BIRS Workshop on Coupled Mathematical Models . . .

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Tumor induced angiogenesis

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Outline

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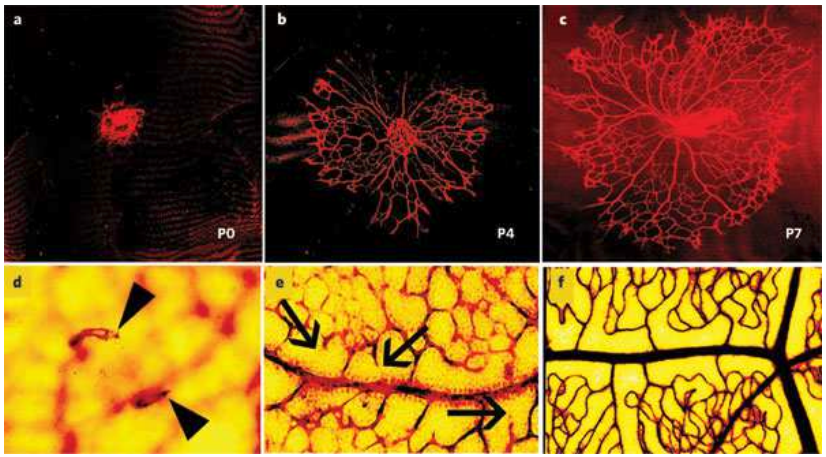
The formation of blood vessels

★ Angiogenesis is essential for organ growth & repair

↪ Figure: *Gariano and Gardner, Nature (2005)*



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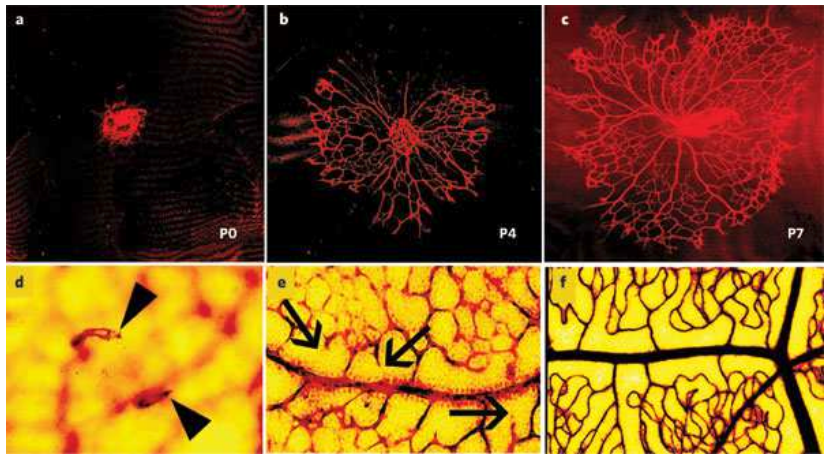
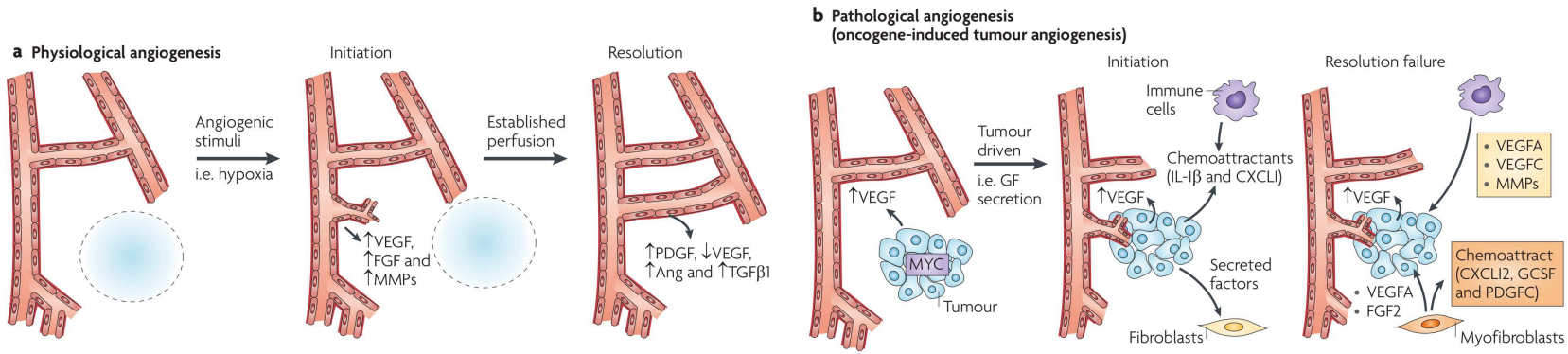


★ Angiogenesis can be either physiological or pathological (*tumor induced*) ↪ Figure: *Chung et al., Nature Reviews (2010)*



Angiogenesis treatment

Experimental dose-effect analysis is routine in biomedical laboratories, but these still lack *methods of optimal control to assess effective therapies*

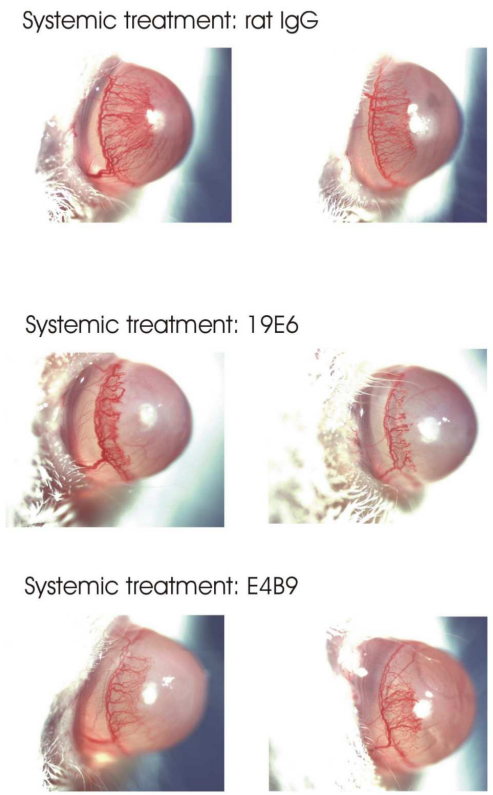


Figure: angiogenesis on a rat cornea – E. Dejana *et al.* (2005)

