CHAPTER 1 INTRODUCTION

Biotechnology is generally accepted to be the next economical wave of the future. In order to attain the many benefits associated with this growing industry simulation modelling techniques have to be implemented successfully. One of the simulations that need to be performed is that of the human energy system. In this chapter the background regarding human energy system simulation and its potential beneficiaries are discussed. The objectives and contributions of the study are highlighted and a brief outline of the methodology is presented.

1.1 Preamble

Biotechnology can be defined as "using a combination of life sciences, high technology and innovative research to drive progress and profits in healthcare" [1]. According to Time Digital, biotechnology companies, most of which did not exist 10 to 15 years ago, are currently developing more than 50% of the world's new medications [1]. Today 14 pharmaceutical giants are listed in the top 60 most valuable companies in the world [2]. In the "Fortune global 5 hundred" survey the pharmaceutical industry was ranked at the top of both the "return on revenues" and the "return on assets" lists [3]. The benefits of having a tool to take a lead in this vast market are obvious.

One such a tool is simulation modelling. Simulation is one of the oldest and also among the most important tools available to engineers. It is usually easier, quicker and less expensive to simulate a real life event than to actually observe it in practice. Through simulation the age-old question, "What would occur if …" may be answered [4]. However, to date simulation techniques have not been used to much effect in the biotechnology field. Therefore, taking the step and applying this well-researched method in the biotechnological field can have vast repercussions.

The ultimate goal is to find a way to perform virtual experiments that can speed up the discovery of new medical treatments and reduce the cost of clinical trails. According to Tom Paterson, Chief Scientific Officer of Entelos Inc., "If Boeing developed aircraft the way the pharmaceutical industry develops drugs, they would develop ten very different aircraft, fly them, and the one that stayed in the air would be the one they would sell" [5]. With the aid of simulation modelling this tedious and costly procedure could obviously be avoided.

Many scientists and researchers have started to employ simulation techniques for faster development, but the accuracy of their models has not yet been thoroughly verified [6]. In future, if these models can be utilised in practice, according to Alfred G. Gillman of the University of Texas South-Western Medical Centre, "it will be the most incredible drug discovery engine there ever was" [6].

1.2 Background

In the following sections a short background concerning simulation of the human energy system is given. It is divided into seven subsections.

1.2.1 The human energy system

The human body behaves to a certain extent much like a machine or engine [7]. It has the ability to utilise energy input (similar to fuel), which is converted in the body into other forms of energy output such as physical and mental energy. Unlike its mechanical counterpart, however, the human body has the further ability to generate and repair itself. This involves mobilising and sustaining internal processes for self-preservation and prevalence in a variety of situations and applications [8].

Understanding the principles of operation of the human engine may seem a complex and almost insurmountable task when viewed from the physiological or biochemical perspective. Many unknowns still exist and full understanding of the exact nature of all biochemical processes in the human body is at present an ongoing quest [8].

The energy system of the human body can however be isolated and described by means of distinct energy pathways and controls. (This will be discussed in more detail in later sections.) The major problem facing researchers up to now has been quantification of the energy flow. To date the quantification and application of a practical measurement unit has been unsuccessful.

Glucose in the blood circulation system (blood sugar) is one of the primary energy sources that drive the human engine. It is made available to the body primarily through ingestion and digestion of food, and from extracting stored energy from the reserves [9]. Control of the flow of energy through the system is a complex matter and is mainly accomplished by means of endocrine regulation and concentration imbalance between the system components [10].

The human system components require a constant energy input to sustain itself and fuel its processes. As with the case of mechanical engines, fuel shortage may result in "engine" starvation, underperformance or even cessation. Oversupply, on the other hand, must be controlled to avoid "flooding" and damaging of the system [10].

Regulation of the human fuel in the blood circulation system happens largely without conscious intervention in most normal functioning individuals. The requirements for special performance, fuel residue build-up, as well as malfunctioning of the regulatory systems have been the catalysts for enormous amounts of research during the past years. Much has been learned, but indications are that in all probability a substantial amount still awaits discovery and understanding [10].

