Université de Montréal

Modélisation pharmacocinétique du rythme circadien

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Mémoire accepté le: . . . . . .

RÉSUMÉ

L'être humain est organisé selon une horloge interne d'une période d'environ 24 heures. La pharmacocinétique de certaines classes de médicaments est donc influencée par le rythme circadien. En effet, l'aire sous la courbe de la concentration en médicament en fonction du temps, la concentration maximale en médicament et le temps auquel on obtient la concentration maximale peuvent varier en fonction de l'heure à laquelle a été consommé le médicament. Le but de ce travail est de modéliser la variation de la concentration maximale de ces médicaments selon le moment de la journée auquel ils sont pris.

On étudie d'abord un modèle présenté par Godfrey permettant de trouver la concentration en médicament en fonction du temps et tenant compte des variations circadiennes. Ce modèle ne permet pas d'illustrer les variations dans la concentration maximale selon le moment de la journée auquel le médicament est pris. Un nouveau modèle à deux compartiments sera donc développé pour les trois modes d'absorption (orale, intraveineuse, intraveineuse bolus). Les systèmes d'équations différentielles résultants seront étudiés. L'effet de la variation des paramètres de phase sur la concentration maximale sera aussi étudié. La preuve de l'existence des solutions, de leur unicité et de leur positivité sera faite en annexe.

Mots clés : Modélisation mathématique, équations différentielles, pharmacocinétique, rythme circadien, modèles compartimentaux.

ABSTRACT

Humans are organised according to an internal clock with a period of approximatively 24 hours. The pharmacokinetic of several classes of drugs are then influenced by circadian rhythms. Indeed, the area under the curve (of the drug concentration as a function of time), the maximal concentration and the time to maximal concentration can change according to the time at which the drug is taken. The objective of this present work is to find a model to represent the variations in the maximal drug concentration according to the absorption's time.

We first study a model presented by Godfrey. It allows to find the drug concentration as a function of time while taking into account circadian rhythms. Unfortunately, this model could not represent the variations in the maximal concentration according to the time at which the drug is taken.

We developed a new two-compartmental model for the three ways of absorption (oral, intravenous and intravenous bolus). The resulting systems of ordinary differential equations will be studied. The effect of the phase parameters on the maximal concentration will also be studied. Finally, the proof of well-poseness of the model will be developed in the Annex.

Keywords : Modelling, ordinary differential equations, pharmacokinetics, circadian rhythms, compartmental models.

TABLE DES MATIÈRES

Ce sont nos choix qui montrent ce que nous sommes vraiment, beaucoup plus que nos aptitudes.

-Albus Dumbledore

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INTRODUCTION

La pharmacocinétique est l'étude de l'effet de l'organisme sur une substance médicamenteuse. Elle peut être divisée en quatre étapes : l'absorption, la distribution, le métabolisme et l'excrétion. Différentes quantités pharmacocinétiques sont typiquement calculées pour étudier l'effet d'un médicament telles que l'aire sous la courbe de concentration plasmatique en fonction du temps, la concentration maximale obtenue, le temps où la concentration maximale est obtenue,... Nous nous intéresserons ici principalement à l'influence du rythme circadien sur la concentration maximale en médicament dans le plasma.

Le mot circadien provient du latin "circa" et "dies" qui signifie "environ un jour". Le rythme circadien est donc tout processus biologique comportant des oscillations d'une période d'environ 24 heures. Les humains sont organisés selon une horloge interne. Cette horloge est responsable des rythmes circadiens. Ces rythmes internes sont influencés par différents facteurs extérieurs comme les Zeitgeber, soit la lumière, la température et la nourriture. Les stimulateurs du rythme circadien se trouvent dans le noyau suprachiasmatique situé dans l'hypothalamus antérieur [2].

Le rythme circadien a une influence sur les quatre étapes pharmacocinétiques soit l'absorption, la distribution, le métabolisme et l'excrétion.

L'absorption désigne le transport du site d'absorption à la circulation systémique. L'administration par voie orale est la plus commune des voies d'absorption. Elle dépend de plusieurs facteurs tels les propriétés physico-chimiques du médicament, le pH dans l'estomac, le taux auquel l'estomac se vide,... Des études ont montrées que ces processus ont un rythme circadien. Par exemple, certains médicaments comme la nifedipine ou le digoxin sont mieux absorbés durant le jour que durant la nuit. De plus, l'activité des gènes MDR1, MCT1 et BCRP1 montre des variations circadiennes et joue un rôle important dans le transport du médicament de l'intérieur de la cellule à l'intestin [15].

La distribution désigne le transport du médicament de la circulation systémique

aux différents tissus et organes. Elle est influencée par la vitesse de circulation du sang aux organes ou tissus, la présence de transporteurs pour le médicament et la présence de liaisons de protéines dans le plasma et les tissus. Ces processus démontrent des variations circadiennes qui donc influencent le taux de distribution [15].

La métabolisation désigne la transformation biochimique du médicament qui se fait principalement dans le foie. Les facteurs inluençant la métabolisation sont le débit sanguin, les activités enzymatiques et la présence de liaisons aux protéines. Ces processus sont encore une fois influencés par les variations circadiennes. Il a été montré que certains enzymes qui jouent un rôle dans le métabolisme des médicaments sont influencés par le rythme circadien. Leur transcription serait régulée par des gènes de l'horloge centrale [15].

L'excrétion désigne le processus par lequel le médicament est éliminé de l'organisme. L'excrétion se produit surtout dans les reins, mais peut se produire aussi dans le foie pour certains médicaments. Elle est influencée par la filtration glomérulaire (filtration dans le rein), la sécrétion tubulaire (excrétion des substances vers l'urine) et réabsorption tubulaire. La sécrétion glomérulaire est influencée par les variations circadiennes. Elle est maximale durant la période active et minimale durant la période inactive [15].

Ainsi, le rythme circadien influence les différents processus pharmacocinétiques.

Nous utiliserons ici un modèle compartimental. Ces modèles sont souvent utilisés en modélisation pharmacocinétique. Un compartiment est un ensemble homogène de molécules. Le passage du médicament dans le corps y est représenté par une suite de compartiments reliés entre eux. Le médicament est administré dans le premier compartiment et peut passer d'un compartiment à l'autre. Il peut aussi être éliminé en partie dans chacun des compartiments. Les vitesses de transfert entre les compartiments et les vitesses d'élimination de la substance médicamenteuse sont proportionnelles à la quantité de médicament dans le compartiment de départ. Les compartiments ne représentent pas nécessairement des organes spécifiques, mais plutôt un processus général.

Nous présenterons ici des modèles pour trois voies d'absorption : orale, intraveineuse et intraveineuse bolus. Lorsque le médicament est pris par voie orale, il doit passer par le système digestif avant d'atteindre la circulation systémique par diffusion. L'absorption de la dose n'est donc pas immédiate. Elle l'est dans le cas d'une injection intraveineuse bolus. Une injection intraveineuse est presque immédiate, comme un vaccin. Celle sous forme de perfusion (zero order input) se fait pendant un certain laps de temps. La voie d'absorption aura comme incidence de faire changer les conditions initiales du modèle et de rajouter une fonction d'absorption.

Certaines classes de médicaments sont influencées par le rythme circadien, par exemple les antiasthmatiques, les anticancéreux, les diurétiques,...[2] Selon le moment de la journée auquel ils sont consommés, il y aura des variations dans les différentes quantités pharmacocinétiques mentionnées plus haut. Nous nous concentrerons ici sur l'influence de l'heure de prise du médicament sur la concentration maximale (C_{max}). Cette dernière est une quantité importante, car elle doit rester dans l'intervalle d'efficacité du médicament. C'est-à-dire qu'elle doit être suffisamment grande pour que le médicament soit efficace, mais pas trop élevée pour ne pas que le médicament soit toxique. Il est donc important de savoir la contrôler. De plus, pour certains médicaments, elle est proportionnelle à l'effet du médicament sur le patient, et donc on veut optimiser l'effet tout en évitant l'intoxication. Le propanolol (un bêta-bloquant), par exemple, montre une concentration maximale presque deux fois plus grande lorsqu'il est pris à 8h00 du matin plutôt que 14h00 [8].

Un modèle compartimental fut proposé par Godfrey tenant compte des variations circadiennes [6]. Ce modèle permettait de représenter les variations de différentes quantités pharmacocinétiques selon l'heure de prise du médicament. Toutefois, il ne permettait pas d'obtenir différentes concentrations maximales selon l'heure à laquelle est pris le médicament. Les concentrations maximales étaient identiques pour différentes valeurs de phase. Ces paramètres de phase représentent le décalage des différents processus (absorption, distribution, métabolisme et élimination) durant la journée. Le but de ce travail

est donc de trouver un modèle capable de représenter l'influence du rythme circadien sur la concentration maximale en médicament. On voudra développer un modèle pour chacune des trois voies d'absorption (orale, intraveineuse et intraveineuse bolus). Finalement, les systèmes d'équations différentielles résultants des modèles seront analysés.

ARTICLE

Modelling Circadian Fluctuations of Pharmacokinetic Parameters

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0.1 Abstract

The pharmacokinetic profile of a number of drugs has been shown to vary as a function of the time of day in the administration and thus apparently be under the influence of circadian rhythms : antiasthmatic, anticancer and cardiovascular products are but a few examples. Circadian rhythms may have influence on each of the processes of absorption, distribution, metabolism and elimination (ADME). Variations in pharmacokinetics quantities such as the Area under the curve (AUC), Mean Residence Time (MRT), time to the peak of concentration (t_{max}) and value of the peak of concentration (C_{max}) may therefore be expected. In this paper, we focus on possible variations in the peak of concentration C_{max}. In contrast to a one-compartment model for time-varying pharmacokinetics quantities which has been shown [6] to *not* display variations in this quantity, we present a bi-compartmental model for time-varying systems to account for rapid intravenous dose, oral dose and intravenous injection (zero order input). The effects of circadian rhythms on the maximal concentration of the drug in the body are studied for both single dose and multiple dosing, showing significant changes in values, induced by the time-varying coefficients in the PK model.

Keywords : Circadian rhythms, pharmacokinetics, two-compartmental models

0.2 Introduction

The influence of circadian rhythms on a number of physiological functions is well established [1], [2] [9], [7], [13], [14]. This variation in turn leads to fluctuations in the the behaviour of certain classes of drug as a function of the time of the day at which they are taken [8], [10], [18]. This behaviour is quantified by a number of classical measures [4], including the maximal concentration of the drug in the body, C_{max}, and the time at which this concentration is reached, t_{max}. However, mathematical representations of this circadian fluctuation and its consequence for these pharmacokinetic parameters have been the object of limited investigations.

In one such work, Godfrey [6] analyses a one-compartment model with time-varying, periodic parameters. To first describe the autonomous system, let x(t) denote the concentration of drug in the compartment, k_e the elimination rate of the drug and u(t) its rate of input, then the model is described by the differential equation

$$\dot{x}(t) = -k_e x(t) + u(t)$$

To represent the circadian variation, the coefficient k_e is taken as a periodic function, with a period of 24 hours, and the fluctuation is represented in the elimination process, so that

$$k_e(t) = k_e(1 + \gamma \sin(\omega t + \phi))$$

where ω represents the frequency of the oscillations, ϕ is the phase angle and γ is a constant used to describe the variation of the k_e coefficient. This equation is used, in both the constant and the periodic cases, to represent the time evolution following a rapid intravenous injection and the ingestion of an oral dose.

The Area Under the Curve (AUC) and Mean Residence Time (MRT) for these mo-

dels are given, since $x(t)$ represents the plasmatic drug concentration, by

$$AUC = \int_0^\infty x(t)dt$$
$$MRT = \frac{\int_0^\infty tx(t)dt}{\int_0^\infty x(t)dt} .$$

The volume of the compartment is considered to be constant and is normalized to the value one. Different values of AUC and MRT are obtained when the phase ϕ changes for both intravenous injection and oral administration [6]. Also, the time at which the concentration curves of the time-invariant and the time-varying systems intersect varies as the phase ϕ is modified. The consequences of varying k_e are also investigated. For the intravenous injection, the limiting cases of $k_e \ll \omega$ and $k_e \gg \omega$ illustrate little differences between the two corresponding concentration curves. This model does not produce changes in the maximal concentration of drug in the compartment by changing the phase ϕ, as the maximal concentration is found for all the values of phase. No systematic investigation of multiple dose administrations was performed.

