Introduction to some topics in Mathematical Oncology

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Stochastic Analysis and applications in Biology, Finance and Physics, Berlin 2014
The field received considerable attentions in the past 10 years

One of the plenary talks at ICM 2014 was on this subject (B. Perthame)

Some people believe it could be a revolution in the next 10 years if properly developed (see Forbes)

For people interested in stochastic systems it is an opportunity to touch an applied field of basic importance for society where stochasticity plays a role

The following discussion is the outcome of an initial investigation with Michele Coghi, Mauro Maurelli, Manuela Benedetti and other young collaborators.
Most common models

1. Macroscopic models (tissue level)
2. Microscopic models (cell level)
3. Mixed or multi-scale models.

Remarks.

- Usually, in Physics, microscopic means molecular. Cell scale is in a sense a meso-scale, but I will call it microscopic.
- Cell motion is stochastic to a large extent.
Objects studied by the models

1. Macroscopic models: density of cells, oxygen concentration etc.
2. Microscopic models: single cells
3. Multi-scale models: single cells and oxygen concentration, etc.
Equations

1. Macroscopic models: Fokker-Planck equations with nonlinear reaction terms
2. Microscopic models: interacting particle systems (based on SDE or discrete models)
3. Mixed or multi-scale models: both
Example of Macroscopic model


Among several other models I have chosen this one due to three facts:

- it is a very good paper
- the team is a leading one in quantitative oncology (e.g. Kristine Swanson)
- it does not require deep biological training.

This model is made of 7 coupled PDE-ODE. I will spend some time on it in order to explain the level of complexity and realism that is usually reached in such papers.
Normoxic, hypoxic and apoptotic cells

- **normoxic** cells: healthy, proliferating tumor cells, with *normal oxygen* supply
- **hypoxic** cells: quiescent tumor cells, with *poor oxygen* supply
- **apoptotic** cells: death or *programmed to death* tumor cells
The PDE for normoxic cells

\[ \frac{\partial N}{\partial t} = k_1 \Delta N \]  
background diffusion

\[ \text{div} (\sigma (N) \nabla N) \]  
crowding-driven diffusion

\[ + c_1 N (V_{\text{max}} - V) \]  
proliferation

\[ - \chi_1 \text{div} (N \nabla m) \]  
transport along ECM gradient

\[ - \alpha_{N \rightarrow H} 1_{O \leq o_H} N + \alpha_{H \rightarrow N} 1_{O \geq o_H} H \]  
normoxic \rightarrow hypoxic hypoxic \rightarrow normoxic

I will come back later to the diffusion and crowding-driven diffusion.

\[ V = N + H + A + E + m = \text{total volume occupied by cells and ECM} \]
ODEs for hypoxic and apoptotic cells and for ECM

\[
\frac{d\mathcal{H}}{dt} = \alpha_{N \rightarrow H} 1_{0 \leq o_{H} \mathcal{N}} - \alpha_{H \rightarrow N} 1_{o \geq o_{H} \mathcal{H}} \\
\quad \text{normoxic \rightarrow hypoxic \quad hypoxic \rightarrow normoxic}
\]

\[
\quad - \alpha_{H \rightarrow \mathcal{A}} 1_{o \leq o_{\mathcal{A}}} \mathcal{H} \\
\quad \text{hypoxic \rightarrow apoptotic}
\]

\[
\frac{d\mathcal{A}}{dt} = \alpha_{H \rightarrow \mathcal{A}} 1_{o \leq o_{\mathcal{A}}} \mathcal{H} \\
\quad \text{hypoxic \rightarrow apoptotic}
\]

\[
\frac{dm}{dt} = - \beta m \mathcal{N} \\
\quad \text{degradation by normoxic cells}
\]

\( \mathcal{H} (t, x) = \text{hypoxic cell density} \)

\( \mathcal{A} (t, x) = \text{apoptotic cell density} \)

\( m (t, x) = \text{ExtraCellular Matrix} \)
The endothelial cascade

- hypoxic cells: need more oxygen to survive. They initiate a cascade of cellular interactions. The result is angiogenesis: new vascularization to supply the tumor (microvessels branching from main vessels in the direction of the tumor).
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- **Messenger from hypoxic cells to endothelial cells**: VEGF (Vascular Endothelial Growth Factor)
PDEs for the endothelial cascade

\[
\frac{\partial g}{\partial t} = k_4 \Delta g + \alpha_{H\rightarrow g} H - \alpha_{g\rightarrow E} E
\]

\[\text{diffusion} \quad \text{production by hypoxic cells} \quad \text{uptake by endothelial cells}\]

\[
\frac{\partial E}{\partial t} = k_2 \Delta E - \chi_2 \text{div} (E \nabla g) + c_2 E (V_{\text{max}} - V)
\]

\[\text{diffusion} \quad \text{transport along VEGF gradient} \quad \text{proliferation under VEGF presence}\]
PDEs for oxygen concentration

$$\frac{\partial o}{\partial t} = k_3 \Delta o \quad (o(t,x) = \text{oxygen concentration})$$

$$+ c_3 \mathcal{E} (o_{\text{max}} - o) \quad - \alpha_{o \rightarrow N,H,E} (N + H + E) o \quad - \gamma o$$

