplantations of the heart rudiment in Amblystoma embryos. Proc. Natl. Acad. Sci. U. S. A. 13, 484.
Copenhaver, W., 1930. Results of heteroplastic transplantation of anterior and posterior parts of the heart rudiment in Amblystoma embryos. J. Exp. Zool. 55, 293–318.
Copenhaver, W., 1939. Some observations on the growth and function of heteroplastic heart grafts. J. Exp. Zool. 82, 239–271.
Couzin, I., 2007. Collective minds. Nature 445, 715.

Couzin, I.D., 2009. Collective cognition in animal groups. Trends Cogn. Sci. 13, 36–43.
Couzin, I.D., Krause, J., 2003. Self-organization and collective behavior in vertebrates. Adv.Stud.Behav. 32 (10), 1016.
Csete, M.E., Doyle, J.C., 2002. Reverse engineering of biological complexity. Science 295, 1664–1669.
Daane, J.M., Lanni, J., Rothenberg, I., Seebohm, G., Higdon, C.W., Johnson, S.L., Harris, M.P., 2018. Bioelectric-calcineurin signaling module regulates allometric growth and size of the zebrafish fin. Sci. Rep. 8, 10391.
Darwin, C., 1897. The Variation of Animals And Plants Under Domestication. D. Appleton.
Decaestecker, E., De Meester, L., Mergeay, J., 2009. Cyclical parthenogenesis in Daphnia: sexual versus asexual reproduction. In: Lost Sex. Springer, pp. 295–316.
Deisboeck, T.S., Couzin, I.D., 2009. Collective behavior in cancer cell populations. BioEssays 31, 190–197.
Dhouailly, D., 1975. Formation of cutaneous appendages in dermo-epidermal recombinations between reptiles, birds and mammals. Wilhelm Roux's Arch.Dev. Biol. 177, 323–340.
Doolittle, W.F., 2008. Uprooting the tree of life. Evolution 87–98.
Doursat, R., Sanchez, C., 2014. Growing fine-grained multicellular robots. SoftRobot. 1, 110–121.
Doursat, R., Sayama, H., Michel, O., 2013. A review of morphogenetic engineering. Nat. Comput. 12, 517–535.
Dunning Hotopp, J.C., 2011. Horizontal gene transfer between bacteria and animals. Trends Genet. 27, 157–163.
Durant, F., Morokuma, J., Fields, C., Williams, K., Adams, D.S., Levin, M., 2017. Long-term, stochastic editing of regenerative anatomy via targeting endogenous bioelectric gradients. Biophys. J. 112, 2231–2243.
Ebisuya, M., Briscoe, J., 2018. What does time mean in development? Development 145.
Ebrahimkhani, M.R., Levin, M., 2021. Synthetic living machines: a new window on life. iScience 24, 102505.
Eis, S., 1972. Root grafts and their silvicultural implications. Can. J. For. Res. 2, 111–120.
Elabd, C., Cousin, W., Upadhyayula, P., Chen, R.Y., Chooljian, M.S., Li, J., Kung, S., Jiang, K.P., Conboy, I.M., 2014. Oxytocin is an age-specific circulating hormone that is necessary for muscle maintenance and regeneration. Nat. Commun. 5, 1–11.
Fankhauser, G., 1945a. The effects of changes in chromosome number on amphibian development. Q. Rev. Biol. 20, 20–78.
Fankhauser, G., 1945b. Maintenance of normal structure in heteroploid salamander larvae, through compensation of changes in cell size by adjustment of cell number and cell shape. J. Exp. Zool. 100, 445–455.
Farinella-Ferruzza, N., 1950. Risultati di esperimenti di trapianti eterogenei dell'abbozzo codale negli Anfibi. Boll.Zool. 17, 113–119.
Farinella-Ferruzza, N., 1956a. The transformation of a tail into a limb after xenoplastic transformation. Experientia 15, 304–305.
Farinella-Ferruzza, N., 1956b. The transformation of a tail into limb after xenoplastic transplantation. Experientia 12, 304–305.
Fielde, A.M., 1903. Artificial mixed nests of ants. Biol. Bull. 5, 320–325.
Fields, C., Levin, M., 2017. Multiscale memory and bioelectric error correction in the cytoplasm–cytoskeleton-membrane system. Wiley Interdiscip. Rev. Syst. Biol. Med. e1410. -n/a.
Fields, C., Levin, M., 2018. Are planaria individuals? What regenerative biology is telling us about the nature of multicellularity. Evol. Biol. 45, 237–247.
Fields, C., Levin, M., 2020. Scale-free biology: integrating evolutionary and developmental thinking. BioEssays 42, e1900228.
French, V., 1980. Positional information around the segments of the cockroach leg. J. Embryol.Exp.Morphol. 59, 281–313.
Friston, K., Levin, M., Sengupta, B., Pezzulo, G., 2015. Knowing one's place: a free-energy approach to pattern regulation. J. R. Soc. Interface 12.
Fuhrmann, J.F., Buono, L., Adelmann, L., Martinez-Morales, J.R., Centanin, L., 2020. Genetic developmental timing revealed by inter-species transplantations in fish. Development 147.
Furusawa, C., Kaneko, K., 1998. Emergence of rules in cell society: differentiation, hierarchy, and stability. Bull. Math. Biol. 60, 659–687.
Gahr, M., 2003. Male Japanese quails with female brains do not show male sexual behaviors. Proc. Natl. Acad. Sci. 100, 7959–7964.
Garber, B., Moscona, A., 1964. Aggregation in vivo of dissociated cells. I. Reconstruction of skin in the chorioallantoic membrane from suspensions of embryonic chick and mouse skin cells. J. Exp. Zool. 155, 179–201.
