UPPSALA
UNIVERSITET

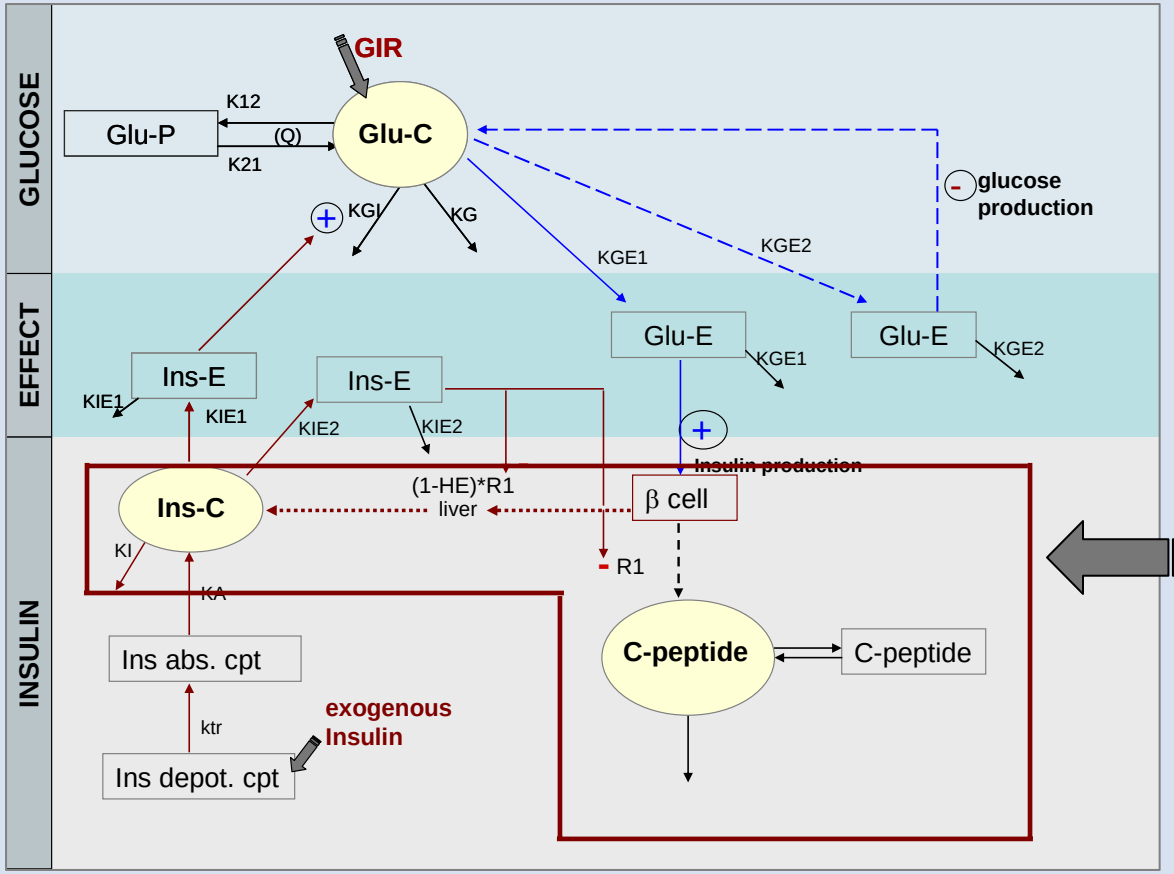
Insulin Secretion and Hepatic Extraction during Euglycemic Clamp Study: Modelling of Insulin and C-peptide data

Chantaratsamon Dansirikul
Mats O Karlsson

Division of Pharmacokinetics and Drug Therapy
Department of Pharmaceutical Biosciences
Uppsala University

Goal & Aim

Goal: ”To develop an integrated glucose-insulin model”



Aim: ”to characterize endogenous insulin secretion profile and to estimate hepatic extraction of insulin”

