Birth-and-death evolutions in random environments

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Setting

What is modelled?

1. Tumour evolution and related quantities such as
   - Volume/size of tumour
   - Growth of tumour patters, speed of growth, shape of growth
   - Mutations, heterogenity and homogenity
2. Interplay between the tumour and
   - Immune system
   - Healthy cells
   - Environmental factors
3. And many other ...

Models should be as simple as possible, but as detailed as necessary.
Simplification: Tumour can be described on different scales

$$\textbf{microscopic} < \textbf{mesoscopic} < \textbf{macroscopic}$$

Setting

How do we model?

1. Ordinary differential equations (also systems of ODEs)
   - Mesoscopic or macroscopic desription.
   - Describe specific quantities of the tumour in certain regimes.
   - Comparably easy for the analysis and simulations $\rightarrow$ compare with data.
   - In many cases deterministic.

   - No spatial structure.
   - How to justify such equations?

   What are the right equations?

2. Stochastic models
   - microscopic description of cells, mutations, interactions
   - Describe collection of cells as a stochastic process.
   - Analysis and simulations are more challenging $\rightarrow$ how to compare with experimental data?
   - Include a spatial structure.

   What are the right models?

Setting

What are we interested in?

1. Description of microscopic tumours by spatial birth-and-death models.
2. Reducing complexity
   - What are the main building blocks?
   - Derivation of effective equations from these models
     $\rightarrow$ spatial analogues of ODEs
   - What is the effect of: immune system, other cells, environmental factors?
3. Time evolution of (spatial) correlations
4. Invariant states, equilibrium states

What is not done: Comparison with data

Going beyond

What could/should, in principle, be done

1. Cells with additional marks (mutations, fitness, ...)
2. Motion of cells (migration, metastasis, go-or-growth, ...)
3. Non-Markov dynamics (equations with delay, fractional derivatives in time, ...)
4. Time-inhomogeneous models (time-dependent parameters due to therapy)

System of Tumour cells

We suppose that

- Tumour cells are indistinguishable (among one type)
- Sufficiently many cells, i.e. statistical description is adequate.
- Each cell has position and maybe other traits.
  It can be represented as an element $x \in \mathbb{R}^d$.

The collection of all cells forms a microscopic state

$$\gamma = \{x_n \in \mathbb{R}^d \mid n \geq 1\}.$$

System may be:

- finite, i.e. $|\gamma| < \infty$.
- infinite, i.e. $|\gamma \cap K| < \infty$ for all balls $K \subset \mathbb{R}^d$.

$$\Gamma^S = \{\gamma \subset \mathbb{R}^d \mid |\gamma \cap K| < \infty \text{ for all balls } K \subset \mathbb{R}^d\}.$$

We mainly focus on the infinite case.

Environment

Environment is another particle system with microscopic state

$$\omega = \{y_n \in \mathbb{R}^d \mid n \geq 1\}.$$

Configuration space

$$\Gamma^E = \{\omega \subset \mathbb{R}^d \mid |\omega \cap K| < \infty \text{ for all balls } K \subset \mathbb{R}^d\}.$$

Environment could be

- Fixed configuration $\omega \in \Gamma^E$.
- An equilibrium process on Γ^E with some invariant measure.
- Non-equilibrium spatial birth-and-death process.

Joint microscopic state is (γ, ω), i.e. an element in

$$\Gamma^2 := \Gamma^S \times \Gamma^E.$$

Statistical description

Observable quantities are

$$\langle F\rangle_\mu := \int\limits_{\Gamma^S\times\Gamma^E} F(\gamma,\omega)\mathrm{d}\mu(\gamma,\omega)$$

where μ is a probability measure ($=$ state) on $\Gamma^S \times \Gamma^E$

- Number of tumour cells in volume Λ^S

$$\int\limits_{\Gamma^S} |\gamma \cap \Lambda^S| \mathrm{d}\mu(\gamma,\omega).$$

- Second order correlations: $\Lambda^S \times \Lambda^E \subset \mathbb{R}^d \times \mathbb{R}^d$

$$\int\limits_{\Gamma^S\times\Gamma^E} |\gamma \cap \Lambda^S||\omega \cap \Lambda^E| \mathrm{d}\mu(\gamma,\omega).$$

