A Multiscale Approach in the Mathematical Modelling of Angiogenesis: the Role of Randomness.

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VASCULOGENESIS – ANGIOGENESIS

The outstanding milestone in the early history of biological quantitation was the work of a physician to the King of England

William Harvey
Exercitatio Anatomica De Motu Cordis at Sanguinis in Animalibus, first published in 1628.

Harvey had studied Medicine in Padua (1600-1602, while Galileo was active there)....he was not able to see those small vessels.

His theoretical prediction, based on his meticolous anatomical observations and his mathematical calculations, was spectacularly confirmed more than half a century later when Marcello Malpighi in 1661, saw the capillaries under a microscope

A Vascular Network
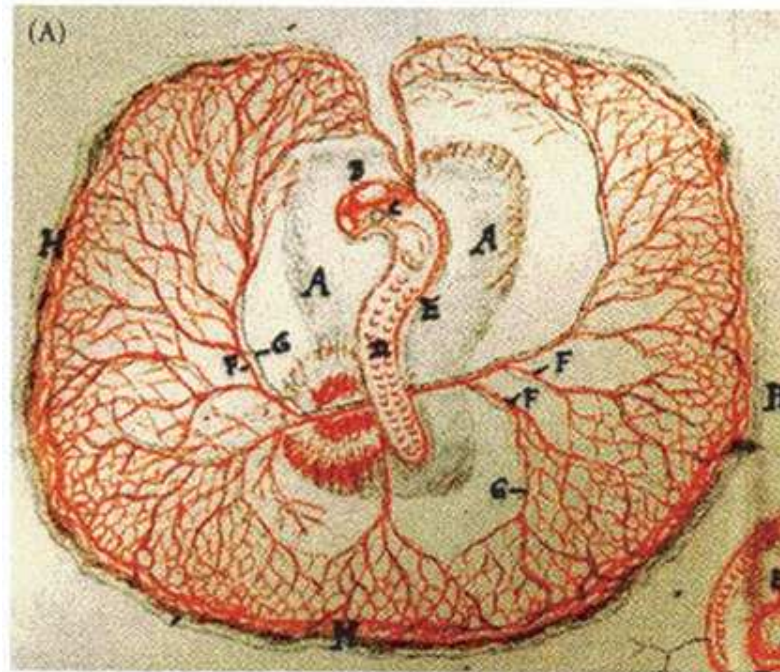
A network of arteries, capillaries and veins in a developing chicken embryo.

Drawing by M. Malphighi (1661).

Harvey's discovery illustrates the enormous power of simple... mathematics combined with careful observation and clear reasoning.

"Mathematics is Biology Next Microscope, Only Better;

Biology is Mathematics Nest Physics, Only Better."

[J.E. Cohen, PLoS Biol. 2, 2004]

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The growth of blood vessels (a process known as angiogenesis) is essential for organ growth and repair.

An imbalance in this process contributes to numerous malignant, inflammatory, ischaemic, infectious and immune disorders.

....

Angiogenesis research will probably change the face of medicine in the next decades, with more than 500 million people worldwide predicted to benefit from pro- or anti-angiogenesis treatments.

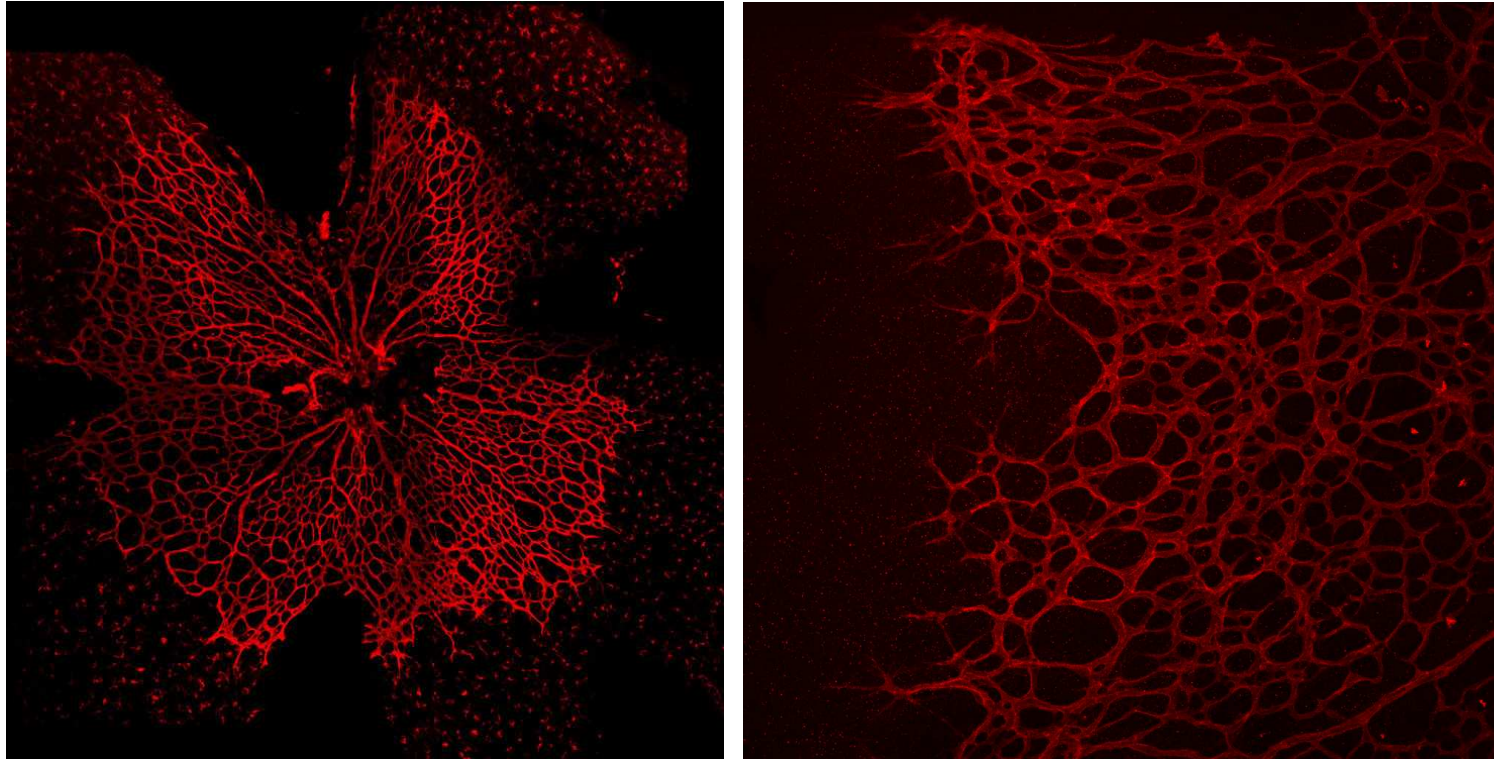[Peter Carmeliet, Angiogenesis in life, disease and medicine, NATURE,438 (2005].

TUMOUR-INDUCED ANGIOGENESIS
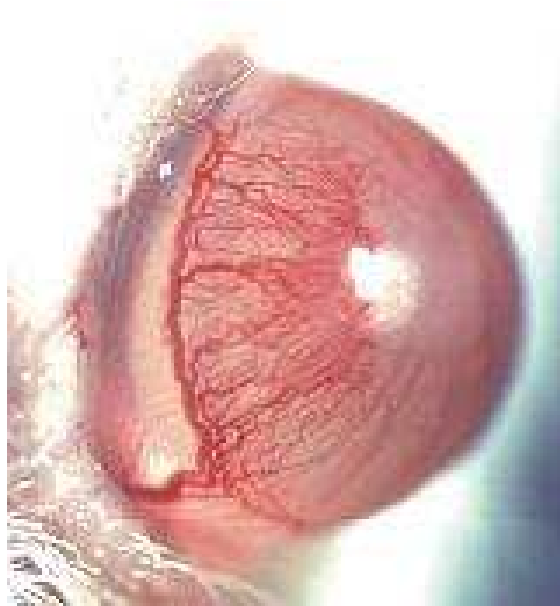
Angiogenesis on a rat cornea

[Credit: Dejana et al., 2005]

RETINAL ANGIOGENESIS

Developing postnatal retinal vasculature
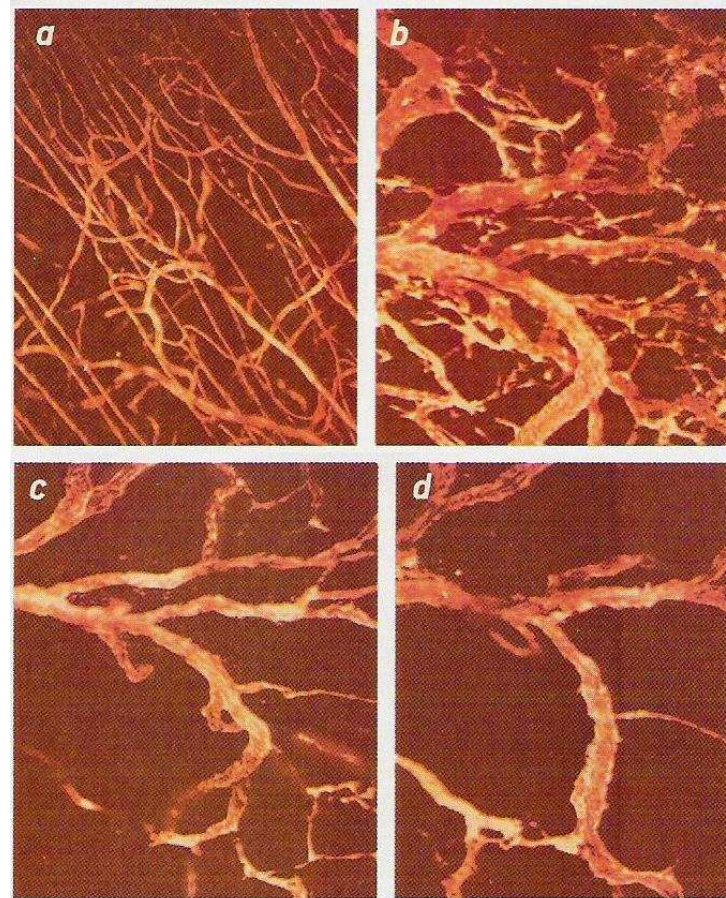
[Credit:Fruttiger, 2007]

Figure 1: Response of a vascular network to an antiangiogenic treatment.
[Credit: R.K. Jain- P.F. Carmeliet, 2001]

Figure 2: Angiogenesis on a rat cornea.

[Credit: Dejana et al 2005]

THE BIOMEDICAL PROBLEM

•• MORPHOLOGY $\Longrightarrow$ DIAGNOSIS

•• CONTROL THE BIRTH-AND-GROWTH PROCESS $\Longrightarrow$ THERAPY

THE MATHEMATICAL PROBLEM

In a detailed description, this process can be modelled as a birth-and-growth process in a stochastic geometric setting:

BIRTH = VESSEL BRANCHING

GROWTH = VESSEL EXTENSION

Various authors have given important contributions to the field; quoting all of them would need more than the time slot allocated for this presentation.

