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ORAL GLUCOSE TOLERANCE TEST MODELLING: PHYSIOLOGICAL PLAUSIBILITY AND ROBUST PARAMETER ESTIMATION

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Oral Glucose Tolerance Test modelling: physiological plausibility and robust parameter estimation.

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1 Abstract

Due to the increasing importance of identifying insulin resistance from the Oral Glucose Tolerance Test, a need exists to have a robust mathematical model representing the glucose/insulin control system. Such a model should be simple enough to allow precise estimation of insulin sensitivity on a single patient, yet exhibit stable dynamics and reproduce accepted physiological behavior. The present work introduces a new model for the interpretation of glucose and insulin concentrations observed during an OGTT.

2 Introduction

The measurement of insulin sensitivity in humans from a relatively non-invasive test procedure is being felt as a pressing need, heightened in particular by the increase in the social cost of obesity-related dysmetabolic diseases [1-8]. Several methods are available for the estimation of insulin sensitivity, ranging from approximate, widely applicable computations involving fasting insulinemia and glycemia, to complex, labor intensive perturbation procedures like the Euglycemic Hyperinsulinemic Clamp (EHC).

Among perturbation procedures, the Oral Glucose Tolerance Test would seem to excel both for the ease of its performance and for the close similarity to physiological nutrient administration and assimilation. These desirable characteristics, however, are accompanied by the fact that glucose absorption after oral administration is determined to a significant extent by irregular gut absorption. In the framework of a possible mathematical interpretation of the experiment, this introduces additional uncertainty and adds to the number of model parameters which need to be estimated.
Several attempts to the mathematical modelling of the OGTT already in fact exist in the literature, showing however different shortcomings.

The goal of the present work is to describe a relatively simple mathematical model of the OGTT, discuss the characteristics which differentiate it from existing contributions, and show that these characteristics determine in fact a good performance of the model in simultaneously assessing tissue insulin sensitivity and pancreatic glucose sensitivity.

