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APPLICATION OF QUEUEING THEORY WITH MONTE CARLO SIMULATION TO THE STUDY OF THE INTAKE AND ADVERSE EFFECTS OF ETHANOL

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Abstract — A deterministic approach has so far been used in the modelling of the intake, metabolism, and elimination of ethanol. However, a well-structured deterministic model needs to consider numerous factors, e.g. anatomical structure, metabolic rate, perfusion rates, non-steady-state and steady-state. In the present study, a stochastic approach was used for modelling the study of ethanol because there is a phenomenological analogy between a queueing system and the systems in the body dealing with ethanol. When using queueing theory, both the consumption of ethanol and the removal of the adverse effects associated with its consumption from the body can be random processes; and the requirement for detailed information on the anatomical structure etc. can be minimized. Using queueing theory, estimations can be made with regard to the accumulated adverse effects of ethanol in the body, the time needed to remove the adverse effects etc. Monte Carlo simulation was performed to analyse the drinking of beer and the removal of the adverse effects associated with it, and to show the potential use of queueing theory in the study of ethanol.

INTRODUCTION

Numerous mathematical models have been developed to study the issues related to intake, metabolism and elimination of ethanol (Gullberg, 1990; Johanson, 1991; Smith *et al.*, 1993; George *et al.*, 1995; Lubkin *et al.*, 1996; Pastino *et al.*, 1996, 1997; Wu, 1997*a*,*b*, 1998). The deterministic approach has been used in all of these models; this needs to consider numerous factors, such as anatomical structures, metabolic rate, non-steady-state, steady-state etc. The deterministic approach provides a deeper insight into the study of ethanol, but there is a need for many parameters to be determined in a well-structured model. The determination of these parameters usually requires a huge amount of experimental work and is therefore time-consuming. Because of the uncertainties in the intake, metabolism, and elimination of ethanol, the deterministic approach may face difficulties, for example, in inter-species extrapolation, mathematical modelling, risk assessment, and experimental settings.

However, it is reasonable to consider that the consumption of ethanol is a random process in most real-life cases (Dole and Gentry, 1984; Gill *et al.*, 1986), i.e. ethanol is taken more frequently on unfixed occasions, rather than on fixed ones. Similarly, it is also reasonable to consider that the removal from the body of the adverse effects associated with the consumption of ethanol is a random process, because: (i) the absorption, metabolism, and elimination of ethanol are affected by numerous factors of varying degrees (Seitz and Pöschl, 1997); (ii) a random consumption of ethanol would result in a random beginning of the removal of the adverse effects associated with this consumption; and (iii) the absorption, metabolism, and elimination systems in humans would not be expected to work at the same rate throughout life. When both the consumption of ethanol and the removal of adverse effects associated with it are random processes, the stochastic approach may be helpful in the modelling of these processes, and could provide useful information that cannot be obtained using the deterministic approach.

Queueing theory is a stochastic approach dealing with random input and servicing processes. As

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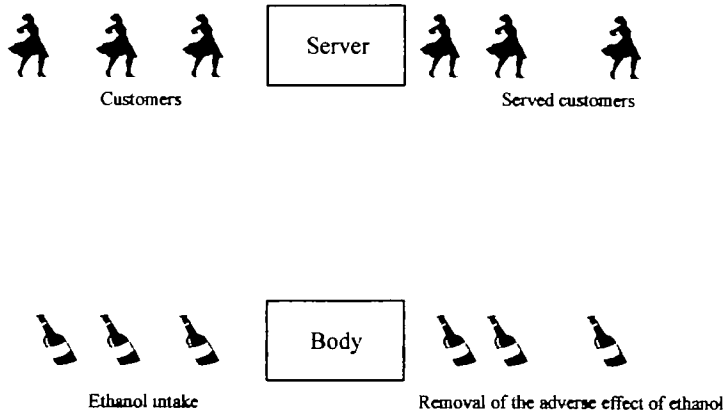

Fig. 1. Analogy between a servicing system and the consumption of ethanol and the removal from the body of the adverse effects associated with such consumption from a queueing theory viewpoint.

there is a phenomenological analogy between a queueing system and the systems in humans in dealing with the intake, metabolism, and elimination of ethanol, the aim of the present study was to apply queueing theory with Monte Carlo simulation to the study of ethanol.

