A DYNAMIC SIMULATION MODEL FOR INSULIN RESISTANCE AND TYPE II DIABETES IN THE CONTEXT OF OBESITY

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ABSTRACT

A DYNAMIC SIMULATION MODEL FOR INSULIN RESISTANCE AND TYPE II DIABETES IN THE CONTEXT OF OBESITY

Type 2 diabetes, is a frequently seen endocrinological disease leading to other serious health problems such as heart disease and kidney dysfunction that may eventually lead to a premature death. Insulin resistance is seen as the starting point of this disorder. Obesity, hyperglycemia (high blood sugar), hyperinsulinemia (excess levels of insulin in the blood) are the main reasons for developing insulin resistance and type 2 diabetes, ultimately. Other factors are indicated as age, gender and genetic factors. The aim of this study is to construct a dynamic simulation model that can realistically reproduce the long term behavior of developing insulin resistance and type 2 diabetes related to obesity. For this purpose, a system dynamic model is constructed which focuses on the interaction between the body weight of an average individual and the glucose and insulin regulation in the body. Firstly, a model which shows the relationship between body weight and glucose-insulin mechanism for a healthy body is generated. In the validation part, the effect of obesity on glucose regulation is demonstrated. According to the available research on this topic, doing exercise and changes in the diet may reduce the severity of insulin resistance or even eliminate this disorder completely. Simulation experiments with the model show that different physical activity levels and dietary intakes have impact on developing insulin resistance. Yet in the long run, insulin secretion level and beta-cell dysfunctionality play a more significant role for developing type II diabetes. In conclusion, the obesity factor on insulin resistance and type II diabetes is demonstrated in the model in a major scope, by using available information and data in the literature.

ÖZET

İNSÜLİN DİRENCİ VE TİP II DİYABETİN ORTAYA ÇIKMASINDA OBEZİTENİN ETKİSİ ÜZERİNE BİR DİNAMİK BENZETİM MODELİ

Tip 2 diyabet, günümüzde oldukça sık görülen ve başka ciddi sağlık problemlerine de yol açan, hatta ölüme neden olabilen endokrinolojik bir hastalıktır. İnsülin direnci ise, bu hastalığın başlangıç noktası olarak görülmektedir. Obezite, hiperglisemi (kan şekeri yüksekliği), hiperinsulinemi (kandaki insülin değerinin yüksekliği) insülin direncinin ve dolayısıyla tip 2 diyabetin ortaya çıkmasındaki başlıca nedenlerdendir. Diğer etkenler olarak; yaş, cinsiyet ve genetik faktörler gösterilmektedir. Bu çalışmanın amacı, obeziteyle ilişkili olarak insülin direncinin ve tip 2 diyabetin uzun dönemde gelişiminin gerçekçi bir şekilde üreten dinamik benzetim modeli kurmaktır. Bu amaca yönelik olarak, tıbbi verileri kullanarak ortalama bir bireyin kilosu ile vücuttaki glikoz ve insülin dengesi arasındaki ilişki üzerine odaklanmış bir dinamik benzetim modeli kurulmuştur. Yapılan araştırmalara göre, kişinin egzersiz yapması ve diyetini değiştirmesi gibi durumlar, insülin direncinin derecesini etkileyebilmekte, hatta problemin tamamen ortadan kalkmasında etkili olabilmektedir. Benzetim deneyleri, farklı fiziksel aktivite düzeyleri ve yiyecek alımlarının insülin direncinin üzerindeki etkisini göstermektedir. Uzun dönemde ise, insulin salgı düzeyi ve beta-hücrelerindeki işlevsel bozulmalar, tip II diyabetin ortaya çıkmasında önemli bir rol oynamaktadır. Sonuç olarak, literatürde mevcut bilgiler ve veriler ışığında, obezitenin insulin direnci ve tip II diyabetin ortaya çıkmasındaki etkisi, model üzerinde genel bir çerçevede yansıtılmaktadır.

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LIST OF ACRONYMS/ABBREVIATIONS

Adj	Adjustment
Avg	Average
BMI	Body mass index
BW	Body weight
coeff	Coefficient
conc	Concentration
comp	Component
CHO	Carbohydrate
del	Delay
ECW	Extracellular water mass
eff	Effect
FBD	Fat breakdown
FFA	Free fatty acids
HOMA-IR	Homaostatis Model Assessment-Insulin Resistance
Graph func	Graphical function
MPD	Muscle protein degradation
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIDDM	Non-insulin-dependent diabetes mellitus
PA	Physical activity
REE	Resting energy expenditure
sec	Secretion
TEE	Thermic effect of exercise
TEF	Thermic effect of food
TURDEP	Turkish Diabetes Epidemiology Study
WHO	World Health Organization

1. INTRODUCTION

Diabetes mellitus is a condition that shows a significant problem in glucose and insulin regulation because of an impaired carbohydrate, fat and protein metabolism, which causes an inadequate secretion of insulin, or a reduction in insulin sensitivity of the target tissues for insulin hormone. There are mainly two cases for this condition, type I diabetes (insulin-dependent diabetes mellitus) and type II diabetes (Guyton, 2006).

Type II diabetes, also known as non-insulin-dependent diabetes mellitus (NIDDM), is one of the most common endocrine disorders, which causes serious physiological problems, leading to premature death. About 80-95% of the diabetic patients have type II diabetes (Sizer and Whitney, 2010).

Type II diabetes occurs when the sensitivity of body tissues, such as muscle and liver, decreases and cannot respond adequately to the effect of insulin hormone (Guyton, 2006). This disease is mostly seen in obese individuals who are generally middle aged (older than 30 years). Insulin resistance is indicated as one of the most significant causes for this disorder. Insulin resistance is the inappropriate response to insulin in insulin receptors and target tissues (Tortura and Grabowski, 2004). Besides insulin resistance, there are several risk factors of type II diabetes, which are obesity, hyperglycemia, genetic factors, age and gender. In this study, the effects of obesity factor on developing hyperglycemia and insulin resistance, and ultimately type II diabetes is taken into consideration.

In the United States, the fourth leading cause of death by disease is diabetes, as it causes major damage in the cardiovascular system (Tortura and Grabowski, 2004). 11.3% of the U.S. population (about 25.6 million people), who are 20 years or older, have diabetes (NIDDK, 2011). According to the statistical results done by World Health Organization, there are approximately 310 million patients who have type II diabetes in the world (WHO, 2011).

Obesity is one of the most important factors in developing insulin resistance, and ultimately having type II diabetes. It occurs when there is an imbalance between energy intake and energy expenditure of the body in the long term. In order to prevent this condition, the factors that cause the imbalance should be well-understood, and necessary precautions have to be taken with respect to the related circumstances (Abdel-Hamid, 2002). Currently, obesity has become one of the most prevalent "disorders" in the world. According to the statistics in Turkey; the prevalence of obesity is 32% of total population, and the prevalence of diabetes is 13.7% of the total population in 2010. When it is compared with the previous study TURDEP-I, held in 1998, it is found that the prevalence of obesity and diabetes has been increased about 44% and 90% respectively, in the last 12 years (TURDEP-II, 2010).

To supply sufficient energy for the body, a person needs to get nutrients according to his resting metabolic rate, which is affected by the factors of age, gender, weight and height. Furthermore, the composition of dietary intake is also important, because the energy-yielding nutrients which are fat, protein and carbohydrate give different amounts of energy, and can be converted to each other. When an individual takes one of these nutrients in excess, it is stored as fat in the body. A healthy person can lose fat (and consequently, lose weight) by doing exercise, which is a process governed by a negative feedback mechanism. Therefore, the relationship between food intake and gaining/losing weight is constructed in the model by using the components of energy intake and energy expenditure, which also includes doing physical activity and muscle build up.

On the other hand, fat storage level affects glucose and insulin regulation in the body that constitutes several negative feedback loops. The link between obesity and insulin resistance is represented with this relation. Because of the complexity by human nature, some assumptions have been made for these mechanisms. The key factor of inducing disorder of glucose homeostasis is known as non-esterified fatty acids (free fatty acids), which is a product of fat breakdown. Besides, functionality of beta-cells is also vital during the process of developing type II diabetes, ultimately. Beta-cells are responsible for regulating insulin release, located in the pancreas. Therefore, a dysfunction of beta-cells will induce an inadequate response to glucose stimulation according to the insulin secretion level, which also works in a negative feedback mechanism.

In this study, a dynamic simulation model of developing insulin resistance and Type II diabetes in obese people will be constructed. The aim of the study is to observe the long term behavior of developing insulin resistance when the obesity factor is considered.

In the following chapter, a review of body weight mechanisms and glucose and insulin regulation will be provided. Next, a system dynamics model will be constructed to represent the relationship between body weight maintenance and developing insulin resistance and type II diabetes in two sectors. In Chapter 5, base behavior and relevant formulations of the complete model will be demonstrated. In Chapter 6, validation analyses will be investigated according to the associated data. Furthermore, principal interventions for both food intake and doing physical activity will be tested in the scenario analysis section, and finally the results will be summarized and discussed in the conclusion part.

2. LITERATURE REVIEW

It is stated that the resistance to the impacts of insulin on glucose metabolism, storage and uptake commonly implies the term of "insulin resistance". When there is an increase in glucose transport to adipose tissues and muscles by stimulation of insulin, there will be a decrease in glucose production in the liver due to the impaired suppression. Thus, this condition is indicated as the insulin resistance in obesity and type II diabetes. According to the studies for all ethnic groups with wide range of body weight, the relationship between insulin resistance and obesity is clearly observed. Nevertheless, it is declared that when the body fat percentages of lean and obese individuals increase, which is determined by using the body mass index (BMI) formula, there is also an increase in the risk of insulin resistance and diabetes, which indicates that insulin sensitivity is affected by the fat content in the body. Hence, there is a relationship between obesity and insulin resistance, also type II diabetes, and this relationship has significant clinical and methodical inferences as a long-recognized issue (Kahn and Flier, 2000).

Insulin production is contributed by the secretion in pancreatic beta-cells, primarily with reference to the increased glucose concentration level. Glucose is known as the most vital secretagogue for releasing insulin despite other stimulates such as some amino acids and free fatty acids (Li *et al.*, 2006). Contrary to popular belief, insulin hormone is not absent or does not exist in insufficient amounts but presents in higher than normal values in the blood circulation, which is known as hyperinsulinemia, in many cases of type II diabetes. Actually, the secretion processes in beta-cells of pancreas work properly; however there is an impairment of the reaction to the insulin in target tissues. It is found in some examples that there might be a primary failure in the insulin receptors. Yet, it is determined in most cases that the receptor functionality is normal, so a post-receptor defect is attributed to the impairment in the insulin action. Actually, the mechanism of insulin activity is not precisely explained and well-understood; thus the causes of insulin resistance cannot be determined with all aspects thoroughly (Rhoades, 2003).

On the other hand, it is declared that plasma free fatty acids (FFA) play important physiological roles in some body parts such as heart, skeletal muscle, pancreas and liver.

According to the recent data, increased plasma FFA concentration has an important effect on insulin resistance. There is a link between elevated FFA concentration and insulin resistance that occurs in the liver. When FFA concentration is increased in the blood circulation, glucose uptake by muscles is decreased, because FFA is used for providing the required energy of muscle activity. About 80% of the patients who have type II diabetes are obese, and practically all of them are also insulin resistant. Moreover, it is indicated that there is a cause and effect relationship between insulin resistance and obesity, by the reason of a positive correlation between weight and insulin sensitivity, as concluded from human and animal studies. Skeletal muscle plays a major role in developing insulin resistance and type II diabetes. In the study of Randle *et al.* (1963), it is asserted that elevated FFA concentration causes muscle insulin resistance exclusively by fat oxidation corresponding with carbohydrate. Furthermore, it is examined in the paper of Boden *et al.* (2001) that insulin-induced glucose uptake is suppressed by the elevated FFA in both healthy and diabetic individuals. Abnormally elevated plasma FFA concentrations are observed in obese people. Therefore, skeletal muscle tissues develop insulin resistance which triggers liver and pancreas to take extra actions that eventually leads to type II diabetes (Boden and Shulman, 2002). It is also expressed in another study that the link between increased fat mass with insulin resistance and elevated FFA most likely demonstrates the relationship of obesity and the condition of developing type II diabetes (Kovacs and Stumvoll, 2005).

Kahn *et al.* state that an individual who developed insulin resistance has greater insulin responses and lower hepatic insulin clearance than insulin-sensitive individuals. A feedback loop exists between beta-cells in the pancreas and insulin-sensitive tissues such as muscle tissue, adipose tissue, liver for healthy people. With respect to the increase in beta-cells, the demand for insulin supply also increases by these insulin-sensitive tissues. If a failure occurs in this feedback loop, glucose tolerance will no longer be kept at the normal level, which leads to developing diabetes. Besides, if beta-cells are functioning healthily, the normal glucose tolerance is preserved because of the effect of efficient adaptive response in functionality and changes in the mass to insulin resistance of beta-cells. However, if there is a dysfunction in beta-cells, the glucose tolerance and fasting glucose concentration levels will be elevated. Hence, this condition may lead to developing type II diabetes (Kahn *et al.*, 2006).

As a consequence, there are two interconnected impairments: insulin resistance and beta-cell dysfunction as the main causes of type 2 diabetes. It is asserted that a possible dysfunction in beta-cells can be observed as an attribute previously seen in diabetic patients, and their relatives who have this tendency because of the genetic factors. Aside from this, insulin resistance is also known as a kind of main activator for developing type II diabetes, eventually. Insulin resistance predisposition increases in many different countries, mainly due to the tremendous increase in the sedentary lifestyle and prevalence of obesity. In order to keep the plasma glucose concentration level as its normal value, two significant factors should be considered: the capacity of beta-cells to insulin secretion and insulin sensitivity of the target tissues that helps to suppress the plasma insulin concentration (Matthews, 2001).

It is denoted that during maintained physical activity, glucose level considerably decreases because of the drop in the glucose production level in the liver. Thus, doing exercise has an effect on increased glucose uptake rate due to the working tissues, and increased glucose release from the liver in order to preserve the glucose homeostasis in the body. Moreover, if the time spent for exercising escalates, then hepatic glycogen degradation rate will decrease by the reason of limited glycogen store in the liver. But glucose breakdown rate is induced, concurrently. In spite of that, the glucose production in the liver is not equal to the glycogen synthesis rate, since it is a slower process. Hence, there will be a deficit in the glucose release via liver, throughout a sustained physical exercise. On account of the fact that there is an imbalance between hepatic glucose release and glucose uptake by the tissues, the plasma glucose concentration level will decline, and finally hypoglycemia (low sugar blood) will occur. Nevertheless, it is observed in many studies that the glycogen level in the liver decreases faster due to an increase in the exercising intensity. Both elevated glucose uptake rate by working skeletal muscles and hepatic glucose release rate decay steadily to their respective basal levels during the recovery period after physical activity done in the short-term (Roy and Parker, 2007).

There are several studies that are related with the subject of this study, which use the system dynamics methodology. Foster presented a nonlinear feedback mechanism for the blood glucose regulation in the short term, in his Master Thesis (Foster, 1970). Another study shows the control on glucose metabolism on a daily time horizon, which also

considered the roles of insulin, glucagon hormones, pancreas and liver in the management of the diabetes (Hillman, 1978). Besides, in Sorensen's PhD Thesis, a dynamic simulation model is constructed for glucose metabolism for a normal man and a type I diabetic patient, in addition to the glucose regulation metabolism, by using pancreatic and hepatic functions in the system (Sorensen, 1985). Similarly, in another PhD Thesis, a model that has an automatic insulin delivery system for the management of type I diabetes is constructed, which also considers the effects of FFA metabolism and exercising in the system (Roy, 2008).

According to the literature survey, all studies are done only for short term regulation of glucose metabolism, and obesity factor is not totally considered. Thus, there is no study directly shows the dynamic modeling for the whole structure of developing insulin resistance and type II diabetes in the context of obesity factor.

3. RESEARCH OBJECTIVE AND OVERVIEW OF THE MODEL

The purpose of this study is to develop a dynamic model which would present long-term dynamics of developing insulin resistance and type II diabetes with specific focus on obese people. Since the glucose regulation metabolism in the body is very complex, and the changes occur in a very short time, some assumptions have been made in order to construct the model to obtain the long term results.

The main focus of the model is the body weight maintenance and its properties. Depending on food intake and physical activity, the body weight can be kept at its baseline level. In order to find these, energy levels can be observed. If the energy intake and energy expenditure are equal, then there will be no change in the body weight. However, if energy intake is greater than energy expenditure, the difference which is not used in the body is converted to fat as an energy reserve, and stored in the fat depot, leading to weight gain. Similarly, if energy intake is lower than energy expenditure, then fat in the storage will break down to meet the energy requirement of the body, which leads to lose weight. Furthermore, doing exercise will help to regulate the body weight, by increasing the level of energy expenditure. If the person continues to gain weight, he ultimately will become obese. In this case, the glucose and insulin regulation metabolism will change with respect to the severity of obesity.

On the other hand, the glucose regulation system in the body is also integrated in the model, and the consequences of impaired glucose metabolism, which is directly related with the diabetes, are discussed in this study. Even though the feedback mechanism of the glucose-insulin regulatory system in the body occurs in a very short span of time, main variables related with the disorder are constructed within the scope of the cause-and-effect relationships. According to fat mass in the body and physical activity endurance, glucose and insulin production and their functionality may be disrupted. Moreover, the insulin secretion from beta-cells, and glucose release and uptake by liver has a significant impact on maintaining glucose homeostasis in the body. Therefore, these variables and their effects are also considered during the model construction step.

In this study, System Dynamics methodology is used for understanding the dynamics of glucose and insulin metabolism, insulin resistance and type II diabetes, which are affected by the dietary intake and muscular activity in the long term. This methodology gives us a point of view in analyzing and determining the structure of complex systems via the set of tools (Sterman, 2000). In order to study a physiological system, especially for a long term, dynamic modeling is one of the best approaches. Also, it is easier to control and make interventions to the system in the determined time period, and apply different policies according to the responses of the main variables.

The overall causal-loop diagram is given in Figure 3.1, in order to demonstrate the general mechanism of the system. Since the mechanisms in human body are very complex, this study concentrates only on the long term effects of the main components. Thus, some variables in the mechanism are considered as constants for making simplification in the model. For instance, the glucagon hormone, which increases plasma glucose concentration, and also secreted by pancreas, is not considered in the model. Besides, other hormones, such as leptin and adiponectin, which play important roles in regulation of energy metabolism, and cytokines such as TNF-α, IL-2 and IL-6, which play key roles in the regulation of immune system, are also not shown in the model. On the other hand, the individual in the model is considered as an average male, who has almost sedentary lifestyle, and the reference values are used for this assumption. Furthermore, the values of bone mass and extracellular water mass (ECW) are assumed to be constant for all experiments.

The 1st loop represents the negative feedback mechanism on energy balance-body weight axis. The 2nd loop demonstrates that there is a positive feedback mechanism on energy balance-physical activity-body weight axis. In addition, the 3rd loop displays the glucose transport rate-physical activity feedback mechanism for carbohydrate and body weight. The 4th loop represents the feedback effect of essential protein on body weight change. The 5th loop represents the delayed feedback effect between the physical activity level and muscle mass in the related axis. The 6th and 7th loops demonstrate short-term hormone control mechanisms for glucose and insulin regulation in the body. In addition to the short term effects, delayed effects between insulin secretion and the beta-cell functionality are observed in the 8th negative feedback mechanism.

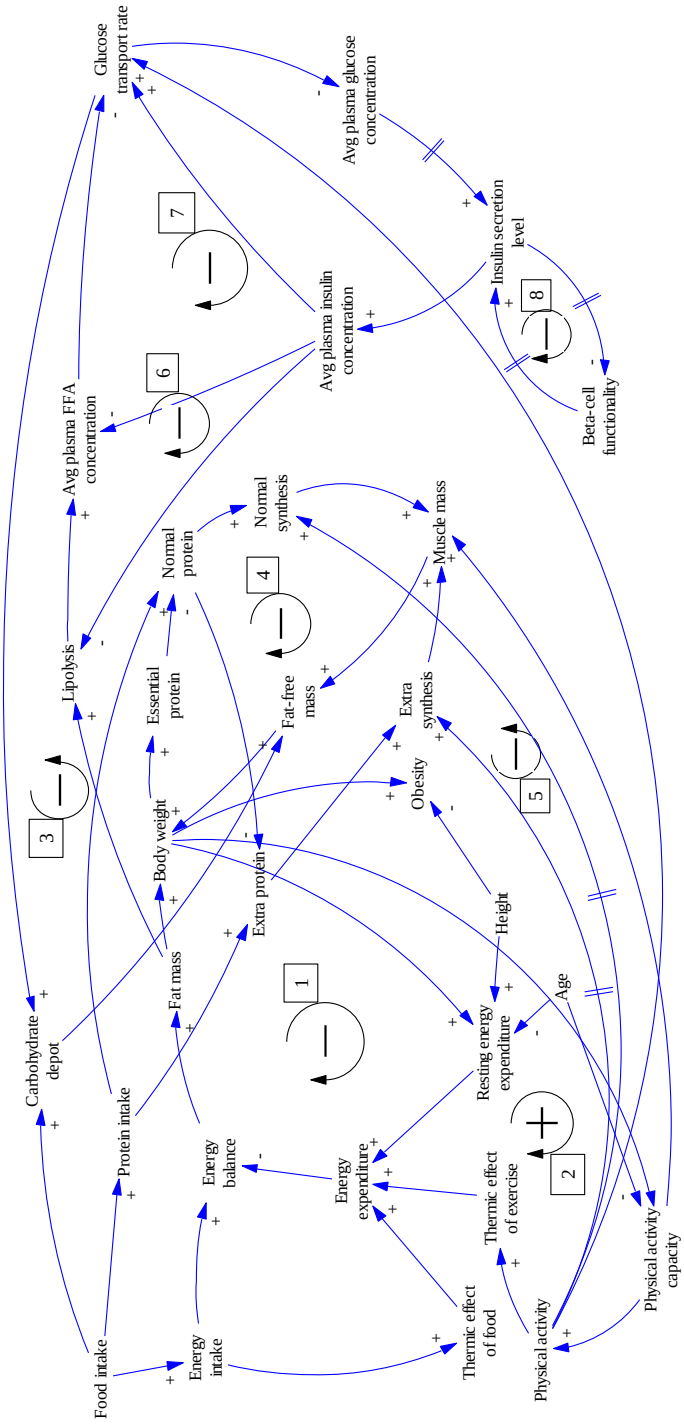

Figure 3.1. A Causal-loop diagram representing the major loops and variables

4. DESCRIPTION OF THE MODEL

4.1. Body Weight Sector

4.1.1. Background Information

As discussed in the first chapter, obesity is the leading factor on developing insulin resistance. Therefore, the starting point for building the model is constructing the body weight dynamics. The main issues considered in this part are food intake and energy expenditure. Energy expenditure contains three different components which are known as resting energy expenditure (REE), thermic effect of exercise (TEE), and thermic effect of food (TEF). Resting energy expenditure refers to the minimum energy requirement that maintains the functions of the body at awake and resting state, which is measured by three standardized conditions: body weight, age and height (McArdle *et al.*, 2010). This value also differs according to the gender; however, in the model, the individual is assumed as male. Thermic effect of exercise refers to the energy expenditure by doing physical activity, which is also indirectly related to the body weight. Furthermore, thermic effect of food which is also known as diet-induced thermogenesis refers to the energy expenditure for breaking down the food, digestion, transform and absorption of them (Yamada, 2009).

Furthermore, the importance of nutrition intake in weight management is taken into consideration for constructing the model in this study. When the recommendations concerning macronutrients, which are carbohydrates, fats and proteins, are considered, different energy-yielding food intakes will change the fat mass, muscle mass and body weight, consequently. The experiments regarding to this case will be discussed in Section 4.1.4.

In the long term, it can be considered that there are mainly two relationships between energy expenditure and body weight. Since body weight has two main components in the model, one of the relationships can be shown between energy expenditure and muscle mass, through fat-free mass, which is constructed via the link of physical activity level. Besides, the other relationship is modeled between energy expenditure and fat mass by using energy balance effect on fat synthesis / breakdown.

4.1.2. Fundamental Approach and Assumptions

In order to make simplification, energy conversion processes in food groups are not shown in the model; therefore, energy intake represents food intake directly with the consideration of diet composition and their caloric values. Similarly, thermic effect of food component is indicated by the energy expenditure of energy intake part that corresponds to the heat production during food absorption, digestion and storage processes after food intake (Guyton, 2006; Abdel-Hamid, 2002). Moreover, the variables in this sector are given as daily in the relevant literature, all of them are converted to weekly values.

The constants and variables used in the body weight sector are given in Table 4.1 and Table 4.2, accordingly with their units as follows. As mentioned previously, TEE refers to thermic effect of exercise. Normal physical activity capacity is used for the capacity of the human body for doing exercise with respect to body weight. "Normal BW" is normal body weight which is considered as the reference value for an average male individual. "MPD coefficient" refers to muscle protein breakdown coefficient, similarly "CHO coefficient" is carbohydrate coefficient, "FBD fraction" refers to fat breakdown fraction that are used in the outflows of the relevant stocks. ECW is extracellular water mass, which is taken as constant in the system. In the model, the individual is assumed to be male. Therefore, the coefficients of age, height and body weight for REE are calculated for an average male individual.

Table 4.1. Constants in Body Weight Sector.

Constants	**Value**	**Unit**	**Reference**
Normal TEE	2458	kcal/Week	Assumption
Normal PA capacity	4130	kcal/Week	(Velardo and Ducelay, 2012)
Normal physical activity	2478	kcal/Week	(Velardo and Ducelay, 2012)
Normal BW	70000	Grams	(Sizer and Whitney, 2010)
Height	1.77	Meters	(Sizer and Whitney, 2010)
Normal age	30	Years	Assumption
Essential protein coefficient	0.56	1/Week	(Bilsborough and Mann, 2006)
MPD coefficient	0.007	1/Week	Assumption

Table 4.1. Constants in Body Weight Sector (cont.).

CHO coefficient	4.39	1/Week	Assumption
FBD fraction	0.0602	1/Week	Assumption
ECW	15000	Grams	(Guyton, 2006)
Bone mass	10500	Grams	(Sizer and Whitney, 2010)
Kcal-to-grams	1/7.7	grams/kcal	(Abdelhamid, 2002)
Protein balance	220.5	grams/Week	(Azouz, 2011)
Protein limit	170	grams/Week	(Bilsborough and Mann, 2006)
Age coefficient of REE	47.6	kcal/Week/year	(McArdle *et al.*, 2010)
Height coefficient of REE	35	kcal/Week/cm	(McArdle *et al.*, 2010)
BW coefficient of REE	95.9	kcal/Week/kg	(McArdle *et al.*, 2010)

Table 4.2. Variables and Initial Values in Body Weight Sector.

Variable Name	**Initial Value**	**Unit**	**Reference**
Carbohydrate	500	Grams	(McArdle *et al.*, 2010)
Fat	12500	Grams	(Sizer and Whitney, 2010)
Muscle	31500	Grams	(Sizer and Whitney, 2010)
PA factor	0.6	Dimensionless	Assumption
Food intake	20000	Kcal/Week	(Hargrove, 1998)

4.1.3. Description of the Body Weight Sector Structure

There are three main stocks in this sector. Fat stock refers to the total fat mass in the body. Carbohydrate stock refers to the total glycogen store in muscles and liver. Muscle stock refers to the total muscle mass in the body which changes with respect to muscle protein synthesis and degradation rates. Besides, there are two stocks of first-order information delay in this sector, "delayed effect of physical activity on normal synthesis" and "delayed effect of physical activity on extra synthesis", which indicate the delay physical activity effect on the muscle protein synthesis. However, muscle protein synthesis should be managed according to the amount of protein that is affected by the required minimum protein intake. Therefore, *essential protein coefficient* refers to the accepted

level of our daily protein requirement with regard to the body weight, when the effect of protein on the energy metabolism is not considered. This coefficient is given as 0.8 g/kg/day in the related literature (Bilsborough and Mann, 2006; McArdle *et al.*, 2010). However, due to selecting the time step of the model as one week, the coefficient is converted to its weekly value.

As it is reviewed in the literature survey, the change in body weight is affected by the difference between energy intake and energy expenditure. And, resting energy expenditure (REE) constitutes almost 60% of the total energy expenditure. REE can be calculated by several different standardized formulations. The Harris-Benedict (1919) formula, a commonly used equation, is used in this model. There are four factors that mainly affect the REE. Since it is assumed that the individual in the model is male, the REE formula developed for males is used in the formulation, which can be implied as follows: Resting Daily Energy Expenditure = 66.0 + (13.7*Body Weight in kg) + (5.0*Stature in centimeters) – (6.8*Age in years) (McArdle *et al.*, 2010). Related variables of these components on resting energy expenditure (see Table 4.1) are generated by taking this formula as a reference. Thus, the following equation is generated according to the formula in the model:

*Resting energy expenditure = (66*7) + BW comp of REE + Height comp of REE – Age comp of REE* (4.1)

The energy expenditure for the muscular activity is known as “thermic effect of exercise” (TEE), which is the second largest energy component that generally accounts for 15% to 30% of the total energy expenditure. It is mainly affected by the body weight and physical activity level. Therefore, the formulation is as follows:

*Thermic effect of exercise = Normal TEE * Effect of physical activity on TEE* (4.2)

Similarly, the level of physical activity will also affect thermic effect of exercise (TEE). According to the muscular work performance during a certain time (for a week, in this case), and the variety of the activities; heat production and expended energy will change respectively. However, due to the limitation of the muscular activities, this thermic

effect will reach to saturation. Hence, there is a positive relationship between the level of the physical activity (including duration and intensity of the related work) and thermic effect of exercise, which is shown in the following graph, Figure 4.1.

Furthermore, according to the literature survey, there are numerous approaches for the calculation of the reference value for thermic effect of exercise. Hence, after making comparisons between the formulations, the value is assumed as 2458 kcal/week in order to meet the energy requirement, which is about 20% of total energy expenditure, as it is given in Table 4.1. The frequency of exercises performed during a week is significant on constructing the graphical function of the effect of physical activity on TEE. Thus, different lifestyles which have impact on calorie expenditure of an individual are considered, according to his exercise intensity (Sizer and Whitney, 2010).

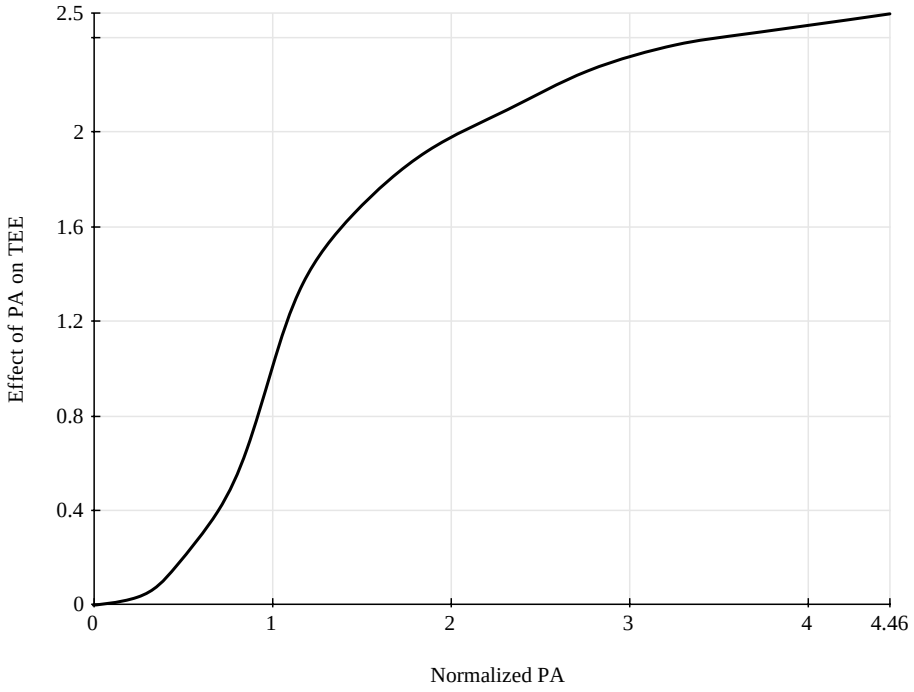

Figure 4.1. Graphical function for the effect of physical activity on thermic effect of exercise.

Nevertheless, it should also be considered that there is a direct relationship between the level of physical activity and muscle build-up. In order to increase the skeletal muscle mass, adequate level of protein synthesis is required. Therefore, the relationship between

physical activity and muscle mass are indicated as in the following graphs (Figure 4.2 and 4.3), because of the limitation of the protein amount expended during the physical activity.

Before determining the protein levels for muscle protein synthesis, essential protein should also be considered. The amount of protein used for muscle synthesis is the quantity when the essential part for repair and recovery used for various parts of the body is extracted from the total protein taken periodically. Amount of essential protein can be calculated by using the essential protein coefficient that is given in several different studies, and it changes according to the body weight of the individual, which is shown in Table 4.1.

Furthermore, there is a delay between doing physical exercise and muscle protein synthesis, for both normal and extra synthesis, which will be discussed in the following part. Muscle protein synthesis rate cannot change instantaneously after the physical activity. Therefore, the time lag associated with the physical activity effect and developing muscle mass is considered in this model. It is shown by using the first-order information delay structures for both parts of syntheses, with a delay time of 8 weeks for normal synthesis and 6 weeks for extra synthesis.

