Feedback mechanisms and systems medicine: Modelling cholesterol homeostasis for drug discovery

Ales Belic¹, Jure Acimovic² and Damjana Rozman²

¹Laboratory for Modelling, Simulation and Control, Faculty of Electrical Engineering, University of Ljubljana,
²CFGBC, Institute of Biochemistry, Medical Faculty, University of Ljubljana, Slovenia

Funders:
Slovenian: ARRS
EU: FP6-Steroltalk
FP7-ITN-Fighting DrugFailure

An advantage of object-oriented modelling is the re-usability of general equations and model object classes with a user-friendly graphical interface.

One can define user-specific model objects and libraries, handle large, dynamic, multi-domain models and generate simulations rapidly.
In the case applied also in your practical example a systems biology library of objects was generated based on ordinary differential equations (ODEs) corresponding to biological pathway entities (Belič et al., Modelling Practice and Theory 33: 18-27, 2013).

The basic objects of the library include enzymes, metabolites, non-enzyme proteins, mRNAs, genes, flux sources and positive and negative regulatory objects for gene expression and protein activity. Objects are linked with connectors, thus forming a closed multi-pathway network of the user’s choice.

Dymola not freely available thus OpenModelica software will be used.
What will we model?

Cholesterol synthesis pathway

Rozman & Monostory, Pharmacology & Therapeutics, 2010
Hafner et al., Pharmacogenet.Genomics 2011
What will we model?

Cholesterol synthesis pathway

Why?

Rozman & Monostory, Pharmacology & Therapeutics, 2010
Hafner et al., Pharmacogenet.Genomics 2011
What will we model?

**Cholesterol synthesis pathway**

Why?

**Potential targets for cholesterol lowering drugs**

Rozman & Monostory, Pharmacology & Therapeutics, 2010
Hafner et al., Pharmacogenet.Genomics 2011
What will we model?

Cholesterol synthesis pathway

Why?

Potential targets for cholesterol lowering drugs

Rozman & Monostory, Pharmacology & Therapeutics, 2010
Hafner et al., Pharmacogenet.Genomics 2011
Statins

- Secondary metabolites of fungi
- Potent inhibitors of cholesterol biosynthesis
SYSBIO library specifications

► Valid ONLY for steady state
► Example:
  ► You are perfectly healthy – one steady state
  ► You cut yourself – you start “leaking”
  ► Scab is formed to prevent “leaking”
  ► You are in another steady state
  ► Normal functions but you are different – you have a scab
► We can model changes from one steady state to another
  ► KO vs. WT

► No kinetic parameters needed, just flux distributions
Expert-based simplified mathematical model of cholesterol biosynthesis

- Green – metabolites;
- Red - enzymes and their biochemical control;
- Yellow blocks - gene expression;
- Orange blocks - enzyme production;
- Blue blocks - biochemical reactions;
- Brown blocks - gene expression control through SREBF2.
Mathematical background

1. \[
\frac{dX}{dt} = \phi_{in} - \phi_{out}
\]
   Substance container model for metabolites, enzymes and mRNAs – describing concentrations of substances (X) and integrating in/out fluxes.

   \[
   \phi_{in} = S \cdot E \cdot k_C - C \cdot k_{CR}
   \]

   \[
   \phi_{out} = C \cdot k_P - P \cdot E \cdot k_{PR}
   \]

   Enzyme reaction model - to describe reactions that define fluxes.

2. \[
\frac{dC}{dt} = \phi_{in} - \phi_{out}
\]
   \[
   \phi_{in} = \phi_{inE}
   \]

   \[
   \phi_{out} = \phi_{outE}
   \]

   \[
   k_{CR} = r \cdot k_p
   \]

   \[
   k_{PR} = r \cdot k_C
   \]

3. \[
\phi_{E_{form}} = X_{mRNA} \cdot k_{Ef}
\]
   Enzyme formation and degradation.

   \[
\phi_{E_{deg}} = E \cdot k_{Ed}
\]

4. \[
\phi_{X_{deg}} = X_{mRNA} \cdot k_{Xd}
\]
   mRNA formation and degradation.

Cholesterol model: training by experimental data; validation of statins effects, drug development, endocrine metabolism, etc.

Acimovic et al., 2009
Rozman & Monostory, 2010
Acimovic et al., 2011
Hafner et al., 2011
Belič et al., 2012
Basic concept

\[
\begin{align*}
\frac{dS}{dt} &= \Phi_I - \Phi_{OA} - k_C \cdot E \cdot S + k_{CR} \cdot C \\
\frac{dC}{dt} &= k_C \cdot E \cdot S + k_{PR} \cdot E \cdot P - k_P \cdot C - k_{CR} \cdot C \\
\frac{dP}{dt} &= k_P \cdot C - \Phi_O - k_{PR} \cdot E \cdot P \\
\frac{dE}{dt} &= \Phi_{EI} + k_P \cdot C + k_{CR} \cdot C - k_C \cdot E \cdot S - k_{PR} \cdot E \cdot P - \Phi_{EO}
\end{align*}
\]
Hands-on tutorial

► Now open OpenModelica programme

► Upload SysBio library
Smith–Lemli–Opitz syndrome (SLOS)

- 7-dehydrocholesterol (DHCR7) reductase deficiency
- An inborn error of cholesterol synthesis.
- It is an autosomal recessive, multiple malformation syndrome caused by a mutation DHCR7.
- It causes a broad spectrum of effects, ranging from mild intellectual disability and behavioural problems to lethal malformations.
Model predicts novel branches from the cholesterol synthesis pathway

- Hypothesis: cholesterol synthesis intermediates are in the studied animal system (testis Crem KO) removed from the pathway by CYP11A1 and E3 – E6 enzymes

- Branching from late cholesterol synthesis valid also for the liver?

Acimovic et al., unpublished