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Modeling Nonsteady-State Metabolism From Arteriovenous Data

Erica Manesso
Department of Information Engineering, University of Padova, Padova 35129, Italy. She is now with the Division of Computational Biology and Biological Physics, Department of Theoretical Physics, Lund University, Lund 22362, Sweden (erica.manesso@thep.lu.se)

Gianna M. Toffolo
Department of Information Engineering, the Uni versity of Padova, Padova 35129, Italy (toffolo@dei.unipd.it)

Rita Basu
Department of Internal Medicine at Mayo Clinic and Foundation, Rochester, MN 55905 USA (basu.rita@mayo.edu)

Robert A. Rizza
Department of Internal Medicine at Mayo Clinic and Foundation, Rochester, MN 55905 USA (rizza.robert@mayo.edu)

Claudio Cobelli [Fellow, IEEE]
Department of Information Engineering, the University of Padova, Padova 35129, Italy (cobelli@dei.unipd.it)

Abstract

The use of arteriovenous (AV) concentration differences to measure the production of a substance at organ/tissue level by Fick principle is limited to steady state. Out of steady state, there is the need, as originally proposed by Zierler, to account for the nonnegligible transit time of the substance through the system. Based on this theory, we propose a modeling approach that adopts a parametric description for production and transit time. Once the unknown parameters are estimated on AV data, the transition time of the substance can be assessed and production can be reconstructed. As a case study, we discuss the estimation of pancreatic insulin secretion during a meal from C-peptide concentrations measured in femoral artery and hepatic vein in 12 subjects. Results support the importance of accounting for nonnegligible transit times, even if C-peptide mean transit time across the splanchnic bed is rather limited (3.3±1.3 min), it affects the estimation of pancreatic insulin secretion which shows a significantly different profile in the early portion of the postprandial period when estimated either with the novel modeling approach or with the simplified steady state equation.

Keywords

Arteriovenous (AV) measurements; beta cell function; insulin secretion; mean transit time; physiological model

Correspondence to: Claudio Cobelli.

I. Introduction

THE use of arteriovenous (AV) concentration differences to study the metabolism of a substance at organ/tissue level by Fick principle is limited to steady state, that is: 1) arterial and venous concentrations of the substance "x" of interest are constant; 2) blood flow is constant; and 3) metabolism of "x" is constant. Under conditions in which the steady state is perturbed, simple steady-state equations are not applicable due to nonnegligible transit time of the molecules of "x" across the system of interest. Under these circumstances, there is the need, as originally proposed by Zierler [1], to use a probabilistic description for transit times of "x" in the expressions that link production/utilization of a substance to AV concentration measurements, based on principles developed for analysis of indication dilution data.

Practical application of Zierler theory has been limited. For instance, with reference to the problem of measuring glucose and insulin fluxes across the splanchnic bed by hepatic catheterization in a nonsteady-state condition, such as an oral glucose tolerance test (OGTT), Tura *et al.* [2] adopted steady-state equations to measure insulin secretion from C-peptide AV differences; Morishima *et al.* [3] assumed a constant C-peptide transit time, equal to 25 s, and thus hepatic vein was sampled 25 s after femoral artery; and Mari *et al.* [4] estimated glucose absorption and production by using Zierler theory, but the transit time density function was assumed constant in all individuals and known *a priori*.

Here, focusing on the assessment of production at organ/tissue level, Zierler theory is revisited and the reasons why its practical implementation is difficult are discussed. Then, a modeling approach based on parametric descriptions of production and of transit time density functions is proposed. The rationale is to estimate model parameters by fitting model equations to AV data. To illustrate a practical application of this modeling approach, estimation of postprandial insulin secretion from AV concentration difference is used as a case study.

II. Theory

Considering a system of organs and tissues that produces a substance "x," Fick principle states that in steady-state conditions, the production P (mass/time) of "x" equals the blood flow F (volume/time) multiplied by the difference between arterial C_A and venous C_V concentrations (both in mass/volume) of "x," that is

$$P = F \cdot (C_V - C_A) \quad (1)$$

which is equivalent to assume the following link:

$$C_V = C_A + \frac{P}{F}. \quad (2)$$

In a nonsteady state, such as during a perturbation, application of the AV model, i.e., (2), is not correct due to the nonnegligible transit times of the molecules of "x" across the system. In this situation, assuming that: 1) the system is linear; 2) blood flow is constant; and 3) the system is in steady-state conditions before the perturbation, the link between arterial and venous concentrations (2) becomes [1]

$$C_V(t) = \int_{-\infty}^{t} C_A(\tau) \cdot f(t-\tau)\, d\tau + \frac{1}{F}\int_{-\infty}^{t} P(\tau) \cdot n(t-\tau)\, d\tau \quad (3)$$

where $f(t)$ (time^{-1}) is the distribution function of transit times from the arterial to the venous site of the system and $n(t)$ (time^{-1}) is the distribution function of transit times from site of

release to the venous site. In other words, the concentration of "x" in vein can be expressed as the sum of two terms: the first one depends on the concentration of "x" in artery and $f(t)dt$ represents the fraction of molecules of "x" that reaches the vein t time units after entering the system from the arterial site and the second term is linked to the production of "x" in the system and $n(t)dt$ represents the fraction of molecules of "x" that reaches the vein t time units after having been produced from points of release in the system.

