Introduction

Stochastic Model

Ensemble Averages

Deterministic Equations

Soliton

Final Comments

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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

★ Angiogenesis is essential for organ growth & repair

→ Figure: Gariano and Gardner, Nature (2005)

★ 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)
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
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)
Main features of the model

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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: \( x = (x, y) \in [0, L] \times [-1.5 L, 1.5 L] \)

★ 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)
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

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

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

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

- ♣ initial position equal to \(x\)
- ♣ initial velocity selected out of a normal distribution with mean \(v_0\) (a constant non-random velocity)
Vessel extension is modeled by tracking the trajectories of all tips

Description is based on the Langevin equations

\[
\begin{align*}
    dX^i(t) &= \mathbf{v}^i(t) \, dt \\
    dv^i(t) &= -k \mathbf{v}^i(t) \, dt + \mathbf{F}\left(C(t, X^i(t))\right) \, dt + \sigma dW^i(t)
\end{align*}
\]

where \(W^i(t)\) are i.i.d. standard Brownian motions

The force due to the underlying TAF field is given by

\[
F(C) = \frac{d_1}{1 + \gamma_1 C} \nabla_x C
\]

\((k, \sigma, d_1, \gamma_1\) are positive parameters)
TAF EVOLUTION

The TAF diffuses & is consumed due to capillary enlargement

\[ \text{locally degraded by each tip proportionally to its velocity (in a region } \sim \text{ tip size)} \]

The evolution equation is

\[
\frac{\partial}{\partial t} C(t, x) = d_2 \Delta_x C(t, x) - \eta C(t, x) \sum_{i=1}^{N(t)} v^i(t) \delta_{\sigma_x} (x - X^i(t))
\]

where \( d_2, \eta, \sigma_x \) are positive parameters

✓ an initial Gaussian-like concentration \( C(0, x) \) is considered

✓ the production of \( C(t, x) \) due to tumor is modeled by a TAF flux boundary condition at \( x = L \) (zero flux at \( x = 0 \) and \( C(t, x, \pm 1.5 L) = 0 \))
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):

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

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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LAW OF LARGE NUMBERS

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✓ Define rescaled density of active tips \((N \) is a fixed large number representative of the existing number of tips):

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✓ Prove deterministic equation is well-posed (unique solution smoothly dependent on data).

✓ Investigate convergence of stochastic to deterministic tip density (math research program).

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

Remedy: Enter a large number of replicas \(N\) of stochastic process and work with ensemble averages. (If it was good for Gibbs, it is good for us!)
**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 $(x, v)$ phase space

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

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

$$\tilde{p}_{\mathcal{N}}(t, x) = \frac{1}{\mathcal{N}} \sum_{\omega=1}^{\mathcal{N}} \left[ \sum_{i=1}^{N(t,\omega)} \delta_{\sigma_x}(x - X^i(t,\omega)) \right] \xrightarrow{\mathcal{N} \to \infty} \tilde{p}(t, x)$$
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)
As $N \to \infty$, the tip density $p(t, x, v)$ satisfies the Fokker-Planck-type equation (Bonilla et al. PRE 2014, well-posed: Carpio et al. NARWA 2016, AMM 2017)

$$
\frac{\partial}{\partial t} p(t, x, v) = \alpha(C(t, x)) p(t, x, v) \delta_{\sigma v} (v - v_0)
$$

birth term (tip branching)

$$
- \gamma p(t, x, v) \int_0^t \tilde{p}(s, x) \, ds
$$

death term (anastomosis) $\rightarrow \gamma > 0$

$$
- v \cdot \nabla_x p(t, x, v) + k \nabla_v \cdot [vp(t, x, v)]
$$

transport

$$
- \nabla_v \cdot [F(C(t, x)) p(t, x, v)] + \frac{\sigma^2}{2} \Delta_v p(t, x, v)
$$

chemotactic forcing by TAF

$$
\text{with}
$$

$$
\frac{\partial}{\partial t} C(t, x) = d_2 \Delta_x C(t, x) - \eta C(t, x) \left| \int v' p(t, x, v') \, dv' \right|
$$

tip flux density
**Deterministic description: source and sink terms**

- **Birth term (tip branching):** \( r_b(t, x) p(t, x, v) \), \( r_b = \alpha(C(t, x)) \delta v (v - v_0) \) (factorization assumed)

- **Anastomosis:** \(- r_d(t, x) p(t, x, v)\). At time \( t \), one tip meets a vessel at volume \( dx \) about \( x \), 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 \( \int_0^t \tilde{p}(s, x) ds \). Missing in all previous work!

- **Anastomosis:** \( r_d \) proportional to average occupation time density of a volume \( dx \) about \( x \): \( \langle \int_0^t ds \sum_{i=1}^{N(s)} \delta_x (x - X_i(s)) \rangle = \int_0^t ds \tilde{p}(s, x) \). We are making a factorization assumption similar to Boltzmann’s molecular chaos assumption (ensemble average of a product is product of ensemble averages).
Deterministic description: source and sink terms

♠ Birth term (tip branching): $r_b(t, x) p(t, x, v)$, $r_b = \alpha(C(t, x)) \delta_{\sigma_v}(v - v_0)$ (factorization assumed)

♠ Anastomosis: $-r_d(t, x) p(t, x, v)$. At time $t$, one tip meets a vessel at volume $dx$ about $x$, 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 $\int_0^t \tilde{p}(s, x) \, ds$. Missing in all previous work!

♠ Anastomosis: $r_d$ proportional to average occupation time density of a volume $dx$ about $x$: $\langle \int_0^t ds \sum_{i=1}^{N(s)} \delta_{\sigma_x}(x - X^i(s)) \rangle = \int_0^t ds \tilde{p}(s, x)$. We are making a factorization assumption similar to Boltzmann’s molecular chaos assumption (ensemble average of a product is product of ensemble averages).

