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Multiple Dose Pharmacokinetic Models Predict Bioavailability of Toxins in Vertebrate Herbivores

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Abstract

In this paper, compartmental pharmacokinetic models are built to predict the concentration of toxic phytochemical in the gastrointestinal tract and blood following oral intake by an individual vertebrate herbivore. The existing single and multiple dose pharmacokinetic models are extended by inclusion of impulsive differential equations which account for an excretion factor whereby unchanged toxins are excreted in the feces due to gastrointestinal mobility. An index α is defined to measure the fraction of bioavailability attributed to the excretion factor of gastrointestinal motility. Sensitivity analysis was conducted and suggests, for any toxin, the bioavailability index α depends mostly on absorption rate of toxin from gastrointestinal tract into the blood, frequency of elimination due to gastrointestinal motility, and the frequency of toxin intake, under the model assumptions.

Keywords Pharmacokinetics modeling · Bioavailability · Gastric motility

Introduction

Physiologically based pharmacokinetic (PBPK) modeling is a mathematical modeling technique for predicting the absorption, distribution, metabolism, and excretion (ADME) of synthetic or natural chemical substances in animal species based on physiological parameters (Kiyoshi et al. 1978). These models have been widely used to study the concentrations of chemicals in body compartments (i.e., pharmacokinetics) and the effects of these concentrations on the animal (i.e., pharmacodynamics) (Derendorf and Meibohm 1999; Meibohm and Derendorf 1997). Koch et al. (2014) proposed delay differential equation models to investigate the impact of delays on responses, such as drug concentration and cell count. General speaking, in biological systems delays occur when the change in time of the variable of interest depends on past states of one or more variables. For example, for oral drug administration, the drug concentration measured in plasma may be delayed compared to the dosing time points. Sukumaran et al. (2015) developed a pharmacokinetic/pharmacodynamic(PKPD) model to describe and predict the dynamics of antibody in mice and can be used to guide future drug optimization and in-vivo studies. McLean and Duncan (2007) used a pharmacokinetic approach to the study of plant secondary metabolites (PSMs) metabolism had much to offer in terms of quantifying the impact of PSMs on large herbivores under different feeding scenarios and to suggest explanations for observed patterns of feeding behavior. However, the existing PBPK models, to our knowledge, do not incorporate the potential that the toxin can be removed out of body due to gastrointestinal motility.

In a typical ADME pharmacokinetic model, the fraction of toxin which reaches the systemic blood compartment unchanged is known as the bioavailability of the toxin (Kiyoshi et al. 1978). By definition a toxin given intravenously has a bioavailability of 100%, whereas an orally ingested toxin has many factors which can affect bioavailability. While many factors impact bioavailability of a toxin, we focus on the toxin removal due to gastrointestinal motility, which can have a considerable

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effect on toxin bioavailability, especially in the case of a toxin which has a low absorption rate through the gut wall (Amidon et al. 1995). While several studies indicate toxins can be excreted unchanged in feces (Sorensen et al. 2004; Thacker et al. 2012). Gastrointestinal motility has not been investigated as a potential mechanism for this observation. The benefit of gastrointestinal motility to limit bioavailability of toxins could explain variation in morphology of gastrointestinal tracts and dietary specialization among herbivores (Shipley et al. 2009). The main goal of this paper is to use mathematical models to study how the excretion factor, defined as the amount of toxin ingested which is excreted unchanged out of the body due to gastrointestinal motility, impacts the bioavailability. We assess the excretion factor on bioavailability under different scenarios, such as single dose intake or multiple dose intake, the different absorption rates of toxin from the gastrointestinal tract (GIT), and the different elimination rates from the body. This phenomenon, where toxin is removed out of body due to gastrointestinal motility, is described by a system of impulsive differential equations.

We consider the case where an orally ingested dose of toxin moves through the GIT and is excreted before having adequate absorption time for the entire dose to be absorbed. In Section 3, a single dose model is introduced first to explore the impact of fecal excretion of unchanged toxin due to the gastrointestinal motility on the bioavailability. An index α is defined to measure the fraction of bioavailability attributed to the excretion factor of gastrointestinal motility. In Section 3, we then build a parallel multiple dose model which is more biologically representative of a foraging herbivore and provide numerical simulations of the model. Finally, sensitivity analysis was conducted. The results suggest the bioavailability index α depends mostly on absorption rate of toxin from gastrointestinal tract into the blood, frequency of elimination due to gastrointestinal motility, and the frequency of toxin intake, under the model assumptions.