OUTLINE

- WORKING EXAMPLES: 1. TUMOUR-INDUCED ANGIOGENESIS

- WORKING EXAMPLES: 2. RETINAL ANGIOGENESIS

- MATHEMATICAL MODELS

- MULTIPLE SCALES $\implies$ HYBRID MODELS

- ASYMPTOTICS $\implies$ MEAN FIELD MODELS

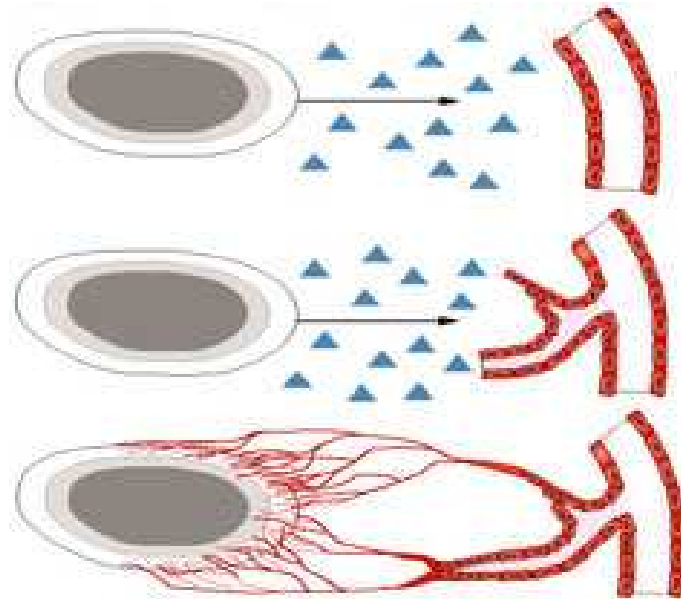# Interaction with underlying fields

Figure 3: Angiogenesis coupled with a capillary growth factor (CGF).

A "CONCEPT" MODEL

The main features of the process of formation of a tumour-driven vessel network are

i) vessel branching;

ii) vessel extension:

- chemotaxis in response to a generic tumour angiogenic factor (TAF), released by tumour cells;

- haptotaxis in response to fibronectin gradient, generated in the ECM (extracellular matrix), as the ECs (endothelial cells) migrate (a combination of degradation and production);

iii) anastomosis, when a capillary tip meets an existing vessel, thus forming loops;

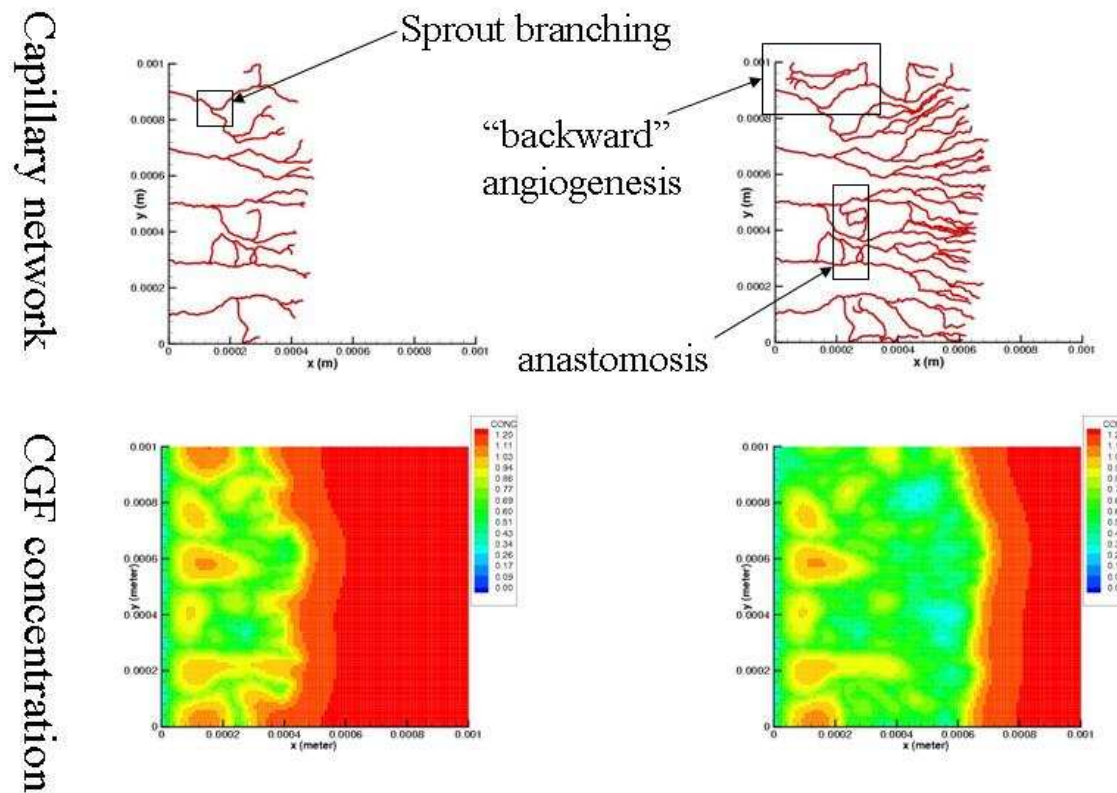iv) blood circulation;

v) therapy.

Figure 4: Key features of a mathematical model of angiogenesis.

THE MATHEMATICAL MODEL

[C. − Morale,2007]

- **THE CAPILLARY NETWORK**

Let

$$N(t) \in \mathbb{N} \quad \text{the random number of tips at time } t,$$
$$X^i(t) \in \mathbb{R}^d \quad \text{the random location of the } i\text{-th tip at time } t,$$
$$T_i \in \mathbb{R}_+ \quad \text{the random birth time of the } i\text{-th tip;}$$

We model sprout extension by tracking the random trajectory of individual capillary tips.

$$X(t) = \bigcup_{i=1}^{N(t)} \{X^i(s), T_i \le s \le t\}$$

is the random network of endothelial cells, i.e. the union of the random trajectories described by all existing tips $\Longrightarrow$ **A STOCHASTIC FIBRE SYSTEM**.

THE UNDERLYING FIELDS

TAF, fibronectin and matrix degrading enzymes activate the migration of endothelial cells.

The Chemotactic field **TAF** diffuses, and it decreases where endothelial cell are present.

As a first simplified model we assume

MODEL 1: consumption is due to the additional endothelial cells producing vessels' extensions. It is proportional to the velocity $v_i, i = 1, \ldots,$ of the tips

$$\frac{\partial}{\partial t}C(t,x) = \kappa \mathbb{I}_A(x) + d_1 \triangle C(t,x) - \eta C(t,x)\frac{1}{N}\sum_{i=1}^{N(t)}(v_i(t)\delta_{X^i(t)} * K_N)(x)$$

where $\delta_{X^i(t)}(x)$ denotes the random Dirac distribution localized at the tip $X^i(t)$, for $i = 1, \ldots, N(t)$

Parameters $\kappa, d_1, \eta \in \mathbb{R}^+$ represent the rate of production of a source located in a region $A \subset \mathbb{R}^d$, modelling e.g. a tumour mass, the diffusivity, and the rate of consumption, respectively.

The consumption terms

In this model we have been considering a dependence upon the (mollified) empirical distribution of the variation in length of the existing vessels, per unit time.

$$\frac{1}{N} \sum_{i=1}^{N(t)} (v_i(t) \delta_{X^i(t)} * K_N)(x)$$

Rescaling by N:

the parameter N represents a scale parameter, corresponding to the order of magnitude of the number of vessels in the network, so that the action of each existing vessel is reduced accordingly;

Convolution with the kernel $K_N(x)$

it provides a mollified version of the relevant random distributions; from a modelling point of view this may correspond to a nonlocal reaction with the relevant underlying fields [Wheeler, 2005].

For the rescaling, the mollifier kernel K_N is chosen such that $\lim_{N \to \infty} K_N(x) = \delta_0(x)$.

Convergence

Later specific choices about the dependence of the kernel K_N upon N will allow the convergence to corresponding densities, for N tending to infinity, by means of suitable laws of large numbers.

Haptotactic field

Fibronectin is attached to the extracellular matrix and does not diffuse [Birdwell,80].

Degradation of fibronectin, characterized by a coefficient γ, depends on the concentration of **matrix degrading enzyme**(MDE), produced by the cells [Chaplain, 2006].

$$\frac{\partial}{\partial t}f(t,x) = \beta\frac{1}{N}\sum_{i=1}^{N(t)}(\delta_{X^i(t)}*K_N)(x) - \gamma m(x,t)f(t,x)$$

The **MDE**, once produced, diffuses locally with a diffusion coefficient ϵ_1, and is spontaneously degraded at a rate ν.

$$\frac{\partial}{\partial t}m(t,x) = \epsilon_1\triangle m(t,x) + \nu_1\frac{1}{N}\sum_{i=1}^{N(t)}(\delta_{X^i(t)}*K_N)(x) - \nu_2 m(t,x)$$

All these random partial differential equations are subject to suitable boundary and initial conditions.

Branching

Two kinds of branching have been identified; either from a tip or from a mature vessel; here for the sake of simplicity, we shall consider only **tip branching**.

The birth process of new tips can be described in terms of a marked point process, by means of the random measure

$$\Phi = \sum_n \epsilon_{(T^n, X^n)}.$$

where T^n and X^n are the birth time and location of the n-th tip, $\epsilon_{t,x}$ denotes the usual Dirac measure on $\mathcal{B}_{\mathbb{R}^+} \times \mathcal{B}_{\mathbb{R}^d}$, $\mathcal{B}_{\mathbb{R}^d}$ is a Borel σ-algebra on $\mathbb{R}^d$.

Hence, for any measurable set $A \subseteq \mathcal{B}_{\mathbb{R}^+} \times \mathcal{B}_{\mathbb{R}^d}$,

$$\Phi(A) := \sum_n \epsilon_{(T^n, X^n)}(A) = \text{card}\{n : (T^n, X^n) \in A\}$$

is the random variable which counts those tips which are born in A, (out of existing tips at the relevant times).

TIP BRANCHING

The jump process $N(t)$, which counts all tips born up to time t, is then defined by

$$N(t) = \Phi([0, t] \times \mathbb{R}^d).$$

A (simple) marked point process is characterized by its stochastic intensity, i.e. by the infinitesimal probability of branching, conditional upon the history $\mathcal{F}_{t-}$ of the whole process up to time $t - $.

Given that at time $t-$, the existing parental tips are $X^i(t), i = 1, ..., N(t-)$, and TAF's concentration is $C(t, x)$, the stochastic intensity is given by

$$
\begin{aligned}
\mu(dt \times dx) &= P(\Phi(dt \times dx) = 1 | \mathcal{F}_{t-}) \\
&= \alpha_1(t, x) dx\, dt \\
&= \alpha(C(t, x)) \sum_{i=1}^{N(t)} \delta_{X^i(t-)}(x) dx\, dt
\end{aligned}
$$

When a tip located in x branches, the initial value of the state of the new tip is $\left(X^{N(t)+1}, v^{N(t)+1} \right) = (x, v_0)$, where v_0 is a non random velocity.

