Branching Process Models of Cancer

Rick Durrett

...

A report on joint work

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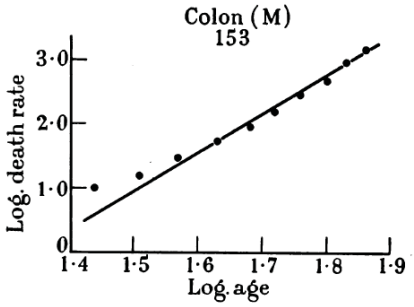
Stan Ulam once said:

"I have sunk so low that my last paper contained numbers with decimal points."

Figure: Feynman, Ulam, von Neumann

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.



Multi-stage theory of carcinogenesis

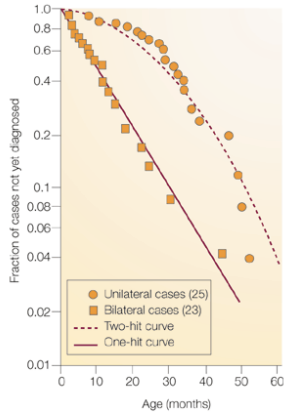
Armitage and Doll (1954) use the observation that the slopes were 5.18 in men and 4.97 in women to argue that colon cancer is a six stage process. The math was very simple

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

$$u_1 \cdots u_k \frac{t^{k-1}}{(k-1)!} \qquad \text{as } t \to 0$$

Incidence of Retinoblastoma

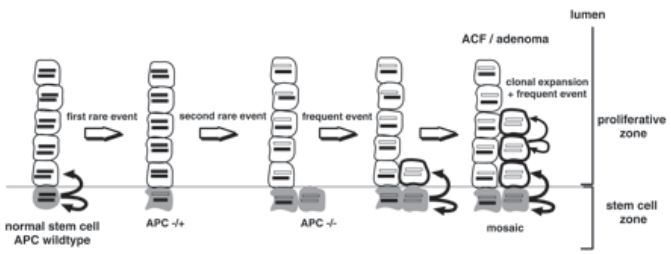
Knudson's two hit hypothesis → tumor-suppressor genes



Nature Reviews | Cancer

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 are inactivation of the tumor suppressor gene *APC* adenomatous polyposis coli.
- KRAS is an **oncogene** (one mutation turns it on). 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 *TP*53 the gene which makes $p53$. Mutant p53 can no longer bind DNA in an effective way, and as a consequence the p21 protein whose production it stimulates is not made available to act as the 'stop signal' for cell division.

Multitype Markovian binary branching process

$Z_i(t) \equiv$ is the number of type i cells

Type i cell give birth at rate a_i and die at rate b_i.

Yes we have deaths at rate b.

Type i cells produce offspring of type $i+1$ at rate u_{i+1}.

Type 0's are a branching process

Birth at rate a_0, death at rate b_0, $\lambda_0 = a_0 - b_0$.

$$P(Z_0(t) = 0 \text{ for some } t \geq 0) = b_0/a_0$$

As $t \to \infty$, $e^{-\lambda_0 t} Z_0(t) \to W_0$ a.s.

$$W_0 =_d \frac{b_0}{a_0}\delta_0 + \frac{\lambda_0}{a_0}\,\text{exponential}(\lambda_0/a_0)$$

exponential(r) has density re^{-rt}, mean $1/r$.

If we condition on nonextinction the limit is exponential(λ_0/a_0).

Type 1's: Durrett and Moseley (2009)

For simplicity suppose V_0 is a constant

$$EZ_1(t) = \int_0^t V_0 e^{\lambda_0 s} u_1 e^{\lambda_1 (t-s)}\, ds$$

Theorem. *As $t \to \infty$, $e^{-\lambda_1 t} Z_1^*(t) \to W_1$ a.s. with*

$$EW_1 = \frac{V_0 u_1}{\lambda_1 - \lambda_0}$$

This overestimates $Z_1(t)$ because the dominant contribution to the integral comes from s near 0, where mutations are rare but have a huge effect.

A better approach

Let $Z_1^*(t)$ be the number of 1's when $Z_0^*(t) = V_0 e^{\lambda_0 t}$, $t \in (-\infty, \infty)$. The expected number of mutations at times ≤ 0 is $V_0 u_1/\lambda_0$ which is small for typical values $u_1 = 10^{-5}$, $s = 0.02$.

