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Design of Predictive Alarm System for Artificial Pancreas

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This paper designs a predictive alarm system for artificial pancreas, which judges whether the closed-loop control of artificial pancreas is in a safe state according to the information transmitted by CGM and insulin pump. It also grades threat degree of different indicators to human safety when various information changes (such as connection information of equipment, blood glucose history, and prediction data). According to the different levels, the system prompts the corresponding warning signal and takes measures to effectively avoid the risk of warning system. Based on the existing human blood glucose metabolism model and Sage-Husa adaptive model, an improved adaptive Kalman filter algorithm is designed to predict the blood glucose data of the model to obtain the blood glucose future blood glucose prediction value and improve the accuracy of multi-step blood glucose prediction firstly. And then simulate the prediction algorithm. Next, the prediction value is used as the information source of the prediction alarm system, and the prediction alarm system for artificial pancreas is established to increase the security control constraints, so as to effectively avoid risks. Finally, experiments are carried out on UVA/Pavoda T1DM hardware in the loop simulation platform to test and verify the effectiveness of the predictive alarm system.

Keywords: Artificial pancreas; Blood glucose prediction; Kalman filter prediction; Alarm system

1. Introduction

Diabetes is mainly caused by the absolute or relatively insufficient secretion of insulin or the disorder of metabolism of carbohydrate and protein caused by impaired insulin use. It is one of terrible diseases which leads to cardiovascular and cerebrovascular diseases, amputation, blindness, renal failure and even death. It is usually marked by hyperglycemia. According to the current statistics, diabetes has a huge impact on the whole society. It is one of the important health problems that human society must face and solve in the world today. As one of the effective ways to treat diabetes in contemporary society, artificial pancreas system has been widely concerned by scholars from all over the world.

However, there are also some time delays in the transmission of simulated pancreatic function which affect the effectiveness of artificial pancreas, including the delay between the CGM (continuous glucose monitoring sensor) and the real blood glucose value, the delay in data processing and signal transmission, and the delay caused by the different basal insulin metabolic rate after insulin input into the human body etc. This requires that in the process of research and development of artificial pancreas, not only the accurate blood glucose data should be used, but also the existing historical data and insulin input level should be used to make up for the lag cycle compensation caused by time lag [1].

Therefore, to complete the design of artificial pancreas prediction alarm system, the first step is to complete the prediction of blood glucose. At present, the research of blood glucose prediction algorithm mainly includes the following three directions [2]: The most commonly used physiological models of insulin action and glucose kinetic system, which needs to identify and set the corresponding physiological parameters, include Dalla man model [3], Hovorka model [4], and Bergman model [5]. The data model is completely based on CGM data and other monitoring data to simulate the physiological response of patients without involving physiological variables, including time series model, genetic algorithm model, grammar evolution model, fuzzy logic model, rule-based model, Gaussian mixture model, regular learning, reinforcement learning, Kalman filter, vector model and artificial neural network model. And the hybrid model of the two. The hybrid model blood glucose prediction method mainly includes the mixed model blood glucose prediction method studied by Cescon [6] and others. Balakrishnan [7] mainly uses Berger's insulin kinetic model and Hovorka's dietary absorption model, and then added neural network method for blood glucose prediction to mix, so that the prediction model has a certain learning ability.

The method of blood glucose prediction studied in this paper innovatively introduces the adaptive Kalman algorithm, which organically combines the system identification and signal filtering prediction, into the field of blood glucose prediction.

In this paper, a blood glucose data filtering and prediction method based on adaptive Kalman filter to provide a more accurate information for the artificial pancreas prediction alarm system will be studied and designed firstly. It is theoretically feasible and innovative to apply this method to the field of blood glucose data filtering and prediction. Then, according to the designed blood glucose data filtering and prediction method based on adaptive Kalman filter, the establishment and improvement of artificial pancreas prediction and alarm system are completed. Through theoretical derivation, software implementation, in loop verification and other methods, the design of predictive alarm system for artificial pancreas is completed.

Blood glucose prediction is the core function of predictive alarm system for artificial pancreas. As a medical device directly connected with the human body and directly controlling the internal environment of the human body, any slight error may bring fatal danger to patients. The establishment of predictive alarm system for artificial pancreas is not only a necessary condition for the practical application of artificial pancreas, but also a necessary condition for it to enter the market.