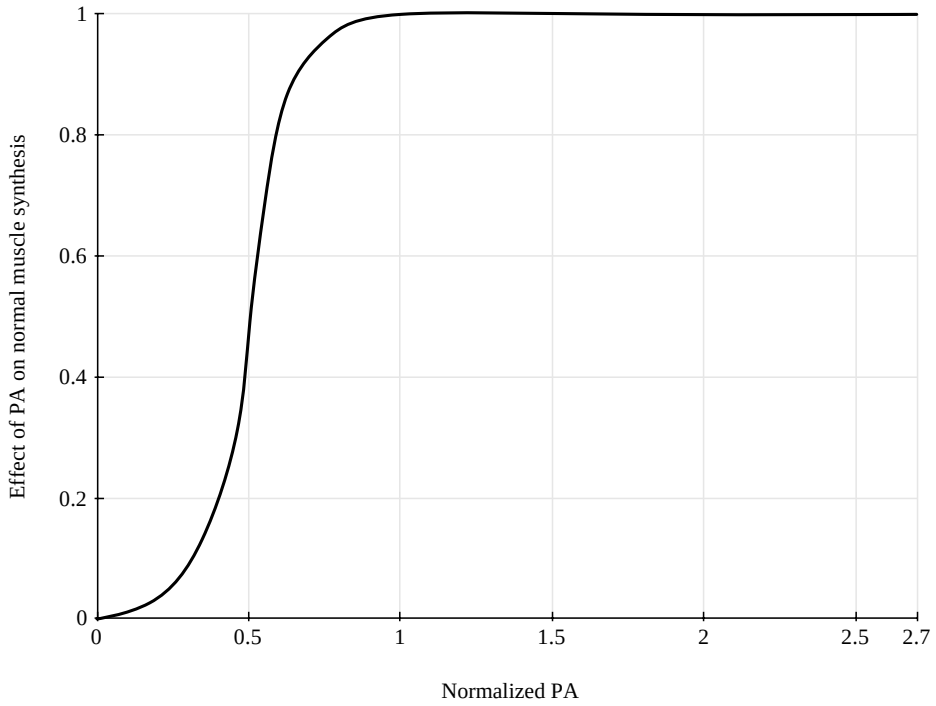

Figure 4.2. Graphical function for the effect of physical activity on normal muscle synthesis.

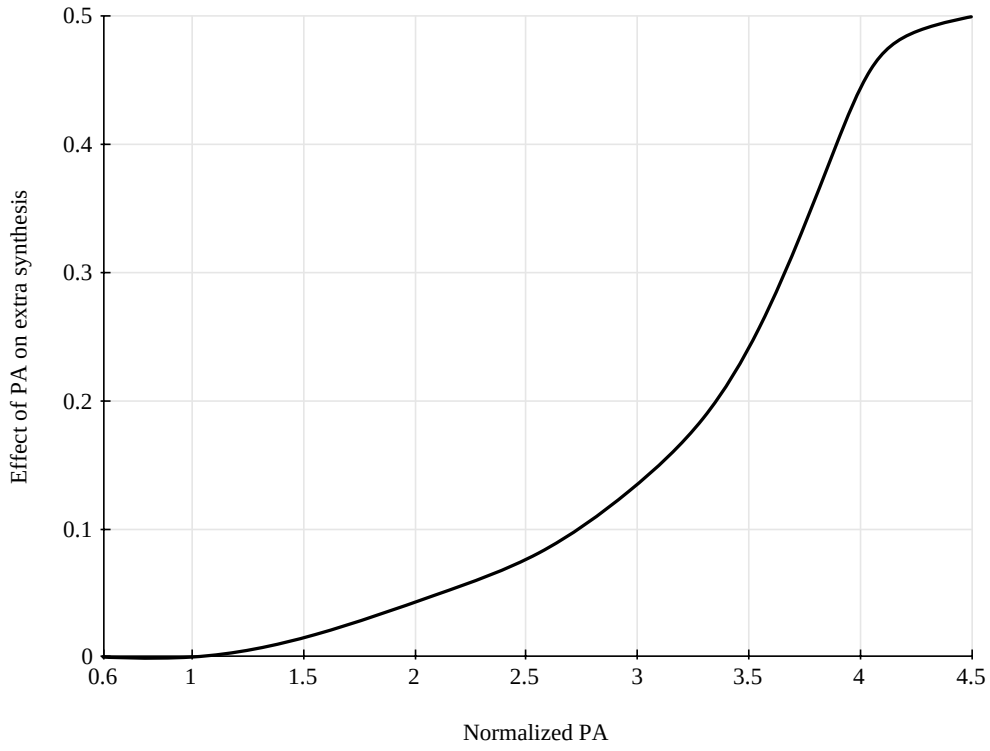

Figure 4.3. Graphical function for the effect of physical activity on extra muscle synthesis.

In the model, a different approach is applied in this part of formulation. The inflow of *Muscle* stock "Muscle protein synthesis" is considered in two different components, named as *normal synthesis* and *extra synthesis*. The reason behind this assumption is that muscle protein synthesis is possible if both physical activity and sufficient amount of protein exist in the system at the same time. Thus, the inflow with regard to the stock of muscle mass is implied as follows:

Muscle protein synthesis = Normal synthesis + Extra synthesis (4.3)

"Normal synthesis" refers to the muscle protein synthesis when the sufficient amount of protein is present in the body for fulfilling the muscle building task. And, its effect function is given in the Figure 4.2, with the following equation as shown below:

*Normal synthesis = Delayed eff of PA on normal muscle synthesis*Normal protein* (4.4)

Normal protein is calculated as in the equation (4.5), which shows that if there is sufficient amount of protein for doing physical activity that corresponds to a greater level of being sedentary, then the muscle protein synthesis is possible. The daily sufficient amount is chosen as 0.45 grams/kg, which is based on the study of the Food and Agriculture Organization of the United Nations (Azouz, 2011). This amount is converted to the weekly value for an average male (see Table 4.1), which is named as *Protein balance.*

Normal protein = IF THEN ELSE (Protein level > Protein balance, Protein balance, Protein level) (4.5)

Besides, extra protein can be used for muscle build-up, if the dietary protein intake is higher than the protein requirement of a specific individual, and this individual also does muscular activity more than the baseline value. In order to determine the extra physical activity level, an effect formulation is used in this part (see Figure 4.4). However, protein limit should also be taken into consideration in this case. *Protein limit* refers to the protein amount that remained from the required protein for the essential activities in the body and the protein used for muscles. In literature, it is stated that the requirement of protein for athletes who do strength training regularly is between 1.4 and 1.8 g/kg/day. Considering this range, total daily protein need is assumed to be 1.6 g/kg in the model, and the remaining part from essential protein and normal protein is considered as the protein limit (Bilsborough and Mann, 2006). Therefore, *extra protein* is determined by the following equation:

*Extra protein = IF THEN ELSE((Protein level - Normal protein) > Protein limit, Protein limit*Effect of PA on extra protein, (Protein level-Normal protein)*Effect of PA on extra protein)* (4.6)

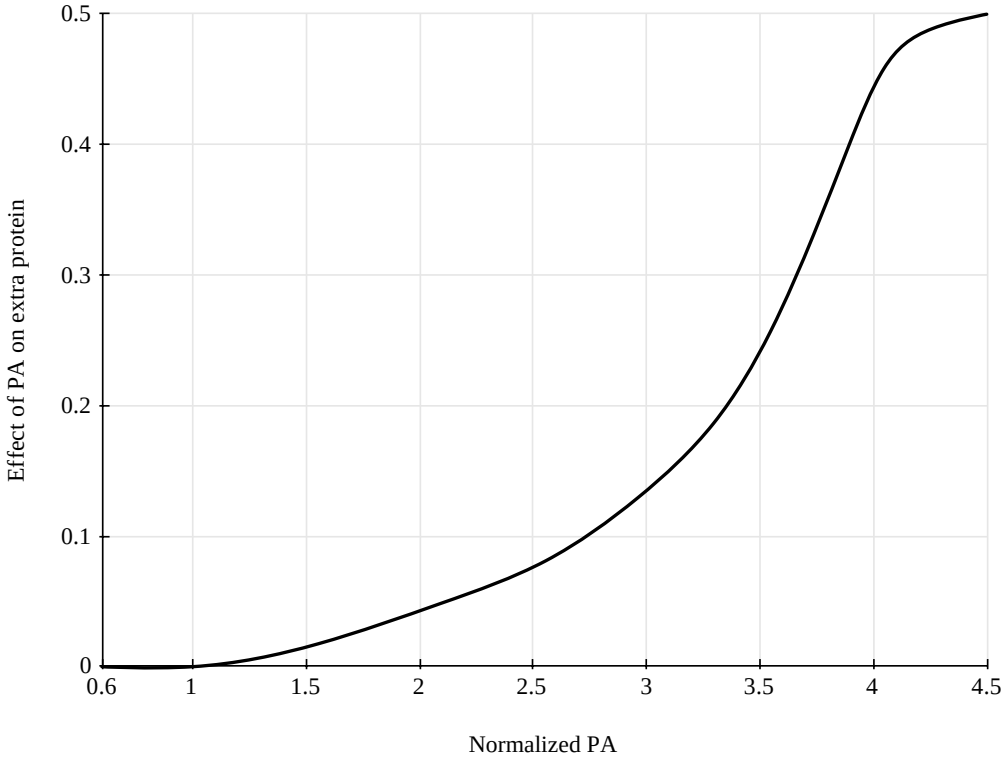

Figure 4.4. Graphical function for the effect of physical activity on extra protein.

Similar to “normal synthesis”, the equation with regard to “extra synthesis” can be stated in Equation 4.7, as follows:

*Extra synthesis = Extra protein*Delayed eff of PA on extra muscle synthesis* (4.7)

If the amount of protein intake is greater than the protein limit of the individual, then this amount is excreted in the urine, which is named as e*xcess protein* in the model. The equation for excess protein is formulated as shown in Equation 4.8.

Excess protein = MAX(Protein level-Normal protein-Extra protein, 0) (4.8)

The amount of “Excess protein” also shows the protein level sent to the kidneys for the excretion of the excess nitrogen that is the main constituent of protein. If this metabolism does not work properly, there will be a failure in kidneys, which will be another physiological problem observed in such condition. However, this problem is not considered in the study.

In this sector, physical activity capacity is defined as a variable, PA, which is altered with respect to the changes in one's body weight and age. Therefore, PA factor refers to the coefficient of doing physical activity, according to one's activeness for a long period. There are various definitions and formulations regarding this factor; however, it is considered as an effect on the capacity of physical activity performance in this model, and it can be changed according to the lifestyle of the individual. The relevant equation is given as follows:

$$\textit{Physical activity} = \textit{PA factor} * \textit{Physical activity capacity} \tag{4.9}$$

In addition, regarding the "lifestyle", there are five main levels of doing activity during the lifetime. The minimal physical exertion is defined as the sedentary lifestyle. "Sedentary" means that the person does not exercise at all. "Lightly active" means that a person engages in light exercise or sports 1-3 days per week, which corresponds to approximately 4130 kcal/week. "Moderately active" means that an individual exercises at least half an hour per day, five days per week, coincides with about 6090 kcal/week. "Very active" means that the person engages in fairly strenuous exercise or sports 6-7 days a week, expends about 8050 kcal/week. Lastly, "extra active" means that the person has a physical job where he is very active throughout a day, which corresponds to approximately 11060 kcal/week (Velardo and Ducelay, 2012).

For instance, an average-70 kg person who walks 4 miles per hour expends about 300 kcal energy per hour (5 kcal/min). According to the change in physical activity factor, *lightly active* corresponds to walking 2 hours per day, *moderately active* corresponds to walking 3 hours per day, *very active* corresponds to walking 4 hours per day, and *extra active* corresponds to walking 5 hours per day. *Sedentary* would include those sitting at a desk all day with no other activity or those confined to a wheelchair or mobility scooters who are not able to exercise at all.

However, besides the lifestyle of the individual, his age and body weight have impact on doing the exercises in the same manner regularly. When the person gets older, he will become less active for maintaining the physical exercises. Similarly, gaining weight and becoming obese will affect the physical activity performance negatively because

completing the same work load will be harder with the overweight. Therefore, the physical activity capacity is formulated below:

*Physical activity capacity = Effect of age on PA capacity*Effect of BW on PA capacity* Normal PA capacity* (4.10)

According to the relationship between the age and physical activity capacity, the effect formulation is drawn as given, in Figure 4.7. The physical activity capacity of an individual peaks at age 30, and then decreases slightly between ages 30 and 40. This decrease accelerates after age 40, and physical activity capacity declines about 40% at age 80 (Oxenham and Sharpe, 2003; Fleg *et al.*, 2005). Thus, regarding to the graphs shown in Figure 4.5 and 4.6, the graphical function for effect of age on exercise capacity is constructed in the model.

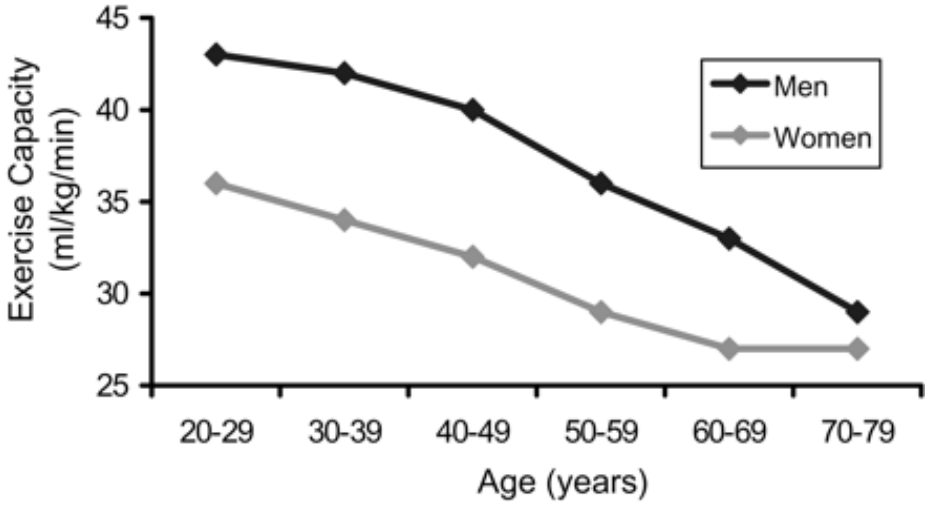

Figure 4.5. The relationship between exercise capacity and age (Oxenham and Sharpe, 2003).

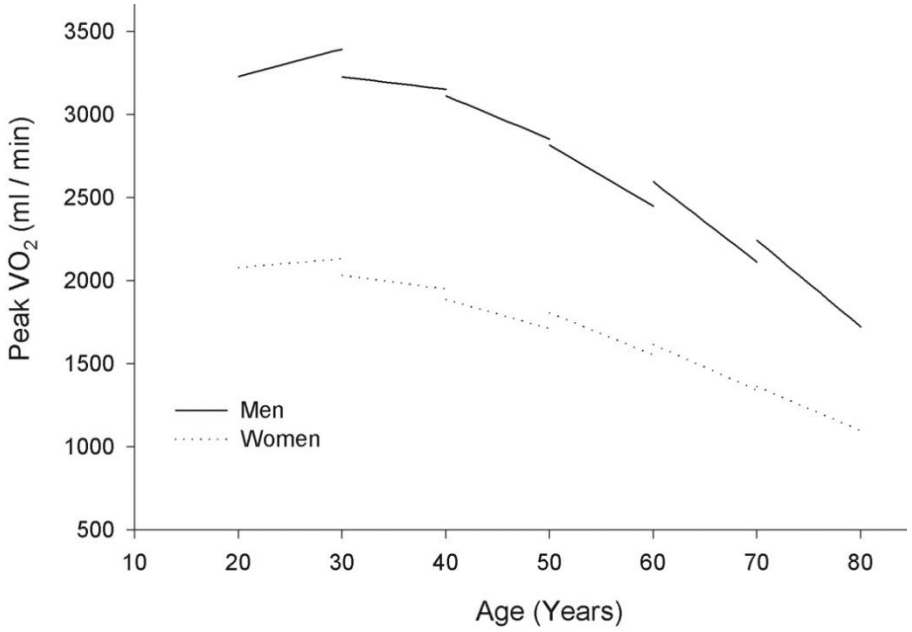

Figure 4.6. The relationship between exercise capacity and age (Fleg *et al.*, 2005).

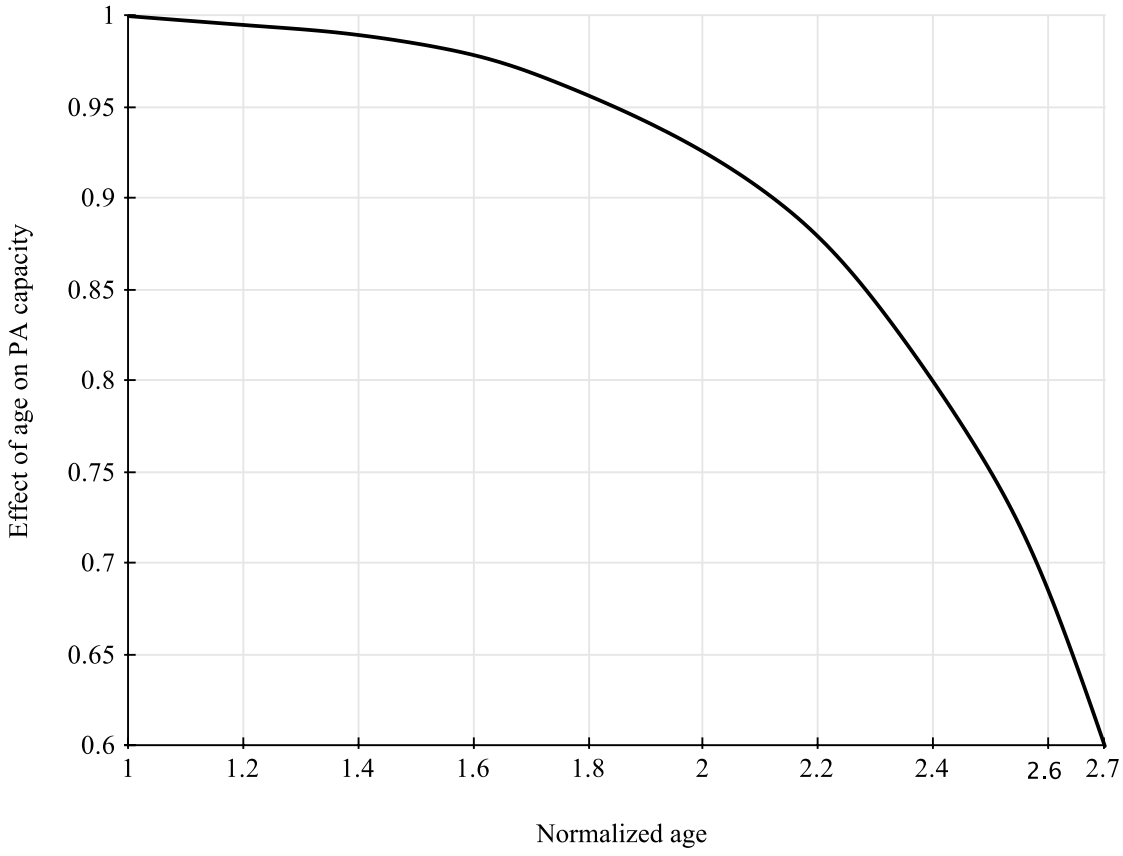

Figure 4.7. Graphical function for the effect of age on physical activity capacity.

As it is discussed previously, effect of body weight on exercise capacity should also be taken into consideration in the model. Since there is a negative correlation between body weight and exercise capacity, the graphical function is shown as follows:

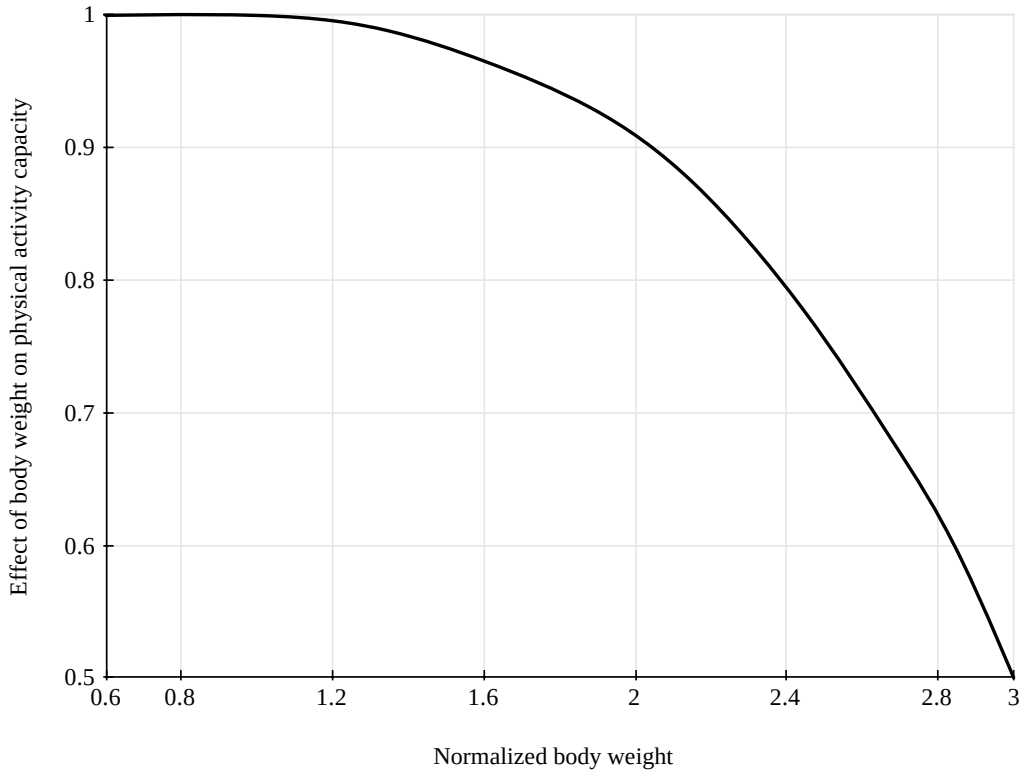

Figure 4.8. Graphical function for the effect of body weight on physical activity capacity.

On the other hand, the effect of energy balance on changing fat mass is also considered in the model. In order to avoid having negative values for fat mass, the effect functions are formulated separately, both inflow and outflow of the stock variable. The function for the inflow (fat synthesis) is shown in Figure 4.9:

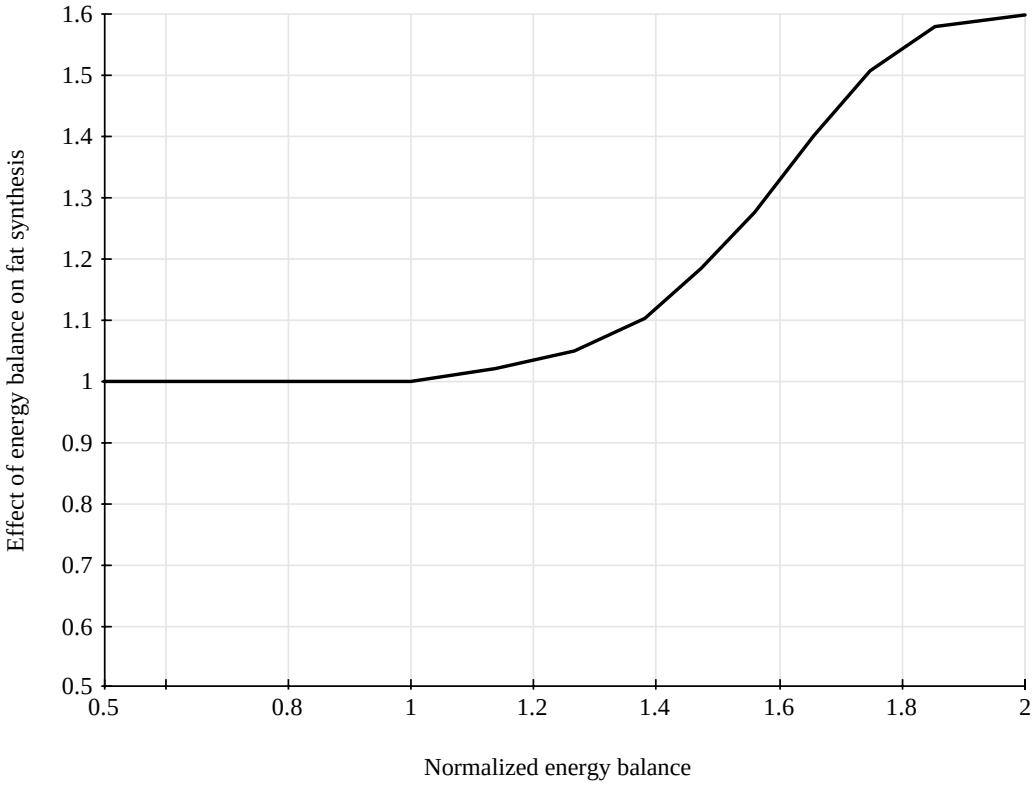

Figure 4.9. Graphical function for the effect of energy balance on fat synthesis.

If there is an energy deficit, fat breakdown is triggered to maintain the necessary energy for the human body. Besides, if there is an excess amount of energy, it is converted to fat and stored in the adipose tissues in order to use when necessary.

One of the most important factors in this formulation is normalizing energy balance as shown in the equation below:

$$Normalized\ energy\ balance = \frac{Energy\ intake}{Energy\ expenditure} \quad (4.11)$$

By using the Equation 4.11, the inflow of fat mass, named as *fat synthesis* is formulated as follows. Besides the effect of energy imbalance, excess amount of carbohydrate is stored in fat mass, as it is shown in the Equation 4.12.

*Fat synthesis = (Effect of energy balance on fat synthesis*Normal fat synthesis) + IF THEN ELSE (CHO breakdown>2660, CHO breakdown-2660, 0)* (4.12)

Similarly, by using the normalized energy balance, the effect of energy balance on fat breakdown is also generated, which can be seen in Figure 4.10.

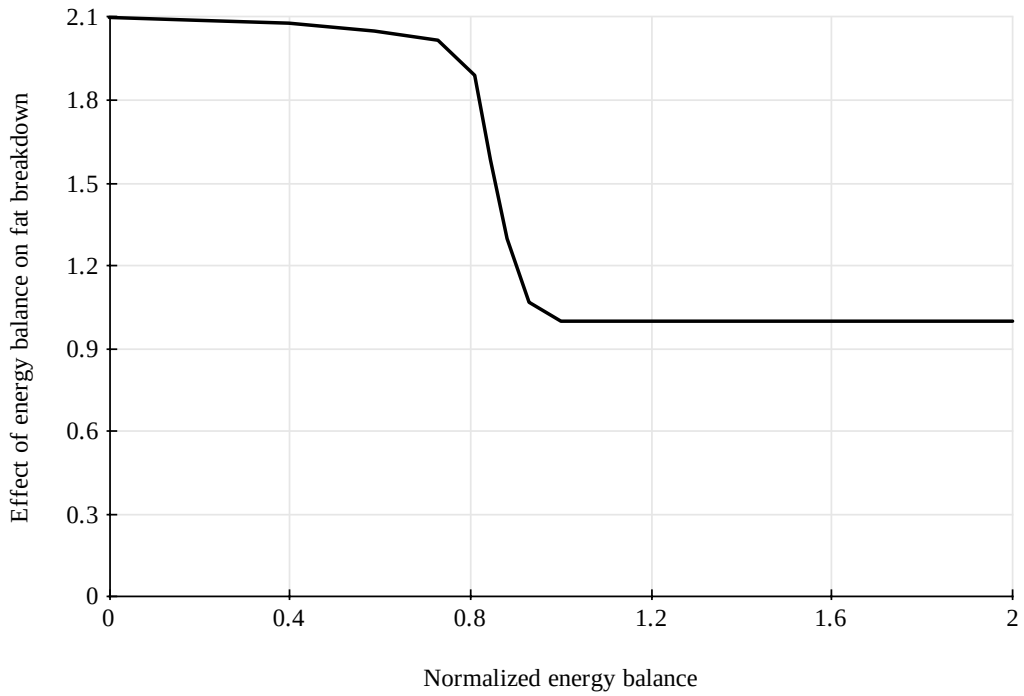

Figure 4.10. Graphical function for the effect of energy balance on fat breakdown.

The equation of the outflow of fat mass, named as *fat breakdown*, is shown as follows:

*Fat breakdown = (Fat*FBD fraction)*Effect of energy balance on fat breakdown* (4.13)

As a result, after implementing all of the main variables and relationships in the model, the whole structure of body weight sector is obtained as below:

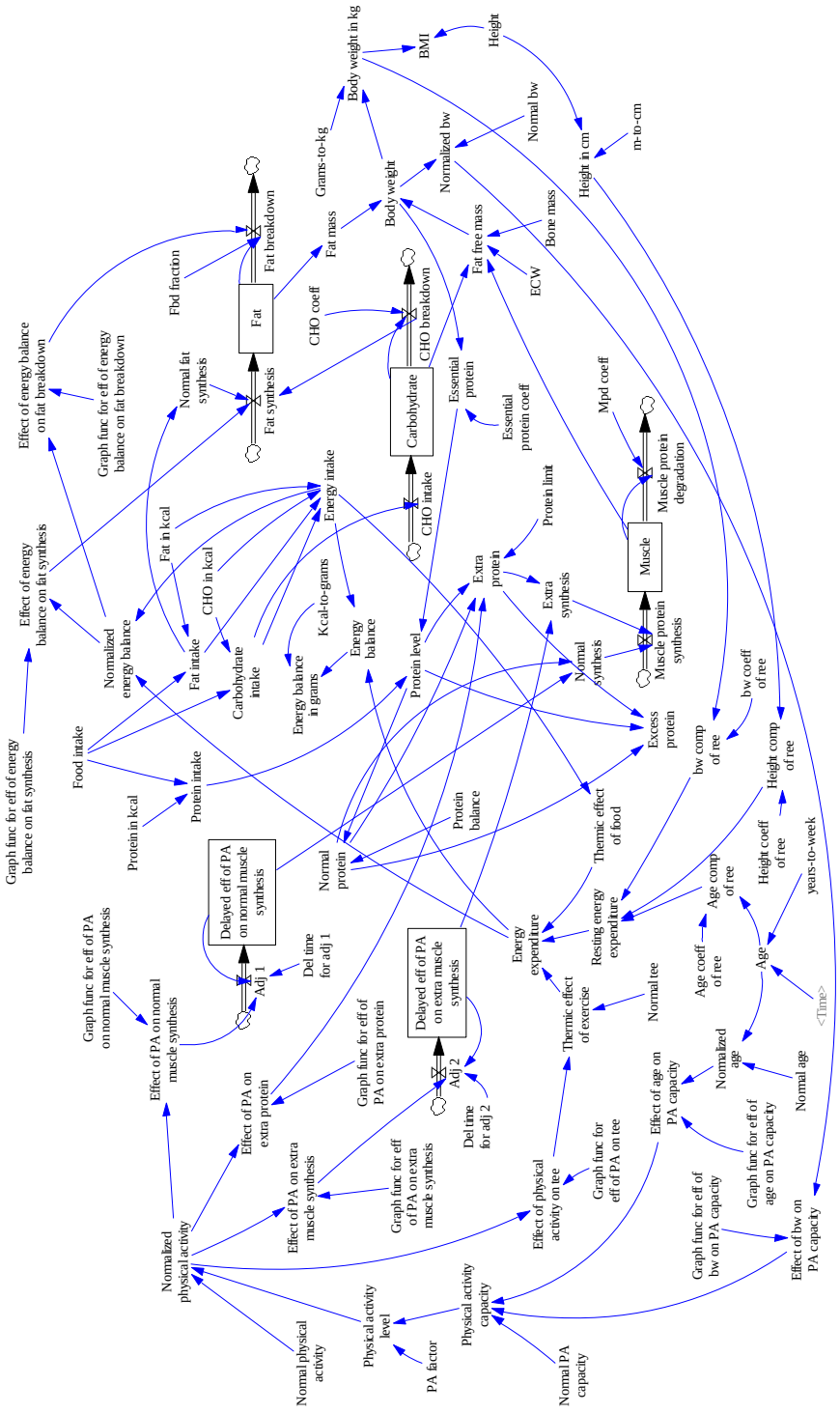

Figure 4.11. Stock-flow diagram of the body weight sector.

4.1.4. Dynamics of Body Weight Sector in Isolation

In this section, a number of runs will be executed for the purpose of verifying that body weight structure works properly. In order to demonstrate the experiments, fat mass and muscle mass values and sudden increases in food intake, nutrient composition and physical activity level will be conducted. The behavior of key variables such as body weight, energy expenditure and its components will be demonstrated for a simulation period of 520 weeks. Besides, only the experiments which show the aging factor will be demonstrated for 2600 weeks.