UPPSALA UNIVERSITET

Introduction
Insulin Secretion & C-peptide

Insulin Secretion

- Secretion: basal & prandial
- Direct assessment of insulin secretion from blood concentration is not so easy!
- ~50% (40-85%)[1-3] is lost during single pass through liver

C-peptide

- Co-secreated with insulin from beta-cell on an equimolar basis
- A negligible amount is lost during single pass through the liver[4]
- A measure of pre-hepatic insulin secretion

1. Cobelli C, et al. *Diabetes* **37**: 223-31 (1988)
2. Tura A, et al. *Am J Physiol Endocrinol Metab* **281**: E966-74 (2001)
3. Meier JJ, et al. *Diabetes* **54**: 1649-56 (2005)
4. Polonsky K, et al. *J Clin Invest* **72**:1114-23 (1983)

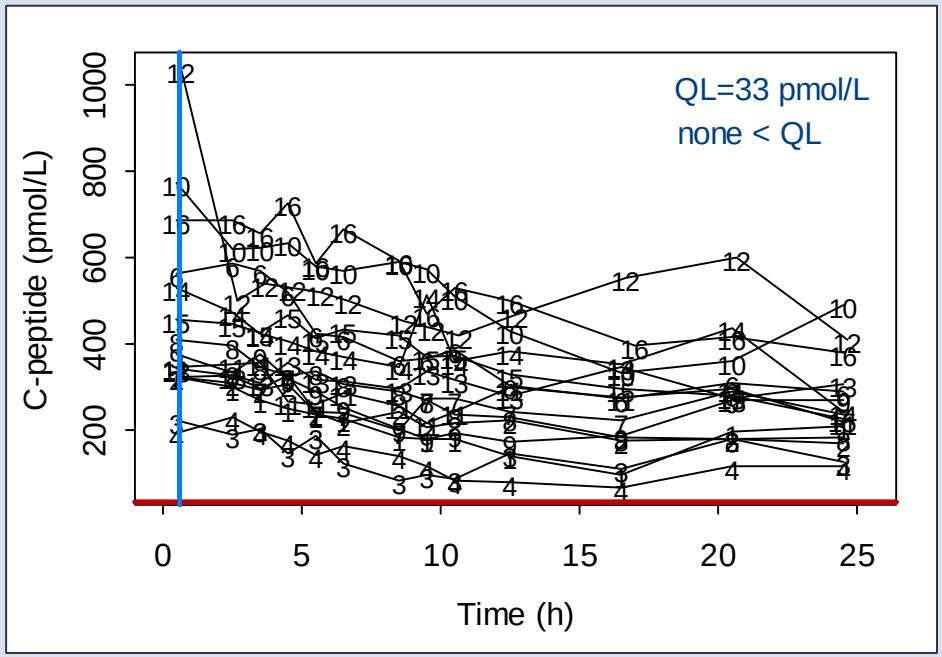
UPPSALA UNIVERSITET

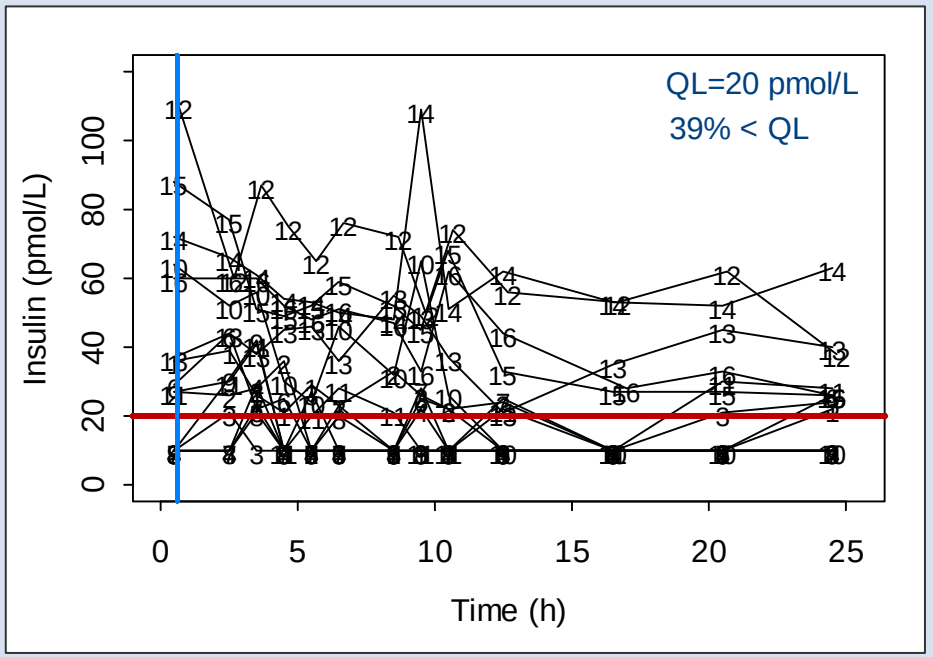
Data

