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1. Introduction

In this Chapter, we are mainly concerned with mathematical modelling (using differential equations) of controlled continuous subcutaneous infusion of insulin in Type 1 diabetes using pumps. It occurs mainly in children where controlling levels of sugar is entirely dependent on external infusion of insulin. Type I diabetes is a result of loss of beta-cell functions in the body due to an autoimmune reaction. There is vast literature concerning continuous infusion of insulin where feedback is intermittent and the dosage is ad hoc. Other ways of combating Type I diabetes include transplantation of insulin producing tissues or introducing artificial beta cells. We mathematically model the sugar concentration in the body and use it to dovetail a previously medically prescribed sugar concentration curve. The modelling, for the first time, aids the continuous infusion of insulin based upon individuals requirements in terms of the curve of decay of sugar concentration in a prescribed time. For each individual, depending on many personal factors like obesity, age, kidney functions, etc., a prescription is made of the desirable curve of sugar concentration from its highest level to the desired lowest level in a given period of time. This fine tunes the delivery of insulin as it takes away much guesswork of amounts of insulin given intermittently or continuously. Devices attached to continuous monitoring device will infuse insulin continuously and as per prescribed curve of reduction of sugar concentration. Thus, the pumps delivery takes into consideration the time profile of the insulin release, with the release stopping after the prescribed values are attained. The amount released in a dual wave shaped insulin bolus combining [8] both the usual normal and square wave methods. The therapy described will be the forerunner of intense clinical research work. Mathematical models with numerical simulations and analysis based on experimental data can be more effective in terms of costs and an extraordinary amount of time dealing with diverse physiological situations. This is particularly so in view of the complexities of the functions in the human body and incomplete existing knowledge.

This chapter provides an overview of mathematical modelling of type 1 diabetes, with particular focus on pump therapy as a management strategy for continuous subcutaneous insulin infusion. Previous models describing the mechanism of glucose metabolism have mostly focused on type 2 diabetes, most notably the classical minimal model for explaining the profile of glucose concentration over time.[4,5] Here we summarize the conclusions of
these studies for management of diabetes, and attempt to lay out a framework for further development of these models to include pump therapy. These models are often formulated as a system of differential equations that describes the profile of insulin release and the dynamics of glucose concentration over specified period of time. In addition to providing background on existing modelling frameworks, the practical implications of their outputs are discussed.

The main goals are (a) formulation of the model using the pump mechanism (b) defining the parameters (c) profiling the insulin release (d) simulating using estimated parameter values and (e) modelling extensions to include obesity as it had been well established that obesity promotes insulin resistance through the inappropriate inactivation of a process called gluconeogenesis, where the liver creates glucose for fuel. The model consists of blood glucose concentration, remote insulin action and amount of insulin. The model predictions include insulin secreted, if any, in pancreas, role of other organs, tissue uptake etc. This chapter closes with future direction in mathematical modelling of type 1 diabetes for optimal usage of external insulin and measuring insulin dependency with an insight into the role of obesity in developing diabetes.

2. Diabetes

2.1 What is diabetes?
Diabetes is a global problem with devastating human, social and economic impact. Diabetes is a growing epidemic threatening to overwhelm global healthcare services, wipe out some indigenous populations and undermine economies worldwide, especially in developing countries. Today more than 250 million people worldwide are living with diabetes and by 2025, this total is expected to increase to over 380 million people. Approximately 24 million people are diabetics in United States which is about 8 percent of the total population. The number of people with diabetes is increasing due to population growth, aging, urbanization, and increasing prevalence of obesity and physical inactivity. Diabetes is a highly prevalent disease in India where more than 35 million people suffer from diabetes. Alarmingly, as much as 13 million cases remains undiagnosed which leads to long term complications. The prevalence of diabetes is greater amongst the urban South Asian population (12-15%) compared to urban population in the West (6%).[9] That is why Diabetes has been one of the most important subjects for biomedical research for many years.
Diabetes Mellitus, commonly referred to as Diabetes, means sweet urine. Consistently elevated levels of blood glucose lead to spillage to glucose into urine, hence the term sweet urine. When the blood sugar level consistently runs too high in our blood stream, the condition is named as Diabetes. In patients with Diabetes Mellitus, the absence or insufficient production of insulin by the liver causes hyperglycemia. Diabetes Mellitus is a syndrome characterized by chronic hyperglycemia resulting from absence or relative impairment in insulin secretion and/or insulin action. It can also be referred to as a condition characterized by the disturbances of carbohydrate, protein and fat metabolism, the way our bodies use digested food for growth and energy. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels.[7] Diabetes is the most common endocrine disorder. It is a chronic medical condition meaning it can last a lifetime which can be controlled but can not be cured completely.
\begin{align}
\frac{dX}{dt} &= -p_1 X + p_2 (I - I_0), \\
\frac{dI}{dt} &= -I_2 (G - G_c) f(t) - I_3 (I - I_0),
\end{align}

where $G$ is the blood glucose concentration, $X$ is an auxiliary function representing remote insulin action, and $I$ is the insulin plasma concentration. A description of the model parameters and their values are given in Table 1.

