



A Stochastic Model for the Ethanol Pharmacokinetics

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Abstract

Background: The aim of this study was to propose a new stochastic model to study the time course of ethanol elimination in human bodies.

Methods: The times and amount of alcohol ingested are assumed to be random in controllable intervals. Constant elimination rate follows zero order kinetics and is replaced by first order kinetics when the effects of alcohol increase due to alcohol ingestion. Simulation studies of three different models were made to compare the statistical characteristics of the ethanol effects obtained using analytical expressions. For each model, three cases were considered depending on the drinking pattern and by classifying the drinker as heavy, normal or sparse.

Results: From the model formulation, we noted that as the rate of drinking increases for a given elimination rate, the expected time between overflows goes towards zero. Furthermore, as the average amount of alcohol in each drink increases, the corresponding time between overflows decreases.

Conclusion: Variations in times of alcohol intakes as well as the amount of alcohol consumption can be accounted through the final created formula. The model proves that overflows occur when alcohol is ingested before the adverse effects of alcohol from the previous drink are completely eliminated. Being the first stochastic model of such a kind, we do hope that it will throw more light on interpreting experimental data of alcohol abuse.

Keywords: Alcohol ingestion, Elimination rate, Overflow, Multiple doses, Zero order kinetics, First order kinetics

Introduction

Alcohol abuse has ramifications not only in public health and highway safety but also has effects on a nation's Gross domestic product (GDP) which underscores the extensive literature on the subject (1). The ethanol pharmacokinetics in human body consists of three distinct phases marked by absorption, distribution and elimination (2). Roughly 95% of the alcohol ingested is metabolized through enzymatic oxidation in the liver and the rest excreted through breath, sweat and urine. The metabolic elimination of alcohol has been modeled using zero order kinetics (con-

stant elimination rate) or first order kinetics (dose dependent elimination rate) (3). The enzymatic elimination process is governed by two main hepatic enzymes known as alcohol dehydrogenase (ADH) and cytochrome (CYP2E1) (4, 5).

ADH enzyme has a low k_m (Michaelis constant) which gets saturated very early and hence fits easily into a constant elimination process. However, cytochrome enzymes have a much higher k_m and provided that the alcohol concentration stays below the k_m . The elimination process with this enzyme will apparently produce first order kinet-

ics that is the mechanism for blood alcohol clearance, which only becomes effectively operative at high blood alcohol concentrations (3). Existing models on ethanol elimination use either zero order or first order kinetics while more appropriate modeling should consider zero order kinetics followed by first order kinetics which comes into play with a higher ethanol concentration in the body.

Studies on ethanol metabolism have mainly been built on single dose experimental studies from the highway safety aspects or to chart the time course of ethanol elimination (6). The highway safety manual was introduced by the American Association of State Highway and Transportation Officials (AASHTO) that aim to help different deputations to unify safety in all processes related to decision making (7). Additional complications arise when alcohol is ingested in multiple doses (8).

Simulating multiple ingestions increases the complexity and analysis of the model. Thus, experimentalists as well as modelers have conveniently stuck to single dose studies staying away from multiple doses (9). However, consumption of multiple drinks in a short span of time is quite common and hence a better understanding of ethanol elimination with multiple dose ingestions is desirable. Such studies are addressed relatively easily with mathematical models, more specifically compartment models which surveyed the fluxes between the compartments (10, 11). Existing compartment models on alcohol elimination are mostly deterministic in nature. Although such models provide a good deal of information on the pharmacokinetics of ethanol, the need for the determination of the model parameters such as the anatomical structure of the assumed compartments, metabolic rates as well as transient and steady state solutions, requires extensive and sophisticated experimental studies and inhibits their efficacy. Because of the variability in the instants of alcohol consumption, absorption and elimination times which are random in nature, a front runner for modeling such phenomena are stochastic models which provide useful information with minimal complexity. One study (12),

used Markov or hidden Markov models to describe the drinking behavior of subjects. These models are better suited to describe processes that make sudden changes rather than being gradual over time. Another study (13), suggested the use of multivariate time models for alcohol consumption.

