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Original Article

Tutorial on Physiology-based Pharmacokinetic (PBPK) Modeling in an Open Access Program

Tutorial de Modelagem Farmacocinética Baseada em Fisiologia (PBPK) em Programa de Acesso Livre

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ABSTRACT

Objectives: To broaden the study of PBPK (Physiology-based Pharmacokinetic) modeling for Portuguese-speaking professionals and students by developing a basic simple PBPK modeling tutorial using free access software. **Methods**: Descriptive study for the development of a Portuguese tutorial dedicated to the use of the PK-Sim® software (version 11.2). **Results**: A tutorial was developed in PK-Sim®, entirely in Portuguese, which enables individuals interested in Pharmacometrics to perform a PBPK analysis in order to study and predict the pharmacokinetics of drugs based on the physiological and anatomical characteristics of a population of interest, as well as the physical and chemical properties of a specific drug. **Conclusions**: Considering the importance of health technologies and their subsequent assessment, this tutorial proves as a relevant tool, both for research and development and for clinical practice, as well as leveraging the democratization of the teaching and research of Pharmaceutical Sciences among Portuguese-speaking people.

Keywords: Pharmacokinetics; Physiology-Based Pharmacokinetic Modeling; Health Technology; Pharmacy Teaching; Tutorial

RESUMO

Objetivo: Ampliar o estudo da modelagem PBPK (Farmacocinética Baseada em Fisiologia) para profissionais e estudantes falantes de português, ao desenvolver um tutorial básico de modelagem PBPK simples usando um programa de acesso livre. **Métodos**: Estudo descritivo para o desenvolvimento de um tutorial em português dedicado à utilização do software PK-Sim® (versão 11.2). **Resultados**: Foi desenvolvido um tutorial no PK-Sim®, todo em português, que viabiliza a pessoas interessadas em Farmacometria a possibilidade de realizar uma análise PBPK, a fim de estudar e prever a PK de medicamentos a partir das características fisiológicas e anatômicas de uma população de interesse, bem como das propriedades físicas e químicas de um determinado fármaco. **Conclusão**: Considerando a importância das tecnologias em saúde e sua posterior avaliação, este tutorial se prova como ferramenta relevante, tanto para pesquisa e desenvolvimento quanto para a prática clínica, além de alavancar a democratização do ensino e pesquisa das Ciências Farmacêuticas entre pessoas falantes de língua portuguesa.

Palavras-chave: Farmacocinética; Modelagem Farmacocinética Baseada em Fisiologia; Tecnologias em Saúde; Ensino em Farmácia; Tutorial

Introduction

According to Ordinance No. 2.510/2012, technologies in health encompass a broad concept of products through which health care and attention are provided to the population. These can include "medications, equipment and technical procedures, organizational, informational, educational, and support systems, as well as assistance programs and protocols."[1,2] The inevitable technological advancement exponentially supports research and development, in addition to promoting health benefits.[3]

Classical pharmacokinetics (PK) is a segment of pharmacology that typically employs mathematical compartmental models to extrapolate and predict the behavior of a substance after administration through the pharmacokinetic processes of absorption, distribution, metabolism , and elimination (ADME). However, it is worth noting that external factors (such as route of administration, multiple dosing, nonlinear PK, etc.) can affect these estimates and should also be considered during PK evaluation concerning the pharmacological and toxicological effects under analysis.[4, 5]

Physiologically Based Pharmacokinetic (PBPK) modeling is a mathematical modeling approach in which a pharmacokinetic model mimics human physiology and is capable of predicting concentration-time profiles of the active substance. Therefore, it has been used for various purposes: from the discovery and development of new drugs to optimizing dose adjustments. [6, 7] In this sense, PBPK proves to be an essential tool for predicting drug exposure in several other clinically relevant scenarios, such as predicting efficacy and toxicity, since it enables the possibility of combining pharmacodynamic (PD) models, allowing the relationship between exposure in target tissues and pharmacological effects.[8]

Generic whole-body PBPK modeling and simulation models aim to simulate the concentration-time profiles of compounds administered via any other route of interest for any species, integrating with a physiological structure, measured or calculated, and physical-chemical properties (such as logP and solubility, for example). [9] It can also be said that PBPK modeling aims to create knowledge by allowing predictions of the kinetic behavior of a drug under different administration routes, dosages, and physiological conditions.[10]

In contrast to classical PK, PBPK seeks to structure, mechanistically and quantitatively, pharmacological parameters by combining in vitro and in vivo extrapolation techniques (IVIVE) and applying them comparatively to data from healthy populations and/or those with some physiological differences. This enables a more efficient prediction of drug dose adjustment, based on the usual dose in healthy or non-pregnant individuals, for example.

