A Pharmacokinetic-Pharmacodynamic model for insulin to guide optimal drug delivery

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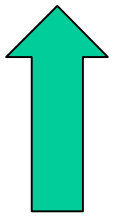
Insulin- Today & Tomorrow

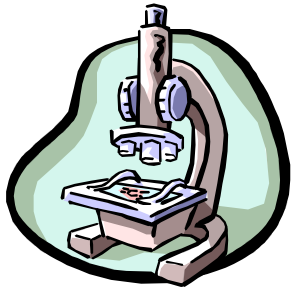
Features	Subcutaneous	Pulmonary
Administration	Inconvenient	Convenient
Onset of action	Slow	Fast
Offset of action	Slow	Fast
Bioavailability	High	Low (5-10%)

Pulmonary Insulin Bioavailability



Low molecular weight aminoacids (Delivery/carrier agents)

Hydroxy methyl amino propionic acid (HMAP)



Modeling Objective

- To characterize the dose-plasma insulin concentration-time relationship (PK) administered via
  - Subcutaneous injection (S.C)
  - Spray-Instillation - insulin alone (S.I)
  - Spray-Instillation insulin + HMAP (S.I HMAP)
- To develop a model to describe the effect of insulin on glucose suppression (PD)

Rat Study (n=77)

Insulin (mU/kg)	Insulin (mU/kg)	Insulin+HMAP (mU/kg)+mg/kg
Subcutaneous (S.C)	Spray-Instillation (S.I)	Spray-Instillation(S.I)
260	260	16,25
1300	1300	5,10,16,25
2600	2600	10,16,25
-----	13000	-----
-----	26000	-----

Suarez, S., et al., *Facilitation of pulmonary insulin absorption by H-MAP: pharmacokinetics and pharmacodynamics in rats.* Pharm Res, 2001. 18(12): p. 1677-84.

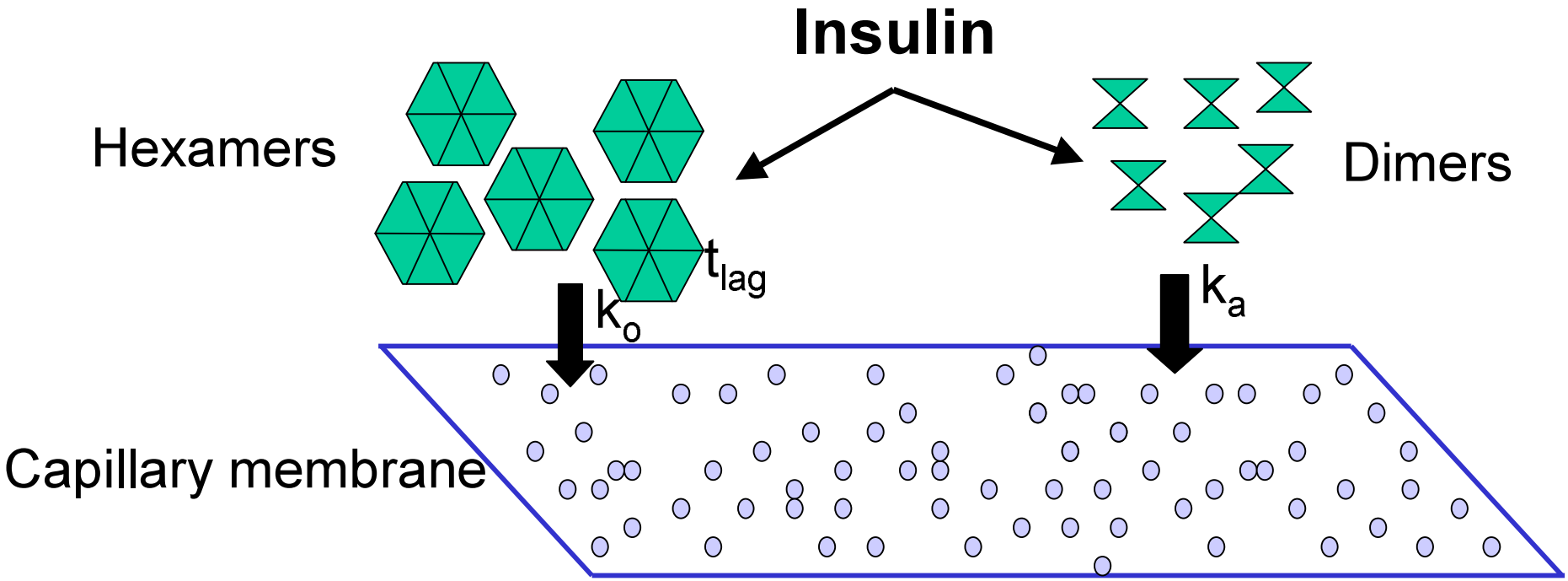
Population Pharmacokinetics

- NONMEM Ver V – Digital Fortran Compiler (Ver 6.5)

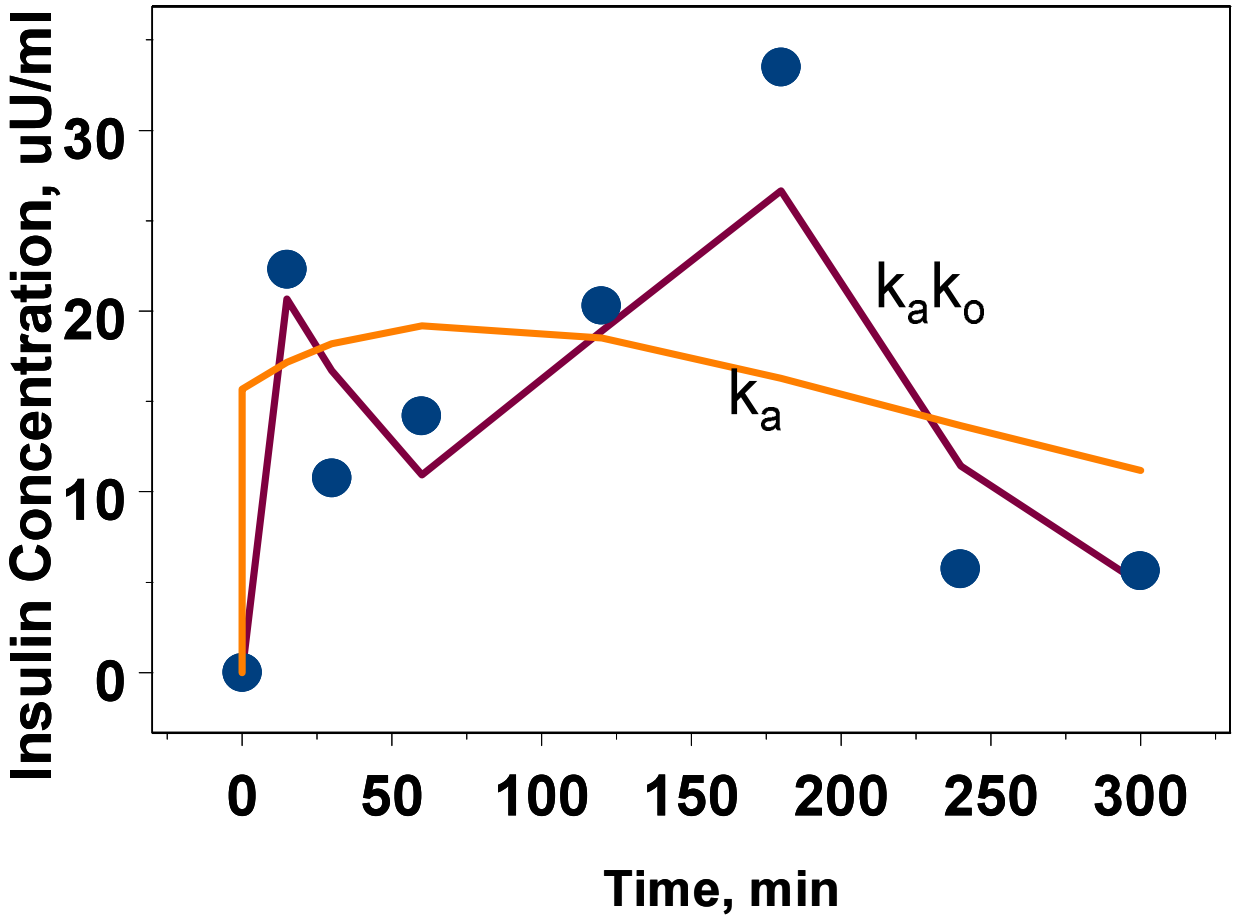
- One compartment model
  - First order absorption model (k_a)
  - Sequential first order – zero order absorption model ($k_a k_o$)