In the first experiment, it will be tested whether fat mass stays stable in the normal levels with respect to the changes in the amount of food intake. The stimulator of the changes in fat mass storage is the energy balance value increased by energy intake, and decreased by energy expenditure. To observe positive changes in the energy balance, food intake and composition of these nutrients can be changed. Here, age is considered as constant in these experiments. Thus, the following dynamic behaviors are obtained when the food intake is increased to different values:

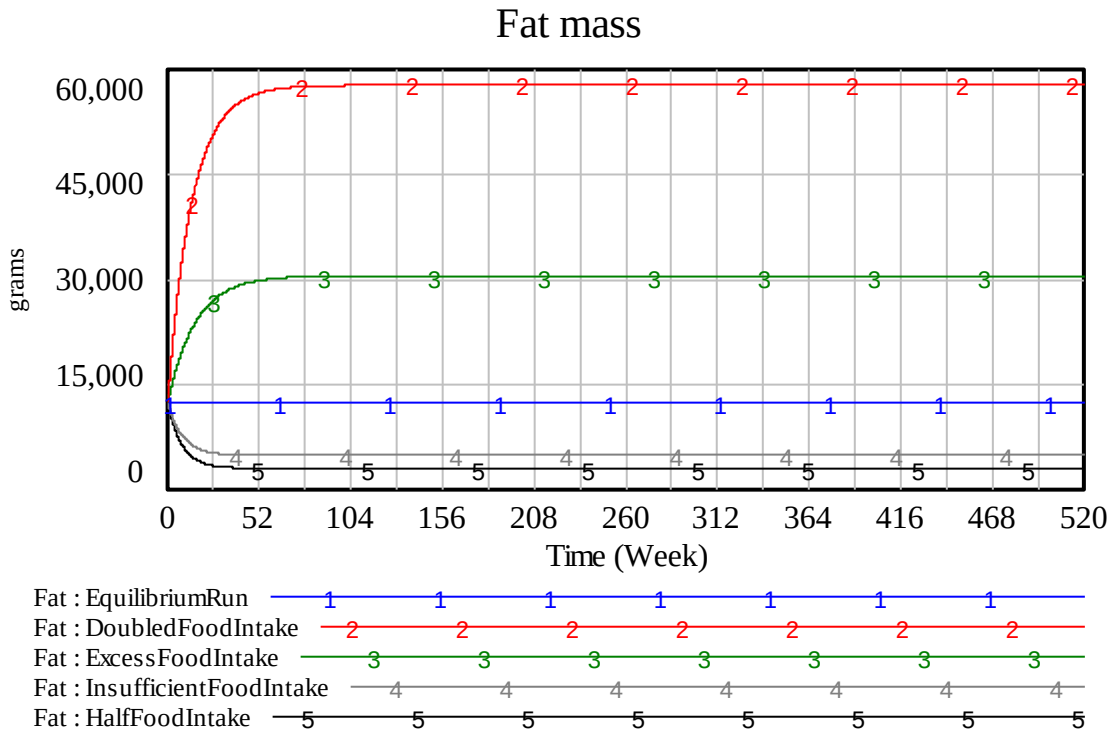

Figure 4.12. Dynamics of fat mass with respect to changes in food intake.

At equilibrium, food intake for an average man is approximately 20000 kcal/Week. This value is chosen by taking the recommended dietary allowances into consideration (Hargrove, 1998; Sizer and Whithey, 2010). In the run, named as *DoubledFoodIntake*, food intake is doubled, 40000 kcal/Week, and in the run *ExcessFoodIntake*, the amount of food intake is taken as 30000 kcal/Week, for determining the dynamic behavior of fat storage level. In the runs, named as *InsufficientFoodIntake* and *HalfFoodIntake*, decreased amount of food intake is observed. For these two runs, weekly food intake is given as 15000 kcal and 10000 kcal, respectively.

As it can be seen from Figure 4.12, there is a change observed in the fat storage with respect to the modification only in the amount of food intake, and physical activity level is kept as the same as its baseline value, which shows that the individual is almost sedentary. When the amount of food intake is increased, fat mass also increases according to the level of increase. Similarly, when the amount is decreased, fat mass decreases, and fat stock reaches equilibrium about in approximately one year, which is an expected result of negative feedback effect of the as it is shown in the first loop, in Figure 3.1.

Furthermore, body weight shows similar dynamic behavior as the fat mass, in Figure 4.12, according to different amount of dietary intakes, while keeping the proportions of food composition intact. The physical activity level is kept the same as in the "Current" run. Thus, the following graph is obtained in Figure 4.13:

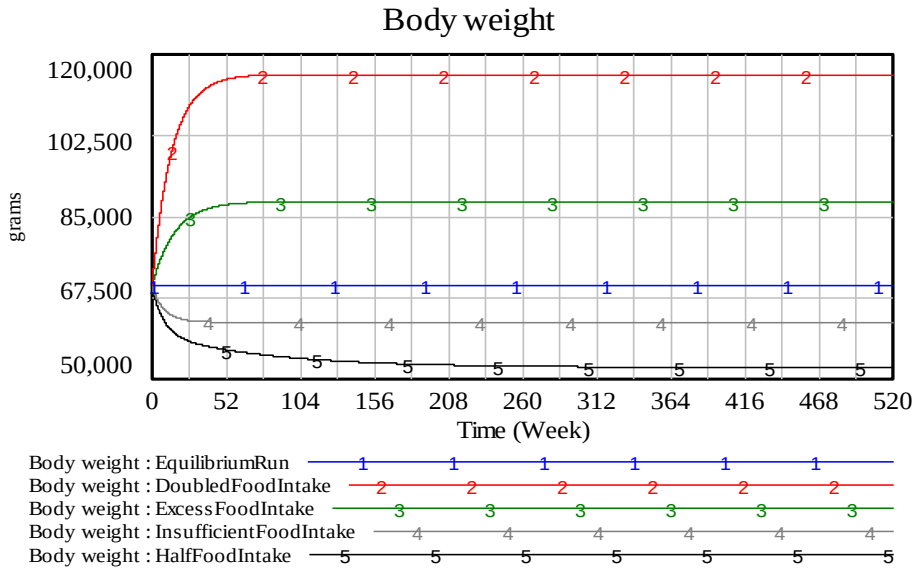

Figure 4.13. Dynamics of body weight with respect to changes in food intake.

Since food intake is increased, the amount of protein intake also increases which is necessary for muscle protein synthesis. Therefore, when the changes explained above are applied to the model, the dynamic behavior of muscle mass is obtained in Figure 4.14. Even the amount of protein increases in the body, muscle mass does not change so much in the runs *DoubledFoodIntake*, *ExcessFoodIntake* and *InsufficientFoodIntake*; because there is no change in the level of physical activity. However, when this amount is reduced by half, as in the experiment of *HalfFoodIntake*; muscle mass decreases, because the individual uses a smaller value of protein for muscle protein synthesis with the same level of physical activity. Thus, there is an exponential decay in normal synthesis and muscle mass observed, as it is shown in Figure 4.14.

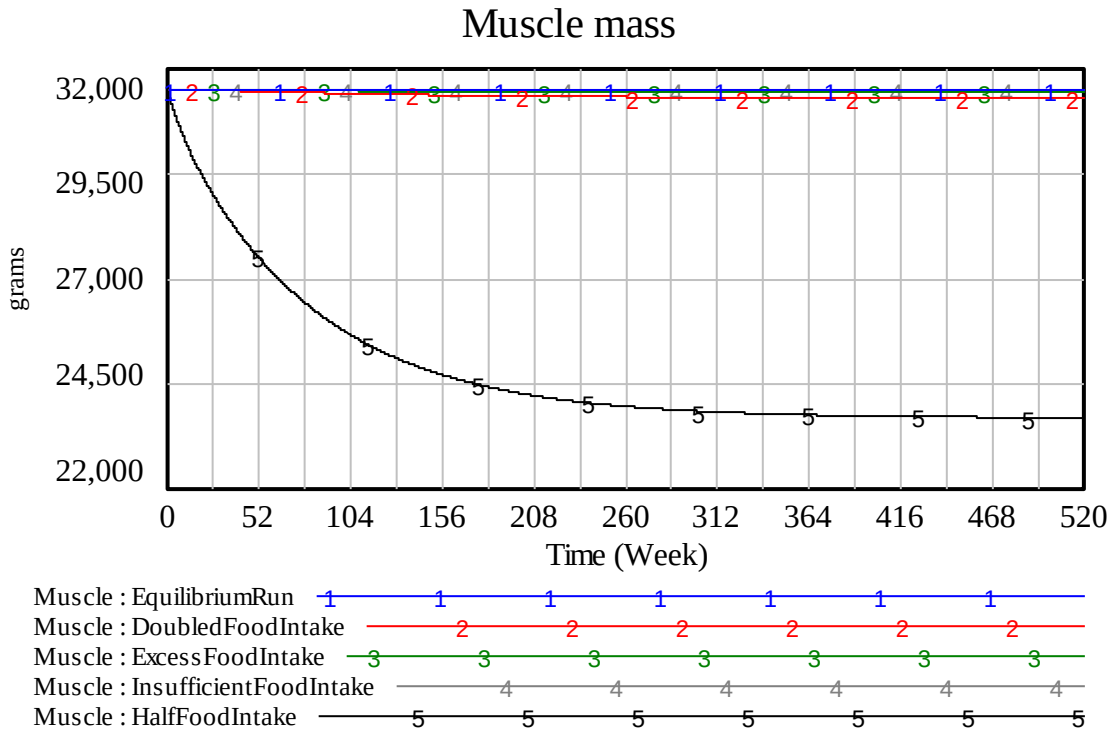

Figure 4.14. Dynamics of muscle mass with respect to changes in food intake.

In the second experiment, some changes are applied to physical activity level, and body weight and energy components in the sector will be observed. According to several physiological studies, when a person increases his muscular activity for a long term, he will lose weight because of the increase in the rate of fat breakdown, and decrease in fat storage (McArdle *et al.*, 2010; Sizer and Whitney, 2010; Hargrove, 1998).

Therefore, four different “lifestyles” are considered for the simulation runs of observing the changes in the body weight and energy components. Since the physical activity capacity can change by age and body weight, the physical activity factor can be considered as the key factor for the change in the physical activity level. At equilibrium, the individual is assumed to be almost sedentary by expending about 2478 kcal in a week; even he does not exercise at all, but expends some energy for doing his daily activities. Therefore, PA factor is taken as 0.6.

Thus, in the run that is named as “Light”, the individual is “lightly active”, who spends about 4130 kcal in a week. In the run named as “Moderate”, the person is “moderately active” who spends around 6090 kcal per week, which let us take PA factor as 1.475. Similarly, in the run named “Active”, it is supposed that the energy expenditure by exercising is nearly 8050 kcal/week as being “very active” and PA factor is about 1.98. In the run named “Strenuous”, the person is doing vigorous physical exercise, also known as being “extra active”, and spending nearly 11060 kcal/week, that PA factor is taken as 2.67. During these experiments are conducted, age effect is also considered. Therefore, the dynamics of body weight according to different physical activity levels, when age effect is overleaped, is shown in Figure 4.15:

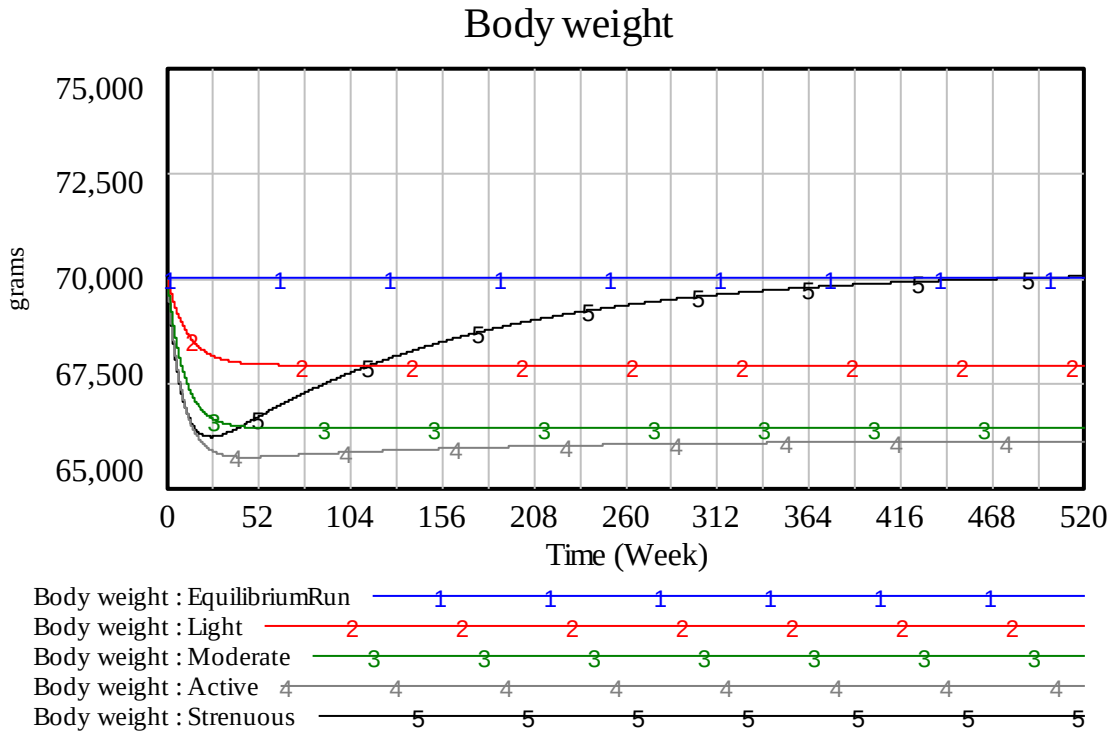

Figure 4.15. Dynamics of body weight with respect to the changes in PA factor.

In Figure 4.15, body weight decreases according to the increase in the level of physical activity. When an individual increases his muscular activity, fat storage will start to decrease after some time. Since more glucose is necessary for a higher level of exercise, rate of fat breakdown will increase. Fat will be converted to carbohydrate, to be used for maintaining the requirement of the exercise. Therefore, if the "lifestyle" requires more physical activity, then fat mass will decrease, and muscle mass will increase. Since the individual we consider in the model is lean, he will not be able to lose too much fat, even he does strenuous exercise. However, muscle mass will increase because of sufficient protein and a very high level of exercise.

When age effect is also taken into consideration, the dynamic behaviors of body weight, fat mass and muscle mass with respect to the changes in PA factor are constructed in Figure 4.16, 4.18, and 4.23, respectively. As it is discussed in Section 4.1.3, both physical activity capacity and resting energy expenditure decrease, when the individual gets older. Therefore, when a person keeps his food intake and physical activity as his baseline values, he will gain some fat. Since muscle mass decreases more than the increase in fat, he will eventually lose weight just because of aging. When both age and PA factor are considered, an individual will again lose some weight, because he performs some physical activity. Thus, the individual will start to lose weight in the long term, because of losing physical activity capacity, and muscle mass will also decrease, which is an expected consequence.

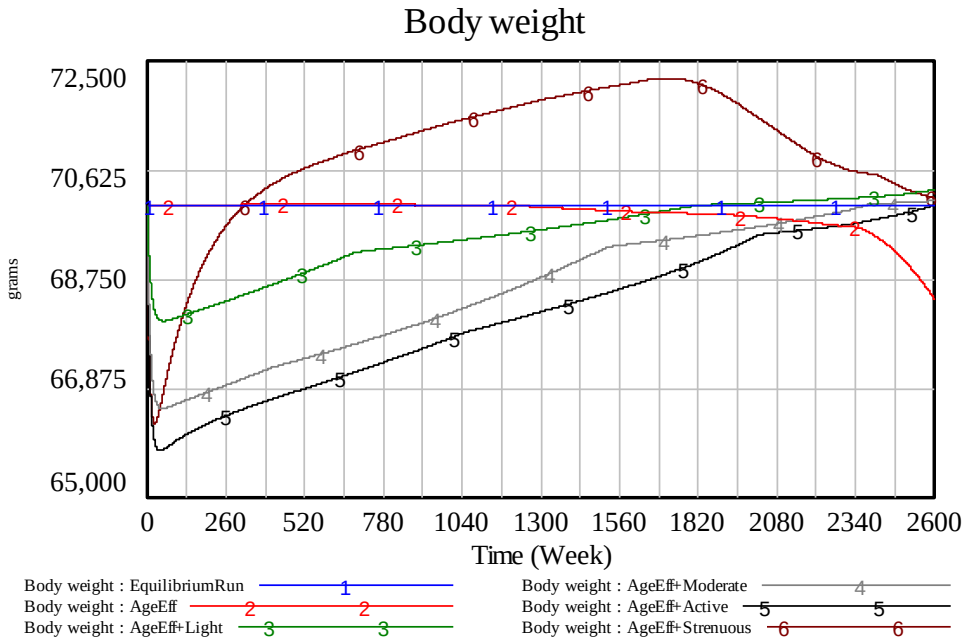

Figure 4.16. Dynamics of body weight with respect to the changes in PA factor and aging.

When age effect and changes in physical activity level are considered, it is observed from the dynamic behavior of fat mass that his fat mass decreases according to the increase in PA factor, because the person increases his physical activity performance. Thus, the most decrease is observed when the person does strenuous physical activity. In Figure 4.17, the graph shows the changes in body weight and fat mass by aging (Goodman, 2009), which is similar to the dynamic behaviors obtained in Figure 4.16 and 4.18.

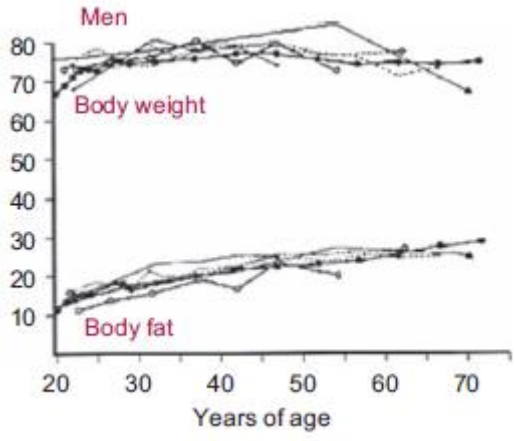

Figure 4.17. Data showing changes in body weight and fat content with aging (Goodman, 2009).

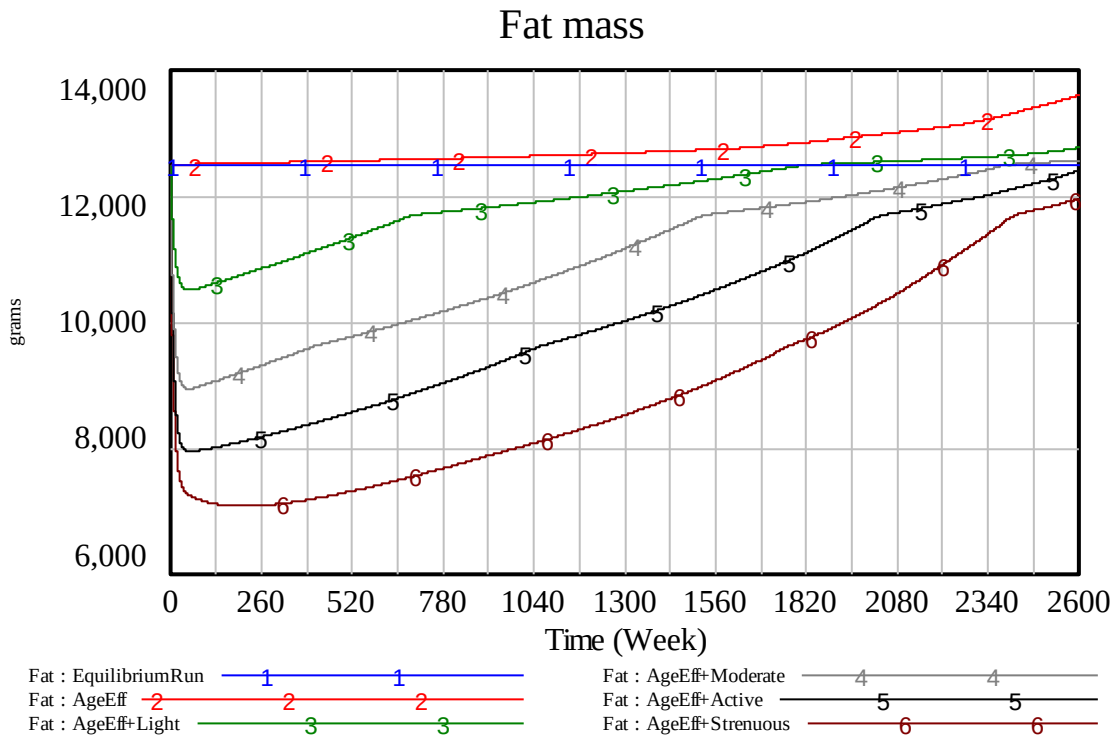

Figure 4.18. Dynamics of fat mass with respect to the changes in PA factor and aging.

As it is expected, when aging is not considered in the model, and PA factor is increased in different experiments, the individual loses weight in the long term, and later reaches equilibrium. Therefore, similar dynamic behavior of body weight can be observed in the fat mass storage, as it is shown in Figure 4.19:

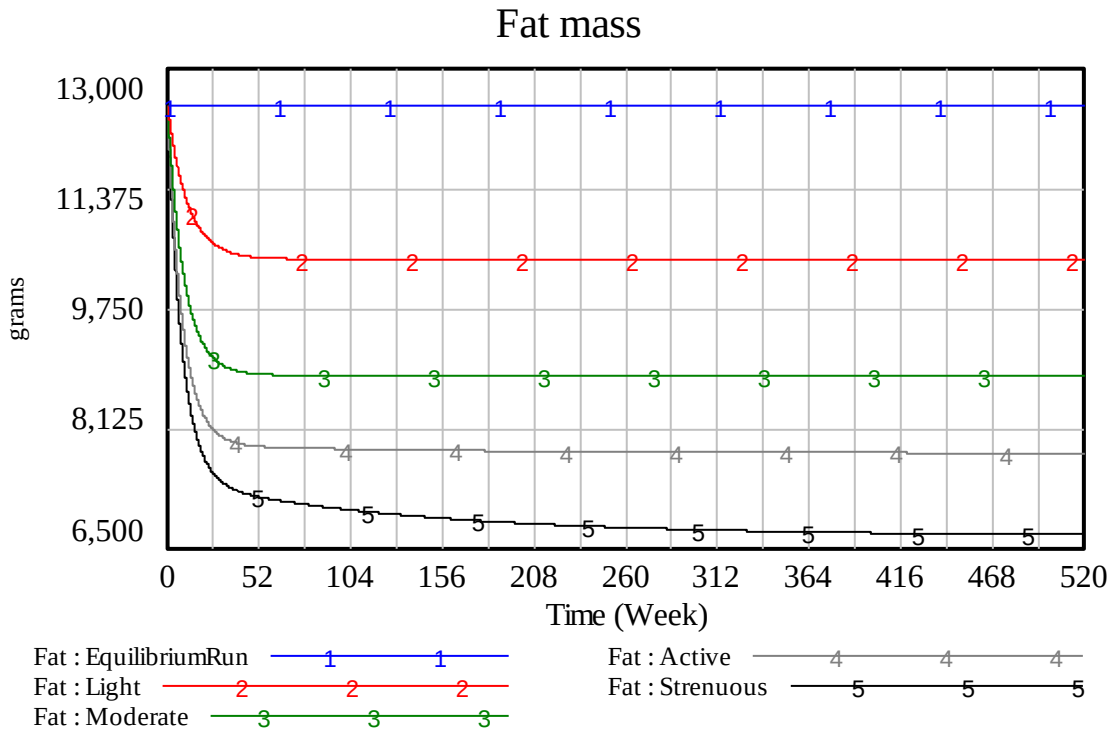

Figure 4.19. Dynamics of fat mass with respect to the changes in PA factor.

The decrease in fat mass can be considered as a result of the small increase in the energy expenditure. It might be expected that thermic effect of exercise (TEE), and consequently total energy expenditure will increase according to the exercising performance level; which are observed in Figure 4.20 and 4.21, respectively. Since the body weight of the individual changes according to different levels of physical activity, resting energy expenditure also changes respectively, as it is shown in Figure 4-19. When the person performs strenuous exercise during 50 years, the increase in muscle mass is greater than the decrease in fat mass; therefore, the person gains weight regarding to the formulation in the model. As a result, the rise in REE of a physically active person is more than the REE of a sedentary person.

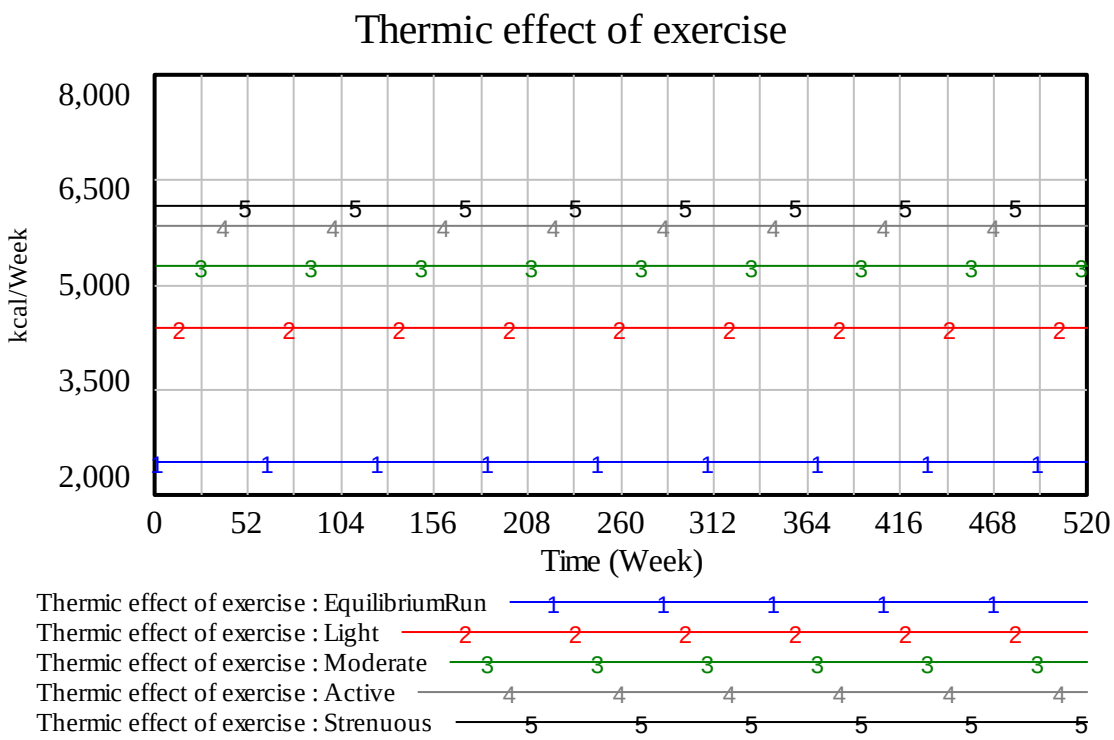

Figure 4.20. Dynamics of TEE with respect to the changes in PA factor.

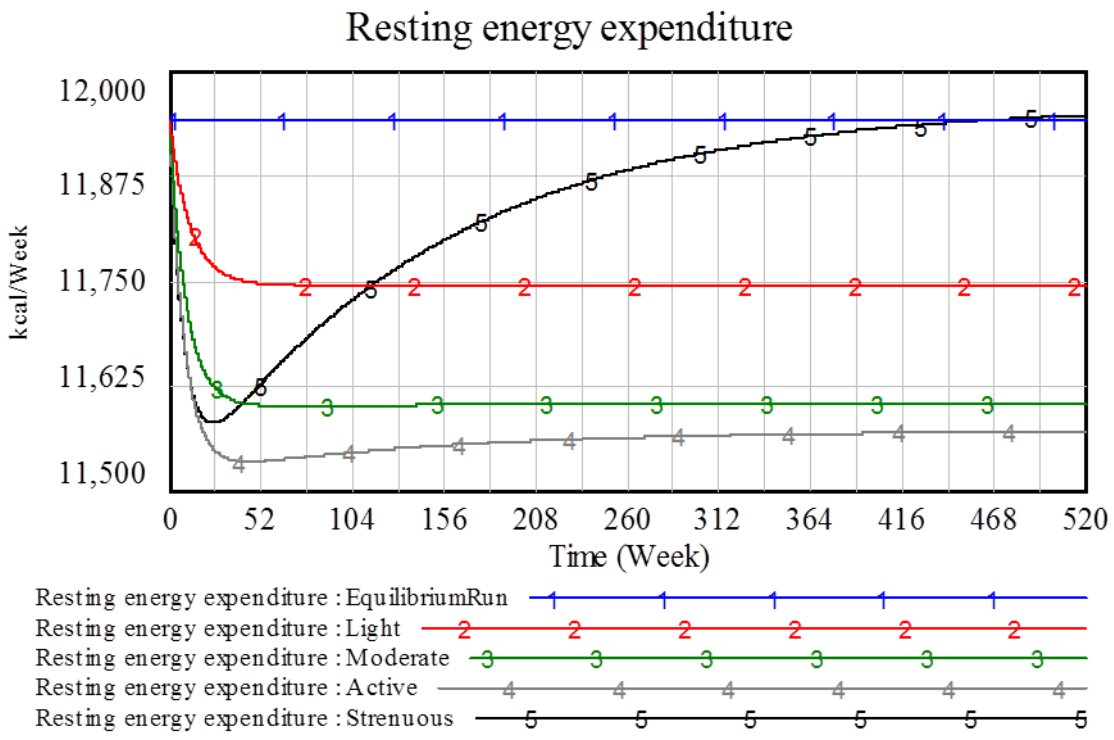

Figure 4.21. Dynamics of REE with respect to the changes in PA factor.

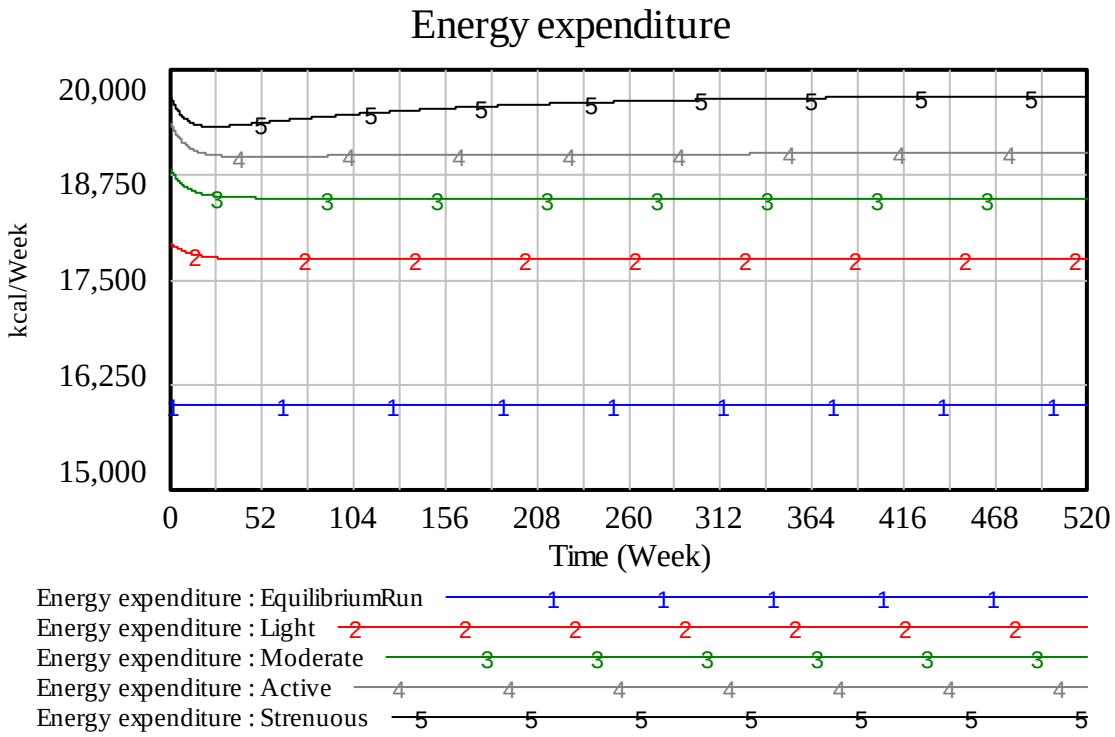

Figure 4.22. Dynamics of energy expenditure with respect to the changes in PA factor.

Furthermore, it should also be discussed on the change in muscle mass according to the change in PA factor. In this experiment, both PA factor and age effect on the behavior of muscle mass are observed, which is shown in Figure 4.23. According to the graphs, it is seen that the most increase in muscle mass is observed in strenuous exercise. On the contrary, the most decrease in muscle mass is observed in sedentary lifestyle, which is an expected result when energy expenditures of each physical activity and effects of muscle building are considered.

On the other hand, when aging effect on the muscle mass is not considered, the dynamic behavior in Figure 4.24 is observed, which shows that there is a greater increase in the muscle mass when PA factor is increased. When a sedentary person is considered, muscle mass decreases because of not exercising.

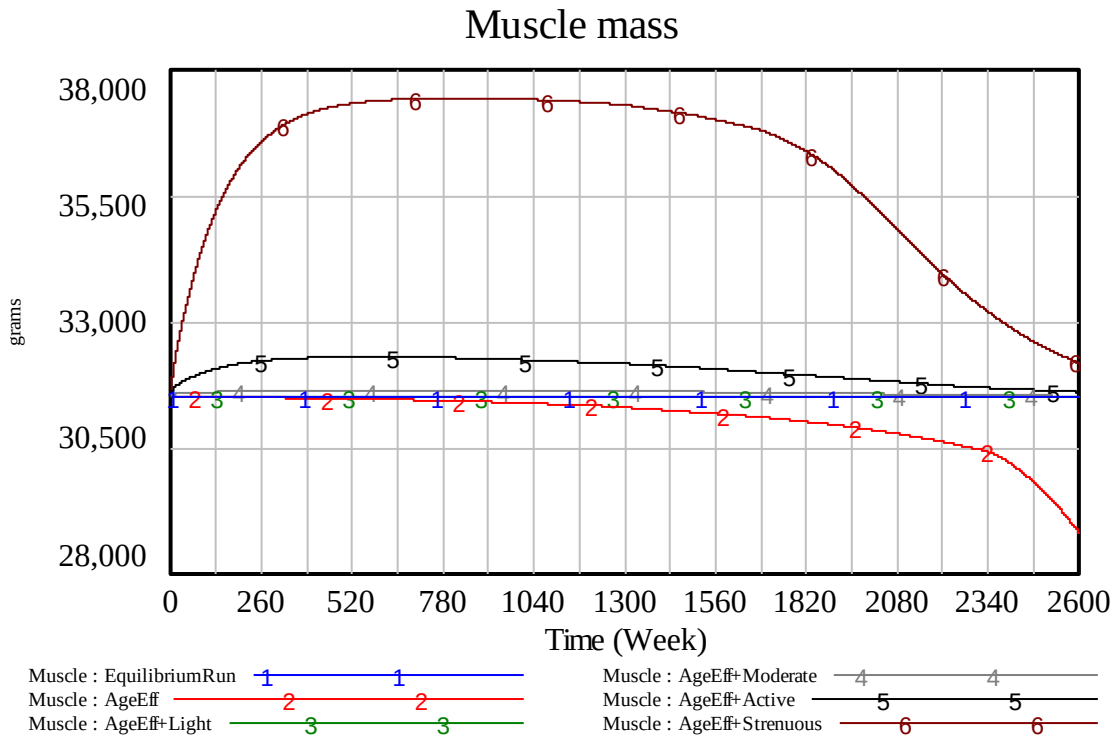

Figure 4.23. Dynamics of muscle mass with respect to the changes in PA factor and aging.

