Interstitial insulin kinetic parameters for a 2-compartment insulin model with saturable clearance

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Keywords: Biomedical system modelling; simulation and visualization; Control of physiological and clinical variables;

Abstract

Glucose-insulin system models are commonly used for identifying insulin sensitivity. With physiological, 2-compartment insulin kinetics models, accurate kinetic parameter values are required for reliable estimates of insulin sensitivity. This study uses data from 6 published microdialysis studies to determine the most appropriate parameter values for the transcapillary diffusion rate (n_I) and cellular insulin clearance rate (n_C).

The 6 studies (12 data sets) used microdialysis techniques to simultaneously obtain interstitial and plasma insulin concentrations. The reported plasma insulin concentrations were used as input and interstitial insulin concentrations were simulated with the interstitial insulin kinetics sub-model. These simulated results were then compared to the reported interstitial measurements and the most appropriate set of parameter values was determined across the 12 data sets by combining the results.

Interstitial insulin kinetic parameters values $n_I = n_C = 0.0060$ min^{-1} were shown to be the most appropriate. These parameter values are associated with an effective, interstitial insulin half-life, $t_{½} = 58$ minutes, within the range of 25-130 minutes reported by others.

1 Introduction

Glucose-insulin system models are commonly used for identifying insulin sensitivity, either for glycaemic control or diagnostic purposes [1, 2]. Insulin sensitivity quantifies the glycaemic response to insulin. Thus, accurate kinetic parameter values describing the transport of insulin are necessary to obtain reliable estimates of insulin sensitivity.

Insulin-mediated glucose uptake primarily occurs from the interstitial fluid. Insulin from plasma diffuses to the interstitial fluid surrounding tissue cells where it binds to cell-wall receptors, activating glucose uptake [3]. Modelling this behaviour with two insulin compartments is relatively common [4-7]. However, directly measuring the kinetic parameter values is difficult, if not impossible.

This study determines the kinetic parameter values for a two-compartment physiological model with saturable clearance, using data from a number of published microdialysis studies. The specific model used is that described by Lin et al. [5], which treats the insulin kinetics parameters as population constants. Although this model is very similar to those described by Lotz et al. [2] and Pielmeier et al. [6], the published insulin kinetic parameter values are quite different. Hence there is a need for clarification based on physiological measurements.

2 Subjects and Methods

This study used data from 6 published studies (see Table 1) that used microdialysis techniques to assay interstitial insulin levels simultaneously with plasma insulin levels. These measurements enabled direct determination of the kinetic parameter values.

2.1 Interstitial insulin kinetics model

The interstitial insulin kinetics model used in this study was described by Lin et al. [5] and is shown in Equation (1) and graphically in Figure 2. Unlike many other models in this field, the interstitial insulin compartment in this particular model represents a physiological fluid space, rather than an effect compartment, thus permitting back-diffusion to the plasma compartment. Plasma and interstitial insulin concentrations are denoted I and Q, respectively. Receptor-bound insulin saturation dynamics are characterised by a Michaelis-Menten function with saturation parameter α_G = 1/65 l.mU^{-1} [5].

$$\dot{Q} = n_I(I - Q) - \frac{n_C Q}{1 + \alpha_G Q} \qquad 1$$

There are only two parameters that affect interstitial insulin kinetics at physiological concentrations. The parameter n_I represents the transcapillary diffusion rate between the I and Q compartments. The parameter n_C represents the irreversible cellular insulin clearance rate. Thus, only one equation is required, and the desired variables are separated from any other equations, data, or parameter values, eliminating any other potential biases.

