A SIMULATION MODEL FOR BLOODCHOLESTEROL DYNAMICS AND RELATED DISORDERS[1]

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ABSTRACT

Cholesterol metabolism and other factors affecting its dynamics comprise a complex system. The goal of this study is to construct a system dynamics simulation model that can generate long term dynamics of cholesterol metabolism in healthy and hypercholesterolemic subjects, with respect to body weight, diet, and exercise. For both healthy and hypercholesterolemic subjects, the model generates realistic behavior patterns for different types of blood cholesterol and body weight. It is shown in this study that a person can have healthier cholesterol levels by changing her diet and/or doing more exercise. Also it's observed that exercise is more effective than diet even in cases when the subject does not lose weight. In the case of hypercholesterolemic patients, the model effectively mimics the way typical drugs work and shows how the patient can reach healthier cholesterol levels.

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1. INTRODUCTION

Different parts of human body have different characteristics; but, through blood, all of them must receive micronutrients from the central system for their metabolic or structural needs. Some of these micronutrients such as glucose, fatty acids, and amino acids are required in large amounts. Though needed in minimal amounts, cholesterol is no less vital than others. Cholesterol is essential for survival. This lipid is found in parts of the outer membrane that surrounds every cell and used to produce hormones, vitamin D, and bile acids that are essential in digesting fat. (Murray, Granner, & Rodwell, 2006)

Cholesterol is synthesized virtually within all of the nucleated cells. The liver also synthesizes cholesterol and sends it to the peripheral tissues via the blood stream. Since cholesterol, like other lipids, is insoluble in water it is bound to blood lipoproteins for its transport. Low-density lipoprotein (LDL) is responsible for the uptake of cholesterol from liver to the other tissues. High-density lipoprotein (HDL) removes free cholesterol from the tissues and arteries and takes them back to the liver. (Murray, Granner, & Rodwell, 2006; Bhagavan, 2002 ;Guyton, et al., 1991)

Very-low density lipoprotein (VLDL) is the vehicle of transport of triacylglycerols from the liver to the other tissues. Reaction with the extrahepatic tissues results in the loss of most of the triacylglycerols in the VLDL. The resulting remnant is called intermediate-density lipoprotein (IDL). The liver takes up about half of the IDL, while the other half is converted to low-density lipoprotein (LDL), which is rather rich in cholesterol. (Bhagavan, 2002)

Because LDLs are the remnants of the remnants of the VLDLs in the blood, the density of LDL in the blood is determined by the rate of VLDL secreted from the liver. Hepatic triacylglycerol synthesis is followed immediately by the formation and secretion of VLDLs. In humans, the fatty acids used in this process are mainly from the uptake of free fatty acids from the circulation.

High-density lipoproteins (HDL) are synthesized and secreted from the liver and intestines. HDL has a part in the removal of excess unesterified cholesterol from lipoproteins and tissues. The class B scavenger receptor B1 (SR-B1) is an HDL receptor that has dual role in HDL metabolism. In the liver and steroidogenic tissues, it selectively uptakes cholesteryl ester to the cells; while in the tissues SR-B1 mediates the acceptance of cholesterol from the cells to the HDL. HDL transports these cholesterols to the liver for excretion via bile or bile acids. Absorption of bile and bile acids back from the intestines to the liver is thus an important determining factor of cholesterol pool in the liver. This process is known as reverse cholesterol transport, or RCT (Murray, Granner, & Rodwell, 2006). Because HDL lowers the amount of cholesterol in the extrahepatic tissues, extrahepatic tissues become more willing to take up cholesterol from blood which is mainly from LDL. Thus increased levels of HDL or HDL choleterol have an indirect effect on LDL cholesterol stocks in the blood. Figure 2.2 depicts the stocks and flows that correspond to the main agents involved in the cholesterol metabolism described above.

Though the most significant determinants of cholesterol in blood are of hereditary nature, there are numerous dietary and environmental factors. These can be listed as diet, exercise, drugs, and stress. Diet has a direct effect on blood cholesterol levels. Taking too much cholesterol and saturated fatty acids instead of taking polyunsaturated and monounsaturated fatty acids tends to increase blood LDL levels (Dietschy, Turley, & Spady, 1993). Bile acids, which are secreted from cholesterol of liver origin, are also a determining factor on the blood levels of cholesterol. Exercise, depending on its intensity and frequency, has a positive effect on the cholesterol levels in the blood. In most of the studies, it has increased blood HDL levels.

There are several types of medication for cholesterol disorders. The most common type is statin related drugs. Statins interfere with the ability of the liver to synthesize cholesterol by blocking some necessary enzymes. Statins increase the uptake of blood cholesterols to the liver by increasing LDL-receptor activity. (Bhagavan, 2002; Murray, Granner, & Rodwell, 2006) But these drugs come with their costs. Toxicity is an issue in statin therapy and its long-term dynamics is not known. (Bhagavan, 2002)

Because atherosclerosis is related to HDL density lower than 60 mg/dl and LDL density higher than100 mg/dL, people are advised to keep their HDL and LDL within safe limits (HDL> 60 mg/dL, LDL< 100mg/dL). Borderline high and low levels are defined for LDL as 130 mg/dL and for HDL as 40 mg/dL (Ma, 2006). Also, the ratio of LDL to HDL - the higher the riskier- is regarded as a risk factor in some studies. (Murray, Granner, & Rodwell, 2006)

People who have cholesterol levels in the upper 5-10% of the whole population are considered to have a lipoprotein - associated disorder (Bhagavan, 2002). Familial hypercholesterolemia (FH) is amongst the most common lipoprotein disorders. It results from a genetic problem in which LDL receptors of a patient are partly or mostly defective. FH heterozygotes have normal levels of HDL and triacylglycerol, yet their LDL cholesterol levels are generally between 320 and 500 mg/dL (Bhagavan, 2002). Residence time of LDL may increase up to 2.5 times the normal values.

There are many modeling studies about the cholesterol metabolism in the literature. Their purpose, generally, is either identifying/quantifying some parameters, or testing alternative hypotheses about the underlying structure of the cholesterol mechanism/metabolism (Schwartz, Zech, VandenBroek, & Cooper, 1993). In terms of methodology, there are simulation models and mathematically analyzable models (August, Parker, & Barahona, 2007). Simulation models are mostly at the cellular level and generally lack a systemic point of view. On the other hand, mathematically analyzable models make several assumptions for the sake of analytical tractability, but this fact raises questions about the validity of such models. Thus there seems to be a need for systemic simulation modeling of cholesterol dynamics that does not compromise model realism for the sake of mathematical tractability.

The purpose of this study is to construct and analyze a dynamic model of cholesterol balance in the blood stream in order to reduce the risk of atherosclerosis. The person who is assumed to be in the borderline or high-risk group of atherosclerosis may consider lowering his or her cholesterol levels in a number of ways like changing diet, exercise, taking drugs, or any combination of these. Though medication has favorable results on the blood cholesterol levels, they come with some side or unknown effects both in the short and long term. Difficulty of patient's sticking to strict diets or exercise programs is another problem. So the constructed model tries to answer the following question: "Are there efficient mixes of diet, exercise and minimal medication to keep blood cholesterol levels within safe limits?" The study takes into consideration the people's selection of different diets, exercise programs, taking medication; and the genetic disorders that may result in higher cholesterol levels.

2. OVERVIEW OF THE MODEL

The relationships between important factors that affect cholesterol levels in blood can be seen in Figure 2-1 and Figure 2-2 at a macro level.

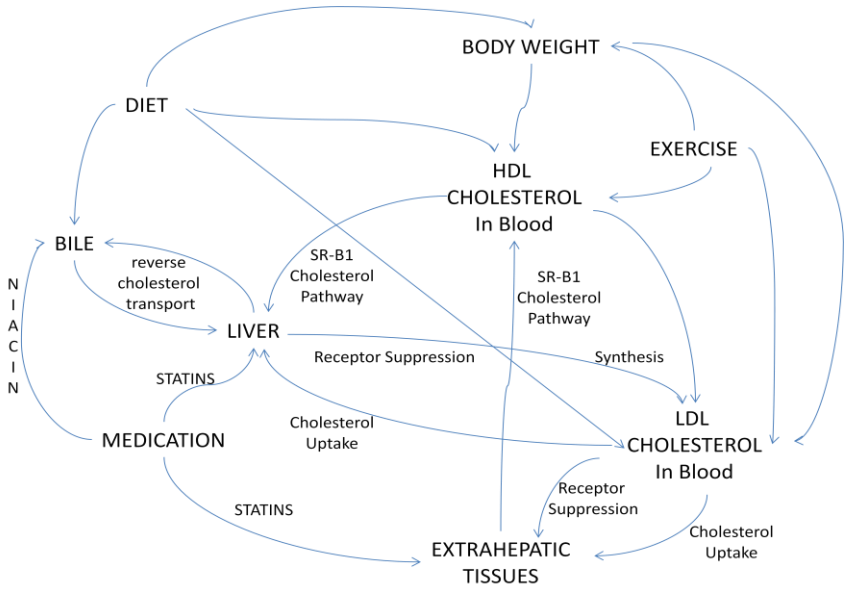

Figure 2-1 Interactions of Main Factors Affecting Blood Cholesterol Levels

There is not a direct feedback loop controlling the blood cholesterol level, yet other feedback loops or dynamics indirectly play with blood cholesterol levels to keep other critical stocks, namely the cholesterol pools in the liver and extrahepatic cells, within safe limits. If cholesterol in the liver becomes higher/lower than its normal level, then by decreasing/increasing its cholesterol uptake receptor activities, the liver adapts itself to take lesser/higher amounts of cholesterol from the blood. The effort of the liver, trying to stabilize its cholesterol pool, can be seen in more detail in Figure 2-3. HP stands for hepatic in this figure. A very similar feedback mechanism also exists in the extrahepatic cells.

Apart from the cholesterol pool feedback loops in the hepatic and extrahepatic cells, though indirect or patient-intervened, other feedback loops can be defined. There are loops which include the effects of dietary elements on blood cholesterol levels. The effect of saturated fat intake on LDLC can be seen in Figure 2-4.

Exercise tends to increase HDLC, and decrease body weight after a delay, but becoming fatter decreases HDLC and increases LDLC. Having healthier HDLC, LDLC, and body weight levels tend people to have less willingness to pursue the exercise programs. Figure 2-5 summarizes this feedback or control mechanism.

Defining the causal relations simply as balancing or reinforcing loops might be rendered erroneous when the effect of weight change on blood cholesterols is taken into account. Weight change, which is a delayed response to the diet, may reverse the working direction of these loops in the long run. Also a particular nutritional ingredient can increase HDL and LDL, or increase HDL and decrease LDL. These relationships or feedback loops add to the complexity of the model even in the absence of the effect of weight change on blood cholesterol levels.

