

New approach based on mathematical modelling to compute drug bioavailability using the PhysPK™ biosimulation system



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Objectives and introduction

According to FDA and EMEA *bioavailability means the rate and extent to which the active substance or active moiety is absorbed from a pharmaceutical form, and becomes available at the site of action* [1]. Due to the difficulty of evaluation, the **rate and amount** of the active substance **delivered to the systemic circulation** are accepted as **surrogate indices**. The amount based - bioavailability, F, is defined as the **proportion of a drug which is absorbed and available to produce systemic effects**. Although F could vary with time, standard mathematical equations neglect time dependency, and use asymptotic or steady-state values. Additional equations are needed in the case of non-linear clearance [2]. Many more complications emerge in the case of extensive first-pass effect in lungs [1], and in other situations like non-negligible influence of circadian cycles. The key point is that despite the importance of bioavailability value in bioequivalence and pharma studies in general, current measurement and mathematical procedures are limited to asymptotic and steady state values in systemic circulation. In addition, the fulfillment of a set of assumptions is also necessary to guarantee the accurate of each mathematical formulation.

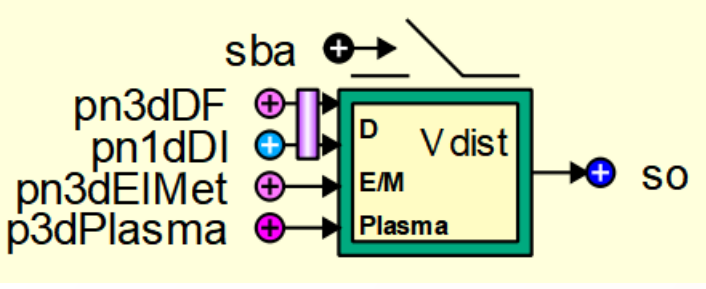
This preliminary work presents a novel approach to calculate F(t) much more close to the original definition by means of pharmacokinetics and physiological mathematical models, using a set of signal computational components included in PhysPK™.

1. Toutain, P.L. and a. Bousquet-Mélou, Bioavailability and its assessment. Journal of veterinary pharmacology and therapeutics, 2004, 27: p. 455-66
2. Berrozpe, J.D., J.M. Lanao, and C.P. Guitart, eds. Tratado general de Biofarmacia y Farmacocinética. Volumen I. 2013, Editorial Síntesis. 700.

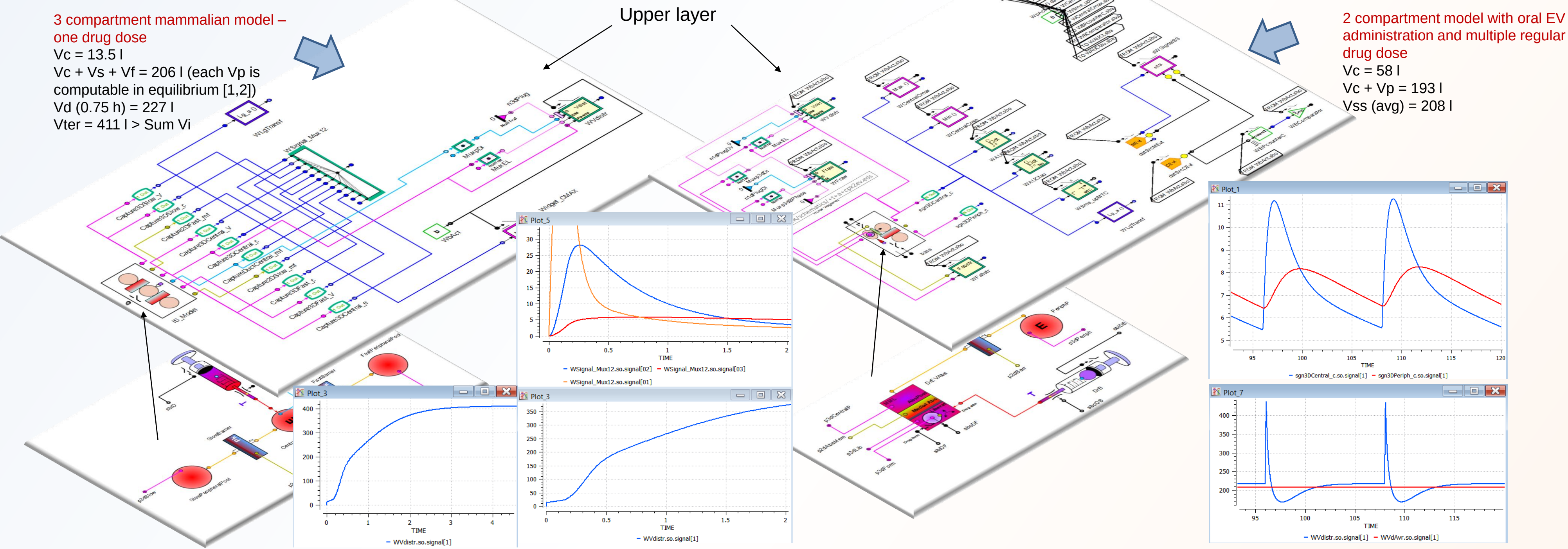
Signal layer in PhysPK™: biosimulation metrics with the Widgets library

