SUPPLEMENTAL INFORMATION

A hierarchical whole body modeling approach elucidates the link between in vitro insulin signaling and in vivo glucose homeostasis

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Supplemental Figures S1-S5

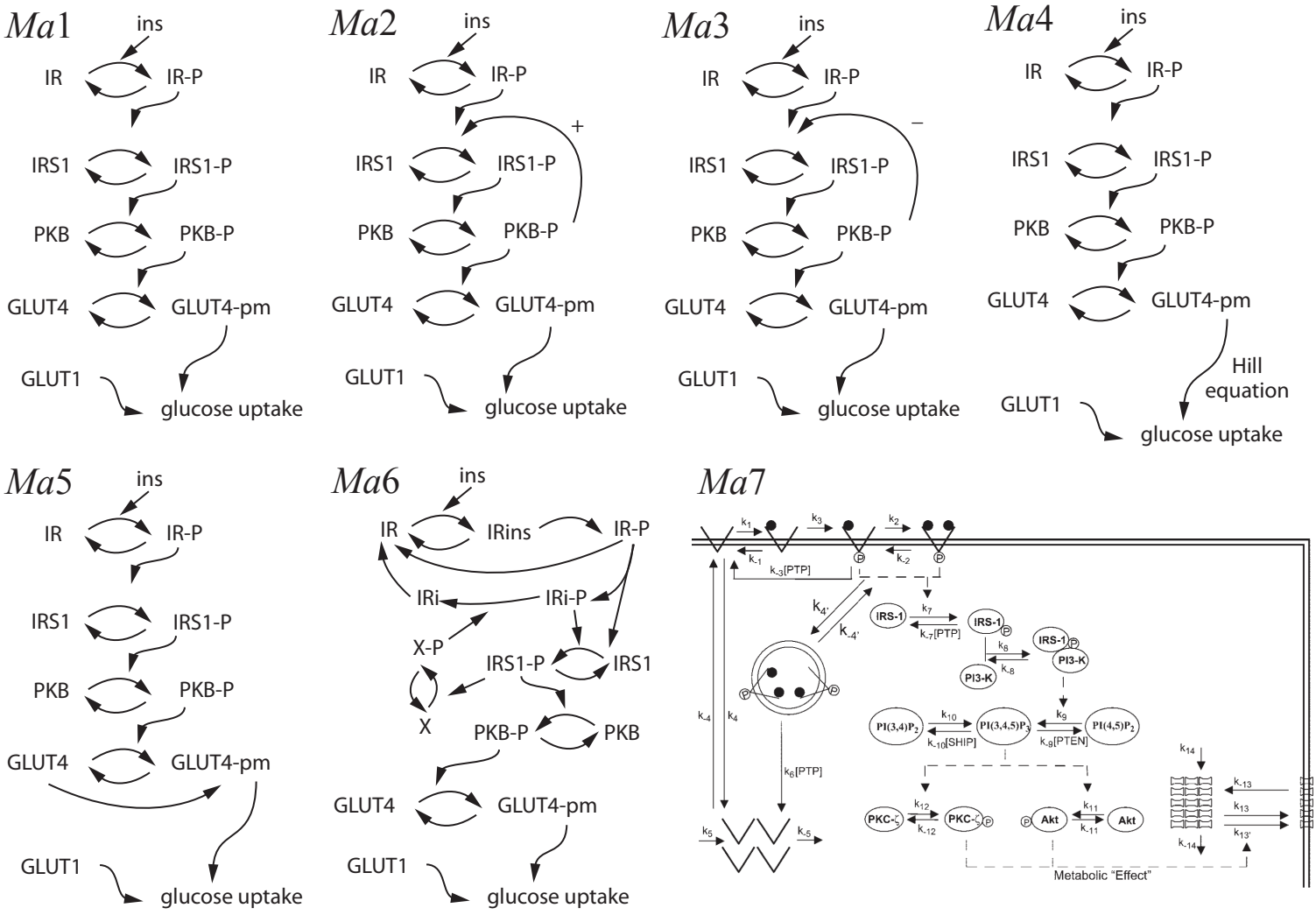


Figure S1. The model structures within the hypothesis *Ma*. The corresponding differential equations can be found in the simulation files for each model. All chosen model structures only deal with the essential dynamics, and are no attempts to include all known reactions or components of the system. ins, insulin; IR, insulin receptor; IR-P, phosphorylated IR; IRins, IR with bound insulin; IRi-P, internalized and phosphorylated IR; IRi internalized IR; IRS1, insulin receptor substrate 1; IRS1-P, phosphorylated IRS1; X and X-P, non-active and active form of an unknown protein; PKB, protein kinase B; PKB-P, phosphorylated PKB; GLUT1, glucose transporter 1; GLUT4, glucose transporter 4; GLUT-pm, GLUT4 translocated to the plasma membrane. *Ma*7 from (1).

