Modelling drug administration regimes for asthma: a Romanian experience

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Motto: We must love and care for error, it is the womb of knowledge.
Friedrich Nietzsche

Abstract. In this paper we present a modelling activity, which was a part of the project DQME II[3] and some general observations regarding the maladjustments and rational errors arising in such type of activities.

Keywords: compartment model, medication schemas, regression analysis, rational errors

Mathematical Subject Classification: 97B40, 97C30, 97U70

1 Introduction

The compartment models and Markov chain models are very often used to describe the absorbtion of drugs in the human body (see [8], [6], [7], [5] [10]). Real-life drug administration encounters a wide range of problems which can be tackled by mathematical models, for example: the estimation of parameters, the use of incomplete data ([12]), the controlling of drug administration ([9]), etc. In biology the mathematical models usually have the role of basic laws (such as the principle of thermodynamics in physics), but a given biological phenomena can be modelled by several mathematical models. The main scope of our activities was to study several mathematical models for drug absorbtion and to compare the developed medication schemas (each based on a different model) starting from a given data set ([11]). We used the problem described in Appendix A and we used four different compartment models (for the model specifications see the appendix).

In all descriptions we denote by $y(t)$ the amount of theophylline in the blood and by $z(t)$ the amount of theophylline in the liver where

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that is the case. We assume that the total quantity of blood is not changed by a few injections, so if we consider the total amount of blood as a unit quantity, then $y(t)$ and $z(t)$ also represent the concentration of this drug in the blood respectively in the liver. The simplest model is to consider a single compartment (the blood, in this case). If we denote by k_1 the rate of absorbtion, then in the interval $[t, t + \Delta t]$ (with very small Δt) from the initial amount $y(t)$ the organism uses $k_1 y(t) \cdot \Delta t$, so we have the following equation

$$y(t + \Delta t) = y(t) - k_1 y(t) \cdot \Delta t. \tag{1}$$

This implies (for $\Delta t \to 0$) the following differential equation

$$y'(t) = -k_1 y(t) \tag{2}$$

with the solution $y(t) = ae^{-k_1 t}$.

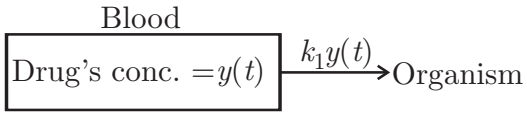

Figure 1: Compartment model with 1 compartment

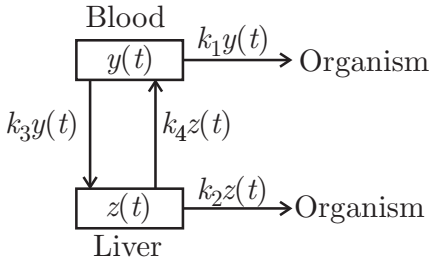

Figure 2: Compartment model with 2 compartments

From the second specification we obtain (as in the first case) the following system of differential equations:

$$\begin{cases} y'(t) &= -(k_1 + k_3)y(t) &+k_4 z(t) \\ z'(t) &= k_3 y(t) &-(k_2 + k_4)z(t) \end{cases} \tag{3}$$

This is a homogeneous linear system with constant coefficients which has the solutions $y = c_1 \cdot e^{r_1 t} + c_2 \cdot e^{r_2 t}$, where r_1 and r_2 are the roots of the equation

$$r^2 + (k_1 + k_2 + k_3 + k_4)r + k_1k_2 + k_1k_4 + k_3k_2 = 0. \tag{4}$$

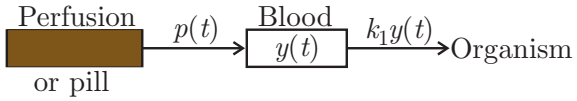

Figure 3: External dosing in a 1 compartment model

From the specification of the third case we deduce the differential equation

$$y'(t) = -k_1 y(t) + p(t).$$

We considered that p is a constant function, so the solution of the equation is $y = a \cdot e^{bt} + y_0$, where $y_0 \in \mathbb{R}$.