In this paper, we introduce and investigate a two-compartment model in which the elimination rates and transfer rates are sinusoidally varying. Unlike the one-compartment model, no explicit analytical solutions are available for the periodic system, and thus no explicit expression can be derived for the pharmacokinetic parameters of interest. One original feature of our model is that the phases of all the rates of transfer will be allowed to change independently from one another. Since different modes of administration will be considered, we present three versions of the model, corresponding to rapid intraveneous administration, oral ingestion and intraveneous injection (zero order input). These derivations are detailed in Section 2. We then compare the solutions of the time-invariant systems with the corresponding periodic systems in Section 3. The administration of multiple dose at a regular interval is analysed in Section 4, and applications of the model to physiological perturbations are considered in Section 5.

0.3 The Mathematical Model For Single Dose

Our two-compartment model for intravenous injection takes the form illustrated on Figure 1. The variables A_1 and A_2 denote respectively the quantity of drug in the first and second compartment : the first one is called the central compartment, and is where the drug is administered, whereas the second one is considered the peripheral one, and corresponds to the target site, that is the site of action of the drug. The coefficients k_{mn} represent first-order transfer rates of the drug from compartment m to compartment n, the compartment labeled 0 being considered as the exterior of the body (for administration or elimination). We are mainly interested in the concentration as a function of time in the second compartment, since it is the location of the target site.

0.3.1 Rapid intravenous dose

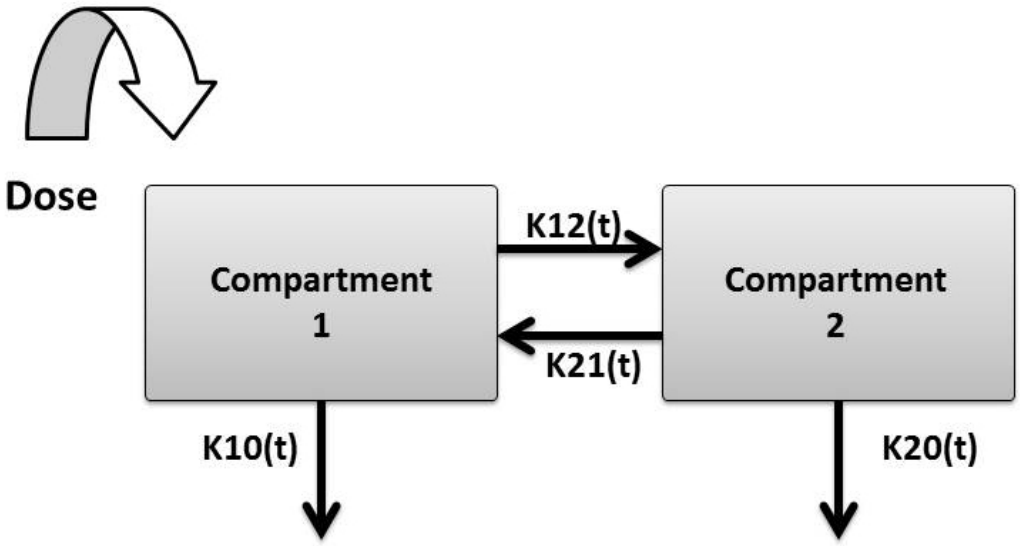

Figure 1 – Bi-compartmental model for intravenous injection

0.3.1.1 Time-invariant System

In the time-invariant system, the coefficients k_{mn} are constant because they ignore circadian rhythms. The notation A_{1i} and A_{2i} will be used throughout to denote respectively the concentration for the time-invariant system in compartment one and two. The model is then represented by the pair of differential equations :

$$\frac{dA_{1i}}{dt} = k_{21}A_{2i} - (k_{12}+k_{10})A_{1i},$$
$$\frac{dA_{2i}}{dt} = k_{12}A_{1i} - (k_{21}+k_{20})A_{2i}\ .$$

We consider that the drug is administered through a rapid intravenous injection, and thus represent it as instantaneously absorbed in the organism. This hypothesis leads to the set of initial conditions

$$A_{1i}(0^+) = Dose$$
$$A_{2i}(0) = 0$$

so that the dose appears instantly in the first compartment just after the initial time, and the second compartment is initially empty. This autonomous linear system can be analytically solved by eigenvalue methods ; together with the initial conditions, one readily obtains

$$A_{2i}(t) = Dose(\frac{-e^{\lambda_2 t}k_{12}}{2\lambda_1+k_{10}+k_{12}+k_{20}+k_{21}} + \frac{e^{\lambda_1 t}k_{12}}{2\lambda_1+k_{10}+k_{12}+k_{20}+k_{21}})$$

with

$$\lambda_1 = \frac{-(k_{12}+k_{10}+k_{21}+k_{20}) + \sqrt{((k_{12}+k_{10}+k_{21}+k_{20})^2 - 4(k_{12}k_{20}+k_{10}k_{21}+k_{10}k_{20}))}}{2}$$
$$\lambda_2 = \frac{-(k_{12}+k_{10}+k_{21}+k_{20}) - \sqrt{((k_{12}+k_{10}+k_{21}+k_{20})^2 - 4(k_{12}k_{20}+k_{10}k_{21}+k_{10}k_{20}))}}{2}$$

0.3.1.2 Time-varying System

In the time-varying system, the circadian rhythm is incorporated to modify the rates of transfer, entering as well as exiting, for both compartments. The coefficients k_{mn} now become periodic functions, and will be in line with the previous work mentioned above.

We consider that the four functions K_{mn} are not only independent from one another, but that they can also be different, in that the rates of transfer from one compartment to another are changing in different ways over the course of a day. This difference is expressed as a phase lag, so that the coefficients K_{mn} are taken as

$$\begin{aligned}
K_{12}(t) &= k_{12}(1+\gamma_1 \sin(\omega_1 t+\phi_1)),\\
K_{21}(t) &= k_{21}(1+\gamma_2 \sin(\omega_2 t+\phi_2)),\\
K_{10}(t) &= k_{10}(1+\gamma_3 \sin(\omega_3 t+\phi_3)),\\
K_{20}(t) &= k_{20}(1+\gamma_4 \sin(\omega_4 t+\phi_4)).
\end{aligned}$$

We assume $0 \leq \gamma_1, \gamma_2, \gamma_3, \gamma_4 \leq 1$, so that the coefficients K_{mn} remains positive, and $\omega_1, \omega_2, \omega_3, \omega_4$ and $\phi_1, \phi_2, \phi_3, \phi_4$ are constant. The notation A_{1v} and A_{2v} will be used throughout to denote respectively the concentration for the time-varying system in compartments one and two. The ensuing differential equations related to this model are different from the one above, since the formerly constants k_{12}, k_{21}, k_{10} and k_{20} have been replaced by functions

of time :

$$\frac{dA_{1v}}{dt} = K_{21}(t)A_{2v}(t) - (K_{12}(t) + K_{10}(t))A_{1v}(t),$$
$$\frac{dA_{2v}}{dt} = K_{12}(t)A_{1v}(t) - (K_{21}(t) + K_{20}(t))A_{2v}(t),$$

with the coefficients :

$$K_{12}(t) = k_{12}(1 + \gamma_1 \sin(\omega_1 t + \phi_1)),$$
$$K_{21}(t) = k_{21}(1 + \gamma_2 \sin(\omega_2 t + \phi_2)),$$
$$K_{10}(t) = k_{10}(1 + \gamma_3 \sin(\omega_3 t + \phi_3)),$$
$$K_{20}(t) = k_{20}(1 + \gamma_4 \sin(\omega_4 t + \phi_4)),$$

and the same initial conditions :

$$A_{1v}(0^+) = Dose,$$
$$A_{2v}(0) = 0.$$

Our main objective is to solve this system in A_{1v} and A_{2v}, and infer from these solutions the pharmacokinetic parameters described in the Introduction.

0.3.2 Oral dose

For an oral administration, an explicit way of distribution must be accounted for, so the drug does not appear instantaneously in the plasma. An intermediate compartment must therefore be added to the model : it will be denoted as *Dose* and assumed to satisfy a linear first order process with rate k_a, as represented on Figure 2.

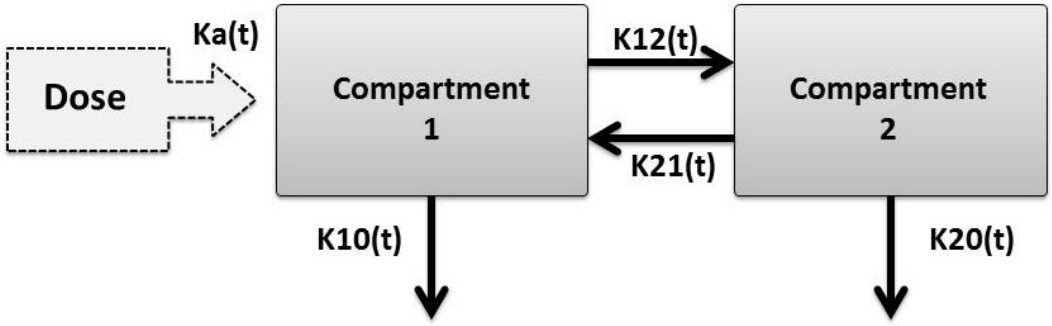

Figure 2 – Bi-compartmental model for oral dose

0.3.2.1 Time-invariant System

We consider first a time-invariant system, in which the coefficients k_{mn} are constant :

$$\begin{aligned}
\frac{dA_{di}}{dt} &= -k_a A_{di}, \\
\frac{dA_{1i}}{dt} &= k_{21}A_{2i} - (k_{12}+k_{10})A_{1i} + k_a A_{di}, \\
\frac{dA_{2i}}{dt} &= k_{12}A_{1i} - (k_{21}+k_{20})A_{2i}.
\end{aligned}$$

As mentioned in the construction of the model, the dose is not represented as instantaneously appearing in the plasma, so the initial conditions are taken to be

$$\begin{aligned}
A_{1i}(0) &= 0, \\
A_{2i}(0) &= 0, \\
F \cdot Dose &= \int_0^\infty A_{di}(0) e^{-\kappa_a t} \mathrm{d}t \\
&= \frac{A_{di}(0)}{\kappa_a}.
\end{aligned}$$

where F is the bioavailability fraction (the fraction of drug that will go in the plasma unchanged). As in the previous time-invariant case, an analytical solution can be obtained by eigenvalue methods, this time applied to a three compartment system, yielding as the general solution in the peripheral compartment

$$A_2(t) = C_1 e^{\lambda_1 t} + C_2 e^{\lambda_2 t} + C_3 e^{\lambda_3 t},$$

with the constant :

$$\lambda_1 = -k_a,$$
$$\lambda_2 = \frac{-(k_{12}+k_{10}+k_{21}+k_{20}) + \sqrt{(k_{12}+k_{10}+k_{10}+k_{21}+k_{20})^2 - 4(k_{12}k_{20}+k_{10}k_{21}+k_{10}k_{20})}}{2},$$
$$\lambda_3 = \frac{-(k_{12}+k_{10}+k_{21}+k_{20}) - \sqrt{(k_{12}+k_{10}+k_{10}+k_{21}+k_{20})^2 - 4(k_{12}k_{20}+k_{10}k_{21}+k_{10}k_{20})}}{2},$$
$$C_1 = \frac{FDosek_a}{k_{20}-k_a},$$
$$C_2 = \frac{FDosek_a(2k_20+2k_{21}-k_a-\lambda_1)}{(k_{20}-k_a)(\lambda_1-\lambda_2)},$$
$$C_3 = \frac{-FDosek_a(2k_20+2k_{21}-k_a-\lambda_2)}{(k_{20}-k_a)(\lambda_1-\lambda_2)}.$$

0.3.2.2 Time-varying System

As in the case of intravenous injection, we also consider the system where the k_{mn} coefficients are periodic functions of time, with the same functional form as above.

