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## CHAPTER 7

## HUMAN ENERGY SYSTEM SIMULATION

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*In order for a simulation model to represent the complex processes of the human energy system shown in Chapter 6, a vast amount of resources are required. This is however impractical. Therefore, a simplified model for predicting glycaemic response is presented in this chapter. The discussion is divided into two parts. The first is the design of the component models used for simulations of internal processes and the second is the strategies implemented for the control system of the entire simulation model.*

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## 7.1 Introduction

Due to the complexity of the human energy system, as described in the previous chapter, the need was identified to simplify the model and its approach toward simulation of the entire system. Therefore the system was divided into its major energy pathways. The first efforts went towards simulating the glucose energy pathway since it has such a tremendous and well-defined impact on society (more detail in Chapter 1). Once this attempt proves successful the other pathways will be dealt with accordingly in future studies.

From a systems point of view the glucose pathway, as described in Section 6.3, is relatively complex due to the integrated nature of the processes involved. Simplification of the subsystem was therefore essential in order to solve the system events dynamically within realistic resource constraints. However, the simplified system was still required to simulate realistic glycaemic response to an acceptable degree. The criteria for evaluation of the proposed simulation are specified in more detail in Chapter 8.

A further aspect to consider was the availability of characterisation data. Both system component parameters and control parameters had to be specified for every model component. As explained in Section 5.2, the less complex the proposed model is, the greater the availability of the data and hence, the greater the potential impact on a specific target market.

In this chapter the simplified simulation model is firstly presented schematically. Then the derivation and properties of all the model components are described. Lastly the control components responsible for energy flow regulation between the model components are discussed.

## 7.2 Integrated glucose energy flow

In order to simulate the dynamic effect of the entire glucose energy subsystem, the model was subdivided into the major energy components and energy flow pathway connections. These were all schematically linked in the required fashion to construct the final (generic) human energy system simulation model for glucose energy.

The flow of energy in the form of glucose ( $\dot{G}$ ) between the model components is shown schematically in Figure 7.1. For simplicity sake Figure 7.1 does not include the controller components and connections. These connections will be discussed in more detail in Section 7.4.

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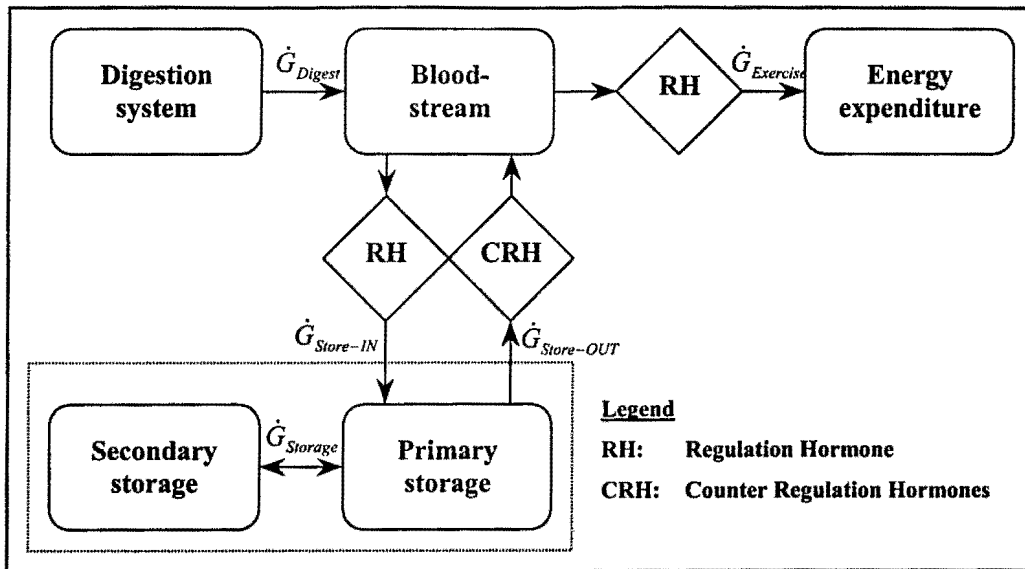


Figure 7.1 – Schematic layout of the integrated human energy simulation model

Each of the energy components (such as the digestion system, bloodstream, etc) as well as the connection lines and control components (RH and CRH) were individually modelled by using the virtual technique of object oriented programming (described in Section 5.5). A class object was created for each, incorporating all the properties and methods necessary for solving that component dynamically [1].

As can be seen from the figure, glucose flows from the digestion system into the bloodstream ( $\dot{G}_{Digest}$ ). From there it is either utilised in the energy expenditure component ( $\dot{G}_{Exercise}$ ), or it is stored in the storage component ( $\dot{G}_{Store-IN}$ ). For both these flows (to expenditure and / or storage) a regulation hormone is required. In the absence of such a hormone, the glucose will simply not be able to flow from the bloodstream and a glucose build-up in the bloodstream will be the result.

This scenario is typically the case with Type 1 diabetes mellitus. Insulin is the so-called “regulation” or “storage” hormone [2]. A Type 1 diabetic’s pancreas often does not produce any or sufficient amounts of insulin and therefore the patient experiences glucose build-up in the bloodstream. In order to control the glucose concentration in the blood the diabetic patient hence has to inject insulin externally on a regular basis [3],[4],[5]. This was described in earlier chapters in more detail.

The storage system in Figure 7.1 (blocked in dotted lines) has two major components, namely a primary and a secondary storage component. It is modelled this way to mimic the actual human

energy system which also has two main storage components, namely the liver (or short-term) and fat (or long-term) stores respectively.

Glucose is firstly stored in the primary storage unit because it can easily be stored and retrieved from there. Whenever the primary storage is “full” (the concentration is higher than preferred) it offloads the excess glucose to the secondary component that has a much larger capacity, but is more difficult and therefore slower to access. If conversely the primary storage is “empty”, glucose is slowly retrieved from the secondary storage component until the primary storage levels are replenished. (The variable used to denote the flow between the two storage components is  $\dot{G}_{Storage}$ .

If  $\dot{G}_{Storage}$  is positive the flow is towards the primary storage unit.)

The storage mode of the secondary unit is not in the form of glucose, but in fatty acids and the adipose tissue from where it is difficult to recover glucose (see Chapter 6). This is why the glucose is retrieved slowly from this component. These storage and recovery processes are described in more detail in Section 6.2.

The primary storage component on the other hand stores glucose in the form of glycogen, which is easily converted back into glucose as long as counter regulation hormones are present in the bloodstream. The primary storage component is therefore the main component responsible for blood sugar counter regulation.

In order to solve the energy balance of the flow through the entire system component model the method described in Section 5.4 was used. The consequence was that the dynamic control of blood glucose could therefore be simulated iteratively in conjunction with the individual components. The following steps in the iterative process however were to solve the flow, utilisation, storage, release and discharge of glucose to and from the individual components in Figure 7.1.

### 7.3 Component models

The following sections consist of detailed descriptions of each of the component models that were used for the integrated simulations shown in Figure 7.1. A virtual computer class object was created for each of the components [1]. The properties and methods of the classes were required to simulate the following specifications.

The component models described in this section are:

- The digestion system model;
- The bloodstream model;
- The energy expenditure model;
- The primary storage model, and;
- The secondary storage model.

### 7.3.1 Digestion system model

The methods for the digestion model object mainly consist of a few calculations to simulate the flow of glucose into the bloodstream due to consumed ets (in other words effective glucose ingested). This glucose flow ( $\dot{G}_{Digest}$ ) is dependant on a few correction factors and restrictions regarding the specific person being modelled.

The exact amount of glucose released at a specific time step ( $\dot{G}_{Digest}$ ) is however dependent on the control parameters as characterised for the specific person. For simplification sake a function was derived by which the release of glucose can be calculated as a basic function of the following parameters:

- the effective amount of ets consumed in a meal ( $ets_{Effective}$ );
- the time of day the meal was taken ( $t_{Meal}$ );
- the time elapsed after the meal was taken ( $t_{Elapsed} = t_{Current} - t_{Meal}$ );
- the total digestion time of the specific meal ( $t_{Digest}$ ).

This glucose release function can be expressed as follows

$$\dot{G}_{Digest} = f(ets_{Effective}, t_{Meal}, t_{Elapsed}, t_{Digest}). \quad (7.1)$$

The release function (Equation (7.1)) and its application will be discussed in more detail in the section concerning control of the system (Section 7.4). What is relevant for this section is that the flow of energy (in the form of glucose) from the digestion system towards the bloodstream component ( $\dot{G}_{Digest}$ ) is calculated analytically.

The amount of ets used in the analytical function is however critically dependent on a combination of both the properties of the food and the characteristics of the person. Correction factors for the various influences affecting the effective amount of ets were implemented in the methods of the component model objects. The following influences were calculated:

### Second meal effect correction

If a meal is consumed within four hours after a previous meal the digestion system model takes a correction factor called the “second meal effect” into account [6]. Physiologically it is implied that the digestion model has to incorporate the effect of a stomach that is still digesting the “difficult to ingest” portion of the previous meal. The stomach can therefore not digest and release the same amount of glucose energy as an empty stomach would be able to.