PBPK modeling can be applied, for example, to incorporate data related to the reduction of the CYP450 enzyme complex expression in patients with chronic liver disease or to perform simulations in pregnant individuals, considering that this is a sensitive group for participation in clinical trials. Additionally, PBPK modeling has also been widely used in industry and academia for predicting drug interactions (whether drug-drug or drug-food). In other words, PBPK modeling is an important and growing health technology.

Therefore, it is evident that PBPK modeling presents many clinical advantages. However, it is also known that it has considerable limitations: such as the need to input data appropriately into the program, as an organization may not generate this data correctly or as desired for the study, compromising the utility of the modeling; understanding how factors such as age, disease, or organ dysfunction quantitatively affect enzymology, potentially impacting the application of modeling; and the low usability of certain programs for non-programmers, something that has been changing with the development of more comprehensive and specific programs like PK-Sim and GastroPlus, for example. Currently, there are many programs available on the market for conducting PBPK modeling, according to the study's demand and the financial accessibility of the researcher.

From another perspective, another relevant disadvantage to mention is the quantity of articles and other scientific publications addressing PBPK modeling in Portuguese, which corroborates the low access of professionals and students in the pharmaceutical field in Brazil (and other Portuguese-speaking countries) to this tool, which is recognized as an

important health technology already adopted in industry and some academic environments. The lack of materials available in this language significantly limits these individuals' ability to understand and effectively apply the principles and techniques of this important technology.

Thus, understanding the urgent need to democratize and expand pharmaceutical education and learning in all its nuances, it is considered imperative to disseminate knowledge of PBPK modeling to students and professionals in Brazil and other countries that adopt Portuguese as their primary language.

The use of software facilitates PBPK modeling in industry and clinical practice, allowing the simulation of scenarios and the prediction of outcomes. Access to detailed tutorials is crucial for understanding and effectively applying these tools, promoting good practices and standards in the creation and validation of PBPK models. Investing in educational materials about software that performs PBPK modeling is essential for empowering professionals and promoting its proper use.

Objective

This study aimed to describe a basic tutorial for simple PBPK modeling using a freely accessible program for Portuguese-speaking professionals and students.

Methodology

The present tutorial emerged from the execution of the master's thesis of the first author, under the guidance of the second. During this process, it was necessary to consult various materials, which are available on different platforms and organized according to the platform on which the material is located, making the academic process less efficient. Therefore, the steps described in the schemes presented in the results were executed concurrently with writing in Portuguese using the graphical tools of Microsoft® Word (2021). Thus, a descriptive study regarding the development of the tutorial using the software PK-Sim®, version 11.2 (Bayer Technology Services GmbH, Leverkusen, Germany) was developed. PK-Sim® is a free and open-source tool developed by Open Systems Pharmacology (OSP) for constructing PBPK models. The program can be used for modeling and simulating different species based on a whole-body configuration, which characterizes the biological organism in 18 different compartments, considering biological factors (such as volume, weight, and pH of organs, as well as blood flow in and out of these for the different species). To assess the effectiveness of the instructions provided in this tutorial, it was presented to an evaluative committee during a partial evaluation of the master's program, in addition to being shared with colleagues from the same research group who wished to work with the software.

Results

The OSP software package contains different software tools and was designed using a modular concept to enable efficient modeling and simulation at various scales. The core software tools PK-Sim® and MoBi® utilize building blocks according to this modular structure, with PK-Sim® based on the whole-body concept and MoBi® focusing on the molecular level.

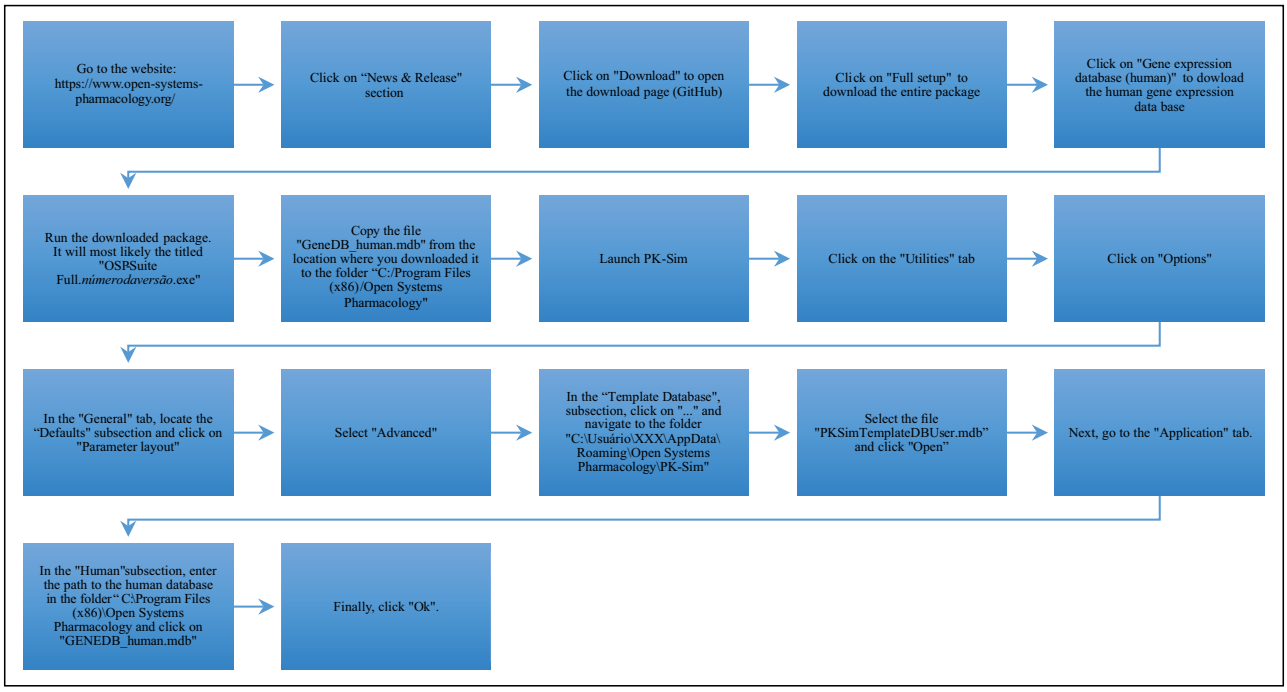
To install the mentioned software package, one should proceed as outlined in Scheme 1.

