Enzyme Simulation and Ethanol Metabolism

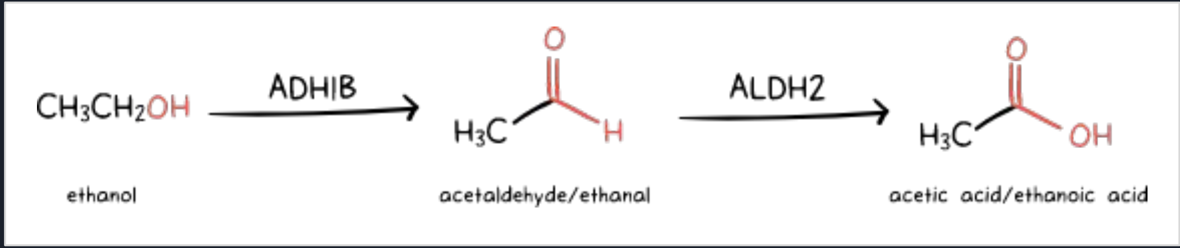
By Celine Lee, Yufei Gao, Jeffrey Liu, Lingbin Wu, Yueshan Liang

Background

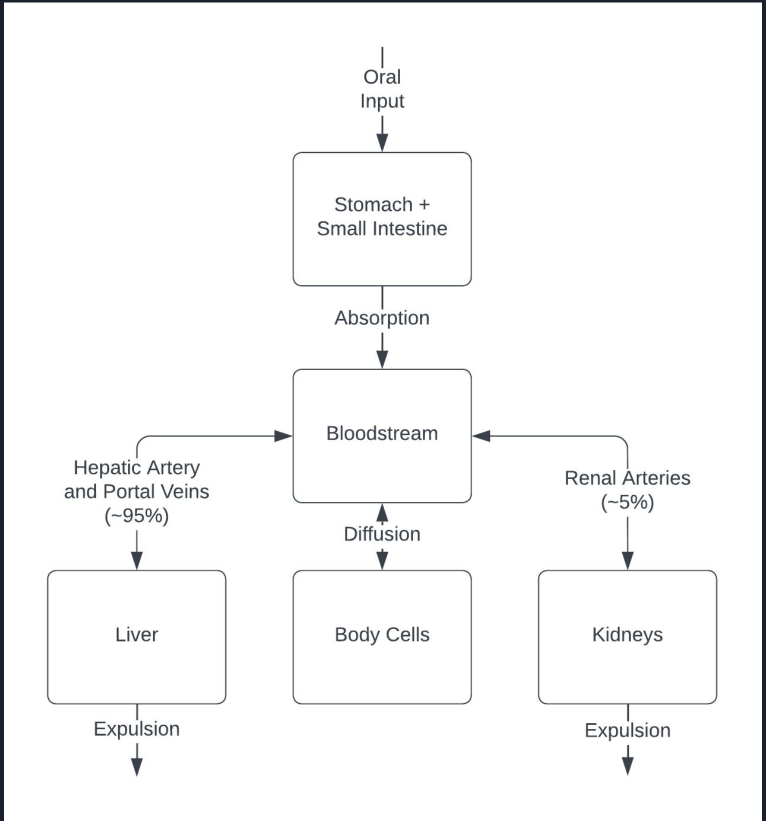
- Alcohol is commonly used
  - 54.9% of adults report drinking in the past month
  - 25.8% of adults report binge drinking within the last month
- Alcohol poisoning causes 6 deaths/day in the US
- Each person’s response to alcohol is highly individualized
  - Try to quantify the differences
  - See the effect of treatments

Background (Continued)

- Ethanol metabolism in the body
  - Converts to acetaldehyde by alcohol dehydrogenase (ADH)
  - Later converts to acetic acid by aldehyde dehydrogenase (ALDH)
- Asian flush



Physiology



- Assumptions:

- Ignore other reactions happening outside of liver
- Not accounting the excretion of alcohol in breath and sweat

Equations (Components)

1. Oral input:

$$\frac{d[\mathrm{EtOH}]_{\mathrm{SSI}}}{dt} = \frac{I}{V_{\mathrm{SSI}}}$$

2. Absorption:

$$\frac{d[\mathrm{EtOH}]_{\mathrm{SSI}}}{dt} = -k_1[\mathrm{EtOH}]_{\mathrm{SSI}}$$

$$\frac{d[\mathrm{EtOH}]_{\mathrm{blood}}}{dt} = \frac{V_{\mathrm{SSI}}}{V_{\mathrm{blood}}}k_1[\mathrm{EtOH}]_{\mathrm{SSI}}$$

3. Diffusion into liver:

$$\frac{d[\mathrm{EtOH}]_{\mathrm{blood}}}{dt} = -k_2([\mathrm{EtOH}]_{\mathrm{blood}} - [\mathrm{EtOH}]_{\mathrm{liver}})$$

$$\frac{d[\mathrm{EtOH}]_{\mathrm{liver}}}{dt} = \frac{V_{\mathrm{blood}}}{V_{\mathrm{liver}}}k_2([\mathrm{EtOH}]_{\mathrm{blood}} - [\mathrm{EtOH}]_{\mathrm{liver}})$$

4. Diffusion into kidneys:

$$\frac{d[\mathrm{EtOH}]_{\mathrm{blood}}}{dt} = -k_3([\mathrm{EtOH}]_{\mathrm{blood}} - [\mathrm{EtOH}]_{\mathrm{kidneys}})$$

$$\frac{d[\mathrm{EtOH}]_{\mathrm{kidneys}}}{dt} = \frac{V_{\mathrm{blood}}}{V_{\mathrm{kidneys}}}k_3([\mathrm{EtOH}]_{\mathrm{blood}} - [\mathrm{EtOH}]_{\mathrm{kidneys}})$$

5. Diffusion into cells:

$$\frac{d[\mathrm{EtOH}]_{\mathrm{blood}}}{dt} = -k_4([\mathrm{EtOH}]_{\mathrm{blood}} - [\mathrm{EtOH}]_{\mathrm{cells}})$$

$$\frac{d[\mathrm{EtOH}]_{\mathrm{cells}}}{dt} = \frac{V_{\mathrm{blood}}}{V_{\mathrm{cells}}}k_4([\mathrm{EtOH}]_{\mathrm{blood}} - [\mathrm{EtOH}]_{\mathrm{cells}})$$

6. Urination:

$$\frac{d[\mathrm{EtOH}]_{\mathrm{kidneys}}}{dt} = -\frac{Q_{out}}{V_{\mathrm{kidneys}}}[\mathrm{EtOH}]_{\mathrm{kidneys}}$$

7. ADH conversion of EtOH to MeCHO:

$$\frac{d[\mathrm{EtOH}]_{\mathrm{liver}}}{dt} = -V_{max,1}\frac{[\mathrm{EtOH}]_{\mathrm{liver}}}{K_{M,1} + [\mathrm{EtOH}]_{\mathrm{liver}}}$$

$$\frac{d[\mathrm{MeCHO}]_{\mathrm{liver}}}{dt} = V_{max,1}\frac{[\mathrm{EtOH}]_{\mathrm{liver}}}{K_{M,1} + [\mathrm{EtOH}]_{\mathrm{liver}}}$$

