Model Implementation of Cholesterol Biosynthesis

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I. INTRODUCTION

This paper mainly talks about cholesterol biosynthesis pathway in hepatocyte [1]. Cholesterol is a sterol, biosynthesized by all animal cells. It is a significant structural component of all animal cell membranes and is essential to maintain both membrane structural integrity and fluidity. Because not only high level of cholesterol in blood is the major risk of cardiovascular disease, but also insufficient cholesterol causes cytotoxicity through compromised membrane structure. The intracellular cholesterol levels are strictly regulated, which make it vital to understand the mechanism of the cholesterol biosynthesis pathway. Biosynthesis of cholesterol is a multistep catalyzed by the enzyme HMG-CoA reductase (HMGCR).

$$\begin{array}{l} \bar{G}+x\bar{S} \underset{\bar{\kappa}_{-1}}{\overset{\bar{\kappa}_1}{\rightleftharpoons}} \bar{G}:x\bar{S} \xrightarrow{\bar{\mu}_d} \bar{M} \xrightarrow{\bar{\mu}_h} \bar{H} \xrightarrow{\bar{\mu}_c} \bar{C} \\ \qquad\qquad\qquad\qquad\quad \downarrow \bar{\delta}_m \qquad\quad \downarrow \bar{\delta}_h \qquad\quad \downarrow \bar{\delta}_c \\ \qquad\qquad\qquad\qquad\quad \emptyset \qquad\qquad \emptyset \qquad\qquad \emptyset \end{array} \tag{1}$$

By analyzing this pathway, the author simplified this biological system into a model of gene expression response to cellular cholesterol concentration. They summarized the model as a series of reaction equation. This is an end-product negative feedback loop system.

$$\bar{S}+y\bar{C} \underset{\bar{\kappa}_{-2}}{\overset{\bar{\kappa}_2}{\rightleftharpoons}} \bar{S}:y\bar{C} \tag{2}$$

The transcription of DNA, will not deplete$[G:xS]$; and the synthesis of H will not deplete M.

After a series of calculation and simplification, the author then obtained three mainly functions that describe the relationship of HMGCR, HMGCR mRNA and cholesterol. The author used these tree function to implement ODE15s to investigate the system behavior and to show the stable steady state.

$$\frac{dm}{d\tau} = \frac{\mu_m}{1+(\kappa_m \times (1+c/\kappa_c)^y))^x} - \delta_m \times m = f(m,h,c) \tag{3}$$

$$\frac{dh}{d\tau} = m - \delta_h \times h = g(m,h,c) \tag{4}$$

$$\frac{dc}{d\tau} = \mu_c \times h - \delta_c \times c = j(m,h,c) \tag{5}$$

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And these are all non-dimensional equation. Then they gave us the parameter value in table 2 and the Appendix A to show how these parameter values was derived.

II. MODEL IMPLEMENTATION

There are three cases. The first case can eventually come to a steady state, which will be discussed in the later section, and is the mainly case to solve. This case is classified into 2 part. Case 1a: eigenvalues are real and negative, which result in a stable node, and the concentrations of mRNA, protein and cholesterol will tend monotonically to a steady state. Case 1b: one eigenvalue is real and negative, and two eigenvalues are complex conjugates with negative real part. In this case the fixed point is stable spiral, and the concentration of mRNA, protein and cholesterol will demonstrate oscillatory convergence to a steady state. I will recreate the computational figures and findings in this case, which is the major part of the paper, to show the tendency of all these two aspects in Case 1

The second case will also go to a steady state, but it cannot be directly arrived. And for the last case, it is biologically infeasible, and the author ignored it.