In the digestion system component model a correction factor is applied to the actual amount of ets to calculate the “effective dose” of ets that is ingested. The relationship between the actual and effective ets ingestion ( $ets_{Actual}$  and  $ets_{Effective}$  respectively) is represented by the Equation (7.2).

$$ets_{Effective} = CF_{SM} ets_{Actual} \quad (7.2)$$

The second meal correction factor ( $CF_{SM}$ ) is defined between 0 and 100 and is further dependent on two variables. These are:

- a correction factor for the elapsed time from the previous meal ( $CF_{Elapsed}$ );
- a correction factor for the glycaemic index (GI) of the previous meal ( $CF_{GI}$ ).

The first correction factor to calculate is  $CF_{Elapsed}$ . The following argument is used: if the previous meal was taken more than four hours earlier than the current one (for which the ets dose has to be

corrected), no correction of the actual ets dose ( $ets_{Actual}$ ) is necessary (i.e.  $CF_{Dose} = 0$  when  $t_{Elapsed} \geq 4$  h). If however the current meal does fall within four hours from the previous meal,  $ets_{Actual}$  can be reduced by up to 40%.

To calculate  $CF_{Elapsed}$  for  $t_{Elapsed} \leq 4$  h linear scaling from  $CF_{Elapsed} = 0.6$  to  $CF_{Elapsed} = 1.0$  is assumed. In other words, at  $t_{Elapsed} = 0$  h,  $CF_{Elapsed}$  is at maximum (which is 0.6), but at  $t_{Elapsed} \geq 4$  h,  $CF_{Elapsed}$  is assumed to be zero. This is shown graphically in Figure 7.2.

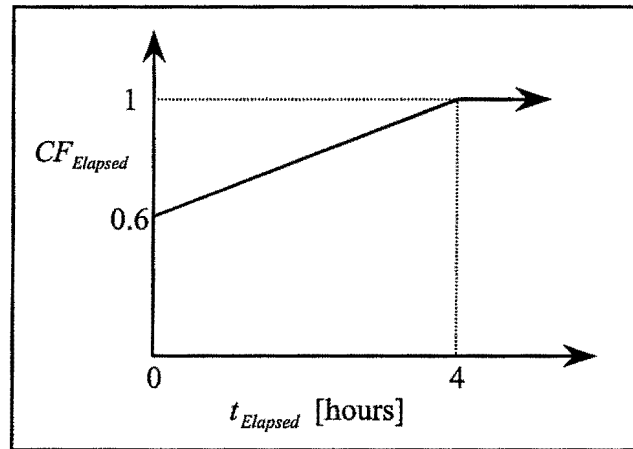


Figure 7.2 – Linear scaling for the calculation of  $CF_{Elapsed}$

Therefore, for  $t_{Elapsed}$  between 0 hours and 4 hours,  $CF_{Elapsed}$  can be calculated with:

$$CF_{Elapsed} = (0.1)t_{Elapsed} + 0.6. \quad (7.3)$$

The other correction factor required for  $CF_{SM}$  is  $CF_{GI}$ . It is the correction due to the GI of the previous meal and it is calculated in a similar manner as  $CF_{Elapsed}$ . This correction factor is necessary if the previous meal the person ingested contained high percentages of fat and / or protein. The resulting low GI (i.e. high protein and fat) food lowers the digestion efficiency by up to 40% because of the “difficult to digest” protein and fat contained in the meal.

A similar argument to the one followed for  $CF_{Elapsed}$  is used for the calculation of  $CF_{GI}$ . It is also assumed to be linear from  $CF_{GI} = 0.6$  to  $CF_{GI} = 1.0$  according to the GI of the previous meal. This calculation is presented graphically in Figure 7.3.

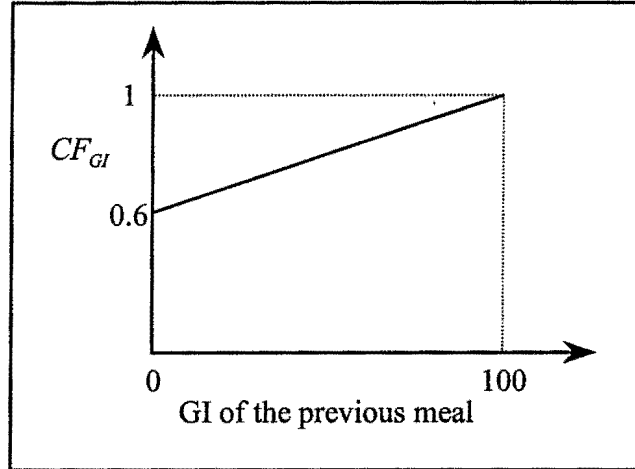


Figure 7.3 – Linear scaling for the calculation of  $CF_{GI}$

Therefore, since GI is defined between 0 and 100,  $CF_{GI}$  can be calculated with:

$$CF_{GI} = 0.1GI_{previous} + 0.6. \quad (7.4)$$

The final step in determining  $CF_{SM}$  is to combine the two correction factors,  $CF_{Elapsed}$  and  $CF_{GI}$ . The calculation is however not as straight forward as one might expect. Simple multiplication of the two variables will result in  $CF_{GI}$  having a correction effect for an undetermined time after any previous meal. The desired result is however that  $CF_{Elapsed}$  should force  $CF_{SM}$  to 1 after  $t_{Elapsed} \geq 4[h]$ . It is therefore proposed that Equation (7.5) is used for the calculation of  $CF_{SM}$ .

$$CF_{SM} = 1 - \left( \frac{1}{CF_{Elapsed}} - 1 \right) \left( \frac{1}{CF_{GI}} - \frac{2}{3} \right) \quad (7.5)$$

(This function was determined with a process of trial and error by comparing answers to a few measurements until acceptable results were obtained. Further studies are required for more accurate predictors.)

For the defined ranges of both  $CF_{Elapsed}$  and  $CF_{GI}$ ,  $CF_{SM}$  will range from 0.333 to 1. This means the unlikely maximum correction of  $CF_{SM} = 0.333$  will only occur when a person consumes the second meal directly after the first meal and the first has a GI of zero (only contains protein and fat). Figure 7.4 shows the values for  $CF_{SM}$  for the defined ranges of  $CF_{Elapsed}$  and  $CF_{GI}$ .

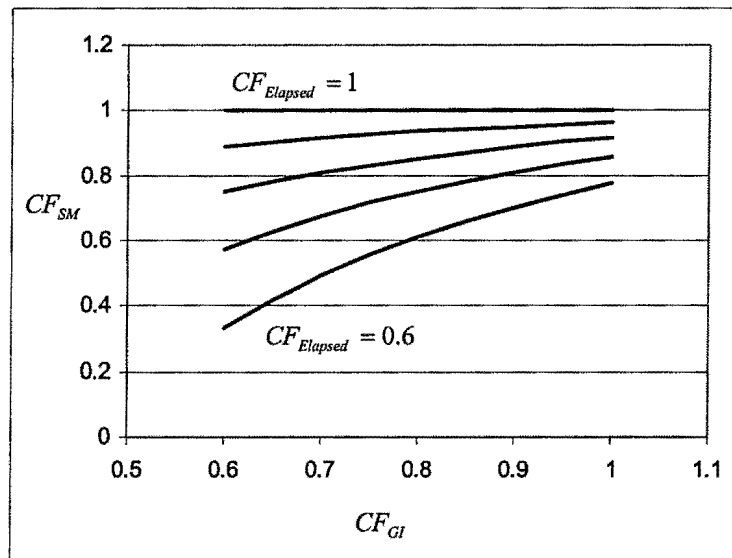


Figure 7.4 –  $CF_{SM}$  values for different values of  $CF_{Elapsed}$  and  $CF_{GI}$ .

Finally, to calculate the effective amount of ets consumed ( $ets_{Effective}$ ) after the second meal, the value of  $CF_{SM}$  should be substituted back into Equation (7.2).

### Maximum intake restriction

Some empirical measurements performed for this study have shown that the glucose energy flowing from the digestive track to the bloodstream ( $G_{Digest}$ ) is restricted to a certain maximum. Even though the person consumes more ets (i.e. increases the ets dose ( $ets_{Actual}$ ) beyond this maximum) the flow of energy in the form of glucose from the digestion system component does not increase. It

was found that there exists a maximum restriction concerning the amount of ets that can be digested.

A mathematical correlation was drawn between the maximum amount a person can digest and the person's physical properties. The result of the correlations was an empirical equation that describes the maximum ets uptake ( $ets_{Max}$ ) in terms of the person's weight ( $W$ ) and length ( $L$ ). The correlation yielded an approximate  $ets_{Max}$  for an average person according to Equation (7.6).

$$ets_{Max} = \frac{W}{2L} \quad (7.6)$$

$W$  is the person's weight measured in kg and  $L$  is the person's length measured in meters. This approximate value for  $ets_{Max}$  is used in the digestion model as a restrictor. When the person consumes more ets than  $ets_{Max}$ , the total dose used for  $ets_{Actual}$  is restricted to  $ets_{Max}$  and the flow of glucose to the bloodstream is calculated accordingly. Therefore, from the maximum intake restriction point of view, the following is always true:  $ets_{Effective} \leq ets_{Actual} \leq ets_{Max}$ .

