Mixed Meal Model in Type 1 Diabetes
—Minimal Compartments of Triglycerides and Non-esterified Fatty Acids*

Claudia Cecilia Yamamoto Noguchi† and Eiko Furutani†

In keeping with the recent recognition of the additive impact of dietary fat on postprandial blood glucose (BG) levels in type 1 diabetes mellitus (T1DM), we include a number of physiologically-relevant improvements to a previous conceptual minimal mixed meal model by considering independent signals for gut transit of carbohydrates and dietary fat, and explicit representation of fatty acid spillover in the compartmental representation of non-esterified fatty acids (NEFA) to represent lipid-derived insulin resistance as the complementary increase in triglycerides (TG) and NEFA levels. Simulation results of postprandial plasma lipids and BG excursion compared with clinical data in the literature demonstrate the validity and potential of the minimal mixed meal model proposed.

1. Introduction

Type 1 diabetes mellitus (T1DM) is a chronic disease caused by β-cell apoptosis, which results in a complete inability to secrete endogenous insulin and such characterized by extremely high blood glucose (BG) levels, especially post-meal. Currently, T1DM has no cure but a continuous management of BG levels through intensive insulin therapy—which consists of exogenous insulin administration in a basal-bolus combination—in order to prevent long-term complications. Specifically, bolus insulin requires an exact dose calculation at every mealtime according to the specific carbohydrate content of the meal in order to maintain diurnal BG levels within the normal range of 70–180 mg/dL (3.9–10.0 mmol/L) post-meal[1].

To assist T1DM patients with their BG management, recent technologies—several of them relying on mathematical modeling of glucose-insulin metabolism—include diabetes diagnostics, decision support systems for insulin dosing and smart BG sensors[2]. In recent years, BG control systems that maintain normoglycemia automatically by closed-loop continuous infusion of insulin have taken particularly large strides towards its commercial development. Some studies[3] already have had successful results for overnight free-living conditions, whereas more recently there is focus on postprandial BG control[4] and its compliance with clinical guidelines considers patient input of the carbohydrate content of the meal. Nonetheless, BG control performance has been shown to be undermined by consumption of high-fat mixed meal[5], thus revealing that not only glucose but also fatty acid metabolism is indispensable in the mathematical representation of postprandial glucose-insulin metabolism in T1DM.

Representative models of fatty acid dynamics include Boston model[6] and others with detailed consideration of counter-regulatory hormones[7], whereas mixed meal models that include gut transit and the ultimate impact on BG levels are, to our knowledge, limited to that of Roy and colleagues[8]. Its physiological representation, nonetheless, includes two ‘remote’ compartments with unknown physiological conceptualization and a questionable direct incorporation of fatty acid into the glucose compartment to represent insulin resistance. In view of this, we previously developed a minimal mixed meal model in T1DM[9] that includes an explicit representation of the two major effects of lipids on postprandial glucose-insulin metabolism given by the delaying effect of dietary fat on gut transit of carbohydrates and lipid-derived insulin resistance due to dietary fat consumption in a mixed meal[10]. More complex mechanisms involved in postprandial lipid dynamics and its intricate interaction with glucose-insulin metabolism, however, are not appropriately represented in such conceptual model, which additionally reflects on a poor ability to reproduce clinical data in patients with T1DM in particular.

In the present study, we improve our original model proposal to obtain a more accurate representation of the impact of a mixed meal on postprandial glucose and fatty acid metabolism by including relevant physiological mechanisms intertwining the two of them, as theorized by the well-known Randle cycle[11] and glucose-fatty acid cycle reversed[12]. In Section 2,
we first provide an overview of the conceptual mixed meal model, and then give a detailed explanation of the improvements proposed to the mathematical representation of gut transit of dietary fat and lipid-derived insulin resistance. In Section 3, model parameters are validated with simulations in Matlab utilizing clinical data in the literature. Lastly, in Sections 4 and 5, we include substantial discussion and conclusions, respectively.

2. Mixed Meal Model in T1DM

In the present section, we first introduce our previous conceptual mixed meal model with a minimal compartmental representation of glucose-insulin and fatty acid metabolism in T1DM[9], followed by the improvements proposed in the present study by considering physiologically-relevant mechanisms as detailed in the forthcoming subsections.

