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BIOCHEMICAL MATHEMATICAL MODELING WITH MODELICA AND THE BIOCHEM LIBRARY

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Abstract.. Considering the large amounts of data that is nowadays produced in the biochemistry (functional genomics) it is difficult to extract the information from the measurements. There is currently also a great interest in the development of novel analytical technologies for rapid screening of disease symptoms in pharmaceutical and clinical applications. Modeling and simulation can provide a useful help in understanding the relations of the measured substances and to minimize the need for measurements. The BioChem library presented here is the first free Modelica library available for mathematical modeling of biochemical processes. Three examples are shown to illustrate the library. First, a simple insulin model is presented. Then a simplified model of cholesterol together with simulations are shown. Next, a simple drug model together with parameter estimation in NONMEN are presented. The BioChem library allows for fast and end-user friendly modeling of biomedical systems. The graphical user interface provides graphics similar to that used in the description of metabolic pathways in biochemistry.

Keywords. cholesterol metabolic pathways, feedback control, functional genomics

Mathematics Subject Classification: 37N25, 37N35.

1 Introduction

There is currently a great interest in the development of novel analytical technologies for rapid screening of disease symptoms in pharmaceutical and clinical applications. However, developing new drugs is a costly and time-consuming process involving tests of many compounds. To speed up the development, models have developed that eliminate the need for certain experiments. In most of these system models, computerized modeling and simulation of the lead compound's effects on different metabolic pathways are included. A metabolic pathway can be seen as a complex web made up of several hundred substances and reactions. Substances that are expected to interact in a harmful or lethal way with essential metabolic pathways can be removed at an early stage and a reduced number of promising lead compounds can be chosen for the concluding tests.

In this context we have developed a library of model components, called BioChem, intended for building metabolic pathway models for analysis and simulation. The library has been developed in the Modelica modeling language. In the following, we will briefly describe the most recent version of the BioChem library and its use for some applications.

2 The Modelica Modeling Language and Biochemical Systems

Modelica [1], [2], [3] is one of the more recently developed object-oriented equation-based modeling languages, and was originally developed for hierarchical physical and technical modeling. Primarily, Modelica is a modeling language that allows the user to specify mathematical models of complex systems, but it is also an object-oriented equation-based language, oriented towards computational applications with high complexity requiring high performance.

Biological and biochemical systems can often be described using mathematical relations and expressions, provided that enough knowledge of the system is available. This makes the equation-based Modelica a suitable modeling language for mathematical modeling of such systems. First of all, Modelica classes are acausal, i.e., can adapt to more than one data flow context, which is a great benefit when dealing with chemical reactions where the flow of matter can move in two directions. The complexity of biological and biochemical models can be rather high, containing several hundreds of items. However, this is not be a problem since Modelica's strength as a modeling language for complex technical systems with hundreds or thousands of components is already well proven. It is also possible to model both discrete and continuous systems, as well as hybrid systems.

3 The BioChem Library and its Subpackages

Most substances and reactions, respectively, have some common basic features. For instance, all substances must have a concentration and all reactions must have at least one substrate and one product. The design objective behind the BioChem library is to collect these basic features of substances and reactions along with units, compartment properties, and other attributes that are commonly used in these kinds of systems in a general-purpose biological and biochemical Modelica library. The library contains several subpackages holding classes and partial models. The classes can be used as they are, while the partial models must be extended to fully functional models.

```
  package BioChem
    package Compartments "Different types of compartments"
    package Interfaces "Basic model properties and graphical
interface"
      package CompartmentProperties "Basic properties for
compartments"
      package ConnectionPoints "Connector interfaces used in the
package"
      package Icons "Icons used in the package"
      package Reactions "Partial reaction models"
        package Basics "Basic properties of reactions"
        package Modifiers "Basic properties of modifiers"
        package ReactionTypes "Partial reaction models"
        package SBML "Partial SBML reaction models"
      package Substances "Partial substance models"
    package Reactions "Reaction edges"
```

```
    package MassAction "Mass action kinetics reactions"
    package SBML "Pre-defined reactions in SBML"
  package Substances "Reaction nodes"
  package Units "Units used in BioChem"
  package Examples "Some examples of BioChem models"
end BioChem;
```