8. ALDH conversion of MeCHO to AcO^-:

$$\frac{d[\mathrm{MeCHO}]_{\mathrm{liver}}}{dt} = -V_{max,2}\frac{[\mathrm{MeCHO}]_{\mathrm{liver}}}{K_{M,2} + [\mathrm{MeCHO}]_{\mathrm{liver}}}$$

Equations (Combined)

$$\frac{d[\text{EtOH}]_{\text{SSI}}}{dt} = \frac{I}{V_{\text{SSI}}} - k_1[\text{EtOH}]_{\text{SSI}}$$

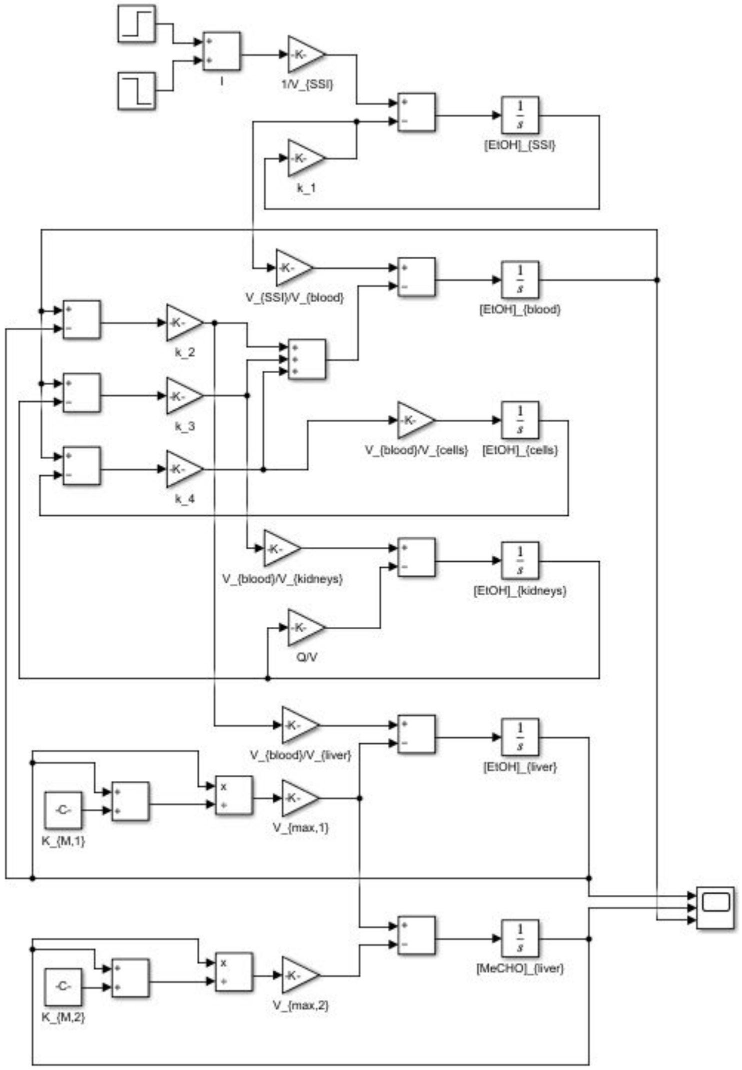
$$\frac{d[\text{EtOH}]_{\text{blood}}}{dt} = \frac{V_{\text{SSI}}}{V_{\text{blood}}}k_1[\text{EtOH}]_{\text{SSI}} - k_2([\text{EtOH}]_{\text{blood}} - [\text{EtOH}]_{\text{liver}}) - k_3([\text{EtOH}]_{\text{blood}} - [\text{EtOH}]_{\text{kidneys}}) - k_4([\text{EtOH}]_{\text{blood}} - [\text{EtOH}]_{\text{cells}})$$

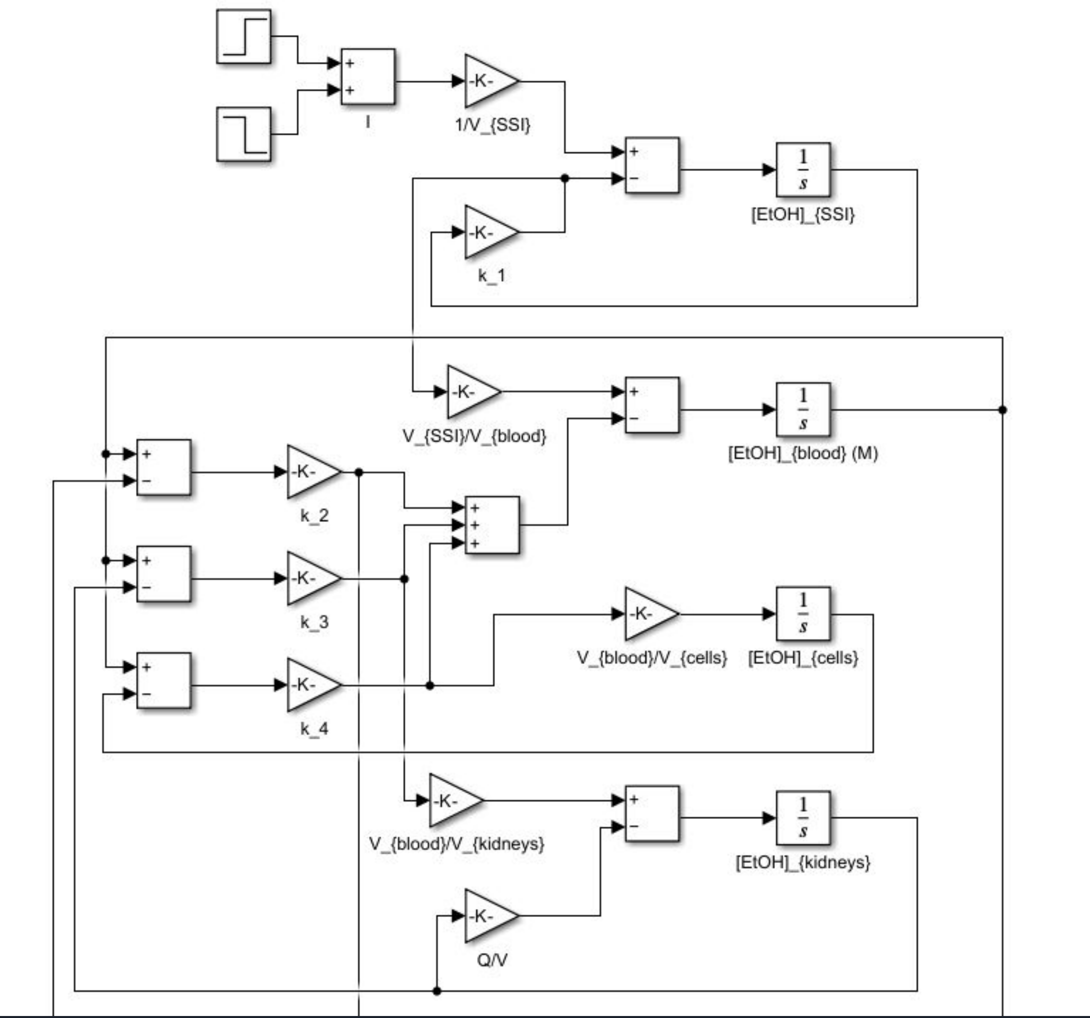
$$\frac{d[\text{EtOH}]_{\text{cells}}}{dt} = \frac{V_{\text{blood}}}{V_{\text{cells}}}k_4([\text{EtOH}]_{\text{blood}} - [\text{EtOH}]_{\text{cells}})$$