VESSEL EXTENSION

We consider a Langevin model

$$
\begin{aligned}
dX^i(t) &= v^i(t)(1 - p_a \mathbb{I}_{X(t)})(X^k(t))dt, \\
dv^i(t) &= a(X^i(t), v^i(t), t)dt + \sigma dW^i(t), \qquad t > T^i,
\end{aligned}
$$

where $v^i(t)$ is the speed of the i-th tip at time t.

The drift $a(x, v, t)$:

$$
a(X^i(t), v^i(t), t) = -kv^i(t) + F\left(C(t, X^i(t)), f(t, X^i(t))\right),
$$

i.e. we consider an inertial component and a bias due to the underlying fields.

Tip-vessel anastomosis:

The term $(1 - p_a \mathbb{I}_{X(t)})(X^k(t))$ models the phenomenon of impingement.

$\mathbb{I}_{X(t)}$ denotes the indicator function associated with the existing vessel network $X(t)$.
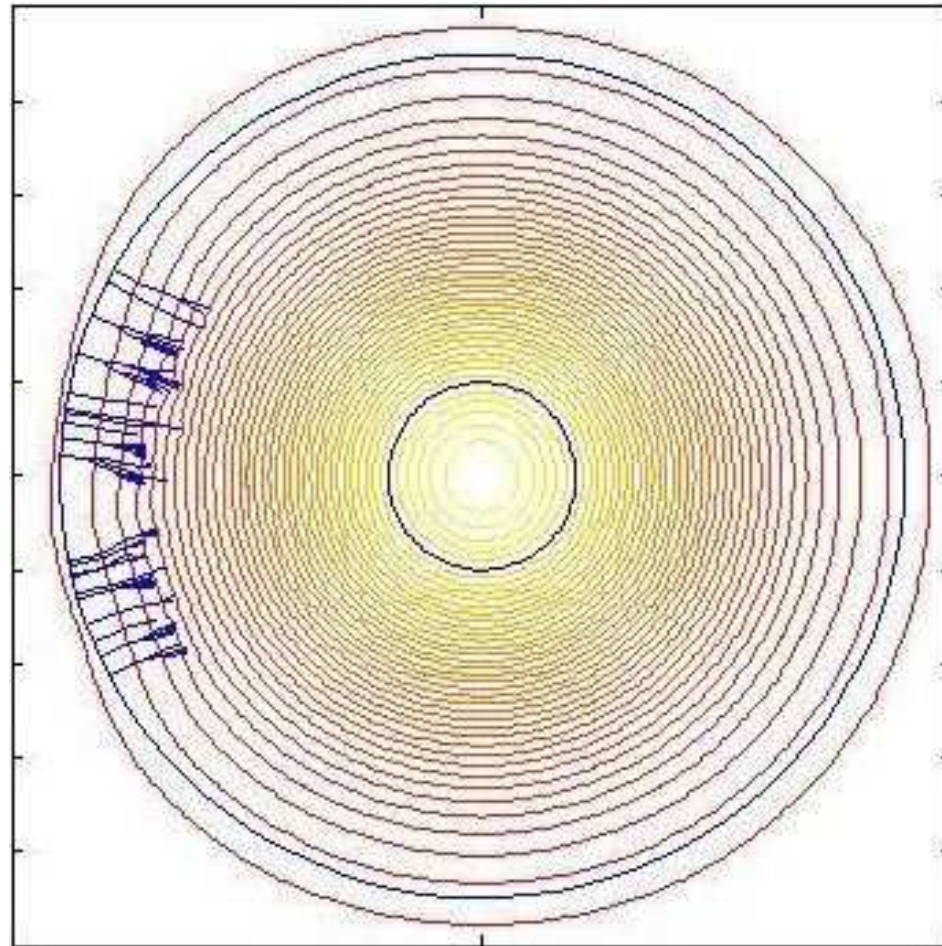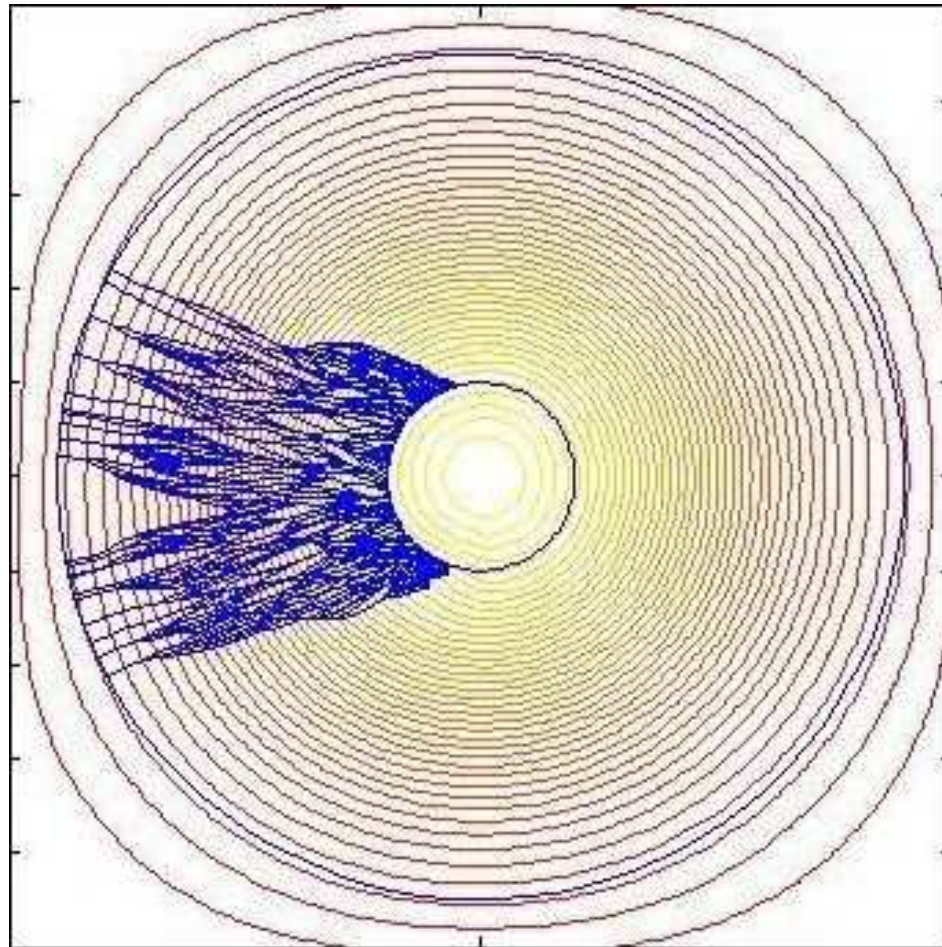
Figure 5: Time t=150. [Credit: Capasso-Mattavelli, 2008]
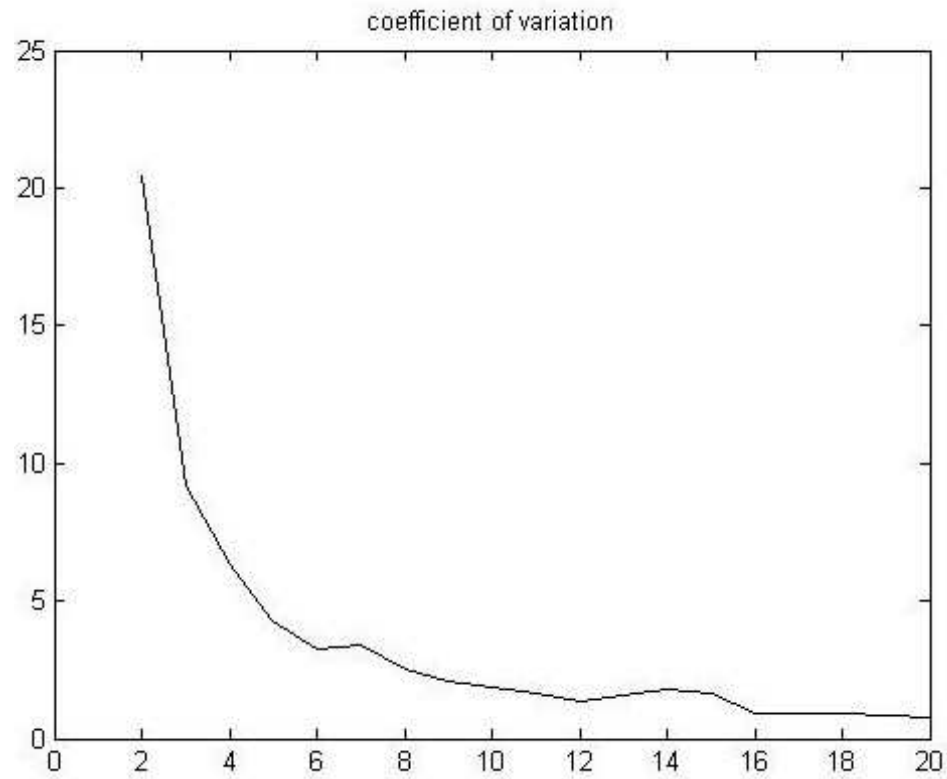
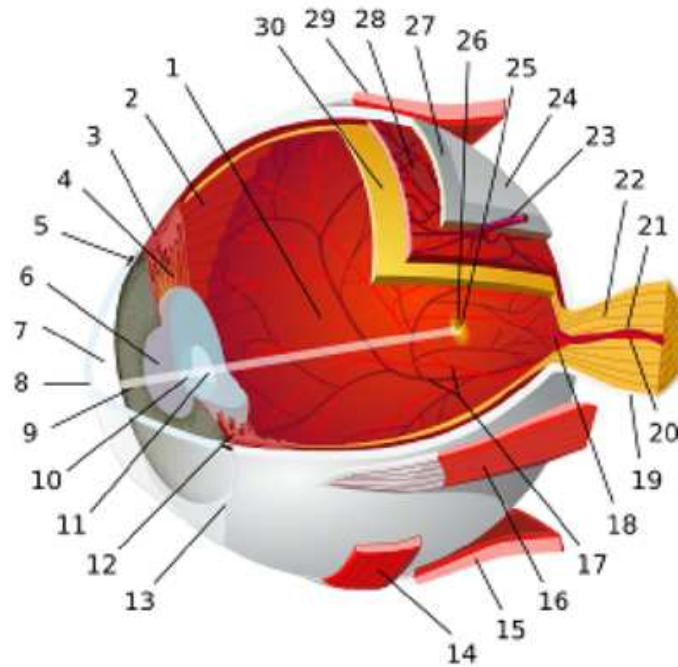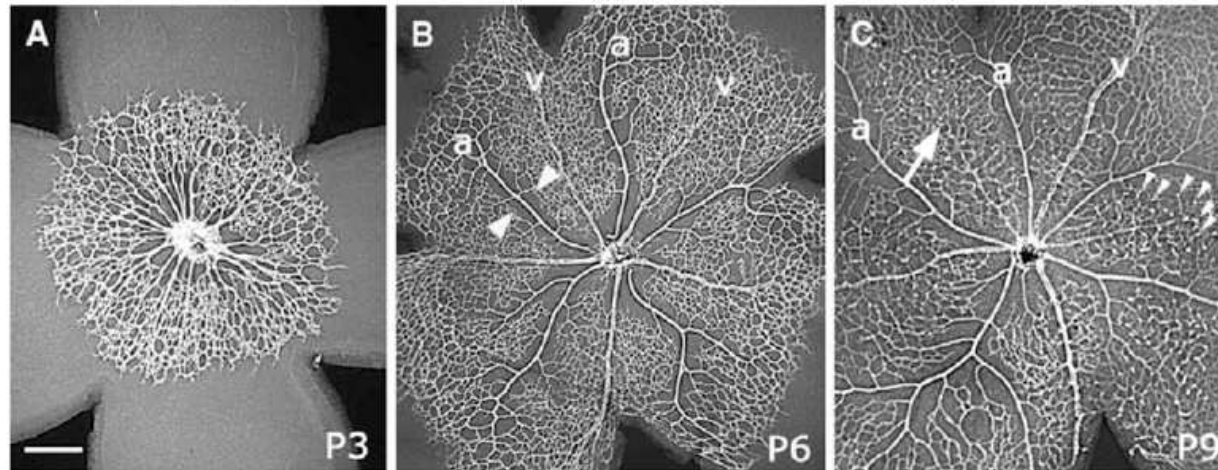Figure 6: Time t=400. [Credit: Capasso-Mattavelli, 2008]

Figure 7: [Credit: Mattavelli, 2008]

Real experiment: Rat Retina

Immediately after birth, the retinal vascular system starts to develop as a sprout from the optic disc (18)

and

initially forms a primitive vascular plexus which is rapidly remodelled into large and small vessels (28).

