



NSF JUMPSTART

From Flatland to Jupiter: Searching for Rules of Interaction Across Biological Scales

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Synopsis In this future-spanning perspective, we examine how an agent-based model could be used to define general rules for interactions across biological systems and evolutionary time. To date, there have been a number of attempts to simulate the emergence of ecological communities using agent-based models of individuals that have evolving traits. Here we speculate whether it is possible to use this computational modeling to simulate self-organizing systems and, importantly, to decipher universal principles that govern biological interactions. This perspective is a thought exercise, meant to extrapolate from current knowledge to how we may make Jupiter-shot leaps to further advance the biosciences in the 21st century.

The importance of breaking silos

In Edwin A. Abbott's novel *Flatland* (Abbott 1952), a line questions its two-dimensional world to abstract about hierarchical structures. The science of *Flatland* is based on rules of geometry, which benefit from being abstract spaces that are scale invariant, allowing the line to conceive of other dimensions. While biology is not scale invariant, is it possible to examine the field at different dimensions and obtain hierarchical meanings in a similar sense as the *Flatland* line? Scientists are at a tipping point in which the questions we can examine have the potential to dramatically expand our field of knowledge, enabling us to decipher governing principles, referred to as “rules,” that guide biological processes. How would scientific research change if there were general rules for interactions across biological systems and evolutionary time? In physics, rules vary across scales. For example, in fluid dynamics, very

different strategies are required to move in a fluid depending on the size of the organism. A small organism like the basilisk lizard (Jesus Christ lizard) avoids predators by skimming across lakes and rivers, taking advantage of viscosity and surface tension. However, the abilities of larger organisms to “walk on water” are hampered by rules of inertial forces and turbulence. For many biological processes, scale seems to be critical. However, is it possible that, like the line, perhaps we have not extrapolated far enough to determine features that can be applied across spatial, temporal, and hierarchical scales? Answering these questions would allow us to predict, modulate, and interpret biology for diverse objectives. Here we examine the feasibility of addressing this question, highlighting why now is an opportune time, and identifying key barriers and ideas for how to overcome them in a manner that gives rise to new strategies to enable transformative breakthroughs.

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Seizing opportunities for advancement

Recent advances in biology have been staggering—whole genomes can now be sequenced in a single day for the price of a small laptop computer and then modified to the precision of a single base pair (Doudna and Charpentier 2014; Lee et al. 2020); the entire molecular contents of the human cell can be catalogued and localized to nanometric precision (Uhlén et al. 2015; Dahlberg and Moerner 2021); the effects of climate change on whole ecological communities can be mapped through space and time (Walther et al. 2002); and our ancestry can be traced to the earliest life forms about 4 billion years ago (Nielsen et al. 2017). With the emergence of new technological capabilities, which enable the acquisition of experimental data, comes the challenge and opportunity to generate new overarching theories for explaining biological processes. In 2019, the U.S. National Science Foundation launched its initiative “Understanding the Rules of Life” (NSF 2019), aiming to elucidate the sets of rules that predict an organism’s observable characteristics, or phenotype. In parallel, a community shift is emerging among scientists to work collaboratively and integrate data across fields, breaking pre-existing walls that separate sub-disciplines and delay transformative advances. The combination of technology, funding, and the scientific community’s interdisciplinary focus provides the foundation for tackling what are often described as moon-shot or even Jupiter-shot problems, such as identifying universal principles of biological interaction that apply across the spatial, temporal, and hierarchical scales of biology.

To find universal rules, we need to examine biological processes at several levels, from molecular to organismal to ecological and systems networks (e.g., from cellular metabolism to neuronal function, brain architecture and, finally, biotic and behavioral interactions such as animal predator/prey interactions) (Fig. 1). Additionally, taking full advantage of the recent advances in measurement and analysis technologies will require training of the next generation of scientists in an interdisciplinary manner that equips them with new analytical and technical skills. It is through integration and synthesis of approaches from many disciplines that we will reveal universal truths, assuming they exist, ultimately allowing us to shape our future.

