Mathematical Modeling and Computational Methods for the Tumor Microenvironment

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Outline

1. Overview of Ductal Carcinoma and Tumor Microenvironment
2. Cells-based Model
3. TGF-β/SMAD autocrine signaling pathway
4. Metabolism and Acidification
5. Numerical Results
6. Future Work

Some References

Casciari et al, Cell Proliferation, 1992

Clark et al, TGF-beta depletion is the primary determinant of Smad signaling kinetics, Molecular and Cell Biology, 2009.

Gatenby, R. A., and Gillies, R. J., 2008, Hypoxia and metabolism - Opinion -A microenvironmental model of carcinogenesis, *Nature Reviews Cance*

Warburg, O.,The metabolism of tumors, Constable Press, London, 1930.

Rejniak and Dillon, A single cell based model of the ductal tumor microarchitecture, *Comput Math Methods in Medicine*, 2007

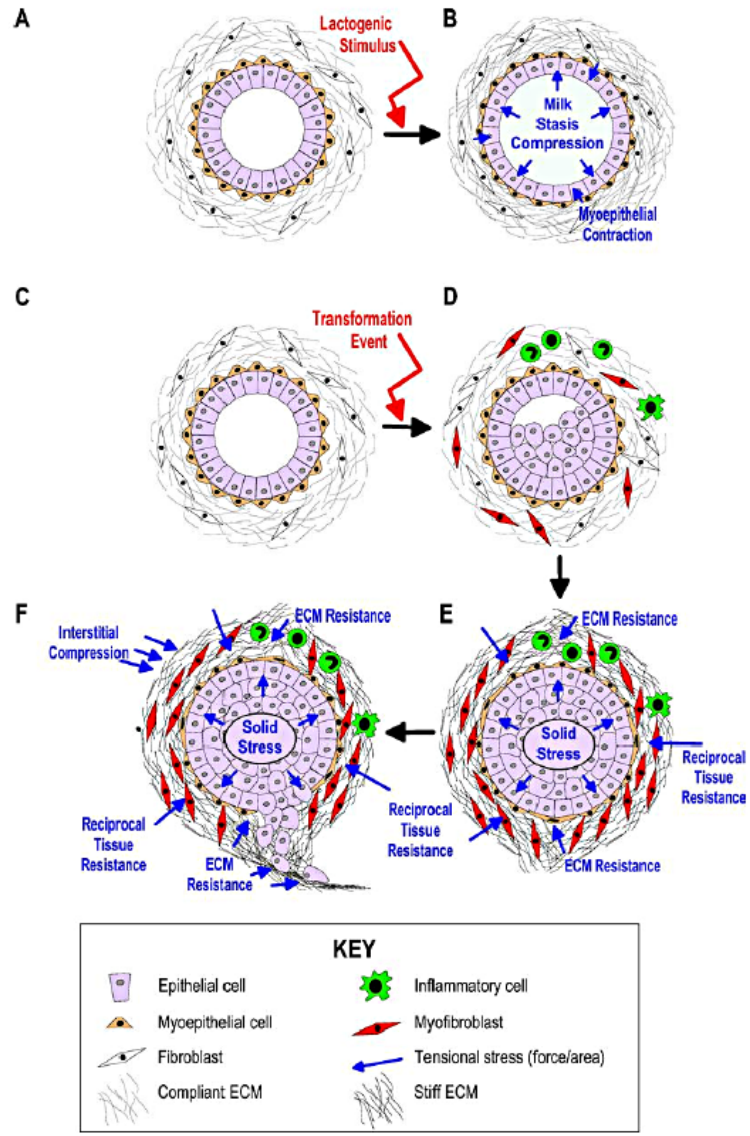
Komjima et al, "Autocrine TGF-beta and …. SDF-1 … ", *PNAS*, 2010

Kim and Othmer, A hybrid model of tumor-stromal interactions in breast cancer, *Bull Math Biol*, 2013

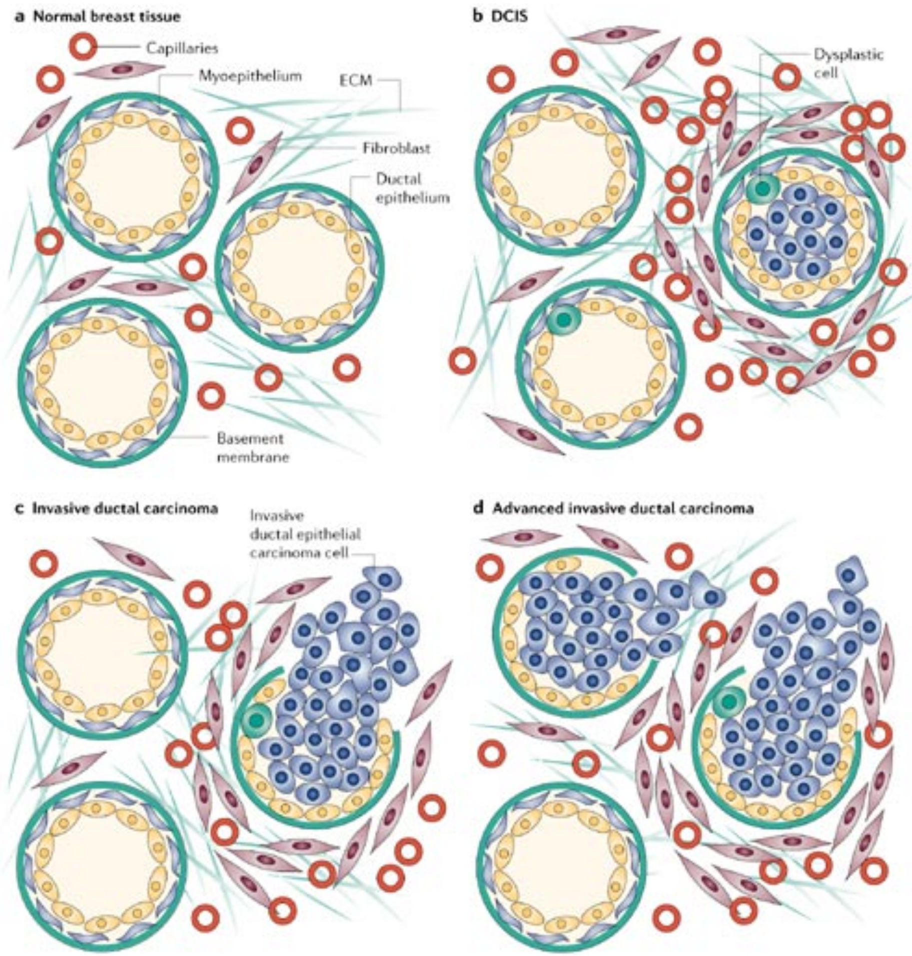
Li, ZL, Siam Journal on Numerical Analysis, 1998

Hossan, Dillon, and Dutta, Hybrid immersed interface –immersed boundary methods for AC dielectrophoresis, JCP, 2014

Transition from normal duct to invasive tumor



Progression of Ductal Carcinoma



Nature Reviews | Cancer

Kalluri *et al. Nature Reviews Cancer* advance online publication;
published online 30 March 2006 | doi:10.1038/nrc1877

nature REVIEWS CANCER

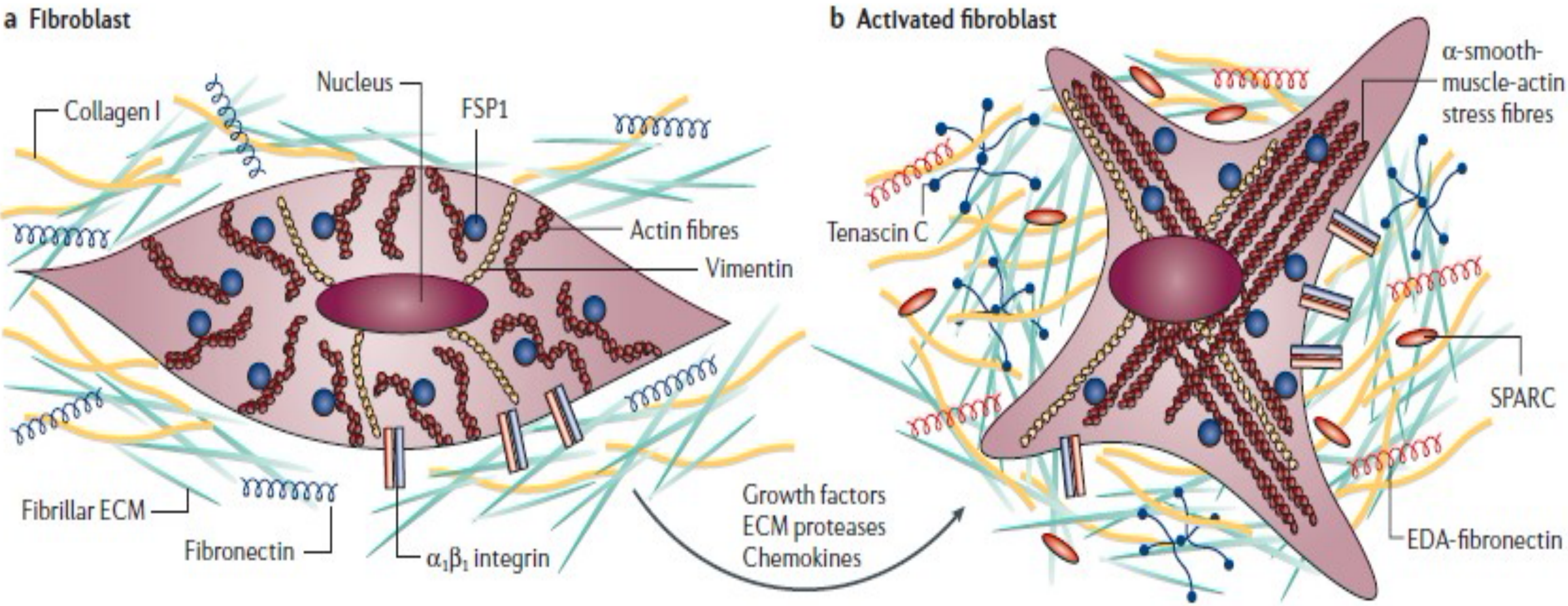


Figure 1 | **Activated fibroblasts. a** | Normal fibroblasts are embedded within the fibrillar extracellular matrix (ECM) of connective tissue, which consists largely of type I collagen and fibronectin. Fibroblasts interact with their surrounding microenvironment through integrins such as the $\alpha_1\beta_1$ integrin. Typically, fibroblasts appear as fusiform cells with a prominent actin cytoskeleton and vimentin intermediate filaments. Although the detection of fibroblasts can be challenging because most known markers are not specific to fibroblasts, fibroblast-specific protein 1 (FSP1), which is a member of the family of S100 Ca^{2+}-binding proteins, is specific for fibroblasts in normal tissues. **b** | Fibroblasts can acquire an activated phenotype, which is associated with an increased proliferative activity and enhanced secretion of ECM proteins such as type I collagen and tenascin C, and also fibronectin that contains the extra domain a (EDA-fibronectin) and SPARC (secreted protein acidic and rich in cysteine). Phenotypically, activated fibroblasts are often characterized as expressing α-smooth-muscle actin. Numerous growth factors such as transforming growth factor-β (TGFβ), chemokines such as monocyte chemotactic protein 1 (MCP1), and ECM-degrading proteases have been shown to mediate the activation of fibroblasts.

Raghu Kalluri‡§ and Michael Zeisberg* 2006*

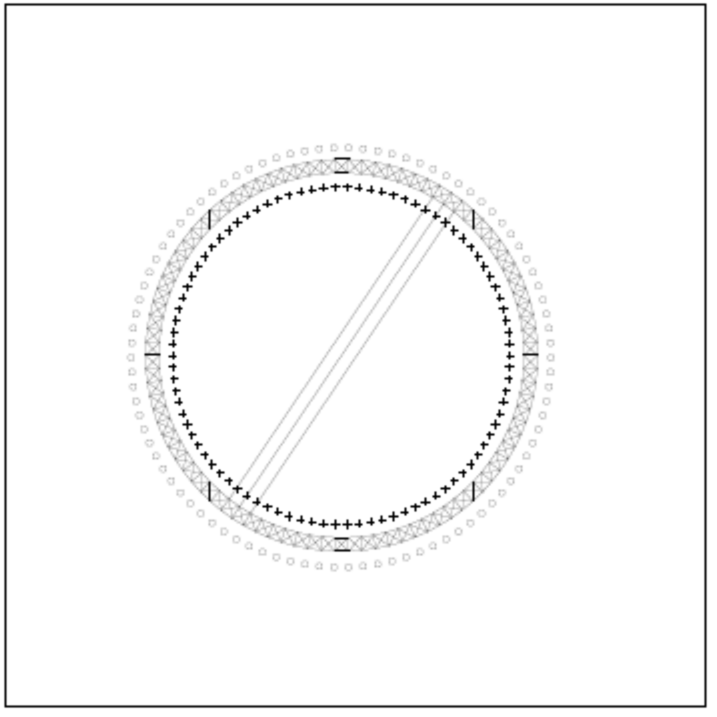
Many Mathematical Models

Continuum models for cell population

Agent based models

Cells-based models: hybrid models with discrete cells coupled with continuous fluid-mechanical, chemical and ion fields.

Single-cell model



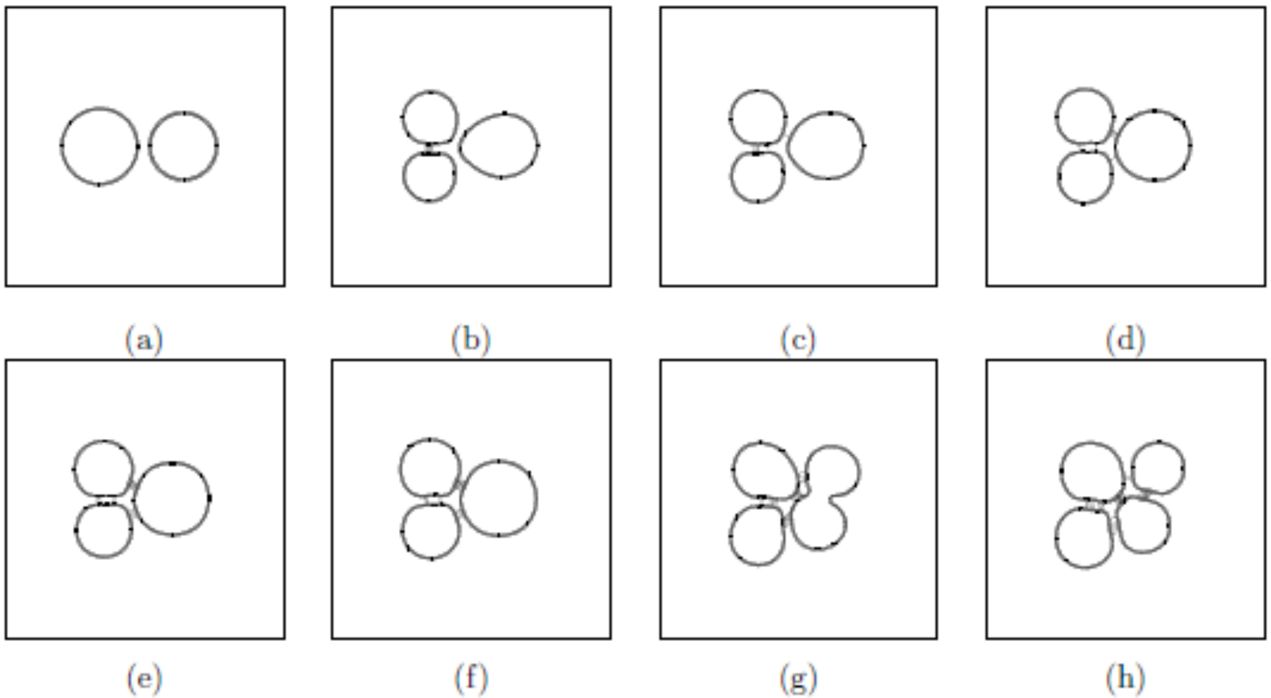
Rejniak and Dillon
A single-cell model of the ductal tumor architecture,
Comput Math Methods in Medicine, 2007

Immersed Boundary Model Equations

$$\left.\begin{aligned} \rho\frac{\partial \mathbf{u}}{\partial t} + \rho(\mathbf{u}\cdot\nabla)\mathbf{u} &= -\nabla p + \mu(\nabla^2\mathbf{u} + \tfrac{1}{3}\nabla S) + \mathbf{F} \\ \nabla\cdot\mathbf{u} &= S(c,\mathbf{x},t) \end{aligned}\right\} \quad \textbf{Fluid Equations}$$

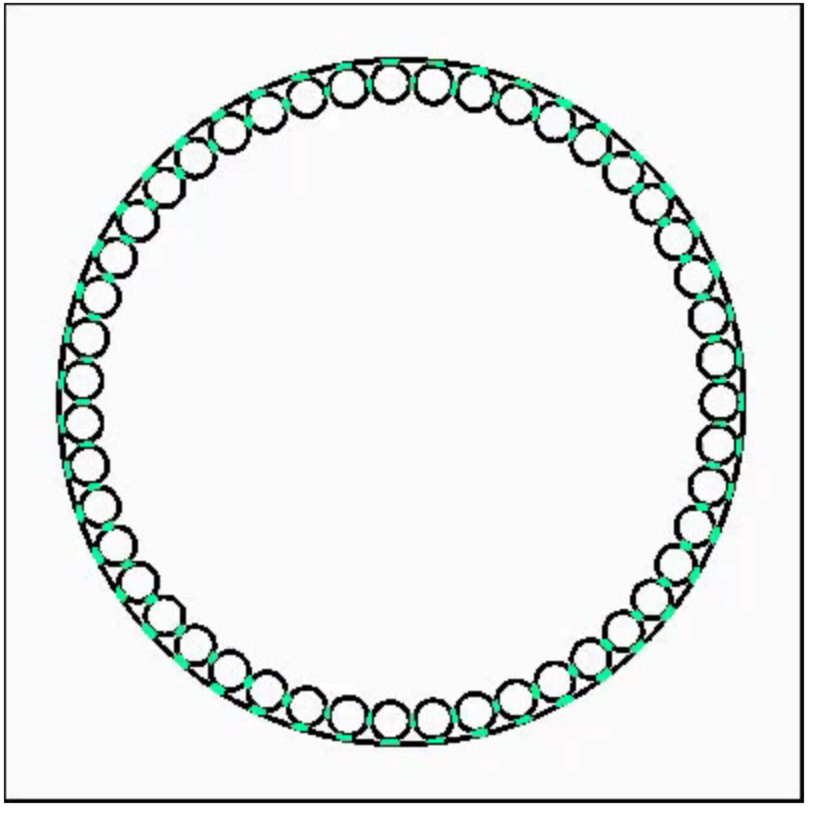
$$\left.\begin{aligned} \frac{\partial \mathbf{X}}{\partial t} &= \mathbf{u}(\mathbf{X}(s,t),t) \\ \mathbf{F}(\mathbf{x},t) &= \int_\Gamma \mathbf{f}(s,t)\delta(\mathbf{x}-\mathbf{X}(s,t))ds \end{aligned}\right\} \quad \textbf{Boundary Motion}$$

Growth and Cell Division

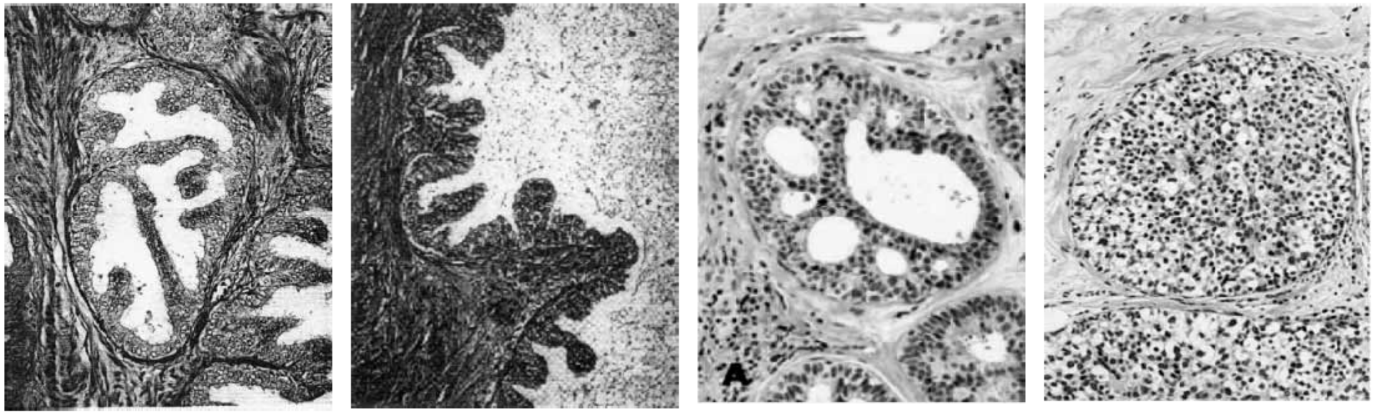


Rejniak and Dillon, 2007

DCIS (ductal carcinoma in situ)



