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Integrating Evolutionary and Developmental Thinking Into a Scale-free Biology

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Abstract: When the history of life on Earth is viewed as a history of cell division, all of life becomes a single cell lineage. The growth and differentiation of this lineage in reciprocal interaction with its environment can be viewed as a developmental process; hence the evolution of life on Earth can also be seen as the development of life on Earth. Here we highlight some potentially-fruitful research directions suggested by this change in perspective. Variation and selection become, for example, bidirectional information flows between scales, while the notions of "cooperation" and "competition" become scale-relative. The language of communication, inference, and information processing becomes more useful than the language of causation to describe the interactions of both homogeneous and heterogeneous living systems at any scale. Emerging scale-free theoretical frameworks such as predictive coding and active inference provide conceptual tools for reconceptualizing biology as the study of a unified, multiscale dynamical system.

Keywords: Active inference; Evo-Devo; Extended synthesis; Free-energy principle; Hierarchical dynamics; Holobiont; Individuality

Running Title: Scale-free Evo-Devo

Introduction

Evolutionary and developmental biology have remained distinct disciplines since their emergence in the 19th century from classical naturalism and embryology, respectively [1]. The Modern Synthesis and later, the adoption of molecular tools and techniques refocused the attention of both of these disciplines on the genome, with the Evo-Devo insights that developmental mechanisms evolve, and that their evolution drives coordinated phenotypic changes [2, 3] as the result. Evo-Devo does not yet, however, fully integrate evolutionary and developmental biology into a single discipline with a unified conceptual basis and domain of application [4]. Evolutionary biology remains largely focused on selection and adaptation, whether at the level of genes, individual organisms, or communities, while developmental biology remains largely focused on the life-histories of individual organisms. As Szathmáry and Maynard Smith [5] put it, "[d]evelopmental biology can be seen as the study of how information in the genome is translated into adult structure, and evolutionary biology of how the information came to be there in the first place" (p. 231).

This traditional division of labor is challenged, in complementary ways, by two emerging ideas. The first is that the traditional, intuitive concept of an "individual organism" with a well-defined genotype, phenotype, and boundary – and in consequence, a well-defined environment comprising "everything else" – has lost its utility and possibly even its meaning. Turner [6] provides a powerful statement of this critique, arguing from the specific case of *Macrotermes* – *Termitomyces* termite-fungal symbiosis that distinct lineages of genes, morphologies, behaviors, and constructed abiotic environments co-evolve as "extended organisms" with heterogeneous phylogenetic histories and ill-defined boundaries. The discovery of obligate symbiotic microbiomes in animals, now extending even to "basal" organisms like sponges [7], and the emergence of the holobiont concept [8, 9] move this heterogeneity inside the traditional individual. Extending the notion of a "biological individual" to include such heterologous systems is further supported by the ever-expanding list of symbiotic and mutualistic relationships above the holobiont level, including plant – pollinator (e.g. in Agavaceae [10]), nutrient-exchange (e.g. mycorrhiza [11]), and agricultural (e.g. by ants [12]) relationships.

Complementing the expansion of the "individual" to the holobiont is an increased recognition of the ubiquity and importance of competition within multicellular bodies [13, 14]. The presence of intra-organism competition was realized already at the very dawn of developmental biology by Roux, who presciently wrote of the *struggle of the parts* [15]. Competition between developing neurons for trophic factors and activity [16] and between stem cells for niche resources [17] are well-characterized examples. Such competition is particularly relevant in cancer; some model a tumor as an organ [18] that can take over other cell types [19] in the same way that embryonic instructor cells control other cells in normal development [20].

