Age Incidence of Cancers, Evolutionary Dynamics, Unlucky Events & Numbers

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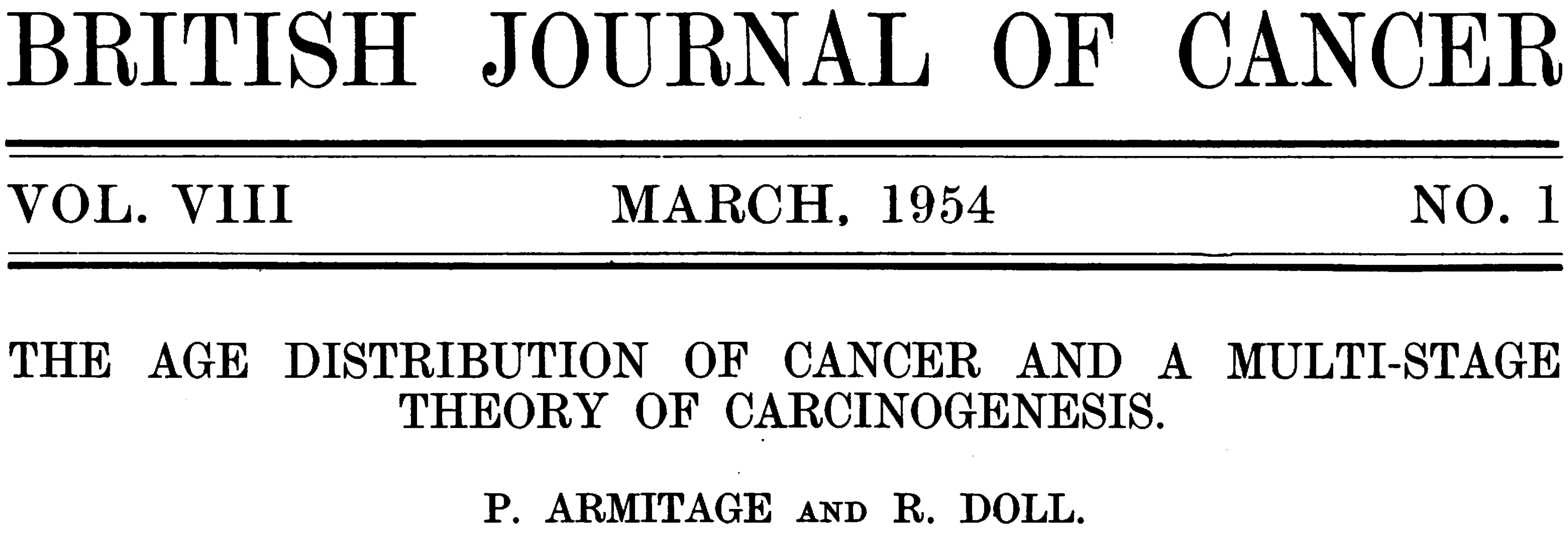
Outline:

- History: inferences from age incidence
- Basic dynamics and numbers
- Stochasticity and unlucky events
- Simple mutation + selection scenarios
- Prospects?

