Mathematical Modeling to Analyze Diabetes and Optimize Personally Insulin Bolus Therapy

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Outline

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About Diabetes

- Diabetes is a chronic disease characterized by high levels of sugar (glucose) in the blood. It occurs when the body either does not produce enough insulin or does not use insulin effectively.
- It is estimated that over 422 million people globally are living with diabetes. In Vietnam, that number is over 5 million and projected to continue to rise in the coming years.
- Customizing therapy to meet the unique needs of each individual is a contemporary approach to addressing diabetes in therapy.

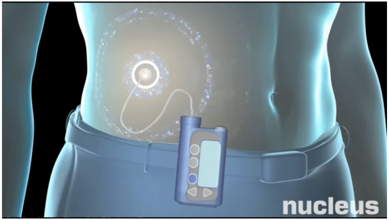
Our Goal

On the try of preventing diabetes

- Continuous glucose monitoring (CGM) uses a sensor fixed on arm, reports blood glucose every 15 min for a 2-week period.
- Daily insulin dose is supplied as the main cure.

Our Goal

- Design a mathematical model describing glucose-insulin metabolism, which is easy to analyze the insight of mellitus.
- Proposing a strategy for insulin bolus therapy.



Procedure

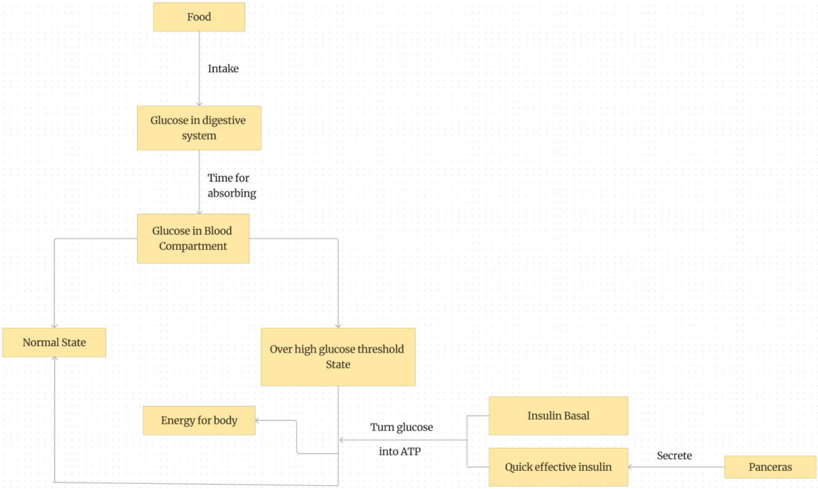
Modeling $\rightarrow$ Parameter Estimation $\rightarrow$ Bolus Strategy

Outline

Meet the Challenge

- Balancing the need for a well-captured model with its complexity is a trade-off in mathematical modeling.
- Our goal is to build a model which is simple but captures well the phenomenon.

Knowledge of the model



Criteria

- The quantities of glucose and insulin present in each compartment should be positive and finite at all times.
- Given sufficient time and in the absence of any external inputs, the concentrations of glucose and insulin in each compartment should approach zero.
- The model should account for a time delay representing the period between food consumption and its subsequent conversion within the digestive system into glucose in the blood compartment.
- Blood glucose concentrations should primarily be regulated by the hormone insulin. However, the model should also consider the influence of insulin-independent factors that contribute to glucose clearance even in the absence of metabolism.
- Rapid-acting insulin is released only when blood glucose concentrations exceed a certain threshold.
- Over time, the amount of rapid-acting insulin should naturally decrease.

