Massachusetts Institute of Technology

INSTITUTE FOR MEDICAL ENGINEERING & SCIENCE

Cancer as an evolutionary process

Leonid Mirny (MIT)

Mutational landscape of cancer [phenotypes]

Cell, Vol. 100, 57–70, January 7, 2000, Copyright ©2000 by Cell Press

The Hallmarks of Cancer

Douglas Hanahan* and Robert A. Weinberg†

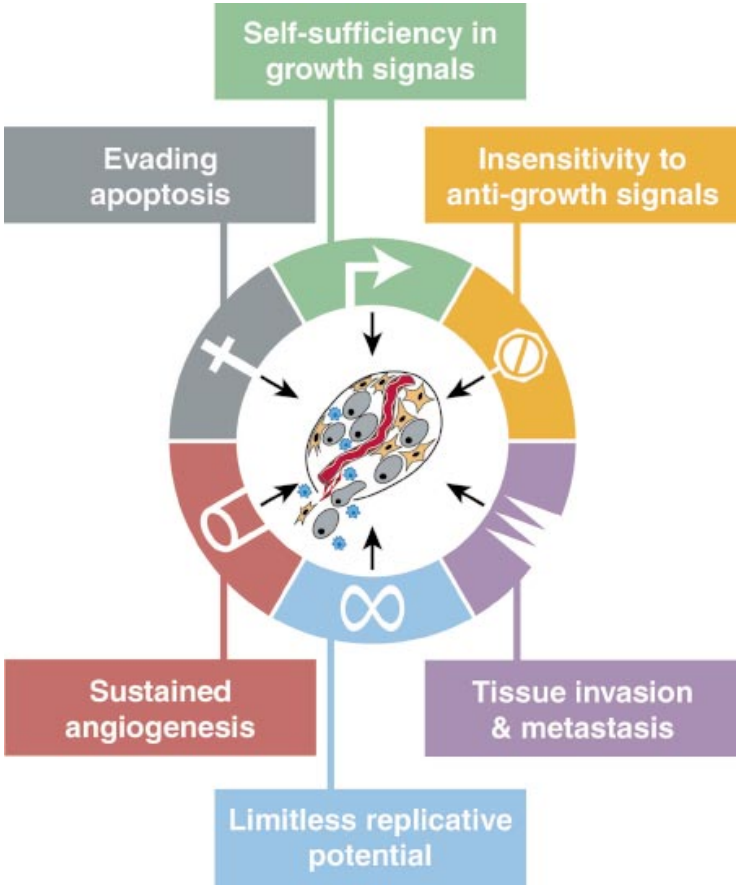


Figure 1. Acquired Capabilities of Cancer

We suggest that most if not all cancers have acquired the same set of functional capabilities during their development, albeit through various mechanistic strategies.

Oncogenes and tumor suppressors **[drivers]**

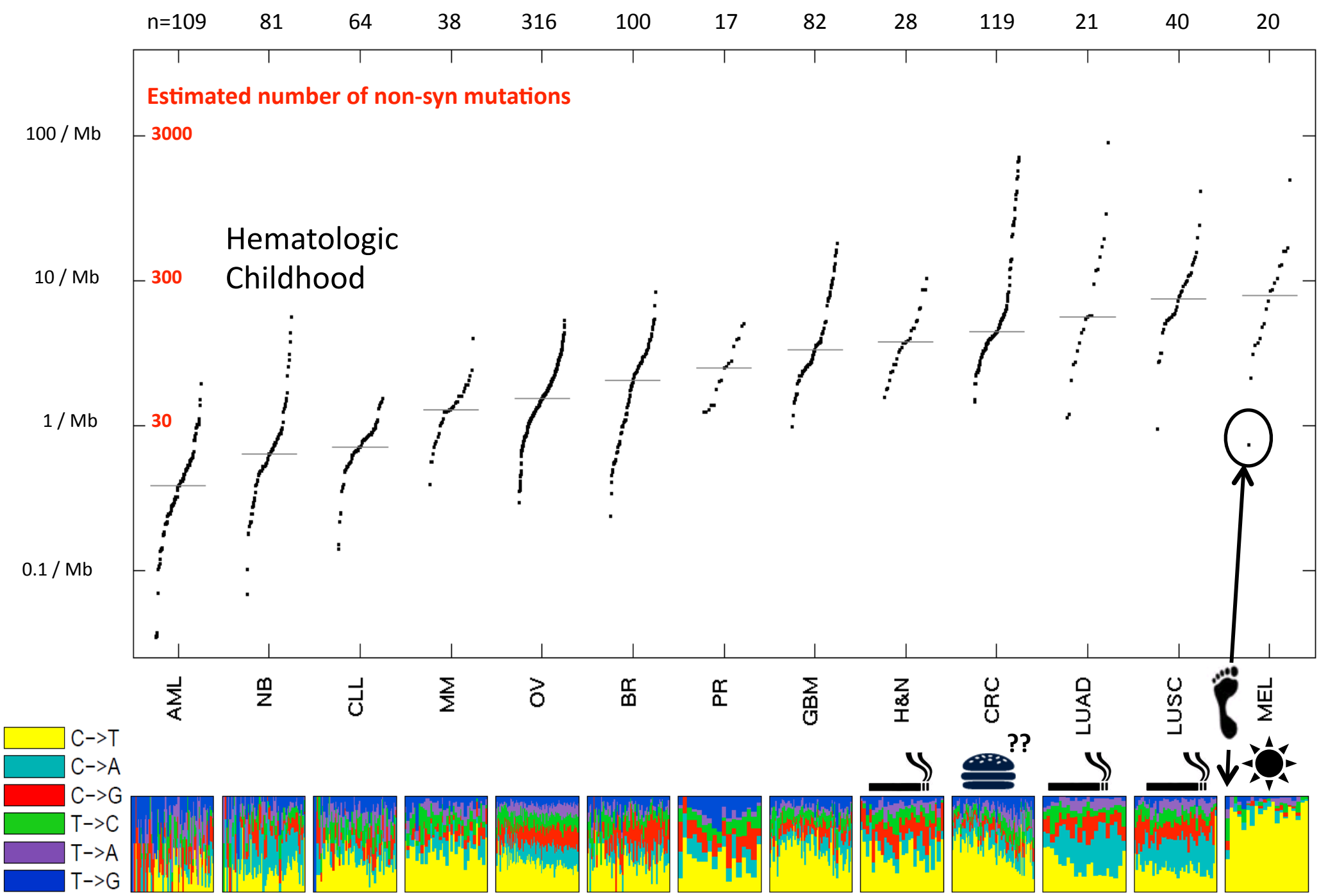
- Oncogenes -- need to be activated
  - by mutations (within a gene or regulatory regions)
  - by chromosomal alterations
  - overexpression/modifications

  one copy is enough
- Tumor suppressors -- need to be inactivated

  - mutations, chromosomal loss, modifications

  second copy needs to be affected (e.g. lost, LOH)

Rates of somatic mutation vary across cancers: [G.Getz]



