Adaptive Control Solution for T1DM Control

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***Abstract*—The *"Type 1 Diabetes Mellitus (T1DM)"* is a dangerous illness that concerns yearly increasing population. The control of the glucose level in the human body is a widely investigated subject area that also has serious technical difficulties as the lack of reliable system model for each individual patient, the limitations regarding the observability of the complete internal state of the patient (at least in the view of the system model). On this reason the *"Model Predictive Control (MPC)"* needs either robust or adaptive completion in this field of application. In the lack of observable data the traditional state estimators may have only limited relevance. The *"Robust Fixed Point Transformation (RFPT)"* based method was elaborated for the design of adaptive controllers typically for such situations. It does not need any sophisticated system model, it can work on the basis of observations that concern only the controlled quantity without the need of complete state estimation. In the present paper the use of the RFPT-based adaptive controller is reported in simulation investigations in which the validity of Bergman's "Minimal Model" is assumed. Promising simulation results are presented.**

I. Introduction

Type 1 Diabetes Mellitus (T1DM) is a subclass of the so-called Diabetes Mellitus (DM), which is chronic metabolic disease. The T1DM is related to the insulin hormone, since during the emergence of the disorder, the insulin producer β-cells are *"burned out"* due to intense autoimmune reaction in which the patient's own immune cells destroy them. Insulin is the key hormone that is responsible for facilitating the inflow of the glucose molecules (which are the general source of energy in the body of human beings) into the body cells through the cell membrane. When a patient gets into such a diabetic condition, external insulin injection is needed, without it, most of the patient's cells suffer energetic fatigue in short term and energetic collapse over longer period [1], [2].

DM researches are hot topics on the biomedical engineering field due to the dramatically increasing number of diabetic patients. According to the newest estimations for the number of people who live with such form of diagnosed and undiagnosed diabetes is about 386 million worldwide in 2013 [3]. Furthermore, the short term prospects suggest that this number can be reached the 592 million, the 10.1% of the expected global population by 2035 [3].

The control of a diabetic patient's condition from the viewpoint of diabetes is crucial because the uncontrolled disease can cause several side effects [1]. Furthermore, the quality of control is important as well [4]. Modeling and control have absolute relevance on the diabetes research field. The main problems are associated with the fact that the processes in human body are non-linear, thus, the control design is not trivial and demands individual approach case-by-case [5]. The nonlinearities can be handled in several ways. The most common strategies from the recent years were the *"Non-linear Model Predictive Control (NMPC)"* [6], *"Linear Parameter Varying (LPV)"* based robust control methods [7]–[9] and *"Soft Computing"* techniques [10], [11].

In this paper we investigate how the lately developed RFPT based control design can give a useful solution to diabetes control [12], [13]. This method has several benefits that will be detailed below.

The paper is structured as follows. At first we introduce the selected models, which were used during the examinations and give an introduction about the RFPT method. Secondly, we present the applied control design technique in this concrete case. At last, we show a few notable results and draw conclusions. Finally, we give an outline to our future work.

II. Diabetes Model

Our purpose was to give a proof of concept, hence, we selected the *"Minimal Model of Bergman"* in the form, which was presented by [5]. This is the most widely used T1DM model that can be tested in relation with different control approaches due to its simplicity. There are other forms of this model, which were made for different purposes [14]. The used form is appropriate from control perspective and, if it necessary, there is an option to extend it to T2DM case, as well. Naturally, we will test this controller design approach on other, more complex models as well. The model is represented by the (1).

The model has two inputs: $p(t)\,[mg/dL/min]$ denotes the glucose rate of appearance and $u(t)\,[\mu U/mL/min]$ represents the subcutaneously injected insulin flow; at the same time this input is the control input as well. The output of the model is $G(t), [mg/dL]$, what is the plasma glucose level.