$$\frac{d[\text{EtOH}]_{\text{kidneys}}}{dt} = \frac{V_{\text{blood}}}{V_{\text{kidneys}}}k_3([\text{EtOH}]_{\text{blood}} - [\text{EtOH}]_{\text{kidneys}}) - \frac{Q_{out}}{V_{\text{kidneys}}}[\text{EtOH}]_{\text{kidneys}}$$

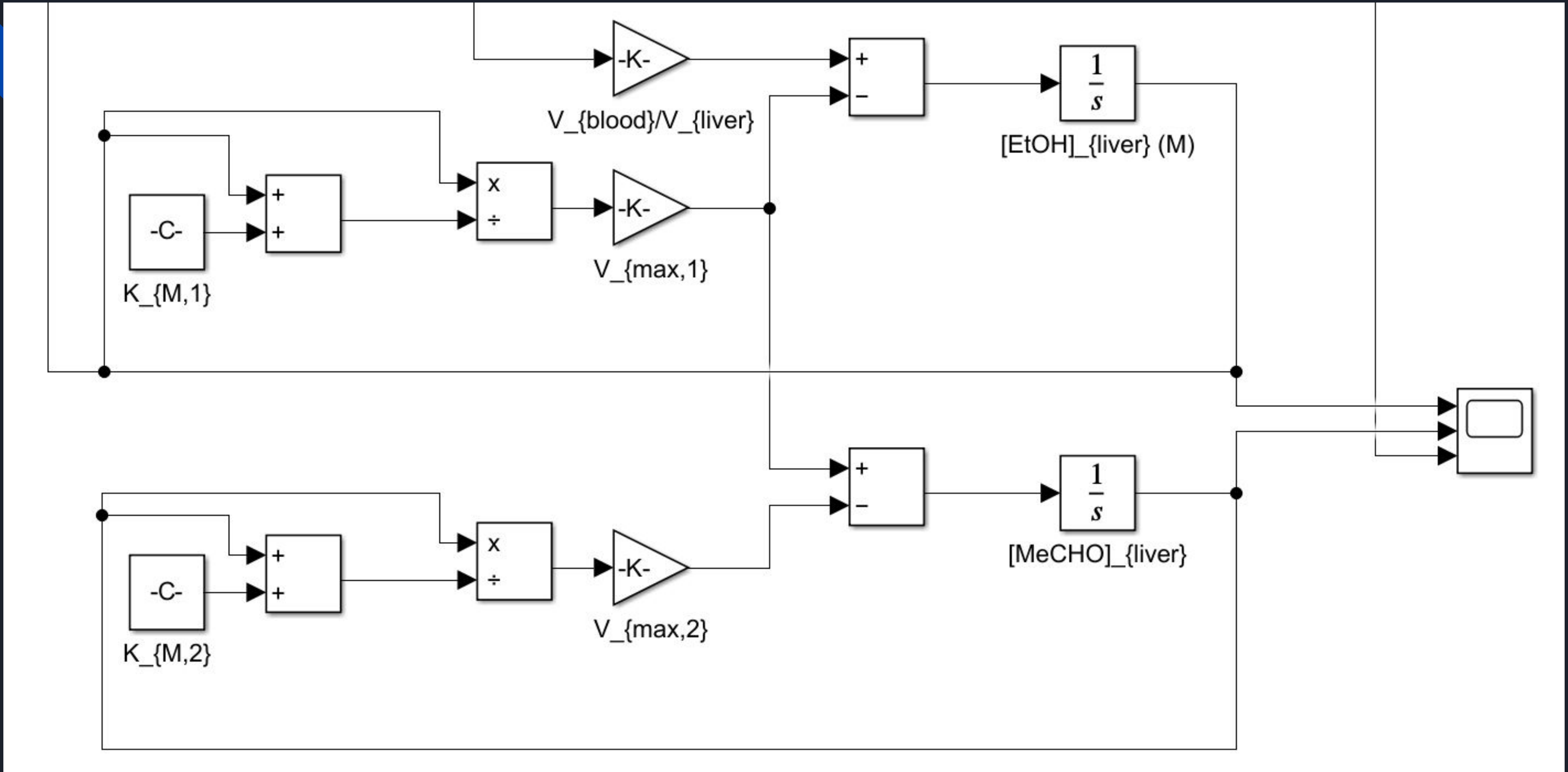
$$\frac{d[\text{EtOH}]_{\text{liver}}}{dt} = \frac{V_{\text{blood}}}{V_{\text{liver}}}k_2([\text{EtOH}]_{\text{blood}} - [\text{EtOH}]_{\text{liver}}) - V_{max,1}\frac{[\text{EtOH}]_{\text{liver}}}{K_{M,1} + [\text{EtOH}]_{\text{liver}}}$$

$$\frac{d[\text{MeCHO}]_{\text{liver}}}{dt} = V_{max,1}\frac{[\text{EtOH}]_{\text{liver}}}{K_{M,1} + [\text{EtOH}]_{\text{liver}}} - V_{max,2}\frac{[\text{MeCHO}]_{\text{liver}}}{K_{M,2} + [\text{MeCHO}]_{\text{liver}}}$$


1/V_{SSI}
[EtOH]_{SSI}
k_1
V_{SSI}/V_{blood}
[EtOH]_{blood}
k_2
k_3
k_4
V_{blood}/V_{cells}
[EtOH]_{cells}
V_{blood}/V_{kidneys}
[EtOH]_{kidneys}
Q/V
V_{blood}/V_{liver}
[EtOH]_{liver}
K_{M,1}
V_{max,1}
[MeCHO]_{liver}
K_{M,2}
V_{max,2}



I
1/V_{SSI}
-K-
1
s
[EtOH]_{SSI}
k_1
V_{SSI}/V_{blood}
[EtOH]_{blood} (M)
k_2
k_3
k_4
V_{blood}/V_{cells}
[EtOH]_{cells}
V_{blood}/V_{kidneys}
[EtOH]_{kidneys}
Q/V



