Modeling Diversity in Tumor Populations

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Joint work with 
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Outline of Talk

- Describe the biological background and motivation.
- Give too much detail about the mathematical results.
- Ramble incoherently about the connection to one-sided stable laws.
- Apply the results to compute the probability that a chronic myeloid leukemia patient is resistant to imatinib at diagnosis.
Multi-stage theory of carcinogenesis

Armitage and Doll (1954) noticed that log-log plots of cancer incidence data are linear for a large number of cancer types; for example, colorectal cancer incidence has a slope of 5.18 in men and 4.97 in women. The authors used this observation to argue that colon cancer is a six stage process. The math was very simple.

Suppose $X_i$ are independent and have an exponential distribution with rates $u_i$. The sum $X_1 + \cdots + X_k$ has a density function that is asymptotically

$$u_1 \cdots u_k \frac{t^{k-1}}{(k-1)!} \quad \text{as } t \to 0,$$
Incidence of Retinoblastoma

Knudson’s two hit hypothesis → tumor-suppressor genes
Progression to Colon Cancer

Luebeck and Moolgavakar (2002) PNAS fit a four stage model to incidence of colon cancer by age.
What are the stages?

- In sporadic cases of colon cancer the first two stages inactivation of the tumor suppressor gene \textit{APC} \textit{adomatous polyposis coli}.
- \textbf{KRAS} is an \textbf{oncogene} (one mutation turns it on). It acts as a molecular on/off switch, once it is turned on it recruits and activates proteins necessary for the propagation of growth factor.
- The final stage is thought to involve the inactivation of \textit{TP53} the gene which makes \textit{p53}. \textit{p53} regulates the cell cycle and, thus, functions as a tumor suppressor that is involved in preventing cancer.
Things are not so simple

- One of the main aims of large scale sequencing of cancer tumors is to find mutations that are potential drug targets. However many statistically significant mutations are “passengers” that occurred on the same chromosome with a causative mutation.

- In 20% of colon cancers, \( APC \) is not mutated but instead the oncogene \( \beta \)-catenin (in the same pathway) is. This and other examples suggest that features of the disease are due to disrupting certain molecular pathways not necessarily specific mutations.

- Clinical observations of disease and histology studies identify subtypes in many cancers, but it is difficult to correlate these subtypes to mutational signatures. For example, a $10M sequencing study of glioblastoma found a number of mutations but they did not serve to delineate clinically useful subtypes.
Within Tumor Heterogeneity

Even more problematic than heterogeneity between patients is the large amount of intra-tumor diversity seen in sequencing and cytogenetic studies of many tumor types. Heterogeneity in tumors has a major clinical impact:

- Different subpopulations within a tumor may have varying types of response to any given treatment, making total tumor reduction and prevention of resistance difficult.
- Heterogeneity levels are associated with aggressiveness of disease (e.g., in Barrett’s esophagus and prostate cancer).
- Studies have also shown mutational heterogeneity between primary tumors and metastases in breast cancer, explaining lack of response to EFGR antibody therapy in patients that appeared to have no mutation in KRAS.
Wild type cells (type 0) give birth at rate $a_0$ and die at rate $b_0$. If we let $\lambda_0 = a_0 - b_0$, $Z_0(t)$ be the number of type-0 cells at time $t$ and suppose $Z_0(1) = 1$ then $e^{-\lambda_0 t} Z_0(t) \rightarrow W$ where

$$W \overset{d}{=} \frac{b_0}{a_0} \delta_0 + \frac{\lambda_0}{a_0} \text{exponential}(\lambda_0/a_0).$$

The first term (point mass at 0) corresponds to the process dying out.
Multitype Markovian binary branching process

\( Z_i(t) \equiv \text{Type } i \text{ cells that have exactly } i \text{ mutations at time } t \)

To simplify suppose \( Z_0(t) = V_0 e^{\lambda_0 t} \), \( V_0 \) constant.

Type \( k \) cells mutate at rate \( u_k \), creating Type \( k + 1 \) cells.

Mutations confer a random change \( \nu \) to the birth rate.

(A) \( \nu \) has a density \( g(\cdot) \) on \([0, b]\), \( g(b) > 0 \) and \( g \) is left-continuous at \( b \).

If \( \nu \) is unbounded, e.g., Weibull, growth is faster than exponential.
In early models type $i$ cells had birth rate $a_i$ and death rate $b_i$.


