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GLUCOSE LEVEL REGULATION VIA INTEGRAL HIGH-ORDER SLIDING MODES

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Abstract. Diabetes is a condition in which the body either does not produce enough insulin, or does not properly respond to it. This causes the glucose level in blood to increase. An algorithm based on Integral High-Order Sliding Mode technique is proposed, which keeps the normal blood glucose level automatically releasing insulin into the blood. The system is highly insensitive to inevitable parametric and model uncertainties, measurement noises and small delays.

1. Introduction.

Diabetes is a chronic disorder of glucose metabolism, caused by inadequate production or improper use of insulin. Insulin is a hormone produced in specialized cells in the pancreas, whose function in the body is to use and to store glucose.People with normal pancreatic function produce it to cover their needs. Upon digestion of carbohydrates, glucose levels in the blood begin to rise. As the blood and the glucose flow into the pancreas and the blood glucose level raises, insulin is directly secreted by the pancreatic beta cells into the bloodstream. Insulin causes the blood glucose to be removed from the bloodstream and to be stored in the liver and muscle cells. Thus, as the blood sugar goes higher, additional insulin brings the blood sugar back down. As the blood sugar level goes back to normal, the beta cells stop spurting insulin. As the glucose level approaches a low mark, the pancreatic alpha cells release glucagons directly into the bloodstream. Glucagons cause the liver to release the stored glucose back into the bloodstream. These hormones form two inverse feedback loops in controlling the blood glucose level.

Normal blood glucose levels are in a narrow range of 70-110 mg/dl. If someone's glucose level stays constantly high out of this range, the person is considered to have diabetes. When the decease is not carefully managed by keeping the amount of glucose in the blood at the right level, the resulting high glucose amounts wreak havoc on nearly every organ system in the body. Complications of diabetes can range from sudden, urgent issues to those that develop slowly over the years. These complications include heart disease and stroke, vision loss and blindness, kidney failure, diabetic ketoacidosis, diabetic coma, and are not limited only by them. Implementing accurate glucose control in patients is the most important issue in diabetes management. The current medical practice suggests three to four daily glucose measurements and the same number of subcutaneous insulin injections. The development of less invasive methods with less frequent injections has been the subject of interest for many researchers working in this area. The ultimate goal of

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most of them is to create a fully automatic glucose control system which works like an artificial pancreas.

The existing insulin pumps dispense the insulin according to a preset program or when they have been triggered manually, and not according to body's needs. Obviously, the main task is to develop an effective computer-based feedback controller that interprets the data from a real-time glucose sensor and respectively instructs the pump how much insulin to release.

The number of control algorithms have been developed for various models of glucose-insulin dynamics. In particular, they include controllers, belonging to the proportional-integral-derivative (PID) control family [2],[5], pole placement, and model predictive control (MPC) methods [13]. The PID methods are applicable to the linearized models only. On the other hand, in order to apply the MPC approach one has to predict accurately the future values of blood glucose concentration level using the analysis of the glucose- insulin dynamics in the past. Unfortunately, such an approach becomes impractical, as patient's medical condition varies in time, and the model parameters change in an unpredictable way. In additional, the above controllers do not address the unmodeled dynamics of the system, like patient-model mismatch, which in general may significantly affect system performance.

It is clear that in practice the control algorithm, employed for blood glucose regulation, has to deal with the uncertainty existing between the model, used in the controller design, and the actual patient. Such controller has been developed by Kienitz [7] within the H-infinity framework, but its robustness has never been proven. Shtessel and Kaveh [14] have developed controller based on the High-Order Sliding Mode (HOSM) technique [9] which operates with the information from the real-time system measurements. Although the HOSM algorithm features high accuracy and robustness with respect to various internal and external disturbances, its application in [14] has some restrictions. In particular, the insulin release cannot be negative, only the model describing the system dynamics after one food intake is considered; the results are only valid for patients, whose insulin secretory function is completely disabled, the uncertainty of transient process has not been treated.

The closed-loop control system of the glucose level regulation which is proposed in this paper can also be described as "artificial pancreas". The system consists of three parts: the real-time subcutaneous glucose sensor; the control system that calculates the necessary insulin dosage based on the real time glucose levels; and the pump, which releases the desired amount of insulin.

The controller is based on the Integral High-Order Sliding Mode (IHOSM) technique [11]. This approach preserves the main advantages of traditional HOSM - robustness and high accuracy in presence of parameter variations and external disturbances. Having been compared to the HOSM methods, the presented algorithm enables choosing transient dynamics and assigning the transient time function of the initial conditions, avoids all kinds of uncertainties and extreme changes in the blood glucose concentration level from the very beginning.

