

# NSF Reintegrating Biology Workshop Vision Paper

## Finding common rules of robustness and resilience that span multiple levels of biological organization

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### Summary:

Today, humans as a species face significant global challenges: meeting the needs of an ever-expanding human population for food and energy from limited land, water and other resources; finding ways to counter rapidly changing pathogens that become resistant to current treatments; adapting to climate change that is linked to more frequent flooding, drought, wildfires and temperature extremes; and reversing the deterioration of ecosystems associated with human-induced alterations of the environment. Owing to its resilience and robustness, life in one form or another will likely persist, but it is unknown by what mechanisms or in what forms. Much is now known about the mechanisms of life, including the biochemical reactions of information and energy processing within microbial cells, programs that define the development and evolution of multi-cellular organisms, from worms to humans, and how interactions among diverse life forms contribute to ecosystem emergence and dynamics. Moreover, we now possess technologies to manipulate, observe, analyze and synthesize our understanding of model and non-model systems in controlled lab environments as well as in the field and encompassing up to the global scale. We have an abundance of in-depth data that if coalesced into user-accessible databases may enable scientists to understand systems in a broad sense, discovering overarching strategies used at different scales. But the big question remains: **are there common rules that govern resilience and robustness across different levels of biological organization-- from molecules to ecosystems?** The study of resilience and robustness is a transdisciplinary field that may be amenable to network science framework across levels of biological organization, where the one network at one scale (e.g., within cells) becomes a node in a network at a different scale (e.g., across cell populations). Moreover, scientists in the fields of psychology, anthropology, sociology, and economics can contribute to and benefit from a central theory of biological robustness and resilience. There are many barriers to this paradigm shift. Engineers, computer scientists, and biologists in different research communities lack of a common language for describing what robustness or resilience mean across different levels of biological organization. In addition, there are many institutional and structural barriers that need to be overcome. For a unified theory of robustness and resilience to emerge, meaningful incentives to promote collaborative research must be implemented, traditional departmental barriers must be dismantled. Most importantly, science education from K-12 through the post-doctoral level must be re-designed to focus on problem-based scientific thinking that requires integration of knowledge from different scientific disciplines so that it becomes a common way of thinking for the next generation of scientists and innovators.

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## 1. The Big Question

Biological systems, regardless of scales, must be robust and resilient in order to survive and reproduce in a continuously fluctuating and changing environment. Here, we define robustness as the ability of a system to resist internal and external perturbations in order to maintain a stable state over a long period of time (Fig. 1A). We define resilience as the ability of a system to recover from functional decline caused by adverse forces in order to return to a stable state (Fig. 1B). A stable state of a system can be considered as a local energy minimum described by a set of parameters or characteristics (Fig. 1C).

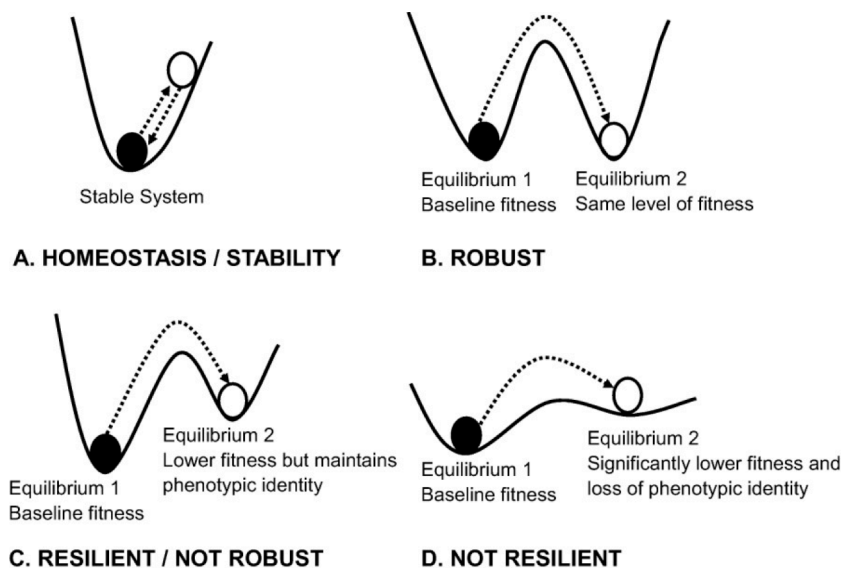


Figure 1: Energy/stability schematic diagram of robustness and resilience from [Varadhan et al. 2018](#).

