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Cross-hierarchy systems principles

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Abstract

One driving motivation of systems biology is the search for general principles that govern the design of biological systems. But questions often arise as to what kind of general principles biology could have. Concepts from engineering such as robustness and modularity are indeed becoming a regular way of describing biological systems. Another source of potential general principles is the emerging similarities found in processes across biological hierarchies. In this piece, I describe several emerging cross-hierarchy similarities. Identification of more cross-hierarchy principles, and understanding the implications these convergence have on the construction of biological systems, I believe, present exciting challenges for systems biology in the decades to come.

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Introduction

Systems biology is often defined by the tools it uses, *e.g.*, mathematical modeling, high-throughput measurements, large statistical analysis. Apart from the tools, systems biology may also be defined as a way of thinking, in the kinds of questions the students ask, and the kinds of answers the students search for [1]. Systems thinking is a consideration of the behavior that a biological process gives rise to as a whole. An apt demonstration of what systems thinking is came from the systems scientist Donella Meadows, who sadly died too young. Meadows described how in the beginning of her class, she would bring a slinky [2]. She would hold one end of the slinky, and then with the most dramatic gesture she could muster, she would flip it so the slinky ended up hanging from her hand and oscillating up and down. She would then ask the class what caused the slinky to oscillate. Some students would say, *e.g.*, 'you hold it upside down' or 'gravity'. She would then take the box that the slinky came in, and performed a similar ritual. This time, of course, nothing happened, just the box hanging upside down. This demonstration illustrates a different view of causation: The slinky oscillated up and down not because it was held upside down or experienced gravitational force. In systems view, the slinky is constructed in such a manner and from such a material that it responds to those external factors by oscillating. Similarly, for example, we do not catch a cold because of a virus; our body provides the conditions that allow the virus to flourish.

A system is, in Meadows' words, "an interconnected set of elements that is coherently organized in a way that achieves something" [2]. A system may be a circuit of two proteins, a metabolic pathway with tens of proteins, a cell with hundreds of pathways, a tissue with millions of cells, an organism with multiple organs. Systems consideration transcends biological hierarchies, but what of the principles? Natural selection acts on the macro-scale organism, and an organism functions through coordination of numerous processes at multiple lower hierarchies, from the organ-, tissue-, cell- to eventually molecular levels. It is far from clear that processes across hierarchies should evolve similar governing principles, for instance that the workings of the organism would converge with the workings of the molecular processes within. In spite of which, strikingly, recent studies and discussions are beginning to uncover similar strategies across hierarchies. Here, I present some examples of cross-hierarchy systems principles (Figure 1).

Beyond analogies, these similarities may indicate convergence of evolutionary pressures these processes across hierarchies face, and may reveal new insights about the construction of biological systems.

Exploratory behavior: from ant foraging to microtubule

Ants set out from their nest in random directions to explore for food. They lay pheromones along the way to help them return home. In many ant societies, discovery of food is followed by recruitment of other ants to the food location, largely by chemical signaling. The ants that encounter the food lay more pheromones on the way back and reinforce the trail. More ants are then biased to follow the trail to the food source, and subsequently lay more pheromones on their way. In this way, the successful trail becomes increasingly reinforced. But strangely, no matter how strong the trail is, there are

always some ants that get lost. These ants may end up finding another source of food nearby, and perhaps even better ones. Without the lost ants, the search process ends with the first food source found. The built-in error ensures that the forage process remains flexible, and the ants to keep exploring for possible better food sources [3,4].

Within organisms, the cell regulates its shape using a conceptually analogous strategy. Microtubules are a component of the cell's cytoskeleton. In a typical cell, hundreds of microtubule polymers radiate out from an organizing center to the cell membrane. And yet these structural pillars, far from static, are highly dynamic: microtubule polymers continually grow and disintegrate, with a half life of ~5 min [5,6]. At any given time, some microtubules shrink, and new ones grow in random direction — maintaining, overall, a constant distribution of number and spatial arrangement. Notably, keeping the dynamic assembly and disassembly requires energy. This process, named microtubule dynamic instability, allows the microtubule array to readily repolarize in response to signal. When a signal arrives on one side of the cell, stabilizing agents are activated at that local site. Microtubules that reach those stabilizing agents by chance are stabilized. The dynamic instability allows the microtubule array to remain flexible, and the cells to modulate shape rapidly [4].