The differential equations become

$$\begin{aligned}
\frac{dA_{dv}}{dt} &= -K_a(t)A_{dv},\\
\frac{dA_{1v}}{dt} &= K_{21}(t)A_{2v} - (K_{12}(t)+K_{10}(t))A_{1v} + K_a(t)A_{dv},\\
\frac{dA_{2v}}{dt} &= K_{12}(t)A_{1v}(t) - (K_{21}(t)+K_{20}(t))A_{2v}(t),
\end{aligned}$$

with coefficients,

$$\begin{aligned}
K_{12}(t) &= k_{12}(1+\gamma_1\sin(\omega_1 t+\phi_1)),\\
K_{21}(t) &= k_{21}(1+\gamma_2\sin(\omega_2 t+\phi_2)),\\
K_{10}(t) &= k_{10}(1+\gamma_3\sin(\omega_3 t+\phi_3)),\\
K_{20}(t) &= k_{20}(1+\gamma_4\sin(\omega_4 t+\phi_4)),\\
K_a(t) &= k_a(1+\gamma_5\sin(\omega_5 t+\phi_5)),
\end{aligned}$$

and the same initial conditions as before :

$$\begin{aligned}
A_{dv}(0) &= F\times Dose\times k_a,\\
A_{1v}(0) &= 0,\\
A_{2v}(0) &= 0.
\end{aligned}$$

Since the solutions A_{1v} and A_{2v} can no longer be obtained analytically, we rely on numerical solutions computed using a fourth-order Runge-Kutta scheme in the programming language Matlab.

0.3.3 Intravenous injection (zero order input)

For this kind of intravenous injection, the injection rate of the drug in the first compartment is a constant or a periodic function. It will not depend on the quantity of drug and can be represented as in Figure 3.

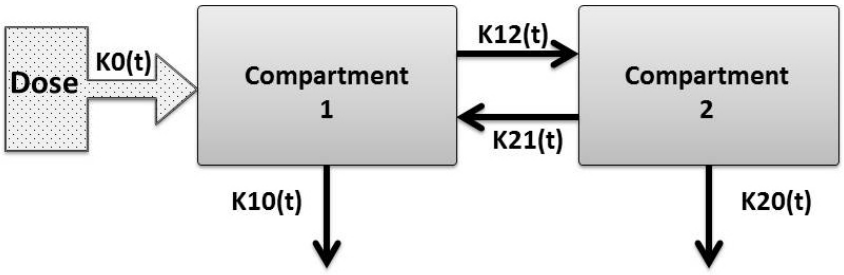

Figure 3 – Bicompartmental model for Intravenous Injection (zero order input)

0.3.3.1 Time-invariant System

The equations for the time-invariant system are

$$\frac{dA_{1i}}{dt} = k_{21}A_{2i} - (k_{12}+k_{10})A_{1i} + k_0,$$
$$\frac{dA_{2i}}{dt} = k_{12}A_{1i} - (k_{21}+k_{20})A_{2i},$$

with the initial conditions :

$$A_{1i}(0) = 0,$$
$$A_{2i}(0) = 0.$$

Again the notation A_{1i} and A_{2i} will be used to denote the concentration in drug in each of the compartments for the time-invariant model.

0.3.3.2 Time-varying System

As in the model for intravenous injection, we now consider that the k_{mn} coefficient are periodic in time, the constants k_{12}, k_{21}, k_{10}, k_{20} having to be replaced. The differentials

equations become

$$\frac{dA_{1v}}{dt} = K_{21}(t)A_{2v} - (K_{12}(t) + K_{10}(t))A_{1v} + K_0(t),$$
$$\frac{dA_{2v}}{dt} = K_{12}(t)A_{1v}(t) - (K_{21}(t) + K_{20}(t))A_{2v}(t),$$

with the coefficients

$$K_{12}(t) = k_{12}(1 + \gamma_1 \sin(\omega_1 t + \phi_1)),$$
$$K_{21}(t) = k_{21}(1 + \gamma_2 \sin(\omega_2 t + \phi_2)),$$
$$K_{10}(t) = k_{10}(1 + \gamma_3 \sin(\omega_3 t + \phi_3)),$$
$$K_{20}(t) = k_{20}(1 + \gamma_4 \sin(\omega_4 t + \phi_4)),$$
$$K_0(t) = k_0(1 + \gamma_5 \sin(\omega_5 t + \phi_5)),$$

and the same initial conditions as before :

$$A_{1v}(0) = 0,$$
$$A_{2v}(0) = 0.$$

The solutions of these equations are also computed numerically, and the notation A_{1v} and A_{2v} is used to denote the concentration of drug in the compartments for the time-varying model.

0.4 Comparison of time-invariant and time-varying systems

In [6], a one-compartment model with an identical phase for each of the periodic coefficients k_{mn} is considered. Under those conditions, no variation of the maximal concentration of the drug appears. Here, we are looking for ways to induce differences of maximal concentration between the time-invariant and time-varying system for each absorption ways. Only the phase will change, the other parameters will stay the same troughout the analysis. We chose values close to the one considered in [6] , namely

$$\text{volume=F=Dose=1, } k_{12} = 0.3,\ k_{21} = 0.4,\ k_{10} = 0.231,\ k_{20} = 0.231,$$

$$\gamma_1 = \gamma_2 = \gamma_3 = \gamma_4 = 0.2$$

and

$$\omega_1 = \omega_2 = \omega_3 = \omega_4 = 0.262 = 2\pi/24$$

the latter values being aligned on a period of 24 hours. The differences in values of the maximal concentration in the different models will be expressed as a relative error, namely a percentage of change (% error) for C_{max} defined as :

$$C_{max}\%error = \frac{C_{imax} - C_{vmax}}{C_{imax}} \times 100\%$$

where C_{imax} is the maximal concentration in the second compartment for the time-invariant system and C_{vmax} is the maximal concentration in the second compartment for the time-varying system. We are thus using the time-invariant systems baseline.

0.4.1 Intravenous injection

Simulations were performed with the values given above, to identify the variations in the maximal concentration in the second compartment (peripheral) between the time-invariant and periodic models.

We observe that there is no difference in the value of C_{max} between the time-varying and time-invariant systems when all phase lags are identical. The t_{max} (time to peak of concentration), however, does change in value.

In Figure 4(a), the values of both C_{max} and t_{max} are different. In Figures 4(b), (c), (d) the values of C_{max} are very close and the phase differences ϕ_{1-4} are all equal. Finally, we observe differences again in the values of C_{max} in Figure 4(e). This extends the results of [6] when all the phases are the same. Differences in C_{max} begin to appear when the phases are not all identical. As we see in Figure 4, the maximal concentration of the time-varying system can be close to the one of the time-invariant system, but the difference may also be important. Some values for these differences in $C_{max}\%error$ are shown in Table 0.I below.

Tableau 0.I – Values of C_{max}%error for the model with intravenous injection

ϕ_1	ϕ_2	ϕ_3	ϕ_4	$C_{max}\%error$
$\pi/2$	$3\pi/2$	$3\pi/2$	$3\pi/2$	-31.83
0	0	$3\pi/4$	$7\pi/8$	0.6728
π	π	π	π	0.0349
...	...	...	...	...
$\pi/2$	$\pi/2$	$\pi/2$	$\pi/2$	-0.0014
$3\pi/2$	$3\pi/2$	$3\pi/2$	$3\pi/2$	0.0103
$3\pi/2$	$\pi/2$	$\pi/2$	$\pi/2$	26.529

0.4.1.1 Relations between the ϕ and the C_{max}%error

The relation between the phase differences ϕ and the values of C_{max}%error can be represented as three-dimensional surfaces when the influence of two phase differences are considered simultaneously. This is illustrated in Figure 5 where the maximal concentration is displayed as a function of ϕ_1 and ϕ_2 at the fixed values $\phi_3 = \phi_4 = 3\pi/2$, and as a funciton of ϕ_3 and ϕ_4 for $\phi_1 = \phi_2 = 3\pi/2$.

0.4.2 Oral Dose

For the oral dose model, an additional constant, for absorption, k_a, is present. We set its value at $k_a = 0.693$ as in [6]. The other phase parameters have the same values as before with $\gamma_5 = 0.3$ and $\omega_5 = 2\pi/24$. The same calculations are performed on the model for the oral dose, but different results are found. In this case, in fact, even identical phases give different maxima for the concentration curves, as shown in Figure 6.

In Figure 6(a), with the values $\phi_1 = \phi_5 = \pi/2$ and $\phi_2 = \phi_3 = \phi_4 = 3\pi/2$, we see that the maximal concentration from both systems are very different. A noticeable difference also appears in figure 6(e) where $\phi_1 = \phi_5 = 3\pi/2$ and $\phi_2 = \phi_3 = \phi_4 = \pi/2$. Much smaller differences are oberved in the maximal concentration when the ϕ are all the same in Figures 6(b),(c) and (d). Some C_{max}%error are shown in Table 2 below. Oscillations in

Tableau 0.II – Values of C_{max}%error for the model with oral dose

ϕ_1	ϕ_2	ϕ_3	ϕ_4	ϕ_5	$C_{max}\%error$
$\pi/2$	$3\pi/2$	$3\pi/2$	$3\pi/2$	$\pi/2$	-36.0160
0	0	$\pi/2$	$\pi/2$	$\pi/2$	0.2767
π	π	π	π	π	1.3009
...	...	...	...	...	
$\pi/2$	$\pi/2$	$\pi/2$	$\pi/2$	$\pi/2$	-1.8113
$3\pi/2$	$3\pi/2$	$3\pi/2$	$3\pi/2$	$3\pi/2$	2.3855
$3\pi/2$	$\pi/2$	$\pi/2$	$\pi/2$	$3\pi/2$	26.2341

the concentration curves begin to appear when the constant k_a is decreased. Recall that the smaller that constant is, the longer it takes for the drug to be introduced in the plasma.

0.4.3 Intravenous injection (zero order input)

The new constant k_0 of this model is set to the value 1, value which is chosen somewhat arbitrarily. We also have $\gamma_5 = 0.3$ and $\omega_5 = 2\pi/24$. Like in the oral dose model, oscillations appear in the concentration curve for the time-varying system. Here, the different phases alter the amplitude rather than the period of the oscillations. Significant changes do appear for certain values of the phase lags. We can see in figure 8 that oscillations appear in the concentration curve for the time-varying system. By changing the phases ϕ_i we can either obtain close maximal concentration or very different ones. Some C_{max}%error of this model are shown in the table below.

0.5 The Mathematical Model for Multiple Dose

Some drugs have to be given more than once to be efficient. Considering that the maximal concentration can be significantly different depending on which system is used for a single dose, it may matter also after the administration of multiple doses. The period

Tableau 0.III – Values of C_{max}%error for the model with bolus injection

ϕ_1	ϕ_2	ϕ_3	ϕ_4	ϕ_5	$C_{max}\%error$
$\pi/2$	$3\pi/2$	$3\pi/2$	$3\pi/2$	$\pi/2$	64.8313
0	0	$\pi/2$	$\pi/2$	$\pi/2$	8.6896
π	π	π	π	π	5.6970
...	...	...	...	...	
$\pi/2$	$\pi/2$	$\pi/2$	$\pi/2$	$\pi/2$	5.7217
$3\pi/2$	$3\pi/2$	$3\pi/2$	$3\pi/2$	$3\pi/2$	5.7217
$3\pi/2$	$\pi/2$	$\pi/2$	$\pi/2$	$3\pi/2$	64.8466

of time at which the dose is given here is set to 6 hours, because it is a commonly used dosage corresponding to four times a day. The same computations have been done on the C_{max} for the models but this time administrating multiple doses at a periodic frequency. The quantities of interest in these calculations are :

A_1[t] : Quantity of drug in the compartment 1 in function of the time

A_2[t] : Quantity of drug in the compartment 2 in function of the time

To find A_1[t] and A_2[t] , the differential equations of Section 0.3 are solved numerically.