2.1 The Model

$$\frac{dS}{dt} = -V_{jsmax}\frac{S}{K_m + S} \quad (1)$$

$$\frac{dJ}{dt} = V_{jsmax}\frac{S}{K_m + S} - k_{gj}J \quad (2)$$

$$\frac{dG}{dt} = -k_{xgi}IG + k_g + fk_{gj}\frac{J}{V} \quad (3)$$

$$\frac{dI}{dt} = -k_{xi}I + k_{ig}G^{\gamma} + k_{ij}\frac{J}{V} \quad (4)$$

with initial conditions

$$S(0) = D, J(0) = 0, G(0) = G_b, I(0) = I_b$$

3 Results

3.1 Subject 1

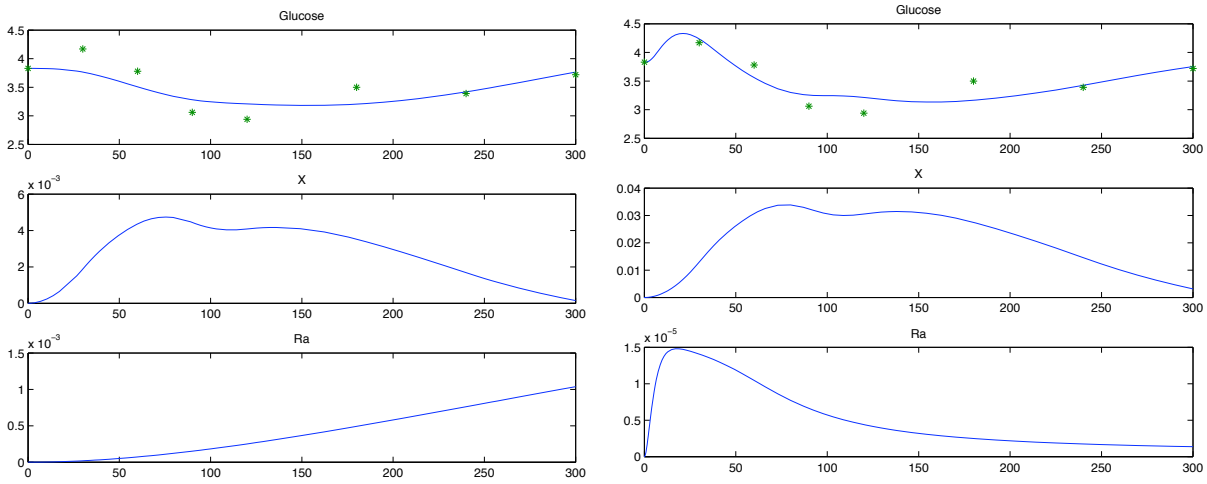

Figure 1: Subject 1 fittings with DallaMan 2006, model 1 (above) and DallaMan 2006, model 2 (below). Top figures: glucose data (stars) and fitting. Middle figures: X compartment predictions. Bottom figures: R_a compartment predictions.

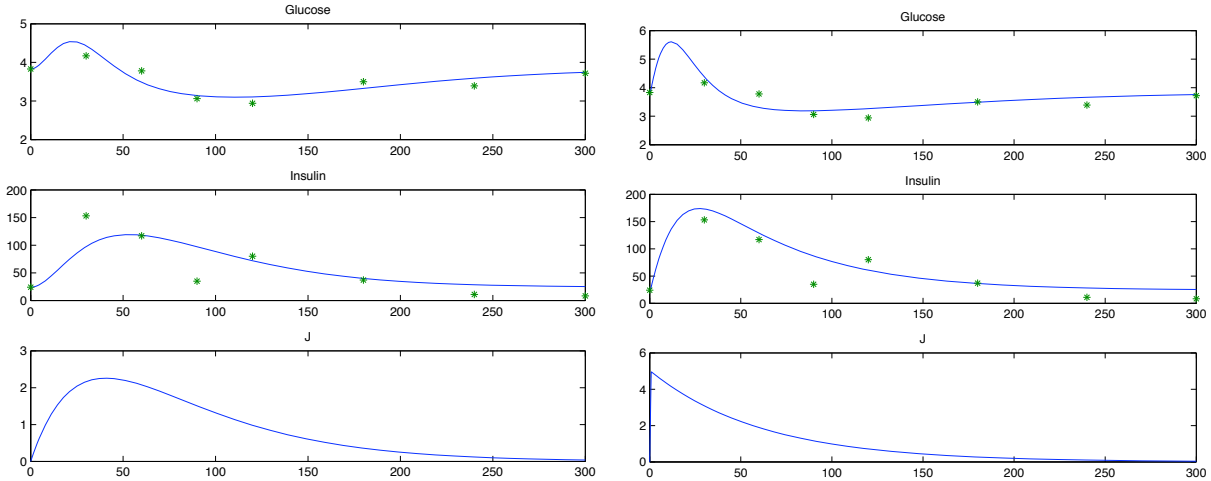

Figure 2: Subject 1 fittings with our model 3, model 3 version 2 (above) and model 3 version 3 (below). Top figures: glucose data (stars) and fitting. Middle figures: insulin data (stars) and predictions. Bottom figures: J compartment predictions.

Model	BIC	Parameters									
DallaMan,1	1828	p_1	p_2	p_3	k_{21}	k_{abs}	σ				
parameters		0.0167	0.0117	0.0000	0.0026	0.0017	0.2358				
SE		0.0020	0.0020	-	-	-	-				
DallaMan,2	2790	p_1	p_2	p_3	k_{empt}	k_{min}	k_{max}	b	c	k_{abs}	σ
parameters		0.1127	0.0101	0.0000	0.0044	0.0004	0.2785	0.8021	0.1930	0.4776	0.1914
SE		0.0004	0.0117	-	0.0007	0.0007	0.0000	0.0000	0.0446	0.0427	0.0001
Model 3.2	61.31	k_{xi}	k_{xgi}	γ	k_{is}	k_{gj}	k_{js}	σ_G	σ_I		
parameters		0.0697	0.0007	1.4558	0.4441	0.0158	0.0326	0.0284	0.2482		
SE		-	-	-	-	-	-	0.0042	-		
Model 3.3	65.38	k_{xi}	k_{xgi}	γ	k_{is}	k_{gj}	V_{jsmax}	K_m	σ_G	σ_I	
parameters		0.0611	0.0006	0.7472	0.3072	0.0123	29.941	10.0740	0.0454	0.1845	
SE		0.0016	0.0003	-	-	0.0061	0.0068	0.0000	0.0502	0.0402	

