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A smart medical system for dynamic closed-loop blood glucose-insulin control

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ABSTRACT

Recent years have witnessed the rapid development of healthcare devices. The connections between patients and medical cyber-physical systems are becoming tighter and many patients have got enormous benefits from these convenient systems. Our research, mainly refer to blood glucose-insulin control system, is a hot topic in the field of connected health as the development of diabetes has attracted more and more attention during the past several decades. Mainstream methods for treating diabetes in hospitals is mainly confined to manually injecting insulin to patients, which is inconvenient and highly expensive. Meanwhile, they are not fine-grained for doctors to accurately control insulin levels, so we try to improve the whole system for blood glucose-insulin control. Medical cyber-physical system on blood glucose-insulin control consists of three parts; CGMS (Continuous Glucose Monitoring System), insulin pump and closed-loop control algorithm. CGSM and insulin pump have made great advances in recent years, but we are still trying to find a better method to decrease errors introduced by mechanical measurement. Closed-loop control algorithm is vitally important and complex to study in this system. We introduce a novel algorithm which can better control blood glucose and insulin levels. To optimize this algorithm and solve storage problem, we also add back end analysis to this system. Our simulations are based on real data from patients in Shanghai No.9 hospital. We have finally concluded that our system performs well.

1. Introduction

Medical cyber-physical systems have brought enormous benefits to human beings and promoted great development to the society. It is known to us that it can monitor some part of our body and support specific feedbacks. In other words, it aims to use real-time feedbacks to provide intelligent monitoring of patients. Wearable monitoring system assists in managing the treatment of chronic diseases such as heart diseases, asthma, and diabetes and the monitoring of vital signs such as heart rate, blood oxygen level, respiration, and body fat. They normally provide noninvasive sensing, local processing, user feedbacks, and communication capabilities (Fotiadis, Glaros & Likas, 2006). There are more and more products streaming into the market such as intelligent bracelets, heart beat detector, CGMS and so on. There are also some challenges during the research of medical cyber-physical systems, such as function, wearability, accuracy and security. The size and requirement of medical cyber-physical systems have defined these difficulties. In this paper, we will pay more attention to one kind of medical cyber-physical system which shows good performance on the blood glucose-insulin control.

For many decades, the control of diabetes has gone through many stages. However, external control cannot reach the perfect

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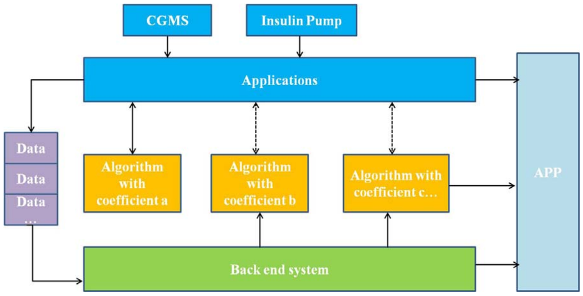


Fig. 1. The workflow of the whole system.

effect as the physiological insulin secretion pattern (Russell, El-Khatib, Nathan, Magyar, Jiang & Damiano, 2012). Human body system is complex, and it is difficult to construct a manual system to realize its function (Brown & Worthington, 2012). Especially for these patients who nearly cannot control the insulin by their own pancreas, the manual control can hardly give good performance as the blood glucose changes greatly. Artificial pancreas is a novel research direction in recent years, and it can imitate the pattern of pumping up of insulin by pancreas and inject insulin automatically (Phillip et al., 2013). Compared with the manual control, it is more reliable, more convenient and more flexible. Artificial pancreas in this paper consists of three parts, CGMS, insulin pump and closed-loop control algorithm. Medtronic is the biggest company which dedicated to research medical devices, and it has the best sale on CGMS and insulin pump. However, they have not given a complete system with closed-loop control algorithm.

(Except these, another question we have to consider is the communication or data exchange between CGMS and insulin pump. The communication between CGMS and closed-loop control can guarantee that the values of blood glucose can be transferred to the algorithm in time. The communication between insulin pump and closed-loop control can guarantee that the signal of insulin can be executed correctly. The closed-loop control algorithm can be embedded into insulin pump if the data processing is not too complex. However, if we want to make this algorithm accurate, we have to get enormous data, and we have to consider the storage of insulin pump algorithm memory and we call it back end system. In this paper, we introduce another part which is especially designed to process data and optimize the algorithm. Fig. 1 shows the whole workflow in the system. The first level is Applications, and it includes CGMS and insulin pump. Applications level mainly provides devices for users. The second level is Algorithms. For each patient, the original algorithm is same, we can call it algorithm with coefficient *a* and we embedded it in the insulin pump algorithm memory. After the system generate data with algorithm with coefficient *a*, it will transfer data to back end system. Next, back end system will analyze the control effectiveness. If necessary, it will generate a new algorithm which we think is better for the current patient, this is algorithm with coefficient *b*. Next is Algorithm with coefficient *c*, Algorithm with coefficient *d* and so on. Obviously, the third level is back end system. Finally, we make an app to integrate these components and provide a friendly interactive interface for patients and doctors. The essence of the whole system is dynamic iteration and optimization.

There are three innovative contributions in this paper and they can be summarized as follows:

- *Design of a system for blood glucose-insulin control:*We design the whole system for blood glucose-insulin control. This wearable medical system for blood glucose control consists of CGMS, insulin pump and closed-loop control algorithm. These three parts guarantee the automatic control.
- *The proposal of a complete control algorithm for blood glucose control:*To better control blood glucose and insulin, we put forward a kind of algorithm based on Model Predictive Control (MPC). We have done many kinds of experiments to validate the performance of this algorithm. Compared to other blood glucose control algorithms, the algorithm in this paper has excellent robustness and individuation.
- *The proposal of a kind of control mechanism in back end:*On one hand, we hope that the insulin carrier is portable, but it will influence the storage of data. Thus, we put forward one method which can solve the storage problem. Meanwhile, we introduce back end optimization which can dynamically optimize our closed-loop algorithm and make our algorithm adaptive to individuals.

This paper is organized as follows: First of all, we introduce the design of the system framework and the closed-loop control algorithm. Also, in this section, we will provide some optimization methods to algorithm including constraints. Next, we will introduce back end system which is designed to better store data and dynamically optimize control algorithm. Section 4 presents the simulation results of this system and introduce the application based on our design. Section 5 discusses some related work and describes future work. Finally, we give the conclusion of this paper.

