BioSim
EU NETWORK OF EXCELLENCE

Advantages and challenges of mechanism-based modeling approach to drug development and testing

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BioSim group at the 1st BioSim conference

Activity Areas and Work Packages

The purpose of the BioSim Network is to illustrate how the use of simulation models can contribute to a more rational drug development process and a better health care.

1 Regulatory issues

- Public relations
- Simulation / 3R
- Drug absorption
- PK/PD models

2 Diabetes

- Pancreatic cells
- Fat cells
- Metabolic regulation
- Disease models

3 Hypertension

- Heart cells
- Full heart model
- Kidney models
- Vascular system

4 Cancer

- New drugs
- Drug testing
- Circadian rhythms
- Chronotherapy

5 Mental disorders

- Gene expression
- Trauma
- Cell communication
- Deep brain stimulation

6 Methodology

- Network models
- Complex systems
- Nonlinear data analysis
- Simulation tools

The mechanism-based modeling approach

In mechanism-based modeling

- We try to represent the assumed biological and pharmacological processes as realistically as possible. In many cases, we do not know what these processes are, and the modeling exercise therefore serves to examine different sets of assumptions.

- The models must respect conservation laws, dimension relations and time scales. In practice this often means that the models are constructed around the material conservation equations.

- We try to base the functional form of the nonlinear relations on chemical and physical considerations, and all parameters are in principle determined from independent experiments.

- The models are initially validated on their ability to reproduce observed wave forms, frequencies, amplitudes, phase relationships, parameter dependences, and stability properties.

- Further validation of the models is based on their ability to predict the outcome of new experiments, performed under conditions not previously investigated.

Two Complementary Modeling Approaches

The generic model: $$\frac{d\bar{x}}{dt} = \bar{F}(\bar{x}, \bar{p}, t)$$

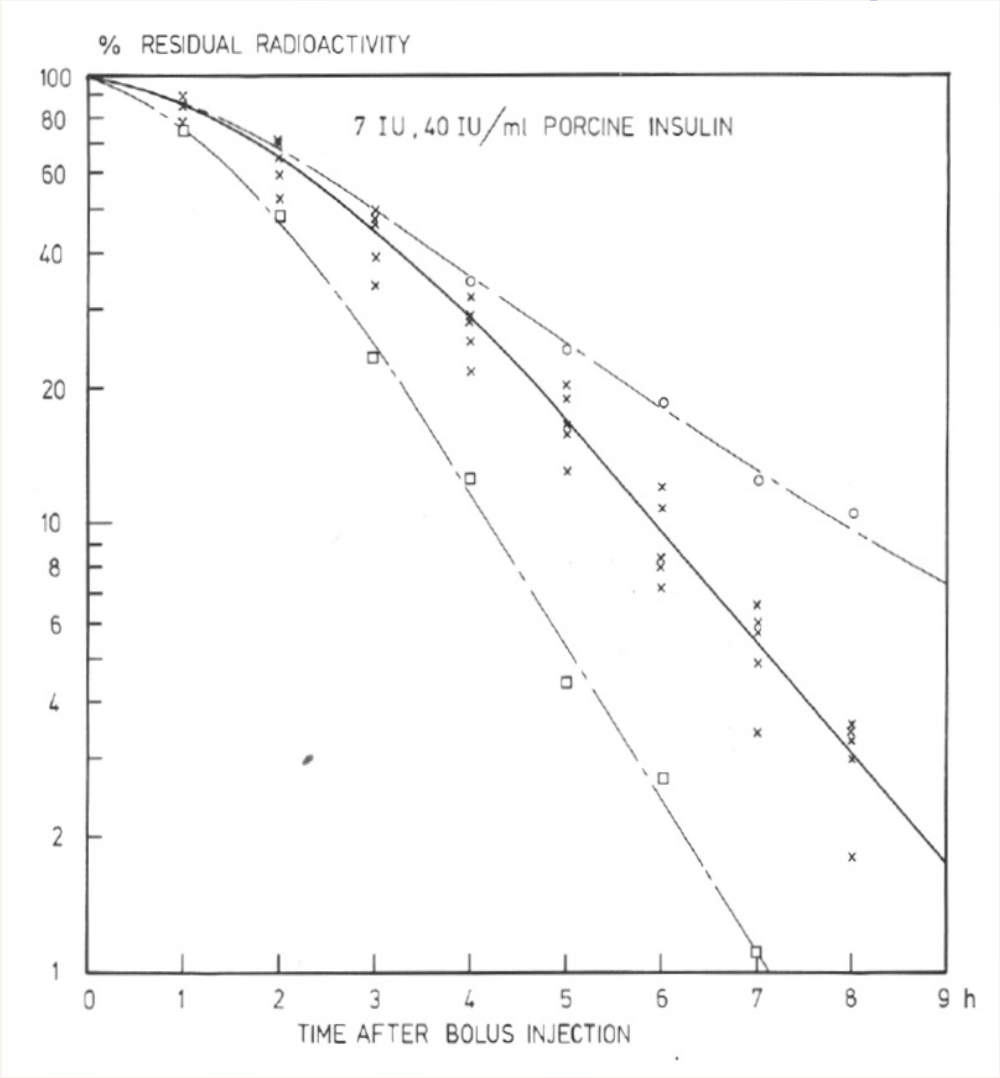
has variables $\bar{x}$, parameters $\bar{p}$, and a structure $\bar{F}$ that describes the interrelations between variables and parameters.

A One can assume the structure $\bar{F}$ to be known. With appropriate statistical methods one can then use the model to determine the parameter values that best reproduce a given set of experimental results.

This usually requires that the model is linear and fairly limited in size. Moreover, the approach in general does not allow neither accumulation of knowledge nor use of information from other sources.

B One can consider determination of the structure $\bar{F}$ to be the purpose of the investigation. In this case the parameters must be known, i.e., determined through independent experiments, and one can then use the experimental observations to determine the most appropriate structure.

Subcutaneous Absorption of Soluble Insulin



Absorption curves for 7 type-I diabetic patients following a bolus injection of 0.2 ml radio-labelled 40 IU/ml soluble insulin (Velosulin®).

