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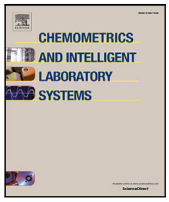

Optimal designs for a non-linear model for the pharmacokinetics of ethanol elimination in the human body

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ABSTRACT

The equation most commonly used to estimate a person's blood alcohol concentration after consuming alcoholic drinks assumes zero-order kinetics in the ethanol elimination phase. This implies that the elimination process occurs in the body at a uniform rate as a function of the ethyl-oxidation constant. The model, formulated by Widmark, does not consider the phase of increase in concentration, and approximates the phase of elimination in a linear way, which may be insufficient if the tests are carried out in the first phases of alcohol intake. In this paper, a non-linear model that fits the different phases of the pharmacokinetic process of ethanol in the human body (absorption, distribution, metabolism, and elimination) is proposed. Optimal experimental designs methods are used in order to find the most informative observation times for the estimation of the parameters of the model.

1. Introduction

Alcohol is probably the most extended legal drug consumed by humans [1]. Moreover, alcohol use increased during the epidemic in several countries, for example, in the United States, Spain, and France [2,3]. In the human body, most of the ingested alcohol (90–98%) is processed in the liver, with the remaining 2–10% eliminated unchanged by breath, perspiration, and urine [4].

There are several equations that can be used to model the pharmacokinetics of ethanol and thus the Blood Alcohol Concentration (BAC) in the body [5] but it has traditionally been modeled making use of the Widmark equation, which was first developed in the 1930s [6]. In these equation, it is assumed that the BAC decreases at a constant rate per a unit time, i.e. zero-order elimination rate. Although BAC is the most reliable indicator of alcoholic drunkenness, police frequently use a Breath Alcohol Concentration (BrAC) estimate obtained with a breathalyzer, which is a less intrusive and more practical tool and, therefore, the Widmark equation has been adapted for these type of tests [7,8]. In order to match the estimates of blood and breath concentration temporal patterns, a blood/breath alcohol ratio of 2,300:1 is commonly advised Jones [9].

As explained in Jones [10], since the main metabolizing enzyme is saturated at low blood alcohol concentrations, ethanol is a good example of a drug that usually displays dose-dependent or saturation kinetics and, for questions arising in forensic science and legal medicine (BAC of 50–500 mg%[1]), zero-order kinetics is a reasonable assumption for characterizing the elimination of ethanol from blood [11]. However, below a BAC of 5–10 mg% the metabolizing enzymes are no longer saturated with substrate and first-order kinetics apply [12]. The linear model relates to the one-compartment model with zero-order elimination kinetic, leaving the absorption kinetics out of the study [13]. This implies that the traditional linear model may be ineffective at forecasting BAC at various time points, as well as estimating the time when the maximum is reached.

The Widmark model is the most used in forensic medicine and by traffic officers, due to its simplicity and because it adjusts quite well the alcohol elimination phase. However, in some situations the interest is not in estimating the level of alcohol at the present time, but in past temporal points (e.g. forensic science trying to estimate the level of alcohol of the driver at the exact time of a car accident that happened some time ago: minutes, hours...). In this scenario, it would not be reasonable to estimate the level of alcohol in the past by the decreasing linear trend. The linear regression model works well in a local environment of the lab test, but it does not when going backwards. As can be seen in Fig. 1, the green point would represent the real alcohol concentration and the red point the estimate made with the Widmark line. A non-linear trend model is needed, more specifically, a

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[1] mg% indicate the mass (in milligrams) of that chemical in 100 milliliters of solution.

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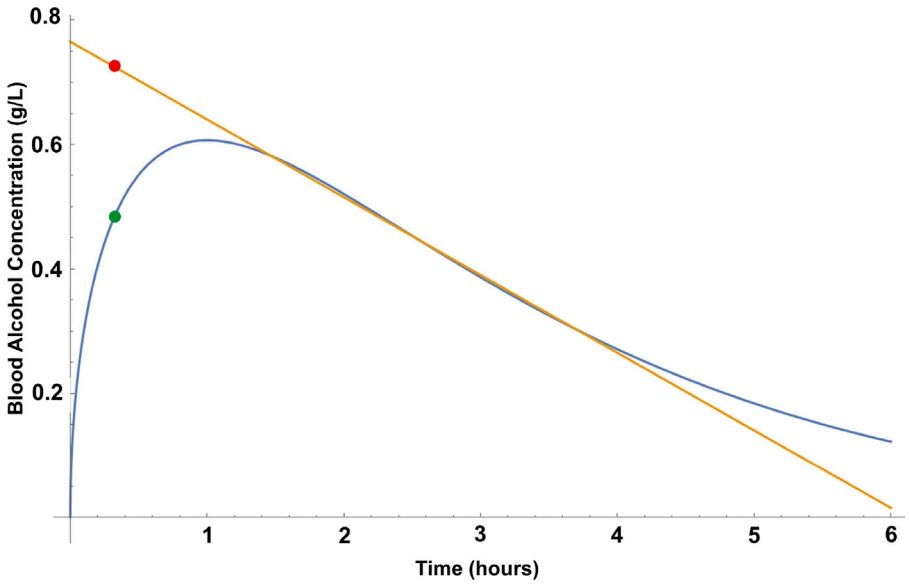


Fig. 1. Widmark line versus blood alcohol concentration.

hill-shaped function that could describe not only the clearance but also the absorption phase of alcohol intake.

Li et al. [14] performed an experiment based in non-linear regression models, with a non-zero right-skewed bell-shaped assumption for the model. They considered different alternatives, but the gamma regression model with parameters based on the alcohol dosage, gender, weight and age outperformed the other candidate models. The non-linear alcohol elimination model was as well proved better than its linear equivalent in terms of prediction accuracy. Other hill-shaped models worth studying are Weibull, Log-Normal and Wagner models [15].

Regardless of the model used, it is very important to obtain good estimation of the parameters. In Li et al. [14] disparities in peak levels were startling, which indicate an urgent need for better estimates of a subject's peak alcohol level, since breath tests are usually conducted a long time after an accident or a police intervention in a drunk-driving case. When these type of experiments are performed, it is important to take observations at the moments that give more information. For this reason, it is essential to use optimal designs to estimate the parameters of the model.

To fit the model parameters, the first important thing to do is set up an experiment (clinical trial) so that the pharmacokinetics of the ethanol elimination can be properly studied. An experiment with a good design and a proper model not only yields more information than an experiment with a worse design, but it also makes it possible to provide the best conditions for the experiment [16]. Moreover, in chemometrics experiments quite often an approximate model is used instead of the true one when the latter is hard to deal with. Space-filling designs are usually used for such situation [17]. However, when the underlying regression model is known, D-optimal designs (see Section 3) is the most effective on parameter estimation. Atkinson et al. [18] first introduced D-optimal design to estimate rate constants in chemical kinetic model of a reversible reaction by computer experiments. The aim is to find the time points $t_1, t_2, \ldots$ at which to take samples in order to get the best estimators of the parameters of model, that is, the estimators with minimum variance. Nonlinear models arise in scientific experiments in a variety of areas, such as pharmacology, biology and agriculture. Determination of optimal designs for these models is more tricky and it often involves linearization.

In Section 2, the Widmark model is introduced, followed by two Hill-shaped models, the Gamma model employed in Li et al. [14] and a simplified version proposed in the present work. In Section 3, a general introduction to optimal experimental designs is given, focusing on D-optimality, which provides good estimations of all the parameters jointly. The calculation of optimal designs for the proposed simplified Gamma model is shown in Section 4 and an example of application is presented in Section 5. Equally-spaced designs, a special type of designs frequently-used in this kind of experiments is studied in Section 6. Section 6 provides a brief discussion, specially on the subject of equally-spaced designs presented is Section 6. Finally, a summary of the work and further lines of investigation are gathered in the Conclusion Section.

