Deleterious passengers in cancer

By Christopher McFarland, Kirill Korolev, and Leonid Mirny

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Advantageous and deleterious mutations

- ***Driver Mutations****: increase a cell's rate of division (or decrease death/senescence) in the hyperplasia. E.g. recurrent mutations in cancer causing genes.*

- ***Passenger Mutations:*** *non-recurrent mutations in cancer, not associated with cancer-causing genes.*

  -May be neutral or deleterious

All happy families are all alike; each unhappy family is unhappy in its own way.

Leo Tolstoy

If drivers cause cancer, why study passengers?

- Passengers slow down **evolution** of cancer
- Passengers **constrain** evolution of cancer
- Passengers affect interpretation of **sequencing** data
- Passengers could be targets for cancer **therapies**
- Passengers could become **drivers**

Passengers vs. Drivers

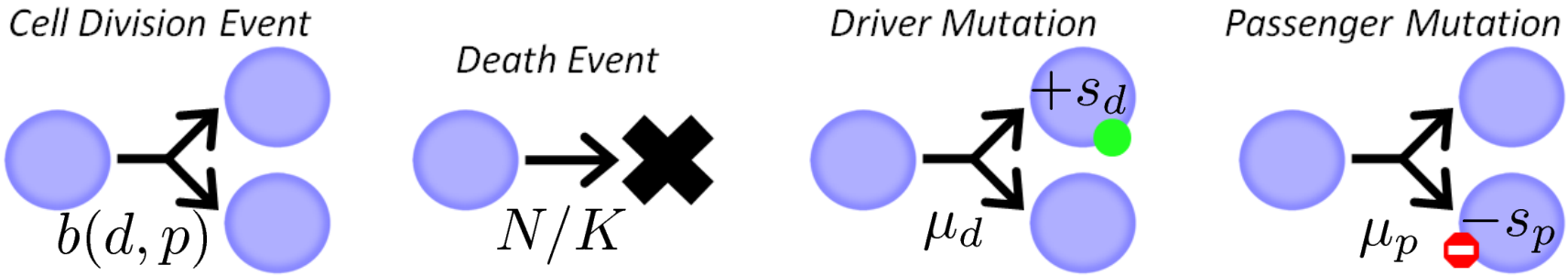
tumor type	protein coding mutations	putative driver mutations
breast cancers	209.8	5.1
colon cancers	136.4	4
astrocytomas	254.3	5.5
leukemia (AML)	11.8	2
malignant melanoma	281.2	7
averages	**10^3**	**10^1**

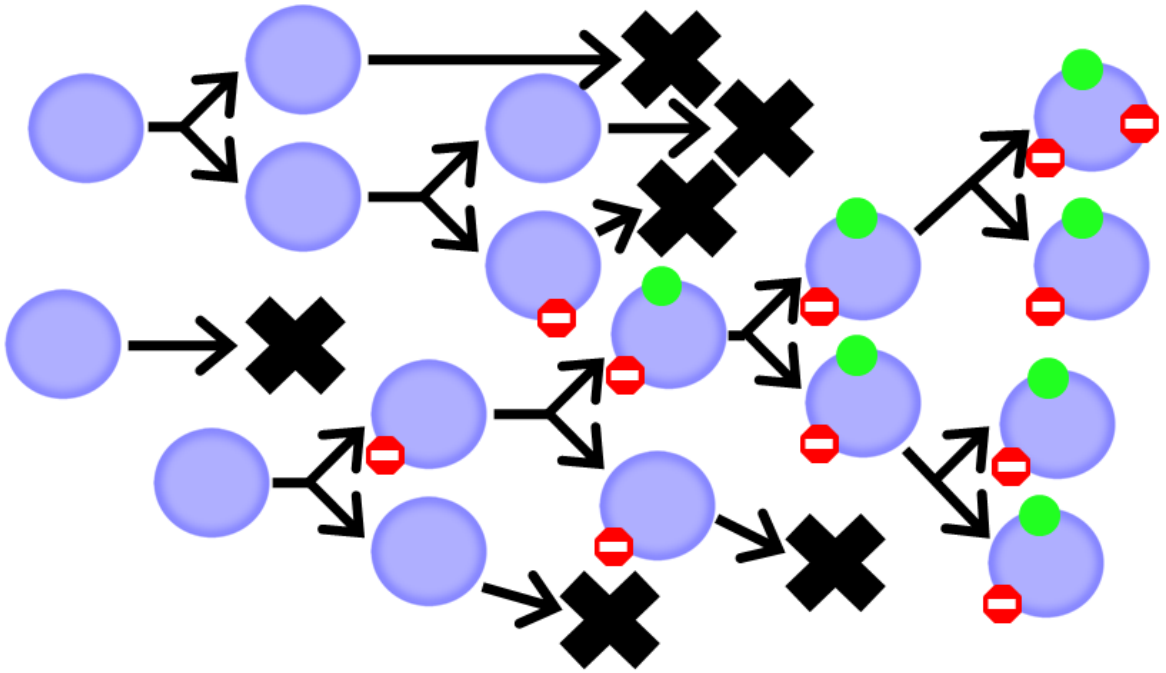
Outline

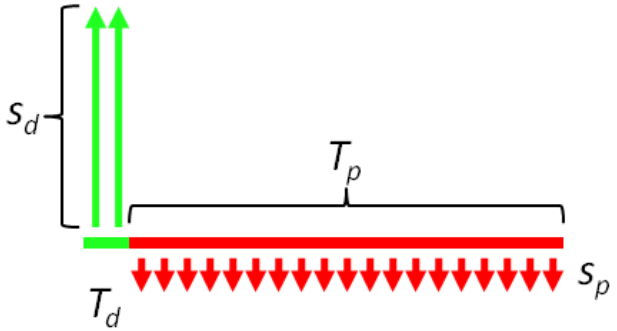
1. Passenger mutations may be deleterious to cancer, yet still accumulate in tumors.

2. Deleterious passengers prevent and slow cancer under specific conditions and these conditions may be exploited by therapies.

Our evolutionary model of cancer





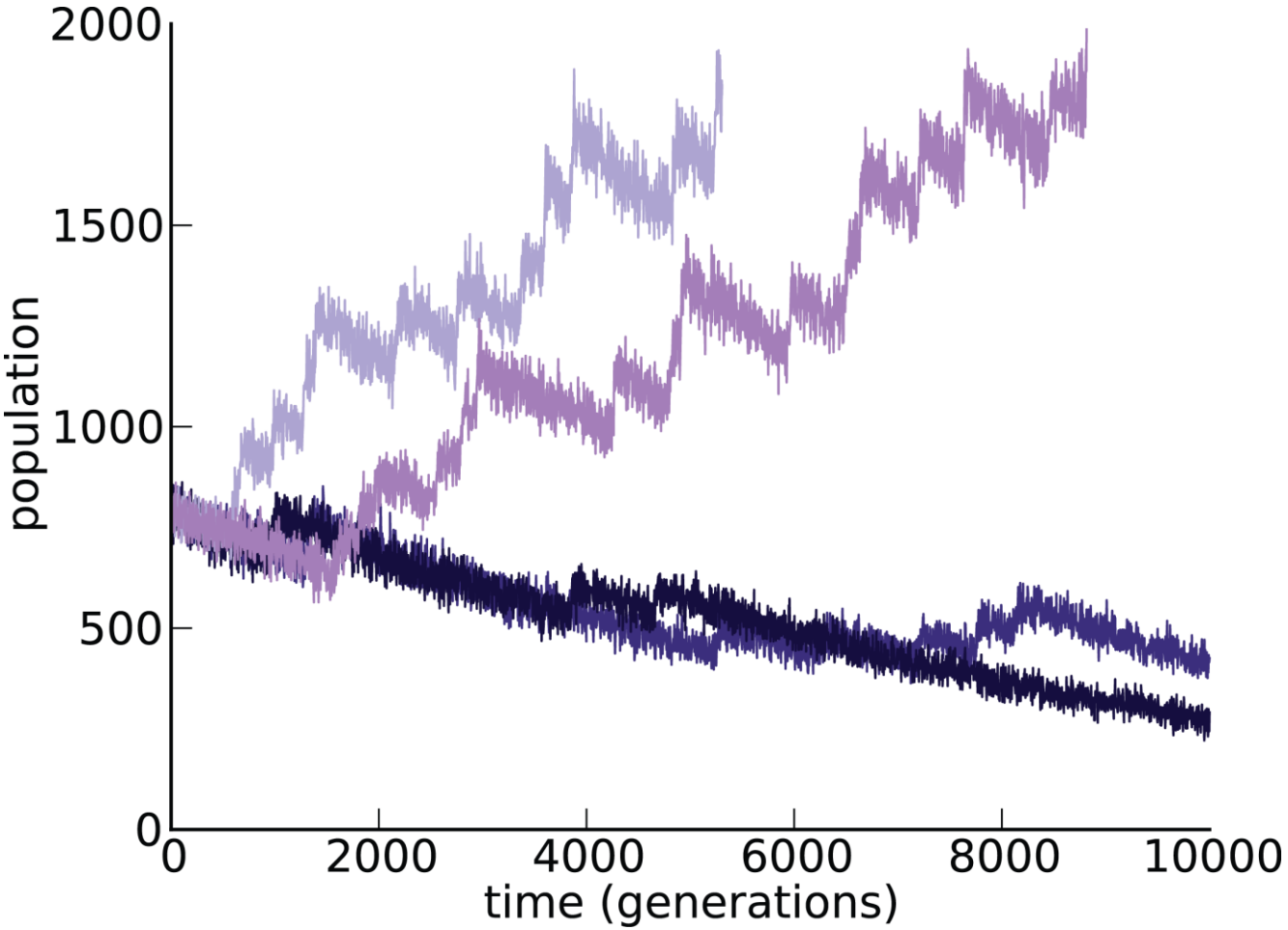


Parameters

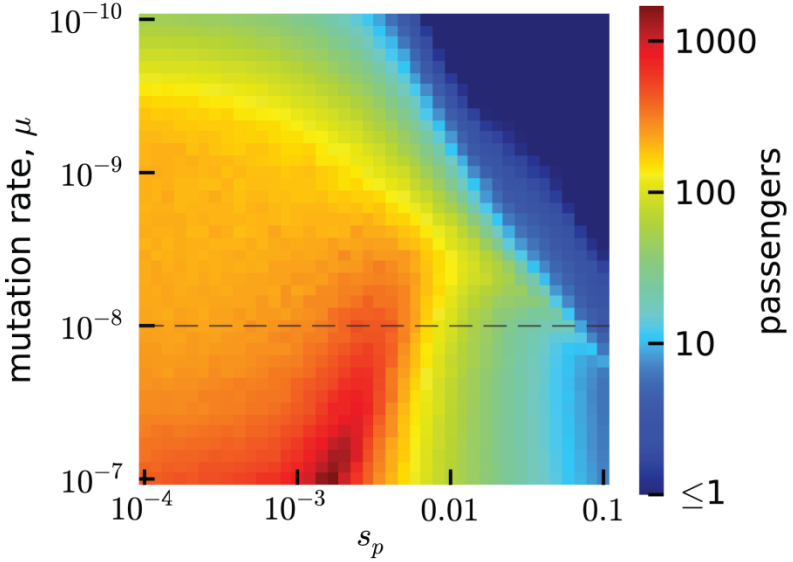
Parameter	Symbol	Literature estimate	Range
mutation rate per nucleotide	μ	10^{-8}	$10^{-10} – 10^{-6}$
number of driver loci	T_d	700	-
number of passenger loci	T_p	5,000,000	-
selective advantage of driver	s_d	0.1	0.001-1
selective disadvantage of passenger	s_p	0.001	0.0001-0.1
Initial carrying capacity of lesion	K	1000	100-10,000

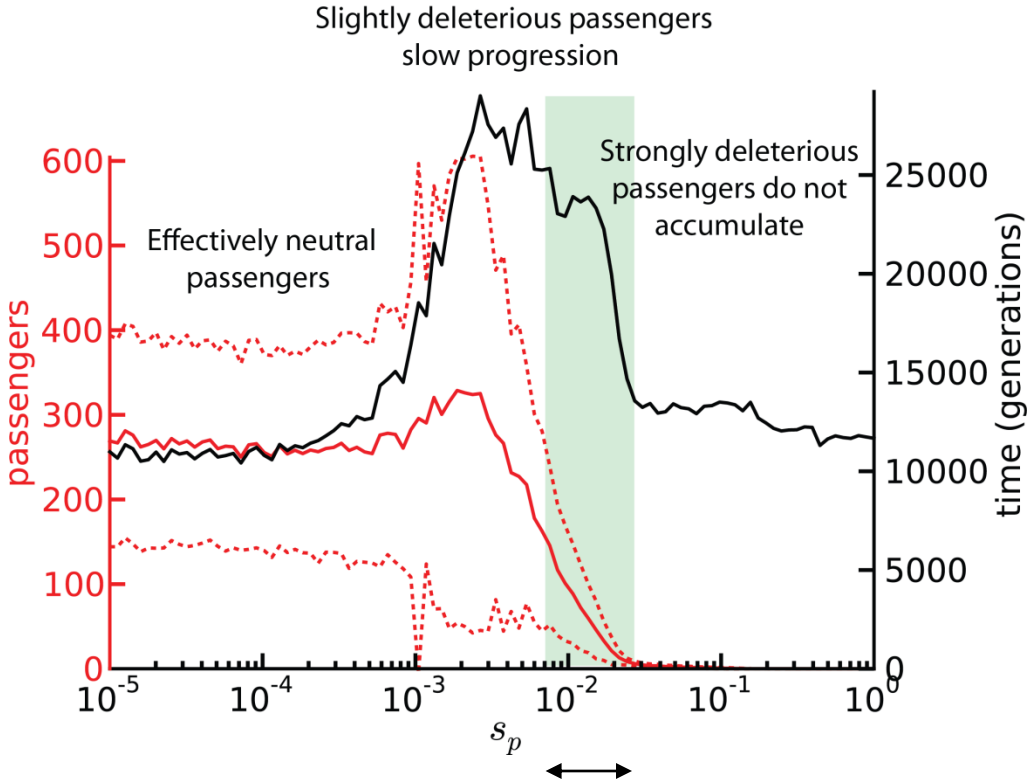
Cole et. al. (2010); Beerwinkel et. al. (2007); Geller-Samerotte et. al. (2010); Loeb, Bielas, and Beckman (2008); Jackson and Loeb (1998); Beerwinkel et. al. (2007);Beckman and Loeb (2005).