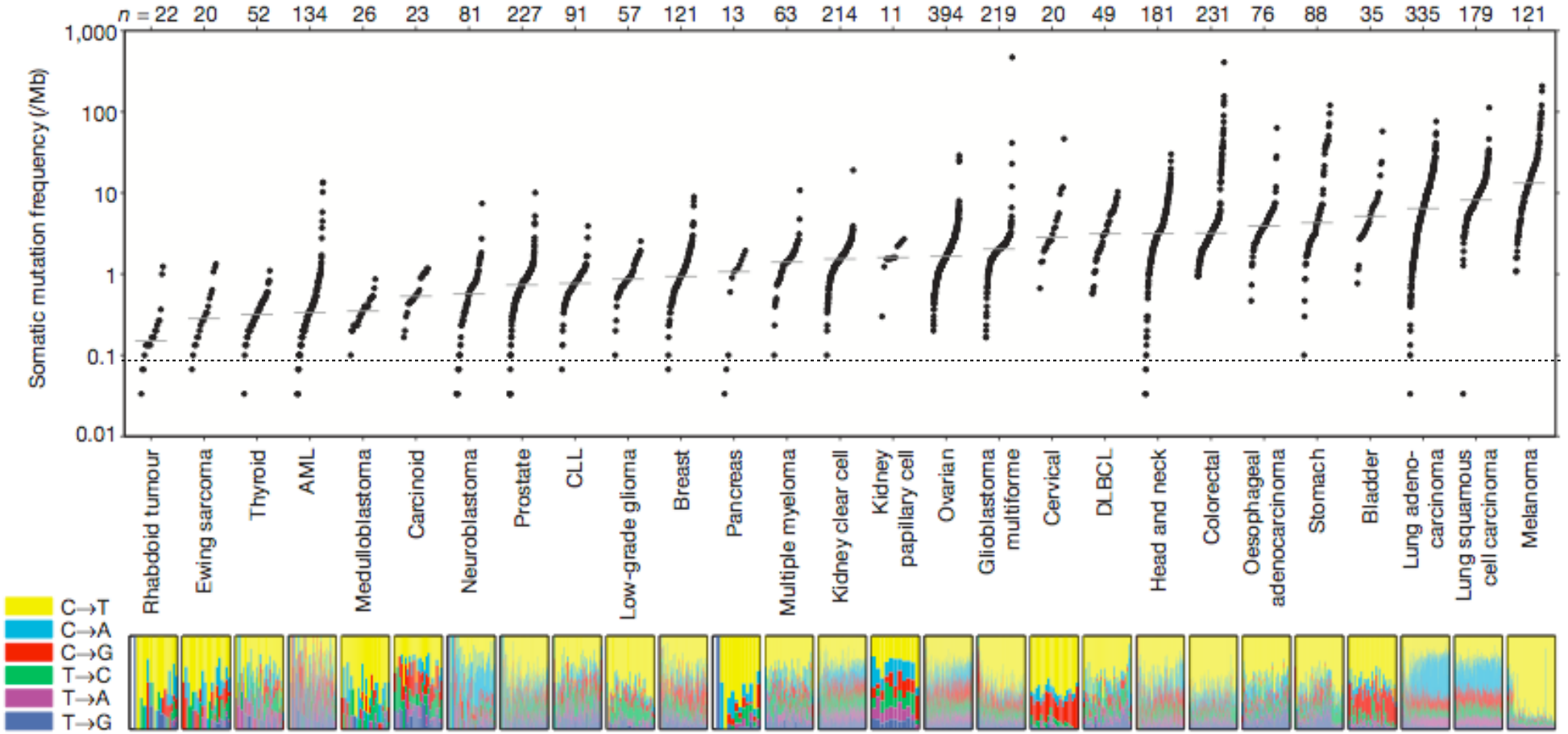
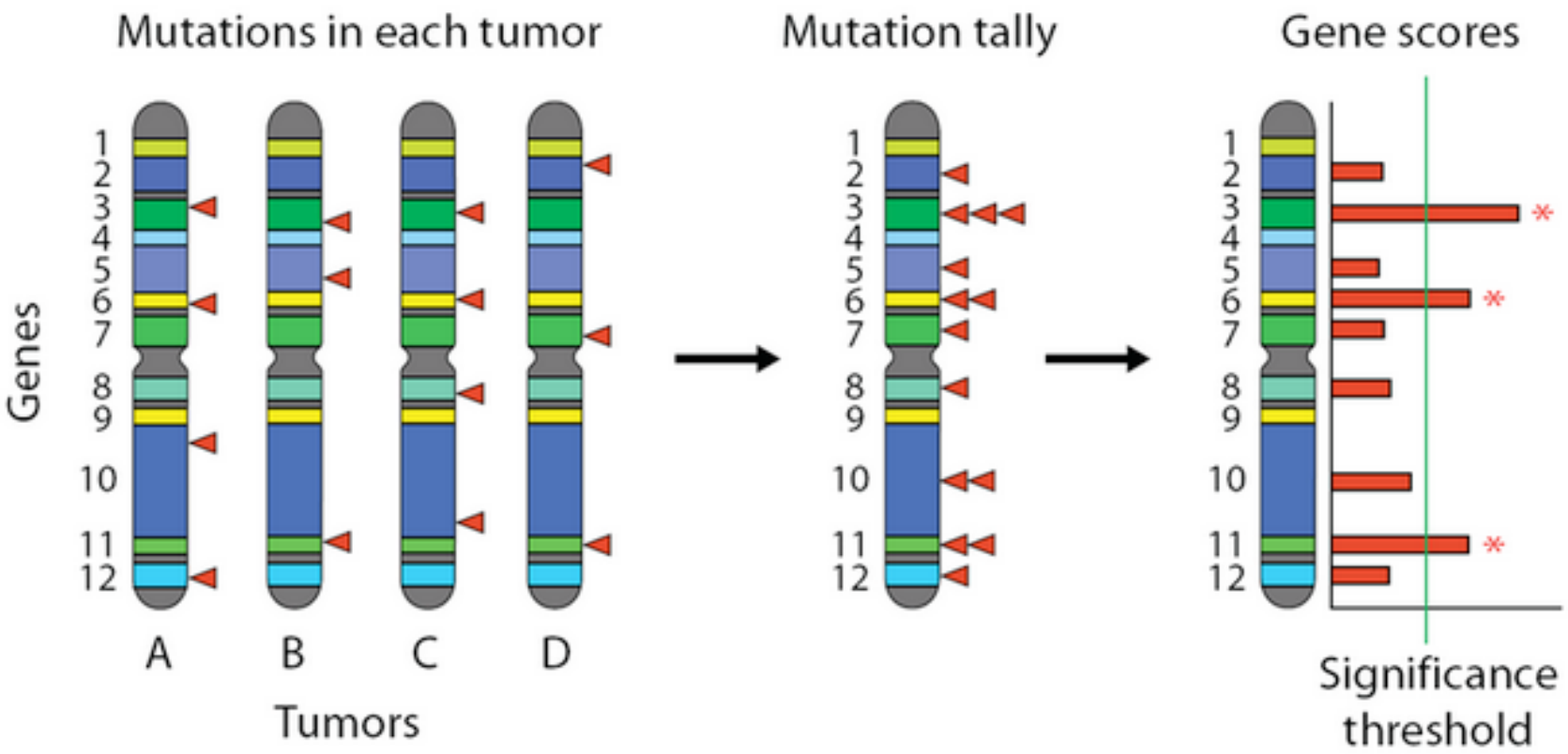


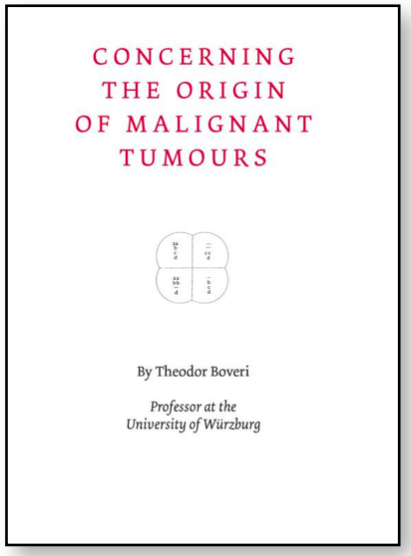
Figure 1 | Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs. Each dot corresponds to a tumour–normal pair, with vertical position indicating the total frequency of somatic mutations in the exome. Tumour types are ordered by their median somatic mutation frequency, with the lowest frequencies (left) found in haematological and paediatric tumours, and the highest (right) in tumours induced by carcinogens such as tobacco smoke and ultraviolet light. Mutation frequencies vary more than 1,000-fold between lowest and highest across different cancers and also within several tumour types. The bottom panel shows the relative proportions of the six different possible base-pair substitutions, as indicated in the legend on the left. See also Supplementary Table 2.