2.1 Conceptual Mixed Meal Model

The original conceptual model in T1DM[9] (Fig. 1) was based on a minimal compartmental representation of gut transit of carbohydrates as glucose equivalent according to their food-specific absorption rate, subcutaneous insulin absorption kinetics and a minimal compartmental representation of glucose-insulin metabolism in T1DM (Fig. 1, solid lines)[13,14] with single-compartmental model of interstitial insulin concentration $X(t)$ and plasma glucose concentration $G(t)$ given respectively by

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3 I(t), \quad (1)$$

$$\frac{dG(t)}{dt} = -X(t)G(t) + p_1 (G_b - G(t)) + \frac{G_{eq}(t)}{V_1}. \quad (2)$$

In the above, $I(t)$ is plasma insulin concentration, $p_1$ is total non-insulin-mediated glucose uptake, $p_2$ indicates the rate of spontaneous decrease of tissue glucose uptake ability, $p_3$ expresses the rate of insulin-dependent glucose uptake ability in peripheral tissue and liver, $G_{eq}(t)$ is meal-derived glucose appearance and $V_1$ is volume of distribution.

Such mathematical model was extended to a mixed meal models (Fig. 1, dotted lines) that includes gut transit of dietary fat and a novel minimal compartmental proposal of fatty acid metabolism specifically for exogenous and endogenous pathways represented by triglycerides (TG) and non-esterified fatty acids (NEFA), respectively.

The biphasic delaying effect in gut transit of carbohydrates by the presence of dietary fat was represented with a gastric emptying delay $\tau_{mix}$ and a pure delay $L_{mix}$ as

$$\frac{dG_{eq}(t)}{dt} = \frac{1}{\tau_{dg} + \tau_{mix}} \left( -G_{eq}(t) + \bar{G}_{eq}(t - L_{mix}) \right), \quad (3)$$

where $G_{eq}(t)$ is gut absorption of glucose-equivalent from carbohydrate, $\bar{G}_{eq}(t)$ is glucose-equivalent with maximum rate of glucose appearance and $\tau_{dg}$ is delay of food-specific carbohydrates as detailed elsewhere[14]. The representation of gut transit of dietary fat is derived from the glucose-equivalent signal of carbohydrates, based on the assumption that food-specific carbohydrates absorption affected dietary fat as well.

Moreover, such conceptual proposal included two single-compartmental models for TG and NEFA dynamics given respectively by

$$\frac{dT(t)}{dt} = -p_4 X(t)T(t) + p_5 (T_b - T(t)) + \frac{F_{cho}(t)}{V_T}, \quad (4)$$

$$\frac{dF(t)}{dt} = -p_6 X(t)F(t) + p_7 (F_b - F(t)). \quad (5)$$

Here, $T(t)$ is plasma TG levels with steady-state basal value $T_b$, $p_4 X(t)T(t)$ is plasma TG clearance by insulin-dependent activation of lipoprotein lipase, $F_{cho}(t)$ is plasma TG appearance as chylomicron-triglyceride (CM-TG), $p_5 (T_b - T(t))$ is hepatic TG balance from very-low-density-lipoprotein (VLDL-TG) and $V_T$ is distribution space of plasma TG; whereas $F(t)$ is plasma NEFA concentration with basal levels $F_b$, $-p_6 X(t)F(t)$ is the antilipolytic effect of insulin and $p_7$ is rate of NEFA release from adipose tissue into plasma due to hormone-sensitive lipase.

Considering the original definition of insulin sensitivity $S_i = p_b/p_2[15]$, $T(t)$ was particularly utilized to represent lipid-derived insulin resistance after consumption of a high-fat mixed meal as

$$p_3(t) = p_{30} - p_b(T(t) - T_b), \quad (6)$$

where $p_{30}$ is the original parameter of the minimal
model previously proposed[13] and $p_8$ adjusts the degree of lipid-derived insulin resistance.

The mathematical representation of $p_9(t)$ in eq. (6), however, does not include the most well-known effect of free fatty acids on increase in insulin resistance as postulated by the Randle cycle. Thus, in the following subsections we incorporate some physiologically-relevant improvements (see Fig. 1, thick lines) including (a) representation of gut transit of dietary fat independently from carbohydrates, and (b) lipid-derived insulin resistance.