A balance between drivers and passengers



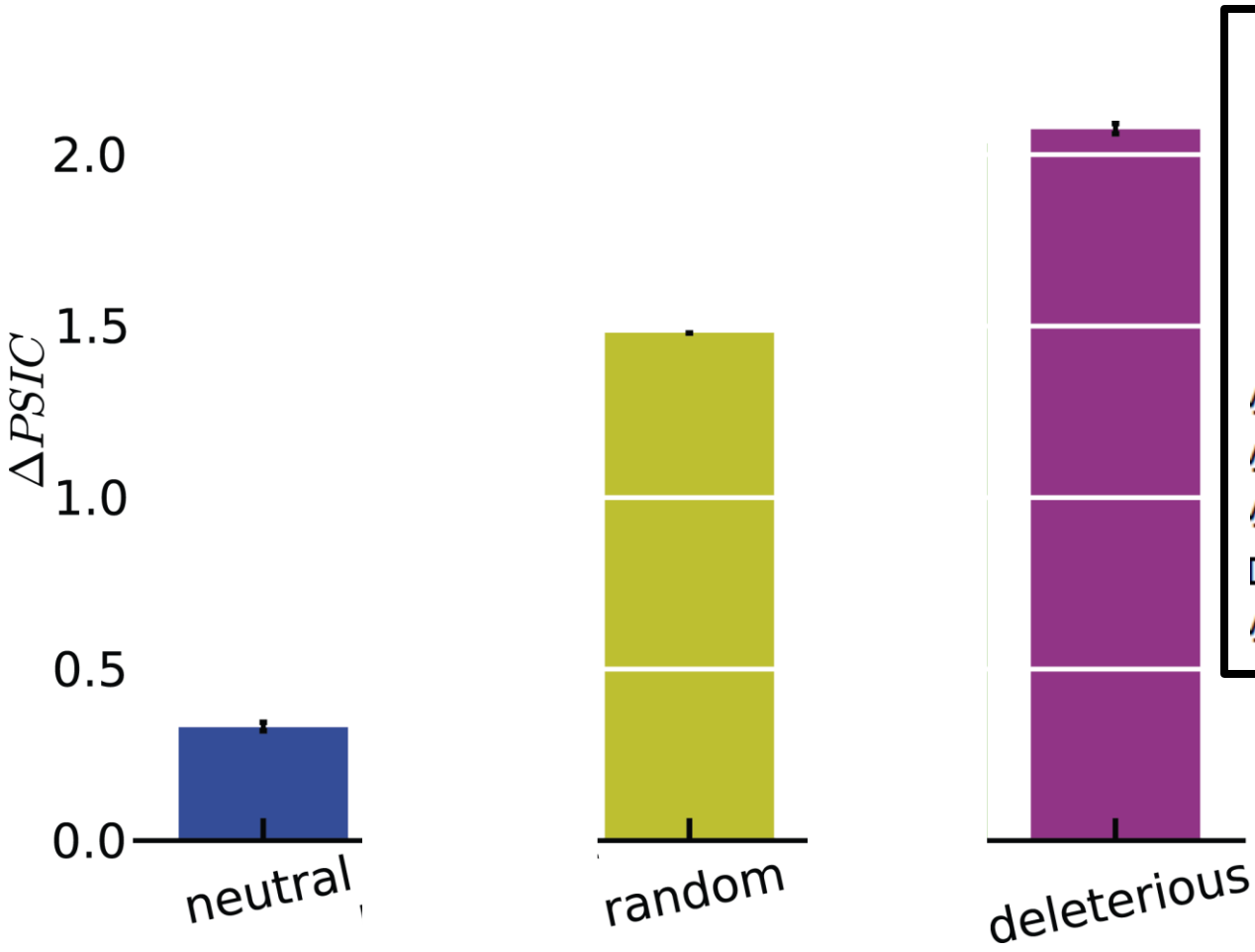
Mildly deleterious passengers accumulate

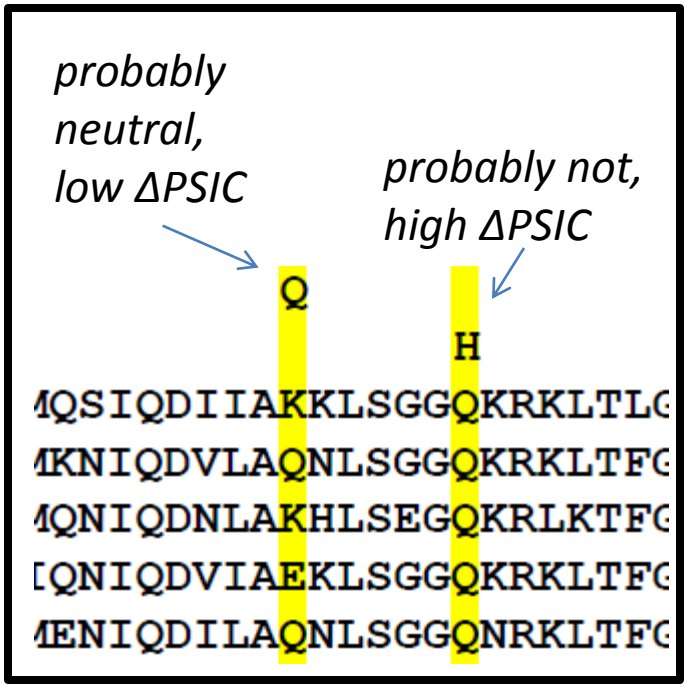




Effects of random mutations introduced into *YFP* in yeast under strong (*GAL1)* expression (Geller-Samerotte et. al. 2010)

Comparative genomics: many sequenced passengers are deleterious





Outline

1. **Passenger mutations can be deleterious to cancer, yet still accumulate in tumors.**

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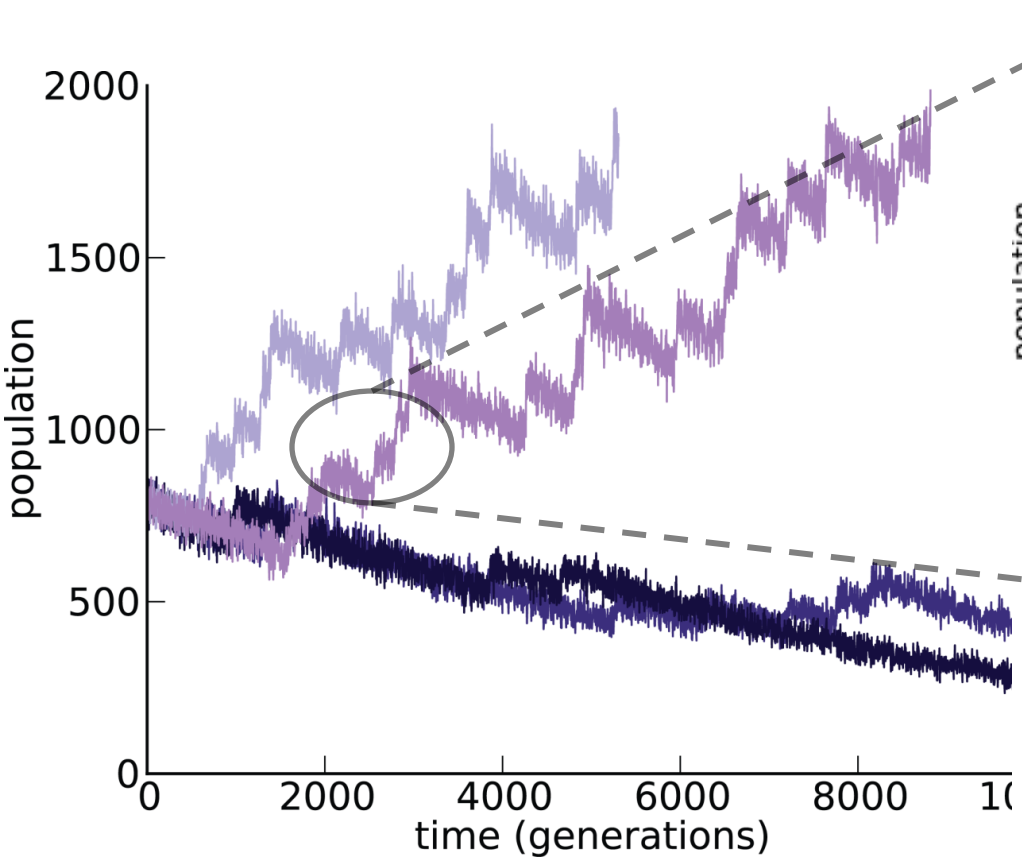
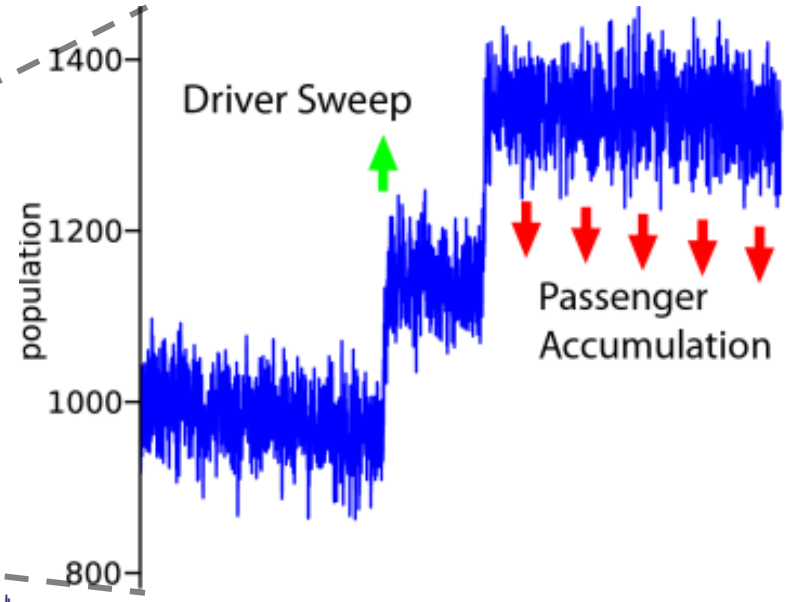
2. **Deleterious passengers can prevent or slow cancer under specific conditions and these conditions may be exploited by therapies.**

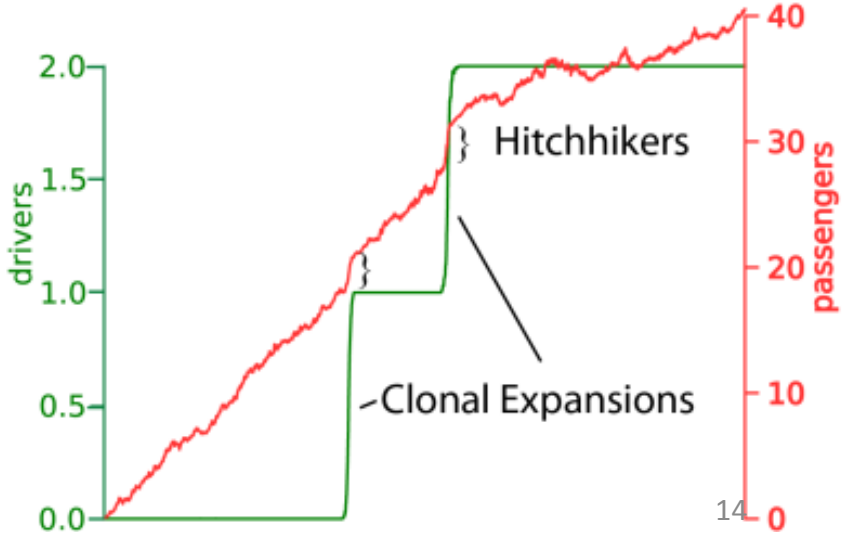
Limitations of our computational model

- Grew populations from 10^3 to $>10^6$
- M ions
- (How/when/where/why
- F do our results
  r generalize?
- (
- I neity

