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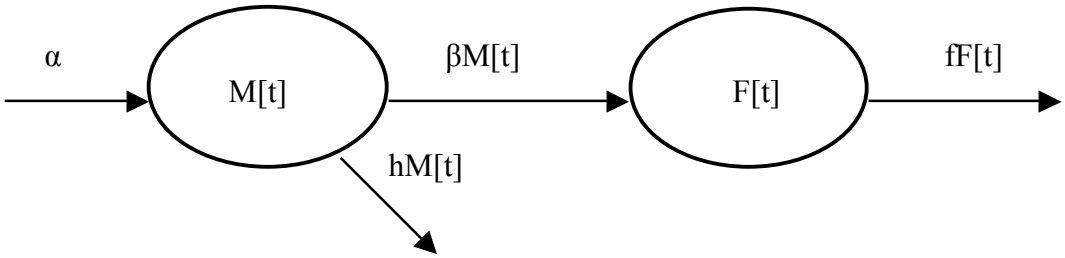
Caffeine levels in maternal and fetal blood with constant daily consumption.

Description of model and relevance

During pregnancy, the mother and developing fetus are intricately connected through the placenta. With highly vascularized tissues, the placenta emerges as an organ for nutrient uptake, waste elimination, and gas exchange between maternal and fetal blood. As a result of this unique connection, nutrients consumed in the mother's diet and absorbed into her bloodstream can be transported through the placenta to nourish the growing fetus. At the same time however, substances that may be harmful to fetal development also cross the placental tissues, and consequently, the mother's diet during pregnancy is critical to the health of the future newborn. One chemical present in many foods and beverages that may cause potentially damaging effects is caffeine. Caffeine consumed in an individual's diet first enters the body through the digestive system, where it is rapidly absorbed into the bloodstream. Extreme levels of caffeine intake result in overdoses, which are not only detrimental to the mother's health, but may also disrupt normal development of the fetus, possibly leading to harmful or lethal effects. Assuming that a pregnant female consumes a constant amount of caffeine per day, a certain proportion is metabolized by the liver, and another fraction is introduced into fetal blood via placental transfer, how will caffeine levels in maternal and fetal blood change over time?

The proposed model will describe the amount of caffeine in maternal blood at time t, M[t], and the amount of caffeine in fetal blood at time t, F[t]. We assume that in a pregnant female who maintains caffeine consumption at a constant daily amount, α, all is rapidly absorbed into her bloodstream from the digestive tract. From her bloodstream, a fixed proportion, h, is metabolized per day by the liver and associated physiological processes, while another fraction, β, enters fetal blood by crossing the placenta. Further, a constant proportion, f, of the caffeine in fetal blood is degraded per day via premature metabolic mechanisms in the developing fetus. The dynamics of circulating caffeine levels are illustrated in the following flow diagram.



Therefore, the model can be represented by the following recursion equations, describing the change in caffeine levels in maternal and fetal blood from one time step to the next:

$$M[t+1]= (1-\beta-h)M[t] + \alpha$$
$$F[t+1]= (1-f)F[t]+ \beta M[t]$$

Analysis of the model

Based on the recursion equations, the caffeine levels at equilibrium in our model are $M_{EQ}=\alpha/(\beta+h)$ in maternal blood, and $F_{EQ}= (\alpha\beta)/(f(\beta+h))$ in fetal blood. To be

biologically valid, both M_{EQ} and F_{EQ}, reflecting caffeine levels at equilibrium, have to be positive. This condition will be satisfied in all cases since daily caffeine consumption, α, cannot be negative and the parameters β, h, and f, representing proportions, will also be positive values between 0 and 1.

Using a transformation, we can describe the distance of M[t] from its equilibrium value M_{EQ} as $\varepsilon_M[t]$, and the distance of F[t] from its equilibrium value F_{EQ} as $\varepsilon_F[t]$. In other words, the new variables are $\varepsilon_M[t]= M[t]-M_{EQ}$ and $\varepsilon_F[t]= F[t]-F_{EQ}$. Therefore, the transformed recursion equations in terms of the new variables are:

$\varepsilon_M[t+1]= M[t+1]-M_{EQ}= (1-\beta-h)\varepsilon_M[t]$, and

$\varepsilon_F[t+1]= F[t+1]-F_{EQ}= (1-f)\varepsilon_F[t]+ \beta\varepsilon_M[t]$.