2.2 Gut Transit of Dietary Fat

After consumption of a mixed meal, dietary fat—which mainly consists of TG and cholesterol—is broken down into monoglycerides and fatty acids in the stomach by the action of gastric lipase and sent to the small intestine for its absorption through the lysosomal system independent of the rate of absorption of carbohydrates[16]. Hence, in the present model, gastrointestinal transit of dietary fat is represented by considering not only increase in TG but also NEFA (fatty acid spillover) afterwards. The compartmental diagram of the present model is shown in Fig. 2, wherein fatty acid metabolism includes fatty acid cycle reversed. Thus, in the follow-

\begin{align*}
\frac{dV(t)}{dt} &= -k_FV(t) + F_{\text{food}}(t), \\
\frac{dF_{\text{fat}}(t)}{dt} &= \frac{1}{\tau_{\text{chy}}} (F_{\text{fat}}(t) - L_{\text{mix}} - F_{\text{chy}}(t))
\end{align*}

where $F_{\text{fat}}(t)$ is gut transit of dietary fat, $k_F$ is rate of absorption of lipids and $\tau_{\text{chy}}$ is the time-constant to represent the biphasic gut transit pattern of fat absorption.

2.3 Insulin Resistance

The mathematical representation of lipid-derived insulin resistance in the present study is improved by considering not only increase in TG but also NEFA (see Fig. 1) as an alternative source according to the theoretical explanation of fuel selection between glucose and fatty acids as proposed by the Randle cycle[11]. Thus, we include fatty acid spillover from CM-TG into the NEFA pool in the single-compartmental model in eq. (5) as

\begin{align*}
\frac{dF(t)}{dt} &= -p_6X(t)F(t) + p_7(F_b - F(t)) + \frac{F_{\text{sp}}(t)}{V_{\text{sp}}}
\end{align*}

where $V_{\text{sp}}$ is distribution space of fatty acid spillover, which is represented by

\begin{align*}
\frac{dT_{\text{sp}}(t)}{dt} &= \frac{1}{\tau_{\text{sp}}} (T(t) - T_{\text{sp}}(t))
\end{align*}

$F_{\text{sp}}(t) = T_{\text{sp}}(t) - T_b$

given that $T_{\text{sp}}$ is spillover from postprandial CM-TG appearance, $\tau_{\text{sp}}$ is the time-constant for spillover during late postprandial state and $F_{\text{sp}}(t)$ is spillover-derived NEFA appearance from the splanchnic bed.

Considering the above single-compartmental models for TG and NEFA dynamics, the novel proposal of lipid-derived insulin resistance is extended to

\begin{align*}
p_3(t) &= p_{30} - p_4 \Delta T(t) - p_5 \Delta F(t),
\end{align*}

where variation in $p_3(t)$ includes the representation of glucose-fatty acid cycle reversed[12], $\Delta T(t)$ and $\Delta F(t)$ are increase in insulin resistance due to postprandial TG and NEFA dynamics, respectively, as given by

\begin{align*}
\Delta T(t) &= \Delta T(t),
\Delta F(t) &= \begin{cases} c_4 (1 - e^{-c_5 \Delta F(t)}), & \Delta F(t) > 0 \\
0, & \text{otherwise.}
\end{cases}
\end{align*}

In eq. (13), $\Delta T(t)$ is the postprandial increase in TG levels caused by dietary fat consumption since $T(t)$ is characterized by circulating TG-rich lipoprotein particles in plasma due to the presence of cycling VLDL in the liver and CM-TG appearance after a high-fat meal; whereas in eq. (14), $\Delta F(t) = F(t) - F(0)$ is NEFA-derived insulin resistance due to elevation above basal levels.

Hence, the physiological representation of lipid-induced insulin resistance in eq. (12) includes increase in TG in the following 7 hours after dietary fat consumption, with an extended state due to increase in NEFA (fatty acid spillover) afterwards. The compartmental diagram of the present model is shown in Fig. 2, wherein fatty acid metabolism includes fatty acid spillover, the Randle cycle and glucose-fatty acid cycle reversed.

