In Silico Testing of a Closed-Loop Artificial Pancreas Based on Generalized Predictive Control

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Abstract. The artificial pancreas (AP) system is a promising approach to maintain blood glucose concentration (BGC) of patients with type 1 diabetes (T1D) in a euglycemic range (70–180 mg/dl). A controller based on generalized predictive control (GPC) with an adaptive reference glucose trajectory and an adaptive softening factor (GPC+AA) was proposed for AP system in our previous research. It was built and tested with the University of Virginia/Padova type 1 diabetes mellitus simulator (T1DMS), which embodies the biophysiological parameters of in-silico population accepted by the US Food and Drug Administration. It was showed that the GPC+AA controller realized effective control of the BGC of in-silico patients with T1D. Here, the effectiveness of the GPC+AA controller was further tested with strict conditions, including a pump with noise and error, a continuous glucose monitoring sensor and a high carbohydrate intake. Test results showed that the BGC of adolescent group was not effectively controlled with the GPC+AA controller. Then, the adaptive softening factor strategy was further optimized and a GPC controller with an adaptive reference glucose trajectory and an optimized adaptive softening factor (GPC+AO) was proposed here. It was demonstrated that the optimized adaptive softening factor strategy significantly improved the performance of the GPC controller, and the average BGC percentage within the euglycemic range of 9 adults and 10 adolescents increased to 80% and 70%, respectively. Thus, our GPC+AO controller is effective for patients with T1D and can be potentially applied in the AP systems.

1. Introduction

Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by insulin deficiency and resultant hyperglycaemia. The artificial pancreas (AP) system, also known as the closed-loop control system, is a promising approach to maintain blood glucose concentration (BGC) of patients with T1D in a euglycemic range (70–180 mg/dl) [1, 2]. The AP system consists of three devices, including a continuous glucose monitoring (CGM), an intelligent controller and an insulin–infusion pump (Figure 1). The control algorithm adopted in the intelligent controller plays a key role because it determines the optimum amount of insulin to be infused through a series of mathematical calculations. At present, several control algorithms have been applied to AP systems, including proportional-integral-derivative (PID) control, model-based and model predictive control (MPC) and adaptive control et.al.

Generalized predictive control (GPC) has been widely applied to the AP systems [3-5]. It is fairly robust and can be easily implemented because it is based on the data-based model and does not require a precise glucose–insulin dynamics model. We have developed a GPC controller with two strategies, namely, an adaptive reference glucose trajectory and an adaptive softening factor (GPC+AA). It was
tested by using the UVA/Padova type 1 diabetes mellitus simulator (T1DMS) approved by the US Food and Drug Administration. It was showed that the GPC+AA controller realized effective control of the BGC of in-silico patients with T1D [6].

![Figure 1. Sketch map of an artificial pancreatic system](image)

Here, the GPC+AA controller was further tested with strict conditions, including a pump with noise and error, a CGM sensor, and a high carbohydrate (CHO) intake. Results showed that the average BGC percentage within the euglycemic range was not satisfactory, especially for the adolescent patients. Then, the adaptive softening factor strategy was optimized with the introduction of BGC deviation. And a GPC controller with an adaptive reference glucose trajectory and an optimized adaptive softening factor (GPC+AO) was proposed here. Test results with the UVA/Padova T1DMS demonstrated that the optimized adaptive softening factor strategy further improved the performance of the GPC controller, and the average BGC percentage within the euglycemic range of 9 adults and 10 adolescents increased to 80% and 70%, respectively. Thus, the optimized adaptive softening factor increases the effectiveness of the GPC controller and the GPC+AO controller can be potentially applied in the AP systems.

2. Materials and methods

2.1. GPC+AA controller

A GPC controller with two adaptive strategies (GPC+AA), namely, an adaptive reference glucose trajectory and an adaptive softening factor is applied for blood glucose regulation [6]. It was proposed in our previous research and had a good performance. Insulin injection rate is computed by minimizing $J$ in the following function.

$$ J = \sum_{j=1}^{n} [y(k+j) - w(k+j)]^2 + \sum_{j=1}^{m} \lambda(j)[\Delta u(k+j-1)]^2 $$

where $y(k+j)$ represents the $j$ -step-ahead prediction of the process output, $\Delta u(k+j-1)$ donates the incremental control input at the $k$th sampling step, $n$, denoting the output prediction horizon is set as 8, $m$ denotes the control horizon, is set as 4. $\lambda(j)$, denoting the weighting parameter toward deviation of the control input, is set as 3. $y(k)$ denotes the current process output, and $y_r$ denotes the reference glucose trajectory. $\alpha$ denotes the weight of $y(k)$, also known as softening factor.