The model has three state variables, which are connected to the blood plasm, these are: $G(t)\,[mg/dL]$ the blood glucose (BG) concentration, $X(t)\,[1/min]$ insulin-excitable tissue glucose uptake activity, $I(t)\,[\mu U/mL]$ the blood insulin concentration. The detailed descriptions about the model parameters

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are available in [5]. Figure 1 shows the schematic structure of the detailed model.

$$\begin{aligned}\dot{G}(t) &= -(p_1 + X(t))G(t) + p_1 G_B + p(t)\\ \dot{X}(t) &= -p_2 X(t) + p_3[I(t) - I_B]\\ \dot{I}(t) &= -n[I(t) - I_B] + u(t)\ .\end{aligned} \tag{1}$$

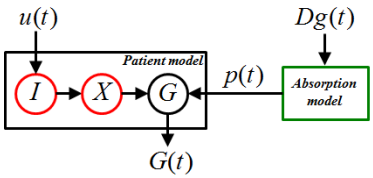

Figure 1. The schematic structure of the used T1DM model, complemented by a simple absorption model.

The selected T1DM model does not have absorption model. Thus, we complemented our simulation environment with a simple absorption model from [6], to reach more realistic operation. This model approximates the glucose absorption from the gut, with an exponential equation:

$$d(t) = \frac{D_g(t)\ A_g\ t\ e^{-\frac{t}{t_{max,G}}}}{t^2_{max,G}}\ , \tag{2}$$

where $D_g(t)$ $[g/min]$ represents the time function of the external glucose input, t $[min]$ is the actual time and the others are scalers. The exact definitions and physiological meanings of these parameters can be found in the cited literature above. The With this model, a more realistic glucose input can be reached. However, during the simulations we assumed, that the output of this model is known and not a direct part of the T1DM model.

III. The RFPT Method

In control engineering the use of high complexity models have significant practical disadvantages. Typical problem is the reliability of the model parameters for the particular person under control. Furthermore, such models are difficult to handle. Often complicated state estimators should be applied but these estimators can work on the basis of "indirect observations" that practically cannot be carried out. The presence of directly not observable environmental disturbances mean further complications. The available signals normally are burdened with various noises. On this reason either *model reduction techniques* have to be applied (e.g. [15]) or alternative approaches should be found. (Regarding model reduction the *physical interpretation* of the "state variables" is often dubious.)

The RFPT-based adaptive control is just a possible alternative to the use of the model reduction techniques. The basic idea is that the only variable that must be observed is the *response of the system* to the *control signal*. This signal is calculated by the use of a *deformed input* to an approximate system model for a predefined *"desired system response"*. This desired response can be determined by the use of "purely kinematic terms" without using any information on the system's dynamics. The necessary "deformation" can be determined in iterative manner i.e. by the application of a sequence of control signals that (under certain conditions) converge to the solution of the control task.

The sequence of the control signals is generated on the basis of Stefan Banach's *"Fixed Point Theorem"* that states that if a mapping is *contractive* over a *complete linear metric space* (Banach Space) the sequence generated by it converges to its fixed point [16]. The appropriate mapping is constructed from the control signal and the system's response generated by it in the preceding control cycle and the actually desired response that for *Single Input - Single Output (SISO)* systems is constructed as follows:

$$\begin{aligned}r_{n+1} = G(r_n; r^{Des}) \overset{def}{=} (r_n + K_c)\times\\ \left\{1 + B_c\left[\tanh(A_c(f(r_n) - r^{Des}))\right]\right\} - K_c\ ,\end{aligned} \tag{3}$$

where K_c, A_c, and $B_c = \pm 1$ are the *adaptive control parameters*. Clearly we have two fixed points as $r = -K_c$ (that is trivial and useless for the controller), and $r_\star$ for which $f(r_\star) = r^{Des}$, that is the solution of the control task. The condition $\left|\frac{\mathrm{d}f}{\mathrm{d}r}\right| < 1$ guarantees convergence. Further details regarding the appropriate setting of the control parameters was given in [13].

