IHP Stochastic Dynamics out of Equilibrium: Workshop Life Sciences

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Tumor induced angiogenesis: Ensemble averages and solitons

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Outline

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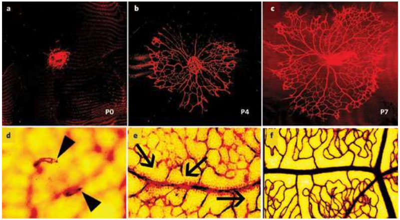
THE FORMATION OF BLOOD VESSELS

★ Angiogenesis is essential for organ growth & repair

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



The formation of blood vessels

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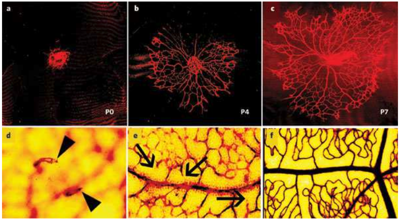
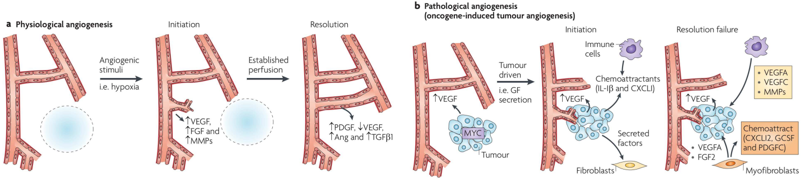


★ Angiogenesis can be either physiological or pathological (*tumor induced*) ↪ Figure: *Chung et al., Nature Reviews (2010)*



Angiogenesis mechanisms

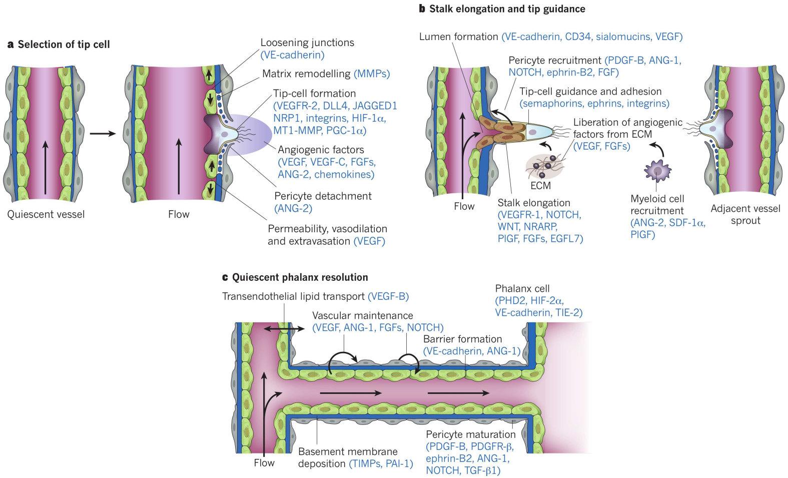


Figure: molecular basis of vessel branching – Carmeliet & Jain, *Nature* (2011)

ANGIOGENESIS TREATMENT

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

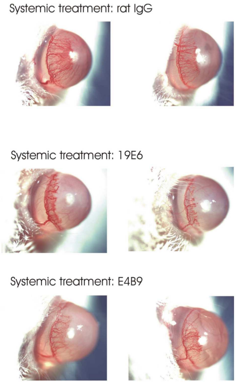


Figure: angiogenesis on a rat cornea – E. Dejana lab (2005)

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, Sleeman, Anderson, Stokes, Lauffenburger, Capasso, Morale, Wheeler, Bauer, Bentley, Gerhardt, Travasso

★ Some experiments: Folkman, Jain, Carmeliet, Dejana, Fruttiger

★ Mostly numerical outcomes, no stat-mech study

Outline

Main features of the model

Early stage formation of a *tumor induced* vessel network involves:

(*i*) tip branching: birth process of tips

(*ii*) vessel extension: Langevin equations

(*iii*) chemotaxis in response to a generic *tumor angiogenic factor* (TAF), released by tumor cells: reaction-diffusion equation

(*iv*) anastomosis: death process of capillary tips that encounter an existing vessel

(*v*) vessel = tip trajectory

(haptotaxis, blood circulation, vessel pruning & other processes are ignored; haptotaxis: Capasso-Morale 2009)