- Standard Two Stage Approach
  - Proportional & Additive Residual error model

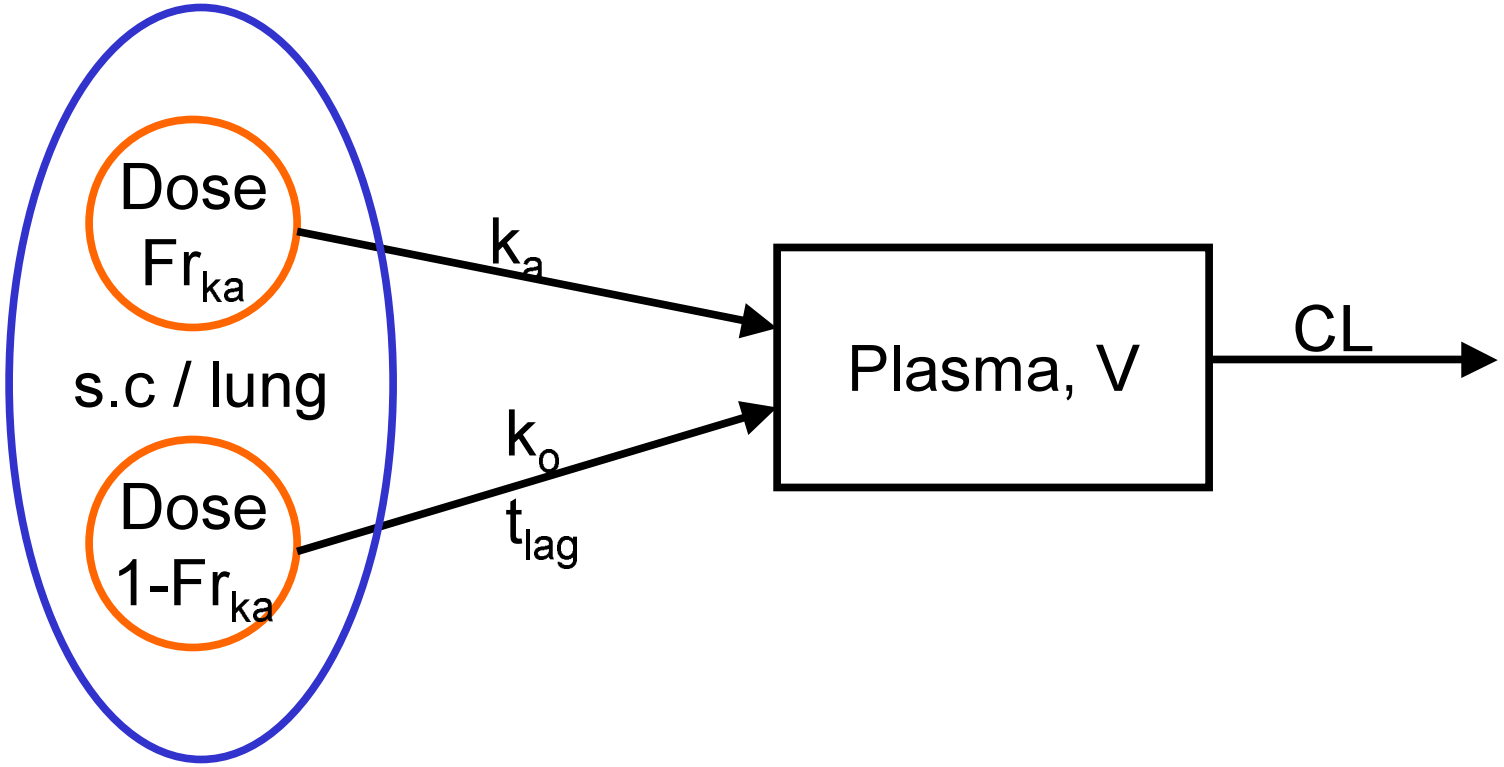
Why - Mixed order absorption



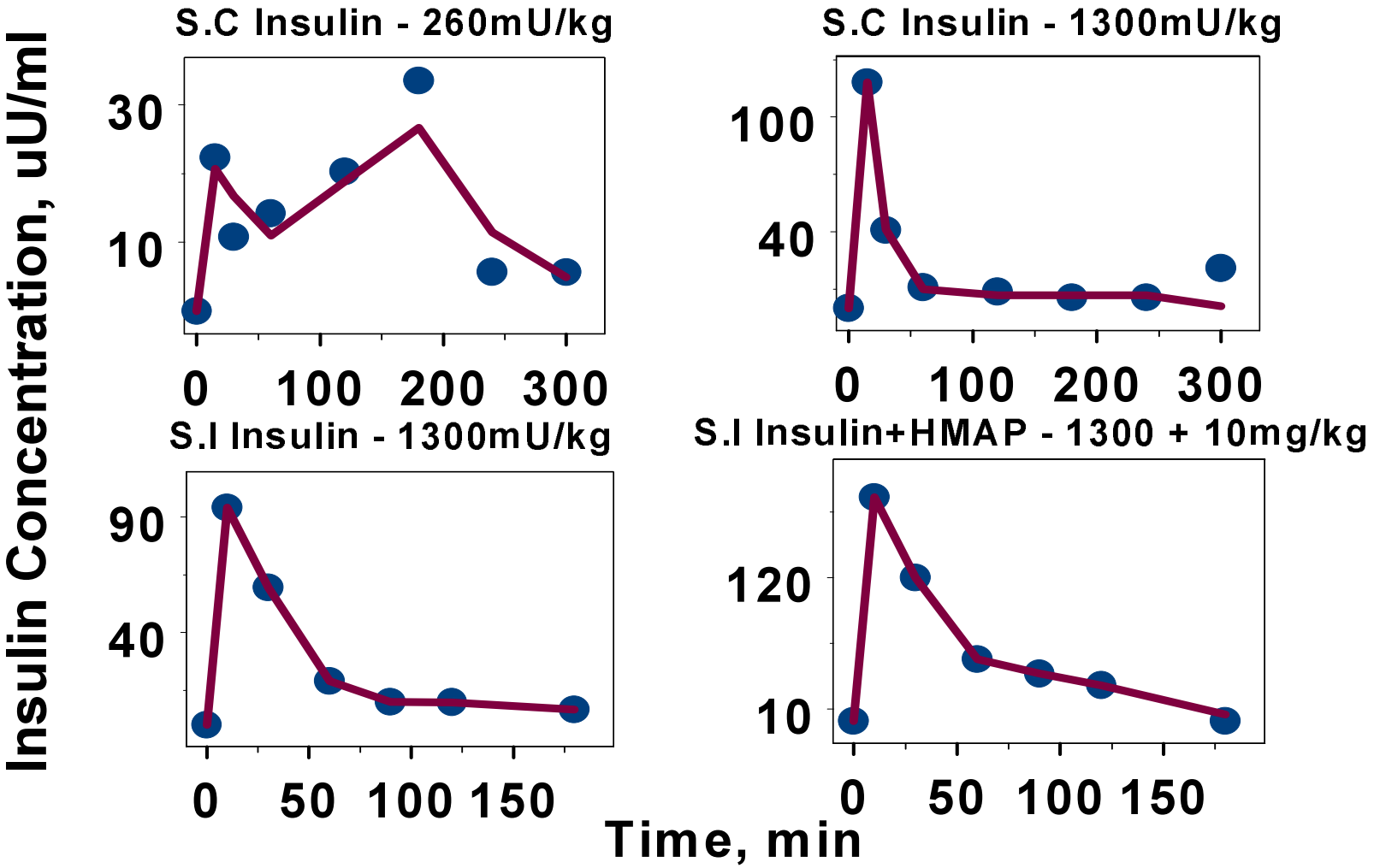
$k_a k_o$ is better than k_a



Structural PK model



Individual Insulin profile



Circles - Individual Observed/Lines - Individual Predicted