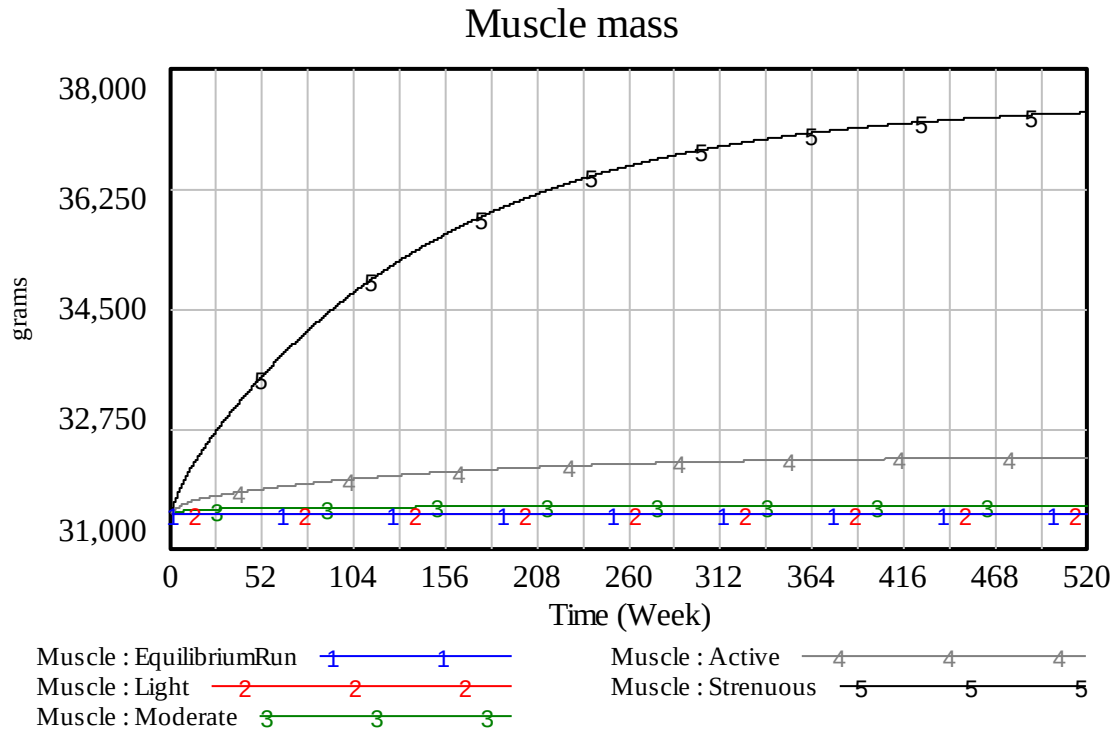

Figure 4.24. Dynamics of muscle mass with respect to the changes in PA factor.

In the last experiment, the tests will demonstrate the responses of the model to the changes in food composition without changing the total food intake amount for a week. Since the amount of energy of each nutrient when burned is different, the reference values for carbohydrate, fat and protein intake are constant at about 2195, 752.68 and 919.54 kcal/week, respectively. All of these values are determined according to Recommended Dietary Allowances (RDA)" and "Adequate Intakes (AI)" which are standardizations of "Dietary Reference Intakes (DRI) Committee" (Sizer and Whitney, 2010). According to the different resources, the proportions determined for nutrient intakes that provide the adequate energy for the body are conflicting with each other. Thus, in the equilibrium run of this model, these proportions are taken as 45%, 35% and 20% for carbohydrate, fat and protein intakes, respectively.

Therefore, in run2, the amount of fat is kept as its initial value, but carbohydrate intake is decreased to 40%, and protein intake is increased to 25% of total intake, and fat intake is not changed. In run3, the protein intake is not changed, but fat intake is decreased to 30%, and carbohydrate intake is increased to 50% of total food intake.

In run4, carbohydrate is kept the same as the baseline value, but this time, fat intake is decreased to 25%, and protein intake is increased to 30% of the total quantity. Finally, in run5, carbohydrate takes 75% of food intake, fat 20%, and protein 5%, in order to show protein inadequacy (see Table 4.3). As a result, the dynamic of these simulations for the fat mass is shown in Figure 4.25.

Table 4.3. Experiments for different food intake compositions.

Name of the run	Percentage of Carbohydrate	Percentage of Fat	Percentage of Protein
EquilibriumRun	45%	35%	20%
run2	40%	35%	25%
run3	50%	30%	20%
run4	45%	25%	30%
run5	75%	20%	5%

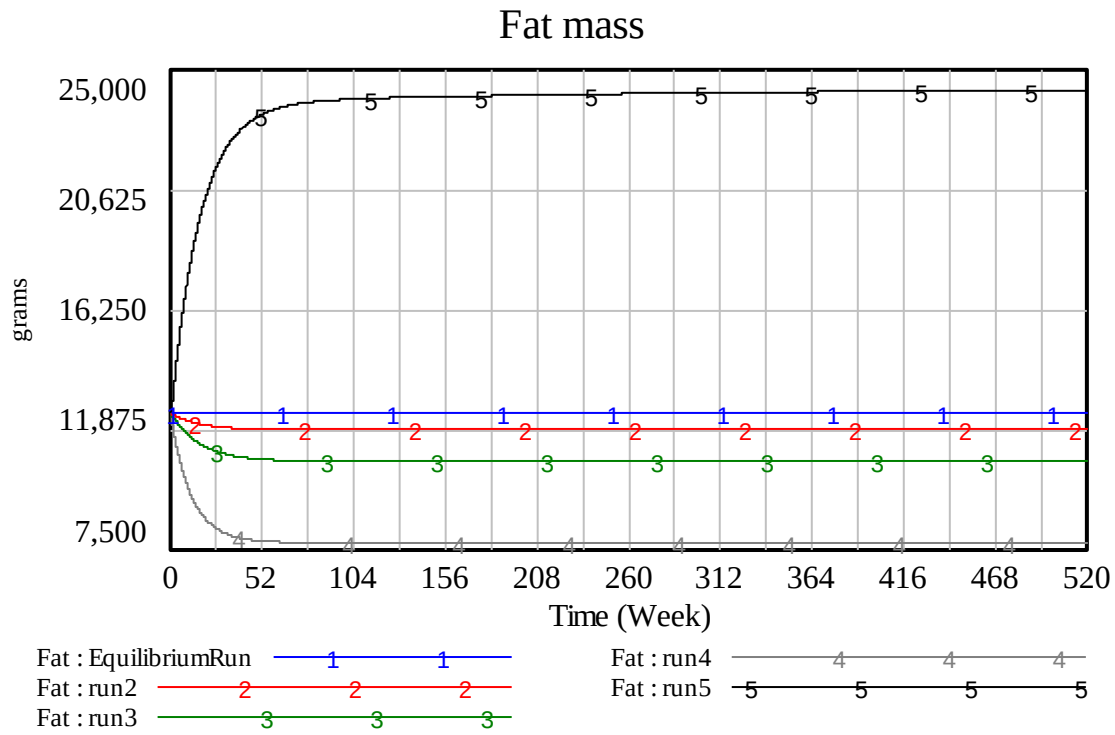

Figure 4.25. Dynamics of fat mass according to different food intake compositions.

As it can be seen from the behavior that since the proportion of fat intake is always increased in all experiments, the fat mass stock also decreases and saturates after some time. In run3 and run4, fat mass decreases, because fat intake is decreased in both experiments. However, in run5, an increase in fat mass is observed, although fat intake is decreased. As it is discussed previously, when the amount of carbohydrate is greater than the body's needs, excess carbohydrate is converted to fat and stored in adipose tissue to be used when necessary. Therefore, when the changes are applied in run5, fat mass increases in this experiment more than the others. On the other hand, in run2, although the amount of fat intake is same as the baseline value, the fat mass decreases because of the increase in total energy expenditure. The reason behind the increase in total energy expenditure is that there is a rise in resting energy expenditure. In this condition, due to the increase in body weight, the resting energy expenditure also increases.

Similarly, the changes in the muscle mass can also be observed according to the results of the relevant experiments. The dynamic behavior of these simulation runs is shown in Figure 4.26:

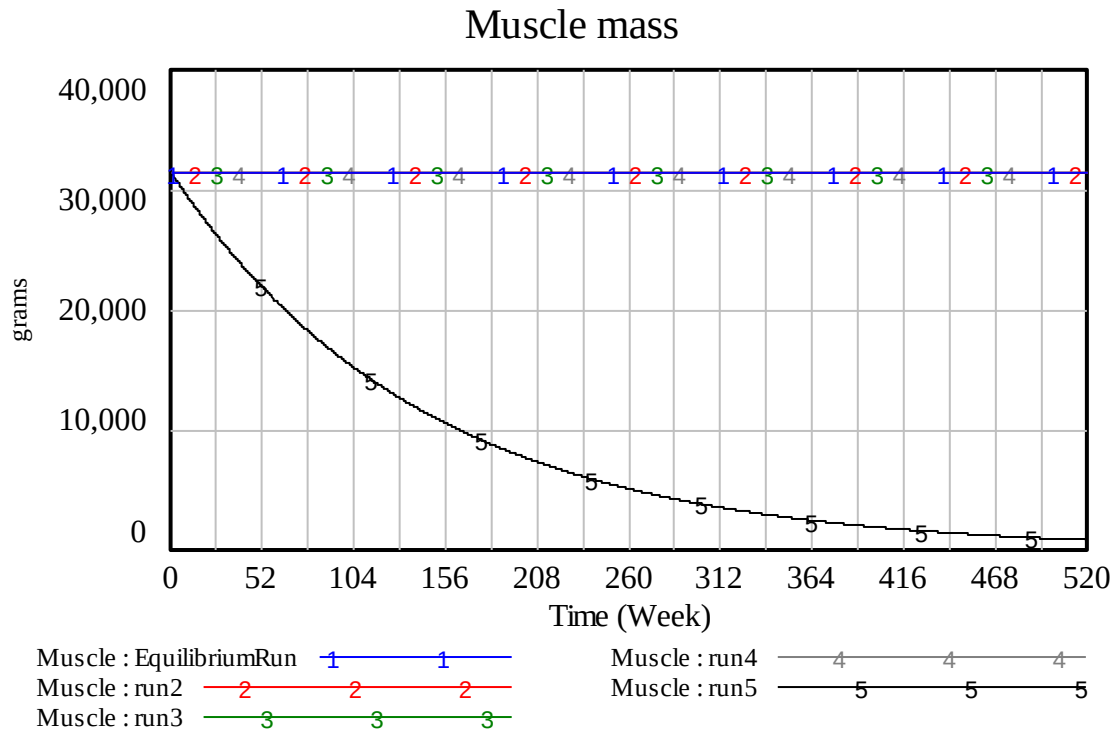

Figure 4.26. Dynamics of muscle mass according to different food intake compositions.

There is no change observed in muscle mass in run2, run3 and run4, even the proportions of food intake have been changed, because the level of muscular activity is kept as the same as the normal value. However, in run5, the case of protein inadequacy is considered. Since the individual does not take adequate protein in order to keep his muscle mass at equilibrium, there is a sharp decrease in muscle mass. In other words, he takes less protein than normal protein. For other cases, muscle mass can only change, if there is also a change in physical activity level. Therefore, the experiments are conducted for a lightly active person in order to see that the changes in the muscle mass, which is shown in Figure 4.28.

Besides, the dynamics in body weight are obtained according to the different runs, shown in Figure 4.27, which is the following graph:

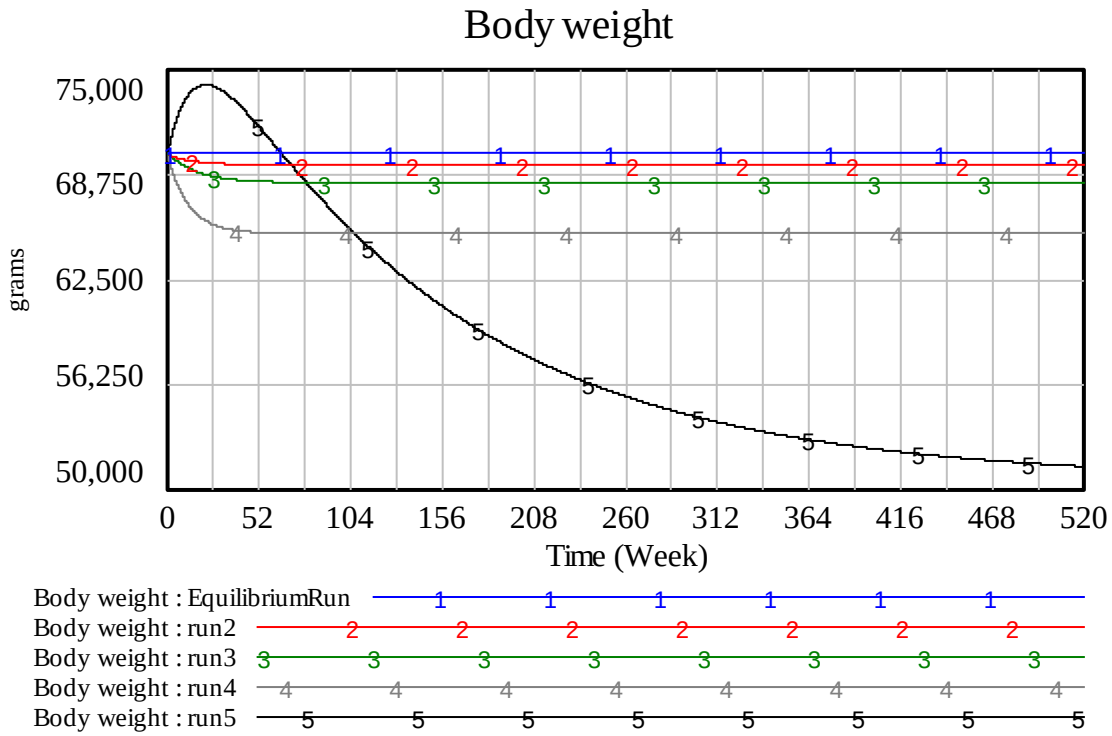

Figure 4.27. Dynamics of body weight according to different food intake compositions

When the proportions of food intake are changed, there will also be changes in the body weight, accordingly. Even the total amount of food intake is kept as its baseline value; each nutrient has different quantity of energy. Thus, it is clearly observed that the values of energy intake and energy balance also change in these experiments. The gradual decrease in body weight for run2 is because of the decrease in fat mass, as it can be seen in Figure 4.25. In run3, a greater rate of decrease can be observed. Since the fat mass decreases in this run, and muscle mass does not change; thus the body weight also decreases. Similarly, in run4, there is a decrease observed in the body weight level, because of the sharp decrease in fat mass. In run5, fat mass increase, but also a sharp decrease is observed in muscle mass. Thus, body weight will increase at first because of the increase in fat mass, and then will decrease because the rate of decrease in muscle mass becomes greater after some time.

When a lightly active person is considered, and the experiments named as run2, run3 and run4, that it is discussed above are reapplied, the dynamic behavior of muscle mass is obtained as shown in the following graph, in Figure 4.28.

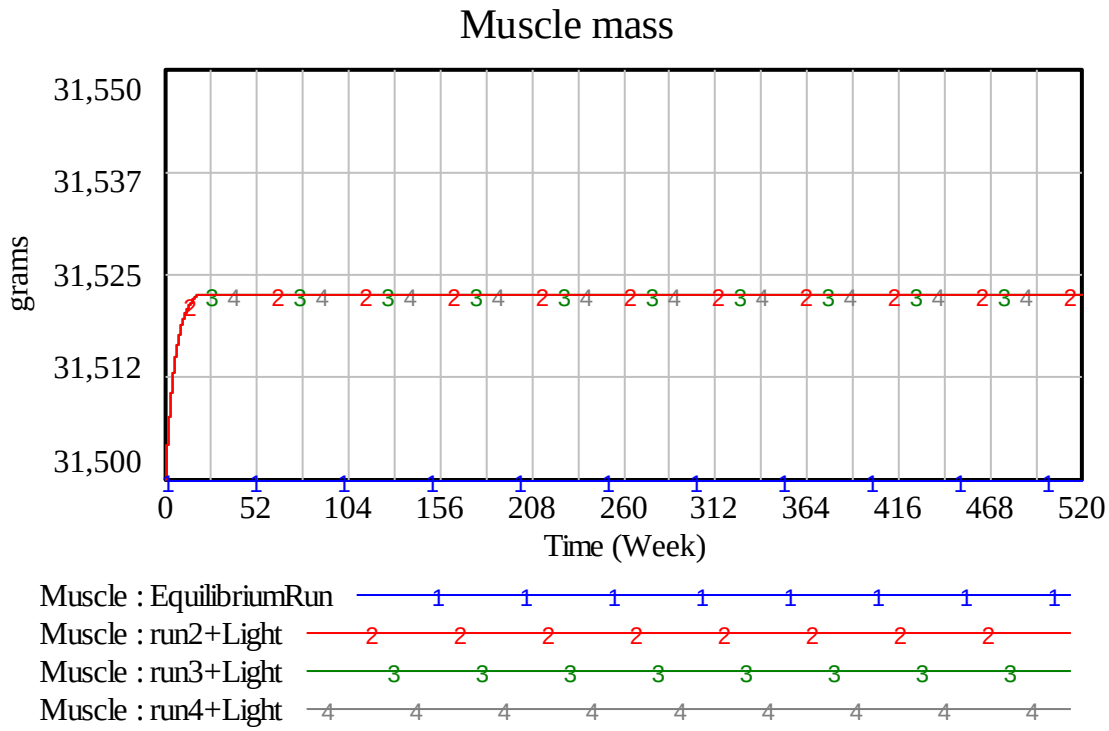

Figure 4.28. Dynamics of muscle mass for a lightly active person, according to different food intake compositions.

In run3, since the protein level is kept as its initial value, muscle mass increases because of the decrease in the body weight, which causes an increase in physical activity capacity. Since the physical activity level is increased, and the amount of protein intake for each experiment is sufficient for muscle protein synthesis, muscle mass also increases in each case. The amount of increase in each case is the same, because muscle mass is only affected by the level of protein, and the proportions of protein for each experiment are sufficient to maintain light activity.

4.2. Glucose-Insulin Regulation Sector

4.2.1. Background Information

Average plasma FFA concentration level refers to average free fatty acid concentration in blood, in units of *mEq/L*. Since this level changes in minutes (especially after food intake), we take weekly average value for this variable. Similarly, average plasma glucose concentration level and average plasma insulin concentration level are also taken as their weekly average values in blood. Besides, insulin secretion level refers to the amount of insulin release from pancreas (β-cells) in a week that changes according to the plasma glucose concentration level in order to decrease and keep it in the normal values. Secretion from pancreas is triggered when the blood glucose concentration is greater than *70 mg/dL* (Li *et al.,* 2006). In healthy subjects; when insulin hormone is released to blood, insulin receptors play an important role of transporting glucose from blood to the target tissues such as adipose tissue, liver and muscle. Beta-cell functionality refers to the ability of reaction for the rise of the blood glucose level. In healthy subjects, beta-cells respond to the level of glucose concentration in a normal way. However, in obese individuals, beta-cell dysfunction may be present which leads to type II diabetes, as the extreme condition. HOMA-IR index refers to "Homeostatic Model Assessment" of insulin and glucose regulation, and used for quantifying insulin resistance (Matthews *et al.,* 1985).

4.2.2. Fundamental Approach and Assumptions

The relationship between obesity and insulin resistance is as follows: when fat mass increases, which means that the amount of adipose tissues increases as well, the rate of lipolysis increases. In the healthy individuals, lipolysis is suppressed by the level of insulin secretion, and kept in the normal ranges. Lipolysis is the breakdown of the fat tissues into the triglycerides and the free fatty acids (FFA). Therefore, when this rate increases, plasma FFA concentration which inhibits the glucose transport from the blood to the cells gets higher. So, the glucose uptake by muscle tissues will decrease, and FFA will be used in the muscles for the energy, instead of glucose, which leads to a reduction in efficiency of energy expenditure. Hence, muscles will not be able to synthesize glycogen by using the glucose which is transported from the bloodstream. Besides, elevated FFA concentration

in blood will also affect hepatic glucose production, which is compensated by the effect of insulin. When hepatic glucose production increases, which is triggered by the FFA concentration level; plasma glucose concentration will also increase. And, the plasma glucose concentration level will be much higher according to the normal values (70-110 mg/dL). When plasma glucose concentration is greater than 110 mg/dL, the insulin signaling will decrease, because the insulin hormone becomes incapable of decreasing plasma glucose concentration adequately (Makroglou *et al.*, 2006).

On the other hand, dysfunction in pancreatic beta-cells is considered as a significant determinant in developing type II diabetes. According to the statistical results, it is denoted that only about 20% of obese people develop the disorder, most likely by the reason of a genetic prevalence to beta-cell dysfunction. These 20% of people cannot equilibrate the insulin resistance efficiently, in spite of elevated FFA concentration levels in their blood. Thus, the imbalance between insulin secretion level and insulin resistance, those individuals will ultimately develop hyperglycemia (excessive amount of glucose in blood). Besides, the remaining 80% are able to compensate the elevated FFA concentration in blood by increasing insulin secretion from the pancreas, and increasing their plasma insulin concentration, even they are insulin resistant. This ability helps them not to become diabetic. Unavoidably, there may be a slight overcompensation in insulin secretion which causes to a characteristic property in these patients: the hyperinsulinemia, which means the level of insulin circulating in blood is much higher than the average (Boden and Shulman, 2002). On the other hand, excess insulin causes major circulatory diseases due to the odd shape of the insulin molecule. Hence, preventing obesity even if it will not lead to type II diabetes is an important issue. However, these consequences are not considered in this model.

As a result of these relationships between the main components of the system, the variables are constructed in the model according to their effects to each other. It can be clearly seen from this sector that numerous effect formulations are used to define the connections between the variables which play important role in this mechanism. As it is discussed in the previous chapter, there are various negative feedback loops in the system that provides the homeostasis in the body.

The constants used in the sector can be seen as below, in Table 4.4. Some of the values given in the table are converted to weekly values according to relevant literature.

Table 4.4. Constants in the glucose-insulin regulation sector.

Constants	**Values**	**Units**	**Reference**
Basal lipolysis	980	grams/Week	(Hall, 2006)
Normal plasma FFA concentration	0.6	mEq/L	(Shigetoh *et al.*, 2009)
Lower limit of normal blood glucose conc	70	mg/dL	(Makroglou *et al.*, 2006)
Glucose transport rate	1	Dimensionless	(Thorell *et al.*, 1999)
Basal plasma insulin concentration	10	μU/mL	(Abbasi *et al.*, 2000)
Normal insulin secretion	245	Units/Week	(Gale, 2012)
Max beta-cell functionality	100%	Dimensionless	(Kahn *et al.*, 2006)

4.2.3. Description of the Glucose-Insulin Regulation Sector Structure

We can consider the insulin resistance as a wall between the blood vessel and the cells. This wall (insulin resistance) prevents the glucose in the blood to enter muscle and fat cells. When insulin resistance increases, more insulin is secreted from the beta-cells in pancreas. However, insulin secretion decreases because of the decrease in performance of pancreas. When the need for insulin rises more than the normal level, the pancreas gradually loses its ability to produce insulin. Insulin resistance is mostly effective in muscle and adipose tissues, and liver (Kahn *et al.*, 2006).

However, the regulation of glucose and insulin mechanism occurs in a very short time. For instance, typical half-life of plasma glucose concentration is around 30 minutes, and this regulation is processed several times in the body during a day. Therefore, all of the variables are considered as their weekly average values, and the changes occur in a week. Since the variables used in the model are not directly converted to each other, and this study observes the system as a macro structure, numerous effect formulations are used in order to express the relationships between the factors present in developing insulin

resistance and type II diabetes, in a better way. Firstly, the following function shows the effect of lipolysis on plasma FFA concentration level, in Figure 4.29:

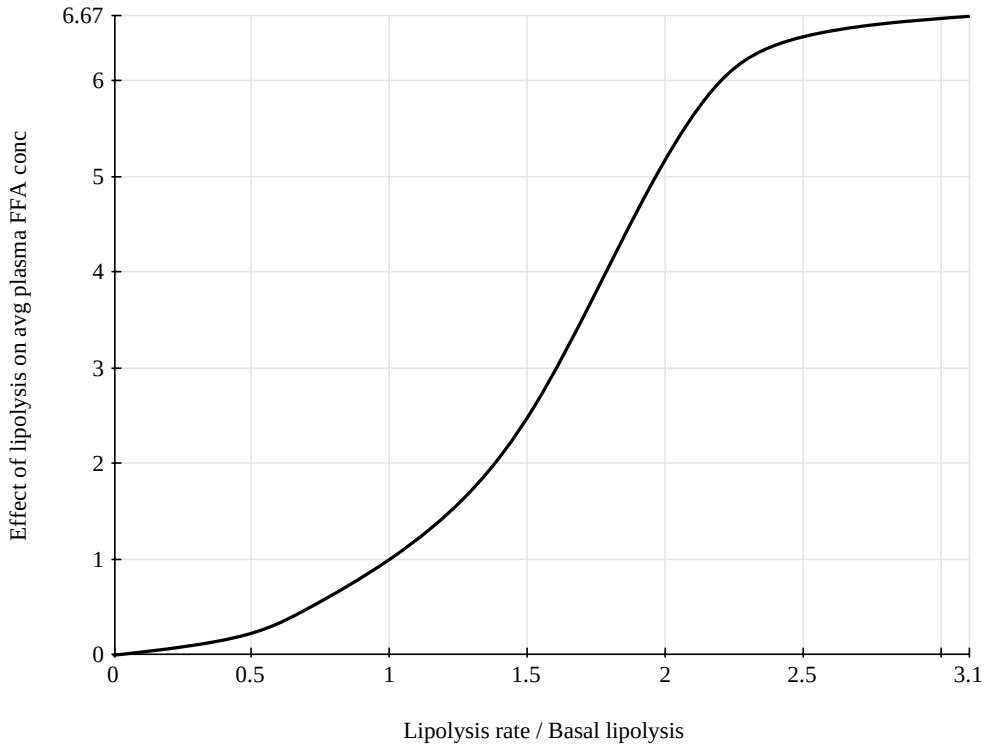

Figure 4.29. Graphical function for the effect of lipolysis on average plasma FFA concentration.

When the lipolysis rate increases, which means that fat breakdown rate rises, free fatty acids and glycerol (main constituents of triglycerides) will be released to the blood vessel. Thus, the concentration of FFA will increase. In literature, it is stated that the maximum rate of lipolysis can be 3.1 times of the basal value (Hall, 2006). By using the graphical function in Figure 4.29, the average plasma FFA concentration level can be calculated with the following formula:

*Average plasma FFA concentration = Effect of lipolysis on average plasma FFA concentration * Normal plasma FFA concentration* (4.12)

Normally, this concentration changes very frequently during a day. Since a long term model is constructed in this study, a possible change on average values is considered for the dynamic behaviors of the simulation.

As it can be seen from the cause-and-effect diagram, in Figure 3.1, the level of FFA concentration in blood has several impacts in the glucose regulation mechanism. It should not be forgotten that FFA concentration is the key factor for this disorder, as it is discussed previously.

Moreover, the elevation in plasma FFA concentration has impact on another variable, named as *glucose transport rate* in the model which refers to the transportation of glucose in blood to the muscle tissues. When plasma FFA concentration rises in the blood, uptake of glucose by muscles decreases, because FFA will be transported to the muscle tissues instead of glucose in order to maintain FFA in the blood in normal ranges. Since the rate changes frequently during a day, this value is considered as a coefficient that affects the carbohydrate stock in the body, where liver and muscle tissues are included. The effect formulation is shown in Figure 4.30.

Furthermore, related literature reports that glucose transport rate increases, if plasma insulin concentration becomes larger in the plasma membrane according to direct comparisons between these two variables. Glucose transport rate can increase about 180% above its basal value with respect to the increase in plasma insulin concentration (Thorell *et al*., 1999). Therefore, a direct relationship is depicted between glucose transport rate and plasma insulin concentration in the formulation, as it is shown in Equation 4.13. The graphical function for this effect is shown in Figure 4.31. The equation of glucose transport rate is formulated as follows:

*Glucose transport rate = Effect on plasma FFA conc on glucose transport rate*Effect of physical activity on glucose transport rate*Effect of insulin conc on glucose transport rate*Normal glucose transport rate* (4.13)

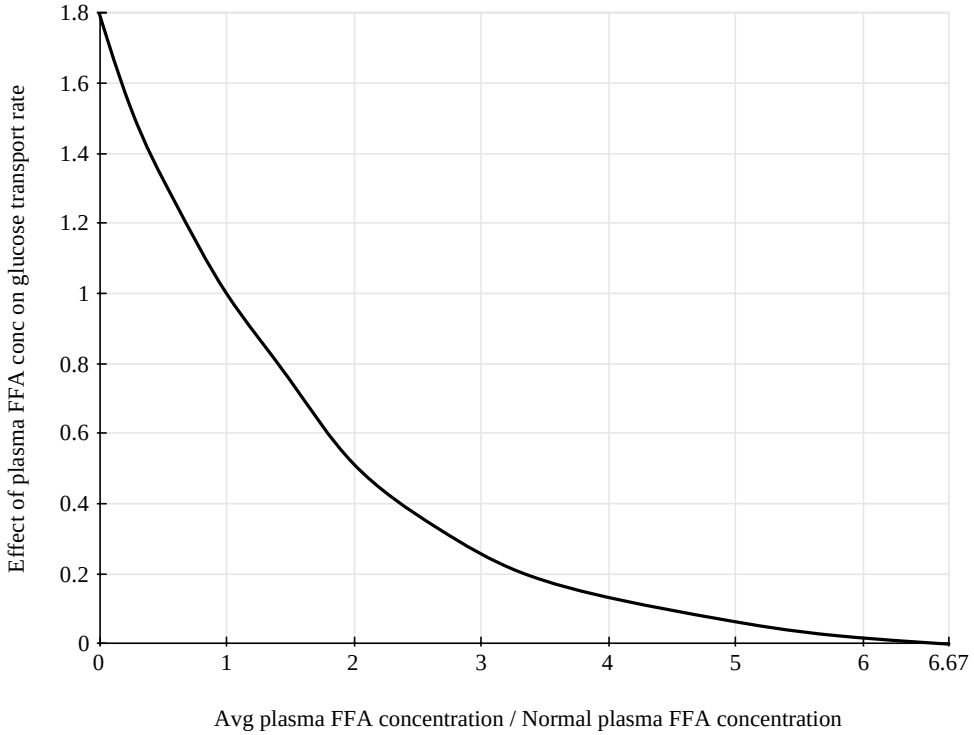

Figure 4.30. Graphical function for the effect of plasma FFA concentration on glucose transport rate.

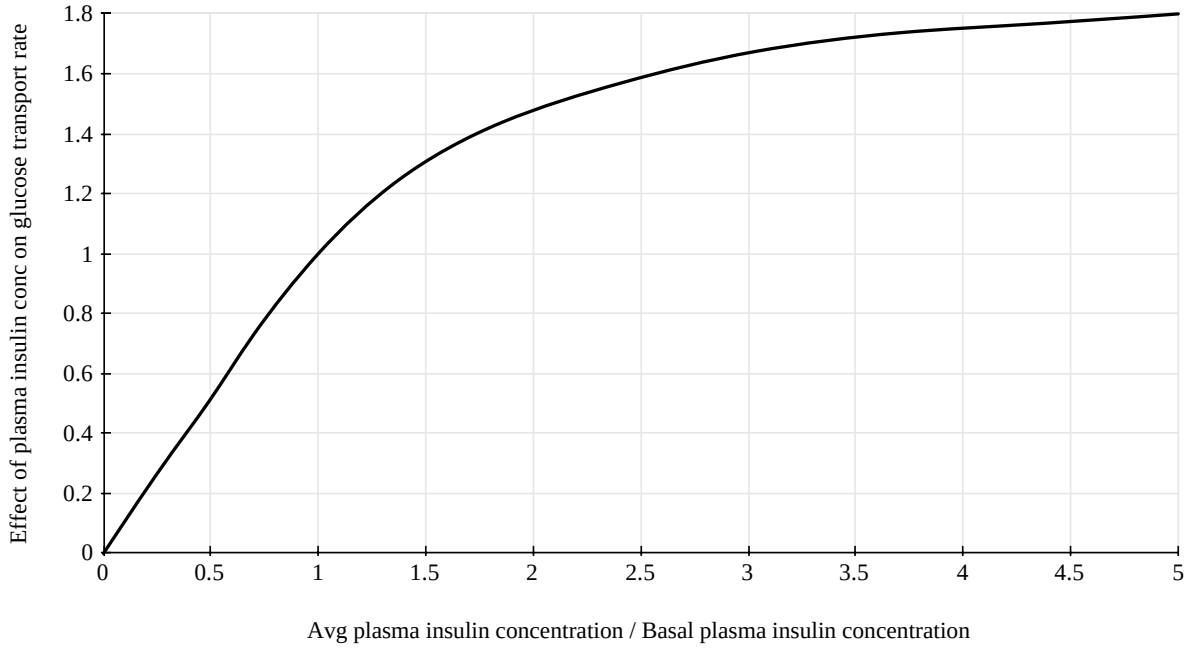

Figure 4.31. Graphical function for the effect of plasma insulin concentration on glucose transport rate.

