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Modeling and simulating the effects of atorvastatin on the central carbon metabolism of rat hepatocytes using SBMLsimulator

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Biological motivation, model building and parameter estimation

The cholesterol lowering drug atorvastatin (Lipitor) acts by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. To investigate the effects of atorvastatin on the central carbon metabolism and the bile acid synthesis we used rat hepatocyte as a model system [1] and constructed a corresponding model based on HepatoNet1 and literature knowledge, e.g. the KEGG knowledgebase. To gain a high-quality model we fully balanced the model and checked the realizability by performing flux balance analysis including thermodynamical constraints.
We generated kinetic equations applying General Mass Action Kinetics (GMAK) using an improved version of the SBMLsqueezer [2] resulting in an Ordinary Differential Equation (ODE) system of 104 uncertain values to estimate. Our newly developed SBMLsimulator was subsequently used to optimize these parameters. We achieved a medium relative euclidean distance of 0.3229. This work demonstrates the usefulness, correctness and efficiency of SBMLsqueezer and the newly developed software SBMLsimulator.

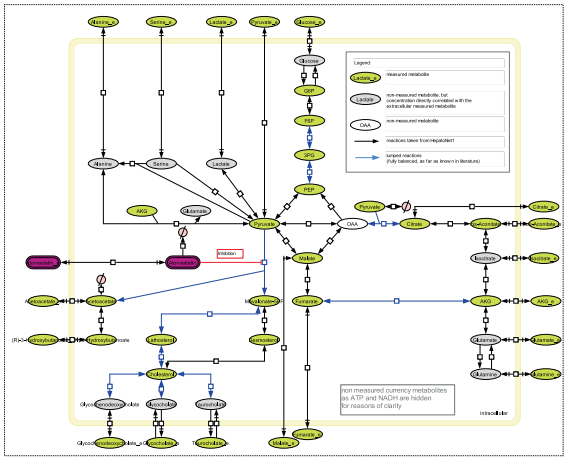
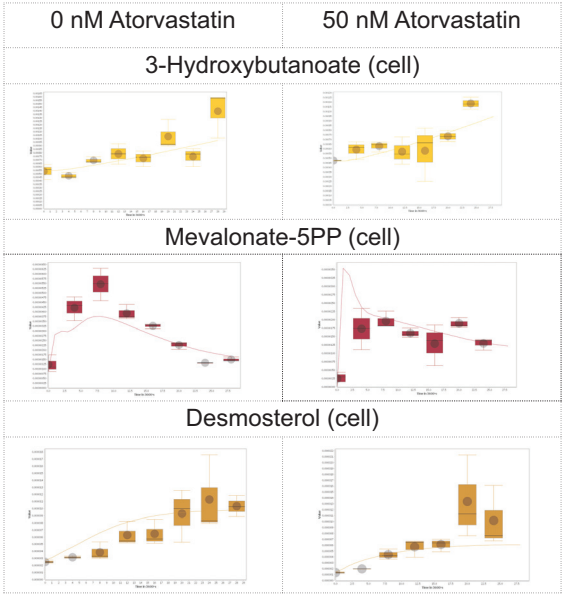


Fig. 1 (above): The resulting rat hepatocyte model with in total 77 metabolites (non measured currency metabolites are hidden for reasons of clarity).

Fig. 2 (below): Comparison of selected optimized curves (not influenced vs. influenced); box plots are obtained from the three replicates.



Facts:

DATA:

# measured metabolites:	34
# intracellular:	16
# extracellular:	18
# time points:	8
# perturbation variants:	3
# replicates:	3

MODEL:

# compartments:	2
# metabolites:	77
# reactions:	39
# lumped reactions:	10
# transports:	21

ODE SYSTEM:

# kinetic equations:	60
# uncertain parameters:	104

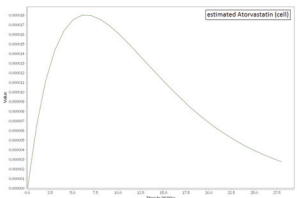
OPTIMIZATION:

method: differential evolution
number of steps: 20,000
population size: 50
F = 0.8
ê = 0.6
ë = 0.6

RESULTS:

relative euclidean distance:

without Atorvastin:	0.3016
with 50nM Atorvastin:	0.3442



SBMLsimulator and Simulation Core Library

The SBMLsimulator [3] interprets the content of models given in the SBML (Systems Biology Markup Language) format [4] and predicts the dynamic behavior of the model's components. It is based on the Java™ library JSBML [5], a specifically developed data structure to read and write models from and into SBML files and to deal with their structure in memory.

The program SBMLsimulator consists of two parts:
Firstly, a generic solver core library, which is completely decoupled from any graphical user interface and can hence easily be integrated as an API (Application Programming Interface) into third-party programs.
Secondly, a graphical and command-line user interface that provides a connection to the heuristic optimization framework EvA2 [6]. The combination of SBMLsimulator and EvA2 estimates the values of all parameters with respect to given time-series of metabolite or gene expression values. The simulation core is also be integral part of the widely used program CellDesigner version 4.2 [7]. The core can be downloaded under the terms of LGPL at http://sourceforge.net/projects/simulation-core/ .

Fig. 3: The graphical user interface of SBMLsimulator provides several options to perform a dynamic simulation of the given SML model. Currently, the simulator includes nine numerical integration methods. The fit of a model to experimental data can be evaluated with eight quality measures.

References

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virtual liver network
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