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Medical Drug Kinetics

Numerical Methods Report

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Concept

Drug kinetics describe the way the body of a given patient reacts to the administration of a given drug. Different drugs, as well as different intake frequencies or the way a drug is administrated, may produce different results on the aforementioned. It is possible to recreate the admnistration of a drug mathematically, in order to predict the quantity of drug product in each of the compartments of the body (dual-compartment model - [1.1]), at any given time, given an administration function.

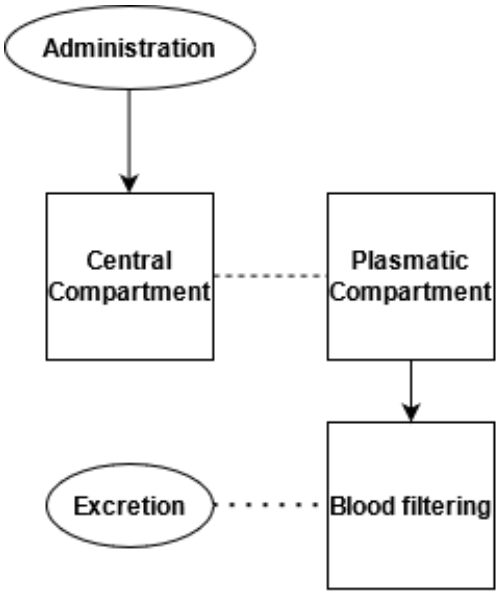


Figure 1.1: Schema of a dual-compartment drug kinetic model via intravenous route

Problem Description

This group was assigned Ceftazidima, an useful antibiotic for the treatment of a number of bacterial infections. The drug characteristics and administration parameters are as follows:

K_{et}	t_{max}	V_{ap}	Dosage	Treatment Duration
0,0959 h^{-1}	5 min	3250 mL	1 $g/24h$	4 $days$

where:

K_{et} = the kinetic total elimination constant
t_{max} = time where the plasmatic drug concentration is the highest
V_{ap} = the apparent volume of plasma

Using the following system of equations:

$$\begin{cases} \frac{\mathrm{d}m_i}{\mathrm{d}t} = D(t) - K_a m_i \\ \frac{\mathrm{d}m_p}{\mathrm{d}t} = K_a m_i - K_{et} m_p \end{cases} . \tag{2.1}$$

where:

m_i = the mass of the given drug in the central compartment
m_p = the mass of the given drug in the plasmatic compartment
$D(t)$ = the administration/transfer function
K_a = the kinetic absorption constant
K_{et} = the kinetic total elimination constant
t = time elapsed

the problem is to calculate, numerically, the concentrations of the given drug in both the central and plasmatic compartments during the treatment duration.

Methodology

3.1 On Calculating K_a

First of all, to solve the system shown in the last chapter, it is necessary to calculate the value of K_a. That value is closely related to K_{et}, by the following non-linear equation:

$$K_a e^{(-K_a t_{max})} - K_{et} e^{(-K_{et} t_{max})} = 0 \tag{3.1}$$

where:

K_a = the kinetic absorption constant
K_{et} = the kinetic total elimination constant
t_{max} = time where the plasmatic drug concentration is the highest

Plotting this function with the K_{et} value given, we obtain:

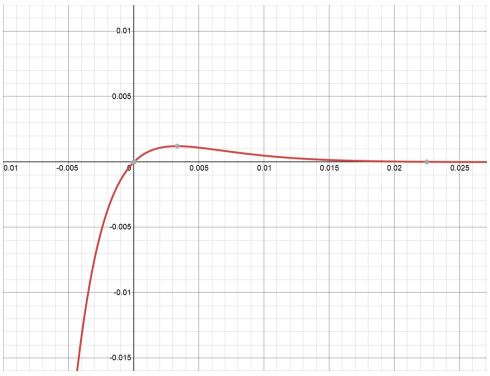


Figure 3.1: Graphic representation of the problem equation

It is possible to detect two solutions, near $x = 0$ and $x \approx 0.025$. However, it is important to assure that these two solutions are unique (that there are no others). The derivative is solvable analytically ($e^{-300x}(1 - 300x)$). It has a root at $x = \frac{1}{300}$, and it is a monotonous decreasing function up until $x = \frac{1}{150}$. From that moment on, it starts increasing, but it never reaches positive values, as its limit towards positive infinity is 0 and has no other roots.

