Probability models for cancer development and progression

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Armitage and Doll (1954)

log-log plots of incidence versus age

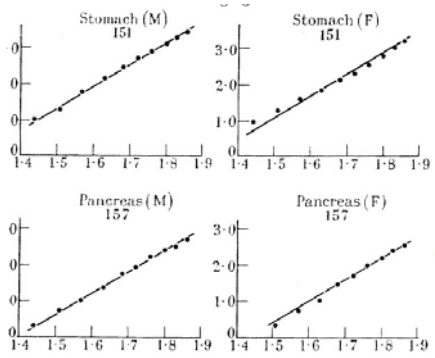


Figure: Slopes Stomach: 5.91 M, 5.27 F; Pancreas M 5.76, F 6.48

Why a power law?

If mutations from stage $i-1$ to stage i occur at rate u_i, the probability density of reaching stage k at time t is

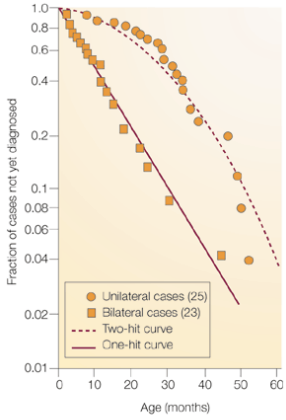
$$\approx u_1 u_2 \cdots u_k \frac{t^{k-1}}{(k-1)!}$$

so the slope is the number of stages -1.

Slopes Stomach: 5.91 M, 5.27 F; Pancreas M 5.76, F 6.48

Incidence of Retinoblastoma

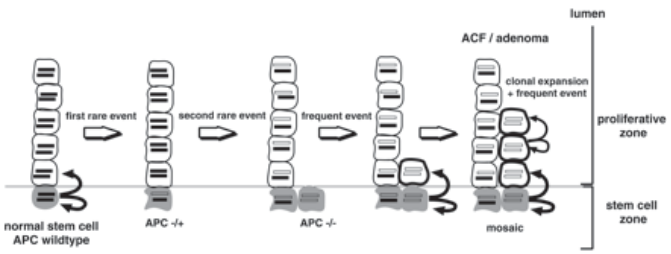
Knudson's two hit hypothesis



Nature Reviews | Cancer

Progression to Colon Cancer

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



The Problem

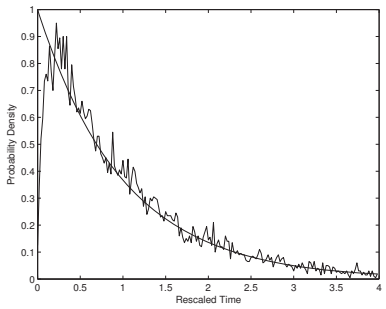
Given a population of size N, how long does it take until τ_k the first time we have an individual with a prespecified sequence of k mutations?

- Initially all individuals are type 0.
- Each individual is subject to replacement at rate 1.
- A copy is made of an individual chosen at random from the population.
- Type $j-1$ mutates to type j at rate u_j.

Theorem. If $Nu_1 \to 0$ and $N\sqrt{u_2} \to \infty$

$$P(\tau_2 > t/Nu_1\sqrt{u_2}) \to e^{-t}$$

10,000 simulations of $n = 10^3$, $u_1 = 10^{-4}$, $\sqrt{u_2} = 10^{-2}$



Idea of Proof

Since 1's mutate to 2's at rate u_2, τ_2 will occur when there have been $O(1/u_2)$ births of individuals of type 1.

The number of 1's is roughly a (time change of) symmetric random walk, so τ_2 will occur when the number of 1's reaches $O(1/\sqrt{u_2})$.

$N \gg 1/\sqrt{u_2}$ guarantees that up to τ_2 the number of 1's is $o(N)$, so 1 mutations occur at rate Nu_1, and 1's that have 2 descendants occur at rate $Nu_1\sqrt{u_2}$

The waiting time from the 1 mutation until the 2 mutant appears is of order $1/\sqrt{u_2}$. For this to be much smaller than the overall waiting time $1/Nu_1\sqrt{u_2}$ we need $Nu_1 \ll 1$.

Waiting for k mutations

Total progeny of a critical binary branching process has $P(\xi > k) \sim Ck^{-1/2}$, so the sum of M such random variables is $O(M^2)$.

To get 1 individual of type 4, we need of order

$1/u_4$ births of type 3.

$1/\sqrt{u_4}$ mutations to type 3.

$1/u_3\sqrt{u_4}$ births of type 2.

$1/u_3^{1/2}u_4^{1/4}$ mutations to type 2.

$1/u_2u_3^{1/2}u_4^{1/4}$ births of type 1.