Garber, B., Kollar, E., Moscona, A., 1968. Aggregation in vivo of dissociated cells. III. Effect of state of differentiation of cells on feather development in hybrid aggregates of embryonic mouse and chick skin cells. J. Exp. Zool. 168, 455–471.
Gartler, S.M., Goldman, M.A., 2001. X-Chromosome Inactivation. e LS.
Gawne, R., McKenna, K.Z., Levin, M., 2020. Competitive and coordinative interactions between body parts produce adaptive developmental outcomes. BioEssays 42, e1900245.
Gehring, W.J., Ikeo, K., 1999. Pax 6: mastering eye morphogenesis and eye evolution. Trends Genet. 15, 371–377.
Gibson, G., Gehring, W.J., 1988. Head and thoracic transformations caused by ectopic expression of Antennapedia during Drosophila development. Development 102, 657–675.
Giersberg, H., 1935. Gehirntransplantationen bei amphibien. Verh. Dtsch. Zool. Ges 37, 160–168.
Gilbert, P.W., 1944. The alga-egg relationship in Ambystoma maculatum, a case of symbiosis. Ecology 25, 366–369.
Gilbert, W., 1978. Why genes in pieces? Nature 271, 501-501.
Gloag, E.S., Javed, M.A., Wang, H., Gee, M.L., Wade, S.A., Turnbull, L., Whitchurch, C.B., 2013. Stigmergy: a key driver of self-organization in bacterial biofilms. Commun. Integr.Biol. 6, 11541–11546.
Gloag, E.S., Turnbull, L., Javed, M.A., Wang, H., Gee, M.L., Wade, S.A., Whitchurch, C.B., 2016. Stigmergy co-ordinates multicellular collective behaviours during Myxococcus xanthus surface migration. Sci. Rep. 6, 26005.
Goldenfeld, N., Woese, C., 2011. Life is physics: evolution as a collective phenomenon far from equilibrium. Annu. Rev. Condens. Matter Phys. 2, 375–399.
Gomes, J., Urbano, P., Christensen, A.L., 2013. Evolution of swarm robotics systems with novelty search. Swarm Intell. 7, 115–144.
Goodwin, B.C., 1994. How the Leopard Changed Its Spots: The Evolution of Complexity. Charles Scribner's Sons, New York.
Goodwin, B.C., Pateromichelakis, S., 1979. The role of electrical fields, ions, and the cortex in the morphogenesis of acetabularia. Planta 145, 427–435.
Green, A.M., Kalaska, J.F., 2011. Learning to move machines with the mind. Trends Neurosci. 34, 61–75.
Gurdon, J., 1961. The transplantation of nuclei between two subspecies of Xenopus laevis. Heredity 16, 305–315.
Gurdon, J., 1986. Nuclear transplantation in eggs and oocytes. J. Cell Sci. 1986, 287–318.
Hadorn, E., 1936. Übertragung von Artmerkmalen durch das entkernte Eiplasma beim merogonischen Triton-Bastard, palmatus-Plasma X cristatus-Kern. Akadem. Verlagsgesellschaft.
Hadorn, E., 1937. Die entwicklungsphysiologische Auswirkung der disharmonischen Kern-Plasmakombination beim Bastardmerogon Triton palmatus (♀)× Triton cristatus.♂. In: Wilhelm Roux'Archiv für Entwicklungsmechanik der Organismen, 136, pp. 400–489.
Halder, G., Callaerts, P., Gehring, W.J., 1995. Induction of ectopic eyes by targeted expression of the eyeless gene in Drosophila. Science 267, 1788–1792.
Hämmerling, J., 1932. Entwicklung und Regeneration beiAcetabularia mediterranea. Z. Indukt.AbstammungsVererbungsl. 62, 92–93.
Hämmerling, J., 1934. Über formbildende Substanzen bei Acetabularia mediterranea, ihre räumliche und zeitliche Verteilung und ihre Herkunft. In: Wilhelm Roux'Archiv für Entwicklungsmechanik der Organismen, 131, pp. 1–81.
Hämmerling, J., 1943a. Ein-und zweikernige Transplantate zwischen Acetabularia mediterranea und A. crenulata. Z. Indukt. Abstammungs. Vererbungsl. 81, 114–180.
Hämmerling, J., 1943b. Entwicklung und Regeneration von Acetabularia crenulata. Z. Indukt.AbstammungsVererbungsl. 81, 84–113.
Hämmerling, J., 1953. Nucleo-cytoplasmic relationships in the development of Acetabularia. In: International Review of Cytology. Elsevier, pp. 475–498.
Harris, W.A., 1980. Regions of the brain influencing the projection of developing optic tracts in the salamander. J. Comp. Neurol. 194, 319–333.
Harris, A.K., 2018. The need for a concept of shape homeostasis. Biosystems 173, 65–72.
Harris, S.A., Robinson, J.P., Juniper, B.E., 2002. Genetic clues to the origin of the apple. Trends Genet. 18, 426–430.
Harrison, R.G., 1898. The growth and regeneration of the tail of the frog larva. Roux's Arch.Dev.Biol. 7, 430–485.
Harrison, R.G., 1903. Experimentelle Untersuchungen Über die Entwicklung der Sinnesorgane der Seitenlinie bei den Ampkibien. Arch. Mikrosk. Anat. 63, 35–149.
Harrison, R.G., 1924. Some unexpected results of the heteroplastic transplantation of limbs. Proc. Natl. Acad. Sci. U. S. A. 10, 69.
Harrison, R.G., 1929. Correlation in the development and growth of the eye studied by means of heteroplastic transplantation. Wilhelm Roux'Arch.Entwicklungsmech.Org. 120, 1–55.