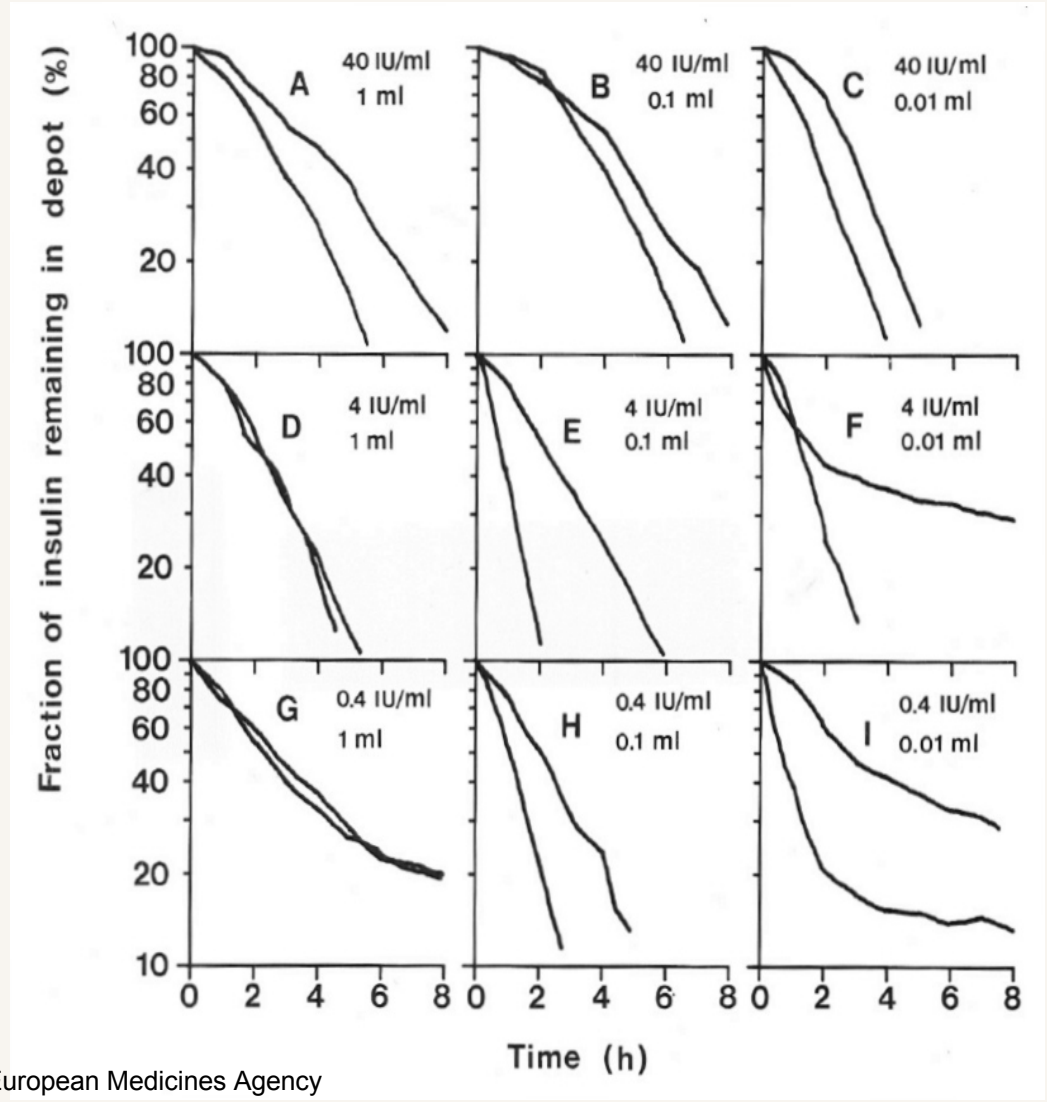
The fraction of insulin remaining in the subcutaneous depot was measured over an 8h period.

Note the initial reduced absorption rate.

With Christian Binder, Steno Memorial Hospital.

Updated in collaboration with Tue Søborg, Danish Medicines Agency and Morten Colding-Jørgensen, Novo Nordisk

