TGFb\_VEGF\_model

- TGF\_b model

- VEGF\_model #Modified from Imoto et al., Cancers (2020)

#Abbreviation

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v: rate reaction

t: time

y: state variable

x: constant parameter

dydt: time derivative of y

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#Description of variable names

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1. TGF\_b model (v[1] ~ v[27])

- inact: inactive form

- act: active form

- S: SMAD

- p: phosphorylation

- m: mRNA

2. VEGF\_model (v[28] ~ v[79])

- E: VEGF

- E1: VEGFR

- G: Grb2.

- sigmaG: Grb2-containing species in which the Grb2 SH2 domain is bound to

tyrosine-phosphorylated receptor dimer (EijP) or to tyrosine-phosphorylated Shc (SP),

and both Grb2 SH3 domains are unbound.

- S: Shc.

- sigmaS: Shc-containing species in which the Shc SH2 domain is bound to

tyrosine-phosphorylated receptor dimer (EijP) or to membrane-localized,

tyrosine-phosphorylated GAB1 (AP), and Shc is unphosphorylated.

- I: PI-3K.

- sigmaI: PI-3K-containing species in which PI-3K is bound to

tyrosine-phosphorylated receptor dimer (EijP) or to membrane-localized,

tyrosine-phosphorylated GAB1 (AP).

- R: RasGAP.

- sigmaR: RasGAP-containing species in which RasGAP is bound to

tyrosine-phosphorylated receptor dimer (EijP) or to membrane-localized,

tyrosine-phosphorylated GAB1 (AP), but is not phosphorylated.

- T: PTP-1B.

- sigmaT: PTP-1B-containing species in which PTP-1B is bound to

tyrosine-phosphorylated receptor dimer (EijP) or to membrane-localized,

tyrosine-phosphorylated GAB1 (AP).

- A: GAB1.

- sigmaA: Gab1-containing species in which the GAB1 PH domain is bound to

PIP3 or the PRD is bound to Grb2, and GAB1 is unphosphorylated.

- O: SOS.

- sigmaO: SOS-containing species that are bound to

a membrane- localized N-terminal SH3 domain of Grb2.

- c: cytoplasmic

- n: nuclear

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# extracellular volume to cytoplasmic volume ratio

VeVc = 33.3

# fraction definitions

if y[V.sigmaS] + y[V.sigmaSP] + y[V.sigmaSP\_G] > 0.0:

fsigmaS = y[V.sigmaS]/(y[V.sigmaS] + y[V.sigmaSP] + y[V.sigmaSP\_G])

else:

fsigmaS = 0.0

if y[V.sigmaG] + y[V.sigmaG\_A] + y[V.sigmaG\_O] + y[V.A\_sigmaG\_O] > 0.0:

fsigmaG = y[V.sigmaG]/(y[V.sigmaG] + y[V.sigmaG\_A] + y[V.sigmaG\_O] + y[V.A\_sigmaG\_O])

else:

fsigmaG = 0.0

if y[V.sigmaA] + y[V.sigmaAP] + y[V.sigmaAP\_S] + y[V.sigmaAP\_R] + y[V.sigmaAP\_I] + y[V.sigmaAP\_T] > 0.0:

fsigmaA = y[V.sigmaA]/(y[V.sigmaA] + y[V.sigmaAP] + y[V.sigmaAP\_S] + y[V.sigmaAP\_R] + y[V.sigmaAP\_I] + y[V.sigmaAP\_T])

else:

fsigmaA = 0.0

if y[V.sigmaR] + y[V.sigmaRP] > 0.0:

fsigmaR = y[V.sigmaR]/(y[V.sigmaR] + y[V.sigmaRP])

else:

fsigmaR = 0.0

sigmaEP = y[V.E11P]

if sigmaEP > 0.0:

f11 = y[V.E11P]/sigmaEP

else:

f11 = 0.0

v = {}

# Rate reactions

# TGFb\_model

v[1] = x[C.kf\_1\_TGFbeta]\*y[V.THBS1]\*y[V.TGFb\_inact]/(x[C.Kmf\_1\_TGFbeta] + y[V.TGFb\_inact])

v[2] = x[C.k\_on\_FMOD]\*y[V.FMOD]\*y[V.TGFb\_act]

v[3] = x[C.Rec\_act]\*y[V.TGFBR\_inact]\*y[V.TGFb\_act]

v[4] = x[C.pRec\_debind]\*y[V.TGFBR\_act]