Relative bioavailability (RelF) model

- Route (S.C / S.I)
- Dose (Insulin)
- Formulation (Insulin / Insulin + HMAP)

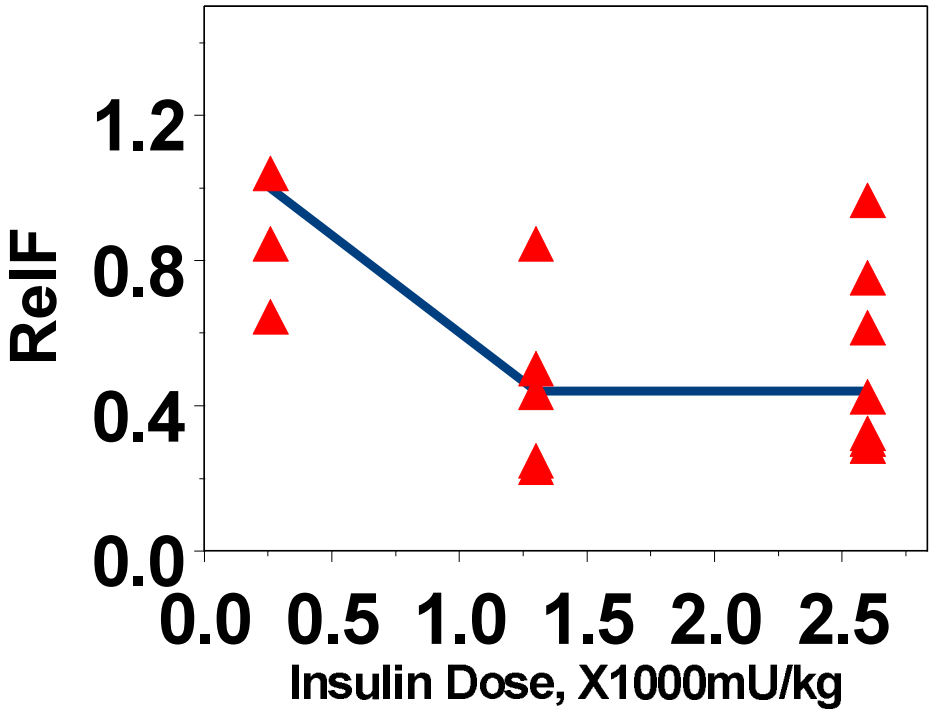
Discrete model for S.C

$$RelF_{s.c} = RelF_{(s.c0.26)} + RelF_{(s.c1.3+s.c2.6)}$$

RelF of 260mU/kg (s.c) ~ 1

RelF of 1300 & 2600mU/kg (s.c)