A consequence of this work is that there is not much difference between the two models.
Growth rate of expected value of $Z_1$

Throughout we assume (A)

$$EZ_1(t) \sim \frac{u_1V_0g(b)}{bt}e^{(\lambda_0+b)t}$$

where $a(t) \sim b(t)$ means $\lim_{t \to \infty} a(t)/b(t) = 1$.

- Mean behavior has polynomial correction (as compared to discrete mutational advances)
- Asymptotic mean behavior only depends on endpoint of density.
- Prove by establishing that contributions from mutations within $1/t$ of endpoint $b$ dominate.
Growth rate of $Z_1(t)$

Let $p \equiv b/\lambda_0$ and assume (A). Then for every $\theta > 0$

$$E \exp \left( -\theta t^{1+p} e^{-(\lambda_0+b)t} Z_1(t) \right) \to \exp \left( -u_1 V_0 c_1(\lambda_0, b) \theta^{\lambda_0/(\lambda_0+b)} \right)$$

where $c_1(\lambda_0, b)$ is

$$
g(b) \frac{(a_0 + b)^{-b/(\lambda_0+b)}}{\lambda_0} \left( \frac{\lambda_0}{\lambda_0 + b} \right)^{-b/(\lambda_0+b)} \Gamma \left( \frac{\lambda_0}{\lambda_0 + b} \right) \Gamma \left( 1 - \frac{\lambda_0}{\lambda_0 + b} \right).$$

In other words

$$t^{1+p} e^{-(\lambda_0+b)t} Z_1(t) \Rightarrow V_1.$$

Note that $EZ_1(t) \sim \frac{u_1 V_0 g(b)}{bt} e^{(\lambda_0+b)t}$, so $Z_1(t) \ll EZ_1(t)$. 
When are asymptotic approximations valid?

Parameter values: $a_0 = 0.2$, $b_0 = 0.1$, $u_1 = 10^{-3}$, $\nu$ is uniform on $[0, .01]$. At time 120 the population size is $10^5$-$10^6$ the number of cells in $(1 \, mm)^3$. 

[Diagram showing LT(θ) vs. θ with different lines and markers for exact LT at different times and limiting LT, with MC simulations indicated by black dots.]
Growth rate of Wave-\(k\) population

To study the growth rate of type-\(k\) let \(\lambda_j = \lambda_0 + jb\)

\[
k + p_k = \sum_{j=0}^{k-1} \frac{\lambda_k}{\lambda_j} \quad \text{and} \quad u_{1,k} = \prod_{j=1}^{k} u_j^{\lambda_0/\lambda_{j-1}}.
\]

If (A) holds, then for \(\theta \geq 0\)

\[
E \exp(-\theta t^{k+p_k} e^{-\lambda_k t} Z_k(t)) \to \exp(-c_k \lambda_0, b) V_0 u_{1,k} \theta^{\lambda_0/\lambda_k})
\]

and hence \(t^{k+p_k} e^{-\lambda_k t} Z_k(t) \Rightarrow V_k\).
When are asymptotic approximations valid?

Plot of the approximations to the LT of $t^2 + p^2 e^{-(\lambda_0 + 2b)t} Z_2(t)$ from Monte Carlo (MC) simulations at times $t = 80, 100, 120$ along with the asymptotic LT. Parameter values: $a_0 = 0.2$, $b_0 = 0.1$, $b = 0.01$, and $u_1 = u_2 = 10^{-3}$. $g$ is uniform on $[0,0.01]$. 

![Graph showing the LT approximations](image-url)
In this simulation, $\lambda_0 = 0.1$, $a_0 = 0.2$, $\nu \sim U([0, 0.05])$, $u = 0.001$. 
Transitions between waves

The limit result gives

\[ \log Z_k(t) \approx \lambda_k t - \sum_{j=0}^{k-1} \frac{\lambda_k}{\lambda_j} \log(1/u) + \log(V_k) \]

Dividing both sides by \( L = \log(1/u) \) and letting \( u \to 0 \)

\[ \frac{1}{L} \log^+ Z_k(t) \to \lambda_k (t - \beta_k)^+ \]

where \( \beta_k = \sum_{j=0}^{k-1} 1/\lambda_j \)
Transitions between waves

Population size $1/u$

\[ z_k(t) = \frac{1}{L} \log^+ Z_k(t) \approx \lambda_k (t - \beta_k)^+ \quad L = \log(1/u) \]
Intra-wave diversity for Wave-1