In this part, we will introduce current research status and challenges of this system including CGMS, insulin pump and loop control algorithm.

1.1. Current status

1.1.1. CGMS

CGMS is a kind of wearable medical device (Mastrototaro, 1998) which can detect patients' blood glucose level. A sensor, which is beneath your skin, will collect some information about blood glucose. Based on the complex algorithm, CGMS can calculate the final statistics and show them on the screen. Doctors can judge whether patients blood glucose level are in a security range by the statistics. In recent years, many companies have invented some practical products which can detect the blood glucose level in high accuracy.

1.1.2. Insulin pump

Insulin pump can relieve patients pain and ache, and it can inject insulin to the body automatically via a micro-motor (Pickup, 2012) which is different from manual injection. To imitate the mechanism of body control, insulin pump has two kinds of injections including basic quantity and incremental quantity. When the patients have meals, insulin pump will inject according to incremental quantity and the other one work at other time. In the field of insulin pump, most of them are disposable because insulin is difficult to store.

1.1.3. Loop control algorithm

The development of CGMS and insulin pump has been stable while the loop control algorithm is difficult to be put into practice. On one hand, the experiment to be tested in the body is long-time because of considerations of security. On the other hand, due to the complexity of blood glucose system, there are various kinds of conditions which can have influence on the injection of insulin. It is extremely difficult for researchers to propose an ideal algorithm to imitate the process of insulin adjustment completely.

Some researchers and doctors have conducted some clinical tests on patients. They use different kinds of algorithms to test their performance. For example, one kind of algorithm is to control blood glucose at night, aiming to guarantee the level of blood glucose at night. The result shows that their algorithm can make hypoglycemia lower than 20% (Hovorka et al., 2011).

In this paper, we put forward a kind of algorithm named Dynamic Closed-loop Control (DCLC) of Insulin which is based on the predictive model. Unlike open-loop control mode, feedback results are added to this algorithm to guarantee accurate operation (Kovatchev et al., 2010). We also take some constraint conditions into consideration. Therefore, it can be called an Enhanced Dynamic Closed-loop Control algorithm (EDCLC). By analyzing our simulation results, it shows realistic and stable control over the changes of blood glucose.

1.2. Challenges and expectations

There are some challenges and expectations about each part of this system. The first problem about current invasive CGMS is that most of these devices need the assistance of blood glucose meter which will definitely introduce much trouble. Secondly, there are differences among different devices when blood glucose at low levels Garg et al., 2009. It is serious because hypoglycemia might cause other diseases. Finally, no matter how we improve the accuracy, time-delay always exists, because of the existence of biological response in the body (Garg, Voelmle & Gottilieb, 2010). We can hardly overcome it at least in these several years. Like CGMS, insulin pump is also faced with time-delay. Because of biological response, insulin from insulin pump needs time to reach internal. Therefore, it is of great importance to solve this kind of problem (Steiner et al., 2008).

Closed-loop algorithm has to overcome the following problems: Firstly, the relationship between blood glucose and insulin is not stable. Secondly, the relationship between blood glucose and insulin is not liner. Thirdly, blood glucose systems are different in different kinds of people and we have to find a model to be adaptive to this difference. Fourthly, some external conditions like diet, exercise and so on can have a big impact on blood glucose control.

Nowadays, wireless communication between CGMS and insulin pump becomes hot because its convenience. Meanwhile, some security problems emerge. Anyone can detect information from wireless channel, and hackers can modify data if he use special technologies. We have to study a kind of wireless communication with highly reliability. Closed-loop control algorithm is significant because it combines CGMS with insulin pump. It can affect the levels of blood glucose and insulin. Moreover, there are no perfect algorithms which can control blood glucose completely. In our paper, we put forward one kind of algorithm which can be used together with CGMS and insulin pump.

2. Requirements and design

Because CGMS and insulin pump have mature technology, the most difficult part of this system is control algorithm. We have studied some famous and effective algorithms which have been published. There are some drawbacks, although they can show good performance in some parts. Our algorithm is based on model predictive control which is a kind of auto control algorithm, and we research the requirements of this system and confirm the main structure of this algorithm. In this algorithm, we have to take various kinds of factors into consideration including values of blood glucose, insulin and so on. We also give a specific equation about how we get certain values.

2.1. Requirements

The purpose of this system is to control blood glucose and insulin automatically. In a word, we need to imitate the function of pancreas. So we have to think about some factors which will affect the blood glucose, such as diet, exercise, daily habit and so on. On the other hand, we can refer to the values from the past, they contain lots of information, and we can study one algorithm which can mix these values together and calculate the exact values we want to know. In the next several parts, we will introduce our design thought, and the algorithm in this system.

2.2. Closed-loop control

The main difference between open-loop control and closed-loop control is whether the output values are used. Obviously, inputs and outputs are necessary in our algorithm Steil et al., 2011.Meanwhile, outputs can take effects on inputs. The key points are how can we turn input values into outputs as we want and which conditions should be paid more attention during this process (Patek et al., 2012).

2.3. Predictive model

There are several algorithms which have been widely studied during these years, Proportion Integration Differentiation (PID) and MPC show good performance according to the experiment results, and both of them includes closed-loop control (Camacho and Bordons, 1999). PID is a kind of algorithm which calculates the optimal amount of insulin by analyzing the patient's past and current situation analysis of blood sugar, blood glucose fluctuation rate. But there are a lot of people think that this method does not cope well with complex blood glucose control system (including food digestion and absorption of insulin, insulin and physical half-life movement and other factors, A˙ström and Hägglund, 2006), while MPC is able to predict the future based on the physiological characteristics of blood sugar levels in patients and look for the best control strategy for next some time Mayne et al., 2000. In this paper, we introduce Dynamic Closed-Loop Control (DCLC) which is based on predictive model.

2.4. Variables

DCLC can make predictions for the future results based on past data, it fuses all kinds of proper information in the past. It doesn't pay much attention on specific formula but focuses on the process of finding a core variable which can optimize the final results.

