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Therapeutic Modelling of Type 1 Diabetes

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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 adhoc. 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.

Human body functions best at a certain level of sugar in the blood stream. Blood sugar levels are tightly controlled by insulin, the principal hormone that makes it possible for many cells (primarily muscle and fat cells) to use glucose from the blood. It is manufactured by the beta cells of the pancreatic islets of Langerhans, a small section of the pancreas. Secretion of insulin primarily occurs in response to increased concentration of glucose in the blood. Insulin helps the glucose from food get into the body cells. If body does not make enough insulin or if the insulin does not work the way it should, glucose can not get into the cells. It stays in the blood instead and blood glucose level gets too high causing to have Diabetes. Deficiency of insulin or its action plays a central role in all forms of diabetes. There are three major forms of diabetes:[18]

2.1.1 Type 1 diabetes

Type 1 diabetes is one of the most challenging medical disorder because of the demands it imposes on day-to-day life. It was formerly known as insulin dependent diabetes mellitus (IDDM) or juvenile onset diabetes mellitus.

In this type of diabetes, the pancreas undergoes an autoimmune attack by the body itself and is rendered incapable of making insulin. It is an autoimmune disorder, in which body's own immune system attacks the beta cells in the islets of Langerhans of the pancreas destroying them or damaging them sufficiently to reduce insulin production. The pancreas then produces little or no insulin. At present, scientists do not know exactly what causes the body's immune system to attack the beta cells, but it is believed that autoimmune, genetic, and environmental factors, possibly viruses, are involved. It develops most often in children and young adults, but can appear at any age.Type 1 diabetes, which predominately affects youth, is rising alarmingly worldwide, at a rate of 3% per year. Some 70,000 children worldwide are expected to develop type 1 diabetes annually. If not diagnosed and treated with insulin, a person with type 1 diabetes can lapse into a life-threatening diabetic coma, also known as diabetic ketoacidosis.

2.1.2 Type 2 diabetes

Type 2 diabetes, formerly called adult-onset diabetes or non-insulin- dependent diabetes mellitus (NIDDM), is the most common form of diabetes. Type 2 diabetes is responsible for 90 -95% of diabetes cases and is increasing at alarming rates globally as a result of increased urbanization, high rates of obesity, sedentary lifestyles and stress. Type 2 diabetes is increasingly being diagnosed in children and adolescents though it can occur at any age. Millions of people don't even know they have it because it can arise with minimal outward signs or symptoms. It is diagnosed with insulin resistance in which the pancreas is producing enough insulin but for unknown reasons, the body can not use the insulin effectively. This leads to a situation similar to type 1 diabetes in which the pancreas can't secrete enough insulin because of which glucose builds up in the blood and the body cannot make efficient use of its main source of fuel. This form of diabetes is associated with obesity, older age, a family history of diabetes, a history of gestational diabetes, certain medications, impaired glucose metabolism, psychological factors, and physical inactivity. Type 2 diabetes can be controlled with exercise, diet and lifestyle modifications.[6] This type of diabetes may develop microvascular complications, which may lead to retinopathy, nephropathy and peripheral and autonomic nephropathies, and macrovascular complications include atherosclerotic coronary and peripheral arterial disease.

2.1.3 Gestational diabetes

This type of diabetes develops just before or during the pregnancy. Though the patient may have diabetes before the onset of the pregnancy, it is termed gestational only if it is first identified after the pregnancy has occurred. Gestational diabetes is caused by the hormones of pregnancy which is produced when the placenta supports the growing fetus. These hormones may interfere with the mother's ability to produce and use her own insulin. Usually this form of diabetes goes away after the delivery but women who have had gestational diabetes have a 20 to 50 percent chance of developing type 2 diabetes within 5 to 10 years especially those who require insulin during pregnancy and those who are overweight. Untreated Gestational Diabetes Mellitus (GDM) can lead to fetal macrosomia, hypoglycemia, hypocalcemia and hyperbilirubinemia. Also chances of cesarean delivery and chronic hypertension increases in women with GDM.