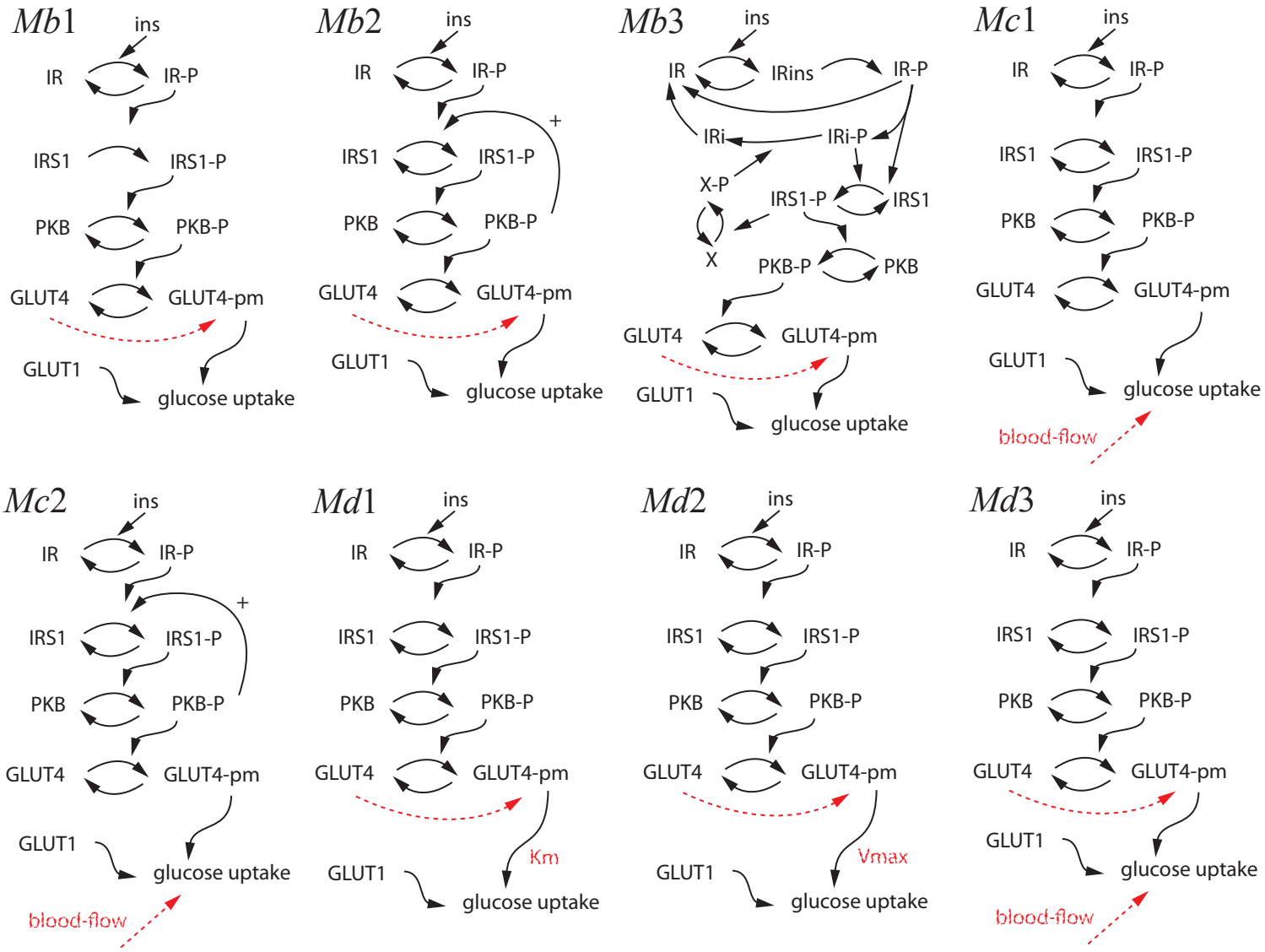


Figure S2. The model structures within the hypotheses *Mb, Mc* and *Md.* Red, dashed lines and text denotes *in vitro/vivo*-differences. All other notations as in Figure S1. The corresponding differential equations can be found in the simulation files for each model. All chosen model structures only deal with the essential dynamics, and are no attempts to include all known reactions or components of the system.

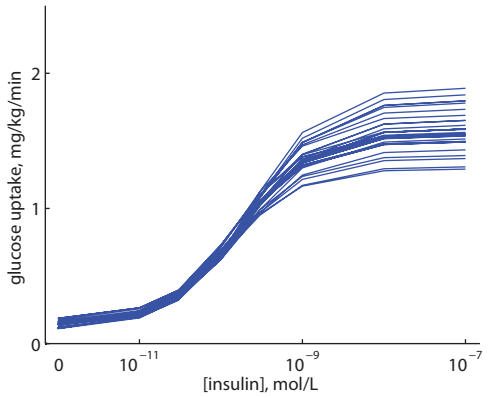


Figure S3. Core-prediction . Core-prediction of glucose uptake with 5.0 mM glucose from model *Ma*6.