In DCLC, we can set up some variables for blood glucose values and insulin values. To clearly describe values for blood glucose and insulin, we introduce two-dimensional variables to represent these parameters. Two-dimension means one variable have two parameters. First and foremost, $G(d, t)$ represents patients blood glucose in d day and t moment, which comes from CGMS. As a result, $G(d, t-1)$ is the blood glucose value before this moment, and $G(d-1, t)$ is the blood glucose value before this day. We do not only need real time statistics, but also review types. Therefor we should take these past data into consideration. In order to measure the current level of patients blood glucose, we need the security values of blood glucose which are a set of referable blood glucose values at every moment. For example, at 7:00 p.m., a patient is supposed to have breakfast, so his secure blood glucose value can be set 10 mmol/L. We use $Gs(t)$ to represent this kind of values. To show the difference between $G(d, t)$ and $Gs(d, t)$. We use $Gx(d, t)$ which equals $Gs(t) - G(d, t)$. In addition, for insulin values, we use $I(d, t)$ to represent the insulin value in d day and t moment. To reflect the changes of the insulin values, we introduce another variable which is $R(d, t)$, it equals $I(d, t) - I(d-1, t)$. $R(d, t)$ is also an important variable, because it can decide the trend of the changes of the insulin values and it is the variable we just mentioned above which is very important. Last but not least, we introduce a new concept which is called control difference. It consists of some data from negative to positive and is calculated by the cost function which has many variables including blood glucose values and insulin values. We use F to represent the dependent variable in the function and R to represent the control difference. In the later parts, we will introduce this function. Because R has many values, F is variable. We select the minimum F and get the corresponding R, which is the $R(d, t)$ we want to get. And then, we can get $I(d, t)$. $I(d, t)$ can have impact on $G(d, t)$, thus the algorithm forms cycle and iteration.

2.5. Algorithm structure

The structure of the algorithm can be divided into three parts. The first part is the collection of blood glucose values, we can get $G(d, t)$, $Gs(d, t)$ and their past values. The second part is mainly about calculating the control difference. The third part is to get the insulin values. Fig. 2 shows the structure of this algorithm.

2.6. Algorithmic process

(1)We get blood glucose values from CGMS, the current value is recorded as $G(d, t)$, and then we can calculate $Gx(d, t)$.

$$Gx(d, t) = Gs(t) - G(d, t) \quad (1)$$

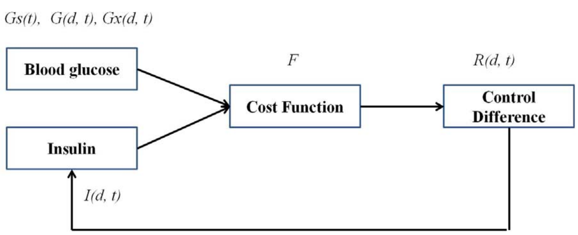


Fig. 2. The structure of the algorithm.

(2)To get precise data, we should take various kinds of factors into consideration. We have mentioned some variables above,such as $G(d,t)$, $Gx(d,t)$, $I(d,t)$, $R(d,t)$. Each of them is related to the current value of insulin, $I(d,t)$. The value of insulin is variable, therefore we introduce R and $R(d,t)$ to represent change and then we can get $I(d,t)$. $R(d,t)$ equals to $I(d,t)-I(d-1,t)$, and we can calculate $Gx(d,t)-Gx(d-1,t)$, $G(d,t)-G(d-1,t)$, $G(d,t)-G(d,t-1)$ and $I(d,t)-I(d,t-1)$. All of them are called D-value. To improve the accuracy, we can sum up the values from several days and moments. With $G(d,t)$, $Gx(d,t)$, $I(d,t)$, $R(d,t)$, we can substitute into function F and we can get $R(d,t)$. There are many ways to form function F by combining these variables, we have tried many possible functions and get one which has the best effect. Function F can be:

$$\begin{aligned} F = & \sum_{i=0}^{m} [Gx(d+i,t)-Gx(d+i-1,t)] \\ & + \sum_{i=0}^{n} [G(d+i,t)-G(d+i-1,t)] \\ & + \sum_{i=0}^{k} [G(d,t+i)-G(d,t+i-1)] \\ & + \sum_{i=0}^{l} [I(d+i,t)-I(d+i-1,t)] \\ & + \sum_{i=0}^{p} [I(d,t+i)-I(d,t+i-1)] + R \end{aligned} \tag{2}$$

One point we should emphasize here is that there are some extra variables like *m*, *n*, etc. They are introduced because of the differences of each kind of patient, we can adjust these variables in order that function F can be adaptive to a specific patient.

Then, $R(d,t)$ is:

$$R(d,t) = argmin(F) \tag{3}$$

$R(d,t)$ is the control difference we need, it can lead to the changes of the insulin values.

(3)Then we can get $G(d,t)$ in Eq. 4:

$$I(d,t) = I(d-1,t) + R(d,t) \tag{4}$$

And now, we get the current value of insulin, then the injection of insulin can lead to the changes of blood glucose. The cycle process has formed and it can be as Algorithm 1.

Algorithm 1. Framework of blood glucose control algorithm.

Input:

The value of blood glucose for current date and moment, $G(d,t)$;

The value of blood glucose for last date and moment, $G(d,t-1)$, $G(d-1,t)$;

The value of insulin for last date and moment, $I(d,t-1)$, $I(d-1,t)$;

Security values of blood glucose, *Gs*(*t*);

Control difference, *R*;

Output:

The value of insulin for current date and moment, $I(d,t)$;

1: Calculate the cost function, *F*;

2: Get $R(d,t)$;

3: Get $I(d,t)$ with $R(d,t)$ and $I(d-1,t)$;

4: **return** $G(d,t+1)$**;**

.

Because the variables of blood glucose and insulin are two-dimensional, there are two loop statements in the code. Thus, the time complexity of algorithm 2 is $o(n^2)$. During each computation, the number of needed values is stationary. Thus, the space complexity is $o(1)$.

2.7. Optimization

Although this algorithm can show good performance on the relationship between the blood glucose values and insulin values, we have come across some problems. For instance, when a patient's blood glucose value suddenly drops, it may cause hypoglycemia. At the same time, the insulin pump will inject insulin continuously, due to our previous blood glucose values and insulin values, which is extremely dangerous to patients. Meanwhile, we hope that this algorithm can perform well on various kinds of patients, but it is extremely difficult. Therefore, we have to make some changes and optimizations to get Enhanced Dynamic Closed-Loop Control (EDCLC). In this part, we mainly talk about the optimizations about this algorithm and system. Obviously, we can modify or add some parts to achieve satisfying results. On one hand, we can add some constraint conditions which can eliminate unstable results. On the other hand, we can select some variables in this algorithm and change them via the history data analysis and we can make them different to different patients. It will be introduced in the next section.