v[5] = x[C.kf\_2\_TGFbeta]\*y[V.S2]\*y[V.TGFBR\_act]/(x[C.Kmf\_2\_TGFbeta]\*(1+y[V.S7]/x[C.k\_inhibit\_TGF])+y[V.S2])

v[6] = x[C.S\_dephosphos]\*y[V.ppS2]

v[7] = x[C.S\_dephos]\*y[V.pS2]

v[8] = x[C.kf\_3\_TGFbeta]\*y[V.S3]\*y[V.TGFBR\_act]/(x[C.Kmf\_3\_TGFbeta]\*(1+y[V.S7]/x[C.k\_inhibit\_TGF])+y[V.S3])

v[9] = x[C.S\_dephosphos]\*y[V.ppS3]

v[10] = x[C.S\_dephos]\*y[V.pS3]

v[11] = x[C.k\_on\_ppS2\_ppS3]\*y[V.ppS3]\*y[V.ppS2]

v[12] = x[C.S\_dephosphos]\*y[V.ppS2\_ppS3]

v[13] = x[C.k\_on\_ppS2\_ppS3\_S4]\*y[V.ppS2\_ppS3]\*y[V.S4]

v[14] = x[C.prod\_mS7]\*y[V.ppS2\_ppS3\_S4]\*\*x[C.n1\_TGF]/(x[C.Km\_1\_TGF]\*\*x[C.n1\_TGF]+y[V.ppS2\_ppS3\_S4]\*\*x[C.n1\_TGF])

v[15] = x[C.mS7\_turn]\*y[V.mS7]

v[16] = x[C.prod\_S7]\*y[V.mS7]

v[17] = x[C.prod\_mcFOS]\*y[V.TGFBR\_act]\*\*x[C.n2\_TGF]/(x[C.Km\_2\_TGF]\*\*x[C.n2\_TGF]+y[V.TGFBR\_act]\*\*x[C.n2\_TGF])

v[18] = x[C.mcFOS\_turn]\*y[V.mcFOS]

v[19] = x[C.prod\_cFOS]\*y[V.mcFOS]

v[20] = x[C.k\_off\_FMOD]\*y[V.FMOD\_complex]

v[21] = x[C.k\_off\_ppS2\_ppS3\_S4]\*y[V.ppS2\_ppS3\_S4]

v[22] = x[C.k\_off\_ppS2\_ppS3\_S4\_cFOS]\*y[V.ppS2\_ppS3\_S4\_cFOS]

v[23] = x[C.k\_on\_ppS2\_ppS3\_S4\_cFOS]\*y[V.ppS2\_ppS3\_S4]\*y[V.cFOS]

v[24] = x[C.prod\_mTHBS1]\*y[V.ppS2\_ppS3\_S4\_cFOS]\*\*x[C.n4\_TGF]/(x[C.Km\_4\_TGF]\*\*x[C.n4\_TGF]+y[V.ppS2\_ppS3\_S4\_cFOS]\*\*x[C.n4\_TGF])

v[25] = x[C.THBS1\_turn]\*y[V.mTHBS1]

v[26] = x[C.prod\_THBS1]\*y[V.mTHBS1]

v[27] = x[C.degrad\_cFOS]\*y[V.cFOS]

# VEGF\_model

v[28] = (x[C.kon1]\*y[V.E]\*y[V.E1] - x[C.EGF\_off]\*y[V.E\_E1])

v[29] = (x[C.kon4]\*y[V.E\_E1]\*y[V.E\_E1] - x[C.koff4]\*y[V.E11])

v[30] = (x[C.kf10]\*y[V.E11] - x[C.VmaxPY]\*y[V.E11P]/(x[C.KmPY] + y[V.E11P]) - x[C.kPTP10]\*y[V.sigmaT]\*y[V.E11P])

v[31] = (4\*x[C.kon16]\*y[V.E11P]\*y[V.G] - x[C.koff16]\*fsigmaG\*y[V.E11G])

v[32] = (8\*x[C.kon17]\*y[V.E11P]\*y[V.S] - x[C.koff17]\*fsigmaS\*y[V.E11S])

v[33] = (2\*x[C.kon18]\*y[V.E11P]\*y[V.R] - x[C.koff18]\*fsigmaR\*y[V.E11R])

v[34] = (x[C.kf38]\*y[V.sigmaS]\*sigmaEP - x[C.VmaxPY]\*y[V.sigmaSP]/(x[C.KmPY] + y[V.sigmaSP]) - x[C.kPTP38]\*y[V.sigmaT]\*y[V.sigmaSP])

