**Table of inputs**

|  |  |  |
| --- | --- | --- |
| **Constant** | **Meaning** | **Unit** |
| I | Insulin input | Molecules |
| Amino\_Acids | Amino acid input | Molecules |

**Table of constants**

|  |  |  |  |
| --- | --- | --- | --- |
| **Constant** | **Meaning** | **Value** | **Unit** |
| NA | Avogadro constant | 6.02E+23 | molecules |
| Vo | Volume outside the cell | 1.00E-10 | L |
| V | Volume inside the cell | 3.00E-12 | L |
| u | number of molecules/cell per nM concentration | NA\*V\*1e-9 | molecules |

**Table of Initial Concentrations**

The initial concentration of not reported species are assumed to be equal to 0

|  |  |  |
| --- | --- | --- |
| **Molecule** | **# molecules/cell** | **Ref.** |
| AKT\_unphos | 180600 | 1 |
| PI3K | 361200 | 1 |
| IRS1\_unphos | 541800 | 1 |
| IR\_free\_memb\_init | 270900 | 1 |
| IR\_free\_cyt\_init | 30100 | 1 |
| GRB2/SOS\_active | 361200 | 1 |
| RasGAP | 90300 | 1 |
| SHP2 | 541800 | 1 |
| SRC\_inactive | 935508 | 1 |
| RasGDP | 270900 | 1 |
| RAF\_inactive | 180600 | 1 |
| MEK\_unphos | 361200 | 1 |
| ERK\_unphos | 722400 | 1 |
| AKT\_unphos | 180600 | 1 |
| AMPK\_unphos | 586920 | 2 |
| mTORC1­\_unphos | 719538 | 2 |
| mTORC2\_unphos | 537961 | 2 |
| p70S6K\_unphos | 409311 | 2 |
| TSC1\_TSC2\_pT1462 | 426957 | 2 |
| PI3K\_variant­\_unphos | 541929 | 2 |
| PI(4,5)P2 | 538549 | 3 |
| PI(3,4,5)P3 | 1680 | 3 |
| PI(3,4)P2 | 1571 | 3 |
| PKC\_unphos | 180600 | 3 |
| GLUT4\_memb | 21672 | 3 |
| GLUT4\_cyt | 520128 | 3 |

Ref: 1Borisov et al.(2009); 2Sonntag et al. (2012); 3Sonntag et al. (2002)