Modeling angiogenesis

- ★ Continuum models: reaction-diffusion equations for densities of endothelial cells, growth factors, ... (e.g. Chaplain) or kinetic equations for distributions of *active particles* (cells, agents, ...) (e.g. Bellomo)
- ★ Cellular models (T. Heck's 2015 classification):
  - *tip cell migration,*
  - *stalk-tip cell dynamics,*
  - *cell dynamics at cellular scale (e.g. cellular Potts models).*
- ★ Many are *multiscale models*, combining randomness at the natural microscale/mesoscale with numerical solutions of PDEs at the macroscale
- ★ Some mathematical models: Chaplain, Bellomo, Preziosi, Byrne, Folkman, Sleeman, Anderson, Stokes, Lauffenburger, Wheeler, Bauer, Bentley, Gerhardt, Travasso
- ★ Some experiments: Jain, Carmeliet, Dejana, Fruttiger
- ★ Mostly numerical outcomes, no stat-mech study

Outline

Stochastic Model and Deterministic Description

Vessel Extension

$$d\mathbf{X}^i(t) = \mathbf{v}^i(t)\,dt$$

$$d\mathbf{v}^i(t) = \underbrace{-\beta\,\mathbf{v}^i(t)}_{\text{friction}}\,dt + \underbrace{\beta\,\mathbf{F}\big(C(t,\mathbf{X}^i(t))\big)}_{\text{chemotactic force}}\,dt + \underbrace{\sqrt{\beta}\,d\mathbf{W}^i(t)}_{\text{random noise}}, \quad \mathbf{F}(C) = \frac{\delta\,\nabla_x C}{\beta\,(1+\Gamma_1 C)}$$

Tip Branching

$$\text{prob}\Big\{N(t+dt)-N(t)=1\Big\} = \sum_{i=1}^{N(t)} \underbrace{\alpha\left(C(t,\mathbf{X}^i(t))\right)}_{\text{response to TAF}}\ \underbrace{\delta_v(\mathbf{v}^i(t)-\mathbf{v}_0)}_{\text{velocity selector}}\,dt\,, \quad \alpha(C) = \frac{A\,C}{1+C}$$

Anastomosis

$$\frac{\partial}{\partial t}p(t,\mathbf{x},\mathbf{v}) = \underbrace{\alpha(C(t,\mathbf{x}))\,p(t,\mathbf{x},\mathbf{v})\,\delta_v(\mathbf{v}-\mathbf{v}_0)}_{\text{tip branching}}$$
$$\underbrace{-\,\Gamma\,p(t,\mathbf{x},\mathbf{v})\int_0^t\int p(s,\mathbf{x},\mathbf{v}')\,d\mathbf{v}'\,ds}_{\text{anastomosis}}$$
$$\underbrace{-\,\mathbf{v}\cdot\nabla_x\,p(t,\mathbf{x},\mathbf{v})}_{\text{transport}} + \underbrace{\beta\,\nabla_v\cdot\Big[\mathbf{v}\,p(t,\mathbf{x},\mathbf{v})\Big]}_{\text{friction}}$$
$$\underbrace{-\,\beta\,\nabla_v\cdot\Big[\mathbf{F}(C(t,\mathbf{x}))\,p(t,\mathbf{x},\mathbf{v})\Big]}_{\text{chemotactic forcing}} + \underbrace{\frac{\beta}{2}\,\Delta_v\,p(t,\mathbf{x},\mathbf{v})}_{\text{diffusion}}$$

Tumor Angiogenic Factor (TAF)

$$\frac{\partial}{\partial t}C(t,\mathbf{x}) = \kappa\,\triangle_x C(t,\mathbf{x}) - \chi\,C(t,\mathbf{x})\,|\,\underbrace{\mathbf{j}(t,\mathbf{x})}_{\text{tip flux}}\,|$$

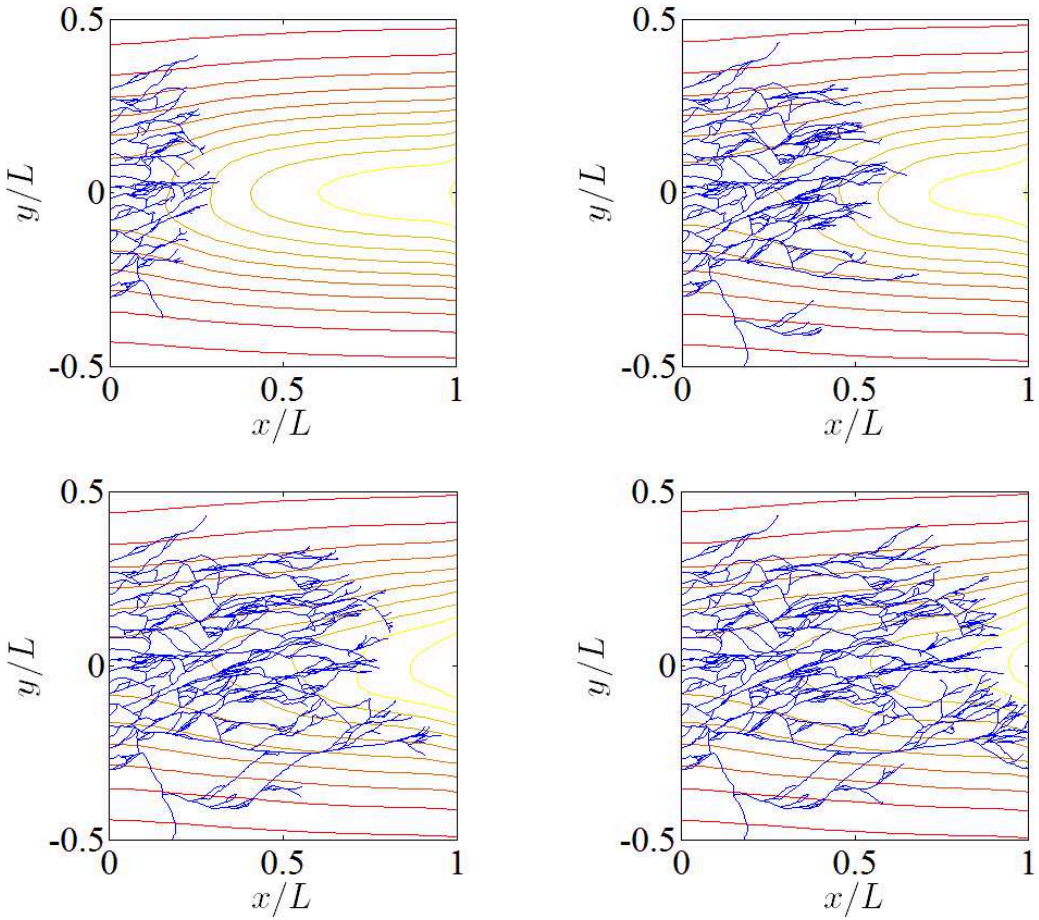
$$\sum_{i=1}^{N(t)}\mathbf{v}^i(t)\,\delta_x\left(\mathbf{x}-\mathbf{X}^i(t)\right)\ \text{(stochastic)} \qquad \int\mathbf{v}'\,p(t,\mathbf{x},\mathbf{v}')\,d\mathbf{v}'\ \text{(deterministic)}$$

