Generating Metabolic-Signaling Network Hypotheses Using ODE and Petri Net Simulations

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Motivation

Background

The complexity of cellular networks makes analysis of their dynamic behavior difficult without the use of computational models. Simulation algorithms implement either ordinary differential equations or Petri net state machines, which are fundamentally different methods of determining network behavior.

Ordinary Differential Equations
- Primary input/output relationship represented by transfer function
- Parameterization (e.g., knowledge of reaction rates) required
- Existence of several solution algorithms yielding approximate results

Petri Nets
- Primary input/output relationship represented by abstract state machine
- No parameterization required
- Execution algorithm aims to simulate signaling mechanisms of real biological systems
- Model checking verifies experimental data and refines simulation algorithms

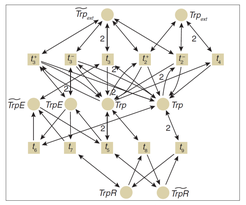

Figure 1 Petri net representation of the Trp regulatory network.

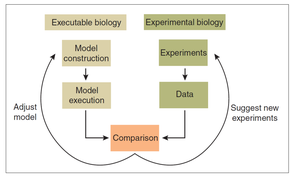

Figure 2 Computational model-checking.

Problem

- Metabolic and signaling pathways in cell networks usually studied independently; doesn't allow for dynamic interaction analysis
- Petri net algorithms for metabolic signaling pathways largely unexplored
- Understanding of metabolic-signaling pathways needed for cancer research and drug development

General Solution

- Modification of our existing Petri net/ODE simulation program, PetriBug, to include graphical user interface (GUI) network modification capabilities
- Simulation of our metabolic-signaling network's behavior under different initial conditions and perturbations
- Simulations allow for hypothesis generation for further lab experiments and development of a Petri net algorithm for metabolic signaling networks

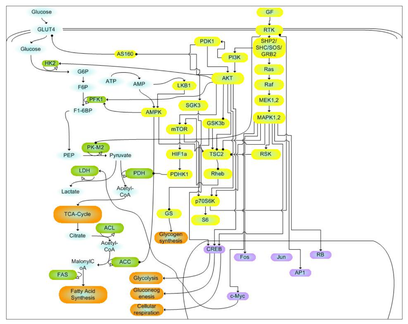

Figure 3 The metabolic-signaling network which we analysed.

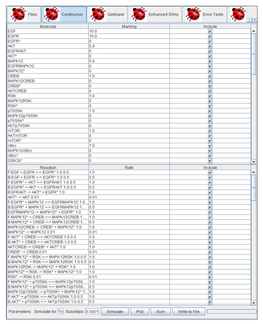

Figure 4 The PetriBug GUI.

Results

Effects of HK2 and GLUT4 initial concentrations on AKT* and MAPK1,2* production

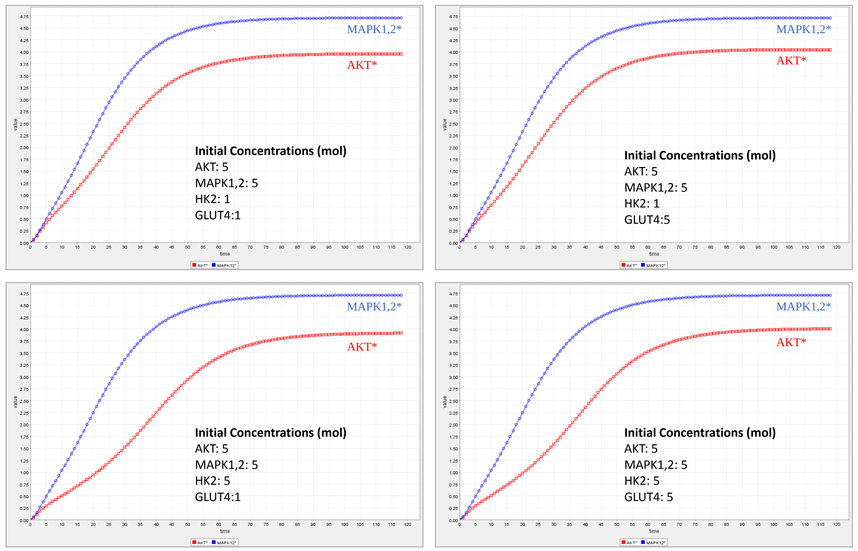

Figure 5 Visualization of the behavior of phosphorylated AKT and MAPK1,2, which are involved in the network's signaling pathways, over a period of 120 minutes given different initial concentrations of HK2 and GLUT4, which are involved in the network's metabolic pathways.