Rejniak and Dillon, Comput Math Methods in Medicine, 2007



(a) micropapillary (b) tufts (c) cribriform (d) solid

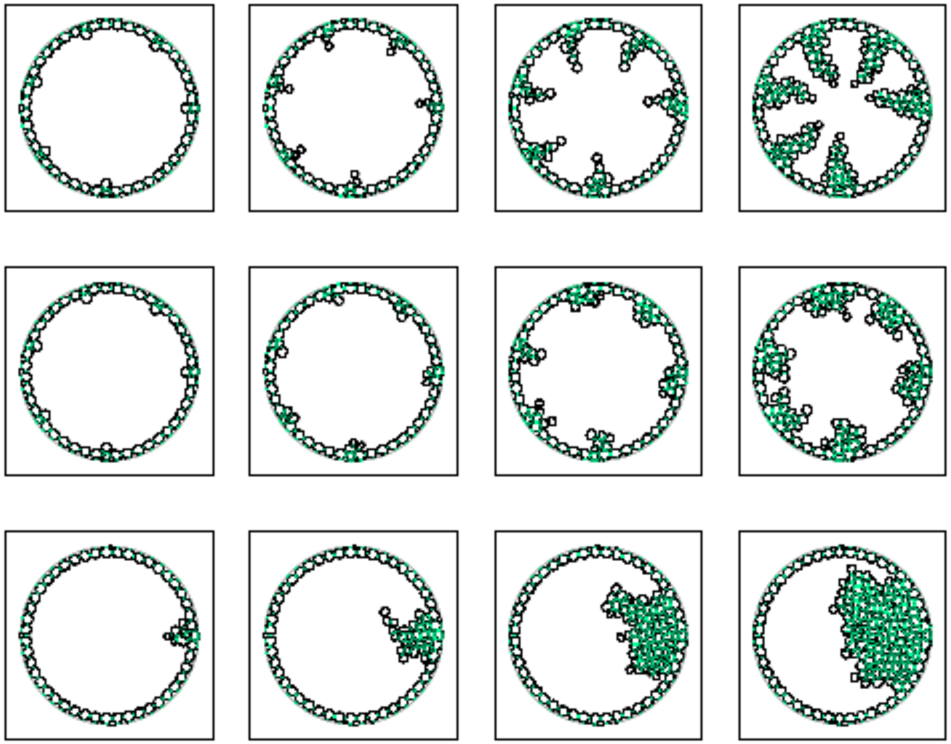
Histological patterns of four ductal carcinomas:
(a) micropapillary with trabecular bars, (b) tufts

both in the prostate tissue
Bostwick, et al, *Human Pathology*, 1993

(c) cribriform, (d) solid

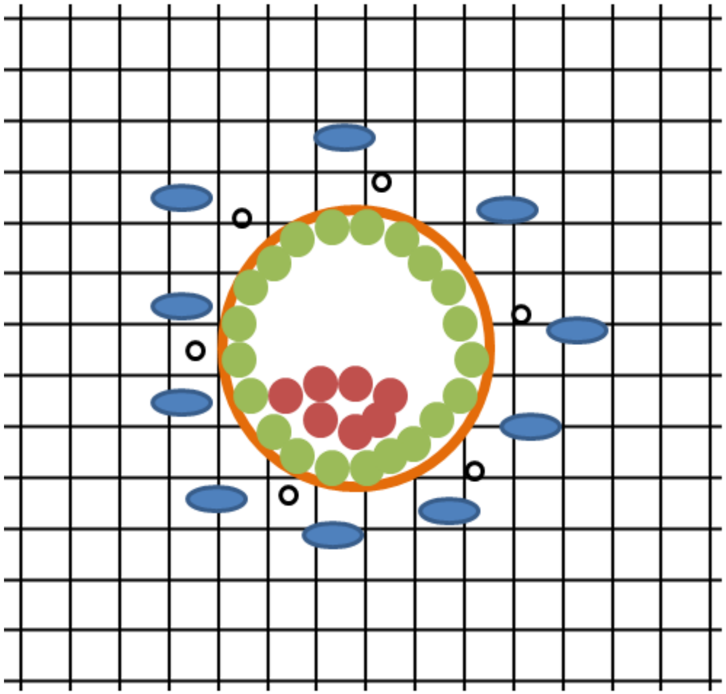
both in the breast tissue.
Winchester et al, *Cancer Journal for Clinicians*, 2000

Tufting, Micropapillary, and Solid Patterns in DCIS



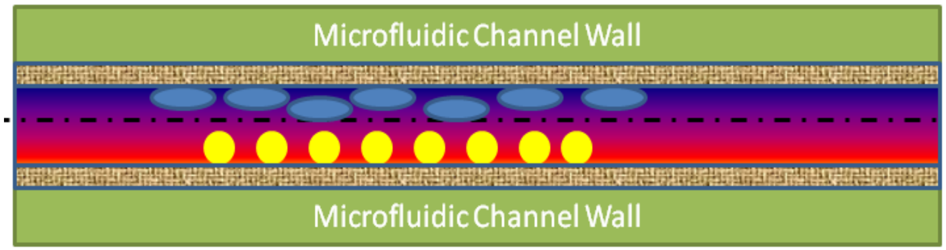
Rejniak and Dillon, 2007

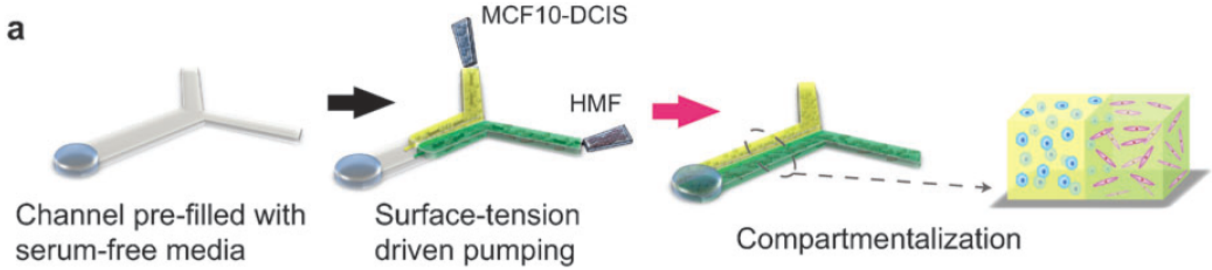
Cells-based *in vitro* model



Similar in concept to Kim and Othmer, 2013

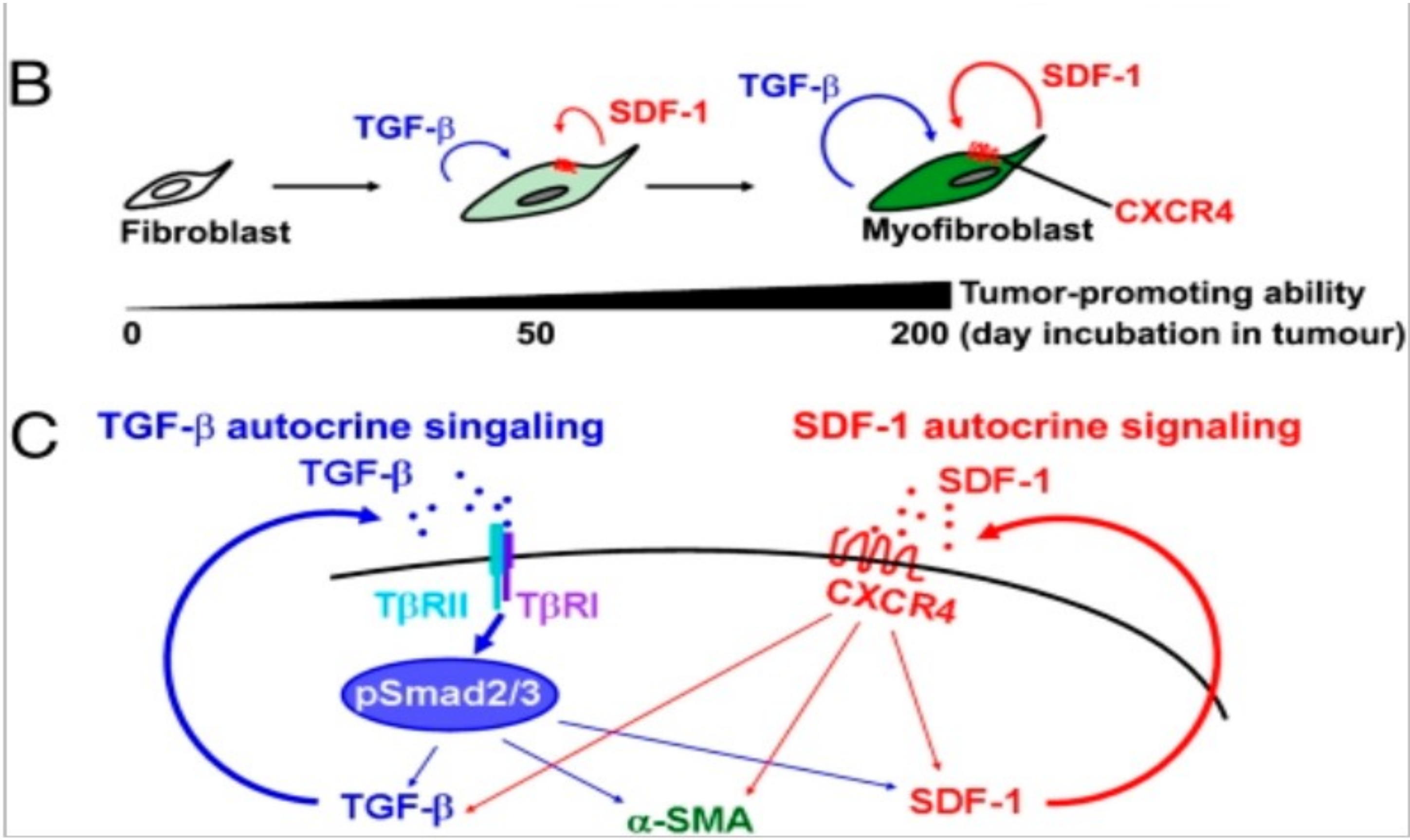
Cells-based microfluidic model





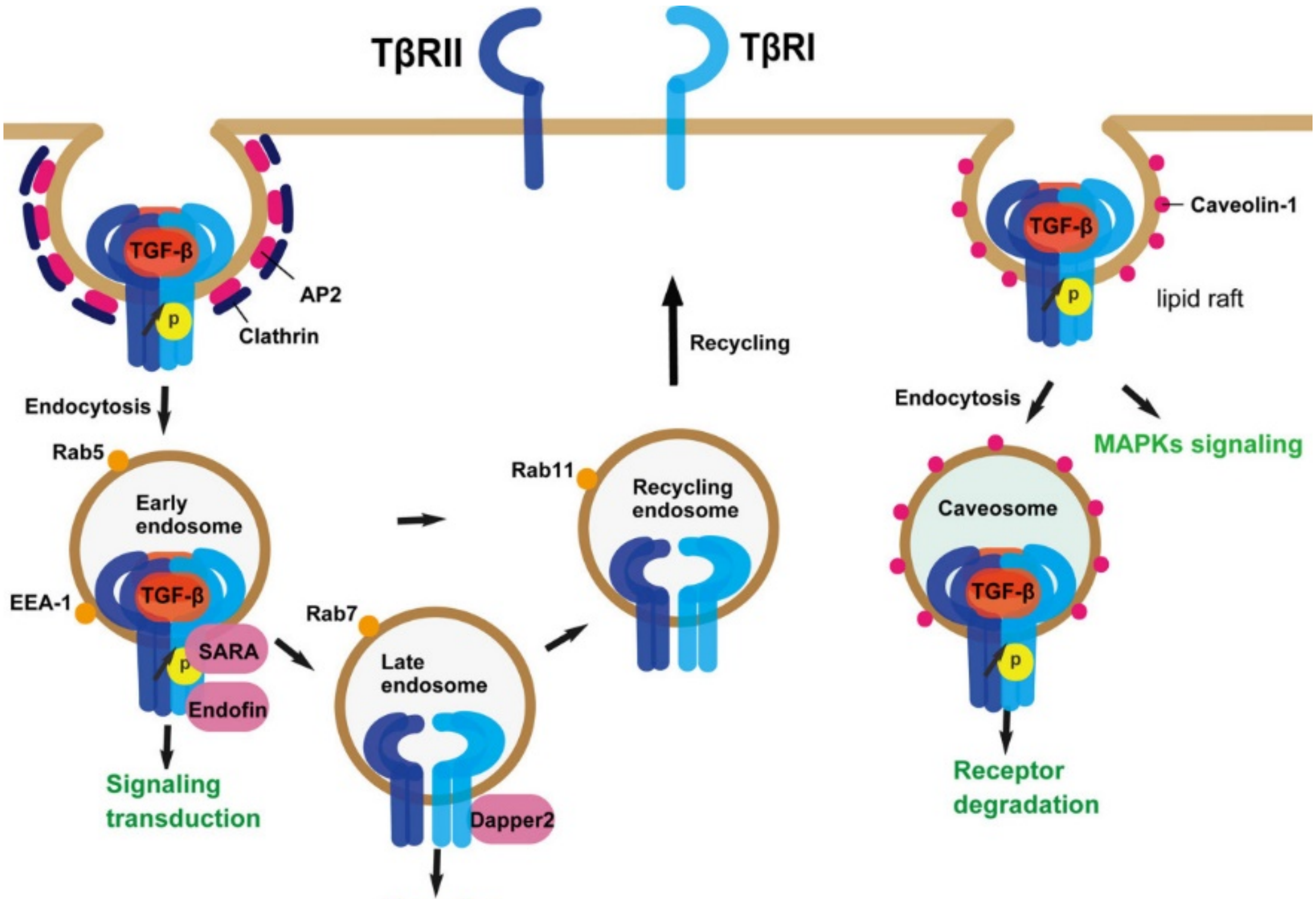
Sung et al, *Integrative Biology*, 2011

TGF-Beta and SDF-1 Autocrine Signaling

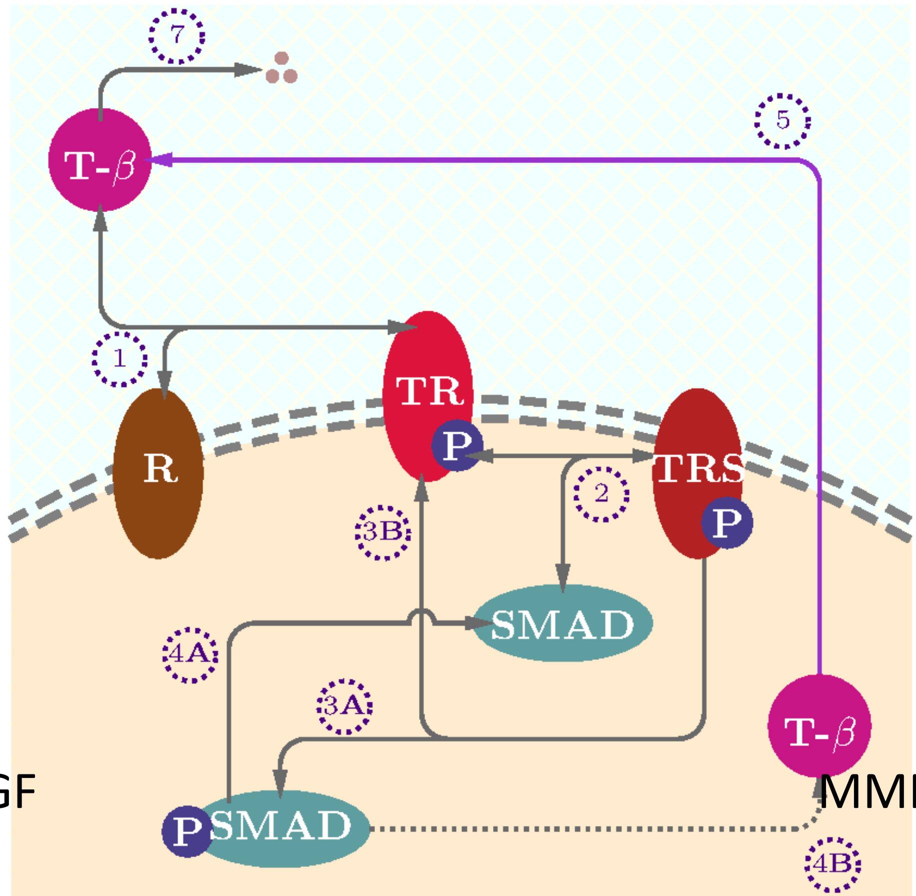


Kojima et al, PNAS, 2010

Receptor Trafficking



TGF/SMAD



Cell Surface

$$\frac{dR}{dt} = k_1^- TR - k_1^+ T \cdot R + k_d TR$$

$$\frac{dTR}{dt} = k_1^+ T \cdot R - k_1^- TR + k_T^- TRS - k_T^+ TR \cdot S + k_T^0 TRS - k_d TR$$

$$\frac{dTRS}{dt} = k_T^+ TR \cdot S - k_T^- TRS - k_T^0 TRS$$

Cell Interior

$$\frac{dS}{dt} = k_T^- TRS - k_T^+ TR \cdot S + k_S S_P$$

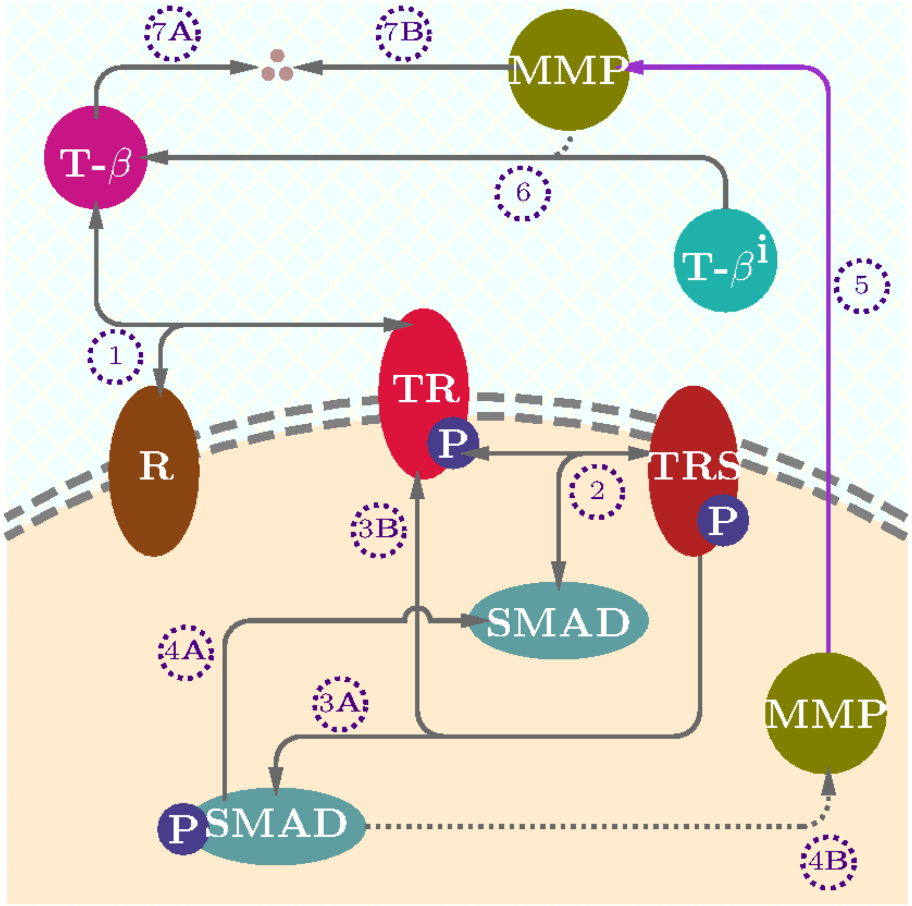
$$\frac{dS_P}{dt} = k_T^0 TRS - k_S S_P$$

$$\frac{dT^{in}}{dt} = \frac{r_1 S_P^2}{r_2^2 + S_P^2} - k_3 T^{in}$$

Exterior Domain

$$\nabla \cdot [-D_T \nabla T] = \int \left[\left(k_1^- TR - k_1^+ T \cdot R \right) \delta\{x(s) - x\} \right] ds$$

