Robust Nonlinear Model Predictive Control of Diabetes Mellitus

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***Abstract*—The purpose of this paper is to present a Robust Nonlinear Model Predictive Control controller design opportunity and the results of three *in silico* test scenarios, where a nonlinear glucose model had to be controlled, and a desired blood glucose level had to be maintained. The chosen glucose model was a two compartmental, nonlinear model with time delay whose parameters were burdened with uncertainty. During the three test scenarios the controller performed well. It could keep the blood glucose level in the desired range without dangerous undershoots. In the third test scenario, during the simulation of 28 full days, 80% of the daily extremes lied between 5,5 - 10 mmol/l. The performance and computational bounds that are present at the moment are addressed and possible solutions are given at the end of the paper.**

I. Introduction

Diabetes Mellitus (DM) is a chronic metabolic disease of the living organisms which frequently occur in case of human beings as well [1]. DM is connected to the insulin hormone which is responsible for maintaining the energy household (via the regulation of the inflow of glucose into body cells) and determinant hormone of the metabolism. Several types of DM are exists. The most common types are the Type 1 DM (T1DM) and Type 2 DM (T2DM) [1]. Most of the researches which use engineering based approaches to deal with the control of blood glucose level are focusing to these types [2]–[4]. In case of T1DM the diabetic patient's insulin producer β cells necrose and the patients need external insulin intakes to keep their glycemia on a healthy level. Without external insulin, these patients suffer from cell level starving due to the lack of insulin and hyperglycemia at the same time which state holds for long term may cause diabetic coma and becomes fatal [2]. The T2DM evolves in the patient's body over long period of time caused by lifestyle, genetics, environmental effects and else. Most determinant effect of T2DM is that the patients insulin regulated glucose consumer body cells become more and more neutral to the effect of the insulin hormone – building up resistance to insulin. Even though the internal insulin production is still active, the efficiency of it becomes lower over time. Although, this state do not cause visible side effects at the beginning, the permanently high blood glucose level requests more and more production of insulin which lead to the "burn-out" of the β-cells over time. This results in T2DM turning into a T1DM diabetic state and these patient need external insulin intake as well [2]. Besides, high glucose variability can cause several side effects over the years [5].

In the recent years the importance of those modeling and control approaches became high which are tunable and which are capable to describe and handle both diabetic disease at the same time [3], [6], [7] - for example the complex model of Wu Zimei [8] or the simple model of De Gaetano et al [9]. These models are using Delay Differential Equations (DDE) in order to describe the natural latencies inside the body regarding the insulin production and secretion and the insulin resistance. In T1DM case the models' equations become Ordinary Differential Equations (ODE).

Model Predictive Controls (MPC) have long history regarding the DM researches [3], [6], [7]. Successfully adaption of different MPC-, Nonlinear MPC (NMPC)-, Stochatic MPC (SMPC) and Robust MPC (RMPC)-based controller design solution have been published over this decade [10]–[13].

However to best of our knowledge the usability of Robust Nonlinear MPC (RNMPC) in case of DDE DM models were not investigated previously. This framework may has several benefits, such as realistic Double Diabetes simulation with considered parameter variation – the RNMPC controllers are able to deal with these situations.

The structure of this article is the following: firstly, the used RNMPC algorithm is introduced. Secondly, we present the the DM model, which was used during the research. After that we demonstrate the RNMPC-based controller design in this particular case. Thereafter, we present our results and achievements. Finally, we conclude our work and present our future goals.