Table 1: Subject 1, estimated parameters and BIC

3.2 Subject 2

Model	BIC	Parameters									
Dalla Man, 1 parameters	253.14	p_1	p_2	p_3	k_{21}	k_{abs}	σ				
		0.0048	0.0013	0.0000	0.0052	0.0047	0.7564				
SE		0.0027	0.0004	0.0000	0.0000	0.0000	0.0028				
DallaMan, 2 parameters	201.19	p_1	p_2	p_3	k_{empt}	k_{min}	k_{max}	b	c	k_{abs}	σ
		12437	0.0000	0.0000	0.0000	0.0001	0.3553	0.9308	0.1178	0.3700	0.8871
SE		-	-	-	-	-	-	-	-	-	-
Model 3.2 parameters	72.79	k_{xi}	k_{xgi}	γ	k_{is}	k_{gj}	k_{js}	σ_G	σ_I		
		0.0997	0.0007	1.8420	0.3806	0.0130	0.0503	0.6476	0.1272		
SE		0.0657	0.0004	0.5090	0.1870	0.0094	0.0842	0.6305	0.1419		
Model 3.3 parameters	86.20	k_{xi}	k_{xgi}	γ	k_{is}	k_{gj}	V_{jsmax}	K_m	σ_G	σ_I	
		0.2442	0.0000	1.0463	0.2756	0.0001	11.6004	0.2607	0.7304	0.3086	
SE		-	0.0000	0.0239	0.0000	-	0.0000	0.0000	-	-	

Table 2: Subject 2, estimated parameters and BIC

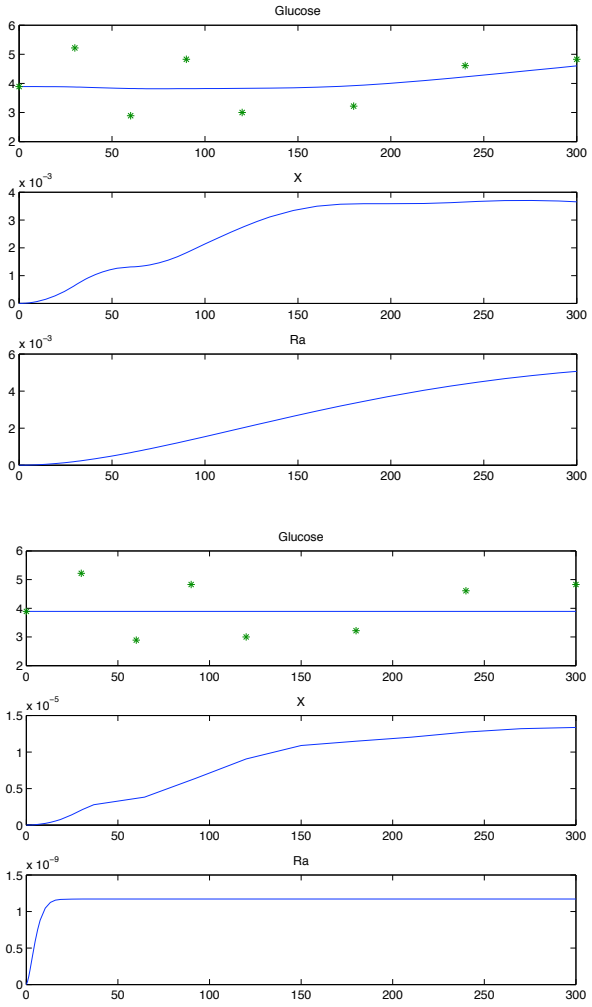

Figure 3: Subject 2 fittings with DallaMan 2006, model 1 (above) and DallaMan 2006, model 2 (below). Top figures: glucose data (stars) and fitting. Middle figures: X compartment predictions. Bottom figures: R_a compartment predictions.

