Comparative computational analysis of enzyme allosteric sites and the binding of allosteric effectors

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Kinetic modeling of biochemical networks requires the correct modeling of allosteric effects. One of the challenges in modeling allosteric effects is that these can differ considerably between related organisms. In the European SysMO-LAB project, the central metabolism of four Lactic Acid Bacteria (LAB), *Lactococcus lactis, Enterococcus faecalis, Streptococcus pyogenes*, and *Lactobacillus plantarum*, is compared using experimental and computational systems biology approaches, including modelling of the metabolic pathways and the reaction kinetics.

With a focus on the central metabolic pathway, we have studied the allosteric regulation of the enzymes L-lactate dehydrogenase (LDH, EC number 1.1.1.27) and pyruvate kinase (PYK, EC number 2.7.1.40), two particularly important enzymes of the primary anaerobic energy metabolism. The activity of LDHs is known to be strongly activator-dependent, with the allosteric activation mostly being due to fructose-1,6-bisphosphate (FBP). Furthermore, the enzymatic activity is influenced by inorganic phosphate (P_i). Both compounds, FBP and P_i, are also involved in the regulation of PYK and other enzymes. Therefore, to understand the cross-talk between pathways, it is important to investigate the role of these compounds.

We used comparative modelling, molecular interaction fields, Protein Interaction Property Similarity Analysis (PIPSA), data mining and molecular docking techniques, to study the binding of effectors at the allosteric binding sites of these enzymes in LABs. Despite the similarity in the allosteric activators, the allosteric binding sites in LDH and PYK differ strongly. Moreover, the results show significant differences in the binding of allosteric effectors to these enzymes in the four LABs studied. Whereas LDHs from *L. lactis* and *S. pyogenes* are expected to behave similarly in the presence of FBP and P_i, the LDH from *L. plantarum* does not appear to be FBP-regulated. For PYKs, there is also a high similarity between *L. lactis* and *S. pyogenes*, whereas differences are observed for the activator binding site in the *E. faecalis* and *L. plantarum* enzymes.

In extension to the comparisons of particular enzymes of different organisms, we are working on data mining and modelling techniques for comparing interactions between compounds and enzymes in a broader and more systematic way. It is planned to make this accessible as a workflow via the modelling platform http://sycamore.h-its.org.