

Research Statement

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My research sits at the intersection of control theory, system identification, nonlinear systems theory and network science. Inspired by these disciplines, my research program aims to develop mathematically rigorous theory in order to understand, diagnose and control complex networked systems in engineering, biology and medicine.

Network structure and functionality of complex dynamic systems. Part of my research focus on understanding the interplay between the network structure (i.e., organization) of complex systems and their dynamic behavior. Real networks such as gene regulatory networks or the World-Wide-Web have macroscopic organization properties like scale-free degree distribution [32] and microscopic properties like network motifs [2]. Do these organization properties provide functional advantages when dynamics are considered?

The microscopic principles organizing dynamic units in complex networks —from proteins and neurons to power-grid generators— can be understood in terms of network “motifs”: small interconnection patterns that appear much more frequently in real networks than expected in random networks [2]. When considered as subgraphs isolated from a larger network, these motifs are more robust to parameter variations, easier to synchronize than other possible subgraphs, and can provide specific functionalities [28, 35, 1]. But one can only isolate these subgraphs by assuming, for example, a significant separation of time scales, and the origin of network motifs and their functionalities when embedded in larger networks remain unclear. Combining *contraction theory* with a simple model reduction methodology, we have shown that most motifs emerge from interconnection patterns that best exploit the intrinsic stability characteristics at different scales of interconnection, from simple nodes to whole modules [7]. This functionality suggests an efficient mechanism to stably build complex systems by recursively interconnecting nodes and modules as motifs. We presented direct evidence of this mechanism in several biological networks, including the gene transcription network of the *E.Coli* bacteria and the neural network of the *C.Elegans* nematode.

From a macroscopic perspective, understanding how new behavior emerges from aggregating simple agents remains a fundamental problem in modern physics, with deep branches that extend to biology [3], technology [33] and the nature of consciousness [42]. Complex behavior emerges due to nonlinear dynamics —through bifurcations [40], catastrophes [18], chaos or strange attractors [41]— but may also emerge due to the aggregation only, in particular, in the *thermodynamic limit* of an infinite number of nodes (or agents). A famous and controversial example is Boltzmann’s *H*-theorem, where nodes with time reversible dynamics give rise to irreversible behavior in the thermodynamic limit [44]. Yet, in such situation, it is not clear how and when the architecture (that is, complexity) of the aggregation —given by a network describing how nodes directly interact— influences the system dynamics and, in particular, the emergence of new behavior in the thermodynamic limit.

Together with my collaborators, we have shown how networks with scale-free degree distributions —common in many real systems— provide functional advantages for the emergence of new mean-field behavior in the thermodynamic limit [6]. We derived new formulas for the eigenvectors of random graphs in the thermodynamic limit, allowing us to characterize necessary conditions under which the mean-field behavior of the thermodynamic limit cannot be approximated by the dynamics of a single node. In other words, conditions characterizing when new behavior emerges. These conditions can be interpreted as ensuring that not all nodes synchronize. We found that new behavior does not emerge in most cases, such as in systems with Erdős-Renyi, small-world or lattice interconnection networks. New behavior emerges only in systems with networks with power-law degree distribution, where “islands” of nodes with different behavior survive in the thermodynamic limit.

Fundamental limitations of network reconstruction. Network reconstruction (NR) is the first step towards understanding, diagnosing and controlling complex systems in physics, engineering, biology and medicine [19]. NR aims to infer some *property* of the interaction matrix (i.e., interconnection network) of a networked system from measuring the temporal response of its nodes. Properties of interest include its sign pattern (i.e., if an interaction is an “activation” or “repression”), its adjacency pattern (i.e., if there is an interaction or not) or its degree sequence (i.e., number of incoming/outgoing interactions per node). Indeed, a key insight of network science is that fundamental properties of complex systems —from stability and epidemic thresholds to observability and controllability— can be determined from these properties without knowing the interaction matrix itself [26, 27, 25, 20]. Yet, NR remains an outstanding challenge after a decade of extensive studies [45, 43]. Existing NR algorithms do not perform significantly better than random guesses [36] and can even provide contradictory results for relatively simple systems [34]. Most of these problems originate from a simple fact: our lack of understanding of the fundamental limitations of NR, governing our ability to infer properties of the interaction matrix regardless of the NR algorithm used. Without understanding these fundamental limitations, it is impossible to decide if an NR algorithm fails due to its design limitations, or due to the limitations imposed by the available data of the system or/and our uncertainty of the system’s coupling functions that describe the interactions between nodes.

