Max Planck Graduate Center
mit der Johannes Gutenberg-Universität Mainz

imb Institute of Molecular Biology

JOHANNES GUTENBERG UNIVERSITÄT MAINZ

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Modeling and simulation of EMT and tumor cell heterogeneity in cancer invasion

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joint with

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Workshop on mathematical perspectives in the biology and therapeutics of cancer

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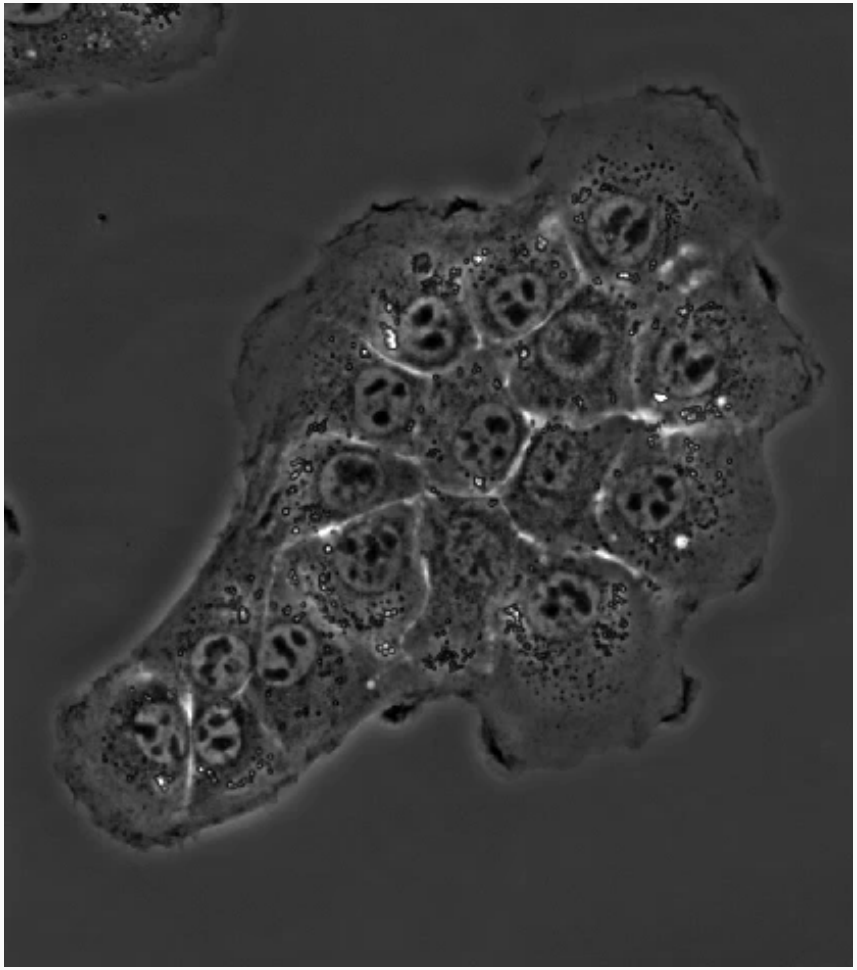
Model of EMT in tumor invasion

On the existence of solutions

Numerical simulations

Model of EMT in tumor invasion

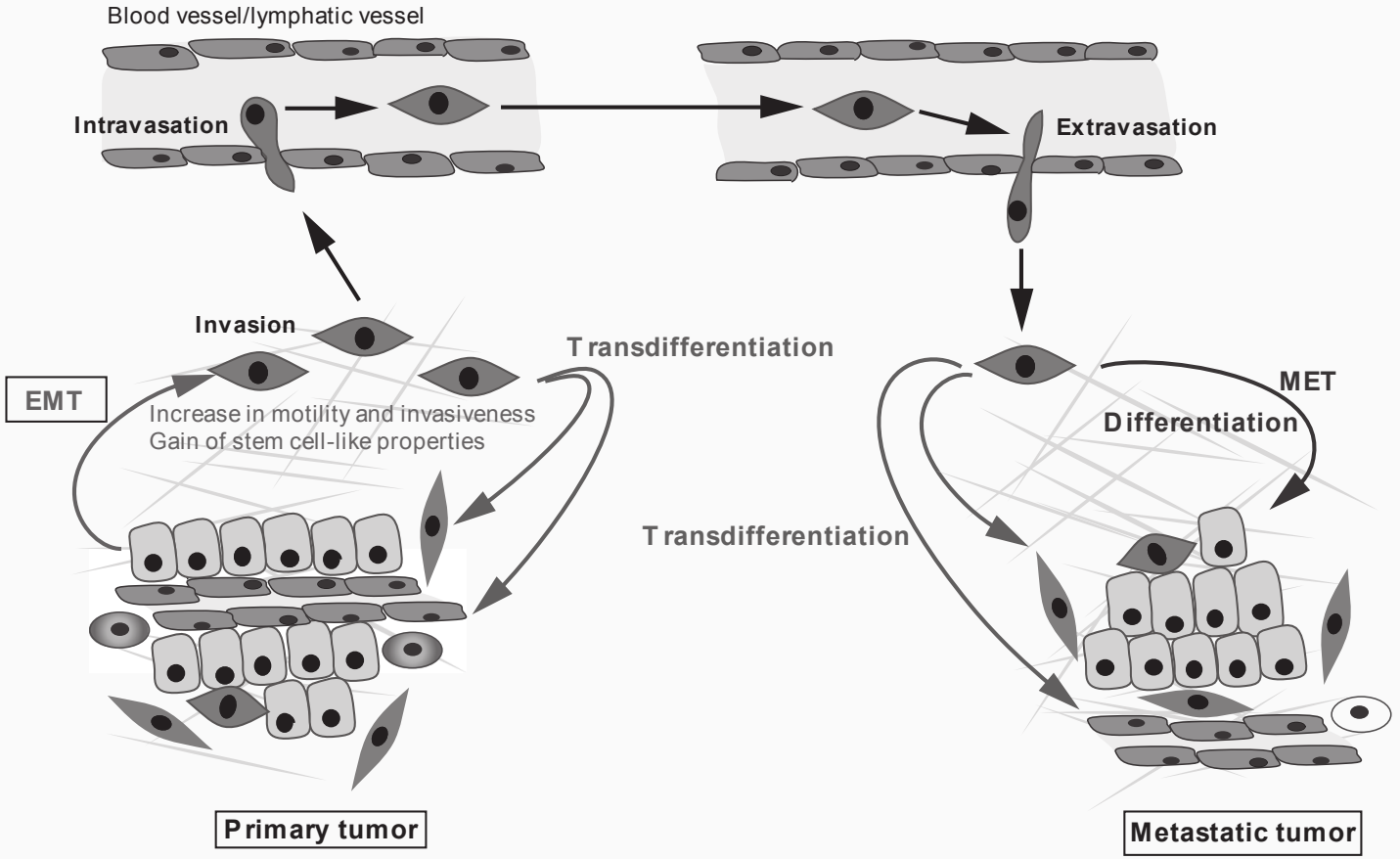
Epithelial-Mesenchymal transition



[Haynes et al., Mol Biol Cell (2011)]

