A multiphase model to understand how aggressive tumor cell behavior is linked to elevated fluid pressure

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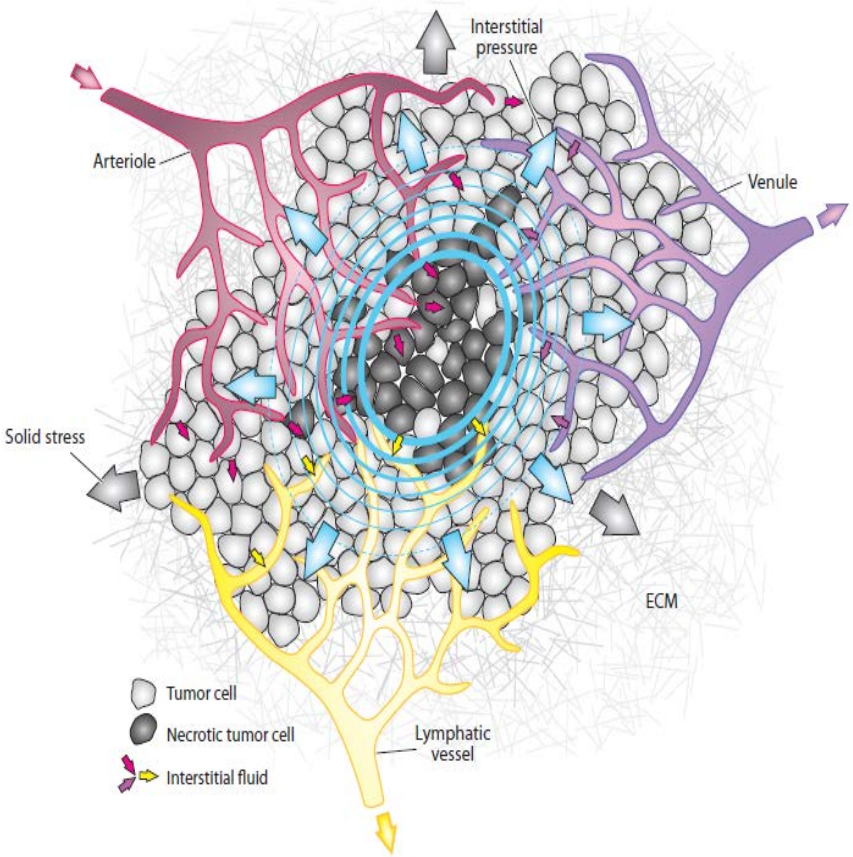
Setting the scene:

Physical forces and Tumor behavior

The Fluid Mechanics of Cancer and Its Therapy, Koumoutsakos, Pivkin, Milde (Annu. Rev. Fluid Mech. 2013)



Components

- Extracellular matrix (ECM)
  - collagen, and other fibers
- Cancer cells, fibroblasts, immune cells
- Interstitial fluid

Mechanisms

- Growing tumor creates pressure and is under pressure from surrounding tissue
- Increased mechanical stresses on and deformation of extracellular matrix (ECM)
- Interstitial fluid and cancer cells escape from the tumor boundary and enter the lymphatic system

How are cancer cells sensitive to the increased fluid velocity ?

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Metastasis: A major problem

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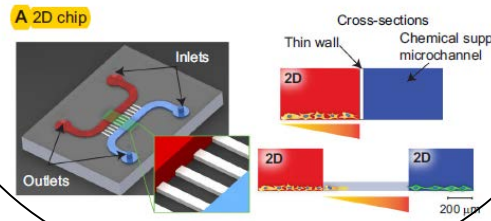
Problem:

Why is it so that aggressive tumor cells are able to break loose from the primary tumor site and migrate to nearby lymphatics and spread to other organs (metastatic behavior)?

