Modeling Ethanol Metabolism

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Introduction

This paper attempts to establish a mathematical model to examine the time course of acetaldehyde concentration in the blood following the consumption of ethanol. Ethanol, also known as alcohol, is metabolized through a series of chemical reactions. Acetaldehyde, a toxic compound, is produced when ethanol is oxidized by the enzyme alcohol dehydrogenase. It is responsible for many of the immediate negative effects of alcohol, including increased skin temperature, facial flushing, increased heart rate, lower blood pressure, dry mouth, nausea, and headache, and is further implicated in the development of alcoholic diseases [4]. Building upon a differential equation model for the blood ethanol concentration as a function of time, an additional equation allows for a model of the theoretical acetaldehyde concentration in the blood following the consumption of alcohol.

Modeling Ethanol

Model assumptions

Blood alcohol concentration depends on many factors including number of drinks, gender, body weight, consumption of food, and speed of consumption. A few preliminary assumptions are used to build the model:

- The subject is 75 kg individual with zero alcohol in their stomach at time $t = 0$.
- Only the main mechanism for metabolizing ethanol is observed. This model is treating them as one specific enzyme, as opposed to the numerous different versions that can exist in the body.
- Any interplay between the rates of alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ADLH) is disregarded, and thus treating them as constants.
- Alcohol must directly pass from the stomach into the bloodstream. No further metabolism processes are observed in this model.
- The subject drinks 15 mls of 95% alcohol.

Compartmental model

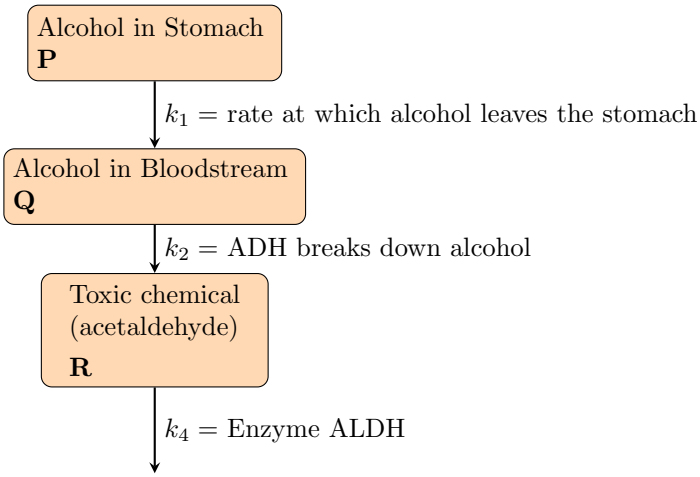

Figure 1: Three compartment model of ethanol metabolizing in human system.

The Compartmental Model shown in Figure 1 describes the transfer of ethanol from the stomach, where it is absorbed into the bloodstream and ultimately gets metabolized.The model functions as a three compartment system i.e. the concentration of ethanol in the stomach, concentration of ethanol in the bloodstream and the concentration of the toxic chemical (acetaldehyde). The ethanol leaves the first compartment and enters the second compartment at a rate k_1 where it is absorbed into the bloodstream. Additionally, from the second compartment the ethanol in the blood is oxidized into acetaldehyde alcohol dehydrogenase(ADH) at a rate k_2. Lastly, from the third compartment the acetaldehyde is broken down by aldehyde dehydrogenase (ADLH) at a rate k_4.

Let P be the concentration of ethanol in the stomach (mg per L), Q be the concentration of ethanol in blood (mg per L), and R be the concentration of acetaldehyde (mg per L). Also, let k_1 be the rate at which ethanol leaves the stomach into the blood stream (per minute), k_2 be the rate at which ADH breaks down ethanol (per minute), k_3 be the rate at which acetaldehyde is produced, and k_4 be the rate at which ADLH breaks down acetaldehyde (per minute).