24-hour Euglycemic clamp study

C-peptide & Insulin Data

- 15 healthy volunteers
- 13 samples/subject





UPPSALA UNIVERSITET

Methods
Modelling

- NONMEM VI
- Log-transformed data
- Estimation method
  - First Order Conditional Estimation (FOCE) method
  - Laplacian method (handling of data below quantification limit (BQL))

Methods

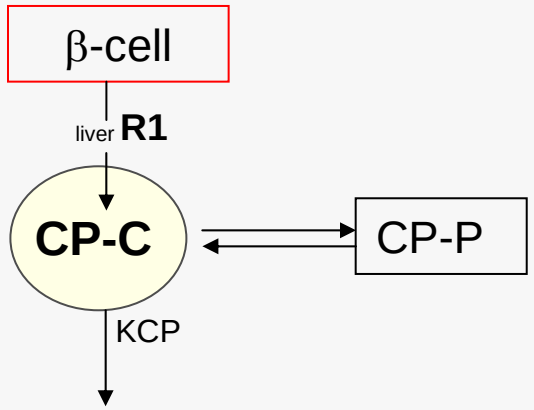
Model & Modelling Steps

1

C-peptide data:

- Population disposition parameters were fixed[1]

✓ Insulin pre-hepatic secretion (R1) was characterised using a flexible staircase input model[2]



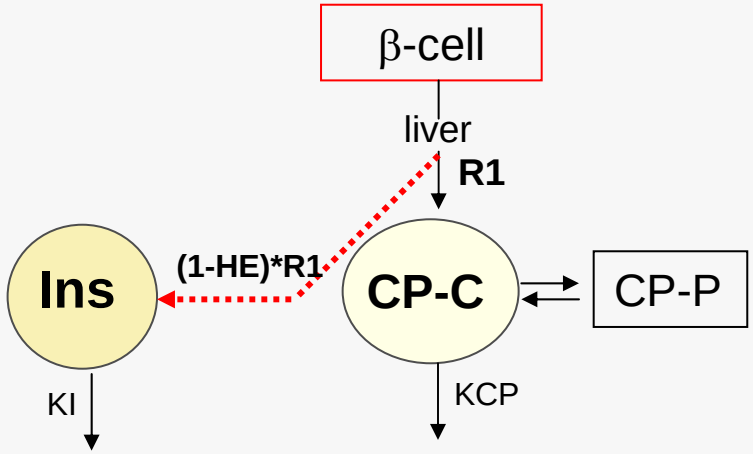
Sequential approach

2

C-peptide & Insulin data:

- Population disposition parameters of insulin were fixed[3]
- Pre-hepatic secretion (R1) estimated from C-peptide data was used