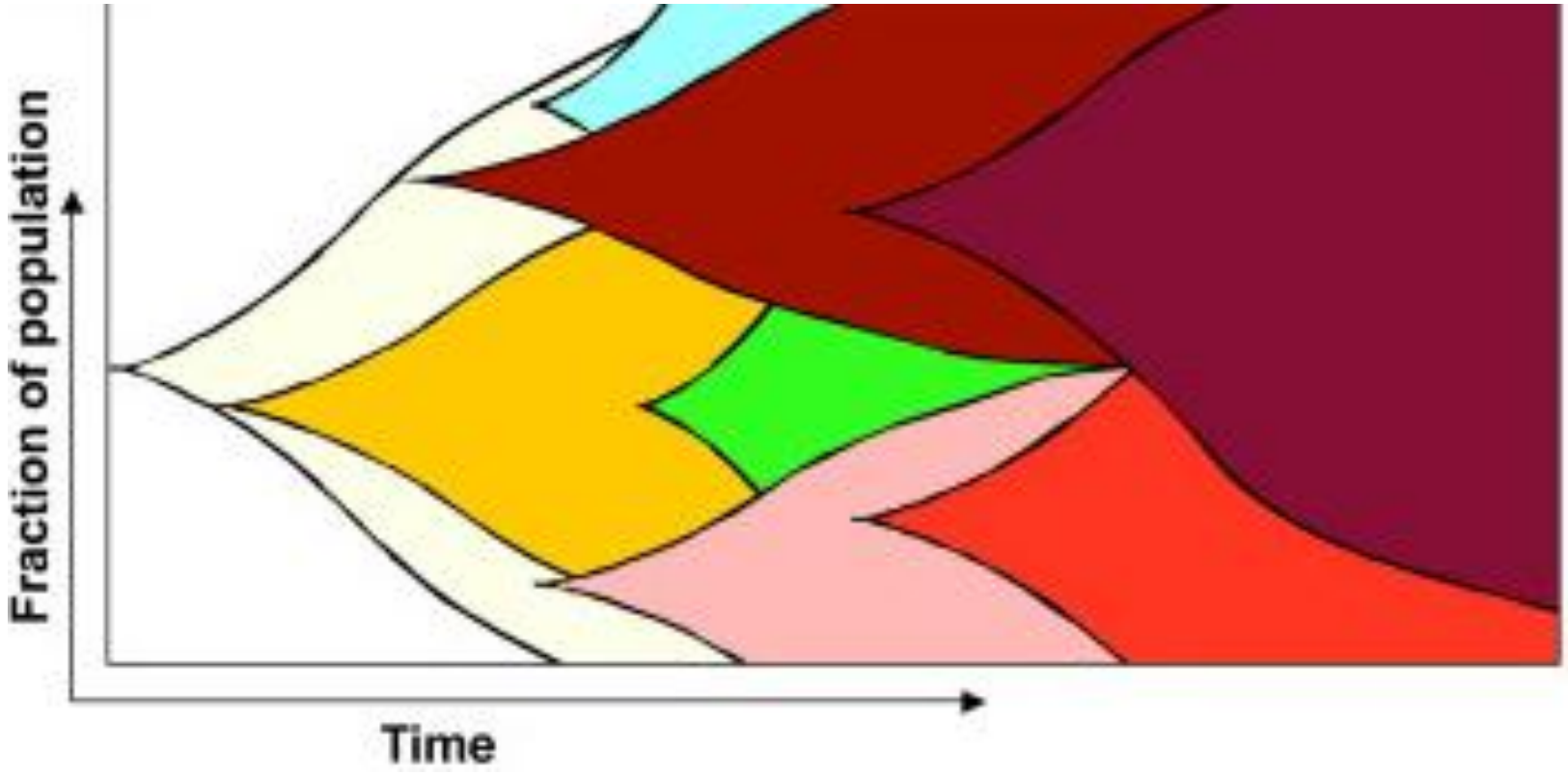
Why do passengers accumulate?



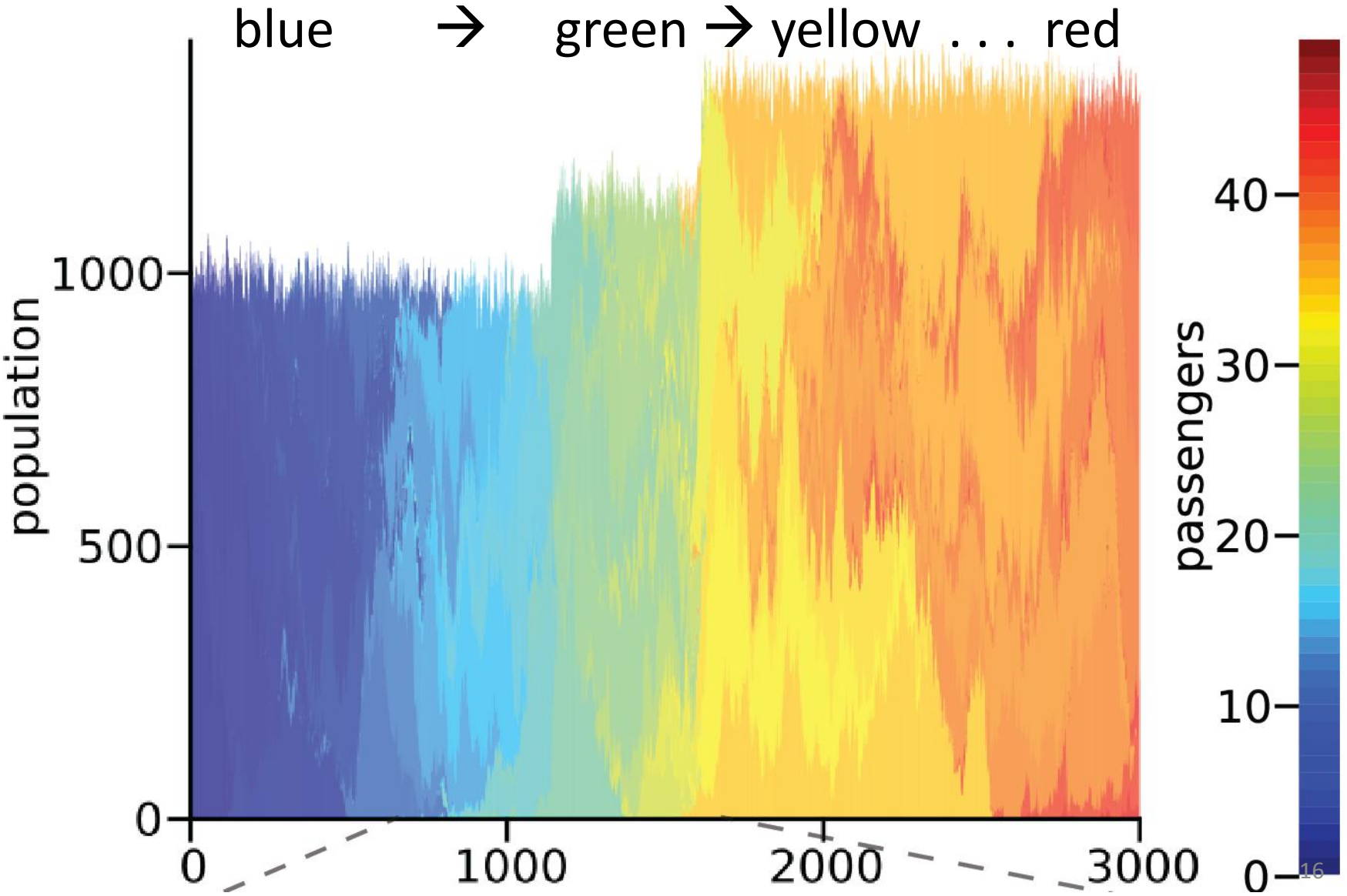




Idealized heterogeneity of progression



Observed heterogeneity of progression



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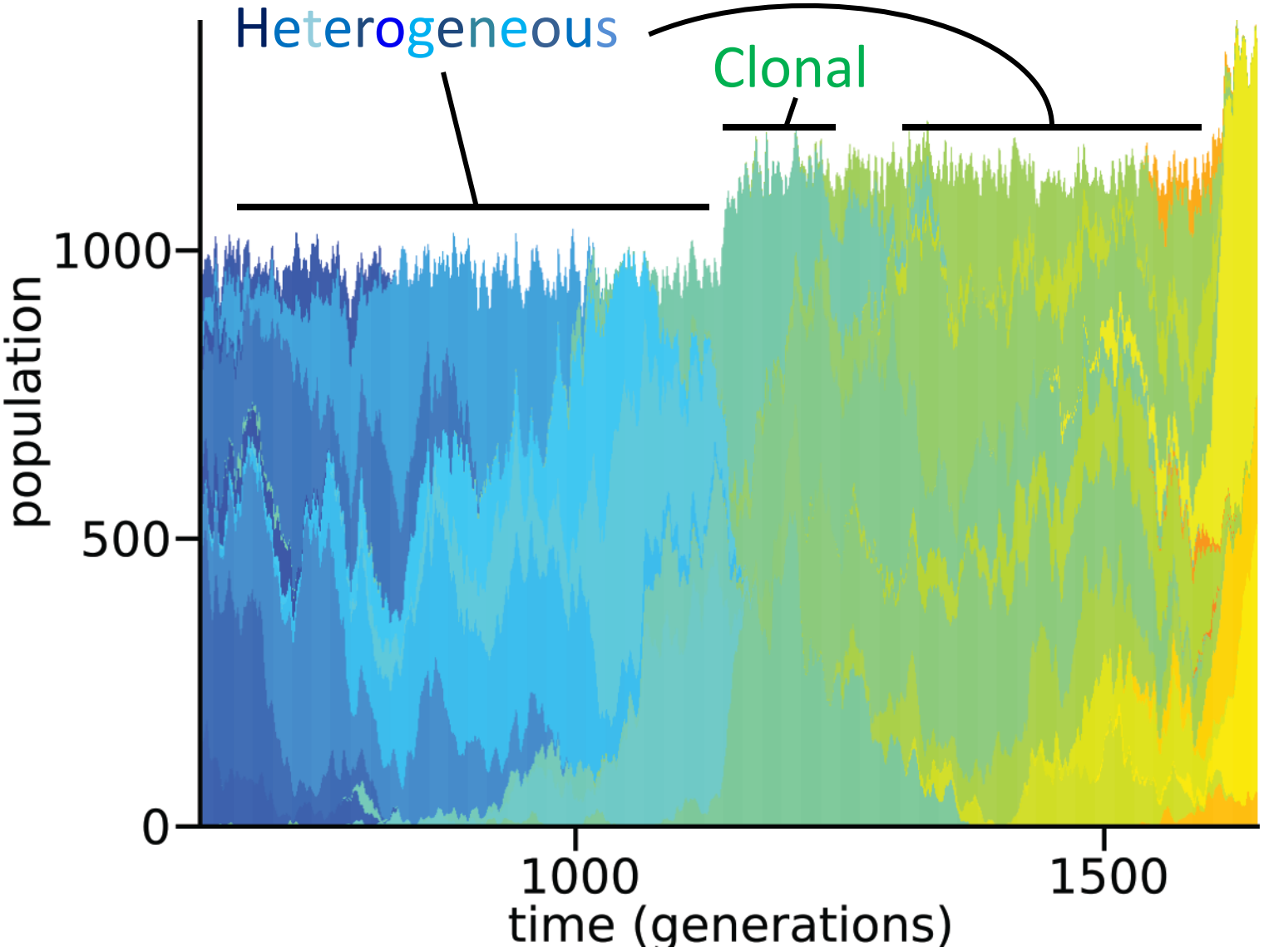


Why two fates?

$$\frac{dN}{dt} = v_{\mathrm{d}}(N) - v_{\mathrm{p}}(N)$$

population growth due to drivers

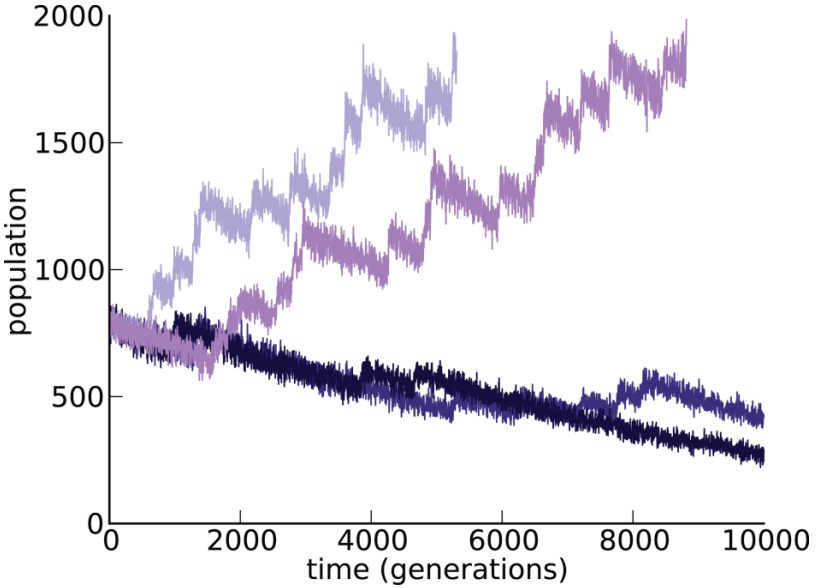
$$v_{\mathrm{d}} = \mu_{\mathrm{d}} N \cdot \pi_{\mathrm{d}} \cdot N s_{\mathrm{d}} = \mu_{\mathrm{d}} s_{\mathrm{d}}^2 N^2$$

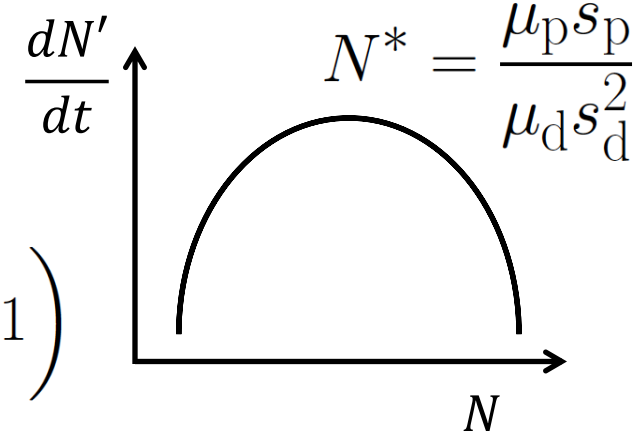
population decline due to passengers

$$v_{\mathrm{p}} = \mu_{\mathrm{p}} N \cdot \pi_{\mathrm{p}} \cdot N s_{\mathrm{p}} = \mu_{\mathrm{p}} s_{\mathrm{p}} N$$