2. Method

In this section, Kalman filter algorithm is selected as the main body of prediction algorithm, and the adaptive Kalman filter algorithm which is developed and improved on the basis of Kalman filter algorithm is further studied. Firstly, the model of human blood glucose metabolism process is established. Then, based on the theoretical research of adaptive Kalman filter algorithm, the blood glucose filtering method and prediction method based on adaptive Kalman filter algorithm are studied and designed. The results of filtering algorithm and prediction algorithm are verified by experimental simulation, and the corresponding performance indexes are established to evaluate the filtering and prediction results. In order to complete the establishment and implementation of blood glucose filtering and prediction algorithm.

2.1. Theoretical Research

The mathematical model of Kalman filter algorithm is as follows:

$$X_k = FX_{k-1} + GU_{k-1} + \Gamma_{k-1}W_{k-1}, \ldots\ldots(1)$$

$$Z_k = HX_k + V_k, \ldots\ldots\ldots\ldots\ldots\ldots(2)$$

where, the state variables X_k of the system at k time; X_{k-1} represents the state variables of the system at k-1 time; The control variables U_{k-1} representing the control function k-1 time of the system; W_{k-1} represents the process dynamic noise at k-1 of the system; Γ_{k-1} is the process noise figure matrix; Z_k represents the observation variable of the system at k time; V_k represents the process observation noise of the system at k time; F represents the state transition variables of the system from k-1 time to K time; G represents the control matrix of the system, which is the gain of the optional control input $U \in R^l$; H is the transformation relationship between the state vector and the observation vector.

Equation (1) is the state equation. It represents the relationship among the state variables X_k at k time, the control variables U_{k-1} at k-1 time and the state variables X_{k-1} at k-1 time. Eq. (2) is the observation equation.

Generally, the statistical characteristics of dynamic systems are stationary random processes. Therefore, it can be assumed that the dynamic noise and the observation noise are uncorrelated Gaussian white noise sequences:

$$\mathrm{E}(W_k) = 0, \quad \mathrm{E}(V_k) = 0, \ldots\ldots\ldots(3)$$

$$\begin{cases} p(w) \sim N(0,Q) \\ p(v) \sim N(0,R) \end{cases}, \ldots\ldots\ldots\ldots(4)$$

According to the least square principle, we can get the recursive calculation formula of Kalman filter, which is mainly as follows:

$$\hat{X}_{k/k-1} = F_{k/k-1}\hat{X}_{k-1}, \ldots\ldots\ldots\ldots\ldots(5)$$

$$\hat{X}_k = \hat{X}_{k/k-1} + K_k(Z_k - H_k\hat{X}_{k/k-1}), \ldots(6)$$

$$K_k = P_{k/k-1}H_k^{\mathrm{T}}(H_kP_{k/k-1}H_k^{\mathrm{T}} + R_k)^{-1}, \ldots(7)$$

$$P_k = (I - K_kH_k)P_{k/k-1}, \ldots\ldots\ldots\ldots(8)$$

$$P_{k/k-1} = \Phi_{k/k-1}P_{k-1}\Phi_{k/k-1}^{\mathrm{T}} + \Gamma_{k-1}Q_{k-1}\Gamma_{k-1}^{\mathrm{T}}, \ldots\ldots\ldots\ldots\ldots\ldots(9)$$

where, K_k is the filter gain matrix, R_k is the matrix observation noise variance matrix. Q_{k-1} is the process dynamic variance matrix.

Based on the standard Kalman filter algorithm, the mean and covariance of the process noise and measurement noise are estimated in real time to adjust the filter gain in real time. This is the core idea of adaptive Kalman filter.

This section mainly uses Sage-Husa adaptive Kalman filter algorithm to improve the calculation accuracy [8]. The adaptive filtering algorithm proposed by A. P. Sage and G. W. Husa introduces the idea of self-adaptive into the calculation process of filtering algorithm. It uses fading factor to adjust the noise parameters of the system in real time by sensing the output value, so as to adjust the degree of on-line state estimation in real time.

