Milan mathematical biology papers

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Agenda

1. Paper 1: Tumour-induced angiogenesis
   - Modelling problem
   - Modelling approach
2. Paper 2: Modelling population aggregation behavior
   - Modelling problem
   - Modelling approaches

Vincenco Capasso, Daniela Morale

"Stochastic modelling of tumour-induced angiogenesis."

"The mathematical modelling of an angiogenic process derives from the strong coupling of the kinetic parameters of the relevant stochastic branching-and-growth of the capillary network with a family of interacting underlying fields. The aim of this paper is to propose a novel mathematical approach for reducing complexity by (locally) averaging the stochastic cell, or vessel densities in the evolution equations of the underlying fields, at the mesoscale, while keeping stochasticity at lower scales, possibly at the level of individual cells or vessels. (...) The branching mechanism of blood vessels is modelled as a stochastic marked counting process describing the branching of new tips, while the network of vessels is modelled as the union of the trajectories developed by tips, according to a system of stochastic differential equations á la Langevin."

"The normal, healthy body maintains a perfect balance of angiogenesis modulators. In many serious diseases states, the body looses control over angiogenesis. Angiogenesis-dependent diseases result when new blood vessels either grow excessively or insufficiently. Nowadays angiogenesis is very widespread studied in relation with the growth of tumours."

Network dynamics:

- vessel branching;
- vessel extension;
- chemotaxis in response to a generic tumour angiogenetic factor (TAF), released by tumour cells;
- haptotatic migration in response to fibronectin gradient, emerging from the extracellular matrix and through degradation and production by endothelial cells themselves;
- anastomosis, when a capillary tip meets an existing vessel.

Let N_0 denote the initial number of tips, $N(t)$ the number of tips at time t, and $X^i(t)$ the location of the i-th tip at time t. We model sprout extension by tracking the trajectory of each individual capillary tips. As a consequence

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

will be the network of endothelial cells, i.e. the union of trajectories of the tips, where T_i is the birth time of the i-th tip and

$$Y(t) = \bigcup_{i=1}^{N(t)} \{X^i(s),\ \tilde{t}_1 \leq t - s \leq \tilde{t}_2\}$$

is the union of the mature parts of vessels that may branch at time t.

Given a TAF's concentration $C(t,x)$

- tip branching occurs with rate per unit of volume:

$$\alpha_1(t,x) = \alpha_1\beta_1(C(t,x))\sum_{i=1}^{N(t)}\delta_{X^i(t)}(x)$$

- vessel branching occurs with rate per unit of volume:

$$\alpha_2(t,x) = \alpha_2\beta_2(C(t,x))\delta_{Y(t)}(x)$$

- probability of having a new tip:

$$P = \left(\sum_{i=1}^{N(t)}\alpha_1(t,X^i(t)) + \int_{\mathbb{R}^d}\alpha_2(x,t)dx\right)dt =: \alpha_N(t)dt$$

As far as vessel movement (extension) is concerned, we consider a Langevin model:

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

where $v^i(t)$ is the velocity of the i-th tip at time t. The drift function $a(x, v, t)$ is a function of the concentration $C(t, x)$ of TAF.

Chemotatic field:

$$\frac{\partial}{\partial t}C(t,x) = c_1\delta_A(x) + d_1\Delta C(t,x) - \eta C(t,x)\frac{1}{N}\sum_{i=1}^{N(t)}(v^i(t)\delta_{X^{i(t)}} * V_\epsilon)(x)$$

Haptotatic field:

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

The chemotatic and haptotatic fields depend upon the stochastic geometric process $X(t)$ of the vessel network. A direct consequence is the stochasticity of the underlying fields, and consequently the stochasticity of the kinetic parameters of birth and growth of vessels.

