

Supplementary

Table S1: Patient summary of sex, age, BW, and BMI. For further patient characteristics see Ranjan *et al.* [25].

Patient	Sex	Age [Years]	BW [kg]	BMI [kg/m ²]
1	F	52	54	22.8
2	F	64	50	20.0
3	M	48	81	24.5
4	F	31	69	24.2
5	M	35	87	25.4
6	M	58	72	23.8
7	F	19	73	25.3
8	F	45	59	20.9

Table S2: Prior distributions of insulin PK and glucose PD model parameters with mean, 95% CI, and references.

Parameter	Mean (95% CI)	Distribution	Reference
t_{max}	51 (32-70)	$t_{max} \sim \mathcal{N}(51, 9.5)$	SD changed from 19 [28] due to PK reported in [34]
$Cl_{F,I}$	18.9 (14.0-25.5)	$\log(Cl_{F,I}) \sim \mathcal{N}(2.94, 0.15)$	[28]
E_{max}	60 (30-90)	$E_{max} \sim \mathcal{N}(60, 15)$	Derived from [22]
C_{E50}	338 (168-508)	$C_{E50} \sim \mathcal{N}(338, 85)$	Derived from [22]
F_{01}	15.7 (11.4-20.0)	$F_{01} \sim \mathcal{N}(15.7, 2.1)$	Mean changed from 9.7 [29] due to explicit inclusion of G_{GNG} in PD model

$k_{I2} * 10^{-4}$	595 (236-1502)	$\log(k_{I2}) \sim \mathcal{N}(-2.8, 0.46)$	[29]
$k_{a1} * 10^{-4}$	34 (3.6-316)	$\log(k_{a1}) \sim \mathcal{N}(-5.7, 1.1)$	[29]
$k_{a2} * 10^{-4}$	555 (137-2252)	$\log(k_{a2}) \sim \mathcal{N}(-2.9, 0.70)$	[29]
$k_{a3} * 10^{-4}$	237 (51-1098)	$\log(k_{a3}) \sim \mathcal{N}(-3.7, 0.77)$	[29]
$S_D * 10^{-4}$	5 (0.5-53)	$\log(S_D) \sim \mathcal{N}(-7.6, 1.2)$	[29]
$S_E * 10^{-4}$	412 (72-2357)	$\log(S_E) \sim \mathcal{N}(-3.2, 0.87)$	[29]
$S_T * 10^{-4}$	42 (10-179)	$\log(S_T) \sim \mathcal{N}(-5.5, 0.73)$	[29]

Table S3: Comparison of PD model parameters estimated during leave-one-out validation and final PD model parameters for patient 1.

Training Data	Test Data	Accept?	C_{E50}	E_{max}	F_{01}	$k_{12} * 10^{-4}$	$k_{a1} * 10^{-4}$	$k_{a2} * 10^{-4}$	$k_{a3} * 10^{-4}$	$S_D * 10^{-4}$	$S_E * 10^{-4}$	$S_I * 10^{-4}$
BCD	A	N	329	70.6	12.0	288	31	408	83	7.2	286	31
ACD	B	Y	407	65.7	11.8	276	39	555	198	5.1	287	31
ABD	C	N	436	56.4	14.2	244	16	522	215	1.5	155	23
ABC	D	N	266	87.1	11.6	241	42	531	58	5.6	508	30
BD	A	Y	431	57.5	14.9	263	15	510	192	1.5	136	22
AD	B	Y	488	54.7	13.8	227	16	502	242	1.4	173	19
AB	D	N	394	66.2	14.3	236	28	554	218	1.6	207	24
ABD	ABD	3/3	436 (355-517)	56.4 (51.1-61.8)	14.2 (12.9-15.5)	244 (181-330)	16 (7-35)	522 (221-1233)	215 (59-778)	1.5 (0.6-3.3)	155 (83-289)	23 (16-31)

Table S4: Comparison of PD model parameters estimated during leave-one-out validation and final PD model parameters for patient 2. *Visit A did not have MPE and MAPE values less than $\pm 15\%$ and 20% , respectively.