- diffusion
- production by endothelial cells
- uptake by all living cells
- oxygen decay
Summary of variables

\( \mathcal{N}(t, x) \) = density of normoxic cells
\( \mathcal{H}(t, x) \) = density of hypoxic cells
\( \mathcal{A}(t, x) \) = density of apoptotic cells
\( \mathcal{E}(t, x) \) = density of endothelial cells (or density of vasculature)
\( o(t, x) \) = oxygen concentration
\( g(t, x) \) = angiogenic growth factor (VEGF) concentration
\( m(t, x) \) = ECM (ExtraCellular Matrix)
$k_1 = \text{background random motility coefficient of normoxic cells}$

$k_2 = \text{random motility coefficient of endothelial cells}$

$k_3 = \text{diffusion coefficient of oxygen}$

$k_4 = \text{diffusion coefficient of angiogenic factor}$

$\chi_1 = \text{transport coefficient of normoxic cells along ECM gradient}$

$\chi_2 = \text{transport coefficient of endothelial cells along VEGF gradient}$

$V_{cr} = \text{threshold for crowding-driven diffusion}$

$V_{\text{max}} = \text{limit to total volume of cells and ECM}$

$c_1 = \text{proliferation rate of normoxic cells}$

$c_2 = \text{proliferation rate of endothelial cells}$

$c_3 = \text{production rate of oxygen}$
\( \alpha_{N \rightarrow H} \) = decay rate from normoxic to hypoxic cells
\( \alpha_{H \rightarrow N} \) = restoration rate from hypoxic to normoxic cells
\( \alpha_{H \rightarrow A} \) = decay rate from hypoxic to apoptotic cells
\( \alpha_{H \rightarrow g} \) = production rate of VEGF from hypoxic cells
\( \alpha_{O \rightarrow N, H, E} \) = uptake rate of oxygen from all living cells
\( \alpha_{g \rightarrow E} \) = uptake rate of VEGF from endothelial cells
\( o_{\text{max}} \) = maximum oxygen concentration
\( o_{H} \) = oxygen threshold for transition normoxic \( \leftrightarrow \) hypoxic
\( o_{A} \) = oxygen threshold for transition hypoxic \( \leftrightarrow \) apoptotic
\( \beta \) = rate of ECM degradation
\( \gamma \) = oxygen decay rate
Blue: density of normoxic cells; light blue (green): extracellular matrix
Dotted black: density of hypoxic cells; red: density of endothelial ramification.
"Although this does not give any new insight into the dynamics of tumor invasion it nevertheless gives us a reference with which we can compare the different treatment strategies we apply."

- Cytostatic drugs inhibit cell division or some other function of tumor or host cells (e.g. angiogenesis).
- Cytotoxic drugs actively kill proliferating tumor (and healthy) cells.
  - Drugs that specifically target proliferation of the endothelial cells could be more efficient than agents which reduce chemotaxis.
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  - Drugs that specifically target proliferation of the endothelial cells could be more efficient than agents which reduce chemotaxis.
  - Under very weak supply of cytotoxic therapy the tumor could even increase (only the boundary of normoxic cells is destroyed so more hypoxic cells became again normoxic).
Other macroscopic models

There are a lot of models, for specific tumors, for specific phenomena. Among the differences, let us only emphasize the variety of diffusion terms:

\[ \text{div} \left( A(x) \nabla C \right) \quad \text{diffusion of cells } C \text{ in a realistic medium (Fick)} \]
\[ \sum \partial_i \partial_j (A_{ij}(x) C) \quad \text{Fokker-Planck instead of Fick} \]
\[ \text{div} \left( \max ((C - C_{\text{min}}) \wedge 0) \nabla C \right) \quad \text{crowding-driven diffusion} \]
\[ \text{div} \left( (V_{\text{max}} - V) \nabla C \right) \quad \text{diffusion limited by volume constraint} \]

- A problem around which we concentrate at present our attention is a careful discussion of the diffusion terms and their microscopic (stochastic) justification.
Example of realistic medium, complex geometry
By microscopic models we mean models at the cell level. They are always stochastic. They can be discrete or continuous:

- exclusion models, Potts models, etc.
- stochastic differential equations (SDEs) for a single typical cell or for interacting cells