How do biological systems maintain robustness and resilience in a continuously fluctuating and changing environment? Importantly, **are there common rules that govern resilience and robustness across different levels of biological organizations-- from molecules to ecosystems?** If we could deduce these rules, strategies, and mechanisms, and any necessary variations, we could then describe, predict, and encode resilience and robustness in systems across different levels.

More specifically, we ask the following questions:

- **What common mechanisms and system properties determine robustness, and what determines resilience?**
  - a) Is there a key principle governing robustness across all biological organizations, such as **redundancy** or a noise-buffering **network**? What is the minimal requirement for such a key factor? For example, how redundant a system and how big a network need to be in order to maintain the robustness of the system?
  - b) Similarly, is there a key principle governing resilience across all biological organizations, such as **diversity** in properties? What is the minimal requirement for such a key factor? For example, how large the size of a population or the number of variations in genetic mutations needs to be in order to maintain the resilience of the system?
- **How do robustness and resilience relate to each other?**

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- a) Do robustness and resilience reinforce or antagonize each other, and how these relationships vary under fitness and other evolutionary pressures?
- b) Is **adaptability** the key to unite robustness and resilience in order to maximize the likelihood of a systems' survival and reproduction?
- **Can we construct a universal, scale-free mathematical model to describe robustness and resilience, and the relationship between them? If so, how?**
  - a) How can we use existing big data and integrate insights from available models of community and population dynamics that are successfully used for metabolism, viruses, microbiomes and ecosystems ([Mathias et al. 2017](#)) to construct a universal mathematical model that will elucidate common rules underlying for resilience and robustness across different scales?
  - b) How can we go beyond commonly practiced pattern-finding in the analysis of big data to gain mechanistic insights and generate good predictions?
  - c) Can we conceptualize each level of biological organization as a network consisting of nodes and edges, and the emergent collective behavior of the network as a node for the network of the next higher level of organization?
  - d) How does the connectivity (and feedbacks therein) among different components of a system, such as that in metabolic networks, gene-regulatory networks, cytoskeletal networks, social networks, and contagion networks contribute to the robustness and resilience of the system?
  - e) Can we use the knowledge gained above to construct a “theory of the thermodynamics of robustness and resilience” in biology across scales drawing insights from dynamical systems and statistical mechanics, including our knowledge of scale-free networks?
  - f) Finally, can we write a master mathematical equation to depict the qualitative or quantitative relationship between robustness and resilience and how they contribute to the system's survival and reproduction?
- **How can we use the above understanding of robustness and resilience of natural biological systems, i.e. the rules of life for robustness and resilience, to address and to solve societal problems?**
  - a) Can we reprogram synthetic systems that recapitulate specific functions of living systems?
  - b) Can we manipulate existing systems or even design new systems that will thrive under even the most undesired conditions? For example, can we build new ecosystems to help balance global processes and address the climate crisis?

### 2. How does the pursuit of these questions reintegrate biology?

Biological processes related to robustness and resilience are studied by scientists not only across biological disciplines, but also in social sciences, computer science and engineering. By focusing on generating conceptual properties that relate to robustness and resilience across levels of biological organization, we can unify the vocabulary and research questions at each level of biology, and ultimately advance to an integrative science of robustness and resilience.