### Uptake duration correction

Foods containing high percentages of fat and / or protein digest less efficiently and also take longer to digest than foods containing pure CHO (see Chapter 2). This is due to the complex processes involved with digestion of mixed meals [7]. For the sake of the human energy simulation this presents a problem since the model and energy flows are solved dynamically (next time step is dependent on the previous).

$t_{Digest}$  was mentioned earlier in this section. It is the variable that describes the duration of the digestion of a specific meal.  $t_{Digest}$  is required for the analytical equation that is used to calculate the specific glucose release from the digestion component model (Equation (7.1)).

Since the glycaemic index (GI) of a meal is also very sensitive to the amount of protein and fat contained in the meal, it is assumed that GI gives a good correlation to the digestion time required to fully absorb the nutrients from the meal. This assumption holds true if it can be assumed that pure

glucose is fully absorbed into the bloodstream before other carbohydrates as well as before protein and fat. For the purpose of this study both these assumptions were used.

It is interesting to note that the original definition of GI is coincidentally: “rate of absorption” [8]. This would imply that using GI does indeed provide a good correlation for digestion time ( $t_{Digest}$ ) as assumed above. However, in Section 2.3 this definition was shown to be possibly flawed.

Nevertheless, if the assumptions hold true, it then follows that the higher the GI of the meal the quicker the glucose is absorbed in the bloodstream (or the smaller the value of  $t_{Digest}$ ). From some unpublished empirical measurements it was observed that for some low GI meals the blood glucose response curves take up to 50% longer to reach their peak values than for some high GI meals with the same amount of ets.

Therefore, a linear approximation was used to determine the value of  $t_{Digest}$  for lower GI foods. If  $t_{Glucose}$  is the normal time elapsed from time of ingestion to peak blood glucose level, in response to pure glucose ingestion, then  $t_{Digest}$  can be found as a function of  $t_{Glucose}$  and GI. This relationship is presented by

$$t_{Digest} = \left( \frac{GI}{200} + 1 \right) t_{Glucose} \quad (7.7)$$

(This preliminary function was also determined with a trial and error method, using some empirical measurements and assumptions, until acceptable results were found. Further study is required for a more accurate equation.)

The GI value in Equation (7.7) is the total GI of the ingested meal and is defined as a fractional percentage, therefore between 0 and 100. The resulting values for  $t_{Digest}$  are presented graphically in Figure 7.5.

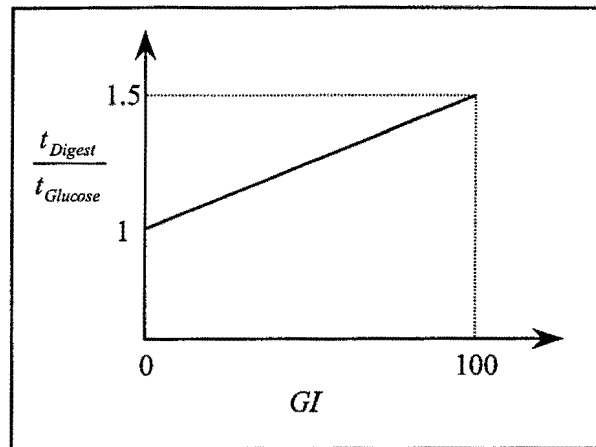


Figure 7.5 – Defined range of values for  $t_{Digest}$

Extrapolation of empirical measurements done by Holtschlag et al have shown that for many people the uptake duration of pure glucose ( $t_{Glucose}$ ) is normally approximately 15 minutes [9]. Since people rarely ingest pure glucose, the time correction factor plays a significant role in determining the amount of energy that flows from the digestion system component to the bloodstream component at any specific time step of the simulation.

### 7.3.2 Bloodstream model

Central to the human energy system simulation model (Figure 7.1) is the component that handles all the main energy flows, control connections and feedback loops. This component is the bloodstream model. The major purpose of the bloodstream model is to act as the conduit through which the energy (in the form of glucose) is channelled towards and from the other components. Flow of glucose energy is denoted with  $\dot{G}$ .

Even though it is so important, from an object-oriented point of view the bloodstream component model was one of the simpler components to develop. It is a standard linear storage tank model with two energy in-flow and two energy out-flow connections.

It also makes provision for controller feedback connections. These feedback connections are necessary for the control system to determine what the current blood glucose concentration is at any given time step ( $G_{Blood(t)}$ ). The bloodstream component is the model that contains the setpoint variable to which the main control system can then act and react. A schematic representation of the bloodstream component model is presented graphically in Figure 7.6.

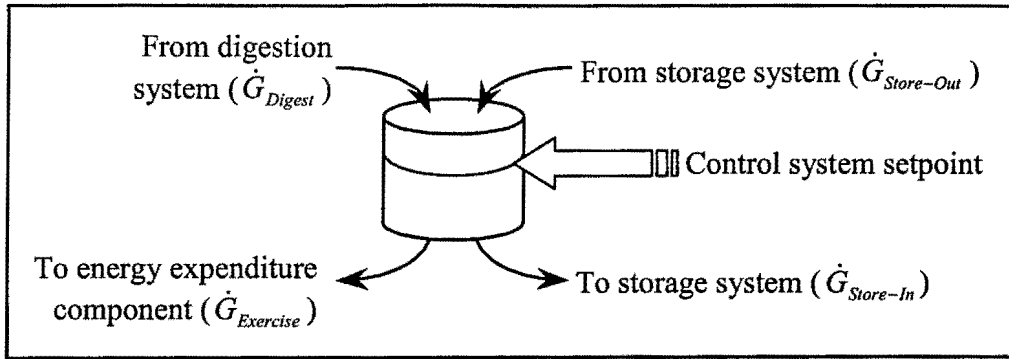


Figure 7.6 – Schematic representation of the energy flow through the linear storage tank model of the bloodstream component.

To dynamically solve the amount of blood glucose energy in the bloodstream component at any given time step ( $G_{Blood(t)}$ ), the total flow of glucose energy from the in- and out-flow connections are linearly added to the glucose amount of the previous time step ( $G_{Blood(t-1)}$ ). This calculation is done with Equation (7.8).

$$G_{Blood(t)} = G_{Blood(t-1)} + \left( \dot{G}_{Digest} + \dot{G}_{Store-Out} - \dot{G}_{Store-In} - \dot{G}_{Exercise} \right)_{(t)} \quad (7.8)$$

In the equation the connections that add glucose to the bloodstream component are denoted as positive, while the connections that subtract glucose are marked as negative. Since ets is a good quantity for measuring energy,  $G_{Blood(t)}$  is measured in ets. Similarly, ets is also used to quantify the flow of glucose energy ( $\dot{G}$ ), and therefore the unit for measuring all the flows in Equation (7.8) is the time derivative of ets, i.e. ets/time.

### Zero and minimum restrictions

The only restriction that is put on the blood glucose value in the bloodstream component ( $G_{Blood}$ ) is that it cannot be negative (less than zero blood sugar concentration). Therefore whenever Equation (7.8) yields a value for  $G_{Blood(t)}$  that is less than zero, the value is artificially reset to be zero. (i.e. if  $G_{Blood(t)} < 0$  then  $G_{Blood(t)} = 0$ .) In that case the two out-flows ( $\dot{G}_{Store-In}$  and  $\dot{G}_{Exercise}$ ) are restricted and no glucose energy flows to the components connected by those flows.

The minimum restriction is also relevant for all the energy flow variables individually. If any of the flow rates at any time step are calculated to be negative, the flow of the glucose energy is artificially forced to zero. Implementation of this rule through an object-oriented programming approach enabled the zero restriction rule to be implemented in a base class from which the individual classes were then derived.

The zero restriction is however not applied for all the flow connections in Figure 7.1.  $\dot{G}_{Exercise}$  (the glucose energy flow connection from the bloodstream to the energy expenditure component) will never be zero anyway due to the fact that energy always has to flow to the basal metabolism in order to sustain life. For the virtual person to “stay alive” a minimum restriction is used instead of a zero restriction. This is described in more detail in Section 7.3.3.

### Blood glucose concentration

The output (simulated result) of the bloodstream component is blood glucose energy contained in the blood at any time step ( $G_{Blood(t)}$ ). However, to be implemented for every-day application, the result people are more interested in is blood sugar concentration ( $BS_{Blood(t)}$ ) provided in mmol/l and not in the amount of glucose energy ( $G_{Blood(t)}$ ) measured in ets. The problem is that the conversion of  $G_{Blood(t)}$  into  $BS_{Blood(t)}$  requires knowledge of the amount of blood a person has ( $V_{Blood}$ ). ( $G_{Blood(t)}$  is an absolute value while  $BS_{Blood(t)}$  is a concentration.)

$V_{Blood}$  is however dependant on many variables such as body weight, age, gender, percentage body fat, etc. To simplify the problem it was assumed, for the purpose of this study, that the volume of blood in a person is only dependent on the person’s body weight. Therefore, the equation that was used to convert blood glucose energy into blood glucose concentration is presented in Equation (7.9).

$$BS_{Blood(t)} = \frac{K}{V_{Blood}} G_{Blood(t)} \quad (7.9)$$

In the equation  $K$  is a constant with units: mmol/ets. The value of  $K$  can be calculated with the following argument.