Assuming that the substance "x" is not utilized in the system, the sum of all $f(t)$ and $n(t)$ values is 1, since all molecules that enter the system, either from the artery or the site of production, will sooner or later reach the vein, that is

$$\int_0^{+\infty} f(t)\,dt = 1 \quad (4)$$

$$\int_0^{+\infty} n(t)\,dt = 1. \quad (5)$$

The first moment of the distribution function f provides the mean transit time (MTT) (time) between artery and vein

$$MTT = \int_0^{+\infty} t \cdot f(t)\,dt. \quad (6)$$

Equation (3) thus requires the handling of two distribution functions of transit times, from the arterial to the venous site and from the site of release to the venous site. However, there are two situations that lead to a simplification of (3). First, when the points of release are close to the arterial site across the system, the behavior of the molecules of "x" either produced by the system or coming from the arterial site is approximately the same in terms of transit times. In this case, the distribution function of transit times from the site of release to the venous site, i.e., $n(t)$ is comparable to the distribution function of transit times from the arterial to the venous site of the system, which is $f(t)$. Thus, (3) is simplified as

$$C_V(t) = \int_{-\infty}^{t} \left[C_A(\tau) + \frac{P(\tau)}{F} \right] \cdot f(t-\tau)\,d\tau. \quad (7)$$

Second, when the points of release are close to the venous site, the transit times of the released molecules of "x" are negligible with respect to the transit times of those molecules that, from the arterial site, have to cross all the system before reaching the venous site. In this case, $n(t) \approx \delta(t)$ and thus (3) becomes

$$C_V(t) = \int_{-\infty}^{t} C_A(\tau) \cdot f(t-\tau)\,d\tau + \frac{P(t)}{F}. \quad (8)$$

Practical implementation of (3), or of its simplified versions (7) and (8), requires the measurement of arterial and venous concentrations by catheterization technique, blood flow by indocyanine green dye, and the distribution functions of transit times $f(t)$ [and eventually $n(t)$)] by additional tracer experiments [1]. When all these variables are available, production P can be obtained either from (3), (7), or (8) by deconvolution.

However, in most of the situations, $f(t)$ and $n(t)$ are not available. Under these circumstances, a parametric approach offers a possible solution based on postulating parametric models for $f(t)$, $n(t)$, and $P(t)$. A sum of two exponentials is a good candidate for the distribution of transit times $f(t)$ and $n(t)$, since it is among the simplest (minimum number of parameters) descriptions able to reproduce the asymmetric bell shape of transit time distribution as described in the indicator dilution theory [1], [5], [6], e.g., for $f(t)$

$$f(t) = A \cdot \left(e^{-\gamma t} - e^{-\mu \cdot t}\right). \quad (9)$$

Parameters A (time^{-1}), γ (time^{-1}), and μ (time^{-1}) are constrained to satisfy (4), resulting in the following condition:

$$A \cdot \left(\frac{1}{\gamma} - \frac{1}{\mu}\right) = 1. \quad (10)$$

The MTT (time) spent in the system by "x" molecules entering from the artery can be expressed as a function of model parameters, e.g., for the two exponential models

$$MTT = A \cdot \left(\frac{1}{\gamma^2} - \frac{1}{\mu^2}\right). \quad (11)$$

As to modeling the production P, different approaches can be explored. If some knowledge is available on how P changes in time during the perturbation, e.g., an exponential rise or a sigmoid function, the model consists in a parametric description of this time course, as a function of parameters, e.g., the plateau value and the time constant in the case of the exponential rise. A very flexible parametric description of P is the piecewise linear function, with a given number of breaks points, as the one used to describe the rate of appearance of glucose during an OGTT [7]. This approach requires to set the number of break points as well as the times when the break points are allocated. The values of P at the break points are the unknown parameters. While these approaches allow the reconstruction of the time course of P, an interesting alternative is represented by a mechanistic model, describing the control exerted on P by some variable, accessible to measurements, e.g., the concentration of some substrate/hormone. Model parameters can be given a mechanistic interpretation in terms of the sensitivity of P to the control variable. In any case, once the unknown parameters of the model are estimated by fitting (3), or its simplified versions (7) or (8), on venous concentration data, assuming arterial concentration data as known input, the transition time of the substance can be assessed and production can be reconstructed.

