Enzyme Simulation and Ethanol Metabolism*

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Abstract— **The breakdown of ethanol, the active substance in alcohol, is tightly regulated by the body, yet alcohol intoxication occurs in thousands of Americans annually. Many factors contribute to the concentration of ethanol in the bloodstream and the tolerance an individual has, including body size, previous drinking experience, and liver functionality. We created a model that estimates both the blood alcohol concentration and the concentration of acetaldehyde (the toxic intermediate during catabolism) in the liver over time for an average person. From the literature, we derived ordinary differential equations that govern the absorption of ethanol in the body and extended it with the metabolic enzyme mechanisms. We also altered the parameters of our system in order to demonstrate the effects of Asian flush. Our model was able to accurately describe the clearance time of ethanol, but was unable to capture the magnitude of concentrations.**

Clinical relevance— **With some improvements and personalization, our model would be able to quantitatively describe the effects of alcohol consumption without requiring a subject to drink alcohol. Liver damage can also be estimated with the acetaldehyde build-up predicted by the model.**

I. INTRODUCTION

Alcohol is commonly used as a commercially-available recreational drug. According to the 2019 National Survey on Drug Use (NSDUH), around 54.9 percent of people ages 18 and older reported drinking and 25.8 percent of adults reported binge drinking in the past month [1]. The Centers for Disease Control and Prevention (CDC) reported an average of 6 deaths per day from direct alcohol poisoning in the United States from 2010 to 2012, which was caused by drinking large quantities of alcohol within a short period of time, shutting down critical areas of the brain [2]. As such, being able to predict safe levels of alcohol consumption could prove to be a useful tool for heavy drinkers and healthcare professionals in order to prevent alcohol-related deaths.

More than 90% of the body's consumed ethanol is metabolized into acetaldehyde and acetic acid [3]. Ethanol is metabolized in the liver through three enzymatic pathways, and the primary pathway for ethanol breakdown is regulated by alcohol dehydrogenase (ADH) [3]. Alcohol dehydrogenase (ADH) facilitates the conversion of ethanol into acetaldehyde, while aldehyde dehydrogenase (ALDH) facilitates the conversion of acetaldehyde into acetic acid. The intermediate product, acetaldehyde, is a toxic metabolite that promotes adduct formation, which facilitates genetic mutation by impairing proteins and damaging DNA [4]. Acetaldehyde can also cause a host of other bodily responses by stimulating the release of adrenaline and norepinephrine in the brain and increasing the amount of histamine and bradykinin produced in other cells, resulting in vasodilation, bronchoconstriction, facial flushing, faster heart and breathing rates, and headaches [5]. As a result, acetaldehyde is the main chemical involved in alcohol poisoning and liver damage.

Our study also examines the "Asian flush" phenomenon, which disproportionately affects patients with Asian heritage. Compared to patients who do not display the Asian flush syndrome, these patients quickly experience redness in the face after consumption of a few drinks. Individuals who suffer from Asian flush generally lack a functional aldehyde dehydrogenase 2 (ALDH2) enzyme, which is the dominant ALDH enzyme involved in breaking down acetaldehyde [6]. The absence of functional ALDH2 means that these patients rely on cytosolic ALDH and ALDH1, which are much less efficient; the Michaelis-Menten constant (K_M) has been estimated to be 900 times higher for these other isoforms [7]. Consequently, acetaldehyde accumulates rapidly in patients who suffer from Asian flush.

II. METHODS

A. Physiological Model

The physiological model of ethanol metabolism is shown in Figure 1. First, alcohol enters the stomach and small intestine via oral input. Next, ethanol will be absorbed into the bloodstream before diffusing into other organs. Blood flow in the hepatic artery and portal veins enables alcohol diffusion into the liver, and blood flow in the renal arteries allows alcohol to diffuse into the kidneys. Body cells surrounding the vasculature also effectively have a capacitive effect by storing ethanol without processing any significant amount. To account for this, we model diffusion between the bloodstream and the liver, kidneys, and body cells as bidirectional; the rate of diffusion depends on the concentration gradient between two interfacing compartments. Ultimately, about 95% of the ethanol will be eliminated by the liver, and 5% of the ethanol will be eliminated by the kidneys [8].