- Widgets library features:
- GUI – based computational components
 - OO design, extensible by the user
 - Support of upper model layer in PhysPK biosimulation software
 - Seamless Integration with physiological and pharmacokinetic models
 - Main categories: Computing, Auxiliary, **Metric**, Pharmacodynamics
 - Metric category components include **standard measures** like half-time, AUC, F, MRT, R (cumulative index), latency time, or distribution volume. They all use free-assumption time - based mathematical formulation
 - Widgets components include logic to automate the activation and deactivation as a function of other Widgets components or experiment variables (simulation scenarios).

An example: distribution volume - Widget



$$V_d(t) = \frac{\text{Amount}(t)}{C_p(t)} = \frac{\sum_R \int_{t_0}^t (\varphi_i - \varphi_e) dt}{C_c}$$



Mathematical approach for calculating the bioavailability

Standard mathematical approach

- Linear pharmacokinetic system and one dose

$$F \cdot D = \int_0^\infty CL_p c(t) dt = CL_p \int_0^\infty c(t) dt = CL_p \cdot AUC_0^\infty \Rightarrow F = \frac{CL_p \cdot AUC_0^\infty}{D}$$

- Linear pharmacokinetic system and multiple regular doses

$$AUC_0^\infty = AUC_{\tau SS} \Rightarrow F \cdot D = CL_p \cdot AUC_{\tau SS} \Rightarrow F = \frac{CL_p \cdot AUC_{\tau SS}}{D}$$

- Linear pharmacokinetic system and relative extravasal F

$$F_{ev/iv} = \frac{CL_{pev} \cdot AUC_{ev}}{CL_{piv} \cdot AUC_{iv}} \cdot \frac{D_{ev}}{D_{iv}} \stackrel{D_{iv}=D_{ev}}{=} \frac{AUC_{ev}}{AUC_{iv}} \stackrel{F_{iv}=1}{=} F_{ev}$$

- **Lacks:**
 - ✓ Linear systems use to be gross approximations, including CLp
 - ✓ CLp can vary for a subject or can be better approximated with a Michaelis Menten (MM) law

CLp intra-subject variation [2]

CLp following MM law – one dose [1]

CLp following MM law – multiple regular doses [3]

$$F_{ev/iv} \stackrel{D_{iv}=D_{ev}}{=} \frac{AUC_{ev}}{AUC_{iv}} \cdot \frac{t_{1/2iv}}{t_{1/2ev}} \stackrel{F_{iv}=1}{=} F_{ev}$$

$$F = \frac{1}{D} \sum CL_i \cdot AUC_i$$

$$F = \frac{V_M \cdot \overline{C_{SS}}}{\frac{D}{\tau} (K_M + \overline{C_{SS}})}$$