Initial condition of all variable concentration: $m(0) = 3.65\times10^{-8}, h(0) = 1.10\times10^{-5}, c(0) = 2.30\times10^{-2}$

Fig. 1 is the stable node equilibrium (corresponding to Case 1a). As analyzed in paper, there are three negative real eigenvalues. We can easily see from this figure that HMGCR and mRNA goes up at first while cholesterol goes down. But these three variable concentrations all show unchangeable eventually. We can see because cholesterol is much more than HMGCR mRNA and HMGCR, the SCAP-SREBP complex is inactivate leading to no SREBP, which cannot activate HMGCR mRNA transcription and HMGCR synthesis. Thus, cholesterol synthesis decreased its concentration in cell. After such processing, this pathway will go to a stable steady state.

Fig. 2 demonstrates the Case 1b. This is a stable spiral equilibrium with one negative real eigenvalue and a pair of complex conjugate eigenvalues with negative real part. In this figure, we can see a fluctuation before the concentration comes to a stable level. As the author claimed that this is different from Case 1a. The association rate of cholesterol from HMGCR transcription is two folds than the first situation. After changing the rate, the eventual trend is almost the same but at the beginning they are more fluctuate. But as we expected, they are stable finally.

Fig. 3 using a quite large rate of cholesterol from HMGCR transcription. The variable concentrations are always oscillatory without going to a stable state. But the fluctuation shows

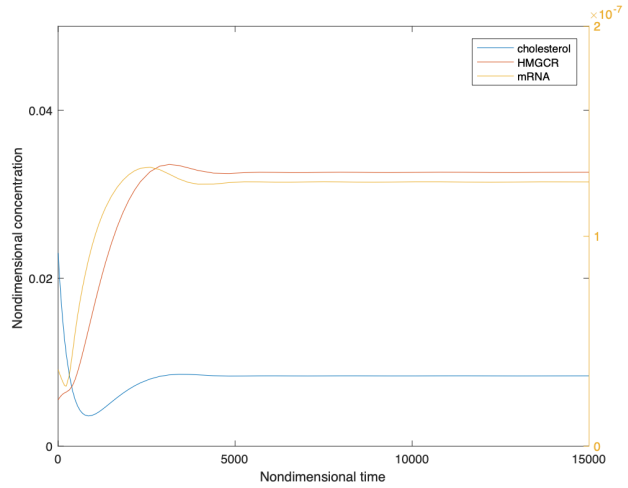

Fig. 1. (Fig. 3 in paper)Stable node equilibrium(Corresponding to Case 1a)

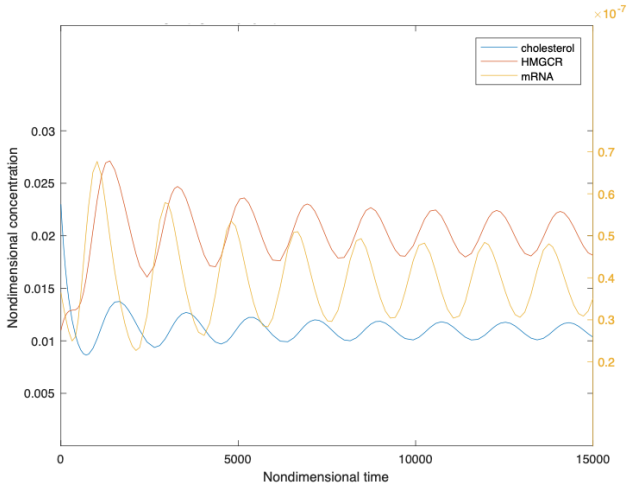

Fig. 3. (Fig. 5 in paper)Transition from Case 1b to Case 2

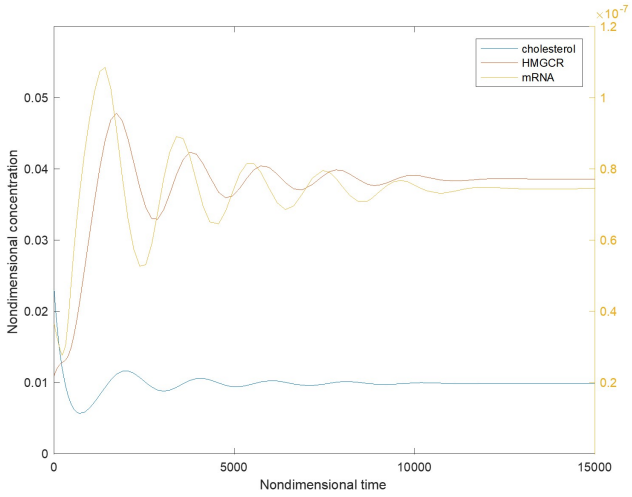

Fig. 2. (Fig. 4 in paper)Stable spiral equilibrium(Corresponding to Case 1b)