Approach:

I) In vitro lab experiments using advanced microfluidic devices



train model

II) Development of mathematical models that can explain observed behavior in laboratory

$$(n)_t + \nabla\cdot(nu_c) = \rho_c S_c, \qquad S_c = \lambda_{11}\alpha_c - \lambda_{12}\alpha_c^2 - \lambda_{13}\alpha_c\frac{\rho}{\rho_M}$$

$$(m)_t + \nabla\cdot(mu_w) = -\rho_w S_c$$

$$\nabla[\alpha_c\Lambda(G,\rho)] + \alpha_c\nabla P_c = -\hat{\zeta}_c u_c + \hat{k}(u_w - u_c) + \varepsilon_c\nabla\cdot(n\nabla u_c)$$

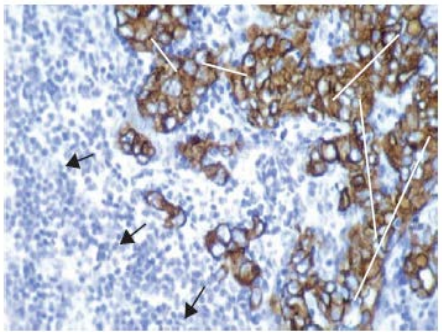
$$\alpha_w\nabla P_w = -\hat{\zeta}_w u_w - \hat{k}(u_w - u_c) + \varepsilon_w\nabla\cdot(m\nabla u_w), \qquad \Delta P = \Delta P(m) = P_c - P_w$$

$$\rho_t = -\lambda_{21}G\rho + \lambda_{22}\rho(1 - \frac{\rho}{\rho_M})$$

$$G_t = D_G\nabla^2 G - \lambda_{31}G + \lambda_{32}\alpha_c, \qquad x\in\Omega, \quad t>0,$$

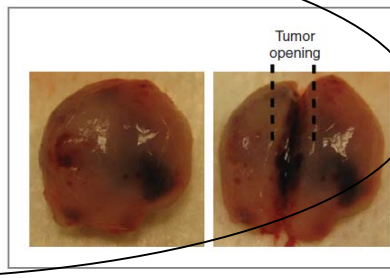
dig into patient data

tumor cell characteristics



III)

How can the math models bridge the gap between in vitro experiments and a real-life tumor? Use the model as a more fine-tuned tool to «dig» in the available data



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Outline

(A) How is metastatic behavior (spreading) linked to interstitial fluid flow ?

- An example from The Radium Hospital (Oslo)

(B) Experimental observations (microfluidic system)

- competing migration mechanisms

(C) A multiphase model

- tumor cells as an active fluid (in contrast to passive)
- training of the model with 1D data from experiments in (B)
- simulations of a more realistic 2D/3D from (A)

(D) Mathematical aspects of the model

- compressible/incompressible
- two-phase (cell-fluid) model
- simplified versions

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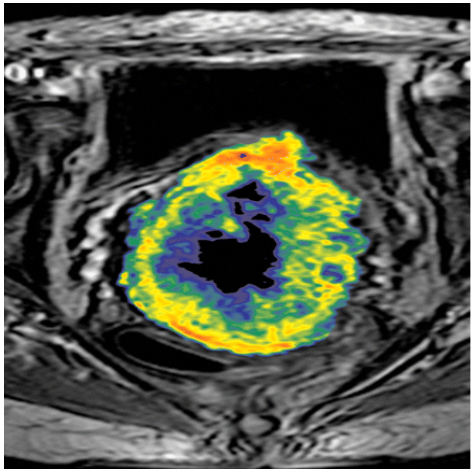
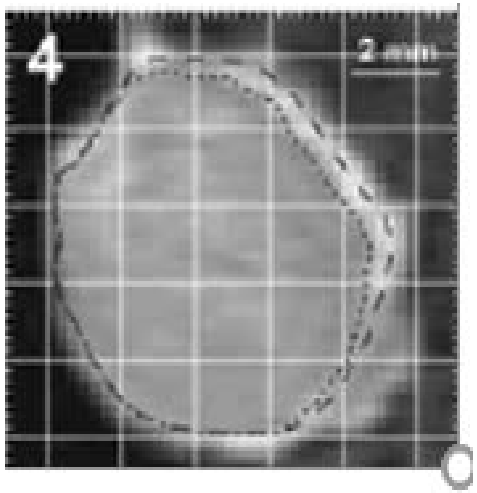
A) Metastatic behavior versus fluid flow