IV. Controller Design

A. Design Considerations

During the development, quite a few general control, physiological and phenomenological constraints have to be considered, as listed below:

- Those state variables, that are concentrations, are only interpreted in the positive range, because physiologically the negative range is meaningless (e.g. the blood glucose and insulin concentration cannot be negative).
- On the same reason the time-derivative of any concentration can only be positive or zero when the concentration itself is zero.
- The control signal is the injected insulin, $u(t) \geq 0$, since negative insulin cannot be injected.
- Furthermore, the blood glucose concentration cannot be decreased under a positive limit level due to physiological reasons (55 mg/dL [3]).
- The equations in (1) do not take into account these constraints. Therefore in the simulations these constraints must be built in additionally while using (1).
- In our controller, the only known state variable is the externally measured blood glucose level, normally available with sensor noise. The other states are not known during the operation. For simplicity reasons, we did not consider the additive noises in this research.
- It is assumed that because of physiological reasons, a state estimator is not usable. (Practically it is impossible to insert sensors into various parts of the patient's body.)

B. The Effect Chain of the Control Action

The external insulin input $u(t)$ is not connected to the output $G(t)$ directly, the control signal affects the controlled variable through an effect chain. To adapt the RFPT method, the control signal's "route" has to be elaborated. This route determines the control action and the control parameters as well.
This input appears in the third equation of (1) and reach the $G(t)$ through the $X(t)$ state variable. The second derivative of $X(t)$ contains the $\dot{I}(t)$:

$$\ddot{X}(t) = -p_2\dot{X}(t) + p_3\dot{I}(t) \ . \tag{4}$$

The quantity $\ddot{X}(t)$ occurs in the third derivative of $G(t)$, if we rearrange the equation for $\dddot{G}(t)$:

$$\dddot{G}(t) = -(p_2 + X(t))\ddot{G}(t) - \ddot{X}(t)G(t) - 2\dot{X}(t)\dot{G}(t) + \ddot{p}(t) \ . \tag{5}$$

The above equations show that the relative order of the control chain is 3. By step-by-step substitutions it can be shown that $u(t)$ effects directly only the third derivate of $G(t)$:

$$\ddot{X}^{Desired}(t) = -\frac{\dddot{G}(t)}{G(t)} - \\ -\frac{(p_2 + X(t))\ddot{G}(t) - 2\dot{X}(t)\dot{G}(t) + \ddot{p}(t)}{G(t)} \tag{6a}$$

$$A = -\frac{(p_2 + X(t))\ddot{G}(t) - 2\dot{X}(t)\dot{G}(t) + \ddot{p}(t)}{G(t)} \tag{6b}$$

$$\ddot{X}^{Desired}(t) = -\frac{\dddot{G}(t)}{G(t)} + A \tag{6c}$$

$$\dot{I}^{Desired}(t) = \frac{\ddot{X}^{Desired}(t) + p_2\dot{X}(t)}{p_3} \tag{7}$$

$$\dot{I}^{Desired}(t) = \frac{-\frac{\dddot{G}(t)}{G(t)} + A + p_2\dot{X}(t)}{p_3} \tag{8}$$

$$B = \frac{A + p_2\dot{X}(t)}{p_3} \tag{9}$$

$$\dot{I}^{Desired}(t) = -\frac{\dddot{G}(t)}{p_3 G(t)} + B \tag{10}$$

$$u^{Desired} = \dot{I}^{Desired}(t) + n(I(t) - I_B) \tag{11}$$

$$u^{Desired} = -\frac{\dddot{G}(t)}{p_3 G(t)} + B + n(I(t) - I_B) \tag{12}$$

$$\textit{Additive term} = B + n(I(t) - I_B) \tag{13}$$

$$u^{Desired} = -\frac{\dddot{G}(t)}{p_3 G(t)} + \textit{Additive term} \tag{14}$$

Equation (14) shows the control opportunity in this specific case: with prescribed kinematic requirements for the third time-derivate of $G(t)$ at a given moment, it determines the necessary control input $u(t)$ exactly in the same moment. Thus, the controller affects the controlled variable through an effect chain. Obviously, the strongest requirement from the control viewpoint is the existence of the third derivate of $G(t)$. The equation contains an $Additive\ term$ as well, but the effect of this term from the RFPT-based control law viewpoint is insignificant therefore it can be a constant.