- Higher order correlations

$$\int\limits_{\Gamma^S\times\Gamma^E} \prod_{k=1}^{n} |\gamma \cap \Lambda_k^S| \cdot \prod_{k=1}^{m} |\gamma \cap \Lambda_k^E| \mathrm{d}\mu(\gamma,\omega).$$

Space of admissible measures

μ state on Γ^2. Correlation function $k_\mu^{(n,m)}$ is locally integrable function s.t.

$$\int\limits_{\Gamma^S \times \Gamma^E} \prod_{k=1}^{n} |\gamma \cap \Lambda_k^S| \cdot \prod_{k=1}^{m} |\gamma \cap \Lambda_k^E| \mathrm{d}\mu(\gamma, \omega) = \frac{1}{n!} \frac{1}{m!} \int\limits_{\Lambda_1^+ \times \cdots \times \Lambda_n^+} \int\limits_{\Lambda_1^- \times \dots \Lambda_m^-} k_\mu^{(n,m)} \mathrm{d}x \mathrm{d}y.$$

Example:

- $k^{(0,0)} = \mu(\Gamma^2) = 1$.
- $n + m = 1$ yields for $\Lambda \subset \mathbb{R}^d$ compact

$$\int\limits_{\Gamma^2} |\gamma^+ \cap \Lambda| \mathrm{d}\mu(\gamma) = \int\limits_{\Lambda} k_\mu^{(1,0)}(x) \mathrm{d}x, \quad \int\limits_{\Gamma^2} |\gamma^- \cap \Lambda| \mathrm{d}\mu(\gamma) = \int\limits_{\Lambda} k_\mu^{(0,1)}(y) \mathrm{d}y.$$

Up to some mathematical aspects, we obtain a one-to-one correspondence

$$\text{states } \mu \longleftrightarrow \text{correlation functions } k_\mu = (k_\mu^{(n,m)})_{n,m=0}^{\infty}$$

Dynamics

Model time evolution by an evolution of states

$$\mu_0 \longmapsto \mu_t \quad \text{or} \quad k_{\mu_0}^{(n,m)} \longmapsto k_{\mu_t}^{(n,m)}.$$

Elementary events:

- Birth: Each particle creates a new particle, a particle may appear from the outside.

  $$\gamma \longmapsto \gamma \cup \{x\}, \quad x \notin \gamma.$$

  Birth rate: $b(x, \gamma, \omega) \geq 0$.
- Death: Particles have a lifetime and compete for resources.

  $$\gamma \longmapsto \gamma \backslash \{x\}, \quad x \in \gamma.$$

  Death rate: $d(x, \gamma, \omega) \geq 0$.
- Motion, migration, mutations and many others are possible.

$\omega \in \Gamma^E$ takes influence of environment into account.

Markov operator

Let $L_\gamma^S(\omega)$ be the Markov operator for the tumour cells, i.e.

$$(L_\gamma^S(\omega)F)(\gamma) = \sum_{x\in\gamma} d(x,\gamma\backslash x,\omega)(F(\gamma\backslash x) - F(\gamma)) + \int_{\mathbb{R}^d} b(x,\gamma,\omega)(F(\gamma\cup x) - F(\gamma))\mathrm{d}x.$$

Environment is assumed to be of similar form but with different birth-and-death rates. These rates will be specified later on.

Dynamics

Markov evolution is described by solutions to (backward) Kolmogorov equation

$$\frac{\partial F_t}{\partial t} = (L^S_\gamma(\omega) + L^E_\omega)F_t, \quad F_t|_{t=0} = F.$$

Then $\langle F_t \rangle_\mu$ is the time evolution of the expected value of F in state μ.