EMT in vitro

EMT in tumor growth



[Katsuno et al. Curr Opin Oncol (2013)]

differentiated cancer cells (DCCs)

cancer stem cells (CSCs)

extracellular matrix (ECM)

The model

$$\partial_t c^D = \overbrace{\nabla \cdot \left(D_D \nabla c^D - \chi_D c^D \nabla v \right)}^{\text{cell movement}} \quad \overbrace{+\mu_D \, c^D \, R^+}^{\text{proliferation}}$$

$$\partial_t v = \overbrace{-\delta_v \, m v}^{\text{proteolysis}}$$

$$\partial_t m = \overbrace{D_m \Delta m}^{\text{diffusion}} \quad \overbrace{+\alpha_D \, c^D}^{\text{activation}} \quad \overbrace{-\beta_m \, m}^{\text{decay}}$$

$$R^+ = \max\{0, \, 1 - v - c^D \quad \}$$

c^D : DCC density v : ECM density m : MMP density

[Sfakianakis, Kolbe, Hellmann, Lukáčová Bull Math Biol (2017)]

The model

$$\partial_t c^D = \overbrace{\nabla \cdot \left(D_D \nabla c^D - \chi_D c^D \nabla v\right)}^{\text{cell movement}} \quad \overbrace{+\mu_D\, c^D\, R^+}^{\text{proliferation}} \quad \overbrace{-\mu_{EMT}\, c^D}^{\text{EMT}},$$

$$\partial_t c^S = \nabla \cdot \left(D_S \nabla c^S - \chi_S c^S \nabla v\right) \quad + \mu_S\, c^S\, R^+ \quad + \mu_{EMT}\, c^D$$

$$\partial_t v = \overbrace{-\delta_v\, m v}^{\text{proteolysis}}$$

$$\partial_t m = \overbrace{D_m \Delta m}^{\text{diffusion}} \quad \overbrace{+\alpha_D\, c^D + \alpha_S\, c^S}^{\text{activation}} \quad \overbrace{-\beta_m\, m}^{\text{decay}}$$

$$R^+ = \max\{0,\, 1 - v - c^D - c^S\}$$

c^D : DCC density v : ECM density m : MMP density
c^S : CSC density

[Sfakianakis, Kolbe, Hellmann, Lukáčová Bull Math Biol (2017)]

The EMT rate

epidermal growth factor (EGF) promotes the EMT

$$\mu_{\text{EMT}} = \mu_0 \frac{[EGF]^{\text{DCC}}_{\text{bnd}}}{\mu_{1/2} + [EGF]^{\text{DCC}}_{\text{bnd}}}$$

EGF dynamics at cell receptors

$$\partial_\tau [EGF]_{\text{free}} = \overbrace{D_f \Delta [EGF]_{\text{free}}}^{\text{diffusion}} \overbrace{-k_+ [EGF]_{\text{free}} [EGFR]_{\text{free}}}^{\text{binding}} \overbrace{+k_- [EGF]_{\text{bnd}}}^{\text{unbinding}}$$

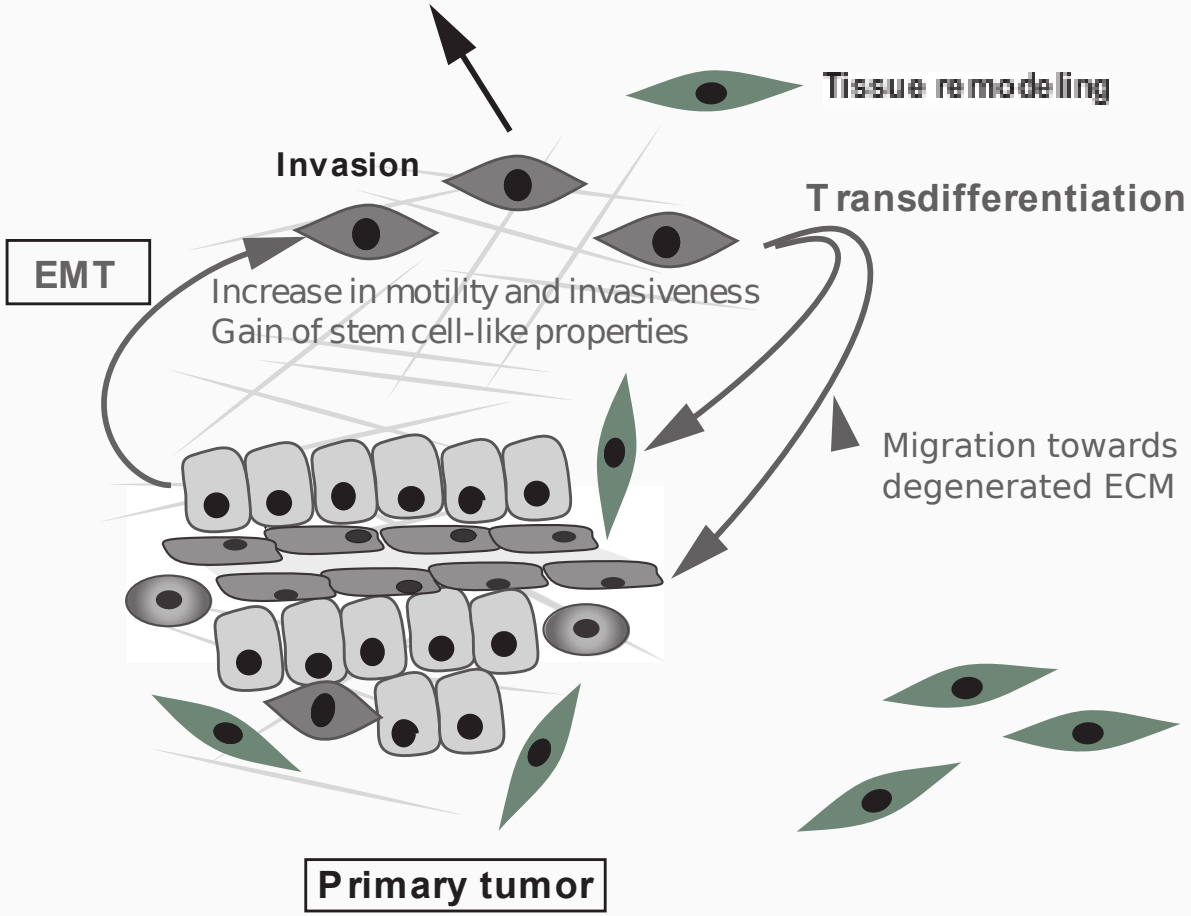
$$\partial_\tau [EGF]_{\text{bnd}} = k_+ [EGF]_{\text{free}} [EGFR]_{\text{free}} - k_- [EGF]_{\text{bnd}}$$