C. The Control Law

The control law can be formalized with the kinematic requirements. Since the control signal affects a third derivate, the requirements should be given by the same order law. From simplicity reasons we can take the tracking error as a prescription and such a PID kind feedback with a proportional term $\Lambda > 0$ could be suitable:

$$(\frac{\mathrm{d}}{\mathrm{d}t} + \Lambda)^4 \int_{t_0}^{t_1} \left(G^N(\xi) - G(\xi)\right) \ d\xi = 0 \tag{15}$$

where $G^N(t)$ is the nominal blood glucose concentration of the nominal model, $G(t)$ is the realized blood glucose concentration and the exact requirement is that the error signal, $G^N(t) - G(t)$, should converge to zero as $t \to \infty$. From here, the desired third derivate is equal to

$$\dddot{G}^{Desired}(t) = \left(\frac{\mathrm{d}}{\mathrm{d}t}\right)^3 G^N(t) + \\ + \sum_{s=0}^{3} \binom{4}{s} \Lambda^{4-s} \left(\frac{\mathrm{d}}{\mathrm{d}t}\right)^s \int_{t_0}^{t_1} \left(G^N(\xi) - G(\xi)\right) \ d\xi \ . \tag{16}$$

Such a prescription can work well in the case of e.g. mechanical systems allowing the application of negative control force or torque terms. However, in our case, when we have to cope with the restriction $u \geq 0$, if too much insulin were injected to the system, we have to wait until it decays by the natural processes. (The speed of decrease of the insulin concentration cannot be increased by negative u.) During such a "dead period" the controller actually cannot be active, and the integrated error can drastically increase. To avoid this unacceptable consequence, we can take a PD kind controller given by

$$(\frac{\mathrm{d}}{\mathrm{d}t} + \Lambda)^3 \ \left(G^N(\xi) - G(\xi)\right) \ = 0 \tag{17}$$

which implies the following desired $\dddot{G}^{Desired}(t)$:

$$\dddot{G}^{Desired}(t) = \left(\frac{d}{dt}\right)^3 G^N(t) + \\ + \sum_{s=0}^{2} \binom{3}{s} \Lambda^{3-s} \left(\frac{d}{dt}\right)^s \left(G^N(\xi) - G(\xi)\right) \tag{18}$$

where it can be considered that the possibly diverging integrated tracking error is missing.

D. Rough Model Selection

The final step during the controller design is to select a "Rough Model" (RM), which provides the control signal. The big advantage of the RFPT-based method is that this can be as simple as it is possible and the external noise, which comes from the BG measuring method is reflected in the output of this model. In this given case the (14) equation can be taken as starting point during the selection. Since, the adaptivity law can guarantee the appropriate control action certain variables can be substituted by constants in this very approximate model. In this case instead of the actual $G(t)$ the constant G_b (from 1), can be used in (14), because of the mentioned adaptivity, the system can tolerate this high approximation as well. We have chosen the following RM:

$$u^{Desired} = -\frac{\dddot{G}(t)}{p_3 G_b} + Additive\ \ term \tag{19}$$

The effect of $Additive\ term$ is negligible and it can be chosen as constant. It is clearly visible that the control action will be based only on the third derivative of $G(t)$ and in this given case no other variables were considered due to the simplicity of the used T1DM model. With more complex model, other effects and signals could be considered depending on the structure of the nominal model.