M. Lawrence et al *Nature* 2013

Finding **driver** events



Somatic Copy Number Alterations (SCNAs)



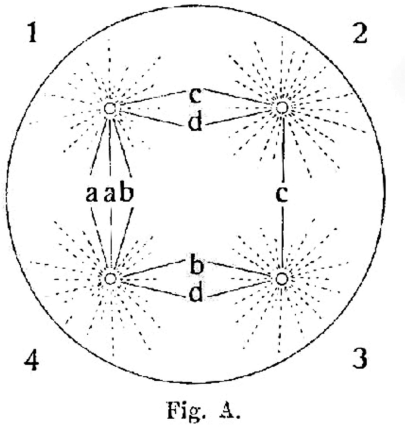
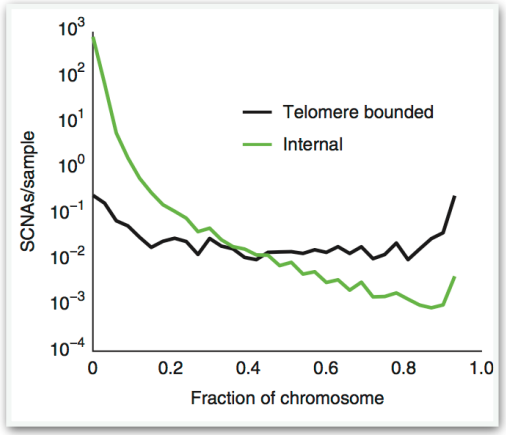
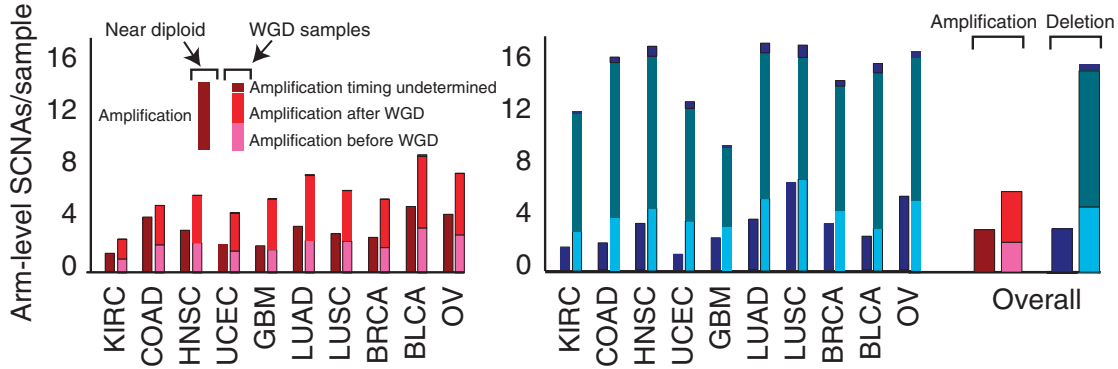
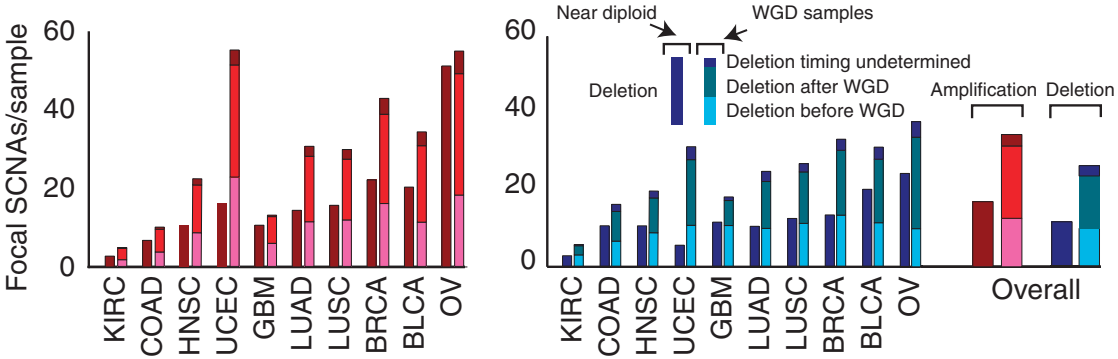


Fig. A.







Cancer genomics

100-400 amino acid substitutions

10-40 chromosomal rearrangements

2-5 drivers

the rest are passengers

High rate of somatic mutations/alterations

Can some passengers

... be deleterious to cancer cells?

... affect progression?

Drivers and passengers

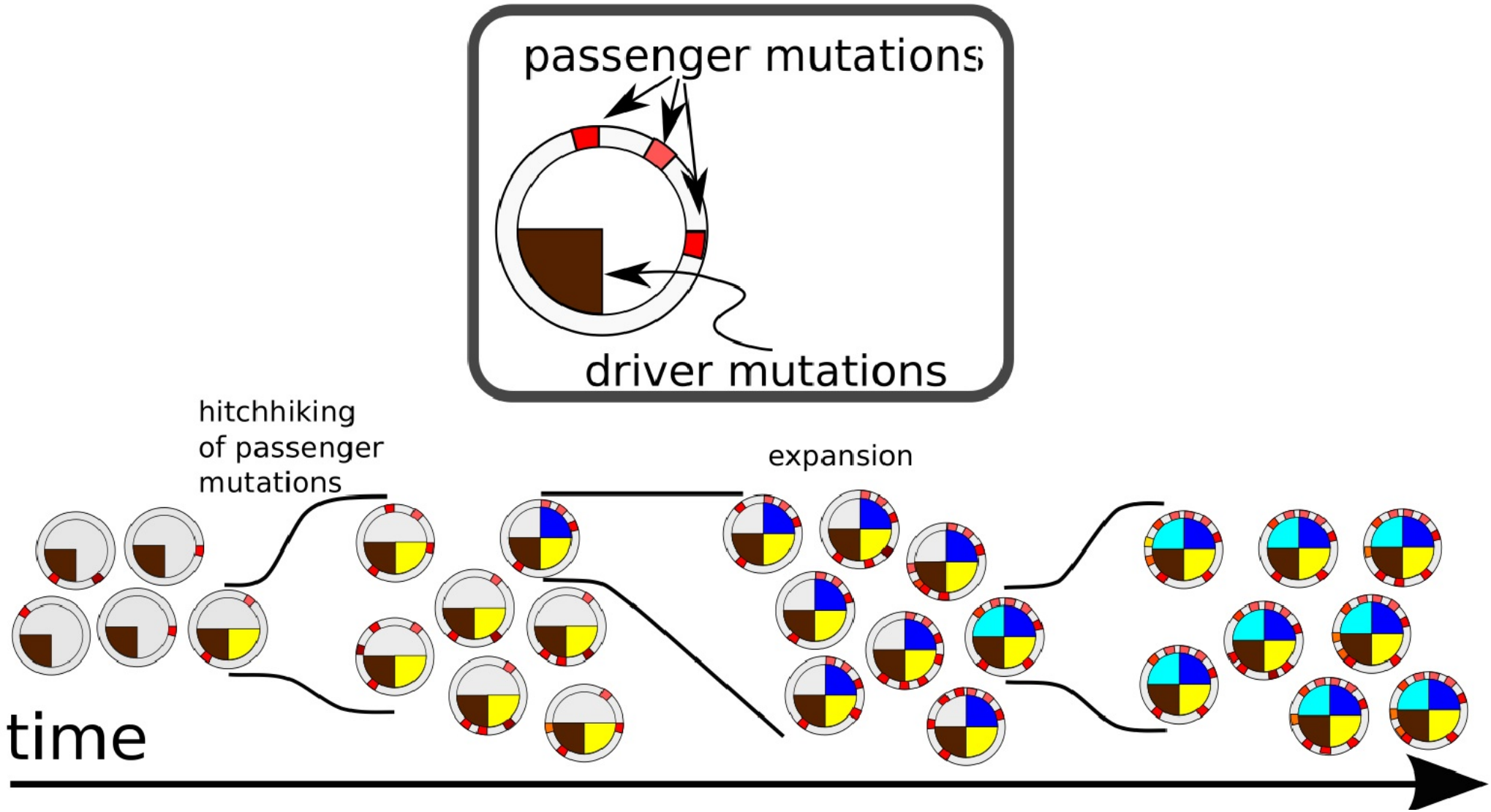
Table 1. Passenger mutations in whole-genome sequences

Cancer(s)	Protein-coding mutations	Driver mutations*	Ref(s).
11 breast	115.4	5.1	(4)
10 colon	75	4	(4)
4 astrocytomas	206	5.5	(52)
Acute myeloid leukemia	10	2	(53)
26 melanomas	366	4	(1, 32)
Small-cell lung	100	4	(2)

In most tumors, hundreds of protein-coding mutations accrue, yet only a few are putative drivers. These values are consistent with our model's results. Deleterious passengers may be most exploitable in carcinomas, because leukemia and many blood cancers are generally more sensitive to DNA damage and have earlier incidence rates.

