Stochastic dynamics of cancer initiation

Jasmine Foo

Dana-Farber Cancer Institute
Harvard School of Public Health
Department of Biostatistics and Computational Biology

June 4, 2011

Cancer initiation: an evolutionary perspective

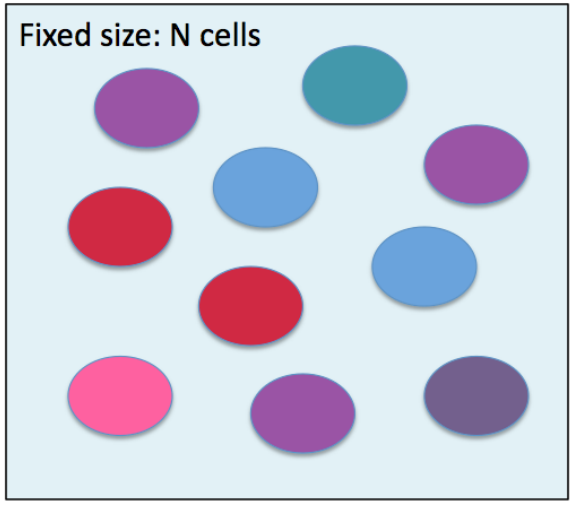
- Tissues of multi-cellular organisms are organized into morphologically stable compartments or niches.
- In healthy tissues, compartment sizes are stabilized by homeostatic mechanisms.
- Genetic/epigenetic alterations may arise during cellular replication within a compartment. These alterations may sometimes confer a change in cellular fitness.
- If a cell evolves a sufficiently aggressive phenotype, it can escape from homeostatic control mechanisms and initiate clonal expansion.
- Interesting questions: How does initiation occur? with what probability? when? What are the characteristics of the initiating cell? (e.g. genetic characteristics, mutations accumulated)

Overview of the mathematical model

- Within a single compartment, cells at risk of accumulating oncogenic mutations proliferate and die according to a stochastic process.
- Cells may accumulate mutations, conferring random changes in fitness during proliferation.
- Clonal expansion initiates when a cell gains fitness sufficiently high to escape from homeostatic mechanisms of the compartment.
- We consider a ‘race’ between a process governing the reproductive fitness of cells in the compartment and an aging process.

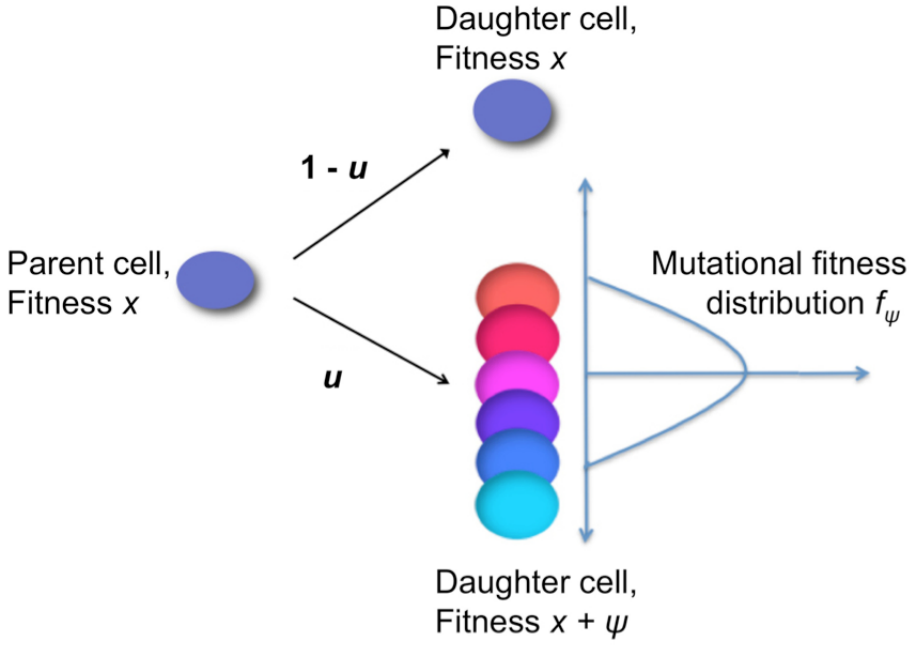
Dynamics in fitness space

Cells proliferate according to a multi-type Moran process with random mutational background.