The statistical characteristics of the noise sequence are:

$$\begin{cases} \mathrm{E}[W(k)] = q(k) \\ \mathrm{E}[V(k)] = r(k) \\ \mathrm{E}[W(k)W^{\mathrm{T}}(j)] = Q_k\delta_{kj}, \\ \mathrm{E}[V(k)V^{\mathrm{T}}(j)] = R_k\delta_{kj} \\ \mathrm{E}[W(k)V^{\mathrm{T}}(j)] = 0 \end{cases} \quad \ldots\ldots\ldots(10)$$

The noise update equation with fading factor d_k is:

$$\hat{R}(k) = (1-d_k)R(k-1) + d_k \begin{Bmatrix} [I - H(k)w(k-1)] \\ \varepsilon(k)\varepsilon^{\mathrm{T}}(k)[I - H(k)w(k-1)]^T + H(k)P(k/k)H^{\mathrm{T}}(k) \end{Bmatrix}, \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots..(11)$$

The fading factor measured in the laboratory is generally 0.94 ~ 0.99, which depends on different situation.

2.2. Prediction Algorithm Design

The human blood glucose insulin system is usually considered as a discrete, linear time invariant model [9-10]. Its transfer function is:

$$\frac{y(z^{-1})}{u(z^{-1})} = \frac{1800Fc}{u_{TDI}} * \frac{z^{-3}}{(1-p_1z^{-1})(1-p_2z^{-1})^2}, \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots..(12)$$

where, p_1=0.980, p_2=0.965, c=-60$(1-p_1)(1-p_2)^2$, F=1.5.

The state space model are as follows:

$$x_{i+1} = Ax_i + Bu_i, \ \ldots\ldots\ldots..\ldots(13)$$

$$y_i = Cx_i\ , \ldots\ldots\ldots\ldots\ldots\ldots\ldots(14)$$

where, $A = \begin{bmatrix} p_1+2p_2 & -2p_1p_2 & p_1{p_2}^2 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \end{bmatrix} \in R^{3*3}$,

$B = \frac{1800Fc}{u_{TDI}}[1 \quad 0 \quad 0]^T$, and $C = [0 \quad 0 \quad 1]$.

Then, the establishment of blood glucose prediction algorithm and the realization process of simulation will be described.

According to the basic principle of the adaptive Kalman filter method described in Section 2.1, the blood glucose prediction method is established by using the mathematical model of human blood glucose metabolism process. The idea of blood glucose prediction method is based on the adaptive Kalman filter algorithm (as shown in Fig.1.).

Firstly, the three-dimensional blood glucose data model is used to set the state variable X :

$$X(k) = [x_{k-1}\ x_k\ x_{k+1}] \quad \ldots\ldots..\ldots(15)$$

where, x_k represents the blood glucose value at this moment, x_{k-1} represents the blood glucose value at the previous moment, and x_{k+1} represents the predicted blood glucose value at the next moment. The state space model of blood glucose metabolism established in Section 3.1, which is used to determine the size of A, B and C matrices.

After the mathematical model of the system is determined, the initial value is set for the system according to the adaptive Kalman filter algorithm. And then the next time state estimation and the next state error estimation are carried out according to the formula. Next Kalman gain and the optimal estimation value are calculated, and calculates the prediction error of the current system. A fading factor is introduced to update the covariance matrix of measurement noise and process noise. Then, the system state after prediction is used for model iteration. According to Turksey [11], when the model is iterated for 6 times, the prediction alarm effect is the best, so choose the model iterating for 6 times. After that, the next step is prediction and estimation to complete the real-time prediction process of the whole process.

And then, in order to reduce the larger tail error than the last model iteration, the fading factor d_m is also used to adjust the predicted value in real time when the model iteration is approaching the last iteration, so as to achieve the effect of reducing the error.

