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Mathematical Two-compartment Model of Human Cholesterol Transport in Application to High Blood Cholesterol Diagnosis and Treatment

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Abstract

Cholesterol plays a vital role in human body. Its unbalanced homeostasis, however, leads to health related problems. The elevated blood cholesterol levels are now considered a classic coronary risk factor and are suspected to lead to coronary artery diseases, causing 2.6 millions of deaths each year. Here, we develop a two-compartment mathematical model to investigate cholesterol transport in the circulatory system and its de novo synthesis in the liver. The model is described with a set of two simultaneous linear differential equations, which solutions yield changes over time of the cholesterol levels in the liver (compartment I) and bloodstream (compartment II). We show the applicability of the model to investigate the processes associated with the high blood cholesterol, e.g. lowering the cholesterol levels by inhibiting de novo cholesterol synthesis. Taking advantage of the analytically derived relationships for the steady state (equilibrium), we show how the model could aid diagnosis of high blood cholesterol by identifying whether the disturbances in the cholesterol homeostasis are due to impaired transport from the liver to the bloodstream, or *vice versa*.

Keywords: high blood cholesterol, metabolic syndrome, mathematical modelling

1 Introduction

Cholesterol plays a vital role in human body. It is an essential structural component of cell membranes where it modulates membrane permeability and fluidity

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over a range of physiological conditions[1,30]. Furthermore, within cell membranes it supports the structure of lipid rafts, stabilizing proteins that perform a wealth of cellular function, including transporting substances into and out of cell, attaching to and communicating with other cells or responding to endocrine hormones[9,26]. Cholesterol itself is also involved in the modulation of intracellular transport, cell signalling and nerve conduction[5,19] and acts as an important precursor molecule in several biochemical pathways[4]. Bile salts are synthesized from the cholesterol in liver to be stored in gallbladder and released to duodenum to solubilize dietary lipids, aiding their digestion and absorption[23]. Other cholesterol derivatives include steroid hormones, both adrenal gland hormones involved i.e. in stress response and in maintaining body's salt and water levels and sex hormones such as estrogen, progesterone or testosterone[10]. In addition, cholesterol is involved in the synthesis of vitamin D that plays an essential role in the control of calcium and phosphorus metabolism[4,31].

To provide sufficient amount of cholesterol in the human body, ca. 1g of cholesterol per day is *de novo* synthesized in human liver and ca. 2-3g is obtained with food (dietary cholesterol)[24]. Cholesterol is almost insoluble in water and therefore by itself cannot freely travel in the bloodstream. To maintain its adequate and targeted delivery to body sites (cells or tissues), cholesterol is transported in the circulatory system encapsulated in the lipoprotein complexes that are made of hydrophobic lipids core surrounded by a shell of more-polar lipids and proteins[6] (Figure 1). These are classified according to increasing density as chylomicrons, chylomicron remnants, very low density lipoproteins (VLDLs), intermediate-density lipoproteins (ILDs), low-density lipoproteins (LDLs) and high-density lipoproteins (HDLs)[21]. The body regulates the transport and amount of cholesterol present. This is done at the various levels and the detailed description is beyond the scope of this paper, but among others, the increased intake of dietary cholesterol is compensated by the decreased *de novo* cholesterol synthesis by the feedback regulation of the amount and activity of 3-hydroxy-3-methylglutaryl CoA reductase (HMG-CoA reductase), an important intermediate of the cholesterol biosynthesis pathway[4,29].