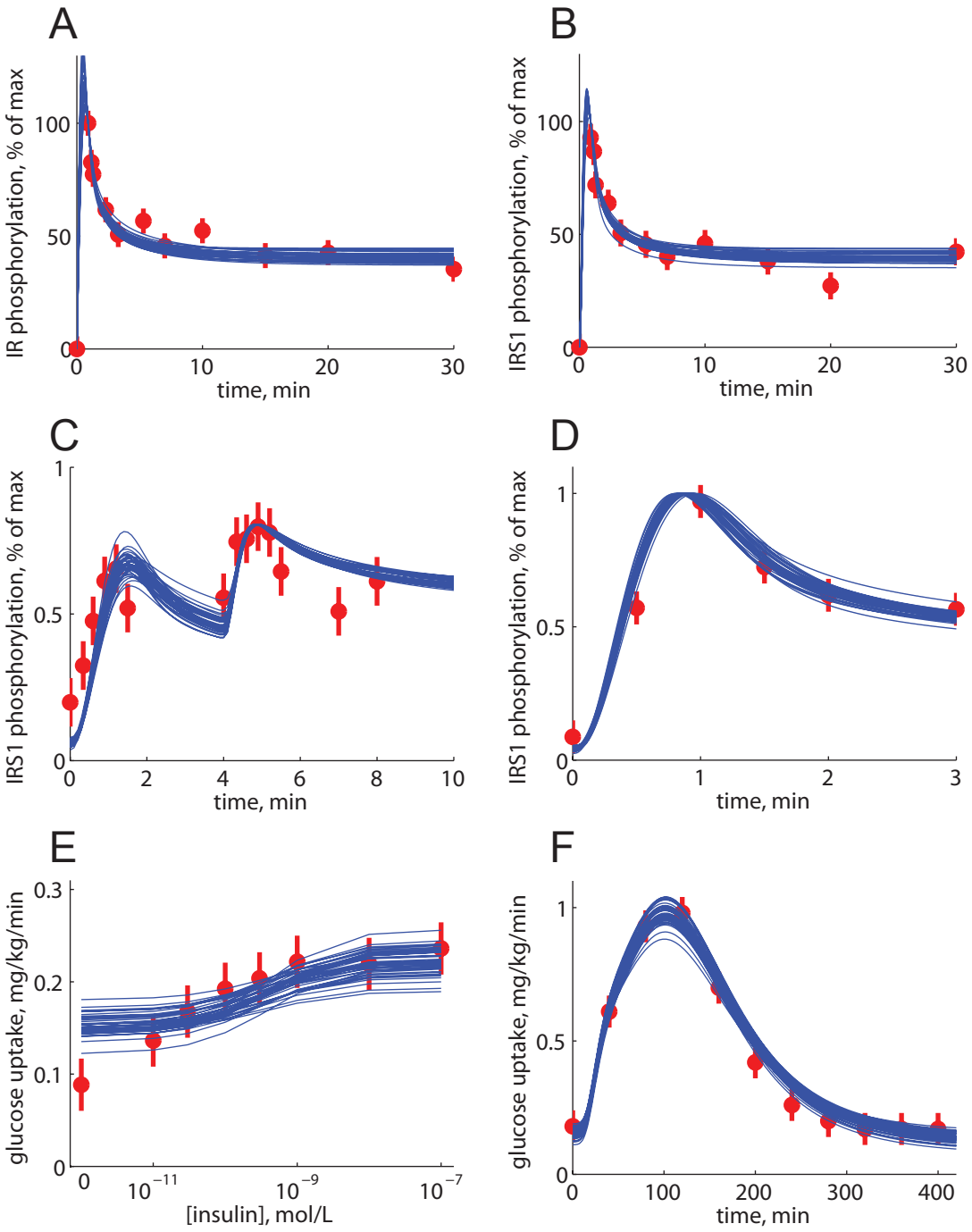


Figure S4. Simulations of the hierarchical model, M^1, compared with dataset Z_3.

Simulated results are depicted as blue solid lines (one line for each extreme acceptable parameter-set), and experimental data are depicted as red, filled circles with error-bars (± one SE). A) IR phosphorylation in response to 100 nM insulin. Experimental data from isolated adipocytes. B) IRS1 phosphorylation in response to 100 nM insulin. Experimental data from isolated adipocytes. C) IRS1 phosphorylation in response to first 1.2 nM at 0 min, and then 10 nM insulin at 4 min. Experimental data from isolated adipocytes. D) IRS1 phosphorylation in response to 10 nM insulin. Experimental data from isolated adipocytes. E) Dose-response for glucose uptake in response to increasing concentrations of insulin. Experimental data from isolated adipocytes. F) Glucose uptake by the adipose tissue in response to a meal. Experimental data from the Dalla Man-model.