In other study (9), proposed a stochastic model applying queuing theory to describe the adverse effects of ethanol in the system. That drew an analogy between customers and the ethanol intake, server and the body and service and ethanol elimination. The serious short comings of the model were the assumptions of the larger elimination rate compared to the rate of alcohol ingestion and the infinite system capacity. But as a preliminary model, it established the success of the stochastic approach.

The purpose of the present work is to develop a new stochastic model to describe the adverse effects of ethanol in the body taking into account the randomness in the times of alcohol ingestion as well as elimination times. The model accounts for multiple doses as well as alcohol metabolizing enzymes ADH and CYP2E1 known to contribute to the observed variability of alcohol elimination rates.

Methods

Two compartments for ethanol metabolism disappear alcohol from the blood stream (3). The first compartment cleared by a process showing zero order kinetics and the second one shows the first order kinetics. To propose the mathematical formula and simulate the alcohol ingestion in the human body, at first some parameters should be defined.

Let X_i denoted the time between the $(i-1)^{\text{th}}$ and i^{th} drink. It was assumed that the sequence of random variables $\{X_i; i \geq 1\}$ were independently and identically distributed with the distribution function $D(\cdot)$ (With probability density function $d(\cdot)$). The adverse effect of alcohol due to the i^{th} drink was random and represented by the random variable Y_i . It should be mentioned that one could correspond to the adverse effects of alcohol with

the well-known blood alcohol content (BAC) (4). However, it should have been done with caution as the model did not take into account the absorption and distribution phases. The sequence of random variables $\{Y_i; i \geq 1\}$ were assumed to be a sequence of independently and identically distributed random variables and independent of the sequence $\{X_i\}$. The effect of the i^{th} drink Y_i was eliminated at a constant rate r (zero order elimination shown in window A) Fig. 1 presents a typical sample path of the model). Thus the time needed to completely eliminate the effects of the i^{th} drink is $Y_i / r = E_i$ say. The adverse effects of alcohol in the system can be taken to be directly proportional to the amount of alcohol consumed. Thus, in this sequel we interchangeably used the random variable E to denote the elimination time of effects of alcohol, adverse effects of alcohol or the amount of alcohol consumed. The sequence $\{E_i; i \geq 1\}$ was therefore a sequence of independently and identically distributed random variables with distribution function $E(\cdot)$ (With probability density function $e(\cdot)$).

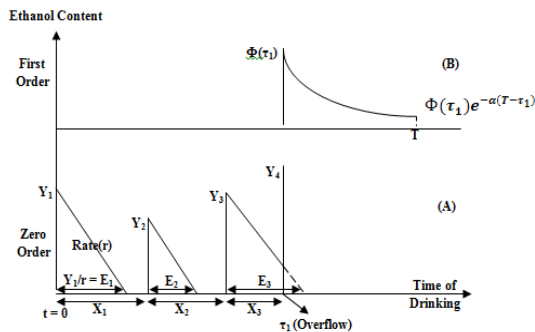


Fig. 1: A typical sample path of the time course of alcohol intake and assimilation covering zero order (A) and first order (B) elimination kinetics. X_i is the time between the $(i-1)^{\text{th}}$ and i^{th} drink; Y_i is the effect of the i^{th} drink; E_i is the elimination time of the i^{th} drink and $\phi(\tau)$ is the random amount added to the alcohol content at time τ .

In the second compartment, when alcohol is ingested, before the adverse effects of alcohol from the previous drink are completely eliminated, there is a spurt in the alcohol concentration in the system. Hence, we called such an event as "overflow" in 4th Y (Fig. 1). Probabilistically, this

event corresponds to the case when $X_i < E_i$. Such events are important from the study of alcohol concentration in the system, as they provide instants of the discontinuities of the alcohol concentration curve with a positive jump leading to the alteration of the elimination kinetics.