The interval of time between successive administration is i hours, so the equations after each dose become

After the first dose, the equations are :

$A_1^1[t]$ with $A_1^1[0] = Dose$ and $0 \leq t < i$

$A_2^1[t]$ with $A_2^1[0] = 0$

After the second dose, the equations are :

$A_1^2[t]$ with $A_1^2[0] = A_1^1[i] + Dose$ and $i \leq t < 2i$

$A_2^2[t]$ with $A_2^2[0] = A_2^1[i]$

After the third dose, the equations are :

$A_1^3[t]$ with $A_1^3[0] = A_1^2[i] + Dose$ and $2i \leq t < 3i$

$A_2^3[t]$ with $A_2^3[0] = A_2^2[i]$

etc.

To determine the maximum C_{max}%error, the phases $\phi_1 = \pi/2$, $\phi_2 = 3\pi/2$, $\phi_3 = 3\pi/2$ and $\phi_2 = 3\pi/2$ have been chosen thoughout these calculations. Also, the same values for the coefficients were used : $k_{12} = 0.3$, $k_{21} = 0.4$, $k_{10} = 0.231$, $k_{20} = 0.231$ with the same Dose=1, the volume of each compartment is set at 1, and $\gamma_1 = \gamma_2 = \gamma_3 = \gamma_4 = 0.2$ and, finally, $\omega_1 = \omega_2 = \omega_3 = \omega_4 = 2\pi/24$.

0.5.1 Intravenous Injection

We see in Figure 9 that the maximal concentration can be really different when one considers either the invariant or the time-varying model . The maximal concentration of the time-varying model oscillates in time with a period of 24 hours.

While keeping the same dose for the time-invariant system to 1, the doses for the time-varying system has been change so that the two systems have the same peaks (the same C_{max} after each dose). The number of the first dose is one. Figure 10 shows the adjusted dose.

We see that the adjusted dose also seems to have a period of 24 hours.

0.5.2 Oral Dose

A new constant appears again in the Oral dose model, and the same value was chosen, $k_a = 0.693$. The other constant values are the same as the one used above. In Figure 11, we see that the maximal concentration for the time-varying model oscillates in time. The maximal concentration remains the same for the time invariant model when it reaches a steady state. The maximal concentrations are very different in the invariant and time-varying model. Here the dose given every 6 hours was always the same, 1. In order to have the same maximal concentration for the time-varying and invariant systems, the adjusted dose for the time-varying model was found. Figure 12 shows the dose we have to give in the time-varying model in order to have the same maximal concentration as the one in the invariant model. The dose given multiple times in the invariant model remains

equal to 1. Again, we observe that the adjusted dose seems to be periodic with a period of 24 hours.

0.6 Application of the model : jet lag recovery

The most present, and annoying, manifestation of circadian rhythms is experienced by long distance travellers who cross multiple time zones from origin to destination. A possible application of the model presented here is a the determination of the impact of Jet Lag on the concentration of drugs. Indeed, a drug inflenced by circadian rhythms could also be influenced by time shift. Consider a drug taking orally, periodically. We want to see what the impact of changing time zone will be on the drug concentration profiles.

We considered here that Jet Lag will influence the absorption, distribution, metabolism and elimination of the drug in the body. Thereby, the phases ϕ_i will change when changing time zone which will make the coefficients k_{mn} change at the same time. In the modelling equations, the phases ϕ_i will now be modified by a shift and become $\phi_i(t)$. The modified equations are :

$$\begin{aligned}
\frac{dA_d}{dt} &= -K_a(t)A_d(t), \\
\frac{dA_{1v}}{dt} &= K_a(t)A_d(t) + K_{21}(t)A_{2v}(t) - (K_{12}(t) + K_{10}(t))A_{1v}(t), \\
\frac{dA_{2v}}{dt} &= K_{12}(t)A_{1v}(t) - (K_{21}(t) + K_{20}(t))A_{2v}(t),
\end{aligned}$$

with the coefficients

$$K_{12}(t) = k_{12}(1+\gamma_1 \sin(\omega_1 t + \phi_1(t))),$$
$$K_{21}(t) = k_{21}(1+\gamma_2 \sin(\omega_2 t + \phi_2(t))),$$
$$K_{10}(t) = k_{10}(1+\gamma_3 \sin(\omega_3 t + \phi_3(t))),$$
$$K_{20}(t) = k_{20}(1+\gamma_4 \sin(\omega_4 t + \phi_4(t)))$$
$$K_a(t) = k_a(1+\gamma_5 \sin(\omega_5 t + \phi_5(t)))$$

and the initial conditions

$$A_d(0) = F \times Dose \times k_a,$$
$$A_{1v}(0) = Dose,$$
$$A_{2v}(0) = 0.$$

The shift in the phase difference function yields $\phi_i = c_i \pm f(t)$ in which $f(t) = 0$ for $t \in [0, T_1]$ and is a function of time for $t > T_1$, where T_1 denotes the time at which the time shift is initiated. Also, $c_1, c_2, c_3, c_4, c_5 \in \mathbb{R}$ are constant all taking values in $[0, 2\pi]$.

The function f is called the shift function. It has the following form :

$$f(t) = -Ae^{-\alpha(t-T_1)} + Ae^{-\beta(t-T_1)}$$
$$\text{with } A, \alpha, \beta \in \mathbb{R}^*$$

This function is increasing for $t \in [T_1, \frac{log(\alpha/\beta)}{(\alpha-\beta)}]$ and decreasing for $t > \frac{log(\alpha/\beta)}{(\alpha-\beta)}$ as we can see in figure 13. The difference $\frac{log(\alpha/\beta)}{(\alpha-\beta)} - T_1$ represents the time it takes to change time zone, so approximately the time spent in the plane for the case of air transportation. The maximum value of this function is $\max = A[(\frac{\alpha}{\beta})^{\frac{-\alpha}{\alpha-\beta}} - (\frac{\alpha}{\beta})^{\frac{-\beta}{\alpha-\beta}}]$. The Jet Lag can then be

evaluated as $\frac{max*24h}{2\pi}$. Once the person is in the new time zone, he will begin to adjust his drug ingestion to this new clock. Thereby, once the Jet Lag is in effect, the shift function f will start to decrease. It will tend to 0, rather rapidly, corresponding to the physiological adjustments to the new time zone.

We use, in the shift function defined above, the parameter values $\alpha = 0.2$, $\beta = 0.15$, $A = 15$, $T_1 = 73$. This will lead to a Jet Lag of 6.0429 hours and it will take 5.7536 hours to obtain it. Figure 13 illustrates the shift function f(t). As mentioned above, we consider a dose given orally multiple times. The time T_1 is significant, so the concentration has time to reach steady state before the changing of time zone can take place. We also use the following values for the parameters :

$$\omega = 2 * \pi/24; \gamma_1 = 0.2; \gamma_2 = 0.2; \gamma_3 = 0.2; \gamma_4 = 0.2; \gamma_5 = 0.3; k_{12} = 0.3; k_{21} = 0.4;$$
$$k_{20} = 0.231; k_{10} = 0.231; k_a = 0.693; \phi_1 = 0; \phi_2 = \pi/2; \phi_3 = \pi; \phi_4 = 0; \phi_5 = \pi/2.$$

We can observe an adjustment in drug concentration as time progresses : the drug concentration approches the value observed in the absence of jet lag.

Here again we compare the maximal concentration with the effect of jet lag at each dose to the one without the effect of jet lag. The absolute value of the error percentage was taken at each dose, as shown in Figures 15 and 16. We see that the error is bigger when travelling with a negative shift. Thereby, the error is bigger when the time in the arrival place is in advance.

However, with the Jet Lag the dose is not taken at the same time. We consider next that the time of day at which the drug is taken, is the same locally in both time zone when the drug is taken over a 24 hours cycle. For example, if the drug is taken at 6 o'clock in the departure's country, it will be taken at 6 o'clock in the arrival destination as well. At some point, there will then be an interval of more or less than 24 hours between two doses.

We see on Figures 17 and 18 that, in these cases, the maximal concentration never

adapts completely in either case. We also see that the difference between the two curves is larger when travelling east rather than travelling west.

0.7 Discussion

A bi-compartmental model has been used to represent the influence of the circadian changes in the behavior of a drug in the body. The circadian rhythm was assumed to have a sinusoidal form. This model was used for single dose of intravenous injection, oral dose and intravenous injection (zero order input). This model was compared with one that does not consider circadian variations. The effects of changing the phase of the transfer coefficients on the maximal concentration were evaluated.

The model for intravenous injection gave the same maximal concentration when the phases of the different transfer coefficients were the same. On the other hand, when the phases change independently, significant difference between the time-varying and time-invariant system appears. For instance, a $C_{max}\%error$ up to -31%,-36% and 64% was found for, respectively, an intravenous dose, an oral dose and a bolus dose. For the intravenous model and oral dose model the biggest |C_{max}%error| obtained was with the phases $\phi_1 = \pi/2, \phi_2 = 3\pi/2, \phi_3 = 3\pi/2$, and $\phi_4 = 3\pi/2$, and with the phases $\phi_1 = 3\pi/2, \phi_1 = \pi/2, \phi_1 = \pi/2$ and $\phi_1 = \pi/2$. Oscillations in the curve of the concentration as a function of time appear when the constant k_a was small in the model for oral dose and always with the model for intravenous injection (zero order input). The smaller the k_a is, the smaller the period of the oscillations are. The same tests were done on the models for multiple dosing for oral and intravenous dose. The C_{max}%error again could be significantly big according to the choice of the phases.

This analysis suggests, in view of the significant values of C_{max}%error, that circadian variability should be considered in designing administration protocols. This consideration has been identifed [5] as one of many challenges that modelers should address to incorporate the dynamics of fluctuating physiological functions.

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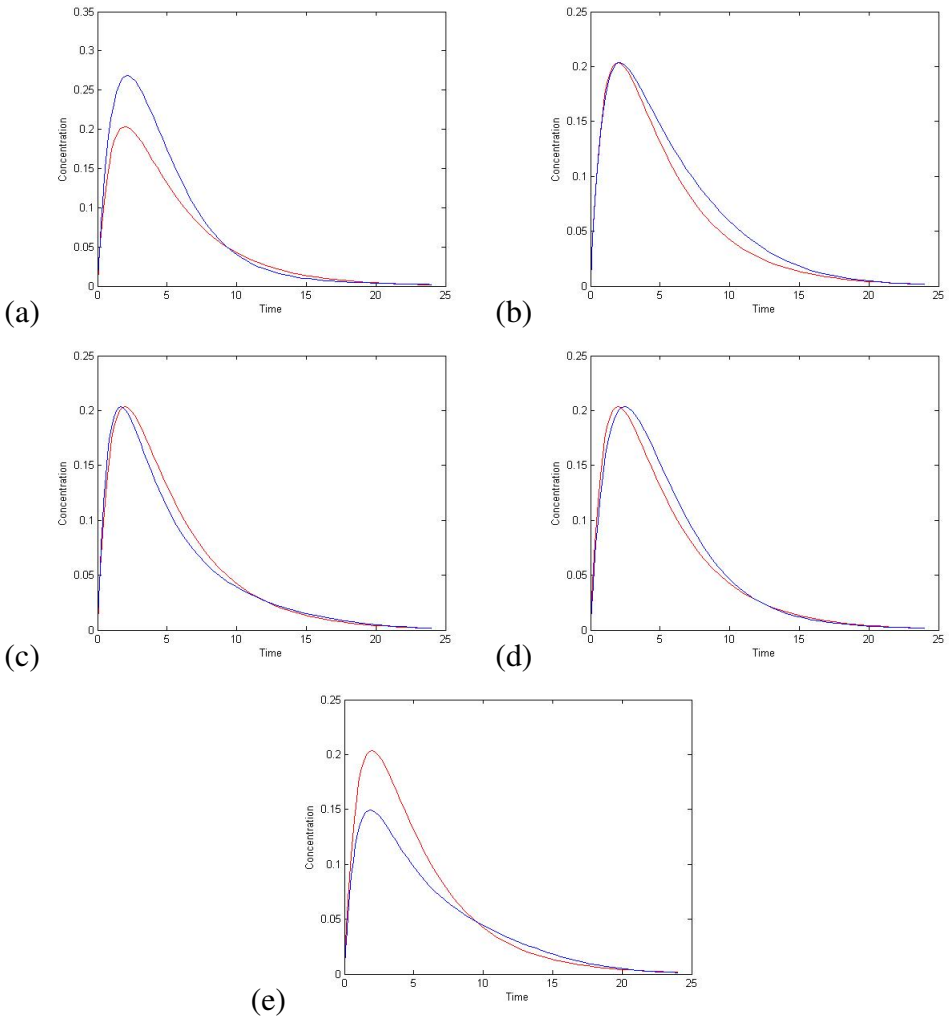

Figure 4 – Concentration in time for IV dose for the time-invariant (red curve) and time-varying systems (blue curve). Values of the phase differences are (a) $\phi_1 = \pi/2$, $\phi_2 = \phi_3 = \phi_4 = 3\pi/2$ (b) $\phi_1 = \phi_2 = \phi_3 = \phi_4 = \pi$ (c) $\phi_1 = \phi_2 = \phi_3 = \phi_4 = \pi/2$ (d) $\phi_1 = \phi_2 = \phi_3 = \phi_4 = 3\pi/2$ (e) $\phi_1 = 3\pi/2$, $\phi_2 = \phi_3 = \phi_4 = \pi/2$.