*Classified as drivers by COSMIC (8).

Somatic evolution of cancer



Passengers hitchhike to fixation

Questions

1. Can *deleterious* passenger mutations accumulate during cancer development?

2. How deleterious are passenger mutations found in genotyped tumors?

3. How can passengers affect neoplastic progression?

Questions

1. Can *deleterious* passenger mutations accumulate during cancer development?

   Simulations

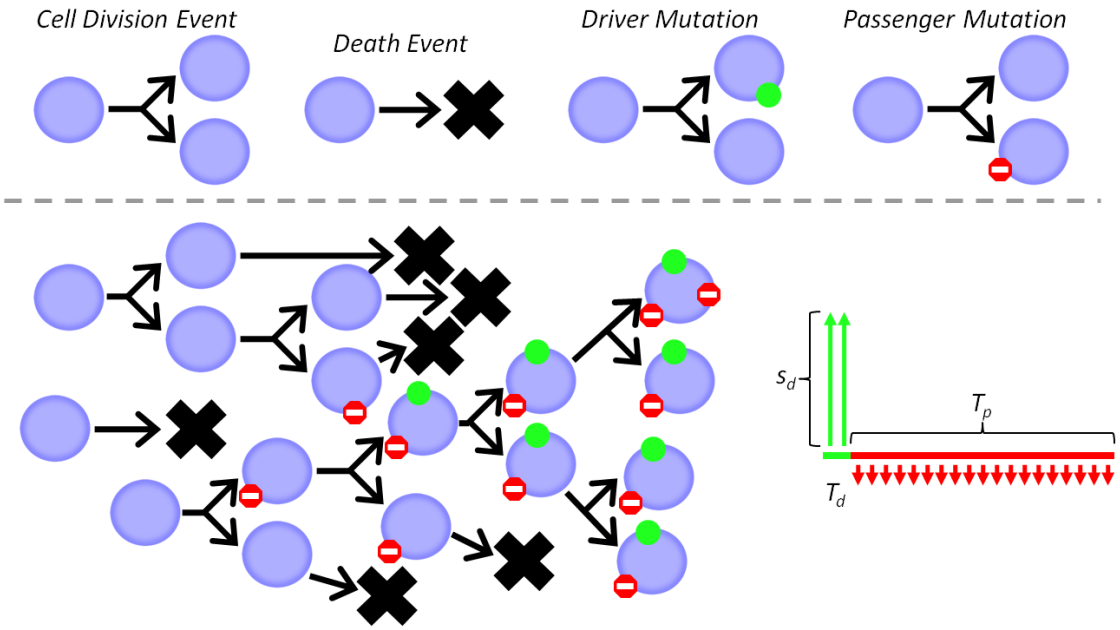
2. How deleterious are passenger mutations found in genotyped tumors?

   Genomics

3. How can passengers affect neoplastic progression?

   Simulations - Experiment

Model of cancer progression

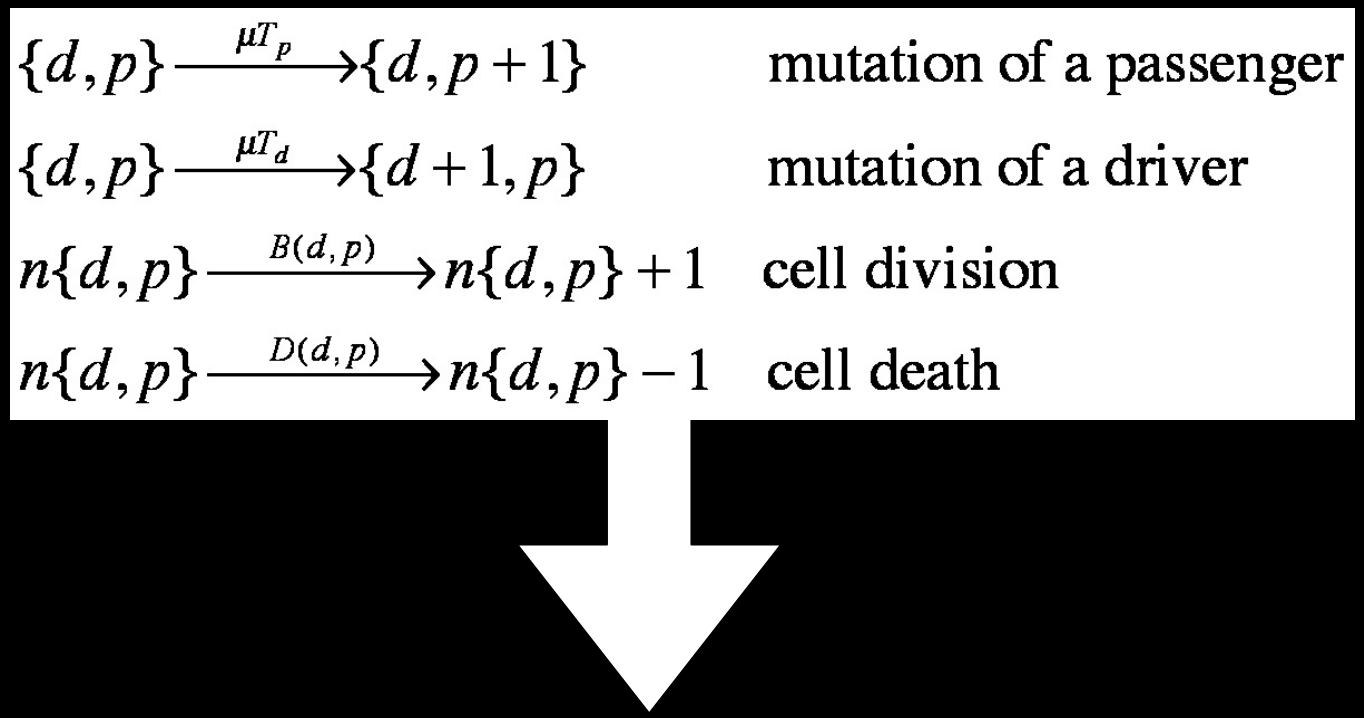


$$\{d,p\} \xrightarrow{\mu T_p} \{d,p+1\} \qquad \text{mutation of a passenger}$$

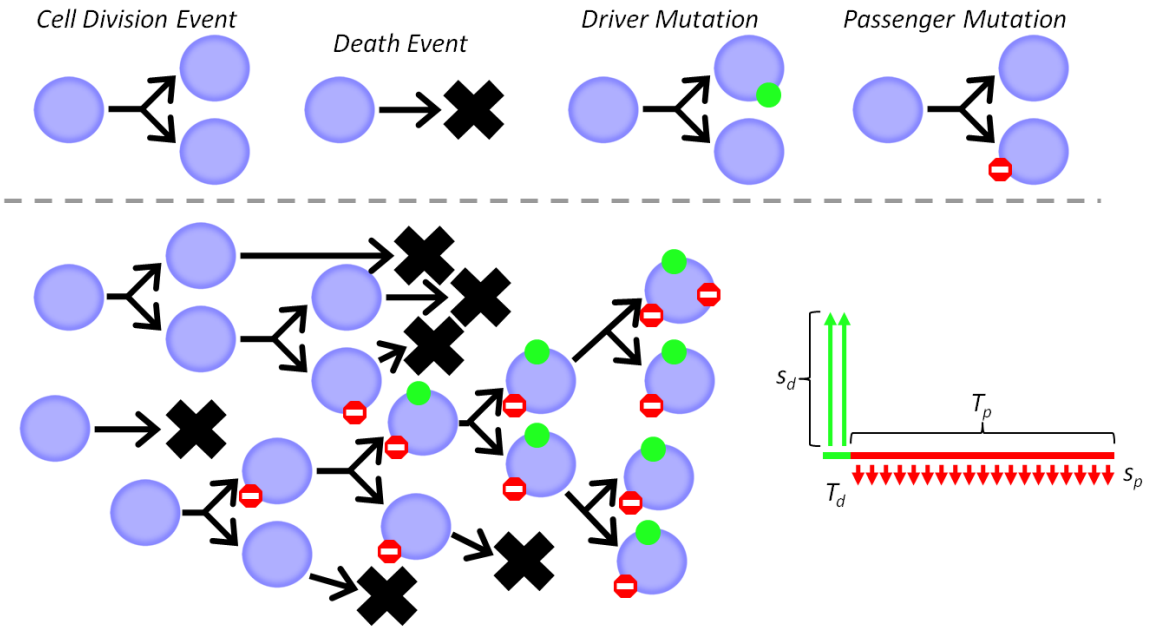
$$\{d,p\} \xrightarrow{\mu T_d} \{d+1,p\} \qquad \text{mutation of a driver}$$

