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WebPK, a web-based tool for custom pharmacokinetic simulation

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I: Introduction

Novel drug development is an expensive and time-intensive process, despite advances in large throughput screening procedures over the past 100 years. Due in part to increases in complexity, regulations, and the length of pre-market studies, the typical cost to bring a new drug to the public is over 800 million USD, an increase of 30% over the past ten years[1].

Previous studies have shown that the major reason for the failure of candidate drugs is drug distribution, delivery, and retention in the human body (pharmacokinetics). The typical strategy to alleviate human pharmacokinetic issues, i.e. *in vivo* evaluation in an animal model, does not solve these problems conclusively. Studies often show that there is little correlation between bioavailability in humans and in common animal models[2]. Due to this general trend, there has been a push in recent years towards computational modeling and simulation of drug pharmacokinetic (PK) characteristics for improved accuracy and expedited results. Previous comparative studies have shown that computational PK models can produce accurate representations of experimental data for both animal and human models[3]. These promising results point toward increased utilization of computational methods to ascertain drug behavior and drug-body interactions before any clinical trials are undertaken. Furthermore, for existing drugs, simulation represents an opportunity to personalize therapeutic drug regimens on a patient to patient basis.

A. Existing Tools

PK Solutions is a Microsoft Excel-based application that can be used to calculate a wide variety of PK model parameters from several types of concentration data, including blood, serum, plasma, and lymphatic fluid. Using curve-stripping and under-the-curve methods, the application can determine up to 75 different parameters and compare model results automatically. Several important user interaction methods are incorporated: users can input a number of PK parameters from which to start the simulation, and can dynamically update

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the model to observe the effect of perturbation. PKSolutions is a powerful tool, but it is neither free, nor portable, which makes it unlikely to have widespread clinical impact.

There are already several previous PK modeling tools available on the market, including PKSolutions[4], PKCalculator[5], and WinNonlin[6]. While these tools offer a multitude of capabilities, they are either costly, require extensive installation, are not portable, or are not flexible to a variety of drugs. WebPK solves these issues by providing an open-use, online platform for pharmacokinetic analyses, accessible from any device with an internet connection. The target users for WebPK are the academic drug developer and the primary care physician. We keep these users in mind for the following survey of existing tools.

Like PKSolutions, WinNonlin is a powerful Excel-based PK software package that focuses on non-compartmental analyses. In addition to similar computational capabilities, WinNonlin emphasizes reuse and combination of preexisting models, as well as the ability to run multiple models within the same project space. For compartmental models however, WinNonlin requires users to create complicated model definition files which are beyond the expertise of the novice user.

PK Calculator is a cell-phone based application for PK analysis. While it is extensive in its capabilities, it is restricted to work only with two drug types: aminoglycosides or vancomycin. Many of the capabilities provided by PKCalculator depend on establishing a database of patient records, and are too specialized to be used in a widespread research basis in which new drugs are being developed.

Despite the capabilities that existing applications offer, there are no widespread, easy-to-use platforms for PK biomodeling. With our new WebPK application, we aim to circumvent these barriers to usage by providing an online interface to conduct compartmental PK analyses of arbitrary size. Because all computational work is done on the host-side server, an internet connection is all that is required for use. An important implication of this is that WebPK is suitable for use on mobile devices.

II. Methodology

A. General Pharmacokinetic Model

WebPK implements a compartmental model with flow rates described by a first order kinetic model commonly used in a variety of chemical and biological systems[2][7]. In this scheme, each compartment represents a division of the body, which can be interpreted as blood supplies, specific organs (liver, kidney, etc.), collections of tissue, or states (i.e. free or protein-bound). Analogously, PK rate constants represent relative volumetric flow rates between compartments and clearance due to metabolic degradation or bodily excretion[3]. Each compartment's concentration is governed by a first order linear differential equation, which dictates that the rate of change for a concentration at any given time is the sum total of the inflow and outflow rates. A system of three compartments is shown in Figure 1. above, with each arrow representing the flow between any two compartments, i.e., k_{12} is the coefficient of flow from compartment 1 to compartment 2, k_{21} is the coefficient of flow from compartment 2 to compartment 1, and d_1 is the clearance rate in compartment 1.

The representative differential equations for this example are as follows, with clearance/outflow rates shown as negative terms, inflow as positive terms, and S_n is the current concentration in the n th compartment:

$$\begin{aligned}\frac{dS_1}{dt} &= -d_1S_1 - k_{12}S_1 - k_{13}S_1 + k_{12}S_2 + k_{31}S_3 \\ \frac{dS_2}{dt} &= -d_2S_2 - k_{21}S_2 - k_{23}S_2 + k_{12}S_1 + k_{32}S_3 \\ \frac{dS_3}{dt} &= -d_3S_3 - k_{31}S_3 - k_{32}S_3 + k_{13}S_1 + k_{23}S_2\end{aligned}\quad (1)$$

This can be generalized for an arbitrarily large system:

$$\frac{dS_n}{dt} = -d_nS_n - S - n \sum_{j \neq n} k_{nj} + \sum_{j/\text{neqn}} k_{jn}S_j \quad (2)$$

Time series concentrations of S_n can be generated by integrating these equations, given initial conditions. Typically, concentrations all begin at zero in order to reflect the fact that the patient enters the study without any drug in their system. Administration of drug is discussed in the following section.

B. Dosing

In addition to the unforced system dictated by the PK rate equations, bolus and continuous intravenous (IV) dosing can also be used to introduce drug to the system. To utilize this optional capability, the user must specify a compartment to receive the dose (e.g. one representing plasma) and the dose amount. For bolus dosing, an addition time vector, consisting of a start time, end time, and frequency of dosing, is required. During the subsequent simulation, the specified compartment's concentration is incremented by the bolus dose appropriately at the specified times.