Accordingly for modeling purposes we assumed that each overflow event induces cytochrome enzymes leading to first order kinetics. More specifically, an overflow event at time τ results in the addition of a random amount $\phi(\tau)$ to the alcohol content eliminated as a first order process (See window B in Fig. 1). Thus, this addition alcohol content $\phi(\tau)$ at time τ was reduced to $\phi(\tau) e^{-\alpha(T-\tau)}$ at time T where α was the first order elimination rate. If the overflows occur at instants $\tau_1, \tau_2, \dots, \tau_n$ with $\tau_1 < \tau_2 < \dots < \tau_n < T$, then the accumulated alcohol effects due to these jumps at time T was given by $Y(T) = \sum_{i=1}^n \phi(\tau_i) e^{-\alpha(T-\tau_i)}$. τ_i 's are random in nature. Based on study (14) time and cumulative of alcohol usage plays a vital role in relevant investigations. Therefore, in this study we focus on the time between overflows and the cumulative alcohol effects in the system, discussed in the following sections.

In order to gain an understanding about performance of the proposed model, we used simulation for certain special cases and compared the statistical characteristics of the simulated model with that of the analytical results. The motivation for the resort to simulation is twofold: firstly the numerical results give us an insight into the working of the model. Secondly, the simulation procedure gives us the results when the Laplace transforms are not amenable for inversion and numerical inversions are to be employed. It was done through varying the rate of drinking λ . In order to make a comparison between the random and deterministic times of drinking / elimination times, we choose the constant in the deterministic case to be the mean of the corresponding random variable. The choice of the parameter $\mu = 0.125$ used in the three cases was motivated by the following facts: The peak blood alcohol concentration on healthy men given an alcohol dose of 1g/kg is expected to reach around 150 mg/dl

and a mean blood alcohol decrease rate of 18.5 mg/dl/hour (2). Thus the mean time to eliminate the alcohol effects $1/\mu=150/18.5$. The simulation procedure was carried out using MATLAB software and each run was replicated 1000 times and the averages taken.

Time between overflows

In this section we proceed to derive the probability density function of the time between two successive overflows. In order to do so, this time interval O consists of the sum of a random number of intervals of which all the intervals excepting the last one have the property $X>E$ (we have dropped the suffixes for the random variable as they are identically distributed). The last interval is such that $X \leq E$. Thus

$$O = \sum_{i=1}^{N-1} U_i + V_N \tag{2.1}$$

Where the number of terms, N , in the summation is a geometric random variable with probability distribution

$$P(N = n) = pq^{n-1}, \quad n = 1, 2, \dots \quad \text{where } p = P(X \leq E) \text{ and } q = 1-p.$$

The variables $U_i, i = 1, \dots, N-1$ are distributed as X but conditional on $X>E$ whereas V_N has the same distribution but conditional on $X \leq E$. Define the conditional distributions of U_i and V_N respectively as

$$a(t) = P[t < X < t + dt | X > E] = \frac{d(t).E(t)}{P(X>E)} \tag{2.2}$$

and

$$b(t) = P[t < X < t + dt | X \leq E] = \frac{d(t).E(t)}{P(X \leq E)} \tag{2.3}$$

Then we could write the probability density function of the time between two overflows as

$$\begin{aligned} f_0(t) &= P[t < O \leq t + dt] \\ &= \sum_{n=0}^{\infty} P[t < O \leq t + dt | N = n] \cdot P[N = n] \\ &= \sum_{n=0}^{\infty} [a^{(n)} * b(t)] P[X \leq E] (P[X > E])^n \end{aligned} \tag{2.4}$$

Where $a^{(n)} * b(t)$ is the convolution of the n -fold convolution of $a(t)$ with $b(t)$. Taking the Laplace transform of both the sides of (2.4), and simplifying, we obtain

$$L_0^*(s) = \frac{L_{dE}(s)}{1 - L_{dE}(s)} \tag{2.5}$$

Where $L_0(s), L_{dE}(s)$, and $L_{dE}(s)$ are the Laplace transform of the functions $f_0(t), d(t)E(t)$ and $d(t)E(t)$ respectively. $L_0^*(s)$ could be inverted to obtain $f_0(t)$ for specific forms of the functions $d(t)$ and $e(t)$. However, when the inversion of $L_0^*(s)$ is not amenable for analytic expressions one can do it using the algorithm of Abate (15).