The molecular structure of glucose is  $C_{12}H_{22}O_{11}$  and therefore the atomic weight of one glucose molecule is 342 [10]. From the definition of atomic weight it entails that, since its weight is 342, a measure of 342 g of glucose will contain in 1 mol of glucose molecules. From the definition of ets it follows that there are effectively 5 g of glucose contained in 1 ets. But, if 342 g represent 1 mol then 5 g represent 14.6 mmol of glucose. Therefore, 1 ets contains 14.6 mmol of glucose molecules and hence  $K = 14.6$  mmol/ets.

### 7.3.3 Energy expenditure model

The energy expenditure component in Figure 7.1 is the only component through which glucose energy can be “burnt” or expended from the human energy system. It represents the combination of all the components that consume glucose energy from the body. It should be noted that energy can be expended in many organs, muscle tissues, nervous system, etc. (more detail is given in Section 6.2). The energy expenditure component model however provides the simulation of glucose energy flow from the bloodstream ( $\dot{G}_{Exercise}$ ) to any combination of all these elements.

As long as insulin (the regulation hormone) is present in the system, the expenditure component is able to extract glucose from the bloodstream. By doing so it also consumes insulin and therefore lowers the total amount of available insulin in the system.

The energy expenditure system consists of two main energy-consuming agents. These are

- the glucose energy required to maintain the vital organs and “stay alive”. It includes the energy required to perform normal daily activities. This energy is also referred to as the basal energy requirement ( $\dot{G}_{Basal}$ ).
- the glucose energy flow required by the muscles to perform movements and exercises other than those performed during normal day activities ( $\dot{G}_{Movement}$ );

The total amount of glucose that flows from the bloodstream into the energy expenditure component is therefore given in Equation (7.10).

$$\dot{G}_{Exercise} = \dot{G}_{Basal} + \dot{G}_{Movement} \quad (7.10)$$

### Minimum restriction

As mentioned in Section 7.3.2,  $\dot{G}_{Exercise}$  can never be below a certain minimum value ( $\dot{G}_{Exercise-Min}$ ). This is because the vital organs require at least the minimum amount of glucose energy at any given time step in order to sustain life ( $\dot{G}_{Basal} \geq \dot{G}_{Exercise-Min}$ ). The only scenario that might present a problem is if there is too little insulin present in the system to allow for the required flow rate. In this case  $\dot{G}_{Exercise}$  is artificially restricted to the minimum flow rate ( $\dot{G}_{Exercise-Min}$ ), i.e. if  $\dot{G}_{Exercise} \leq \dot{G}_{Exercise-Min}$  then  $\dot{G}_{Exercise} = \dot{G}_{Exercise-Min}$ .

The value of  $\dot{G}_{Exercise-Min}$  is obtained through the following argument. It was assumed that the critical amount of energy that is required in order to sustain life in the vital organs is at least half the amount recommended for daily ingestion at any time of the day ( $\dot{G}_{RDA(t)}$  where "RDA" is the abbreviation for "recommended daily allowance"). Therefore,  $\dot{G}_{Exercise-Min}$  can be calculated with Equation (7.11).

$$\dot{G}_{Exercise-Min} = \frac{1}{2} \dot{G}_{RDA(t)} \quad (7.11)$$

For example: it is recommended that a certain person ingests 288 kCal of energy per day through CHO ingestion and the human energy system simulation is performed for that person in 1 minute time step intervals. Since there are 1440 minutes in one day it follows that  $\dot{G}_{RDA(t)} = 0.2$  kCal/minute. If this is substituted into Equation (7.11), it yields that for that person  $\dot{G}_{Exercise-Min} = 0.1$  kCal/minute.

But, there are 20 kCal in 1 ets, so  $\dot{G}_{Exercise-Min} = 0.005$  ets/minute.

### Insulin consumption

In the majority of the cases the insulin level is however not near zero. In this case the glucose energy flow to the energy expenditure model ( $\dot{G}_{Exercise}$ ) is calculated with Equation (7.10). If incidentally more insulin is present than is required for energy expenditure flow, the value of

$\dot{G}_{Exercise}$  is still calculated with Equation (7.10), independent of the absolute amount of insulin in the system.

However,  $\dot{G}_{Exercise}$  does bring about the consumption of insulin from the system ( $\dot{I}_{Exercise}$ ). The greater the value of  $\dot{G}_{Exercise}$ , the more insulin is “used” or extracted. A linear consumption relationship was assumed. The total amount of insulin that is consumed (flow of insulin out of the system) is dependent on the characteristics of the person being simulated and can be calculated with Equation (7.12).

$$\dot{I}_{Exercise} = CF_{Exercise} \dot{G}_{Exercise} \quad (7.12)$$

In the equation  $CF_{Exercise}$  is an empirical constant that describes the amount of insulin a person expends in order to perform exercises (or stay alive). For the purpose of this study the value of  $CF_{Exercise}$  was simply determined empirically through a method of trial-and-error. The value was adjusted during the construction phase of each model (see Section 8.3) and the simulations were performed iteratively until acceptable values for the models were attained.

### Basal energy requirement

To determine the amount of glucose energy (measured in ets) that should flow towards the energy expenditure component for normal every-day life ( $\dot{G}_{Basal}$ ), the following assumption is made. The amount of energy required to maintain a constant weight (zero net glucose flow to the secondary storage component ( $\dot{G}_{Storage} = 0$ )) has to equal the amount of energy published in recommended daily allowance (RDA) tables for glucose consumption [11]. In other words, if the person has a constant weight and negligible extra exercises are performed,  $\int(\dot{G}_{Basal})dt = G_{Basal}$  must be equal to the person’s RDA of glucose energy.

This assumption further implies that any extra energy expended by the energy expenditure component has to be totalled and assigned to  $\dot{G}_{Movement}$ . The sum calculated in Equation (7.10) then consists of the RDA of energy (in the form of glucose) as the basal requirement ( $\dot{G}_{Basal}$ ), as well as any other exercise that the person may do other than normal activity ( $\dot{G}_{Movement}$ ).

To find  $\dot{G}_{Basal}$  for a specific person, a method similar to the argument in Section 3.3.2 is proposed: While expending energy during endurance events, 20% of the energy is released by the liver in the form of blood glucose [12],[13].  $\dot{G}_{Basal}$  can be compared to the flow of glucose energy due to an endurance event with very light intensity. Therefore, if the total amount of daily energy required by the person is then denoted by  $E_{RDA}$  (as can be found in published energy tables), the total amount of energy required from glucose ( $\int(\dot{G}_{Basal})dt = G_{Basal}$ ) is then 20% of  $E_{RDA}$ .

$$G_{Basal} = 20\%E_{RDA} \quad (7.13a)$$

In Equation (7.13a) both variables ( $G_{Basal}$  and  $E_{RDA}$ ) are measured in the same units, i.e. either kCal or ets. However, for the sake of simulation  $G_{Basal}$  has to be measured in ets, while  $E_{RDA}$  is usually listed in terms of kCal. A conversion is therefore required. In Section 3.3 it was shown that there are 13 kCal in 1 ets. Thus, Equation (7.13a) can be rewritten as

$$G_{Basal}[ets] = \frac{20\%}{13} E_{RDA}[kCal] = (0.0154)E_{RDA}[kCal]. \quad (7.13b)$$

The only remaining step is to calculate  $\dot{G}_{Basal}$  in terms of ets for every time step. Since  $\dot{G}_{Basal}$  is the time derivative of  $G_{Basal}$  (or  $\dot{G}_{Basal} = \frac{dG_{Basal}}{dt}$ ), the value of  $G_{Basal}$  can simply be divided by the total number of time step intervals in the simulation for one day to find  $\dot{G}_{Basal}$ .

### Exercise energy requirement

The second component of Equation (7.10) is  $\dot{G}_{Movement}$ . This variable describes the flow of energy in the form of blood glucose from the bloodstream to the energy expenditure component model in order to perform physical exercise other than normal daily activities. This entails any kinetic movement that is not included in  $\dot{G}_{Basal}$ . (Normal daily movements are excluded because they are already incorporated in  $\dot{G}_{Basal}$  through  $E_{RDA}$ .)

To calculate the amount of glucose energy required by the energy expenditure component to perform exercises, the same reasoning as with  $\dot{G}_{Basal}$  is applied. Measurements by Bosch et al showed that only 20% of the energy burnt during exercise is oxidised from glucose [12]. Hence, if the person knows how much total energy is required by the body to perform a certain exercise, the total integrated flow of glucose energy from the bloodstream to the energy expenditure component due to the exercise ( $G_{Movement} = \int(\dot{G}_{Movement})dt$ ) can be calculated. This calculation is shown in Equation (7.14), which is very similar to Equation (7.13b).

$$G_{Movement} [ets] = \frac{20\%}{13} E_{Movement} [kCal] = (0.0154) E_{Movement} [kCal] \quad (7.14)$$

In Equation (7.14)  $E_{Movement}$  is the amount of energy that the person requires for exercising, measured in kCal. This value is often published in energy expenditure tables or it can be calculated with the Equation suggested in Section 3.3.2 [11],[14].  $G_{Movement}$  is the total amount of glucose energy required from the bloodstream component measured in ets. The constant conversion factors in Equation (7.14) follow the same reasoning as the conversion factors used in Equation (7.13b).