- no EGF consumption
- homogeneous Neumann boundaries
- fast EGF binding allows for scaling $t/\tau \to 0$

$$[EGF]_{\text{free}} = \text{const} \left(\int_\Omega [EGFR]_0 \, dx \right)$$

$$[EGF]^{\text{DCC}}_{\text{bnd}} = \frac{[EGF]_{\text{free}}}{k_D + [EGF]_{\text{free}}} [EGFR]^{\text{DCC}}_0$$

The role of cancer associated fibroblasts



[Katsuno et al. Curr Opin Oncol (2013)]

DCCs

CSCs

ECM

fibroblasts

The extended model

$$\partial_t c^{\mathrm{D}} = \overbrace{\nabla \cdot \left(D_D \nabla c^{\mathrm{D}} - \chi_D c^{\mathrm{D}} \nabla v\right)}^{\text{cell movement}} \quad \overbrace{+\mu_D\, c^{\mathrm{D}}\, R^+}^{\text{proliferation}} \quad \overbrace{-\mu_{\mathrm{EMT}}\, c^{\mathrm{D}}}^{\text{EMT}}, \qquad (\mathrm{M})$$

$$\partial_t c^{\mathrm{S}} = \nabla \cdot \left(D_S \nabla c^{\mathrm{S}} - \chi_S c^{\mathrm{S}} \nabla v\right) \quad + \mu_S\, c^{\mathrm{S}}\, R^+ \quad + \mu_{\mathrm{EMT}}\, c^{\mathrm{D}}$$

$$\partial_t v = \overbrace{-\delta_v\, m v}^{\text{proteolysis}}$$

$$\partial_t m = \overbrace{D_m \Delta m}^{\text{diffusion}} \quad \overbrace{+\alpha_D\, c^{\mathrm{D}} + \alpha_S\, c^{\mathrm{S}}}^{\text{activation}} \quad \overbrace{-\beta_m\, m}^{\text{decay}}$$

$$R^+ = \max\{0,\, 1 - v - c^{\mathrm{D}} - c^{\mathrm{S}} \qquad \}$$

c^{D} : DCC density v : ECM density m : MMP density

c^{S} : CSC density

[Sfakianakis, Kolbe, Hellmann, Lukáčová Bull Math Biol (2017)]

The extended model

$$\partial_t c^{\mathrm{D}} = \overbrace{\nabla \cdot \left(D_D \nabla c^{\mathrm{D}} - \chi_D c^{\mathrm{D}} \nabla v\right)}^{\text{cell movement}} \quad \overbrace{+\mu_D\, c^{\mathrm{D}}\, R^+}^{\text{proliferation}} \quad \overbrace{-\mu_{\mathrm{EMT}}\, c^{\mathrm{D}}}^{\text{EMT}}, \qquad (\mathrm{M})$$

$$\partial_t c^{\mathrm{S}} = \nabla \cdot \left(D_S \nabla c^{\mathrm{S}} - \chi_S c^{\mathrm{S}} \nabla v\right) \quad + \mu_S\, c^{\mathrm{S}}\, R^+ \quad + \mu_{\mathrm{EMT}}\, c^{\mathrm{D}} \quad \overbrace{-\mu_{\mathrm{T}}\, c^{\mathrm{S}}}^{\text{differentiation}},$$

$$\partial_t c^{\mathrm{F}} = \nabla \cdot \left(D_F \nabla c^{\mathrm{F}} + \chi_F c^{\mathrm{F}} \nabla v\right) \quad + \mu_F\, c^{\mathrm{F}}\, R^+ \quad \overbrace{-\beta_F\, c^{\mathrm{F}}}^{\text{apoptosis}} \quad + \mu_{\mathrm{T}}\, c^{\mathrm{S}},$$

$$\partial_t v = \overbrace{-\delta_v\, m v}^{\text{proteolysis}} \quad \overbrace{+\mu_v\, c^{\mathrm{F}}\, R^+}^{\text{ECM remodelling}},$$

$$\partial_t m = \overbrace{D_m \Delta m}^{\text{diffusion}} \quad \overbrace{+\alpha_D\, c^{\mathrm{D}} + \alpha_S\, c^{\mathrm{S}}}^{\text{activation}} \quad \overbrace{-\beta_m\, m}^{\text{decay}}$$

$$R^+ = \max\{0,\, 1 - v - c^{\mathrm{D}} - c^{\mathrm{S}} - c^{\mathrm{F}}\}$$

c^{D} : DCC density v : ECM density m : MMP density

c^{S} : CSC density c^{F} : fibroblast density

[Sfakianakis, Kolbe, Hellmann, Lukáčová Bull Math Biol (2017)]

On the existence of solutions

Global existence of a simplified model in 2D

Simplified model

$$
\begin{aligned}
\partial_t c^{\mathrm{D}} &= \nabla \cdot \left(\nabla c^{\mathrm{D}} - \chi_D c^{\mathrm{D}} \nabla v \right) - \mu_{\mathrm{EMT}}\, c^{\mathrm{D}} + \mu_D\, c^{\mathrm{D}}\, R, \\
\partial_t c^{\mathrm{S}} &= \nabla \cdot \left(\nabla c^{\mathrm{S}} - \chi_S c^{\mathrm{S}} \nabla v \right) + \mu_{\mathrm{EMT}}\, c^{\mathrm{D}} + \mu_S\, c^{\mathrm{S}}\, R, \\
\partial_t v &= -m v + \mu_v\, v\, R, \\
\partial_t m &= \Delta m + c^{\mathrm{S}} + c^{\mathrm{D}} - m
\end{aligned}
\tag{S}
$$