We propose to establish a unifying concept that biological systems at any level function in networks. A **network** is defined as a collection of nodes and edges, which are abstract and universal to systems of all levels but can also be embodied with specific substances

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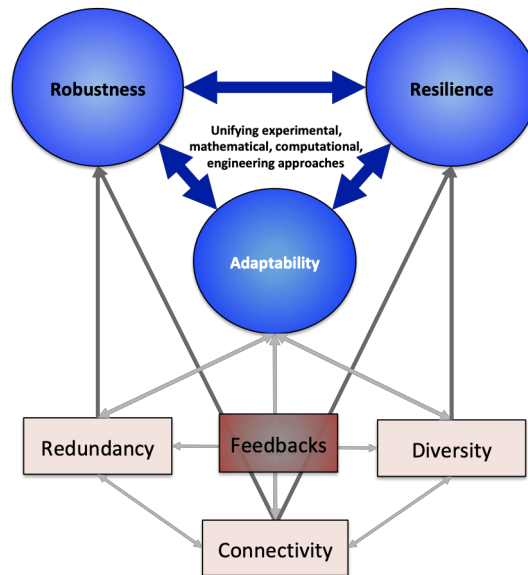


Figure 2: Schematic of the properties relating to robustness and resilience based on a network science framework. In this model, robustness and resilience, and adaptability are emergent properties (blue circles) of the dynamic workings of networks that have redundancy, diversity and connectivity, which includes functional feedbacks among nodes.

particular to individual systems. For example, communities can be thought of as network of interacting species. Diverging but interconnecting species can be considered a network of populations of varying connectivity. In dynamic conditions, individuals in colonies of social insects operate in a functional network. Physiological regulatory networks (Cohen et al. 2012) maintain organismal function, and within organ systems, metabolic networks maintain cellular function (see Box 1).

Borrowing from mathematical theory of networks, we propose that key properties determining the robustness and resilience of biological systems at any level of organization are **redundancy, diversity, and connectivity** of the network (**Fig. 2**). Below we provide definitions and some examples of the relationship between these network properties and robustness and resilience.

- **Redundancy:** Multiple nodes in a network could have the same essential functions. If one node loses function, others can compensate. Redundancy is widely observed in developmental biology, where essential developmental events are often under the control of many genes having a similar function. Redundancy is often used to explain how embryos tolerate developmental errors to result in the successful development of canalized body plans and morphogenesis (Lachowiec et al. 2018). Similarly, food webs with redundant species at different trophic levels are considered more stable against environmental perturbations and diseases. Lastly, redundancy of endocrine and genetic mechanisms regulating energy balance and food intake are necessary to maintain homeostasis.
- **Diversity:** Each node in a network could be molecules, genes, cellular transduction pathways, individuals or genotypes in a population, species in a community and trophic levels in an ecosystem. Diversity of a network can be regarded as the number, variations and complexity of nodes of differential identities or functions in a network. For example, genetic variations or differential gene expression states in microbial populations allows for

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the survival of resistant or persistent cells, which could revive the entire population upon the retrieval of adverse antibiotic treatment; high virus mutation rates create variants escaping host immune systems and resulting in robust viral infections (Drake 1993; Fitzsimmons et al. 2018). Communities with more diverse species composition and of larger population sizes are more stable and resistant to invasive species compared to the ones of smaller sizes (Hopf et al. 2019).

- **Connectivity:** We broadly define connectivity as the extent to which nodes communicate with each other, or specifically, the number and types of connections (edges) connecting nodes in a network. Connectivity is a universal property of networks, but the specific connectivity depends on the structure of the network and mechanisms of communication. Networks can be described as distributed, decentralized or centralized, each of which having different patterns of connectivity. Connectivity plays a critical role in determining the robustness and resilience of a network. For example, distributed networks with high levels of edges connecting nodes confer stability, as demonstrated in the stability and persistence of metapopulations linked with migration (Hopf et al. 2019). During gastrulation, sheets of cells are robust against any “weak links” of individual cells in the population to allow for successfully differentiation into germ layers. Decentralized or centralized networks could also confer stability and resilience in the metapopulation contexts.