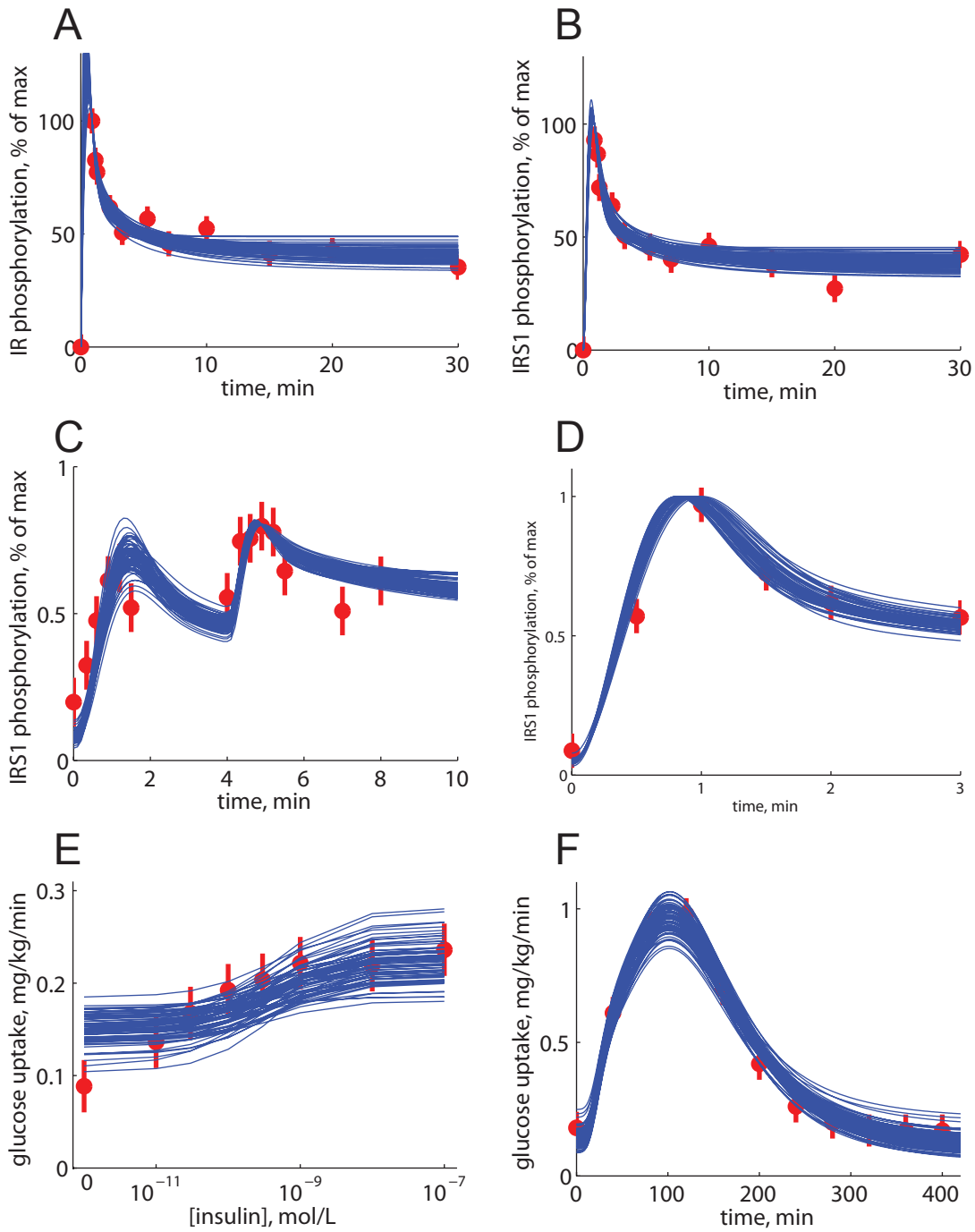


Figure S5. Simulations of the hierarchical model, M^2, compared with dataset Z_3.

Simulated results are depicted as blue solid lines (one line for each extreme acceptable parameter-set), and experimental data are depicted as red, filled circles with error-bars (± one SE). A) IR phosphorylation in response to 100 nM insulin. Experimental data from isolated adipocytes. B) IRS1 phosphorylation in response to 100 nM insulin. Experimental data from isolated adipocytes. C) IRS1 phosphorylation in response to first 1.2 nM at 0 min, and then 10 nM insulin at 4 min. Experimental data from isolated adipocytes. D) IRS1 phosphorylation in response to 10 nM insulin. Experimental data from isolated adipocytes. E) Dose-response for glucose uptake in response to increasing concentrations of insulin. Experimental data from isolated adipocytes. F) Glucose uptake by the adipose tissue in response to a meal. Experimental data from the Dalla Man-model.

TABLE S1

Model rejections for different degrees of freedom and levels of significance

		Dataset Z_1				Dataset Z_2
	Degrees of freedom	34	34	31	28	36
	Level of significance	1%	5%	5%	5%	1 %
*Ma*1	Simple model	OK	Rejected	--	--	
*Ma*2	*Ma*1 + positive feedback (PKB → IRS1)	OK	OK	OK	OK	Rejected
*Ma*3	*Ma*1 + negative feedback (PKB → IRS1)	OK	Rejected	--	--	
*Ma*4	*Ma*1 + Hill equation (GLUT4 glucose uptake)	OK	OK	OK	Rejected	
*Ma*5	*Ma*1 + basal translocation of GLUT4	OK	Rejected	--	--	
*Ma*6	*Ma*1 + *Mifa* (2)	OK	OK	OK	OK	Rejected
*Ma*7	Sedaghat model (1)	OK	Rejected	--	--	

TABLE S2

Model rejections for different degrees of freedom and levels of significance

		Dataset Z_2			
	Degrees of freedom	36	36	33	30
	Level of significance	1%	5%	5%	5%
Basal GLUT4 translocation hypothesis					
*Mb*1	*Ma*1 + basal-translocation	Rejected	--	--	--
*Mb*2	*Ma*2 + basal-translocation	OK	Rejected	--	--
*Mb*3	*Ma*6 + basal-translocation	Rejected	--	--	--
Blood-flow hypothesis					
*Mc*1	*Ma*1 + blood-flow	OK	Rejected	--	--
*Mc*2	*Ma*2 + blood-flow	OK	Rejected	--	--
Multiple *in vivo/vitro*-differences					
*Md*1	*Mb*1 + *in vivo/vitro*-different Km GLUT4	OK	OK	Rejected	--
*Md*2	*Mb*1 + *in vivo/vitro*-different Vmax GLUT4	OK	OK	OK	Rejected
*Md*3	*Mb*1 + *Mc*1	OK	OK	OK	OK

Supplemental Methods

Principles of constructing and simulating a model using module constraints

Consider model structure *Ma*1 in Figure S1. We assume that all reactions follow mass action kinetics and act through simple multiplication. We also assume that the basal activation is given by a basal activation of the insulin receptor. With these assumption, the set of differential equations become

$$\dot{IR} = k1b \cdot IRp - k1f \cdot IR \cdot insulin - k1basal \cdot IR$$
$$\dot{IRp} = -k1b \cdot IRp + k1f \cdot IR \cdot insulin + k1basal \cdot IR$$
$$\dot{IRS} = k2b \cdot IRSp - k2f \cdot IRS \cdot IRp$$
$$\dot{IRSp} = -k2b \cdot IRSp + k2f \cdot IRS \cdot IRp$$
$$\dot{PKB} = k3b \cdot PKBp - k3f \cdot PKB \cdot IRSp$$
$$\dot{PKBp} = -k3b \cdot PKBp + k3f \cdot PKB \cdot IRSp$$
$$\dot{GLUT4} = k4b \cdot GLUT4pm - k4f \cdot GLUT4 \cdot PKBp$$
$$\dot{GLUT4pm} = -k4b \cdot GLUT4pm + k4f \cdot GLUT4 \cdot PKBp$$

The total amounts of the proteins are unknown and we thus use relative amounts to describe the initial conditions of the states. All model simulations are initiated by a steady-state simulation to assure that the system is at rest and to allow for different ratios of the proteins for different parameter values. The initial values are denoted

$$IR(0) = 10$$
$$IRp(0) = 0$$
$$IRS(0) = 10$$
$$IRSp(0) = 0$$
$$PKB(0) = 10$$
$$PKBp(0) = 0$$
$$GLUT4(0) = 10$$
$$GLUT4pm(0) = 0$$

The parameters of the model are

$$k1basal \;\; k1f \;\; k1b \;\; k2f \;\; k2b \;\; k3f \;\; k3b \;\; k4f \;\; k4b \;\; k_{glut1} \;\; k_{glut4} \;\; Km_{G1} \;\; Km_{G4}$$