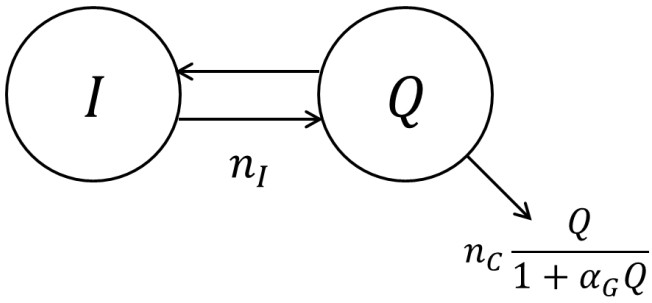

Figure 1. Schematic representation of compartmental interstitial insulin transport kinetics model.

The transformation shown in (2) defines γ, the steady state ratio of interstitial insulin (Q) to plasma insulin (I) concentrations, in the absence of any saturation effects [6].

$$\gamma = \frac{n_I}{n_I + n_C} \qquad 2$$

The results of this study are presented in terms of n_I and γ as the parameter γ provides a more intuitive insight than n_C to the relative interstitial insulin concentrations at physiological levels. However, the modelling was performed using n_C from which γ was subsequently calculated. Thus saturation and non-steady-state effects were treated correctly.

2.2 Microdialysis analysis

To identify n_I and γ in a direct, physiological manner, data were used from 6 published studies (12 data sets). These studies used microdialysis to determine interstitial insulin concentrations. Plasma insulin concentrations were taken simultaneously. The 6 independent studies were conducted using infused and endogenous insulin at varying physiological and supra-physiological levels. Data used in this analysis was taken from the published reports of the studies listed in Table 1.

Using reported arterial insulin concentrations (I) as input, interstitial concentrations (Q) were simulated with the interstitial insulin kinetics sub-model described in (1). These simulated results were then compared to the reported interstitial measurements.

A grid-search was performed over a range of n_I and γ values to find the region of minimum error between simulated and measured interstitial insulin concentrations. The resolution of the grid was 0.0001 min^{-1} for n_I and 0.01 for γ. For any given parameter pair, the error value was defined as the sum of absolute differences between the simulated and measured concentrations at the experimental sampling points, divided by the number of sample points (mean absolute error), normalised by the mean interstitial insulin level during the experiment. Errors across all data sets were evaluated by two methods to ensure

robust parameter values that were not skewed by data from a single study. Specifically:

I. Each error value was weighted equally, by summing error magnitude at each (n_I, γ) pair across all data sets.

II. Each study was weighted equally by scaling the calculated errors into the range [0-1] prior to summing across all data sets.

Table 1. Published microdialysis studies used to investigate interstitial insulin kinetic parameters. N = number of subjects.

Study	Study Method	Study Population	N	Interstitial sampling location
Jansson et al. [8]	Euglycaemic-hyperinsulinaemic clamp	Healthy non-obese	5	Abdominal subcutaneous fat
Castillo et al. [9]	Euglycaemic-hyperinsulinaemic clamp	Healthy: Body fat <=12%	3	Subcutaneous lymph vessel; lower leg
	Euglycaemic-hyperinsulinaemic clamp	Healthy: Body fat 13-21%	5	Subcutaneous lymph vessel; lower leg
	Euglycaemic-hyperinsulinaemic clamp	Healthy: Body fat 22-35%	3	Subcutaneous lymph vessel; lower leg
	Euglycaemic-hyperinsulinaemic clamp	Healthy: Body fat >=36%	2	Subcutaneous lymph vessel; lower leg
Sjostrand et al. [10]	Euglycaemic-hyperinsulinaemic clamp	Healthy lean	10	Forearm muscle
	Euglycaemic-hyperinsulinaemic clamp	Healthy obese	10	Forearm muscle
Gudbjornsdottir et al. [11]	Euglycaemic-hyperinsulinaemic clamp	Healthy lean	10	Forearm muscle
Herkner et al. [12]	Oral glucose tolerance test	Healthy lean	8	Mid-thigh muscle
	Euglycaemic-hyperinsulinaemic clamp	Healthy lean	8	Mid-thigh muscle
Sjostrand et al. [13]	Oral glucose tolerance test	Healthy lean	10	Forearm muscle
	Oral glucose tolerance test	Healthy obese	10	Forearm muscle

It should be noted that the data from the Sjostrand et al. study [13] was corrected prior to use in this analysis for the labelling error present in the original article, as per their retraction [14].