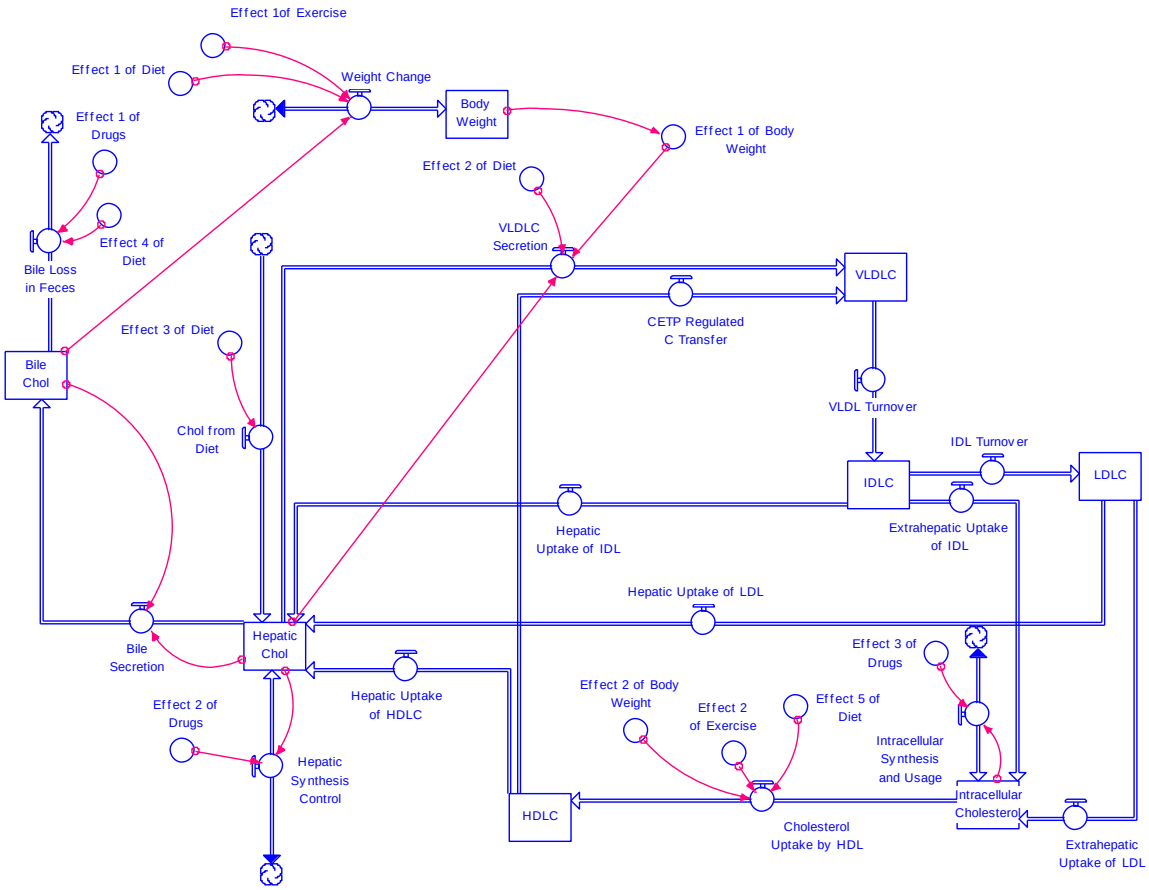

Figure 2-2 Condensed Stock-Flow Diagram of the Main Variables

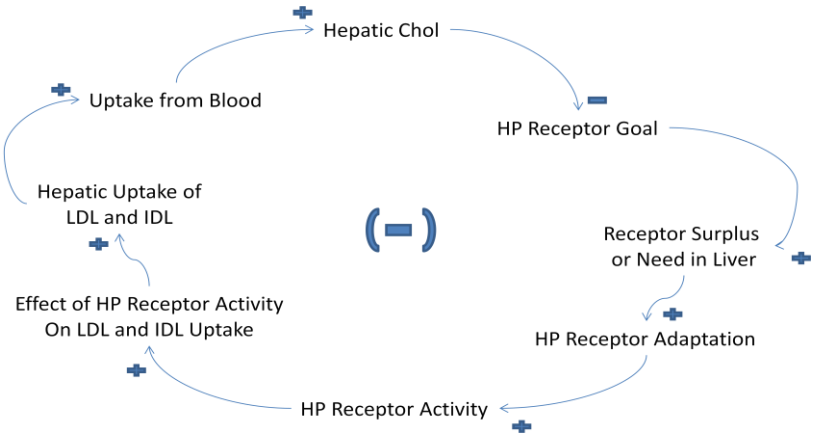

Figure 2-3 Hepatic Cholesterol – HP Receptor Activity Causal Loop Diagram

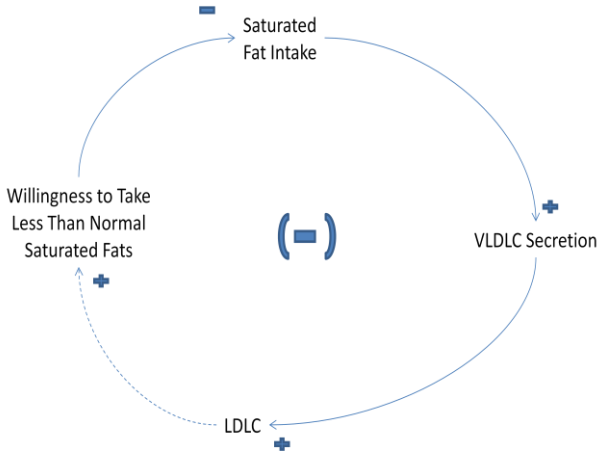

Figure 2-4 Saturated Fat–LDLC Patient-intervened Causal Loop Diagram

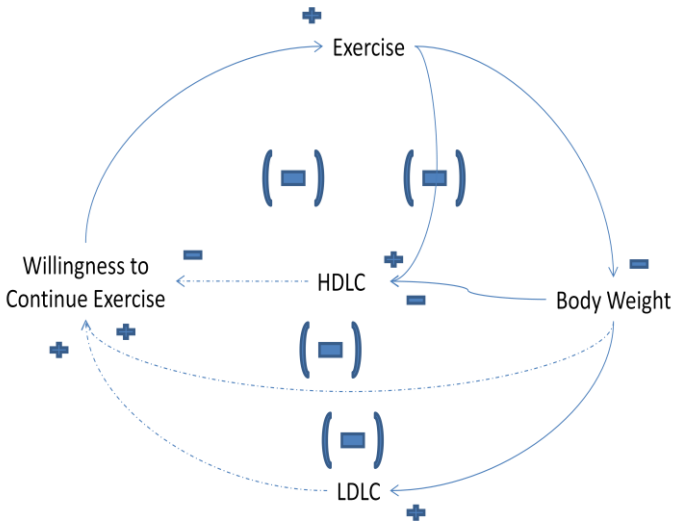

Figure 2-5 Exercise Loops

For simplicity the model is divided into six sectors. These are liver, blood, extrahepatic tissues, digestive system, and body weight sectors. All of these sectors are analyzed in detail in the next section. In a nutshell, liver sector defines relationships which synthesize blood cholesterol and regulate cholesterol uptake from blood. Blood sector includes relationships about transportation of cholesterol among lipoproteins, liver and extrahepatic tissues. Extrahepatic tissue sector defines relationships that regulate cholesterol uptake from blood lipoproteins. Diet & exercise sector represents diet and exercise, together with their effects on digestive system and body weight. Digestive system sector includes relationships about absorbed nutrients and their effects on blood cholesterol levels and reverse cholesterol transport. And finally body weight sector represents dynamics of weight change, diet, exercise and their effects on the blood cholesterol levels.

3. DESCRIPTION OF THE MODEL

3.1.Blood Sector

3.1.1. Background and Assumptions

VLDL is secreted from the liver. VLDL turns into IDL in the blood. Nearly half of the IDLs are taken up by the liver and extrahepatic tissues, whereas the other half is converted to LDL. Thus the level of cholesterol bound to LDL (LDLC) is mainly from the cascading process of VLDLC turning into IDLC and finally to LDLC, where VLDLC and IDLC stand for the level of cholesterol bound to VLDL and IDL respectively. (Bhagavan, 2002; Murray, Granner, & Rodwell, 2006)

HDL is secreted from the steroidogenic tissues; mostly from the liver and the intestines. Main responsibility of HDL is to transfer cholesterol from extrahepatic cells to other lipoproteins, liver, and intestine. Movement of cholesteryl-ester to VLDL, IDL, and LDL is due to the activity of cholesteryl-ester transfer protein or CETP. Half of the cholesterol bound to HDLs (HDLC) is taken up by steroidogenic tissues while the other half goes to the other lipoproteins via the stimulation by CETP (Murray, Granner, & Rodwell, 2006).

In the model, for simplicity, steroidogenic tissues and their functions in the HDL metabolism are limited to liver. Also the liver is assumed to be maintaining a constant level of HDL productivity. CETP related cholesterol transfer is also assumed to be occurring only between HDL and VLDL, not taking IDL and LDL as receivers of cholesterol into account.

3.1.2. Description of the Blood Sector Structure

There are four stocks in this sector. *VLDLC*, *IDLC*, and *LDLC* have a relationship as a cascading process, while *HDLC* is related to these stocks via the flow *CETP Regulated C Transfer*. (Stock-flow diagram is shown in Figure 3.1). HDLC is short for cholesterol bound to HDL particles. HDLC has one inflow and two outflows. HDLC is increased with the HDL particles collecting cholesterol from extrahepatic tissues via SR-B1 regulated pathways or with other methods. This increase is represented with the inflow *Cholesterol Uptake by HDL* and analyzed in below in more detail. Because life of HDL particles is 4 days (Barter, Kastelein, Nunn, & Richard, 2003), HDLC are assumed to have the same clearance rate from the liver and this is modeled as *HDLC Transport to Liver* outflow in the model. The other outflow is *CETP Regulated C Transfer*. *CETP Activity Rate* converter in the model is short for the rate or speed of this CETP regulated transfer of cholesterol from HDL to VLDL particles. Because CETP regulated cholesterol transfer is nearly equal to the amount of cholesterol transferred to the liver by HDL (Kwiterovich, 2000), it should be equal to the reciprocal of the life of an HDL particle. So, it is equal to 0.25 day^{-1}. Also the initial level of HDLC is set to 31.5 mg/dL. The relationship of HDLC with its flows can be seen in the Equation 3-1 as an example. Complete set of equations can be found in the online Appendix.

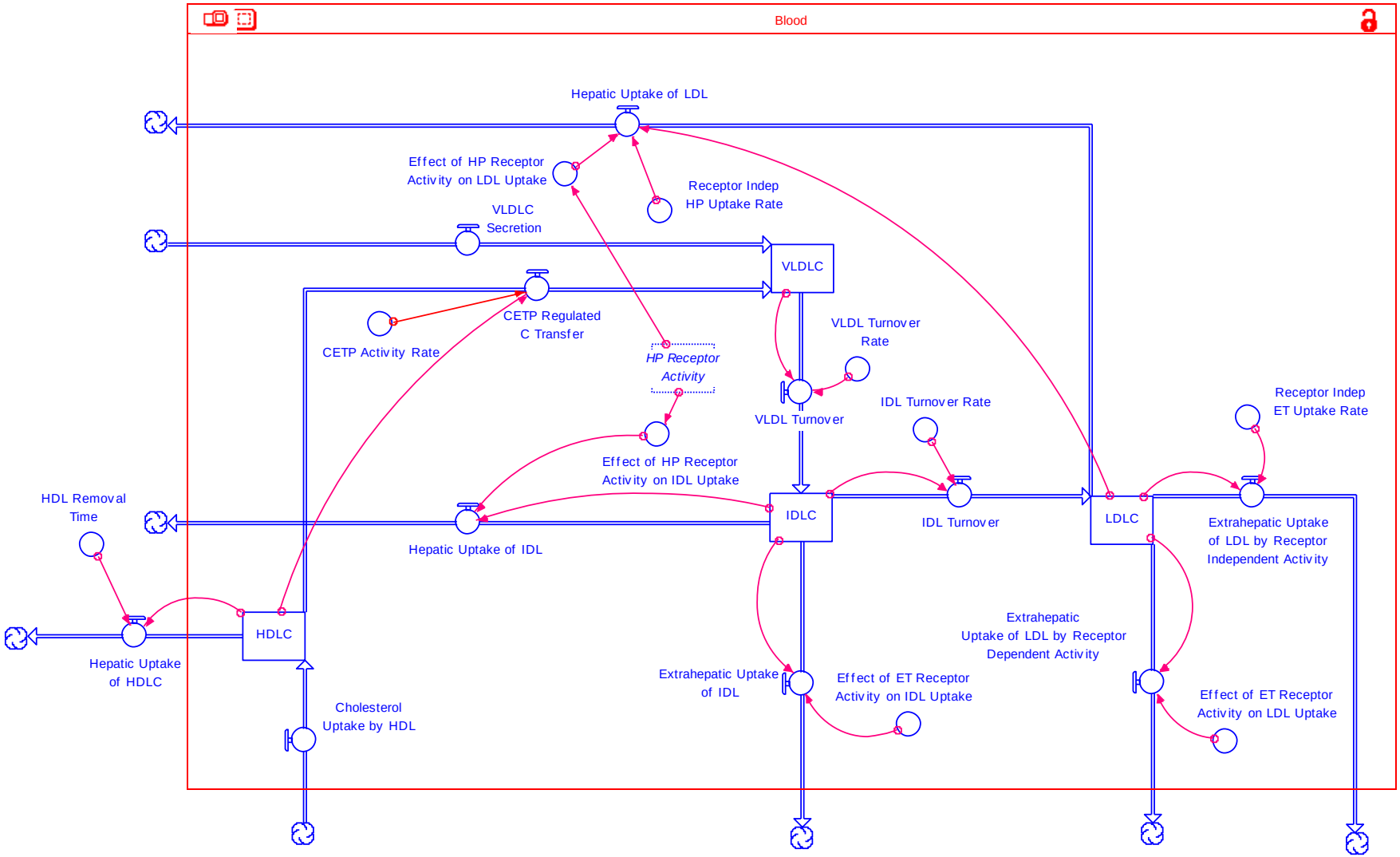

Figure 3-1 Stock – Flow Diagram of Blood Sector

$$HDLC(t) = HDLC(t - dt) + (Cholesterol\ Uptake\ by\ HDL - HDLC\ Transport\ to\ Liver - CETP\ Regulated\ C\ Transfer) * dt \quad 3\text{-}1$$

Cholesterol bound to VLDL (*VLDLC*) has two inflows and one outflow. Its first inflow is *VLDLC Secretion*. This inflow is the outflow of the *Hepatic Cholesterol Pool* stock which is located in the *liver section* and this flow is analyzed in the liver section in more detail. The normal value of this inflow is 128.6 mg/dL per day. The other inflow of *VLDLC* is *CETP Regulated C Transfer*. Cholesteryl ester transfer protein is responsible in the process of cleaving cholesterol form HDL particles and letting VLDL to capture these cholesterols. Because *HDLC* is set to be 31.5 mg/dL at the beginning and *CETP Regulated C Transfer* equals to *HDLC * CETP Activity Rate*, then the normal value of this transfer equals to 31.5*0.25, or nearly 7.88 mg/dL per day. The outflow of *VLDLC* is *VLDL Turnover* and is equal to *VLDLC* times *VLDL Turnover Rate*. The latter rate is set to be 5.5 day^{-1} in the model (Packard, et al., 2000).

Cholesterol bound to IDL (*IDLC*) has one inflow, which is the only outflow of *VLDLC* just mentioned above, and three outflows. Two of the outflows are *Hepatic Uptake of IDL* and *Extrahepatic Uptake of IDL*. The first uptake is done by the liver receptors while the latter is done by the receptors of the extrahepatic cells. Nearly two thirds of the IDL are taken up by these pathways- 70% by liver and 30% by extrahepatic tissues (Murray, Granner, & Rodwell, 2006). Hepatic uptake equals to *IDLC*Effect of ET Receptor Activity on IDL Uptake*, and extrahepatic uptake equals to *IDLC*Effect of HP Receptor Activity on IDL Uptake*. More will be said about the receptor activities in the liver and extrahepatic tissues sections. The remaining cholesterol which is not taken up, or namely one third of IDLC, is degraded into *LDLC* which is represented by the *IDL Turnover* outflow. This outflow equals to *IDLC*IDL Turnover Rate*. *IDL Turnover Rate* is 2.4 day^{-1} (August, Parker, & Barahona, 2007), and the initial level of IDLC is set to 18.6 mg/dL. So the initial value of the *IDL Turnover Rate* is around 44.6 mg/dL per day.

IDL Turnover Rate is the only input of the stock *LDLC*, or cholesterol bound to LDL. *LDLC* also has three outflows: *Hepatic Uptake of LDL, Extrahepatic Uptake of LDL by Receptor Dependent Activity, Extrahepatic Uptake of LDL by Receptor Independent Activity*. LDLC is taken up by liver and extrahepatic tissues via both receptor dependent and receptor independent activities. The first of the outflows *Hepatic Uptake of LDL* represents the degradation of LDL in liver. It equals to *LDLC * Effect of HP Receptor Activity on LDL Uptake + LDLC * Receptor Indep HP Uptake Rate*. These uptake rates are delineated in the liver section. The other outflows equal to *LDLC * Effect of ET Receptor Activity on LDL Uptake* and *LDLC * Receptor Indep ET Uptake Rate* respectively. The details of these uptake rates will be given in the extrahepatic tissue section. Initial values of LDLC and three outflows are about 111.5 mg/dL, 31.2 mg/dL per day, 10 mg/dL per day, 3.2 mg/dL per day respectively.