The moments of overflow could be obtained using the following formula,

$$\mu'_n = (-1)^n \left. \frac{d^n L_0^*(s)}{ds^n} \right|_{s=0} \tag{2.6}$$

Specifically, the mean time between overflow is obtained as

$$\mu'_1 = \left. \frac{-dL_0^*(s)}{ds} \right|_{s=0} = \frac{E[X]}{P[X \leq E]} \tag{2.7}$$

The variance and higher order moments of the overflow could be obtained using (2.6).

Number of drinks between two overflows

We could obtain the probability distribution of N , the number of drinks, consumed between two overflows by observing that overflow occurs when for the first time a drink is consumed before the completion of the elimination of the effects of the previous drink, formally denoted by $X \leq E$. Thus, the probability distribution of N follows a geometric distribution with

$$P(N = n) = pq^{n-1}, \quad n = 1, 2, \tag{2.8}$$

where

$$q = P(X > E) = \int_0^{\infty} P(X > E | E = t) P(E = t) dt = \int_t^{\infty} \bar{D}(t) e(t) dt \tag{2.9}$$

And

$$p = P(X \leq E) = \int_0^{\infty} P(X \leq E | E = t) P(E = t) dt = \int_0^t D(t) e(t) dt \tag{2.10}$$

Thus the mean and variance of the number of drinks between two overflows were obtained as

$$E(N) = \frac{q}{p} \quad \text{and} \quad \text{Var}(N) = \frac{q}{p^2}.$$

Specific models

For illustration purposes, we assumed the following three specific models for the underlying probability distributions of the model:

Model 1: The subject drinks randomly, so that the time between drinks is exponentially distributed as $d(t) = \lambda e^{-\lambda t}$, $t > 0$.

The amount of alcohol consumed (or the effects of alcohol) in each drink is a constant C so that

$$E(t) = \begin{cases} 0 & t < C \\ 1 & t \geq C \end{cases}$$

The Laplace transform of the density function of the time between overflows given in (2.5), in this case reduces to the following formula. (Derivations are given in Appendix A).

$$L_0^*(s) = 1 - \frac{s}{s + \lambda - \lambda e^{-(s+\lambda)c}}$$

The mean and variance of the overflows are given by

$$E(O) = \frac{1}{\lambda - \lambda e^{-\lambda c}}$$

$$Var(O) = \frac{1 + 2\lambda c e^{-\lambda c}}{(\lambda - \lambda e^{-\lambda c})^2}$$

Finally, the mean and variance for number of drinks between overflows were obtained as

$$E(N) = \frac{1}{1 - e^{-\lambda c}}$$

$$Var(N) = \frac{e^{-\lambda c}}{(1 - e^{-\lambda c})^2}$$

Model 2: The subject drinks at fixed intervals of length C so that

$$D(t) = \begin{cases} 0 & t < C \\ 1 & t \geq C \end{cases}$$

The amount of alcohol consumed is random so that $e(t) = \mu e^{-\mu t}$, $t > 0$.

In this case the statistical characteristics are given by

$$L_0^*(s) = \frac{e^{-(s+\mu)c}}{1 - e^{-sc} + e^{-(s+\mu)c}}$$

$$E(O) = \frac{c}{e^{-\mu c}}$$

$$Var(O) = \frac{c^2(1 - e^{-\mu c})}{e^{-2\mu c}}$$

$$E(N) = \frac{1}{\mu e^{-\mu c}}$$

$$Var(N) = \frac{1 - \mu e^{-\mu c}}{(\mu e^{-\mu c})^2}$$

Model 3: Finally, we assumed that both the time between drinks and the amount of alcohol consumed each time are random with $d(t) = \lambda e^{-\lambda t}$, $t > 0$ and $e(t) = \mu e^{-\mu t}$, $t > 0$.