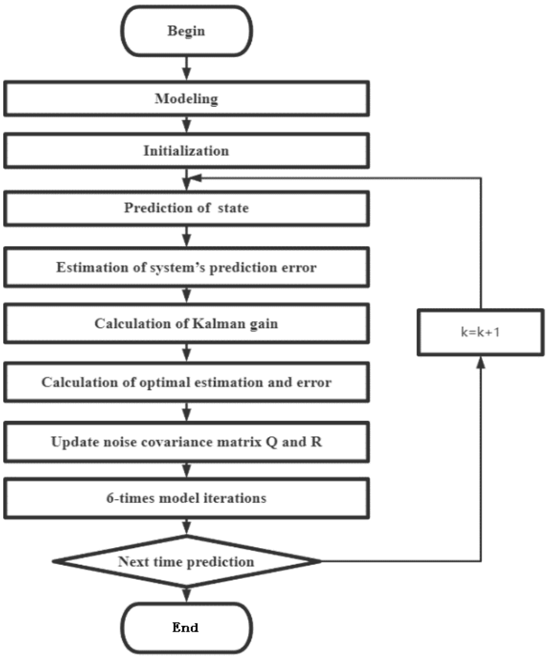

Fig. 1. Flow chart of blood glucose prediction method

2.3. Simulation and Evaluation

The UVA/Pavoda T1DM blood glucose simulator was selected to simulate the data of diabetic patients with a serial number of 001. The simulation time was simulated for 12 hours, and 25g glucose was taken in 0.5 hours. The noise figure was set to 1, and the 6-step prediction was carried out.

The 6-step prediction of blood glucose data refers to the process of multi-step prediction, in which the parameters calculated by the adaptive Kalman algorithm are substituted into the model for 6 iterations to further calculate the predicted values of blood glucose data in the next 6 moments while CGM reads one data at a time. That is to say, the actual value of one blood glucose data and the predicted value of six blood glucose data are displayed at each time.

The experimental simulation diagrams of three blood glucose prediction methods which is using Kalman filter algorithm, using adaptive Kalman filter algorithm and improved prediction method by using fading factor to reduce error are shown in Fig.2., Fig. 3. and Fig.4. respectively.

In order to better evaluate the prediction effect of the designed blood glucose prediction algorithm, the mean absolute error (MAE) and mean square error (MSE) are introduced to complete the error analysis by calculating the predicted data

$$MAE = \frac{\sum|y-\hat{y}|}{n}, \qquad (16)$$

$$MSE = \sqrt{\frac{\sum(y-\hat{y})^2}{n}}, \qquad (17)$$

Select the other UVA/Pavoda T1DM blood glucose simulator in the other numbered diabetes simulation data, calculate its value, the calculation results are shown in Table.1.

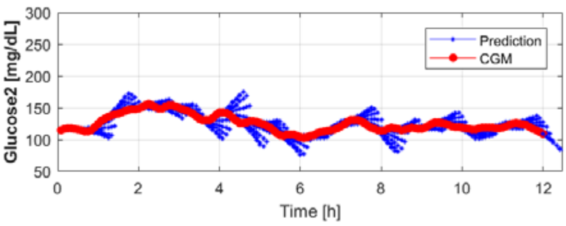

Fig. 2. Result with Kalman filter algorithm

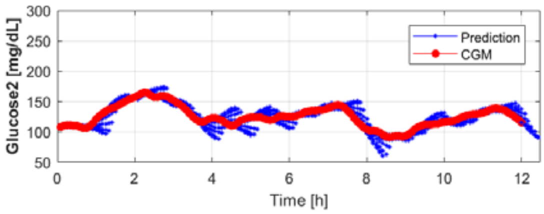

Fig. 3. Result with Adaptive Kalman filter algorithm

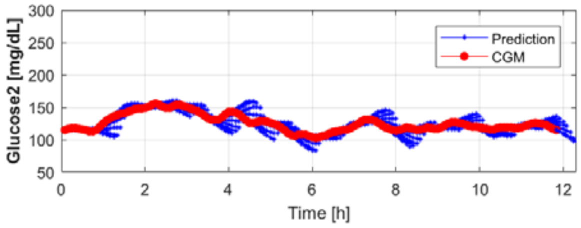

Fig. 4. Result with Improved Adaptive Kalman filter

Table. 1 Comparison of the results of three prediction methods.