The above linear equations can be presented in matrix form.

$$\begin{pmatrix} \varepsilon_M[t+1] \\ \varepsilon_F[t+1] \end{pmatrix} = \begin{pmatrix} 1-\beta-h & 0 \\ \beta & 1-f \end{pmatrix} \begin{pmatrix} \varepsilon_M[t] \\ \varepsilon_F[t] \end{pmatrix}, \text{where} \begin{pmatrix} 1-\beta-h & 0 \\ \beta & 1-f \end{pmatrix}$$ is the transition matrix, **M**, describing the change in the perturbation of caffeine levels in maternal blood and fetal blood from their equilibrium values from one time step to the next. To simplify our analysis, we change the coordinate system of the transition matrix into one where the transition matrix is a diagonal matrix, **D**, with the eigenvalues of **M** as its diagonal elements. The eigenvalues of the transition matrix **M** are $\lambda_{1=}$ 1-f and λ_2= 1-β-h. Therefore, the diagonal matrix, **D**, is

$$\mathbf{D}= \begin{pmatrix} (1-f) & 0 \\ 0 & (1-\beta-h) \end{pmatrix}, \text{ which becomes } \mathbf{D}^t= \begin{pmatrix} (1-f)^t & 0 \\ 0 & (1-\beta-h)^t \end{pmatrix}$$ when taken to the t^{th} power.

The right eigenvectors associated with the above eigenvalues of **M** are:

$$v_1= \begin{pmatrix} 0 \\ 1 \end{pmatrix}$$ for $\lambda_{1=}$ 1-f, and $v_2= \begin{pmatrix} (f-\beta-h)/\beta \\ 1 \end{pmatrix}$ for λ_2= 1-β-h.

Consequently, the transformation matrix, A, and its inverse matrix, A^{-1}, are

$$\mathbf{A}= \begin{pmatrix} 0 & \frac{f-\beta-h}{\beta} \\ 1 & 1 \end{pmatrix} \text{ and } \mathbf{A}^{-1}= \begin{pmatrix} \frac{\beta}{\beta+h-f} & 1 \\ -\frac{\beta}{\beta+h-f} & 0 \end{pmatrix}$$

Using the above matrices, the original transition matrix, **M**, taken to the t^{th} power becomes $\mathbf{M}^t=(\mathbf{A}\,\mathbf{D}^t\mathbf{A}^{-1})$. Therefore, the general solution for the perturbation from equilibrium, $\varepsilon[t]= \mathbf{M}^t\varepsilon[0]=(\mathbf{A}\,\mathbf{D}^t\,\mathbf{A}^{-1})\varepsilon[0]$, can be written in matrix form as

$$\begin{pmatrix} \varepsilon_M[t] \\ \varepsilon_F[t] \end{pmatrix} = \begin{pmatrix} 0 & \frac{f-\beta-h}{\beta} \\ 1 & 1 \end{pmatrix} \begin{pmatrix} (1-f)^t & 0 \\ 0 & (1-\beta-h)^t \end{pmatrix} \begin{pmatrix} \frac{\beta}{\beta+h-f} & 1 \\ -\frac{\beta}{\beta+h-f} & 0 \end{pmatrix} \begin{pmatrix} \varepsilon_M[0] \\ \varepsilon_F[0] \end{pmatrix}$$

As a result, the general solutions describing the distance of caffeine levels in maternal blood and fetal blood from their equilibrium values at any time t in the future are:

$\varepsilon_M[t]= \varepsilon_M[0](1-\beta-h)^t$ and

$\varepsilon_F[t]= \varepsilon_F[0](1-f)^t + \varepsilon_M[0][(1-f)^t-(1-\beta-h)^t]\ (\beta/(\beta+h-f))$

Finally, transforming back to our original variables, the general solutions for caffeine levels in maternal blood and fetal blood are

$M[t]= (1-\beta-h)^t (M[0]-M_{EQ})+M_{EQ}$ and

$F[t]= (F[0]-F_{EQ})(1-f)^t +(M[0]-M_{EQ})[(1-f)^t-(1-\beta-h)^t] (\beta/(\beta+h-f)) +F_{EQ}$

where $M_{EQ}= \alpha/(\beta+h)$ and $F_{EQ}= (\alpha\beta)/(f(\beta+h))$.

Using these equations, we can predict the amount of circulating caffeine in the mother and the fetus at any time t during the course of pregnancy as a function of their initial states if the mother's caffeine intake is maintained at the same amount.