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II. RNMPC ALGORITHM

NMPC is an optimization based method for the feedback control of nonlinear systems [14]. Its primary applications are stabilization and tracking problems [15]. In case of NMPC the current value of the control signal $u(k)$ is obtained by solving, at each sampling instant t_n, a finite horizon open-loop optimal control problem. The type of the optimal control problem depends on the type of the control task, the given limitations and constraints to be applied and other factors. Using the previous state of the plant $x(k-1)$ as current initial state x_0, the optimization yields an optimal control sequence. The first element of the control vector in this sequence $u(k)$ is applied to the nonlinear plant. An important benefit of this type of control is its ability to cope with hard constraints on control inputs and states [14], [15]. The basic control algorithm of NMPC-based controller consists of three main steps. For constant reference $x^{ref} \equiv x_*$, where the sampling time t_n and $n = 0, 1, 2, ...$ denotes the finite horizon [15]:

1) Measure the states $x(n) \in \mathbb{X}$, where $\mathbb{X} \subset \mathbb{R}$ is the possible values of the states
2) Set $x_0 := x(n)$ and solve the optimal control problem for the finite horizon t_n:

$$\textbf{min } J(x(t), U) = \sum_{k=0}^{N-1} d(x_u(k), u^*(k)) \ . \quad (1)$$

$$d(x_u(k), u^*(k) = \\ = \lambda * \mid\mid x_u(k) - x^*(k) \mid\mid^2 + \kappa \mid\mid u(k) - u^*(k) \mid\mid^2 \ , \quad (2)$$

where $x_u(0) = x_0$, $x_u(k+1) = f(x_u(k), u(k))$, and $d(x_u(k), u(k))$ is the cost function penalizing the deviation of the state variables and control values from their desired reference values.

3) Determining the value of the control signal. The control signal for the next time frame will be the first element of the calculated U^* optimal control value sequence:

$$\mu(x(n)) = U^*(0) \quad (3)$$

The NMPC's property of handling constraints of state and control variables on the algorithmic level without causing additional nonlinearities in the system makes the usage of it desirable in biological applications where the controlled system's physiological constraints cannot be neglected.

Despite it's positive properties, one problem arises with the use of NMPC, namely the increased levels of error-proneness caused by uncertainties and modeling errors. This results in an ever increasing interest in robust NMPC research. Many research groups have worked out solutions to the problem, for example Hovorka et al. from the field of biomedical engineering. They used an NMPC control scheme with adaptive capabilities for blood glucose regulation [11].

RNMPC is based on the algorithm described above with additional ability to handle uncertainties of the controlled system. For the robustification process we have chosen the Minimax method [14]. The main idea behind is to optimize the output of the system while affected by the worst-case values of the uncertainties. This might not give the optimal solution of the nominal system, however the output will be feasible in the whole range of the uncertainties. The algorithm of the robust controller is basicly the same as the normal NMPC's, with additional constraints that represent the uncertainties.

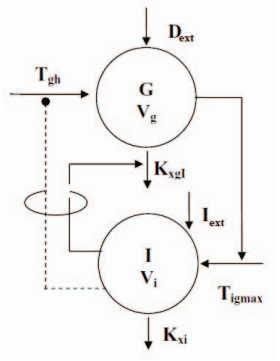

Figure 1. Schematics of the two compartment Single Delay Model [16]. V_g and V_i are the distribution volumes respectively for Glucose ($G(t)$) and Insulin ($I(t)$). D_g stands for the glucose bolus administered; $K_{xg}I$ is the second-order net elimination rate of glucose per unit of insulin concentration; K_{xi} is the first order elimination rate of insulin; T_{gh} is the net difference between glucose production and glucose elimination; T_{igmax} is the maximal rate of second phase insulin release.

III. THE SINGLE DELAY MODEL

The blood glucose model chosen for further research was originally described by Panunzi et. al in 2007 [16]. The model is based on IVGTT results and physiological considerations, providing a relatively easily handled yet accurate description of the glucoregulatory system.

The state variables of the nonlinear two compartmental system are the plasma glucose $G(t)$ and plasma insulin $I(t)$ concentrations:

$$\dot{G}(t) = -K_{xgl} I(t) G(t) + T_{gh} V_g + \frac{G_{ext}(t)}{V_g} \quad (4)$$

$$\dot{I}(t) = -K_{xi} I(t) + \frac{T_{igmax}}{V_i} \frac{\left(\frac{G(t-\tau_g)}{G^*}\right)^\gamma}{1 + \left(\frac{G(t-\tau_g)}{G^*}\right)^\gamma} + \frac{I_{ext}(t)}{V_i} \quad (5)$$

where $G(0) = G_b$, $I(0) = I_b$.