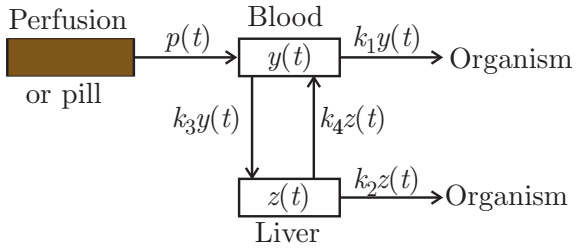

Figure 4: External dosing in a 2 compartments model

In the last case we obtain the following system:

$$\begin{cases} y'(t) &= -(k_1 + k_3)y(t) &+k_4 z(t) &+p(t) \\ z'(t) &= k_3 y(t) &-(k_2 + k_4)z(t) & \end{cases} \tag{5}$$

If we assume that p is a constant, we obtain the solutions

$$y = c_1 \cdot e^{r_1 t} + c_2 \cdot e^{r_2 t} + y_0.$$

In order to answer the given questions the students were expected to fit the models to the given data using regression analysis and then to develop (by numerical experiments or by formal calculations) the required medication schemas.

2 Student background and getting started

Due to the complexity of the problem we involved not only high school students but university students too.

Before starting the main activities (for solving the proposed problem) we had to organize a few special classes to prepare the background:

- for the high school students we needed to introduce basic notions of mathematical analysis (limit, derivative, differential equation), regression analysis (parameter estimation, curve fitting) and we also needed to develop some skills in manipulating special softwares (Excel - solver, curve fitting);

- for the university students (who already had a first course on differential equations) we needed lessons on regression analysis and the use of computer softwares (Excel).

These preparations required 6+4 classes for the high school students and 4 classes for the university students. These lectures were held in 3 weeks. All the activities were organized in a traditional setting, without any special assessment. At the end of each activity our students were able to handle the main concepts and tools, to use them in simple modelling tasks.

For the main activity we organized four groups, so each group had its own model. The groups were composed by $3-4$ university students (freshmen/19 years old) and $2-3$ high school students ($16-18$ years old). Each group had a computer for calculations (calculations were made in Excel) and a video projector for the oral presentation of the results. During the preparatory activities the students got acquinted with the models (the differential equations and the solutions of these equations), but they did not know about the questions they had to answer. The activity was supposed to take in $2-3$ hours, but it actually took 5 and a half hours. During this period we answered any technical question but we tried not to influence the groups in designing and structuring their calculations. At the end each group made an oral presentation based on their own Excel sheet.

3 Solutions and maladjustments

I. model. Outline of the expected solution. The requested function has the explicit form $f(t) = a \cdot e^{bt}$, so $a = f(0)$ and b can be determined from the measured data. Using regression analysis we obtain $a = 10$ and $b = -0,167$. In the time period $[0, T]$ the concentration can be described by the function $f_1(t) = a \cdot e^{bt}$. At moment T the concentration is $a \cdot e^{bT}$ and the patient gets a further dose D, so the concentration becomes $D/6 + a \cdot e^{bT}$. In this way in the time interval $[T, 2T]$ the concentration can be described by the function $f_2(t) = \left(D/6 + a \cdot e^{bT}\right) \cdot e^{b(t-T)}$.

By a very similar argument we obtain for the interval $[2T, 3T]$ the function $f_3(t) = (D/6 + f_2(2T)) \cdot e^{b(t-2T)}$ and generally (by a recurrence relation)

$$f_k(t) = \frac{D}{6} \cdot \frac{1 - e^{kbT}}{1 - e^{bT}} \cdot e^{b(t-(k-1)T)}, \ t \in [(k-1)T, kT).$$

If L_1 and L_2 is the lower, respectively the upper limit, from the conditions $L_1 \leq f_k(t) \leq L_2$ we obtain:

$$L_1 \leq \frac{D}{6} \cdot \frac{1 - e^{kbT}}{1 - e^{bT}} \cdot e^{bT} < \frac{D}{6} \cdot \frac{1 - e^{kbT}}{1 - e^{bT}} \leq L_2. \tag{6}$$

