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

Ma1          Ma2          Ma3          Ma4
IR  ins  IR  ins  IR  ins  IR  ins
IR-P  IRS1  IR-P  IRS1  IR-P  IRS1  IR-P  IRS1
PKB  PKB-P  PKB  PKB-P  PKB  PKB-P  PKB  PKB-P
GLUT4 GLUT4 GLUT4 GLUT4 GLUT4 GLUT4 GLUT4 GLUT4
GLUT1 glucose uptake glucose uptake glucose uptake glucose uptake

Ma5          Ma6
IR  ins  IR  ins  IR  ins  IR  ins
IR-P  IRS1  IR-P  IRS1  IR-P  IRS1  IR-P  IRS1
PKB  PKB-P  PKB  PKB-P  PKB  PKB-P  PKB  PKB-P
GLUT4 GLUT4 GLUT4 GLUT4 GLUT4 GLUT4 GLUT4 GLUT4
GLUT1 glucose uptake glucose uptake glucose uptake glucose uptake

Ma7

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. Ma7 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 Ma6.
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

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**Basal GLUT4 translocation hypothesis**

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**Blood-flow hypothesis**

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**Multiple in vivo/vitro-differences**

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Supplemental Methods

Principles of constructing and simulating a model using module constraints

Consider model structure $M_{al}$ 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 assumptions, the set of differential equations become

\[
\begin{align*}
IR &= k_{1b} \cdot IRp - k_{1f} \cdot IR \cdot insulin - k_{1basal} \cdot IR \\
IRp &= -k_{1b} \cdot IRp + k_{1f} \cdot IR \cdot insulin + k_{1basal} \cdot IR \\
IRS &= k_{2b} \cdot IRSp - k_{2f} \cdot IRS \cdot IRp \\
IRS &= -k_{2b} \cdot IRSp + k_{2f} \cdot IRS \cdot IRp \\
PKB &= k_{3b} \cdot PKBp - k_{3f} \cdot PKB \cdot IRSp \\
PKBp &= -k_{3b} \cdot PKBp + k_{3f} \cdot PKB \cdot IRSp \\
GLUT4 &= k_{4b} \cdot GLUT4pm - k_{4f} \cdot GLUT4 \cdot PKB \\
GLUT4pm &= -k_{4b} \cdot GLUT4pm + k_{4f} \cdot GLUT4 \cdot PKBp
\end{align*}
\]

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

\[
\begin{align*}
IR(0) &= 10 \\
IRp(0) &= 0 \\
IRS(0) &= 10 \\
IRS(0) &= 0 \\
PKB(0) &= 10 \\
PKBp(0) &= 0 \\
GLUT4(0) &= 10 \\
GLUT4pm(0) &= 0
\end{align*}
\]

The parameters of the model are

\[k_{1basal} \ k_{1f} \ k_{1b} \ k_{2f} \ k_{2b} \ k_{3f} \ k_{3b} \ k_{4f} \ k_{4b} \ k_{glut1} \ k_{glut4} \ Km_{G1} \ Km_{G4}\]
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

\[ \text{insulin} = f_1(t) \]
\[ \text{glucose} = f_2(t) \]

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

\[ \text{glucose uptake} = k_{glu1} \cdot \frac{\text{glucose}}{K_{m1} + \text{glucose}} + k_{glu4} \cdot \frac{\text{glucose}}{K_{m4} + \text{glucose}} \cdot \text{GLUT4pm} \]

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.

**Glucose kinetics**

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.

\[
\frac{d}{dt}(G_p) = EG_P + Ra - E_{iii} - k_1 G_p + k_2 G_t \\
G_p(0) = 178
\]

\[
\frac{d}{dt}(G_t) = (-U_{id}) + k_1 G_p - k_2 G_t \\
G_t(0) = 135
\]
\[ G = \frac{G_p}{V_G} \]

- \( G_p \) 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.

\[
\frac{d}{dt}(I_l) = (-m_1*I_l) - \frac{m_3*I_l+m_2*I_p+S}{m_4*I_p+m_l*I_l} \\
\frac{d}{dt}(I_p) = (-m_2*I_p) - \frac{m_4*I_p+m_l*I_l}{m_4*I_p+m_l*I_l}
\]

\[ I = \frac{I_p}{V_I} \]

- \( I_l \) insulin mass in liver
- \( I_p \) insulin mass in plasma
- \( HE \) hepatic extraction
- \( m_3 = HE \cdot m_1 / (1 - HE) \)