E. Controller Considerations

The developed controller is able to control the actual blood glucose level based only on the past (realized) blood glucose level, because of the applied method. In order to introduce our method of full value, we have taken into account a few considerations, detailed below:

- We used the suggested adaptivity law from [13], described in (3). Thus, the adaptive control parameters are the A_c, B_c and K_c, which are changeable.
- We have not used optimization method to select the A_c, B_c and K_c parameters, however, "better" results could be reached with different optimization methods [17], [18].
- Other adaptivity laws can be used, since it has the same geometric properties (based on sigmoid functions) [13], with other tunable variables.
- The control law's parameter, which can be changed is the Λ. During the control action, the Λ's value was constant.

From this list above, it can be realized that the RFPT-based controller design method allows several kind of tuning options. However, earlier studies have shown various optimization methods [17], [18], the usability of these in this given case is not proven and we are going to investigate the controller tuning options in further studies.

V. Results

In this section we present three different scenarios, which provide good representation of the achievable results with RFPT-based control design methods.

A. Results of RFPT-based PID Control with Different Λ Gains

Figure 2 shows a time diagram of a 24 hours long simulation based on PID-type control law, with three high glucose loads in case of different Λ parameters. As it was expected, with higher gain, the controller provides higher control signal and the control action is faster than in the case of lower Λ. The following glucose input schemes were used: 7 am: 60g, 12.30 pm: 85 g, 19.30 pm: 75 g.

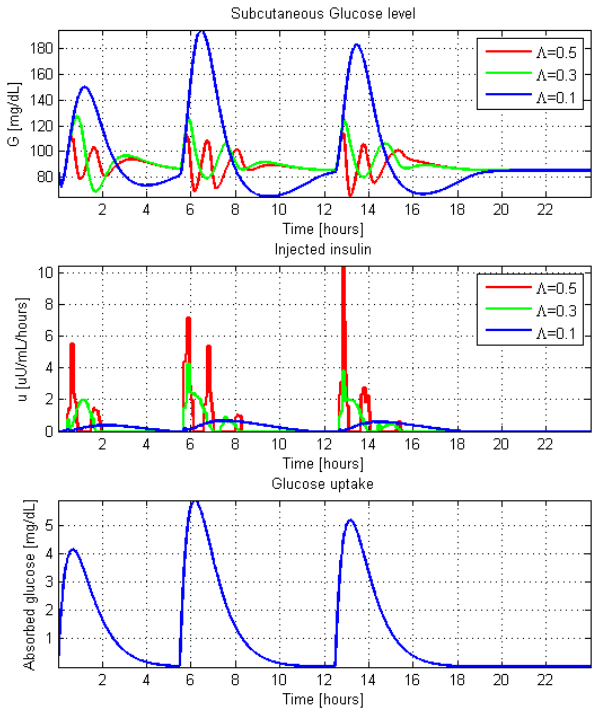

Figure 2. BG level ($G(t)$) with PID-type control, at heavy glucose load [Control parameters: $\Lambda = 0.08$, $A_{ctrl} = \frac{1}{10|K_{ctrl}|} = 5 \cdot 10^{-4}$, $K_{ctrl} = -200$, $B_{ctrl} = 1$, Set-point (G_N)=100 mg/dL]

On the above figure it can be seen well that after the control action (i.e. injection of some insulin), the controller *"switches off"* itself because the zero insulin intake is the best possible approximation of the kinematically desired negative value.

B. Comparison of Different Approaches

The result of the second scenario can be seen on Fig. 3. In this case, we have compared different situations, namely:

1) Without control. The controller was eliminated.
2) Using of PD control law. We have used the control law which was detailed in (17).
3) Using of PID control law. In this case (15) was used as control law.