By setting $k \to \infty$ and solving the obtained system of inequalities we get:

$$\frac{1}{b} \ln \left(1 - \frac{D}{6L_2}\right) \leq T \leq -\frac{1}{b} \ln \left(1 + \frac{D}{6L_1}\right),$$

so for the existence of a real T we must have $D < 6(L_2 - L_1)$. If we fix the length of the interval (T) we can calculate a minimal and a maximal dose corresponding to this interval:

$$6L_1 \cdot \frac{1 - e^{bT}}{e^{bT}} \leq D \leq 6L_2 \cdot \left(1 - e^{bT}\right) \tag{7}$$

and T must satisfy the inequality $T \leq \frac{1}{b} \ln \frac{L_1}{L_2}$. For the given data we obtain $a = 9,8637$ and $b = -0,1696$ and so the maximal value of T is approximately $6,57$. So for $T \in \{1, 2, 3, 4, 5, 6\}$ we can make the following table (the values are rounded to 2 digits):

Time interval between doses, T (hours)	1	2	3	4	5	6
Minimal dose	5,55	12,12	19,90	29,13	40,05	53,00
Maximal dose	14,03	25,88	35,89	44,33	51,45	57,46

To have a more realistic image about the phenomena we illustrated a few medication schemas. In figure 5 and 6 one can see that the system tends to a periodic solution, the period of which is the length of the time interval between doses (T). The dose influences the values of this periodic solution (with the minimal dose the concentration attains the lower clinical limit L_1 at the end of every period of length T while the upper clinical limit is attained with a maximal dose at the beginning of every period T). Figure 6 shows also that for some T the concentration can be smaller than the lower clinical limit in the first few periods.

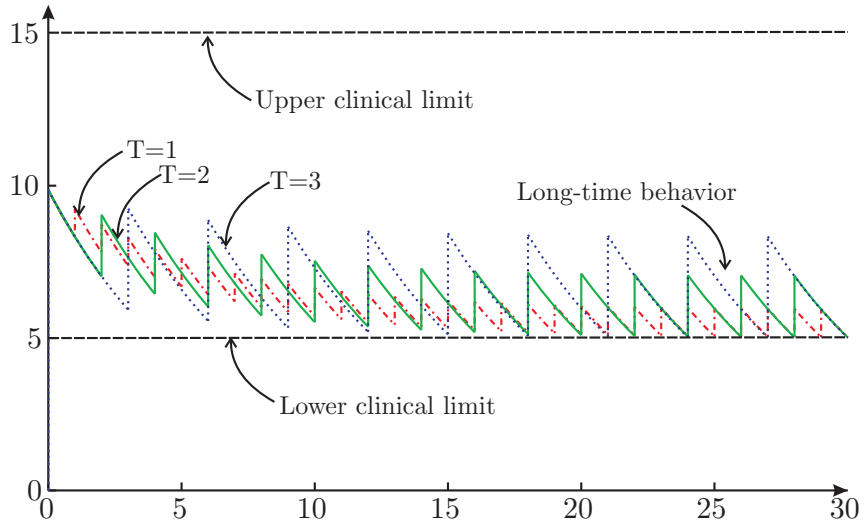

Figure 5: Medication schemas for $T \in \{1, 2, 3\}$ and a minimal dose

In figure 7 we can see what happens if we fix T and we increase the dose (from the minimal value to the maximal value). With the minimal dose the concentration reaches the lower clinical limit in each time period (and it is possible not to reach the upper clinical limit)

