Network-level dynamics of diffusively coupled cells

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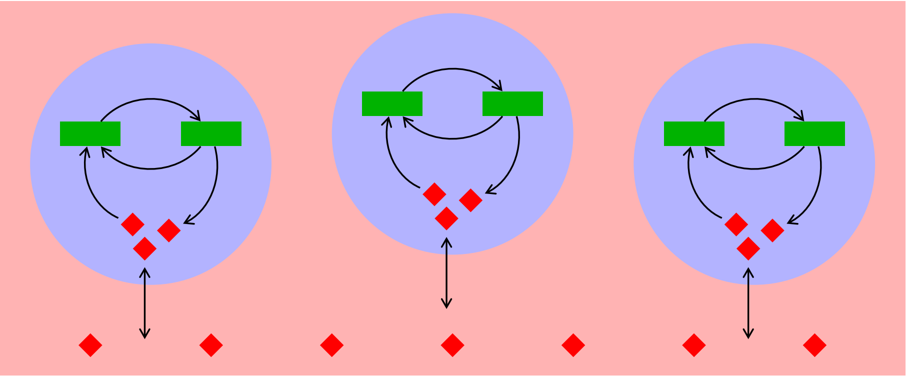
Biological mechanisms of cellular coupling

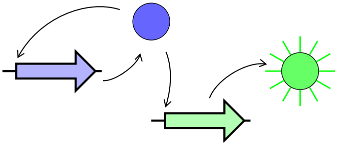
- Intracellular dynamics of communication molecules (autoinducers)
- Exchange of autoinducers via a joint chemical medium

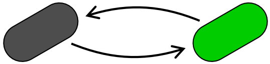
Illustration of the autoinducer mechanism



From bistability in single cells to population bistability?

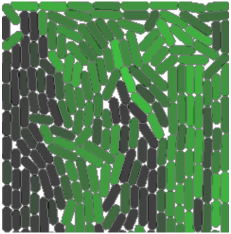
Bistable genetic switches in a single cell



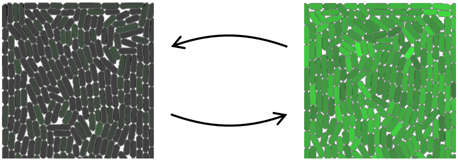


Switching triggered by extrinsic perturbations

Desynchronized population



Synchronized switching in populations?



Outline

1. Modeling formalism
2. Synchronized bistability in cell populations
3. Example: an autoregulatory gene switch

Outline

Preliminaries for the modeling

Simplifying assumptions

1. Homogeneous intracellular dynamics.
2. All cells have equal volume.
3. The volume of the extracellular medium is proportional to the number of cells.
4. All molecular species are exchanged by diffusion.

Assumptions 1–3 can be relaxed to come to the same conclusion, but lead to a more complicated model.

Definitions

$\xi^{(0)} \in \mathbb{R}^n$ – molecular concentrations in the medium

$\xi^{(i)} \in \mathbb{R}^n$ – molecular concentrations in the i-th cell

N – number of cells

V_c – volume of a cell

Modeling a coupled cell population

Dynamics in extracellular medium:

$$\dot{\xi}^{(0)} = -k_d \xi^{(0)} + \sum_{j=1}^{N} \frac{k_c}{N V_c} (\xi^{(j)} - \xi^{(0)})$$

Intracellular dynamics:

$$\dot{\xi}^{(i)} = F(\xi^{(i)}) - \frac{k_c}{V_c} (\xi^{(i)} - \xi^{(0)}), \quad i = 1, \ldots, N.$$

Terms

$F(\xi^{(i)})$ – intracellular dynamics

$k_d \xi^{(0)}$ – extracellular decay / dilution

$\frac{k_c}{V_c}(\xi^{(i)} - \xi^{(0)})$ – diffusive exchange rate

Transformation to the singular perturbation form

Determination of a small parameter

- **Assumption** of fast diffusive exchange: large value for k_c
- Small parameter $k_c^{-1} = \varepsilon$

Key step: Separation into slow and fast variables

- Candidate slow variable: *Averaged concentration*

$$x = \xi^{(0)} + \frac{1}{N}\sum_{j=1}^{N}\xi^{(j)}$$

Dynamics of the transformed system

$$\dot{x} = -k_d\left(x - \frac{1}{N}\sum_{j=1}^{N} z^{(j)}\right) + \frac{1}{N}\sum_{j=1}^{N} F(z^{(j)})$$

$$k_c^{-1}\dot{z}^{(i)} = k_c^{-1}F(z^{(i)}) - \frac{1}{V_c}\left(z^{(i)} - x + \frac{1}{N}\sum_{j=1}^{N} z^{(j)}\right),$$

Outline

Singular perturbation: The quasi-steady state

Dynamics of the fast variables

$$\varepsilon \dot{z}^{(i)} = \varepsilon F(z^{(i)}) - \frac{1}{V_c}\left(z^{(i)} - x + \frac{1}{N}\sum_{j=1}^{N} z^{(j)}\right),$$

For the quasi-steady state, we need to solve the equations

$$z^{(i)} - x + \frac{1}{N}\sum_{j=1}^{N} z^{(j)} = 0, \qquad i = 1, \ldots, N.$$

Unique quasi-steady state solution

$$z^{(i)} = \frac{x}{2}$$

Lemma

The matrix $E_N = \frac{1}{N}\underline{\mathbf{1}} + I \in \mathbb{R}^{N \times N}$, where $\underline{\mathbf{1}}$ is a $N \times N$ matrix of all ones, has one eigenvalue at 2 and $N - 1$ eigenvalues at 1.