The duration and onset time of the exercise event in Equation (7.14) is very important for the purpose of simulation. It was found empirically from trial data and some literature sources that the full impact of the exercise on blood glucose concentrations is not effective at the onset of the exercise [15]. Also, the influence of the exercise does not cease immediately after the full duration of the exercise has passed. A “time delay” equation is therefore required to dynamically simulate the actual effect of the exercise for every time step.

As a sufficient approximation this “time delay” was found to be a very similar equation to the release function mentioned in Section 7.3.1 for the digestion system component (Equation (7.1)). In that section the release function was presented as a calculation of how much ets is released into the bloodstream at any given time step. That same equation can be used to approximate the impact of exercise at any time step.

The time delay function is dependent on the following variables:

- the effective amount of ets “burnt” during the event ( $G_{Movement}$ );

- the time of day the exercise event started ( $t_{Movement}$ );
- the total duration of the exercise that is performed ( $t_{Event}$ ).

The time delay function is inherently a control system concern and will therefore be discussed in more detail in Section 7.4. The specific amount of energy required by the energy expenditure component at any specific time step ( $\dot{G}_{Movement}$ ) is then found with

$$\dot{G}_{Movement} = f(G_{Movement}, t_{Movement}, t_{Event}) \quad (7.15)$$

The only remaining issue regarding the energy expenditure component model is to calculate the total flow of energy in the form of glucose from the bloodstream ( $\dot{G}_{Exercise}$ ). This is done by substituting  $\dot{G}_{Movement}$  and  $\dot{G}_{Basal}$  back into Equation (7.10) for every time step in the solving process.

### 7.3.4 Primary storage model

After ingestion of a meal the digestion system component releases glucose energy into the bloodstream component ( $\dot{G}_{Digest}$ ). This flow causes the blood glucose concentration of the bloodstream component to rise. Because the flow of energy towards the energy expenditure component ( $\dot{G}_{Exercise}$ ) is primarily only determined by the requirements of the energy expenditure component itself (it is therefore relatively small), the level of glucose in the bloodstream component will therefore remain high for a relatively long period.

In the actual human energy system (the human body) high blood glucose levels are unacceptable due to the negative health implications associated with it [16]. The body therefore has a temporary storage facility to which the glucose can be transferred and from where it can later be retrieved if necessary [17]. However, a distinction can be made between short-term and long-term storage. In Figure 7.1 these are modelled by the primary and secondary storage components respectively.

The primary storage component is the storage component where glucose is stored first for relatively easy access. This component is very similar to the bloodstream component model in that it is also a linear “storage tank” model. (In the human body this component would fulfil the same role as the

liver storage would [18].) Figure 7.7 shows how the glucose energy flows in and out of the primary storage component model.

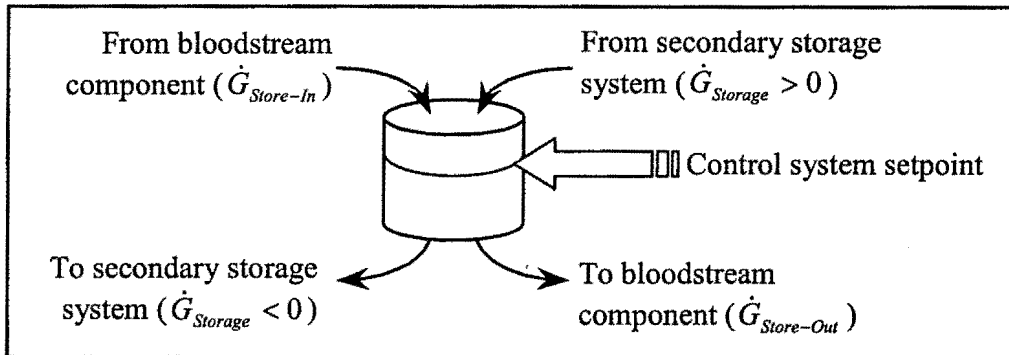


Figure 7.7 – Schematic representation of the energy flow through the linear storage tank model of the primary storage component.

Unlike the bloodstream model (Figure 7.6), the in and out flow connections of the component are only connected to two components (not three): the bloodstream and the secondary storage components. It is through the connections to the bloodstream component that the primary storage component is able to perform blood glucose level control. The control of the bloodstream glucose level ( $G_{Blood}$ ) is however accomplished by control hormones (regulation and counter regulation hormones) that induce glucose energy flow ( $\dot{G}_{Storage-In}$  and  $\dot{G}_{Storage-Out}$ ) and consequently raise and lower blood glucose levels in the bloodstream component.

To dynamically solve the amount of glucose energy stored in the primary storage component for any given time step ( $G_{Storage(t)}$ ), the energy flow to and from the component has to be considered. The energy flow rate of glucose into and out of the primary storage component ( $\dot{G}_{Storage-In}$  and  $\dot{G}_{Storage-Out}$  respectively) at a specific time step have to be added to the level of glucose at the previous time step ( $G_{Storage(t-1)}$ ). Therefore Equation (7.16) can be written as

$$G_{Storage(t)} = G_{Storage(t-1)} + (\dot{G}_{Storage-Out} - \dot{G}_{Storage-In} + \dot{G}_{Storage})_{(t)}. \quad (7.16)$$

To follow the same sign convention as before, for the variables connected to the bloodstream component ( $\dot{G}_{Storage-In}$  and  $\dot{G}_{Storage-Out}$ ) a positive value describe the flow of energy out of the primary

storage and into the bloodstream component. Concerning the connection with the secondary storage,  $\dot{G}_{Storage}$  is considered positive if the glucose energy flows towards the primary storage component and negative otherwise.

### Blood glucose energy regulation

In Section 7.4 the topic of control hormones and its control regimes will be discussed. These hormones (regulation and counter regulation) are responsible for the induced flow of glucose energy between the primary storage component and the bloodstream. Insulin (the only regulation hormone) causes absorption of glucose energy from the blood stream [2]. The counter regulation hormones on the other hand cause the release of glucose energy from the primary storage component back into the bloodstream [3].

The amount of regulation and counter regulation hormones present in the system are denoted with two variables:  $I_{Control}$  and  $C_{Control}$  respectively. The definitions of these variables are such that they linearly represent the flow rate of glucose energy into and out of the primary storage component. Therefore, the energy flows are calculated:  $\dot{G}_{Store-In} = I_{Control}$  and  $\dot{G}_{Store-Out} = C_{Control}$ . Observably it implies that the more insulin is present in the system, the more energy will be stored, and also, the more counter regulation hormones are present, the more glucose energy will be released from storage.

### Zero restriction

Another flow connection, the connection to the secondary storage component, is further necessary for active control of the level of glucose energy stored in the primary storage ( $G_{Storage}$ ). This control strategy will also be discussed in more detail in Section 7.4. However, there is one condition that must be adhered to at all the time steps throughout the simulation process.

Similar to the bloodstream component storage tank model, a zero restriction rule is applied. It states that the level of glucose energy, measured in ets, stored in the primary storage component must always be positive. Therefore, if at any time step  $G_{Storage}$  is calculated to be less than zero ( $G_{Storage} \leq 0$ ) then  $G_{Storage}$  will be adjusted to be zero ( $G_{Storage} = 0$ ). In that event all the glucose energy connections flowing from the primary storage component are also reset to equal zero.

## Control hormone consumption

Similar to the exercise expenditure component the primary storage component also has a hormone consumption effect. Whenever glucose energy flows into or out of the primary storage component ( $\dot{G}_{Store-In}$  and  $\dot{G}_{Store-Out}$  respectively), the hormones responsible for inducing the energy flow are consumed.

The flow of glucose energy into the primary storage unit ( $\dot{G}_{Store-In}$ ) stimulates regulation hormone (insulin) consumption ( $\dot{I}_{Storage}$ ) while the flow out of the component ( $\dot{G}_{Store-Out}$ ) brings about consumption of counter regulation hormones ( $\dot{C}_{Storage}$ ). The amount that is consumed can be determined with a method similar to Equation (7.12). Equation (7.17) and (7.18) represent the consumption of the control hormones.

$$\dot{I}_{Storage} = CF_{Storage} \dot{G}_{Store-In} \quad (7.17)$$

and

$$\dot{C}_{Storage} = CF_{Storage} \dot{G}_{Store-Out} \quad (7.18)$$

In both the equations a consumption factor ( $CF_{Storage}$ ) was used to describe how much of the control hormones are consumed according to the amount of glucose that flows towards and from the primary storage component. Like the consumption factor used for exercise in Equation (7.12) ( $CF_{Exercise}$ ), these factors were determined empirically through iterative trial-and-error simulations.

### 7.3.5 Secondary storage model

The role of the secondary storage component model is to aid in the control of the level of energy stored in the primary storage unit. If at any time step the primary storage component contains more glucose energy than preferred (higher than control setpoint) the excess glucose energy is transferred from the primary storage component to the secondary one. In that case  $\dot{G}_{Storage}$  in Equation (7.16) is negative.