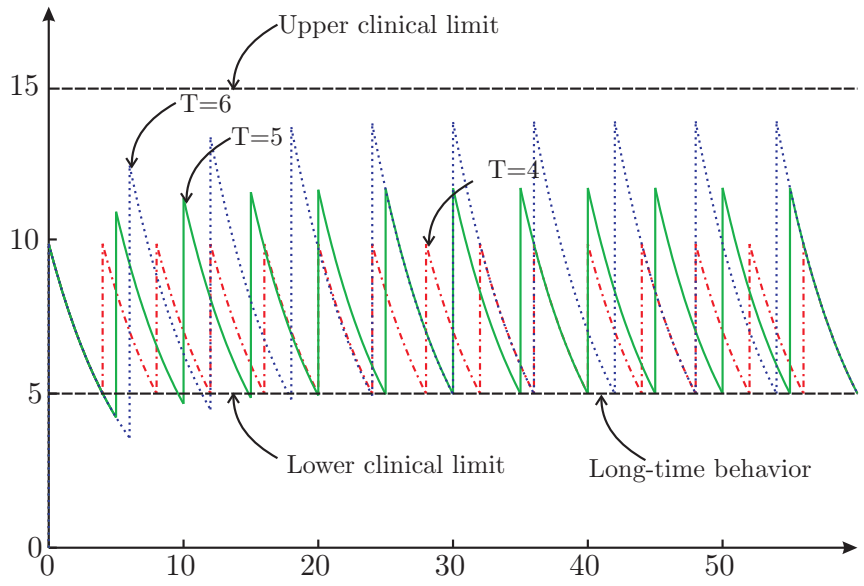

Figure 6: Medication schemas for $T \in \{4, 5, 6\}$ and a minimal dose

and with the maximal dose the concentration reaches the upper limit L_2 (after a few periods of length T).

To avoid the first few periods in which the concentration may become lower than L_1 we can use a starting dose S and then a fixed dose D. In this case

$$f_k(t) = \left(\frac{S}{6} e^{(k-1)bT} + \frac{D}{6} \cdot \frac{1 - e^{(k-1)bT}}{1 - e^{bT}} \right) \cdot e^{b(t-(k-1)T)},$$

so from the conditions $L_1 \leq f_k(t) \leq L_2$, for all $t \in [(k-1)T, kT]$ we obtain the same minimal and maximal dose as in the previous case and for the starting dose we get

$$6L_1 e^{-bT} \leq S \leq 6L_2,$$

where $T \leq \frac{1}{b} \ln \frac{L_1}{L_2}$.

Figure 8 illustrates the effect of the starting dose on the variation of the concentration. We can observe that the starting dose has no influence on the long-time behavior of the solution.

The group's solution for this model. The answer to the first question was correct (and it was obtained using the Excel's curve fitting options). A part of the medication schemas they obtained (with