2. Alcohol clearance models

The kinetics of ethanol metabolism have been extensively studied, in both healthy and alcohol-dependent men and women, with many models focusing on how the blood's ethanol concentration changes over time. A more extensive review of some mathematical models can be found in, for example in Lands [19] or Heck et al. [15].

2.1. Widmark model

Widmark [20] proposed an equation to model the pharmacokinetics of ethanol and it is commonly used to predict blood alcohol concentration some time after drinking alcohol. Widmark equation is still widely used in forensic research since it performs well with real data over a wide range of values. It assumes a zero-order elimination process, i.e. the alcohol is eliminated at a constant rate in the human body. The hypothetical BAC at zero time is calculated as:

$$C_0 = \frac{A}{rW},$$

where r is the so-called Widmark factor, A is the mass of alcohol consumed and W the body weight (in kg). The Widmark factor r is variable and depends on body mass, percentage body fat, age, and sex.

Widmark tested a large number of individuals and found that the average value of r for males is 0.68 ± 0.17 and for females is 0.55 ± 0.11 [21].

The quantity consumed, A, is sometimes expressed as the product of volume of alcoholic beverage consumed (ml), represented by v, the strength of alcoholic beverage (%v/v), z, and the density of ethanol (l/kg), d [22]. Moreover, some versions utilize the total body water (TBW) of an individual:

$$C_0 = \frac{100vzdF_{water}}{TBW},$$

where F_{water} is the fraction of blood volume that is water. It is generally assumed to be 0.838%w/v in women and 0.825%w/v in men. TBW is an individual's total body water (in liters).

The blood alcohol concentration (BAC) at time t can then be determined from the following equation:

$$C_W(t) = C_0 - \beta t$$

where β is the clearance rate (in g/L/h), and t is the time (in hours) after consuming alcohol [15]. This zero-order (linear) model assumes an alcohol elimination rate, β which is constant, independently of the alcohol taken.

2.2. Hill-shaped models

As previously mentioned, the rate of alcohol elimination in humans is not necessarily constant, and in fact the study of the absorption phase may be interesting for different purposes. In the following, different non-linear regression models, based on a non-zero right-skewed bell-shaped assumption are presented. The Gamma, Weibull and Log-Normal densities are similar in shape and mainly differ at the tails (i.e., long time after consumption) [23].

2.2.1. Gamma model

The BAC at time t can be expressed as:

$$C_G(t) = s\frac{\beta^\alpha}{\Gamma(\alpha)}t^{\alpha-1}e^{-\beta t},$$

where $\alpha > 1$ is the shape parameter and $\beta > 0$ the scale parameter (sometimes $1/\beta$ is considered instead). These parameters determine the shape, skewness and dispersion of the model and represent a combination of the subject characteristics. For example, Li et al. [14] consider them as a linear combination of the gender, age and weight. The parameter s specifies that BAC is directly proportional to the alcohol dose consumed by the subject: $s = K \times A$, where A, as before, represents the alcohol dose taken (in grams) and K is the constant of proportionality.

If $\alpha \leq 1$ the derivative is negative for $t > 0$, thus the function is always decreasing. The hill-shape shows up when $\alpha > 1$, having a maximum value (maximum BAC) of:

$$C_G(t^*) = s\frac{\beta}{\Gamma(\alpha)}\left(\frac{\alpha-1}{e}\right)^{\alpha-1},$$

which is reached at a time $t^* = (\alpha - 1)/\beta$.

2.2.2. Simplified-Gamma (SG) model

The Gamma model can be simplified so that it can capture all the different phases of the BAC while remaining user-friendly. It can be expressed as:

$$C_{SG}(t) = st^a e^{-bt}, \tag{1}$$

with a, $b > 0$. This model has always a hill shape, and the maximum value is attained at $t^* = a/b$. The simplified model, just like the Gamma function, enables the fitting of a wide range of hill-shape models. However, since the most important fact is indeed this hilly shape, there is no need for the density-function constraints; these can be removed to obtain a model that is easier to handle and work with.

Fig. 2 shows the graphs corresponding to the SG model (1) for different values of the parameters a and b. On the left (Fig. 2(a)), $s = b = 1$ are kept constant. It can be noted how increasing the value of a increases the value of the function. In addition, the maximum is reached at higher values of time, changing the slope of the descending phase after the maximum. On the right (Fig. 2(b)), with $s = a = 1$, the slope, on the contrary, is maintained after the peak. The graph for fixed values for a and b and varying s, has been omitted since the latter is a linear parameter in the model.

3. Optimal designs of experiments background

Let x represent the experimental conditions in the design space $\mathcal{X}$. An exact design, ξ, is a collection of points, $\{x_1, x_2, \ldots, x_n\}$ where samples are to be taken. Let $\mathbf{Y} = (y_1, \ldots, y_n)$ denote the vector of observations of a one-response linear model $y = f(x;\theta)$, where $\boldsymbol{\theta}$ is the m-parameter vector and $\mathbf{X} = (\mathbf{f}(x_1), \ldots, \mathbf{f}(x_n))^T$, the design matrix, with $\mathbf{f}(x) = (f_1(x), \ldots, f_m(x))^T$. If there is a correlation structure $\boldsymbol{\Sigma} = \mathrm{Var}(\mathbf{Y})$ between the samples, the information given by a design ξ is reflected in the Fisher Information Matrix (FIM), defined as

$$\mathbf{M}(\xi, \theta) = \mathbf{X}^T\boldsymbol{\Sigma}^{-1}\mathbf{X}.$$

The FIM describes essentially the amount of information about the unknown parameters provide by the data. The inverse of the FIM, $M^{-1}(\xi, \theta)$, is proportional to the asymptotic covariance matrix for the maximum likelihood estimate of $\boldsymbol{\theta}$. The covariance between the observations taken at different points will be assumed to be dependent only on the distance between points, which is a logical assumption when studying the incorporation-elimination phases in alcohol consumption.

For non-linear models the usual approach is to linearize them (by computing the derivates with respect to the parameters) and proceed as above. In this case $\mathbf{M}$ will depend on the unknown parameters, thus nominal values are needed for them and the designs computed will be locally optimal. Linearizing may be a problem when it is not possible to have an analytical expression of the model; in this case the procedures described in Rodríguez-Díz and Sánchez-León [24] can be used for computing the derivatives.

The aim is to find optimal designs that produce precise estimators of the model parameters. This is achieved minimizing (a characteristic of) the covariance matrix of the estimators of the model parameters. Since the covariance matrix is proportional to the inverse of the information matrix, usually a function ϕ of the latter, called the optimality criterion, is employed. Amongst the different criteria for optimal designs, the D-criterion is the most popular. A design ξ is D-optimal if it maximizes the determinant of the FIM, which is equivalent to minimizing that of the covariance matrix of the parameters' estimators, or minimizing the volume of the confidence ellipsoid of these parameters [25,26].

When we are interested in obtaining the best design for the estimation of a specific linear combination of the parameters $c^T\beta$ (where c is a vector of length m, the proper criterion function to employ is c-optimality. c-optimal designs are not to easy to compute in general. Elfving [27] shows a very nice graphical procedure for finding c-optimal designs for two-parameter models assuming independent observations, and later on López-Fidalgo and Rodríguez-Díaz [28] extended it for m-parameter models.