2.2 History and causes of diabetes

Diabetes is not a newly born disease, it has been with human race from long back but, we came to knew about it in 1552 B.C. Since after than, many of Greek as well French **physicians** had worked on it and threw some light on the nature of disease, organs responsible for it etc. Diabetes was recognized and categorized with complete details and its types, Type 1and Type 2 in 1959. In 1870s, a French physician had discovered a link between Diabetes and diet intake, and then diabetic diet was formulated with inclusion of milk, oats and other fiber containing foods in 1900-1915. Dr. Frederick Banting, Prof. Macleod and Dr. Collip discovered the function of **insulin**, its nature, along with its use started at the University of Toronto from 1920 -1923, who were awarded a Noble prize. In 1922, 14 year old Leonard Thompson becomes the first human to receive insulin. In the decade of 1940, it has been discovered that different organs like kidney and skin are also affected if diabetes is creeping from a long term. A major turn in this **research** was in 1955, when the oral hypogycemic drugs had been manufactured. Paul E. Lacy, a JDRF – funded researcher at Washington University School of Medicine performs the first successful islets transplantation in diabetic animal models in 1976. The first experimental insulin pump was developed in 1979 which leads to further refined pumps to provide the infusion of insulin in a way which closely mimics the glucose response of human islets. Since then, scientists are trying their best to produce results with the most impact.

Diabetes and its complications occur among Americans of all ages and ethnicities but the elderly and certain racial/ethnic groups are more commonly affected. In comparison of non – Hispanic whites, African Americans and Hispanics/Latino Americans are about two times more likely to be affected by the disease. It has been found that one tribe in Arizona has the highest rate of diabetes in the world, with about 50 percent of the adults between the ages of 30 and 64 with the disease. Population of type 2 diabetes sufferers has officially reached epidemic proportions.

Diabetes mellitus is developed when pancreatic tissue responsible for the production of insulin is absent because it is destroyed by disease such as chronic pancreatitis, trauma or surgical removal of pancreas. It can also result from other hormonal disturbances such as excessive growth hormone production (acromegaly, in which a pituitary gland tumor at the base of the brain causes excessive production of growth hormone leading to hyperglycemia) and Cushing's syndrome, in which the adrenal glands produce an excess of cortisol which promotes blood sugar elevation. Several other factors that make it more likely that a person develop diabetes are as follows:

- Age-older than 45 years
- Obesity
- Family history of diabetes in a first degree relative (parent or sibling)
- History with gestational diabetes mellitus
- Hispanic, Native American, African American, Asian American or Pacific Islander descent
- Hypertension (>140/90 mm Hg) or dyslipidemia (high-density lipoprotein HDL cholesterol <35mg/dl or triglyceride level >250mg/dl)

2.3 Symptoms and diagnosis of diabetes mellitus

Diabetes mellitus (DM) has diverse intial presentations. The early symptoms of diabetes are related to elevated blood sugar levels in the body and loss of glucose in the urine. It usually presents with symptomatic hyperglycemia. Common sign and symptoms may include any of the following:

- Being very thirsty
- Urinating often
- Feeling very hungry or tired
- Losing weight without trying
- Repeated or slow healing infections
- Having dry, itchy skin
- Extreme fatigue
- Blurred vision
- Tingling or loss of feeling in the hands or feet

2.4 Biological terms commonly used in diabetes

Insulin: An anabolic hormone, produced by the beta cells of the islets of Langerhans of pancreas in response of elevated blood sugar level in the body. It helps to control the blood sugar level in the desirable range.

Glucose: Glucose is a simple sugar present in everyone's body. It is an essential nutrient that provides energy for the proper functioning of the body cells. After meals, food is digested in the stomach and intestines. The glucose in digested food is absorbed by the intestinal cells into the blood stream and is carried by the blood to all the cells in the body. Glucose needs insulin to enter into the body as it can not get into the cells alone.

Glucagon: Glucagon is a hormone synthesized and secreted from alpha cells of the pancreatic islets used for carbohydrate metabolism. Its secretion increases rapidly when the sugar level is too low in the body. It maintains the level of glucose in the blood by binding to specific receptors on hepatocytes causing the liver to release its intracellular stores of glucose. As these stores become depleted, glucagon then encourages the liver to synthesize glucose by gluconeogenesis which will be released to prevent the development of hypoglycemia, low sugar level.

Insulin Resistance: Sometimes the cells throughout the body become resistant to the insulin produced by the pancreas due to which it becomes difficult for the sugar to enter the cells. This condition is known as insulin resistance.

Diabetic Ketoacidosis: It is a condition in which the cells of muscle, liver and other body parts are unable to take up glucose for producing energy due to the absence of insulin. It is a

state of absolute or relative **insulin deficiency** aggravated by hyperglycemia, dehydration, and acidosis-producing derangements in intermediary metabolism. To avoid starvation the body begins to break down fat for energy. Fatty acids and ketone bodies are released due to the break down of fat causing chemical imbalance (metabolic imbalance) called Diabetic Ketoacidosis. Moderate or large amounts of **ketones** in urine are dangerous. They upset the chemical balance of the blood.