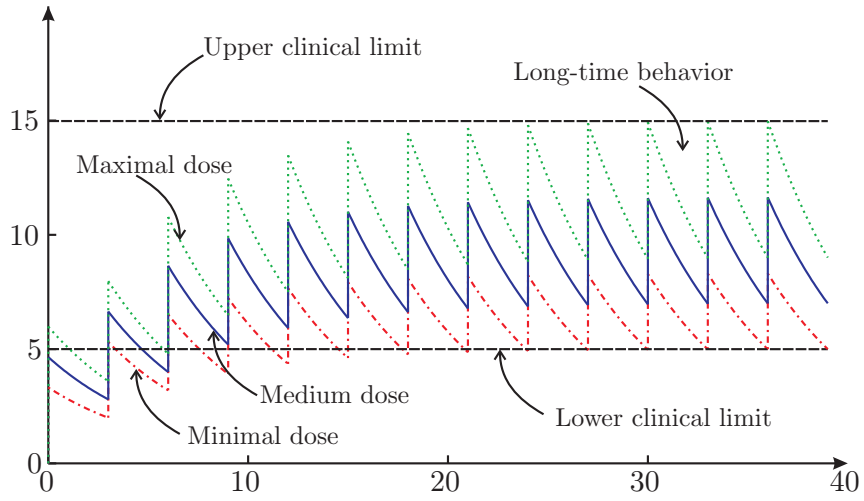

Figure 7: Increasing the dose for fixed T

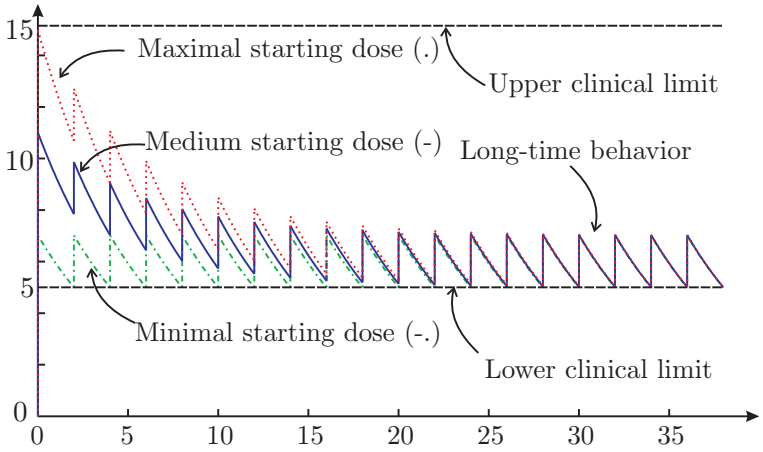

Figure 8: The effect of the starting dose

or without starting dose) was also correct, but they gave incorrect schemas too. Their tables did not contain the maximal and the minimal dose for a fixed T, but for correct values of T, their dose was in between the corresponding minimal and maximal dose. The team did not calculate the explicit form of the function f_k : they obtained only the recurrence relation and they calculated the values of this function in $(k-1)T$ and kT. As a consequence they could not use inequality (6) analytically. At this stage they turned to a numerical experimentation. For fixed T and D they calculated the concentration in kT and they found some values for which the dosing schema seemed to be good. Unfortunately they had not observed the upper limit for T and so they gave also uncorrect schemas. This error occurred basically because for every moment kT they calculated only one value (the value of $f_k(kT)$ without $f_{k+1}(kT)$). Due to the numerical point of view they couldn't handle all values $f_k(kT)$ (they only tackled a few values which covered just 1-2 days of medication), so they did not calculate the maximal respectively the minimal doses. ♦

Student behaviors. All the members were much engaged in the activity, they started their calculations only after a half an hour brainstorm. The students were working assiduously for more than 3 hours and they had no questions during the activity.

Concluding remarks for the first group. The oral presentation of the first group was clear, but it did not contain the basic key elements of the phenomena (the periodicity of the long-time behavior, the necessity of the starting dose, the effect of the starting dose). The main difficulty of their activity was that they were unable to combine the numerical techniques with the formal calculations, they wanted to obtain the results only by numerical experimentations.

II. model. Expected solution. The students were expected to discover that the given data is not sufficient to give a correct and verified answer or in the worst case to reduce their model to the first one using regression analysis for the given data. This is possible because if we look for a regression function of the form $f(t) = c_1 e^{r_1 t} + c_2 e^{r_2 t}$, we obtain (using Excel's Solver function)

$$r_1 = -0,171730399, r_2 = -0,171730399, c_1 = 4,976891104$$

and $c_2 = 4,976891104$. Hence the function is

$$f(t) = 9,953782209e^{-0,171730399t}$$

(because r_1 and r_2 are very closed).

