

# Optimization for Parameter Estimation in Mathematical Model to Predict the Behaviour of Immune System

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## Abstract:

This paper surveys and compares various optimization functions related to diabetes to study the various parameter affecting on diabetes. The most important stage in improving the precision and predictive ability of mathematical models is parameter estimation. Mathematical models for immunity are used to describe and predict the behaviour of the immune system in response to infections, vaccinations, and various other immunological processes. These models are quite complex, involved differential equations and various parameters. Ongoing research aims to better understand these immune-related conditions and develop targeted treatments to modulate immune responses appropriately related to diabetes disease.

**Keywords:** Immunotherapy, Decision Variable, Multistage Model, Auto immune, Diabetes Mellitus.

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## Introduction:

### 1.1 Background

An immune system always protects the human body from infections, diseases, and other threats. Understanding the compatible dynamics of immune responses is essential for developing effective treatments, vaccines, and therapies. Human health is totally depending on the immune system if it is strong then human health is strong and if one of the parameters related to immune system is weaken then its directly affect the human health. Mathematical modelling offers a powerful approach to study the complexities of the immune system, providing insights that can guide experimental research and clinical interventions. The relationship between diabetes and the immune system is complex, and it varies depending on the type of diabetes [1]. Diabetes which is also known by the name diabetes mellitus. If one of the persons suffered from the diabetes then it can't end by just taking a medicine or stop within 5 to 6 days, with proper medicine, diet, exercise it can just control. So, diabetes is also known to be a one of the most killer diseases in the world. Diabetes occurs in human being when pancreas is unable to secrete the proper insulin so that the glucose level in the body cannot be controlled. Insulin is one of the hormones produce by the pancreas to regulates the blood sugar [2]. Again, person suffered from the diabetes having the different kind of sugar level. Most of the higher risk diseases like heart stroke, brain disorder, effects on eye sight, improper kidney function, effects on the nervous system etc. are occurred in human being only due to the diabetes.

Diabetes is of two types mainly: Type-1 or T1 diabetes and Type-2 or T2 diabetes. Type-1 diabetes is characterized by an autoimmune response. Beta cells in the pancreas responsible for producing the insulin which is required to control the glucose in the blood. In auto immune response insulin-producing beta cells in the pancreas destroys and attacks by the immune system mistakenly. 2 types of T cell mainly regulatory T cells and autoreactive T cells involved in the diabetes [3,6]. Autoreactive T cell kills the cells which is responsible for creating the insulin to control the glucose level in human body while regulatory cells control the autoreactive T cells. Hereditary and environmental factors might cause this autoimmune reaction. The immune system's T cells and antibodies are responsible in the breakdown of beta cells in individuals who have Type 1 diabetes. Insulin, a hormone required for controlling blood sugar (glucose) levels, is thus lacked [4-5].

Type-2 diabetes is not be considered as an autoimmune disorder, as research suggests in the development of insulin resistance that chronic low-grade inflammation may play a role. Due to insufficient secretion of insulin, blood glucose levels rise. Which is the body's cells ineffective response to insulin. Insulin resistance is generally associated with the Obesity. Hence obesity is also responsible for type 2 diabetes. Not all obese human being suffered from type 2 diabetes as it depends on immunity of persons and heredity [7]. Gestational diabetes is again one of the types of the diabetes but it occurs only during the stage of pregnancy and it goes away when baby is born, later on it can convert to the type 2 diabetes depending upon the immune system level [8]. Study of diabetes is most important as now a days its frequently occurred is all age levels and also the human being suffered from diabetes having different range of glucose level (Pre meal or post meal), it varies person to person. The reading regarding the diabetes of a single person also varies day by day.