The resulting control presents the amount of insulin released to the blood and should be always positive. The restriction holds, for the control value is kept very close to the insulin release level maintaining the transient glucose level assigned in advance (i.e. the equivalent control [15]. Due to the integral sliding mode the influence of system uncertainties is suppressed starting from the very moment of the control application. To increase the model feasibility it was modified by adding some casual food intake as a disturbance.

Section 2 describes some fundamentals of HOSM design [8],[9]. In Section 3 a mathematical model which describes the glucose- insulin dynamics in human body is introduced. The model is based on the minimal model commonly used in the literature, which belongs to Bergman [1]. Section 4 deals with the design of IHOSM controller. Simulations are presented in Section 5.

2. **High-order sliding mode fundamentals.** Consider a single input-single output dynamic (SISO) system

$$\dot{x} = a(t, x) + b(t, x)u, \quad u \in R, \sigma = \sigma(t, x) \in R, x \in R^n, \tag{1}$$

with output σ. Assume that $a, b\ \sigma$ are unknown smooth functions, the dimension n can also be uncertain. The task is to make the output function vanish in finite time and to keep it zero afterwards by means of possibly discontinuous feedback. The solution is understood in Fillipov sense, and system trajectories are supposed to be infinitely extendable in time for any bounded Lebesgue- measurable input.

Let the relative degree of the system is constant and known, and equals r. The equality of relative degree of the system (1) to r means that control u appears for the first time in the r-th total time derivative of the output, i.e

$$\sigma^r = h(t, x) + g(t, x)u, \quad g(t, x) \neq 0 \tag{2}$$

holds with some uncertain functions

$$h(t, x) = \sigma^r|_{u=0}, \quad g(t, x) = \frac{\partial}{\partial u}\sigma^r \neq 0. \tag{3}$$

Suppose that

$$0 < K_m \leq \frac{\partial}{\partial u}\sigma^r \leq K_M, \quad |\sigma^r|_{u=0} \leq C \tag{4}$$

for some $K_m, K_M, C > 0$.These inequalities are satisfied at least locally for any smooth system (1) which has a well-defined relative degree at a given point with

$$\sigma = \dot{\sigma} = ... = \sigma^{r-1} = 0. \tag{5}$$

Assume that (3) hold globally. Then we can replace equations (2), (3) by the differential inclusion

$$\sigma^r \in [-C, C] + [K_m, K_M]u. \tag{6}$$

The problem of nullifying of output in finite time and keeping it zero afterwards is solved in two steps. First, a bounded feedback control

$$u = -\varphi_r(\sigma, \dot{\sigma}, ..., \sigma^{r-1} \tag{7}$$

is constructed such that all trajectories of (6), (7) converge in finite time to $\sigma = \dot{\sigma} = ... = \sigma^{r-1} = 0$ - the origin of the r - sliding phase space $\sigma, \dot{\sigma}, ..., \sigma^{r-1}$. Then the lacking derivatives are real-time evaluated by means of robust exact differentiator, producing an output-feedback controller. Since the inclusion (6) does not "remember" the original system (2), such controller is robust with respect to any perturbations preserving the system relative degree and (4). If the relative degree r of the system is 1, i.e. control appears in the first derivative of output function and $\sigma'_u > 0$, then the standard sliding mode control (SM) $u = -\alpha sign\sigma$ accomplishes the task. Arbitrary-order sliding-mode controllers with finite-time convergence were developed by Levant [8, 9]. Following are quasi continuous higher order sliding mode controllers for r=1–4:

1. $u = -\alpha sign\sigma$,
2. $u = -\alpha(\dot{\sigma} + |\sigma|^{1/2} sign\sigma)(|\dot{\sigma}| + |\sigma|^{1/2})^{-1}$,
3. $u = -\alpha((\ddot{\sigma} + 2(|\dot{\sigma}| + |\sigma|^{2/3})^{-1/2}(\dot{\sigma} + |\sigma|^{2/3} sign\sigma))/(|\ddot{\sigma}| + 2(|\dot{\sigma}| + |\sigma|^{2/3})^{1/2})$,
4. $\varphi_{3,4} = \sigma^3 + 3(\ddot{\sigma} + (|\dot{\sigma}| + 0.5|\sigma|^{3/4}))^{-1/3}(\dot{\sigma} + 0.5|\sigma|^{3/4} sign\sigma)$
$(|\ddot{\sigma}| + |\dot{\sigma}| + 0.5\sigma|^{3/4})^{2/3})^{-1/2}$
$N_{3,4} = |\sigma^3| + 3(|\ddot{\sigma}| + (|\dot{\sigma}| + 0.5|\sigma|^{3/4})^{2/3})^{1/2}$
$u = -\alpha\varphi_{3,4}/N_{3,4}$