Training Data	Test Data	Accept?	C_{E50}	E_{max}	F_{0I}	$k_{12} \cdot 10^{-4}$	$k_{a1} \cdot 10^{-4}$	$k_{a2} \cdot 10^{-4}$	$k_{a3} \cdot 10^{-4}$	$S_D \cdot 10^{-4}$	$S_E \cdot 10^{-4}$	$S_T \cdot 10^{-4}$
BCD	A	N	452	68.0	13.2	246	14	456	235	1.2	380	16
ACD	B	N	413	81.6	13.7	367	41	517	119	2.9	434	26
ABD	C	Y	416	60.1	13.9	283	12	507	277	0.8	201	19
ABC	D	Y	426	68.6	14.4	317	15	512	180	0.8	204	21
ABCD	ABCD	3/4*	405 (339-471)	67.4 (59.3-75.5)	13.8 (12.8-14.7)	285 (223-363)	15 (7-35)	495 (236-1039)	231 (137-389)	1.2 (0.6-2.3)	334 (232-481)	19 (15-25)

Table S5: Comparison of PD model parameters estimated during leave-one-out validation and final PD model parameters for patient 3.

Training Data	Test Data	Accept?	C_{E50}	E_{max}	F_{01}	$k_{12} * 10^{-4}$	$k_{a1} * 10^{-4}$	$k_{a2} * 10^{-4}$	$k_{a3} * 10^{-4}$	$S_D * 10^{-4}$	$S_E * 10^{-4}$	$S_T * 10^{-4}$
BCD	A	Y	414	55.3	15.3	392	13	524	327	1.2	260	24
ACD	B	Y	408	57.8	15.6	387	17	538	333	1.3	241	24
ABD	C	N	406	55.0	15.8	370	21	559	276	1.1	133	22
ABC	D	N	352	54.8	14.6	422	47	585	104	1.7	254	29
ABCD	ABCD	4/4	401 (327-475)	57.4 (49.8-65.0)	15.5 (14.2-16.8)	397 (277-568)	18 (8-42)	548 (268-1121)	327 (168-638)	1.4 (0.7-2.5)	237 (183-308)	25 (17-36)

Table S6: Comparison of PD model parameters estimated during leave-one-out validation and final PD model parameters for patient 4.

Training Data	Test Data	Accept?	C_{E50}	E_{max}	F_{01}	$k_{12} * 10^{-4}$	$k_{a1} * 10^{-4}$	$k_{a2} * 10^{-4}$	$k_{a3} * 10^{-4}$	$S_D * 10^{-4}$	$S_E * 10^{-4}$	$S_I * 10^{-4}$
BCD	A	N	275	85.8	13.2	224	20	245	61	3.0	412	17
ACD	B	Y	295	89.6	12.6	202	18	398	58	2.5	435	18
ABD	C	N	397	57.4	12.2	250	18	439	122	1.6	195	22
ABC	D	N	329	81.9	13.2	214	16	510	188	1.6	192	17
ABCD	ABCD	4/4	285 (226-344)	84.4 (73.9-94.8)	12.8 (11.3-14.4)	213 (157-289)	18 (9-36)	437 (183-1044)	68 (42-113)	2.0 (1.0-3.8)	415 (347-496)	18 (13-25)

Table S7: Comparison of PD model parameters estimated during leave-one-out validation and final PD model parameters for patient 5.

Training Data	Test Data	Accept?	C_{E50}	E_{max}	F_{01}	$k_{12} * 10^{-4}$	$k_{a1} * 10^{-4}$	$k_{a2} * 10^{-4}$	$k_{a3} * 10^{-4}$	$S_D * 10^{-4}$	$S_E * 10^{-4}$	$S_T * 10^{-4}$
BCD	A	Y	232	78.8	13.2	316	31	558	351	1.3	436	42
ACD	B	N	245	77.7	13.8	311	54	522	253	3.5	239	36
ABD	C	N	261	70.9	11.3	385	31	562	305	0.7	526	62
ABC	D	N	339	65.4	12.0	281	15	517	235	1.1	229	31
BC	A	Y	339	66.0	12.1	276	15	512	237	1.1	222	30
AC	B	Y	373	66.8	13.4	339	14	491	171	1.3	161	26
AB	C	Y	267	70.3	9.5	201	14	365	276	2.3	547	28
ABC	ABC	3/3	339 (251-427)	65.4 (53.8-77.1)	12.0 (10.6-13.5)	281 (194-406)	15 (7-32)	517 (223-1201)	235 (95-586)	1.1 (0.4-2.6)	229 (127-415)	31 (20-47)