The person, whom blood cholesterol level is being modeled, is assumed to have cholesterol levels as borderline high. Initially HDLC, VLDLC, IDLC, and IDLC are set to 31.5, 25.0, 18.6, and 111.5 mg/dL respectively.

3.2. Liver Sector

3.2.1. Background and Assumptions

Liver has control over blood cholesterol levels through HDL activity, VLDL cholesterol secretion, bile secretion, and hepatic receptor activities or uptake of cholesterol. HDL is secreted from liver. It is responsible for the reverse cholesterol transport, which is the mechanism through which the excess cholesterol of extrahepatic tissues is transferred to liver and other blood lipoproteins.

Though VLDL is mainly produced for the purpose of transferring triacylglycerols to muscle and adipose tissue, some cholesterol is incorporated in them while they are secreted to the blood stream in liver. VLDL cholesterol secretion is dependent on hepatic cholesterol pool, some dietary nutrients, and body weight. Thus the origin of blood cholesterol level is mainly VLDL secretion and reverse cholesterol transport.

Lipids and cholesterol are not soluble in water. Bile is used to solve and uptake them in the digestive system. Bile and bile acids are secreted in the liver from cholesterol. Therefore their loss in the feces determines how much cholesterol in the liver will be utilized for new bile production. Because hepatic cholesterol pool determines the receptor dependent cholesterol uptake and VLDL-cholesterol secretion, bile metabolism is an indirect mechanism by which the liver plays with blood cholesterol levels.

The receptors are responsible for cholesterol uptake in the form of IDL cholesterol and LDL cholesterol. LDL cholesterol is also taken up by receptor independent activities by liver and extrahepatic tissues. Activities of the hepatic receptors are adjusted such that hepatic cholesterol pool does not exceed safe limits. If hepatic cholesterol pool is lower (higher) than its normal level, then hepatic receptor activity is increased (decreased) to allow more (less) cholesterol to be taken up from blood. This is another mechanism which involves liver and blood cholesterol interaction.

Bile and bile acids are secreted and absorbed 4 to 10 times a day in the body, which is called enterohepatic circulation, and some portion of them is lost in the feces (Bhagavan, 2002). Bile loss and the compensation of this loss by the liver are modeled by using total daily values rather than treating every enterohepatic circulation individually. Because bile is accompanied with free cholesterol while it is secreted in the liver, some cholesterol, which amounts to be about 0.4 gr, is also lost to the feces (Guyton, et al., 1991). This loss is assumed to be compensated by the liver. Any other cholesterol use or loss, like structural use of cholesterol, is also assumed to be regulated by the liver. This compensation is to be represented with the flow *Hepatic Synthesis Control* in the model.

3.2.2. Description of the Liver Sector Structure

There are two stocks in this section: *HP Receptor Activity* and *Hepatic Chol*. The first one represents the activeness or efficiency of liver receptors in taking up cholesterol from blood, while the second one represents the cholesterol amount in the liver.

HP Receptor Activity has only one bi-flow named *HP Receptor Adaptation*. If the *Hepatic Chol* pool is less (more) than its base level, then more (less) receptors are utilized in the liver

surface. According to the ratio of hepatic cholesterol to its base level, HP Receptor Goal is calculated as in Figure 3-2.

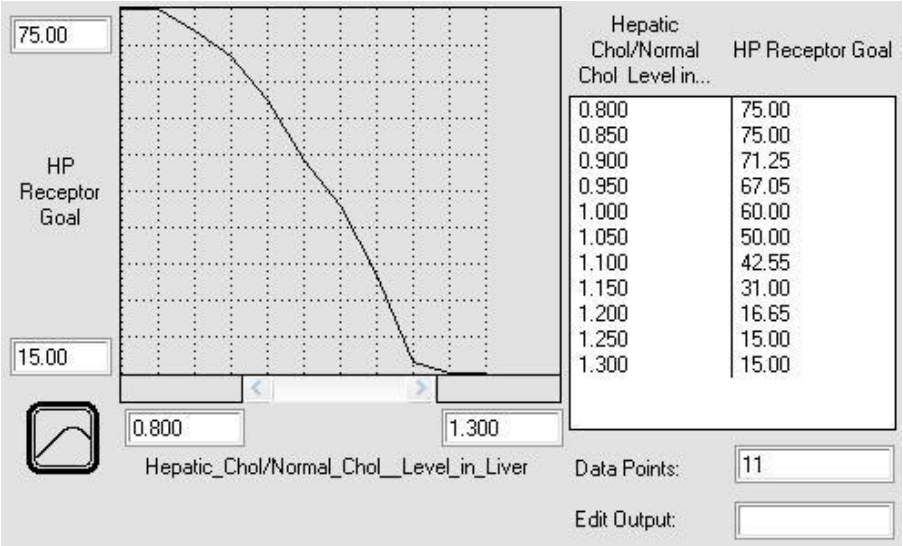

Figure 3-2 HP Receptor Goal

If there is a lot of cholesterol in the liver, then the liver wants minimum of its receptors working which is a relatively low number, 15. And in the contrary, if the liver needs more cholesterol, the receptor goal increases to 75. The rationale behind these numbers 15 and 75 is the fact that a cell has between 15,000-75,000 LDL receptors (Goldstein & Brown, 1997), and the assumption that these numbers represent the receptor activity or efficiency of each cell and in turn liver. Normal level of receptors is assumed to be 60,000. Afterwards, the liver checks the surplus or need of the receptors by comparing the goal with the current level of the stock *HP Receptor Activity*. According to the resulting surplus or need the activity is decreased or increased. The adjustment time of this process is 2.5 days (Goldstein & Brown, 1997). Therefore the formula for *HP Receptor Adaptation* becomes:

$$HP\_Receptor\_Adaptation = Receptor\_Surplus\_or\_Need\_in\_Liver / HP\_Receptor\_Adaptation\_Time \quad 3\text{-}2$$

The second stock of this sector is *Hepatic Chol*. It has two outflows, two inflows, and one bi-flow. Its outflows, inflows, and bi-flow are *VLDLC Secretion*, *Bile Secretion*; *Uptake from Blood*, *Chol from Diet*; and *Hepatic Synthesis Control* respectively. The normal or base level *Hepatic Chol* is taken to be 1700 mg (Schwartz, Zech, VandenBroek, & Cooper, 1993).

VLDLC Secretion is the cholesterol loss rate in which cholesterol is bound to VLDL particles. This flow has a complicated formula which depends on the *Hepatic Chol* stock, saturated and unsaturated fat intake, and body weight.

Base VLDLC Secretion is adjusted to be about 130 mg/dL a day in its normal or initial level (August, Parker, & Barahona, 2007). *Hepatic Chol* has effect on how much VLDL cholesterol is

secreted from the liver. Therefore, base level secretion is multiplied with this effect in the formula above. The graphical function, which has the ratio of the stock to its base level or 1700 mg as its x-axis, can be seen in Figure 3-3.

The bi-flow of *Hepatic Chol* is named as *Hepatic Synthesis Control*. If the pool deviates from this level, the liver adjusts its production mechanisms so that cholesterol amount approaches the base level. If there is more cholesterol in the pool than that of the base level, then new cholesterol synthesis rate is reduced. The rate or speed of this process is assumed to be 0.5 days. Also, all of the other synthesis and usages of cholesterol in the liver and steroidogenic tissues are aggregated into this bi-flow. This flow has a constant 245 mg per day cholesterol input to the stock as a result of this aggregation.

$$\text{Hepatic\_Synthesis\_Control} = 245 + (\text{Normal\_Chol\_\_Level\_in\_Liver} - \text{Hepatic\_Chol}) / \text{Hepatic\_Synthesis\_Control\_Rate} \quad \text{3-3}$$

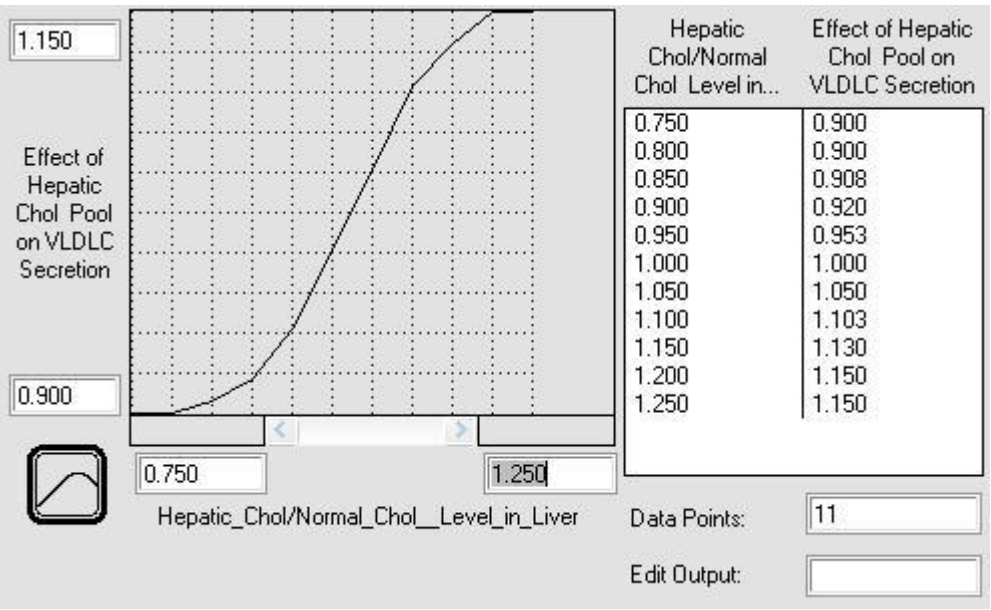

Figure 3-3 Effect of Hepatic Cholesterol Pool on VLDLC Secretion

Chol from Diet and *Uptake from Blood* are the inflows of the stock *Hepatic Chol*. *Chol from Diet* is merely the absorbed cholesterol from the diet. The latter represents the total receptor dependent uptake of cholesterol from IDL and LDL particles. *Uptake from Blood* also includes receptor independent cholesterol uptake from LDL particles.

Hepatic Uptake of IDL is *IDLC* times *Effect of HP Receptor Activity on IDL Uptake*. The effect formula is calculated as *HP Receptor Activity* times 0.0583, with the help of the paper (Packard, et al., 2000), after assuming that the effect is linear in HP Receptor Activity, and 70 per cent of the total IDL uptake from the blood occurs in liver (Goldstein & Brown, 1997; Murray, Granner, &

Rodwell, 2006).*Hepatic Uptake of LDL* includes receptor dependent and independent uptake of LDLC.

$$Hepatic\_Uptake\_of\_LDL = LDLC*Effect\_of\_HP\_Receptor\_Activity\_on\_LDL\_Uptake + LDLC*Receptor\_Indep\_HP\_Uptake\_Rate$$

3-4

After taking the same assumptions as in the case of IDL uptake, *Effect of HP Receptor Activity on LDL Uptake* equals to *HP Receptor Activity* times 0.0035 (Packard, et al., 2000). *Receptor Indep HP Uptake Rate* is taken to be 0.07 (Murray, Granner, & Rodwell, 2006; Dietschy, Turley, & Spady, 1993).

Stock - Flow diagram can be seen in Figure 3-4. Complete set of equations can be found in the online Appendix.

3.3. Extrahepatic Tissue Sector

3.3.1. Description of the Extrahepatic Tissue Sector Structure

Extrahepatic tissue represents all of the tissues or parts of the body that receive cholesterol from IDL and LDL; and give away cholesterol to HDL.This sector is very similar to the liver sector. Some assumptions made in the liver sector are also made in this sector. These are using daily average values for the parameters, and assuming a linear relationship between receptor number and receptor activity.

Extrahepatic tissue sector has two stocks: *Intracellular Cholesterol* and *ET Receptor Activity*. The first represents the amount of cholesterol in the extrahepatic tissues, and the second represents the activeness or efficiency of the receptors in taking up cholesterol from blood. *Intracellular Cholesterol* has a base level of 1450 mg (Schwartz, Zech, VandenBroek, & Cooper, 1993).The same mechanisms and assumptions of *HP Receptor Activity* apply for *ET Receptor Activity*, and it has a base level of 60. It doesn't have a unit because it represents efficiency.

Intracellular Cholesterol has one inflow, two outflows, and one bi-flow. Its only inflow is cholesterol taken up from blood or *C from Blood*. It includes receptor dependent uptake of cholesterol from IDL and LDL particles together with receptor independent cholesterol uptake from LDL particles.

$$C\_from\_Blood = Extrahepatic\_Uptake\_\_of\_IDL + Extrahepatic\_\_Uptake\_of\_LDL\_by\_Receptor\_Dependent\_Activity + Extrahepatic\_Uptake\_of\_LDL\_by\_Receptor\_Independent\_Activity$$

3-5

Extrahepatic Uptake of IDL is *IDLC* times *Effect of ET Receptor Activity on IDL Uptake*. The effect formula is calculated as *ET Receptor Activity* times 0.025, with the same assumptions as in its hepatic counterpart (Packard, et al., 2000), namely assuming that the effect is linear in ET Receptor Activity, and 30 per cent of the total IDL uptake from the blood occurs in extrahepatic tissues (Goldstein & Brown, 1997).

