Mathematical Modeling of Insulin Secretion & Kinetics

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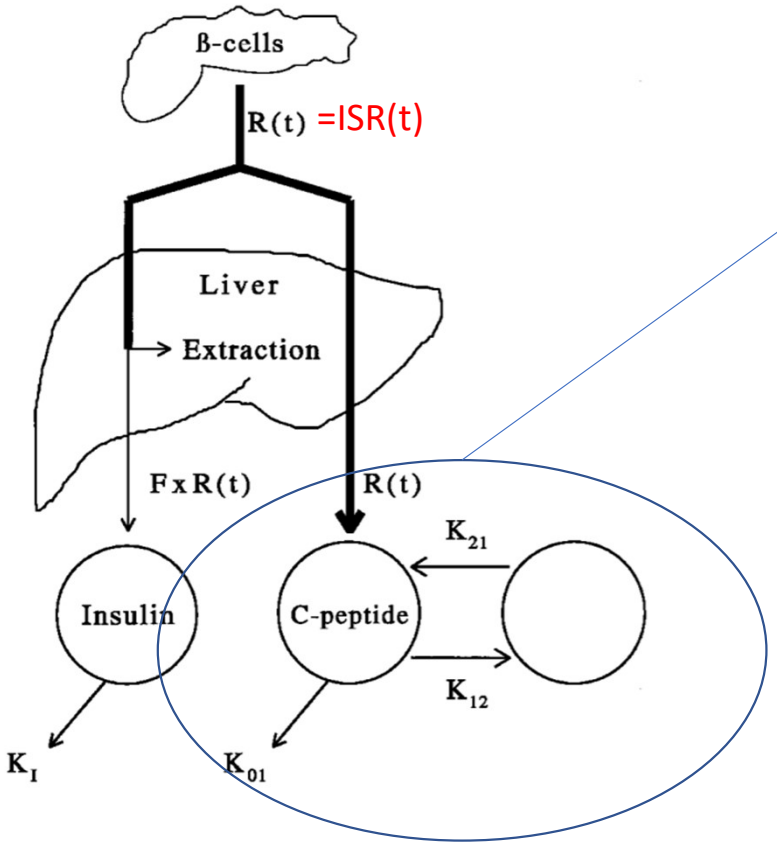
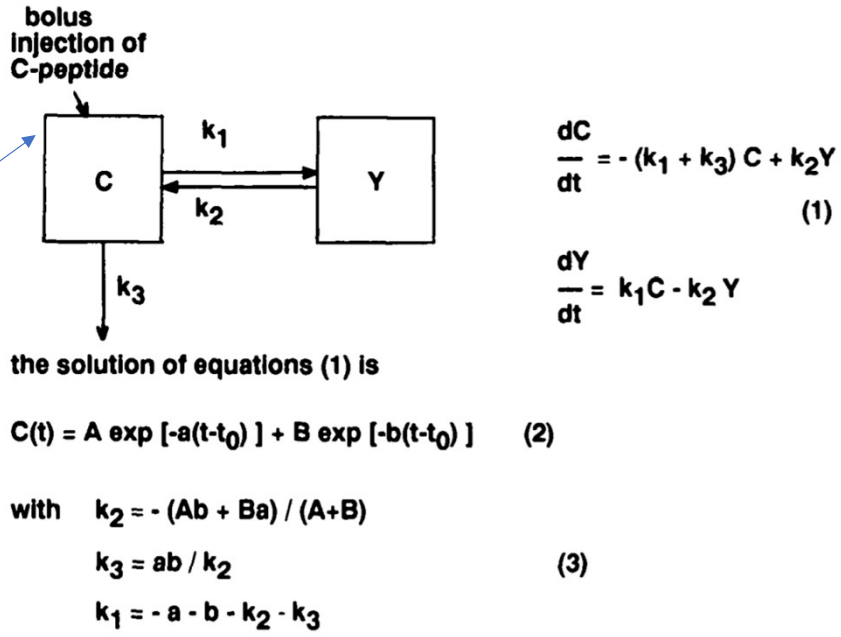
Mathematical model of insulin secretory rate (ISR)