The statistical characteristics of this model are

$$L_0^*(s) = \frac{\lambda s + \lambda^2}{s^2 + 2\lambda s + \lambda^2 + s\mu}$$

$$E(O) = \frac{\lambda + \mu}{\lambda^2} \tag{2.11}$$

$$Var(O) = \frac{(\lambda + \mu)^2 + 2\mu\lambda}{\lambda^4} \tag{2.12}$$

$$E(N) = \frac{\lambda + \mu}{\lambda}$$

$$Var(N) = \frac{\mu(\lambda + \mu)}{\lambda^2}$$

Accumulated effects of ethanol

The accumulated ethanol effects at time T due to overflows at $\tau_1, \tau_2, \dots, \tau_n$ eliminated by first order kinetics were given by

$$Y(T) = \sum_{i=1}^n \phi(\tau_i) e^{-\alpha(T-\tau_i)} \tag{2.13}$$

Noting that τ_i , the instants of overflow are random, we can write Y(T) as a stochastic integral

$$Y(T) = \int_0^T \phi(\tau) e^{-\alpha(T-\tau)} dN(\tau) \tag{2.14}$$

where

$$dN(\tau) = \begin{cases} 1 & \text{if there is overflow in } (\tau, \tau + d\tau) \\ 0 & \text{if not} \end{cases}$$

Note that the overflows form a renewal process, $E[dN(\tau)] = m(\tau)$ where $m(\tau)$ is the renewal density corresponding to the overflow process. Thus

$$\bar{Y}(T) = E[Y(T)] = \int_0^T E(\phi(\tau)) e^{-\alpha(T-\tau)} m(\tau) d\tau \tag{2.15}$$

Without loss of generality let us choose the constant $E(\phi(\tau)) = 1$. In order to evaluate $E[Y(T)]$ we take Laplace transforms on both sides of (2.15) to get

$$\bar{Y}^*(s) = \frac{m^*(s)}{\alpha + s}$$

where $m^*(s) = \frac{L_0^*(s)}{s(1-L_0^*(s))}$

and $L_0^*(s)$ is the Laplace transform of the overflow density function given in (2.5). Inverting $Y^*(s)$ either analytically if possible or numerically yields $\bar{Y}(\tau)$.

Results

We present below the simulation results of the three models discussed in the previous section. For each model, we consider three different cases

depending on the drinking pattern by classifying the drinker as heavy, normal or sparse. For all the models, the first order elimination rate α is chosen to be 0.1 mg/dl/hour, $E(\phi(\tau)) = 1$ and the time $T=9$. The values in the parentheses in each of the cells in the tables were obtained using the analytical results while the other value in the same cell was obtained using simulated result. Table 1 shows the results when the subject drinks randomly and the time between drinks is exponentially distributed and the amount of alcohol consumed in each drink is a constant.

Table 1: Statistical characteristics of the elimination process for model 1 (drinks are consumed randomly)

$$d(t) = \lambda e^{-\lambda t}, t > 0 \text{ and } E(t) = \begin{cases} 0 & t < C \\ 1 & t \geq C \end{cases} \text{ where } C=1/\mu.$$

Model 1	E(O)	STD(O)	E(N)	STD(N)	E[Y(T)]
Heavy drinker	9.5737	12.4270	1.4259	0.7834	0.8400
$\lambda = 0.150, \mu = 0.125$	(9.5401)	(12.5221)	(1.4310)	(0.7854)	(0.8472)
Normal drinker	12.5576	16.0894	1.5757	0.9607	0.6909
$\lambda = 0.125, \mu = 0.125$	(12.6558)	(16.6738)	(1.5820)	(0.9595)	(0.6980)
Sparse drinker	18.3242	24.0361	1.8232	1.2098	0.5418
$\lambda = 0.100, \mu = 0.125$	(18.1597)	(23.8087)	(1.8160)	(1.2173)	(0.5507)

E (O): mean time between overflows; E (N): mean of the number of drinks between overflows; E[Y(T)]: average of the accumulated effects of alcohol; STD: standard deviation; λ : drinking rate; μ : elimination rate. Values in parenthesis were obtained using the analytical results and the other value in the same cell was obtained by simulation.

Table 2 considers the situation that the subject drinks at fixed intervals of length and the amount of alcohol consumed is random.