The produced controllers are discontinuous functions of σ and of its real-time calculated successive derivatives $\sigma, \dot{\sigma}, ..., \sigma^{r-1}$. They provide for n- th order accuracy with respect to sampling interval. It is proven by Levant that this is the best possible accuracy with discontinuous control [8].

Originally HOSMs were proposed in order to remove the chattering effect, caused by is discontinuity of the control. The main idea of the HOSM is to consider the k-th-order time derivative of the actual control as the new control input. As a result, the relative degree raises, and a new $(r + k)$-sliding controller is applied, corresponding to the new relative degree $r + k$. The real control becomes output of an integrator chain, thus it is smooth of the needed order k. Note that when the relative degree is increased, the input u and its (k-1) successive derivatives are considered as as additional system coordinates.

A specific problem arises due to the artificial increase of the relative degree. Some interaction of u and its derivatives during the convergence to the $(r + k)$-sliding mode $\sigma = \dot{\sigma} = ... = \sigma^{r+k-1} = 0$ is inevitable. Generally speaking, such an $(r + k)$- sliding controller is for sure effective only in some vicinity of the $(r + k)$-sliding mode, where u is close to the so-called equivalent control [14], which is independent on u. The global convergence was provided only for the transfer from $r = 1$ to $r = 2$ by a suitable controller modification [9].

An additional drawback of the approach is an uncertainty of transient process. The SM technique assures the ultimate robustness of the system motions only when the sliding mode occurs. However, during the reaching phase, i.e. before establishment of the SM, there is no guarantee of robustness of the system and ever trajectories remain uncertain.

The recently developed IHOSM technique successfully treats on all these drawbacks. The idea is to choose a transient trajectory in advance and to keep it from the very beginning by means of HOSM. As the result, the interaction between the control and its derivatives is excluded and the semi-global convergence is assured. Also the robustness of the system performance is ensured from the beginning.

3. **Integral r-sliding mode.** The main idea of IHOSM is to provide the equality of sliding variable and it's first r+k, $k > 0$ derivatives to some chosen-in-advance transient values from the very beginning. Let the above requirements are fulfilled if

$$\sigma(t, x(t)) = s(t),$$

which means, in particular, that

$$s(t_0) = \sigma(t_0), \dot{s}(t_0) = \dot{\sigma}(t_0), ..., s^{r-1}(t_0) = \sigma^{r-1}(t_0) \quad (8)$$

at the initial moment and

$$s(t) = 0, \text{ with } t \geq t_f \quad (9)$$

Let $s^{(r-1)}(t)$ be a Lipshitz function, i.e. it is absolutely continuous, almost everywhere differentiable, and its derivative is bounded by the Lipschitz constant in its absolute value. Thus, $s^{(r)}(t)$ is a globally bounded function. The last statement implies that the function $S(t,x) = \sigma(t,x) - s(t)$ satisfies conditions (2), (3) with some changed constants, and the equality $S(t,x) \equiv 0$ can be kept by any known r-sliding controller.

3.1. **Transient time assignment for r-sliding mode.** Obviously, any constant value of the transient time $T = t_f - t_0$ requires unacceptably large control values in order to steer the trajectory to the r-sliding mode $\sigma \equiv 0$ from far-distanced initial values, and leads to very low convergence rate if the initial values of $\overrightarrow{\sigma} = (\sigma, \dot{\sigma}, ..., \sigma^{(r-1)})$ are close to zero. Thus, choose transient time being a continuous positive-definite r-sliding homogeneous function of the initial conditions of the degree 1, i.e.

$$\forall\ \kappa\, 0\ T(d_k\vec{\sigma}) \equiv \kappa T(\overrightarrow{\sigma}). \tag{10}$$

For example, the choice

$$T(\overrightarrow{\sigma}) = \lambda(|\sigma(t_0)|^{p/r} + |\dot{\sigma}(t_0)|^{p/r-1} + ... + |\sigma^{(r-1)}(t_0)|^p)^{1/p},\ \text{with } p, \lambda > 0 \tag{11}$$

is valid.

