



# A MARKOV CHAIN METHOD FOR SIMULATING THE TIME EVOLUTION OF DRUGS IN PHARMACOKINETICS SYSTEMS

*A stochastic method based on discrete Markov chains is employed to simulate numerically the time course of drugs, without either solving differential equations or supplying closed form rate equations. The method is general, simple, accurate and fast. The method is applied to several linear and nonlinear pharmacokinetic models.*

## INTRODUCTION

The time evolution of the concentrations of molecular species during a chemical reaction can be formulated in a probabilistic or in a deterministic framework. Deterministic approaches are generally favoured, because, in chemical kinetics, the stochastic master equation is very often mathematically intractable [1]. However, recently, methods have been developed that allow exact numerical calculations within stochastic formulations without having to deal explicitly with the master equation [2-4]. One of such methods employs discrete Markov chains for the numerical integration of coupled chemical reactions. This Markov chain method (MCM) has proved to be a simple, accurate and general technique for the study of homogeneous and nonhomogeneous [3] systems. Here MCM is applied to the study of several models of interest in pharmacokinetics, to reveal the possibilities of the method in this field.

## MARKOV CHAIN METHOD

### MARKOV CHAINS

The concept of a Markov chain is associated with systems whose states change with time in a random manner, such that the outcome of any trial depends only on the outcome of the directly preceding trial [4]. Hence the probability,  $p_{ij}$ , of the system going from a state  $a_i$  at a time  $t$  (discrete variable) to a state  $a_j$  at a time  $t + 1$  depends only on the states at  $t$ , but is independent of the states of the system at times prior to  $t$ . The probability that  $a_i$  will remain unchanged between  $t$  and  $t + 1$  is  $p_{ii}$ . The transition probabilities can be presented in a matrix form

$$\tilde{T} = \begin{bmatrix} p_{11} & p_{12} & \dots & p_{1m} \\ p_{21} & p_{22} & \dots & p_{2m} \\ \vdots & \vdots & \ddots & \vdots \\ p_{m1} & p_{m2} & \dots & p_{mm} \end{bmatrix} \quad (1)$$

the so-called transition matrix. If we assume that the process begins at some particular state at time  $t$ , characterized by independent variables,  $X_1, X_2, X_3, \dots$ , represented also in a matrix form

$$\tilde{C}_t = [X_1(t), X_2(t), X_3(t), \dots] \quad (2)$$

then the state after one step of time is given by the matrix  $\tilde{C}_{t+1}$  where

$$\tilde{C}_t \times \tilde{T} = \tilde{C}_{t+1} \quad (3)$$

The  $\tilde{C}$  matrixes represent the absolute probabilities of the system being in its different possible states  $i = 1, \dots, m$ . In addition to the so called one-step transition probabilities  $p_{ij}$ , it is of interest to consider  $n$ -step probabilities  $p_{ij}^{(n)}$ . These express the probability of a transition from a state  $i$  to a state  $j$  in  $n$  steps. A relationship between these different kinds of probabilities can be established recursively through the "Chapman-Kolmogorov functional equation"

$$\tilde{T}^{m+n} = \tilde{T}^m \times \tilde{T}^n \quad (4)$$

where  $\tilde{T}^n$  represents the matrix of the  $n$ -step transition probabilities.

A Markov chain is stationary when  $\tilde{C}_{t+1} = \tilde{C}_t$  and in this case the absolute probability of being at any state is the same for all steps of the process. Stationary situations occur after a large number of steps, as long as  $\tilde{T}$  is a stochastic regular matrix, i.e.,

$$p_{ij} \geq 0 \quad \sum_{j=1}^m p_{ij} = 1 \quad \text{and} \quad \sum_{n=1}^{\infty} p_{ij}^{(n)} \text{ converges.}$$

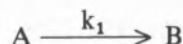
On the other hand if the series  $\sum_{n=1}^{\infty} p_{ij}^{(n)}$  diverges the state  $i$  is called recurrent. In general the divergence of this series implies the divergence of  $\sum_{n=1}^{\infty} p_{jj}^{(n)}$  [4]. It is of interest in statistical applications to consider the relationship between the mean and the variance of a variable  $X^{(n)}$  once the mean,  $m$ , and the variance,  $\sigma$ , of  $X^{(1)}$  are known. For a simple branching process

$$\begin{aligned} \text{mean } X^{(n)} &= m^n \\ \text{variance } X^{(n)} &= n \sigma^2. \end{aligned} \quad (5)$$