The variable “glucose transport rate” is the one of the variables that makes the connection between two sectors. It shows increase in the inflow of *Carbohydrate* stock, because the glucose that is transported to muscle tissues is used for synthesizing glycogen or expending energy (for the case of doing physical activity).

Besides, doing physical activity has an impact on muscle glucose transport rate, which also shows another connection between two sectors. When the level of doing physical exercise increases, glucose transport to muscle tissues will also increase to maintain the required amount of glucose for muscle activity. The relationship between these two variables has been shown in Figure 4.32, as follows:

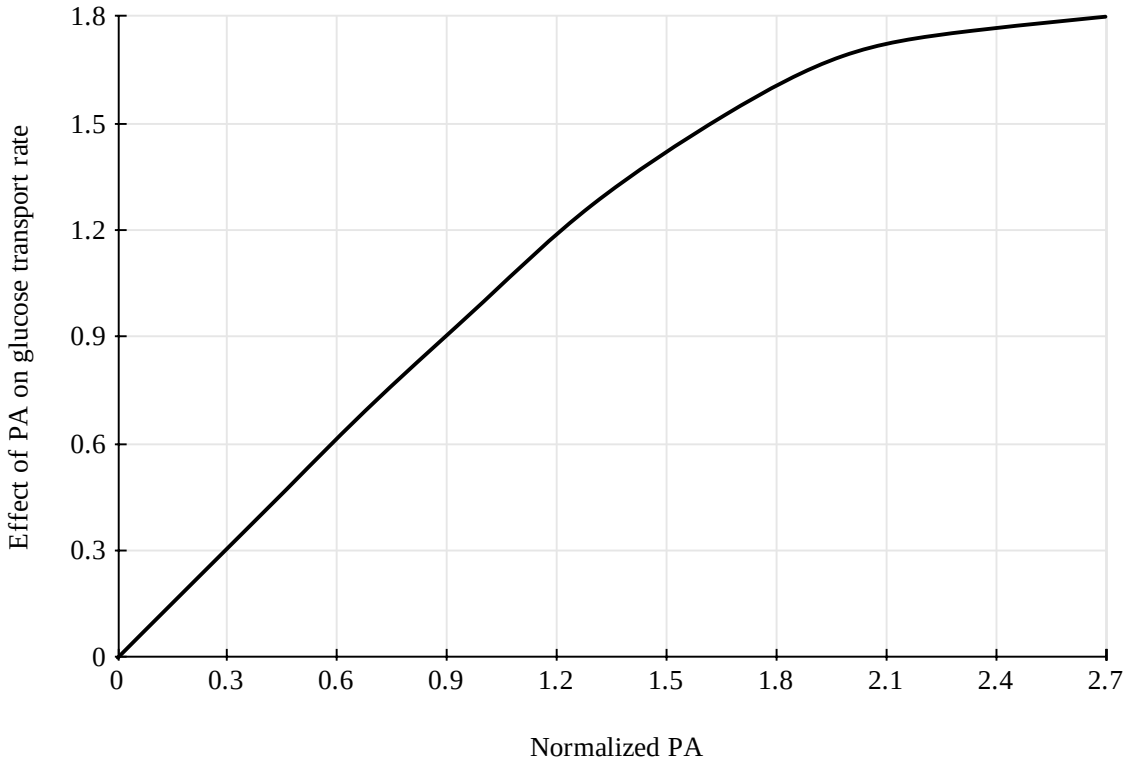

Figure 4.32. Graphical function for the effect of physical activity on glucose transport rate.

On the other hand, when glucose is transported from the blood vessel to the muscles, the concentration of glucose will decrease accordingly. Thus, the relationship between glucose transport rate and glucose concentration is shown in Figure 4.33:

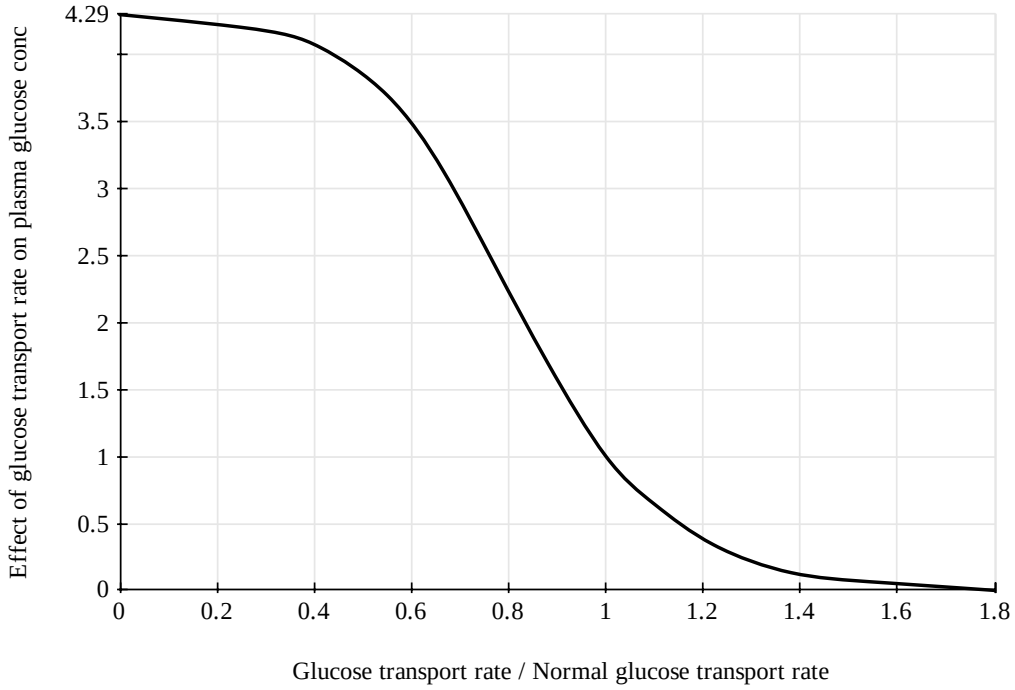

Figure 4.33. Graphical function for the effect of plasma glucose transport rate on plasma glucose concentration.

Plasma glucose concentration is the most significant variable in this sector, because when the level of this variable cannot be maintained in the normal ranges, one might expect that the individual most likely will develop insulin resistance. There are several variables that affect this concentration in blood. The main factor on maintaining the level in the normal ranges is insulin hormone. When the glucose in the blood is greater than the normal value, beta-cells are triggered to secrete insulin hormone into the bloodstream.

Besides, when the glucose regulation mechanism works properly, skeletal muscles will uptake the glucose from the blood into the tissues in a normal way, which induces the plasma glucose concentration level to decrease because of the transportation. On the other hand, elevated FFA concentration in the blood will result in an increase in hepatic glucose production, which causes an increase in plasma glucose production (DeFronzo, 2004). The graphical function of this effect is shown in Figure 4.33. Thus, the equation for this variable can be formulated as follows, in Equation 4.14:

*Average plasma glucose concentration = Lower limit of normal blood glucose concentration*Effect of glucose transport rate on plasma glucose concentration* (4.14)

The glucose-insulin regulation is a reciprocal process, which is also shown in this sector. According to the level of insulin concentration in the blood, glucose concentration level changes, and vice versa. In order to specify this negative feedback mechanism, a first-order information delay between these two concentrations has been defined in the model. It means that when plasma glucose concentration increases, it will take some time to trigger the pancreas, and to release the hormone into the bloodstream. However, in this model, this effect is considered as a long term effect. Thus, the effect formulation is obtained by using a first-order delay structure with delay time 10 weeks, as shown in Figure 4.34:

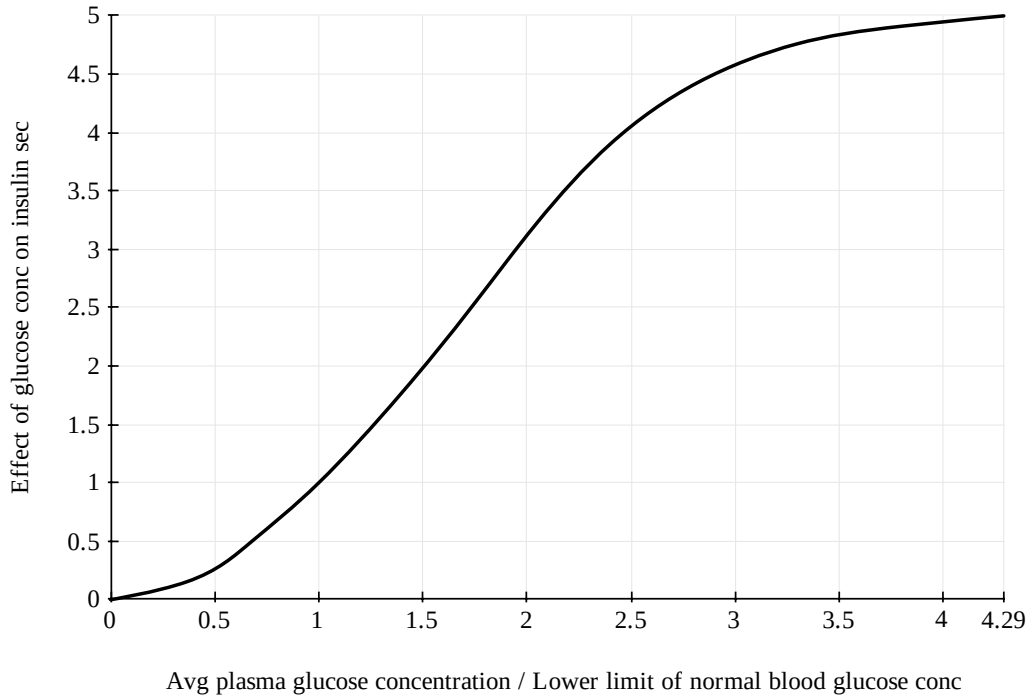

Figure 4.34. Graphical function for the effect of plasma glucose concentration on insulin secretion.

Not only plasma insulin concentration is regulated by the glucose concentration level, but also the insulin secretion via pancreatic islets. Therefore, average plasma insulin concentration level is formulated as below:

*Average plasma insulin concentration = Normal average plasma insulin concentration * Effect of insulin secretion on plasma insulin concentration* (4.15)

The following graphical function shows the effect of insulin secretion on plasma insulin concentration, in Figure 4.35. When the insulin hormone is secreted from the beta-cells, the concentration of insulin in the blood will increase.

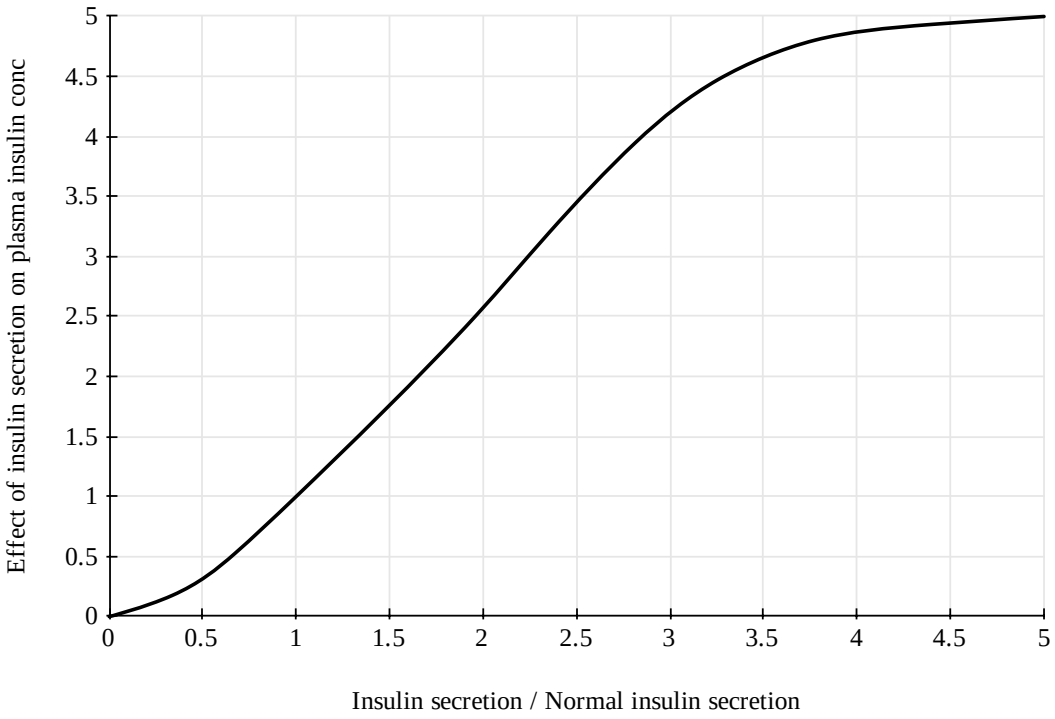

Figure 4.35. Graphical function for the effect of insulin secretion on plasma insulin concentration.

Insulin hormone has a significant impact on suppressing the lipolytic activity, which is also a part of the negative feedback loop of this mechanism. When insulin resistance is present, insulin might start to respond to the glucose concentration level properly, and not to function appropriately. At this time, the suppression on lipolysis will be removed, and FFA concentration will increase in the blood. This negative correlation between insulin concentration and lipolysis is shown in the following graphical function, Figure 4.36:

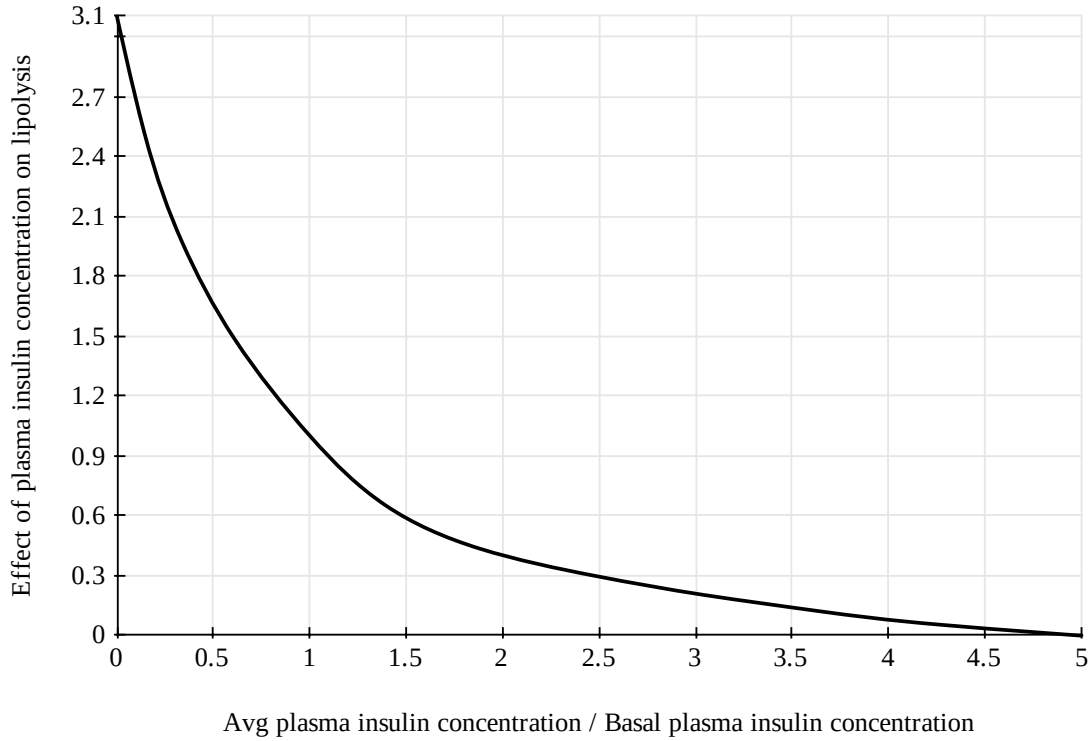

Figure 4.36. Graphical function for the effect of plasma insulin concentration on lipolysis.

As it is discussed in the insulin-glucose feedback mechanism, there is a similar reciprocal process between insulin secretion level and beta-cell functionality. When beta-cells in the pancreas work properly during the regulation processes, the amount of insulin secreted into the blood will be in the normal values, which is changed according to the serum glucose concentration. However, when the beta-cell dysfunction is present, the insulin secretion will be inadequate for keeping the glucose concentration in the normal range.

The negative relationship between insulin secretion and beta-cell functionality is shown in Figure 4.37. According to the level of insulin secretion, beta-cells may lose their functionality with some percentage. When the individual develops hyperglycemia, then pancreas is stimulated to secrete more insulin into the bloodstream; therefore, beta-cell functionality decreases to 25% of its healthy capacity (Kahn *et al.*, 2006). The effect of insulin secretion level is smoothed with a first-order information delay structure with a delay time of 15 weeks.

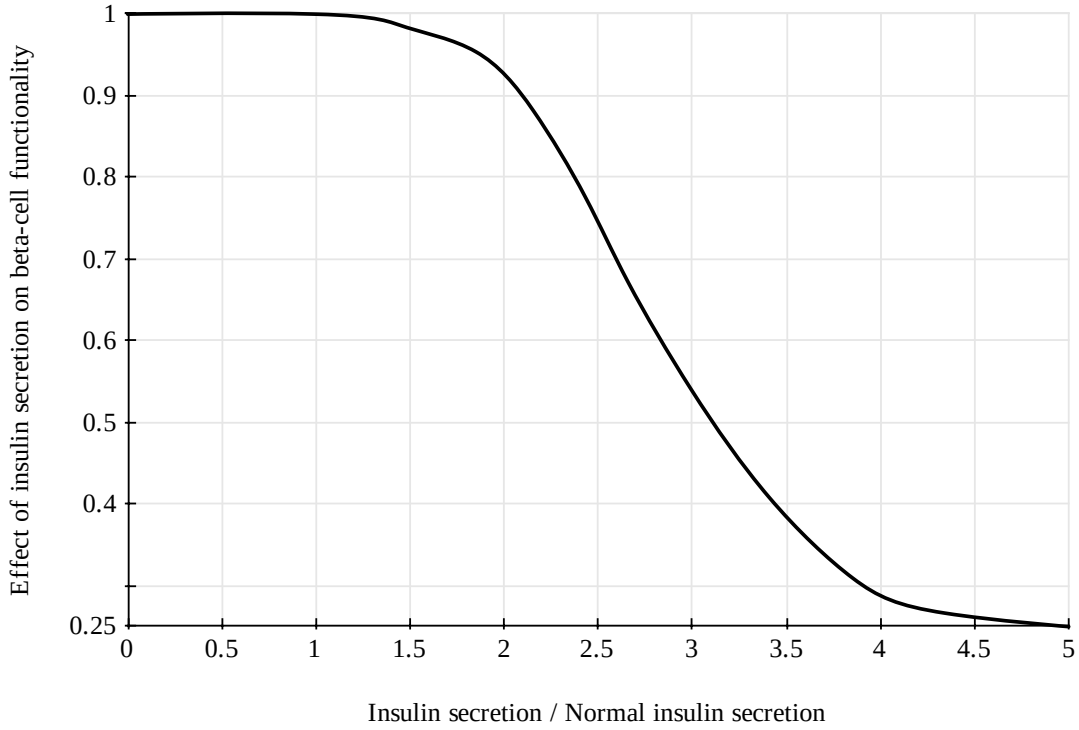

Figure 4.37. Graphical function for the effect of insulin secretion on beta-cell functionality.

In accordance with considering the effect of beta-cell functionality, insulin secretion level is formulated as given in the following Equation 4.16:

*Insulin secretion = Delayed eff of beta-cell func on insulin secretion*Delayed eff of glucose concentration on insulin secretion*Normal insulin secretion* (4.16)

Nevertheless, the other way around of this process is also considered in the model. The effect of beta-cell functionality on insulin secretion is displayed in this sector (see Figure 4.38) with a delay function. There is a first-order information delay structure between beta-cell functionality and the units of insulin secretion. It will take some time to induce beta-cell dysfunction according to the level of stimulation and secretion of insulin. The delay time for the effect of beta-cell functionality on insulin secretion is assumed as 12 weeks.

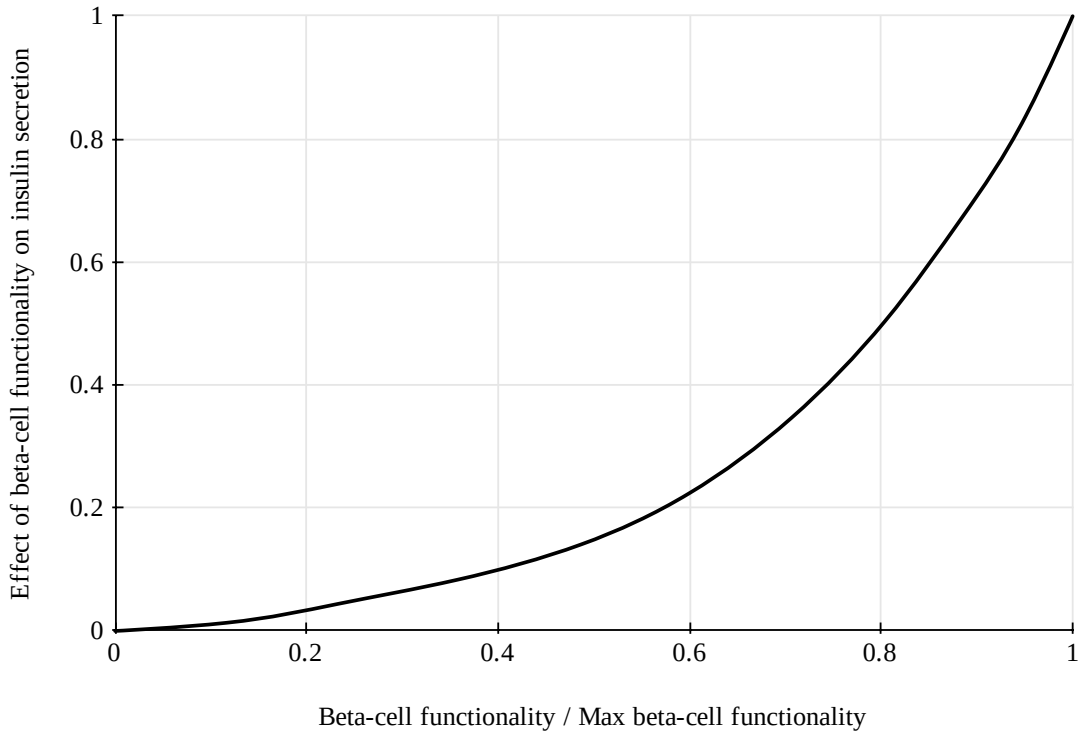

Figure 4.38. Graphical function for the effect of beta-cell functionality on insulin secretion.

Therefore, the formulation for the variable of beta-cell functionality is given in the Equation 4.17:

*Beta-cell functionality = Delayed eff of insulin sec on beta-cell functionality*Max beta-cell functionality* (4.17)

Lastly, the effect of the change in fat breakdown on the lipolysis rate is shown in the following graphical formulation, Figure 4.39:

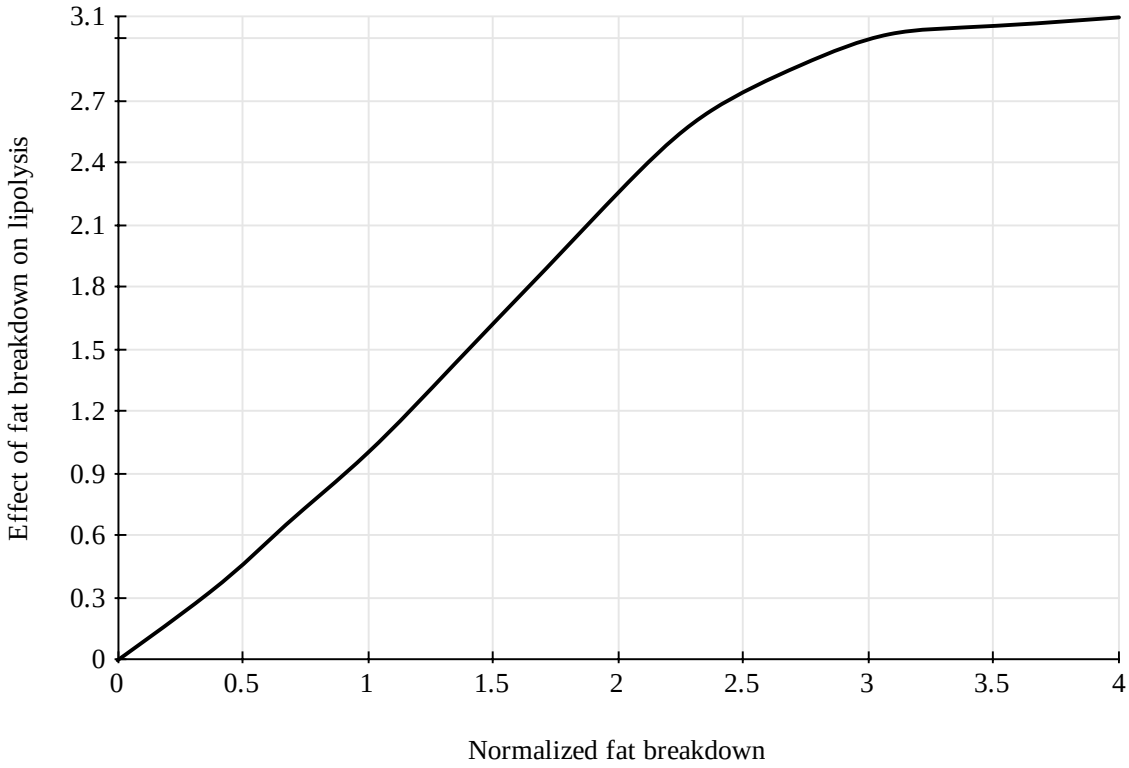

Figure 4.39. Graphical function for the effect of fat breakdown on lipolysis rate

According to the effect of fat breakdown and insulin on lipolysis, the equation regarding to lipolysis rate is formulated as follows:

*Lipolysis rate = Effect of fat breakdown on lipolysis*Effect of plasma insulin concentration on lipolysis*Normal lipolysis* (4.17)

As a result, after implementing all of the main variables and relationships in the model, the whole structure of body weight sector is obtained as below, in Figure 4.40:

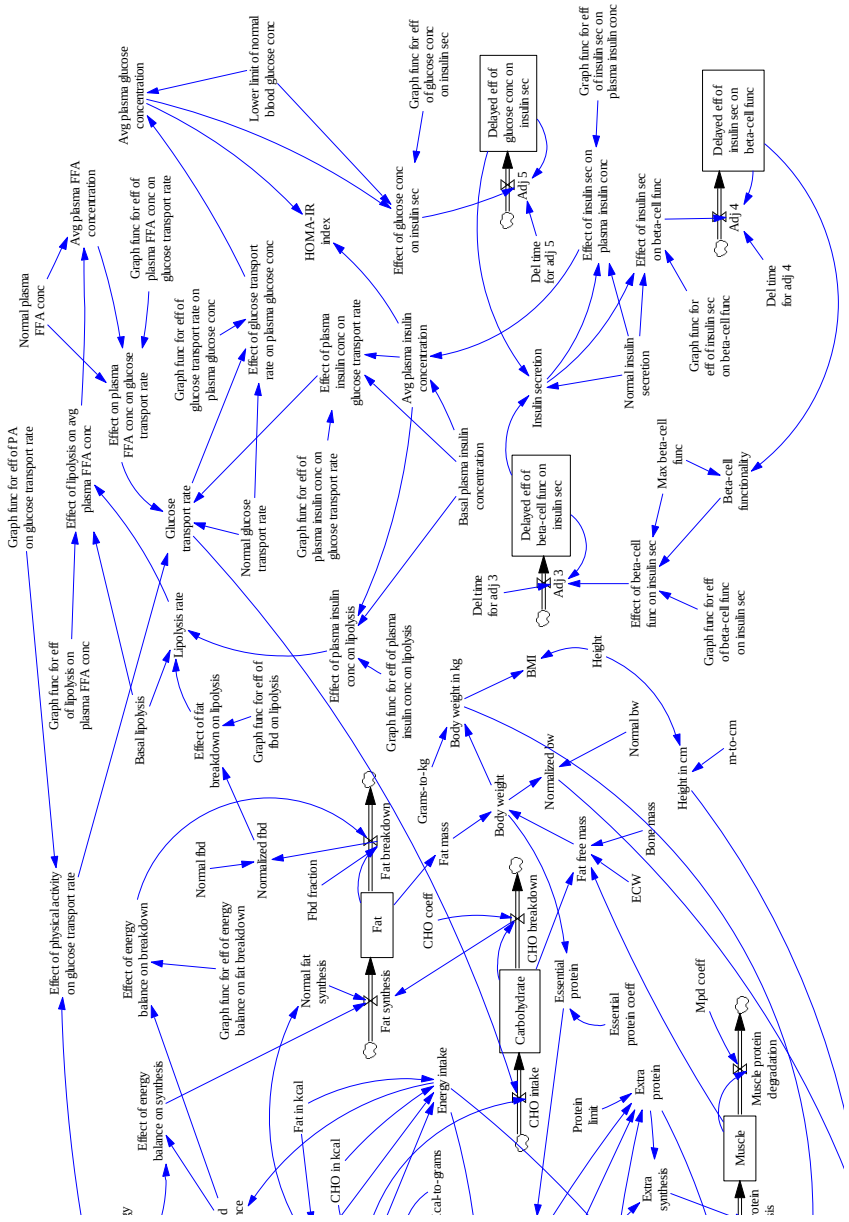

Figure 4.40. Stock-flow diagram of the glucose-insulin regulation sector

4.2.4. Dynamics of Glucose-Insulin Regulation Sector

In this section, in order to verify that glucose-insulin regulation structure works properly, a number of runs will be executed. For the purpose of illustrate the experiments, the changes in the average plasma FFA, glucose and insulin concentrations for different conditions will be conducted. The dynamic behaviors of key variables and the other relevant variables in this sector will be demonstrated for a simulation period of 520 weeks.

In the first experiment, it will be tested whether average plasma concentrations of FFA, glucose and insulin stay stable in the normal ranges with respect to the changes in the energy expenditure. In this case, the physical activity level will be changed in order to observe the regulation of glucose metabolism, and all other variables will be kept as their baseline values. In the run *Light2*, a lightly active person is considered, and PA factor is selected as 1. In *Moderate2* and *Active2*, PA factor is chosen as 1.475 and 1.95, respectively, which are the values used for the moderate and very active individuals. Lastly, PA factor is chosen as 2.67 for an individual who does strenuous exercise, in *Strenuous2*. The relevant graphs for plasma FFA, glucose and insulin concentrations are shown in Figure 4.41, 4.42 and 4.43, accordingly:

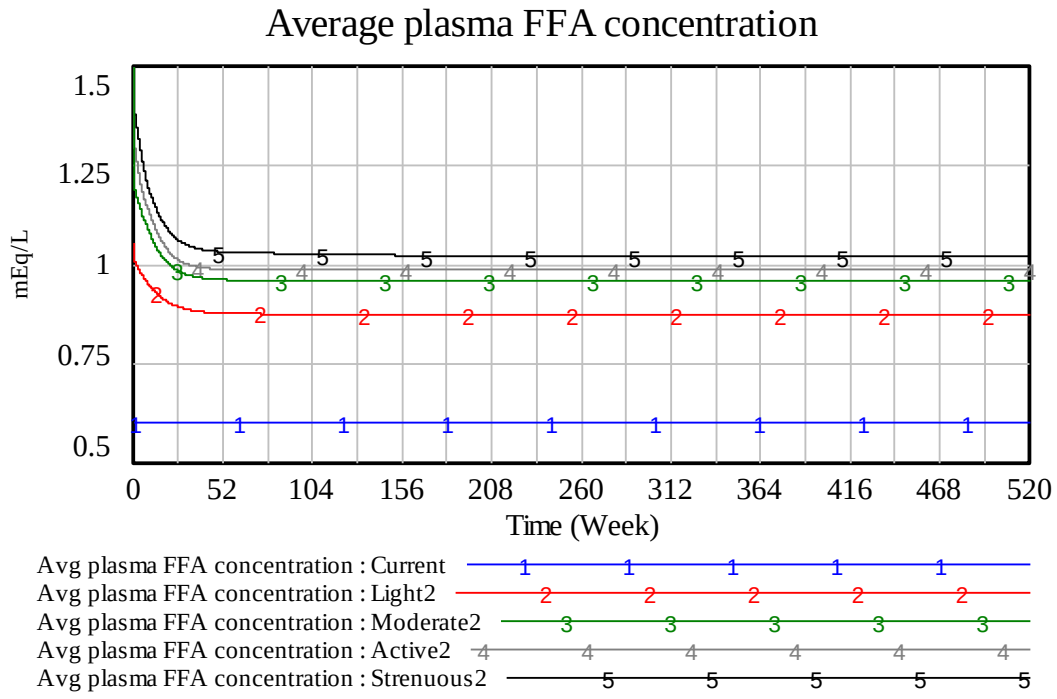

Figure 4.41. Dynamics of average plasma FFA concentration with respect to the changes in PA factor.