A Single Dose Model

First, we start with a single dose ADME pharmacokinetic model. It is assumed that an initial toxin dosage, denoted D_0, is consumed orally by an individual and then moves through the GIT. We then assume the toxin is absorbed into the body through a first order process, as the majority of toxins are absorbed through first order kinematics (Clements et al. 1978), where the amount of toxin being absorbed is linearly dependent on the total amount of toxin remaining in the GIT. This absorption rate, denoted by k_a, is dependent on physiochemical properties of the toxin, intestinal permeability, as well as detoxification of the parent compound into metabolites by both the host, and the intestinal microbiome (Karasov and Douglas 2013). After some amount of time, the remaining toxin passes through the entire GIT and is excreted unchanged (including both fecal and cecal excretion) due to the gastrointestinal motility, thus the absorption phase of the toxin halts. We term this process as the excretion factor. After first pass metabolism by the liver, the absorbed toxin is distributed from the systemic blood compartment to various other compartments throughout the body, where the toxin can be metabolized by these various compartments, and finally excreted out of the body. For simplicity, we divide the body into two compartments: the GIT, where the toxin is absorbed; and the body compartment where the toxin can be distributed to tissues, metabolized, and excreted, where excretion of the toxin is typically through renal filtration then urinary excretion, or through bile processing then fecal excretion. The single dose model can be described by the diagram in Fig. 1.

In order to capture the fact that the toxin will be excreted from the GIT due to the gastrointestinal motility, we denote δt as the duration of time the toxin remained in the GIT. Therefore, from the time the dosage is taken, $t = 0$, to $t = \delta t$, the toxin is available in the GIT for absorption, after $t = \delta t$, the toxin is excreted and no longer available for absorption. Lack of absorption in the GIT could be due to impermeability of toxin across enterocytes, metabolism by host or microbiome, or because the toxin has been excreted. Here, we focus on the excretion factor of toxin caused by gastrointestinal motility.

The equation describing this process is as follows,

$$\begin{cases} GI_0(0) = D_0, & t = 0 \\ \dfrac{dGI_0(t)}{dt} = -k_a GI_0(t), & 0 < t < \delta t \\ GI_0(t) = 0, & \delta t \le t \end{cases} \tag{1}$$

where $GI_0(t)$ is the amount of toxin in the GIT with respect to time t.

Once toxin is in the body compartment of the individual, the toxin is available to be metabolized and eliminated from the animal. Therefore the rate of change in systemic blood toxin concentration in the body is given by the amount

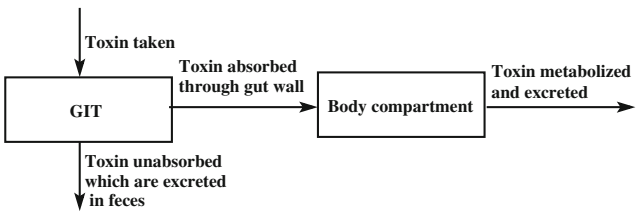

Fig. 1 The single dose model diagram for the toxin absorbed into the body from the gastrointestinal tract (GIT)

Table 1 The definition of parameters in models

Symbol	Definition
C	The concentration of toxin in the body compartment (Figure 1).
GI_0	The amount of toxin available for absorption in GIT (Figure 1).
D_0	The initial dosage of toxin ingested.
k_e	Elimination rate of toxin after absorption in the body compartment.
k_a	Absorption rate of toxin from the GIT into the body compartment.
V	The volume of the body compartment.
δt	Duration between toxin being ingested and when toxin is excreted in feces.
Δt	Duration between two consecutive oral ingested toxin.
F	Bioavailability coefficient of orally ingested toxin.
α	Fraction of bioavailability due to excretion factor in the GIT.

absorbed through the GIT, minus the amount being excreted in the feces. We assume the process of elimination of toxin from the body is a first order process, with the rate k_e. The equation which governs the change in toxin concentration in the body compartment is then given by

$$\begin{cases} \dfrac{dC(t)}{dt} = \dfrac{1}{V} k_a GI(t) - k_e C(t) \\ C(0) = 0 \end{cases} \tag{2}$$

where V is the total volume of the body compartment.

The parameters in the models are defined in Table 1. The excretion factor in this model pertains to all toxins which are ingested orally, but is most drastically seen in toxins with relatively low absorption rate from the GIT into the body compartment.

In a typical model, this fraction of unabsorbed toxin is considered in the parameter of bioavailability. A typical single dose model has the following analytic solution (Holford and Sheiner 1982; Shargel et al. 1999).

$$C(t) = \frac{F D_0 k_a}{V(k_a - k_e)} (e^{-k_e t} - e^{-k_a t}) \tag{3}$$

where the parameter F is the coefficient related to the bioavailability of the toxin. In this model, a fraction of the initial toxin dosage will be completely absorbed through the GIT into the body compartment. Our new model looks to assess the fraction of the coefficient of bioavailability attributed to gastrointestinal motility. To ensure the excretion factor is somewhat prominent we focus on toxins which have a low coefficient of absorption to ensure some amount of toxin is eliminated from the GIT without being absorbed into the body. Typically, the rate of absorption of a toxin can be dependent on many factors, including the type of toxin, the health and age of the animal, and chemical or enzymatic changes made to the toxin

