Modeling Intake and Clearance of Alcohol in Humans

André Heck
heck@science.uva.nl
AMSTEL Institute
Universiteit van Amsterdam
The Netherlands

Abstract: *Students can be provided insight into pharmacokinetics via compartmental models. Graphical modeling software supports this. In this paper we discuss various models that students at pre-university level 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 modeling of biological, chemical or physical phenomena. All models presented, ranging from a simple linear elimination model to a sophisticated physiologically based compartmental model, are used in real pharmacokinetic studies. This implies that the students' investigation work is not only fun to do, but also resembles professional research practice.*

1 Introduction

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 Influence' has been designed recently for the vocational and pre-university streams (the Dutch lesson material can be found at the website www.betavak-nlt.nl). In this material, the so-called Widmark 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 liter).

In our own course materials discussed in this paper various mathematical models that predict BAC during and after alcohol consumption are investigated. All models originate from research on alcohol metabolism and are in mathematical terms compartmental models. They can be implemented in a computer program: we have used the graphical modeling environment of the computer learning environment Coach 6 [1], but it can also be done with system dynamics modeling software like STELLA or Powersim. In the computer modeling approach, students can rather easily investigate various scenarios of alcohol consumption. Questions of interest include: 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. Investigating questions like these gives the students a broad idea of alcohol pharmacokinetics and it provides them with examples of compartmental models that can also be applied in investigations of similar processes. Results of computer models have been compared with real data collected with breath analyzing equipment. Such data are anyway useful in discussions of the various mathematical models. It reminds students of the fact that understanding of the mathematical models is not the main goal, but understanding of the

phenomenon under investigation. This holds even under circumstances that measurements of the biological processes in the human body are complicated.

2 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 gives 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].

2.1 The 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., alcohol is transported rapidly from the stomach and small intestine via the liver to the systemic circulation, and further distributed in 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 of change. The process is schematically drawn in Figure 2.1.
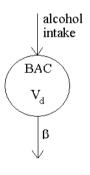

Figure 2.1 The Widmark Model.

After absorption of alcohol, the blood alcohol level is represented in this model by the formula

$$\mathrm{BAC} = \frac{D}{r \cdot W} - \beta \cdot t, \tag{2.1}$$

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 can be 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 in which the alcohol is distributed. V_d is considered in most models of alcohol pharmacokinetics equal to the amount of 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 [5]. For example, Seidl et al. [6] gave the following formulas:

$$r(\text{men}) \quad = 0.3161 - 0.004821 \cdot W + 0.004632 \cdot H, \tag{2.2a}$$

$$r(\text{women}) = 0.3122 - 0.006446 \cdot W + 0.004466 \cdot H, \tag{2.2b}$$

where H is the body height (in cm). Assuming a percentage of 80% water in blood, Watson et al. [7] determined various linear regression formulas. Two of the formulas, in which AGE is in years, are:

$$0.8 \cdot V_d(\text{men}) \quad = 0.3626 \cdot W - 0.1183 \cdot AGE + 20.03, \tag{2.3a}$$

$$0.8 \cdot V_d(\text{women}) = 0.2549 \cdot W + 14.46. \tag{2.3b}$$

2.2 A Hybrid Open 1-Compartment Model with Zero-Order Elimination

In reality it takes some time before consumed alcohol gets distributed in the total body water compartment. You can deal with this explicitly in the formula of the Widmark model: for example,

$$\text{BAC} = D/\ r \cdot W \ - \beta \cdot\ t - 0.5 \tag{2.4}$$

expresses a time difference of half an hour between consumption and absorption of alcohol. A more reliable method is the following [8]: assume that alcohol intake is a first-order absorption process and that clearance is linear in time, just as in the Widmark model, then the blood alcohol concentration is given by:

$$\text{BAC} = C_0 + \alpha \cdot\ 1 - H(t - t_0) \cdot e^{-k_a\ t - t_0}\ - \beta \cdot t, \tag{2.5}$$

where C_0 is the BAC at time $t = 0$, α is a constant proportional to the amount of alcohol consumed at time $t = 0$, k_a is the absorption coefficient, t_0 is the retardation time for absorption, and H is the Heaviside function (defined by $H(x) = 0$ for negative x, and $H(x) = 1$ elsewhere). Formula 2.5 can be rewritten for $t \geq t_0$ as:

$$\text{BAC} = B \cdot e^{-k_a \cdot t} + A - \beta \cdot t \tag{2.6}$$

where k_a is estimated by Hahn et al. [9] at 0.08 min^{-1} with standard deviation 0.03, which corresponds with a half-life of 8.7 min, for drinking with an empty stomach. t_0 is estimated at 1.6 minutes with standard deviation 0.5. A third way of dealing with delayed absorption of consumed alcohol in the body in a mathematical model is to assume that absorption of a dose D takes a certain amount of time T_0 (say 30 minutes) and that alcohol distribution in the total body water compartment during this time interval happens at constant speed D/T_0.