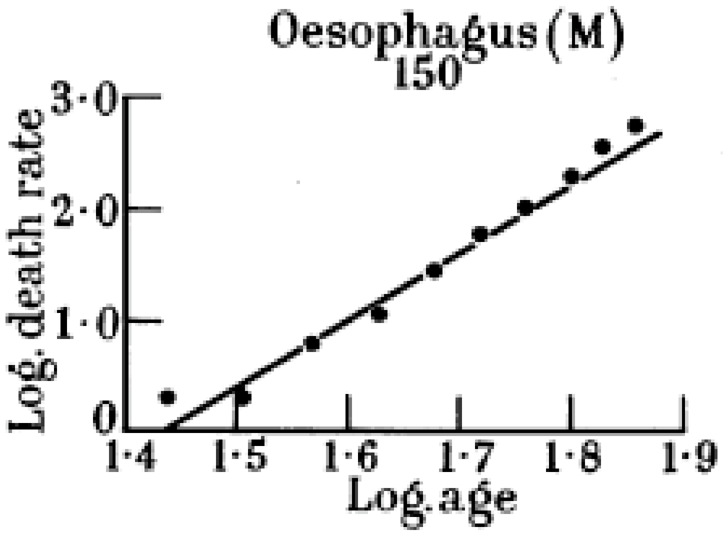


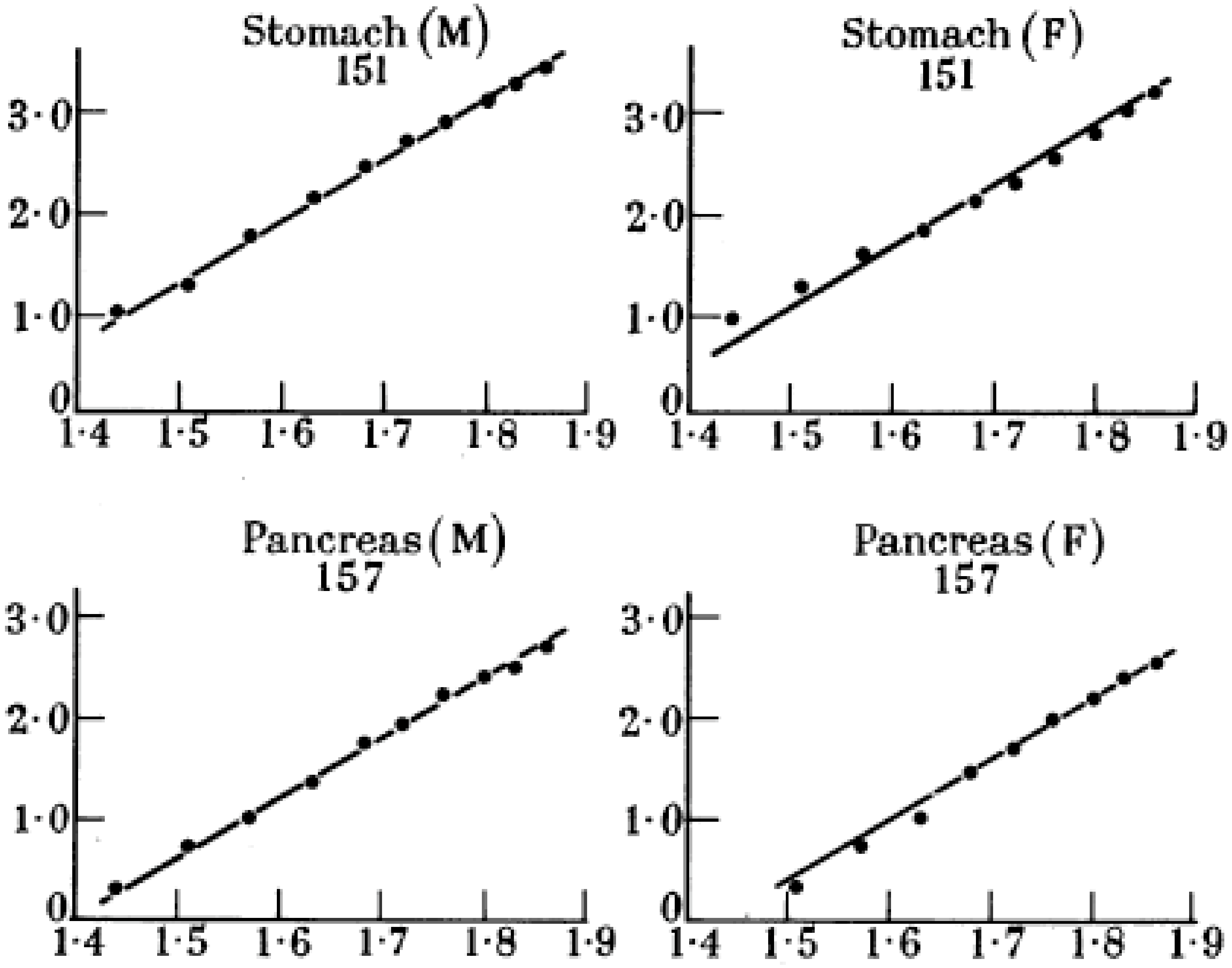
BRITISH JOURNAL OF CANCER

VOL. VIII MARCH, 1954 NO. 1

THE AGE DISTRIBUTION OF CANCER AND A MULTI-STAGE THEORY OF CARCINOGENESIS.