We are interested in the evolution of states $\mu_0 \longmapsto \mu_t$.
We should have $\langle F_t \rangle_\mu = \langle F \rangle_{\mu_t}$.

Can rewrite this into a system of equations

$$\frac{\partial k_t^{(n,m)}}{\partial t} = (L^\Delta k_t)^{(n,m)}, \quad k_t^{(n,m)}|_{t=0} = k_0^{(n,m)}$$

where L^Δ is a double-matrix. Then

$$(k_t^{(n,m)})_{n,m=0}^\infty \longleftrightarrow \mu_t.$$

Evolution of correlation functions

$$\frac{\partial k_t^{(n,m)}}{\partial t} = (L^{\Delta} k_t)^{(n,m)}, \quad k_t^{(n,m)}|_{t=0} = k_0^{(n,m)}$$

- L^{Δ} can, for many models, be computed explicitly from $L_{\gamma}^{S}(\omega), L_{\omega}^{E}$.
- Explicit form in coordinates

$$\frac{\partial k_t^{(n,m)}}{\partial t} = \sum_{k,l=0}^{\infty} L_{kl,nm}^{\Delta} k_t^{(k,l)}, \quad k_t^{(n,m)}|_{t=0} = k_0^{(n,m)}.$$

- In some cases the right-hand side has recursive structure, i.e.

$$\frac{\partial k_t^{(n,m)}}{\partial t} = \sum_{k,l=0}^{n,m} L_{kl,nm}^{\Delta} k_t^{(k,l)}, \quad k_t^{(n,m)}|_{t=0} = k_0^{(n,m)}.$$

Hence it may be solved explicitly.

Aim: Simplification

1. We are interested in the projections μ_t^S of μ_t onto Γ, i.e.

$$\mu_t^S(A) := \mu_t(A \times \Gamma^E) \longleftrightarrow k_{\mu_t^S}^{(n)} = k_{\mu_t}^{(n,0)}.$$

   Equation for $k_{\mu_t^S}^{(n)}$ depends on all $k_{\mu_t}^{(n,m)}$. Projection is not Markov.

   - Find a closed equation (after proper scaling) for μ_t^S or $k_{\mu_t^S}$.
   - The limiting equation should recover the Markov property.
   - Works in a certain regime of parameters on the interactions.

2. Find closed equations for particle densities $k_t^{(1,0)}, k_t^{(0,1)}$, i.e.

$$\frac{\partial \rho_t^S(x)}{\partial t} = v^S(\rho_t^S, \rho_t^E)(x), \quad \frac{\partial \rho_t^E(x)}{\partial t} = v^E(\rho_t^E)(x).$$

   Mesoscopic equations which are obtained after certain scalings.

Environment

Environment is Glauber dynamics with formal Markov operator

$$(L^E_\omega F)(\omega) = \sum_{x\in\omega}(F(\omega\backslash x) - F(\omega)) + z\int_{\mathbb{R}^d} e^{-E_\varphi(x,\omega)}(F(\omega\cup x) - F(\omega))\mathrm{d}x$$

- $z \geq 0$ activity parameter.
- Relative energy

$$E_\varphi(x,\omega) = \sum_{y\in\omega}\varphi(x-y), \quad x\in\mathbb{R}^d, \quad \omega\in\Gamma^E.$$

- Death rate is constant to 1.
- Birth rate is given by $ze^{-E_\varphi(x,\omega)}$.