## 1.2 Objective:

The next step in an optimization method is to assign values to the unknowns from the permitted domain so that all constraints are satisfied and the objective function is optimized. The optimization method looks for a solution in a search space,  $S$  of solutions, in order to accomplish this goal. In the context of a diabetes model, parameter estimation involves determining the values of the model's parameters to best fit the available data. Diabetes models can range from simple to complex, often involving mathematical equations that describe the relationships between variables related to glucose and insulin dynamics [9].

Multi-objective optimization is a part of multiple-criteria decision making that includes mathematical optimization problems having multiple objective functions that must be maximized simultaneously. In numerous biological domains, multi-objective vector optimization has been utilized [10]. When creating a mathematical model for immunotherapy, it's essential to carefully define the decision variables based on the specific goals of the model, whether it's optimizing treatment outcomes, resource allocation, or other objectives.

Additionally, the model may include constraints, such as safety limits and ethical considerations, to ensure realistic and practical solutions. identifying parameters for a number of associated diseases and using those parameters to compute usefully the impact of a big immunization program. Multiline objective functions typically refer to optimization problems with objectives that span multiple lines or equations [11]. In mathematical optimization, an objective function is a function that is to be

optimized, either minimized or maximized, by choosing the values of the decision variables. When the objective function involves multiple criteria or components [12].

### **Multistage Modelling**

Explore the potential for developing multistage models that integrate different levels of biological information to capture complexity. In mathematical modelling, decision variables represent the quantities or factors that decision-makers can control or manipulate to optimize a certain outcome. In the context of immunotherapy, the decision variables may vary depending on the specific goals, constraints, and characteristics of the model[13]. Here are some potential decision variables of immunotherapy related to the diabetes considered. Glucose levels of patients are not constant, even individual patients glucose levels are not constant its always varies according to the intake of food and the physical activities. So, treatment on a specific disease is also varies according to glucose level, insulin secretion, and immunity of the person.

#### **1. Dosage Levels:**

**Decision Variable:** The amount or concentration of the immunotherapy drug administered to the patient. Dosage may vary according to glucose level of person. If glucose concentration is high insulin secretion is low then person need to take more dosages of medicine to control the glucose level. Sometime high intake of medicines may affect on other organs so its objectives should be to minimize the side effects.

**Objective:** Minimizing potential side effect.

**2.Duration of Treatment:** If the immunity of one of the persons is strong then it helps to cure the diseases within short period of time. But if the diabetes damaged the one of the essential organs of the human body or it attacked vigorously on one of the body parts then immune system takes more times to cure the diseases.

**Decision Variable:** The total duration of the immunotherapy.

**Objectives:** Optimize the treatment duration to achieve sustained.

#### **3.Combination of Therapies:**

**Decision Variable:** Selection and dosage of additional therapies in combination with immunotherapy.

**Objectives:** Identify the most effective combination of treatments to enhance overall therapeutic outcomes.

In the context of diabetes and multistage mathematical modelling, decision variables can be used to represent parameters that healthcare providers adjust to optimize diabetes management Here are some potential decision variables related to diabetes: Diabetes is a long-term illness that impacts the body's utilization of glucose, or blood sugar. Uncontrolled diabetes can lead to various complications and side effects. It's essential to remember that individuals may experience side effects differently in terms of intensity and frequency. And proper management of diabetes can help mitigate these risks. Here are some common side effects and complications associated with diabetes:

**Minimize:**  $\{f_1(x,y,z), f_2(x,y,z), f_3(x,y,z), f_4(x,y,z), f_5(x,y,z)\}$

Subject to the constraint:

$$g(x,y,z) \leq 0 \quad \text{and} \quad h(x,y,z) \leq 0$$

**Cost constraints:**

**Decision Variable:** Consideration of the budget or cost constraints associated with the immunotherapy.

**Objective:** Balance treatment with the economic feasibility of the immunotherapy strategy.

**Treatment schedule:**

**Decision Variable:** The timing and frequency of immunotherapy administrations.

**Objectives:** Develop an optimal treatment schedule that balances effectiveness with patient convenience.

In this case, the objective is to minimize  $f_1(x, y, z), f_2(x, y, z), f_3(x, y, z), f_4(x, y, z), f_5(x, y, z)$  simultaneously.