✓ Hepatic extraction (HE) of insulin



[1] Van Cauter E, et al. *Diabetes* **41**: 368-77 (1992) ; [2] Lindberg-freijs A et al. *Biopharmaceutics & Drug Disposition* **15**: 75-86 (1994);
[3] Silber H, et al. *J Clin Pharmacol (in press)*

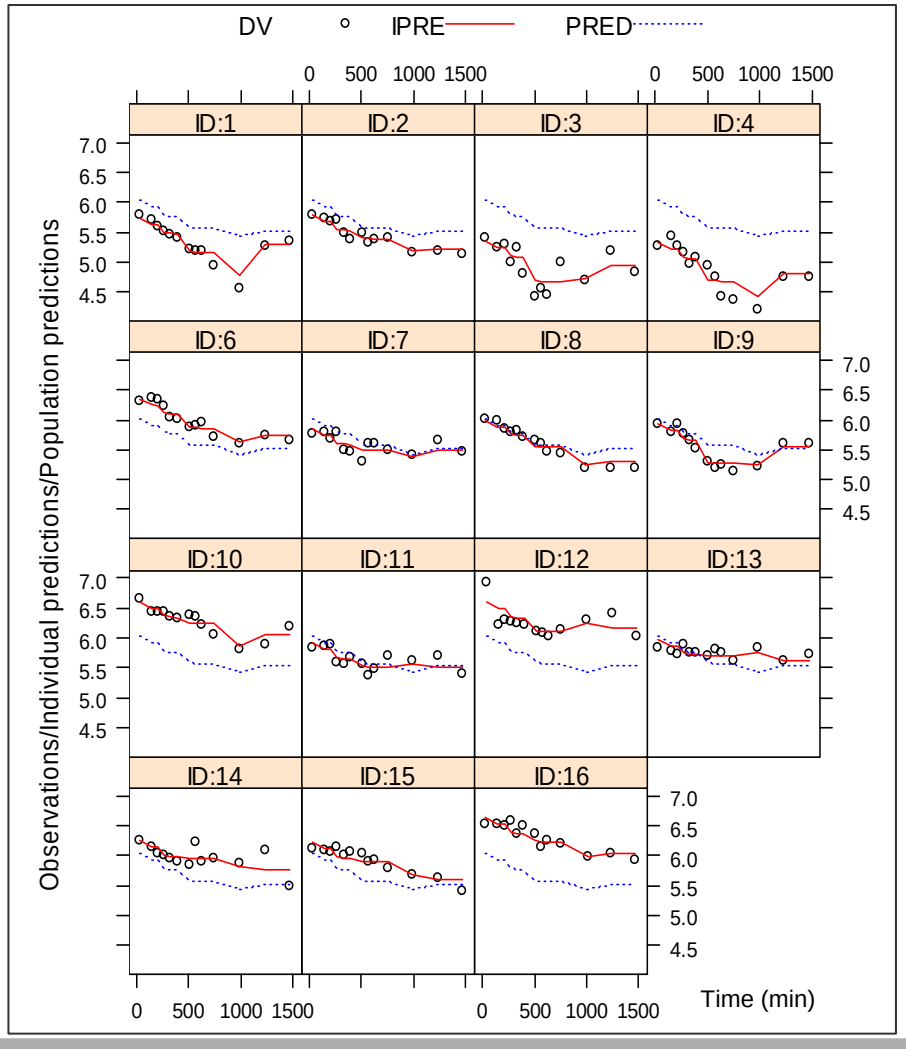
UPPSALA UNIVERSITET

Step 1

Results

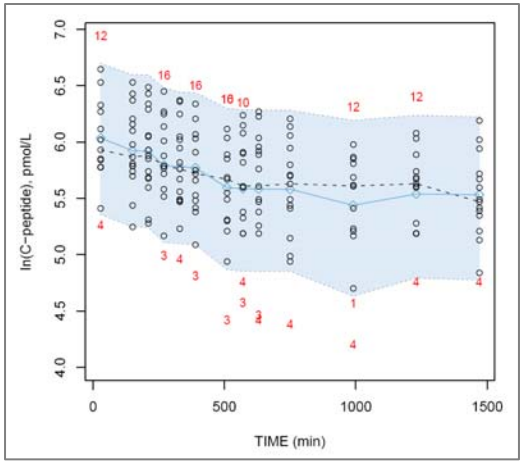
C-peptide secretion (Pre-hepatic secretion of Insulin)