3.1 BioChem.Compartments

In order to be able to control the environment of the reaction during a simulation a chemical reaction must take place in a restricted screened-off container. Within this container the basic physical properties, e.g. volume and temperature, are the same for all reactions that take place and all substances contained in that container. In BioChem.Compartments this is solved using the Modelica inner-outer construct, i.e., providing a "semi-global" variable for a whole compartment declared using the inner prefix. Thus, all substances in a compartment can automatically refer to the compartment volume. The package so far only contains partial models for a few kinds of containers that can be found in cells.

3.2 BioChem.Interfaces

BioChem.Interfaces contains connections points, icons and partial models. The partial models are extended by models in BioChem.Compartments, BioChem.Reactions and Biochem.Substances.

3.3 BioChem.Interfaces.CompartmentProperties

The partial models in BioChem.Interfaces.CompartmentProperties collect some basic properties of compartments, such as volume and temperature. These partial models are extended by models in BioChem.Compartments, and the compartment properties can be accessed by all substances in the compartment.

3.4 BioChem.Interfaces.ConnectionPoints

The package BioChem.Interfaces.ConnectionPoints contains the connector class SubstanceConnector (see below) that is used when connecting the different components in a model. In order to be able to make simulations using a connected model, the connector has to have a flow variable. For chemical reactions this flow variable is the molar flow rate of a substance (mol s^{-1}). There are also two non-flow variables in the connector, the concentration of a substance and the volume of the compartment where the substance is located. The concentration and compartment volume are later on used in equations with relations to the reaction rate in reaction models.

The connector class is used in several partial models in BioChem.Interfaces. ConnectionPoints. Each partial model relates to the graphical interface of at least on icon in BioChem.Interfaces.Icons (Not more than one icon at a time though.). For the reaction arrows, connectors are placed at each intended connectable end. For the enzymes regulating the reactions the connectors are placed at the enzyme signs. Finally for substances, eight connectors are placed on the rim of the circle that represents the node of substance.

```
connector SubstanceConnector "Connector between substances and
reactions"
extends BioChem.Interfaces.Icons.SubstanceConnector;
```

```
BioChem.Units.Concentration c
                    "Concentration of substance at the connection";
BioChem.Units.Volume V
                    "Volume of compartment where the substance is
located";
flow BioChem.Units.MolarFlowRate r
                    "Molar flow rate of substance at the
connection";
end SubstanceConnector;
```

3.5 BioChem.Interfaces.Icons

The package BioChem.Interfaces.Icons contains icons used in the drag-and-drop interface of the Model Editor in MathModelica. A substance is represented by a circle and the fill color is changed depending on the type of substance represented, i.e., substance in solution, fixed concentration, etc. Since the substance only come in a few flavors there is one icon for each type of node.

The reactions on the other hand come in many different variations. A reaction is represented by an arrow with two or more ends. The number of ends of an arrow is determined by the number of substrates and products that are involved in the reaction. Substrate-ends are, by convention, at the left side of the arrow, while product-ends are at the right side. Arrowheads indicate the direction of the reaction, i.e., irreversible reactions only have heads on the product-ends while reversible reactions have heads on both ends.

Instead of creating one icon for each type of reaction, the final graphical interface for a reaction is built out of several partial icons. The reaction arrow is divided into three parts, substrates side (left part of the reaction arrow), middle, and products side (right part of the reaction arrow). The middle is the same for all reactions, while the two other parts differentiate depending on the number of substrates and products participating in the reaction.