(haptotaxis, blood circulation, vessel pruning & other processes are ignored)

Bonilla et al, PRE 90, 062716, 2014, Terragni et al, PRE 93, 022413, 2015

A typical vessel network simulation

- ★ 2D spatial domain: $\mathbf{x} = (x, y) \in [0, L] \times [-1.5\,L, 1.5\,L]$
- ★ Primary vessel at $x = 0$, tumor at $x = L$; level curves depict the TAF field



↪ **Figure**: (a) 12 h (46 tips), (b) 24 h (60 tips), (c) 32 h (78 tips), (d) 36 h (76 tips)

Key point: Ensemble averaged tip densities

GOAL: a deterministic description of the vessel tip mean density

★ Anastomosis keeps the number of tips $N(t)$ relatively low

▲ No laws of large numbers can be applied

▲ The stochastic model is not self-averaging (fluctuations do not decay)

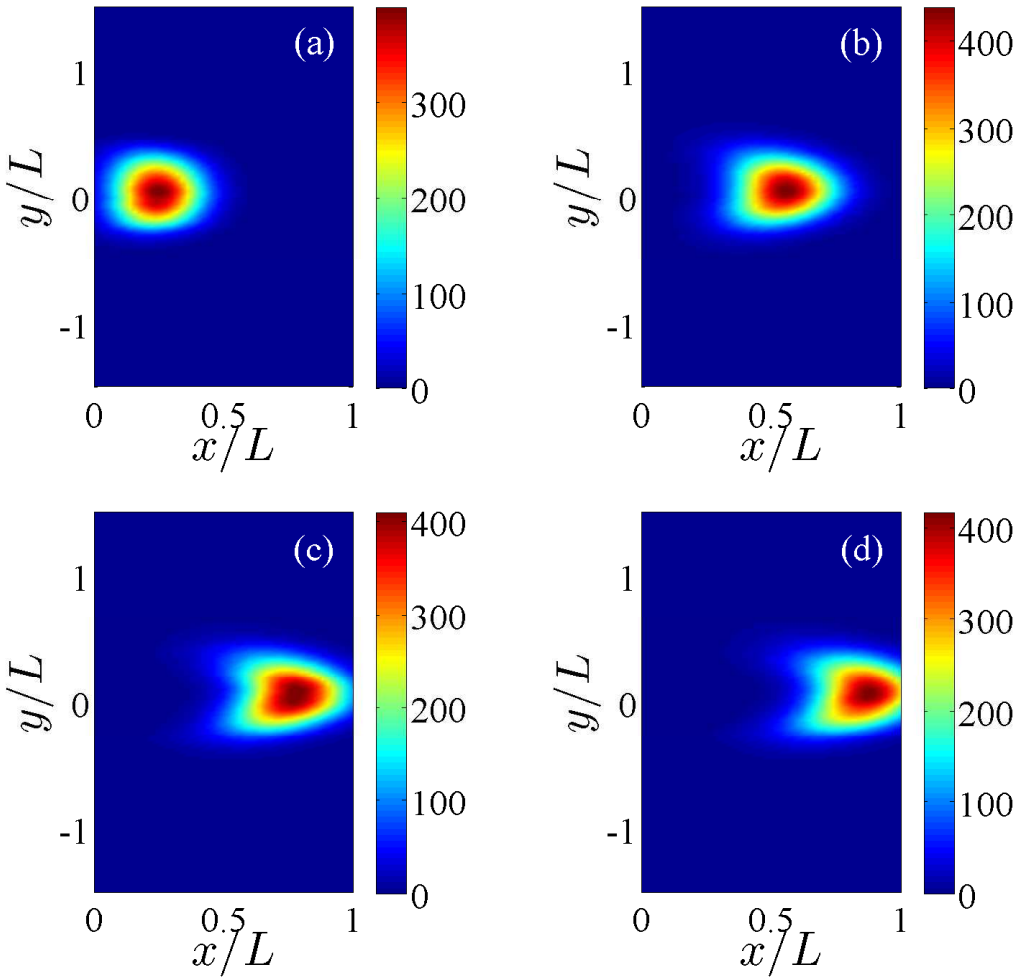
♠ Set $\mathcal{N}$ *independent* replicas of the angiogenic process. Empirical distribution of tips, per unit volume, in $(\mathbf{x}, \mathbf{v})$ phase space

$$p_{\mathcal{N}}(t, \mathbf{x}, \mathbf{v}) = \frac{1}{\mathcal{N}} \sum_{\omega=1}^{\mathcal{N}} \left[\sum_{i=1}^{N(t,\omega)} \delta_{\sigma_x}(\mathbf{x} - \mathbf{X}^i(t,\omega)) \delta_{\sigma_v}(\mathbf{v} - \mathbf{v}^i(t,\omega)) \right] \xrightarrow[\mathcal{N}\to\infty]{} p(t, \mathbf{x}, \mathbf{v})$$