Implications of the model

From this model, we can infer several conclusions about how caffeine levels in maternal and fetal blood change over time. To begin with, examining the eigenvalues of the transition matrix **M**, 1-f and 1-β-h, the equilibrium caffeine levels in maternal and fetal blood are stable. This follows from the fact that none of the eigenvalues will be greater than 1 in magnitude, since in our model, the parameters f, and the sum of h and β, are all positive values, representing proportions that are between 0 and 1. Consequently, the transition matrix $\mathbf{M}^t$, and hence the perturbation from equilibrium, will shrink over time. Further, the approach to equilibrium will be smooth with no oscillatory behaviour, as all eigenvalues are non-negative.

The above conclusions can also be drawn from the general solutions for caffeine levels in maternal blood, M[t], and fetal blood, F[t]. The terms $(1-f)^t$ and $(1-\beta-h)^t$ all approach 0 over time as t approaches infinity since 1-f and 1-β-h both have magnitudes less than 1, and a stable equilibrium is reached. With large values of f, indicating high efficiency of caffeine metabolism in the fetus, and large values of β and h, reflecting high rates in caffeine removal from the mother's circulatory system, the system will equilibrate more rapidly. As expected under these conditions, the equilibrium caffeine levels in both maternal and fetal blood, given respectively as $\alpha/(\beta+h)$ and $\alpha\beta/(f(\beta+h))$, will also be low since metabolic processes in the body are actively removing caffeine from the circulatory system in the mother and the fetus.

Moreover, if we perturb the caffeine levels in either the mother or the fetus, the system will eventually return to the same equilibrium over time, given the daily caffeine consumption remains constant. This is because the equilibrium caffeine levels do not depend on initial amounts, but instead, only rely on the rates of metabolism in the mother and fetus (h and f) the rate of transfer via the placenta (β) and the amount consumed per day (α) during the course of pregnancy. Therefore, even if a mother was originally a heavy caffeine consumer, with large amounts of caffeine circulating in her bloodstream at the start of pregnancy, her eventual levels will reach the same equilibrium as a mother with initially lower levels, as long as they both maintain the same consumption rate during pregnancy.

Other points arise when considering the equilibrium amounts of caffeine circulating in maternal and fetal blood. Namely, the equilibrium caffeine level in fetal blood is β/f times that of maternal blood. Therefore, if the rate of caffeine transfer from the mother,

β, is equal to the rate of caffeine metabolism in the fetus, f, caffeine levels in maternal and fetal blood will equilibrate at the same amount. Conversely, M_{EQ} will be higher than F_{EQ} when f is greater than β, and lower than F_{EQ} if f is lower than β. Since metabolic functions in the growing fetus are premature and not fully developed, f is expected to be low. Therefore, with the assumption that the caffeine transferred to the fetus through the placenta is not efficiently metabolized within a day, and f is less than β, the amount of caffeine in fetal blood is predicted be higher than in maternal blood at equilibrium, based on this model.

The following figure illustrates the dynamics of caffeine levels in maternal blood and fetal blood during the first 100 days of pregnancy, with initially high amounts of circulating caffeine in the mother (M[0]=200) and no caffeine in the fetus (F[0]=0). Using some sample parameters, we assume that the mother consumes one cup of coffee per day during pregnancy, containing about 100mg of caffeine (α= 100), 60% of caffeine is metabolized from maternal blood per day (h=0.6), while 30% is transferred to the fetus via the placenta (β=0.3). Further, we set the rate of caffeine degradation in fetal blood per day as 20% (f=0.2).

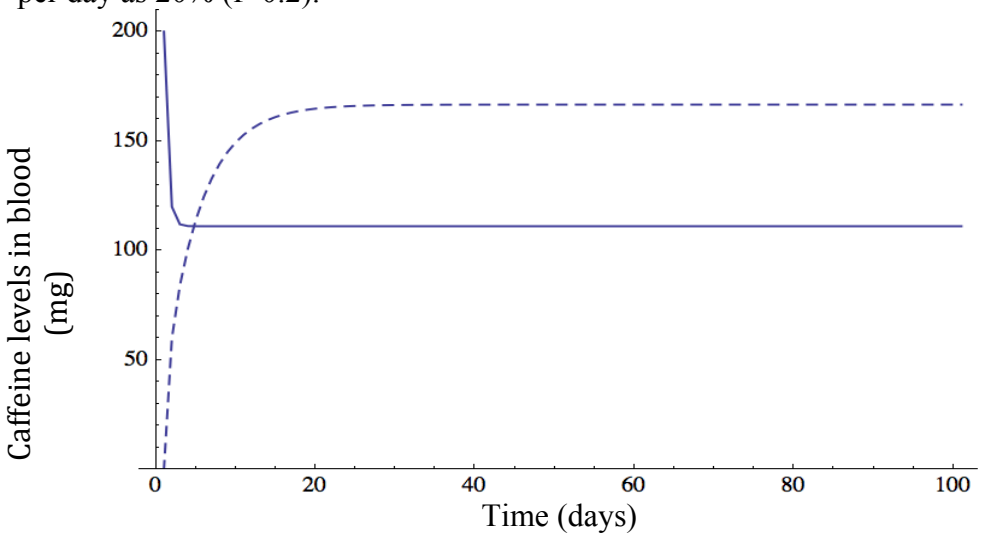


Figure 1. Dynamics of caffeine levels in maternal blood (solid line) and fetal blood (dashed line) during the first 100 days of pregnancy using sample parameters: α=100, β=0.3, h=0.6, and f=0.2.