$$n\{d,p\} \xrightarrow{B(d,p)} n\{d,p\}+1 \qquad \text{cell division}$$

$$n\{d,p\} \xrightarrow{D(d,p)} n\{d,p\}-1 \qquad \text{cell death}$$


$\{d,p\} \xrightarrow{\mu T_p} \{d,p+1\}$ mutation of a passenger
$\{d,p\} \xrightarrow{\mu T_d} \{d+1,p\}$ mutation of a driver
$n\{d,p\} \xrightarrow{B(d,p)} n\{d,p\}+1$ cell division
$n\{d,p\} \xrightarrow{D(d,p)} n\{d,p\}-1$ cell death

Model of cancer progression



$$\{d,p\} \xrightarrow{\mu T_p} \{d,p+1\} \qquad \text{mutation of a passenger}$$

$$\{d,p\} \xrightarrow{\mu T_d} \{d+1,p\} \qquad \text{mutation of a driver}$$

$$n\{d,p\} \xrightarrow{B(d,p)} n\{d,p\}+1 \qquad \text{cell division}$$

$$n\{d,p\} \xrightarrow{D(d,p)} n\{d,p\}-1 \qquad \text{cell death}$$

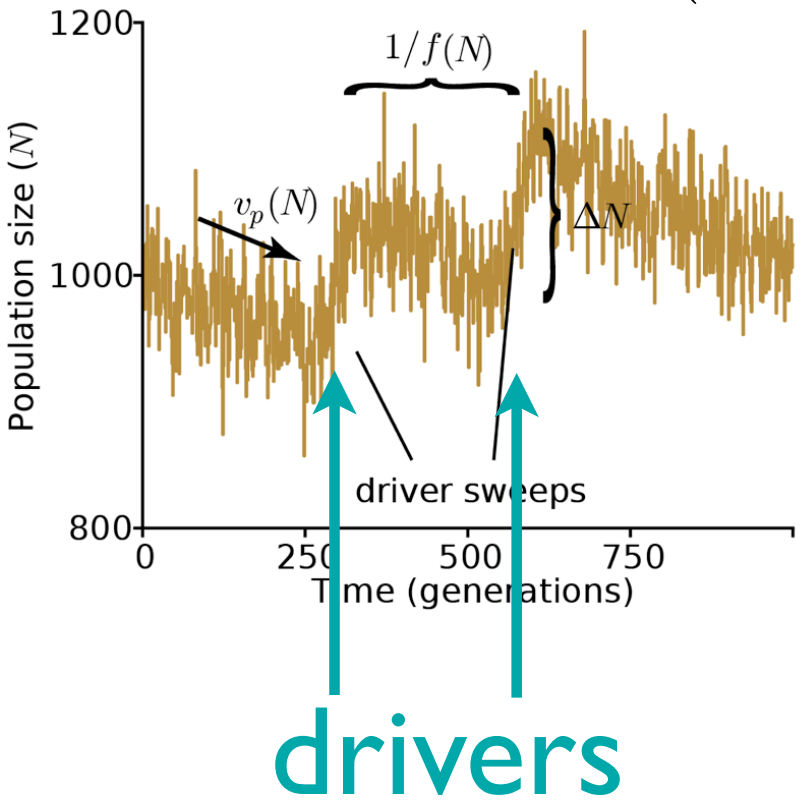
$$B(d,p) = \frac{(1+s_d)^d}{(1+s_p)^p} \qquad D(N) = \frac{N}{K}$$

Alternative model for $N>10^6$

$$D(N) = log(1 + N/K)$$

Model of cancer progression

$$B(d,p) = \frac{(1+s_d)^d}{(1+s_p)^p} \qquad D(N) = \frac{N}{K}$$



$s_p \approx 10^{-3}$

$s_d \approx 0.1$

$T_p \approx$ 5000 expressed genes x 1000

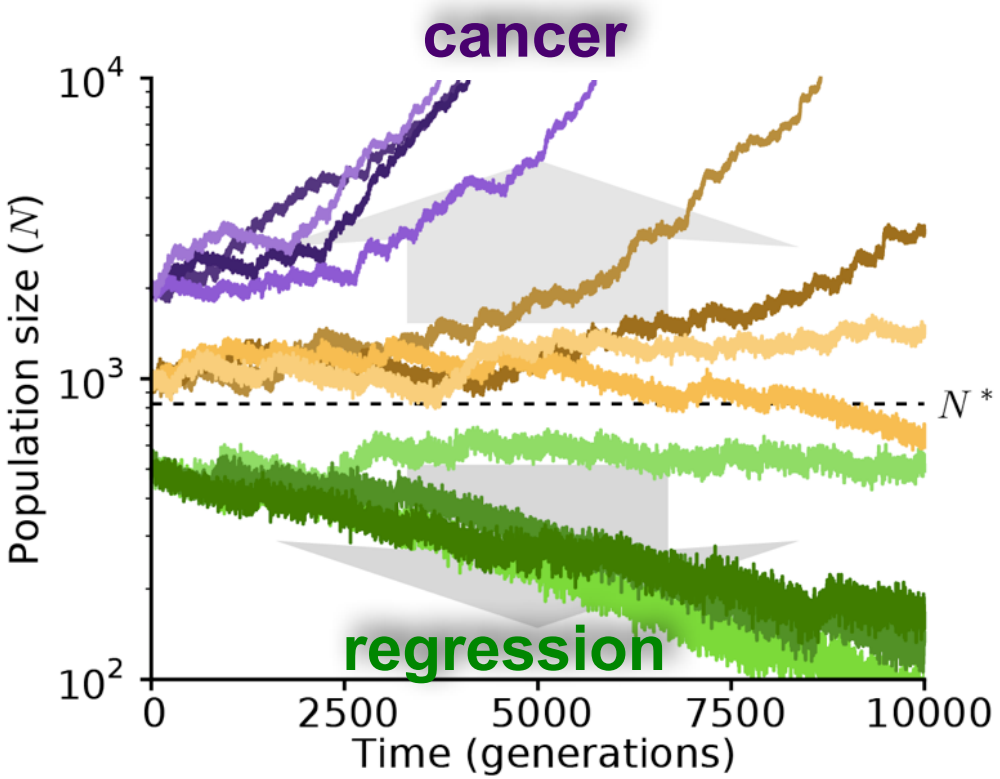
$T_d \approx$ 70 genes x 10 hotspots

$K = 5000$ carrying capacity

$s_d >> s_p$

$T_d << T_p$

Model of cancer progression

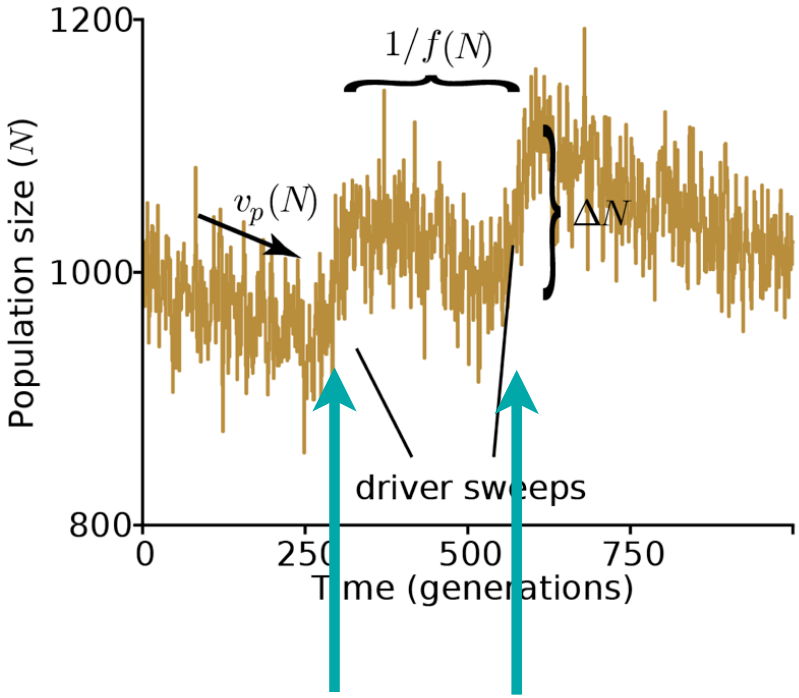


- Two possible outcomes:
  population growth (**cancer**)
  population collapse (**regression**)

