ABC FOR GRASPing ENZYME KINETICS IN METABOLIC MODELS

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Large scale kinetic models of metabolism are required to explore and explain the molecular basis for homeostasis, the self-regulating processes evolved to maintain metabolic equilibrium. Studying homeostasis is relevant for the understanding and treatment of complex diseases, particular with the emergence of personalized medicine. It is equally important when we seek to repurpose the cellular machinery for the production of desired chemicals, materials and pharmaceuticals. In the latter process, the cells' homeostatic control mechanisms must be either disabled or exploited. However, estimation of *in vivo* parameters is hard due to the large amount of data needed and the fact that homeostatic control typically renders many parameters practically unobservable. We have developed a General Reaction Assembly and Sampling Platform (GRASP) capable of consistently parameterizing and sampling thermodynamically feasible kinetics using minimal reference data (1). The former integrates the concerted MWC model and elementary reaction formalism to describe both simple and complex (e.g., allosteric) kinetics. Application of this approach enabled assessment of the impact of thermodynamics on reaction kinetics, as well as the exploration of complex allosteric behaviours (2). Formulation of the sampling problem within the Bayesian framework provides a natural interface for the addition of experimental data, hereby improving sampling accuracy. Approximate Bayesian Computation (ABC) methods were used to unravel the dynamic properties of metabolic networks (3). A posteriori analysis of the parameter distribution enabled prediction of metabolic states, identification of critical parameters as well as unravelling the control structure of the network. We have illustrated the capabilities of our framework in several cases ranging from simple enzymatic mechanisms to tightly-regulated pathways. Overall, this framework demonstrates that detailed kinetic representation is possible without sacrificing complexity and with low amounts of data. Expanding this framework to large metabolic networks requires further algorithmic advances, including the development of efficient and robust sequential sampling schemes. Recent advances in algorithmics will be discussed.

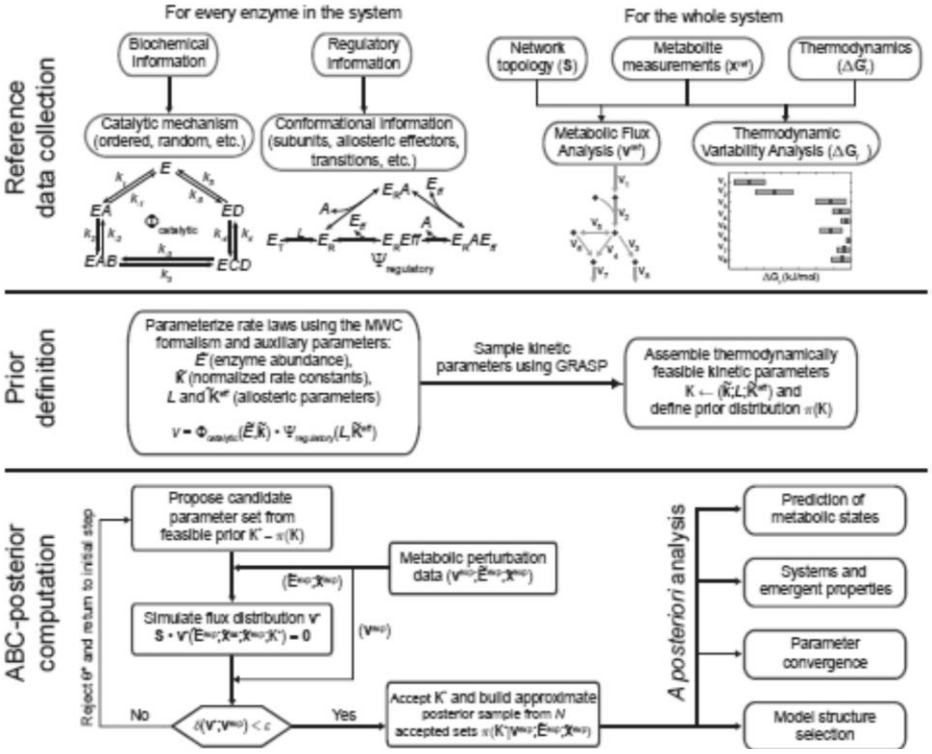

Figure 1 – ABC-GRASP Framework for kinetic modeling

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