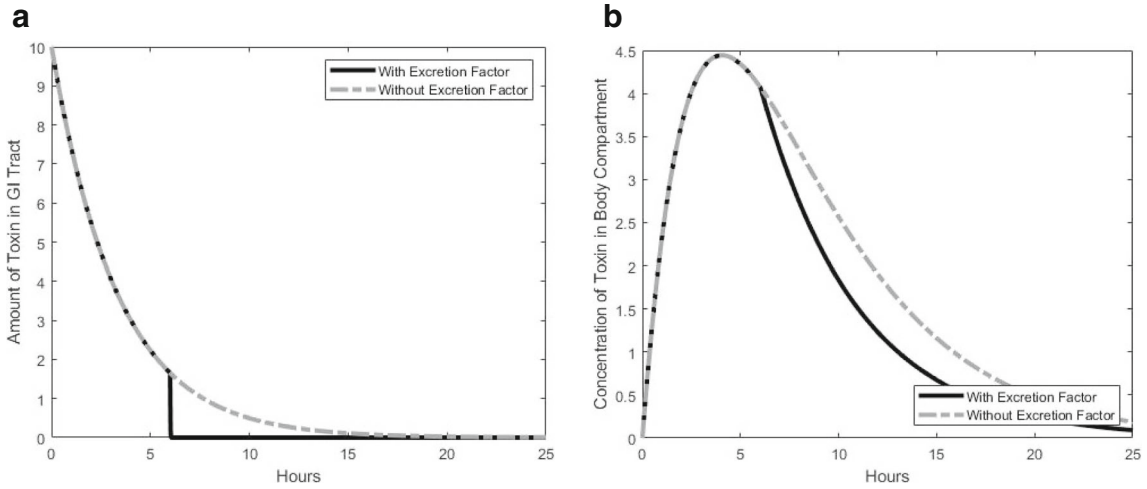

Fig. 2 The amount of toxin in the gastrointestinal tract (GIT) vs time (panel (**a**)) and the concentration of toxin in the body (panel (**b**)) for model (1) and (2) with excretion factor (black solid line) and a typical model (3) without this effect (grey dashed line). In the model (1) and (2), after time $\delta t = 6$ hours all remaining toxin is excreted from the body. In this simulation, other parameter values are $k_a = 0.3$ hour^{-1}, $k_e = 0.2$ hour^{-1}, $D_0 = 10$mg, $V = 1$L

through the stomach or small intestine. Therefore many toxins can have a range of absorption rates based on these factors, however, toxins which act as calcium supplements usually have low coefficients of absorption. We also assume the time the toxin spends in the GIT where the majority of absorption takes place, the small intestine, is somewhat short, again to ensure this effect is noticeable. We can then compare numerically the two models, the model which includes the excretion factor accounting for gastrointestinal motility, and one which does not, for a single dose of toxin. This numerical simulation is shown in Fig. 2.

From this simulation, we can immediately see the concentration of toxin in the body compartment is lower after the time of fecal excretion, and identical before the time of fecal excretion. For this simulation we choose a toxin profile, which highlights this effect more predominantly, i.e. a toxin which is ingested with a low coefficient of absorption and a relatively long half life, or a low rate of elimination. From this, we can hypothesize which parameters in our model contribute most to the coefficient of bioavailability. The rate of absorption, k_a, into the organism and the time the toxin spends in the GIT readily available for absorption, δt, will most likely have the largest impact on the difference in toxin concentrations. To compare the outcomes of these two models analytically by integrating over the two curves, we can look at the Area Under the Curve (AUC) and assess the percentage difference in concentrations between the two models. If we attribute all of the gastrointestinal motility to the parameter of bioavailability, we can then say the excretion factor is a fraction of the bioavailability. We then have the ratio of the two AUCs is proportional to some fraction of bioavailability, F, or

$$\frac{AUC_2}{AUC_1} = 1 - \alpha \tag{4}$$

where α is the fraction of bioavailability attributed to the excretion factor. For this simulation, in the typical model we calculate the AUC_1 as 49.99, and for the proposed model which includes the excretion factor we calculate the AUC_2 as 41.77. The percent of F attributed to the coefficient α can then be calculated as 16.46%.

A Multiple Dose Model

We are most interested in a multiple dose scenario, where we assume doses of toxin are ingested by herbivores at regular intervals, and each dose of toxin remains in the GIT for time δt before being excreted out of body due to the gastrointestinal motility. Normally, the concentration of toxin in the body compartment influences the dosing interval time by influencing the behavior of the animal to consume or avoid ingesting the toxin to keep toxin concentration levels within a range where they are high enough to elicit beneficial effects, and low enough to avoid harmful effects (McLean et al. 2007; Torregrossa and Dearing 2009). However in this model for simplicity we consider the dosing interval to be constant. After several doses are taken, the system reaches a steady state where toxin concentration in the body compartment remains within a particular range of concentration, or tolerable concentration. Here again we omit the inclusion of the parameter of bioavailability, and look at the difference between a typical model without an excretion factor and the case with an excretion factor. We then find the fraction of the bioavailability coefficient which can be attributed to this excretion factor.