3.2. **Integral high order sliding mode controller based on optimal control technique.** One of the natural ways to choose a smooth function s(t) satisfying (8), (9) is to choose a control which connects the initial point with the origin by a trajectory optimal in some sense [12]. Note that due to the uncertainty of the original system the optimality will take place for the auxiliary dynamic system (8), (9) only.

Define $\overrightarrow{z}(t) = (z(t), \dot{z}(t), ..., z^{(r-1)}(t))$. Consider an auxiliary control system

$$\dot{z} = Az + Bv, \tag{12}$$

$z \in R^n,\ \nu \in R,\ A\ is\ n \times n$ order quadratic matrix.

$$A_{n,n} = \begin{pmatrix} 0 & 1 & 0 & \cdots & 0 \\ 0 & 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 & 1 \\ 0 & 0 & \cdots & 0 & 0 \end{pmatrix} \tag{13}$$

and

$$B_{1,n} = \begin{pmatrix} 0 & 0 & 0 & \cdots & 1 \end{pmatrix}^T \tag{14}$$

The control objective is to drive the state $\vec{z}(t_0)$ *to* $\vec{z}(t_f) = 0$ during the time $T = t_f - t_0$ (10). The task can be fulfilled by minimizing the cost function

$$I(\vec{z}(t_0, \nu(\cdot)) = \int_0^T v^2(t)dt.$$

Since the system (12)–(14) is reachable, the minimal energy control that drives the initial state to the origin exists. Let v^* be the optimal control which fulfills the task. Then v^* can be calculated by

$$v^*(t) = -B^T e^{A^T(t_f - t)})G^{-1}(t_0, t_f)e^{A(t_f - t)}\vec{z}(t_0), \tag{15}$$

where

$$G(t_0, t_f) = \int_0^T e^{A(t_f - \tau)} B B^T e^{A^T(t_f - \tau)} d\tau \tag{16}$$

is the continuous reachability Grammian [12]. Solving the differential equation (12) and substituting (15) into the solution, get the optimal trajectory

$$z(t) = e^{A(t-t_0)} z(t_0) + \int_0^t e^{A(t-\tau)} B B^T e^{A^T(t-\tau)} G^{-1}(t_0, t_f) z(t_0) e^{A^(t_f - \tau)} d\tau \tag{17}$$

Note that in order to derive the reachability gramian there is no need to perform the integration (16) which can be very messy. Taking into account that the grammian is actually solution of Lyapunov's differential equation [12]

$$\dot{P} = AP + PA^T + BB^T, \ t > t_0 \tag{18}$$

with the initial condition

$$P(t_0) = 0 \tag{19}$$

one has only to solve the initial value problem (18), (19). Since in [12] the grammian is calculated of-line, it's computation must be redone for any given initial condition. Let solve the system (18), (19) in real time. Recall that $P(\mathrm{t})$ is a quadratic symmetric matrix which depends on the reaching time T. Define

$$P_{n,n} = \begin{pmatrix} p_{1,1} & p_{1,2} & \cdots & p_{1,n} \\ p_{2,1} & p_{2,2} & \cdots & p_{2,n} \\ \vdots & \vdots & \ddots & \vdots \\ p_{n,1} & p_{n,2} & \cdots & p_{n,n} \end{pmatrix}.$$

Substituting P in (18) and solving it with initial conditions (16) get

$$v^* = -\begin{pmatrix} \frac{(T-t)^{n-1}}{(n-1)!} & \frac{(T-t)^{n-2}}{(n-2)!} & \cdots & T-t & 1 \end{pmatrix} \times$$

$$\begin{pmatrix} \frac{a_{11}}{T^{2n-1}} & \cdots & \cdots & \frac{a_{1n-1}}{T^{n+1}} & \frac{a_{1n}}{T^n} \\ \frac{a_{21}}{T^{2n-2}} & \cdots & \cdots & \frac{a_{2n-1}}{T^n} & \frac{a_{2n}}{T^{n-1}} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ \frac{a_{n1}}{T^n} & \cdots & \cdots & \frac{a_{n(n-1)}}{T^2} & \frac{a_{nn}}{T} \end{pmatrix} \times$$

$$\begin{pmatrix} 1 & T & \cdots & \frac{T^{n-2}}{(n-2)!} & \frac{T^{n-1}}{(n-1)!} \\ 0 & 1 & \cdots & \cdots & \frac{T^{n-2}}{(n-2)!} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & T & 1 \\ 0 & 0 & \cdots & \cdots & 1 \end{pmatrix} \times \begin{pmatrix} z(0) & \dot{z}(0) & \cdots & \cdots & z^{(n-1)}(0) \end{pmatrix}^T. \tag{20}$$

The optimal control $v^*(t, \vec{z}(t))$ is a uniformly bounded function in the whole space [3].