**Table of rules and functions (BioNetGen syntax)**

|  |  |  |
| --- | --- | --- |
| **Reaction Rule** | **Function** | **Ref.** |
| # Receptor binding 1st insulin molecule  IR(alpha,beta,Y999~u,NPXY,loc~m) + I(bs) <-> IR(alpha!1,beta,Y999~u,NPXY,loc~m).I(bs!1) k1,k\_1 |  | 3 |
| # Receptor phosphorylation  IR(alpha!1,beta,Y999~u,NPXY,loc~m).I(bs!1) -> IR(alpha!1,beta,Y999~p,NPXY,loc~m).I(bs!1) k3 |  | 3 |
| # Receptor binding 2nd insulin molecule  IR(alpha!1,beta,Y999~p,NPXY,loc~m).I(bs!1) + I(bs) <-> IR(alpha!1,beta!2,Y999~p,NPXY,loc~m).I(bs!1).I(bs!2) k2,k\_2 |  | 3 |
| # Receptor unbinding and dephosphorylation (on the cell membrane)  IR(alpha!1,beta,Y999~p,NPXY,loc~m).I(bs!1) -> IR(alpha,beta,Y999~u,NPXY,loc~m) + I(bs) f\_3() | f3()=(k\_3)\*PTP\*(1-Vmax/2\*(Akt\_pT)^n/(Kd\_akt+(Akt\_pT)^n)) | 3 |
| # Free receptor internalization/externalization  IR(alpha,beta,Y999~u,NPXY,loc~m) <-> IR(alpha,beta,Y999~u,NPXY,loc~c) k4, k\_4 |  | 3 |
| # Phosphorylated receptor internalization/externalization  IR(alpha!+,Y999~p,NPXY,loc~m) <-> IR(alpha!+,Y999~p,NPXY,loc~c) k4p, k\_4p |  | 3 |
| # Receptor synthesis  SynthIR() -> SynthIR() + IR(alpha,beta,Y999~u,NPXY,loc~c) k5 |  | 3 |
| # Receptor degradation  IR(alpha,beta,Y999~u,NPXY,loc~c) -> Degr() k\_5 |  | 3 |
| # Receptor unbinding and dephosphorylation (inside the cell)  IR(alpha!+,Y999~p,NPXY,loc~c) -> IR(alpha,beta,Y999~u,NPXY,loc~c) f6() | f6()=(k6)\*PTP\*(1-Vmax/2\*(Akt\_pT)^n/(Kd\_akt+(Akt\_pT)^n)) | 3 |
| # IRS-1 phosphorylation/dephosphorylation in Tyr  IRS1(YXXM,Y896,Y~u,S636~u) <-> IRS1(YXXM,Y896,Y~p,S636~u) f7(),f\_7() | f7()=k7\*IR\_phos\_memb/IR\_free\_memb  (k\_7)\*PTP\*  (1-Vmax/2\*(Akt\_pT)^n/(Kd\_akt+(Akt\_pT)^n)) | 3 |
| # IRS-1 phosphorylation/dephosphorylation in Ser  IRS1(YXXM,Y896,Y~u,S636~u) <-> IRS1(YXXM,Y896,Y~u,S636~p) f7p(), k\_7p | f7p()=k7p\*Vmax\*(PKC\_pT410)^n/  (Kd\_pkc+(PKC\_pT410)^n) | 3 |
| # IRS-1\_PI3-K complex formation (PI3-K activation)  IRS1(YXXM,Y896,Y~p,S636~u) + PI3K(SH2) <-> IRS1(YXXM!1,Y896,Y~p,S636~u).PI3K(SH2!1) k8,k\_8 |  | 3 |
