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A Robust Fuzzy-logic-based Analysis of the Stochastic Dynamics of a Genetic Toggle Switch in the Presence of Uncertainty

University of Neyshabur

Alireza Rowhanimanesh

Assistant Professor of Control Engineering, University of Neyshabur, Neyshabur, Iran.

rowhanimanesh@neyshabur.ac.ir

Objective and background

One of the most practical biological circuits is a genetic toggle switch that can be implemented inside a biological cell using biotechnology (Gardner et al. 2000). Such a biological circuit is able to perform logical functions at molecular level. Consequently, it can be severely used in gene regulation and cell fate control (Loinger et al. 2009). The dynamics of a genetic toggle switch is nonlinear (Jing et al. 2005), stochastic (Ribeiro et al. 2006), and very sensitive to the uncertainty and external noise. Hence, analysis and control of this dynamical system is complex (Fiore et al. 2018). One of the most important problems is the accurate and robust identification of the attractors (Strasser et al. 2012). The central question is how the attractors of a genetic toggle switch can be accurately and robustly identified from gene expression time series in the presence of uncertainty and external noise. This paper addresses this issue by fuzzy logic.

Keywords: Genetic Toggle Switch, Fuzzy Logic, Nonlinear Systems, Attractor, Stochastic Differential Equations.

Methodology

The nonlinear dynamics of a genetic toggle switch was modeled by four benchmark mathematical models, including: a) Ordinary differential equations, b) Stochastic differential equations, c) Ordinary differential equations with uncertain parameters, d) Stochastic differential equations with uncertain parameters. The robustness of these dynamical models was investigated in the presence of uncertainty and external noise through computer simulation. A fuzzy-logic-based procedure was designed to convert the gene expression time series to fuzzy signals. These fuzzy signals could efficiently handle the uncertainty available in gene expression profiling. Using the notion of fuzzy granulation, the state space of the phase plane analysis method was fuzzified into a number of fuzzy granules. A fuzzy scheme was developed to analyze the fuzzy signals and accordingly identify the attractors of the dynamical system in terms of fuzzy granules. Also, a confidence metric was defined to determine the robustness of the identified fuzzy attractors.

Results

The results revealed that the most robust model among the benchmark dynamical models was stochastic differential equations with uncertain parameters. Bifurcations and multi-stability were observed in the nonlinear dynamics of a genetic toggle switch. The Waddington landscape of the system was quantified, and the attractors and the trajectories of the dynamical system were precisely computed for different rates of uncertainty and external noise.

Computer simulation demonstrated that uncertainty and external noise, particularly in the higher rates, could drastically alter the number, type, and the position of the attractors as well as the trajectories of the dynamical system. To evaluate the efficiency of the proposed approach, several distinguishing experiments were designed. One of them is shown in Figure 1. This figure illustrates three independent random tests, in which, the rate of uncertainty and external noise was set to 1%, 5%, and 15%, respectively. In each test, the number of expression time series is 20 for each gene. The proposed approach independently analyzed the expression time series of each test and identified the fuzzy granules that pass the confidence threshold as the attractors of the system. As expected, in all tests, granules 3 and 11 were identified as the attractors.

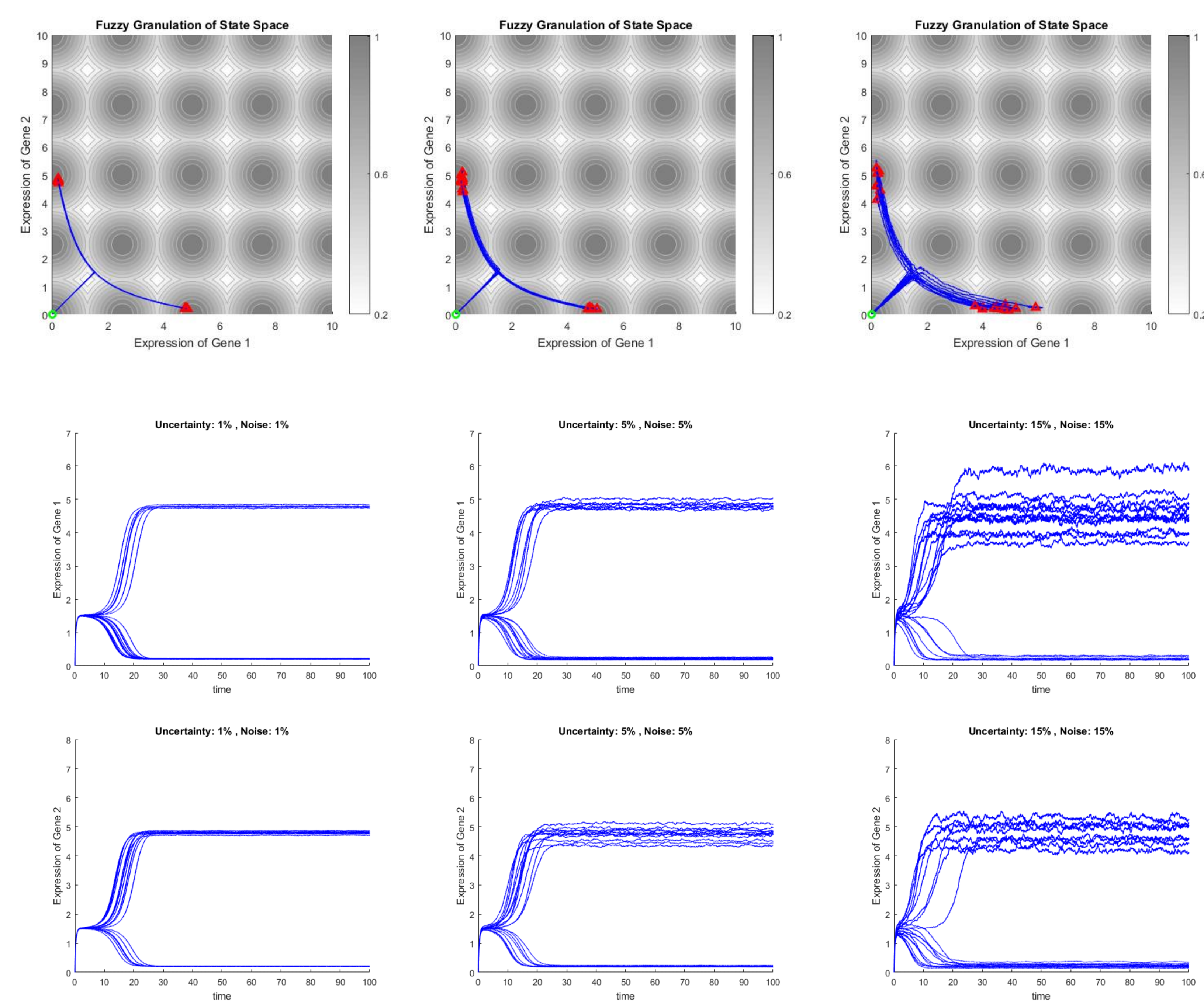

Figure 1. The fuzzy attractors identified by the proposed approach are robust against different rates of uncertainty and external noise.

Conclusions

Computer simulation showed that the proposed approach could accurately and robustly identify the fuzzy attractors of the genetic toggle switch in the presence of uncertainty and external noise. In addition to the position of attractors, the region and the potential of attraction can be calculated.

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