Proposed Model

Our model focus on three main factors

- $G_1(t)$: Glucose disturbance of the digestive system at time t (mg/dl)
- $G_2(t)$: Glucose disturbance in the blood at time t (mg/dl)
- $I(t)$: The effective insulin level at time t (μU/ ml)

here, we separate $I(t)$ into two components: insulin basal I_b and quick effective insulin $\bar{I}(t)$. i.e. $I(t) = I_b + \bar{I}(t)$

Proposed Model

We proposed a new formula of dynamical system, which has the form

$$\begin{aligned}
\frac{dG_1(t)}{dt} &= -\alpha G_1(t) \\
\frac{dG_2(t)}{dt} &= \alpha G_1(t) - \left(\beta_1 + \beta_2 \left(\bar{I}(t) + I_b\right)\right) G_2(t) \\
\frac{d\bar{I}(t)}{dt} &= \gamma \ln\left(\exp\left(G_2(t) - T_{upper}\right) + 1\right) - \delta \bar{I}(t)
\end{aligned}$$

where

- α is rate constant of decreasing glucose level in the digestive system
- β_1 is rate constant of the hormone-independent decrease of glucose level in the blood.
- β_2 is rate constant of the hormone dependent decrease of glucose level in the blood.
- γ is rate constant of release of the hormone due to blood glucose disturbance
- δ is rate constant for the removal of the hormone due to disturbance of the blood hormone level.
- T_{upper} is threshold for high blood glucose concentration

Valid the system

We proposed a new formula of dynamical system, which has the form

$$\frac{dG_1(t)}{dt} = -\alpha G_1(t)$$
$$\frac{dG_2(t)}{dt} = \alpha G_1(t) - \left(\beta_1 + \beta_2 \left(\bar{I}(t) + I_b\right)\right) G_2(t)$$
$$\frac{d\bar{I}(t)}{dt} = \gamma \ln\left(\exp\left(G_2(t) - T_{upper}\right) + 1\right) - \delta \bar{I}(t)$$

- The system describe quite exactly glucose - insulin metabolism in above flow charts.
- All $G_1(t), G_2(t), I(t)$ are positive and have upper bound.

Outline

Table of Notation

Symbol	Meaning	Unit
$G_1(t)$	Glucose disturbance of the digestive system at time t	mg/dl
$G_2(t)$	Glucose disturbance in the blood at time t	mg/dl
$I(t)$	The effective insulin level at time t	μU/ml
I_b	Basal insulin level	μU/ml
$\bar{I}(t)$	Rapid-acting insulin level at time t	μU/ml
T_{upper}	Threshold for high blood glucose concentration	mg/dl
T_{lower}	Threshold for low blood glucose concentration	mg/dl
$G_2^{\text{obs}}(t)$	Observed data of G_2 at time t	mg/dl
$u(t)$	Insulin pump dosage at time t	μU/ml
α	Rate of decreasing glucose level in the digestive system	mg/dl/h
β_1	Rate of hormone-independent decrease of glucose level in the blood	mg/dl/h
β_2	Rate of hormone-dependent decrease of glucose level in the blood	mg/dl/h
γ	Rate of release of hormone due to blood glucose disturbance	μU/ml/h
δ	Rate of removal of hormone due to disturbance of blood hormone level	μU/ml/h

Numerical integration techniques for solving ODEs.

One common way for numerical solving ODEs is using Runge-Kutta methods. We need modify a little for adaptation (Dorman Prince method)

Parameter Estimation

The goal is to estimate the parameters, $\hat{p}$, that best fit the observed data. i.e the minima of this optimization problem

$$\min_p \sum_{i=1}^{n} q_G \frac{||G_2(t_i,p) - G_2^{\text{obs}}(t_i)||^2}{2} = \min_p \mathcal{L}(p)$$

We can choose shooting approach, which could be described as a search strategy including two stages

- First Stage: find a suitable initial guess, p_0
- Second Stage: Apply a suitable local optimizer to find $\hat{p}$

Shooting with Smoother

- First Stage (Smooth and Match Estimator - SME)

$$\boldsymbol{p}_{\text{sme}} = \arg\min_{\boldsymbol{p}} \int_0^T \left\| \left(\tilde{\boldsymbol{G}}_{\boldsymbol{2}}{}'(t) - \boldsymbol{G}_2(t, \boldsymbol{p}) \right) \right\|^2 dt$$

  where $\tilde{\boldsymbol{G}}_{\boldsymbol{2}}{}'(t)$ is obtained by smoothing the observations by spline or kernel regression

