Modelling the suitable pharmacokinetic profile of Erythromycin.

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Abstract: Erythromycin is the oldest macrolide antibiotic. The mechanism of action of these antibiotics is to inhibit protein biosynthesis in bacterial cells by binding to the 50S ribosomal subunit and interfering with the elongation of the protein chain (ribosome is an element of the cell used to produce proteins, composed of two subunits - large 50S and small 30S). Because the cell's development is inhibited and not killed, we say that macrolides are bacteriostatic antibiotics. They are characterized by a broad spectrum of activity, i.e. they are active against numerous species of bacteria. To get better informed with the mechanics of the antibiotic tried to model the suitable pharmacokinetic profile of the erythromycin. Because the concentration of erythromycin in the blood does not change linearly, we used two nonlinear function modeling methods in our studies: polynomial interpolation and automatic nonlinear regression. The aim of the experiment was to assess the suitability of the erythromycin pharmacokinetic profile model depending on the method chosen for modeling (using polynomial interpolation or automatic non-linear regression). From the conducted experiment, it can be concluded that the selected modeling method strongly influences the usefulness of the model in terms of the pharmacokinetic profile of erythromycin, because this method determines the type of functions obtained and, consequently, the behavior and properties of the curves. In the case of this

exploration, it is the Hoerl function that fits more clearly into the pharmacokinetic profile of erythromycin than the cubic polynomial model. In general, the Hoerl model has a smaller percentage error than the cubic polynomial model.

Keywords: modelling; pharmacokinetic profile; Erythromycin

------- Introduction ----------

— Fundament of interest —

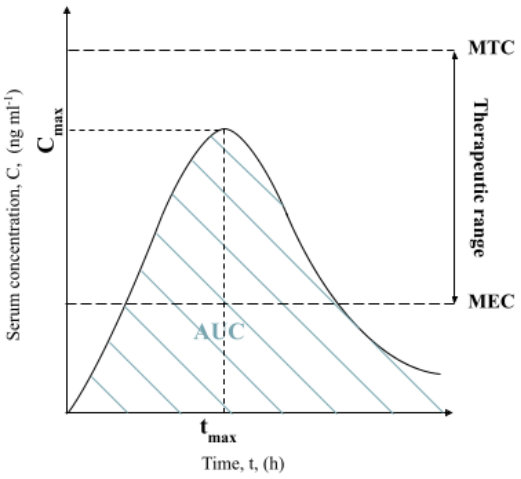
Erythromycin – this is the oldest macrolide antibiotic. The mechanism of action of these antibiotics is to inhibit protein biosynthesis in bacterial cells by binding to the 50S ribosomal subunit and interfering with the elongation of the protein chain (ribosome is an element of the cell used to produce proteins, composed of two subunits - large 50S and small 30S). Because the cell's development is inhibited and not killed, we say that macrolides are bacteriostatic antibiotics. They are characterized by a broad spectrum of activity, i.e. they are active against numerous species of bacteria. In respiratory tract infections, macrolides are considered an alternative to β-lactam antibiotics. For an antibiotic to work effectively, it must reach the concentration at the site of infection necessary to inhibit the growth or kill the pathogenic microorganism, and at the same time this concentration must remain safe for human cells. If both of these conditions are met, we say that the microorganism is sensitive to the antibiotic; if not, we are dealing with antibiotic resistance. Antibiotic resistance may be innate or acquired as a result of genetic mutation of bacteria and selection of resistant strains, or by transferring resistance genes between bacterial cells (this is the so-called horizontal transfer). Resistance to macrolide antibiotics may arise as a result of active removal of the drug from inside the cell, production of ribosomal proteins that displace the drug from the connection with the 50S subunit, enzymatic inactivation or as a result of chromosomal mutations causing changes in the 50S protein. Side effects that may occur after the use of macrolide antibiotics include gastrointestinal problems, such as nausea, vomiting, loose stools and diarrhea. These are usually mild and often disappear during or after treatment. It may also be beneficial to take preparations that restore the proper composition of the intestinal bacterial flora.

— Background knowledge —

To get better informed with the mechanics of the antibiotic We try to model the suitable pharmacokinetic profile of the erythromycin. Pharmacokinetics is a study of kinetics of how the antibiotic is absorbed, distributed, metabolised and excreted by the organism, in other words, how the organism deals with the medicament (Saghir and Ansari). Pharmacokinetics use the mathematical equations to create models of pharmacokinetic profile of a drug, which allow us to predict the

biological response of the body to the substance (Saghir and Ansari).

Since erythromycin concentration in our blood does not change linearly (Ďurišová), in my investigation We use two nonlinear methods of modelling a function: polynomial interpolation and automated nonlinear regression. Polynomial interpolation is the method in which We will calculate the function's formula by hand based on the data used in the investigation (*Table 1*), whereas automated linear regression will be the function found by the computer as the most suitable to the gathered data. The functions will be examined to see whether there is a difference in accuracy of those models. Then both functions will be further analysed with use of differential and integral calculus intending to obtain two pharmacokinetic profiles, which in turn will give the information about C_{max}, t_{max}, and AUC (*Figure 1*).