Hashimura, H., Morimoto, Y.V., Yasui, M., Ueda, M., 2019. Collective cell migration of Dictyostelium without cAMP oscillations at multicellular stages. Commun.Biol. 2, 1–15.
Heidelberg, J.F., Eisen, J.A., Nelson, W.C., Clayton, R.A., Gwinn, M.L., Dodson, R.J., Haft, D.H., Hickey, E.K., Peterson, J.D., Umayam, L., 2000. DNA sequence of both chromosomes of the cholera pathogenVibrio cholerae. Nature 406, 477–483.
Heylighen, F., 2013. Self-organization in communicating groups: the emergence of coordination, shared references and collective intelligence. In: Complexity Perspectives on Language, Communication And Society, pp. 117–149.
Heylighen, F., 2016a. Stigmergy as a universal coordination mechanism I: definition and components. Cogn. Syst. Res. 38, 4–13.
Heylighen, F., 2016b. Stigmergy as a universal coordination mechanism II: varieties and evolution. Cogn. Syst. Res. 38, 50–59.
Hibbard, E., 1959. Central integration of developing nerve tracts from supernumerary grafted eyes and brain in the frog. J. Exp. Zool. 141, 323–351.
Hirose, E., Nakashima, K., Nishino, A., 2011. Is there intracellular cellulose in the appendicularian tail epidermis? A tale of the adult tail of an invertebrate chordate. Commun.Integr.Biol. 4, 768–771.
Holt, G., Bentz, G., 1983a. Interanimal memory transfer of a barpress response through brain and liver RNA injections. Bull. Psychon. Soc. 21, 51–53.
Holt, G.L., Bentz, G., 1983b. Interanimal memory transfer of a barpress response through brain and liver RNA injections. Bull. Psychon.Soc. 21, 51–53.
Holtfreter, J., 1955. Transformation of a tail into a limb or gill-like structures. J. Exp. Zool. 129, 623–648.
Honegger, R., 1991. Functional aspects of the lichen symbiosis. Annu. Rev. Plant Biol. 42, 553–578.
Ishikawa, T., Omori, T., Kikuchi, K., 2020. Bacterial biomechanics—from individual behaviors to biofilm and the gut flora. APL Bioeng. 4, 041504.
Itaya, M., Tsuge, K., Koizumi, M., Fujita, K., 2005. Combining two genomes in one cell: stable cloning of the synechocystis PCC6803 genome in the Bacillus subtilis 168 genome. Proc. Natl. Acad. Sci. 102, 15971–15976.

Jack, C.N., Ridgeway, J.G., Mehdiabadi, N.J., Jones, E.I., Edwards, T.A., Queller, D.C., Strassmann, J.E., 2008. Segregate or cooperate-a study of the interaction between two species of Dictyostelium. BMC Evol. Biol. 8, 1–10.
Jacob, E.B., Aharonov, Y., Shapira, Y., 2004. Bacteria harnessing complexity. Biofilms 1, 239–263.
Johnson, M.D., Oldach, D., Delwiche, C.F., Stoecker, D.K., 2007. Retention of transcriptionally active cryptophyte nuclei by the ciliate Myrionecta rubra. Nature 445, 426–428.
Jones, C.D., Begun, D.J., 2005. Parallel evolution of chimeric fusion genes. Proc. Natl. Acad. Sci. 102, 11373–11378.
Kamm, R.D., Bashir, R., 2014. Creating living cellular machines. Ann. Biomed. Eng. 42, 445–459.
Kamm, R.D., Bashir, R., Arora, N., Dar, R.D., Gillette, M.U., Griffith, L.G., Kemp, M.L., Kinlaw, K., Levin, M., Martin, A.C., McDevitt, T.C., Nerem, R.M., Powers, M.J., Saif, T.A., Sharpe, J., Takayama, S., Takeuchi, S., Weiss, R., Ye, K.M., Yevick, H.G., Zaman, M.H., 2018. Perspective: the promise of multi-cellular engineered living systems. APLBioeng. 2.
Katsimpardi, L., Litterman, N.K., Schein, P.A., Miller, C.M., Loffredo, F.S., Wojtkiewicz, G.R., Chen, J.W., Lee, R.T., Wagers, A.J., Rubin, L.L., 2014. Vascular and neurogenic rejuvenation of the aging mouse brain by young systemic factors. Science 344, 630–634.
Kauffman, S.A., 1993. The Origins of Order: Self Organization And Selection in Evolution. Oxford University Press, New York.
Khuong, A., Gautrais, J., Perna, A., Sbai, C., Combe, M., Kuntz, P., Jost, C., Theraulaz, G., 2016a. Stigmergic construction and topochemical information shape ant nest architecture. Proc. Natl. Acad. Sci. U. S. A. 113, 1303–1308.
Khuong, A., Gautrais, J., Perna, A., Sbaï, C., Combe, M., Kuntz, P., Jost, C., Theraulaz, G., 2016b. Stigmergic construction and topochemical information shape ant nest architecture. Proc. Natl. Acad. Sci. 113, 1303–1308.
Korb, J., 2003. Thermoregulation and ventilation of termite mounds. Naturwissenschaften 90, 212–219.
Korb, J., 2014. Robots acting locally and building globally. Science 343, 742–743.
Korochkin, L., Saveliev, S., Ivanov, A., Evgeniev, M., Bessova, N., Gulimova, V., 1991. Nerve cells of Drosophila Notch mutant are differentiated inside amphibian brain: a new approach for the analysis of genetic control of nerve cell differentiation. Genetica 85, 23–34.
von Kraft, A., 1999. Symmetry and asymmetry in the development of inner organs in parabiotic twins of amphibians (Urodela). Laterality 4, 209–255.