Enzymes can affect reactions, which is represented by a small arrow and an enzyme sign. The sign represent the type of effect that the enzyme have on the reaction, i.e., inhibition, activation, or a combination of both, and are indicated with a ─, +, and M respectively.

3.6 BioChem.Interfaces.Reactions

All reactions need some basic components in order to work properly. In BioChem.Interfaces.Reactions, these basic components are collected as partial reaction models in the sub packages Basics, ReactionTypes, and SBML.

3.7 BioChem.Interfaces.Reactions.Basics

Basic properties, common to all reactions, such as a reaction rate and the middle part of the reaction arrow are collected in BioChem.Interfaces.Reactions.Basics.

The package also contains components that are not needed in all types of reactions, but can rather be seen as roles assigned in some reactions while left vacant in others. Using the role-approach, the directions of a reaction can be seen as two roles. The role for a forward directed reaction is almost always appointed, while the role for a backward directed reaction only is assigned for reversible reactions.

The different types of enzymes that can affect a reaction can also be seen as a set of roles. When no enzymes affect the reaction, all enzyme roles are vacant. The different roles that are pos-

sible to assign are activator, inhibitor, and modifier. A modifier is a situation dependent enzyme that can react as either an inhibitor or an activator, depending on the environmental context. These roles are also directional, i.e., they can be appointed in both a forward and a backward context.

3.8 BioChem.Interfaces.Reactions.Modifiers

Activators, inhibitors and modifiers share some common properties. They are captured in the partial models in BioChem.Interfaces.Reactions.Modifiers. The roles of the modifiers are directional, i.e., there is one partial model for forward inhibition and another for backward inhibition etc.

3.9 BioChem.Interfaces.Reactions.ReactionTypes

BioChem.Interfaces.Reactions.ReactionTypes contains a collection of partial models for different types of reactions that can take place in biological and biochemical systems. The reaction types are obtained by combining different types of classes from other packages in BioChem. First, there is the combination of substrates and products. Then there is the appointment of the two reaction-direction roles. Finally, there is the possibility to appoint an enzyme role. At this point only three substrates and three products can be appointed at a time.

Given the above restrictions, there are nine irreversible and nine reversible reaction types to choose from.

Along with the graphical interface the partial models for connector interfaces in BioChem.Interfaces.ConnectionPoints are also extended. Since each of the connector interfaces have been defined in relation to an icon the extensions are quite straightforward.

Parts of the graphical interface for the MathModelica Model Editor are also defined in this package. Each partial model has a graphical representation in the form of a reaction arrow. If the role for the backward directed reaction is appointed, all the arrow-ends have heads, otherwise only the product-ends have heads. A small arrow perpendicular to the reaction arrow is used to indicate that there is an enzyme-role assigned in the reaction. An enzyme-arrow above the reaction arrow indicate that the enzyme is involved in the transformation of substrate into product, while an enzyme arrow below the reaction arrow indicate that the enzyme is involved in the reverse transformation.

3.10 BioChem.Interfaces.Reactions.SBML

In BioChem.Interfaces.Reactions.SBML are partial reactions, extended by the reaction models in BioChem.Reactions.SBML, collected. The reactions are of different types, e.g., activation kinetics, inhibition kinetics, Hill kinetics, Michaelis-Menten kinetics, etc.

3.11 BioChem.Interfaces.Substances

The BioChem.Substances sub package contains partial models of different kinds of nodes needed to represent substances in biological and biochemical systems. The basic attributes corresponding to the properties that are studied during simulations, i.e., the amount and the concentration of the substance, are declared in these partial models. All partial substance models also extend the partial model BioChem.ConnectionPoints.Node, which contains the connector interface.

3.12 BioChem.Reactions

BioChem.Reactions contains a collection of models for different types of reactions that can take place in biochemical systems. The reaction models are divided into two sub package; BioChem.Reactions.MassAction and BioChem.Reactions.SBML.