#### TRANSITION PROBABILITIES FOR CHEMICAL REACTIONS

In homogeneous chemical reactions time is a continuous variable, but Markov chains discrete in time can be employed to study the time evolution of chemical systems, so long as the discreteness in the time variable does not hinder an accurate interpolation of molecular concentrations between any two instants. In order to apply MCM to reaction kinetics rate

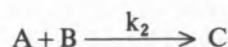
constants must be related to the Markovian transition probabilities [3]. For a first order process characterized by a rate constant  $k_1$



the probability of conversion of A into B during a single step is

$$p_{AB} = k_1 \Delta t, \quad (6)$$

where  $\Delta t$  is the duration of each step, such that  $p_{AB} \ll 1$ . The probability that A will remain unchanged during one step is  $p_{AA} = 1 - k_1 \Delta t$ . For a second order process



The probability of conversion of A into C is

$$p_{AC} = k_2 [B] \Delta t$$

and  $p_{AA} = 1 - k_2 [B] \Delta t$ ,  $p_{BC} = k_2 [A] \Delta t$  and  $p_{BB} = 1 - k_2 [A] \Delta t$ . In the definition of these transition probabilities care must be exercised to preserve the stoichiometry of the reaction. For example if C is considered to be formed simultaneously from A and from B then  $p_{AC}$  and  $p_{BC}$  should be multiplied by  $\frac{1}{2}$  [3].

Concentrations or doses of drugs at different times can be determined through an iterative process by eq (3). The matrix  $C_t$  represents the concentrations or doses of the different substances at time  $t$  and through eq. (3) the concentrations after one step, i.e., at  $t + \Delta t$ , can be determined. For example the concentration of  $[X_i(t + \Delta t)]$  is related to the molecular concentrations at time  $t$  by

$$\begin{aligned} [X_i(t + \Delta t)] &= p_{1i} [X_1(t)] + p_{2i} [X_2(t)] + \dots \\ &\dots + p_{mi} [X_m(t)] \end{aligned} \quad (7)$$

For any substance the area,  $A$ , under the concentration curve is given by

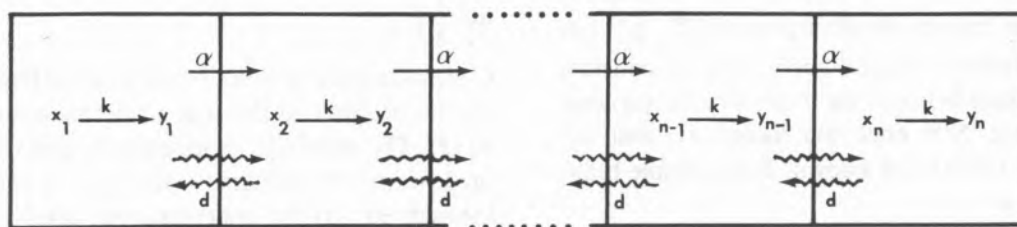
$$A = \sum_{t=0}^{t=n\Delta t} [X_i(t)] \quad (8)$$

The properties of matrices ensure that MCM verifies the Rule of Corresponding Areas [5].

The use of one-step transition matrix  $\tilde{T}$  can sometimes lead to a time consuming iterative process. However such iteration can be much faster if one employs an  $n$ -step transition matrix  $\tilde{T}^n$ . The use of  $\tilde{T}^n$  is always possible when the transition probabilities are time-independent. When this is not so, e.g. in nonlinear kinetics, the use of such matrices is permissible under certain conditions that will be discussed later on.

#### NONHOMOGENEOUS SYSTEMS

To study spatial nonhomogeneous kinetic systems Markov chains discrete in time and in space must be employed [3]. The spatial coordinates of the system are represented as discrete variables. The reaction system is considered to be divided into several compartments. Molecular concentrations are the same at all points of any compartment but vary in a discrete manner from compartment to compartment. Molecular concentrations are therefore space,  $l$ , and time,  $t$ ,  $[X_i(l,t)]$  dependent. The Markov chain transition probabilities contain not only the probabilities of transitions between different substances through chemical reaction, but also the conversion of a substance in a compartment  $i$  to a compartment  $j$  through mass transfer.