Environment

Assumptions

- Interaction potential $\varphi(x) = \varphi(-x) \geq 0$ with integrability condition

$$\beta(\varphi) := \int_{\mathbb{R}} (1 - e^{-\varphi(x)}) \mathrm{d}x < \infty.$$

- Small activity regime

$$z < \frac{1}{e\beta(\varphi)}.$$

Then

- There exists an evolution of states $(\mu_t)_{t \geq 0}$.
- There exists a unique invariant measure (Gibbs measure) μ_{inv}.
- Evolution of states is ergodic, i.e.

$$\mu_t \longrightarrow \mu_{\mathrm{inv}} \quad \text{or} \quad k_{\mu_t}^{(n)} \longrightarrow k_{\mu_{\mathrm{inv}}}^{(n)}, \ \forall n, \quad t \longrightarrow \infty.$$

System

Free branching with rates

$$d(x,\gamma\backslash x,\omega) = m + g\sum_{y\in\omega} d(x-y)$$

$$b(x,\gamma,\omega) = \sum_{y\in\gamma} a^+(x-y)$$

- $m \geq 0$ mortality rate of cells.
- $a^+(x-y) = a^+(y-x) \geq 0$ integrable and bounded, proliferation kernel for cells
- $d(x-y) = d(y-x) \geq 0$ integrable and bounded, interaction with environment.
- $g \geq 0$ coupling constant for interaction with environment.

Consider **finite system** such that $m < \lambda := \int_{\mathbb{R}^d} a^+(x)\mathrm{d}x$.

Reduced description

Scaling Markov operator $L^S_\gamma(\omega) + \frac{1}{\varepsilon} L^E_\omega$ for $\varepsilon > 0$ yields when $\varepsilon \to 0$ reduced description:

$$\overline{d}(x, \gamma \backslash x) = m + \overline{g}(x)$$

$$\overline{b}(x, \gamma) = \sum_{y \in \gamma} a^+(x - y)$$

where

$$\overline{g}(x) = g \int_{\Gamma^E} \sum_{y \in \omega} d(x-y) \mathrm{d}\mu_{\mathrm{inv}}(\omega) = gz \int_{\Gamma^E} \int_{\mathbb{R}^d} d(x-y) e^{-E_\varphi(y,\omega)} \mathrm{d}y \mathrm{d}\mu_{\mathrm{inv}}(\omega)$$

$$= g \int_{\mathbb{R}^d} d(x-y) k^{(1)}_{\mu_{\mathrm{inv}}}(y) \mathrm{d}y.$$

Reduced description

Consequences

1. System is effectively a free branching process with modified mortality rate.
2. Space inhomogeneous death rate may be a consequence of interactions with environment.
3. Different environments yield the same reduced description:
   - depends only on invariant state and interactions.
4. Environment may regulate the system:
   - Without environment or interactions the number of particles grows exponentially, since

     $$m < \lambda := \int\limits_{\mathbb{R}^d} a^+(x)\mathrm{d}x.$$

   - For $g \cdot z$ large enough all particles die, i.e. $\overline{\mu}_t \longrightarrow \delta_\emptyset$ as $t \to \infty$. Equivalently $k_{\overline{\mu}_t}^{(n)} \longrightarrow 0$ for $n \geq 1$ as $t \to \infty$.

System

Free branching with birth-and-death rates

$$d(x,\gamma\backslash x,\omega) = m + \sum_{y\in\gamma\backslash x} a^{-}(x-y) + g_0 \sum_{y\in\omega} d(x-y)$$

$$b(x,\gamma,\omega) = \sum_{y\in\gamma} a^{+}(x-y) + g_1 \sum_{y\in\omega} b(x-y)$$

- $a^{-}(x-y) = a^{-}(y-x) \geq 0$ integrable and bounded, competition kernel for cells.
- $b(x-y) = b(y-x) \geq 0$ integrable and bounded, proliferation kernel from environment.
- $g_0, g_1 \geq 0$ coupling constant for interaction with environment.

Reduced description

Suppose the following conditions:

- There exists $\Theta > 0$ such that $\Theta a^{-} - a^{+}$ is a stable potential.
- There exists $c > 0$ such that $b \leq c \cdot d$.
- m is sufficiently large.