MMP



7A
7B
MMP
T-β
6
T-β^i
5
1
TR
P
R
2
TRS
P
3B
SMAD
4A
3A
MMP
P
SMAD
4B

Cell Surface

$$\frac{dR}{dt} = k_1^- TR - k_1^+ T \cdot R + k_d TR$$

$$\frac{dTR}{dt} = k_1^+ T \cdot R - k_1^- TR + k_T^- TRS - k_T^+ TR \cdot S + k_T^0 TRS - k_d TR$$

$$\frac{dTRS}{dt} = k_T^+ TR \cdot S - k_T^- TRS - k_T^0 TRS$$

Cell Interior

$$\frac{dS}{dt} = k_T^- TRS - k_T^+ TR \cdot S + k_S S_P$$

$$\frac{dS_P}{dt} = k_T^0 TRS - k_S S_P$$

$$\frac{dM^i}{dt} = \frac{r_1 S_P^2}{r_2^2 + S_P^2} - k_M M^i$$

Exterior Domain

$$\nabla \cdot \left[-D_{M^o} \nabla M^o \right] = \oint_s [k_a k_M M^i \delta\{\mathrm{x(s)} - \mathrm{s}\}] ds - \gamma_1 M^o$$

$$\nabla \cdot \left[-D_T \nabla T \right] = \oint [(k_1^- \overline{TR} - k_1^+ T \cdot R) \delta\{\mathrm{x(s)} - \mathrm{s}\}] ds + \gamma_2 T^i M^o$$

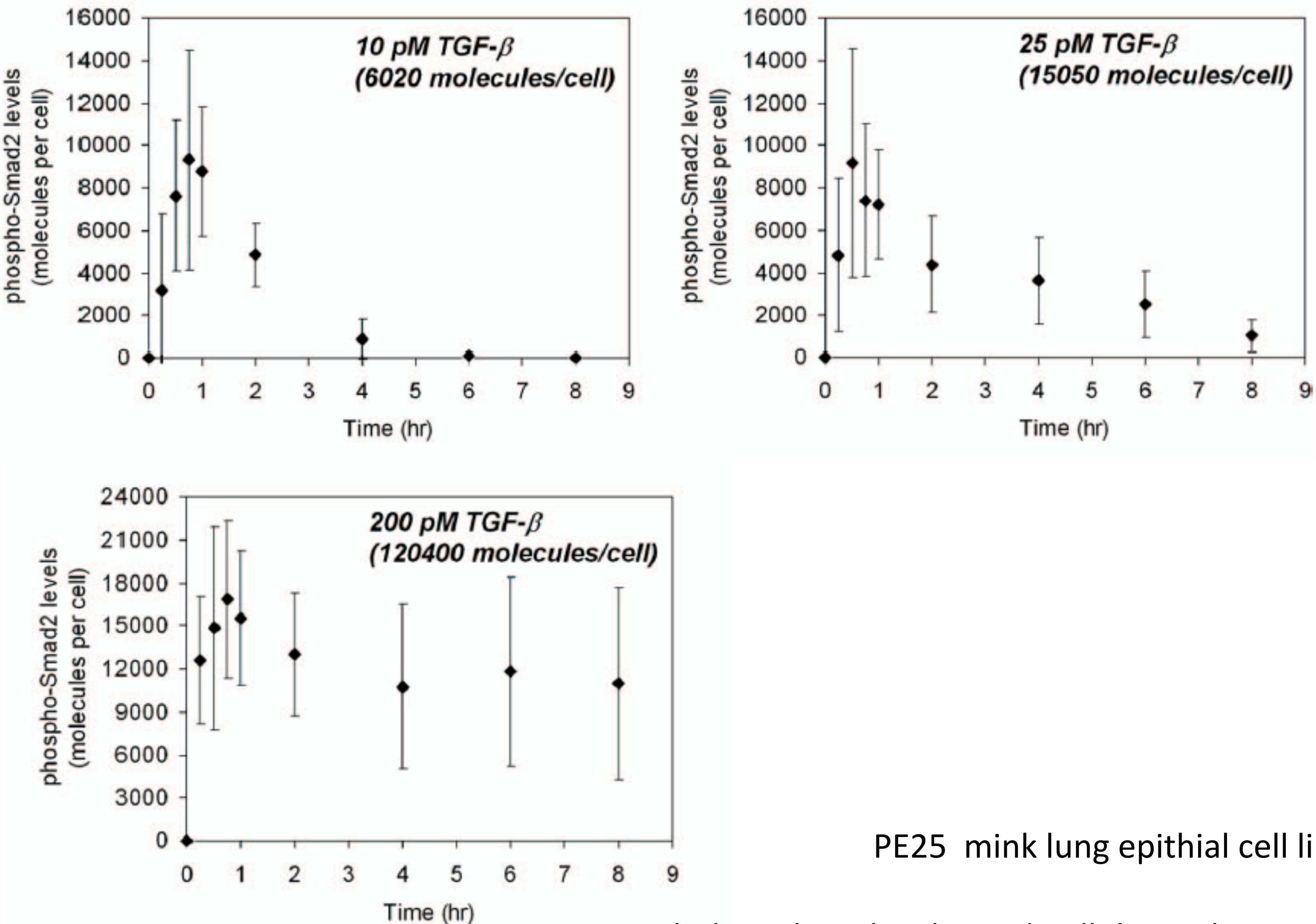
Immersed Interface Method

$$\nabla \cdot [-D_T \nabla T] = \int \left[\left(k_1^- TR - k_1^+ T \cdot R \right) \delta\{x(s) - x\} \right] ds$$

$$T^{out} - T^{in} = [T] = w(s)$$

$$D_{T,out} \frac{\partial T^{out}}{\partial n} - D_{T,in} \frac{\partial T^{in}}{\partial n} = \left[D \frac{\partial T}{\partial n} \right] = v(s)$$

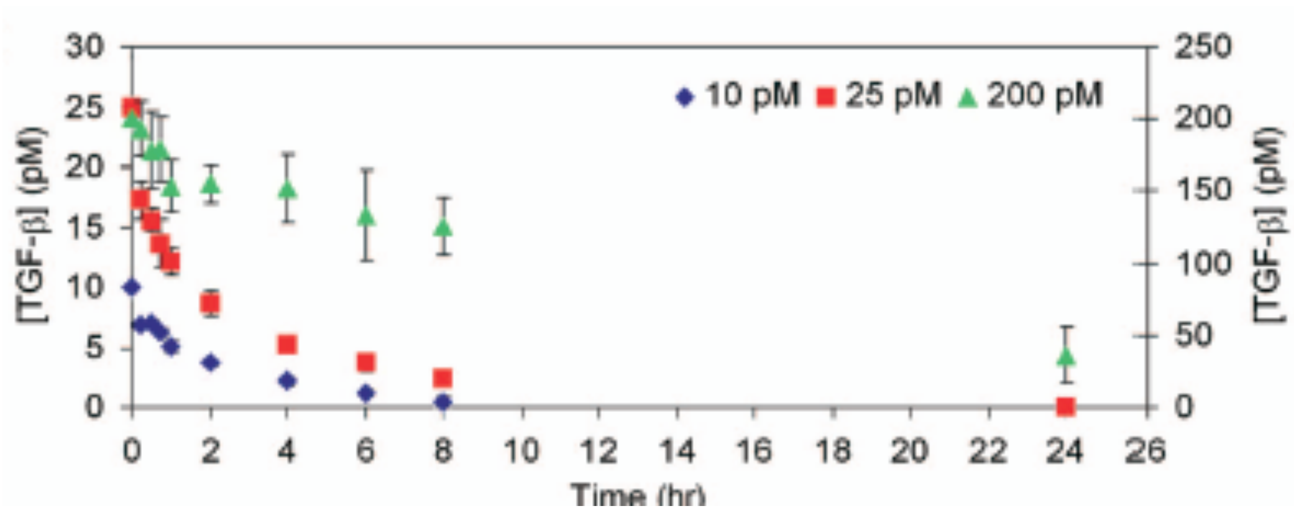
LI, Zhilin , A fast iterative algorithm for elliptic interface problems,
SIAM J. Num Anal, 1998



PE25 mink lung epithial cell line

Clark et al, Molecular and Cellular Biology, 2009

Comparison with experimental data



Clark et al, Molecular and Cellular Biology, 2009

Parameter	Description	Value	Refs
k_1^+	Association (TGF- β)	4.44 $nM^{-1}min^{-1}$	(Chung et al., 2009; Schmierer et al., 2008)
k_1^-	Dissociation (TGF- β)	2.4×10^{-1} min^{-1}	(Chung et al., 2009; Schmierer et al., 2008)
k_T^+	Association (Smad)	2.4×10^{-2} $nM^{-1}min^{-1}$	(Chung et al., 2009)
k_T^-	Dissociation (Smad)	3.96×10^{-1} min^{-1}	(Chung et al., 2009)
k_T^0	Phosphorylation (Smad)	2.4×10^{-1} min^{-1}	(Chung et al., 2009)
k_S	Dephosphorylation (Smad)	3.96×10^{-1} - 3.96×10^{1} min^{-1}	(Chung et al., 2009)
[illegible]	[illegible]	[illegible]	[illegible]

Cell Surface

$$\frac{dR}{dt} = k_1^- TR - k_1^+ T \cdot R + k_d TR$$

$$\frac{dTR}{dt} = k_1^+ T \cdot R - k_1^- TR + k_T^- TRS - k_T^+ TR \cdot S + k_T^0 TRS - k_d TR$$

$$\frac{dTRS}{dt} = k_T^+ TR \cdot S - k_T^- TRS - k_T^0 TRS$$

Cell Interior

$$\frac{dS}{dt} = k_T^- TRS - k_T^+ TR \cdot S + k_S S_P$$

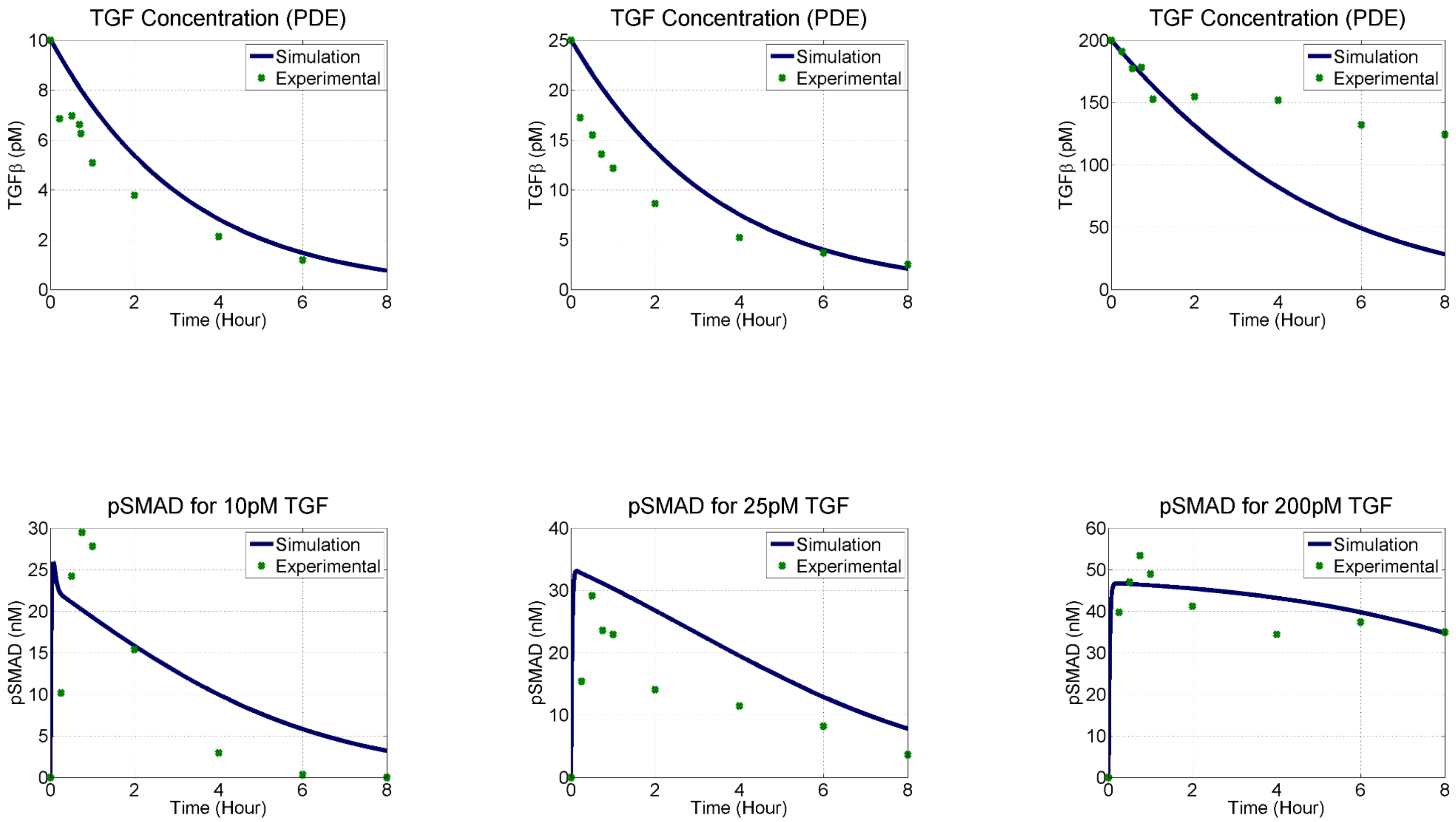
$$\frac{dS_P}{dt} = k_T^0 TRS - k_S S_P$$

$$\frac{dT^{in}}{dt} = \frac{r_1 S_P^2}{r_2^2 + S_P^2} - k_3 T^{in}$$

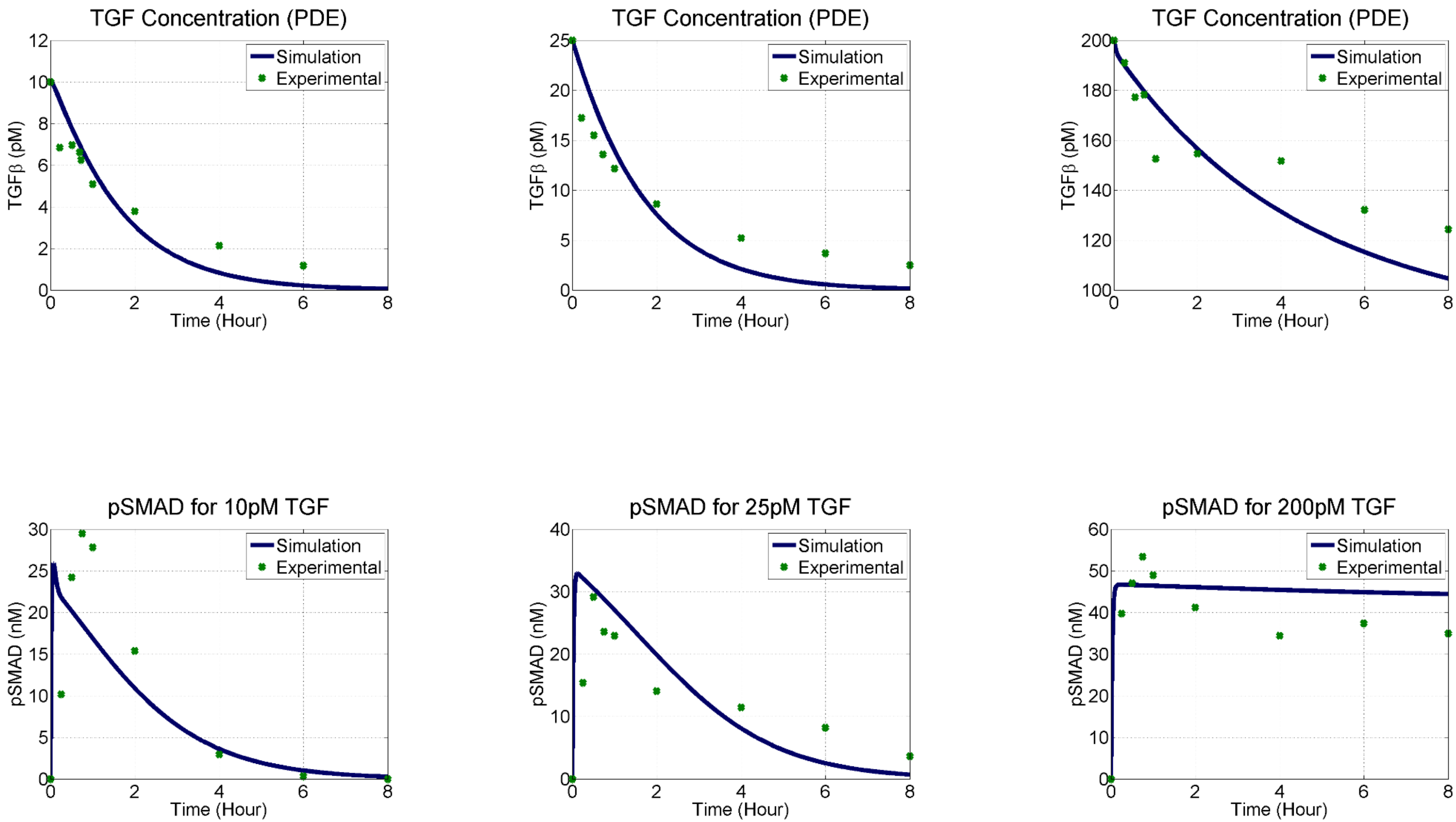
Exterior Domain

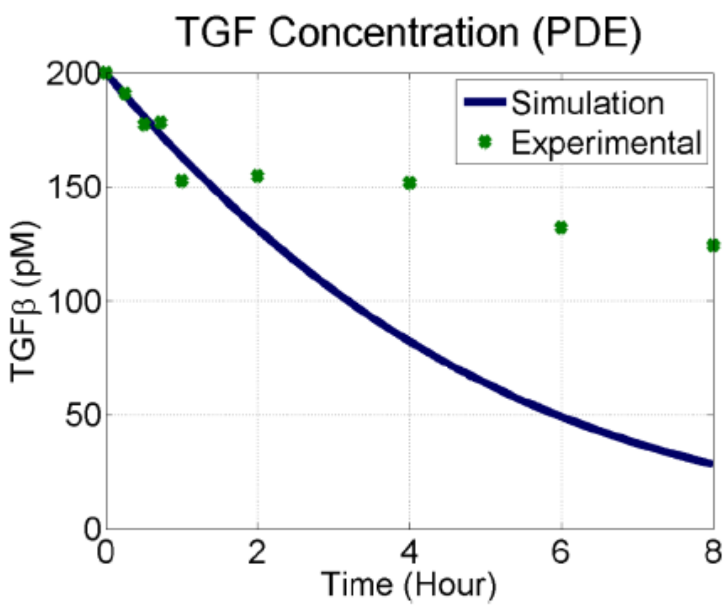
$$\nabla \cdot [-D_T \nabla T] = \int \left[\left(k_1^- TR - k_1^+ T \cdot R \right) \delta \{ x(s) - x \} \right] ds$$