Table 2: Statistical characteristics of the elimination process for model 2 (drinks consumed at fixed intervals C)

$$D(t) = \begin{cases} 0 & t < C \\ 1 & t \geq C \end{cases}, t > 0, \text{ where } C=1/\lambda \text{ and } e(t) = \mu e^{-\mu t}, t > 0.$$

Model 2	E(O)	STD(O)	E(N)	STD(N)	E[Y(T)]
Heavy drinker	15.224	11.4229	2.2934	1.7021	0.3449
$\lambda = 0.150, \mu = 0.125$	(15.3398)	(11.5345)	(2.3010)	(1.7302)	(0.3465)
Normal drinker	22.0072	17.3768	2.7192	2.1715	0.3367
$\lambda = 0.125, \mu = 0.125$	(21.7463)	(17.2896)	(2.7183)	(2.1612)	(0.3187)
Sparse drinker	34.7850	29.3204	3.5284	2.9909	0.0000
$\lambda = 0.100, \mu = 0.125$	(34.9034)	(29.4825)	(3.4903)	(2.9482)	(0.0000)

E (O): mean time between overflows; E (N): mean of the number of drinks between overflows; E[Y (T)]: average of the accumulated effects of alcohol; STD: standard deviation; λ : drinking rate; μ : elimination rate. Values in parenthesis were obtained using the analytical results and the other value in the same cell was obtained by simulation.

Table 3: Statistical characteristics of the elimination process for model 3 (time between drinks and the amount alcohol consumed each time are random)

$$d(t) = \lambda e^{-\lambda t}, t > 0 \text{ and } e(t) = \mu e^{-\mu t}, t > 0.$$

Model 3	E(O)	STD(O)	E(N)	STD(N)	E[Y(T)]
Heavy drinker $\lambda = 0.150, \mu = 0.125$	12.1562 (12.2222)	14.8014 (14.9485)	1.8455 (1.8333)	1.2087 (1.2360)	0.6154 (0.6111)
Normal drinker $\lambda = 0.125, \mu = 0.125$	16.1248 (16.0000)	19.9370 (19.5959)	1.9914 (2.0000)	1.3864 (1.4142)	0.4958 (0.4964)
Sparse drinker $\lambda = 0.100, \mu = 0.125$	22.5223 (22.5000)	27.3548 (27.5000)	2.2281 (2.25000)	1.6684 (1.6771)	0.3869 (0.3858)

E (O): mean time between overflows; E (N): mean of the number of drinks between overflows; E[Y (T)]: average of the accumulated effects of alcohol; STD: standard deviation; λ : drinking rate; μ : elimination rate. Values in parenthesis were obtained using the analytical results and the other value in the same cell was obtained by simulation.

Finally, Table 3 contains the results when both the time between drinks and the amount of alcohol consumed each time, are random

Discussions

From the model formulation, as the rate of drinking of alcohol (λ) increases for a given rate of alcohol elimination (μ), the expected time between overflows decreases and reaches to reverse of rate of alcohol elimination ($1/\lambda$). Thus with reduced time between drinking, there is a reduction in the time between overflows, so that ultimately every drink leads to an overflow. On the other hand, as the rate of alcohol elimination increases, for a given rate of drinking of alcohol, the expected time between overflows increases so that overflows do not occur. Furthermore, as the average amount of alcohol in each drink increases, the corresponding time between overflows decreases also mentioned by some studies (16).

From the tables, the mean time between overflows (E[O]) as well as the mean number of drinks between two overflows (E[N]) are decreasing functions of drinking rate (λ). However, the average accumulated effects of ethanol (E[Y(T)]) is an increasing function of drinking rate so that the faster a subject drinks, the more effects of ethanol accumulates in the system.

Another interesting observation can be made in the case of fixed drinking times (Table 2), when the drinking rate is less than the elimination rate,

the times between overflows are sufficiently large, so the effects of alcohol due to first order kinetics do not accumulate at all (E[Y(T)] = 0).