PK-Sim® offers two interesting functionalities for tracking modeling: History and Journal. In History, it is possible to see all the steps completed (after clicking "Ok") in the program. In Journal, users can write, paste figures, and utilize other functionalities that they wish to insert while working with the software.

According to the course from the Academic Learning Center at esqLabs, the steps for developing the model are:

1. Creation of the necessary building blocks (individual, compound, formulation, administration protocol, and observed data);
2. Configure and run a simulation;
3. Refine the model with sensitivity analysis and parameter identification;
4. Integrate in vitro knowledge about metabolism;
5. Optimize the final intravenous model.

Scheme 1 – Install the OSP package and insert the human database.



Thus, the construction of a simple PBPK model aims to: utilize in vitro data; perform sensitivity analysis of the model; optimize the model by identifying parameters; and compare the simulation results with observed data.

To construct an individual, the parameters (dimensions) of that individual must be defined, including modifying anatomy and physiology, and adding metabolizing or transport enzymes. If necessary, it is also possible to clone and scale individuals, as shown in Scheme 2.

If individual data is available, it is possible to modify the parameters in the "Biometrics" tab. In the "Anatomy & Physiology" tab, parameters such as glomerular filtration rate can be inserted, along with their values if available.

Next, it is possible to construct the compound of interest, as shown in Scheme 3.

It should be noted that it is suggested to enter "1.00" for the glomerular filtration rate because, being a small molecule, it is believed to be freely filtered by the kidneys.