Evolutionary biology has responded to this challenge to the notion of biological individuality with proposals to redefine "an individual" as a locus of maximum cooperation at some given scale [21, 22] and to formally extend the conceptual structure of the Modern Synthesis to incorporate heterogeneous systems [23-25]; see [26, 27] for arguments that this extension is insufficient. Expanding or redefining the concept of "individual" also impacts developmental biology, raising the question of what counts as the "unit of development" [9]. Within human developmental biology, with its practical medical implications, the response has been to merge the holobiont back into the traditional individual (e.g. [28]). Outside of this context, however, the question can be addressed more broadly. We have argued, for example, that the unit of maximum cooperation in asexual planaria is the clonal stem-cell lineage,

which is simultaneously one of many such lineages within, and extends in both time and space far beyond, what would traditionally be called an "individual" planarian [29].

From a deep phylogenetic perspective, all descendants of the last universal common ancestor (LUCA) together compose one continuous cytoplasm contained within one continuous cell membrane; hence all descendants of LUCA together compose one continuous cell lineage, i.e. one biological individual [30-32]. Multilevel evolutionary theory describes the life-history of this individual as a sequence of major transitions in which new levels of organization, e.g. eukaryotic cells and multicellular organisms, emerge in response to selection for increased cooperation [5, 33-36]. Individual life-histories are, however, also the domain of developmental biology, where they are described as processes of cell proliferation and differentiation driven by regulatory interactions at multiple scales. Crucially, every developing structure imposes boundary conditions on processes at smaller scales [37-40] as well as constraints on higher-scale development. Is it more productive to describe the history of life as a whole as evolution or as development? We suggest a third option: that fully integrating evolutionary and developmental concepts into a single, scale-free description may enable novel insights.

The elaboration of theoretical methods and concepts equally applicable to evolutionary and developmental biology, but formulated independently of either, poses the second challenge to the traditional distinction between these disciplines. If evolutionary and developmental processes can be given the same formal, mathematical description, it becomes hard to argue that they are distinct in any fundamental way. The "free-energy principle" (FEP) – the idea that systems at any scale execute internal dynamics that minimize the difference between expected and detected conditions – is the best-developed candidate for such a description. Initially developed within computational neuroscience to describe the apparently Bayesian inferences implemented by neural networks at multiple scales [41], it is increasingly being applied to evolutionary [42] and developmental [43, 44] processes. We have suggested recently that FEP minimization provides a purely thermodynamic account of the transition from unicellularily to obligate multicellularily in sufficiently harsh environments [45].

As a thermodynamic model of inference, the FEP supports a broad conception of organisms as information-processing systems [46, 47] and of biological processes as implemented computations. Such a conception is intrinsically scale-free, describing biological systems in terms of common, abstract processes that are implemented from the subcellular or even deep physical [48] scales to the ecosystem scale and beyond. In such a conception, apparent teleology is redefined from an intractable philosophical problem to a practical, empirical problem of how (approximately) invariant outcomes at some scale are jointly encoded by memory structures or processes at both lower and higher scales [31, 39, 40].

In what follows, we take seriously the possibility that evolutionary and developmental biology are, or are becoming, a single science with one domain – all of life – and a shared toolkit of theoretical and experimental methods and concepts. In this case, the existing concepts and tools of evolutionary and developmental biology should either be, or be modifiable to become, both mutually consistent and cross-applicable. We examine several cases in which concepts of the two disciplines are *prima facie* mutually inconsistent or significantly conflicting, beginning with the conflict between the largely stochastic versus largely deterministic concepts of mechanism in evolutionary and developmental biology, respectively. We ask how the theoretical roles of these conflicting concepts might be made mutually compatible and what new research questions emerge when this is done. We do not claim definitive answers to any of these questions; we rather offer them as potentially-fruitful new research

directions and highlight work that has already started. We conclude by suggesting that a conceptual unification of evolutionary and developmental biology has the potential to significantly increase our understanding of biological processes on multiple scales.