Absorption curves for Different Volumes and Concentrations

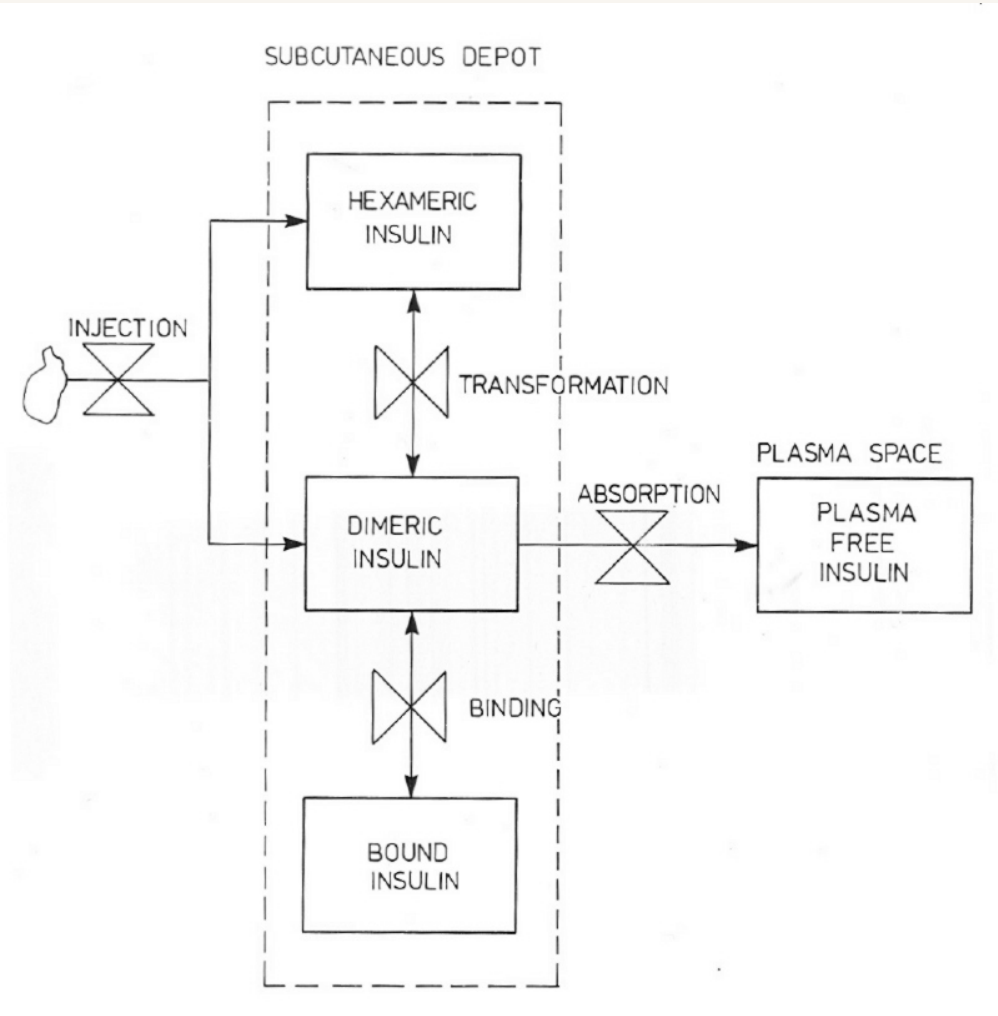


There is both a volume and a concentration effect.

The delayed initial absorption is observed only for high volumes and high concentrations.

At low volumes and low concentrations a tail phenomenon develops.

Absorption Model of Soluble Insulin



$$\frac{\partial C_H}{\partial t} = P(QC_D^3 - C_H) + D\nabla^2 C_H$$

$$\frac{\partial C_D}{\partial t} = -P(QC_D^3 - C_H) + D\nabla^2 C_D - BC_D - SC_D(C - C_B) + \frac{C_B}{T}$$

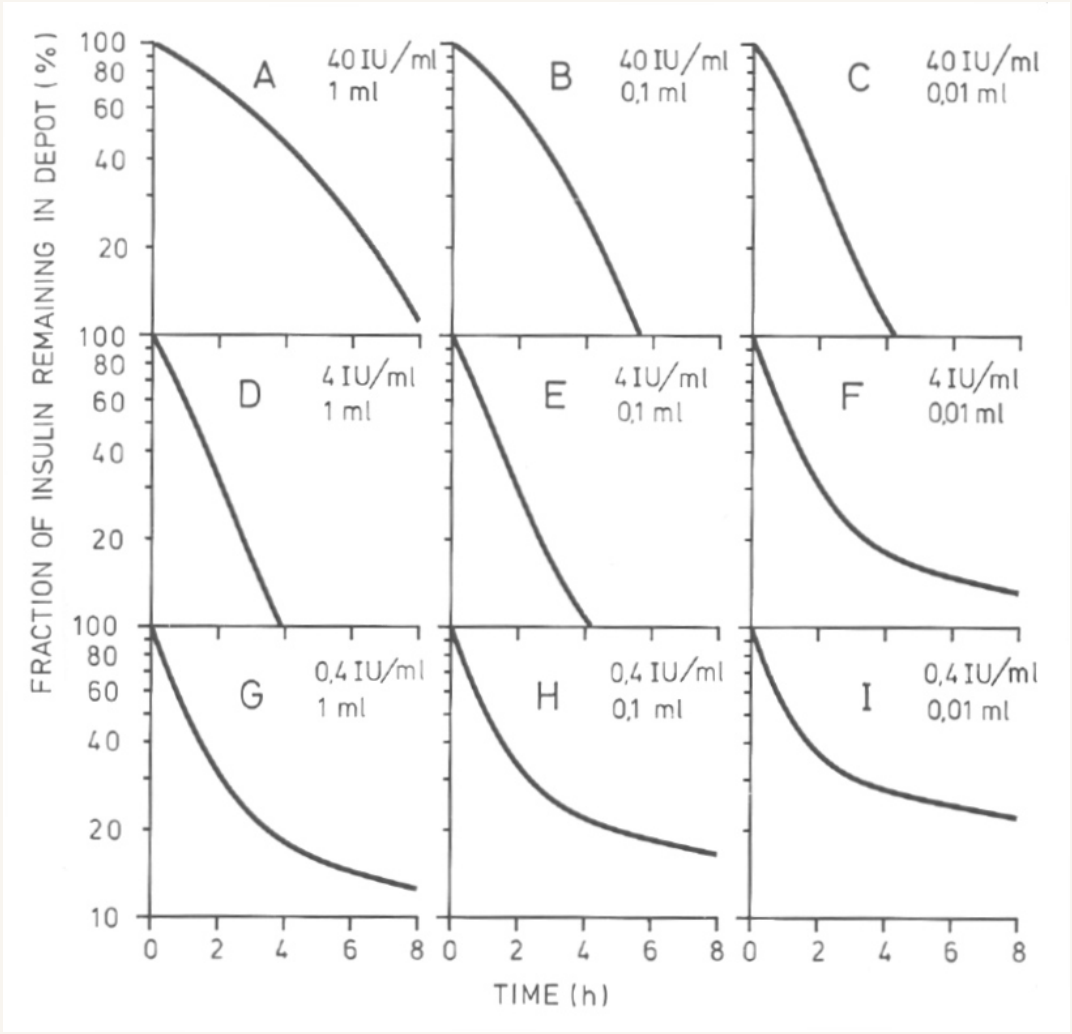
$$\frac{\partial C_B}{\partial t} = SC_D(C - C_B) - \frac{C_B}{T}$$

C_H, C_D and C_B represent the local concentrations of hexameric, dimeric, and bound insulin, respectively.

The terms $D\nabla^2 C_H$ and $D\nabla^2 C_D$ describe the rates of diffusion of the mobile insulin.

P and S are assumed to be large enough to establish quasiequilibrium.

