The Open Systems Pharmacology Suite (PK-Sim® & MoBi®): An open source solution for whole-body physiologically based pharmacokinetics and -dynamics

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www.open-systems-pharmacology.org

Objectives

Vision & Mission of Open Systems Pharmacology

Vision
Robust and reliable, easy-to-use modeling & simulation tools, processes and models for pharmaceutical and other life-sciences applications qualified and accepted by a scientific community from academia, regulatory agencies and industry available and open to everyone.

Mission
Provide a platform for joint development, review & qualification, and application of state-of-the-art tools for PBPK and Systems Pharmacology modeling and an open library of models for application as well as method & tool qualification purposes. Promote the idea of pre-competitive open collaboration for the advancement of modeling & simulation sciences in pharmaceutical and life science.

Methods

Open Systems Pharmacology makes formerly commercial software tools PK-Sim® and MoBi® [1,2] available as freeware under the GPLv2 License [3] . All source code is publicly available on GitHub (github.com). A number of sub-pages have been established for easier navigation and orientation.

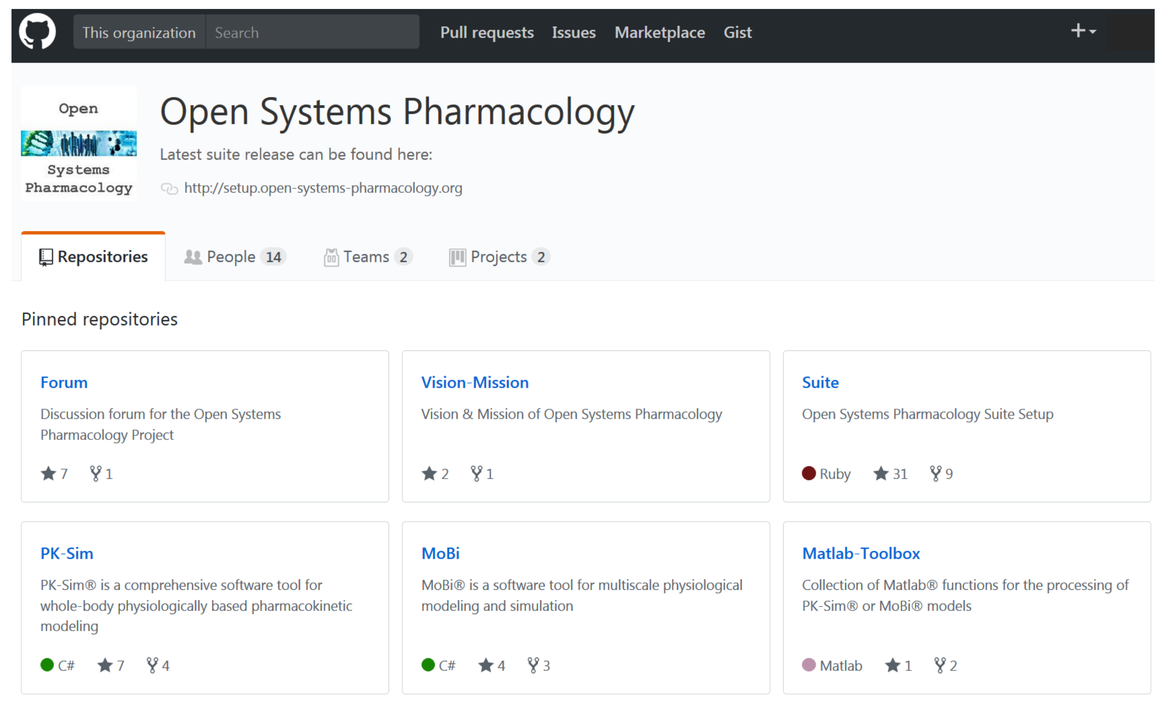

Figure 1: Screenshot of the Open Systems Pharmacology website on github.com

Top: Links to all sub-pages: Suite, PK-Sim®, MoBi®, Matlab Toolbox, other add-ons (e.g. R Toolbox) and models (such as Glucose/Insulin metabolism model), GPLv2 License information, information and tools required or helpful for coding.