3.13 BioChem.Reactions.MassAction

The mass-action reactions are obtained by extending the reaction types in BioChem.Interfaces.Reactions.ReactionTypes and then adding an equation for the relation between the reaction rate and the participating substances, i.e., substrates, products, and interacting enzymes. The mass-action kinetics package is divided into the sub packages Irreversible and Reversible to facilitate in finding the desired reaction.

3.14 BioChem.Reactions.SBML

The Systems Biology Markup Language (SBML) is a computer-readable format for representing models of biological and biochemical systems. SBML is, amongst other, applicable to metabolic pathways, cell-signaling pathways, and genomic regulatory networks. SBML (level 1, version 2) has 32 predefined reactions, which are common in SBML-models, although the predefined reactions are absent in the current SBML document (level 2, version2). All of these SBML-reactions are included in BioChem.Reactions.SBML in order to facilitate the translation of SBML-models into Modelica, and vice versa.

3.15 BioChem.Substances

The package BioChem.Substances contains different types of nodes needed for representing a substance in a biochemical pathway. The substance models are specified by extending the partial models of substance nodes in BioChem.Interfaces.Substances and adding some additional attributes and equations. Thus both normal substance nodes and nodes with different types of restrictions, e.g. on the concentration of the substance, can be specified.

Typically the concentration in a substance node is allowed to change without restrictions during a simulation, while the total amount of substance in the node is conserved at all times. Some of the models have an assert statement that checks that the concentration never drop more than the tolerance below zero. The tolerance is a parameter and can thus be changed for every node in a model as well as for each simulation run.

3.16 BioChem.Units

A number of physical types are needed in order to be able to declare most parameters and variables in the BioChem package. Some of the types can be found in Modelica.SIunits and are here redefined in order to avoid long name paths. The SI-types used in BioChem are volume (m^{-3}), amount of substance (mol), and concentration (mol m^{-3}).

Most of the other types in the package are non-SI types and thus need to be fully declared. In order for a reaction to actually transport something it has to have a flow of some kind. For a chemical reaction this flow is the volumetric reaction rate (mol m^{-3} s^{-1}). Together with the concentration, the molar flow rate of a substance (mol s^{-1}) is used in the interfaces between connected components.

3.17 BioChem.Examples

BioChem.Examples contains some small examples of how to build models using the components in BioChem, including models using several compartments. Below is an example of a BioChem implementation of an insulin receptor signaling pathway. The model in this example is based on the insulin signaling model proposed by Sedaghat et al. [8].

The model describes insulin receptor (IR) activation, internalization and recycling in response to insulin. Figure 1 shows a graphical editor view of the model. The circles represent substances with variable concentration. The arrows represent reactions, some are uni-uni, and some are bi-uni reactions. Substances and reactions are connected via their SubstanceConnectors. In contrast to substances, reaction arrows need to be connected to substances from each arrowhead. Once the structure of the model has been established by connections between substances and reactions, initial concentrations of the substances, compartment properties and kinetic parameters can be set.

In Figure 1, x_1 represents free insulin, and $x_2 - x_8$ represents different forms of the IR.

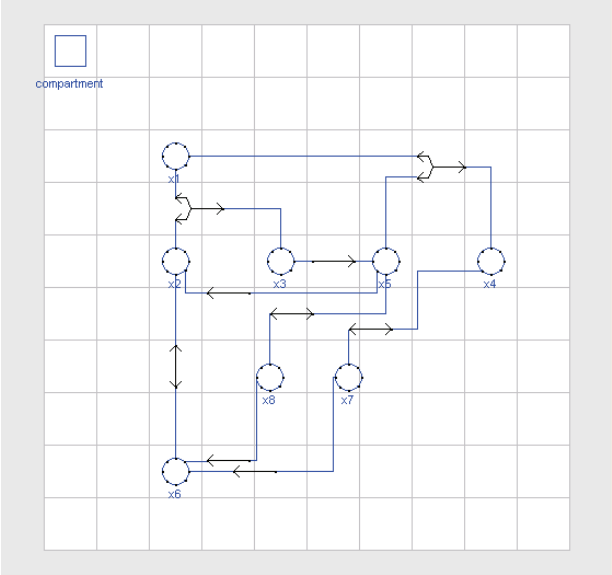

Figure 1. Model editor view of the insulin receptor model.