v[35] = (x[C.kf39]\*y[V.sigmaA]\*sigmaEP - x[C.VmaxPY]\*y[V.sigmaAP]/(x[C.KmPY] + y[V.sigmaAP]) - x[C.kPTP39]\*y[V.sigmaT]\*y[V.sigmaAP])

v[36] = (x[C.kon40]\*y[V.sigmaG]\*y[V.O] - x[C.koff40]\*y[V.sigmaG\_O])

v[37] = (x[C.kon41]\*y[V.sigmaG]\*y[V.A] - x[C.koff41]\*y[V.sigmaG\_A]\*fsigmaA)

v[38] = (x[C.kon42]\*y[V.sigmaSP]\*y[V.G] - x[C.koff42]\*y[V.sigmaSP\_G]\*fsigmaG)

v[39] = (3\*x[C.kon43]\*y[V.sigmaAP]\*y[V.S] - x[C.koff43]\*y[V.sigmaAP\_S]\*fsigmaS)

v[40] = (3\*x[C.kon44]\*y[V.sigmaAP]\*y[V.I] - x[C.koff44]\*y[V.sigmaAP\_I])

v[41] = (2\*x[C.kon45]\*y[V.sigmaAP]\*y[V.R] - x[C.koff45]\*y[V.sigmaAP\_R]\*fsigmaR)

v[42] = (x[C.kon46]\*y[V.P3]\*y[V.A] - x[C.koff46]\*y[V.P3\_A]\*fsigmaA)

v[43] = (x[C.kf47]\*y[V.P3]\*y[V.Akt]/(x[C.Kmf47] + y[V.Akt]) - x[C.Vmaxr47]\*y[V.Aktstar]/(x[C.Kmr47] + y[V.Aktstar]))

v[44] = (x[C.kf48]\*(1 - y[V.fint]\*f11)\*y[V.sigmaI]\*y[V.P2]/(x[C.Kmf48] + y[V.P2]) - 3\*x[C.PTEN]\*y[V.P3]/(x[C.Kmr48] + y[V.P3]))

v[45] = (x[C.kf49]\*y[V.sigmaO]\*y[V.RsD]/(x[C.Kmf49] + y[V.RsD]) - x[C.kr49]\*y[V.sigmaR]\*y[V.RsT]/(x[C.Kmr49] + y[V.RsT]) - x[C.kr49b]\*y[V.sigmaRP]\*y[V.RsT]/(x[C.Kmr49b] + y[V.RsT]) - x[C.kcon49]\*y[V.RsT])

v[46] = (x[C.kf50]\*y[V.sigmaR]\*sigmaEP - x[C.VmaxPY]\*y[V.sigmaRP]/(x[C.KmPY] + y[V.sigmaRP]) - x[C.kPTP50]\*y[V.sigmaT]\*y[V.sigmaRP])

v[47] = (x[C.kf51]\*y[V.RsT]\*y[V.Raf]/(x[C.Kmf51] + y[V.Raf]) - x[C.Vmaxr51]\*y[V.Rafstar]\*y[V.Aktstar]/(x[C.Kmrb51] + y[V.Rafstar]))

v[48] = (x[C.kf52]\*y[V.Rafstar]\*y[V.MEK]/(x[C.Kmf52] + y[V.MEK]) - x[C.Vmaxr52]\*y[V.ppMEKc]/(x[C.Kmr52] + y[V.ppMEKc]))

v[49] = (x[C.kf54]\*y[V.O]\*y[V.ppERKc]/(x[C.Kmf54] + y[V.O]) - x[C.Vmaxr54]\*y[V.OP]/(x[C.Kmr54] + y[V.OP]))

v[50] = (x[C.kf55]\*y[V.A]\*y[V.ppERKc]/(x[C.Kmf55] + y[V.A]) - x[C.Vmaxr55]\*y[V.AP]/(x[C.Kmr55] + y[V.AP]))

v[51] = (x[C.kon57]\*y[V.P3\_A]\*y[V.G] - x[C.koff57]\*y[V.sigmaA\_G])

v[52] = (x[C.kon58]\*y[V.sigmaA\_G]\*y[V.O] - x[C.koff58]\*y[V.sigmaA\_G\_O])

v[53] = (x[C.kon59]\*y[V.sigmaG\_O]\*y[V.A] - x[C.koff59]\*y[V.A\_sigmaG\_O]\*fsigmaA)

