Circulator Is a New Technique for Systems Pharmacology

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Introduction

Modern pharmacology is impossible without theoretical and computational methods for drug development and testing. The most popular methods of the theoretical pharmacology are Pharmacokinetics/Pharmacodynamics (**PK/PD**) modeling, **population analysis**, biostatistics, physiologically based pharmacokinetic modeling (**PBPK**) and other approaches which have become the ”gold standard” for any drug development for decades. The approaches help the pharmacologists:
• to integrate heterogeneous clinical and biomedical data;
• to improve and formalize the process of the decision making during drug development;
• to design a program of clinical trial;
• to check different hypotheses of drug mechanism;
• to estimate optimal regimes and doses for safety and maximal therapeutic effect.

Today new and more advanced methods are developed. The **“systems pharmacology”** approach represents the further evolution of theoretical pharmacology combining the methods mentioned above with the **“systems biology”** approach. These methods include the **mechanistic modeling** of drug and disease. One of the **main challenge** of such methods is combining of all possible kinds of information (pre-clinical, clinical, physico-chemical, biochemical) for all levels (molecular, cell, tissue and whole organism) from all sources (literature, measurements, clinical data).

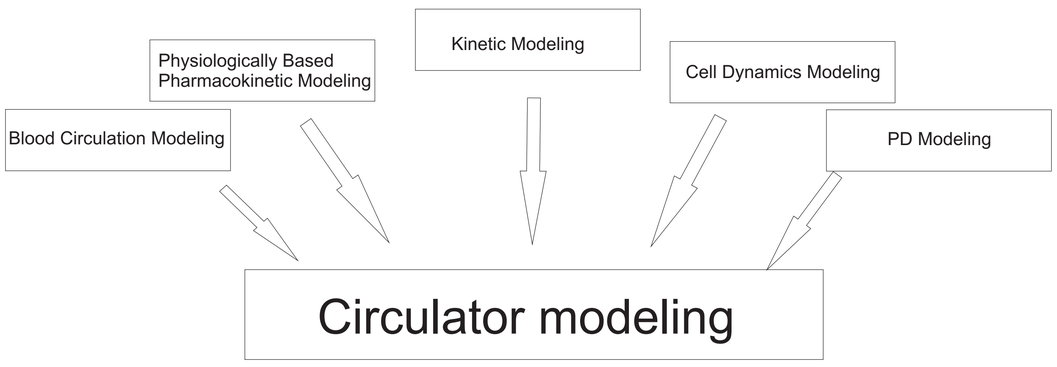
The limitations of the methods

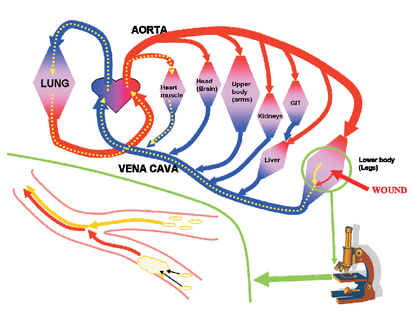
All the existing methods of system pharmacology work well only in the framework of conditions that dictated by their approximations but show unsatisfactory results for the wide range of other conditions. For example classical PBPK approach can simulate and predict the concentration of drug in different tissues in quasi-equilibrium approach but cannot simulate the biochemical reactions, pharmacodynamics or cell development for many cases. The **kinetic modeling** approach can simulate very complex systems including multiple compartments but it is unsuitable for simulation of processes in blood flow that is very important for drug simulation.

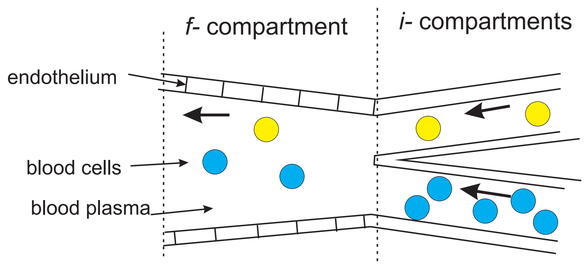
The main goal of Circulator modeling approach is the simulation of cellular and whole body processes in a wide range of conditions with detailed description of bichemical and cellular processes.

Institute for Systems Biology SPb have been developing the technique and software for modeling of complex biochemical system that simulate the behavior of metabolites and cells in vivo for whole organism.

Circulator Modeling Approach







Appoach description

Circulator describes the whole organism as the system of interconnected compartments which can exchange their liquid medium (blood) with the constant rate. Each compartment can be described as the kinetic model that includes fixed phase (tissues) and movable phase (blood). The blood includes plasma and blood cells.
Let’s look at compartment f in details. The main characteristics of the compartment are:
. blood cells number of of each type, subtype and group;
. concentrations of metabolites in plasma;
. concentrations of metabolites in blood cells;
. concentrations of metabolites in fixed cells.
The main problem for Circulator software is to answer how these values are changing within the time.

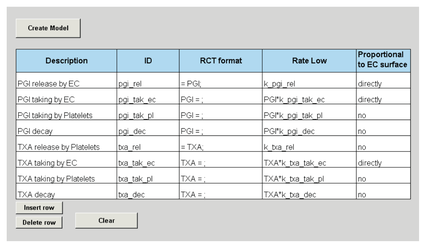
The capabilities of Circulator

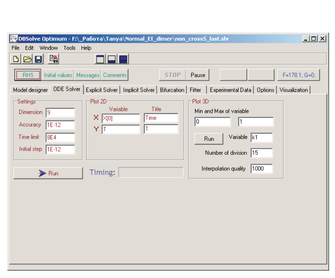
. Simulation of kinetics of “fast” and “slow” reactions in body;
. Modeling of non-equilibrium metabolites transport between cells and blood;
. Description of pharmacokinetics for short-lived molecules;
. Simulation of blood cell dynamics;
. Modeling of enzymatic reactions in tissue cells, flowing blood cells and plasma;
. Simulation of different states of blood cells.