Figure 3.2: Graphic representation of the derivative of the problem equation

With this in mind, since the left limit of the initial function is negative infinity, and the maximum at $x = \frac{1}{150}$ is positive, the function has one root within this interval $\left]-\infty, \frac{1}{150}\right[$. From this point on, the function decreases (confirmed by the derivative, which is always negative), and as its right limit is ≈ -0.000026, it must have one root in this interval as well $\left]\frac{1}{150}, +\infty\right[$ (both conclusions were made using Bolzano's Theorem).

As such, it is possible to conclude that there are 2 solutions to this equation. One of them is trivial, where $K_a = K_{et}$. However, this solution was not considered valid.

To solve this issue, several methods were tested, them being *Brent's*, *Newton's*, *Regula Falsi* and *Ridder's Derivation of Regula Falsi* methods, with different halting conditions.

3.2 On Calculating The System of Differential Equations

For the problem itself, a system of non-linear differential equations was to be dealt with. As such, several methods were also tested. These methods were *Euler's*, *Runge-Kutta 2* and *Runge-Kutta 4* methods.

For all of the methods referred above, the convergence coefficients were calculated and, when possible, its corresponding absolute errors.

3.3 On Determining $D(t)$

Given the dosage and characteristics of the administration of the drug, it was important to choose a function that was a good replication of the real life occurance and that followed the aforementioned parameters. Therefore, this function had to have an *integral* of 1g (or 1000mg, as all units are in mg) and, as it is given intravenously, be *relatively quick*, following a *pulse-like* function.

It was also important that the t_{max} parameter was respected. Some experimenting was necessary, so that when the max of m_p was achieved, the time elapsed was around 5 minutes (or 300 seconds). On the other hand, m_i had to be around 1.2g on that instant, as the max of m_p would occur on $\frac{\mathrm{d}m_p}{\mathrm{d}t} = 0$, or, in other words, $m_p \approx 844.173 m_i$.

For that, a function of the family xe^{-x} was considered, has it approximately replicated the real life application of the drug.

3.4 Methodology Note

It is important to note that all calculations were made in seconds, instead of hours or even minutes, due to the administration function being extremely volatile in the first few instants. Using greater orders of magnitude would considerably and negatively impact the results, as much of the administrated drug would be unnoticed by the differential equations (this would be solved by an using a smaller step, but using seconds would simply be clearer, as the calculations would, in fact, be in that order of magnitude).

Results

4.1 K_a

The following tables show the results for each of the methods tested, for a margin of error of ± 0.000001, in the interval $[0.02, 0.03]$, when the halting condition was absolute precision, relative precision and function annulment, respectively.

Method	Result	Number Of Iterations
Regula Falsi	0.02248783032563428	29
Newton	0.02248783024699512	6
Ridder's	0.02248783032563428	4
Brent's	0.02248783032563428	8

Table 4.1: Results using absolute precision halting condition

Method	Result	Number Of Iterations
Regula Falsi	0.02248783032563428	29
Newton	0.02248783032563428	7
Ridder's	0.02248783032563428	5
Brent's	0.02248783032563428	8

Table 4.2: Results using relative precision halting condition

Method	Result	Number Of Iterations
Regula Falsi	0.02248783032563428	29
Newton	0.02248703360595367	5
Ridder's	0.02248783033255841	3
Brent's	0.02248322399996300	3

Table 4.3: Results using function annulment halting condition

It was important to choose a fairly small interval, as both solutions to the equation were very close to each other. It was also important to guarantee that it bracketed that root only. Choosing a greater interval for Newton's Method, for example, would make it diverge, due to the nature of the equation.

