

What does evolution make? Dynamics underlying learning in living lineages and machines.

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WHENCE THE ENDLESS FORMS MOST BEAUTIFUL?

Living forms present three fundamental challenges to our understanding: First, they self-assemble – performing all of the decision-making needed to construct a functional, complex body while the computational material itself is being reorganized on-the-fly. Second, they reach the correct target morphology reliably, utilizing heredity mechanisms to propagate specific patterns of form and behavior through time. Crucially, third, this process is almost never hard-wired, but instead offers immense plasticity, able to complete morphogenetic tasks despite perturbations of external environment and internal components¹. This capacity to navigate the morphospace of possible anatomies, to produce the correct final pattern in the face of novel situations, or to create something completely different (never before seen by evolution) but nevertheless coherent and adaptively functional², is an example of problem-solving ability in a high-dimensional latent space. This lynchpin capacity ties together fields of evolutionary developmental biology, non-equilibrium thermodynamics, computational and information science, and the emerging field of diverse intelligence. The implications of understanding the multiscale behavior of the active matter of life during embryogenesis, regeneration, and cancer suppression range across biomedicine, bioengineering, robotics, and bio-inspired AI. Central to this set of questions is the relationship between the genetically-specified hardware inside cells and the resulting physiological software that produces phenotypes acted upon by selection. Given the plasticity and context-sensitive decision-making of the all-important morphogenetic layer lying between genotype and phenotype, what are useful conceptual frameworks for understanding what genomes actually do (or encode), on evolutionary and ontogenetic timescales?

A FRESH PERSPECTIVE ON THE GENERATIVE GENOME

The paper “*The Genomic Code: The genome instantiates a generative model of the organism*” by Mitchell and Cheney³ offers an unconventional and insightful analogy between the genome and generative models in machine learning, thus significantly advancing our understanding of how genetic information is encoded and decoded during evolution and development. The authors elegantly bridge concepts from biology, neuroscience, and artificial intelligence, offering a formalizable and timely framework that could advance both theoretical and empirical research; especially the listed *Outstanding Questions* are a valuable, thought-provoking contribution to the community. Here, we provide a brief overview of related ideas and ways to extend this approach in theoretical and experimental biology.

Evolution through developmental reproduction involves encoding the features and functionality necessary for high-fidelity reconstruction of an organism into the compact form of the genome. The authors rightly argue that the genome does not encode organismal traits or developmental processes directly, departing from the genetic “blueprint” or “program” metaphors. Instead,

they identify the genome as compressed latent variables - analogous to Waddington's gene landscape and biologically implemented via protein-encoding sequences and gene regulatory factors - that instantiate organismal development literally as a generative model. They argue that the genome comprises compressed latent variables that are shaped or encoded by evolution and natural selection, and decoded by a generative model implemented by the cells of the developing embryo. Development can thus be interpreted as hierarchical generative decoding process from a single cell into a mature organism that is similar but not identical to its ancestors, a reconstruction with variational adaptations and mutations. As we argue below, this kind of architecture enables not only fidelity (reliability) in reaching the correct species-specific target morphology, but also creative problem-solving that maximizes adaptive saliency to new scenarios, not just hardwired replication of what happened before. The line of thinking described herein integrates across scales of space and time, identifying this flexible, creative process as conserved across evolutionary, developmental, and behavioral contexts.

EVOLUTIONARY DEVELOPMENT AS GENERATIVE MODEL

In machine learning (ML) terms, such an architecture is reminiscent of variational auto-encoders (VAEs^{4–7}), two-stage Artificial Neural Networks (ANNs^{8–12}) consisting of an encoder and a decoder part (see Fig. 1 (A)). The encoder and decoder are jointly trained to compress input data into a lower-dimensional bottleneck representation, from which the original data is reconstructed via decompression. Typically, the decoding-stack of VAEs occurs hierarchically, going from abstract representations through adding modular features to detailed reconstructions of the original data, closely resembling, in turn, the developmental stack of embryogenesis. The latent space can capture emergent properties of the data, such as clusters or manifolds that represent different classes or features (modularity). Generative models, including VAEs, generate data by sampling from this latent space, variational latent variables allowing for the creation of novel examples conforming but not identical to the training data (adaptation). Thus, generative processes relying on compressed latent variables arguably leverage modularity and evolvability in developmental biology. Such work speaks to the fundamental question of the meaning of “genetics” – what precisely is encoded in the biochemical medium of the genes, and how is it read out and interpreted by the active cellular material whose hardware it specifies?