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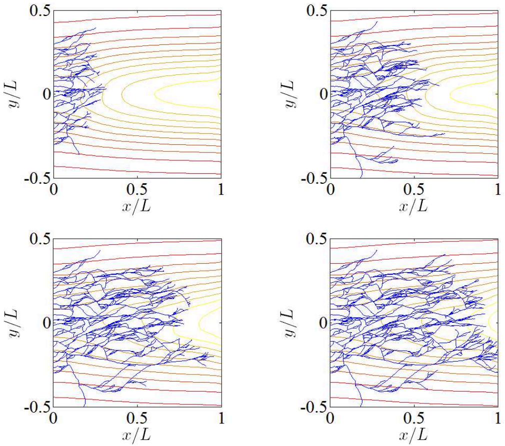
At time t, there are $N(t)$ active tips, with position $\mathbf{X}^i(t)$ and velocity $\mathbf{v}^i(t)$

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)

Tip branching

New capillaries branch out of vessel tips (not from mature vessels)

The 'probability' that a tip branches from an existing one in $(t, t + dt]$ is measured by

$$\sum_{i=1}^{N(t)} \alpha\left(C(t, \mathbf{X}^i(t))\right) dt\,, \quad \text{with} \ \ \alpha(C) = \alpha_1 \frac{C}{C_R + C}\,,$$

where C_R is a reference value for the TAF concentration $C(t, \mathbf{x})$ $(\alpha_1 \in \mathbb{R}^+)$

A 'successful' branching (birth) at $\mathbf{x} = \mathbf{X}^i(t)$ generates a *new tip* with

- initial position equal to $\mathbf{x}$
- initial velocity selected out of a normal distribution with mean $\mathbf{v}_0$ (a constant non-random velocity)

Vessel extension

Vessel extension is modeled by tracking the trajectories of all tips

Description is based on the Langevin equations

$$\begin{aligned} d\mathbf{X}^i(t) &= \mathbf{v}^i(t)\,dt \\ d\mathbf{v}^i(t) &= \underbrace{-k\,\mathbf{v}^i(t)}_{\text{friction}}\,dt + \underbrace{\mathbf{F}\Big(C(t,\mathbf{X}^i(t))\Big)}_{\text{chemotactic force}}\,dt + \underbrace{\sigma\,d\mathbf{W}^i(t)}_{\text{random noise}} \end{aligned}$$

where $\mathbf{W}^i(t)$ are i.i.d. standard Brownian motions

The force due to the underlying TAF field is given by

$$\mathbf{F}(C) = \frac{d_1}{1+\gamma_1 C}\,\nabla_{\mathbf{x}} C$$

(k, σ, d_1, γ_1 are positive parameters)

TAF EVOLUTION

The TAF diffuses & is consumed due to capillary enlargement

$\hookrightarrow$ locally degraded by each tip proportionally to its velocity (in a region $\sim$ tip size)

The evolution equation is

$$\frac{\partial}{\partial t} C(t,\mathbf{x}) = d_2 \triangle_{\mathbf{x}} C(t,\mathbf{x}) - \eta\, C(t,\mathbf{x}) \left| \underbrace{\sum_{i=1}^{N(t)} \mathbf{v}^i(t)\, \delta_{\sigma_x}\left(\mathbf{x} - \mathbf{X}^i(t)\right)}_{\text{tip flux}} \right|$$

where d_2, η, σ_x are positive parameters

- ✓ an initial Gaussian-like concentration $C(0,\mathbf{x})$ is considered
- ✓ the production of $C(t,\mathbf{x})$ due to tumor is modeled by a TAF flux boundary condition at $x = L$ (zero flux at $x = 0$ and $C(t, x, \pm 1.5\, L) = 0$)

Law of large numbers

- ✓ After some time, so many active tips exist that process is self-averaging: realizations follow the mean, *negligible fluctuations*.
- ✓ Define rescaled density of active tips (N is a fixed large number representative of the existing number of tips):

$$\frac{1}{N}\sum_{i=1}^{N(t)}\delta(\mathbf{x}-\mathbf{X}^i(t))\delta(\mathbf{v}-\mathbf{v}^i(t))\sim p(t,\mathbf{x},\mathbf{v}),\quad N\to\infty.$$

- ✓ Get deterministic (integrodifferential) eq. for density: Fokker-Planck equation plus source & sink terms, Bonilla *et al*, PRE 2014.
- ✓ Prove deterministic equation is well-posed (unique solution smoothly dependent on data).
- ✓ Investigate convergence of stochastic to deterministic tip density (math research program).