1.2.2 Diabetes mellitus

One of the human energy system's fuels, blood glucose, is regulated by means of two mechanisms to maintain glycaemic homeostasis [11]. These mechanisms are designed to actively monitor the blood glucose concentrations and react to any external disturbance [12]. By controlling the blood glucose concentrations at the desired level all the energy system components can function correctly.

The two control mechanisms are referred to as the regulation and the counter regulation systems [12]. Simply put, whenever the blood glucose concentration falls below a certain control setpoint, the counter regulation system activates a number of glands to secrete certain hormones into the bloodstream. These hormones then activate the energy storage cells in the body to release glucose into the bloodstream and the desired blood glucose level is restored [10].

Conversely, whenever the blood glucose level rises too high, the regulation system activates the pancreas to secrete the hormone insulin. The primary function of insulin is to activate cellular uptake of available blood glucose. By absorbing the excess glucose in the bloodstream into the storage cells, the desired blood glucose concentration is again restored [13].

As mentioned earlier, malfunctions of the control system do occur. The most common malfunction is that of a condition called diabetes mellitus. Diabetes is the condition where the pancreas either fails to produce insulin (Type 1) or the person becomes resistant to insulin (Type 2) and hence inhibits the regulation system to lower blood glucose levels. Since regular high blood glucose concentrations (hyperglycaemia) entail many health complications, a diabetic patient has to manually inject insulin or take medication to consciously control his / her own blood sugar level. A too low blood sugar level (hypoglycaemia) on the other hand is even more dangerous with consequences, like loss of consciousness and possibly death [10].

Accurate glycaemic control is no easy feat [14]. Today the disease is reaching epidemic proportions. There are currently an estimated 110 million diabetes sufferers in the world. This number is expected to double by the year 2010 and, if no cure can be found, it can increase to 300 million by 2025 [15],[16]. Of these about 30 million are insulin dependant and have to inject insulin on a daily basis [13].

Studies in the USA showed a growing concern that the onset of especially Type 2 diabetes is occurring more frequently in the younger population [17]. During 1990 to 1998 the prevalence of diabetes increased by 33% throughout the whole population of the USA, but alarmingly the prevalence in individuals from age 30 to 39 increased by 70% [18]. The total increase in diabetes since 1990 is estimated at 49% [19].

In total there are currently 16 million diabetics in the USA and diabetes is the third largest cause of death [20]. This is an outright epidemic with a significant impact on the worldwide economy [21]. The USA has an estimated expenditure of between $92 billion and $103 billion annually to combat the disease [20]. The biotechnological industry is constantly thriving towards developing new treatments and cures and having a competitive edge in this field may prove a large advantage.

1.2.3 Obesity

Obesity can be defined as "excess adiposity for a given body size" [22]. The International Obesity Task Force has defined being "overweight" as having a Body Mass Index (BMI) of more than 25 kg/m^2 and being "obese" as having a BMI of more than 30 kg/m^2. According to these criteria 55% of the United States adult population is overweight and 22.5% is classified as obese [23]. A South African study performed by Mollentze et al confirmed a similar local problem in 1995. It showed that the overall average BMI of women in rural areas of South Africa was above 25 kg/m^2 [24].

Obesity is therefore a major public health problem [24],[25]. Costs attributable to obesity totalled $99.2 billion in the United States in 1995 of which more than half is associated with medical expenditure [26]. The prevalence of obesity has increased by 61% since 1991 and according to the Centres for Disease Control and Prevention (CDC): "If we continue on this course for the next decade, the public health implications in terms of both disease and health-care costs will be staggering" [19].

As mentioned in the previous section, the hormone insulin is the major role-playing agent in human energy storage control [13],[27]. A direct link therefore exists between adipose tissue growth (gaining weight) and disorders regarding insulin [27]. This is the reason for obesity being associated with conditions like glucose intolerance, hyperinsulinemia, dyslipidemia, insulin resistance and diabetes mellitus [22],[28],[29],[30].

Successful simulation of the human energy system will yield better understanding of the response to food and the resulting insulin secretion. The new insight might provide answers to the growing problem of obesity.