The first thing which we take into consideration is the curve slope. As known to all, food is the main factor that affect the patients' blood glucose. When a patients' blood glucose values increase or decrease in a short time, it is difficult for our original algorithm to change the insulin values quickly. As a result, it is necessary for us to add some constraint conditions to it. We introduce the constraint of curve slope. For example, the difference of blood glucose values and insulin values between two adjacent moments represents the changing speed, and we can call it curve slope. If the curve slope of the blood glucose is beyond the secure value, it may cause some problems. So we should set a constraint to make the curve slope maintain the secure ranges.

When we sleep, the blood glucose values are stable because we do not have any food. However, some little changes will also lead to the changes of the insulin values. To simplify the running system and save the energy, we set a stationary insulin value when the patient falls asleep. For example, if the patient goes to bed before 10 p.m. every night, and wakes up at about 6 a.m. We can set the $G(d, t)$ equals a constant like 0.3 during this period, which means the insulin value during this period is regular. However, if there are some huge changes at night, the patient may have some snack after 10 p.m., we will set a constraint function which will adds some insulin temporarily to ensure maximum security.

The core of our algorithm is the cost function which can decide the control difference, and we should pay more attention to it. The cost function includes many kinds of factors, but not each factor has equal effect on the final values. As we know, the values of the last day and moment are the most important while the effect of previous two or three days or moments are limited which is still useful as well. We should take different weight to different values, and the cost function can be optimized with some weights. For example, for the last moment value $G(d, t) - G(d, t-1)$ we can set the weight 1.5. For $G(d, t-1) - G(d, t-2)$, we can set 0.5. This method can fully take advantages of the latest values.

Considering all these optimization method, we can supplement the algorithm which is mentioned in the last section. These constraint factors can be put after we calculate F and get $I(d, t)$ as described in Algorithm 2.

Algorithm 2. Process of optimization for blood glucose control algorithm.

Output:
The value of insulin for current date and moment from cost function and control difference, $I(d, t)$;

foreach $t \in [0, m]$ **do**
  foreach $d \in [0, n]$ **do**
    $F = 1.5*(G(d, t) - G(d, t-1)) + 0.5*(G(d, t-1) - G(d, t-2))\ldots$
  end for
end for
$R(d, t) = argmin(F)$
if $G(d, t) - G(d, t-1) > securevalue$ **then**
  $I(d, t)$ = blood glucose;
else
  I(d,t) = I(d-1,t) + R(d,t);
end if
if $t > bedtime$ **then**
  $I(d, t)$ = night value;
else
  I(d,t) = I(d-1,t) + R(d,t);
end if
return $I(d, t)$;

.

Because the variables of blood glucose and insulin are two-dimensional, there are two loop statements in the code. Thus, the time complexity of algorithm 2 is $o(n^2)$. During each computation, the number of needed values is stationary. Thus, the space complexity is $o(1)$.

2.8. Data error solution

Now, the control algorithm has been optimized with some constraints above. However, it is not robust enough. There are still some problems when blood glucose values are lost or abnormal, and we call data error. We cannot guarantee CGMS is accurate enough with no error. Thus, there is some possibilities of occurring data error when CGMS cannot provide us with actual data. For example, we do not receive a blood glucose value at a specific time point, therefore we cannot get corresponding insulin value. Another situation is that we receive an abnormal blood glucose value which is too high or too low. To solve data error problem, we add LaGrange Interpolation method to the system.

First of all, we should judge when data error occurs. Data exception is not easy to judge, and we need to know which kind of data is abnormal. The normal blood glucose level ranges from 4.0 to 15.0 mmol/L. Thus, if one patients blood glucose value exceeds 20, we can tag it data error.

Next, assumes one value should be discarded at time point x because of data loss or exception. And now we try to use LaGrange Interpolation to get a new value. The concept of LaGrange Interpolation is that first we calculate LaGrange polynomial L(x):

$$L(x) = \sum_{i=0}^{m} (y_i * P_i(x)) \tag{5}$$

$$P_i(x) = \prod_{j} ((x - x_i)/(x_j - x_i)) \tag{6}$$

according to the given set of distinct points x_i (x_1, x_2, x_3 …x_n) and numbers y_i (y_1, y_2, y_3 …y_n), and then put the value we want to interpolate into L(x).

To reduce the computation load, we can directly use a secure value to interpolate the target position. For most people, the secure blood glucose value is 7 mmol/L. Thus, if data error occurs, we can set a secure value which can guarantee the system normally operates.

3. Back end system

We have optimized the algorithm we put forward, but there is another question. As we know, this algorithm can be embedded into insulin pump. However, insulin pump is so mini that it cannot store too much data generated by this algorithm. For each time point, the data we need are not only current values of blood glucose or insulin, the previous values are also necessary. It will cause the problem that the storage device can not process these large datasets. In this part, we will introduce a kind of method which can solve the storage problem. Meanwhile, it can optimize our algorithm dynamically. We add another part called back end system and it can exchange data with insulin pump.

Insulin pump stores recent data and most data are stored in back end system. At first, insulin pump has an original algorithm and it can control blood glucose and insulin roughly. When it has enough data to analyze, it will transfer these data to back end system which we can call BES. However, if we accumulate data during 3 or 4 days and we sample it every 30 minutes, insulin pump probably cannot store so much data. So we adopt one storage method which can change the quantity of data as time changes. For example, in first 5 hours, we store data every 30 minutes. Between 5 hours and 10 hours, we store data every 1 hour. Between 10 hours to 20 hours, we store data every 2 hours. Over 20 hours, we store data every 3 hours. It can be described in Fig. 3.

This method can store more data and keep effectiveness to the maximum extent. CGMS collects values of blood glucose every 30 minutes, and insulin pump gets values of insulin every 30 minutes. Once insulin pump connects BES successfully, it will transfer all data to BES and then it will store data with the method in Fig. 3.