2.3 Sensitivity to dynamic parameters

The sensitivity of the results to the specific value of the parameter α_G was also investigated. Although it is a dynamic parameter, the value of α_G could

potentially impact the observed kinetics by saturating the clearance of receptor-bound insulin in this type of simulation. The grid-search was repeated for two extreme values of α_G = 0 l.mU^{-1} and α_G = 2x $\alpha_{G\_nominal}$, representing conditions of no saturation and receptor saturation at very low insulin concentrations.

3 Results and Discussion

Grid-search results for the parameter optimisation using published microdialysis data are shown in Figure 2. The left panel shows the results from method I where each error value was weighted equally. The right panel shows the results from method II where each study was weighted equally. Data from the Herkner et al. [12] clamp study have been omitted as the minimum error was located at $n_I = 0$, which was not physiologically reasonable.

Figure 2 shows the regions around the minimum error points, where the contours enclose errors 1% and 5% greater than the minimum values. The parameter set, n_I =0.0060 min^{-1}, γ = 0.5 ($n_I = n_C$) is enclosed within the 5% region and thus provides a good compromise between the two identified minima and previous results, while indicating limited precision with only one significant figure. The choice of γ = 0.5 is consistent with that used by Lin et al. [5] and similar to the value of 0.6 used by Lotz et al. [2] and Pielmeier et al. [6].

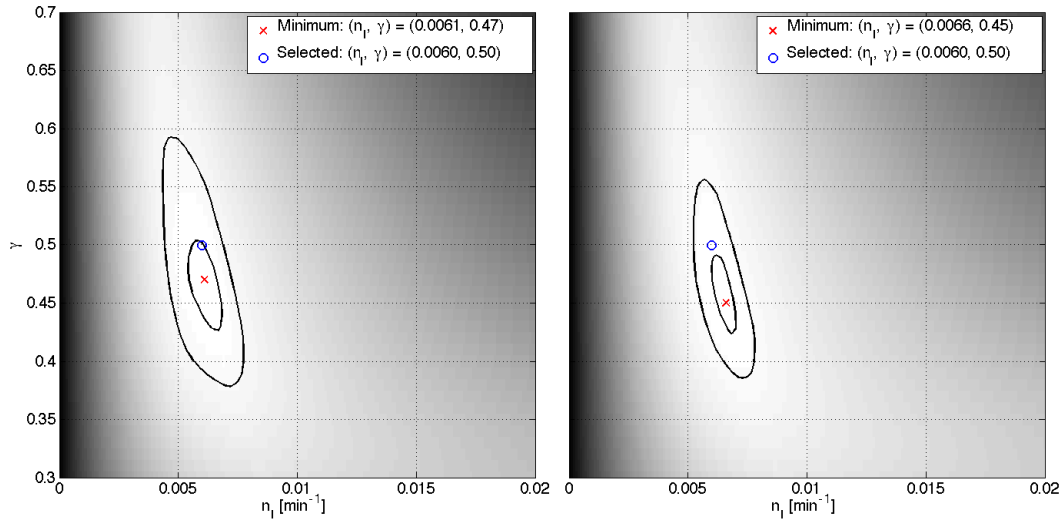

Figure 2. Grid-search error results from microdialysis analysis showing optimal parameter values. The left panel shows the results where each error value was weighted equally (method I), and the right panel shows the results where each study was weighted equally (method II). Contours are at error 1% and 5% greater than the minimum. Lighter areas represent lower error and darker areas, greater.