Patient	Kalman Filter		Adaptive Kalman Filter		Improved Adaptive Kalman filter	
	MAE	*MSE*	*MAE*	*MSE*	*MAE*	*MSE*
001	7.0	10.5	6.2	9.0	6.0	8.6
002	6.8	10.0	6.0	9.0	5.8	8.4
003	7.4	10.3	6.4	8.9	5.9	8.4

According to Table.1, it is easy to see that the prediction result of adaptive Kalman filter is better than that of Kalman filter under the two indexes of average error and mean square error, and the adaptive method improves the accuracy of Kalman filter prediction to a certain extent; The prediction result of the improved adaptive Kalman filter is better than that of the original one. It can be seen that adding fading factor method in the process of model iteration can improve the accuracy of adaptive Kalman filter prediction to a certain extent.

3. Predictive Alarm System

The predictive alarm system for artificial pancreas mainly refers to the system which judges whether the closed-loop control of artificial pancreas is in a safe state according to the information transmitted by CGM and insulin pump, and grades the degree of deviation warning and the threat degree of different indicators to human safety when various information changes (such as connection information of equipment, blood glucose history and prediction data), to determine the level of different risks. According to the different levels, the system prompts the corresponding warning signal and takes measures to effectively avoid the risk of alarm system.

3.1. Framework Design

According to the requirements of predictive alarm system for artificial pancreas, it is designed as follows (as shown in the Fig.5 below): Hardware alarm system, hypoglycemia alarm system, hyperglycemia alarm system and insulin information alarm system. Among them, hypoglycemia alarm system is the core functions of the predictive alarm system. The following risk levels are classified according to the emergency degree of different alarm situations:

- High risk information: danger may occur in a short time (5 minutes), which is a first-class early warning situation. The software will send a prompt message and vibrate, and automatically exit the closed-loop control, stop the use of insulin pump. It is necessary to check the relevant equipment and indicators immediately.

- Medium risk information: danger may occur in a period of time (30 minutes) in the future, which is a level II early warning situation. The software sends inquiry information and vibrates. The user can judge whether to close the software and exit the closed-loop control by checking the equipment and relevant indicators.

- Low risk information: it is a three-level early warning situation. If the internal data of the software is abnormal, it can be adjusted and constrained by software algorithm design.

Red means high risk event, orange means medium risk event, and green means low risk event in Fig.5.

According to the blood glucose prediction method, the flow chart of hypoglycemia alarm system is designed, as shown in Fig.6.

Firstly, the hypoglycemia alarm system first judges whether the data reception is normal (i.e. Bluetooth connection interruption problem, etc.), and under the normal condition of data reception, the true value of

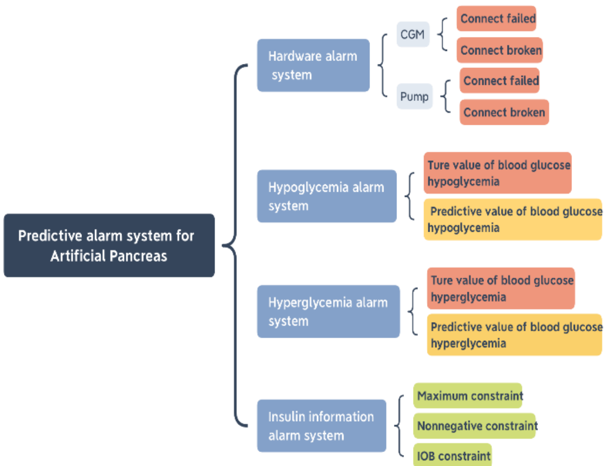

Fig. 5. Framework of Predictive alarm system

blood sugar data is obtained. When the true value of blood glucose data is lower than 70mg/dl (there is a certain amount left relative to the threshold value of hypoglycemia), it indicates that hypoglycemia has occurred, and it is already extremely dangerous, the alarm system responds immediately. The closed-loop control system should be shut down immediately, and the blood glucose value shall be adjusted manually to avoid falling into danger. This is the last line of defense for hypoglycemia alarm system, but also the most important one.