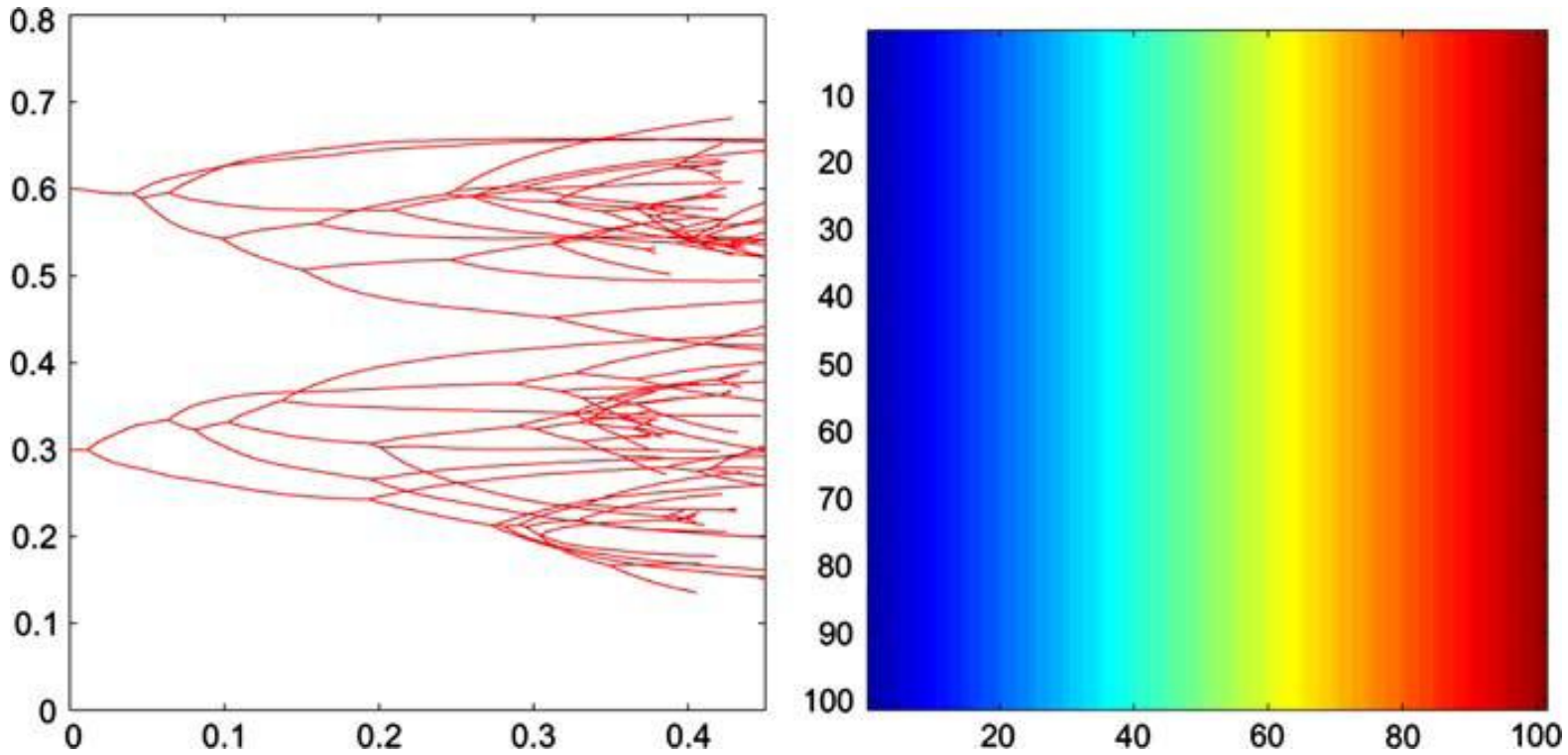

Figure: A vessel network (on the left) driven by a constant in time TAF field (on the right).

