A coupled stochastic differential reaction-diffusion system for angiogenesis

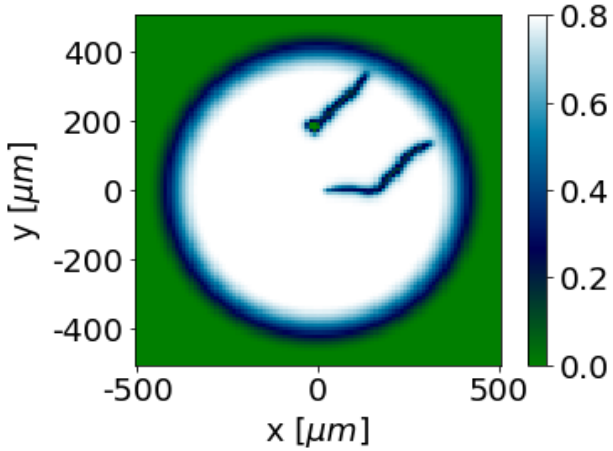
Ansgar Jüngel

Vienna University of Technology, Austria

www.asc.tuwien.ac.at/∼juengel

Joint work with M. Fellner (Vienna)

1. Introduction
2. Modeling
3. Analysis
4. Numerical simulation



Extracellular fluid fraction

European Research Council
Established by the European Commission

FWF
Der Wissenschaftsfonds.

Motivation

Vision: To understand emergence of network structures

Growing connections

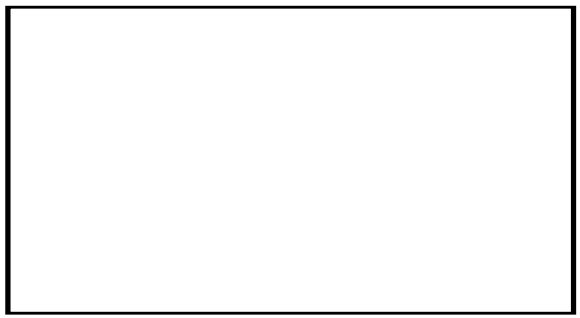
- Ion transport and axon growth
- Vasculogenesis (formation of vascular networks)
- Angiogenesis (growth from existing vessels)

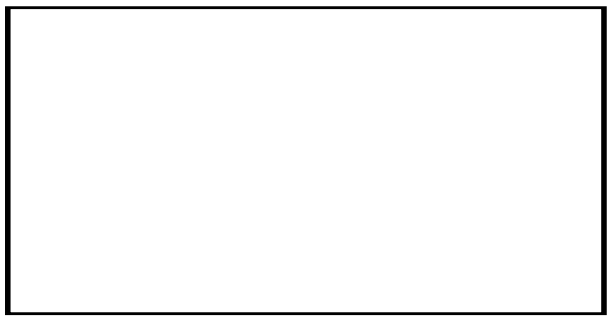
Emerging networks

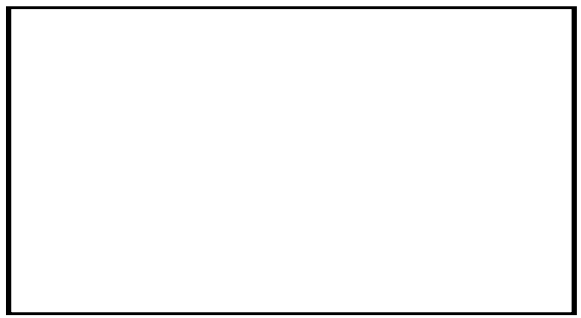
- Chemical-signal driven dynamics
- Self-wiring by feedback
- Mean-field description

Applying networks

- Simulate synapse by memristor device
- Memristor device-circuits
- Neuromorphic networks







Motivation

Vision: To understand emergence of network structures

Growing connections

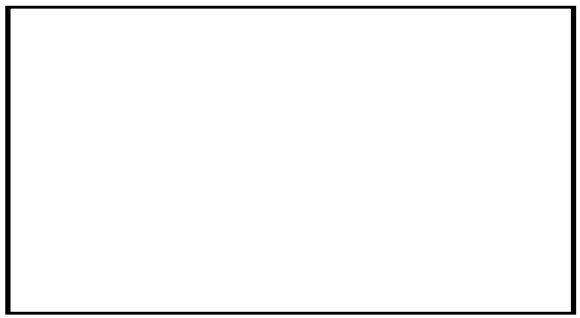
- Ion transport and axon growth
- Vasculogenesis (formation of vascular networks)
- **Angiogenesis (growth from existing vessels)**

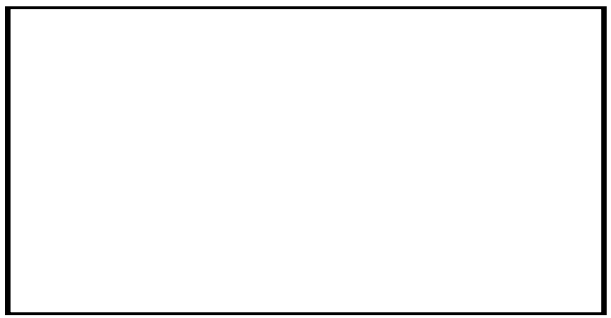
Emerging networks

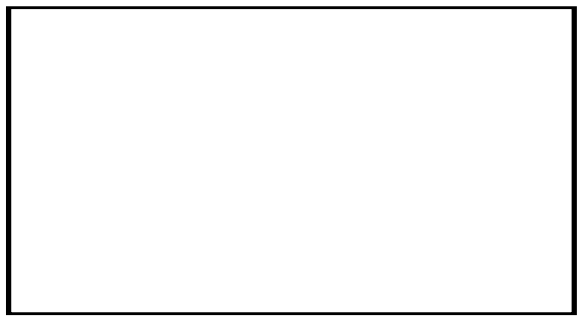
- Chemical-signal driven dynamics
- Self-wiring by feedback
- Mean-field description

Designing circuits

- Simulate synapse by memristor device
- Memristor device-circuits
- Neuromorphic networks

