Modelling the spreading of metastases: a stochastic approach

Livio Triolo
Dipartimento di Matematica
Università di Roma Tor Vergata, Italy

Plan.

- Introduction: the description of the metastases system
- The deterministic model for the metastases distribution function
- The stochastic model: motivations, description and results
- Comparisons and perspectives

"Make your theory as simple as possible, but no simpler"

A.Einstein

1. Introduction: the description of the system

A primary tumor grows somewhere;

- through angiogenesis, the tumor spreads (independent) cells which form secondary tumors (metastases); they grow and spread cells as the primary one.
- Aim: to describe the distribution of the metastases as a function of size and time.

Reference work ([IKS]: description of the system, deterministic approach and comparison with experimental data):

K.Iwata, K.Kawasaki, N.Shigesada,
A Dynamical Model for the growth and size distribution of multiple metastatic tumors.
J.Theor. Biol. **203**, 177-186,(2000)

2. The deterministic model

A revised version of IKS:

J.Struckmeier,
A mathematical investigation of a dynamical model for the growth and size distribution of multiple metastatic tumors.
Preprint Inst Angew. Math. Hamburg **277**, (2003)

The IKS model:

- Deterministic growth law in the continuum (i.e. the number of its cells is considered as a continuous variable $x_p \in [1, \infty]$),

$$\dot{x}_p = g(x_p)$$

g is Gomperztian i.e. $g(z) = az \log b/z$, $a \approx 3 \cdot 10^{-3}\text{day}^{-1}$, $b \approx 10^{10}$.

Explicit solution, with $x_p(0) = 1$,

$$x_p(t) = b \exp(-(\log b) \exp(-at))$$

(from these data: it takes 300 days to reach the size 10^6, and 700 to get 10^9)

- Spreading of sparse, one-cell secondary tumours (i.e. metastases) happens with a rate
  $\beta(x_p) = m x_p^\alpha$, $m \approx 5 \cdot 10^{-8}$, $\alpha \in (0, 1]$

  The parameter α describes the (fractal) geometry of the capillary network in the tumor: $\alpha \approx 2/3$ means that the network is essentially on the surface of the tumors, while $\alpha \approx 1$ means a bulk structure of the network; m is the colonization rate.

  These metastases grow and produce other me–tastases with the same laws as the primary.
- Issue: to determine the distribution $\rho(x, t)$ as a function of the size x and the time t.

ρ is the solution of a linear first order PDE (i.e. the Liouville eq. for the growth flow in the continuum approximation),

$$\partial_t \rho(x,t) + \partial_x (g(x)\rho(x,t)) = 0, \quad x > 1, t > 0$$

Boundary condition at $x = 1$ (=incoming flux there, due to the primary and to the proliferation process):

$$g(1)\rho(1,t) = \int_1^\infty \beta(x)\rho(x,t)dx + \beta(x_p)$$

Initial condition

$$\rho(x,0) = 0, \ x > 1$$

Remarks:

- The solution is discontinuous along the growth curve $\{(t, x_p(t),\ t > 0\}$ in the $(t, x)-$plane.
- From asymptotic analysis: the distribution grows in time with a dominant exponential, and for fixed large time the dependence on x may be either decreasing or U-shaped (i.e. with an internal minimum). This depends on the parameters: given a, m, b as before, a change in α from .66 to .4 determines this qualitative change ([IKS]).

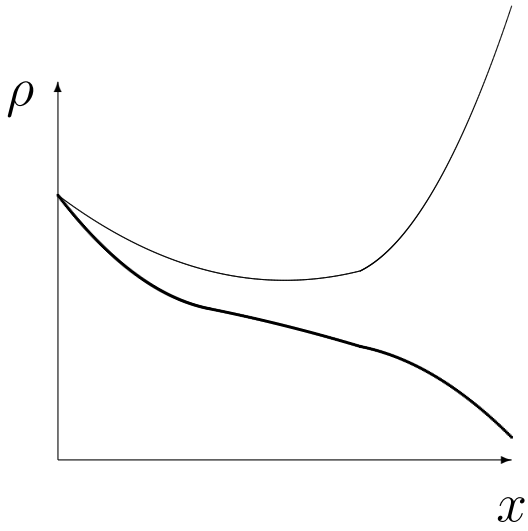

FIGURE 1. Qualitative graphs of two distribution functions for $\alpha = .66$ (thick) and $\alpha = .4$ (thin).

