Supplemental material

1 Mathematics of the PDE model

Describing metastatic growth by means of a transport equation is motivated by an analogy to particle motion. There, the transport equation is derived from *mass conservation.* (see [2] for a clearly illustrated derivation in the particle case). The solution of this equation is a density, which, when integrated over a control domain, yields the number of particles inside the domain. In the metastatic model, transport does not take place in a physical space but in the "size space", with metastatic growth being transport in the size space.

Consider the model

$$\begin{aligned} &\frac{\partial}{\partial t}\rho(x,t) + \frac{\partial}{\partial x}\left(g_m(x)\rho(x,t)\right) = 0, && t > 0,\ x \in (1,b) \\ &g_m(1)\rho(1,t) = f(t) + \int_1^b \beta(x)\rho(x,t)dx,\ t > 0, && \\ &\rho(x,0) = \rho_0(x), && x > 0. \end{aligned} \tag{1}$$

Global existence of a unique strong solution ρ can be shown if the compatibility condition

$$g_m(1)\rho_0(1) = f(0) + \int_1^b \beta(x)\rho_0(x)dx$$

is fulfilled. In the metastatic model, this condition is not met because $f(0) = \beta(x_p(0)) > 0$ and $\rho_0 \equiv 0$. In this case, the model has a unique weak solution $\rho \in C(\mathbb{R}^+, L^1(1,b))$, which is discontinuous along $(t, x_m(t))$ (see [1, 3]). However, it can be shown that the number of metastases $N(t) = \int_1^b \rho(x,t)dx$ and the metastatic burden $M(t) = \int_1^b x\rho(x,t)dx$ are smooth functions.

2 Equivalence of the PDE and Volterra formulations

Here we sketch the reformulation of the PDE model into a Volterra equation. See [3] for a rigorous account which also explains why it is numerically advantageous to work with the Volterra formulation.

Recall that x_m is the solution of $\frac{dx_m}{dt}(t) = g_m(x_m(t))$, $x_m(0) = 1$. The solution of the transport equation satisfies the conservation property

$$\frac{d}{dt}\left(g_m(x_m(t))\rho(x_m(t), t + t')\right) = 0.$$

Let us write $\varepsilon(t) := g_m(1)\rho(1, t)$, which is the metastatic emission rate. We have

$$\begin{aligned} M(t) &= \int_1^{x_m(t)} x\rho(x, t)dx = \int_0^t x_m(s)g_m(x_m(s))\rho(x_m(s), t)ds \\ &= \int_0^t x_m(s)g_m(1)\rho(1, t - s)ds = (x_m * \varepsilon)(t), \end{aligned}$$

denoting by $*$ the convolution product. Similarly,

$$\int_\Omega \beta(x)\rho(x, t)dx = (\beta(x_m) * \varepsilon)(t).$$

Using the boundary condition and the associativity of the convolution product,

$$\begin{aligned} M &= x_m * \left(\beta(x_p) + \int_\Omega \beta(x)\rho(x, \cdot)dx\right) \\ &= x_m * (\beta(x_p) + \beta(x_m) * \varepsilon) = x_m * \beta(x_p) + M * \beta(x_m). \end{aligned}$$

3 PDE formulation of the final model

The final model can equally be written in the original PDE formulation. Let

$$g(x; a, b) := \min\left(a_{exp}x, ax\log(b/x)\right)$$

be the Gomp-Ex model with parameters a, b and the exponential growth rate a_{exp}. The primary tumor size $x_p(t)$ is the solution of the Gomp-Ex model

$$x_p'(t) = g(x_p(t), a_p, b), \qquad x_p(0) = x_0.$$

The total metastatic burden is defined by

$$\begin{aligned}
&\frac{\partial}{\partial t}\rho(x,t) + \frac{\partial}{\partial x}\left(g_m(x)\rho(x,t)\right) = 0, \\
&g_m(1)\rho(1,t) = \beta(x_p(t)), \\
&\rho(x,0) = 0, \\
&M(t) = \int_1^b x\rho(x,t)dx,
\end{aligned}$$

where

$$g_m(x) = g(x; a_m, b), \qquad \beta(x) = \mu x^{2/3}.$$

Parameters Estimated primary tumor-related parameters are the Gompertzian primary tumor growth parameters a_p, b (common for primary and metastatic tumors) and the initial size of the primary x_0. Metastasis-related parameters are the Gompertzian metastatic growth rate a_m and the metastatic emission rate μ. The exponential growth rate a_{exp} is determined experimentally.

References

[1] D. Barbolosi, F. Verga, A. Benabdallah, and F. Hubert. Mathematical and numerical analysis for a model of growing metastatic tumors. *Math Biosci*, 218(1):1–14, 2009.

[2] L. Edelstein-Keshet. *Mathematical Models in Biology*. Classics in Applied Mathematics. SIAM, 2005.

[3] N. Hartung. Efficient Resolution of Metastatic Tumour Growth Models by Reformulation into Integral Equations. Submitted, preprint at HAL: `http://hal.archives-ouvertes.fr/hal-00935233`.