P. ARMITAGE AND R. DOLL.





Cumulative cancer

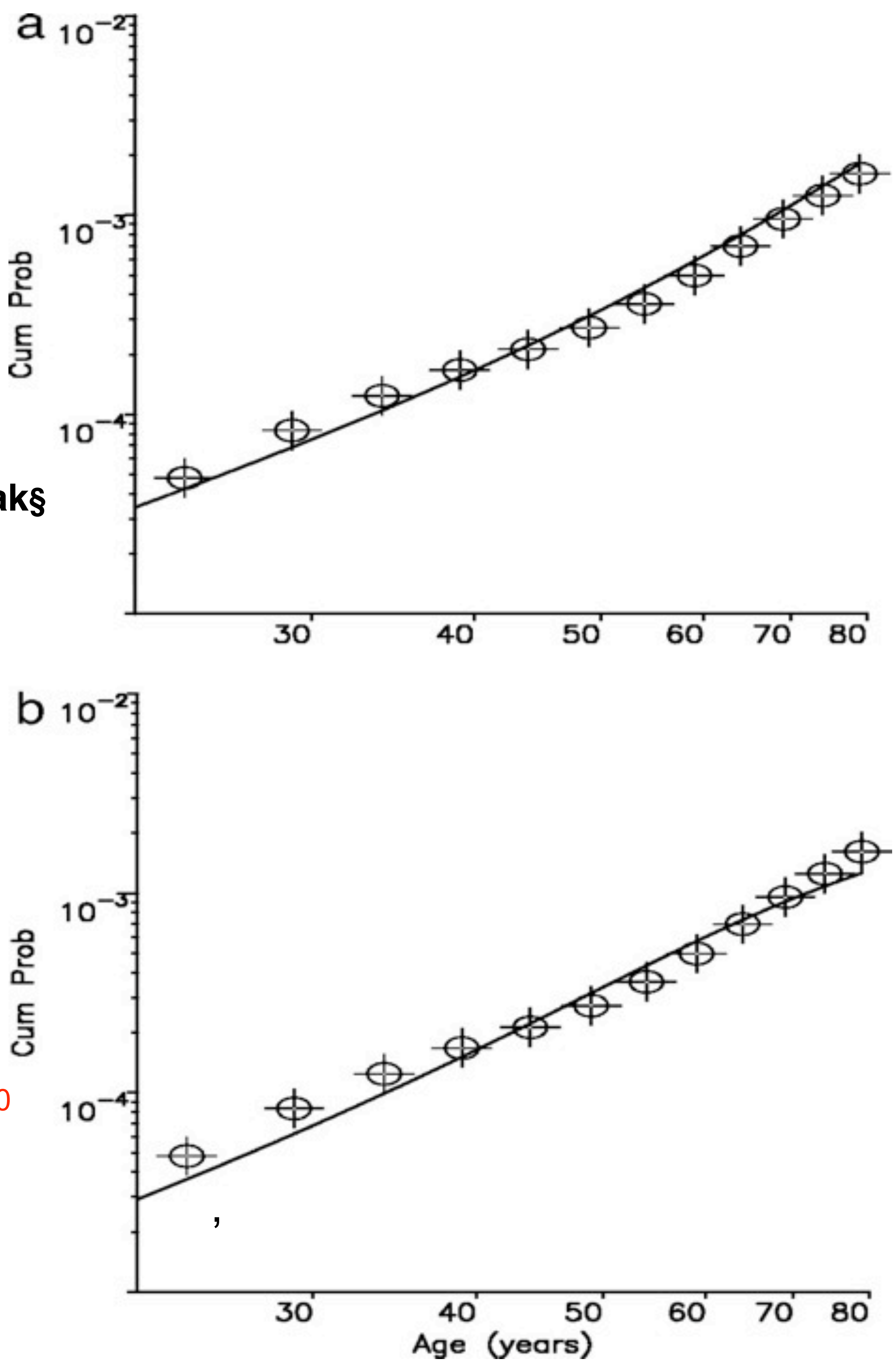
mortality ~ (age)^K

¿¿ => ?? K mutations

K~ 7 for many cancers

“The age incidence of chronic myeloid leukemia can be explained by a one-mutation model”

Franziska Michor*†, Yoh Iwasa‡§, and Martin A. Nowak§
PNAS 2006;103:14931-14934



Power law fit:

