Visit Research Plan:

Theoretical Dynamics and Evolution of Modular-Hierarchical Structures

1. Background

A common feature of many biological systems is that they are organized as a hierarchy of embedded subsystems or modules (see Fig. 1). Complex organisms are composed of multiple substructures and often host a variety of sub-organisms (e.g.: bacteria or viruses). These can contain in turn their own substructures and sub-organisms, a pattern that can repeat multiple times and span many spatiotemporal scales. It is becoming clear that the dynamics and evolution of living systems is strongly conditioned by these embedded substructures and sub-organisms. This multi-scale Modular and Hierarchical (MH) organization also appears to be a crucial factor when engineering biological functions, such as those resulting from genetic and metabolic networks created artificially using synthetic biology. Indeed, while many arbitrary structures can be built, these will be discarded through natural selection if they are not as robust and adaptable as required by biological conditions (and as MH systems appear to be).

In a starting collaboration between Prof. Dirk Brockmann (Robert Koch-Institute & Humboldt U, Berlin), Prof. Joshua Leonard (Chemical & Biological Engineering, Northwestern U), and Prof. Cristián Huepe (Engineering Sciences and Applied Mathematics, Northwestern U) we have been considering theoretically and experimentally the dynamical features, adaptability and evolution of MH structures in living systems. The Leonard Lab has developed experimental platforms, using tools from synthetic biology to engineer cellular ecosystems wherein genes and other intracellular and extracellular components are connected through defined interaction networks with different degrees of modular and hierarchical organization, in order to compare their fitness, adaptability, and functional capabilities. These types of structures are being built in two different systems: a bacterial Toxin-Antitoxin system (Fig. 2a) and groups of interacting immune cells. Both systems combine dynamics at the intracellular level with interactions between cells, which allows us to implement MH structures that span at least these two distinct hierarchical levels. The Leonard Lab also has unique capabilities to measure single-cell data of various internal population dynamics, allowing us to closely monitor dynamical processes in the engineered MH biological interaction networks (Fig. 2b).

The experimental framework described above must be paired with adequate theoretical tools in order to make sense of the complex structural and dynamical features of MH systems. Despite the apparent ubiquity of MH structures in biology, there are very few formal tools for analyzing or modeling them and a limited understanding of their typical dynamics and potential origin. To address this, we are developing a set of, both, specific and generic models that explore the properties of MH systems, which will help guide experiments and carry out model-based predictions and data analysis. Our models are formulated in terms of networks, since these can readily represent abstract MS structures by imposing the right connectivity and are commonly used to translate real-world biological interaction structures into mathematical language by describing biological networks such as genetic networks, metabolic networks, signaling networks, and even neural networks or ecological networks.

Our objective with this parallel experimental and theoretical work is to examine comparable MH structures using experiments, models, and theory to investigate the key questions: (1) what types of dynamics are supported by MH structures; (2) do MH structures improve fitness or confer other evolutionary advantages; and (3) how do MH structures emerge and evolve? Ultimately, we seek to achieve conceptual understanding that helps design MH synthetic structures that are more robust and adaptable within biological systems and also understand natural MH dynamics, to be able to consistently disrupt or restore existing biological functions.

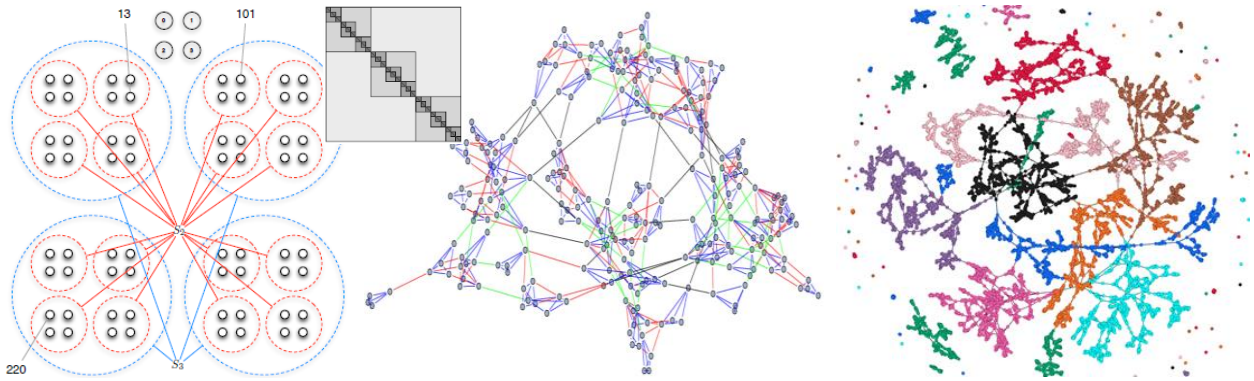

Figure 1: Examples of the structure, topology, and dynamics of MH systems generated using a Random MH Network (RMHN) algorithm. Left: Structure of the RMHN algorithm and of its adjacency matrix (inset); we observe a hierarchy of embedded modules (four nodes within each red-circle module, four red-circle modules within each blue-circle module, etc.) that is typical of MH systems. Center: RMHN with 4 levels and 4 modules per level; links are colored by level. Right: Preliminary calculations of percolation on RMHN; modules initially percolate independently.

2. Specific aims

The objective of the proposed visits is to develop and study a new class of simple (and hopefully universal) network-based models specifically designed to describe the dynamics and evolution of MH structures in living systems. We will focus on two different types of models: (1) detailed descriptions of the connectivity structures that are currently being engineered by the Leonard Lab through synthetic biology, in order to contrast them with specific experiments, and (2) minimal, generic models where connectivity is random but follows a certain MH structure, in order to represent a variety of systems with common MH properties.