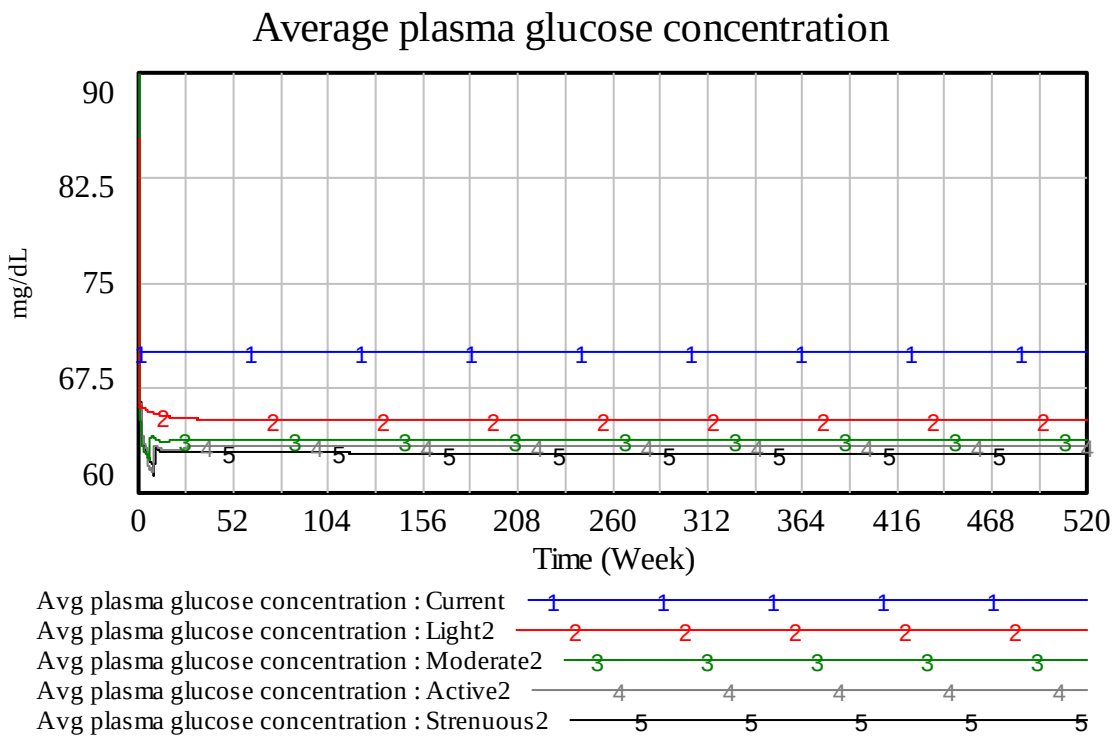

Figure 4.42. Dynamics of average plasma glucose concentration with respect to the changes in PA factor.

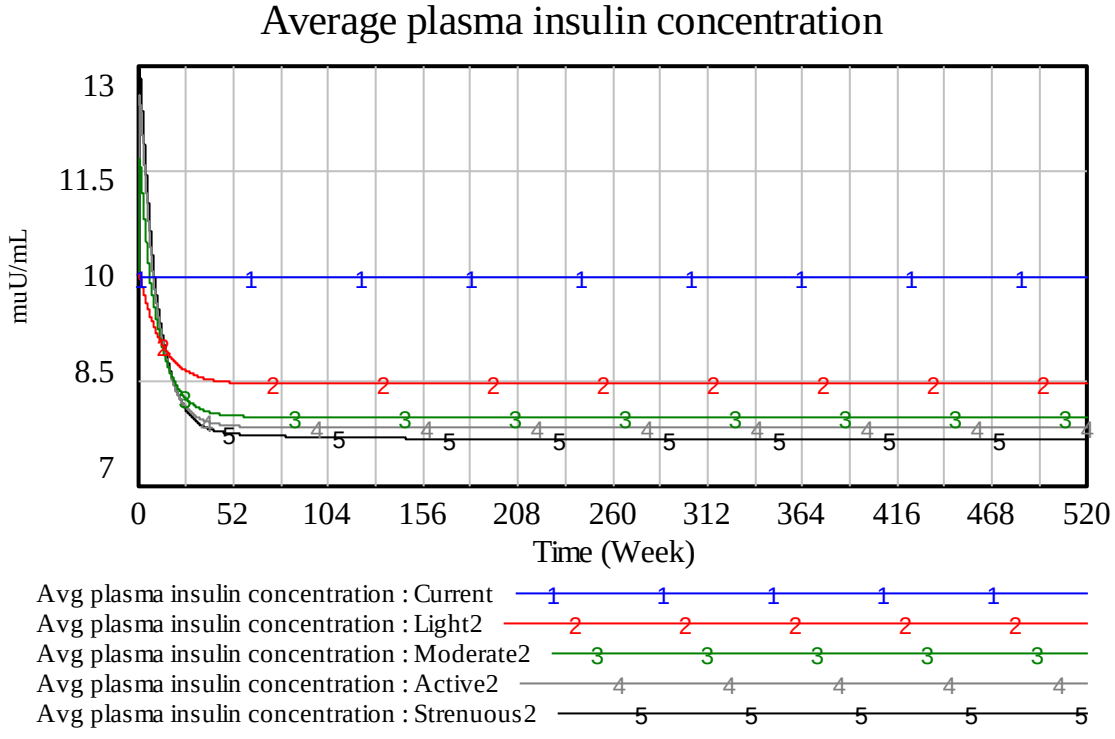

Figure 4.43. Dynamics of average plasma insulin concentration with respect to the changes in PA factor.

In Figure 4.41, average plasma FFA concentration increases according to the level of physical activity. As it is discussed previously, FFA will be used in order to maintain necessary amount of glucose for muscle tissues. Therefore, more FFA will be released to the bloodstream.

As it can be seen from Figure 4.42; average plasma glucose concentration level decreases with respect to the increase in physical activity level. When a person performs more physical activity, muscle tissues use more glucose for fulfilling the exercising task. Thus, there is a decrease in the plasma glucose concentration level because of the increase in glucose transport from blood to muscles according to the feedback loop mechanism in the model, which also confirms our hypothesis. In Figure 4.43, average plasma insulin concentration will change according to the levels of average plasma glucose concentration. Therefore, a similar dynamic behavior as in Figure 4.42 is observed in the dynamics of plasma insulin concentration.

Second experiment tests the responses of average plasma FFA, glucose and insulin concentrations to low and high food intakes. In the run named as *DoubledFoodIntake2*, food intake will be increased to 40000 kcal/week, and in the run *ExcessFoodIntake2*, this amount will be taken as 30000 kcal/week. In the run *InsufficientFoodIntake2*, food intake will be decreased to 15000 kcal/week, and lastly, in the run named as *Starvation*, the food intake is chosen as 0 kcal/week in order to test the body's response in case of starvation.

The dynamic behaviours for these experiments are shown as follows, in Figure 4.44, 4.45 and 4.47:

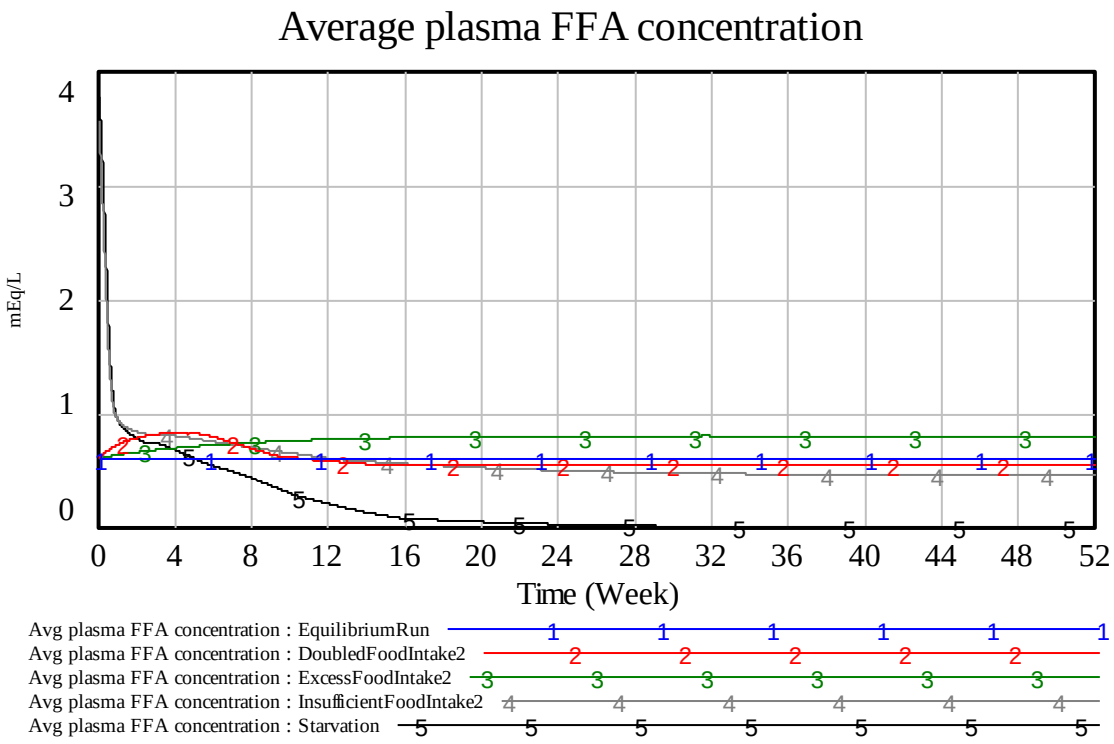

Figure 4.44. Dynamics of average plasma FFA concentration with respect to the changes in food intake.

As it can be seen from Figure 4.44, when food intake is increased too much, there will be an increase at the beginning, and a sudden decrease in plasma FFA concentration. In order to show the changes in plasma FFA concentration more clearly, simulation time is selected as 52 weeks. Since the individual continues to eat more than the sufficient amount, the concentration increases in some time. However, in the opposite case, when food intake is decreased, plasma FFA concentration will stay stable under the average value. In addition, if the individual is in a fasting condition, then FFA concentration in the blood will hit the maximum at first, and decrease by the reason of one's body will start to consume the fat storage at the beginning. After the storage is totally consumed, FFA in the blood will decrease sharply in a shorter time.

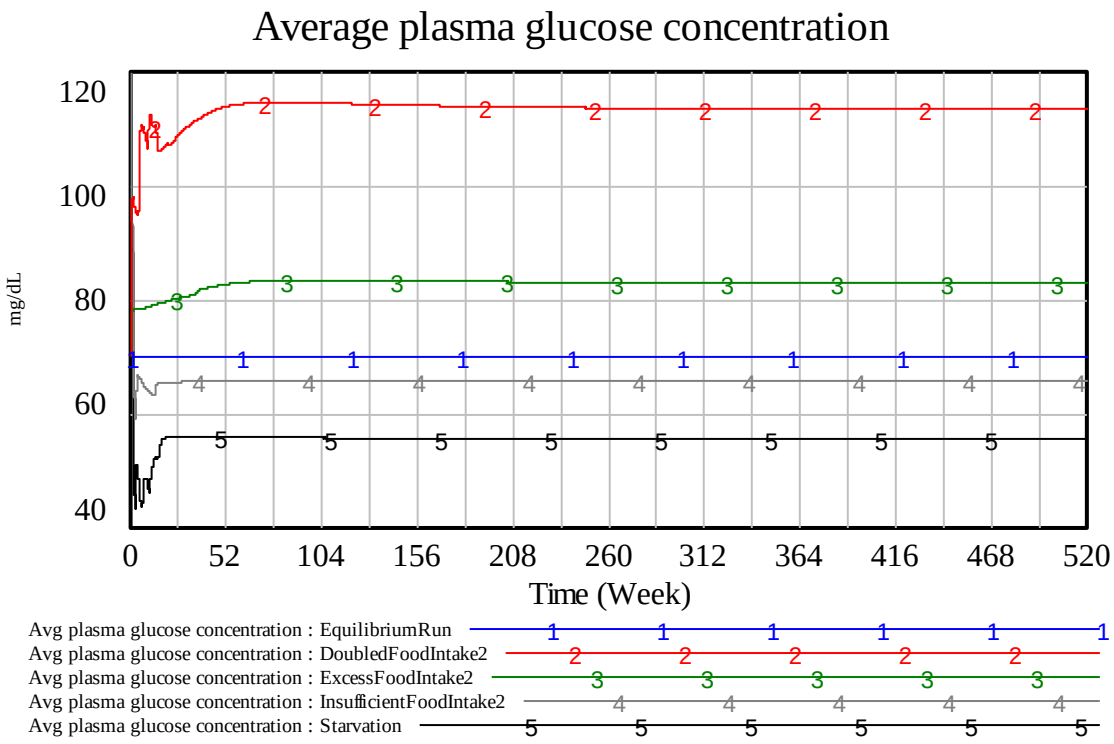

Figure 4.45. Dynamics of average plasma glucose concentration with respect to the changes in food intake.

In Figure 4.45, it is shown that the increase in food intake will result a sharp increase in glucose concentration in blood, and it reaches equilibrium at a level above the normal range. However, if the individual get nutrition below the adequate level, then the glucose concentration will decrease and reach equilibrium at the level which is in the normal range, since the amount of food intake is closer to the baseline value. In the prolonged fasting condition, glucose concentration will decrease dramatically because the body uses all of the carbohydrate stock in the liver in order to keep itself in the homeostasis, as shown in Figure 4.46:

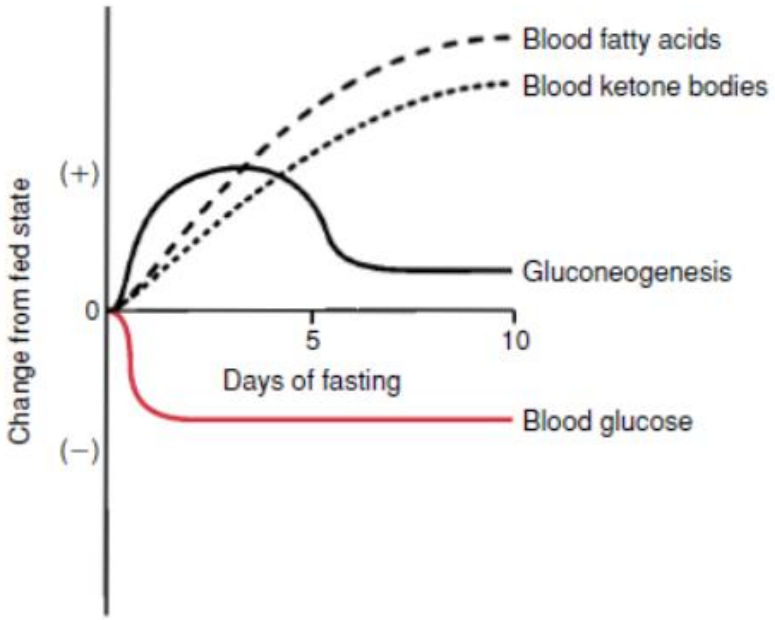

Figure 4.46. Metabolic adaptations in the body in prolonged fasting condition (Guyton, 2006).

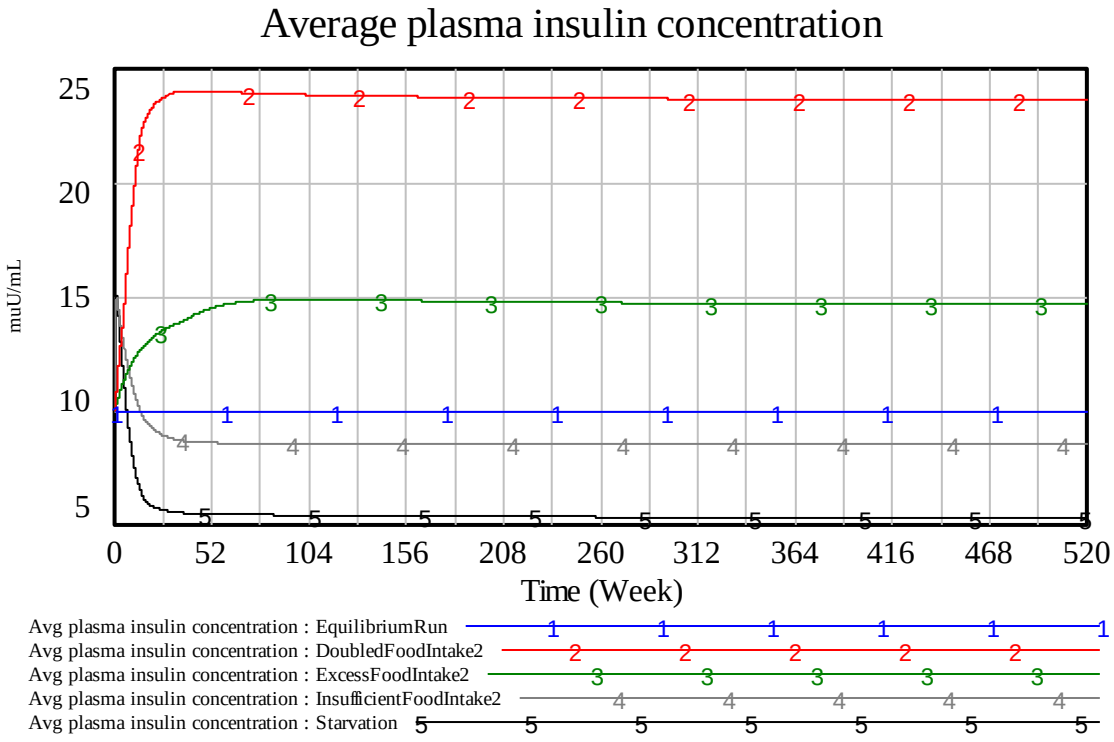

Figure 4.47. Dynamics of average plasma glucose concentration with respect to the changes in food intake.

In Figure 4.47, similar results are observed as in Figure 4.45, the dynamic behavior of plasma glucose concentration. Since insulin hormone is secreted according to the rise in plasma glucose concentration, the concentration of insulin in blood will also increase and reach equilibrium at a higher level, which is above the normal range (10-20 μU/mL) in the case of having higher amounts of food intake. When this amount is decreased to 15000 kcal/week, the concentration will be also kept in the normal ranges as it is observed in plasma glucose concentration, because the glucose level is in the normal range. However, the fasting condition is considered, then a similar behavior will be observed as in glucose concentration. There will be a sudden increase at the beginning, in order to regulate the higher level of glucose, and then insulin level will decrease according to the decrease in glucose level.

5. BASE BEHAVIOUR OF THE INTEGRATED MODEL

5.1. Structure of the Integrated Model

The whole structure of the model is given in the following stock-flow diagram in Figure 5-1. *CHO intake* (the inflow of the Carbohydrate stock), *Fat breakdown* (the outflow of the Fat stock) and *Physical activity* are the common variables which connect the two sectors. The values of these variables are not directly changed during the simulation runs in Glucose-Insulin Regulation Sector. In the body weight sector, in order to see isolated dynamics of the body weight, CHO intake was limited with the food intake only. However, after integrating two sectors, CHO intake has two different components coming from different sectors.

Besides, rate of fat breakdown is displayed as the main effect on glucose-insulin regulation mechanism. With the increase in fat breakdown, lipolysis rate increases accordingly. Similarly, in order to see isolated dynamics of the body weight in the body weight sector, the effect of fat breakdown on the glucose-insulin regulation sector is not shown.

On the other hand, level of physical activity has impact on the amount of muscle glucose transport. When the physical activity increases, muscle cells need more glucose in order to perform that activity, which triggers the muscle glucose transport from blood to muscle cells.

As a consequence, the whole structure of the model after the integration of two sectors can be seen as follows, in Figure 5.1:

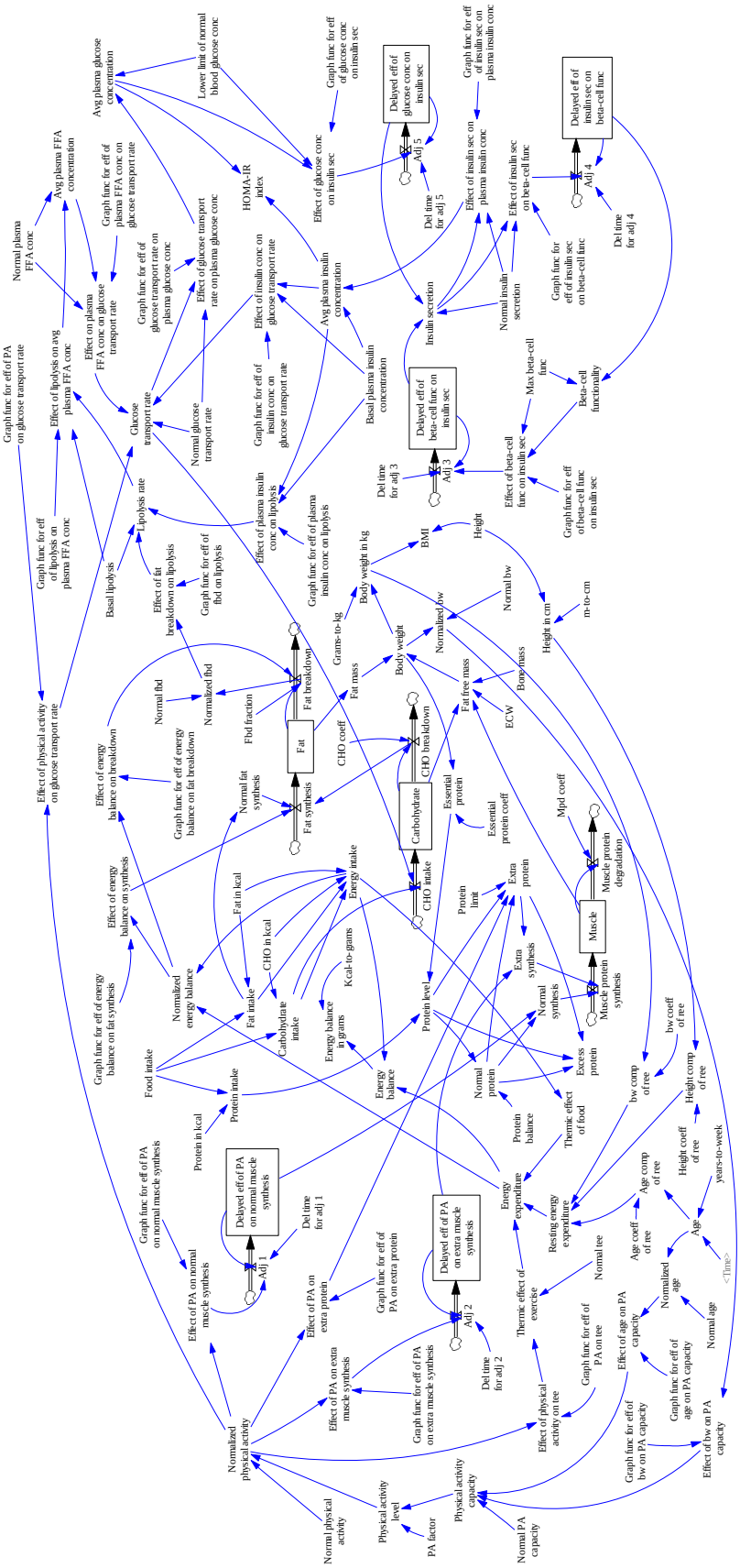

Figure 5.1. The stock-flow diagram of the whole model

5.2. Equilibrium Behaviour of the Complete Model

The start of the simulation for the equilibrium runs, week zero, represents an average, 30-year old male, who is healthy and almost sedentary individual, also has not experienced any diabetic problems, which means that plasma glucose and insulin concentrations are in the normal ranges. The simulation ends after about 10 years, which is sufficient to observe the maintenance of body weight with performing physical activity, and taking adequate amount of food according to reference values for that individual. The parameters in the equilibrium are selected as it is shown in Table 4.1, 4.2 and 4.3.

When all the variables are initially set to their equilibrium (normal) levels, all concentration levels and body weight components stay constant at their equilibrium values, as expected, which can be seen in the Figures 5.2 to 5.4:

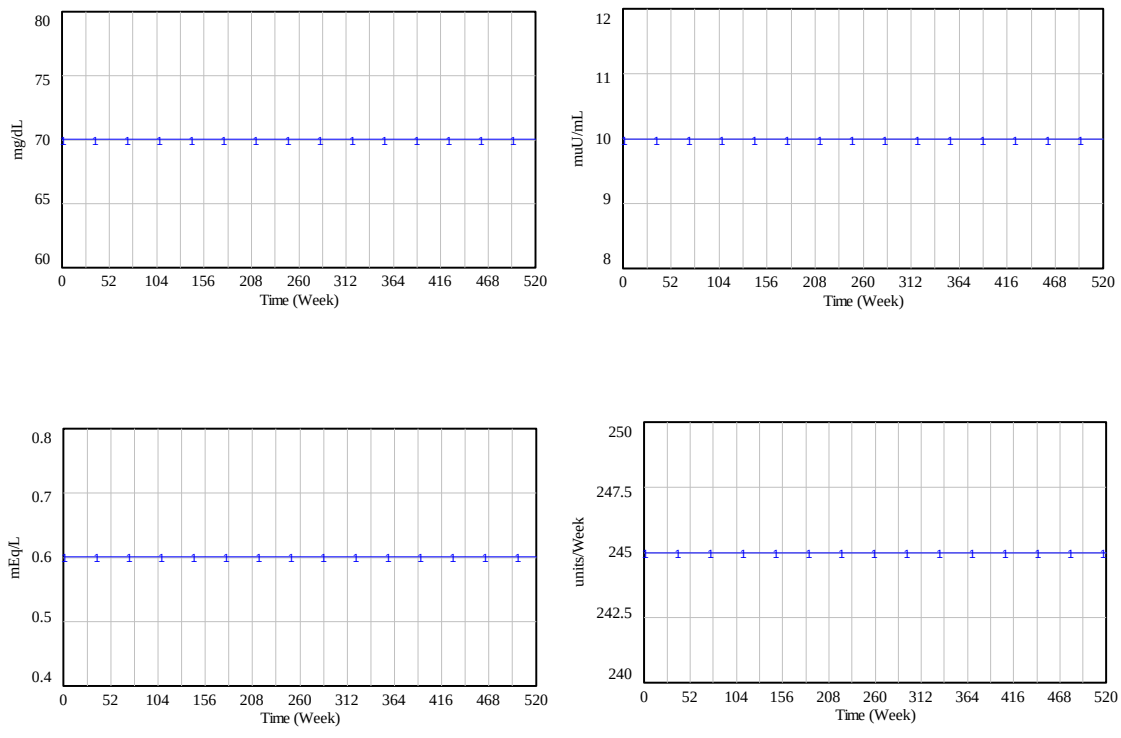

Figure 5.2. Plasma FFA, glucose, insulin concentrations, and insulin secretion at equilibrium.

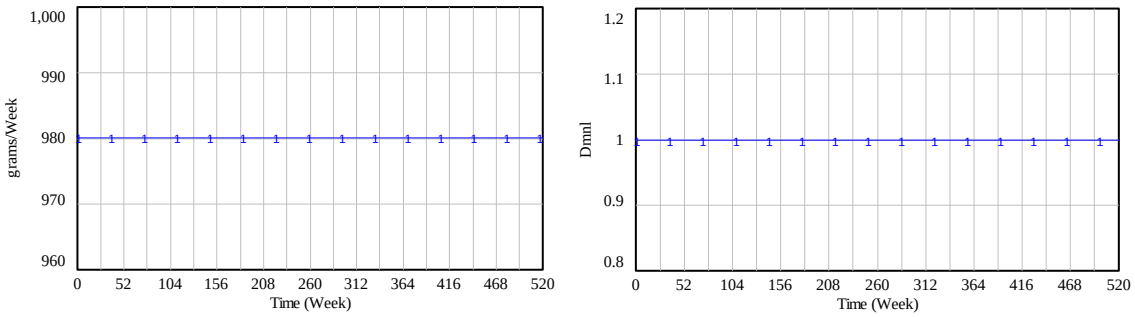

Figure 5.3. Lipolysis and glucose transport rates at equilibrium.

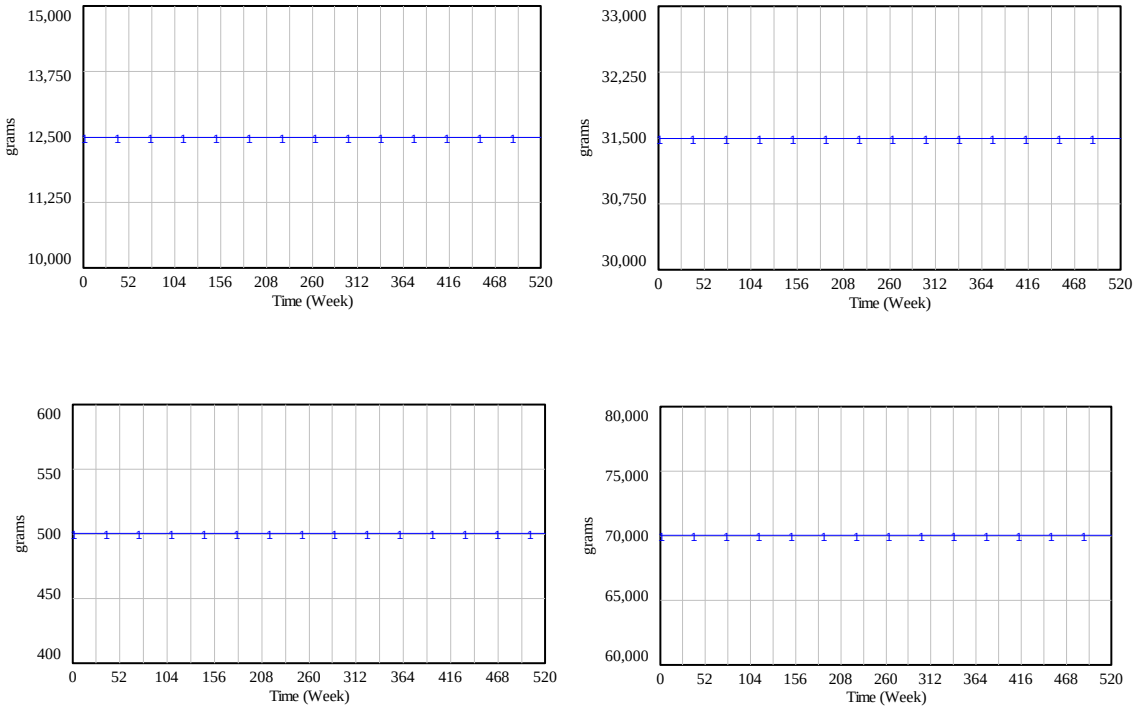

Figure 5.4. Fat, muscle, carbohydrate stocks and body weight at equilibrium.

According to the dynamic behaviors shown in Figure 5.2 to 5.4, if an average male individual takes the adequate amount of food which is determined for his body, and expends energy as being about sedentary person, then his plasma concentration levels will stay at their initial values (small changes can be ignored for a long term). Therefore, a healthy person will not develop insulin resistance and type 2 diabetes, because all of the values are in the range of normal levels at the equilibrium.

5.3. Base Behaviour of the Complete Model

In order to observe the base dynamics of the model, the amount of food intake is increased to 40000 kcal/week at time t = 52, and all other parameters are selected as in the equilibrium run. As it can be seen in Figure 5.5, fat storage and body weight increase, and reach equilibrium at a higher level than their initial values. Since the individual performs a lower level of physical activity, muscle mass will decrease and reach equilibrium at a smaller level than its initial value.

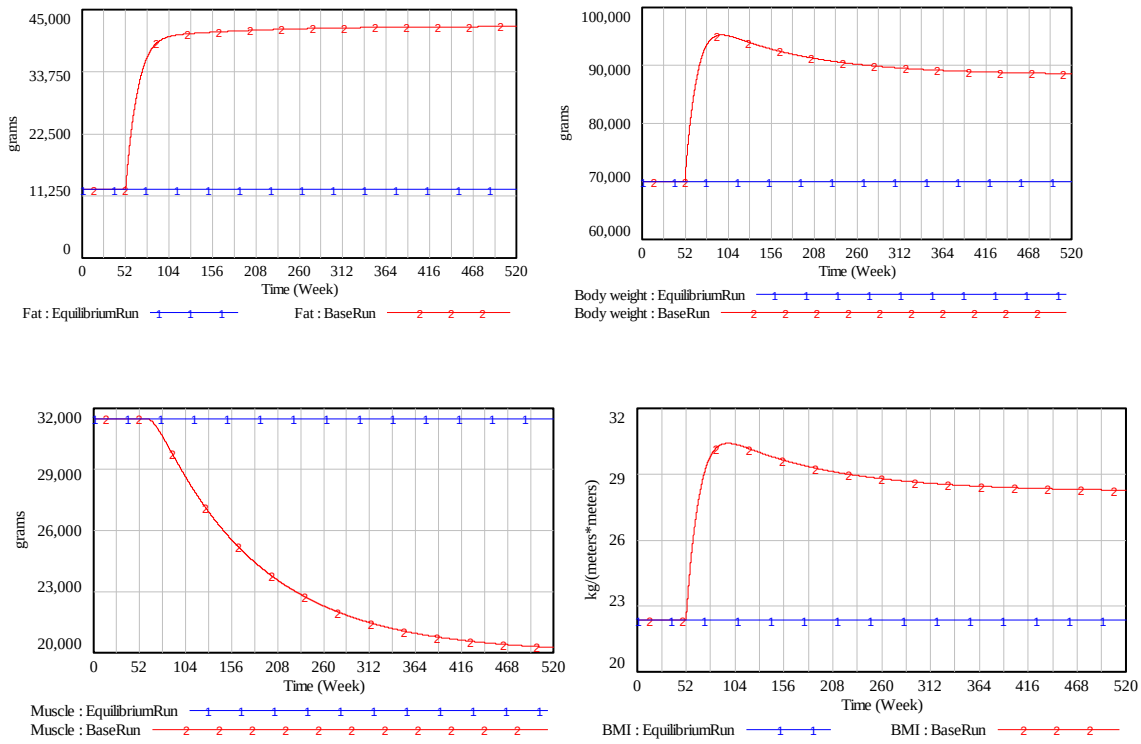

Figure 5.5. Fat, body weight, muscle mass and body mass index (BMI) in the base run.