The probability of mass transfer in a flow system of velocity  $v$  is

$$\alpha = \frac{v \Delta t}{\Delta l} \quad (9)$$

where  $\Delta l$  is the dimension of the compartments in a given direction. The probability through diffusion is

$$d = \frac{D \Delta t}{(\Delta l)^2} \quad (10)$$

where  $D$  is the diffusion coefficient. Chemical conversion is only considered within each compart-

ment. The transition matrix  $\tilde{T}$  for a nonhomogeneous system contains the one-step spatial and temporal transition probabilities, but obviously  $n$ -step transitions in space and in time can also be considered.

#### NUMERICAL ERRORS

To assess the errors involved in the numerical simulation of concentrations through MCM let us consider a first order reaction  $A \xrightarrow{k_1} B$  which can be represented by a simple branching process. The errors can be calculated for different transition probability values,  $p = k_1 \Delta t$ , through eqs. (5). With  $k_1 \Delta t = 0.1$  the error in  $[A]$  is 10% after 3 periods and 16% after 5 periods, an error which is similar to the experimental errors in pharmacokinetics. The error decreases linearly with the decrease in the transition probability  $k_1 \Delta t$ , and consequently with the decrease in  $\Delta t$ . The error in the area under the curve (eq. (8)), after 5 periods, is only 1%, with  $k_1 \Delta t = 0.1$  and also decreases linearly with a decrease in  $\Delta t$ .

The accuracy of MCM is dependent on the time scale of iteration, with respect to the magnitude of rate constants, and depends consequently on the number of iteration steps that one is prepared to

carry out. For time-independent transition probabilities the accuracy of the method depends only on the one-step transition probabilities, but is independent of the order of the multistep transition probabilities. For most purposes the accuracy provided by the transition probabilities  $k \Delta t = 0.1$  or  $k[A] \Delta t = 0.1$  is good enough and, therefore, in the examples considered in the following section  $\Delta t$  is chosen such that  $k \Delta t = 0.1$  for the highest kinetic rate constant.

Time dependent transition probabilities are required to simulate non-linear kinetics and for time-dependent first order rate constants. An example of such kinetics is provided by some models of

enzyme induction [6]. For a first-order process whose rate constant varies between  $k_0$  at  $t=0$  to  $k_\infty$  at  $t=\infty$  with  $k=k_\infty-(k_\infty-k_0)e^{-\gamma t}$  the concentration is given by

$$C(t) = C_0 \exp\left\{k_\infty t - \frac{k_\infty - k_0}{\alpha} [1 - \exp(-\gamma t)]\right\} \quad (11)$$

where  $\gamma$  is a constant and  $C_0$  the concentration at time zero. The MCM equation for this process is

$$C(t_{i+1}) = C(t_i) (1 - k_i)$$

where  $k_i = (k_\infty - (k_\infty - k_0)e^{-\gamma t_i}) \Delta t$ .

Fig. 1 compares  $C(t)$  given by eq. (11) with the results of MCM, with  $k_0 \Delta t = 0.01$ ,  $k_\infty \Delta t = 0.1$  and  $\gamma = 0.2 \text{ time}^{-1}$ . The agreement is excellent with an error of 12% after five periods of reaction. Multistep transition probability matrices can also be employed in the calculation. However for time-dependent probabilities the matrices  $\tilde{T}^n$  introduce an additional error in the calculation. This error is reasonable as long as the survival probabilities do not vary, by more than 5% during each multistep transition. Fig. 1 illustrates the employment of a five-step transition which, after the first step, gives an error  $\leq 25\%$ ; the error decreases along the course of reaction since the variation with time decreases