Ultimately, while a network with appropriate levels of redundancy, diversity and connectivity could confer robustness and resilience under set conditions, these networks must also be able to **adapt** under fluctuating and changing environments over time (see Figure 1). Here, we broadly define adaptability as the ability of the system to change in response to perturbations, either maintaining the original stable state but with better stability or moving to a new stable state with changed properties. This concept is commonly referred as physiological acclimation, phenotypic plasticity, or evolutionary adaptation depending on the level of biological organization.

What are possible mechanisms contributing to the adaptability of a system? In the context of biological networks, beside the aforementioned redundancy and diversity, **feedback** mechanisms encoded in connectivity could play a central role. Feedbacks in a network refer to special connections among different nodes that allow these nodes to send out signals to downstream nodes in response to feedback signals they receive from these nodes. A network with feedback connections will be able to measure the state it is in, compare to a set state, and adjust its output to meet the set state. In the scenario where the original set state cannot be met, a network with the appropriate connectivity could activate different feedbacks to break old connections, make new connections to establish a new stable state. Feedback mechanisms allow a network to correct/repair nodes and connections that are perturbed or become dysfunctional under certain conditions. Common examples include negative feedbacks in predator-prey systems that result in population oscillations, gene regulation systems that lead to constant gene expression output, or DNA proofreading and repair systems, and positive feedbacks in excitable organism behaviors or memories in gene regulatory networks.

Adaptability can both contribute to and result from robustness and resilience under dynamic conditions. A better integration of adaptive processes that occur at different levels of organization is therefore needed to understand generalizable strategies. These strategies can then be modeled across scales to predict how robustness and resilience at one level relates to those at another. Evolutionary biologists can help us understand how stability and resilience systems change over time in response to selection different pressures, or how the diversity of mechanisms that create systems that confer stability and control have been derived.

## Box 1. Cellular metabolic networks: Robustness, resilience and adaptability

Robustness, resilience, and adaptability of metabolic networks makes possible the maintenance of cellular functions in the face of different internal and environmental perturbations. **Robustness** in metabolic networks emerges from the kinetic properties of the individual enzymes of the network in conjunction with the steady state-pool sizes of the set of metabolites the enzymes are operating upon. Pool sizes tend to hover at the  $K_m$  value of the enzyme, which is the linear portion of the saturation behavior of the enzyme, such that the rate of the enzyme changes maximally in response to fluctuations in pool size. This even applies to metabolite pools that have extremely high rates of turnover due to high rates of metabolic flux through the pathway. Overall, this situation results a robust maintenance of metabolic pool sizes throughout the network. **Resilience**, likewise, has evolved through the myriad of homeostatic mechanisms modulating enzyme abundance and allosteric feedback mechanisms adjusting enzyme activities according to changing conditions.

**Adaptability** is apparent in metabolic networks as observed in long-term natural and laboratory experiments that are revealing adaptive genetic changes fixed in populations that have transitioned to new environmental conditions (La Rosa et al. 2018, Baez & Shiloach 2014). Much of this has only been possible by the development of big data and computational modeling approaches. For example, the field of metabolomics has hybridized advanced analytical biochemistry, genomics, and mathematical modeling. With advances in large-scale experimental metabolic analysis, it is possible to trace hundreds of metabolites simultaneously in a single experiment and, thus, it is now becoming possible to quantitatively evaluate fluctuations in metabolite concentrations for key metabolites across entire metabolic networks (Neilson 2017; Basan et al. 2015, Sauer 2006; Orth et al. 2010).

