



Review

Artificial Pancreas Control Strategies Used for Type 1 Diabetes Control and Treatment: A Comprehensive Analysis

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Abstract: This paper presents a comprehensive survey about the fundamental components of the artificial pancreas (AP) system including insulin administration and delivery, glucose measurement (GM), and control strategies/algorithms used for type 1 diabetes mellitus (T1DM) treatment and control. Our main focus is on the T1DM that emerges due to pancreas's failure to produce sufficient insulin due to the loss of beta cells (β -cells). We discuss various insulin administration and delivery methods including physiological methods, open-loop, and closed-loop schemes. Furthermore, we report several factors such as hyperglycemia, hypoglycemia, and many other physical factors that need to be considered while infusing insulin in human body via AP systems. We discuss three prominent control algorithms including proportional-integral-derivative (PID), fuzzy logic, and model predictive, which have been clinically evaluated and have all shown promising results. In addition, linear and non-linear insulin infusion control schemes have been formally discussed. To the best of our knowledge, this is the first work which systematically covers recent developments in the AP components with a solid foundation for future studies in the T1DM field.

Keywords: type-1 diabetes mellitus; insulin; closed loop and open loop schemes; artificial pancreas; PID controller; β -cells; model predictive controller; and fuzzy logic controller

1. Introduction

1.1. What Is Diabetes?

Diabetes is a metabolic disease in which one's blood sugar, or blood glucose (BG), levels are very high. Glucose comes from the foods one eats. Insulin is a hormone that helps the glucose enter human cells to provide them with energy, and it helps in maintaining the homeostatic BG levels. Insulin is produced by the specialized type of cells of the pancreas known as beta-cells (β -cells), which are necessary to exploit glucose as a source of energy from the digested food. Chronic hyperglycemia (high blood glucose concentration (BGC)) can lead to further complications such as microvascular and macrovascular damage leading to kidney disease, neuropathy, amputations, cardiac disease, stroke and retinopathy. Hence, diabetes includes a broad range of heterogeneous diseases [1]. Diabetes has been classified in to three major types based on the presumed etiology which are explained below:

- Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease in which the human body does not produce enough insulin while insulin inoculations are required on a daily basis. T1DM

was further classified into two subgroups: immune mediated and idiopathic by the American Diabetes Association (ADA) in 2007. Meanwhile, the idiopathic type-1 diabetes is considered to be type-2 diabetes by several researchers and clinicians. Patients of T1DM become entirely dependent on externally administered insulin, and it is the only treatment available in medicine. However, the daily dose of insulin varies and depends heavily on a range of other factors including age, gender, daily exercise, and physique. However, an average daily dose is about 1-unit of insulin per kg weight per day [2].

- Type 2 diabetes mellitus (T2DM) also known as non-insulin dependent diabetes mellitus (NIDDM), it is characterized by the defect in both insulin secretion and insulin resistance. High levels of BG are managed with the reduced food intake, improved physical activity, and ultimately oral medications or insulin [3].
- Gestational diabetes (GD) can occur temporarily during pregnancy, and recent findings suggest that it can occur in 2~10% of the all pregnancies. During pregnancy, significant hormonal changes can lead to the blood sugar elevation in genetically predisposed individuals which is known as gestational diabetes (GD).

1.2. What Causes Diabetes in the Human Body?

The common causes of diabetes are: insufficient production of the insulin (either absolutely or relative to the body's requirements), production of the defective insulin (which is uncommon in a human body), or the inability of cells to use insulin properly and efficiently leading to hyperglycemia. It can also occur due to the flaw in the insulin secretion or insulin action or both. There can be multiple causes for each diabetes type outlined earlier. The causes for each diabetes are summarized below:

- T1DM diabetes causes are not as well documented compared to T2DM. Family history is a known risk factor for the T1DM. Other risk factors can include having certain infections or diseases of the pancreas. T1DM is primarily characterized as an autoimmune disease resulting in damage of the insulin-producing β -cells in the pancreas by T-cells (CD^{4+} and CD^{8+}), and macrophages penetrating the islets. Both genetic as well as environmental factors as yet unclear trigger autoimmune responses against β -cells and destroy them, thus significantly proliferating the disease in humans [4]. According to the latest studies, genetic factors are becoming more evident in causing T1DM disease [5–7].
- T2DM develops when the body becomes resistant to insulin or when the pancreas is unable to produce enough insulin. The main cause of this is as yet unknown, although genetics and environmental factors, such as being inactive, and overweight seem to be main causes for the T2DM disease.
- GD can occur due to the significant hormonal changes during the pregnancy period, and blood sugar elevation in genetically predisposed individuals.

The morbidity and mortality rates of diabetes mellitus have increased throughout the world in recent years. Diabetes has influenced 463 million people around the globe [8]. Furthermore, the World Health Organization (WHO) predicts that the number of patients can soar to 552 million approximately worldwide by 2030, which is approximately a 19.2% increase in the current patients [9].

1.3. Current Treatment Modalities Available for Diabetes in Medicine

The ensemble learning technique has been used to forecast the early outset of the diabetes. The main purpose of these techniques is two-fold: (i) whether the person has a possibility of contracting diabetes in near future or not, and (ii) the risk probability of having diabetes linked with the person. These findings help to train the model itself for the prediction of the diabetes [10]. People affected by T1DM require day-to-day management of exogenous insulin with firsthand help or by using an insulin pump. A stability inspection is carried out and the dynamics of glucose are demonstrated by a simulation using different parameters [11]. Artificial neural networks (ANNs) are promising machine-learning algorithms that are very beneficial in figuring out the complicated patterns, and classification markers

without making any presumptions. The formally approved current treatment modalities used for the T1DM treatment and diagnosis are summarized in Figure 1.

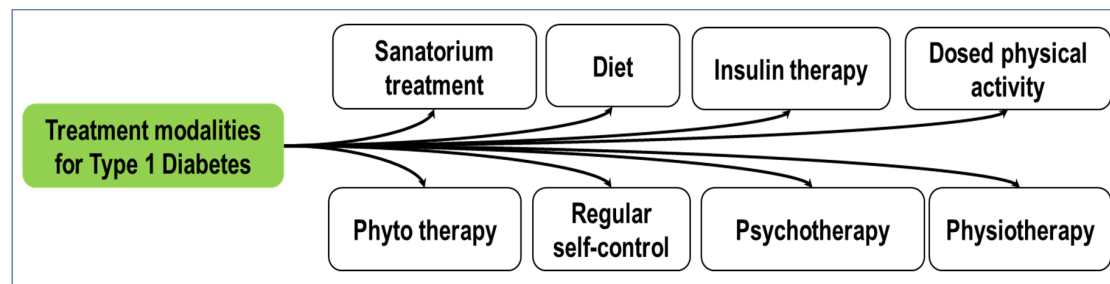


Figure 1. Current treatment modalities used for type 1 diabetes mellitus treatment and diagnosis.

Farias et al. [12] devised a long short-term memory (LSTM) ANN to identify T1DM patients. The auto antibodies have been used for the clinical diagnosis of the T1DM. Auto antibodies against insulin, glutamic acid decarboxylase (GAD), and insulinoma linked protein-2 (IA-2) are stable in the T1DM panels. Both predictive and screening T1DM requires sensitive detection techniques [13]. An automated insulin delivery system is designed to roll together consistently the glucose levels of the patients, insulin dosing, and food intake and then calculate how much an insulin pump should deliver to maintain the BG level at normal range while giving a clear, precise report [14]. An Android game has been developed for the T1DM to check their BG level and keep updated about the health of child while playing the game and also notify them through the game to inject insulin and also about the food which is suitable for the child body [15]. The MyDi framework is presented which integrates a smart glycemic diary for Android users, which automatically records the activity of patients via pictures and deep learning-based technology which monitor their meals and sports via pictures and store them. The proposed method is helpful to predict the diabetic patients using smart technology [16]. Zhang et al. [17] proposed an Internet-of-things (IoT)-based self-management technique named MyDay tool for the T1DM control and treatment. This tool fuses heterogeneous data sources for diabetes self-management patterns analysis and promotes data sharing of diabetic patients in real time. Wei et al. [18] proposed a reinforcement learning-based algorithm for the control of BG level in the T1DM's patients. The main purpose of the proposed model is to inject insulin, and its performance was verified through simulations on the aggregation of the minimum model, and part of the Hovorka model. Cescon et al. [19] proposed a model for once a day dosing of long acting insulin using iterative learning control. With the help of this model, insulin can act for a longer time rather than being injected multiple times in a single day.

A growing body of literature has explained the various control strategies based on model predictive control (MPC) strategy for the T1DM's treatment and control [20,21]. MPC uses a model to predict and augment future process behavior. In each time step, an optimization problem is solved to obtain an ideal control sequence that reduces a cost function and accomplishes constraints as the system progresses. Furthermore, the stability of the MPC can be guaranteed by accumulating a terminal cost and a terminal constraint, or by extension of the prediction horizon [22]. Sinclair et al. [23] explained various recommendations in the areas of: clinical diagnosis, establishing management plans and glucose regulation, diabetes self-management education, nutritional therapy, physical activity, exercise and lifestyle modification, insulin treatments and regimens, use of technology in diabetes management, hypoglycemia, managing cardiovascular risk, management of microvascular risk, and inpatient management of T1DM and ketoacidosis. A comprehensive guideline for dealing with glucose-related emergencies in T1DM are summarized by Dhatariya et al. [24].

The challenges involved in diagnosing T1DM in older adults are explained by Jones1 et al. [25]. Andrej et al. [26] summarized various treatment algorithm for T1DM, and diagnostic criteria for T1DM in adults. Singh et al. [27] explained serological, biochemical, and genetic aspects related to gene

HLA-DQB1 and its association with the T1DM. Nadia et al. [28] explained the paradigm shift in treating T1DM by coupling inflammation to islet regeneration. Buzzetti et al. [29] comprehensively explained the role of obesity in the increasing incidence of T1DM around the globe. Dayal et al. [30] discussed the possible risks to children and adolescents with T1DM during the current pandemic and the special considerations in management in those affected with COVID-19. Anna et al. [31] presented a study focusing on adults with congenital heart disease (CHD) who also develop T1DM disease. The study reported that increasing number of adults with CHD will significantly affect cardiologist practice in the coming years. Cobelli et al. [32] presented a comprehensive review about artificial pancreas (AP) systems and their components. They also discuss the improvements needed in the AP systems for better monitoring of T1DM.

1.4. Manuscript Contribution in the Field of Study

The contributions of this research in the field of T1DM treatment and control can be summarized as follows: (i) it explains relevant details about the diabetes concept, different types of diabetes, causes of the diabetes, and practical control strategies used in the T1DM treatment and diagnosis; (ii) it summarizes various factors with sufficient details that need to be considered in AP systems for insulin delivery in a human body; (iii) it describes various insulin delivery and administration methods used for T1DM patients; (iv) it explains three advanced controller and strategies used in the AP for BG regulation in a human body; (v) it provides a comparison of the different controllers used for T1DM assessment and control; and (vi) to the best of our knowledge, this is the first survey that systematically covers recent strategies used in T1DM treatment and control with AP systems.