B. Key Assumptions

We make the following assumptions with our model.

- The fluid volume of the alcohol consumed is negligible since the volume of fluid in the body is much greater. Our input only takes the raw ethanol content; we do not account for the type of alcohol.

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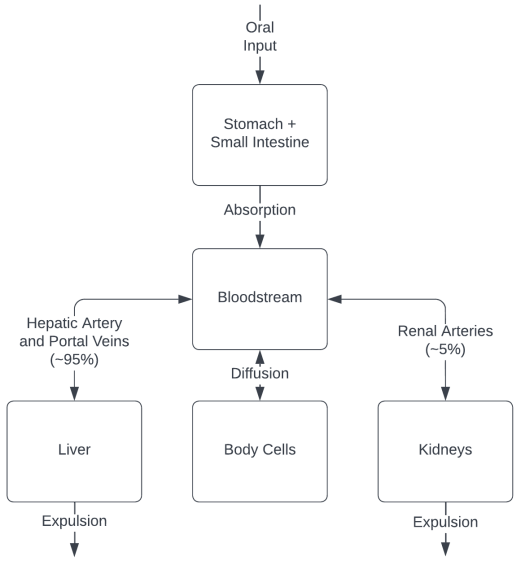

Fig. 1. Physiological diagram of alcohol metabolism.

- Alcohol consumed reaches the stomach and small intestine instantaneously.
- Ethanol diffuses unidirectionally from the stomach and small intestine into the bloodstream.
- The elimination of ethanol through breathing and sweating is negligible compared to the ethanol eliminated by the liver and kidney.
- Other alcohol decomposition reactions outside of the liver are negligible.
- Urination occurs at a constant rate.
- Acetaldehyde in the liver does not diffuse into the bloodstream.

C. Mathematical Model

Our model takes into account: (1) the oral alcohol input, (2) absorption by the bloodstream, (3) ethanol diffusion into the organs and cells, (4) ethanol expulsion via urination, and (5) Michaelis-Menten enzyme kinetics for ADH and ALDH. The system of ordinary differential equations is given below.

$$\frac{dA}{dt} = \frac{I}{V_{\text{SSI}}} - k_{AB}A \tag{1}$$

$$\frac{dB}{dt} = \frac{V_{\text{SSI}}}{V_{\text{blood}}}k_{AB}A - k_{BC}(B-C) - k_{BD}(B-D) - k_{BE}(B-E) \tag{2}$$

$$\frac{dC}{dt} = \frac{V_{\text{blood}}}{V_{\text{cells}}}k_{BC}(B-C) \tag{3}$$

$$\frac{dD}{dt} = \frac{V_{\text{blood}}}{V_{\text{kidneys}}}k_{BD}(B-D) - \frac{Q_{out}}{V_{\text{kidneys}}}D \tag{4}$$

$$\frac{dE}{dt} = \frac{V_{\text{blood}}}{V_{\text{liver}}}k_{BE}(B-E) - \frac{V_{max,1}E}{K_{M,1}+E} \tag{5}$$

$$\frac{dF}{dt} = \frac{V_{max,1}E}{K_{M,1}+E} - \frac{V_{max,2}F}{K_{M,2}+F} \tag{6}$$

The V_i constants refer to the fluid volume of compartment i, k_{ij} represents the diffusion rate constant between i and j, Q_{out} gives the rate at which urine is expelled, and the $V_{max,i}$ and $K_{M,i}$ parameters refer to the Michaelis-Menten kinetics of ADH ($i = 1$) and ALDH ($i = 2$). Table I shows what each variable represents.

