Modelling Intake and Clearance of Alcohol in Humans

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Students can be provided insight into processes of enzyme kinetics and physiology via compartmental models. Graphical modelling software supports this. In this paper we discuss various models that students could implement and use to investigate blood alcohol concentration after consumption of one or more alcoholic drinks. Results from these computer models are compared with measured data that were obtained with breath analysis equipment. The broad range of models for intake and clearance of alcohol in the human body ensures that students have great opportunity to practice evaluation and revision of their models. They can develop the critical attitude that is necessary for successful modelling of biological, chemical or physical phenomena. All models presented, ranging from the simplest linear elimination model to a sophisticated physiologically based compartmental model, are used in pharmacokinetic studies. This implies that the students' investigation work is not only fun to do, but also resembles professional research practice ICT tools that help to develop mathematical understanding and mathematical skills.

Introduction

Alcohol is widely used by secondary school pupils. Binge drinking under teenagers is not unusual anymore, especially during school holidays. It is difficult to prevent children from experimenting with alcohol; most of them consume their first alcoholic drink between the age of 11 and 14. The number of children who go into a coma because of severe alcohol abuse and who are taken into hospital is growing fast. Teenagers, but also their parents seem to realize insufficiently that alcohol is a poisonous substance that can be damaging. If they would realize how easily one gets drunk and how long it takes before alcohol is removed from the human body, they might think twice before turning to alcohol abuse and they might be more careful in participating to traffic after consumption of alcoholic beverages.

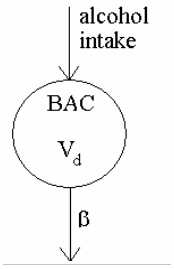
Education plays a crucial role in getting children better informed about alcohol and its effects on the human body. At Dutch secondary school level, in the new subject 'Nature, Life and Technology' that is under active development, lesson material entitled 'Driving under the influence' has been designed recently for the vocational and pre-university streams. In this material, Wick's formula is used to calculate the blood alcohol concentration (BAC) after consumption of alcoholic drinks. BAC must be understood as the total amount of alcohol (in gram) in the body divided by the total amount of body water (in litre). In this paper we will discuss various mathematical models that predict BAC during and after alcoholic consumption. All models originate from research on alcohol metabolism and are in mathematical terms compartmental models. They can be implemented on a computer: We have used the graphical modelling environment of Coach 6 [1]. In this way, pupils can investigate various scenarios of alcohol consumption: Does it matter in the long term whether you drink fast or slowly? Does it matter whether you consume drinks after a meal or not? Do there exist ways to speed up the clearance of alcohol from your body? Are there gender differences in alcohol intake and clearance? And so on. This type of work gives the pupils a broad idea of alcohol pharmacokinetics and it provides them with examples of compartmental models that can also be applied in investigations of other processes. Results of computer models have been compared with real data collected with breath analysing equipment. Such data are anyway useful in discussions of the various mathematical models, not in the least to remind pupils of the fact that not understanding of the mathematical models is important, but understanding of the phenomenon under investigation, even under circumstances that measurements of the biological processes in the human body are complicated. We have also developed computer games with which pupils can experience how reaction time, spatial skills, and memory already change after moderate alcohol consumption.

Mathematical Models of Alcohol Metabolism

First we will review some mathematical models found in the research literature that discusses what happens after alcohol consumption. The range of models give a good view on issues that concern

researchers who try to model clearance of alcohol from the human body [2]. More mathematical models and computer implementations can be found in [3].

Fig. 1. Widmark model.



Widmark Model

Widmark [4] developed a model that predicts the blood alcohol concentration after consuming alcohol and that is still much used in forensic research because it works well with real data for a large range of values. This model is an open 1-compartment model with a zero-order elimination process: it is assumed that the alcohol after consumption is quickly taken into the body and spread over the total body water, i.e., is distributed rapidly into the bloodstream from the stomach and small intestine, and further into the watery fluids in and around somatic cells. Alcohol does not dissolve into body fat. Hereafter, the alcohol in the human body is eliminated at a constant rate. The process is schematically drawn in Figure 1. After absorption of alcohol, the blood alcohol level is represented in this model by the formula