3. The stochastic model: generalities

Individual evolution of primary and secondary tumors is modeled as a birth-death process, where drift (=birth-death rates) behaves as the deterministic one, but with the new feature of being absorbed in 0 (a.s. extinction).

For large sizes: the behavior is not very different from the predicted by the deterministic model,

E. Renshaw (1991) *Modelling Biological Populations in Space and Time*. Cambridge

For small sizes (e.g. $x = 1$), fluctuations are more relevant, in particular absorption in 0 may change things qualitatively.

This is particularly relevant in the colonization process, where single clonal cells (i.e. minimum size) are created.

3.1. Stochastic description of the single-tumor evolution. A single tumor evolves like an inhomogeneous Random Walk $X(\cdot)$ on $\overline{\mathbb{Z}}_+$, the one-dimensional space of nonnegative sizes (= sites)

$$\overline{\mathbb{Z}}_+ = \{0, 1, 2, ..\} \equiv \{0\} \cup \mathbb{Z}_+$$

with nonnegative rates of one-step jump λ_n (up) and μ_n (down), which are positive for $n > 0$ and null in 0.

Let λ_n and μ_n be such that the net drift $\lambda_n - \mu_n \approx$ the deterministic, Gompertz law.

E.g.

$$\lambda_n = an\log(b+1);\ \mu_n = an\log(n+1),\ n = 0, 1, 2, ...$$

Let Q be the tridiagonal matrix:

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

Let $P(t)$ denote the transition probability matrix, we then get for the nonhomogeneous random walk on $\overline{\mathbb{Z}}_+$:

$$\dot{P} = QP,\ \text{(Backw. Equ.)}$$
$$\dot{P} = PQ,\ \text{(Forw. Equ.)}$$

3.2. Stochastic description of the many-tumor evolution. The system is a like a gas of identical independent RW's.

$\eta_k(t)$, $k = 1, 2, ..$ is the occupation number of the site k, at time t; their expected values are

$$\rho_k(t) =< \eta_k(t) >= (\underline{\rho}(t))_k$$

Colonization rate and its expected value:

$$C(\eta) = \sum \beta_n \eta_n, \; c(t) = \langle C(\eta) \rangle = \sum \beta_n \rho_n(t)$$

$\underline{e}_1$ is the vector s.t. $(\underline{e}_1)_k = \delta_{1k}$, $k = 1, 2, ...$

Equation of motion for the vector $\underline{\rho}(t)$, with Q restricted to the transient set $\mathbb{Z}_+$.

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

A closed equation for the expected colonization rate $C(\underline{\rho}(t) \equiv c(t)$:

$$\rho_k(t) = P_{1,k}(t) + \int_0^t c(s) P_{1,k}(t-s) ds, \; k = 1, 2, ..$$

$$\underline{\rho}^0 = \underline{e}_1$$

Multiplying by β_k and summing up,

$$\sum \beta_k \rho_k(t) =$$

$$\sum \beta_k P_{1,k}(t) + \int_0^t c(s) \sum \beta_k P_{1,k}(t-s) ds$$

Let

$$\gamma_1(t) \equiv \sum \beta_k P_{1,k}(t) = \langle \beta_{X(t)} \rangle > 0$$

In compact form

$$c(t) = \gamma_1(t) + \int_0^t c(s) \gamma_1(t-s) ds$$

Proposition

If the colonization constant m in the definition of β. is suitably chosen, the asymptotic behavior of $c(t)$ may be exponentially small, constant, or exponentially increasing as $t \to \infty$.

Sketch of the proof.

