Modeling the Two-Peak Phenomenon in Pharmacokinetics Using a Gut Passage Model with two Absorption Sites

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INTRODUCTION

Background

- The first study with a new compound in humans showed PK characteristics that can be characterized by a single compartment model.
- Higher doses exhibited a two-peak phenomenon: a second drug concentration peak occurred that became more pronounced with higher doses.
- Preclinical data suggested that the underlying mechanism could be a gut passage with two absorption sites in the upper and lower intestinal tract, respectively.

Objectives

- Characterization of the pharmacokinetic (PK) two-peak phenomenon with pronounced second peak on higher doses by a gut passage model with two absorption sites and an absorption limit on the first site of absorption.

METHODS

Software

- The Monolix Model Explorer, MlxPlore [1], was used to visualize model candidates and simulate variability. Monolix version 4.1.3 was used to implement the model and estimate parameters [2].

Data

- Single ascending doses of an entry-into-man study.
- Drug concentrations measured up to 24 hours after drug intake.

Implementation

- A PK model with the desired properties was implemented in MlxPlore and in Monolix.
- The model comprises two separate dose administration compartments, one with direct first order absorption and one that consists of a set of transit compartments (with the number of transit compartments estimated).
- The drug is absorbed in the upper part of the gut (absorption compartment 1) up to an absorption (rate) limit. The drug not absorbed here travels through the gut (modeled as transit compartments) and gets absorbed into the same central compartment afterwards.
- In the model, the dose is split into two fractions, F1 and (1-F1). The amount F1 enters the compartment that transfers into the central compartment directly, the amount 1-F1 goes through the transit compartments and the last transit compartment transfers into the central compartment again. The amounts transferred are characterized as fractions of the total amount in the gut, p1 and p2, and the fraction p1 is limited by the ratio of the maximum absorption and the amount of drug in the gut.
- In addition, we modeled the possibility of different absorption rates for different tablet strengths using 3 individual dose administration compartments with different absorption rates. The data file must be set up accordingly by specifying the administration compartment for the particular dosing event (using the variable adm). A mix of tablet strengths requires more than one dosing record in the data set: for example, 120 mg = 100 mg (adm=3) + 20 mg (adm=2).

Figure 1. *Model-predicted concentration-time profiles for 2 dosing regimen. Uncertainties simulated based on variability in volume of distribution and body weight as covariate on volume. Shaded areas indicate 10, 20, ..., 90% quantiles.*
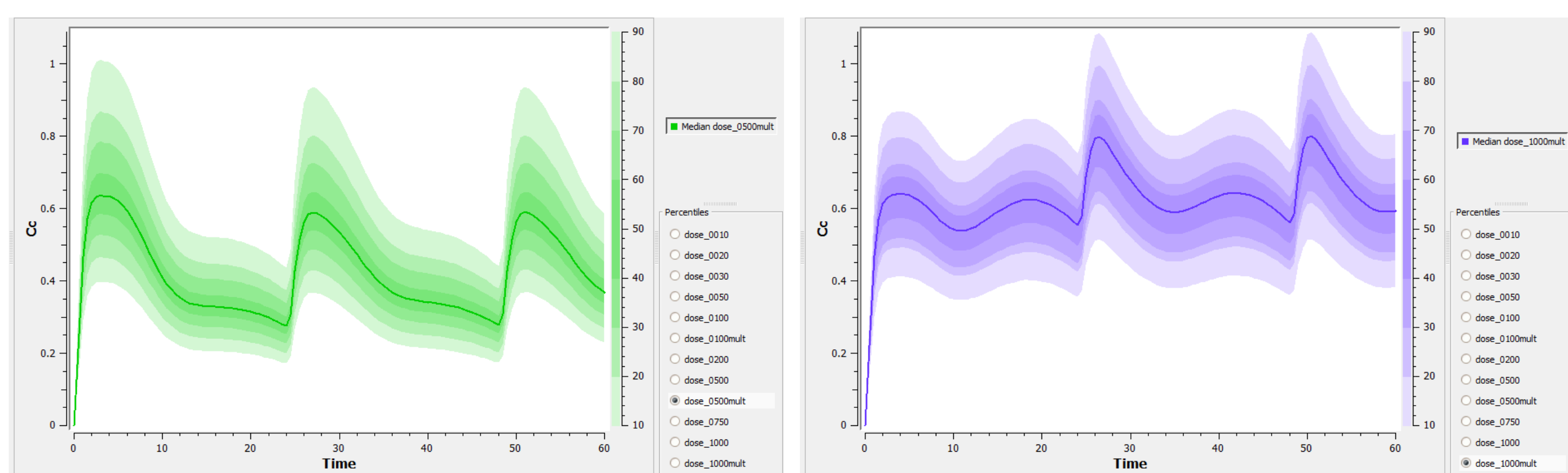