1.5. Manuscript Organization

The rest of the paper is structured as follows: Section 2 explains the physiological methods of insulin delivery. Section 3 discusses the open loop administration of insulin and Section 4 presents the closed loop administration of insulin. Section 5 comprehensively explains the proportional integral derivative (PID) controller. Section 6 explains about the linear and non-linear insulin infusion control schemes. Section 7 explains about the most widely used MPC strategy in the T1DM therapy. Section 8 discusses the glucose measurement (GM), and latest approaches. The assimilation of data from other groups and our own synthesis on the subject matter (i.e., control algorithms) are presented in Section 9. Finally, conclusions and promising future directions are offered in Section 10.

2. Physiological Methods of Insulin Delivery

This section presents the physiological methods of the insulin delivery in the human body. The β -cell response to the glucose system is explained which is very important, as it highlights how an artificial system should behave in practice/real-world scenarios [33]. There are two phases “first” and “second” phase responses of the β -cell [33]. Both phases are briefly summarized in Section 2.1.

2.1. Significance of First and Second Phase Insulin Secretion in Human Body

The immediate release of insulin after a meal is known as “first-phase insulin release”. The first-phase insulin secretion has a major effect on extinguishing hepatic glucose production [34]. Small change in the plasma insulin can have a significant effect on the hepatic glucose output [34]. Normally, insulin production in an early phase is actually less than the total insulin needed to yield a similar area under the glucose curve [33,35]. Improving first-phase response is related to glucose tolerance [36]. A person whose system is insulin-resistant without the variation in the insulin secretion becomes diabetic. Meanwhile, a person’s system which maintains the required level of glucose tolerance by adopting the “control gain” is regarded as a non-diabetic individual [33]. The first and second phases of insulin secretion occur all the time in the body. However, the second phase insulin secretion has a major effect on the glucose production as well as its utilization in a human body [34]. The importance of second phase insulin secretion cannot be ignored as it is necessary to maintain

plasma glucose at a set point (i.e., normal range) [33]. In addition, the loss of first phase insulin secretion is the first indicator of the development of T2DM in a human body [37].

2.2. Hyperglycemia and Hypoglycemia

Insulin cannot be infused until the BG level exceeds 180–200 mg/dL. This condition is referred as hyperglycemia [38]. The condition of hyperglycemia is found to be common in intensive care units (ICU) [37]. According to existing surveys presented by Krinsley et al. [39], even a small level of hyperglycemia can lead to an increased rate of hospital mortality in ICUs [39]. Sugar level control with insulin infusion has a risk of hypoglycaemia. Sugar level which is <50 mg/dL is called hypoglycemia. The hypoglycemia can be diagnosed by the Whipple's triad, with three steps. (i) neuroglycemia symptoms, (ii) immediate glucose of <40 mg/dL, and (iii) symptoms of the relief after glucose intake [40].

2.3. Biological Perspective on How β -Cell Achieves Glucose Control and Energy Metabolism in Type 1 Diabetes Mellitus (T1DM)

The biological perspective on how a β -cell achieves glucose control can be summarized in four steps as: (i) after a person takes a meal, the small intestine absorbs glucose from the digested food. Consequently, the BG levels rise; (ii) increase in BG levels stimulate the β -cells in the pancreas to produce insulin; (iii) after that, insulin triggers liver, muscle, and fat tissue cells to absorb the glucose, where it is stored. As glucose is absorbed in the related parts, the BG levels fall; (iv) Once the glucose levels drop below a certain threshold, there is no longer a sufficient stimulus for insulin release, and the β -cells stop releasing further insulin. The conceptual overview of the whole process is shown in Figure 2. Due to the synchronization of the insulin release with the β -cells, basal insulin concentration oscillates in the blood following a meal. The oscillations are clinically important, since they are believed to help maintain sensitivity of insulin receptors in the target cells. The key role of the β -cells is to sense the BG levels, and regulate insulin accordingly. For example, when the BG increases following food intake, β -cells sense this change in concentration, and subsequently secrete insulin into the blood. On the other hand, when blood glucose levels are low, such as following a prolonged fasting period, the release of insulin from β -cells is inhibited [41].

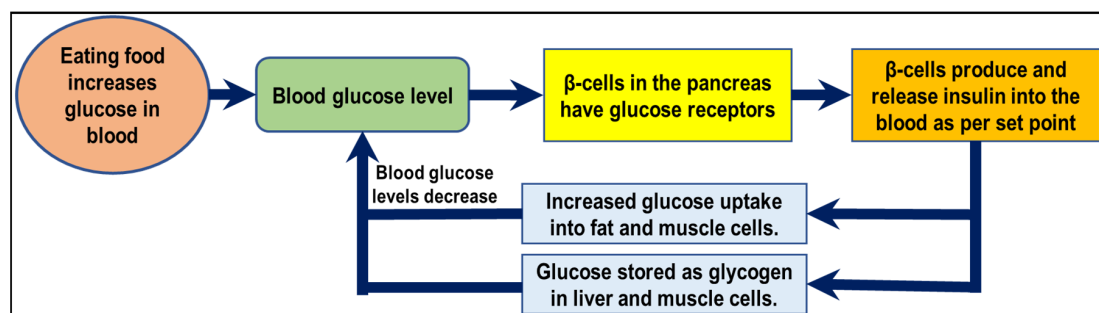


Figure 2. Conceptual overview of the biological perspective on how a β -cell achieves glucose control.

Doctors have tried to help patients of T1DM to maintain their glucose values as close to the normal range as possible to delay the onset and slow the progression of long-term diabetes complications such as renal disease, retinopathy, neuropathy, and heart disease. Monitoring glucose levels is vital for achieving desirable glycemia and avoiding hypoglycemia. Continuous Glucose Monitoring (CGM) is a recent glucose monitoring device that assists to achieve these aims. CGM has been shown to improve glycemia without an increase in the hypoglycemia for adults with T1DM who wear it most days [42–44]. Furthermore, studies have reported the positive psychosocial changes such as decreased partners' anxiety, vigilance and negative experiences surrounding hypoglycemia, and improved patients' mood and general quality of life [45,46]. Currently, flash glucose monitoring is emerging

as an innovative technology, it enables self-monitoring of blood glucose [47]. With the help of CGM and other related technologies, doctors and clinicians are able to gain more insight into the glucose variability, temporarily improved sense of control, reduced distress and reduced dependency on the others physical devices. However, some participants experienced confrontation with the CGM output as intrusive, whereas others reported frustration due to the technical failures and difficulty in trusting the devices. Active and passive self-management behaviours were reported by the participants, mirroring individual differences in attitudes and coping styles [48].

Insulin making and subsequent release from the β -cells is controlled by multiple players, including glucose, peptide hormones, neurotransmitters, and other related compounds [49,50]. Briefly, the rise in the BG levels that follows food intake is sensed by the β -cells, which subsequently take glucose up from the blood, and metabolize it to more fuel for the mitochondria to shunt towards adenosine triphosphate (ATP) production, increased levels of which result in the inhibition of the cell's K_{ATP} channels. This ultimately leads to depolarization at the plasma membrane (PM), an electrical change that functions to activate the L-type Ca^{2+} channels, which allows an influx of Ca^{2+} into the β -cell. Finally, this wave of Ca^{2+} triggers the release of secretory granules containing insulin, to be released from the cell by exocytosis. The conceptual overview of the whole process is depicted in Figure 3. The flow is marked with red-arrows in Figure 3 for clarity.

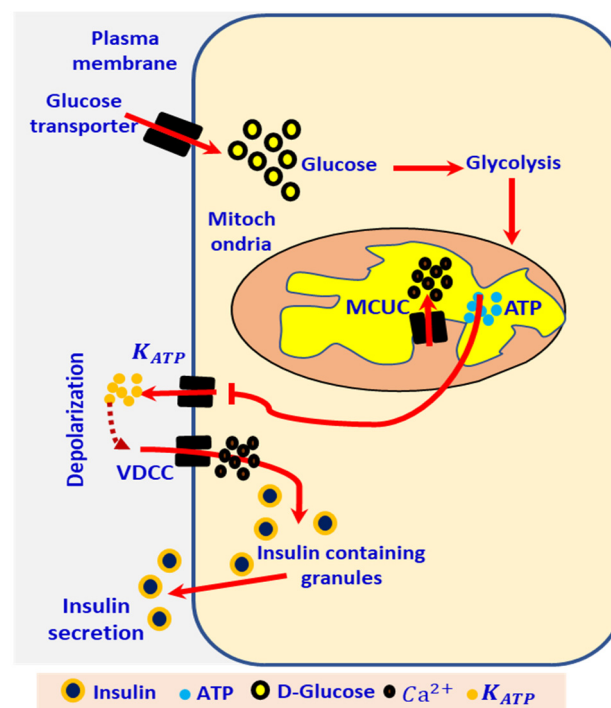


Figure 3. Conceptual overview of the glucose-stimulated insulin secretion (GSIS) and brief excerpt of glucose sensing, oxidation into adenosine triphosphate (ATP) energy equivalents, potassium-ATP (K_{ATP}) channels working together, leading to calcium entry and insulin exocytosis in the pancreatic β -cells (shown with red arrow flow). (Adopted from [41]).

3. Open Loop Administration of an Insulin

The requirement/need of an automated AP system has been present since 1921, the time when insulin was discovered first time [33]. The produced insulin needs definition in terms of prehepatic insulin as well as portal insulin concentration in order to work as closely in a non-diabetic state [51].

3.1. Timing of Insulin Delivery

With the increase in the demand of the insulin infusion and its mechanism, it is recommended to take the dose with almost every meal [52]. However, one major concern is the timing of insulin delivery [53]. Depending on the type of insulin, rapid-acting insulin should be infused 15 min before the meal. Short-acting or regular insulin can be infused 30 min before the meal. Having food activity straight away after regular insulin can cause hypoglycemia (i.e., low sugar level) [53]. Changing the interval between insulin infusion and meal shows remarkable effect in the postprandial hyperglycemia in insulin dependent patients. Recent studies show that a near-normal glucose level can be achieved only when patient had their insulin administered 60 min before the meal [52]. Results infer that adjusting the time and the amount of insulin can be helpful in the management of the diabetes [41]. As shown in Figure 4, delayed insulin infusion before meals can be linked to greater hyperglycemia up to three hours after the meal [54].

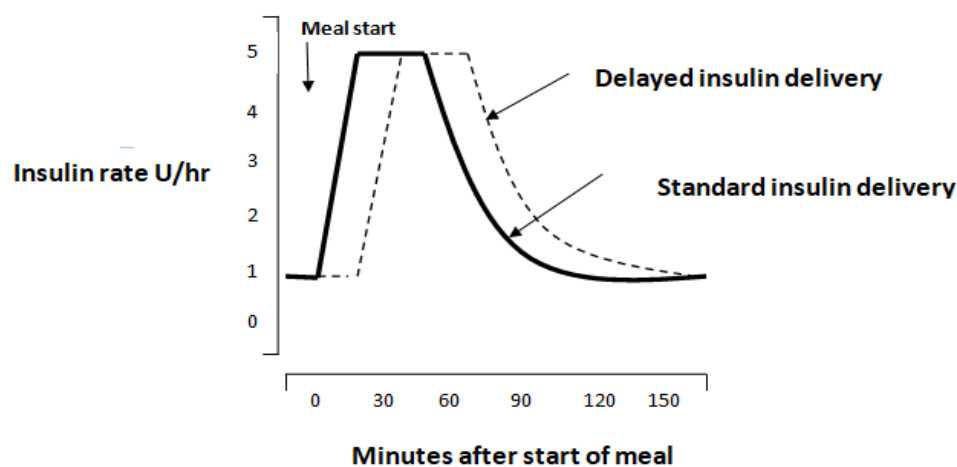


Figure 4. Comparison of delayed and standard insulin delivery with the meal (adopted from [38]).

