BEYOND IC_{50} AND SIMPLE PK MODELS – CONSIDERATIONS FOR DISCOVERY CHEMISTS

Robert Fraczkiewicz, Michael B. Bolger, Walter S. Woltosz

Simulations Plus, Inc., 42505 10th Street West, Lancaster CA 93534

Introduction

What are the so-called "nonlinearities" in pharmacokinetics (PK) for multiple dosage of oral drugs? What are their causes and implications? While developing the Simulation Module [1] – an *in silico* tool for conducting PK simulations based on the Advanced Compartmental Absorption and Transit (ACAT™) model [2] – we have discovered a handful of interesting cases of nonlinear PK behavior.

Methods

1. The ACAT Model

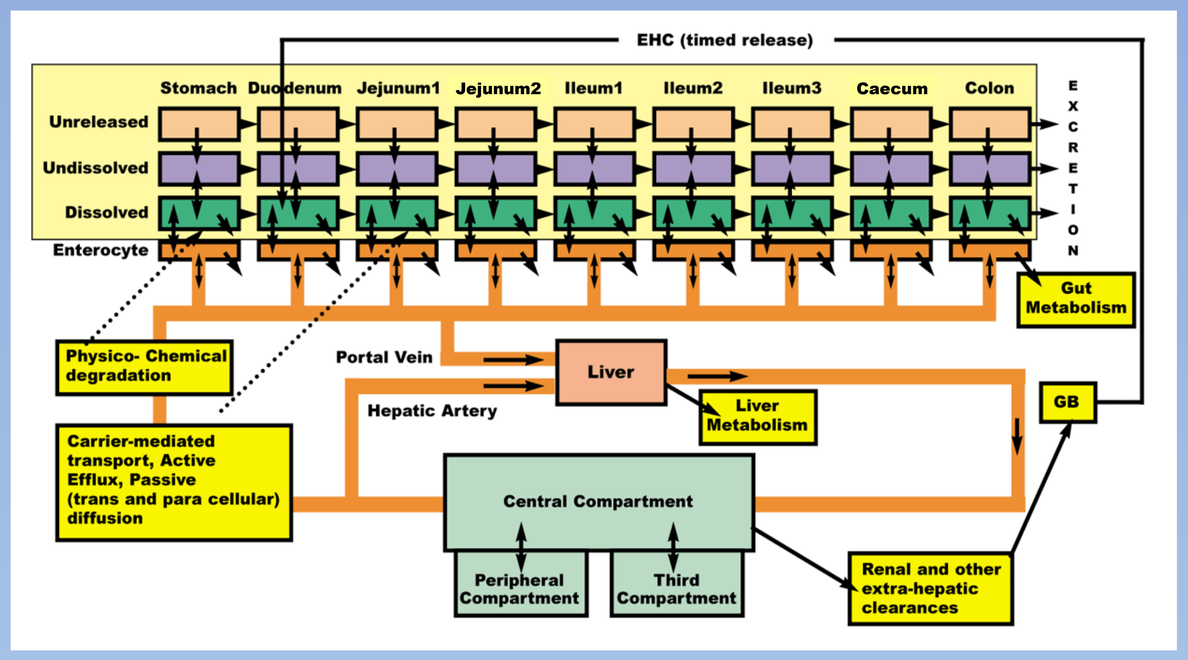

Figure 1. The ACAT model is composed of 9 intestinal compartments: stomach (St), duodenum (D), jejunum 1 (J1), jejunum 2 (J2), ileum 1 (I1), ileum 2 (I2), ileum 3 (I3), caecum (C), and ascending colon (AC). In our simulations we use only two systemic compartments: liver (L) and central compartment (CC).

