

Sirius platform as environment for evolutionary development of mathematical models of complex biological systems

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Motivation and Aim: Development of mathematical models of complex biological systems is impossible from scratch. Such models can be developed only step-by-step, with incremental increasing of their complexity. This process is similar to the evolutionary one. However, this process is very time- and labor-consuming. For example, the most modern modular model of the human cardiovascular and renal systems for blood pressure regulation [1] still contains some part of the original Guyton model for overall regulation of circulation [2], that is already 50 years old. A rapid evolutionary development of mathematical models of complex biological systems requires a specialized software platform where models can evolve like living creatures (Table 1).

Table 1. Basic evolutionary processes for living creatures and mathematical models

Living creatures	Mathematical models
Multiplying	Easy copying from a repository
Living	Reproducibility – possibility to simulate and reproduce the original results
Mutagenesis	A model editing
Recombinations	Composing complex models from modules
Natural selection	Passing tests, correspondence to experimental results

Thus, the corresponding software environment should provide:

- a repository from which mathematical models can be easily copied. Thorough documentation about the models structure and parameters is also essential for further models development;
- editor (preferably both visual and textual) for model editing;
- support of modular approach for composing complex models from modules;
- simulation engine;
- test engine that checks the compliance of the model with certain conditions and experimental data;

- parameters fitting.

Methods and Algorithms: BioUML (<https://www.biouml.org>) – is a web-based integrated platform for systems biology and data analysis [3]. It supports visual modeling and development of hierarchical biological models that allow us to construct the most complex modular models of blood pressure regulation [1], skeletal muscle metabolism [4], and COVID-19 epidemiology [5].

Jupyter notebook/lab/hub (<https://jupyter.org/>) – Jupyter notebooks are widely used in biosciences for interactive and reproducible data analysis and visualization. We have integrated Jupyter notebooks into the BioUML platform using the Jupyter hub technology and developed Jupyter kernels for R, Python and JavaScript languages that provide access to BioUML functionality inside the corresponding notebooks. Jupyter notebooks can be used to reproduce the original results and model testing.

BioStore (<https://bio-store.org/>) – is the central hub, which provides collaborative research using the BioUML platform. For this purpose, it contains a registry of users, their projects, access rights to projects (several users can have access to the same project) and a list of publicly available servers where the BioUML platform or its derivatives are installed. Sirius (<https://sirius-web.org/>) – an information platform for projects related to the data analysis and modeling for educational and research projects of Sirius University. This platform combines the possibilities of the BioUML platform for modeling and data analysis and GitLab for project storage, management and documentation.

Results: To demonstrate the suggested approach, we have deposited into the Sirius platform the following complex mathematical models:

- blood pressure regulation [2]
<https://gitlab.sirius-web.org/virtual-patient/blood-pressure-regulation>
- skeletal muscle metabolism [3]
<https://gitlab.sirius-web.org/virtual-patient/muscle-metabolism>
- COVID-19 epidemiology [5]
<https://gitlab.sirius-web.org/covid-19/dde-epidemiology-model>

A user can easily clone the corresponding model from the git repository. A repository contains not only the model SBML code, but also detailed description, as well as Jupyter notebooks to reproduce the original results. Using the appropriate links from README file on the start page of the respective git project, a user can open the model in one click in the BioUML platform, edit it visually, simulate its behavior, as well as reproduce original simulation results using Jupyter notebooks.

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