

Research Statement

Marco Tulio Angulo

m.anguloballesteros@neu.edu

My research sits at the intersection of control theory, system identification, nonlinear system 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.

CURRENT RESEARCH

Network structure and functionality of complex dynamic systems. Real networks such as gene regulatory networks and the World-Wide-Web have macroscopic organization properties like heavy-tailed degree distributions and microscopic properties like network motifs. Do these organization properties provide functional advantages when dynamics are considered?

The microscopic organization of complex networks can be understood in terms of network “motifs”: small interconnection patterns that appear much more frequently in real networks than expected in random networks [1]. 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 [2–4]. 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 remains unclear. Combining recent methods to analyze stability of nonlinear systems 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 [5], see Fig. 1. 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* and Yeast bacteria and the neural network of the *C.Elegans* nematode. Our results established the functionalities of network motifs when embedded in large systems for the first time, and they were published in the special edition of *Nature Physics* commemorating its 100th anniversary.

From a macroscopic perspective, the organization properties of the network influence the average behavior that emerges from the aggregation of the node’s dynamics. Indeed, new behavior may emerge from aggregation in the *thermodynamic limit* of an infinite number of nodes. A famous and controversial example is Boltzmann’s H -theorem, where nodes with time reversible dynamics give rise to irreversible mean-field behavior in the thermodynamic limit [6]. Nevertheless, it is not clear if very coarse macroscopic properties of the aggregation —such as the degree distribution of the interconnection network of the system— are sufficient to determine the emergence of new behavior. Together with my collaborators, we combined classical tools from system theory with new results of random-graph theory in order to reveal the role of the macroscopic properties of the interconnection network in the emergence of new behavior. We shown that networks with heavy-tailed degree distributions favour the emergence of new mean-field behavior in the thermodynamic limit [7], see Fig. 2. 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 —thus providing an effective definition for “emergence” of new behavior behavior.

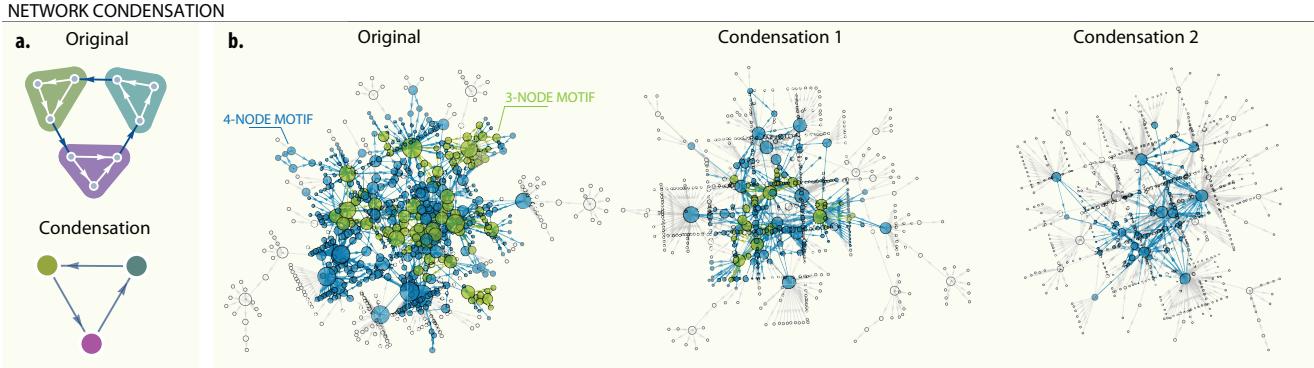


Fig. 1: **The microscopic properties of real network favour stability.** **a.** Interconnection of motifs as motifs. The original network is condensed, and stability of the condensed network ensures stability of the original network. **b.** Original and two consecutive condensations for the Yeast transcription network. Network motifs are recursively found and condensed into a single node. **c.** Number of motifs vs. relative contraction loss for the original and condensed networks. We introduced the notion of “contraction loss” in order to quantify the contribution of an interconnection network to the stability of the system (the lower the most favorable for stability).