Unbalanced cholesterol homeostasis leads to health related problems and especially the elevated blood cholesterol levels are now considered a classic coronary risk factor and are suspected to lead to the third of the coronary artery disease (top prevalent disorder) causing 2.6 millions of deaths each year (World Health Organization). Coronary artery disease is caused by the plaque building up along the inner walls of the arteries of the heart, narrowing them and reducing blood flow to the heart[11]. It is believed that it is caused by a chronic inflammatory response in the walls of arteries due to accumulation of macrophages and white blood cells and promoted by LDLs (bad cholesterol) without the adequate removal of fats and cholesterol form the macrophages by HDLs (good cholesterol)[16]. At the molecular level the regulation of cholesterol homeostasis is quite complex and not still fully understood, hence the diagnosis of the underlying problems of the unbalanced cholesterol transport remain challenging. The elevated blood cholesterol levels are battled with changes in lifestyles (e.g. reducing the amount of dietary cholesterol,

increased physical activity) and lowering cholesterol drugs with various modes of actions (e.g. reducing *de novo* cholesterol synthesis)[25,27]. However, quite often finding the right treatment is based on the trial and error approach. Mathematical modelling of the cholesterol transport and *de novo* synthesis could help understanding the underlying mechanisms of the disturbances in the cholesterol homeostasis. However, this would require modelling of the complex processes, both at the genetic, molecular (e.g. HMG-CoA reductase effects) and physiological and/or tissue level (e.g. cholesterol uptake by the liver), whose exact mechanisms are not yet fully understood[12]. This could reflect a very limited number of mathematical models within the field. The previous work included models of lipoprotein dynamics (e.g. a model of the fluid dynamics of lipid accumulation on the arterial walls[14] and chemical kinetics of LDL oxidation[7]) as well as of lipoprotein metabolism[2]. Here, we aim at developing a simple mathematical model of cholesterol transport and *de novo* synthesis that could offer insights into high blood cholesterol diagnosis and treatment.

2 Materials and Methods

2.1 Overview of the current knowledge of cholesterol transport

Based on the literature search, we have identified and presented the overview of the current knowledge of cholesterol transport in the lipoproteins (Figure 1). Cholesterol (C), along triacylglycerols, obtained from diet is carried away from the intestine in the form of large chylomicrons (CM), the lowest density lipoproteins containing ca. 90% of triacylglycerols (TAGs) and ca. 4% of cholesterol. In muscles and other tissues using fatty acids as fuels, triacylglycerols from CM are released as free fatty acids (FFA) and the liver takes up the cholesterol-rich residues (chylomicron remnants)[4]. Liver is the major site of *de novo* cholesterol (and TAGs) synthesis (in addition to the cholesterol obtained from diet, dietary cholesterol) that is regulated by the cholesterol levels present and the excess of cholesterol is exported into the blood in the form of VLDLs[12,22]. As in CM, TAGs are hydrolysed by lipases (released) at the muscles and tissues, transforming VLDLs into IDLs. Half of IDLs is taken up by the liver and the other half is converted to LDLs by the removal of more TAGs[4]. LDLs are the major carrier of cholesterol in the blood and their role is to transport cholesterol to the peripheral tissues and regulate *de novo* cholesterol synthesis at these sites. HDLs, on the other hand, binds the esterified cholesterol released from the peripheral tissues and transports it back to the liver for the synthesis of bile and steroid hormones[4,21]. Finally, ca. half of the cholesterol in bile released to digestive tract is recycled, i.e. reabsorbed by the small bowel back into the bloodstream[4]. The chemical reactions are catalysed by enzymes and regulated by proteins: ABCA1, cholesterol efflux regulatory protein; CEPT, cholesteryl ester transfer protein; LCAT, lecithin-cholesterol acyltransferase; LIPC, hepatic lipase; LIPG, endothelial lipase; LPL, lipoprotein lipase; LIPC, hepatic lipase and PLTP, phospholipid transfer protein.