Cumulative cancer probability to age T

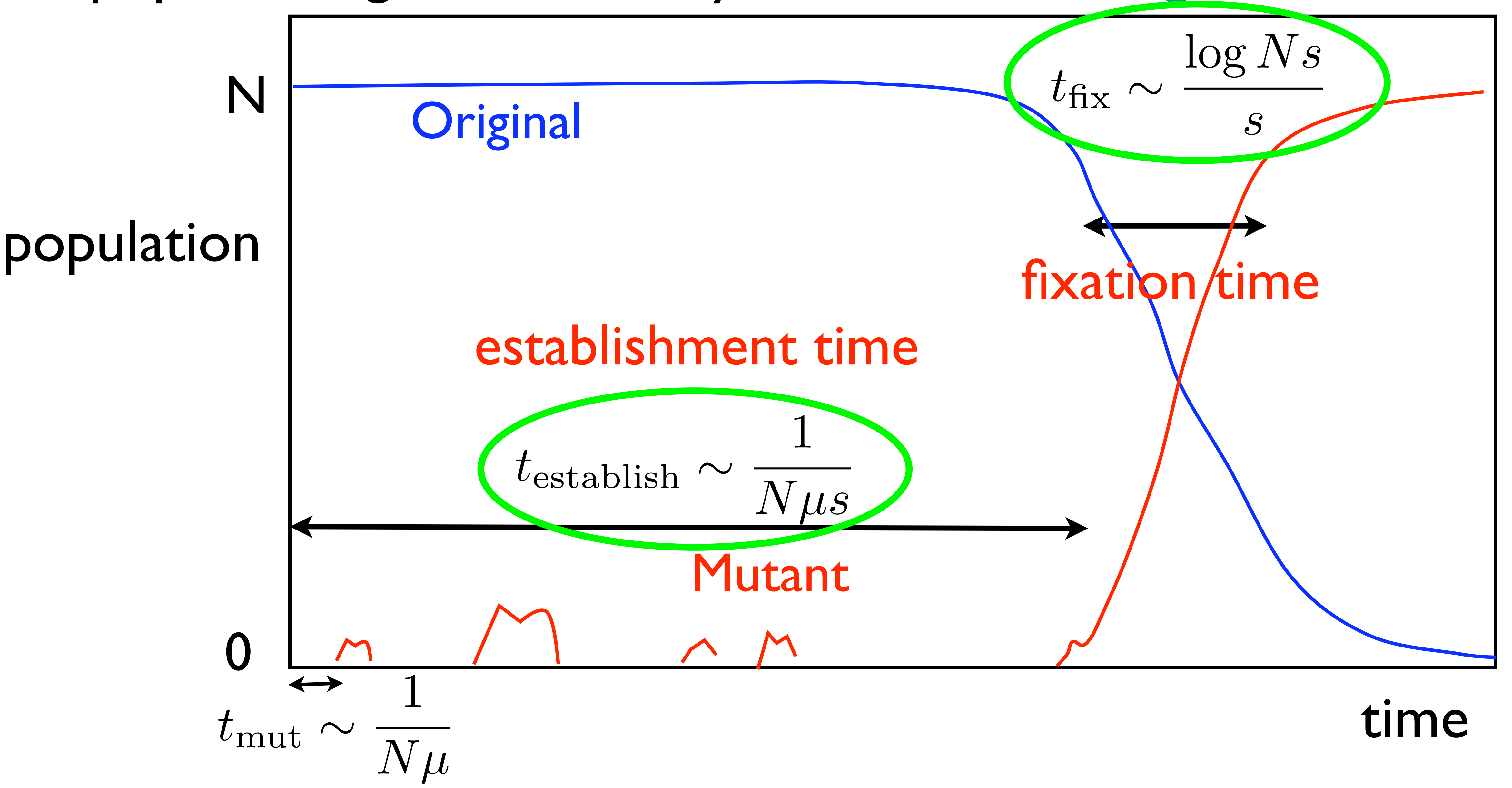
$P_C(T) \sim T^K$ w/ $K \sim 3$

Parameters:	(a)	(b)
Mutation rate	$m = 3 \times 10^{-8}$,	5×10^{-10}
Population size:	$N = 10^5$	10^6
Selective advantage	$s = 1\%$	2%
Cell division rate	r = 60/yr	100
Detection probability	10^{-3}	10^{-1}

Mutation, Selective Sweep, and Time Scales

Original population n_0 mutates at rate μ to n_1 population

Mutant population grows faster by selective advantage s => e^{st}



Stochastic mutations at rate $N\mu$

but die out with prob. $1-s$ => $t_{est} \sim 1/(N\mu s)$

Deterministic selective sweep => $t_{fix} \sim {}^{1}/_{s} \log Ns$

What are the Numbers that Determine Cumulative Cancer Incidence, $P_C(T)$?

N Population size of susceptible cells (stem cells? others?):

Hematapoetic stem cells: N ~ 10^7- 10^8

Solid tissues: up to 10^{12} total cells

Mutation rates per somatic cell division:

Point mutations: ~ 10^{-9} Deletions? Copy # changes?

Target sizes? For one gene knockout: 10^2-10^3

m Total rate for pre-oncogenic genetic changes?

s Selective advantage of mutants

beneficial, neutral, or deleterious

r Rates of cell division: 10^{-2}-10^3 /yr

T Age

Drastically simplified:

global competition, no niches, etc.

Processes that give $P_C \sim T^K$?

K sequential sweeps of "beneficial" mutations

Mutation limited: time between sweeps ~ $1/(Nms)$

with fixation time of sweep $^1/_s \log(Ns)$ shorter

$P_C \approx$ Prob(K sweeps before T) ~ $(NmsrT)^K e^{-NmsrT}/_{K!}$

But: for K=7 would need

$srT > K \log(Ns) \sim 10^2 \Rightarrow Nm < 10^{-2}$

unreasonably small mutation rate

Cf:. single mutation and single sweep (Michor, Iwasa, Nowak)

Can have slow fixation with s very small,

but: need $Nm \sim 10^{-3}$ unreasonably small

Processes that give $P_C \sim T^K$?

K-1 neutral then one beneficial

N = total pop'n $\quad$ n_j = popul'n w/ j neutral mut'ns

m_j = mut'n rate for j^{th} mut'n

s = selective advantage of K^{th} (cancerous) mutant

Simple deterministic approximation for intermediaries

$dn_1/dt = m_1 N \quad \Rightarrow n_1 = N m_1 t$

$dn_2/dt = m_2 n_1 \quad \Rightarrow n_2 = {}^1/_2 N m_1 m_2 t^2$

$dn_K/dt \approx s\, n_K + m_3 n_2$ stochastic w/ fixation prob. $\propto s$

$\Rightarrow P_C(T) \equiv$ Prob(cancer by T) $\approx {}^1/_{K!}\ N m_1 m_2 \dots m_K\ (rT)^K s$