Singular perturbation: Fast and slow dynamics

Fast dynamics: the boundary layer model

$$\frac{dy^{(i)}}{d\tau} = -\frac{1}{V_c}(y^{(i)} + \frac{1}{N}\sum_{j=1}^{N} y^{(j)})$$

Key conclusion

The fast dynamics exponentially approach the quasi-steady state.

Slow dynamics: the long timescale approximation

$$\dot{x} = F(\frac{x}{2}) - k_d\frac{x}{2}$$

Singular perturbation result

The population dynamics of order Nn are well approximated by the slow dynamics of order n in a time range $\mathcal{O}(\varepsilon) \leq t \leq \mathcal{O}(1)$.

Synchronized bistability

$$\dot{x} = F(\frac{x}{2}) - k_d \frac{x}{2}.$$

Main result

Multistability of the slow dynamics implies synchronized multistability of the cell population.

Proposition: If

1. F is globally Lipschitz,
2. a Lyapunov condition is satisfied around an equilibrium of the slow dynamics,
3. the slow variable x_0 starts in the corresponding neighbourhood of the equilibrium,

then all cells in the population converge to an ε-neighborhood of this equilibrium.

Conditions 1–2 are satisfied for typical multistable intracellular networks.

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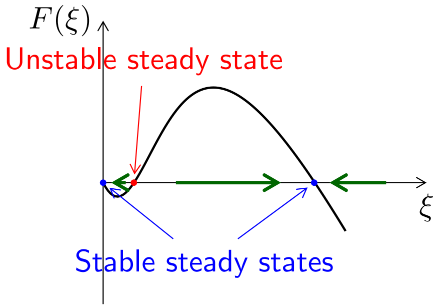
Intracellular dynamics of an autoregulatory switch

Bistable model with one intracellular component

$$\dot{\xi} = F(\xi) = \frac{3\xi^2}{1+\xi^2} - \xi$$

Illustration of steady state behavior

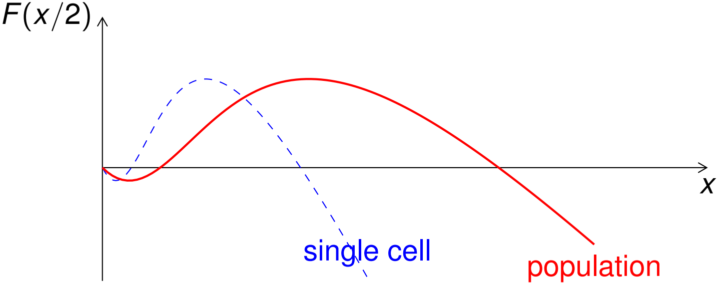


Dynamics of coupled switches

Slow dynamics: $\xi^{(i)} = x/2$

$$\dot{x} = F(\frac{x}{2}) = \frac{3x^2}{4 + x^2} - \frac{x}{2}$$

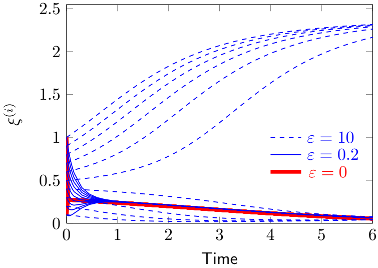
Population-level steady state behavior



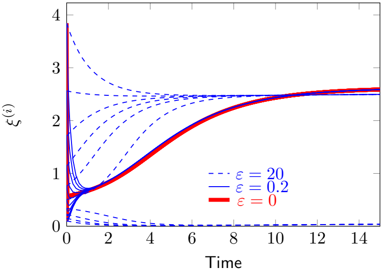
Bistable with same steady states $\xi_s^{(i)} = \frac{x_s}{2}$ as in the single cell.

Coupled switches: simulation results

Convergence to the **“off”** state



Convergence to the **“on”** state



- Decoupled switches for large ε
- Synchronized switches for small ε

Discussion of biological implications

Occurence of multistable cellular switches

- Differentiation decisions in multicellular organisms
- Generating start signals for cellular programs (cell death, cell cycle, ...)
- Phenotype variations in bacterial populations

Biological relevance of synchronized switching

- Advantages of stochastic heterogeneity within a population.
- Tissue differentiation requires coordinated switching of many cells.
- Increased robustness of tissue differentiation by synchronized switching?
- Engineering a population of synchronously switching cells.

Conclusions

Synchronized bistability in coupled cells under fast diffusive coupling.

- Biophysical model for a cellular network with diffusive coupling.

$$\dot{\xi}^{(0)} = -k_d \xi^{(0)} + \sum_{j=1}^{N} \frac{k_c}{NV_c}(\xi^{(j)} - \xi^{(0)})$$

$$\dot{\xi}^{(i)} = F(\xi^{(i)}) - \frac{k_c}{V_c}(\xi^{(i)} - \xi^{(0)}), \quad i = 1, \ldots, N.$$

- Used a singular perturbation approach to establish sufficient conditions for synchronized switching.

$$\dot{x} = F(\frac{x}{2}) - k_d \frac{x}{2}$$

- Biological implications in tissue differentiation and synthetic biology.