Simulation in Biomedicine

Group 01

# Estimation of nonlinear differential equation model for glucose-insulin dynamics in type I diabetic patients using generalized smoothing[1]

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# Contents:

# Introduction:

Diabetes mellitus is a chronic metabolic disease associated with changes in glucose metabolism that affect the glucose levels in tissues and causes issues in the blood. Type I Diabetes Mellitus is defined based on the whole insulin deficiency. Based on the insulin percentage in a person's body, the insulin is injected or infused using various therapies. But infrequent testing of blood sugar levels does not show or provide with possible glucose control levels. Alos it is said, there is no proper algorithm in calculating or validating the regulation of glucose levels. From the article, we would like to introduce a parsimonious model, which could used to in validating the glucose-insulin dynamics for the patients, along with algorithms for automated insulin delivery system.

Most of the existing models describe glucose-insulin dynamics in terms of a system of non linear ordinary differential equations which has not been feasible in converting it into estimating statistical models because of the large number of variables describing the time-level dependents of glucose, insulin and other parameters.

# Project Task

## Task 1

Outline of model

A glucose-insulin dynamics models in Type 1 Diabetes Mellitus patients are comprised of three components:

- glucose metabolism model

- meal model

- insulin kinetics model.

The article suggests a model below:

$$\mathbf{G}(t) = b_0 + b_1 G(t) + b_2 G(t) I(t) + \sum_{i=1}^{L} \mu_i (t - t_{Mi})_+ exp(v_i (t - t_{Mi})_+),$$

$$\mathbf{I}(t) = -c_1 I(t) + c_2 r(t)$$

Where,

x1(t) = G(t) plasma glucose concentration

x2(t) = I(t) Plasma Insulin Concentration

Θ = [2.08;-4.60;-7.99;-2.91; 0.08;2.15;-0.07; 0.39;-0.03];

b0 = Θ(1); %is the constant increase in plasma glucose concentration due to constant baseline liver glucose release

b1 = exp(Θ(2)); %is the spontaneous glucose 1st order disappearance rate,

b2 = exp(Θ(3)); %is the insulin-dependent glucose disappearance rate.

Meal and Glucose release in the blood from Gut,

Starting time of the meal,

v1 = -abs(Θ(7)) - is the parameter related to the rate of glucose absorption from the gut meu1 = abs(Θ(6)) - is the product of the distribution volume and the constant related to the total amount of carbohydrates consumed

meu2 = abs(Θ(8));

v2 = -abs(Θ(9));

c1 = exp(Θ(4)); % is the insulin 1st order disappearance rate

c2 = Θ(5); % is the reciprocal of the volume of the insulin distribution space

r(t) [mU/min] is the IV insulin infusion rate

For Type 1 Diabetes Mellitus patients, the pancreas does not release insulin, and insulin concentration I(t) is independent of G(t). Thus, we consider the following non-homogeneous nonlinear ODE model for an individual Type 1 Diabetes Mellitus subject on IV insulin delivery and consuming L meals at times tM1, . . . , tML

## Solution:

Model Description

Model 2.2 presents a parsimonious model of glucose-insulin dynamics in Type 1 Diabetes (T1DM) patients who are receiving intravenous (IV) insulin infusion and consuming meals.

Components of the Model

Glucose metabolism model: Describes regulation of glucose uptake and production, represented by the derivative of plasma glucose concentration (G(t)) as a function of glucose and insulin concentrations.

Meal absorption model: Describes the rate of glucose appearance from intestinal absorption of meals.

Insulin kinetics model: Describes the rate of change of plasma insulin concentration (I(t)) based on IV insulin infusion rate and insulin clearance/distribution kinetics.

Model Equations

Equation 2.2: Differential equation describing the derivative of plasma glucose concentration (G(t)) as a function of baseline glucose production, glucose clearance, insulin-dependent glucose clearance, and glucose absorption from meals.

Equation 2.3: Differential equation describing the derivative of plasma insulin concentration (I(t)) as a function of insulin clearance and IV insulin infusion rate.

Parameters

Parameters in the model equations include: baseline glucose production (b0), glucose clearance rates (b1, b2), insulin clearance rate (c1), insulin distribution volume (c2), glucose appearance from meals (μ, ν).

So in summary, model 2.2 presents a system of nonlinear ordinary differential equations to model glucose-insulin dynamics in T1DM

patients receiving IV insulin and consuming meals, based on submodels of glucose metabolism, meal absorption, and insulin kinetics.

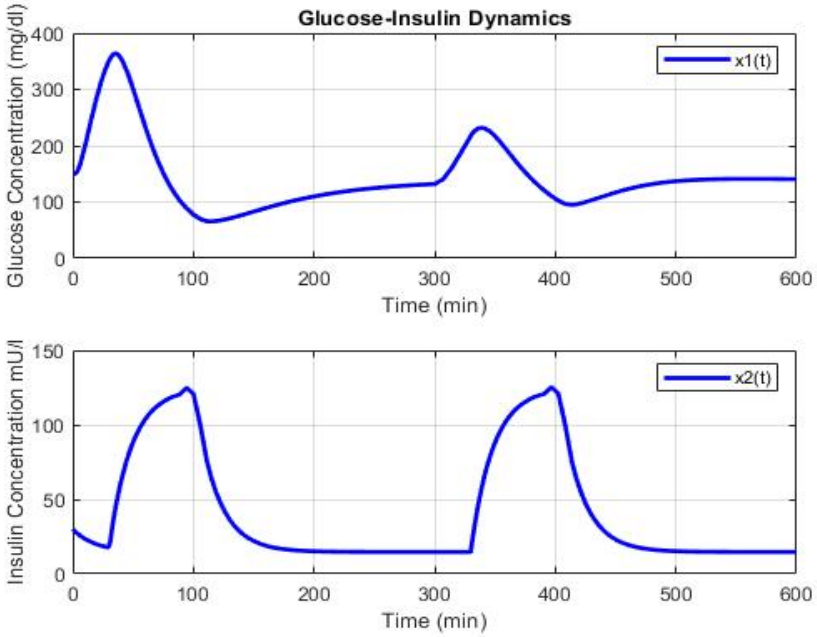
## Task 2

Solve the ODE system using the parameters Θ.