$$R = 1 - v - c^{\mathrm{D}} - c^{\mathrm{S}}$$

Assumptions

- $\Omega \subset \mathbb{R}^2$ is a C^{2+l} domain, $Q_T = \Omega \times (0, T),\ 0 < l < 1$
- $\partial_\nu c^{\mathrm{D}} = \partial_\nu c^{\mathrm{S}} = \partial_\nu m = 0$ in $\partial\Omega$
- $c_0^{\mathrm{D}}, c_0^{\mathrm{S}}, v_0, m_0 \geq 0, \quad v_0 \leq 1, \quad c_0^{\mathrm{D}}, c_0^{\mathrm{S}}, m_0, v_0 \in C^{2+l}(\bar{\Omega})$
- $\mu_{\mathrm{EMT}} : \mathbb{R}^4 \to \mathbb{R}$ is a bounded function of $c^{\mathrm{D}}, c^{\mathrm{S}}, \int_\Omega c^{\mathrm{D}}\, dx, \int_\Omega c^{\mathrm{S}}\, dx$ with bounded first derivatives
- $\mu_D \geq \chi_D \mu_v, \quad \mu_S \geq \chi_S \mu_v.$

[Giesselmann, Kolbe, Sfakianakis, Lukáčová Disc Cont Syst B (2018)]

Global existence of a simplified model in 2D

Simplified model

$$
\begin{aligned}
\partial_t c^{\mathrm{D}} &= \nabla \cdot \left(\nabla c^{\mathrm{D}} - \chi_D c^{\mathrm{D}} \nabla v \right) - \mu_{\mathrm{EMT}}\, c^{\mathrm{D}} + \mu_D\, c^{\mathrm{D}}\, R, \\
\partial_t c^{\mathrm{S}} &= \nabla \cdot \left(\nabla c^{\mathrm{S}} - \chi_S c^{\mathrm{S}} \nabla v \right) + \mu_{\mathrm{EMT}}\, c^{\mathrm{D}} + \mu_S\, c^{\mathrm{S}}\, R, \\
\partial_t v &= -m v + \mu_v\, v\, R, \\
\partial_t m &= \Delta m + c^{\mathrm{S}} + c^{\mathrm{D}} - m
\end{aligned}
\tag{S}
$$

$$R = 1 - v - c^{\mathrm{D}} - c^{\mathrm{S}}$$

Theorem (Global existence of an unique classical solution)
There exists an unique solution $c^D, c^S, v, m \in C^{2+l,1+l/2}(\bar{Q}_T)$ *of system* (S) *for any* $T > 0$ *with* $c^D, c^S, v, m \geq 0$ *and* $v \leq 1$.

[Giesselmann, Kolbe, Sfakianakis, Lukáčová Disc Cont Syst B (2018)]

Towards global existence

1. Variable transformation $a^{\mathrm{D}} = c^{\mathrm{D}} e^{-\chi_D v}$ and $a^{\mathrm{S}} = c^{\mathrm{S}} e^{-\chi_S v}$
2. Local existence via contraction mapping theorem
3. $\|a^{\mathrm{D}}(t)\|_{L^\infty(\Omega)}, \|a^{\mathrm{S}}(t)\|_{L^\infty(\Omega)} \leq C_1$ via Moser-Alikakos iteration
4. $\|\nabla v(t)\|^p_{L^p(\Omega)} \leq C_2(T,p) \left(\|\nabla a^{\mathrm{D}}\|^p_{L^p(Q_T)} + \|\nabla a^{\mathrm{S}}\|^p_{L^p(Q_T)} + 1 \right)$
5. $\|\nabla a^{\mathrm{D}}(t)\|_{L^4(\Omega)}, \|\nabla a^{\mathrm{S}}(t)\|_{L^4(\Omega)} \leq C_3(T)$,
6. Bootstrapping

Numerical simulations

Numerical discretization

Method

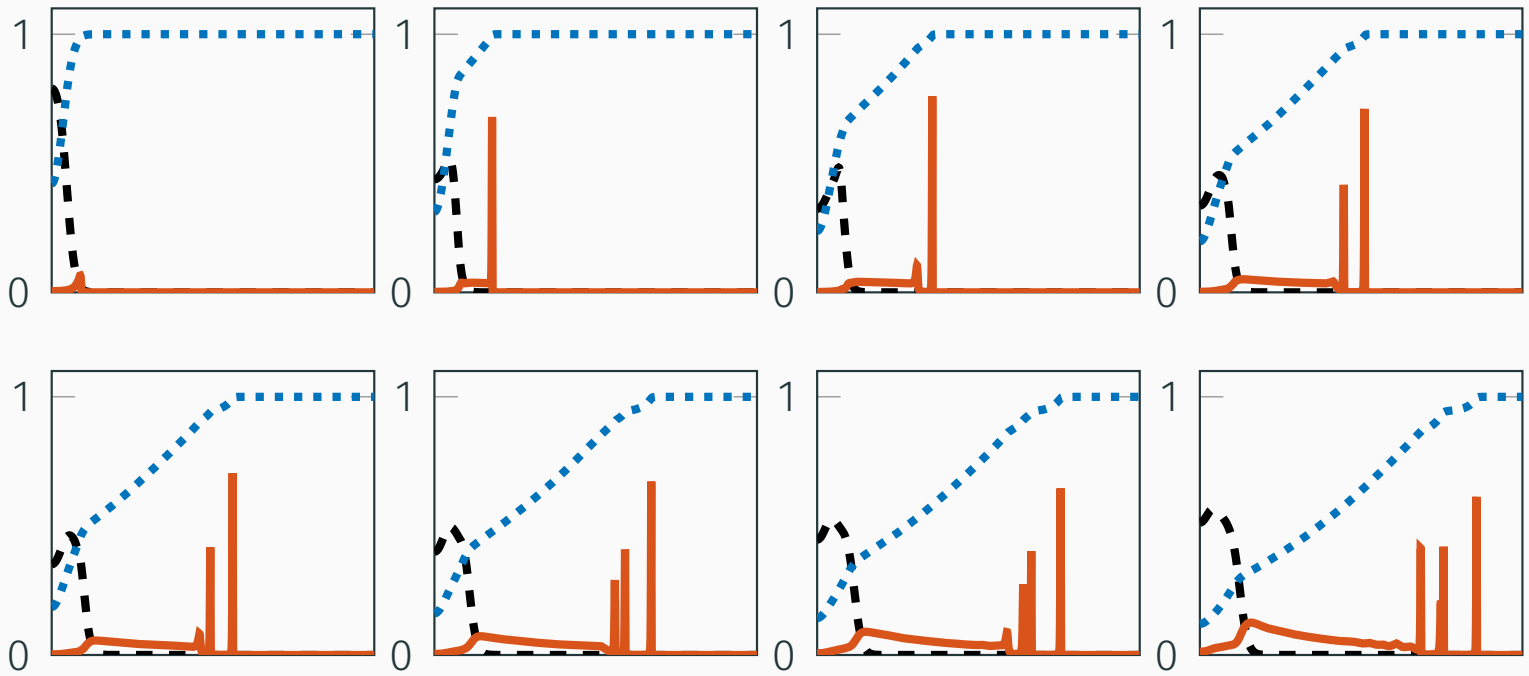
		haptotaxis	diffusion	reaction
spatial	Finite Volumes	Central Upwind + MC limiter	central differences	midpoint rule
temporal	IMEX-RK	explicit	implicit	explicit