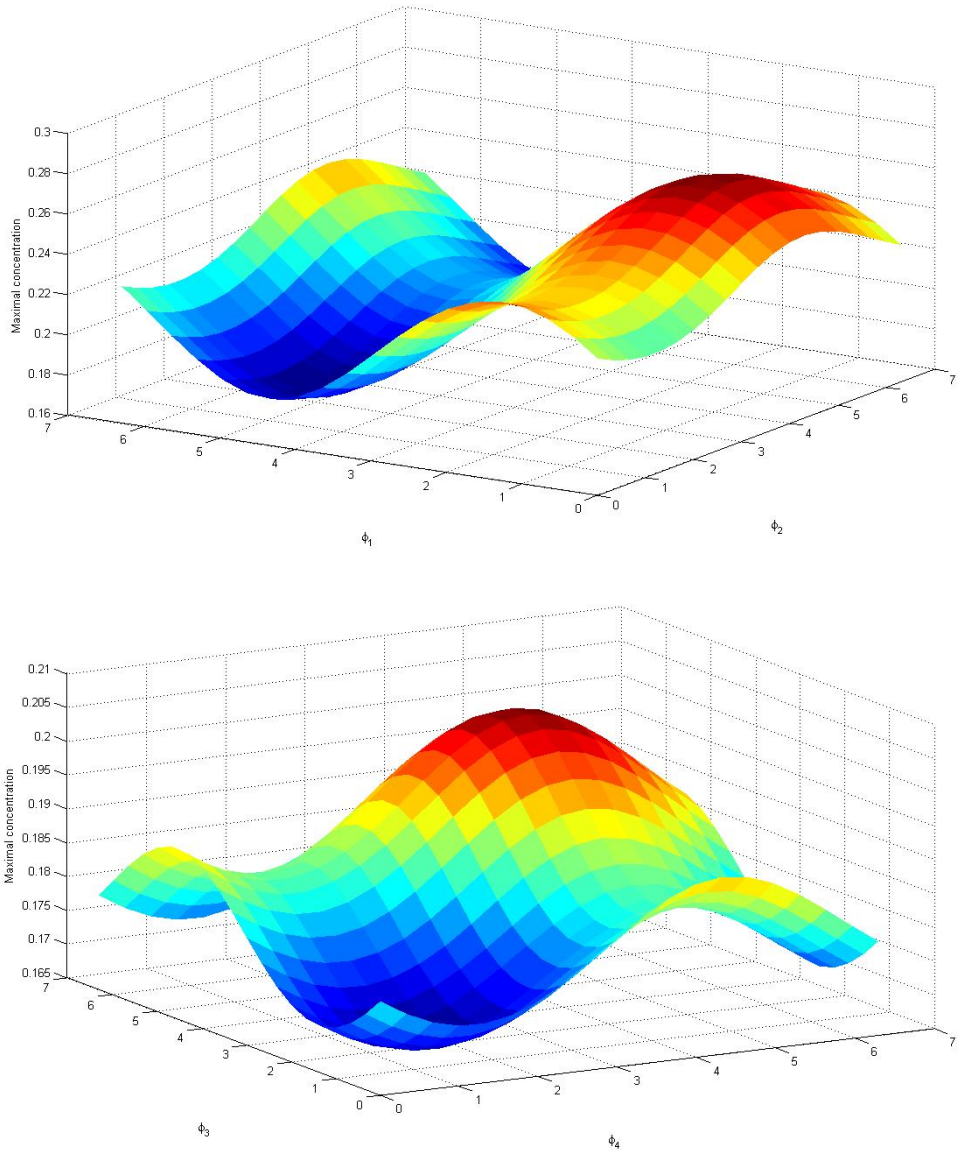

Figure 5 – Maximal concentration for the intravenous dose according to different phases ϕ_i. In the top graph, the dependent variables are ϕ_1 and ϕ_2 ; in the bottom graph, the dependent variables are ϕ_3 and ϕ_4. In both cases, the values of the complementary phases lags are set at $3\pi/2$.

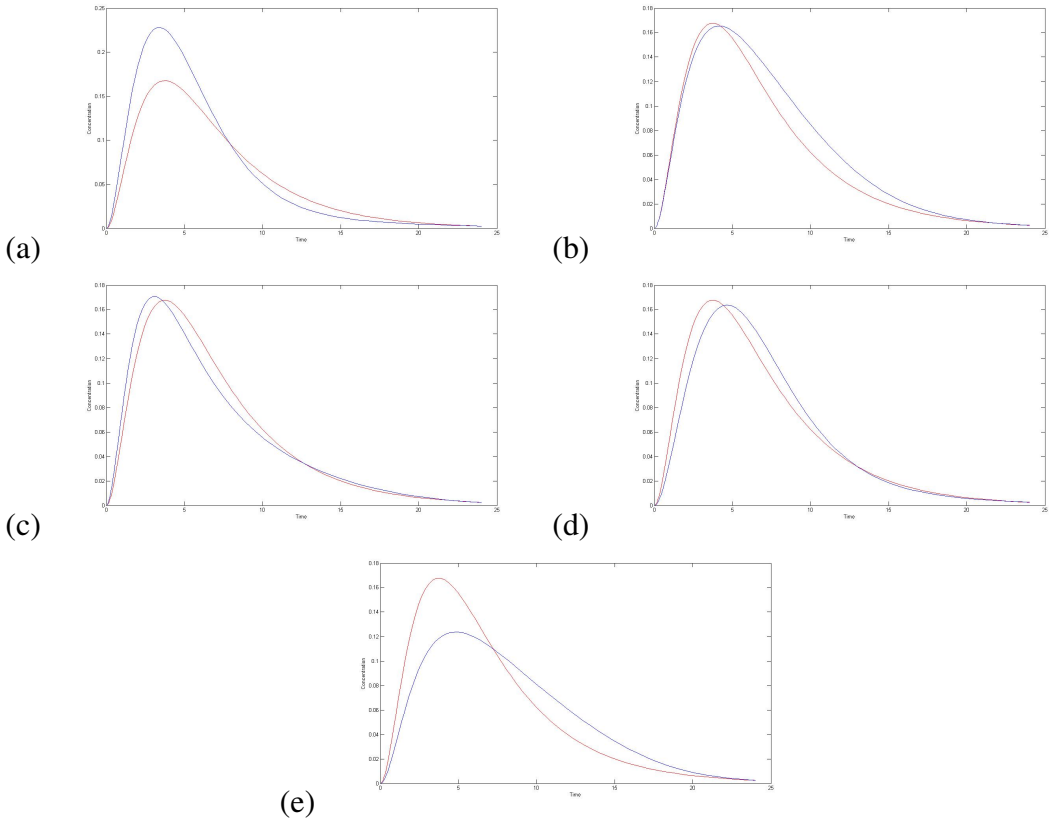

Figure 6 – Concentration in time for oral dose administration for the time-invariant (red curve) and time-varying systems (blue curve). Values of the phase differences are (a) $\phi_1 = \pi/2$, $\phi_2 = \phi_3 = \phi_4 = 3\pi/2$ (b) $\phi_1 = \phi_2 = \phi_3 = \phi_4 = \pi$ (c) $\phi_1 = \phi_2 = \phi_3 = \phi_4 = \pi/2$ (d) $\phi_1 = \phi_2 = \phi_3 = \phi_4 = 3\pi/2$ (e) $\phi_1 = 3\pi/2$, $\phi_2 = \phi_3 = \phi_4 = \pi/2$.

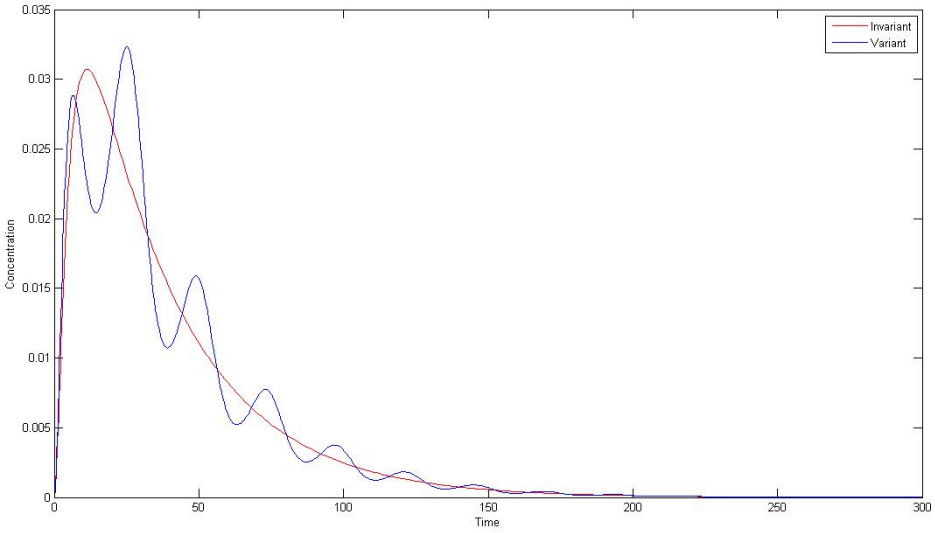

Figure 7 – Comparison of time-invariant and time-varying systems with $\phi_1 = \pi/2, \phi_2 = 3\pi/2, \phi_3 = 3\pi/2, \phi_4 = 3\pi/2$, and $k_a = 0.03$ for oral administration.