3.2. Manual Administration of the Insulin

The injection technique is the most common and early cure for a diabetic patient. Dosage is different for different individuals. People with T1DM do not produce enough insulin to meet the glucose level of a normal person so they need an external insulin. Most of the T2DM patients do not require external insulin. The timing of the insulin injection depends on the glucose level, and various other factors [53]. Injection site selection is important to yield appropriate results. Insulin can be injected into subcutaneous tissue of the upper arm or the anterior aspect of thighs and buttocks [54].

3.3. Subcutaneous Versus Inhaled Insulin

Inhaled insulin has been proven way more effective and reliable in the T1DM and T2DM. Infusion of regular insulin through lungs by inhalation has shown insulin absorption and lowering of the BG [55]. As shown in Figure 5, the maximum insulin concentration is more rapid in case of inhaled insulin as compared to the subcutaneous (SC) injection [56]. In subcutaneous insulin (SCI), the short-acting insulin driven by a mechanical force and delivered via a needle or soft cannula under the skin is undertaken on a continuous and constant basis [57]. Although SCI is expensive, but it provides greater flexibility for the individuals having diabetes in managing their condition, and it allows more precise insulin dosing than multiple daily injections (MDI) [58]. According to systematic reviews, potential benefits of SCI include improved glycaemic control, reduction in the hypoglycaemia unawareness, lower insulin doses, high absorption, and a lower frequency of severe hypoglycaemia [59–61]. Due to the development of sensor augmented insulin therapy with or without suspend functions [62,63], the T1DM control and quality of life for patients have significantly enhanced [64,65]. Moreover, SCI is most successful

in individuals motivated to manage their condition and supported by a multidisciplinary team with expertise in the delivery of SCI [66]. In contrast, inhalable insulin is a powdered form of insulin, delivered with an inhaler into the lungs where it is absorbed [67].

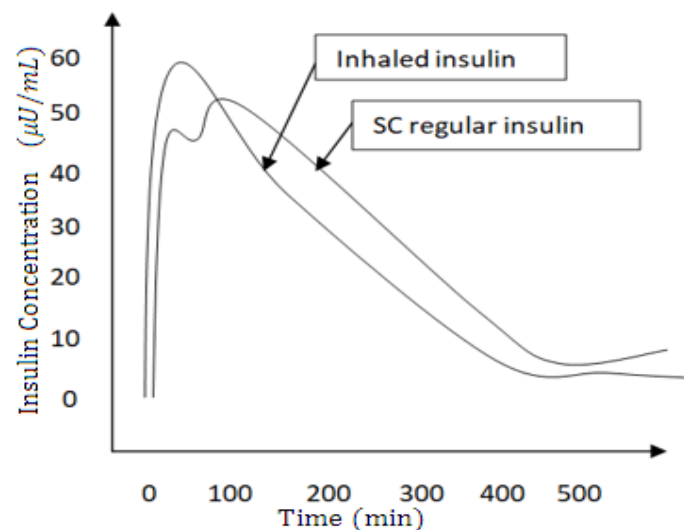


Figure 5. Comparison of the inhaled insulin with the subcutaneous (SC) injection [45].

In general, inhaled insulins absorb more rapidly than SCI insulin, with faster peak concentration in serum and more rapid metabolism [68]. Sanofi-Aventis developed the first commercial inhaled insulin product (Exubera), which was approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2006 and marketed by the Pfizer [69]. Although Exubera offered the advantage of painless insulin administration by the pulmonary route of administration, its pharmacokinetics (PK) and pharmacodynamics (PD) (i.e., PK/PD) characteristics were similar to the SCI injected rapid-acting insulin analogs (aspart, glulisine, and lispro) and, thus, offered no additional clinical benefit in postprandial glycemic control [70]. Furthermore, the inhaler device was large and the handling procedure for insulin administration was cumbersome [71,72]. Afrezza, an inhaled insulin with ultra-rapid PK/PD properties that enable improved postprandial glycemic control in adults with T1DM or T2DM has been suggested as a promising tool [73]. Improvements in the PK/PD characteristics of today's SC insulins provide more physiological coverage of basal and prandial insulin requirements than inhaled insulin, that why SC is most widely used. Furthermore, the treatment with SC offers a safe and efficacious option for managing diabetes in patients with T1DM and T2DM [74]. The inhaled insulin delivery may cause safety issues in lungs. We refer interested readers for more detailed understanding about both these two insulin methods to the latest findings in recent studies [75–80]. Pharmacokinetics deals with the absorption and distribution process of the insulin in a human body. Insulin is absorbed into the blood stream directly [81]. The rate of the absorption truly depends on the state of insulin, volume of the injection, and rate of the blood flow. It has been reported in literature that the absorption rate decreases with an increase in the concentration and the volume. Existing studies demonstrated that inhaled insulin can absorb faster in the human body [82]. Pharmacodynamics deals with effect of insulin on the human body. It is basically called the euglycaemic clamp study, and glucose infusion rate is used to represent the pharmacodynamics of an insulin [83].

3.4. Multiple Daily Insulin Therapy

The most renowned method of insulin therapy consists of the regular periodic injection of basal (baseline) insulin multiple times in a day—known as multiple daily insulin injections (MDI)—supported by the additional insulin doses (boluses), and oral glucose or glucagon as required to maintain normoglycemic conditions (e.g., at mealtimes) [84]. While calculating the required basal and bolus

insulin doses, practical guidelines need to be followed. Due to the significant complications, there is now an array of options/factors that allow for the personalization and situational evaluation of the treatments [84]. MDI using short- and long-acting doses are currently the main strategies of the insulin administration in this population. Depending upon the scenarios, some injections are developed as a mix of rapid acting (i.e., quick onset and peak times with short duration) and long acting (i.e., delayed onset time, low or no peak, and long duration) insulin to provide both basal and bolus action from a single injection, thereby reducing the number of injections required per day [85,86]. In addition, in some cases, it may be helpful to perform islet transplantation or that of the pancreas, in place of insulin therapy to significantly lower the treatment costs [85].

Generally, MDI comprise of three or more injections per day. It contains one injection of long-acting (LA) insulin in the evening, and an injection of the short-acting (SA) insulin ahead of every meal. LA insulin is drafted in such a way that it delivers insulin steadily and remains in the body for around 24 h. Meanwhile, the SA insulin needs to be adjusted to match the meal using the insulin-to-carbohydrate ratio [87]. The presentation of MDI and its use in diabetes control and complications trials (DCCT) study has been the ideal case to protect the patients with T1DM. The recent evolution of automated bolus calculations for the MDI is available to help patients to perform complex calculations that are required for functional insulin therapy (FIT) [88,89]. But there are some limitations of MDI to be considered: those patients who use very small amount of insulin doses or are insulin-sensitive may conflict with the MDI as it comes up with the limitations and accuracy's issues. Similarly, for patients who require large doses, the use of continuous subcutaneous insulin infusion (CSII) may be very helpful from the pharmacodynamics aspect. Continuous infusion works better on delivery of basal insulin rather than using a large subcutaneous depot. MDI is not very effective on those who eat frequently or living soft lifestyle, demanding a large number of injections of the SA insulin, and it becomes difficult to manage through MDI [88]. The Hypo-Ana research study shows that using an analogue-based regimen decreases the severe hypoglycemia in patients with impaired knowledge of hypoglycemia [88,89]. Data also suggests it is being taught already as a way of adjusting the insulin, but many patients ignore the fact and underestimate the insulin doses face difficulty while calculating appropriate amount of insulin adjustments and which acts like a barrier. In early study, the use of bolus calculator recommended reduced errors of insulin and fear hypoglycemia [90,91]. The use of a bolus automated calculator is linked with revised HbA1c and reduced glycemic fluctuations even in the younger patients with T1DM on MDI [92]. The list of distinct categories of the insulin available in medicine (adopted from [93]) is summarized in Table 1.

Table 1. Description about distinct types of the insulin available in medicine for T1DM treatment.

Type of Insulin	Time Action Profile	Dose
Short acting	Begins from the 30-min after the subcutaneous with reaching peak action in 2–4 h	3 times in a day, 30 min before taking a meal
Long acting	Beyond 24 h and up to 36 h	Once daily subcutaneous, at the same time with at least 8h interval between consecutive doses
Rapid acting	Generally, 4–20 min after subcutaneous injection with peak at 20–30 min.	Three times a day up to 15 min before food intake
Intermediate acting	Peak onset from 4–6 h, with the duration of action until 14–16 h	1 or 2 time daily subcutaneous

3.5. Continuous Subcutaneous Insulin Therapy

Insulin pump therapy also known as continuous subcutaneous insulin infusion (CSII) is a way of providing intensive insulin therapy which consistently leads to enhances glucose and reduced hypoglycemia. CSII was developed about 40 years ago. CSII systems are portable pump therapy devices that are generally constructed as a combination of an onboard insulin reservoir, an infusion apparatus

(tubing and cannula), and an electromechanical infusion pump [94,95]. According to numerous studies, these systems can be operated easily using the synthetic human insulin or rapid-acting insulin analogs (RAIA), with the help of RAIA, it provides superior performance to the synthetic human insulin [94]. In most cases, CSII uses the same basal dosage as MDI, with the basal insulin dosage applied more consistently over the day in CSII [95].

The CSII is an efficient self-management tool for T1DM patients. It is recommended that insulin therapy should initiate at the start of the week, it is because patient has access to the clinical help for the rest of the week [96]. In fact, across Europe, there are less than 30% T1DM patients which are using insulin pumps, while in the USA, the use of insulin pump is relatively higher [97]. The key dominance of insulin pumps is the additional flexibility, allowing patients to adjust basal insulin in response to the requirement changes due to illness, alcohol and exercise. Many pumps also provide on-board automated bolus calculators, allowing persistent boluses for corrections by the day. Moreover, wellbeing and increased flexibility using CSII in patients may increase their attachment to intensified therapy [98]. A short randomized trial revealed that increased glucose in the target but too short to report HbA1c levels [99]. Despite the fact that CSII is effective, it must be appropriately maintained and used, as device performance heavily depends on proper operation (i.e., timely replacement of consumables) to avoid failure modes such as impeded or clogged infusion pathways, which can lead to the insulin deficiency and hyperglycemia. The tools used by the T1DM subjects for insulin dosing are summarized in Figure 6, and the detailed description about each method/tool, and their advantages and disadvantages are summarized by Rima et al. [100].