Also, we use history data to optimize the control of blood glucose and insulin and we hope that the distinguish of different kinds of patients will be clear. In the last section, we mentioned that we needed to select some variables to change them via the analysis of history data. The main difference among patients is the human blood glucose system. Different people react differently to different amount of insulin. Therefore, we can change these variables placed before insulin values including l and p in Eq. 2. Now the problem is that when we should change these variable values and under which conditions we can decide to change. In the third part, we introduce $Gs(t)$ which represents the security value of blood glucose, and we can get $G(d, t)$ from Algorithm 1. We can set a safe point for each security value for each period. Below is Table 1 which indicates different $Gs(t)$ in different periods.

Therefore, we can calculate the variance σ^2 between $Gs(t)$ and $G(d, t)$ as shown in Eq. 5:

$$\sigma^2 = (Gs(t) - G(d, t))^2 \tag{7}$$

The value of σ^2 indicate the security of the current blood glucose level. If σ^2 is a bit large, $G(d, t)$ is supposed to change. It also shows that the patient is more sensitive to insulin, because the same amount of insulin can make more impact on blood glucose than others. When we want to change $G(d, t)$, we can change l and p. If we decrease l and p, $R(d, t)$ we get in Eq. 3 will become smaller and values of insulin will change more slowly. Therefore, to those who are more sensitive to insulin, less amount of insulin will have the same impact on their blood glucose. To different σ^2, the system will give different judgments. For instance, if $\sigma^2 = 10$, l and p will be decreased to 75%, if $\sigma^2 = 3$, l and p will be decreased to 90%. After we get the latest l and p, BES will transfer to insulin pump to update Eq. 2, there will be a new and more suitable algorithm for this patient. It is important for early treatment because the original algorithm is not suitable to each kind of patients. After several weeks, when BES gets stable coefficients, the algorithm can have a stable performance to a specific patient. Algorithm 3 will show the process of big data analysis.

Algorithm 3. Back end analysis in algorithm optimization.

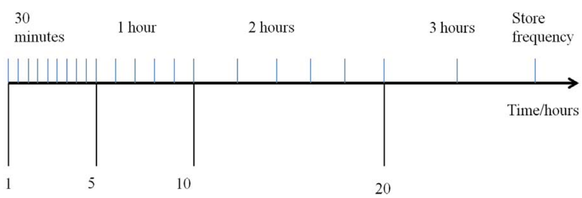


Fig. 3. Store method in insulin pump.

Table 1
$Gs(t)$ in different periods.

Period	range	$Gs(t)$
7 a.m.- 9 a.m.	5-12 mmol/L	8 mmol/L
9 a.m. - 11 a.m.	5-12 mmol/L	10 mmol/L
11 a.m. - 1 p.m.	8-18 mmol/L	13 mmol/L
1 p.m. - 5 p.m.	5-12 mmol/L	8 mmol/L
5 p.m. - 8 p.m.	8-18 mmol/L	13 mmol/L
8 p.m. - 7 a.m.	3-8 mmol/L	5 mmol/L

Input:
The value of blood glucose for current date and moment, $G(d, t)$;
Security values of blood glucose, $Gs(t)$;
Output:
coefficient l, p in Eq. 2;
1: Calculate σ^2;
2: Calculate l and p;
3: Transfer l and p to insulin pump;
4: **return** l **and** p;
.

In our project, we use wireless communication to ensure data exchange between insulin pump and BES. Bluetooth is a kind of wireless communication and it can provide stable data transmission. On the other hand, it is easy to carry out. We assume a scene that patients use our system at home with BES as described in Fig. 4.

Insulin pump connects with BES via Bluetooth. After the patient use the whole system, CGMS detects values of blood glucose and transfer to insulin pump. Insulin pump gets these data and then calculates values of insulin by the embedded algorithm. Because BES and insulin pump are connected, insulin pump will transfer all data to BES regularly. If BES is connected with insulin pump, insulin pump will store data with the algorithm in Fig. 3 momentarily. Once they are connected successfully, insulin pump will transfer all historical data to BES. BES can calculate suitable coefficients and then transfer to insulin pump to update closed-loop control algorithm. When we use wireless communication, we have to think about security. It is important to communication and patients treatment. If some coefficients are falsified, it is difficult to imagine. Because of Bluetooth, insulin pump and BES should authenticate with a private key which can protect data security to a certain extent.

4. Experiments and application

In this section, we introduce the simulation environment setup, describe the simulation results, discuss the causes behind the simulation results and introduce the application based on our design.

To ensure the reliability and practicability, we have monitored the real-time conditions of 8 patients including their blood glucose and insulin injection. First of all, we have got 24-hour values of blood glucose and insulin for three days of 8 patients in hospital. CGMS can get the values of blood glucose every 30 minutes, and doctors inject insulin by insulin pump at each specific time point. Fig. 5 shows the realistic scene in the hospital. The left one shows a patient who is using CGMS and the right one is the insulin pump and CGMS.

We use an embedded development board to store data and the algorithm. Our computer can give the values of blood glucose to the board and get the values of insulin from it. The chip is from Freescale which can perform excellent computing and storage power as described in Fig. 6. The USBDM port is designed to burn the program and the serial port is for communicating with the computer.

To make it more convenient to record data of blood glucose and insulin and make our system into reality, we have developed an app for blood glucose-insulin recording and display. Patients or doctors can use this app to input blood glucose values. This app can

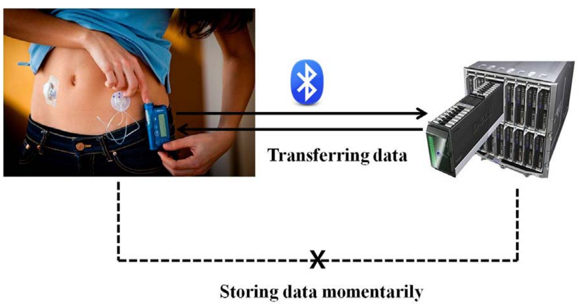


Fig. 4. Communication between insulin pump and BES.

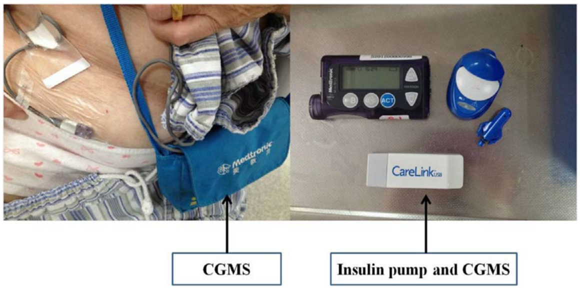


Fig. 5. Realistic operation of CGMS and insulin pump in the hospital.

present charts which can clearly show patients' health conditions. Meanwhile, to make this app have more close relations with this medical cyber-physical system in this paper, we are now developing new functions including real-time insulin computation and treatment plans.