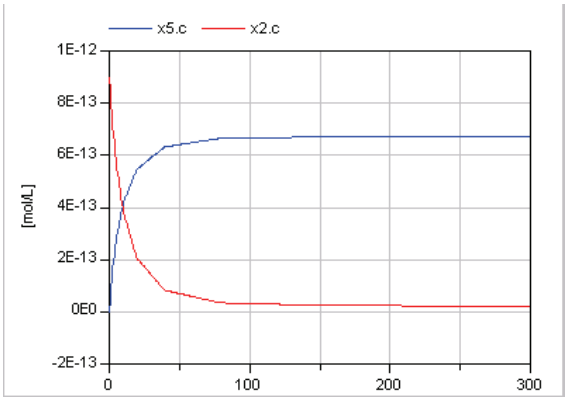

Figure 2. Time course of free IR (red) and twice insulin-bound, phosphorylated IR (blue).

After a simulation, the properties of every reaction and substance in the model, e.g. the concentrations, can be plotted. Figure 2 shows the result of a simulation of the insulin receptor model.

The blue graph shows the rise in concentration of insulin bound IR as a response to the presence of free insulin. It also shows the decrease in free surface IR concentration since the free IR molecules bind to insulin and become activated.

4 A Cholesterol Model with Feedback Control

Practically all endogenous substances that are of high importance to the organisms are controlled with feedback mechanisms. Thus, optimal concentrations of the substance are achieved within the organism. However, when a feedback loop is damaged, serous illnesses may occur, that are in most cases lethal to the organism. Cholesterol is a substance that is essential for building of cell membranes in animals, therefore, the lack of it causes decay of the cell, on the other hand, constantly raised levels of cholesterol can cause damage to the cardiovascular system (hypercholesteremia).

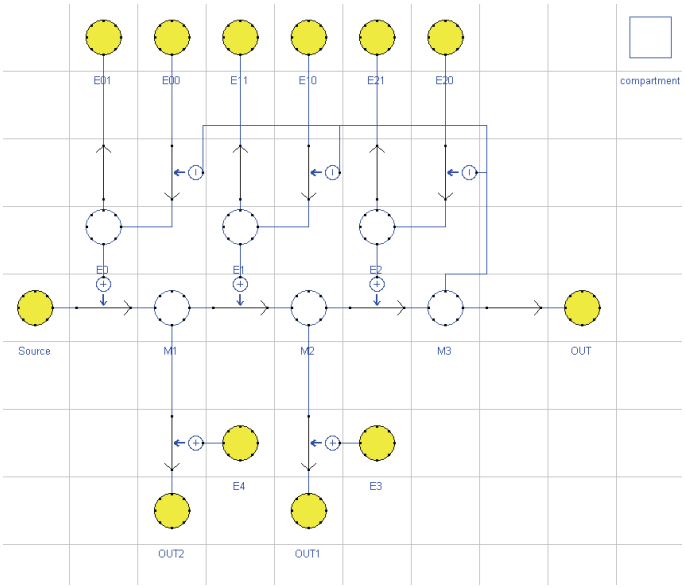

Figure 3. A model of cholesterol metabolism built with the BioChem library. Metabolite M3 represents cholesterol, metabolites M1 and M2 represent the intermediates. Enzymes E0 to E2 activate the metabolism pathway and its levels depending on the level of cholesterol.