The following impulsive differential equations describe the multiple dose scenario,

$$\begin{cases} GI_i(i\Delta t) = D_0, & t = i\Delta t, i = 0, 1, \cdots n \\ \frac{dGI_i(t)}{dt} = -k_a GI_i(t), & i\Delta t < t < i\Delta t + \delta t \\ GI_i(t) = 0, & 0 < t < i\Delta t \text{ or } t > i\Delta t + \delta t, \end{cases} \tag{5}$$

where i denotes the i-th orally ingested dose, $n+1$ is the total number of ingested doses, $GI_i(t)$ is the amount of toxin in the GIT due to the i-th ingested dose, δt is the duration that toxin remains in the GIT, and Δt is the duration between two consecutive orally ingested doses of toxin.

The term $k_a GI_i(t)$ is the amount of toxin absorbed from the GIT to the body compartment for i-th particular dose intake. The total amount of toxin in the body compartment is given by the summation of these terms for i from 0 to n,

$$\sum_{i=0}^{n} k_a GI_i(t)$$

We can then write the equation which describes the concentration of toxin in the body compartment with multiple doses, $C_m(t)$, as

$$\frac{dC_m(t)}{dt} = \frac{1}{V}\sum_{i=0}^{n} k_a GI_i(t) - k_e C_m(t) \tag{6}$$

where the meaning of other parameters are the same as the ones in the Table 1.

The standard equation for a multiple oral dose model is given as

$$\frac{dC_p(t)}{dt} = \frac{FD_0k_a}{V(k_a - k_e)}\left[\left(\frac{1 - e^{-nk_e\Delta t}}{1 - e^{-k_e\Delta t}}\right)e^{-k_e t} - \left(\frac{1 - e^{-nk_a\Delta t}}{1 - e^{-k_a\Delta t}}\right)e^{-k_a t}\right] \tag{7}$$

where $C_p(t)$ is the concentration of drug in the blood and other parameters are the same as the previous models (Holford and Sheiner 1982; Shargel et al. 1999).

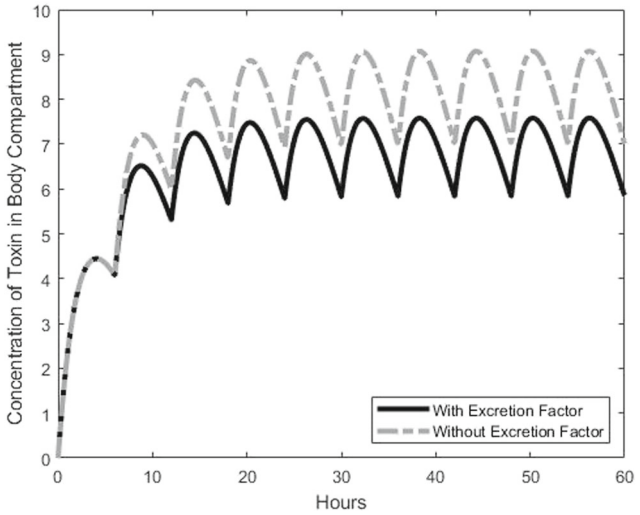

Fig. 3 Plot of concentration of toxin in the body vs time for our model (5)–(6) with excretion factor (black solid curve), and a typical model without this factor (gray dashed curve). The parameter values are $k_a = 0.3$ hour^{-1}, $k_e = 0.2$ hour^{-1}, $D_0 = 10$mg, $V = 1$L, $\delta t = 6$ hours, and $\Delta t = 6$ hours

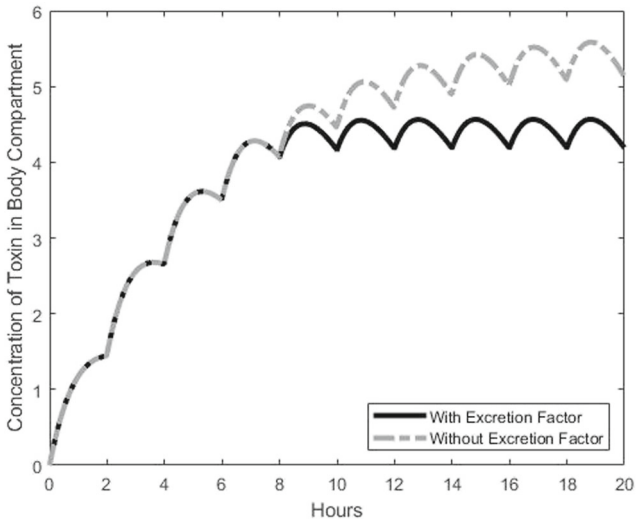

Fig. 5 Plot of concentration of toxin in the body vs time for our model with excretion factor, and a typical model without this factor. Parameters for this model are chosen as follows: $k_a = 0.2$, $k_e = 0.9$, $\Delta t = 2$, $\delta t = 8$

To gain insight into comparing our model (5)–(6) with an excretion factor to a typical model with no excretion factor, an analytic solution to the model with an excretion factor is given in the Appendix through the use of Laplace transforms and step functions. However, the analytic model is complex and difficult to compare to the standard analytic model as the model must be broken into different cases depending on the parameters δt and Δt. We instead use numerical simulations to explore the impact of parameters of the model to the concentration of toxin in the body compartment.