$1/u_2^{1/2}u_3^{1/4}u_4^{1/8}$ mutations to type 1.

Durrett, Schmidt, and Schweinsberg

Probability type j has a type k descendant.

$$\sim r_{j,k} = u_{j+1}^{1/2}u_{j+2}^{1/4}\cdots u_k^{1/2^{k-j}} \quad \text{for } 1 \le j < k$$

Theorem. Let $k \ge 2$. Suppose that:
(i) $Nu_1 \to 0$.
(ii) For $j = 1, \ldots, k-1$, $u_{j+1}/u_j > b_j$ for all N.
(iii) There is an $a > 0$ so that $N^a u_k \to 0$.
(iv) $Nr_{1,k} \to \infty$.
Then for all $t > 0$, $\lim_{N\to\infty} P(\tau_k > t/Nu_1r_{1,k}) = \exp(-t)$.

Small time behavior

Most cancers occur in less than 1% of the population so we are looking at the lower tail of the distribution. Let $g_k(t) = Q_1(\tau_k \le t)$ where Q_1 is the probability for the branching process started with one type 1. In the case $u_j \equiv \mu$

$$g_j'(t) = \mu g_{j-1}(t) - (1-\mu)g_j(t)^2 - 2\mu g_j(t)$$

One can inductively solve the differential equations and finds

If $t \ll \mu^{-1/2}$ then $g_k(t) \approx \mu^{k-1}t^{k-1}/(k-1)!$

Schweinsberg (2008) *Electronic J. Probab.* 13, 1442–1478

Exponentially growing population, 1

Joint work with Stephen Moseley.

Some chronic myeloid leukemia patients show resistance to imatinib at diagnosis, and many others develop resistance during the first year of treatment. Iwasa, Nowak, and Michor (2006) and Haeno, Iwassa, Michor (2007), both in Genetics.

Model is a multi-type branching process in which type i cells have $i \ge 0$ mutations.

Type i cells give birth at rate a_i and die at rate b_i.
$\lambda_i = a_i - b_i$ increases in i.

Type i's mutate at rate u_{i+1} becoming type $i+1$.

Math questions

Compute the distribution of τ_k be the time of the occurrence of the first type k. $k = 1, 2$ most relevant to development of immunity.

Let $Z_k(t)$ be the number of type k cells at time t. Find the limiting behavior of $e^{-\lambda_k t} Z_k(t)$.

$$P(\tau_1 > t | Z_0(s), s \le t, \Omega_\infty^0) = \exp\left(-u_1 \int_0^t Z_0(s) ds\right)$$

$(e^{-\lambda_0 s} Z_0(s) | \Omega_\infty^0) \to V_0 = \text{exponential}(\lambda_0/a_0)$ so

$$P(\tau_1 > t | \Omega_\infty^0) \approx E \exp\left(-u_1 V_0 e^{\lambda_0 t}/\lambda_0\right)$$
$$= \frac{\lambda_0}{\lambda_0 + a_0 u_1 e^{\lambda_0 t}/\lambda_0}$$

Growth of the 1's

$(Z_t^0, Z_t^1, \ldots Z_t^k)$ is a decomposable Galton-Watson process, which Kesten and Stigum studied in discrete time.

For any $k \ge 1$

$$M_t^k = e^{-\lambda_k t} Z_k(t) - \int_0^t u_k e^{-\lambda_k s} Z_{k-1}(s)\, ds \text{ is a martingale}$$

Show that M_t^1 is L^2 bounded and conclude

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

$$EW_1 = u_1/(\lambda_1 - \lambda_0).$$

W_1 has a power law tail

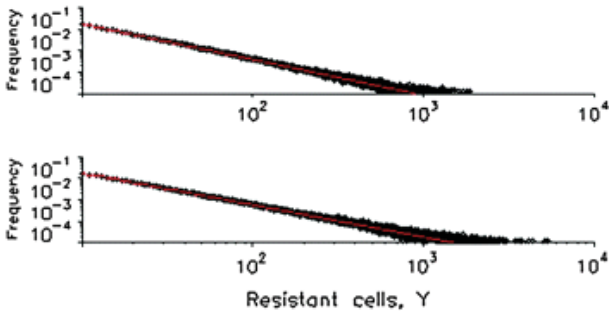


Figure: Simulated distribution

Proof of power law tail

Let $Z_i^*(t)$ be the number of type-i's at time t in a system with $Z_0^*(t) = e^{\lambda_0 t} V_0$ for all $t \in (-\infty, \infty)$.

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

$$Ee^{-\theta V_1} = 1/(1 + u_1 c_{\theta,1} \theta^{\lambda_0/\lambda_1})$$

and hence

$$P(V_1 > x) \sim c_{V,1} x^{-\lambda_0/\lambda_1}$$

Actually W_1 does not have a power law tail but $P(W_1 \neq V_1) = u_1 a_0/\lambda_0^2$ is small.