1.2.4 Endurance energy expenditure (exercise)

One of the main purposes of the human energy system is to provide energy for the body to perform kinetic functions (movements). These include movements like breathing and cardiac functions. In order to achieve this the muscles, as "engine components", utilise energy in the form of glucose (blood sugar) [31]. Consequently, whenever an athlete exercises, his / her blood sugar concentrations fall because of the extraction of available blood glucose from the bloodstream. (This is provided that enough basal (normal control level) insulin is available to activate the muscle cells for glucose uptake.) [32]

The counter regulation control system of the body (discussed in section 1.2.2) has the important task of replenishing the blood glucose in order to constantly fuel the vital components of the energy system [10]. Depletion of any one of the counter regulation system components will result in a tired state called "hypoglycaemia" or "hitting the wall". Apart from being unpleasant, this state can in some cases be very dangerous. This is a common but poorly understood phenomenon many athletes encounter [33].

Many empirical studies have been conducted to establish the required food ingestion in order to prevent hypoglycaemia during exercise [34],[35]. Because successful simulation techniques were not available yet, the studies were unable to accurately account for physiological differences in various individuals. Some researchers, like Noakes, therefore adopted a common one-size-fits-all approach [33]. With successful simulation of the human energy system these differences might also be addressed.

Exercising also has many advantageous health aspects. Many links have been made between exercise and weight loss, cardiovascular disease control, insulin sensitivity improvement, diabetes avoidance, blood pressure control, prevention of osteoporosis, stroke and cancer, management of depression, etc. [36],[37],[38],[39],[40]. It is for this reason that large campaigns are frequently launched to inspire people to exercise regularly.

According to a survey, less than a third of the adults in the United States get enough exercise each day and 40% are almost completely sedentary [40]. Persuading people to exercise can however only be accomplished once some important questions regarding exercise in general can be answered; questions like required intensity, duration, frequency and optimal food ingestion [41]. Finding the answers rely on accurate quantification and simulation of the effects of exercise on the human energy system.

1.2.5 Stress

Mental stress is a modern phenomenon that affects most people [42]. Many negative health consequences have been linked to stress and a recent survey even concluded that traumatic (stressful) events like wartime displacement causes increased risk of cardiovascular disease and mortality [43],[44]. Quantification of the effects of stress on the body is however not yet defined.

It has long been known that mental or psychological stress directly causes blood glucose increase [45]. Stress triggers the counter regulation system (described in section 1.2.2) to secrete hormones that both raise the blood glucose concentration as well as impairs insulin action [45]. The higher blood sugar levels consequently also have an adverse effect on general well-being and health. As will be shown in later sections a direct link can therefore be made between stress, high blood sugar levels and therefore increased health risk.

Other studies have concluded that short-term stressors, like examination stress, have a similar effect on the human energy system as exercise energy expenditure [46]. This is due to accelerated heart rate, hastened breathing and increased neurological action [46],[47]. If the effects of exercise on the human energy system could be successfully simulated, the possibility of examining at least some stress effects also exists.

Due to the size of the world population affected by stress, many opportunities exist to improve the quality of life for a large group of people. As of yet, quantification and therefore good understanding is unavailable. If a "treatment" or "cure" could be developed for this epidemic, the owner of such a cure will control the market with phenomenal revenue prospects.

1.2.6 Other blood glucose connections

The blood sugar tract in the human energy system can be linked to many other occurrences in the body. Inaccurate control often has negative health implications. For example, as mentioned before, studies have confirmed that cardiovascular diseases, hypertension (high blood pressure), and strokes are direct causes of elevated blood glucose concentrations [48].

Long-term complications associated with diabetes mellitus are also evidence of regular high blood sugar posing a health risk. Because diabetics want to prevent hypoglycaemia (comas), they usually overcorrect their glycaemic control and deliberately induce higher blood glucose concentrations. Long-suffering diabetics then often have failing eyesight due to retinal damage, kidney failure resulting in dialysis or transplantation, neuropathy (abnormality of the nervous system) sometimes leading to amputations due to poor blood circulation, arteriosclerosis, etc. [16],[49].

On the other hand, some other studies have shown the connection between frequent low blood sugar and incidents like insomnia [50]. Whenever counter regulation hormones due to low blood glucose levels prevail in the bloodstream, lighter sleep (and often waking) is the result. This is also a possible explanation why people struggle to sleep while they experience stressful situations. More stress implies more counter regulation hormones in the bloodstream (section 1.2.5).