Let me discuss the second possibility, just because of my personal background.
A first natural strategy (it was our first idea) to build a microscopic model based on SDEs, is to apply the well known relation between Fokker-Planck equations and SDEs: the solution $p(t, \cdot)$ of the PDE

$$\frac{\partial p}{\partial t} = \frac{1}{2} \sum \partial_i \partial_j (a_{ij} p) - \chi \text{div}(p \nabla g), \quad p|_{t=0} = p_0$$

is the law of the solution $X_t$ of the SDE

$$dX_t = \nabla g(t, X_t) \, dt + \sigma(t, X_t) \, dW_t, \quad a = \sigma \sigma^T$$

if $p_0$ is the density of the law of $X_0$. Reaction terms (proliferation, death, change of type) can be described by birth-death-like processes added to this SDE.
The SDE associated to the PDE

This viewpoint, of building (mathematically) the SDE associated to the PDE may be useful for numerical purposes and may throw some initial light into the microscopic phenomena. However, it is basically an artificial exercise.

It nevertheless arises interesting questions. Let me mention one. Most papers assume Fick structure of the diffusion term:

$$\text{div} \left( a(t, x) \nabla u \right) \quad \text{(Fick type).}$$

This is not the term we have in a Fokker-Planck equation:

$$\sum \partial_i \partial_j \left( a_{ij}(t, x) u \right) \quad \text{(Fokker-Planck type).}$$

Which one is correct?
A better approach is to investigate directly the microscopic system and build a model (discrete or continuous). Let us discuss only normoxic cells. Normoxic cells are free to move (opposite to normal cells which are bounded by adhesion constraints; hypoxic cells do not move)

1. The motion of a normoxic cell has a random component (it is attracted at random in all possible directions by chemical impulses, like an animal who look at random for food).

2. It has also a systematic component in the direction of chemical or nutrient gradients (like ECM).

3. (This point is specific of the model above) it has an additional diffusivity due to crowding: it tends to escape more crowded regions (crowding is also caused by proliferation).
Non-interacting particles

If we take into account only 1 and 2 (random component and nutrient gradients) we model the position of cell $i$ by the SDE

$$dX_t^i = \sqrt{2k_1}dW_t^i + \chi_1 \nabla m(t, X_t^i)\, dt$$

which corresponds to the PDE ($N(t, x) =$ density of normoxic cells)

$$\frac{\partial N}{\partial t} = k_1 \Delta N - \chi_1 \text{div} (N \nabla m)$$
Fisher-Kolmogorov model (with transport)

If we add proliferation, in the sense that we have $N(t)$ particles $X_t^1, \ldots, X_t^{N(t)}$, where $N(t)$ is a non-homogeneous Poisson process with rate $c_1(N_{\text{max}} - N(t))$, subject to the equations

$$dX_t^i = \chi_1 \nabla m(t, X_t^i) \, dt + \sqrt{2k_1} \, dW_t^i$$

and with a suitable rule for the initial position of the new particles, in a suitable limit as $N_{\text{max}} \to \infty$ the empirical density

$$\frac{1}{N_{\text{max}}} \sum_{i=1}^{N(t)} \delta_{X_t^i}$$

converges (in the weak topology of measures) to the solution of the equation

$$\frac{\partial N}{\partial t} = k_1 \Delta N + c_1 N (N_{\text{max}} - N) - \chi_1 \text{div} (N \nabla m).$$

This is already an interesting model with a traveling wave structure of solutions (similar to the simulations above).
Let us try to model also the interactions between particles. A cell may react to messages arriving from other cells, of two classes:

- short range (namely from cells composing the same tissue or very close tissues; e.g. VEGF)
- long range (namely from cells belonging to other parts of the body; e.g. hormones).

Moreover, it reacts to contact inputs:

- adhesion (but we exclude it for normoxic cells)
- exclusion (two cells cannot occupy the same space).

The crowding-driven diffusion is an enhanced form of exclusion, a tendency to go apart other cells in order not to compete with them for oxygen and other nutrients.
Modelling the crowding-driven diffusion

The purpose of this last part of the talk is more specialized: how to model, at the level of interacting particles, the crowding-driven diffusion?

Let us repeat its features: it includes the exclusion constraint but also with some tendency to go apart from very nearest neighbor cells.

