Title

Building a universal theoretical framework to understand robustness and resilience within and across scales of biological organization, space, and time

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Goal

Can we create a theoretical framework to understand robustness and resilience? In particular, a framework that can be used to identify connections, strength, and importance of those connections as they operate within and across scales of space, time, and biological organization.

Summary

Research across a range of biological subdisciplines and scales ranging from molecular to ecosystems, has provided evidence that living systems generally exhibit both a degree of resistance to disruption and an ability to recover following disturbance. Not only do mechanisms of robustness and resilience exist across and between systems, those mechanisms also seem to exhibit commonalities in pattern and function. Mechanisms such as redundancy, plasticity, interconnectivity, and coordination of subunits seem to be crucial internal players in the determination of stability. Similarly, factors external to the system such as the amplitude, frequency, and predictability of disruptors, or the prevalence of key limiting resources, may constrain pathways of response. In the face of a changing environment, the time is right to develop a common framework for describing, assessing, and predicting robustness and resilience within and across living systems.

Introduction

Robustness of a living system is the ability of that system to survive disturbances largely intact. In contrast, resilience of a living system is the ability of that system to be restored after disturbance. Understanding how systems persist over time in response to changing conditions is essential. This knowledge will provide novel insight into fundamental rules of biological and system organization and adaptability. Principles of robustness and resilience operate at systems of different scales (e.g., molecular - cellular - organismal - community - ecosystem - landscape - biosphere). The genetic code, the very basic signature of life as we know it, exhibits a degree of robustness that precisely specifies a mapping between DNA and proteins yet has inbuilt redundancy and error correction mechanisms that provide resiliency and make genomes stable yet evolvable over millions of years. While system components not only interact within these systems, they also have strong interactions across systems at different levels of organization, space, and time. What are the key connections that influence robustness and resilience within and across these parameters? How can we advance our understanding of systems connections and interconnections across such complex and disparate interacting scales?

Robustness and resilience are essential for the biological response to stress. For example, the capacity to respond to heat stress is one of the most universal and evolutionarily conserved cellular stress signaling pathways. In eukaryotic cells, heat exposure triggers a multitude of responses that, in turn collectively upregulate a suite of chaperones to assist with protein folding and stress recovery, maintaining cell viability, and ensuring robustness. However, an acute heat stress causes massive aggregation of unfolded peptides, and leads to the activation of programmed cell death (PCD). The heat-triggered PCD is an example of a biologically resilient response: by selectively removing damaged cells it allows restoration to local homeostasis at the tissue and/or organismal levels.

At the organismic level robustness and resilience are tightly connected to the concepts of stress, homeostasis, and allostasis. We might see robustness in an organism that, when faced with increased environmental temperatures, maintains a relatively constant internal temperature through means of alterations in its physiology, such as sweating or vasodilation, and behavior, such as shade-seeking or burrowing. The same organism might show resilience after facing heat stress that exceeds its ability to resist in that it is able to recover through regrowth, reallocation of internal resources to compensate for damaged tissues, or shifts in behavior to acquire new resources and avoid additional energy expenditures.

How an individual organism responds to heat stress could alter the dynamics at the population, community, and ecosystem levels simultaneously. For instance, some corals are robust to warming temperature via containing unusual algal symbionts, thus increasing their ability to survive thermal stress while other corals die. Similarly, if we have variability of the algal symbiont community across the corals, that may contribute to greater resilience of ecosystem to variable thermal stress. The ability of some corals to survive the thermal perturbation may allow the community and ecosystem to remain robust. In contrast, if a coral population lacks any of the thermally-resistant algal symbionts, then thermal stress could result in major disruption in community structure and ecosystem function.

Despite the critical importance of having a framework to understand the robustness and resilience of systems within and across scales, we lack a common language and approach to study this complex field of inquiry. This lack of commonality leads us to pose the question: **Can we build a universal theoretical framework to understand robustness and resilience?** In particular, a framework that can be used to identify dynamic connections and strength and importance of those connections as they operate within and across scales of space, time, and biological organization.