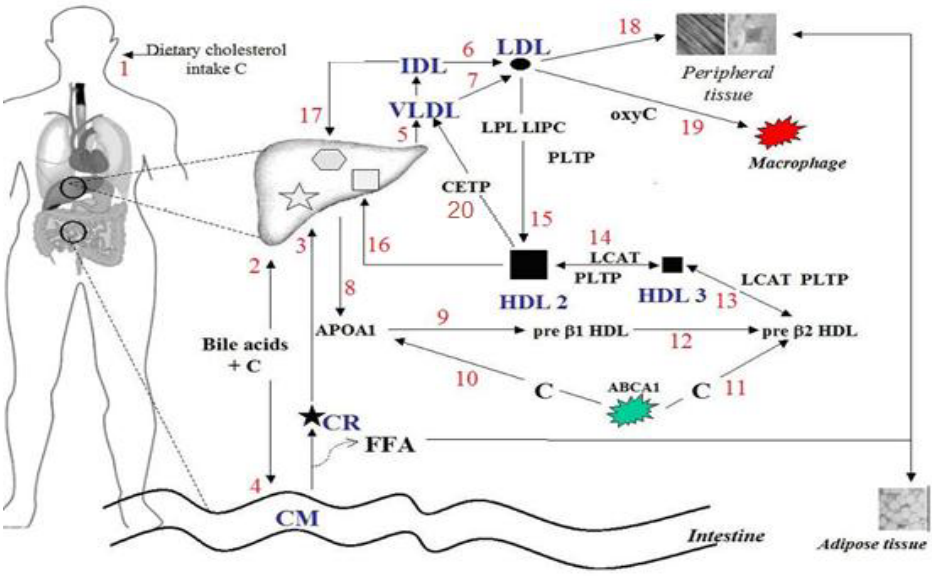

Fig. 1. Overview of the keys biochemical processes behind cholesterol transport by lipoproteins. Dietary and de novo synthesized cholesterol is redistributed to muscles and peripheral tissues (LDLs) as well as removed from the bloodstream (HDLs) to maintain cholesterol homeostasis.

2.2 Modelling cholesterol circulatory transport and de novo synthesis

To analyse the disturbances in the cholesterol homeostasis we have developed a simple mathematical model based on the key aspects of the available current knowledge of cholesterol transport within lipoproteins and its *de novo* synthesis in the liver (main site of the *de novo* cholesterol synthesis). We have simplified and represented the biochemical processes shown in Figure 1 in a two-compartment model with the first compartment (I) representing the total cholesterol present in the liver and the second compartment (II) representing the total cholesterol present in the circulatory blood (bloodstream) as in Figure 2.

A set of two simultaneous differential equations describes the rate of changes of the total amount of cholesterol (m_1 and m_2) in the two compartments respectively (Eq.1 and Eq. 2; Figure 2).

$$\frac{dm_1}{dt} = \frac{k}{m_1} + k_{21}m_2 - k_{12}m_1 + m_{in} - m_{out} \tag{1}$$

$$\frac{dm_2}{dt} = -k_{21}m_2 + k_{12}m_1 - m_{tis} + m_{diet} \tag{2}$$

The amount of cholesterol in the first compartment is dependent on the *de novo* cholesterol synthesis (inversely proportional to m_1 with rate k), transport of the cholesterol from compartment II to I (directly proportional to m_2 with rate k_{21}, reverse cholesterol transport), transport of the cholesterol from compartment I to II (directly proportional to m_1 with rate k_{12}),m_{in} cholesterol obtained from intestine

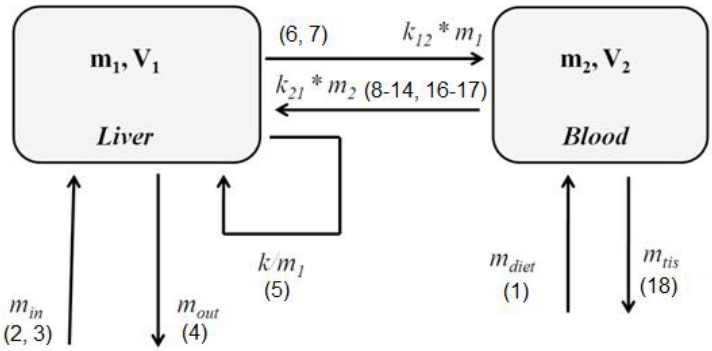

Fig. 2. A schematic representation of the two-compartment model of cholesterol transport in the lipoproteins; First compartment reflects liver, the main site of *de novo* cholesterol synthesis, the second compartment reflects bloodstream. Numbers in parentheses indicate corresponding biochemical processes from Figure 1.