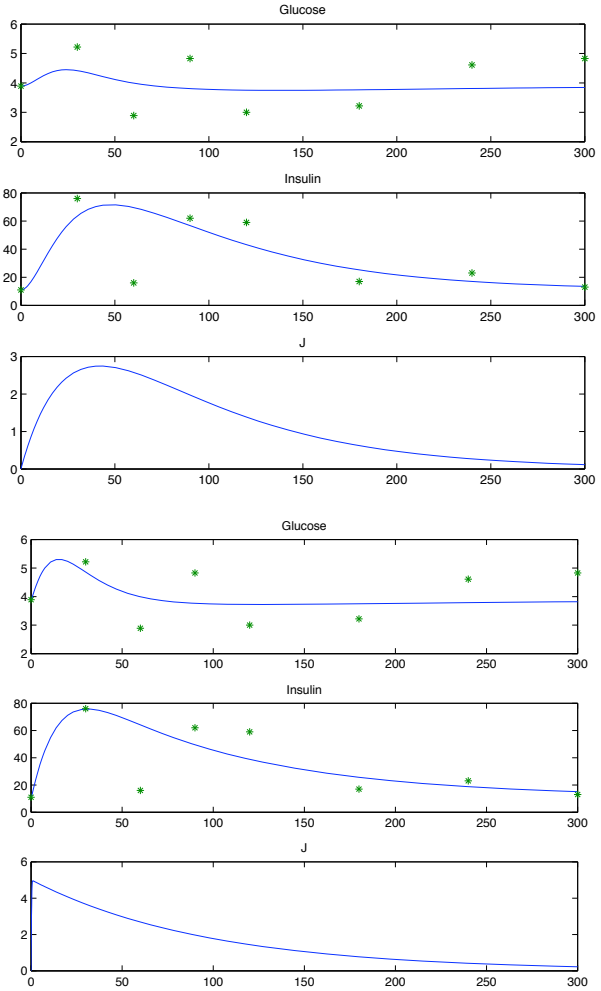

Figure 4: Subject 2 fittings with our model 3, model 3 version 2 (above) and model 3 version 3 (below). Top figures: glucose data (stars) and fitting. Middle figures: insulin data (stars) and predictions. Bottom figures: J compartment predictions.

3.3 Subject 3

Model	BIC	Parameters									
Dalla Man, 1 parameters	211.67	p_1	p_2	p_3	k_{21}	k_{abs}	σ				
		0.0067	0.0184	0.0000	0.0013	0.0054	1.0762				
SE		-	-	-	0.0001	-	-				
DallaMan, 2 parameters	970.56	p_1	p_2	p_3	k_{empt}	k_{min}	k_{max}	b	c	k_{abs}	σ
		0.0384	0.4714	0.0001	0.0196	0.0012	0.1277	0.7640	0.1361	0.3468	0.4863
SE		0.0038	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0038	0.0000	0.0001
Model 3.2	66.62	k_{xi}	k_{xgi}	γ	k_{is}	k_{gj}	k_{js}	σ_G	σ_I		
parameters		0.0405	0.0004	3.1834	0.8358	0.0688	0.0180	0.2342	0.1222		
SE		0.0206	0.0002	0.2784	0.2815	0.0498	0.0078	0.2347	0.1381		
Model 3.3	74.22	k_{xi}	k_{xgi}	γ	k_{is}	k_{gj}	V_{jsmax}	K_m	σ_G	σ_I	
parameters		0.0576	0.0003	1.3126	0.5177	0.0200	31.7096	0.1044	0.2886	0.1605	
SE		-	0.0090	0.0001	-	0.0139	0.0025	0.0000	0.0025	-	