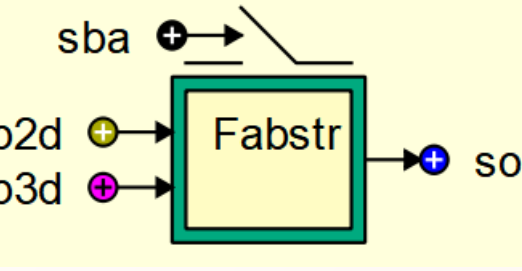
- **Are they effective solutions to lacks?:**
 - ✓ Upper equations are estimations limited to restricted assumptions (regular doses, number of compartments, type of drug administration, ...)
 - ✓ Many more approximated equations have been developed, compartmental or non-compartmental based (NCA)
 - ✓ All equations try to compute asymptotic F by means of the drug elimination
 - ✓ In physiological models the extraction rate or escaping first pass values in tissues are taken into account, but they are not used to compute a more accurate metric according to regulatory definition (rate and extend in the site of action).
 - ✓ Dynamic component of bioavailability are approximated by means of surrogates like Cmax, tmax, or MAT, in NCA.

3. Lam, G. and W. L. Chiou (1979). "Integrated Equation to Evaluate Accumulation Profiles of Drugs Eliminated by Michaelis-Menten Kinetics." Journal of Pharmacokinetics and Biopharmaceutics 7(2): 227-232

Novel mathematical approach

- Based on a mathematical model fitted for drug and population/subject
- Supports non-compartmental (NCA) and compartmental approaches
- Assumptions independent (limited only by model accuracy)
- Mathematical equations associated to original definitions, are implemented into the Widgets library of PhysPK™

Absorption modelling structure based F(t)

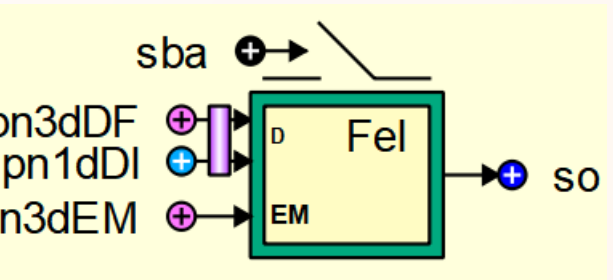


$$F(t) = \frac{\int_{t_0}^t \varphi_b dt}{\int_{t_0}^t (\varphi_b + \varphi_e) dt}$$

Drug flow mass through absorption membrane

Numerator + drug flow mass eliminated from liberation place

System elimination based F(t)

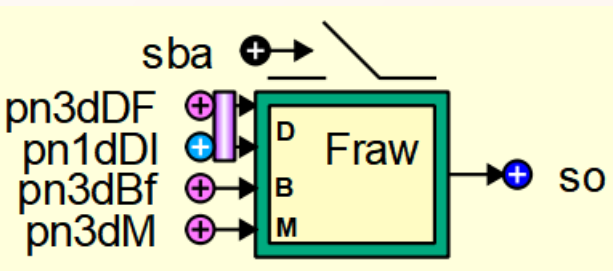


Drug + active metabolites eliminated in whole body

$$F = \frac{\sum_{ME} \sum_M \int_{t_0}^t (\varphi_e - g) dt}{\sum_{DR} \int_{t_0}^t \varphi_{Din} dt}$$

Drug + active metabolites available to reach biophase regions

Biophase based F(t)



Drug + active metabolites reaching selected biophase in selected form (bound / unbound)

$$F = \frac{\sum_{BR} \int_{t_0}^t \varphi_{in} dt}{\sum_{DR} \int_{t_0}^t \varphi_{Din} dt + \sum_{MR} \sum_M \int_{t_0}^t g dt}$$

Drug + active metabolites available to reach biophase regions

Equations are slightly simplified in order to clarify their meaning.

Scenarios for testing the new approach

- **Models:**
 - ✓ 2 compartmental PK with extravasal administration for tacrolimus
 - ✓ PBPK with four tissues (liver, Fat, GI, other) + blood region and oral administration of tacrolimus
- **Population**
 - ✓ Fitted to paediatric renal transplanted population with tacrolimus orally administrated each 12 hours. Two sets of population parameters: with linear CL and MM-CL, obtained by the FOCE PhysPK implementation.
- **Scenarios for F analysis**
 - ✓ One random extracted patient from each set (linear & MM CL), used in simulations to compare standard with novel mathematical F approaches
 - ✓ NCA combined with compartmental simulation analysis with the same patients to complete the previous comparison.

