

Appendix

MODEL EQUATIONS

Diffusion of compounds in the extracellular space

FGF dimerization and soluble HSPG binding with FGF monomer and dimer are considered. Compounds represented in the following equations are VEGF, FGF, soluble HSPG, complex of FGF with soluble HSPG, FGF dimer, and complex of FGF dimer with soluble HSPG.

$$\frac{\partial V}{\partial t} = D_v \left(\frac{\partial^2 V}{\partial x^2} + \frac{\partial^2 V}{\partial y^2} \right)$$

$$\frac{\partial F}{\partial t} = D_F \left(\frac{\partial^2 F}{\partial x^2} + \frac{\partial^2 F}{\partial y^2} \right) - k_{onFh} F * h - k_{onF_2h} Fh * F - k_{onF_2} F * F + k_{offFh} Fh + 2 * k_{offF_2} F_2$$

$$\frac{\partial h}{\partial t} = D_h \left(\frac{\partial^2 h}{\partial x^2} + \frac{\partial^2 h}{\partial y^2} \right) - k_{onFh} F * h - k_{onF_2h} F_2 * h + k_{offFh} Fh$$

$$\frac{\partial Fh}{\partial t} = D_{Fh} \left(\frac{\partial^2 Fh}{\partial x^2} + \frac{\partial^2 Fh}{\partial y^2} \right) + k_{onFh} F * h - k_{offFh} Fh - k_{onF_2h} Fh * F$$

$$\frac{\partial F_2}{\partial t} = D_{F_2} \left(\frac{\partial^2 F_2}{\partial x^2} + \frac{\partial^2 F_2}{\partial y^2} \right) + k_{onF_2} F * F - k_{offF_2} F_2 - k_{onF_2h} F_2 * h$$

$$\frac{\partial F_2h}{\partial t} = D_{F_2h} \left(\frac{\partial^2 F_2h}{\partial x^2} + \frac{\partial^2 F_2h}{\partial y^2} \right) + k_{onF_2h} Fh * F + k_{onF_2h} F_2 * h$$

Binding of FGF and VEGF to cell surface receptors

$$- D_v \left. \frac{\partial V}{\partial y} \right|_{y=0} = k_{onVR} R_V * V - k_{offVR} B_{VR}$$

$$-D_F \left. \frac{\partial F}{\partial y} \right|_{y=0} = k_{onFR} R_F * F + k_{onFH} F * H + k_{onFFHR} B_{FHR} * F + k_{onFFhR} B_{FhR} * F$$

$$-k_{offFR} B_{FR} - k_{offFH} B_{FH} - k_{offFHR} B_{FHR}$$

$$-D_{Fh} \left. \frac{\partial Fh}{\partial y} \right|_{y=0} = k_{onFhR} Fh * R_F - k_{offFhR} B_{FhR}$$

$$-D_{F_2} \left. \frac{\partial F_2}{\partial y} \right|_{y=0} = k_{onF_2R} F_2 * R_F + k_{onF_2H} F_2 * H - k_{offF_2R} B_{F_2R}$$

$$-D_{F_2h} \left. \frac{\partial F_2h}{\partial y} \right|_{y=0} = k_{onFFhR} F_2h * R_F$$

Concentration change of complex on cell surface

Various complexes are formed by binding of the compounds in the extracellular space with corresponding receptors, and HSPGs on cell-surface.

$$\frac{\partial R_V}{\partial t} = S_V - k_{inVR} R_{VR} - k_{onVR} V * R_V + k_{offVR} B_{VR}$$

$$\frac{\partial B_{VR}}{\partial t} = S_{VR} - k_{inVR} B_{VR} + k_{onVR} V * R_V - k_{offVR} B_{VR}$$

$$\begin{aligned} \frac{\partial R_F}{\partial t} = & S_F - k_{inFR} R_F - k_{onFR} F * R_F - k_{onFhR} Fh * R_F - k_{onFHR} B_{FH} * R_F - k_{onFFhR} B_{F_2h} * R_F \\ & - k_{onF_2R} F_2 * R_F - k_{onFFHR} B_{F_2H} * R_F + k_{offFR} B_{FR} + k_{offFHR} B_{FHR} + k_{offF_2R} B_{FHR} + k_{offF_2R} B_{F_2R} \end{aligned}$$

$$\begin{aligned} \frac{\partial H}{\partial t} = & S_H - k_{inH} H - k_{onFH} F * H - k_{onFHR} B_{FR} * H - k_{onF_2H} F_2 * H - k_{onFFHR} B_{F_2R} * H \\ & + k_{offFH} B_{FH} + k_{offFHR} B_{FHR} \end{aligned}$$