v[54] = (x[C.kon60]\*y[V.sigmaG\_A]\*y[V.O] - x[C.koff60]\*y[V.A\_sigmaG\_O])

v[55] = (4\*x[C.kon73]\*y[V.E11P]\*y[V.T] - x[C.koff73]\*y[V.E11T])

v[56] = (x[C.kf81]\*y[V.E1]\*y[V.ppERKc]/(x[C.Kmf81] + y[V.E1]) - x[C.Vmaxr81]\*y[V.E1\_PT]/(x[C.Kmr81] + y[V.E1\_PT]))

v[57] = (x[C.kf84]\*y[V.E\_E1]\*y[V.ppERKc]/(x[C.Kmf84] + y[V.E\_E1]) - x[C.Vmaxr84]\*y[V.E\_E1\_PT]/(x[C.Kmr84] + y[V.E\_E1\_PT]))

v[58] = (x[C.kon86]\*y[V.E]\*y[V.E1\_PT] - x[C.EGF\_off]\*y[V.E\_E1\_PT])

v[59] = (2\*x[C.kon88]\*y[V.sigmaAP]\*y[V.T] - x[C.koff88]\*y[V.sigmaAP\_T])

v[60] = x[C.kdeg]\*y[V.E11P]

v[61] = x[C.kdeg]\*y[V.E11G]

v[62] = x[C.kdeg]\*y[V.E11S]

v[63] = x[C.kdeg]\*y[V.E11R]

v[64] = x[C.kdeg]\*y[V.E11T]

v[65] = x[C.V1] \* y[V.ppMEKc] \* y[V.ERKc] / ( x[C.Km1] \* (1 + y[V.pERKc] / x[C.Km2]) + y[V.ERKc] )

v[66] = x[C.V2] \* y[V.ppMEKc] \* y[V.pERKc] / ( x[C.Km2] \* (1 + y[V.ERKc] / x[C.Km1]) + y[V.pERKc] )

v[67] = x[C.V3] \* y[V.pERKc] / ( x[C.Km3] \* (1 + y[V.ppERKc] / x[C.Km4]) + y[V.pERKc] )

v[68] = x[C.V4] \* y[V.ppERKc] / ( x[C.Km4]\* (1 + y[V.pERKc] / x[C.Km3]) + y[V.ppERKc] )

v[69] = x[C.V5] \* y[V.pERKn] / ( x[C.Km5] \* (1 + y[V.ppERKn] / x[C.Km6]) + y[V.pERKn] )

v[70] = x[C.V6] \* y[V.ppERKn] / ( x[C.Km6] \* (1 + y[V.pERKn] / x[C.Km5]) + y[V.ppERKn] )

v[71] = x[C.KimERK] \* y[V.ERKc] - x[C.KexERK] \* (x[C.Vn]/x[C.Vc]) \* y[V.ERKn]

v[72] = x[C.KimpERK] \* y[V.pERKc] - x[C.KexpERK] \* (x[C.Vn]/x[C.Vc]) \* y[V.pERKn]

v[73] = x[C.KimppERK] \* y[V.ppERKc] - x[C.KexppERK] \* (x[C.Vn]/x[C.Vc]) \* y[V.ppERKn]

v[74] = x[C.kf\_16\_vegf]\*y[V.TF\_inact]\*y[V.ppERKn]/(x[C.Kmf\_16\_vegf]+y[V.TF\_inact])

v[75] = x[C.kr\_17\_vegf]\*y[V.TF\_act]/(x[C.Kmr\_17\_vegf]+y[V.TF\_act])

v[76] = x[C.prod\_mFMOD]\*(y[V.TF\_act])\*\*x[C.n1\_vegf]/((x[C.Km\_18\_vegf])\*\*x[C.n1\_vegf]+(y[V.TF\_act])\*\*x[C.n1\_vegf])

v[77] = x[C.degrad\_mFMOD]\*y[V.mFMOD]

v[78] = x[C.prod\_FMOD]\*y[V.mFMOD]

v[79] = x[C.act\_PI3K]\*y[V.TGFBR\_act]\*y[V.I] - x[C.inact\_PI3K]\*y[V.sigmaI]