Theorem. *As $t \to \infty$, $e^{-\lambda_1 t} Z_1^*(t) \to V_1$ a.s. with*

$$E(\exp(-\theta V_1)|V_0) = \exp(-c_{h,1} u_1 V_0 \theta^{\alpha_1})$$

and $\alpha_1 = \lambda_0/\lambda_1$. $(V_1|V_0)$ is one sided stable law with index $\alpha_1 \in (0,1)$.

$P(V_1 > x) \sim cx^{-\alpha_1}$ so $EV_1 = \infty$.

Growth rate of type k's

Suppose $Z_0^*(t) = V_0 e^{\lambda_0 t}$ for $t \in (-\infty, \infty)$ where V_0 is exponential(λ_0/a_0).

$$e^{-\lambda_k t} Z_k^*(t) \to V_k \quad \text{a.s.}$$

Let $\mathcal{F}_\infty^{k-1}$ be the σ-field generated by $Z_j^*(t)$, $j \leq k-1$, $t \geq 0$.

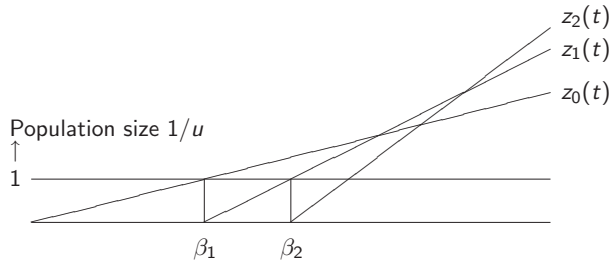
$$E(e^{-\theta V_k}|\mathcal{F}_\infty^{k-1}) = \exp(-c_{h,k} u_k V_{k-1} \theta^{\alpha_k})$$

where $\alpha_k = \lambda_{k-1}/\lambda_k$ and hence $Ee^{-\theta V_k} = \left(1 + c_{\theta,k}\mu_k \theta^{\lambda_0/\lambda_k}\right)^{-1}$.

$$c_{h,k} = \frac{1}{a_k}\left(\frac{a_k}{\lambda_k}\right)^{\alpha_k} \Gamma(\alpha_k)\Gamma(1-\alpha_k)$$

$c_{\theta,k} = c_{\theta,k-1} c_{h,k}^{\lambda_0/\lambda_{k-1}}$, $c_{\theta,0} = a_0/\lambda_0$ and $\mu_k = \prod_{j=1}^k u_j^{\lambda_0/\lambda_{j-1}}$.

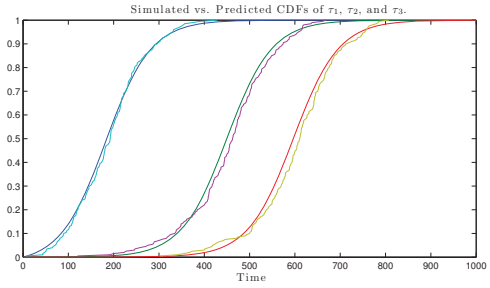
Transitions between waves



$$z_k(t) = \frac{1}{L}\log^+ Z_k(t) \approx \lambda_k(t-\beta_k)^+ \quad L = \log(1/u) \quad \beta_k = \sum_{j=0}^{k-1} 1/\lambda_j$$

$\tau_k = \min\{t : Z_k(t) > 0\}$

$$P(\tau_k > t_{1/2}^k + x/\lambda_0) \to \frac{1}{1+e^x}$$

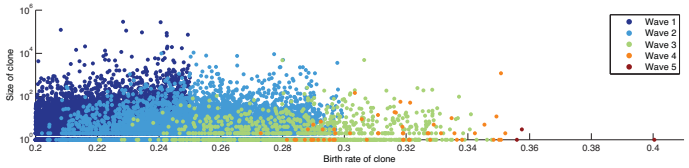


Within Tumor Heterogeneity

Problems in cancer treatment caused by intra-tumor diversity:

- 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.

Intra-tumor diversity generated by model



In this simulation, $b_i = 0.1$, $a_0 = 0.2$, $a_i - a_{i-1} \sim U([0, 0.05])$, $u = 0.001$.