QUEUEING MODELLING

Queueing theory was developed to study the queueing phenomena in commerce, telephone traffic, transportation, business–industrial servicing systems, variable reservoirs etc. (Cooper, 1981; Gross and Harris, 1985). Although there are completely different mechanisms operating in various systems, queueing theory studies their common properties in the queueing process, because the phenomenological laws governing the queueing processes are similar.

Figure 1 shows the simplest comparison between the customer–server servicing system and the consumption of ethanol and removal of adverse effects associated with such consumption in humans from the queueing theory viewpoint. In a commercial servicing system, the server can be a payee, the customers are the individuals wanting to pay, the served customers are the individuals having paid. In a transportation servicing system, the server can be a bridge, the customers are the cars wanting to cross the bridge, the served customers are the cars that crossed the bridge.

In the ethanol study, a 'server' can be defined as the systems in humans, the 'service' is to remove from the body the adverse effects associated with the consumption of ethanol, the accumulated adverse effects of ethanol in the body can be defined as the queue waiting to be 'served', and the 'served' adverse effects are the adverse effects removed from the body. In this manner, a servicing system is analogous to the systems in humans in dealing with the intake, metabolism, and elimination of ethanol from the queueing theory viewpoint.

Although the mathematics underlying queueing theory are quite complicated, the deduced equations and simulation are less complex. As a first stage in the application of queueing theory to the study of ethanol we hope to use the theory to estimate several parameters in the consumption of ethanol and the removal of the adverse effects associated with such consumption, such as (i) the accumulated amounts of adverse effects of ethanol in the body in terms of bottles of beer and (ii) the time needed to remove the adverse effects of ethanol from the body.

In order to determine these parameters, one needs to know the following data: (1) the probability distributions of inter-arrival times, which is the probability distributions of lengths of time between any two equal successive amounts of ethanol consumption and characterizes the process of ethanol intake, i.e. random intake, fixed time intake etc.; (2) the probability distributions of service times, which is the probability

distributions of lengths of time in the removal of equal amount of adverse effects of ethanol from the body, and characterizes the removal of the adverse effects of ethanol, i.e. random removal, constant rate removal etc.; (3) the queue discipline, being the regulation by which an equal amount of adverse effects of ethanol is selected to be removed, i.e. first-come-first-served, last-come-first-served, priority service, random service etc.; and (4) the number of servers, i.e. the body can be defined as one server, or gastrointestinal absorption, gastrointestinal metabolism, and liver metabolism can be defined as three different servers etc. When these data are readily available, the deduced equations can be used, otherwise the simulation would be restored (Gordon, 1978; Cooper, 1981; Hammersley and Handscomb, 1983; Gross and Harris, 1985).

MONTE CARLO SIMULATION ON ETHANOL DRINKING AND REMOVAL

We arbitrarily assume that a person consumes 3 bottles of beer during non-sleeping and non-working time per day and that the body can also remove the adverse effects associated with the consumption of 3 bottles of beer per day. Usually, the occasions when the person drinks would differ from time to time, but there may be several fixed occasions, thus we may consider that the person drinks somewhat pseudo-randomly. Similarly, we may reasonably assume that the removal of the adverse effects associated with the consumption of 3 bottles of beer per day from the body is not at the same rate, i.e. the time needed to remove the adverse effects associated with the consumption of each bottle of beer is different. Clearly, it would be difficult to use the deterministic models to estimate issues such as the magnitude of the adverse effects in terms of how many bottles of beer in the body, and the time needed to remove the adverse effects from the body, because of the random properties of both consumption of beer and removal of the adverse effects. In such a case, the queueing model (the stochastic model) with Monte Carlo simulation can be helpful in making an estimate.

