Application of systems biology to construct and simulate glycosylation reaction networks

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Glycosylated proteins play structural and functional roles in diverse biological processes including inflammation, cancer and development. Recent advances in analytical tools now enable the characterization of entire glycomes. In this paper, we present our efforts to develop a mathematical modeling framework that can be applied to analyze such experimental data. This approach uses object-oriented programming and graph theory to construct glycans, enzymes, reactions, pathways and compartments *in silico*. Such definitions allow the integration of XML (eXtensible Markup Language) based glycan structures in Systems Biology Markup Language (SBML) files. High-quality visualization of glycosylation reaction networks and integration with glycomics based databases is also enabled. Thus, information cataloged in these databases is used to inform model structure. Quantitative simulation of the glycosylation network is performed by simulating the 'Master Pathway' which describes the "maximum-size" glycosylation pathway that includes all reactions in a given system. Additional analysis is performed by analyzing subsets of this master model, and by collating the findings using hierarchical clustering, principal component and sensitivity analysis. These post-simulation analyses identify key regulating enzymes and reactions that control system behavior. They also generate experimentally testable hypotheses. All procedures are implemented in a new MATLAB based toolbox called Glycosylation Network Analysis Toolbox (GNAT). Examples are presented for mathematical models that: 1) simulate N-linked glycosylation initiation and branching, 2) model O-glycosylation networks, and 3) determine "feasible" glycosylation reaction networks that can fit experimentally measured mass spectrometry data. In summary, we present a structured modeling approach for the synthesis of glycosylation reaction network models. Beyond the use of statistical methods alone, such a framework may allow querying of experimental data using biological or mechanistic hypothesis.