**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.

\[
\frac{d}{dt}(Q_{sto1}) = -k_{gri}Q_{sto1} \\
\frac{d}{dt}(Q_{sto2}) = -k_{empt}Q_{sto2} + k_{gri}Q_{sto1} \\
\frac{d}{dt}(Q_{gut}) = -k_{abs}Q_{gut} + k_{empt}Q_{sto2}
\]

\[ Q_{sto} = Q_{sto1} + Q_{sto2} \]

\[ Ra = f \cdot k_{abs} \cdot Q_{gut} / BW \]

\[ k_{empt} = k_{min} + (k_{max} - k_{min}) / 2 \cdot \left( \text{tanh}(a \cdot (Q_{sto} - b \cdot D)) - \text{tanh}(c \cdot (Q_{sto} - d \cdot D)) + 2 \right) \]

- \( Q_{sto1} \) 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.

\[
\frac{d}{dt}(I_1) = -k_i \cdot (I_1 - I) \\
\frac{d}{dt}(I_d) = -k_i \cdot (I_d - I_1)
\]

- \( I_1(0) = 25 \)
- \( I_d(0) = 25 \)
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.

\[
U_{id} = U_{idm} \cdot v_{glucoseuptake}
\]

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} \cdot INS) + p_{2U} \cdot (I - I_b)

U_{idm} = 0.8 \cdot (V_{m0} + V_{mX} \cdot INS) \cdot 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 \cdot I_po) + S_po

S = gamma \cdot I_po
S_po = Y + K \cdot (EGP + Ra - E_{ii} - k_1 \cdot G_p + k_2 \cdot 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.

\[E = 0\]
renal excretion

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

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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 acts 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.

\[
\begin{align*}
\frac{d}{dt}(\text{IRS1}) &= v_2b - v_2f \\
\frac{d}{dt}(\text{IRS1iP}) &= -v_2b + v_2f \\
\frac{d}{dt}(X) &= v_3b - v_3f \\
\frac{d}{dt}(X_P) &= -v_3b + v_3f \\
\end{align*}
\]

\[
\begin{align*}
v_2f &= k_{21}^*\text{IRS1}^*((r_1x^2+r_11x^2+r_1x^2+d+r_11x^2d+r_Pbasal)+k_{22}^*r_{endP}) \\
&\quad \times (1+k_{23}^*PKC_P+k_{24}^*mTOR) \\
v_2b &= k_{2b}^*\text{IRS1iP} \\
v_3f &= k_{3f}^*X\cdot\text{IRS1iP} \\
v_3b &= k_{3b}^*X_P \\
\end{align*}
\]

IGS1 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.

\[
\begin{align*}
\frac{d}{dt}(\text{PI3K}) &= v_4b - v_4f \\
\frac{d}{dt}(\text{PI3K}_-) &= -v_4b + v_4f \\
\frac{d}{dt}(\text{PDK1}) &= v_5b - v_5f \\
\frac{d}{dt}(\text{PDK1}_-) &= -v_5b + v_5f \\
\end{align*}
\]

\[
\begin{align*}
v_4f &= k_{4f}^*\text{PI3K}\cdot\text{IRS1iP} \\
v_4b &= k_{4b}^*\text{PI3K}_- \\
v_5f &= k_{5f}^*\text{PDK1}\cdot\text{PI3K}_- \\
v_5b &= k_{5b}^*\text{PDK1}_- \\
\end{align*}
\]

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.

\[
\begin{align*}
\frac{d}{dt}(PKC) &= v_6b - v_6f \\
\frac{d}{dt}(PKC_P) &= -v_6b + v_6f \\
\frac{d}{dt}(PKB) &= v_7b - v_7f \\
\frac{d}{dt}(PKB_P) &= -v_7b + v_7f
\end{align*}
\]

\[
\begin{align*}
v_6f &= k_6f*PKC*PDK1_\text{P} \\
v_6b &= k_6b*PKC_P \\
v_7f &= k_7f*PKB*PDK1_\text{P} \\
v_7b &= k_7b*PKB_P
\end{align*}
\]

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.