Multiline objective functions often arise in real-world optimization problems where there are multiple criteria to be considered, and the aim is to find the set of decision variables which optimize these criteria subject to certain constraints. The values of the specified variables that produce the best overall solution that corresponds with the objectives are then determined using optimization algorithms.

Minimize:  $\{f_1(x, y, z), f_2(x, y, z), f_3(x, y, z), f_4(x, y, z), f_5(x, y, z)\}$

**Insulin Dosage:**

$G(t)$ : Concentration of Plasma at time  $t$ .

$X(t)$ : Action of the Insulin at time  $t$ .

$G_b$ : glucose concentration

**Rate of change of glucose concentration**

$$\frac{dG(t)}{dt} = -p_1 \cdot [G(t) - G_b] - X(t) \cdot G(t)$$

This equation describes the rate of change of glucose levels with respect to time  $t$ .  $p_1$  represents the rate of glucose disappearance,  $G_b$  is the basal glucose concentration, and  $X(t)$  represents action of the Insulin at time  $t$ . Concentration of the glucose is totally depending on the secretion of insulin. Minus sign is used as to minimize the glucose concentration in the plasma.

**Rate of change of Insulin decay**

$$\frac{dX(t)}{dt} = -p_2 \cdot X(t) + p_3 \cdot [I(t) - I_b]$$

This derivative describes change of insulin action with respect to time.  $p_2$  represents the rate of insulin action decay,  $I_b$  represents the basal insulin concentration. Where  $I(t)$  represent concentration of the insulin at time.

### Insulin Secretion:

$$I(t)=S(t) \cdot (G(t)-G_b)$$

This equation represents a simple model of insulin secretion  $S(t)$ , based on the difference between actual and basal glucose levels. It's necessary to keep in mind that the frequency and severity of side effects can vary from person to person, and that managing diabetes well can reduce these risks. Here are some common side effects and complications associated with diabetes:

### General Diabetes Model:

Diabetes may consider as slow poisoned diseases which destroys the working ability of the important organs and always effect on how the body uses the blood glucose Diabetes which is uncontrolled can lead to various complications hyperglycemia, hypoglycemia, Cardiovascular complications, Neuropathy, Nephropathy, Retinopathy, skin complications Gastroparesis, complications in pregnancy. Sometimes these kind of diseases leads to the death.

Creating a mathematical model that encompasses all the mentioned complications of diabetes involves a complex system of equations and parameters [14]. Developing a comprehensive model requires consideration of various physiological processes, interactions, and feedback mechanisms.

The model simulates the dynamic interaction between glucose and insulin, considering glucose production utilization, and insulin action. Insulin action is influenced by both the insulin concentration and its decay rate. The model can be extended to include meal intake, physical activity, and more sophisticated representations of insulin secretion.

**Minimize  $\{f(x)\}$**   $\{(G(t), I(t), X(t), H(t), C(t), N(t), K(t), R(t), S(t), Gp(t), P(t))\}$

### Decision Variable:

$G(t)$ : concentration of plasma glucose at time t.

$I(t)$ : Concentration of Insulin at time t.

$X(t)$ : Action(effectiveness) of the Insulin at time t.

$H(t)$ : Plasma glucagon concentration at time t.

$C(t)$ : Cardiovascular health metric.

$N(t)$ : Neuropathy index.

$K(t)$ : Kidney function index.

$R(t)$ : Retinopathy index.

$S(t)$ : Skin health metric.

$Gp(t)$ : Gastric motility index (for gastroparesis).

$P(t)$ : Pregnancy-related index.