| # lipids formation  PI45() <-> PI345() f9(),k\_9\*PTEN  PI34() <-> PI345() k10,k\_10\*SHIP | f9()=k9a\*IRS1\_PI3K\_complex+k9b | 3 |
| # Akt phosphorylation/dephosphorylation in Tyr  Akt(T309~u) <-> Akt(T309~p) f11(),k\_11 | f11()=k11\*(PI345-PI345)/(PI345\*10-PI345) | 3 |
| # PKC phosphorylation /dephosphorylation  PKC(T410~u) <-> PKC(T410~p) f12(), k\_12 | f12()=k12\*(PI345-PI345)/(PI345\*10-PI345) | 3 |
| # GLUT4 translocation  GLUT4(loc~c) <-> GLUT4(loc~m) f13(), k\_13 | f13()=k13+k13p\*((0.2\*(Akt\_pT309+Akt\_pS474+Akt\_pp)/Akt)+(0.8\*PKC\_pT410/PKC)) | 3 |
| # GLUT4 synthesis  SynthG4() -> SynthG4() + GLUT4(loc~c) k14 |  | 3 |
| # GLUT4 degradation  GLUT4(loc~c) -> Degr() k\_14 |  | 3 |
| # PI3K\_variant phosphorylation/dephosphorylation by IRp  PI3K\_variant(Y~u) <-> PI3K\_variant(Y~p) fp15(),p\_15 | fp15()=p15\*IR\_phos\_memb | 2 |
| # IRS1 phosphorylation by P70S6K  IRS1(YXXM,Y896,Y~u,S636~u) + p70S6K(T389~p) -> IRS1(YXXM,Y896,Y~u,S636~p) + p70S6K(T389~p) f15() | f15()=k15\*(Vmax)\*(p70S6K\_pT389)^n\_p70/(Kd\_p70+(p70S6K\_pT389)^n\_p70) | 2 |
| # AMPK\_T172\_phosphorylation/dephosphorylation mediated by IRS1\_pY  AMPK(T172~u) <-> AMPK(T172~p) f16(),k\_16 | f16()=k16\*IRS1\_pY | 2 |
| # Akt phosphorylation/dephosphorylation in Ser mediated by mTORC2\_pS2481  Akt(S474~u) <-> Akt(S474~p) f17(),k\_17 | f17()=k17\*mTORC2\_pS2481 | 2 |
| # TSC1-TSC2 S1387\_phosphorylation\_by\_AMPK\_pT172 and T1462\_phosphorylation\_by\_Akt\_pT308  TSC1\_TSC2(T1462~p,S1387~u) <-> TSC1\_TSC2(T1462~u,S1387~p) f21(),f\_21() | f\_21()=k\_21\*Akt\_pT  f21()=k21\*AMPK\_pT172 | 2 |
| # mTORC1 phosphorylation/dephosphorylation mediated by TSC1\_TSC2\_pS1387 and Aminoacids  mTORC1(S2448~p) <-> mTORC1(S2448~u) f\_18(),f18() | f\_18()=k\_18\*TSC1\_TSC2\_pS1387  f18()=k18\*Aminoacids | 2 |
| # mTORC2 phosphorylation/dephosphorylation mediated by phosphorylated PI3K\_variant  mTORC2(S2481~u) <-> mTORC2(S2481~p) f19(),k\_19 | f19()=k19\*PI3K\_variant\_p | 2 |
| # p70S6K phosphorylation/dephosphorylation mediated by mTORC1\_pS2448  p70S6K(T389~u) <-> p70S6K(T389~p) f20(),k\_20 | f20()=k20\*mTORC1\_pS2448 | 2 |