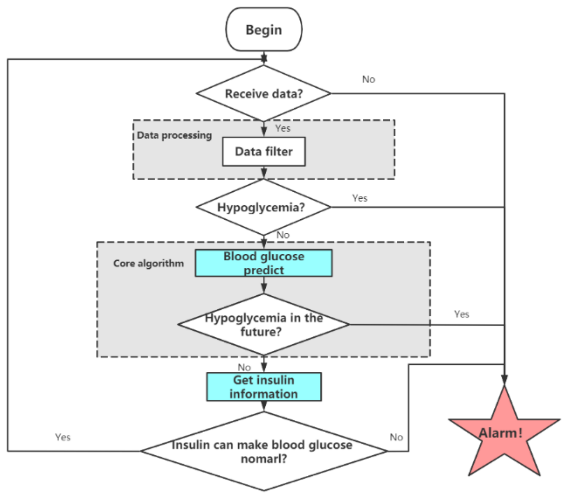

Fig. 6. Framework of Predictive alarm system

The main purpose of the predictive alarm system for artificial pancreas is to prevent hypoglycemia events. Therefore, the core algorithm is to use the adaptive Kalman filter algorithm established in Chapter 2 to predict blood glucose data, and set up a safety threshold for blood glucose prediction value. When the blood glucose prediction data reaches the early warning value, the key algorithm is to use the prediction algorithm based on Adaptive Kalman filter algorithm established in Chapter 2, It means that there may be dangerous situation in the future, and then warning information shall be sent to start the alarm response; Even if the predicted value of blood glucose data is within the normal range, the insulin history information IOB quantity (IOB is the insulin quantity which still has hypoglycemic effect in the patient) needs to be further considered. If the dose of IOB is injected, whether it may cause the risk of hypoglycemia after the injection of the dose IOB is completed, the alarm response will be activated.

The formula for calculating whether the risk of hypoglycemia caused by low blood glucose after the whole injection of IOB is as follows:

$$Value_P = CGM_P - u_{BASAL} * u_{IOB} * \Delta t \;....(18)$$

$Value_P$ refers to the predicted value of blood glucose after considering the historical information of insulin, CGM_P is the predicted value of blood glucose based on the Adaptive Kalman Filter algorithm, u_{BASAL} is the basal metabolic rate of insulin, u_{IOB} is the amount of insulin remaining in the patient's body at this time, Δt is time difference between the predicted time and the present time. When $Value_P <$ 70mg / dL, it is considered that hypoglycemia may occur in the future, that is, an alarm response should occur.

After completing the above detection, the next data can be read and judged, so as to realize real-time monitoring.

3.2. Simulation and Evaluation

The performance index of the effectiveness of the artificial pancreas predictive alarm system is established. The sensitivity of the predictive alarm system [11] S is defined as the ratio of correctly predicting the number of alarm events to all the alarm events required. The calculation formula is as follows:

$$S = \frac{\text{Number of correct alarm events}}{\text{Number of alarm events required}} ,.....(19)$$

The error rate FAR is defined as the ratio of the number of incorrect predicted alarm events to the number of all required alarm events:

$$FAR = \frac{\text{Number of incorrect alarm events}}{\text{Number of alarm events required}} ,...(20)$$

The following is the effectiveness test: The hardware in the loop simulation is carried out by using the artificial pancreas system simulation platform based on mobile devices [10]. The simulation platform is mainly composed of artificial pancreas controller app, UVA / Padova T1DM blood glucose metabolism simulation platform accepted by FDA, a HC-05 Bluetooth module simulating CGM data transmission and a HC-05 Bluetooth module simulating insulin pump. The computer side of the simulation platform uses the T1DM blood glucose metabolism simulation platform to simulate the process of human blood glucose metabolism. Two Bluetooth (simulating the data transmission of CGM and insulin pump) are used for wireless connection to transmit information to each other. According to the received data, the app of the artificial pancreas controller on the mobile terminal uses the internal control algorithm to complete the calculation of the required insulin injection volume and control the injection of the simulated insulin pump, So as to achieve the effect of closed-loop control of human blood glucose level.

The effectiveness of the system is tested by man-made dangerous situation. The statistical results are as Table.2. The average sensitivity and error rate of the system are 91.33% and 13.33%, respectively. The system can effectively detect and predict risks, and has certain application value.

However, it should be noted that the dangerous situations in the hardware in the loop simulation process are man-made, predictable, with certain rules to follow, and have certain particularity. Therefore, the simulation experiment results have certain reference value. For the effectiveness test of the system, further experiments in real environment are needed.

Table. 2 Evaluation of predictive alarm system for artificial pancreas.

