Integral feedback in synthetic biology: Negative-equilibrium catastrophe [1]

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Summary. A central goal of synthetic biology is the design of molecular controllers that can manipulate the dynamics of intracellular networks in a stable and accurate manner. To address the fact that detailed knowledge about intracellular networks is unavailable, integral-feedback controllers (IFCs) have been put forward for controlling molecular abundances. These controllers can maintain accuracy in spite of the uncertainties in the controlled networks. However, this desirable feature is achieved only if stability is also maintained. In this paper, we show that molecular IFCs can suffer from a hazardous instability called *negative-equilibrium catastrophe* (NEC), whereby all nonnegative equilibria vanish under the action of the controllers, and some of the molecular abundances blow up. We show that NECs place a fundamental limit to design and control of molecular networks.

Extended Abstract

A main objective in synthetic biology is to control living cells [1, 2]. This challenging problem requires addressing a number of complicating factors displayed by intracellular networks:

(N) **Nonlinearity**. Intracellular networks are *bimolecular* (nonlinear), i.e. they include reactions involving two reacting molecules.

(HD) **Higher-dimensionality**. Intracellular networks are *higher-dimensional*, i.e. they contain larger number of coupled molecular species.

(U) **Uncertainty**. The experimental information about the structure, rate coefficients and initial conditions of intracellular networks is *uncertain* (noisy).

To mitigate challenge (U), molecular *integral-feedback controllers* (IFCs) have been put forward, which can maintain accurate control of molecular abundances in spite of some of the uncertainties in the controlled networks [3, 4]. However, this desirable feature is achieved only if stability is also maintained - an important problem which has been predominantly studied when unimolecular and/or lower-dimensional networks are controlled [4, 5, 6, 7]; in contrast, intracellular networks are generally bimolecular and higher-dimensional (challenges (N) and (HD) stated above). To bridge the gap, in this paper we focus on the question of fundamental importance to intracellular control: How do molecular IFCs perform when applied to biochemical networks which are bimolecular, higher-dimensional and uncertain?
We show that at the center of this question are equilibria - stationary solutions of the reaction-rate equations that govern the deterministic dynamics of biochemical networks. In particular, molecular concentrations can reach only equilibria that are nonnegative. In this context, we show that molecular IFCs can destroy all nonnegative equilibria of the controlled system and lead to a control failure; furthermore, this failure can be catastrophic, as some of the molecular abundances can then experience an unbounded increase with time (blow-up) at both deterministic and stochastic (chemical master equation) levels. We call this hazardous phenomenon, involving absence of nonnegative equilibria and blow-up of some of the underlying species abundances, a *negative-equilibrium catastrophe* (NEC), which we outline in Figure 1. In context of electro-mehanical systems, analogous phenomenon is known as integrator windup. We show that unimolecular IFCs do not exist due to a NEC. We then derive a family of bimolecular IFCs that are safeguarded against NECs when uncertain unimolecular networks, with any number of molecular species, are controlled. However, when IFCs are applied on uncertain bimolecular (and hence most intracellular) networks, we show that the problem of preventing NECs generally suffers from the *curse of dimensionality* - the problem becomes intractable as the number of interacting molecular species increases. NECs therefore have broad implications for design and control of molecular networks at both deterministic and stochastic levels.

