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PUTTING "SYSTEMS" BACK INTO SYSTEMS BIOLOGY

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Metabolic modelling, control analysis, supply-demand analysis, regulatory design, biotechnological manipulation

A central tenet of systems biology is that organisms, cells, genes and proteins are complex structures whose relationships and properties are largely determined by their functional organisation. Systems biology, therefore, should therefore go beyond the properties and amounts of individual biomolecules, and take seriously their organisation into a living whole. Sadly, much of what currently passes for systems biology has degenerated into what can be called the"system-wide" biology of all the -omics, which seems to be based on the belief that if we measure everything that can be measured in the cell we will understand cellular physiology. In this talk I shall argue for the necessity of a "systems view" for gaining the required understanding.

In terms of functional organisation metabolism can be regarded as a chain of coupled factories: a catabolic factory transforms nutrients into carbon skeletons and captures chemical energy and reducing power. These catabolic products serve as input to an anabolic factory that synthesizes the building blocks for macromolecular syntheses (amino acids, nucleotides, simple lipids, etc.). The factories for protein, polynucleotide, complex carbohydrate and lipid synthesis form the end of the chain and lead to growth. I show how this view of the functional organisation of the cell underlies a quantitative formalism and a general theory for understanding the cell as a integrated molecular economy of coupled supply and demand systems that have evolved regulatory mechanisms that enable them to fulfill specific functions such as control of flux or homeostatic maintenance of metabolite concentrations. In “classical” accounts of metabolic regulation the rates at which metabolic products are made are purported to be controlled by so-called rate-limiting steps within the supply pathways. Our supply-demand analysis[1] allows the control and regulation of metabolism as a whole to be understood quantitatively in terms of the elasticities of supply and demand, which are experimentally measurable properties of the individual pathways or processes. The kinetic and thermodynamic aspects of regulation[2] can be clearly distinguished, and a major consequence of enzyme regulation is that fluxes can respond to changes in demand or supply, depending on the type of function that the system fulfils, while the system remains both far from equilibrium and homeostatic. Supply-demand analysis shows that flux and concentration control are inextricably linked: the more control either supply or demand block has over flux, the less it determines the degree of homeostasis of the concentration of the linking intermediate, which becomes the function of the other block.

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[2] Rohwer, J.M. & Hofmeyr, J.-H.S. (2010) Kinetic and thermodynamic aspects of enzyme control and regulation. J. Phys. Chem. B 114, 16280–16289.