The glucose intakes were exactly the same as in the previous case. It is clearly visible that the controllers (Case 2-3.) can handle the high glucose load and the characteristic of the controlled variable is more favorable than without control

when the BG level reaches higher values. Otherwise, the injected insulin causes lower BG levels. After the controllers' turning-off, the system's variables approach their equilibrium values. On the bottom diagram (Fig. 3) the integrator causes *"insulin spikes"* in the control signal, which immediately disappear and the control signal decreases to a given value. The control action is faster in this case than in the PD-type one. On the other hand, we can take the conclusion that with these control parameters, the PD and PID based controllers provide similar results without individual parameter settings.

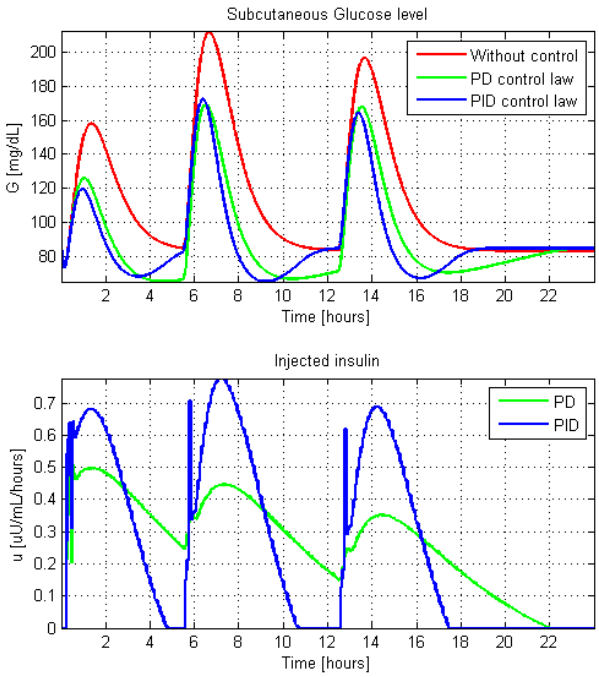

Figure 3. Different BG levels ($G(t)$), at heavy glucose load [Control parameters: $\Lambda = 0.1$, $A_{ctrl} = \frac{1}{10|K_{ctrl}|} = 5 \cdot 10^{-4}$, $K_{ctrl} = -200$, $B_{ctrl} = 1$, Set-point (G_N)=85 mg/dL]

C. 8 Days Long Simulation

The last scenario was an 8 days long simulation with PID control law. The used glucose intake protocol can be seen in Table I. Six intakes were considered, with the same time moments at every day, however, we have used a $\pm$ 10% deviation in the amounts of glucose, as *"soft"* randomization.

Time moments	6.00 am	9.30 am	12.30 pm	16.00 pm	20.00 pm	22.00 pm
Amounts of glucose intake with $\pm$ 10% deviation	45g	20g	60g	15g	55g	10g

Table I
GLUCOSE INTAKE PROTOCOL OVER THE 8 DAYS LONG SIMULATION

The results are displayed on Fig. 4, which is a *"Control-Variability Grid Analysis"* (CVGA) diagram that is a commonly used tool [19] to investigate the eligibility of BG control.

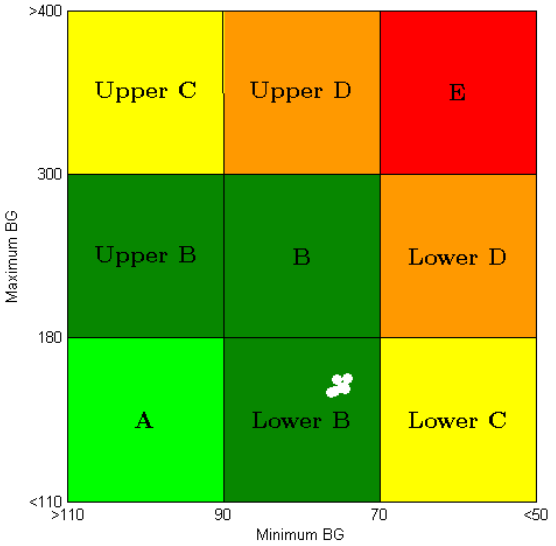

Figure 4. CVGA plot of the 8 days long simulation with the randomized feeding protocol. [Control parameters: $\Lambda = 0.1$, $A_{ctrl} = \frac{1}{10|K_{ctrl}|} = 5 \cdot 10^{-4}$, $K_{ctrl} = -200$, $B_{ctrl} = 1$, Set-point (G_N)=100 mg/dL]