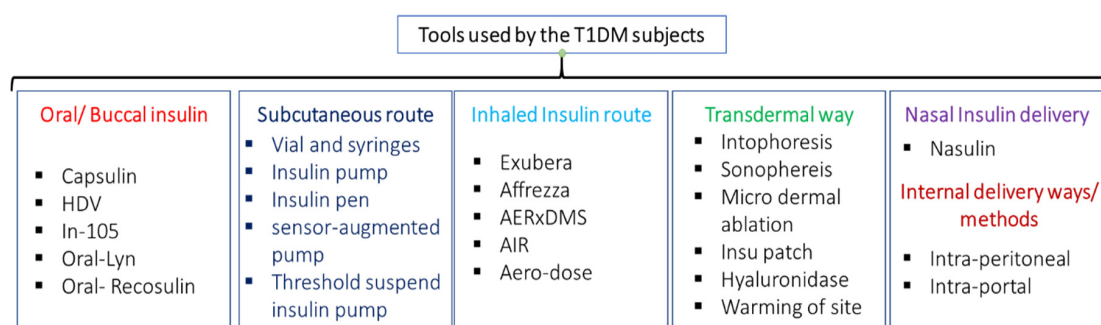


Figure 6. Overview of the tools used by T1DM subjects for insulin dosing (adopted from [100]).

4. Closed Loop Administration of Insulin

Current treatment methods such as SC injections and continuous delivery of insulin can result in frequent variations in the BG levels due to their open-loop nature [101]. In order to keep a stable basal glycemia with the continuous insulin infusion, we require a feedback system [102]. The main aim of the feedback system is to maintain a set point which is predefined. Variable transfer functions like proportional, integral or derivative terms are used to implement a feedback system [102]. The diabetes control and complications trial (DCCT) published in 1993 showed that it is very important to tightly control the BG in a human body [103]. The trial showed that there is an increased risk of hypoglycemia by combining the results of SC injections and insulin pumps [103]. A person with T1DM has always a long-term risk related to hyperglycemia, and short-term risks of the hypoglycemia, so they need to have a tight BG control. However, the T2DM patients' needs an insulin treatment when oral anti-diabetic agent and changing lifestyle do not provide glucose control [104]. A closed-loop AP system shown in Figure 7a,b requires three main things: (i) a glucose sensor or continuous glucose monitor (CGM), (ii) an insulin pump, and (iii) a control device that receives CGM values and uses a control algorithm to convey signal to the insulin pump for appropriate amount of insulin delivery [104].

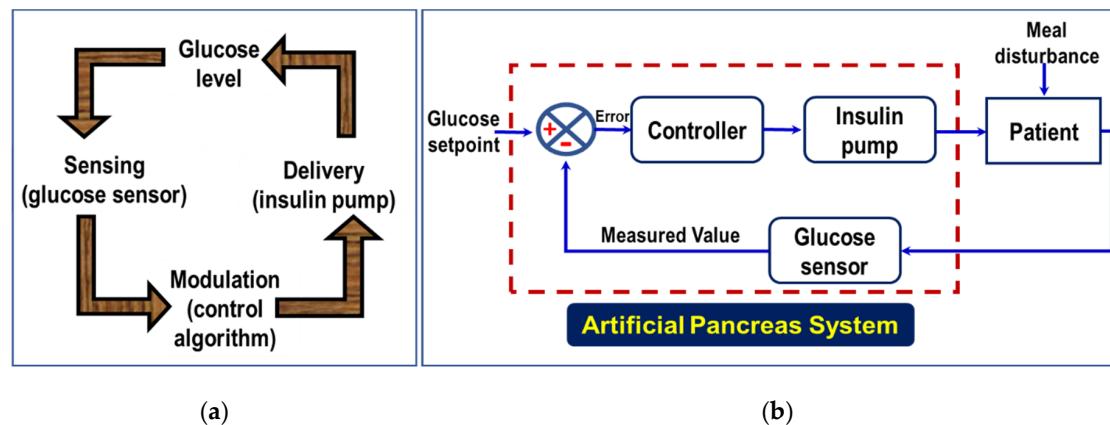


Figure 7. Example of the closed loop insulin delivery system using artificial pancreas (AP) [104]. (a) Abstract overview of AP system components. (b) Detailed overview of the AP system.

Different control algorithms have been proposed in literature for closed loop administration of insulin so far, but two of the most commonly used algorithms are: (i) *proportional integral control (PID)*- it regulates insulin by noticing variations from the target glucose levels, and (ii) *model predictive control (MPC)*- it regulates the insulin by minimizing the difference of forecasted and target glucose levels [105]. The different control challenges which need to be considered for the APs [106] are: (i) in the closed loop system, insulin is delivered when there is only glucose deviation without consideration of information about the meal size, and timing; (ii) the hypoglycemia condition is risky as it can cause coma, seizures, and mental illness. Also, hyperglycemia is not good as it causes cardiovascular disease and other chronic diseases. Therefore, these conditions must be considered; (iii) different treatments for diabetes patients have different requirements. In some cases, rapid insulin delivery is required, and vice versa. Exercise can also create the hypoglycemia condition, so all of these physical factors are important to consider while designing an AP system; (iv) when creating a rapid insulin delivery control algorithm mostly the maximum BG lowering effect occur after up to 90–120 min. When designing control algorithm this time range should be considered. Furthermore, sometimes there occurs noise in the sensor measurements so different estimation techniques should be employed for compensating these noise values. Also, the self-calibration methods with self/auto correction ability are required for the success of the APs.

5. Proportional Integral Derivative (PID) Controller

The proportional integral derivative (PID) controller is one of the most widely used controllers in industrial applications. In T1DM treatment and control, it is used to emulate β -cell's insulin secretion in the body in response to the glucose, and it is also called external physiological insulin delivery (e-PID) [107,108]. The insulin is rapidly secreted by the β -cells in the bolus during the first phase in response to the increased BG (proportional component), and in the second phase (integral component), it is released slowly, called basal insulin, to account for the insulin required in between meals to keep BG at a normal level [108,109]. In order to reduce the hypoglycemic cases, that is, to reduce over delivery of the insulin, insulin feedback was included to make the controller more robust [107,110,111]. For critically ill patients, Chee et al. [112] developed a rule-based PID controller. Marchetti et al. [113] developed a switching PID controller using the Hovorka model. The developed controller works in such a way that the controller is turned on only after meals and is off before the meal bolus. Various schemes for tuning the hybrid-PID and PID controller parameters to obtain significantly optimized results are developed using soft computing techniques such as the cuckoo search algorithm [114], genetic algorithm [115], and fire-fly algorithm [116].

Huyett et al. [117] conducted experiments *in silico* for inter-peritoneal (IP; deliver in or administer through the abdominal cavity or peritoneum) insulin delivery and IP glucose sensing (IP-IP) for

an implantable AP [118,119]. The working mechanism of the PID controller is shown in Figure 8. The brief overview of the PID working is summarized as: the PID controller utilizes proportional, integral and derivative gain to control a process variable (system/process output). They obtained input from the process output and compared it with a set point value to calculate error signal or deviations. Error/deviation value was processed using the proportional, derivative and integration controllers. This input from the PID controller was used to control the process variable. To stabilize a PID controller is very challenging because it requires the proper understanding of the proportional, integral, and derivative gain values. There exist plenty of methods for PID controller tuning. PID control algorithms are the simplest way to design a robust control system for the T1DM treatment and control. Turksoy et al. [120] presented a comprehensive review about the adaptive control techniques and their use in the AP systems. Klemen et al. [121] summarized the most recent advances in the closed-loop systems in adolescents and children with T1DM, using both single- and dual-hormone closed-loop systems.

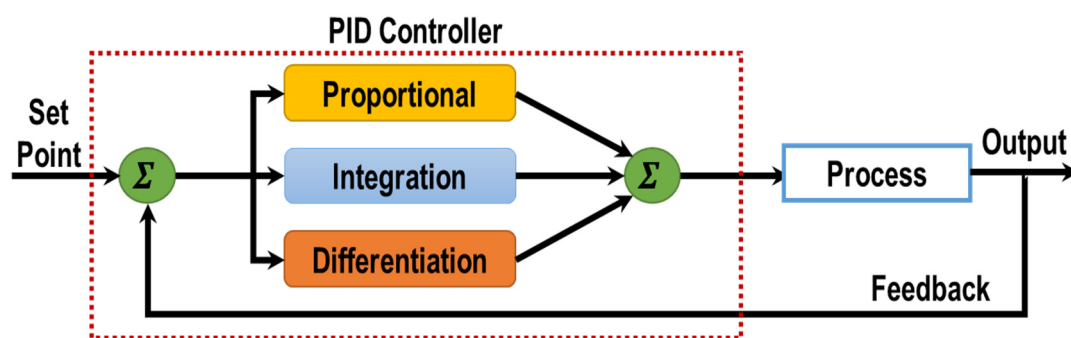


Figure 8. Conceptual overview of the proportional integral derivative (PID) controller used in T1DM treatment and control.

Trevor et al. [122] proposed a new insulin controller from a complementary metal oxide semiconductor microprocessor (CMOS) which works on wake-up cycle; each cycle occurs after 2.86 ms. The CMOS operational amplifier and direct current (DC) driver provide voltage to motor from 0 to 7.5 volt in 29.41 mV. A feedback loop is used having three parts as outlined in Section 4. The input of the system is output of glucose sensor, and output of the system is the input to the insulin pump. Shainer et al. [123] developed a model and controller design for concentration of glucose, the system instructs the insulin pump how much insulin is required to be injected. A PID controller is constructed by computer-aided design (CAD) tools, and 81 mg/dL is taken as a normal glycemia set point. Strategies are implemented in a discrete manner. The device has three major parts: (i) mechanical pump, (ii) in vivo glucose sensor, and (iii) a mathematical algorithm. The pump is driven using the readings of a sensor. It is the classic PID controller which is based upon the CAD methodology having a dynamic model of the control system. CAD is based upon frequency response (FR) tool [124].

An expert PID controller is designed to regulate the BG levels. It uses clinical sliding table technique. The sliding table contains multiple insulin concentration rates. The sliding table implements the proportional control scheme and this table is improved with the condition of the intended patient [125]. The proportional integral (PI) controller is the most common used controller in it. The P and I controller are implemented for the individual purposes. There are many methods to tune the PI controller, one of those is trial and error method. In this method, the gains of the proportional and integral were set randomly to boost the performance of insulin delivery system. Controller designers improved the steady and transient achievement of the PI controller by introducing fuzzy theory [108]. Sanaul et al. [126] explained a PID controller strategy which is evaluated in silico using the physiological Hovorka model. There are some key points of the strategy: (i) switching strategy for the PID initiating, (ii) a novel time varying set point trajectory, (iii) reducing the sensor noise and noise derivative with a filter, and (iv) a strategy is used to tune the controller. The proposed PID strategy is widely used in

the industrial applications. The PID controller is best because it mimics the first and second phase responses. The controller is based upon novel PID controller. The authors explained various control strategies, which are: (i) bolus only (ii) PID control only (iii) bolus plus PID control (iv) bolus plus PID control with switching criteria, and (v) bolus plus PID control with switching criteria and time varying glucose set point which are called improved PID (IPID).