By extending the notion of *distinguishability* —originated in system identification theory— and its analysis to consider uncertain coupling functions, my collaborators and I have recently revealed these fundamental limitations of network reconstruction [12]. We first derived necessary and sufficient conditions to reconstruct any property of the interaction matrix, and then used these conditions to characterize two classes of fundamental limitations of network reconstruction. The first class implies a natural trade-off: the more information we want to reconstruct the more certain we need to be about the coupling functions between the nodes of the network. Consequently, reconstructing less information —such as adjacency pattern instead of edge weights— helps us decrease the needed knowledge of the system dynamics. The second class originates from the measured temporal data only and produce a rather counterintuitive limitation: even if we know the coupling functions exactly, reconstructing any property of the interaction matrix is as difficult as reconstructing the interaction matrix itself, requiring equally informative temporal data. To circumvent this limitation, we show that prior knowledge of the interaction matrix —such as bounds on the edge weights— can be very helpful. We also showed how revealing these fundamental limitations shed light on our ability to design better network reconstruction algorithms that offer practical improvements over existing methods.

Qualitative stability of nonlinear networked systems. Usual *quantitative* methods to determine the stability of a dynamic system —such as computing the eigenvalues of the Jacobian/linearization or finding a Lyapunov function— require detailed knowledge of the system dynamics (i.e., the structure and parameters of a model, and a measure of how far is the true system from the fitted model). Although quantitative methods have been extended to analyze large systems [31], their application has been restricted to relatively small systems only, because knowing the required details of the dynamics of large/complex systems —such as gene regulation, protein interaction or ecological systems— is currently impossible. For such large complex systems, available information is limited to an exquisite description of their organization properties in the form of a network. These networks characterize how components (nodes) interact between each other, and if such interactions are inhibitory or excitatory (i.e., the sign-pattern of the network). Since the edge weights and dynamic model associated to these networks are almost always unknown, they provide *qualitative* information of the system only.

The classical *sign-stability criterion* opened the door to study the *qualitative* stability of linear systems, requiring to know only the sign-pattern of the associated network to determine their stability [30, 23]. The impact of this criterion was profound in diverse fields including ecology [29], economy [37], and more recently control [22] and network science [8]. Due to its linearity, its application is

restricted to systems operating close to an equilibrium point. However, important phenomena in biology, physics and economy such as oscillations, chaos and so on emerge from inherently nonlinear dynamics. Small-gain conditions have been proposed to partially extend the qualitative stability conditions to nonlinear systems with particular interconnection networks [39]. Yet, a more general stability result for nonlinear systems beyond the “cascade of stable systems is stable” remains unknown.

In collaboration with Prof. Jean-Jacques Slotine from MIT, I have used contraction theory to extend the sign-stability criterion to nonlinear systems [13]. To our surprise, almost the same conditions as in the linear sign-stability criterion imply contraction in a nonlinear system. We proved that a nonlinear system is contracting provided that: (i) nodes are stable when isolated, (ii) reciprocate interactions have the same functional form but opposite signs, and (iii) the network does not contain cycles of length 3 or more. The proof of this theorem is based on two observations. First, that the network of sign-stable systems consists of “feedback chains” interconnected in cascade. A feedback chain is a recursive negative feedback interconnection with the constraint of avoiding cycles of length 3 or more. Second, feedback chains are contracting (indeed in a diagonal metric) provided that their nodes are stable when isolated. This nonlinear sign-stability theorem opens the door to study stability properties of complex nonlinear systems, such as gene regulation networks.