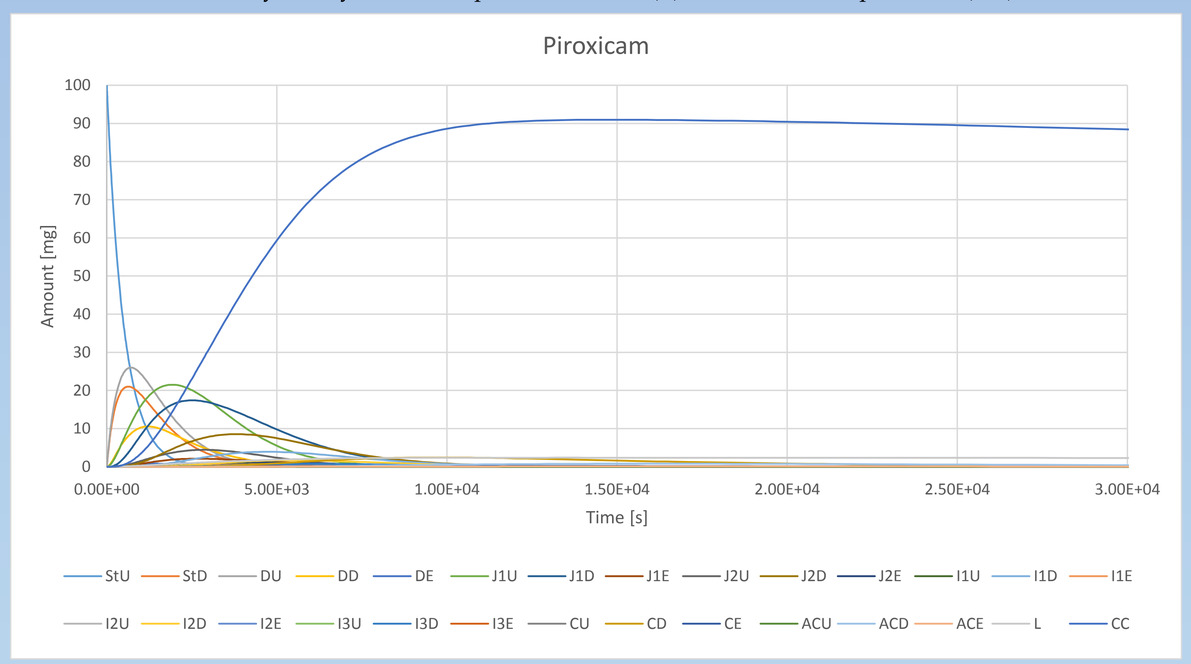

Figure 2. A typical output of the ACAT model after single dose administration yields time-amount (or concentration) curves in each compartment. Curve labels are composed of the compartment symbol, as defined in Figure 1, and the drug state: undissolved (U), dissolved in lumen (D), and in enterocytes (E).

2. The Linear Model of Multiple Dosing

A simple two compartment PK model can be postulated for the following amounts:

- S(t) = sum of all amounts from stomach to liver at time t, representing total input into central compartment.
- C(t) = amount in central compartment at time t. The k and m are the respective elimination constants

$$\frac{dS}{dt} = -kS$$

$$\frac{dC}{dt} = kS - mC$$

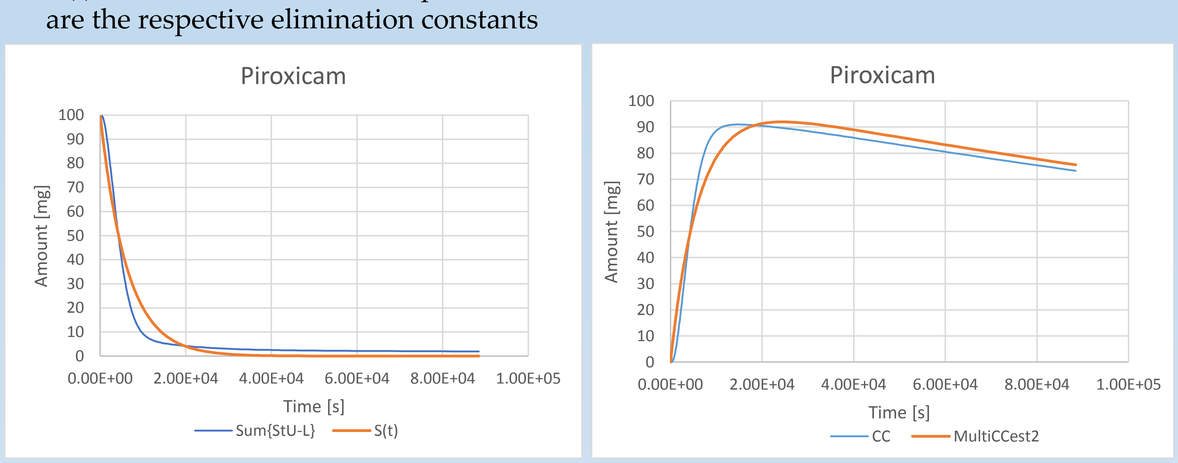

Figure 3. Elimination constants, k and m, are obtained from single dose simulations by fitting the ACAT's S(t) and C(t) curves (blue). The model curves are displayed in orange.

Repetitive solution of the above system of differential equations, with proper boundary conditions, at subsequent multiple dosing intervals leads to the well-known Dost formulas for the amounts in n-th period of administration. [3, 4]

$$S^{(n)}(t) = D\frac{1-a^{(n+1)}}{1-a}e^{-kt}$$

$$C^{(n)}(t) = \frac{kD}{m-k}\left[\frac{1-a^{n+1}}{1-a}e^{-kt} - \frac{1-b^{n+1}}{1-b}e^{-mt}\right]$$

$$a \equiv e^{-k\tau}$$
$$b \equiv e^{-m\tau}$$

Where D = dose; τ = dosing interval; k, m = linear elimination constants.

