Dynamic Properties of the Non-linear Cholesterol-level Control in the Cell

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Abstract. Current research in biomedicine is still mostly based on purely experimental discoveries while modelling and simulation are almost unused. Systems biology and systems medicine try to improve the situation, however, mathematical models are being treated in similar manner as biological models, therefore, their contribution is still limited. In this article we show a simplified model of cholesterol metabolism in the body and analyse its properties with respect to system dynamics. Cholesterol metabolism system shows high robustness on metabolic level, while gene expression regulation is susceptible to external disturbances. The model suggests that it is possible to push similar metabolic systems to alternative stable equilibrium point and cause severe problems (disease) without actually damaging the structure of any of the involved molecular species. This new concept of disease understanding my help solve many disease treatment problems.

Introduction

Dynamical properties of biological systems are still largely neglected. Non-linear high-order systems with a complex network of positive and negative feedback loops can exhibit a wide variety of dynamical behaviours, from critically damped and oscillatory to chaotic. One of the most interesting properties of such systems are multiple equilibrium points. Current opinion on disease onset and progression is mostly associated with some kind of a defect in the metabolic machinery of life, such as genetic mutation, ageing effects, and biological or chemical agents.

However, complex dynamical systems can spontaneously shift to an alternative equilibrium point. A disease is generally defined as persistence of one or more system states out of their normal value ranges accompanied with harmful effects to biological processes. Body temperature is one of themost commonlymonitored body states that can indicate on a variety of harmful processes. In linear systems it is not possible to shift from one equilibrium point to another without changing the system parameters. This concept is also widely accepted in biology and medicine, where each disease would want to be described by system parameters such as gene mutations, chemical or isomeric alteration of a molecule etc. On the other hand, nonlinear dynamic systems can spontaneously shift from one equilibrium to another or the shift can be a consequence of environmental effects.

As non-linear systems can persist in any stable equilibrium point, some of the equilibrium points may be harmful to the organism. Many widespread diseases that also cause high costs to the healthcare system [1] such as metabolic syndrome, some cancers, etc., effectively elude all attempts to be classified as genetic disorders of wide range of genes while they may be caused by a complex shift of equilibrium point of several interconnected processes. The idea is further supported by a few cases of spontaneous remissions. The biggest problem is an adequate monitoring of the states in metabolic processes. Each time point requires either blood or tissue sample and can, therefore, not be performed routinely. Brain activity is much easier to monitor, since electroencephalography (EEG) recorders are common equipment and can measure electric activity of the brain with several non-invasive scalp-surface mounted electrodes with sampling frequencies in the range of kHz.