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But it is all wrong! Anastomosis eliminates active tips! $N \approx 100$.

Remedy: Enter a large number of replicas $\mathcal{N}$ of stochastic process and work with ensemble averages. (If it was good for Gibbs, it is good for us!)

Outline

Key point: Ensemble averaged tip densities (PRE 93, 022413)

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)

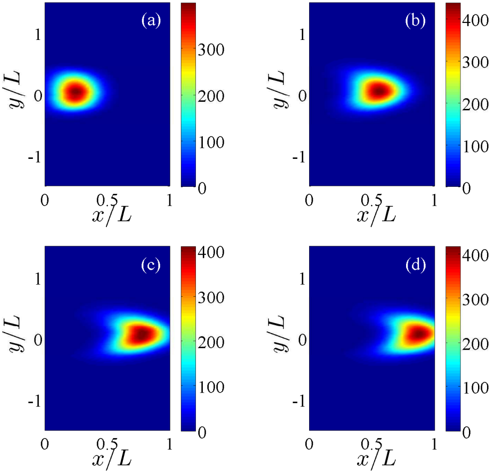
♠ Set $\mathcal{N}$ *independent* replicas of the angiogenic process. Empirical distribution of tips, per unit volume, in $(\mathbf{x}, \mathbf{v})$ phase space

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

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

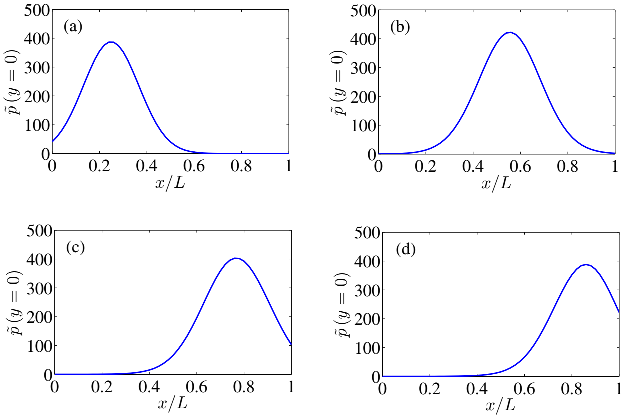
$$\tilde{p}_{\mathcal{N}}(t, \mathbf{x}) = \frac{1}{\mathcal{N}} \sum_{\omega=1}^{\mathcal{N}} \left[\sum_{i=1}^{N(t,\omega)} \delta_{\sigma_x}(\mathbf{x} - \mathbf{X}^i(t,\omega)) \right] \xrightarrow[\mathcal{N}\to\infty]{} \tilde{p}(t, \mathbf{x})$$

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)



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Deterministic description (Terragni *et al.*, PRE, 2016)

As $\mathcal{N} \to \infty$, the tip density $p(t, \mathbf{x}, \mathbf{v})$ satisfies the Fokker-Planck-type equation (Bonilla *et al* PRE 2014, well-posed: Carpio *et al* NARWA 2016, AMM 2017)

$$\frac{\partial}{\partial t} p(t,\mathbf{x},\mathbf{v}) = \underbrace{\alpha(C(t,\mathbf{x}))\, p(t,\mathbf{x},\mathbf{v})\, \delta_{\sigma_v}(\mathbf{v}-\mathbf{v}_0)}_{\text{birth term (tip branching)}}$$

$$\underbrace{-\,\gamma\, p(t,\mathbf{x},\mathbf{v}) \int_0^t \tilde{p}(s,\mathbf{x})\, ds}_{\text{death term (anastomosis)} \;\longrightarrow\; \gamma > 0}$$

$$\underbrace{-\,\mathbf{v}\cdot\nabla_{\mathbf{x}}\, p(t,\mathbf{x},\mathbf{v})}_{\text{transport}} + \underbrace{k\, \nabla_{\mathbf{v}} \cdot \Big[\mathbf{v}\, p(t,\mathbf{x},\mathbf{v})\Big]}_{\text{friction}}$$