# Equations of the model

# TGFb\_model

dydt[V.TGFb\_inact] = - v[1]

dydt[V.TGFb\_act] = + v[1] - v[2] - v[3] + v[20]

dydt[V.FMOD] = - v[2] + v[20]

dydt[V.FMOD\_complex] = + v[2] - v[20]

dydt[V.TGFBR\_inact] = - v[3] + v[4]

dydt[V.TGFBR\_act] = + v[3] - v[4]

dydt[V.S2] = - v[5] + v[7]

dydt[V.S3] = - v[8] + v[10]

dydt[V.S4] = - v[13] + v[21]

dydt[V.pS2] = + v[6] - v[7] + v[12]

dydt[V.pS3] = + v[9] - v[10] + v[12]

dydt[V.ppS2] = + v[5] - v[6] - v[11]

dydt[V.ppS3] = + v[8] - v[9] - v[11]

dydt[V.ppS2\_ppS3] = + v[11] - v[12] - v[13] + v[21]

dydt[V.ppS2\_ppS3\_S4] = + v[13] - v[23] - v[21] + v[22]

dydt[V.mS7] = + v[14] - v[15]

dydt[V.S7] = + v[16]

dydt[V.mcFOS] = + v[17] - v[18]

dydt[V.cFOS] = + v[19] - v[27] - v[23] + v[22]

dydt[V.ppS2\_ppS3\_S4\_cFOS] = + v[23] - v[22]

dydt[V.mTHBS1] = + v[24] - v[25]

dydt[V.THBS1] = + v[26]

# VEGF\_model

dydt[V.E] = (-v[28] - v[58])/VeVc

dydt[V.E1] = -v[28] - v[56]

dydt[V.E\_E1] = v[28] - v[29] - v[29] - v[57] #VEGF\_VEGFR

dydt[V.E11] = v[29] - v[30] #VEGF\_VEGFR\_dimer

dydt[V.E11P] = v[30] - v[31] - v[32] - v[33] - v[55] - v[60] #VEGF\_pVEGFR\_dimer

dydt[V.G] = -v[31] - v[38] - v[51] + v[61] #Grb2

dydt[V.S] = -v[32] - v[39] + v[62] #Shc

dydt[V.I] = - v[40] - v[79] #PI3K

dydt[V.R] = -v[33] - v[41] + v[63] #RasGAP

dydt[V.O] = -v[36] - v[49] - v[52] - v[54] #SOS

dydt[V.A] = -v[37] - v[42] - v[50] - v[53] #GAB1

dydt[V.E11G] = v[31] - v[61]

dydt[V.E11S] = v[32] - v[62]

dydt[V.E11R] = v[33] - v[63]

dydt[V.sigmaG] = v[31] - v[36] - v[37] + v[38] - v[61]

dydt[V.sigmaS] = v[32] - v[34] + v[39] - v[62]

dydt[V.sigmaI] = v[40] + v[79]

dydt[V.sigmaR] = v[33] + v[41] - v[46] - v[63]

dydt[V.sigmaA] = -v[35] + v[37] + v[42] + v[53]

dydt[V.sigmaSP] = v[34] - v[38]

dydt[V.sigmaAP] = v[35] - v[39] - v[40] - v[41] - v[59]

dydt[V.sigmaG\_O] = v[36] - v[53]

dydt[V.sigmaG\_A] = v[37] - v[54]

dydt[V.sigmaSP\_G] = v[38]

dydt[V.sigmaAP\_S] = v[39]

dydt[V.sigmaAP\_I] = v[40]

dydt[V.sigmaAP\_R] = v[41]

dydt[V.P3\_A] = v[42] - v[51]

dydt[V.P2] = -v[44]

dydt[V.P3] = -v[42] + v[44]

dydt[V.Akt] = -v[43]

dydt[V.Aktstar] = v[43]

dydt[V.RsD] = -v[45]

dydt[V.RsT] = v[45]

dydt[V.sigmaRP] = v[46]

dydt[V.Raf] = -v[47]

dydt[V.Rafstar] = v[47]

dydt[V.MEK] = -v[48]

dydt[V.ppMEKc] = v[48]

dydt[V.OP] = v[49]

dydt[V.AP] = v[50]

dydt[V.A\_sigmaG\_O] = v[53] + v[54]

dydt[V.sigmaA\_G] = v[51] - v[52]

dydt[V.sigmaA\_G\_O] = v[52]

dydt[V.sigmaO] = v[36] + v[52] + v[54]

dydt[V.T] = -v[55] - v[59] + v[64]

dydt[V.E11T] = v[55] - v[64]

dydt[V.sigmaT] = v[55] + v[59] - v[64]

dydt[V.E1\_PT] = v[56] - v[58]