III. Insulin Secretion Case Study

To discuss practical application of the AV model with transit times, TT-AV model [([3]), or its simplified versions [7] or [8]], let us consider the estimation of pancreatic insulin secretion during a meal. Insulin has a central role in glucose homeostasis. During a meal, blood glucose level increases, beta cells sense the prevailing blood glucose level and secrete insulin in a manner dependent on glucose concentration. The secreted insulin constrains circulating blood glucose concentrations by its actions to inhibit hepatic glucose release and stimulate glucose uptake and storage by skeletal muscle and fat [8]. To measure insulin secretion during a meal, AV measurements were taken across the splanchnic bed, by sampling femoral artery and hepatic vein in 12 nondiabetic subjects [9] (see Appendix 2 for glucose and C-peptide concentrations). Since insulin measurements only provide secretion corrected by hepatic extraction, (see Fig. 1, upper panel) C-peptide, an hormone that is released by beta cells in equimolar proportion with insulin, but not extracted by the liver (see Fig. 1, lower panel) [10], [11] was used to reconstruct pancreatic secretion, (3) describes the system, where C_V and C_A (pmol/L) are C-peptide concentrations, respectively, in femoral artery and hepatic vein and the production P is pancreatic secretion, i.e., SR. Since the pancreas is very close to the arterial site (see Fig. 1, lower panel), we can safely assume that $\pi(t) \approx f(t)$ and thus use the simplified (7). The distribution function f is modeled as the sum of two exponentials (9), while for SR, the mechanistic model describing the

control exerted by glucose on SR, built in the minimal model of C-peptide secretion [12] is adopted, namely SR is described as the sum of three components:

1) basal value of insulin secretion SR_b (pmol/min) resulting from (1)

$$SR_b = F \cdot (C_{Vb} - C_{Ab}) \quad (12)$$

2) dynamic insulin secretion SR_d (pmol min^{-1}) proportional to the rate of increase of glucose ($\dot{G}(t) \equiv D(t)$, in mmol L^{-1} min^{-1}) through the dynamic responsivity parameter Φ_d (10^9 L), which represents the stimulatory effect of the rate of increase of glucose on secretion of stored insulin

$$SR_d(t) = \begin{cases} \phi_d \cdot D(t), & \text{if } D(t) \geq 0 \\ 0, & \text{if } D(t) < 0 \end{cases} \quad (13)$$

3) static insulin secretion SR_s (pmol/min) controlled by glucose concentration G (mmol/L) in a linear dynamic fashion, i.e., in response to a glucose step increase above a threshold level h (mmol/L, practically coinciding with basal glucose concentration), SR_s tends with a rate constant α (min^{-1}) toward a steady-state value that is linearly related to the glucose step through the static responsivity parameter Φ_s (10^9 L· min^{-1})

$$\dot{SR}_s(t) = -\alpha \cdot \{SR_s(t) - \phi_s \cdot [G(t) - h]\}, SR_s(0) = 0. \quad (14)$$

All parameters of the TT-AV model (7), both related to insulin secretion (Φ_s, Φ_d, and α) and C-peptide transit time (A, γ, and μ constrained by (10) are *a priori* uniquely identifiable (see Appendix 1). They were identified by nonlinear least squares [13] on C-peptide postprandial venous concentrations assuming arterial C-peptide and glucose concentration, linearly interpolated between data, as error free model input. The splanchnic blood flow F was set equal to the average of values measured by indocyanine green infusion, as detailed in Appendix 2 [9]. Measurement error of C-peptide concentration was assumed to be independent and Gaussian, with zero mean with a variance linked to C-peptide concentration C_V: $\sigma^2(t_i) = 2000 + 0.001 \times C_V^2(t_i)$ [14], where suffix "i" stays for sample ith. When parameter α was elevated and estimated with poor precision, the Bayesian approach implemented by MATLAB software (The Mathworks, Natick, MA) was used. A Bayesian prior was also used on parameters γ and μ to improve their numerical identification. Since there is no prior information available in the literature for these parameters, different combinations corresponding to MTT = 0.5, 1, 2.5, 5, 7.5 min were tested.

IV. Results

The TT-AV model, (7), was able to reproduce satisfactorily the venous C-peptide data of our subjects. Estimated parameters of transit time distribution were not affected by the Bayesian prior: A = (1.0 ± 2.2) min^{-1}; γ = (0.93 ± 0.15) min^{-1}; and μ = (4.993 ± 0.0017) min^{-1}, resulting in an average C-peptide MTT (11) equal to (3.3 ± 1.3) min. Estimated parameters of insulin production were: Φ_s = 141 ± 13 × 109 L·min^{-1}; Φ_d = 1363 ± 468 × 10^9 L; and α = 0.115 ± 0.014 min^{-1}. The reconstructed SR profile is shown in Fig. 2. Despite of its low value, C-peptide MTT influenced SR estimation, especially in the early postprandial period, since TT–AV model predictions are consistently higher than values (see Fig. 2) obtained by applying the simpler AV model (1), which neglects the transit time.