- Second Stage (Gauss - Newton optimizer)
  From initial point p_0, at step k, Gauss-Newton reads the update:

$$p^{(k+1)} = p^{(k)} - \alpha^{(k)} \cdot d^{(k)}$$

  where we use the notation

$$J_i(p) = G_2^{\text{obs}}(t_i) - G_2(t_i, \boldsymbol{p})$$

$$J(p) = (J_1, J_2, ..., J_n)^T,$$

$$\mathbf{d}^{(k)} = -\left(\nabla J^T(p^{(k)}) \cdot \nabla J(p^{(k)}) \right)^{-1} \nabla \mathcal{L}\left(\mathbf{p}^{(k)}\right),$$

  and $\alpha^{(k)}$ is the learning rate.

Numerical Simulation

- The data is from Jaeb Center for Health Research (https://public.jaeb.org/datasets/diabetes)
- We simulation for a normal and a diabetic person who both eat three meals per day

```
RecID|PtID|ParentFLAIRDeviceUploadID|CarelinkIndex|DataDtTm|CGM|SensorCal|ISIG|DataDtTm_adjusted|Unusuable|UnusableReason
1|26|144|18164|5/15/2019 9:18:15 PM|136||27.47||False
2|26|144|18165|5/15/2019 9:13:15 PM|146||29.02||False
3|26|144|18166|5/15/2019 9:08:15 PM|157||30.48||False
4|26|144|18167|5/15/2019 9:03:15 PM|166||31.75||False
5|26|144|18168|5/15/2019 8:58:15 PM|174||32.6||False
6|26|144|18169|5/15/2019 8:53:15 PM|183||33.21||False
7|26|144|18170|5/15/2019 8:48:15 PM|193||33.83||False
8|26|144|18171|5/15/2019 8:43:15 PM|202||34.55||False
9|26|144|18172|5/15/2019 8:38:15 PM|208||35.09||False
10|26|144|18173|5/15/2019 8:33:15 PM|207||35.02||False
11|26|144|18174|5/15/2019 8:28:15 PM|203||34.6||False
12|26|144|18175|5/15/2019 8:23:15 PM|197||33.61||False
13|26|144|18176|5/15/2019 8:18:15 PM|197||33.04||False
14|26|144|18177|5/15/2019 8:13:15 PM|201||33.18||False
15|26|144|18178|5/15/2019 8:08:15 PM|204||33.27||False
16|26|144|18179|5/15/2019 8:03:15 PM|197||32.61||False
17|26|144|18180|5/15/2019 7:58:15 PM|191||31.94||False
18|26|144|18181|5/15/2019 7:53:15 PM|189||31.39||False
19|26|144|18182|5/15/2019 7:48:15 PM|188||31.08||False
20|26|144|18183|5/15/2019 7:43:15 PM|189||31.15||False
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23|26|144|18186|5/15/2019 7:28:15 PM|179||30.5||False
24|26|144|18187|5/15/2019 7:23:15 PM|180||30.67||False
25|26|144|18188|5/15/2019 7:18:15 PM|188||31.24||False
26|26|144|18189|5/15/2019 7:13:14 PM|197||31.87||False
27|26|144|18190|5/15/2019 7:08:14 PM|205||32.28||False
28|26|144|18191|5/15/2019 7:03:14 PM|211||32.99||False
29|26|144|18192|5/15/2019 6:58:14 PM|212||33.31||False
30|26|144|18193|5/15/2019 6:53:14 PM|209||33.11||False
31|26|144|18194|5/15/2019 6:48:14 PM|205||32.91||False
32|26|144|18195|5/15/2019 6:43:14 PM|203||32.83||False
33|26|144|18196|5/15/2019 6:38:14 PM|207||33.3||False
```