Why is it important?
By its nature life strikes a balance between change and stability; it walks a line between constancy and inconstancy. Change is a prerequisite for adaptation, but simultaneously living

systems are selected to maintain their integrity (at least to some substantial degree) whereas unstable systems fail to cohere. There is a need for understanding the balance between maintaining the fundamental principles of life and progressive change. As such, we posit that mechanisms to achieve robustness and resilience are ubiquitous and fundamental aspects of life.

Why now?
Recent developments have produced a broad range of models of disruption and stress across multiple scales and fields. Conceptual paradigms from various sub-disciplines of biology have been used to understand robustness and resilience; however, each paradigm has a limited scope of applicability across different levels of biological organization, and individual models and findings remain largely unallied. We have reached critical levels in our understanding of living systems, and that should facilitate the mapping of a common core of principles and the ability to push into a new frontier of synthesis. This type of reintegration will pull biology closer together as a field and bring us closer to conceptualizing foundational rules of life. In addition, our ability to collect and process very large data sets reached a point where synthesis and large-scale pattern recognition in such data sets is feasible in a way that was previously cost and time prohibitive.

We also occupy a point in time where biological systems are faced with an almost unanticipated degree of challenge. Increasing and ongoing climate change and accelerating global anthropogenic disturbance threaten to disrupt organisms in a variety of heretofore unanticipated ways. Systems that have evolved under and proven robust against previous forms of disturbance will be forced to cope with this mismatch. A strong framework for resilience and robustness will prove inestimably valuable in navigating these changes.

What's the exciting science?
Understanding how ecosystems respond and persist in a changing environment is a central scientific question. The ability to withstand perturbations is now becoming even more urgent to understand in the face of the constantly changing and increasingly heterogeneous environment. Data yielded by network biology indicate that different types of perturbations tend to be commonly stabilized by similar mechanisms. Some ecosystems are more robust than others when facing changes and perturbations, so these systems may have a higher chance to persist under the changing environment. At the population or community level, there might not be many significant differences in response to changing environment, which ultimately leads to serious consequences at the ecosystem level. For instance, the disappearance/death of a single individual or species may not result in a collapse at the ecosystem level. However, we might find a more sensitive response to the changing environment at the organismic and molecular levels. For example, a hypothetical disease might kill the majority of the population. However, if there is high genetic variability underlying the population, some individuals might be more resistant to the disease. Following the die-off of vulnerable members those resistant individuals would be most likely to reproduce and repopulate and, as a result, the whole population may persist and be robust to the disease.

If we want to understand, change or increase the robustness of a system, we need to examine responses to environmental change across scales. We need to understand what is the mechanism of response at the molecular level, which genes control the change, and how to scale the response from individual to ecosystem level (and vice versa). The framework that we propose to develop here will make it possible to develop tools to predict system stability, to select the most essential variables to study through model sensitivity analysis, to generate testable hypotheses, to create unification across scales and allow us to explore "rules of life" across spatial, temporal, and biological organization levels, and to modulate that stability to ensure more stable systems. Though the framework, we will be able to identify key scales and components that need to be examined for specific questions. Some questions may require consideration across most or all scales, while others may focus more on fewer scales.

What's the potential impact?

The potential applications of a universal framework for robustness and resilience are manifold. The ability to predict which systems are vulnerable to collapse would allow us to anticipate pathways of disease and dysfunction, to identify agriculture and extractive resource models that are non-sustainable, and to predict and prevent the collapse of threatened species, populations, and environments. A holistic model of resilience and robustness will also lead inevitably to the capacity to manipulate those self-same systems to further our goals. These developments would allow us to create sustainable ecosystem services of increased effectiveness, to develop novel and minimally invasive treatments for illness based on modification of existing systems, and even to destabilize and thus remove or reduce undesirable biological systems such as pathogens, pests, and invasive species. In general, a deep model of robustness and resilience will allow us to understand biological systems in a way that maximizes their efficiency and effectiveness.