Summary

- Compartmental analysis showed that values of F obtained by the novel approach agree with those obtained by the standard one when the assumptions required by the later are fulfilled.
- Combined NCA with compartmental analysis showed the good agreement of NCA values with their homologous compartmental values, validating the accuracy of the models.
- NCA F values given by standard method in linear case agreed with the F values of novel method. The non linear case was not solved by Lam and Chiou's well-known F equation, in opposition to the novel method.
- The F value at a selected tissue was provided also in the PBPK model, together with the absorption structure based - F. The agreement of the later value with the standard F value validated the accuracy of the model, and it suggests the possibility to compute the rate and extent of drug and metabolites at any selected site considered in the model.

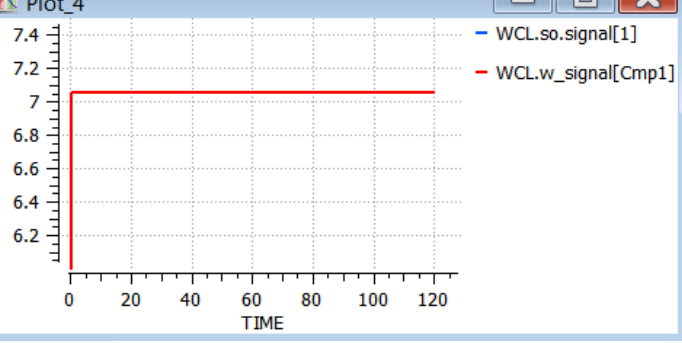
This preliminary work has presented a novel technique based on mathematical models, which has not limiting assumptions, to compute drug bioavailability, which could provide measures more close to the original definition. Additional studies are needed to know the scope and reliability of this Widget based technique of PhysPK™.

NCA comparison of standard against Widget – based technology of PhysPK

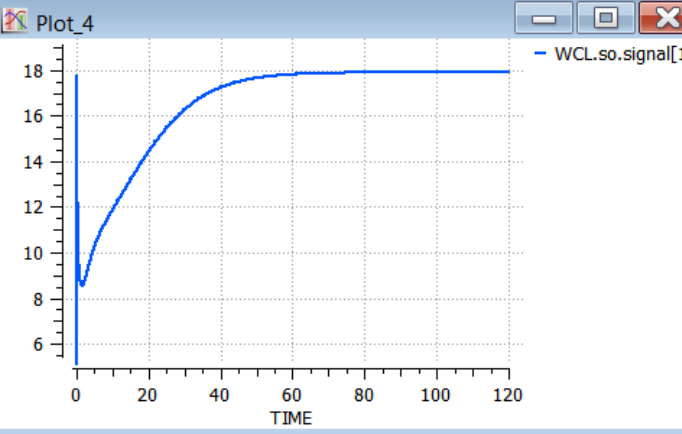
Compartmental analysis

Fasympt is given by linear standard equations

CL linear

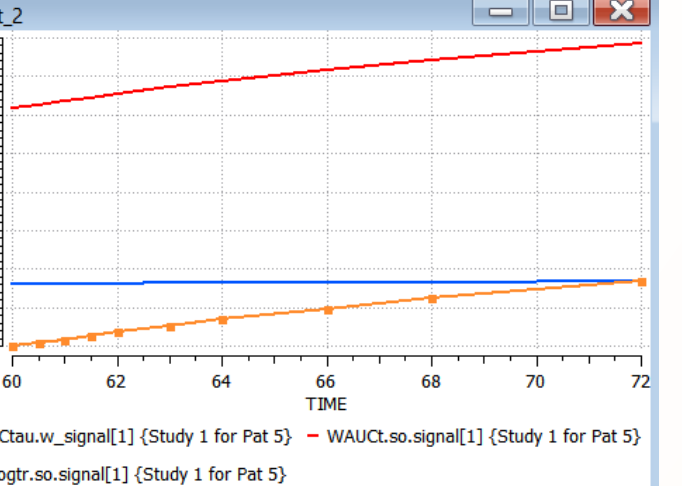
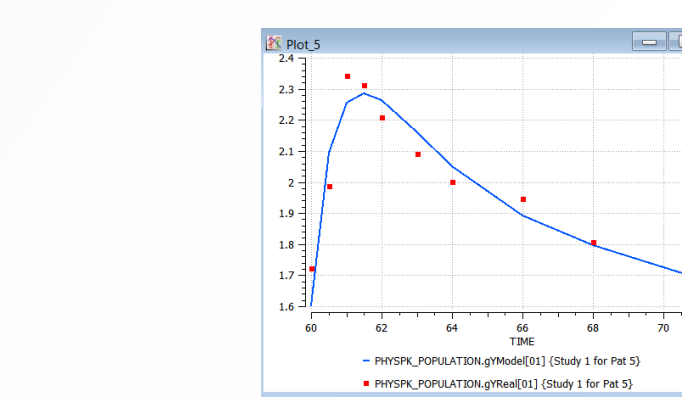