Observation I (Hompland, …, Rofstad, UiO, Cancer Research, 2012):





- Maximal IF velocity v_0 at tumor periphery relatively uniform
- Maximal travelled distance s_0 is heterogenous
- High IFP gives larger s_0

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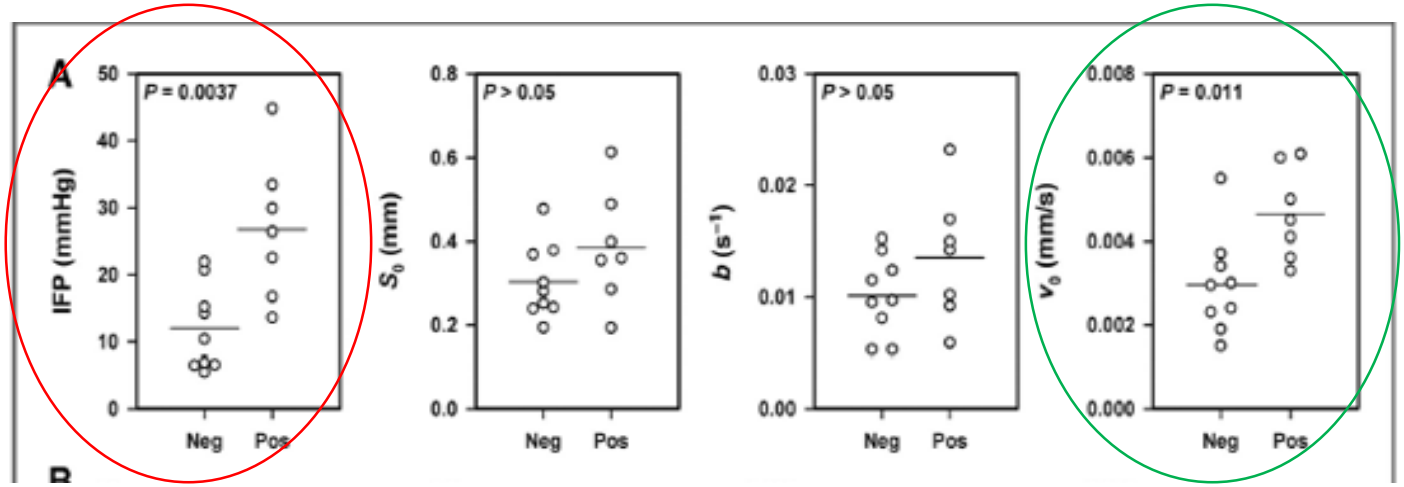
A) Metastatic behavior versus fluid flow

Observation II (Hompland et al, 2012):



High IFP ⇔ High fluid velocity ⇔ high risk for metastasis

(migration of tumor cells to nearby lymphatic vessels)

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B) Microfluidic experiment

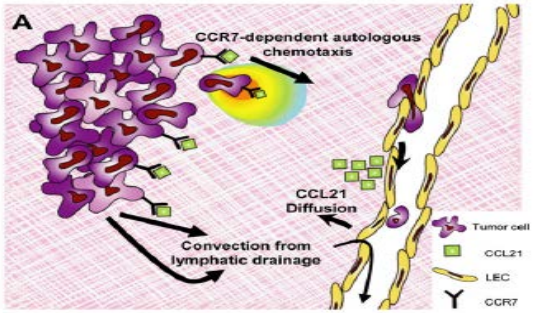
- Interstitial fluid (IF) flow as driver for cell migration