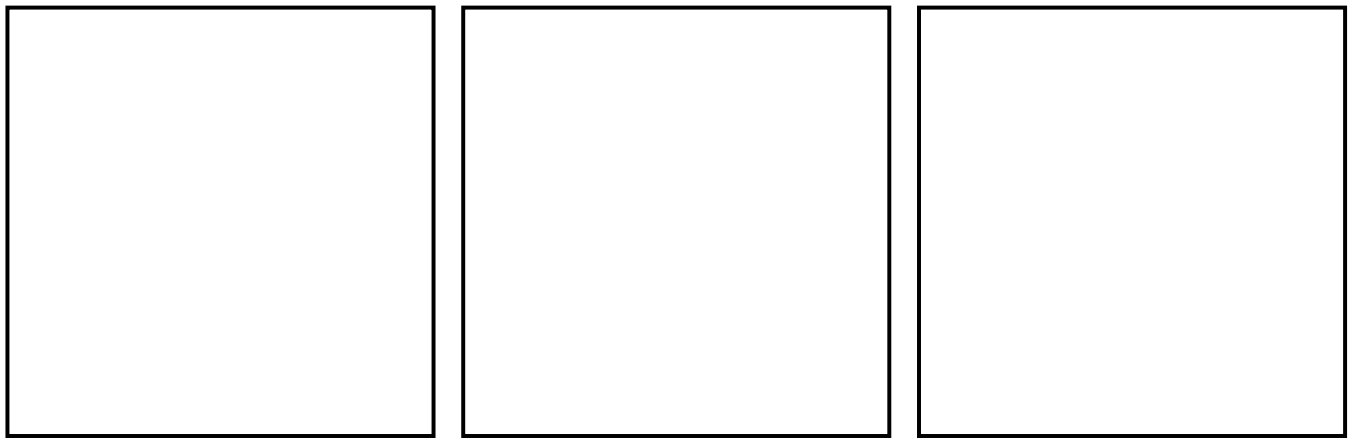




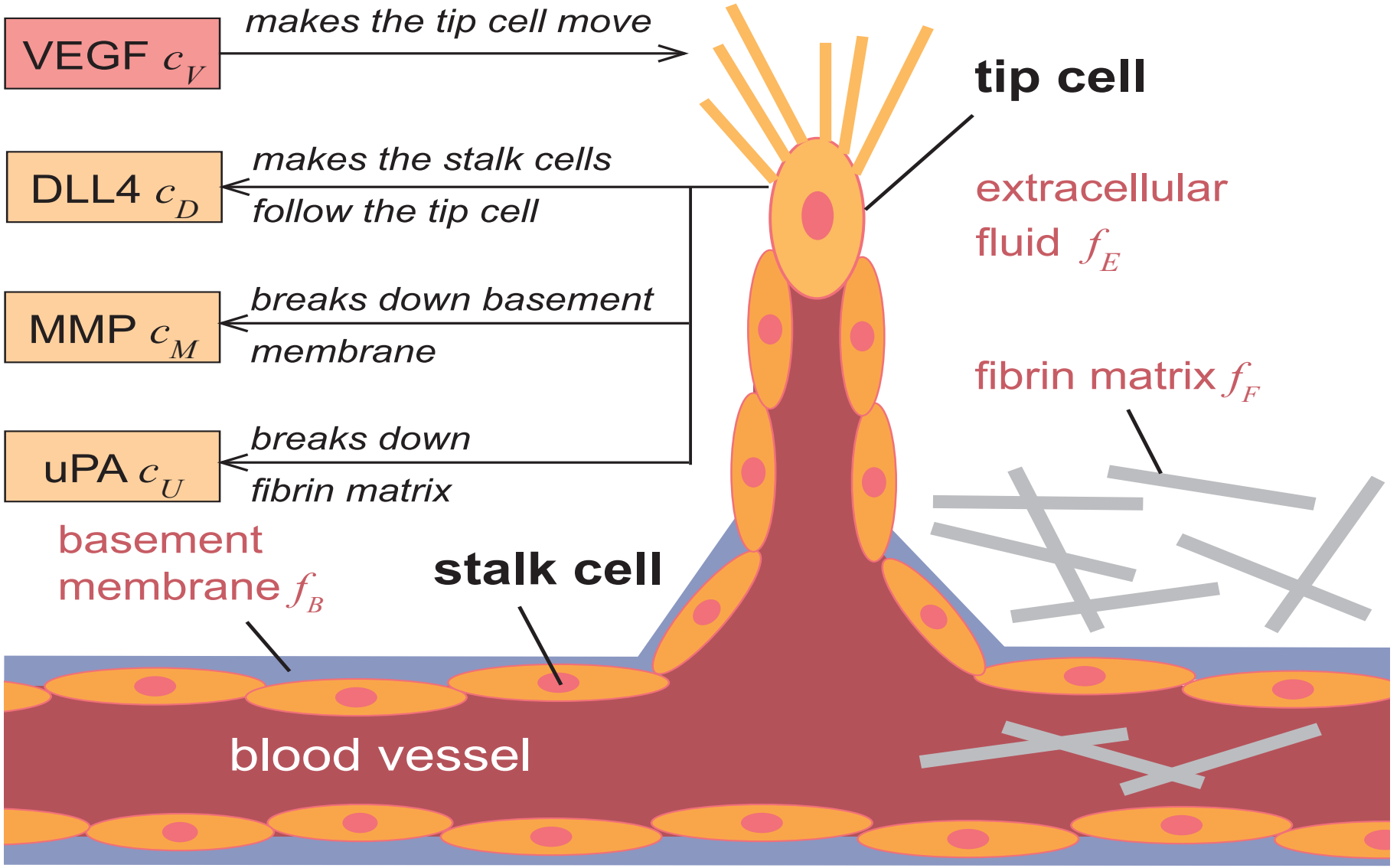


Angiogenesis

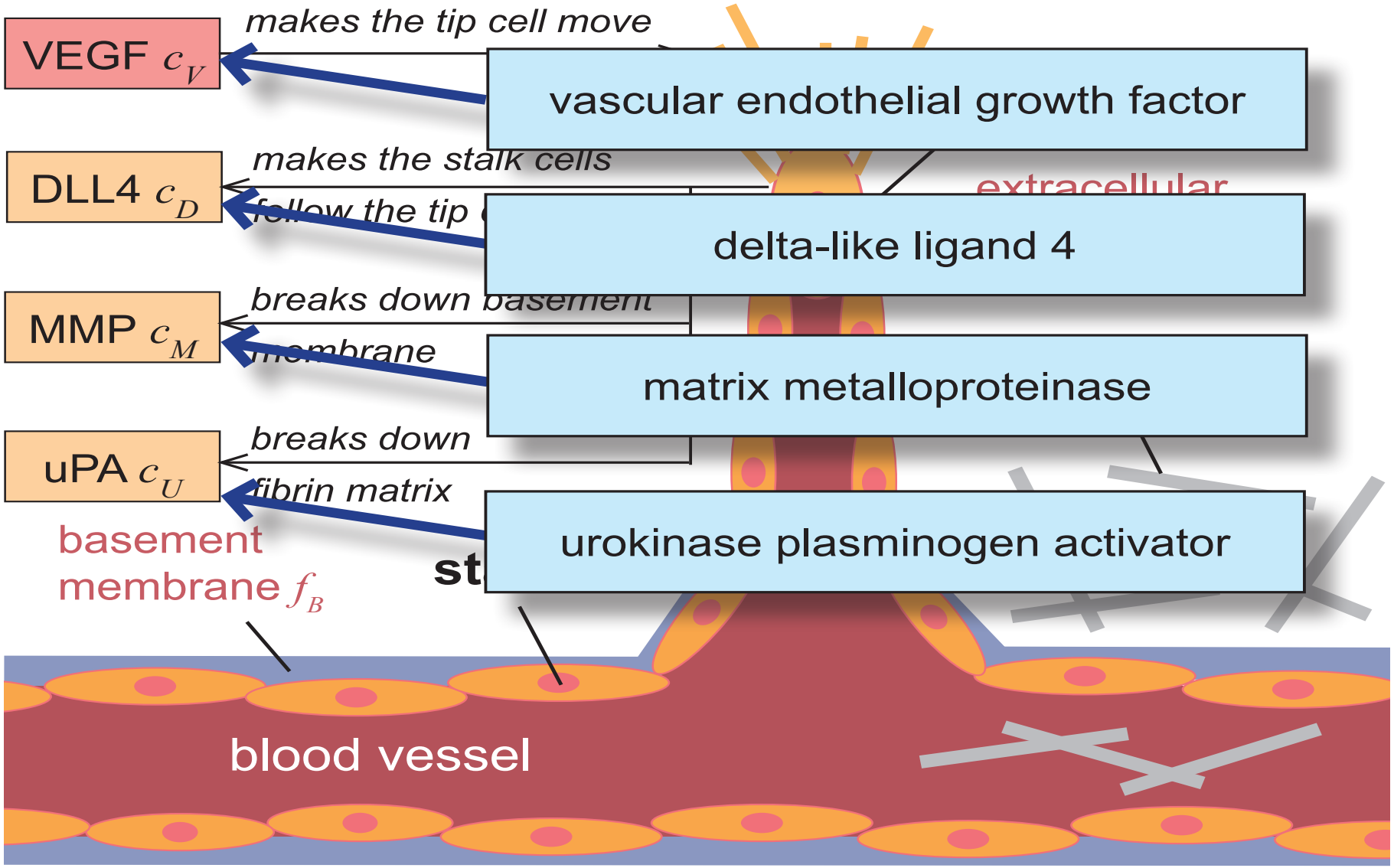
- Emergence of new blood vessels from existing ones
- Angiogenesis may be triggered by tissue hypoxia (low oxygen level)
- Activates production of VEGF (vascular endothelial growth factor)
- VEGF activates endothelial cells that release enzymes
- Enzymes degrade basement membrane (sheet-like structure)
- Endothelial cells becomes tip cells or stalk cells
- Tip cells follow source of VEGF, stalk cells follow tip cells



