Numerical approximation of mathematical model for absorption of subcutaneously injected insulin

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Abstract—*A pharmacokinetic model is modified to enable quantitation of subcutaneous insulin absorption following insulin injections of soluble insulin and monomeric insulin analogues. The model for soluble insulin includes diffusion, equilibration between hexameric and dimeric insulin and absorption of dimeric insulin molecules. Numerical approximation is carried out by modelling the whole system as a capacitor–resistor network with lumped elements and discrete sources and sinks. By means of the analytical solution for monomeric-insulin absorption, it can be shown that the approximation scheme yields sufficiently accurate results. The modified model for soluble insulin demonstrates dose- and concentration-dependent insulin absorption within the range of therapeutic concentrations and volumes. Additionally, parameters are estimated from published glucose-clamp data. The results of the data fitting indicate that the model presented is adequate for pharmacological studies. The model is suitable for individual parameter estimation from the time course of plasma insulin or from the disappearance curves of radiolabelled injected insulin.*

Keywords—*Analytical solution, Diffusion, Insulin absorption, Mathematical model, Parameter estimation*

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List of symbols

t = continuous time, min
r = radial distance, cm
h, d, m = concentration of hexameric, dimeric, and monomeric insulin, U ml^{-1}
$\bar{I}$ = average insulin concentration of the depot, U ml^{-1}
$\bar{h}, \bar{d}, \bar{m}$ = initial concentration of hexameric, dimeric and monomeric insulin, U ml^{-1}
M_0 = initial concentration of injected monomeric insulin, U m^{-1}
i = concentration of plasma insulin, mU ml^{-1}
h_{ij} = hexameric insulin concentration at locus i, time j, U ml^{-1}
f_i = flux of insulin from shell i to shell $i + 1$, U min^{-1}
Δt = time step, min
∇^2 = Laplacian operator
$\tilde{u}(s)$ = Laplace transform of $u(t)$
$\hat{u}(p)$ = Fourier transform of $u(r)$
Q = chemical equilibrium constant, m U^{-2}
P = rate constant, min^{-1}
D = diffusion constant, cm^2 min^{-1}
B = absorption rate constant, min^{-1}
K_e = insulin elimination-rate constant, min^{-1}
V_0 = injection volume, ml
V_p = distribution volume for insulin, l
V_{SC} = volume of subcutaneous depot, ml
R_i = radius of the outer surface of the spherical shell i, cm
$\bar{R}_i$ = average radius that divides the volume of the spherical shell i in two equal parts, cm
R_d = initial radius of the insulin depot, cm
N = largest number of a shell for the initial insulin depot

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1 Introduction

KNOWLEDGE OF subcutaneous (SC) insulin absorption kinetics is an important clinical prerequisite for adjusting therapy in patients with diabetes mellitus. The factors affecting the absorption rate of insulin from the SC tissue have been widely studied (BERGER *et al.*, 1982; BINDER, 1969; BINDER *et al.*, 1984; GALLOWAY *et al.*, 1981; VORA *et al.*, 1992). However, the detailed mechanisms of SC absorption are still unknown, and constructing a model that describes all

known aspects of the absorption process is difficult. It is a common approach to use mathematical modelling and describe the absorption process approximately (FURLER and KRAEGEN, 1989). A deconvolution approach (COBELLI *et al.*, 1987), empirical models (BERGER and RODBARD, 1989) or compartment models (FISCHER *et al.*, 1983; KOBAYASHI *et al.*, 1983; KRAEGEN and CHISHOLM, 1984; DE MEUER *et al.*, 1989; VORA *et al.*, 1992) have been used in the past. These simplified models are not adequate for predicting insulin absorption kinetics following insulin administration with various volumes and concentrations. On the other hand, a comprehensive model based on *a priori* knowledge and assumptions about absorption kinetics was proposed by Mosekilde *et al.* (1989). This model is able to explain the slow initial absorption phase and the observed inverse relationship between both volume and concentration of the injected insulin and the absorption rate. However, the use of such a complex model in clinical investigations is restricted (COBELLI *et al.*, 1984).