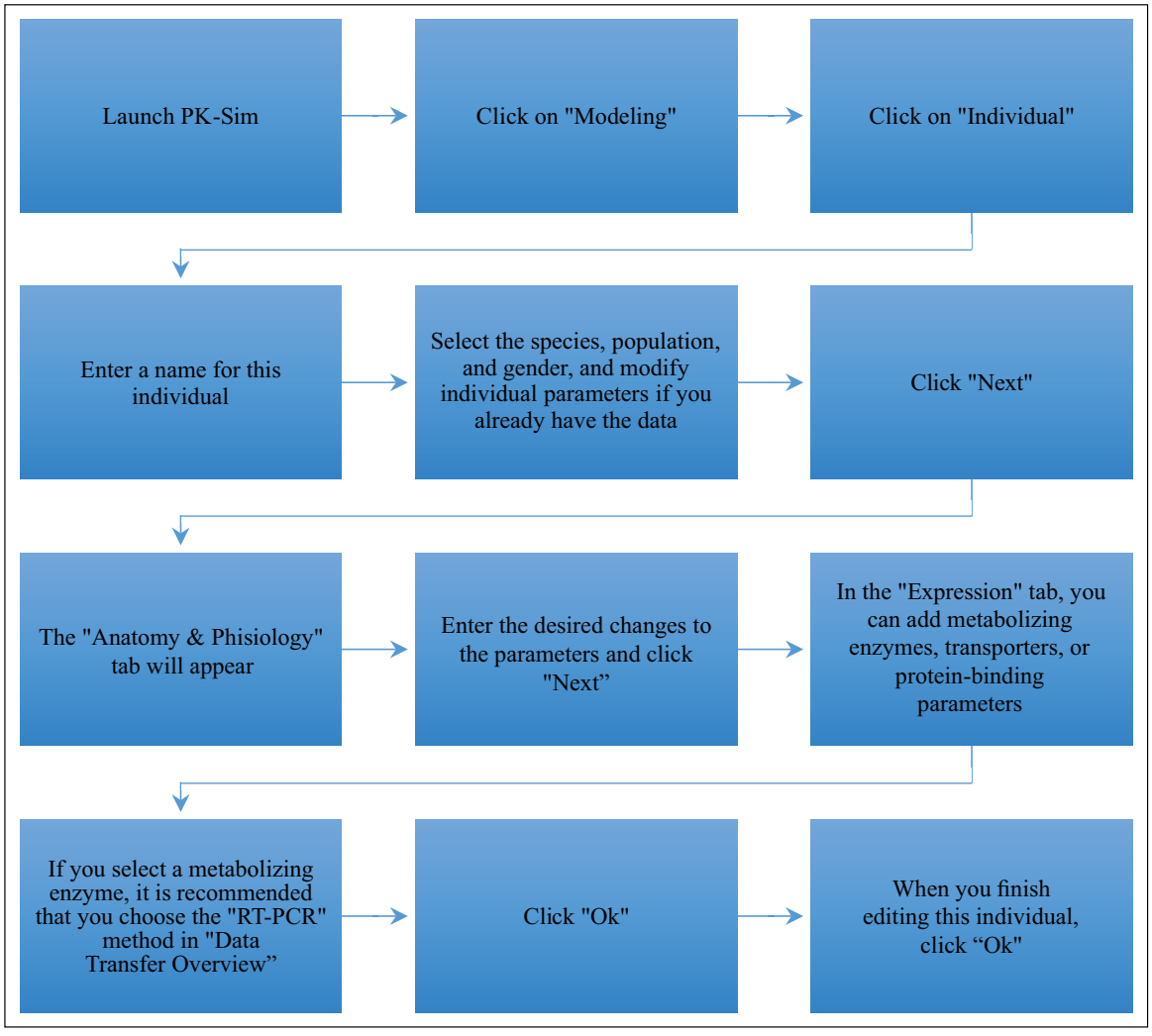
Subsequently, a formulation should be created for the previously entered compound, as shown in Scheme 4.

If the focus of your modeling does not require a faithful delineation of dissolution profiles, which are requested in some formulations, it is suggested to use the "Dissolved" formulation for immediate-release pharmaceutical forms, and for pharmaceutical forms with different release profiles, the use of the "Weibull" formulation is proposed.

The administration protocols can be: intravenous, oral, or advanced. For each one, the process begins the same way (by opening the software, clicking on "Modeling" and then clicking on "Administration Protocol") but concludes differently, depending on the protocol being studied. The advanced protocol should be selected when there is more than one type of administration, for example. In Scheme 5, the procedure for inserting a simple administration protocol is outlined.

It is important to note that if the "oral" route is selected, the volume of water per kg can be entered or the program's default can be maintained. If the selected route is "infusion," it will be necessary to enter the infusion time. When selecting the advanced protocol, at least one administration scheme must be selected.

Scheme 2 – Construction of an Individual.



The last item in the Building Blocks is Observed Data. In this section, observed data (from literature or clinical trials) should be entered. Observed data can be added for the constructed compound (in "Add Observed Data for"), loaded from the OSP package template (in "Load from Template"), or simply added without a specific compound (in "Add Observed Data"). It is also possible to create subfolders or delete this data. In Scheme 6, the steps for entering observed data are outlined.

Finally, a simulation must be created to actually simulate the clinical pharmacokinetic data based on the entered data (Scheme 7).