Alarm System	S	FAR
Hypoglycemia	91.55%	18.00%
Hyperglycemia	82.45%	22.05%
Hardware	100%	100%
Insulin information	/	/
Total	91.33%	13.33%

Note: the insulin information early warning system is the internal constraint of the controller, excluding the performance index.

4. Conclusion

In this paper, the design of predictive alarm system for artificial pancreas mainly based on the established state space model of human blood glucose metabolism process, then using Kalman filter algorithm and adaptive Kalman filter algorithm to predict blood glucose data, and using Sage-Husa adaptive model to get the predicted value of blood glucose. And then through the experimental simulation which uses the UVA/Pavoda T1DM blood glucose simulation platform accepted by FDA, the error of different prediction algorithms is tested, so as to evaluate the prediction effect. According to the experimental results, the mean absolute error of adaptive Kalman filter is about 8.5, and the relative error is less than 8%. The performance is better than Kalman filter; In the process of model iteration, the improved method is adding a fading factor appropriately to reduce the prediction error of a certain extent, which optimizes the blood glucose prediction algorithm.

Then, based on the prediction results of adaptive Kalman filter algorithm and insulin history information, an appropriate predictive alarm system for artificial pancreas is established, which adds early warning function module and safety control constraints for artificial pancreas app, so as to effectively avoid risks. The predictive alarm system for artificial pancreas is mainly divided into four subsystems: hypoglycemia alarm system, hyperglycemia alarm system, hardware alarm system and insulin information alarm system. Finally, the effectiveness of the predictive alarm system is verified by the UVA / Pavoda T1DM hardware in the loop simulation platform accepted by FDA. According to simulation results, the average sensitivity of the predictive alarm system designed in this paper is 91.33%, and the error rate is 13.33%. It can effectively detect and predict risks, and has practical value.

Acknowledgements

References:

[1] Wang W. Research status and progress of artificial pancreas [J]. Chinese Journal of Pancreatology, 2018, 18(05):359-361.

[2] Silvia O. A Review of Personalized Blood Glucose Prediction Strategies for T1DM Patients[J]. International Journal for Numerical Methods in Biomedical Engineering, 2017, 33(6): 2833-2854.

[3] Chiara D. M., Robert A. R. Meal Simulation Model of The Glucose - insulin System[J]. IEEE Transactions on Biomedical Engineering, 2007, 54(10):1740–1749.

[4] Hovorka R., Canonico V., Chassin Ludovic J., et al. Nonlinear Model Predictive Control of Glucose Concentration in Subjects with Type 1 Diabetes[J]. Physiological Measurement, 2004, 25(4): 905–920.

[5] Bergman RN, Y Z Ider, Bowden C. R., Cobelli C. Quantitative Estimation of Insulin Sensitivity[J]. American Journal of Physiological, 1979, 236(6): 667–677.

[6] Marzia C., Rolf J., Eric R. Subspace-based Linear multi-step Predictors in Type 1 Diabetes Mellitus[J]. Biomedical Signal Processing and Control, 2015, 22:99–110.

[7] Naviyn P. B., Lakshminarayanan S., Rangaiah G.P. Personalized Hybrid Models for Exercise, Meal, and Insulin Interventions in Type 1 Diabetic Children and Adolescents[J]. Industrial and Engineering Chemistry Research, 2013, 52 (36):13020–13033.

[8] Gao X. Seam Tracking Monitoring Based on Adaptive Kalman Filter Embedded Elman Neural Network During High-Power Fiber Laser Welding[J]. IEEE Transactions on Industrial Electronics, 2012, 59(11):4315-4325.

[9] Klaske van H., Dassau E., Zisser H. C., et al. Control-relevant Models for Glucose Control Using a Priori Patient Characteristics[J]. IEEE Transactions on Bio-medical Engineering, 2012, 59(7):1839-1849.

[10] Cai D., Liu W., Dassau E., et al. An Adaptive Disturbance Rejection Controller for Artificial Pancreas[C]. 21th IFAC World Congress. 2020, 53(2): 16372-16379.

[11] Turksoy K., Elif S. B., Lauretta Q., et al. Hypoglycemia Early Alarm Systems Based on Multivariable Models[J]. Industrial and Engineering Chemistry Research, 2013, 52(35): 12329–12336.