- **Autologous chemotaxis**

  (Swartz et al, 2007)

  - cells secrete proteases that release ECM-bound chemokine CCL21 (molecule that binds to CCR7 receptor) that follows the fluid flow towards nearby lymphatics

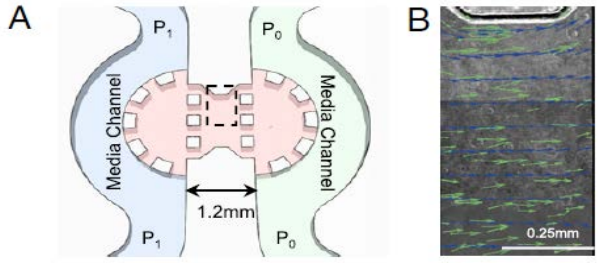
  - cancer cells move by chemotaxis towards gradient in CCL21

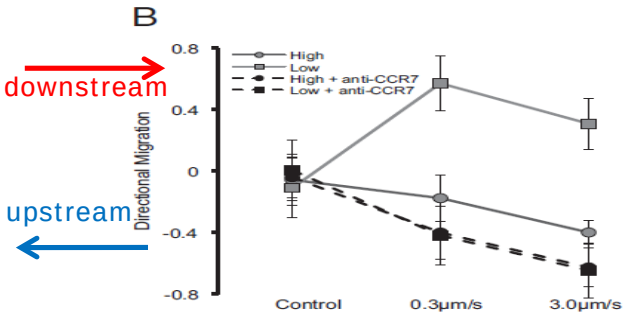


Autologous chemotaxis as a mechanism of tumor cell homing to lymphatics via interstitial flow and autocrine CCR7 signaling,
Shields, Fleury, Yong, Tomei, Randolph, Swartz
Cancer Cell, 2007

- **«Rheotaxis»** (sensitivity to fluid flow) (Kamm et al, 2011 and 2014)

  → P_1 > P_0





- low density cell aggregate gives downstream migration
- high density cell aggregate gives upstream migration
- upstream migration is sensitive to magnitude of fluid velocity

Interstitial flow influences direction of tumor cell migration through competing mechanisms
Polacheck, Charest, Kamm. *PNAS*, 2011 and 2014

C) A multiphase model for cancer cell migration

matrix vol + pore vol = total volume

$$\phi_m + \phi_p = 1.$$

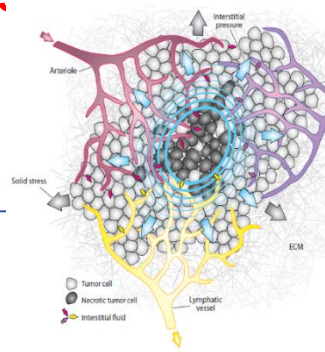


Figure 5
Mechanical properties of the tumor microenvironment: radial solid stress exerted by the gro
(*gray arrows*), enhanced extracellular matrix (ECM) stiffness (*gray fibers*), elevated levels of in
pressure (*blue arrows*), and increased interstitial flow (*red, purple, and yellow arrows*).

Mass balance

Cell proliferation/apoptosis

$$(\phi\alpha_c\rho_c)_t + \nabla\cdot(\phi\alpha_c\rho_c\mathbf{u}_c^p) = \rho_c S_c, \qquad S_c = \alpha_c\left(\lambda_{11} - \lambda_{12}\alpha_c - \lambda_{13}\frac{\rho}{\rho_M}\right)$$

$$(\phi\alpha_w\rho_w)_t + \nabla\cdot(\phi\alpha_w\rho_w\mathbf{u}_w^p) = -\rho_w S_c + \rho_w Q, \qquad Q = Q_v - Q_l$$

Fluid produced/adsorbed

cell vol + fluid vol = pore vol

$$\alpha_c + \alpha_w = 1, \quad (\text{i.e.}, \quad \phi\alpha_c + \phi\alpha_w = \phi)$$