Krause, K., 2015. Grand-scale theft: kleptoplasty in parasitic plants? Trends Plant Sci. 20, 196–198.
Kriegman, S., Blackiston, D., Levin, M., Bongard, J., 2020. A scalable pipeline for designing reconfigurable organisms. Proc. Natl. Acad. Sci. U. S. A. 117, 1853–1859.
Kriegman, S., Blackiston, D., Levin, M., Bongard, J., 2021. Kinematic self-replication in reconfigurable organisms. Proc. Natl. Acad. Sci. U. S. A. 118.
Kuchling, F., Friston, K., Georgiev, G., Levin, M., 2020. Morphogenesis as Bayesian inference: a variational approach to pattern formation and control in complex biological systems. Phys. Life Rev. 33, 88–108.
Kwapich, C.L., Valentini, G., Hölldobler, B., 2018. The non-additive effects of body size on nest architecture in a polymorphic ant. Philos.Trans.R.Soc.BBiol.Sci. 373, 20170235.
Langton, C.G., 1995. Artificial Life: An Overview. MIT Press, Cambridge, Mass.
Lanni, J.S., Peal, D., Ekstrom, L., Chen, H., Stanclift, C., Bowen, M.E., Mercado, A., Gamba, G., Kahle, K.T., Harris, M.P., 2019. Integrated K+ channel and K+Cl- cotransporter functions are required for the coordination of size and proportion during development. Dev. Biol. 456, 164–178.
Lartigue, C., Glass, J.I., Alperovich, N., Pieper, R., Parmar, P.P., Hutchison, C.A., Smith, H.O., Venter, J.C., 2007. Genome transplantation in bacteria: changing one species to another. Science 317, 632–638.
Le Douarin, N.M., Catala, M., Batini, C., 1997. Embryonic neural chimeras in the study of vertebrate brain and head development. In: International Review of Cytology. Elsevier, pp. 241–309.
Levin, M., 1998. Left-right asymmetry and the chick embryo. Semin. Cell Dev. Biol. 9, 67–76.
Levin, M., 1999. Twinning and embryonic left-right asymmetry. Laterality 4, 197–208.
Levin, M., 2001. Asymmetry of body and brain: embryological and twin studies. In: Smelser B.P., N. (Ed.), International Encyclopedia of Social And Behavioral Sciences. Elsevier, Oxford, UK, pp. 853–859.
Levin, M., 2019a. The computational boundary of a "self": developmental bioelectricity drives multicellularity and scale-free cognition. Front. Psychol. 10, 2688.
Levin, M., 2019b. The computational boundary of a "Self": developmental bioelectricity drives multicellularity and scale-free cognition. Front. Psychol. 10.
Levin, M., 2020. Life, death, and self: fundamental questions of primitive cognition viewed through the lens of body plasticity and synthetic organisms. Biochem. Biophys. Res. Commun. 564, 114e133.
Levin, M., 2021. Bioelectrical approaches to cancer as a problem of the scaling of the cellular self. Prog. Biophys. Mol. Biol. 165, 102–113.
Levin, M., Pagan, S., Roberts, D.J., Cooke, J., Kuehn, M.R., Tabin, C.J., 1997. Left/right patterning signals and the independent regulation of different aspects of situs in the chick embryo. Dev. Biol. 189, 57–67.
Levin, M., Pietak, A.M., Bischof, J., 2018. Planarian regeneration as a model of anatomical homeostasis: recent progress in biophysical and computational approaches. Semin. Cell Dev. Biol. 87, 125–144.
Liu, Y., Wang, Q., Li, B., 2010. New insights into plant graft hybridization. Heredity 104, 1.
Lobo, D., Solano, M., Bubenik, G.A., Levin, M., 2014. A linear-encoding model explains the variability of the target morphology in regeneration. J. R. Soc. Interface 11, 20130918.
Long, K.D., Kennedy, G., Balaban, E., 2001. Transferring an inborn auditory perceptual predisposition with interspecies brain transplants. Proc. Natl. Acad. Sci. 98, 5862–5867.
Lorch, I., Danielli, J., 1953a. Nuclear transplantation in amoebae. II: the immediate results of transfer of nuclei between amoeba proteus and amoeba discoides. J. Cell Sci. 3, 461–480.
Lorch, I.J., Danielli, J., 1953b. Nuclear transplantation in amoebae. I: some species characters of amoeba proteus and amoeba discoides. J. Cell Sci. 3, 445–460.
Macia, J., Vidiella, B., Sole, R.V., 2017. Synthetic associative learning in engineered multicellular consortia. J. R. Soc. Interface 14, 20170158.
Maden, M., 2008. Axolotl/newt. Methods Mol. Biol. 461, 467–480.
Mallet, J., 2005. Hybridization as an invasion of the genome. Trends Ecol. Evol. 20, 229–237.
Mallet, J., 2007. Hybrid speciation. Nature 446, 279–283.
Mangold, H., 1929. Organisatortransplantationen in verschiedenen Kombinationen bei Urodelen. In: Wilhelm Roux'Archiv für Entwicklungsmechanik der Organismen, 117, pp. 697–710.
Mangold, O., 1931. Versuche zur Analyse der Entwicklung des Haftfadens bei Urodelen; ein Beispiel für die Induktion artfremder Organe. Naturwissenschaften 19, 905–911.
Margulis, L., 2004. Serial endosymbiotic theory (SET) and composite individuality. Microbiol. Today 31, 172–175.