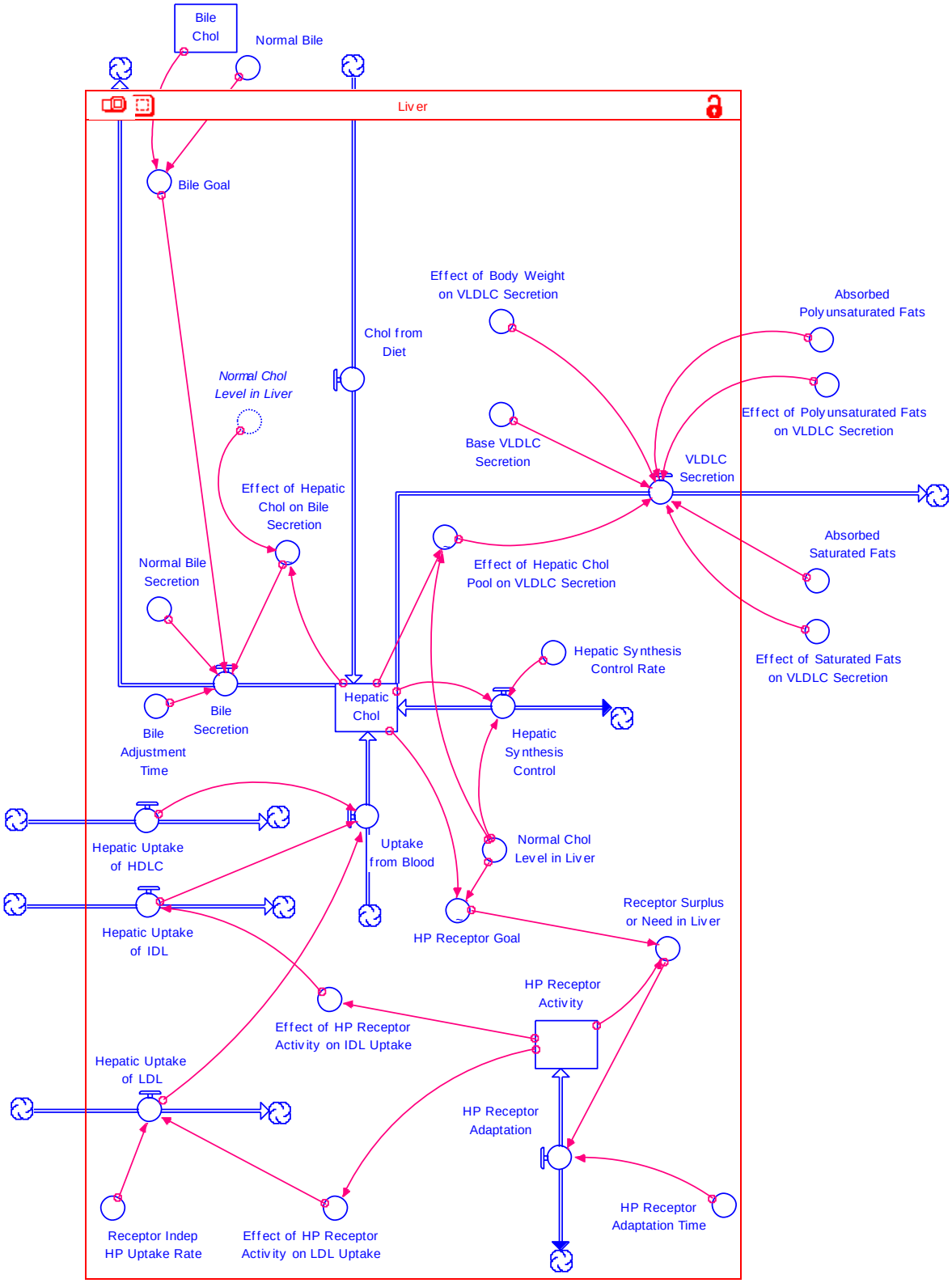

Figure 3-4 Stock – Flow Diagram of Liver Sector

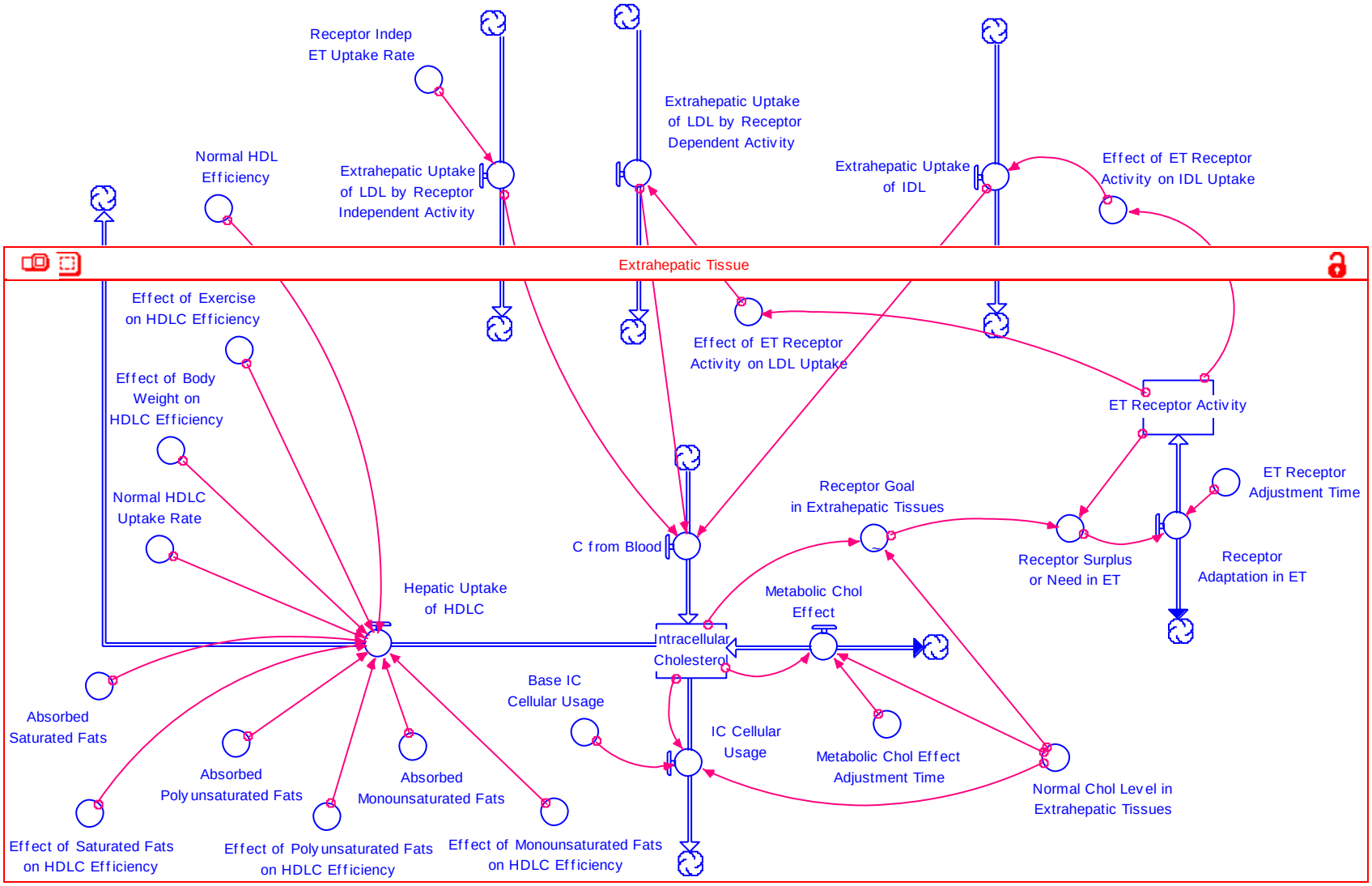

Figure 3-5 Stock – Flow Diagram of Extrahepatic Tissue Sector

Extrahepatic Uptake of LDL includes receptor dependent and independent uptake of LDLC. *Extrahepatic Uptake of LDL by Receptor Dependent Activity* equals to *IDLC* times *Effect of ET Receptor Activity on LDL Uptake*. *Extrahepatic Uptake of LDL by Receptor Independent Activity* equals to *LDLC* times *Receptor Indep ET Uptake Rate*. After taking the same assumptions as in the case of IDL uptake, *Effect of ET Receptor Activity on LDL Uptake* equals to *ET Receptor Activity* times 0.0015. *Receptor Indep ET Uptake Rate* is taken to be 0.03 (Murray, Granner, & Rodwell, 2006; Packard, et al., 2000; August, Parker, & Barahona, 2007).

Cholesterol Uptake by HDL and *IC Cellular Usage* are the outflows of *Intracellular Cholesterol*. The first is the determining factor for the HDLC level in the blood. It is affected by dietary elements, body weight, and exercise. Its formula can be seen in the online Appendix. *Normal HDL Efficiency* represents the uptake that should be made in normal conditions. That means if all of the parameters that affect this flow are kept constant at their base levels in the model, then there would be no change in the value of the flow and it would be equal to this base or normal level which is set to be about 16 (August, Parker, & Barahona, 2007). *Normal HDLC Uptake Rate* represents the diminishing rate of HDL cholesterol in the blood which is 0.5 $days^{-1}$ (Barter, Kastelein, Nunn, & Richard, 2003). All of the effects are analyzed in more detail at their corresponding sections.

Cholesterol is synthesized in virtually every living cell which has nucleus, yet cholesterol taken up from blood is a vital source. About 60 per cent of the cholesterol taken up from blood is used in cells (Aidels, 2002). Therefore in a given day, about 41 mg of cholesterol is taken up from blood, 25 mg of it is used in metabolic activities in the cell and about 16 mg is taken away by HDL. Assuming other cholesterol synthesis within the cells equal their usage throughout the simulation means their net effect is always zero. So in the beginning of the simulation the above 25 mg is taken to be *IC Cellular Usage* or the intracellular cholesterol used in the cell within a day. But this flow is also dependent on the relative level of the intracellular cholesterol to its base level in an assumed linear fashion. Therefore *IC Cellular Usage* equals to *Base IC Cellular Usage* times *Intracellular Cholesterol* divided by *Normal Chol Level in Extrahepatic Tissues*.

If there is a difference between intracellular cholesterol and its normal level 1450 mg, *Metabolic Chol Effect* bi-flow works to diminish this gap. A similar bi-flow is also present in the liver sector, but this one is assumed to have a rather slow speed, or *Metabolic Chol Effect Adjustment Time*, as 2 days compared to 0.5 days in its liver counterpart. Stock - Flow diagram of this sector can be seen in Figure 3-5. All of the equations can be found in the online Appendix.

3.4.Digestive System Sector

3.4.1. Background and Assumptions

Bile salts are used in the absorption of fats and cholesterol from the diet. Also, they are produced from cholesterol in the liver and most of them are recycled to the liver from the intestines. This is called enterohepatic circulation. The loss of bile from the intestines, thus, affects how much new bile will be produced and, though indirectly, how much cholesterol will be taken up from blood (Stein & Stein, 1999).

Absorbed cholesterol indirectly plays with blood cholesterol levels. It increases the cholesterol pool in the liver and causes hepatic receptor activity to decrease which in turn causes blood cholesterol levels to rise. Dietary fats increase HDL cholesterol. Saturated fats increase, polyunsaturated fats decrease, and monounsaturated fats do not affect LDL cholesterol (Hegsted,

Ausman, Johnson, & Dalla, 1993). High fibers in the diet promote bile loss in the feces. Loss in the absorption of bile and bile salts mean lesser absorption of cholesterol and dietary fats in the diet (Cohen, 2007).

3.4.2. Description of the Digestive System Sector Structure

The only stock in this sector is *Bile Chol*. Its normal or base level is 3000 mg (Cohen, 2007). Its inflow is *Bile Secretion* and outflow is *Bile Loss in Feces*. The latter flow is taken to have a base level of 500 mg a day (Bhagavan, 2002; Cohen, 2007). This base level is affected by dietary high fibers so that *Bile Loss in Feces* equals to *Base Bile Loss Rate* multiplied by *Effect of High Fibers on Bile Loss*. High fibers cause less bile to be absorbed in the intestines. So they increase bile loss in feces. Their contribution to lower blood cholesterol is about 5 per cent (Citkowitz, 2007). So the graphical function *Effect of High Fibers on Bile Loss* is adjusted to cause this level of change in blood cholesterol level. Figure 3-6 shows this effect formula in detail.

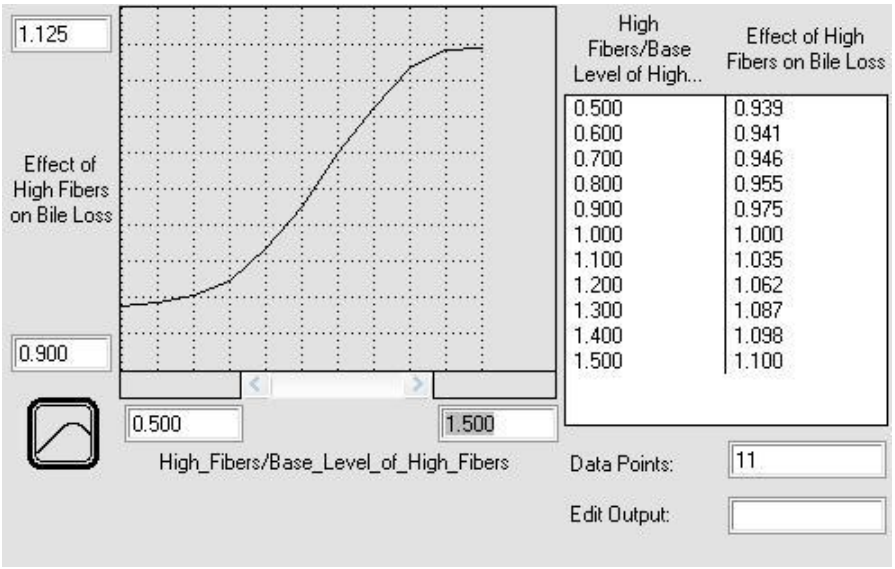

Figure 3-6 *Effect of High Fibers on Bile Loss*

Bile is strictly monitored in the liver and intestines; and the liver takes action to return the bile pool to its normal level accordingly. Normal Bile Secretion equals to normal bile loss level 500 mg. *Bile Discrepancy* is defined to be normal level of bile minus the current level of bile, or *Normal Bile - Bile_Chol*. Also *Hepatic Chol*, the cholesterol stock in the liver, has control over how much new bile will be produced from cholesterol in the liver. The formula for *Bile Secretion* is:

$$Bile\ Secretion = Normal\ Bile\ Secretion * Effect\ of\ Hepatic\ Chol\ on\ Bile\ Secretion + Bile\ Discrepancy / Bile\ Adjustment\ Time$$

Effect of Hepatic Chol on Bile Secretion can be seen in the online Appendix. *Normal Cholesterol Absorption Ratio* is 0.55. *Absorbed Cholesterol* is also assumed to be affected by the level of bile in the sector. So the formula for *Absorbed Cholesterol* is *Cholesterol Intake* * *Normal Cholesterol Absorption Ratio* * *Effect of Bile on Cholesterol Absorption per cent*. The latter effect formulation is assumed to be equal to *Bile_Chol* / *Normal Bile*. *Absorbed Cholesterol* is an inflow to the hepatic cholesterol pool, which is discussed in the liver sector in detail.