No Internal TGF Production

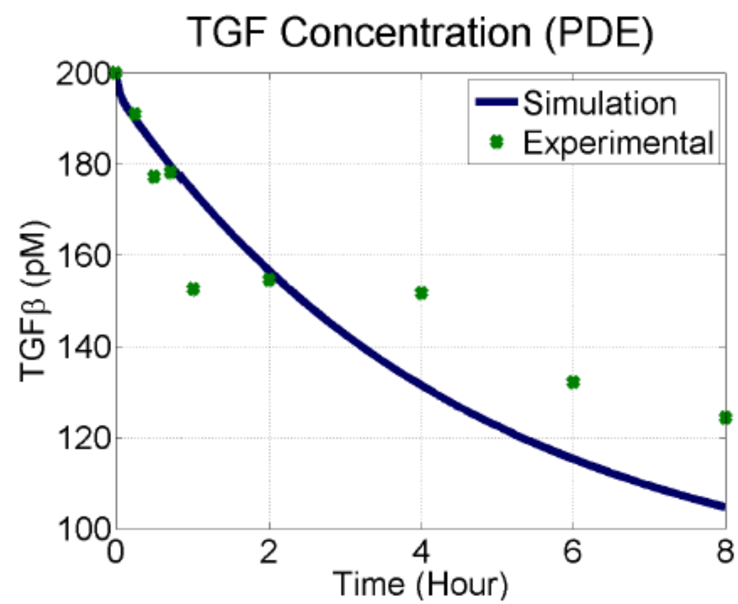


With Internal TGF Production



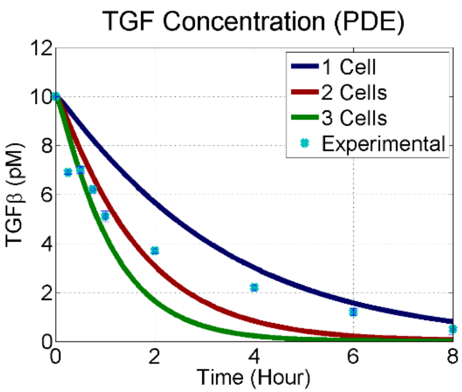


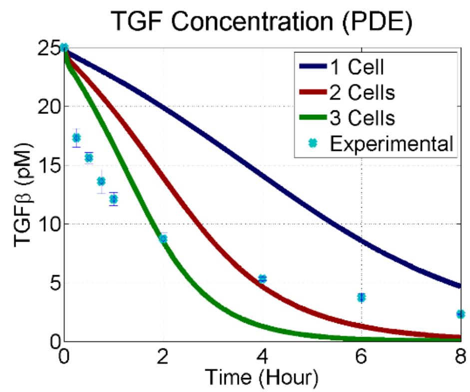
NO TGF Productiom

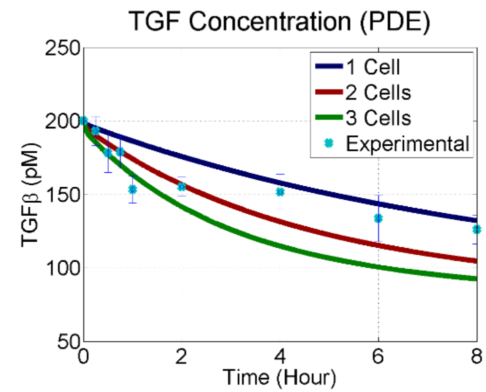


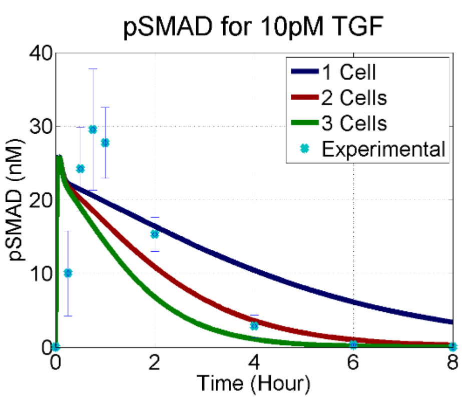
With cellular TGF production

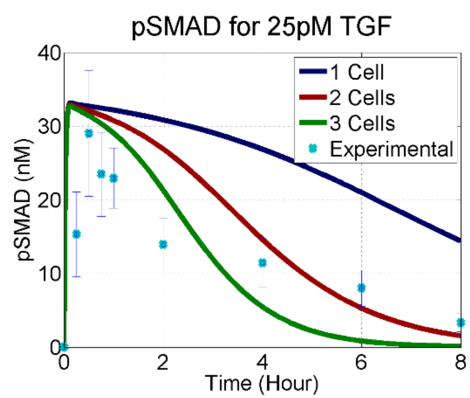
1-3 Cells With Internal TGF Production

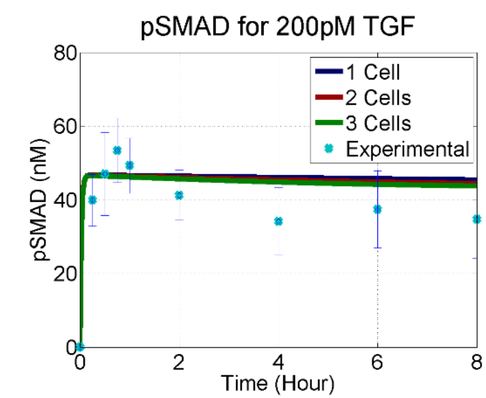










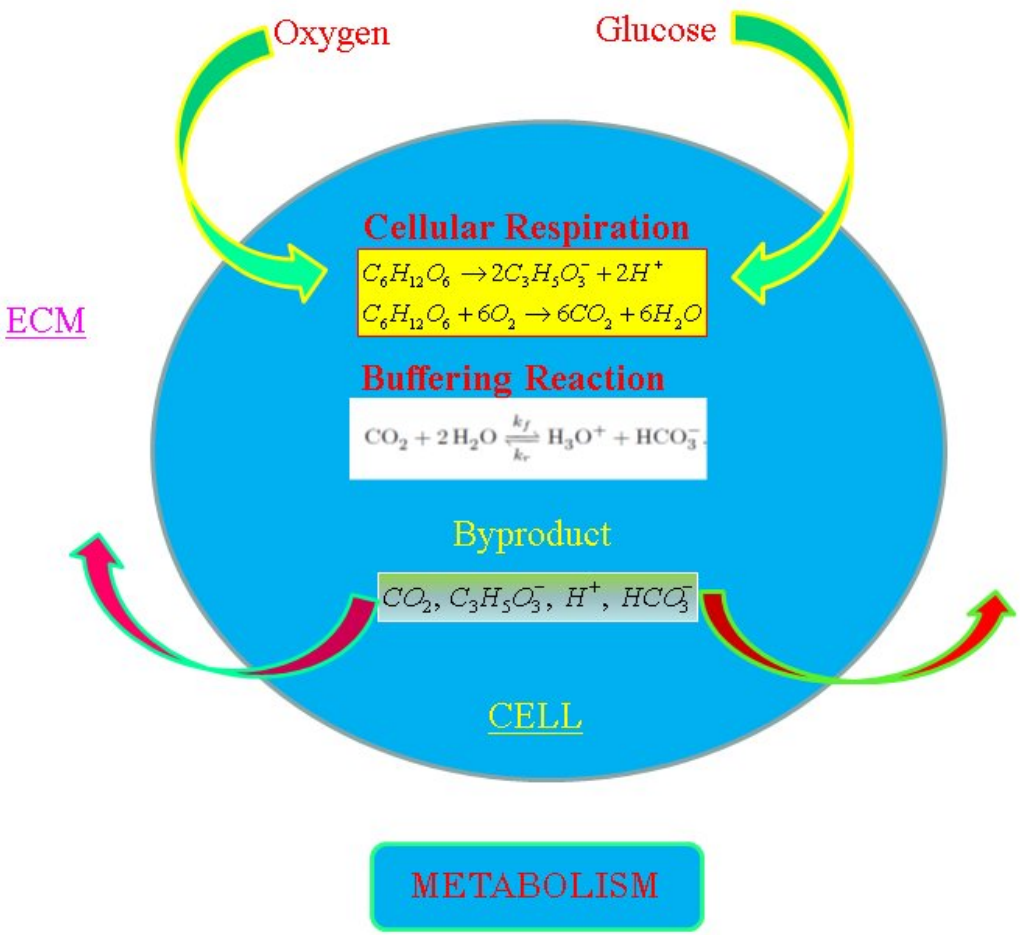


Glycolysis Model

Under normal oxygen levels glucose is converted to pyruvic acid and through the Krebs cycle to ATP

Under low oxygen levels the pyruvic acid ferments to lactic acid with a reduced level of ATP production

In what is known as the Warburg effect, tumor cells continue to convert glucose to ATP with enhanced lactate production even in the presence of normal oxygen levels. This results in an increased production of H+ , a lowering of the pH and increased acidity in the tumor environment.



Oxygen
Glucose
Cellular Respiration
$C_6H_{12}O_6 \rightarrow 2C_3H_5O_3^- + 2H^+$
$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$
ECM
Buffering Reaction
$CO_2 + 2H_2O \underset{k_r}{\overset{k_f}{\rightleftharpoons}} H_3O^+ + HCO_3^-$.
Byproduct
$CO_2, C_3H_5O_3^-, H^+, HCO_3^-$
CELL
METABOLISM

Kinetics of the Casciari model

$$\frac{dC_i}{dt} = P_i$$

$$P_O = -\rho_c\left[A_O + \frac{B_O}{C_g C_k^m}\right]\left[\frac{C_O}{C_O + k_{mO}}\right]$$

$$P_g = -\rho_c\left[A_g + \frac{B_g}{C_O}\right]\left[\frac{1}{C_k^n}\right]\left[\frac{C_g}{C_g + k_{mg}}\right]$$

$$P_c = -k_f C_c + k_r C_b C_h$$

$$P_h = k_f C_c - k_r C_b C_h - P_O + P_l$$

$$P_l = 2P_g + \frac{P_O}{3}$$

$$P_b = k_f C_c - k_r C_b C_h - P_O$$

$$P_{cl} = 0$$

$$P_s = 0$$

o, g, c, h, l, b, cl, s:
oxygen, glucose, CO2, hydrogen ion, lactate, bicarbonate, chloride, sodium

Casciari et al, Cell Proliferation, 1992

Nernst-Planck Equations for ions and chemicals

$$\frac{\partial C_i}{\partial t} + \nabla \cdot N_i = S_i$$

$$N_i = -D_i \nabla C_i + \omega_i z_i C_i E + C_i V$$

Electrical Potential

$$\nabla \cdot (\varepsilon_e \nabla \phi) = -\rho_e = -F \sum_i z_i C_i$$

Electric Field

$$E = -\nabla \phi$$

Inside Cells

$$\frac{dC_i}{dt} = P_i + Flux_i$$

Interface Conditions

$$[D_i \frac{\partial C_i}{\partial n}] = J_i$$

Nonionic Species

$$J_i = k_i (C_i^{out} - C_i^{in}),$$

Goldman-Hodgkin-Katz

$$J_i = -k_i \frac{z_i F}{RT} \Delta\phi \left[\frac{C_i^{in} - C_i^{out} \exp\left(-\frac{z_i F}{RT} \Delta\phi \right)}{1 - \exp\left(-\frac{z_i F}{RT} \Delta\phi \right)} \right]$$

$$\Delta\phi = \phi^{in} - \phi^{out} = \frac{RT}{F} \ln \left[\frac{\sum_{Cation} k_+ C_+^{out} + \sum_{Anion} k_- C_-^{in}}{\sum_{Cation} k_+ C_+^{in} + \sum_{Anion} k_- C_-^{out}} \right]$$

$$[C_i] = (C_i^{out} - C_i^{in})$$

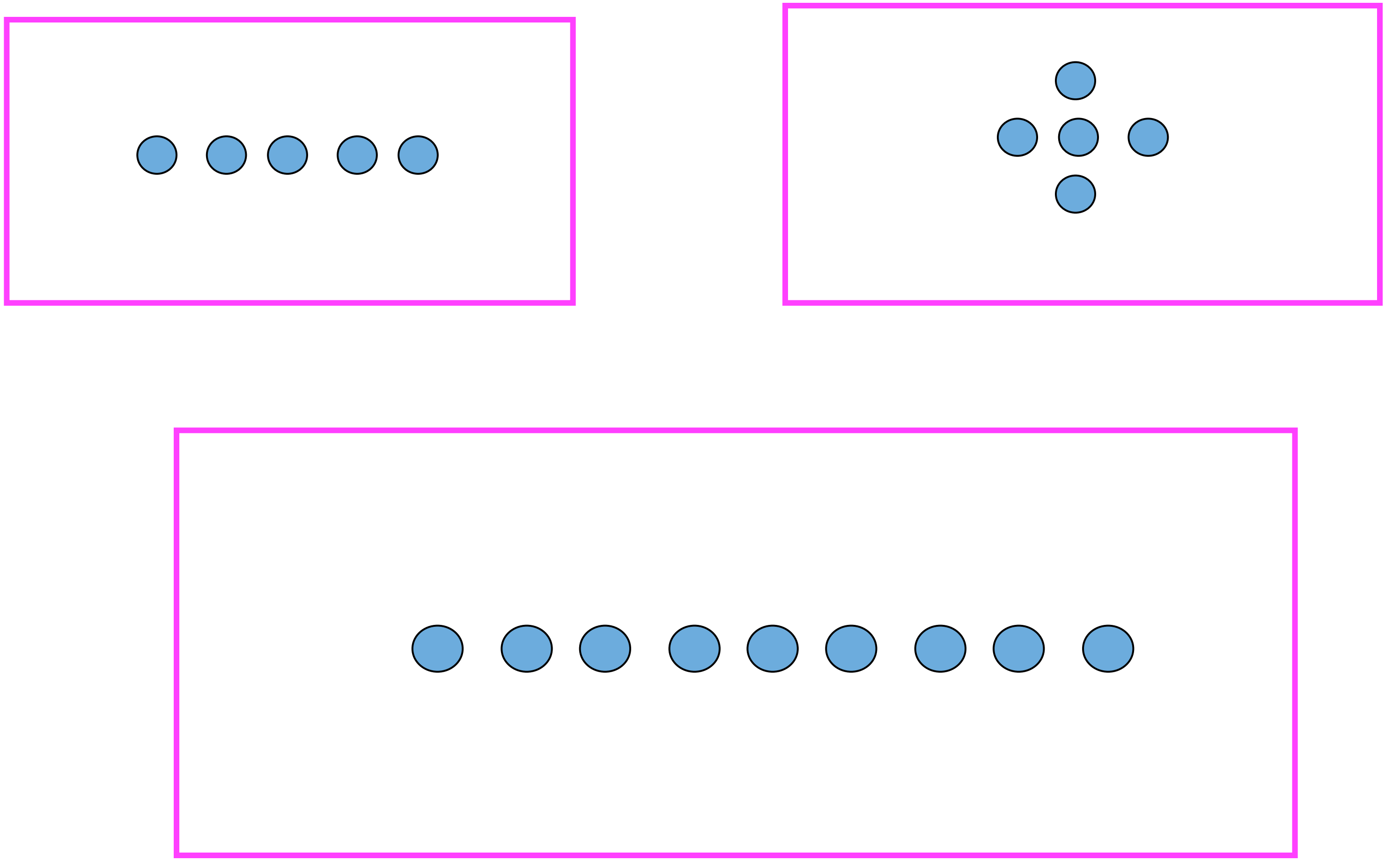
PDEs have the form: $\nabla \cdot \left(\beta(x) \nabla c(x) \right) = f(x)$

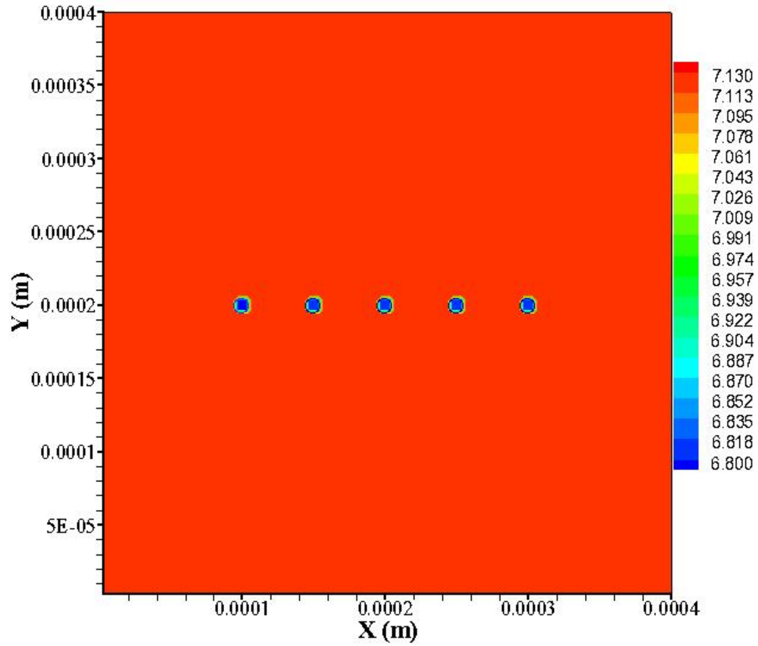
Can be solved with the immersed interface method * with an appropriate choice of interface jump conditions

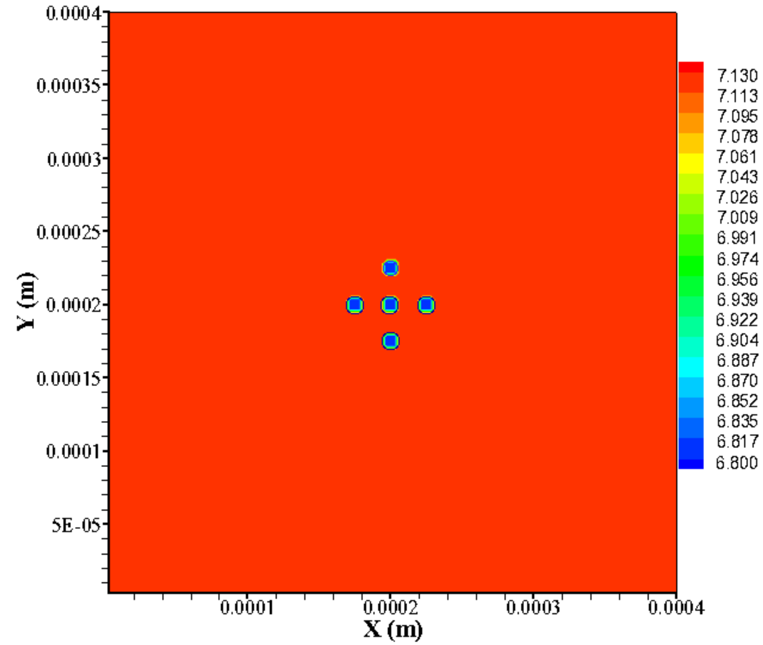
$$[c] = g(x) \qquad\qquad [\beta c_n] = h(x)$$

Note that with periodic boundary conditions the solution is not unique.
At each time step we add a constant chosen to enforce conservation of mass so that the net change in the ECM equals the net secretion from the cells.