Maschlanka, H., 1943. Zweikernige transplantate zwischenAcetabularia crenulata undAcicularia schenckii. Naturwissenschaften 31, 549-549.
Matthysse, A.G., Deschet, K., Williams, M., Marry, M., White, A.R., Smith, W.C., 2004. A functional cellulose synthase from ascidian epidermis. Proc. Natl. Acad. Sci. 101, 986–991.
McGinnis, W., Levine, M.S., Hafen, E., Kuroiwa, A., Gehring, W.J., 1984. A conserved DNA sequence in homoeotic genes of the Drosophila antennapedia and bithorax complexes. Nature 308, 428–433.
McKay, D., 2002. Inter-kingdom sex: the mating of bacterial and mammalian cells. Trends Biotechnol. 20, 94–95.
Meinhardt, H., 1983. A boundary model for pattern formation in vertebrate limbs. J. Embryol Exp. Morphol. 76, 115–137.
Metcalf, D., 1963. The autonomous behaviour of normal thymus grafts. Aust.J.Exp.Biol. Med.Sci. 41, 437–447.
Miller, B., Holt, G., 1977a. Memory transfer in rats by injection of brain and liver RNA. J. Biol. Psychol. 19 (1), 4–9.
Miller, B.E., Holt, G.L., 1977b. Memory transfer in rats by injection of brainand liver RNA. J. Biol. Psychol. 19, 4–9.
Mitchell, M., 2009. Complexity: A Guided Tour. Oxford University Press, Oxford England, New York.
Mittenthal, J.E., Nuelle, J.R., 1988. Discontinuities of pattern and rules for regeneration in limbs of crayfish. Dev. Biol. 126, 315–326.
Moore, D., Walker, S.I., Levin, M., 2017. Cancer as a disorder of patterning information: computational and biophysical perspectives on the cancer problem. Converg.Sci. Phys.Oncol. 3, 043001.
Mordvintsev, A., Randazzo, E., Niklasson, E., Levin, M., 2020. Growing neural cellular automata. Distill. https://doi.org/10.23915/distill.00027.002.
Mudge, K., Janick, J., Scofield, S., Goldschmidt, E.E., 2009. A history of grafting.
Muneoka, K., Murad, E.H., 1987. Intercalation and the cellular origin of supernumerary limbs in Xenopus. Development 99, 521–526.
Murugan, N.J., Kaltman, D.H., Jin, P.H., Chien, M., Martinez, R., Nguyen, C.Q., Kane, A., Novak, R., Ingber, D.E., Levin, M., 2021. Mechanosensation mediates long-range spatial decision-making in an aneural organism. Adv. Mater. 33, e2008161.
Narbonne, P., Gurdon, J.B., 2012. Amphibian interorder nuclear transfer embryos reveal conserved embryonic gene transcription, but deficient DNA replication or chromosome segregation. Int. J. Dev. Biol. 56, 975–986.
Narbonne, P., Simpson, D.E., Gurdon, J.B., 2011. Deficient induction response in a Xenopus nucleocytoplasmic hybrid. PLoS Biol. 9, e1001197.
Narbonne, P., Halley-Stott, R.P., Gurdon, J.B., 2012. On the cellular and developmental lethality of a Xenopus nucleocytoplasmic hybrid. Commun. Integr. Biol. 5, 329–333.
Needham, J., 1936. New Advances in the Chemistry And Biology of Organized Growth. SAGE Publications.
Negrini, S., Gorgoulis, V.G., Halazonetis, T.D., 2010. Genomic instability—an evolving hallmark of cancer. Nat. Rev. Mol. Cell Biol. 11, 220–228.
Nelsen, E.M., Frankel, J., 1989. Maintenance and regulation of cellular handedness in Tetrahymena. Development 105, 457–471.
Newman, S.A., 2016. 'Biogeneric' developmental processes: drivers of major transitions in animal evolution. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 371.
Nishikawa, N., Suzuki, R., Arita, T., 2016. Coordination control design of heterogeneous swarm robots by means of task-oriented optimization. Artif. Life Robot. 21, 57–68.
Norris, V., Zemirline, A., Amar, P., Audinot, J.N., Ballet, P., Ben-Jacob, E., Bernot, G., Beslon, G., Cabin, A., Fanchon, E., Giavitto, J.L., Glade, N., Greussay, P., Grondin, Y., Foster, J.A., Hutzler, G., Jost, J., Kepes, F., Michel, O., Molina, F., Signorini, J., Stano, P., Thierry, A.R., 2011. Computing with bacterial constituents, cells and populations: from bioputing to bactoputing. Theory Biosci. 130, 211–228.
Nowack, E.C., Melkonian, M., 2010. Endosymbiotic associations within protists. Philos. Trans.R.Soc.BBiol.Sci. 365, 699–712.
O'Malley, M.A., 2015. Endosymbiosis and its implications for evolutionary theory. Proc. Natl. Acad. Sci. 112, 10270–10277.
de Oca, M.A.M., Ferrante, E., Mathews, N., Birattari, M., Dorigo, M., 2010. Opinion dynamics for decentralized decision-making in a robot swarm. Swarm Intell. 6234, 251–262.

Ocko, S.A., Heyde, A., Mahadevan, L., 2019. Morphogenesis of termite mounds. Proc. Natl. Acad. Sci. 116, 3379–3384.
Olle-Vila, A., Duran-Nebreda, S., Conde-Pueyo, N., Montanez, R., Sole, R., 2016. A morphospace for synthetic organs and organoids: the possible and the actual. Integr. Biol. (Camb.) 8, 485–503.
Onuma, R., Horiguchi, T., 2015. Kleptochloroplast enlargement, karyoklepty and the distribution of the cryptomonad nucleus in Nusuttodinium (= Gymnodinium) aeruginosum (Dinophyceae). Protist 166, 177–195.