We choose Δt, the duration between two consecutive doses, to be roughly the amount of time for large foods to move through the gastrointestinal tract of an individual with the assumption the toxin has maximal absorption time. The value of δt, the frequency of fecal excretion due to gastrointestinal motility, is taken to be a value for a toxin which is ingested frequently, more often than excretion usually takes place, to highlight the effect this excretion factor has on the concentration of toxin in the body. We choose our remaining model parameters to be the same as those as in our single dose model (1)–(2).

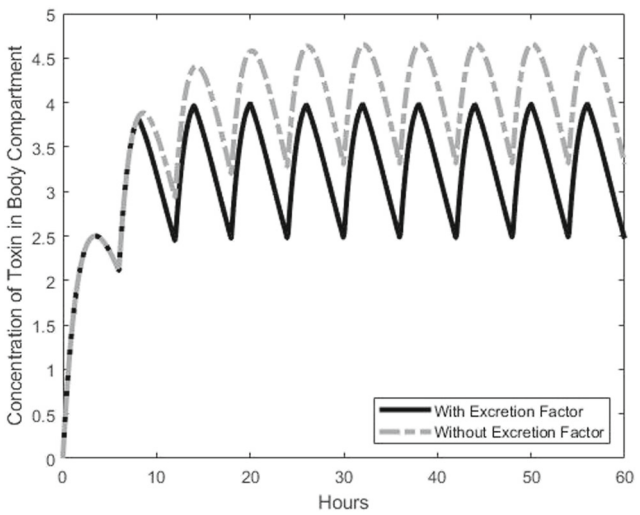

Fig. 4 Plot of concentration of toxin in the body vs time for our model with excretion factor, and a typical model without this factor. Parameters for this model are chosen as follows: $k_a = 0.2$, $k_e = 0.4$, $\Delta t = 6$, $\delta t = 8$

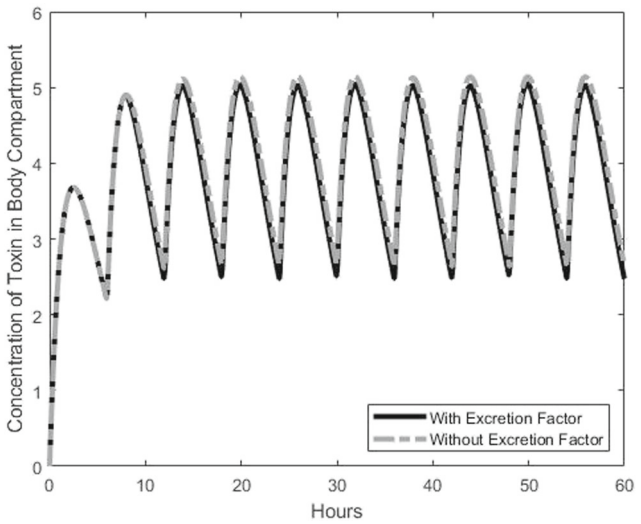

Fig. 6 Plot of concentration of toxin in the body vs time for our model with excretion factor, and a typical model without this factor. Parameters for this model are chosen as follows: $k_a = 0.4$, $k_e = 0.4$, $\Delta t = 6$, $\delta t = 8$

We explore several different toxin profiles with varying values of parameters to showcase the effects of the excretion factor on the overall concentration in the body after 10 doses of toxin. Figure 3 shows how the concentration of toxin in the body compartment changes with respect to time with the excretion factor (black solid curve) and without this factor (gray dashed curve). Under this set of parameters we observe, three doses are required for the concentration of toxin in the blood to achieve the steady state stage, and the maximum and minimum values for the steady state solutions in these two scenario are roughly 20% different.

Figures 4, 5, 6 and 7 give similar results as Fig. 3 with different sets of parameters. Biologically, each of these can be interpreted differently. For Fig. 4, parameters are chosen to represent a toxin which is slowly absorbed through the GIT into the body compartment, and is also slowly metabolized in the body compartment and then excreted, while the time between orally ingested toxin doses, Δt, and the time require for the toxin to be excreted δt are similar. Figure 5 attempts to represent a toxin which is ingested very frequently, while also being absorbed slowly into the body compartment, and being metabolized quickly from the body compartment. Figure 6 has parameters exactly the same as those in Fig. 4, except that it has a faster rate of absorption from the GIT into the body compartment. Figure 7 is chosen with both increased absorption and elimination rates, and a high rate of toxin ingestion. In all of these figures, the time between the toxin being ingested and excreted, δt, remains the same.