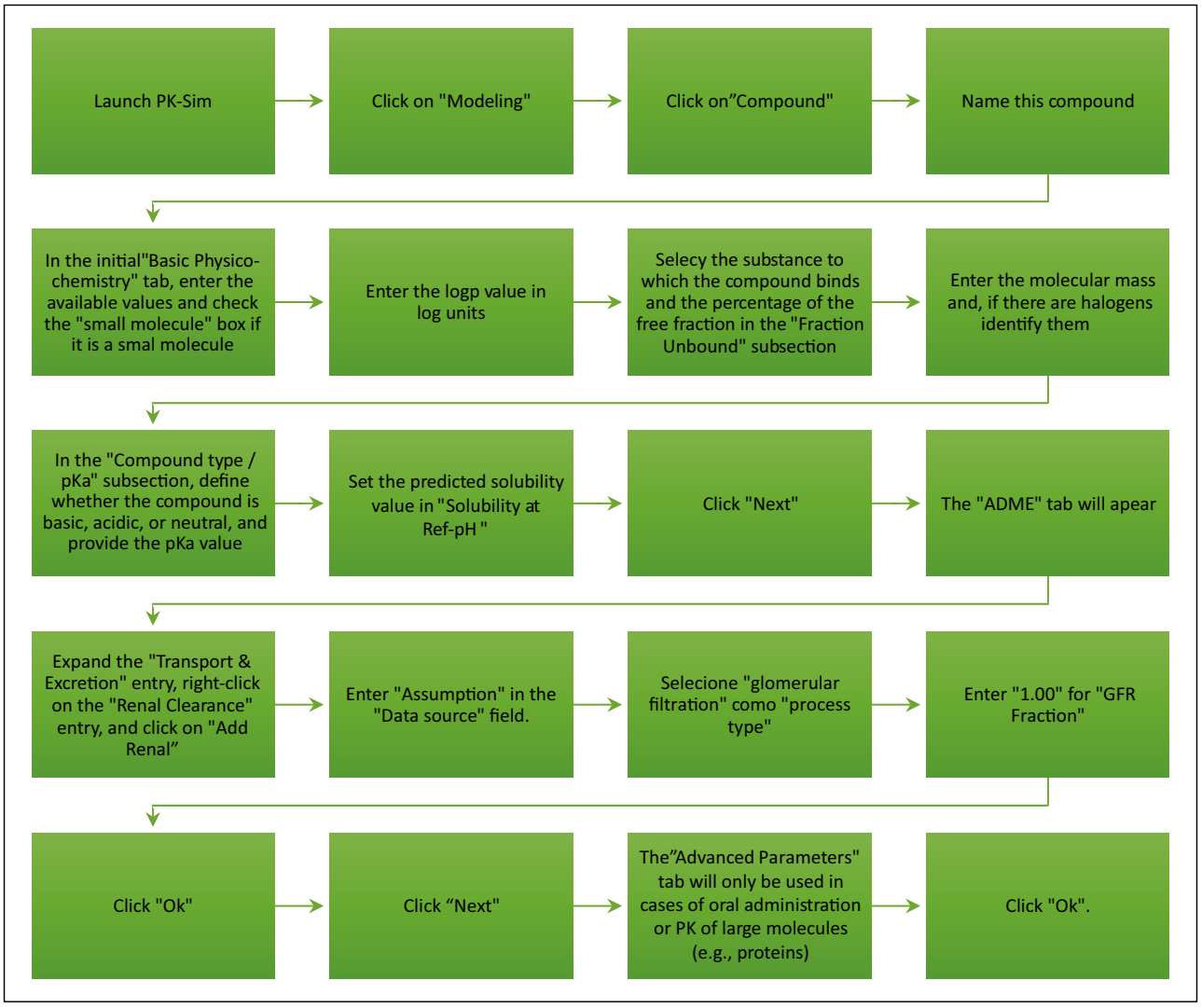
The simulation will appear on the left side, in the "Simulations" section. It is possible to explore the open tabs after the simulation is run. The "Parameters" tab can be used to change specific parameters only in the simulation, allowing for testing without altering the building blocks, and the "Reaction Diagram" tab aims to show the processes specified earlier (such as clearance, if this parameter was affected by the data insertion).

To simulate the plasma concentrations vs. time of the compound after a specific administration, double-click on the desired simulation and proceed according to Scheme 8:

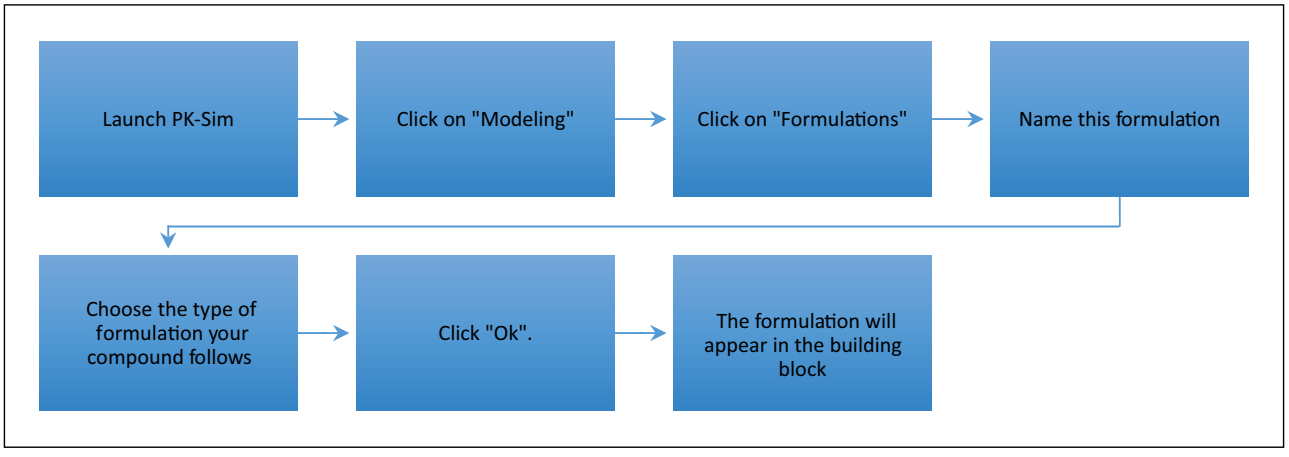
The next step is to visually verify whether the observed data aligns with the simulation proposed by the program's calculations. If they do not align, the model parameters must be optimized to obtain simulated data that resemble the observed data.