In this study, we have tried to adapt the model of Mosekilde *et al.* (1989) in order to be able to use it in clinical investigations. The model should mimic absorption of soluble insulin in the range of therapeutic concentrations and injection volumes. Moreover, individual parameter estimation from the time course of plasma insulin should be possible.

2 Methods

The distributed parameter model by Mosekilde *et al.* (1989) is based on physical and pharmacokinetic principles: diffusion, dissociation, reversible binding of insulin molecules in the tissue and absorption. It has been assumed that the injected soluble insulin is present in the SC tissue in hexameric and dimeric form and that only dimeric molecules can penetrate the capillary membrane. According to the study by Binder (1969), at very low concentrations and injection volumes (4 U ml^{-1} and 0·01 ml, or 0·4 U ml^{-1} and less than 1 ml), a fraction of the injected insulin is slowly absorbed, a feature that has been explained as temporary binding of insulin in the SC tissue. As the therapeutic concentrations (40 U ml^{-1} and 100 U ml^{-1}) and doses (1 U and above) used are much higher, the binding of insulin is clinically not relevant (MOSEKILDE *et al.*, 1989), and it can be neglected. The model equations corresponding to the modified model are

$$\frac{\partial h}{\partial t} = P(Qd^3 - h) + D\nabla^2 h \tag{1a}$$

$$\frac{\partial d}{\partial t} = -P(Qd^3 - h) + D\nabla^2 d - Bd \tag{1b}$$

Owing to the nonlinear structure of the equations, an analytical solution does not exist. The process of the spatial discretisation is accomplished by dividing the SC region into spherical shells (Fig. 1), in analogy with an electrical network model (Fig. 2). In this capacitor– resistor network model, the volume of a spherical shell corresponds to a capacitor, the insulin concentration corresponds to the voltage, and the insulin flux between the shells corresponds to the electric current. If we assume a spatially constant insulin flow f_i from the shell with radius $\bar{R}_i$ to the shell with radius $\bar{R}_{i+1}$, the following equation is valid:

$$\frac{f_i}{4\pi r^2} = -D\frac{\partial h}{\partial r} \ldots \bar{R}_i < r < \bar{R}_{i+1} \tag{2}$$

After integrtaion with respect to r from $\bar{R}_i$ to $\bar{R}_{i+1}$, we obtain

$$f_i = \frac{4\pi D\bar{R}_i\bar{R}_{i+1}}{\bar{R}_i - \bar{R}_{i+1}}(h_{i+1} - h_i) \tag{3}$$

with

$$\bar{R}_{i+1} = \frac{1}{\sqrt[3]{2}}\sqrt[3]{R_{i+1}^3 + R_i^3} \tag{4}$$

Using the approximation of the time derivative of the concentration in the shell $i + 1$

$$\frac{h_{i+1,n+1} - h_{i+1,n}}{\Delta t} = -\frac{1}{V_{i+1}}(f_{i+1,n} - f_{i,n}) \tag{5}$$

and considering the dissociation of hexameric and the absorption of dimeric molecules in the shell $i + 1$, the following equations for the hexameric and dimeric insulin concentration can be written:

$$\frac{h_{i+1,n+1} - h_{i+1,n}}{\Delta t} = \frac{-3D}{R_{i+1}^3 - R_i^3}\left[\frac{\bar{R}_{i+1}\bar{R}_{i+2}}{\bar{R}_{i+2} - \bar{R}_{i+1}}(h_{i+2,n} - h_{i+1,n}) - \frac{\bar{R}_i\bar{R}_{i+1}}{\bar{R}_{i+1} - \bar{R}_i}(h_{i+1,n} - h_{i,n})\right] + P(Qd_{i+1,n}^3 - h_{i+1,n}) \tag{6a}$$

$$\frac{d_{i+1,n+1} - d_{i+1,n}}{\Delta t} = \frac{-3D}{R_{i+1}^3 - R_i^3}\left[\frac{\bar{R}_{i+1}\bar{R}_{i+2}}{\bar{R}_{i+2} - \bar{R}_{i+1}}(d_{i+2,n} - d_{i+1,n}) - \frac{\bar{R}_i\bar{R}_{i+1}}{\bar{R}_{i+1} - \bar{R}_i}(d_{i+1,n} - d_{i,n})\right] + P(Qd_{i+1,n}^3 - h_{i+1,n}) - Bd_{i+1,n} \tag{6b}$$