EXTENDING THE AUTOENCODER ANALOGY

Mitchell and Cheney's framework focuses on the powerful idea of interpreting the genome as latent variables of a generative model. The assertion that “DNA instantiates a generative model of the organism” is spot on, and has been actively debated^{13–19}. However, the authors seem not to commit to whether their proposed generative model covers (i) the entire developmental stack from the genome to the organism, or targets (ii) a single decoding layer between the genome and a cellular phenotype. This raises questions about how such a model might be applied across different scales of biological organization (c.f., Fig. 1 (B)):

- i Biology is organized in layers within layers of abstraction, where the components of each organizational level efficiently navigate their respective problem domains^{14,15,17}, including metabolic, transcriptomic, physiological, anatomical, and behavioral state spaces. More than that: biological agents, even those comprising the same organism continuously influence, *i.e.*, “hack”, each other either in symbiotic or adversarial relations, including among the organs of a single organism^{20–22}.

- ii Even individual cells dynamically respond to environmental cues but can also reconfigure internally via gene regulatory networks (GRNs), displaying significant structural and operational plasticity, including several different kinds of learning^{13,16,17,23}.

VAEs are single-shot generators with limited generative variability stemming from noise applied at the latent space level. The subsequent decoder is a deterministic down-stream process with no room for further variability or creativity. In contrast, organismal development is inherently distributed with a collective of agents constantly reinterpreting and reacting to signals and noise across scales^{16,17}. Following the VAE metaphor, this is fundamentally different from variations only in the latent space, and would rather affect every node within the decoder, massively departing from the typical deterministic downstream decoding processes. Moreover, embryonic viability requires adherence to stringent physiological and energetic criteria throughout development, while vanilla VAEs do not enforce physical constraints on intermediate states during decoding.

The hierarchical and recurrent complexity and multiplicity of the genetically instantiated generative model of organismal development poses significant challenges for current ML architectures, greatly departing from the VAE analogy. Here, we intend to expand on the more general generative model framework and discuss inherently collective self-regulatory ML approaches bridging the gap between artificial and biological life.

FROM BOWTIES TO DARWIN'S AGENTIAL MATERIAL

One exciting aspect of using deep concepts from ML to shed light on biology is that it provides a rigorous formalism for unifying dynamics of cognitive and morphological change. The idea that the self-assembly of the body had important symmetries with the construction of minds must have already been apparent to Turing, who famously was not only interested in unconventional embodiments of intelligence and patterns of mental activity²⁴ but also in the self-assembly of structural patterns during development²⁵. Another notable contribution to this field was Grossberg's prescient "Communication, Memory, and Development"²⁶. However, advances in connectionist approaches to problem-solving in synthetic media have provided more specific architectural principles around which somatic and cognitive competency can be organized.^{27–33}

Starting in 2016, Pezzulo and Levin discussed¹³ how top-down approaches, such as the free energy principle^{34–37} (FEP), can model developmental processes through nested bowtie architectures, *i.e.*, where diverse molecular mechanisms converge on critical intermediates to achieve high-level goals through distributed self-orchestration. This concept highlights the efficiency and robustness of the generative developmental and evolutionary process of biological systems. Subsequent works^{14,15} further explore scale-free and hierarchical dynamics in development, emphasizing the FEP's unifying role in evolution and development and introducing the concept of biology as a multiscale competency architecture (MCA), with causal top-down and bottom-up control pathways. They specifically proposed that tissue, organs, organ systems, and other levels of biological organization arise as the generalization of compressed information at molecular levels, as occurs in multi-layer ANNs, and framed regeneration as a kind of pattern completion task³⁸.

This led to the idea that each individual within an MCA is an autonomous agent, actively navigating their respective environments and problem spaces¹⁵. In turn, a unified approach to understanding biological self-organization is arguably rooted in localized homeostatic agents following cooperatively coordinated error correction principles (see Fig. 1 (C)).