In the first equation the term $-K_{xg} I(t) G(t)$ represents the net balance between insulin-dependent glucose uptake from peripheral tissues and insulin-dependent hepatic glucose output, whereas the term $\frac{T_{gh}}{V_g}$ represents the net difference between insulin independent glucose uptake and hepatic glucose output [16]. In the second equation $-K_{xi}$ represents the rate of insulin degradation, whereas the second term represents second-phase insulin delivery from the β-cells. The term is

limited, the maximal rate of release is $\frac{T_{igmax}}{V_i}$. The exponent γ represents the capability of the pancreas to accelerate its insulin secretion in response to progressively increasing blood glucose concentrations [16]. By increasing the value of $G^*, \lim_{\infty} \frac{T_{igmax}}{V_i} \frac{\left(\frac{G(t-\tau_g)}{G^*}\right)^{\gamma}}{1+\left(\frac{G(t-\tau_g)}{G^*}\right)^{\gamma}} \to 0$, thus the model can be used to simulate Type I diabetic conditions. The full list of parameters and their values used in the following simulations can be found in [16].

IV. Controller design

A. The YALMIP framework

The possible robustification methods applicable for the NMPC all demand a deep mathematical understanding of both the system and the robustification algorithms. Applying the theoretical knowledge of the mathematics of robustification is often tedious, error-prone and time consuming. The main idea during the implementation of our controller was to focus on the actual problem rather than the mathematical challenges of the robustification. In order to achieve this, YALMIP's Robust Optimization Framework [17], a freely available MATLAB toolbox was used.

YALMIP is a modeling language for advanced modeling and solution of convex and nonconvex optimization problems, consistent with standard MATLAB syntax. It allows the user to concentrate on the high-level model, while YALMIP takes care of the low-level modeling to obtain as efficient and numerically appropriate models as possible. [18]. Even though YALMIP heavily relies on efficient external solvers for the low-level numerical solution of optimization problems [18], for the solution of the problem derived from the nonlinear Single Delay Model, MATLAB's built in nonlinear solver, *fmincon* was used.

With YALMIP, defining the model affected by uncertainties and deriving its robust counterpart can be done in only several dozen lines of code, this way greatly reducing development time.

B. Steps of implementation

The frame of the robust NMPC controller is based on a robust MPC description available on the YALMIP's webpage [19], which has been adapted to handle the given nonlinear glucose system.

The first step of the realization of the algorithm was the declaration of the glucose model burdened with uncertainties with the help of YALMIP's symbolic variables. After, the uncertainties are declared via a list of equations and inequations containing the uncertain symbolic variables. By defining an objective function we provided the reference signal for the controlled system. During the tests only constant reference signals have been used. YALMIP's ***robustify*** function provides the system's robust counterpart which can be repeatedly solved by the nonlinear solver in the program's main loop.

The main loop is responsible for the execution of the RN-MPC algorithm: sampling the state of the system at every time instant t_n, solving the robust control problem with *fmincon* and applying the resulting control signal as the control input of the system. After every sampling, the current state of the system is saved to an array that can be plotted or otherwise evaluated.

C. Test scenarios

During the *in silico* tests three scenarios have been examined: first the nominal system model burdened with an unknown but limited external glucose signal as disturbance and with K_{xi} as a limited but uncertain parameter (scen. A). Next both K_{xgl} and K_{xi} as limited but uncertain parameters (scen. B), finally a system similar to scen. B, but with several modifications to achieve better undershoot prevention (scen. C). In scen. B and C the systems are only robust explicitly to the changing of the external glucose disturbance signal and K_{xi}, but not to the changing of K_{xgl}. This means that the change in the value of K_{xgl} affects the system as an uncompensated disturbance, this way simulating extreme circumstances that the controller has to handle.