### Rate of change of concentration of glucose

$$\frac{dG(t)}{dt} = -p_1 \cdot (G(t) - G_b) - X(t) \cdot G(t)$$

### Rate of change of Insulin decay

$$\frac{dI(t)}{dt} = S(t) \cdot (G(t) - G_b) - p_2 \cdot I(t)$$

### Rate of change of action of the Insulin

$$\frac{dX(t)}{dt} = -p_3 \cdot X(t) + p_4 \cdot I(t)$$

### Rate of Hypoglycaemia Risk

$$\frac{dH(t)}{dt} = p_5 \cdot (G(t) - G_b) - p_6 \cdot I(t)$$

### Rate of Cardiovascular Risk

$$\frac{dC(t)}{dt} = p_7 \cdot G(t) - p_8 \cdot X(t) + p_9 \cdot (I(t) - I_b)$$

### Rate of Neuropathy Risk

$$\frac{dN(t)}{dt} = p_{10} \cdot (G(t) - G_b) - p_{11} \cdot X(t)$$

### Rate of Nephropathy Risk

$$\frac{dP(t)}{dt} = p_{12} \cdot G(t) - p_{13} \cdot X(t) + p_{14} \cdot [I(t) - I_b]$$

### Rate of Retinopathy Risk

$$\frac{dR(t)}{dt} = p_{15} \cdot (G(t) - G_b) - p_{16} \cdot X(t)$$

### Rate of Skin complication Risk

$$\frac{dS(t)}{dt} = p_{17} \cdot G(t) + p_{18} \cdot X(t) - p_{19} \cdot I(t)$$

### Rate of Gastroparesis Risk

$$\frac{dGp(t)}{dt} = p_{20} \cdot (G(t) - G_b) - p_{21} \cdot X(t)$$

### Rate of pregnancy complications Risk

$$\frac{dPp(t)}{dt} = p_{22} \cdot (G(t) - G_b) + p_{23} \cdot X(t) - p_{24} \cdot I(t)$$

### Parameters:

$P_i$  -parameters affecting rate of glucose, insulin decay, changes in insulin concentration and risks associated with complications.

$P_j$  -parameters used to evaluate skin health, cardiovascular complications, neuropathy, nephropathy, retinopathy, skin complications, gastroparesis, and complications in pregnancy

**parameter estimation methods:** In the context of diabetes modelling, both least squares and maximum likelihood methods can be applied, depending on the nature of the data and the specific goals of the modelling effort [15]. Understanding and managing these parameters is essential for optimizing glucose and insulin regulation and reducing the risks associated with diabetes complications.

Initial conditions:

### Data collection:

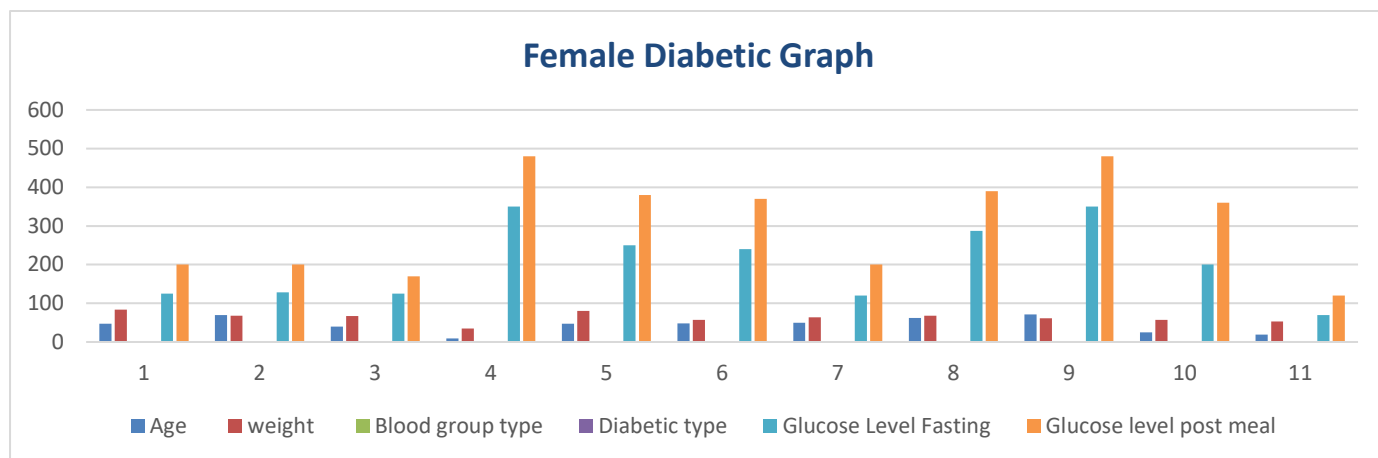
Data related to the diabetic patients both male and female of all age categories was collected. This data included the blood glucose levels, insulin levels, meal intake, physical activity, medicine type and other relevant variables. Data collected by creating a google form distributed amongst diabetic patient of all age level including both male and females. The parameters in model that need to be estimated could include parameters related to insulin sensitivity, beta-cell function, glucose clearance rates, and other factors. Data included age, weight their physical activities, their diabetic type, pre meal and the post meal sugar, the kind of the disease patients suffered after post diabetics. The kind of the treatments they included in their daily life to control the glucose levels etc. From the collected data it has been observed that diabetes diseases occurred more in male as compare to the women. Generally, women suffered from diabetes due to obesity and post pregnancy hormonal changes. Stress may be one of the reasons to occur diabetes in the females [16].

Tabulated data is as follow.