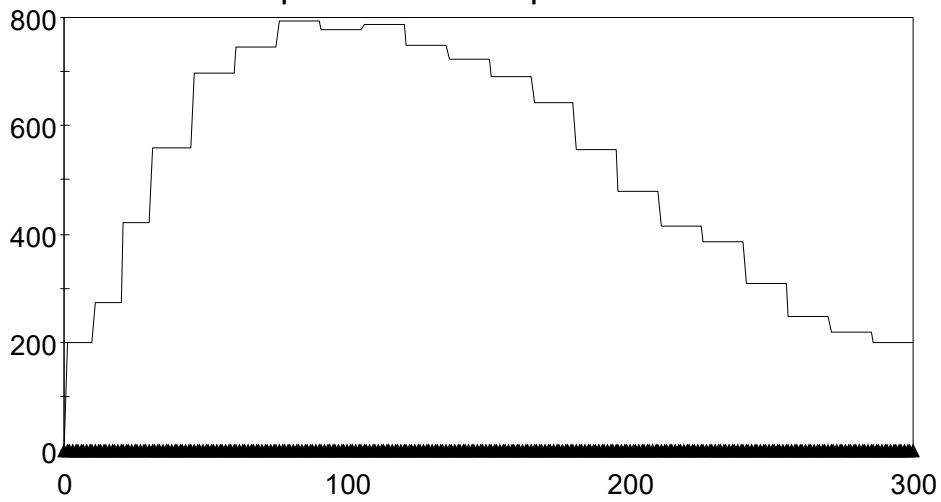


Watanabe RM and Bergman RN, Diabetes 2000

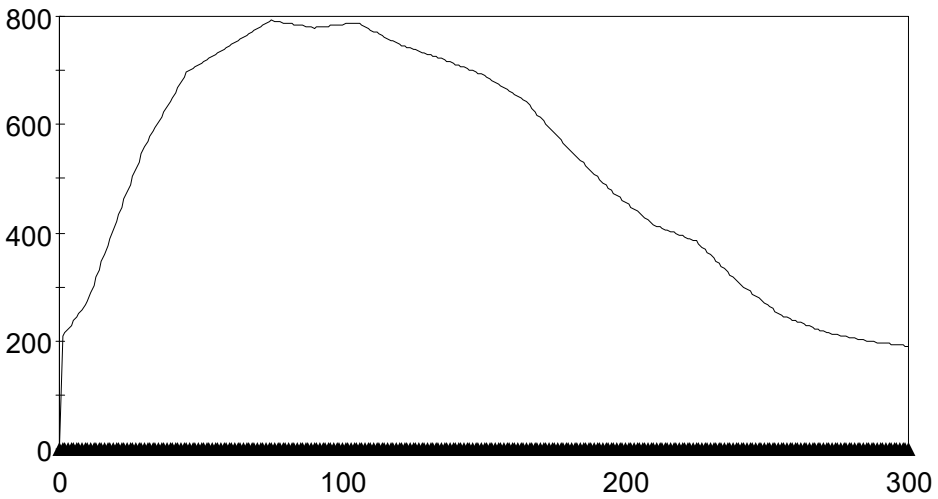
Van Cauter E et al., Diabetes 1992

QO vs. QL Functions

QO turned into Forcing Function
Step function interpolation



QL turned into Forcing Function
Linear function interpolation



Mathematical Model of Insulin Secretion

$$\frac{dI}{dt} = -p_I I(t) + p_{fp} R_a(t) \quad (1)$$

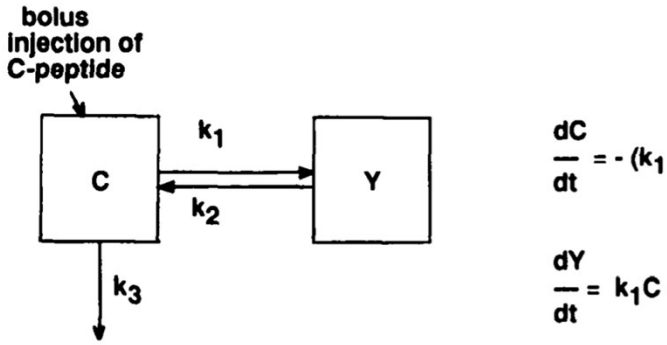
$$\frac{dC_{p1}}{dt} = -(k_{12} + k_{10}) C_{p1}(t) + k_{21} C_{p2}(t) + R_a(t) \quad (2)$$

$$\frac{dCp1}{dt} \approx \frac{C_{p1}(t+h) - C_{p1}(t)}{h} = \frac{\Delta C_{p1}}{h} \quad (3)$$

$$R_a(t) = \frac{\Delta C_{p1}}{h} + (k_{12} + k_{10}) C_{p1}(t) - k_{21} C_{p2}(t) \quad (4)$$

