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Enzyme sharing as a cause of multistationarity in signaling systems

Bistability, and more generally multistability, in biological systems is seen as a mechanism of cellular decision making. Compared to systems with a single steady state, the presence of multiple stable steady states provide a possible switch between different responses and increased robustness with respect to environmental noise. To understand cellular signaling, it is therefore of fundamental importance to know i) which systems can exhibit multistationarity and ii) what are the biological conditions enabling it.

Here, we consider biological systems where a signal is transmitted by phosphorylation. Kinases catalyze phosphorylation of (protein) substrates, and phosphatases catalyse dephosphorylation of the same substrates. Biological systems are known in which several different kinases phosphorylate a single substrate and others where a single kinase phosphorylate several different substrates. Furthermore, phosphorylation in more than one site can be carried out by a unique kinase or, as in the case of priming kinases, different ones. The same phenomena are observed concerning phosphatases and dephosphorylation.

The interplay between kinases, phosphatases and their substrates increases the complexity of signaling pathways. In this presentation we determine the emergence of multistationarity in small motifs that repeatedly occur in signaling pathways. Our simple modules are built on a one-site modification cycle and contain one or two cycles combined in all possible ways with the above features regarding the number of modification sites, and competition and non-specificity of enzymes, incorporated.

We conclude that

a) Multistationarity arises whenever a single enzyme is responsible for catalyzing the modification of two different but linked substrates.
b) The presence of multiple steady states requires substrate saturation and two opposing dynamics acting on the same substrate.
c) Multistationarity in some of the systems occurs independently of the reaction rates.

The mathematical modeling is based on mass-action kinetics. This implies that steady states are solutions to a system of polynomial equations in the chemical concentrations and enables the use of algebraic arguments as previously proven successful, e.g. [1], [3]. In particular, the conclusions are derived in full generality without restoring to simulations or random generation of parameters. See [2].

References

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