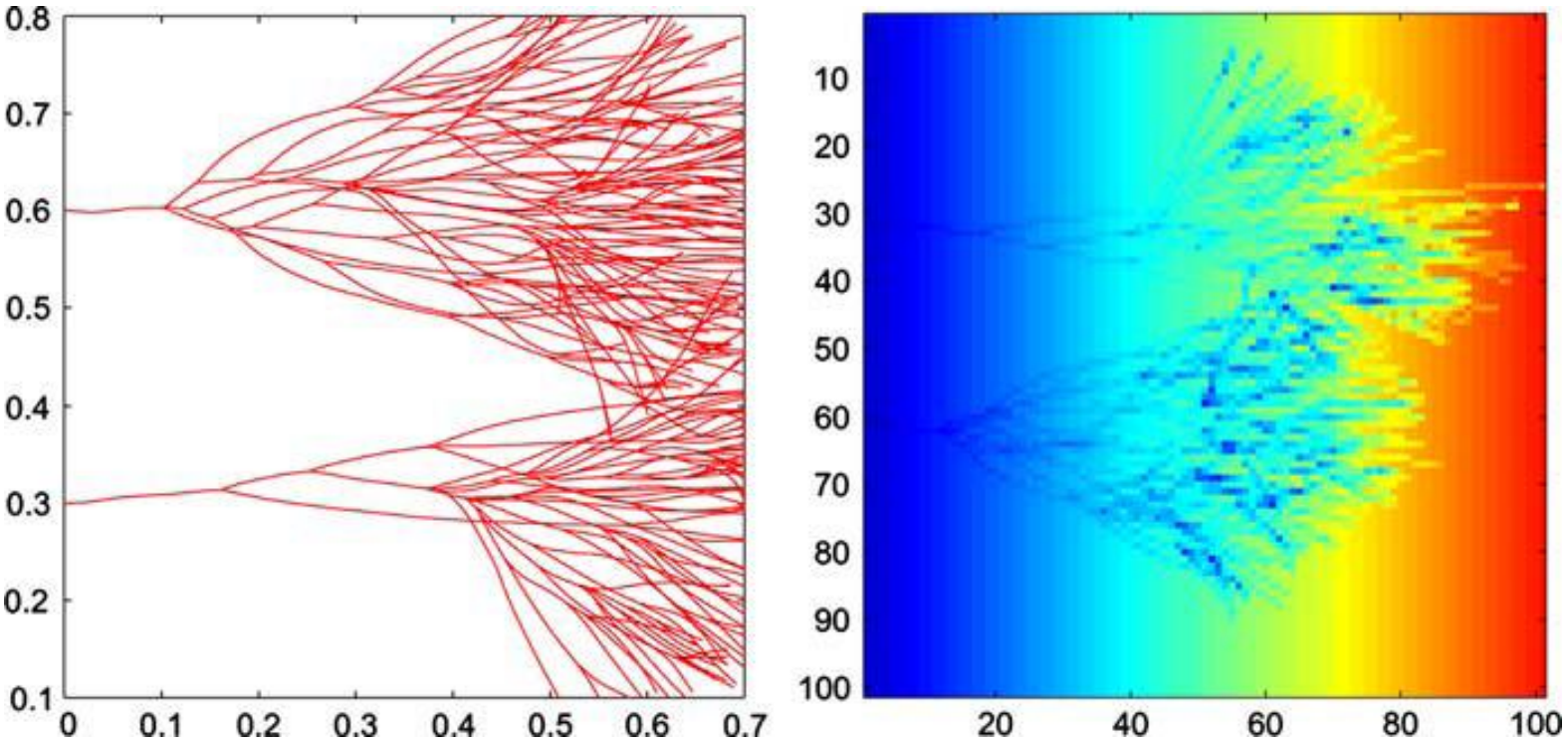

Figure: A vessel network (on the left) interacting with a degrading TAF field (on the right).

Daniela Morale, Vincenco Capasso, Karl Oelschlager

"An interacting particle system modelling aggregation behavior: from individuals to populations."

Modelling problem

"Complexity of the biological clustering raises very interesting mathematical problems. Aggregation patterns are usually explained in terms of forces, external and/or internal, acting upon individuals. A remarkable aspect of these global organization is that individuals move altogether in a coordinated (though random) fashion. (...) The aim of the modelling is to catch the main features of the interaction at the lower scale of single individuals that are responsible, at a larger scale, for a more complex behavior that leads to the formation of aggregating patterns."

Eulerian approach

Eulerian models are based on continuum equations, typically (deterministic) nonlinear partial differential equations of the advection-reaction-diffusion type:

$$\rho_t + \nabla \cdot (\mathbf{v}\rho) = \nabla \cdot (D\nabla\rho) + \nu(\rho)$$

where ρ is the population density, $\mathbf{v}$ is the velocity field and $\nu(\rho)$ is a possible additive reaction term which may include birth and death processes.

Lagrangian approach

In *Lagrangian approach* individuals are followed in their motion. Variation in time of the (random) location of the k-th individual in the group at time $t \geq 0$, $X_N^k(t) \in \mathbb{R}^d$, $k = 1, \ldots, N$ is described by a system of stochastic differential equations:

$$dX_N^k(t) = F_N[X_N(t)]\left(X_N^k(t)\right) dt + \sigma_N dW^k(t), \qquad k = 1, \ldots, N,$$

where each particle moves randomly with a mean free path σ_N. F_N is drift term with two additive components responsible for aggregation and repulsion.

The interaction among particles is mathematically modelled by an interaction kernel depending on the distance between two particles. The main three types of interactions are:

- *McKean-Vlasov interaction* (macroscale)
- *hydrodynamic interaction* (microscale)
- *moderate interaction* (mesoscale)

The three types of interaction may be obtained in terms of an appropriate rescaling of a given reference function V_1. Let V_1 be a sufficiently regular probability density; and assume that the interaction of two particles out of N, located in x and y respectively is modelled by

$$\frac{1}{N} V_N(x - y)$$

where

$$V_N(z) = N^{\beta} V_1(N^{\beta/d} z),$$

which expresses the rescaling of V_1 with respect to the total number N of particles in terms of a scaling coefficient $\beta \in [0, 1]$.

The force exerted on the k-th (out of N) single particle located at $X_N^k(t)$ due to the interaction of the single k-particle with all the others in the population is given by

$$I^k \equiv I^k(X_N^1(t), \ldots, X_N^N(t)) = \sum_{i=1}^{N} \frac{1}{N} V_N \left(X_N^k(t) - X_N^i(t)\right)$$
$$= \sum_{i=1}^{N} N^{\beta-1} V_1 \left(N^{\beta/d} \left(X_N^k(t) - X_N^i(t)\right)\right)$$

where we obtain a McKean-Vlasov interaction for $\beta = 0$, a hydrodynamic interaction for $\beta = 1$, and a moderate interaction for $\beta \in (0, 1)$.

Comparison of approaches

- *Eulerian models:*
  Identity of individuals is compromised.
  Some important features of the dynamics may be hidden.
- *Lagrangian models:*
  Stochastic Lagrangian models offer the advantage of being directly related to experimental data on the behavior of individuals of a real population, especially when dealing with a relatively "small" number of individuals per unit space (Poisson like spatial processes).

Dziękuję za uwagę