Fat Absorption per cent is affected from the level of bile. The normal absorption of fats is about 95 per cent. Details of the parameter *Fat Absorption per cent* can be seen in the online Appendix. The absorbed saturated, monounsaturated, and polyunsaturated fats are defined to be the multiplication of *Fat Absorption per cent* with their corresponding dietary intakes.

Base levels of carbohydrate and protein absorption are taken to be 99 and 90 per cent respectively. They are assumed to be constant throughout the simulation. *Absorbed Carbohydrates* and *Absorbed Proteins* are defined to be equal to these per cent values of the corresponding caloric intakes of the nutrients.

1 gr of fat has 9 kcal, whereas 1 gr of carbohydrate and protein has 4 kcal. Of all the available dietary calories, 10 per cent is lost in the processes of digestion mainly in the intestines and it is called *Thermic Effect of Food*. *Total Available Dietary Energy* is thus equals to:

$$\begin{aligned} \textit{Total Available Dietary Energy} = (&(\textit{Absorbed Polyunsaturated Fats} \\ &+\textit{Absorbed Saturated Fats} \\ &+\textit{Absorbed Monounsaturated Fats}) \\ &*\textit{energy per gr fat} \\ &+\textit{Absorbed Carbohydrates} \\ &*\textit{energy per gr carbodydrate} \\ &+\textit{Absorbed Proteins}*\textit{energy per gr protein}) \\ &*(1-\textit{Thermic Effect per cent of Foods}) \end{aligned} \qquad 3\text{-}7$$

Effects of dietary nutrients on LDL and HDL cholesterol levels are calculated from the information given on (Hegsted, et.al., 1993) and (Mensink, et.al., 2003). Exact values can be found in the online Appendix.

The incorporation of these effect formulations into the flow formulas are adjusted such that the normal or initial amount of dietary intakes does not affect the level of the flows. For example, *Effect of Saturated Fats on VLDLC Secretion* equals to 0.774 (cholesterol mg) / (fat gr) in the model. This effect appears in the formulation of *VLDLC Secretion* as: *VLDLC Secretion* = *Base VLDLC Secretion* ... *-9.18* + *Effect of Saturated Fats on VLDLC Secretion* * *Absorbed Saturated Fats*. The number *-9.18* is chosen such that Absorbed Saturated Fats (11.875 gr) times the effect (0.774 mg / gr) is equal to 9.18 and the net effect in the base level of the parameters is zero. Stock - Flow diagram of this sector can be seen in Figure 3-7. Complete set of equations can be found in the online Appendix.

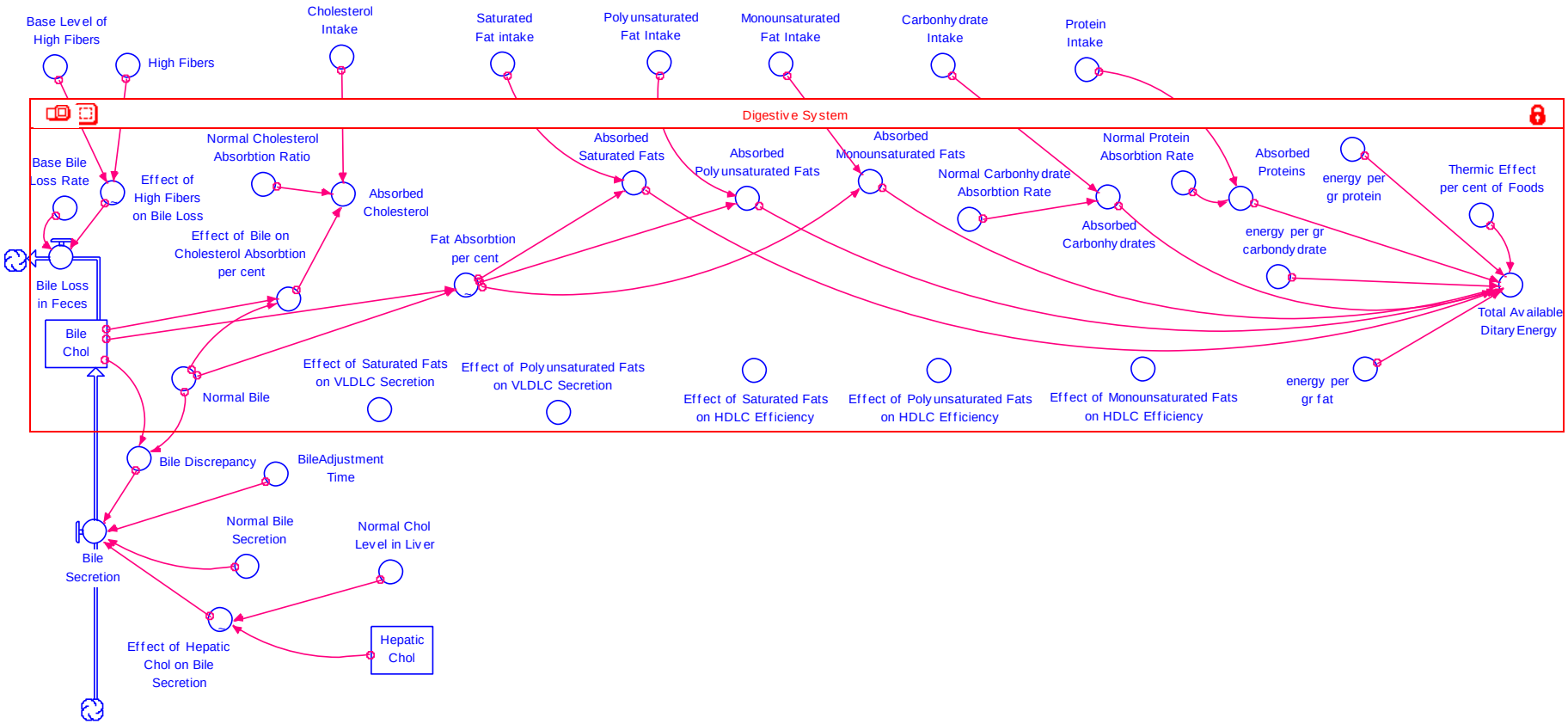

Figure 3-7 Stock– Flow Diagram of Digestive System Sector

3.5.Body Weight, Diet and Exercise Sector

3.5.1. Background and Assumptions

Body weight dynamics are well studied in the literature. In the widely shared mental model, it is transparent enough that if daily energy intake is more (less) than daily energy expenditure, then daily energy surplus (deficit) causes body mass to increase (decrease). (Whitney & Rolfes, 1999)Energy expenditure can be divided into three. Resting energy expenditure is defined as the energy need of an individual who is awake and at rest. This component is the biggest of all the energy expenditure components in a sedentary individual (Abdel-Hamid, 2002). The second one is energy used for muscular activities or thermic effect of exercise. The last one is thermic effect of food, which is mentioned in the digestive system sector.

Body gains weight mainly in the form of fat or adipose tissue independent of the form of dietary components: fat, carbohydrates, or proteins. There are about 7716 kcal in human fat. Therefore, 7716 kcal of deficit in energy balance is considered to be causing 1 kg of body weight loss. The assumption in this estimate is that, energy need of the body remains stable even when the body weight changes (Weinsier, Bracco, & Schultz, 1993).

The complexity in body weight change dynamics is represented in the model via taking the viewpoint of (Westerterp, Donkers, Fredrix, & Boekhoudt, 1994). First it is assumed that if there is an energy surplus that is going to be converted to body mass, there is a cost in converting these nutrients to fat. Secondly, if there is energy deficit, then basal metabolism is reduced by 10 per cent by the body for the purpose of not losing its energy deposits rapidly.

Moreover, basal metabolism is changed with the body weight. In the normal range of weight values, it is assumed that weight change is linear as in the case of the basal metabolism approximation formulation of Friedervald's. It is assumed that when the body weight increases to 40 per cent above its normal level, basal metabolism increases more than that would increase in the linear case. Also when the body weight drops to about 80 per cent of its base level, basal metabolism decreases more than it would be in the Friedervald's formulation to not lose more weight or energy deposits.

3.5.2. Description of the Body Weight Sector Structure

The mentioned conceptual model is used with the added complexities with the help of the paper *energy intake, physical activity and body weight* and the Fiedervald's method (Westerterp, Donkers, Fredrix, & Boekhoudt, 1994). As explained in the digestive system sector, *Total Available Dietary Energy* is the calories taken from the blood minus the thermic effect of food. *Total Energy Need* is defined as *Basal Metabolism* plus *Exercise and Normal Activities*. The difference between them is *Energy Surplus or Shortage*. If there is energy surplus, the cost of converting nutrients to adipose tissue is added to this auxiliary variable. This cost is represented in the model as the graphical formulation *Effect of Fat Conversion to Energy balance*, which can be found in the online Appendix.

There are two stocks in the model. The first is *Body Weight* and the second is *Basal Metabolism*. *Body Weight* has one bi-flow. *Energy Surplus or Shortage* is used for calculating *Weight Change*.

Weight Change = Energy Surplus or Shortage
/ Adjustment Time for Weight Change/ energy kg convertor

3-8

Adjustment Time for Weight Change is taken to be 1 day, and *energy kg converter* as 7716 kcal per gr. Base and initial *Body Weight* is taken to be 74 kg.

The other stock *Basal Metabolism* also has one bi-flow. It's named as *BM Change*. It's formulated as:

*BM Change = (Base Basal Metabolism * Effect of Body Weight on Basal Metabolism*
-Basal Metabolism)/BM Change Rate+Metabolic Adjustment Effect

3-9

Base Basal Metabolism and the initial level of the stock is set to 1800 kcal. But this level depends on the body weight as described in the above sections. *Effect of Body Weight on Basal Metabolism* is defined as:

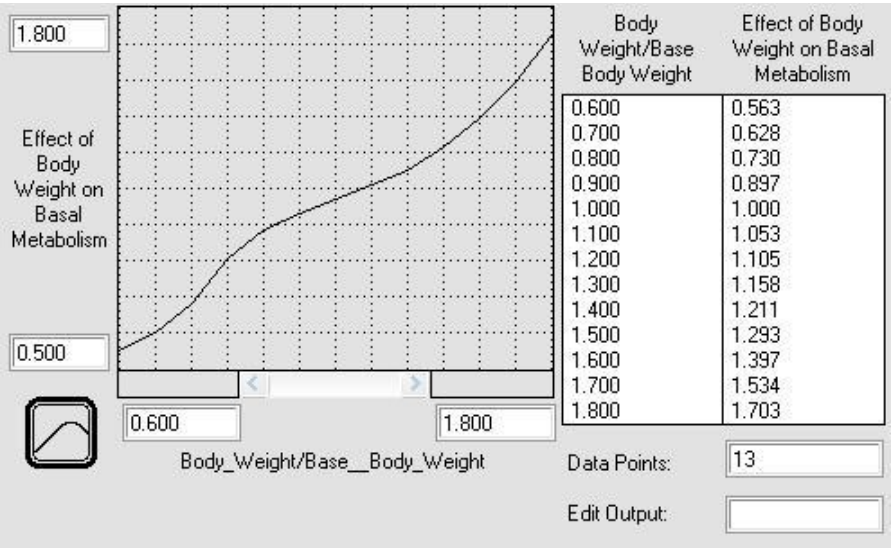

Figure 3-8 *Effect of Body Weight on Basal Metabolism*

BM Change Rate is set to 0.5, assuming the speed of change in *Basal Metabolism* is 0.5 days. Metabolic Adjustment Effect represents the body's effort of reducing basal metabolism by 10 per cent if there is energy shortage in a given day.

Body weight has effect on LDL and HDL cholesterol levels. Its effect on LDL is modeled as an adjustment in the production of VLDL cholesterol or VLDLC. *Effect of Body Weight on VLDLC Secretion* is formulated as (*Body Weight-Base Body Weight) * 1.95* (Dattilo & Kris-Etherton, 1992). Its effect on HDL cholesterol level is represented with *Effect of Body Weight on HDLC Efficiency*. It's defined as: (*Body Weight-Base Body Weight) * 0.351*.

At the base level the person is assumed to be doing 150 kcal of exercise and daily activities each day so that he has a sedentary life style. There is one graphical function that represents the effect of exercise on HDL cholesterol. *Effect of Exercise on HDLC Efficiency* is defined as an S-shaped curve and can be seen in the online Appendix (Trejo-Gutierrez & Fletcher, 2007).

Converters about diet and their base levels in parentheses are: Cholesterol Intake (510 mg/d), Saturated Fat Intake (12.5 gr/d), Monounsaturated Fat Intake (50 gr/d), Polyunsaturated Fat Intake (25 gr/d), Carbohydrate Intake (281.25 gr/d), Protein Intake (84.375 gr/d), High Fibers (10 gr/d), and Base Level of High Fibers (10 gr/d).

Stock - Flow diagram of this sector can be seen in Figure 3-9. Complete set of equations can be found in the online Appendix.

