Supporting Information

Tomasetti and Levy 10.1073/pnas.1007726107

SI Text

We consider here the model where both populations are represented by branching processes and show how to derive Eq. **4** in the paper. The standard theory for these multitype branching processes can be found in the book by Mode (1) as well as partially in refs. 2 and 3.

Let $p^{(1)}(j,k)$ denote the probability for one wild-type cancer stem cell to give birth to j wild-type cancer stem cells and k drug-resistant cancer stem cells. Let $p^{(2)}(j,k)$ denote the same probability when the cancer stem cell is drug resistant.

Then the only values for which $p^{(i)}(j,k)$ are nonzero are the following: $p^{(1)}(2,0) = (1-u)(1-a-b)$, $p^{(1)}(1,1) = u(1-a-b)$, $p^{(1)}(1,0) = (1-u/2)a$, $p^{(1)}(0,1) = (ua)/2$, $p^{(1)}(0,0) = b$; $p^{(2)}(0,2) = (1-a-b)$, $p^{(2)}(0,1) = a$, $p^{(2)}(0,0) = b$. Let $D = 0$.

Let $f^{(1)}(s_1,s_2)$ and $f^{(2)}(s_1,s_2)$ be the probability generating functions of these distributions. Thus

$$\begin{aligned} f^{(1)}(s_1,s_2) &= (1-u)(1-a-b)s_1^2 + u(1-a-b)s_1s_2 \\ &\quad + \left(1-\frac{u}{2}\right)as_1 + \frac{ua}{2}s_2 + b, \\ f^{(2)}(s_1,s_2) &= (1-a-b)s_2^2 + as_2 + b. \end{aligned} \quad \textbf{[S1]}$$

Let $Z_1(t)$ and $Z_2(t)$ be the number of cancer stem cells at time t, which are wild type and drug resistant, respectively. Note that these are both random variables now. Let $F^{(1)}(s_1,s_2;t)$ be the probability generating function of the total number of cancer stem cells (both types) at time t, for the process that was started at time 0 by one wild-type cancer stem cell, that is

$$\begin{aligned} F^{(1)}(s_1,s_2;t) &= \sum_{j,k} P(Z_1(t) = j, Z_2(t) = k | Z_1(0) = 1, \\ &\qquad Z_2(0) = 0) s_1^j s_2^k. \end{aligned} \quad \textbf{[S2]}$$

Similarly, let $F^{(2)}(s_1,s_2;t)$ be the probability generating function of the total number of cancer stem cells (both types) at time t, for the process that was started at time 0 by one drug-resistant cancer stem cell. Note that because we do not consider backward mutations, $F^{(2)}(s_1,s_2;t)$ is not a function of s_1 and is given by

$$F^{(2)}(s_1,s_2;t) = \sum_{0,k} P(Z_1(t) = 0, Z_2(t) = k | Z_1(0) = 0, Z_2(0) = 1) s_2^k. \quad \textbf{[S3]}$$

By Eq. **S2** in ref. 2, page 225, we have that the two probability generating functions satisfy the following system:

$$\begin{aligned} F^{(1)}(s_1,s_2;t) &= e^{-Lt}s_1 \\ &\quad + \int_0^t f^{(1)}(F^{(1)}(s_1,s_2;t-y), F^{(2)}(s_2;t-y)) L e^{-Ly} dy, \\ F^{(2)}(s_2;t) &= e^{-Lt}s_2 + \int_0^t f^{(2)}(0, F^{(2)}(s_2;t-y)) L e^{-Ly} dy. \end{aligned} \quad \textbf{[S4]}$$

These equations can be differentiated to yield the following system (see, e.g., ref. 3, pages 70 and 88):

$$\begin{aligned} \frac{dF^{(1)}}{dt} &= -LF^{(1)} + Lf^{(1)}(F^{(1)}, F^{(2)}), \\ \frac{dF^{(2)}}{dt} &= -LF^{(2)} + Lf^{(2)}(F^{(1)}, F^{(2)}). \end{aligned} \quad \textbf{[S5]}$$

Thus, substituting Eq. **S1** into Eq. **S5**, we obtain the following system:

$$\begin{aligned} \frac{dF^{(1)}}{dt} &= L(1-u)(1-a-b)(F^{(1)})^2 - L\left(1-a+\frac{au}{2}\right)F^{(1)} \\ &\quad + Lu(1-a-b)F^{(1)}F^{(2)} + L\frac{ua}{2}F^{(2)} + Lb, \\ \frac{dF^{(2)}}{dt} &= L(1-a-b)(F^{(2)})^2 - L(1-a)F^{(2)} + Lb. \end{aligned} \quad \textbf{[S6]}$$

Note that we have already solved the second equation in Eq. **6**; it is Eq. **16** in the main paper, with $\tilde{D} = Lb$,

$$F^2(s_2;t) = \frac{(s_2-1)(\tilde{D}/\tilde{L})e^{(\tilde{L}-\tilde{D})t} - (s_2 - \tilde{D}/\tilde{L})}{(s_2-1)e^{(\tilde{L}-\tilde{D})t} - (s_2 - \tilde{D}/\tilde{L})}. \quad \textbf{[S7]}$$

All that is left is to substitute Eq. **7** into the first equation of Eq. **6** and solve for $F^{(1)}$. The probability to develop resistance by the time the tumor is detected is then given by $P_R = 1 - F^{(1)}(1,0;T)$, where T is the time of detection of the tumor.

1. Mode C (1971) *Multitype Branching Processes* (American Elsevier Publishing Company, New York).
2. Athreya KB, Ney PE (1972) *Branching Processes* (Springer, Berlin).
3. Kimmel M, Axelrod DE (2002) *Branching Processes in Biology* (Springer, New York).