Thus, a critical missing piece in our understanding of development and evolution is the fact that cells are problem-solving agents themselves, with agendas of their own¹⁶. The various

competencies of cells and subcellular components, in terms of problem-solving, memory, and flexible, context-sensitive navigation of physiological and anatomical landscapes have been reviewed elsewhere^{39–42}. We argue that an organism’s genotype and phenotype are connected by an agential layer of irreducible physiological computation, fundamentally implemented by self-orchestrated biological agents that are - at all scales - capable of dealing with novel situations on the fly¹⁷. Moreover, such an MCA demonstratively^{43–45} impacts the process of an underlying evolutionary process operating on the structural and functional plasticity of an agential substrate, leading to more efficient and robust evolutionary and developmental search dynamics, adaptability, transferability, and evolvability.

GENERATIVE BOWTIES EVERYWHERE

Mitchell and Cheney identify the genome as latent variables of a generative model for organismal development that is facilitated through GRNs and shaped by evolution. Their proposed VAE architecture leverages developmental plasticity through complexity of the connectionist decoder stack, and evolvability through variability in latent variables. In contrast and complement, our framework^{13–19} emphasizes the fundamental role of goal-directed problem-solving and collective intelligence of biological systems across scales in developmental and evolutionary pathways.

The paradox of change is a profound invariant across spatio-temporal scales, materials, and problem spaces, equally affecting embryos, behaving individuals, and evolutionary lineages. If a system stays the same, it will not survive when circumstances call for novel form or function. But if it changes and adapts, it is no longer the same system and the original has likewise, to an extent, disappeared. Thus, the question of what it is that persists through evolutionary change, morphogenesis/metamorphosis, and learning can be better visualized as a process of contextual sense-making, not an object. We have visualized it as a bowtie dynamic, which is traversed by active agents continuously (Fig. 1). In the case of learning, the center of the bowtie is the “now” moment. The left side of the bowtie is the deductive, algorithmic process of learning and generalization, which their cognitive system compressed from individual instances of experience. But beings never have access to the actual past – what they have access to is the engrams stored in their brain (and possibly body⁴⁶). Thus, the right side of the bowtie is a creative process in which the cognitive system must reconstruct the meaning of these engrams, but optimizing for saliency in the current situation, not constancy of the meaning these biophysical messages had for their past self.

The same dynamic occurs in embryonic development and evolution. Counter to the familiar model in which the genetics reproduces a map of a fixed body structure, morphogenesis is a creative, problem-solving process which utilizes information in the genome but is not a hardwired, mechanical result of it. The experience of past members of a lineage is stored in a generative seed – the genome, which does not directly code for phenotypic features. The process of producing a functional body given the prompt of the genome is as much a sense-making effort, executed by the biomechanical, biochemical, and bioelectrical networks of protoplasm to navigate physiological and anatomical spaces as is the memory-interpretation task of neural networks in brains as an animal navigates the 3D space of behavior. We propose that what evolution builds are not fixed solutions to fixed environments, but problem-solving agents, exerting well-demonstrated competencies to use genetically-provided affordances in new ways as needed (discussed in detail in Refs. 17,19).

We have proposed that biology strongly leans in to the fact that it is operating on an unreliable substrate (guaranteed to change due to mutation over long timescales, and noise on short timescales), and favors architectures that take the lessons of the past seriously but not literally, and exhibit considerable regulative and creative ways to navigate their problem spaces.

Viewing biology as operating over an active, computational, decision-making material (as opposed to fixed mappings between genetic information and phenotypic outcomes) has many implications for how we relate to it in biomedical settings (recent emphasis being on prompts and behavior-shaping communication⁴⁷), but also for evolution. Recent computational modeling efforts showed that the competency of the material hides information from selection, leading much of the work to be done on the competency mechanisms themselves^{43,44}. This results in augmented ability of the material to creatively adapt to changes in its genetics, thus accelerating the evolutionary process, and kickstarting a positive feedback loop which scales primitive competencies of living matter into the more obvious intelligence of brainy animals.

It is essential to develop a rigorous understanding of the substrate- and scale-invariant learning and creative problem-solving dynamics that tie together morphogenesis, evolution, and learning^{28,31}.