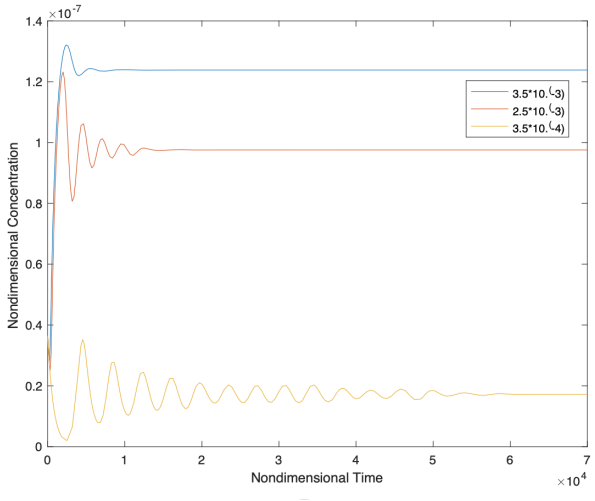

Fig. 4. (Fig. 6 in paper)mRNA Response to variation of cholesterol degraded rate

a stable trend. The phenomenon means that there is a stable oscillatory state. On the other hand, although it cannot come to a stable state, it changes in a limited range, which make sure that the concentration of cholesterol in a safe state.

Fig. 4 is the response of mRNA concentration to variation of cholesterol degraded rate. They used three different values of cholesterol degraded rate to draw the figure.

According to the figures and what they wrote in the paper, we can see the author mainly discussed how the biosynthesis of cholesterol affects the concentration of HMGCR mRNA, HMGCR and cholesterol. But they did not consider the initial condition may have impact on the pathway. Because as I mentioned before, this is a negative end-product feedback loop system, the cholesterol level plays an essential role in this system. Furthermore, I will not only consider the cholesterol level but also mRNA and HMGCR at the beginning of the system. I will still use ODE15s to draw the figure to compare the tendency. There is another difference between my assumption and the paper. I will set the rate of association of cholesterol from HMGCR transcription and degraded of cholesterol as a constant. Each time change one concentration to see how that initial concentration affects the system.

First, to investigate how mRNA affect the system, I change the initial concentration of mRNA to a larger one, that is m (0) =0.365, and maintain other parameters. I then scale the evolution of HMGCR to allow for easier comparison. I also use ODE15s (fig. 5). And in addition, changing it to a smaller one (Fig. 6).

Second, to see the effect of HMGCR on this system, I changed the initial concentration of HMGCR to a larger one and a smaller one, respectively. Shown as fig. 7 and fig. 8.

Last, changing the initial concentration of cholesterol. Fig. 9 shows the effect of sufficient cholesterol and fig. 10 shows the lack of cholesterol.