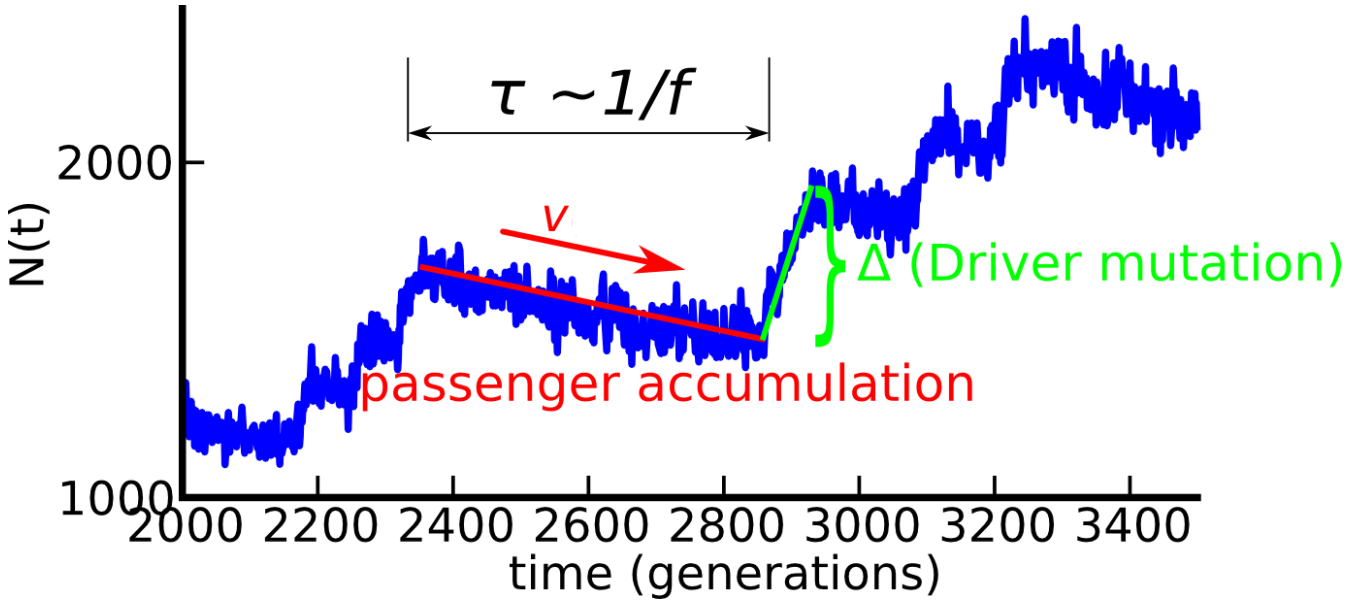
unstable fixed point

$$\frac{dN}{dt} = N(\mu_{\mathrm{d}} s_{\mathrm{d}}^2 N - \mu_{\mathrm{p}} s_{\mathrm{p}}) = \mu_{\mathrm{p}} s_{\mathrm{p}} N \left(\frac{N}{N^*} - 1 \right)$$





Stochastic drivers and deterministic passengers



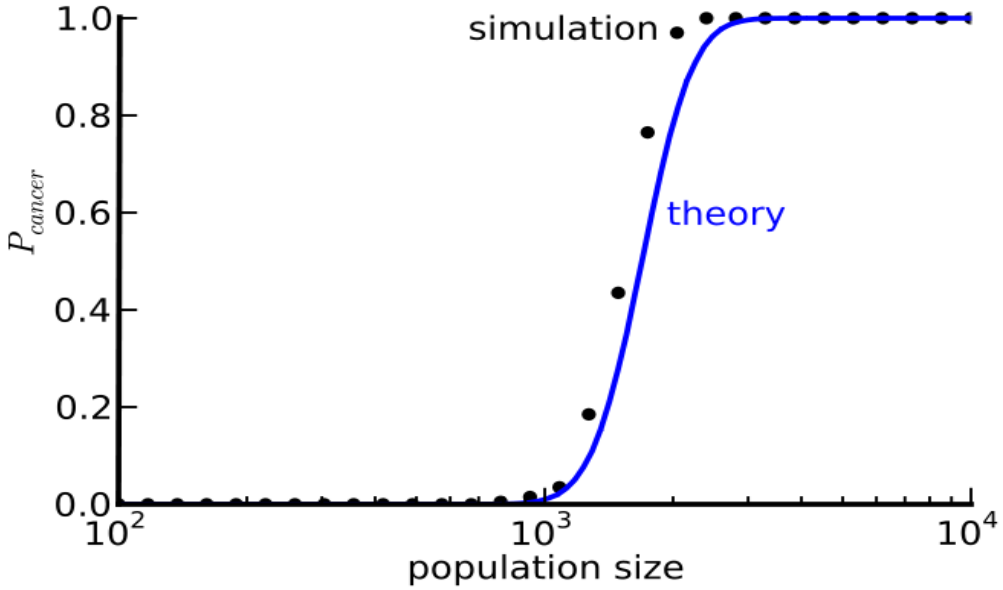
$$dN = -v(N) + \Delta(N)dn_d$$

$$n_{\mathrm{d}} \xrightarrow{f(N)} n_{\mathrm{d}} + 1$$

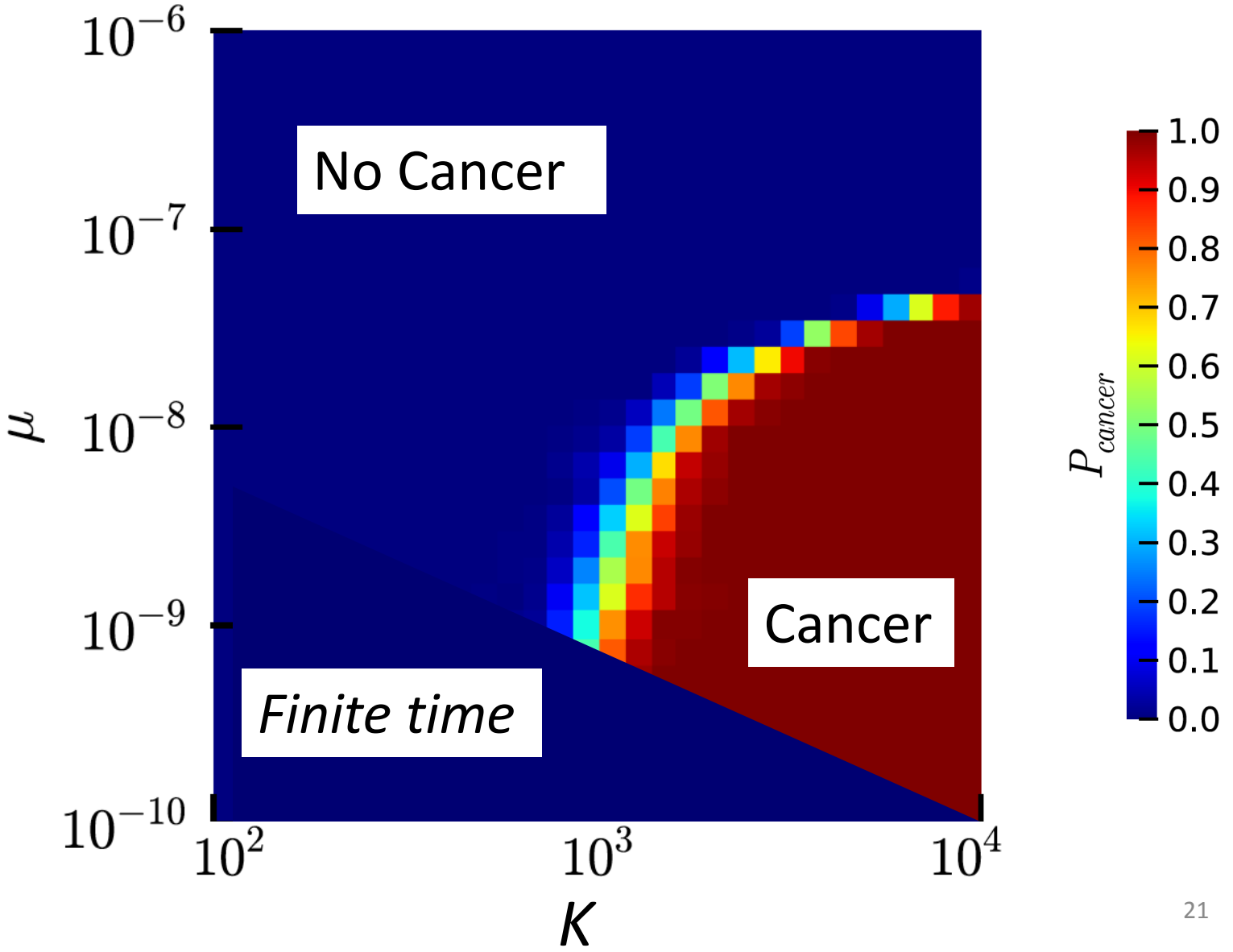
Estimating the probability of cancer

$$dN = -v(N) + \Delta(N)dn_d$$

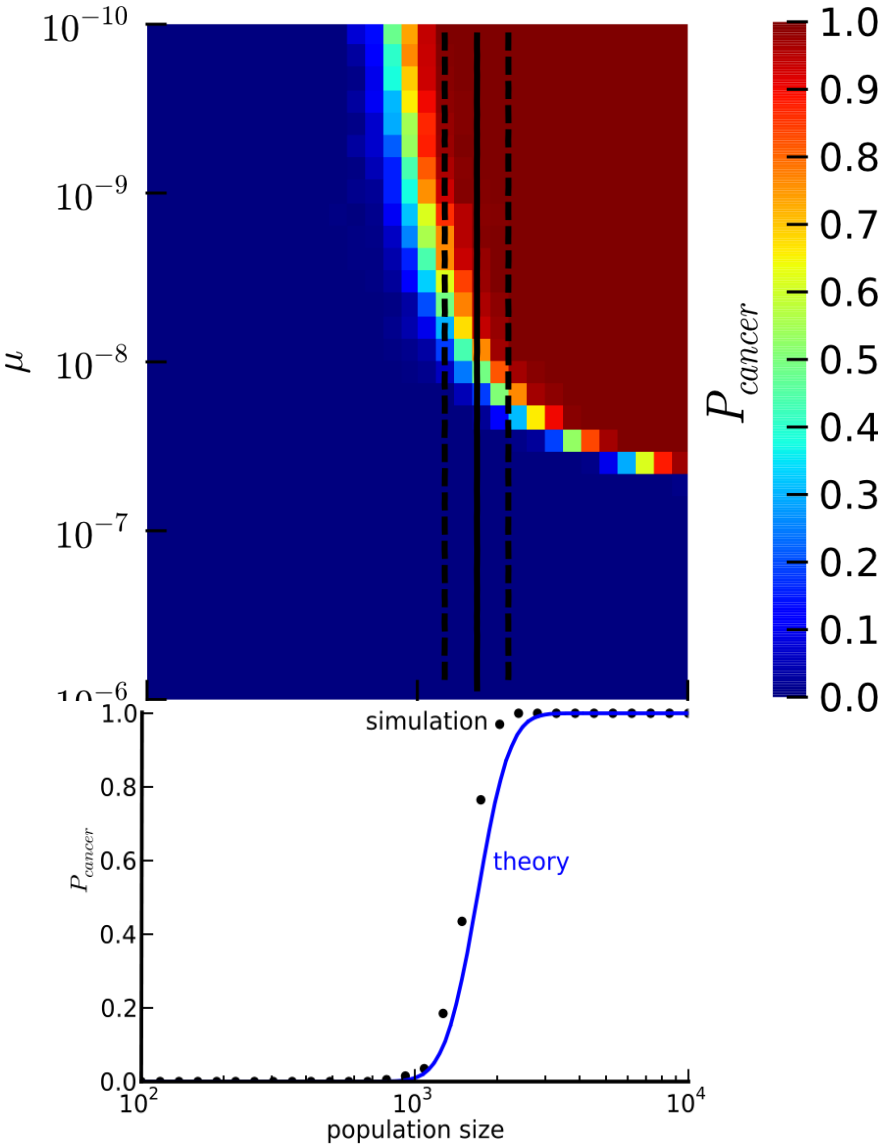
Parameter	Estimate	Assumption
$v(N)$	$N\mu_p s_p$	Effectively neutral
$\Delta(N)$	Ns_d	No hitchhikers
$f(N)$	$N\frac{\mu_d s_d}{1+s_d}$	Moran Process (two alleles)



Simulated results



Comparing to our first theory



Perhaps passengers fixate slower?