Cells reproduce proportional to fitness, die at random.

Fitness ranges in [1 -1/N, 1 + 1/N] (cutoffs for neutral evolution).



Mutation kernel $M(x, y) = f_\psi^x(y - x)$

Cumulative fitness-based initiation

We model initiation as a consequence of an *accumulated* effect of fitness changes conferred by (epi)genetic alterations during a lifetime.

Initially, all cells in a compartment have normalized fitness 1. Initiation occurs when any cell acquires a fitness of greater than 1 + 1/N.

A simplification:

- Homogenization time is shorter than time to produce new mutants: $P(T_{mut} < T_{hom}) \leq 3Nu(\log N + \gamma)$.
- Thus we study the process Z which tracks the fitness of the homogenized compartment over time. Z has an intensity matrix:

$$Q(x, y) = Nu\rho_{x,y}M(x, y)$$

  where $\rho_{x,y}$ is fixation probability of a mutant with fitness y in a compartment of fitness x.
- An egalitarian view: there are many paths to initiation

Dynamics in aging space

We use US population mortality data to construct a calibrated Markov process in an aging dimension.

Process is tuned to fit distribution of time until absorption (at death) with mortality statistics in the population of interest.

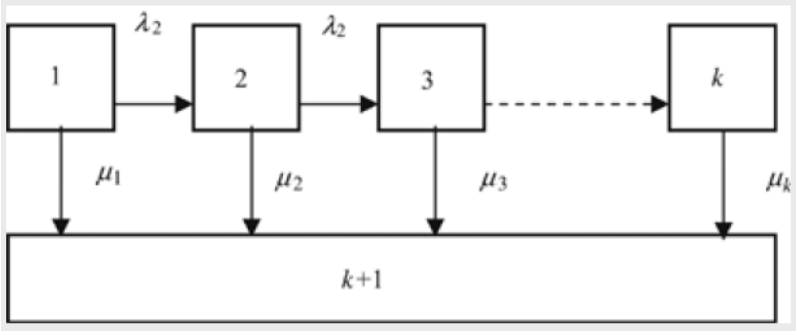
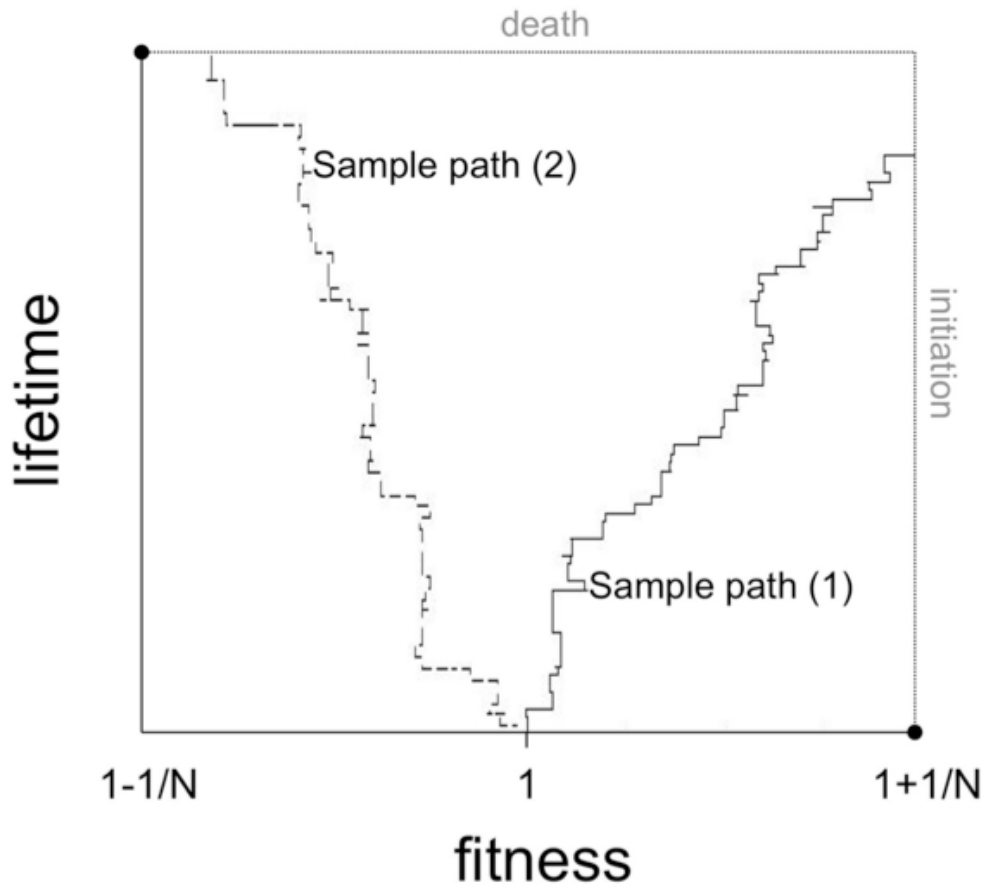