The $j$-step-ahead prediction prediction $y(k+j)$ is estimated using an autoregressive integrated moving-average model with exogenous inputs (function 2) and the Diophantine equation (function 3), where $y(k)$ denotes the BGC at $k$th sampling step, $u(k)$ is the control input variable (insulin infusion rate), $\xi(k)$ denotes the zero-mean white noise and $\Delta = (1 - z^{-1})$ denotes the integration. The
minimization of function (1) gives the optimal control action (insulin infusion rate) and its solution process is introduced in our previous research in detail.

\[ A(z^{-1})y(k) = B(z^{-1})u(k - 1) + C(z^{-1})f(k)/\Delta \]

\[ A(z^{-1}) = 1 + a_1 z^{-1} + \cdots + a_{na} z^{-na} \]

\[ B(z^{-1}) = b_0 + b_1 z^{-1} + \cdots + b_{nb} z^{-nb} \]

\[ C(z^{-1}) = 1 + c_1 z^{-1} + \cdots + c_{nc} z^{-nc} \]

\[ 1 = E_j(z^{-1})A(z^{-1})\Delta + z^{-1}F_j(z^{-1}) \]

\[ E_j(z^{-1}) = e_{j0} + e_{j1} z^{-1} + \cdots + e_{nj-1} z^{-j+1} \]

\[ F_j(z^{-1}) = f_{j0} + f_{j1} z^{-1} + \cdots + f_{jn} z^{-n} \]

An adaptive reference glucose trajectory was designed for GPC controller, instead of a desired glucose value or a time-varying trajectory. It avoids the sudden decrease of BGCs and increases the effectiveness of the GPC controller for patient subjects. The slopes of the trajectory were adjusted in real time in accordance with the increasing (or decreasing) BGC rates measured in the past steps (Figure 2).

![An adaptive reference glucose trajectory](image)

**Figure 2.** An adaptive reference glucose trajectory

The softening factor \(\alpha\) of the GPC system can vary from 0 to 1 and significantly affects the integral time and output of the GPC system. When \(\alpha\) is set to 0, the GPC system will likely have low robustness and high tracking speed; when \(\alpha\) is set to 1, it will have high robustness and slow tracking speed. An adaptive softening factor strategy was proposed to ensure the balance between track speed and system robustness, that is,

\[ \alpha = m^{-|y_k - y_{k-1}|} \]

where \(m=1.1, y(k)\) and \(y(k - 1)\) denote the BGCs measured in the past two steps.

### 2.2. GPC+AO controller

\(\alpha\) in function (4) is only determined with the increasing (or decreasing) BGC rates, neglecting the real BGCs of patients. The tracking speed of the controller was not fast enough when patients have high BGC. Thus, the adaptive softening factor strategy was further optimized here. The deviation of BGC is introduced and \(\alpha\) is redefined as follows:

\[ \alpha = m^{-|y_k - y_{k-1}|} \]

\[ m = 1 + \frac{|y_k - \bar{y}|}{\bar{y}} \]

Where \(\bar{y} = 130\) mg/dl. \(\alpha\) will decrease more violently to ensure an increased reference tracking speed for the control system when the BGC is high above the desired value \(\bar{y}\). A GPC controller with an adaptive reference glucose trajectory and an optimized adaptive softening factor (GPC+AO) is proposed here and tested the UVA/Padova T1DMS.
2.3. Software and parameter settings
The AP system with GPC controllers was built and tested with the UVA/Padova T1DMS version 3.2.1, which embodies the biophysiological parameters of the FDA-accepted in silico populations, including 10 adults and 10 adolescents [7-9]. Adult 09 was excluded because the endogenous glucose production of this patient was suppressed even 6 hours after meals, leading to hypoglycemia [10].

A pump with noise and error, and a CGM sensor were used. The same scenario used by Kamuran Turksoy et al. was demonstrated in this study [11]. All patients from the simulator were simulated over three days (72 hours). Twelve unannounced meals were provided and lasted for 15 min each. The multiple meals provided during the testing period were as follows: 48 g of CHO at the 9th hour, 47 g at the 13th hour, 75 g at the 18th hour, 31 g at the 22nd hour, 55 g at the 33rd hour, 70 g at the 37th hour, 65 g at the 42nd hour, 20 g at the 46th hour, 40 g at the 57th hour, 68 g at the 61st hour, 75 g at the 66th hour, and 25 g at the 70th hour.