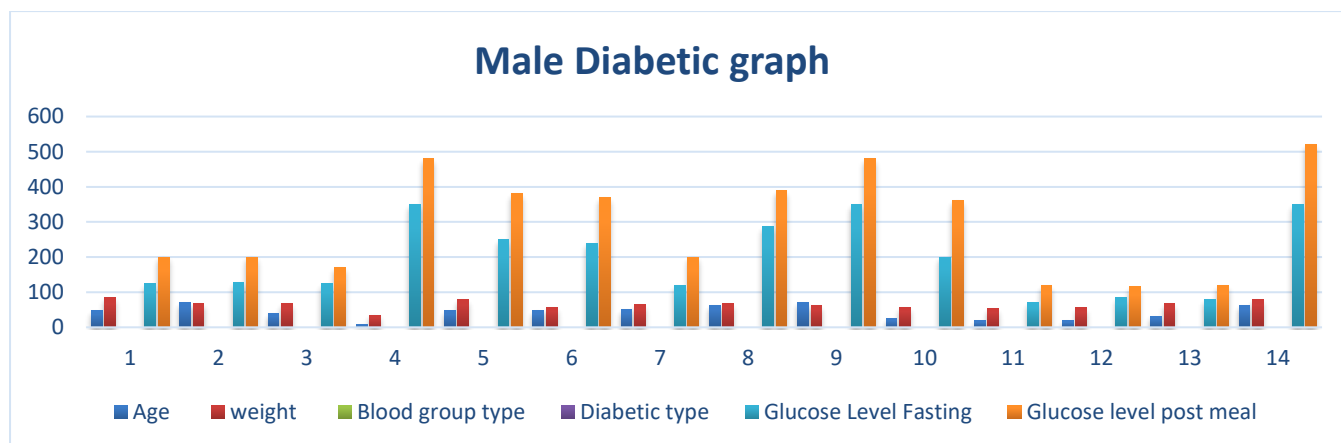
Timestamp	Gender	Age	weight	Blood group type	Diabetic type	Glucose Level Fasting	Glucose level post	consumption of	Sugar control by	Physical activity	Blood pressure is always	Any disease which is occur after due to diabetes	Diabetes is Here	Timing of Breakfast ,lunch and Dinner
12/27/2023 19:49:26	Male	47	83.6	Arh+	Type 2	125	200	No	other	High	normal	No	No	Irregular timing
12/27/2023 19:55:17	Female	59	65	O+	Type 1	160	270	No	insulin injections	Moderate	Very high	Cardio	Yes	Regular timing
12/27/2023 20:11:40	Female	61	71	O+	Type 1	400	560	No	tablet medicine	Low	Very high	Left Kidney is at high risk	No	Irregular timing
12/27/2023 20:14:58	Male	70	68	O+	Type 1	128	200	tobacco	tablet medicine	High	Very high	Late Cure of any diseases	No	Irregular timing
12/27/2023 22:12:25	Male	40	67	A+	Type 2	125	170	No	tablet medicine	Moderate	normal	Nil	Yes	Regular timing
12/27/2023 22:49:23	Male	9	35	A+	Type 1	1	1	No	insulin injections	Moderate	normal	Thyroid	No	Regular timing
12/29/2023 22:43:22	Female	40	76	B+ve	Type 2	168	180	No	tablet medicine	Moderate	very low	Effect on eyes	No	Regular timing
12/30/2023 11:33:51	Male	47	80	A+ve	Type 2	250	380	alcohol	tablet medicine	Moderate	Very high	Thyroid	No	Irregular timing
12/31/2023 11:24:37	Female	38	67	B positive	Type 2	230	380	No	other	Moderate	normal	Kidney Damage	No	Regular timing
12/31/2023 12:52:44	Male	48	57	A positive	Type 2	240	370	No	other	Moderate	normal	Kidney disease	No	Regular timing
12/31/2023 18:12:21	Female	18	43	O+	Type 1	340	530	No	insulin injections	Low	normal	Kidney	Yes	Regular timing
12/31/2023 23:17:53	Male	50	64	A +ve	Type 1	120	200	No	tablet medicine	Low	normal	No	No	Irregular timing
1/8/2024 20:44:41	Male	62	68	o+ve	Type 2	287	390	tobacco	tablet medicine	Moderate	Very high	Eye sight	No	Regular timing
1/8/2024 20:48:29	Male	71	61	A+ve	Type 1	350	480	tobacco	insulin injections	Low	normal	Kidney damage	No	Regular timing
1/9/2024 14:00:04	Female	41	78	B+ve	Type 2	180	245	No	tablet medicine	Moderate	Very high	Thyroid	No	Irregular timing
1/9/2024 14:00:29	Female	25	63	AB+ve	Type 2	180	220	No	tablet medicine	Moderate	normal	Thyroid	No	Irregular timing
1/9/2024 14:01:21	Male	25	57	B+	Type 2	200	360	No	tablet medicine	Moderate	Very high	Thyroid	No	Irregular timing
1/9/2024 14:01:23	Female	18	62	B+	Type 1	180	240	No	tablet medicine	Moderate	Very high	Thyroid , kidney , eye sight	No	Irregular timing
1/9/2024 14:01:27	Male	19	53	A+	Type 2	70	120	No	tablet medicine	Moderate	Very high	Sugar	No	Irregular timing
1/9/2024 14:01:53	Male	19	55	B positive	Type 1	85	115	No	tablet medicine	Moderate	Very high	Thyroid	Yes	Irregular timing
1/9/2024 14:01:59	Female	22	57	O+ve	Type 2	210	330	No	tablet medicine	Moderate	Very high	Eye sight	No	Irregular timing
1/9/2024 14:02:06	Female	19	50	O+	Type 1	98	218	No	tablet medicine	Moderate	Very high	Thyroid , kidney , eyesight	No	Irregular timing

### 1.1 Table related to diabetic male and female

### Category wise graphs are: Collected data distributed



1.2 Female Diabetic Graph



1.3 Male Diabetic Graph

### Model Fitting:

Apply the chosen optimization algorithm to find the values of the parameters that minimize the difference between model predictions and observed data.