Forum: Discussion forum for the Open Systems Pharmacology Project. Users can access a list of all ongoing and past discussions and start new discussions, requests, questions etc.

Vision-Mission: Short summary of the idea, goals and fundamental principles of the OSP community.

Suite: Description of Suite releases and components, system requirements, download of Suite setup, links to OSP code of conduct, coding standard, information on how to contribute.

PK-Sim/MoBi/Matlab-Toolbox: Description of PK-Sim® and MoBi®, access to source code, links to OSP code of conduct, coding standard, information on how to contribute.

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Results

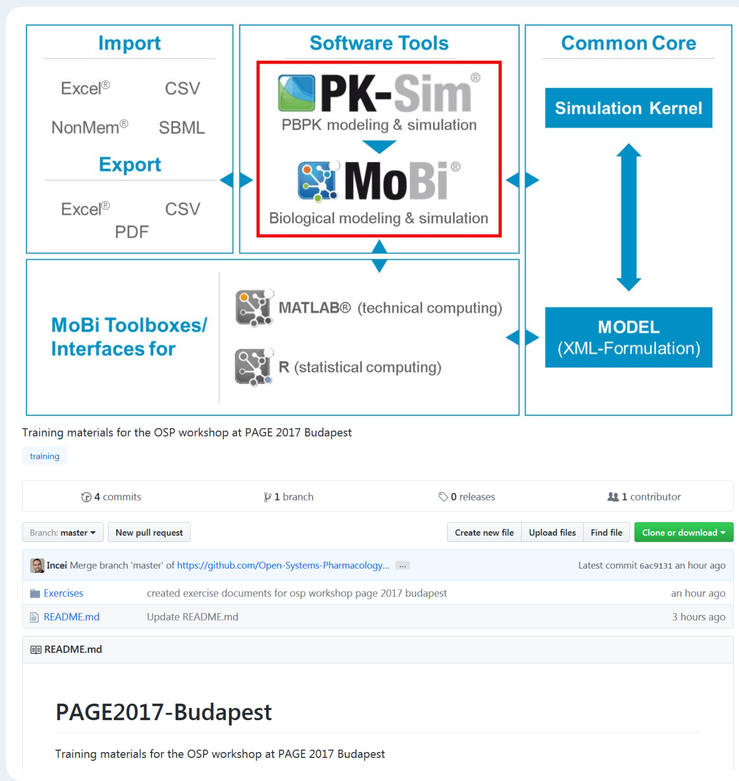
The Open Systems Pharmacology Suite: Unlimited Transparency and Modeling Flexibility

The OSPS comprises a set of individual software tools and has been designed using a modular concept to allow efficient, flexible, and transparent multi-scale systems pharmacology modeling and simulation. The central tools PK-Sim® and MoBi® [1,2] make use of building blocks for individual datasets like e.g. individuals, populations, administration protocols, compounds, reactions, spatial structures, etc. and models can be commonly used by both. While PK-Sim® is designed using a whole-body PBPK concept, the focus of its counterpart, MoBi®, is on allowing complete modeling flexibility and including interactions at the molecular level.

Figure 2.

Top: Overview of OSPS software tools, their interplay and import and export functions. PK-Sim® and MoBi® offer interfaces to other commonly used software tools Matlab® and R via toolboxes that are part of the OSPS.

Bottom: Training materials and exercises for learning and getting familiar with the OSPS software are available for everyone on the OSP website. Furthermore, a comprehensive manual including background information on the scientific basis of the software is installed together with the OSPS [4].