Oppenheimer, J.M., 1936. Structures developed in amphibians by implantation of living fish organizer. Proc. Soc. Exp. Biol. Med. 34, 461–463.
Panning, B., 2008. X-chromosome inactivation: the molecular basis of silencing. J. Biol. 7, 1–4.
Panoutsopoulos, A.A., 2020. Organoids, assembloids, and novel biotechnology: steps forward in developmental and disease-related neuroscience. Neuroscientist 1073858420960112.
Patil, M., 2014. Design And Implementation of Heterogeneous Robot Swarm.
Patton, A.H., Lawrance, M.F., Margres, M.J., Kozakiewicz, C.P., Hamede, R., Ruiz-Aravena, M., Hamilton, D.G., Comte, S., Ricci, L.E., Taylor, R.L., 2020. A transmissible cancer shifts from emergence to endemism in Tasmanian devils. Science 370.
Perathoner, S., Daane, J.M., Henrion, U., Seebohm, G., Higdon, C.W., Johnson, S.L., Nusslein-Volhard, C., Harris, M.P., 2014. Bioelectric signaling regulates size in zebrafish fins. PLoS Genet. 10, e1004080.
Pezzulo, G., Levin, M., 2015. Re-membering the body: applications of computational neuroscience to the top-down control of regeneration of limbs and other complex organs. Integr. Biol. (Camb.) 7, 1487–1517.
Pezzulo, G., Levin, M., 2016. Top-down models in biology: explanation and control of complex living systems above the molecular level. J. R. Soc. Interface 13.
Pietsch, P., 1972. In: Scrambled Salamander Brains-Test of Holographic Theories of Neural Program Storage, Anatomical Record. Wiley-Lis Div John Wiley & Sons Inc., 605 Third Ave, New York, NY 10158-0012, p. 383.
Pietsch, P., 1981. The Quest of Hologramic Mind. Citeseer.
Pietsch, T.W., 2005. Dimorphism, parasitism, and sex revisited: modes of reproduction among deep-sea ceratioid anglerfishes (Teleostei: Lophiiformes). Ichthyol. Res. 52, 207–236.
Pietsch, P., Schneider, C.W., 1969. Brain transplantation in salamanders: an approach to memory transfer. Brain Res. 14, 707–715.
Rainey, P.B., Monte, S.D., 2014. Resolving Conflicts During the Evolutionary Transition to Multicellular Life. Annu. Rev. Ecol. Evol. Syst. 45, 599–620.
Raper, K.B., Thom, C., 1941. Interspecific mixtures in the Dictyosteliaceae. Am. J. Bot. 69–78.
Reinis, S., 1968. Block of memory transfer by actinomycin D. Nature 220, 177.
Rubenstein, M., Cornejo, A., Nagpal, R., 2014. Programmable self-assembly in a thousand-robot swarm. Science 345, 795–799.
Rumpho, M.E., Worful, J.M., Lee, J., Kannan, K., Tyler, M.S., Bhattacharya, D., Moustafa, A., Manhart, J.R., 2008. Horizontal gene transfer of the algal nuclear gene psbO to the photosynthetic sea slug Elysia chlorotica. Proc. Natl. Acad. Sci. 105, 17867–17871.
Rumpho, M.E., Pelletreau, K.N., Moustafa, A., Bhattacharya, D., 2011. The making of a photosynthetic animal. J. Exp. Biol. 214, 303–311.
Saccucci, M., Denton, R., Holding, M., Gibbs, H., 2016. Polyploid unisexual salamanders have higher tissue regeneration rates than diploid sexual relatives. J. Zool. 300, 77–81.
Sahu, S., Sharan, S.K., 2020. Translating embryogenesis to generate organoids: novel approaches to personalized medicine. iScience 23, 101485.
Saito, Y., Koinuma, S., Watanabe, K., Agata, K., 2003. Mediolateral intercalation in planarians revealed by grafting experiments. Dev. Dyn. 226, 334–340.
Sandquist, E.J., Essner, J.J., Sakaguchi, D.S., 2018. Xenotransplantation of adult hippocampal neural progenitors into the developing zebrafish for assessment of stem cell plasticity. PloS one 13.
Sasakura, Y., Ogura, Y., Treen, N., Yokomori, R., Park, S.-J., Nakai, K., Saiga, H., Sakuma, T., Yamamoto, T., Fujiwara, S., 2016. Transcriptional regulation of a horizontally transferred gene from bacterium to chordate. Proc. R. Soc. B Biol. Sci. 283, 20161712.
Saveliev, S., Korochkin, L., Ivanov, A., Evgen'ev, M., 1989. Transplantation of Drosophila cells in amphibian embryos. In: Doklady Biological Sciences. Pleiades Publishing, Ltd.(Плеадес Паблишинг, Лтд), pp. 209–211.
Saveliev, S., Korochkin, L., Ivanov, A., Evgenev, M., Besova, N., Gulimova, V., 1990. Transplantationof embryonic neural cells of Notch Drosophila melanogaster into the neural-tubeof amphibia. Dokl. Akad. Nauk SSSR 313, 1491. -+.
Saveliev, S., Lebedev, V., Evgeniev, M., Korochkin, L., 1997. Chimeric brain: theoretical and clinical aspects. Int. J. Dev. Biol. 41, 801–808.
Schneider, C.W., Pietsch, P., 1968. The effects of addition and subtraction of eyes on learning in salamander larvae (Amblystoma punctatum). Brain Res. 8, 271–280.