Figure: Coxian process

We construct a Coxian process L that governs dynamics in the aging dimension. The process L has intensity matrix S.

Paths to initiation of clonal expansion



The conditioned process

We can derive equations for the probability of initiation prior to death starting from state (x, r) for general mutation kernel M:

$$I(x,r) = \sum_y I(y,r)\frac{Nu\rho_{x,y}M(x,y)}{-Q(x,x)-S} + \sum_s I(x,s)\frac{S}{-Q(x,x)-S}$$

Using the result I, we can then derive properties of the process conditioned on initiating before death, such as:

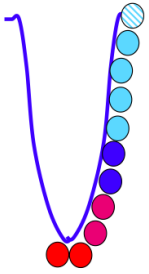
- Waiting time until initiation
- Number of passenger (neutral) mutations in the initiating cell
- Number of advantageous/disadvantageous mutations in the initiating cell

Application to colorectal cancer

Colonic tumors arise from the rapidly proliferating epithelium of the colon.

- Epithelium organized into approx 10^7 crypts.
- Each crypt contains 4-10 stem cells, residing at the base.
- Adenomatous polyps (benign growths) observed in approximately 50% of people above age 70 (Kinzler, Vogelstein 2002).
- Define initiation probability from a single crypt to be p_i.

  If $p_i \sim 10^{-6}$, probability of having at least one initiated crypt before death is ~ 1.



Application to colorectal cancer

We consider a crypt of $N = 10$ stem cells, with overall mutation rate $u = 0.001$ per cell division.

Mutational fitness distributions from a parametrized family of functions (algebraic decay rate controlled by shape parameters α and β).