If conversely the primary storage component has too little stored glucose energy, the secondary storage unit is required to supply energy and  $\dot{G}_{Storage}$  is positive. The control of the energy flow between the secondary and primary storage components ( $\dot{G}_{Storage}$ ) will be discussed in more detail in the following Sections.

The secondary storage component model is different from the other storage components (bloodstream and primary storage component models) in that it is not a linear storage tank model. Instead there is no limit to the glucose energy capacity of this component. A closer description would be an endless source. This approach is required for modelling the dynamic effect of liver depletion and replenishing from fat stores [18].

The trouble is that in reality the fat stores are not infinite. However, the purpose of this study was not to simulate weight gain and loss over long periods of time. The objective was merely to simulate relatively short-term blood glucose response (typically daily). Therefore the assumption of an infinite secondary storage capacity (fat store) is legitimate.

## 7.4 Glucose energy control system

The control of the human energy system (Figure 7.1) is conducted through four primary control components. Like the system component models described in Section 7.3, these components were also constructed as class objects with methods and properties required to calculate the control system response to certain inputs [1].

Solving the control system was performed with a similar procedure as the one used for solving the energy system. The major difference however is that no energy flow needs to be calculated prior to solving the component models. Instead the required inputs to all the components are taken as the properties of the energy components. At each time step, through iterative solving, the amount of control hormones (or release of energy) can then be calculated for each component before recalibrating the glucose energy flow network and executing the next iteration.

The following four control components are used in the human energy system simulation model:

- an empirical “release” or “time delay” function;
- a controller unit for the release of the regulation hormone, insulin;

- a controller component for the release of counter regulation hormones;
- a control strategy to regulate the stored energy level in the primary storage component.

The application of the controller components in the human energy system simulation model is shown schematically in Figure 7.8. This layout is an extension of Figure 7.1 in which the control connections were not shown due to the complexity of the system.

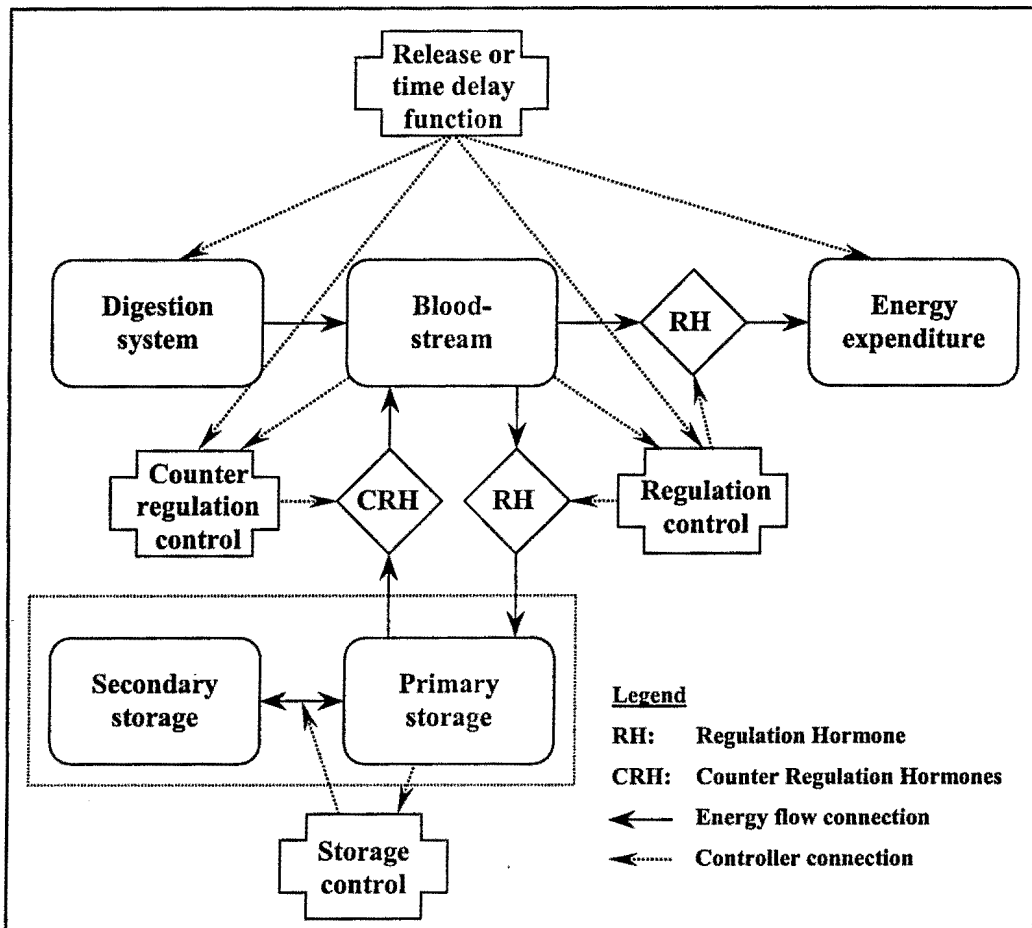


Figure 7.8 – Schematic layout of the controller component connections.

As can be seen from Figure 7.8 all the controllers, except the release function, receive input variables from certain energy components. The controller properties are then implemented to determine how much glucose energy should be allowed to flow through the various energy connections that are controlled.

### 7.4.1 Release or time delay function

As mentioned in Sections 7.3.1 and 7.3.3 the release and / or time delay function (as it was referred to in those sections) was used to approximate the amount of digested glucose or exercise energy that was “release” or “consumed” at specific time steps respectively. Empirical measurements for the blood glucose release rate from the digestion system ( $\dot{G}_{Digest}$ ) have yielded a distinctively recognisable response curve [9],[19],[20]. Due to the repeatability of the response curve it is therefore suggested to calculate the release of glucose analytically rather than using tedious simulation techniques.

The following function is proposed for this analytical calculation. The glucose release rate ( $\dot{G}_{Digest}$ ) can be approximated with the sum of the following two sine curves ( $f_1(t)$  and  $f_2(t)$ ). The two functions, which were determined with trial and error methods, are shown in Equations (7.19) and (7.20).

$$f_1(t) = \sin\left(\frac{2\pi}{t_{total}}(t_x - t_0)\right) \quad (7.19)$$

$$f_2(t) = 2 \sin\left(\frac{\pi}{t_{total}}(t_x - t_0)\right). \quad (7.20)$$

In the equations the functions are both dependent on one variable  $t$ . This is the current time step of the simulation procedure. If the two sine functions ( $f_1$  and  $f_2$ ) are totalled, the sum ( $\dot{G}' = f_1 + f_2$ ) yields a function that is shown graphically in Figure 7.9. For the function  $\dot{G}'$  is only defined between  $t = t_0$  and  $t = t_{Total}$ .

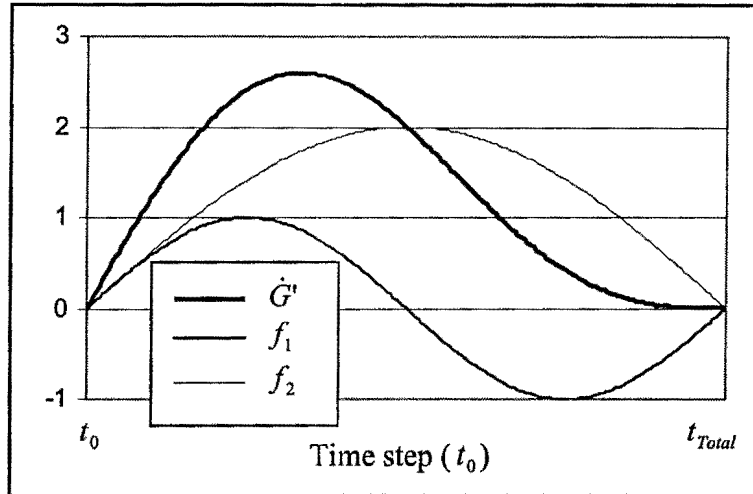


Figure 7.9 – A graphical representation of the release function: the sum of the two sine curves, namely ( $f_1$  and  $f_2$ ).

In the function  $\dot{G}'$ , the variable concerning time ( $t_x$ ,  $t_0$  and  $t_{Total}$ ) are used to describe the duration of the curve from the onset time ( $t_0$ ) to the completion time ( $t_{Total}$ ). The magnitude of the function is however not scaled yet, so in order to adjust the total amount of energy released (or consumed through a time delay),  $\dot{G}'$  is multiplied with a scaling factor. This scaling factor can be determined by approximating the total amount of energy released (or consumed) and then adjusting the integral of the function accordingly.