$$\underbrace{-\,\nabla_{\mathbf{v}} \cdot \Big[\mathbf{F}(C(t,\mathbf{x}))\, p(t,\mathbf{x},\mathbf{v})\Big]}_{\text{chemotactic forcing by TAF}} + \underbrace{\frac{\sigma^2}{2} \Delta_{\mathbf{v}}\, p(t,\mathbf{x},\mathbf{v})}_{\text{diffusion}}$$

with

$$\frac{\partial}{\partial t} C(t,\mathbf{x}) = d_2\, \triangle_{\mathbf{x}} C(t,\mathbf{x}) - \eta\, C(t,\mathbf{x}) \left| \underbrace{\int \mathbf{v}'\, p(t,\mathbf{x},\mathbf{v}')\, d\mathbf{v}'}_{\text{tip flux density}} \right|$$

Deterministic description: source and sink terms

- Birth term (tip branching): $r_b(t,\mathbf{x})\,p(t,\mathbf{x},\mathbf{v})$, $r_b = \alpha(C(t,\mathbf{x}))\,\delta_{\sigma_v}(\mathbf{v}-\mathbf{v}_0)$ (factorization assumed)
- Anastomosis: $-r_d(t,\mathbf{x})\,p(t,\mathbf{x},\mathbf{v})$. At time t, one tip meets a vessel at volume $d\mathbf{x}$ about $\mathbf{x}$, whose leading tip was there at past time in $(s, s+ds)$, no matter its velocity. Death term for all previous time is proportional to the ensemble average $\int_0^t \tilde{p}(s,\mathbf{x})\,ds$. Missing in all previous work!
- Anastomosis: r_d proportional to average occupation time density of a volume $d\mathbf{x}$ about $\mathbf{x}$: $\langle\int_0^t ds\sum_{i=1}^{N(s)}\delta_{\sigma_x}(\mathbf{x}-\mathbf{X}^i(s))\rangle = \int_0^t ds\,\tilde{p}(s,\mathbf{x})$. We are making a factorization assumption similar to Boltzmann's molecular chaos assumption (ensemble average of a product is product of ensemble averages).

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- Similar factorization assumption made to get the force term in the deterministic equation for tip density:
- ★

$$\nabla_{\mathbf{v}} \cdot [\mathbf{F}(C(t,\mathbf{x}))\,p(t,\mathbf{x},\mathbf{v})].$$

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

Ensemble-averaged *vs.* deterministic descriptions

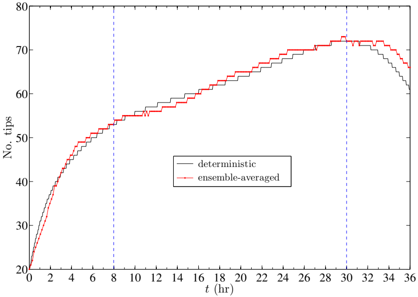
- ✓ All parameters appear in both models (with the same values)
- ✓ Main parameter values are extracted from experiments

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 $8\,\text{h} < t < 30\,\text{h}$ calculated with the two approaches

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

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

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



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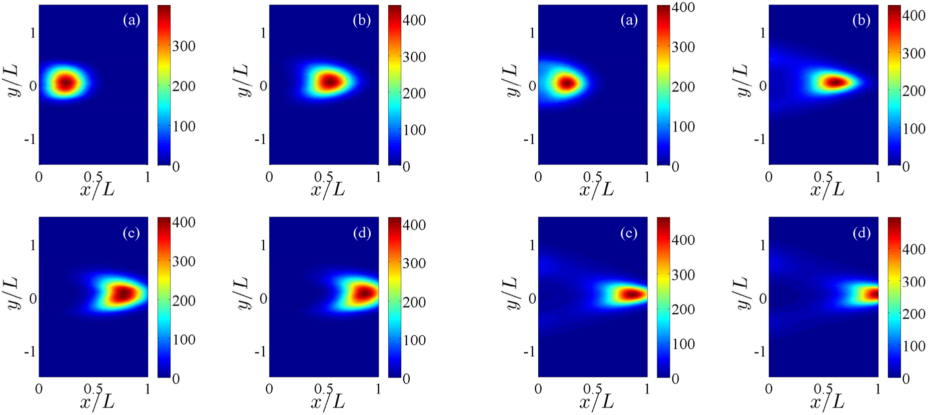