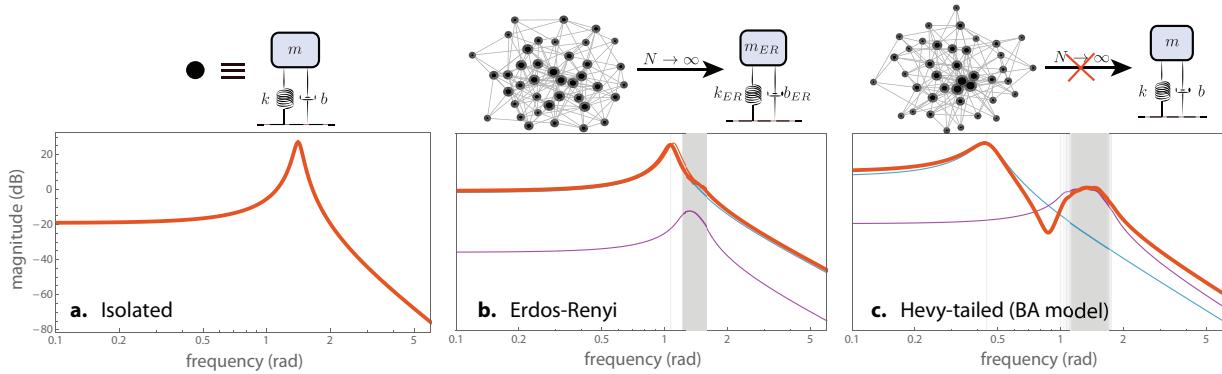


Fig. 2: **Heavy-tailed degree distributions favour the emergence of new macroscopic behavior.** We use harmonic oscillators (spring-mass-damper systems) as illustration. **a.** The frequency response of an isolated oscillator —characterizing its dynamic behavior— has a single peak corresponding to its resonant frequency. **b.** A network with homogenous degree distribution is generated using the Erdős-Renyi model for $N = 2048$ nodes (10411 edges and average degree of 10.167). Harmonic oscillators (each one corresponding to a node) are interconnected using this network architecture. The average frequency response of the system (orange line) has a single peak that can be approximated by the dynamics of a single oscillator, implying that new behavior did not emerge. This same phenomena is observed in networks generated using the (Watts-Strogatz) Small-World model, geometric graphs, etc. **c.** An heterogenous network with heavy-tailed distribution is generated using the Barabási-Albert (BA) model (10225 edges and average degree 9.985). Harmonic oscillators are interconnected with this network architecture and their average frequency response (orange line) has two resonance peaks. This shows that new behavior emerged because it cannot be approximated with the dynamics of an isolated oscillator.