$G(0)$ : Initial plasma glucose concentration at time  $t=0$

$I(0)$ : Insulin concentration at time  $t=0$ .

$X(0)$ : Action of the Insulin at time  $t$ .

$H(0)$ : Concentration of the plasma glucagon at time  $t=0$ .

$C(0)$ : Cardiovascular health metric at time  $t=0$ .

$N(0)$ : Neuropathy index at time  $t=0$ .

$K(0)$ : Kidney function index at time  $t=0$ .

$R(0)$ : Retinopathy index at time  $t=0$

$S(0)$ : Skin health metric at time  $t=0$ .

$Gp(0)$ : Gastric motility index (for gastroparesis) at time  $t=0$ .

$P(0)$ : Pregnancy-related index at time  $t=0$ .

### Calculations:

By using values in table 1.1 and normal diabetic range values

$p_1$ : This parameter represents the rate at which glucose disappears from the bloodstream, reflecting factors such as glucose uptake by tissues and organs, glycogen synthesis, and glucose utilization for energy. Higher  $p_1$  value indicates faster glucose disappearance, while a lower value suggests slower clearance. Assume the following parameter values and initial conditions for our numerical simulation:

Basal glucose concentration  $G_b$ : 90 mg/dL

$p_1$  Rate constant: 0.1 1/min

Initial concentration of glucose:  $G(t)$ : 120 mg/dL (slightly elevated)

Insulin action effectiveness:  $X(t) = 0.01$

$$\frac{dG(t)}{dt} = -p_1 \cdot (G(t) - G_b) - X(t) \cdot G(t)$$

This is ordinary differential equation

$$\begin{aligned} \int dG(t) &= \int [-p_1 \cdot (G(t) - G_b) - X(t) \cdot G(t)] dt \\ &= \int [-0.11 \cdot (120 - 90) - 0.01 \cdot 120] dt \end{aligned}$$

$$G(t) = -4.5 t \text{ mg/dl glucose concentration rate}$$

$$\frac{dI(t)}{dt} = S(t) \cdot [G(t) - G_b] - p_2 \cdot I(t)$$

Insulin sensitivity factor  $S(t) = 0.05$

$p_2$ : clearance rate constant 0.02

Basal glucose concentration  $G_b$ : 90 mg/dL

$I(t) = 15$  current insulin concentration

$$\begin{aligned} \int dI(t) &= \int [S(t) \cdot (G(t) - G_b) - p_2 \cdot I(t)] dt \\ &= \int [0.05 \cdot (120 - 90) - 0.02 \cdot 15] dt \end{aligned}$$

$$I(t) = 1.2 t \text{ unit/L Insulin concentration over time}$$

Adjust the model parameters, initial conditions, and glucose concentration function as needed to fit the specific scenario or data.

### Conclusion:

A mathematical model included hyperglycaemia, hypoglycaemia, cardiovascular complications, neuropathy, nephropathy, retinopathy, skin complications, gastroparesis, and complications in

pregnancy. Developing a model that accounts for all these complications is challenging due to the complexity and heterogeneity of diabetes. Model simulates the dynamic interaction between glucose and insulin, considering glucose production, utilization, and insulin action. Insulin action is influenced by both the insulin concentration and its decay rate. The model can be extended to include meal intake, physical activity, and more sophisticated representations of insulin secretion.

Summarize the key challenges, approaches, and recent advances in parameter estimation for mathematical model. Emphasize the crucial role of accurate parameter estimation in advancing our understanding of cellular processes and potential applications in precision medicine and synthetic biology. These references provide insights into the diverse applications of immunotherapy beyond cancer. Immunotherapeutic strategies continue to evolve, offering new hope for the treatment of various medical conditions. It's necessary that people with diabetes work closely with medical professionals to create personalized treatment programs that take these variables into account. Lifestyle modifications, medication management, and regular monitoring are key components of diabetes care.

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