↪ **Figure**: marginal tip density by ensemble averages over $\mathcal{N} = 400$ replicas (**left**) and deterministic equations (**right**), for (a) 12 h, (b) 24 h, (c) 32 h, (d) 36 h

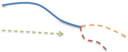
Stochastic Model and Deterministic Description

Vessel Extension

$$dX^i(t) = v^i(t)\, dt$$

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

Tip Branching



$$\text{prob}\left\{N(t+dt)-N(t)=1\right\} = \sum_{i=1}^{N(t)} \underbrace{\alpha\left(C(t, X^i(t))\right)}_{\text{response to TAF}}\, \underbrace{\delta_v(v^i(t) - v_0)}_{\text{velocity selector}}\, dt, \quad \alpha(C) = \frac{AC}{1+C}$$

Anastomosis

$$\frac{\partial}{\partial t} p(t,x,v) = \underbrace{\alpha(C(t,x))\, p(t,x,v)\, \delta_v(v - v_0)}_{\text{tip branching}}$$
$$\underbrace{-\Gamma\, p(t,x,v) \int_0^t \int p(s,x,v')\, dv'\, ds}_{\text{anastomosis}}$$
$$\underbrace{-v \cdot \nabla_x p(t,x,v)}_{\text{transport}} + \underbrace{\beta \nabla_v \cdot \left[v\, p(t,x,v)\right]}_{\text{friction}}$$
$$\underbrace{-\beta \nabla_v \cdot \left[F(C(t,x))\, p(t,x,v)\right]}_{\text{chemotactic forcing}} + \underbrace{\frac{\beta}{2} \Delta_v p(t,x,v)}_{\text{diffusion}}$$

Tumor Angiogenic Factor (TAF)

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

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

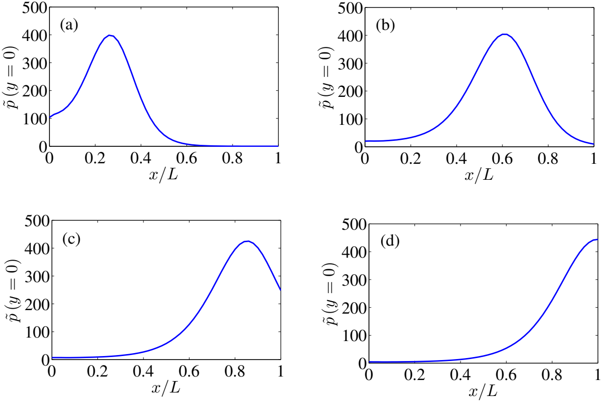
(haptotaxis, blood circulation, vessel pruning & other processes are ignored)

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

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; PRE 94, 062415, 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

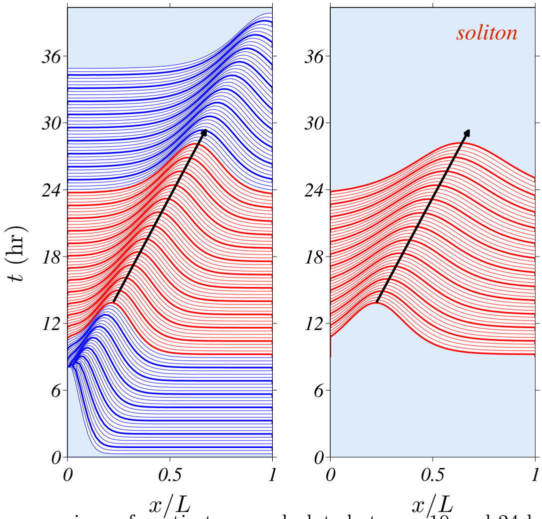
$$s(t,x) = \frac{(2K\Gamma + \mu^2)c}{2\Gamma(c - F_x/\beta)} \operatorname{sech}^2 \left[\frac{\sqrt{2K\Gamma + \mu^2}}{2(c - F_x/\beta)} (x - X) \right]$$