2.3 The Wagner Model

Wagner ([10]) developed another open 1-compartment model, with the difference that the clearance of alcohol is now described by Michaelis-Menten kinetics (see Figure 2.2). This means that after absorption of alcohol, the rate of change in blood alcohol concentration is given by the following formula:

$$V_d \cdot \frac{d}{dt} \text{BAC} = -\frac{v_{\max} \cdot \text{BAC}}{k_m + \text{BAC}}, \tag{2.7}$$

where V_d is the volume of distribution of the total body water compartment (the amount of total body water used in the mathematical description), k_m is the Michaelis-Menten constant, and $v_{\max}$ is

the maximum disappearance rate. In Figure 2.2 we use the clearance rate CL that is associated with Michaelis-Menten kinetics. For a high value of BAC, the value of the clearance rate (the negative value of the right-hand side of formula 2.7) is almost equal to the maximum removal rate v_{max} ($\approx$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.
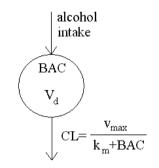

Figure 2.2 The Wagner Model.

2.4 The Norberg 2-Compartment Model

Norberg et al. [11] used a 2-compartment model consisting of the central compartment, which is in this case the blood plasma and the tissues that are in rapid equilibrium with it (liver and kidney), and the peripheral compartment, which contains the rest of the body fluids in other tissues. From the central compartment there is in parallel alcohol clearance through the liver following Michaelis-Menten kinetics and through the kidneys (unmodified alcohol clearance in urine) following a linear first-order kinetics. By the way, only a small portion of the consumed alcohol (2-5%) is actually excreted in breath, sweat and urine. We denote the blood alcohol concentration and the volume of the central and peripheral compartment by C, V_C and by C_T, V_T, respectively. The increase in the amount A_u of unmodified alcohol in the urine is determined by the elimination constant CL_d. The distribution of alcohol over the two compartments is determined by the intercompartmental distribution parameter CL_d. The relation

$$CL = v_{max} / k_m + C \tag{2.8}$$

corresponds with Michaelis-Menten kinetics. So, in this pharmacokinetic model, the following three equations hold after absorption of alcohol in the central compartment:

$$V_C \cdot \frac{dC}{dt} = -CL \cdot C - CL_d \cdot C + CL_d \cdot C_T - CL_u \cdot C \tag{2.9a}$$

$$V_w \cdot \frac{dC_T}{dt} = CL_d \cdot C - CL_d \cdot C_T \tag{2.9b}$$

$$\frac{dA_u}{dt} = CL_u \cdot C \tag{2.9c}$$

Norberg and colleagues came to the following parameter values in clinical trials with intravenous infusion of alcohol and via analysis of blood samples at various times:

$$v_{max} = 95.0 \pm 25.1 \,(\text{mg/min}), \quad k_m = 27.0 \pm 18.9 \,(\text{mg/L}),$$
$$CL_d = 809 \pm 232 \,(\text{mL/min}), \quad CL_u = 3.65 \pm 2.04 \,(\text{mL/min}), \tag{2.10}$$
$$V_C = 14.5 \pm 4.3 \,(\text{L}), \quad V_T = 21.2 \pm 4.4 \,(\text{L}).$$

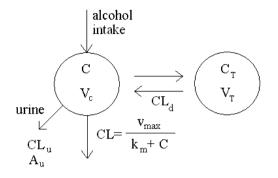The Norberg 2-compartment model is schematically drawn in Figure 2.3.

Figure 2.3 The Norberg 2-Compartment Model.

2.5 The Pieters 3-Compartment Model

Pieters et al. [12] modeled alcohol clearance in humans with a semi physiological 3-compartment model. Their model considers the central compartment, in which alcohol is metabolized 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 in the central compartment. Figure 2.4 illustrates the model, in which the volumes of distribution of the compartments are not specified, but hidden in the parameters.
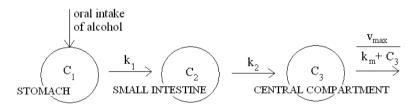

Figure 2.4 The Pieters 3-Compartment Model.