CL MM



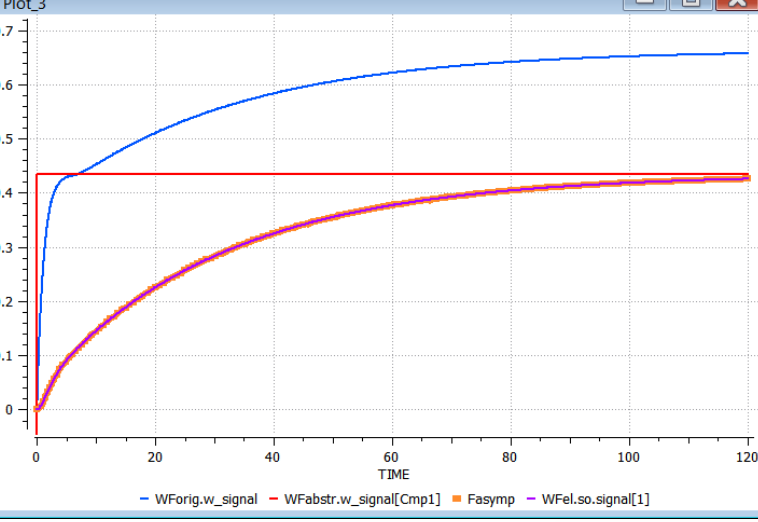
Combined NCA analysis

- ✓ CL linear multiple regular doses

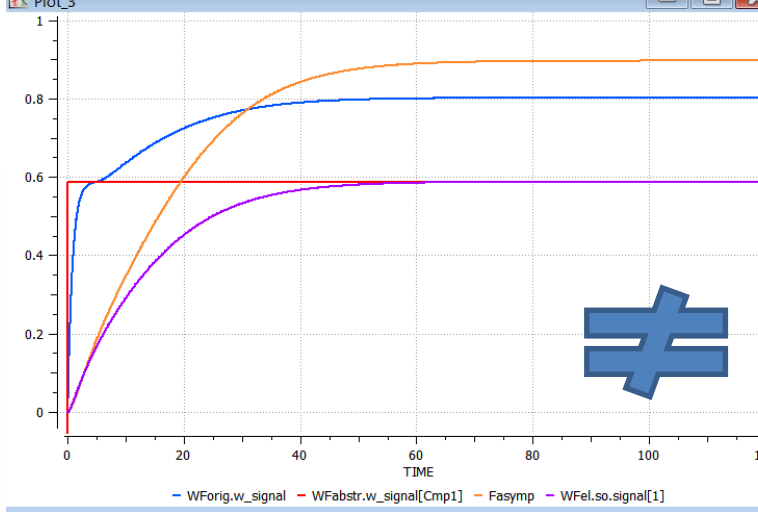


NAC AUC_{12h} from log-trapezoidal formula is accurate. Fasympt tends F computed through absorption structure. Elimination based – F also converges.