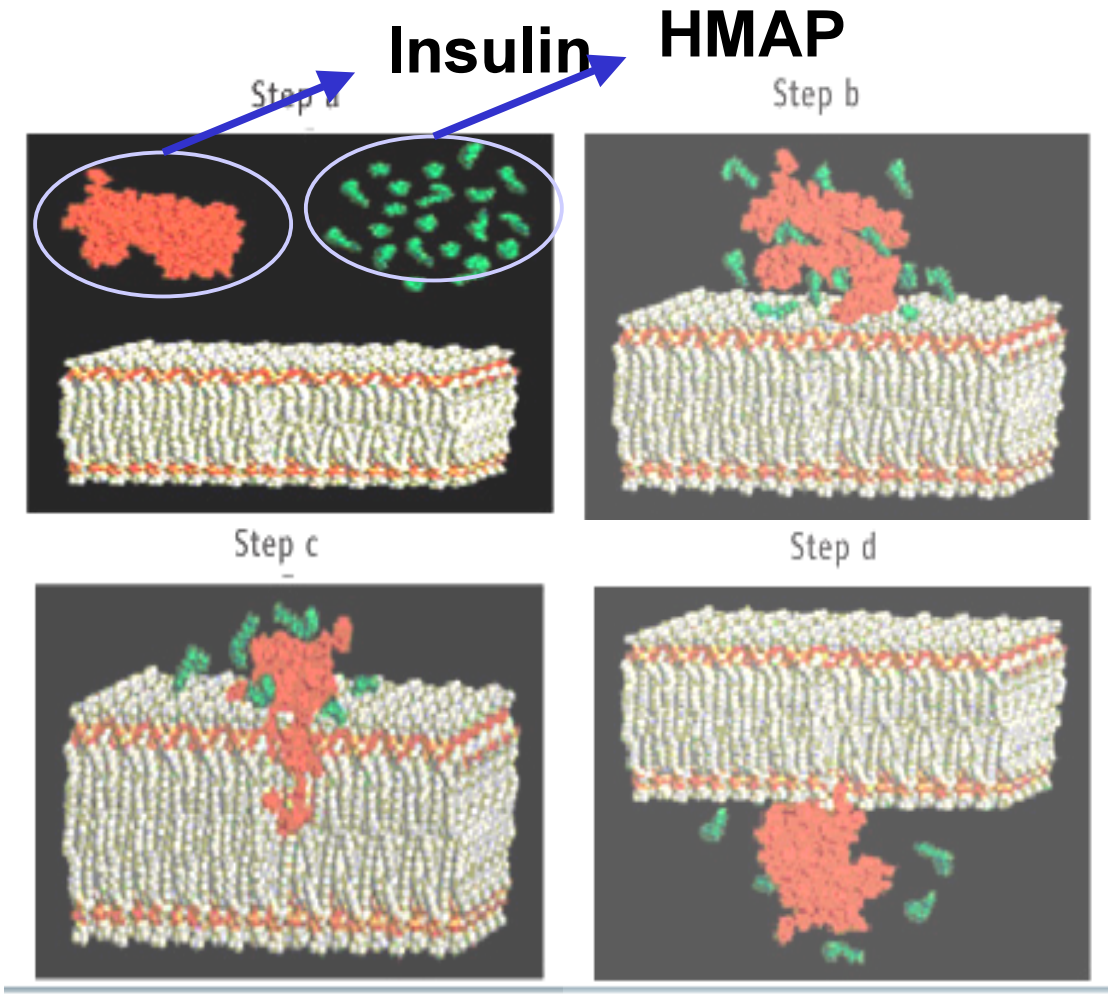
RelF – S.C insulin



- Discrete RelF model used for s.c insulin
- Decreased RelF at high doses may be due to precipitation
- Considerable variability seen

Mosekilde, E., et al., *Modeling absorption kinetics of subcutaneous injected soluble insulin.* J Pharmacokinet Biopharm, 1989. 17(1): p. 67-87.

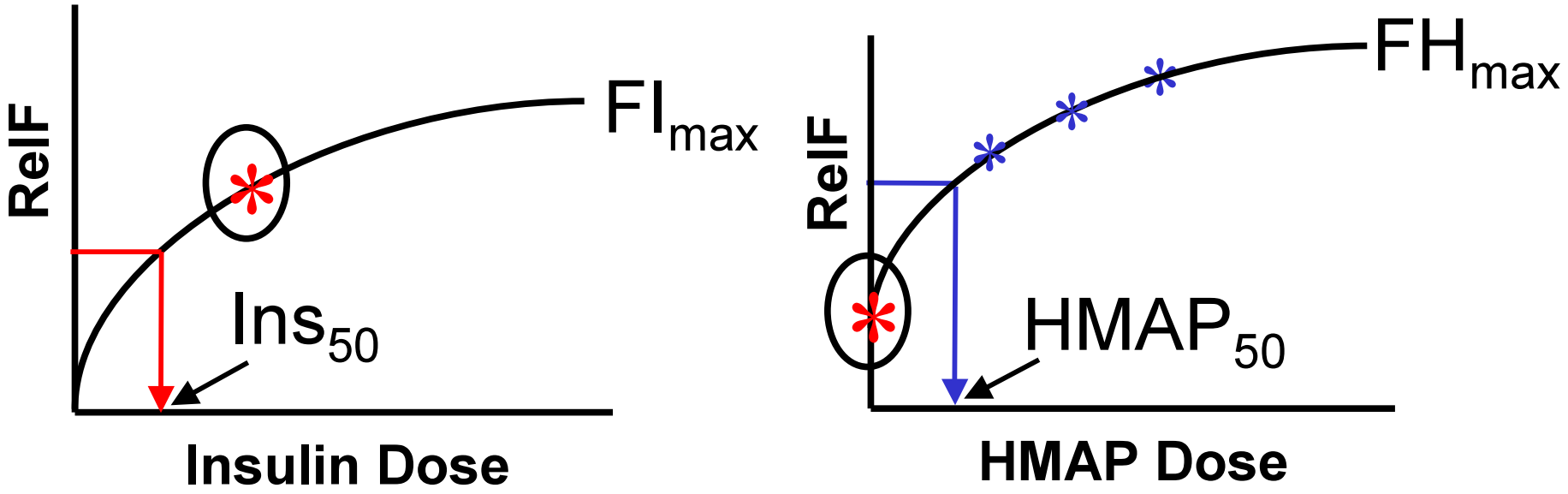
Bioavailability enhancement by HMAP



- HMAP binding to insulin-site specific
- Saturation of binding sites may limit bioavailability

Milstein, S.J., et al., *Partially unfolded proteins efficiently penetrate cell membranes--implications for oral drug delivery.* J Control Release, 1998. 53(1-3): p. 259-67.

RelF model – S.I



$$RelF_{s.i} = \frac{FI_{max} \bullet Insulin}{Ins_{50} + Insulin} \bullet (1 + (\frac{FH_{max} \bullet HMAP}{HMAP_{50} + HMAP}))$$