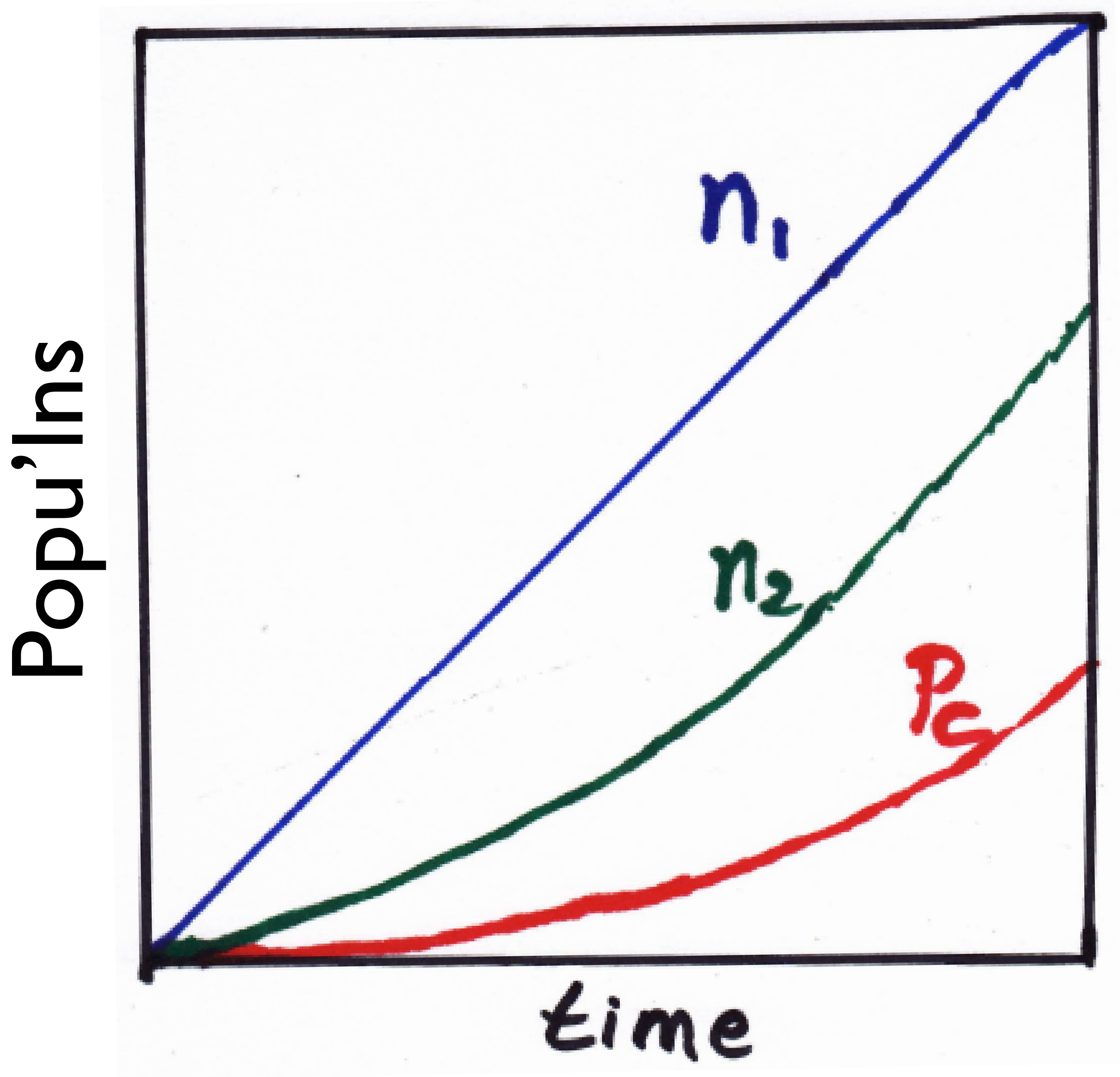
But: Need enormous N for det'c approx'n

Need unreasonably large m's for K=7

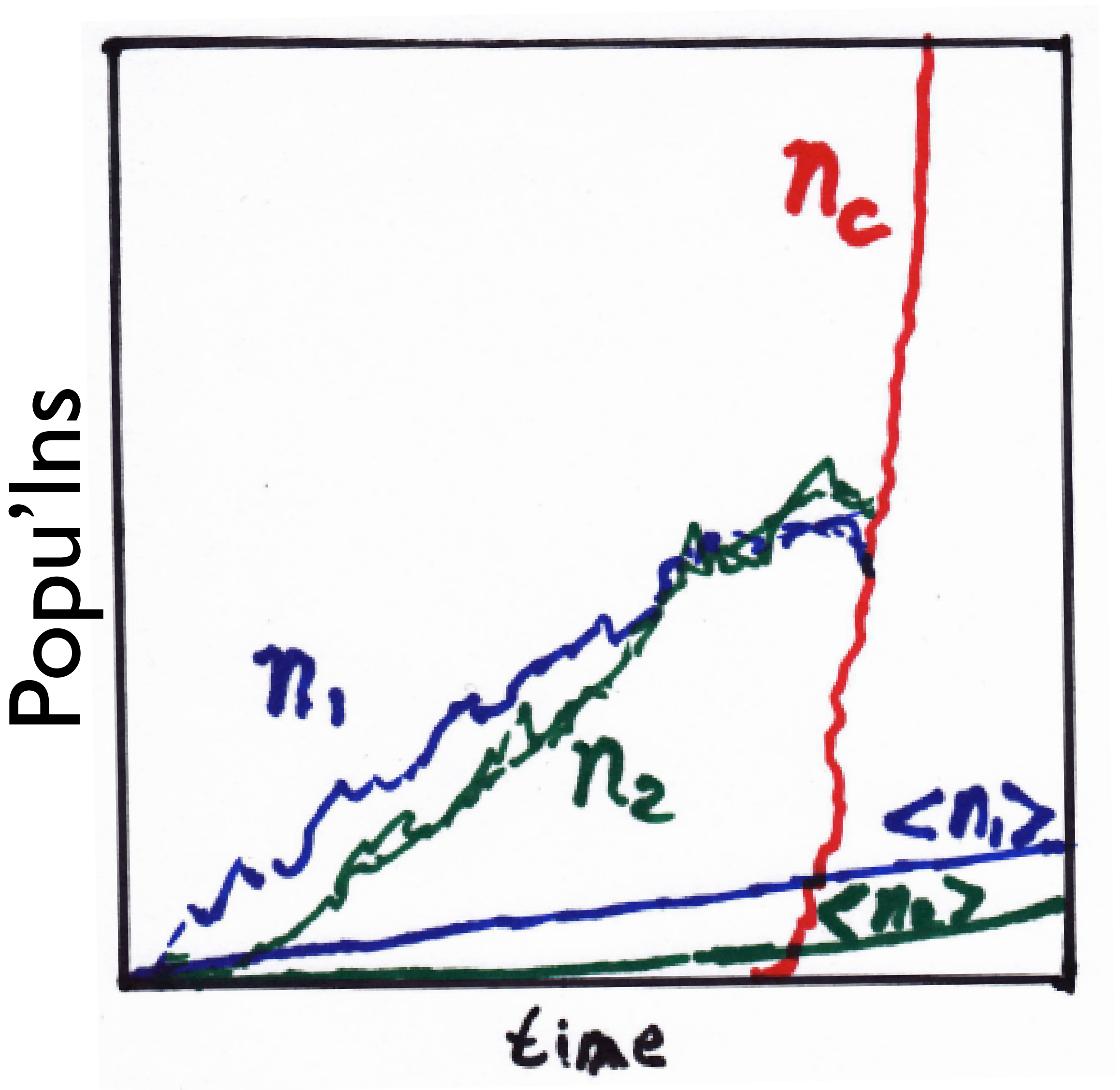
Need almost exact neutrality