Point process representation of V_1

$Z_0(t) = V_0 e^{\lambda_0 t}$, V_0 nonrandom.

Define a two dimensional point process $\mathcal{X}_t$ with a point at (s, w) if there was a mutation to type 1 at time s and the resulting type 1 branching process $\tilde{Z}_1(t)$ has $e^{-\lambda_1(t-s)}\tilde{Z}_1(t) \to w$.

A point at (s, w) contributes $e^{-\lambda_1 s} w$ to $V_1 = \lim_{t\to\infty} e^{-\lambda_1 t} Z_1(t)$.

$V_1 = \sum_{(s,w)\in\mathcal{X}_t} e^{-\lambda_1 s} w$, the sum of points in a Poisson point process with mean measure $\mu(z, \infty) = A_1 u_1 V_0 z^{-\alpha}$ where $\alpha = \lambda_0/\lambda_1$.

True for $(V_k | \mathcal{F}_\infty^{k-1})$ 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 $P(Y_i > x) \sim cx^{-\alpha}$ with $0 < \alpha < 1$. Let $S_n = Y_1 + \cdots + Y_n$. Then

$$S_n/n^{1/\alpha} \to V$$

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

Simpson's index

We define Simpson's index to be the probability two randomly chosen individuals in wave k are descended from the same mutation.

$$R_2 = \sum_{i=1}^{\infty} \frac{X_i^2}{V_k^2}$$

where $X_1 > X_2 > \ldots$ are points in the Poisson process and V_k is the sum. In genetics this is the homozygosity.

Theorem. $ER_2 = 1 - \alpha$ where $\alpha = \lambda_{k-1}/\lambda_k$ for wave k.

Proof. Apply results of Fuchs, Joffe and Teugels (2001) about convergence to stable laws. ER does not depend on V_{k-1}.

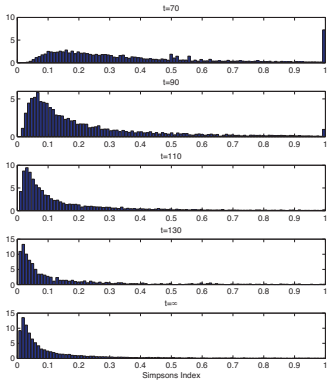


Figure: Empirical distribution of Simpson's Index for wave 1 at times $t = 70, 90, 110, 130, \infty$. Parameters: $b_i = 0.1$, $a_0 = 0.2$, $a_i - a_{i-1} \sim U([0, 0.01])$, mean is $1 - \alpha = 1/11$.

Poisson-Dirichlet Distribution(α,0)

The points $Y_i = X_i/V_k$ have this famous distribution introduced by Kingman (1975) *J. Roy. Stat. Soc. B.* 37, 1-22 and which has been extensively studied, see 75 references in Pitman and Yor *Ann. Prob.* 25 (1997), 855–900 and Pitman's 2006 book *Combinatorial Stochastic Processes*.

$$E\sum_{i=1}^{\infty} f(Y_i) = \frac{1}{\Gamma(\alpha)\Gamma(1-\alpha)} \int_0^1 f(u) u^{-\alpha-1}(1-u)^{\alpha-1}\, du$$

we find that $R_p = \sum_i X_i^p / V_k^p$ has

$$ER_p = E\sum_i Y_i^p = \frac{\Gamma(p-\alpha)}{\Gamma(1-\alpha)\Gamma(p)}$$

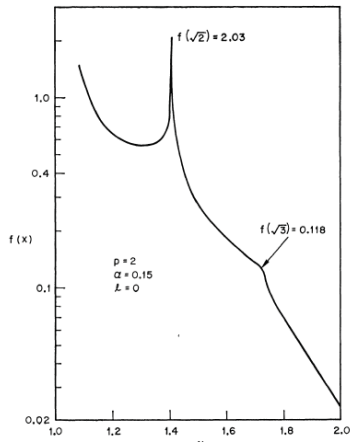
which is $1 - \alpha$ when $p = 2$.