Example for a model as part of the community's growing repository: The physiologically-based whole-body model of the glucose-insulin-glucagon regulatory system

Within this repository, we distribute the physiologically-based whole-body model of glucose-insulin-glucagon regulation based on the model developed at Bayer and first published in [5]. The model (referred to as the Glucose Insulin Model or GIM in following) includes physiologically-based pharmacokinetics/pharmacodynamics (PBPK/PD) models of glucose, insulin, and glucagon, coupled by complex regulatory interactions on various mechanistic levels.
The model was updated to reflect software development over the years. The general description of implemented process provided in [5] is still valid and the user is encouraged to read the publication to get insight into model structure. Selected publications addressing the application of GIM are [6,7,8]. Extensions and updates are under development.

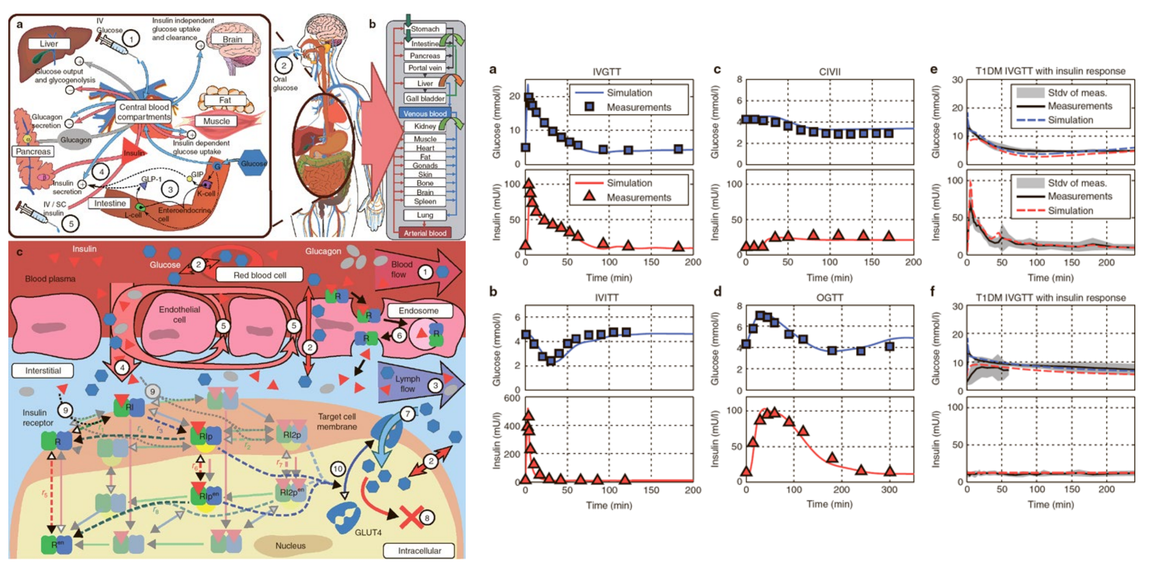


Figure 3: Overview of the Glucose-Insulin metabolism model. For details, see Schaller et al. [5]

The Forum: Active Participation and exchange

The Forum represents the starting point for exchange and communication between users of the platform. Topics regarding e.g. coding, model building, exchange of ideas and suggestions for improvement are discussed openly here, providing users with access to the knowledge pool of the community.