While the VAE architecture in particular might not yet capture such recurrent multiscale dynamics, the crisp ideas of Mitchell and Cheney raise fundamental questions about the differences and similarities between active inference systems, collective goal-directed agents, and (self-regulatory) generative models, especially in distributed and hierarchical systems. One might interpret every biological agent as a generative model - with an informational bowtie at its core - sampling or generating actions from a policy subordinate to a higher-level goal state. Consequently, organismal development would be characterized as a highly noisy, recurrent, and hierarchically multiplexed generative process.

PARALLELS BETWEEN CONSTRUCTION OF BODY AND MIND

The idea of seeing development as distributed agential process can be expanded to memory and cognition¹⁹: A developing “Self”, capable of learning through subjective cognitive experience, is ultimately in charge of reinterpreting its own thoughts, constantly reconstructing its story without having objective ground truth of the semantics of its memories⁴⁸. By interpreting memory as compressed embedding, remembering is an active decoding process of information captured in “creative” bowties¹⁹. The process of remembering parallels a context-sensitive generative process akin to associative-memory-based attention mechanisms^{49–51} or, in turn, development, rendering “memories” to be potentially hierarchical and contextually agential, constantly reinterpreted by the same “Self”.

The concept of an MCA is applicable across biological systems, including development, evolution, and cognitive processes: it’s agents all the way up and down, turtles both ways. In turn, this suggests a unified approach to understanding biological organization - from cells to mind - can not be explained via complexity and (nested) indirect encodings alone, but rather fundamentally rooted in collective intelligence¹⁸.

NEURAL CELLULAR AUTOMATA FOR SELF-ORCHESTRATED MORPHOGENESIS

Dating back to von Neumann’s self-replicating machines⁵², Cellular Automata (CAs) have provided a foundational framework for modeling distributed biological phenomena and *Artificial Life*, such as replication, growth, and morphogenesis, simply through local interactions of neighboring cells on a discrete grid. Exemplified by, e.g., Conway’s *Game of Life*⁵³ and Wolfram’s *New Kind of Science*⁵⁴, even basic update rules amongst a CA’s cells can give rise to emergent

system-level dynamics with complex, life-like, and even Turing-complete behavior. Since explicitly programming CAs for target applications proved difficult, a relatively recent but promising extension termed Neural Cellular Automata^{55,56} (NCAs) replaces the hard-wired update rules in CAs with more flexible and generalizable ANNs. Like the bowtie continuous sense-making of life mentioned above, an NCA's cells make dynamic decisions about how to interpret the current state of their neighborhood in order to generate their next state. Such NCAs have been successfully trained via differentiable^{56–62} and evolutionary learning frameworks^{44,63} to perform, amongst others, the inverse task of targeted pattern formation (c.f., Fig. 1 (D)).

Just like CAs, the artificial cells (A-cells) of NCAs maintain numerical cell states, substituting differentiation of biological cells (B-cells). The A-cell's internal ANN computes how to update the cell's state based on the states of its neighbors, modelling decision-making competencies of B-cells. Mirroring the structural and functional plasticity of biological development, a single A-cell can instantiate the growth of a cybernetic tissue via recurrent and fully decentralized inter-cellular communication and internal computation. This leads to the formation of diverse tissue types, composite organs, etc., by this multi-cellular substrate until the system-level goal-morphology is achieved. Thus, the functionality of such A-cells can be evolved to “grow” diverse high-fidelity target patterns *in-silico*, operating as a generative morphogenetic model.

NCAs describe a iterative multi-scale generative process capable of solving the inverse pattern formation task of embryogenesis fundamentally based on distributed, multi-agential communication protocols and local iterative error-correction principles¹⁴. This not only represents a generative morphogenetic process, but also parallels the dynamical self-regulatory architecture of GRNs: an A-cell's state broadly captures the physiological state of B-cells, such as gene expressions or transcription factors, while its ANN substitutes the GRN. The operational point of both networks, ANNs and GRNs, is susceptible to noise, environmental cues, cell state expressions, and memory. In context of this Commentary, the NCA's ANN can be interpreted as a generative genome representing the latent variables of an evolvable multi-cellular substrate – an informational bowtie compressed into a single A-cell – while cell states may carry epigenetic information.