For example, if the function is used to calculate the release of glucose energy from the digestion system into the bloodstream, the total amount of ets released after  $t_{Total}$  should be equal to the integral of  $\dot{G}'$  from  $t_0$  to  $t_{Total}$ . Therefore, if the total effective amount of ets released is  $ets_{Effective}$  (see Section 7.3.1) then Equation (7.21) should hold true.

$$\int_0^{t_{Total}} (\dot{G}') dt = ets_{Effective} \quad (7.21)$$

Let  $\dot{G}$  be the product of  $\dot{G}'$  and the scaling factor. After performing the integral calculation and substituting the scaling factor back into  $\dot{G}'$ , the final equation for the digestive release function is then

$$\dot{G} = \frac{\pi}{4} \frac{ets_{Effective}}{t_{Total}} \left[ \sin\left(\frac{2\pi}{t_{Total}}(t - t_0)\right) + 2 \sin\left(\frac{\pi}{t_{Total}}(t - t_0)\right) \right]. \quad (7.22)$$

An equivalent equation can also be applied to describe the release function for any substance as well as the consumption function for exercise expenditure (Section 7.3.3). Simply substitute the variable,  $ets_{Effective}$  with the total amount of the other substance that should be released (or with the total amount of energy required for the specific exercise performed). Of course the time dependent variables in Equation (7.22) should also be substituted with the applicable onset and duration times for the specific substance.

As shown in Figure 7.8, the release or time delay function has control connections with the digestion system and the energy expenditure system, but also with the regulation and counter regulation controllers. The digestion and expenditure components were already described in Sections 7.3.1 and 7.3.3 respectively. However, the release of regulation hormones and counter regulation hormones is also determined by a release function similar to Equation (7.22). These controllers will be described in more detail in the following two sections.

## 7.4.2 Regulation hormone controller model

Whenever a person ingests ets, the digestion system component model releases glucose energy into the bloodstream component [3]. This is shown schematically in Figure 7.1 and Figure 7.8. The magnitude of the effective ets dose ( $ets_{Effective}$ ) is determined with the procedures described in Section 7.3.1. The specific amount of energy that flows into the bloodstream component at any time step can be calculated with Equation (7.22).

The primary role of the regulation controller component is to lower the rising amount of energy contained in the bloodstream component back to an acceptable level. This is accomplished by releasing the regulation hormone, insulin ( $I_{Control}$ ). (The organ in a healthy person's body that performs an equivalent task is the pancreas described in Chapter 6 [3].)

Insulin is responsible for activation of the primary storage component to absorb glucose energy from the bloodstream. The more insulin is available, the more glucose energy is extracted from the bloodstream component and stored in the primary storage unit ( $\dot{G}_{Store-In}$ ). As described in Section

7.3.4 the flow of energy further also causes the insulin to be consumed according to a consumption factor defined in Equation (7.17). The insulin level is henceforth lowered to stabilise at the basal insulin level ( $I_{Basal}$ ).

In order to calculate the level of insulin hormone present in the system at any time step, the insulin level at the previous time step is totalled together with the changes in insulin due to the various processes such as insulin secretion and insulin consumption (described Sections 7.3.3 and 7.3.4). Therefore the total amount of insulin in the system at time step ( $t$ ) can be calculated with Equation (7.23).

$$I_{Control(t)} = I_{Control(t-1)} + (\dot{I}_{Control} + \dot{I}_{Injected} - \dot{I}_{Exercise} - \dot{I}_{Storage})_{(t)} \quad (7.23)$$

If a Type 1 diabetic's energy system is simulated  $\dot{I}_{Control}$  is zero because the person is unable to secrete insulin for blood glucose control. In this case  $\dot{I}_{Injected}$  will be used to simulate the injected insulin. Conversely, if a healthy person is simulated  $\dot{I}_{Control}$  will be calculated at every time step and usually  $\dot{I}_{Injected}$  will be zero. It is however not a prerequisite that  $\dot{I}_{Injected}$  must be zero (Although not common practice, a healthy person may also inject insulin experimentally.) This procedure might be useful in future studies for simulation of blood glucose response in Type 2 diabetes.

### Insulin injection strategy (diabetic patients)

Type 1 diabetes mellitus patients do not have insulin available in their bodies to actively control their blood glucose levels. They have to inject insulin regularly in order to activate the primary storage component to absorb glucose energy for storage [3],[4],[5].

Many types of injected insulin have an absorption effect similar to the release function described in the previous section [21]. The duration and onset of the insulin is normally a matter of hours rather than seconds like pancreatic insulin [21],[22]. Therefore, the release function can be used to simulate the effect and impact of the insulin at any given time step. To accomplish this, simply substitute  $ets_{Effective}$  in Equation (7.22) with the total amount of insulin injected (measured in ets).

It should be noted that if a specific insulin is used that require a different release function than the one in Equation (7.22), the function should be derived with a similar procedure as described in

Section 7.4.1. For the purpose of this study and the types of insulin used by the test subjects, Equation (7.22) was sufficient.

### PID control strategy (healthy people)

The amount of insulin that is released at any time step is determined through a control strategy analogous to a proportional integral differential (PID) controller that is often used in engineering control applications [23]. It is a linearised strategy by which the regulation hormone secretion ( $\dot{I}_{Control}$ ) at any time step is determined by the level of glucose energy contained in the bloodstream component ( $G_{Blood}$ ). Figure 7.10 shows the implemented strategy for insulin release control.

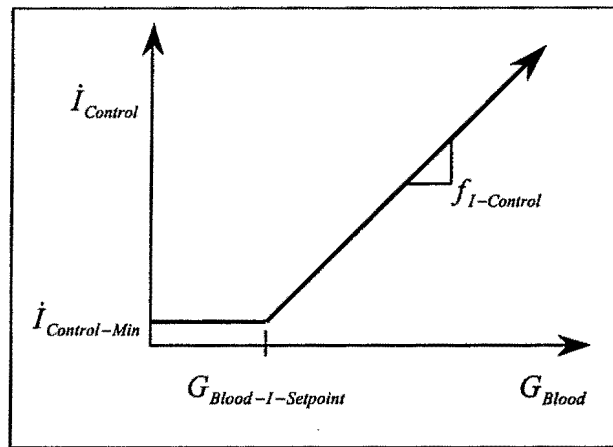


Figure 7.10 – PID control strategy for the regulation hormone (insulin) controller component.

In Figure 7.10  $G_{Blood-I-Setpoint}$  is the blood glucose energy setpoint at which the insulin controller is activated. It is measured in ets (absolute amount not concentration), but it is equivalent to the blood glucose level that can be measured with glucometers. To convert the values of  $G_{Blood-I-Setpoint}$  and  $G_{Blood}$  to blood sugar concentration ( $BS_{Blood}$ ), Equation (7.9) can be used.

$\dot{I}_{Control-Min}$  in Figure 7.10 is the minimum amount of regulation hormone that is released at any time step. This restriction is necessary because (as explained in Section 7.3.3) the energy expenditure component requires insulin to absorb glucose energy from the bloodstream component. A certain minimum amount of energy has to flow towards the energy expenditure component in order to sustain life ( $\dot{G}_{Exercise-Min}$ ).

$\dot{I}_{Control-Min}$  can be calculated by using  $CF_{Exercise}$  found in Equation (7.12). It is suggested that the amount of insulin available in the system ( $I_{Control}$ ) should never be less than the minimum amount required for insulin consumption by the exercise expenditure minimum energy flow ( $\dot{G}_{Exercise-Min}$ ). Therefore, from Equation (7.12) it follows that  $\dot{I}_{Control-Min}$  can be calculated with the following equation:

$$\dot{I}_{Control-Min} = CF_{Exercise} \dot{G}_{Exercise-Min} \quad (7.24)$$

$f_{I-Control}$  in Figure 7.10 is the gradient of the PID regulation control strategy. It is equivalent to the insulin sensitivity of the person (amount of insulin secreted in response to an amount of ets ingested) discussed in Section 3.2. To calculate  $f_{I-Control}$  for a healthy person the following argument is presented:

If it can be assumed that a linear relationship between the area under the blood sugar response curve ( $AUC_{BS}$ ) and the area under the insulin response curve ( $AUC_I$ ) for some ingested amount of ets exists, then  $f_{I-Control}$  represents that relationship. In other words  $f_{I-Control}$  is the correlation between insulin response and blood sugar response described by Equation (7.25).

$$f_{I-Control} = \frac{AUC_I}{AUC_{BS}} \quad (7.25)$$

### 7.4.3 Counter regulation hormone controller model

The specific counter regulation hormones that are found in the human energy system are described in more detail in Section 6.5.2. The main purpose of these hormones is to raise blood glucose levels by releasing stored glucose from the storage system [3].

Unlike the regulation control system (using insulin) the counter regulation control system does not consist of only one type of hormone. There are in fact several hormones that all perform the same purpose: they all act to ensure elevation of blood glucose levels whenever it is required [24]. For the sake of simplifying the simulation process of the human energy system, the effect of the counter

regulation hormones is combined into one virtual hormone. The amount of that hormone available to the system is denoted as  $C_{Control}$ .

As shown in Section 7.3.4, the larger the value of  $C_{Control}$  (amount of counter regulation hormones) the larger the flow of glucose energy from the primary storage component into the bloodstream component. Consequently, the counter regulation hormone controller, shown in Figure 7.8, is used to control the level of glucose energy in the bloodstream component according to a feedback setpoint from the bloodstream model. Whenever the blood glucose energy contained in the bloodstream component falls below the required setpoint value,  $C_{Control}$  is increased ( $\dot{C}_{Control}$ ).

To accomplish this control a PID controller similar to the model used for regulation (insulin) control is used [23]. This control strategy is shown schematically in Figure 7.11.