2.4 Parameters Setting

For a physiologically-relevant mixed meal model, clinical values from the literature are carefully considered as follows. Parameters of gut transit of carbohydrates and dietary fat are $\tau_{\text{mix}} = 20\text{ min}$ and $L_{\text{mix}} = 23\text{ min}$ in eq. (3) according to clinical data in patients.
with T1DM specifically\cite{17}, \( k_F = 0.01 \text{ min}^{-1} \) in eq. (7) and \( \tau_{\text{chy}} = 170 \text{ min} \) in eq. (8) are determined from a clinical test\cite{18} wherein the difference in the half-time gastric retention between a low-fat (30 min) and TG-rich (200 min) meal.

Considering that the maximum postprandial increase in TG levels is IR\(_{p,max} = 1 \text{ mmol/L} \) after a very large fat load in patients with T1DM\cite{19}, and the maximum reduction in insulin sensitivity due to postprandial increase in TG levels is one-half\cite{20}, we set parameter \( p_8 = p_{30}/2 \) in eq. (12). Moreover, the degree of insulin resistance due to NEFA levels in eq. (14) is determined from previous studies\cite{21} that indicate a dose-response relationship with a decrease in glucose uptake of 22\%, 30\% and 34\% for lipid-infused plasma NEFA increases above basal levels of 294 \( \mu \text{mol/L} \) (from 401 to 695 \( \mu \text{mol/L} \)), 865 \( \mu \text{mol/L} \) (386 to 1251 \( \mu \text{mol/L} \)) and 1272 \( \mu \text{mol/L} \) (from 416 to 1688 \( \mu \text{mol/L} \)), respectively. Having set \( p_8 = p_{30} \), parameters in the exponential function in eq. (14) are fitted with \( c_1 = 0.33 \) and \( c_5 = 3.6 \) (see Fig. 3) for a maximum reduction of IR\(_{p,max} = 34\% \) for NEFA increases above \( F_b \).

To represent postprandial lipid metabolism in patients with T1DM, parameters are fitted to clinical data as follows. Fitting of model parameters for plasma TG compartment in eq. (4) include \( p_7 = 0.35 \text{ min}^{-1} \), \( p_8 = 6.4 \times 10^{-2} \text{ min}^{-1} \) and \( V_T = 370 \text{ L} \), whereas for NEFA dynamics in eq. (9), in particular, we follow a two-step procedure given by (a) validation of parameter \( p_7 = 2.5 \times 10^{-2} \text{ min}^{-1} \) for rate of lipolysis and steady-state value \( F_b = 1.5 \text{ mmol/L} \) under insulin-deprived conditions specifically for T1DM\cite{22} and (b) parameter fitting of \( p_6 = 89 \text{ min}^{-1} \), \( V_{sp} = 7.8 \text{ L} \) and fatty acid spillover \( \tau_{sp} = 180 \text{ min} \) with clinical data of postprandial NEFA dynamics in T1DM\cite{23}.

3. Simulation

In this section we present simulation results of the proposed mixed meal model with parameter fitting considering clinical data in patients with T1DM.

3.1 Simulation Settings

Initial settings for each simulation are set to basal conditions given by \( T_{sp}(0) = T_b \) and \( p_{30}(0) = p_{30,b} \), with remaining parameters of glucose-insulin metabolism in T1DM specified elsewhere\cite{13,14}. Initial conditions for lipid metabolism consider each specific study as:

i) Postprandial TG\cite{19}: Large dietary fat intake of 100 g with initial values \( G(0) = 113 \text{ mg/dL} \) (6.25 \( \text{mmol/L} \)), \( T(0) = 0.71 \text{ mmol/L} \), \( F(0) = 0.55 \text{ mmol/L} \) and basal insulin \( u_b(t) = 6.7 \times 10^{-3} \text{ IU/min} \).

ii) Insulin-deprived NEFA\cite{22}: Initial values are set to \( G(0) = 113 \text{ mg/dL} \) (6.25 \( \text{mmol/L} \)), \( T(0) = 0.71 \text{ mmol/L} \), \( F(0) = 0.85 \text{ mmol/L} \) with remaining values set to zero due to insulin-deprived conditions and absence of meal consumption.

iii) Postprandial NEFA\cite{23}: Mixed meal with carbohydrate intake of 65.3 g, dietary fat intake of 28 g, and initial values \( G(0) = 130 \text{ mg/dL} \) (7.25 \( \text{mmol/L} \)), \( T(0) = 0.71 \text{ mmol/L} \), \( F(0) = 0.24 \text{ mmol/L} \), constant basal insulin \( u_b(t) = 15.9 \times 10^{-3} \text{ IU/min} \) and single-bolus \( u_c(t) = 6 \text{ IU} \) at \( t = -5 \text{ min} \).