TABLE I
VARIABLES USED

Simplified Name	Variable
A	$[\text{EtOH}]_{\text{SSI}}$
B	$[\text{EtOH}]_{\text{blood}}$
C	$[\text{EtOH}]_{\text{cells}}$
D	$[\text{EtOH}]_{\text{kidneys}}$
E	$[\text{EtOH}]_{\text{liver}}$
F	$[\text{MeCHO}]_{\text{liver}}$

The consensus for the rate constants and Michaelis-Menten reaction parameters is weak in the literature [9-15]. Different authors sometimes provided values varying by several orders of magnitude, especially for the enzyme kinetics. We took a rough average of the values from literature for our model (Table II).

TABLE II
CONSTANT VALUES USED

Constant	Value
V_{SSI}	2.4 L
V_{blood}	5.28 L
V_{cells}	31.83 L
V_{kidneys}	0.21 L
V_{liver}	1.08 L
k_{AB}	0.083 min^{-1}
k_{BC}	0.003 min^{-1}
k_{BD}	0.005 min^{-1}
k_{BE}	0.100 min^{-1}
Q_{out}	2 L day^{-1}
$V_{max,1}$	3.9 mmol min^{-1}
$K_{M,1}$	0.4 mM
$V_{max,2}$	4.05 mmol min^{-1}
$K_{M,2}$	1.2 μM

D. Simulink Implementation

The Simulink model is shown in Figure 2.

E. Linearization and Laplace Transform

Our system of ODEs is mostly linear; only the enzyme kinetics are nonlinear. To get the transfer function, we will first linearize around the equilibrium point: just the steady-state $A = B = C = D = E = F = 0$ exists. Doing so yields the transfer functions

$$\frac{\tilde{B}}{\tilde{I}} = \frac{0.0157(s+10.239)(s+0.139)(s+5.53\times10^{-4})}{(s+10.244)(s+0.153)(s+0.090)(s+0.083)(s+3.58\times10^{-6})} \tag{7}$$

$$\frac{\tilde{E}}{\tilde{I}} = \frac{0.0077(s+0.139)(s+5.53\times10^{-4})}{(s+10.244)(s+0.153)(s+0.090)(s+0.083)(s+3.58\times10^{-6})} \tag{8}$$

$$\frac{\tilde{F}}{\tilde{I}} = \frac{0.0747(s+0.139)(s+5.53\times10^{-4})}{(s+3375)(s+10.244)(s+0.153)(s+0.090)(s+0.083)(s+3.58\times10^{-6})}. \tag{9}$$

Since all the poles are negative, this linearized system is stable. However, it will not mimic the nonlinear behavior

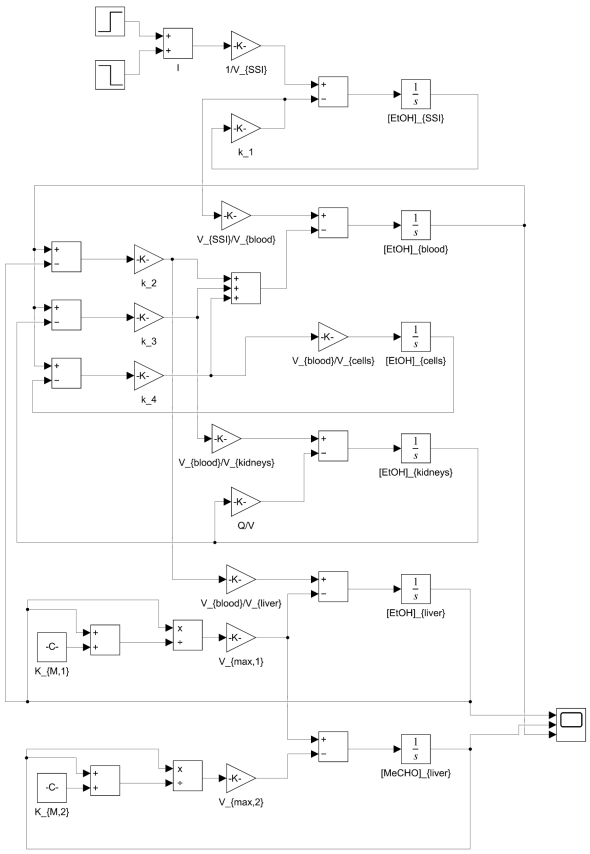

Fig. 2. Simulink model.