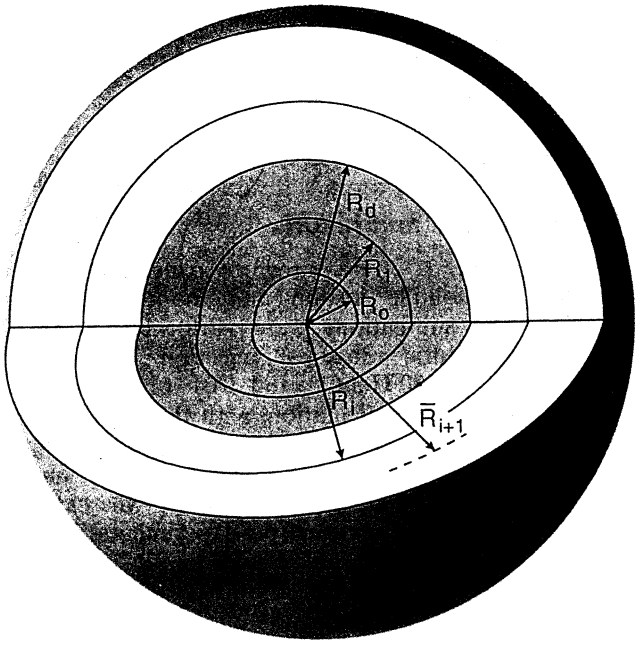

Fig. 1 *Spatial discretisation of subcutaneous depot*

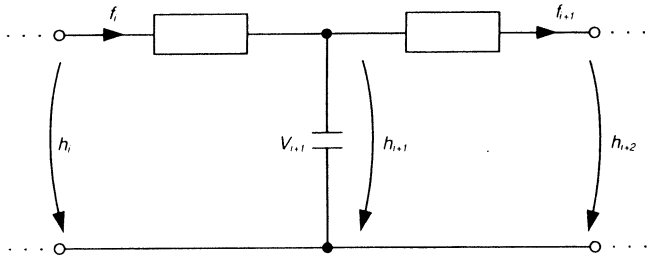

Fig. 2 *Electrical network model for diffusion process*

The next step in the modelling process is the determination of the boundary and initial conditions. We assign zero concentration to a shell with a sufficiently large radius. We have assumed that for $i = 0$ ($R_{-1} = 0$) no insulin flux from the hypothetical shell $i = -1$ takes place. Therefore, the time derivative of the concentration in the zeroth shell can be calculated as follows:

$$\frac{h_{0,n+1}-h_{0,n}}{\Delta t}=\frac{3D}{R_0^3}\frac{\bar{R}_0\bar{R}_1}{\bar{R}_0-\bar{R}_1}(h_{1,n}-h_{0,n}) \tag{7}$$

The initial conditions are

$$h_{n,0}=\begin{cases}\bar{h}\ldots 0<n<N\\ 0\ldots n>N\end{cases} \tag{8a}$$

$$d_{n,0}=\begin{cases}\bar{d}\ldots 0<n<N\\ 0\ldots n>N\end{cases} \tag{8b}$$

with

$$Q\bar{d}^3=\bar{h} \tag{9a}$$

$$R_N=\sqrt{\frac{3V_0}{4\pi}} \tag{9b}$$

$$\bar{I}=\bar{d}+\bar{h} \tag{9c}$$

The time course of plasma insulin concentration was calculated with a single compartment model for insulin distribution and elimination (KRAEGEN and CHISHOLM, 1984). Assuming no endogenous insulin secretion and no circulating antibodies, the plasma insulin can be calculated according to the equation

$$\frac{di}{dt}=\frac{1}{V_p}\int_{V_{sc}}(Bd)dV-K_e i \tag{10}$$

Advances in genetics and molecular biology have provided methods for developing a series of human insulin analogues (BRANGE *et al.*, 1988; KANG *et al.*, 1991). These novel insulins have a reduced tendency to self-association. Several insulin analogues have been produced that remain monomeric at pharmaceutical concentration (BRANGE *et al.*, 1990). Thus the equation for the SC absorption of these monomeric insulin analogues in spherical co-ordinates can be written as

$$\frac{\partial m(r,t)}{\partial t}=D\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial m}{\partial r}\right)-Bm \tag{11}$$