References

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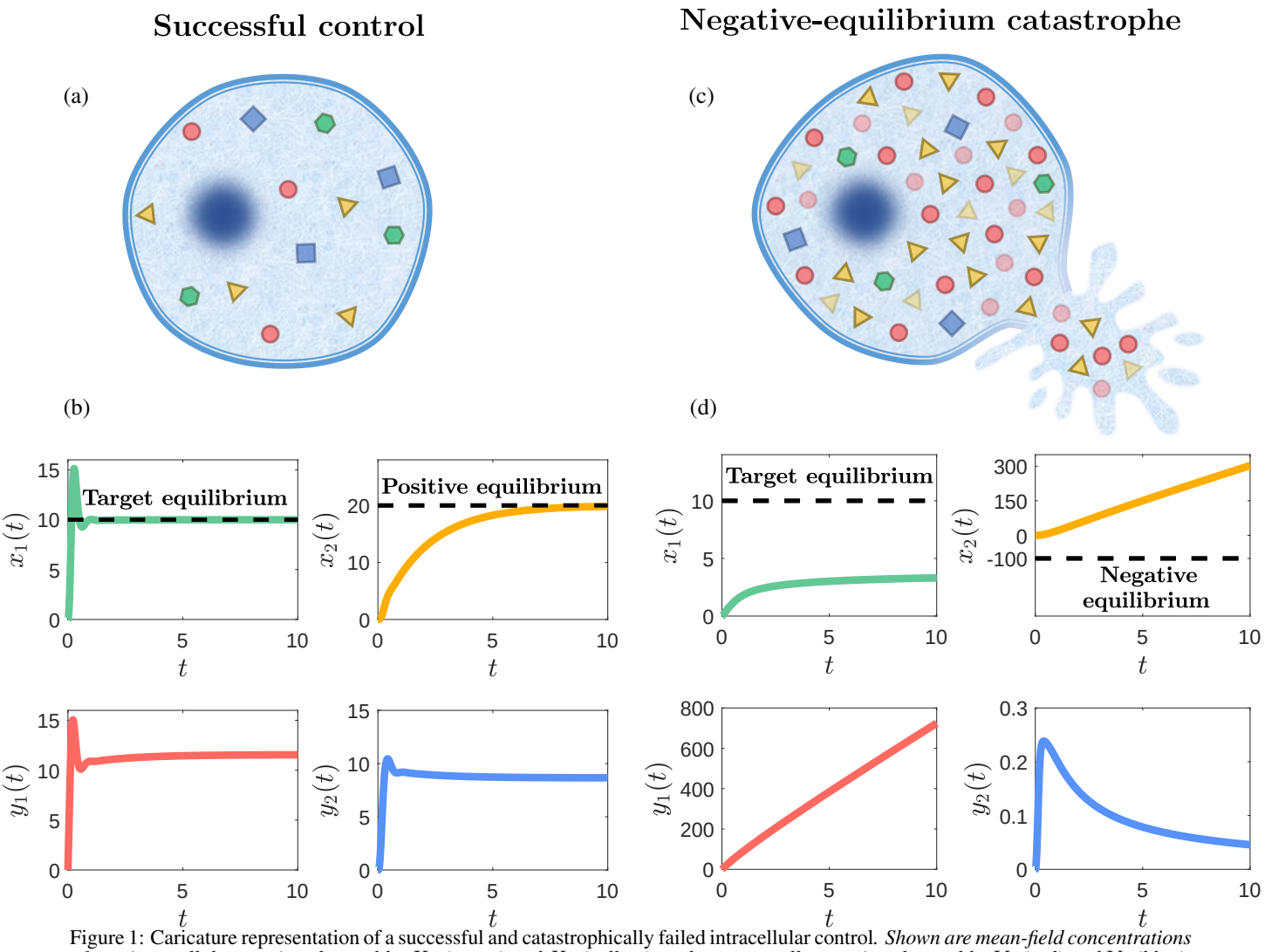

Figure 1: Caricature representation of a successful and catastrophically failed intracellular control. *Shown are mean-field concentrations of two intracellular species, denoted by X_1 (green) and X_2 (yellow), and two controller species, denoted by Y_1 (red) and Y_2 (blue); the goal is to steer the equilibrium of X_1 to a desired set-point.*
Panels (a)–(b) *display a cell successfully controlled with a molecular* IFC. *In particular, panel* (b) *shows that the species X_1 approaches a desired equilibrium, shown as a black dashed line, while the equilibria for the remaining species X_2, Y_1 and Y_2 are positive.*
Panels (c)–(d) *display a cell that has taken lethal damage due to a failure of the* IFC. *In particular, as shown in panel* (d), *the target equilibrium for X_1 enforces a negative equilibrium for the species X_2. However, since molecular concentrations are nonnegative, this equilibrium cannot be reached and, therefore, control fails. Furthermore, the failure is catastrophic, as concentrations of some of the underlying species (in this example, species X_2 and Y_1) blow up, placing a lethal burden on the cell. Analogous phenomenon occurs at the stochastic level.*