Properties

- stable for large time steps in $\mathcal{O}(h)$
- second order in time and space (experimentally verified)
- positivity preserving

[Kolbe, Kat'uchová, Sfakianakis, Hellmann, Lukáčová Appl Math Comp (2015)]

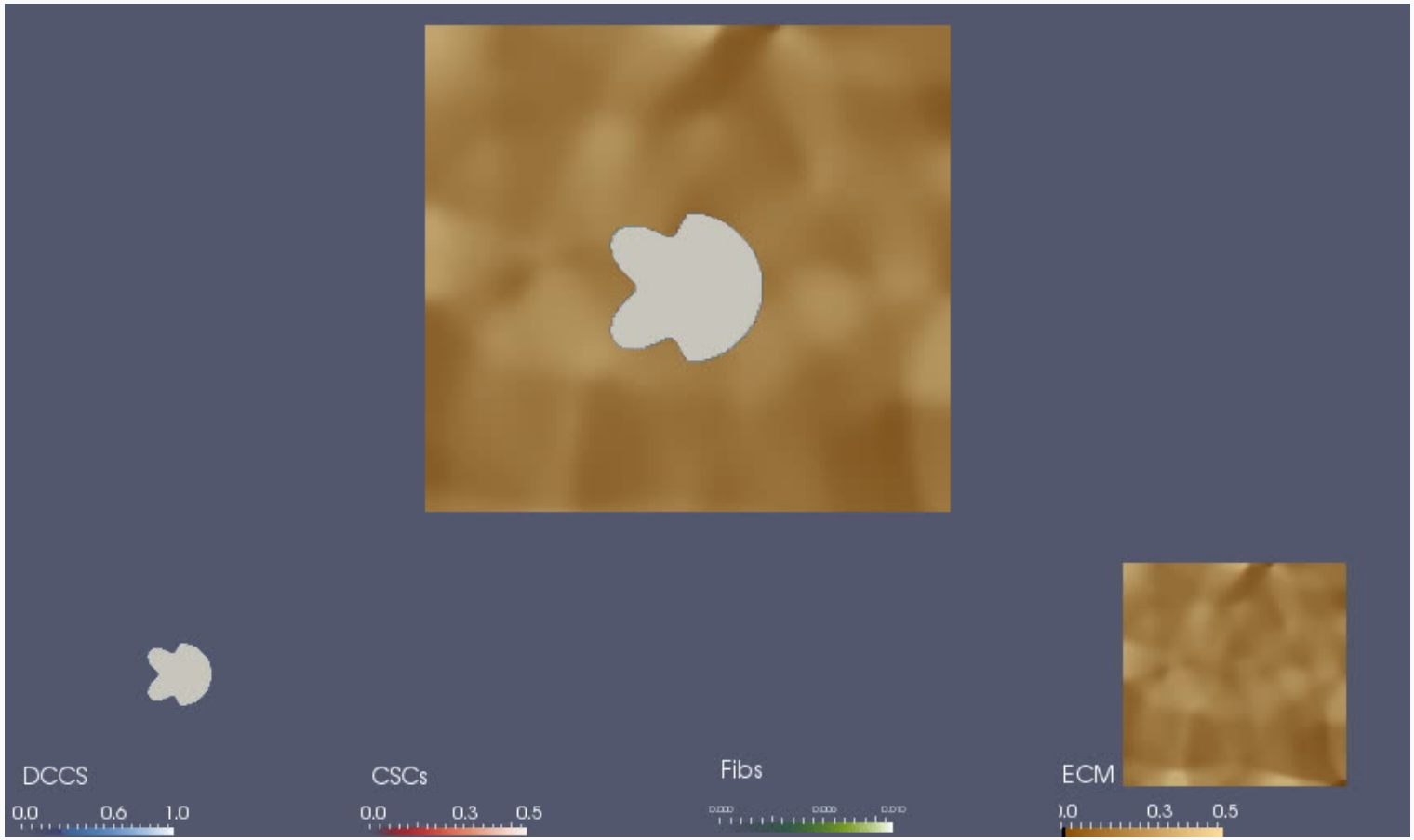
Model dynamics in 1D