dydt[V.E\_E1\_PT] = v[57] + v[58]

dydt[V.sigmaAP\_T] = v[59]

dydt[V.fint] = x[C.a98]\*(-y[V.fint] + x[C.b98])

dydt[V.ERKc] = -v[65] + v[67] - v[71]

dydt[V.ERKn] = v[69] + v[71]\*(x[C.Vc]/x[C.Vn])

dydt[V.pERKc] = v[65] - v[66] -v[67] +v[68]-v[72]

dydt[V.pERKn] = -v[69] + v[70] + v[72]\*(x[C.Vc]/x[C.Vn])

dydt[V.ppERKc] = v[66] - v[68] - v[73]

dydt[V.ppERKn] = -v[70] + v[73]\*(x[C.Vc]/x[C.Vn])

dydt[V.TF\_inact] = + v[75] - v[74]

dydt[V.TF\_act] = + v[74] - v[75]

dydt[V.mFMOD] = + v[76] - v[77]

dydt[V.FMOD] = - v[2] + v[20] + v[78]

# Best fit parameter

x[C.kf\_1\_TGFbeta] = 4.923e-01

x[C.Kmf\_1\_TGFbeta] = 2.529e+00

x[C.k\_on\_FMOD] = 2.168e+02

x[C.k\_off\_FMOD] = 2.045e+00

x[C.Rec\_act] = 5.970e-01

x[C.pRec\_debind] = 8.082e-03

x[C.S2tot] = 6.000e-02

x[C.S3tot] = 3.800e-01

x[C.S4tot] = 4.400e-03

x[C.kf\_2\_TGFbeta] = 4.664e-01

x[C.Kmf\_2\_TGFbeta] = 4.889e+00

x[C.k\_inhibit\_TGF] = 1.569e+00

x[C.S\_dephosphos] = 1.001e-01

x[C.S\_dephos] = 1.947e+00

x[C.kf\_3\_TGFbeta] = 9.264e-01

x[C.Kmf\_3\_TGFbeta] = 1.004e-01

x[C.k\_on\_ppS2\_ppS3] = 8.995e-01

x[C.k\_on\_ppS2\_ppS3\_S4] = 9.071e-01

x[C.k\_off\_ppS2\_ppS3\_S4] = 3.579e-01

x[C.prod\_mS7] = 2.069e-01

x[C.n1\_TGF] = 1.000e+00

x[C.Km\_1\_TGF] = 2.299e-01

x[C.mS7\_turn] = 8.564e+00

x[C.prod\_S7] = 2.258e-01

x[C.prod\_mcFOS] = 1.848e+01

x[C.n2\_TGF] = 1.000e+00

x[C.Km\_2\_TGF] = 2.049e-02

x[C.mcFOS\_turn] = 2.056e-02

x[C.prod\_cFOS] = 1.134e-01

x[C.k\_on\_ppS2\_ppS3\_S4\_cFOS] = 6.391e-01

x[C.k\_off\_ppS2\_ppS3\_S4\_cFOS] = 2.785e-01

x[C.prod\_mTHBS1] = 2.157e+02

x[C.n4\_TGF] = 1.000e+00

x[C.Km\_4\_TGF] = 1.102e-01

x[C.THBS1\_turn] = 5.464e-03

x[C.prod\_THBS1] = 3.524e+00

x[C.w\_THBS1] = 1.234e-01

x[C.w\_TGFBR1] = 2.282e-01

x[C.w\_TGFBR2] = 3.128e-01

x[C.w\_SMAD7] = 1.021e-01

x[C.w\_cFOS] = 1.047e-01

x[C.degrad\_cFOS] = 1.000e-01

x[C.VmaxPY] = 2.209e+03

x[C.KmPY] = 4.197e+02

x[C.kdeg] = 2.220e-02

x[C.kf47] = 2.441e+02

x[C.Vmaxr47] = 3.040e+02

x[C.Kmf47] = 6.986e+01

x[C.Kmr47] = 1.218e+03

x[C.kf48] = 7.758e+00

x[C.Kmf48] = 1.543e+03

x[C.Kmr48] = 3.083e+03

x[C.PTEN] = 7.689e+01

x[C.kf49] = 1.340e+02

x[C.kr49] = 4.429e+03

x[C.Kmf49] = 1.923e+02

x[C.Kmr49] = 8.206e+02

x[C.Kmr49b] = 5.209e+02

x[C.kr49b] = 5.056e+02

x[C.kf51] = 8.832e-01

x[C.Vmaxr51] = 2.239e+01

x[C.Kmf51] = 5.166e+03