Term	Definition
C_{max}	Expressed in: ng ml^{-1}. Maximum concentration of serum after taking the antibiotic.
t_{max}	Expressed in: hours. Time in which the drug reaches its C_{max}.
AUC	Expressed in: h ng ml^{-1}. Area under the function of pharmacokinetic profile of the antibiotic. Represents the overall exposure of the body to the drug.
MEC	Minimum Effective Concentration that is needed to achieve the positive pharmacological response of the body.
MTC	Minimum Toxic Concentration after which the adverse effects start to occur.
Therapeutic range	Concentration range in which desired therapeutic response takes place.

Figure 1. Sketch of a pharmacokinetic profile of the antibiotic and list of key terms concerning the pharmacokinetic profile in the investigation.

Information about those parameters will be crucial in studying the properties of the erythromycin characteristics since they play a role as an indicator of the antibiotic toxicityand effectiveness.

— Research question —

Is suitability of the model of the pharmacokinetic profile of erythromycin dependent on the method chosen for the modelling, investigated with the use of polynomial interpolation and automated nonlinear regression?

— Hypothesis —

There is a significant difference in accuracy and suitability of the pharmacokinetic profiles of erythromycin derived from different methods of modelling: polynomial interpolation and automated nonlinear regression.

------- Analysis of the data ----------

As We were not able to obtain this kind of data through independently conducted experiment, We decided to take it from: "Mathematical Model of the Pharmacokinetic Behavior of Orally Administered erythromycin to Healthy Adult Male Volunteers" by Mária Ďurišová (*Table 1*).**Table 1.** Concentration of the Erythromycin over time (Ďurišová).

Time, t, (h)	0.0	0.5	1.0	2.0	4.0	6.0	9.0
Concentration of Erythromycin, C, (ng ml^{-1})	0.0	47.4	185.0	293.0	254.0	158.0	76.9

In purpose of better understanding the data, values have been plotted on the scatter graph (*Figure 2*). All functions' models in the investigation were prepared with the use of a modelling tool called SciDaVis.

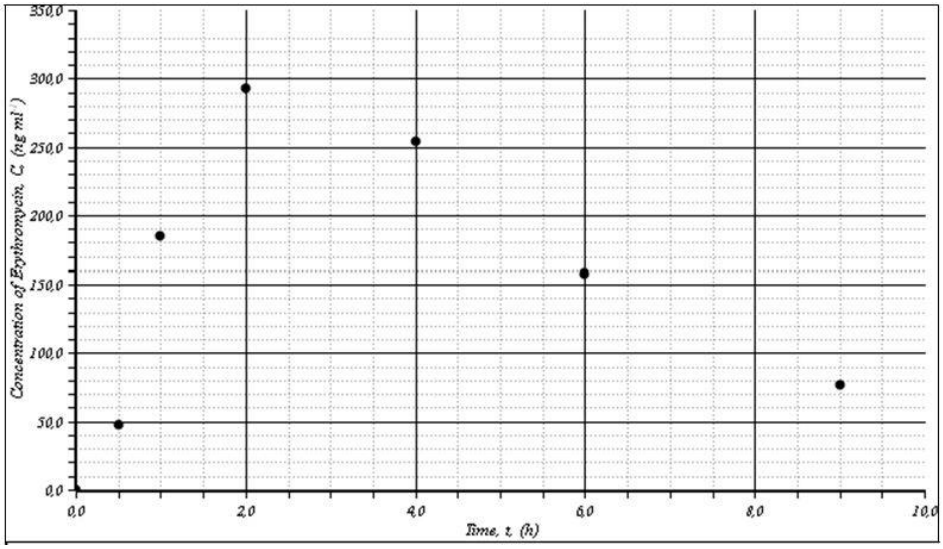


Figure 2. Scatter graph representation of dependency between Time, t, (h) and Erythromycin concentration, C, (ng ml^{-1})

Now, the first, $\frac{\Delta C}{\Delta t}$, and the second, $\frac{\Delta^2 C}{\Delta t^2}$, rates of change were calculated in order to provide the information about potential changes in shape of the future function. Since the first derivative shows whether the function is increasing or decreasing at a given point, so whether the gradient of the tangent is positive or negative, its symbol may be considered the same as the symbol of the first rate of change (Boelkins). If the rate of change is positive, the function is increasing, the gradient of the tangent is positive, hence, the first derivative also must be positive. When it comes to the second derivative, it indicates the concavity of the original function, and the rate of change of the first derivative (Boelkins). Thus, when the second rate of change, so the rate of change of the first derivative, is positive, then the original function isconcave up, and when it is negative, the function is concave down (Boelkins).

Calculated rates of changes and responding function's behaviour were gathered in *Table 2*.

Table 2. First and second rates of change with highlighted function's behaviours.