$$\frac{\partial B_{FR}}{\partial t} = -k_{inFR} B_{FR} + k_{onFR} F * R_F - k_{onFHR} B_{FR} * H - k_{offFR} B_{FR}$$

$$\frac{\partial B_{FH}}{\partial t} = -k_{inFH} B_{FH} + k_{onFH} F * H - k_{onFHR} B_{FH} * R_F - k_{offFH} B_{FH}$$

$$\frac{\partial B_{FHR}}{\partial t} = -k_{inFHR} B_{FHR} + k_{onFHR} B_{FH} * R_F + k_{onFHR} B_{FR} * H - k_{offFHR} B_{FHR} - k_{onFFHR} B_{FHR} * F$$

$$\frac{\partial B_{FhR}}{\partial t} = -k_{inFhR} B_{FhR} + k_{onFhR} B_{Fh} * R_F - k_{offFhR} B_{FhR} * H - k_{onFFhR} B_{FhR} * F$$

$$\frac{\partial B_{FFHR}}{\partial t} = -k_{inFFHR} B_{FFHR} + k_{onFFHR} B_{FHR} * F + k_{onFFHR} B_{F_2H} * R_F + k_{onFFHR} B_{F_2R} * H$$

$$\frac{\partial B_{FFhR}}{\partial t} = -k_{inFFhR} B_{FFhR} + k_{onFFhR} B_{FhR} * F + k_{onFFhR} B_{F_2h} * R_F$$

$$\frac{\partial B_{F_2R}}{\partial t} = -k_{inF_2R} B_{F_2R} + k_{onF_2R} F_2 * R_F - k_{offF_2R} B_{F_2R} - k_{onFFHR} B_{F_2R} * H$$

$$\frac{\partial B_{F_2H}}{\partial t} = -k_{inF_2H} B_{F_2H} + k_{onF_2H} F_2 * H - k_{onFFHR} B_{F_2H} * R_F$$

Intracellular concentration change of calcium and IP₃

Calcium transport events include IP₃ generation, calcium uptake into the ER, influx and leak of calcium across cell plasma membrane.

$$\frac{\partial I}{\partial t} = J_B + J_P - k_3 I + D_I \frac{\partial^2 I}{\partial x^2}$$

$$J_B = k_1 (B_{VR} + B_{FR} + B_{FHR} + B_{FFHR} + B_{F_2R} + B_{FhR} + B_{FFhR}) * \left(\frac{C_a}{C_a + K_1} \right)$$

$$J_P = k_2 \frac{C_a^2}{K_2^2 + C_a^2}$$

$$\frac{\partial C_a}{\partial t} = J_{REL} - J_{IER} + J_{IN} - J_{OUT} + D_C \frac{\partial^2 C_a}{\partial x^2}$$

$$J_{REL} = \left[k_4 + k_5 \frac{RC_a^2 I^2}{(K_5^2 + C_a^2)(K_i^2 + I^2)} \right] (C_{ER} - C_a)$$

$$J_{IER} = k_6 C_a, \quad J_{IN} = k_7 + k_8 * \frac{I^2}{K_8^2 + I^2}, \quad J_{OUT} = k_9 C_a$$

$$\frac{\partial C_{ER}}{\partial t} = r(J_{IER} - J_{REL})$$

$$\frac{\partial R}{\partial t} = k_{10} \left[\frac{K_{10}^2}{K_{10}^2 + C_a^2} - R \right]$$

Glossary

B_{F2h}	Concentration of FGF dimer-soluble HSPG on cell surface
B_{F2H}	Concentration of FGF dimer-HSPG
B_{F2R}	Concentration of FGF dimer-FGFR1
B_{FFhR}	Concentration of FGF dimer-soluble HSPG-FGFR1
B_{FFHR}	Concentration of FGF dimer-HSPG-FGFR1
B_{Fh}	Concentration of FGF-soluble HSPG on cell surface
B_{FH}	Concentration of FGF-HSPG on cell surface
B_{FhR}	Concentration of FGF-soluble HSPG-FGFR1
B_{FHR}	Concentration of FGF-HSPG-FGFR1
B_{FR}	Concentration of FGF-FGFR1
B_{VR}	Concentrations of VEGF-VEGFR2
C_a	Concentrations of calcium in cytoplasm
C_{ER}	Concentrations of calcium in ER
C_{ER0}	The initial concentrations of calcium in ER
D_F	Diffusivity of FGF monomer
D_{F2}	Diffusivity of FGF dimer