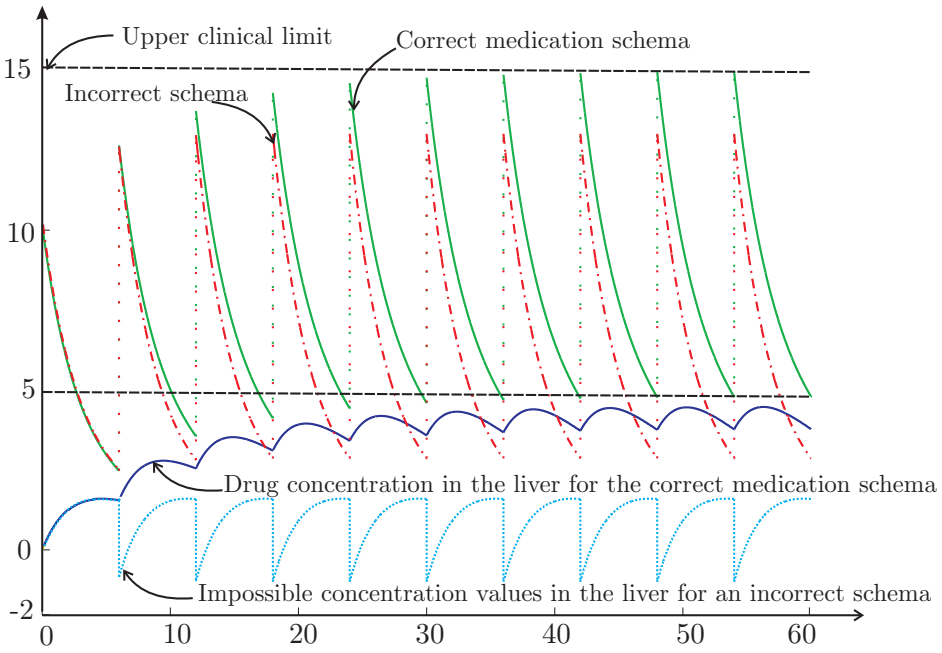

Figure 9: Dosing in the compartment model with 2 compartments

If $r_1 \neq r_2$ we need to solve a Cauchy problem on each interval $[kT, (k+1)T)$ but we do not have sufficient data to estimate all the parameters of the model because the given data concern only one of the compartments. Figure 9 shows a correct medication schema for this model based on a sequence of Cauchy problems and also an uncorrect medication schema based on a similar reasoning the students have used. Although the same phenomenon appears in all the models (upper bound for T, the asymptotically periodic solution, necessity of the starting dose, ...) the calculations are different for these models and may become very complicated if we use a multiple compartment model.

The group's solution for this model. The second team used a geometrical motivation to derive the function f_2 from the function f_1.

Obviously they did not have sufficient data to generate the Cauchy problems for each time period T. They considered that the graphs of the functions f_k can be obtained from the same curve by translation. This idea works only for the first model, not for the second model, hence the reasoning of the second team was completely wrong. However the numerical values they obtained were almost correct. Their results were also obtained by numerical experimentation, so they had problems with the validation of the results. The only validation was the comparison between teams. ♦

Student behaviour. It was very interesting that they needed a very long time (more than 2 hours) to give up the idea of finding some explicit formulas for the function f_2 in the case $r_1 \neq r_2$ and to concentrate just on the special case they obtained. At the beginning they were not looking for a minimal and a maximal dose for a fixed T but for a minimal and a maximal T in the case of a fixed D. After the presentation of the first team they changed this and in their presentation they used the same structure as the first team. This change of variables was performed because initially they didn't obtain medication schemas for $T > 6$. Unfortunately by choosing $T > 6$ they obtained invalid medication schemas due to the same error as the first team.

Concluding remarks for the second group. The expected solution was far too strange for this group. They did not realize that they have to change the settings of the problem (the model) although a deeper understanding of the mathematical model would have implied this.

III. model. The expected solution. The required function has the form $f(t) = ae^{bt} + c$ and the Excel's Solver function gives $a = 9,91$ $b = -0,17$ and $c = 0,06$. Using a similar argument as in the first case and denoting by f_k the function which describes the concentration on the interval $[(k-1)T, kT)$ we obtain

$$f_k(t) = \left(\frac{D}{6} \frac{1 - e^{kbT}}{1 - e^{bT}} - ce^{(k-1)bT} \right) e^{b(t-(k-1)T)} + c.$$

Hence in order to maintain the concentration values between the lower and upper limit we need

$$L_1 - c \leq \frac{D}{6} \frac{e^{bT}}{1 - e^{bT}} < \frac{D}{6} \frac{1}{1 - e^{bT}} \leq L_2 - c.$$

This implies that for fixed T the dose D may vary between the following minimal and maximal dose:

$$6(L_1 - c) \cdot \frac{1 - e^{bT}}{e^{bT}} \leq D \leq 6(L_2 - c) \cdot \left(1 - e^{bT}\right).$$

In order to obtain a proper D we need $T \leq \frac{1}{b} \ln \frac{L_1 - c}{L_2 - c}$, so from the given data we deduce $T \leq 6,33$. Using the previous inequalities we can recommend the following medication schemas:

Time interval between doses, T (hours)	1	2	3	4	5	6
Minimal dose	5,66	12,40	20,42	29,97	41,35	54,90
Maximal dose	14,36	26,43	36,56	45,06	52,21	58,21

If S is the starting dose, we obtain

$$f_k(t) = \left(\left(\frac{S}{6} - c\right) e^{(k-1)bT} + \frac{D}{6} \cdot \frac{1 - e^{(k-1)bT}}{1 - e^{bT}}\right) \cdot e^{b(t-(k-1)T)} + c$$

and using a similar monotonicity argument as in the first case we obtain the necessary and sufficient conditions for S :

$$6\left((L_1 - c)e^{-bT} + c\right) \leq S \leq 6L_2,$$

hence we obtain the following table:

Time interval between doses, T (hours)	1	2	3	4	5	6
Minimal starting dose	35,66	42,40	50,42	59,97	71,35	84,90
Maximal starting dose	90	90	90	90	90	90

The group's solution for this model. The third team used an equivalent formulation of the geometric idea for generating the functions f_k. They calculated the translation (t_0) from the inverse function of f_1. They found the upper limit for T and all their results were correct. Their minimal and maximal doses were obtained by numerical experimentations.

Student behaviour. This group had several questions during the activity. Every time they had ambiguities or disagreements regarding some aspects, they presented their problems, their ideas and asked for advice.

Concluding remarks for the third group. The success of this team can be explained by their efficient working style.

IV. team. The students were expected to reduce their model to the previous one or to the first one (based on the parameter values they obtained from the curve fitting) and to observe that a single data set concerning only one of the compartments is not sufficient to perform an analysis using the fourth model.

Fitting the curve $f(t) = c_1 e^{r_1 t} + c_2 e^{r_2 t} + c$ to the given data (using the Solver function and the least squares method) we obtain $r_1 = -0,17470162$, $r_2 = -0,17470162$, $c_1 = 4,9554490$, $c_2 = 4,9554490$ and $c = 0,061231823$. This implies that the desired function is

$$f(t) = 9,9108980e^{-0,17470162t} + 0,061231823,$$

so we can repeat the arguments from the previous model.

The group's solution for this model. The fourth team finished on the last position (both as far as time and solutions were concerned). Initially they wanted to use Matlab instead of Excel, but they didn't know how to obtain estimations for the parameters. This issue set them back for almost 1 hour, when they restarted their calculations in Excel. Using the Excel's Solver function they obtained the values $c_1 = 0,177$, $c_2 = 9,813$, $c_3 = 0,00016$, $r_1 = -1097,03$ and $r_2 = -0,169$ (the result given by the Solver depends also on the initial values from which this function is initialized). Since $e^{r_1 t}$ is extremely small, they neglected it. Their calculations were very similar to the calculations of the third team but unfortunately they had a wrong cell reference, so their numerical results were incorrect.

Student behaviour. They made an initial plan of what they wanted to visualize. Due to this plan they wanted to use Matlab. A problem occurred because they did not find the Matlab keywords for minimizing nonlinear functions (and they did not ask for any help on this issue). Due to their initial lag, they became hurried and made a few mistakes on the Excel sheet. They noticed some of their errors but they were not able to correct all of them.

Concluding remarks for the fourth group. The overall conception of this group was probably the best, but they didn't manage to handle their problems.

4 Concluding remarks

1. Since our students are not familiar with such an approach (real problem+ modelling+statistical data+computer oriented organization of the hole calculations) they wanted very often to create some formulas even if it was not possible, so we can conclude that some mathematical notions (such as the notion of function, inverse function, equation, result of a problem) must be reanalyzed and sometimes extended to be usable and useful in this kind of situations. The use of computers during the Mathematics classes is recommended and both the teaching staff and the students have to understand the benefits. The computer can be used as a helpful tool (see also [6]). The Romanian curriculum needs to be changed in order to include mathematical modelling and computer based simulation.