Table 3: Subject 3, estimated parameters and BIC

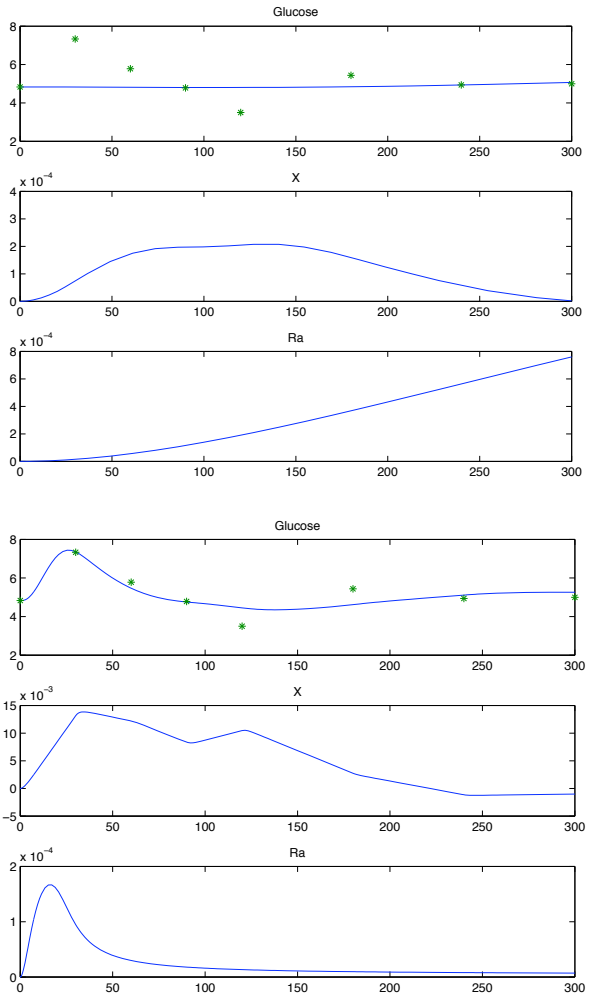

Figure 5: Subject 3 fittings with DallaMan 2006, model 1 (above) and DallaMan 2006, model 2 (below). Top figures: glucose data (stars) and fitting. Middle figures: X compartment predictions. Bottom figures: R_a compartment predictions.

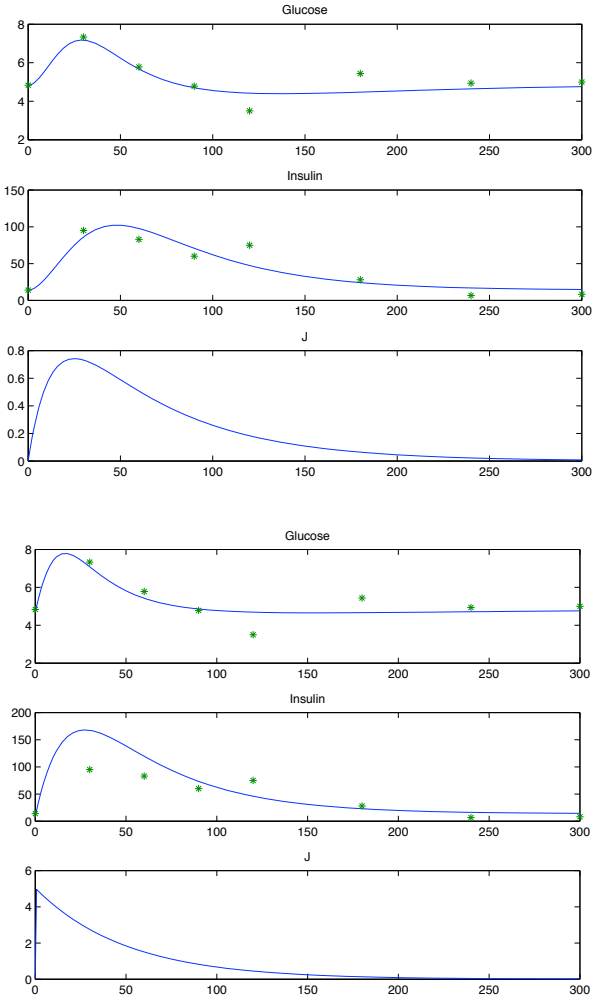

Figure 6: Subject 3 fittings with our model 3, model 3 version 2 (above) and model 3 version 3 (below). Top figures: glucose data (stars) and fitting. Middle figures: insulin data (stars) and predictions. Bottom figures: J compartment predictions.

