A stochastic model of metastatic proliferation

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Plan:

- The deterministic results
- The stochastic model
- The reduced equations

The deterministic results

K.Iwata, K.Kawasaki and N.Shigesada [IKS] model for the growth and spread of secondary tumors (metastases):

- the primary tumor, of size x_p (the cell number, being very large, is considered as a continuous variable), grows with a Gompertzian deterministic law $\dot{x}_p = g(x_p)$ and $g(x) := ax\log(N/x)$ here $a > 0$, $0 << N$ (i.e. N is "macroscopic", e.g. 10^{11}).
- meanwhile, it produces one-cell metastases with a size-dependent rate $\beta(x_p) = mx_p^\alpha$, with parameters $m > 0$ and $\alpha \in (0, 1]$: α is related to the connection between tumor and blood circulation (angiogenesis), vascularization is on the surface $\Rightarrow \alpha \simeq 2/3$.
- the new metastases grow with the same law and produce other metastases with the same mechanism.

The evolution (von Forster) equation for the size distribution, in the continuum approximation:

$$\frac{\partial \rho(x,t)}{\partial t} + \frac{\partial (g(x)\rho(x,t))}{\partial x} = 0,\ x > 1 \tag{1.1}$$

$$g(1)\rho(1,t) = \int_1^\infty \beta(x)\rho(x,t)dx + \beta(x_p(t)); \quad \rho(x,0) = 0 \tag{1.2}$$

Remark: $x_p(t) = N^{(1-\exp(-at))}$ solves the Gompertz equation with $x_p(0) = 1$.

Accurate analysis in more recent papers by two french groups [DGL, BBHV].

The main point is the evaluation of the malthusian rate associated to the asymptotic exponential growth of the metastatic population.

The stochastic model

First step: modelling growth of a single tumour.

- It is a BD (birth-death) process (equivalently, a random walk on the space of sizes $\mathbb{Z}_+ = \{0, 1, 2, ...\}$), with suitable rates.
- In the initial segment $[1, N]$, its size tends to increase (B > D), while beyond N , the size tends to decrease (D > B).
- 0 is a.s. absorbing.

Remark: the stochastic model of a single tumor has a behavior not so different from the deterministic one; if the tumor reaches a macroscopic size the mean time to extinction becomes extremely long. What is actually observed in the long run, if no extinction occurred, is the quasi-stationary state, i.e. the distribution of sizes, conditioned to not being absorbed, see the recent review on quasi-stationary distributions [vDP]

Proposed rates:

- birth rate, $\lambda_n = an \log(N+1), \quad n \in \mathbb{Z}_+$
- death rate $\mu_n = an \log(n+1), \quad n \in \mathbb{Z}_+$.

Remark: N is a large bounding size, the drift $\lambda_n - \mu_n$ is positive from 1 to $N-1$, zero on N and negative after N, such that asymptotically reproduces the deterministic, Gompertzian law.

For general positive rates of a birth-death process, we consider the potential coefficients $\pi_n, \quad n \in \mathbb{N}$, i.e. on the set of transient states $\mathbb{N} = \{1, 2, ..\}$

$$\pi_1 = 1,\ \pi_n = \frac{\lambda_1 \lambda_2 \ldots \lambda_{n-1}}{\mu_2 \mu_3 \ldots \mu_n}, \quad n = 2, 3, .. \tag{2.1}$$

and suppose that the following conditions are fulfilled:

$$\sum_{n=1}^{\infty} \left(\frac{1}{\lambda_n \pi_n}\right) = \infty \text{ i.e. non-explosion}$$

and

$$\sum_{n=1}^{\infty} \left(\frac{1}{\lambda_n \pi_n} \sum_{i=1}^{n} \pi_i\right) = \infty$$

These conditions (fulfilled in our case) imply that absorption in 0 is certain. The transition probabilities

$$P_{i,j}(t) = \mathbb{P}\{X(t) = j | X(0) = i\}$$

are the unique solution of the Kolmogorov Backward and Forward Equation (KBE, KFE) systems.

These equations can be compactly formulated by introducing the generator Q of the process: Q is a tridiagonal matrix such that

$$Q_{i,i} = -(\lambda_i + \mu_i),\ i = 0, 1, .., \ Q_{i,i-1} = \mu_i,\ i = 1, 2, ..;$$
$$Q_{i,i+1} = \lambda_i,\ i = 0, 1, ..;\ Q_{i,k} = 0 \text{ otherwise}$$

Let $P(t)$ denote the transition probability matrix, we shortly write the two Kolmogorov equations:

$$\dot{P} = QP,\ \text{(KBE)}$$
$$\dot{P} = PQ,\ \text{(KFE)}$$

Remark: as absorption in 0 is certain, the stationary distribution of the process is just δ_0.