In order to check whether the individual becomes obese or not, one of the most frequently used measurements is body mass index (BMI). Therefore, for the base run, BMI shows that the individual becomes overweight after the change in t = 52 (see Table 5.1).

A classification of obesity has been demonstrated according to the body mass index by World Health Organization (WHO), which is shown in Table 5.1 (McArdle *et al.*, 2010).

Table 5.1. Classification of obesity with respect to the body mass index.

BMI	Classification
< 18.5	Underweight
18.5-24.9	Normal weight
25.0-29.9	Overweight
30.0-34.9	Class I obesity
35.0-39.9	Class II obesity
≥ 40.0	Class III obesity

Besides, when the changes in average plasma concentrations of the individual are observed in Figure 5.6, it is obtained that plasma glucose and insulin concentration levels are above the upper limit of the normal ranges. Furthermore, the changes in HOMA-IR index, which also is a measurement for determining the insulin resistance, can be observed. Since the limit value of HOMA-IR index for insulin resistance is 2.7, it can be said that the individual becomes insulin resistant after t = 52, as a result of increase in obesity level of that individual. Therefore, we can say that these results support our hypothesis: the individual develops insulin resistance, and ultimately type II diabetes by the effect of obesity factor, in the long term.

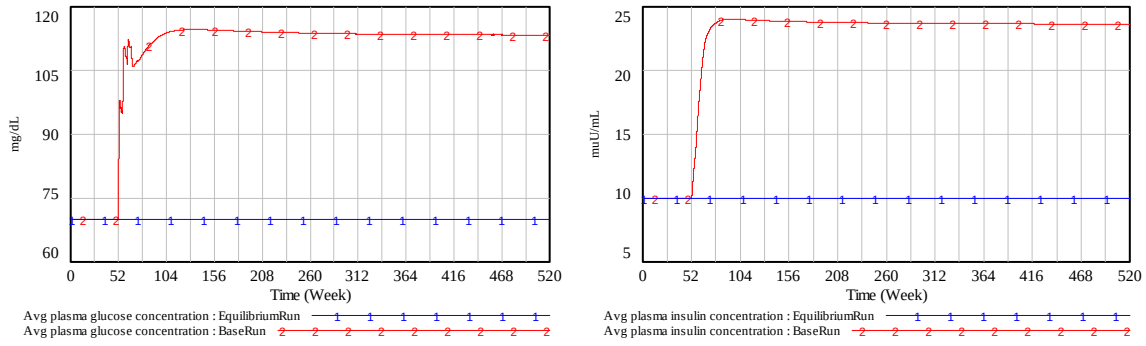

Figure 5.6. Dynamics of average plasma glucose and average plasma concentrations in the base run.

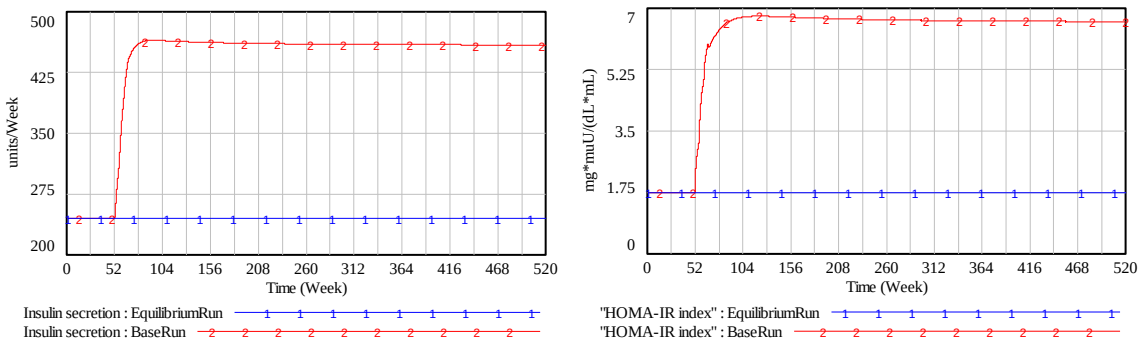

Figure 5.7. Dynamics of insulin secretion and HOMA-IR index in the base run.

Furthermore, the changes in beta-cell functionality are vital in order to determine if the individual may develop type II diabetes, ultimately. As it can be seen in Figure 5.8, there is a decrease observed in beta-cell functionality. Since only the amount of food intake is changed in the base run, and other factors which play a significant role in this disorder are not considered, beta-cell functionality does not decrease as it is expected. However, it can be said that the individual is a possible candidate for being a diabetic patient, when other factors which are assumed to be constant in the model.

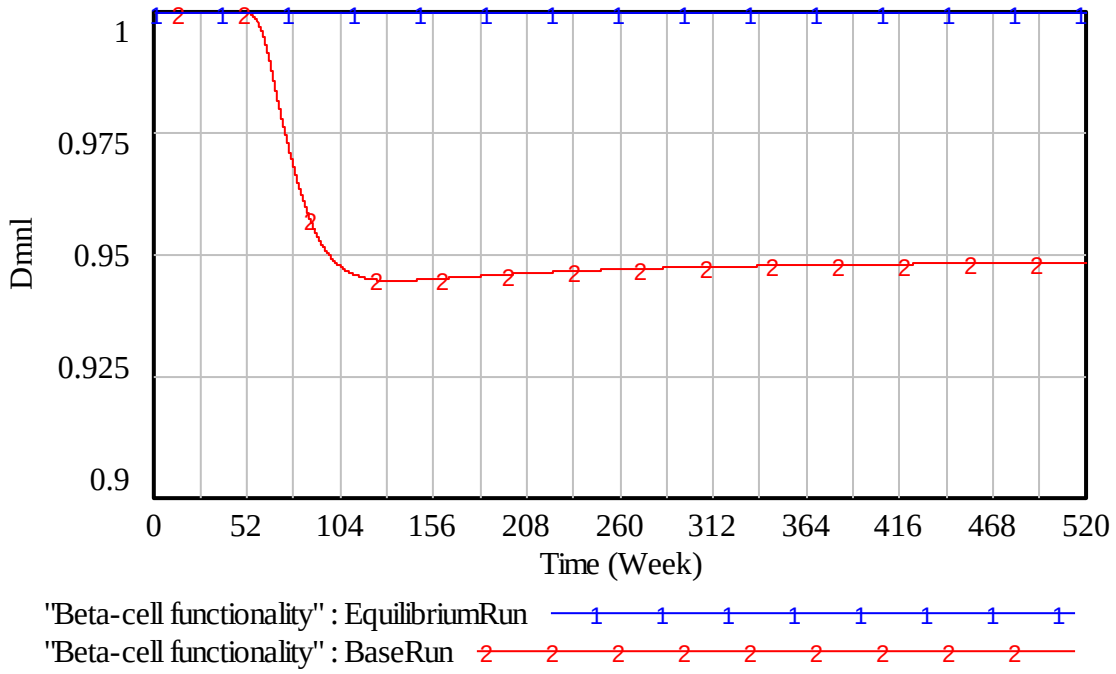

Figure 5.8. Dynamics of beta-cell functionality in the base run.

6. VALIDITY TESTS AND ANALYSIS OF THE MODEL

In this chapter, validation tests of the model will be conducted by using the relevant literature. The model is simulated by using Vensim 5.9c software, and the simulation time unit is chosen as one week, in order to monitor the long term behavior of developing insulin resistance and type II diabetes. Therefore, most of the runs are conducted for 520 weeks (10 years), only the runs which are testing the aging effect are demonstrated for 2600 weeks. Moreover, time step (DT) is chosen as 0.0078125 (1/128) that is considered as sufficiently small for the simulation.

In order to illustrate validation analysis of the model, two different tests should be conducted, which are known as structural and behavior tests. In structural tests, the robustness of the model is shown under extreme conditions, for indicating that the real problem has the similar relationships as shown in the model. Besides, in behavior tests, the dynamic behaviors of different variables in the model are demonstrated in order to show that the real behaviors give the similar patterns with the hypothetical behaviors (Barlas, 1999; Barlas, 2002).

As it is discussed in the Literature Review chapter, there is no research found which directly shows the whole structure. Therefore, validation tests are performed according to different data sets that consider different components of the model.

6.1. Direct Extreme Condition Test

In this section, some tests are performed by assigning extreme values to the key variables, fat mass and muscle mass, and the dynamic behaviours of some variables are observed according to the tests. In the run named as *ext1*, the initial value of fat stock is given as 0 grams. With respect to this change, dynamic behaviours of fat mass, average plasma glucose, insulin and FFA concentrations are shown in the figures from 6.1 to 6.4, respectively.

In Figure 6.1, fat mass increases and reaches equilibrium in about 1.5 years, since the individual takes the normal amount of food intake during the experiment.

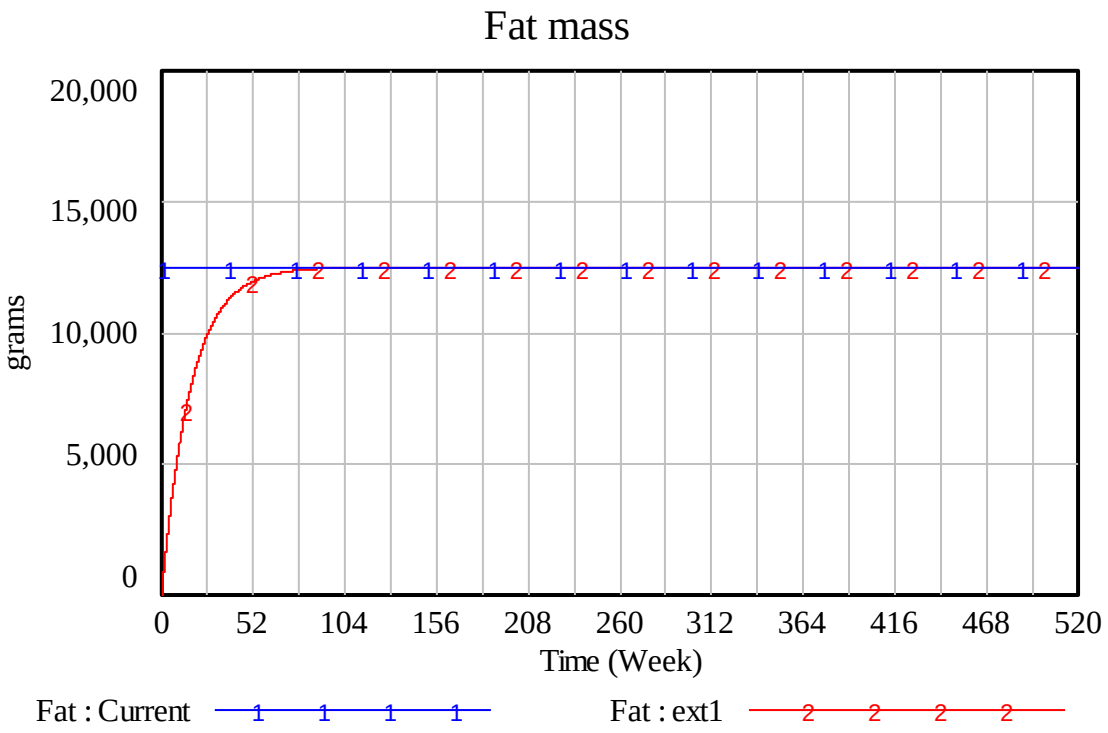

Figure 6.1. Dynamics of fat mass for the extreme condition test.

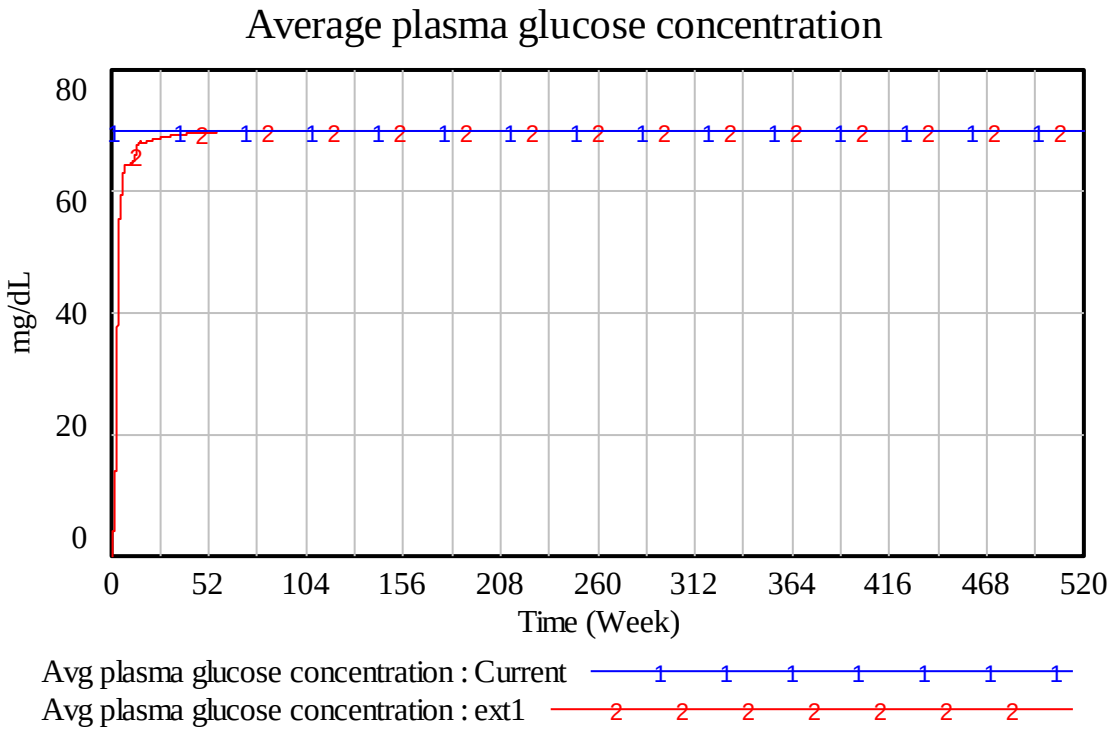

Figure 6.2. Dynamics of average plasma glucose concentration for the extreme condition test.

In Figure 6.2, it is observed that average plasma glucose concentration starts from 0 at the beginning, and reaches equilibrium at the basal value about in a year. Similarly, in Figure 6.3, average plasma insulin concentration starts from its baseline value at t = 0, and decreases sharply, since plasma glucose concentration is equal to 0 mg/dL at first and then increases. With respect to the increase in glucose concentration in blood, plasma insulin concentration also rises, and reaches equilibrium at the basal value, which is similar to plasma glucose concentration.

Besides, in Figure 6.4, plasma FFA concentration is equal to zero at t = 0, because there is no fat storage in the body at the beginning, and fat breakdown rate will be zero. Thus, glycerol and FFA production from triglycerides will not be possible. Since fat mass increases during the first 52 weeks and reaches equilibrium at its baseline value, FFA concentration will increase and reach equilibrium at the basal value, accordingly.

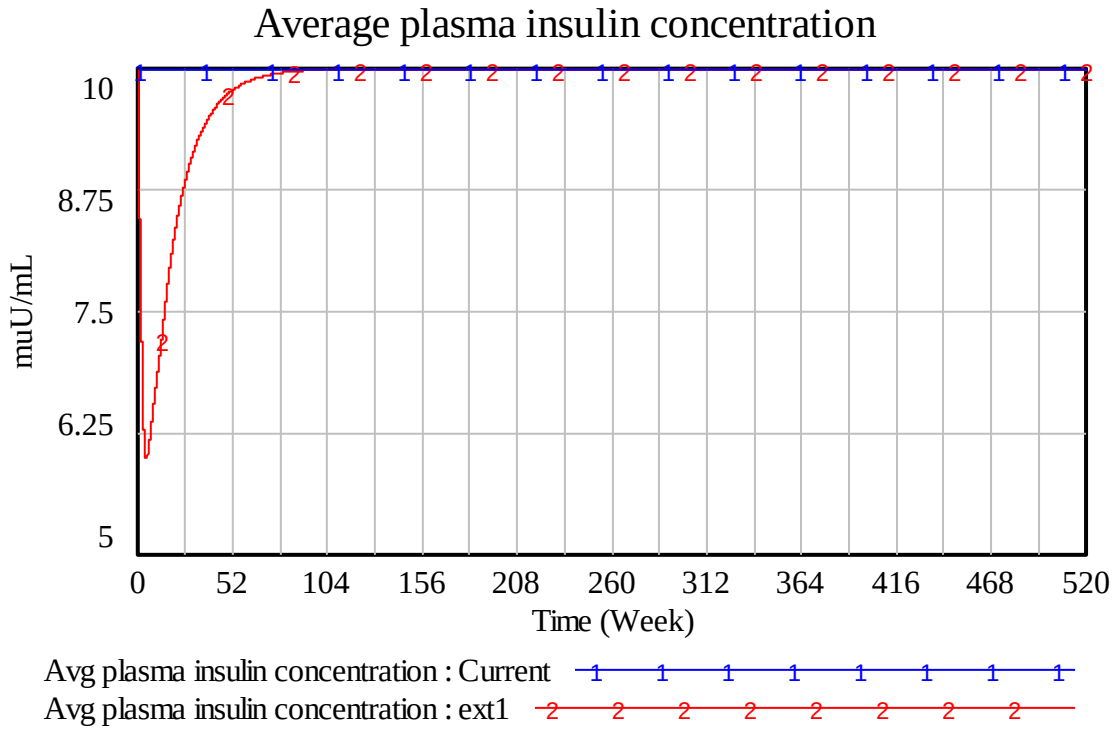

Figure 6.3. Dynamics of average plasma insulin concentration for the extreme condition test.

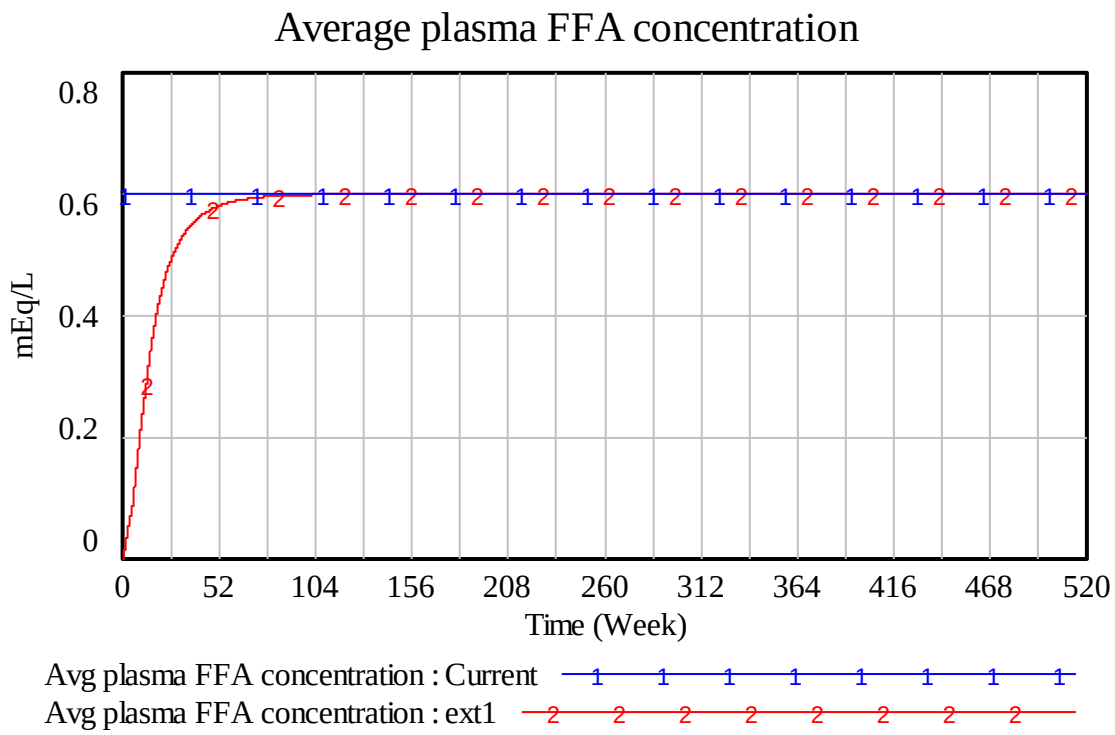

Figure 6.4. Dynamics of average plasma FFA concentration for the extreme condition test.

6.2. Body Weight Management

In the research of Anderson *et al.*, the effect of weight management for diabetic individuals on plasma glucose concentration levels is investigated. It is shown that if the individuals lose weight, plasma glucose concentrations will decrease accordingly. This research is conducted for 48 weeks in total, and the values are measured in every 6 weeks (Anderson *et al.*, 2003).

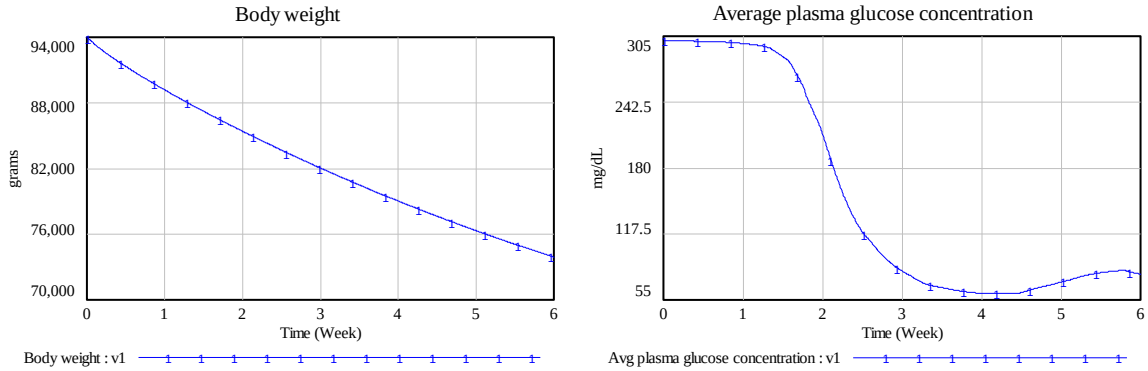

Figure 6.5. Dynamics of body weight and average plasma glucose concentration.

In the analyses, it is indicated that the individuals who are obese and diagnosed with type II diabetes, are treated in a weight management program, with a very-low-energy diets. In the practice, their energy intake is between 800-1200 kcal/day. At t=0, their average body weight is about 93.8 kg, and baseline fasting plasma glucose value is 15.9 mmol/L (286.2 mg/dL). Therefore, the dynamic behaviours are obtained, which is shown in Figure 6.1., according to the information in the study.

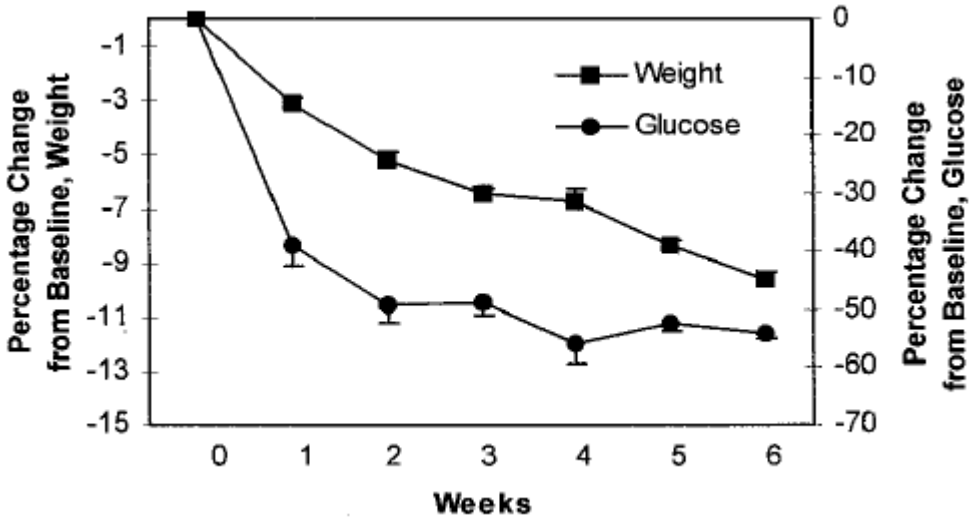

Figure 6.6. Effects of weight loss on plasma glucose concentration values of obese patients with type II diabetes (Anderson *et al.*, 2003).

Since the other factors, such as physical activity level, age, percentage of lean mass, are not totally clarified in the study, the changes in body weight and plasma glucose concentration values are not totally matched by the value, but the sudden decrease is observed in plasma glucose concentration during the first 6 weeks, and there is a small decrease in body weight, observed in the model result.

7. SCENARIO ANALYSIS

In this chapter, an average man who has prevalence of diabetes will be tested. As it is discussed previously, genetic factors for this disease are ignored in the model. With respect to genetic factors, there is a possibility that some people may not develop this disorder, because of no dysfunctionality in beta-cells, even he becomes obese. Therefore, it is assumed that if the individual we consider in this study already developed insulin resistance and type II diabetes, eventually, and it is likely to decrease the resistance by exercising and diet. The simulation starts with a 30-year-old adult, healthy male in both scenarios. In the other experiment, the simulation starts with an adult, who is an insulin-resistant man, and tested whether the insulin resistance disappears or not, by the treatment.

7.1. Effect of Diet and Exercise on Obesity and Insulin Resistance

The first scenario tests the effects of diet and exercise on obesity and the development of insulin resistance and type II diabetes. Thus, several variables are taken into consideration for this experiment: food intake, physical activity level, body weight and body mass index (from the body weight sector), average plasma glucose, FFA and insulin concentrations, and HOMA-IR index (from the glucose-insulin regulation sector).

In the Da Qing Study, if these interventions (diet and exercise) are applied to the patients who are diagnosed type II diabetes, the incidence of diabetes significantly decreases according to the results obtained in 6-years study (Pan *et al.*, 1997). Since there were differences between the values, such as glucose concentrations, age and BMI, of the patients in the study, a general case will be applied in the scenario.

Firstly, an individual is assumed to be sedentary, and have a high level of BMI, who is also getting high amount of energy from nutrients. Therefore, at t = 0, food intake is assumed to be 25000 kcal/week, PA factor is 0.6, and body weight is 95000 grams, which results his BMI is about 30.3 kg/m^2.

With regard to this classification, in this scenario, the individual is assumed to be class-I obese (see Table 5.1).

In order to show the effects of diet and exercise, PA factor will be increased at every 52 week, according to the different levels of physical activity as it is discussed in Section 4.1.1. Besides, food intake will be decreased 500 kcal at every 52 week, and the simulation will be conducted for a time horizon of 520 weeks.

Therefore, according to the assumptions, the dynamic behavior of body weight is obtained as shown in Figure 7.1.

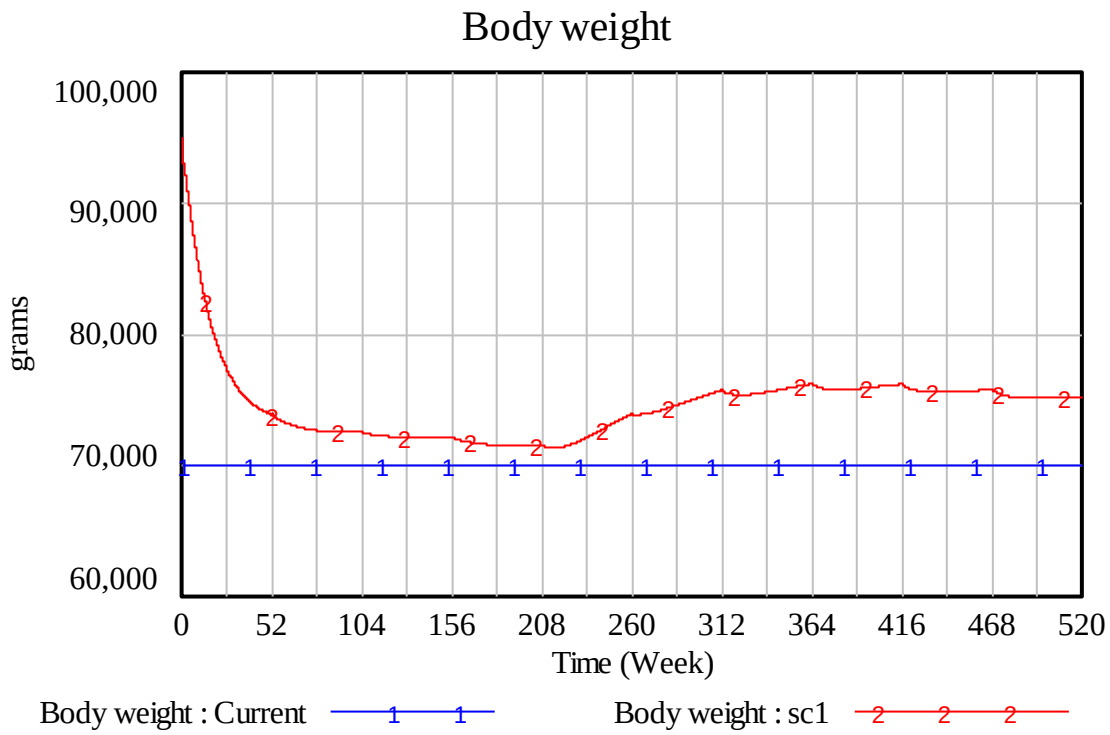

Figure 7.1. Dynamics of body weight according to the first scenario.

According to the interventions which are mentioned above, body weight decreases because of doing more physical activity, and the decrease in food intake. However, since the amount of food intake is higher than the protein balance, body starts to synthesize muscle proteins, and consequently, muscle mass increases. Therefore, in a longer term, body weight starts to increase gradually. With respect to the changes in the body weight, a similar behavior can be observed in BMI, which is shown in Figure 7.2.

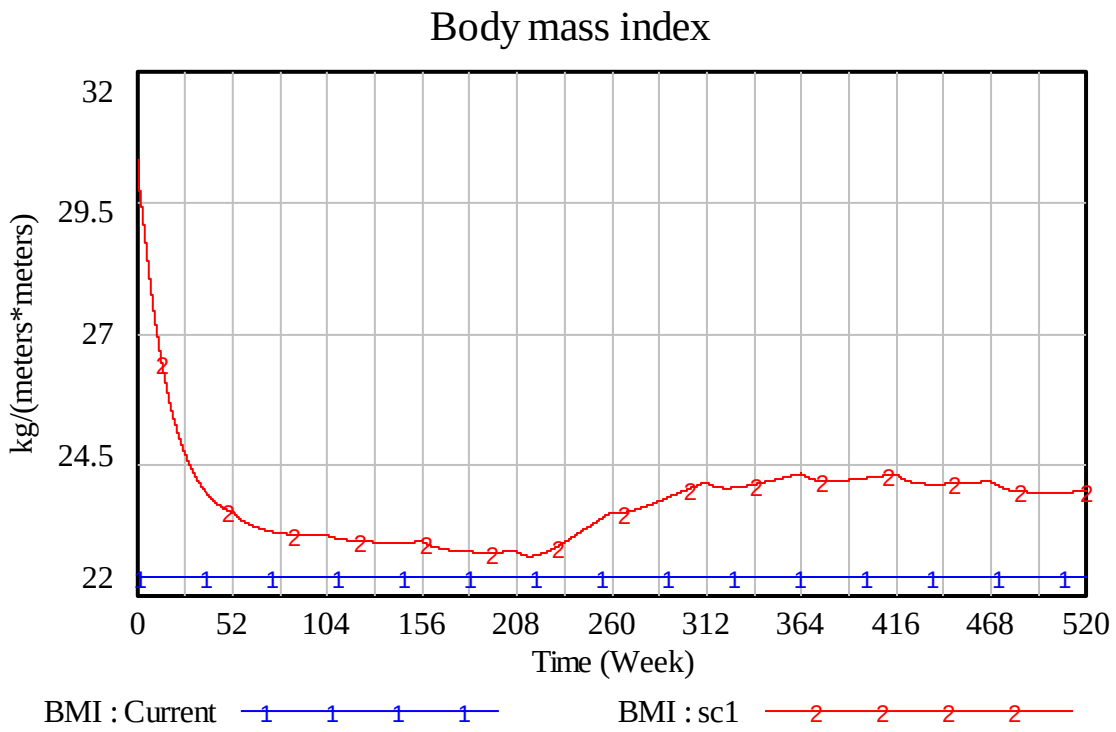

Figure 7.2. Dynamics of body mass index (BMI) according to the scenario.

Besides, the dynamic behaviors of average plasma glucose, FFA and insulin concentrations are shown in Figure 7.3, 7.4 and 7.5, respectively. As it can be observed from Figure 7.3, at the beginning of the simulation, plasma glucose concentration is above the normal range, even at a critical value. However, with the effects of both decreasing food intake and increasing muscular activity, this level reaches equilibrium at a point which is approximately 70 mg/dL.