Figure 2 shows the simulation on drinking 21 bottles of beer and removal of the adverse effects associated with the consumption of these 21 bottles of beer in terms of the behaviour predicted by queueing theory. Figure 2A shows the assumed drinks during non-sleeping and non-working time from Monday to Sunday; this panel can be regarded as the arrival of customers to a servicing system. The position of the lower-left corner of each bottle represents the drinking time. Figure 2B shows the accumulated adverse effects in the body in terms of how many bottles of beer; this panel can be regarded as the queue waiting to be served in a servicing system. The position of each bottle is changed along the time course, and the panel constructs the dynamics of the queue. Figure 2C shows the removal of the adverse effects from the body; this panel can be regarded as the service provided by the servicing system. The lower-left corner of each bottle represents the start time to remove the adverse effects in terms of each bottle of beer and the rectangle (from the left line to the right line) is the time needed to remove the adverse effects in terms of each bottle of beer. Figure 2D shows the removal of the adverse effects from the body in terms of each bottle of beer; this panel can be regarded as the served customers who have left the servicing system. The upper-left corner of each bottle represents the finishing time for the removal of the adverse effects in terms of each bottle from the body (all the data are given in the caption to Fig. 2).

For example, when drinking the first bottle of beer at 12:30 on Monday (Fig. 2A), there are no adverse effects of ethanol in the body (Fig. 2B), thus the adverse effects associated with the drink of the first bottle of beer immediately begin to be removed (Fig. 2C). When drinking the second bottle of beer at 21:00 on Monday (Fig. 2A), the systems in the body are busy removing the adverse effects associated with the first bottle of beer (Fig. 2C), thus the adverse effects associated with the second bottle of beer have to wait, and there are the adverse effects in terms of 1 bottle of beer in the queue (Fig. 2B). When drinking the third bottle of beer at 21:30 on Monday (Fig. 2A), the systems in the body are still busy removing the adverse effects associated with the first bottle of beer (Fig. 2C) and the adverse effects in terms of the second bottle of beer are waiting (Fig. 2B), thus the adverse effects associated with the third bottle of beer have to wait, and there are the adverse effects in terms of 2 bottles of beer in the queue (Fig. 2B). When the time reaches 07:20 on Tuesday, the adverse effects associated with the