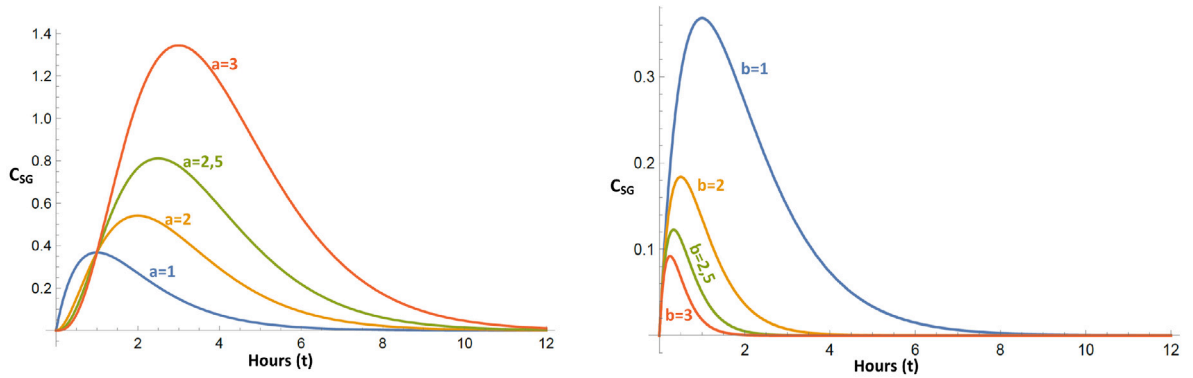
In order to check the goodness of a design, its efficiency can be computed. The D-efficiency of a design ξ is

$$\frac{n_2}{n_1}\left[\frac{|\mathbf{M}(\xi)|}{|\mathbf{M}(\xi_D^*)|}\right]^{\frac{1}{m}}, \tag{2}$$

where ξ_D^* is the optimal design and n_1, n_2 are the number of observations of designs ξ and ξ_D^* respectively. If N experiments can be performed under the design ξ, which has D-efficiency p, this means that the same accuracy (measured in terms of the D criterion) in the estimations would be achieved by performing only pN experiments under the optimal design ξ_D^* [29].

4. Optimal designs for the Simplified-Gamma model

In the literature, studies of the proposed model have been already performed from the point of view of optimal design of experiments, considering the model as a modification of the Arrhenius equation or the generalized exponential model. In Rodríguez-Díaz and Santos-Martín [30] a study of the best designs for modifications of the Arrhenius equation was carried out; the equation is similar to the proposed model but assuming that one of the parameters is known (the parameter



(a) Graphs for different values of a, all other parameters constant equal to 1.

(b) Graphs for different values of b, all other parameters constant equal to 1.

Fig. 2. Graphs of SG model for different values of the parameters.

m, which is now called a). In Rodríguez-Díaz et al. [31] filling and D-optimal designs for the correlated generalized exponential models were calculated. The correlation was also incorporated assuming that the parameter was known. The Michaelis–Menten equation is as well used sometimes to model the pharmacokinetics of ethanol elimination, and D-optimal designs for this model have been obtained (see Mariñas-Collado et al. [32]). In this section, optimal designs for the proposed Simplified Gamma model will be computed.

For the alcohol clearance models, the BAC or BrAC for one subject is observed at different times, t_i. Thus from now on $\mathcal{T}$ will denote the design space, and every observation will be taken at time $t \in \mathcal{T}$. A sensible and common assumption is that the covariance between observations from the same subject taken at different points depends on the distance between points, that is:

$$Cov[y(t_i), y(t_j)] = \rho(|\, t_i - t_j \,|),$$

where ρ is a stationary covariance kernel, which is assumed to be known. The fact that the covariance function is assumed to be known while the parameters of the model are unknown is a controversial issue (see discussion on page 9 of Näther [33]), but nevertheless this situation appears quite often in bibliography. The assumption, however, seems to be more acceptable when working with locally optimal designs.

The simplified-Gamma model (SG) introduced before, $C_{SG}(t;\theta) = st^a e^{-bt}$, is a triparametric model with parameter vector $\theta = (s,a,b)^T$. The model can be linearized as

$$f(t;\theta)^T = \frac{\partial C_G(t;\theta)}{\partial \theta} = t^a e^{-bt}\,(1, s\log(t), -st)\,.$$

It appears obvious that samples collected on the same subject at different times should be regarded as correlated. However, very often in the literature (see for instance Li et al. [14] and references therein), the alcohol clearance model assumes independent observations because it simplifies the modeling process, but it may not accurately reflect the true nature of alcohol metabolism in the body [34]. Nonethless, in the following, optimal designs will be obtained for different levels of correlation, even for independent observations, in order to be able to compare the results with those found in the literature. When the number of support points is the number of parameters in the model, the design is said to be minimally supported or saturated. Having a minimally supported design reduces the difficulty of the computation of optimal designs, since the criterion becomes a function of the m unknown support points only [35]. When the number of design points is the same than the number of parameters, $\mathbf{X}$ is a square matrix and $|\mathbf{X}^T\mathbf{X}| = |\mathbf{X}|^2$. Very often, in order to deal with a three-point design $\xi = \{t_1, t_2, t_3\}$, $t_i > 0$, it will be more convenient to write it as $\xi = \{t, t+d_1, t+d_2\}$ where $t_1 = t$, $t_2 = t + d_1$, $t_3 = t + d_1 + d_2$ and $t, d_1, d_2 > 0$.

Then the determinant of the information matrix (FIM) when there is no correlation structure can be expressed as

$$|\mathbf{M}(\xi)| = s^4 t^{2a} e^{-2b(3t+2d_1+d_2)}(t+d_1)^{2a}(t+d_1+d_2)^{2a} \times \left(d_2\log(t) - (d_1+d_2)\log(t+d_1) + d_1\log(t+d_1+d_2)\right)^2. \quad (3)$$

This notation may be more convenient when there is a non-trivial correlation structure given by a kernel function that depends only on the distance between points, $cov(y(t_i), y(t_j)) = \rho(|t_i - t_j|)$. In this work, the quite used exponential covariance kernel, $\rho(d) = e^{-\lambda d}$, where λ is characteristic of the subject, will be assumed, producing the following covariance matrix.

$$\Sigma = \begin{pmatrix} 1 & e^{-\lambda d_1} & e^{-\lambda(d_1+d_2)} \\ e^{-\lambda d_1} & 1 & e^{-\lambda d_2} \\ e^{-\lambda(d_1+d_2)} & e^{-\lambda d_2} & 1 \end{pmatrix}.$$

Then the determinant of the FIM, $\mathbf{M}(\xi,\theta) = \mathbf{X}^T\boldsymbol{\Sigma}^{-1}\mathbf{X}$, when there exists correlation structure is:

$$|\mathbf{M}_\Sigma(\xi)| = \frac{e^{2\lambda(d_1+d_2)}}{(e^{2\lambda d_1}-1)(e^{2\lambda d_2}-1)}|\mathbf{M}(\xi)| \quad (4)$$

The usual procedure for estimating the level of alcohol (either in breath or blood) is taking the first test as soon as possible, and a second one some time later (not quite exactly defined); in this scenario t represents the first moment after the ingestion when the subject can be tested. In most of the cases the optimal time $t_2 = t + d_1$ has been found to be close to the peak of alcohol concentration and $t_3 = t + d_1 + d_2$ would be at the end of the elimination phase. In order too find the optimal times for a set of nominal values of the parameters, $\theta_0 = (s,a,b)^T$, the determinant of the FIM has to be maximized. The following propositions show the main results for the uncorrelated and correlated case respectively:

Proposition 1. *The D-optimal design $\xi_D^* = \{t, t+d_1, t+d_1+d_2\}$ for the Simplified-Gamma model $C_{SG}(t) = st^a e^{-bt}$ with parameter vector (s,a,b) and assuming independent observations can be computed as the solution of the system*

$$\begin{aligned} Q_1\log(t) + Q_2\log(t+d_1) + Q_3\log(t+d_1+d_2) &= 1, \\ R_1\log(t) + R_2\log(t+d_1) + R_3\log(t+d_1+d_2) &= 1, \\ S_1\log(t) + S_2\log(t+d_1) + S_3\log(t+d_1+d_2) &= 1, \end{aligned}$$

where Q_i, R_i and S_i are parameter and time dependent functions, which satisfy that the sum of the functions that multiply the logarithms of the optimal times is always zero: $\sum Q_i = \sum R_i = \sum S_i = 0$. The explicit expressions of Q_i, R_i and S_i are shown in Appendix A.1. Due to the complexity of the equation system above, it is not possible to obtain an analytical expression of the design, which should be computed numerically.

