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Modern Approaches to Drugs Research and Development Using Mathematical Modeling

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Abstract. Modern drug design and development is a complex process that brings together numerous chemical, biological and clinical disciplines. The paper considers modern approaches to the research and development of new drugs based on pharmacodynamics and pharmacokinetics modeling. The basic concepts are considered. Software tools for such kind` of modeling under large amounts of data are described. As an example, the model of a drug impact on tumor growth, built in MATLAB SimBiology, is presented.
Keywords: drug research and development, PK PD modeling, MATLAB SimBiology.

1. Introduction

Present difficulties in drug development include an increase in cost and duration of drug development, and only few new medical entities reach approval. According to [1], it takes from 10 to 15 years to bring a new drug to market — at a cost of more than $1 billion. A key contributor to these racking costs is a late-stage failure: of every 250 compounds that enter preclinical testing, only five proceed into clinical trials, and only one will be approved by the U.S. Food and Drug Administration (FDA). Many new potential drugs fail because researchers lack reliable information about their behavior. That leads to problems for both pharma industry and public health. Moreover, one can observe some lack of interest of drug pharma for some disease areas due to high potential costs of research.

At the same time, with only a partial understanding of the link between dose and response, and knowing little about the drug concentration in the body over time, researchers often cannot guarantee a drug safety until it is too late in the development process. The FDA's 2004 Critical Path Report proposed, among other solutions, the increased use of model-based approaches to drug development–including pharmacokinetic and pharmacodynamic (PK/PD) modeling [2].

In a confirmation of the need for such approaches, the FDA announced funding for the UCSF-Stanford Center of Excellence in Regulatory Science and Innovation, a joint effort created to get more advantages out of diverse data sets and to create computational tools to accelerate drug development [3].

Recently, it has also been suggested to expand the use of simulations in support of clinical drug development for predicting outcomes of planned trials. This approach is

based on using PK/PD models on the population level together with random sampling techniques. Modern simulation techniques assist in assessing disease progression and behavioral features like compliance, drop-out rates, adverse event dependent dose reductions, etc. Computer simulation helps to evaluate consequences of design features on safety and efficacy assessment of the drug, enabling identification of statistically valid and practically implementable study designs [4].

2. PK/PD modeling — the core of drug research and development

Modeling and simulation are based on the use of mathematical models that, in turn, are simplified representations of the considered complex system. It has been proposed to integrate pharmacokinetic (PK) and pharmacodynamic (PD) principles into drug development to make it more rational and efficient. A survey on 18 development projects showed that a PK/PD guided approach can aid to boost the drug development process [4].

Pharmacokinetics is the study of what the body does to a drug after administration. It studies absorption, distribution, metabolism, and excretion` of drugs in the body. It can be summarized in two main processes: absorption and disposition [5, 6]. It is possible to build models of varying complexity. In single compartment models, one can concentrate on what happens in the central system. At the same time, multi-compartment models are more accurate, as there is an opportunity to consider peripheral compartments, such as surrounding tissue, and the drug transfer between these compartments. Pharmacodynamics is the study of what the drug does to the body [5, 6]. It examines biochemical and physiological effects of a drug on the body, as well as relationship between drug concentration and effect.

In pharmacokinetic models a human body is described as a set of compartments. A drug is injected into the blood with profile $u(t)$ (Fig. 1). It moves from the central compartment C to the peripheral compartment P with profiles $x_c(t)$ and $x_p(t)$. The main task is to identify the parameters in the reactions and to use this knowledge to infer the hidden state responses. Such physiological parameters as clearance of elimination, volume of distribution, and rate constants are taken into account.