Time, t, (h)	Erythromycin concentration, C, (ng ml^{-1})	$\frac{\Delta C}{\Delta t}$	Function	$\frac{\Delta^2 C}{\Delta t^2}$	Concavity
0.0	0.0	0.0	-	0.0	-
0.5	47.4	94.8	Increases	189.6	Concave up
1.0	185.0	275.2	Increases	360.8	Concave up
2.0	293.0	108.0	Increases	-167.2	Concave down
4.0	254.0	-19.5	Decreases	-63.8	Concave down
6.0	158.0	-48.0	Decreases	-14.3	Concave down
9.0	76.9	-27.0	Decreases	7.0	Concave up

By looking at the *Table 1*, *Figure 2*, and *Table 2*, one may observe the following behaviour ofthe data:

- In the interval: $0 \leq t \leq 2$, concentration of erythromycin increases very quickly and drastically just to reach its C_{max} of 293.0ng ml^{-1} at t_{max} of 2h.
- The function is concave up to $t = 1$ and concave down at $t = 2$, which suggests thatthere is a point of inflection in the interval: $1 < t < 2$, when the second derivative equals 0.
- After $t = 2$, the function starts decreasing, being concave down at once.
- In the interval $4 \leq t \leq 6$, the function is decreasing with increasing rate of change, however, in the interval $6 \leq t \leq 9$, the function is decreasing slower, as the rate of change decreased when compared to the previous interval.
- Since the sign of the second rate of change changes in the interval: $6 < t < 9$, there is another point of inflection on the graph of the original function.
- The data implies that there is only one root of the function in (0,0).

Taking into consideration the fact that the values are non linearly distributed on the graph (*Figure 2*), creating a model of a linear function would be completely incorrect. However, due to the presence of the root of the function, and points of inflection, the polynomial function would be a good choice to prepare a model function of this data set. As there are two points of inflection, and the data is unevenly spread on the graph, the model function must be a polynomial of degree > 2. Moreover, the degree cannot be too high, as the function would be too precise and would reach to meet every known point, omitting the points not described in Table *1*. Hence, We have decided to fit a cubic function to the data, and with the use of Microsoft Excel check if it would suit the values. Excel has shown R^2, the coefficient of determination, value = 0.9545. The closer the R^2 value to 1, the more suited are the results. For example: the R^2 of 0.9545 tells that 95.45% of changes on one axis are explained by the changes on the second axis, which is high enough to assume that the cubic function fits the data very well.

------- Polynomial interpolation ----------

— Searching for cubic polynomial —

Polynomial interpolation is a method of estimating the values of a polynomial function, given that n + 1 values of a function are known, where n = the degree of the polynomial (Fulber-Garcia). Therefore, 4 points are needed in order to estimate the cubic function formula. As We have 7 different values of erythromycin concentration (*Table 1*), and need only

4 are required, there is $C_4^7 = 35$ combinations of different polynomials that We can choose, each

of which would have a different formula and would fit the data set non identically. Since solving 35 different equations for functions and seeking for the highest R^2 value among them would be extremely tedious, We have decided to use Lagrange interpolation. This method permits finding the formula of a function based on arbitrary chosen points that are supposed to lay on a final curve (Arashiro et al.), which in my case, makes the process of establishing the formula of the polynomial much more efficient. Lagrange interpolation formula:

$$P(x) = \sum_{i=1}^{n} P_i(x) y_i \qquad [1]$$

For the formula, the following theorem must be obeyed:

With n distinct real values given as $x_1, x_2, x_3, \ldots, x_n$ and n real values given as $y_1, y_2, y_3, \ldots, y_n$, and data points given as $(x_1, y_1), (x_2, y_2), (x_3, y_3), \ldots, (x_n, y_n)$, there exists a polynomial P with coefficients satisfying the assumption that $P(x_i) = y_i$ where $i \in \{1, 2, 3, \ldots, n\}$ and degree of $P < n$ (Arashiro et al.). On the other hand, $P_i(x)$ is a Lagrange polynomial of a degree $n - 1$, which can be expressed by:

Taking into consideration all of the assumptions,

$$P(t) = \sum_{i=1}^{4} P_i(t)C_i = P_1(t)C_1 + P_2(t)C_2 + P_3(t)C_3 + P_4(t)C_4 \quad [2]$$

During the choosing process We tried to take points so that they were relatively equally distributed between each other on the scatter graph (*Figure 2*). Points are presented in *Table 4*.

Table 4. Coordinates of the four chosen points.

Time, t, (h)	Concentration of Erythromycin, C, (ng ml^{-1})
0.0	0.0
1.0	185.0
4.0	254.0
9.0	76.9

4 unique Lagrange polynomials are obtained:

$$P_1(t) = \left(\frac{t-1}{0-1}\right)\left(\frac{t-4}{0-4}\right)\left(\frac{t-9}{0-9}\right)$$

$$P_2(t) = \left(\frac{t-0}{1-0}\right)\left(\frac{t-4}{1-4}\right)\left(\frac{t-9}{1-9}\right)$$

$$P_3(t) = \left(\frac{t-0}{4-0}\right)\left(\frac{t-1}{4-1}\right)\left(\frac{t-9}{4-9}\right)$$

$$P_4(t) = \left(\frac{t-0}{9-0}\right)\left(\frac{t-1}{9-1}\right)\left(\frac{t-4}{9-4}\right)$$

Then the equation was solved:

$P(t) \approx 3.689t^3 - 58.943t^2 + 240.254t + 0$ (rounded to 3 decimal places)