An agent-based modeling approach to identify scalable breakthroughs

To identify rules that are scale-independent and apply across temporal, spatial, and/or hierarchical scales, we need to define relevant minimal systems, sufficient to capture complex, emergent behaviors, while being elementary enough to translate across multiple scales. The

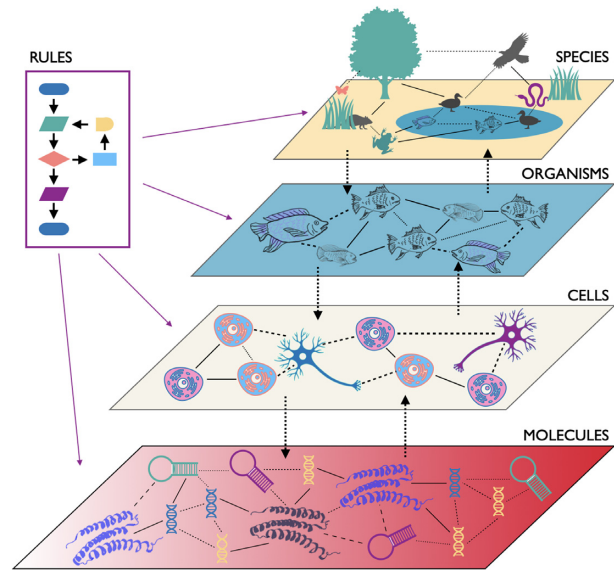


Fig. 1 An agent-based modeling approach to identify scalable breakthroughs. Independent agents interact with each other and their environment across spatiotemporal and hierarchical scales, from single molecules to ecosystems. Various rules of interaction apply within and between scales. Lines between agents and arrows between scales represent interactions. The inset shows an example algorithm for an interaction rule that can be applied at any scale.

challenge here will be to determine key features and simple mechanisms of the system that give rise to collective emergent behaviors. For example, to what extent could models, developed within a spatial scale, be applied to problems within a temporal scale? How does the directionality of time limit our ability to deduce future outcomes from sampling the space of agents and interactions in a given moment? Developing new theoretical and modeling frameworks and testing them in relevant minimal systems will facilitate our ability to predict outcomes of interactions at every scale.

There exists already a large body of work aiming to formulate general rules of biological systems through simulations that try to understand how rules arise. For example, several postulates explore the emergence of complexity (Morowitz 2004), the flow of energy in biological organization (Morowitz 1968; Morowitz and Smith 2007), and the order’s structure and instabilities (Prigogine and Nicolis 1971). The subject is too large to easily summarize, but the literature demonstrates a desire of scientists to uncover, analyze, and apply a universal language for understanding biology similar to the achievements of mathematics (Miller 1978).

To uncover potential invariant interaction principles, we envision taking an agent-based modeling approach, applied across spatial, temporal, and hierarchical scales (Fig. 1). Agent-based modeling is a bottom-up computational approach that predicts how system-

level complexity arises from the behavior of individual “agents” (Bonabeau 2002). This approach has been used to model emergent phenomena in a wide variety of contexts, from predicting the behavior of economic markets (Arthur et al. 1997), through modeling molecular self-organization (Troisi et al. 2005), to capturing the spread of COVID-19 (Stevens 2020).

The three essential components of the proposed models are: (1) agents, (2) their environment, and (3) the rules by which agents interact with each other and respond to the environment (Bodine et al. 2020). To apply this modeling to finding universal rules of biological processes, we first need to identify the relevant interacting agents. An agent is an independently acting object that can be defined at any scale: from single molecules and subcellular organelles through tissues and organisms, to entire ecosystems over time. To this end, we will benefit from integrating existing and developing collections of data from a variety of sources (e.g., GenBank, Protein Data Bank [PDB], Barcode of Life Data System [BOLD], Plant List of Accepted Nomenclature Taxonomy and Symbols [PLANTS], and Global Biodiversity Information Facility [GBIF]), as well as by expanding beyond the cadre of current model systems to less studied organisms to discover potentially novel agents (Russell et al. 2017). Second, we will need to define the agent’s *environment*—this may involve various degrees of complexity, including, for example, gradients (e.g., of signaling morphogens) or local inhomogeneities (e.g., spatiotemporal fluctuations in population density). And third, we will need to determine the possible rules of interactions, which can adopt a myriad of features. For example, agents may be governed by non-linearity, displaying switch-like behavior when a certain threshold or an if/then condition is met (e.g., lactose level triggering gene expression). Additionally, rules can have a local character, such that they apply only based on the conditions in close vicinity of an agent, rather than a global average—this feature enables the ability to determine at which spatial, temporal, and hierarchical scales the rules apply. Rules also may be context-dependent, deterministic versus stochastic, or constrained in a manner that limits the possibilities for future interactions. Importantly, rules in biology can adapt, displaying memory or change over time through a learning process. In this fashion, a complex system self-organizes on multiple spatial and temporal scales, giving rise to emergent behaviors that could not have been predicted solely from the sum of its components. It is their inherent ability to display emergent behaviors that makes agent-based modelling a potentially effective strategy for determining guiding principles of biology.