Figure 3 presents the same contours as Figure 2 (shown in red) with additional contours for two extreme values of the saturation parameter, α_G = 0 and 2/65 l.mU^{-1}. The nominal value used in the glucose-insulin model is α_G = 1/65 l.mU^{-1}. This dynamic parameter has little impact on the value of n_I, as expected, but does cause a shift in the optimal values of n_C (γ), which directly models insulin clearance from the receptor. The black circle indicates the selected parameter set. This result suggests that the identified insulin transport kinetic parameters are not unduly influenced by the choice of saturation parameter value.

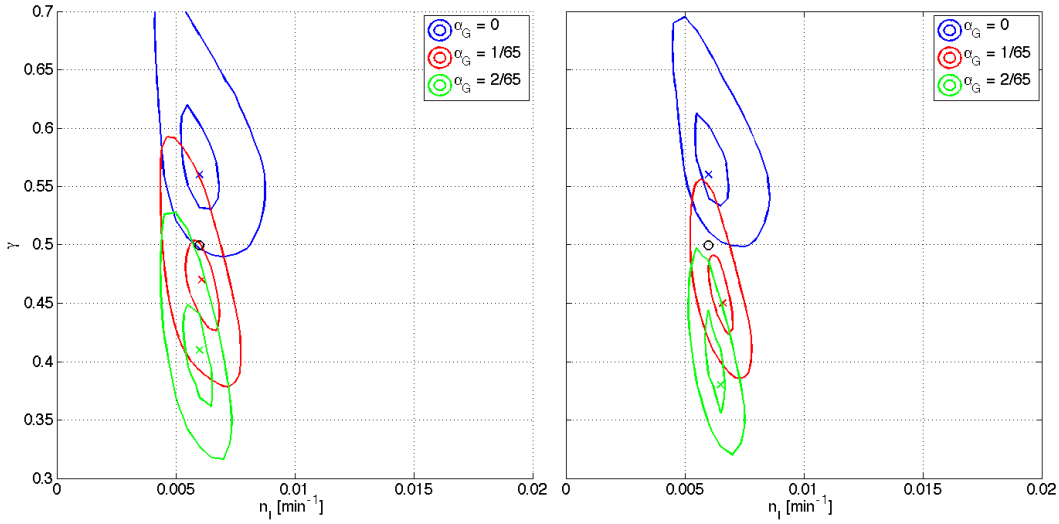

Figure 3. Error contours from Figure 2 (red) supplemented by two further sets of contours representing the impact of varying the value of α_G. The black circle shows the location of the selected parameter set as a good compromise between the nominal value of α_G and two extreme values.

Table 2 shows the individual optimal parameter values for each dataset. The associated errors are shown along with the error obtained using the selected parameter set, n_I =0.0060 min^{-1}, γ = 0.5. The errors presented are unitless and represent the mean absolute error across the experimental sampling points for that study, normalised by the average interstitial insulin concentration during the experiment. The associated standard deviations are also shown in brackets.

Table 2. Individual results from published microdialysis studies. Study minimum error is associated with the study optimal n_I and γ. The error at the selected parameter set, n_I =0.0060 min^{-1}, γ = 0.5 is also shown. Errors are unitless and represent mean absolute error (standard deviation) across the measurement points, normalised by the average interstitial insulin concentration. Abbreviations; Clamp: Euglycaemic-hyperinsulinaemic clamp; OGTT: Oral glucose tolerance test.