*Real experiment: Rat Retina*

[Fruttiger, Angiogenesis (2007) 10,7788]

During the first postnatal week, retinal vessels continue to extend radially over the superficial layer of the retina to form a two-dimensional vascular structure.

On the other hand, around postnatal day 7, the retinal vessels start to sprout into deeper layers, which finally leads to the formation of a three-layered vascular system.

The Dynamics
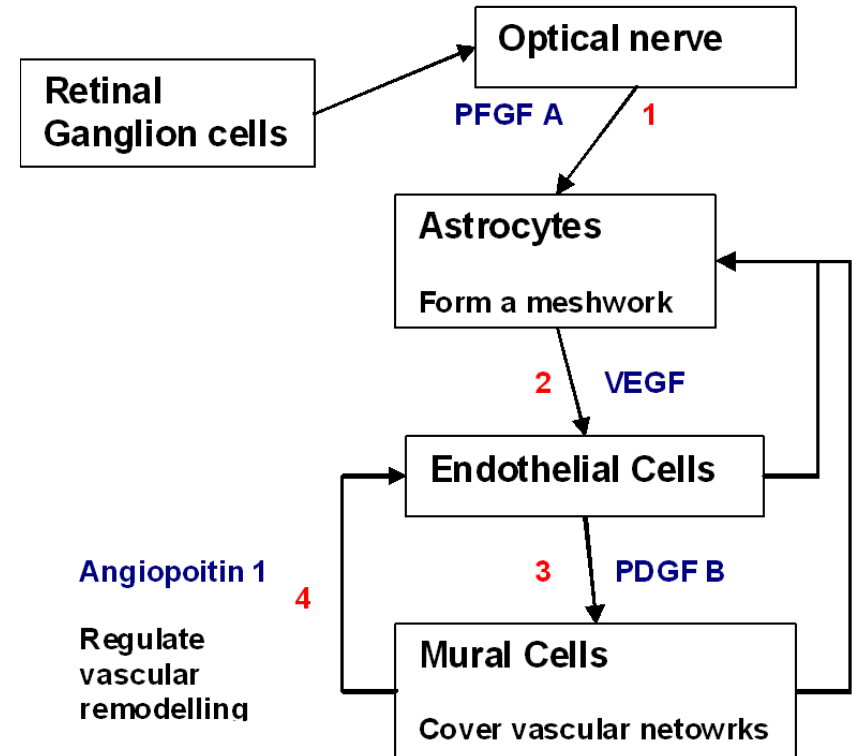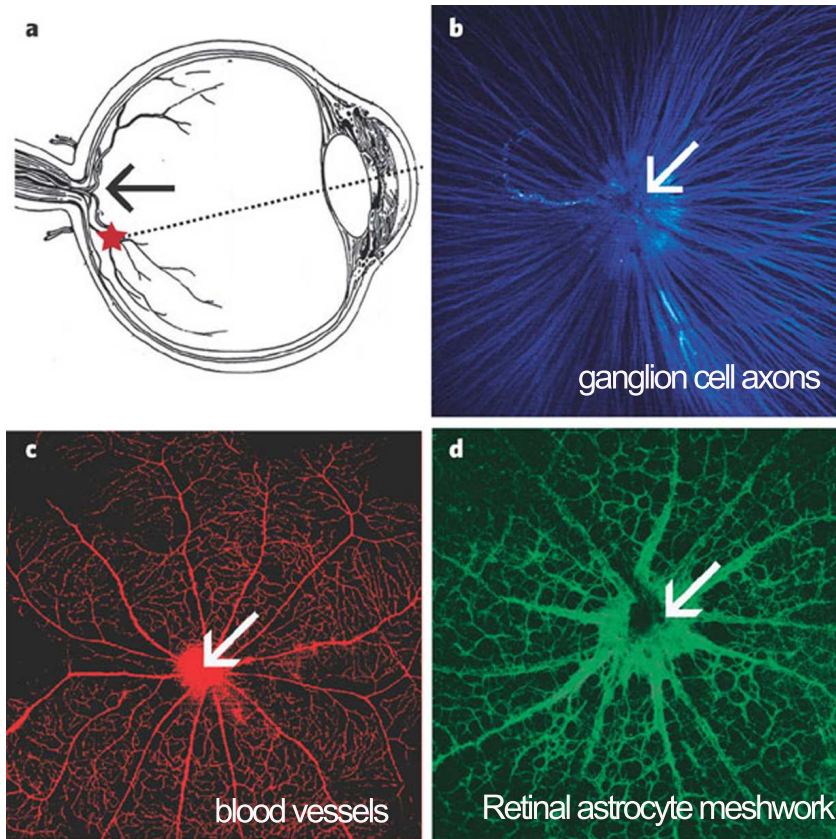
[Gariano, Gardner, Nature, 438, 2005, 960-966]

The VEGF
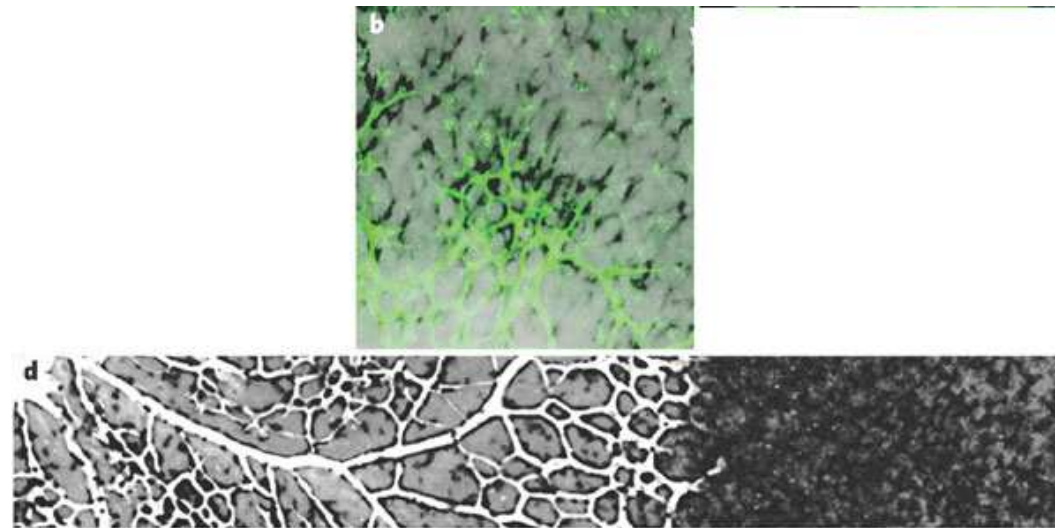
[Gariano, Gardner, Nature, 438, 2005, 960-966]

b. VEGF expression (black) is greatest just in advance of the most distal growing blood vessels (green).

d, VEGF expression (black) is higher beyond the extent of retinal vascularization (right) than where vessels (white) are present.

A "CONCEPT" MODEL

[Fruttiger, Angiogenesis (2007) 10,7788]

The main features of the process of formation of a retinal vessel network are

- type of cells and conversion:

    - specialized *endothelial tip cells* at the leading edge of the growing vascular network (type 2);
    - the *stalk cells*, located in the neighborhood of tip cells (type 2);
    - the *mural cells* which are the mature cells (type 1).

- vessel branching: due to proliferation and change of state of cells;
- vessel extension;

    - aggregation chemotaxis on type 2 cells in response to Vascular Endothelial Growth Factor (VEGF), released by astrocytes at the front of the vessel network;
    - repulsion in response to nutrients produced by type 1 cells;

- remodelling;
- blood circulation.

Let $N \in \mathbb{N}$ be the total number of cells in the system and, $N(t) \in \mathbb{N}$ be the random number of cells entered in the dynamics at time t, $T_i^b, T_i^d \in \mathbb{R}_+$ the random birth and death time of the i-th cell.

Cells: a bivariate stochastic process

$$(X^i(t), C^i(t)) \in \mathbb{R}^d \times \mathbb{S}, \quad \mathbb{S} = \{1, 2, 3\}, \quad i = 1, ..., N(t),$$
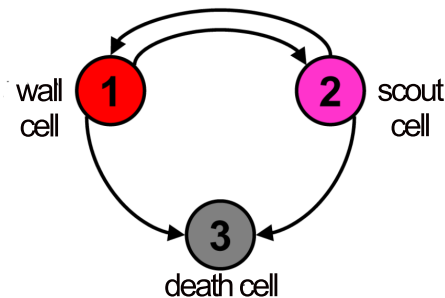
The Vessel Network: a stochastic fiber process

$$X(t) = \bigcup_{i=1}^{N(t)} \{X^i(s), T_i^b \leq s \leq min(t, T_i^d)\}$$

Lagrangian description

The state of the k-th tip:

$$\epsilon_{(X^k(t),C^k(t))} \in \mathcal{M}(\mathbb{R}^d \times \mathbb{S}),$$

which is the *degenerate Dirac measure* localized in $(X^k(t), C^k(t))$, i.e.

for any $B \in \mathcal{B}_{\mathbb{R}^d}, s \in \mathbb{S}$,

$$\epsilon_{(X^k(t),C^k(t))}(B \times \{s\}) = \begin{cases} 1, & X^k(t) \in B, C^k(t) = s \\ 0, & \text{otherwise} \end{cases}$$

for any sufficiently smooth $g : \mathbb{R}^d \times \mathbb{S} \to \mathbb{R}$

$$\int_{\mathbb{R}^d} \sum_{s=1}^{3} g(y,s) \epsilon_{(X^k(t),C^k(t))}(dy \times \{s\}) = g\left(X^k(t), C^k(t)\right)$$