Table S8: Comparison of PD model parameters estimated during leave-one-out validation and final PD model parameters for patient 6.

Training Data	Test Data	Accept?	C_{E50}	E_{max}	F_{01}	$k_{12} * 10^{-4}$	$k_{a1} * 10^{-4}$	$k_{a2} * 10^{-4}$	$k_{a3} * 10^{-4}$	$S_D * 10^{-4}$	$S_E * 10^{-4}$	$S_T * 10^{-4}$
BCD	A	N	404	66.0	15.2	201	34	463	170	2.6	254	19
ACD	B	Y	387	67.0	11.8	179	31	404	180	3.7	328	24
ABD	C	N	424	60.1	13.1	238	10	353	74	2.6	404	21
ABC	D	Y	351	57.1	11.4	165	44	475	156	2.8	384	22
BD	A	Y	472	60.2	14.1	315	14	212	75	3.7	279	22
AD	B	N	439	50.8	13.5	221	10	431	132	1.3	194	20
AB	D	Y	328	63.4	12.9	195	10	441	120	2.6	461	19
ABD	ABD	3/3	424 (333-515)	60.1 (46.3-74.0)	13.1 (11.7-14.5)	238 (172-330)	10 (4-22)	353 (102-1221)	74 (23-232)	2.6 (1.1-6.2)	404 (185-882)	21 (14-32)

Table S9: Comparison of PD model parameters estimated during leave-one-out validation and final PD model parameters for patient 7.

Training Data	Test Data	Accept?	C_{E50}	E_{max}	F_{01}	$k_{12} \cdot 10^{-4}$	$k_{a1} \cdot 10^{-4}$	$k_{a2} \cdot 10^{-4}$	$k_{a3} \cdot 10^{-4}$	$S_D \cdot 10^{-4}$	$S_E \cdot 10^{-4}$	$S_T \cdot 10^{-4}$
BCD	A	N	281	91.4	14.5	250	34	558	32	2.0	321	15
ACD	B	N	293	81.9	16.2	268	189	607	283	2.0	104	15
ABD	C	Y	151	86.9	12.1	309	253	791	218	4.7	194	20
ABC	D	Y	146	82.8	15.0	357	58	616	113	4.4	143	20
ABCD	ABCD	4/4	141 (96-187)	78.0 (68.9-87.1)	14.2 (12.2-16.1)	358 (252-509)	49 (23-105)	624 (319-1221)	178 (69-459)	4.4 (3.2-6.0)	140 (99-199)	21 (16-29)

Table S10: Comparison of PD model parameters estimated during leave-one-out validation and final PD model parameters for patient 8.

Training Data	Test Data	Accept?	C_{E50}	E_{max}	F_{01}	$k_{12} * 10^{-4}$	$k_{a1} * 10^{-4}$	$k_{a2} * 10^{-4}$	$k_{a3} * 10^{-4}$	$S_D * 10^{-4}$	$S_E * 10^{-4}$	$S_T * 10^{-4}$
BCD	A	Y	362	39.7	16.8	429	273	546	280	0.6	125	36
ACD	B	N	390	40.4	17.8	369	323	538	286	0.3	92	27
ABD	C	N	344	36.1	16.2	451	83	549	264	0.8	197	45
ABC	D	N	307	75.3	13.4	289	37	518	154	4.2	463	29
BC	A	N	328	85.5	9.0	367	58	184	94	13.6	279	38
AC	B	N	378	59.1	16.7	276	73	554	269	1.3	262	26
AB	C	N	359	71.5	13.9	306	30	379	191	3.5	197	27
ABC	ABC	3/3	307 (228-386)	75.3 (61.5-89.1)	13.4 (11.4-15.4)	289 (197-424)	37 (18-75)	518 (203-1324)	154 (68-348)	4.2 (2.8-6.5)	463 (377-569)	29 (20-42)