NCAs have been successfully trained to perform robust embryogenesis^{44,56,57,64,65}, symbiotic or parasitic behavior^{59,60}, and even intricate self-orchestrated computational tasks such as collective classification⁶², medical imaging^{66,67}, or pathfinding in a maze⁶⁸. Moreover, the cellular competencies of morphogenetic NCAs have significant implications for an underlying evolutionary process⁴⁴, facilitating enhanced evolvability and transferability to novel problems, and potentially enabling open-ended evolution through concepts from the paradox of robustness^{69,70}. Moreover, the A-cells' ANNs may exhibit graph-like recurrent architectures⁴⁴, and thus potentially model active inference agents with an internal worldmodel whereas cell states represent communication boundaries or Markov blankets. Thus, NCAs are promising models for understanding the multiscale competency architecture of biology and exploiting it in novel ways for top-down control in biomedical⁷¹ and bioengineering^{72,73} settings.

A MODEL FOR DISTRIBUTED DECISION-MAKING

Current research aims to explicitly extend NCAs towards hierarchical architectures^{74–76}. While potentially improving their applicability, this might not be necessary conceptually to achieve multiscale dynamics: At the critical point, the Ising model - the simplest CA-like model for a magnetic material - displays self-similar organization patterns of magnetic islands. An NCA operating near such a critical point may exhibit scale-free spatio-temporal activation patterns in its distribution of cell states⁷⁷, potentially leading to collective interactions of such higher-level structures. Mirroring the near-critical activation patterns observed in neuronal tissue^{78–80}, this yet again blurs

the line between morphogenesis and behavioral information processing, which is essential for capturing the nature of living things that process information while actively remodeling the processing medium itself.

While indirect encoding paradigms in the domain of reinforcement learning⁸¹ (RL) demonstrate impressive performance^{82–86}, encoding innate behavior in a genomic bottleneck⁸⁷, NCAs have been utilized to facilitate both morphogenetic development and robust, decentralized, and transferable behavioral control in composite RL agents^{64,88–90}. Similarly, neural developmental programs have been used to grow an agent's controller ANN during its lifetime^{91,92}. Other promising RL approaches^{93–95} maintain distributed sensors whose individual recurrent perceptions are analyzed for importance by attention-based mechanisms to retain a compressed environmental representation for subsequent decision-making. Such informational bowties, be it in the single-agent or collective intelligence domain⁹⁶, or even in worldmodel architectures^{97–99}, allow correspondingly trained – or evolved – agents to generalize well to environmental rules and navigate their respective problem spaces robustly.

DIFFUSION MODELS: DEVELOPMENT AND EVOLUTION AS INCREMENTAL DENOISING

Although progress has been made⁶³, NCAs are still limited in their capacity of generating multiple patterns from different seed cells. However, NCAs are closely related to probabilistic diffusion models^{100–104} (DMs), cutting-edge generative techniques that demonstrate versatility and control over - so-far - mainly multi-media content generation.

Both methods iteratively refine an originally incomplete or noisy data sample through incremental error correction until it conforms to a target data distribution. Different training and denoising paradigms based on non-equilibrium thermodynamics^{104,105} allow DMs to generate realistic samples conforming to a versatile data distribution, a process that can even be guided by text prompts^{106,107}. To name but a few examples, DMs have revolutionized guided generation of synthetic images¹⁰⁶, videos¹⁰⁸, and protein-folding predictions¹⁰⁹, and even facilitate fully generative game-play¹¹⁰ demonstrating agential behavior.

Notably, we have recently demonstrated^{111,112} that DMs can serve as highly efficient generative models in evolutionary algorithms, substituting conditional genotypic offspring generation through iterative denoising of genomic parametrizations in various optimization domains. Moreover, the generative process of DMs is capable of adapting a given data instance conditionally to some external cues or constraints, such as modularly replacing details in sceneries¹¹³, transforming an image to a particular target style without corrupting its content¹¹⁴, or adjusting an RL agent's policy dynamically to achieve targeted behavior shaping¹¹². Thus, DMs (and similarly NCAs) are promising candidates to model the modular, internal and external context-sensitive reconfiguration capabilities of B-cells.