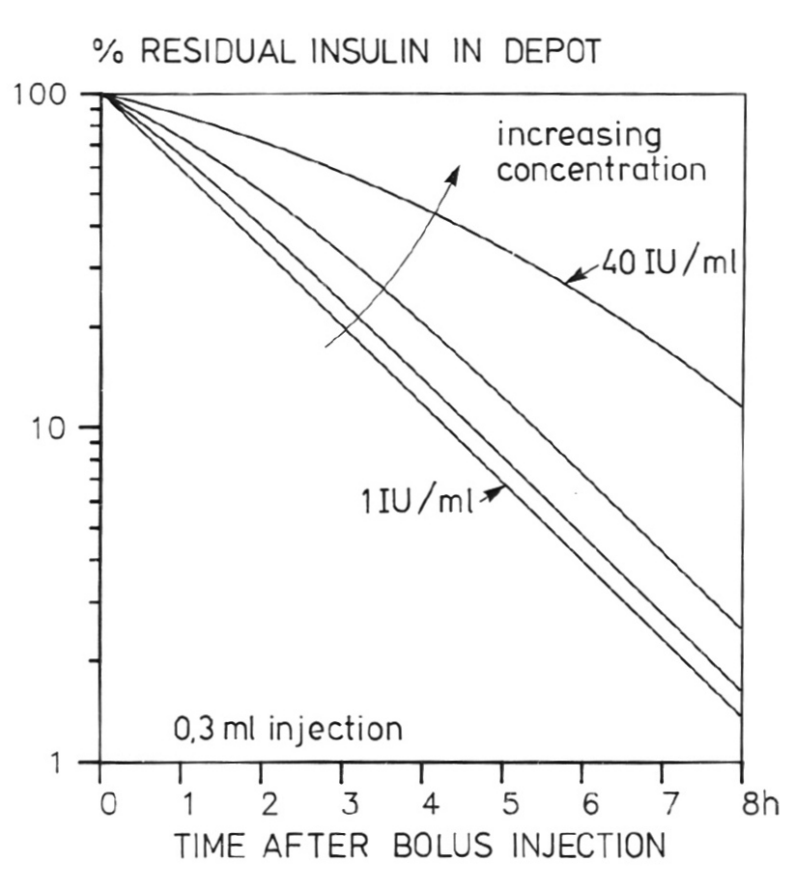
Simulation Results

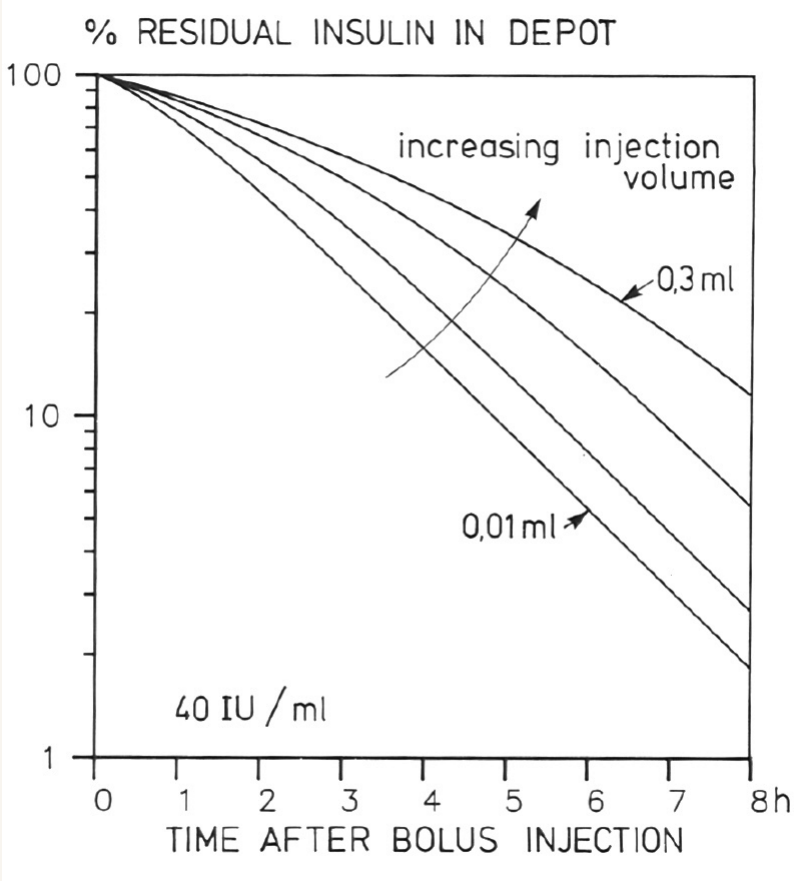


The model can reproduce the general characteristics of the observed insulin absorption curves.

By fitting the model to individual patients one can determine all the involved parameters.