Chronic hyperglycemia: Chronic hyperglycemia means elevated blood sugar level in the blood.

2.5 Treatment therapies for diabetes

Type 1 Diabetes is very serious, with a sudden and dramatic onset, usually in youth. Type 1 diabetes is an autoimmune condition, where the body attacks its own insulin producing cells. The body's immune cells, or white blood cells, include B cells and T cells. B cells make antibodies and present 'antigens' to T cells, allowing them to recognize, and kill invaders. People with Type 1 diabetes must maintain an insulin-monitoring and insulin-injecting regimen for the rest of their lives as the islets of Langerhans are destroyed in this type of diabetes. Treatment for type 1 diabetes includes taking insulin shots or insulin pump to deliver insulin in the body, making wise food choices, exercising regularly and controlling blood pressure and cholesterol.

Type 2 diabetes can be treated successfully with diet, physical activity and medication, if necessary.[23] Physical activity can help to control blood sugar levels and increases body's sensitivity to insulin.[6] Also, it helps delays or stop heart diseases, a leading complication of diabetes. Diet plays an extremely important role in controlling this type of diabetes. Being overweight can increase the chances of developing type 2 diabetes. Usually GDM in pregnant women disappears itself after delivery.

2.6 Mathematical model

The first approach to measure the insulin sensitivity *in vivo* was introduced by Himsworth and Ker [24] and the first mathematical model to estimate the glucose disappearance and insulin sensitivity was proposed by Bolie. In this model, he assumed that glucose disappearance is a linear function of both glucose and insulin. The insulin secretion and disappearance is proportional to glucose and plasma insulin concentration respectively.

The main objective here is to prescribe a more accurate, but less simple, method of arranging the palatable composition of a diabetic diet.

The modified coupled differential equations for the plasma glucose and insulin concentration [1-14, 16-22], when the normal fasting level of plasma glucose is 70 - 120 mg/dl, are given as follows

$$\frac{dg}{dt} = -l_1 h\bar{g} + l_2\left(g_0 - g\right)U\left(g_0 - g\right) + l_3 F\left(t\right) \tag{1}$$

$$\frac{dh}{dt} = l_4\left(g - g_0\right)U\left(g - g_0\right) - l_5 h_0 + l_6 I\left(t\right) \tag{2}$$

where, g(t) - plasma glucose concentration, h(t) - insulin concentration, l_i - sensitivity constants, i = 1,2,3,4,5,6, F(t) - food source input for plasma glucose, I(t) – insulin input and $U(g_0 - g)$ is unit step function.

The insulin input I(t) will be given through injection at subcutaneous level at periodic intervals, which leaks its contents into the system over a period of time. Therefore, I(t) may be defined as

$$I(t) = \frac{\rho t}{\bar{t} - t_0} + b$$

At $t = t_0$, $I(t) = 0$

$$\Rightarrow b = -\frac{\rho t_0}{\bar{t} - t_0} \qquad \therefore I(t) = \frac{\rho (t - t_0)}{\bar{t} - t_0} \qquad = \lambda + \mu t \tag{3}$$

where, $\lambda = -\frac{\rho t_0}{\bar{t} - t_0}$, $\mu = \frac{\rho}{\bar{t} - t_0}$, ρ - quantity of injection, t_0 – time of injection, $\bar{t}$ -time lag to maximum.

Food input source term, F(t), is the source for food input to the plasma glucose level, the contents of which are reduced in a simple exponential manner. Therefore, F(t) may be modeled as

$$F(t) = \begin{cases} Se^{-\alpha(t-t_0)}, & t > t_0 \\ 0, & t \le t_0 \end{cases} \tag{4}$$

where, S - quantity constant of meal, α - delay parameter.

For $t \ge t_0$, in non – diabetic case, $F(t) \neq 0$ and $I(t) = 0$ and for diabetic case, $F(t) \neq 0$, $I(t) \neq 0$.

A mathematical model for the dynamics of glucose concentration in patients with type 1 diabetes using CSII [15] therapy as an external source of insulin has been developed by us. We attempt to model the effect of an external source of insulin release, as a prescribed function of time, on glucose levels. The model is then used to assess the optimal insulin release profile, and the threshold amount required to bring the level of glucose to within a normal physiological range.