Let us introduce two convolution kernels:

\[ k_\epsilon (x) = (2\pi)^{-d/2} \epsilon^{-d/2} \exp \left( -\frac{1}{2\epsilon} |x|^2 \right) \] (heat kernel)

\[ K_\epsilon (x) = -\nabla k_\epsilon (x) = \frac{x}{\epsilon} k_\epsilon (x), \quad K_\epsilon : \mathbb{R}^d \to \mathbb{R}^d. \]
Modelling the crowding-driven diffusion

The first kernel,

$$k_\epsilon (x) = (2\pi)^{-d/2} \epsilon^{-d/2} \exp \left( -\frac{1}{2\epsilon} |x|^2 \right)$$

when applied to the position of particles,

$$\sum_{j \neq i} k_\epsilon \left( X^i_t - X^j_t \right)$$

measures the number of particles $X^j_t$ very close to $X^i_t$. 
Recall

\[ K_\varepsilon(x) = -\nabla k_\varepsilon(x) = \frac{x}{\varepsilon} k_\varepsilon(x), \quad K_\varepsilon : \mathbb{R}^d \rightarrow \mathbb{R}^d. \]

The second kernel, when applied to the position of particles,

\[ \sum_{j \neq i} K_\varepsilon \left( X^i_t - X^j_t \right) = \sum_{j \neq i} k_\varepsilon \left( X^i_t - X^j_t \right) \frac{X^i_t - X^j_t}{\varepsilon} \]

gives us a force acting on \( X^i_t \) in the direction opposite to \( X^j_t \), but only when \( X^j_t \) is very close to \( X^i_t \). It is a form of crowding-driven force.
The limit kernels

We have

$$
\lim_{\epsilon \to 0} \int k_\epsilon (x - y) \mathcal{N} (t, y) \, dy = \mathcal{N} (t, x)
$$

$$
\lim_{\epsilon \to 0} \int K_\epsilon (x - y) \mathcal{N} (t, y) \, dy = -\nabla \mathcal{N} (t, x)
$$

if $\mathcal{N} (t, x)$ is of class $C^1$. This means: if we replace the empirical density

$$
\frac{1}{N_{\text{max}}} \sum_{i=1}^{N(t)} \delta_{X_t^i}
$$

by a continuum density, the first kernel acts (in the limit as $\epsilon \to 0$) as pointwise evaluation, the second one as a derivative.

Again we see the interpretation of the second kernel:

$$
\frac{1}{N_{\text{max}}} \sum_{j \neq i} K_\epsilon (X_t^i - X_t^j) \sim -\nabla \mathcal{N} (t, X_t^i)
$$

(large $N_{\text{max}}$, small $\epsilon$). It gives us a force in the direction of decreasing concentration of cells.
Interacting cells with crowding-driven motility. Mean field limit

\[ dX_t^i = \sqrt{2k_1} dW_t^i + \chi_1 \nabla m(t, X_t^i) \, dt + \frac{1}{N_{\text{max}}} \sum_{j \neq i} K_\epsilon \left( X_t^i - X_t^j \right) \, dt \]

The natural conjecture (we still have to prove it) is that, in a suitable limit when \( \epsilon \to 0 \) and \( N_{\text{max}} \to \infty \), each particle is subject to the nonlinear SDE (of McKean type)

\[ dX_t = \sqrt{2k_1} dW_t + \chi_1 \nabla m(t, X_t) \, dt - \nabla \mathcal{N}(t, X_t) \, dt \]

where \( \mathcal{N}(t, x) \) is the law of \( X_t \) itself. Hence

\[ \frac{\partial \mathcal{N}}{\partial t} = k_1 \Delta \mathcal{N} - \chi_1 \text{div}(\mathcal{N} \nabla m) + \text{div}(\mathcal{N} \nabla \mathcal{N}) \]
Different nonlinear diffusion terms

We have found the nonlinear diffusion term

\[
\text{div}(\mathcal{N} \nabla \mathcal{N}).
\]

The model at the beginning prescribed

\[
\text{div}(\max((\mathcal{N} - \mathcal{N}_{\text{min}}) \land 0) \nabla \mathcal{N})
\]

which is similar. Even if not equal, it is of Fick type! Which one is more correct is not clear but I tend to vote for \(\max((\mathcal{N} - \mathcal{N}_{\text{min}}) \land 0)\). If so, we have found a microscopic interacting model which is very similar to the expected one but not exactly. We are working to find microscopic models which are more flexible, to produce

\[
\text{div}(g(\mathcal{N}) \nabla \mathcal{N})
\]

for suitable functions \(g\).

Remark. It is known that hydrodynamic limits of discrete exclusion-type models also give rise to such Fick terms but perhaps not so flexible again.
Concluding remarks and open questions

- This is not like fluid mechanics, or electromagnetism etc. where the governing equations are known.
- The models illustrated above are just examples, among several others based on different elements.
- What makes a mathematical model potentially better than classical approach to medicine?
  - the possibility to change the parameters and study the differences in outcomes of computer simulations

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- Gompertz law is a more classical example of qualitative law described in all books of clinical oncology.
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  - in particular, to compare the efficacy of different anti-cancer treatment protocols (control theory)
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  - Each model contains several constants which are poorly known.
  - The "geometry" where the equations take place is very complex.
  - Genetic mutations play a fundamental role and are unpredictable.

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Thank you for your attention