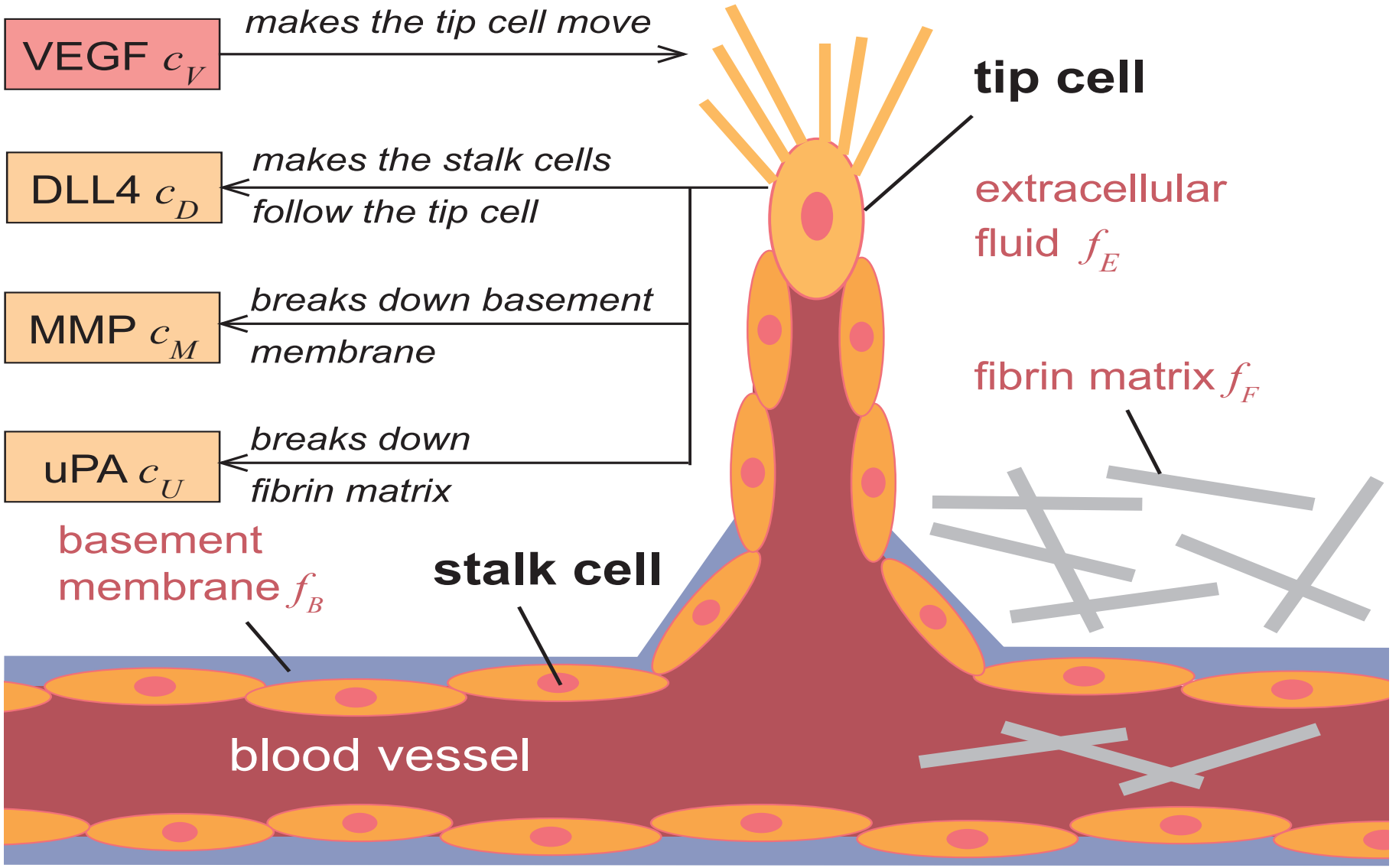
Angiogenesis



Angiogenesis



Angiogenesis



Overview

1. Introduction
2. Modeling
3. Analysis
4. Numerical simulation

Modeling of angiogenesis

- Cellular automata models: flexible but computationally expensive (Graner-Glazier 1992)
- Individual-based off-lattice models: Langevin/Newton eqs. (Byrne-Drasdo 2009)
- Continuum-scale models: PDEs (Gaffney-Pugh-Maini 2002)
- Hybrid models: vessel network on lattice, tip cells movement lattice free, other cells modeled as densities (Carlier et al. 2012)
- Off-lattice cell-based model: ODE-SDE-PDEs (Bookholt et al. 2016)

Model equation classes:

- SDE: positions of tip cells $X_1^k(t)$ and stalk cells $X_2^k(t)$
- ODE: volume fractions of basement membrane $f_B(x,t)$, extracellular fluid $f_E(x,t)$, fibrin matrix $f_F(x,t)$
- PDE: concentrations of proteins VEGF $c_V(x,t)$, DLL4 $c_D(x,t)$, MMP $c_M(x,t)$, uPA $c_U(x,t)$

Stochastic differential equations

- Itô SDE for position of tip cell $X_1^k(t)$ and stalk cell $X_2^k(t) \in \mathcal{D} \subset \mathbb{R}^3$:

$$dX_i^k(t) = g_i[c,f](X_i^k,t)dt + \sigma_i(X_i^k)dW_i^k(t), \ t>0, \quad X_i^k(0) = X_i^0$$

- Number of cells: $k = 1,\dots,N_i$, $i = 1,2$
- Drift terms: $g_i[c,f] = g_i(c,f,\nabla c,\nabla f)$ with $(c,f) \mapsto g_i[c,f](x,t)$ Lipschitz in C^1 and $(x,t) \mapsto g_i[c,f](x,t)$ Lipschitz in $W^{2,\infty}$
- Example for drift terms (used for simulations): $X = (X_1, X_2)$

$$g_1 = M_1(f_S,X_1)z_1(f_E,X) + \gamma(f_S)\nabla c_V(X_1) + \lambda(f_S)\nabla f_S(X_1),$$
$$g_2 = \underbrace{M_2(f_S,X_2)z_2(f_E,X)}_{\text{strain energy direction}} + \underbrace{\gamma(f_S)\nabla c_D(X_2)}_{\text{chemotaxis force}} + \underbrace{\lambda(f_S)\nabla f_S(X_2)}_{\text{durotaxis force}}$$

- Solid volume fraction = basement membrane + fibrin matrix: $f_S := f_B + f_F$

Ordinary differential equations

- Volume fractions of basement membrane f_B, extracellular fluid f_F, and fibrin matrix f_F

$$\frac{df_B}{dt} = -s_B c_M f_B, \quad t > 0, \quad f_B(0) = f_B^0,$$
$$\frac{df_F}{dt} = -s_F c_U f_F \quad t > 0, \quad f_F(0) = f_F^0,$$
$$\frac{df_E}{dt} = s_B c_M f_B + s_F c_U f_F, \quad t > 0, \quad f_E(0) = 1 - f_B^0 - f_F^0$$

- Rate constants: $s_B > 0$, $s_F > 0$
- Volume filling: $f_B + f_E + f_F = 1$ implies that $f_E = 1 - f_B - f_F$
- Pathwise explicit solution for $(x,t) \in \mathcal{D} \times (0,T)$, $\omega \in \Omega$:

$$f_B(\omega,x,t) = f_B^0 \exp\left(-s_B \int_0^t c_M(\omega,x,s)ds\right),$$
$$f_F(\omega,x,t) = f_F^0(0) \exp\left(-s_F \int_0^t c_U(\omega,x,s)ds\right).$$

Reaction-diffusion equations

- Concentrations of VEGF c_V, DDL4 c_D, MMP c_M, uPA c_U:

$$\partial_t c_V - \mathrm{div}(D_V(f)\nabla c_V) + \alpha_V(x,t)c_V = 0 \quad \text{in } \mathcal{D},\ t>0,$$
$$\partial_t c_D - \mathrm{div}(D_D(f)\nabla c_D) + \beta_D(x,t)c_D = \alpha_D(x,t)c_V \quad \text{in } \mathcal{D},\ t>0,$$
$$\partial_t c_M - \mathrm{div}(D_M(f)\nabla c_M) + s_M f_B c_M = \alpha_M(x,t)c_V \quad \text{in } \mathcal{D},\ t>0,$$
$$\partial_t c_U - \mathrm{div}(D_U(f)\nabla c_U) + s_U f_F c_U = \alpha_U(x,t)c_V \quad \text{in } \mathcal{D},\ t>0,$$

- Initial and no-flux boundary conditions:

$$c_j(0) = c_j^0 \text{ in } \mathcal{D}, \quad \nabla c_j \cdot \nu = 0 \text{ on } \partial\mathcal{D}, \quad j = V, D, M, U$$

- Diffusion coeff.: $D_j(f) = D_j^B f_B + D_j^E f_E + D_j^F f_F > 0 \Rightarrow$ unif. parabolic
- Rate functions: $\alpha_V = s_V\widetilde{\alpha}_V$, $\alpha_j = r_j\widetilde{\alpha}_j$, $j = D, M, U$

$$\widetilde{\alpha}_j(x,t) = \sum_{k=1}^{N_1} V_j^k(X_1^k(t) - x), \quad \beta_D(x,t) = s_D \sum_{k=1}^{N_2} V_D^k(X_2^k(t) - x)$$