3.2 Simulation Results: Triglycerides

Based on i) above, simulation of postprandial TG in patients with T1DM after consumption of a mixed meal with 100 g of dietary fat content is shown in Fig. 4, wherein not only the peak in TG levels but the excursion throughout the postprandial state is accurately represented by the single-compartmental model given in eq. (4).

3.3 Simulation Results: NEFA

Considering the initial settings in ii) and iii), simulation of plasma NEFA dynamics by the minimal compartmental proposal in eq. (9) are given in Fig. 5 and Fig. 6 for insulin-deprived conditions\cite{22} and single-meal consumption\cite{23}, respectively. The former shows the adequacy in parameter fitting for rate of lipolysis under complete absence of insulin from clinical data of T1DM patients, whereas the latter demonstrates the accurately representation of postprandial NEFA excursion and specifically the increase in NEFA levels above \( F(0) > t > 270 \text{ min} \) as a result of fatty acid spillover, which in comparison our previous conceptual model is unable to reproduce. Nonetheless, the peak in postprandial BG excursion does not reflect clinical data as expected, particularly during early postprandial excursion at \( t < 200 \text{ min} \) arguably due to the lack of further specification of the type of carbohydrate included in the clinical test design.

4. Discussion

In the present study we consider a number of improvements to a previous mixed meal model in T1DM to enhance the physiological representation of glucose and fatty acid metabolism for postprandial state. Different from the original proposal\cite{9}, gut transit of carbohydrates and dietary fat are represented separately, and the mathematical representation of fatty acid metabolism includes postprandial fatty acid
spillover $F_{sp}(t)$, the Randle cycle as IR$_F$ and glucose-fatty acid cycle reversed in $p_3(t)$, although the limited clinical data only permits model parameter setting and model validation for plasma BG and lipid dynamics. As shown in Fig. 4, the impact of dietary fat on TG levels is accurately represented throughout the postprandial state for the carbohydrate-independent signal $F_{chy}(t)$, whereas NEFA dynamics in Figs. 5 and 6 demonstrate an accurate representation of the rate of lipolysis and the gradual increase in NEFA levels due to fatty acid spillover from postprandial CM-TG metabolism, respectively, which our previous conceptual model[9] is neither able to reproduce.

Although carbohydrates and dietary fat from a mixed meal are digested as chyme in the same physiological chamber, the biphasic nature of gut transit of mixed meals is represented separately for each macronutrient since the rate of gastric emptying of the fat component is basically slower than that of carbohydrates[24]. Moreover, despite the existence of some evidence, there is no absolute consensus about the relationship between BG levels and gastric emptying due to conflicting results from clinical studies[25], except for an apparent normal gastric emptying at normoglycemia[26]. Such a complex mechanism has not been explicitly considered in any mathematical representation of gut transit to this date[27], and thus the model proposed in the present study is not associated with instantaneous BG levels but only the macronutrient content of the mixed meal.

The minimal compartmental representation for plasma TG and NEFA dynamics proposed in the present study have an identical structure to that of the glucose compartment of Bergman minimal model. Nonetheless, since the activation/deactivation of insulin-dependent TG and NEFA uptake depends on different enzymes, i.e., lipoprotein lipase and hormone-sensitive lipase, respectively, different parameter values for each compartment are deemed necessary. The representation of insulin-dependent NEFA uptake follows a nonlinear dose-response relationship as quantified in previous studies[28], and excessive lipolysis due to absence of endogenous insulin secretion in patients with T1DM is determined by elevated values of $F_{b}$. Instantaneous variation in $p_3(t)$ within the physiologically-relevant range of $0.5 \leq p_3(t) \leq 1.33$ $p_{30}$ as proposed in the present study responds to the careful parameter setting of $p_8$ and $p_9$, provided that the concomitant effect of TG and NEFA metabolism does not occur simultaneously. Specific conditions such as hypertriglyceridemia and high fasting NEFA levels are beyond normal postprandial lipid metabolism, and thus are not considered in our study.