Deriving the discretised equation for monomeric insulin analogues is straightforward. However, in this special case, an analytical solution can be obtained. Using the substitution

$$m(t,r)=\frac{R_d}{r}u(t,r) \tag{12}$$

eqn. 11 can be rewritten as

$$\frac{\partial u(t,r)}{\partial t}=D\frac{\partial^2}{\partial r^2}u(t,r)-Bu(t,r) \tag{13}$$

By applying a Laplace transform with respect to t we obtain

$$\frac{\partial^2}{\partial r^2}\tilde{u}(s,r)-\frac{s+B}{D}\tilde{u}(s,r)=-\frac{u(0,r)}{D} \tag{14}$$

and, by applying Fourier transform with respect to r, the following equation can be obtained:

$$\hat{u}(s,p)=\frac{\hat{u}(0,p)}{Dp^2+B+s} \tag{15}$$

Inverse transformation to the time domain leads to

$$\hat{u}(t,p)=e^{-Bt}\hat{u}(0,p)e^{-Dp^2t} \tag{16}$$

The initial conditions for the substituted function are given by

$$u(0,r)=\begin{cases}\dfrac{\bar{m}}{r}\ldots -R_d<r<R_d, |r|<R_d\\ 0\ldots |r|>R_d\end{cases} \tag{17}$$

With the Fourier transformation of this function

$$\hat{u}(0,p)=\frac{\bar{m}}{R_d}\int_{-R_d}^{+R_d}re^{-jpr}dr \tag{18}$$

we can obtain

$$\hat{u}(t,p)=e^{-Bt}e^{-Dp^2t}\times\frac{\bar{m}}{R_d}\left[-\frac{R_d}{jp}(e^{-jR_dp}+e^{jR_dp})-\frac{1}{p^2}(e^{-jR_dp}-e^{jR_dp})\right] \tag{19}$$

After partial integration of the second part of eqn. 19 in the inverse Fourier-transform integral and using the relationships (MAGNUS *et al.*, 1966)

$$-\frac{1}{p^2}e^{-Dtp^2}e^{\pm jR_dp}\xrightarrow{\text{inverse-transformation}}\sqrt{\frac{Dt}{\pi}}e^{-(r\pm R_d)^2/4Dt}$$

$$-\frac{1}{jp}(e^{-Dtp^2}e^{+jR_dp}+e^{-Dtp^2}e^{-jR_dp}\xrightarrow{\text{inverse-transformation}}-\frac{1}{2}\Phi\left(\frac{r+R_d}{2\sqrt{Dt}}\right)+\frac{1}{2}\Phi\left(\frac{r-R_d}{2\sqrt{Dt}}\right)$$

where $\Phi(x)$ denotes the error function

$$\Phi(x)=\frac{2}{\sqrt{\pi}}\int_0^x e^{-\xi}d\xi \tag{20}$$

the analytical solution of eqn. 11 can be written as follows:

$$m(r,t)=\bar{m}\frac{e^{-Bt}}{2}\left[\Phi\left(\frac{r+R_d}{2\sqrt{Dt}}\right)-\Phi\left(\frac{r-R_d}{2\sqrt{Dt}}\right)+\frac{2}{r}\sqrt{\frac{Dt}{\pi}}\left[e^{-(r+R_d)^2/4Dt}-e^{(r-R_d)^2/4Dt}\right]\right]$$

3 Computations and results

Eqns. 6 and 21 were used to calculate the SC absorption of soluble insulin and monomeric insulin analogues. The simulations were performed within an extended therapeutic range of injection volumes and concentrations (1–100 U ml^{-1} and 0·01–1 ml). The parameter set used for the calculation, with the corresponding References, is given in Table 1. Additionally, model predictions were also calculated including insulin binding in eqn. 6 and using the reported parameters (MOSEKILDE *et al.*, 1989). Parameter estimation from experimental data was performed using the Levenberg–Marquardt method for non-linear least-square optimisation (MARQUARDT, 1963). Data were used from plasma insulin measurements from 12 normal weight healthy volunteers after a glucose-clamp experiment (BOTTERMANN *et al.*, 1985). In this case, the