✓ describe data



✓ simulate new data

1. Visual Predictive Check e.g. 90% PI



2. Numerical Predictive Check e.g.

	%Observation (95%CI)[1]		Expectation
above simulated median	**49.7**	**(28.2-71.8)**	**50**
below simulated median	**50.3**	**(28.2-71.8)**	**50**
above simulated 90%PI	**4.1**	**(0-16.9)**	**5**
below simulated 90%PI	**7.2**	**(0-15.4)**	**5**
above simulated 50%PI	**29.2**	**(8.21-44.6)**	**25**
below simulated 50%PI	**23.1**	**(8.21-45.1)**	**25**

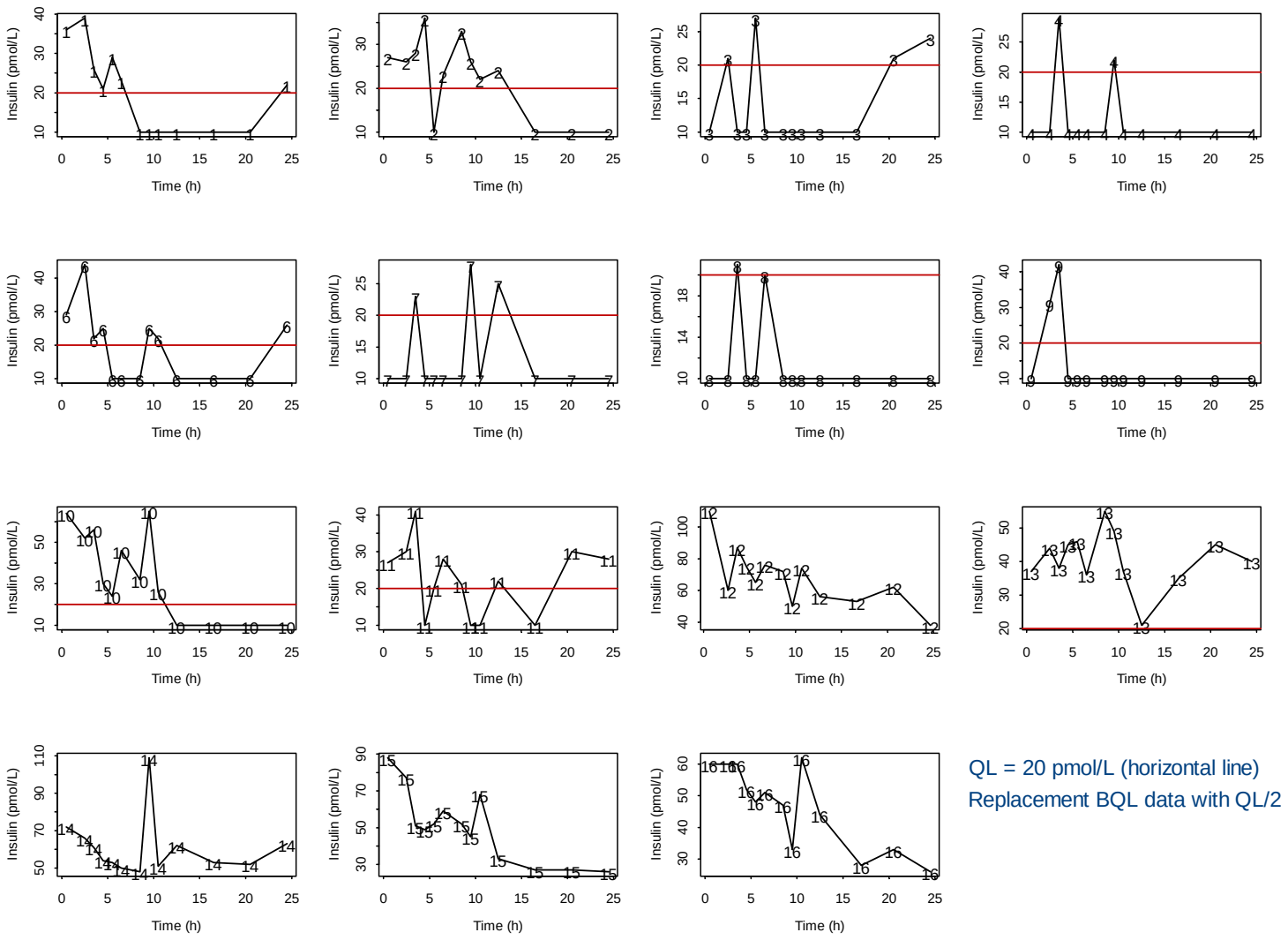
[1] obtained based on 1000 simulated datasets