-K-
V_{blood}/V_{liver}
+
−
1/s
[EtOH]_{liver} (M)
-C-
K_{M,1}
+
+
x
÷
-K-
V_{max,1}
+
−
1/s
[MeCHO]_{liver}
-C-
K_{M,2}
+
+
x
÷
-K-
V_{max,2}

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_1	0.083 min^{-1}
k_2	0.100 min^{-1}
k_3	0.005 min^{-1}
k_4	0.003 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

Transfer Function (aka hours of work summarized in 30 seconds)

$$\frac{d[\mathrm{EtOH}]_{\mathrm{SSI}}}{dt} = \frac{I}{V_{\mathrm{SSI}}} - k_1[\mathrm{EtOH}]_{\mathrm{SSI}}$$

$$\begin{aligned}\frac{d[\mathrm{EtOH}]_{\mathrm{blood}}}{dt} = & \frac{V_{\mathrm{SSI}}}{V_{\mathrm{blood}}}k_1[\mathrm{EtOH}]_{\mathrm{SSI}} - k_2([\mathrm{EtOH}]_{\mathrm{blood}} - [\mathrm{EtOH}]_{\mathrm{liver}}) \\ & - k_3([\mathrm{EtOH}]_{\mathrm{blood}} - [\mathrm{EtOH}]_{\mathrm{kidneys}}) - k_4([\mathrm{EtOH}]_{\mathrm{blood}} - [\mathrm{EtOH}]_{\mathrm{cells}})\end{aligned}$$

$$\frac{d[\mathrm{EtOH}]_{\mathrm{cells}}}{dt} = \frac{V_{\mathrm{blood}}}{V_{\mathrm{cells}}}k_4([\mathrm{EtOH}]_{\mathrm{blood}} - [\mathrm{EtOH}]_{\mathrm{cells}})$$

$$\frac{d[\mathrm{EtOH}]_{\mathrm{kidneys}}}{dt} = \frac{V_{\mathrm{blood}}}{V_{\mathrm{kidneys}}}k_3([\mathrm{EtOH}]_{\mathrm{blood}} - [\mathrm{EtOH}]_{\mathrm{kidneys}}) - \frac{Q_{out}}{V_{\mathrm{kidneys}}}[\mathrm{EtOH}]_{\mathrm{kidneys}}$$

$$\frac{d[\mathrm{EtOH}]_{\mathrm{liver}}}{dt} = \frac{V_{\mathrm{blood}}}{V_{\mathrm{liver}}}k_2([\mathrm{EtOH}]_{\mathrm{blood}} - [\mathrm{EtOH}]_{\mathrm{liver}}) - V_{max,1}\frac{[\mathrm{EtOH}]_{\mathrm{liver}}}{K_{M,1} + [\mathrm{EtOH}]_{\mathrm{liver}}}$$

$$\frac{d[\mathrm{MeCHO}]_{\mathrm{liver}}}{dt} = V_{max,1}\frac{[\mathrm{EtOH}]_{\mathrm{liver}}}{K_{M,1} + [\mathrm{EtOH}]_{\mathrm{liver}}} - V_{max,2}\frac{[\mathrm{MeCHO}]_{\mathrm{liver}}}{K_{M,2} + [\mathrm{MeCHO}]_{\mathrm{liver}}}$$

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

Transfer Function (aka hours of work summarized in 30 seconds)

$$r = V_{max} \frac{[\mathrm{X}]}{K_M + [\mathrm{X}]}$$

$$r = V_{max} \left(1 - \frac{K_M}{K_M + [\mathrm{X}]} \right)$$

$$\tilde{r} = \frac{\partial r}{\partial [\mathrm{X}]} \bigg|_{[\overline{\mathrm{X}}]=0} [\tilde{\mathrm{X}}]$$

$$\tilde{r} = -\left(\frac{-V_{max} K_M}{(K_M + [\mathrm{X}])^2} \right) \bigg|_{[\overline{\mathrm{X}}]=0} [\tilde{\mathrm{X}}]$$

$$\tilde{r} = \left(\frac{V_{max} K_M}{(K_M + 0)^2} \right) [\tilde{\mathrm{X}}]$$

$$\tilde{r} = \left(\frac{V_{max}}{K_M} \right) [\tilde{\mathrm{X}}]$$

Transfer Function (aka hours of work summarized in 30 seconds)

$$\frac{d\tilde{A}}{dt} = \frac{\tilde{I}}{V_{\text{SSI}}} - k_1\tilde{A}$$

$$\frac{d\tilde{B}}{dt} = \frac{V_{\text{SSI}}}{V_{\text{blood}}}k_1\tilde{A} - k_2(\tilde{B} - \tilde{E}) - k_3(\tilde{B} - \tilde{D}) - k_4(\tilde{B} - \tilde{C})$$

$$\frac{d\tilde{C}}{dt} = \frac{V_{\text{blood}}}{V_{\text{cells}}}k_4(\tilde{B} - \tilde{C})$$

$$\frac{d\tilde{D}}{dt} = \frac{V_{\text{blood}}}{V_{\text{kidneys}}}k_3(\tilde{B} - \tilde{C}) - \frac{Q_{out}}{V_{\text{kidneys}}}\tilde{D}$$

$$\frac{d\tilde{E}}{dt} = \frac{V_{\text{blood}}}{V_{\text{liver}}}k_2(\tilde{B} - \tilde{E}) - \frac{V_{max,1}}{K_{M,1}}\tilde{E}$$

$$\frac{d\tilde{F}}{dt} = \frac{V_{max,1}}{K_{M,1}}\tilde{E} - \frac{V_{max,2}}{K_{M,2}}\tilde{F}$$

Transfer Function (aka hours of work summarized in 30 seconds)

$$(s + k_1)\tilde{A} = \frac{\tilde{I}}{V_{\text{SSI}}}$$

$$(s + k_2 + k_3 + k_4)\tilde{B} = \frac{V_{\text{SSI}}}{V_{\text{blood}}} k_1 \tilde{A} + k_2 \tilde{E} + k_3 \tilde{D} + k_4 \tilde{C}$$

$$\left(s + \frac{V_{\text{blood}}}{V_{\text{cells}}} k_4\right)\tilde{C} = \frac{V_{\text{blood}}}{V_{\text{cells}}} k_4 \tilde{B}$$

$$\left(s + \frac{V_{\text{blood}}}{V_{\text{kidneys}}} k_3 + \frac{Q_{out}}{V_{\text{kidneys}}}\right)\tilde{D} = \frac{V_{\text{blood}}}{V_{\text{kidneys}}} k_3 \tilde{B}$$

$$\left(s + \frac{V_{\text{blood}}}{V_{\text{liver}}} k_2 + \frac{V_{max,1}}{K_{M,1}}\right)\tilde{E} = \frac{V_{\text{blood}}}{V_{\text{liver}}} k_2 \tilde{B}$$

$$\left(s + \frac{V_{max,2}}{K_{M,2}}\right)\tilde{F} = \frac{V_{max,1}}{K_{M,1}} \tilde{E}$$