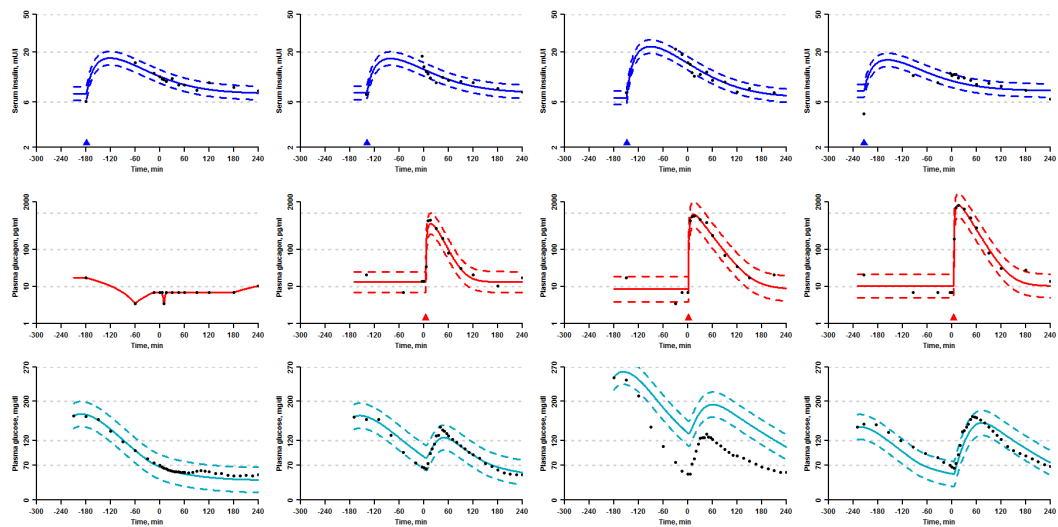


Figure S1: Data from all patient 1's visits (left to right: visit A to D) with insulin PK model fits (top row, logarithmic y-axes) and glucagon linear interpolation or PK model fits (middle row, logarithmic y-axes) both used as inputs to the glucose PD model for simulation built with data from visits A, B and D (bottom row). The dynamics during visit C are clearly different from the three other visits. The triangles indicate dose time of the insulin and glucagon boluses, respectively.