Figure 2. *MlxPlore screenshots. Left: interface with parameter sliders (left), exploration setup (middle), and model code (right). Right: corresponding visualization window with setup options and dose administration selection.*
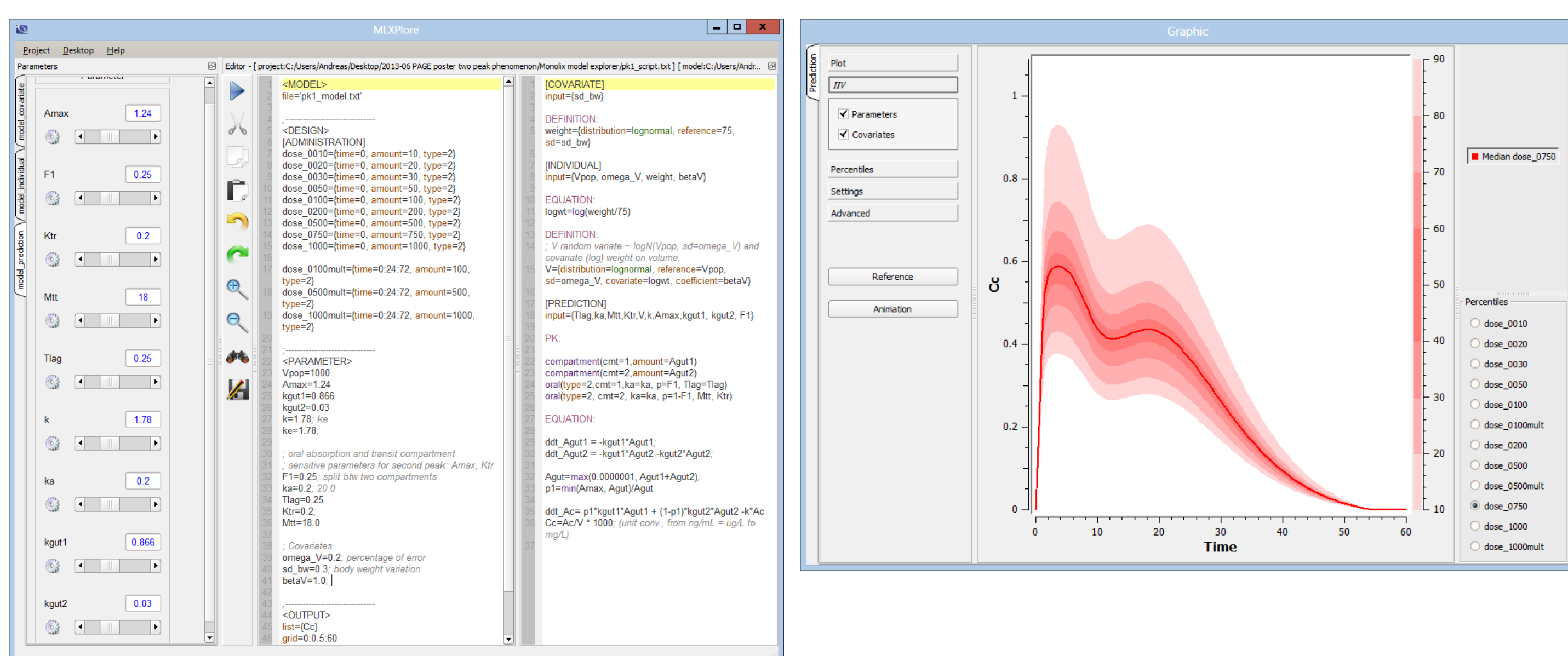