To simulate the model to mimic the different diagrams in the dataset Z1 we use both the module constraints and the different experimental settings. The input constraints of the module – insulin and glucose – are functions of time

$$insulin = f_1(t)$$
$$glucose = f_2(t)$$

A simulation of the model with the input constraints as input signals must fit the output constraint, i.e. the glucose uptake

$$glucose\ uptake = k_{glut1} \cdot \frac{glucose}{Km_{G1} + glucose} + k_{glut4} \cdot \frac{glucose}{Km_{G4} + glucose} \cdot GLUT4pm$$

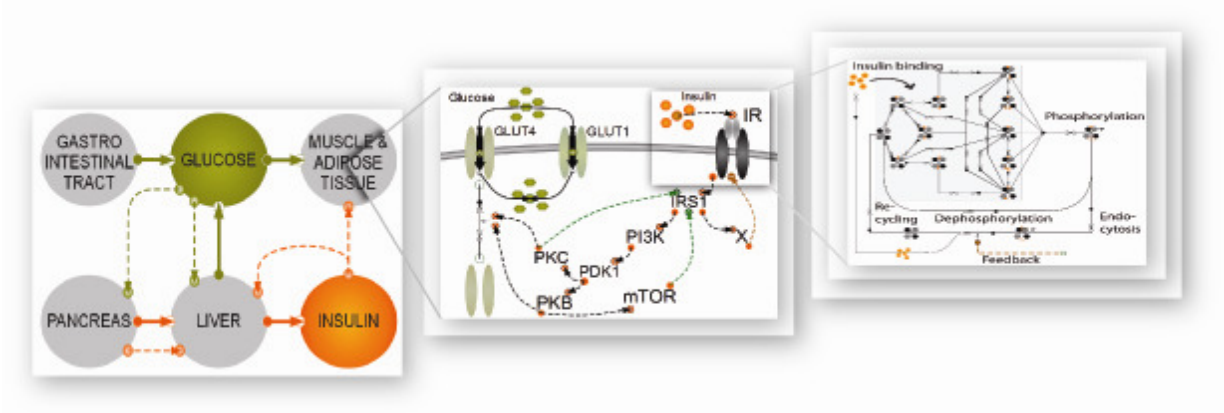
Insulin and glucose are also kept at values according to the performed experiments to simulate these and to compare with glucose uptake but also with IRp, IRSp and PKBp.

Recall that all chosen models only deal with the essential dynamics, and are no attempts to include all known reactions and components of the system.

All model equations are found in the supplemental file ModelFiles.zip and all simulations of the models are found in the supplemental file SimulationFiles.zip.

Supplemental Description of Model M^3

The final model M^3 consists of three levels: whole-body level, adipose tissue level, and insulin binding level. A schematic overview of the system is found below. Here we present the model equations for all these levels and show how we merge the levels into one multi-level model. The connections between the whole-body level and the other levels are in **red**, and connections between the adipose tissue level and the insulin binding level in **green**.



The whole-body level

The whole-body level is taken from (3) with one small modification. We sub-divided the insulin-responding glucose uptake module in two parts; muscle and adipose tissue, with static 80/20 proportions. We did not change the values of the parameters. A schematic overview of the whole-body level is given by the following figure.

<u>Glucose kinetics</u>

The glucose kinetics module describes the dynamic change in glucose concentration in the two compartments plasma and tissues. More motivations for these equations are given in (3). The same holds for all equations relating to the whole-body level.

```
d/dt(G_p) = EGP+Ra-E-U_ii-          G_p(0) = 178
            k_1*G_p+k_2*G_t
d/dt(G_t) = (-U_id)+k_1*G_p-         G_t(0) = 135
            k_2*G_t
```

```
G = G_p/V_G
```

G_p	glucose mass in plasma and rapidly equilibrating tissues
G_t	glucose mass in slowly equilibrating tissues
G	plasma glucose concentration

Insulin kinetics

The insulin kinetics module describes the dynamic changes in insulin concentration in the two compartments plasma and liver.

```
d/dt(I_l) = (-m_1*I_l)-                 I_l(0) = 4.5
            m_3*I_l+m_2*I_p+S
d/dt(I_p) = (-m_2*I_p)-                 I_p(0) = 1.25
            m_4*I_p+m_1*I_l

I = I_p/V_I
HE = (-m_5*S)+m_6
m_3 = HE*m_1/(1-HE)
```

I_p	insulin mass in plasma
I_l	insulin mass in liver
HE	hepatic extraction

Glucose Rate of Appearance (gastrointestinal tract)

In the gastrointestinal tract the glucose enter the system and travel through three compartments before it appears in the plasma.

```
d/dt(Q_sto1) = -k_gri*Q_sto1            Q_sto1(0) = 78000
d/dt(Q_sto2) = -k_empt*Q_sto2           Q_sto2(0) = 0
            +k_gri*Q_sto1
d/dt(Q_gut) = -k_abs*Q_gut              Q_gut(0) = 0
            +k_empt*Q_sto2

Q_sto = Q_sto1+Q_sto2
Ra = f*k_abs*Q_gut/BW
k_empt = k_min+(k_max-k_min)/2*(tanh(a*(Q_sto-b*D))-tanh(c*(Q_sto-
d*D))+2)
```

Q_sto1	first stomach compartment
Q_sto2	second stomach compartment
Q_gut	mass of glucose in the intestine
Q_sto	amount of glucose in the stomach
Ra	glucose rate of appearance

Endogenous Glucose Production (liver)

The glucose production in the liver is dependent on glucose in the plasma, a delayed insulin signal from the plasma and insulin in the portal vein.

```
d/dt(I_1) = -k_i*(I_1-I)                I_1(0) = 25
d/dt(I_d) = -k_i*(I_d-I_1)              I_d(0) = 25
```

```
EGP = k_p1-k_p2*G_p-k_p3*I_d-k_p4*I_po
```