Stochastic Dynamics with Neutral Mutations

Deterministic Approx'n



Stochastic



Rare events:

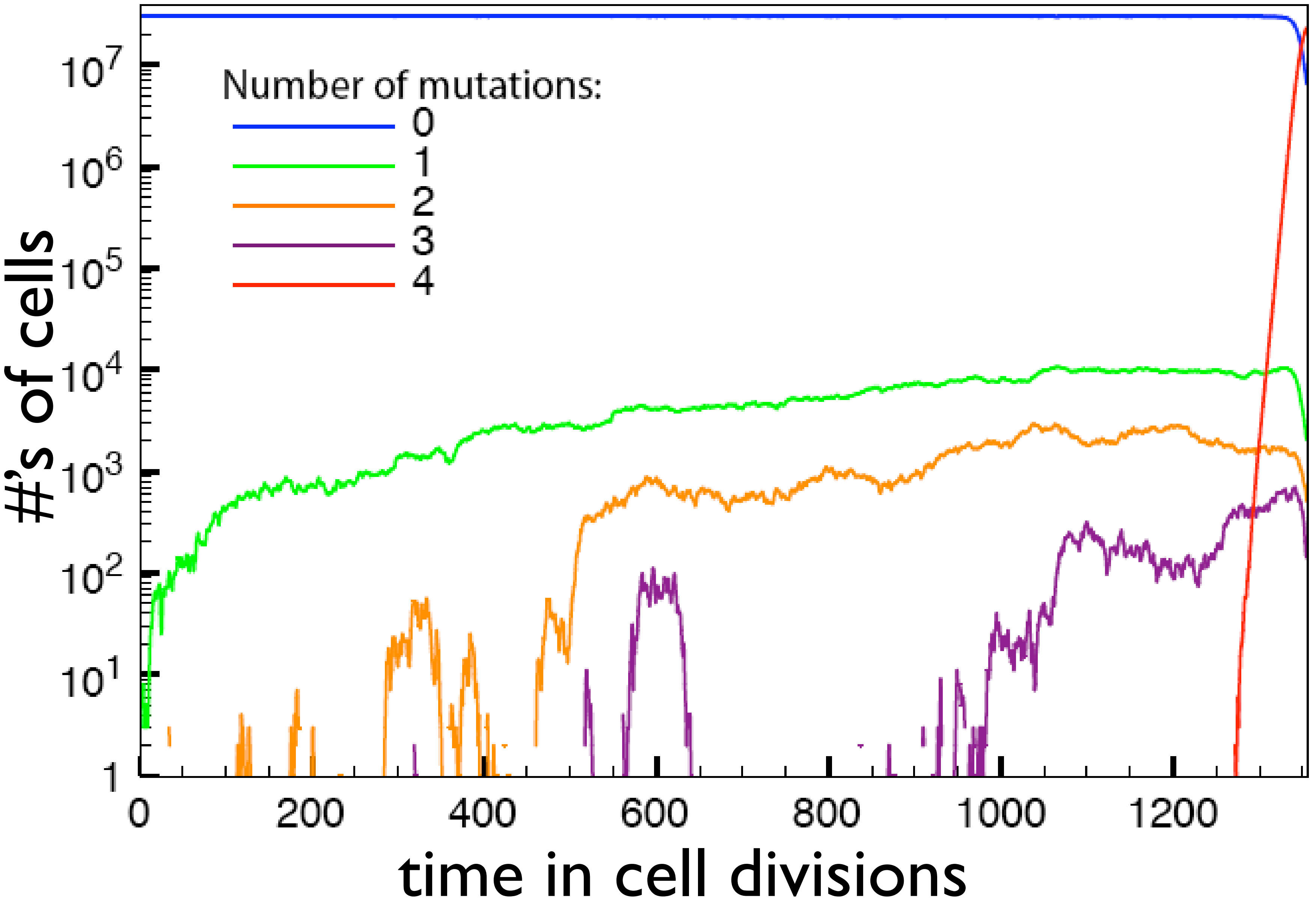
least unlikely ones => early onset cancer

4-Mutation Neutral Scenario: for CM Leukemia?