Results from Sjoblom et al (2006): 35 tumors

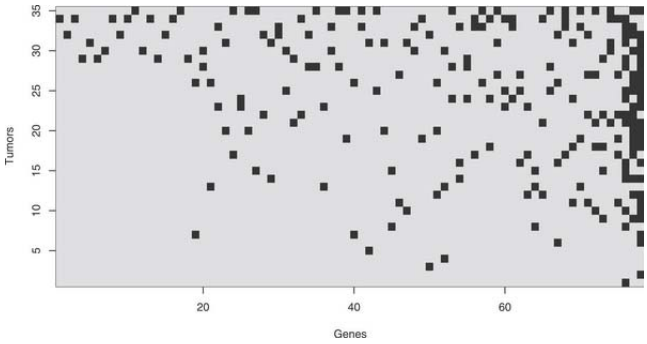
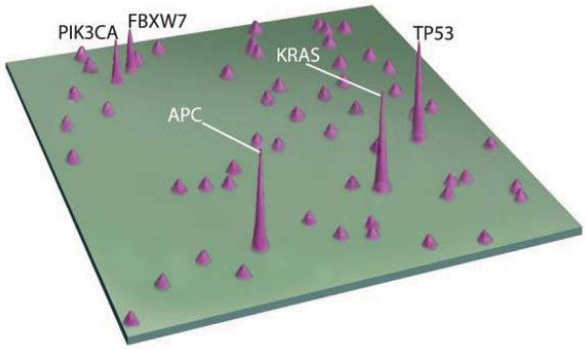


Figure: Last three columns: APC (24), p53 (17), K-ras (16)

Results from Wood et al. (2007) Science



Flawed Methodology?

Wood et al. (2007): 40 of the top 119 genes, selected based on the pathways in which they occur, were chosen for further sequencing.

15 of the 40 genes (38%) were not mutated in any of the 96 tumors studied.

False Discovery Rate of 10 % ??

Exponentially growing population, 2

Joint work with John Mayberry

In some cancers, e.g., colon cancer, an early stage is the growth of a "benign tumor," before progression to malignancy.

Genetic Progression and the Waiting Time to Cancer

Niko Beerenwinkel, Tibor Antal, David Dingli, Arne Traulsen, Kenneth W. Kinzler, Victor E. Velculescu, Bert Vogelstein, Martin A. Nowak

PLoS Computational Biology 3 (2007) e225

Wright-Fisher model in exponentially growing population. Cells with k mutations have relative fitness $(1+\gamma)^k$.

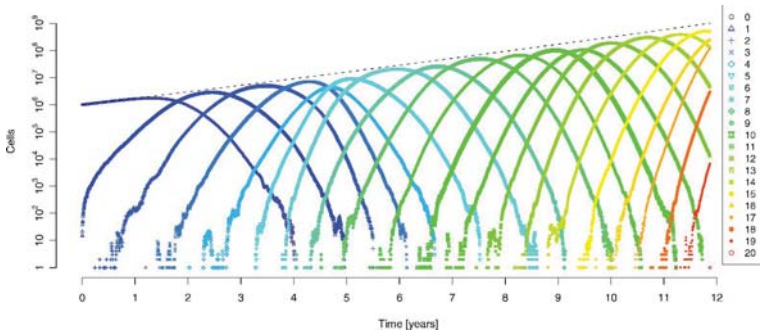


Figure: Simulation from Beerenwinkel et al.

Populations of fixed size

Theorem. Suppose that $X_0(0) = N$ and $N = \mu^{-\alpha}$ for some $\alpha > 1$. Let $L = \log(1/\mu)$. As $\mu \to 0$,

$$Y_k^N(t) \equiv \frac{1}{L}\log^+(X_k(Lt/\gamma)) \to y_k(t)$$

uniformly on compact subsets of $(0,\infty)$.

The limit $y_k(t)$ is deterministic and piecewise linear. In applications γ is small, e.g., 0.01, and the limit process is almost independent of γ.

Inductive definition

Suppose we have defined the timit to time s_n.