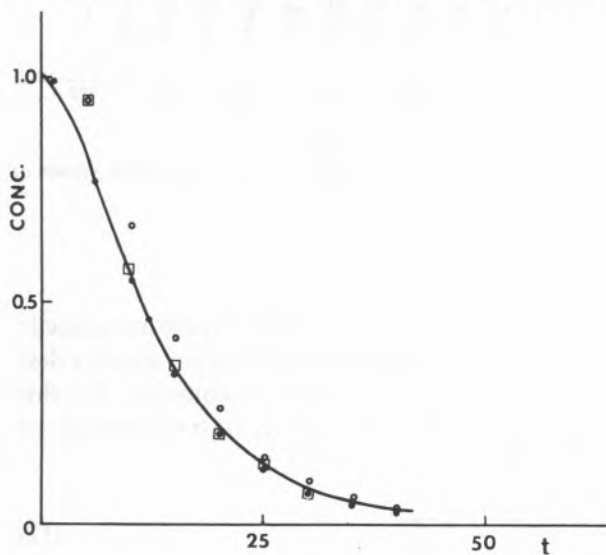


Fig. 1

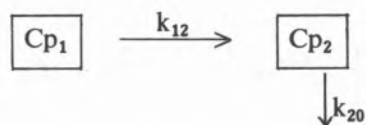
First-order time-dependent induction kinetics  $k = k_\infty - (k_\infty - k_0)e^{-\gamma t}$ ;  $k_0 = 0.01$ ,  $k_\infty = 0.1$  and  $\gamma = 0.2$ : — exact solution;  $\circ \Delta t = 1$  1-step transition;  $\Delta \Delta t = 1$  5-step transition;  $\square \Delta t = 0.1$  50-step transition

with increase in time. The error of the numerical simulation can be decreased by decreasing  $\Delta t$  and increasing, in the same proportion, the multistep transition. For example at  $t=10$  the error is 25% with  $\Delta t = 1$  and  $n = 5$ , but decreases to 6% if  $\Delta t = 0.1$  and  $n = 50$ . Consequently in MCM, the judicious employment of multistep transition matrices can considerably decrease the time of computation without any significant loss of accuracy.

## APPLICATIONS

### MULTI-EXPONENTIAL KINETICS

In contrast with the analytical and numerical integration techniques, MCM provides a general method to deal with any kind of linear pharmacokinetics model [7]. To illustrate the applicability of MCM let us consider a two compartment model



Where  $Cp_i$  is the concentration in compartment  $i$ . This system [7] has an exact analytical solution, the so called "Bateman function". The one-step transition matrix for this kinetic scheme is

$$\begin{array}{l} Cp_1 \\ Cp_2 \\ elim. \end{array} \begin{bmatrix} 1 - k_{12} \Delta t & k_{12} \Delta t & 0 \\ 0 & 1 - k_{20} \Delta t & k_{20} \Delta t \\ 0 & 0 & 1 \end{bmatrix}$$

Equation (7) leads to the one-step recurrence equations for the concentration of drug in any of the compartments. For example for the central compartment

$$[Cp_2]_{t+\Delta t} = [Cp_1]_t k_{12} \Delta t + [Cp_2]_t (1 - k_{20} \Delta t)$$

Fig. 2 compares the computed time dependence of the drug in the central compartment with the theoretical one for a system where  $\frac{k_{12}}{k_{20}} = 100$ . The fit is very good throughout, with an error that does not exceed 5%. The calculation at the earlier stages used a step  $n = 1$ , at the middle stages  $n = 23$  and for the later stages  $n = 1024$ . Multicompartment models do

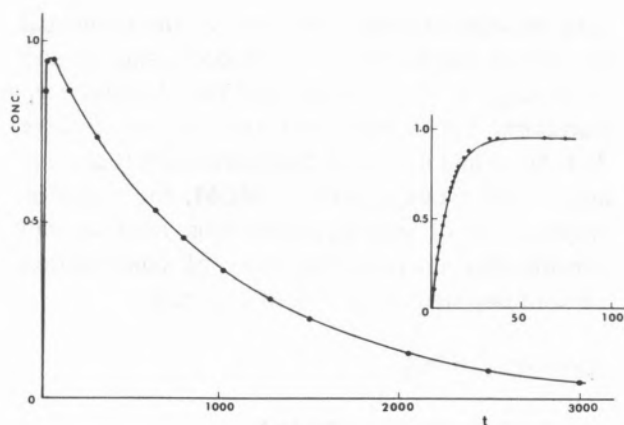
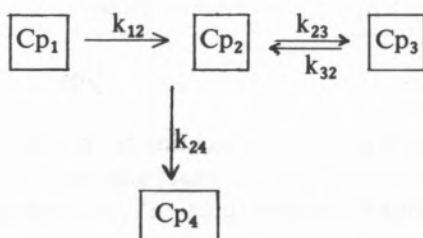