1.2.7 Simulation of the human energy system

The intricacies of the human energy system are being researched on a physiological and a molecular level and a vast compendium of knowledge has been accumulated. Only in recent years has medical science been able to put together a number of pieces of the puzzle [6]. This has led to the pursuit of simulation modelling as a key to advanced testing, analysis and prediction of system behaviour [51].

Most biotechnological simulation efforts throughout the world have been directed at the biochemical level. These results have been mostly inaccurate due to too many variables that cannot be sufficiently quantified. Here follows a short description of some of the known attempts at biotechnological simulation.

AIDA AIDA contains a simple model of glucose-insulin interaction in the human body. It is intended for simulating the effects on the blood glucose profile due to changes in insulin and diet for a typical insulin-dependent (Type 1) diabetic patient. The creators acknowledge that it is not possible for AIDA to accurately predict a patient's blood glucose profile. Therefore the software cannot be used for therapy planning. It is only intended to be used for educational, teaching and demonstration purposes [52].

Caltech The Caltech group published research results on the development of genomic regulatory networks. They investigated a gene regulatory network in sea urchin embryos, using simulation techniques. They suggest similar processes for the development of simulation models for humans, but no models have been developed yet [53],[54].

DARPA The USA Department of Defence is conducting research projects to construct simulation models for complex biological systems. Their aim is to develop "smart cells" to be used in security and warfare applications. The project is in its preliminary stages and no published simulation models of the human energy system could be found [55].

Diabetex Diabetex is a decision support system for the treatment of diabetic patients. It includes a network and a database of rules on the basis of known glucose-insulin relationships under different situations. According to a host of inputs the system follows two classification methods in order to suggest insulin doses for Type 1 diabetics. No active integrated simulations are performed, but empirical condition matching is performed [56].

DiasNet DiasNet is a decision support system via the Internet to aid in insulin application planning. The system is intended to incorporate a blood glucose simulation package for individual education. It is however still an on-going research effort. The simulation accuracy has not been verified or evaluated yet [52],[57].

Entelos Entelos partners with pharmaceutical and biotechnology organizations worldwide to develop treatments for diseases. They intend to accomplish this by constructing large-scale localised models of diseases using their patented "PhysioLab" technology. With their aim only at drug discovery, no evidence of dynamic integrated simulation of the full human energy system could be found [5],[53],[58],[59],[60],[61].

ISB & ARSC The Institute for Systems Biology (ISB) and the Arctic Region Supercomputing Centre (ARSC) supports genomic and proteomic research in which extremely large datasets are analysed with supercomputers. They primarily focus on data mining and not so much on process simulation. Again empirical condition matching is their main aim [53],[61].

MSC The Materials and Process Simulation Centre (MSC) is developing and validating tools for a new approach to biocatalysis and biotechnology. They use techniques of macromolecular simulation. So far they have done much research on protein design and hierarchical protein folding strategy, as well as some work on protein binding on specific DNA. However, no mention of human energy simulations could be found [62],[63].

PharSight PharSight has joint ventures with 18 of the 20 largest pharmaceutical companies in the world. They develop computer techniques and simulations (Advanced Continuous Systems Language (ACSL)) to mine existing pre-clinical and clinical trial data in order to design more efficient drug trials. They however do not perform dynamic simulations on physiochemical processes [60],[64],[65].

Physiome Physiome Sciences, in conjunction with IBM, performs research into biological systems, disease and potential drug targets. They use supercomputers to speed up research into simulating complex models of cells, organs and disease states. They also promote open standards such as CellML™ (an XML-based language to develop computer models of cells, tissues and organs) to widen their research inputs. As of yet only publications on localised cellular simulations could be found, but no publications on full body simulations are available [60],[61].

Vertex Vertex Pharmaceuticals uses a supercomputer dedicated to "in silico" drug design applications. The supercomputer analyses complex data and information generated using cell-based evaluations. Their research groups specialise in bioinformatics and pharmacology. Full body and energy system simulations were not mentioned in their publications [61].

To summarise, many companies and organisations are currently in pursuit of accurate biochemical and biotechnological simulations. However, none could be found that construct full body human energy system simulation models. A fast closing window of opportunity therefore exists for developing a simulation model that can successfully predict energy system response.