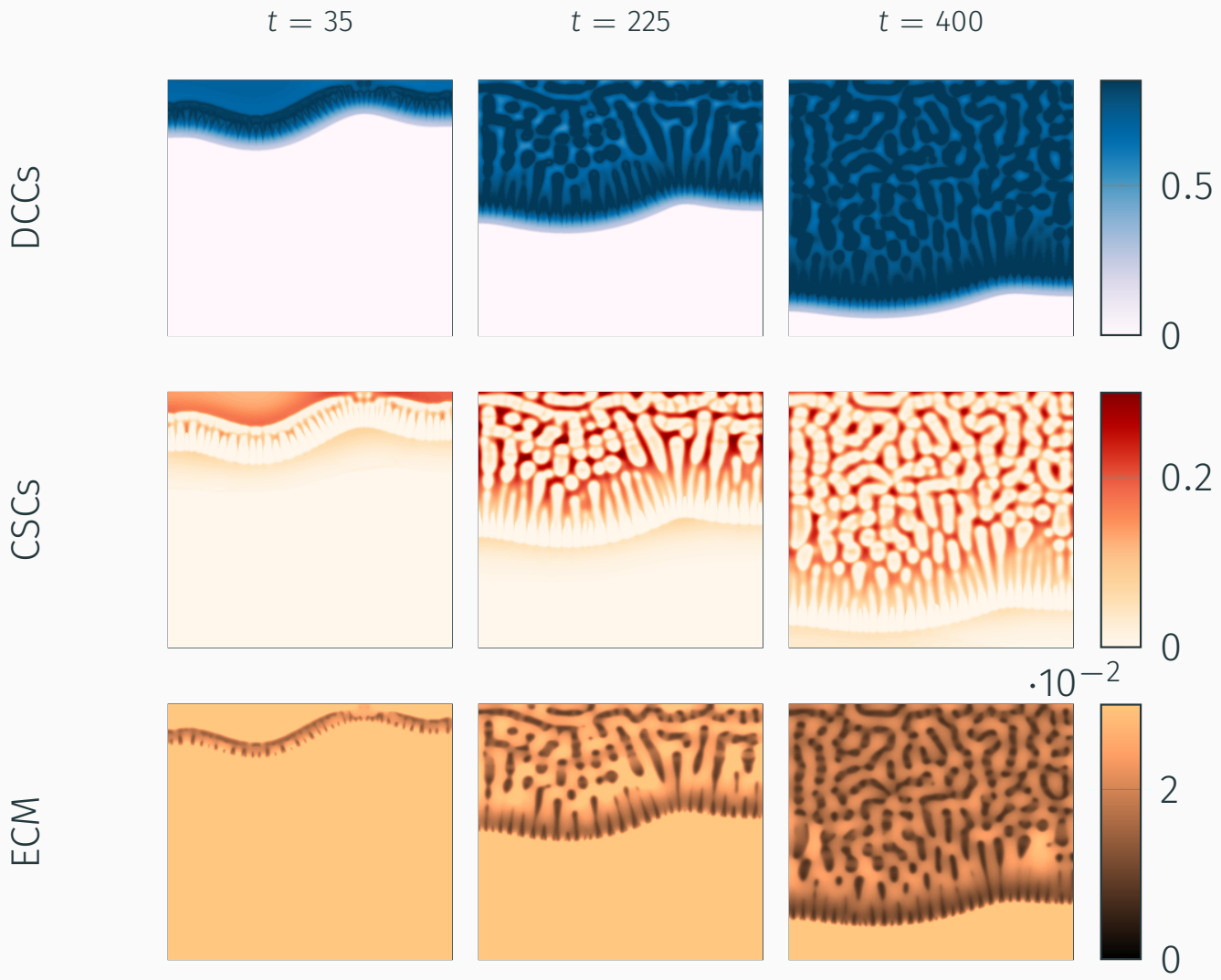
Spatial densities in 1D experiment in time instances $t = 1, 5, 12, 18, 20, 24, 27, 32$.

DCCs CSCs ECM

Model dynamics in 2D



Increased tissue remodeling/adhesion

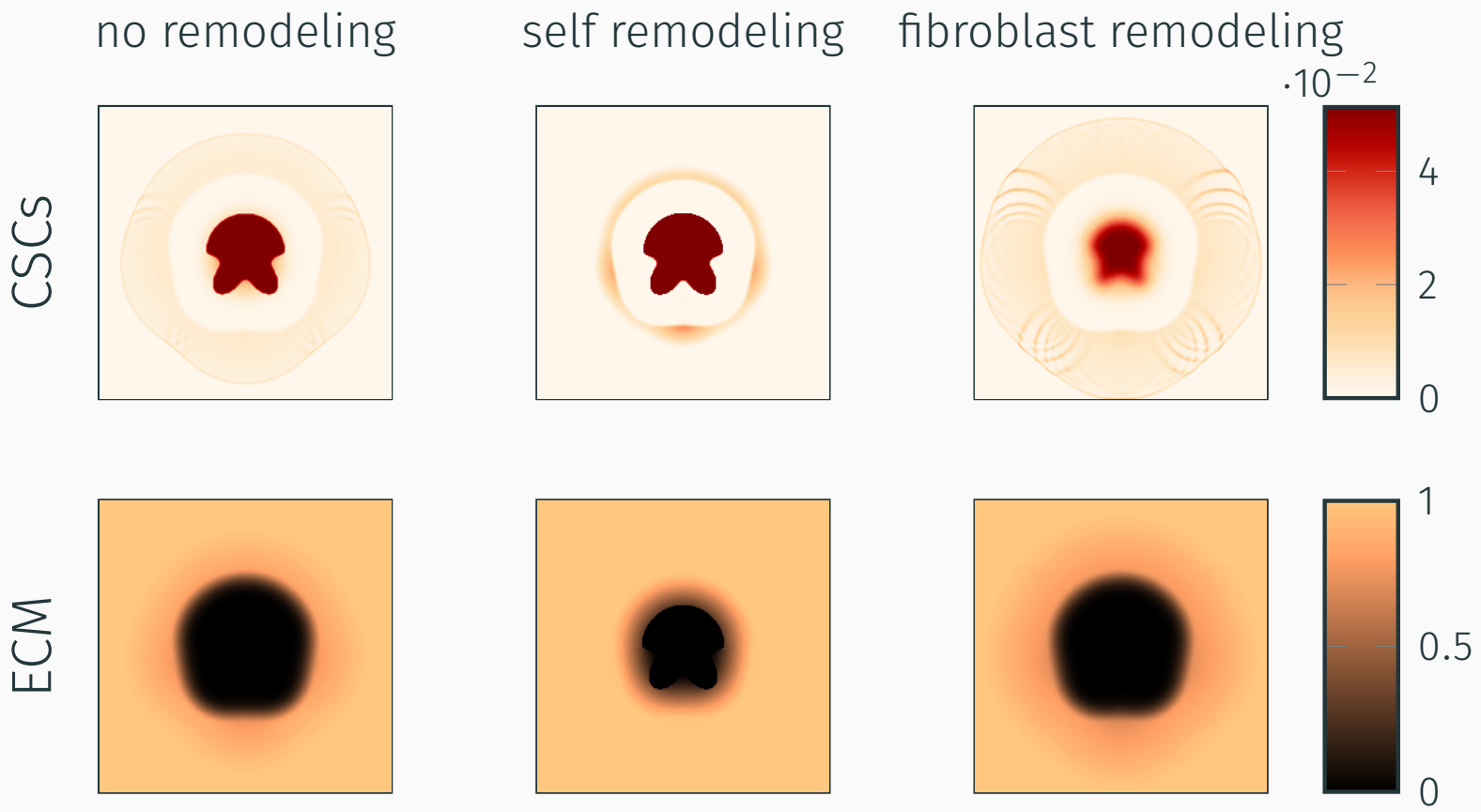


Experiment with initially homogeneous ECM.