At the end of the proposed visits, we expect to have:

- A set of algorithms that generate MH-networks and help us classify different types of topological MH structures
- A strong understanding of the characteristics of the dynamical (biochemical) processes that can be supported by MH biological interaction networks
- A set of artificial-life simulations using MH structures that show how they may improve fitness (especially in changing environments) and how they emerge and evolve
- A detailed analysis of the specific biological networks that are being developed at the Leonard Lab, including their structural and functional features, stability, and adaptability.

The visit conditions are ideal to achieve these objectives. Prof. Brockmann is a leading expert on complex network topology and dynamics, and has vast experience modeling and analyzing data from biological networks. Prof. Huepe has significant know-how on developing theory that describes complex self-organized biological systems and MH structures. Since he is based in Chicago, he interacts regularly with the Leonard Lab and will thus help bridge the experimental and theoretical work, while his adjunct position provides him with the flexibility to carry out the proposed extended visits to focus on the theoretical collaboration for the project. In addition, Prof. Brockmann's position at the Robert Koch-Institute (one of the leading institutions for health protection and the study of biomedicine in Germany) will provide an environment where our abstract network analyses can be discussed in a broader biomedical context, in order to further link them to various real-world genetic or metabolic processes.

In sum, the activities listed below aim to result in set of modelling and theoretical tools that will help analyze and control the synthetic biology experiments at Leonard Lab, as well as a broad class of biological and biomedical systems with MH organization.

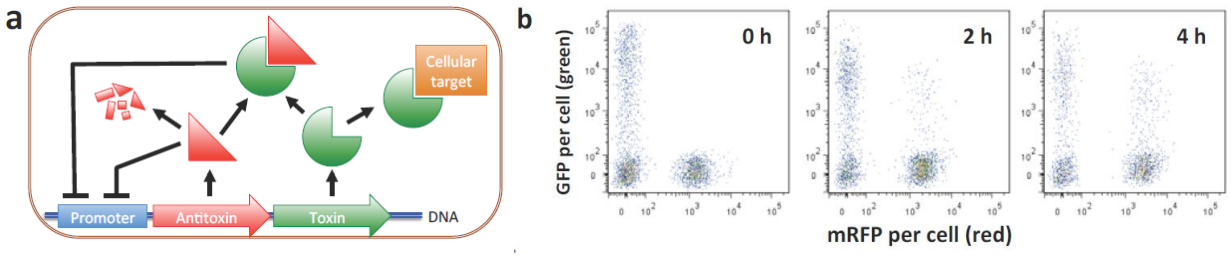

Figure 2: Experimental framework. (a) One of the Leonard Lab systems is based on bacterial toxin-antitoxin (TA) networks. This cartoon shows the general architecture of natural type II TA systems, in which TA components are co-expressed from a single promoter, antitoxin inhibits toxin-mediated interference with cellular processes, antitoxin and toxin-antitoxin complexes negatively regulate expression of TA components, and antitoxin is degraded rapidly relative to the toxin. (b) Single-cell data showing population dynamics, here illustrating transfer of a GFP-encoding plasmid (green) from donor cells to recipient cells expressing mRFP (red) over 4 hours of conjugative transfer.

3. Research activities and career development potential

During my visit to Prof. Dirk Brockmann at the Robert Koch-Institute in Berlin, we will study a novel class of network models that generate MH structures analogous to those constructed in the Leonard Lab's experiments. The visit will allow us to focus together on their topological and dynamical features and explore their potential evolutionary origins. Our activities will include:

- Continue to develop MH network-generating algorithms; program them in different platforms
- Search for analytical and numerical results describing the type of topology and dynamics that characterizes the resulting MH networks, and use these to classify MH structures
- Perform artificial life simulations where MH networks are evolved based on their ability to support dynamical processes on the node states that satisfy specific fitness criteria
- Survey the literature for similar algorithms that generate MH networks and for connections to our synthetic biology experiments and other biological systems
- Interact with biologists related to the Brockmann group in Berlin, at the Robert Koch-Institute and Humboldt University, to find other biological examples of our abstract MH networks
- Establish a larger future research plan, building on the visit results

In preliminary work, we developed a new algorithm to generate multi-scale Random MH Networks (RMHN – see Fig. 1). We will analyze these theoretical MH structures and compare them to our experiments. We will carry our analytical and numerical investigations on the topology and dynamics of these networks. Our topological work will include: studying if standard community detection algorithms correctly identify modules on MH networks, examining network topology (including biologically relevant features such as robustness), and exploring percolation and network growth properties. Our work on node-state dynamics will include: analyzing network spectral properties, studying canonical dynamical processes on RMHN (diffusion, synchronization, infection, etc.), and exploring phase-transitions and evolutionary dynamics on RMHN. Evolutionary studies will be guided by recent results showing that modular structures spontaneously emerge in systems that are adapted to alternating conditions, since each module can be activated independently when required, to address a given biological challenge.

The PI's career development will strongly benefit from this opportunity to serve as a critical link between the US and German teams in this ambitious project. The visit will also allow the PI to further learn about biological networks and the biomedical implications of their structure and dynamics. This project could lead to breakthroughs in the beneficial utilization and manipulation of living systems and in the fundamental cross-disciplinary understanding of biological dynamics and self-organization. It could also improve medical practice by helping identify critical nodes or structures in human or pathogen physiology that convey functional properties such as adaptability and robustness, thus largely increasing the PI's impact on biomedical research.