

Cellerator: A System for Simulating Biochemical Reaction Networks

Although a vast amount of information is stored by biological systems, realistic computational descriptions are limited by the potentially combinatoric growth in biochemical interactions. In the past it has been necessary to manually translate chemical networks from cartoon-diagrams to chemical equations and thence to ordinary differential equations. This process is tedious and highly error prone, and impractical for all but the simplest of systems because of the combinatoric increase in the number of equations with the number of chemical species. Cellerator, developed at JPL, provides a framework for automatically generating computational models of signal transduction networks (STNs) from high-level biochemical descriptions.

Cellerator does this using a compact, optionally palette-driven, arrow-based notation to represent biochemical reactions and transcriptional activation. Larger systems are represented as graphs with STNs embedded in each node. Interactions include mass-action, enzymatic, allosteric and connectionist models. Reactions are translated into ODEs and can be solved numerically to generate predictive time courses or output as systems of equations to be read by other programs. Implemented as a Mathematica package, Cellerator simulations are fully extensible and transportable and can be indefinitely nested within larger data structures, thereby providing a framework for generating, translating, and numerically solving a potentially unlimited number of biochemical interactions.

Reactions are specified as $A+B+\dots \text{ arrow } C+D+\dots$, where the reactants on the left hand side of the arrow are converted into the reactants on the right hand side of the arrow. Various arrows represent different reactions and additional catalysts are specified using an over-script/under-script notation. After being collected the reactions are then symbolically translated into differential equations. The Cellerator implementation allows explicit input editing so that "power-users" can modify the equations at any stage desired, and all reactions have equivalent text-commands that can be nested to any level within a Mathematica data structure.

Multicellular systems are represented by graphs containing a list of *nodes* (representing cells), a list of *links* (representing intercellular interaction), and a *lineage tree* (a familial history of cell birth). Cell division occurs (optionally) whenever a user-specified variable passes a threshold. STNs and mitotic oscillators are embedded within nodes; large genetic regulatory networks are described with a connectionist model.

Cellerator is being used at JPL to support NASA programs to study muscle atrophy during long-duration space missions and radiation-induced leukemia. Elsewhere in academia it is being applied to the study of ordinary muscle and bone development; the development of pediatric cancers and AIDS; and to model cell cycle, locomotion and apoptosis in eukaryotes.

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