The reason for this design lies in the limitations of YALMIP. Setting both parameters as uncertain variables leads to an intractable problem, which YALMIP is unable to handle effectively. Even setting only K_{xi} as an uncertain variable leads to a problem category whose complexity is O(N^2), where N is the length of the prediction horizon. This heavily affects the need of computational resources and thus sets a limit for N.

Considering this, the following settings have been used during the tests:

– The nominal values of the system parameters have been set based on the values published in [16]. The prediction horizon of the robust controller was $N = 6$.

– Scenario A: the external disturbance signal was limited to: $0 <= G_{ext}(t) <= 10[mmol/l]$. K_{xi} was limited to: $0.0314 < K_{xi} < 0.48$

– Scenario B: both K_{xi} and K_{xgl} were limited: $0.0314 < K_{xi} < 0.48$, $4.34e-5 < K_{xgl} < 4.28e-4$

– Scenario C: $0.0314 < K_{xi} < 0.48$, $1.34e-4 < K_{xgl} < 3.28e-4$

V. Results

In this section the results of the tests are presented. Based on the results of the three different test cases the robustness of the controlled system has been examined and evaluated. In all test cases 7 days long periods have been simulated, with the glucose intakes of 5 meals every day. Glucose intakes have been generated based on WHO's recommendations of daily calory intake [20], weighted with a random value in the range of $80-120\%$.

A. Scenario A

The first version of the simulated system was robust only to the uncertainty of the glucose intake and K_{xi}. The simulation results are shown in Figure 2.

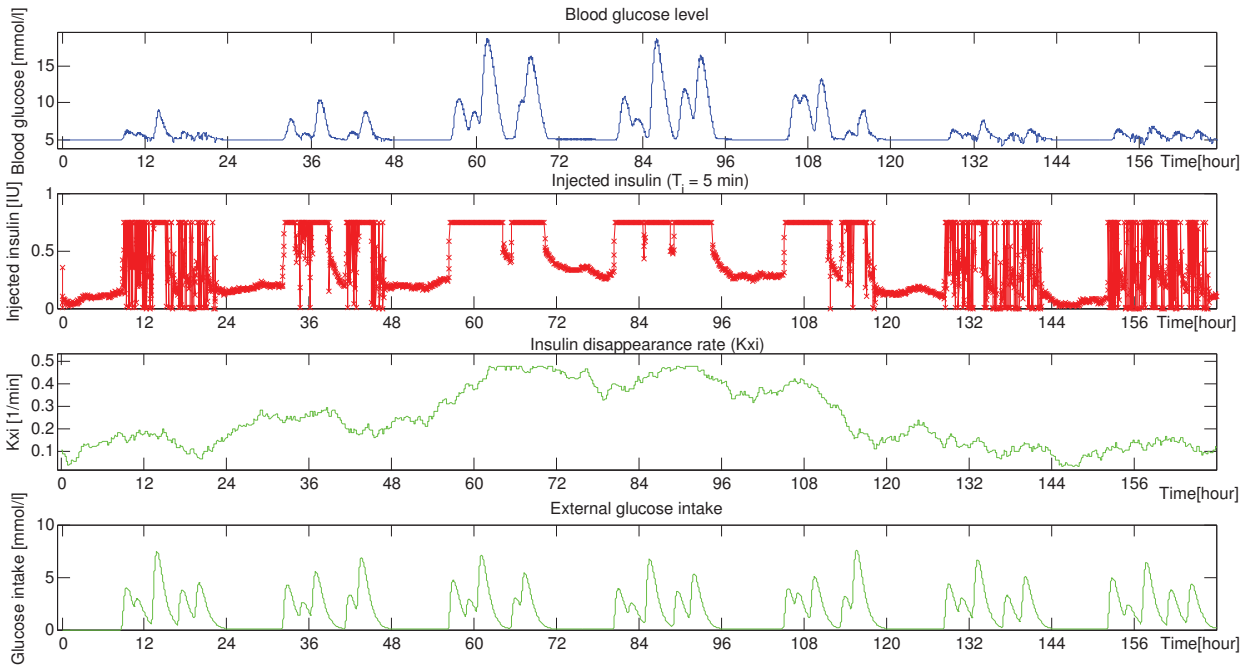

Figure 2. Results of test case A: blood glucose level, insulin control signal, glucose intake

