Caffeine Control on Brain Stimulation

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Abstract – **Caffeine is one of the most widely used drugs in the world. Its most important effect on brain function is that it inhibits the sleep-stimulating neurotransmitter adenosine. Caffeine's relationship with adenosine results in the inhibition of dopamine release, increasing the amount of dopamine in the brain of an individual who has consumed caffeine. In this report, caffeine intake and flow will be modeled to simulate how caffeine moves through the body and into the brain such that it will bind to adenosine receptors and promote the release of dopamine. The results of this model align with physiological expectations, showing that both caffeine and dopamine concentrations peak in the body shortly after ingestion and then diminish over time.**

I. Introduction

Caffeine is a naturally occuring chemical found in a variety of plants. It is a central nervous system stimulant, increasing alertness, energy, and attention [3]. Once consumed, caffeine's effect only lasts for a few hours. After ingestion, caffeine travels to the stomach and small intestine, where it is absorbed into the bloodstream. Eventually, it arrives at the blood-brain barrier, where caffeine crosses diffusively and the direction of flow is dependent on concentration gradients. In the brain, caffeine competes with adenosine for binding to A1 adenosine receptors - both substances belong to the xanthine group and have similar chemical structures. Caffeine binds to these receptors with a similar affinity to adenosine, preventing their activation. Adenosine binding to A1 receptors inhibits dopamine release, so by blocking this binding, caffeine leads to an increase in dopamine release. The heart, which also has A1 receptors, is also affected by caffeine, which causes vasodilation and increased heart rate [3]. Eventually, caffeine travels to the liver via the bloodstream, where it is metabolized. It is processed in the kidneys and a small amount is excreted through the urine.

II. Methods

A. Assumptions and Limitations

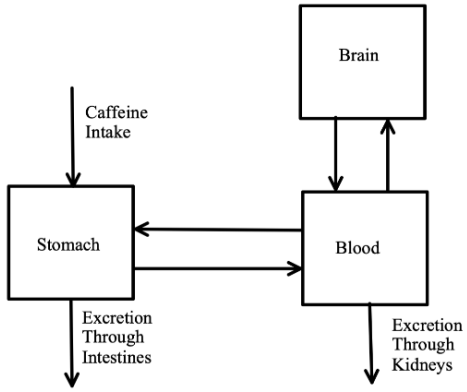

Figure 1: Block diagram of the caffeine flow through the body and into the brain.

The flow of caffeine in the model is simplified according to Figure 1. In this model, the flow of caffeine is simplified such that there is an intake of caffeine at a specific rate into the stomach, where it will either diffuse into the blood or be excreted through the intestines. Furthermore, it is assumed that flow out of the stomach is constant, whereas in reality the stomach contracts and pushes contents out at an interval. It is also assumed that the blood flow is constant whereas in reality the flow would increase as caffeine takes effect due to its properties in increasing heart rate and blood pressure. Another assumption is that caffeine binding to adenosine receptors in the brain and allowing for the release of dopamine is a first order reaction where one unit of caffeine releases one unit of dopamine. Caffeine tolerance varies from person to person, which is not accounted for in the relation between caffeine concentration and dopamine release. This is a limitation of our study because the brain responds to regular caffeine consumption by increasing the number of adenosine receptors; therefore it takes more caffeine to achieve the same effect. An additional limitation is that organ sizes and therefore their fluid volumes and flow also vary, making many of our parameters inapplicable to various persons.

B. Equations

Based on the previous assumptions made, a mathematical model for caffeine intake and resulting caffeine concentrations in the body as well as dopamine concentration in the brain was made. Table

1 contains the variables used in the model and equations (1)-(3) describing the flow of caffeine. Equations (3) and (4) describe the reaction of caffeine in allowing the release of dopamine.