Results of the theory:

1. **Critical population size: N***
2. **Deleterious passengers can accumulate**
3. **Critical mutation rate μ***

Critical population size



drivers

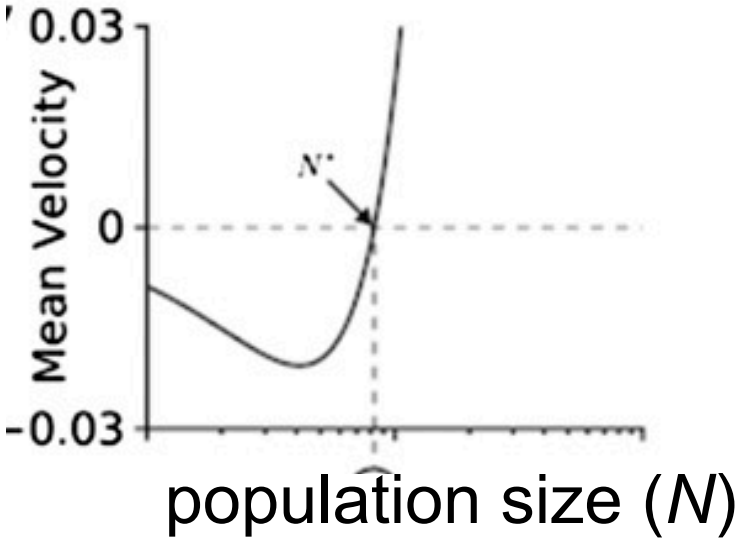
drivers

$$\Delta N = Ns_d$$

$$f = \mu_d N s_d$$

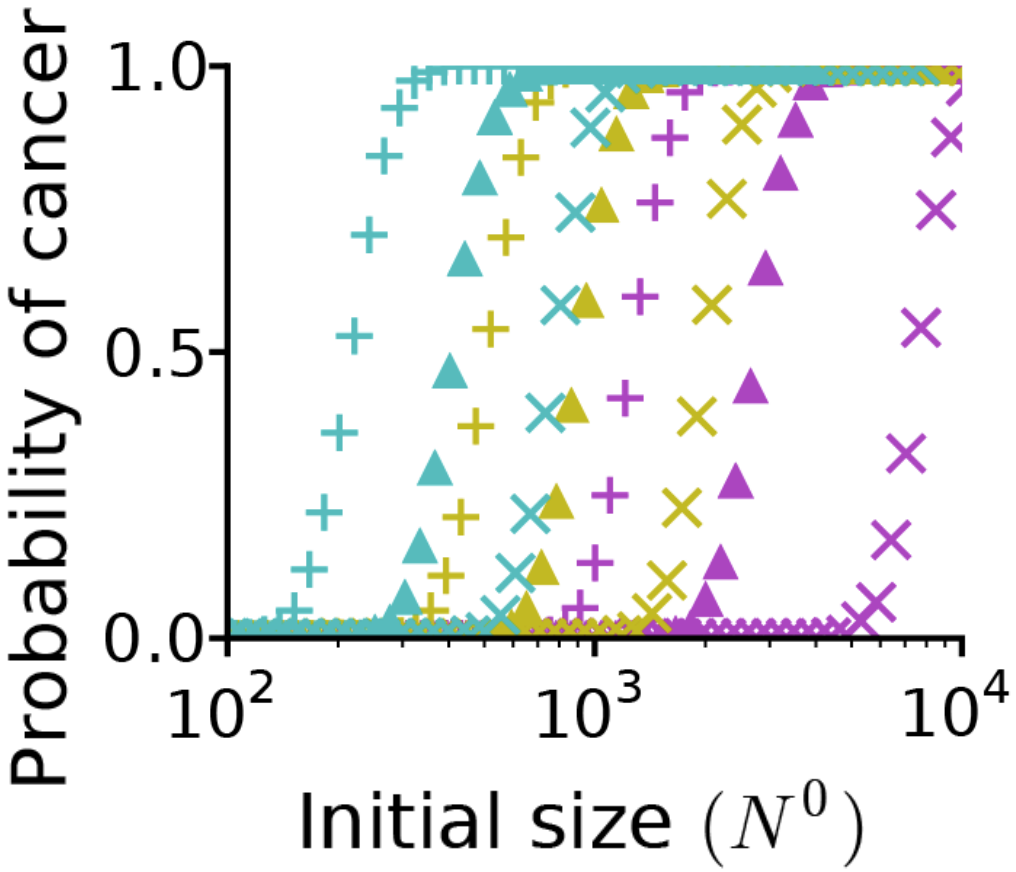
$$v_d = f\Delta N = \mu_d N^2 s_d^2$$

$$V = v_d - v_p$$



$$N^* = \frac{T_p s_p}{T_d s_d^2}$$