Define a 3D point process $\mathcal{M}(t)$ on $[0, t] \times [0, b] \times (0, \infty)$: Point at $(s, x, v)$ if a type-1 mutant with birth rate $a_0 + x$ is created at time $s$, and its type-1 descendants at time $t$, $Z_{s,x,v}^1(t)$ satisfies

$$e^{-(\lambda_0 + x)(t-s)} Z_{s,x,v}^1(t) \to v \text{ as } t \to \infty.$$

For $(s, x, v) \in \mathcal{M}(t)$ consider its contribution to $V_1$

$$F(s, x, v) = t^{1+p} e^{-(\lambda_0 + b)t} \cdot v e^{(\lambda_0 + x)(t-s)}.$$

Thus we expect that for large $t$,

$$t^{1+p} e^{-(\lambda_0 + b)} Z_1(t) \approx \sum_{(s,x,v) \in \mathcal{M}(t)} F(s, x, v)$$
Point process representation of $V_1$

As $t \to \infty$, $F(\mathcal{M}(t)) \Rightarrow \Lambda$, where $\Lambda$ is a Poisson process on $(0, \infty)$ with mean measure $\mu(z, \infty) = A_1(\lambda_0, b)u_1V_0z^{-\alpha}$, and $\alpha = \lambda_0/\lambda_1$. In addition, $V_1$ is the sum of the points $X_1 > X_2 > \ldots$ in $\Lambda$.

In wave-$k$, this holds for $V_k$ with $\alpha = \lambda_{k-1}/\lambda_k$.

**Flash back to stable laws.** Let $Y_1, Y_2, \ldots$ be independent and identically distributed nonnegative random variables with $P(Y_i > x) \sim cx^{-\alpha}$ where $0 < \alpha < 1$. Let $S_n = Y_1 + \cdots + Y_n$. Then

$$S_n/n^{1/\alpha} \Rightarrow W$$

where $W$ is the sum of the points in a Poisson process with mean measure $\mu(z, \infty) = cx^{-\alpha}$
Simpson’s Index

We define Simpson’s index (the probability two randomly chosen individuals are from the same family) for the point process by

\[ R = \frac{\sum_{i=1}^{\infty} X_i^2}{V_1^2} \]

The formula for \( ER \) is remarkable simple.

**Theorem.** \( ER = 1 - \alpha \) where \( \alpha = \lambda_{k-1}/\lambda_k \) for wave \( k \).

To prove this we use a result of Fuchs, Joffe and Teugels (2001) about convergence to stable laws

\[ R_n = \frac{\sum_{i=1}^{n} Y_i^2}{S_n^2} \Rightarrow R \quad \lim_{n \to \infty} ER_n = 1 - \alpha \]
Figure: Empirical distribution of Simpson’s Index for wave 1 at times $t = 70, 90, 110, 130, \infty$. Parameters: $\lambda_0 = 0.1$, $a_0 = 0.2$, $\nu \sim U([0, 0.01])$, mean is $1 - \alpha = 1/11$. 
Studied the “self-normalized sums”

\[ S_n(p) = \frac{\sum_{i=1}^{n} X_i}{(\sum_{j=1}^{n} X_j^p)^{1/p}} \equiv \frac{U_n}{V_n} \]

They proved convergence in distribution by studying the limit of \((U_n, V_n)\).

Can compute moments of the limit.

Cannot invert Fourier transform to find formula for density.

When \(p = 2\),

\[ f(x) \sim \pi^{-1}(x - 1)^{\alpha - 1} \sin(\pi \alpha) \quad \text{as} \quad x \to 1. \]

\[ \sim ae^{-bx^2} \quad \text{as} \quad x \to \infty \]
$f(\sqrt{2}) = 2.03$

$p = 2$
\[\alpha = 0.15\]
\[L = 0\]

$f(\sqrt{3}) = 0.118$
Largest Clone

Let $V_n \equiv Y_1/S_n$ be the contribution of the largest term to the sum of the first $n$ points.

Darling (1952) Theorem 5.1. As $n \to \infty$, $V_n^{-1} \Rightarrow W$ where $W$ has a density on $(1, \infty)$ with characteristic function $e^{it}/f_\alpha(t)$ where

$$f_\alpha(t) = 1 + \alpha \int_0^1 (1 - e^{itu})u^{-(\alpha+1)} du.$$ 

$EW = 1/(1 - \alpha)$ and $\text{var}(W) = 2/(1 - \alpha)^2(2 - \alpha)$.
Monte Carlo estimates for $E(1/V_n)$ and $EV_n$ plotted versus $1/(1 - \alpha)$ and $(1 - \alpha)^+$. Recall that by Jensen’s inequality $E(1/V_n) > 1/EV_n$. 