The principle of exploratory behavior was proposed by Kirschner and Gerhart [4]. In ant foraging and microtubule regulation, they propose that exploratory behavior mediates versatile uses: the built-in instability allows microtubule to function in diverse cell types, the built-in error allows ants to forage for food in different environments. Beyond the two examples highlighted here, exploratory behavior may also describe other processes, such as bacterial chemotaxis [7], patterning of neuronal connections [4], and noise in gene transcription, which increasingly proves to have functional roles in cellular activities [8] (Figure 1).

It is all relative: from sensory systems to cell signaling

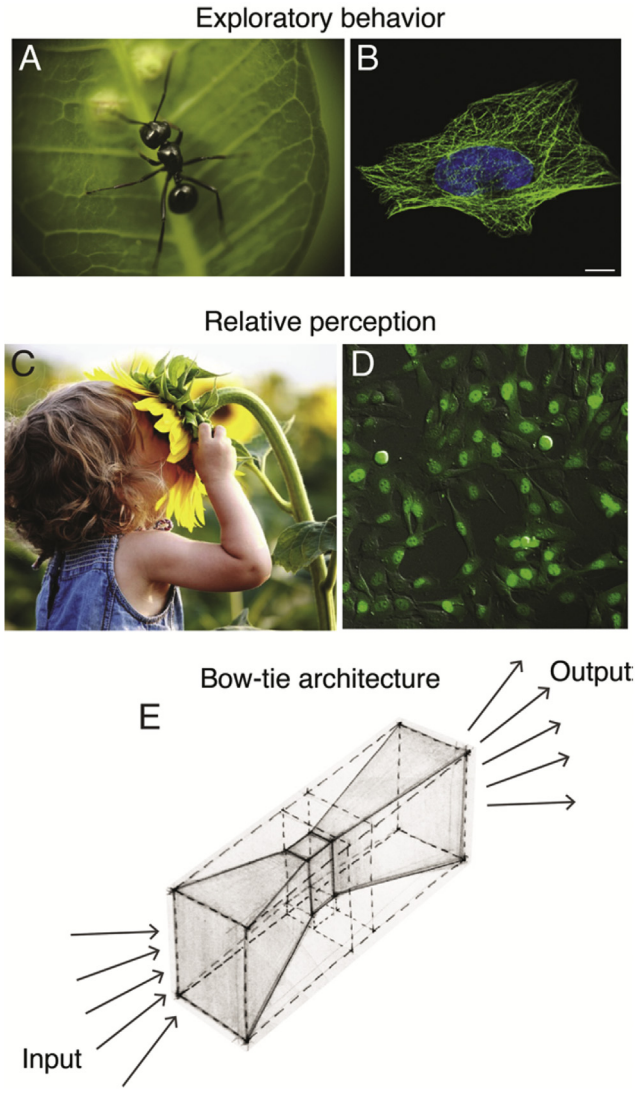
A distinguishing feature of our sensory systems is their broad dynamic range. For instance, we distinguish over twelve orders of magnitude of sounds, one million colors, and one trillion unique odors. Thought to contribute to this impressive dynamic range is the ability of our sensory systems to adjust detection to background stimulus. This is in essence captured by Weber's Law [9],

$$\Delta S/S_{background} = \text{constant}$$

from one of the earliest studies to measure sensory discrimination. Weber's Law is approximately true for many sensory modalities, including weight perception, vision, hearing, as well as in our cognitive perception of time and number. Weber's Law underscores that we do not perceive stimuli in their absolute terms, but in relative terms.

Sensing signal in a relative manner may not only apply to the sensory systems at whole organismal level, but also to the way individual cells signal. In multicellular animals, signaling between cells is important to coordinate

Figure 1



Examples of cross-hierarchy systems principles. (**A**–**B**) Exploratory behavior describes the strategy of ant foraging and how cells modulate their shapes. In B, staining of microtubule in human cell U-2 OS. Scale bar is 10 μm. (**C**–**D**) Relative perception describes how we sense our world, as well as individual cells within us sense their surrounding. In D, mouse C2C12 cells expressing fluorescently tagged Smad protein. (**E**) Bow-tie architecture describes various molecular, cellular and technological networks. **Credits**. A, photograph by Dylan O'Donnell. B, Human Protein Atlas (www.proteinatlas.org/learn/dictionary/cell/cytoskeleton+(microtubules)+2). C, Photograph by Yaruta at Getty Images. D, Cells generated and imaged by Christopher Frick. E, Sketch by Reza Aliabadi (www.rzlbd.com/). Courtesy of atelier rzlbd. A sketch of a bow-tie installation in Toronto Harbourfront Centre, Winter 2012 Architecture Exhibition, Canada.

growth, development, and homeostasis. Cells signal to one another using a set of highly conserved signaling pathways. In a typical signaling pathway, an external ligand (*e.g.*, growth factor) binds to a surface receptor and activates a cascade of reactions inside the cells, which leads to activation of a transcription factor and subsequently transcription of specific genes. Studies have now shown in multiple contexts that gene transcription, rather than responding to the absolute level of the transcription factor, responds to the fold change in the magnitude relative to the background level [10–13]. It was proposed that fold-change detection allows the cells to respond to signals accurately despite fluctuations over time, and allows the signaling pathways to be used across tissues where biochemical parameters might vary [12,14].