Disturbance suppression (keeping blood glucose at the desired 5 mmol/l level) is highly dependent on the value of K_{xi}: a higher value means faster insulin degradation, which leads to lower blood insulin levels and thus to higher blood glucose values. When K_{xi}'s value is lower, the controller can keep the blood glucose under 8 mmol/l even when a considerably large disturbance is applied. During the 7 simulated days BG level peaked over 15 mmol/l only 4 times (for a total duration of 2 hours), and only if K_{xi} was more than 0.45. During the whole simulation no serious undershoots occurred. BG level's absolute minimum was 4.6 mmol/l.

During the longer fasting periods between meals the value of the injected insulin (the control signal) clearly follows the changes in K_{xi}. The controller administered appropriate amount of insulin in order to keep the blood insulin level constant during these periods.

B. Scenario B

In the first test case the controller could handle the disturbances come from the external glucose uptake and the uncertainty of K_{xi}. To test the robustness of the controller, in the second test case an uncertain K_{xgl} has been implemented. As stated in IV-C the uncertainty of K_{xgl} affects the system as an uncompensated disturbance, since computational limitations prevented explicit robustification for both parameters. However, the results of the tests showed that the effects of this simplification on the controller's performance are limited.

Fig. 3 and Fig. 4 show the simulation's outputs. It's easy to see, how "'fuzzy"' the BG level is, with heavy sawtooth-like oscillation. The extent of this oscillation mainly depends on two factors: the actual value of K_{xgl} and the length of the controller's prediction horizon. Bigger value of K_{xgl} causes faster BG's disappearance from the plasma. If its actual value is greater than the nominal (see Fig. 4), the controller's calculations become inaccurate, the applied doses of insulin become higher than needed which leads to a steep decrease in the amount of plasma glucose. The other factor is the length of the prediction horizon: the heavy limitations on the number of future states taken into account during the optimization step causes higher overshoots in the control signal.

Even though the "quality" of the BG signal is desirable, despite the disturbances caused by the inconstant parameter K_{xgl} the controller keeps the BG level in a physiologically acceptable region ($4.1 - 10$ mmol/l, with one outlying value [3.6 mmol/l]).

The performance of the controller can be easier evaluated using CVGA plots [21]. On Fig. 5 each dot represents a 24 hour period from the week long simulation with the given day's minimum and maximum BG value. Every dot lies in the lower B region, meaning that the controller could compensate the external glucose signal's effects, however smaller undershoots occurred.

C. Scenario C

Even though the undershoots of the second test case weren't dangerous, the results showed that corrective steps had to be taken. For the third test case the reference signal has been increased from 5 mmol/l to 6 mmol/l. Even though the value of K_{xgl} can vary considerably from patient to patient, it's safe to assume that it's value can't vary between those same bounds