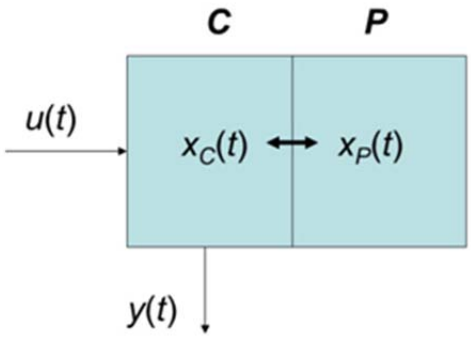

Figure 1. Simple pharmacokinetic model

In summary, we can say that PK model is a model that describes the time course of drug concentrations over time; PD model is a model that describes the relationship "effect vs. concentration"; and there is also a model that links PK measurements to the PD observations and that plays a role of a link between PK and PD models (Fig. 2). Together they represent PK/PD model which is extremely important for the pharmaceutical industry. With the help of PK/PD modeling and simulation, there is a possibility of earlier understanding of the link between drug and response [1]. This knowledge leads to better characterizing of a drug's absorption, distribution, and elimination properties. Such models may be of help when prescribing the right amount of drug to a patient. They may also be applied when predicting the pattern of the body's response to different drug dosages. With good models, chemists that examine new potential drugs can test out formulations of various drugs to see their effects. This saves time and avoids potential hazardous testing. Another benefit of PD modelling is monitoring any unwanted side-effects of drugs.

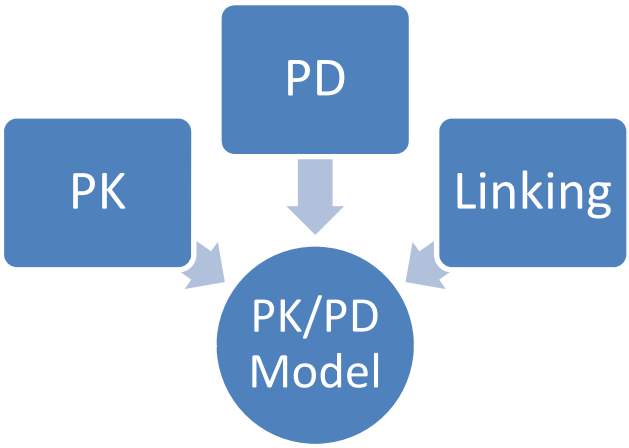

Figure 2. Scheme of PK/PD model parts interaction

In general, such models can be presented in the form of linear ordinary differential equations system (ODEs). In the simplest case, for the model shown in fig. 1 it will have the following form:

$$\begin{aligned} \frac{dx_c}{dt} &= \left(-k_{el} - k_{cp}\right)x_c(t) + k_{pc}x_p(t) + u(t), \\ \frac{dx_p}{dt} &= k_{cp}x_c(t) - k_{pc}x_p(t), \end{aligned} \qquad x(t_0) = x_0.$$

As an output, we can observe one noisy transformed drug concentration

$$y(t) = x_c(t)/V + \varepsilon(t).$$

Here the additive measurement noise ε (errors) is assumed to be i. i. d. $\aleph(0, \sigma^2)$;. $\mathbf{x} = \{x_c(t), x_p(t)\}$, and $u(t)$ are the state and input column vectors; x_0 is the initial states

vector at time t_0; V is compartment volume, and positive parameters $\{k_{el}, k_{cp}, k_{pc}\}$ characterize reaction rates.

Linear state space model in this problem can be rewritten as:

$$\begin{bmatrix} \dot{x}_c(t) \\ \dot{x}_c(t) \end{bmatrix} = \begin{bmatrix} -k_{el} - k_{cp} & k_{pc} \\ k_{cp} & -k_{pc} \end{bmatrix} \begin{bmatrix} x_c(t) \\ x_p(t) \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \end{bmatrix} u(t),$$

$$y(t) = \begin{bmatrix} 1/V & 0 \end{bmatrix} \begin{bmatrix} x_c(t) \\ x_p(t) \end{bmatrix} + \aleph(0, \sigma^2),$$

or, in the matrix form:

$$\dot{\mathbf{x}}(t) = \mathbf{A}\mathbf{x}(t) + \mathbf{B}\mathbf{u}(t),$$

$$\mathbf{y}(t) = \mathbf{C}\mathbf{x}(t) + \aleph(0, \sigma^2).$$

For such a system there are two problem types: the first one is simulation: Given $\mathbf{u}(t)$, x_0 and $\{\mathbf{A}, \mathbf{B}, \mathbf{C}\}$, one needs to calculate $\mathbf{x}(t)$ and $\mathbf{y}(t)$. The second one is parameter estimation: Given $\mathbf{u}(t)$, x_0 and $\mathbf{y}(t)$, one needs to estimate $\{\mathbf{A}, \mathbf{B}, \mathbf{C}\}$ matrices and noise model.