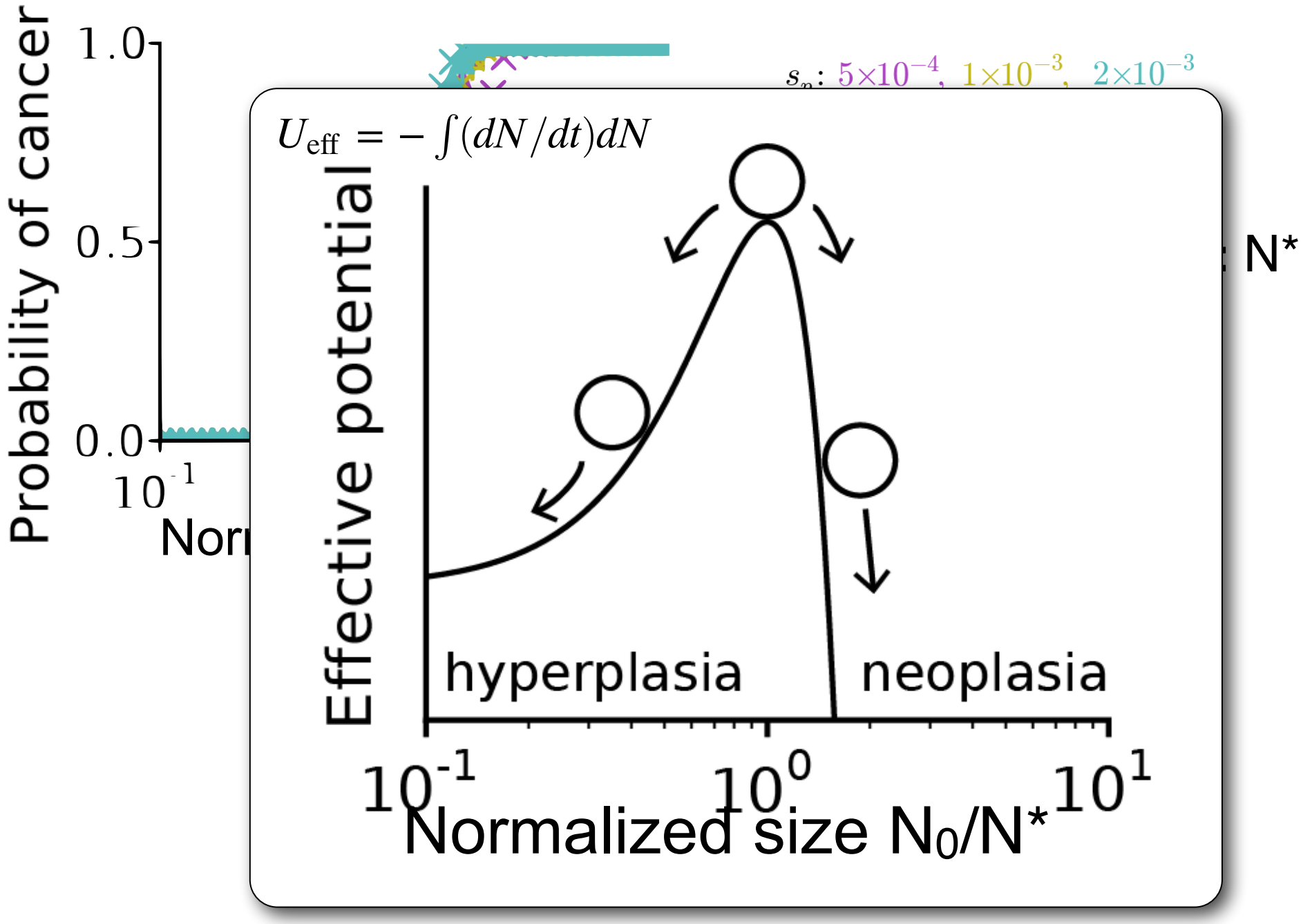
Critical population size



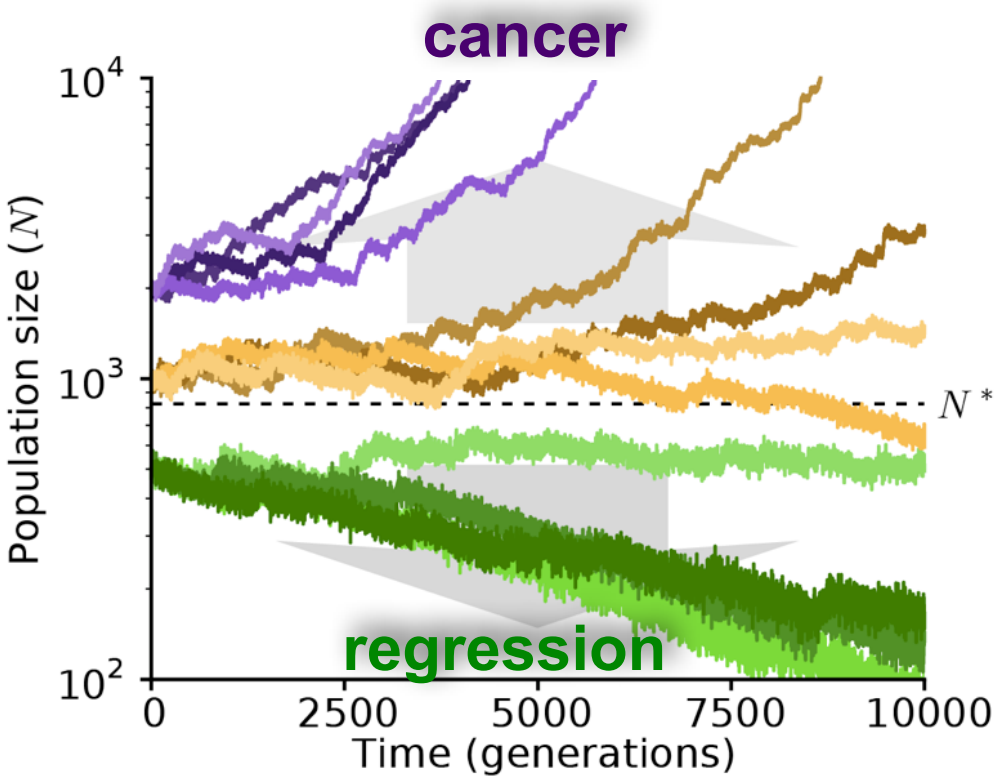
s_p: 5×10^{-4}, 1×10^{-3}, 2×10^{-3}

$\frac{T_d}{T_p}$: + 5×10^{-5}, ▲ 1.4×10^{-4}, × 3×10^{-4}

Critical population size



Model of cancer progression

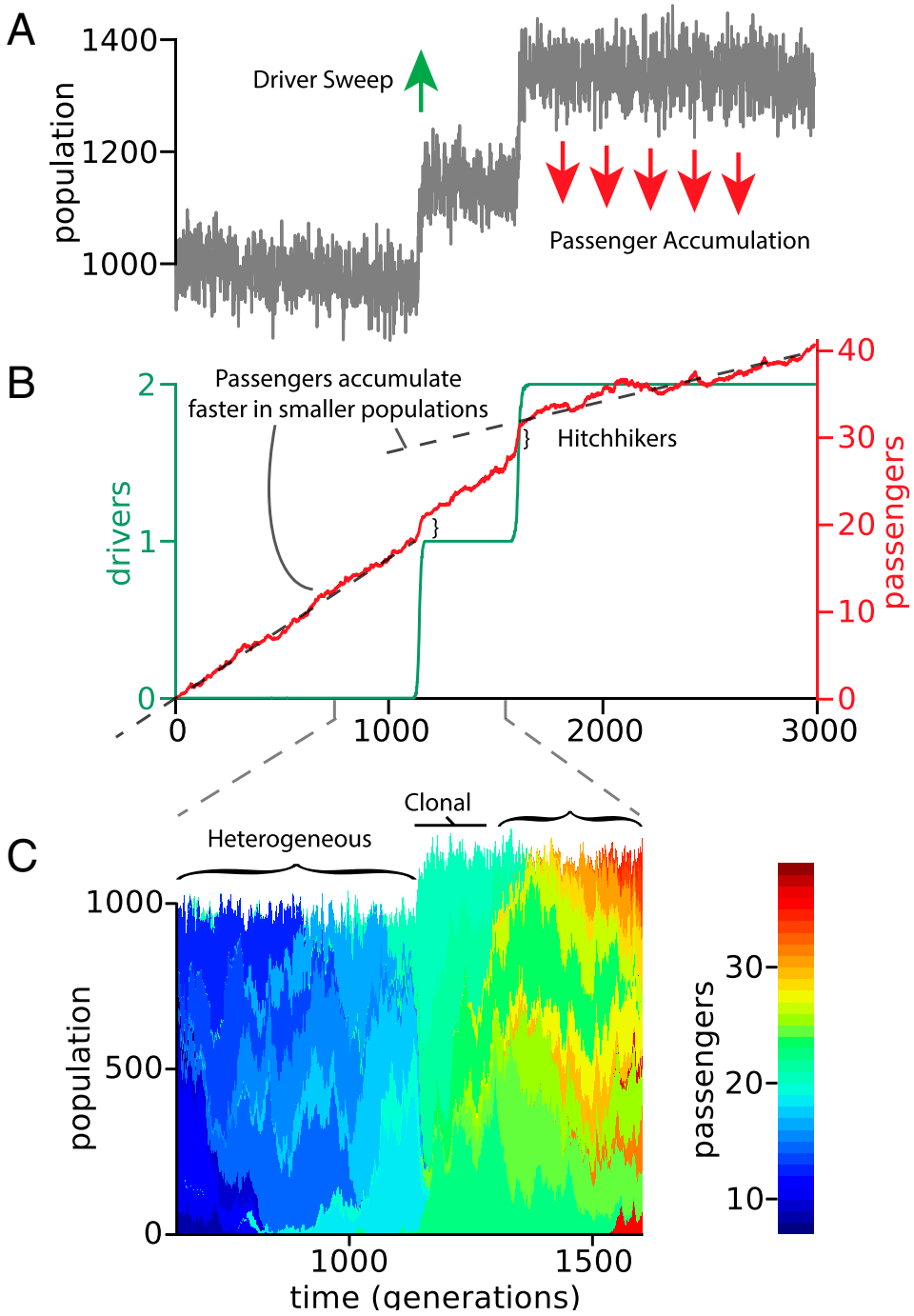


- Two possible outcomes:
  population growth (**cancer**)
  population collapse (**regression**)