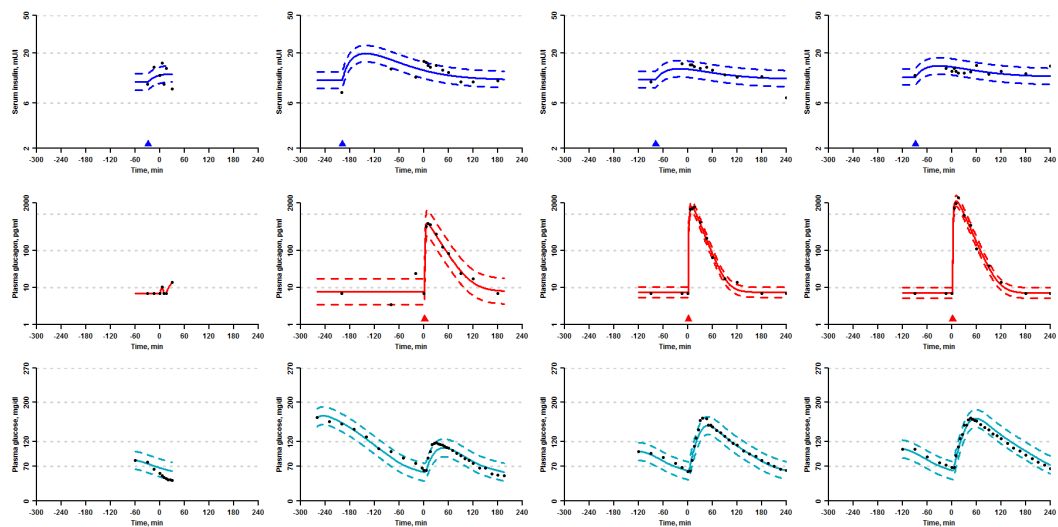


Figure S2: Data from all patient 2's visits (left to right: visit A to D) with insulin PK model fits (top row, logarithmic y-axes) and glucagon linear interpolation or PK model fits (middle row, logarithmic y-axes) both used as inputs to the glucose PD model for simulation **built with data from all four visits** (bottom row). The triangles indicate dose time of the insulin and glucagon boluses, respectively.

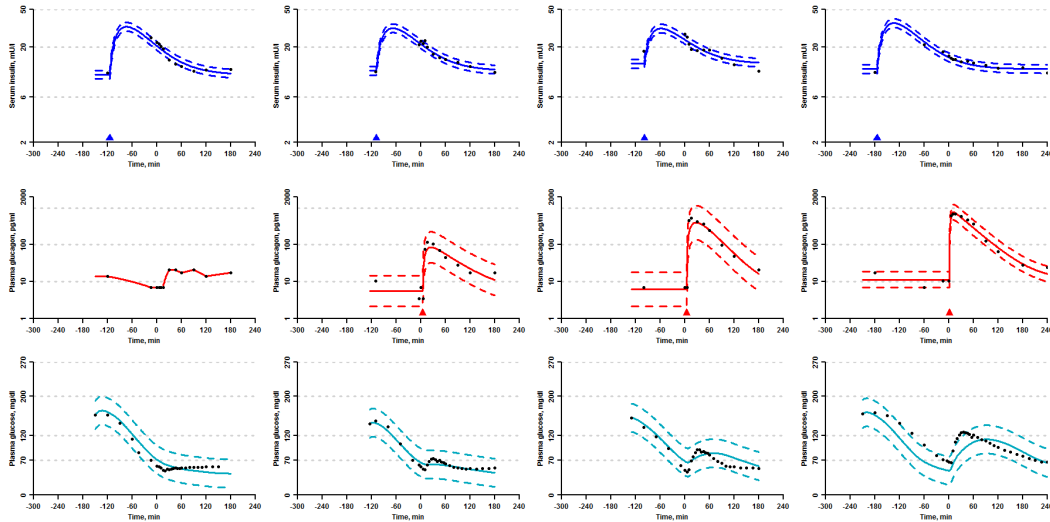


Figure S3: Data from all patient 3's visits (left to right: visit A to D) with insulin PK model fits (top row, logarithmic y-axes) and glucagon linear interpolation or PK model fits (middle row, logarithmic y-axes) both used as inputs to the glucose PD model for simulation **built with data from all four visits** (bottom row). The triangles indicate dose time of the insulin and glucagon boluses, respectively.