Interestingly, these developments have productively collided with developments in completely different fields: genomics and computational modeling. The result has been a renaissance in the understanding of metabolism which are likely to lead to new understandings of metabolic system resilience and robustness. Already, it is clear the the topology of metabolic networks, with highly interconnected metabolites in 'modules' such as the TCA cycle, connected by a much smaller number of common intermediates, including ATP, influences the robustness of the network [10.1073/pnas.0703262104], although the 'rules' are still being worked out. Also, it is clear that some of the mathematical formalism for this (linear programming of simultaneous reactions, network analysis) share features that are in common with biological networks at different scales of time and space. For example, HIV viral levels belie that fact that the turnover rate is very high can be mathematically described in the same form as findings that metabolites present in cells at very low concentrations often correspond to pathways that have the highest flux (traffic) through them (Xiong et al. 2015; Liang & Lindblad 2016). In both cases, low steady state levels reflect high turnover due to high rates of production matched by high rates of consumption. No doubt ecological and population dynamic process have parallel dynamical features. This illustrates, how entirely different biological processes, studied using very different experimental techniques, and by scientists in different disciplines can find common ground in describing and integrating different phenomena.

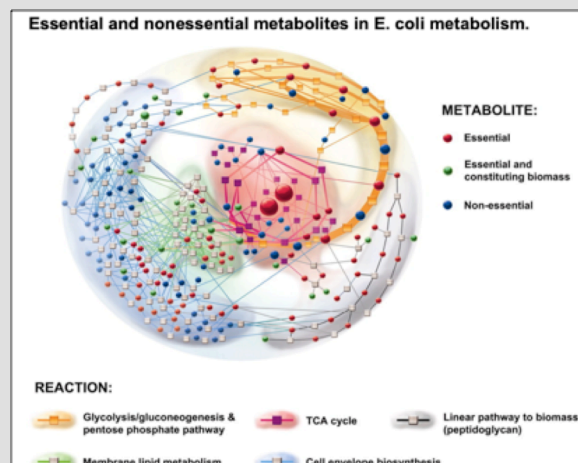


Figure 3. Cellular metabolic network adapted from Kim et al. 2007.

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### **3. Potential Impact**

Addressing above questions requires combined approaches from experimental, mathematical, computational and engineering sub disciplines (Fig. 2). These joint efforts will no doubt generate unique collaborative opportunities, new tools and new research directions that will improve future research of biological systems. For example, useful experimental datasets, mathematical models, and computational tools for validating and predicting behaviors of complex systems may be generated. New software incorporating improved parameter definitions and modeling techniques could facilitate the investigation and understanding of intra- and inter-level connections of complex biological systems. Synthetic datasets with standardized format could also result from these research to allow downstream applications for other multiscale studies.

At the larger scientific community level, these joint efforts will boost communications among researchers of different expertise, promoting common language to describe diverse biological systems. Such common language for biological systems would have long-lasting implications for future researchers discovering and elucidating the rules of life on Earth.

Finally, finding common rules of robustness and resilience across scales in natural systems will transform the way we understand biological systems and revolutionize synthetic biology. We will begin elucidating design and engineering principles of living systems and use them to deploy stable and viable synthetic systems. As biological systems of different organization levels are interconnected across scales, we may be able to predict how changes at one organization level affect the other levels, contributing to a holistic understanding of all biological systems as a whole. Mechanisms discovered in these researches could also be targeted for interventions and manipulations of systems to deliver desired outcomes.

In summary, we anticipate that research to find common rules of robustness and resilience of biological systems will provide complex and predictive models of biological systems ranging from a single-cell's development into complex tissues to diversified species in ecosystems in the face of climate change. Access to such predictive models will have enormous impacts on social, economic, science policy decision-making and beyond (see 6. Broader Impacts).

### **4. Why now?**

We face grand challenges, such as meeting the needs for food, fiber and energy produced from the arable land by the continuously increasing human population; adapting to climate changes that lead to more frequent flooding, drought, and high temperature; and remedying deteriorating ecosystems (forests, oceans, etc.). All these challenges call for innovative solutions that will be derived from fundamental and applied research including basic biological research funded by NSF. Revealing and applying common rules that govern the robustness and resilience of biological systems will be an important and indispensable part of the solution. Biological systems by themselves are complex across all molecular, cellular, tissue, organ, species and ecosystem levels. These pressing challenges and their prevalent complexity require integrative strategies and approaches to find the common rules of biological systems.