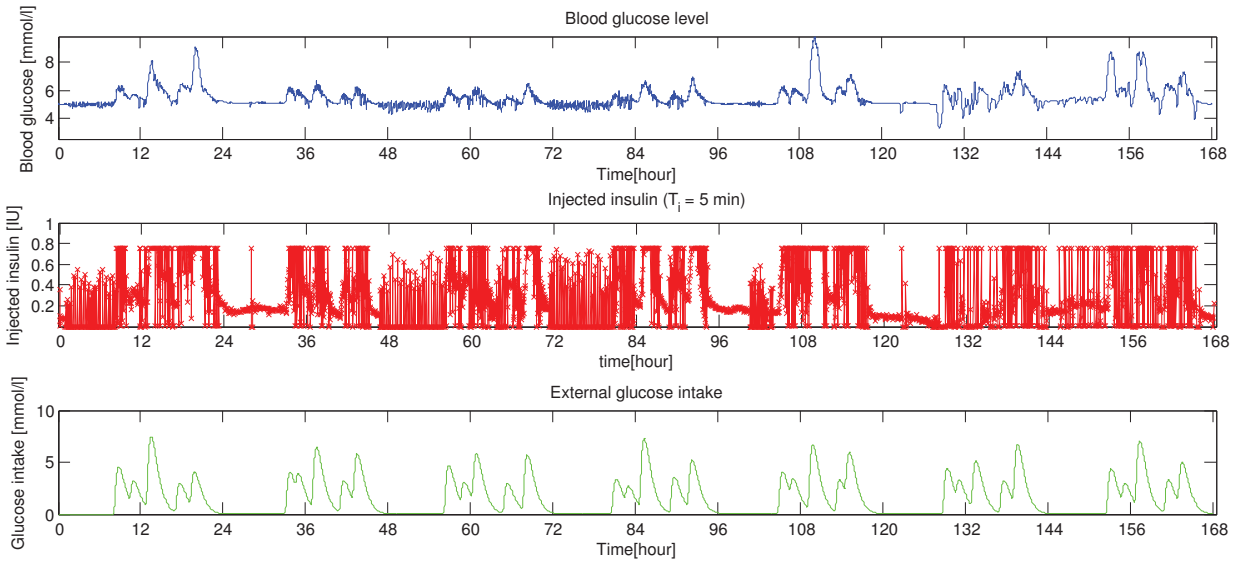

Figure 3. Results of test case B: blood glucose level, insulin control signal, glucose intake

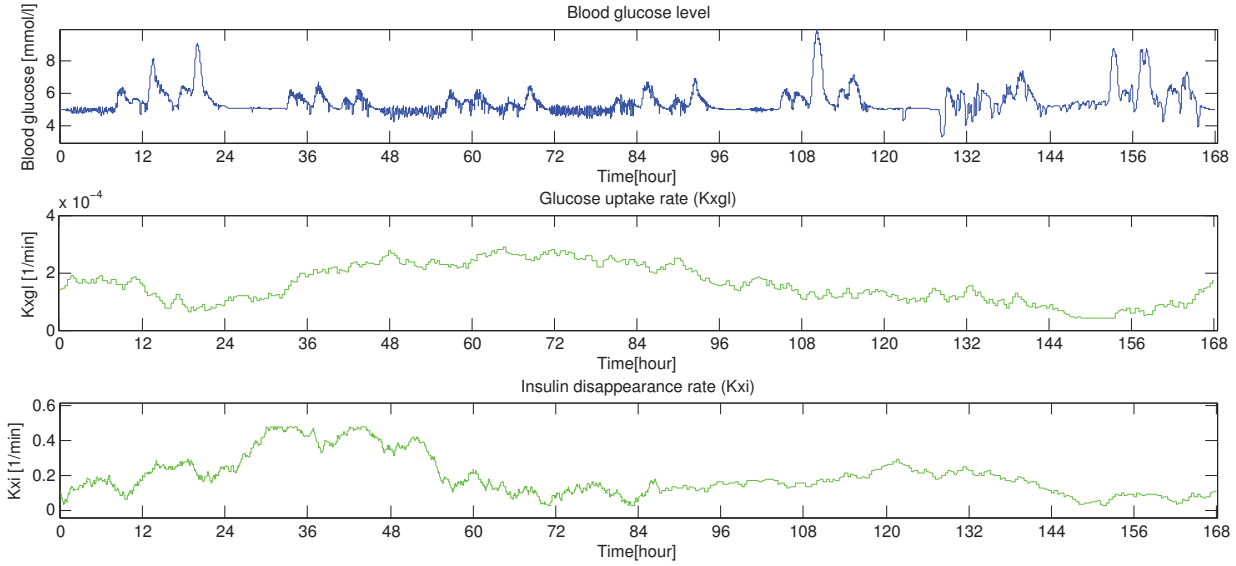

Figure 4. Results of test case B: blood glucose level, glucose uptake rate, insuling disappearance rate

in case of one patient. Considering this, the new, more realistic bounds of the uncertain K_{xgl} have been set to $1.34e-4 < K_{xgl} < 3.28e-4$. The maximum of the control signal has been decreased by 25% (from 12 IU/h to 9 IU/h). The length of the simulation has been increased from 7 days to 28 days. The results of the simulation can be seen on Fig. 6.