Let $m = \max\{j : y_j(s_n) = \alpha\}$. Suppose that

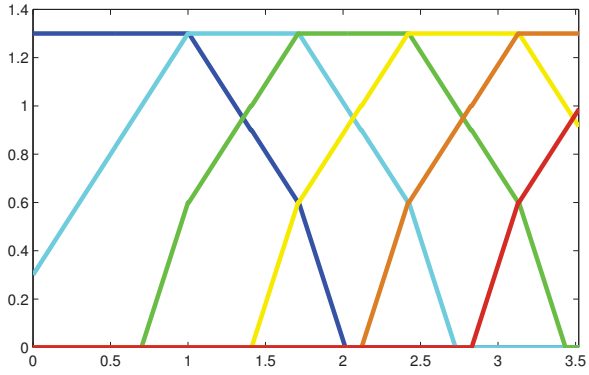
(i) $y_j(s_n) = 0$ for $j > k$, $y_j(s_n) > 0$ for $m < j \le k$,

(ii) $y_{j+1}(s_n) \ge y_j(s_n) - 1$

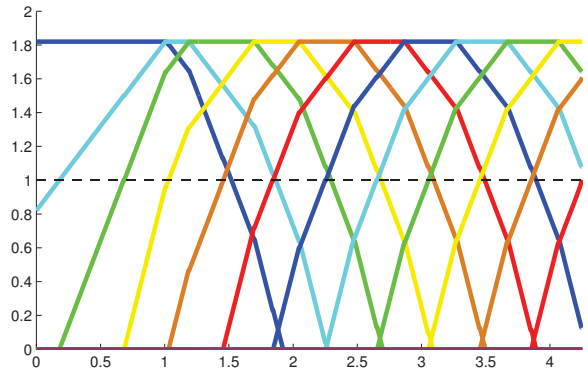
Let $K = k$ if $y_k(s_n) < 1$, and $K = k+1$ if $y_k(s_n) = 1$.
$\gamma_m = (1+\gamma)^m - 1$. Then for $t \le \Delta_n$

$$y_j(s_n + t) = \begin{cases} (y_j(s_n) + t\gamma_{j-m}/\gamma)^+ & j < m \\ y_j(s_n) + t\gamma_{j-m}/\gamma & m \le j \le K \\ 0 & j > K \end{cases}.$$

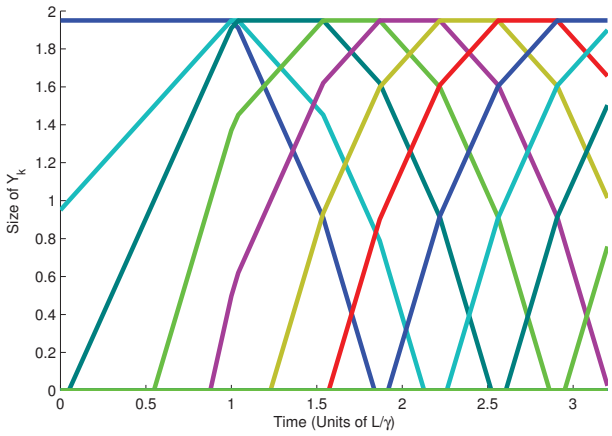
First regime $\alpha \in (1, 3/2)$. Limit when $\alpha = 1.3$



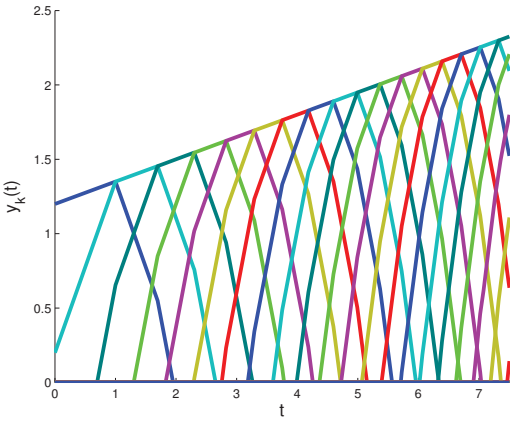
Second regime $\alpha \in (3/2, 11/6)$. Limit for $\alpha = 1.82$



Third regime $\alpha \in (11/6, 25/12)$. Limit for $\alpha = 1.95$



Exponentially growing population



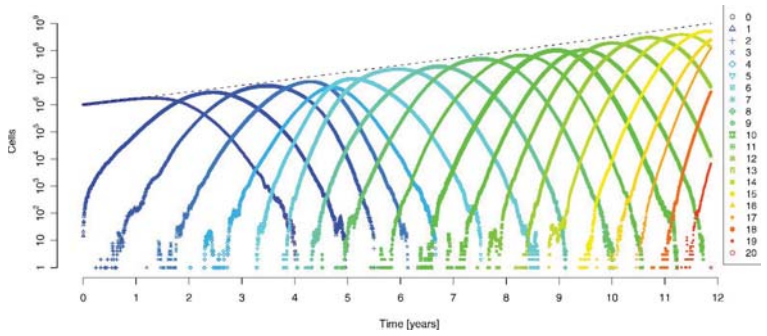


Figure: Simulation from Beerenwinkel et al.