Indeed, the flexibility of agent-based modeling has already been successfully employed in many biologi-

cal contexts, including gene expression (Thomas 2019), immune response (Chavali et al. 2008; Castiglione and Celada 2015), cancer growth (Wang et al. 2015), morphogenesis and development (Thorne et al. 2007; Glen et al. 2019), tissue mechanics (van Liedekerke et al. 2015), epidemics (Cisse et al. 2013; Tracy et al. 2018), and ecology (DeAngelis and Diaz 2019). Combined with novel measurement approaches, such as real-time monitoring of unperturbed dynamic systems ranging from single molecules to organismal networks, agent-based modeling coupled with advances in high-speed computing and algorithms may allow us to discern interactions between entities within and across scales. Importantly, agent-based modeling approaches are particularly suitable for introducing computational modeling to students in the life sciences, as they require almost no previous computational background (Bodine et al. 2020). In fact, agent-based modeling software environments, including NetLogo (Wilensky 1999) and SimBio Virtual Labs (simbio.com), provide attractive and accessible platforms, already widely used by students and educators to model biological phenomena across scales.

A future of scientific possibilities

Deciphering the rules of interactions across biological scales will allow us to identify the drivers of biodiversity, predict adaptive evolutionary processes, and design genes for robustness and resilience. Imagine it were possible to look solely at a sequence of deoxyribonucleic acid, ribonucleic acid, or protein and be able to identify its molecular function and predict the temporal, spatial, and hierarchical interactions it will have within a cellular systems network. Now imagine how those interactions will impact organismal behavior and how that behavior will influence evolutionary processes from the neofunctionalization of genes, to the birth of a new species, to the inhibition of enzymes, to the extinction of taxa. The analyses of these rules of interaction combined with newly available technology will decipher the code of communication, where communication is defined as the transfer of information between agents. For example, we will be able to explain why there are so many different biological species, and how diverse organisms assemble, inhabit, and share the same environment. If we understand communication among different biological entities and their common environment through millions of years, we will be able to predict how they will adapt to change in the future. Even more importantly, we will learn how to cope with unexpected changes that have potentially catastrophic consequences. For example, we can determine if we should intervene when an ecologically important species is in danger of extinction, or we can predict when a novel

zoonotic virus will likely jump the interspecies barrier to humans and vice versa, setting off a vicious cycle of infection. Perhaps the most salient opportunity for new science that may emerge from the knowledge of the rules of interaction across biological species and evolution will be the establishment of a roadmap for synthetic life from single cells to organoids to complex organisms. This potential will certainly raise ethical questions about what is life and who gets to create it. In an ironic twist, knowing the rules manifests a God syndrome that may require restricting the rules. While we may think this is still years away, consider that we are celebrating the twentieth anniversary of the human genome and in those 20 years sequencing throughput has grown by exponential orders of magnitudes, spawning the revolution of precision genome editing.

Grappling with ethical ramifications of determining the rules of life will manifest also as a challenge for training future generations of scientists. Multifaceted problems require multifaceted solutions. Universities may need to migrate from departments to interdisciplinary centers as the focal home for training graduate students. In this setting, students are free agents themselves, training in an environment of interdisciplinary expertise, learning the technical skills to navigate complex biological questions as well as the societal skills to understand the enabling role of scientists on an increasingly interdependent global stage.

Broader impacts beyond flatlands

Identifying the principles that govern interactions across biological systems and evolutionary time will explain the connections that enable and facilitate function. In determining principles that can be applied across spatial, temporal, and hierarchical scales, we will begin to illuminate the evolutionary arc from the origin of life to the present into the future. One exciting aspect about such horizon-spanning initiatives is that they force a re-examination of existing scientific approaches. To this end, pursuing an initiative that identifies interactions across biological systems and evolutionary time will enable paradigm shifts in education that will, in turn, facilitate the interdisciplinary training of students and restructuring of academic departments. Finally, tackling this problem will provide tools to mitigate a myriad of societal challenges related to natural disasters and global health.

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Data availability

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