Logan, Mallows, Rice and Shepp (1973)

Consider the "self-normalized sums"

$$S_n(p) = \frac{\sum_{i=1}^n X_i}{(\sum_{j=1}^n X_j^p)^{1/p}} \qquad S_n(2) = R_n^{-1/2}$$

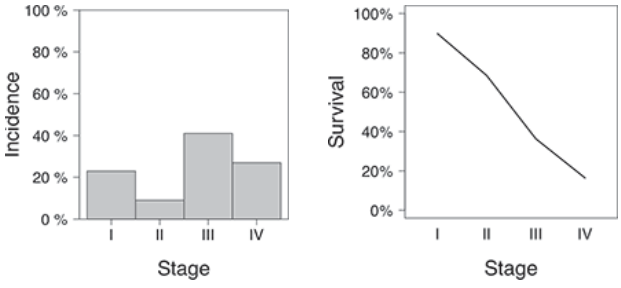
They proved convergence in distribution and identified the Fourier transform of the limit.



Ovarian Cancer

Ovarian cancer is the fifth leading cause of cancer death among women in the United States.

21,800 new cases and 13,850 deaths in 2010.



Can screening reduce mortality?

In the June 8, 2011 issue of the JAMA, results were published of a study of 78,216 women aged 55–74. Screening used tests for the bio-marker *CA*125 (cancer antigen) and transvaginal ultrasound.

	n	diagnosed	death
annual screening	39,105	212	118
routine care	39,111	176	100

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routine care	39,111	176	100

3,285 women in the screening group had false positive results, 1080 had surgery and 163 had serious complications from surgery.

Multitype model

Lengyel (2010) Am. J. Pathology 177, 1053–1064

An epidermal to mesenchymal transition in the tumor allows its cells to detach. Cells float in the peritoneal fluid as single cells or small groups. Some cells adhere to the omentum, followed by invasion of the extracellular matrix, angiogenesis etc. There are no significant genetic differences between the main tumor and metastases indicating that no additional mutations are needed beyond those that created the initial tumor.

type 0 = primary tumor, type 1 = cells in peritoneal fluid, type 2 = metastasis. u_i = rate at which cells change from type $i-1$ to type i.

Brown and Palmer (2009) PLoS Medecine Vol. 6, Issue 7, e1000114

$\lambda_0 = (\ln 2)/4$, $\lambda_2 = (\ln 2)/2.5$ per month, $\lambda_1 < \lambda_0$ u_i =?

Brown and Palmers' parameter estimation

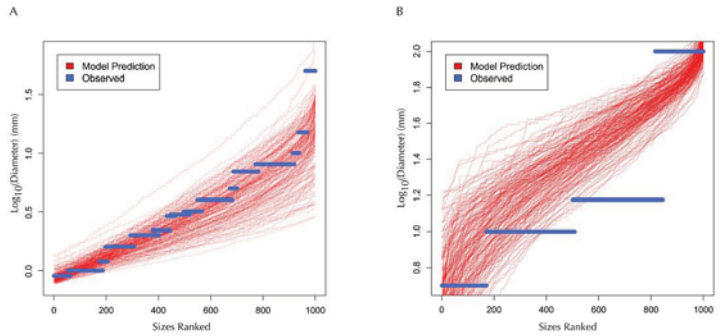


Figure: A. Growth in stages I and II, B. Stages III and IV, versus 625 parameter combinations

Type 0

Type 0's are a branching process. $Z_0(t) \sim W_0 e^{\lambda_0 t}$

$$W_0 =_d \frac{b_0}{a_0}\delta_0 + \frac{\lambda_0}{a_0}\,\text{exponential}(\lambda_0/a_0)$$

exponential(r) has density re^{-rt}, mean $1/r$.

Condition on not dying out and $Z_0(t) \sim V_0 e^{\lambda_0 t}$, $V_0 =$ exponential(λ_0/a_0).

Time t since original mutation is not observable so we simplify.

Assume $Z_0(t) = e^{\lambda_0 t}$.

Type 1

Type 1's leave from the surface of the primary tumor at rate u_1 times the surface area.

$$\begin{aligned} EZ_1(t) &= \int_0^t u_1 e^{2\lambda_0 s/3} e^{\lambda_1 (t-s)}\, ds \\ &= \frac{u_1}{(2\lambda_0/3) - \lambda_1}\left(e^{2\lambda_0 t/3} - e^{\lambda_1 t}\right) \end{aligned}$$

Let $\gamma_1 = 2\lambda_0/3$. To remove the unknown rate λ_1, we set $\lambda_1 = 0$. Dominant contribution comes from times near t. Many mutations so result is deterministic.