| # RasGAP module  IR(Y999~p,NPXY,loc~m) + RasGAP(bs) <-> IR(Y999~p,NPXY!1,loc~m).RasGAP(bs!1) k22,k\_22 |  | 1 |
| # Src module  Src(state~i) <-> Src(state~a) f24(), f25() | f24()=(0.1/10)\*kcat24\*(alpha24\*IR\_phos\_memb)/(Km24+iSrc)  f25()=V25/(Km25+aSrc) | 1 |
| # IRS1-GS complex formation |  | 1 |
| IRS1(Y896,Y~p,S636~u) + GS(SH2,state~a) <-> IRS1(Y896!1,Y~p,S636~u).GS(SH2!1,state~a) k26,k\_26 |  | 1 |
| # IRS1-SHP2 complex formation  IRS1(Y896,Y~p,S636~u) + SHP2(SH2) <-> IRS1(Y896!1,Y~p,S636~u).SHP2(SH2!1) k27,k\_27 |  | 1 |
| # Ras module  Ras(state~GDP) <-> Ras(state~GTP) f28(), f29() | f28()=kcat28\*(IRS1\_GS\_complex)/(Km28+RasGDP)  f29()=kcat29\*(bRasGAP+IR\_RasGAP\_complex)/(Km29+RasGTP) | 1 |
| # Raf module  Raf(state~i) -> Raf(state~a) f30()  Raf(state~a) -> Raf(state~aa) f31()  Raf(state~aa) -> Raf(state~i) f32() | f30()=kcat30\*RasGTP/(Km30+Raf)  f31()=kcat31\*aSrc/(Km31+aRaf)  f32()=kcat32\*PKA/(Km32+aaRaf)+alpha32\*(Akt\_pT309+beta32\*Akt\_pp) | 1 |
| # Mek module  Mek(S218\_S222~u) <-> Mek(S218\_S222~p) f33(), f34() | f33()=kcat33\*aaRaf/(Km33+Mek)  f34()=V34/(Km34+Mek\_pS218\_S222) | 1 |
| # ERK module  Erk(T202\_T185~u,Y204\_Y187~u) <-> Erk(T202\_T185~p,Y204\_Y187~u) f35(), f38()  Erk(T202\_T185~p,Y204\_Y187~u) <-> Erk(T202\_T185~p,Y204\_Y187~p) f36(), f37() | f35()=kcat35\*Mek\_pS218\_S222/(Km35+Erk+Erk\_pT202\_T185\*Km35/Km36)  f36()=kcat36\*Mek\_pS218\_S222/(Km36+Erk\_pT202\_T185+Erk\*Km36/Km35)  f37()=V37/(Km37+Erk\_ppY204\_Y187+Erk\_pT202\_T185\*Km37/Km38)  f38()=V38/(Km38+Erk\_pT202\_T185+Erk\_ppY204\_Y187\*Km38/Km37) | 1 |
| # GS inhibition  GS(SH2,state~a) <-> GS(SH2,state~i) f39(),f\_39() | f39()=kcat39\*Erk\_ppY204\_Y187/(Km39+GS)  f\_39()=k\_39 | 1 |
| # IRS1-GS and IRS1-SHP2 complex disruption and IRS1 dephosphorylation  IRS1(YXXM,Y896!1,Y~p,S636~u).GS(SH2!1,state~a) -> IRS1(YXXM,Y896,Y~u,S636~u) + GS(SH2,state~a) f40()  IRS1(YXXM,Y896!1,Y~p,S636~u).SHP2(SH2!1) -> IRS1(YXXM,Y896,Y~u,S636~u) + SHP2(SH2) k41 | f40()=V40/(Km40+IRS1\_GS\_complex) | 1 |
| # SHP2 activity against RasGAP  IR(Y999~p,NPXY!1,loc~m).RasGAP(bs!1) -> IR(Y999~p,NPXY,loc~m) + RasGAP(bs) f42() | f42()=k42\*IRS1\_SHP2\_complex | 1 |