$X(t)$: RW with a drift which is positive just in $\mathbb{Z}_+ \cap [1, b]$: there is a positive decay constant Λ_+ for the transition probabilities restricted to the transient class $\mathbb{Z}_+$. The exponential estimate (actually, in time t and in space $k \in \mathbb{Z}_+$)

$$P_{1,k} \leq M_k e^{-\Lambda_+ t}$$

gives

$$\gamma_1(t) \leq m\overline{\beta} e^{-\Lambda_+ t}, \qquad \text{where } \overline{\beta} = \sum k^\alpha M_k$$

Let

$$A_0 = \int_0^\infty \gamma_1(t)dt, \quad A_1 = \int_0^\infty t\gamma_1(t)dt$$

(their values depend on the colonization parameter m). $\hat{\gamma}_1(z)$ is the Laplace transform of the positive function γ_1.

$$\hat{\gamma}_1(z) = \int_0^\infty e^{-zt}\gamma_1(t)dt$$

$$\hat{c}(z) = \frac{\hat{\gamma}_1(z)}{1 - \hat{\gamma}_1(z)}$$

Laplace transform for small $z \Rightarrow$ asymptotics in large t:

- if $A_0 = \hat{\gamma}_1(0) < 1$,

$$\hat{c}(z) = \frac{\hat{\gamma}_1(z)}{1 - \hat{\gamma}_1(z)} = \frac{\hat{\gamma}_1(z)}{1 - \hat{\gamma}_1(0) + o(z)}$$

so that

$$c(t) \to 0, \quad \text{for } t \to \infty$$

- if $A_0 = \hat{\gamma}_1(0) = 1$,

$$c(t) \to \frac{A_0}{A_1}, \quad \text{as } t \to \infty$$

- if $A_0 = \hat{\gamma}_1(0) > 1$, calling $\sigma > 0$ the positive root of $\hat{\gamma}_1(z) = 1$, and defining

$$A_0' = \int_0^\infty e^{-\sigma t} \gamma_1(t) dt, \quad A_1' = \int_0^\infty t e^{-\sigma t} \gamma_1(t) dt$$

we get

$$c(t) \sim e^{\sigma t} \frac{A_0'}{A_1'}, \quad \text{as } t \to \infty$$

This result on the colonization rate may be plugged in the equation for $\underline{\rho}$ obtaining the analogous results for the expected occupation numbers.

Proposition.

The expected occupation numbers for the "meta–static" process go to zero, to a constant, or grow asymptotically in an exponential way, according to suitable values of the colonization constant m.

Sketch of the proof:

by passing to Laplace transform, and using the preceding results on $c(t)$, we get first

$$\hat{\rho}_k(z) = \hat{P}_{1,k}(z) + \hat{c}(z)\hat{P}_{1,k}(z) =$$
$$\hat{P}_{1,k}(z)(1 + \hat{c}(z)) = \hat{P}_{1,k}(z)(\frac{1}{1 - \hat{\gamma}_1(z)})$$

In this Laplace-transform form, the resolvent is the same which appears before, so that we get the same asymptotics as before.

4. Comparisons and perspectives

This behavior is clearly very different from the deterministic one, and it may give a way to model the "dormancy", (i.e. long time survival of very small metastases, as particles in a metastable situation).

Seminars in Cancer Biology, n.4, **11**, (2001)

It should be interesting to study the whole process by introducing the notion of "quasistationarity".

E.A. van Doorn Quasi-stationary distributions and convergence to quasi-stationarity of birth-death process. *Ann. Appl. Probab.* **23** , 683-700, (1991)

A difficulty is the procedure sketched above: the ergodic behavior for the individual evolution is established in a very long time, and this sure event happens after (astronomically) long times. What is really observed in the long time for the individual evolution? It is a stationary distribution, *conditioned* of not having been absorbed before (quasistationary distribution).

Further perspective: model the system in the continuum, like [IKS], but adding a stochastic fluctuation.

I.e. Diffusion approximation of the population process:

Ricciardi, Luigi M., Stochastic population theory: diffusion processes, in Mathematical Ecology, *Biomathematics*, **17**, Springer, 1986

The diffusion coefficient comes out to be proportional to the size, and the drift coefficient may be corrected near the origin with a small trap, i.e. the associated potential has a deep minimum in the large asymptotic site, and a narrow (how deep?) one near the origin.

An exploration of the combined effect of this correction together with the absorption may give some information on a possible metastable situation, where particles stay long time around the origin.

G.N.Naumov, I.C. McDonald, A.F.Chambers, A.C. Groom, Solitary cancer cells as a possible source of tumour dormancy?, *Sem. in Cancer Biology*, **11**, 271-276, (2001)