Momentum balance

$$\alpha_c\nabla P_c = -\hat{\zeta}_c\mathbf{u}_c^p + \hat{\zeta}(\mathbf{u}_w^p - \mathbf{u}_c^p)$$

$$\alpha_w\nabla P_w = -\hat{\zeta}_w\mathbf{u}_w^p - \hat{\zeta}(\mathbf{u}_w^p - \mathbf{u}_c^p)$$

(+ viscous terms)

Cell-ECM interaction

Cell-fluid interaction

Fluid-ECM interaction

Active fluid -> possibly negative sign

$$P_c = P_w + \Delta P(\alpha_c) + \Lambda(C).$$

diffusive spread chemotactic migration

ECM (rho) + protease (G) + chemokine (C) (system required to describe autologous chemotaxis)

$$(\rho)_t = -\lambda_{21}G\rho + \rho\left(\lambda_{22} - \lambda_{23}\alpha_c - \lambda_{24}\left(\frac{\rho}{\rho_M}\right)\right)$$

$$(\phi\alpha_w G)_t + \nabla\cdot(\phi\alpha_w G\mathbf{u}_w^p) = \nabla\cdot(D_G\nabla G) - \lambda_{31}G + \alpha_c\left(\lambda_{32} - \lambda_{33}\left(\frac{G}{G_M}\right)^{\nu_1}\right)$$

$$(\phi\alpha_w C)_t + \nabla\cdot(\phi\alpha_w C\mathbf{u}_w^p) = \nabla\cdot(D_C\nabla C) + G\rho\left(\lambda_{41} - \lambda_{42}\left(\frac{C}{C_M}\right)^2 - \lambda_{43}\left(\frac{C}{C_M}\right)^{\nu_2}\right) - \lambda_{44}\alpha_c,$$

Story:
"Tumor cells secrete protease which will follow the fluid flow, and through proteolytic activity release ECM-bound chemokine that in turn is skewed in flow direction"

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C) A multiphase model for cancer cell migration

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Compact version

$$\alpha_{ct} + \nabla \cdot (\alpha_c \mathbf{u}_c) = S_c,$$

$$\rho_t = -\lambda_{21}\phi G\rho + \phi\rho\left(\lambda_{22} - \lambda_{23}\alpha_c - \lambda_{24}\frac{\rho}{\rho_M}\right)$$

$$G_t + \nabla \cdot (G\mathbf{u}_w) = \nabla \cdot (D_G \nabla G) - \lambda_{31} G + \alpha_c\left(\lambda_{32} - \lambda_{33}\left(\frac{G}{G_M}\right)^{\nu_1}\right)$$

$$C_t + \nabla \cdot (C\mathbf{u}_w) = \nabla \cdot (D_C \nabla C) + G\rho\left(\lambda_{41} - \lambda_{42}\left(\frac{C}{C_M}\right)^2 - \lambda_{43}\left(\frac{C}{C_M}\right)^{\nu_2}\right) - \lambda_{44}\alpha_c$$

Protease produced + ECM-released chemokine skewed in flow direction by u_w

cell velocity = sum of 3 components

$$\mathbf{U}_c = \underbrace{\mathbf{U}_T \hat{f}_c(\alpha_c)}_{\text{flow-generated stress}} - \underbrace{\hat{h}(\alpha_c)\nabla(\Delta P(\alpha_c))}_{\text{diffusion}} - \underbrace{\hat{h}(\alpha_c)\nabla\Lambda(C)}_{\text{autologous chemotaxis}}$$

Cell migration sensitive to fluid flow, i.e., Kamm + Swartz

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C) Model behavior II – tumor cell migration