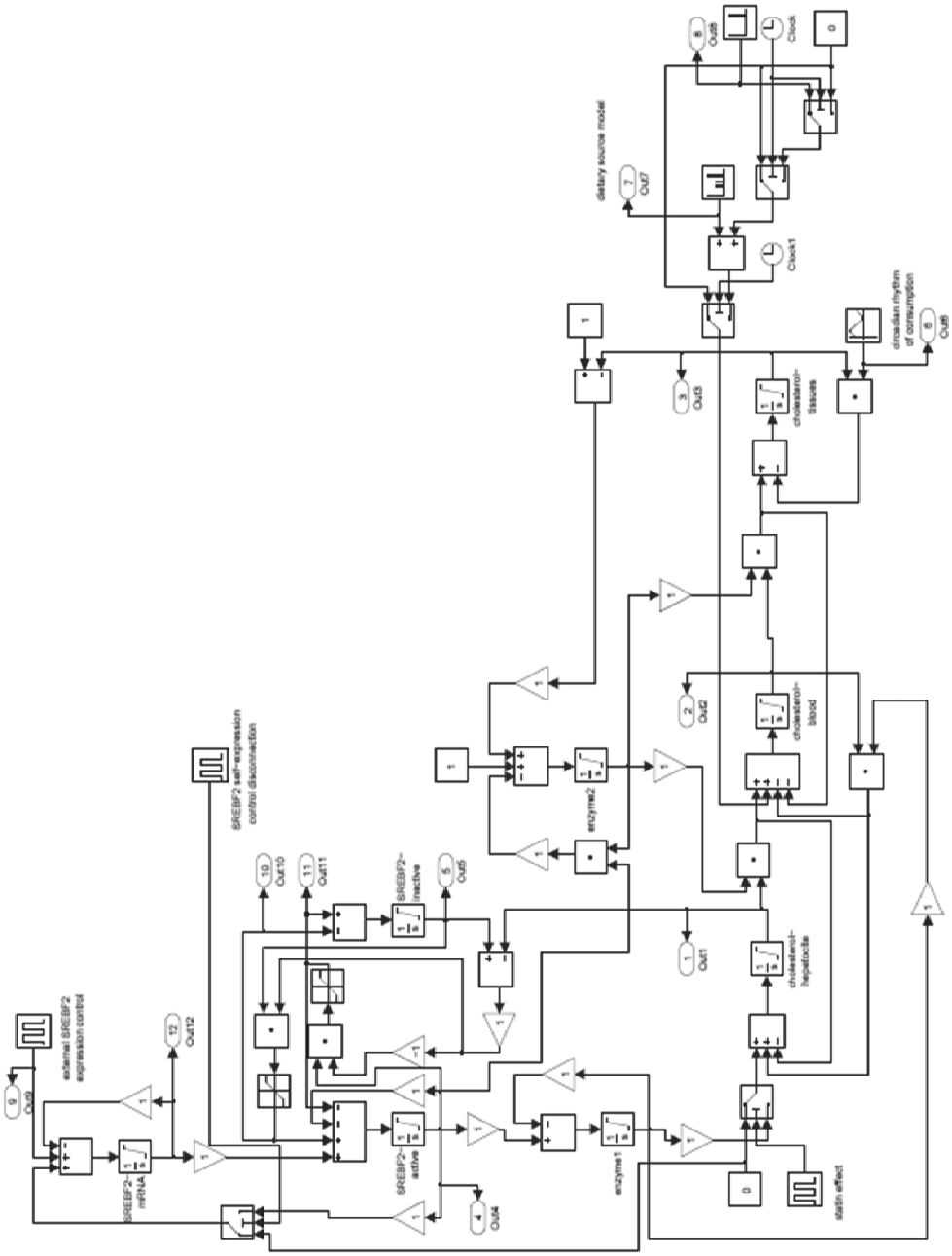

Figure 1: Simulink implementation of the model.

Therefore, it is not surprising that the field of brain activity research adopted system dynamics ideas quite early and currently, epileptic seizures are being interrupted by applying simple vocal disturbance applied at the most convenient time, regarding oscillations around equilibrium point, to push the system toward equilibrium that does not cause seizures [2].

In the absence of suitable monitoring systems, we can only rely on mathematical models when exploring dynamic properties of metabolic systems [3, 4]. In this study we present a cholesterol level regulation mechanism that has some required properties that could result in multiple stable equilibrium points.

1 Simple Model of Cholesterol Regulation in the Body

Cholesterol is one of the most important metabolites in the body, since it is the building block for cell membranes. Any disorder in cholesterol supply can cause severe body malformation of foetus and/or mental retardation since the cells cannot divide properly. Cholesterol is obtained from two sources, one is de-novo biosynthesis and other are dietary sources (Φ_D). Hepatocites are cells that mainly produce cholesterol (C_{CH}) and supply other organs with the necessity amounts. Hepatocites also remove excess cholesterol from the blood stream and convert it to bile. Peripheral tissues mostly consume cholesterol (C_{CP}) and are able to signal their needs for cholesterol.

The cell-level regulation of cholesterol is achieved by equilibriumof transcription factor SREBF2 and cholesterol. At high levels of cholesterol SREBF2 is kept inactive (C_{SI}), bound to cell membrane. SREBF2 controls the expression of all cholesterogenic genes (E_1) which act as a valve on cholesterol biosynthesis pathway. As the levels of cholesterol drop, SREBF2 is released and activated (C_{SA}), transported to nucleus and all the cholesterogenic genes are up-regulated. Since positive loop of SREBF2 on its gene expression (C_{SmRNA}) is a part of cascade regulatory system it does not cause unstable system but rather results in PI-controller like system that is capable of very precise control of cholesterol levels in the cell.