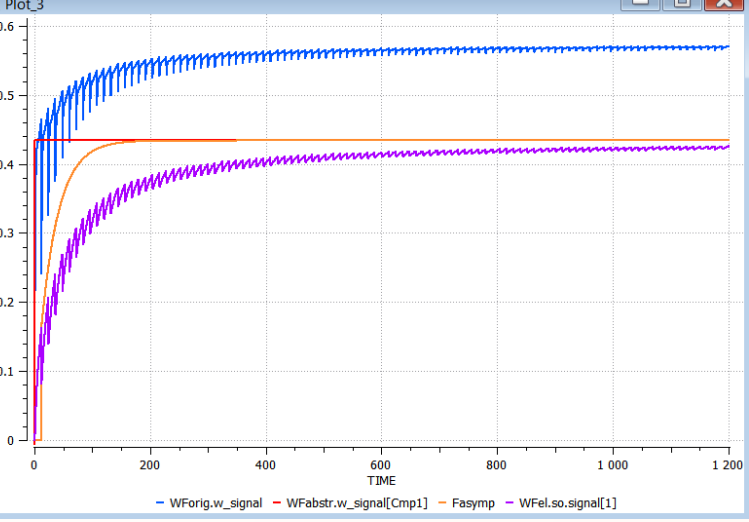
✓ One dose



✗ One dose

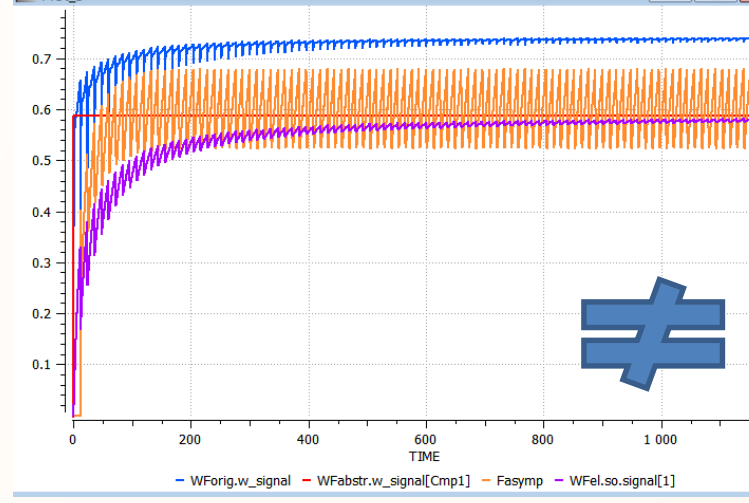


✓ Multiple regular doses

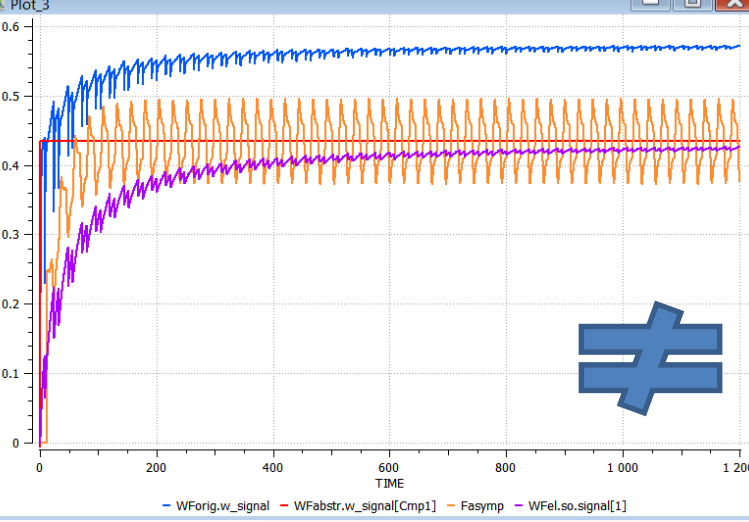


Non regular doses induce greater deviation in standard mathematical equation

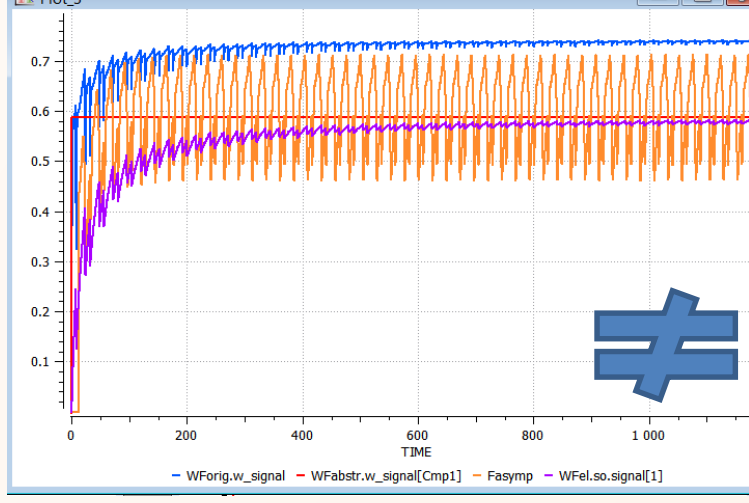
✗ Multiple regular doses



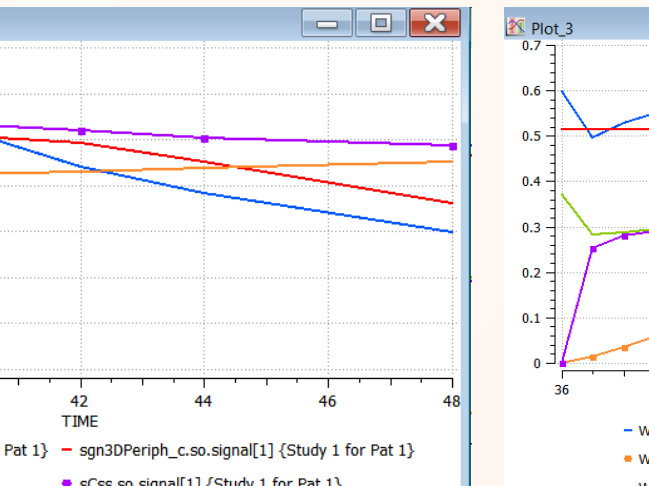