It needs to be mentioned that in [7] it is shown that such kind of linear ODEs is not prevalent for representation of most biochemical reactions. More generally, and more applicably, we can consider ODEs that are linear in their unknown parameters, but not necessarily states. For instance, the Michaelis-Menten enzyme kinetics, models are all bilinear in the states but linear in parameters [7]. It should also be noted that using ODEs to model biochemical reactions assumes that the system is well-stirred in a homogeneous medium, spatial effects (such as diffusion) are irrelevant, and the system has a large number of molecules for each species [7, 8]. If this constraints are not valid, either partial differential equations should be used or a discrete stochastic model will be more appropriate, as in such models individual molecular interactions may be considered.

3. Modern simulation tools and there advantages

What are the challenges with in silico biochemical modeling? First of all, often it is very difficult to accumulate knowledge from experimental data, intuition, literature, and other models. Secondly, modelers and scientists have difficulty communicating knowledge and sharing work. Mathematical methods for solving these models sometimes are developing faster than the corresponding computer tools. Finally, several different tools are needed to complete entire workflow. There is an increasing demand for software packages that allow to integrate the main parts of modeling process under a single programming environment: building a model using both predefined blocks and one's own programmable modules, simulation, estimation of model parameters using experimental data, and conducting sensitivity analysis of model key parameters to changes in input data.

As more and more frequently used packages the following software products should be mentioned: NONMEM® (ICON Company), Phoenix® (Certara Company), Monolix®

(Lixoft Company), and MATLAB (MathWorks Company). NONMEM® is a well-known and widely used software tool, mostly for modeling population pharmacokinetic [9]. Phoenix® is a software platform for managing, analyzing and reporting pharmacokinetic, pharmacodynamic and toxicokinetic data [10]. Below I would like to elaborate on the possibilities of a rather new software tool, namely, MATLAB SimBiology [11].

MATLAB SimBiology package provides one environment for both graphical and programmatic pathway analysis (Fig. 3–4). It may be considered as a tool for modeling, simulating and analyzing dynamic systems, focusing on pharmacokinetic/pharmacodynamic models and systems biology applications.