Additional expression control (Φ_{EX}) was added to the model to describe possible independent effects of other processes. Cholesterol is transported through blood (C_{CB}) mostly encapsulated in proteins and actively exported in or out of the cell with a series of transporters (E_2) which are controlled internally as well as externally (Φ_2). The following model was used to describe the presented situation.

$$\frac{dC_{CH}}{dt} = E_1k_1 + C_{CB}E_1k_2 - C_{CH}E_2k_3 \quad (1)$$

$$\frac{dC_{CB}}{dt} = C_{CH}E_2k_3 + \Phi_D - C_{CB}E_1k_2 - C_{CB}E_2k_4$$

$$\frac{dC_{CP}}{dt} = C_{CB}E_2k_4 - C_{CP}k_5\sin(\omega t)$$

$$\frac{dE_1}{dt} = C_{SA}k_6 - E_1k_7$$

$$\frac{dE_2}{dt} = \Phi_D + (R_{CP} - C_{CP})k_8 - C_{SA}E_2k_9$$

$$\frac{dC_{SA}}{dt} = C_{SmRNA}k_{10} + f\big((C_{CH} - C_{SI})C_{SI}\big)k_{11} - C_{SA}k_{12} - f\big((C_{SI} - C_{CH})C_{SA}\big)k_{13}$$

$$\frac{dC_{SI}}{dt} = f\big((C_{CH} - C_{SI})C_{SA}\big)k_{13} - f\big((C_{SI} - C_{CH})C_{SI}\big)k_{11}$$

$$\frac{dC_{SmRNA}}{dt} = C_{SA}k_{14} - C_{SmRNA}k_{15} + \Phi_{EX}$$

$$f(x) = \begin{cases} 0; & x < 0 \\ x; & x \geq 0 \end{cases}$$

In the Equation 1 the k_i represent the model parameters. Since we have no realistic information on the values of the model parameters, because the models is so drastically simplified that they cannot be related to any specific reaction and because systems dynamics of the process is so poorly characterised, the values were chosen such that the system has at least one stable non-oscillatory nonzero equilibriumpoint and reasonably quick transient phenomena. Model simulation and analysis was performed in Matlab/Simulink 2009b (Mathworks Inc., Natick, Mass. USA). The simulink implementation of the model is presented in Figure 1.

2 Simulation Experiments

With simulation experiments the effects of several conditions on cholesterol level control in the hepatocites were tested. Since the control algorithm is a type of ratio control, it is always possible that concentration level set-point could shift, as long as the ration of the involved species stays within range defined by a controller design. Therefore, we tested several conditions that pushed the controlling sub-system to saturation. It was shown in [5] that PI-like control controls the cholesterol levels in the cell, however, the character changes when the system is overloaded. The most important goal was to test if such high disturbances could push the system into a new equilibrium point.

The following conditions were tested: extreme increase in cholesterol uptake from dietary sources, no cholesterol diet, complete blocking of cholesterol biosynthesis (statin activity), elevated demand on cholesterol in peripheral tissues, external influence on SREBF2 expression, and breaking of SREBF2 feedback loop on its expression. The simulation results are presented in Figures 2 to 7. The first simulation experiment was intended to test the capacity of the regulatory mechanisms. The dietary uptake of cholesterol was increased 30 times for a short time, which simulated a large feast. After the large meal, levels decreased to normal values, although the control system was operating in saturation for a while (see Figure 2).

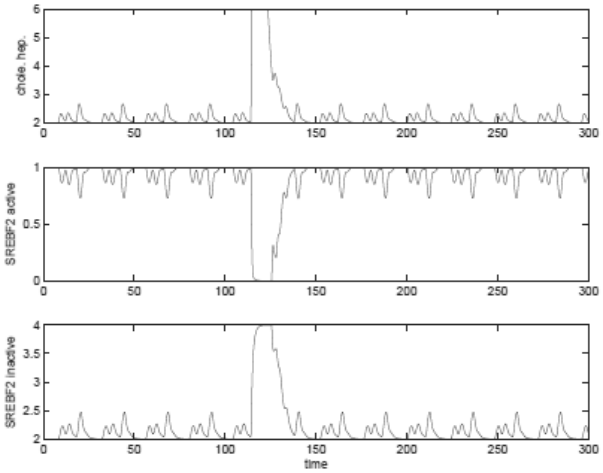

Figure 2: Simulation of large dietary uptake (30 times larger than normal uptake).