Fig. 2

Concentrations as a function of time for a two-compartment first-order model ( $k_{12} = 100$ ,  $k_{20} = 1$  and  $\Delta t = 10^{-3}$ ): — exact solution; • MCM solution

not add any special difficulty to the method, except by the requirement of a larger computer memory. A reasonable complex system of 4 compartments such as



leads to a transition matrix

$$\begin{bmatrix} 1 - k_{12} & k_{12} & 0 & 0 \\ 0 & 1 - k_{23} - k_{24} & k_{23} & k_{24} \\ 0 & k_{32} & 1 - k_{32} & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

with the rate constants expressed in units of  $\Delta t$ . Fig. 3 illustrates the time evolution of the drug in some of the compartments. Although MCM provides a discrete set of concentration values, such values allow the evaluation of the continuous functions of concentration *versus* time, as fig. 3 shows. To speed up the computation 1-step and 8-step transitions were considered. The effect on the dose in the central compartment of a repeated administration of an unitary dose in compartment 1, at every 20 units of time, is illustrated in fig. 4. Within the model this effect can be easily simulated by the addition of a dose of 1, in  $Cp_1$ , every 20 units of time.

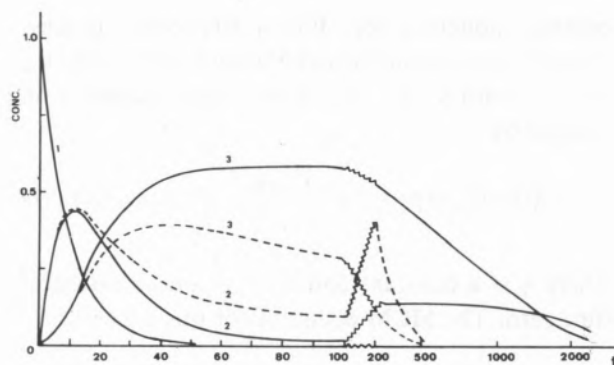


Fig. 3

Time evolution of a drug in a 4-compartment model:  $k_{12} \Delta t = 0.1$ ,  $k_{23} \Delta t = 0.05$ ,  $k_{24} \Delta t = 0.03$ ; — linear  $k_{32} \Delta t = 0.025$ ; — nonlinear  $k_{32} \Delta t = \frac{0.00125}{0.05 + [Cp_3]}$

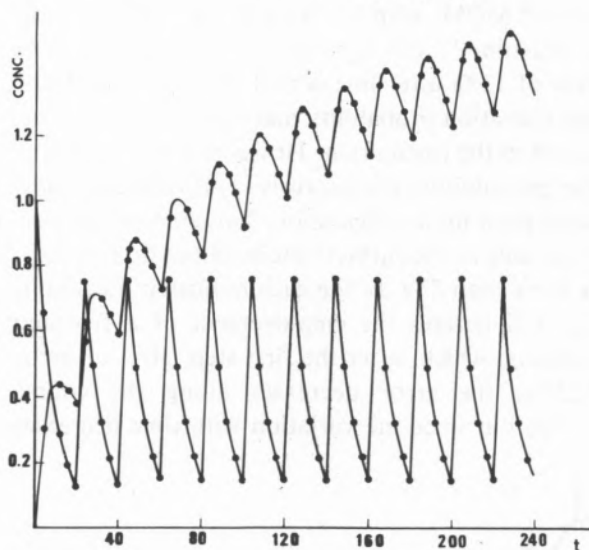


Fig. 4

Multidose administration in the linear 4-compartment system of fig. 3

#### NONLINEAR KINETICS

As an illustration of a nonlinear pharmacokinetic model we will consider the saturation kinetics described by the Michaelis-Menten equation. For this kind of kinetics the probability of transition can be given by

$$p_{ij} = \frac{V_M \Delta t}{K_M + [S]} \quad (12)$$

where  $V_M$  is the maximum rate of reaction or elimination,  $[S]$  the substrate concentration and  $K_M$  the Michaelis constant, which is the concentration at which the rate of elimination is one-half of the ma-



ximum possible value. Let us consider a process with a rate law

$$-\frac{d[A]}{dt} = \frac{V_M[A]}{K_M + [A]} \quad (13)$$

for which the recurrence equation is

$$[A]_{t+\Delta t} = \left(1 - \frac{V_M \Delta t}{K_M + [A]_t}\right) [A]_t \quad (14)$$

Eq. (13) can be integrated and gives

$$K_M \ln \frac{[A]_0}{[A]} + [A]_0 - [A] = V_M t \quad (15)$$

where  $[A]_0$  is the initial concentration of the substance A. Eq. [15] reveals that  $\ln [A]$  is a linear function of  $V_M t + [A] - [A]_0$ . Markov chain data conform well with this prediction, with an error  $< 1.5\%$  after 3 periods of reaction and an error of  $7.5\%$  when 20-step transitions are employed (fig. 5).