The fact that the value of the derivative of the equation is extremely small in the chosen domain makes Newton's method not as precise as the others, even though it still converged fairly quickly. It is also clear Ridder's algorithm was, by far, the best one, as it needed the smallest number of iterations to converge (it obtained the same result of Regula Falsi's algorithm in approximately 7 times less iterations).

Due to all methods converging to a specific solution in different halting conditions, the value for K_a that was chosen was 0.0224878303256342.

4.2 Drug Concentration Over Time

4.2.1 Administration Function

As stated previously, the chosen administration function was of the family xe^{-x}. It was important that in a 24 hour period, the administrated mass of the drug (or, in other terms, the integral of the function) was 1000mg. It was also important that most of it was integrated very quickly, and for realistic terms that some residue was incorporated over time.

This function had to be replicated every 24 hours, for 4 days. It was considered a 5 second time frame for the administration. As such, the function equation and graphic are as follows:

$$\begin{cases} \text{ke}^{-3t}, & \text{if } 0 \geqslant t > d \\ \text{k(t-d)e}^{-3(t-d)}, & \text{if d} \geqslant t > 2d \\ \text{k(t-2d)e}^{-3(t-2d)}, & \text{if 2d} \geqslant t > 3d \\ \text{k(t-3d)e}^{-3(t-3d)}, & \text{if t} > 3\text{d} \end{cases} . \tag{4.1}$$

where:

k = the chosen constant = $9{\times}10^3$
d = the number of seconds in an day = 86400

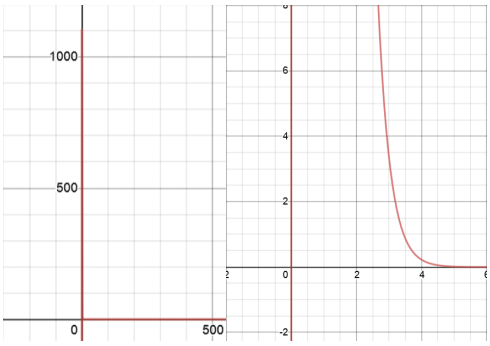


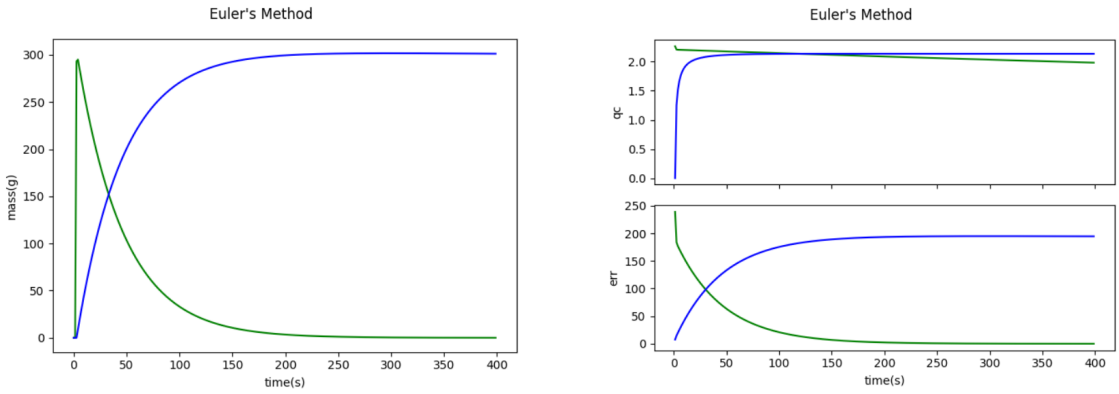
Figure 4.1: Graphic representation of the administration function

4.2.2 Drug Concentration Modeled Prediction

With K_a calculated and the administration function defined, it was possible to predict the concentration, over time, of the given drug in the human body. The system of equations was, already, in its simplest form, so no adjustments were made.