Table 1 Base parameter set

parameter	value
Q^*, ml^2 U^{-2}	0·13
P^*, min^{-1}	0·5
D^*, cm^2 min^{-1}	9×10^{-5}
B^*, min^{-1}	$1{\cdot}3 \times 10^{-2}$
K_e†, min^{-1}	0·09
V_p†, l	12

* MOSEKILDE *et al.*, 1989
† KRAEGEN *et al.*, 1984

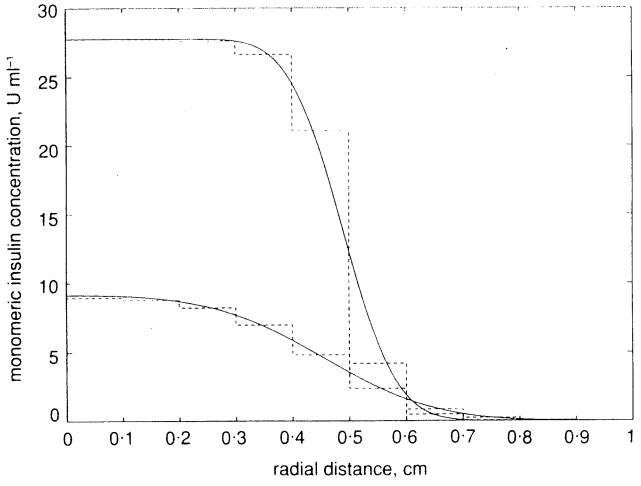

Fig. 3 *Concentration of monomeric insulin analogues following injection of 10 U, 40 U ml^{-1} after 30 (upper solid line) and 180 min (lower solid line) obtained by the analytical solution and the numerical approximation (dashed lines)*

physicochemical parameters (P, Q, D) were held constant, and the absorption rate B and elimination rate constant K_e were estimated. For the distribution-elimination model, 12 l distribution volume was assumed. All simulations were performed on a Digital DECstation 5000/240* using the MATLAB†software package and in-house written extensions.

The results obtained by the analytical solution (eqn. 21) and the approximation of the equation for monomeric insulin analogues with the assumed boundary and initial conditions are given in Fig. 3.

The elapsed time until 50% and 90% (T_{50} and T_{90}) of the injected amount of 1 U (the smallest amount of insulin that can be injected by standard injection pens) and concentration of 40 and 100 U ml^{-1}, using eqn. 6 and the same equation including binding of insulin, is given in Table 2. As can be seen, the process of insulin binding in the SC tissue can indeed be neglected.

Fig. 4 illustrates the effect of the concentration of the injected soluble insulin on the absorption, whereas Fig. 5

* DEC, Massachussets
† MathWorks Inc., Massachussets

Table 2 Influence of insulin binding for therapeutic concentrations of soluble insulin

	T_{50}, min	T_{90}, min
1 U, 40 U ml^{-1}, no binding	108·4	236·2
1 U, 40 U ml^{-1}, binding included	110·0	237·6
1 U, 100 U ml^{-1}, no binding	107·8	220·0
1 U, 100 U ml^{-1}, binding included	108·6	220·4

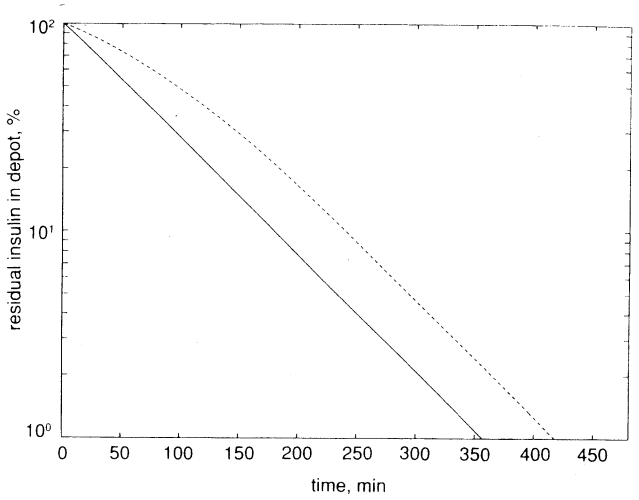

Fig. 4 *Simulations of SC absorption of soluble insulin following injection of 0·3 ml and concentra tion of 1 (solid line), 10 (dashed line), and 100 U ml^{-1} (dotted line)*