With the above notations, the global random empirical measure of the process is given by

$$Q_N(t) = \frac{1}{N} \sum_{i=1}^{N(t)} \epsilon_{(X^k(t), C^k(t))},$$

and the empirical spatial distribution of the cells of type $s \in \mathbb{S}$ is given by

$$
\begin{aligned}
Q_N^{[s]}(t) &= Q_N(t)(\cdot \times \{s\}) \\
&= \frac{1}{N} \sum_{k \in H(s,t)} \epsilon_{X^k(t)} \in \mathcal{M}(\mathbb{R}^d),
\end{aligned}
$$

where $H(s,t) = \{k \in \{1, ..., N(t)\} : C^k(t) = s\}, \ s \in \mathbb{S} = \{1, 2, 3\}.$

The dynamics of the underlying fields

Aggregation field **VEGF** diffuses, it is produced around the scout (type 2) cells and it naturally decays:

$$
\begin{aligned}
\frac{\partial g(x,t)}{\partial t} &= -d_g g(x,t) + D_g \Delta g(x,t) + \alpha_g \frac{1}{N} \sum_{j=1}^{N(t)} \left(\epsilon_{(\cdot, C^j(t))}(x,2) * K_\epsilon \right) (X^j(t)) \\
&= -d_g g(x,t) + D_g \Delta g(x,t) + \alpha_g \left(Q_N^{[2]} * K_\epsilon \right) (X^j(t))
\end{aligned}
$$

Repulsion field **nutrients** diffuses, it is produced around the mural (type 1) cells and it naturally decays:

$$
\begin{aligned}
\frac{\partial u(x,t)}{\partial t} &= -d_u u(x,t) + D_u \Delta u(x,t) + \alpha_u \frac{1}{N} \sum_{j=1}^{N(t)} \left(\epsilon_{(\cdot, C^j(t))}(x,1) * V_\epsilon \right) (X^j(t)) \\
&= -d_u u(x,t) + D_u \Delta u(x,t) + \alpha_u \left(Q_N^{[1]} * V_\epsilon \right) (X^j(t))
\end{aligned}
$$

VESSEL EXTENSION : Lagrangian Dynamics

VEGF (g) and the nutrient (u) (e.g. oxygen) activate the migration and the dynamics of endothelial cells. We suppose that

$-$ only Type 2 cells are subject to the action of the underlying fields (attraction by the VGEF g, repulsion by the nutrient u).

$-$ Type 1 cells are only subject to a possible randomness.

Randomness is modelled by additive independent Wiener processes $\{W_t^i\}_{t \in \mathbb{R}_+}$. Hence, for $i = 1, ..., N(t)$ and $t > T_i^b$.

$-$ Type 3 cells do not move anymore.

For $i = 1, ..., N(t)$ and $t > T_i^b$,

$$dX^i(t) = \delta_{C^i(t),2}\alpha_2[\nabla g(X^i(t), t) - \nabla u(X^i(t), t)]dt + \sigma(C^i(t))dW_t^i dt.$$

where

$$\sigma(C^i(t)) = \begin{cases} \sigma_j, & C^i(t) = j, \text{ for } j = 1, 2; \\ 0, & C^i(t) = 3. \end{cases}$$

$\delta_{i,j}$ is the Kroenecker delta, and $\beta, \sigma_1, \sigma_2 \in \mathbb{R}_+$.

CELL PROLIFERATION

Proliferation is described by a branching process, modelled as a marked counting process. Random measure Φ on $\mathcal{B}_{\mathbb{R}_+ \times E \times \mathbb{S}}$

$$\Phi = \sum_i \epsilon_{(T_i^b, X^i, C^i)}.$$

Stochastic intensity, for $(t, x, s) \in \mathbb{R}_+ \times E \times \mathbb{S}$

$$\mu(dt \times dx \times \{s\}) = prob(\Phi(dt \times dx \times \{s\}) = 1 | \mathcal{F}_{t-}) = \Lambda_t(dx \times \{s\}) \, dt;$$

where $\mathcal{F}_{t-}$ denotes the "history" of ($\sigma-$ algebra generated by) the process up to time $t-$;

$$\Lambda_t(dx \times \{s\}) = h(x, s) \sum_{i=1}^{N(t^-)} \epsilon_{(X^i(t), C^i(t))}(dx \times \{s\}),$$

with

$$h\left((X^i(t), C^i(t))\right) = \lambda_1 \delta_{C^i(t), 1} + \lambda_2 \frac{1}{1 + N(Q_N^{[2]} * K)(X^i(t))} \delta_{C^i(t), 2}.$$

The type 1 cell proliferation rate is constant, while the type 2 cell proliferation rate decreases with their local density number.

The counting process $N(t)$

$N(t)$ is a stochastic counting process with intensity

$$\nu(dt) = \Lambda_t(\mathbb{R}^d \times \mathbb{S}) = \sum_{i=1}^{N(t)} h(X^i(t), C^i(t))dt = N \sum_{s \in \mathbb{S}} \int_{\mathbb{R}^d} h(x, s) Q_N(t)(dx, \{s\})\, dt.$$

Since $h(x, s)$ is uniformly bounded, the process

$$Z(t) = \frac{N(t)}{N} = \langle Q_N(t), 1 \rangle$$

is stochastically dominated by the process $\dfrac{1}{N} Y_{N\langle T_N(0),1\rangle}$, where Y_k is a Yule process with birth rate given by $\tilde{h} = \sup h(x, s), \quad Y_k(0) = k$. This implies that

$$\lim_{n \to \infty} \sup_{N \in \mathbb{N}} P\left(\sup_{t \leq T} \langle Q_N(t), 1 \rangle \geq n \right) = 0.$$

CELL STATE EVOLUTION

The change of state of each cell is described via a continuous time Markov chain. The associated time-dependent transition intensity matrix for the i-th cell is given by the following

$$\mathbf{M}(X^i(t), C^i(t), t) = \begin{bmatrix} -(m_{12} + m_{13}) & m_{12} & m_{13} \\ m_{21} & -(m_{21} + m_{23}) & m_{23,} \\ 0 & 0 & 0 \end{bmatrix},$$

where

$$m_{hk} := m_{hk}(X^i(t), C^i(t)) = \lim_{\Delta t \to 0} \frac{\mathbb{P}\{C^i(t + \Delta t) = k | C^i(t) = h\}}{\Delta t}$$

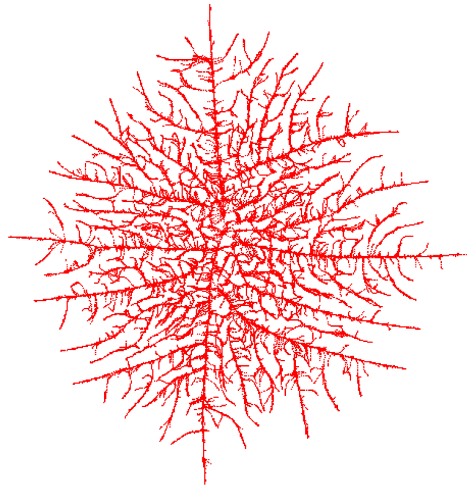are given by (for $i, j = 1, 2, 3, \ \lambda_{ij} > 0$).

$$m_{12}(x, 1) = \frac{\lambda_{12}}{u(x,t)}, \qquad m_{21}(x, 2) = \lambda_{21}(Q_N^{[2]} * K)(x),$$

$$m_{13}(x, 1) = \frac{\lambda_{13}}{(Q_N^{[1]} * K)(x)}, \qquad m_{23}(x, 2) = \lambda_{23},$$
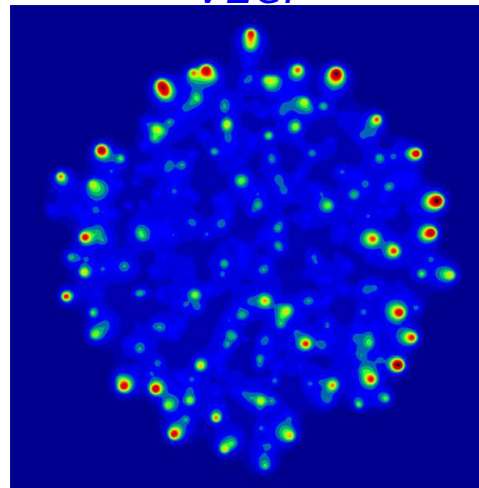
The stochastic system

$$\text{random} \quad dX^i(t) = \alpha_2[\nabla g(X^i(t), t) - \nabla u(X^i(t), t)]dt + \sigma_2 dW_t^i$$

$$\text{random} \quad \frac{\partial g(x, t)}{\partial t} = -d_g g(x, t) + D_g \Delta g(x, t) + \frac{\alpha_g}{N(t)} \sum_j \delta_{(X^j(t), C^j(t))}(x, 2);$$

$$\text{random} \quad \frac{\partial u(x, t)}{\partial t} = -d_u u(x, t) + D_u \Delta u(x, t) + \frac{\alpha_u}{N(t)} \sum_j \delta_{(X^j(t), C^j(t))}(x, 1).$$
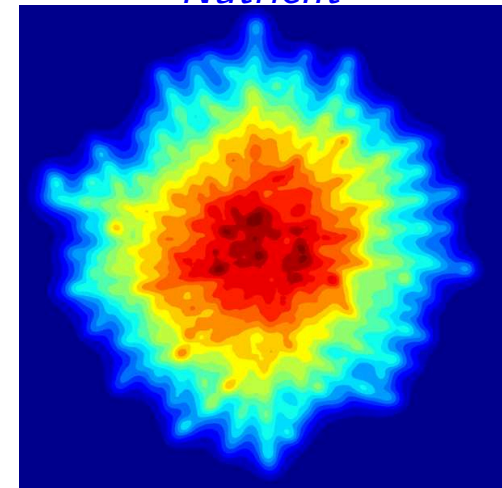
Endothelial Cells *VEGF* *Nutrient*

- network

- feedback of the stochasticity on the underlying fields

Summarizing ...

At the microscale, the Lagrangian description is based on the stochastic behavior of individual cells, given by

- the system of stochastic differential equations modelling extension;

- the branching process $\Phi_N(t)$ modelling cell proliferation;

- the Markov chain modelling the change of state.

The evolution of the stochastic processes of branching and extension is driven by parameters which depend upon the underlying fields; since the evolution of these ones is viceversa coupled with the above stochastic processes, they are themselves stochastic.

We are dealing at the microscale with a doubly stochastic system.

Such a strong coupling with the underlying fields is a source of complexity which may tremendously increase as the number of cells becomes extremely large, as it may happen in many cases of real interest.

The source terms in the PDEs of $g(x, t)$, and $u(t, x)$ depend upon the stochastic geometric process $X(t)$

$\Downarrow$

RANDOM PDE's

$\Downarrow$

stochasticity of the kinetic parameters of branching and growth of vessels.

$\Downarrow$

Multiple Scales - An Hybrid Model

For many practical tasks, the stochastic models presented above, which are able to describe the process on microscopic scales, are too sophisticated. On the other hand in many applications parameters are such that multiple scales can be identified . It suffices to use averaged quantities at the larger scale, still using stochastic quantities at the lower scales. The advantage of using averaged quantities at the larger scale is convenient, both from a theoretical point of view, and for computational affordability.