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

$$\nabla_v \cdot [F(C(t, x)) p(t, x, v)].$$
**Deterministic description: boundary conditions for $p$**

★ Since $p$ has 2nd-order derivatives in $v$

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

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

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 \( x \): 2 one-half boundary conditions at \( x = 0, \ x = L \):

\[
\begin{align*}
p^+(t, 0, y, v, w) &= \frac{e^{-\frac{k|v-v_0|^2}{\sigma^2}}}{\int_{-\infty}^{0} \int_{-\infty}^{0} e^{-\frac{k|v'-v_0|^2}{\sigma^2}} \, dv' \, dw'} \left[ j_0(t, y) - \int_{-\infty}^{0} \int_{-\infty}^{\infty} v' p^-(t, 0, y, v', w') \, dv' \, dw' \right] \\
p^-(t, L, y, v, w) &= \frac{e^{-\frac{k|v-v_0|^2}{\sigma^2}}}{\int_{0}^{\infty} \int_{-\infty}^{\infty} e^{-\frac{k|v'-v_0|^2}{\sigma^2}} \, dv' \, dw'} \left[ \tilde{p}_L(t, y) - \int_{0}^{\infty} \int_{-\infty}^{\infty} p^+(t, L, y, v', w') \, dv' \, dw' \right]
\end{align*}
\]

where

- \( \mathbf{v} = (v, w) \); \( p^+ = p \) for \( v > 0 \) and \( p^- = p \) for \( v < 0 \)
- \( v_0 \) is the mean velocity of the vessel tips
- \( \sigma^2/k \) 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.

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

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

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

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L. L. Bonilla  |  Tumor Induced Angiogenesis  |  25 / 37
**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**

(haptotaxis, blood circulation, vessel pruning & other processes are ignored)
Bonilla et al, PRE 90, 062716, 2014, Terragni et al, PRE 93, 022413, 2015
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

♠ Overdamped limit of vessel extension: \( \frac{dX_i}{dt} = F + \beta^{-1/2} \frac{dW_i}{dt} \), yields simple equation for \( \tilde{p}(t, x) \):

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

♠ Renormalized \( \mu \) can be obtained by a Chapman-Enskog perturbation method (assuming that the tip density rapidly approaches local equilibrium in \( v \))

♠ Ignore diffusion, assume almost constant \( \mu \) & \( F \) produce 1D soliton

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

★ 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 \( (K, c, \xi_0) \)
SOLITON COLLECTIVE COORDINATES

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

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 \( \tilde{p}(t, x) \) behavior after formation stage.
Determinedistic 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**

![Graph showing the position of maximum marginal density for different replicas](image)

- **Soliton**: Red line
- **Stochastic pulse of replica n.10**: Black line
- **Stochastic pulse of replica n.19**: Green line
- **Stochastic pulse of replica n.100**: Blue line
- **Stochastic pulse of replica n.350**: Orange line

*Graph title: Location of Maximum*

*Axes labels:*
- **t (hr)**
- **0.2** to **0.7**

*Graph description:*
- The graph illustrates the position of maximum marginal density for different replicas over time (t in hours).
- The soliton curve (red) acts as a reference and is followed by the stochastic pulses of replicas n.10, n.19, n.100, and n.350, each represented by different colored lines.

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TWO REALIZATIONS FOR DIFFERENT FRICTION

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

- **Blueprint for other models** (master equation $\rightarrow$ Fokker-Planck eq)

- **Haptotaxis, anti-angiogenic drugs** added as extra field RDE and extra forces in Langevin equations (haptotaxis in Entropy 19, 209, 2017)

- **Stability of soliton, initial stage and arrival to tumor**

- **Effect of haptotaxis, anti-angiogenic drugs on soliton:** *control of angiogenesis, therapy*
**PERSPECTIVES**

- **Blueprint for other models** (master equation $\rightarrow$ Fokker-Planck eq)

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THANK YOU!!!
Derivation of a mean field equation for the vessel tip density, as $N \to \infty$

- Itō’s formula is applied for a smooth $g(x, v)$ & the process in Langevin eqns

- For any replica $\omega$, at time $t$, the number of tips per unit volume in the $(x, v)$ phase space is given by the empirical distribution

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

- If $N$ is sufficiently large, $Q^*_N$ may admit a density by laws of large numbers

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

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

- Tip branching & anastomosis are added as source & sink terms to the obtained equation for $p(t, x, v)$ in strong form
Anastomosis

If a tip meets an existing vessel, they join at that point & time → the tip stops the evolution

The “death” rate of tips is a fraction of the occupation time density

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

which is the concentration of vessels per unit volume, at \( t \) and \( x \)

Note: tips occupy a volume \( dx \) about \( x \) when they reach it, or by branching, or during anastomosis (this depends on the past history of a given stochastic replica)
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$$p^-(t, L, y, v, w) = \frac{e^{-\frac{k|v-v_0|^2}{\sigma^2}}}{\int_{-\infty}^0 \int_{-\infty}^\infty e^{-\frac{k|v'-v_0|^2}{\sigma^2}} dv' dw'} \left[ \tilde{p}_L(t, y) - \int_{\infty}^\infty \int_{-\infty}^0 p^+(t, L, y, v', w') dv' dw' \right]$$

where

★ $v = (v, w)$; $p^+ = p$ for $v > 0$ and $p^- = p$ for $v < 0$

★ $v_0$ is the mean velocity of the vessel tips

★ $\sigma^2 / k$ is the temperature of the local equilibrium distribution