



# EPISIM Platform

## Semantic SBML Model Integration

Movies

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### Abstracts

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We created a series of movies to demonstrate the semantic SBML model integration features of the EPISIM Modeling and Simulation platform. The original movie resolution is 1280 x 1024 pixels. Each movie can be played in the web browser (flash) or downloaded in wmv (Windows Media Video) format.

If you want to become familiar with the EPISIM platform we recommend taking a look at our video tutorials in which most of the platform's features are demonstrated. The tutorials are available under: <http://tiga.uni-hd.de/tissue-modelling.html> (flash movies as well as avi-files). The avi-files can be viewed in any video player if the XviD codec is installed.

In the following you will find a brief abstract for each movie of our series **“Semantic Integration of SBML models in graphical cell behavioral models and their simulation”**

### **Movie M1: Import of EPISIM SBML Demo Project and Tyson's Cell Cycle model**

We provide two EPISIM SBML Demo projects that can be imported by EPISIM Modeller.

These projects are available on our supplements website:

<http://www.tiga.uni-hd.de/supplements/SemSBMLIntegration.html>

The first project is the starting point used in our movies to demonstrate the semantic SBML Model integration capabilities. The second project reflects the final result that is used for simulation. The first movie shows how to build a EPISIM Modeller workspace and how the import of the provided projects works. Moreover, we demonstrate how EPISIM Modeller's working environment can be customized. Finally, a SBML is imported. We download Tyson's cell cycle model in the 2 variable and 6 variable version from BioModels database. Subsequently, the 2 variable version is imported. EPISIM Modeller's SBML Model editor enables to access the SBML model's species, parameters and fluxes.

### **Movie M2: Building a cell behavioral model a semantic link to a SBML model**

Here we give instruction how graphical cell behavioral models (CBM) can be semantically linked to an imported SBML model. We show step by step how to build such a graphical cell behavioral model. We build a cell cycle model that will control mitosis in our overall model of human epidermis. For the cell cycle model we define a mitotic threshold (MT) and a minimum time period between two cell divisions (MIN\_AGE\_DELTA). We reference the active MPF concentration in Tyson's cell cycle model (species *u*, here: *sbml\_u*). A cell divides when '*sbml\_u*' exceeds the threshold 'MT' and the minimum time 'MIN\_AGE\_DELTA' has elapsed. Subsequently, we embed this cell cycle model into the already existing keratinocyte model included in the demo project.

The EPISIM SBML Model Editor allows to sets two parameters a SBML model's time course simulation in COPASI. This allows modifying the time course simulation's precision and mapping of discrete simulation steps to time units. We show how and where to set these parameters.

In human epidermis only stem cells and transit amplifying (TA) cells proliferate. Therefore, we extend the existing cell differentiation model with an additional state element. The state element sets the SBML model parameter 'k6' from 1 to 2. This causes the transition from oscillating to steady state



behavior in the imported cell cycle model. 'k6' is set to 2 when a TA cell differentiates to a spinosum cell. This in turn corresponds to the cell state transition from proliferation to differentiation.

Finally, we use EPISIM Modeller's automated model validation to check the final cell cycle model. After correcting the errors we translate the graphical model into executable code. This code is stored together with the imported SBML model in a model archive file.

### **Movie M3: Import of a second SBML model and handling of namespace conflicts**

Multiple SBML models can be imported into one cell behavioral modeling project. In practice, the namespaces of two SBML models might overlap. However, the name of each species, parameter or flux must be unique in order to be unambiguously referenced in a CBM. For this reason we implemented an automated resolution of namespace conflicts. The name of the SBML model entities within the SBML model file remains unchanged. An automatically generated intermediate software layer maps the original name to the name after resolving the namespace conflicts during simulation.

To demonstrate this we import the 6 variable version of Tyson's cell cycle model. The SBML parameter 'k6' for example is defined in the 6 variable version as well as in the already imported 2 variable version of the model. The resulting namespace conflict is automatically resolved by adding a suffix to the parameter's name.

### **Movie M4: Optimization of simulation speed**

As mentioned before only stem cells and TA cells proliferate. After differentiation to a spinosum cell, the imported SBML model's parameter 'k6' is set to 2. This in turn leads to a change from oscillating to steady state model behavior in spinosum and granulosum cells. The time course simulation of this steady state in each spinosum and granulosum cell is computationally expensive and not necessary from the cell behavioral modeling perspective. As we have 90% spinosum and granulosum cells in the later tissue simulation we are able to increase the simulation speed significantly by turning off the time course simulation for these cells. Moreover, we are able to decrease main memory usage.

We demonstrate how to use the command 'SBMLSim' of EPISIM Modeller's function library to turn off time course simulation of a particular SBML model in a particular cell. We build a graphical cell behavioral sub-model which is controlling the time course simulation state. Finally, we embed this model in the overall epidermis model.

### **Movie M5: Model simulation and monitoring of simulation outputs**

After we completed the modeling part in our movie series, we proceed to the simulation part. We show how a model archive file can be loaded with EPISIM Simulator. After an exemplary simulation run, we define a chart to monitor the simulation output. In particular, we want to monitor a single stem cell and visualize the integrated SBML model's time course simulation by a chart. EPISIM Simulator provides an extendable algorithm library to evaluate the simulation output. There are algorithms to monitor a single cell as well as the tissue as a whole. A chart definition for a particular loaded model archive can be stored and reloaded. The so called 'chart-set' we defined in this movie is available on the supplements website (see abstract movie 1). We demonstrate step by step how to



define such a chart-set. Finally, we run the simulation again and show the real time monitoring of Tyson's cell cycle model simulation in a stem cell.

### **Movie M6: Link a cell behavioral model to 3D biomechanical model**

A cell behavioral model (CBM) is per default linked to a 2D biomechanical model. EPISIM Simulator automatically detects the connected biomechanical model. EPISIM Modeller can link a CBM to a different biomechanical model by importing a so called biomechanical model connector. We provide a 3D biomechanical model connector on the supplements website. We demonstrate how to import this connector into the existing Semantic SBML Integration project with EPISIM Modeller. After compilation of a model archive we start a 3D Tissue simulation. We re-use the chart-set of movie 5 to monitor the cell cycle model behavior in stem cells.

### **Movie M7: Cell cycle model behavior in different cells during simulation**

EPISIM Simulator allows storing of tissue simulation states at each simulation step in an xml-based format. Such snapshots can be used to share simulation results or as starting point of further evaluation with different parameter sets. We stored a 2D and a 3D tissue simulation state at step 3000 (available on supplements website). Moreover, we provide a chart-set with charts to monitor the behavior of Tyson's model (2 variable version) in stem cells and TA cells. The 6 variable model version is monitored in stem cells. We show how to load a tissue simulation state and how to load an existing chart set. During simulation we see the transition of oscillating to steady state cell cycle model behavior in a TA cell. This corresponds to the differentiation of this TA cell to an early spinosum cell.