1.3 Mission statement and objectives

As will be discussed in later chapters, the human energy system is a very complex and integrated system. Therefore the first step towards simulation of the entire human energy system is the successful implementation of a simulation model for a certain part or subsystem. Because of the relatively higher degree of understanding of the blood sugar energy system this subsystem was chosen as the first attempt at simulating the entire human energy system.

The mission statement for this study therefore is the following:

"To develop a simulation model and procedure to dynamically simulate the integrated energy processes of the blood sugar energy subsystem and its controls as part of the complete human energy system."

From the above statement the following objectives were established:

- To quantify the energy as well as the flow of energy in the human energy system;
- To establish a common link between the primary role-players in the system;
- To verify this link with empirical measurements;
- To perform a thorough literature study regarding the entire human energy system;
- To develop a simplified model that represents and accurately simulates the complex system;
- To verify the accuracy of the simulation model according to certain evaluation criteria.

1.4 Beneficiaries of the study

The motivation for conducting this study can be subdivided into a few major beneficiary groups. A short description of the potential impact on each of the groups is discussed below.

Diabetes management

The first and obvious practical application of a successful simulation model is the possibility of self-managed diabetes control with a far superior degree of accuracy as opposed to the guesswork or the hit-and-miss methods currently employed [66]. The diabetic community therefore directly benefits from this study.

Weight loss

Adipose tissue growth is an important function of the human energy system [27]. Simulation and prediction of the processes regarding energy control in the system may result in future research for treatments and perhaps even cures for obesity. In the biotechnological community the benefit of faster and less expensive clinical testing as a result of simulation could also provide a much-needed competitive advantage.

Endurance exercise

Quantifying the effect of exercise on the human energy system is very beneficial to the large group of individuals concerned with endurance exercises. In future the results from accurate simulations may provide solutions to medical hurdles like diabetes control, or it may supply insight for new discoveries and products (like energy supplements, dietary enhancement, etc.) for endurance athletes.

Stress management

Successful simulation of the human energy system entails successful quantification of the effects of physiological stress and illness on humans. "Treatment" for stress may be developed with the simulations since the cost and required time to perform clinical trails are dramatically reduced. With stress growing into a widespread dilemma the impact and potential benefit of successful simulations are considerable.

Other

Human energy system simulation also provides resolution to many other medical complications like cardiovascular diseases, cancer, etc. Pharmaceutical companies and manufacturers stand first in a long line of beneficiaries when these tools are implemented. Of course the one party in control of the intellectual property is the one that has a considerable competitive advantage.

Further down the line medical practitioners can also benefit because of the development of improved treatment and solutions for their patients. This increases the productivity, understanding of the field, as well as credibility of medical practice in general.

The end-users or general public are however the largest benefactors as a result of successful simulations. Possibilities of improved treatment and products due to the simulations may result in less expensive medical cost, better quality of life and improved general well-being.

1.5 Contributions of this study

In order to achieve the objectives mentioned in Section 1.3 a few contributions were made in this study. Here follows a short description of the main contributions that are described in the preceding chapters:

- A considerable amount of confusion currently exists regarding the dietary value of food, especially that of carbohydrates (CHO). This study points out that the commonly accepted amount of energy that is available from ingested CHO is inaccurate since the human energy system cannot utilise 100% of the available energy contained in the food. In this study a method for determining the correct energy value is proposed.

- The Glycaemic Index (GI) of foods was investigated. It was found that the universal definition of GI, which is "rate of digestion", is inaccurate. A new definition as well as a new application of GI is proposed.

- To date energy flow in the human energy system could not be quantified successfully in order to simulate the processes involved in the body. To solve this problem the concept of equivalent teaspoons sugar (ets) is derived. The concept is a novel unit for quantifying energy and energy flow in the human energy system. A detailed derivation of the concept is provided as well as a comprehensive empirical verification.

- The application of the ets concept is also discussed in detail. The first of the applications is the link that can be established between ingested ets and the amount of insulin secreted by a healthy person as a result of rising blood glucose levels. It is shown that a linear relationship exists between the insulin response and the ingested ets from which the insulin requirement for Type 1 diabetics can also be calculated.