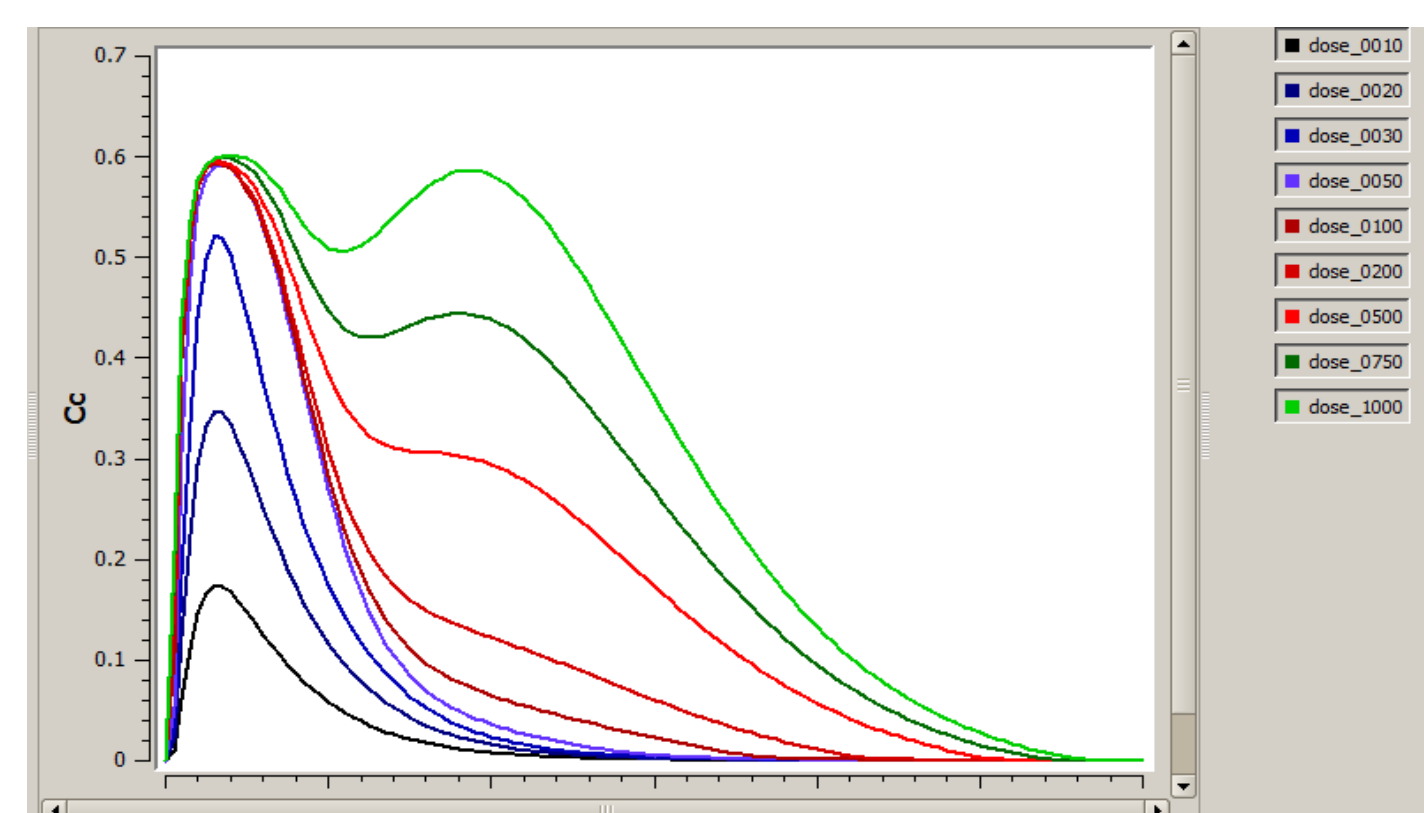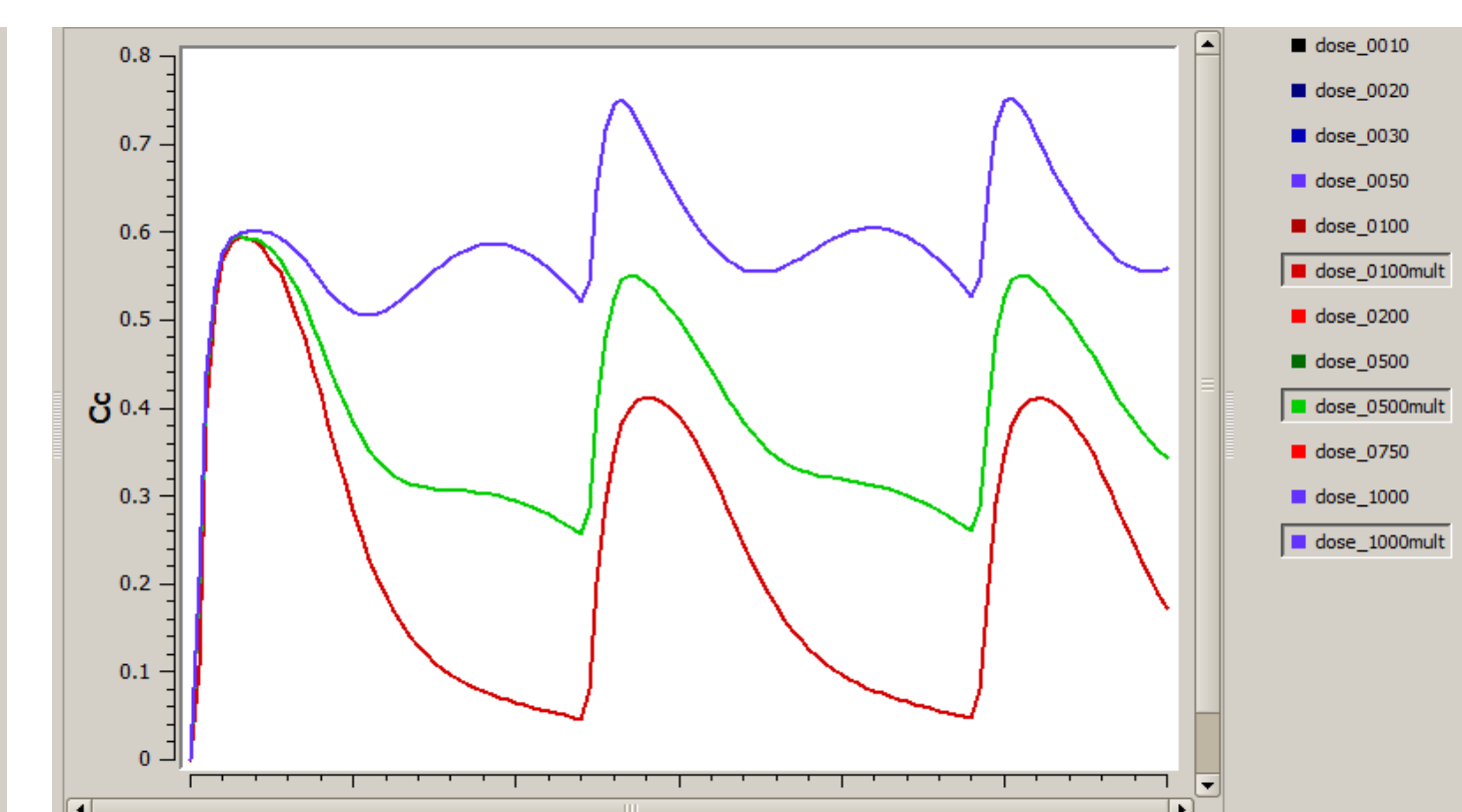**Figure 3.** *Model-predicted concentration-time profiles for selected single doses.*