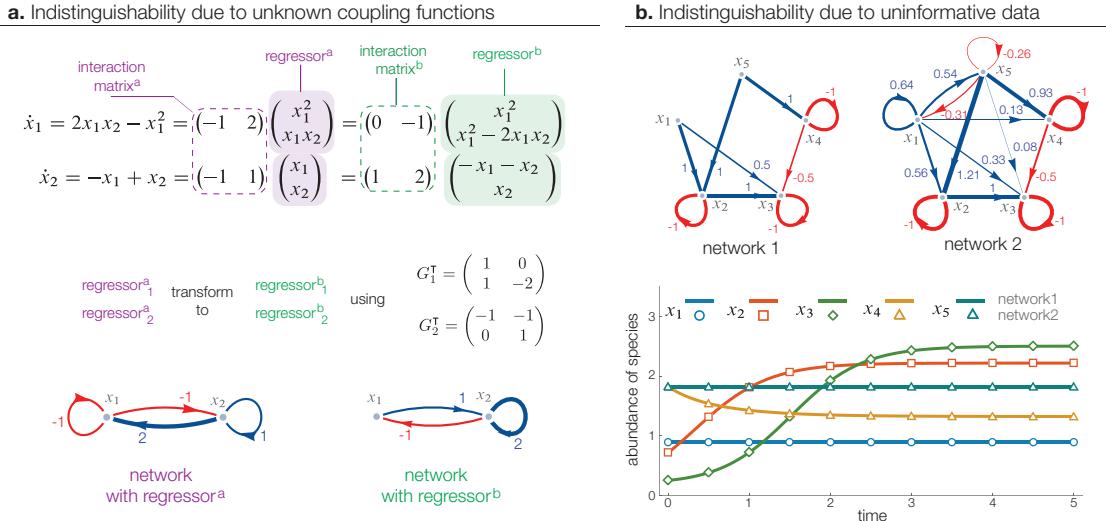


Fig. 3: Indistinguishability characterizes the fundamental limitations of network reconstruction. Two networks are indistinguishable if they produce the same node trajectories under some coupling functions of the nodes. **a.** The same dynamics can be written using two regressors with different coupling functions (purple and green), yielding indistinguishable networks that differ in their edge-weights, sign patterns, connectivity patterns and degree sequences. **b.** After fixing the coupling functions using the generalized Lotka-Volterra (GLV) model $\dot{x}_i = r_i x_i + \sum_j a_{ij} x_i x_j$, the two different networks shown in the top panel —representing two different inter-species interaction produce identical node trajectories (bottom panel). In these two examples, it is impossible to reconstruct the edge-weights, sign-pattern, connectivity-pattern or degree sequence of the network simply because we cannot decide which one of the two networks produced the measured node trajectories.

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 [8]. 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 (e.g., if the interaction between two genes in a gene regulatory system 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 [9–12]. Yet, NR remains an outstanding challenge after a decade of extensive studies [13, 14]. Existing NR algorithms do not perform significantly better than random guesses [15] and can even provide contradictory results for relatively simple systems [16]. 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 the fundamental limitations of network reconstruction [17], Fig. 3. We 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. Revealing these fundamental limitations shed light on our ability to design better network reconstruction algorithms that offer practical improvements over existing methods.

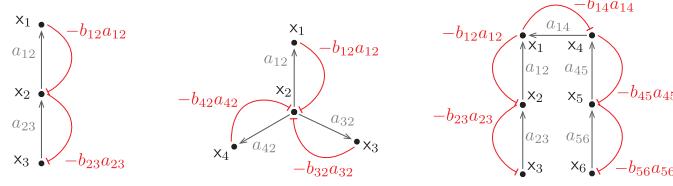
Qualitative stability of nonlinear networked systems. Usual *quantitative* methods to determine the stability of a dynamic system —such as computing the location of eigenvalues of the Jacobian/linearization or finding a Lyapunov function— require detailed knowledge of the system dynamics (i.e., the structure and parameters of a model, and a measure of how far is the true system from the fitted model). Knowing these details for large/complex systems —such as gene regulation, protein synthesis or ecological systems— is currently impossible. For such large complex systems, available information is usually limited to an exquisite description of their organization properties in the form of an interconnection network [8]. In addition, we often know if the interactions in the network are positive or negative (i.e., the sign-pattern of the network). In gene regulation, for example, nodes corresponds to genes, positive interactions to “activations” and negative interactions to “repressions”. Since the edge weights and dynamic model associated to these networks are unknown, they provide *qualitative* information of the system only.

The classical *sign-stability criterion* introduced in the 70’s 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 [18, 19]. The impact of this criterion was profound in diverse fields including ecology [20], economy [21], and more recently control [22] and network science [5]. 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 [23]. For nonlinear systems, stability is preserved under cascade (i.e., series) interconnections under quite general conditions. Small-gain conditions have also been proposed to understand the stability of nonlinear systems with particular interconnection networks [24, 25], but these conditions are not completely qualitative precisely because we need to establish the small-gain property of the node’s dynamics. Thus, a qualitative stability criterion for nonlinear systems beyond the “cascade of stable systems is stable” was lacking.

Together with my collaborator, I have used contraction theory to extend the sign-stability criterion to nonlinear systems [26], see Fig. 4. To our considerable surprise, almost the same conditions as in the linear sign-stability criterion imply stability in nonlinear systems. Indeed, we show that the conditions for sign-stability of linear and nonlinear systems are identical if the “asymmetries” of the system are constant. In other case, we show it becomes necessary that the intrinsic stability of isolated nodes is large enough. As a byproduct of this observation, we also proved that a pure qualitative criterion for the stability of nonlinear systems with time-varying asymmetries is impossible. As science and engineering face increasingly more complex systems, we expect that our nonlinear sign-stability criterion will allow to isolate modules inside complex system that are stable by the design of their internal interconnection network. This, in turn, will help us improve our understanding of the qualitative factors that determine stability in complex systems.

