Reconciling a Biochemical Switch Catalog with Network Theories of Bistability

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Abstract

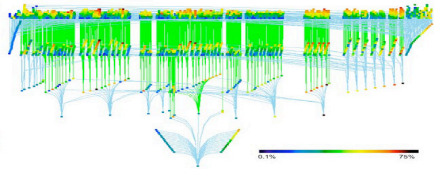
What characteristics of biochemical circuits endow them with potential for bistability?

In this work we conduct an exhaustive comparison of classical network theories, i.e. Feinberg's deficiency theorems and Craciun-Feinberg Species-Reaction (S-R) graphs, and catalog-based approaches, e.g., the CSPACE bistable catalog published by Ramakrishnan and Bhalla. We try to determine how well these approaches agree and, when they do not agree, what are the situational assumptions that lead to discordance. By studying these discordances, we highlight the diverse assumptions under which a circuit can be modeled and which would affect its stability characterization.

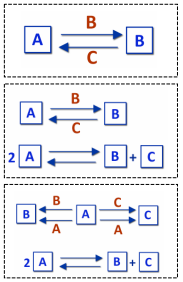
Background

CSPACE

- Generate candidate systems from biologically relevant reactions using mass action kinetics
- Eliminate stoichiometric inconsistencies and redundancies
- Generate >100 parameters for each topology
- Find stationary points by homotopy tracking
- Calculate eigenvalues, classify stationary points
- Published master set of bistables at http://docss.ncbs.res.in/
- "Banyan tree" diagram showing the relationship between CSPACE catalog of bistables

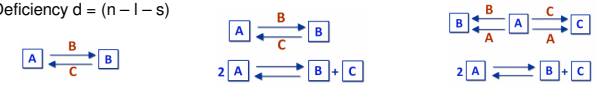


CSPACE examples



Deficiency theorems

- For every system which obeys mass action kinetics, calculate number of complexes (n), number of linkage classes or interconnected subnetworks (l), and rank (s) of stoichiometric matrix.
- Deficiency d = (n – l – s)



d = 6 – 2- 3 = 1 d = 7 - 2 – 4 = 1 d = 10 – 1 – 6 = 5

- If d = 0 , system cannot admit more than one *positive* steady state (i.e., no multistationarity)
- If d >= 1, l > = 2, system is "*regular*", and each linkage class has d = 0, then the system has the potential to admit multiple *positive* steady states
- Deficiency theorems are available as a DOS program as Chemical Reaction Network Toolbox (CRNT)

S-R Graph

- Model networks as bipartite graphs of systems where nodes are species and reactions and edges are labeled with complexes which connect species and reactions. A complex pair in the S-R graph is a pair of edges with the same complex label adjacent to the same reaction node

Comparison

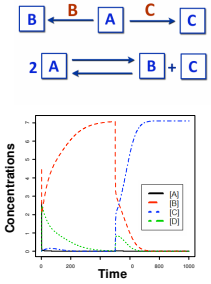
Total CSPACE bistable networks: 3562, Total CSPACE "silent" networks: 35967

	CRNT: no potential for multi-stationarity	CRNT: potential for multi-stationarity	CRNT: inconclusive	CRNT: aborted	S-R graph: no potential for multi-stationarity	S-R graph: does not negate potential for multi-stationarity
CSPACE bistable	82	2797	683	--	1	3561
CSPACE silent	20044	5429	9861	633	729	35238

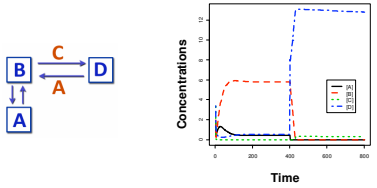
Discussion

Discrepancy between CSPACE and CRNT/S-R-graph theorems

- There are bistable networks for which CRNT or S-R graph report that the network cannot have multiple positive stationary states
  - **Reason for discrepancy**: CSPACE analysis includes principal axes; CRNT considers only the positive space
  - The figure on the right is a bistable system for which CRNT concludes that it cannot have multiple stationary points

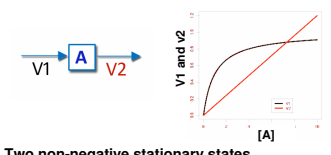


- Shown below is a bistable system where S-R graph precludes multistationarity. S-R Graph considers only positive space, whereas CSPACE includes principal axes



Factors affecting bistability analysis

Multistationarity versus multistability

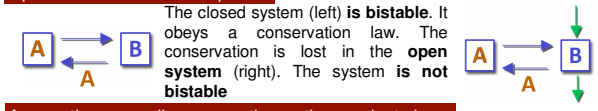


Two non-negative stationary states *(multistationary)* but **only one stable state *(monostable)***

Three non-negative stationary states *(multi-stationary)*, but **only one *positive stable* state**

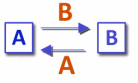
Multistationarity may not imply multistability

Open versus closed Assumptions



The closed system (left) **is bistable**. It obeys a conservation law. The conservation is lost in the **open system** (right). The system **is not bistable**

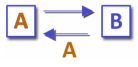
Assumptions regarding enzymatic reactions and rate laws



The system (left) is bistable for a large set of parameters if **Michaelis-Menten** kinetics is used, assuming steady state of enzyme complexes. But it **will not be bistable** if **mass-action** kinetics is used, because then steady state assumption for enzyme complexes is not valid

Zeroness: positive plane versus inclusion of principal axes

Zeroness = number of species' concentrations that are zero at steady state



The system to the left has two stable states where one of the two species' concentrations always reaches **zero**

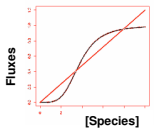


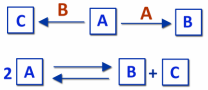
Figure (left) shows a system with **two non-negative stable states** - **only one stable state is positive.** The other is on the principal axis

Number of stable states identified can change depending on whether or not principal axes are included in the analysis

References

- Craciun, G & Feinberg, M. (2005) SIAM Journal on Applied Mathematics 65, 1526-1546.
- Craciun, G & Feinberg, M. (2006) SIAM Journal on Applied Mathematics 66, 1321-1338
- Craciun, G. & Feinberg, M. (2006) IEE Proceedings Systems Biology 153, 179-186
- Feinberg, M. (1987) Chem. Eng. Sci 42, 2229-2268.
- Feinberg, M. (1988) Chemical Engineering Science 43, 1-25.
- Ramakrishnan, N & Bhalla, U. (2008) PLoS Computational Biology 4.

- Calculate all cycles in the S-R graph
- If each cycle has odd number of complex pairs



and no complex pair is split by two cycles of an even complex pair, S-R graph theorem states that the corresponding system

cannot admit more than one positive steady state

- If above conditions are not met, chances of precluding multistationarity cannot be demonstrated