Delgado et al. [127] discussed a fuzzy logic-based controller for glucose regulation in the T1DM patients. To get rid of daily injection insulin and to obtain professional education about the treatment of the disease, Mamdani type fuzzy logic controller is simulated. Chengwei et al. [128] discussed an IPID controller and explained some new features of it. The controller is on “silico” using the physiologic model of Hovorka which is the best glucose–insulin dynamics model. The key features of the proposed control strategies are (i) switching strategy, (ii) novel time-varying set point (iii) noise and derivate filters, and (iv) systematic controller tuning strategy. The IPID controller of this type are built upon the novel PID controller and bolus injection for the meal [128]. Maleki et al. [129] described a glucose insulin system model with only few parameters. The model is designed using Mamdani type fuzzy structure. It has two input and one output variables. The inputs are error and its rate, and output is rate of the insulin infusion. To make the mathematical model, the Stolwijk–Hardy glucose–insulin interaction model is employed. The exogenous insulin infusion term is added in the modified model to yield superior results.

The glucose dynamics are formally expressed as:

$$A_g \frac{dG}{dt} = \mu_g + P_g - \pi G - vGI, \quad G \leq \vartheta \quad (1)$$

$$A_g \frac{dG}{dt} = \mu_g + P_g - \pi G - vGI - \sigma(G - \vartheta), \quad G > \vartheta \quad (2)$$

The insulin dynamics are formally expressed as:

$$C_i \frac{dI}{dt} = \mu_i - \gamma I, \quad G \leq \omega \quad (3)$$

$$C_i \frac{dI}{dt} = \mu_i - \gamma I + \delta(G - \omega), \quad G > \omega \quad (4)$$

where $G(t)$ represents instantaneous BGL in mg/mL, $I(t)$ denotes the instantaneous blood insulin level mU/mL, $\mu G(t)$ represents exogenous glucose infusion in mg/h, $\mu I(t)$ denotes the exogenous insulin infusion in mU/h, A_g represents the glucose capacitance in the extracellular space, C_i represents the insulin capacitance in the extracellular space, $PG(t)$ is a glucose inflow into blood in mg/h, π is tissue usage rate of the glucose that is independent of $I(t)$, v denotes the tissue usage rate of glucose that is dependent on $I(t)$, γ : Insulin destruction rate, δ represents the insulin production rate by the pancreas, ϑ is a threshold for renal discharge of the glucose, Φ is a threshold for pancreatic production of an insulin, and σ denotes the glucose excretion rate [130].

In the open loop control systems, specialists direct a pre-determined dose of insulin hypodermically based on an invasive method of finger prick GM on a daily basis 3~4 times managed by the patients. This procedure is painful, inappropriate, and untrustworthy because of the fuzzy evaluation of the type and amount of insulin dosage. The semi-closed loop control is dissatisfactory, and unable to adjust the BG level properly. It also experiences long sampling as it depends upon infrequent BG readings. The closed loop control is the most effective method. It acts as an AP, and it can upgrade the life expectancy of the patients. AP enables diabetic patients to maintain the normal BG levels by providing accurate amount of the insulin at the right time without human interaction, even when there is need of human-based decision [131]. The term AP is becoming a reality by using a closed loop strategy. There are two loop strategies inner loop and outer loop. The inner loop provides an amount of both rapid and intermediate acting insulin (RSAI and ILAI), and outer loop adjusts the max amount

of the insulin provided in a time scale of the days [132]. Figure 9 explains Simulink model of a normal person using a PID controller [130].

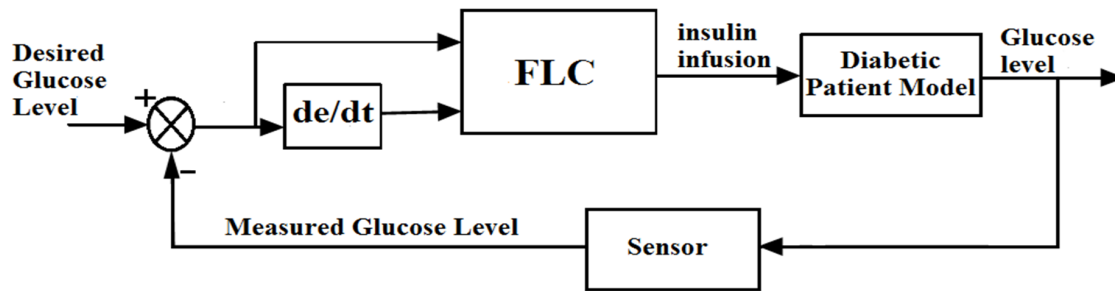


Figure 9. Schematic diagram of the fuzzy logic controller (adopted from [133]).

6. Linear and Non-Linear Insulin Infusion Control Schemes

This section explains the seven different types of the linear and non-linear insulin infusion control schemes used in the APs. We present formalization and general description for the clarity and better understanding of each scheme.

6.1. Self-Tuning Control

A self-tuning controller is basically a non-linear control scheme which was developed on a micro-controller unit (MCU) [134]. This scheme was verified through computer simulations, and it concluded that glycemia control is insensitive to changes in a patient's behavior; also, the insulin concentration it produced was the more physiological. A discrete-time model is assumed for the controlled system to implement a self-tuning controller.

$$y_{k+h} = \sum_{i=0}^{n-1} f_i y_{k-i} + \sum_{i=0}^{m+h-1} g_i u_{k-i} + d \quad (5)$$

where u_k and y_k are the k th samples of $u(t)$ and $y(t)$, n and m are number of poles and zeros, respectively. Self-tuning control uses an estimator, and the coefficients in Equation (5) are estimated by the least-squares method; it compares the true output of the model and controlled systems so that estimation is sensitive to slow changes in the patient response.

$$J_k = (y_{k+h} - y_{ref})^2 + Q u_k^2 \quad (6)$$

where Q is the arbitrary weighting factor. Putting Equation (5) in Equation (6) and equating to zero the derivative of J_k with respect to u_k , result is given in Equation (7).

$$u_k = \frac{1}{g_0 + Q/g_0} \left(y_{ref} - \sum_{i=0}^{n-1} f_i y_{k-i} - \sum_{i=0}^{m+h-1} g_i u_{k-i} - d \right) \quad (7)$$

where arbitrary parameters h , m , n and Q and sampling time characterize the controller in Equation (7).

The self-tuning controller has the following structure (see Figure 10) where both controller and estimator work as a self-tuner for accurate insulin infusion in a human body.

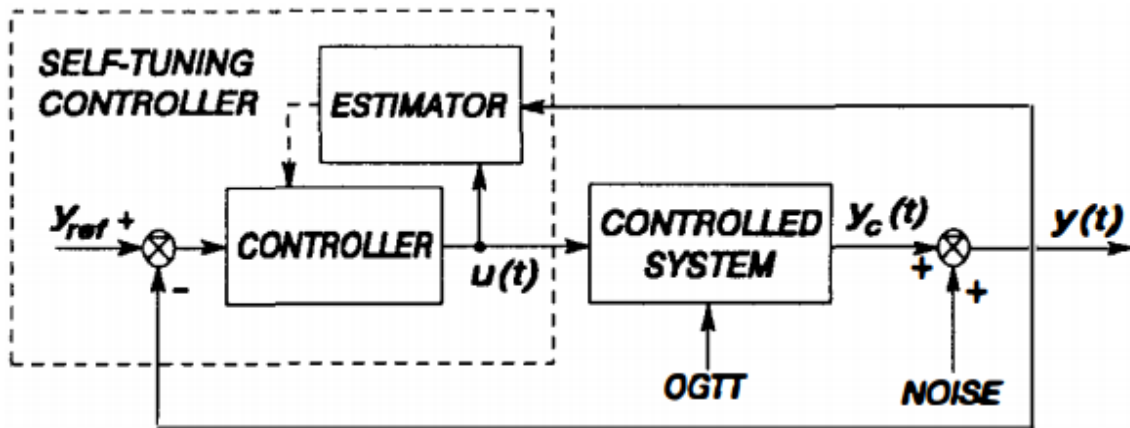


Figure 10. Self-tuning controller with the help of estimates and adjustments [134].

The controller in Figure 10 is characterized by the transfer function, which is given below.

$$G(s) = \frac{K_s}{1 + \tau s} \quad (8)$$

where K_s is arbitrary coefficient which can be figured out according to the y_{ref} .

6.2. Adaptive Control

This control method is used by the controllers which must adapt to a controlled system with varying parameters which are initially uncertain. For adaptive modeling, the “Minimal Model of Bergman” [135] is commonly used due to its conceptual simplicity. Most of the existing T1DM models are designed via the Bergman model. The T1DM model can be extended for the T2DM with ease. The model has two inputs: (i) glucose rate $p(t)$, and (ii) the subcutaneously injected insulin flow $u(t)$; at the same time this input is the control input as well. The output of the model is the plasma glucose level $G(t)$. The model has three state variables that are connected to the blood plasma which are: (i) the blood glucose concentration $G(t)$, (ii) insulin-excitabile tissue glucose uptake activity $X(t)$, and (iii) the blood insulin concentration $I(t)$. Figure 11 shows the detailed model of an adaptive control using the T1DM model.

$$\dot{G}(t) = -(p1 + X(t)) G(t) + p1G_B + p(t) \quad (9)$$

$$\dot{X}(t) = -p2X(t) + p3[I(t) - I_B] \quad (10)$$

$$\dot{I}(t) = -n[I(t) - I_B] + u(t) \quad (11)$$

where G_B and I_B are the basal pre injection level of glucose and insulin in blood, $p1$: insulin-independent rate constant of glucose uptake in muscles and liver in (1/min), $p2$: rate for decrease in tissue glucose up take ability (in 1/min), $p3$: insulin-dependent increase in glucose uptake ability in tissue per unit of insulin concentration above the basal level in $((\mu\text{U/mL})^{-1} \text{ min}^{-1})$.

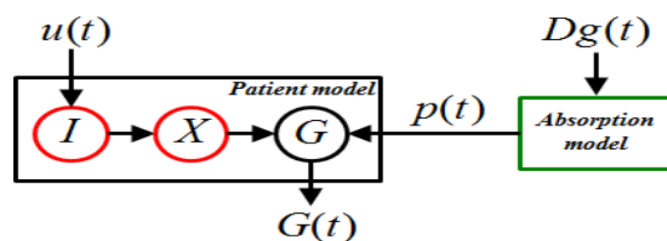


Figure 11. The schematic structure of the T1DM model used [135].

The controller reacts promptly to large and rapid variations in the insulin action [108]. The absorption model is approximated as the exponential equation given below.

$$D(t) = \frac{D_g(t) A g t e^{\frac{-t}{t_{max,G}}}}{t^2_{max,G}} \quad (12)$$

where $D_g(t)$ represents the time function of the external glucose input.

Then, a robust fixed point transformation (RFPT) method is applied to overcome problems like reliability of the model parameters and environmental disturbances [136]. The RFPT method is an alternative for the model reduction techniques. Only the response of the system to the control signal is observed. The deformed input is used to calculate this signal to approximate the model for already defined “desired system response” and “purely kinematic terms” are used to determine the desired response without using any information on the system’s dynamics. Fixed point theorem is used to map the control signal and the system’s response generated in the control cycle and actual desired response for single- input/single-output (SISO) is as follows:

$$r_{n+1} = G(r_n; r^{Des}) = (r_n + K_c) * \{1 + B_c [\tanh(A_c(f(r_n) - r^{Des}))]\} - K_c \quad (13)$$

where K_c , A_c , $B_c = \pm 1$ are the adaptive control parameters. For the adaption of the RFPT method a route for control signal is elaborated which determines control actions and parameters. Bergman equations and RFPT equations are solved to obtain the desired values.

$$u^{Desired} = -\frac{\ddot{G}(t)}{p3G_b} + \text{Additive term} \quad (14)$$

The control parameters can be set without any optimization. Controller is efficient to control BG levels that are very close to basal value for a patient.