With the known equation of cubic polynomial, the function of erythromycin concentration (ng ml^{-1}) changing over time has been graphed:

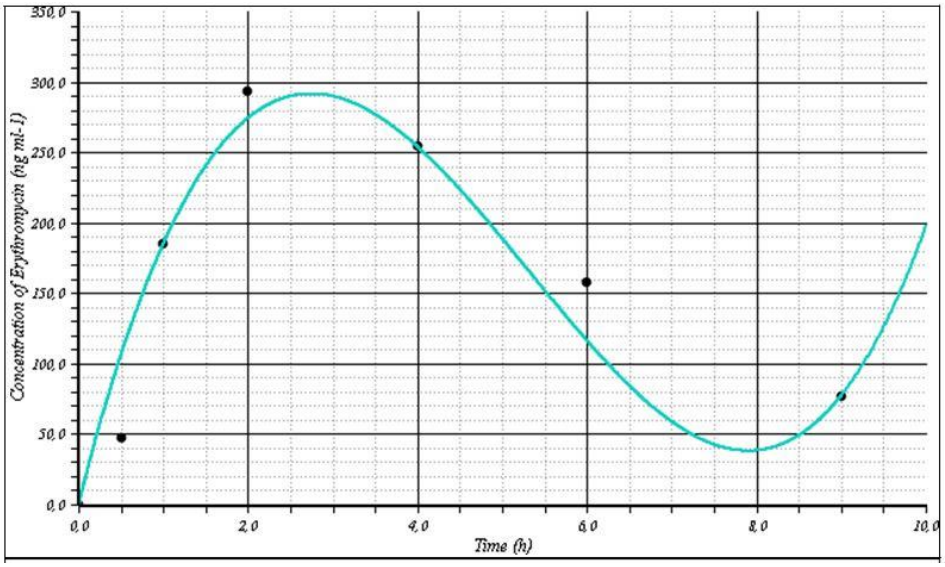


Figure 3. Graph of cubic polynomial model of erythromycin concentration, C, (ng ml^{-1}) changing over time, t, (h)

— Analysis of the cubic polynomial —

Analysing the graph from *Figure 3* one may see that the C_{max} is reached after about 3 hours, so it is shifted in time. The rest of the points of the function are quite well suited with the model, especially for t = 0. However, although the model resembles most of the assumptions about the behaviour of the function (*Table 2*), it could not be introduced as a correct pharmacokinetic profile of erythromycin due to the huge error occurring after the interval of decrease from t = 6. Under normal conditions, the erythromycin is supposed to be metabolised in the organism and finally excreted (Ďurišová), so as $t \rightarrow \infty$, $C \rightarrow 0$, nonetheless in the cubic polynomial function as $t \rightarrow \infty$, $C \rightarrow \infty$, which is not possible in reality. To accurately compare the original data set to the data obtained from cubic polynomial, We used the differential calculus to get the values of the highest importance in pharmacokinetics: C_{max} and t_{max} of erythromycin. To find those values, the derivative of the polynomial equation has been calculated:

$$f(x) = x^{n} \Rightarrow f'(x) = nx^{n-1} \quad [3]$$

$$P(t) = 3.689t^{3} - 58.943t^{2} + 240.254t + 0$$

$$\Rightarrow P'(t) = 11.067t^{2} - 117.886t + 240.254$$

C_{max} is a local maximum, and local maximum occurs for t_{max} when $P'(t) = 0$, so:

$$11.067t^{2} - 117.886t + 240.254 = 0$$

$$\Delta = 117.886^{2} - 4 \cdot 11.067 \cdot 240.254$$

$$\Delta = 3261.545$$

$$\sqrt{\Delta} = 57.110$$

$$t = \frac{117.886 + 57.110}{2 \cdot 11.067}$$

$$t_1 \approx 7.906$$

$$t_2 \approx 2.746$$

Since the t_{max} of the original data set is 2, and no more than 3 *Figure 3*, $t \approx 7.906_{1}$ wasrejected, and the $t \approx 2.746_{2}$ was accepted as a correct value to calculate C_{max}:

$$P(2.746) = 3.689 \cdot 2.746^{3} - 58.943 \cdot 2.746^{2} + 240.254 \cdot 2.746 + 0$$

$C_{max} = P(2.746) \approx 291.7$ ng ml^{-1} (rounded to original erythromycin concentration)

Now, to find AUC, the integral calculus was applied, and the definite integral was calculatedfor the domain: $0 \leq t \leq 9$, as these are the hours between which the concentration is known.

$$\text{Area under the curve} = \int_{a}^{b} f(x)\,dx \quad [4]$$

Where a and b are consecutively the lower and upper boundaries of the integral, hence:

$$\text{AUC} = \int_{0}^{9} (3.689t^{3} - 58.943t^{2} + 240.254t + 0)\,dt$$

Since integral of x^{n}equals:

$$\int x^{n}\,dx = \frac{x^{n+1}}{n+1} + Q \quad [5]$$

Then, by applying a definite integration method, we get rid of constant Q and integrate withinthe $0 \leq t \leq 9$ domain. The following equation is obtained:

$$\text{AUC} \approx 1458.020 - 0.000 = 1458.020 \text{ h ng ml}^{-1}$$

The final results are presented on *Figure 4*:

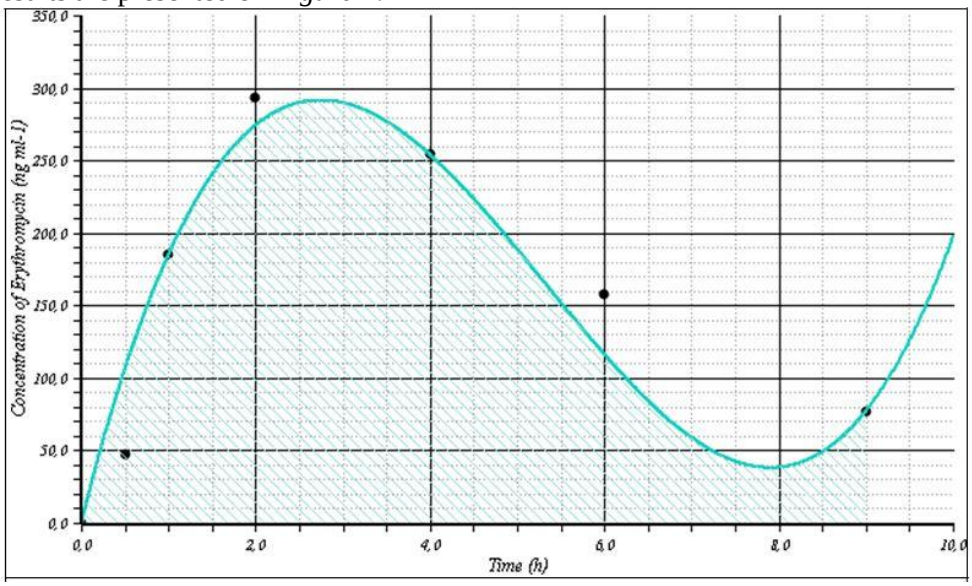


Figure 4. Graph of cubic polynomial model of erythromycin concentration, C, (ng ml^{-1}) changing over time, t, (h), with highlighted area under the curve, which represents the AUC value

— Verifying the polynomial of a higher degree —

Out of curiosity, at the end We have decided to verify the thesis introduced at the end of the *Analysis of the data* section, and check whether the degree of the polynomial really cannot be too high, as it would be somehow too precise, which would make it even less reliable than polynomial of a smaller degree. To verify it, We used all the data presented in *Table 1* and using

the same combination of steps We calculated the polynomial of 6th degree. The final equation ofsuch function is presented below:

$$P_6(t) = 0.831t^6 - 18.496t^5 + 147.946t^4 - 517.998t^3 + 731.562t^2 - 158.845t + 0$$

Which when placed on the graph, looks as following:

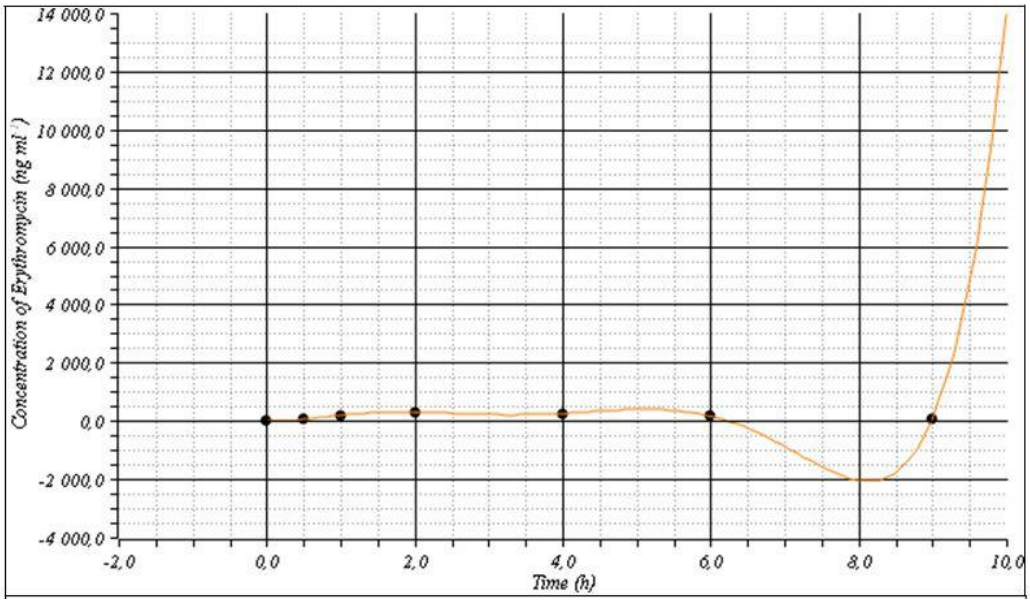


Figure 5. Graph of 6th degree polynomial model of erythromycin concentration, C, (ng ml^{-1}) changing over time, t, (h)

As presented on Figure 5, a polynomial of too high degree is also undesired, since it indeed omits every potential and unknown point just to fit the given data. Moreover, in the polynomial of 6th degree, the erythromycin concentration goes into negative values, which is also incorrect, since it must be bigger or equal 0. In addition, after 9 hours the erythromycin concentration also increases, similarly to the cubic model, but with much higher pace. Therefore, the polynomial of 6th was correctly rejected, and the analysis of the cubic polynomial was much more reliable than the analysis of the polynomial of 6th degree.