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

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

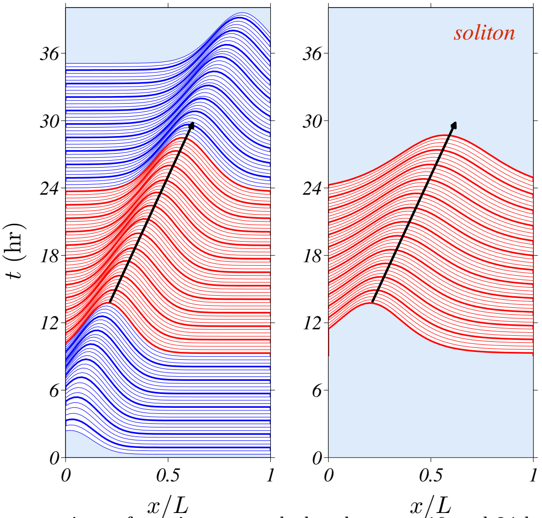
- ★ *Collective coordinates* $K(t)$, $c(t)$, $X(t)$ satisfy ODEs reflecting influence of diffusion and non-constant TAF. Coefficients are spatial averages
- ★ Good predictions on the soliton position & amplitude can be obtained as to *mimic the behavior of the vessel tips pulse*
- ★ Soliton controls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

Deterministic pulse *vs.* soliton



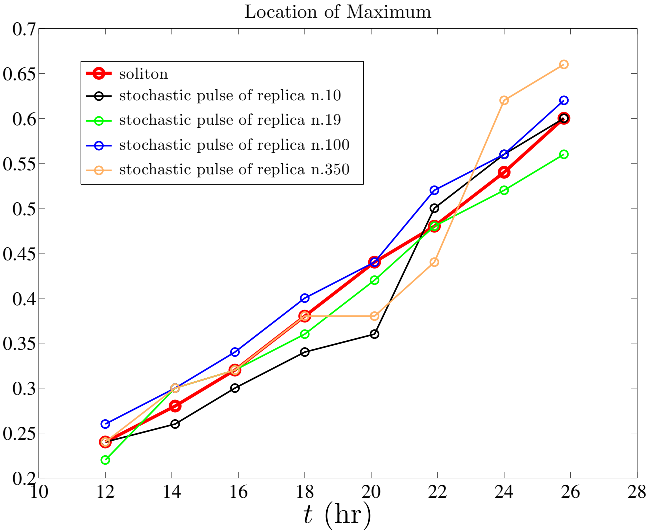
↪ **Figure**: comparison of spatio-temporal plots between 10 and 24 hours

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

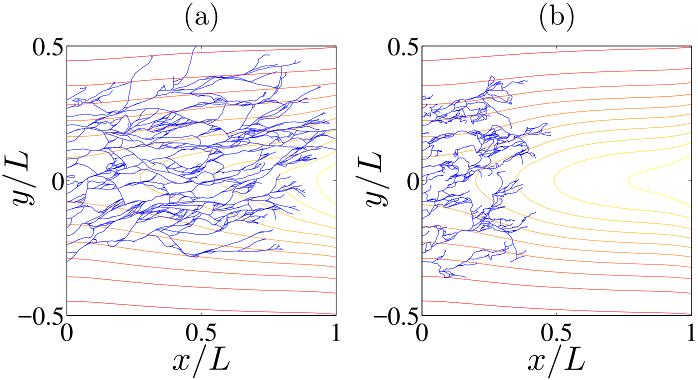


↪ **Figure**: comparison of spatio-temporal plots between 10 and 24 hours

Position of maximum marginal density for different replicas



Two realizations for different friction



Angiogenic network for (a) $\beta = 5.88$, (b) $\beta = 29.4$, after 36 h.

Outline

Perspectives

1. *Blueprint for other models* (master equation → Fokker-Planck eq)
2. *Haptotaxis, anti-angiogenic drugs* added as extra field RDE and extra forces in Langevin equations (haptotaxis in Entropy 19, 209, 2017)
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!!!

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

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

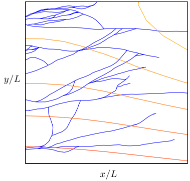
$$\Longrightarrow \quad \frac{1}{\mathcal{N}} \sum_{\omega=1}^{\mathcal{N}} \left[\sum_{i=1}^{N(t,\omega)} g(\mathbf{X}^i(t,\omega), \mathbf{v}^i(t,\omega)) \right] \sim \int g(\mathbf{x}, \mathbf{v})\, p(t, \mathbf{x}, \mathbf{v})\, d\mathbf{x}\, d\mathbf{v}$$

- 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