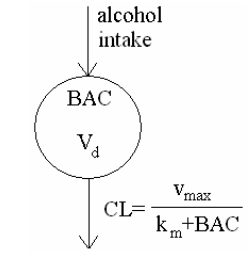
$$\mathrm{BAC} = \frac{D}{r \cdot W} - \beta \cdot t\,,$$

where D is the amount of alcohol consumed (in gram), r is the so-called Widmark factor, W is the body weight (in kg), β is the rate of metabolism (clearance rate in g/l/h), and t is the time (in hours) after consuming alcohol. The rate of alcohol metabolism is individual (e.g., different for men and women, and age dependent), it depends on circumstances (e.g., before or after a meal) and it varies from 0.10 to 0.20 g/l/h. The Widmark factor is also individual and depends mainly on body composition. Mean values are 0.68 for men and 0.55 for women (the lower value for women is explained because the female body contains in general a higher percentage of body fat and therefore less body water than the male body). The product $r \cdot W$ is equal to the volume of distribution V_d, i.e., the theoretical volume of the total body water compartment into which the alcohol is distributed. V_d is considered in most pharmacokinetic models equal to the total body water. Various methods can be found in the research literature to estimate the Widmark factor or the volume of distribution from variables such as height, weight and age. For example, Seidl et al [5] gave the following formulas:

$$r(\mathrm{men}) = 0.3161 - 0.004821 \cdot W + 0.004632 \cdot H, \quad r(\mathrm{women}) = 0.3122 - 0.006446 \cdot W + 0.004466 \cdot H,$$

where H is the body height (in cm).

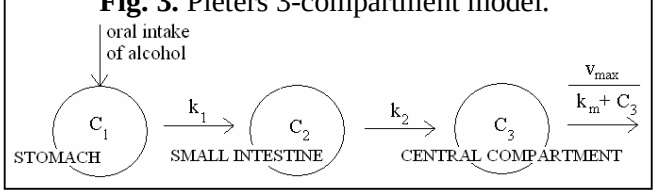
Fig. 2. Wagner model.



Wagner Model

Wagner [6] developed another open 1-compartment model, with the difference that the clearance of alcohol is now described by Michaelis-Menten kinetics (see Figure 2). This means that after absorption of alcohol, the rate of change in blood alcohol concentration is given by the following formula: $V_d \cdot \frac{\mathrm{d}}{\mathrm{dt}}\mathrm{BAC} = -\frac{v_{\max} \cdot \mathrm{BAC}}{k_m + \mathrm{BAC}}$, where V_d is the volume of distribution of the total body water compartment (the total amount of body water), k_m is the Michaelis-Menten constant, and $v_{\max}$ is the maximum disappearance rate. For a high value of BAC, the value of the clearance rate (the negative value of the right-hand side of the formula) is almost equal to the maximum removal rate $v_{\max}$ (≈140 mg/min) and the graph of BAC vs. time looks like a straight line. Curvature in the graph becomes noticeable when BAC reaches half of the maximum removal rate.

Fig. 3. Pieters 3-compartment model.



Pieters 3-compartment model

Pieters et al [7] modelled alcohol clearance with a semi physiological 3-compartment model. Their model considers the central compartment, in which alcohol is metabo-

lised following Michaelis-Menten kinetics, the stomach and the small intestine. The alcohol goes into the stomach first, hereafter into the small intestine, and finally from there it is absorbed into the bloodstream and rapidly distributed over the central compartment. Figure 3 illustrates the model. The model equations are:

$$\frac{dC_1}{dt} = -\frac{k_1}{1 + a \cdot C_1^{\,2}} \cdot C_1, \qquad \frac{dC_2}{dt} = \frac{k_1}{1 + a \cdot C_1^{\,2}} \cdot C_1 - k_2 \cdot C_2, \qquad \frac{dC_3}{dt} = k_2 \cdot C_2 - \frac{v_{\max}}{k_m + C_3} \cdot C_3,$$

with initial conditions $[C_1(0), C_2(0), C_3(0)] = [C_0, 0, 0]$, where $C_0 = D_0 / V$, the initial amount of alcohol D_0, divided by the volume of distribution V of the central compartment, and where C_1, C_2, and C_3 are the alcohol concentrations in the stomach, small intestine and central compartment, respectively, related to the volume of distribution of the third compartment. The first differential equation in the Pieters model, which models emptying of the stomach, does not represent a simple first-order process, but a feedback control is built-in that depends on the instantaneous concentration in the stomach, C_1. In this way, the effect of an empty or full stomach on alcohol clearance can be taken into account mathematically.

Graphical Computer Models of Alcohol Metabolism

In general, computer implementation of a mathematical model consists roughly of two phases: specification of the mathematical model and simulation of the model. For the first phase, Coach 6 has a graphical interface to describe a model qualitatively (see the screen shots in the examples below). In the graphical model you specify which quantities in the mathematical model play a role (distinguishing between parameters and state variables), how they depend on each other, which formulas for quantities are used and which values parameters have. The graphical model is automatically translated into a system of equations that is used in a computer simulation, i.e., in running the model. We will look at some examples of alcohol clearance from the human body.