\[
\begin{align*}
\frac{d}{dt}(mTOR) &= v_8b - v_8f \\
\frac{d}{dt}(mTOR_) &= -v_8b + v_8f \\
\frac{d}{dt}(GLUT4_C) &= v_9b - v_9f \\
\frac{d}{dt}(GLUT4_M) &= -v_9b + v_9f
\end{align*}
\]

\[
\begin{align*}
v_8f &= k_8f*mTOR*PKB_P \\
v_8b &= k_8b*mTOR_\text{P} \\
v_9f &= k_91*GLUT4_C*PKC_P+k_92*GLUT4_C*PKB_P+k_5BasicWb*GLUT4_C \\
v_9b &= k_9b*GLUT4_M
\end{align*}
\]

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.
\[ \text{vglucoseuptake} = k_{\text{glut1}} G_t/(KmG1+G_t) + k_{\text{glut4}} \times \text{GLUT4}_M/(KmG4+G_t) + k_{bf} \times (\text{INS}+5) \]

**Parameters**

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>k21</td>
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<td></td>
</tr>
<tr>
<td>k6f</td>
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<tr>
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<tr>
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<tr>
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<td>k_{glut1}</td>
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<td>KmG1</td>
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<tr>
<td>KmG4</td>
<td></td>
</tr>
<tr>
<td>k_{bf}</td>
<td></td>
</tr>
</tbody>
</table>

**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.

\[
\begin{align*}
\frac{d}{dt}(r0) &= -R1-R2+R5+R8+R37-R46+R47 & r0(0) &= 9.96820 \\
\frac{d}{dt}(r1) &= +R1-R3-R5-R6-R9+R12+R15+R19 & r1(0) &= 0.02214 \\
\frac{d}{dt}(r2) &= +R2-R4-R7-R8-R10+R13+R16+R22 & r2(0) &= 0.00935 \\
\frac{d}{dt}(r11) &= +R3-R12-R17+R26 & r11(0) &= 1.22887e-005 \\
\frac{d}{dt}(r12) &= +R4+R6-R13-R15+R18-R20+R27+R28 & r12(0) &= 1.03764e-05 \\
\frac{d}{dt}(r22) &= +R7-R16-R21+R29 & r22(0) &= 2.18683e-06
\end{align*}
\]
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).

\[
\begin{align*}
d/dt(r1x2) &= +R9+R10-R11-R14- \quad r1x2(0) = 1.36476e-06 \\
&\quad R19-R22- \\
&\quad R23+R24+R25+R34-R39 \\
d/dt(r11x2) &= +R11+R17+R20-R24- \quad r11x2(0) = 1.51514e-09 \\
&\quad R26-R28-R31+R36-R40 \\
d/dt(r1x22) &= +R14+R18+R21-R25- \quad r1x22(0) = 6.39352e-10 \\
&\quad R27-R29-R30- \\
&\quad R32+R33+R35-R41 \\
d/dt(r1x22d) &= +R23+R32-R33-R34- \quad r1x22d(0) = 5.59231e-20 \\
&\quad R42 \\
d/dt(r11x22) &= +R30+R31-R35-R36- \quad r11x22(0) = 1.78726e-14 \\
&\quad R43
\end{align*}
\]

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).

\[
\begin{align*}
d/dt(rend) &= -R37+R44 \quad rend(0) = 3.31712e-05 \\
d/dt(rendP) &= -R44+R39+R40+R41+R42+R43+R48 \quad rendP(0) = 0.0002125 \\
&\quad +R42+R43+R48 \\
d/dt(iendIR) &= +R39+2*R40+2*R41+3*R42+3*R43+R45 \quad iendIR(0) = 7.25519e-06 \\
&\quad +3*R42+3*R43+R45 \\
&\quad +3*R42+3*R43+R45 \\
d/dt(iend) &= -R38+R45 \quad iend(0) = 1.13228e-06 \\
d/dt(rPbasal) &= R46-R47-R48 \quad rPbasal(0) = 3.87230e-05
\end{align*}
\]

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).

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

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.

\[
S1 = (\text{INS} + 5) \times 10^{-12} \\
S2 = 0
\]

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.

\[
K4 = 1400 \\
K8 = 0.01
\]

<table>
<thead>
<tr>
<th>(a1)</th>
<th>(a2)</th>
<th>(d1)</th>
<th>(d2)</th>
<th>(Kcr)</th>
<th>(Kex)</th>
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<td>(Kdp)</td>
<td>(Kcat)</td>
<td>(Km)</td>
<td>(kfbasal)</td>
<td>(krbasal)</td>
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References