Now is a prime time to make the integration possible because we have many state-of-the-art, enabling technologies across all scales of biological organization. For example, at the molecular scale, next-generation sequencing (NGS)-based technologies can access genomic and transcriptomic information across conditions and species. Advanced mass spectroscopic techniques provide quantitative proteomic and metabolomic analyses to address a wide range of biological questions. Cryo-electron microscopy and tomography can visualize structures of macromolecular complexes in native or near native environment with atomic resolutions. Super-



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resolution and single-molecule imaging push the detection of molecules and cellular structures in live cells beyond the diffraction limit of light microscopy. We also possess incredible powers in manipulating organisms through gene editing and targeted perturbations. At the organism level, we start to build synthetic cells and grow organoids that recapitulate essential features of life. At the population level, we have the most advanced tracking technologies to monitor the dynamics of large populations of animals and changes in ecosystems. Various social media offer new platforms to gather and disseminate information at the society level. Our growing computational and mathematical powers, coupled with mechanistic modeling, machine learning algorithms and artificial intelligence algorithms, are able to describe systems and predicate outcomes at different scales, whether it be levels of biological organization (molecules to ecosystems), time scales (seconds, min, hours), or by some metric of complexity (e.g., reaction, pathway, network, hairball).

Furthermore, we have an abundance of in-depth data from not only model systems, but also diverse, non-lab adapted systems. If coalesced into standardized, user-accessible databases, they can be used to understand systems and find overarching strategies at a broad level, examining overarching strategies universal to different scales. There is also a substantial amount of historical genetic and ecological data that can be harnessed and integrated with current data to develop algorithms of hindcasts to forecast robustness and resilience of systems.

Finally, we are also at a time that funding agencies such as the National Science Foundation have acknowledged that they can play a major role in promoting cross-disciplinary training of a new generation of scientists by changing funding schemes and training programs. These changes will promote cross-disciplinary training of a new generation of scientists who have the skills to discover and describe the important overarching questions of life on Earth.

### 5. Key barriers and challenges

Terms like resilience and robustness depend on context (molecular, cellular, multi-cellular, population) and differ depending on scientific training or field (math/systems/engineering vs molecular/cell /biology/ecology). One challenge is that the same term can be applied to different or even foreign concepts; despite this these activities offer an grand opportunity where a common “language” can be developed to identify unifying threads across biological levels and across scientific fields. Different fields/training will likely have “solved” the problems of “resilience” or “robustness” for some more narrowly defined problems, but scientists outside the field (or approach) may struggle with adapting these solutions to novel areas. Learning solutions from other systems may provide insights within a different domain/level of biological organization). We have identified 10 barriers to progress in addressing our overarching questions:

1. Lack of a common language for describing what robustness or resilience means across different levels of biological organization.
2. Is math/engineering/computer science (MEC) the common language? If it is, then a key barrier becomes translation of the biological description into a MEC one, resulting in the related questions:
3. If MEC is a common language, then what form of MEC is most useful for describing the essential biology at any particular level or across levels of organization?
4. How do we translate results from MEC back into biological insight?