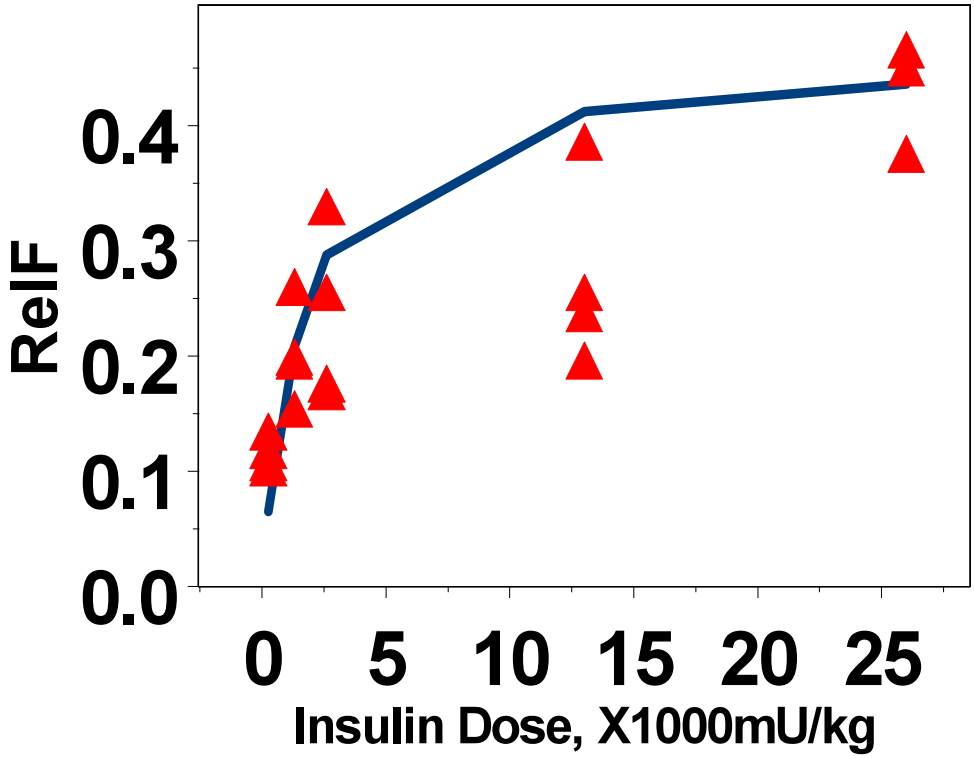
FI_{max} : maximum RelF of s.i insulin

Ins_{50} : insulin dose at half FI_{max}

FH_{max} : maximum fraction of increase in RelF of s.i HMAP w.r.t to s.i insulin

$HMAP_{50}$: HMAP dose at half FH_{max}

RelF – S.I insulin

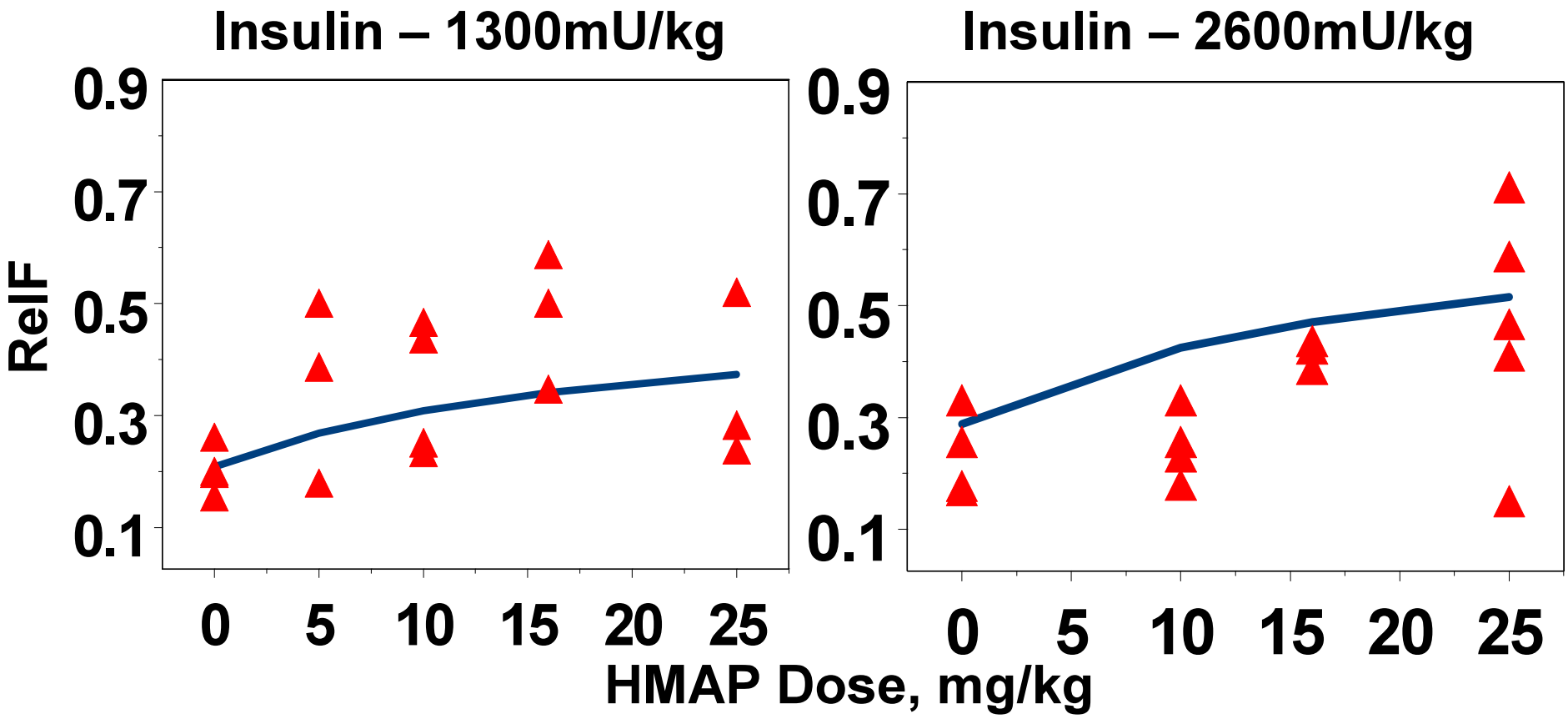


- RelF increases as insulin dose increases
- Saturable metabolism in the lung may increase bioavailability