♠ Empirical distribution of tips, per unit volume, in physical space

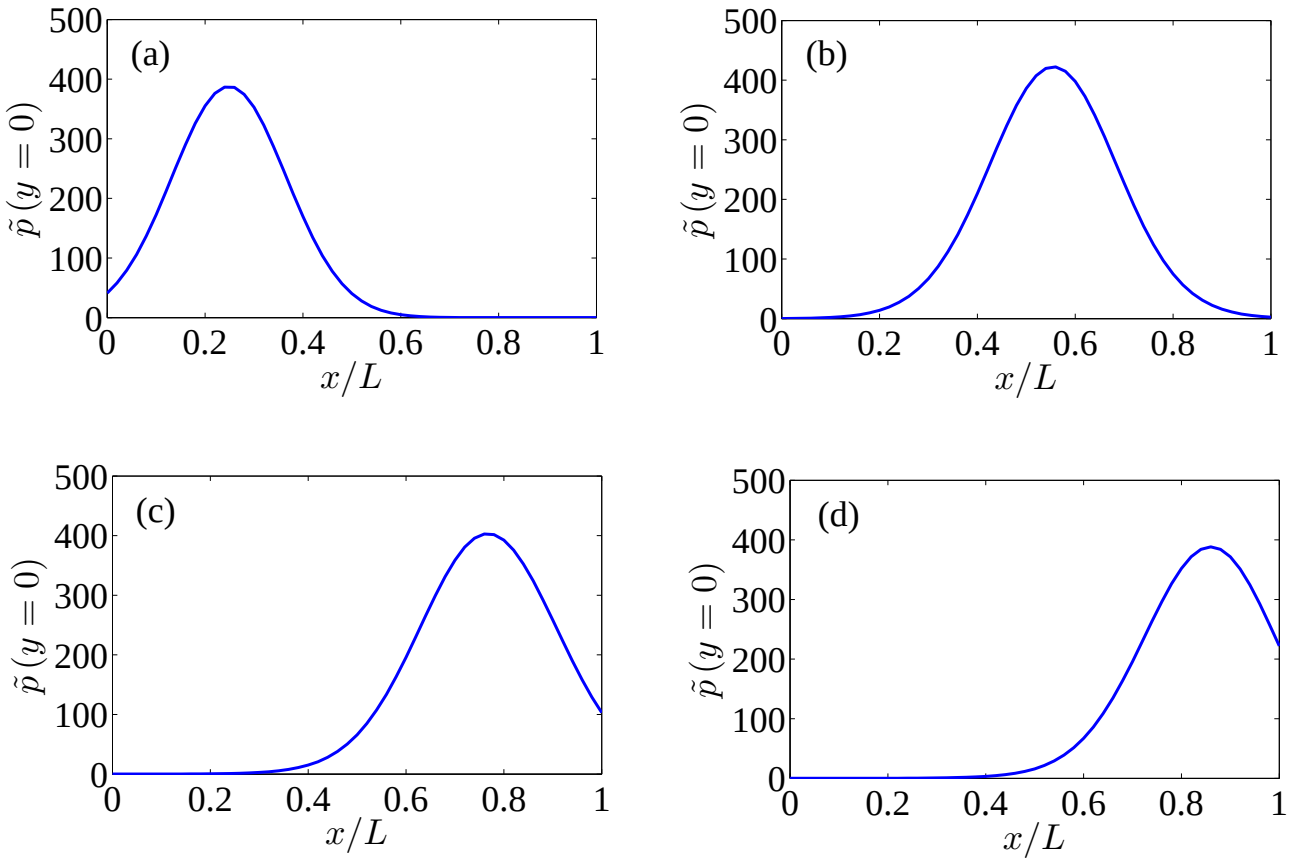
$$\tilde{p}_{\mathcal{N}}(t, \mathbf{x}) = \frac{1}{\mathcal{N}} \sum_{\omega=1}^{\mathcal{N}} \left[\sum_{i=1}^{N(t,\omega)} \delta_{\sigma_x}(\mathbf{x} - \mathbf{X}^i(t,\omega)) \right] \xrightarrow[\mathcal{N}\to\infty]{} \tilde{p}(t, \mathbf{x})$$

Marginal tip density from $\mathcal{N} = 400$ replicas (lump)



↪ **Figure**: (a) 12 h (56 tips), (b) 24 h (69 tips), (c) 32 h (72 tips), (d) 36 h (66 tips)

Marginal tip density from $\mathcal{N} = 400$ replicas (soliton)



↪ **Figure**: (a) 12 h (56 tips), (b) 24 h (69 tips), (c) 32 h (72 tips), (d) 36 h (66 tips)

Ensemble-averaged *vs.* deterministic descriptions

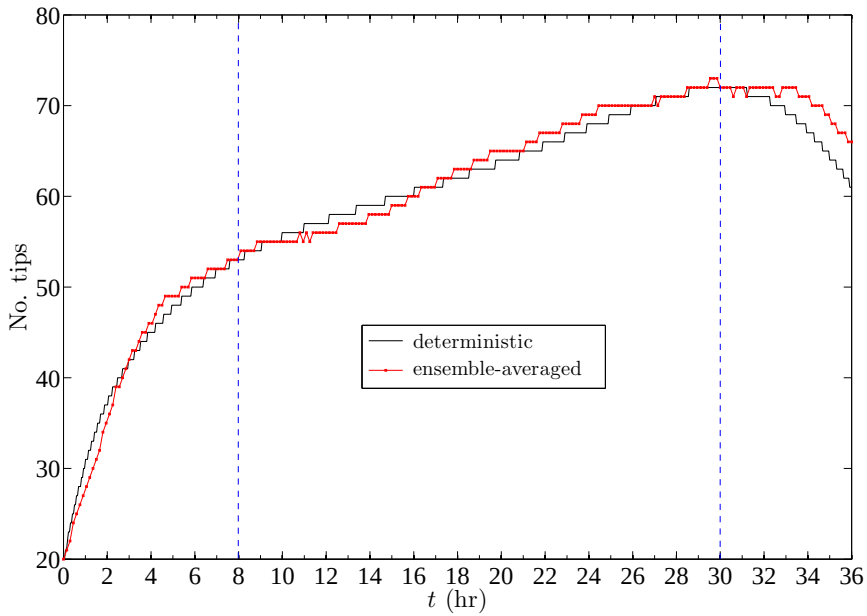
- ✓ All parameters appear in both models (with the same values)
- ✓ Main parameter values are extracted from experiments

The two descriptions agree quite well (qualitatively) as far as the anastomosis coefficient is suitably estimated: our fit minimizes the relative RMS error on the number of tips for $8\,\mathrm{h} < t < 30\,\mathrm{h}$ calculated with the two approaches