Ref: 1Borisov et al.(2009); 2Sonntag et al. (2012); 3Sonntag et al. (2002)

**Table of Parameters (Rate Constants)**

|  |  |  |
| --- | --- | --- |
| **Parameter** | **Value** | **Unit** |
| k1 | (6e7/(NA\*Vo)) | 1/(molecules\*min) |
| k\_1 | 0.2 | 1/min |
| k2 | (6e7/(NA\*Vo)) | 1/(molecules\*min) |
| k\_2 | 20 | 1/min |
| k3 | 2500 | 1/min |
| k\_3 | 0.2 | 1/min |
| PTP | 1 | - |
| PTEN | 1 | - |
| SHIP | 1 | - |
| n | 4 | - |
| n\_p70 | 2 | - |
| Kd\_akt | 2.955e12 | molecules^n |
| Kd\_pkc | 2.955e12 | molecules^n |
| Kd\_p70 | 4e8 | molecules^n\_p70 |
| k4 | 0.003/9 | 1/min |
| k\_4 | 0.003 | 1/min |
| k4p | 2.10E-03 | 1/min |
| k\_4p | 2.10E-04 | 1/min |
| k\_5 | ln(2)/(9\*60) | 1/min |
| k5 | 38.63653729 | molecules/min |
| k6 | 0.461 | 1/min |
| k7 | 4.16 | 1/min |
| k\_7 | 2.22 | 1/min |
| k7p | ln(2)/2 | 1/min |
| k\_7p | 1.386 | 1/min |
| k8 | 5.18091E-06 | 1/(molecules\*min) |
| k\_8 | 10 | 1/min |
| k9s | ln(2)\*2 | 1/min |
| k\_9 | (94/3.1)\*k9s | 1/min |
| k9b | (0.31/99.4)\*k\_9 | 1/min |
| k9a | 1.99817E-05 | 1/min |
| k\_10 | ln(2)\*4 | 1/min |
| k10 | (3.1/2.9)\*k\_10 | 1/min |
| k11 | ln(2)/2 | 1/min |
| k\_11 | 10\*k11 | 1/min |
| k12 | ln(2)/2 | 1/min |
| k\_12 | 10\*k12 | 1/min |
| k13 | (4/96)\*0.167 | 1/min |
| k\_13 | 0.167 | 1/min |
| k13p | ((40/60)-(4/96))\*0.167 | 1/min |
| k14 | 0.001155\*GLUT4\_cyt | molecules/min |
| k\_14 | 0.001155 | 1/min |
| p15 | 6.113E-07 | 1/min |
| p\_15 | 10 | 1/min |
| k15 | 12 | 1/min |
| k16 | 3.423E-04 | 1/min |
| k\_16 | 1.072E-02 | 1/min |
| k\_17 | 3.415E-02 | 1/min |
| k17 | 4.592E-04 | 1/min |
| k\_18 | 3.726E-07 | 1/min |
| k18 | 1.481E-08 | 1/min |
| k\_19 | 1.837E-02 | 1/min |
| k19 | 1.311E-05 | 1/min |
| k20 | 3.927E-06 | 1/min |
| k\_20 | 6.931E-01 | 1/min |
| k21 | 1.277E-06 | 1/min |
| k\_21 | 1.765E-05 | 1/min |
| k22 | 6.66e-8/(u\*1/60) | 1/(molecules\*min) |
| k\_22 | 2e6\*k22\*u | 1/min |
| kcat24 | 6.66/(1/60) | 1/min |
| alpha24 | 2.50E-04 | - |
| Km24 | 110\*u | molecules |
| V25 | 6.66\*u/(1/60) | molecules/min |
| Km25 | 50\*u | molecules |
| k26 | 6.66e-4/(u\*1/60) | 1/(molecules\*min) |
| k\_26 | 1e5\*k26\*u | 1/min |
| k27 | 6.66e-4/(u\*1/60) | 1/(molecules\*min) |
| k\_27 | 1000\*u\*k27 | 1/min |
| kcat28 | 5.33/(1/60) | 1/min |
| Km28 | 50\*u | molecules |
| bRasGAP | 1e-5\*u | molecules |
| kcat29 | 2e4/(1/60) | 1/min |
| Km29 | 50\*u | molecules |
| kcat30 | 0.1/(1/60) | 1/min |
| Km30 | 400\*u | molecules |
| kcat31 | 3.33/(1/60) | 1/min |
| Km31 | 10\*u | molecules |
| kcat32 | 0.666/(1/60) | 1/min |
| PKA | 100\*u | molecules |
| Km32 | 1e4\*u | molecules |
| alpha32 | (1e-6)/(u\*(1/60)) | 1/(molecules\*min) |
| beta32 | 2 | - |
| kcat33 | 0.133/(1/60) | 1/min |
| Km33 | 50\*u | molecules |
| V34 | 16.6\*u/(1/60) | molecules/min |
| Km34 | 675.299\*u | molecules |
| kcat35 | 0.333/(1/60) | 1/min |
| Km35 | 500\*u | molecules |
| Km36 | 500\*u | molecules |
| kcat36 | 0.666/(1/60) | 1/min |
| V37 | 33.3\*u/(1/60) | molecules/min |
| Km37 | 500\*u | molecules |
| Km38 | 500\*u | molecules |
| V38 | 23.33\*u/(1/60) | molecules/min |
| kcat39 | 0.0466/(1/60) | 1/min |
| Km39 | 5000\*u | molecules |
| k\_39 | 6.66e-5/(1/60) | 1/min |
| V40 | 333\*u/(1/60) | molecules/min |
| Km40 | 143.3\*u | molecules |
| k41 | 0.666/(1/60) | 1/min |
| k42 | 0.0133/(u\*1/60) | 1/(molecules\*min) |