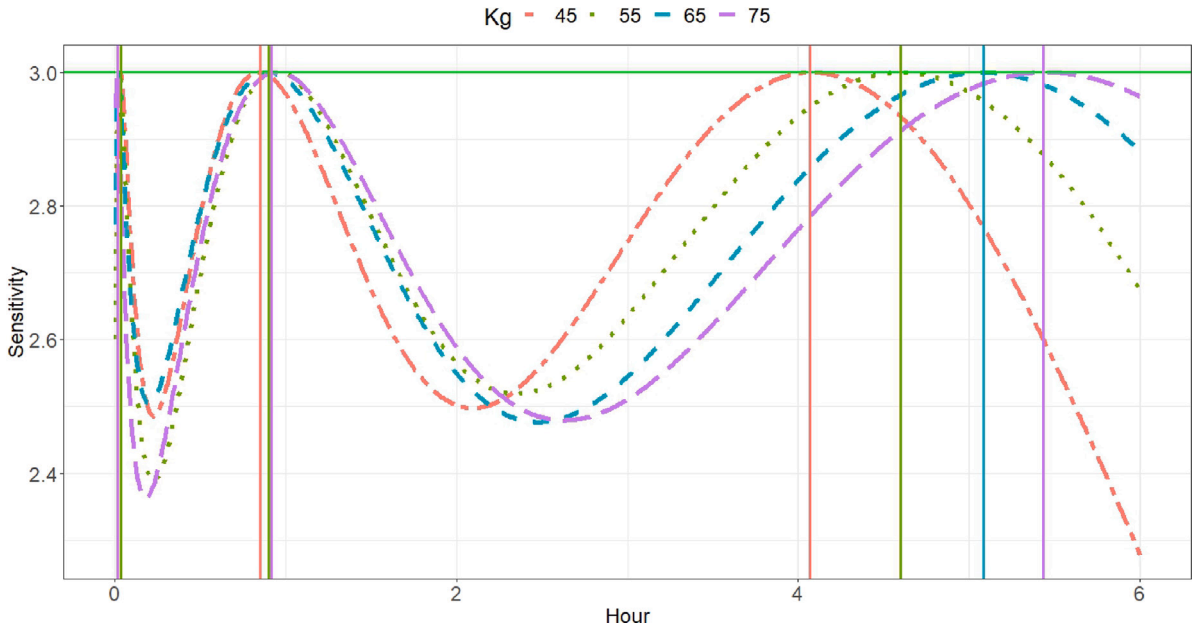


Fig. 3. Sensitivity function for the D-optimal designs, without correlation, over the time range. Vertical lines represent the corresponding design support points.

Proposition 2. *The optimal points of the D-design* $\xi_D^* = \{t, t+d_1, t+d_1+d_2\}$ *for the Simplified-Gamma model* $C_{SG}(t) = st^a e^{-bt}$*, with parameter vector* (s, a, b) *and assuming a correlation structure between the samples given by an exponential kernel function, are the solutions of the system*

$$\begin{aligned} Q_1 \log(t) + Q_2 \log(t+d_1) + Q_3 \log(t+d_1+d_2) &= 1, \\ V_1 \log(t) + V_2 \log(t+d_1) + V_3 \log(t+d_1+d_2) &= 1, \\ W_1 \log(t) + W_2 \log(t+d_1) + W_3 \log(t+d_1+d_2) &= 1, \end{aligned}$$

where Q_i*,* V_i *and* W_i *are parameter and time dependent functions. The functions* Q_i *are the same than that in Proposition 1, and the expressions of* V_i *and* W_i *as functions of* R_i *and* S_i *of Proposition 1 respectively are shown in Appendix A.2.*

In order to check that a design is, indeed, D-optimal, the General Equivalence Theorem (GET) for D-optimality [36] may be used. The GET states that an approximate design, $\tilde{\xi}$, is D-optimal if and only if

$$\psi_a(\tilde{\xi}, \theta, t) = f(t,\theta)^T \tilde{\mathbf{M}}^{-1}(\tilde{\xi}) f(t,\theta) \leq m \qquad \forall t \in \mathcal{T}, \tag{5}$$

where $\tilde{\mathbf{M}}$ denotes the information matrix of the approximate design $\tilde{\xi}$. The function $\psi(\xi, \theta, t)$ is known as the *sensitivity function*, and equality is reached at the support points of the design.

An approximate design is a set of design points, $x_1, \ldots, x_n$, each of one having an associated weight w_i ($\sum_{i=1}^n w_i = 1$), which indicates the proportion of observations to be taken at that point, and the FIM is calculated using the corresponding weight for each point in the design. An exact design can always be thought as an approximate design with equal weights (every of them equal to $1/n$), thus if $\mathbf{M}$ is the FIM of an exact design ξ, then the FIM of the corresponding approximate design $\tilde{\xi}$ is $\tilde{\mathbf{M}} = \mathbf{M}/n$. Therefore (5) can be expressed as

$$\psi(\tilde{\xi}, \theta, t) = n f(t,\theta)^T \mathbf{M}^{-1}(\xi) f(t,\theta) \leq m \qquad \forall t \in \mathcal{T}. \tag{6}$$

5. Case study

In order to find the best estimates for the model parameters, samples should be taken at least at three different time points, representing minutes after the consumption. Tables 1 and 2 show optimal designs $\xi_D^* = \{t, t+d_1, t+d_1+d_2\}$, using initial values from Li et al. [14], where observations were made every 10 minutes for the first hour after consumption (absorption phase) and then every 30 minutes, up to 8 hours after the intake (elimination phase). The times taken into account are from the instant that alcohol can be detected in blood. Although that this moment depends on factors such as weight, health, quantity of alcohol consumed, type of beverages, etc., is usually accepted to be around 5 minutes after consumption. Moreover, a BAC test is only accurate within 6 to 12 hours after someone has had their last drink. The results and calculations have been done with the help of softwares: *R* [37] and *Mathematica* [38]. More specifically, computations have been done using Mathematica functions `FindMaximum` and `NMaximize`. The first one may produce a local maximum, thus it has been employed several times for each case, using different starting points. NMaximize attempts to find a global maximum by using one of the four direct search algorithms (Nelder–Mead, differential evolution, simulated annealing, and random search), then fine-tunes the solution by using a combination of KKT solution, the interior point, and a penalty method. Both procedures have been used for each parameter combination, in order to double-check the results.

Note that, as $\lambda \to \infty$, $\Sigma \to I$ and the designs with correlation structure tend to be the same as when the correlation is not considered. When there is no previous information regarding the value of λ, an intermediate value could be used, e.g. $\lambda = 1$. A sensitivity study regarding the choice of λ has shown that the designs are quite robust for the actual value of λ. If the advisable optimal design for $\lambda = 1$ is chosen, the loss in efficiency is not very big even when the actual value of λ is as far as 0.25 or 4. For instance, assuming the case of a Chinese 65-kg male, the efficiency of the D-optimal design for $\lambda = 1$ is 98.1% when it is assumed that the actual value of λ is 0.25, and 87.3% when the true λ is taken to be 4. Similar values are found for the rest of the cases. It can be observed that the designs indicate that the first observation should be taken as soon as possible, while the last one should be between 4 and 6 hours after consumption, when alcohol is believed to be almost eliminated from the body. The midpoint corresponds approximately to the alcohol concentration peak, that is around time a/b. The D-optimality of the designs is checked using condition (6), which is shown in Fig. 3 for different body weights.