Unlucky individual with age at onset 65 yrs
when cumulative prob. $P_C \sim 2\%$

$N=3 \cdot 10^7$ stem cells
r= 20 cell divisions/yr
neutral 1,2,3
s of 4th mutant: 20%

mut'ns: 1st: $m_1 = 10^{-7}$
breaks DNA repair
mut'ns 2,3,4: $m=10^{-4}$

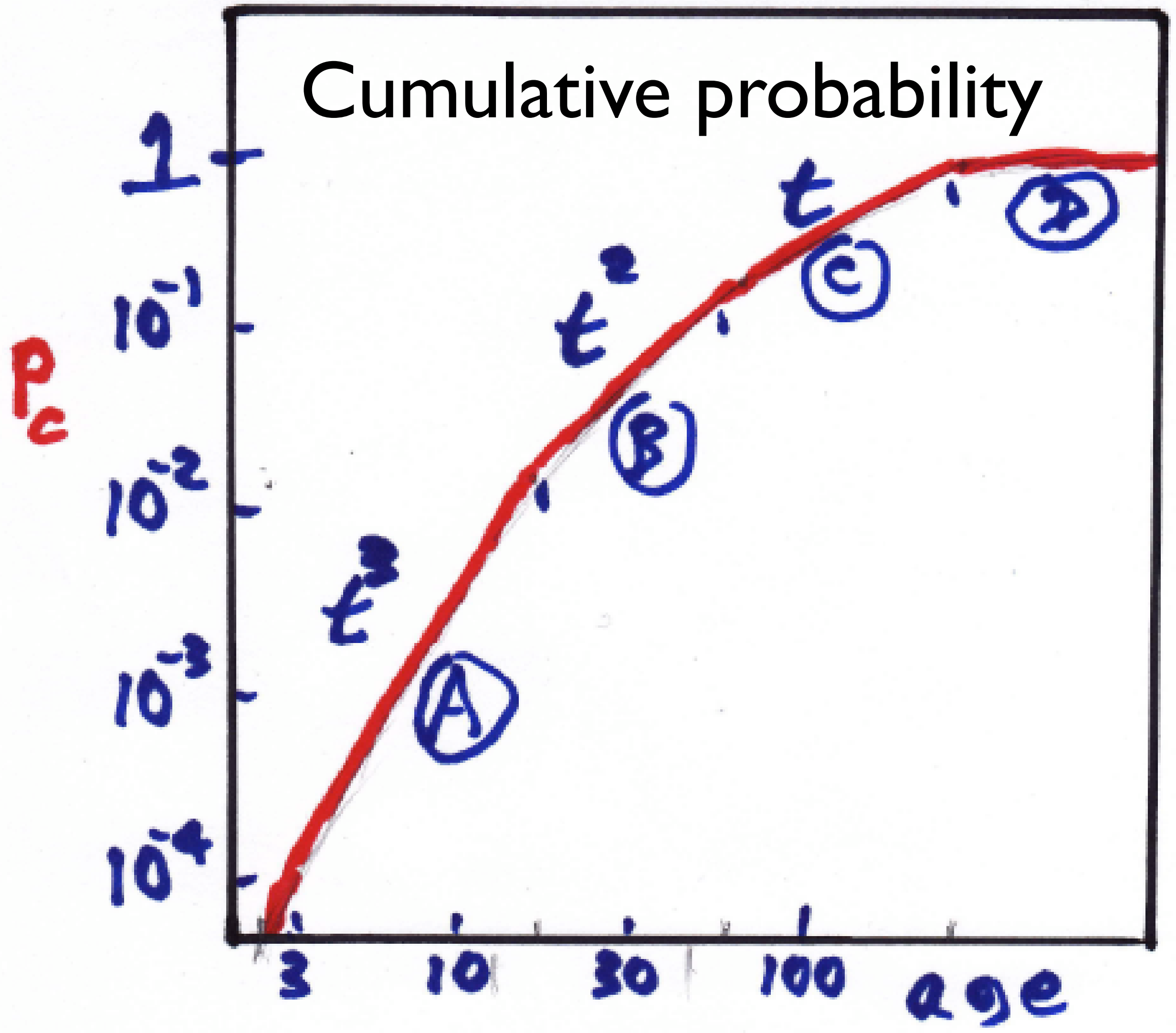


Age incidence looks approx like K=3

Multiple Regimes:
& different unlucky events

A “common cancer”

2 neutral + 1 beneficial
Mutation limited: $Nm_1 \ll 1$



Regime:	A	B	C	D
Pr(mut’n 1)	Nm_1	Nm_1	$Nm_1\ m_2^{1/2}(m_3 s)^{1/4}\,rt$	likely
Pr(mut’n 2)	$m_2\,rt$	$m_2(m_3 s)^{1/2}(rt)^2$	likely	likely
Pr(mut’n 3)	$m_3\,(rt)^2 s$	likely	likely	likely
Cumulative:				
P_C/Nm_1	$m_2 m_3\, s(rt)^3$	$m_2(m_3 s)^{1/2}(rt)^2$	$m_2^{1/2}(m_3 s)^{1/4}\,rt$	

4-Mutation Overlapping Sweep Scenario: for CML?