The CVGA plot shows that the modifications have been effective: 80% of the daily results are in the desired region and the absolute minimum value of the BG level is 5.5 mmol/l, far above dangerous hypoglycemic values. 93% of the values lie in the region of 5.5-12 mmol/l, with two outliers at 16 mmol/l.

VI. Conclusion

In the previous section three different scenarios have been tested and the results have been showed.

In general the results are satisfactory. The robust controller could compensate the effects of the external and internal disturbances and uncertainties, thus keeping the BG level in a physiologically acceptable region without dangerous over- or undershoots. On the other hand the test results raise some issues. The characteristics of the uncertainties in the

system cause rapid growth of computational time even in case of short prediction horizons. This severely affects the prediction abilities of the controller, resulting in a "'fuzzy"' BG signal, with frequent undershoots. There are possible improvements that may help to solve this issue: considering another glucose model is one of them. With an appropriately chosen glucose model the robust optimization problem might fall into a simpler problem category, that could be solved more easily. Another aspect is the broader use of parallel programming, which can positively affect computational time. Apart from these, a demanding, however potentially more promising aspect would be an in-depth and focused research in robust optimization theory. YALMIP is a powerful tool for rapid development, however it's generality and easy usage might come with suboptimality in the particular cases we have examined.

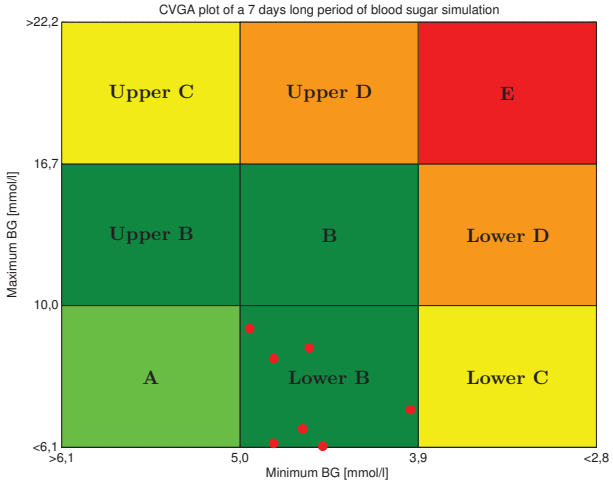

Figure 5. CVGA plot of test case B.

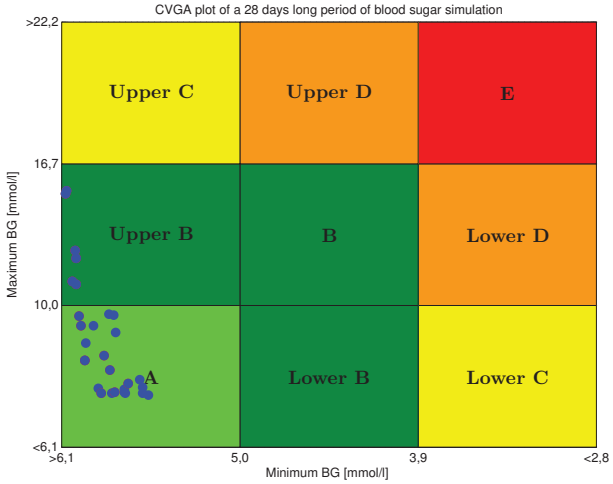

Figure 6. CVGA plot of test case C.

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