Transfer Function (aka hours of work summarized in 30 seconds)

$$\alpha = k_2 + k_3 + k_4$$

$$\beta = \frac{V_{\text{blood}}}{V_{\text{liver}}} k_2 + \frac{V_{max,1}}{K_{M,1}}$$

$$\gamma = \frac{V_{\text{blood}}}{V_{\text{kidneys}}} k_3 + \frac{Q_{out}}{V_{\text{kidneys}}}$$

$$\delta = \frac{V_{\text{blood}}}{V_{\text{cells}}} k_4$$

Transfer Function (aka hours of work summarized in 30 seconds)

$$\frac{\tilde{B}}{\tilde{I}} = \frac{k_1(s+\beta)(s+\gamma)(s+\delta)}{V_{\text{blood}}(s+k_1)}\Bigg((s+\alpha)(s+\beta)(s+\gamma)(s+\delta) - \frac{k_2^2 V_{\text{blood}}}{V_{\text{liver}}}(s+\gamma)(s+\delta)$$

$$- \frac{k_3^2 V_{\text{blood}}}{V_{\text{kidneys}}}(s+\beta)(s+\delta) - \frac{k_4^2 V_{\text{blood}}}{V_{\text{cells}}}(s+\beta)(s+\gamma)\Bigg)^{-1}$$

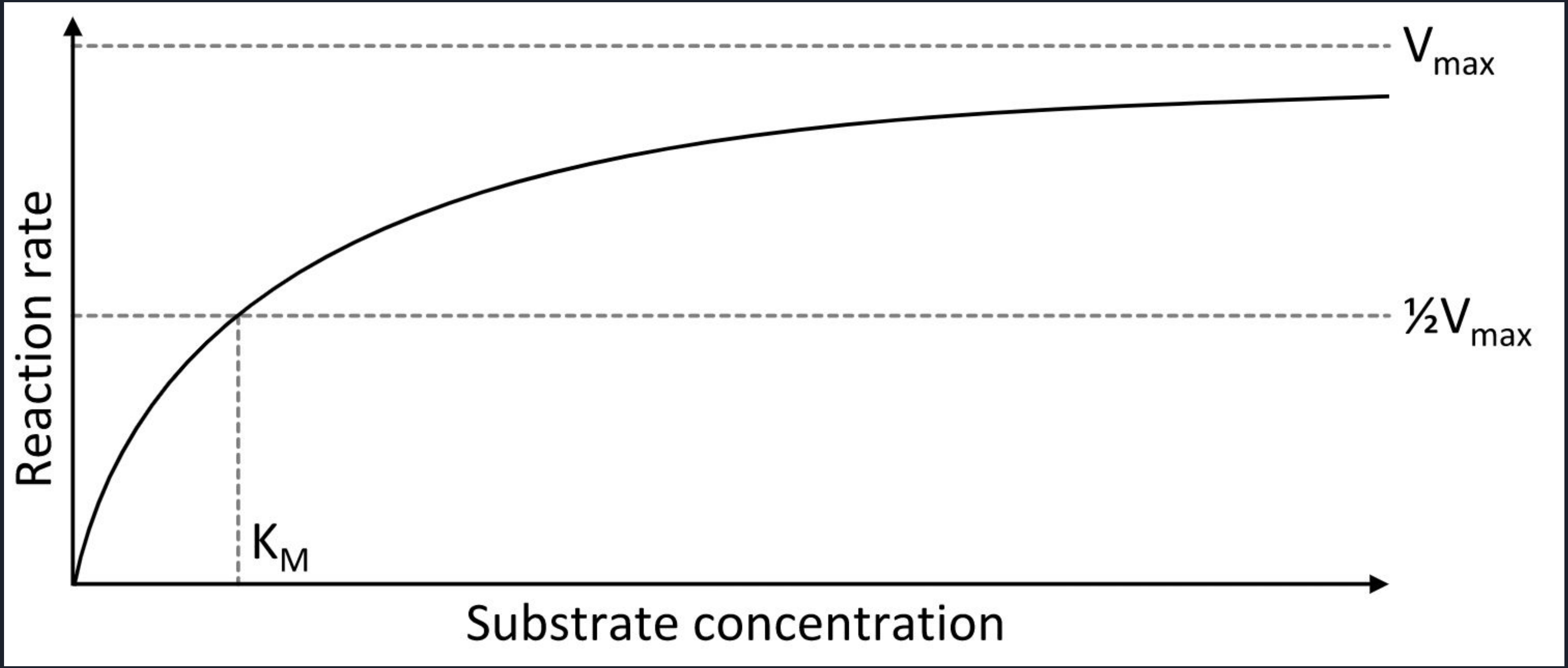
Transfer Function (aka hours of work summarized in 30 seconds)

$$\frac{\tilde{B}}{\tilde{I}} = \frac{0.0827s^3 + 0.8580s^2 + 0.1182s + (6.51 \times 10^{-5})}{5.28s^5 + 55.81s^4 + 17.82s^3 + 1.842s^2 + 0.0618s + (2.21 \times 10^{-7})}$$

$$\frac{\tilde{E}}{\tilde{I}} = \frac{0.0437s^3 + 0.4534s^2 + 0.0624s + (3.44 \times 10^{-5})}{5.702s^6 + 118.6s^5 + 636.4s^4 + 199.0s^3 + 20.44s^2 + 0.6836s + (2.45 \times 10^{-6})}$$