There are 8 subfigures in Figs. 7 and 8, they stand for blood glucose curve for 8 patients, and each subfigure has three curves with different colors and shapes for different days. The x-coordinate represents time, every two points equal 30 minutes because we get the data every 30 minutes. The y-coordinate represents specific numerical value, we can read the value of blood glucose and insulin. Meanwhile, from each figure, we find that there are three peaks which represent the meal time during the whole day.

The normal values of blood glucose range from 4 mmol/L to 15 mmol/L. However, in Figs. 7 and 8, some of their values ranges from 4.0 mmol/L to 15.0 mmol/L which is beyond the normal standard. With the process of the algorithm, we can simulate the values of insulin according to their blood glucose value. Finally, we can compare the simulation insulin values with the actual insulin values and evaluate the performance of our algorithm Ahmed et al., 2008.

Our experiment includes four parts. The first one is to simulate the insulin values with the original algorithm which we have introduced in Section 3. And then, in the second part, we turn to the algorithm which has been optimized. These two parts can indicate the superiority of performance clearly. The third part and fourth part mainly focus on the robustness of this algorithm. To express the figures of simulation clearly, the meanings of some proper expressions are shown in Table 2.

On the first stage, we test the insulin values with DCLC algorithm. Now, we take patient 1 for example. We have got the statistics of blood glucose values for completely three days. According to the algorithm, the first-day statistic is necessary, and the values of the second and the third day is based on the iteration of first-day statistic. For each day, we have 48 data, which is sampled by 30 minutes during 24 hours. Now we use the first-day data and simulate insulin results on the second day and the third day. For patient 1, some variables like *m*, *n*, ect are different from other patients, and we have tried many times to get good results. The simulation results can be shown in Fig. 9a.

Fig. 9a shows insulin values change along with the changes of blood glucose values. It is based on DCLC algorithm and we can find some waves in the blue curve. We can see that the three peaks of the curve of blood glucose values stand for the meal time, because when a person have meals, his or her blood glucose will increase. Also, the curve of insulin values has three peaks which are correspond to the curve of blood glucose values. However, there are some problems. Because the simulation result is different from original values at some points and we want to decrease the rate of difference, we add some constraints conditions as mentioned above. We can get Fig. 9b by simulating EDCLC algorithm. Comparing Fig. 9a with Fig. 9b, we can validate the stability of EDCLC algorithm. Next, we increase the blood glucose values deliberately. For example, we have three days simulation results, and the blood glucose values on the fourth day are increased twice as that on the third day. As shown in Fig. 9c, insulin values on the fourth day are about twice as much as blood glucose values. In Fig. 9d, when we decrease the blood glucose values on the sixth day, we can find the insulin values also decreased. Fig. 9c and d indicate that the insulin curve can change along with the blood glucose curve obviously.

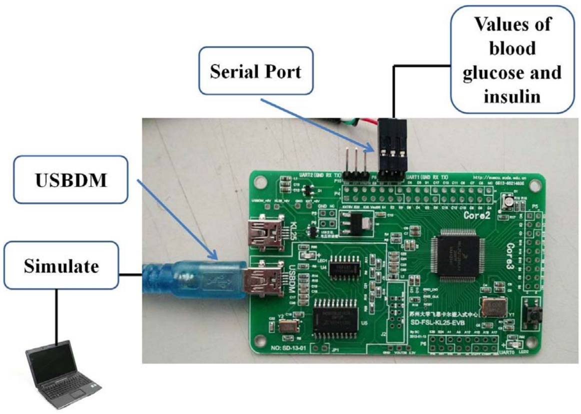


Fig. 6. Communication and storage tools.

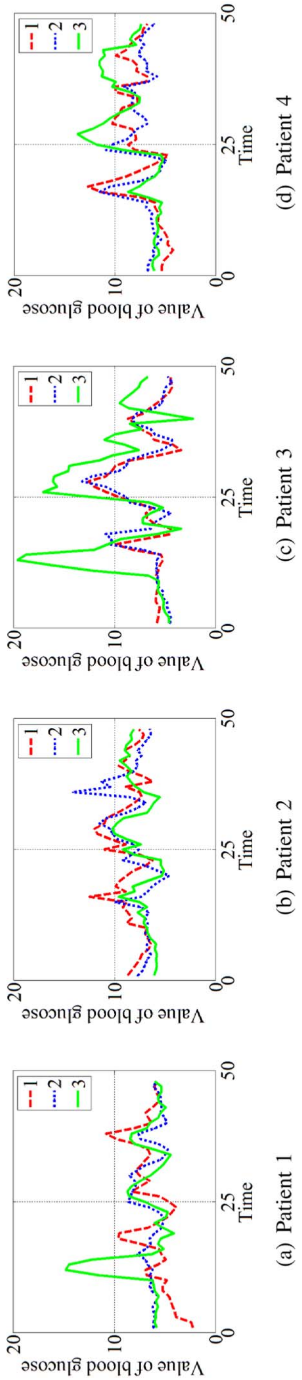
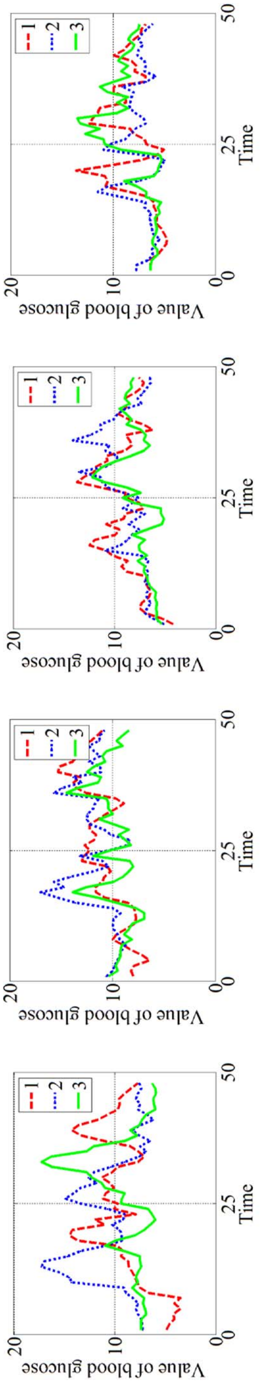


Fig. 7. Original blood glucose curve: patient 1-4.