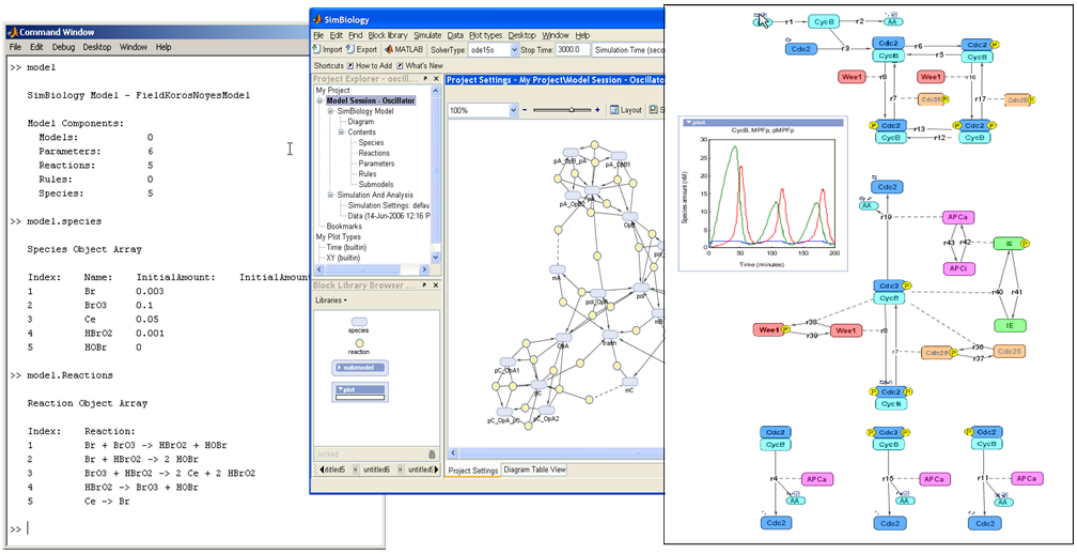

Figure 3. SimBiology interface example

Similar to MATLAB Simulink, the key features of SimBiology include building a model (possibility of using block-diagram editor and MATLAB code, as well as importing SBML files), running a simulation, both deterministic and stochastic, and analyzing a model (estimating parameters, conducting sensitivity analysis, and examining model in parts). The last one is of particular interest when one tries to consider a pathway without some part of it.

4. Case study — evaluating the effect of therapy on tumor growth using SimBiology

The following example illustrates the behavior of a tumor growth in the presence of an antitumor drug or a combination of drugs.

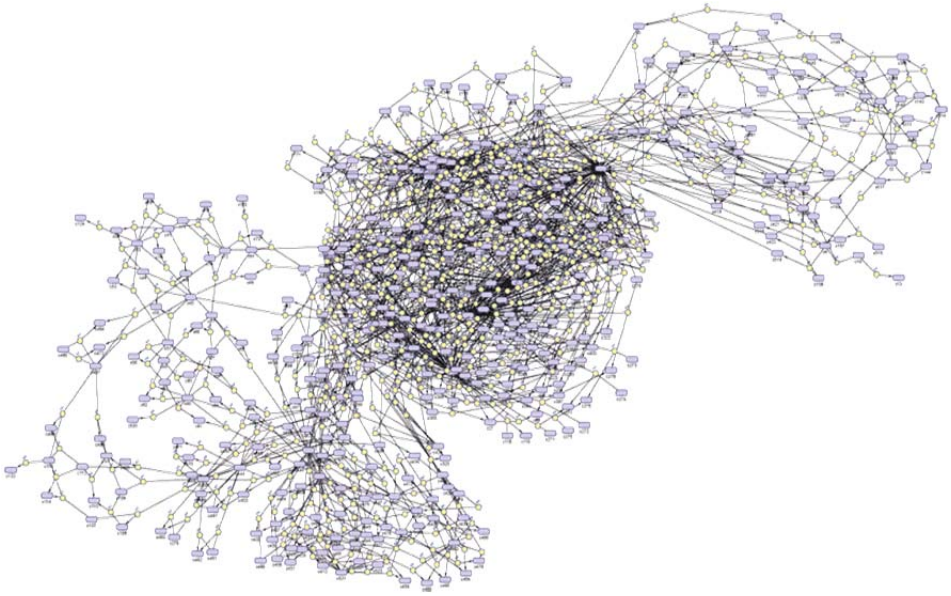

Figure 4. SimBiology Model created by Merrimack Pharmaceuticals [12]

Impressive progress in our understanding of the molecular and cellular biology of cancer has been made in the past three decades. However, studies show that only about 10% of oncology products have proven to be successful in clinical development, with the cost of a new drug being brought to market of over $1 billion [13, 14]. Using simulation PK/PD modeling it is possible to examine whether there is an interaction between several drugs or if the drug effect is purely additive. After building the model it is also possible to simulate different scenarios and dosing strategies to understand how they affect tumor growth over time.

As an example, the model developed in [15] will be used. In this paper authors examine the tumor growth in mice. The model with two anticancer agents was considered. A detailed review and analysis of the implementation of this model in SimBiology can be found in [16].