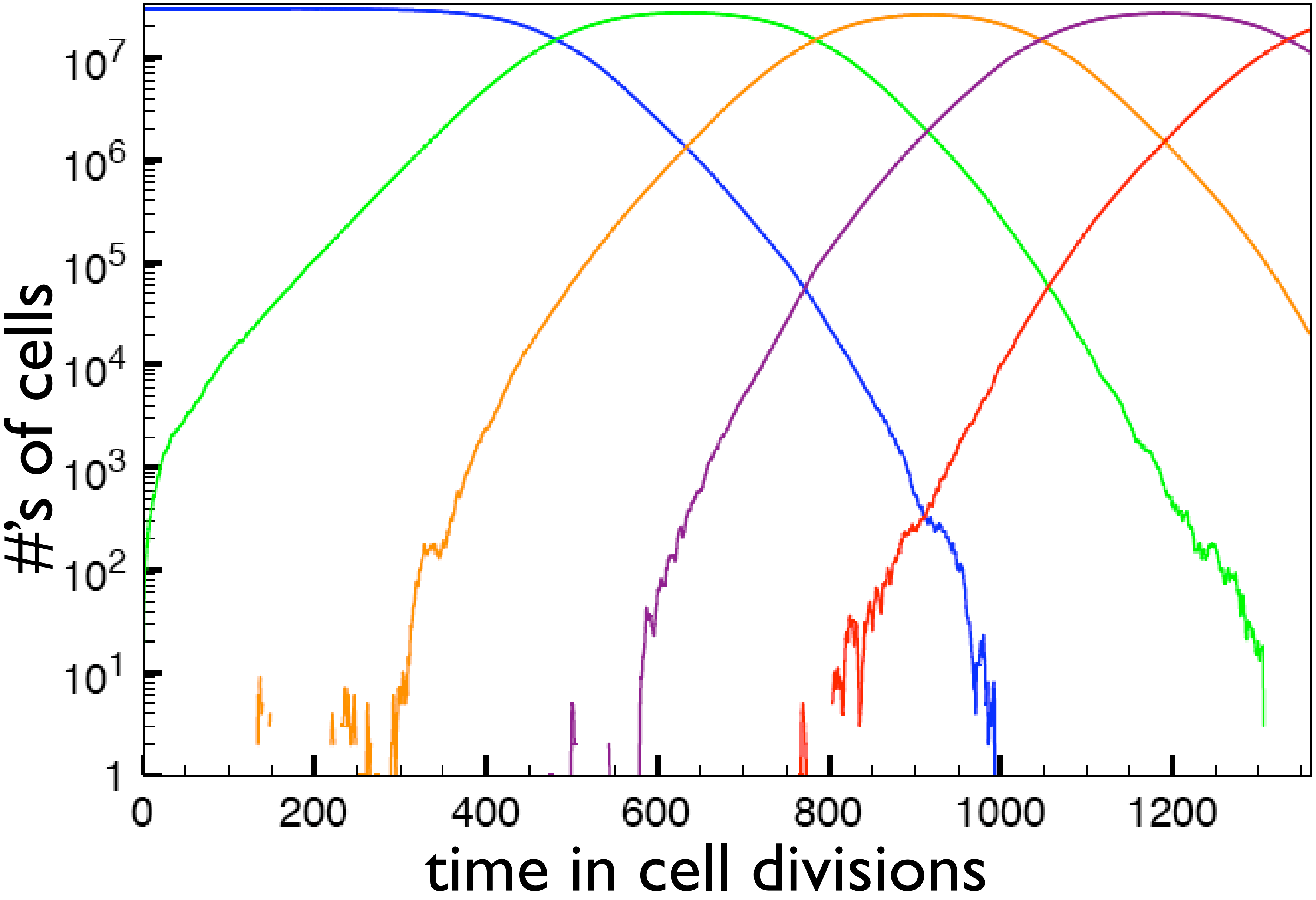
Unlucky individual with age at onset 65 yrs
when cumulative prob. $P_C \sim 2\%$

$N=3 \cdot 10^7$ stem cells
r= 20 cell divisions/yr

$s_1 = s_2 = s_3 = s_4 = 2\%$
(cancerous mutant:
8% faster than normal)

$m_j = 10^{-6}$

Age incidence looks
approx like K=3



Almost the same quantitatively if $m \sim 10^{-8}$

Complications -- Even When "Simple"

Interplays: selection limited & mutation limited. Hard to infer

Stochastic & deterministic aspects
Different for unusually early incidences

Numbers crucial, but still many plausible scenarios

Multiple overlapping sweeps
Valley crossing
Neutral wandering and selection on genomes

And in real life ... Phenotypes crucial, niches, heterogeneties

Local or global competition
Spatial and temporal dependence
Aggravating factors, etc, etc.

Some hopes?

Delicate balance cancer vs normal cells and rare events
=> small subtle changes could be crucial
For understanding: Big and small numbers limit viable scenarios