Study	Study Method	Study Population	Study optimal n_I [min^{-1}]	Study optimal γ	Study min. error	Error at selected (n_I, γ)
Jansson et al. [8]	Clamp	Healthy non-obese	0.0051	0.30	0.14 (0.15)	0.23 (0.20)
Castillo et al. [9]	Clamp	Healthy: Body fat <=12%	0.0031	0.52	0.10 (0.09)	0.31 (0.22)
	Clamp	Healthy: Body fat 13-21%	0.0048	0.61	0.04 (0.03)	0.09 (0.07)
	Clamp	Healthy: Body fat 22-35%	0.0041	0.60	0.03 (0.03)	0.10 (0.05)
	Clamp	Healthy: Body fat >=36%	0.0041	0.42	0.04 (0.04)	0.20 (0.09)
Sjostrand et al. [10]	Clamp	Healthy lean	0.0128	0.45	0.06 (0.05)	0.19 (0.12)
	Clamp	Healthy obese	0.0053	0.70	0.06 (0.06)	0.07 (0.07)
Gudbjornsdottir et al. [11]	Clamp	Healthy lean	0.0060	0.69	0.14 (0.18)	0.18 (0.19)
Herkner et al. [12]	OGTT	Healthy lean	0.0110	0.30	0.30 (0.53)	0.46 (0.49)
	Clamp	Healthy lean	0	0	0.14 (0.16)	1.55 (0.76)
Sjostrand et al. [13]	OGTT	Healthy lean	0.0600	0.56	0.10 (0.15)	0.61 (0.40)
	OGTT	Healthy obese	0.0500	0.44	0.06 (0.06)	0.52 (0.32)

The optimal parameter values vary widely across the 12 data sets, particularly for n_I. This variability could reflect the inter-patient differences, poor mixing of interstitial fluid, the difficulty of microdialysis techniques or lack of sensitivity to these parameter values.

Figure 4 shows two contrasting examples of the simulated and measured interstitial insulin concentrations using the selected parameter values. Panels A and B show data from the Castillo study [9] for subjects with body fat in the range of 13-21%. Panels C and D show data from the oral glucose tolerance test (OGTT) study by Herkner et al. [12]. Measured arterial insulin is presented in the top panels (A and C), with measured and modelled interstitial insulin in the bottom (B and D) along with the absolute error between them. These two studies had similar insulin concentrations and thus make a good comparison.

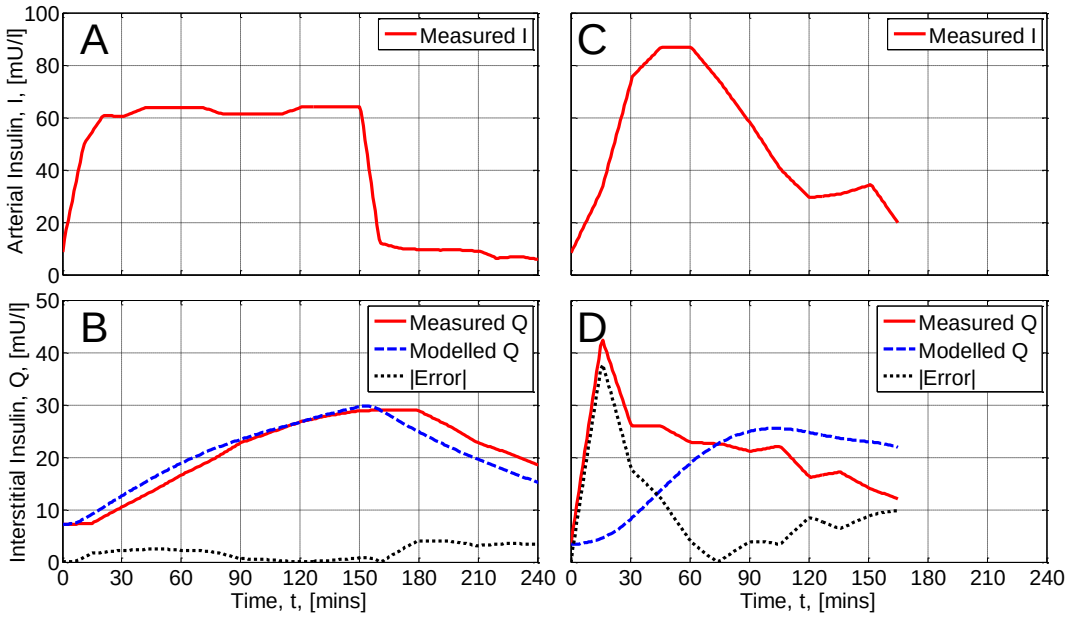

Figure 4. Two contrasting examples from the simulation of microdialysis data using selected parameter set, n_I =0.0060 min^{-1}, γ = 0.5. The panels on the left show a good model fit to measured data from Castillo et al. [9] (body fat 13-21%). The panels on the right show a poor fit from Herkner et al. [12] (OGTT). The upper panels present plasma insulin concentrations and the lower panels measured and modelled interstitial insulin concentrations.