Maximum RelF of Spray Instillation Insulin (FI_{max}) = 46%

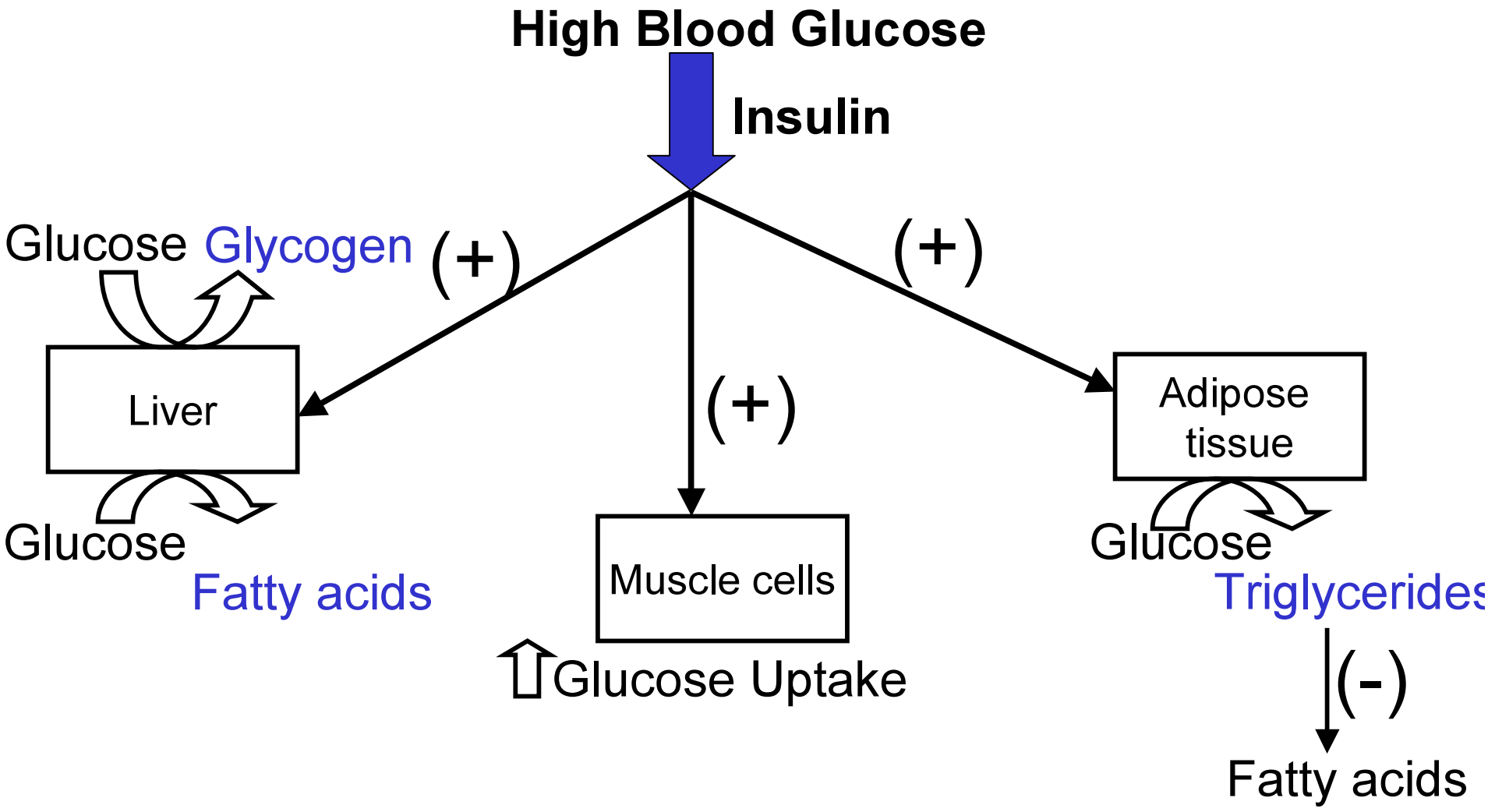
Liu, F.Y., D.O. Kildsig, and A.K. Mitra, *Pulmonary biotransformation of insulin in rat and rabbit.* Life Sci, 1992. 51(21): p. 1683-9.

RelF-S.I insulin+HMAP



Maximum RelF of Spray-Instillation Insulin+HMAP = 65%

Insulin action on Glucose



Literature PD model

Effect compartment model

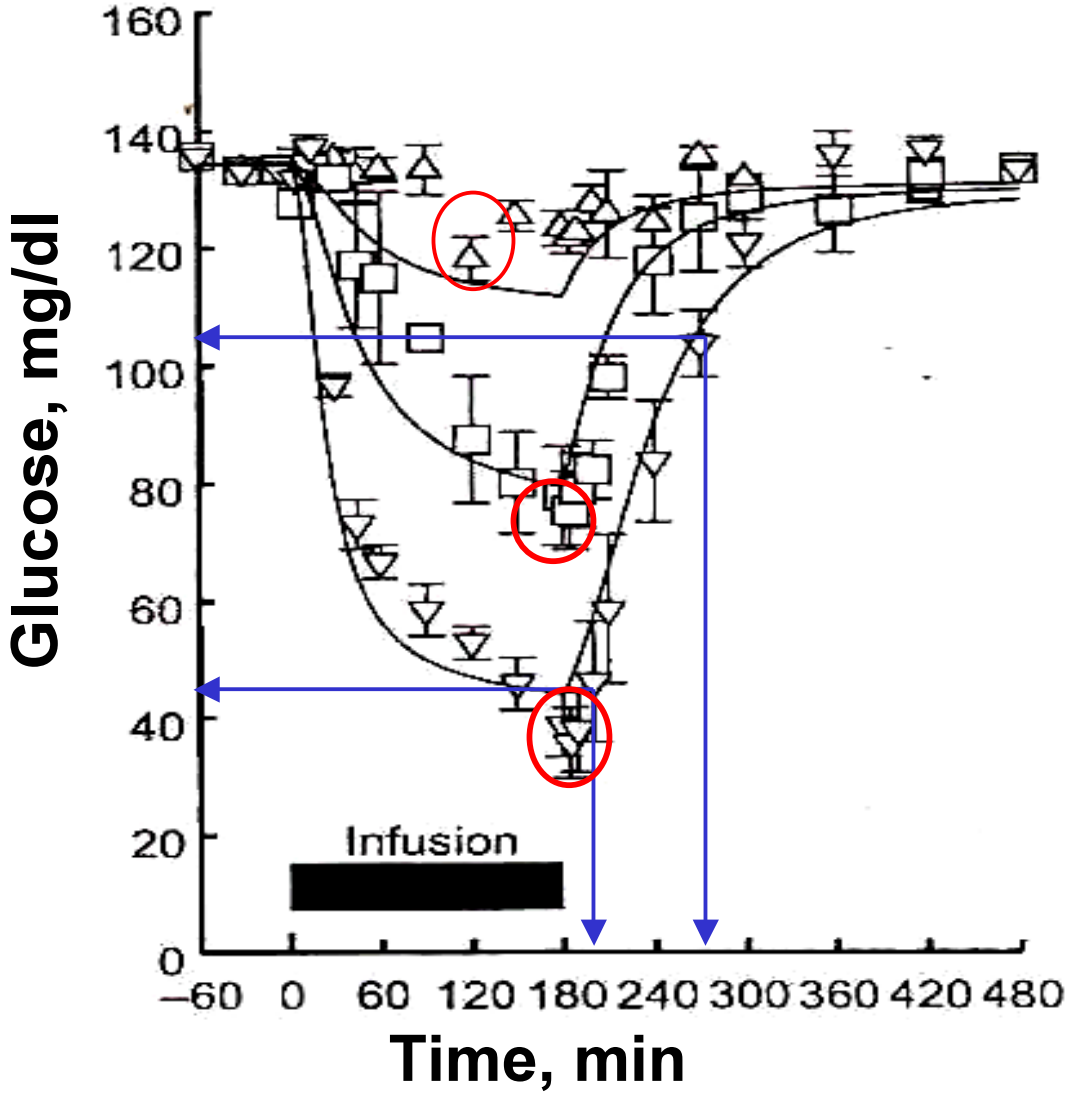
Limitations

- Not a mechanistic model
- EC_{50} estimates are dose dependant.
- Optimal dose depend on EC_{50} used.

•Miyazaki etal., *Pharmacokinetic-pharmacodynamic modelling of human insulin: validity of pharmacological availability as a substitute for extent of bioavailability* JPP,2001 : 53: 1235-1246

•Woodworth etal.,*Establishment of time-action profiles for regular and NPH insulin using pharmacodynamic modeling.*Diabetes Care. 1994 Jan;17(1):64-9.