3. Results and discussion
3.1. Tests of the GPC+AA controller
First, the GPC+AA controller were tested with 9 adults with strict conditions including a pump with noise and error, a CGM sensor, and a high CHO intake. The BGC percentages within the euglycemic region of 9 subjects was 84.30%, 90.16%, 65.23%, 83.84%, 58.39%, 74.30%, 72.22%, 47.79% and 87.20%, respectively. The merged BGC density of 9 adults was shown in Figure 3 (Green line). The average BGC percentage within the euglycemic region of the 9 subjects was 73.71% ± 14.35% (average ± standard deviation).

![Figure 3. Merged BGC densities of 9 adults with GPC+AA controller (green) or GPC+AO controller (red).](image)

Then, the GPC+AA controller were tested with 10 adolescents. The BGC percentages within the euglycemic region of 10 subjects were 71.88%, 74.50%, 78.64%, 41.56%, 35.89%, 80.89%, 53.58%, 45.51%, 44.59% and 62.65%, respectively. The merged BGC density of 10 adolescents was shown in Figure 4 (Green line). The average BGC percentage within the euglycemic region of the 10 subjects was 58.97%±16.81%.

![Figure 4. Merged BGC densities of 10 adolescents with GPC+AA controller (green) or GPC+AO controller (red).](image)
3.2. Tests of the GPC+AO controller
The effectiveness of the GPC+AA controller did not meet our expectations, especially for the adolescent. The reason might be that the tracking speed of the GPC+AA controller was not fast enough when patients have high BGC. Thus, the adaptive softening factor strategy was optimized with the introduction of BGC deviation to ensure a faster tracking speed of the controller. A GPC+AO controller was proposed here and tested with the T1DMS.

The BGC percentages within the euglycemic region of 9 adults was 86.88%, 85.92%, 92.43%, 83.28%, 79.56%, 80.18%, 78.79%, 76.99% and 95.94%, respectively. The merged BGC density of 9 adults was shown in Figure 3 (Red line). The average BGC percentage within the euglycemic region of the 9 subjects was 84.44%±6.47%. F-tests showed that the variance of the BGC percentages of 9 adults with the GPC+AO controller was unequal to that in Section 3.1 (F = 3.44, p = 0.02). Thus, heteroscedastic T-tests were performed to further examine the difference (Figure 5). Consequently, the average BGC percentage within the euglycemic region for the adult group (84.44% ± 6.47%) was significantly higher than that shown in Section 3.1 (73.71% ± 14.35%).

![Figure 5](image1.png)
**Figure 5.** T-test of BGC percentages within the euglycemic region with different GPC controllers for 9 adults. * p < 0.05.

The BGC percentages within the euglycemic region of 10 adolescents was 65.67%, 70.87%, 72.88%, 53.28%, 79.21%, 69.43%, 52.95%, 73.44%, 81.42% and 79.91%, respectively. The merged BGC density of 10 adolescents was shown in Figure 4 (Red line). The average BGC percentage within the euglycemic region of those 10 subjects was 69.91%±10.13%. F-tests showed that the variance of the BGC percentages of 10 adolescents with GPC+AO controller was equal to that in Section 3.1 (F = 3.18, p = 0.07). According to the following heteroscedastic T-test analysis, the average BGC percentage within the euglycemic region for the adolescent group (69.91%±10.13%) was significantly higher than that in Section 3.1 (58.97%±16.81%) (Figure 6).

![Figure 6](image2.png)
**Figure 6.** T-test of BGC percentages within the euglycemic region with different GPC controllers for 10 adolescents. * p < 0.05.
4. Conclusion
The optimized adaptive softening factor strategy prominently improved the quality of the GPC controller. The GPC controller with an adaptive reference glucose trajectory and an optimized adaptive softening factor is effective and can be potentially applied in the AP systems.

Acknowledgements
The authors would like to acknowledge that this study is supported by Guangdong Province Science and Technology (Project No. 2015A020214016), Science and Technology Program of Guangzhou (Project No. 201904010207), Young Innovative Talents Program in Universities and Colleges of Guangdong Province (Project No. 2018GkQNCX002) and GDHVPS 2016, as well as the funding support from Guangdong Province Medical Scientific Research Foundation (No. A2019142) and from the Research Gant of Guangdong Food and Drug Vocational College (No. 2018ZR028)

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