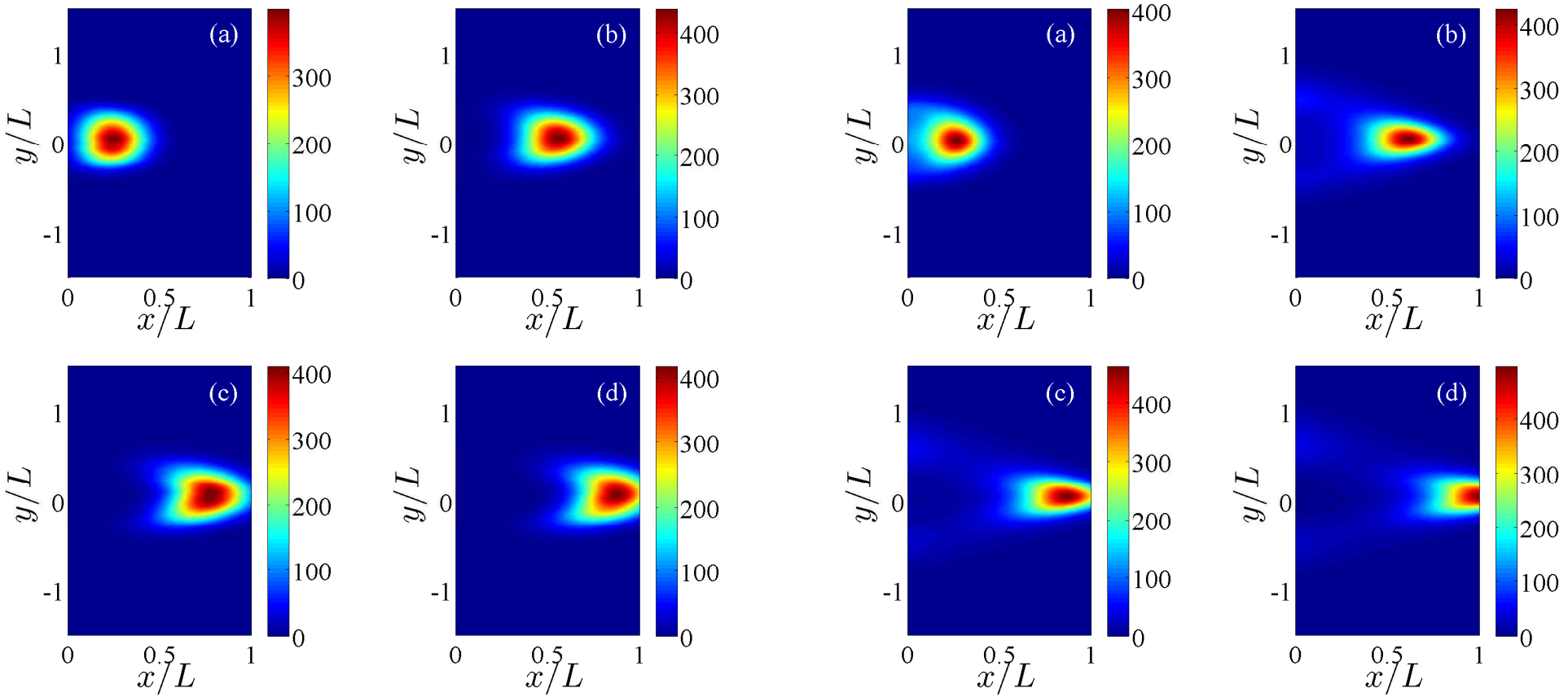
$$N(t) = \left[\int \tilde{p}(t,\mathbf{x})\,d\mathbf{x}\right] \quad \text{(deterministic)}$$

$$N(t) = \left[\frac{1}{400}\sum_{\omega=1}^{400} N(t,\omega)\right] \quad \text{or}$$

$$\left[\int \tilde{p}_{400}(t,\mathbf{x})\,d\mathbf{x}\right] \quad \text{(ensemble-averaged)}$$



Ensemble-averaged *vs.* deterministic descriptions



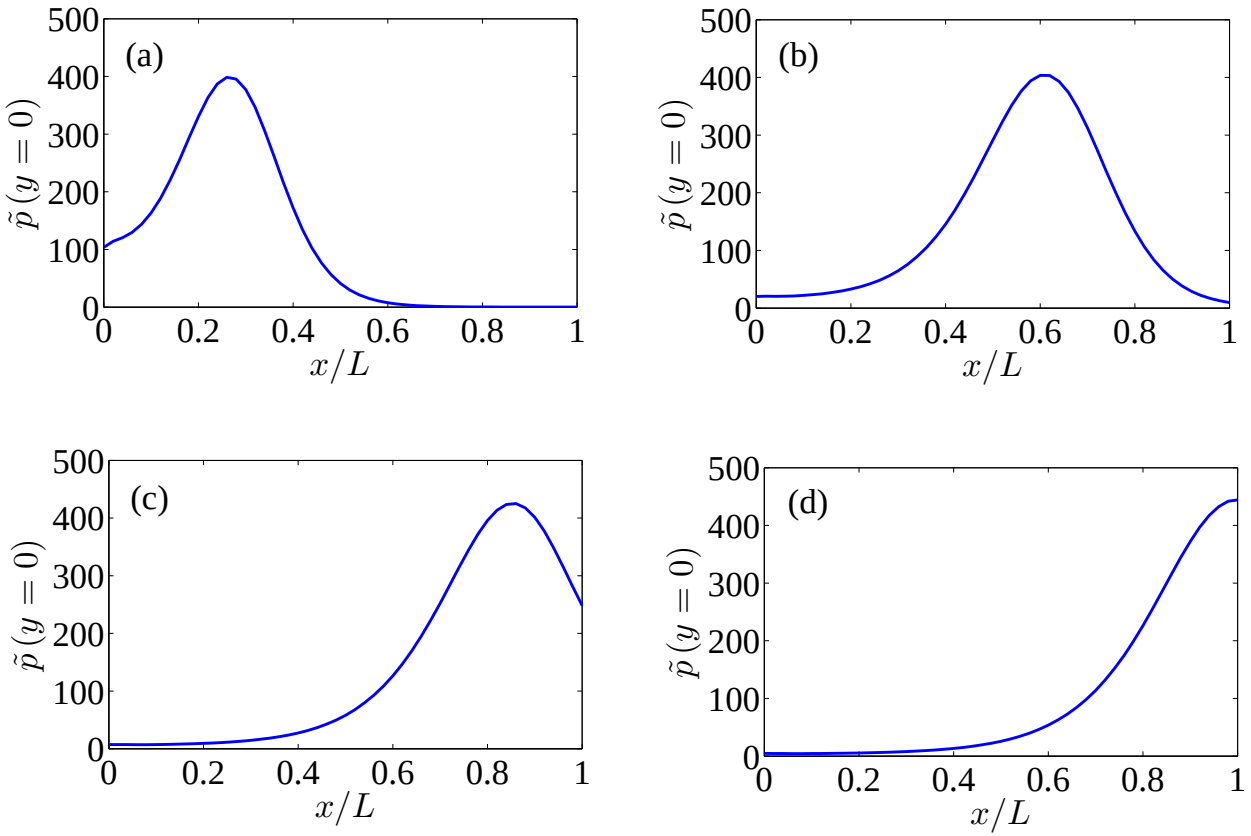
↪ **Figure**: marginal tip density by ensemble averages over $\mathcal{N} = 400$ replicas (**left**) and deterministic equations (**right**), for (a) 12 h, (b) 24 h, (c) 32 h, (d) 36 h

Outline

Vessel tips advance as a pulse

★ Deterministic marginal tip density at the x-axis, $\tilde{p}(t, x, y = 0)$

★ Tips form a growing pulse moving toward the tumor $(x = L)$ by chemotaxis



↪ **Figure**: (a) 12 h, (b) 24 h, (c) 32 h, (d) 36 h

Soliton (Bonilla et al, Sci. Rep. 6, 31296, 2016)