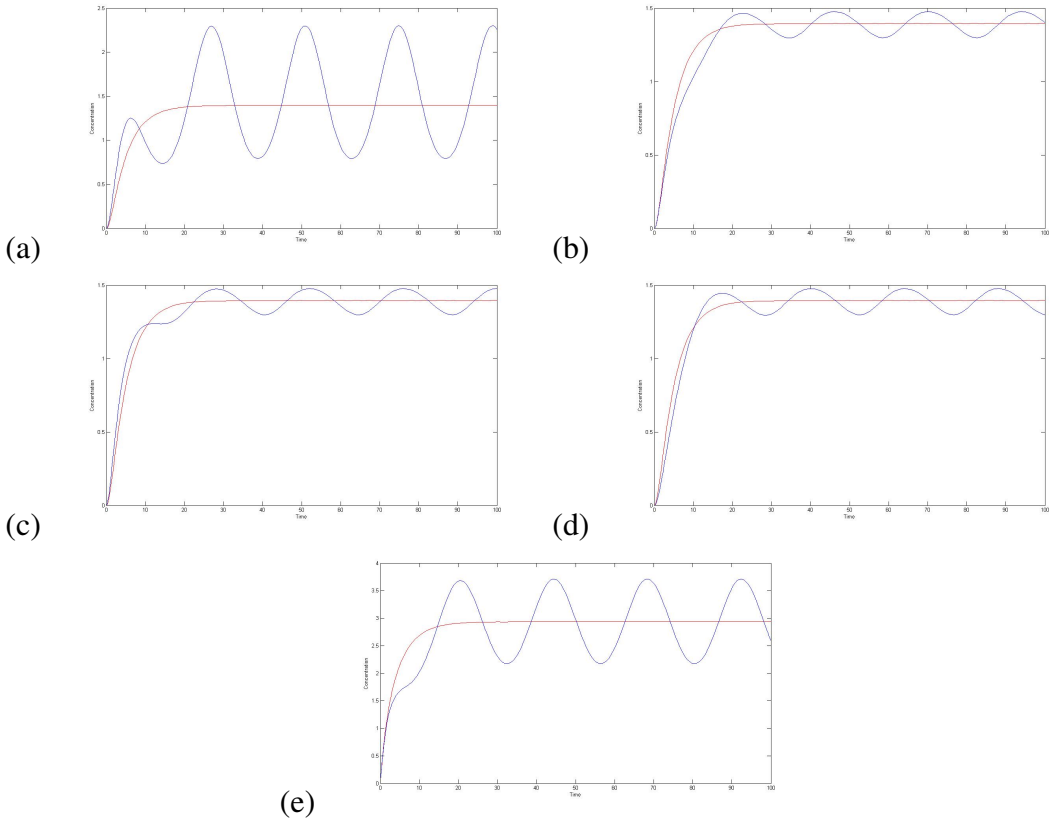

Figure 8 – Concentration in time for bolus injection for the time-invariant (red curve) and time-varying systems (blue curve) . Values of the phase differences are (a) $\phi_1 = \pi/2$, $\phi_2 = \phi_3 = \phi_4 = 3\pi/2$ (b) $\phi_1 = \phi_2 = \phi_3 = \phi_4 = \pi$ (c) $\phi_1 = \phi_2 = \phi_3 = \phi_4 = \pi/2$ (d) $\phi_1 = \phi_2 = \phi_3 = \phi_4 = 3\pi/2$ (e) $\phi_1 = 3\pi/2$, $\phi_2 = \phi_3 = \phi_4 = \pi/2$.

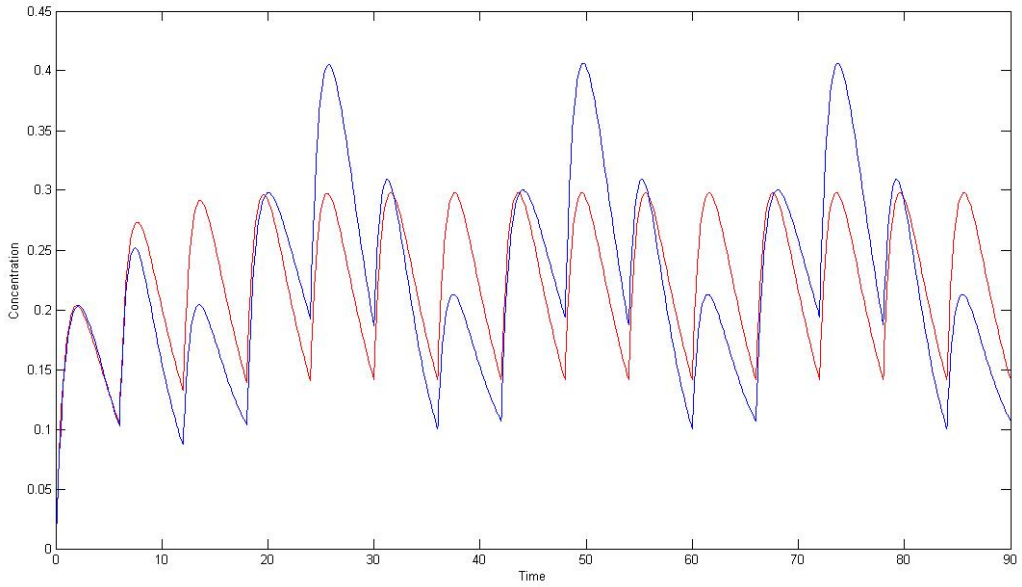

Figure 9 – Concentration in time for an intravenous dose given every 6 hours with the values of the coefficient mentionned in the text.

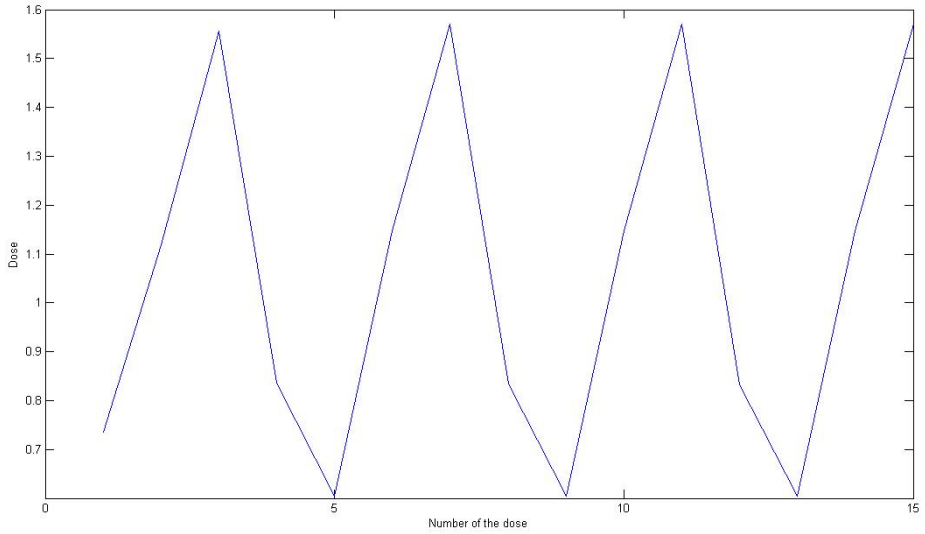

Figure 10 – Adjusted dose in the time-varying model in order to have the same maximal concentration as in the invariant model for an intravenous dose.

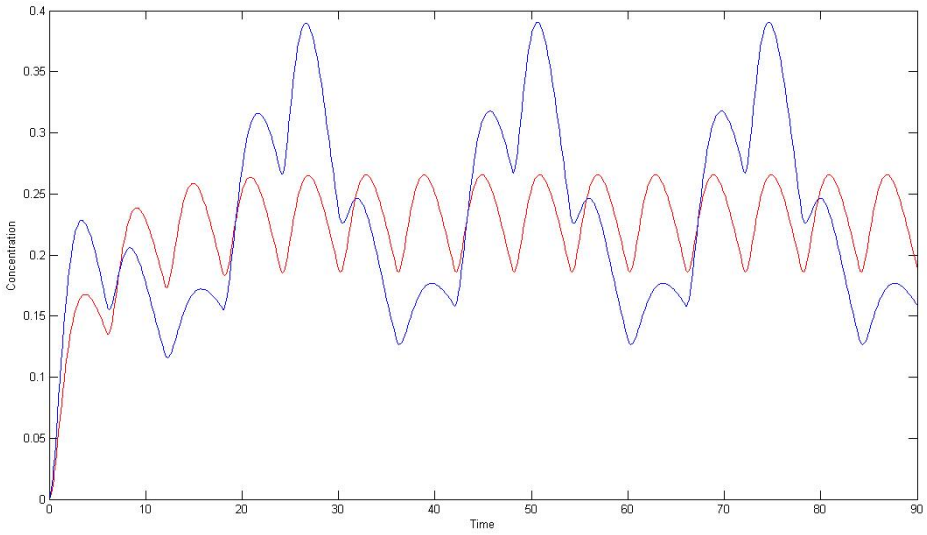

Figure 11 – Concentration in time for an oral dose given every 6 hours with the values of the coefficients mentionned above. The time-invariant concentration is drawed in red, the periodic curve in blue.

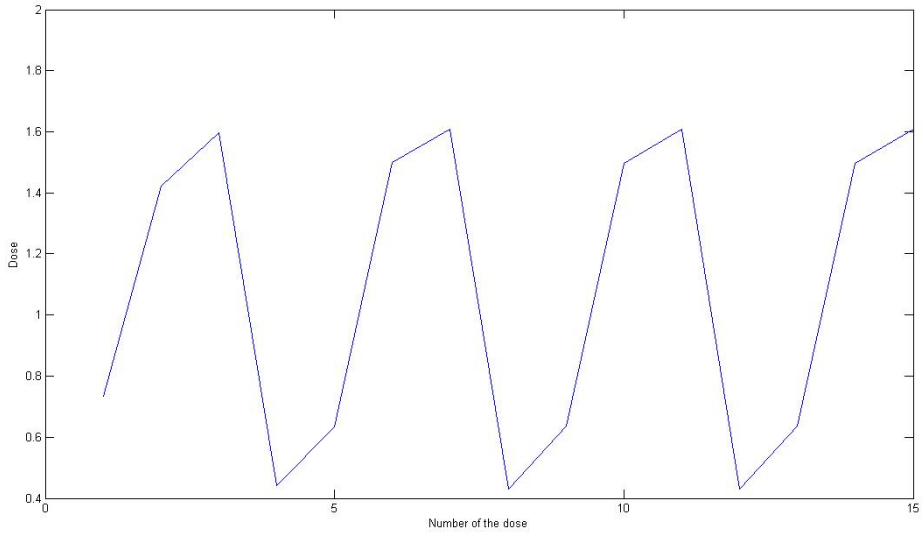

Figure 12 – Adjusted dose in the time-varying model in order to have the same maximal concentration as in the invariant model for an oral dose.

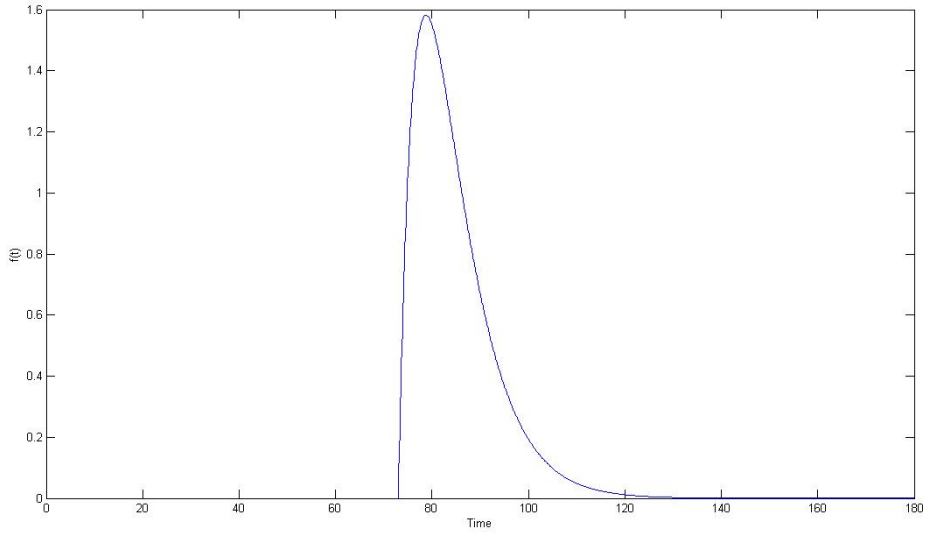

Figure 13 – Shift function f(t)

