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Systems Biology: Simulation of Dynamic Network States

Winter semester 2016

Research Project

Due: 2 p.m. at January 30, 2017

Problem 1 Introduction

- ✎ Do reading about *Staphylococcus aureus*. What is its importance, why is it relevant?
- ✎ Download the model iSB619 (Becker et al., 2005) from BiGG Models database[1] (King, Lu, et al., 2015) in the formats SBML (Level 3 Version 1 Release 2 by Hucka, Bergmann, et al., 2016) and JSON (JavaScript Object Notation).
- ✎ What are subsystems and what is the *groups* package (Hucka and Smith, 2016) in SBML?
- ✎ Select one of the predefined subsystems in *S. aureus* as depicted in Table 1.
- ✎ Create a model slice from the SBML model only comprising subsystems in your list.
- ✎ What can you learn from MIRIAM[2] annotations (Juty et al., 2012; Le Novère et al., 2005) in your model?
- ✎ Which information can you obtain from SBO[3] terms (Courtot et al., 2011)?

Problem 2 Formulation of dynamic mass balances

Problem 2.1 Graphical display

- ✎ Use the online tool Escher (King, Dräger, et al., 2015) to build one metabolic map for each subsystem in your list.
- ✎ Build one larger map that combines all your generated maps.
- ✎ Use EscherConverter[4] to compile your maps in SBML+Layout (Gauges et al., 2015) and include them into your model slice.
- ✎ Create a meaningful variation of models that combine the subsystems.

[1] `http://bigg.ucsd.edu`
[2] Minimal Information Required In the Annotation of Models, see `http://co.mbine.org/standards/miriam`.
[3] Systems Biology Ontology terms, see `http://www.ebi.ac.uk/sbo/main/`.
[4] `https://github.com/SBRG/EscherConverter/`

Table 1: List of selected subsystems in iSB619. Subsystems are collections of reactions that form a larger unit. The SBML extension package *groups* is used to compile subsystems. The identifiers in the column 'ID' correspond to the ids of individual groups in the SBML file.

Nº	ID	Team	Name	Reaction count
1	g4	Blue	Pyruvate Metabolism	11
2	g6	Blue	Amino Acid Metabolism	24
3	g12	Blue	Citric Acid Cycle	14
4	g14	Blue	Cofactor and Prosthetic Group Biosynthesis	25
5	g11	Green	Cell Envelope Biosynthesis	12
6	g15	Green	Purine and Pyrimidine Biosynthesis	54
7	g28	Green	Sterol Biosynthesis	14
8	g3	Yellow	Fatty Acid Degradation	21
9	g20	Yellow	Glycerolipid Metabolism	10
10	g21	Yellow	Tyrosine, Tryptophan, and Phenylalanine Metabolism	17
11	g27	Yellow	Lipid & Cell Wall Metabolism	13
12	g38	Yellow	Fatty Acid Synthesis	13

Problem 2.2 Analysis of the dynamic mass balances

- ✎ Formulate the dynamic mass balance equation.
- ✎ Calculate the rank of the stoichiometric matrix.
- ✎ What are the conservation relationships?
- ✎ How are the eigenvalues distributed?

Problem 3 Dynamic modeling

- ✎ Generate kinetic equations for your model by using SBMLsqueezer[5] (Dräger et al., 2015).
- ✎ Define boundary fluxes that are required to fill and drain your system and annotate them with SBO terms for *demand*, *exchange*, or *sink reaction* as appropriate.
- ✎ Specify initial conditions and numerical values for the kinetic parameters.

Problem 4 Simulation

Run simulation to obtain the numerical solution.

- ✎ Estimate meaningful orders of magnitude for initial conditions and parameter values.
- ✎ Simulate each subsystem in isolation using Tellurium (Sauro et al., 2016).
- ✎ Simulate the combined model.

Problem 5 Analyze the result

Problem 5.1 Plotting

Find meaningful ways of plotting the simulations. Since the simulated models are can be rather big now, it is important to find condensed visual representations which still convey relevant information. Examples include:

[5] available for download at `http://www.cogsys.cs.uni-tuebingen.de/software/SBMLsqueezer/`

- defining biochemically relevant pools based on research, or
- plotting biochemically relevant subsystems, etc.

Here, as in many other phases of the project, there are no unique "right" answers, so just be creative (in a biochemically informed way).

Problem 5.2 Post processing of the result

Analyze your subsystems and the combined model for meaningful pools, such as

- conservation relationships,
- time invariants, or
- distances from equilibrium, etc.

Plot the movement of the pools. Which graphical display is most useful (such as transient responses or tiled arrays)?

Problem 5.3 Regulation and sensitivities

✎ What are the parametric sensitivities, i.e., which parameters have the largest effects on the system's dynamic behavior?

✎ Can you spot statistical regularities by sampling kinetic parameters and/or initial conditions.

✎ How many stable steady states can you identify?

Problem 6 Term paper

Write a summary report about your term project of approximately 15 pages. This should include five major sections:

1. Abstract: a brief description in up to 300 words summarizing all subsequent sections.
2. Background: a general introduction including a description of the importance of the subject under study.
3. Results and discussion: a description of your findings, i.e., your observations from solving the individual problems above.
4. Conclusion: a short summary including a perspective on possible future investigations.
5. Material and methods: a short overview of what was used and how the study was executed.

References

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