- Overdamped limit of vessel extension: $\frac{d\mathbf{X}^i}{dt} = \mathbf{F} + \beta^{-1/2}\frac{d\mathbf{W}^i}{dt}$, yields simple equation for $\tilde{p}(t, \mathbf{x})$:

$$\frac{\partial \tilde{p}}{\partial t} + \nabla_x \cdot [\mathbf{F}(C)\tilde{p}] = \frac{1}{2\beta}\Delta_x \tilde{p} + \mu(C)\tilde{p} - \Gamma\tilde{p}\int_0^t \tilde{p}(s, \mathbf{x})ds.$$

- Renormalized μ can be obtained by a Chapman-Enskog perturbation method (assuming that the tip density rapidly approaches local equilibrium in $\mathbf{v}$)
- Ignore diffusion, assume almost constant μ & $\mathbf{F}$ produce 1D soliton

$$s(t,x) = \frac{(2K\Gamma + \mu^2)c}{2\Gamma(c - F_x/\beta)}\,\mathrm{sech}^2\left[\frac{\sqrt{2K\Gamma + \mu^2}}{2(c - F_x/\beta)}(x - ct - \xi_0)\right]$$

- ★ Analogy with the soliton of the Korteweg-de Vries equation
- ★ Blue parameters (dimensionless) come from the angiogenesis model (those depending on TAF are computed by considering $C(t_0, x, y)$, setting $y = 0$, and averaging over x)
- ★ Red parameters (dimensionless) are related to the soliton (K, c, ξ_0)

Soliton collective coordinates

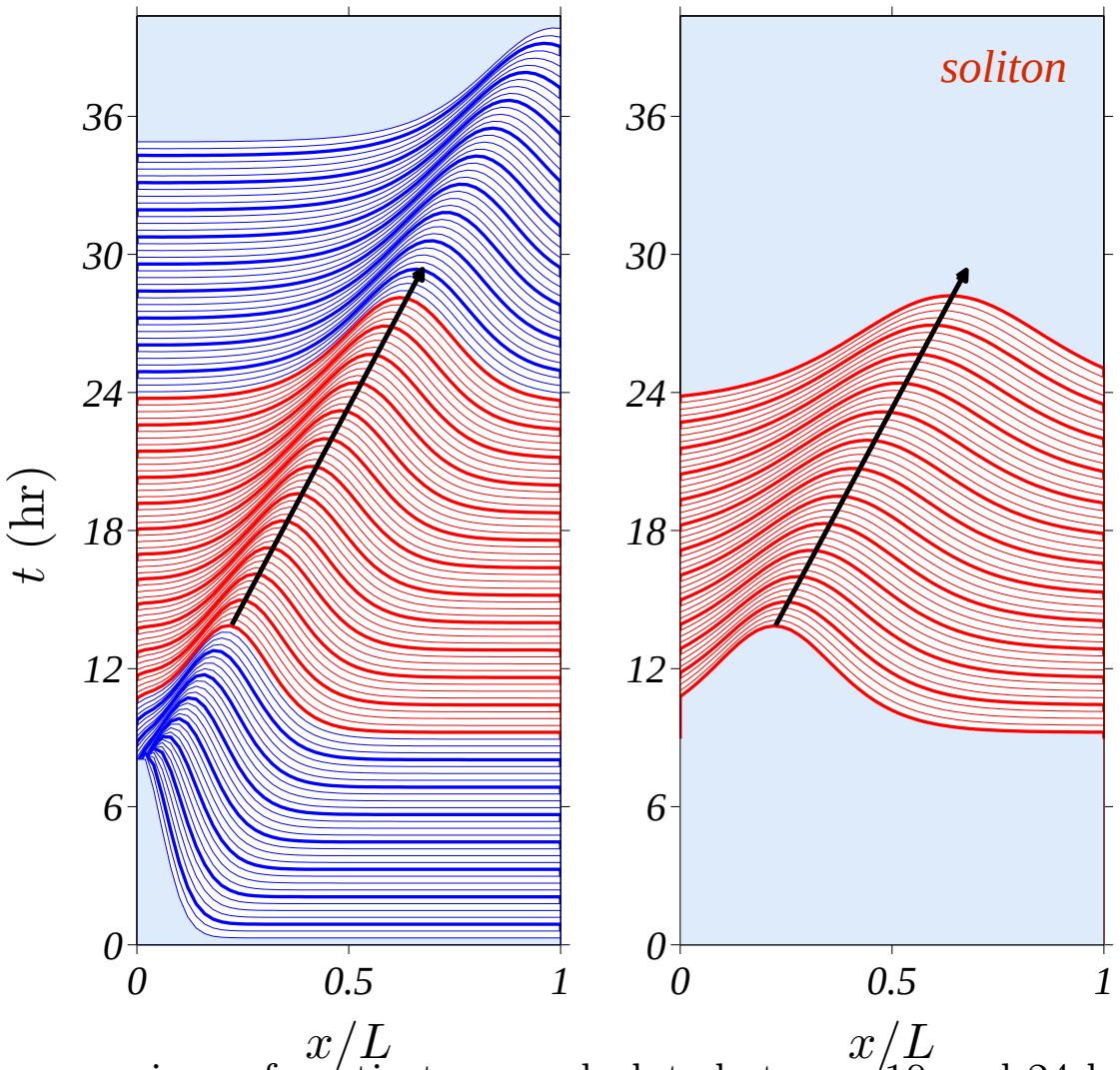
$$s(t,x) \;=\; \frac{(2K\Gamma+\mu^2)c}{2\Gamma(c-F_x/\beta)}\,\mathrm{sech}^2\left[\frac{\sqrt{2K\Gamma+\mu^2}}{2(c-F_x/\beta)}(x-X)\right]$$