In the case of IV dosing, the specified amount will be added at every time epoch; no additional timing information is required. Thus, IV dosing is essentially bolus dosing with a maximally dense timing vector.

C. Implementation

The WebPK web interface is implemented using PHP, while computations are executed using a number of Matlab scripts on a remote server. A workflow diagram is shown in Figure 2.

The user is first prompted to either (1) provide the name of a previous session to be restored, (2) upload a file which specifies all system parameters, or (3) specify the number of compartments for a new model. For newly created models, a new web form is dynamically generated, containing input fields for describing a PK system with the user-supplied number of compartments. A list of fields is shown in Table 1. Note that in Table 1, N is the number of compartments in the model. Once the user has completed this web form and has thus fully

described the model, the user is shown a visualization of the model topology and asked to verify that the visualization matches the input. If the user has uploaded a parameters file, this visualization is the first thing the user will see. Once the user verifies the model visualization, the model is simulated on the server, and the user is directed to a results page. The results page includes files specifying time series concentration data for each compartment, as well as graphs showing these concentration profiles over time. The user is also provided with a model parameters file which is suitable for uploading to WebPK. Each simulation is saved under a user-specified name so that previous simulation results can be reviewed quickly by specifying the experiment's name on the homepage. Conversely, the user can delete all simulation-specific files from the server upon completion.

D. Visualization

Prior to calculation of simulation results, WebPK displays a simple visualization of the entered model for user confirmation. This diagram is created using Graphviz, an open-source graph visualization software package[8]. The visualization is a directed graph, with compartments as nodes, and the PK rate constants shown as labels on the graph's edges. For clarity, all edges with rate constants equal to zero, i.e. no flow, are omitted from the diagram. Figure 3. shows an automatic topology visualization running on an iPhone for an arbitrary model with five compartments.

E. File Formats

WebPK provides limited support for SBML parameter file upload. Parameter sets created through WebPK's standard interface are also made available in SBML format for download and subsequent use. A template document is provided on the homepage for download and editing. Uploaded SBML files are parsed into the computation routine using Matlab's SimBiology Toolbox capabilities.

In addition to the output graphs produced, WebPK also provides a comma-separated-values (CSV) file with all compartments' concentrations at all time points. As discussed earlier, all of these files can be retrieved at any future time by providing the simulation name.

III. Results and Discussion

A. Clinical Use Case

As an example of WebPK utilization, we take a previously published two-compartment model[9] which has previously been used with bolus dosing[10]. This model simulates the effect of a periodic Taxol dosing regimen similar to those used in cancer treatment protocols, but in a mouse model. The parameters used in this simulation, shown in Table 2, are taken from the original study[9].

For our case study, we use the experimental Taxol dosing regimen as tested by Wang et al. [11]. The five distinct bolus doses occur at 7, 14, 21, 28, and 35 days. The Graphviz representation of this model is shown in Figure 4.

The effect of these doses is better observed in the log-scale. WebPK provides two output graphs for this simulation, shown in Figure 5. The changes in tissue concentration

(compartment 2) are better seen with the vertical axis log plotted. As can be seen in the figure, bolus doses in compartment 1 (plasma) are quickly eliminated relative to the increase the concentration in compartment 2 (tissue).

IV. Conclusions

We have presented a novel web-based tool for customized pharmacokinetic simulation on the organ level. Our system incorporates a compartmental PK model with user-specified timing, rate parameters, and optional bolus dosing. Inputs may be entered by hand, or uploaded, and output time series data is made available in both graphical and textual format. Resultant data is accurately calculated according to well-established PK mathematics, with no load on the client machine.

This application represents a significant advantage over previously established PK software methods; WebPK is open to the entire community and accessible on any mobile, web-capable device. As such, WebPK overcomes several of the barriers to usage shared by other proprietary applications, and makes PK analysis available to a wider audience of potential researchers, physicians, and other professionals.

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Fig. 1.
Example of a three compartment PK system, with transfer rates for each pathway.

Fig. 2.

WebPK work flow diagram. User interface is shown as single lines, computation scripts in shaded arrows.

Fig. 3.

Five compartment PK model visualization on iPhone. Note that the screen capture is authentically from an iPhone, while the surrounding image of the iPhone has been added for scale.

Fig. 4.
Graphviz visualization for case study taxol dosing regimen.

Fig. 5.

Left: Sample WebPK output for 2-compartment case study. Right: Same data plotted in semilogy.

Table I
Number of Fields for an N -Compartment Model

Parameter	Units	Number of Instances
Start Time	time	1
Time Step	time	1
End time	time	1
Dose Compartment	none	1
Dose Start Time	time	1
Dose Period	time	1
Number of Doses	none	1
Dose Amount	concentration	1
Initial Concentration	concentration	N
PK Clearance Constant	time^{-1}	N
PK Flow Rate Constant	time^{-1}	$N^2 - N$

Table II
Parameters for sample bolus dosing

Parameter	Value
Start Time	0 d
Time Step	0.0625 d
End Time	25 d
Comp. 1 Initial Concentration	0
Comp. 2 Initial Concentration	0
Comp. 1 Clearance Rate	0.868 d ⁻¹
Comp. 2. Clearance Rate	0
k12	0.006 d ⁻¹
k21	0.0838 d ⁻¹
Bolus Compartment	1
Bolus Start Time	7 d
Bolus Time Step	7 d
Bolus End time	21 d
Bolus Amount	16 g/L