Schneuwly, S., Klemenz, R., Gehring, W.J., 1987. Redesigning the body plan of Drosophila by ectopic expression of the homoeotic gene Antennapedia. Nature 325, 816–818.
Seilern-Aspang, F., Kratochwil, K., 1962. Induction and differentiation of an epithelial tumour in the newt (Triturus cristatus). Development 10, 337–356.
Sengel, P., 2003. Pattern formation in skin development. Int. J. Dev. Biol. 34, 33–50.
Sengel, P., Dhouailly, D., 1977. Tissue interactions in amniote skin development. Cell Interact.Differ. 153–169.
Sero, D., Zaidi, A., Li, J., White, J.D., Zarzar, T.B.G., Marazita, M.L., Weinberg, S.M., Suetens, P., Vandermeulen, D., Wagner, J.K., Shriver, M.D., Claes, P., 2019. Facial recognition from DNA using face-to-DNA classifiers. Nat. Commun. 10, 2557.
Setlow, B., 1997. Georges Ungar and memory transfer. J. Hist. Neurosci. 6, 181–192.
Sharma, S., Hollyfield, J., 1980. Specification of retinotectal connexions during development of the toad Xenopus laevis. Development 55, 77–92.
Shi, X.B., Qiu, Z.I., He, W., Frankel, J., 1991. Microsurgically generated discontinuities provoke heritable changes in cellular handedness of a ciliate, Stylonychia mytilus. Development 111, 337–356.
Slavkov, I., Carrillo-Zapata, D., Carranza, N., Diego, X., Jansson, F., Kaandorp, J., Hauert, S., Sharpe, J., 2018. Morphogenesis in robot swarms. Sci. Robot. 3.
Sole, R., 2016a. The major synthetic evolutionary transitions. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 371, 20160175.
Sole, R., 2016b. Synthetic transitions: towards a new synthesis. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 371, 20150438.
Sole, R., Amor, D.R., Duran-Nebreda, S., Conde-Pueyo, N., Carbonell-Ballestero, M., Montanez, R., 2016. Synthetic collective intelligence. Biosystems 148, 47–61.
Spemann, H., 1918. Über die Determination der ersten Organanlagen des Amphibienembryo I-VI. Arch.Entwicklungsmech.Org. 43, 448–555.
Spemann, H., 1921. Die Erzeugung tierischer Chimären durch heteroplastische embryonale Transplantation zwischen Triton cristatus und taeniatus. Arch. Entwicklungsmech.Org. 48, 533–570.
Spemann, H., 1924. Über Organisatoren in der tierischen Entwicklung. Naturwissenschaften 12, 1092–1094.
Spemann, H., Mangold, H., 1924. Über induktion von Embryonalanlagen durch Implantation artfremder Organisatoren. Archiv für mikroskopische Anatomie und Entwicklungsmechanik 100, 599–638.
Spemann, H., Schotté, O., 1932. Über xenoplastische Transplantation als Mittel zur Analyse der embryonalen Induktion. Naturwissenschaften 20, 463–467.
Stegemann, S., Bock, R., 2009. Exchange of genetic material between cells in plant tissue grafts. Science 324, 649–651.
Streit, A., Stern, C.D., 2014. Transplantation of neural tissue: quail-chick chimeras. In: Brain Development. Springer, pp. 235–251.
Sun, Y.H., Zhu, Z.Y., 2014. Cross-species cloning: influence of cytoplasmic factors on development. J. Physiol. 592, 2375–2379.
Sun, Y.-H., Chen, S.-P., Wang, Y.-P., Hu, W., Zhu, Z.-Y., 2005. Cytoplasmic impact on cross-genus cloned fish derived from transgenic common carp (Cyprinus carpio) nuclei and goldfish (Carassius auratus) enucleated eggs. Biol. Reprod. 72, 510–515.
Sun, Y., Do, H., Gao, J., Zhao, R., Zhao, M., Mogilner, A., 2013. Keratocyte fragments and cells utilize competing pathways to move in opposite directions in an electric field. Curr.Biol. 23, 569–574.
Swanson, D.J., Goldowitz, D., 2011. Experimental Sey mouse chimeras reveal the developmental deficiencies of Pax6-null granule cells in the postnatal cerebellum. Dev. Biol. 351, 1–12.
Swanton, C., 2012. Intratumor heterogeneity: evolution through space and time. Cancer Res. 72, 4875–4882.
Szathmary, E., Maynard Smith, J., 1997. From replicators to reproducers: the first major transitions leading to life. J. Theor. Biol. 187, 555–571.
Theraulaz, G., Bonabeau, E., 1999. A brief history of stigmergy. Artif. Life 5, 97–116.
Thyssen, G., Svab, Z., Maliga, P., 2012. Cell-to-cell movement of plastids in plants. Proc. Natl. Acad. Sci. 109, 2439–2443.
Tiedemann, R., 1989. Graft union development and symplastic phloem contact in the heterograft Cucumis sativus on Cucurbita ficifolia. J. Plant Physiol. 134, 427–440.
Topoff, H., Zimmerli, E., 1991. Formica wheeleri: Darwin's predatory slave-making ant? Psyche 98, 309–317.
Torralba, D., Baixauli, F., Sánchez-Madrid, F., 2016. Mitochondria know no boundaries: mechanisms and functions of intercellular mitochondrial transfer. Front.CellDev. Biol. 4, 107.
Trianni, V., Campo, A., 2015. Fundamental collective behaviors in swarm robotics. In: Springer Handbook of Computational Intelligence, pp. 1377–1394.
Triantaphyllou, A., Hirschmann, H., 1964. Reproduction in plant and soil nematodes. Annu. Rev. Phytopathol. 2, 57–80.