Let the soliton parameters depend on time & consider a new "center"

$$K \;=\; K(t)\,, \quad c \;=\; c(t)\,, \quad X \;=\; X(t), \quad \dot{X} = c$$

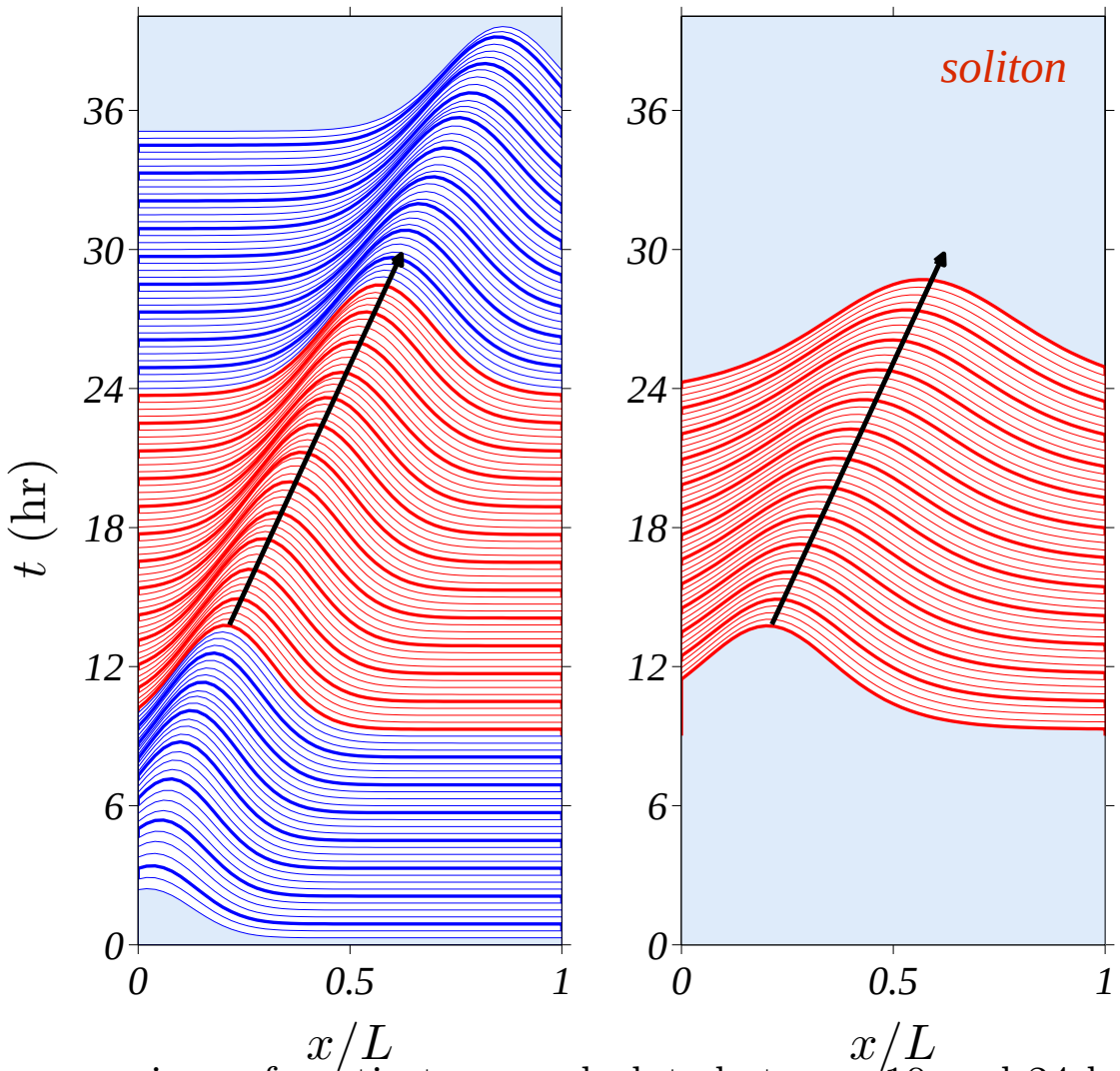
- ★ *Collective coordinates* $K(t)$, $c(t)$, $X(t)$ satisfy ODEs reflecting influence of diffusion and non-constant TAF
- ★ Good predictions on the soliton position & amplitude can be obtained as to *mimic the behavior of the vessel tips pulse*
- ★ Soliton controls $\tilde{p}(t,\mathbf{x})$ behavior after formation stage

Deterministic pulse *vs.* soliton



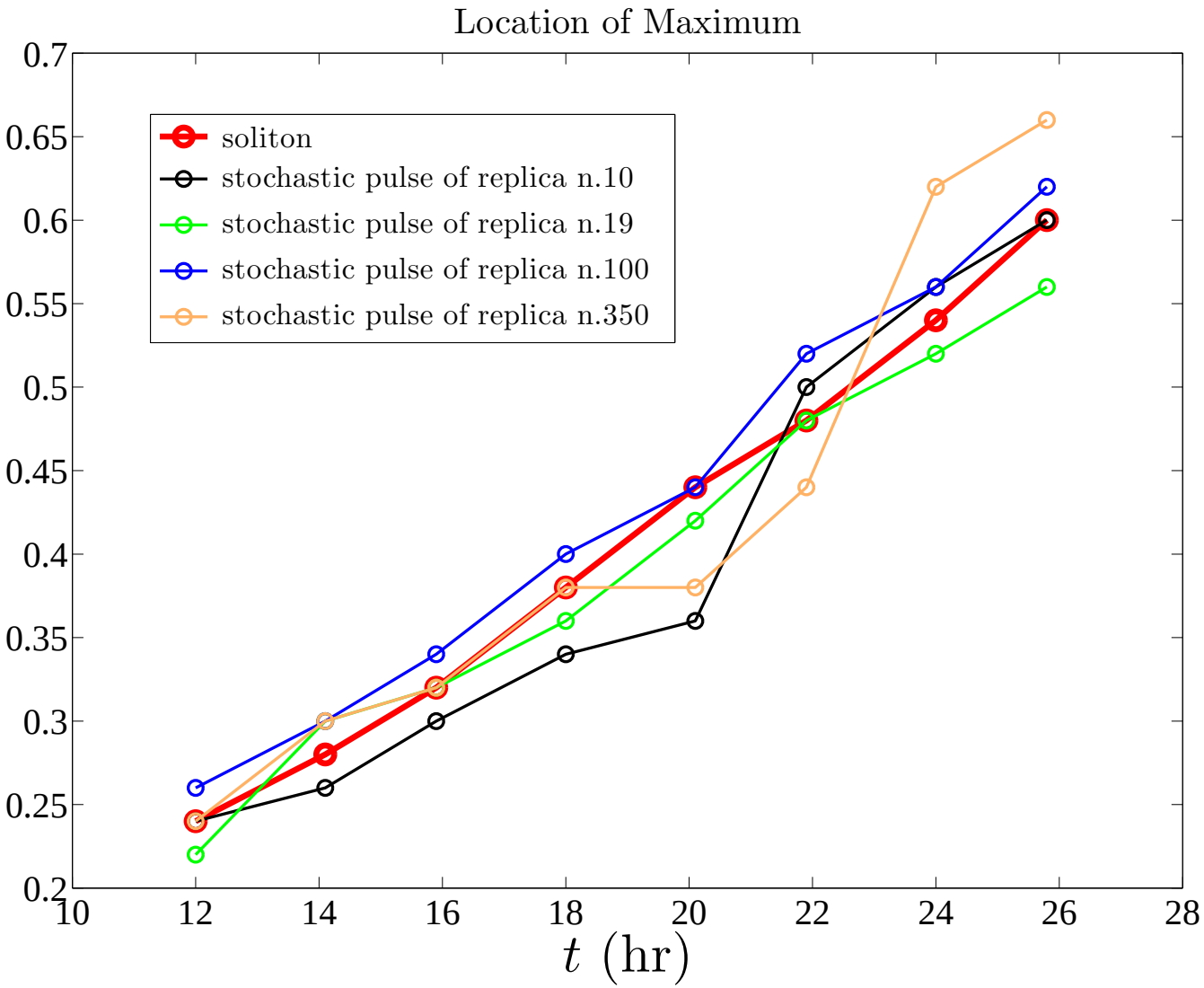
↪ **Figure**: comparison of spatio-temporal plots between 10 and 24 hours

