The Role of Dynamic Stimulation Pattern in the Analysis of Bistable Intracellular Networks


Bistable intracellular networks play an important role in the functioning of living cells. Besides the well-established steady-state properties, some important characteristics of bistable systems arise from their dynamics. We demonstrate that:

- A supercritical stimulus amplitude is not sufficient to move the system from the lower to the higher branch for either a step or a pulse input.
- A switching surface can be identified for the system as a function of the initial condition, input pulse amplitude and duration (a supercritical signal).
- A minimal signal power is necessary to change the steady state of a bistable system.
- We investigate and characterize the role of the duration of the stimulus.

These results are relevant for the design of experiments, where it is often difficult to create a defined pattern for the stimulus.

Model System

- Mutually-activated system [1]
- Linear system coupled with a sigmoidal system through a positive feedback loop.
- Mathematical representation

\[
\frac{dx}{dt} = k_1 x + k_2 y - k_3 y \quad \text{and} \quad \frac{dy}{dt} = k_3 y - k_4 z
\]

- Response function of the external stimulus

\[
S(x) = \frac{k_5 x}{k_6 + x}
\]

- Critical signal duration

\[
\Delta t_{crit} = \frac{k_7}{k_8 k_9}
\]

- Positive feedback loop regulates the production rate of R in an autocatalytic manner.

Steady-State Properties

- Steady state with step input:
  - Determined by the balance equation
  - Balance equation
  - Two stable branches, \( a_k \) (upper) and \( b_k \) (lower), are separated by an unstable one, \( c_k \).

- Unstable and unphysical states define a forbidden region, Fig. 2.

- Depending on the feedback strength, the network can be bistable in a reversible or irreversible manner [1] or monostable.

Dynamic Behaviour

- Transient dynamics of the irreversible bistable network for different initial states \( R_i \) and different supercritical stimulus pulses of different durations \( \Delta t \).
- Superconstant stimulus constant switches the system to the upper stable branch.
- Unstable branches are separated for supercritical signals.
- Upper branch is approached for \( R_i \) otherwise the lower branch, Fig. 5.

Critical Signal Duration

- The original system of differential equations cannot be solved analytically due to the high nonlinear characteristics of the Goldbeter-Koshland function [1].
- Taylor expansion to approximate the enzyme concentration \( R_i \) [4]

\[
R_i(\Delta t) = C_1 R_i + C_2 R_i^2 + C_3 R_i^3
\]

- Linear approximation with respect to the minimal signal component \( R_i \).
- Positive feedback decreases the degradation of \( R_i \).
- Linear differential equation

\[
\frac{dR_i}{dt} = \frac{k_{10}}{k_{11}} \left( R_i - C_1 R_i - C_2 R_i^2 - C_3 R_i^3 \right)
\]

- Analytical solution can be transformed with respect to critical signal duration [4].
- Decreased degradation rate constant \( k_{11} \) and displacements between initial state \( R_i \) and stable steady state \( R_s \) and unstable state \( R_u \), respectively, determine the critical duration.

\[
\Delta t_{crit} = \frac{1}{k_{11}} \left( R_s - R_u \right)
\]

- Good agreement for high stimuli, Fig. 8.
- Deviations for small supercritical stimuli because of neglect of higher feedback terms in the approximation.
- Asymptote for strong stimuli \( R_i \rightarrow R_s / k_{11} \).

Critical Signal Power

- Signal power (dose) sums over the whole applied external stimulus

\[
F(\Delta t) = 0 \quad \text{for} \quad \Delta t \leq \Delta t_{crit}
\]

- \( F(\Delta t) \) measures the dosage which is required to switch the system from a lower to a upper stable state applying a constant time stimulus \( \Delta t \).

Switching Surface

- Signal amplitude, signal duration, and initial state can be combined in a three-dimensional plot, Fig. 7.
- Switching surface separates the parameter combinations which switch the bistable intracellular network to the upper stable branch and which not.
- Different characteristic behaviour are identified.

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