Theorem 3.1. *Let the function $s(t, \vec{\sigma}(t_0))$ satisfies conditions (8), (9) and have the uniformly bounded r-th order derivative $s^{(r)}(t, \vec{\sigma}(t_0))$ within the segment $t_0 \leq$*

$t_f(\vec{\sigma}(t_0))$. Then, with sufficiently large constant any r- sliding order finite-time convergent homogeneous controller,

$$u = -\alpha \Psi_r(\Sigma, \dot{\Sigma}, ..., \Sigma^{(r-1)}), \ \ with \ \ \Sigma = \sigma - s$$

establishes the finite-time-stable r-sliding mode $\sigma \equiv 0$ independently of the initial conditions. The equality $\sigma(t, x(t)) = s(t, \vec{\sigma}(t_0))$ is kept during the transient.

Proof. The uniform boundedness of $s^{(r)}(t)$ means that it is bounded by a certain constant which does not depend on initial condition and time. Thus the new constraint function $\Sigma = \sigma - s$ satisfies condition (6),(7) with some changed constants problem of stabilization can be solved by a corresponding-order sliding-mode controller. For example the quasi continuous controller can fit. See [9]for detailed proof. □

3.2.1. *Chattering attenuation process.* Choose some integer $k > r$ and consider $u^{(k-r)}$ as a new control. The new relative degree of the system is k. The k-th order smooth function s which satisfies conditions

$$s(t_0) = \sigma(t_0), \dot{s}(t_0) = \dot{\sigma}(t_0), ..., s^{k-1}(t_0) = \sigma^{k-1}(t_0)$$

at the initial moment and

$$s(t) = 0, \ \text{with } t \geq t_f$$

is considered. Take the transient time

$$T(\overrightarrow{\sigma}) = \lambda(|\sigma(t_0)|^{p/r} + |\dot{\sigma}(t_0)|^{p/r-1} + ... + |\sigma^{(k-1)}(t_0)|^{p})^{1/p}, withp, \lambda > 0, k > r. \tag{21}$$

Consider the new constraint function

$$\Sigma = \begin{cases} \sigma(t,x) - s(t), & t_0 \leq t \leq t_f \\ \sigma(t,x), & t > t_f \end{cases}$$

and define the bounded feedback controller by

$$u^{(k-r)} = -\alpha \Psi_k(\Sigma, \dot{\Sigma}, ..., \Sigma^{(k-1)}). \tag{22}$$

with arbitrary initial values $u(t_0), ..., u^{(k-1)}(t_0)$.

Theorem 3.2. *Let the initial conditions $t_0, s(t, \vec{\sigma} t_0), u(t_0), \dot{u}(t_0), ..., u^{(k-r-1)}(t_0)$ belong to some compact set in $R^{n+k-r+1}$. Then controller (22) with sufficiently large constant establishes the k-sliding mode $\sigma \equiv 0$ with the transient time (21). The equality $\sigma(t, x(t)) = s(t, \vec{\sigma}(t_0))$ is kept during the transient.*

Proof. The proof explicitly follows from the theorem (3.1) and boundness of optimal controller (20). □

4. **Model of insulin-glucose dynamics regulation.** The physiological model commonly used in the interpretation of the intravenous tolerance test is a so called Minimal Model developed by Bergman [1]. In this paper a modified model is considered, where some patient food intake is assumed:

$$\begin{aligned} \dot{G} &= -p_1(G(t) - G_b) - X(t)G(t) + D(t) \\ \dot{X} &= -p_2 X(t) + p_3(I(t) - I_b) \\ \dot{I} &= -n(I(t) - I_b) + \rho(t) + u_t \\ \dot{\rho} &= \frac{1}{\rho_M^{2l}} \gamma(G(t) - h)(\rho_M^{2l} - (2\rho(t) - \rho_M)^{2l}) \end{aligned} \tag{23}$$