Fixation probability in the Moran model

$$\pi = \frac{1 - 1/r}{1 - (1/r)^N}$$

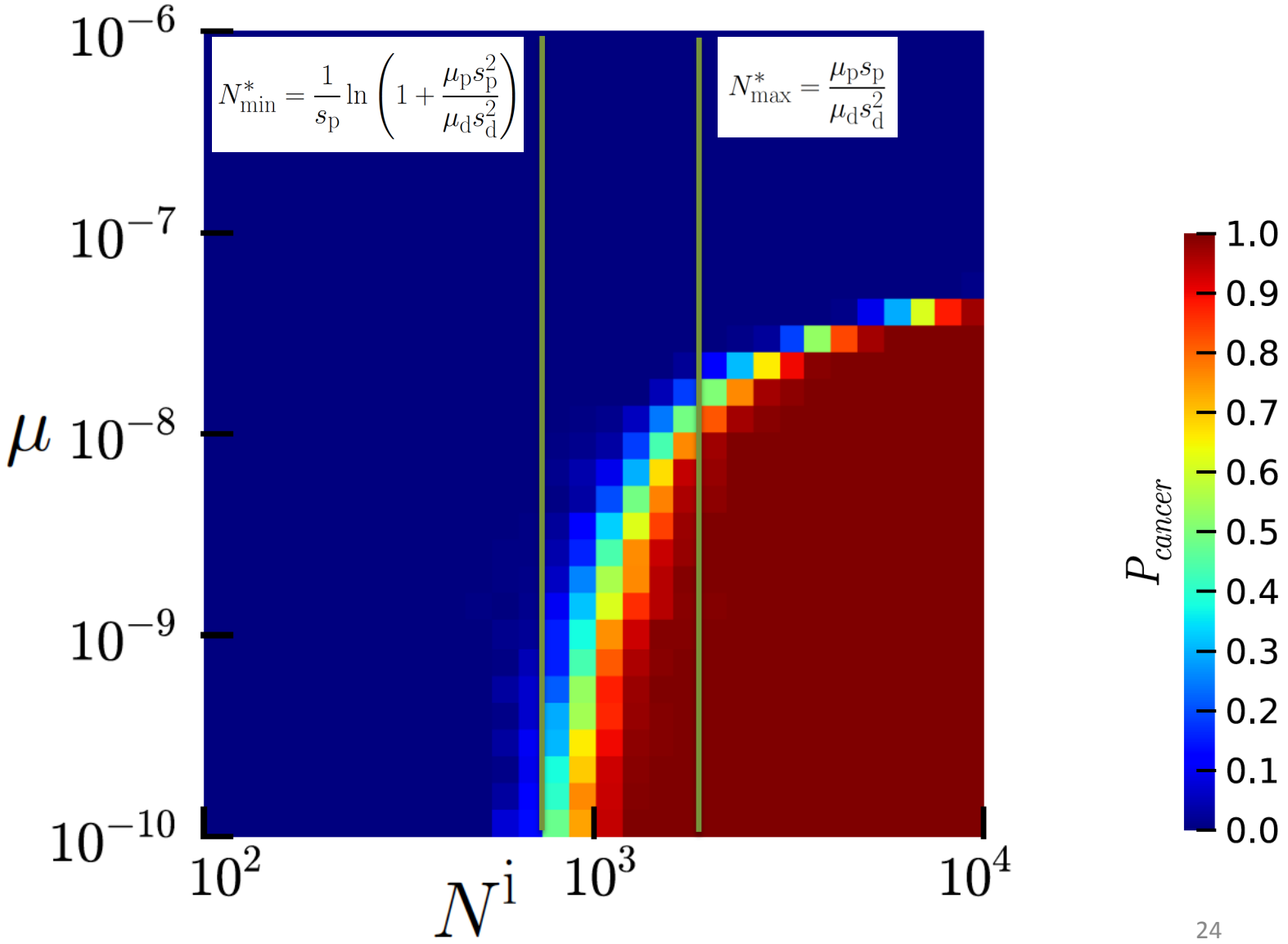
r is the ratio of the mutant growth rate and wild type growth rate

$$\pi_{\mathrm{p}} = s_{\mathrm{p}} e^{-\ln(1+s_{\mathrm{p}})N} \approx s_{\mathrm{p}} e^{-s_{\mathrm{p}}N}$$

Lower bound on fixation rate of passenges

$$N^*_{\min} = \frac{1}{s_{\mathrm{p}}} \ln\left(1 + \frac{\mu_{\mathrm{p}} s_{\mathrm{p}}^2}{\mu_{\mathrm{d}} s_{\mathrm{d}}^2}\right)$$

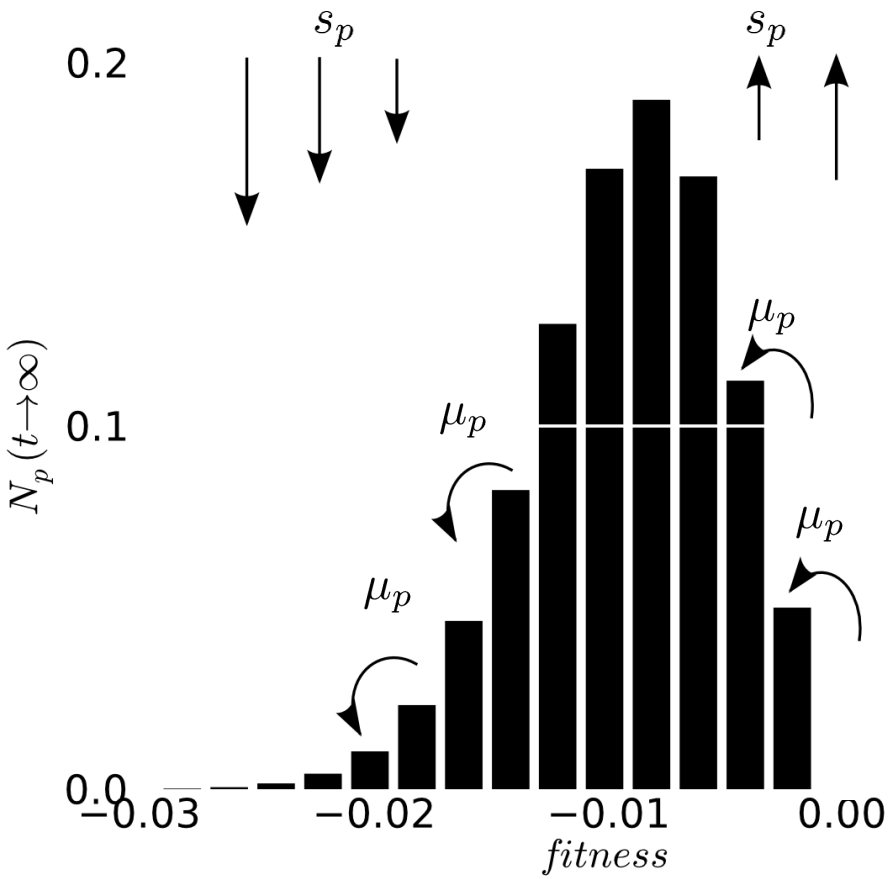
π_p explains part of the deviation from simulations



In reality, π_p is even more complicated

$$\frac{dN_P}{dt} = N\left(\frac{b}{(1+s_p)^P} - \frac{N}{K}\right) + \mu_p(N_{P-1} - N_{P+1})$$

$$N_P(t \to \infty) = \frac{P^\lambda e^{-\lambda}}{P!} \qquad : \ \lambda = \frac{\mu_p}{s_p}$$



In reality, π_p is even more complicated

neutral

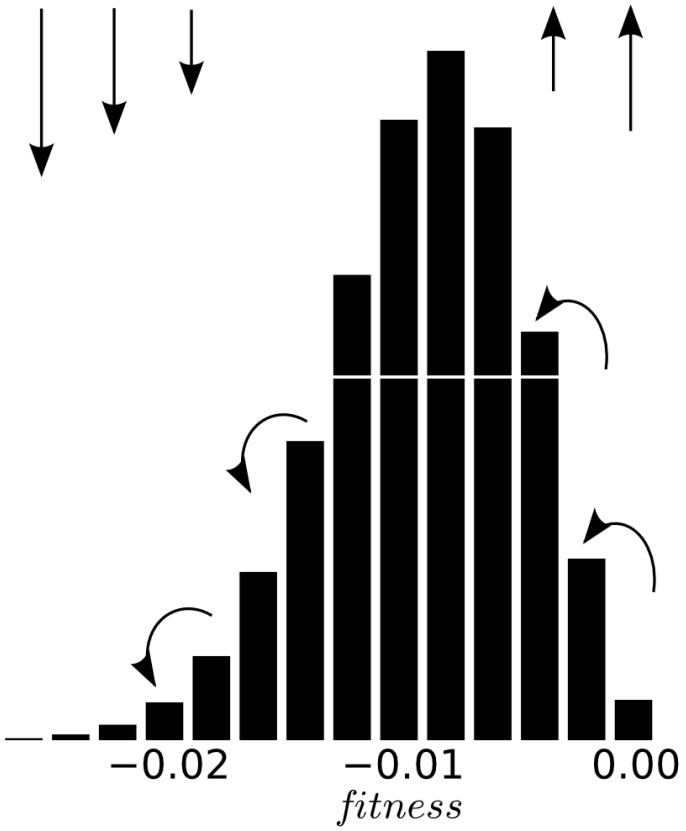
wave

Tsimring, Levine, Kessler (1996)
Rouzine, Brunet, and Wilke (2003, 2008)

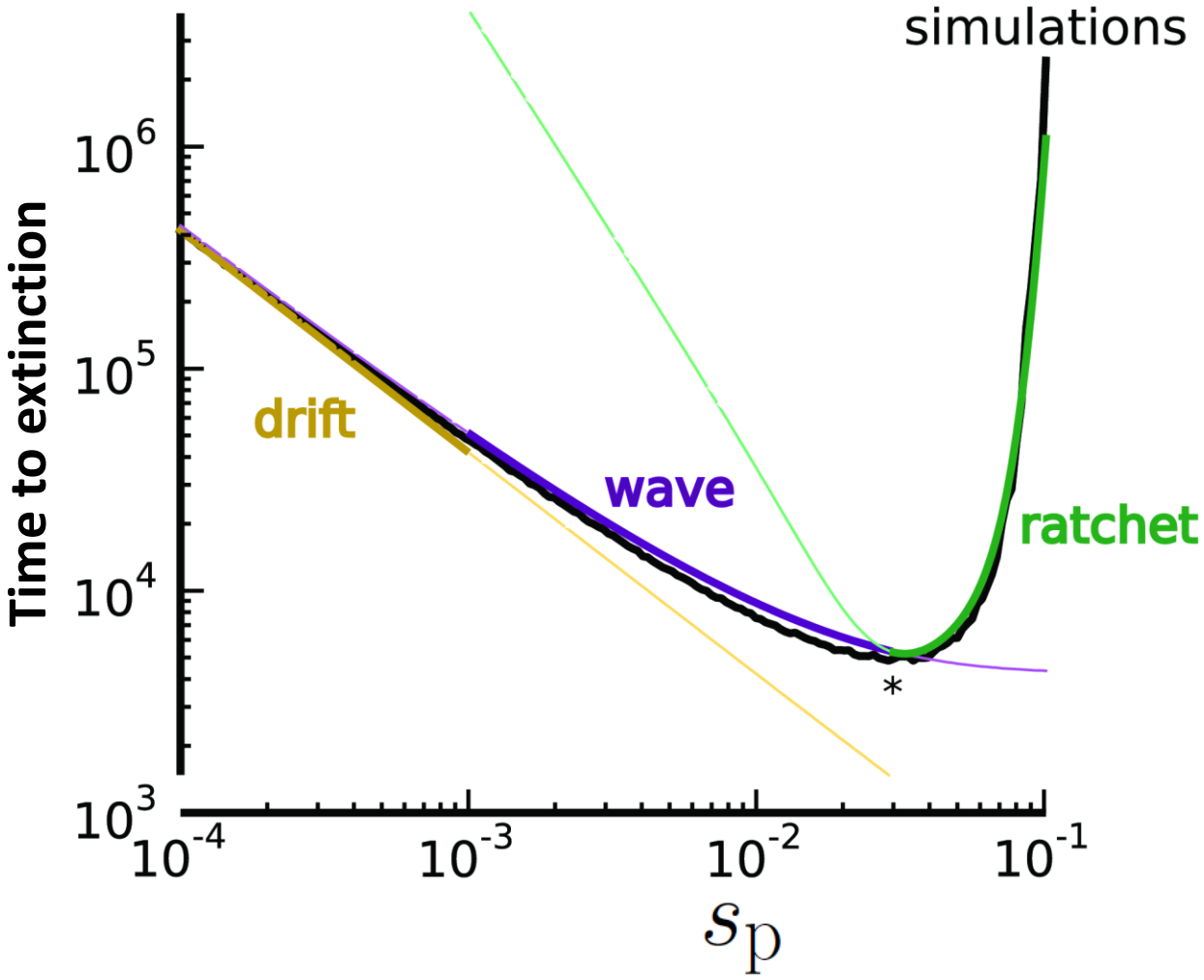
ratchet

Haigh (1978)
Gordo and Charlesworth (2000)

independent



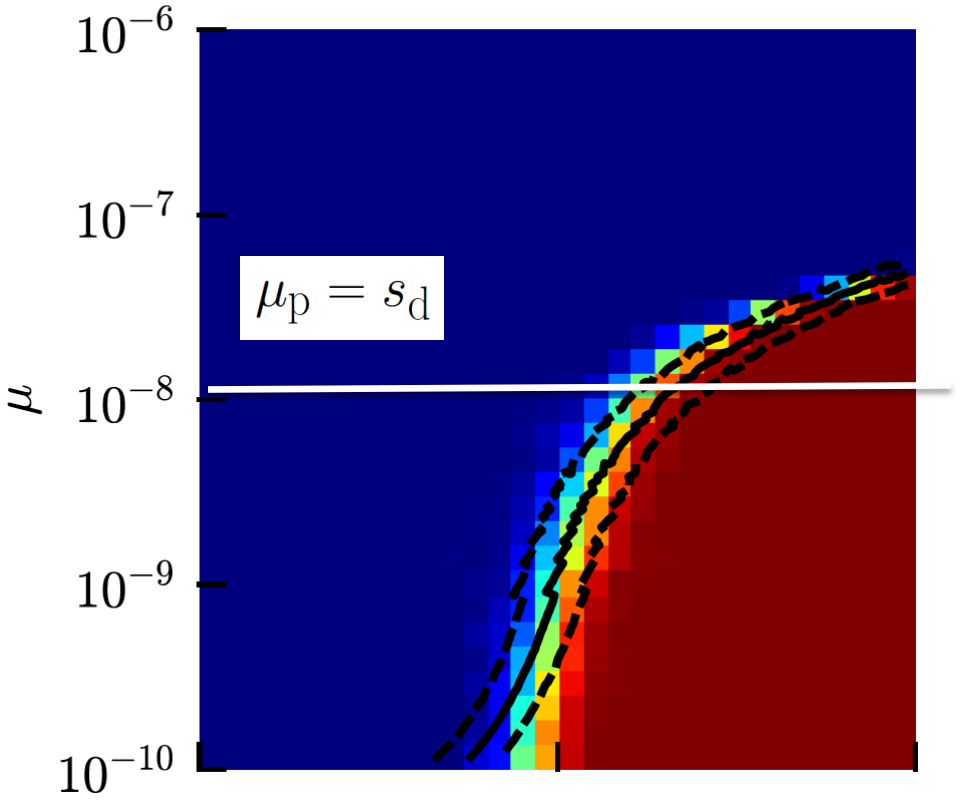
These regimes capture the non-monotonic behavior of passenger accumulation