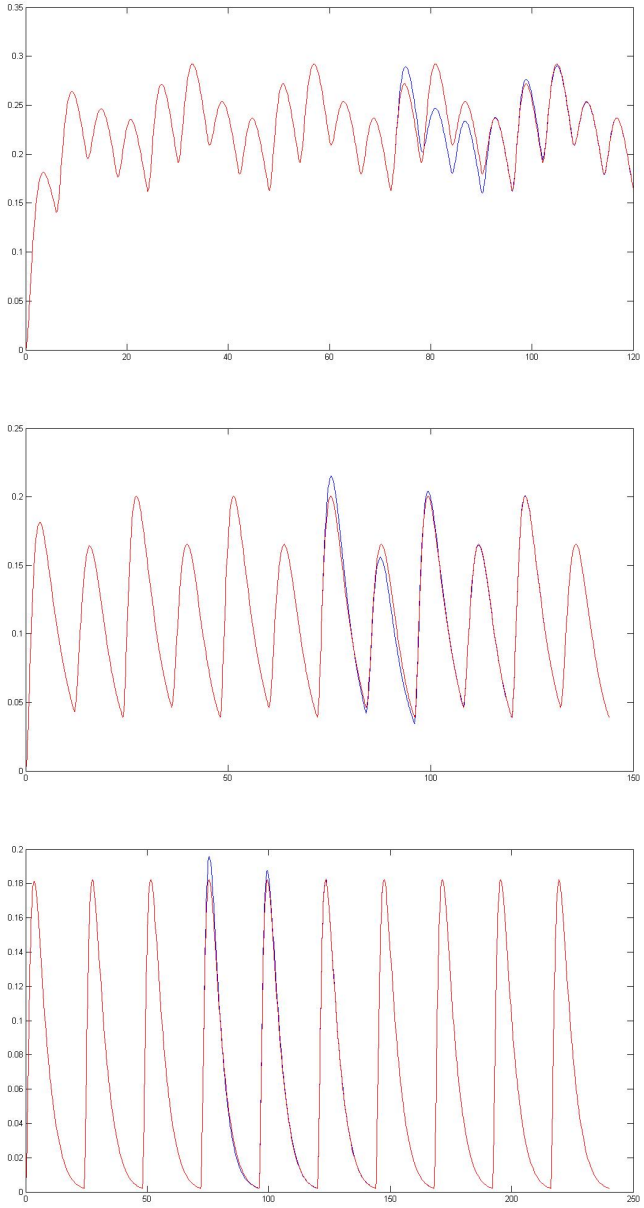

Figure 14 – Effect of time shifts correspond to travel across time zones. The red curve is the concentration without time shift and the blue one with a time shift. In the first graph, on top, the dose is given every 6 hours, on the second, every 12 hours and on the last one, at the bottom, 24 hours.

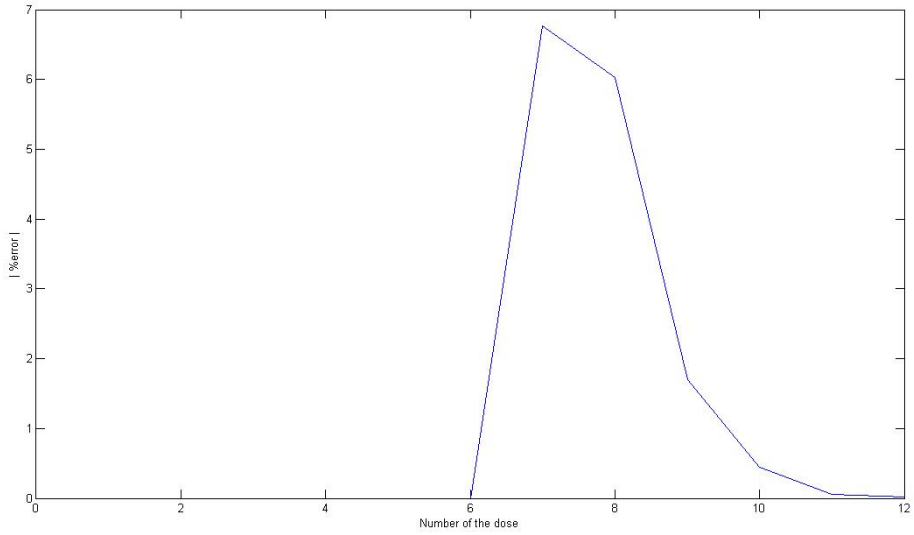

Figure 15 – Error percentage in drug concentration after a time shift across time zones. The time shift is +6 hours between the arrival place and the departure place.

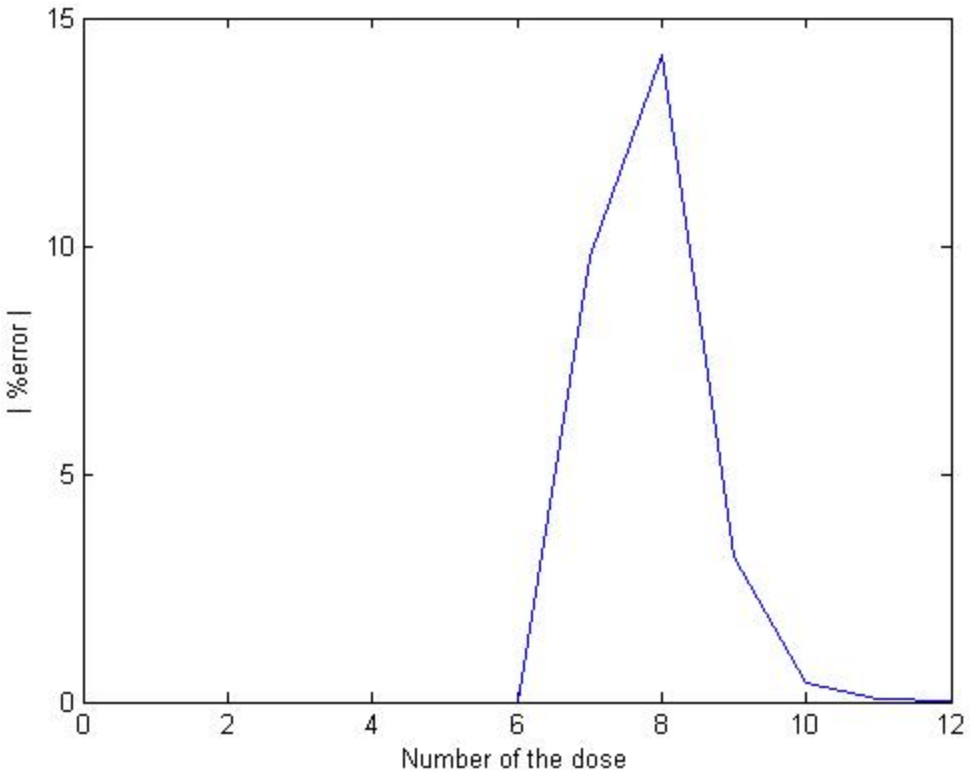

Figure 16 – Error percentage in drug concentration after a time shift across time zones. The time shift is -6 hours between the arrival place and the departure place.

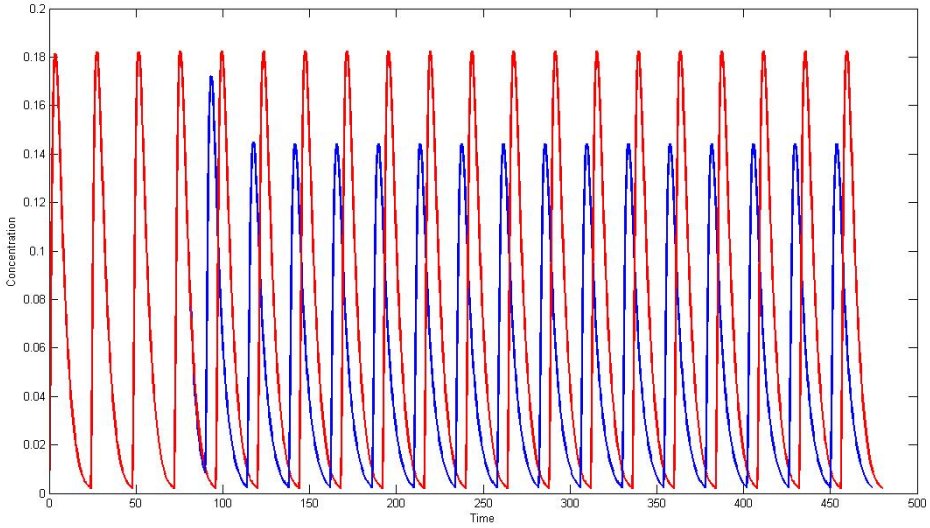

Figure 17 – Concentration in time with or without JetLag when travelling eastward. The red curve is the one without time shift and the blue one with it.

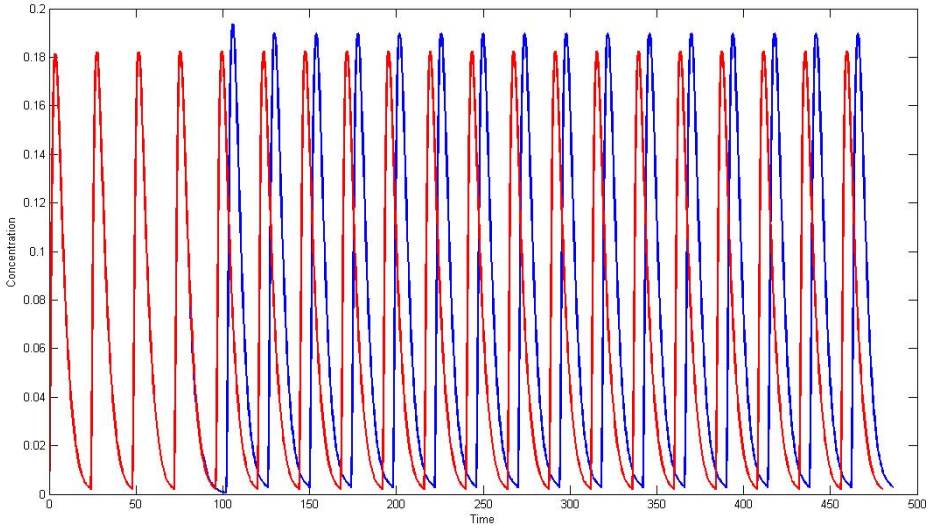

Figure 18 – Concentration in time with or without JetLag when travelling westward. The red curve is the one without time shift and the blue one with it.

CONCLUSION

Le but de ce travail était de modéliser l'influence du cycle circadien sur la pharmacocinétique des médicaments. Il fut donc d'abord essentiel de se familiariser avec les modèles compartimentaux utilisés en pharmacocinétique. Il fallut aussi comprendre comment modéliser les différentes voies d'absorption des médicaments. De plus, l'influence du rythme circadien sur les différentes étapes (absorption, distribution, métabolisme et excrétion) pharmacocinétiques a été étudiée. La concentration plasmatique maximale de certains médicaments comme le propanolol ou le ketoprofène varient en fonction de l'heure d'absorption.

Un précédent modèle sur l'influence du rythme circadien sur la pharmacocinétique avait été présenté par Godfrey. C'était un modèle pharmacocinétique représentant le corps humain comme un seul compartiment. Il ne permettait toutefois pas de représenter la variation de la concentration maximale selon le moment de la journée auquel est pris le médicament.

Nous avons donc développé un modèle mathématique permettant de trouver la concentration en médicament en fonction du temps tenant compte des variations circadiennes. Ce modèle en est un à deux compartiments. Il mène à un système d'équations différentielles non-autonomes. Le modèle fut développé pour une absorption par voie orale (la plus fréquente), par voie intraveineuse et par voie intraveineuse (zero order input). L'existence, la positivité et la borne de ces systèmes furent étudiées en annexe dans le but de vérifier que le problème est bien posé.

Les solutions de ces systèmes furent trouvées numériquement. Leur concentration maximale fut comparée au modèle classique à deux compartiments ne tenant pas compte des variations circadiennes. Les paramètres de phase (par multiples de $\pi/2$) furent variés pour voir leur influence sur la concentration maximale. Notre modèle permet de retrouver le même résultat que Godfrey, soit aucune variation dans la concentration maximale pour certains paramètres de phase. Il permet par contre aussi d'obtenir de très grandes

variations dans la concentration maximale pour certaines autres valeurs de paramètres, comme ce que l'on observe, par exemple, avec le propanolol. Le fait de rajouter un compartiment et de permettre que les phases d'absorption, de distribution, de métabolisme et d'excrétion soient différentes a permis d'obtenir des variations significatives dans la concentration maximale en médicament. Ceci a été observé pour les trois modes de consommation du médicament.