and $V_j^k : \mathbb{R}^3 \to \mathbb{R}$ approximates delta distribution

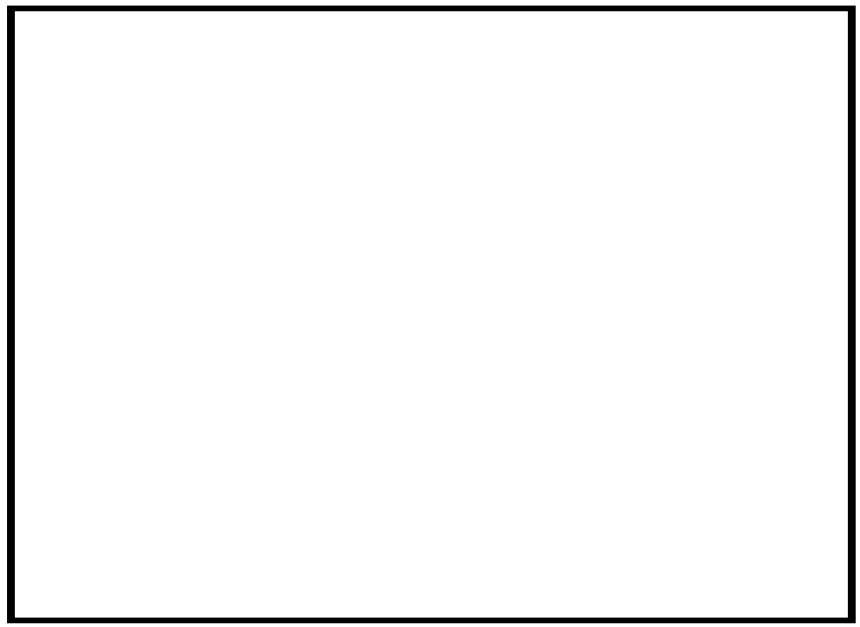
Discussion of the model

We model ...

... early stages of angiogenesis

... cells migrate by chemotaxis and durotaxis forces

... and distinguish tip and stalk cells (which is new)



Dermal endothelial cells stimulated with VEGF

We do not model ...

... transition between phenotypes *tip cell* and *stalk cell*

... sprouting from existing vessels, branching, anastomosis (= interconnection between blood vessels)

... other growth factors, like tumor necrosis growth factor

... vasculogenesis (first stage of formation of vascular network)

Overview

1. Introduction
2. Modeling
3. Analysis
4. Numerical simulation

Analysis

$$dX_i^k = g_i[c,f](X_i^k)dt + \sigma_i(X_i^k)dW_i^k, \ \ k = 1,\ldots,N_i, \ \ i = 1,2$$
$$\partial_t c_j - \operatorname{div}(D(f)\nabla c_j) + R(c,f,X) = Q(c_V,X), \quad f = f[c] \text{ solves ODE}$$

Mathematical difficulties: $(j = V, D, M, U)$

- Nonlocal diffusivities, mixed-type equations, nonlinearities
- Hölder continuous drift needed in SDE $\to c \in C^{1+\delta}(\overline{\mathcal{D}})$ needed
- Paths $X_i^k(t)$ should not leave domain $\mathcal{D}$
- Choice of space in fixed-point theorem

Mathematical ideas:

- Coupling not too strong: X_i feeds into reaction terms in PDE
- Combine existence results for SDE & parabolic regularity theory
- Apply stochastic analysis results to guarantee progressive measurability of $g_i[c,f]$ and σ_i

Existence analysis

$$dX_i^k = g_i[c,f](X_i^k)dt + \sigma_i(X_i^k)dW_i^k, \quad k = 1,\dots,N_i, \quad i = 1,2$$

$$\partial_t c_j - \operatorname{div}(D(f)\nabla c_j) + R(c,f,X) = Q(c_V, X), \quad f = f[c] \text{ solves ODE}$$

Main assumptions:

- Filtered probability space: $(\Omega, \mathcal{F}, (\mathcal{F}_t)_{t\geq 0}, \mathbb{P})$
- $(W_i^k(t))_{t\geq 0}$ independent Wiener processes on $\mathbb{R}^3$
- Initial data: $X_i^0 \in \mathcal{D}$, $c^0 \in L^\infty(\Omega; C^{2+\delta}(\overline{\mathcal{D}}))$, $f^0 \in L^\infty(\Omega; C^{1+\delta}(\overline{\mathcal{D}}))$
- Diffusion: σ_i Lipschitz, linear growth, and $\sigma_i = 0$ on $\partial\mathcal{D}$ a.s.
- Drift: g_i Lipschitz, $g_i[c,f] = 0$ on $\partial\mathcal{D}$ if (c,f) solution
- Potential: $V_j^k \in C^{0,1}(\mathbb{R}^3)$ nonnegative (used in PDE rate terms)

Theorem (Global existence, Fellner-AJ 2022)

There exists unique (f,c,X) such that $f_i \in C^0([0,T]; L^2(\mathcal{D}))$, c classical solution, $X_i^k \in C^{1/2}([0,T]; L^4(\Omega))$ strong solution.

Strategy of proof

$$\partial_t c_V - \operatorname{div}(D_V(f)\nabla c_V) + \alpha_V(x,t)c_V = 0 \quad \text{in } \mathcal{D},\ t>0,$$
$$\partial_t c_D - \operatorname{div}(D_D(f)\nabla c_D) + \beta_D(x,t)c_D = \alpha_D(x,t)c_V \quad \text{in } \mathcal{D},\ t>0,$$
$$\partial_t c_M - \operatorname{div}(D_M(f)\nabla c_M) + s_M f_B c_M = \alpha_M(x,t)c_V \quad \text{in } \mathcal{D},\ t>0,$$
$$\partial_t c_U - \operatorname{div}(D_U(f)\nabla c_U) + s_U f_F c_U = \alpha_U(x,t)c_V \quad \text{in } \mathcal{D},\ t>0,$$

Step 1: Solvability of ODE-PDE

- Given $\widetilde{X}_i^k \in Y_R(0,T;\mathcal{D})$, where
  $Y_R(0,T;\mathcal{D}) = \{X \in C^{1/2}([0,T];L^4(\Omega)) : \|X\|_{C^{1/2}([0,T];L^4(\Omega))} \le R,\ X(t) \in \overline{\mathcal{D}}\}$
- Then $\widetilde{\alpha}_j = \sum_k V_j^k(\widetilde{X}_1^k(t) - x)$, $\beta_D = s_D \sum_k V_D^k(\widetilde{X}_2^k(t) - x)$ Hölder continuous in (x,t) a.s.
- Prove uniform estimates for c independent of $\widetilde{X}$: Moser iteration for L^∞, regularity theory gives c Hölder continuous
- Thus $D_j(f[c])$ Hölder cont. and, by regularity, c classical solution
- Existence of (c,f) by Schauder fixed-point theorem