Theorem. $Z_1(t)/EZ_1(t) \to 1$ in probability as $t \to \infty$.

Type 2 Asymptotics

At time s mutations occur to type 2 at rate $u_2(u_1/\gamma_1)e^{\gamma_1 s}$ so we let

$$s_2 = \frac{1}{\gamma_1}\log\left(\frac{\gamma_1}{u_1 u_2}\right)$$

be the time at which the mutation rate is 1.

Theorem *$e^{-\lambda_2(t-s_2)}Z_2(t) \to V_2$ where V_2 is the sum of points in a Poisson process with mean measure $\mu(x,\infty) = C_2 x^{-\alpha_2}$ where $\alpha_2 = \gamma_1/\lambda_2$,*

$$C_2 = \frac{1}{a_2}\left(\frac{a_2}{\lambda_2}\right)^{\alpha_2}\Gamma(\alpha_2)$$

and $\Gamma(r) = \int_0^\infty t^{r-1}e^{-t}\,dt$ is the usual gamma function.

What is the detection window?

A commonly quoted fact is that $1\text{cm}^3 = 10^9$ cells.
We define the window of opportunity for detection to be $[T_0, T_2]$ where

$$T_0 = \inf\{t : Z_0(t) = 6.5\times 10^7\}, \quad \text{diameter 0.5 cm}$$
$$T_2 = \inf\{t : m_2(t) > 10^9\}. \quad \text{one gram}$$

Recall $\lambda_0 = (\log 2)/4 = 0.1733$ and $\lambda_2 = (\log 2)/2.5 = 0.2772$. Setting

$$e^{0.1733 T_0} = 6.5\times 10^7 \quad \text{gives} \quad T_0 = \frac{1}{0.1733}\log(6.5\times 10^7) = 103.8$$

months or 8.65 years.

$T_0 = 103.8$. To make a crude calculation note that the first mutation to type 2 occurs at time

$$s_2 = \frac{1}{\gamma_1}\log\left(\frac{\gamma_1}{u_1 u_2}\right)$$

From this point for the 2's to grow to size 10^9.it will take time roughly

$$\frac{1}{\lambda_2}\log(10^9) = 74.76 \quad \text{months}$$

If we let $u_1 u_2 = 10^{-4}$ and note $\gamma_1 = 0.1155$ then

$$s_2 = \frac{1}{.1155}\log(1115) = 61.05$$

so $T_2 = 7476 + 61.05 = 138.51$ months, and $T_2 - T_0 = 32$ months or 2.66 years.

Need to do screening every one or two years.

Size of the Primary at $T_1 = \inf\{t : Z_1(t) > 10^9\}$

In the previous calculations we ignored the fact that $Z_1(t) \sim V_1 e^{-\lambda_1 t}$.

$$T_1 = \frac{1}{\lambda_1}\ln(10^9/V_1)$$

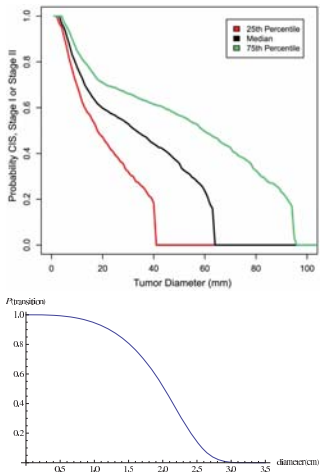
At this time

$$Z_0(T_1) = \exp(\lambda_0 T_1) = (10^9 V_1)^\alpha \quad \alpha = \lambda_0/\lambda_1$$

Brockwell and Brown (1978) ZfW (aka PTRF), $V_1^{-\alpha}$ has density

$$\sum_{k=0}^{\infty}\frac{(-x)^k}{\Gamma(k+1)\Gamma(1-\alpha-\alpha k)}$$

Probability of Progression vs. Size



Summary

Growth, progression, and metastasis of cancer can be modeled with multi-type branching processes, and these models can be used to evaluate screening strategies and treatment regimens.

Results about stable laws can be used to obtain quantitative results about tumor heterogeneity and other quantities of interest, which in contrast to simulation, reveal the dependence on underlying parameters.