UPPSALA UNIVERSITET

Step 2

Issue

39% of Insulin data are BQL



QL = 20 pmol/L (horizontal line)
Replacement BQL data with QL/2

UPPSALA UNIVERSITET

Step 2

Method

How to handle BQL?

- Omission BQL data
- Replacement observation
  - QL/2 for all BQL data
  - QL/2 for the first BQL data, discard the rest
  - Replacing with ’zero’
- Likelihood approach: maximizing likelihood ...
  - For ’all data’ taken into account likelihood of a BQL observation being below QL
    - e.g. F_FLAG functionality in NONMEM VI
  - For ’data above QL’ conditional on the likelihood of being above QL
    - e.g. YLO functionality in NONMEM VI

UPPSALA UNIVERSITET

Step 2

Results
Hepatic Extraction (HE) of Insulin

- Slightly different parameter estimates

Method	HE		P-RV	
	Typical	95%CI	Typical	95%CI
1. Omission	0.474	(0.393-0.542)	0.236	(0.205-0.269)
2. QL/2	0.618	(0.50-0.699)	0.373	(0.313-0.430)
3. F_FLAG	0.561	(0.458-0.646)	0.275	(0.232-0.334)

HE= hepatic extraction, P-RV = proportional residual variablity (on untransformed scale), 95%CI = bootstrap 95% confidence interval (1000 bootstrap samples)

- Neither the inclusion of additive residual error (fixed or estimated) nor ETA on EPS improved OFV value for each method

UPPSALA UNIVERSITET

QL/2 or F_FLAG, which method should I go for?

Step 2

Criteria	Relevance for comparison	Results	
		QL/2	F_FLAG
• Objective function value (OFV)	no	inapplicable	inapplicable
• Goodness of fit plots (GOF)	limited		
• Model estimation stability	yes		
• Different initial estimates		stable	stable
• Bootstrapping		74% Cov step success	72% Cov step success
• Bias & Imprecision	yes	ME < 1%	ME < 1%
(Simulation & re-estimation[1])		RMSE < 10%	RMSE < 10%
• Numercial Predictive Check	yes	✓	✓ (slightly better)
• Run time	yes	< 10 min	< 10 min

[1] 100 datasets was simulated using final estimates from each method. Parameters were then re-estimated. Mean error (ME) and root mean squared error (RMSE) were computed and presented as a percentage of the true value.