V. Discussion

To address the general problem of measuring the rate of production of a substance "x" from AV measurement in nonsteady-state conditions (i.e., when Fick principle is not valid), Zierler [1] developed an elegant formalism, resorting to the notion of distribution function of transit times. Due to the complexity of blood vessels between entrance and exit of an organ, molecules entering the system at a given time are dispersed, so that they reach the exit at different times according to the distribution function of transit times. Based on this function, the concentration at exit of an organ (venous site) can be related to the concentration at entrance (arterial site), production within the organ of "x," and blood flow (3).

In the present study, Zierler theory was revisited and the reasons why its practical employment is difficult were discussed. In detail, the application of Zierler theory requires to measure not only arterial and venous concentrations by catheterization technique and blood flow by indocyanine green dye, but also the distribution function of transit times across the organ/tissue by proper tracer experiments. In most situations where these additional experiments are either unpractical or unfeasible, a parametric approach offers a possible solution, based on postulating parametric models for the distribution function of transit times and production. While the former can be easily modeled by a sum of exponentials able to reproduce the asymmetrical bell shape of transit time distribution, modeling the production requires some knowledge on how this quantity changes in time during the perturbation, either in terms of time course, or of functional dependence on some variable, known to exert a control on production and accessible to measurement. Formulating the model, a balance between the needs to describe well the data and to keep the number of the parameters as smallest as possible must be considered since excessively complex models suffer from overfitting and have a poor predictive power. In this contest, the simplifications of (3) into (7) or (8), where possible, result useful since they require only the parametric description of the distribution function of transit times from the arterial to the venous site. Once the model has been formulated and the *a priori* identifiability of model parameters has been established, model parameters are estimated by fitting (3) on venous concentration data, assuming arterial concentration data as known input.

To illustrate a practical application of this modeling approach, the estimation of postprandial insulin secretion (production) from AV concentration difference was used as a case study. In this case, the distribution function of C-peptide in the splanchnic bed was modeled by a sum of two exponentials (9), while secretion was modeled according to the description built in the minimal model of C-peptide secretion and kinetics [12] that describes the control exerted by glucose on insulin secretion.

When identified on AV concentrations measured during a meal in 12 nondiabetic subjects, the TT–AV model (7) was able to reproduce the data satisfactorily. Furthermore, all its unknown parameters, related to both secretion and distribution function of transit times (f), were identifiable, both *a priori*, i.e., it was theoretically possible to derive unique value for them, and *a posteriori*, i.e., precise estimates were derived in all individuals. In particular, nonnegligible values were estimated for parameters describing the transit time distribution, irrespective of the value of the Bayesian prior used to improve their numerical identification, thus indicating that both SR and f can be reliably estimated from AV data. From the parameters of f distribution, an MTT of C-peptide molecules close to 3 min as an average was estimated. This value was consistently higher than the value assumed in [3] for C-peptide hepatic transit time, i.e., 25 s. However, the estimated value was not significantly different ($P = 0.14$) to its approximation (1.24 ± 0.12 min) with the ratio between C-peptide splanchnic volume (25% [15], [16] of the total C-peptide blood volume estimated by a population approach [17]) and the measured blood flow. Despite the low value of MTT,

transit times influenced SR estimation since the average insulin secretion rate profile obtained from the simple AV model (1), thus neglecting the transit times, showed differences from SR estimated by the TT–AV model (see Fig. 2). In particular, transit times biased SR estimation during the first 45 min since the areas under the two curves were significantly different ($P = 0.0049$) in the same period, thus indicating that neglecting transit times led to the loss of the dynamic component of insulin secretion. Application of the AV model (1) only provides the secretion profile. In order to quantify the responsivity parameters, the secretion model was used in (2) to fit C-peptide venous data. Even neglecting the transit times, a dynamic component was identified, even if the estimated Φ_d was significantly lower than the correspondent obtained by the AV model (i.e., $488 \pm 117 \times 10^9$ L versus $1363 \pm 468 \times 10^9$ L; $P < 0.01$, Wilcoxon signed rank test). As expected, the static phase was similar, i.e., $132 \pm 14\ 10 \times 10^9$ L·min^{-1} versus $141 \pm 13 \times 10^9$ L·min^{-1} ($P > 0.05$).

The model proposed for the distribution function of C-peptide in the splanchnic bed (9) is among the simplest (minimum number of parameters) descriptions able to reproduce the asymmetric bell shape of transit time distribution and it is in accordance with the indicator dilution theory [1], [5], [6]. Other models, such as the Weibull function, which has been used very successfully for lifetime and reliability engineering problems, did not provide the best performances according to the generalized information criterion of parsimony (40 ± 7 for the sum of exponentials versus 43 ± 8 for the Weibull function).