Literature Glucose data



- 500, 1000, 2000 mU/kg by i.v infusion
- T_{Rmax} increases as dose increases
- R_{max} not captured well
- Roughly,
  Ascending slope
  = 105 – 45/ 270-200
  = 0.85 mg/dl/min

Literature PD model

Inhibition of glucose production model

Insulin stimulates

- Glucose uptake into muscle cells for energy
- Glucose storage as glycogen in liver and as triglycerides in adipose tissue.

Insulin inhibits

- Conversion of triglycerides to fatty acids

Limitations

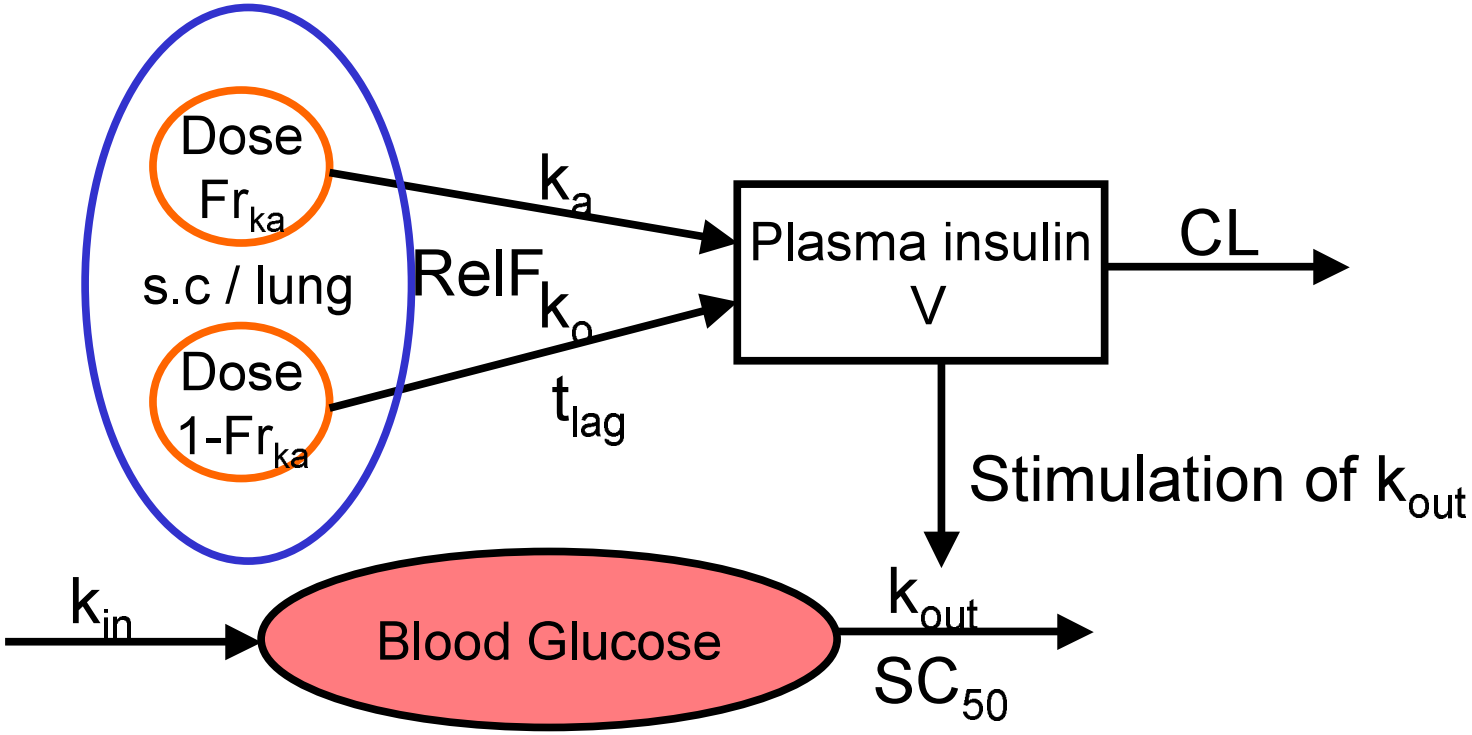
- Unlikely mechanistic possibility
- Could lead to erroneous dosing interval decisions

Lin etal.,*Pharmacokinetic-pharmacodynamic modelling of insulin: comparison of indirect pharmacodynamic response with effect-compartment link models.* J Pharm Pharmacol. 2002 Jun;54(6):791-800

Population Pharmacodynamics

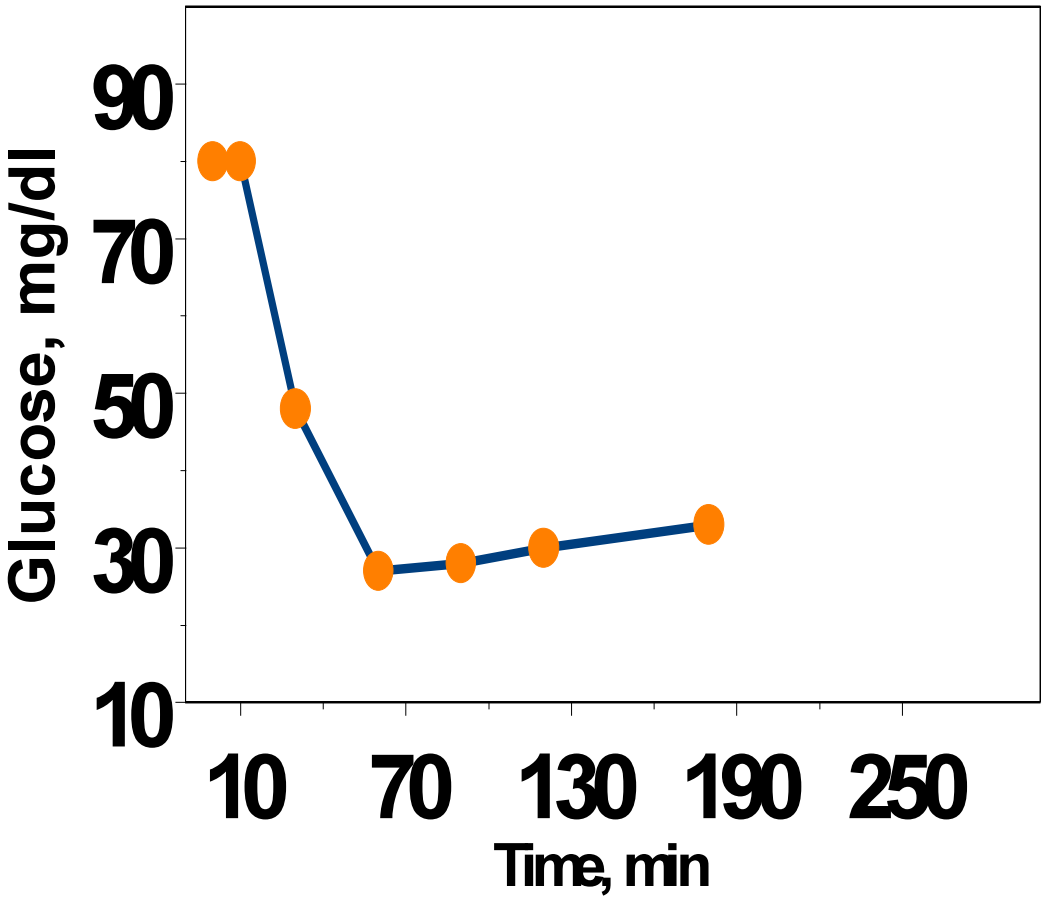
- Sequential PK-PD modeling – Individual PK parameters
- Indirect response model (Stimulation of k_{out})
  - Insulin action involves complex signalling mechanism (Tyrosine kinase receptor)
  - Stimulates glucose uptake into cells by activating GLUT4 transporters
- Exponential Inter- rat variability model
- Proportional & Additive residual error model