Numerical Simulation - Normal Person

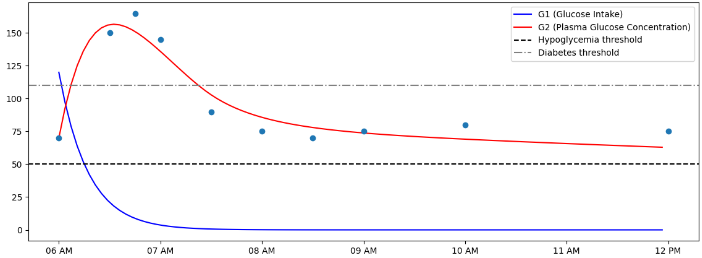

Figure: Simulation for a normal person with initial point $(G_{10}, G_{20}, I_0) = (120, 70, 10)$ and the parameter $\alpha = 2.489663451182711, \beta_1 = 0.455887849907597, \beta_2 = 0.6635348806614735, \gamma = 1.6307128293153201, \delta = 0, 2$

Numerical Simulation - Normal Person

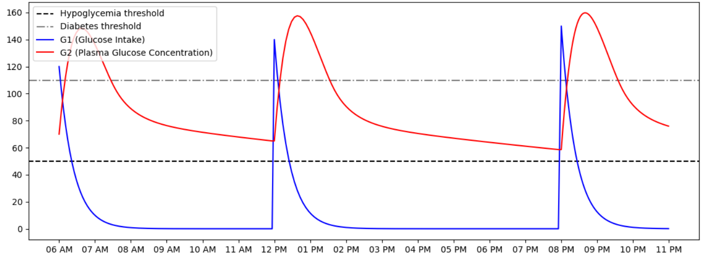

Figure: Simulation for one day with three meals

Numerical Simulation - Diabetic Person

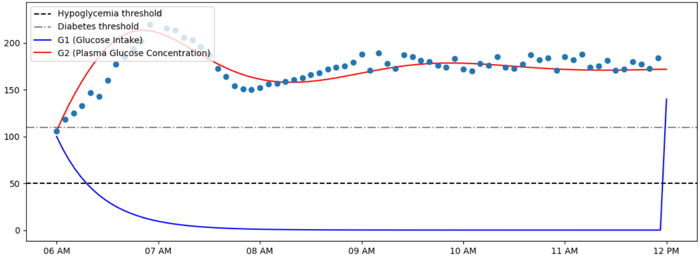

Figure: Simulation for a diabetic person with initial point $(G_{10}, G_{20}, I_0) = (120, 100, 5)$ and the parameter $\alpha = 2.3624595, \beta_1 = 0.47694835, \beta_2 = 0.29979771, \gamma = 0.08884565, \delta = 1.31002741$

Numerical Simulation - Diabetic Person

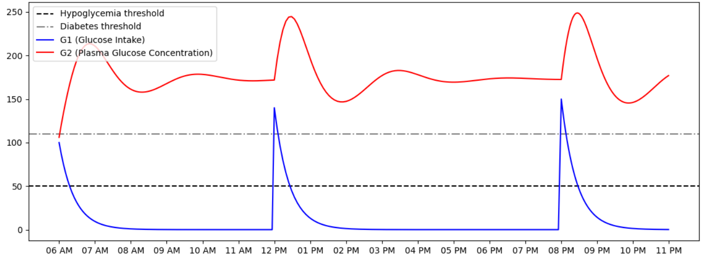

Figure: Simulation for one day with three meals

Outline

Method

Using control variable $u(t)$ which is insulin pump due to time

$$\frac{dG_1(t)}{dt} = -\alpha G_1(t)$$

$$\frac{dG_2(t)}{dt} = \alpha G_1(t) - \left(\beta_1 + \beta_2 \left(\bar{I}(t) + I_b\right)\right) G_2(t)$$

$$\frac{d\bar{I}(t)}{dt} = \gamma \ln\left(\exp\left(G_2(t) - T_{upper}\right) + 1\right) - \delta \bar{I}(t) + u(t)$$

to minimize objective function

$$\int_0^{t_0} (G_2(t) - T_{lower})(G_2(t) - T_{upper}) + \frac{1}{2}u^2(t)dt$$

Framework

- One of the way to solve this optimal control problem is Pontryagin-Differentiable-Programming framework. [Wanxin Jin, 2020]
- PDP is an end-to-end learning method that unifies learning and control by integrating deep neural networks with the Pontryagin's Maximum Principle (PMP).