Unpublished work

Mathematical model of C-Peptide



$$\frac{dC}{dt} = -(k_1 + k_3)\,C + k_2 Y \qquad (1)$$

$$\frac{dY}{dt} = k_1 C - k_2 Y$$

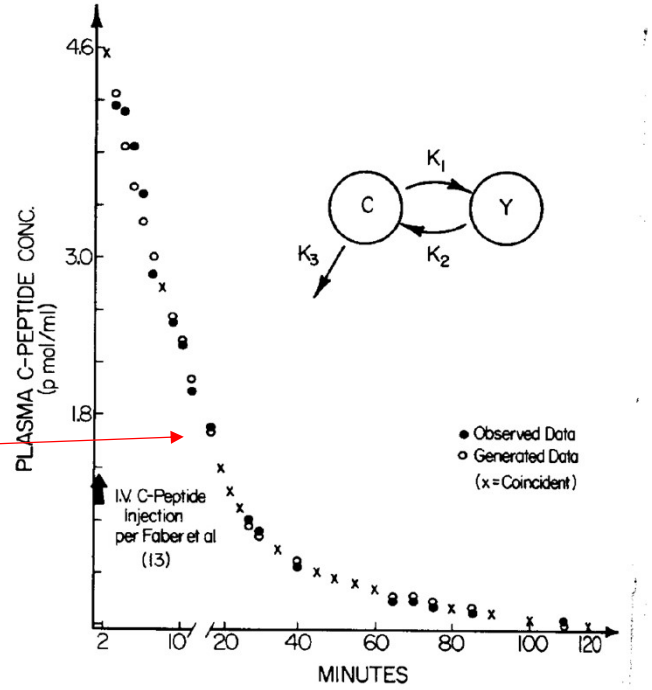
the solution of equations (1) is

$$C(t) = A \exp[-a(t-t_0)] + B \exp[-b(t-t_0)] \qquad (2)$$

with $k_2 = -(Ab + Ba)/(A+B)$

$k_3 = ab / k_2$ (3)

$k_1 = -a - b - k_2 - k_3$

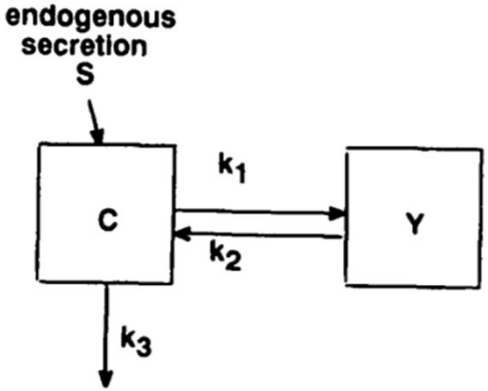


Van Cauter E et al., Diabetes 1992

Eaton RP et al., JCEM 1979

Model of insulin secretory rate (ISR)

- Assumption: The unique parameter estimates (k1, k2, k3) of a subject are equal across given cohort of subjects (normal, obese or T2D).
  - Consequence of the assumption: The data and the model (including the parameters) are taken as to be known (absolute) and we need to estimate the temporal profile of the secretion (appearance of insulin). This is also known as <u>parametric deconvolution</u>



$$\frac{dC}{dt} = S - (k_1 + k_3)\,C + k_2 Y$$

$$\frac{dY}{dt} = k_1 C - k_2 Y$$

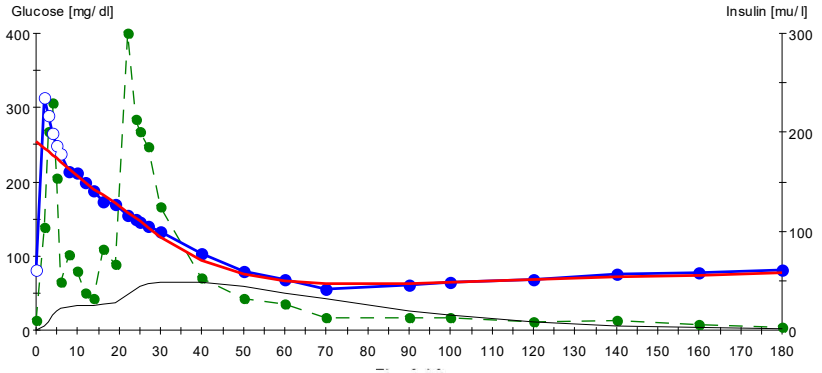
(4)

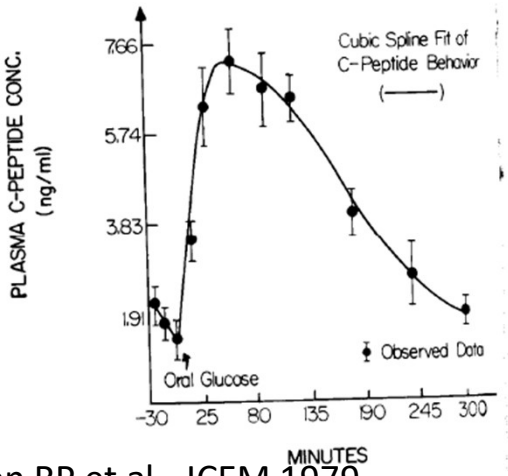
$$S(t) = -k_1\,C(t_0)\exp[-k_2(t-t_0)] - k_1 k_2 \int_{t_0}^{t} C(s)\exp[-k_2(t-s)]\,ds + \frac{dC}{dt} + (k_1 + k_3)\,C(t)$$