C_{brain}	Concentration of caffeine in the brain
C_{blood}	Concentration of caffeine in the blood
$C_{stomach}$	Concentration of caffeine in the stomach
V_{brain}	Volume of blood in the brain
V_{blood}	Volume of blood in the stomach
$V_{stomach}$	Volume of blood in the stomach
D_{brain}	Concentration of dopamine in the brain
R_b	Resistivity of the blood brain barrier
R_s	Resistivity of the stomach
k_f	Rate of conversion of caffeine to dopamine
τ_D	Time constant of dopamine
Q_b	Flow of blood through the body
Q_s	Flow of fluid through the stomach to the intestines

Table 1. Summary of variables used to quantify caffeine flow throughout the body and into the brain to release dopamine. Specific values can be found in the appendix.

$$\frac{dC_{stomach}}{dt} = \frac{I(t)}{V_{stomach}} + \frac{1}{R_s V_{stomach}}(C_{blood} - C_{stomach}) - \frac{Q_s}{V_{stomach}} C_{stomach} \quad (1)$$

$$\frac{dC_{blood}}{dt} = \frac{1}{R_s V_{blood}}(C_{stomach} - C_{blood}) + \frac{1}{R_b V_{blood}}(C_{brain} - C_{blood}) - \frac{Q_b}{V_{blood}} C_{blood} \quad (2)$$

$$\frac{dC_{brain}}{dt} = \frac{1}{R_b V_{brain}}(C_{blood} - C_{brain}) - k_f C_{brain} \quad (3)$$

$$\frac{dD_{brain}}{dt} = k_f C_{brain} - \frac{1}{\tau_D} D_{brain} \quad (4)$$

In the model, I(t) which is shown in equation (1) is the rate at which caffeine is entering the stomach which was defined as 150 mg/min. The time at which caffeine was entering was also defined to be for 1 min, therefore the total concentration of caffeine entering the system was 150mg. The diffusion of blood in the ODEs were defined by the inverse of the time constants RV multiplied by the difference in caffeine concentrations, and the flow of caffeine was defined as Q/V multiplied by the concentration of caffeine in the volume. From equations (1)-(4) it can be seen that the system is linear and time invariant such that if the input concentration is changed, the system will scale linearly.

C. Block Diagram

To simulate the mathematical models, the block diagram depicted in Figure 2 was generated with values based on the average person used in the ordinary differential equations (ODEs) and the input rate of caffeine was modeled using step functions. The laplace transformation of the equations (1)-(4) were taken to obtain the equivalent model in Figure 3 which was then simplified further to obtain the simplified transfer function shown in equation (5). The ODEs were simplified by ignoring the concentration of caffeine in the blood, as it was assumed to be significantly lower than that in the stomach. A similar assumption was made for the change in caffeine concentration in the brain, which was assumed to be significantly less than the concentration of caffeine in the blood. Thus produced the transfer function represented in the block diagram in Figure 3, and the simplified transfer function in equation 5 and shown in the block diagram in Figure 4.

$$H(s) = \frac{D_{brain}(s)}{I(s)} \frac{0.0007}{(s+0.1144)(s+0.333)(s+0.6145)(s+12)} \quad (5)$$

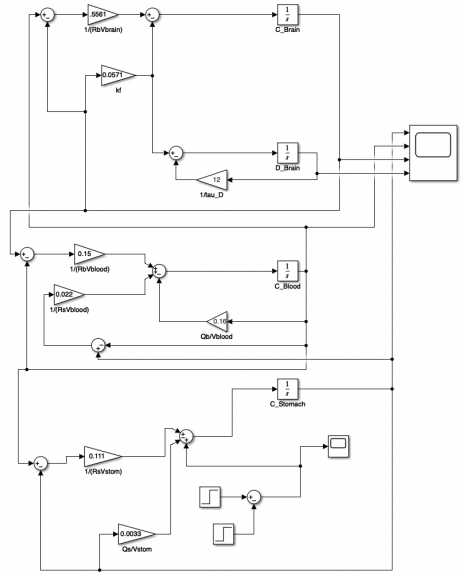

Figure 2 Simulink block diagram of the ODEs shown in equations (1)-(4).

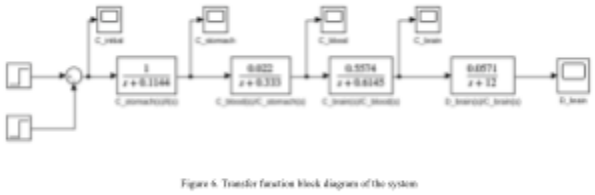

Figure 3 Block diagram of transfer functions relating caffeine intake to dopamine release in the brain