(from membranes of the enterocytes (epithelial cells) that underwent programmed cell death and recycled from bile acids) and m_{out} cholesterol used as a precursor of bile acids and being a part (8%) of bile. The amount of cholesterol in the second compartment is dependent on the transport of the cholesterol between compartments, m_{tis} cholesterol transported to muscles and peripheral tissue (membrane component) as well as used as a precursors in biochemical reactions (vitamin D, steroid hormones) and m_{diet} dietary cholesterol. These two equations embrace in a simplified form all the physiological processes in cholesterol transport and *de novo* synthesis as outlined in Figure 1 (corresponding processes numbers shown on Figure 2) and their solutions show the changes over time of the total cholesterol in the two compartments (liver and bloodstream).

2.3 Values of the model parameters

The values of the model parameters were assigned based on the literature search (for most of the parameters) and mathematically derived (or assumed) given the known values of the remaining parameters, where literature data were not available (k_{12} and k_{21}). The values of model parameters are shown in Figure 3. We have set the volume of blood in the liver compartment, V_1, equal to 12 dl and in the second compartment, V_2, equal to 43 dl (overall 55 dl of blood in the human body)[2] and assumed no changes in these blood volumes. In addition, we assumed that the total amount (C_2, concentration) of the cholesterol in blood is equal to or below 200 mg/dl, healthy physiological values[11]. The kinetic changes of the parameters (m_{in}, m_{out}, m_{diet}, m_{tis}) are expressed in mg/min (units of the literature data were changed (rescaled / recalculated) accordingly given the assumed values of V_1 and V_2).

3 Calculations

The set of two simultaneous linear differential equations has been coded in Matlab (version 2007b), a high-level technical computing language and environment, and

Parameter	Literature value	Rescaling / calculations	Model value	Source
k	k/m$_1$: 0.324 ÷ 0.624 mg/min	for C_1=C_2 and max rate of synthesis (0.625 mg/min) k=0.625 / 2400 mg^2/min	1500 mg^2/min	[4]
k_{21}	value assumed	k_{21}	1.0 min^{-1}	[11]
k_{12}	mathematically derived	k_{12}= V_2*k_{21}/V_1	3.58 min^{-1}	NA
m_1	assumption: C_1 is equal to C_2	m_1 = C_1 * V_1 = 200 mg/dl * 12 dl	2400 mg	NA
m_2	max C_2=200 mg/dl	m_2 = C_2 * V_2 = 200 mg/dl * 43 dl	8600 mg	[11]
V_1	12 dl	NA	12 dl	[2]
V_2	43 dl	NA	43 dl	[2]
m_{in}	1.44 g/day	1440mg / (24 h * 60 min)	1 mg/min	[23]
m_{out}	2 g/day	2000 mg / (24 h * 60 min)	1.4 mg/min	[23]
m_{diet}	0 ÷ 3 g daily intake 0.33 g daily absorption	Time of cholesterol absorption 180 min	0 ÷ 1.1 mg/min	[23]
m_{tis}	350 mg/day	350 mg / (24 h * 60 min)	0.234 mg/min	[23]

Fig. 3. Values of the model parameters: literature derived and calculated.

numerically solved using Runge Kutta Method (ode45 solver). This yielded equations for the change of total cholesterol (m_1 and m_2) over time in the corresponding compartments. We have found the stationary solutions to the differentiation equations, i.e. for which there is no change of cholesterol mass over time ($dm_1/dt = 0$ and $dm_2/dt = 0$) (Eq. 3 and Eq. 4).