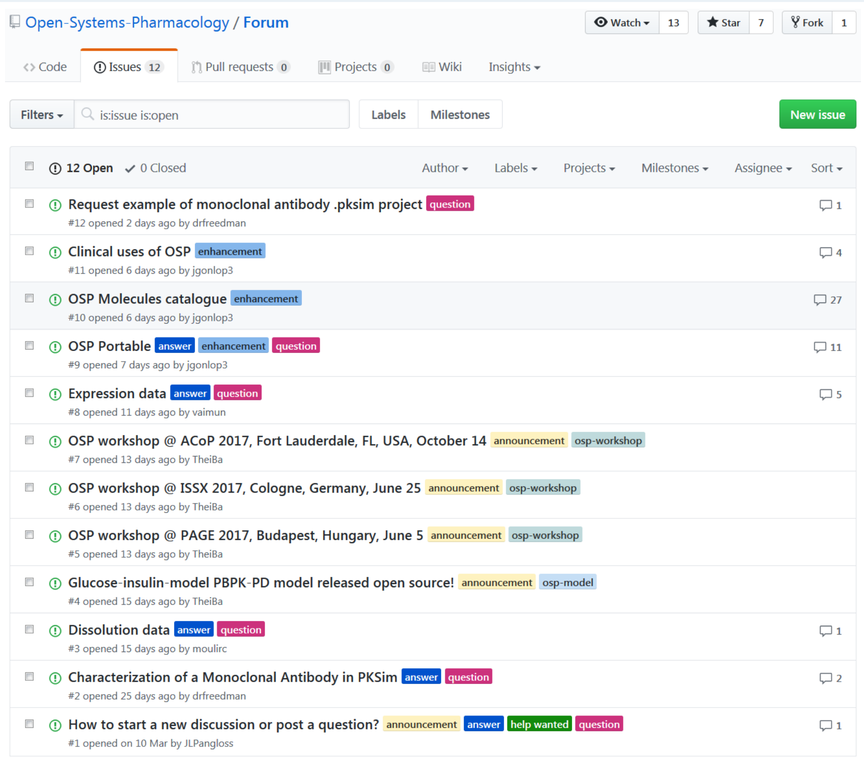


Figure 4: Screenshot of the Open Systems Pharmacology Forum on github.com

Conclusions

The Open Systems Pharmacology Suite makes powerful and flexible tools for PBPK and systems pharmacology modeling available open source under GPLv2. We invite everyone in the field of Systems Pharmacology, be it in academia, industry or regulatory bodies, to use the platform. Active participation of computer and modeling & simulation scientists in the further development of the modeling & simulation platform, the incorporated systems models, processes for their qualification and application etc. is encouraged and highly welcome. Please follow the community's activities on GitHub [4].

References

[1] Willmann S, Lippert J, Sevestre M, Solodenko J, Fois F, Schmitt W. PK-Sim®: a physiologically based pharmacokinetic 'whole-body' model. Biosilico. 2003; 1 (4): 121-124.

[2] Eissing T, Kuepfer L, Becker C, Block M, Coboeken K, Gaub T, Goerlitz L, Jaeger J, Loosen R, Ludewig B, Meyer M, Niederalt C, Sevestre M, Siegmund H, Solodenko J, Thelen K, Telle U, Weiss W, Wendl T, Willmann S, Lippert J. A computational systems biology software platform for multiscale modeling and simulation: Integrating whole-body physiology, disease biology, and molecular reaction networks. Front Physio 2:4.

[3] https://github.com/Open-Systems-Pharmacology/PK-Sim/blob/develop/LICENSE

[4] Open Systems Pharmacology Suite website and user manual at www.open-systems-pharmacology.org.

[5] Schaller S, Willmann S, Lippert J, Schaupp L, Pieber TR, Schuppert A, Eissing T. A generic integrated physiologically based whole-body model of the glucose-insulin-glucagon regulatory system. CPT: Pharmacometrics & Systems Pharmacology (2013) 2:e65; doi:10.1038/psp.2013.40.

[6] Schaller S, Willmann S, Schaupp L, Pieber TR, Schuppert A, Lippert J, Eissing T. A new Perspective on Closed-Loop Glucose Control using a Physiology-Based Pharmacokinetic/Pharmacodynamic Model Kernel. IFAC Proceedings Volumes (2012), 45(18):420-425.

[7] Schaller S, Lippert J, Schaupp L, Pieber T, Schuppert A, Eissing T. Robust PBPK/PD-Based Model Predictive Control of Blood Glucose. IEEE Transactions on Biomedical Engineering (2016), 63(7):1492-1504.

[8] Lahoz-Beneytez J, Schaller S, Macallan D, Eissing T, Niederalt C, Asquith B. Physiologically Based Simulations of Deuterated Glucose for Quantifying Cell Turnover in Humans. Frontiers in Immunology (2017), 8:474. doi: 10.3389/fimmu.2017.00474