Random versus outcome-directed processes

Variation, selection, and inheritance are the three fundamental components of evolution as a process [49]; hence they are the three fundamental explanada of evolutionary theory. The default explanation of variation, and the foundation of evolutionary theory as an alternative to theological or other explicitly teleological views of the world, is the assumption that variation is "random" or occurs by "chance" [50]. As Michod [35] puts it, "[d]esign in biology … is created through differential replication and survival operating on random variation (p. 161). More precisely, the process(es) that produce variants (at some given scale) are stochastic (at that scale) and the variants that they produce are mutually statistically independent [51, 52]. The idea of "chance" variation suggests, moreover, a default expectation of uniform probabilities of variants, both across variable characters and across variational outcomes. Variation becomes, in this case, a uniform-probability random walk through character-value space, an idea consistent with the "pure contingency" championed by Gould [53]. This model of variation as a stochastic process acting with uniform probabilities on statistically-independent characters is typically assumed for molecular sequences, and is inherited by evolutionary models that assume that sequences are the basis of both inheritance and selection. Uniform probabilities of variation underlie, in particular, molecular clock models based on molecular sequence similarity [54]. Stochastic variation also occurs above the level of the genome, generating phenotypic diversity in isogenic clonal populations of both unicellular and multicellular organisms [55-57].

Under constraints imposed by directional selection, equiprobable variations do not imply equiprobable outcomes; indeed specific evolutionary models [58], evolutionary games [59], the general utility of genetic algorithms as search procedures [60], and the existence of identifiable species living in identifiable niches all indicate that evolution can "progress" in the sense of better adapt to imposed conditions. As Watson and Szathmáry [61] point out, evolution and learning can both generate nonrandom macroscale outcomes from random microscale variation given appropriate macroscale constraints, and in some domains are formally equivalent. Equiprobable variation is, however, the antithesis of the directed, apparently outcome-oriented generation of cellular diversity that characterizes developmental processes. Here a precisely-orchestrated combination of lineage-based gene expression and intercellular signaling results in the consistent production of particular terminally-differentiated cell types arranged in a consistent spatial pattern, and thus a particular "target" morphology by every genetically-typical individual experiencing a species-typical environment (e.g. [62]). These processes are essentially invariant from individual to individual within a species, on multiple scales from gene expression patterns in specific cell lineages [63-65] to the gross morphology of organ systems and limbs; departures from process invariance produce the outcome variants on which population-scale selection acts. Development is, moreover, "progressive" in a natural and obvious sense. The most remarkable examples of this invariant plasticity are illustrated by the anatomical homeostasis implemented by regulative development and adult organ regeneration: injury and drastic deformation of tissue relationships induce cells to drive morphogenesis and remodeling until they achieve correct anatomical outcomes [66, 67].

Equiprobable, independent, stochastic variation as an evolutionary mechanism has been challenged at

multiple scales, from locus-specific differences in mutability or the probability of DNA repair (e.g. [68, 69]) to the sequence-specificity of recombination or transposon mobility [70-73] to the ideas of gene duplication, gene conversion, gene families, and cassettes [74-76]. Evo-Devo is based in part on the observation that highly mechanistically nonrandom duplication events that copy entire clusters of developmental regulators, e.g. the Hox cluster [77], can drive major evolutionary events [2, 3]. Mechanistically nonrandom variational processes such as gene-cluster duplication may produce outcomes that are uncorrelated with, and hence still "random" with respect to fitness. Randomness with respect to fitness is challenged by evidence supporting forms of developmental bias [78], pre-adaptation [79] or adaptive prediction [80], and adaptive mutation [81]. Active modification of the environment, moreover, effectively channels selection and hence the variational outcomes that survive and reproduce, as emphasized by extended synthesis theorists [23-25]. For all eukaryotes the "environment" includes the other organisms comprising the intact, viable holobiont, which becomes the unit of survival and reproduction [8, 9]. Such storage of information in the environment can be considered a form of active inference [42] as discussed below.

One can ask whether some of the forms of non-randomness highlighted above are just artifacts of our inability to observe cells, organisms, or developmental trajectories that do not survive. Conversely, one can question whether "randomness" in any form is not merely an artifact of our limited ability to observe causal chains. These questions are to some extent philosophical, but they do suggest that the seemingly fundamental conflict between randomness in evolution and non-randomness in development may be less an empirical than a conceptual issue.