Currently, statins are the only commercially available drugs for treating hypercholesteremia. They act by inactivating an HMGCR enzyme in endogenous cholesterol metabolism pathway in order to reduce the flux of endogenous cholesterol production. However, since the metabolism has internal feedback loops that control the levels of cholesterol, the drugs disturb the levels of substances in the whole pathway, thus generating causes for some possible adverse effects. For the purpose of analysis of statins and other drugs that work in similar way, a simplified model was developed for studying metabolic system responses to drugs (Figure 3).

The model simulation shows that when drug inactivates the enzyme E2, the levels of M3 are reduced only if M2 is metabolised in a parallel pathway. If the only metabolic pathway of M2 is towards M3, the inactivation of M2 only causes raised levels or accumulation of M2 with no reduction of M3. The same effect can be observed if the feedback control of E0 to E2 levels on the basis of M3 levels is eliminated from the model.

However, when a parallel pathway for the M2 exists, feedback control reduces the effect of the E2 inactivation, such that M3 levels are not reduced as much as was observed when feedback loop was eliminated. In the case of inactive feedback loop, the levels of M1 are not affected. However, when the loop was active, the levels of M1 were slightly changed, because, the changes in M3 caused the changes in E0 levels that controls the M1 production. If the proposed structure is correct, it suggests that any treatment with enzyme inactivation will result in high intermediate metabolite levels, unless the metabolite that is used as a substrate in the affected reaction, is also metabolised in a parallel pathway. A feedback control has a significant influence on the metabolism when parallel pathways exist, otherwise the effect of the control loop is not significant.

5 A Simple Drug Model Test Case for NONMEM with Parameter Estimation

NONMEM (Nonlinear Mixed Effects Model) is a software developed by Stuart L. Beal and Lewis B. Sheiner and the NONMEM Project Group at the University of California. The program is written in FORTRAN 77 and is the most frequently used software for so-called population pharmacokinetics. Population pharmacokinetics is concerned with model development from data from patient populations rather than from data from single patients. Measurement data usually consists of drug concentrations in blood plasma. Other data used for modeling can be age, weight of the patient or the patient genotype related to the enzyme involved in the metabolic pathway of the drug.

5.1 Nonlinear Mixed Effects Models

The structure of a Nonlinear Mixed Effects Model can be divided in two levels, a structural model (1.1) and a parameter model (1.2)

$$y_{ij} = f(x_{ij}, \phi_i) + h(x_{ij}, \phi_i)\varepsilon_{ij} \tag{1.1}$$

$$\phi_i = g(z_i, \theta, \eta_i) \tag{1.2}$$

where y_{ij} is the j:th measurement from the i:th individual. x_{ij} and z_i are so called fixed effects, i.e., behavior that can be explained by a certain variable, while ϵ_{ij} and η_i are random effects, i.e. the behavior of the system that can not be explicitly modeled, e.g., measurements errors. The function *f()* in (1.1) is quite often modeled as a system of ODE:s and have a connection to the kinetics of the system. The function *g()* is on the other hand derived on non-kinetic basis [10].

5.2 Building a two-compartment model in MathModelica System Designer

The course of biochemical processing of a drug in the body is divided into different phases. The phases for an oral dose are described by absorption, distribution and elimination. In the case of an intravenous dose, the absorption phase is usually ignored since the drug is injected directly into the blood circulatory system. From this compartment the drug may then be disposed to another compartment, e.g., the liver, where the drug is eliminated [11].