Scaling Markov operator $L^S_\gamma(\omega) + \frac{1}{\varepsilon} L^E_\omega$ for $\varepsilon > 0$ yields when $\varepsilon \to 0$ reduced description:

$$\overline{d}(x, \gamma \backslash x) = m + \overline{g}(x) + \sum_{y \in \gamma \backslash x} a^{-}(x - y)$$

$$\overline{b}(x, \gamma) = \sum_{y \in \gamma} a^{+}(x - y) + \overline{z}(x)$$

where $\overline{z}(x) = g_1 \int_{\Gamma^E} \sum_{y \in \omega} b(x - y) \mathrm{d}\mu_{\mathrm{inv}}(\omega)$ and

$$\overline{g}(x) = g_0 \int_{\Gamma^E} \sum_{y \in \omega} d(x - y) \mathrm{d}\mu_{\mathrm{inv}}(\omega)$$

Consequences

Without presence of environment:

- Dynamics is asymptotically degenerated, i.e. $\mu_t \longrightarrow \delta_\emptyset$ as $t \to \infty$. Equivalently $k_{\mu_t}^{(n)} \longrightarrow 0$ for all $n \geq 1$ as $t \to \infty$.

In the presence of environment

- Dynamics has non-trivial invariant measure μ_∞ such that $\mu_t \longrightarrow \mu_\infty$ as $t \to \infty$. Equivalently $k_{\mu_t}^{(n,m)} \longrightarrow k_{\mu_\infty}^{(n,m)}$ for all $n, m \geq 0$ as $t \to \infty$.

After reduced description

- Dynamics has non-trivial invariant measure $\overline{\mu}_\infty$ such that $\overline{\mu}_t \longrightarrow \overline{\mu}_\infty$ as $t \to \infty$. Equivalently $k_{\overline{\mu}_t}^{(n)} \longrightarrow k_{\overline{\mu}_\infty}^{(n)}$ for all $n \geq 0$ as $t \to \infty$.

Consequences

Without presence of environment:

- Kinetic equation is

$$\frac{\partial \rho_t(x)}{\partial t} = -m\rho_t(x) - \int\limits_{\mathbb{R}^d} a^-(x-y)\rho_t(y)\mathrm{d}y\rho_t(x) + \int\limits_{\mathbb{R}^d} a^+(x-y)\rho_t(y)\mathrm{d}y.$$

In the presence of environment

$$\frac{\partial \rho_t^E(x)}{\partial t} = -\rho_t^E(x) + ze^{-\int\limits_{\mathbb{R}^d}\varphi(x-y)\rho_t^E(y)\mathrm{d}y}$$

$$\frac{\partial \rho_t^S(x)}{\partial t} = -m\rho_t^S(x) - \int\limits_{\mathbb{R}^d} a^-(x-y)\rho_t^S(y)\mathrm{d}y\rho_t^S(x) - \int\limits_{\mathbb{R}^d} d(x-y)\rho_t^E(y)\mathrm{d}y\rho_t^S(x)$$

$$+ \int\limits_{\mathbb{R}^d} a^+(x-y)\rho_t^S(y)\mathrm{d}y + \int\limits_{\mathbb{R}^d} b(x-y)\rho_t^E(y)\mathrm{d}y.$$

After reduced description

$$\frac{\partial \overline{\rho}_t(x)}{\partial t} = -(m+\overline{g}(x))\overline{\rho}_t(x) + \int\limits_{\mathbb{R}^d} a^+(x-y)\overline{\rho}_t(y)\mathrm{d}y + \overline{z}(x).$$

Dynamics

Tumour cells

$$d(x, \gamma \backslash x, \omega) = \sum_{y \in \omega} a^{-}(x-y)$$

$$b(x, \gamma, \omega) = \sum_{y \in \gamma} a^{+}(x-y)$$

Immune system

$$d^{E}(x, \gamma, \omega \backslash x) = m + \sum_{y \in \gamma} b^{-}(x-y)$$

$$b^{E}(x, \gamma, \omega) = \sum_{y \in \omega} \left(1 - e^{-E_{\varphi}(y, \gamma)}\right) b^{+}(x-y) + z$$

Derive kinetic equations.