I_1	helping state to describe a delayed insulin signal
I_d	helping state to describe a delayed insulin signal
EGP	endogenous glucose production

Glucose Uptake

The glucose uptake by the insulin sensitive tissues is a sum of glucose uptake in muscle and adipose tissue. Recall that we mark a connection between the whole-body level and the other levels with **red**.

```
U_id = U_idm+vglucoseuptake
```

U_id	insulin dependent glucose uptake

Glucose Uptake (muscle tissue)

Glucose is taken up in the muscle tissue and the uptake depends on the interstitial insulin and the glucose tissue concentrations.

```
d/dt(INS) = (-p_2U*INS)+p_2U*(I-I_b)        INS(0) = 0

U_idm = 0.8*(V_m0+V_mX*INS)*G_t/(K_m0+G_t)
```

INS	insulin in the interstitial fluid
U_idm	insulin dependent glucose uptake by the muscle tissue

Glucose Uptake (adipose tissue)

The glucose uptake by the adipose tissue (**vglucoseuptake**) is described below in the adipose tissue level, in the section Glucose uptake dynamics.

Insulin Secretion (beta cells)

Insulin is produced and secreted from the beta cells in the pancreas. The amount of insulin that is secreted is calculated from the glucose concentration in the plasma

```
d/dt(I_po) = (-gamma*I_po)+S_po          I_po(0) = 3.6
d/dt(Y) = -alpha*(Y-beta*(G-G_b))        Y(0) = 0

S = gamma*I_po
S_po = Y+K*(EGP+Ra-E-U_ii-k_1*G_p+k_2*G_t)/V_G+S_b
```

I_po	amount of insulin in the portal vein
Y	helping state to calculate the insulin secretion
S	insulin secretion to beta cells
S_po	insulin secretion to the portal vein

Glucose Renal Excretion

When the concentration of glucose in the blood is high glucose will be excreted to the kidneys. However, this will not happen for healthy individuals so we set the renal excretion to 0.

```
E = 0
```

E renal excretion

Parameters

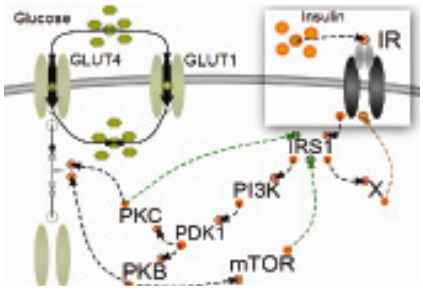
We use the parameters that have been determined and further described in (3).

V_G	1.88	dl/kg
k_1	0.065	/min
k_2	0.079	/min
V_I	0.05	l/kg
m_1	0.190	/min
m_2	0.484	/min
m_4	0.194	/min
m_5	0.0304	min·kg/pmol
m_6	0.6471	dimensionless
HE_b	0.6	dimensionless
k_max	0.0558	/min
k_min	0.0080	/min
k_abs	0.057	/min
k_gri	0.0558	/min
f	0.90	dimensionless
a	0.00013	/mg
b	0.82	dimensionless
c	0.00236	/mg

d	0.010	dimensionless
k_p1	2.70	mg/kg/min
k_p2	0.0021	/min
k_p3	0.009	mg/kg/min per pmol/l
k_p4	0.0618	mg/kg/min per pmol/kg
k_i	0.0079	/min
U_ii	1	mg/kg/min
V_m0	2.50	mg/kg/min
V_mX	0.047	mg/kg/min per pmol/l
K_m0	225.59	mg/kg
P_2U	0.0331	/min
K	2.30	pmol/kg per mg/dl
alpha	0.050	/min
beta	0.11	pmol/kg/min per mg/dl
gamma	0.5	/min
BW	78	kg
D	78000	mg

The adipose tissue level

The adipose tissue level is developed by us in this study. We have tested a number of hypotheses to find a minimal model (*Md3*), partly based on (2), that can explain all our experimental data and fit the module constraints from the whole-body level. This hypothesis we have then expanded to include interesting proteins within the adipocyte. The parameters of this level were optimized to gather all the acceptable parameter sets. A schematic overview of the adipose tissue level is the following figure.



IRS1 and X dynamics

The insulin receptor substrate is activated by phosphorylation from active insulin receptor states from the insulin binding level described below. Also, positive feedbacks from downstream proteins further activate `IRS1`. The unknown protein `X` is activated by `IRS1iP` and act as a negative feedback to the insulin receptor. This part of the adipose tissue level is adopted from and further described in (2), with the difference that we have now replaced the insulin receptor states with corresponding ones from the insulin binding level. Recall that we mark connections between the adipose tissue level and the insulin binding level with **green**.

```
d/dt(IRS1) = v2b-v2f                    IRS1(0) = 9.99982
d/dt(IRS1iP) = -v2b+v2f                 IRS1iP(0) = 0.00018
d/dt(X) = v3b-v3f                       X(0) = 9.92463
d/dt(X_P) = -v3b+v3f                    X_P(0) = 0.07537

v2f = k21*IRS1*((r1x2+r11x2+r1x22+r1x22d+r11x22+rPbasal)+k22*rendP)
           *(1+k23*PKC_P+k24*mTOR)
v2b = k2b*IRS1iP
v3f = k3f*X*IRS1iP
v3b = k3b*X_P
```

`IRS1`	insulin receptor substrate-1
`IRS1iP`	phosphorylated (active) form of IRS1
`X`	downstream intermediate which dephosphorylates IR in its active form
`X_P`	active form of X