6.3. Sliding Mode Control (SMC)

The advantages of sliding mode control (SMC) are ultimate accuracy, insensitivity to the internal and external disturbances, robustness and convergence in finite time that are important characteristics of the SMC which are a suitable choice for the control algorithms related to the human body because it is important to obtain extreme precision [137]. Also, the robustness against the parameter variation is better in the SMC compared to the PID. The SMC is basically a simple and robust procedure to synthesize controllers for both the linear and non-linear processes. The design problem of the SMC consists of defining the switching logic and parameter tuning of each controller structure. The first step in SMC is to define a surface $s(t)$, along which the process can slide to its desired final value. The sliding surface breaks the phase plane into regions where the switching function $s(t)$ has different signs. The structure of the controller is intentionally altered as its state crosses the surface in accordance with a prescribed control law [138]. It was designed for T1DM. As SMC is for the first-order, the higher-order sliding mode (HOSM) is a technique suitable to design the control function $u(t)$ to stabilize the BG level. Bergman model (see Section 6.2) is considered for designing. State space is considered for designing, state space equations are:

$$\dot{x}_1 = -p1[x_1 - G_b] - x_{1 \times 2} + D(t) \quad (15)$$

$$\dot{x}_2 = -p2x_2 + p3[x_3 - I_b] \quad (16)$$

$$\dot{x}_3 = -n[x_3 - I_b] + [x_1 - h]^+ t + u(t) \quad (17)$$

Y : is the rate of the pancreatic β -cells release of insulin.

$D(t)$: rate at which glucose is absorbed to the blood following food intake (mg/dL/min).

$$D(t) = 0.5 \exp(-0.05t) \quad (18)$$

The output tracking error is defined as:

$$e = G_b - G(t) = G_b - x_1 \quad (19)$$

Relative degree was found to be $r = 3$. So, the desired sliding variable (σ) for Equation (18) is:

$$\sigma = e^{r-1} + c_{r-2}e^{r-2} + \dots + c_0e \quad (20)$$

After the calculation in [44] we obtain the control function designed as:

$$u = -\alpha |\sigma|^{1/2} \text{sign}(\sigma) - \beta \int \text{sign}(\sigma) d\tau \quad (21)$$

This control function is used with appropriate α and β to stabilize sliding variable σ to zero in a finite time. This model is simulated in MATLAB to obtain the desirable responses.

6.4. Model Predictive Control (MPC)

Mostly, work done in the MPC is for the glucose control in T1DM. Flexibility to independently define the precise parameters such as body weight, total insulin dose, and control specifications must be considered [139]. The feed forward ability of MPC that acts in anticipation of the future variations due to disruptions is enhanced when considering a reference meal plan of definite size and time that is always given to the patient. Thus, the system is ready to provide the optimal insulin infusion to satisfy for a small in size reference meal, in order to conquer the effect of long. For a detailed model and equations, we refer interested readers to study [139]. In recent years, the MPC strategy has been widely used in T1DM therapy and clinical trial, more than PID and fuzzy logic. A detailed description of the MPC strategy and its working is explained in Section 7.

6.5. H_∞ Control

When using linear time-invariant (LTI) models, H_∞ is a practical controller synthesis approach. There is an effective trade-off between the strength of control action, and the tracking error when considering a low-order robust controller characterized by the H_∞ . This tradeoff is known as the mixed-sensitivity problem, and the optimal solution in terms of the lowest gain between the input disturbance and the output errors is achieved by this optimal control procedure. The glucose-insulin response obtained by the simulations show that it became stabilized in a reasonable time interval [140]. A Bergman model (see Sections 6.1 and 6.2 for details) along with the H_∞ control is studied. A self-contained route is used to design H_∞ control as shown in the Figure 12.

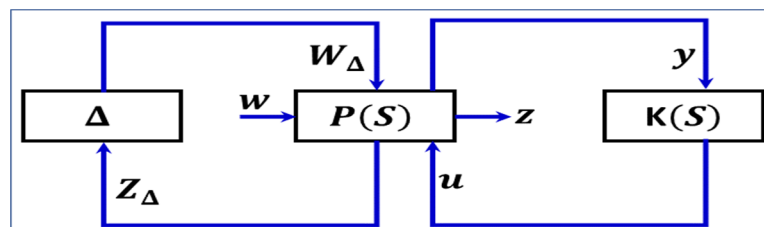


Figure 12. Schematic overview of the H_∞ controller (adopted from [125]).

The symbols given in Figure 12 are: $P(s)$: transfer matrix of the plant, $K(s)$: transfer matrix of controller, and Δ denotes the system uncertainty model. The plants transfer matrix is related to the input and output matrices, respectively. For $Y > 0$ an internally stabilized controller exists such that $\|G_{ZW}\| < Y$, G_{ZW} : closed loop transfer matrix from w to z , Y : is the rate of the pancreatic β -cells release of insulin, G_{ZW} is given by: $G_{ZW} = F(P,K)$, Controller $K(s)$ was found under the conditions given in [123]. It is simulated in the MATLAB to obtain the desired responses. It was observed that

BG levels were stabilized at basal level of 81mg/dL using H_∞ controller. Also, even in the presence of disturbances, it falls to satisfactory level of 67 mg/dL [140]. The simulations results validate the effectiveness of the H_∞ controller.

6.6. State-Dependent Riccati Equation (SDRE)

This technique is used to design a BG regulator for T1DM patients. There is a tracking problem defined so that BG concentration tracks exponential decreasing desired trajectories. Hypoglycemia and hyperglycemic problems are limited by time-varying the desired trajectory. Effects of uncertainties like meals and exercise have been investigated for 10 different patients. Important advantages of this treatment are that for T1DM patients there are no hypoglycemia conditions, and it has robustness against parametric uncertainties in glucose insulin system [141].

6.7. Fuzzy Logic Control

The feedback fuzzy logic control (FLC) model is devised for the T1DM. It is Mamdani-type fuzzy architecture which has two input and one output methods. It is configured with the PID [127]. The structural overview of the FLC along with its principal components is shown in Figure 13.

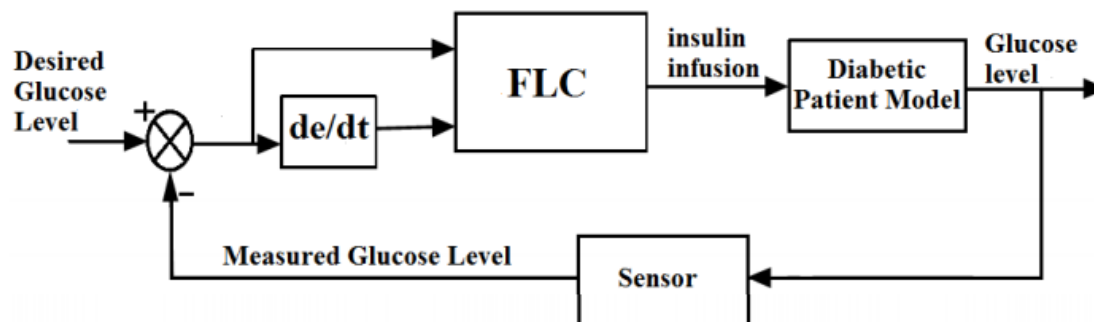


Figure 13. Structural overview of the fuzzy logic controller (adopted from [133]).

7. Model Predictive Control (MPC) Strategy Used in T1DM Therapy

MPC is a promising strategy used in AP, it assists in maintaining the glucose level within the normal glycaemias range and achieving good regulation in lowering the hypoglycemia risk in a human body [142]. MPC is one of the most efficient control strategies developed in recent years for control design. This control model predicts the future system outputs/states, considering the current values as well as past, and on the proposed control action of the future [143–145]. It has many exceptional features, which makes it more competitive for BG regulation compared to other methods [142]. The five unique features of the MPC are summarized below:

- MPC's prediction property makes it suitable for anticipatory and measured insulin delivery in a human body.
- MPC can exceed the physiological delays associated with the subcutaneous flow.
- MPC can resolve the compensation of the dead time, commonly seen in the glucose concentration problem.
- The efficient feed-forward control technique embedded in the MPC can handle the known disturbances such as meal intake or metabolic changes.
- MPC can easily handle the constraints on the system inputs and outputs.

Apart from the unique features stated above, in MPC, the control parameters can easily be tuned for each patient. The controller can yield acceptable performance even with no external information such as time and quantity of meal intake [146]. The control model collects the data from both past inputs as well as outputs, and then combines them with the future inputs predicted and gives a

predicted output for that particular time. This attained predicted output can be combined with the referral trajectory, then giving the predicted future errors possible in the system [147]. To eliminate the error from the measurements, the attained error can be fed into an optimizer, which can implement the present constraints of the system on to the predicted outputs, and then minimize the operating cost function [147]. With the help of MPC, dual control of insulin is easily designed with such an algorithm [148,149]. The conceptual working of the MPC strategy taking insulin input as an impulse is shown in Figure 14.

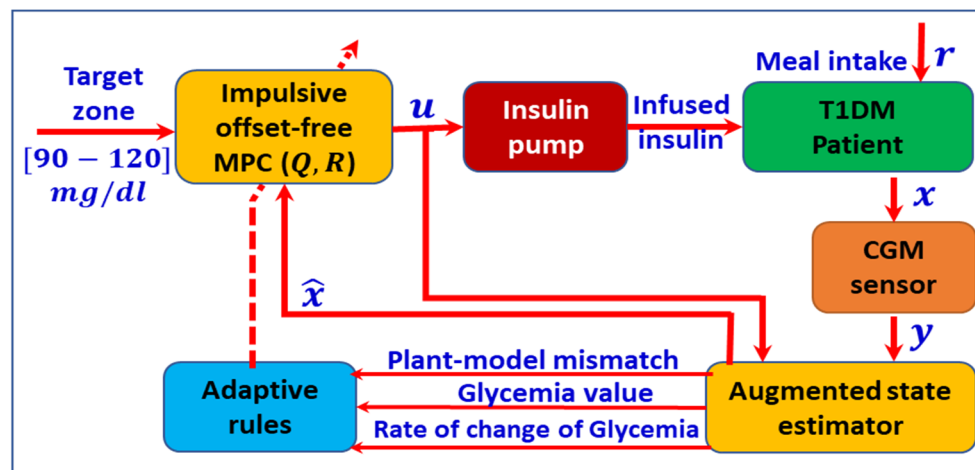


Figure 14. Conceptual overview of a model predictive control (MPC) strategy used in T1DM treatment and control (adopted from [150]).