Bolus therapy result

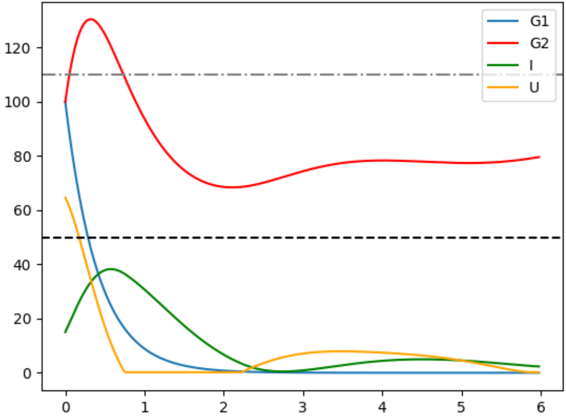

Figure: Therapy result for parameter of diabetic person with choosing $t_0 = 6, T_{lower} = 50, T_{upper} = 100$

Conclusion

- Developing a new mathematical model that accurately captures the dynamics of glucose and insulin in the human body.
- Personalizing model parameters for each patient based on their individual characteristics and medical history.
- Proposing an insulin bolus strategy that optimizes blood glucose control for each patient based on the personalized model.

Further study

- Administer the therapy of injections three times a day with meals, with one injection given every other day, for other types of diabetes therapy.
- Use a mixed dose of fast-acting and intermediate-acting insulin.
- Enlarge the size of the mathematical model, we suggest a model that

$$E(t) = A_g(t) + A_F\left(\mathrm{Relu}\left(t - \tau_1\right)\right) + A_l\left(\mathrm{Relu}\left(t - \tau_2\right)\right)$$

$$\begin{cases} \frac{dG_D}{dt} = -\frac{G_D(t)}{\alpha_1} + E(t) \\ \frac{dG_B}{dt} = \frac{G_D(t)}{\alpha_1} - \alpha_2 G_B(t) - \alpha_3 I(t) G_B(t) + Y(t) \end{cases}$$

$$\frac{dY}{dt} = \alpha_4\left(\alpha_2 G_B(t) - \alpha_5 Y(t)\right) - \beta R(t) Y(t)$$

$$\begin{cases} \frac{dI}{dt} = \frac{1}{\beta_1}\left(-I(t) + \varphi\left(V_i(t) + V_{s_c}\left(\mathrm{ReLu}\left(t - r_3\right)\right)\right)\right) \\ \frac{dS}{dt} = \frac{1}{\beta_2}\left(\left(-S(t)\right) + V_{sc}(t)\right) \\ \frac{dR}{dt} = \frac{1}{\beta_3}\left(-R(t) + Y(t)\right) \end{cases}$$

References

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Thanks for your attention!

Fourth-order Runge-Kutta method

Algorithm 1 Runge-Kutta method of order 4

$t_n \leftarrow t_0$
$u_n \leftarrow u_0$
while $t_n < T$ **do**
    $h \leftarrow \min(h_{\max}, T - t_n)$
    $k_1 \leftarrow hf(t_n, u_n)$
    $k_2 \leftarrow hf(t_n + \frac{h}{2}, u_n + \frac{k_1}{2})$
    $k_3 \leftarrow hf(t_n + \frac{h}{2}, u_n + \frac{k_2}{2})$
    $k_4 \leftarrow hf(t_n + h, u_n + k_3)$
    $u_{n+1} \leftarrow u_n + \frac{1}{6}(k_1 + 2k_2 + 2k_3 + k_4)$
    $t_{n+1} \leftarrow t_n + h$
    $n \leftarrow n + 1$
end while
return $u(T)$