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5. There are also vocabulary differences among disciplines within the biological sciences, such that the same phenomena are studied independently, preventing the integration of these disciplines. For example, we have amazing tools for searching primary literature that combine sources of information across diverse scientific disciplines (e.g., Web of Science), but literature searches are restricted to the terms used. Unless this terminology is standardized, or “smart” searches that translates those terms into others that are known to vary across fields are utilized (e.g., “transgenerational plasticity” and “developmental programming” and “carry-over effects”), relevant information will be forever segregated in the minds of researchers.. Creating interdisciplinary educational programming will also enhance this merging of language and terminology so that discipline-specific jargon will be erased.
6. How do we blend the best of different MEC approaches (i.e., traditional vs. “big data” methods of MEC)? Traditional mechanistic (mathematical) models are based on relatively sparse data, but they can offer mechanistic insights; they generally cannot extract insight from big data. Emerging bioinformatic/machine learning or statistical methods of MEC can use big data to find patterns and develop predictive models, but they often provide little mechanistic insight. So one specific challenge is: how can we gain deeper mechanistic insights from the analysis of big data (go beyond finding patterns to generating robust predictions).
7. Inevitably, the scientific community needs to decide on one or a few model systems to probe for universal roles. Which ones are optimal and what criteria are used to select these systems?
8. How do we use the synthetic systems approach to design for robustness or resilience in systems? And how does a designed system differ from one that came about natural processes (e.g. trial/error, natural selection, stochasticity, phylogeny)?
9. How do scientists gain access to the physical infrastructure and tools needed to study transdisciplinary robustness and resilience across scales, despite laboratory and institutional limitations?
10. What incentives can be created to promote novel transdisciplinary collaborations, such as funding mechanisms and considerations for individual tenure and review, over traditional, individual PI awards?

### 6. What might be broader impacts?

These activities will transform how we view the minutiae and grandeur of biodiversity; understanding how biological systems respond to changing conditions over time and space has a multiplicity of broader applications. These questions will address how biological systems react with current, rapidly changing environmental conditions, which affects everyone on Earth (e.g. Hammerschlag et al. 2019). Outcomes of these efforts have consequences for an array of applications that will improve the quality of life for humans. Study of robustness and resilience at sub-cellular, physiological and tissue levels has medical implications; research in this area can set the stage for advancements in disease biology and cancer treatments. Robustness and resilience can also be viewed through the lens of organismal biology and responses to environmental changes; outcomes from this area will influence conservation strategies for species in threatened ecosystems as well as providing a unique view of many potential and realized threats to biodiversity (e.g.. Donelan et al. 2019). Finally, understanding resilient and robust biological systems can also facilitate improved design of energy storage/transport, urban transportation systems, and movement of resources across the globe.

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All activities will require the use of large datasets in novel ways, ranging from online, public genetic databases to traditional specimen-based collections. These activities will necessitate using these resources in a novel way, and require new ways of curating complex, integrated datasets. Once these resources are available to the scientific community, the benefits will be wide-ranging and future innovative applications will be realized. The synthesis of separate resources will also require increased communication between individuals responsible for these disparate resources, which, in turn, will allow for collaborations resulting in novel research directions.

Education is central to the advancement of this research and will also benefit from these activities. Undergraduates will benefit from a merger of approaches from these research areas, integrating traditional biological topics with quantitative and machine-learning approaches. These efforts will produce a cohort of broadly trained graduate students and post-doctoral researchers. Established scientists in diverse areas will have the ability to acquire new skill sets and establish unique interdisciplinary networks to answer questions about robustness and resilience at different biological scales. Societal impacts could be that the development of the language and concepts of the integrative 'systems' thinking developed by the center could provide a more unified way of teaching/learning science. Practically, this can lead to improvements in K-12 standards and curricula that, for example, better facilitate math and language skills. As one of the goals will be to develop example venues and collaborative science projects between MEC scientists and biologists, an important aim will be to understand and propagate methodologies and tools that foster this type of collaboration. Accordingly, outreach activities would include sharing the lessons learned in this process.

### **8. What disciplines might be needed?**

The study of resilience and robustness is a transdisciplinary field, encompassing molecular biology to ecosystem science, and extending into biophysics and biochemistry. Similarly, collaborations with scientists in psychology, anthropology, sociology, and economics that also study resilience and robustness using conceptual frameworks and theory could manifest in new ideas across biology and these fields. Engineers and computer scientists also tackle the question of stability and resilience from an applied information and power systems context, which also applies. Ultimately, a transdisciplinary community of scientists can yield unified properties of stability and resilience across any system, as well as identifying, essential context-specific mechanisms. Importantly, science communicators are needed to translate this transdisciplinary understanding of resilience and robustness to international policy makers, consultants and business leaders so that these principles can be applied to global decisions that impact the whole of humanity.