The word equations for each compartment in any instant of time are given by:

$$\left\{\begin{array}{c}\text{time rate change of}\\ \text{ethanol concentration}\\ \text{in stomach}\end{array}\right\} = \left\{\begin{array}{c}\text{rate that}\\ \text{ethanol enters}\\ \text{the stomach}\end{array}\right\} - \left\{\begin{array}{c}\text{rate that}\\ \text{ethanol leaves}\\ \text{the stomach}\end{array}\right\}$$

$$\left\{\begin{array}{c}\text{time rate change of}\\ \text{ethanol concentration}\\ \text{in the bloodstream}\end{array}\right\} = \left\{\begin{array}{c}\text{rate that ethanol}\\ \text{enters the}\\ \text{bloodstream}\end{array}\right\} - \left\{\begin{array}{c}\text{rate that ethanol}\\ \text{leaves the}\\ \text{bloodstream}\end{array}\right\}$$

$$\left\{\begin{array}{c}\text{time rate change of}\\ \text{concentration of}\\ \text{acetaldehyde in}\\ \text{the bloodstream}\end{array}\right\} = \left\{\begin{array}{c}\text{rate at which}\\ \text{acetaldehyde is}\\ \text{produced by}\\ \text{oxidizing ethanol}\end{array}\right\} - \left\{\begin{array}{c}\text{rate at which}\\ \text{acetaldehyde is broken}\\ \text{down by ADLH}\end{array}\right\}$$

Formulating the differential equations

At time $t = 0$ the initial amount of ethanol in the stomach is zero since the subject has not yet ingested the assumed 15 mls of 95% alcohol, thus we have $P(0) = 0$. The rate of change of ethanol present in the stomach is given by :

$$\frac{dP}{dt} = -k_1 P, \quad P(0) = 0 \tag{1}$$

where k_1 is the rate constant or constant of proportionality.

At time $t = 0$ the initial amount of ethanol in the bloodstream is zero, thus we have $Q(0) = 0$ then rate of change of ethanol in the bloodstream is given by:

$$\frac{dQ}{dt} = k_1 P - k_2 Q, \quad Q(0) = 0 \tag{2}$$

where k_2 is another rate constant or constant of proportionality.

The equation describing the behavior of the rate of change of the toxic chemical, acetaldehyde, can be written as :

$$\frac{dR}{dt} = k_3 Q - k_4 R, \quad R(0) = 0 \tag{3}$$

where $R(0) = 0$ is the initial amount of toxic chemical in the bloodstream and k_3 and k_4 are the rate constants or constants of proportionality.

Solving the differential equations

To understand the behavior of the following model we start by solving Eq.(1)

$$\frac{dP}{dt} = -k_1 P$$

integrating both the sides and separating the variables we get

$$\frac{dP}{P} = -k_1 dt \Rightarrow \int \frac{dP}{P} = \int -k_1 dt \Rightarrow ln|P| = -k_1 t + C_1 \Rightarrow e^{ln|P|} = e^{-k_1 t + C_1}$$

$$\boxed{\Rightarrow P(t) = C_2 e^{-k_1 t}} \qquad \text{where} \quad e^{C_1} = C_2 \tag{4}$$

Substituting Eq.(4) in Eq.(2) we get

$$\frac{dQ}{dt} = k_1 P - k_2 Q = k_1 C_2 e^{-kt} - k_2 Q$$

rearranging and hence integrating the first order linear differential equation :

$$\frac{dQ}{dt} + k_2 Q = k_1 C_2 e^{-kt}$$

Note, the integrating factor $= e^{\int k_2 \, dt} = e^{k_2 t}$

$$\Rightarrow Q e^{k_2 t} = \int k_1 C_2 e^{-k_1 t} e^{k_2 t} \, dt = k_1 C_2 \int e^{-k_1 t} e^{k_2 t} \, dt = k_1 C_2 \int e^{(k_2 - k_1) t} \, dt$$

$$\Rightarrow Q e^{k_2 t} = \frac{k_1 C_2}{k_2 - k_1} e^{(k_2 - k_1) t} + C_3$$

$$\boxed{\Rightarrow Q(t) = \frac{k_1 C_2}{k_2 - k_1} e^{-k_1 t} + C_3 e^{-k_2 t}} \tag{5}$$