To determine the difference in the toxin concentrations for the two models, sensitivity analysis is conducted to determine which of the parameters, $k_e, k_a, \Delta t, \delta t$ contribute most to the index α, defined in Eq. 4, which represents the fraction of bioavailability attributed to gastrointestinal motility. We compare the AUC of the two models for an N^{th} toxin dosage where N is large enough to ensure a steady state concentration behavior. Figure 8 shows how the parameter k_a, the absorption rate of toxin into body compartment from the GIT, while ranging between values for 0.1 and 0.9, impacts the value of the difference between the percent difference in the two AUCs. We can see the difference in bioavailability fractions is larger when k_a is small. Figure 9 demonstrates how the parameter k_e, the

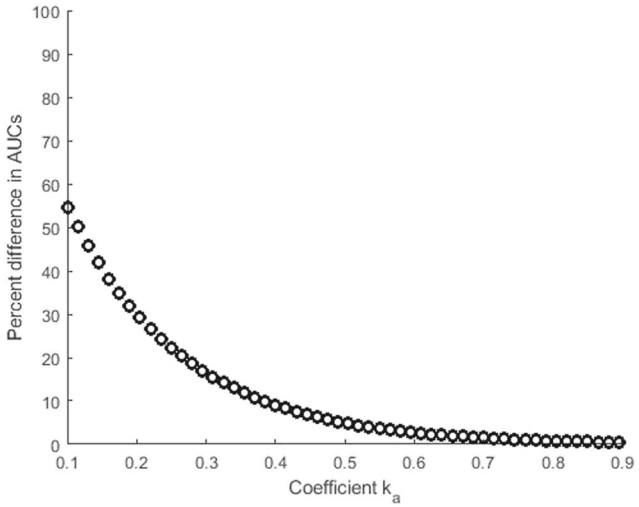

Fig. 8 Plot of the coefficient of absorption, k_a vs the percent difference in AUC's. Parameters for this model are chosen as follows: $k_e = 0.3$, $\Delta t = 6$, $\delta t = 6$, with k_a varying between varying between 0.1 and 0.9

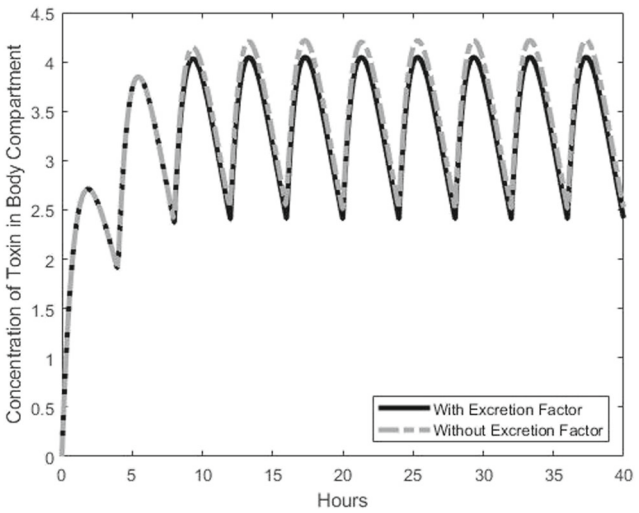

Fig. 7 Plot of concentration of toxin in the body vs time for our model with excretion factor, and a typical model without this factor. Parameters for this model are chosen as follows: $k_a = 0.4$, $k_e = 0.7$, $\Delta t = 4$, $\delta t = 8$

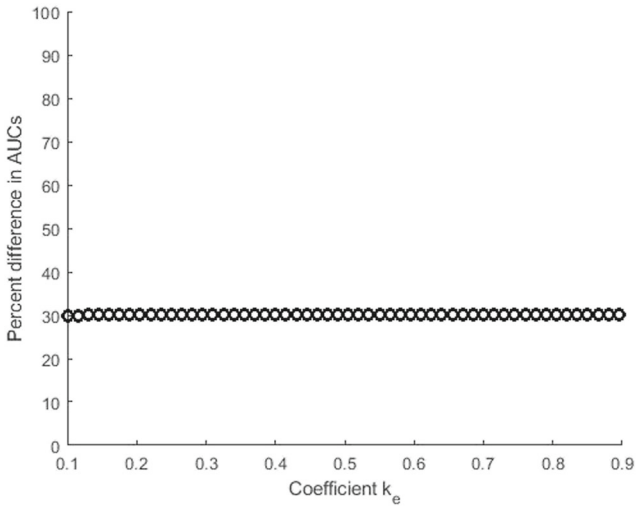

Fig. 9 Plot of the coefficient of elimination, k_e vs the percent difference in AUC's. Parameters for this model are chosen as follows: $k_a = 0.2$, $\Delta t = 6$, $\delta t = 6$, with k_e varying between 0.1 and 0.9

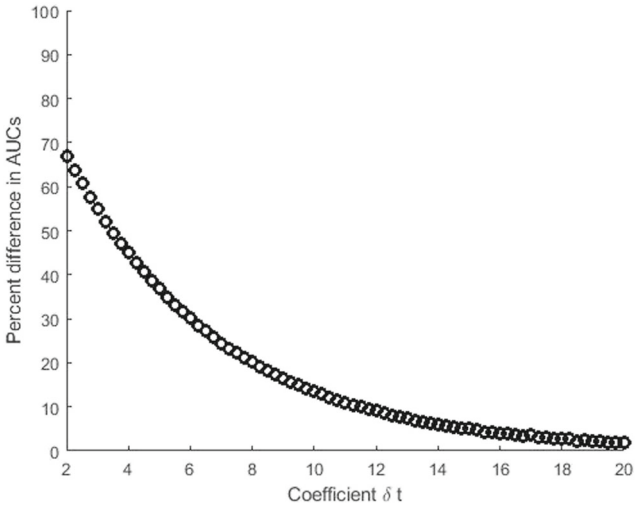

Fig. 10 Plot of the coefficient of the parameter δt vs the percent difference in AUC's. Parameters for this model are chosen as follows: $k_a = 0.2$, $k_e = 0.3$, $\Delta t = 6$, with δt varying between 2 and 20

elimination rate from body compartment impacts the results while also ranging between values from 0.1 to 0.9. This figure shows regardless of the value of k_e, the percentage difference in the two different models remains the same. This suggests the parameter k_e has minimal impact on the system if we assume the elimination rate of liver is linear, where as k_a has a large impact on the system. Similarly we range the values of Δt and δt, while holding all other parameters constant, and range the values between two and twenty hours.