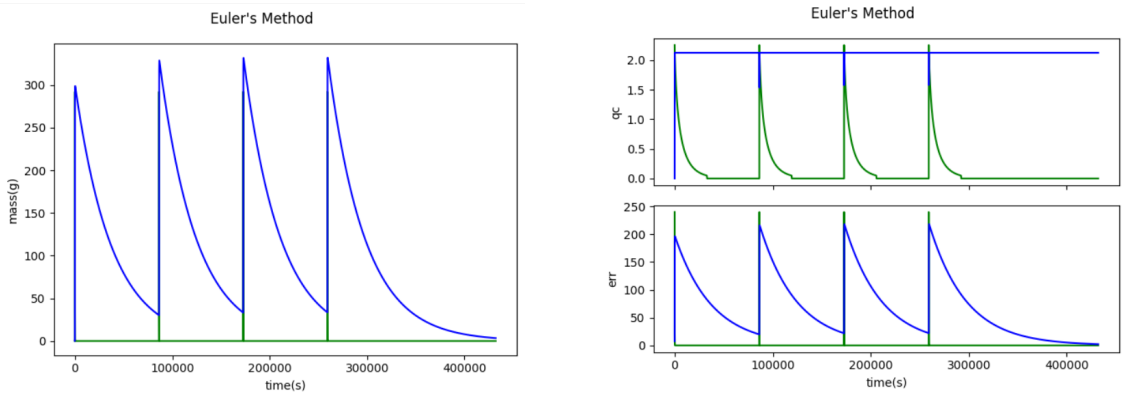
Several methods were tested. Their results, as well as the Convergence Coefficients and errors are displayed below. M_i and M_p are represented, in all graphics, by the green and blue colors, respectively.

Euler



(a) M_i and M_p (b) QC and Error

Figure 4.2: Graphic representation of the first 600 seconds of the problem



(a) M_i and M_p (b) QC and Error

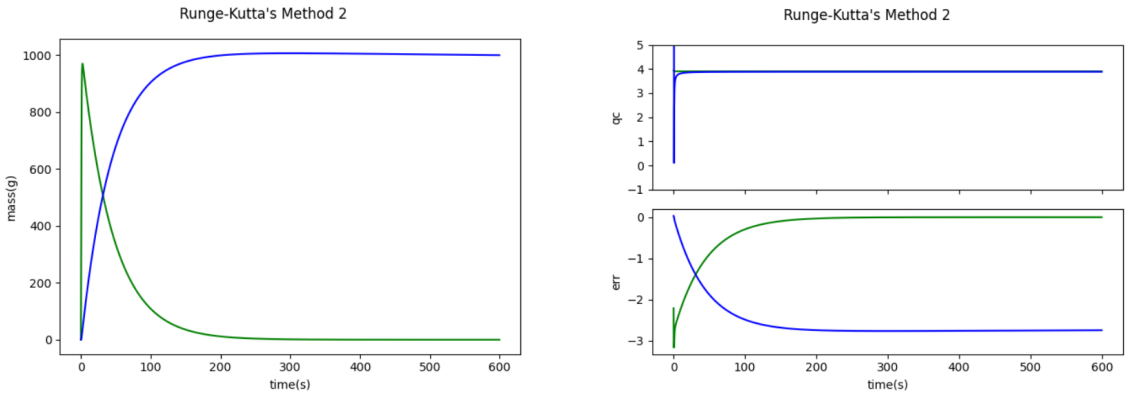
Figure 4.3: Graphic representation of 5 days of the problem

This method was iterated 430 times for the first 600 seconds, and 322500 times in the full duration of the 5 days to achieve the correct convergence coefficient (Euler's Method is a first order method, so QC ≈ 2 to evaluate its error correctly). It took $t = 6.28s$ to process the method for the full 5 days.