The model equations are:

$$\frac{dC_1}{dt} = -\frac{k_1}{1+a\cdot C_1^2}\cdot C_1, \quad \frac{dC_2}{dt} = \frac{k_1}{1+a\cdot C_1^2}\cdot C_1 - k_2\cdot C_2, \quad \frac{dC_3}{dt} = k_2\cdot C_2 - \frac{v_{max}}{k_m+C_3}\cdot C_3, \quad (2.11)$$

with initial conditions

$$C_1(0), C_2(0), C_3(0) = C_0, 0, 0, \quad (2.12)$$

where $C_0 = D_0/V$, i.e., 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. Tabulated parameter values are listed in Table 2.1

The first differential equation in the Pieters 3-compartment 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. The parameter a in the quadratic term of the denominator determines whether gastric emptying is faster (negative a) or slower (positive a) than the first-order rate k_1 under normal conditions. So, the effect of an empty or full stomach on

alcohol clearance can be taken into account mathematically (see [13]). By the way, food promotes alcohol clearance, even when alcohol intake takes place via an intravenous infusion (see [14]). The Pieters model cannot explain this.

Table 2.1 Parameter Values for the Pieters 3-Compartment Model.

		Mean Values	
Parameter	Dimension	Men	Women
v_{max}	$g \cdot L^{-1} \cdot h^{-1}$	0.470	0.480
k_m	$g \cdot L^{-1}$	0.380	0.405
C_0	$g \cdot L^{-1}$	0.455	0.703
k_1	h^{-1}	5.55	4.96
k_2	h^{-1}	7.05	4.96
a	$L^2 \cdot g^{-2}$	0.42	0.75

3 Graphical Computer Models of Alcohol Metabolism

All mathematical models that were described in the previous section can be converted into computer models. In general, computer implementation of a mathematical model consists roughly of two phases: specification of the model and simulation of the model. For the first phase, the computer learning environment 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, state variables, and flows), 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. In this section we look at some examples of alcohol intake and clearance from the human body.

3.1 The Widmark Computer Model

We start with the Widmark model, in which we work with the formulas of Seidl et al. [6] for the Widmark factor. Thus, after immediate consumption of n drinks, each holding D grams of alcohol, holds:

$$\frac{d\,\text{BAC}}{dt} = -\beta \cdot t, \quad \text{BAC}(0) = \frac{n \cdot D}{r \cdot W}, \quad r(\text{men}) = 0.3161 - 0.004821 \cdot W + 0.004632 \cdot H, \tag{3.1}$$

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

Figure 3.1 shows the graphical model and a computer run for a man who has consumed two alcoholic drinks. The graph illustrates a weakness in the computer model: the computed BAC becomes negative after about two hours. In reality this is not possible. But having a critical look at the quality of a (computer) model is actually something that students have to learn or that has to become second nature.
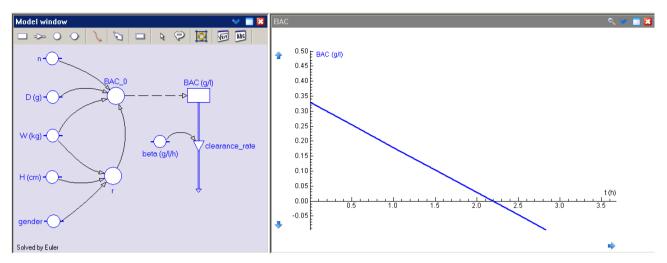
Figure 3.1 Screen shot of the simple Widmark computer model after two alcoholic drinks.

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 take 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 (Figure 3.2) you see the graphical model, the graph of computed BAC against time, and a measured BAC curve of the author emptying eight glasses of red wine in one draught every half hour.
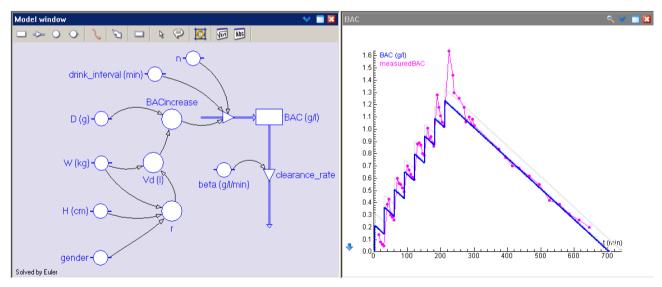

Figure 3.2 Screen shot of the Widmark computer model for regular consumption of 8 drinks.