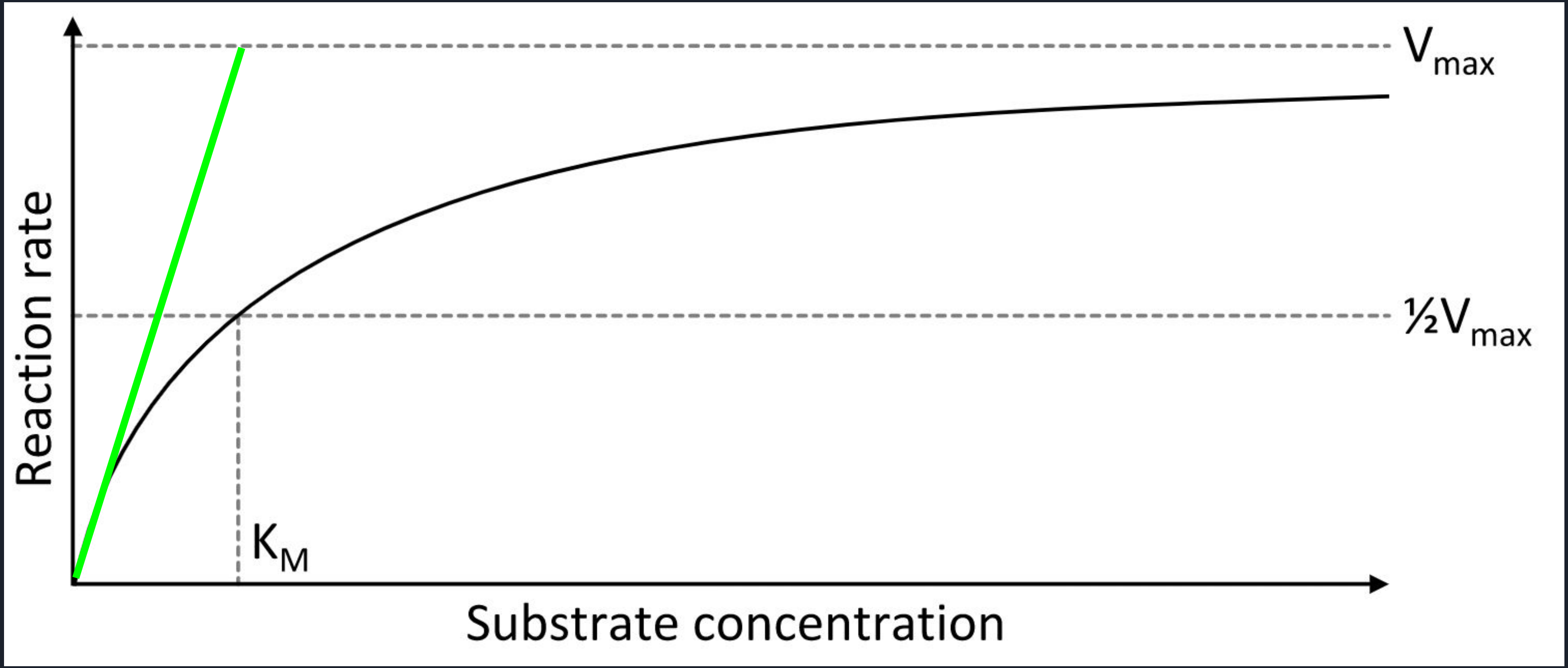
$$\frac{\tilde{F}}{\tilde{I}} = \frac{(1.70 \times 10^{-4})s^3 + 0.0018s^2 + (2.44 \times 10^{-4})s + (1.34 \times 10^{-7})}{0.0023s^7 + 7.746s^6 + 160.5s^5 + 859.3s^4 + 268.7s^3 + 27.59s^2 + 0.9228s + (3.30 \times 10^{-6})}$$

Transfer Function (aka why those hours of work were wasted)

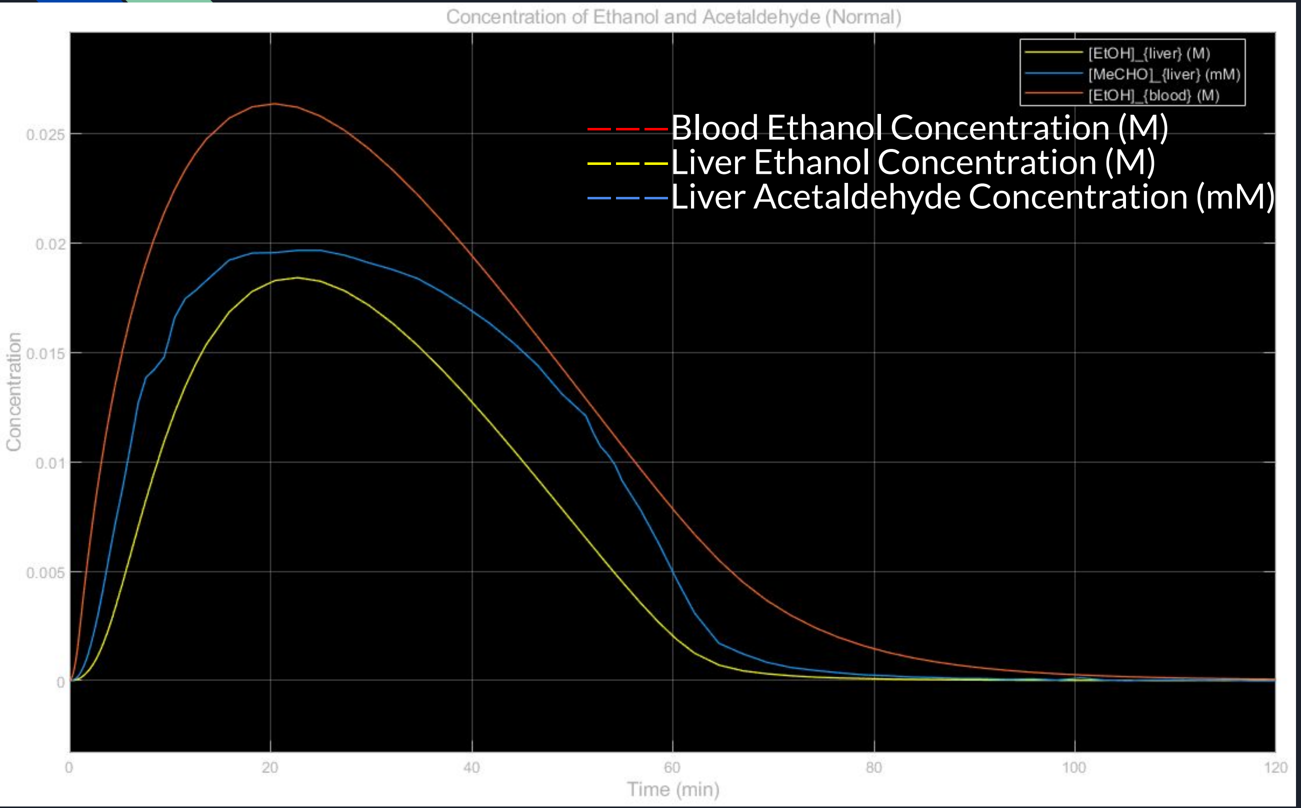


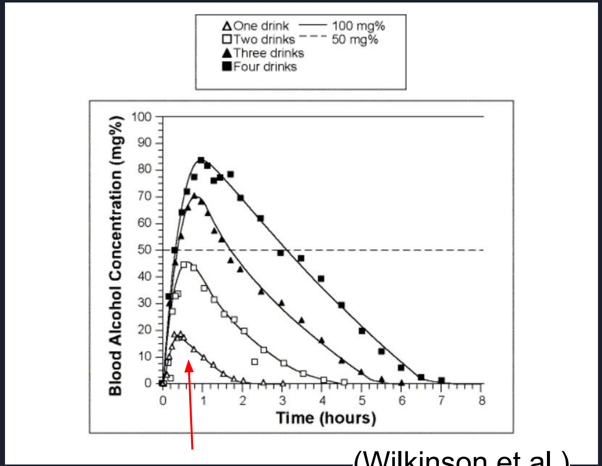
Constant	Value
V_{SSI}	2.4 L
V_{blood}	5.28 L
V_{cells}	31.83 L
V_{kidneys}	0.21 L
V_{liver}	1.08 L
k_1	0.083 min^{-1}
k_2	0.100 min^{-1}
k_3	0.005 min^{-1}
k_4	0.003 min^{-1}
Q_{out}	2 L day^{-1}
$V_{max,1}$	3.9 mmol min^{-1}
$K_{M,1}$	0.4 mM
$V_{max,2}$	4.05 mmol min^{-1}
$K_{M,2}$	1.2 μM