With regard to the model of insulin secretion, a flexible alternative parametric description is a piecewise linear function. Among different ways of setting the number of break points as well as of allocating the times related to the break points, we identified a piecewise linear function with break points at 0, 10, 20, 30, 60, 120, 180, and 360 min which led to a satisfying fit of C-peptide venous data (7). To enhance the precisions of the estimated parameters, the break points at time 0 and 360 min where fixed to the values obtained from (1). The mean insulin secretions obtained applying to (7) either the mechanistic model (13)–(14) or the piecewise function were in excellent agreement both in terms of profile (see Fig. 3) and of area under the curve (AUC). In detail, in the interval 0–360 min, the AUC was $103 \pm 8 \times 10^3$ in the first case versus $104 \pm 11 \times 10^3$ in the second case ($P = 0.83$, Wilcoxon signed rank test); in the first 45 min, AUC was $18.5 \pm 2.3 \times 10^3$ in the first case versus $18.4 \pm 2.2 \times 10^3$ in the second case ($P = 0.91$), thus confirming the presence of a dynamic component for insulin secretion. Furthermore, the mean residence times estimated with the two approaches were similar ($P = 0.27$): 3.4 ± 1.6 min with the piecewise linear function approach versus 3.3 ± 1.3 min with the mechanistic model. Despite the piecewise linear function was better than the model proposed by Breda *et al.* [12] in terms of fit (objective function = 20 ± 4 in the first case, 39 ± 7 in the second case) since it had more degrees of freedom, the precisions of the estimates obtained with the piecewise linear function approach were poor, i.e., the coefficient of variation for the break point at 10 min was greater than 100%. Thus, we conclude that, in this case study, the mechanistic model applied to (7) is better than a parametric description as a piecewise linear function, underlying the importance of providing physiological parameters where possible (i.e., dynamic and static phases).

An alternative and less invasive estimation of insulin secretion in humans is provided by the whole-body “oral” minimal model [12]. This model requires only arterialized venous measurements of glucose and C-peptide levels from the forearm, since it combines the parametric description of insulin secretion with a population model of C-peptide kinetics [17]. When identified from arterial data of our 12 subjects and expressed in proper units, average SR predicted by the whole-body model was in excellent agreement with the AV counterpart (7), both in terms of profile (see Fig. 4) and beta cell responsivity parameters:

$\Phi_d = 1363 \pm 468 \times 10^9$ L versus $1927 \pm 433 \times 10^9$ L ($P = 0.18$, Wilcoxon signed rank test); $\Phi_S = 141 \pm 13 \times 10^9$ L·min^{-1} versus $132 \pm 17 \times 10^9$ L·min^{-1} ($P = 0.47$). Since AV measurements are often considered as a golden standard method to validate whole-body models, this excellent agreement suggests that the whole-body model can be widely applied to estimate insulin secretion in view of its minimum invasiveness.

In conclusion, Zierler theory [1] was revisited and a modeling approach based on parametric descriptions of the unknown fluxes and of transit time density functions was described. To illustrate a practical application of this modeling approach, a TT-AV model to assess postprandial mean C-peptide transit time and insulin secretion from AV concentrations was proposed. The resulting insulin secretion rate confirmed the importance of considering transit times at organ/tissue level in nonsteady state. Furthermore, insulin secretion estimated by the TT-AV model was concordant with its counterpart obtained independently by applying the whole-body "oral" minimal model [12] to arterial concentrations, thus supporting the validity of whole-body model as a minimally invasive method to assess insulin secretion.

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Appendix I

Priori Identifiably

Substituting the production $P(t)$ with the secretion $SR(t)$ and making explicit $f(t)$, over basal (7) equals

$$C_V(t) = A \cdot \int_0^t \left[C_A(\tau) + \frac{\phi_d \cdot D(\tau) + SR_s(\tau)}{F} \right] \cdot \left[e^{-\gamma \cdot (t-\tau)} - e^{-\mu \cdot (t-\tau)} \right] d\tau. \quad \text{(A1)}$$

Assuming that $C_A(t)$, $D(t)$, $SR_s(t)$, $G(t)$, and $C_V(t)$ are Laplace transformable, the Laplace transform of (A1) is

$$\begin{aligned} C_V(s) = & \left\{ C_A(s) + \frac{\phi_d}{F} \cdot D(s) + \frac{1}{F} \cdot \frac{\alpha \cdot \phi_s \cdot \left[G(s) - \frac{h}{s} \right]}{s+\alpha} \right\} \cdot \frac{\gamma \cdot \mu}{s^2 + (\gamma+\mu) \cdot s + \cdot \mu} \\ = & \frac{\gamma \cdot \mu}{s^2 + (\gamma+\mu) \cdot s + \gamma \cdot \mu} \cdot C_A(s) \\ & + \frac{\gamma \cdot \mu \cdot \phi_d / F}{s^2 + (\gamma+\mu) \cdot s + \gamma \cdot \mu} \cdot D(s) \\ & + \frac{\gamma \cdot \mu \cdot \alpha \cdot \phi_s / (F \cdot s)}{s^3 + (\alpha+\gamma+\mu) \cdot s^2 + (\alpha \cdot \gamma + \alpha \cdot \mu + \gamma \cdot \mu) \cdot s + \alpha \cdot \gamma \cdot \mu} \cdot G(s) \\ & - \frac{\gamma \cdot \mu \cdot \alpha \cdot \phi_s \cdot h / F}{s^3 + (\alpha+\gamma+\mu) \cdot s^2 + (\alpha \cdot \gamma + \alpha \cdot \mu + \gamma \cdot \mu) \cdot s + \alpha \cdot \gamma \cdot \mu}. \end{aligned} \quad \text{(A2)}$$