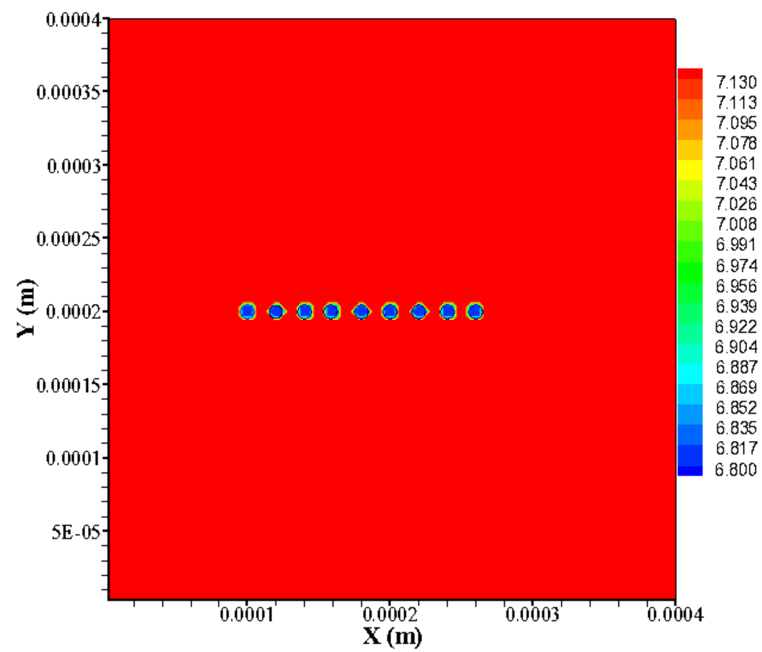
* Leveque and Li, SIAM J. Num Anal, 1994

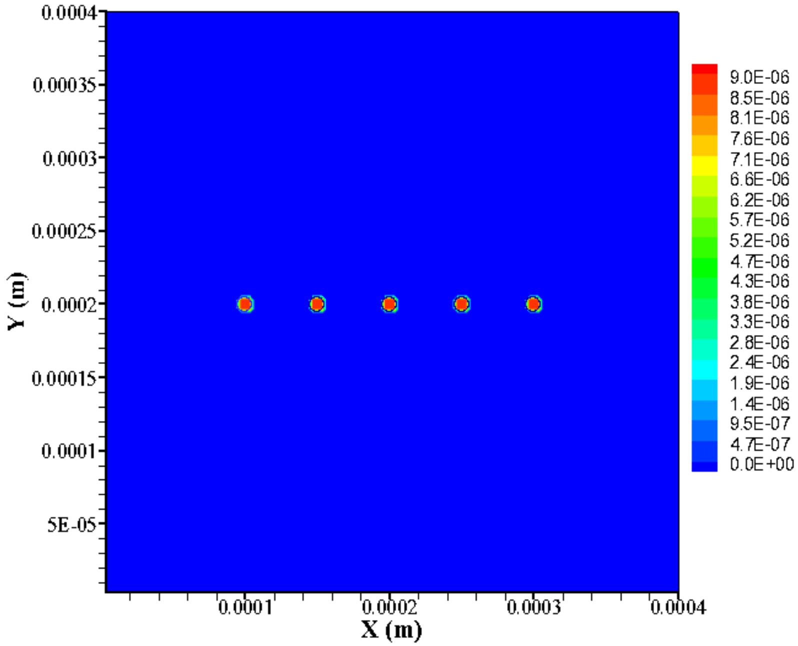


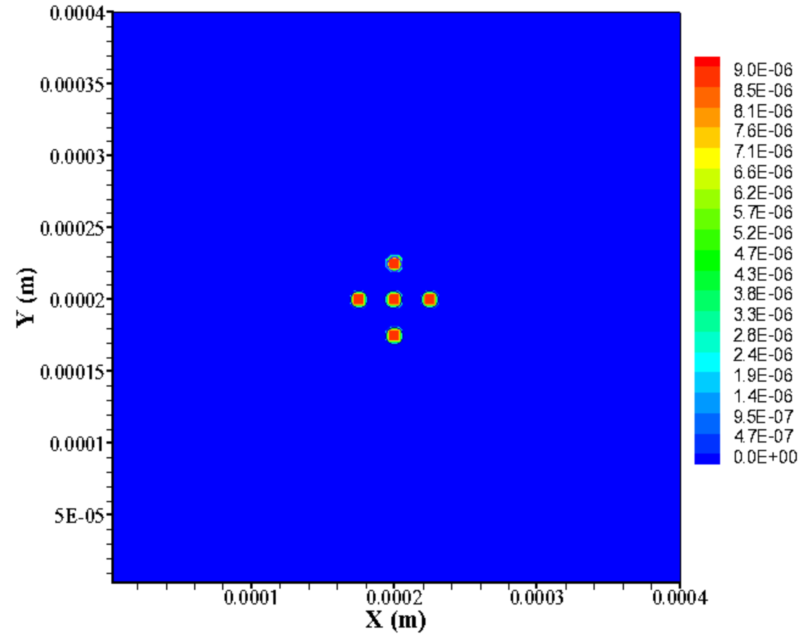




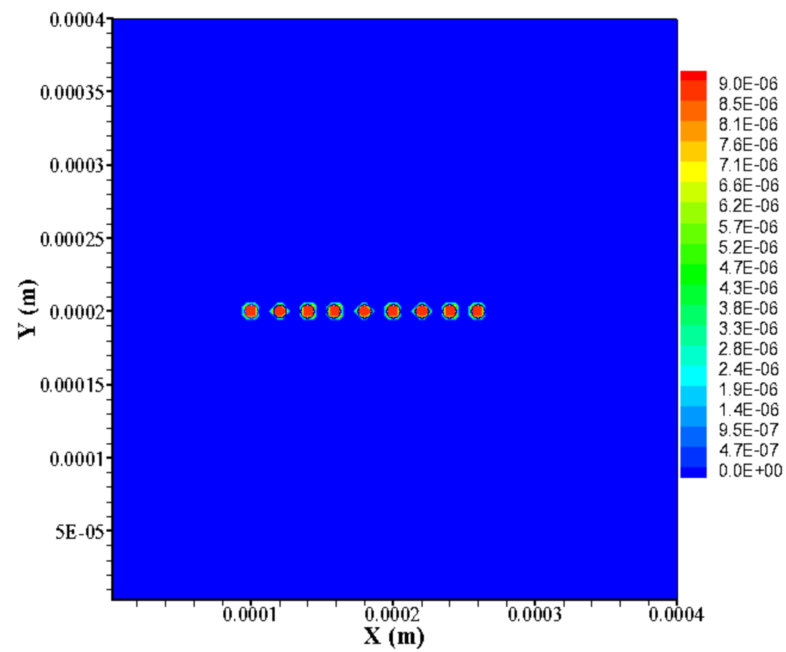
pH Variation

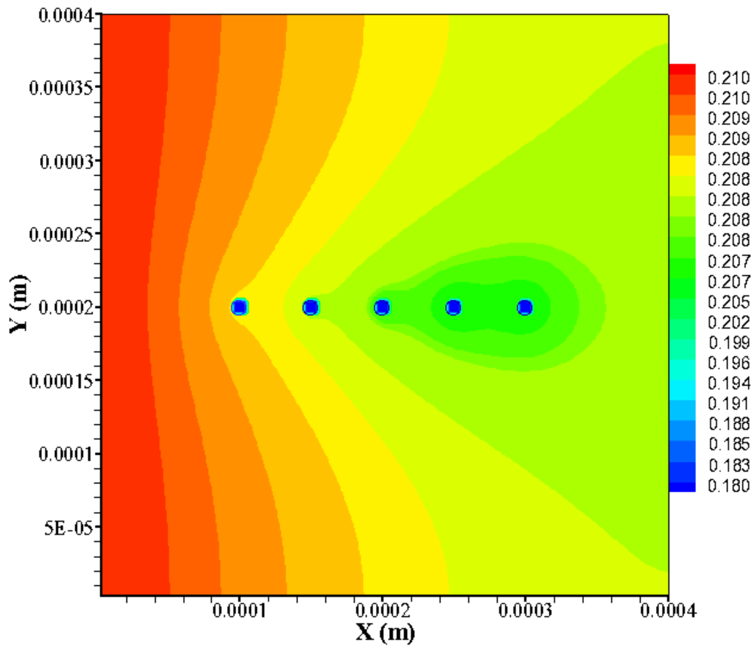


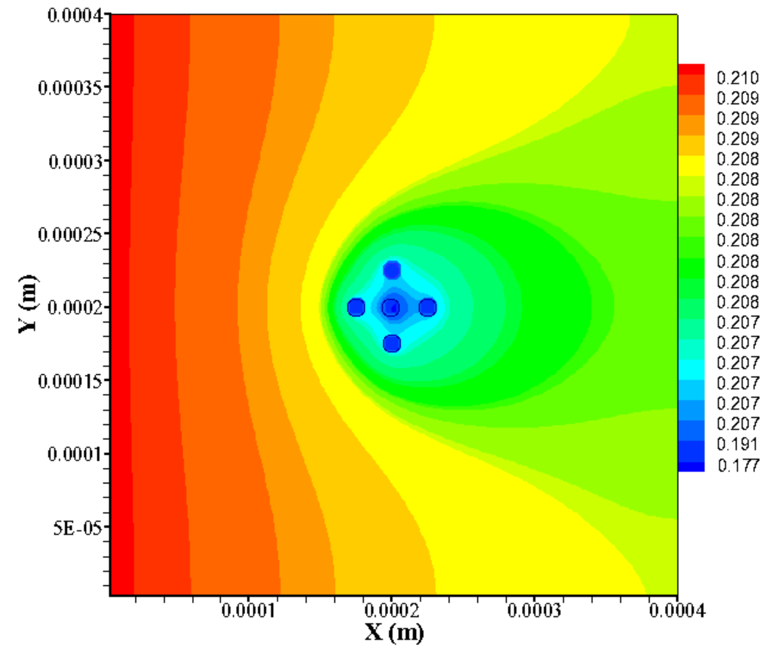




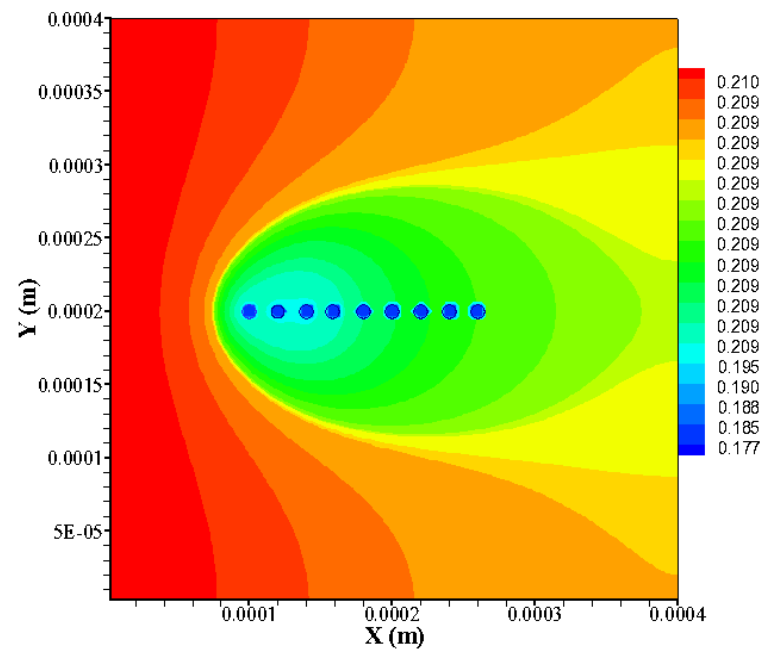
ϕ Variation

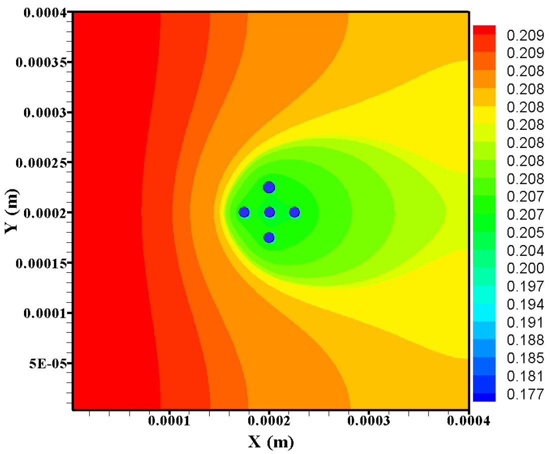




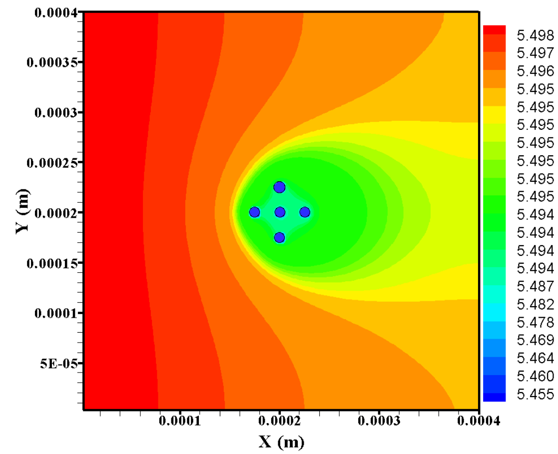


Oxygen Concentration

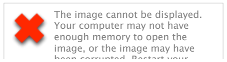


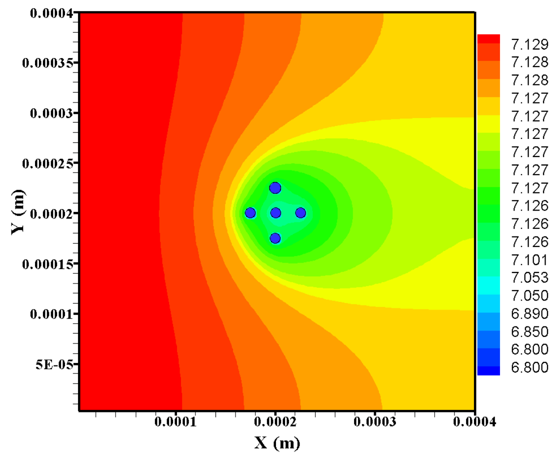


Oxygen



Glucose





CO2

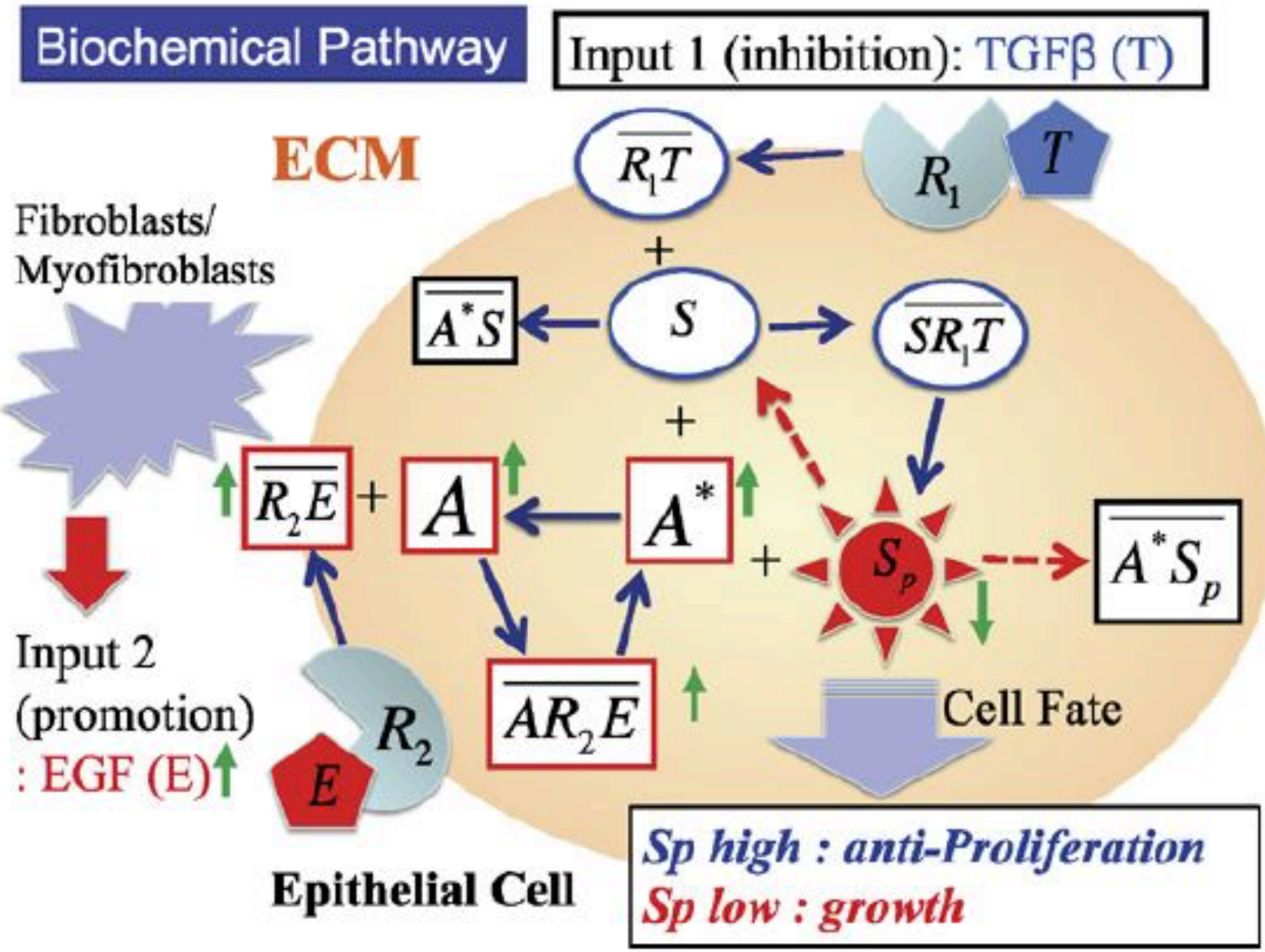
In progress and future work

Develop full multicellular models for both in vitro and microfluidic cell culture

Develop TGF-β models with SDF-1 and EGF cross talk

Develop a fluid/mechanical model of the ECM based on an IB Lagrangian mesh model (Dillon and Zhuo, 2011)

Longer timescale model for cell growth



Biochemical Pathway
Input 1 (inhibition): TGFβ (T)
ECM
$\overline{R_1T}$
R_1
T
Fibroblasts/
Myofibroblasts
+
$\overline{A^*S}$
S
$\overline{SR_1T}$
+
$\overline{R_2E}$
+
A
A^*
+
S_p
$\overline{A^*S_p}$
Input 2
(promotion)
: EGF (E)
R_2
E
$\overline{AR_2E}$
Cell Fate
Sp high : anti-Proliferation
Sp low : growth
Epithelial Cell

Glycolysis Kinetics

$dc_i/dt = P_i + Flux_i$

Component	Reaction term
Oxygen (a)	$P_a = -\Omega\left(A_a + \frac{B_a}{C_b C_g^m}\right)\left(\frac{C_a}{C_a + K_{ma}}\right)$
Gluocose (b)	$P_b = -\Omega\left(A_b + \frac{B_b}{C_a}\right)\left(\frac{1}{C_g^n}\right)\left(\frac{C_b}{C_b + K_{mb}}\right)$
Lactate ion (c)	$P_c = -(2P_b - P_a/3)$
Carbon dioxide (d)	$P_d = -k_f C_d + k_r C_e C_g$
Bicarbonate (e)	$P_e = k_f C_d - k_r C_e C_g - P_a$
Chloride (f)	$P_f = 0$
Hydrogen ion (g)	$P_g = k_f C_d - k_r C_e C_g - P_a + P_c$

Casciari et al, *Cell Prolif*, 1992

Interface Conditions for Concentration

Uncharged Species

$$[c_i] = c_i^{out} - c_i^{in}$$

$$[D_i \frac{\partial c_i}{\partial n}] = D_i^{out} \frac{\partial c_i^{out}}{\partial n} - D_i^{in} \frac{\partial c_i^{in}}{\partial n} = k_i (c_i^{out} - c_i^{in}) = J_i$$

$$k_i = mass\ transfer\ coeffiecient$$

Interface Conditions for Concentration

Charged Species

$$[c_i] = c_i^{out} - c_i^{in}$$

$$[D_i \frac{\partial c_i}{\partial n}] = D_i^{out} \frac{\partial c_i^{out}}{\partial n} - D_i^{in} \frac{\partial c_i^{in}}{\partial n} = J_i$$

$$J_i = -k_i \frac{z_i F}{RT} \Delta\phi \left[\frac{c_i^{in} - c_i^{out} \exp\left(-\frac{z_i F}{RT} \Delta\phi \right)}{1 - \exp\left(-\frac{z_i F}{RT} \Delta\phi \right)} \right]$$

$$\Delta\phi = \phi^{in} - \phi^{out} = \frac{RT}{F} \ln \left[\frac{\sum_{cation} k_+ c_+^{out} + \sum_{anion} k_- c_-^{in}}{\sum_{cation} k_+ c_+^{in} + \sum_{anion} k_- c_-^{out}} \right]$$

Interface Conditions for Concentration

Charged Species

$$[c_i] = c_i^{out} - c_i^{in}$$

$$[D_i \frac{\partial c_i}{\partial n}] = D_i^{out} \frac{\partial c_i^{out}}{\partial n} - D_i^{in} \frac{\partial c_i^{in}}{\partial n} = J_i$$

$$J_i = -k_i \frac{z_i F}{RT} \Delta\phi \left[\frac{c_i^{in} - c_i^{out} \exp\left(-\frac{z_i F}{RT}\Delta\phi\right)}{1 - \exp\left(-\frac{z_i F}{RT}\Delta\phi\right)} \right]$$