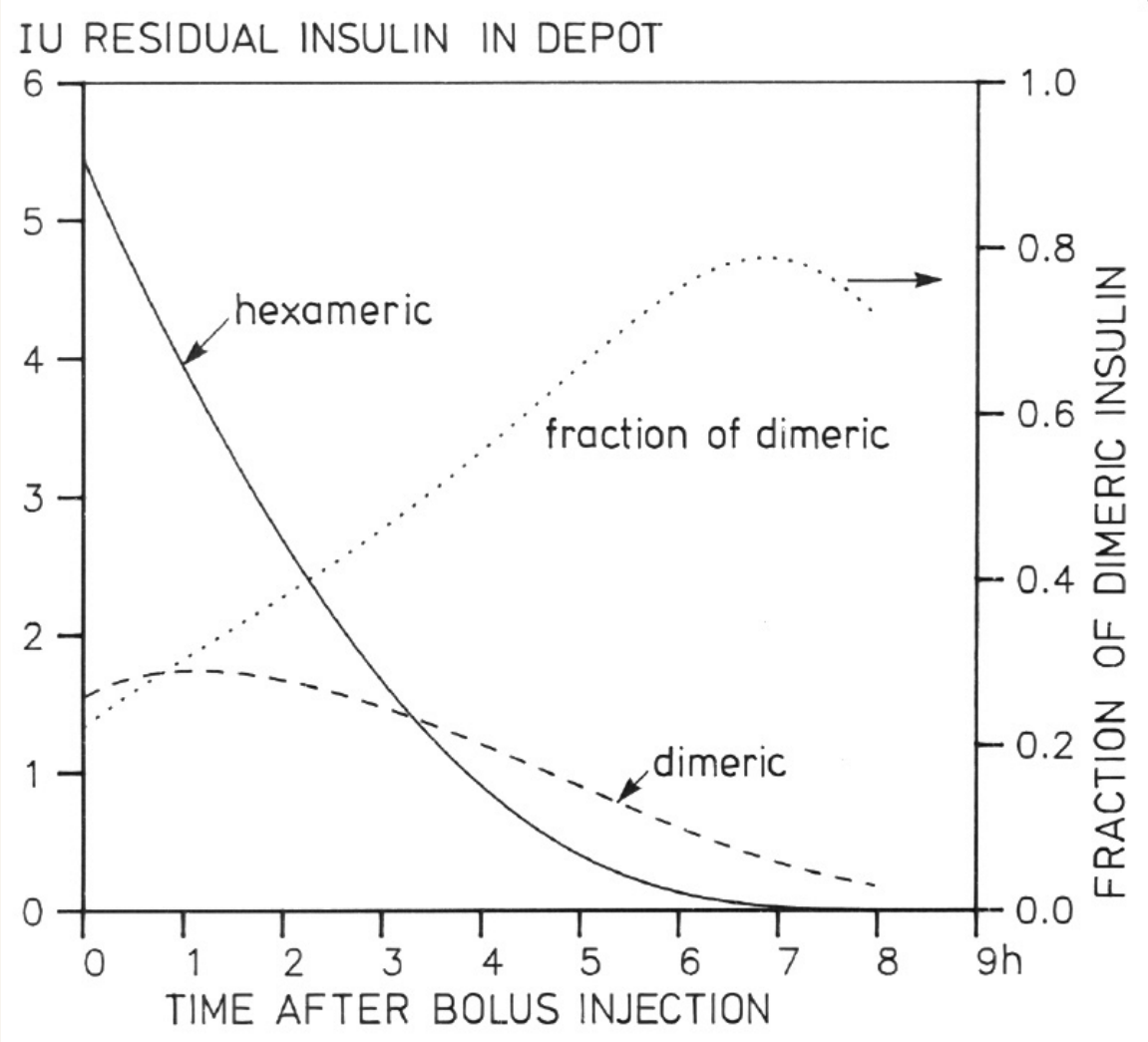
Volume and Concentration Effects





The model can be used to predict the results of experiments not previously performed, e.g. absorption of 100 IU/ml in different volumes.

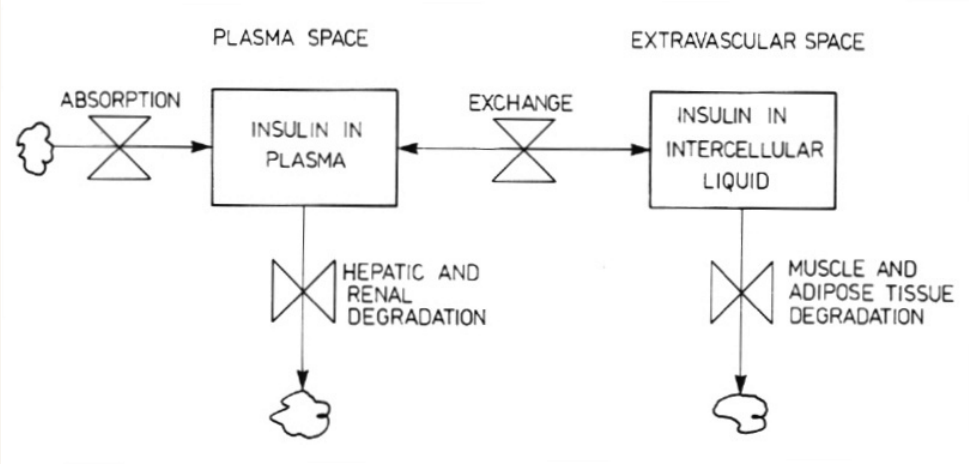
Fraction on Dimeric Form



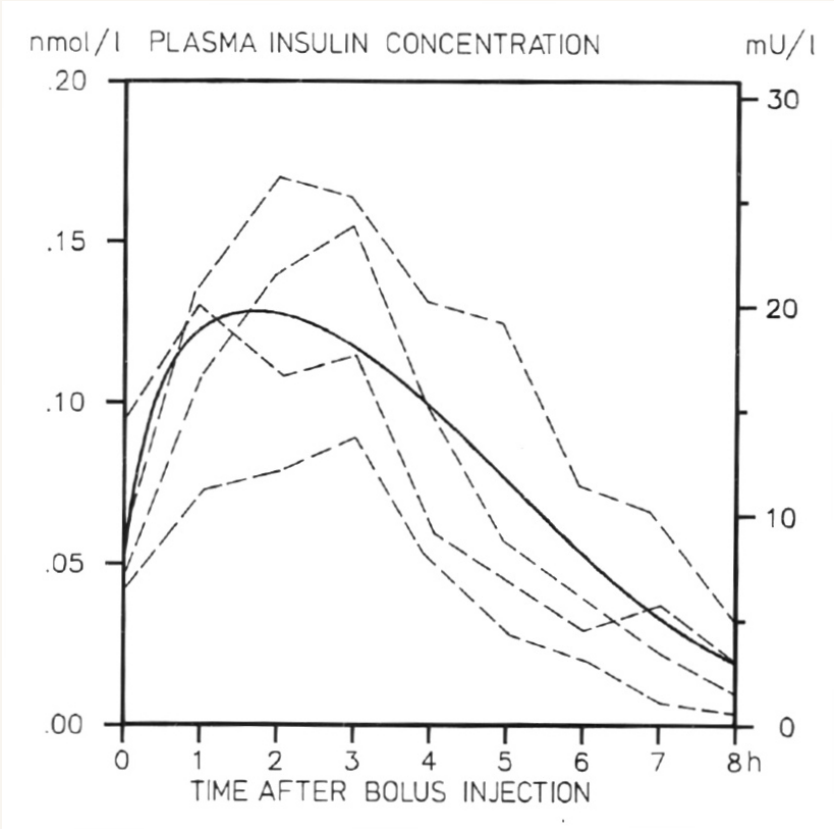
The model can be used to explain the individual variations of the three different concentrations, including, for instance, the fraction of dimeric insulin.

To the extent that these curves develop in an explainable manner, they provide an additional consistency check on the model.

