Large fluctuations in coupled metabolic reactions

Johan Elf
Dept. of Cell & Molecular Biology
Uppsala University
Sweden
Johan.Elf@icm.uu.se

Måns Ehrenberg
Dept. of Cell & Molecular Biology
Uppsala University
Sweden
Ehrenberg@xray.bmc.uu.se

ABSTRACT

The reactions in metabolic networks are far from equilibrium. Therefore, even relative fluctuations in metabolite pools consisting of hundreds of thousands of molecules can be very large [1]. This is in particular true for irreversible, multisubstrate reactions. These are ubiquitous in anabolic biochemical pathways and among them we find replication of DNA, transcription and translation of messenger RNA. When these reactions are unsaturated and when the inflows of their substrates are nearly balanced, the sizes of the substrate pools are almost degenerate, i.e. an increase in one pool can be compensated by a decrease in another, so that the overall flow characteristics remain unchanged.

The flux-coupled system represents a multidimensional version of the classical zero order mechanism [2], the mesoscopic implications of which only recently has been clarified [3]. In resemblance to the classical case the coupled system display three closely related properties.

Firstly, the rates by which average substrate pool sizes adjust to their steady states may be extremely slow. Secondly, the pool sizes are ultrasensitive to imbalances in the inflows of substrates and, thirdly, the pools display giant fluctuations making mesoscopic descriptions necessary for realistic modelling of this type of intracellular kinetics.

To maintain homeostasis despite of this inherent instability of metabolic pathways, other molecular regulatory systems besides transcriptional control are necessary. We demonstrate how feedback inhibition of substrate synthesis can tame the fluctuations, speed up the relaxation rates and reduce the hypersensitivity of the substrate pools. We use these results to show how fast growth of bacterial populations depends on a delicate balance of the beneficial and deleterious effects of feed back inhibition. On one hand, this mechanism reduces pool fluctuations, which is necessary for proper intracellular regulation of transcription, and on the other it reduces the activity of enzymes.

By adiabatic elimination of fast variables [4] we have derived approximate, analytical solutions to the Master equations that describe the stochastic behavior of coupled substrate pools. The analytical approximations are important, since these in contrast to Monte Carlo simulations clarifies the underlying principles.

REFERENCES

[1] Van Kampen N.G. *Stochastic Processes in physics and chemistry*. North Holland, Amsterdam, 1992.

[2] Goldbeter, A. & Koshland, D.E., Jr. An amplified sensitivity arising from covalent modification in biological systems. *PNAS* 78, 6840-6844, 1981.

[3] O.G. Berg, J. Paulsson, & M. Ehrenberg, Fluctuations and quality of control in biological cells: zero-order ultrasensitivity reinvestigated. *Biophysical J*. 79, 1228-1236, 2000.

[4] C.W. Gardiner, *Handbook of Stochastic Methods*, Springer, Berlin, 1985.