Figure 10 demonstrates how the parameter δt, the duration of toxin staying in the GIT, impacts the index α. As δt increases, the index α is monotonically decreasing.

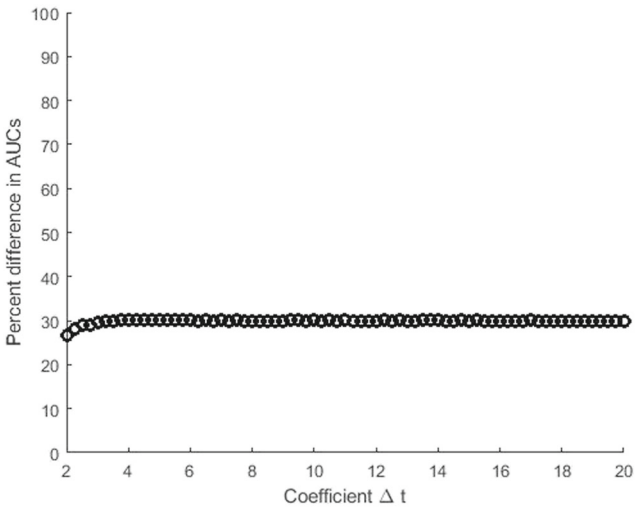

Fig. 11 Plot of the coefficient of the parameter δt vs the percent difference in AUC's. Parameters for this model are chosen as follows: $k_a = 0.2$, $k_e = 0.3$, $\Delta t = 6$, with δt varying between 2 and 20

The impact of the parameter Δt, the interval between two consecutively ingested oral doses of toxin, is shown in Fig. 11. These two figures suggest the impact of Δt is negligible, as the percent difference in bioavailabilities remains unchanged through varying values for Δt, and the parameter δt has a strong impact on the system.

Conclusions

We conclude for any orally intaken toxin, the coefficient of bioavailability which is attributed to the excretion factor of gastrointestinal motility depends mostly on the factors of absorption rate of toxin from GIT (k_a) and duration for toxin staying in GIT (δt), if it is assumed that the absorption rate and elimination rate are linear. From a biological standpoint, this means the bioavailability of a toxin is more dependent on the time the toxin spends in the GIT, and how quickly the toxin is absorbed through the GIT, rather than the rate of elimination from the system and the frequency at which toxin is ingested. This may suggest the mechanism in the GIT could be under relatively higher selective pressure and adaptations than detoxification mechanisms in the body compartment. If the coefficients for a particular toxin are known, we conclude the percentage of bioavailability attributed to gastrointestinal motility can be determined exactly, meaning the remaining mechanisms of bioavailability, including the first pass effect, gastric digestion, and gut microbiomes, can be more accurately determined. In this current paper, all the rates are modeled by a linear function. In reality, the rates might be nonlinear (Ludden 1991), and a combination of both zeroth and first-order processes. Our future work will extend this model to nonlinear functional responses. In the case of nonlinear absorption through the GIT into the body compartment, toxins would need to spend a sufficient amount of time in the GIT before a majority of toxin is absorbed. If, however, the toxin is moved through the GIT due to gastrointestinal motility before this has taken place, a majority of the toxin might move through the organism completely unabsorbed. We hypothesize in the case of nonlinear absorption, this excretion factor might contribute an even greater effect on the bioavailability of a toxin. Also, we would like to incorporate the metabolism of the intestinal enzymes of the host and the microbiome in the model to explore their impact on concentration in body compartments. These parameters could further affect toxin bioavailability independent of gastrointestinal motility.

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Appendix

Analytical solution of the single dose model with excretion factor.

$$\begin{cases} \dfrac{dGI_i(t)}{dt} = -k_a GI_i(t), i\Delta t < t < i\Delta t + \delta t \\ GI_i(i\Delta t) = D_0, t = i\Delta t, i = 0, 1, \cdots n \\ GI_i(t) = 0, 0 < t < i\Delta t \text{ or } t > i\Delta t + \delta t \end{cases} \tag{8}$$

Solving for $GI(t)$ and rewriting the equation in terms of Heaviside or unit step functions yields the following analytical solution for $GI(t)$.

$$GI(t) = \sum_{i=0}^{n-1} D_0 e^{-k_a(t-i\Delta t)}(1 - u_{i\Delta t+\delta t}(t))u_{i\Delta t}(t) \tag{9}$$

This give the concentration of toxin to be absorbed inside the GIT. The concentration in the body compartment is then given by

$$\frac{dC_m(t)}{dt} + k_e C_m = \frac{1}{V}(k_a GI(t)) \tag{10}$$

Using Laplace transforms the solution can then be determined in two cases.