Appearance Curves

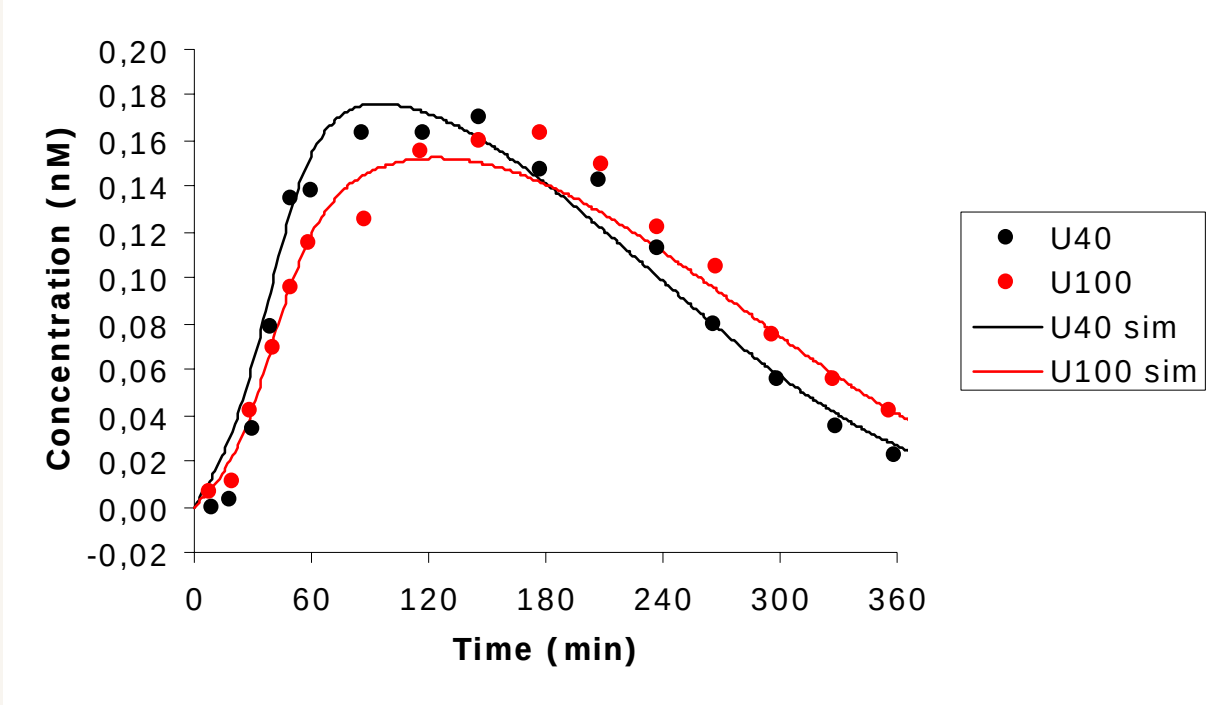


The model has been extended to describe the appearance of insulin in the blood.



The model has also been used to simulate the rate of insulin appearance from a depot supplied by an insulin pump at different pump rates.

Recent Data



Experimental data (n = 6): 6 IU

With the same dose, one observes a delayed appearance in the plasma for higher insulin concentrations.

As the insulin concentration increases further, the delay in appearance becomes even more pronounced.

COMMENTARY

The Use of U-500 in Patients With Extreme Insulin Resistance

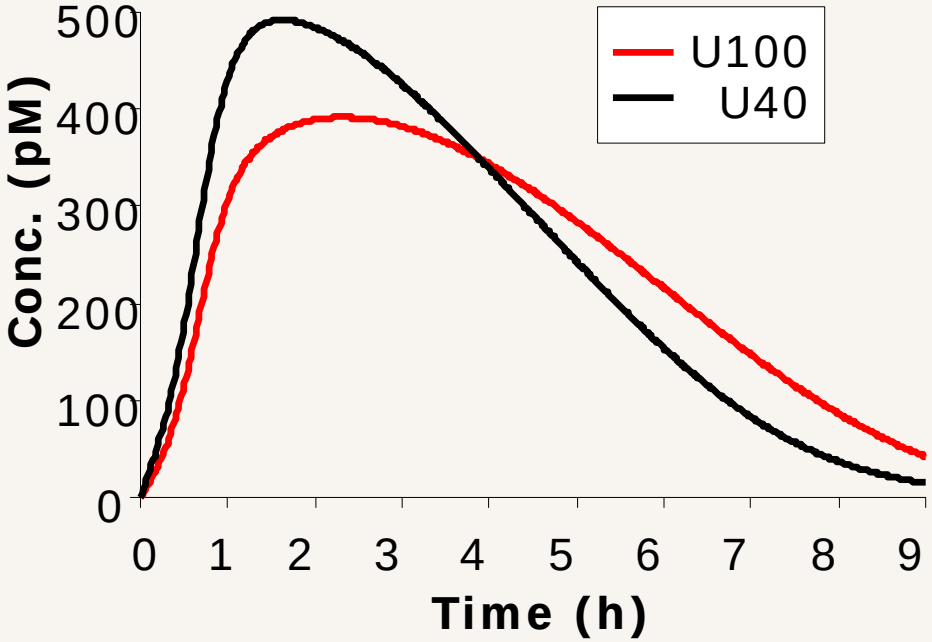
ELAINE COCHRAN, MSN, CRNP
CARLA MUSSO, MD
PHILLIP GORDEN, MD

effect 2–4 h after administration and dur-
ration of action of 5–7 h. U-500 has a pharmacokinetic profile more closely simulating NPH than regular U-100. U-500 insulin does not have anything added during its preparation to change its

insulin (10–14). These therapies seem to have their greatest role when the hyperglycemia is associated with obesity, as is the case with almost all type 2 diabetic patients. Diet and oral agents have a more

U-500 has a pharmacokinetic profile more closely simulating NPH than regular U-100.

Bioequivalence ?



Simulation: 20 IU

There is no dose linearity, and there is no bioequivalence between the same dose administered with different concentrations.

The area under the curve is the same for the two concentrations. However, the ratio of the C_{max} values are (slightly) larger than the factor 1.25 accepted by EMEA.

Endpoints

AUC-ratio

The 90% confidence interval for this measure of relative bioavailability should lie within an acceptance interval of 0.80-1.25. In specific cases of a narrow therapeutic range the acceptance interval may need to be tightened.