Other past research projects. Optimization of uncertain systems using nonlinear Extremum-Seeking algorithms [27], observability and observer design for nonlinear uncertain systems [28–30], performance tradeoffs in the differentiation of noisy signals and the use of nonlinear/discontinuous algorithms [31, 32], design of differentiators with prescribed convergence time [33], and the use of discontinuous algorithms to circumvent structural restrictions of continuous algorithms in observation

a. Examples of negative feedback chains



b. Cascade interconnection of feedback chains

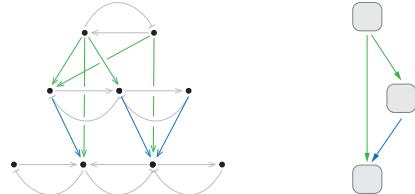


Fig. 4: **Simple qualitative conditions on the signs of the interactions allow us to prove stability of nonlinear networked systems.** An edge $x_i \rightarrow x_j$ represents a direct interaction of x_j on x_i , and its edge-weight shows the functional form of this interaction. In the networks shown in the figure, the sign of $a_{ij}(x, t)$ may change with time because it is a function of the state $x(t)$ and time t . Hence, the different edge representation for pairs of activation “ \rightarrow ” and inhibition “ \dashv ” indicates that a_{ij} and $b_{ij}a_{ij}$ have opposite signs at each time instant. All nodes have negative self-loops $a_{ii} < 0$, which are omitted when a network is displayed in order to improve readability. **a.** We proved that “negative feedback chains” are stable under qualitative conditions involving the sign of their interactions only. **b.** When the network of the system does not have cycles of length 3 or more — and reciprocate interactions have opposite signs — we also proved that the network can be decomposed as a cascade of negative feedback chains. Since the cascade of stable systems is stable under very general conditions, the stability of such systems can be determined using the sign of the interactions only.

and parameter estimation problems (e.g., in induction motors [34] and diagnose of leaks in pipelines [35]).

FUTURE RESEARCH

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 [36]. This interplay offers an alternative way to treat difficult diseases such as the *recurrent C. difficile infection* (abbreviated as 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 [37]. 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 [38]. 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 system perspective, a cure of rCDI occurs by a transition of the patient microbiome state $\mathbf{x}(t)$ (i.e., abundance of microbes) from its “unhealthy” equilibrium \mathbf{x}_u — a stable equilibrium characterized by an overabundance of *C. difficile* — into the “healthy” stable equilibrium \mathbf{x}_h present in a healthy microbiome ecosystem. The effect of FMT is to impulsively control the system trajectory $\mathbf{x}(\cdot)$ by setting $\mathbf{x}(t^+) = \mathbf{x}(t) + K\mathbf{x}_h$ at certain intervention times $t \in \mathcal{T}$ where FMT is performed. Here K is a diagonal positive matrix of appropriate dimensions determining which microbes of the donor 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 \mathbf{x}_u to \mathbf{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 [39]. 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

¹<http://hmpdacc.org>

FMTs). Solving this control problem has, potentially, a direct impact in treating diseases by means of controlling the human microbiome.

Reverse engineering dynamic systems using a finite number of different components. Reverse engineering is a key problem faced by scientist in all disciplines: inferring the constitutive components of a system from its observed behavior. In the discovery of the electron, for instance, Thomson measured how the cathode rays in vacuum tubes responded to electromagnetic fields. Then he did “reverse engineering”, showing that a charged particle with certain properties (ratio of electric charge to mass) fitted the measurements. Biologist want to do something similar, inferring the inner workings of living cells from their response to different stimuli —such as the response of the *Hog1* gene to the osmolarity of the environment [40]. Despite its fundamental importance, the limits of reverse engineering are poorly understood [13].

From a system-theoretic perspective, in the linear time-invariant case, reverse engineering is the problem of realization of a given transfer function using a state-space model. The transfer function corresponds to the available (input-output) measurements of the system, and the state-space model to the inner workings of the system we wish to infer —uncovering the “hidden” variables and how they interrelate between each other. Unfortunately, this same observation show us that solving this problem is impossible: there always exists an infinite number of state-space realizations of a transfer function, making impossible to decide which one is the “correct” one [41]. Indeed, it is a problem of distinguishability very similar to my previous results on network reconstruction. But why did Thomson succeed in discovering the electron? Thomson succeeded because he restricted the possible components that may constitute the system: he was looking to fit his data with particles.