PK - PD model



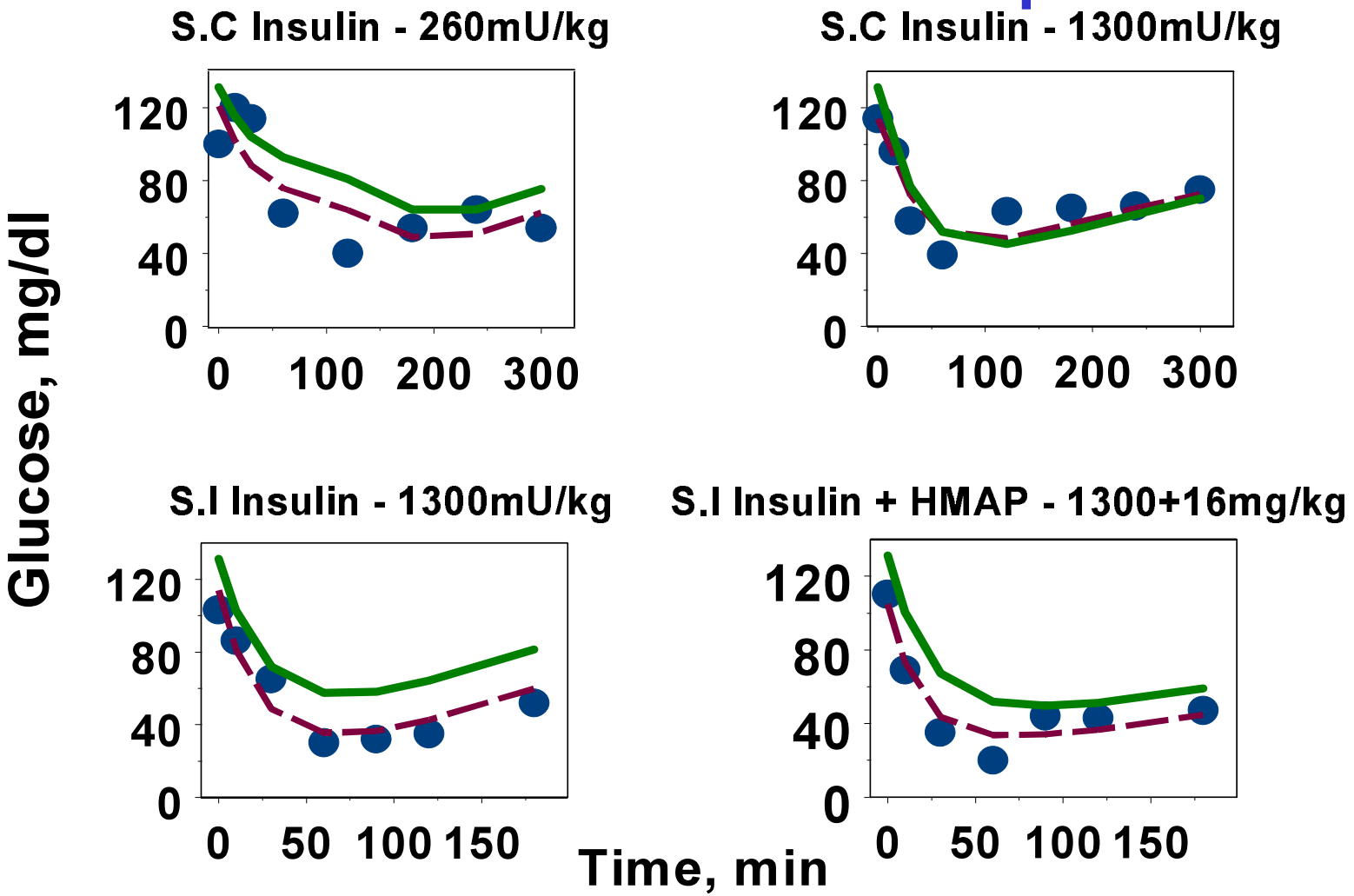
$$\frac{dGlucose}{dt} = k_{in} - k_{out} \bullet \left(1 + \frac{S_{max} \bullet C}{SC_{50} + C}\right) \bullet Glucose$$

Present Glucose data



- Lack of glucose data returning to baseline
- Reliable estimate of k_{in} and SC_{50} could not be obtained.
- SC_{50} fixed to 80uU/ml based on literature

Individual Glucose profile



Circles - Individual Observed, RedLines - Individual Predicted

Green lines-Population Predicted

PD parameters

Parameter	Population mean (%SE)	Random effects(%) (%SE)
k_{in} (mg/dl/min)	0.96 (10)	12 (135)
k_{out} (min^{-1})	0.007 (9)	28 (23)
S_{max}	6.04 (11)	19 (108)
SC_{50} (uU/ml)	80 (--)	88 (37)
Residual error		
Proportional error 14% (35)		
Additive error (mg/dl) 10 (40)		

- Glucose uptake into skeletal muscle cells stimulated 7 times
- SC_{50} similar to k_d reported in skeletal muscle cells ~ 40–150uU/ml

Conclusion

- An integrated PK-PD model developed for insulin administered via subcutaneous and spray-instillation in rats
  - Formulation effects (Insulin/Insulin+HMAP)
  - Effect of route (S.C vs S.I)

PD model for insulin

- Mechanism based pharmacodynamic model used for insulin
  - Stimulation of uptake of glucose into muscle cells
  - Extrapolation to other species easier
  - Between subject variability and Within subject variability explained better

Model Applications

- Project PK and PD in different species e.g pigs (better animal model for insulin)
- Helpful in deciding optimal dosing strategies for future clinical studies
- Could be used to analyze data from human studies

Acknowledgements

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Questions