Finally substituting Eq.(5) in Eq.(3) we get

$$\Rightarrow \frac{dR}{dt} = k_3 \left(\frac{C_2 k_1}{k_2 - k_1} (e^{-k_1 t}) + C_3 e^{-k_2 t} \right) - k_4 R$$

rearranging and hence integrating the first order linear differential equation :

$$\Rightarrow \frac{dR}{dt} + k_4 R = \frac{k_3 C_2 k_1}{k_2 - k_1}(e^{-k_1 t}) + k_3 C_3 e^{-k_2 t}$$

Note, the integrating factor $= e^{\int k_4\, dt} = e^{k_4 t}$

$$\Rightarrow R e^{k_4 t} = \frac{k_3 C_2 k_1}{k_2 - k_1} \int e^{-k_1 t + k_4 t} dt + k_3 C_3 \int e^{-k_2 t + k_4 t} dt$$

$$\Rightarrow R e^{k_4 t} = \frac{k_1 k_3 C_2}{(k_2 - k1)(k_4 - k_1)} e^{(k_4 - k_1)t} + \frac{k_3 C_3}{k_4 - k_2} e^{k_4 - k_2} t + C_4$$

$$\boxed{\Rightarrow R(t) = \frac{k_1 k_3 C_2}{(k_2 - k1)(k_4 - k_1)} e^{-k_1 t} + \frac{k_3 C_3}{k_4 - k_2} e^{-k_2 t} + C_4 e^{-k_4 t}} \tag{6}$$

Numerical solution

Real world data is used to find the estimates for the values of each of the constants. The values for k_1 and k_2 from the table presented in "Blood Alcohol Content" [6] were observed to be as $k_1 = 0.109456$ and $k_2 = 0.017727$. Then using these k_1 and k_2 values, C_2 is calculated as 245.8769.

Next, by substituting these constants in Eq.(5) for initial condition $Q(0) = 0$, C_3 is calculated as 293.3936.

To find k_3, consider the balanced chemical equation below, which shows the oxidation of ethanol into acetaldehyde [2]. The equation given as:

$$CH_3CH_2OH + NAD^+ \rightarrow CH_3CHO + NADH + H^+$$

The inference that can be drawn from the equation above is that one molecule of ethanol becomes one molecule of acetaldehyde. Thus, k_2 and k_3 have a **1:1** relationship and are considered to be equal.

Substituting all the constants in Eq.(6) for initial condition $R(0) = 0$, the equation simplifies to:

$$C_4 = \frac{5.200988}{k_4 - 0.109456} - \frac{5.200988}{k_4 - 0.017727}$$

Putting all the values for $C_2, C_3, C_4, k_1, k_2, k_3$ in Eq.(6), with C_4 as a function of k_4, we get:

$$\boxed{R(t)=\frac{-5.200988}{k_4-0.109456}e^{-0.109456t}+\frac{5.200988}{k_4-0.017727}e^{-0.017727t}+\left(\frac{5.200988}{k_4-0.109456}-\frac{5.200988}{k_4-0.017727}\right)e^{-k_4t}}$$

By selecting various values of k_4, this equation can be used to model blood acetaldehyde concentration in a number of scenarios.

Interpretation of parameters

Case 1

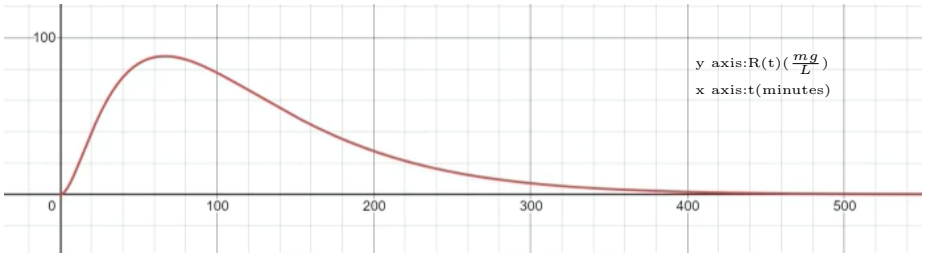

Figure 2: Graph when $k_4 = 0.018$(k_2 and k_4 are approximately equal- paper [6] says that maximal capacities of ADH and ALDH are similar)

According to the graph, Figure 2: the blood acetaldehyde concentration in the average person,with normally functioning ALDH peaks after an hour of consuming 15ml of 95% ethanol. It then drops relatively quickly with no noticeable level after 6.5 hours.