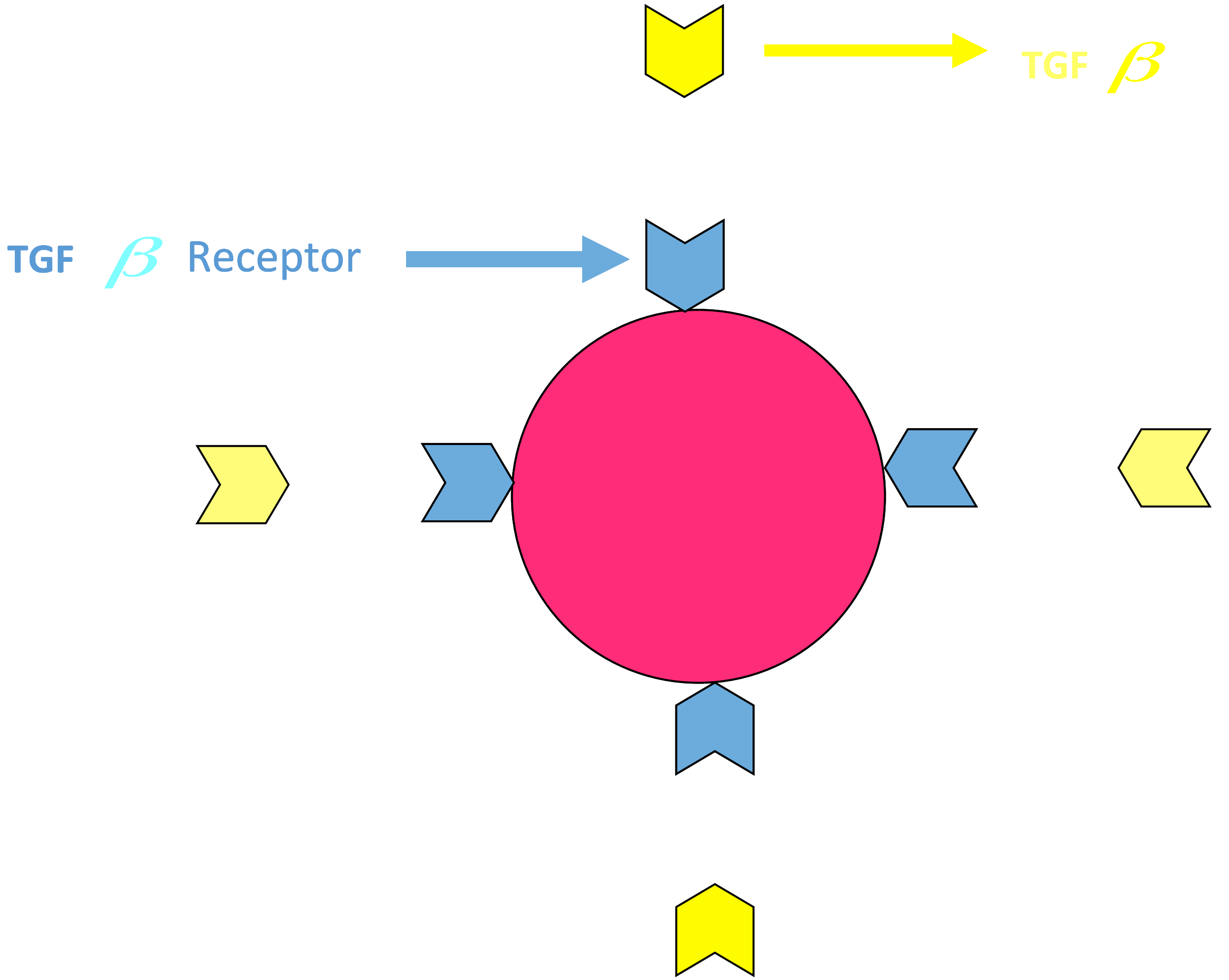
$$\Delta\phi = \phi^{in} - \phi^{out} = \frac{RT}{F} \ln \left[\frac{\sum_{cation} k_+ c_+^{out} + \sum_{anion} k_- c_-^{in}}{\sum_{cation} k_+ c_+^{in} + \sum_{anion} k_- c_-^{out}} \right]$$

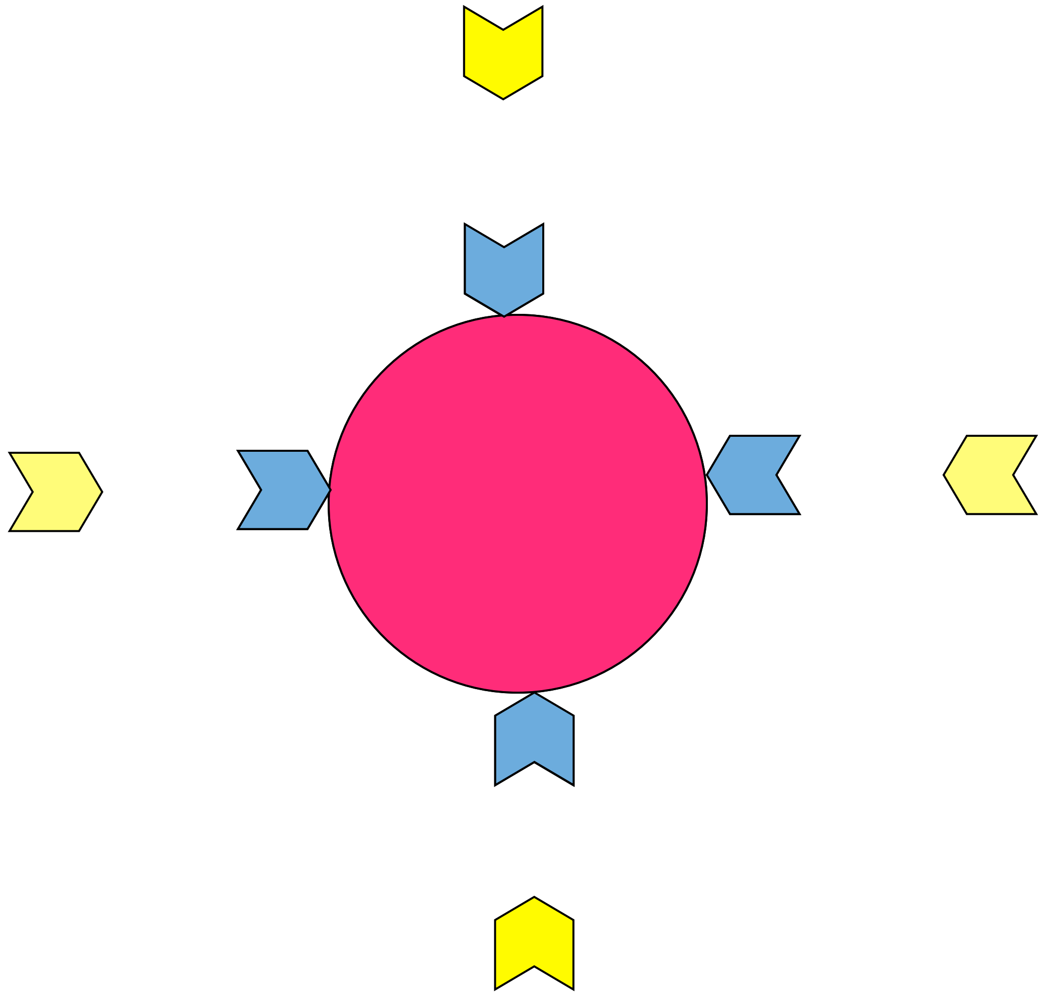
Interface Conditions for Potential

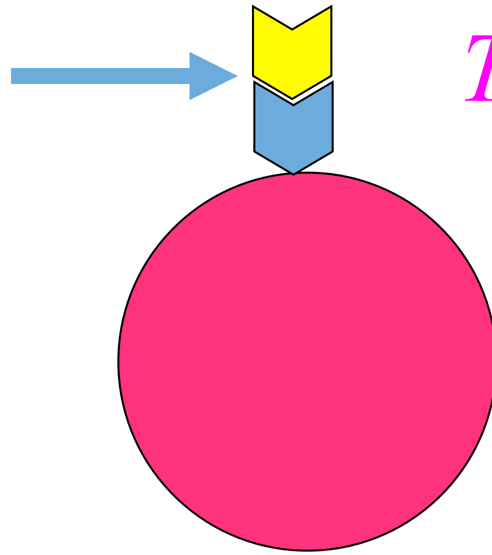
$$\left[\varepsilon_e \frac{\partial \phi}{\partial n}\right] = \varepsilon_e^{out} \frac{\partial \phi^{out}}{\partial n} - \varepsilon_e^{in} \frac{\partial \phi^{in}}{\partial n} = 0$$

$$[\phi] = \phi^{out} - \phi^{in} = -\Delta\phi = -\frac{RT}{F} \ln \left[\frac{\sum_{cation} k_+ c_+^{out} + \sum_{anion} k_- c_-^{in}}{\sum_{cation} k_+ c_+^{in} + \sum_{anion} k_- c_-^{out}} \right]$$

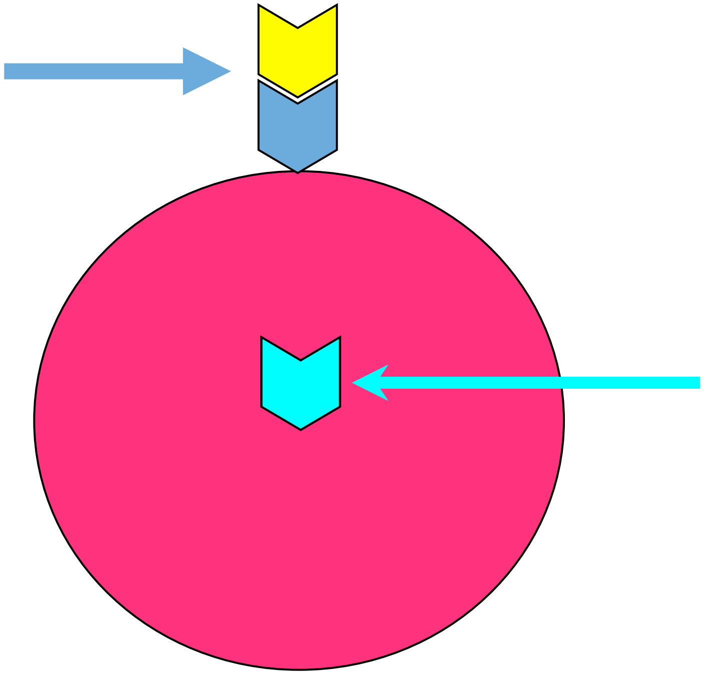
S. G. Shultz, Basic Principles of Membrane Transport, 1980