While the flow of information in the VAE model of evolutionary development is deterministic and unidirectional when traversing a hard-wired and predefined decoder stack - after possible variations in the latent space - both DMs and NCAs iteratively operate on dynamically refined structures. More than that, these increasingly contextualized structures are recursively feedback as refined inputs to successive generative steps, effectively conditioning and reconfiguring the functionality of their governing generative models in a dynamic, context-sensitive manner. This mirrors biological development much more accurately, where the output of computational processes is constantly feedback to the biological hardware, inducing architectural and topological changes to itself, and driving the morphological and functional plasticity of this process.

Given their generative fidelity and context-sensitive versatility, DMs potentially represent pow-

erful models for morphogenesis, and, in the spirit of this Commentary, might be candidates for foundational generative models for DNA or GRNs with deep associative memory capacities^{115,116}: The DM would literally represent the generative and functional genome^{3,13}, while the data sample it operates on relates to gene expressions or transcriptomic data¹¹².

CONCLUSION: BIOMEDICINE AND BEYOND

The material of life exhibits active problem-solving capacities in physiological and anatomical spaces which dwarf our current efforts in biomedicine and bioengineering, in the same way that brains' learning capacities are still unmatched by efforts in machine learning and AI. An especially impressive example are asexual strains of planarian flatworms, which overcome whole-body damage, cancer, and aging (despite a very noisy genome which accumulates mutations due to somatic inheritance¹¹⁷), can implement other species' morphotypes¹¹⁸ and novel, permanent bodyplan architectures in the absence of genetic change^{119,120} (see Fig. 1 (B)), and identify a small number of genes sufficient to counteract the effects of a novel toxin¹²¹. The challenges and opportunities facing the field now is to exploit and extend the deep lessons of connectionist neuroscience and machine learning, with respect to architectures that learn and adapt. Exciting developments in genetics include fundamental changes in how we see the subject of the science itself, and what we are really doing when we track and edit genetic information. The molecular medicine of the future, and our understanding of natural and experimentally-guided evolution, depends on developing omics tools, modeling approaches, and interventions that extend classic views of the mapping between genetics and phenotypes, and tames system-level complex outcomes by targeting the genetic, physiological, and informational structures as active learning agents.

RESOURCE AVAILABILITY

Not applicable

Lead contact

Requests for further information and resources should be directed to and will be fulfilled by the lead contact, Michael Levin (michael.levin@tufts.edu).

Materials availability

Not applicable

Data and code availability

Not applicable

ACKNOWLEDGMENTS

We thank Axel de Baat, Hananel Hazan, Yanbo Zhang, and Patrick Erickson for helpful discussions. We acknowledge support from Astonishing Labs, and the Templeton World Charity Foundation (TWCF0606). B.H. acknowledges an APART-MINT stipend by the Austrian Academy of Sciences

AUTHOR CONTRIBUTIONS

B.H. and M.L. contributed equally.

DECLARATION OF INTERESTS

M.L.'s lab receives funding from a sponsored research agreement with Astonishing Labs, a company that seeks to operate in the space of biomedical advances driven by a better understanding of the computational intelligence of living materials.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES

During the preparation of this work, no AI or AI-assisted technologies were used.