where

- $G[mg/dl]$ is the blood glucose concentration at time $t[min]$;
- $I[\mu Ul/dl]$ is the blood insulin concentration;
- $X(t)[min^{-1}]$ is an auxiliary function describing insulin excitable tissue glucose uptake ability, its is always considered equal zero at initial time;
- $G_b[mg/dl]$ is patient's baseline glucose level;
- $I_b[\mu UL/ml]$ is patient's baseline insulin level;
- $p_1[1/min]$ is the insulin-independent rate constant of glucose uptake in muscles and liver;
- $p_2[1/min]$ is the rate constant expressing the spontaneous decrease of tissue glucose uptake ability;
- $p_3[min^{-2}(\mu Ul/ml)^{-1}]$ is the insulin-dependent rate of increase in tissue glucose uptake ability, per unit of the insulin concentration excess over the baseline insulin;
- $\gamma[\mu Ul/ml]^{-1}[mg/dl^{-1}min^{-2}]$ is the rate of pancreatic release of insulin after the bolus, per minute and per mg/dl of glucose concentration above the "target" glycemia;
- $n[min^{-1}]$ is the first order decay rate for insulin in blood;
- $h[mg/dl]$ is the threshold value of glucose above which the pancreatic cells insulin.

The system (23) assumes repeated food intake, which is not a case in model used in [1, 14]. Since the IHOSM controllers are insensitive to bounded matched disturbances, the last equation in insulin-glucose regulation model (23) can be replaced by any other suitable subsystem, not compromising the performance. One should note that $\rho \in (0, \rho_M)$ is bounded function, and $l > 1$ is some positive number. The term $D(t)$ shows the rate at which glucose is absorbed to blood following food intakes. Since in diabetic patients the normal regulatory system does not exist, this glucose absorption is considered as disturbance for the presented system. The disturbance can be modeled by any continuous non-negative bounded function $D(t) \in [0, D_M]$ and is measured in $[mg/dl/min]$. The control function $u(t)$ defines the insulin injection rate and replaces the normal regulatory system of the body, which does not exist in diabetic patients.

4.1. **Control design.** Let rewrite the model (23) in the state-space form:

$$\begin{aligned}
\dot{x_1} &= -p_1(x_1 - G_b) - x_1 x_2 + D(t)\\
\dot{x_1} &= -p_2 x_2 + p_3(x_3 - I_b)\\
\dot{x_3} &= -n(x_3 - I_b) + \rho(t) + u_t\\
\dot{\rho} &= \frac{1}{\rho_M^{2l}}\gamma(x_1 - h)(\rho_M^{2l} - (2\rho(t) - \rho_M)^{2l}).
\end{aligned}$$

The state variables x_1, x_2 and x_3 represent the blood plasma glucose concentration, the insulin effect on the net glucose disappearance and the insulin concentration in plasma respectively. The task is to stabilize the glucose concentration level in patient's blood at the basal level, which is an output-tracking problem. The tracking error is defined as the difference between the glucose concentration level and its basal value as

$$\sigma = G_b - G(t) = G_b - x_1$$

which in fact is the sliding variable. Suppose that inequalities (3) hold at least locally. Then the relative degree of the system is 3 [6] and it can be rewritten as

$$\sigma^{(3)} = h(t,x) + g(t,x)u, \tag{24}$$

where $h(t,x) = \sigma^{(3)}|_{u=0}, g(t,x) = \frac{\partial}{\partial u}\sigma^{(3)} \neq 0$ are some unknown smooth functions. To ensure the smoothness of control, let increase the relative degree of the system by one, defining the controls derivative as a new control. Then the equation (24) can be rewritten as follows:

$$\sigma^{(4)} = h_1(t,x,u) + g_1(t,x)\dot{u}, \tag{25}$$

and the problem of stabilization of σ at zero can be solved by any known fourth order sliding controllers, e.g., [8, 9].

Let $s(t)$ be a smooth function, which satisfies conditions (8), (9) with $r = 4$. Define an auxiliary function $S = s - \sigma$ and transient time as:

$$T(\overrightarrow{\sigma}) = \lambda(|\sigma(t_0)|^3 + |\dot{\sigma}(t_0)|^4 + |\sigma^{(2)}(t_0)|^6 + |\sigma^{(3)}(t_0)|^{12})^{1/12}.$$