PI3K and PDK1 dynamics

`PI3K` is activated by `IRS1` and subsequently `PDK1` is activated by `PI3K`. We assume that the activations follow simple mass-action kinetics.

```
d/dt(PI3K) = v4b-v4f                    PI3K(0) = 9.97578
d/dt(PI3K_) = -v4b+v4f                  PI3K_(0) = 0.02422
d/dt(PDK1) = v5b-v5f                    PDK1(0) = 8.65877
d/dt(PDK1_) = -v5b+v5f                  PDK1_(0) = 1.34123

v4f = k4f*PI3K*IRS1iP
v4b = k4b*PI3K_
v5f = k5f*PDK1*PI3K_
v5b = k5b*PDK1_
```

`PI3K`	phosphatidylinositol 3-kinases

PI3K_	active form of PI3K
PDK1	3-phosphoinositide dependent protein kinase-1
PDK1_	active form of PDK1

PKC and PKB dynamics

Both PKB and PKC are activated by PDK1 in its active form. We assume that the activations follow simple mass-action kinetics.

```
d/dt(PKC) = v6b-v6f                    PKC(0) = 3.60284e-05
d/dt(PKC_P) = -v6b+v6f                 PKC_P(0) = 9.99996
d/dt(PKB) = v7b-v7f                    PKB(0) = 9.90193
d/dt(PKB_P) = -v7b+v7f                 PKB_P(0) = 0.09807

v6f = k6f*PKC*PDK1_
v6b = k6b*PKC_P
v7f = k7f*PKB*PDK1_
v7b = k7b*PKB_P
```

PKC	protein kinase C
PKC_P	phosphorylated (active) form of PKC
PKB	protein kinase B
PKB_P	phosphorylated (active) form of PKB

mTOR and GLUT4 dynamics

mTOR is activated by PKB in its active form. The glucose transporters (GLUT4) are moving from the cytosol to the plasma membrane both at a basal level and when activated by PKB and PKC. We assume that the activations follow simple mass-action kinetics.

```
d/dt(mTOR) = v8b-v8f                   mTOR(0) = 0.02019
d/dt(mTOR_) = -v8b+v8f                 mTOR_(0) = 9.97981
d/dt(GLUT4_C) = v9b-v9f                GLUT4_C(0) = 9.99317
d/dt(GLUT4_M) = -v9b+v9f               GLUT4_M(0) = 0.00683

v8f = k8f*mTOR*PKB_P
v8b = k8b*mTOR_
v9f = k91*GLUT4_C*PKC_P+k92*GLUT4_C*PKB_P+k5BasicWb*GLUT4_C
v9b = k9b*GLUT4_M
```

mTOR	mammalian target of rapamycin
mTOR_	active form of mTOR
GLUT4_C	glucose transporter 4 in vesicles in the cytosol
GLUT4_M	glucose transporter 4 in the plasma membrane ready to take up glucose

Glucose uptake dynamics

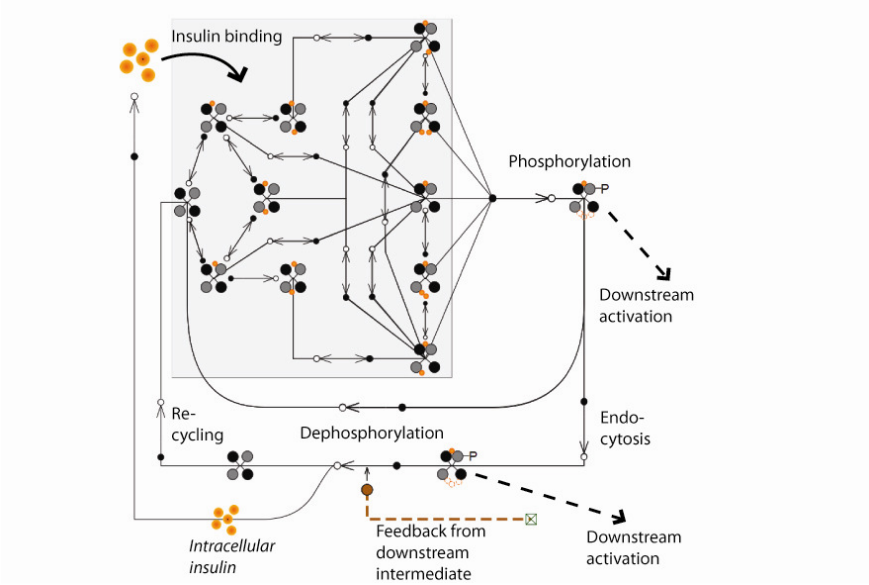
The glucose uptake in the adipose tissue comes in this model from three terms; glucose transporter 1 (non-insulin dependent), glucose transporter 4 (insulin-dependent through the insulin signaling cascade and thus through GLUT4), and blood flow (directly insulin-dependent). We assume that the glucose uptake also depends on the interstitial glucose concentration (**G_t**, from the whole-body level) and that the dependency is saturated.

vglucoseuptake =
k_glut1*G_t/(KmG1+G_t)+k_glut4*GLUT4_M*G_t/(KmG4+G_t)+kbf*(INS+5)

Parameters
The parameters of the adipose tissue level were optimized to find the acceptable solutions. The following parameters are part of this level.

k21	k22	k23	k24	k2b	k3f	k3b	k4f	k4b
k5f	k5b	k6f	k6b	k7f	k7b	k8f	k8b	k91
k92	k9b	k5Basic	k5BasicWb	k_glut4	k_glut1	KmG1	KmG4	kbf

The insulin binding level
The insulin binding level is taken from (4). We took the model structure and merged with our adipose tissue module. The parameters in (4) were fitted to data from other cell types so we used optimization to gather the acceptable parameter sets. A schematic overview of the insulin binding level is found below.