Strategy of proof

$$dX_i^k = g_i[c,f](X_i^k)dt + \sigma_i(X_i^k)dW_i^k,\ k=1,\dots,N,\ i=1,2$$

Step 2: Solvability of SDE

- From Step 1: solution (c,f) and $(\nabla c, \nabla f)$ Hölder
- Show that (c,f) and $(\nabla c, \nabla f)$ progressively measurable
  (i.e. $(\omega,t)\mapsto c(\omega,x,t)$ $\mathcal{B}([0,T])\times\mathcal{F}_t$-measurable for a.e. $x\in\mathcal{D}$)
- Thus $\exists$ unique strong solution X (Liu-Röckner 2015)
- How to prove that $X_i^k(t)\in\overline{\mathcal{D}}$? Assume $X_i^k(t)\in\mathcal{D}^c$. Let $\operatorname{supp}\phi\subset\mathcal{D}^c$, apply Itô lemma:

$$d\phi(X_i^k) = \nabla\phi(X_i^k)\cdot \underbrace{g_i[c,f](X_i^k)}_{=0}\,dt + \tfrac{1}{2}\underbrace{\sigma_i(X_i^k)^2}_{=0}\Delta\phi(X_i^k)dt$$
$$+\nabla\phi(X_i^k)\cdot\underbrace{\sigma_i(X_i^k)}_{=0}dW_i^k = 0$$

Thus, $\phi(X_i^k(t)) = \phi(X_i^k(0)) = 0 \Rightarrow X_i^k(t)\in\overline{(\operatorname{supp}\phi)^c}\subset\overline{\mathcal{D}}$

Strategy of proof

$$dX_i^k = g_i[c,f](X_i^k)dt + \sigma_i(X_i^k)dW_i^k, \quad k=1,\ldots,N, \quad i=1,2$$
$$\partial_t c_j - \operatorname{div}(D(f)\nabla c_j) + R(c,f,X) = Q(c_V,X), \quad f = f[c] \text{ solves ODE}$$

Step 3: Solvability of SDE-ODE-PDE system

- $Y_R(0,T;\mathcal{D}) = \{X \in C^{1/2}([0,T];L^4(\Omega)) : \|X\|_{C^{1/2}([0,T];L^4(\Omega))} \le R,\ X(t) \in \overline{\mathcal{D}}\}$
- (c,f) uniformly bounded $\Rightarrow \exists\, R_0 > 0$: $X \in Y_{R_0}(0,T;\mathcal{D}) =: Y$
- Fixed-point operator $\Phi : Y \to Y$, $\widetilde{X} \mapsto (\alpha,\beta) \mapsto (c,f) \mapsto X$
- Prove that Φ is contraction: Let X, $X' \in Y$

$$\mathbb{E}|X(t)-X'(t)|^4 \le Ct\int_0^t \mathbb{E}\|(c-c')(s)\|_{C^1(\overline{\mathcal{D}})}^4 ds$$
$$\le Ct\big(\|\alpha-\alpha'\|_{L^4_{x,t}}^4 + \|\beta-\beta'\|_{L^4_{x,t}}^4\big) \le Ct\int_0^t \mathbb{E}|X(s)-X'(s)|^4 ds$$

- Iterate:
$\mathbb{E}|\Phi^n(X(t)) - \Phi^n(X'(t))|^4 \le (Ct)^n(t^n/n!)\sup_{0<s<t}\mathbb{E}|X(s)-X'(s)|^4$

Strategy of proof

$$dX_i^k = g_i[c,f](X_i^k)dt + \sigma_i(X_i^k)dW_i^k, \quad k = 1,\dots,N, \quad i = 1,2$$
$$\partial_t c_j - \operatorname{div}(D(f)\nabla c_j) + R(c,f,X) = Q(c_V, X), \quad f = f[c] \text{ solves ODE}$$

Step 3: Solvability of SDE-ODE-PDE system

$$\sup_{0<s<T} \left(\mathbb{E}|\Phi^n(X(t)) - \Phi^n(X'(t))|^4\right)^{1/4} \le \frac{(CT^2)^{n/4}}{(n!)^{1/4}} \sup_{0<s<T} \left(\mathbb{E}|X(s) - X'(s)|^4\right)^{1/4}$$

- $(CT^2)^{n/4}/(n!)^{1/4} \to 0$ as $n \to \infty \Rightarrow \exists\, n \in \mathbb{N}$: Φ^n is contraction
- Banach fixed-point theorem: existence of unique solution

Limitations:

- Transition process between phenotypes *tip cells* and *stalk cells*
- Potentials V_j^k given by delta distributions $\to$ solution c of $-\Delta c = \delta_0$ in $W^{1,p}(\mathcal{D})$ with $p < 3/2 \to c$ may be not Hölder continuous but SDE needs Hölder continuous coefficients
- Generalizations: sublinear growth (Nilssen 2016), continuous drift & weak solution (Bauer/Meyer-Brandis/Proske 2018)

Overview

1. Introduction
2. Modeling
3. Analysis
4. Numerical simulation

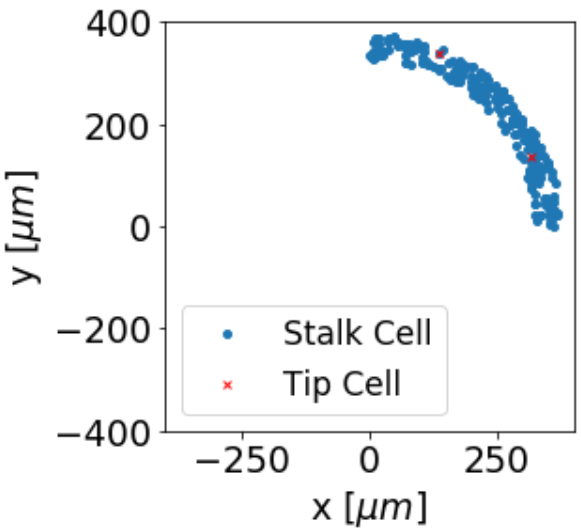
Numerical simulation

- Domain: ball in $\mathbb{R}^2$ with radius 500 μm, space step size 10 μm, time step size $\tau = 1$ s
- SDE: standard Euler-Maruyama scheme
- ODE: trapezoidal rule for integral in $f_B((n+1)\tau) = f_B(n\tau)\exp(-s_B \int_0^\tau c_M(s + n\tau)ds)$ (similar for f_F)
- PDE: semi-implicit central finite-difference scheme
- Scheme is semi-implicit; solution of linear system in *SciPy* using sparse matrices and `spsolve` from `scipy.sparse.linalg`