It is possible to export the complete PK-Sim model to MoBi for various purposes, such as PD modeling or automatic parameter identification.

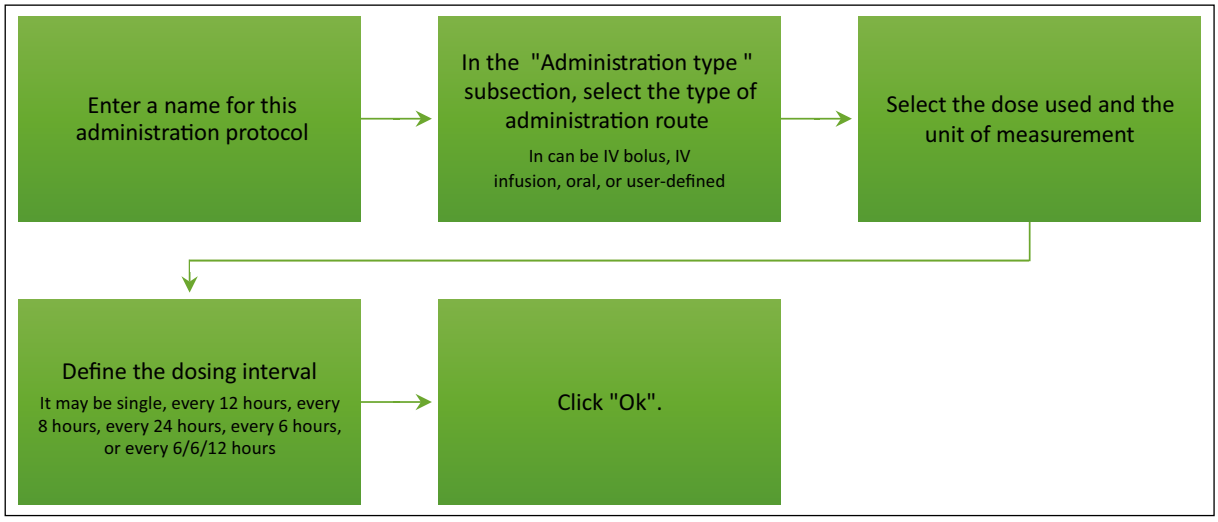
Scheme 3 – Construction of a Compound.



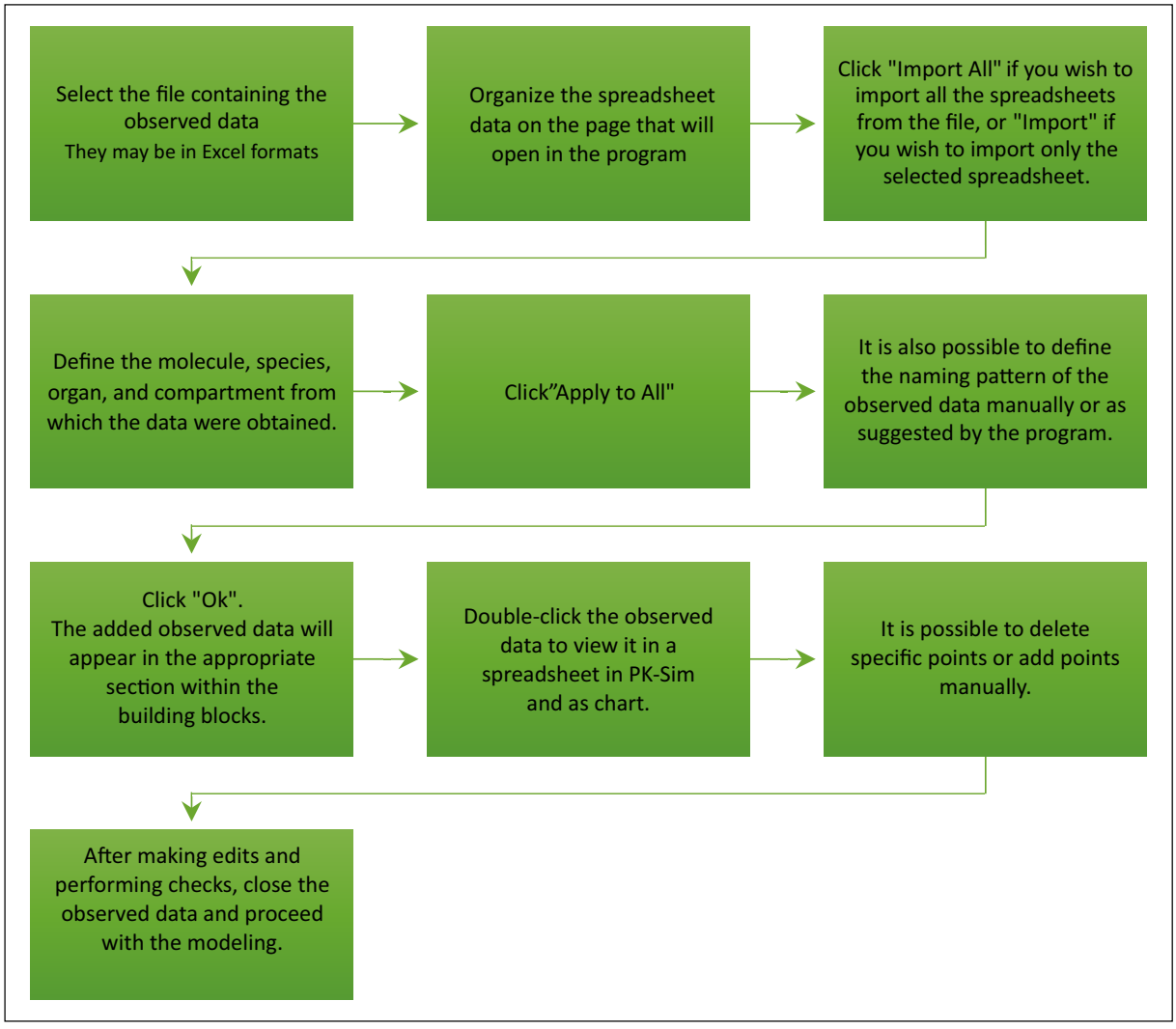
Scheme 4 – Creation of a Formulation.