The unique aspects of the MPC such as constraint handling, an optimal control signal, and flexibility to include different types of objectives, make it one of the preferred controllers for incorporation in AP systems. The use of MPC for different test cases is reported by Anirudh et al. [151]. A robust MPC for automatic BG control was developed in Schaller et al. [152] study, where the robustness to uncertainties was introduced via PID-based offset control [152]. Recently, Tinna et al. [153] proposed an MPC-based dose guidance algorithm to identify an individual's optimal dosing of long-acting insulin. Authors simulated various scenarios with biological variations and distinct levels of adherence to the treatment. Tinna et al. [154] proposed an MPC-based decision support system for fasting glucose and long acting insulin dynamics in T2DM's patients. Gian et al. [155] improved the MPC performance in silico via integral action. The proposed integral MPC (IMPC) keeps the glucose closer to the set point with respect to the MPC. The proposed IMPC significantly reduces time in hyperglycemia without negatively affecting hypoglycemia. Dimitri et al. [156] proposed an adaptive model predictive control (AMPC) algorithm for a dual hormone AP intended for patients with T1DM. The study results show that the controller is robust to daily variations in the model parameters. Furthermore, some latest approaches have improved the MPC strategy for solving complex control problems [157–161].

In 2008, computer simulations were extensively used for the T1DM treatment and control, and a paradigm shift occurred due to the significantly improved results. Consequently, for the first time in history, an automated model was approved by the FDA as a substitute for the preclinical trials of certain insulin treatments, including closed-loop algorithms [162]. This UVA/Padova T1DM simulator (S2008) emulated meal challenges and included a population of the 300 in silico subjects (100 children, 100 adults, and 100 adolescents) for validation. Each virtual subject was represented by a model's parameter vector, which was randomly extracted from an appropriate joint parameter distribution. At that time, the S2008 was successfully used by 32 research groups in academia, as well as by the companies active in the field of the T1DM treatment. The simulation results were explained by 63 publications in peer-reviewed journals. Chiara et al. [163] presented new insights about the non-linearities of insulin action in the glucagon kinetics and hypoglycemic range and developed an updated version of the

UVA/Padova T1DM simulator (S2013), which was submitted to the FDA for approval in 2013. It yields better results compared to the S2008 simulator, and it has been extensively used in T1DM treatment until now. Later, Roberto et al. [164] assessed the rationality of the S2013 simulator against the clinical data and compared its performance with that of the S2008.

Recently, the S2013 simulator has been enriched by three novel features [165], which are: (i) assimilation of intra- and inter-day variability of the insulin sensitivity (SI), (ii) different distributions of the carbohydrate-to-insulin ratio (CR) at lunch, breakfast, and dinner, and (iii) dawn phenomenon. Roberto et al. [166] presented an upgraded version of the UVA/Padova S2013 simulator. The presented simulator reproduces the intra-day glucose variability observed in the clinical data, and also describes the nocturnal glucose increase, and the simulated insulin profiles reflecting real-life data. The FDA's approved UVA/Padova simulator has been tested and improved for fully automated BG control with announced/unannounced meal intake [167]. Roberto et al. [168] evaluated the potential benefits and risks of different insulins or dosing schemes to suggest the design of the clinical studies for T1DM. For this, a module describing the pharmacokinetics of different basal insulins is incorporated into the UVA/Padova T1D simulator. Authors verified the feasibility results through extensive simulations with alternate parameters. Furthermore, the MPC and PID control strategies have been extensively used with the UVA/Padova simulator for the insulin regulation to the target individual in the presence of disturbances and model uncertainties to effectively monitor the T1DM's patients [169–171].

8. Glucose Measurement

Glucose measurement (GM) is one of the fundamental components of modern AP systems. It is extremely important to monitor the glucose levels in the human blood for transparent management and early diagnosis of diabetes as well as an endocrine metabolic disorder [172]. Furthermore, GM plays a vital role in yielding near-normal glycemic control which is extremely important to prevent diabetes. Continuous monitoring of the glucose levels empowers faster treatment decisions, steps to be taken to prevent fluctuations in the BG levels, and to avoid further complications in a human body [173,174]. Recently, due to significant developments in sensor technology, low-cost sensors have been extensively used for GM purposes [175]. In addition, edge computing and fog computing are two latest architectures for a sensor's data handling that can offload data from the cloud, process it in a T1DM patient, and transmit information machine-to-human or machine-to-machine in just a few milliseconds or seconds [176]. Dianne et al. [177] described the detailed understanding about the GM, methods used for the GM, and calibration methods used for the sensor's readings correction for T1DM's control and treatment.

The patients of T1DM can monitor their GM via two methods, (i) self-monitoring blood glucose (SMBG) using home blood glucose meters or (ii) using a CGM to monitor the glucose concentrations continuously [178]. The GM provides the data essential to make daily administration and management decisions related to the insulin dose, food intake, and physical exercise etc. The recent introduction of the CGM enables the GM subcutaneously in interstitial fluid which has a range of advantages compared to the SMBG method. The SMBG test strips were available in the market from approximately 35 years ago. The latest SMBG test strips contains hexokinase or glucose oxidase chemistry and can yield a numerical measure of capillary glucose concentration either via photometry, colorimetry, or electrochemistry after a series of chemical reactions on a small drop of blood ($<1 \mu\text{L}$ for some meters). Nearly 30 home BG meters are obtainable from the market today. All SMBG meters satisfy the minimum standards of accuracy as established by the FDA. Despite the success of the CGM, the SMBG remains the most usual form of glucose monitoring and GM practiced by T1DM patients in recent times.

In contrast, the CGM provides the time-series glucose data which is highly reliable whereas the SMBG gives only snapshots of the BG's concentration. The CGM can report ~ 288 glucose values per day and produce data revealing temporal trends and patterns in the glucose control. The CGM technologies measure glucose subcutaneously, in the interstitial fluid. A sensor is positioned just under the patient's

skin typically in the patients' thighs, buttocks, upper-arm, or abdomen. The sensor is a glucose oxidase platinum electrode [179], which generates an electrical current in the presence of glucose in the interstitial fluid. Each individual CGM monitors measure the electrical current and generates an average glucose value every five minutes which, depending on the monitor, is either displayed in real-time or stored for later downloading. In order to receive or either display or record glucose values, calibration is required for accurate monitoring and analysis [179,180]. Furthermore, in case of the real-time CGM, monitors can be programmed to trigger alerts/alarms for both high or low glucose values, thus permitting T1DM patients to treat for these abnormal readings and significantly reducing fear related to hypo or hyperglycemia [181]. The advantages and disadvantages of both GM techniques used in real-world applications are summarized in Table 2.

Table 2. Advantages and disadvantages of glucose measurement (GM) techniques (adopted from recent studies [182,183]).

GM Method	Advantages	Disadvantage
SMBG	<ul style="list-style-type: none"> • Accurately measure the capillary glucose concentration • Relatively inexpensive • convenient to train patients • Familiar and widely used in practice • Significant help in prioritization of clinical problems and support in clinical decision. 	<ul style="list-style-type: none"> • Require more training and checking • Subject to mis recorded data and user errors • Yield limited data in one point of time • Multiple daily testing is required to achieve good glycaemic control • Inconvenient and painful • Quality of glucose test strip varies • Sporadic measurements can occur which impact the clinical effectiveness.
CGM	<ul style="list-style-type: none"> • Provides the detailed picture of the glucose levels even in abnormal circumstances (i.e., during sleeping and exercise) • Record all readings perfectly • Provide wide range of metrics for personalized diabetes management • More convenient to use compared to strips • No need of daily fingerstick by using the pre-calibrated systems • Helpful for identifying low or high glucoses in patients who cannot recognize or express symptoms • Enables more in-range glucoses • Decrease worry and increase confidence about patients' safety. 	<ul style="list-style-type: none"> • More expensive compared to SMBG • Difficult to wear multiple sensor on a body • Significant complexity involved in understanding • Many models are required for the calibration purposes • Regular replacement is needed (every 3–14 days depending upon the model) • High level of compliance and interactions are needed • Sometime produces disruptive alerts

Ajjan et al. [183] described various GM techniques including CGM and SMBG, guidelines on the use of both CGM and SMBG, and metrics used in the CGM evaluation. Furthermore, they described the latest CGM devices that can overcome the limitations of the HbA1c monitoring and SMBG. Jenine et al. [184] described the limitations and benefits of CGM advancements in the T1DM and explained the future application of this technology in revolutionizing T1DM treatment and control. Klemen et al. [185] presented the recent evolution in the AP systems, T1DM, CGM, insulin pump technology, closed-loop systems, SMBG, and MDI etc. Boucher et al. [186] explored flash glucose monitoring commencement in adolescents and young adults with T1DM who were not meeting glycaemic targets in normal circumstances. This newer GM technology may decrease the management burden and raise the proportion of young adults and adolescents who achieve glycaemic targets. Flash glucose

monitoring is one such modern technology, which delivers comprehensive glucose data when an interstitial glucose sensor is scanned by handheld device. Recently, ensemble methods have emerged as potential solutions for the glucose levels prediction in T1DM patients [187]. The BG prediction involves forecasting a patient's BG levels based on past and current history (i.e., accumulated data). The BG prediction helps in providing the necessary alarm so as to avoid any further complications from the hyperglycemia and hypoglycemia. We present the detailed taxonomy of the latest BG prediction approaches in Figure 15.

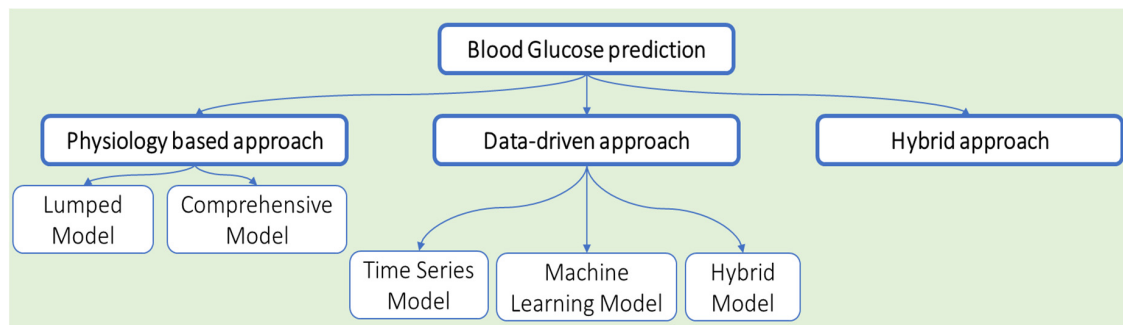


Figure 15. Taxonomy of the blood glucose prediction approaches for T1DM (Adopted from [188]).

Apart from the BG prediction, researchers across the globe have been trying from decades to make functional commercial non-invasive glucose measurement devices [189]. The challenges associated with the such devices are the inaccurate readings, and repetitive replacement over time. The non-invasive GM methods can be categorized based on: (i) blood/tissue properties, (ii) the intrinsic properties of the glucose, and (iii) breath acetone analysis. The latest non-invasive GM techniques based on the glucose and tissue/blood properties are presented in Figure 16. Recently, various mathematical models have been developed for the purpose of GM and analysis in the T1DM's patients [190]. Contador et al. [191] proposed a method for identification of the BG patterns in patients with T1DM using CGM and clustering techniques. The proposed method facilitates mathematical modeling of glucose and extracts useful patterns which in turn can assist healthcare professionals to improve T1DM patient habits and therapies.