D_{F2h}	Diffusivity of FGF dimer-soluble HSPG
D_h	Diffusivity of soluble HSPG
D_{Fh}	Diffusivity of FGF-soluble HSPG
D_V	Diffusivity of VEGF
D_C	Diffusivity of calcium
D_I	Diffusivity of IP_3
F	Concentrations of FGF
F_0	The initial concentrations of FGF
F_2	Concentration of FGF dimer
F_{2h}	Concentration of FGF dimer-soluble HSPG
F_h	Concentration of FGF-soluble HSPG
h	Concentration of soluble HSPG
h_0	The initial concentration of soluble HSPG
H	Concentration of cell-surface HSPG
H_0	The initial concentration of cell-surface HSPG
J_B	The rate of IP_3 generation by cell-surface complexes through $PLC\gamma$
J_{IER}	Calcium pumping into the ER
J_{IN}	Calcium influx across the plasma membrane
J_{OUT}	Calcium extrusion
J_P	The rate of IP_3 generation by the positive feedback through $PLC\delta$
J_{REL}	Calcium released from the ER
k_1	IP_3 generation rate
k_2	Maximal rate of $PLC\delta$

k_3	IP ₃ degradation rate
k_4	Rate of calcium leak from ER
k_5	Rate constant of calcium release through IP ₃ R
k_6	Rate constant of SERCA pump
k_7	Rate of calcium leak across the plasma membrane
k_8	Maximal rate of activation-dependent calcium influx
k_9	Rate constant of calcium extrusion
k_{10}	Rate constant of IP ₃ R inactivation
K_1	Dissociation constant between calcium and PLC γ
K_2	Half-saturation constant for calcium activation of PLC δ
K_5	Half-saturation constant for calcium activation of IP ₃ R
K_i	Half-saturation constant for IP ₃ activation of IP ₃ R
K_8	Half-saturation constant for agonist-dependent calcium entry
K_{10}	Half-saturation constant for calcium inhibition of IP ₃ R
k_{inF}	Internalization rate of FGFR1
k_{inFH}	Internalization rate of FGF-HSPG
k_{inFhR}	Internalization rate of FGF-soluble HSPG-FGFR1
k_{inFHR}	Internalization rate of FGF-HSPG-FGFR1
k_{inFFhR}	Internalization rate of FGF dimer-soluble HSPG-FGFR1
k_{inFFHR}	Internalization rate of FGF dimer-HSPG-FGFR1
k_{inF2R}	Internalization rate of FGF dimer
k_{inF2H}	Internalization rate of FGF dimer-HSPG
k_{inH}	Internalization rate of HSPG

k_{inV}	Internalization rate of VEGF
k_{inFR}	Internalization rate of FGF-FGFR1
k_{inVR}	Internalization rate of VEGF-VEGFR2
k_{offFR}	Dissociation rate of FGF-FGFR1
k_{offF2}	Dissociation rate of FGF dimer
k_{offF2R}	Dissociation rate of FGF dimer-FGFR1
k_{offFh}	Dissociation rate of FGF -soluble HSPG
k_{offFH}	Dissociation rate of FGF-HSPG
k_{offFhR}	Dissociation rate of FGF-soluble HSPG-FGFR1
k_{offFHR}	Dissociation rate of FGF-HSPG-FGFR1
k_{offVR}	Dissociation rate of VEGF-VEGFR2
k_{onFR}	Kinetic rate of FGF binding FGFR1
k_{onF2}	Kinetic rate of FGF binding FGF
k_{onF2R}	Kinetic rate of FGF dimer binding FGFR1
k_{onF2h}	Kinetic rate of FGF dimer binding soluble HSPG
k_{onF2H}	Kinetic rate of FGF dimer binding HSPG
k_{onFh}	Kinetic rate of FGF binding soluble HSPG
k_{onFH}	Kinetic rate of FGF binding HSPG
k_{onFhR}	Kinetic rate of FGF-soluble HSPG binding FGFR1
k_{onFHR}	Kinetic rate of FGF-HSPG binding FGFR1
k_{onFFhR}	Kinetic rate of FGF dimer-soluble HSPG binding FGFR1
k_{onFFHR}	Kinetic rate of FGF dimer-HSPG binding FGFR1
k_{onV}	Kinetic rate of VEGF binding VEGFR2

P_C	Permeability of calcium to gap junctions
P_I	Permeability of IP ₃ to gap junctions
r	Ratio of the volume between cytoplasmic and ER
R	Fraction of IP ₃ R
R_F	Concentrations of FGFR1
R_{F0}	The initial concentration of FGFR1
R_V	Concentrations of VEGFR2
R_{V0}	The initial concentrations of VEGFR2
S_F	Insertion rates of FGF
S_H	Insertion rates of HSPG
S_V	Insertion rates of VEGFR2
V	Concentrations of VEGF
V_0	The initial concentration of VEGF