From Figure 1, we see that if we set the sum of β and h to be less than 1, meaning not all caffeine in maternal blood is removed each day, the caffeine levels in maternal blood decreases from its initial higher levels and equilibrates to an amount greater than its daily intake, α. Further, as expected, the low rate of metabolism in the fetus, f, relative to the rate of caffeine entry via placental transfer, β, results in higher caffeine levels in fetal blood at equilibrium compared to the mother. Caffeine levels also equilibrate more rapidly in maternal blood due to a larger proportion being removed per day. Consistent with our expectations, a stable equilibrium is approached smoothly in both the mother and the fetus, with no oscillatory behaviour, as a result of the eigenvalues being positive and less than 1 in magnitude.

Figure 2 shows caffeine levels in maternal and fetal blood using the same initial conditions, M[0]=200 and F[0]=0, and the same parameters for β, h, and f, except with caffeine consumption doubled (α=200). When daily caffeine consumption during pregnancy is doubled, the equilibrium caffeine levels in maternal and fetal blood are also doubled as expected.

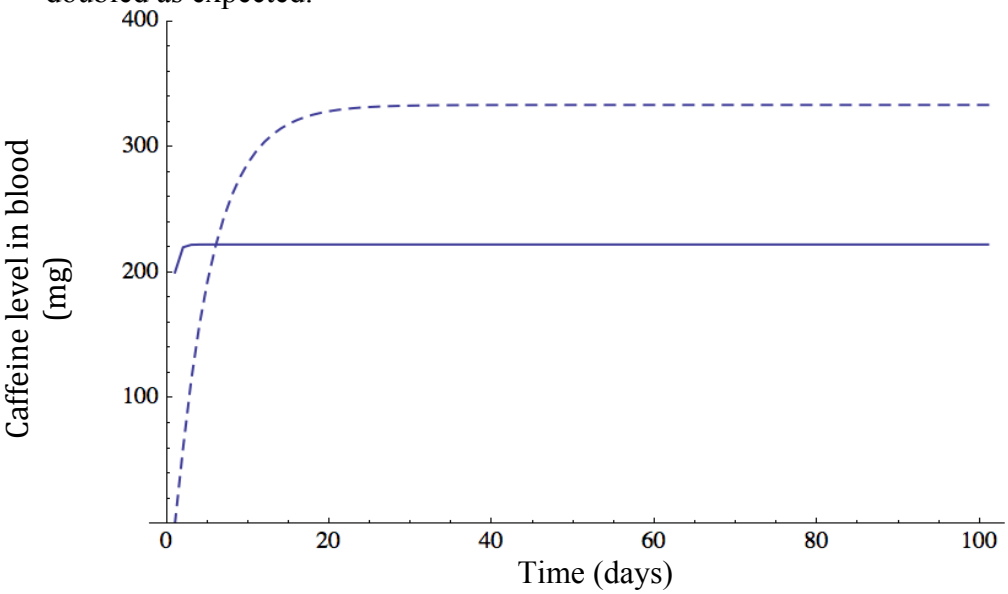


Figure 2. Dynamics of caffeine levels in maternal blood (solid line) and fetal blood (dashed line) during the first 100 days of pregnancy using sample parameters: α=200, β=0.3, h=0.6, and f=0.2.

While the actual effects of caffeine on fetal development remain a topic in many areas of research, we can conclude from our model that regular caffeine consumption during pregnancy can indeed sustain a level of the chemical in both maternal and fetal circulation. Further, several parameters in our model determine the levels of caffeine in maternal and fetal blood over the course of pregnancy. However, the only parameter that can be reasonably monitored is the daily caffeine intake of the mother, α, since we can modify neither the rates of caffeine metabolism in the mother and the fetus, nor the rate of placental transfer. Therefore, as elucidated in this model, to regulate and minimize the equilibrium amount of caffeine circulating in fetal blood, the most direct method is to reduce daily consumption.