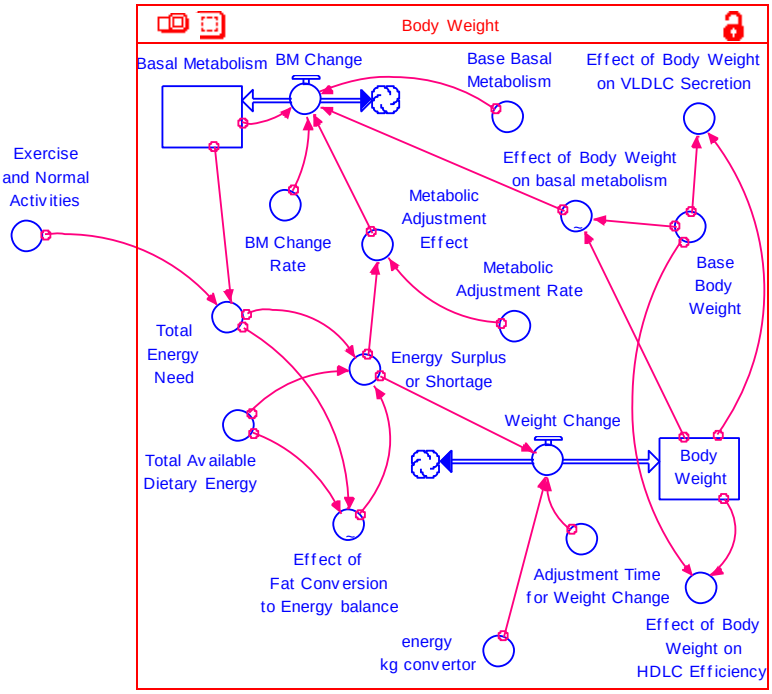

Figure 3-9 Stock– Flow Diagram of Body Weight Sector

4. BASE BEHAVIOR OF THE MODEL and VALIDITY TESTS

4.1.Base Run

The patient has borderline high blood cholesterol values. He weighs 74 kg. If he keeps his diet and exercise constant, he gets the same blood levels throughout time and a total to HDL cholesterol ratio of 5.9. Since this ratio is quite high, he should consider some ways to lower his total cholesterol level and this ratio. His base level of VLDLC, IDLC, LDLC, and HDLC are 25 mg/dL, 18.57 mg/dL, 111.45

mg/dL, and 31.56 mg/dL. His total blood cholesterol is 186.5 mg/dL. All of the stocks stay in their equilibrium levels, if they are so initialized.

Randomness in the model parameters *High Fibers*, *Cholesterol Intake*, *Saturated Fat Intake*, *Polyunsaturated Fat Intake*, *Monounsaturated Fat Intake*, *Carbohydrate Intake*, *Protein Intake*, *Exercise and Normal Activities*, *Normal Bile Secretion*, *Base VLDLC Secretion, Hepatic Synthesis Control Rate, HDL Removal Time, Normal HDL Efficiency, CETP Activity Rate* results in stable oscillations around the equilibrium levels, as would be expected in real life.

4.2. Validity Tests

Sector-wise validity checks are made for each sector in isolation. In this section, the paper by Burke *et al* (2006) is used as a reference point to check the validity of the whole model. In the study, the subjects' dietary intakes are reduced. The experiment was done for 6 months.

The mean and standard deviation, (mean, standard deviation) of the parameters and initial values in the real case are: body weight (94.4, 14.23 kg), total cholesterol (206.31, 41.3 mg/dL), HDLC (52.26, 12.1 mg/dL), and LDLC (127.53, 36.7 mg/dL). Before the experiment, the subjects' diet had (2023.76, 660.66 kcal). This intake was reduced to (1487.78, 475.23 kcal). Also the fat percentage of the diet is reduced: saturated fat from (11.96, 3.27) to (8.20, 3.53), monounsaturated fat from (13.42, 2.94) to (9.23, 3.54), and polyunsaturated fat from (7.20, 2.21) to (6.22, 2.30). Carbohydrate percentage of the diet is increased from (50.31, 7.72) to (61.37, 9.25). Protein percentage remains fairly the same (15.15, 3.41) at first, and (15.07, 3.46) in the experiment.

In simulation, the initial levels of the stocks are set to real case equilibria by changing the necessary flows from their base levels. All of the parameters and equations can be seen in the online Appendix. As seen in the initial phase of Figures 4.1 and 4.2, all stocks stay at their equilibria, if they are so initialized. On day 10, all of the dietary parameters are decreased to the mean levels stated above and simulated for another 6 months or 180 days as in the real experiment. The resulting dynamics can be seen in Figure 4-1 and Figure 4-2.

The starting body weight was 94.40 kg in the simulation and this value also was the average body weight in the real case. In the real case, body weight is reported to decrease to (86.90, 15.55 kg), while in the simulation it became 89.44 kg. In the real case total cholesterol decreased to (197.73, 39 mg/dL) from its average value 206.42 mg/dL. In the simulation it decreased to 179.05 mg/dL from 206.42 mg/dL. The reported LDLC in the paper is (121.29, 33.54 mg/dL), whereas in the simulation (LDLC + IDLC) it is 111.88 mg/dl. The base level in both cases is about 130 mg/dL. HDLC is reported to decline little compared to other factors: it decreased by 1.56 mg/dL with a standard deviation of 7.41 mg/dL. HDLC decreased by 7.1 mg/dL in the simulation.

Figure 4-1 Validity Run Experiment – Blood Cholesterol Levels

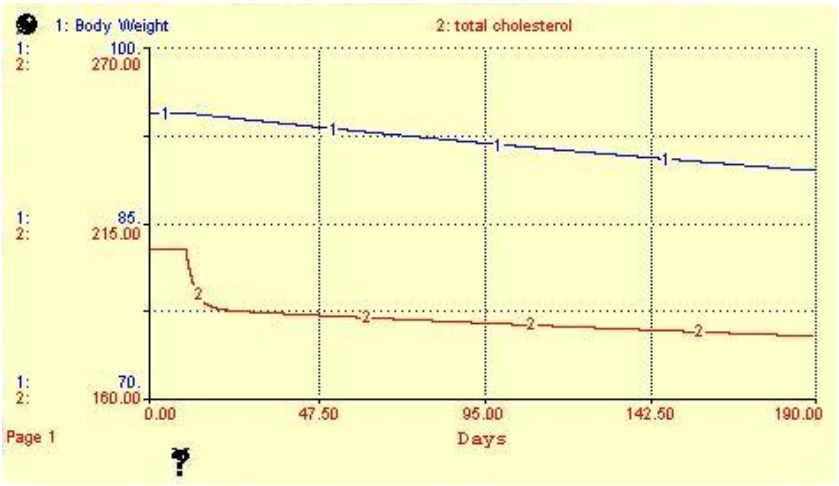

Figure 4-2 Validity Run Experiment – Body Weight, and Total Cholesterol

The reported values have high standard deviations. This may not be due to random error since the number of subjects is 84 and it's fairly a high number for such a costly experiment. The high variations may be due to the nonlinearities in control parameters, or uncontrolled/ unobserved situations like the stress level of the subjects, deviations from the controlled diets, decreasing level of exercise, smoking, gender etc… The most contributing factor for the uncertainty in the response variables like total body weight, and total blood cholesterol is probably due to genetics of the people. Different people respond differently to changing factors like the body weight and diet. The amount of reaction may differ in body weight (Mensink, Zock, Kester, & Katan, 2003), whereas the reaction to some dietary elements like monounsaturated fats may even be positive in some people while negative in the others (Dattilo & Kris-Etherton, 1992).

Though there are variations in the response variables in the real case with possible reasons stated above, the simulation model predicts the behavior in the correct direction and in reasonably valid ranges. The response values are estimated within from 0.3 standard deviation error (LDLC), to one

standard variation error (HDLC). Taking everything into consideration, due to the different genetics of people, it is impossible to build a model that predicts the cholesterol dynamics of each person point-by-point, yet a model can be designed and calibrated such that it represents the cholesterol dynamics of "a specific" person adequately. Such a specific calibration is not the purpose of this research, nor do we have access to any such individual experimental data. We can nevertheless state based on the validity dynamics shown above that our model can capture the fundamental dynamics and levels of the main cholesterol variables adequately.

5. Scenario Analysis

5.1.Normal Subjects

5.1.1. Hazelnut Diet

In the first experiment, the patient adds hazelnuts to his diet, which are argued to decrease blood cholesterol levels, without any change in his lifestyle. The subject eats a handful, or 25 gr, of nuts a day. The extra dietary elements from 25 gr of hazelnuts are: 4.25 gr carbohydrates, 2.5 gr dietary fibers, 1 gr saturated fats, 11.5 gr monounsaturated fats, 2 gr polyunsaturated fats, 3.75 gr proteins.

If he starts to add 25 gr of hazelnut to his diet, does not change any other practice in his life, and considers only the first month of his changed diet, he should think that adding hazelnuts really works. His total cholesterol decreased to 185 mg/dL from 186.6 mg/dL. There is also a slight decrease, 3.2 mg/dL, in LDLC; and 0.5 mg/dL decrease in IDLC. But, HDLC increased by 1.81 mg/dL. This caused his total to HDL cholesterol ratio to decrease to 5.5 from 5.9. But within this first month he gained nearly a half kg, and he should bear in his mind that body weight has effect on LDLC and HDLC. To see the long term dynamics, the model is run till day 2000. The results can be seen in Figure 5-1and Figure 5-2.

His *total cholesterol* was better for about 2.5 months, while his *total to HDL cholesterol ratio* was less than normal, meaning better, for about 8 months. But, as said before, he should keep in mind that he is gaining weight. He only gains about 4 kg at the time his ratio was back to 5.9, though he had seen 5.5 in his first month after starting to eat hazelnuts! At the end of the simulation he gains a total of 10 kgs, and his has *total cholesterol* and his *total to HDL cholesterol ratio* rises to 202 mg/dL and 6.8, from 186.6 mg/dL and 5.9 respectively. Therefore, in the short run this diet is healthful but in the long run it deteriorates his health.

5.1.2. More Hazelnuts, Less Carbohydrates - Unchanged caloric Intake

In the second scenario, he compensates the extra calories from hazelnut by reducing his carbohydrate intake. So he should cut about 40 gr of carbohydrates not to gain weight. His body weight stays constant at 74 kg and his total cholesterol decreased to 184 mg/dL from 186.6 mg/dL. There is a 3.9 mg/dL reduction in LDLC; and 0.4 mg/dL decrease in IDLC. But, HDLC increased by 2.0 mg/dL. This caused his total to HDL cholesterol ratio to decrease to 5.5 from 5.9. Therefore, in this scenario hazelnut recipe works in the short and long run, because body weight does not change throughout the simulation.

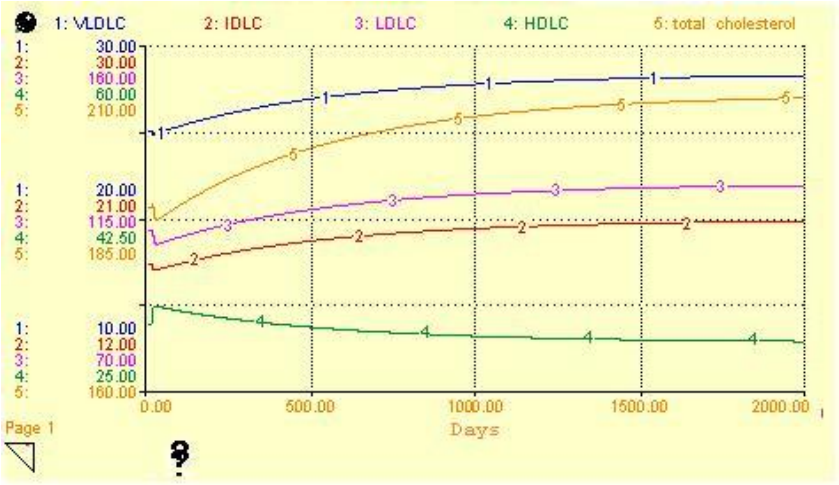

Figure 5-1 Hazelnuts, 2000 days – Blood Cholesterol Levels

Figure 5-2 Hazelnuts, 2000 days – Body Weight, Total Cholesterol and Cholesterol Ratio

5.1.3. Weight Loss

In this case he will have a 150 kcal deficit in his energy balance via either reduced dietary intake, or increased exercise.

Reduced Dietary Intake

In this case he cuts fats, carbohydrates, and proteins proportionally. All of the ingredients in his diet are decreased by 7.67 per cent to make a total of 150 kcal energy reduction. He starts his new diet at day 10. In the first two months he does not see much improvement in his body weight and blood cholesterol levels as seen in Figure 5-3 and Figure 5-4.

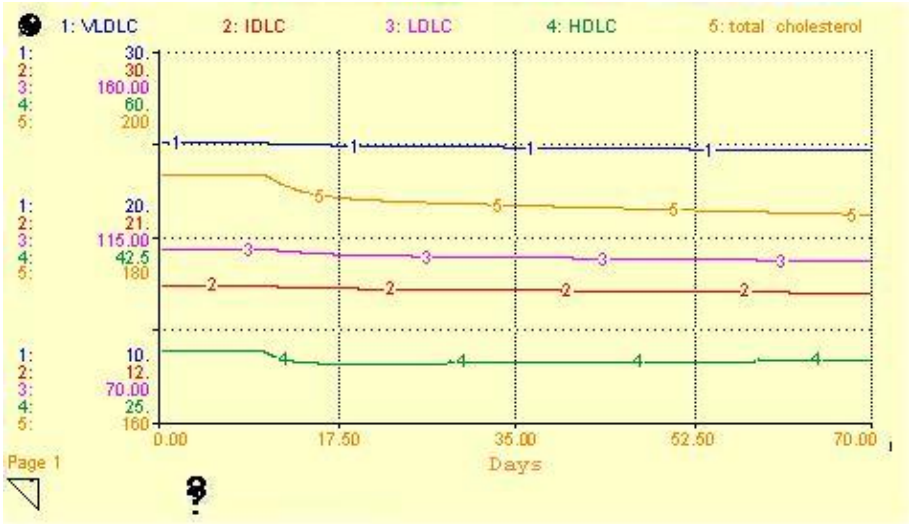

Figure 5-3 Reduced Dietary Intake – Blood Cholesterol Levels

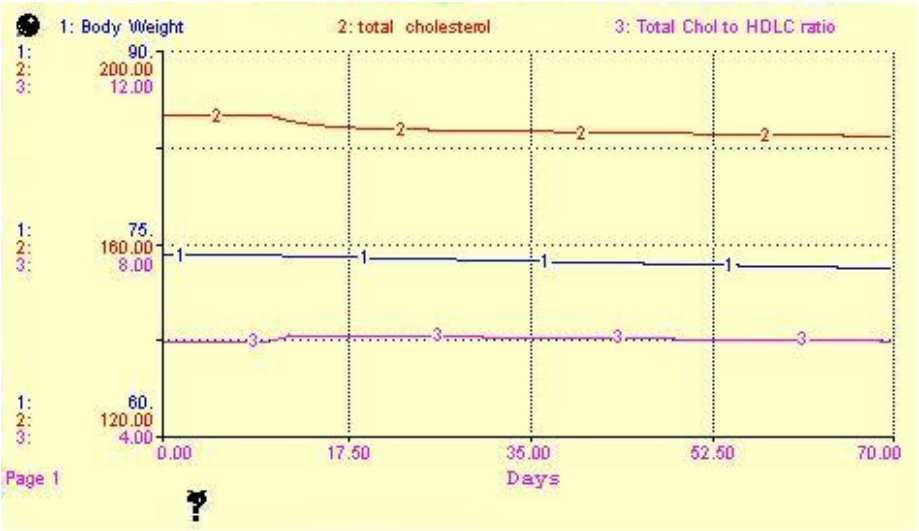

Figure 5-4 Reduced Dietary Intake- Body Weight, Total Cholesterol and Cholesterol Ratio

In the long run, he sees improvements in his blood cholesterol levels and body weight. There is a sharper decrease in HDLC than LDLC, so at first his *total to HDL cholesterol ratio* increases. But, as he begins to lose weight, his HDLC increases while his LDLC increases and this ratio begins to decrease. At the end of the simulation, he loses about 6 kg, his total to HDLC ratio decreases to 5.35 from 5.9, and his total cholesterol decreases to 173.5 mg/dL from 186.6 mg/dL, whereas his HDLC level increases to 32.4 mg/dL from 31.5 mg/dL. These results can be seen in the following figures. Also the initial reduction in the level of HDL cholesterol is reported on the literature as the decrease in HDLC in the period of actively losing weight (Dattilo & Kris-Etherton, 1992). This reduction is also seen in the simulation, but it is due to the reduced intake of fats. If fat content of the diet was not reduced than this initial reduction should not be observed.