3.4 Subject 4

Model	BIC	Parameters									
Dalla Man, 1	201.12	p_1	p_2	p_3	k_{21}	k_{abs}	σ				
parameters		0.0839	0.0000	0.0000	0.0785	0.0786	1.1968				
SE		0.0036	0.0265	-	-	-	0.0033				
DallaMan, 2	233.44	p_1	p_2	p_3	k_{empt}	k_{min}	k_{max}	b	c	k_{abs}	σ
parameters		0.0157	0.0428	0.0000	0.0136	0.0011	0.2475	0.7036	0.1428	0.4626	1.1308
SE		-	0.0086	-	0.0001	0.0093	0.0626	0.0628	0.3196	0.3323	-
Model 3.2	381	k_{xi}	k_{xgi}	γ	k_{is}	k_{gj}	k_{js}	σ_G	σ_I		
parameters		0.0000	0.0000	1.6692	0.0802	0.0000	-	0.0000	1.3461		
SE		0.0064	0.0000	-	0.0789	0.0015	-	4.1705	2.0803		
Model 3.3	136.53	k_{xi}	k_{xgi}	γ	k_{is}	k_{gj}	V_{jsmax}	K_m	σ_G	σ_I	
parameters		0.0316	0.0001	1.7910	0.4964	0.0152	10.1582	0.0238	1.9029	0.2609	
SE		0.0132	0.0000	0.0894	0.0543	0.0036	0.0008	-	-	-	

Table 4: Subject 4, estimated parameters and BIC

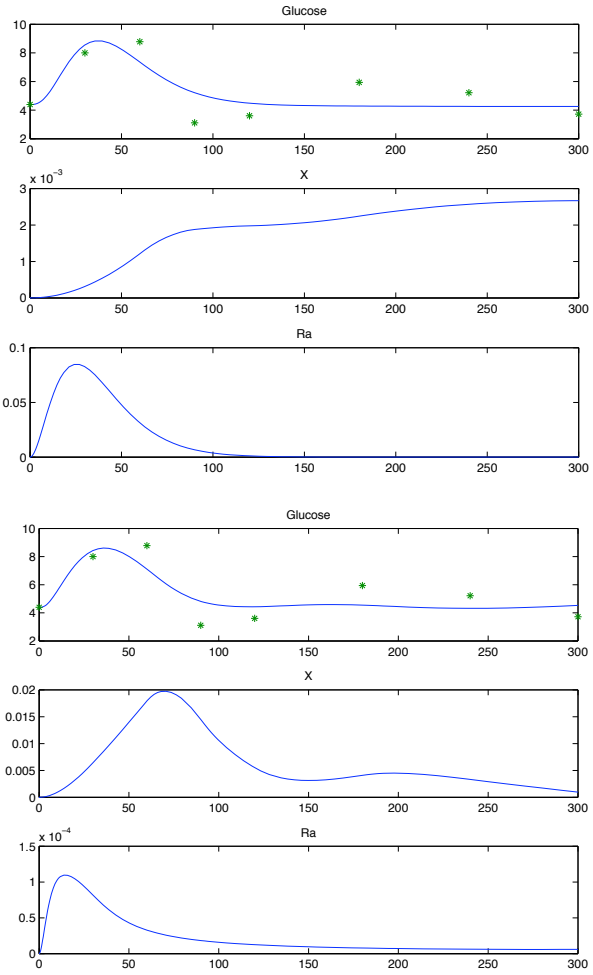

Figure 7: Subject 4 fittings with DallaMan 2006, model 1 (above) and DallaMan 2006, model 2 (below). Top figures: glucose data (stars) and fitting. Middle figures: X compartment predictions. Bottom figures: R_a compartment predictions.