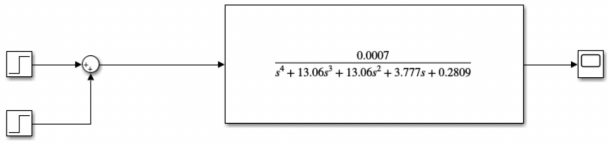

Figure 4 Simulink Block diagram of simplified transfer function

III. Results

A. *Simulink Graphs*

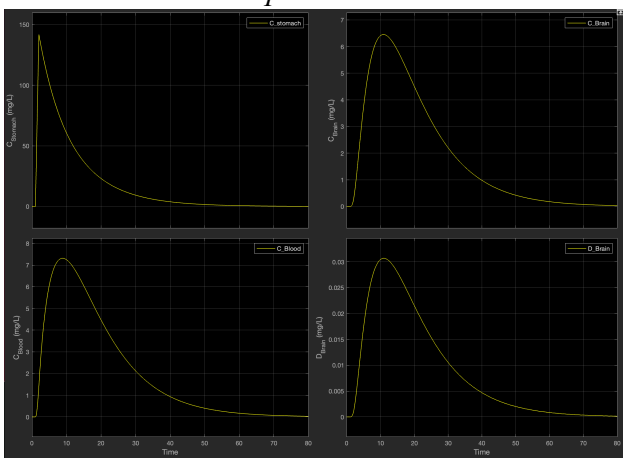

Figure 5 System response of change of caffeine concentration in the stomach over time (top left), change of caffeine concentration in the brain over time (top right), change in caffeine concentration in the blood over time (bottom left) and change in dopamine concentration in the brain over time (bottom right).

In Figure 5 it can be noted that the concentration of caffeine in the stomach (top left) doesn't quite reach 150 mg/L. That is because in the minute that caffeine is being taken in, caffeine is also being diffused through the blood as well as excreted through the intestines. From there the concentrations of the caffeine in the blood, brain, and the concentration of dopamine in the brain are obtained shown in the bottom left, top right, and bottom right of Figure 5. The results from the simulink make sense as physiologically as caffeine peaks in the system after a specific range of time which results in the "caffeine rush". Afterwards, the caffeine and dopamine exponentially decrease as the effects wear off. However, the caffeine flow in our model is significantly faster than what would occur in reality. As our model disregards a number of organ systems that regulate what goes in and out of the body and the absorption of caffeine that may occur in other regions of the body, this rapid rate of caffeine flux is sensible.

B. *Bode Plot*

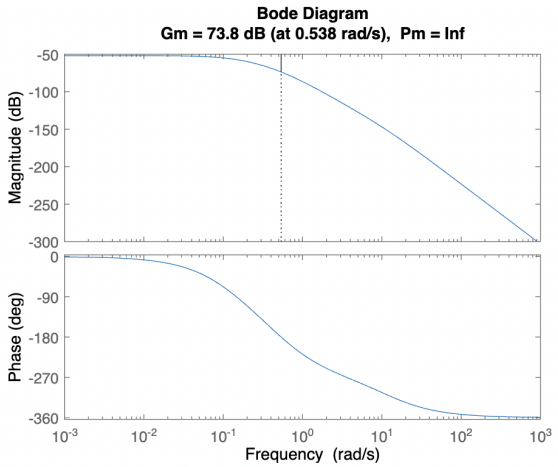

Figure 6 Bode response of dopamine release transfer function

The stability of the system can be determined from the transfer function.The system consists of no zeros and four negative poles (-12, -0.6156, -0.3316, and -0.1147 rad/min) and is thus strictly stable. This is shown in the Bode plot in Figure 6 and shows the system resembles a low-pass filter. There a low gain of 7.0×10^{-4} rad/s and infinite phase margin, which indicates the surety of the system's stability, as with an infinite phase margin, perturbations introduced into the system should not affect its stability. However, the DC gain is -50 dB, suggesting a high DC error, which likely affected the system response.

IV. Discussion

A. *Clinical Applications*

Our model predicts the concentration of caffeine in different organs, at any time after the initial concentration is added. This model can be used for a number of clinical applications. Caffeine directly and indirectly affects bodily processes. While it has been established that caffeine works as an adenosine antagonist [3], it also increases the circulation of chemicals such as cortisol and adrenaline in the rest