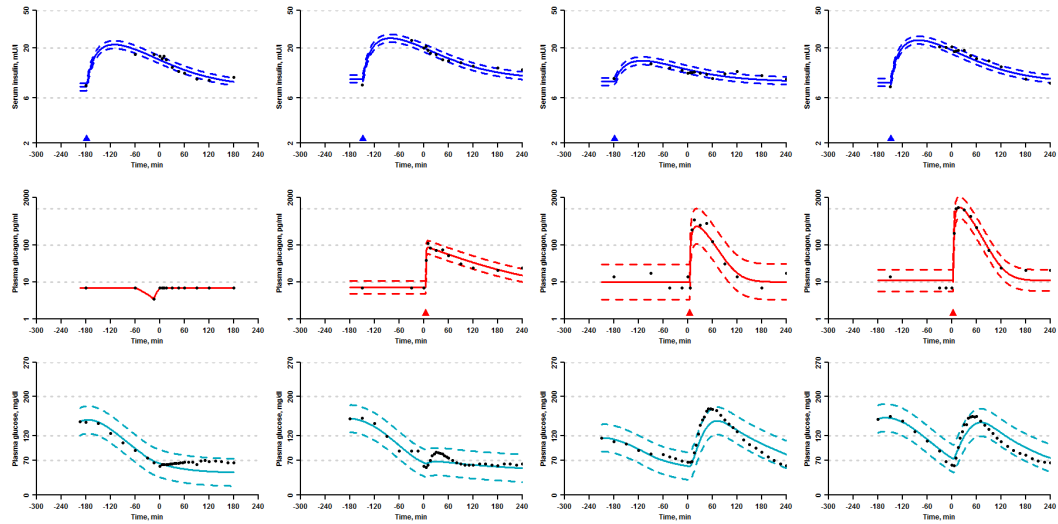


Figure S4: Data from all patient 4's visits (left to right: visit A to D) with insulin PK model fits (top row, logarithmic y-axes) and glucagon linear interpolation or PK model fits (middle row, logarithmic y-axes) both used as inputs to the glucose PD model for simulation **built with data from all four visits** (bottom row). The triangles indicate dose time of the insulin and glucagon boluses, respectively.

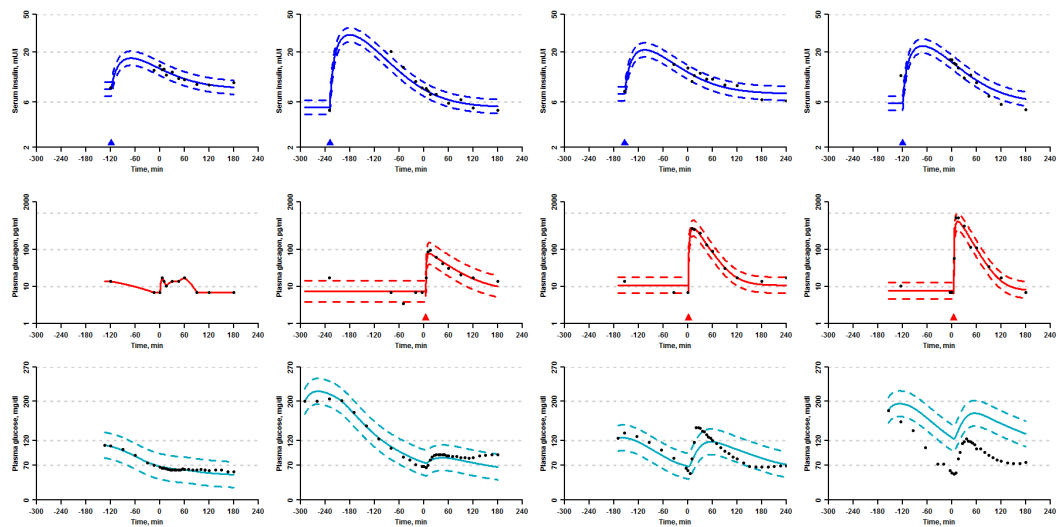


Figure S5: Data from all patient 5's visits (left to right: visit A to D) with insulin PK model fits (top row, logarithmic y-axes) and glucagon linear interpolation or PK model fits (middle row, logarithmic y-axes) both used as inputs to the glucose PD model for simulation **built with data from all four visits** (bottom row). The triangles indicate dose time of the insulin and glucagon boluses, respectively.

simulation built with data from visits A, B and C (bottom row). The dynamics during visit D are clearly different from the three other visits. The triangles indicate dose time of the insulin and glucagon boluses, respectively.