The D-efficiency of the design employed in Li et al. [14], with respect to the optimal designs, is shown in Tables 3 and 4. For instance, an efficiency of around 50% means that the optimal design would obtain the same information with a number of samples that is just a half than the number needed for the other design. Very often practitioners prefer to use designs with more points, thinking that model fitting will

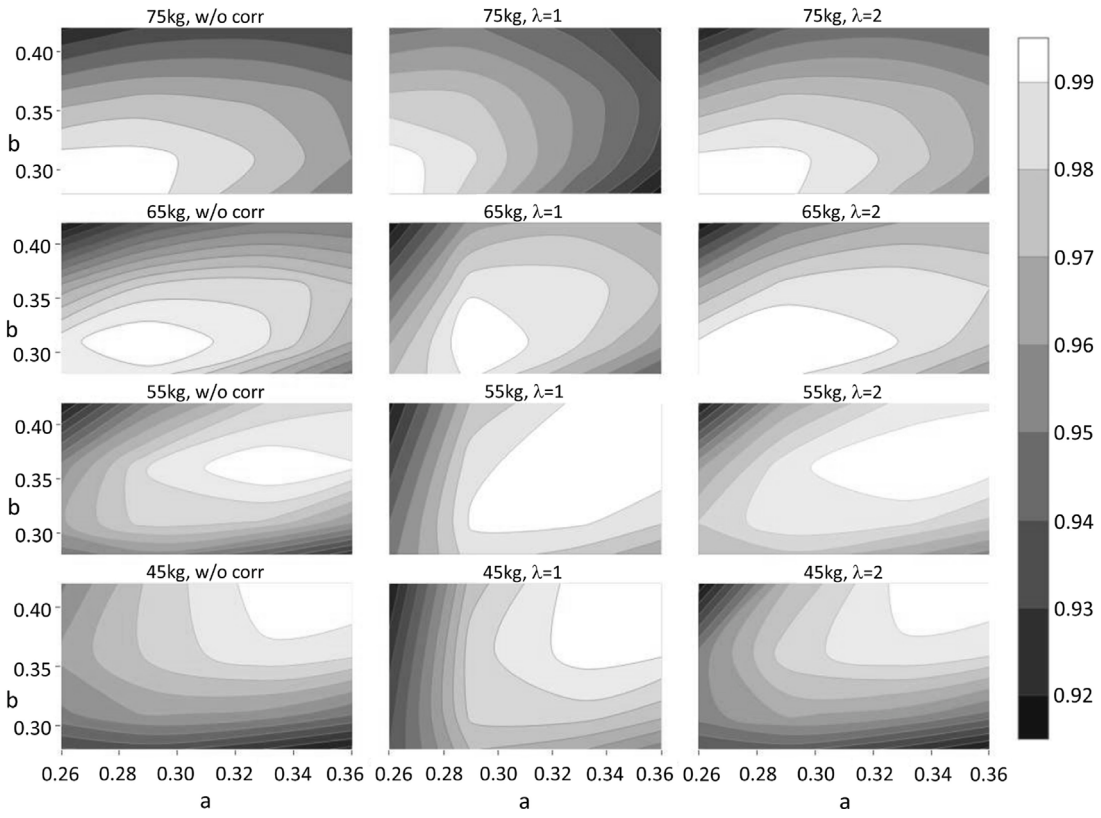


Fig. 4. Efficiency of the D-optimal designs with respect to the choice of initial values for designs in Table 1.

Table 1
D-optimal design in minutes for different weights in 38-year-old men consuming 40 gr. of alcohol.

Weights (kg)	45	55	65	75
$\theta = (s, a, b)$	(48.03, 0.36, 0.42)	(39.75, 0.33, 0.36)	(34.29, 0.29, 0.31)	(30.33, 0.26, 0.28)
w/o corr.	{2, 51, 244}	{2, 54, 276}	{1, 55, 305}	{1, 55, 326}
$\lambda = 0.25$	{1, 16, 180}	{1, 13, 205}	{0, 8, 226}	{0, 2, 239}
$\lambda = 0.5$	{1, 19, 206}	{1, 16, 233}	{0, 10, 256}	{0, 2, 268}
$\lambda = 0.75$	{1, 22, 217}	{1, 21, 244}	{0, 13, 265}	{0, 3, 274}
$\lambda = 1$	{1, 27, 233}	{1, 27, 251}	{1, 19, 272}	{0, 6, 278}
$\lambda = 2$	{2, 44, 238}	{2, 48, 270}	{1, 48, 299}	{1, 46, 318}
$\lambda = 3$	{2, 49, 243}	{2, 53, 275}	{1, 54, 304}	{1, 53, 324}
$\lambda = 4$	{2, 50, 244}	{2, 54, 275}	{1, 55, 305}	{1, 54, 326}

Table 2
D-optimal design in minutes for different doses of alcohol in 38 year-old men weighing 66.7 kg.

Doses (gr.)	20	40	60
$\theta = (s, a, b)$	(14.75, 0.18, 0.25)	(33.35, 0.29, 0.31)	(62.22, 0.39, 0.39)
w/o corr.	{0, 42, 327}	{1, 55, 305}	{3, 60, 272}
$\lambda = 0.25$	{0, 0.6, 248}	{0, 8, 226}	{2, 22, 207}
$\lambda = 0.5$	{0, 0.6, 279}	{0, 10, 256}	{2, 26, 235}
$\lambda = 0.75$	{0, 0.6, 283}	{0, 13, 265}	{2, 32, 246}
$\lambda = 1$	{0, 0.6, 284}	{1, 19, 272}	{2, 38, 253}
$\lambda = 2$	{0, 0.6, 284}	{1, 48, 299}	{3, 55, 268}
$\lambda = 3$	{0, 36, 321}	{1, 54, 304}	{3, 59, 271}
$\lambda = 4$	{0, 41, 326}	{1, 55, 305}	{3, 59, 271}

be better and at the same time for checking the goodness of the chosen model. But usually every test has a cost (time, money,...) and for this reason when comparing designs the number of samples employed by each one should be taken into account.

In order to study the dependency of the D-optimal designs on the initial values of the parameters, the efficiency function (2) can be used. First, given initial values for θ, a D-optimal design ξ is computed. Then, for different values θ_i, the corresponding D-optimal designs, ξ_i, are also calculated. Assuming that the initial θ is actually the true parameter vector, the D-efficiency of the designs ξ_i with respect to ξ may be computed.

Let the values provided in Li et al. [14] be considered as 'true parameters' for $\theta = (s, a, b)$. Fig. 4 shows the efficiencies (in percentage) for some of the designs from Table 1 for different combinations of a and b. It can be seen that the efficiency always surpasses 90%. Moreover, when the differences between the alternative values of the parameters and the assumed trued values are less than two decimal points, the efficiency is always greater than 98%. In general, the efficiency appears to be consistent across the different values of correlation, which proves the robustness of the optimal designs with respect to the choice of the nominal values and the correlation structure.

6. Equally-spaced designs

Very often, optimal designs contain few points, and frequently most of them are concentrated at the extremes of the design interval. However, in experimental science, usually due to operational reasons, practitioners prefer to employ designs that cover the design space

Table 3
D-efficiency of the design used in Li et al. [14] with respect to the optimal designs of Table 1.

Weights (kg)	45	55	65	75
$\theta = (s, a, b)$	(48.03, 0.36, 0.42)	(39.75, 0.33, 0.36)	(34.29, 0.29, 0.31)	(30.33, 0.26, 0.28)
w/o corr.	59.5%	61.3%	60.4%	58.6%
$\lambda = 0.25$	14.3%	14.1%	13.1%	12.0%
$\lambda = 0.5$	16.1%	16.1%	15.3%	14.0%
$\lambda = 0.75$	18.2%	18.4%	17.7%	16.4%
$\lambda = 1$	20.3%	20.6%	20.3%	21.9%
$\lambda = 2$	27.9%	28.5%	28.3%	27.7%
$\lambda = 3$	33.9%	35.0%	34.6%	33.7%
$\lambda = 4$	38.7%	40.0%	39.6%	38.6%

Table 4
D-efficiency of the design used in Li et al. [14] with respect to the optimal designs of Table 2.