If evolution at the biosphere level is in fact the development of a single, unique biological individual comprising all of life, might it be canalized toward some specific outcomes, in the same way that the stochastic cell-level processes of development are canalized, through the action of spatiotemporally local physical and biochemical constraints, toward some specific invariant outcomes? Is there a "target morphology" that this biosphere-scale "developmental" process is building? Would any outcomes, e.g. major transitions such as the eukaryotic cell or multicellularity, be expected to be replicated if evolution could be "run over again" as Gould [53] imagines in his thought experiment? If evolution generically generates complexity, i.e. highly-organized systems as opposed to just highly diverse systems [82], does this mean complex organisms, complex inter-organismal interactions, or both? Would we expect such an abstract global property to be conserved even after global, apparently random perturbations such as mass extinctions? At what scale or scales might we expect such a property to be encoded in the structures or interactions of current organisms and/or their physical environments? Studies of homeostatic plasticity of regulatory molecular networks, cell networks, organs, and swarm constructs in morphogenesis suggest a scale-free concept of complexity, in which the same concepts can be applied from the molecular to the population level [44, 83-85].

Life as a whole is, by definition, a single, unique individual. The process by which it develops cannot be regarded as "selected" or "adapted" in any way. It is, rather, analogous to the development of the physical universe as a whole, a process similarly characterized by a sequence of major transitions (e.g. from pure radiation to elementary particles to atoms) that progressively generate a hierarchy of scale-specific structures. This process is driven by local physical interactions constrained by global boundary conditions. Theoretical study of this unique, individual developmental process has generated significant empirical predictions, many of which have been extensively tested (e.g. [86]).

Genome-centric versus non-genome-centric inheritance

The modern synthesis is based on the recognition that genomes are inherited and that evolution can act directly at the level of DNA. A popular but extreme view is that evolution acts only at the level of the genome [87], and hence that the cell can be considered just a "bag" of manipulable genes (e.g. [88]). Both the existence of epigenetic effects [89, 90] and the encoding of significant heritable information in the cell membrane, cytoplasm, and cytoskeleton [31, 91] challenge this extreme view (see [27] for a general critique of the gene-centric view). In planaria, for example, an epigenetically inherited bioelectric asymmetry along the anterior-posterior (A-P) axis specifies head-tail morphology; induced A-P bioelectric symmetry induces a *heritable* two-headed phenotype that persists across future rounds of amputation and regeneration of middle fragments in plain water, with no further manipulation [92]; this novel anatomical layout can be reversed back to a stable one-headed form by briefly targeting a proton/potassium exchanger complex [93]. Although the two-headed phenotype has only partial penetrance, the ratio of one-headed to two-headed forms in each round of regeneration remains approximately fixed over multiple generations after only a single symmetrization treatment [93]. This heritable bioelectric state acts upstream of all known genetically-encoded mechanisms in determining a whole organism-scale morphological outcome despite a wild-type genome [94].

Multilevel evolutionary theory acknowledges that variation and selection occur at multiple scales, from the molecular to the cultural [5, 33-36]. Extended-synthesis thinking extends this further, emphasizing information storage outside of the traditionally-bounded "organism" altogether. "Extended organisms" as discussed above are a canonical example, as are multigenerational cultural practices employing external memories, e.g. tool-use cultures in humans and other species [95, 96].

Single cells in developing embryos clearly access information encoded in multiple formats, including their own genome/transcriptome/proteome, the current states of their cytoplasm, cytoskeleton, and membrane, including the spatial organizations of receptors, channels, and other membrane-bound, cytoskeleton-coupled proteins, molecular and bioelectric signals from specific neighboring cells, regional or organism-scale molecular and bioelectric signals generated by groups of more distant cells, and light, gravity, osmolarity, and other physical features of their environments [31, 39, 97-101]. Recognition of these diverse encodings at multiple spatial and temporal scales naturally raises the questions of how this developmentally-relevant information is partitioned between scales and how the encoding process is regulated at each scale.