------- Automated nonlinear regression ----------

— Searching for the best fitting function —

As stated in the *Background knowledge*, automated nonlinear regression is a method that assumes computer searching for the function that would fit the behaviour of the data the best, so have the highest R^2 value for the given set of data. For the purposes of research, We have installed the demo version of software called “Curve Expert” (Hyams), which uses the nonlinear least square method to find the functions with highest fitting. In case of my data set, it is the Hoerl function that turned out to be the best fit, with R^2 value ≈ 0.9869 (*Appendix A*).

This function is expressed by the following formula (Lohninger):

$$f(x) = k_0 \cdot k_1^{x} \cdot x^{k_2} \quad [6]$$

Where parameters k_0, k_1, and k_2 are the values calculated by the software to make the function as well fitted as possible. The Hoerl function is adjusted to express pharmacokinetics profile since its k_1 value is such that $0 < k_1 < 1$ (Lohninger), so k_1^{x} indicates the exponential decay, plateauing of the function, hence, when $t \to \infty$, and $C \to 0$. Additionally, it can be concluded that k_0 and k_2 are values responsible for initial exponential growth of the function. These theories are supported by the results from Curve Expert, as it has shown the following values for each parameter: $k_0 \approx 301.161$, $k_1 \approx 0.564$, and $k_2 \approx 1.570$. After substituting the values We obtained the formula for my Hoerl function model:

$$C(t) = 301.161 \cdot 0.564^{t} \cdot t^{1.570}$$

The equation of Hoerl model was visualised:

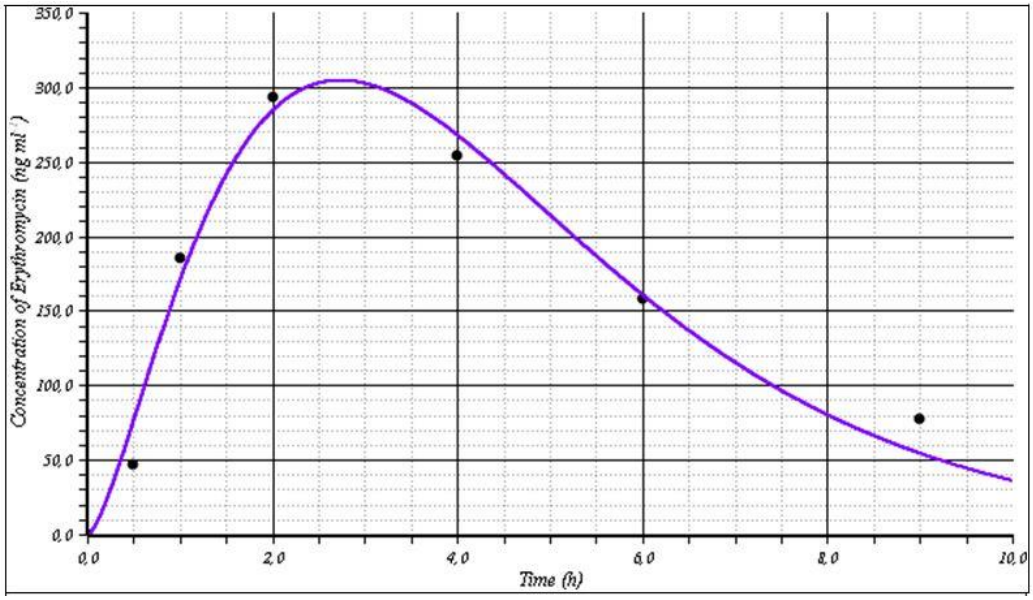


Figure 6. Graph of Hoerl model of erythromycin, C, (ng ml^{-1}) changing over time, t, (h)

— Analysis of the Hoerl model —

In case of Hoerl function there is also a rapid growth in the interval: $0 \leq t \leq C_{max}$, which reflects the reality of the original set of data, however, this time, the C_{max} is a little bit higher than the original one. After reaching C_{max} the concentration is relatively slowly decaying which resembles the normal pharmacokinetic profile of the antibiotics (*Figure 1*). Moreover, the Hoerl function values are closed in range such as $C \geq 0$, which is desired, as the concentration of the antibiotic in the organism cannot be negative. This statement is supported by the fact that as $t \to \infty$, $C \to 0$. Nevertheless, for more accurate comparison of Hoerl model to polynomial model, and original dataset, the same procedure of analysis of Hoerl model as in the case of cubic polynomial was applied. Repeatedly occurring the same schemes of calculations were omitted to achieve better conciseness.