Tissue remodeling

The majority of cancer cells that went through EMT escape from the main tumor

[Thiery Nat Rev Cancer (2002)]



Comparison to trivial EMT model

- CSCs make up only a minor subpopulation of the tumor

[Reya, Morrison, Clarke, Weissmann Nature (2001)]

- EMT is a late stage event in malignant cancer

[Tsai, Yang Genes & development (2013)]

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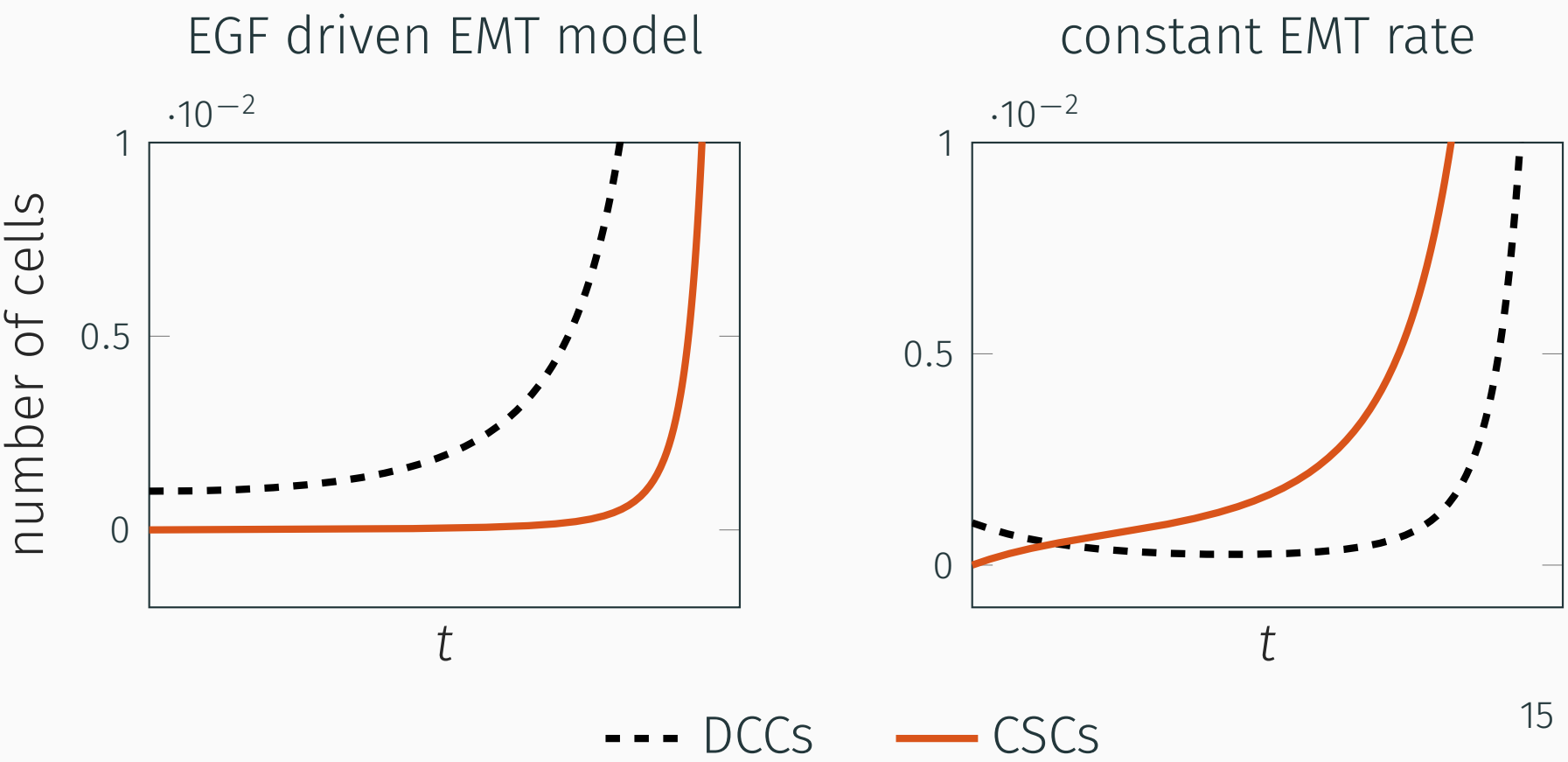


Conclusion

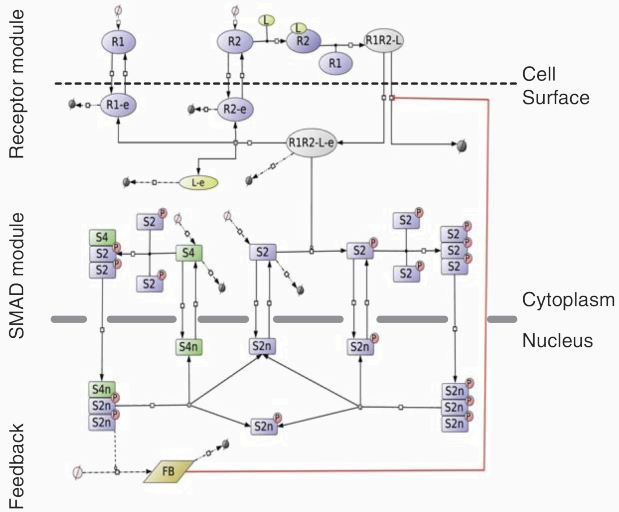
Conclusion

The multiscale PDE model (M)

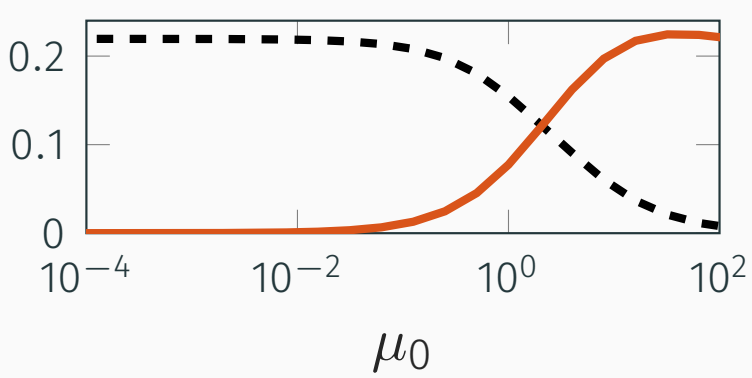
- can qualitatively reproduce the invasion by DCCs and CSCs
- exhibits important role of tumor associated fibroblasts in the modeling
- admits a unique global smooth solution in 2D