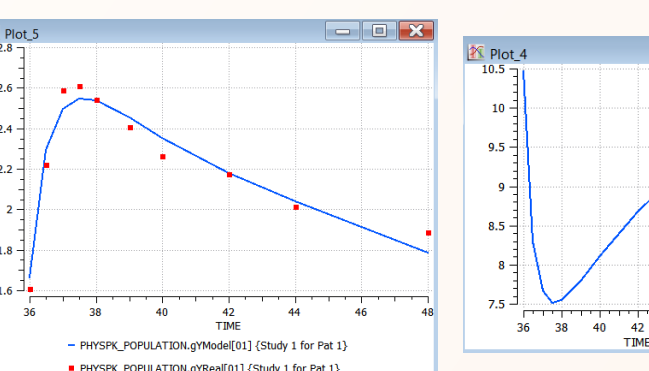
✗ Multiple non-regular doses



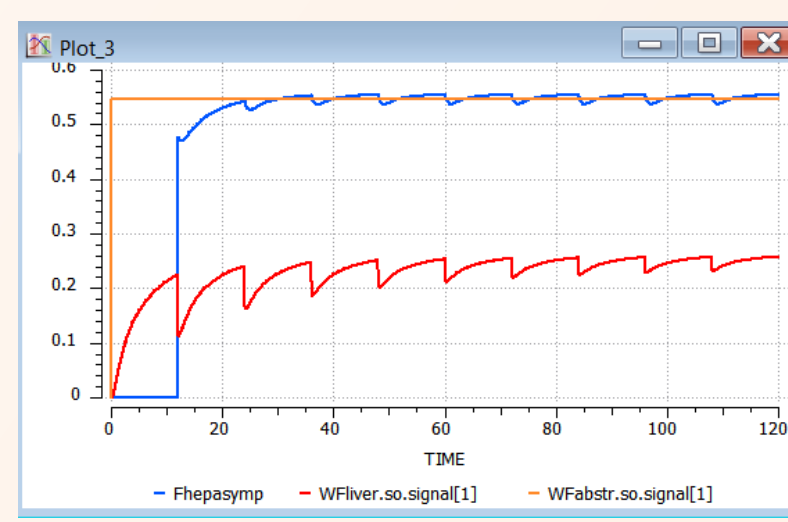
✗ Multiple non-regular doses



✗ CL MM multiple regular doses



- ✓ Biophase – based (liver with MM CL) F in PBPK model with multiple regular doses



Nomenclature: standard method does not fulfil assumptions and fails to evaluate F