From an information-theoretic point of view, "inheritance" is memory: the transfer of information through time, in this case communication between consecutive instances of a living system over time. Any system organized at multiple scales will, moreover, encode memories at each scale just as a consequence of basic physics; as Fig. 1a illustrates, lower scales encode the mechanisms that compose the behavioral possibility space at a given scale, while higher scales set boundary conditions that constrain this possibility space [37, 38]. The dynamics at any scale in such a system both influences and is influenced by the dynamics at all other scales. That there can be no single, preferred "unit of selection" scale at which variation is evolutionarily significant follows immediately [102, 103].

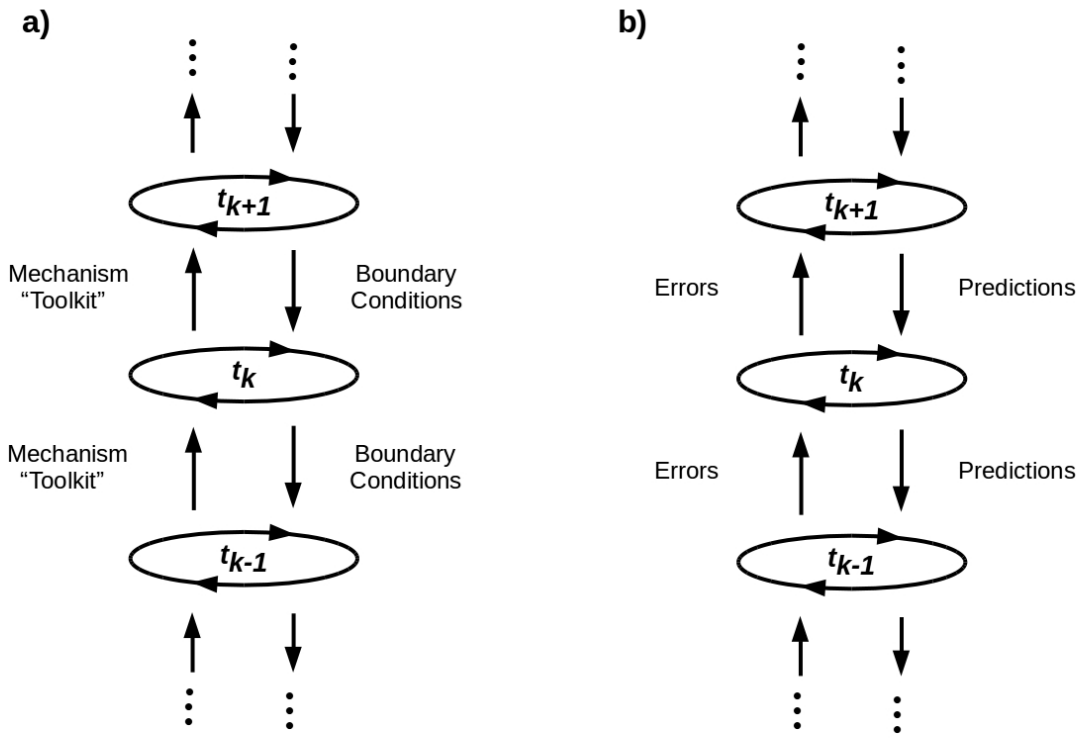

Fig. 1: a) a hierarchy of dynamics (loops with arrows) characterized by scales *k* and a characteristic times t_k exchanges "toolkits" of mechanisms that define the behavioral possibility space in the bottom-up direction and boundary conditions that constrain behavior within that space in the top-down direction. b) any such hierarchy can be represented as a predictive-coding system, with predictions flowing top-down and prediction errors flowing bottom-up.