The second simulation experiment was designed to test low cholesterol diet circumstances. As this is normal situation for most animals, the system replaces all the dietary cholesterol with internally synthesised and normally functions (see Figure 3).

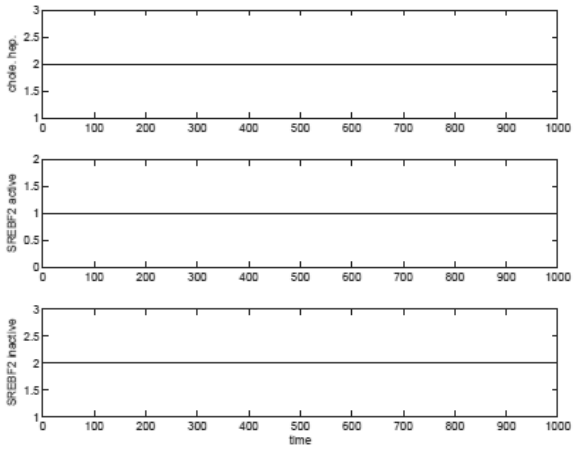

Figure 3: Simulation of no cholesterol diet.

The third simulation experiment explored the influence of statins, cholesterol lowering drugs on cholesterol biosynthesis. Stains are designed to block cholesterol biosynthesis by binding to one of the important synthesis enzymes. Complete blocking of cholesterol biosynthesis resulted in complete depletion of cholesterol in hepatocites, however, as blockade was lifted, the levels were completely restored (see Figure 4).

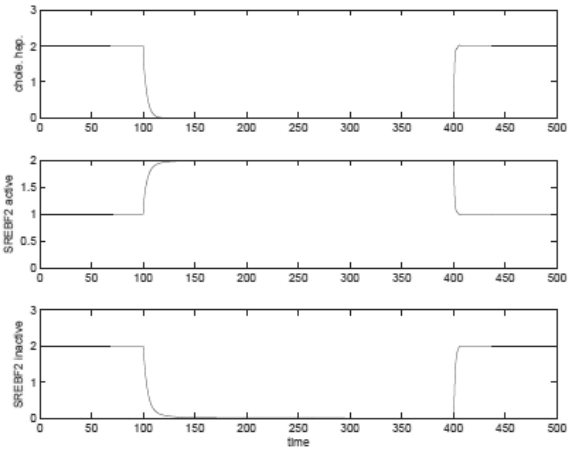

Figure 4: Simulation of complete biosynthesis blocking.

The fourth experiment targeted the influence of increased demand on cholesterol levels in hepatocites. The demand was increased to double value of the usual demand. Only minor reduction in cholesterol levels in hepatocites was observed (see Figure 5).

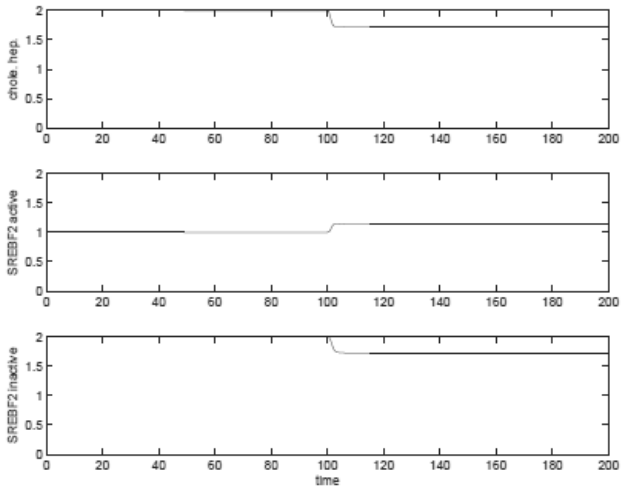

Figure 5: Simulation of increased demand (2x) in peripheral tissues.