$$m_1^* = -\frac{k}{m_{diet} + m_{in} - m_{out} - m_{tis}} \tag{3}$$

$$m_2^* = \frac{m_{diet}^2 + m_{diet}m_{in} - m_{diet}m_{out} - kk_{12} - 2m_{diet}m_{tis} - m_{in}m_{tis} + m_{out}m_{tis} + m_{tis}^2}{k_{21}\left(m_{diet} + m_{in} - m_{out} - m_{tis}\right)} \tag{4}$$

In a special case of no dietary cholesterol ($m_{diet} = 0$, e.g. after overnight fasting or cholesterol free diet), a relationship between the stationary masses ($m_1{}^*$ and $m_2{}^*$) can be obtained in the form of Eq. 5.

$$m_2^* = m_1^* \frac{kk_{12} + m_{in}m_{tis} - m_{out}m_{tis} - m_{tis}^2}{kk_{12}} \tag{5}$$

Using the definition of concentration as the amount of substance (total cholesterol mass) per defined space (volume) (C=m/V), the above equation can be rewritten for the stationary total cholesterol concentrations in the two compartments correspondingly (Eq. 6)

$$C_2^* = C_1^* \frac{V_1}{V_2} \frac{kk_{12} + m_{in}m_{tis} - m_{out}m_{tis} - m_{tis}^2}{kk_{12}} \tag{6}$$

4 Results and Discussion

4.1 Model analysis

The developed two-compartment model allows modelling and analysing a range of physiological processes related to the high blood cholesterol levels (C_2). The high blood cholesterol levels can be modelled, examined and lowered via changing values of the model parameter. This can be carried out in the physiological context since the model parameters represent the underlying biological mechanisms driving cholesterol transport and de novo synthesis (Figure 1 and Figure 2). Few examples of model analysis are shown on Figure 4. The expected changes of blood cholesterol levels (C_2) are observed when changing the values of the rates of cholesterol transport from compartment II to I (from bloodstream to the liver), i.e. increase and decrease of blood cholesterol levels C_2 for k_{21} = 0.8 min^{-1} (lowered, compared to default k_{21} = 1 min^{-1}) and k_{21}= 1.2 min^{-1} (increased) respectively (Figure 4a). In addition, the predicted behaviour of blood cholesterol dynamics can be observed (Figure 4b). Following a cholesterol-rich meal, blood cholesterol levels (C_2) increase 3 h following the meal (during the period of assumed absorption of dietary cholesterol) and then lower to reach the pre-meal (initial) state. To achieve the physiological dynamics of the return to the pre-meal state (within 12 h) the values of m_{out} had to be slightly increased (m_{out} = 1.6 mg/min as oppose to default 1.4 mg/min) to compensate for the fact the model in its current form does not include the processes associated with the circulation of bile acids. Typically, during a meal, bile (containing bile acids synthesized from cholesterol in the liver) is discharged from the gallbladder into the duodenum where it solubilizes fats to aid their absorption as well as fat-soluble vitamins. Following the meal, cholesterol in the bile released to the digestive tract is reabsorbed back into the bloodstream (recycled). To model these processes, a third compartment representing gallbladder would be needed.

Given the model, it is also possible to investigate the therapeutic strategies to lower high blood cholesterol. High blood cholesterol levels (C_2) obtained due to high levels of bad cholesterol (by setting the value of m_{tis} to 0 mg/min) can be counter by inhibiting de novo cholesterol synthesis (by lowering the values of k to 1000 mg/min) (Figure 4c). Statins inhibit HMG-CoA reductase and are the first-line therapy for reducing LDLs blood levels in patients at high risk for coronary art disease [18]. They have been proven to be able to reduce the 5-year incidence of major coronary events by about one fifth per mmol/L reduction in blood LDLs levels[3]. However, they are no side effects free; these tend to be dose related and include raised liver enzymes and muscle problems[13]. Tailoring the values of the model parameters to an individual patient could help selecting the optimal dosage of statins and predict the expected cholesterol levels during the treatment. Another way to counter the increased blood cholesterol levels is to reduce the activity of CETP, plasma lipid transfer protein that facilitates the transport of cholesterol and TGAs between the different fractions of lipoproteins. This can be modelled by simultaneously adjusting the values of rates of cholesterol transport between the