In order to restrict the possible components that may constitute a system, I will chose resistors R , inductors L and capacitors C as components because electric circuits can describe a wide variety of system beyond engineering ones —from Maxwell and Nevier-Stokes equations, to the Schrödinger equation and the well known Hodgkin-Huxley model of neurons [42, 43]. Then the problem becomes “synthesizing” or “realizing” a passive electric circuit whose impedance matches a given transfer function. “Network realization” is a classical problem of electrical engineering that has received lots of attention recently [44, 45]. I will use these recent insights into the network realization problem together with my previous previous experience on distinguishability analysis in order to establish when, how and in which sense it is possible reverse engineer a system using electric circuit analogs. As a basic illustration, suppose we want to reverse engineer a system with transfer function $Z(s) = k/(\tau s + 1)$ for some constants $k, \tau > 0$ and $s \in \mathbb{C}$ the Laplace variable. There is a “unique” electric circuit that fits this transfer function: a resistor in parallel with a capacitor that yields $\hat{Z}(s) = R/(RCs + 1)$. This electric network is “unique” modulo some transformations, such as replacing a single resistor by many resistors in series and so on. My main goal will be to characterize these transformations because they determine if the data constraints the structure of the electric circuit enough to be useful (e.g., to know that its effective form is a parallel RC circuit, as in the example). These transformations are “invariants” that can be studied algebraic invariant theory [46]. I will supplement this theoretical analysis with numerical simulations to reverse engineer known physical laws —such as Newton’s or Maxwell’s equations— by reconstructing their electric circuit analogs [42, 43]. I will also test the theoretical results using experimental data of the frequency response of cells [40] and other organs [47, 48]. Solving the problems formulated above contains the key to build a “mathematical microscope” to explore complex systems.

Early warning signals for extinction and collapse of complex systems using the Koopman operator. Detecting early warning signals for the transition of a system from one equilibrium to another is a key problem [49]. In ecological, economic and climate systems, for example, providing early warnings for extinction or collapse is of the utmost importance [50, 51]. Despite the overwhelming

data we have collected from these systems, their complexity, diversity and our lack of knowledge of their dynamics makes difficult to predict transitions using analytical methods [49]. Currently, detecting a “critically slowing down” in the system is the most frequent method to generate early warning signals because it is model-free [49, 50, 52]. This method measures the recovery time of the system to perturbations, under the rationale that the faster it recovers the more “stable” the equilibrium is and, consequently, the farther away is the system from the tipping point of the transition. However, this method produces qualitative results only: we cannot know or quantify how far is the system from the tipping point since there is no general rule to measure how fast should the system recover under “normal” conditions.

In order to address the problems above, I propose to use the spectral properties of the Koopman operator associated to the system. The Koopman operator is a linear and infinite-dimensional operator —even if the system is finite-dimensional and nonlinear— that describes the evolution of observables in dynamic systems [53]. Due to its linearity, the spectral properties of the Koopman operator (i.e., eigenvalues and eigenfunctions) can be used to fully characterize the stability properties of nonlinear systems [54]. A Koopman eigenvalue with positive real part, for example, corresponds to an “unstable” growing mode of a nonlinear system, in analogy to how positive eigenvalues corresponds to instability in linear systems. In addition, it is possible to estimate the spectral properties of the Koopman operator from data only without requiring any model of the system [55].

I will use these very recent ideas and advances based on the Koopman operator to provide a quantitative and data-driven early warning signal for the transition of complex systems. As a basic illustration, suppose we have data of the system over a time interval $[0, t_f]$. Lets divide this data into N time windows $[t_k, t_f]$, $t_k \in \mathbb{R}$, and approximate the Koopman eigenvalues over each time window. Then the eigenvalue with largest real part over the k -th window λ_k^{\max} corresponds to the most unstable mode over that time interval. Consequently, the condition $\text{Re}\lambda_{k+1}^{\max} > \text{Re}\lambda_k^{\max}$ implies a decrease of stability indicating that the system moves towards a tipping point, and $\text{Re}\lambda_k^{\max} > 0$ if the system has crossed the tipping point. From this observation, it follows that $|\text{Re}\lambda_k^{\max}|$ can be used to quantify how far is the system from the tipping point. I will systematically compare the performance of the Koopman-based early warning signals with those obtained using the critically slowing down method. For this, I will consider synthetic data generated from mutualistic ecological systems because we know necessary and sufficient conditions for their stability [50]. I will also apply this analysis to real data from ecological collapse and climate change [56, 57].

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 we need in order to fully or partially control a system [9, 58]. Nevertheless, in cases such as gene regulatory networks and 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 these 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.

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