The important part of this extension is the first term of (7) which models all three factors mentioned above. This term contributes to the insulin plasma when the glucose concentration exceeds the threshold $G_c$, and is defined as

\begin{equation}
I_2 (G - G_c) \begin{cases}
I_2 (G(t) - G_c) f(t) & \text{if } G(t) > G_c \\
0 & \text{if } G(t) < G_c
\end{cases}
\end{equation}

The function models the profile of insulin release from the pump, and the coefficient represents a scaling factor determining TDD of insulin released by the pump. In the next section, we discuss different profiles of insulin release and compare their effects on the optimal control of glucose concentration. The newer generation of pumps can be programmed to release insulin using three different bolus techniques.

A normal bolus can be used if small amounts of carbohydrates are consumed or if a correction to the blood glucose level outside the physiological range needs to be made. A square wave profile is helpful when eating foods that are high in both fat/protein and carbohydrate (fat and protein delay the absorption of carbohydrates). If a normal bolus is given for a meal high in protein and fat concentrations, circulating insulin levels rise rapidly and may peak before the carbohydrates are absorbed. This mismatch in insulin and blood glucose levels can result in postprandial hypoglycemia. Therefore, a dual wave bolus, as a combination of the normal and square wave bolus techniques, can be introduced. Using this technique, half of the insulin dose is given (over a short period of time) at the onset of the meal, and the remainder over a 2–4 h period. The profile of a dual wave bolus is modeled as a function of time, $f(t)$, in Eq. (4) over a period of 3 h (Fig. 1(a)–(c)).

![Fig. 1. Profile of insulin release by the pump $f(t)$, for 3h: HLL release; (b)LHL release; (c) LLH release, where $H$ stands for high amount release of insulin and $L$ stands for its low amount per hour $f(t)$ is normalized so that $H=L$.](www.intechopen.com)
<table>
<thead>
<tr>
<th>S No</th>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$G_b$</td>
<td>Base line value of glucose concentration in plasma</td>
<td>118</td>
<td>mg dl$^{-1}$</td>
</tr>
<tr>
<td>2</td>
<td>$G_c$</td>
<td>Glucose threshold concentration in plasma</td>
<td>100-107</td>
<td>mg dl$^{-1}$</td>
</tr>
<tr>
<td>3</td>
<td>$I_b$</td>
<td>Baseline value of insulin concentration in plasma</td>
<td>7</td>
<td>µU ml$^{-1}$</td>
</tr>
<tr>
<td>4</td>
<td>$I_1$</td>
<td>The insulin dependent rate of tissue glucose uptake</td>
<td>10</td>
<td>Min$^{-1}$</td>
</tr>
<tr>
<td>5</td>
<td>$I_2$</td>
<td>Scaling factor determining TDD of insulin</td>
<td>Variable</td>
<td>min$^{-1}$ µU mg$^{-1}$</td>
</tr>
<tr>
<td>6</td>
<td>$I_3$</td>
<td>The rate of decay for insulin in plasma</td>
<td>0.264</td>
<td>min$^{-1}$</td>
</tr>
<tr>
<td>7</td>
<td>$P_1$</td>
<td>The rate of spontaneous decrease of glucose uptake</td>
<td>0.0107</td>
<td>min$^{-1}$</td>
</tr>
<tr>
<td>8</td>
<td>$P_2$</td>
<td>The rate of insulin – dependent increase in tissue glucose uptake due to insulin concentration excess over its baseline</td>
<td>0.007</td>
<td>min$^{-2}$ µU ml$^{-1}$</td>
</tr>
</tbody>
</table>

Table 1. Description and values of the model parameters obtained from the published literature


2.7 Future work
More advanced mathematical models can be formulated to explain the effects of obesity on diabetes, effects of exercise on management of type 2 diabetes. Parameters involving glucose sensors can be added to the insulin pump model for a better programmed insulin delivery by insulin pump.

3. References


This book is intended as an overview of recent progress in type 1 diabetes research worldwide, with a focus on different research areas relevant to this disease. These include: diabetes mellitus and complications, psychological aspects of diabetes, perspectives of diabetes pathogenesis, identification and monitoring of diabetes mellitus, and alternative treatments for diabetes. In preparing this book, leading investigators from several countries in these five different categories were invited to contribute a chapter to this book. We have striven for a coherent presentation of concepts based on experiments and observation from the authors own research and from existing published reports. Therefore, the materials presented in this book are expected to be up to date in each research area. While there is no doubt that this book may have omitted some important findings in diabetes field, we hope the information included in this book will be useful for both basic science and clinical investigators. We also hope that diabetes patients and their family will benefit from reading the chapters in this book.

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