As it is clear from (A2), the transfer function of (A1) can be divided in four terms: 1) the first depends on C-peptide concentration in femoral artery; 2) the second is related to glucose rate of increase; 3) the third depends on glucose concentration in femoral artery; and 4) the last one is associated with the threshold glucose level h.

Knowing $C_A(t)$, $D(t)$, and $G(t)$ and their Laplace transforms, through functions in "s" of (A2) the unknown parameters: γ, μ, Φ_d, α, Φ_s, and h can be obtained.

The exhaustive summary (excluding dependent equations) of (A2) is

$$\begin{cases} \gamma \cdot \mu = \beta_1 \\ \gamma + \mu = \beta_2 \\ \frac{\gamma \cdot \mu \cdot \phi_d}{F} = \beta_3 \\ \alpha + \gamma + \mu = \beta_4 \\ \frac{\gamma \cdot \mu \cdot \alpha \cdot \phi_s}{F} = \beta_5 \\ \frac{\gamma \cdot \mu \cdot \alpha \cdot \phi_s \cdot h}{F} = \beta_6 \end{cases} \quad \text{(A3)}$$

where $\beta_1, \beta_2, \ldots, \beta_6$ are observational parameters, so known from the experiment. As it is clear from (A3), all the parameters are *a priori* identifiable (that is, from the first and the second equations of (A3), γ and μ can be obtained; from the third Φ_d, from the fourth α, from the fifth Φ_s, and from the sixth h).

Appendix II

Glucose, Insulin, and C-Peptide Concentrations

To measure insulin secretion during a meal, AV measurements were taken across the splanchnic bed, by sampling femoral artery and hepatic vein in 12 nondiabetic subjects, previously reported in [7]. Glucose and C-peptide concentrations in femoral artery (void squares–dashed line) and hepatic vein (full squares–continuous line) are depicted in Fig. 5. Glucose, insulin, and C-peptide levels were higher in the hepatic vein than in femoral artery before meal ingestion with the difference becoming more marked after meal ingestion. Blood flow following meal ingestion averaged $(0.97 \pm 0.07)\ \mathrm{L \cdot min^{-1}}$ with a coefficient of variation among sampling times of $(19 \pm 2)\%$.

Splanchnic Blood Flow

The splanchnic blood flow F was calculated at sampling times by dividing by (one-hematocrit) the respective plasma flow, estimated from the ratio of indocyanine green infusion rate to its arterial-hepatic venous concentration gradient. F was fixed to the average of values calculated at sampling times once established by the Bonferroni's method that the splanchnic blood flow did not depend on time.

Biographies

Erica Manesso was born in Camposampiero, Italy, on September 24, 1981. She received the Master's degree in computer science engineering and the Doctoral degree in information engineering from the University of Padova, Padova, Italy, in 2006 and 2010, respectively.

Since February 2010, she has been a Postdoctoral Fellow in the Department of Theoretical Physics, Lund University, Lund, Sweden. Her research interests include the development of mathematical models for analysis and control of biological systems.

Gianna M. Toffolo received the Graduate (Hons.) degree in electronic engineering from the University of Padova, Padova, Italy, in 1978.

She is currently a Full Professor of Biological Signal Processing at the University of Padova. She is the author and coauthor of a book and more than 110 full papers on international peer reviewed journals. Her research activity, carried out in collaboration with Italian and foreign investigators, mainly regards modeling of biological and physiological systems, and includes methodological aspects as well as specific applications in biology, physiology and medicine, with particular focus on endocrine-metabolic systems.

Rita Basu received the B.Sc. degree in biology, chemistry, and physics from the University of Punjab, Chandigarh, India. She completed medical school, internship, and residency training from the Jawaharlal Institute of Medical Science and Research, University of Pondicherry, Pondicherry, India. She was a Research Fellow at the Mayo Clinic, Rochester, NY.

She joined Mayo Clinic as a Faculty Member, in 2000 and is currently an Associate Professor of Medicine and an Associate Consultant in the Division of Endocrinology, Diabetes, Metabolism, and Nutrition. She also serves as the Chair of an Institutional Review Board for the Mayo Clinic Office of Human Research Protection. She previously completed a term as the Assistant Medical Director of the Office of Human Research Protection. Her research focuses on the regulation of “splanchnic cortisol metabolism” in humans. She has been well funded by the National Institute of Health, U.S., to conduct complex physiology studies in the field of Diabetes and the role of splanchnic cortisol in modulating various diseased states including diabetes, obesity, and the so called “metabolic syndrome.”