As the present study proposes a mixed meal model of glucose and fatty acid metabolism with a minimal compartmental approach, a direct comparison with the mixed meal model proposed by Roy and colleagues[8] becomes imminent. In Roy model, the representation of fatty acid metabolism considers two remote-compartment for insulin-dependent fatty acid uptake and fatty acid, and one accessible compartment for fatty acids concentration, although the physi-
iological significance of the remote insulin and fatty acid compartments (Y and Z in their proposal) remains to be elucidated. The effect of fatty acids on glucose metabolism is directly included in the glucose compartment $G(t)$ of the minimal model. Compared to this, in our study we emphasize the physiological mechanism involved by making a clear distinction between exogenous (meal-derived) and endogenous lipid metabolism as represented by two single-compartment models for TG and NEFA dynamics, respectively, which are utilized for a physiologically-relevant representation of lipid-derived insulin resistance as the supplementary increase in plasma TG and NEFA above basal levels.

In the current understanding of the etiology of insulin resistance, it is commonly attributed to fatty acids. Nevertheless, the physiological interpretation proposed in the present study (see Fig. 2) includes not only the well-known Randle cycle[11] but also glucose-fatty acid cycle reversed[12]. Despite the apparently opposite theoretical standpoint from their respective authors, we considered an original interpretation with a complementary effect on glucose-fatty acid metabolism. To the best of our knowledge, the present model is the first that explicitly considers the late-postprandial increase in NEFA levels as a result of fatty acid spillover as represented with eqs. (10) and (11) assuming a direct relationship between the amount of dietary fat consumed and degree of spillover[29].

We acknowledge that further identification of model parameters for varying proportions of mixed meals is a necessary process for the complete validation of the present proposal. Even though lipid-derived insulin resistance is the hallmark of high-fat meal consumption, it cannot be directly measured in clinical studies and thus development of alternative methods for its quantitative measurement need further investigation as well.

5. Conclusions

In the present study, we improved an original mixed meal model by including the mathematical representation of a number of physiological mechanisms involving glucose and fatty acid metabolism. Parameter fitting with clinical data in the literature demonstrates the potential of the minimal compartmental approach proposed in the present mixed meal model in T1DM.

Acknowledgements

This research was supported in part by Grant-in-Aid for Scientific Research (C) (KAKENHI) from the Japan Society for the Promotion of Science (#26420414, E. Furutani).

References

[1] American Diabetes Association: Standards of medical care in diabetes—2014; Diabetes Care, Vol. 31, Suppl 1, pp. S14–S80 (2014)
[2] I. Ajmaira, M. Swat, C. Laihe, N. Le Novère and V. Chelliah: The impact of mathematical modeling on the understanding of diabetes and related complications; CPT Pharmacometrics Syst. Pharmacol., Vol. 2, No. 7, p. 545 (2013)
[3] R. Hovorka, D. Eller, H. Thabit, J. M. Allen, L. Lee-larathna, R. El-Khairi, K. Kumareswaran, K. Caldwell, P. Calhoun, C. Kollman, H. R. Murphy, C. L. Acrerini, M. E. Willinska, M. Nodale and D. B. Dunger: Overnight closed-loop insulin delivery in young people with type 1 diabetes: a free-living, randomized clinical trial; Diabetes Care, Vol. 37, No. 5, pp. 1204–1211 (2014)
[4] C. C. Yamamoto Noguchi, S. Hashimoto and E. Furutani: In silico blood glucose control for type 1 diabetics with meal announcement using carbohydrate intake and glycemic index; Adv Biomed Eng, Vol. 5, pp. 124–131 (2016)
[5] H. A. Wolpert, A. Atakov-Castillo, S. A. Smith and G. M. Steil: Dietary fat acutely increases glucose concentrations and insulin requirements in patients with type 1 diabetes: implications for carbohydrate-based bolus dose calculation and intensive diabetes management; Diabetes Care, Vol. 36, No. 4, pp. 810–816 (2013)
[6] R. C. Boston and P. J. Moate: A novel minimal model to describe NEFA kinetics following an intravenous glucose challenge; Am. J. Physiol. Regul. Integr. Comp. Physiol., Vol. 294, No. 4, pp. R1140–R1147 (2008)
[7] K. Thomaseth, A. Brehm, A. Pavan, G. Pacini and M. Roden: Modeling glucose and free fatty acid kinetics during insulin-modified intravenous glucose tolerance test in healthy humans: role of counterregulatory response; Am. J. Physiol. Regul. Integr. Comp. Physiol., Vol. 307, No. 3, pp. R321–R331 (2014)
[8] A. Roy and R. S. Parker: Mixed meal modeling and disturbance rejection in type 1 diabetic patients; Conf. Proc. IEEE Eng. Med. Biol. Soc., Vol. 1, pp. 323–326 (2006)
[9] C. C. Yamamoto Noguchi, N. Kunikane, S. Hashimoto and E. Furutani: Mixed model of dietary fat effect on postprandial glucose-insulin metabolism from carbohydrates in type 1 diabetes; Conf. Proc. IEEE Eng. Med. Biol. Soc., pp. 8058–8061 (2015)
[10] S. Laxminarayan, J. Reifman, S. S. Edwards, H. Wolpert and G. M. Steil: Bolus estimation—Rethinking the effect of meal fat content; Diabetes Technol. Ther., Vol. 17, No. 12, pp. 860–866 (2015)
[11] R. J. Randle: Regulatory interactions between lipids and carbohydrates: the glucose fatty acid cycle after 35 years; Diabetes Metab. Rev., Vol. 14, No. 4, pp. 263–283 (1998)
[12] G. Boden, P. Cheung, T. P. Stein, K. Kresge and M. Mozzoli: FFA cause hepatic insulin resistance by inhibiting insulin suppression of glycogenolysis; Am. J. Physiol. Endocrinol. Metab., Vol. 283, No. 1, pp. E12–E19 (2002)
[13] C. C. Yamamoto Noguchi, E. Furutani and S. Sumi:
Mathematical model of glucose-insulin metabolism in type 1 diabetes including digestion and absorption of carbohydrates; *SICE JCMSI*, Vol. 7, No. 6, pp. 314–320 (2014)