2. The students were working for more than 5 hours, and even so most of them were unable to observe the major phenomena that occur in the drug administration (upper bound for T, asymptotically periodic solution, the role of the starting dose,...). This confirms the observations from [7] regarding the increased need of time for solving modelling tasks. Moreover, in comparison with the tasks from [7], where question (vi) was "the only poorly done section", in our approach inequality (6) was essential in developing correct dosing schemas and it wasn't formulated as a separated task, so the students had to discover it. This created great difficulties for our students.

3. The teamwork helped the students to avoid a lot of impracticable paths during the discovery of the solutions. The students opinion was that it is more than sure that not every student could have reached individually the same results. This opinion confirms the remarks from [7] regarding the reduced effectiveness of such an

activity in students evaluation.

4. The software they used influenced their thinking in the sense that all the teams gave the results in some kind of tables. If they had used other software, such as Matlab, Mathematica, Maple (with more graphical capabilities), they might have given the solutions as graphs or they could have chosen the good medication schemas by simply simulating the variation of the drug's concentration for the changing parameters T and D.

5. The Excel's Solver function uses an iterative process and sometimes for the same sample gives different results depending on the starting values of the variables. The students didn't test this.

6. Most of the errors that occurred can be classified as "rational errors" (for the definition and other examples see [1]). The most relevant example of such an error is the use of the geometric idea in the second and fourth case. The students had a good motivation to use this idea (this worked in the first case) but they did not have sufficient data to develop a correct approach. Unfortunately they didn't realize this.

7. During the preparation of these activities we realized that finding cooperative colleagues was the hardest issue we faced. This experience convinced us about the necessity of a special course on modelling and on computer based mathematics for teachers, which (besides the usual tasks) trains them to avoid these rational error-traps even if using them would be more comfortable.

In an overall evaluation of this experience we think that it is very alarming that in some situations (during a complex modelling activity) the students have no criteria for validating their model or their calculations (just think about the real life validation of a wrong medication schema). These kind of errors are very useful if we have enough time to discuss them and to correct them (unfortunately in a classical setting the time is very limited [3]). Otherwise they should be avoided, because they can lead to dangerous misconceptions.

4.1 Acknowledgements

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5 Appendix A

People that suffer of Asthma are often treated with the medicine theophylline. Theophylline, also known as dimethylxanthine, is a methylxanthine drug used in therapy for respiratory diseases such as asthma under a wide variety of brand names. Patients are often treated with an equally large dose, D mg, over equally large time intervals, T hours. A doctor measured how the concentration of theophylline in the blood of a patient varies after the patient had been injected with a dose of 60 mg.

Time (hours)	Concentration (mg/l)
0	10,0
2	7,0
4	5,0
6	3,5
8	2,5
10	1,9
12	1,3
14	0,9
16	0,6
18	0,5

You are asked to write a report for the doctor answering the following questions

1. How will the concentration of theophylline in the blood decrease over time?

2. How can we plan a continuous medication schema with a fixed dose D over a fixed time interval T, so that the concentration after a couple of injections is always in the interval 5-15 mg/l?

3. How can we plan a continuous medication schema with a start dose S and thereafter a fixed dose D over fixed time intervals T, so that the concentration from the first administration of the medicine should be within the interval 5-15 mg/l?

4. What considerations must be taken into account before one uses this medication plan for a patient?

In order to answer the above questions construct several mathematical models considering the specifications listed below and then compare the obtained medication schemas.

I. the amount of drug used by the organism is directly proportional to the time and to the existing amount of drug in the blood (k_1 is the proportionality constant), or in a more suitable formulation, the speed of assimilation is proportional to the concentration of the drug in the blood;

II. in any unit time interval a fixed rate k_3 of the existing theophylline is transported to the liver and from the liver a fixed rate of theophylline (k_4) is returned to the blood; the absorbtion rate in the liver is k_2 while the absorbtion rate from the blood is k_1;

III. the absorbtion is realized as in the first case, but in any unit time interval (from an external source) a fixed amount p of theophylline is added to the existing theophylline (the external source can be an adhesive patch, a pill or perfusion);

IV. the absorbtion is realized as in the second case under the additional assumption from the third case.

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