The occurred time diagram of the 8 days long simulation (Fig. 5.) shows that the applied controller can not just only handle the system, but also can adapt to the system's "needs", namely, the required amount of insulin injection to reach the control goal can be realized under changing glucose load. During the simulation no hypoglycemic event happened, however sometimes hyperglycemia of short duration appeared very shortly after the maximum glucose absorption.

VI. CONCLUSION

In this paper, the application of an RFPT-based controller design method was reported in the field of diabetes control. Several situations were investigated and encouraging simulation results were obtained. (In the paper only a few of them was presented.) It was found that the RFPT-based method is appropriate from different points of view, which were detailed in the text. The control parameters were set without sophisticated optimization. It is expected that with on-line optimization, beside the adaptation, the control could achieve even better performance. In our future work, we are going to analyze the design method from different directions, namely we will examine the possibilities of parameter identification and optimization, control law and adaptivity function selection and other points of view.

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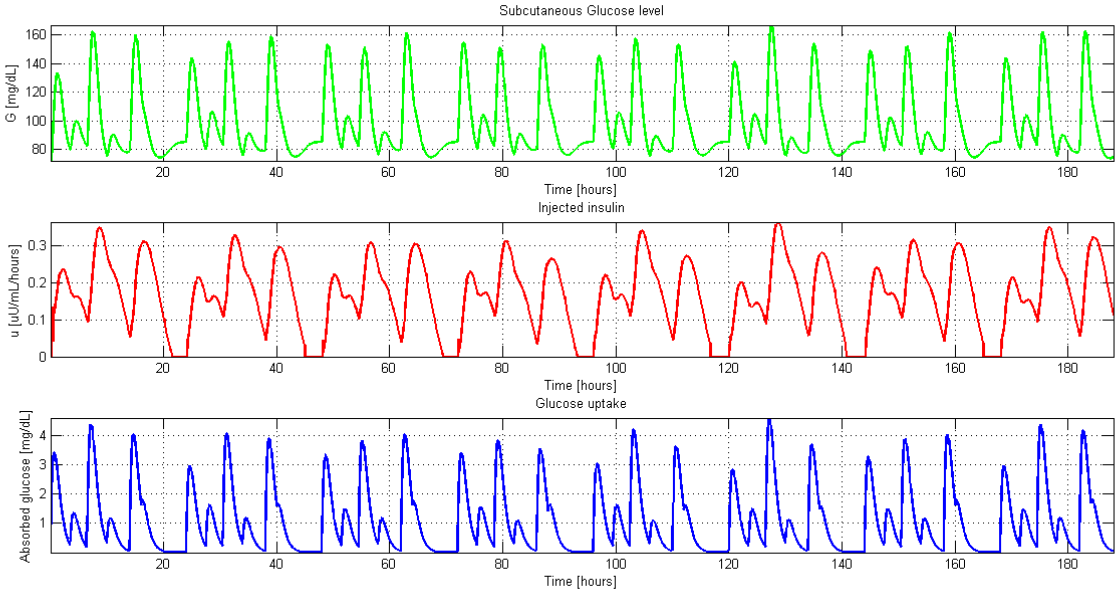

Figure 5. Result of a 8 days long simulation with the randomized feeding protocol [Control parameters: $\Lambda = 0.1$, $A_{ctrl} = \frac{1}{10|K_{ctrl}|} = 5 \cdot 10^{-4}$, $K_{ctrl} = -200$, $B_{ctrl} = 1$, Set-point (G_N)=100 mg/dL]

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