Multiple Scales

Under particular conditions a *mesoscale* may be introduced, which is sufficiently small with respect to the macroscale of the underlying fields and sufficiently large with respect to typical cell size.

A typical size x_{meso} on this mesoscale satisfies

$$x_{micro} << x_{meso} << x_{macro},$$

where x_{micro} and x_{macro} are typical sizes for single cells and for the fields' diffusion.
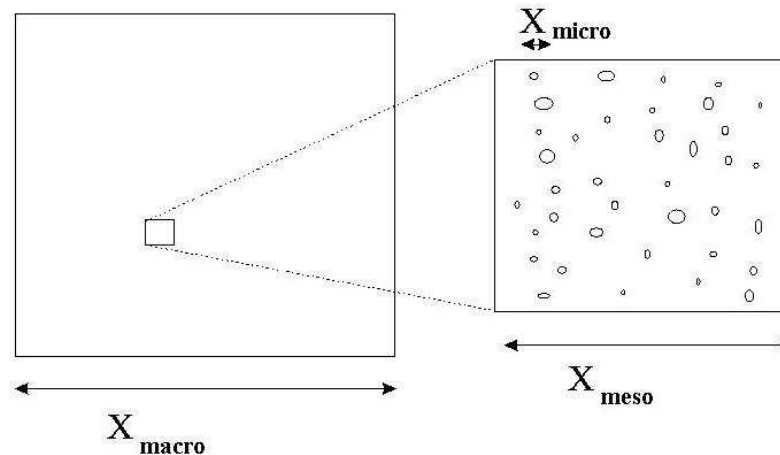
Depending upon a sufficiently high spatial density of vessels, at the level of the mesoscale we might approximate (*law of large numbers*) the contribution due to the vascularization process in the equations for $g(x,t)$, and $u(x,t)$, by suitable local mean densities, thus obtaining purely deterministic PDE's.

[Burger-C -Pizzocchero, 2005]

Consequently, we would be given

deterministic fields for the kinetic parameters for the stochastic processes evolving at the microscale.

With these parameters,

the branching-and-growth process would become stochastically simple.

This approach is called "hybrid", since we are substituting all stochastic underlying fields by their "mean field" approximations; most of the existing literature in this area might be reinterpreted along these lines.

Indeed, one should check that the hybrid system is fully compatible with a rigorous derivation of the evolution for the vessel densities. Nonlinearities in the full model are a big difficulty in this direction; here we are going to present an heuristic derivation, since a rigorous mathematical analysis requires further investigation.

We wish to stress that anyhow substituting mean geometric densities, to the corresponding stochastic quantities leads to an acceptable coefficient of variation (percentage error) only when a law of large numbers can be applied, i.e. whenever the relevant numbers per unit volume are sufficiently large; otherwise randomness cannot be avoided, and, in addition to mean values, the mathematical analysis and/or simulations should provide confidence bands for all quantities of interest.

[Burger-C -Pizzocchero, 2005]

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THE DISCRETE EULERIAN EVOLUTION

A global description of the cell system may be given in terms of stochastic measures.

This means that instead of the evolution of the stochastic processes describing the state of each individual cell, one may consider the temporal evolution of the stochastic empirical process

$$t \in [0, T] \mapsto Q_N(t) = \frac{1}{N} \sum_{i=1}^{N(t)} \epsilon_{(X^k(t), C^k(t))} \in C([0, T], \mathcal{M}(E \times \mathbb{S})).$$
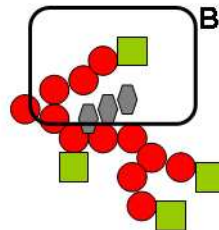
The Eulerian description

The global random empirical measure of the process :

$$Q_N(t) = \frac{1}{N} \sum_{i=1}^{N(t)} \epsilon_{(X^k(t), C^k(t))}$$

The empirical spatial distribution of the cells of type $s \in \mathbb{S} = \{1, 2, 3\}$ is given by

$$
\begin{aligned}
Q_N^{[s]}(t) &= Q_N(t)(\cdot \times \{s\}) \\
&= \frac{1}{N} \sum_{k \in H(s,t)} \epsilon_{X^k(t)} \in \mathcal{M}(\mathbb{R}^d),
\end{aligned}
$$

where $H(s,t) = \{k \in \{1, ..., N(t)\} :$
$C^k(t) = s\}.$

EULERIAN DYNAMICS

By Ito-Levy formula, if $f \in C_b(E \times \mathbb{S})$ is a sufficiently smooth function, we obtain, for any $k = 1, ..., N(t)$

$$d\, f(X^k(t), C^k(t)) =$$

$$= \left(\beta \left[\nabla g(X^k(t), t) - \nabla u(X^k(t), t) \right] \delta_{C^k(t),2} \nabla_x f(X^k(t), C^k(t)) \right.$$

$$+ \quad \frac{\sigma(C^k(t))^2}{2} \Delta_x f(X^k(t), C^k(t))$$

$$+ \quad \sum_{j \neq C^k(t)} \left[f(X^k(t), j) - f(X^k(t), C^k(t)) \right] m_{C^k(t)j}(X^k(t), C^k(t)) \Bigg) dt$$

$$+ \quad M^k(t),$$

$$M^k(t) \quad = \quad \sigma(C^k(t)) \nabla_x f(X^k, C^k(t)) dW^k(s)$$

$$+ \quad \left[f(X^k, C^k) - \sum_{j \neq C^k} \left[f(X^k, j) - f(X^k, C^k) \right] m_{C^k j}(X^j(t), C^j(t)) \right] dt$$

is a zero mean martingale.

EULERIAN DYNAMICS:

Time evolution of the empirical measure $Q_N(t) = \dfrac{1}{N} \displaystyle\sum_{i=1}^{N(t)} \epsilon_{(X^k(t), v^k(t))}$

For any $B \times S \subseteq \mathcal{B}_{\mathbb{R}^2} \otimes \mathcal{P}(S)$

$$\sum_{c=1}^{3} \int_B f(x, c) Q_N(t)(dx, c) = \sum_{c=1}^{3} \int_B f(x, c) Q_N(0)(dx, c)$$

$$+ \int_0^t \left\{ \int_B \sum_{c=1}^{2} \frac{\sigma_c^2}{2} \Delta_x f(x, c) \, Q_N^{[c]}(s)(dx) \right.$$

$$+ \int_B \beta [\nabla_x g(x) - \nabla_x u(x)] \cdot \nabla_x f(x, 2) \, Q_N^{[2]}(s)(dx)$$

$$+ \sum_{\substack{c=1 \\ j \neq c}}^{2} \int_B (f(x, j) - f(x, c)) \, m_{cj}(x, c) \, Q_N^{[c]}(s)(dx)$$

$$+ \sum_{c=1}^{2} \int_B h(x, c) \, f(x, c) \, Q_N^{[c]}(s)(dx) \bigg\} ds + M_N[Q_N, W](t).$$

EULERIAN DYNAMICS: the martingale term

$$
M_N[Q_N, W](t) = \int_0^t \sum_{c=1}^2 \frac{1}{N} \sum_{k=1}^{N_B(s)} \sigma_c \nabla_x f(X^k(s), c) dW^k(s) \delta_{c, C^k(s)}
$$

$$
+ \int_0^t \frac{1}{N} \sum_{k=1}^{N_B(s)} f(X^k(s), C^k(s)) \left[N_B(ds) - \sum_{c=1}^2 h(X^k(s), c) \delta_{c, C^k(s)}] ds \right]
$$

$$
+ \int_0^t \frac{1}{N} \sum_{k=1}^{N_B(s)} \left\{ f(X^k(s), C^k(s)) \right.
$$

$$
\left. - \sum_{j \neq C^k} [f(X^k(s), j) - f(X^k(s), C^k(s)) \; m_{C^k j}(X^k(t), C^k(t)) \right\} ds.
$$

It is a zero mean martingale with respect to the natural filtration $\{\mathcal{F}_t\}_{t \in \mathbb{R}_+}$ generated by the process $\{(X^k(t), C^k(t)), N(t)\}_{t \in \mathbb{R}_+}$.

The Martingale Term: ASYMPTOTICS

For any $t \in [0, T]$, by Doob's inequality and by the control estimate on $N(t)$, the quadratic variation of the zero mean martingale $M_N[Q_N, W]$ is such that

$$\mathbb{E}\left[\sup_{t \leq T} |M_N[Q_N, W](t)| \big| \mathcal{F}_0\right]^2 \leq 4C\mathbb{E}\left[|M_N[Q_N, W](T)|^2 \big| \mathcal{F}_0\right]$$

$$\leq \frac{4T}{N}\left(\sigma_1^2 \|\nabla_x f\|_\infty^2 + \|f\|_\infty^2 (\lambda + \gamma)\right)\mathbb{E}\left[\frac{\sup_{t \leq T} \langle Q_N(t), 1 \rangle}{N} \bigg| \mathcal{F}_0\right]$$

$$\leq C\frac{T}{N}\mathbb{E}\left[\frac{\sup_{t \leq T} \langle Q_N(t), 1 \rangle}{N} \big| \mathcal{F}_0\right]$$

$$< C\frac{T}{N}. \tag{1}$$

where $C, \lambda, \gamma \in \mathbb{R}_+$ are suitable constants.

The Martingale Term: ASYMPTOTICS

From the above estimate we have

$$\mathbb{E}\left[M_N[Q_N, W](t)\right] = 0,$$

and

$$\mathbb{E}\left[\sup_{t \leq T} |M_N[Q_N, W](t)|\right]^2 \xrightarrow{N \to \infty} 0.$$

Hence, the martingale vanishes in probability, i.e.

$$M_N[Q_N, W](t) \xrightarrow{P} 0.$$

Since in the above evolution equation for Q_N, $M_N[Q_N, W](t)$ is the only source of randomness, this is the substantial reason of the deterministic limiting behavior of the process Q_N, as N increases to infinity.

Asymptotics (heuristic)

Suppose it has been proven that, for $N \to \infty$, the sequence of random measures

$\{Q_N(t), \ N \in \mathbb{N}\}$ converges in probability to a deterministic measure $Q_\infty(t)$, which admits a spatial density,

$$Q_N(t)(B \times A) \longrightarrow Q_\infty(t)(B \times A) = \sum_{s \in A} \int_B p_s(x, t) dx$$

for $B \in \mathcal{B}_{\mathbb{R}}^d$ and $A \subset \mathbb{S}$.

$$\Downarrow$$

$$Q_\infty^{[s]}(t)[dx] = p_s(x, t) dx,$$

where we have denoted by $p_s(x, t)$ the spatial density of the $s-$type cells, for $s = 1, 2, 3$; from the above we may derive the following evolution equations, which offer a continuum deterministic description of angiogenic network at the macroscale.