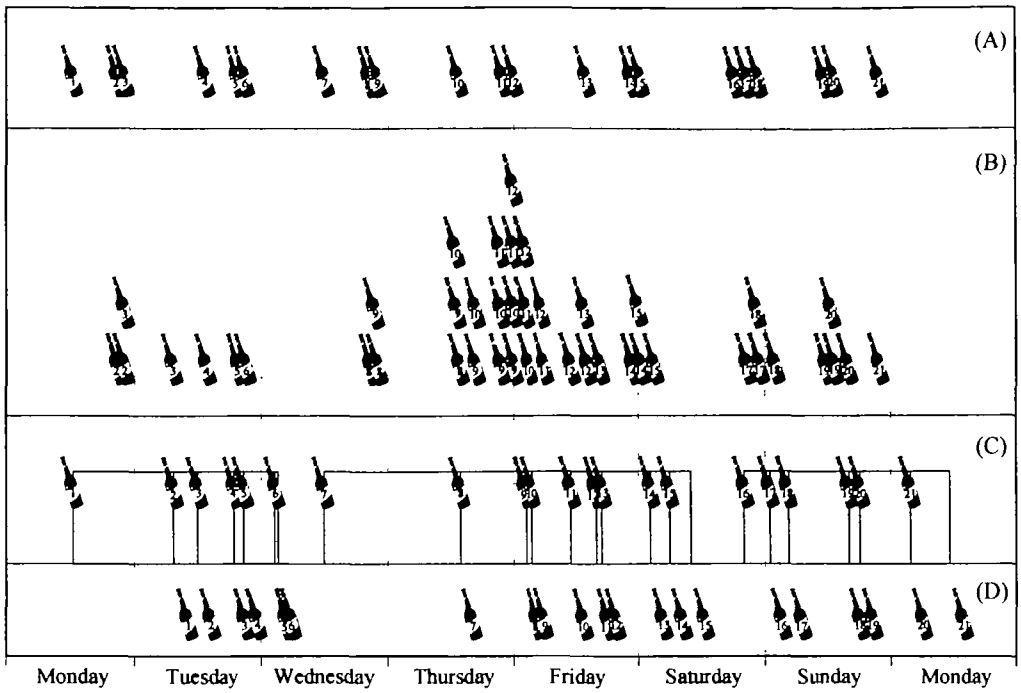

Fig. 2. Simulation of the drinking of 21 bottles of beer and the removal of the adverse effects associated with their intake. (A) The assumed drinking times from Monday to Sunday are 12:30, 21:00, 21:30; 13:06, 20:00, 21:00; 12:00, 20:30, 22:00; 13:30, 22:00, 22:48; 14:00, 23:00, 23:48; 20:00, 21:00, 22:00; 12:00, 13:00, and 21:00. (B) The adverse effects associated with the drinking of bottles of beer accumulated in the body during the second to the 21st bottle of beer. (C) The assumed random lengths of time needed to remove the adverse effects in terms of each bottle of beer are 18.833, 4.473, 7.110, 1.876, 5.841, 0.716, 25.685, 12.769, 1.125, 7.552, 4.872, 1.046, 9.123, 3.781, 3.885, 4.912, 3.527, 11.456, 2.113, 9.652, and 7.622 h. (D) The finishing time for the removal of the adverse effects in terms of each bottle of beer from Tuesday to the following Monday is 07:20, 11:48, 18:55, 20:48; 02:38, 03:21; 13:41; 02:27, 03:35, 11:08, 16:00, 17:03; 02:10, 05:57, 09:50; 00:55, 04:26, 15:54, 18:00; 03:40, and 11:17.

first bottle of beer are removed from the body (Fig. 2D), thus the adverse effects associated with the second bottle of beer immediately begin to be removed (Fig. 2C), and only the adverse effects associated with the third bottle of beer are waiting to be removed (Fig. 2B).

Queueing theory with Monte Carlo simulation further shows: (1) the adverse effects are accumulated to the maximum amount in terms of 4 bottles of beer in the body waiting for removal, in means ± SEM (1.52 ± 1.03 bottles, Fig. 2B); (2) the maximum length of time waiting is 28.45 h (7.87 ± 7.24 h/bottle); (3) the maximum length of time in which the body is not involved in the removal of the adverse effects is 10.16 h (0.89 ± 2.98 h/bottle); (4) the maximum length of time that the adverse effects are in the body is 29.95 h (14.91 ± 7.79 h/bottle); (5) the length of time from the beginning of drinking to the complete removal of the adverse effects associated with the drinking of 21 bottles of beer is 166.78 h (6.95 days); (6) there are about 18.81 h (about 11.28% of 166.78 h) between drinks in which the body is not involved in the removal of the adverse effects; and (7) there are two intervals between drinks in which the body is not involved in the removal of the adverse effects (before the seventh and 17th bottles in Fig. 2C). This simulated example suggests that the body can successfully remove the adverse effects of the consumption of 21 bottles of beer within 166.78 h, the maximum accumulated adverse effects in terms of 4 bottles of beer can result, which may lead to some adverse effects in humans.

Following this example, three other Monte Carlo simulations were performed to further apply queueing theory to ethanol drinking and the removal of its adverse effects. We still assume that a person randomly drinks the average 3 bottles of beer during non-sleeping and non-working time per day for 1 year (1095 bottles of beer).

Example: 10 bottles of beer per day

When the body can remove the average adverse effects associated with the consumption of 10 bottles of beer per day, the simulated results show: (1) the adverse effects can be accumulated to the maximum amount in terms of 2 bottles of beer in the body waiting for removal (0.20 ± 0.54 bottle); (2) the maximum length of time waiting is 15.81 h (0.67 ± 1.74 h/bottle); (3) the maximum length of time in which the body is not involved in the removal of the adverse effects is 29.15 h (5.73 ± 8.41 h/bottle); (4) the maximum length of time that the adverse effects are present in the body is 18.28 h (2.93 ± 2.83 h/bottle); (5) the length of time from the beginning of drinking to the complete removal of the adverse effects associated with the drinking of 1095 bottles of beer is 8742.39 h (364.26 days because the first drink is taken at 20:32 on the first day and the last drink is taken at 23:51 on the 365th day); (6) there are about 6272.94 h (261.37 days, about 71.75% of 364.26 days) between drinks in which the body is not involved in the removal of the adverse effects; and (7) there are 810 intervals between drinks in which the body is not involved in the removal of the adverse effects.