Effects of AKT and MAPK1,2 initial concentrations on G6P and Lactate production

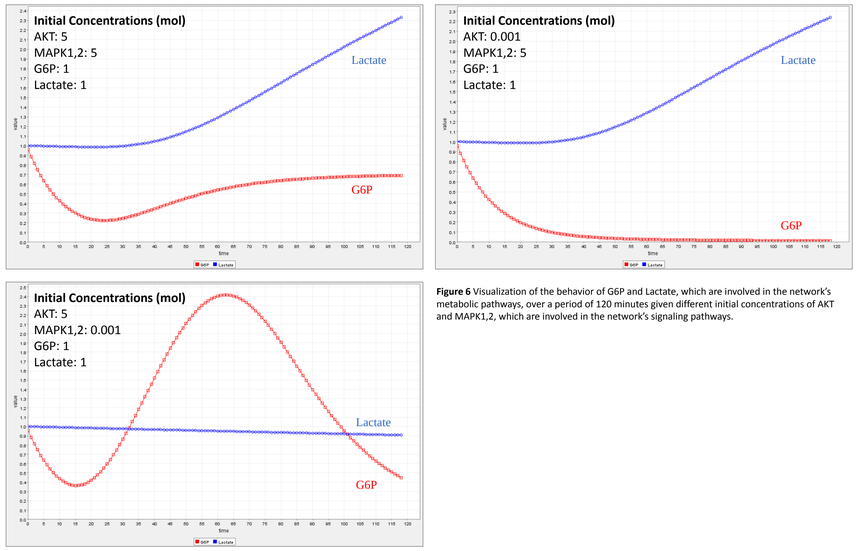

Figure 6 Visualization of the behavior of G6P and Lactate, which are involved in the network's metabolic pathways, over a period of 120 minutes given different initial concentrations of AKT and MAPK1,2, which are involved in the network's signaling pathways.

Conclusions

Analysis

The simulations focused on two sets of molecules involved in metabolic and signaling pathways implicated in causing cancer and were run over a course of 120 minutes.

Simulation 1
- Molecules analysed: HK2 and GLUT4 (metabolic); AKT and MAPK1,2 (signaling)
- Behavior of phosphorylated MAPK1,2 (MAPK1,2*) not affected by changes to either HK2 or GLUT4 initial concentrations
- Production of phosphorylated AKT (AKT*) dampened by increase of HK2 initial concentration from 1 mol to 5 mol; GLUT4 levels did not affect AKT* behavior
- Hypothesis: HK2 levels on metabolic end of the network directly proportional to AKT levels on signaling end of the network

Simulation 2
- Molecules analysed: G6P and Lactate (metabolic); AKT and MAPK1,2 (signaling)
- Given 5 mol AKT and MAPK1,2 initial concentrations, Lactate production steadily rises while G6P levels initially sink before slowly rising
- Very low AKT initial concentration results in G6P levels sinking to 0 over time
- Very low MAPK1,2 initial concentration results in sinusoidal G6P behavior and very slow decrease in Lactate over time
- Hypothesis: AKT levels on signaling end of the network directly proportional to G6P levels on metabolic end of the network; MAPK1,2 levels directly proportional to Lactate levels

Future Research

The purpose of this investigation was to generate hypotheses about metabolic-signaling networks via simulation. This work must be followed up by laboratory experiment to confirm simulation results and progress toward developing a Petri net simulation algorithm for metabolic-signaling networks, an area of research still in its infancy.

There is room for improvement within the PetriBug code base as well. A Petri net simulator will be implemented into this program in conjunction with progressing research in metabolic-signaling network analysis. This tool would then be released for use by the research community. The GUI of the program would benefit from the implementation of other user-friendly features, such as the ability to sort molecules and reactions by name to reduce search time, the addition of plot-editing capabilities (e.g. resolution modification), and the ability to run multiple simulations in series.

References

The images in the "Background" section are taken from the following source:

Jasmin Fisher and Thomas A. Henzinger, "Executable Cell Biology," *Nature Biotechnology*, vol. 25, no. 11, pp. 1239-1249, Nov. 2007

Acknowledgments

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