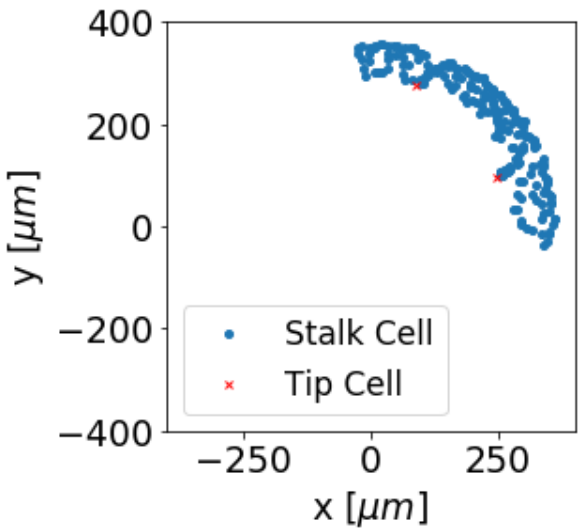
Numerical data:

- Drift: as in Bookholt et al. 2016 (direction from strain energy, chemotaxis, durotaxis)
- Stochastic diffusion: radially symmetric around origin, decreasing
- Potentials: approximation of delta distribution
- Initial data for X_i^k, f_i and c_j, 2 tip cells, 200 stalk cells

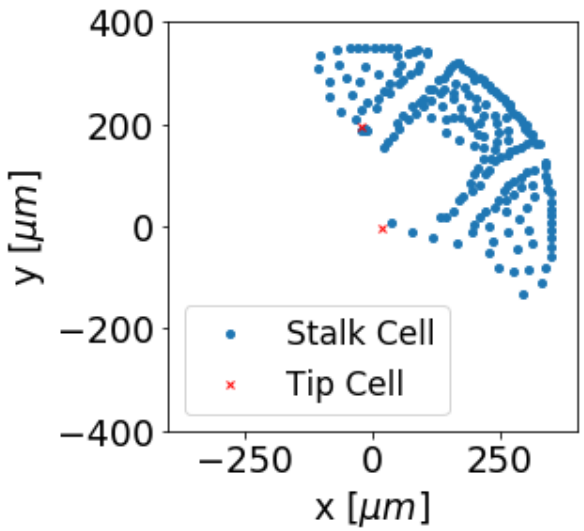
Position of tip and stalk cells



$t = 0\,\mathrm{s}$



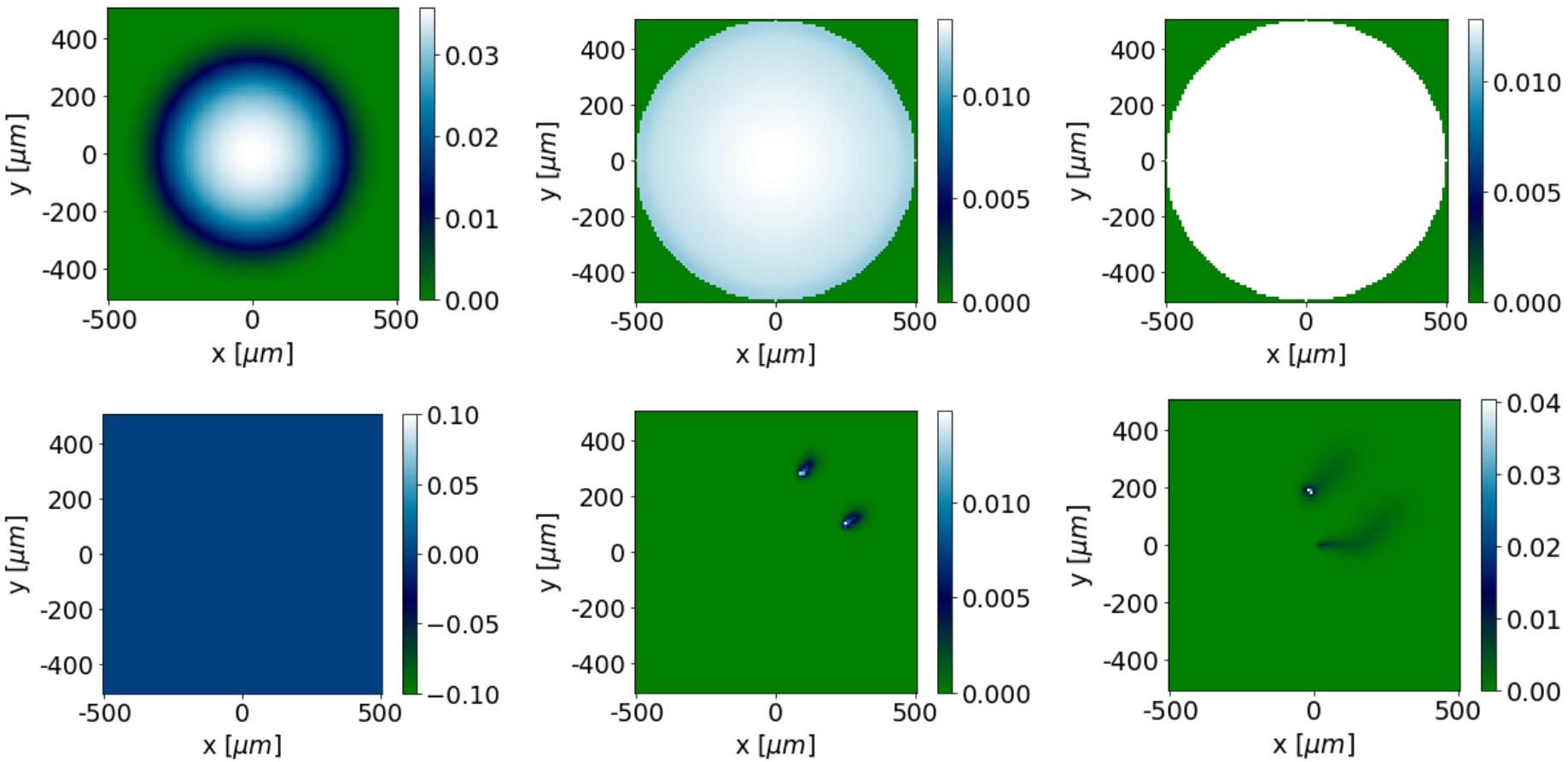
$t = 400\,\mathrm{s}$



$t = 1600\,\mathrm{s}$

- Tip cells segregate DLL4 protein, stalk cells follow tip cells
- Stronger effect for tip cell close to dense stalk cell population
- Other stalk cells spread because of strain energy & stiffness gradient $\nabla f_S = \nabla(f_B + f_F)$ (solid fraction)