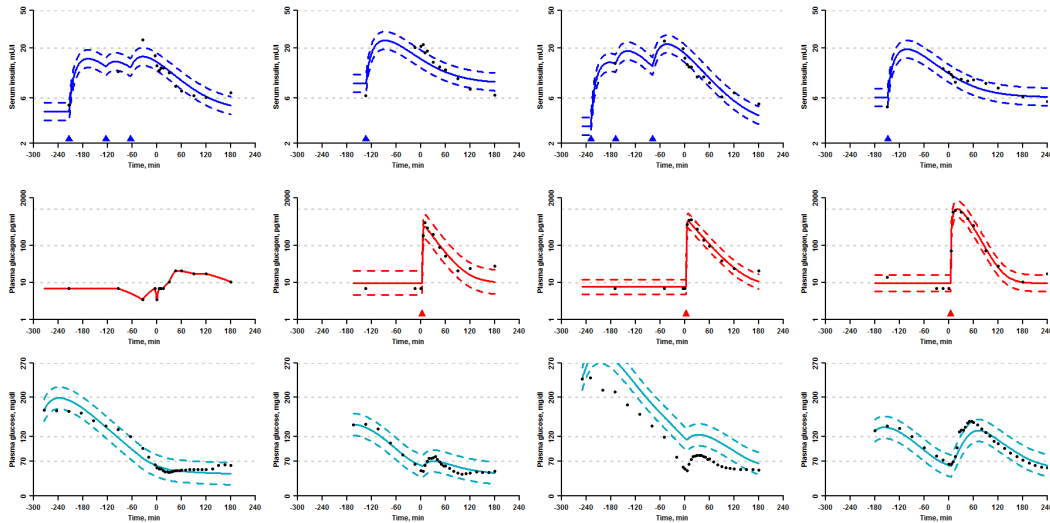


Figure S6: Data from all patient 6's visits (left to right: visit A to D) with insulin PK model fits (top row, logarithmic y-axes) and glucagon linear interpolation or PK model fits (middle row, logarithmic y-axes) both used as inputs to the glucose PD model for simulation built with data from visits A, B and D (bottom row). The dynamics during visit C are clearly different from the three other visits. The triangles indicate dose time of the insulin and glucagon boluses, respectively.

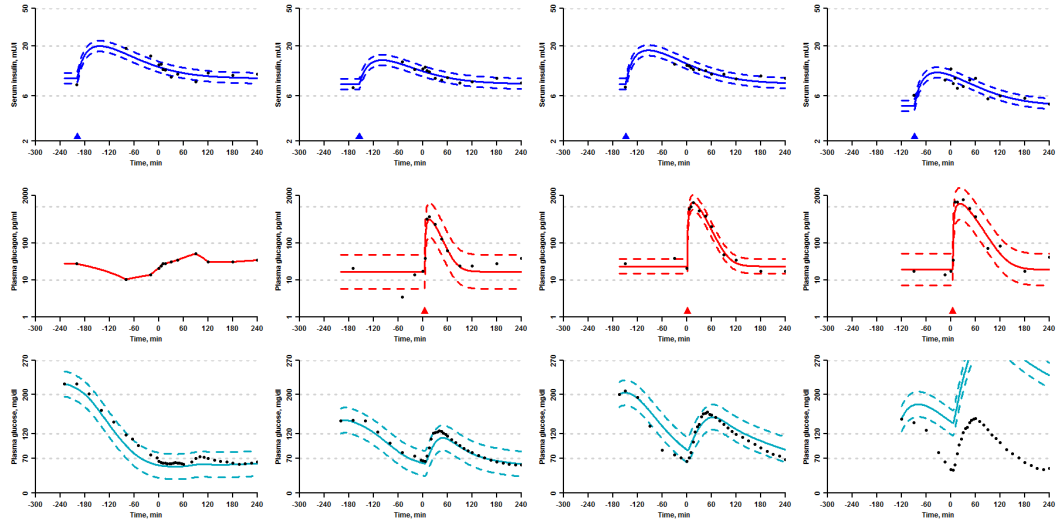


Figure S7: Data from all patient 8's visits (left to right: visit A to D) with insulin PK model fits (top row, logarithmic y-axes) and glucagon linear interpolation or PK model fits (middle row, logarithmic y-axes) both used as inputs to the glucose PD model for simulation built with data from visits A, B and C (bottom row). The dynamics during visit D are clearly different from the three other visits. The triangles indicate dose time of the insulin and glucagon boluses, respectively.