In any system, top-down boundary conditions can be viewed as expectations about where in the space of possible behaviors the actual behavior of the system will be localized. Constant boundary conditions predict a constant environment in which some circumscribed collection of behaviors suffice to maintain homeostasis, using this term in an extended sense that includes metabolic and cell-division cycling. Time-varying boundary conditions enable – indeed demand – exploration of the space of behaviors in response to a changing environment. In this case, the "state" of the boundary condition imposed at scale *k* and time t_k can be viewed as a prediction of the appropriate behavioral response(s) at scale *k* and time $t_k+\Delta t_k$, for some "small" interval Δt_k. With this interpretation of boundary conditions as predictions, the hierarchical dynamics of Fig. 1a can be represented as a hierarchical predictive coding system as in Fig. 1b, in which predictions flow top-down and "errors" or discrepancies between predictions and current (at Δt_k) conditions flow bottom-up. An "error" is, in this case, a change

between t_k and $t+\Delta t_k$ in the activation levels of the mechanisms available in the "toolkit" at scale k.

Hierarchical predictive coding models are ubiquitous in cognitive neuroscience [41, 104-107], and reflect the general observation of tonic top-down regulation of neural activity in "layers" of local circuits organized to represent their target environment at some scale k. Such models implement a general least-action principle, minimization of prediction error, corresponding in the language above to the minimization of changes in the distribution of activation across available mechanisms. Friston [41, 42] gives this least-action principle a thermodynamic formulation as the minimization, at each scale k, of the variational free energy (VFE) of the environment measured at k. Intuitively, environmental VFE measures the environment's ability to change unpredictably; technically, it is the Kullback-Leibler divergence between prior and posterior probabilities minus the system's predictive ability, all defined at scale k. Simulations of VFE minimization reproduce qualitative patterns of biological morphogenesis [43, 44]; formal details are provided in [44].

Within a VFE minimization framework, both action on the environment (to alter the boundary conditions in Fig. 1a) and revision of the internal representation of the environment (altering the activation of available mechanisms in Fig. 1a) can achieve the goal of reducing prediction error; hence the terminology of "active inference" [41, 42]. The "environment" of an active inference system includes its body; minimizing VFE implements an intrinsic motivation toward continued homeostasis and hence survival [108, 109]. This picture motivates a general deployment of cognitive and information-processing concepts in biological systems [40, 47, 110]. As action on the environment effectively stores information in the environment, rendering it a memory resource, the active inference framework naturally represents "extended organisms" Turner's [4] sense.

The representation of organisms as active agents embedded in and interacting with active environments requires a reconceptualization of inheritance as the transfer across time not of a genome or other isolated memory-bearing structure but of a functioning dynamical system – a living cell in continuous interaction with its environment. Although memory is physically encoded and selection acts at multiple scales, what actually survives (or not) is a cell lineage [31]. This raises deep questions for evolutionary biology. In an active inference framework, "variation" can be viewed as bottom-up information flow between scales, while "selection" is top-down constraint flow; this interpretation can also be reversed by low-level variants as "selecting" for compensatory variation at higher scales. Hence both variation and selection can occur at any scale, including scales within the organism and within the environment. The central evolutionary concepts of adaptation and exaptation apply, therefore, to interactions at all scales, not just at the organism-environment interaction. In this setting, adaptation and exaptation are processes, analogous to perception or measurement, that render information flows actionable. They therefore require information-bearing structures that function as reference frames or standards against which incoming information is compared. "Optimal" pH, osmolarity, and membrane voltage may serve as reference frames at the cellular scale, but state variables that serve this function at higher scales remain to be defined. How organisms represent their own geometry and that of their environment, for example, remains poorly understood. The role of mammalian hippocampal place cells in the latter task the best-studied example [111], although work on non-neural bioelectricity is beginning to extend these ideas to the anatomical surveillance required to support the plasticity of bodies that adjust structure and function despite radical deformations [112, 113]. Reference frames for time, particularly circadian rhythm, have similarly been investigated at the neural network scale in mammals [114], and at the level of highly-conserved genetic networks in

diverse organisms from mammals to bacteria [115].