The study conducted a performance evaluation for the optimization for a Non-Linear and Non-Homogeneous for the ODE model. The numeric solution was given to the above model with the given parameters below:

$$\theta = [2.08, -4.60, -7.99, -2.91, 0.08, 2.15, -0.07, 0.39, -0.03]$$

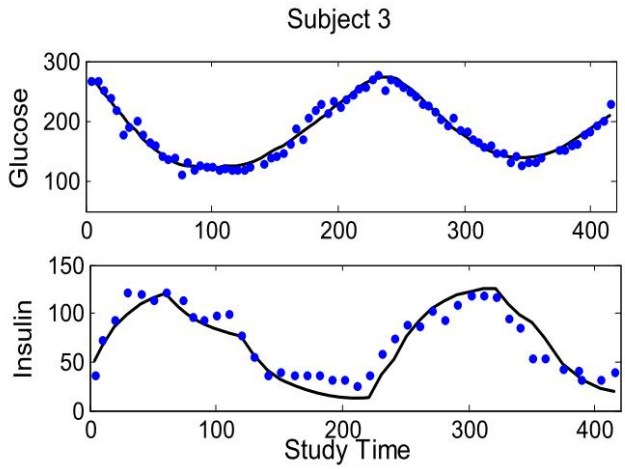
## Solution:



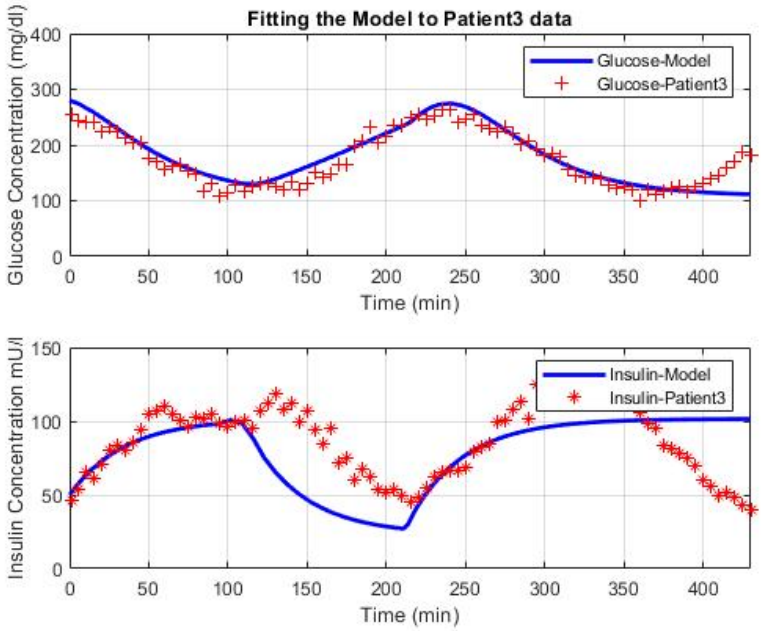

## Task 3

To reproduce the fitting results for subject 3 by transferring the measurements from Fig. 2.

$$\theta = [2.08, -4.60, -7.99, -2.91, 0.08, 2.15, -0.07, 0.39, -0.03]$$




## Solution:




## Observation:

Several issues were encountered while completing the tasks:

For Task 2, the explanation provided for insulin supply was somewhat incomplete and non-quantitative, making it difficult to appropriately parameterize the corresponding value in the model. A more detailed

numerical description would have facilitated model implementation.

In Task 3, extracting the data for Patient 3 from Figure 2 introduced inaccuracies. The large scale used on the axes made finer distinctions between data points values indistinct, precluding exact reading. As a result, the parameters fed to the fminsearch function for model fitting had to be approximated.

Minor modifications were made to the model structure for Task 3 to accommodate input of all required parameters.

Though the model fitting achieved acceptable results, the outcome was not fully accurate. There were detectable divergences between the parameter values generated by fminsearch for Patient 3 and those published in the original study describing that patient.

Overall, more precise explanations, smaller graphical scales, and exact datasets would likely have yielded model parameterization and fitting with higher fidelity to published patient data and model behavior.

let me know if need any thing else, I am sending you the code files with correct names.

## Conclusion:

For this study, our approach was implemented for the optimization in profiling the estimation of models by non-linear and/or non-homogeneous ODE systems. By applying the optimised profile to glucose and insulin

data in Type 1 Diabetes Mellitus patients, a plausible result was obtained for the given parsimonious model of glucose-insulin dynamics. This approach could render a good model in insulin delivery and other issues involving chronic medical management.

## References:

[1] - Chervoneva I, Freydin B, Hipszer B, Apanasovich TV, Joseph JI. Estimation of nonlinear differential equation model for glucose-insulin dynamics in type I diabetic patients using generalized smoothing. Ann Appl Stat. 2014 Jun;8(2):886-904. doi: 10.1214/13-aoas706. Epub 2014 Jul 1. PMID: 33833847; PMCID: PMC8025877.