of the body [2]. A possible future study can be carried out where the effects of caffeine would be studied in the context of different bodily processes, such as brain waves or digestive activity. In this study, a subject can ingest a set amount of caffeine. Then, based on our model, the concentration of caffeine in the blood, brain, and kidneys is known throughout time. Researchers can study brain waves via EEG to find potential differences before and after caffeine intake, or use electrodes to observe muscle activity in the digestive system. Another possible application for our model is to improve the model by accounting for the rise in heart rate after caffeine intake. Our system assumes a constant heart rate to simplify its governing equations, however, it is known that ingesting caffeine will generally result in a rise in heart rate. A possible improvement to this system would be to add an equation that will modify heart rate based on the rising concentration of caffeine in the bloodstream. A third application we can pursue is refining the model to account for the release of dopamine in the brain. Currently, our system models the release of dopamine in the brain based on a time constant from a literature search. This model of dopamine release feeds back into the system, meaning any error in this model can lead to larger error in the resulting concentrations. To fix this, we could run an experiment where subjects ingest caffeine, then use a PET scan to detect an intravenously injected radiolabeled ligand to estimate dopamine concentration in real time [1]. We can use this experimentally determined dopamine concentration over time to create a stronger estimate of dopamine release as a result of caffeine intake, strengthening our model.

Our project made a few simplifying assumptions that may lead to error in applications of our model. First, we assumed in our model that caffeine traveled through the bloodstream, where it was processed by the brain and eventually excreted through the kidneys. In reality, caffeine is processed in significant amounts by the liver, which metabolizes caffeine into useful byproducts such as theophylline, theobromine, and paraxanthine [4]. A future step that can be taken to reduce this error is to modify the excretion of caffeine so metabolization in the liver is taken into account. Another source of error encountered when applying this model to different subjects is that a variety of physiological factors determine the effect and course of caffeine in the body. For example, people who frequently smoke are known to metabolize caffeine almost twice as fast as non-smokers [5]. Genetics can also play a role, where different people have a different amount of receptors for caffeine in their organs [6]. A robust method to address these factors would be to run a study quantifying the effects of caffeine on a wide variety of subjects, then refining the constants of the model to better represent the population. Because of the many variables stated above, this simulation would not be an appropriate alternative to a physiologic experimentation. Rather, it is most valuable as a means for understanding the large-scale response to caffeine consumption.

B. Simulation of Pathologic Behavior

To simulate a caffeine overdose, 3000 mg of caffeine (20 times the amount from the initial simulation) was input into our system. As seen in Figure 6, the shape of the response remains the same, while the peak concentration of caffeine in the blood and brain and dopamine in the brain increase.

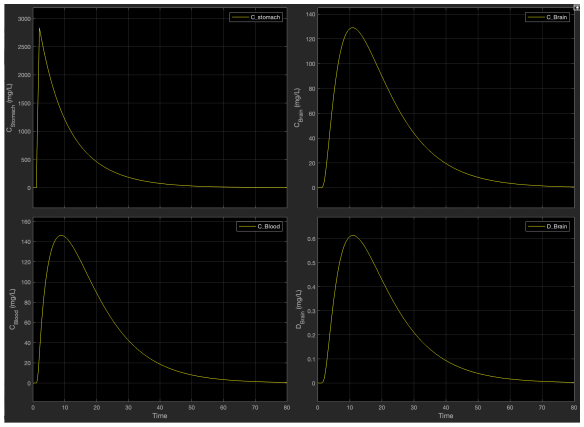

Figure 6 System response of change of caffeine concentration in the stomach, blood, brain, and change in dopamine concentration with a 3000 mg caffeine input

This aligns generally with our physiologic expectations that toxic levels of caffeine will be reached fairly quickly due to rapid absorption by the stomach. However, we expect caffeine to linger in the organs and blood for much longer than 80 minutes as the liver struggles to maintain the metabolization of caffeine. The peak dopamine concentration in the brain increases by a factor of 20 in this overdose state. This is contrary to our expectations as there is only a limited number of dopamine receptors in the brain - dopamine concentration should eventually reach a saturation point at which no more dopamine can be released regardless of how much caffeine is present.

V. References

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Appendix

C_{brain}	Concentration of caffeine in the brain (mg/L)
C_{blood}	Concentration of caffeine in the blood (mg/L)
$C_{stomach}$	Concentration of caffeine in the stomach (mg/L)
V_{brain}	1.349 L
V_{blood}	5 L
$V_{stomach}$	1 L
D_{brain}	Concentration of dopamine in the brain (mg/L)
R_b	1.3 min/L
R_s	9 min/L
k_f	0.057 min^{-1}
τ_D	0.0833 min
Q_b	0.8 L/min
Q_s	0.033 L/min