[14] C. C. Yamamoto Noguchi, S. Hashimoto, E. Furutani and S. Sumi: Model of gut absorption from carbohydrates with maximum rate of exogenous glucose appearance in type 1 diabetes; *SICE JCMSI*, Vol. 9, No. 5, pp. 201–206 (2016)

[15] R. N. Bergman, Y. Z. Ider, C. R. Bowden and C. Cobelli: Quantitative estimation of insulin sensitivity; *American Journal of Physiology*, Vol. 236, No. 6, pp. E667–E677 (1979)

[16] A. Harbis, C. Delfort, H. Narbonne, C. Juwel, M. Senft, C. Latgé, B. Delenne, H. Portugal, C. Atlanger, B. Viallet and D. Lainon: Acute hyperinsulinism modulates plasma apolipoprotein B-48 triglyceride-rich lipoproteins in healthy subjects during the postprandial period; *Diabetes*, Vol. 50, No. 2, pp. 462–469 (2001)

[17] A. M. Caballero-Plasencia, M. C. Muros-Navarro, J. L. Martin-Ruiz, M. Valenzuela-Barranco, M. C. de los Reyes-Garcia, R. Vilchez-Joya, F. J. Casado-Juarez and J. L. Martin-Ruiz, M. Valenzuela-Barranco, M. C. de los Reyes-Garcia, R. Vilchez-Joya, F. J. Casado-Juarez and J. L. Martin-Ruiz, M. Valenzuela-Barranco, M. C. de los Reyes-Garcia: Gastroparesis of digestible and indigestible solids in patients with insulin-dependent diabetes mellitus or functional dyspepsia; *Dig. Dis. Sci.*, Vol. 39, No. 7, pp. 1409–1415 (1994)

[18] H. A. Wolpert, A. Atakov-Castillo, S. A. Smith and G. M. Steil: Dietary fat acutely increases glucose concentrations and insulin requirements in patients with type 1 diabetes; *Diabetes Care*, Vol. 36, No. 4, pp. 810–816 (2013)

[19] G. F. Lewis, N. M. O’Meara, V. G. Cabana, J. D. Blackman, W. L. Pugh, A. F. Druetzler, J. R. Lukens, G. S. Getz and K. S. Polonsky: Postprandial triglyceride response in type 1 (insulin-dependent) diabetes mellitus is not altered by short-term deterioration in glycaemic control or level of postprandial insulin replacement; *Diabetologia*, Vol. 34, No. 4, pp. 253–259 (1991)