demonstrates the ability of the modified model to reproduce the variation of the absorption following different injection volumes and constant concentration. These results are in a very good agreement with the experimentally observed absorption curves (BINDER, 1969). The results of the parameter estimation are given in Fig. 6. The goodness of fit of the model to the data was evaluated from

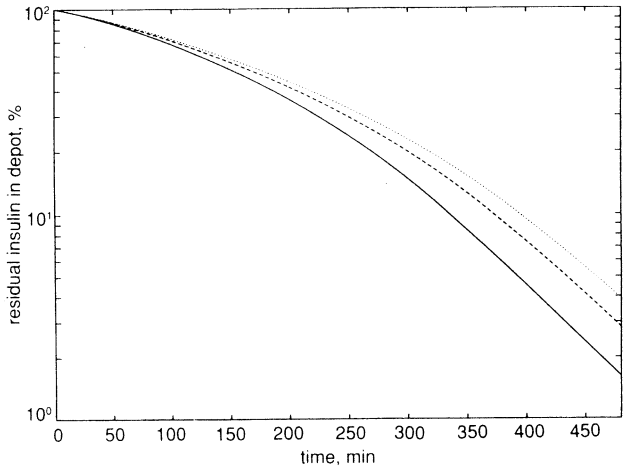

Fig. 5 *Simulations of SC absorption of soluble insulin following injection of 7 (solid line), 14 (dashed line), and 21 U soluble insulin (dotted line), 40 U ml^{-1}*

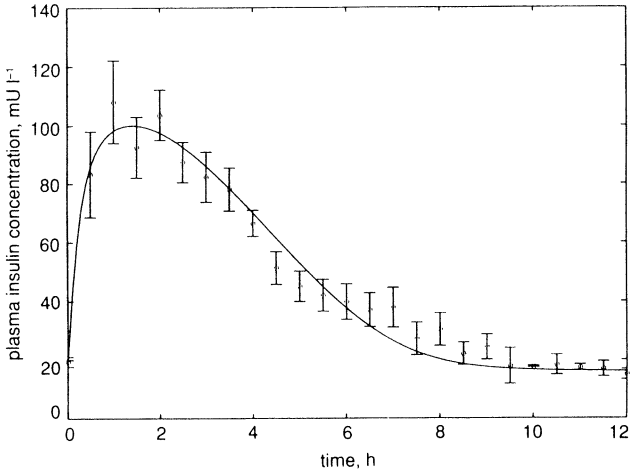

Fig. 6 *Measured plasma insulin concentration (±SEM) and model calculation (continuous line) with estimated parameters; $B = 0{\cdot}017$ min^{-1}, $K_e = 0{\cdot}076$ min^{-1}*

the deviations between measured and model values according to

$$F = 1 - \frac{\sum_{k=1}^{L} (i_{d,k} - i_{m,k})^2}{\sum_{k=1}^{L} i_{d,k}^2} \quad (22)$$

where $i_{d,k}$ is the measured k sample, $i_{m,k}$ is the model value with the estimated parameters, and L is the number of samples ($L = 25$). The goodness of fit (F) was 0·99.

4 Discussion

It is well known that the absorption of SC injected insulin contributes to the day-to-day variability of the insulin requirements. Thus, a mathematical model with special emphasis on the major factors yielding variability can be an important clinical tool for the prediction of plasma insulin levels. As the therapeutic concentrations are either 40 U ml^{-1} or 100 U ml^{-1}, the phenomenon of the dosage dependency of the SC absorption is of great clinical interest. An empirical model (BERGER and RODBARD, 1989) that considers this dependency has been presented in the past. However, this model has not been validated, and its parameters have no physical interpretation. The complete model by Mosekilde *et al.* (1989) has a complex structure, and individual parameter estimation is very difficult to perform. In this study, we have modified the model by Mosekilde *et al.* (1989) in order to allow simulations of SC insulin absorption in a restricted range, i.e. for clinically used insulin concentrations and injection volumes. We have made several assumptions for simplification (but not oversimplification), and it could be shown that these assumptions do not change the results significantly for the defined region of interest.