In fig. 5 the initial concentration of mRNA, HMGCR

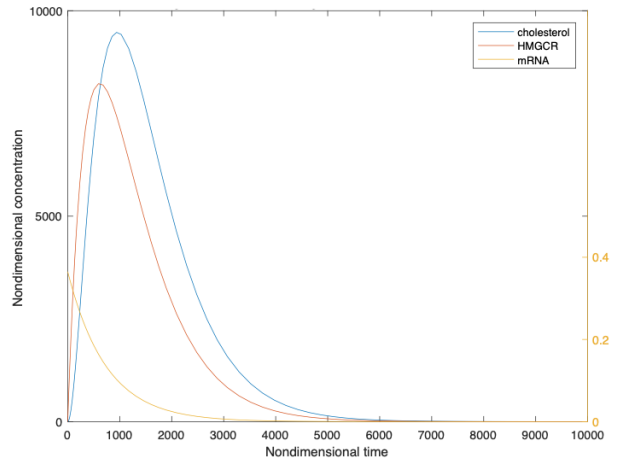

Fig. 5. Effect of increasing initial mRNA concentration

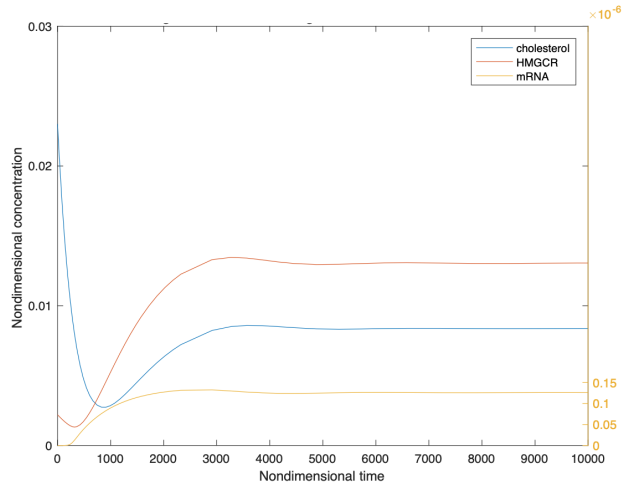

Fig. 6. Effect of decreasing initial mRNA concentration

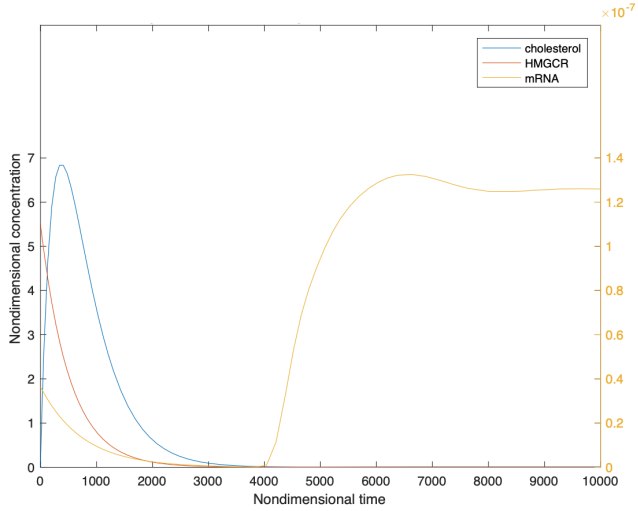

Fig. 7. Effect of increasing initial HMGCR concentration

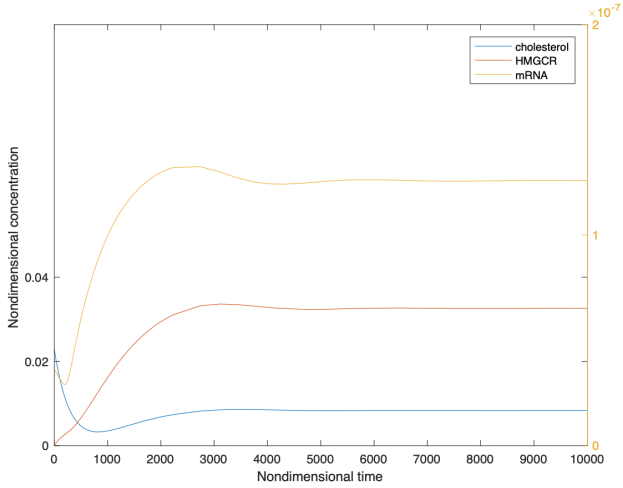

Fig. 8. Effect of decreasing initial HMGCR concentration

and cholesterol are 0.365, 0.000011, 0.023 respectively. Compared with fig. 1, we can see when increase the mRNA, HMGCR will be activated and thus increased. In such condition, HMGCR will in turn transcript to cholesterol. Thus, cholesterol will be also increased.