Next, we compare tables 1 and 3 where the only difference is in the time for elimination of the effects of a drink (or the amount of alcohol in a drink). In Table 3 it is random with a mean time of $1/\mu$ while in Table 1 it is deterministic with $C=1/\mu$. The comparison in the accumulated alcohol effects E[Y (T)] for the two cases shows that random amounts of alcohol ingested per drink has a reduced ethanol accumulation in the system as compared to constant amounts of drinking. Similarly, comparing the two tables 1 and 3 for the mean number of drinks consumed in between two overflows, we conclude that there is a significant increase in the number of drinks consumed when the amount of alcohol consumed is random. We also observe that in such a case the overflows are delayed considerably when the amount of alcohol consumed is random. A similar analysis could be carried out by considering the random and deterministic nature of the times of drinking as a queuing system (9), used a stochastic approach to model alcohol ingestion in human bodies. Additionally, the approach of our study can be applied for a study (17) where they developed a pharmacokinetic model and considered a metabolic series approach for the ethyl series.

Conclusion

The paper proposed a new model for the process of ethanol elimination. The salient features of the model were that it accounts for multiple doses as well as zero and first order elimination. The results were able to account for the variations in the times of alcohol intake as well as the amount of alcohol consumed. Being the first stochastic model of such a kind, we do hope that it will throw more light on interpreting experimental data of alcohol abuse. In this regard, there are only three effective model parameters to be estimated namely λ , μ and α (assuming exponential underlying distributions). Given the two moments of the overflows, one can easily estimate as $\hat{\lambda}$ and $\hat{\mu}$ using moment estimators (from equations (2.11) and (2.12)).

The model assumed that overflows occur when alcohol is ingested before the adverse effects of

alcohol from the previous drink are completely eliminated. However, it is eminently possible to have this event occur at the k^{th} drink and k could be random, although the analytical expressions get messier, but simulation is always possible.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Appendix A

$$\begin{aligned}
 L_{d\bar{E}}(s) &= \int_0^{\infty} e^{-st} d(t)\bar{E}(t)dt \\
 &= \int_0^c e^{-st} d(t)\bar{E}(t)dt + \int_c^{\infty} e^{-st} d(t)\bar{E}(t)dt \\
 &= \int_0^c e^{-st} d(t)dt + 0 \\
 &= \int_0^c e^{-st} \lambda^{-\lambda t} dt = \frac{-\lambda}{s + \lambda} (e^{-(s+\lambda)c} - 1) \\
 L_{dE}(s) &= \int_0^{\infty} e^{-st} d(t)E(t)dt \\
 &= \int_0^c e^{-st} d(t)E(t)dt + \int_c^{\infty} e^{-st} d(t)E(t)dt \\
 &= \int_c^{\infty} e^{-st} \lambda^{-\lambda t} dt \\
 &= \int_c^{\infty} \lambda e^{-(s+\lambda)t} dt = \frac{\lambda}{s + \lambda} (e^{-(s+\lambda)c}) \\
 L_0^*(s) &= \frac{L_{d\bar{E}}(s)}{1 - L_{dE}(s)} = \frac{\frac{-\lambda}{s + \lambda} (e^{-(s+\lambda)c} - 1)}{1 - (\frac{\lambda}{s + \lambda} (e^{-(s+\lambda)c}))} = 1 - \frac{s}{s + \lambda - \lambda e^{-(s+\lambda)c}}
 \end{aligned}$$

$$\frac{dL_0^*(s)}{ds} = \frac{-\lambda + (1+sc)\lambda e^{-(s+\lambda)c}}{(s+\lambda - \lambda e^{-(s+\lambda)c})^2}$$

$$E(O) = \left. \frac{dL_0^*(s)}{ds} \right|_{s=0} = \frac{-\lambda + \lambda e^{-\lambda c}}{(\lambda - \lambda e^{-\lambda c})^2} = \frac{1}{\lambda - \lambda e^{-\lambda c}}$$

$$\left. \frac{d^2 L_0^*(s)}{ds^2} \right|_{s=0} = \frac{2(1+\lambda c e^{-\lambda c})}{(\lambda - \lambda e^{-\lambda c})^2}$$

$$Var(O) = \frac{2(1+\lambda c e^{-\lambda c})}{(\lambda - \lambda e^{-\lambda c})^2} - \left(\frac{1}{\lambda - \lambda e^{-\lambda c}} \right)^2 = \frac{1+2\lambda c e^{-\lambda c}}{(\lambda - \lambda e^{-\lambda c})^2}$$

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