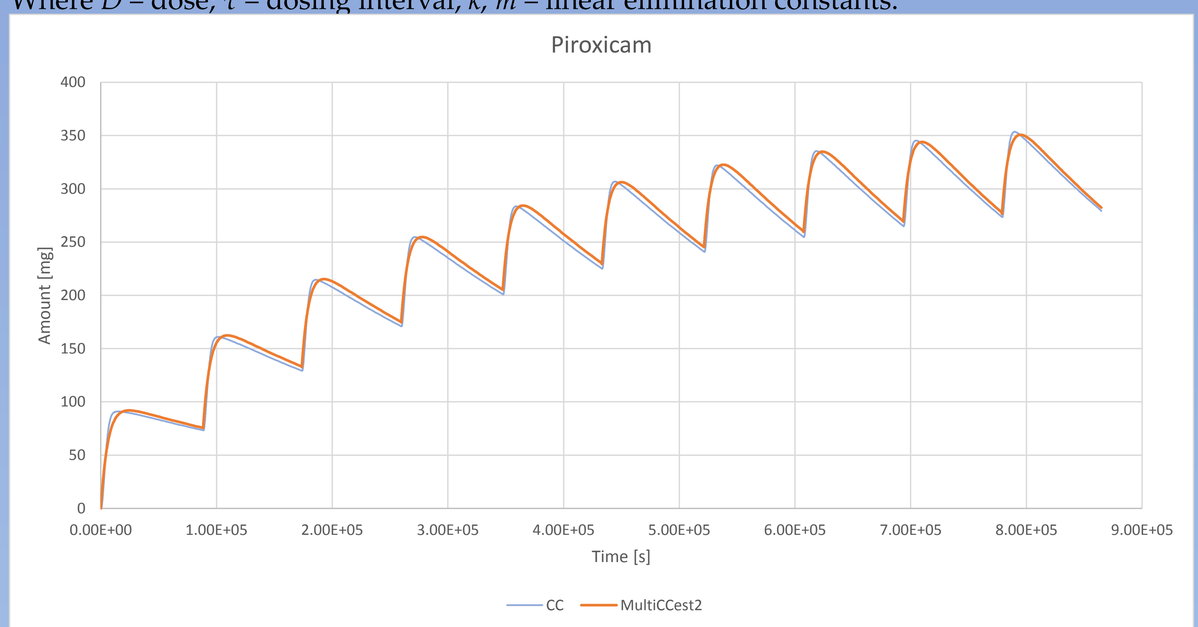

Figure 4. Piroxicam's multiple dosing profile obtained from expensive ACAT simulations (blue) is almost perfectly matched by fast, analytical Dost equations (orange).

Results

In our experience, the multiple dose response of many drugs is well predicted by the Linear Model, as exemplified by Figure 4. In these cases, only a single dose ACAT run is sufficient to predict the outcome for all periods of multiple dosing regime with fixed dosing interval. This is particularly attractive in computationally intensive dose optimization algorithm implemented in our Simulation Module [1]. However, there are exceptions from this behavior.