Stochastic pulse *vs.* soliton (ensemble average 400 replicas)



↪ **Figure**: comparison of spatio-temporal plots between 10 and 24 hours

Position of maximum marginal density for different replicas



Outline

Perspectives

1. *Blueprint for other models*
2. *Haptotaxis, anti-angiogenic drugs* added as extra field RDE and extra forces in Langevin equations
3. *Stability of soliton, initial stage and arrival to tumor*
4. Effect of *haptotaxis, anti-angiogenic drugs on soliton: control of angiogenesis, therapy*

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THANK YOU!!!

Appendix: deterministic description

Derivation of a mean field equation for the vessel tip density, as $\mathcal{N} \to \infty$

- ★ Itō's formula is applied for a smooth $g(\mathbf{x}, \mathbf{v})$ & the process in Langevin eqns
- ★ For any replica ω, at time t, the number of tips per unit volume in the $(\mathbf{x}, \mathbf{v})$ phase space is given by the *empirical distribution*

$$Q_N^*(t, \mathbf{x}, \mathbf{v}, \omega) = \sum_{i=1}^{N(t,\omega)} \delta_{\sigma_x}(\mathbf{x} - \mathbf{X}^i(t, \omega)) \delta_{\sigma_v}(\mathbf{v} - \mathbf{v}^i(t, \omega))$$

- ★ If $\mathcal{N}$ is sufficiently large, Q_N^* may admit a *density* by laws of large numbers

$$\frac{1}{\mathcal{N}} \sum_{\omega=1}^{\mathcal{N}} Q_N^*(t, \mathbf{x}, \mathbf{v}, \omega) \sim p(t, \mathbf{x}, \mathbf{v})$$

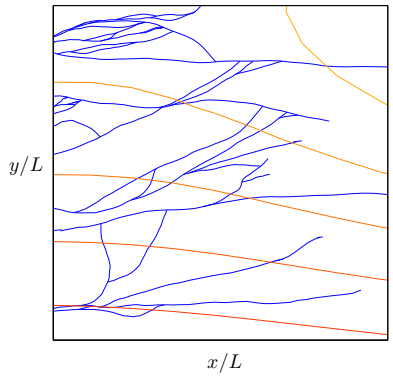
$$\Longrightarrow \quad \frac{1}{\mathcal{N}} \sum_{\omega=1}^{\mathcal{N}} \left[\sum_{i=1}^{N(t,\omega)} g(\mathbf{X}^i(t, \omega), \mathbf{v}^i(t, \omega)) \right] \sim \int g(\mathbf{x}, \mathbf{v})\, p(t, \mathbf{x}, \mathbf{v})\, d\mathbf{x}\, d\mathbf{v}$$

- ★ Tip branching & anastomosis are added as *source* & *sink* terms to the obtained equation for $p(t, \mathbf{x}, \mathbf{v})$ in strong form

Anastomosis

If a tip meets an existing vessel, they join at that point & time

$\hookrightarrow$ the tip stops the evolution



The "death" rate of tips is a fraction of the *occupation time density*

$$\int_0^t ds \sum_{i=1}^{N(s)} \delta_{\sigma_x}(\mathbf{x} - \mathbf{X}^i(s)),$$

which is the concentration of vessels per unit volume, at t and $\mathbf{x}$

Note: tips occupy a volume $d\mathbf{x}$ about $\mathbf{x}$ when they reach it, or by branching, or during anastomosis (this depends on the past history of a given stochastic replica)

Deterministic description: boundary conditions for p

★ Since p has $2nd$-order derivatives in $\mathbf{v}$

$$p(t, \mathbf{x}, \mathbf{v}) \to 0 \quad \text{as} \quad |\mathbf{v}| \to \infty$$

★ Which spatial bcs for p ? (p has $1st$-order derivatives in $\mathbf{x}$)

At each t, we expect to know

✓ the *marginal tip density* at the tumor ($x = L$)

$$\tilde{p}(t, L, y) = \tilde{p}_L(t, y)$$

✓ the normal *tip flux density* injected at the primary vessel ($x = 0$)

$$-\mathbf{n} \cdot \mathbf{j}(t, 0, y) = j_0(t, y)$$

Using these values & assuming p close to a local equilibrium distribution at the boundaries, we impose compatible bcs for p^+ at $x = 0$ and p^- at $x = L$

Deterministic description: boundary conditions for p

First order derivatives in $\mathbf{x}$: 2 *one-half* boundary conditions at $x = 0$, $x = L$:

$$p^+(t,0,y,v,w) = \frac{e^{-\frac{k|\mathbf{v}-\mathbf{v}_0|^2}{\sigma^2}}}{\int_0^\infty\int_{-\infty}^\infty v' e^{-\frac{k|\mathbf{v}'-\mathbf{v}_0|^2}{\sigma^2}} dv'\, dw'}\left[j_0(t,y) - \int_{-\infty}^0\int_{-\infty}^\infty v' p^-(t,0,y,v',w')dv'dw'\right]$$

$$p^-(t,L,y,v,w) = \frac{e^{-\frac{k|\mathbf{v}-\mathbf{v}_0|^2}{\sigma^2}}}{\int_{-\infty}^0\int_{-\infty}^\infty e^{-\frac{k|\mathbf{v}'-\mathbf{v}_0|^2}{\sigma^2}} dv'\, dw'}\left[\tilde{p}_L(t,y) - \int_0^\infty\int_{-\infty}^\infty p^+(t,L,y,v',w')dv'dw'\right]$$

where

- ★ $\mathbf{v} = (v,w)$; $p^+ = p$ for $v > 0$ and $p^- = p$ for $v < 0$
- ★ $\mathbf{v}_0$ is the mean velocity of the vessel tips
- ★ σ^2/k is the temperature of the local equilibrium distribution