Michael Knudsen
Bioinformatics Research Centre, Aarhus University, Denmark
e-mail: micknudsen@gmail.com
Elisenda Feliu
Bioinformatics Research Centre, Aarhus University, Denmark
e-mail: efeliu@birc.au.dk
Carsten Wiuf
Bioinformatics Research Centre, Aarhus University, Denmark
e-mail: wiuf@birc.au.dk

Mathematical Modeling of Phosphorelay Dynamics

Phosphorylation is one of the most prevalent forms of post-translational modifications by which signals are transmitted in living cells. A type of signaling pathway prevalent in bacteria is the two-component system (TCS), in which a signal is transferred through a series of phosphate group transfers moving the phosphate group from the sensor domain of one protein to the regulator domain of another protein. Similar pathways involving more than two proteins exist, and together with TCSs these are known as phosphorelays.

We present a rigorous mathematical analysis of phosphorelays assuming only mass-action kinetics. By combining an algebraic approach, previously applied to linear signaling cascades [1], with theory for monotone systems, we show that phosphorelays converge to unique stable steady states given initial total substrate concentrations. The proof relies on graph theoretical properties of the species-reaction Petri net (SR-net) and an analysis of the phosphorelay system in reaction coordinates. Using reaction coordinates, the system exhibits a special kind of monotonicity (the system is cooperative).

For the TCS, algebraic manipulations of the steady state equation lead to further insight into the system dynamics, for example in relation to stimulus-response curves. We obtain a polynomial equation relating stimulus and response, only depending on the rate constants and the total substrate concentrations. Using this relationship we are able to investigate, without restoring to simulation or further approximation, how the stimulus depends on the number phosphorylation sites of each protein.

Algebraic approaches to phosphorylation networks have been the topic of many recent publications, see [1,2] and references therein, and we believe that such approaches will be helpful for understanding many different types of systems.

References

[1] E. Feliu, M. Knudsen, L.N. Andersen, C. Wiuf: An Algebraic Approach to Signaling Cascades with n Layers, arXiv:1008.0431 (2010).
[2] E. Feliu, L.N. Andersen, M. Knudsen, C. Wiuf: A General Mathematical Framework Suitable for Studying Signaling Cascades, arXiv:1008.0427 (2010).