The inactive receptor states
The following insulin receptor states can bind one or two insulin molecules, or be unbound. The states that bind at least one insulin molecule can be activated.

```
d/dt(r0) = -R1-R2+R5+R8+R37-          r0(0) = 9.96820
           R46+R47
d/dt(r1) = +R1-R3-R5-R6-              r1(0) = 0.02214
           R9+R12+R15+R19
d/dt(r2) = +R2-R4-R7-R8-              r2(0) = 0.00935
           R10+R13+R16+R22
d/dt(r11) = +R3-R12-R17+R26           r11(0) = 1.22887e-005
d/dt(r12) = +R4+R6-R13-R15-R18-       r12(0) = 1.03764e-05
           R20+R27+R28
d/dt(r22) = +R7-R16-R21+R29           r22(0) = 2.18683e-06
```

r0	inactive receptor state with no insulin bound
r1	inactive receptor state with 1 insulin molecule bound to site 1
r2	inactive receptor state with 1 insulin molecule bound to site 2
r11	inactive receptor state with 2 insulin molecules bound to site 1
r12	inactive receptor state with 2 insulin molecules bound to site 1 and 2 respectively
r22	inactive receptor state with 2 insulin molecules bound to site 2

The active receptor states

When insulin is bound to the receptor it can be activated and also phosphorylated. The active states activate IRS1 at the adipose tissue level (above).

```
d/dt(r1x2) = +R9+R10-R11-R14-          r1x2(0) = 1.36476e-06
           R19-R22-
           R23+R24+R25+R34-R39
d/dt(r11x2) = +R11+R17+R20-R24-        r11x2(0) = 1.51514e-09
           R26-R28-R31+R36-R40
d/dt(r1x22) = +R14+R18+R21-R25-        r1x22(0) = 6.39352e-010
           R27-R29-R30-
           R32+R33+R35-R41
d/dt(r1x22d) = +R23+R32-R33-R34-       r1x22d(0) = 5.59231e-020
           R42
d/dt(r11x22) = +R30+R31-R35-R36-       r11x22(0) = 1.78726e-014
           R43
```

r1x2	active receptor state with 2 insulin molecules bound to site 1 and 2 respectively
r11x2	active receptor state with 3 insulin molecules bound, 2 to site 1 and 1 to site 2
r1x22	active receptor state with 3 insulin molecules bound, 1 to site 1 and 2 to site 2
r1x22d	active receptor state with 1 insulin molecules bound to site 1 and an insulin dimer to site 2
r11x22	active receptor state with 4 insulin molecules bound, 2 to site 1 and 2 to site 2

The internalization process

We included internalization in the insulin binding model to be able to relate the insulin binding level with the adipose tissue level. This part is based the *Mifa* model in (2).

```
d/dt(rend) = -R37+R44                  rend(0) = 3.31712e-05
d/dt(rendP) = -R44+R39+R40+R41         rendP(0) = 0.0002125
           +R42+R43+R48
d/dt(iendIR) = +R39+2*R40+2*R41        iendIR(0) = 7.25519e-06
           +3*R42+3*R43-R45
d/dt(iend) = -R38+R45                  iend(0) = 1.13228e-06
d/dt(rPbasal) = R46-R47-R48            rPbasal(0) = 3.87230e-05
```

rend	internalized receptor states
rendP	internalized and phosphorylated receptor states
iendIR	receptor bound internalized insulin molecules
iend	internalized insulin molecules
rPbasal	state that account for the basal phosphorylation of receptor states

Reactions

Here all reactions of the insulin binding level are gathered. Most of the reactions follow simple mass action kinetics, but R44 and R45 that belong to our addition of internalization are saturated. These reactions describe the action of a feedback from a downstream signaling intermediate (X_P) and these equations are based on (2). All other reactions are from Kiselyov *et al.* (4).

```
R1 = 2*a1*S1*r0
R2 = 2*a2*S1*r0
R3 = a1*S1*r1
R4 = a1*S1*r2
R5 = d1*r1
R6 = a2*S1*r1
R7 = a2*S1*r2
R8 = d2*r2
R9 = Kcr*r1
R10 = Kcr*r2
R11 = a1*S1*r1x2
R12 = 2*d1*r11
R13 = d1*r12
R14 = a2*S1*r1x2
R15 = d2*r12
R16 = 2*d2*r22
R17 = 2*Kcr*r11
R18 = Kcr*r12
R19 = d2*r1x2
R20 = Kcr*r12
R21 = 2*Kcr*r22
R22 = d1*r1x2
R23 = a2*S2*r1x2
R24 = d1*r11x2
R25 = d2*r1x22
R26 = d2*r11x2
R27 = d2*r1x22
R28 = d1*r11x2
R29 = d1*r1x22
R30 = a1*S1*r1x22
R31 = a2*S1*r11x2
R32 = K4*S1*r1x22
R33 = K8*r1x22d
R34 = d2*r1x22d
R35 = d1*r11x22
R36 = d2*r11x22
R37 = Kex*rend
R38 = Kex*iend
R39 = (Kend)*r1x2
R40 = (Kend)*r11x2
R41 = (Kend)*r1x22
R42 = (Kend)*r1x22d
R43 = (Kend)*r11x22
R44 = (Kdp+Kcat*(X_P)/
            (Km+(X_P)))*rendP
R45 = (Kdp+Kcat*(X_P)/
            (Km+(X_P)))*iendIR
R46 = kfbasal*r0
R47 = krbasal*rPbasal
R48 = Kend*rPbasal
```

Variables

The variables S1 and S2 describe the interstitial concentration of insulin as a monomer (S1) and as a dimer (S2) in molars. The dimer will not form in the low insulin concentrations in the physiological situation.

```
S1 = (INS+5)*1e-12
S2 = 0
```

Parameters

For two of the parameters, K4 and K8, we used the values from (4), and for the others we used optimization to find the acceptable values.

```
K4 = 1400
K8 = 0.01
```

a1	a2	d1	d2	Kcr	Kex
Kend	Kdp	Kcat	Km	kfbasal	krbasal

References

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