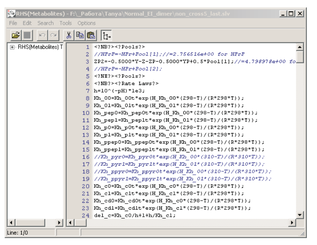
Circulator Software

The presented technology have been realized as the software package **“Circuator 3"**. The current version of software allows:
. To use any number of kinetic models (compartments) based on DBSolve Optimum software;
. To simulate multiple groups of each cell type;
. To describe enzymatic, non-enzymatic reactions and transport in blood plasma, tissues and blood cells;

On the basis of the software “Circulator 3” the models of following diseases and processes have been developed and analyzed:
. The universal model of blood recirculation which includes 20 organs and 2199 compartments. The model can be expanded for the description of any drug and metabolites in organism.
. The model of diabetes I and II types and different treatment regimes;
. The PK/PD model of prostacyclin after bradykinin treatment which describes different pharmacokinetics depending on location of injection;
. Spatial destribution model of Ca2+ dynamics in trombocytes after local activation or inhibition;
. The model of lipid exchange in human;



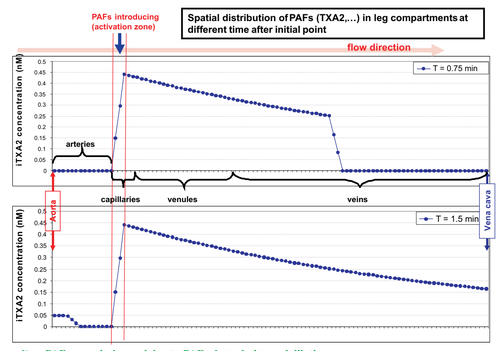




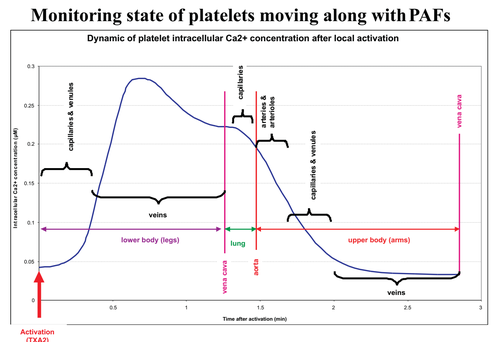
Example: the influence of NSAIDs on clot formation

We have developed mathematical model of blood circulation, kinetic models of platalets and endothelium cells. The model was applied to predict risk of clot formation at different parts of blood circulation system, to monitor effect of COX-2 inhibitors, to predict possible combinations of NSAIDs with low risk of clot formation. Totally the model includes 27170 equations, 39182 rate laws, 352 parameters.

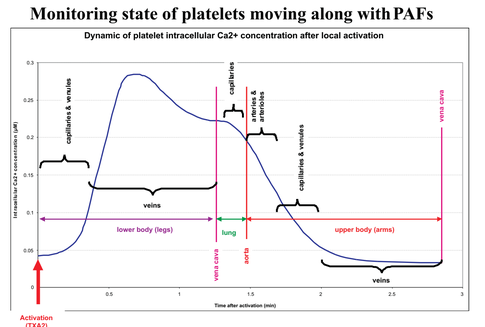
Circulator allows to present results of the virtual experiment in three different modes:
• Fixed time mode. Values of a selected variable are calculated in different parts of blood circulation system at the same time point. As a result we have spatial distribution of the variable across blood circulation system.
• Fixed space mode. Values of a selected variable are calculated in one selected part of blood circulation system at different time points. As a result we have temporal distribution of the variable in the selected part of blood circulation system.
• Drifting mode. Values of a selected variable are calculated for selected portion of blood which moves along the blood circulation system. As a result we have either temporal distribution of the “drifting variable” which is moving across blood circulation system.



1) PAFs wave is damped due to PAFs degradation and dilution
2) It takes about 1.5 - 2 minutes that PAFs wave arrives at place of its initiation (capillaries of legs)



1) We assume that intracellular Ca2+ concentration corresponds to a bility of platelets to form a clot
2) Maximal risk of clot formation is observed in leg veins
3) Capillaries of lungs and arms decrease risk of clot formation su bstantially



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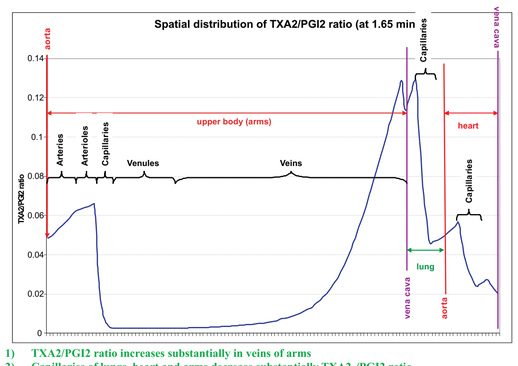

1) TXA2/PGI2 ratio increases substantially in veins of arms
2) Capillaries of lungs, heart and arms decrease substantially TXA2 /PGI2 ratio

Future plans

Today we are developing a new version of “Circulator modeling” software that allows to realize the possibilities. **“Circulator 4”** includes all possibilities of third version and some addition:
. A new interface and data structure which are more user-friendly;
. Description of any numbers of blood cell types;
. Including the subtypes of the cells i.e. states of cells and transitions between them;
. Simulation of blood cells that can flow or bind to endothelium depending on exact state;

* Please, visit **insysbio.ru** to read more about Circulator modeling and examples as well as about other projects of Institute for Systems Biology SPb.

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