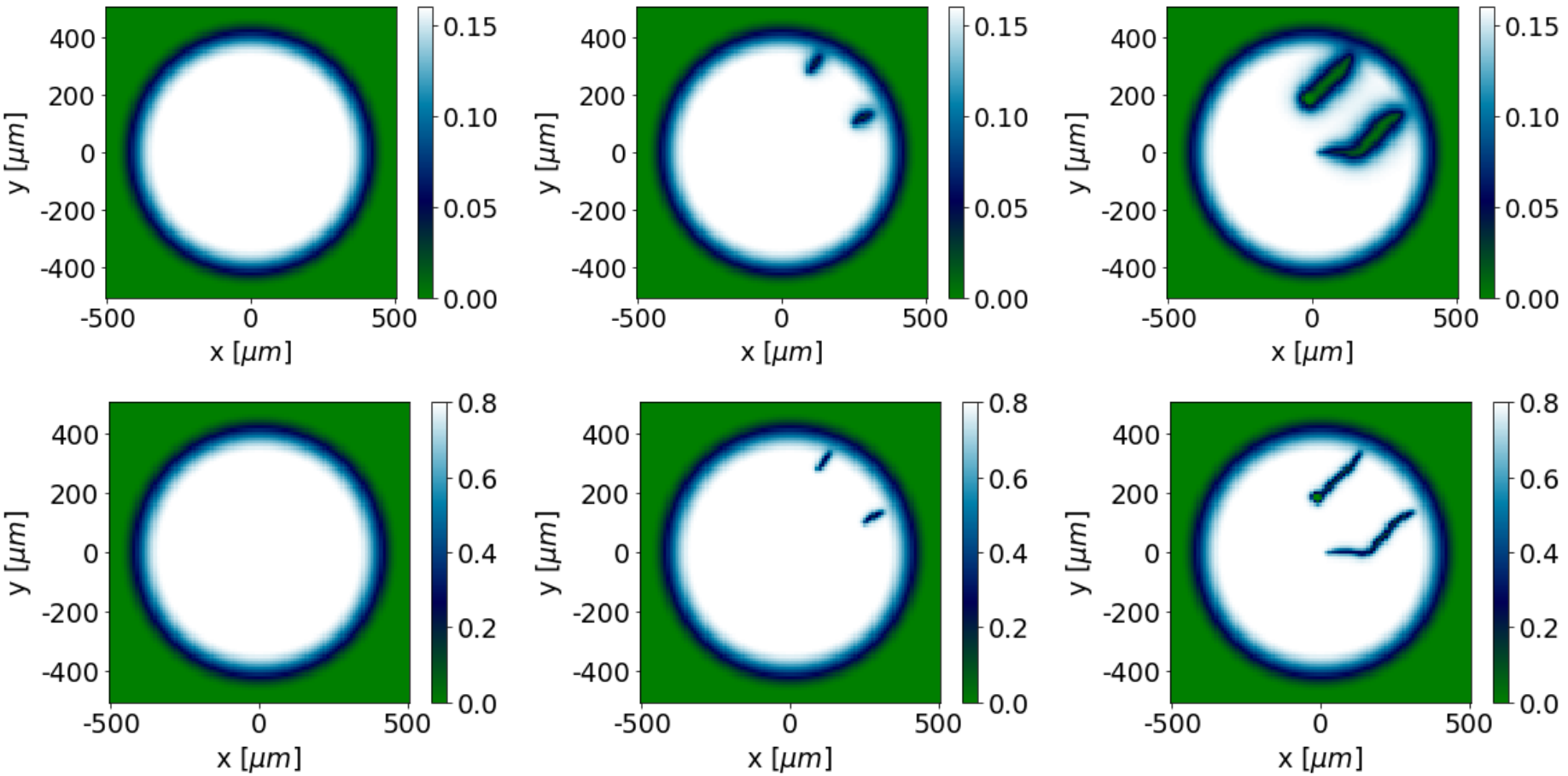
Concentrations of VEGF and DDL4 proteins



$t = 0\,\mathrm{s}$ $t = 400\,\mathrm{s}$ $t = 1600\,\mathrm{s}$

- Diffusion for VEGF "large": c_V becomes uniform for $t \to \infty$
- DLL4 protein produced by tip cells, follow their paths

Volume fractions of basement membrane and fibrin matrix



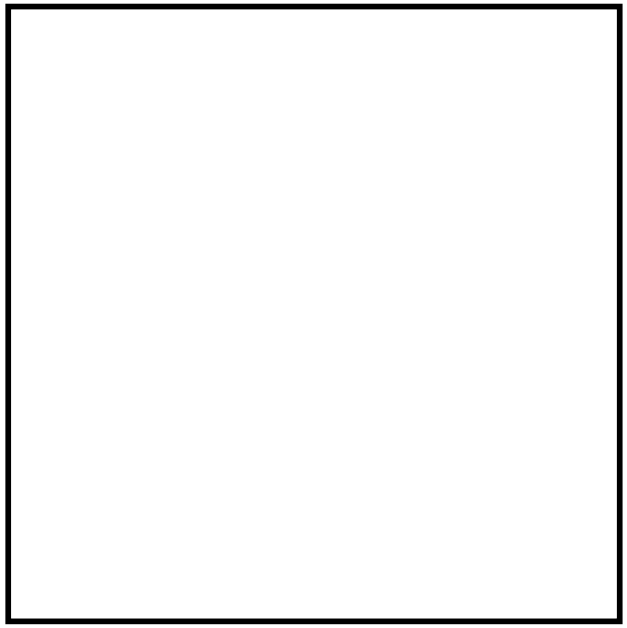
$t = 0\,\mathrm{s}$ $t = 400\,\mathrm{s}$ $t = 1600\,\mathrm{s}$

- Membrane and fibrin matrix degraded by MMP and uPA proteins
- MMP and uPA proteins produced by tip cells, follow their paths

Summary and perspectives

Summary:

- First stages of angiogenesis modeled by nonlinear SDE-ODE-PDE system
- Global existence and uniqueness of strong/classical solutions
- Model able to describe formation of premature sprouts although simple model



Perspectives:

- Understand chemotaxis and durotaxis role to create network structure
- Understand mixed-type systems: Mean-field models appropriate? Fluctuations-corrected models needed?
- Modeling of plasticity of neural networks: memory, (Hebbian) learning
- Combine biology and semiconductor theory for novel electronic devices