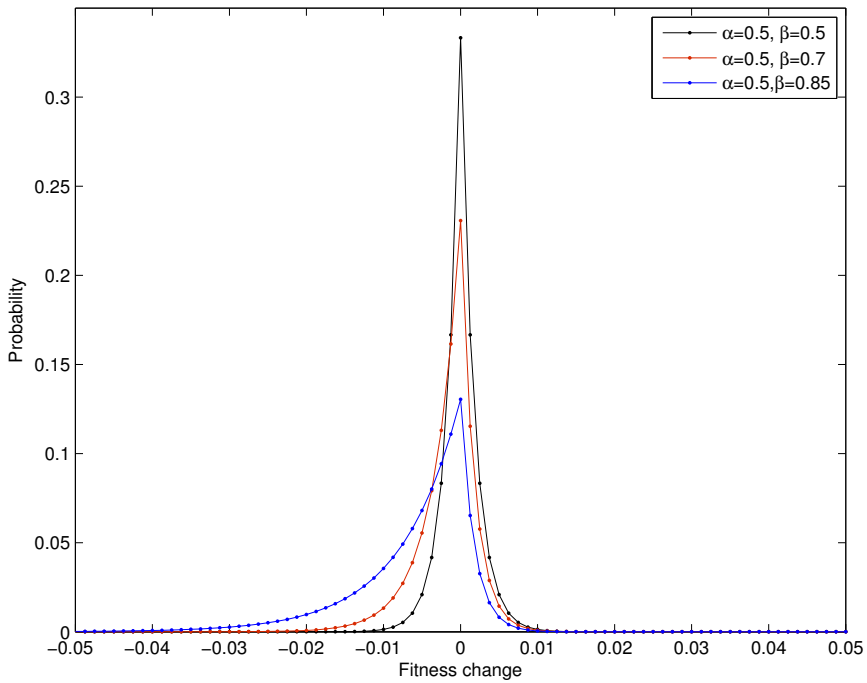
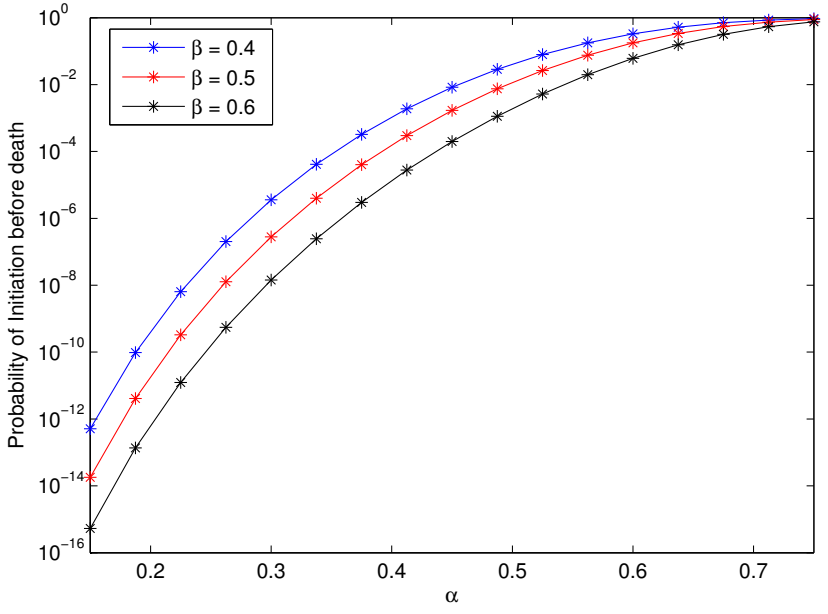


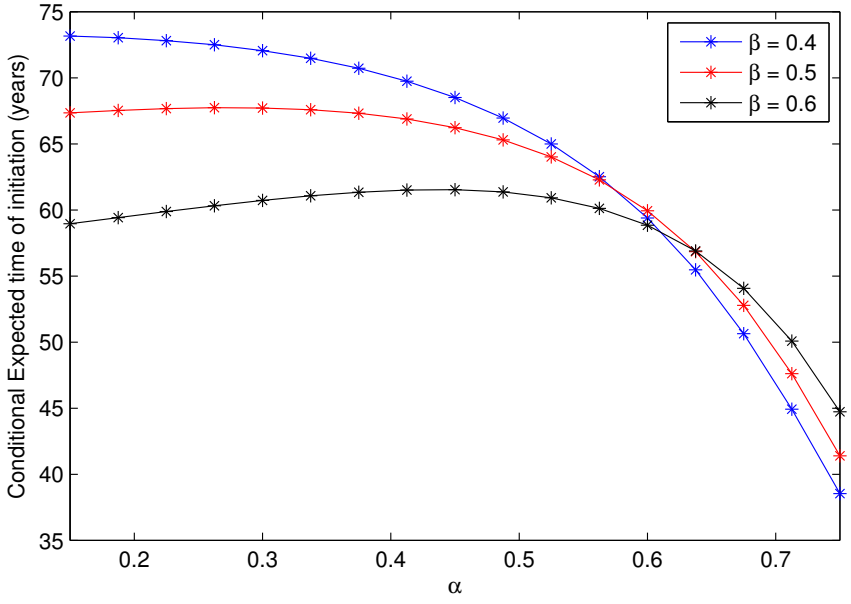
Figure: f_ψ: Distribution of mutational fitness changes

Dynamics of initiation

We investigate the dependence on varying shape parameters α, β of the mutational fitness distribution.