Example: 3 bottles of beer per day

When the body can remove the average adverse effects associated with the consumption of 3 bottles of beer per day, the simulated results show: (1) the adverse effects can be accumulated to the maximum amount in terms of 21 bottles of beer in the body waiting for removal (6.60 ± 5.08 bottles); (2) the maximum length of time waiting is 162.33 h (48.79 ± 39.80 h/bottle); (3) the maximum length of time in which the body is not involved in the removal of the adverse effects is 23.74 h (0.54 ± 2.38 h/bottle); (4) the maximum length of time that the adverse effects are present in the body is 174.47 h (56.31 ± 40.35 h/bottle); (5) the length of time from the beginning of drinking to the complete removal of the adverse effects associated with the drinking of 1095 bottles of beer is 8826.08 h (367.75 days); (6) there are about 593.92 h (24.75 days, about 6.73% of 367.75 days) between drinks in which the body is not involved in the removal of the adverse effects; and (7) there are 91 intervals between drinks in which the body is not involved in the removal of the adverse effects.

Example: 2.5 bottles of beer per day

When the body can remove the average adverse effects associated with the consumption of 2.5 bottles of beer per day, the simulated results show: (1) the adverse effects can be accumulated to the maximum amount in terms of 127 bottles of beer in the body waiting for removal (52.84 ± 38.19 bottles); (2) the maximum length of time waiting is 1208.91 h (487.11 ± 358.36 h/bottle); (3) the maximum length of time in which the body is not involved in the removal of the adverse effects is 11.97 h (0.05 ± 0.68 h/bottle); (4) the maximum length of time that the adverse effects are present in the body is 1222.17 h (496.13 ± 358.72 h/bottle); (5) the length of time from the beginning of drinking to the complete removal of the adverse effects associated with the drinking of 1095 bottles of beer is 9930.84 h (413.78 days); (6) there are about 55.40 h (about 0.56% of 413.78 days) between drinks in which the body is not involved in the removal of the adverse effects; and (7) there are 10 intervals between drinks in which the body is not involved in the removal of adverse effects.

The use of drinking of bottles of beer in the above examples and simulations serves to show the potential applications of queueing theory to ethanol studies; the medical relevance should be considered as marginal. However, it would be of interest to note that: (1) there are always adverse effects accumulated in the body, even though the ability to remove the adverse effects from the body is much larger than the amount of ethanol intake; this is because drinking is concentrated on the non-sleeping and non-working time and the removal of the adverse effects follows drinking; and (2) when the ability of the removal of the adverse effects from the body is less, even slightly less, than the amount of ethanol intake, the adverse effects are increased dramatically in the body.

Table 1. Equations deduced by queueing theory for determination of operating characteristics in the *M/M/*1 queueing model

$L_s = \frac{\lambda}{\mu - \lambda}$	$L_q = \frac{\rho\lambda}{\mu - \lambda}$	$W_s = \frac{1}{\mu - \lambda}$	$W_q = \frac{\rho}{\mu - \lambda}$

In the ethanol study, λ is the parameter used in the Poisson input, i.e. the mean amount of intake of ethanol per time; μ is the parameter used in the negative exponential distributions of service times, i.e. the mean amount of the adverse effects of ethanol removed from the body per time; ρ is the probability of a servicing system being busy and is equal to λ/μ, i.e. the probability of the body being busy removing the adverse effects of ethanol from the body; L_s is the mean number of customers in the queueing system being served and waiting, i.e. the mean amount of the adverse effects of ethanol being removed and waiting to be removed in the body; L_q is the mean number of customers in the queue, i.e. the mean amount of the adverse effects of ethanol waiting to be removed from the body; W_s is the mean length of time that a customer spends in the queueing system including service and waiting time, i.e. the mean length of time that the equal amount of the adverse effects of ethanol spend in the body including removing and waiting time; and W_q is the mean length of time that a customer spends in the queue, i.e. the mean length of time that the amount of the adverse effects of ethanol spend waiting to be removed from the body.