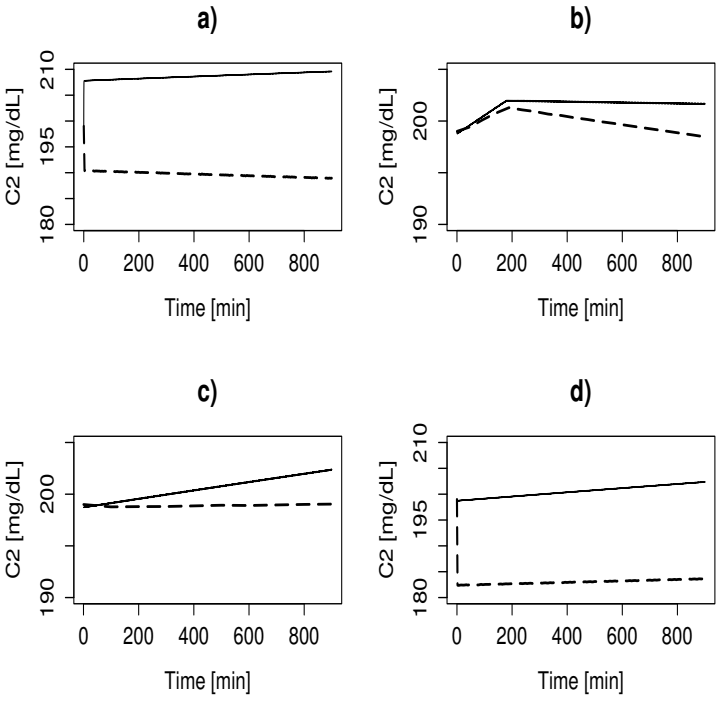

Fig. 4. Examples of the modelling possibilities showing changes in the blood cholesterol levels: a) increase and decrease of the blood cholesterol due to changes in the rates of cholesterol transport from bloodstream to the liver alone; solid line: decreased rates (k_{21} = 0.8 min^{-1}), dashed line: increased rates (k_{21} = 1.2 min^{-1}); b) increase of blood cholesterol levels following uptake of dietary cholesterol (absorption up to 3 h following a meal); solid line: m_{diet} = 1 mg/min, dashed line: m_{diet} = 1mg/min and increased m_{out}= 1.6 mg/min; c) effect of the increased cholesterol level due to decreased cholesterol transport to muscles and peripheral tissues and decreased usage as a precursor of vitamin D and steroid hormones (m_{tis} = 0 mg/min, solid line) and counter-acting this increase by decreasing de novo cholesterol synthesis (k = 1000 mg^2/min, dashed line) and d) increase of blood cholesterol levels due to lowering the activity of the CETP protein (k_{12} = 3.3 min^{-1} and k_{21}=1.3 min^{-1})

two compartments (lowering k_{12} to 3.3 mg/min and increasing k_{21} to 1.3 mg/min) (Figure 4d). Here, the model could be used to test novel drugs regulating the activity of CETP. No such drugs are used in the current medical practise, yet few are being tested in the clinical trials (dalcetrapib, anacetrapib)[15]. It is believed that reducing activity of CETP can not only lower the blood levels of LDLs, but also increase the levels of HDLs (good cholesterol) and restoring the physiological balance between the lipoproteins fractions[28]. However, the relationship between lipoproteins metabolism, pharmacologic CETP inhibition and the development of coronary artery diseases requires further elucidation.