MAIN FIGURE TITLES AND LEGENDS

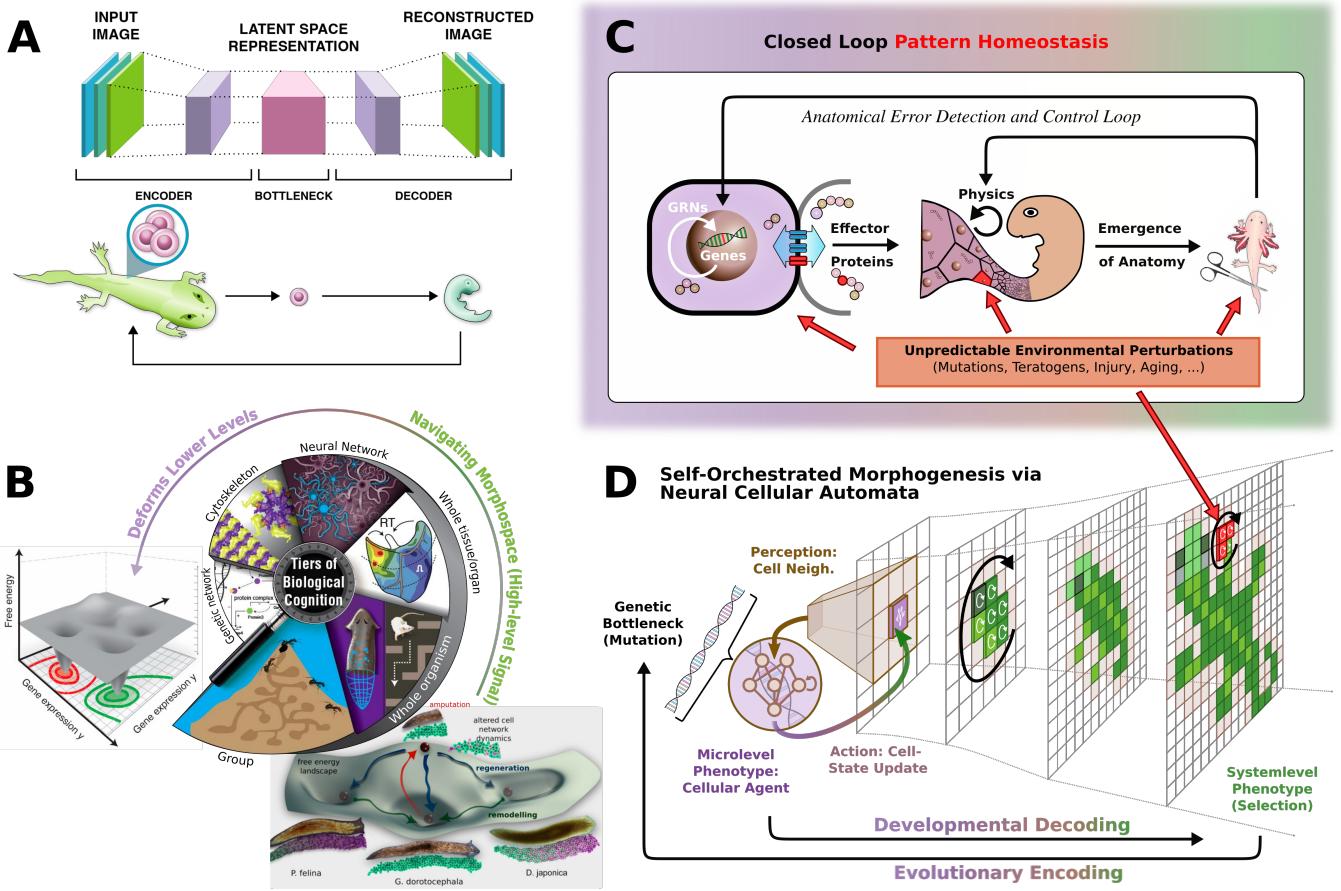


Figure 1: (A) Evolutionary development parallels an autoencoder architecture known from machine learning, but reality is much more complicated: (B) Biology is organized as multiscale competency architecture with interactive agents navigating their respective problem spaces across scales. Lower level components implement the physical substrate for higher levels of emergent abstraction, spanning molecular, cellular, tissue, organ, to organismal and group scales. In turn, higher levels deform the free energy landscape of possible microlevel conformations through top-down behavioral shaping and signaling. (C) Components at every level of organization perform “local” homeostatic control loops capable of handling novel stressors on the fly, yet are susceptible to hierarchical - system-level or environmental - feedback. (D) Neural Cellular Automata (NCA) cover the essence of our current understanding of biology’s multiscale competency architecture by modeling morphogenesis through an explicitly distributed multi-agential architecture. Each cell maintains and regulates its physiological state within a local microscopic environment via successive intercellular communication and intracellular decision-making. In that way, a single cell on an NCA’s grid can initiate morphogenesis of a system level target tissue fully based on decentralized agential control-loops. The NCA’s cell-specific ANNs substitute biological GRNs, and represent the evolutionary genetic bowtie, or latent variables, of a multiscale developmental (generative) model. Panels A, and left, middle panels of B: Images by Jeremy Guay of Peregrine Creative; used with permission from 17, 15, and 16, respectively. Bottom right panel of B: Image by Alexis Pietak; used with permission from 118.

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