Dynamics

Kinetic equations

$$\frac{\partial \rho_t^S(x)}{\partial t} = -\int_{\mathbb{R}^d} a^-(x-y)\rho_t^E(y)\mathrm{d}y\rho_t^S(x) + \int_{\mathbb{R}^d} a^+(x-y)\rho_t^S(y)\mathrm{d}y$$

$$\frac{\partial \rho_t^E(x)}{\partial t} = -\left(m - \int_{\mathbb{R}^d} b^-(x-y)\rho_t^S(y)\mathrm{d}y\right)\rho_t^E(x)$$

$$+ \int_{\mathbb{R}^d} b^+(x-y)\left(1 - e^{-\int_{\mathbb{R}^d}\varphi(w-y)\rho_t^S(w)\mathrm{d}w}\right)\rho_t^E(y)\mathrm{d}y + z$$

Space-homogeneous version: $X = \rho^S$ and $Y = \rho^E$

$$X' = (a^+ - a^- Y)X$$

$$Y' = z - mY + b^+ Y(1 - e^{-\varphi X}) - b^- XY.$$

Dynamics

Tumour cells

$$d(x,\gamma\backslash x,\omega) = m^S + \sum_{y\in\gamma\backslash x} b^-(x-y) + \sum_{y\in\omega}\varphi^-(x-y)$$

$$b(x,\gamma,\omega) = \sum_{y\in\gamma} b^+(x-y) + \sum_{y\in\omega}\varphi^+(x-y)$$

Immune system

$$d^E(x,\gamma,\omega\backslash x) = m^E + \sum_{y\in\omega\backslash x} a^-(x-y)$$

$$b^E(x,\gamma,\omega) = \sum_{y\in\omega} a^+(x-y) + z$$

Environment has still invariant measure μ_{inv} with $\mu_t^E \longrightarrow \mu_{\mathrm{inv}}$ as before.

Reduced description

Have birth-and-death rates

$$\overline{d}(x,\gamma\backslash x) = m^S + \overline{\varphi}^-(x) + \sum_{y\in\gamma\backslash x} b^-(x-y)$$

$$\overline{b}(x,\gamma) = \sum_{y\in\gamma} b^+(x-y) + \overline{z}(x)$$

where $\overline{\varphi}^-(x) = \int\limits_{\Gamma^E} \sum\limits_{y\in\omega} \varphi^-(x-y)\mathrm{d}\mu_{\mathrm{inv}}(\omega)$ and

$$\overline{z}(x) = \int\limits_{\Gamma^E} \sum_{y\in\omega} \varphi^+(x-y)\mathrm{d}\mu_{\mathrm{inv}}(\omega).$$

Kinetic equations

Without environment

$$\frac{\partial \rho_t(x)}{\partial t} = -\left(m^S + \int_{\mathbb{R}^d} b^-(x-y)\rho_t(y)\mathrm{d}y \right) \rho_t(x) + \int_{\mathbb{R}^d} b^+(x-y)\rho_t(y)\mathrm{d}y.$$

Reduced description

$$\frac{\partial \overline{\rho}_t(x)}{\partial t} = -\left(m^S + \overline{\varphi}^-(x) + \int_{\mathbb{R}^d} b^-(x-y)\overline{\rho}_t(y)\mathrm{d}y \right) \overline{\rho}_t(x) + \int_{\mathbb{R}^d} b^+(x-y)\overline{\rho}_t(y)\mathrm{d}y + \overline{z}(x)$$

Kinetic equations

Theorem

Thank You!