The limit deterministic system

$$\frac{\partial p_1(x,t)}{\partial t} = (h(x,1) - m_{12} - m_{13})p_1(x,t) + m_{21}p_2(x,t),$$

$$\frac{\partial p_2(x,t)}{\partial t} = \frac{\sigma_2^2}{2}\Delta p_2(x,t) - \alpha_2\nabla\Big[(\nabla\tilde{g}(x,t) - \nabla\tilde{u}(x,t))\,p_2(x,t)\Big]$$

$$(h(x,2) - m_{21} - m_{23})p_2(x,t) + m_{12}p_1(x,t),$$

$$\frac{\partial p_3(x,t)}{\partial t} = m_{13}p_1(x,t) + m_{23}p_2(x,t),$$

coupled with

$$\frac{\partial \tilde{g}(x,t)}{\partial t} = -d_g\tilde{g}(x,t) + D_g\Delta\tilde{g}(x,t) + \alpha_g\,p_2(x,t)$$

$$\frac{\partial \tilde{u}(x,t)}{\partial t} = -d_u\tilde{u}(x,t) + D_u\Delta u(x,t) + \alpha_u\,p_1(x,t)$$

The Hybrid Model

These mean fields now drive, at the microscale, a simply stochastic evolution for the single cells. More specifically, a typical cell k will satisfy the following system of stochastic differential equations, for any $k = 1, \ldots, N(t)$,

$$dX^k(t) = \beta \, [\nabla \tilde{g}(X^k(t), t) - \nabla \tilde{u}(X^k(t), t)]\delta_{C^k(t),2} \, dt + \sigma(C^k(t))dW_t^k dt,$$

subject to a change of state governed by the matrix $M(Y^k(t), C^k(t))$, proliferation rate

$$h\left((Y^k(t), C^k(t))\right) = \lambda_1 \delta_{C^k(t),1} + \lambda_2 \frac{1}{1 + N\left(p_2(\cdot, t) * K\right)(Y^k(t))}\delta_{C^k(t),2},$$
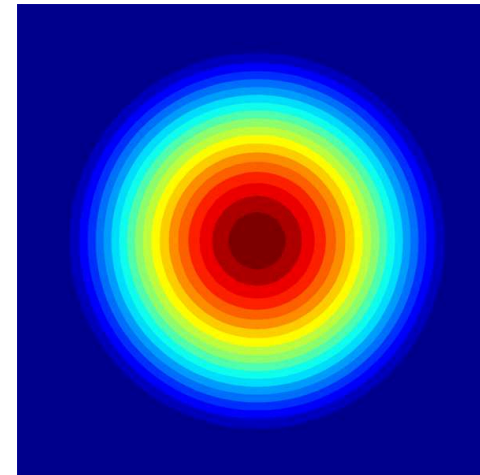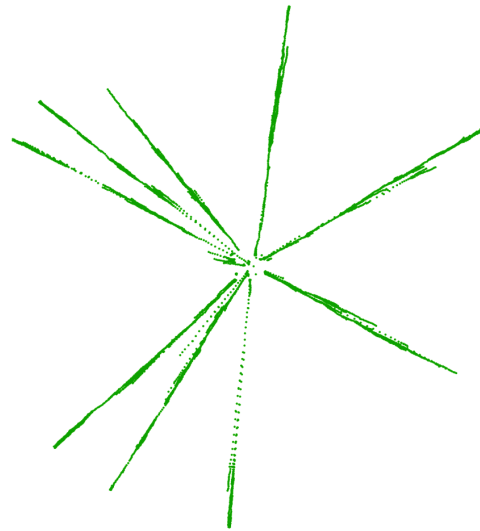
and coupled with the mean fields $p_2(x, t)$, $\tilde{g}(x, t)$, and $\tilde{u}(x, t)$ given above.

This constitutes what we mean by hybrid model.
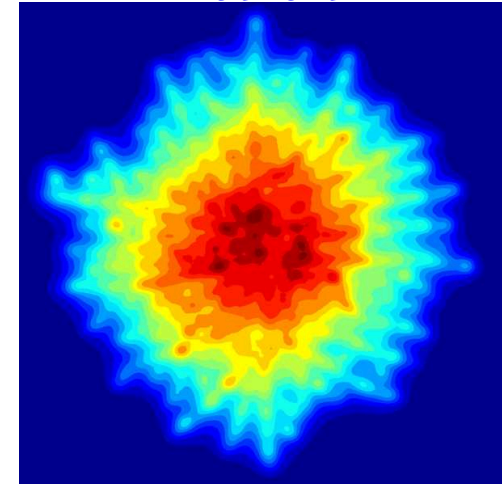
WARNING

If we homogenize ab initio the underlying fields

- we surely obtain reduction of the computing time vs the total stochastic model

- but the network is lost.

In order to obtain the desired network structure, at the start of the process, when a law of large numbers does not apply, we need to follow the purely stochastic system.

Endothelial Cells
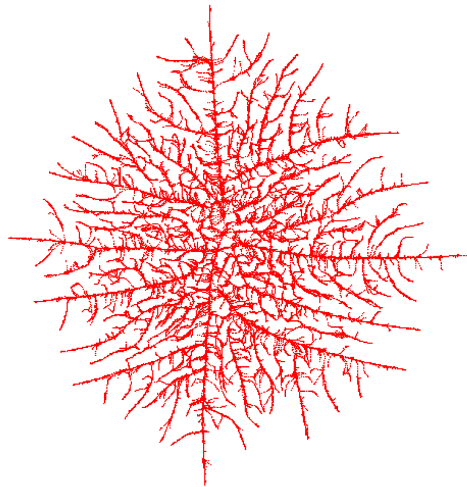
VEGF
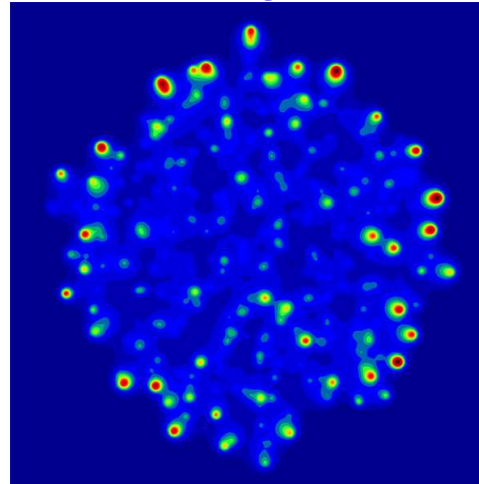
Nutrient

Anyhow, if we are not interested in the geometric structure, the purely deterministic system for densities may offer an interesting qualitative behaviour.

The deterministic system

Endothelial Cells   *VEGF*   *Nutrient*
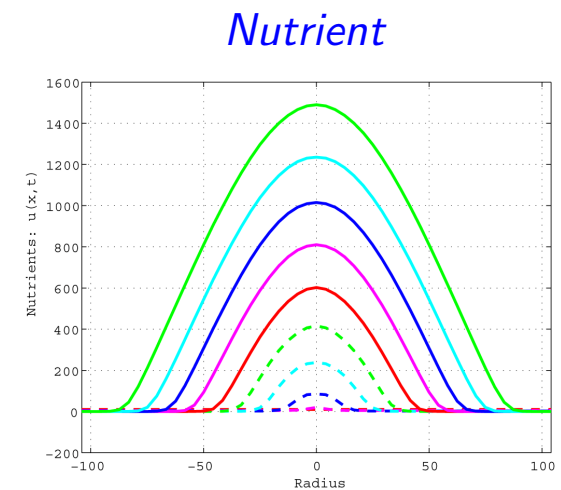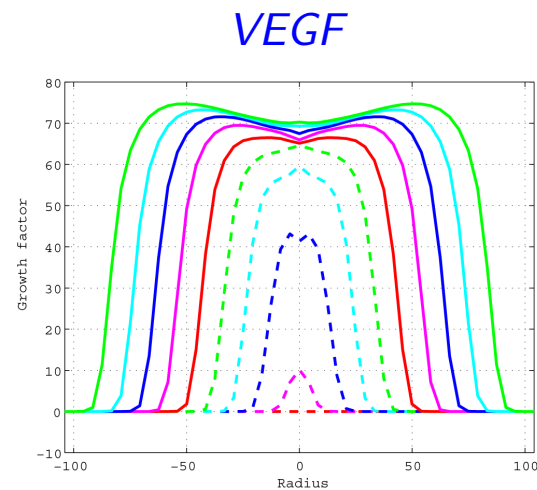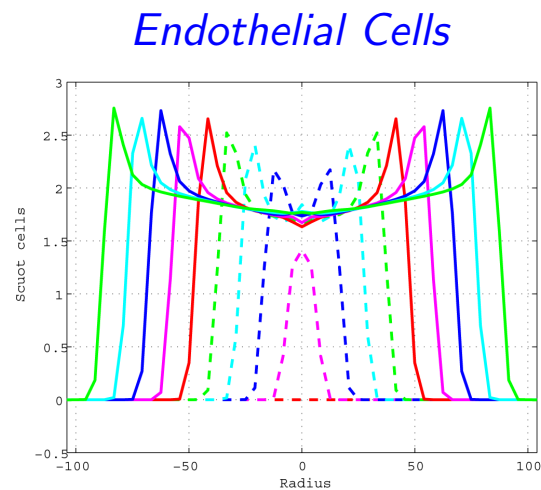
- radial symmetry

- scouts density is higher at the growing front.

- VEGF density is higher at the growing front.

- nutrients are higher where vessels are present.

Various authors, including Wheeler et al (2005) and more recently Travasso et al (2011) have preferred to consider the interaction of the whole vessel network with the underlying fields of the Capillary Growth factors (CGF) and alike.

Again this kind of models can be handled computationally only at low vessel densities. The question which arises in this framework is the following:

- HOW CAN WE OBTAIN AN HYBRID MODEL INCLUDING MEAN FIELD APPROXIMATIONS, FOR LARGE VALUES OF THE VESSEL SPATIAL DENSITIES ?