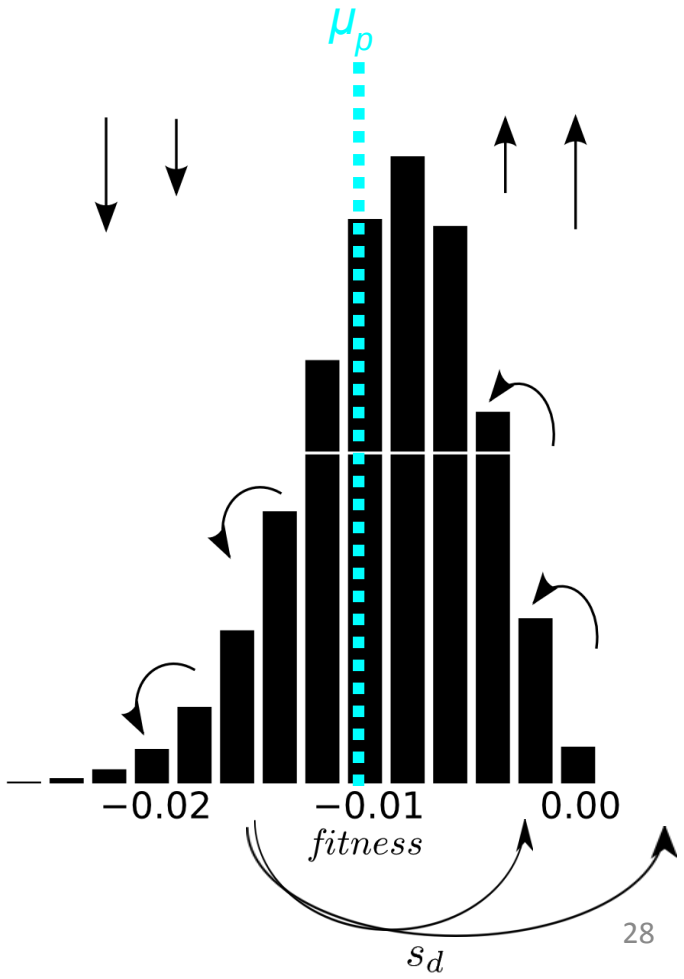


Dynamics for large μ

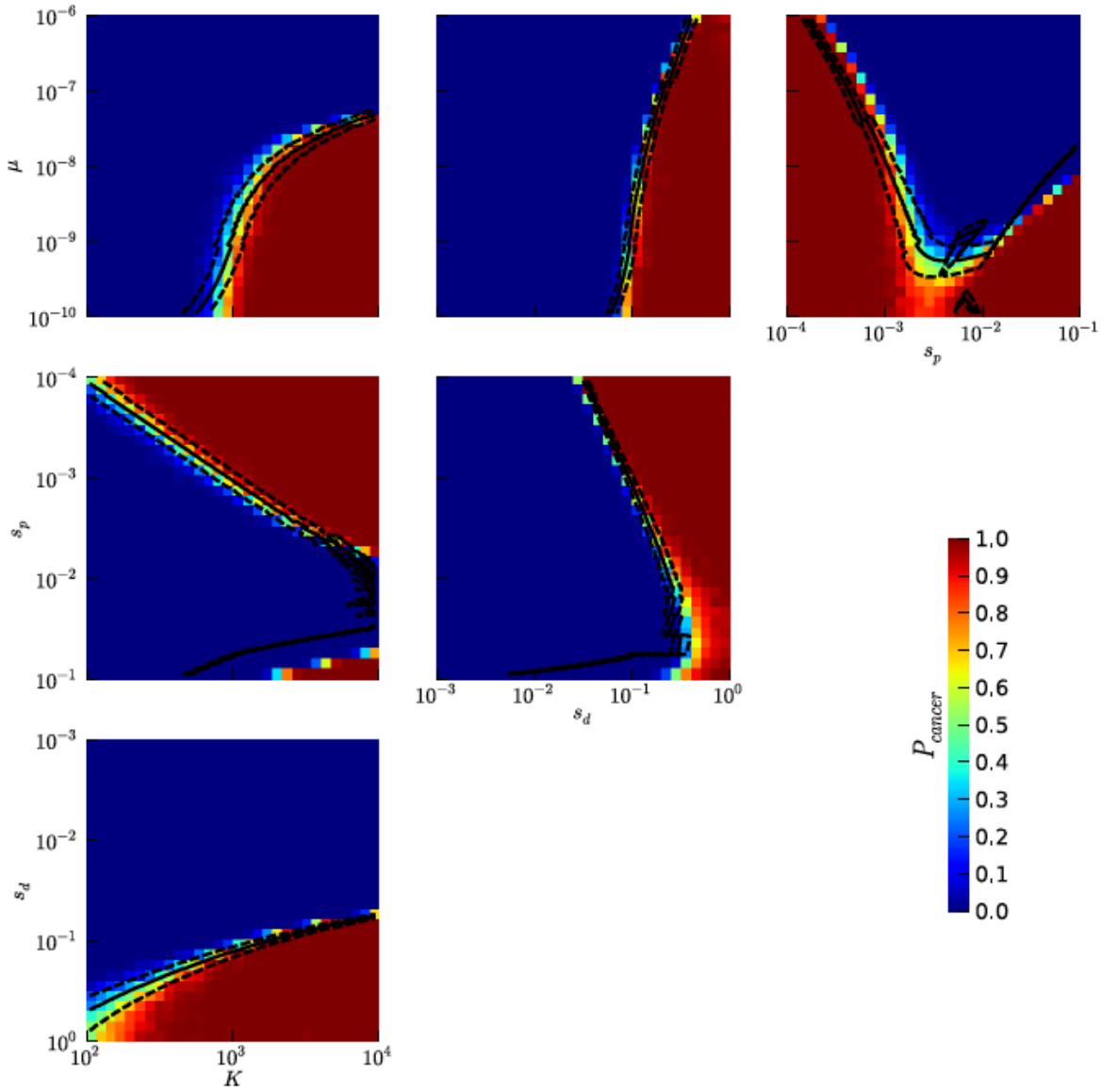
Johnson and Barton (2002)

$$N_P(t \to \infty) = \frac{P^{\lambda} e^{-\lambda}}{P!} \quad : \quad \lambda = \frac{\mu_p}{s_p}$$





Agreement is good across the phase space

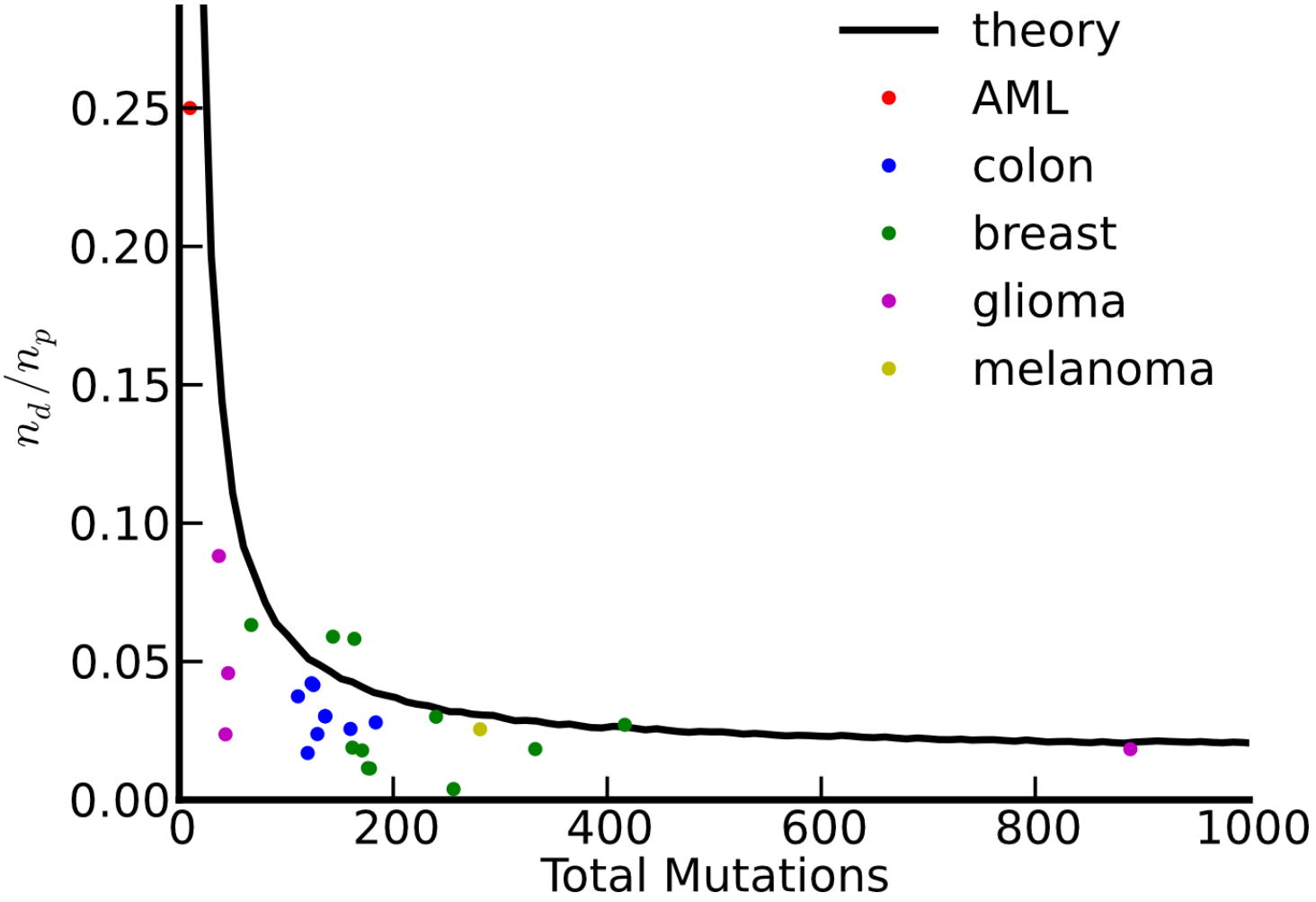


If drivers cause cancer, why study passengers?

- Passengers slow down **evolution** of cancer ✓
  - -Reduce fitness of population
  - -Prevent fixation of drivers
- Passengers constrain evolution of cancer ✓
  - -Two phases of cancer
- Passengers affect interpretation of **sequencing** data
  - -Carry non-neutral phenotypes
  - -Do not fix according to neutral theory?
- Passengers could be targets for cancer **therapies**

- Passengers could become **drivers**

Does our model explain observed accumulation patterns?