Parametric Deconvolution

Known Input
(e.g. bolus)

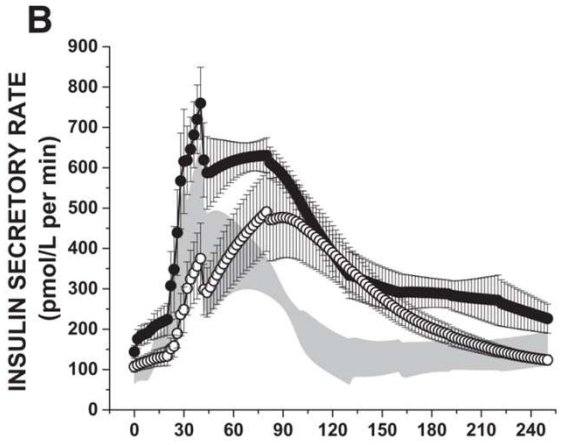
Mathematical Model with unknown parameters





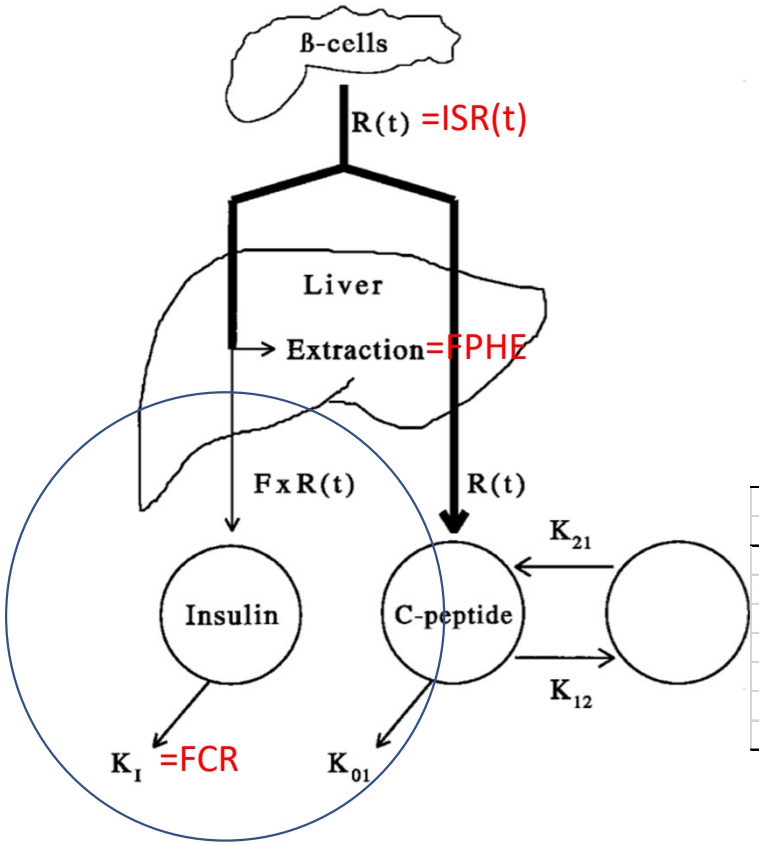
Eaton RP et al., JCEM 1979

Mathematical Model with fixed parameters



Sheikh S et al., Diabetes 2017

Mathematical model of insulin secretory rate (ISR)



Watanabe RM and Bergman RN, Diabetes 2000

Inactivating mutations in the genes encoding the beta-cell KATP channels, cause the most common and severe form of congenital hyperinsulinism (KATPHI), which is unresponsive to available treatments. The aim of this study was to assess pancreatic and extra-pancreatic actions of exendin-(9-39) using non-invasive mixed meal and protein load tests in children with HI.

	MMTT					OPTT				
	Placebo		EX9			Placebo		EX9		
Parameter	Mean	SEM	Mean	SEM	P	Mean	SEM	Mean	SEM	P
AUC Glucose (mg.dl/min)	26259	3306	33470	3498	**≤0.001**	12570	1318	18540	1621	**0.01**
AUC Insulin (pmol/l.min)	25811	6507	25227	5597	0.827	14584	4141	27797	6139	**0.004**
AUC C-peptide (pmol/l.min)	171367	22443	179653	29360	0.534	139776	24075	183620	17283	0.059
AUC ISR (pmol/l.min)	11815	1436	12389	1773	0.562	12135	1802	11329	1373	0.553
FCR (1/min)	0.219	0.086	0.264	0.072	0.383	0.309	0.071	0.225	0.051	**0.017**
FPHE (%)	75	6	54	8	**0.008**	48	9	54	8	0.566

DeLeon D laboratory, unpublished data