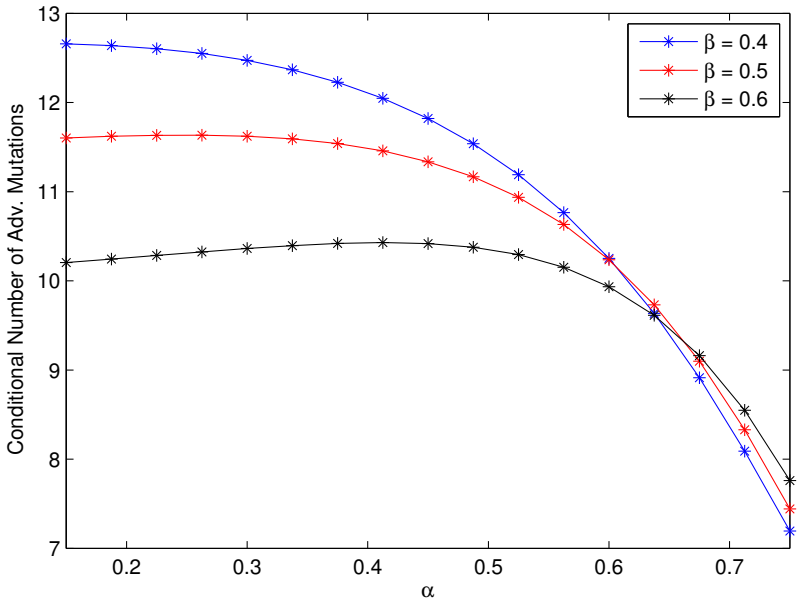


Probability of initiation during lifetime

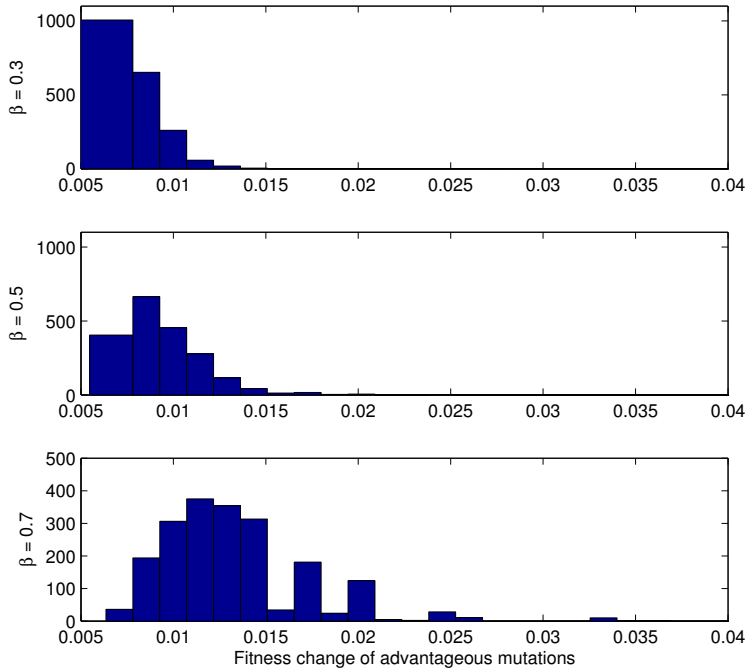


Waiting time until initiation

Rare events: Selection effect favors a few strongly advantageous mutations



Expected number of advantageous mutations in initiating cell



Strength of advantageous mutations in initiating cell ($\alpha = 0.15$)

-> Fewer, more beneficial mutations -> Faster initiation

Effects of varying life expectancy distribution

Mode of the US life expectancy distribution $\sim$ 80 yrs.