We moreover have that a positive decay parameter Λ_+, $\Lambda_+ := \lim_{t\to\infty} 1/t|\log P_{ij}(t)|, i, j \in \mathbb{N}$ exists; this comes from the asymptotic behavior of the π_j for large j, which allows the following result for the quantity $R_n := (\sum_{j=1}^{n} \frac{1}{\mu_j \pi_j})(\sum_{j=n}^{\infty} \pi_j)$ see [SZP]:

$$\sup_{n\geq 1} R_n := R < \infty \tag{2.2}$$

This implies that the decay parameter is positive, as $(4R)^{-1} \leq \Lambda_+ \leq R^{-1}$.

The reduced equations

Model proliferation i.e. the appearance of secondary tumours at small, unit size: it is represented by a given rate of creation of "particles" in the site 1, through a linear functional of the system configuration.

Remark: at the initial stage of growth (size =1!) extinction happens with "reasonable" mean times; this is not present in the deterministic model, hence different results are expected.

The proliferation process is represented in the configuration space $\mathbb{S} = \{\eta : (\eta_1, .., \eta_n, ..), \eta_n = \#\text{metastases of size } n, n = 1, 2, ..\}$, in the following way: the population on the site 1 (i.e. the number of tumours of size one) increases with a rate $C(\eta)$ (the colonization rate) which depends linearly on the current configuration $C(\eta) = \sum \beta_n \eta_n$.

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We just analyze the evolution of the expected values.

Let the expected occupation numbers be $\rho_k(t) = \langle \eta_k(t) \rangle$, $k = 1, 2, ...$. The initial measure is concentrated on the configuration with just one particle in the site 1, i.e. just one (ancestor) cell.

and let $\underline{e}_1$ denote the unit vector on the site 1.

By linearity we get the following system for the vector $\underline{\rho}(t)$, with $C(\underline{\rho}) = \langle C(\eta) \rangle$:

$$\begin{aligned} \dot{\underline{\rho}} &= \underline{\rho} Q + C(\underline{\rho}) \underline{e}_1 \\ \underline{\rho}^0 &= \underline{e}_1 \end{aligned} \tag{3.1}$$

Let $c(t) \equiv C(\underline{\rho}) = \sum \beta_n \rho_n(t)$, and write the associated componentwise integral equation

$$\rho_k(t) = P_{1,k}(t) + \int_0^t c(s) P_{1,k}(t-s) ds \tag{3.2}$$

Multiplying by β_k and sum over k, a Volterra integral equation for the colonization rate $c(t)$ is got:

$$c(t) = \gamma(t) + \int_0^t c(s) \gamma(t-s) ds \tag{3.3}$$

where $\gamma(t) \equiv \sum_k \beta_k P_{1,k}(t) = \mathbb{E}(\beta_{X(t)})$.

Key estimates:

- for the transition probabilities

$$P_{1,k} \le M_k \exp(-\Lambda_+ t) \tag{3.4}$$

- similar for $\gamma(t)$,

The following integral plays a key role:
$\int_0^\infty \gamma(t)dt = \hat{\gamma}(0)$, where $\hat{f}$ denotes Laplace transform of f.
If $\hat{\gamma}(0) < 1$, $c(t)$ decays exponentially, while exponential growth comes out if $\hat{\gamma}(0) > 1$; $c(t)$ goes to a constant if $\hat{\gamma}(0) = 1$. Some properties of the solution $c(t)$ propagate to the distribution function $\rho(t)$, as the inhomogenous term $P_{1,k}(t)$ is decaying to zero and the integral term is a convolution between γ and $P_{1,k}(t)$.

Final observations on possible actions on the parameters in order to get the desired, decaying behavior.

Formula giving the relevant integral $\int_0^\infty \gamma(t)dt$ in terms of the rates:

$$\int_0^\infty \gamma(t)dt = \mathbb{E}(\int_0^\tau \beta_{X(t)}) = \frac{1}{\mu_1}\sum_{k=1}^\infty \beta_k H(k) \tag{3.5}$$

where $H(1) = 1$, $H(k) = \frac{\lambda_1..\lambda_{k-1}}{\mu_2..\mu_k}$, see [SW].

This formula allows to evaluate the role of different parameters in order to decrease the value of the integral below 1, in particular by suitable decreasing the birth rates in a initial segment.

Forthcoming work (with K.Ravishankar) will focus on the full many-particle system, where the absorption competes with proliferation; it may be interesting to investigate the condition for the existence of a stationary distribution on the transient set. A resemblance with the Fleming-Viot system may be noted, see [FM].

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