Transfer Function (aka why those hours of work were wasted)



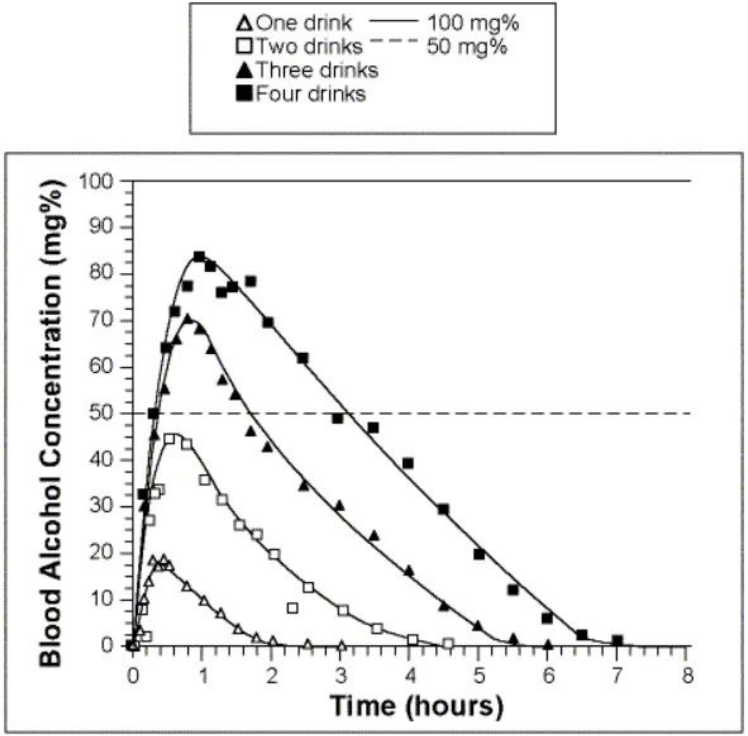
Simulink Model (Normal)





(Wilkinson et al.)

- Input: one standard drink (a can of 12oz beer)
- Similar shape and time it reaches zero
- Limitation: 7 times higher amplitude



One drink
Two drinks
Three drinks
Four drinks
100 mg%
50 mg%
Blood Alcohol Concentration (mg%)
Time (hours)

Model with Alcohol Flush

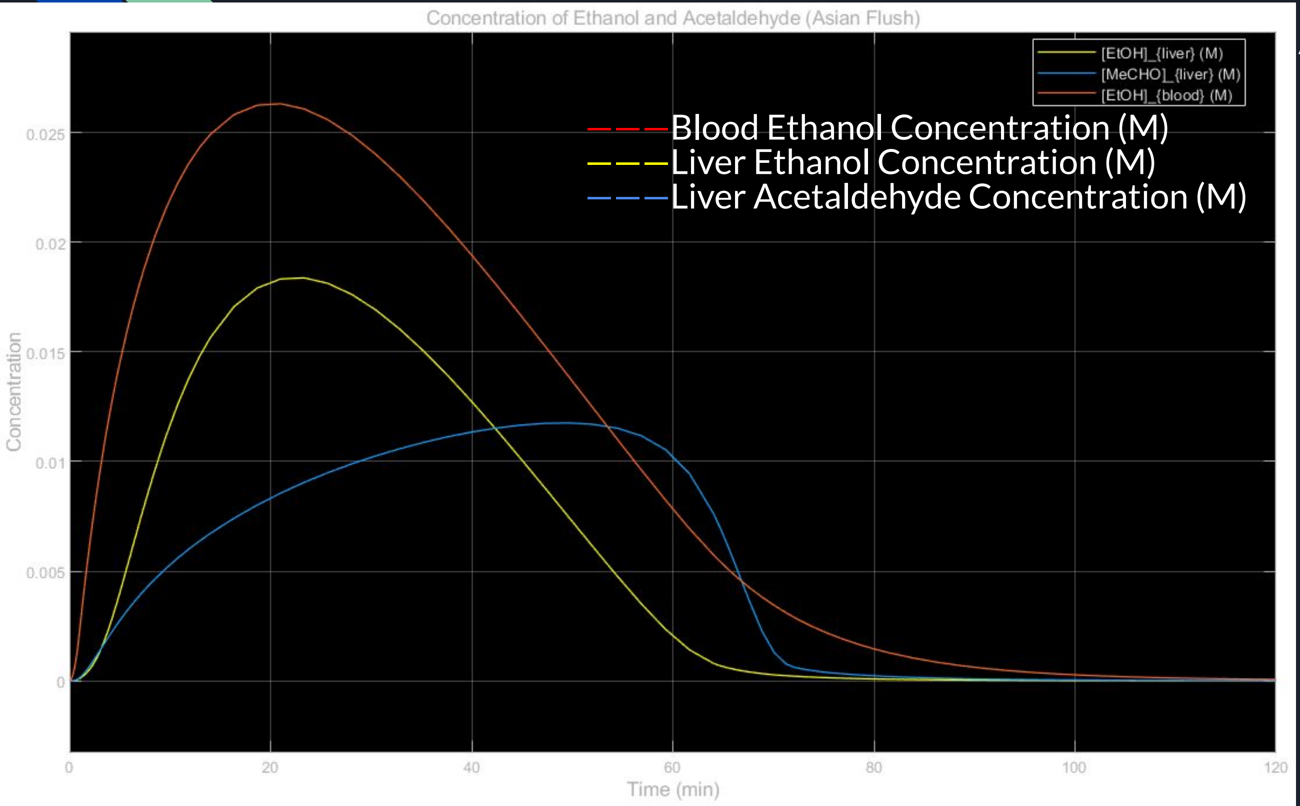
Healthy people:

use ALDH2 (mainly) + ALDH1 to process acetaldehyde

Alcohol Flush Reaction:

lack ALDH2, only rely on ALDH1 to process acetaldehyde

Simulink Model (Alcohol Flush)