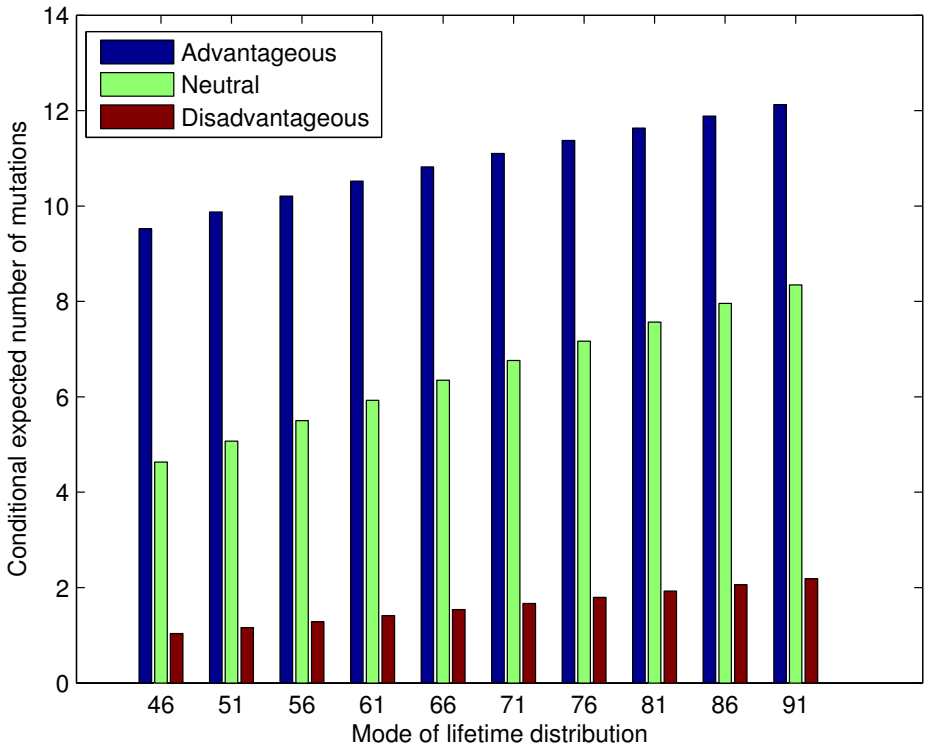
We investigate the dynamics of initiation in populations with different life expectancies by varying the mode of the distribution.

ϕ_{mode}	$\alpha = 0.25, \beta = 0.5$	$\alpha = 0.3, \beta = 0.3$	$\alpha = 0.5, \beta = 0.25$
45	4.0450e-10	1.0608e-06	1.5979e-02
50	6.3142e-10	1.9604e-06	2.4384e-02
55	9.3832e-10	3.4264e-06	3.5433e-02
60	1.3372e-09	5.7100e-06	4.9395e-02
65	1.8381e-09	9.1313e-06	6.6441e-02
70	2.4486e-09	1.4086e-05	8.6642e-02
75	3.1736e-09	2.1050e-05	1.0996e-01
80	4.0147e-09	3.0584e-05	1.3627e-01
85	4.9705e-09	4.3330e-05	1.6533e-01
90	6.0369e-09	6.0017e-05	1.9686e-01

Figure: Probability of initiation during lifetime

Effects of varying life expectancy distribution

Mutational load in the cancer-initiating cell:



Composition of the mutational load varies with life expectancy. The relative frequency of advantageous mutations is higher when life expectancy is low.

Summary (Hypotheses)

Considering this ‘race’ reveals interesting properties about evolutionary paths that lead to initiation of clonal expansion.

- The rare evolutionary paths leading to initiation during a human lifetime are qualitatively different from the majority of paths (i.e. selection effect)
- E.g. Selection effect from more deleterious mutational fitness distributions favors fewer but more beneficial advantageous mutations -> Faster paths to initiation.
- Life expectancy distribution influences the genetic characteristics of the cancers we expect to see in a population of individuals.
- In populations with low life expectancy, we expect that the mutational load is enriched for advantageous (driver) mutations. In populations with high life expectancy we expect a larger frequency of passenger mutations.

[Reference] Foo, Leder, Michor. Phys. Biology (2011) Vol 8: 015002.

Acknowledgements

F. Michor
K. Leder

Funding:
NCI Physical Sciences in Oncology Program
Dana Farber Cancer Institute