Robert A. Rizza received the B.A. degree in biophysics from Johns Hopkins University, Baltimore, MD. He completed medical school from the University of Florida, Gainesville, FL, and internship and residency training from Johns Hopkins University. He completed both a clinical endocrinology and a research fellowship at the Mayo Clinic, Rochester, NY.

He joined Mayo as a Faculty Member, in 1980, where he was the Chair of the Division of Endocrinology, Diabetes, Metabolism and Nutrition, from 1992 to 2002, and the Co-Director of the Mayo Kogod Program of Aging from 2002 to 2004. He is currently the Earl and Annette R. McDonough Professor of Medicine, the Principal Investigator for Mayo's Center for Translational Science Activities, as well as the Executive Dean for Research at Mayo. His clinical interests include diabetes, hypoglycemia, insulin resistance, obesity, and lipid disorders. His research focuses on the regulation of carbohydrate metabolism in humans.

Dr. Rizza has received the American Diabetes Association's Outstanding Physician Clinician Award and Banting Medal for Scientific Achievement, as well as the American Association of Clinical Endocrinologist's Distinguished Service to Endocrinology Award. He was the Ex-President of the Association of the Program Directors of Endocrinology, Diabetes and Metabolism, the Association of Subspecialty Professors and the American Diabetes Association.

Claudio Cobelli (S'67–M'70–SM'97–F'03) was born in Bressanone, Italy, on February 21, 1946. He received the Laurea Degree in electrical engineering in 1970 from the University of Padova, Padova, Italy.

In 1981, he was a Full Professor of Biomedical Engineering at the University of Padova. Since 2000, he has been an Affiliate Professor in the Department of Bioengineering, University of Washington, Seattle. He has published around 280 papers in internationally refereed journals and is co-author of several books on modeling of biomedical systems. His main research interests include modeling and identification of physiological systems, especially endocrine-metabolic systems.

He is a Fellow of the Biomedical Engineering Society.

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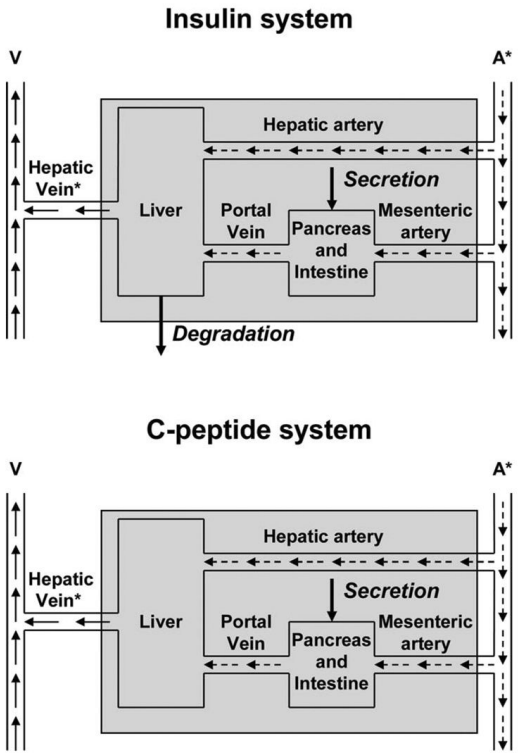

Fig. 1.

Insulin (upper panel) and C-peptide (lower panel) fluxes in the splanchnic bed. Insulin and C-peptide are secreted in equimolar proportion by the pancreas, but only insulin is cleared by the liver. Arterial blood is represented by dashed arrows, venous blood by continuous arrows. Asterisks represent the sampling sites.

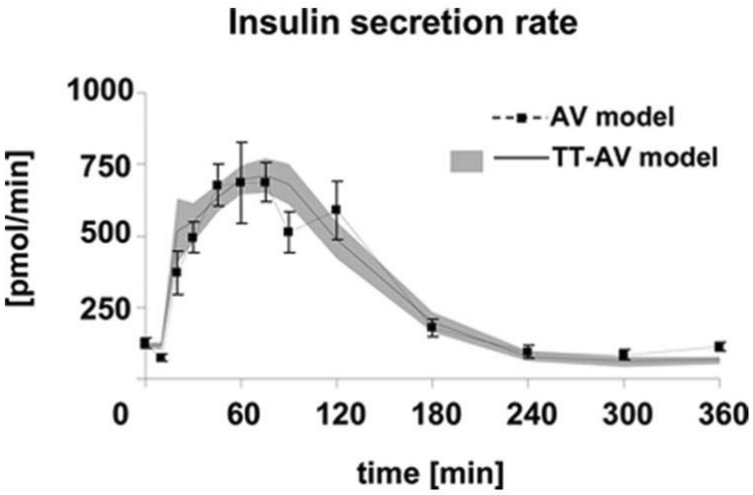

Fig. 2.