Doses (gr.)	20	40	60
$\theta = (s, a, b)$	(14.75, 0.18, 0.25)	(33.35, 0.29, 0.31)	(62.22, 0.39, 0.39)
w/o corr.	51.2%	60.4%	65.19%
$\lambda = 0.25$	7.2%	13.1%	15.6%
$\lambda = 0.5$	8.4%	15.3%	17.7%
$\lambda = 0.75$	9.9%	17.7%	20.0%
$\lambda = 1$	10.7%	20.3%	22.1%
$\lambda = 2$	17.1%	28.4%	30.2%
$\lambda = 3$	27.7%	34.6%	36.9%
$\lambda = 4$	31.7%	39.6%	42.3%

Table 5
Locally optimal t and d in equally-spaced designs for independent (left) and correlated (right) observations assuming the simplified gamma model. Initial values corresponding to a 75-kg male Chinese have been used.

n	Independent		Correlated	
	t	d	t	d
3	0.0197	2.099	0.0191	2.013
4	0.0183	1.649	0.0188	1.738
5	0.0172	1.349	0.0184	1.530
6	0.0164	1.135	0.0175	1.370
7	0.0158	0.975	0.0175	1.243
8	0.0153	0.852	0.0170	1.138
9	0.0148	0.755	0.0167	1.051
10	0.0144	0.677	0.0163	0.977

'uniformly', keeping a constant distance between adjacent points, rather than the optimal designs. Those are called *equally-spaced designs*, and they are related with the space-filling designs [see for instance31]. Equally-spaced designs are used for instance in Li et al. [14], where first measurements are taken every 10 minutes during the first hour after consumption (absorption phase) and then every 30 minutes. Moreover, equally-spaced designs have been used to identify the parameters of alcohol kinetics (see for instance Fujimiya et al. [39]; Maskell et al. [40]) and for this reason it seems convenient to perform a study about the behavior of this type of designs for the alcohol-clearance model.

Thus, in this section, designs $\xi_n = \{t, t+d, \ldots, t+(n-1)d\}$ will be considered. The main advantage of these designs is that each one of them just depends on just two values, namely the time of the first sample, t, and the distance d between adjacent observations. For instance, the determinant of the information matrix of the 3-point design ξ_3 assuming independent observations is

$$d^2 s^4 t^{2a} (d+t)^{2a} (2d+t)^{2a} e^{-6b(d+t)} (-2\log(d+t) + \log(2d+t) + \log(t))^2,$$

and when using the parameter values of a 75-kg Chinese male ($\theta = (s, a, b) = (30.33, 0.26, 0.28)$) the maximum is attained for $t = 0.01968$ hours (1.18 mins.) and $d = 2.0994$ hours (Fig. 5).

When assuming exponential correlation, the covariance matrix for the 3-point design is

$$\Sigma = \begin{pmatrix} 1 & e^{-\lambda d} & e^{-2\lambda d} \\ e^{-\lambda d} & 1 & e^{-\lambda d} \\ e^{-2\lambda d} & e^{-\lambda d} & 1 \end{pmatrix},$$

with determinant $e^{-4\lambda d}\left(e^{2\lambda d}-1\right)^2$. Thus, the determinant of the 3-point design information matrix assuming correlation is:

$$\frac{d^2 s^4 t^{2a} (d+t)^{2a} (2d+t)^{2a} (-2\log(d+t) + \log(2d+t) + \log(t))^2 e^{4d\lambda - 6b(d+t)}}{\left(e^{2d\lambda}-1\right)^2}$$

Table 5 shows optimal values for the parameters t and d when searching for optimal designs with different number of points, with and without correlation. The initial points are quite similar for every design and type of correlation; the variation of the optimal distances with n for both cases is shown in Fig. 6 where it can be checked that the optimal distance between adjacent points decreases as n increases, but the decreasing is faster for the correlated case.

Fig. 7 shows the explicit equally-spaced *D*-optimal designs $\xi_3^* \ldots \xi_{10}^*$ when assuming independent observations, using for the parameters, as before, the nominal values of a 75-kg Chinese male. The time of the first sample is quite similar for all of them, while the pattern of the remaining observations follows a clear symmetry.

The efficiency (2) of these designs, with respect to the 3-point D-optimal design, assuming independent observations, is shown in Fig. 8. It clearly proves that when using equally-spaced designs just three observations are too few, producing an efficiency of less than 75%; but it also shows that there is no need to take too many samples. In fact the 5-point design seems to be the most efficient (more than 80%), which should be the most clever choice when using designs with constant distance between samples.

Regarding the parameters estimations, simulations for different cases have been performed using both the optimal design and the equally-spaced designs. It has been found that the estimation of the parameters is quite similar in average, but the variance of this estimation was smaller when using the optimal designs. For instance, for a 75 kg. Chinese male assuming independent observations, the variance of the estimator of the s parameter was 3.7174 when using the *D*-optimal design, and 13.5782 when the equally-spaced design in three points was employed.

7. Discussion

The study of equally-spaced designs opens new lines of research. For instance, from the shape of the curves described by the points (see Fig. 7) it would be possible to estimate the values of the *D*-optimal designs with more support points from the knowledge of the optimal designs with fewer points, following an iterative procedure. For instance, Fig. 9(a) shows the 11 curves needed for the estimation of an 11-point design from optimal equally-spaced designs with fewer points. Note that this procedure, say P_1, will not produce in general an equally-spaced final design. Another possibility, say P_2, would be to estimate suitable t and d for an n-point design from the two corresponding curves defined by the values of the optimal t and d for the designs with fewer points (Fig. 9(b)). The estimated 11-point design using P_1 is

$$\{0.014086, 0.6109, 1.2078, 1.8349, 2.4547, 3.0906, 3.6941,$$

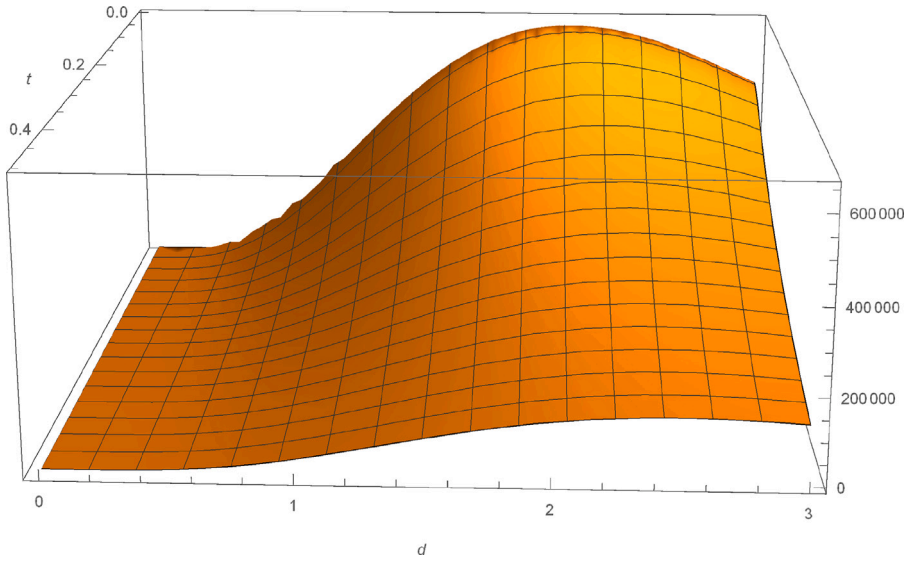


Fig. 5. Determinant of the information matrix of an equally-spaced design as a function of t and d.

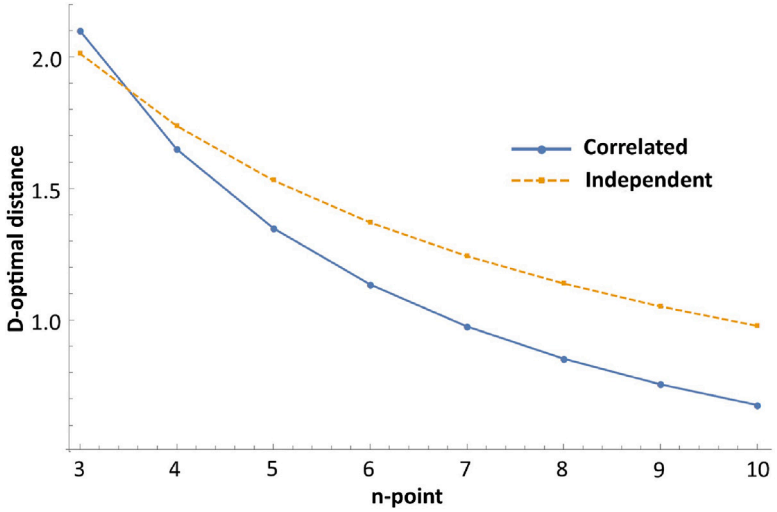


Fig. 6. *D*-optimal distance for equally-spaced *n*-point designs for independent (dashed) and correlated (full line) observations.