In terms of differential equations, we have the system presented in Fig. 5. Here w is natural cell proliferation, and w_0 represents the tumor weight at the inoculation time $(t=0)$. Tumor growth is known to follow an exponential growth followed by a linear growth component [18, 19], therefore, λ_0 and λ_1 are parameters that represent the rate of exponential and linear growth, respectively. The value w_{th} (threshold tumor mass at which the tumor growth switches from exponential to linear) can be expressed as a function of λ_0 and λ_1. Then, one can consider combined model accounting for exponential and linear tumor growth. The ψ parameter, when it is big enough, allows the system to switch from the exponential to linear growth sharply.

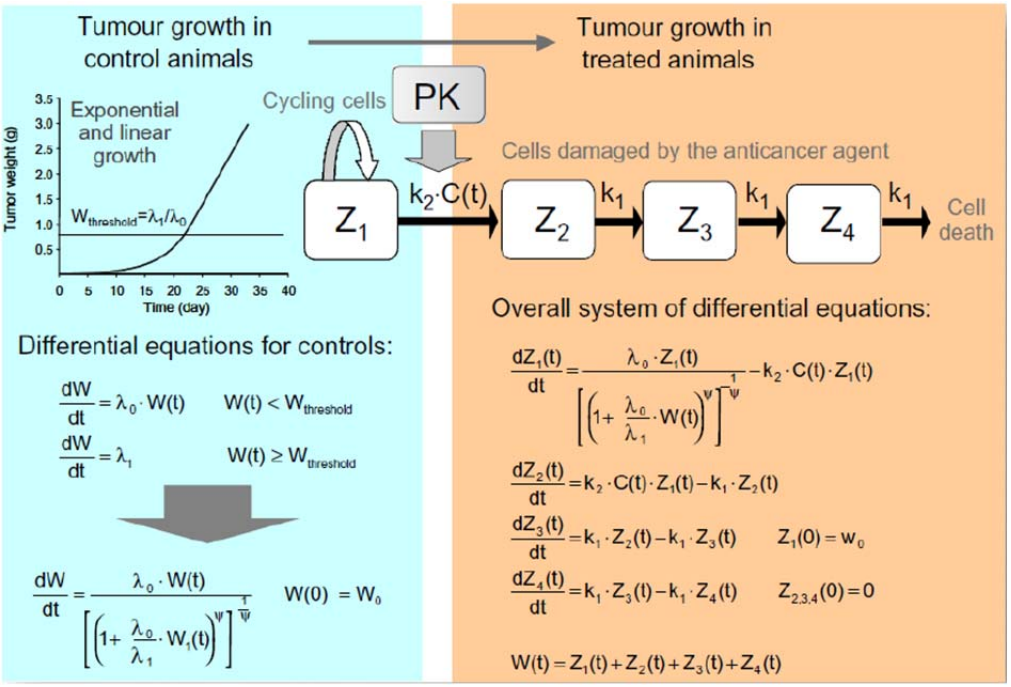

Figure 5. Linking Tumor Growth to Drug Exposure [17]

The delay between drug intake and tumor cells death is modeled using a multi-compartment model (x_1, x_2, x_3 and x_4), this is characterized by a damage rate constant k_1. The average time-to-death of a damaged cell is equal to n/k_1 (where n is the number of compartments).

The model assumes that the drug elicits its effect decreasing the tumor growth rate by a factor proportional to $C_p(t)$ (plasma concentration of the drug) through a constant parameter k_2, which is an index of drug efficacy [14].

Here in the absence of drugs x_1 represents a growing tumor, and x_2, x_3, x_4 describe decaying tumor cells (Fig. 6). Thus, total tumor weight is sum of the mentioned variables. At the presence of an anticancer agent the tumor goes over sequential series of transformations. The first transformation is dependent on the plasma concentration of the drug, given here by C_p.

After creating a model from blocks library in SimBiology using given equations and running a simulation, one can then work with an appeared interactive MATLAB User Interface (UI) and continue to simulate the effective dosing strategies on tumor growth (Fig. 7).