(a) Patient 5 (b) Patient 6 (c) Patient 7 (d) Patient 8

Fig. 8. Original blood glucose curve: patient 5-8.

Table 2
Meanings for proper expressions.

Proper Expressions	Meanings
OIC#1	Original insulin curve on the 1st day
OIC#2	Original insulin curve on the 2nd day
SIC#2	Simulation insulin curve on the 2nd day
SIC#4	Simulation insulin curve on the 4th day
SIC#6	Simulation insulin curve on the 6th day
BGC#1	Blood glucose curve on the 1st day
BGC#2	Blood glucose curve on the 2nd day
BGC#4	Blood glucose curve on the 4th day
BGC#6	Blood glucose curve on the 6th day
OIV#1	Original insulin value on the 1st day
SIV#4	Simulation insulin value on the 4th day
SIV#6	Simulation insulin value on the 6th day

In Fig. 9c, as the values of blood glucose are doubled on the fourth day, the values of insulin are nearly doubled. To get a direct proof, we make a bar chart for the values of insulin on the first day and the fourth day as shown in Fig. 10a.

In Fig. 9d, the values of blood glucose on the sixth day are halved compared with that on the fourth day. Fig. 10b shows the specific value of insulin on the fourth day and the sixth day, and we can understand the relationship between blood glucose and insulin clearly. From these simulations, we can conclude that the enhanced dynamic closed-loop control algorithm has satisfying results.

At the end of section II, we proposed using LaGrange Interpolation to eliminate the effect of data error. We can do some experiments to show the consequence of data error and the processing result when we use LaGrange Interpolation. Fig. 11a shows the simulation result when a value is abnormal. The original blood glucose value is 5, but it is over 30 because external devices' problems. In the red rectangle, the blood glucose value is too high, and it generates a larger insulin value which can cause clinical problems to patients. To avoid the effect of data error, we use LaGrange Interpolation to set a new for value for this time point. According to the calculation result from Eqs. 5 and 6, the blood glucose value at this time point is reset to 4.4, and we can find it in the red circle in Fig. 11b. Thus, the insulin value is normal and there is no bad effect to patients.

Experiments above are focused on the algorithm, now we want to validate the accuracy of back end system, and we want to prove that it can optimize the algorithm when it is carried on different patients. In Fig. 12, there are two pictures which separately show different simulation results of different patients. Patient 1 and patient 2 have different blood glucose levels according to doctors in No.9 hospital. Obviously, patient 2 has a more wide range of blood glucose which means insulin can have more impact on patient than that on patient 1. According to the analysis from their original data, they are set up our control algorithm with different coefficients. Thus, we can clearly find their insulin curves are similar with original insulin curves.

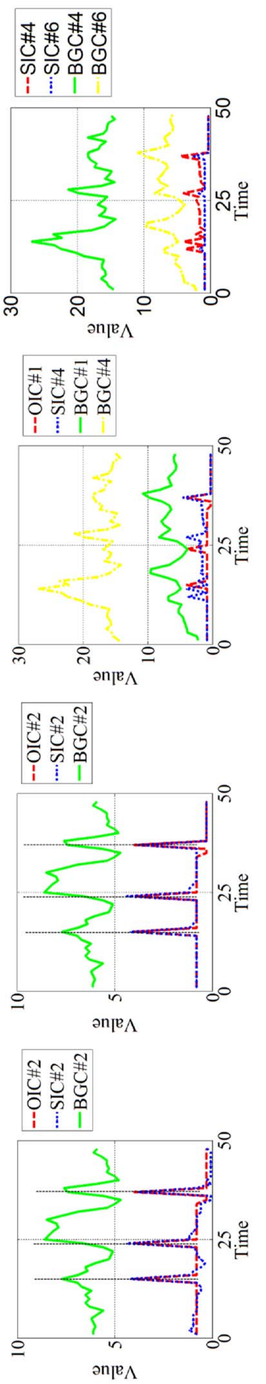
5. Discussions

To advance the study of blood glucose and insulin control system, researchers in different fields are sparing no effort to do experiments. As we have mentioned above, this system mainly consists of three parts, CGMS, insulin pump and closed-loop control algorithm.

Reducing correction times and improving measurement accuracy are two focusing points during these years, and it is a long term process and needs countless process adjustments. To improve measurement accuracy, some scientists propose a new method which is based on humor measurement. Scientists from University of Washington and Microsoft have done experiments to detect glucose concentration in human tear, and it shows good results. Some scientists study noninvasive CGMS to make it be adaptive to more patients and lessen pains. Professor Jin Tuo Yang et al., 2015 from school of pharmacy in Shanghai Jiao Tong University proposed a kind of micro needle which enables highly efficient transdermal delivery of insulin without depositing the needle tip materials to the skin. It is practically applicable to a variety of protein/peptide medicines requiring frequent dosing by offering painless administration, freedom of refrigeration, and minimal safety concerns.

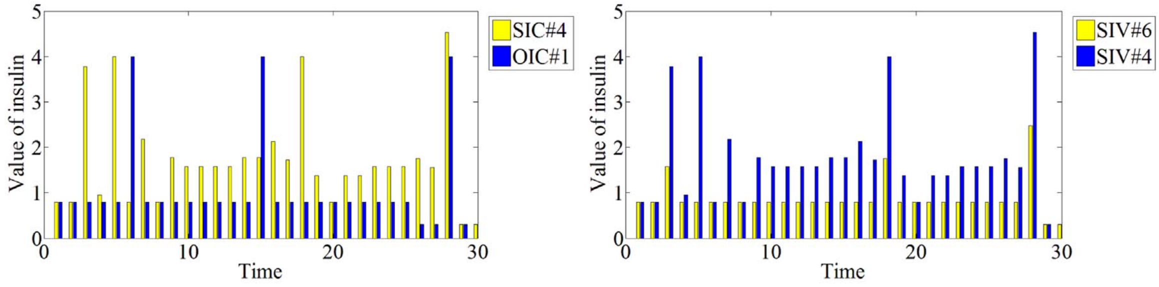
Decreasing response time after injecting insulin is a key point during the study of insulin pump. Researchers are trying different ways to control effectiveness when patients have meals. Daniel E. Vaughn and other researchers have authenticated that insulin being injected with recombinant human hyaluronidase can improve response speed Vaughn et al., 2009. Heating the infusion position Raz and Weiss, 2009 and infusion in the dermis Pettis et al., 2011 can also realize this effect. Most of insulin pumps are unidirectional which means that it can just control the injection of insulin. It can low the blood glucose, but sometimes if blood glucose is too low, we need glucagon to promote the decomposition of blood glucose to raise it. Therefore, some researchers are trying to make insulin pump bidirectional. Meanwhile, adding glucagon can improve security in blood glucose-insulin control. It is more acceptable than unidirectional insulin pumps. Mark Evans introduce next generation in insulin pump technology and put forward this bidirectional bionic pancreas Evans and Hovorka, 2014. The storage of insulin is another problem, it is difficult for patients to provide low temperature environment. There also researchers are searching for better store methods.

