Mapping of deterministic versus stochastic network activity by feedback splitting

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***Short Abstract* — The functioning of cellular regulatory networks is jointly governed by deterministic nonlinear system dynamics and stochastic fluctuations. They can counteract or amplify each other, and their effects are often difficult to separate, particularly, in the context of feedback regulation. We developed an approach to separate these contributions at molecular level. The parameter space of deterministic bistability was mapped and the nonlinearity due to protein homo-dimerization that supports cellular memory was captured. Furthermore, we showed that with additional noise and deterministic transients characterized, the stochastic activity, the transition rates between the two states of the bimodal expression, can be well predicted.**

***Keywords* — Bistability, bimodality, cellular memory, positive feedback, stochastic transition, protein homodimerization, transcriptional regulation.**

NONLINEARITIES are essential to generate complex cellular behavior, such as bistability, pattern formation or oscillations. Modeling and control of nonlinear systems with the help of classical deterministic kinetics is valid when noise is absent. However, stochastic effects arise in cells due to the small number of molecules in single cells and due to the fluctuations in environmental stimuli and pathway components [1]. They can drive the system away from that predicted by classical kinetics [2].

When nonlinearities are incorporated into positive feedback loops the resulting autocatalytic circuit can maintain two stable activity states under identical conditions [3], a phenomenon termed bistability. Bistability can uphold alternative cellular differentiation states and store cellular memory of past stimuli. Noise induces transitions between the two states of the bistable system so that both states (phenotypes) are present in a cell population, termed bimodality, which is commonly considered to be a hallmark of bistability. However, noise can have deviant effects in the context of positive feedback loops. For instance, bimodality can arise in the absence of nonlinearities and even without feedback loops [4-5], which makes the distinction of deterministic and stochastic effects difficult. Since deterministic nonlinearities and stochastic fluctuations have different origins it is important to disentangle their effects to analyze and control network functioning.

Focusing on positive feedback circuits, we combined three concepts to devise a strategy to distinguish stochastic and deterministic effects. Firstly, opening of positive feedback loops reduces nonlinearity and consequently the deviant effects caused by noise, which permits a deterministic characterization. Secondly, a general mathematical theory states that opening of feedback loops yields input/output relations that map uniquely steady-state values of feedback expression states in a large class of systems [6]. Thirdly, the polymeric nature of biomolecules permits the creation of input/output pairs that are metrically equivalent, a strategy we termed feedback splitting. When these conditions are satisfied, deterministic mono- and bistability can be mapped.

We created well-defined synthetic positive feedback loops that incorporate protein dimerization and/or cooperative binding in yeast cells. With feedback splitting, we confirm that homodimerization can support robust cell memory. With the help of equivalence relations, the nonlinear responses obtained by feedback splitting delimit areas of true steady-state bistability from bimodality. Two distinct factors affecting stochastic transition between states were also identified: transient kinetics which predominately affect the transition in the parameter space outside of the bistable region and a fitted noise which determines the rates within. We showed that the kinetics of a feedback system over a two-dimensional parameter space can be well predicted with the model derived from feedback splitting.

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