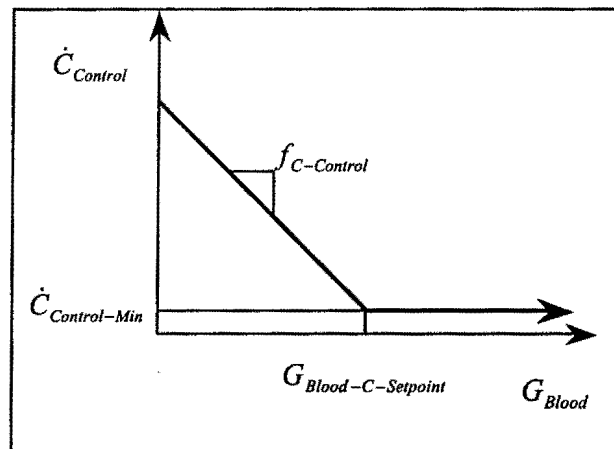


Figure 7.11 – PID control strategy for the counter regulation hormone controller component.

The setpoint under which the counter regulation hormones are released ( $G_{Blood-C-Setpoint}$ ) is critically dependent on the setpoint for which insulin is controlled (Figure 7.10). To prevent the simulation solver from calculating infinite values for  $\dot{C}_{Control}$  and  $\dot{I}_{Control}$ , it must always be ensured that  $G_{Blood-C-Setpoint}$  is less than  $G_{Blood-I-Setpoint}$ .

Mathematically a larger  $G_{Blood-C-Setpoint}$  may result in a condition where the simulation model will be able to release undetermined amounts of both regulation and counter regulation hormones. In that case the energy flow to and from the storage will be undetermined (possibly infinite), but the

control hormones will simply be cancelled with possible oscillatory response. To prevent this scenario from occurring the following condition must therefore always hold true:

$$G_{\text{Blood-C-Setpoint}} \leq G_{\text{Blood-I-Setpoint}}$$

For blood glucose energy levels above  $G_{\text{Blood-C-Setpoint}}$  a minimum secretion rate was used. To determine this minimum amount of counter regulation hormones that may be released ( $\dot{C}_{\text{Control-Min}}$ ) an assumption is made. Since the counter regulation and regulation hormones are supposed to counteract each other in their mechanisms of blood glucose control, it is assumed that  $\dot{C}_{\text{Control-Min}}$  should be equal in magnitude to  $\dot{I}_{\text{Control-Min}}$ . The calculation of  $\dot{I}_{\text{Control-Min}}$  is provided in Section 7.4.2.

The same reasoning was applied to determine  $f_{\text{C-Control}}$ . The hormones, as they are defined for the use in the simulation model, are assumed to be equally effective in their opposing action. Therefore  $f_{\text{C-Control}}$  and  $f_{\text{I-Control}}$  are equal in magnitude, but different in sign.

An interesting observation was made: During the verification study it was found by trial-and error that the above assumption is not always applicable. With some of the long-term diabetics (diagnosed more than 15 years prior to this study) better simulation results were obtained when a smaller value for  $f_{\text{C-Control}}$  was used. It was concluded that long-term diabetics therefore have a poorer than normal counter regulation action. In some cases the reduced capacity was up to four times less (only 25% of  $f_{\text{I-Control}}$ ).

#### 7.4.4 Storage controller model

The secondary storage unit is required in the human energy system (Figure 7.1) to simulate the dynamic and integrated effect of liver depletion as well as long-term energy storage and retrieval response. A third controller, with a step control strategy (shown in Figure 7.8), is used to regulate the flow of glucose energy between the primary and secondary storage components ( $\dot{G}_{\text{Storage}}$ ) [23].

Due to unavailability of measurements and the relative simplicity of a step controller this strategy was chosen. The control strategy is presented in Figure 7.12 below.

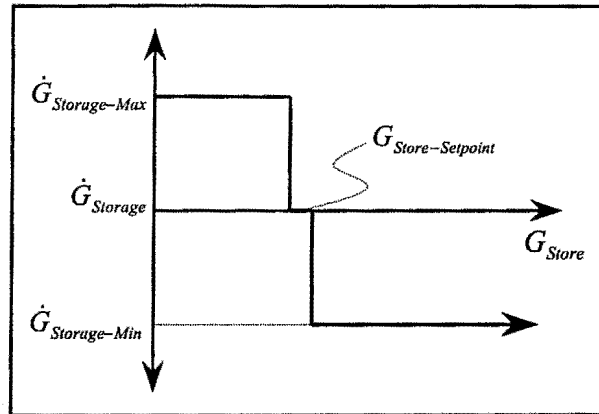


Figure 7.12 – Step control strategy for the storage system controller component.

The regulation of  $\dot{G}_{Storage}$  is direct in that no hormones or induced control is required. The flow is simply determined by the amount of glucose energy stored in the primary storage component, as shown in Figure 7.12. In order to find the maximum and minimum energy flow rates between the two storage components ( $\dot{G}_{Storage-Max}$  and  $\dot{G}_{Storage-Min}$ ) the following argument was followed:

As discussed in Section 3.3.2, some measurements have shown that 20% of the energy used for exercise is retrieved from liver stores [12],[13]. Whenever these stores are depleted, the athlete experiences hypoglycaemia [15]. In addition, Noakes et al performed experiments with people under extreme exercise conditions to observe how long they were able to exercise before suffering hypoglycaemia [25].

Noakes also showed in his book that an average person has a liver storage capacity from which approximately 12 g of blood glucose can be retrieved [15]. (This “capacity” is the setpoint around which the liver store is controlled.) This is equivalent to roughly 30 ets for an average sized person. If it can assumed that an average person weighs 65 kg (same assumption as in previous chapters), the capacity of an average person’s liver storage ( $G_{Liver}$ ) can be approximated with

$$G_{Liver} = \frac{30}{65}W = (0.462)W . \quad (7.26)$$

Now, let the energy required for the exercise in the Noakes et al experiments be  $\dot{E}_{Exercise}$  [25]. Also, let the time to exhaustion be denoted by  $t_{Exhaustion}$ . The change in the stored amount of glucose in the

liver is then  $\dot{G}_{Liver}$ , which is equal to the difference between the amount of energy flowing into the liver ( $\dot{G}_{Storage}$ ) and the amount of energy flowing out of the liver ( $20\%\dot{E}_{Exercise}$ ). This relationship is shown in Equation (7.27).

$$\dot{G}_{Liver} = 20\%\dot{E}_{Exercise} - \dot{G}_{Storage} \quad (7.27)$$

If Equation (7.27) is integrated over the total duration of  $t_{Exhaustion}$ ,  $G_{Liver}$  (which is also used as  $G_{Store-Setpoint}$  in the step controller) is found:

$$G_{Liver} = \int_{t_{Exhaustion}} \dot{G}_{Liver} dt = (20\%\dot{E}_{Exercise} - \dot{G}_{Storage})t_{Exhaustion} \quad (7.28)$$

Since  $G_{Liver}$  is already known from Equation (7.26), and both  $\dot{E}_{Exercise}$  and  $t_{Exhaustion}$  are known from the Noakes et al experiments, Equation (7.28) can be rearranged to calculate  $\dot{G}_{Storage}$  as shown in Equation (7.29) [15].

$$\dot{G}_{Storage} = 0.2\dot{E}_{Exercise} - \frac{G_{Liver}}{t_{Exhaustion}} \quad (7.29)$$

According to the step control strategy proposed in Figure 7.12  $\dot{G}_{Storage}$  was assumed to be constant and equal to either zero,  $\dot{G}_{Storage-Max}$  or  $\dot{G}_{Storage-Min}$ . The magnitude of both  $\dot{G}_{Storage-Max}$  and  $\dot{G}_{Storage-Min}$  can be calculated with Equation (7.29) and the sign convention will determine whether the glucose energy flows towards or from the primary storage component.

The range for which  $\dot{G}_{Storage}$  is zero is relatively small and primarily required to ensure that if the primary storage level is at the required setpoint, no flow from the secondary storage component will be the result. If this condition was not true, unpredictable flows into and out of the primary storage component at sequential time steps may result. It should also be mentioned that a further precaution to prevent this possible problem is to ensure that the magnitude of  $\dot{G}_{Storage-Max}$  and  $\dot{G}_{Storage-Min}$  is small

enough to avoid oscillating control around the setpoint. Fortunately, the values for  $\dot{G}_{Storage-Max}$  and  $\dot{G}_{Storage-Min}$  that are calculated with Equation (7.29) indeed proved small enough.

## 7.5 Conclusion

The model discussed in this chapter is a generic one designed for predicting glycaemic response of the human energy system. However, people differ in physiological make-up, so an individualised model has to be constructed for each person that is to be simulated. Some procedures for calculating characterisation parameters for different people were also suggested.

The solving techniques discussed in Chapter 5 were implemented for the model to predict glycaemic response due to many different influences. Furthermore, the model is a vastly simplified version of the actual human energy system discussed in Chapter 6.

The next step is to apply the model to people in reality and verify the validity of the simulation procedure. This will be discussed in the next chapter where glycaemic responses due to many influences are compared to measured data.

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