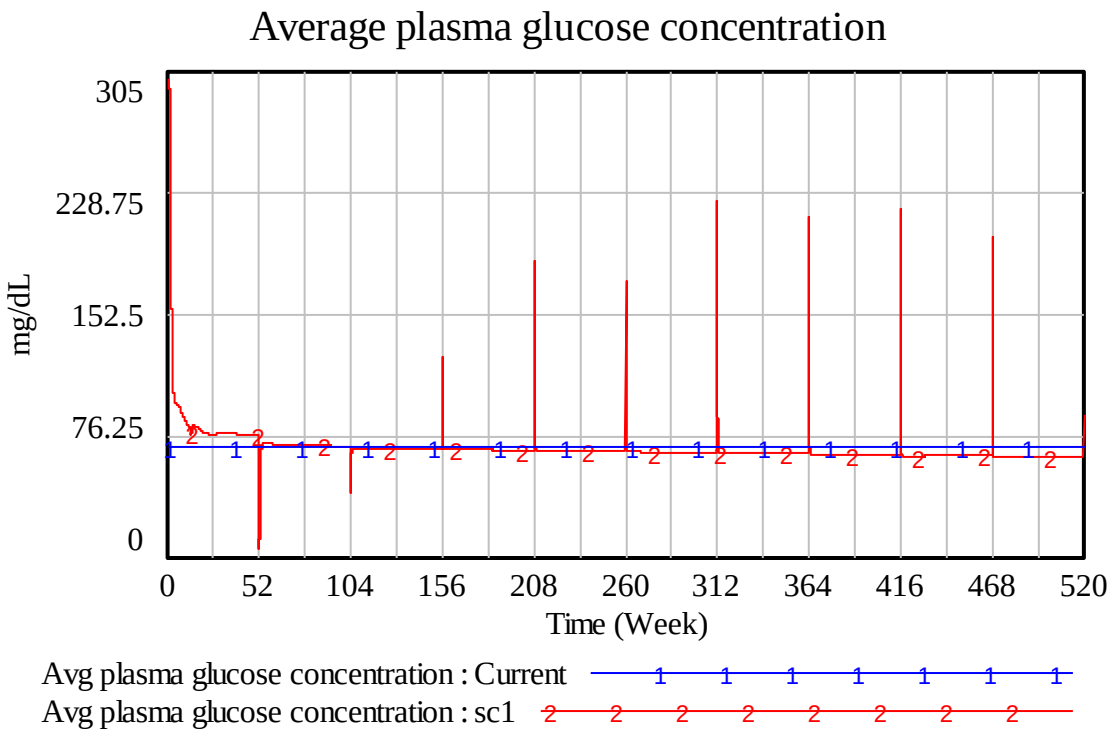

Figure 7.3. Dynamics of plasma glucose concentration according to the scenario.

Since plasma glucose concentration decreases in the long term, FFA concentration will also decrease according to this level. However, with respect to the rise in physical activity, the glucose level will not be sufficient in order to provide necessary glucose uptake for the muscles. Therefore, FFA concentration increases in blood to be used in giving energy to the muscles, as a substitution of glucose.

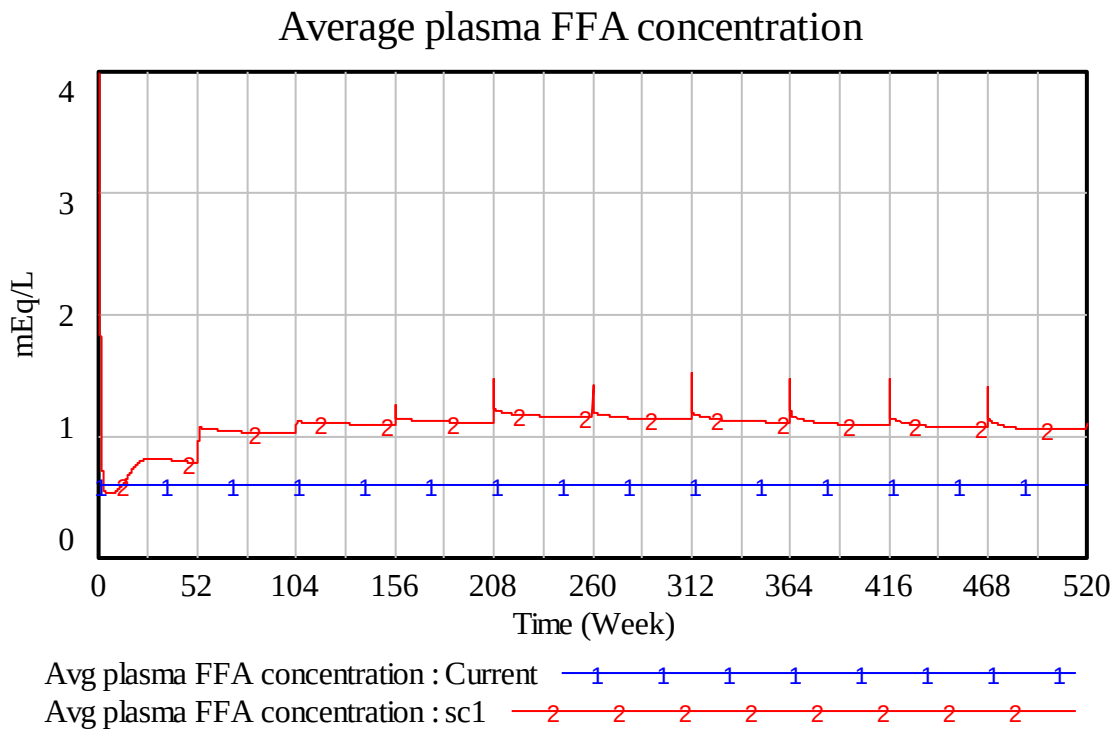

Figure 7.4. Dynamics of plasma FFA concentration according to the scenario.

With respect to the changes in glucose concentration in blood, insulin hormone will be secreted in order to regulate the metabolism. Therefore, as it is observed in Figure 7.5, insulin concentration is above the normal range, similar to the glucose and FFA concentrations at the beginning, and then this level decreases according to the effects of physical activity and diet levels.

Besides, the change in HOMA-IR index is also shown in Figure 7.6. As it is discussed in the literature survey, if the limit for this index is 2.7, which shows that the individual develops insulin resistance. According to the dynamic behavior of HOMA-IR index, one can observe that insulin resistance can disappear with the effects of physical activity and decrease in food intake level.

In the Da Qing Study, these levels are not shown in details, but it is declared that the incidence of diabetes decreases by the help of doing more physical activity and changing the diet (Pan *et al.*, 1997).

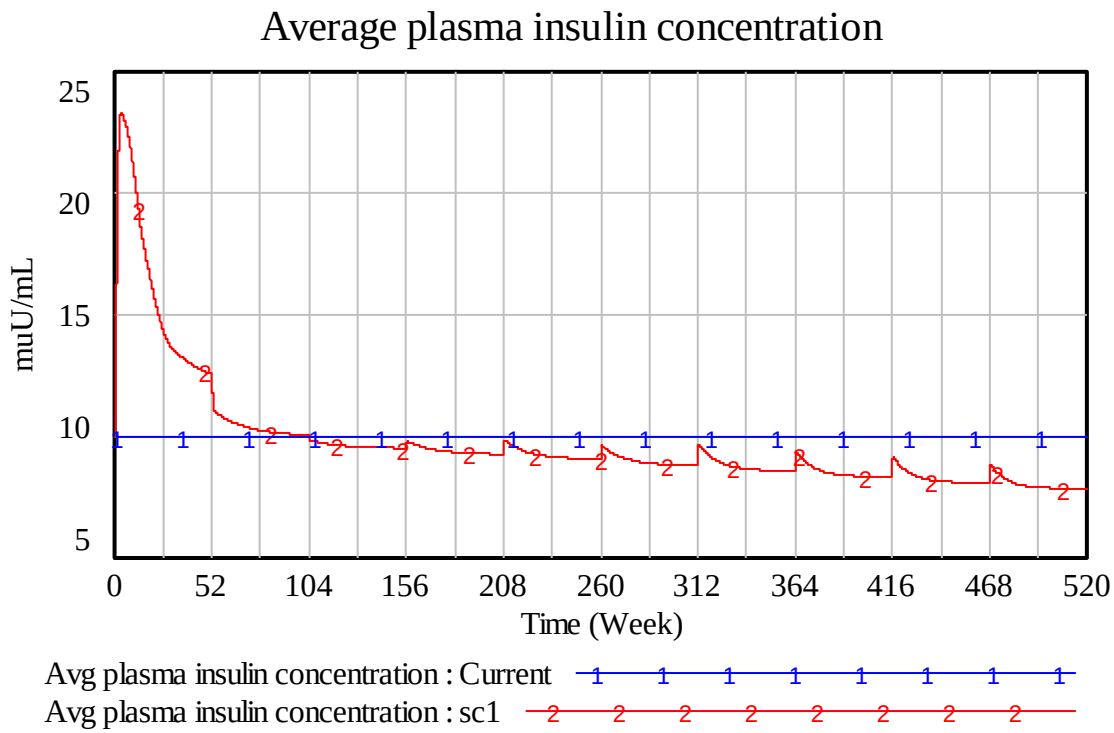

Figure 7.5. Dynamics of plasma insulin concentration according to the scenario.

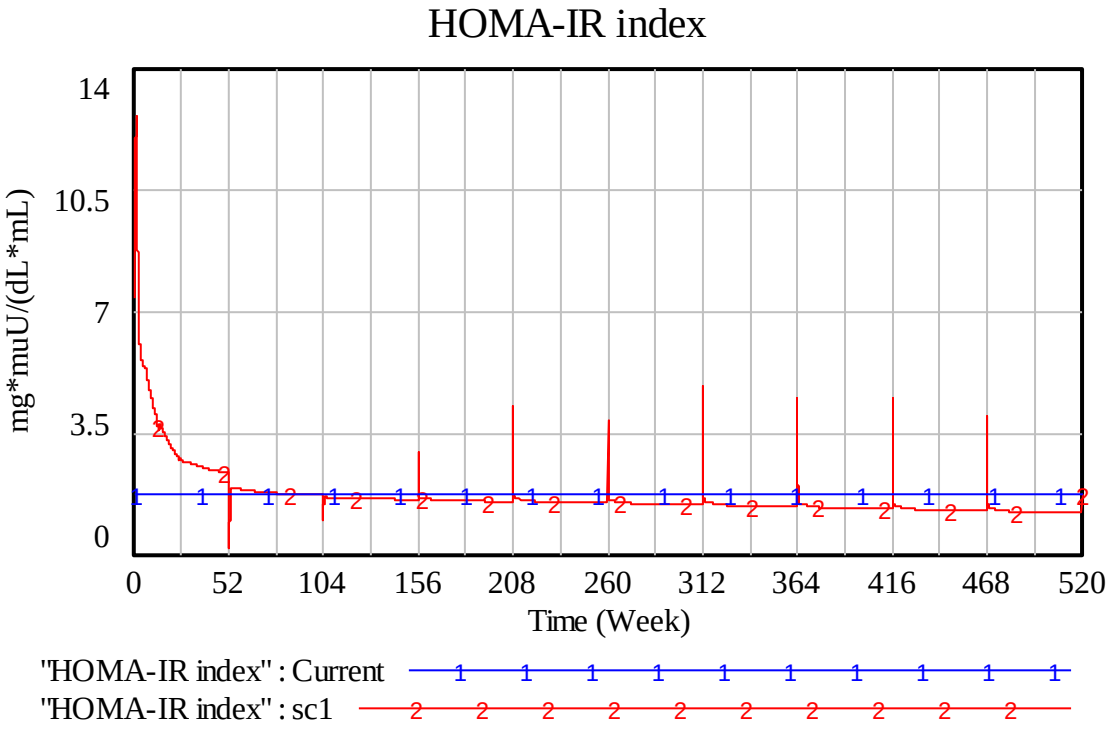

Figure 7.6. Dynamics of HOMA-IR index according to the first scenario.

8. CONCLUSION AND FUTURE RESEARCH

Obesity is shown one of the leading causes for insulin resistance and type II diabetes. In this study, the problem we considered is the dynamics of developing insulin resistance and type II diabetes, ultimately, assuming that a person has prevalence for obesity. In order to show that, a dynamic model which includes both body weight metabolism and glucose-insulin metabolism are constructed for an average man. In body weight metabolism, energy-yielding macronutrients, main body weight stocks and effect of physical activity are indicated in order to show the balance between energy intake and expenditure. In glucose-insulin regulation metabolism, only the main variables and the relationships between them in the system are shown, since the model is constructed for the long term.

The aim of the study is to construct a long term dynamic model which demonstrates the dynamics of developing insulin resistance and type II diabetes which specifically focuses on obesity. Therefore, different experiments which test the effects of aging, changes in diet and different physical activity levels are conducted in this study. Furthermore, these effects on insulin-glucose metabolism are also shown in the simulation runs.

In the equilibrium runs, the dynamics of the regulation in glucose-insulin metabolism by considering body weight components of an average man in the equilibrium state are shown. In the validation analysis of the model, two different cases related with type II diabetic patients are conducted. In the scenario analyses, typical interventions which make the insulin resistance and type II diabetes to disappear, by decreasing glucose and insulin concentrations, and keeping them in the normal ranges. These interventions include the effect of diet management and doing physical activity.

As it is discussed in the Literature Review chapter, type 2 diabetes may induce numerous physiological disorders in the body, such as kidney failure, atherosclerosis, and other cardiovascular problems. However, detailed analyses and the consequences related

with that topic are not demonstrated in this study. Thus, modeling of physiological disorders related with type II diabetes can be a further research topic.

On the other hand, the model is demonstrated only for 10 years (520 weeks), which can be considered as a sufficient time for determining insulin resistance, but not a very long time for developing type II diabetes. In order to show the results for developing type II diabetes, a dynamic model which includes other factors that affect developing type II diabetes by conducting the simulation for a long time (30-50 years) can be demonstrated as a further research.

Furthermore, all of the values of the parameters in the model are set according to the reference values of an average male individual in the literature. In order to make experiments for another individual who is not in the average, the parameters should be changed manually for that specific person. Therefore, constructing a dynamic model of developing insulin resistance and type II diabetes which allows automatic changes according to the specific values for any type of individual can also be a further research topic.

APPENDIX A: LIST OF EQUATIONS

All of the variables used in the model are listed below:

Stocks:

Carbohydrate= INTEG (CHO intake-CHO breakdown, 500)
Units: grams

"Delayed eff of beta-cell func on insulin sec"= INTEG (Adj 3, 1)
Units: Dmnl

Delayed eff of glucose conc on insulin sec = INTEG (Adj 5, 1)
Units: Dmnl

"Delayed eff of insulin sec on beta-cell func"= INTEG (Adj 4, 1)
Units: Dmnl

Delayed eff of PA on extra muscle synthesis = INTEG (Adj 2, 1)
Units: Dmnl

Delayed eff of PA on normal muscle synthesis = INTEG (Adj 1, 1)
Units: Dmnl

Fat= INTEG (Fat synthesis-Fat breakdown, 12500)
Units: grams

Muscle= INTEG (Muscle protein synthesis-Muscle protein degradation, 31500)
Units: grams

Flows:

Adj 1 = (Effect of PA on normal muscle synthesis-Delayed eff of PA on normal muscle synthesis)/Del time for adj 1
Units: Dmnl/Week

Adj 2 = (Effect of PA on extra muscle synthesis – Delayed eff of PA on extra muscle synthesis)/Del time for adj 2
Units: Dmnl/Week

Adj 3 = ("Effect of beta-cell func on insulin sec" – "Delayed eff of beta-cell func on insulin sec")/Del time for adj 3
Units: Dmnl/Week

Adj 4 = ("Effect of insulin sec on beta-cell func" – "Delayed eff of insulin sec on beta-cell func")/Del time for adj 4
Units: Dmnl/Week

Adj 5 = (Effect of glucose conc on insulin sec – Delayed eff of glucose conc on insulin sec)/Del time for adj 5
Units: Dmnl/Week

CHO intake = Carbohydrate intake * Glucose transport
Units: grams/Week

CHO breakdown = Carbohydrate*CHO coeff
Units: grams/Week

Fat synthesis = (Effect of energy balance on synthesis*Normal fat synthesis)+IF THEN ELSE(CHO breakdown>3750, CHO breakdown-3750, 0)
Units: grams/Week

Fat breakdown = (Fat*Fbd fraction)*Effect of energy balance on breakdown
Units: grams/Week

Muscle protein synthesis = Normal synthesis + Extra synthesis
Units: grams/Week

Muscle protein degradation = Mpd coeff*Muscle
Units: grams/Week

Auxiliary variables:

Age = 30 + (Time/"years-to-week")
Units: year

Age coeff of ree = 6.8*7
Units: kcal/Week/year

Age comp of ree = Age*Age coeff of ree
Units: kcal/Week

Avg plasma FFA concentration = Effect of lipolysis on avg plasma FFA conc*Normal plasma FFA conc
Units: mEq/L

Avg plasma glucose concentration = Lower limit of normal blood glucose conc*Effect of glucose transport rate on plasma glucose conc
Units: mg/dL

Avg plasma insulin concentration = Basal plasma insulin concentration*Effect of insulin sec on plasma insulin conc
Units: muU/mL

Basal lipolysis = 980
Units: grams/Week

Basal plasma insulin concentration = 12
Units: muU/mL

"Beta-cell functionality" = "Delayed eff of insulin sec on beta-cell func"*"Max beta-cell func"
Units: Dmnl

BMI = Body weight in kg/(Height*Height)
Units: kg/(meters*meters)

```
Body weight = Fat free mass + Fat mass
Units: grams

Body weight in kg = Body weight*"Grams-to-kg"
Units: kg

Bone mass = 70000*0.15
Units: grams

bw coeff of ree = 13.7*7
Units: kcal/Week/kg

bw comp of ree = Body weight in kg*bw coeff of ree
Units: kcal/Week

Carbohydrate intake = (Food intake*0.45/CHO in kcal)
Units: grams/Week

CHO coeff = 4.39
Units: 1/Week

CHO in kcal = 4.1
Units: kcal/grams

Del time for adj 1 = 6
Units: Week

Del time for adj 2 = 12
Units: Week

Del time for adj 3 = 12
Units: Week

Del time for adj 4 = 15
Units: Week
```

Del time for adj 5 = 10
Units: Week

ECW = 15000
Units: grams

Effect of age on PA capacity = LOOKUP EXTRAPOLATE(Graph func for eff of age on PA capacity, Normalized age)
Units: Dmnl

"Effect of beta-cell func on insulin sec" = LOOKUP EXTRAPOLATE("Graph func for eff of beta-cell func on insulin sec", "Beta-cell functionality"/"Max beta-cell func")
Units: Dmnl

Effect of bw on PA capacity = LOOKUP EXTRAPOLATE(Graph func for eff of bw on PA capacity, Normalized bw)
Units: Dmnl

Effect of energy balance on breakdown = LOOKUP EXTRAPOLATE(Graph func for eff of energy balance on fat breakdown, Normalized energy balance)
Units: Dmnl

Effect of energy balance on synthesis = LOOKUP EXTRAPOLATE(Graph func for eff of energy balance on fat synthesis, Normalized energy balance)
Units: Dmnl

Effect of fat breakdown on lipolysis = LOOKUP EXTRAPOLATE(Graph func for eff of fbd on lipolysis, Normalized fbd)
Units: Dmnl

Effect of glucose conc on insulin sec = LOOKUP EXTRAPOLATE(Graph func for eff of glucose conc on insulin sec, (Avg plasma glucose concentration/Lower limit of normal blood glucose conc))
Units: Dmnl

Effect of glucose transport rate on plasma glucose conc = LOOKUP EXTRAPOLATE (Graph func for eff of glucose transport rate on plasma glucose conc, (Glucose transport rate/Normal glucose transport rate))
Units: Dmnl

"Effect of insulin sec on beta-cell func" = LOOKUP EXTRAPOLATE("Graph func for eff of insulin sec on beta-cell func", (Insulin secretion/Normal insulin secretion))
Units: Dmnl

Effect of insulin sec on plasma insulin conc = LOOKUP EXTRAPOLATE(Graph func for eff of insulin sec on plasma insulin conc, (Insulin secretion/Normal insulin secretion))
Units: Dmnl

Effect of lipolysis on avg plasma FFA conc = LOOKUP EXTRAPOLATE(Graph func for eff of lipolysis on plasma FFA conc, (Lipolysis rate/Basal lipolysis))
Units: Dmnl

Effect of PA on extra muscle synthesis = LOOKUP EXTRAPOLATE(Graph func for eff of PA on extra muscle synthesis, Normalized physical activity)
Units: Dmnl

Effect of PA on extra protein = LOOKUP EXTRAPOLATE(Graph func for eff of PA on extra protein, Normalized physical activity)
Units: Dmnl

Effect of PA on normal muscle synthesis = LOOKUP EXTRAPOLATE(Graph func for eff of PA on normal muscle synthesis, Normalized physical activity)
Units: Dmnl

Effect of physical activity on glucose transport rate = LOOKUP EXTRAPOLATE(Graph func for eff of PA on glucose transport rate, Normalized physical activity)
Units: Dmnl

Effect of physical activity on tee = LOOKUP EXTRAPOLATE(Graph func for eff of PA on tee, Normalized physical activity)
Units: Dmnl

Effect of plasma insulin conc on glucose transport rate = LOOKUP EXTRAPOLATE(Graph func for eff of plasma insulin conc on glucose transport rate, (Avg plasma insulin concentration/Basal plasma insulin concentration))
Units: Dmnl

Effect of plasma insulin conc on lipolysis = LOOKUP EXTRAPOLATE(Graph func for eff of plasma insulin conc on lipolysis, (Avg plasma insulin concentration/Basal plasma insulin concentration))
Units: Dmnl

Effect on plasma FFA conc on glucose transport rate = LOOKUP EXTRAPOLATE(Graph func for eff of plasma FFA conc on glucose transport rate, (Avg plasma FFA concentration/Normal plasma FFA conc))
Units: Dmnl

Energy balance = Energy intake-Energy expenditure
Units: kcal/Week

Energy balance in grams = Energy balance*"Kcal-to-grams"
Units: grams/Week

Energy expenditure = Resting energy expenditure + Thermic effect of food + Thermic effect of exercise
Units: kcal/Week

Energy intake = (Fat in kcal*Fat intake) + (CHO in kcal*Carbohydrate intake)
Units: kcal/Week

Essential protein = Body weight*Essential protein coeff/1000
Units: grams/Week

Essential protein coeff = 0.8*7
Units: 1/Week

Excess protein = MAX (Protein level-Normal protein-Extra protein, 0)
Units: grams/Week

Extra protein = IF THEN ELSE (Protein level - Normal protein > Protein limit, Protein limit, Protein level-Normal protein)*Effect of PA on extra protein
Units: grams/Week

Extra synthesis = Extra protein*Delayed eff of PA on extra muscle synthesis
Units: grams/Week

Fat free mass = ECW + Bone mass + Muscle + Carbohydrate
Units: grams

Fat in kcal = 9.3
Units: kcal/grams

Fat intake = (Food intake*0.35/Fat in kcal)
Units: grams/Week

Fat mass = Fat
Units: grams

Fbd fraction = 752.68/12500
Units: 1/Week

FINAL TIME = 520
Units: Week
The final time for the simulation.

Food intake = 20000
Units: kcal/Week

Glucose transport rate = Effect on plasma FFA conc on glucose transport rate*Effect of physical activity on glucose transport rate*Normal glucose transport rate
Units: Dmnl

"Grams-to-kg" = 1/1000
Units: kg/grams

Graph func for eff of age on PA capacity([(1,0.6)-(2.7,1)],(1,1),(1.205,0.995),(1.38991,0.99),(1.58226,0.98),(1.75,0.963),(1.96697,0.931579),(2.16453,0.889474),(2.32049,0.835088),(2.48685,0.757895),(2.61162,0.677193),(2.7,0.6))
Units: Dmnl

"Graph func for eff of beta-cell func on insulin sec"([(0,0)-(1,1)],(0,0),(0.116208,0.0131579),(0.232416,0.0438596),(0.357798,0.0833333),(0.486239,0.140351),(0.599388,0.223684),(0.706422,0.346491),(0.804281,0.504386),(0.883792,0.671053),(0.95107,0.837719),(1,1))
Units: Dmnl

Graph func for eff of bw on PA capacity([(1,0.545)-(1.3,1)],(1,1),(1.03394,0.996009),(1.06055,0.988026),(1.08624,0.96807),(1.10917,0.932149),(1.12844,0.858311),(1.14771,0.778487),(1.16697,0.706645),(1.18991,0.642785),(1.21835,0.592895),(1.25413,0.554978),(1.3,0.545))
Units: Dmnl

Graph func for eff of energy balance on fat breakdown([(0,0)-(2,2)],(0,2),(0.269113,1.97368),(0.489297,1.89474),(0.66055,1.74561),(0.819572,1.51754),(0.929664,1.24561), (1,1),(1.5,1),(2,1))
Units: Dmnl

Graph func for eff of energy balance on fat synthesis([(0,0)-(2,2)],(0,1),(1,1),(1.08869,
1.31579),(1.24159,1.57018),(1.3945,1.77193),(1.55963,1.89474),(1.737,1.95614),(2,2))
Units: Dmnl

Graph func for eff of fbd on lipolysis([(0,0)-(4,3.1)],(0,0),(0.366972,0.326316),(0.672783,
0.652632),(1,1),(1.34557,1.42763),(1.71254,1.88991),(2.07951,2.35219),(2.37309,2.65132),(2.72783,2.86886),(3.08257,3.01842),(3.5107,3.05921),(4,3.1))
Units: Dmnl

Graph func for eff of glucose conc on insulin sec([(0,0)-(4.29,5)],(0,0),(0.367339,
0.153509),(0.682202,0.504386),(1,1),(1.39064,1.75439),(1.73174,2.5),(2.04661,3.22368),(2.40083,3.90351),(2.82064,4.42982),(3.29294,4.75877),(3.80459,4.91228),(4.29,5))
Units: Dmnl

Graph func for eff of glucose transport rate on plasma glucose conc([(0,0)-(1.8,4.29)],
(0,4.29),(0.247706,4.19592),(0.412844,4.04539),(0.550459,3.68789),(0.666055,3.12342),(0.770642,2.42724),(0.880734,1.69342),(1,1),(1.10092,0.639737),(1.22202,0.338684),(1.38165,0.131711),(1.57431,0.0564474),(1.8,0))
Units: Dmnl

"Graph func for eff of insulin sec on beta-cell func"([(0,0.25)-(5,1)],(0,1),(1,1),(1.48318,
0.983553),(1.85015,0.953947),(2.15596,0.881579),(2.43119,0.776316)

,(2.66055,0.671053),(2.99694,0.539474),(3.40979,0.407895),(3.85321,0.309211),(4.34251,0.266447),(5,0.25))
Units: Dmnl

Graph func for eff of insulin sec on plasma insulin conc([(0,0)-(5,5)],(0,0),(0.336391,
0.175439),(0.672783,0.526316),(1,1),(1.46789,1.71053),(1.95719,2.5),(2.35474,3.20175),(2.81346,3.94737),(3.25688,4.47368),(3.77676,4.80263),(4.40367,4.93421),(5,5))
Units: Dmnl

Graph func for eff of lipolysis on plasma FFA conc([(0,0)-(3.1,6.67)],(0,0),(0.379205,0.146272),(0.692049,0.46807),(1,1),(1.2893,1.69675),(1.5263,2.60364),(1.73486,3.71531),(1.9055,4.6807),(2.07615,5.52908),(2.28471,6.20193),(2.55963,6.49447),(2.85352,6.61149),(3.1,6.67))
Units: Dmnl

Graph func for eff of PA on extra muscle synthesis([(0.6,0)-(4.5,0.5)],(0.6,0),(1,0),(1.55413,0.0175439),(2.09083,0.0482456),(2.55596,0.0811404),(2.96147,0.129386),(3.29541,0.186404),(3.54587,0.256579),(3.7367,0.33114),(3.89174,0.399123),(4.04679,0.458333),(4.26147,0.489035),(4.5,0.5)
Units: Dmnl

Graph func for eff of PA on extra protein[(0.6,0)-(4.5,0.5)],(0.6,0),(1,0),(1.55413,0.0175439),(2.09083,0.0482456),(2.55596,0.0811404),(2.96147,0.129386),(3.29541,0.186404),(3.54587,0.256579),(3.7367,0.33114),(3.89174,0.399123),(4.04679,0.458333),(4.26147,0.489035),(4.5,0.5)
Units: Dmnl

Graph func for eff of PA on glucose transport rate([(0,0)-(2.7,1.8)],(0,0),(0.222936,0.228947),(0.462385,0.473684),(0.710092,0.726316),(1,1),(1.29633,1.27105),(1.65963,1.52368),(1.98165,1.68947),(2.3367,1.76053),(2.7,1.8))
Units: Dmnl

Graph func for eff of PA on normal muscle synthesis([(0,0)-(2.7,1)],(0,0),(0.181651,0.0131579),(0.429358,0.0789474),(0.594495,0.184211),(0.734862,0.350877),(0.833945,0.557018),(0.916514,0.754386),(1,1),(1.33761,1),(2.02294,1),(2.7,1))
Units: Dmnl

Graph func for eff of PA on tee([(0,0)-(1,1)],(0,0),(0.107034,0.153509),(0.211009,0.324561),(0.318043,0.508772),(0.428135,0.679825),(0.562691,0.872807),(0.703364,0.960526),(0.862385,0.991228),(1,1))
Units: Dmnl

Graph func for eff of plasma FFA conc on glucose transport rate([(0,0)-(6.67,1.8)],(0,1.8),(0.244771,1.53158),(0.591529,1.26316),(1,1),(1.48902,0.757895),(1.99896,0.513158),(2.65168,0.331579),(3.3044,0.205263),(4.07951,0.126316),(4.87502,0.0710526),(5.79291,0.0236842),(6.67,0))
Units: Dmnl

Graph func for eff of plasma insulin conc on glucose transport rate[(0,0)-(5,1.8)],(0,0),(0.244648,0.260526),(0.489297,0.505263),(0.703364,0.73421),(1,1),(1.37615,1.24737),(1.85015,1.43684),(2.4159,1.57105),(3.02752,1.67368),(3.70031,1.73684),(4.37309,1.76842),(5,1.8))
Units: Dmnl

Graph func for eff of plasma insulin conc on lipolysis([(0,0)-(5,3.1)],(0,3.1),(0.142,2.52),(0.338,1.97),(0.611621,1.48202),(1,1),(1.39144,0.652632),(1.88073,0.435088),(2.47706,0.299123),(3.04281,0.203947),(3.63914,0.122368),(4.26606,0.054386),(5,0))
Units: Dmnl

Height = 1.77
Units: meters

Height coeff of ree = 35
Units: kcal/Week/cm

Height comp of ree = Height coeff of ree*Height in cm
Units: kcal/Week

Height in cm = Height*"m-to-cm"
Units: cm

"HOMA-IR index" = Avg plasma glucose concentration*(Avg plasma insulin concentration/18)/22.5
Units: (mg*muU)/(dL*mL)

INITIAL TIME = 0
Units: Week
The initial time for the simulation.

Insulin secretion = "Delayed eff of beta-cell func on insulin sec"*Delayed eff of glucose conc on insulin sec*Normal insulin secretion
Units: units/Week

"Kcal-to-grams" = 1/7.7
Units: grams/kcal

Lipolysis rate = Effect of fat breakdown on lipolysis*Effect of plasma insulin conc on lipolysis*Basal lipolysis
Units: grams/Week

Lower limit of normal blood glucose conc = 70
Units: mg/dL

"m-to-cm" = 100
Units: cm/meters

"Max beta-cell func" = 1
Units: Dmnl

Mpd coeff=220.5/31500
Units: 1/Week

Normal age = 30
Units: year

Normal bw = 70000
Units: grams

Normal fat synthesis = Fat intake
Units: grams/Week

Normal fbd = 752.68
Units: grams/Week

Normal glucose transport rate = 1
Units: Dmnl

Normal insulin secretion = 245
Units: units/Week

Normal PA capacity = 4130
Units: kcal/Week

Normal physical activity = 2478
Units: kcal/Week

Normal plasma FFA conc = 0.6
Units: mEq/L

Normal protein = IF THEN ELSE(Protein level > Protein balance, Protein balance, Protein level)
Units: grams/Week

Normal synthesis = Delayed eff of PA on normal muscle synthesis*Normal protein
Units: grams/Week

Normal tee = 2458
Units: kcal/Week

Normalized age = Age/Normal age
Units: Dmnl

Normalized bw = Body weight/Normal bw
Units: Dmnl

Normalized energy balance = (Energy intake/Energy expenditure)
Units: Dmnl

Normalized fbd = Fat breakdown/Normal fbd
Units: Dmnl

Normalized physical activity = Physical activity level/Normal physical activity
Units: Dmnl

PA factor = 0.6
Units: Dmnl

Physical activity capacity = Effect of age on PA capacity*Effect of bw on PA capacity * Normal PA capacity
Units: kcal/Week

Physical activity level = PA factor*Physical activity capacity
Units: kcal/Week

Protein balance = 0.45*7*70
Units: grams/Week

Protein in kcal = 4.35
Units: kcal/grams

Protein intake = (0.2*Food intake/Protein in kcal)
Units: grams/Week

Protein level = MAX (Protein intake-Essential protein, 0)
Units: grams/Week

Protein limit = 150
Units: grams/Week

Resting energy expenditure = (66*7) + bw comp of ree + Height comp of ree – Age comp of ree
Units: kcal/Week

SAVEPER = TIME STEP
Units: Week [0,?]
The frequency with which output is stored.

Thermic effect of exercise = Normal tee*Effect of physical activity on tee
Units: kcal/Week

Thermic effect of food = Energy intake*0.1
Units: kcal/Week

TIME STEP = 0.0078125
Units: Week [0,?]
The time step for the simulation.

"years-to-week" = 52
Units: Week/year

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