well because the linearization is inaccurate for most of the operating area. The Michaelis-Menten constant K_M is rather small; our concentrations of ethanol and acetaldehyde are usually much higher. While the enzyme reaction rate levels off for high concentrations (similar to zero-order kinetics for sufficiently high substrate concentrations), the linearization predicts a linear increase, thus making its error significantly large.

We have also tried linearizing around non-steady-state operating points (where $\overline{E}$ and $\overline{F}$ are 2, 10, or 100 times K_M in order to land in the asymptotic regime). However, in all these cases, the new transfer function has a positive pole, thus making the linearized system unstable and even more unusable.

III. RESULTS

A. Full Nonlinear Model

Figure 3 gives the Simulink simulation results of blood ethanol concentration, liver ethanol concentration, and liver acetaldehyde concentration of healthy individuals after ingesting one standard drink (same as the ethanol content in a 12-ounce can of beer, or 14 grams). The red curve in Figure 3 shows the simulation result of blood ethanol concentration over time, and the shape of the curve is similar to the results from literature. Additionally, the clearance time (when the blood alcohol concentration reaches zero) is about two hours, matching the expected outcome. However, our results'

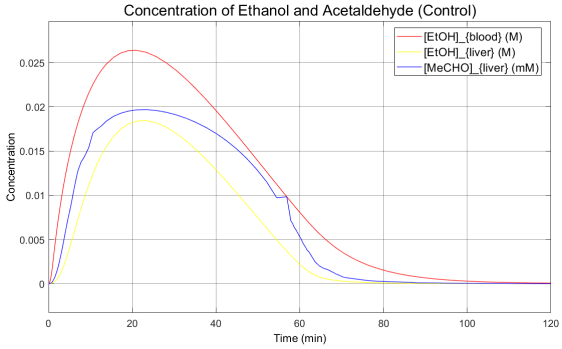

Fig. 3. Simulation results for 1 standard drink. The red curve shows the ethanol concentration in the blood, the yellow curve shows the ethanol concentration in the liver, and the blue curve shows the acetaldehyde concentration in the liver.

amplitude is about 4-7 times higher than what is observed in humans [16].

Figure 4 presents the results of the linearized model. As explained in the methods, the linearization of the Michaelis–Menten equation has a limited operation interval near zero. The enzyme reaction rate was overestimated, causing the ethanol and acetaldehyde to seem to be processed much faster; the ethanol and acetaldehyde concentrations are significantly lower than the ones in reality. However, the peak magnitude of the blood alcohol concentration did not change much. This is due to the fact that only the Michaelis-Menten kinetics required linearization, and no enzyme reaction occurs in the blood. Thus, the transfer function for the blood concentration is relatively accurate to the nonlinear model.

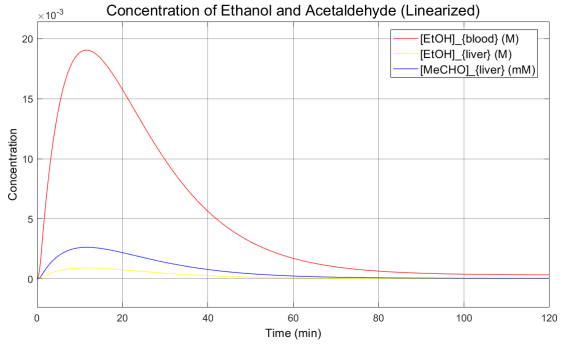

Fig. 4. Simulation results for 1 standard drink with the linearized model. The red curve shows the ethanol concentration in the blood, the yellow curve shows the ethanol concentration in the liver, and the blue curve shows the acetaldehyde concentration in the liver.