1. Digoxin

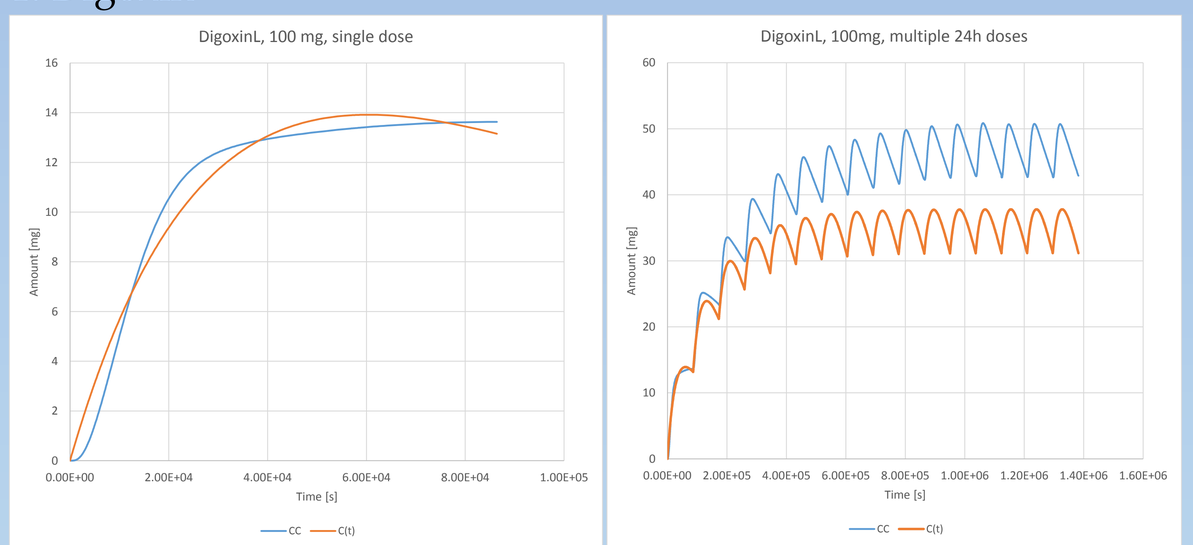

Figure 5. The linear model (orange curves) underestimates multi-dose steady state obtained from ACAT (blue curves) for digoxin. This is caused by transit of digoxin in mainly its *undissolved* form and slow colonic absorption. Thus the single dose data contains inadequate amount of information to properly estimate the m constant.

2. Cimetidine

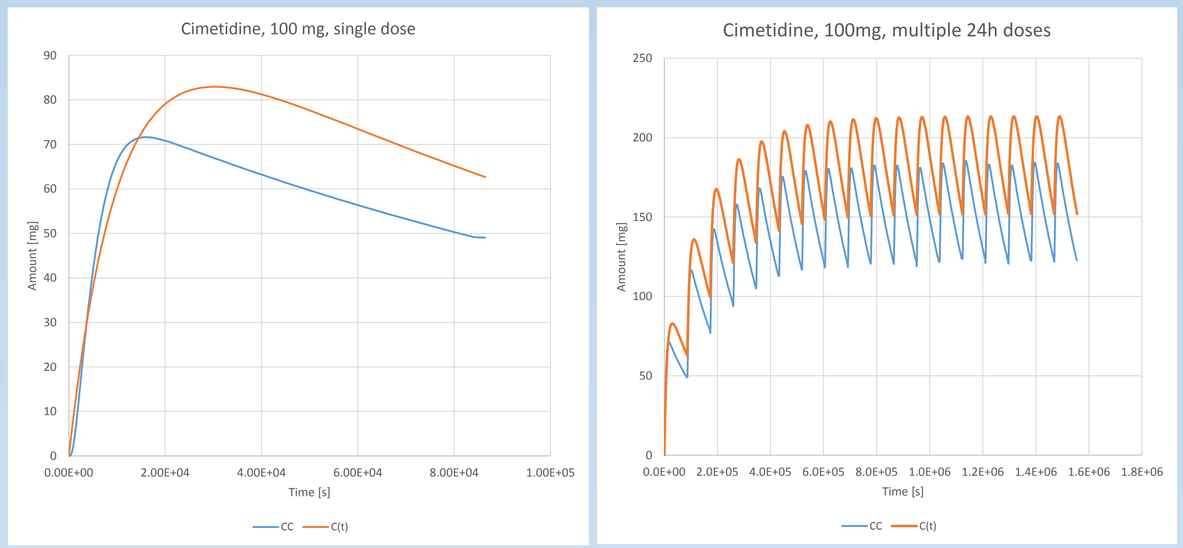

Figure 6. The linear model (orange curves) overestimates multi-dose steady state obtained from ACAT (blue curves) for cimetidine. Unlike digoxin, cimetidine transits through the GI tract in *dissolved* form. Absorption from small intestine is particularly rapid and, although the clearance, m, is estimated properly, the supply part cannot be adequately represented by the linear model involving a single constant k.

Conclusions

- The 64-year old Dost equations still apply to multiple dosing regime of many drugs.
- This allows for rapid estimation of multiple dose response. The speed of analytical formulas is particularly attractive in dose optimization algorithm.
- However, there are cases where the linearity assumption inherent in Dost approach breaks down.
- In these nonlinear cases full ACAT simulation is more appropriate for predicting the multiple dosing outcome. Still, Dost equations provide a good starting point for iterative optimization based on full ACAT.

[1] ADMET Predictor™, version 8.5, Simulations Plus, Inc., 2017.
[2] GastroPlus™, version 9.0, Simulations Plus, Inc., 2016.
[3] Dost, F. H. *Der Blutspiegel - Kinetik der Konzentrationsabläufe in der Kreislaufflüssigkeit*; Georg Thieme Verlag: Leipzig, 1953; 362 pp.
[4] Krüger-Thiemer, E. *Pharmacokinetics and Dose-Concentration Relationships*. In 3rd International Pharmacological Meeting, Sao Paulo, 1966; Ariens, E. J., Ed. Pergamon Press: Sao Paulo, 1966; Vol. 7; pp 63-114.