The absolute error calculated, averaging about 170mg for m_p in the first 10 minutes (600 seconds), the low precision of this method and a clear miss-read of the administration

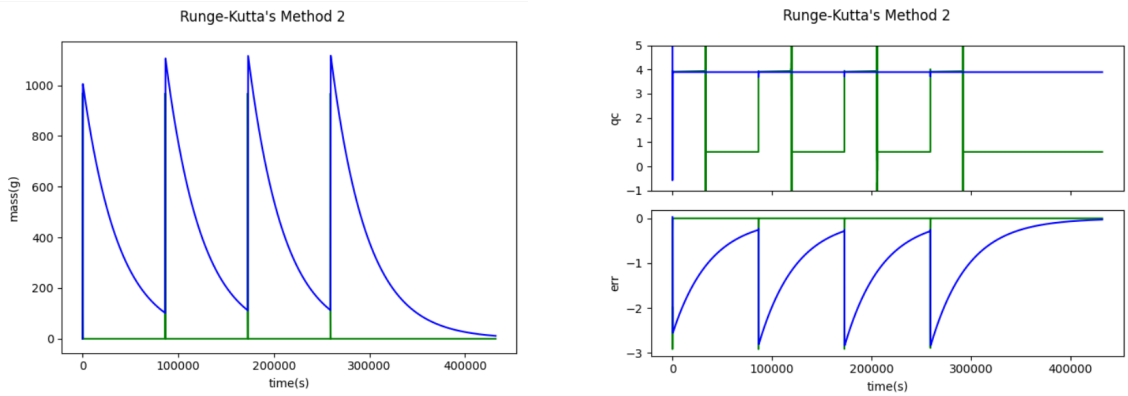
function by the method (m_p maxes out at around 300mg, and it should max out near 1000mg - the administrated drug) are problems that impact negatively the accuracy of this solution to an insurmountable amount, and so these results must be discarded.

Runge-Kutta 2



(a) M_i and M_p (b) QC and Error

Figure 4.4: Graphic representation of the first 600 seconds of the problem



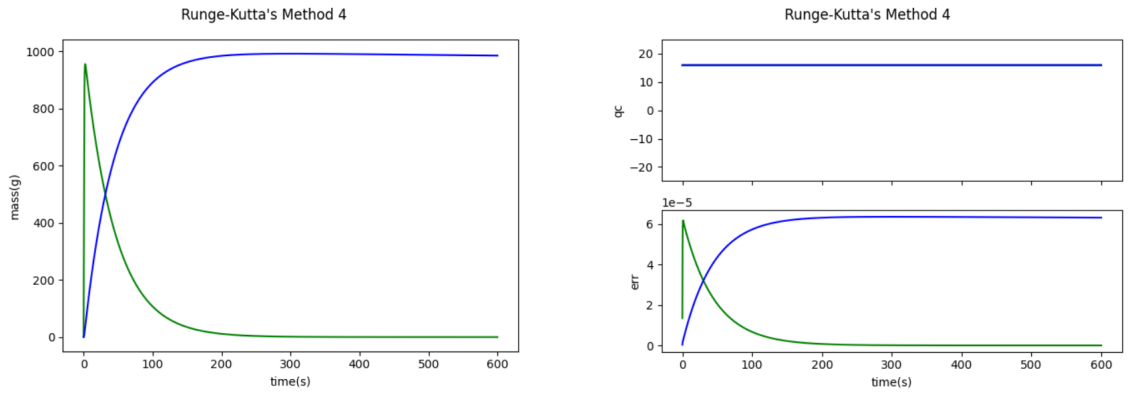
(a) M_i and M_p (b) QC and Error

Figure 4.5: Graphic representation of 5 days of the problem

This method was iterated 3000 times for the first 600 seconds, and 2250000 times in the full duration of the 5 days to achieve the correct convergence coefficient (Runge-Kutta's 2 Method is a second order method, so QC ≈ 4 to evaluate its error correctly). It must be noted that this coefficient was only reliably achieved for m_p. That can be explained by the great variance associated with the administration function (and with m_i, consequently), as it has one big peak each day, followed by incredibly small rate of change (near 0). It took $t = 118.33s$ to process the method for the full 5 days.