CALCULATIONS USING THE DEDUCED EQUATIONS

The parameters in the queueing process can also be calculated using the deduced equations. The model of ethanol intake, metabolism, and elimination in Fig. 1 can correspond to the simplest model in the queueing theory, i.e. *M/M/*1 model, the single-server model with Poisson input and exponential service defined by Kendell's notation, where *M* is a Markovian process, the first *M* is that the probability distributions of inter-arrival times are the Poisson input, the second *M* is that the probability distributions of service times are the negative exponential distributions, and 1 is the single server, the queue discipline is the first-come-first-served (for the meanings of Poisson input and exponential service, see the Appendix).

In the modelling of the consumption of ethanol and the removal of the adverse effects associated with such consumption, the *M/M/*1 model denotes that: (1) the consumption of ethanol is a random process; (2) the removal from the body of the adverse effects associated with the consumption of ethanol would take an identical length of time for the same amount of adverse effects in terms of each bottle; and (3) the body is one 'server'. Table 1 shows several equations used in the *M/M/*1 model, which are suited at the statistical equilibrium state.

We again use the example of drinking of bottles of beer in Fig. 2 to show the possible use of the equations in Table 1. Although the person consumes 3 bottles of beer during non-sleeping and non-working time and the drinking meets the Poisson input (Appendix), we need to consider the drinking to be 3 bottles per day, we have $\lambda = 3/24 = 0.125$ (bottle/h). The body can remove the adverse effects associated with the consumption of 3 bottles of beer per day; as the length of time of removal meets the negative exponential distributions of service times (Appendix), we have $\mu = 3/24 = 0.125$ (bottle/h). Here we have $\lambda = \mu$, i.e. the arrival rate is equal to the service rate, this is also the case in our second Monte Carlo simulation. In these cases, we cannot use the equations in Table 1. Similarly, when the body can remove the adverse effects associated with the consumption of 2.5 bottles of beer from the body per day, and we have $\mu = 2.5/24 = 0.1042$ (bottle/h) the same is true. Thus we have $\lambda > \mu$, i.e. the arrival rate is larger than the service rate and we still cannot use the deduced equations in Table 1. However, we would expect that the adverse effects of ethanol in the body would increase with drinking because the intake rate is larger than that of removal.

In the first Monte Carlo simulation, the person randomly drinks the average 3 bottles during non-sleeping and non-working time per day, $\lambda = 3/24 = 0.125$ (bottle/h), and the body can remove the adverse effects associated with the consumption of 10 bottles of beer from the body per day, and we have $\mu = 10/24 = 0.4167$ (bottle/h). Then we have $\rho = \lambda/\mu = 0.125/0.4167 = 0.72$, $L_s = \lambda/(\mu - \lambda) = 0.125/(0.4167 - 0.125) = 0.43$ (bottle), $L_q = \rho\lambda/(\mu - \lambda) = 0.72 \times 0.125/(0.4167 - 0.125) = 0.13$ (bottle), $W_s = 1/(\mu - \lambda) = 1/(0.4167 - 0.125) = 3.43$ (h), and $W_q = 0.72/(0.4167 - 0.125) = 1.03$ (h). Part of these results is similar to the simulated results, i.e. 0.13 bottles vs 0.20 ± 0.54 bottles, but other

results are different from the simulated results. This difference is due to the fact that the drinks are randomly distributed throughout the day (00:00 to 24:00) in the calculation using the deduced equations, whereas the drinks are randomly distributed only during the non-sleeping and non-working time in the calculation using Monte Carlo simulation.

From the above calculations, we can see the limitations in the use of the deduced equations, however since the deduced equations are very easy to calculate, they are particularly useful for a preliminary estimation.