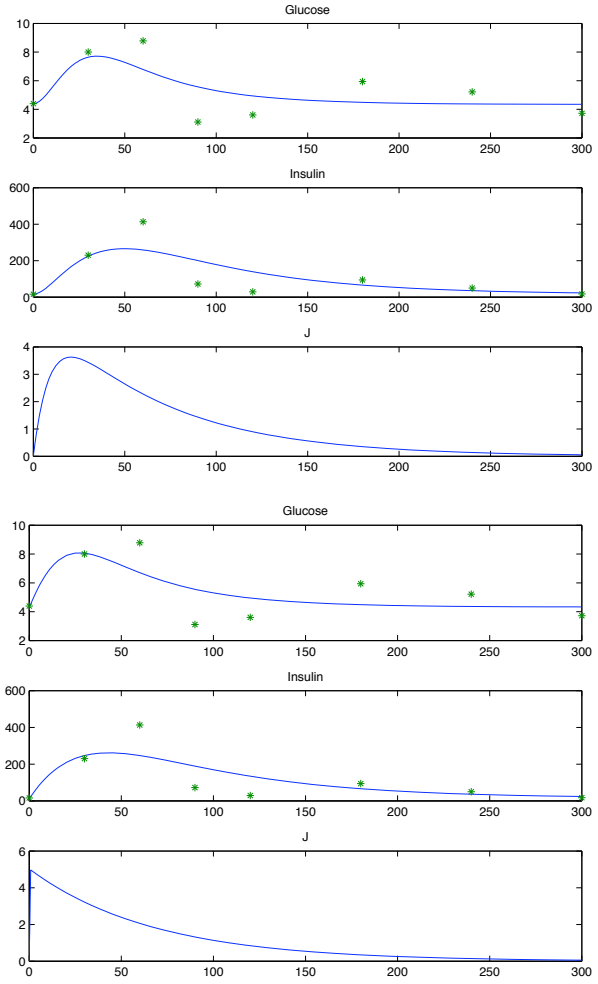

Figure 8: Subject 4 fittings with our model 3, model 3 version 2 (above) and model 3 version 3 (below). Top figures: glucose data (stars) and fitting. Middle figures: insulin data (stars) and predictions. Bottom figures: J compartment predictions.

3.5 Subject 5

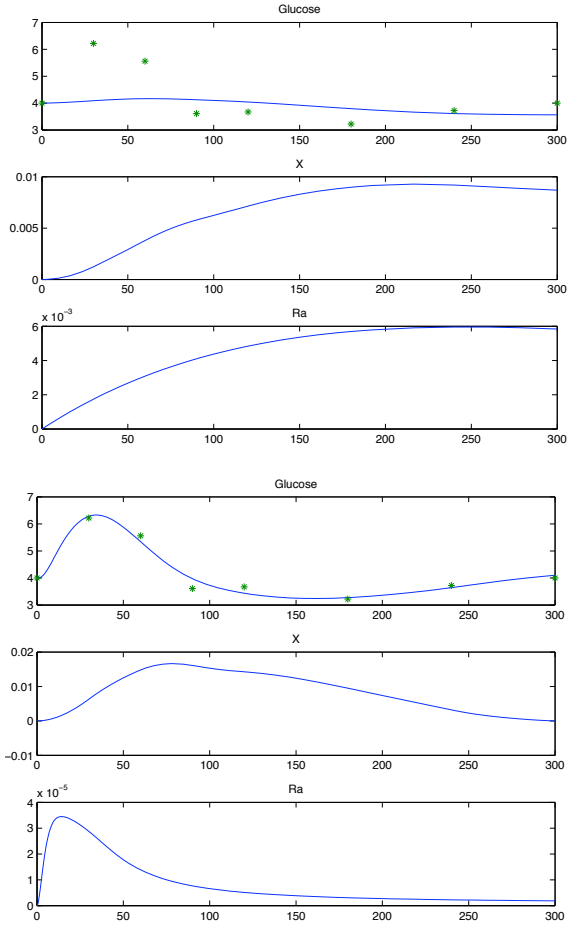

Figure 9: Subject 5 fittings with DallaMan 2006, model 1 (above) and DallaMan 2006, model 2 (below). Top figures: glucose data (stars) and fitting. Middle figures: X compartment predictions. Bottom figures: R_a compartment predictions.