[20] M. T. Pedrini, A. Niederwanger, M. Kranebitter, C. Tautermann, C. Ciardi, T. Tatarczyk and J. R. Patsch: Postprandial lipaemia induces an acute decrease of insulin sensitivity in healthy men independently of plasma NEFA levels; *Diabetologia*, Vol. 49, No. 7, pp. 1612–1618 (2006)

[21] R. Belfort, L. Mandarino, S. Kashyap, K. Wirfel, T. Pratipanawat, R. Berria, R. A. Defronzo and K. Cusi: Dose-response effect of elevated plasma free fatty acid on insulin signaling; *Diabetes*, Vol. 54, No. 6, pp. 1640–1648 (2005)

[22] M. R. Burge, K. J. Hardy and D. S. Schade: Short-term fasting is a mechanism for the development of euglycemic ketoadosis during periods of insulin deficiency; *J. Clin. Endocrinol. Metab.*, Vol. 76, No. 5, pp. 1192–1198 (1993)

[23] S. Panpanelli, E. Torlone, C. Ialli, P. Del Sindaco, M. Ciofetta, M. Lepore, L. Bartocci, P. Brunetti and G. B. Bolli: Improved postprandial metabolic control after subcutaneous injection of a short-acting insulin analog in IDDM of short duration with residual pancreatic beta-cell function; *Diabetes Care*, Vol. 18, No. 11, pp. 1452–1459 (1995)

[24] P. Kunz, C. Feinle-Bisset, H. Faas, P. Boesiger, M. Fried, A. Steingöter and W. Schwizer: Effect of ingesction order of the fat component of a solid meal on intragastric fat distribution and gastric emptying assessed by MRI; *J. Magn. Reson. Imaging*, Vol. 21, No. 4, pp. 383–390 (2005)

[25] M. Samsom, A. Bharucha, J. E. Gerich, K. Herrmann, J. Linmer, R. Linke, D. Maggs, J. Schirra, A. Vella, H. J. Wörle and B. Göke: Diabetes mellitus and gastric emptying: questions and issues in clinical practice; *Diabetes Metab. Res. Rev.*, Vol. 25, No. 6, pp. 502–514 (2009)

[26] C. Folwaczny, R. Wawarta, B. Otto, S. Friedrich, R. Landgraf and R. L. Riepl: Gastric emptying of solid and liquid meals in healthy controls compared with long-term type-1 diabetes mellitus under optimal glucose control; *Exp. Clin. Endocrinol. Diabetes*, Vol. 111, No. 4, pp. 223–229 (2003)

[27] E. J. Mansell, P. D. Docherty and J. G. Chase: Shedding light on grey noise in diabetes modelling; *Biomed. Signal Process Control*, Vol. 31, pp. 16–30 (2017)

[28] M. D. Jensen, M. Caruso, V. Heiling and J. M. Miles: Insulin regulation of lipolysis in nondiabetic and IDDM subjects; *Diabetes*, Vol. 38, No. 12, pp. 1595–1601 (2006)

[29] G. M. Puga, C. Meyer, L. J. Mandarino and C. S. Katsanos: Postprandial spillover of dietary lipid into plasma is increased with moderate amounts of ingested fat and is inversely related to adiposity in healthy older men; *J. Nutr.*, Vol. 142, No. 10, pp. 1806–1811 (2012)

**Authors**

Claudia Cecilia **YAMAMOTO NOGUCHI**  
She received her B.S. from Pontificia Universidad Católica del Perú, Lima, Peru in 2006; and her M.S. and PhD from Kyoto University, Japan in 2013 and 2016, respectively. She is currently Research student in the same university.  
Her research interests include mathematical modeling of postprandial glucosel-insulin metabolism and prandial bolusing algorithms in type 1 diabetes.

Eiko **FURUTANI** (Member)  
He received his B.E., M.E., and Ph.D. degrees from Kyoto University, Japan, in 1987, 1989, and 1997, respectively. In 1991, he joined Kyoto University, where he is currently an Associate Professor of the Department of Electrical Engineering. His research interests include control technologies and their application to medical problems in cooperation with medical doctors. He is a member of IEEE, IEEJ, SICE and JSMBE.