Also, there are lots of researches focusing on closed-loop control. Feedback control real-time scheduling Lu et al., 2002 presents a kind of framework for adaptive real-time systems. An advantage of this system is its use of feedback control theory as a scientific



(a) Results of the original algorithm (b) Results of the optimized algorithm (c) Results after the values in fourth day are increased (d) Results after the values in sixth day are decreased

Fig. 9. Results.



(a) Insulin values on the first day and the fourth day (b) Insulin values on the four day and the sixth day

Fig. 10. Values of insulin on the 1st day, the 4th day and the 6th day.

underpinning. The enhanced dynamic closed-loop control algorithm performs well during the simulation, because we have put forward some concepts to optimize and have integrated this algorithm into the medical system. Distributed Constraint Handling and Optimization Farinelli et al., 2013 shows the effects of constraint conditions. Despite traditional auto control algorithms, we can take other data processing algorithms into considerations, like data mining, deep learning and so on. We can combine some exercise information into these algorithms not only values of blood glucose and insulin. Likely, other kinds of patients' information can also be included.

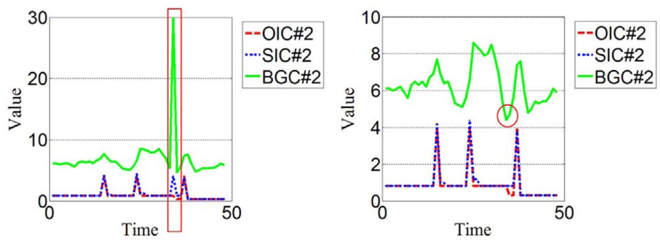
As this system is related to human beings and our daily life, clinical tests are necessary. Most clinical tests are operated in hospitals which can guarantee the safe of volunteers. When patients use this system, they may be in various kinds of places not only in hospitals. Therefore, some experiments are operated in their homes. Some countries have made some regulations to advance these clinical tests carried on in different places and guarantee people's security. As we know, blood glucose is not only related to diet, exercises, social activities and other important conditions cannot be ignored. The diabetes research in children network study group have conducted an experiment and they find that exercises with medium intensity have a higher probability to cause hypoglycemia The Diabetes Research in Children Network (DirecNet) Study Group, 2005. Meanwhile, researches from school of human movement and exercise science, University of Western Australia raise a point that a 10-s sprint performed immediately prior to moderate-intensity exercise prevents glycaemia from falling during early recovery from moderate-intensity exercise in individuals with type 1 diabetes Bussau et al., 2007.

6. Conclusion

Medical cyber-physical systems are becoming extremely prevalent in recent years, and lots of patients are going to use these products because of their convenience and practicability. This paper mainly introduces a kind of medical cyber-physical system for blood glucose-insulin control. It mainly includes CGMS, insulin pump and closed-loop control algorithm.

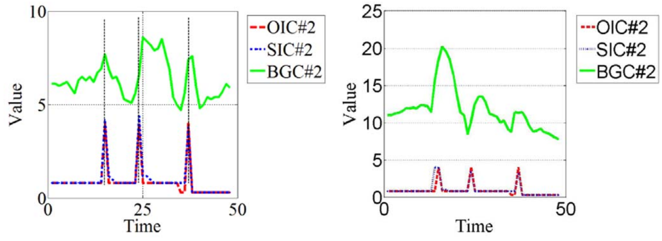
Although CGMS and insulin are mature in technology, there are many scientists spending much time improving their performance. The core of this system is the enhanced dynamic closed-loop control algorithm. It is based on predictive model control, and we add some constraint conditions to it. There is a high probability that CGMS will be out of work, and we should consider how to solve this kind of this problem. We decide to adopt LaGrange Interpolation to supplement the vacant or abnormal value and we have done experiments to validate its effectiveness. From the simulations and experiments we have done, we can conclude that this system is stable, fine-grained and robust, the values of insulin are also reasonable.

We also add another part which is called back end system which is intended to solve the problem of storage in insulin pump and to dynamically optimize the closed-loop control algorithm. CGMS, insulin pump and closed-loop control algorithm are three parts for users, while back end analysis is a backstage processing system. Patients use the same original algorithm when they use it for the first time. As the accumulations of data, the system will analyze a suitable algorithm with individual coefficients for each patient. Therefore, algorithms are supposed to be different to different patients.



(a) Results of occurring data error (b) Results of using LaGrange Interpolation

Fig. 11. Simulations about LaGrange Interpolation.



(a) Results of optimized algorithm: patient1 (b) Results of optimized algorithm: patient2

Fig. 12. Simulations results of different patients.

The road to fine-grained and flexible control of blood glucose-insulin is long. As a kind of medical cyber-phsical systems, blood glucose-insulin control has attracted great attentions in recent years. Likewise, there are also some other medical cyber-physical systems or devices which are beneficial but face similar challenges and problems. Besides some problems about their functions, security should also be taken into consideration. As technology develops, especially medical cyber-physical systems are increasingly related to human health, the demand of security will arise. In the future, we will leverage our previous experience to secure our system (Yi et al., 2016, 2014, 2013, 2012; Zhu et al., 2011; Xiao et al., 2014; Yi et al., 2010), manage the sensing data (Zhu et al., 2015; Zhang et al., 2012), and design more reliable network protocols (Ren et al., 2014; Jun et al., 2014; Yi et al., 2012; Guo et al., 2011; Gu et al., 2009) for health related applications.

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