Fifth-order Runge Kutta method

Algorithm 2 Runge-Kutta method of order 5

$t_n \leftarrow t_0$
$u_n \leftarrow u_0$
while $t_n < T$ **do**
  $h \leftarrow \min(h_{\max}, T - t_n)$
  $k_1 \leftarrow hf(t_n, u_n)$
  $k_2 \leftarrow hf(t_n + \frac{h}{5}, u_n + \frac{k_1}{5})$
  $k_3 \leftarrow hf(t_n + \frac{3h}{10}, u_n + \frac{3k_1}{40} + \frac{9k_2}{40})$
  $k_4 \leftarrow hf(t_n + \frac{4h}{5}, u_n + \frac{44k_1}{45} - \frac{56k_2}{15} + \frac{32k_3}{9})$
  $k_5 \leftarrow hf(t_n + \frac{8h}{9}, u_n + \frac{19372k_1}{6561} - \frac{25360k_2}{2187} + \frac{64448k_3}{6561} - \frac{212k_4}{729})$
  $k_6 \leftarrow hf(t_n + h, u_n + \frac{9017k_1}{3168} - \frac{355}{33}k_2 + \frac{46732k_3}{5247} + \frac{49k_4}{176} - \frac{5103k_5}{18656})$
  $u_{n+1} \leftarrow u_n + \frac{35k_1}{384} + \frac{0k_2}{1} + \frac{500k_3}{1113} + \frac{125k_4}{192} - \frac{2187k_5}{6784} + \frac{11k_6}{84}$
  $t_{n+1} \leftarrow t_n + h$
  $n \leftarrow n + 1$
end while
return $u(T)$

Dorman Prince method

Algorithm 3 Dorman-Prince method

$t_n \leftarrow t_0$
$u_n \leftarrow u_0$
while $t_n < T$ **do**
  $h \leftarrow \min(h_{\max}, T - t_n)$
  $k_1, k_2, k_3, k_4, k_5, k_6 \leftarrow$ **Fifth-order Runge-Kutta update**
  $u_{n+1} \leftarrow u_n + \frac{35}{384} k_1 + \frac{0}{1} k_2 + \frac{500}{1113} k_3 + \frac{125}{192} k_4 - \frac{2187}{6784} k_5 + \frac{11}{84} k_6$
  $u_{\text{hat}} \leftarrow u_n + \frac{5179}{57600} k_1 + \frac{0}{1} k_2 + \frac{7571}{16695} k_3 + \frac{393}{640} k_4 - \frac{92097}{339200} k_5 + \frac{187}{2100} k_6$
  $t_{n+1} \leftarrow t_n + h$
  $n \leftarrow n + 1$
  $e_n \leftarrow u_{\text{hat}} - u_{n+1}$
  if $|e_n| > \text{TOL}$ **then**
    $h \leftarrow \frac{h}{2}$
    continue ▷ Retry with a smaller step size
  end if
  $\text{TOL} \leftarrow 0.84 \left(\frac{\text{TOL} \cdot h}{|e_n|} \right)^{0.25}$ ▷ Adapt the tolerance
  $u_n \leftarrow u_{n+1}$
end while
return $u(T)$

PDP framework

$$\boldsymbol{\Sigma}(\boldsymbol{\theta}): \quad \begin{aligned} \text{dynamics:} \quad & \boldsymbol{x}_{t+1} = \boldsymbol{f}(\boldsymbol{x}_t, \boldsymbol{u}_t) \quad \text{with} \quad \boldsymbol{x}_0, \\ \text{control policy:} \quad & \boldsymbol{u}_t = \boldsymbol{u}(t, \boldsymbol{x}_t, \boldsymbol{\theta}). \end{aligned} \tag{7}$$

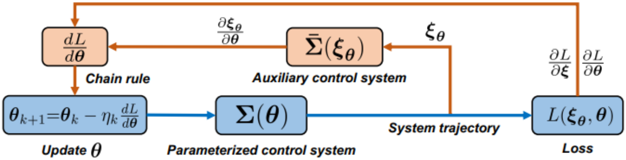

Figure 2: PDP end-to-end learning framework.