Then the controller

$$\xi(t) = \begin{cases} 0, & t < t_0, t > t_f \\ z(t), & t \in [t_0, t_f] \end{cases}$$

$$u = \begin{cases} 0, & t < t_0 \\ -\alpha\Psi_{3,4}(\sigma - \xi, \dot{\sigma} - \dot{\xi}, \ddot{\sigma} - \ddot{\xi}, \sigma^{(3)} - \xi^{(3)}), & t_0 \leq t \leq t_f \end{cases}$$

with $z(t)$ being an optimal trajectory in (17), establishes the 4-th order sliding mode $\sigma \equiv 0$. The equality $\sigma(t) = z(t)$ is kept during the transient. Implementing the corresponding order robust exact differentiator [8] obtain the output-feedback controller

$$\xi(t) = \begin{cases} 0, & t < t_0, t > t_f \\ z(t), & t \in [t_0, t_f] \end{cases}$$

$$u = \begin{cases} 0, & t < t_0 \\ -\alpha\Psi_{3,4}(s_0 - \xi, s_1 - \dot{\xi}, s_2 - \ddot{\xi}, s_3 - \xi^{(3)}), & t_0 \leq t \leq t_f \end{cases}$$

where s_0, s_1, s_2, and s_3 are the outputs of the differentiator estimating respectively $\sigma,\ \dot{\sigma},\ \ddot{\sigma},\ \sigma^{(3)}$:

$$\begin{aligned}
\dot{s_0} &= \nu_0, \nu_0 = -3L^{1/4}|s_0 - \sigma|^{3/4} sign(s_0 - \sigma) + s_1, \\
\dot{s_1} &= \nu_1, \nu_1 = -2L^{1/3}|s_1 - \nu_0|^{2/3} sign(s_1 - \nu_0) + s_2, \\
\dot{s_2} &= \nu_2, \nu_2 = -1.5L^{1/2}|s_2 - \nu_1|^{1/2} sign(s_2 - \nu_1) + s_3, \\
\dot{s_3} &= -1.1L(s_3 - \nu_2).
\end{aligned}$$

Here L is to be larger than $sup|(\sigma^4)|$. In the simulations presented here, L=80. The time t_0 is required to ensure that the differentiator has already converged. The initial values of the differentiator are taken $s_0 = s_1 = s_2 = s_3 = 0$. Define $S_i = s_i - \xi_i$, then the fourth order sliding mode quasi-continuous controller takes form:

$$\begin{gathered}
H_1 = S_3 + 3[|S_2| + (|S_1| + 0.5|S_0|^{3/4})^{-1/3}|S_1 + 0.5|S_0|^{3/4} sign S_0)]^{-1/2} \\
(S_2 + (|S_1| + 0.5|S_0|^{3/4})^{-1/3}(S_1 + 0.5|S_0|^{3/4} sign S_0)), \\
H_2 = |S_3| + 3[|S_2| + (|S_1| + 0.5|S_0|^{3/4})^{-1/3}|S_1 + 0.5|S_0|^{3/4} sign S_0)]^{-1/2} \\
|S_2 + (|S_1| + 0.5|S_0|^{3/4})^{-1/3}(S_1 + 0.5|S_0|^{3/4} sign S_0)|, \\
\Psi_{3,4}(S_0, S_1, S_2, S_3) = -H_1/H_2.
\end{gathered}$$

The missing parameters are $\alpha = 70, \lambda = 12$. The integration was by the Euler method and the sampling step is set to be equal to the numerical integration step $\tau = 10^{-5}$.

5. **Simulation.** The parameters of the model are listed in the following table [14]:

	Normal	Patient 1	Patient 2	Patient3
p_1	0.0317	0	0	0
p_2	0.0123	0.02	0.0072	0.0142
p_3	4.92×10^{-6}	5.3×10^{-6}	2.16×10^{-6}	9.94×10^{-5}
γ	0.0039	0.005	0.0038	0.0046
n	0.2659	0.3	0.2465	0.2814
h	79.0353	78	77.5783	82.9370
G_b	70	70	70	70
I_b	7	7	7	7
G_0	291.2	220	200	180
I_0	364.8	50	55	60

TABLE 1. The values of parameters used in numerical computations

The feasibility of model (23) is shown in Fig.1. The assumption is that the person consumes food every four hours. The glucose level concentration is changing according to the food intakes. In the "healthy person" case, when the glucose level starts to increase, additional insulin is released to reduce it. However, as the glucose level reaches its low mark, insulin also converges to its basal value.

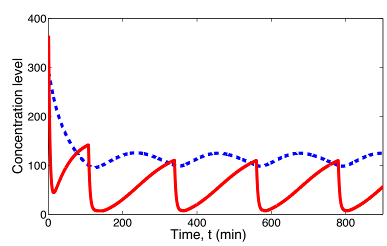

FIGURE 1. Glucose level (mg/dL, *dashed*)/insulin level ($\mu Ul/dL$, *solid*) concentration of the healthy person.

The task of glucose level stabilization in the blood of diabetic patient is completed by the controller presented in Section 4. The insulin-glucose concentration levels of three different patients are demonstrated in Fig. 2.