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 ‰.

3.2 The Wagner Computer Model

In the screen shot below (Figure 3.3) we assume an alcohol consumption of emptying three glasses in one draught 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 6 is actually a hybrid modeling environment for continuous-time and discrete-event dynamic modeling. 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.
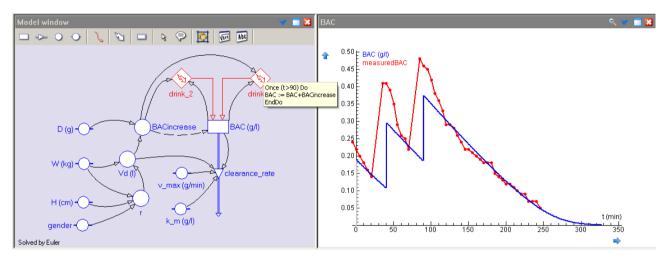

Figure 3.3 Screen shot of the Wagner computer model for regular consumption of 3 standard units.

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 parameters is quite tricky in practice: for instance, the values $v_{max} = 340$ mg/min and $k_m = 290$ mg/L are almost as good.

3.3 The Norberg 2-Compartment Computer Model

Comparing a mathematical model with real data is essential for judging the quality of a model. We use in this subsection data collected for subject no. 19 in the clinical study described in the SWOV report R-2001-19 [15]. Subject no. 19 (female, 66 kg, 20, drinking weekly) consumed one portion of 24 grams of alcohol during a drinking time of 25 minutes. Using the hybrid Widmark formula and using the formulas of Watson et al. (formula 2.3b) for the volume of distribution, the blood alcohol concentration can be predicted as

$$\text{BAC} = \frac{D}{18.075 + 0.3186 \cdot G} - \beta \cdot t - 0.5 \qquad (3.2)$$

where D is the amount of alcohol consumed (in gram), β is the clearance rate (in g/L/h), and t is the amount of time (in hours) passed since alcohol consumption. The measured data and the predicted values (according to the hybrid Widmark model) for the participant are listed in Table 3.1.

Table 3.1 BAC data of subject no. 19 in the SWOV report [14]

Development of BAC after consumption of 24 g pure alcohol by subject no. 19				
Time of measurement (after start, in minutes)	40	70	100	130
Amount of alcohol consumed	24	24	24	24
BAC measurement	0.46	0.32	0.21	0.16
Predicted value (β=0.2)	0.44	0.34	0.24	0.14

The screen shot below (Figure 3.4) illustrates that the Norberg 2-compartment model does not give a good match between measurements and model for subject 19, whereas the hybrid Widmark model worked reasonably (see Table 3.1). In the computer model we have used a rate of intake of alcohol equal to 24/25 = 0.96 g/L/min for time between 0 and 25 minutes, and 0 elsewhere. Such a function can be specified in Coach 6 by means of the Pulse function: Pulse(t; 0; 25; 24/25). Thus, we obtain the following system of differential equations in the 2-compartment model:

$$\frac{dA_C}{dt} = \text{Pulse}\left(t; 0; 24; 24/25\right) - CL \cdot C - CL_d \cdot C + CL_d \cdot C_T - CL_u \cdot C,$$

$$\frac{dA_T}{dt} = CL_d \cdot C - CL_d \cdot C_T, \quad \frac{dA_u}{dt} = CL_u \cdot C, \tag{3.2}$$

where A_C, A_T, and A_u, are the amounts of alcohol in the central compartment, in the peripheral compartment, and in the urine, respectively.
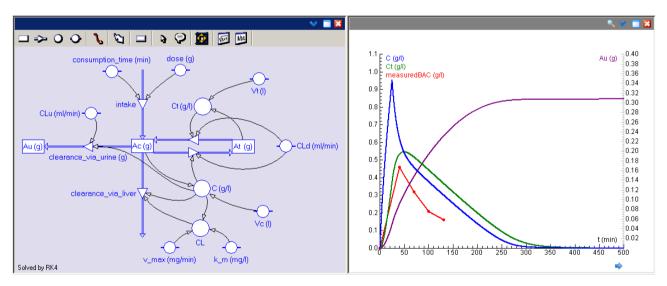

Figure 3.4 Screen shot of the Norberg 2-compartment computer model with data of subject no. 19.