GENERAL DISCUSSION AND COMMENTS

In the past, queueing theory has been mainly used in medical management settings (Gupta *et al.*, 1971; Drdkova, 1973; Kohler *et al.*, 1976; Moore, 1977; Scott *et al.*, 1978; Brill and Moon, 1980; Berger *et al.*, 1982; Pratt and Grindon, 1982; Rosenquist, 1987; Naylor *et al.*, 1993; Myasnikova *et al.*, 1996). As the first stage of application of queueing theory to the study of ethanol, the model and examples used in the present paper are quite simple, may have various drawbacks, and may not be suited for the real-life cases. However, a good outcome is possible in the application of queueing theory to the study of ethanol, for example, gastrointestinal and liver metabolism can be modelled as two 'servers', even more 'servers' can be co-opted into the body.

In the present study, we used the customer–server model to analyse the consumption of ethanol and the removal of the adverse effects associated with such consumption. Certainly, other models in queueing theory may be more suitable to the study of ethanol, for example, the model of fluid flowing from a variable reservoir through a bottleneck. The main consideration in choosing the customer–server model is that the number of bottles of beer is the discrete value, and we do not need to consider the non-integer value such as 0.73 bottles of beer. By contrast, if we use the model of fluid flowing from a variable reservoir through a bottleneck, the intake and removal may be the continuous variables, and the intake can be in the form of the bulk arrivals. In the simulation, the discrete data are more easily produced by the Monte Carlo method, and more easily determined as the Poisson process. In fact, it is usual first to consider the discrete cases in classical mechanics and probability theory, and then to consider the continuous cases (Feller, 1968), thus we chose the customer–server model in this study. We also consider that the number of bottles is more easily used in epidemiological studies.

Queueing theory is particularly suited when input and/or service time are random; if they are not, the deterministic approach would be preferred. However, when the understanding of operating mechanisms underlying ethanol intake, metabolism, and elimination is limited, the stochastic approach can be advantageous. Therefore, either the deterministic approach or the stochastic approach have their own advantages and can help each other in modelling in the study of ethanol.

It is worth mentioning that the results obtained using queueing theory sometimes are counter-intuitive as observed by researchers, who originate and use queueing theory intensively. However, this counter-intuitive phenomenon is thought to be due to the fact that the real nature of the scientific phenomenon is not yet fully understood and thus one perceives the results as counter-intuitive (Cooper, 1981).

We have met such counter-intuitive phenomena in the present study. For example, when the removal rate of the adverse effects is reduced from drinking 3 bottles of beer per day to drinking 2.5 bottles of beer per day in the second and third Monte Carlo simulations, the maximum adverse effects dramatically increase by a factor of 5 (21 bottles of beer vs 127 bottles of beer), which is not proportional. According to queueing theory, the magnitude of the accumulated amount of the adverse effects is dependent on the length of time of drinking. Thus when drinking for 0.5 years (183 days, 549 bottles), the maximum amounts of the adverse effects are in terms of 55 and 16 bottles of beer for the removal rates of 2.5 and 3 bottles of beer per day respectively; when drinking for 1.5 years (548 days, 1644 bottles), the maximum amounts of the adverse effects of ethanol are in terms of 181 and 25 bottles for the removal rates of 2.5 and 3 bottles of beer per day (detailed data not shown).

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APPENDIX

(1) The Poisson input is a random input: (i) the arrivals are independent from one another; (ii) in any sufficiently small time-span, at most, only one arrival occurs, the chance of two arrivals at the same time is very small; and (iii) the chance of an arrival between T_1 and T_2 depends on the time length between T_1 and T_2, not on either T_1 or T_2.

The Poisson input is characterized by the parameter of λ in the queueing theory, the parameter of $1/\lambda$ is the mean length of time between two successive arrivals.

(2) The negative exponential distributions of service times are: (i) the servicing system would spend an identical length of time for each customer for the same kind of service; (ii) the successive servicing times are independent from one another; and (iii) the probability of finishing a service is dependent on the length of time between T_1 and T_2, not on either T_1 or T_2. The probability distributions of service times are characterized by the parameter of μ in queueing theory, the parameter of $1/\mu$ is the mean length of time in a servicing system.