However, the modified model is still a complex model, and the unknown parameters cannot all be estimated by formal identification techniques. As shown by Cobelli *et al.* (COBELLI *et al.*, 1984), the validation of such a complex model is a three-step procedure; enhancing model testability, adaptive fitting and examining plausability of the model. We have followed this approach to validate the modified model. Further increase of the model testability (model simplification or model decomposition) is not possible without rejecting the model structure or without the use of additional *a priori* knowledge. To our knowledge, no additional data for validating are available as investigations have not yet been made into SC insulin absorption with monomeric, dimeric and non-dissociating hexameric insulin over a wide range of concentrations and injection volumes. In the adaptive fitting stage, the parameter set was derived from data from radiolabelled SC injected insulin (MOSEKILDE *et al.*, 1989) and was used to test the model predictions. Additionally, plausible values of the absorption-rate and elimination-rate constants were estimated from an independent data set of plasma insulin concentration (Fig. 6).

However, in applications with other insulin preparations, where individual parameters of the presented model are of interest, it may be necessary to tune the model to appropriate experimental data. Finally, partial sensitivity analysis was performed by varying each of the parameters by 50% about their nominal values, which still resulted in normal patterns of the model predictions. These facts indicate that the modified model is an adequate representation of the SC insulin absorption of soluble insulin and monomeric analogues within the defined range.

The results of the simulations using the analytical solution and the numerical approximation for monomeric insulin analogues confirm the correctness of our discretisation approach. Thus, the modified model and its numerical approximation can be used for investigation of SC insulin absorption in patients with diabetes mellitus. Depending on the technical facilities of the clinical centre, different experimental protocols for the individual parameter estimation can be used; monitoring residual depot activity after injection of radiolabelled insulin, or measuring plasma insulin. In the first case, parameter estimation is straightforward. Monitoring plasma insulin is less expensive and moreover, this method is widely used. However, care should be taken to avoid possible pitfalls. The subject under investigation should have no endogenous insulin secretion and no residual SC depot insulin. Endogenous secretion can be suppressed by an infusion of somatostatin, whereas exclusion of the residual insulin absorption can be achieved by a sufficiently long time interval after the previous SC injection. Furthermore, it is necessary to quantify the insulin-elimination rate and the distribution volume of insulin using the intravenous route. For the parameter estimation in our study, we had no information about the distribution volume of the subjects in the work by Bottermann *et al.* (BOTTERMANN *et al.*, 1985). Despite this uncertainty, the results of the parameter estimation indicate that the modified model can be used not only in a teaching context, but also in pharmacological studies of currently used and novel insulin preparations (dimeric and monomeric insulin analogues) or simulations of closed-loop control of glucose with SC applied insulin. In addition, the presented approximation approach might be of interest in related fields, such as pharmacokinetic investigations of other subcutaneously administered drugs.

The computation time is an important aspect for the use of this model. The equations of the model are of parabolic type, and it should be ensured that the solution converges. Hence, we have used a rather small time step (0·2 min) for the calculations. On a DECstation 5000/240, a simulation of 8 h takes a few minutes. For hardware with a lower computation speed, we suggest the use of look-up tables for predicting plasma insulin concentration after SC insulin injection.

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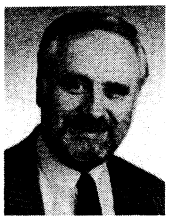
Author's biography



Paul Wach was born in Austria in 1940. H received his diploma and Dr Techn degree in Electrical Engineering from Graz University of Technology, in 1966 and 1967, respectively. Since 1977 he has been Professor and Head of the Department of Biophysics at the Institute of Biomedical Engineering, Graz University of Technology. His main research interests are general field theory, network theory, bioelectricity and biomagnetism and modelling.