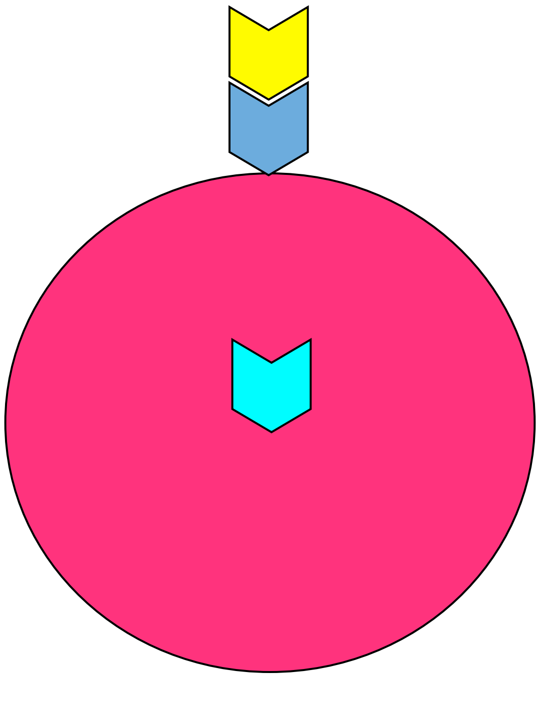

TGF β
TGF β Receptor



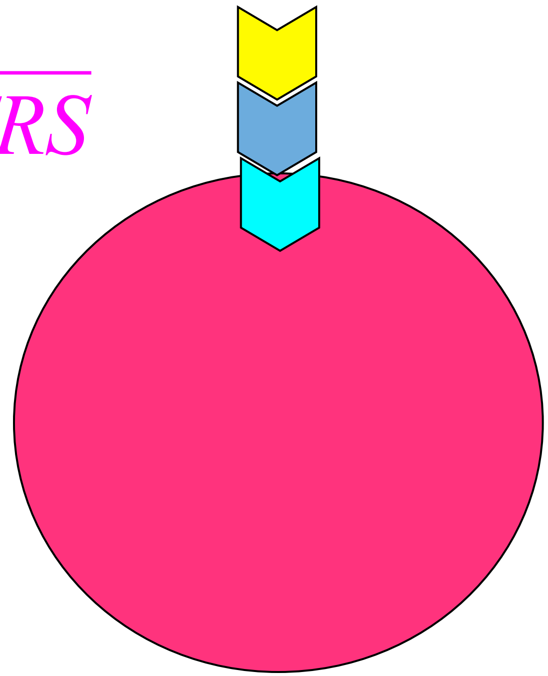


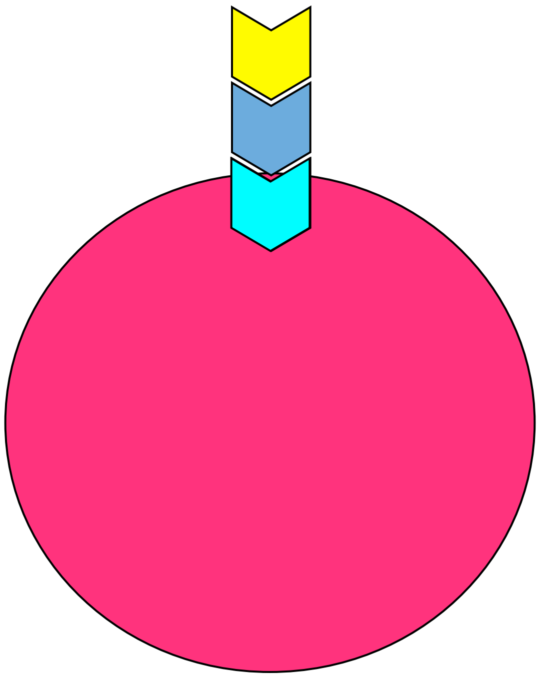
$T + R$ É $\overline{TR}$



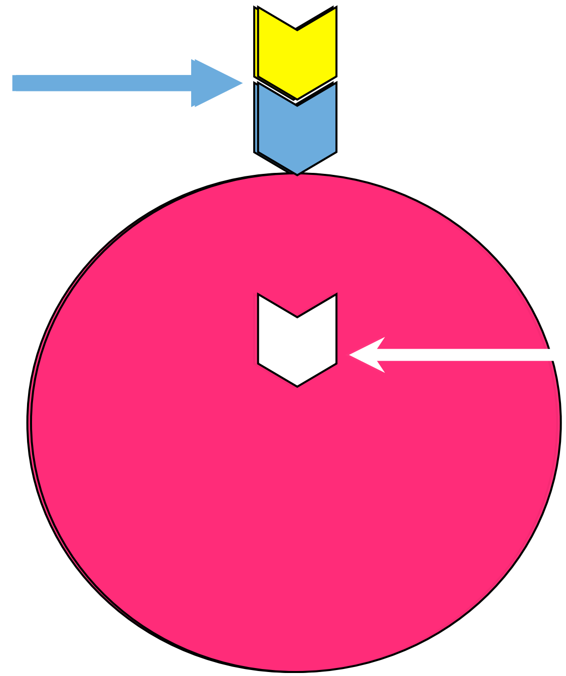


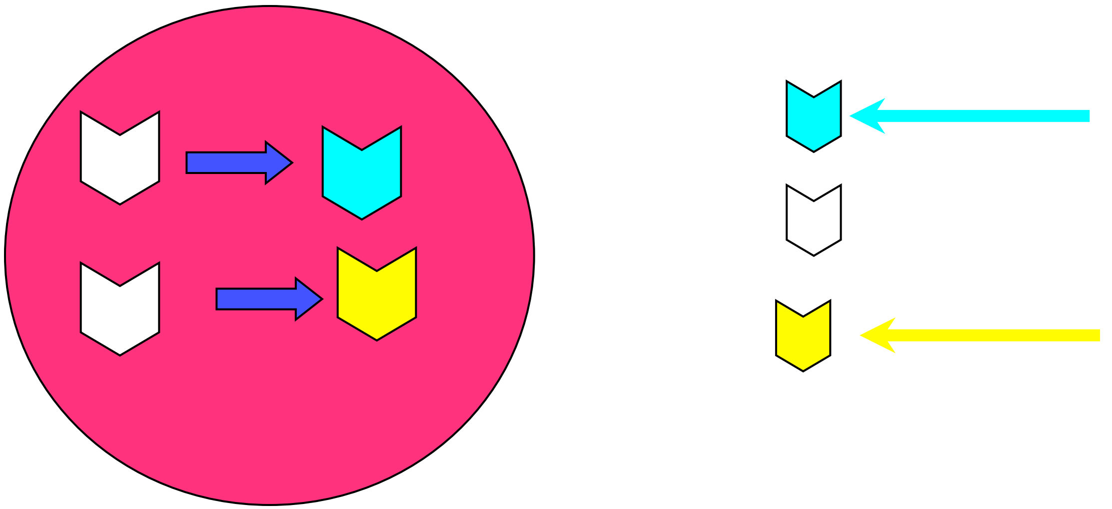
$\overline{TR} + S$ É $\overline{TRS}$





$$\overline{TRS} \rightarrow \overline{TR} + S_p$$





$$S_p \to S$$

$$S_p \to T$$

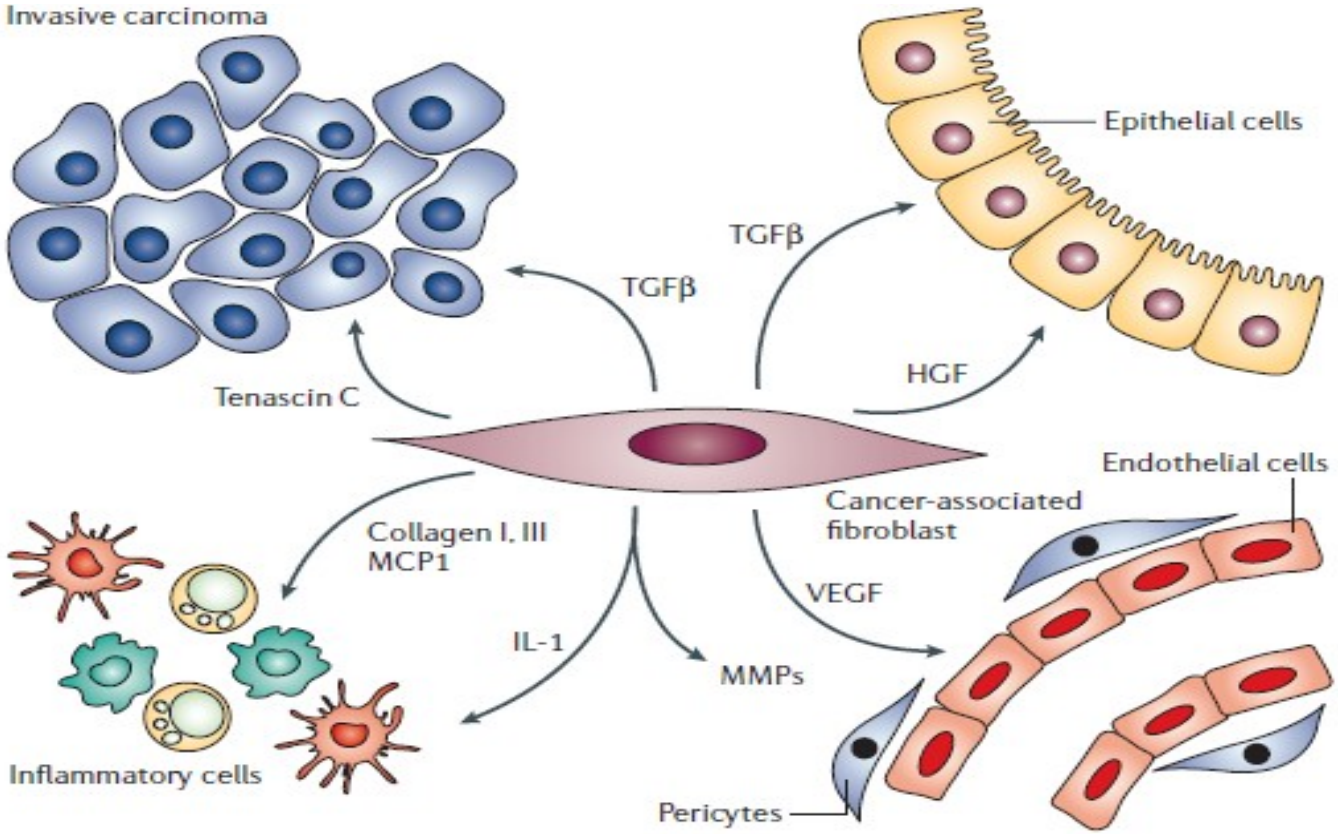
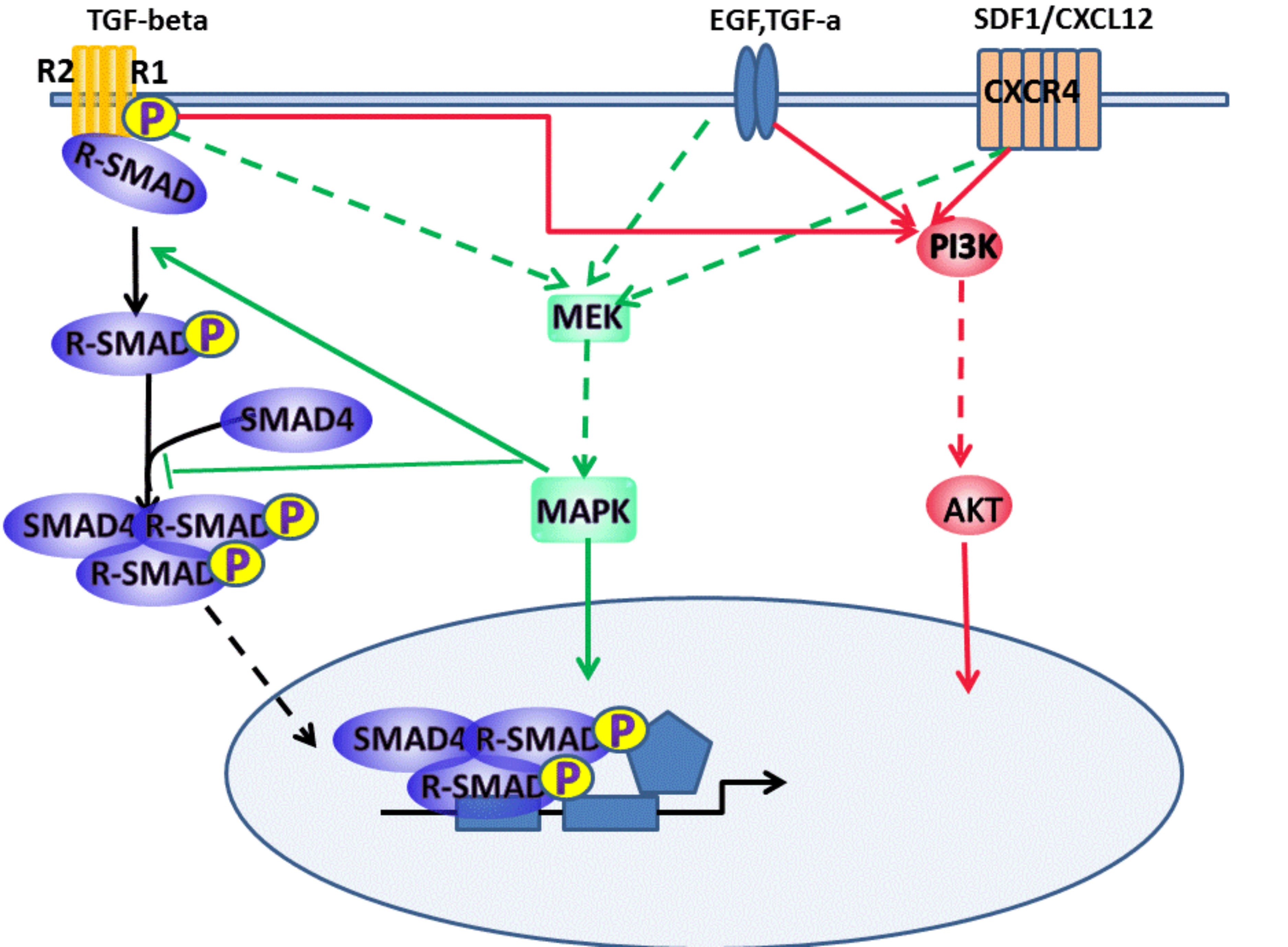
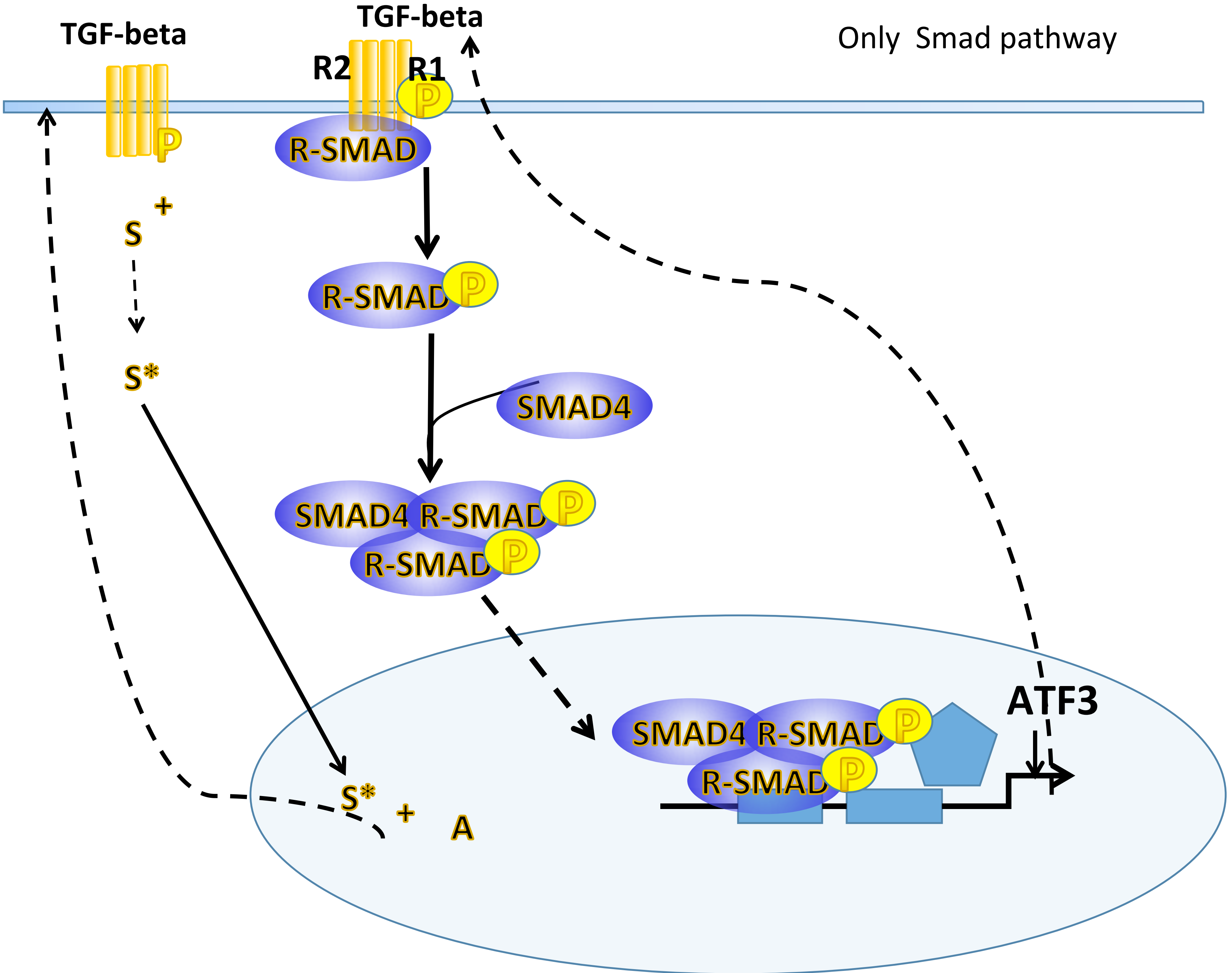


Figure 3 | **Functions of activated fibroblasts in the tumour stroma.** Fibroblasts communicate with cancer cells, resident epithelial cells, endothelial cells, pericytes and inflammatory cells through the secretion of growth factors and chemokines. Through the increased deposition of collagen types I and III and *de novo* expression of tenascin C they induce an altered extracellular-matrix microenvironment, which potentially provides additional oncogenic signals, probably leading to accelerated cancer progression. Fibroblasts mediate the inflammatory response by secreting chemokines such as monocyte chemotactic protein 1 (MCP1) and interleukins such as IL-1. Fibroblasts interact with the microvasculature by secreting matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF). Fibroblasts also provide potentially oncogenic signals such as transforming growth factor-β (TGFβ) and hepatocyte growth factor (HGF) to resident epithelia, and directly stimulate cancer-cell proliferation and invasion by secreting growth factors such as TGFβ and stromal-cell-derived factor 1 (SDF1).

Raghu Kalluri‡§ and Michael Zeisberg* 2006*


TGF-beta
R2
R1
P
R-SMAD
EGF,TGF-a
SDF1/CXCL12
CXCR4
PI3K
MEK
R-SMAD
P
SMAD4
MAPK
AKT
SMAD4
R-SMAD
P
R-SMAD
P
SMAD4
R-SMAD
P
R-SMAD
P


TGF-beta
TGF-beta
Only Smad pathway
R2
R1
P
P
R-SMAD
S
+
S*
R-SMAD
P
SMAD4
SMAD4
R-SMAD
P
R-SMAD
P
SMAD4
R-SMAD
P
R-SMAD
P
ATF3
S*
+
A

Nernst-Planck Equations

$$\vec{J}^{\,i} = -D^i \nabla C^i - \omega^i z^i C^i \nabla \psi + C^i \vec{u}$$

$$\frac{\partial C^i}{\partial t} = -\nabla \cdot \vec{J}^{\,i} + P^i$$

$$\nabla \cdot \left(\varepsilon \varepsilon_0 \nabla \psi \right) = -\rho_e = -F \sum_{i=1}^{N} z^i C^i$$

$$\frac{dR}{dt} = k_1^- \overline{TR} - k_1^+ T \cdot R$$

$$\frac{d\overline{TR}}{dt} = k_1^+ T \cdot R - k_1^- \overline{TR} + k_T^- \overline{TRS} - k_T^+ \overline{TR} \cdot S + k_T^0 \overline{TRS}$$

$$\frac{d\overline{TRS}}{dt} = k_T^+ \overline{TR} \cdot S - k_T^- \overline{TRS} - k_T^0 \overline{TRS}$$

$$\frac{dS}{dt} = k_T^- \overline{TRS} - k_T^+ \overline{TR} \cdot S + k_s S_p$$

$$\frac{dS_p}{dt} = k_T^0 \overline{TRS} - k_s S_p$$

$$\frac{dT}{dt} = k_1^- \overline{TR} - k_1^+ T \cdot R + \frac{r_1 S_p^n}{r_2^n + S_p^n}$$

Mathematical Modeling and Computational Methods for the Tumor Microenvironment

WSU Math/Bio Seminar
February 23, 2016

Robert Dillon
Department of Mathematics
Washington State University
Pullman, WA
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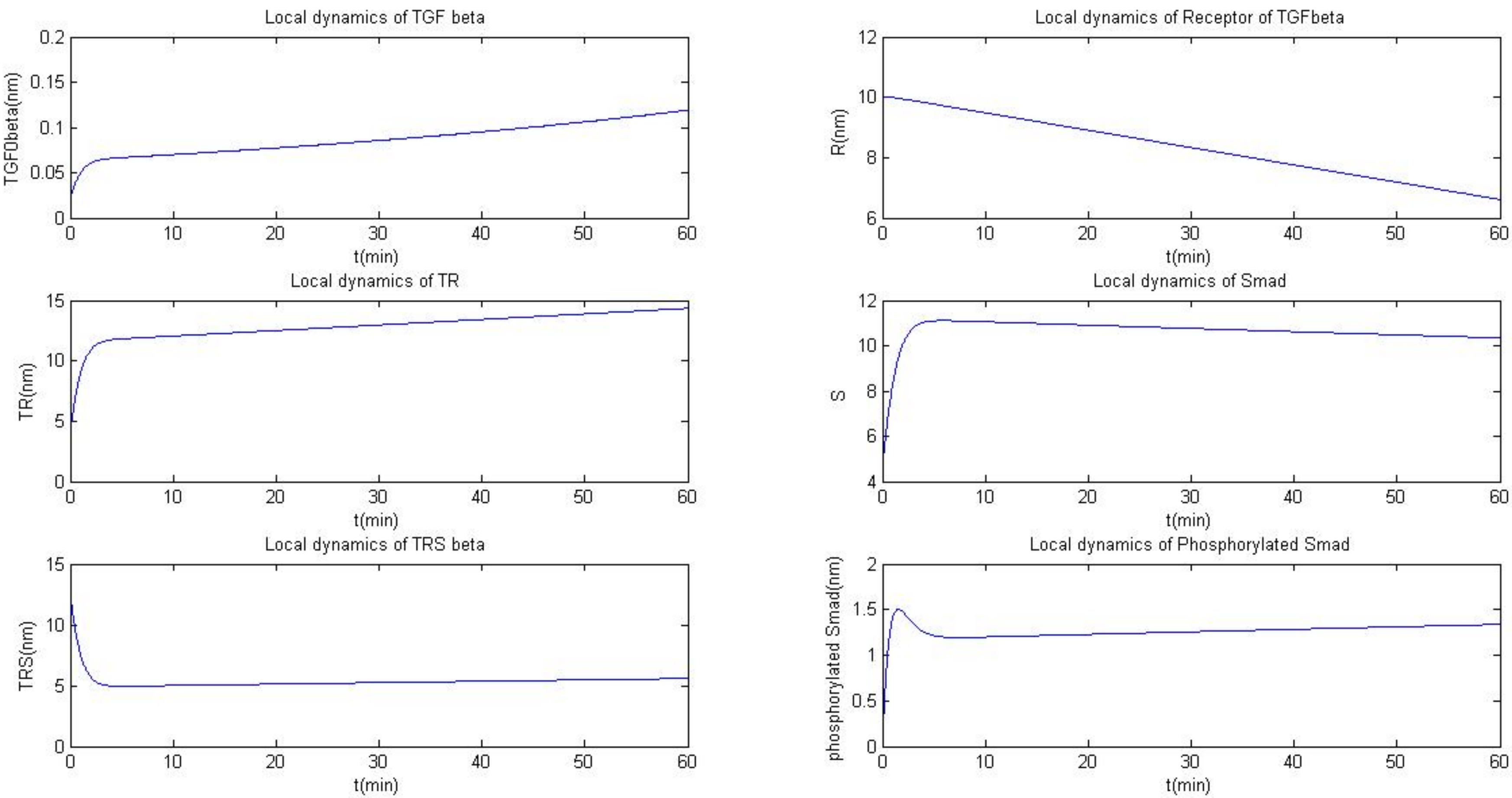
r1 = 0.06, r2=0.035,n=1



Model Equations

$$\frac{dR}{dt} = k_1^- TR - k_1^+ T \cdot R + k_d TR$$

$$\frac{dTR}{dt} = k_1^+ T \cdot R - k_1^- TR + k_T^- TRS - k_T^+ TR \cdot S + k_T^0 TRS - k_d TR$$

$$\frac{dTRS}{dt} = k_T^+ TR \cdot S - k_T^- TRS - k_T^0 TRS$$

$$\frac{dS}{dt} = k_T^- TRS - k_T^+ TR \cdot S + k_S S_P$$

$$\frac{dS_P}{dt} = k_T^0 TRS - k_S S_P$$

$$\frac{dT^{in}}{dt} = \frac{r_1 S_P^2}{r_2^2 + S_P^2} - k_3 T^{in}$$

$$\nabla \cdot [-D_T \nabla T] = \int \left[\left(k_1^- TR - k_1^+ T \cdot R \right) \delta \{ x(s) - x \} \right] ds - \gamma_3 T$$

Extracellular Domain

MMP

$$\nabla \cdot [-D\nabla M^{o}] = \int S_2\, \delta(x(s)-s)\, ds - \gamma_1 M^{o}$$

MMP Secretion

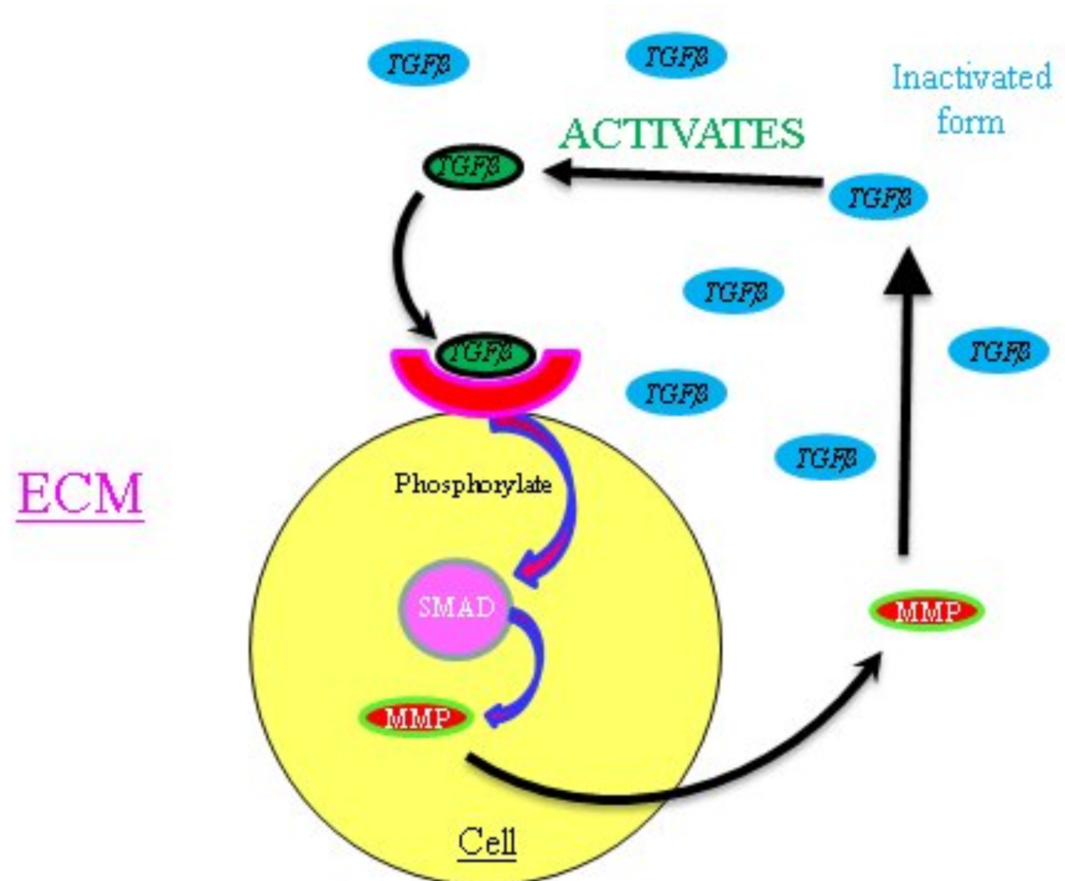
$$AS_1 = LS_2$$

Activated TGF-β

$$\nabla \cdot [-D\nabla T^{a}] = \int (k_1^- \overline{TR} - k_1^+ T^{a} \cdot R)\, \delta(x(s)-s)\, ds + \gamma_2 T^{i} M^{o} - \gamma_3 T^{a}$$

TGF-β Autocrine Signaling Without MMP

$$\nabla \cdot [-D\nabla T^{a}] = \int (S_2 + (k_1^- \overline{TR} - k_1^+ T^{a} \cdot R))\, \delta(x(s)-s)\, ds - \gamma_3 T^{a}$$



MMP (matrix metalloproteinase) SMAD (intracellular protein)

$$T + R \underset{k_1^+}{\overset{k_1^-}{\rightleftharpoons}} \overline{TR}$$

$$\overline{TR} + S \underset{k_T^+}{\overset{k_T-}{\rightleftharpoons}} \overline{TRS} \overset{k_T^0}{\rightarrow} \overline{TR} + S_p$$

$$S_p \overset{r_1}{\rightarrow} T$$

$$S_p \overset{k_s}{\rightarrow} S$$

variable	symbol
TGF-β	T
TGF-β receptor	R
Unphosphorylated Smad	S
PhosphorylatedSmad	S_p

Ligand Binding: $T + R \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} \overline{TR}$

Smad Reaction: $\overline{TR} + S \underset{k_T^-}{\overset{k_T^+}{\rightleftharpoons}} \overline{TRS}$

Phosphorylation of Smad: $\overline{TRS} \xrightarrow{k_T^0} \overline{TR} + S_P$