A number of things catch the eye in the computed BAC curve of Figure 3.4: a fast increase of BAC in the central compartment and after the peak value the alcohol concentration falls rapidly down under the values of the peripheral compartment. For some time there is a decline in alcohol concen-

tration in both compartments that is almost linear. The amount of alcohol that leaves the body via urine is in the computer model about 1% of the total amount consumed. It cannot be denied that the match between measurements and computer model is bad. The main reason for this is that we applied a mathematical model for intake of alcohol via intravenous infusion under completely different circumstances, viz., oral intake of alcohol. Of course the blood alcohol concentration raises rapidly when it is injected directly into the bloodstream. Our graphs are indeed consistent with graphs found in the scientific literature about clinical trials in which alcohol is supplied by intravenous infusion. The 2-compartment model is not really made for oral intake of alcohol. Such a critical look at circumstances under which experiments take place is something that we want to achieve with our students: a critical look at the applicability of methods should be second nature.

For a better match between the measurements and the Norberg 2-compartment model we must use a better model for the intake of alcohol. One solution is to use a smaller dose in the computation, as if just part of the alcohol consumption really matter. Figure 3.5 shows the computed graphs when we use an 'effective dose' of 18 grams of alcohol in 25 minutes. Then we achieve a nice match, but in an artificial way.
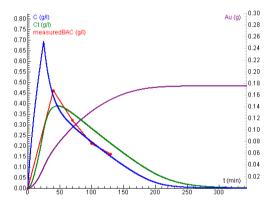

Figure 3.5 Norberg computer model with data of subject no. 19 using an 'effective dose'.

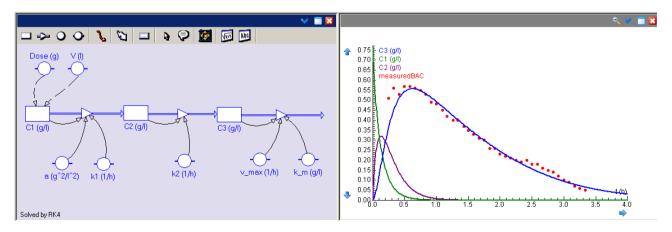## 3.4 The Pieters 3-Compartment Computer Model

Figure 3.6 Screen shot of the Pieters computer model after drinking 3 standard units.

Figure 3.6 shows a graphical implementation of the Pieters 3-compartment model that compares well for suitable parameter values with the measured data of the author drinking 3 glasses of red wine in one draught 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.

4 Conclusion

The power of mathematical modeling 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 student can investigate whether a person who drinks 3 glasses of beer in one draught 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 student can also find clues that explain why women in general get drunk earlier than men when they consume the same amount of alcohol. Another investigation may be about the effect of a meal on the alcohol metabolism. In other words, with a computer implementation of a mathematical model for intake and clearance of alcohol, students can explore many scenarios.

The purpose of students' investigative work is not to figure out how to maximize alcohol intake and still be legally allowed to drive or, even worse, still not get into coma. The main purpose is to give students insight in mathematical modeling and in current applications of mathematics in natural sciences. Great advantage of the ICT supported activities is that many of the models discussed are simple enough that students who have little experience in modeling can still take care of the computer implementation. Our experience in school practice is that students find the topic and the modeling activities quite interesting.

The diversity of the models of alcohol metabolism in humans gives students a good idea of the common method of working in mathematical modeling: 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, too. 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. It is our belief that by looking at various models of one and the same phenomenon a critical attitude of students is promoted.

This progressive aspect of modeling is also a pointer to a suitable manner to introduce it to students: 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 students 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 modeling not only into a fun way of learning, but also makes it exciting, challenging, and concrete work for students. Our

experience is that this is practicable and that students can actually use the same theoretical framework, methods and techniques as professionals.

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Online resources

The Coach 6 activities used to generate the screen shots in this paper are made available at the author's home page, at URL: www.science.uva.nl/~heck/research/alcohol. The classroom materials on intake and clearance of alcohol have become part of lesson materials about pharmacokinetics in general, collected under the title "Drinking, Shooting, and Swallowing". These materials have been translated to English and made available through the aforementioned website. The course materials have been designed for high school students, who already understand the concept of rate of change, but do not yet know about differentiation, and who have not yet knowledge about the exponential function, the logarithm, and the base of the natural logarithm. One of the main purposes of the course material is to give students insight in current applications of mathematics in natural sciences.

For further information about the computer learning environment Coach and sample activities we refer to the website www.cma.science.uva.nl/english.