Competitive versus cooperative interactions

Evolution is traditionally thought of primarily in terms of competition; indeed the very existence of cooperation is generally conceptualized within evolutionary theory as a problem to be solved [116, 117]. Cooperative mechanisms such as group or multilevel [118] selection are interesting and controversial because they challenge this focus on competition. Within multilevel evolutionary theory, major transitions such as the eukaryotic cell or multicellularity are possible only if and when mechanisms for cooperation at the new larger scale have evolved [5, 33-36]. Development, on the other hand, is thought of primarily in terms of cooperation, with the biological individual, the outcome of development, sometimes defined as a system that maximizes cooperation [21, 22]. Informally, we tend to think that more closely related cells are more likely to be allies in a developmental context, while in a social-evolutionary context the assumption that even near kin will be allies can be highly disadvantageous [117, 119].

Detailed studies of particular cases have challenged both of these generalizations [13, 14]. Competition among neurons in the developing brain for both coherent activity [120] and neurotrophic factors [16] is well documented. Here competition is not for reproductive success and hence lineage survival, but for immediate resources and hence individual survival. Stem cells compete for their preferred cellular microenvironments [17], and cells routinely ascertain each other's fitness, removing cells that are judged to be inferior [121, 122]. On the other hand, cross-species metabolic cooperation is well documented in microbial mat communities [123] and in multiple examples of symbiosis; such cooperation is typically transactional as opposed to strictly altruistic. Lateral gene transfer is a cooperative evolutionary mechanism, as the genes transferred typically code for functions facilitating survival in challenging environments [124]. The discovery of symbiotic microbiomes throughout animal lineages [7, 28, 125] and the development of the holobiont concept [8, 9] made it clear that both evolutionary and developmental processes at the holobiont level involve a dynamic balance between cooperation and competition among cells derived from multiple lineages.

When evolution is viewed in terms of bidirectional flows of variation and selection between scales as above, the notions of "cooperation" and "competition" become scale-relative. While small-scale cooperation (e.g. of cells within an organism) supporting larger-scale competition (e.g. between organisms) is familiar, small-scale competition (e.g. among cells within a tissue) may also support larger-scale cooperation (e.g. between tissues). If all of life is a biosphere-scale holobiont inhabiting a planetary-scale environment, what are commonly considered cooperative or competitive interactions between individual organisms become internal processes. Cooperation and competition can, indeed, be considered internal all the way down; in asexual planaria, for example, stem-cell lineages that extend throughout a clonal population both cooperate and compete within individual worms in the population [29]. Such scale-relativity suggests that the right language for describing interactions is the language of information flow and agent-agent communication, both within and between scales.

Causal interaction versus informative communication

Evolutionary biology traditionally employs a language of causation; for example, we tend to think of

organisms causally altering an environment to which other organisms have to adapt. Predators alter the environments of prey and vice-versa, parasites alter the environments of hosts and vice-versa, invasive species alter the environments of native species and vice versa. The extended organism concept is built on a causal-interaction basis [126]. Developmental biology, on the other hand, makes greater use of the language of communication. We think, for example, of cells sending instructive signals to other cells to induce proliferation, differentiation, or apoptosis. Communication is, of course, causal; information must be physically encoded to be communicated, and the tokens encoding the information must be physically exchanged, with both encoding and exchange requiring energetic resources [127]. The information exchanged, however, is also independent, in principle, of the specific encoding chosen. The language of communication naturally raises the questions of how information is stored, accessed, encoded, transmitted, received, and interpreted, questions that are difficult to formulate clearly and at the right level of abstraction in the language of causation.

Developmental signaling mechanisms are often redundant, multimodal, and error-correcting [31]. Neurons represent a major evolutionary innovation not only because they allow fast and specific communication between individual cells, but also because they support two error-correction mechanisms, exact path replication and bidirectional handshaking, that are critical for accurate, long-distance coordination of complex morphology and behavior [128]. Considering evolution and development to be the same process immediately raises the question of whether a “neuron” equivalent specialized for communication between lineages can be identified. It also raises the question of error correction in evolution, and of what an “error” would even be in evolutionary terms. For example, a genetic or epigenetic change that resulted in an embryonic feature with an abnormal shape can be seen as a birth defect, but in some cases it might be appropriate to the shape of another, viable species [129, 130]. Unless obviously deleterious to health, the boundary between developmental defect and evolutionary innovation can be difficult to define. Synesthesia in humans, for example, can be viewed as an example of evolutionary “tinkering” toward a more integrative perceptual interface [131].