The model fit to data is very good for the Castillo study [9] in the left panel, but less so for the Herkner study [12] in the right panel. The interstitial insulin peak at 15 minutes in the Herkner study does not correspond to any feature in the plasma insulin profile. The plasma insulin-sampling scheme may have missed a peak, the interstitial insulin peak may be spurious, or insulin may have been transported to the interstitium independent of plasma as the authors' propose.

The Herkner study was conducted using oral glucose (75 grams) to stimulate insulin secretion. Therefore, a sharp plasma insulin peak would not be expected [15], particularly within 15 minutes of glucose ingestion. The insulin kinetics model used for this analysis relies on passive diffusion of insulin across the endothelium. Hence, with no plasma insulin peak to create a sharp concentration gradient, the model could not reproduce the reported peak in interstitial insulin, resulting in the poor fit. As noted previously, data from the Herkner et al. [12] clamp study were omitted from this analysis.

Modelled interstitial insulin profiles did not fit either data set from the Herkner et al. [12] study very well. The OGTT example from this study is shown in the right panel of Figure 4. The other data set from Herkner involved a euglycaemic-hyperinsulinaemic clamp procedure, in which the interstitial insulin concentrations were lower than during the OGTT study (<10 mU/l), despite sustained higher plasma levels (>65 mU/l for 60 minutes). There were no obvious reasons for these poor fits and they may be due to the complicated and difficult nature of microdialysis sampling of interstitial fluid.

The remaining studies had mean absolute error values at their individual optimal parameter values of less than 15% of their average interstitial insulin concentration. At the selected parameter set, the errors were less than 30%, except for the OGTT study by Sjostrand et al. [13]. The optimal n_I values for these two datasets were very high (n_I = 0.060 and 0.050 min^{-1}, respectively), though similar to those used by Lotz et al. [2]. Hence, the errors for this study were large with the much smaller value of n_I = 0.0060 min^{-1} selected.

When using this insulin kinetics model and these parameter values for modelling insulin-mediated glucose uptake, the impact of the errors is likely to be less than the reported values. The values presented in Table 2 were calculated using the absolute value of error at each sample point, to provide a measure of goodness-of-fit for the model. However, glucose uptake is determined by the area under the curve and thus the signed error values would be more appropriate to gauge this effect and would be equal to, or smaller than those reported. Thus, these values provide an upper bound on the expected model errors.

3.1 Comparison of results

Using direct physiological measurements from 6 published microdialysis studies, the most appropriate parameter values n_I = 0.0060 min^{-1}, γ = 0.5 were identified. The parameter value, γ = 0.5 ($n_I = n_C$) is unchanged from the value reported by Lin et al. [5] and similar to γ = 0.6 used by Lotz et al. [2] and Pielmeier et al. [6]. However, n_I = 0.0060 min^{-1} is higher than that reported by Lin et al. [5] (n_I = 0.0030 min^{-1}), but considerably lower than the values, n_I = 0.0486 min^{-1} and 0.0300 min^{-1} reported by Lotz et al. [2] and Pielmeier et al. [6], respectively.

The value of n_I identified for the ICING model by Lin et al. [5] was approximately 16-times smaller than that used by Lotz et al. [2] for healthy and diabetic subjects. The result of this reduction in transcapillary diffusion (n_I) and cellular insulin clearance rates, was that insulin persisted much longer in the interstitial compartment, reflecting the insulin pooling and delayed utilization effects observed in critically ill patients by Doran et al. [16].