Figure 4. *Model-predicted concentration-time profiles for 3 doses with multiple administration.*

MODEL CODE (Monolix)

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DESCRIPTION:
Two-peak PK phenomenon model.

INPUT:
parameter = {ka1, ka2, ka3, F1, F2, F3, V, kgut1, kgut2, Ktr, Mtt, Amax, ke, tlag}

PK:
compartment(cmt=1,amount=Agut1); absorption compartment 1
compartment(cmt=2,amount=Agut2); absorption comp 2, transit compt.

; Administer different tablet strengths into different administration compts.
; The dose is split between cmt 1 and cmt 2, the transfer compartment(s).
; Both transfer into the central compartment in turn.
; The following code block defines the drug depots (but not the transfers).

oral(adm=1, cmt=1, ka=ka1, p=F1, Tlag=tlag)
oral(adm=1, cmt=2, ka=ka1, p=1-F1, Ktr, Mtt)

oral(adm=2, cmt=1, ka=ka2, p=F2, Tlag=tlag)
oral(adm=2, cmt=2, ka=ka2, p=1-F2, Ktr, Mtt)

oral(adm=3, cmt=1, ka=ka3, p=F3, Tlag=tlag)
oral(adm=3, cmt=2, ka=ka3, p=1-F3, Ktr, Mtt)

EQUATION:
ddt_Agut1 = -kgut1*Agut1; from drug depot into central compartment
ddt_Agut2 = -kgut2*Agut2; from transfer compartment into central compartment

; p1, the fraction absorbed at absorption site 1, must always be > 0 for ODE.
Agut=max(0.0000001, Agut1+Agut2);
p1 = min(Amax, Agut)/Agut;

ddt_Ac   = p1*kgut1*Agut1 + (1-p1)*kgut2*Agut2 -ke*Ac ;
conc=Ac/V * 1000; (unit conversion, from ng/mL to mg/L);

OUTPUT:
output={conc}
```

RESULTS

- The gut passage model as a way of capturing the two-peak PK phenomenon offers a flexible class of models.
- It can capture very different shapes of concentration-time profiles, including large differences in the magnitude of the second peak relative to the first peak (Figure 3, Figure 4).
- An absorption limit on the first absorption site (estimated) drives the magnitude of the second peak (Figure 1).
- Simultaneous model development (coding) and visualization is a very efficient way of model development (Figure 2).

CONCLUSIONS

- The gut passage model represents a viable alternative to enterohepatic recycling models for the two-peak PK phenomenon ([3], [4], [5]).
- Model visualization is very important during the entire model development process.
- Monolix in combination with MlxPlore provides an efficient environment for model development and simulation, visualization, and parameter estimation.

REFERENCES

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