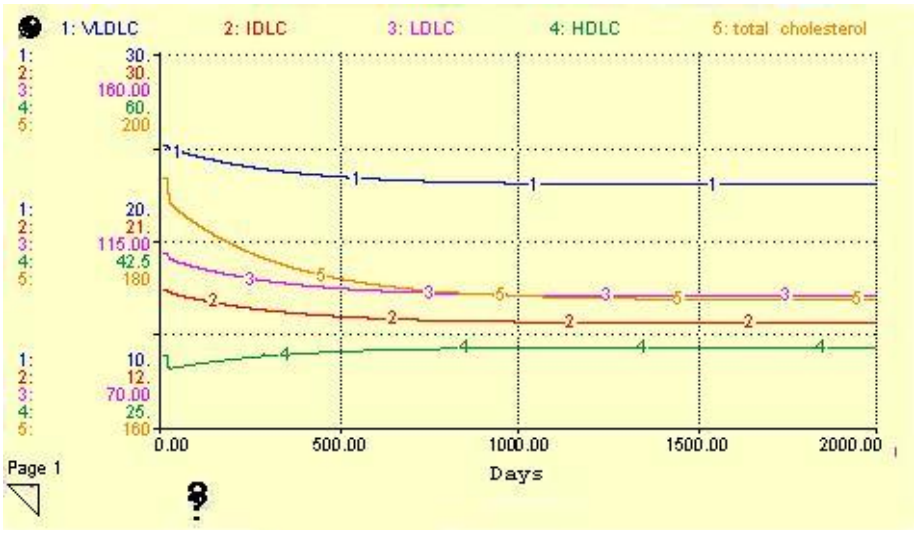

Figure 5-5 Reduced Diet – Blood Cholesterol Levels

Figure 5-6 Reduced Diet - Body Weight, Total Cholesterol and Cholesterol Ratio

Increased Exercise

In this scenario, he increases his daily activities by practicing more to burn 150 more kcal per day.

In the first 10 days of the exercise, there is a sharp change in the blood cholesterol levels. After this time, the effect of losing weight on blood cholesterol begin to show up and help decrease his *total to HDL cholesterol ratio* even further. At the end of the simulation, he loses about 6 kg, his ratio decreases to 4.9 from 5.9, and his total cholesterol decreases to 179.5 mg/dL from 186.6 mg/dL, whereas his HDLC level increases to 36.3 mg/dL from 31.5 mg/dL. Keeping in mind that 1 per cent increase in HDLC level means 2-3 per cent less chance of hearth stroke; it is possible to argue that doing exercise is highly beneficial to the health of the subject.

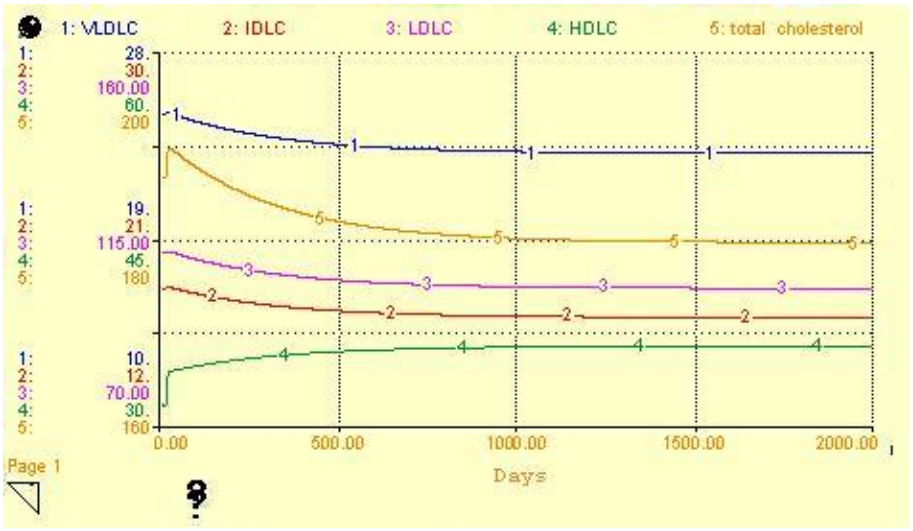

Figure 5-7 Increased Exercise - Blood Cholesterol Levels

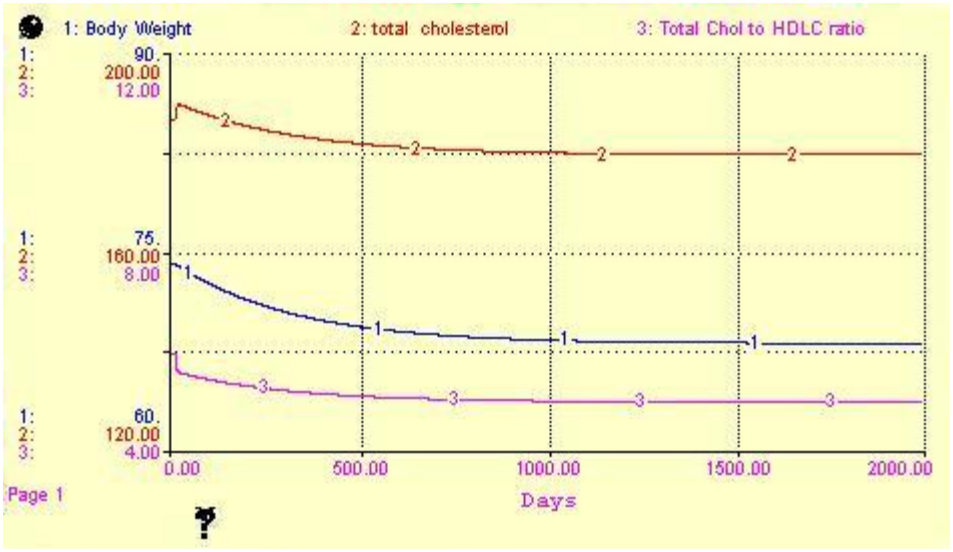

Figure 5-8 Increased Exercise - Body Weight, Total Cholesterol and Cholesterol Ratio

Atheroprotective properties of HDL increase with exercise, but this is out of the model boundary and is not modeled. But it's already possible to conclude that doing more exercise is healthier than merely eating less by comparing the figures and numbers of the two losing weight scenarios. Exercise lowers the ratio to 4.95 and total cholesterol to 179.5 mg/dL, whereas diet decreases the ratio and total cholesterol to 5.35 and 173.5 mg/dL respectively. Total cholesterol in the second scenario is 6 mg/dL higher than the first one, yet it would be erroneous to jump to the conclusion that exercise is not a better solution than diet, because 4 mg/dL of this number adds to the HDLC level of the subject and only about 2 to the other cholesterol stocks in the blood and looking for the *total to HDL cholesterol ratio* is a more appropriate way of assessing the healthiness in terms of cholesterol levels.

5.1.4. More Exercise, Increased Dietary Intake – Constant Weight

In this case the subject exercises 150 kcal more than the base level while increasing his diet by the same calories. He is assumed to be increasing his entire dietary intake proportionately, namely by 7.67 per cent. The results can be seen in Figure 5-9 and Figure 5-10. It can be argued from the figures and numbers that losing weight by any of the two methods in the earlier scenarios is more efficient in getting healthier numbers than this scenario, after noting that this scenario is better than the *do nothing* or the *base run*. In this constant weight scenario his total to HDLC cholesterol ratio decreases to 5.43 from 5.9; total cholesterol increases by 5 mg/dL of 4 mg/dL of which was in HDLC.

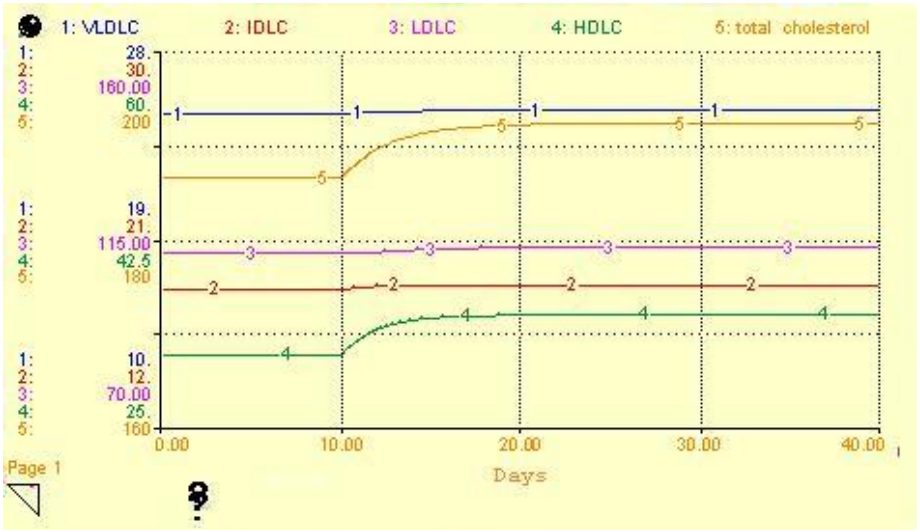

Figure 5-9 More Exercise, Constant Weight – Blood Cholesterol Levels

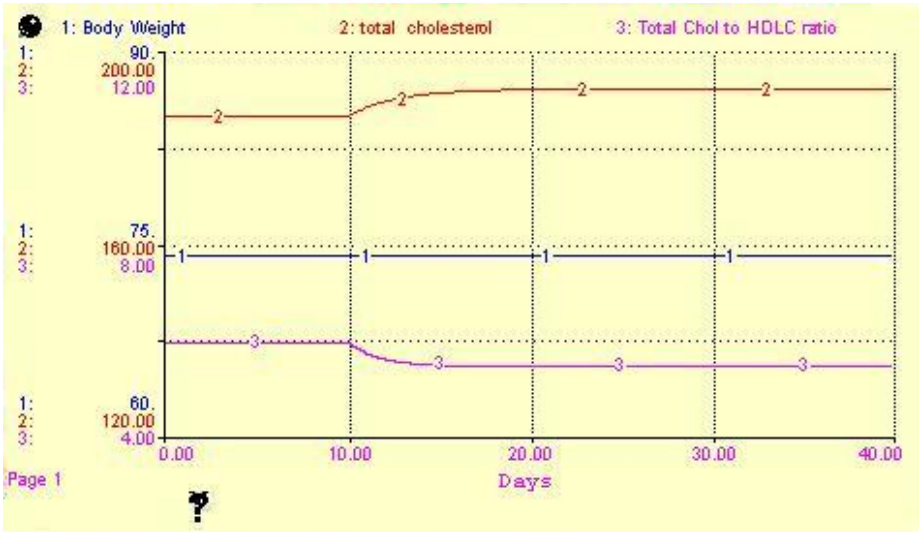

Figure 5-10 More Exercise, Constant Weight – Body Weight, Total Cholesterol and Cholesterol Ratio

5.2. Hypercholesterolemic Subjects

As an extension to the model, familial hypercholesterolemia (FH) can be simulated. In this type of cholesterol disorder, the LDL receptor activity of the patients' is reduced to half. Nearly 50 per cent of the receptors are not functioning (Bhagavan, 2002; Citkowitz, 2007). Reducing the LDL receptor activity results in lower IDLC and LDLC uptakes by hepatic and extrahepatic tissues. HDLC and VLDLC don't seem to change but IDLC and LDLC rise to 28.0 mg/dL and 269.3 mg/dL from 18.5 mg/dL, and 111.5 mg/dL respectively. The total blood cholesterol increases to 353.9 mg/dL from 187 mg/dL. The total cholesterol levels of familial hypercholesterolemic patients' are between 330 and 400 mg/dL, and the model is able to reflect this change. Moreover total to HDL cholesterol ratio increases to 11.2 from 5.9. All of the equations and the parameters can be seen in the online Appendix.

5.2.1. Increased Exercise, Reduced Dietary Intake

In this scenario, the patient tries to do more exercise and eat less. He does 150 kcal worth of exercise each day and has motivation to cut his diet by 50 kcal a day. The results can be seen in the Figure 5-11 and Figure 5-12.

By this diet and exercise program he loses about 8 kg. His total cholesterol level decreased to 324 mg/dL and his HDLC level increased 4 mg/dL. His *total to HDL cholesterol ratio* decreased to 8.9 from 11.2. Though there is a significant decrease, 8.9 is still a risky number (Harvard Health Letter, 2004), it should be lower than 7.0 to count as not risky.