In the example below MathModelica System Designer [6] is used to create a two-compartment model where the first compartment is the blood circulatory system, where a drug is supplied by intravenous infusion. The drug is then disposed into another compartment where elimination takes place by Michaelis–Menten kinetics. This system can be described by (1.3) and (1.4)

$$V_1 \dot{x}_1(t) = -Q(x_1(t) - x_2(t)) + u(t) \tag{1.3}$$

$$V_2\dot{x}_2(t) = Q(x_1(t) - x_2(t)) - V_2\left(\frac{V_{\max}x_2(t)}{K_M + x_2(t)}\right) \tag{1.4}$$

where $u(t)$ is the rate of amount of the injected drug, $x_1(t)$ is the concentration of the drug in the blood compartment, $x_2(t)$ is the concentration of the drug in the elimination compartment, V_1 is the volume of the blood compartment, V_2 is the volume of the elimination compartment, Q is the flow from the blood compartment to the elimination compartment, V_{max} is the maximal rate of elimination and K_M is the Michaelis-constant (which is a measure of affinity between substrate and enzyme). We assume that a patient is receiving an intravenous infusion during 3 hours, which is modeled by a single pulse in MathModelica System Designer, see Figure 4.

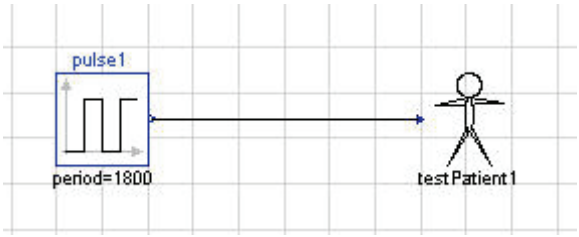

Figure 4. The infusion-patient system as it appears in the model editor.

Some patient groups have a reduced elimination capability because they have another genotype than the wild-type. In our example this is utilized by a 50% reduction for V_{max} and a 100% increase for K_M. Assume that we in our example have 7 patients from a group (Group A) with normal elimination capability and 5 patients (Group B) with reduced elimination capability. The actual drug concentrations in the different compartments during 24 hours for a patient is seen in Figure 5 (Group A to left and Group B to the right). From this figure it is quite clear that Patient Group B has a much slower elimination than Group A.

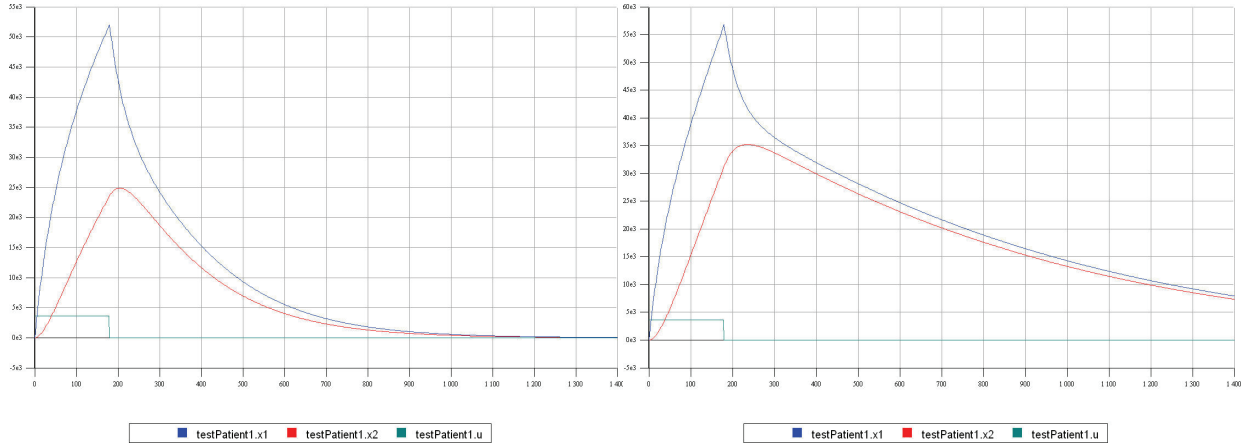

Figure 5. Concentrations during 24 hours in the blood compartment (top curve) and the elimination compartment (lower curve). The 3-hour infusion with constant rate is seen in the lower left corner. Patient Group A to the left and patient Group B to the right. (Note that the top value in the blood compartment for the two patient populations is slightly different, just above 50000 nmolar for Group A and 55000 nmolar for Group B).