The parameter value for n_I used by Lotz et al. [2] was the transcapilliary diffusion rate for C-peptide identified by Van Cauter et al. [17]. This choice was justified on the grounds that insulin and C-peptide have similar molecular weights (5.8 kDa and 3.6 kDa, respectively) and passive properties. Parameter values were identified for each individual based on age, gender, body surface area and diabetic or obese status, as proposed by Van Cauter et al. The mean value identified across the study cohort was $n_I = 0.0486$ min^{-1} [2]. The value of $n_I = 0.0300$ min^{-1} attributed to Pielmeier et al. [6] was calculated in the same way as in Lotz et al. [2], but using example data presented for a single subject.

A possible reason for the discrepancy between the values identified in this study and those of Lotz et al. and Pielmeier et al. is that trans-endothelial insulin diffusion is a saturable process [5]. The experimental diffusion rates adopted from Van Cauter et al. [17] are determined by using C-peptide measurements. Although C-peptide has very similar molecular properties to insulin, it does not go through a high and variable degree of first pass extraction in the portal vein [17]. Therefore, its concentration is several folds higher than insulin in plasma. If the diffusion process is to any level saturable [18], the rates determined using C-peptide measurements would not be reflective of insulin.

The ‘effective’ or interstitial half-life of insulin is defined by the interstitial kinetic parameters in (3) [5]. This half-life characterizes the clearance rate of insulin from the interstitium where it effects the uptake of glucose into tissue cells. Previously published reports suggest values in the range 25-130 minutes [19-21]. The range of effective half-lives for the study-specific optimal parameters of Table 2 is 6-116 minutes, with a mean value of 58.6 minutes.

$$t_{½} = \frac{log_e(2)}{n_I + n_C} \quad (3)$$

The effective half-life associated with the kinetic parameters identified by Lin et al. [5] was t½ = 116 minutes. This value better matched data from previous studies than the short t½ = 9 minutes used by Lotz et al. [2]. The effective half-life insulin determined from the selected values of n_I and n_C identified in this study is t½ = 58 minutes; this value is within the range reported by previous studies and is very close to the mean value for the study-specific optimal values.

3.2 Limitations

A significant limitation of this study is the dearth of reliable interstitial insulin data and the difficulty associated with obtaining it. This lack of reliable data necessitates population constant values for the kinetic parameters in the current model. If more information becomes available, the use of separate values for specific sub-populations could be investigated. For example, critically ill patients are typically sedated and their lack of movement may slow the transport kinetics, as the circulation and mixing of interstitial fluid is achieved by diffusion and the passive effects of muscle contraction and movement [22]. However, at present and within the framework of the glucose-insulin system model, errors arising from differences between the population constant kinetic parameter values and the actual, patient-specific values are captured by the identified insulin sensitivity parameter as noise.

4 Conclusions

This study used data from 6 published microdialysis studies to determine the most appropriate parameter values. Using direct physiological measurement data from the microdialysis studies provided a sound physiological foundation for the kinetic parameter values.

The results of this investigation suggest that the most appropriate values for the interstitial insulin kinetic parameters for this type of model are $n_I = n_C = 0.0060$ min^{-1}. These parameter values are associated with an effective, interstitial insulin half-life $t_{½} = 58$ minutes, within the range of 25-130 minutes reported by others. Further, these identified insulin transport kinetic parameters are not unduly influenced by the value of Michaelis-Menten saturation parameter value, within a physiologically valid range.

Acknowledgments

The authors would like to acknowledge the input of several people with whom discussions and debates culminated in this work. The early work of developing the physiological 2-compartment model was done in collaboration with Steen Andreassen and Ulrike Pielmeier from the University of Aalborg, Denmark. Subsequent debates about the most appropriate parameter values directly prompted this investigation. Paul Docherty from the University of Canterbury, New Zealand has also provided invaluable input to the development of the model and advice during this investigation.

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