UPPSALA UNIVERSITET

Step 2

Results

Numerical Predictive Check

- % observation above 90% and 50% prediction interval (PI)

% observations above	expectation	QL/2		F_FLAG	
		observed	95%CI[1]	observed	95%CI[1]
90%PI	5	**12.3**	**0.51 - 11.8**	**10.8**	**0.513 - 13.3**
50%PI	25	**34.9**	**12.3 - 40.0**	**31.3**	**11.3 - 42.1**

[1] The 95% confidence interval (CI) is obtained based on 1000 simulated datasets

- % BQL observation simulated from each method

method	%BQL observation	
	observed	95%CI[1]
QL/2	**39**	**27 - 56**
F_FLAG	**39**	**15 - 46**

[1] The 95% confidence interval (CI) is obtained based on 1000 simulated datasets

UPPSALA UNIVERSITET

Conclusions

- Endogenous insulin secretion profile was well characterized using a flexible staircase input model
- In the presence of BQL data, F_FLAG method was chosen
  - Theoretically appealing
  - Slightly better with numerical predictive check

UPPSALA UNIVERSITET

Discussion Issue: I

Selection among different methods of handling BQL

- Original Question

  ”How to select which method to be used to handle BQL when the OFV (and GOF) can not be used?”

- Approach
  - Model estimation stability
  - Bias & imprecision (simulation & re-estimation)
  - Numerical Predictive Check
  - Run time

What else can be considered?

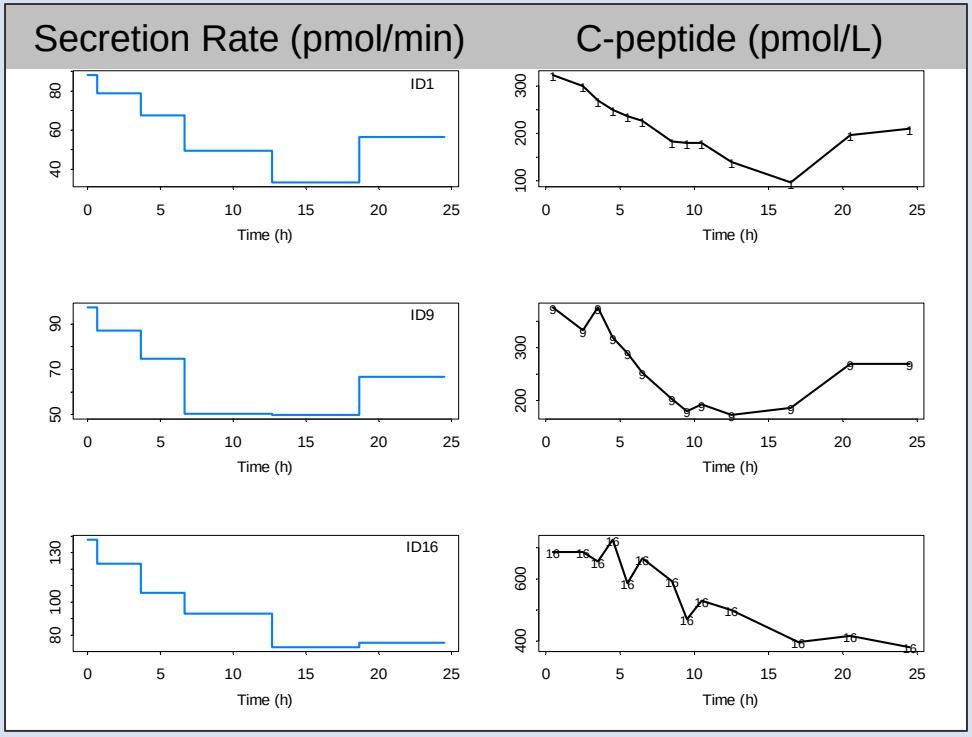
UPPSALA UNIVERSITET

Discussion Issue: II

Flexible staircase input model & Endogenous secretion

Flexible Staircase Input Model

- Secretion rate is the same within a time interval
- Changes are characterised using staircase function
- Secretion at baseline and fraction of changes are estimated



Any comments?