4.2 Diagnostic significance

An advantage of modelling the cholesterol transport and *de novo* synthesis in a form of a simple two-compartment model is that it can be easily described by the two simultaneous linear differential equations, for which the exact analytic solutions in the steady state (equilibrium) can be obtained (Eq.3 and Eq.4). Furthermore, these

analytic solutions can be used to find relationships between the model parameters (e.g. Eq. 6). The sensitivity analysis to these equilibrium solutions showed that the model is not very sensitive to changes of the values of the cholesterol mass parameters of m_{in}, m_{out} and m_{tis} and the rate of *de novo* cholesterol synthesis k. The changes of these values ($0 < m_{in} < 1$ mg/min, $0 < m_{out} < 1$ mg/min, $0 < m_{tis} < 0.4$ mg/min, and $0 < k < 2000$ mg^2/min) yield only a small response of the cholesterol concentration ratio (${C_2}^*/{C_1}^*$) - in the order of magnitude of 4 (10^{-4})(data not shown). However, a model has proved to be sensitive to the changes of the values of the rates of cholesterol transport between the two compartments (k_{12} and k_{21}) (Figure 5). Changing the values of k_{12} and k_{21} from 0 to double their normal, equilibrium state values ($0 < k_{21} < 2$ and $0 < k_{12} < 5$) gave exponential-like (or power) and linear responses for k_{21} and k_{12} respectively.

The rates of cholesterol exchange (transport) between the two compartments are the key parameters affecting the cholesterol concentration and hence are of potential diagnostic application. Screening for high blood cholesterol levels is recommended for all patients with coronary artery diseases or their risk factors (e.g. men aged 45 years or older, women aged 55 years or older, family history of coronary artery diseases, hypertension or smoking) and lipoprotein panel blood tests provides results on the measures of lipids, including total cholesterol and its fractions (incl. HDLs and LDLs)[20]. The elevated cholesterol, in particularly the LDL fraction can be lowered by up to 15% by changes in lifestyle (diet and exercise) and by up to 50% and up to 60% with the maximum dosages of statins and cholesterol-absorption inhibitors respectively[25]. However, not all patients respond well or at all to the medications, and selection of doses as well as a type of treatment is quite often conduced via a trial and error approach. In these problematic patients, according to our model, the measurement of the cholesterol concentration ratio (${C_2}^*/{C_1}^*$) could be informative of the underlying causes of the high blood cholesterol. In particular, low values (${C_2}^*/{C_1}^* << 1$) indicate problems with transport of cholesterol from liver to the bloodstream, that is with processes such as releasing the excess cholesterol from the liver in the form of VLDLs or hydrolysing by lipases TAGs at the muscles and tissues and transforming VLDLs into IDLs (processes labelled on Figure 1 as 6 and 7). High values (${C_2}^*/{C_1}^* >> 1$), on the other indicate the problems with transport of cholesterol from bloodstream to the liver including processes such as i) the maturation process of HDLs molecules (from pre 1 HDL via pre 2 HDL and HDL3 into HDL2, with apolipoprotein (Apo) A1 peptides (principal component of HDLs) acting as recognition sites by the LCAT and PLTP enzymes in this process), ii) uptake of mature HDL2s by the liver, iii) induction of cholesterol efflux from macrophages inside artery walls by ABCA1 gene or iv) uptake by IDLs by the liver (processes labelled on Figure 1 as 8-14 and 16-17)[8]. The knowledge of the direction of the underlying cause of high blood cholesterol (either disturbance of cholesterol transport from the liver to bloodstream or *vice versa*) could be essential in the further diagnostics and treatment of some of the patients in which finding lowering cholesterol interventions are not straightforward. In these patients, the measurement of the cholesterol levels in the blood from the hepatic portal vein or