- HOW IS IT DEFINED A DETERMINISTIC SPATIAL DENSITY OF A STOCHASTIC NETWORK OF VESSELS?
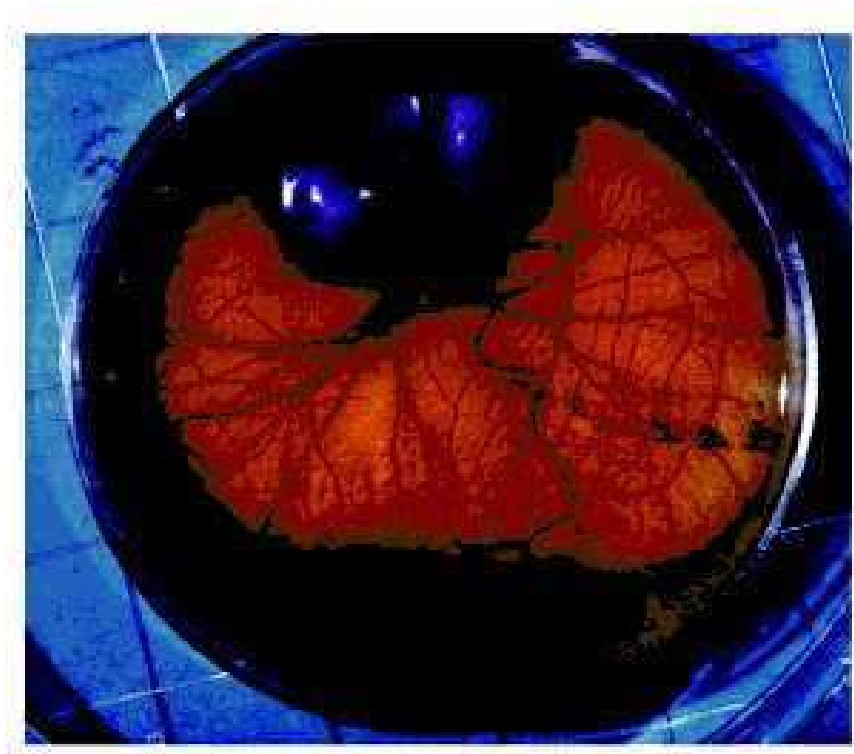
Figure 8: Experimental capillary network [Credit: Auerbach et al 2003]
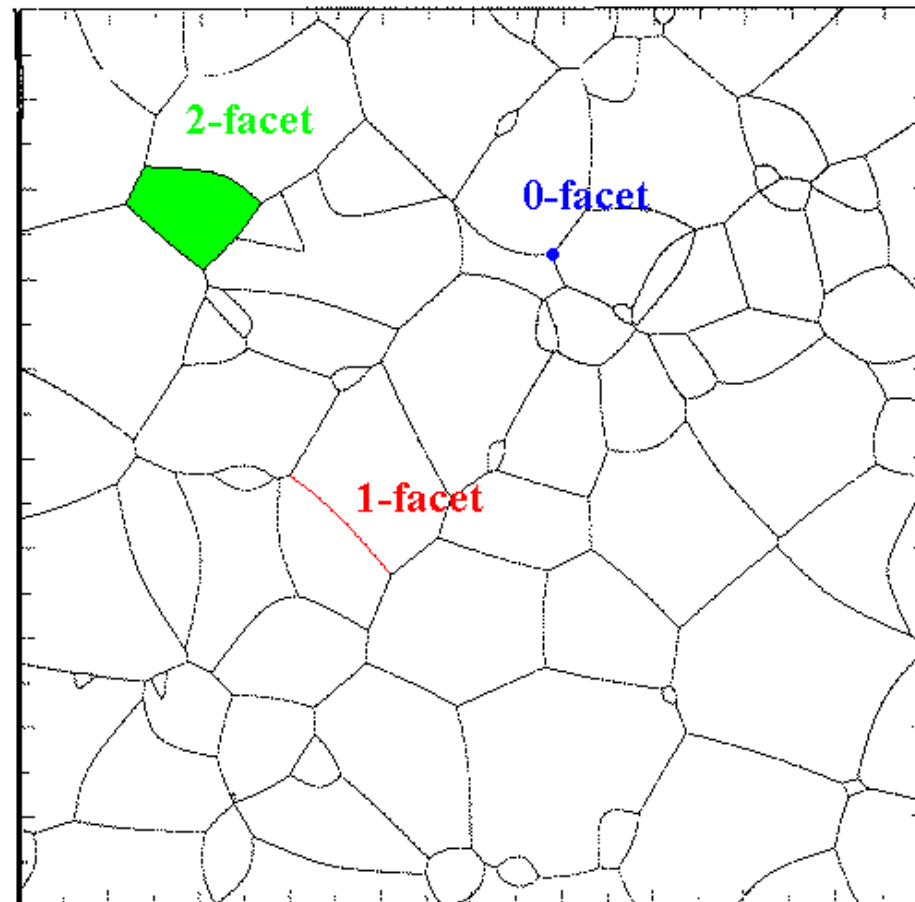
Figure 9: Characteristic features of a stochastic fibre system.

BASIC CONCEPTS OF STOCHASTIC GEOMETRY

A correct mathematical description of these structures requires concepts from stochastic geometry.

Given a probability space $(\Omega, \mathcal{F}, P)$, we introduce the family $\mathbb{F}$ of closed sets in $\mathbb{R}^d$, and a suitable $\sigma-$algebra $\sigma_{\mathbb{F}}$ on it.

A RAndom Closed Set (RACS) Θ is a random object

$$\Theta : (\Omega, \mathcal{F}) \longrightarrow (\mathbb{F}, \sigma_{\mathbb{F}}).$$

Its probabilistic structure is characterized by its hitting functional , defined as

$$T_{\Theta} : K \in \mathcal{K} \longmapsto P(\Theta \cap K \neq \emptyset).$$

Where $\mathcal{K}$ is the family of compact sets in $\mathbb{R}^d$.

CLOSED SETS AS DISTRIBUTIONS
The deterministic case

In the sequel we will refer to a class of sufficiently regular closed sets in the Euclidean space $\mathbb{R}^d$, of integer dimension n. We denote by $B_r(x)$ the ball with center x and radius r.

If θ_n is an n-regular closed set in $\mathbb{R}^d$ with $n < d$, then the measure

$$\mu_{\theta_n}(\cdot) := \mathcal{H}^n(\theta_n \cap \cdot)$$

is a singular measure with respect to ν^d, and so its Radon-Nikodym derivative does not exist as a classical function, but......

In analogy with the usual Dirac delta function $\delta_{x_0}(x)$ associated with a point $x_0 \in \mathbb{R}^d$ (a $0-$regular closed set), we may introduce the following definition.

Definition 1. *Given an n-regular closed set θ_n in $\mathbb{R}^d$, we call* generalized density *(or, briefly,* density*) associated with θ_n, the quantity*

$$\delta_{\theta_n}(x) := \lim_{r \to 0} \frac{\mathcal{H}^n(\theta_n \cap B_r(x))}{b_d r^d},$$

finite or not.

By assuming $0 \cdot \infty = 0$, for $0 \leq n < d$ we have

$$\lim_{r \to 0} \frac{\mathcal{H}^n(\theta_n \cap B_r(x))}{b_d r^d} = \lim_{r \to 0} \frac{\mathcal{H}^n(\theta_n \cap B_r(x))}{b_n r^n} \frac{b_n r^n}{b_d r^d} = \begin{cases} \infty & , \mathcal{H}^n\text{-a.e. } x \in \theta_n, \\ 0 & , \text{elsewhere.} \end{cases}$$

$$(2)$$

In this way $\delta_{\theta_n}(x)$ can be considered as the *generalized density* (or the *generalized Radon-Nikodym derivative*) of the measure μ_{θ_n} with respect to the d-dimensional Lebesgue measure ν^d.

CLOSED SETS AS DISTRIBUTIONS
The stochastic case

If Θ_n is an *n-regular random closed set* in $\mathbb{R}^d$, the measure

$$\mu_{\Theta_n}(\cdot) := \mathcal{H}^n(\Theta_n \cap \cdot)$$

is a random measure, and consequently δ_{Θ_n} is a *random linear functional*

(i.e. (δ_{Θ_n}, f) is a real random variable for any test function f).

By extending the definition of expected value of a random operator à la Pettis (or Gelfand-Pettis, [Araujo- Giné 1980, Bosq 2000]), we may define the *expected linear functional* $\mathbb{E}[\delta_{\Theta_n}]$ associated with δ_{Θ_n} as the unique linear functional for which:

$$(\mathbb{E}[\delta_{\Theta_n}], f) = \mathbb{E}[(\delta_{\Theta_n}, f)] \tag{3}$$

for any $f \in C_c(\mathbb{R}^d, \mathbb{R})$.

Absolute continuity of RACS

Remark 1. *Apart from the case $n = d$, in which $\delta_{\Theta_d}(x) = \mathbf{1}_{\Theta_d}(x)$, ν^d-a.s., it is true that*

$$V_V(x) := \mathbb{E}[\delta_{\Theta_d}](x) = \mathbb{P}(x \in \Theta_d)$$

is a classical function, known in material science as degree of crystallinity,

in general, for any lower dimensional random closed set Θ_n in $\mathbb{R}^d$, the expected measure $\mathbb{E}[\mu_{\Theta_n}]$ it is not absolutely continuous with respect to ν^d, so that it admits a classical Radon-Nikodym density.

But if it happens that the RACS is absolutely continuous, its density

$$\lambda_n(x) := \mathbb{E}[\delta_{\Theta_n}](x)$$

is well defined as a classical function (see [C–Villa,2006], and [Ambrosio–C–Villa,2006].

Going back to the case of a stochastic fibre system, consider the set $\Xi_n(t)$ of all n-facets at time t, for $n < d$

For any Borel set B one can define the *n-facet mean content* of B at time t as the measure

$$\mathcal{M}_{d,n}(t, B) = \mathbb{E}\left[\mathcal{H}^n(B \cap \Xi_n(t))\right],$$

Only when $\mathcal{M}_{d,n}(t, \cdot) \ll \nu_d$, where ν_d is the d-dimensional Lebesgue measure, there exists a density $\mu_{d,n}(x, t)$ such that for all Borel sets B in $\mathbb{R}^d$

$$\mathcal{M}_{d,n}(t, B) = \int_B \mu_{d,n}(x, t)dx. \tag{4}$$

Definition. The function $\mu_{d,n}(x, t)$ is called local mean n-facet density of the fibre system at time t . A characterization of a fibre system at time t is given in terms of the family of densities $\mu_{d,n}(x, t)$ for $n = 0, 1, \ldots, d$.

We may now go back to our case.

With reference to tumour driven angiogenesis,

$\delta_{X^i(t)}(x)$ will denote the random distribution (Dirac density) localized at the tip $X^i(t)$, for $i = 1, \ldots, N(t)$

while

$\delta_{X(t)}(x)$ will represent the random distribution localized at the whole network $X(t)$;

$X^i(t)$ is a random closed set of Hausdorff dimension zero,

$X(t)$ is a random closed set of Hausdorff dimension one.

Whenever the above random sets are absolutely continuous with respect to the usual Lebesgue measure on $\mathbb{R}^d$,

$\mathbb{E}[\delta_{X^i(t)}]$ is the probability density distribution of tips,

while

$\mathbb{E}[\delta_{X(t)}]$ is the mean vessel density .

We may now revisit our first model for tumour driven angiogenesis. Having introduced the above concepts, a model involving the interaction of the whole vessel network $X(t)$ with the spatial distribution $C(t, x)$ of the VGEF would be of the following form

$$\frac{\partial}{\partial t}C(t, x) = \kappa\delta_A(x) + d_1\triangle C(t, x) - \eta C(t, x)\frac{1}{N}(\delta_{X(t)} * K_N)(x);$$

Let us denote by $\lambda(x, t) = \mathbb{E}[\delta_{X(t)}(x)]$.

If we had adopted such a model, we would have obtained for the underlying field in the corresponding hybrid model

$$\frac{\partial}{\partial t}\widetilde{C}(x, t) \quad = \quad d_1\triangle\widetilde{C}(x, t) - \eta\widetilde{C}(x, t)\lambda(x, t), \tag{5}$$

in $E \times \mathbb{R}^+$, $d = 1, 2, 3$ (supplemented by suitable boundary and initial conditions) coupled with the relevant stochastic process of geometric patterning of the vessel network.

The open problem then is to obtain an evolution equation for the mean vessel density $\lambda(x, t)$, as the asymptotics of the stochastic vessel network, by suitable laws of large numbers as in the pointwise particle systems, and this is still an open problem.

... WORK IN PROGRESS

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T H A N K S