Case 2

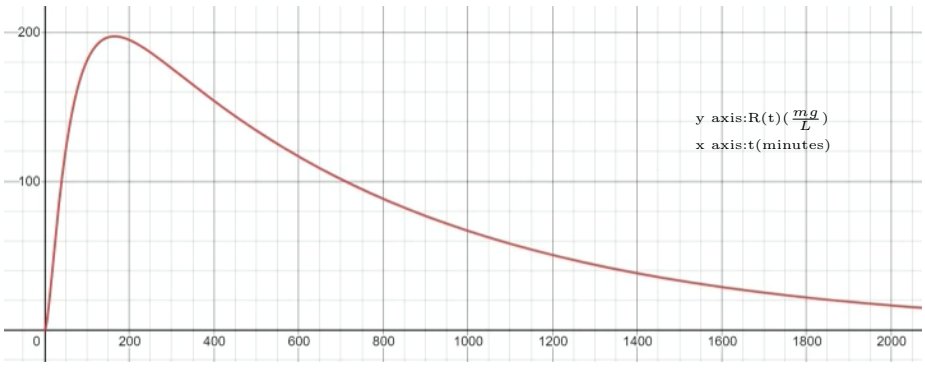

*Figure 3 : Graph when $k_4 = 0.0014$ (this is for the people with the ALDH*2*2 gene whose ALDH works at about 8% of the normal capacity)*

Those with a mutation of ALDH2 gene, ALDH*2*2, have ALDH that works at approximately 8% of its usual capacity. This trait is present in approximately 50% of the Taiwanese, Han Chinese and Japanese populations [10]. In the graph, Figure 3, k_4 is 8% of its usual level. Through observation it is noticed that the blood acetaldehyde concentration reaches its maximum effect in the body after two hours of consumption, but it declines at a much slower rate because of ALDH*2*2's relative ineffectiveness.

Case 3

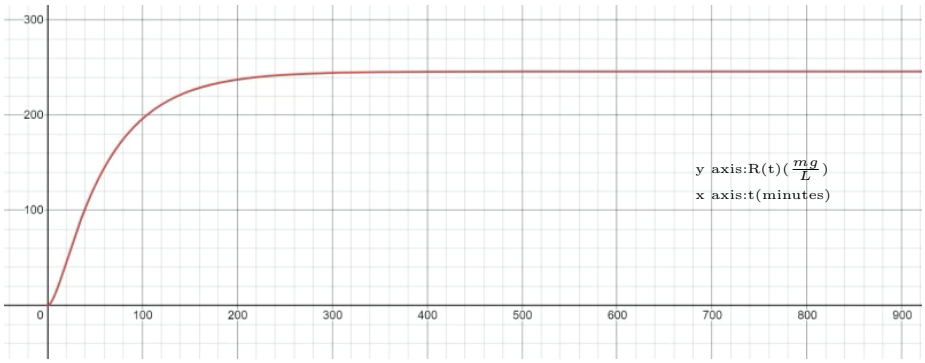

Figure 4 : Graph when k_4=0 (Case where people take a drug that suppresses the action of ADLH)

Finally, one form of treatment for alcoholism is to take Disulfiram, which suppresses the activity of ALDH and magnifies the negative physiological effects. Taking Disulfiram reduces the value of k_4 to zero. When this happens, the acetaldehyde content in the blood peaks after about an hour and remains stable. This will cause an individual who normally tolerates alcohol well to experience negative effects shortly after its consumption. The idea is that this will make drinking so unpleasant that it compels one to quit drinking alcohol altogether [5].

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