Widmark Computer Model

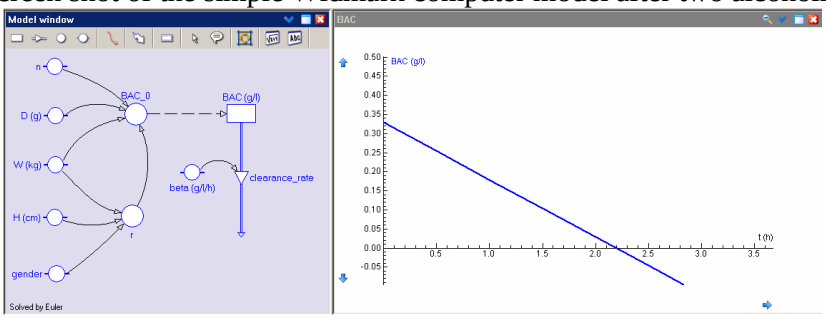
We start with the Widmark model, in which we work with the formulas of Seidl et al [5] for the Widmark factor. Thus, after immediate consumption of n drinks holds:

$$\frac{d\ \mathrm{BAC}}{dt} = -\beta \cdot t, \quad \mathrm{BAC}(0) = \frac{n \cdot D}{r \cdot W}, \quad r(\text{men}) = 0.3161 - 0.004821 \cdot W + 0.004632 \cdot H,$$

$$r(\text{women}) = 0.3122 - 0.006446 \cdot W + 0.004466 \cdot H.$$

Figure 4 shows the graphical model and a computer run for a man who has consumed two drinks. The graph illustrates a weakness in the computer model: the computed BAC becomes negative after about 2 hours. In reality this is not possible. But having a critical look at the quality of a (computer) model is actually something that pupils have to learn or that has to become second nature.

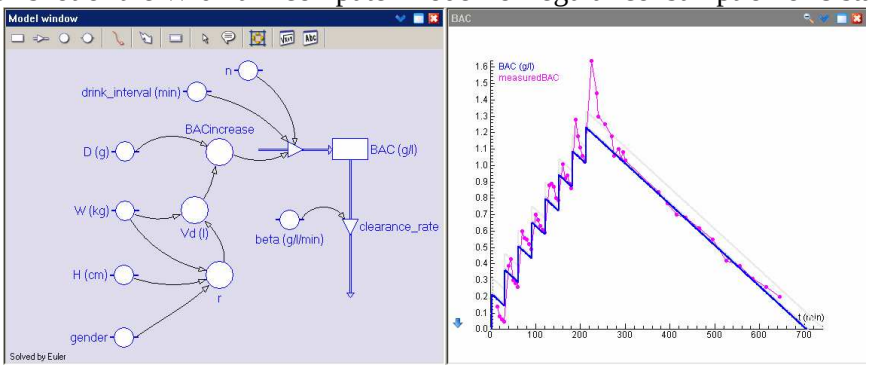
Fig. 4. Screen shot of the simple Widmark computer model after two alcoholic drinks.



We can make the computer model more realistic by choosing a smaller time step and BAC < 0 as stop condition. Furthermore, we can assume that not all drinks are consumed at once, but say one glass every 30 minutes. This means that with each drink the blood alcohol concentration increases instantaneously with D/($r \cdot W$). In the screen shot below (Fig. 5) you see the graphical model, the graph of computed BAC against time, and a measured BAC curve of the author drinking eight

glasses of red whine ‘ad fundum’ every half an hour. Ignoring the overshoot of BAC shortly after each drink, the accordance between model and measurement is good for a clearance rate β of 0.0025 g/l/min. From the computed BAC curve you could draw the conclusion that BAC after consumption of two glasses has come above the legal limit of 0.2‰ for persons under age of 24. Also, this person must wait at least 7 hours after his last drink before the BAC is again below 0.2‰.

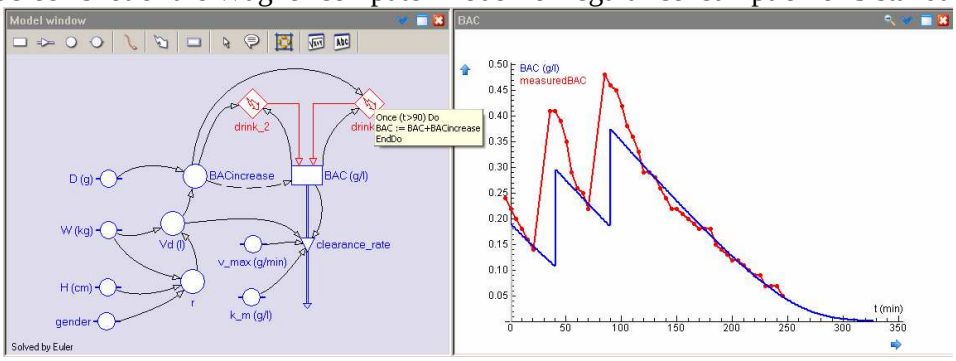
Fig. 5. Screen shot of the Widmark computer model for regular consumption of 8 standard units.