Average insulin secretion rate during a meal predicted by the TT–AV model (continuous line, band stays for SEM). Values obtained by applying the AV model at sampling times are also shown as mean SEM (squares-linearly interpolated by the dashed line). The areas under the ± two curves are significantly different ($P < 0.05$ Wilcoxon signed rank test) in the 0–45-min interval following the meal.

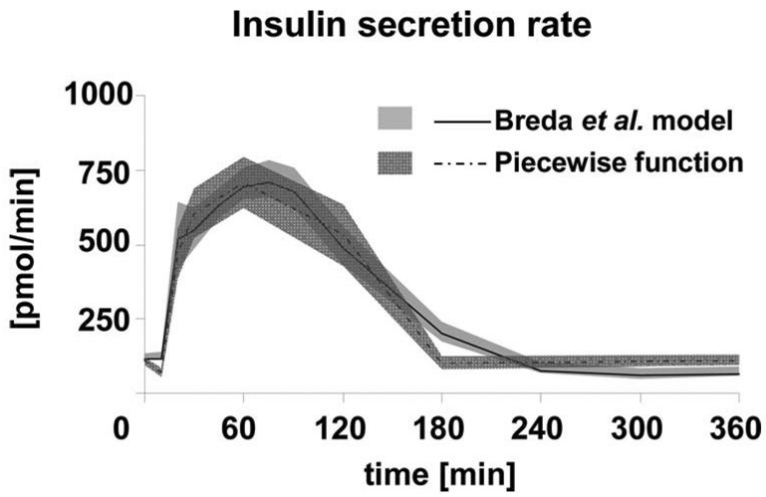

Fig. 3.

Average insulin secretion rate during a meal estimated by the TT–AV model combined either with Breda *et al.* model [12] (continuous line) or with a piecewise function (dashed line) for insulin secretion. Light gray bar stays for SEM of the first, gray for SEM of the second, and overlap of the two is in dark gray.

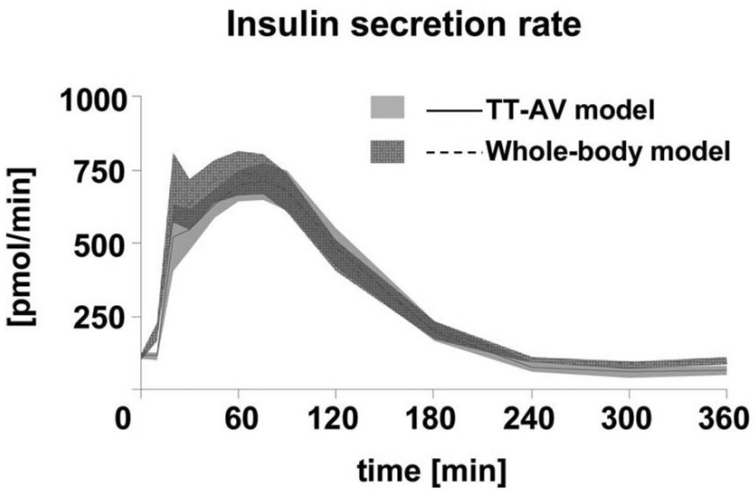

Fig. 4.

Average insulin secretion rate during a meal estimated by TT–AV (continuous line) and whole-body (dashed line) models. Light gray bar stays for SEM of the first, gray for SEM of the second, and overlap of the two is in dark gray.

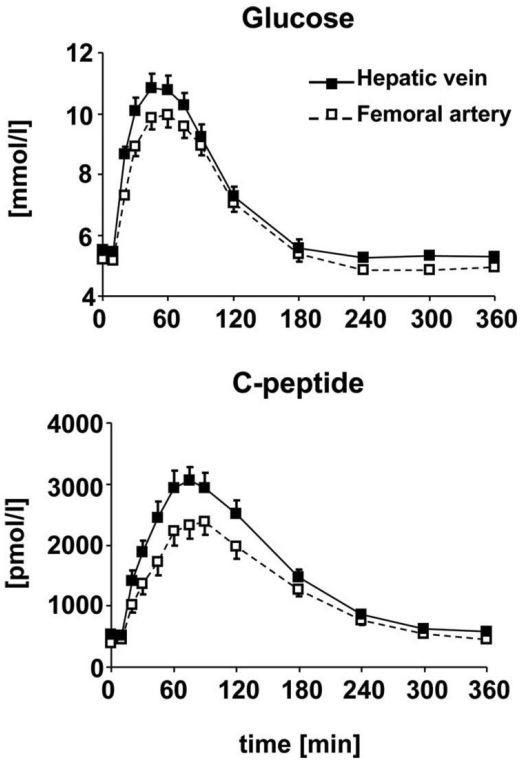

Fig. 5.
Average glucose and C-peptide concentrations in femoral artery (void squares–dashed line) and hepatic vein (full squares–continuous line). Bars denote SEM.