The fifth experiment was designed to test the gene expression of SREBF2 influence on the cholesterol regulation. A short external intervention causes long term disruption of cholesterol level control by changing its set-point (see Figure 6).

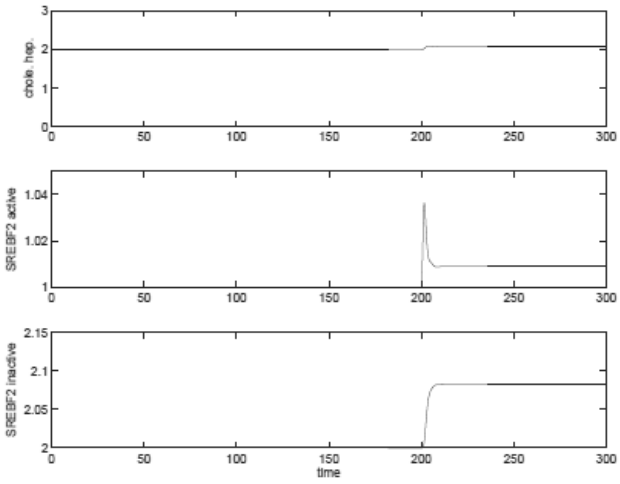

Figure 6: Simulation of external influence on SREBF2 expression (1% of normal expression flux, short pulse).

The sixth simulation experiment also targeted SREBF2 expression regulation, however, this time feedback from SREBF2 protein was disconnected. Again, this resulted in set-point disturbance. As the disconnection was long enough, active and inactive SREBF2 were depleted and the system could no longer regain its functionality (see Figure 7).

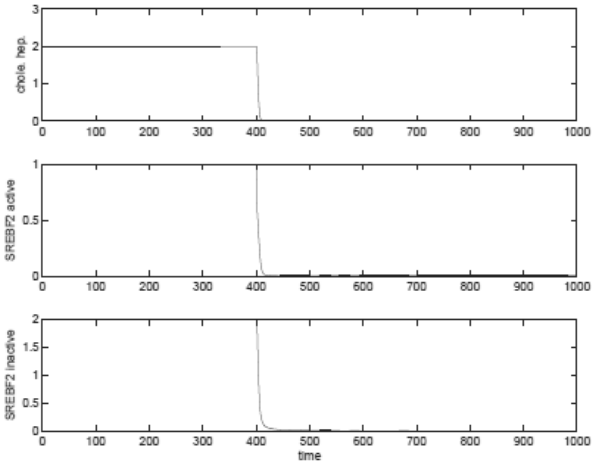

Figure 7: Simulation of a short break of the internal control loop for SREBF2 expression.

3 Discussion

Simulation experiments show interesting property of the metabolic systems. They are extremely robust to any disturbance on metabolic level and their regulation can compensate for more than 10-fold changes in uptake or consumption. Sigmoid type non-linearities arrising from products of variable in enzyme reaction models reduce control problems at high fold changes of levels since they have very low attenuation at high values and thus prohibit the propagation of such spikes through the system. Although we expected problems when system would be pushed to saturation it completely recovered to original equilibrium point.

Saturation of the metabolic pathway means that further elevation of concentration cannot significantly elevate the flux through the network which can beneficial in cases of uptake and quite problematic in cases of elimination since we can expect accummulation of metabolites in tissue, however, regulation system remains intact. The protein and gene expression levels seem to be me more sensitive to perturbations. Any interference with gene expression regulation results in equilibrium point change that is not reversible.

However, such external gene expression controllers exist, since regulatory network is also full of feedback-mechanisms that take care of flux distribution and rational energy consumption of the body. They may not be entirely independent of cholesterol metabolic pathway, however, we can expect that in some specific conditions controller set-point might actually change which would cause system wide problems.

4 Conclusion

Although the presented simulation results do not prove the concept of system dynamics as one of the reasons for entering disease state, they provide some important insights into metabolic systems functioning. Almost all regulatory mechanism operate in ration control mode, which makes them potentially susceptible to spontaneous setpoint changes. As shown in this paper, it takes only short term disturbances at the right place of the system and long-term consequences can occur. This new concept of disease analysis and treatmentmay add a new piece to our understanding of the diversity of biological processes.

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