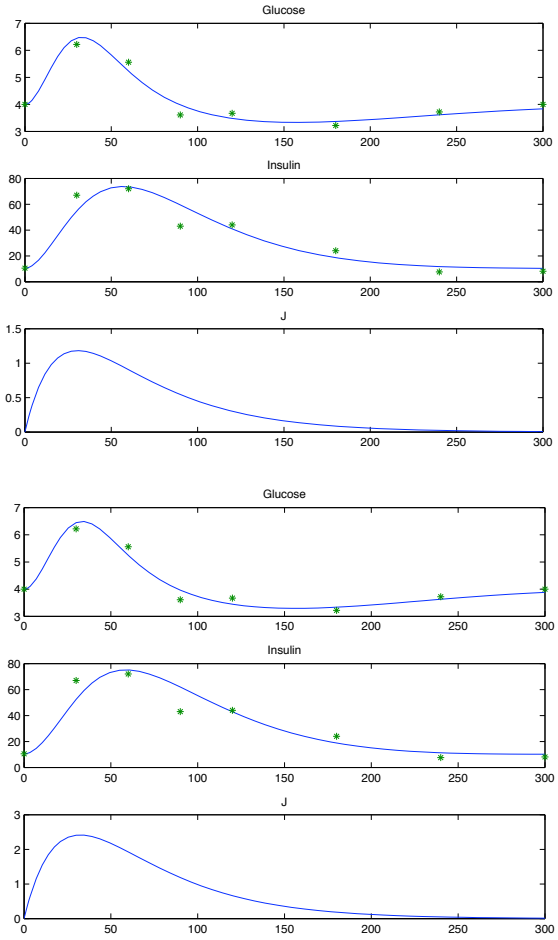

Figure 10: Subject 5 fittings with our model 3, model 3 version 2 (above) and model 3 version 3 (below). Top figures: glucose data (stars) and fitting. Middle figures: insulin data (stars) and predictions. Bottom figures: J compartment predictions.

Model	BIC	Parameters									
Dalla Man, 1	180.81	p_1	p_2	p_3	k_{21}	k_{abs}	σ				
parameters		0.0002	0.0005	0.0000	0.0040	472.9870	1.9614				
SE		-	-	-	0	-	-				
DallaMan, 2	4539	p_1	p_2	p_3	k_{empt}	k_{min}	k_{max}	b	c	k_{abs}	σ
parameters		0.0285	0.0245	0.0000	0.0081	0.0006	0.3345	0.7791	0.1611	0.4623	0.1835
SE		-	0.0015	-	0.0000	-	0.0444	-	-	0.0441	-
Model 3.2	85.72	k_{xi}	k_{xgi}	γ	k_{is}	k_{gj}	k_{js}	σ_G	σ_I		
parameters		2.3597	0.0000	2.7874	2.6247	0.0000	-	1.0388	0.3233		
SE		0.0007	-	0.0123	0.7298	-	0.0944	0.6647	0.3509		
Model 3.3	49.35	k_{xi}	k_{xgi}	γ	k_{is}	k_{gj}	V_{jsmax}	K_m	σ_G	σ_I	
parameters		0.0502	0.0005	1.9181	0.3882	0.0267	0.1095	0.0027	0.0279	0.2900	
SE		0.0028	-	0.0113	0.0020	0.0023	-	-	-	0.0242	

Table 5: Subject 5, estimated parameters and BIC

Table 6: Model parameters

Parameters	Units	Description
t	min	time
G_b	mM	Glucose plasma concentration immediately before glucose injection
I_b	pM	Insulin basal level
V_g	$L/Kgbw$	Glucose distribution volume
D	mM	Dose of glucose injected
γ		
k_{js}		Glucose transfer rate from stomach to jejunum
k_{gj}		Glucose transfer rate from jejunum to available glucose compartment
k_{is}		Insulin entry contribution from stomach
k_{ij}		Insulin entry contribution from jejunum
k_{xgi}	min^{-1}/pM	Glucose elimination rate, insulin dependent
k_g	mM/min	Spontaneous glucose production by the liver ($k_g = k_{xgi} I_b G_b$)
k_{xi}	min^{-1}	Insulin elimination rate, insulin dependent
k_{ig}	min^{-1}	Insulin entry rate, glucose dependent ($k_{ig} = I_b k_{xi}$)