Therefore, from whole organisms to single cells within, sensing relative rather than absolute signal may allow the system to function across different environments. Weber's Law may be an ancient strategy: it has been proposed, by Adler and colleagues, in chemotaxis in bacteria [15] and, by Delbruck and colleagues, in phototaxis in fungi [16]. Moreover, it has been proposed that allosteric proteins can act as logarithmic sensors [17–19], suggesting that broader cellular processes such as metabolism, oxygen transport, and protein degradation may sense substrate concentration on relative terms [17].

Bow-tie architecture: from immune system to metabolism

A bow-tie architecture is one where many inputs fan in to a few intermediates that then fan out to many outputs. Bow-tie architecture describes many molecular processes [20–22]. For instance, in metabolic networks, a vast array of nutrients are broken down to a dozen of universal precursors that are then used to build all biomass (e.g., nucleic acids, proteins, carbohydrates). In signaling, hundreds of signals are transmitted through a dozen of signaling pathways that lead to regulation of thousands of genes. In transcription, numerous genes are processed through a few universal polymerase modules and translational apparatus to produce numerous proteins.

At the cell and tissue level, bow-tie architecture also describes aspects of the immune system, *e.g.*, signals from various pathogens that are transmitted to the naïve CD4+ T-cells to stimulate differentiation and release of various cytokines that direct immune response [23]. In the human visual system, neural images from over a hundred million of retinal photoreceptors are transmitted to the brain by only about a million axons of the ganglion cells, from which rich conscious visual experience is eventually derived [24]. Finally, in the primate cerebral cortex, interactions among cortical areas, which mediate sensory, motor, and cognitive functions, have been proposed to exhibit bow-tie architecture [25].

Performing a mathematical stimulation study, Friedlander and colleagues [26] found that a bow-tie architecture evolves spontaneously when information in the evolutionary goal can be compressed, or mathematically when the rank of the input–output matrix is deficient. It is interesting that many manmade systems have also evolved bow-tie architecture, *e.g.*, the standard 60 Hz AC in power grid, the universal TCP/IP in the internet, and the use of common currency in modern economies. It was proposed that bow-tie architecture facilitates robustness of the knot process by facilitating tight regulation and control over perturbations on many time- and spatial scales [20–22]. The bow-tie architecture can also facilitate adaptation to widely fluctuating environment while still maintaining manageable genome and proteome size [21].

Beyond analogy

Beyond examples discussed here, few more potential cross-hierarchy similarities have been proposed, *e.g.*, weak linkage [27], near decomposability [28], Pareto's optimality [29]. Identifying cross-hierarchy similarity is useful because it allows us to transfer conceptual tools and hypotheses from one field of study to another. The consideration of cross-hierarchy similarity is also useful in identifying a potential organizing principle in one process from a known prominent feature of an analogous process. Finally, the consideration of cross-hierarchy similarity is useful in unifying seemingly different biological processes, toward identifying general design principles in biological systems.

Further, the presence of similar principles governing processes across hierarchical level raises an interesting question: Might processes across hierarchies experience similar selectional pressures? In one argument, perhaps it is all frozen historical inheritance. The molecular processes were already present in our unicellular ancestor, where selection would have shaped them more directly. As multicellularity evolved, similar strategies evolved at the organismal level. On the opposite argument, perhaps organismal and molecular level processes continue evolving together. The convergence of solutions across hierarchy would then suggest that selection at the organismal-level can be felt at processes multiple hierarchies below. This raises question of how the parts are connected together to form the whole. On one hand, if there is extensive compensation between the parts, then changes in parts might be "invisible" on the whole. On the other hand, if changes in parts are faithfully transmitted to the whole, then selection on the whole can be felt down the hierarchical ladder – but such a design would not presumably be very robust. An important fact to remember here is that the hierarchical nature of biological systems is itself an evolved property [28,30]. The questions that cross-hierarchy similarity raises then essentially boil down to the evolved structure of interactions between parts and the nature of

inter-part and inter-hierarchy compensations that regulates transmission of selection across hierarchies. Exciting challenges — theoretically and experimentally — for students of systems biology.

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