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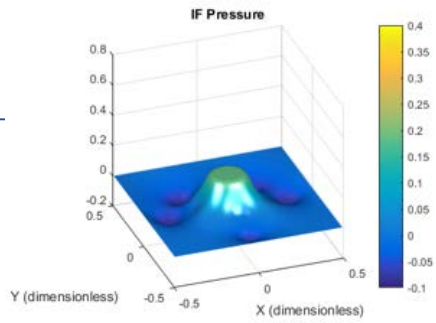
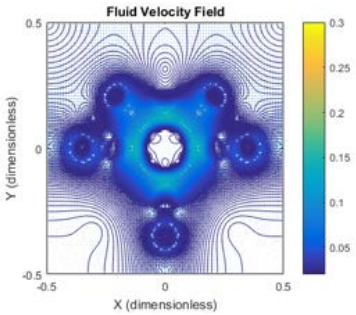
Low microvascular pressure
= low fluid velocity





«weak»

$$U_c = \underbrace{U_T \hat{f}_c(\alpha_c)}_{\text{flow-generated stress}} - \underbrace{\hat{h}(\alpha_c)\nabla(\Delta P(\alpha_c))}_{\text{diffusion}} - \underbrace{\hat{h}(\alpha_c)\nabla\Lambda(C)}_{\text{autologous chemotaxis}}$$

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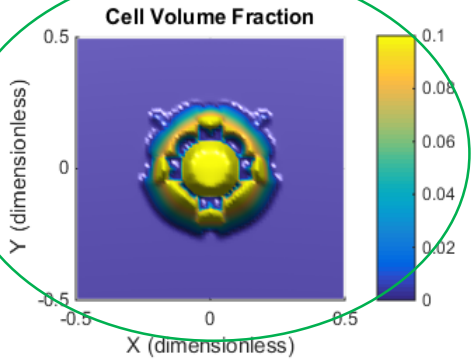
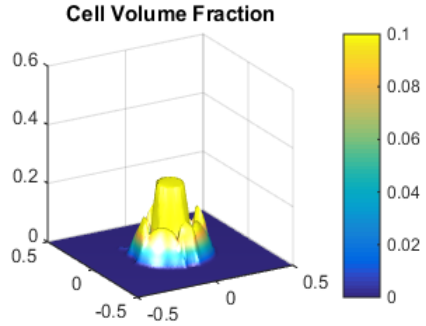
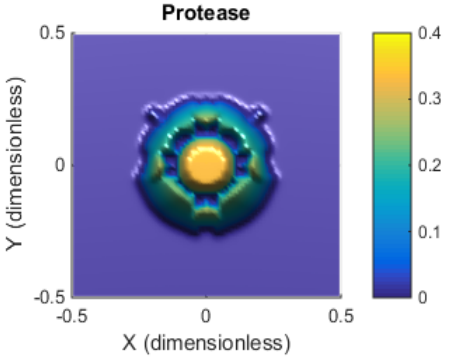
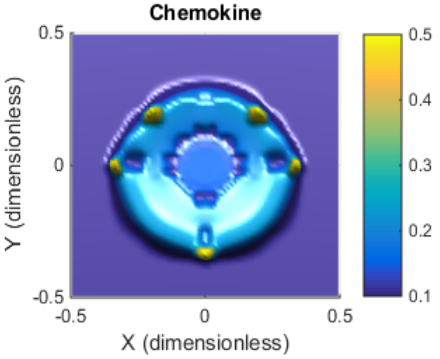
- Large volume fraction of tumor cells move by autologenous chemotaxis
- Homogenous outward-driven migration
- No mechanism that can cleave the «wave» of downstream moving tumor cells









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C) Model behavior II – tumor cell migration

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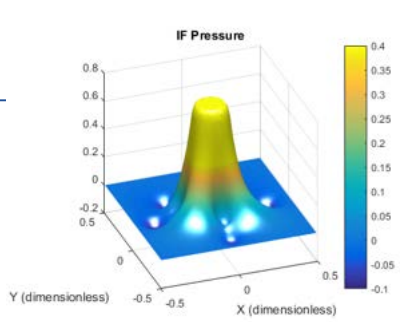
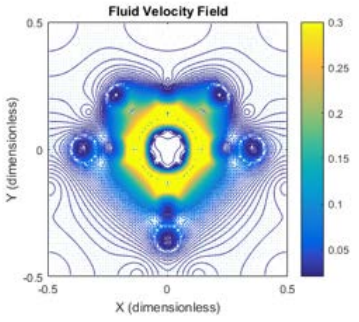
High microvascular pressure
= high fluid velocity