C_{max}-ratio

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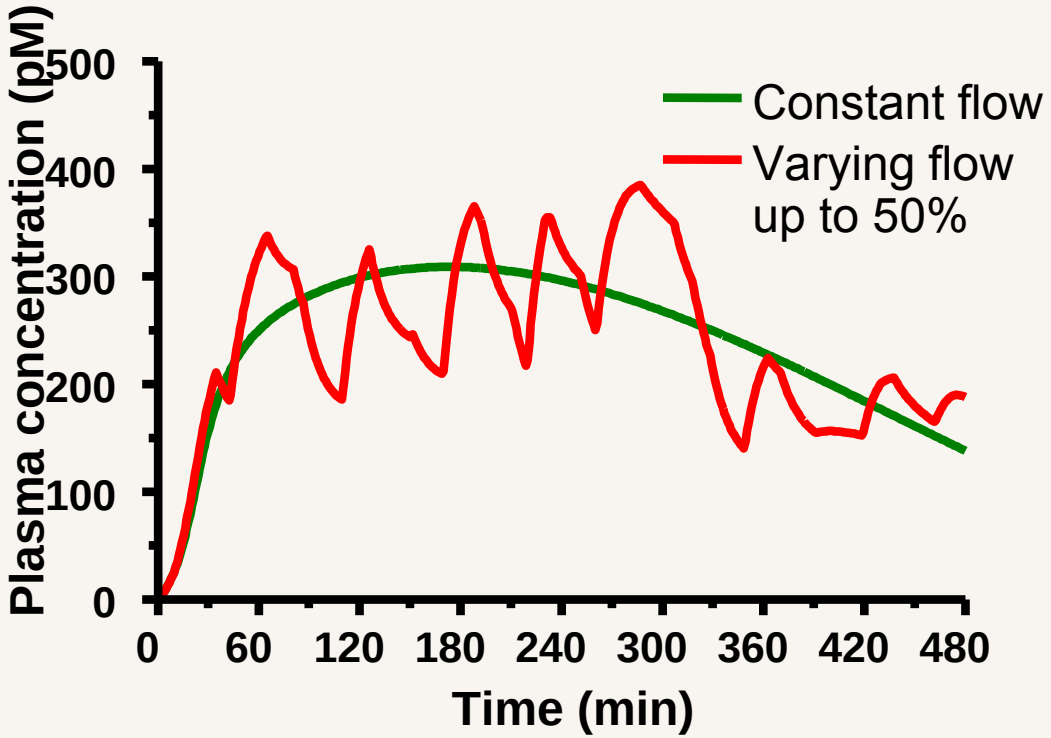
Variations in Blood Flow



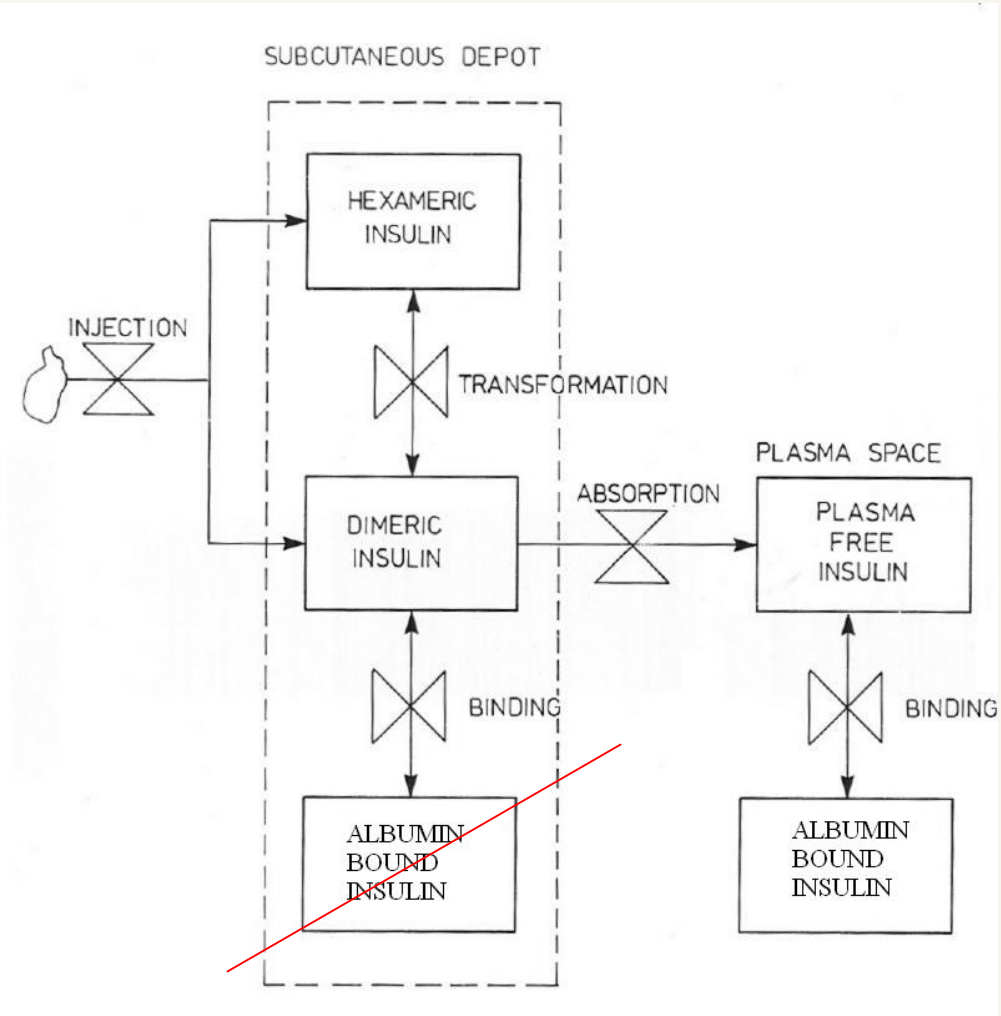
This phenomenon can be modelled by inserting an additional compartment in the model to describe the amount of insulin in the local capillary blood volume.

Variation in the blood flow at the injection site can cause significant variations in the rate of insulin appearance, particularly if the blood perfusion is low (obesity, reduced skin temperature, meals, etc.).

C_{max} and $T(C_{max})$ are not nessesary well defined.

A possible way to avoid the back diffusion of insulin could be to use a protein bound formulation so that free insulin is drained away in the blood vessels.