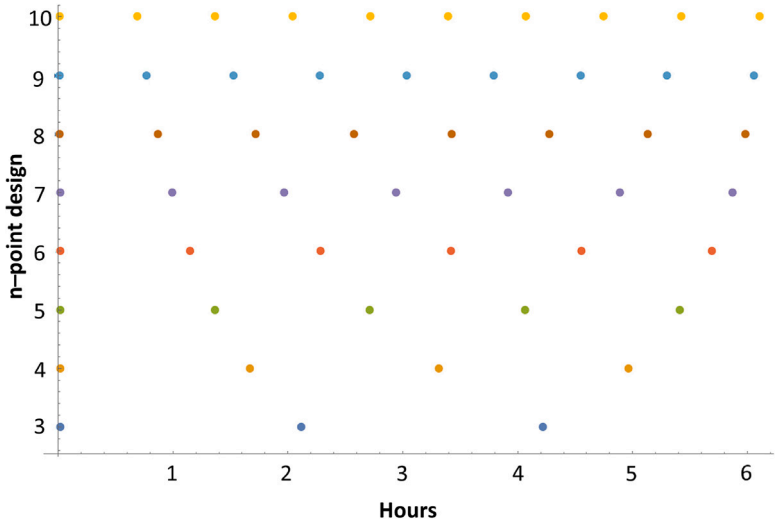


Fig. 7. *D*-optimal *n*-point equally-spaced designs (in rows) for independent observations.

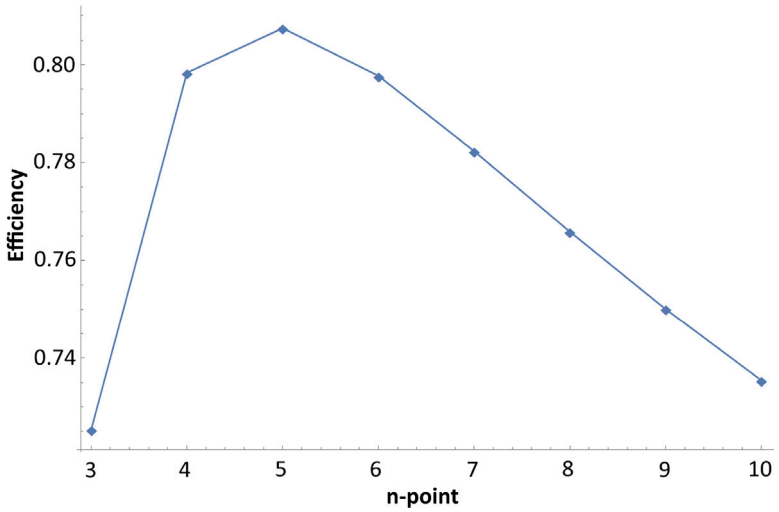
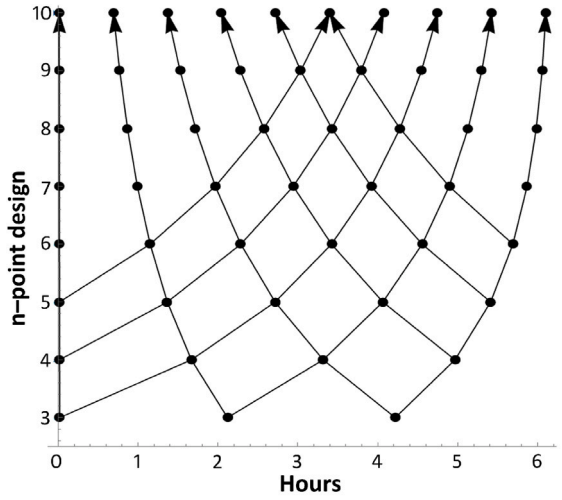
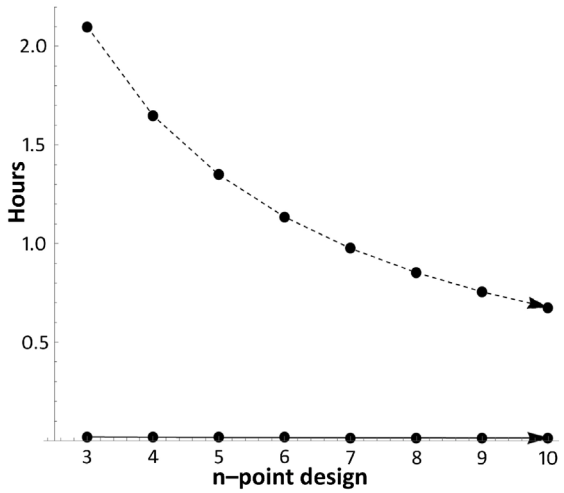


Fig. 8. Efficiency of D-optimal n-point equally-spaced designs for independent observations.



(a) The eleven curves for the estimation of an 11-point design from equally-spaced designs with fewer points (given in rows).



(b) Curves of optimal first observation t (full line) and optimal distance d between adjacent points (dashed) for D-optimal equally-spaced designs. They may be used to estimate the corresponding values of t and d for the 11-point design.

Fig. 9. Procedures for generating designs with more support points from known equally-spaced designs.

4.3206, 4.9686, 5.5655, 6.1623} ,

with determinant 3.2297×10^7 and not exactly equally-spaced. From method P_2, the estimated t and d for the 11-point design are respectively 0.01409 and 0.5969, producing the 11-point equally-spaced design

{0.014086, 0.6109, 1.2078, 1.8047, 2.4015, 2.9984, 3.59526,
4.1921, 4.7890, 5.3859, 5.9827} ,

which has determinant 3.1835×10^7. Finally, the optimal 11-point equally-spaced design computed using numerical procedures is

{0.01410, 0.6258, 1.2376, 1.8493, 2.4610, 3.0727, 3.6844,
4.2962, 4.9079, 5.5196, 6.1313} ,

with determinant 3.1861×10^7. It can be seen that the values of the determinants are quite similar, thus the three designs have roughly the same efficiency. However, in this case the design obtained with the P_1 procedure is slightly better than the other two, that are tied to the restriction of having equally-spaced points while the former is not.

On the other hand, when an exponential correlation is assumed in an equally-spaced design $\{t, d\}$, the covariance matrix for $n+1$ support points will have the shape

$$\Sigma = \begin{pmatrix} 1 & K & K^2 & \dots & K^n \\ K & 1 & K & \dots & K^{n-1} \\ K^2 & K & 1 & \dots & K^{n-2} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ K^n & K^{n-1} & K^{n-2} & \dots & 1 \end{pmatrix} ,$$

where $K = e^{-\lambda d}$. Some characteristics of these matrices could now be studied. For instance, the eigenvalues for the 3-equally-spaced-point covariance matrix are

$$\lambda_1 = 1 - K^2, \quad \lambda_2 = \frac{1}{2}\left(2 + K^2 - K\sqrt{K^2+8}\right),$$
$$\lambda_3 = \frac{1}{2}\left(2 + K^2 + K\sqrt{K^2+8}\right) ,$$

and since the covariance matrix is non-negative definite, $\lambda_1 \geq 0$, $i = 1, 2, 3$. Therefore, a square root of Σ can be obtained, and a

procedure similar to that described in Rodríguez-Díz [41] can be used for computing c-optimal designs even for the correlated case.

8. Conclusion

In this work, a new non-linear model is proposed to adjust the pharmacokinetics of ethanol in the human body. As stated in the introduction, it is necessary to use a non-linear trend model, more precisely, a hill-shaped function, to explain both the clearance and absorption phases of alcohol consumption. The proposed model can be considered a simplification of the Gamma model used in Li et al. [14] or a modified Arrhenius model.

