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Defining excitability via transition path theory

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The functions of many biological systems — including spiking neurons and activating macrophages— depend on excitable dynamics: a small perturbation triggers a rapid, nonlinear ramp followed by a return to equilibrium. **While this behavior is common biologically, excitability lacks a precise mathematical definition, and the generic properties of these systems remain unclear.** We are taking a two-pronged approach to define and classify excitable systems. First, we are extending transition path theory (TPT) to excitable systems and using it to define excitability precisely. Second, we are combining TPT with machine learning to map dynamical behavior over a broad class of models to enumerate the types of excitability. In the longer term, we are applying this new mathematics to study 'flares' in immune response.

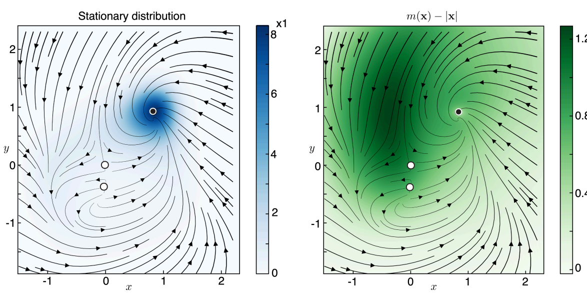

Figure 1: Transition path theory for excitability. Stationary distribution (left) and 'gain' (right) for a two-dimensional system of stochastic differential equations (SDEs) with polynomial terms up to cubic order.

Transition path theory (TPT) is a mathematical theory that was developed to compute the statistics of the ensemble of trajectories that connect two metastable states (e.g., reactant and product states of a molecular process). The core idea of transition path theory is that it defines these statistics in terms of quantities that are local in space, via a Markov assumption. Dinner and his group recently extended TPT to treat augmented processes that can account for history. This opens the door to considering other dynamical behaviors such as limit cycles and excitability.

Qualitatively, we consider a system excitable if a trajectory, x(t), that starts near a stable fixed point x_0 moves away from it before returning to the fixed point. We formalize this idea by computing the expected maximum distance, m, that x(t) moves away from x_0. As is, m cannot be computed from local quantities. **Our innovation is to augment** x(t) with y(t), the maximum distance that was reached by the trajectory up to the present time t. The augmented process (x(t), y(t)) is a Markov process under which m can be computed through local quantities using methods related to those used to solve the Hamilton-Jacobi-Bellman equation in optimal control.

As a demonstration, we apply the theory to a globally stable planar system of stochastic differential equations (SDEs) with polynomial terms up to cubic order in Figure 1. In the left panel, we plot the stationary distribution. In the right panel, we plot the 'gain,' that is, for trajectories starting at an initial point x, how much further the trajectory is expected to move away before returning to x_0. This identifies a 'launch pad' with high gain to the left of the stable fixed point. These tools enable defining precisely our intuitive notion of excitability. We are applying them to large ensembles of such systems to characterize the types of excitability.