Controlling the human microbiome to cure diseases. We carry in our bodies a complex ecosystem of commensal microorganisms (microbiome) that plays key roles in human diseases [21]. This interplay offers an alternative way to treat difficult diseases such as the recurrent *C. difficile* infection (rCDI). *C. difficile* is an opportunistic pathogen poorly responsive to antibiotics, which causes disease in over 500 000 US citizens every year greatly increasing mortality in hospitalized patients [38]. However, a fecal microbiota transplantation (FMT) —that is, transplanting to the patient the microbial ecosystem of a healthy donor— has shown to cure over 90% of rCDI cases that previously resisted antibiotic therapy [24]. Surprisingly, we still don’t understand exactly why FMT treats rCDI so well, nor how to optimize and design new FMT therapies that are less invasive to the patient (e.g., by transplanting only a few selected microbes).

My aim is to understand and answer these questions using a combination of control and system identification tools. From a dynamic systems perspective, a cure of rCDI occurs by a transition of the patient microbiome state $x(t)$ (i.e., abundance of microbes) from its “unhealthy” equilibrium x_u —a stable equilibrium characterized by an overabundance of *C. difficile*— into the “healthy” stable equilibrium x_h present in a healthy microbiome ecosystem. The effect of FMT is to impulsively control the system trajectory $x(\cdot)$ by setting $x(t^+) = x(t) + Kx_h$ at certain intervention times $t \in \mathcal{T}$ where FMT is performed. Here K is a diagonal positive matrix of appropriate dimensions determining which of the donor’s microbes will be transplanted (e.g., $K = \text{Identity}$ corresponds to a full transplantation). The control problem is to find an intervention strategy (K, \mathcal{T}) that moves the system from x_u to x_h . In collaboration with Prof. Yang-Yu Liu at Brigham and Women’s Hospital and Harvard Medical School, we will study this impulsive control problem using the generalized Lotka-Volterra (GLV) as a model for the microbiome ecosystem. First, based on our previous results on network reconstruction, we will fit the parameters of the GLV model from real data of the Human Microbiome Project¹. Then, with the fitted GLV model, we will explore the design of optimal intervention strategies that makes both K and \mathcal{T} sparse (i.e., with the least number of transplanted microbes and the least number of FMTs). Solving this control problem has, potentially, a direct impact in treating diseases by means of controlling the human microbiome.

Finding the essential control circuits built inside complex networks. The question of how to control complex system has been addressed in terms of finding the least number of (driver) nodes that need to be manipulated in order to fully (or partially) control the system [26]. Nevertheless, in cases such as

¹<http://hmpdacc.org>

gene regulatory networks or neural networks, the control circuits (i.e., controller) needed to regulate either gene synthesis or the nervous system are already built inside these networks. Finding these control circuits in real networks will help us better understand how nature solves complex control problems, compromising performance (e.g., robustness) and efficiency (e.g., resource optimization).

To find essential control circuits, I will consider the neural wiring of the *C. elegans* nematode, one of the few organism for which a complete map of its neural wiring (302 neurons with 7,000 synapses) and function (e.g., sensor, motor, etc.) is available. With the annotated function of each neuron, the essential control circuits can be obtained by selecting input (e.g., sensor) and output (e.g., motor) neurons, and searching for the subgraph with minimum number of edges such that the outputs are controllable from the inputs.

Other forthcoming projects. Learning dynamics from data using symbolic regression. Data-driven recovery of ecological systems using robust nonlinear control.

Past research. Other research topics I have covered in the past include the optimization of uncertain systems using nonlinear Extremum-Seeking algorithms [4], observability and observer design for nonlinear uncertain systems [9, 10, 14], performance tradeoffs in the differentiation of noisy signals and the use of nonlinear/discontinuous algorithms [15, 16], design of differentiators with prescribed convergence time [11], and the use of discontinuous algorithms to circumvent structural restrictions of continuous algorithms in observation and parameter estimation problems (e.g., in induction motors [5] and diagnose of leaks in pipelines [17]).

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