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  - -May not fix according to neutral theory
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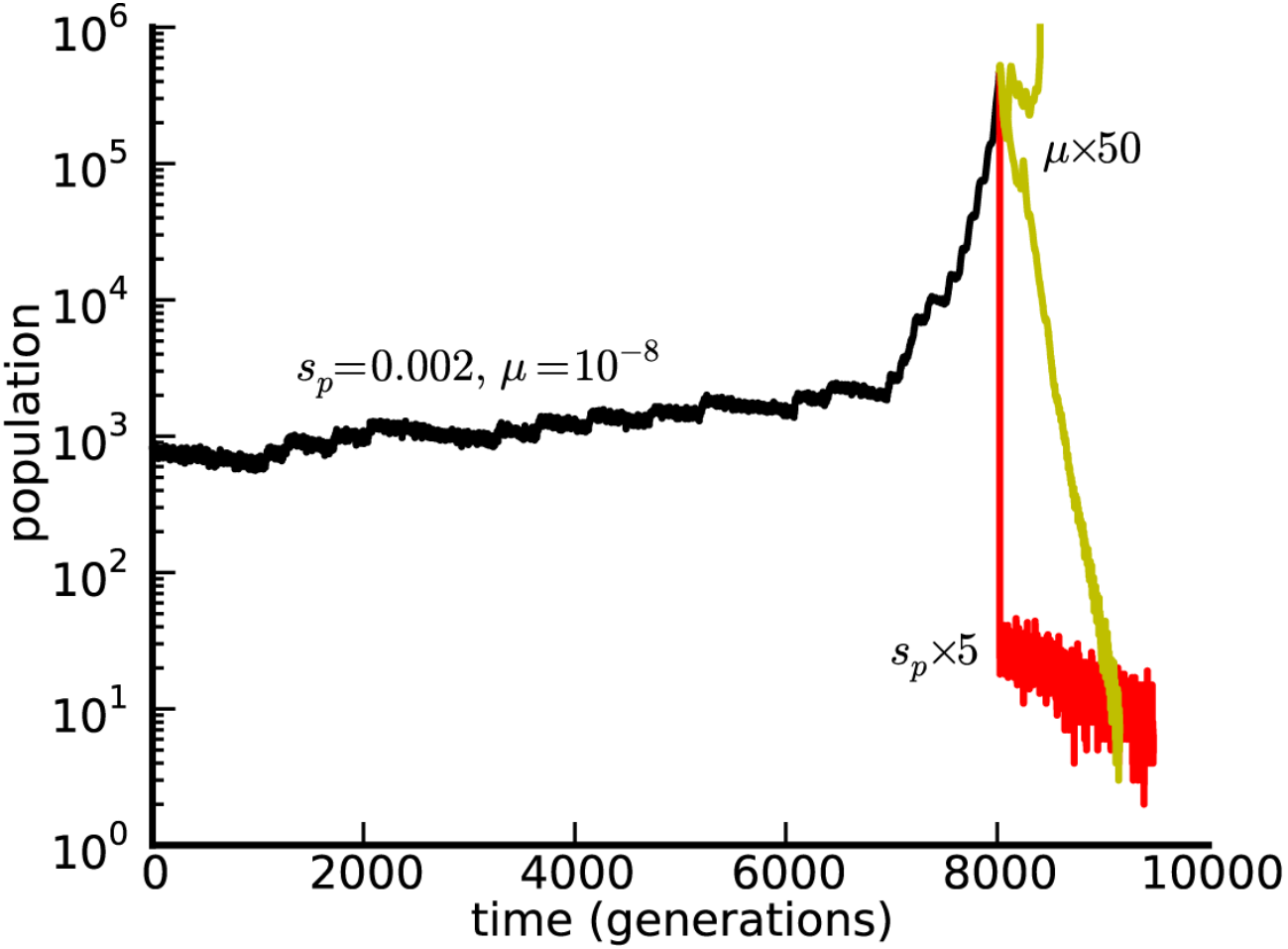
  "We need to trick these cells into developing evolutionary strategies which we can then exploit." Robert Gatenby, Thursday.
- Passengers could become **drivers**

Mutation rate and passenger deleteriousness can be exploited



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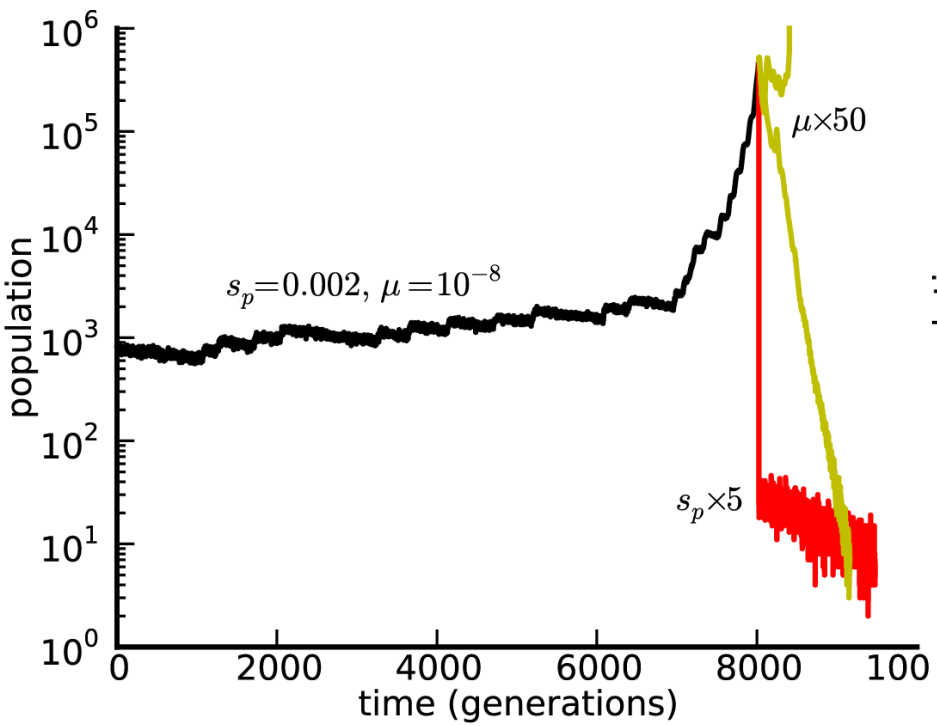
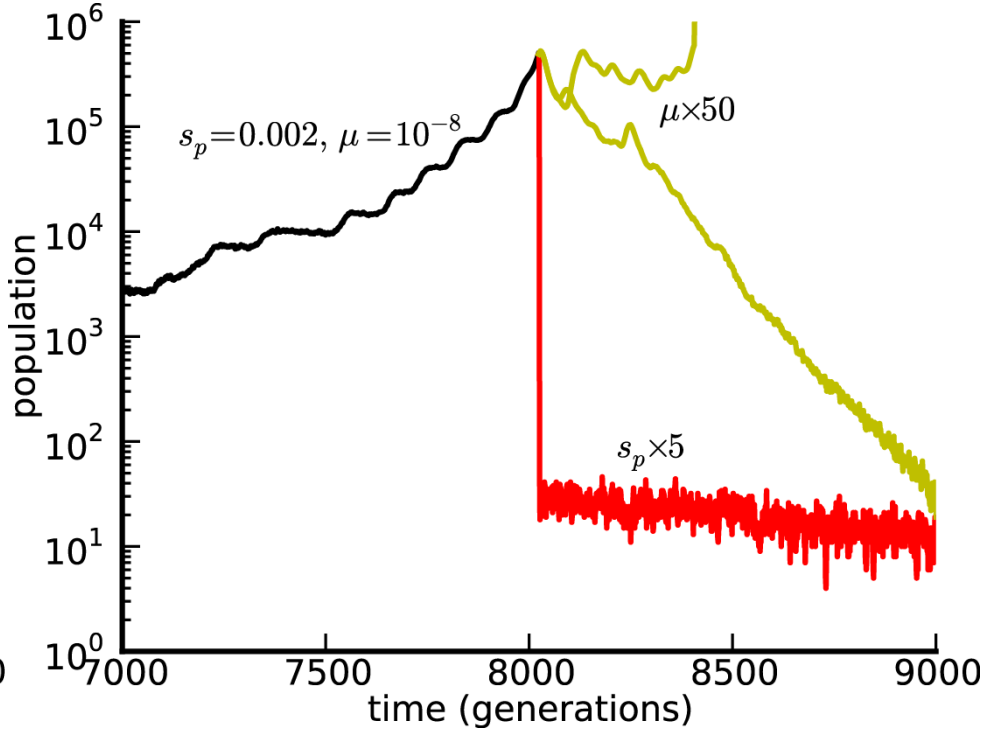


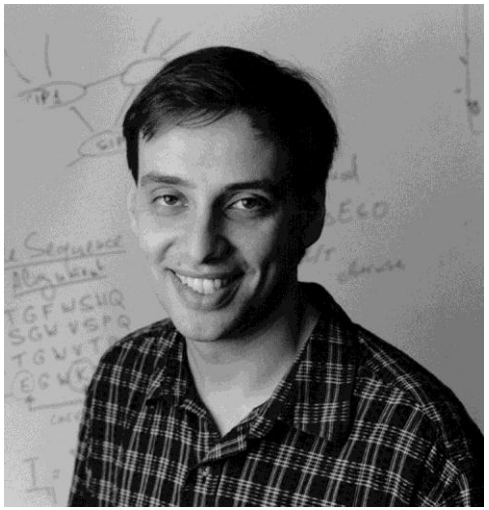


Increasing passenger's deleterious effects through proteotoxicity

- Most point mutations reduce fitness through partial mis-folding of expressed proteins (Geiler-Samerotte et al 2011 *PNAS*).
- Chaperon proteins were found to be widely expressed in cancer and indicative of poor prognosis (Santagata et al 2011 *PNAS*).
- Knockdown of *HSP1,* the master chaperon regulator, can prevent tumorgenesis in mice (Dai et al 2007 *Cell*).
- Greater DNA damage (Silva et al 2000 *Mutation Res*) and chromosomal instability (Birkbak et al. 2011 *Cancer Res*) correlates with positive clinical outcomes.
- Hyperthermia in combined treatment improves clinical outcomes (Wust et al 2002 *Lancet Oncology*).

Thanks!

Kirill Korolev
Analytical models



Leonid Mirny
My advisor

My Labmates:
Geoff Fudenberg
Maksim Imakaev
Jason Leith
Anton Goloborodko

Probability of developing cancer

$P_c(x)$ is the probability to develop cancer from the initial lesion of size $N^i=x$.

infinitesimal step analysis

$$P_c(x) = f(x)dtP_c[x + g(x)] + [1 - f(x)dt]P_c[x - v_p(x)dt]$$

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$$v_p(x)P_c'(x) = f(x)\{P_c[x + g(x)] - P_c(x)\} \qquad x + g(x) = \theta x$$

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$$v_p(x)P_c'(x) = f(x)\{P_c[x+g(x)] - P_c(x)\} \qquad x+g(x)=\theta x$$

$$\lambda \ln^2(\theta)x^2 P_c''(x) + \left[\lambda \ln^2(\theta)x + 2\lambda \ln(\theta)x - 2\nu\right] P_c'(x) = 0$$

boundary conditions $\quad P_c(0)=0 \qquad P_c(\infty)=1$

Probability of developing cancer

$$P_{\mathrm{c}}(N^{\mathrm{i}}) = 1 - \frac{\gamma\left(\frac{2}{s_{\mathrm{d}}}, \frac{2N^*}{s_{\mathrm{d}}N^{\mathrm{i}}}\right)}{\Gamma\left(\frac{2}{s_{\mathrm{d}}}\right)}$$

$$\gamma(s,x) = \int_0^x t^{s-1}e^{-t}dt$$

$$N^* = \frac{\mu_{\mathrm{p}}s_{\mathrm{p}}}{\mu_{\mathrm{d}}s_{\mathrm{d}}^2}$$

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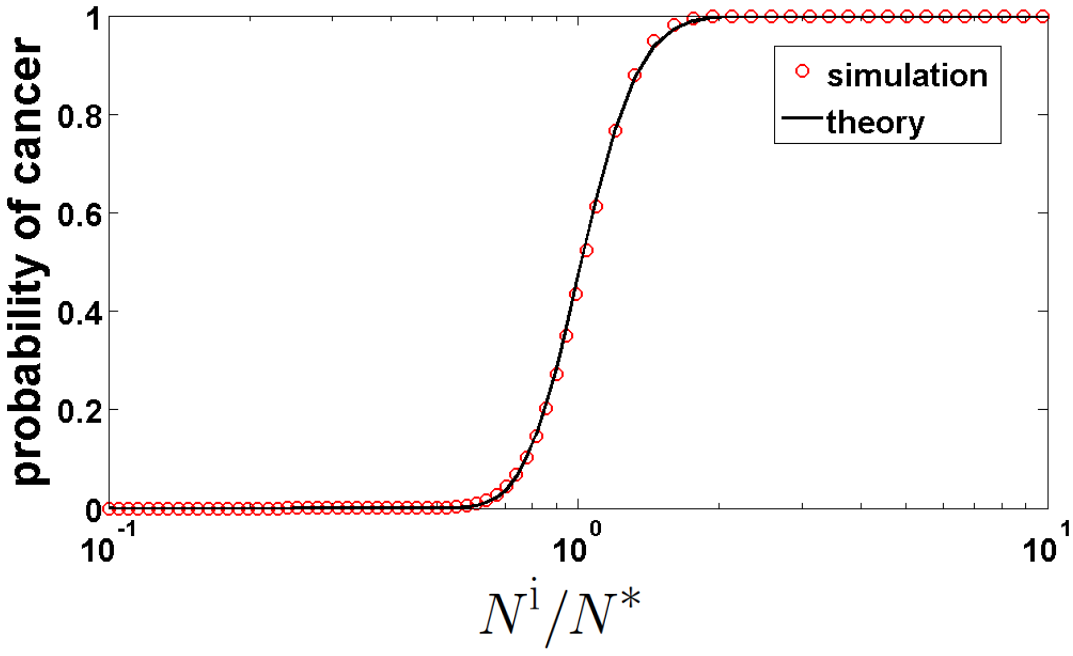

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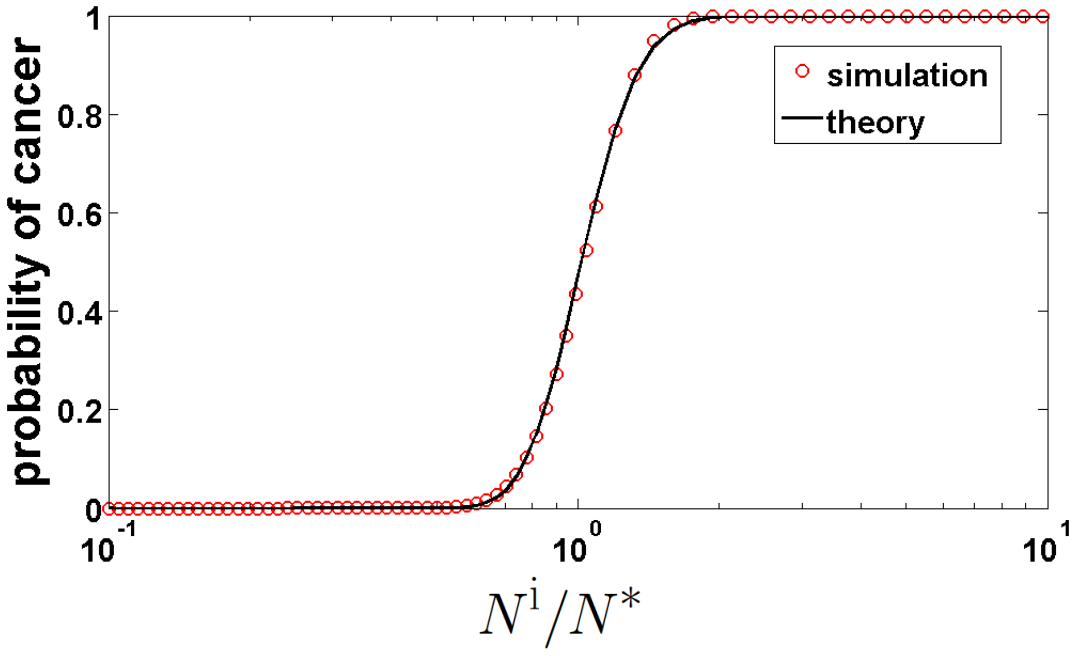
Small initial lesions

$$N^{\mathrm{i}}/N^* \ll 1$$

$$P_{\mathrm{c}}(N^{\mathrm{i}}) \sim (N^{\mathrm{i}})^{2/s_{\mathrm{d}}-1}e^{-2N^*/(s_{\mathrm{d}}N^{\mathrm{i}})}$$