$$C(t) = 301.161 \cdot 0.564^{t} \cdot t^{1.570}$$

$$\Rightarrow C'(t) = 472.823 \cdot 0.564^{t} \cdot t^{0.570} - 172.475 \cdot 0.564^{t} \cdot t^{1.570}$$

$$C'(t) = 0.564^{t}(472.823t^{0.570} - 172.475t^{1.570})$$

Again, local maximum was calculated:

$$0.564\,(472.823t^{0.570} - 172.475t^{1.570}) = 0$$

$$t_1 \approx 2.741 \text{ and } t_2 \approx 0.000$$

Since local maximum is not in point (0, 0), $t_1 \approx 2.738$ value was accepted as a t_{max}. By substituting t_{max} value into the function C_{max} value was obtained:

$$C(2.741) = 301.161 \cdot 0.564^{2.741} \cdot 2.741^{1.570}$$

$$C_{max} = C(2.741) \approx 305.2 \text{ ng ml}^{-1} \text{ (rounded to original erythromycin concentration)}$$

By substituting the Hoerl model equation and setting the boundaries of 0 and9, the AUC of Hoerl model of pharmacokinetic profile of erythromycin was calculated:

$$\text{AUC} \approx 1636.064 \text{ h ng ml}^{-1}$$

The results have been put on the graph (*Figure 7*):

Figure 7. Graph of Hoerl model of erythromycin, C, (ng ml^{-1}) changing over time, t, (h) with highlighted area under the curve, which represents the AUC value

------- Conclusions ----------

— Comparison of key features and behaviours of functions —

To start the comparison, key results of both methods were compared to the values from the original data (*Table 5*) and both functions were put on one graph to facilitate the analysis of behaviours.

Table 5. Key values of the original set of data compared to values obtained from polynomial interpolation and automated nonlinear regression.

	C_{max}, C, (ng ml^{-1})	t_{max}, t, (h)	AUC, (h ng ml^{-1})
Original data	293.2	2.000	-
Polynomial interpolation	291.7	2.746	1458.020
Automated nonlinear regression	305.2	2.741	1636.064

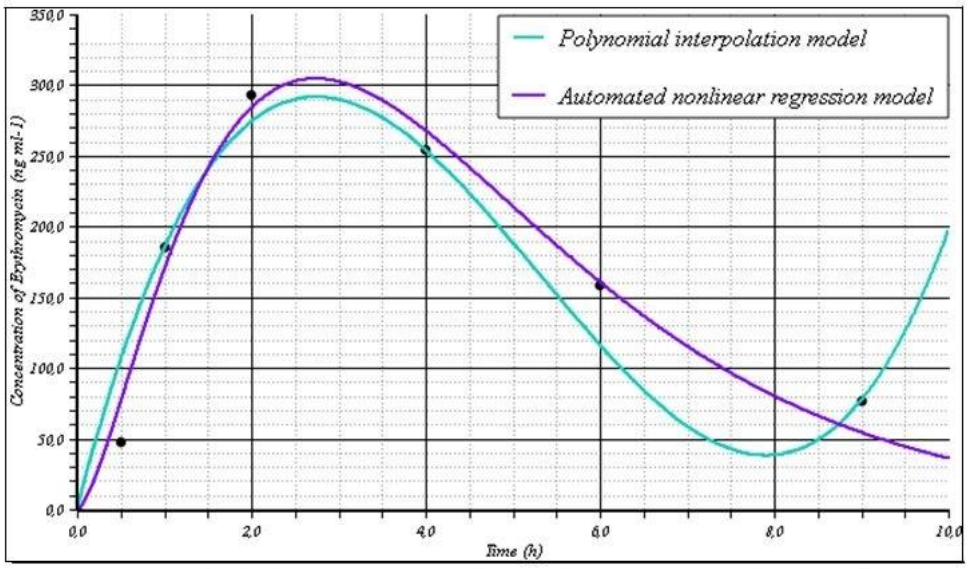


Figure 8. Comparison of graphs of Hoerl and cubic polynomial models of erythromycin concentration, C, (ng ml^{-1}) changing over time, t, (h)

As presented above, there is a visible difference in t_{max} value between the original set of data and both models. The C_{max} remains quite similar between the data sets, yet there is an observable exception in case of automated nonlinear regression, which shows C_{max} to be higher than polynomial interpolation and original data suggest. However, the greatest difference between both models occurs in values of AUC (178.044 h ng ml^{-1}). Such a huge

difference should be resolved, as AUC is the indicator of bioavailability, and its value is often used for estimating the dosage of the antibiotics. When it comes to the behaviours of the functions, one may observe that as $t \rightarrow t_{max}$, both functions experience a really rapid increase in concentration values to reach the C_{max}, just as in the case of the original data points. After reaching C_{max} both functions decrease, however, at different pace. Therefore, We calculated the rate of change of both functions between t = 6, and t = 9, by establishing the $P(6)$, $P(9)$, $C(6)$, $C(9)$ and substituting values with rounding the result to rates' of change number of decimal places:

$$P(6) = 3.689 \cdot 6^{3} - 58.943 \cdot 6^{2} + 240.254 \cdot 6 + 0 = 116.400$$