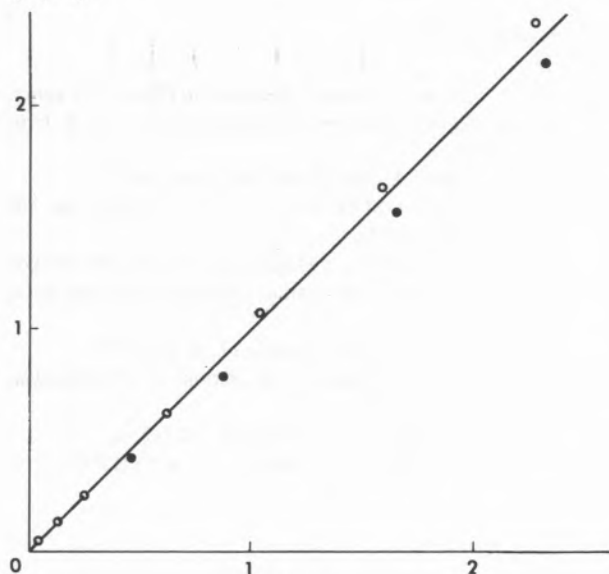


Fig. 5

Plot according to eq. (15) for the disappearance of a substance following Michaelis-Menten kinetics:  $[A]_0 = 1$ ,  $K_M = 0.5$ ,  $V_M = 0.05$ ,  $\Delta t = 1$ ;  $\circ n = 1$ ;  $\bullet n = 10$

To illustrate a drug interaction process, saturation kinetics were considered in the 4-compartment level of the last section for the intercompartmental transition rate  $k_{32}$ ; the first order rate constant, at low  $[Cp_3]$ , is identical to the rate in the linear system. Fig. 3 illustrates this system and comparison with the linear system reveals the drug retention in  $Cp_3$

in the nonlinear situation, with the consequent decrease of the drug concentrations in the central compartment. After the initial stages, the concentrations do not vary strongly with time and consequently n-step transitions can be employed without loss of accuracy. In the calculation, for  $t > 50$ , 16-step transitions were employed.

#### GASTROINTESTINAL ABSORPTION

Gastrointestinal absorption introduces new factors into the kinetic systems. In the models that are going to be considered we will take into consideration the gastrointestinal filling and emptying and the effect of blood flow. MCM can be applied to the different phases of gastrointestinal absorption by considering the intestine divided into several segments of length  $\Delta l$ . In each segment the concentration of drug is the same at all points, but varies in a discrete manner from segment to segment. Absorption into blood occurs from a portion of the intestine tube and is characterized by a rate constant  $k_{abs}$ ; the flow of the chyme has a rate  $v_c$ . The probability of mass transfer through flow in the intestine is  $\alpha_c$  (eq. (9)). In a situation where absorption occurs only from the central segment the transition matrix is

entrance	$1 - \alpha_c$	$\alpha_c$	0	0
middle	0	$1 - \alpha_c - k_{abs}$	$\alpha_c$	$k_{abs}$
exit	0	0	1	0
blood	0	0	0	$1 - k_{el}$

where  $k_{el}$  is the rate constant for the elimination process. Fig. 6 presents the curves for the absorption of the drug into the blood. The chyme is filling the intestine up to a time  $t_g$ , such that the total dose is unity.