Whilst taking into account all the different phases of alcohol concentration in the body (i.e. absorption and elimination), a key aspect of the proposed model is its simplicity, unlike other more complex models such as compartmental models. It is important to use not very complex models so that they can be used to, for example, retrospectively determine the level of alcohol that a driver had in the moment of an accident. This has been so far done using the Widmark equation, which only models the elimination phase in a linear way but is widely used because of its simplicity in forensic medicine.

Among all optimality criteria for precise estimation, the D-criterion is the most popular, minimizing the volume of the confidence ellipsoid of the estimators of the model parameters [25,26]. For this reason, D-optimal designs for the Simplified-Gamma model have been calculated, which determine the observation times at which BAC should be measured to find the best estimations of the model parameters. These parameters, as well as the correlation parameter λ, will depend on factors such as the amount and type of alcohol consumed, sex, age, weight, height... and must be determined after conducting clinical trials. In the future, after the appropriate experimental studies, lambda could be chosen to fit the "standard" individual, i.e. a value that describes the characteristics of the average subject. Being a non-linear model, an initial estimation of the parameters that appear 'non-linearly' in the model [42] has been required. This has been done by calculating the equivalent values from those in Li et al. [14].

Nonetheless, due to the complexity of the system of equations that optimize the designs, these had to be solved analytically, so future work may include the implementation of a web application that allows the calculation of the designs for any initial estimation of the parameters. Additionally, c-optimal designs can be studied in order to obtain good designs for estimating more precisely one particular parameter, if needed. Furthermore, equally-spaced designs have also been presented. These designs, a compromise between D-optimal designs and filling designs, while easier to calculate have been proven to be less efficient than unrestricted D-optimal designs, but offer an alternative when easy to implement designs with more points are needed.

Further lines of investigations may also include a deeper study of how efficient are the more complex models, such as compartmental models, when used for alcohol clearance, in terms of whether their complexity can be justified by a much better adjustment. However, the main drawback for these models is still that they are not as user friendly so that the can be used on the go by, for example, police officers when intervening with a drunk driver.

When both BAC and BrAC tests are conducted on the same subject we get into the field of multiresponse models (see Rodríguez-Díaz and Sánchez-León 43). If, in addition, the study is made over different subjects, the results in Rodríguez-Díaz [44] could be used. In future works, derivations of the proposed model when the intake of alcohol is carried out in multiple steps (which probably fits better the actual situation of an alcohol drinker) should be studied.

To summarize, the purpose of this work is to present a model that could represent a compromise between simplicity and utility for estimating BAC and BrAC. The crucial next step, outside the authors' scope, is to run the appropriate trials so as to estimate the parameters of the model for subject of different type, combining on factors such as age, race, sex, ... For this, the optimal time points at which to take samples are given through the D-optimal designs presented. Moreover, the procedures given in the Discussion could also be used.

CRediT authorship contribution statement

Irene Mariñas-Collado: Conceptualization, Investigation, Methodology, Software, Writing of the paper. **Juan M. Rodríguez-Díaz:** Conceptualization, Investigation, Methodology, Software, Writing of the paper. **M. Teresa Santos-Martín:** Conceptualization, Investigation, Methodology, Software, Writing of the paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article

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Appendix. Sketches of the proofs

A.1. *Proposition* 1

Proof. In order to find the maximum, the derivatives of (3) with respect to t, d_1 and d_2 are calculated. The following expressions are obtained after lengthy computations to obtain simplified terms of the system of equations. The functions Q_i can be computed as

$$Q_1(a,b,t,d_1,d_2) = \frac{-Q(a,b,t,d_1,d_2)}{d_1(d_1+d_2)} \tag{A.1}$$

$$Q_2(a,b,t,d_1,d_2) = \frac{Q(a,b,t,d_1,d_2)}{d_1 d_2} \tag{A.2}$$

$$Q_3(a,b,t,d_1,d_2) = \frac{-Q(a,b,t,d_1,d_2)}{d_2(d_1+d_2)}, \tag{A.3}$$

with

$$Q(a,b,t,d_1,d_2) = a[(t+d_1)^2+2t(t+d_1+d_2)+(d_1 d_2)]-3bt(t+d_1)(t+d_1+d_2). \tag{A.4}$$

Regarding the R_i:

$$R_1(a,b,t,d_1,d_2) = \frac{R(a,b,t,d_1,d_2)}{t+2d_1+d_2} \tag{A.5}$$

$$R_2(a,b,t,d_1,d_2) = \frac{-(d_1+d_2)R(a,b,t,d_1,d_2)-(t+d_1)(t+d_1+d_2)}{d_2(t+2d_1+d_2)} \tag{A.6}$$

$$R_3(a,b,t,d_1,d_2) = \frac{d_1 R(a,b,t,d_1,d_2)+(t+d_1)(t+d_1+d_2)}{d_2(t+2d_1+d_2)}, \tag{A.7}$$

$$R(a,b,t,d_1,d_2) = a[(t+d_1)+(t+d_1+d_2)]-2b(t+d_1)(t+d_1+d_2). \tag{A.8}$$

And finally, the S_i:

$$S_1(a,b,t,d_1,d_2) = \frac{-d_2 S(a,b,t,d_1,d_2)-(t+d_1+d_2)}{d_1} \tag{A.9}$$

$$S_2(a,b,t,d_1,d_2) = \frac{(d_1+d_2)S(a,b,t,d_1,d_2)+(t+d_1+d_2)}{d_1} \tag{A.10}$$

$$S_3(a,b,t,d_1,d_2) = -S(a,b,t,d_1,d_2), \tag{A.11}$$

where

$$S(a,b,t,d_1,d_2) = a-b(t+d_1+d_2). \quad \square \tag{A.12}$$

A.2. Proposition 2

Proof. In the case of correlated observations, the procedure is the same, taking into account the correlation matrix. Now, in the first equation the Q_i functions are the same as those in Proposition 1 (see (A.1),(A.2), (A.3), and (A.4)).

For the second equation:

$$V_1(a,b,t,d_1,d_2) = R_1(a,b,t,d_1,d_2) + \frac{\lambda(t+d_1)(t+d_1+d_2)}{(e^{2\lambda d_1}-1)d_2(t+2d_1+d_2)}$$
$$V_2(a,b,t,d_1,d_2) = R_2(a,b,t,d_1,d_2) + \frac{\lambda(t+d_1)(d_1+d_2)(t+d_1+d_2)}{(e^{2\lambda d_1}-1)d_2(t+2d_1+d_2)}$$
$$V_3(a,b,t,d_1,d_2) = R_3(a,b,t,d_1,d_2) + \frac{-\lambda d_1(t+d_1)(t+d_1+d_2)}{(e^{2\lambda d_1}-1)d_2(t+2d_1+d_2)},$$

with R_1, R_2, R_3 and R from Proposition 1: (A.5), (A.6), (A.7) and (A.8).

For the last equation:

$$W_1(a,b,t,d_1,d_2) = S_1(a,b,t,d_1,d_2) + \frac{\lambda d_2(t+d_1+d_2)}{(e^{2\lambda d_2}-1)d_1}$$
$$W_2(a,b,t,d_1,d_2) = S_2(a,b,t,d_1,d_2) + \frac{\lambda(d_1+d_2)(d_1+d_2)(t+d_1+d_2)}{(e^{2\lambda d_2}-1)d_1}$$
$$W_3(a,b,t,d_1,d_2) = S_3(a,b,t,d_1,d_2) - \frac{\lambda(t+d_1+d_2)}{(e^{2\lambda d_2}-1)},$$

with S_1, S_2, S_3 and S corresponding to (A.9), (A.10), (A.11) and (A.12), respectively.

The expressions above are obtained after lengthy calculations and simplifying the derivatives of (4) with respect to t, d_1 and d_2 in order to find the maximum. □

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