Chronic Myeloid Leukemia is a cancer of the white blood cells driven by an oncoprotein created by a chromosomal translocation that fuses the gene \textit{abl} from chromosome 9 with \textit{bcr} from chromosome 22.

CML is treated with Imatinib, a tryosine kinase inhibitor, but many point mutations in the kinase domain of \textit{bcr} – \textit{abl} confer resistance to TKIs. Approximately 13\% of patients have no major cytogenetic response to imatinib.

Dasatinib and nilotinib overcome some imatinib-resistance mutations but are associated with higher toxicity.
An Evolutionary Model of Resistance

- Sensitive CML cells pop. at time $t$: $Z_0(t) = V_0 e^{\lambda_0 t}$. Unlike earlier, $V_0$ is exponential random variable with mean $a_0/\lambda_0$. $a_0 = 0.008$, $b_0 = 0.003$, $\lambda_0 = 0.005$. Units per day.
- Resistant cells are created with probability $u = 10^{-7}$ each time a sensitive cell divides. Death rate $b_0$, Birth rate $a_0 + X$.
- Values of $X$ have equal probability and correspond to growth rates of each of the 11 most common resistant types. (Given on next slide.)

Focus on Wave-1 of mutants ($Z_1$) since parameters indicate small likelihood of $Z_2$ arising before detection.
In vivo growth rates adapted from in vitro measurements of sensitive cells and 11 resistant types (B. Skaggs, C. Sawyers)

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Birth Rate</th>
<th>Resistant to</th>
</tr>
</thead>
<tbody>
<tr>
<td>T315I</td>
<td>0.0088</td>
<td>all</td>
</tr>
<tr>
<td>E255K</td>
<td>0.0085</td>
<td>imatinib</td>
</tr>
<tr>
<td>Y253F</td>
<td>0.0082</td>
<td>imatinib</td>
</tr>
<tr>
<td>p210</td>
<td>0.008</td>
<td>type-0</td>
</tr>
<tr>
<td>E255V</td>
<td>0.0078</td>
<td>imatinib</td>
</tr>
<tr>
<td>V299L</td>
<td>0.0074</td>
<td>dasatinib</td>
</tr>
<tr>
<td>Y253H</td>
<td>0.0074</td>
<td>imatinib</td>
</tr>
<tr>
<td>M351T</td>
<td>0.0072</td>
<td>imatinib</td>
</tr>
<tr>
<td>F317L</td>
<td>0.0071</td>
<td>imatinib, dasatinib</td>
</tr>
<tr>
<td>T315A</td>
<td>0.0070</td>
<td>dasatinib</td>
</tr>
<tr>
<td>F317V</td>
<td>0.0067</td>
<td>dasatinib</td>
</tr>
<tr>
<td>L248R</td>
<td>0.0061</td>
<td>imatinib, dasatinib</td>
</tr>
</tbody>
</table>
Probability of Resistance at Diagnosis (Approx)

Time of diagnosis $\tau_M$ is time when total population is $M = 10^5$. 

$\lambda_0 = 0.005$. Probability of not dying out is $\lambda_1/a_1$ where $\lambda_1 = a_1 - 0.003$.

$Z_0(s) \sim We^{\lambda_0 s}$ so expected total births before reaching $M$ conditional on the 0’s not becoming extinct

$$E \int_0^{\tau_M} Z_0(s) \, ds \approx \int_0^\infty Me^{-\lambda_0 s} \, ds = M/\lambda_0 = 2 \times 10^7$$

$u_1 = 10^{-7}$. Expected number of mutations that do not die out is

$$2 \times 10^7 \cdot 10^{-7} \cdot a_1 \cdot \lambda_1/a_1 = 2(a_1 - 0.003)$$

Answers range from 0.0116 to 0.0062
Probability of Resistance at Diagnosis (Exact)

Using the probability that the mutation is present at time $T_M$ given that it is occurred at time $T_M - s$ and integrating over $s$, gives a more exact answer.
The discrepancy between the two calculations is due to the fact that when present most mutants are rare.
Evaluating benefits of combination therapy

Benefits of combination therapy significantly greater for patients with late detection.
Acknowledgement

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Figure: Jasmine, Kevin, John, Franziska