Absorption Model of Albumin Bound Insulin



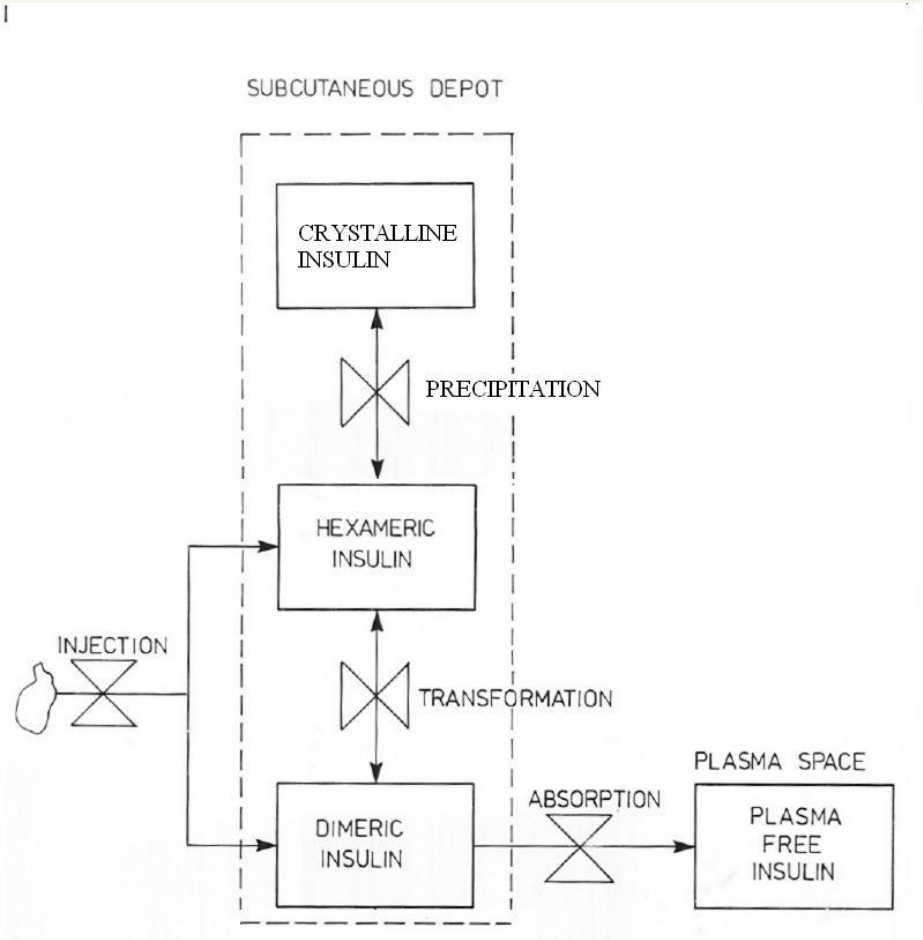
We must know the albumin concentrations in the plasma and interstitial spaces.

We must know the reaction rate constants for the formation and dissociation of the insulin-albumin complex.

We must know if the insulin-albumin complex is degraded in the liver and/or kidney.

The model can then predict the time profiles of free and albumin bound insulin in the blood, and we can examine what the response is to fluctuations in peripheral blood flow.

Crystalline Insulin



Insulin variants in crystalline form are used with both Zn and protamine as promoters of precipitation.

We must know the rate constants that control precipitation and dissolution.

Addition of Zn or protamine will also affect the dimeric/hexameric balance. Hence, we must know, how fast these additives appear from the injection site.

Different insulin formulations require different model structures and involve different parameters.

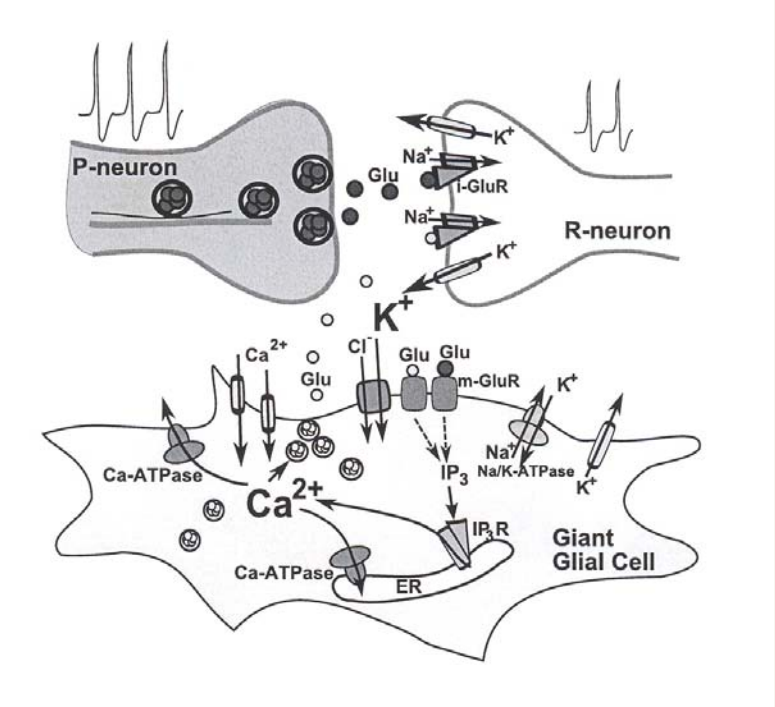
Conclusions

Classic PK/PD modeling provides precisely the information that the Medicines Agencies request in terms of parameter values to characterize the time profile of drug concentration and action.

The weaknesses are primarily that the models do not represent any degree of biological detail, nor do they allow accumulation of knowledge from different studies.

The physiologically based PK/PD models that have evolved over the last years represent an intermediate solution. At the moment these methods presumably also represent an optimal solution.

We can actually not model the simplest living organism. Nonetheless the use of mechanism based modeling is widely spread in physiology, neurology, cell biology, etc.



The strengths of mechanism-based modeling are that it (i) is based on a close interaction between experiment and modeling (ii) allows integration of knowledge from study to study, (iii) provides a detailed understanding of the biological mechanisms, and (iv) allows interpolation between groups.

Paediatric Modeling

		Adult	Child
P	Equilibration rate hexameric/dimeric	✓	✓
Q	Equilibrium constant hexameric/dimeric	✓	✓
B	Dimeric absorption rate	✓	✓
D	Dimeric/hexameric diffusion constant	✓	✓
V_1	Distribution volume for plasma	✓	✗
V_2	Distribution volume for interstitial space	✓	✗
K	Equilibration rate constant between spaces	✓	✗
T_1	Lifetime for insulin in plasma (hepatic)	✓	?
T_2	Lifetime for insulin in interstitial space	✓	✗

In classic PK/PD modeling the obtained parameter values are typically effective values without direct physiological interpretation. This makes it difficult to make an interpolation between groups.