Now assume that the concentrations in the blood compartment are being measured at 0, 30, 60, 180, 185, 210, 240, 300, 420, 600, 780, 1020 and 1440 minutes (24 hours) after the start of infusion in all 12 patients. A 10% measurement noise is added to all concentration values according to (1.5)

$$y_{ij} = x_{1ij} + 0.1 * x_{1ij} * \varepsilon_{ij} \tag{1.5}$$

Here y_{ij} is the measured concentration and ϵ_{ij} is a uniformly distributed random variable within the open interval,]-1,1[.

5.3 Parameter estimation in NONMEM

NONMEM is now used to estimate the parameters from the collected data. In the first run (EST1) a structural model and a parameter model is being used that do not account for different genotypes in Group A and Group B. In the second run (EST2) an indicator variable and an additional parameter *RED* are used in the parameter model to deal with the reduced elimination in Group B caused by the genotype. The reducing factor *RED* is assumed to affect both V_{max} and K_M in opposite but proportional ways, e.g., *RED*=0.5 implies half V_{max} and twice K_M.

True values from the simulations in Figure 5, initial estimates and boundary conditions given to NONMEM and estimated values from the two runs are given in

Table 1.

	True A	*True B*	*Initial*	*Min*	*Max*	*EST1*	*EST2*
V1	5	5	5*	-	-	5	5
V2	10	10	20	1	50	14.5	9.7
Q	0.1	0.1	0.5	0.01	5	0.0634	0.0933
Vmax	500	250**	1000	10	10000	178	793
KM	50000	100000**	10000	100	100000	70300	79300
RED	-	-	0.5***	0	1	-	0.485

Table 1. True values, initial estimates, boundary conditions and estimated values. *The blood volume is assumed to be known. **These values are obtained by multiplying/dividing with RED. ***That the true value for RED is also a good initial guess is not that unlikely.

On the average the estimated values of EST2 are closer to the true values than EST1. The minimum value of the objective function in the optimization is approximately 11.4 % less for EST2 compared to EST1.

6 Related Work

The use of functional genomics provides nowadays more and more information about the structure and dynamics of metabolic systems (including cholesterol metabolism), however, large amounts of data need more systematic approach than was used in biochemistry so far. Modeling and simulation can help by providing an inexpensive environment for quick testing of the ideas, thus reducing the needed biological experiments which are expensive, time consuming, and difficult to control.

Therefore, the relatively new field of Systems Biology is quickly spreading. It is now possible to model metabolic systems with considerable accuracy [9]. However, simulation of such large

complex models represents a serious problem to the simulation algorithms, causing algorithm instabilities and thus providing erroneous results. It is also difficult to extract the important information from such large models. Since metabolic pathways are very complex systems, a lot of partial knowledge of a single metabolic pathway exists that is spread over many groups that each uses different approaches to modeling or the models were created for different purposes.

In order to be able to store and interchange entire models between different pathway tools, several XML-languages have been developed. The non biology specific MathML is commonly used along with other more biology-specific languages such as SBML [4] and CellML [7]. On the other hand, bioinformatics tools that perform some more or less complex statistical analysis of the measurements are widely applied in functional genomics, first to eliminate noise from the measurements and then to extract the information. To compose a useful pathway model, all these aspects must be taken into account, and all the available information must be correspondingly integrated, which can only be achieved by standardizing the interfaces between different modeling and simulation, and bioinformatics tools. Modelica provides excellent support for such modeling and standardization.

7 Conclusions and Future work

In this paper we have briefly presented the BioChem library, the first free Modelica library for biochemical modeling. Its usefulness has been shown for three small applications. In the future, we expect that the power of the Modelica language will be increasingly used to model complex biochemical systems in nature. We will continue to improve the library and associated tools, as well as using it for increasingly complex applications, and are also developing import/export functionality between Modelica and model representations such as SBML.

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