Homogeneous systems versus heterogeneous systems

Evolutionary biology has always been concerned with interactions between heterogeneous organisms, often representing mutually-distant lineages, within a shared environment. Developmental biology, on the other hand, has traditionally been concerned with interactions within an individual, i.e. between members of a single clone of post-zygotic cells. The holobiont and extended organism concepts clearly challenge this focus on homogeneous populations. In the case of human fetal development, this challenge has practical, medical implications [28].

A natural response to the recognition that all multicellular systems of interest to either evolution or development are holobionts is to consider interactions between lineages, with the explicit recognition that lineages may cross the boundaries between traditional “individuals” and between “organism” and “environment.” Microbial lineages, for example, are shared between organismal microbiomes and the external environment, and are exchanged between them [132]. Inter-lineage interactions may differ between compartments due to different selective constraints; the developing host organism, for example, is a rapidly-changing selective environment for its microbiome. In cases of asexual reproduction by whole-body regeneration, e.g. in cnidarians or flatworms, such crossing between “organism” and “environment” compartments even involves stem-cell lineages [29]. Here again, differences in the “environments” of non-stem somatic cells (e.g. genomic heterogeneity [133]) may

lead to differences in inter-lineage interactions within different individuals.

Reconceptualizing both evolution and development in terms of inter-lineage interactions, which may be cooperative or competitive in a scale-dependent way as discussed above, suggests that lineage-homogenizing bottlenecks in evolution are functional analogs of lineage-homogenizing sexual reproduction. Sexual reproduction generates diversity in the germline lineage while suppressing diversity, by organism-level death, in somatic lineages, and is generally viewed as a defensive strategy in evolutionary terms [134]. One can ask whether genetic bottlenecks and extinctions have a similarly defensive function on macro-evolutionary scales.

Conclusions

Evolutionary and developmental biology have traditionally pursued distinct sets of questions using distinct theoretical concepts and experimental tools. Both empirical discoveries and theoretical developments over the past two decades motivate a re-examination of the traditional distinctions between these disciplines. It is now well-established that developmental mechanisms evolve. Here we suggest going beyond this, to a scale-free biology that fully integrates evolutionary and developmental thinking.

What will this integrated biology look like? As outlined above, we expect it to render concepts such as randomness, goal-directedness, competition, cooperation, causation, and communication scale-relative. It will consider both organisms and supra-organismic structures as "environments" for systems at smaller scales (as is already happening on a smaller scale in cancer biology), and ask what constraints these environments impose. It will recognize that all organisms contain functional components from heterogeneous lineages, whether they are exogenous genes, endosymbionts, or chimeric cells. It will treat all biological structures as memories, and all biological processes as (possibly quantum) computations.

This integrated, scale-free biology will be useful to the extent that it motivates new questions and novel experiments. Theoretical work along these lines has already started [40, 45, 47, 110, 135-137]. Both artificial embryogeny and *in silico* evolution [138, 139], as well as the nascent field of synthetic morphology [140-146], suggest that coming decades will enable the running of well-controlled evolutionary experiments that may reveal the presence of organizing principles operating across scales to generate order from the interplay of generic laws of physics and computation with selection imposed on both genetic and epigenetic mechanisms.

In summary, we suggest that biology can be, and progressively is being, reconceptualized as scale-free. This reconceptualization blurs, and in the limit even erases traditional disciplinary boundaries, and offers new concepts, methods, and tools for theory development, experimental design, and both medical and bioengineering practice.

Conflict of Interest

The authors declare that they have no conflicts of interest relevant to this research.

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