Case I. where $\delta t < \Delta t$, or the time for the excretion factor to take effect, the amount of time the toxin spends in the GIT is less than the dosing interval.

$$C_m(t) = \begin{cases} \sum_{i=0}^{n-1} \frac{D_0 k_a}{V(k_e - k_a)} e^{(-k_e t + k_a i\Delta t)} \left[e^{(k_e - k_a)t} - e^{(k_e - k_a)i\Delta t} \right], \\ i\Delta t < t < i\Delta t + \delta t \\ \sum_{i=0}^{n-1} \frac{D_0 k_a}{V(k_e - k_a)} e^{(-k_e t + k_a i\Delta t)} \left[e^{(k_e - k_a)(i\Delta t + \delta t)} - e^{(k_e - k_a)i\Delta t} \right], \\ i\Delta t + \delta t < t < (i+1)\Delta t \end{cases} \tag{11}$$

Case II. where $\Delta t < \delta t < 2\Delta t$, or the time for the excretion factor to take effect, the amount of time the toxin spends in the GIT is between dosing intervals.

$$C_m(t) = \begin{cases} \frac{D_0 k_a}{V(k_e - k_a)} e^{(-k_e t)} \left[e^{(k_e - k_a)t} - 1 \right], 0 < t < \Delta t \\ \sum_{i=0}^{n-1} \frac{D_0 k_a}{V(k_e - k_a)} e^{-k_e t} \left[e^{(k_e - k_a)t + k_a i\Delta t)} - e^{(k_e - k_a)i\Delta t} \right], \\ i\Delta t < t < (i-1)\Delta t + \delta t \\ \sum_{i=0}^{n-1} \frac{D_0 k_a}{V(k_e - k_a)} e^{-k_e t} \left[e^{(k_e - k_a)((i-1)\Delta t + \delta t)} - e^{(k_e - k_a)t} \right], \\ (i-1)\Delta t + \delta t < t < (i+1)\Delta t \end{cases} \tag{12}$$

References

Amidon G, Lennernäs H, Shah V, Crison J (1995) A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharmaceut Res 12(3):413–420

Clements J, Heading R, Nimmo W, Prescott L (1978) Kinetics of acetaminophen absorption and gastric emptying in man. Clin Pharmacol Ther 24(4):420–431

Derendorf H, Meibohm B (1999) Modeling of pharmacokinetic/pharmacodynamic (pk/pd) relationships: concepts and perspectives. Pharm Res 16(2):176–185

Holford N, Sheiner L (1982) Kinetics of pharmacologic response. Pharmacol Therapeut 16(2):143–166

Karasov W, Douglas A (2013) Comparative digestive physiology. Comprehens Physiol 3(2):741–783

Kiyoshi Y, Terumichi N, Toyozo U (1978) Statistical moments in pharmacokinetics. J Pharm Biopharm 6(6):547–558

Koch G, Krzyzanski W, Pérez-Ruixo J, Schropp J (2014) Modeling of delays in pkpd: classical approaches and a tutorial for delay differential equations. J Pharmacokinet Phar 41(4):291–318

Ludden T (1991) Nonlinear pharmacokinetics. Clin Pharm 20(6):429–446

McLean S, Boyle R, Brandon S, Davies N, Sorensen J (2007) Pharmacokinetics of 1, 8-cineole, a dietary toxin, in the brushtail possum (Trichosurus vulpecula): significance for feeding. Xenobiotica 37(9):903–922

Meibohm B, Derendorf H (1997) Basic concepts of pharmacokinetic/pharmacodynamic (pk/pd) modelling. Int J Clin Pharmacol Ther 35(10):401–413

Shargel L, Andrew B, Wu-Pong S (1999) Applied biopharmaceutics and pharmacokinetics. Appleton & Lange Stamford

Shipley L, Forbey J, Moore B (2009) Revisiting the dietary niche When is a mammalian herbivore a specialist? Integr Comp Biol 49(3):274–90

Sorensen J, Turnbull C, Dearing M (2004) A specialist herbivore (Neotoma stephensi) absorbs fewer plant toxins than does a generalist (Neotoma albigula). Physiol Biochem Zool 77(1):139–48

Sukumaran S, Gadkar K, Zhang C, Bhakta S, Liu L, Xu K, Raab H, Yu S, Mai E, Fourie-O'Donohue A (2015) Mechanism-based pharmacokinetic/pharmacodynamic model for THIOMAB, drug conjugates. Pharm Res 32(6):1884–1893

Thacker E, Gardner D, Messmer T, Guttery M, Dahlgren D (2012) Using gas chromatography to determine winter diets of greater sage-grouse in Utah. J Wildl Manag 76(3):588–592

Torregrossa A, Dearing M (2009) Nutritional toxicology of mammals: regulated intake of plant secondary compounds. Funct Ecol 23(1):48–56