In fig. 6 when mRNA is a little, we can see HMGCR and cholesterol both decreased. After a while, when there is an increase in mRNA, HMGCR first increase and then transcript into cholesterol. After all, they all come to the stable steady state.

In all, low concentration of mRNA will cause a decrease of HMGCR and cholesterol, vice versa.

In fig. 7 we can see when the initial condition of HMGCR is increased, cholesterol will be increased too. But mRNA becomes less than before, which may because if HMGCR is sufficient, there is no need to synthesize it using mRNA.

In fig. 8 when taking out HMGCR from the system, cholesterol decreased greatly for no transcription. But mRNA will be largely accumulated to make HMGCR.

In all, more HMGCR means more cholesterol and less mRNA.

In fig. 9 I suppose cholesterol is sufficient, which is the major risk to cardiovascular disease. We can see from the figure mRNA and HMGCR decreased at once, because it gives a signal that there are plenty of cholesterol in blood. And when lack of cholesterol, there will also be a signal to tell the system that HMGCR and mRNA are needed. Corresponding, fig. 10 shows us this feedback regulation.

III. Conclusion

If cholesterol is sufficient, HMGCR and mRNA will decrease. If, lack, they will increase.

After these analyses, we can see no matter how the initial condition of these three, the result will be a balance. Among the reasonable range, this biological system can control each part to maintain a friendly, harmonious and dynamic state.

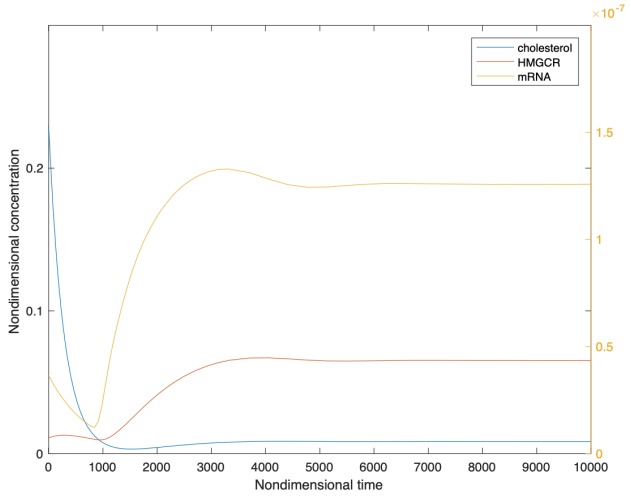

Fig. 9. Effect of increasing initial cholesterol concentration

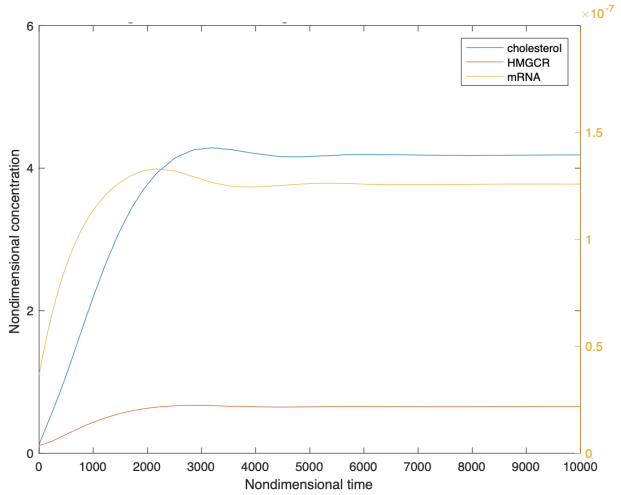

Fig. 10. Effect of decreasing initial cholesterol concentration

REFERENCES

[1] Bonhi S Bhattacharya, Peter K Sweby, Anne-Marie Minihane, Kim G Jackson, and Marcus J Tindall. A mathematical model of the sterol regulatory element binding protein 2 cholesterol biosynthesis pathway. *Journal of theoretical biology*, 349:150–162, 2014.