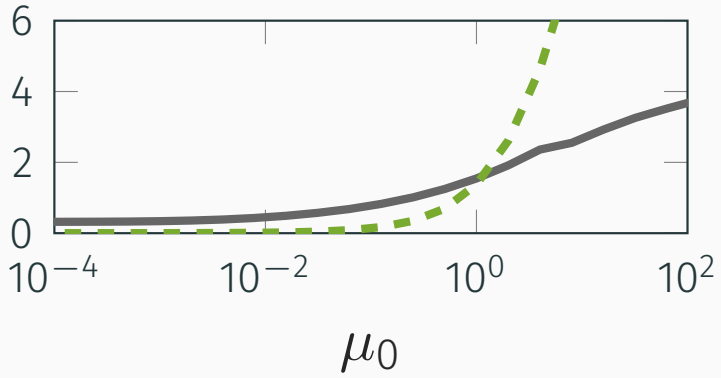
Ongoing work

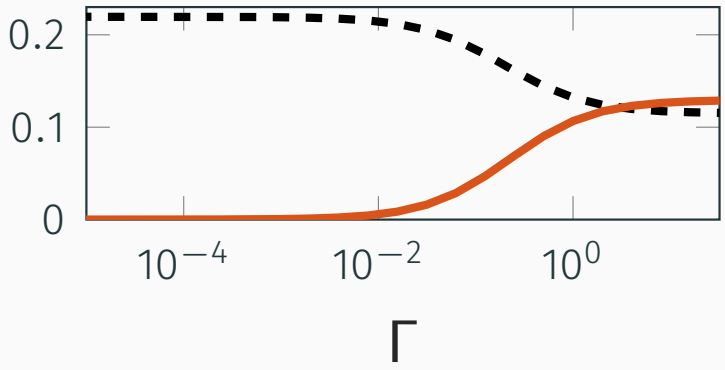
- consider TGFβ pathway
- derivation of SODE model in collaboration with S. Legewie and L. Ripka (IMB Mainz)
- replace role of EGF in spatial model

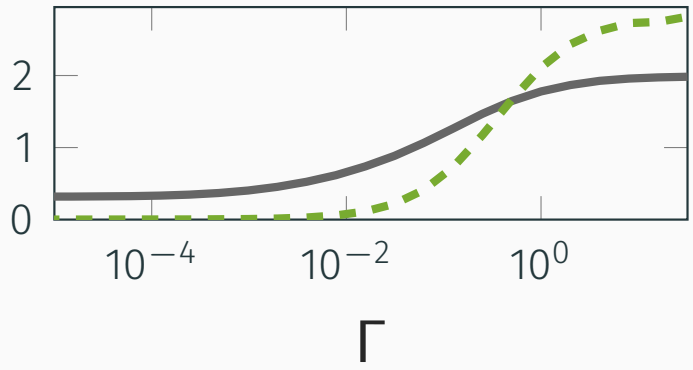


Parameter study





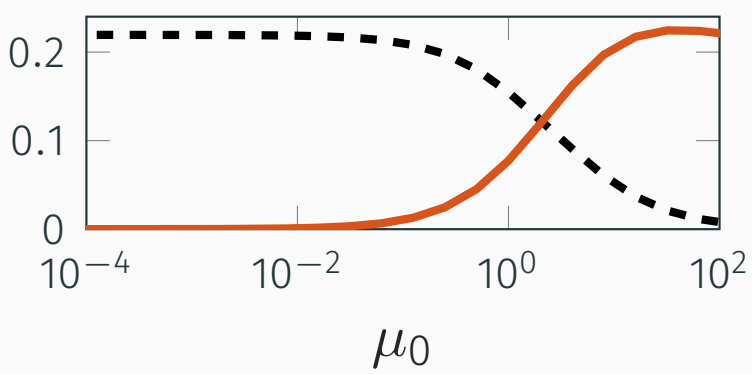


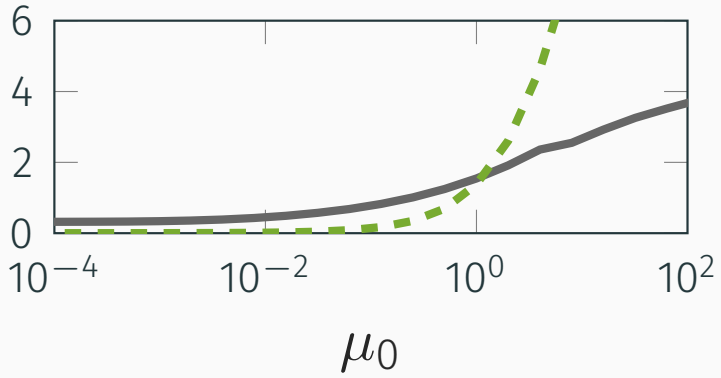


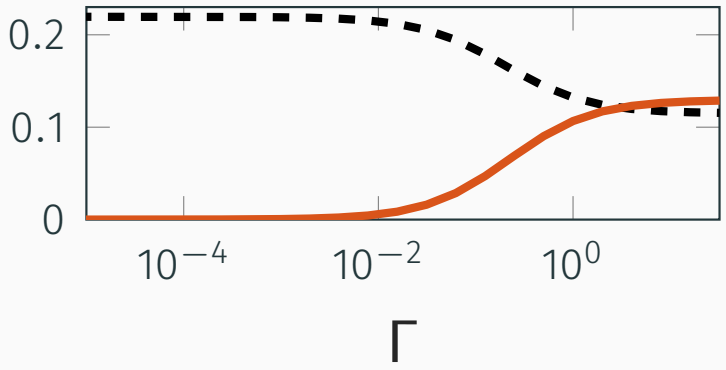
DCC mass — CSC mass

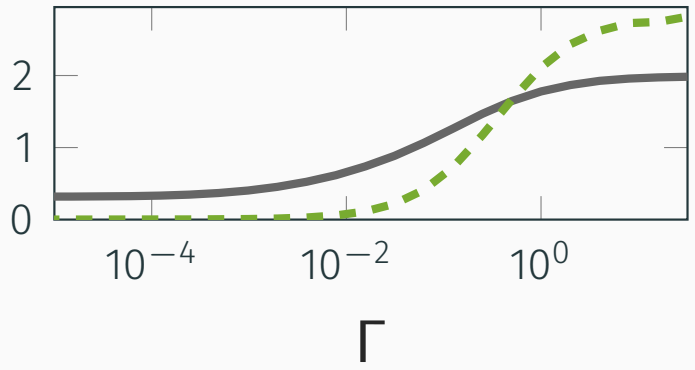
front height — front distance

Parameter study









Sensitivity analysis

- Sensitive (tumor promoting) to ECM remodeling by fibroblasts
- Sensitive (tumor promoting) to fibroblasts apoptosis