$$P(9) = 3.689 \cdot 9^{3} - 58.943 \cdot 9^{2} + 240.254 \cdot 9 + 0 = 77.184$$

Cubic polynomial rate of change in between t = 6 and t = 9 is -13.1

$$C(6) = 301.161 \cdot 0.564^{6} \cdot 6^{1.570} = 161.499$$

$$C(9) = 301.161 \cdot 0.564^{9} \cdot 9^{1.570} = 54.761$$

Hoerl function rate of change in between t = 6 and t = 9 is -35.6

Since the original data points decrease at the rate of -27.0 between t = 6 and t = 9, it can be concluded that Hoerl function decreases too rapidly, and the cubic polynomial too slowly, which burdens those functions with some potential errors. Moreover, at point $t \approx 7.906$, which is the local minimum, second root, of the first derivative of the cubic polynomial (*Analysis of the cubic polynomial*), the polynomial starts increasing again, yet the Hoerl function is still decreasing. Therefore, cubic polynomial cannot be extrapolated after $t \approx 7.906$, in contrast to the Hoerl model, as the concentration of erythromycin in blood cannot start randomly increasing after such a long time.

— Evaluation of the results —

Before making the final conclusion, We have decided not only to compare the behaviours of both models, but also propagate the hypothetical errors of those functions in order to clearly state which method is more accurate. To calculate the error, each value of t was substituted to the equation of the model function to obtain erythromycin concentration in given point.

Table 6. Original data set compared to cubic polynomial model and Hoerl model values of erythromycin concentrations, C, (ng ml^{-1}) in given time, t, (h) points, with their %error in relation to the original data.

Time, t, (h)	Observed concentration, C, (ng ml^{-1})	Cubic model concentration, C, (ng ml^{-1})	%error	Hoerl model concentration, C, (ng ml^{-1})	%error
0.0	0.0	0.0	0.0	0.0	0.0
0.5	47.4	105.9	123.3	76.2	60.8
1.0	185.0	185.0	0.0	169.9	8.2
2.0	293.0	274.2	6.4	284.4	2.9
4.0	254.0	254.0	0.0	267.9	5.5
6.0	158.0	116.4	26.3	161.5	2.2
9.0	76.9	77.2	0.4	54.8	28.7

Hence, the mean %error for cubic polynomial function is 22.3% and for Hoerl model it is only 15.5%. Although the difference between mean %errors of those models is not very high, in cubic polynomial there are some huge outliers, such as 123.3% error for t = 0.5, which suggests that the function of cubic polynomial rises far too rapidly just after taking the erythromycin. Such errors additionally decrease the reliability of the cubic model.

— Final conclusions —

The aim of this exploration was to investigate whether the suitability of the model of the pharmacokinetic profile of erythromycin is affected by the method chosen for the modelling. The report made an attempt to answer this question by comparing models obtained with the use of the polynomial interpolation method and automated linear regression method. Looking at the results of the investigation, following conclusions may be introduced:

- Model values in relation to the original data points are mirrored in obtained %errors, which show to what extent the values estimated by models fit the original values. One may easily observe that depending on the chosen method, the %errors are different.
- Behaviour of the functions is seen on the graphs, which present how the values of erythromycin concentration are changing over time. *Figure 8* shows that both curves are not the same and that they change differently relative to the original data set.
- Finally, R^2 values are different for each model (cubic polynomial model $R^2 = 0.9545$ and Hoerl model $R^2 = 0.9869$), which directly indicates different coefficients of correlation between the model and original data.

Ultimately, when considering all of the provided arguments, one may conclude that the method chosen for modelling strongly affects the suitability of the model in terms of pharmacokinetic profile of erythromycin, since the method determines the type of functions obtained, hence, the behaviour and properties of the curves. In case of this exploration, it is the Hoerl function that unambiguously fits into the pharmacokinetic profile or erythromycin more than the cubic polynomial model. The Hoerl model, in general, shows smaller %error than the cubic polynomial model. Furthermore, the range of the Hoerl model such as concentration of erythromycin ≥ 0 is a huge advantage of this model over the model obtained by polynomial interpolation, since in real life such concentration cannot go below 0. All in all, We are glad with the obtained results as We strongly believe that the knowledge that We got

about the pharmacokinetics in this exploration will be helpful for me in my future career. However, one thing could not let me rest. Despite the fact that the whole method of automated linear regression turns out to be much more efficient in modelling the function than polynomial interpolation, the R^2 value points out that still only the 98.69% of changes occurring in concentration are explained by the changes in time. The remaining 1.31% of uncertainty made me think of the possible cause of such a situation. While doing research We found the information that real modelling of pharmacokinetic profiles is far more complex than the method chosen by me. Both my models leave the space for the uncertainty, since they do not take into account the pharmacokinetic properties of the substance, like: absorption, and elimination (Hull). Hence, as an extension to this work, it would be nice to apply the formula that includes those variables as well. The example of such formula is presented below (Hull):

$$C(t) = Ae^{-\alpha t} + Be^{-\beta t} \quad [7]$$

In the case C(t) means the concentration of the substance at time = t, A and B are extrapolated concentrations in serum, sum of which gives the initial concentration of the substance. α with β consecutively reflect the constants of rate of distribution and elimination of the substance in the body (Hull). With such a precise information about the properties of examined substance, and with the function expressed by this data, one can model pharmacokinetic profiles of many different substances, also dividing them into different profiles depending on the age or gender of the recipients (as the constants α and β would change along with the change in the conditions of the experiment).

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