The basal value of glucose concentration level is considered $100[mg/dl]$ in the simulations. Any deviation of the glucose level from the normal value is immediately treated by additional insulin injection (actual control), thus keeping the glucose concentration into the blood on its basal value. Note that the amount of insulin released in the blood is always positive. The food intake treated as disturbance is $D(t) = 5sin^2(240t)$, where t is a time in $[min]$. The parameter l in the model (23) is equal 2 in the simulations.

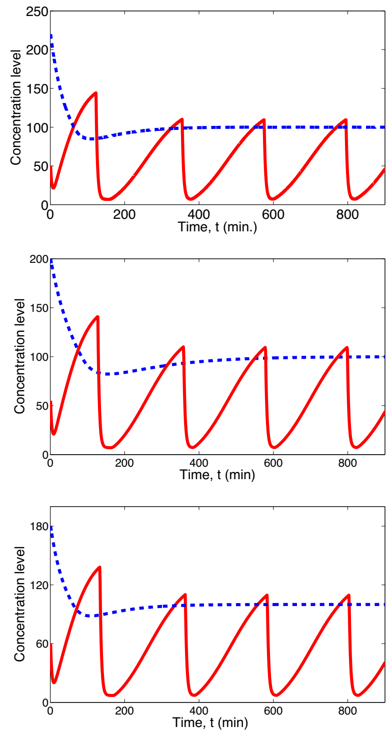

FIGURE 2. Glucose level (mg/dL, *dashed*)/insulin level ($\mu Ul/dL$, *solid*)concentration of the patients 1–3 (from top to bottom).

6. **Concluding remarks.** Robust Controller based on the Integral High Order Sliding Mode technique is proposed for glucose-insulin regulatory system. The control suppresses any kind of uncertainties from the beginning; the amount of insulin released into the blood is recalculated every time according to the body needs. The future extension of this work will take into account the effect of the pump dynamics unmodeled here.

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REFERENCES

[1] R. N. Bergman, S. Phillips and C. Cobelli, *Physiologic evaluation of factors controlling glucose tolerance in man*, J. Clin. Invest, **68** (1981), 1456–1462.
[2] F. Chee, T. L. Fernando and V. V. Heerden, *Closed-loop glucose control in critically ill patients using continuous glucose monitoring system(CGMS) in real time*, IEEE Trans. Information Technology in Biomedicine, **7** (2003), 419–425.
[3] L. Dorel, "Transient features of High Order Sliding Modes," Ph.D thesis, Tel Aviv University, 2010.
[4] A. F. Fillipov, "Differential equations with Discontinuous Right-Hand Sides," Kluwer academic Publishers, Dordrecht, 1988.
[5] U. Fisher, E. Salzsieder, E. J. Freyse and G. Albrecht, *Experimental validation of a glucose-insulin control model to simulate patterns in glucose turnover*, Comput. Methods Programs, **7** (1990), 249–258.
[6] A. Isidori, "Nonlinear Control Systems," Springer Verlag, New York, 1989.

[7] K. H. Kienitz and T. A. Yoneyama, *Robust controller for insulin pumps based on H-Infinity theory*, IEEETrans. Inf. Biomed. Eng, **40** (1993), 1133–1137.

[8] A. Levant, *Sliding order and sliding accuracy in sliding mode control*, Int. Journal of Control, **58** (1993), 1247–1263.

[9] A. Levant, *Higher order sliding modes, differentiation and output-feedback control*, Int. Journal of Control, **76** (2003), 924–941.

[10] A. Levant, *Homogeneity approach to high-order sliding mode design*, Automatica, **41** (2005), 823–830.

[11] A. Levant and L. Alelishvili, *Integral high-order sliding modes*, IEEE Trans. Automat. Control, **52** (2007), 1278–1282.

[12] F. Lewis and V. Syrmos, "Optimal Control," 2^{nd} edition, John Wiley, New York, 1995.

[13] R. S. Parker, F. J. Doyle and N. A. Peppas, *A Model-Based algorithm for Blood Glucose Concentration in Type I Diabetic Patients* IEEE Trans. Biomed. Eng., **46** (1999), 148–157.

[14] Y. B. Shtessel and P. Kaveh, *Blood glucose regulation using higher-order sliding mode control*, Int.J. of Robust and Nonlinear Control, **18** (2008), 557–569.

[15] V. Utkin, "Sliding Modes in Control and Optimization," Springer-Verlag, Germany, 1992.

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