- The second application of the ets concept is the derivation of the link between endurance energy expenditure and ingested ets. An equation is derived and verified which provides a method for calculating the amount of ets an endurance athlete should ingest while exercising. The equation is then simplified even further to make its application practical.

- Next it was shown that there is a link between the ets concept and the effect of stress and illness on the human energy system. For the first time a quantification method is proposed to describe the effect of stress and illness on the human body. The link is also developed further to incorporate Type 1 diabetes and an adjustment for insulin dosages is suggested.

- In order to construct a generic simulation model for the human energy system, some background research was done concerning the major energy pathways and the control strategies involved in the system. The human energy system was summarised and detailed schematic layouts of both the energy pathways and the control system are presented.

- Lastly a detailed description of the final simulation model and the simulation procedure are provided. The system as well as the control strategies implemented for the energy flow are discussed. Also, both the implementation and thorough verification of the simulation model are presented.

1.6 Outline of the study

The study is presented in two major parts. These are shown schematically in Figure 1.1.

The first part involves the development of the ets concept, which is necessary to quantify energy flow through the human energy system. This concept is derived in Chapter 2.

Chapter 3 is a discussion of the verification of the concept. Two distinct studies are presented with which it is shown that the concept is indeed a good unit for representing energy in the human energy system. The two examples are firstly to use ets as a predictor of insulin response to ingested carbohydrates, and secondly to use ets as a quantifier of carbohydrate requirement while exercising.

Chapter 4 is an extension of the verified ets concept. It is shown that ets can be used for many applications. Two examples are presented. The first is to use ets for calculating diabetic insulin requirement. The second is to use ets for quantification of the effects of stress and illness.

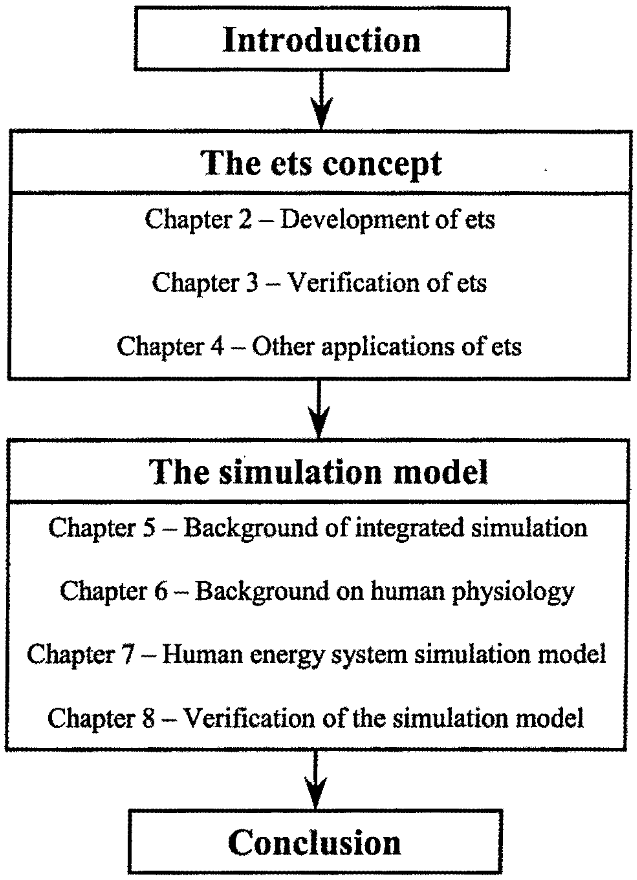

Figure 1.1 – Schematic representation of the layout of this study.

The second part of the study starts at Chapter 5.

Chapter 5 and 6 are provided as background to integrated simulation and human physiology respectively. The chapters serve as a literature study in order to develop the simulation model presented next.

In Chapter 7 the simulation model of the human energy system is presented. The ets concept, derived in the first part of the study, is used extensively for quantification of the energy flow processes.

In Chapter 8 the verification of the simulation model is then performed. It is shown that the simulation model yields acceptable results and that it is very useful as a predictor of blood glucose response to most external influences.

Lastly Chapter 9 is the conclusion of the study. In it a discussion is given on the results of the previous chapters as well as some recommendations for further work.

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