Wagner Computer Model

In the screen shot below (Fig. 6) we assume an alcohol consumption of drinking three glasses ‘ad fundum’ on an empty stomach: one at the start of the experiment, one after 40 minutes, and another drink 50 minutes later. In the computer model we have specified the 2nd and 3rd intake of alcohol by means of ‘events’ (represented graphically by an icon with a thunderbolt). Coach is actually a hybrid modelling environment for continuous-time and discrete-event dynamic modelling. With events one can take actions when a certain condition is met; see the yellow page in the screen shot for the event of consuming the third drink. Alternatively, the intake can be specified by means of mathematical formulas or by drawing a sketch of the drinking behaviour.

Fig. 6. Screen shot of the Wagner computer model for regular consumption of 3 standard units.

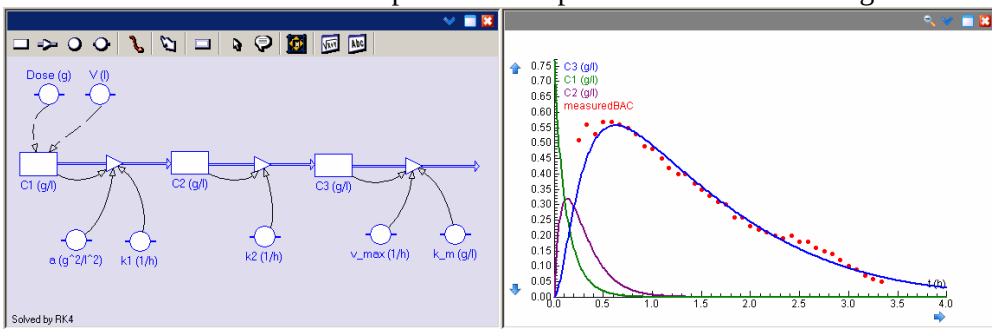


In the comparison of the computer model and the measured data we assume a time delay of half an hour for absorption of the consumed alcohol into the total body water: for this reason we have translated the graph of the measured BAC 30 minutes to the left. Alcohol clearance follows in the Wagner model Michaelis-Menten kinetics. The parameters v_{max} = 170 mg/min and k_m = 45 mg/l have been chosen such that a reasonable match between the measured data and the computer model exists, at least if one ignores overshoot of BAC. But obtaining good values for parameter is quite tricky in practice: for example, the values v_{max} = 340 mg/min and k_m = 290 mg/l are almost as good.

Pieters 3-Compartment Computer Model

Figure 7 shows a graphical implementation of the Pieters model that compares well for suitable parameter values with the measured data of the author drinking 3 glasses of red whine at once on an empty stomach early in the morning. In the computer model we chose a negative value for the feedback parameter to get an accelerated intake of alcohol because drinking happened after fasting.

Fig. 7. Screen shot of the Pieters 3-compartment computer model after drinking 3 standard units.



Conclusion

The power of mathematical modelling really lies in the following: After construction of a mathematical model and a corresponding computer model that describes reality adequately for well-chosen parameter values, one can investigate the influence of various factors in the model by varying the parameter values. With the models of the previous section, a pupil can investigate whether a person who drinks 3 glasses of beer at once may drive a car earlier than a person who consumes the same amount of alcohol, but at a slower speed and with time intervals in between. A pupil can also find clues that explain why women in general get drunk earlier than men when they consume the same amount of alcohol.

The diversity of the models of alcohol metabolism in humans gives a good idea of the common method of working in mathematical modelling: first one simplifies the situation to such an extent that a simple model can be constructed. Hereafter one evaluates this model, preferably by comparing it with experimental data, and one adapts it if necessary. In the process of evaluation, parameter estimation plays an important role as well. The complexity of finding suitable parameter values must not be underestimated. Adaptation of the model normally means that one makes the model more complicated by taking more factors that cannot really be neglected into account or by undoing some earlier simplifications. One comes into the process of simplifying first and then adding step-by-step more details to the model, with the purpose of matching the model better with reality.

This progressive aspect of graphical modelling is also a pointer to a suitable manner to introduce it to pupils: it seems best not to let them construct out of the blue some well-functioning model, but to let them first improve an existing model by changing or adding details. Here it is important that pupils can compare the results of the computer model with real data, preferably collected in an earlier measurement activity. Confrontation of a model with reality turns graphical modelling not only into a fun way of learning, but it also makes it exciting, challenging, and concrete work for pupils. Experience is that this is practicable and that pupils can actually use the same theoretical framework, methods and techniques as professionals.

References

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