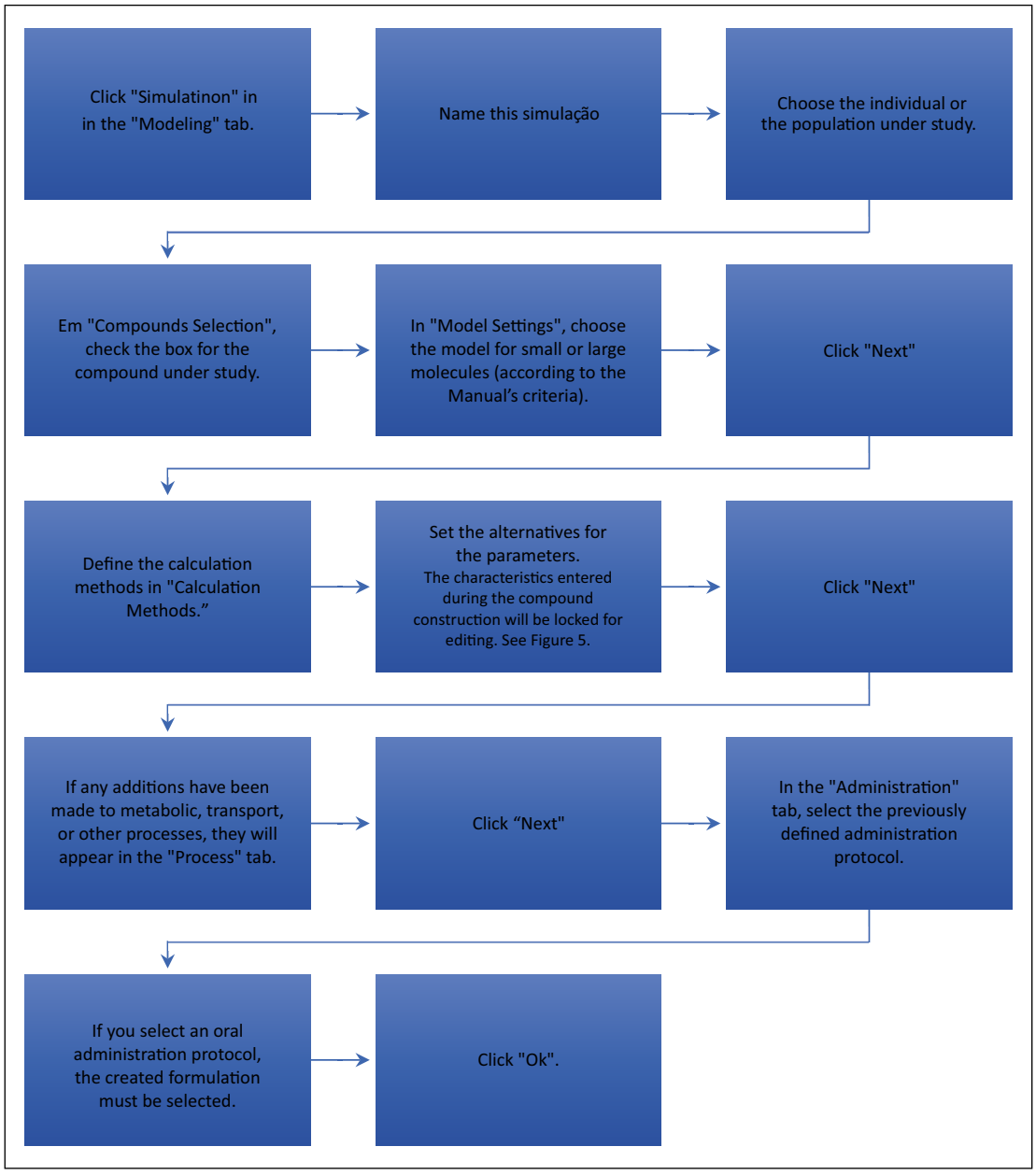
Scheme 5 – Insertion of a Simple Administration Protocol.