x[C.Kmrb51] = 8.959e+03

x[C.kf52] = 3.306e+00

x[C.Vmaxr52] = 1.320e+02

x[C.Kmf52] = 5.670e+01

x[C.Kmr52] = 1.965e+03

x[C.kf54] = 2.758e-02

x[C.Vmaxr54] = 2.994e+02

x[C.Kmf54] = 1.760e+03

x[C.Kmr54] = 1.338e+02

x[C.kf55] = 3.059e-01

x[C.Vmaxr55] = 1.347e+02

x[C.Kmf55] = 8.731e+01

x[C.Kmr55] = 1.127e+03

x[C.kf38] = 6.409e+01

x[C.kf39] = 1.249e+02

x[C.kf50] = 1.029e+02

x[C.a98] = 1.685e-02

x[C.b98] = 7.300e-01

x[C.koff46] = 3.845e-01

x[C.EGF\_off] = 8.144e-03

x[C.koff4] = 2.320e-01

x[C.koff16] = 2.271e+00

x[C.koff17] = 8.975e+00

x[C.koff18] = 6.361e+00

x[C.koff40] = 7.349e+00

x[C.koff41] = 1.709e+00

x[C.koff42] = 1.779e+00

x[C.koff43] = 7.319e-01

x[C.koff44] = 1.339e-01

x[C.koff45] = 1.650e+01

x[C.koff57] = 4.455e+00

x[C.koff58] = 4.199e+00

x[C.koff59] = 1.170e+01

x[C.koff60] = 8.973e-01

x[C.kPTP10] = 1.457e+02

x[C.koff73] = 4.650e-01

x[C.kPTP38] = 1.861e+02

x[C.kPTP39] = 5.194e+01

x[C.koff88] = 2.285e+01

x[C.kPTP50] = 2.738e+02

x[C.kf81] = 1.262e+01

x[C.Vmaxr81] = 7.175e+01

x[C.Kmf81] = 1.533e+03

x[C.Kmr81] = 1.676e+03

x[C.kf84] = 1.951e+00

x[C.Vmaxr84] = 5.420e+02

x[C.Kmf84] = 1.027e+03

x[C.Kmr84] = 5.849e+02

x[C.kcon49] = 2.571e+01

x[C.kon1] = 2.199e-05

x[C.kon86] = 1.320e-02

x[C.kon4] = 2.444e+00

x[C.kf10] = 1.122e+00

x[C.kon16] = 3.510e-03

x[C.kon17] = 3.378e-02

x[C.kon18] = 1.022e-02

x[C.kon73] = 3.401e-02

x[C.kon40] = 3.385e-02

x[C.kon41] = 2.294e-03

x[C.kon42] = 3.881e-03

x[C.kon43] = 5.142e-03

x[C.kon44] = 2.135e-02

x[C.kon45] = 1.039e-03

x[C.kon88] = 1.085e-03

x[C.kon46] = 1.315e-01

x[C.kon57] = 4.061e-03

x[C.kon58] = 2.149e-01

x[C.kon59] = 5.092e-03

x[C.kon60] = 3.622e-04

x[C.V1] = 5.407e-01

x[C.Km1] = 4.461e+02

x[C.V2] = 2.200e-01

x[C.Km2] = 3.500e+02

x[C.V3] = 7.200e-01

x[C.Km3] = 1.600e+02

x[C.V4] = 6.480e-01

x[C.Km4] = 6.000e+01

x[C.V5] = 9.121e+00

x[C.Km5] = 3.254e+00

x[C.V6] = 9.121e+00

x[C.Km6] = 3.254e+00

x[C.KimERK] = 1.200e-02

x[C.KexERK] = 1.800e-02

x[C.KimpERK] = 1.200e-02

x[C.KexpERK] = 1.800e-02

x[C.KimppERK] = 1.100e-02

x[C.KexppERK] = 1.300e-02

x[C.Vn] = 2.200e-01

x[C.Vc] = 9.400e-01

x[C.act\_PI3K] = 5.185e+00

x[C.inact\_PI3K] = 2.077e-01

x[C.kf\_16\_vegf] = 1.792e-01

x[C.Kmf\_16\_vegf] = 1.639e-03

x[C.kr\_17\_vegf] = 4.213e+00

x[C.Kmr\_17\_vegf] = 8.677e+00

x[C.prod\_mFMOD] = 2.758e+01