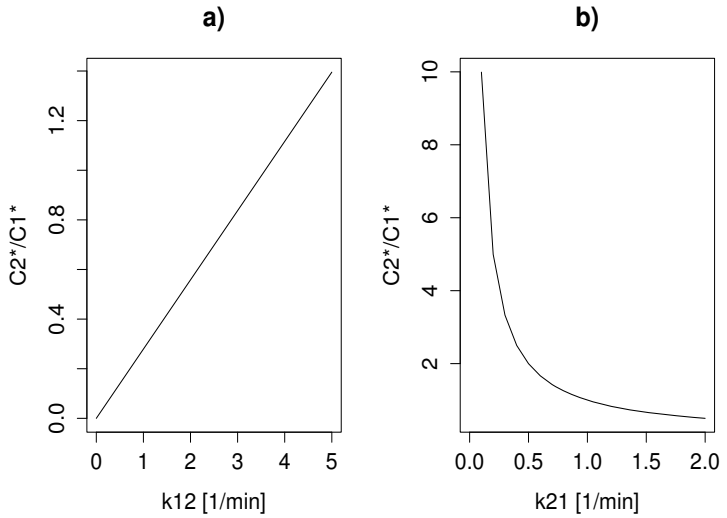

Fig. 5. Plot of equilibrium solutions vs. the changes in the rates of cholesterol transport: a) from compartment II to I and b) from compartment I to II. Low levels of the cholesterol ratio (${C_2}^*/{C_1}^* << 1$) indicate that the underlying cause of the disturbances of the cholesterol homeostasis are due to impaired transport of cholesterol from compartment I to II; high levels (${C_2}^*/{C_1}^* >> 1$) point towards the impaired transport from compartment II to I.

based on the liver biopsy, a more invasive way than the standard blood test, could provide the essential insights into the underlying causes of disturbance of cholesterol homeostasis and direct further diagnosis (e.g. genetic testing of mutations in HDLs and LDLs receptors or the main apolipoproteins components (ApoA1 in HDLs, or ApoB in chylomicrons and LDLs).

5 Conclusions

Maintaining cholesterol homeostasis is a complex process that takes place at the genetic, cellular and tissue levels. Disturbances in the cholesterol balance, especially high levels of blood cholesterol levels lead to coronary artery diseases and are estimated to cause 2.6 millions of deaths each year. Furthermore, statins, lowering *de novo* cholesterol synthesis, are the most common prescribed medications, all showing that our cholesterol health is of importance. Whereas many mathematical models have been developed to better understand the mechanism of glucose-insulin regulatory system [17] (of similar complexity and significance as cholesterol, leading to another prevalent disease, namely diabetes), the modelling approaches to cholesterol homeostasis are limited. Here, we showed that even modelling the keys aspects behind cholesterol homeostasis in the two-compartment model enables investigation of the elevated blood cholesterol levels in the physiological and diagnostic context. We have showed that the changes in the blood cholesterol levels can be obtained in the predictive fashion, when changing the values of the model parameters. Furthermore, we demonstrated the models potential to investigate different treatment strategies to lower high blood cholesterol values (via reduction of *de novo*cholesterol

synthesis or reduction of the activity of the CETP protein). Finally, taking advantage of being able to find analytic solutions to the stationary states, we derived the potential relationship between the ratio of cholesterol levels in the blood and liver (C_2^*/C_1^*) that could be significance when pinpointing the underlying causes of cholesterol homeostasis.

Presenting a relatively simple two-compartment model of cholesterol transport and *de novo* synthesis, we would like to highlight the importance of mathematical modelling in improving understanding of the cholesterol homeostasis as well as in aiding the diagnosis and treatment of the life-treating high blood cholesterol levels. Advanced models could not only help to elucidate the relationships between regulation of cholesterol homeostasis at the gene, cellular and tissue level, but could bring us a step closer to a personalized medicine in preventing and treating high cholesterol levels. We have now started developing such advanced model by focusing first on the inclusion of the aforementioned function of the gallbladder.

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