To model the pump's delivery of insulin, we take into account three major factors: (i) the total amount of insulin released over a specific period; (ii) the time profile of insulin release, f(t); and (iii) the glucose threshold concentration Gc, below which the pump stops releasing insulin. The amount of insulin (TDD) is proportional to the total amount of glucose, whose concentration is assessed by the sensor in the pump's controller. This amount is released by the pump in a dual wave shaped insulin bolus which allows the patient to combine both normal and square wave techniques. The body characteristics of the patient determine how much insulin is needed to maintain the glucose level within the normal physiological range after each meal. The dual wave shape also provides a rapid increase in insulin plasma concentration, and sustained high circulating insulin levels while a meal is being consumed. Here, we extend the minimal model to incorporate the above factors, which leads to the following differential equations:

$$\frac{dG}{dt} = -XG + l_1 (G_b - G)^+, \tag{5}$$

$$\frac{dX}{dt} = -p_1 X + p_2(I - I_b), \tag{6}$$

$$\frac{dI}{dt} = -l_2(G - G_c)^+ f(t) - l_3(I - I_b), \tag{7}$$

where G is the blood glucose concentration, X is an auxiliary function representing remote insulin action, and 1 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 Gc, and is defined as

$$l_2(G - G_c)^+ = \begin{cases} l_2(G(t) - G_c) f(t) & if\ G(t) > G_c \\ 0 & if\ G(t) < G_c \end{cases} \tag{8}$$

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)).

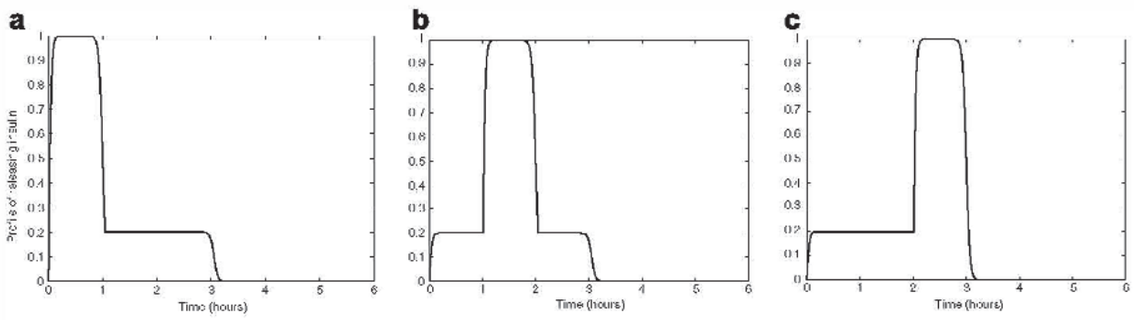

Fig. 1. Profile of insulin release by the pump $f(t)$, for 3h: HLL release; (b)LHL release; (c) LLH release, where H stands for high amount release of insulin and L stands for its low amount per hour $f(t)$ is normalized so that $H=L$

S No	Parameter	Description	Value	Unit
1	G_b	Base line value of glucose concentration in plasma	118	mg dl^{-1}
2	G_c	Glucose threshold concentration in plasma	100-107	mg dl^{-1}
3	I_b	Baseline value of insulin concentration in plasma	7	μU ml^{-1}
4	l_1	The insulin dependent rate of tissue glucose uptake	10	Min^{-1}
5	l_2	Scaling factor determining TDD of insulin	Variable	min^{-1} μU mg^{-1}
6	$l_{3``}$	The rate of decay for insulin in plasma	0.264	min^{-1}
7	p_1	The rate of spontaneous decrease of glucose uptake	0.0107	min^{-1}
8	p_2	The rate of insulin – dependent increase in tissue glucose uptake due to insulin concentration excess over its baseline	0.007	min^{-2} μU ml^{-1}

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

This particular work is published in Applied Mathematics and computation, 2007, pages 1476 – 1483 and has been cited by Kato, R, Munkhjargal, M and Takahashi, D "An autonomous drug release system based on chemo- mechanical energy conversion "Organic Engine" for feedback control of blood glucose", Biosensors and Bioelecetronics in 2010 Vol 26(4), pages 1455 - 1459.

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.

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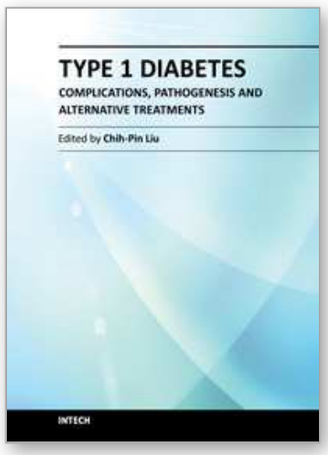

Type 1 Diabetes - Complications, Pathogenesis, and Alternative Treatments

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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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