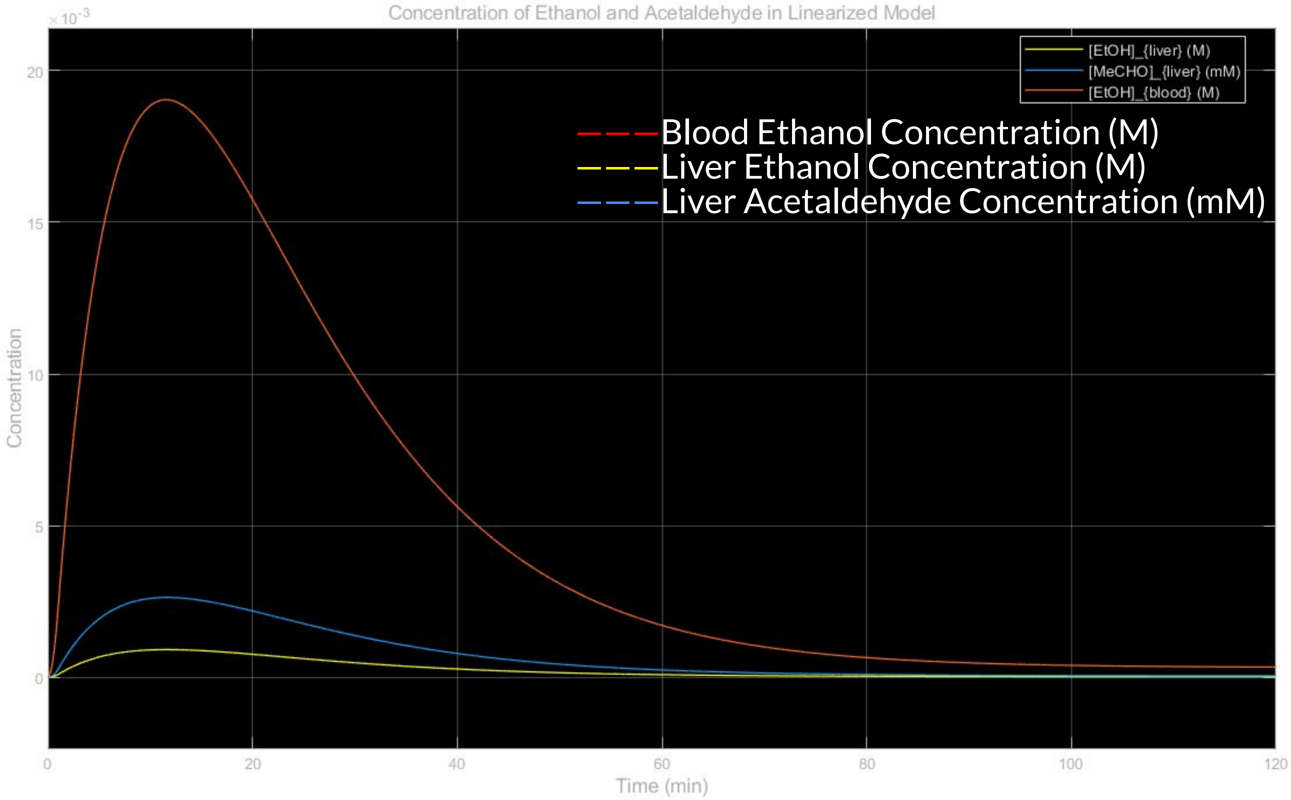


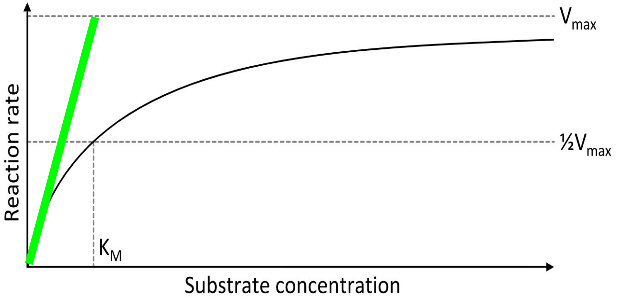
Alcohol flush:

- Normal rate of processing ethanol to acetaldehyde
- +Lack of ALDH2→low rate of processing acetaldehyde
- = accumulation of acetaldehyde

- Maintain high-level acetaldehyde concentration for a long period
- Causing damage at the cellular and genomic levels

Simulink Model
(Linearized model and perturbation)





- Limited operation interval
- Smaller perturbation can increase the accuracy.

Model Evaluation

- The trend matched the curve in the research.
- Successfully represent the consequence of lack ALDH2

- Error
  - Does not match BAC in reality after one shot
  - Might due to rate constants (but we make best guesses here)

Limitations

1. Reductionist approach
    - Simplify based on reasonable assumptions
    - Idealize

2. Rate constant? Variable?
    - Rate constant varies from person to person
    - Drink behavior/Diseases affect these constants

Physiological Significance

1. A clinical syndrome corresponding to a modified version of the system
    - Healthy individuals vs Individuals with Asian flushing syndrome
2. Simulation of pathological behavior
    - Generally summarize the alcohol metabolism pathway
    - Quantitative understandings of alcohol metabolism
3. Use of this simulation as an alternative to actual physiologic experimentation
    - Low risk
    - Ethical

References

A. I. Cederbaum, “Alcohol metabolism,” *Clinics in Liver Disease*, vol. 16, no. 4, pp. 667–685, 2012.

“Alcohol Facts and Statistics,” *National Institute on Alcohol Abuse and Alcoholism*. [Online]. Available: https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-facts-and-statistics. [Accessed: 29-Nov-2022].

A. Paton, “Alcohol in the body,” *BMJ*, vol. 330, no. 7482, pp. 85–87, 2005.

C.-H. Chen, J. C. Ferreira, E. R. Gross, and D. Mochly-Rosen, “Targeting aldehyde dehydrogenase 2: New therapeutic opportunities,” *Physiological Reviews*, vol. 94, no. 1, pp. 1–34, 2014.

D. M. Umulis, N. M. Gürmen, P. Singh, and H. S. Fogler, “A physiologically based model for ethanol and acetaldehyde metabolism in human beings,” *Alcohol*, vol. 35, no. 1, pp. 3–12, 2005.

G. Dam, M. Sørensen, O. L. Munk, and S. Keiding, “Hepatic ethanol elimination kinetics in patients with cirrhosis,” *Scandinavian Journal of Gastroenterology*, vol. 44, no. 7, pp. 867–871, 2009.

J. E. Pieters, G. Schaafsma, and M. Wedel, “Parameter estimation in a three-compartment model for blood alcohol curves,” *Alcohol and Alcoholism*, 1990.

K. Uemura, T. Fujimiya, Y. Ohbora, M. Yasuhara, and K.-ichi Yoshida, “Individual differences in the kinetics of alcohol absorption and elimination: A human study,” *Forensic Science, Medicine, and Pathology*, vol. 1, no. 1, pp. 027–030, 2005.

T. Fujimiya, K. Yamaoka, Y. Ohbora, T. Aki, and H. Shinagawa, “Michaelis-menten elimination kinetics of acetaldehyde during ethanol oxidation,” *Alcoholism: Clinical and Experimental Research*, vol. 26, no. s1, 2002.

W. F. Bosron, D. W. Crabb, and T.-K. Li, “Relationship between kinetics of liver alcohol dehydrogenase and alcohol metabolism,” *Pharmacology Biochemistry and Behavior*, vol. 18, pp. 223–227, 1983.