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ANNEXE A

Problème bien posé

On montrera dans cette section l'existence, l'unicité et la non-négativité de la solution du système lorsque la dose est prise par voie intraveineuse. Nous montrerons aussi que la solution est bornée.

La preuve pour les systèmes lorsque la dose est prise par voie orale ou par voie intraveineuse de type perfusion se fait de façon similaire, mais n'est pas explicitée ici.

Commençons par énoncer quelques théorèmes qui seront utiles pour montrer que le problème est bien posé.

Théorème 1. *Soit un système linéaire de la forme suivante :*

$$y'(t) = A(t)y(t) + b(t)$$
$$y(t_0) = y_0$$

avec $A : I \to \mathbb{R}^{n\times n}$, $b : I \to \mathbb{R}^n$ *et* $y : \mathbb{R} \to \mathbb{R}^n$. *Soit A et b continues, alors il existe une unique solution du système linéaire précédent sur I vérifiant* $y(t_0) = y_0$ *où* $t \in I$, $y_0 \in \mathbb{R}^n$.*[17]*

Théorème 2 (Inégalité de Grönwall)**.** *Soit I un intervalle de la forme* $[t_0, \infty)$, $[t_0, b]$ *ou* $[t_0, b)$ *avec* $t_0 < b$. *Soit* β *et u des fonctions réelles continues sur I. Si u est différentiable dans l'intérieur* I° *de I et u satisfait l'inéquation suivante :*

$$u'(t) \leq \beta(t)u(t).$$

alors u est bornée par la solution de l'équation différentielle correspondante $y'(t) =$

$\beta(t)y(t)$:

$$u(t) \leq u(t_0)e^{\int_{t_0}^{t}\beta(s)ds}.$$

[17]

Preuve :

Définissons la fonction

$$v(t) = e^{\int_{t_0}^{t}\beta(s)ds}, t \in I.$$

On aura alors que

$$v'(t) = \beta(t)v(t), t \in I^{\circ},$$

avec $v(t_0) = 1$ et $v(t) > 0 \; \forall t \in I$. Par la règle du quotient on a

$$\begin{aligned}
\frac{d}{dt}\frac{u(t)}{v(t)} &= \frac{u'(t)v(t) - v'(t)u(t)}{v^2(t)} \\
&= \frac{u'(t)v(t) - \beta(t)v(t)u(t)}{v^2(t)} \\
&= \frac{v(t)(u'(t) - \beta(t)u(t))}{v^2(t)} \\
&= \frac{u'(t) - \beta(t)u(t)}{v(t)} \\
&\leq 0
\end{aligned}$$

Donc la dérivée n'est pas positive et la fonction $\frac{u(t)}{v(t)}$ n'est pas croissante, donc bornée

par sa valeur à la condition initiale sur I. On a donc :

$$\frac{u(t)}{v(t)} \leq \frac{u(t_0)}{v(t_0)} = u(t_0),$$
$$u(t) \leq u(t_0)v(t) = u(t_0)e^{\int_{t_0}^{t}\beta(s)ds},\ t \in I$$

On a donc retrouvé l'inégalité voulue.

Théorème 3. *Soit* k_{12}, k_{21}, k_{10}, k_{20}, γ_1, γ_2, γ_3, γ_4, w_1, w_2, w_3, w_4, ϕ_1, ϕ_2, ϕ_3 *et* ϕ_4 *des constantes positives.* $\gamma_1, \gamma_2, \gamma_3, \gamma_4 < 1$ *pour avoir* $K_{12}(t), K_{21}(t), K_{10}(t), K_{20}(t) > 0\ \forall t$. *Il existe alors une solution unique, bornée et non-négative* (A_1, A_2) *au système*

$$\begin{cases} A_1' = & K_{21}(t)A_2 - (K_{12}(t) + K_{10}(t))A_1, \\ A_2' = & K_{12}(t)A_1 - (K_{21}(t) + K_{20}(t))A_2, \end{cases}$$

avec

$$K_{12}(t) = k_{12}(1 + \gamma_1 \sin(\phi_1 t + \phi_1)),$$
$$K_{21}(t) = k_{21}(1 + \gamma_2 \sin(\phi_2 t + \phi_2)),$$
$$K_{10}(t) = k_{10}(1 + \gamma_3 \sin(\phi_3 t + \phi_3)),$$
$$K_{20}(t) = k_{20}(1 + \gamma_4 \sin(\phi_4 t + \phi_4)),$$
$$A_1(0) = Dose,$$
$$A_2(0) = 0.$$

Preuve : Le système ci-dessus peut s'écrire sous la forme $y'(t) = A(t)y(t) + b(t)$

avec

$$y(t) = \begin{bmatrix} A_1(t) \\ A_2(t) \end{bmatrix},$$
$$A(t) = \begin{bmatrix} -(K_{12}(t) + K_{10}(t)) & K_{21}(t) \\ K_{12}(t) & -(K_{21}(t) + K_{20}(t)) \end{bmatrix},$$
$$b(t) = \begin{bmatrix} 0 \\ 0 \end{bmatrix}.$$

On a que A et b sont continus sur $I = \mathbb{R}$. Par le théorème 1, on a ainsi que la solution du système existe et est unique.

On a ensuite que la solution est non-négative si l'on commence avec une condition initiale non-négative. Posons

$$\begin{bmatrix} A_1' \\ A_2' \end{bmatrix} = \begin{bmatrix} F_1(t, A_1, A_2) := K_{21}(t)A_2(t) - (K_{12}(t) + K_{10}(t))A_1(t) \\ F_2(t, A_1, A_2) := K_{12}(t)A_1(t) - (K_{21}(t) + K_{20}(t))A_2(t) \end{bmatrix}$$

En effet, soit $A_2(t) \geq 0$ et $A_1(0) \geq 0$, alors on aura $A_1(t) < 0$ s'il existe t_1 tel que $A_1(t_1) = 0$ et $A_1'(t_1) < 0$. Toutefois, lorsque $A_1 = 0$ on a que $A_1'(t_1) = F_1(t_1, 0, A_2) \geq 0$. Donc, sous ces conditions A_1 ne deviendra pas négatif.

Maintenant, soit $A_1(t) \geq 0$ et $A_2(0) \geq 0$, alors on aura $A_2(t) < 0$ s'il existe t_2 tel que $A_2(t_2) = 0$ et $A_2'(t_2) < 0$. Toutefois, lorsque $A_2 = 0$ on a que $A_2'(t_2) = F_2(t_2, A_1, 0) \geq 0$. Donc, sous ces conditions A_2 ne deviendra pas négatif.

Ainsi, puisque l'on aura toujours $(A_1(0), A_2(0)) \in \mathbb{R}^2_+$, alors la solution reste donc dans $\mathbb{R}^2_+$.

Finalement, on montre que la solution est bornée.

On a que

$$\begin{aligned}\frac{d}{dt}(A_1(t)+A_2(t)) &= -K_{10}(t)A_1(t)-K_{20}(t)A_2(t),\\ &\leq 0,\end{aligned}$$

car $0 \leq K_{10}(t) \leq 2k_{10}$, $0 \leq K_{20}(t) \leq 2k_{20}$, $A_1(t) \geq 0$ et $A_2(t) \geq 0$. Par le lemme 2 on aura donc

$$\begin{aligned}(A_1+A_2)(t) &\leq (A_1+A_2)(0)e^{\int_0^t 0ds},\\ &= (A_1+A_2)(0),\\ &= Dose.\end{aligned}$$

De plus, puisque l'on a que $A_1, A_2 \geq 0$, on aura $0 \leq A_1 \leq Dose$ et $0 \leq A_2 \leq Dose$. La solution est donc bornée. Ceci est aussi biologiquement cohérent car la concentration en médicament dans le corps ne pourrait pas dépasser la concentration de la dose initiale et ne pourrait pas être négative.

On aura aussi que

$$\lim_{t\to\infty} \begin{bmatrix} A_1(t) \\ A_2(t) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}.$$

En effet, on a

$$\begin{aligned}\frac{d}{dt}(A_1(t)+A_2(t)) &= -K_{10}(t)A_1(t)-K_{20}(t)A_2(t),\\ &\leq -\min\{K_{10}(t),K_{20}(t)\}(A_1+A_2)(t) \quad \forall t \in \mathbb{R}\end{aligned}$$

Soit $p(t) = -\min\{K_{10}(t),K_{20}(t)\}$, $p(t)$ est une fonction continue et réelle. On peut donc

utiliser l'inégalité de Grönwall :

$$(A_1+A_2)(t) \leq (A_1+A_2)(0)e^{\int_0^t p(s)ds}$$

p(t) est continue donc on peut l'intégrer et

$$\int_0^t p(s)ds = \int_0^t -\min\{K_{10}(s), K_{20}(s)\}ds$$

On a ensuite que :

$$\begin{aligned}
\int_0^t -K_{10}(s)ds &= \int_0^t (-k_{10} - k_{10}\gamma_3 \sin(\omega_3 s + \phi_3))ds \\
&= -k_{10}t + \frac{k_{10}\gamma_3}{\omega_3}\cos(\omega_3 t + \phi_3) - \frac{k_{10}\gamma_3\cos(\phi_3)}{\omega_3} \\
&\leq -k_{10}t + \frac{k_{10}\gamma_3}{\omega_3} - \frac{k_{10}\gamma_3\cos(\phi_3)}{\omega_3} \\
\int_0^t -K_{20}(s)ds &= \int_0^t (-k_{20} - k_{20}\gamma_4 \sin(\omega_4 s + \phi_4))ds \\
&= -k_{20}t + \frac{k_{20}\gamma_4}{\omega_4}\cos(\omega_4 t + \phi_4) - \frac{k_{20}\gamma_4\cos(\phi_4)}{\omega_4} \\
&\leq -k_{20}t + \frac{k_{20}\gamma_4}{\omega_4} - \frac{k_{20}\gamma_4\cos(\phi_4)}{\omega_4}
\end{aligned}$$

On a donc que

$$\begin{aligned}
\int_0^t p(s)ds &\leq \min\{\int_0^t -K_{10}(s)ds, \int_0^t -K_{20}(s)ds\} \\
&\leq -\min\{k_{10}, k_{20}\}t + \max\{\frac{k_{10}\gamma_3}{\omega_3} - \frac{k_{10}\gamma_3\cos(\phi_3)}{\omega_3}, \frac{k_{20}\gamma_4}{\omega_4} - \frac{k_{20}\gamma_4\cos(\phi_4)}{\omega_4}\} \\
&\leq -\min\{k_{10}, k_{20}\}t + C_1 \text{ avec } C_1 \in \mathbb{R}
\end{aligned}$$

avec $C_1 = \max\{\frac{k_{10}\gamma_3}{\omega_3} - \frac{k_{10}\gamma_3\cos(\phi_3)}{\omega_3}, \frac{k_{20}\gamma_4}{\omega_4} - \frac{k_{20}\gamma_4\cos(\phi_4)}{\omega_4}\}$.

Les solutions sont non-négatives, on a donc les inégalités suivantes :

$$0 \leq (A_1 + A_2)(t) \leq (A_1 + A_2)(0)e^{-\min\{k_{10},k_{20}\}t+C_1}$$

en passant à la limite on a

$$\lim_{t\to\infty} 0 \leq \lim_{t\to\infty} (A_1 + A_2)(t) \leq \lim_{t\to\infty} (A_1 + A_2)(0)e^{-\min\{k_{10},k_{20}\}t+C_1}$$
$$0 \leq (A_1 + A_2)(t) \leq 0$$

On a donc que $\lim_{t\to\infty}(A_1 + A_2)(t) = 0$ et puisque l'on a $A_1(t) \geq 0$ et $A_2(t) \geq 0 \; \forall \; t \in [0,\infty[$ alors on a

$$\lim_{t\to\infty} \begin{bmatrix} A_1(t) \\ A_2(t) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}.$$

C'est encore une fois cohérent d'un point de vue biologique, car lorsque l'on donne une dose unique de médicament, on s'attend à ce que lorsque le temps t tend vers l'infini, le médicament soit complètement éliminé de l'organisme donc que la concentration tende vers zéro.