Turner, J.S., 2004. Extended phenotypes and extended organisms. Biol. Philos. 19, 327–352.
Turner, S.J., 2005. Extended physiology of an insect-built structure. Am. Entomol. 51, 36–38.
Turner, J.S., 2009a. The Extended Organism: The Physiology of Animal-built Structures. Harvard University Press.
Turner, J.S., 2009b. The Tinkerer's Accomplice. Harvard University Press.
Twitty, V.C., Elliott, H.A., 1934. The relative growth of the amphibian eye, studied by means of transplantation. J. Exp. Zool. 68, 247–291.
Twitty, V.C., Schwind, J.L., 1931. The growth of eyes and limbs transplanted heteroplastically between two species of Amblystoma. J. Exp. Zool. 59, 61–86.
Urrios, A., Macia, J., Manzoni, R., Conde, N., Bonforti, A., de Nadal, E., Posas, F., Sole, R., 2016. A synthetic multicellular memory device. ACS Synth. Biol. 5, 862–873.
Van Steenkiste, N.W., Herranz, M., Husnik, F., Keeling, P.J., Leander, B.S., 2019. A new case of kleptoplasty in animals: marine flatworms steal functional plastids from diatoms. Sci. Adv. 5, eaaw4337.
Vandenberg, L.N., Adams, D.S., Levin, M., 2012. Normalized shape and location of perturbed craniofacial structures in the Xenopus tadpole reveal an innate ability to achieve correct morphology. Dev. Dyn. 241, 863–878.
Varenne, F., Chaigneau, P., Petitot, J., Doursat, R., 2015. Programming the emergence in morphogenetically architected complex systems. Acta Biotheor. 63, 295–308.
Villeda, S.A., Plambeck, K.E., Middeldorp, J., Castellano, J.M., Mosher, K.I., Luo, J., Smith, L.K., Bieri, G., Lin, K., Berdnik, D., 2014. Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. Nat. Med. 20, 659–663.
Vogt, N., 2021. Assembloids. Nat. Methods 18, 27.
Vollmer, J., Casares, F., Iber, D., 2017. Growth and size control during development. Open Biol. 7.

Vollmer, J., Casares, F., Iber, D., 2017b. Growth and size control during development. Open Biol. 7, 170190.
Waddington, C.H., 1935. Cancer And the Theory of Organisers. Nature Publishing Group.
Wang, Y., Dai, G., Gu, Z., Liu, G., Tang, K., Pan, Y.-H., Chen, Y., Lin, X., Wu, N., Chen, H., 2020. Accelerated evolution of an Lhx2 enhancer shapes mammalian social hierarchies. Cell Res. 30, 408–420.
Wang-Chak Chan, B., 2018. Lenia - Biology of Artificial Life p. arXiv:1812.05433.
Waters, V.L., 2001. Conjugation between bacterial and mammalian cells. Nat. Genet. 29, 375–376.
Werfel, J., Petersen, K., Nagpal, R., 2014. Designing collective behavior in a termite-inspired robot construction team. Science 343, 754–758.
Werz, G., Hämmerling, J., 1961. Über die Beeinflussung artspezifischer Formbildungsprozesse von Acetabularia durch UV-Bestrahlung. Z.Naturforsch.B 16, 829–832.
Whiddon, M., Oboyle, M., Lowe, J., 1976. Memory transfer of an escape response by means of brain-tissue homogenate injection. J. Biol. Psychol. 18, 27–32.
Wilson, D.L., Arch, S.W., 1972. Does memory transfer imply limits on human knowledge. Int. J. Neurosci. 3, 43.
Wu, R., Wang, X., Lin, Y., Ma, Y., Liu, G., Yu, X., Zhong, S., Liu, B., 2013a. Inter-species grafting caused extensive and heritable alterations of DNA methylation in Solanaceae plants. PLoS One 8.
Wu, R., Wang, X., Lin, Y., Ma, Y., Liu, G., Yu, X., Zhong, S., Liu, B., 2013b. Inter-species grafting caused extensive and heritable alterations of DNA methylation in Solanaceae plants. PLoS One 8, e61995.
Xiong, L., Cao, Y., Cooper, R., Rappel, W.-J., Hasty, J., Tsimring, L., 2020. Flower-like patterns in multi-species bacterial colonies. eLife 9, e48885.
Yamamoto, K., Mak, T.W., 2017. Mechanistic aspects of mammalian cell size control. Develop. Growth Differ. 59, 33–40.
Yan, D., Lin, X., 2009. Shaping morphogen gradients by proteoglycans. Cold Spring Harb. Perspect. Biol. 1, a002493.
Yan, S., Mao, Z., Yang, H., Tu, M., Li, S., Huang, G., Li, G., Guo, L., Jin, G., He, R., 2004. Further investigation on nuclear transplantation in different orders of teleost: the combination of the nucleus of Tilapia (Oreochromis nilotica) and the cytoplasm of Loach (Paramisgurnus dabryanus). Int. J. Dev. Biol. 35, 429–435.
Yeung, J., Ha, T.J., Swanson, D.J., Goldowitz, D., 2016. A novel and multivalent role of Pax6 in cerebellar development. J. Neurosci. 36, 9057–9069.
Zhou, J.X., Cisneros, L., Knijnenburg, T., Trachana, K., Davies, P., Huang, S., 2018. Phylostratigraphic analysis of tumor and developmental transcriptomes reveals relationship between oncogenesis, phylogenesis and ontogenesis. <sb:contribution><sb:title>Converg. Sci.</sb:title> Phys.</sb:contribution><sb:host><sb:issue><sb:series><sb:title>Oncol.</sb:title></sb:series></sb:issue></sb:host> 4.