x[C.Km\_18\_vegf] = 1.533e+02

x[C.n1\_vegf] = 1.000e+00

x[C.degrad\_mFMOD] = 7.070e-01

x[C.prod\_FMOD] = 3.175e-01

x[C.w\_VEGFR1] = 6.361e-01

x[C.w\_VEGFR2] = 1.185e+01

x[C.w\_G] = 6.101e+00

x[C.w\_SHC1] = 1.996e+00

x[C.w\_SHC2] = 9.208e-01

x[C.w\_SHC3] = 1.451e+01

x[C.w\_SHC4] = 4.376e+00

x[C.w\_PIK3CA] = 3.317e+01

x[C.w\_PIK3CB] = 8.983e+00

x[C.w\_PIK3CD] = 4.935e-01

x[C.w\_PIK3CG] = 4.971e-01

x[C.w\_PTEN] = 1.502e+00

x[C.w\_RASA1] = 3.196e+01

x[C.w\_RASA2] = 8.671e+00

x[C.w\_RASA3] = 6.741e+00

x[C.w\_SOS1] = 1.192e+01

x[C.w\_SOS2] = 1.055e+01

x[C.w\_A] = 7.601e+00

x[C.w\_AKT1] = 2.547e+01

x[C.w\_AKT2] = 1.378e+00

x[C.w\_HRAS] = 8.886e-01

x[C.w\_KRAS] = 7.941e-01

x[C.w\_NRAS] = 1.985e+00

x[C.w\_ARAF] = 1.422e+01

x[C.w\_BRAF] = 3.225e+00

x[C.w\_RAF1] = 9.078e+00

x[C.w\_MAP2K1] = 2.270e+01

x[C.w\_MAP2K2] = 3.834e+00

x[C.w\_T] = 8.234e+00

x[C.w\_MAPK1] = 1.341e+00

x[C.w\_MAPK3] = 7.190e-01

x[C.w\_FMOD] = 1.214e+00

# None zero initial values for 'Control' condition

# y0[V.TGFb\_act] =0 for 'Control'

y0[V.TGFb\_inact] = 0.013

y0[V.TGFBR\_inact] = 4.475e+01

y0[V.S2] = 6.000e-02

y0[V.S3] = 3.800e-01

y0[V.S4] = 4.400e-03

y0[V.mS7] = 2.105e+00

y0[V.mcFOS] = 1.225e-01

y0[V.mTHBS1] = 5.581e+02

y0[V.E] = 1.000e+01

y0[V.E1] = 6.482e+01

y0[V.G] = 7.836e+02

y0[V.S] = 8.693e+02

y0[V.I] = 6.943e+02

y0[V.R] = 3.592e+03

y0[V.T] = 6.927e+02

y0[V.O] = 5.132e+02

y0[V.A] = 5.389e+01

y0[V.P2] = 4.811e+01

y0[V.Akt] = 2.212e+03

y0[V.RsD] = 3.497e+02

y0[V.Raf] = 1.958e+03

y0[V.MEK] = 2.098e+03

y0[V.ERKc] = 1.595e+02

y0[V.TF\_inact] = 6.616e+01

y0[V.mFMOD] = 2.536e+01

# None zero initial values for 'TGFβ1' condition

# y0[V.TGFb\_act] = 0.0902 for 'TGFβ1'

y0[V.TGFb\_inact] = 0.013

y0[V.TGFb\_act] =0.0902

y0[V.TGFBR\_inact] = 4.475e+01

y0[V.S2] = 6.000e-02

y0[V.S3] = 3.800e-01

y0[V.S4] = 4.400e-03

y0[V.mS7] = 2.105e+00

y0[V.mcFOS] = 1.225e-01

y0[V.mTHBS1] = 5.581e+02

y0[V.E] = 1.000e+01

y0[V.E1] = 6.482e+01

y0[V.G] = 7.836e+02

y0[V.S] = 8.693e+02

y0[V.I] = 6.943e+02

y0[V.R] = 3.592e+03

y0[V.T] = 6.927e+02

y0[V.O] = 5.132e+02

y0[V.A] = 5.389e+01

y0[V.P2] = 4.811e+01

y0[V.Akt] = 2.212e+03

y0[V.RsD] = 3.497e+02

y0[V.Raf] = 1.958e+03

y0[V.MEK] = 2.098e+03

y0[V.ERKc] = 1.595e+02

y0[V.TF\_inact] = 6.616e+01

y0[V.mFMOD] = 2.536e+01