Reversion of phosphorylated Smad: $S_P \xrightarrow{k_S} S$

$$\frac{dR}{dt} = k_1^- \overline{TR} - k_1^+ T \cdot R + R_{prod} - k_d R$$

$$\frac{d\overline{TR}}{dt} = k_1^+ T \cdot R - k_1^- \overline{TR} + k_T^- \overline{TRS} - k_T^+ \overline{TR} \cdot S + k_T^0 \overline{TRS} - k_d \overline{TR}$$

$$\frac{d\overline{TRS}}{dt} = k_T^+ \overline{TR} \cdot S - k_T^- \overline{TRS} - k_T^0 \overline{TRS} - k_d \overline{TRS}$$

Cell Surface

$$\frac{dR}{dt} = k_1^- \overline{TR} - k_1^+ T \cdot R$$

$$\frac{d\overline{TR}}{dt} = k_1^- \overline{TR} - k_1^+ T \cdot R + k_T^- \overline{TRS} - k_T^+ \overline{TR} \cdot S + k_T^0 \overline{TRS}$$

$$\frac{d\overline{TRS}}{dt} = k_T^+ \overline{TR} \cdot S - k_T^- \overline{TRS} - k_T^0 \overline{TRS}$$

Cell Interior

$$\frac{dS}{dt} = k_T^- \overline{TRS} - k_T^+ \overline{TR} \cdot S + k_s S_P$$

$$\frac{dS_P}{dt} = k_T^0 \overline{TRS} - k_s S_P$$

$$\frac{dM^i}{dt} = \frac{r_1 S_p^2}{r_2^2 + S_p^2} - S_1$$

MMP Secretion

$$S_1 = \mathrm{k}\,\mathrm{M}^i$$

Extracellular Domain

MMP

$$\nabla \cdot [-D\nabla M^{o}] = \int S_2 \, \delta(x(s)-s)\, ds - \gamma_1 M^{o}$$

MMP Secretion

$$AS_1 = LS_2$$

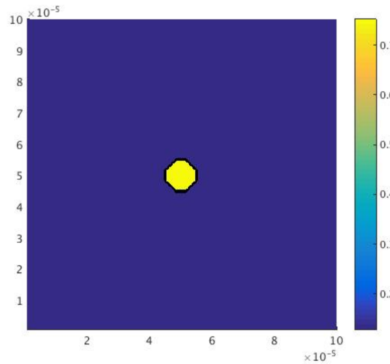
Activated TGF-β

$$\nabla \cdot [-D\nabla T^{a}] = \int (k_1^{-}\,\overline{TR} - k_1^{+} T^{a} \cdot R)\, \delta(x(s)-s)\, ds + \gamma_2 T^{i} M^{o} - \gamma_3 T^{a}$$

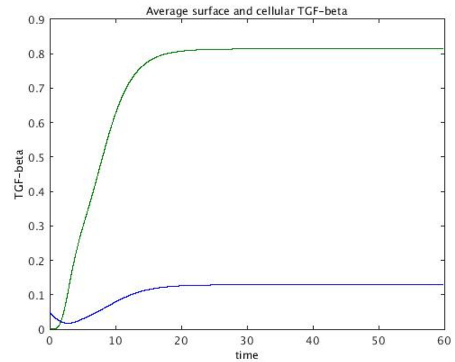
TGF-β Autocrine Signaling Without MMP

$$\nabla \cdot [-D\nabla T^{a}] = \int (S_2 + (k_1^{-}\,\overline{TR} - k_1^{+} T^{a} \cdot R))\, \delta(x(s)-s)\, ds - \gamma_3 T^{a}$$

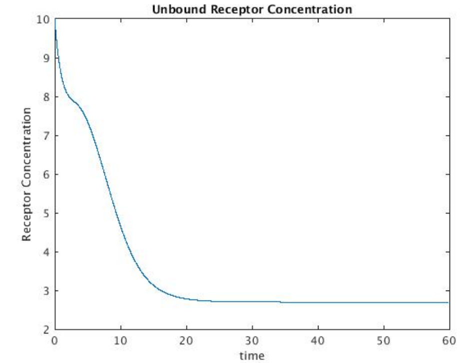
TGF-β Autocrine Signaling (periodic boundary conditions)



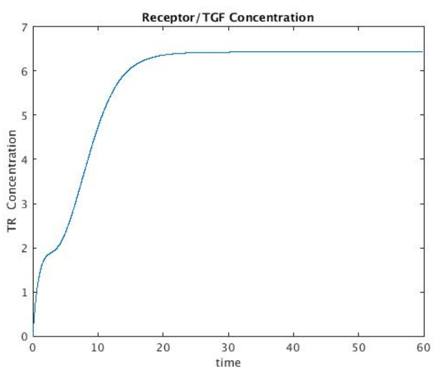
TGF



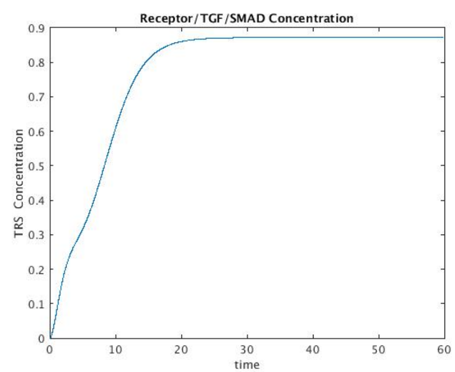
TGF



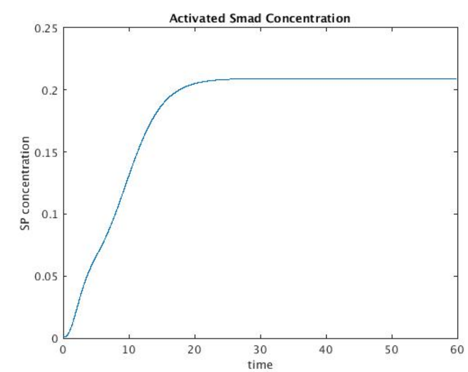
Free Receptors



TR complex

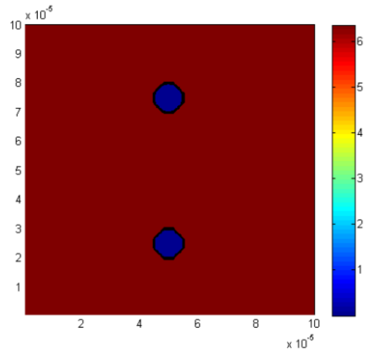


TRS complex

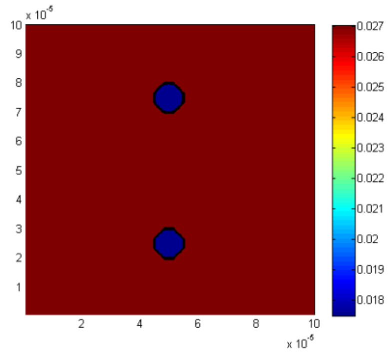


Activated Smad

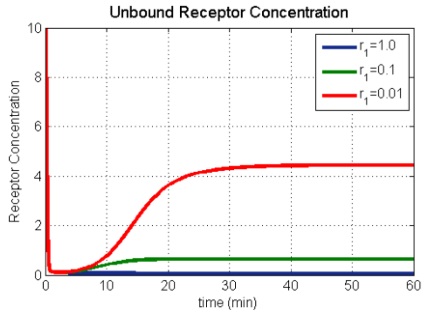
TGF-MMP Autocrine Signaling



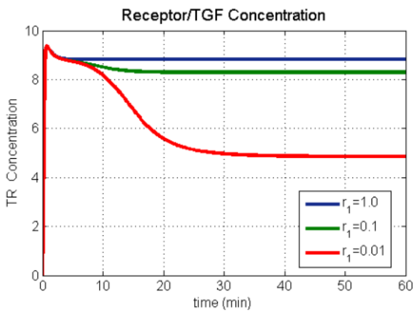
TGF



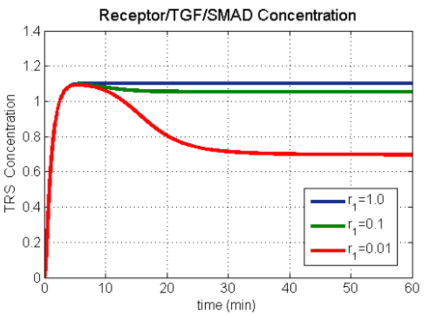
MMP



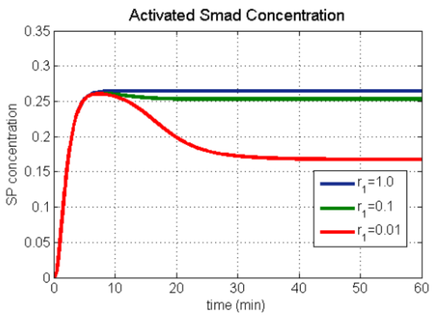
Free Receptors



TR complex

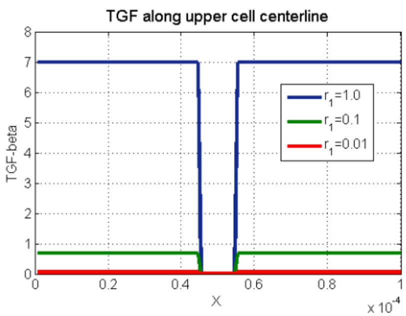


TRS complex

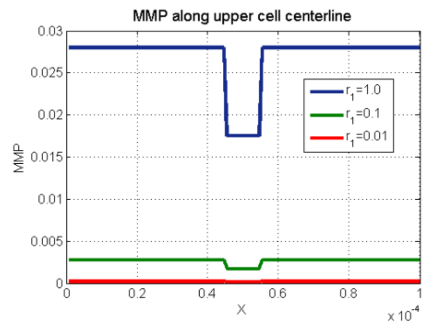


Activated Smad

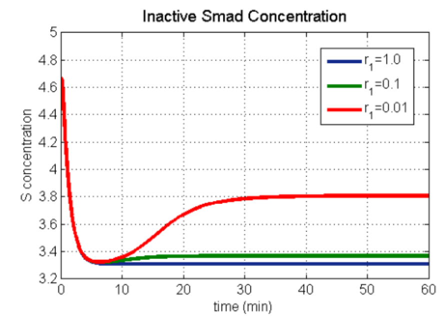
TGF-beta Autocrine Signaling



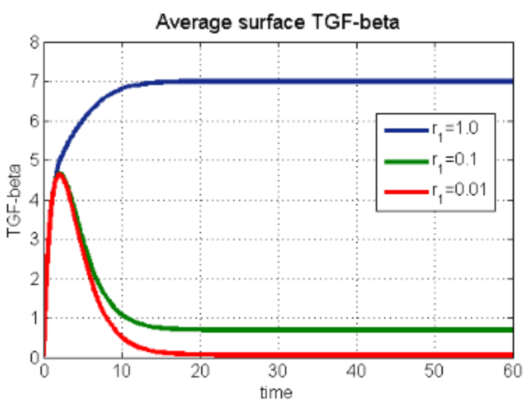
TGF-Line



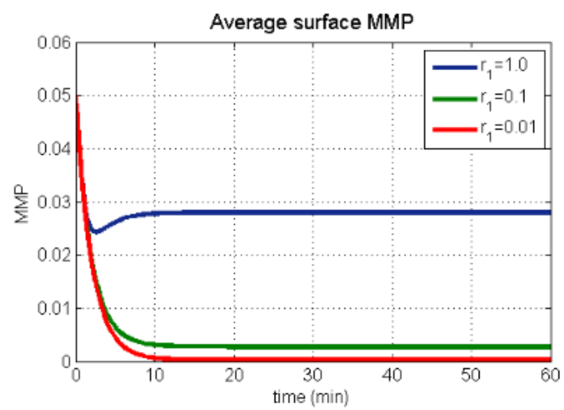
MMP-Line



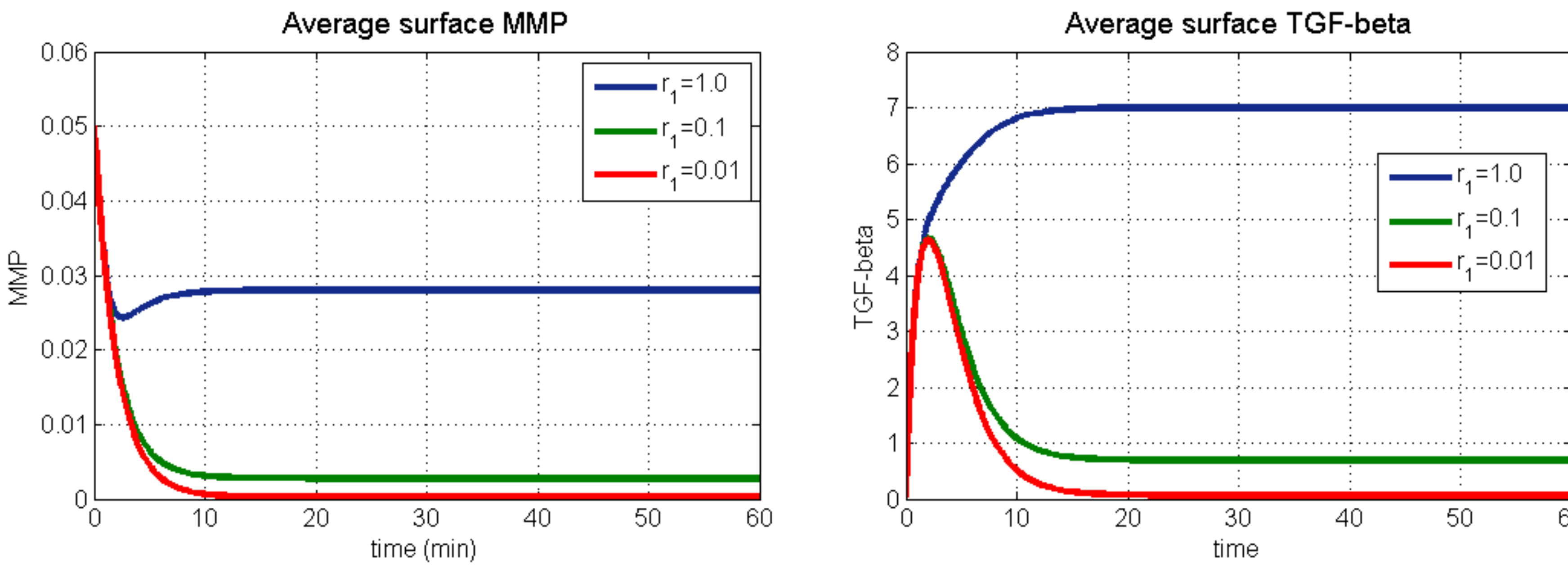
Smad

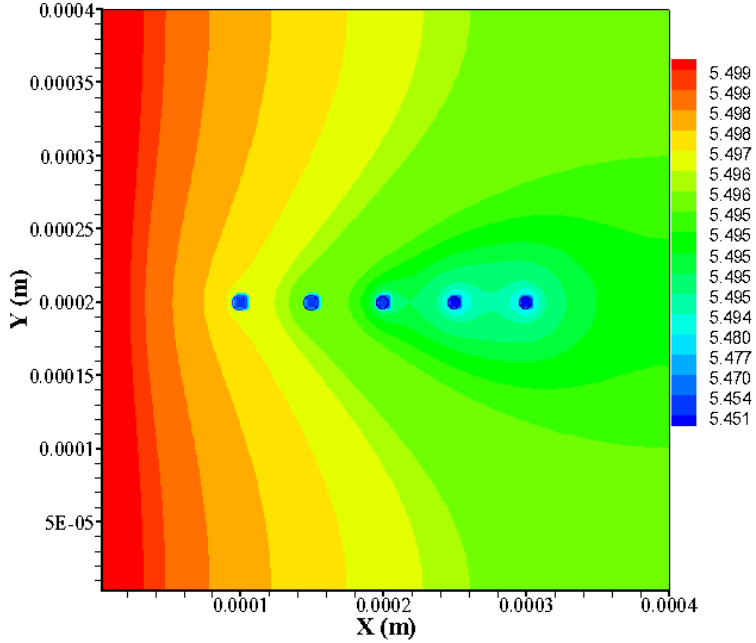


Surface TGF

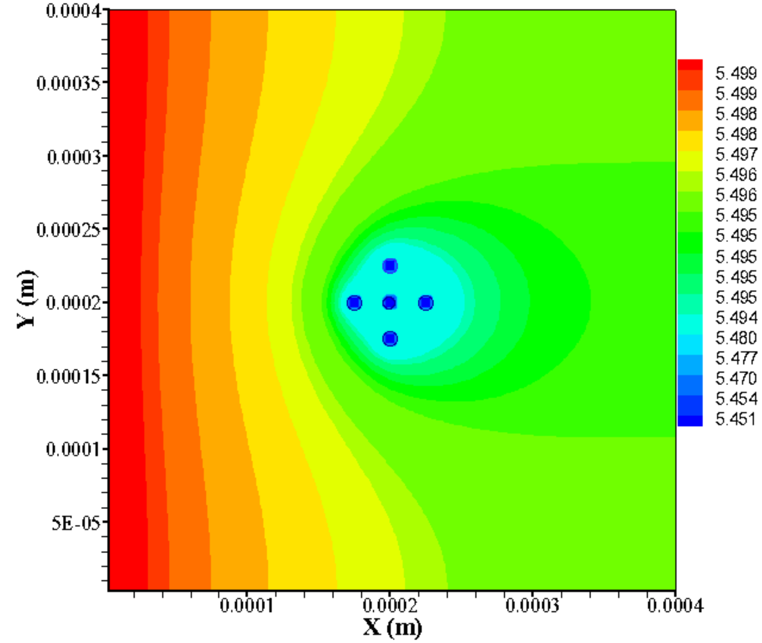


Surface MMP


Average surface MMP
MMP
time (min)
0.06
0.05
0.04
0.03
0.02
0.01
0
0
10
20
30
40
50
60
r_1=1.0
r_1=0.1
r_1=0.01
Average surface TGF-beta
TGF-beta
time
8
7
6
5
4
3
2
1
0
0
10
20
30
40
50
60
r_1=1.0
r_1=0.1
r_1=0.01



Y (m)
0.0004
0.00035
0.0003
0.00025
0.0002
0.00015
0.0001
5E-05
X (m)
0.0001
0.0002
0.0003
0.0004
5.499
5.499
5.498
5.498
5.497
5.496
5.496
5.495
5.495
5.495
5.495
5.495
5.494
5.480
5.477
5.470
5.454
5.451



Y (m)
0.0004
0.00035
0.0003
0.00025
0.0002
0.00015
0.0001
5E-05
X (m)
0.0001
0.0002
0.0003
0.0004
5.499
5.499
5.498
5.498
5.497
5.496
5.496
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5.495
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5.495
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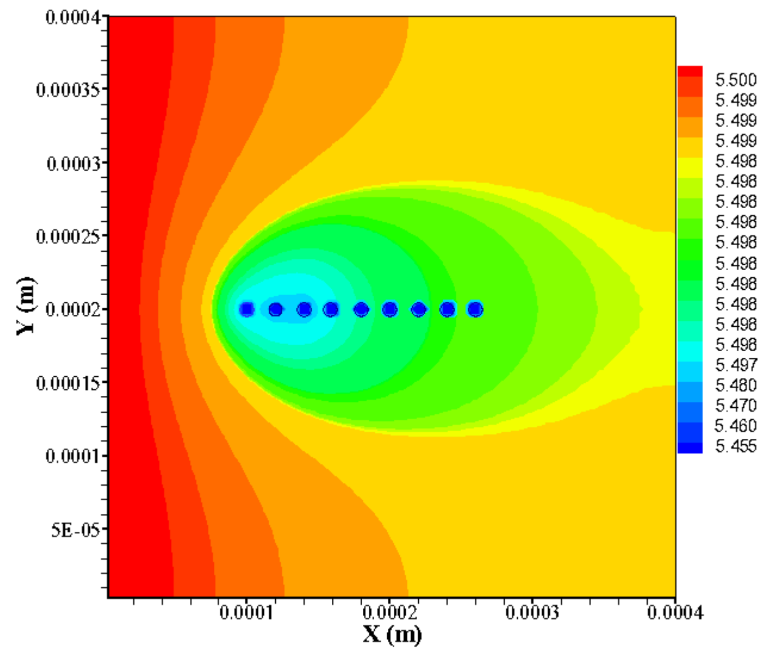
5.480
5.477
5.470
5.454
5.451



Y (m)
0.0004
0.00035
0.0003
0.00025
0.0002
0.00015
0.0001
5E-05
X (m)
0.0001
0.0002
0.0003
0.0004
5.500
5.499
5.499
5.499
5.498
5.498
5.498
5.498
5.498
5.498
5.498
5.498
5.498
5.498
5.497
5.480
5.470
5.460
5.455