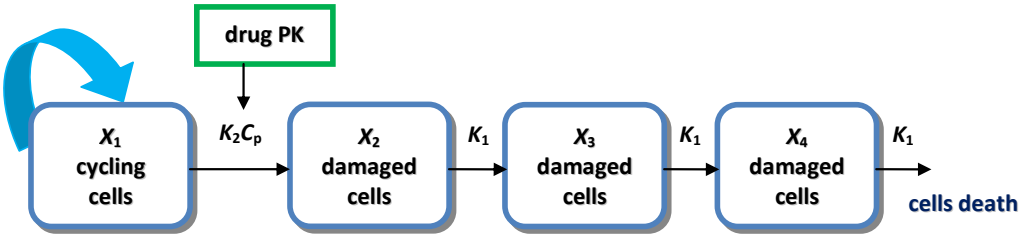

Figure 6. Scheme of the PK/PD model:
k_1 — first-order rate constant of transit; k_2 — measure of drug potency;
$c(t)$ — plasma concentration of the anticancer agent [17]

In the absence of tumor drug one can observe the profile of tumor growth over time (black line on the fig. 7). After introducing a drug A to the system (and in this case we can choose the dosage, starting date, and therapy duration and regimen), we can evaluate the effect on the tumor (red line on fig. 7). Modeling in SimBiology provides a possibility of adding several drugs and, thus, simulating the cumulative effect of combination therapy.

One feature worth mentioning here is the ability to see underlying equations of the model. This is extremely useful while building and exploring models, as it provides a possibility of changing the equations according to one's needs.

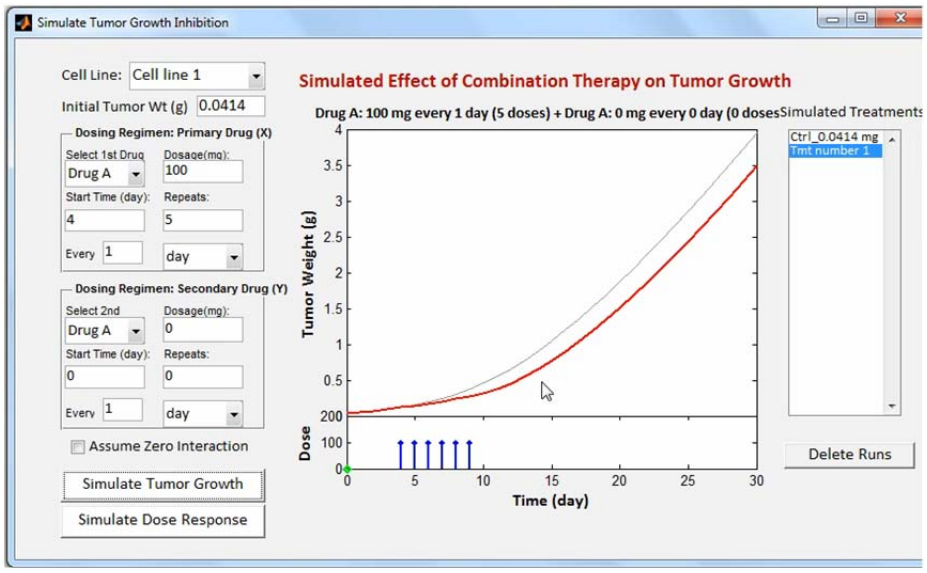

Figure 7. UI showing effect of combination therapy on tumor growth

After finishing PK part, one can move on to assessing the tumor growth using data from experiments. Simulation viewer provides a tool to quickly assess the effect of different parameters on a time profile of a drug uptake. Further simulation allows finding the

best fitted parameters for the model. In the considered example the tumor decay process is a function of concentration of Drug1 and Drug2. Running simulation with different parameters provides an opportunity to evaluate the dynamics of tumor behavior over time (Fig. 8).