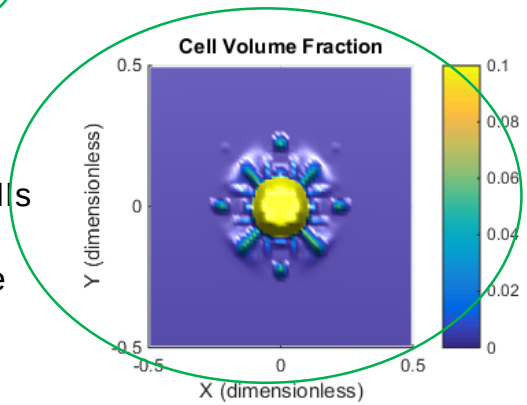


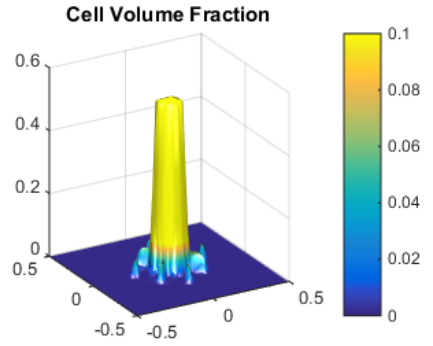
«strong»

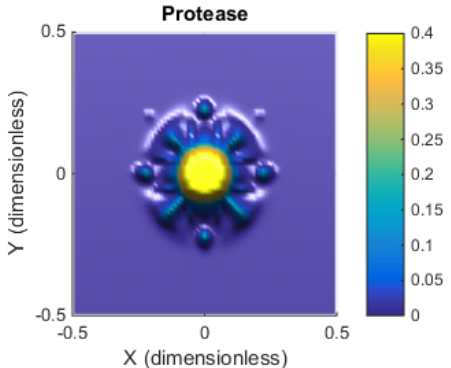
$$U_c = \underbrace{U_T \hat{f}_c(\alpha_c)}_{\text{flow-generated stress}} - \underbrace{\hat{h}(\alpha_c)\nabla(\Delta P(\alpha_c))}_{\text{diffusion}} - \underbrace{\hat{h}(\alpha_c)\nabla\Lambda(C)}_{\text{autologous chemotaxis}}$$

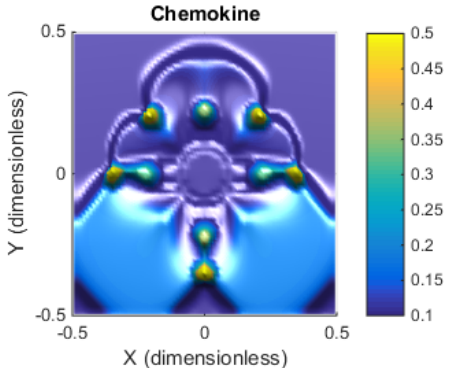
$$U_c = \underbrace{U_T \hat{f}_c(\alpha_c)}_{\text{flow-generated stress}} - \underbrace{\hat{h}(\alpha_c)\nabla(\Delta P(\alpha_c))}_{\text{diffusion}} - \underbrace{\hat{h}(\alpha_c)\nabla\Lambda(C)}_{\text{autologous chemotaxis}}$$

- Small volume fraction of tumor cells tend to accumulate at nearby lymphatics or move in a finger-like pattern towards lymphatics
- Strongly heterogenous migration behavior
- The combination of downstream + upstream gives much more «aggressive» behavior









