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Kinetic Cooperativity, Loop Dynamics, and Allostery from NMR and MD simulations

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The hallmark of glucokinase (GCK), which catalyzes the phosphorylation of glucose during glycolysis, is its kinetic cooperativity whose understanding at atomic detail has remained open since its discovery over 40 years ago. I will discuss how the origin of kinetic cooperativity is rooted in intramolecular protein dynamics using NMR relaxation data of 17 isoleucines distributed over all parts of GCK. Residues of glucose-free GCK located in the small domain display a distinct exchange behavior involving multiple conformers that are substantially populated, whereas in the glucose-bound form these dynamic processes are quenched. The conformational exchange process directly competes with the enzymatic turnover at physiological glucose concentrations, thereby generating the sigmoidal rate dependence that defines kinetic cooperativity. The flexible nature of protein loops and the timescales of their dynamics are critical for many biologically important events at the molecular level, such as protein interaction and recognition processes. Based on a library of proteins, rules about loop dynamics in terms of amplitude and timescales can be derived using molecular dynamics (MD) simulations and NMR data. These rules have been implemented in the new web server ToeLoop (for Timescales Of Every Loop) that permits the prediction of loop dynamics based on an average 3D protein structure (http://spin.ccic.ohio-state.edu/index.php/loop/index).