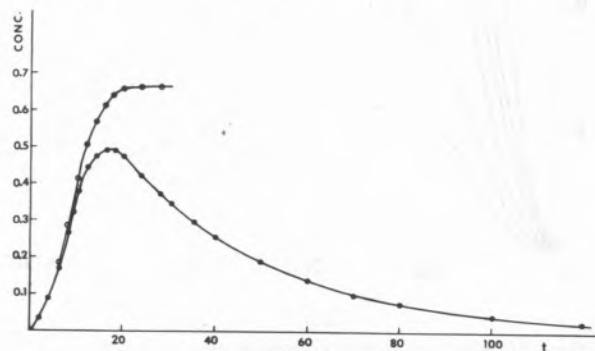
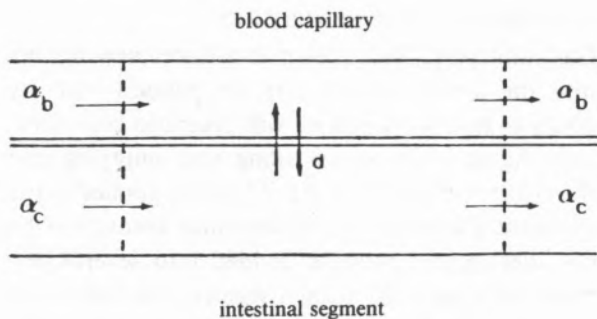


Fig. 6

Absorption ( $\bullet$ ) and invasion ( $\circ$ ) curves gastrointestinal absorption with  $\alpha_c = 0.1$ ,  $k_{abs} = 0.1$ ,  $k_{el} = 0.03$ , dose = 1 and  $\Delta t = 1$

In this model of gastrointestinal absorption the mixing of the drug in the blood compartment is considered to be very fast. However such models do not take into consideration the effect of blood flow rate [8] when this is comparable to the absorption or the chyme flow rate. A model such as the following one can simulate this effect



A reversible diffusion,  $d$ , between chyme and blood is considered. The probability of mass transfer through flow in the blood is  $\alpha_b$  and elimination is only considered from the exit blood compartment with a rate  $k_{el}$ . Fig. 7 presents a family of computed

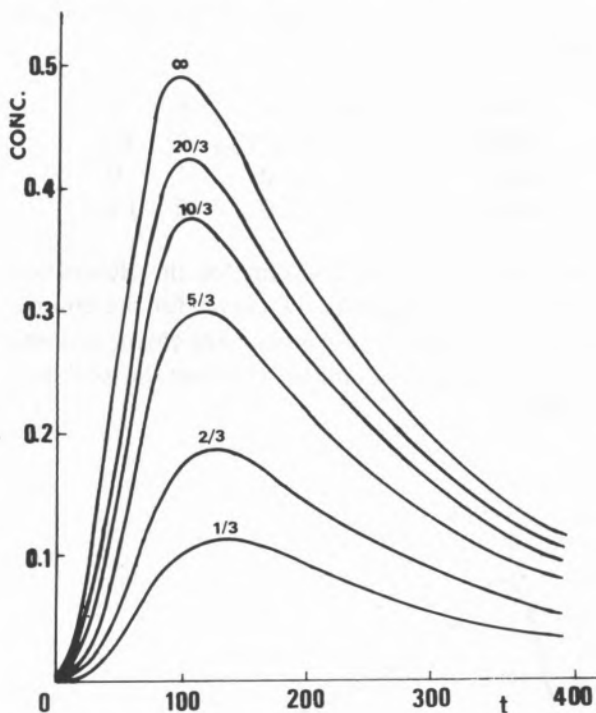


Fig. 7

Effect of blood flow rate on gastrointestinal absorption. Family of curves for different ratios  $\frac{\alpha_b}{d}$ ;  $k_{el} = 5 \times 10^{-3}$ ,  $d = 3 \times 10^{-2}$ ;  $\alpha_c = 1.5 \times 10^{-2}$ ,  $\Delta t = 1$

curves which clearly show that when the blood flow rate approaches the rate of diffusion, there is a decrease in drug absorption.

In conclusion we have shown that MCM can be applied to several situations of relevance in pharmacokinetics. The method is universal, can be made as accurate as one wishes, but can also be a fast method of numerical integration. This allows MCM to be employed in model search. For any given model the method can be used for constructing families of curves of doses or concentrations as a function of time, which may allow estimation of kinetic rate constants.

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## RESUMO

Aplicação do Método das Cadeias de Markov à Evolução com o Tempo de Medicamentos em sistemas Farmacocinéticos

O método estocástico das Cadeias de Markov é aplicado ao estudo da evolução temporal de medicamentos em situações de cinética linear e não-linear. O método que é um processo de integração numérica, é simples, rápido e tão exacto quanto se queira.