Key concepts and approaches in studies of robustness and resilience

Models of robustness and resilience must incorporate a number of factors that contribute across levels and domains. Diversity, redundancy, and variability of subcomponents allow systems to respond to the disruption in a range of possible pathways. Interconnectedness, communication and ability to respond and reallocate resources also contribute to the capacity that a system has to plastically respond. Modularity and response diversity frequently display strong positive associations with robustness and are strong candidates to function as cross-disciplinary paradigms. Similarly, robustness and resilience seem to be amplified in systems that incorporate emergent trans-scalar connections, facilitating coordination of response across levels. It is also essential to work across fields and scales to understand how resilience and robustness themselves interrelate; for instance, how resiliency at lower scale might contribute to robusticity at a higher, or how robusticity of one system might put pressure on another.

Environmental factors may also constrain the potential robustness and resilience of biological systems. Systems operating in environments with highly limiting factors (e.g., water, saline, essential nutrients) may have great difficulty in achieving substantial resilience or robustness along with those metrics. Similarly, the nature of the perturbations encountered, and their duration, amplitude, frequency, and predictability play a key role in determining how systems respond and whether they are able to survive disruptive challenges.

Challenges and key barriers

The fundamental challenge to be addressed is to define ways of making the leap from individual well-studied biological systems to a universal “Rule of Life”. We need to develop a set of common term knowledge, processes and protocols for assaying robustness and resilience across systems. This will allow us to determine whether, and if so, how these processes parallel one another across the scales of biological organizations.

A comprehensive model for robustness and resilience needs to be constructed using data spanning multiple levels. We don’t necessarily need to generate more large-scale data to be able to begin looking for general patterns. We do, however, need to develop new ways to analyze the data, integrating expertise across different biological disciplines, including quantitative biologists/ecologists, modelers, network biologists, applied mathematicians, information data scientists, etc. As we collect future streams of large datasets at various -omics scales, we need to ensure that we capture the entire spectrum of bio-complexity, from genomic and epigenomic level all the way to ecosystems and communities.

Furthermore, the model for multi-scale robustness and resilience needs to incorporate multiple time scales and include the dynamic nature of changes and stasis in the face of challenge. The model also needs to incorporate costs and trade-offs. One of the main evolutionary concepts implies that there is a direct, conflicting relationship between robustness and performance, i.e., a biological entity with a higher robustness capacity will also exhibit poorer fitness. It is anticipated that both robustness and redundancy come at a cost of imposing severe constraints on the underlying architecture of a system, which substantially impacts the principles of the general design motifs found in many networks across scales of biological complexity.

Training and institutional structures

These questions are of such significance that they demand an increase in motivation and a change in culture within the biological research community. To address them we must make a variety of changes not only to funding institutions but to our academic culture. We must work to develop a distributed yet collaborative network of specialists from a range of institutions and levels in which experts from various fields are encouraged and aided in communicating with one another and wherein multiple types of expertise and perspective are valued for their inherent diversity. We must develop a community that incorporates not only a wide range of biologists but also processing specialists, not simply as technicians or core facilities, but as valued and equal participants. We must develop clear pathways of support and incentivization, paired with unambiguous parameters and expectations for collaboration. We must train not only current, but also future generations, in such a way that they focus on the large question without abandoning individual specialization and knowledge.

Conclusions

Studies on the mechanistic underpinnings of robustness and resilience are central to our understanding of how life both persists and evolves. Development of common tools and terminology will be necessary to allow for seamless integration of the vast datasets obtained from sources across scales of biological organization, and inform future research directions. A new framework of training and collaboration of life science experts representing multiple disciplines will promote a cultural shift that stimulates diversity and inclusion.