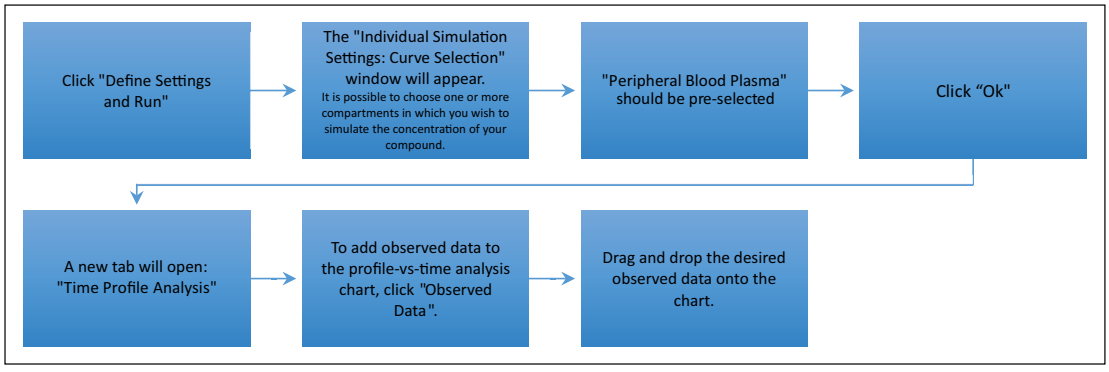
Scheme 6 – Insertion of Observed Data.



Scheme 7 – Creating a Simulation.



Scheme 8 – Simulation of Plasma Concentration versus Time of a Specific Compound after Administration and Verification of Observed Data.



Discussion

The main objectives of writing a tutorial are to educate: solve problems, promote understanding, empower readers, increase efficiency, define standard procedures, build a community, drive engagement, showcase expertise, and provide supporting documentation. Tutorials aim to teach readers step by step, provide hands-on experience, and offer solutions to specific challenges, helping individuals learn and effectively apply new skills or knowledge.

In 2016, Kuepfer and colleagues published a tutorial (in English) aimed at presenting basic concepts of PBPK modeling associated with pharmacodynamics (PBPK/PD), focusing on the practical implementation of typical PBPK modeling work, using ciprofloxacin (an antibacterial drug) as an example, also in PK-Sim.

Five years later, Ezurike and colleagues described the different input parameters needed, as well as the necessary considerations when developing a PBPK model within the Simcyp Simulator, a paid software. A case study demonstrating the development and application of a PBPK model for ondansetron was used to aid the understanding of different PBPK model development concepts.

To develop a simple PBPK model using the OSP software package, tips and information can be found on the OSP website (through the manual provided and the online course offered by esqLabs – which has limited access), in forums, and on video platforms. However, all this information is not organized didactically and is available in English, like most materials found in international databases.

However, just as Brazilian research, research produced by other Portuguese-speaking nations needs to be highlighted and its scientific products disseminated. In this sense, the present tutorial outlines a step-by-step process, from downloading the OSP software package (PK-Sim and MoBi) to developing a simple PBPK model using, exemplarily, a widely used drug today, with the aim of popularizing PBPK modeling as a health technology among professionals and students in the Pharmaceutical Sciences.

Conclusion

Thus, considering the importance of health technologies and their subsequent evaluation, this tutorial proves to be a relevant tool for both the development of new drugs and improvements to already available pharmaceutical forms, as well as for clinical practice, such as dose adjustment and better assessment of drug interactions. Additionally, this tutorial also serves to promote the democratization of education and research in Pharmaceutical Sciences among Portuguese-speaking individuals.

Thinking about the phases following the creation of an individual simulation using PK-Sim, it is important to emphasize that some steps must be followed to evaluate the population performance of the constructed model. We have included the steps for this model as Supplementary Material to this tutorial.

Contributions of the Authors

JMSA: conceptualization of the work and writing; FJA: review and correction.

Conflicts of Interest

There are no conflicts of interest for the authors listed above.

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Responsible Reviewers

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