Individuals with Asian flush syndrome have a deficiency in ALDH2—the primary enzyme in the human body that processes acetaldehyde to acetate. To model ethanol metabolism in individuals with Asian flush, we increased the Michaelis-Menten constant $K_{M,2}$ by 900-fold, as suggested by literature [7]. Figure 5 shows the metabolism of ethanol and acetaldehyde accumulation in Asian flush after the same alcohol intake. The blue curve indicates that the acetaldehyde concentration increased by a magnitude of about 500 (note that the scale is now molar instead of millimolar) and maintained a relatively high concentration for a long period

of time. Also, the ethanol concentration curves have minimal change from the control, which indicates that people with Asian flush syndrome are still able to convert ethanol to acetaldehyde.

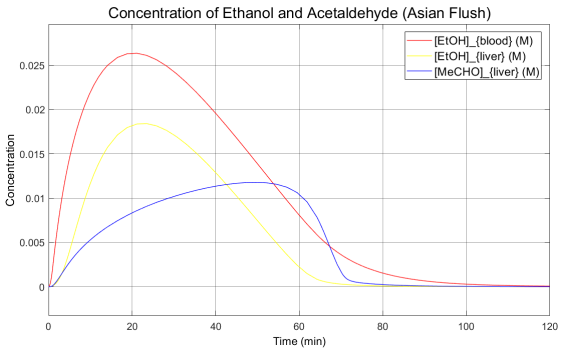

Fig. 5. Simulation results for 1 standard drink for Asian flush syndrome. The red curve shows the ethanol concentration in the blood, the yellow curve shows the ethanol concentration in the liver, and the blue curve shows the acetaldehyde concentration in the liver.

IV. CONCLUSIONS

The model utilizes a reductionist approach to analyzing human alcohol metabolism by simplifying the model based on the assumptions discussed earlier. One limitation of the reductionist approach is that it idealizes and simplifies complex biological systems. For example, the model assumes that there is no excretion of alcohol through breath and sweat since the amount of alcohol excreted through breath and sweat is relatively insignificant in comparison to the amount excreted through urine and digested by enzymes. We are unsure why the magnitude is so inaccurate—it could be due to the rate constants used, or we may also be missing some unknown, critical aspect of the physiological system due to our simplifications.

Another limitation of this model is that rate constants, such as the absorption rate of alcohol, are assumed to be constants. In reality, these rate constants vary significantly from person to person; even for an individual, the rate constants might change due to changes in drinking behaviors or disease development. To address this, the rate constant can be modified to suit personalized needs.

Despite the limitations, this model examines multiple physiological aspects of ethanol metabolism, contributing to the quantitative understanding of how the body responds to alcohol. First, the model may be applied to describe the ethanol metabolism for both healthy individuals and individuals with Asian flush syndrome, which could contribute to the future study of targets for treatment or amelioration of Asian flush. The model's constants can also be modified to display the effects of another clinical disorder relating to alcohol breakdown. Second, by generally summarizing the alcohol metabolism pathway, the model allows for the simulation of pathological behavior after alcohol intake, which supports the quantitative understanding of ethanol metabolism. Third, using a mathematical model for modeling ethanol metabolism results in lower human risk and maintains a high ethical value since the model is based on existing data and does not require volunteers to drink alcohol and get intoxicated. To get a personalized model, a subject would only have to drink alcohol once, and the constants could be calculated based on the bodily measurements taken afterward. Once those constants are obtained, the model could calculate the body's response to a wide range of alcohol intakes, providing an informative basis for the patient and their physician.

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