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D) Compressible version

A compressible, viscous version with one chemical component

- a simplified version but contains the competing migration mechanisms
- numerical approximations (?)
- mathematical analysis (?)

$$
\begin{aligned}
(\alpha_c\rho_c)_t + \nabla\cdot(\alpha_c\rho_c\mathbf{u}_c) &= +S_c \\
(\alpha_w\rho_w)_t + \nabla\cdot(\alpha_w\rho_w\mathbf{u}_w) &= -S_c \\
\alpha_c\nabla P_c &= -\hat{k}_c\mathbf{u}_c + \hat{k}_{cw}(\mathbf{u}_w-\mathbf{u}_c) + \nabla\cdot(\varepsilon_c\nabla\mathbf{u}_c) \\
\alpha_w\nabla P_w &= -\hat{k}_w\mathbf{u}_w - \hat{k}_{cw}(\mathbf{u}_w-\mathbf{u}_c) + \nabla\cdot(\varepsilon_w\nabla\mathbf{u}_w) \\
C_t + \nabla\cdot(C\mathbf{u}_w) &= \nabla\cdot(D_C\nabla C) + R_C
\end{aligned}
$$

with

$$
\begin{aligned}
\alpha_c + \alpha_w &= 1 \\
P_c &= P_w + \Lambda_{\text{diff}}(\alpha_c) + \Lambda_{\text{chemo}}(C) \\
\rho_c &= \rho_c(P_c) \\
\rho_w &= \rho_w(P_w)
\end{aligned}
$$

A *Stokes-chemotaxis* model for cell-fluid dynamics (incompressible)

- a competition between gravity and chemotaxis
- Many mathematical results
  M Winkler (JDE 2018) - review
- energy-based arguments

$$
\begin{aligned}
n_t + \mathbf{u}\cdot\nabla n &= \nabla\cdot(D(n)\nabla n) - \nabla\cdot(n\nabla c) \\
\nabla\cdot\mathbf{u} &= 0 \\
\mathbf{u}_t + \nabla P &= n\nabla\phi + \Delta\mathbf{u} \\
C_t + \mathbf{u}\cdot\nabla C &= \Delta C - nC
\end{aligned}
$$

with

n = cell density, $\mathbf{u}$ = fluid velocity

P = fluid pressure, C = chemical

D) Incompressible version

How to obtain reduced versions ?

$$
\begin{aligned}
\alpha_{ct} + \nabla \cdot (\alpha_c \mathbf{u}_c) &= +S_c \\
\alpha_{wt} + \nabla \cdot (\alpha_w \mathbf{u}_w) &= -S_c \\
\alpha_c \nabla (P_w + \Lambda_{\text{diff}}(\alpha_c) + \Lambda_{\text{chemo}}(C)) &= -\hat{\zeta}_c \mathbf{u}_c + \hat{\zeta}(\mathbf{u}_w - \mathbf{u}_c) \\
\alpha_w \nabla P_w &= -\hat{\zeta}_w \mathbf{u}_w - \hat{\zeta}(\mathbf{u}_w - \mathbf{u}_c) \\
C_t + \nabla \cdot (C \mathbf{u}_w) &= \nabla \cdot (D_C \nabla C) + R_C
\end{aligned}
$$

with

$$\alpha_c + \alpha_w = 1$$

+ simplifying assumptions

$$
\begin{cases}
u_t - f(u)_x &= u_{xx} - (h(u)v_x)_x \\
v_t + v_x &= v_{xx} + u(1-v)
\end{cases}
$$

where $f(u)$ and $h(u)$ are given by

$$f(u) = u^\kappa \quad \text{and} \quad h(u) = u(1-u)^\lambda$$

where $\kappa > 0$ and $\lambda > 0$ are fixed parameters.

- Simplifying assumptions on choice of coefficients related to $\hat{\zeta}_c$, $\hat{\zeta}_w$, and $\hat{\zeta}$.
- The competing upstream migration and downstream migration is preserved

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The End

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