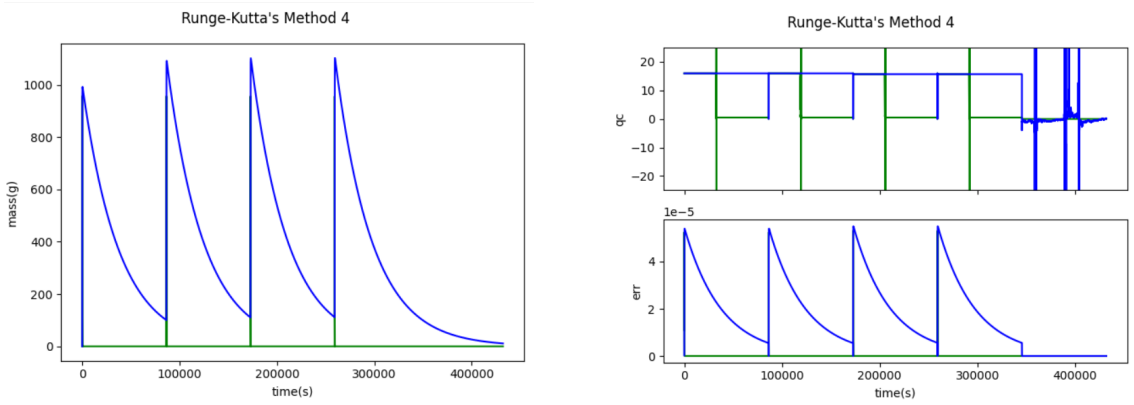
The absolute error calculated averaged about -1mg for m_p in the first 10 minutes (600 seconds). This method took nearly 20 times the time Euler's method took. This is associated with it being a method with greater precision, higher order and the fact that it was used a smaller step to meet the QC criteria, which led to a better result.

Runge-Kutta 4



(a) M_i and M_p (b) QC and Error

Figure 4.6: Graphic representation of the first 600 seconds of the problem



(a) M_i and M_p (b) QC and Error

Figure 4.7: Graphic representation of 5 days of the problem

This method was iterated 10000 times for the first 600 seconds, and 7500000 times in the full duration of the 5 days to achieve the correct convergence coefficient (Runge-Kutta's 4 Method is a fourth order method, so QC ≈ 16 to evaluate its error correctly). It must be noted that this coefficient was only reliably achieved for m_p, for the same reasons Runge-Kutta's 2 Method did. However, it must also be noted that due to the high precision of the method and the small step chosen (to meet the QC condition), some values are so close to one another that make QC erratic (can be seen at the end of the 5th day). Due to the consistency of it and its lower error margins, it is possible to admit that the error behaviour stays the same in that interval. It took $t = 456.52s$ to process the method for the full 5 days.

The absolute error calculated averaged about -$2e^{-5}$mg for m_p in the first 10 minutes (600 seconds). This method took nearly 80(!) times the time took by Euler's method, and that can be explained by the same reasoning used for Runge-Kutta's 2 Method. This method is, by far, the most precise, but its computing time was far superior than any other (and the results are similar to Runge-Kutta's 2), making it less appealing.

Conclusions

With this report it was possible to have an overview on Numerical Methods as a way to envision and predict real life situations, instead of it simply being another branch of Math. Difficult situations to reliably calculate analytically, such as this one, are the ones where these methods shine, as most of them don't require the most exact answer, and having a good approximation to understand the concept at hand will do just fine.

It must also be referred that this report incited every group member to understand more deeply every method used and its intricacies, and even motivated a search for new methods beyond this curricular unit.

In short, this report made clear the utility and importance of Numerical Methods, as a way to strive for a better understanding of complex world situations and problems.