Time to cancer

$$T_{\mathrm{c}}(x) = \frac{2}{\mu_{\mathrm{d}} s_{\mathrm{d}}^3} \int_x^\infty \frac{dy}{y^3} \frac{P_{\mathrm{c}}(y)[1 - P_{\mathrm{c}}(y)]}{P_{\mathrm{c}}'(y)} + \frac{2}{\mu_{\mathrm{d}} s_{\mathrm{d}}^3} \frac{1 - P_{\mathrm{c}}(x)}{P_{\mathrm{c}}(x)} \int_0^x \frac{dy}{y^3} \frac{P_{\mathrm{c}}^2(y)}{P_{\mathrm{c}}'(y)}$$

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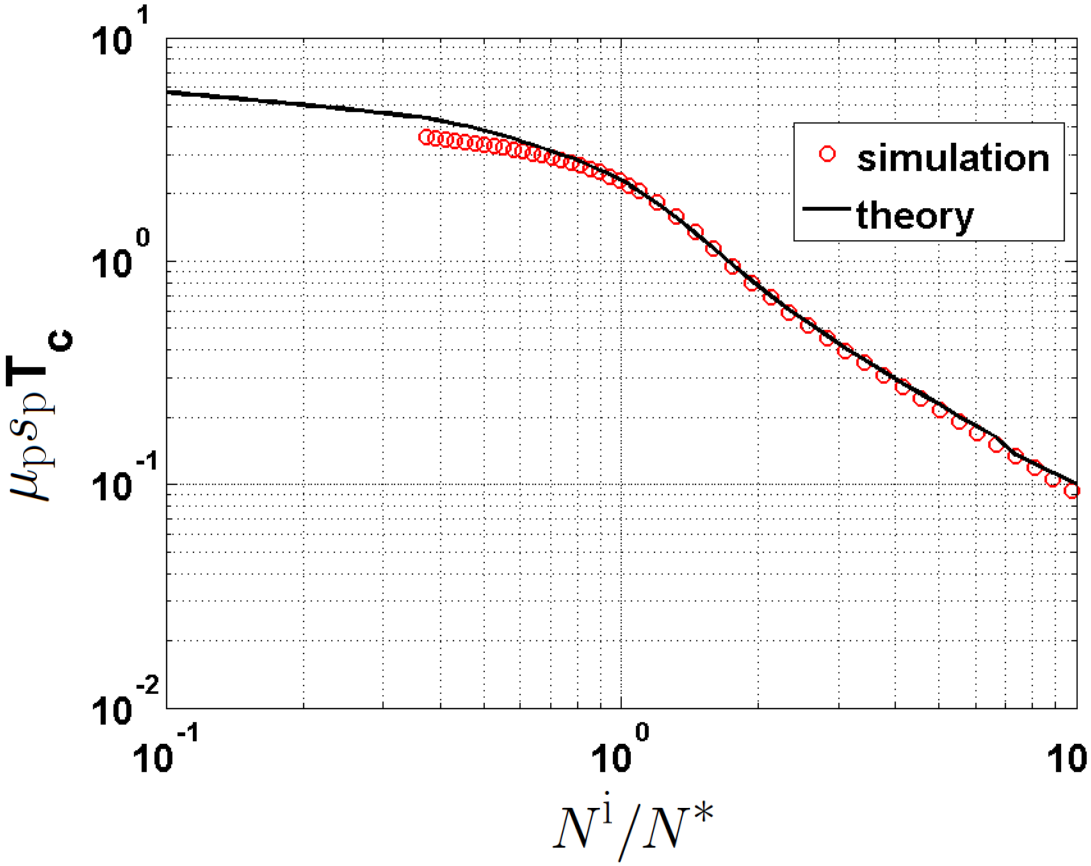
$$T_{\rm c}(x) = \frac{2}{\mu_{\rm d} s_{\rm d}^3} \int_x^\infty \frac{dy}{y^3} \frac{P_{\rm c}(y)[1-P_{\rm c}(y)]}{P_{\rm c}'(y)} + \frac{2}{\mu_{\rm d} s_{\rm d}^3} \frac{1-P_{\rm c}(x)}{P_{\rm c}(x)} \int_0^x \frac{dy}{y^3} \frac{P_{\rm c}^2(y)}{P_{\rm c}'(y)}$$

$$N^* = \frac{\mu_{\rm p} s_{\rm p}}{\mu_{\rm d} s_{\rm d}^2}$$



Time to cancer

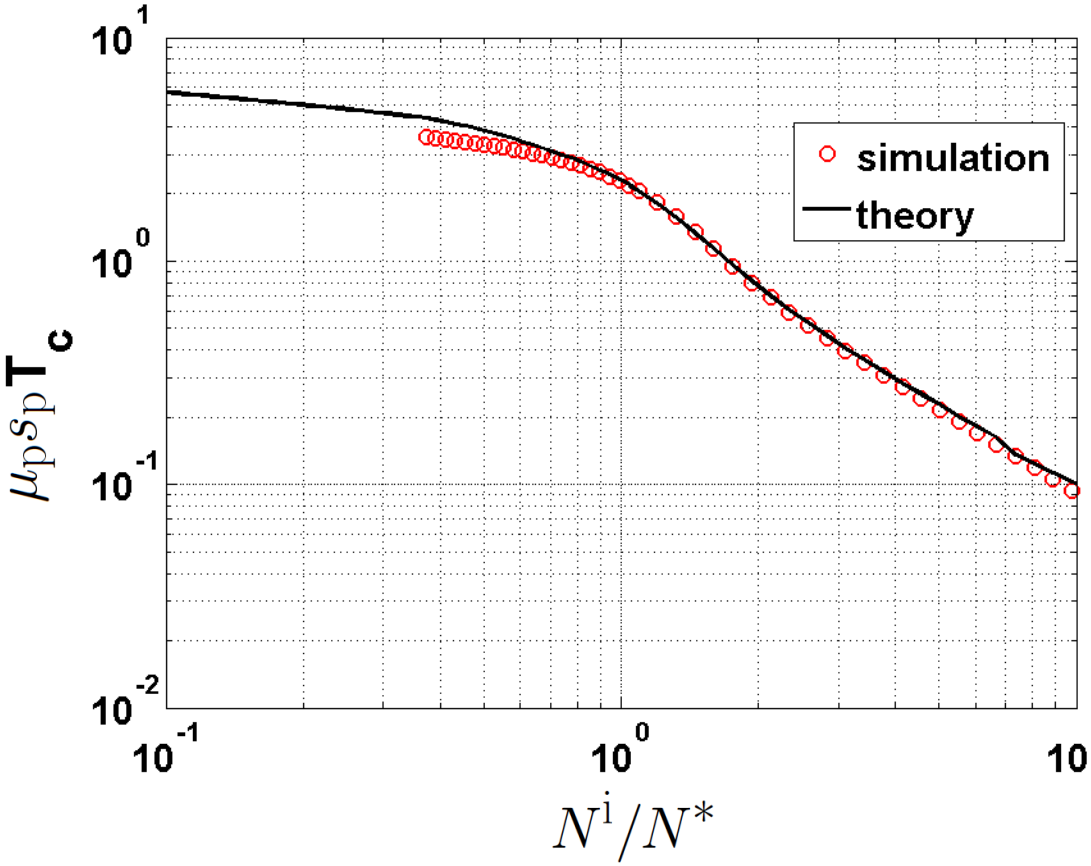
$$T_{\rm c}(x) = \frac{2}{\mu_{\rm d} s_{\rm d}^3} \int_x^\infty \frac{dy}{y^3} \frac{P_{\rm c}(y)[1-P_{\rm c}(y)]}{P_{\rm c}'(y)} + \frac{2}{\mu_{\rm d} s_{\rm d}^3} \frac{1-P_{\rm c}(x)}{P_{\rm c}(x)} \int_0^x \frac{dy}{y^3} \frac{P_{\rm c}^2(y)}{P_{\rm c}'(y)}$$

$$N^* = \frac{\mu_{\rm p} s_{\rm p}}{\mu_{\rm d} s_{\rm d}^2}$$

Small initial populations

$$N^{\rm i}/N^* \ll 1$$

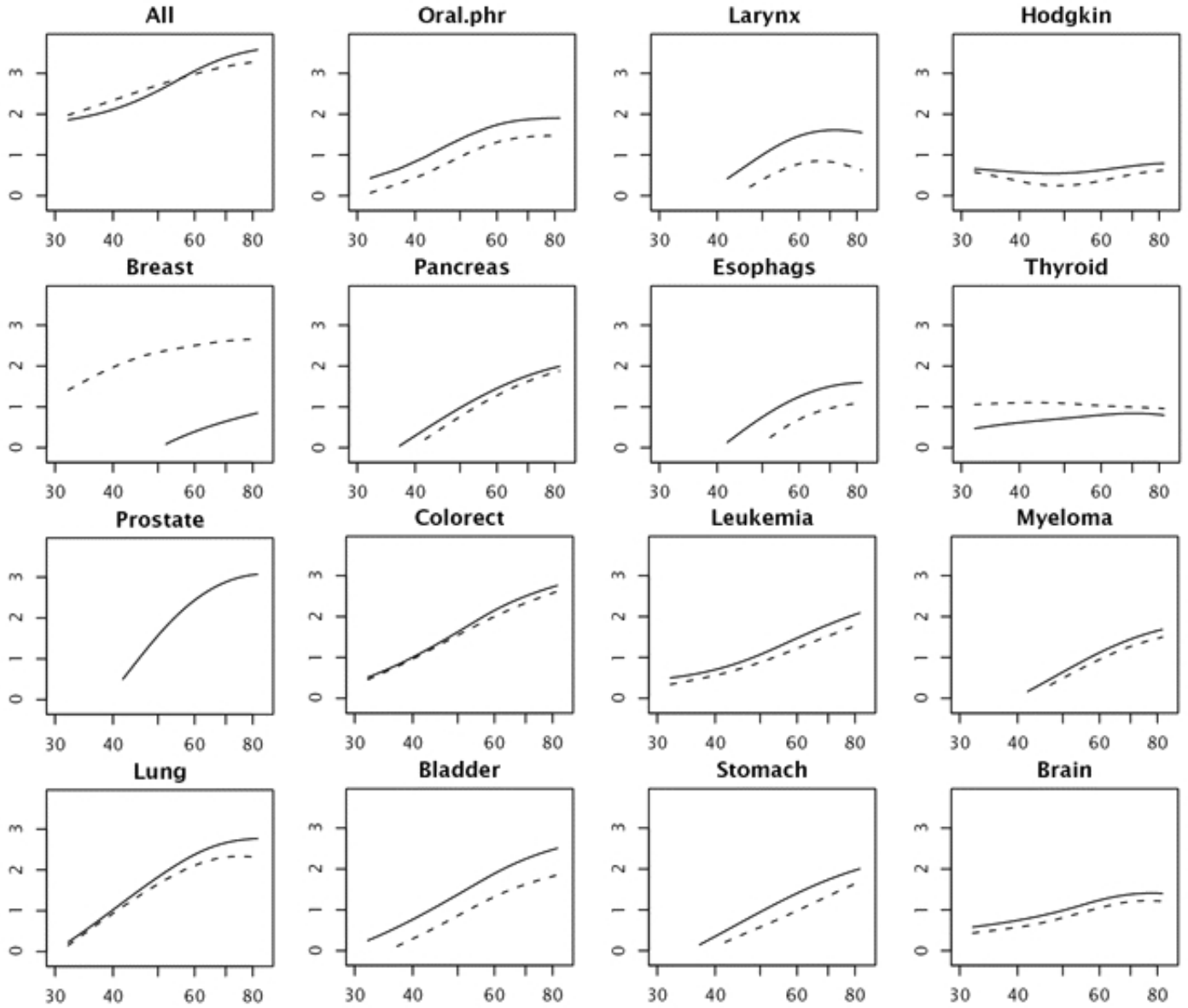
$$T_{\rm c}(N^{\rm i}) \approx \frac{1}{\mu_{\rm p} s_{\rm p}} \ln\left(\frac{N^*}{N^{\rm i}}\right) + \text{const}$$



Main results from the simple model

- There is a critical population size $\mathbf{N^*}$.
- The **probability of cancer** can be very small due to the accumulation of passengers.
- The **width** of the transition depends on the fitness advantage of drivers.
- The **time to cancer** depends weakly on the initial size and is determined by the rate of passenger accumulation.

Different cancers require different number of steps



Frank, Dynamics of Cancer (2007)