### **9. Intended audience of the paper.**

The vision paper is intended for all those involved in the chain of scientific research and education, including funding agencies, peer scientists, educators, as well as the public. First of all, communication of the vision to funding agencies like NSF and NIH is extremely important, because they determine directions taken by the scientific community, impacting the research activities and professional training in the far future. Second, the vision paper advocates the need of breaking down barriers between different disciplines. Thus, the paper aims to reach the working scientists from the entire spectrum of disciplines that are currently or could soon be involved. For example, experimentalists benefit from learning about how models generalize the understanding of robustness and resilience at different levels of biological organization through the mathematical language. In turn, modelers benefit from learning about the specific robustness and resilience that emerge in different biological systems. Third, the vision we advocate will urge the administrators and/or colleagues who make hiring decisions to value

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diverse backgrounds in their new principal investigators. Fourth, it is important to translate the concepts and common language developed for robustness and resilience to *educators*. Educational programs from K-12 through post-doctoral training, must integrate different traditional scientific disciplines (chemistry, biology, physics), mathematics and teach computational skills to produce students who understand the connections among these fields. *Vision and Change* and other undergraduate STEM programs (e.g., POGIL, CURE, etc.) have offered some strategies for effective cross-disciplinary thinking, such as problem/research-based curricula, involving integration and multiple levels of analysis. Unfortunately, programs that use this philosophy are few and in their infancy. Further, development of textbooks and online educational tools that incorporate these concepts and interdisciplinary perspectives will efficiently speed this process. Most importantly, these approaches should be communicated to the general public and voting citizens. Advances in understanding and eventually engineering robustness and resilience will enable us to address the most pressing societal challenges of the day and their potential links to biology (e.g. antibiotic resistance, global warming, fresh water supply, electric grid stability, climate change, food supply).

### **10. What institutional changes are needed to make this vision a reality?**

Robustness and resilience are properties that are studied across levels of biological organization, yet these efforts often occur in isolation within disciplinary communities of scientists. Definitions and vocabulary, research approaches and methods, and metrics vary depending on the scientific discipline, or even across communities even within a discipline, preventing the formation of a unified theory. To integrate biology, we must first incentivize the collaboration of researchers working on biology-related problems across an array of disciplines and approaches. For example, collaborative interdisciplinary research awards must receive as much weight for tenure or promotion as discipline specific awards, and the review process of grants must be changed to increase the likelihood of funding collaborative proposals. Breaking down traditional barriers by merging biology-related departments under one umbrella program, or having umbrella programs that facilitate interdepartmental academic and research activities, is a necessary first step.

Another successful mechanism used to enhance transdisciplinary research is to establish integrated biological centers or programs. Rather than focusing on the subdiscipline, i.e. biochemistry, ecology, genetics, task-driven centers focusing on a common problem will facilitate creating a common language for people across disciplines for examining robustness and resilience in all biological systems. We propose that the establishment of a central Institute for Robustness and Resilience would address many of these issues and spark a new paradigm, promoting transdisciplinary research to address the questions articulated above, just as many of the other NSF centers have done for other focal areas of research and innovation. In addition to stimulating transdisciplinary research, such an institute could develop improved math, engineering, computer science education programs for undergraduate and graduate students in the biological sciences, which is urgently needed. Biologists will more readily adopt quantitative model approaches if the material for these areas is taught through the lens of relevant research application. An especially important role of this institute will be to provide a platform to attract policy makers to consider and eventually embrace data-driven, rational and thoughtful approaches to promote robustness and resilience through governance and solving problems at local, national and global scales.

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