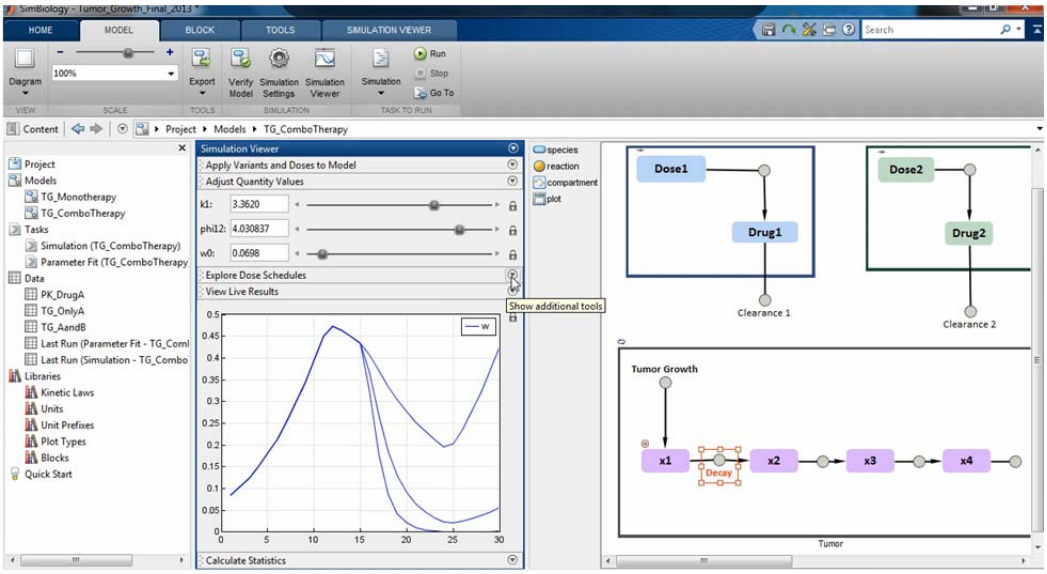

Figure 8. Simulation viewer (tumor growth over time, three lines correspond to different parameters)

5. Conclusions

The role of math modeling in drug development is becoming more mainstream and accepted. Modeling allows a better understanding of mechanisms and provides an opportunity for predictions outside the domain of the studies used to develop the model [6]. Thus, among others we can name two main reasons for creating quantitative biochemical computer models. The first is that biochemical pathways start out simple and quickly grow in complexity. Therefore, testing pathways via experiment is expensive in both time and money [20]. And the second is that computer modeling narrows the range of experiments. Once created and validated, such model can be used for testing new ideas and approaches much faster than through experimentation. Such Big Pharma companies as Novartis, Merrimarck, Merck, Pfizer and others are already using innovative technologies, including MATLAB Simbiology, in their Drug Research and Development [21]. According to Birgit Schoeberl from Merrimarck Pharmaceuticals [22], "Model-based drug design enables us to rapidly identify optimal pathway targets and determine the best approach. The models inform our decisions throughout drug development, enabling us to develop targeted therapeutics with higher efficacy and fewer side effects."

PK/PD modeling may enable the pharmaceutical industry to move into patient studies faster and safer [23]. Being a standard in other knowledge-based industries, computer modeling is a state of art tool that is being widely used to aid drug research and development. As increased volumes of information require sophisticated new analyses and visualization techniques, there are still various problems where academic research is needed. With this approach the future lies with collaborative work between biologists, pharmacologists, chemists, engineers and mathematicians.

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Современные подходы к исследованиям и разработке новых лекарственных средств с использованием математического моделирования

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Аннотация. Создание и разработка современных лекарственных средств представляет собой сложный процесс, который объединяет различные химические, биологические и клинические исследования. В работе рассмотрены актуальные подходы к исследованию и разработке новых лекарств на основе моделирования фармакодинамических и фармакокинетических процессов. Описаны программные средства для такого рода моделирования при больших объемах данных. В качестве примера представлена модель воздействия лекарств на рост опухоли, построенная в пакете MATLAB SimBiology.
Ключевые слова: исследование и разработка лекарственных средств, фармакокинетика, фармакодинамика, моделирование, MATLAB SimBiology.

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