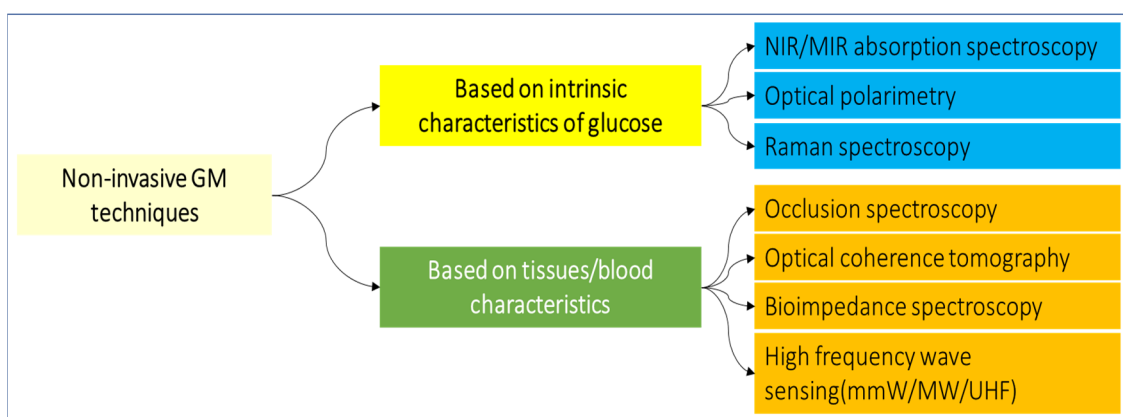


Figure 16. Detailed taxonomy of the latest non-invasive GM techniques (adopted from [189]).

9. Lesson Learned and Discussion

In this review paper, we have summarized the insulin administration, glucose measurements, and control strategies used in artificial pancreas (AP) systems. A large number of control algorithms have been proposed for the AP. Among these, only MPC, PID, and FLC have been used experimentally in clinical trials. The PID controller can be personalized or made patient-specific by tuning its parameters accordingly. In MPC strategy, the weighting function of the objective function or model is used for the individual predictions [192], whereas the adaptive controllers have been used in conjunction with other controllers such as PID and FLC to provide real-time adjustment of the parameters [193]. Meanwhile, it is relatively challenging to decide as to which control strategy is appropriate for desirable performance. Furthermore, due to the diverse factors and hidden complexities, the development of controllers based on personalized mathematical models using the CGM data, and devising computational models, mainly based on machine-learning methods, that reproduce the CGM data/values and controllers based on such data-based models, are very challenging. Meanwhile, the full automation of insulin regulation, and the solution of the underlying closed-loop control problems, are the main elements in the success of the T1DM's treatment based on the AP paradigm. Furthermore, most of the controllers discussed in the study lack implementation in clinical trials. A synthesis of the controllers addressing the large diversity of metabolic factors has not been devised. With the significant advancements in machine-learning methods, determining the accurate medications highly suitable for treating different comorbidities of the diabetic has become reality [194]. Training of the machine-learning models on the sufficiently large datasets can help in suggesting the most appropriate medications for T1DM patients. Apart from this, the scheme which tunes the insulin is based on broad limits and proportional gain. Such schemes provide robust performance considering circadian variations, mixed meals, and the common problems of the disturbance rejections and sensor errors. The invention of the low-cost sensor data-processing technologies in a CGM, and data-driven adaptive controllers that can auto-correct errors and change the insulin infusion rates can revolutionize the T1DM control.

Until now, there have been three major eras which show the improvements of the control strategies in the AP systems [195]: (i) first era covers the closed-loop control algorithms reported between 1963~1981, (ii) second era includes the model-based control algorithms developed from the 1990s to the present, and (iii) the third era includes current control algorithms based on data. In the first era, the control problem heavily depends upon the glycemic target defined by the physician, and the controller is an algorithm able to compute the insulin amount to be infused by the CSII system such that the goal of the treatment could be achieved. In the second era, the new challenge was to develop the control algorithms based on the physiological information of glucose metabolism and the control signal should have physiological meaning. It establishes a new paradigm encouraged by two research problems/areas: the mathematical modeling of glucose metabolism, and the synthesis of model-based control algorithms. In the third era, the paradigm of the AP, its three elements (CGM system, CSII system, and the control algorithm) have evolved considerably. Recently, many clinical trials have proved the usefulness of the AP as an outpatient therapy. Despite the significant developments, the specific model based on the personalization scheme that can adopt with the specific features of each patient is missing. In addition, the multi-criteria such as considering circadian variations, mixed meals, and the common problems of the disturbance rejections and sensor errors need significant developments [196]. Although both the MPC and PID approaches have shown promising results, confirming their validity with real experiments and clinical trials is required. In addition, the very high complexity of the glucose dynamics and limitations in the technology the viable approaches for closed-loop glucose control in T1DM has become imperative [197].

Improved and modern technologies for the treatment of diabetes continue to emerge at an impressive rate. The latest devices such as Medtronic MiniMed 670G hybrid closed-loop (670G HCL) system has demonstrated its effectiveness in terms of the user requirements treatment outcomes [198]. Ghada et al. [199] updated the medical community about both new and old technologies used for the control and management of diabetes mellitus. Diabetes handling technology is improving every day

to make the life of the diabetic patient easier with data-driven models/algorithms. Hjerde et al. [200] implemented and evaluated several hybrid closed-loop deep Q learning (HCL-DQL) algorithms for the task of regulating BG in T1DM patients. Low-cost tools such as tidepool [201] and glucose meters [202], are used to collect, integrate, and visualize the diabetes device data in a pediatric clinic setting. American Diabetes Association (ADA) made standards of the medical care for the diabetes. Diabetes technology comprises both hardware and software devices related to insulin injection and administration in a human body. This technology recently introduced various hybrid devices. Technologies useful for diabetes are real-time CGM, intermittently scanned CGM, blinded (professional) CGM, unblinded CGM etc. Moreover, it is very difficult to manufacture one proper device with all related functionalities because metabolic conditions vary from patient to patient. Hence, despite the latest developments in tools and technologies, there is no single device and technology which can completely handle the task of self-care in T1DM patients [203].

Large uncertainties in intra- and inter-day meal responses and daily and periodic variability in insulin action require AP systems to be equipped with personalized safety and sophisticated mechanisms that adjust insulin titration, titrate the insulin efficiently, and eliminate or reduce insulin's over-delivery. Meanwhile, the HCL systems are equipped with adaptive tools/modules and can solve the aforementioned problems effectively. Benyamin et al. [204] tested the safety and efficacy of the Medtronic HCL in a supervised outpatient setting. The authors suggested that whole HCL system was safe and efficacious during testing. It was concluded that the HCL system is able to significantly reduce the risk of hypoglycemia, while regulating the BG levels automatically. Richard et al. [205] investigated the safety of an HCL system in T1DM patients, and the authors concluded that automated insulin delivery using HCL was associated with fewer serious or device-related hostile events in T1DM patients. The authors further stressed that randomized studies and long-term registry data are needed to verify the effectiveness of the HCL systems. Martin et al. [206] verified exercise-induced hypoglycemia during the insulin delivery using an HCL system. The authors tested the performance of the proposed algorithm with modified parameters and verified the system effectiveness for long-term outpatient trials. Tagougui et al. [207] discussed in detail the development of AP systems over time, how they work, and the glucose control regulation during the physical activities. Riddell et al. [208] claimed that recently approved HCL devices/systems are appropriate for the prolonged aerobic exercise if a temporary (higher level) glucose target is set well before the start of the exercise (i.e., 45–90 min before the exercise starting time). The comprehensive description, functionalities, examples, and working methodologies of the HCL systems can be found in several recent studies [209–213]. The comprehensive description about the advantages and disadvantages of different controllers discussed in this study are summarized in Table 3.

Table 3. Comparison of the different controllers used for T1DM assessment and control.

Controller	Advantages	Disadvantages	References
Self-Tuning	Accurate physiological response with short time.	Parameter optimization and manual tuning is required.	[134]
Sliding Mode Control	Better robustness and insensitivity to the inter-patient variability/diversity in metabolic conditions.	SMC has some intrinsic problems such as discontinuous control that suffers from the chattering. SMC is only applicable for the degree one systems otherwise higher order sliding mode (HOSM) is used.	[137,138]
Adaptive Control	It can react promptly during the large and rapid variations in insulin action.	In the presence/entrance of the unknown parameters in the process model, it becomes relatively difficult to construct a continuously parameterized controller.	[118,119]
Model Predictive Control	It can be tuned for personalized insulin delivery. It has feed-forward insulin action for delayed insulin effect.	There is no compensation for the unknown disturbances, and the metabolic uncertainty is not considered in the MPC.	[122]
H_{∞}	H_{∞} controller works well in the presence of uncertain parameters.	Unable to effectively resolve the tradeoff between the strength of control action and the tracking error.	[123]
SDRE	Can tackle any non-linear terms, and effectively maintains the non-linear characteristics of the system. It exhibits robustness against parametric uncertainties.	It involves very complex mathematical calculations especially when a system is of higher order.	[124]
PID	It is the best controller with situation awareness. It may be proportional (P), proportional-integrative (PI), proportional derivative (PD), and/or PID.	Its physical implementation for the clinical trials is relatively difficult.	[105]
Fuzzy logic	Fuzzy logic is opposite to that of binary logic. It is helpful at any point between 0 to 10.	Simulations wise developed but its validity in clinics has not been rigorously verified.	[116]

10. Conclusions and Future Work

In this review article, we have described the fundamental components of the artificial pancreas (AP) system used for type 1 diabetes mellitus (T1DM) treatment and control. We have explained the different methods of administration and delivery of insulin in T1DM patients, glucose measurement (GM), and the most widely used control algorithms. In addition, we explained the strengths and weakness of the available control strategies used for diabetes treatment and control. We have discussed many techniques related to the insulin infusion in human body. The open loop, closed loop, linear and non-linear schemes, and various controllers have been explained in detail to enable research beginners to understand this domain effectively. The Simulink models has been formally explained and plotted with the mathematical formalization to explain their backend functionality. The control loop strategy has been widely used in AP systems and works like a real human pancreas system. We described three prominent control algorithms such as PID, MPC, and FLC in detail, which are

proven clinically, and they yield promising results. In future work, we intend to explore more advance control techniques used in the AP systems, and their structure and challenges. In addition, we aim to present a comprehensive review about the recent developments in the type 2 diabetes mellitus (T2DM) treatment and control.

Furthermore, the current coronavirus disease 2019 (COVID-19) pandemic has forced clinicians to reconsider the ways in which effective diabetes management is delivered during these challenging times around the globe [214,215]. While many of the technological prospects are now becoming readily available, an improved understanding of patient behaviors and lifestyle choices is needed in order to achieve the full potential for emerging digital health technologies for people with diabetes. In addition, the use of interoperable and connected devices in remote diabetes management will certainly increase, both outside and inside hospitals. As treatment paradigms shift toward more automated insulin delivery systems and remote management, the risks and benefits will become clearer and more nuanced. To this end, we aim to present detailed policies and procedures that are guided by the untainted data and which focus on improved outcomes for those affected by the diabetes. We aim to present the challenges and countermeasures required for the remote monitoring of diabetic patients, and technology-dependent treatment methods leveraging the federated learning concept of infectious diseases. We intend to describe the country-specific experiences in handling the infectious diseases, and their relationship with diabetes.

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