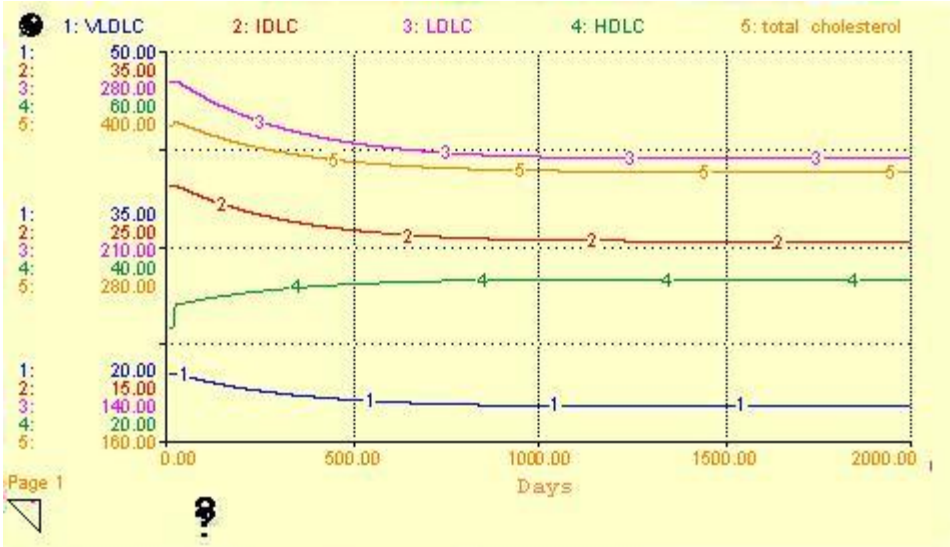

Figure 5-11 FH Patient; More Exercise, Less Dietary Intake. Blood Cholesterol Levels

Figure 5-12 FH Patient; More Exercise Less Dietary Intake. Body Weight, Total Cholesterol and Cholesterol Ratio

5.2.2. Medication

Reducing the dietary intake and doing more exercising may not be not enough to reach to healthy cholesterol levels. Medicine is another option and the patient is assumed to take statins for this purpose. Statins lower or block the synthesis of cholesterol within liver and extrahepatic tissues by inhibiting HmG-CoA reductase – which is an enzyme in the production of cholesterol (Bhagavan, 2002).

The effect of statin in the model is by four factors. It is assumed that the given dose decreases the cholesterol synthesis in the liver and extrahepatic tissues by 300 mg/dL, and 100 mg/dL respectively. Also the metabolic adjustment times in these compartments to reach desired levels of intracellular cholesterol is increased to 2 and 4 days from 0.5 and 2 days in the liver and extrahepatic tissues.

The model as in the real case works like the following. First, statins lower the cholesterol synthesis in these tissues. So, the receptor activities of these tissues increase to compensate this loss. As a final result, more cholesterol is taken up by these tissues and blood cholesterol is thus decreased. This argument can be seen in Figure 5-13.

The total effect of statins is observed after about 4 weeks. This is reported in literature- as the time to see the full potential of statins is 4 weeks (Citkowitz, 2007; Statins, FM, 2008). The remarkable thing here is that we did not include any delay formulation to our model to reflect this 4 week period. Our model successfully gave this result with its parameters and structure unchanged for this purpose. This is sort of a validity check which is successfull but not intended.

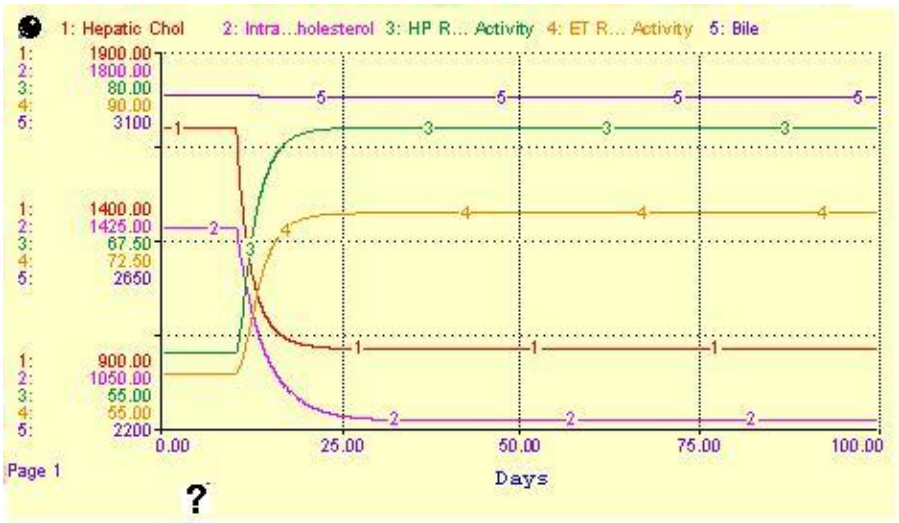

Figure 5-13 FH Patient; Effect of Statins on Cholesterol Pools and Receptor Activities

Total cholesterol level decreased to 265 mg/dL, while *total to HDL cholesterol ratio* decreased to 8.4 from 11.2. Though this decrease is better than the lifestyle change in the previous experiment, it is still not sufficient alone. These findings can be found in the following figures.

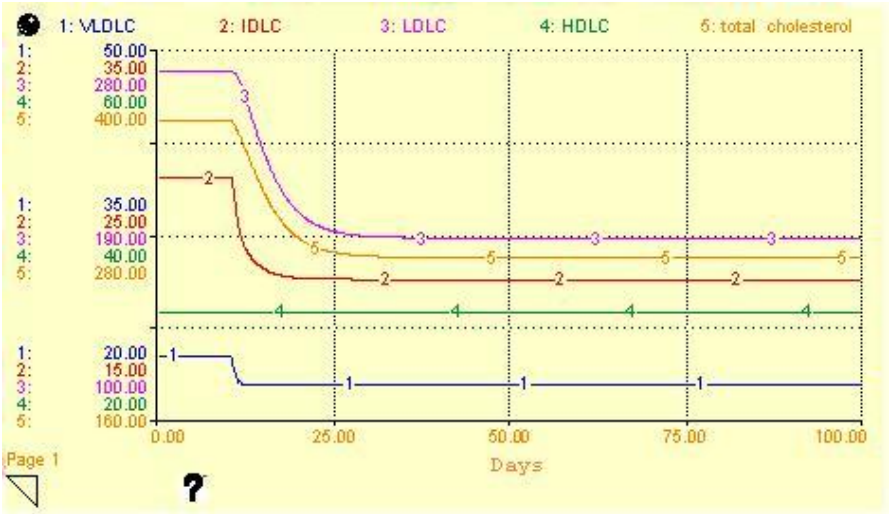

Figure 5-14 FH Patient; Statin Medication- Blood Cholesterol Levels

Figure 5-15 FH Medication - Body Weight, Total Cholesterol and Cholesterol Ratio

5.2.3. Medication, Increased Exercise, and Reduced Dietary Intake

As seen in the above two scenarios, neither taking medication nor changing the lifestyle alone provide sufficient results. So in this case, these two practices will be tried together as it is recommended to familial hypercholesterolemia patients by practitioners in the real world. So he will practice more that his daily exercise is increased by 150 kcal, dietary intake is reduced by 50 kcal, and he takes the same dose of statins as in the above scenario.

This combination is able to lower total cholesterol to 244 mg/dL and the total to HDL cholesterol ratio to 6.7. These numbers are regarded as borderline high, but a lot healthier than the patient's base run values: 354 mg/dL and a ratio of 11.2. The following figures depict this argument.

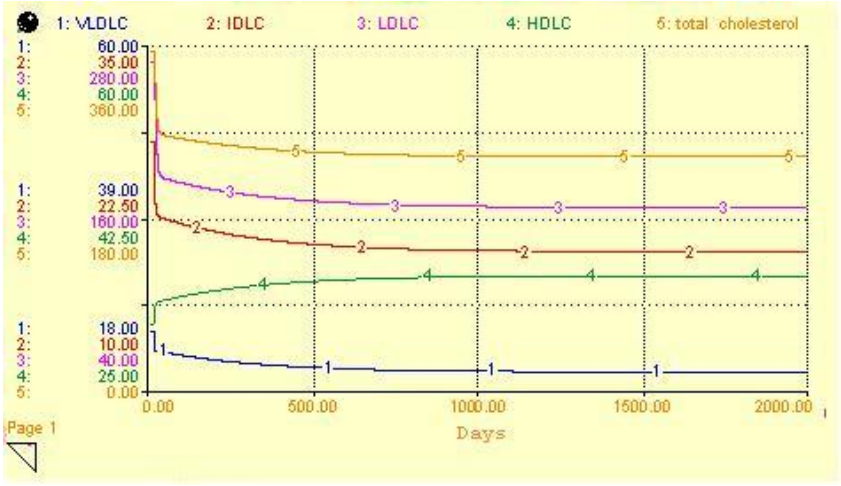

Figure 5-16 FH Patient; Medication, Exercise, and Diet Case. Blood Cholesterol Levels

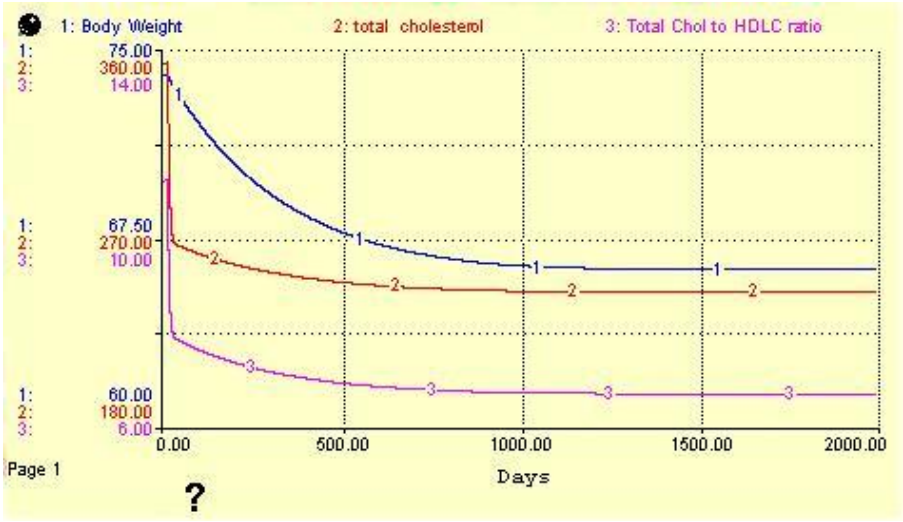

Figure 5-17 FH Patient; Medication, Exercise, and Diet Case.Body Weight, Total Cholesterol and Cholesterol Ratio

6. Conclusion

As stated in the introduction, cholesterol has been the subject of many simulation modeling and mathematical modeling studies. Simulation studies generally try to answer questions at the cellular level, whereas most mathematical models sacrifice model realism for the sake of analytical tractability (August, Parker, & Barahona, 2007). Our model is built using system dynamics methodology and it has a systemic a view, which takes diet, exercise, and the genetics of the person into account.

Reference simulation run for a healthy patient generates a stable and realistic pattern for the variables of interest: HDL cholesterol, IDL cholesterol, LDL cholesterol, VLDL cholesterol, and body weight. Validity checks on a sector by sector basis and on the whole model give no signal of modeling flaws. Moreover, all sectors and the whole model are shown to be robust to random errors in the parameters. Likewise, the simulation run for the hypercholesterolemic patient case successfully generates the behavior of the disorder dynamics.

For healthy subjects, scenario runs include different settings like adding hazelnuts to the patient's diet, replacing carbohydrates with hazelnuts in the diet, weight loss by reducing dietary intake, weight loss by increasing the amount of exercise, and adding calories to the diet together with increased exercise to keep a constant body weight. When hazelnuts are added to the diet, better cholesterol levels are first observed in the short run, while in the long run this situation is reversed since the patient gains weight. If the total caloric intake is kept constant while adding hazelnuts to the diet, the patient reaches healthier cholesterol levels both in the short and long terms. When the subject loses weight by reducing the caloric intake, we first observe a higher (worse) total cholesterol-to-HDL cholesterol ratio. This is due to sharper decrease in HDLC compared to other blood cholesterol pools as a response to decreased fat intake and is consistent with the literature (Mensink, Zock, Kester, & Katan, 2003). As the subject loses weight, HDLC increases while LDLC decreases, so the ratio reduces to values lower than the initial case. If the subject loses weight by increasing his daily exercise, he obtains even healthier results than the reduced dietary intake case. If the subject does more exercise but compensates this energy loss by

eating more, she gets healthier cholesterol measures than the do-nothing case (base run), but worse results than any of the weight losing scenarios.

In the case of hypercholesterolemic subjects, the scenarios include the subject losing weight by increased exercise and reduced caloric intake, medication (taking *statins*), and the combination of medication, reduced caloric intake, and increased exercise. In the medication scenario, the subject takes *statins* to lower her cholesterol. The full effect of statins is observed after 4 weeks of starting the medication and this is in agreement with what is observed in the real world (Statins, FM, 2008; Citkowitz, 2007). A remarkable point here is that we did not include any delay formulation in our model to reflect this 4 week period. Our model successfully yielded this result with its parameters and structure unchanged for this purpose. This is a natural and strong validity check. Although statins result in healthier cholesterol levels than the first scenario (only losing weight), by themselves they are not enough to attain acceptable blood cholesterol levels. In the third scenario, the combination of medication, diet, and exercise are employed, yielding acceptable cholesterol levels which are clearly healthier than the results of all of the other scenarios.

Our model can be used to test other scenarios on both healthy and hypercholesterolemic subjects. The model can also be used as a foundation for a more comprehensive model that takes stress on both behavioral and physiological grounds into account. The subject, whose bodily dynamics are modeled in this study, is sort of a representative individual. His parameter values are average values of various individuals, which are extracted from the literature. So, as an extension to this study, our model could be calibrated in a way to represent the cholesterol dynamics of “specific” persons. Finally, our model can be a starting point of an interactive simulation game which focuses on the management of hypercholesterolemic patients, where users can experiment with alternative diet, exercise & medication combinations.

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