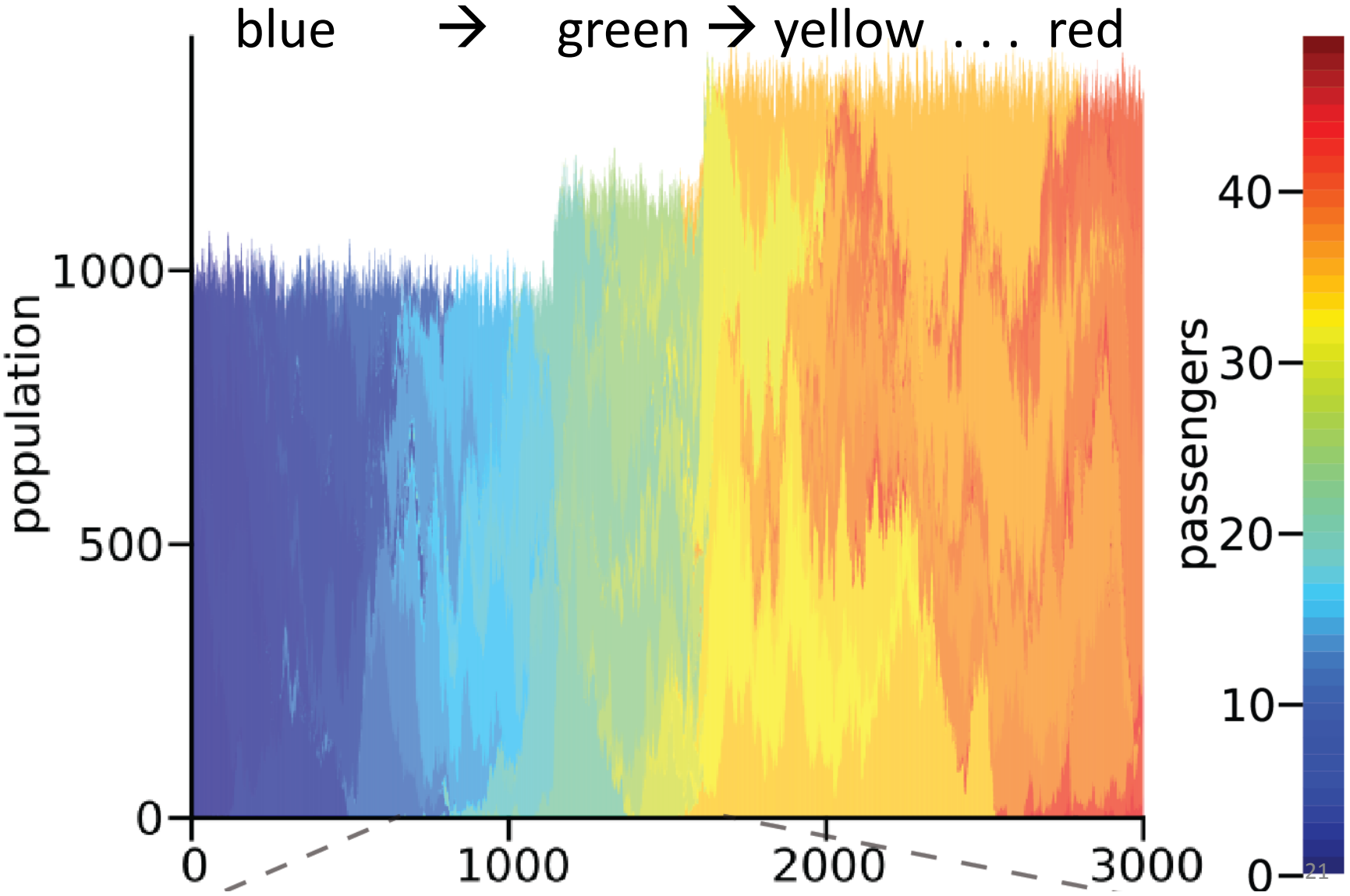
Results of the theory:

1. **Critical population size: N***
2. **Deleterious passengers can accumulate**
3. **Critical mutation rate μ***

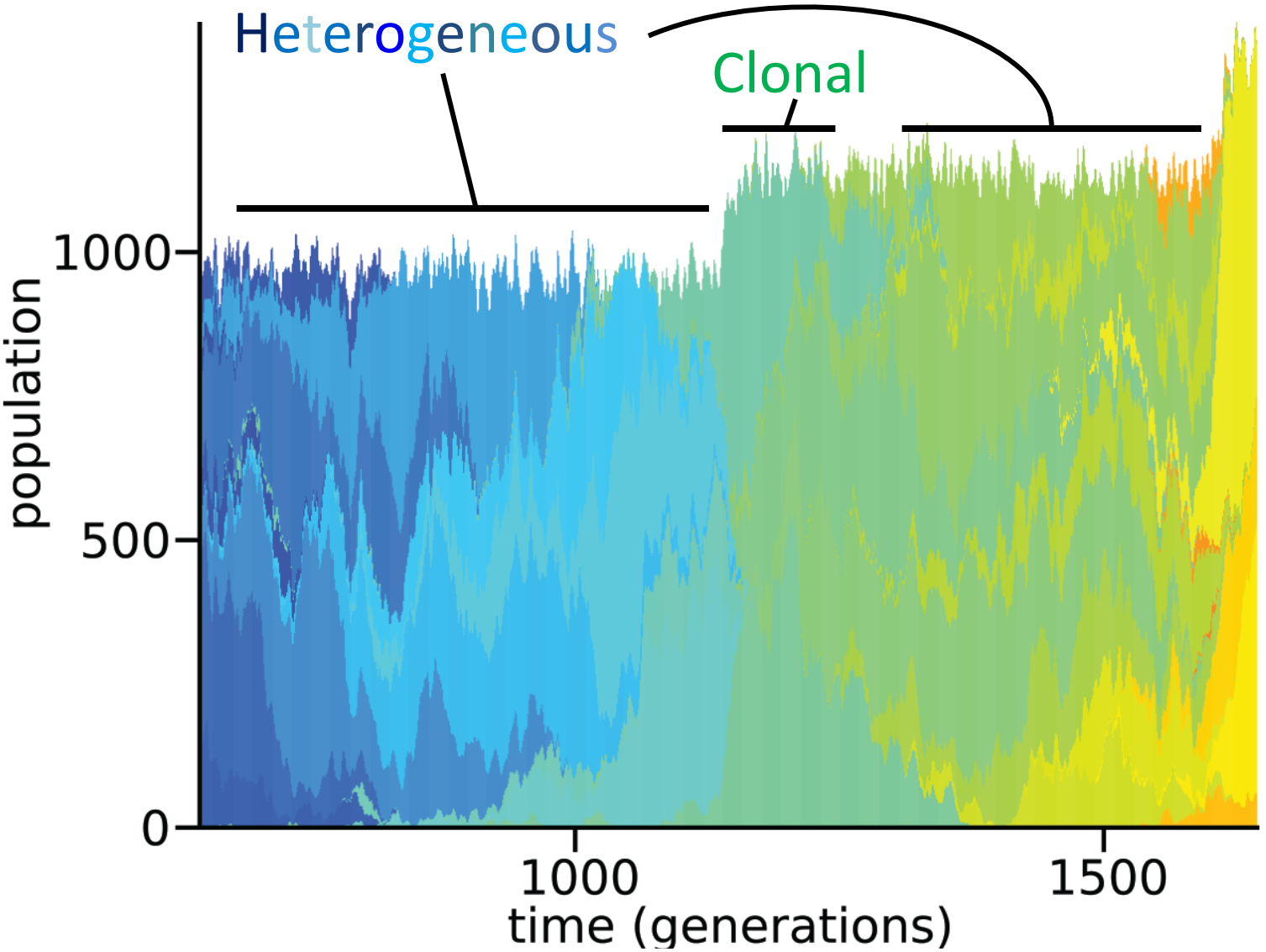
Accumulation of passengers: hitchhiking



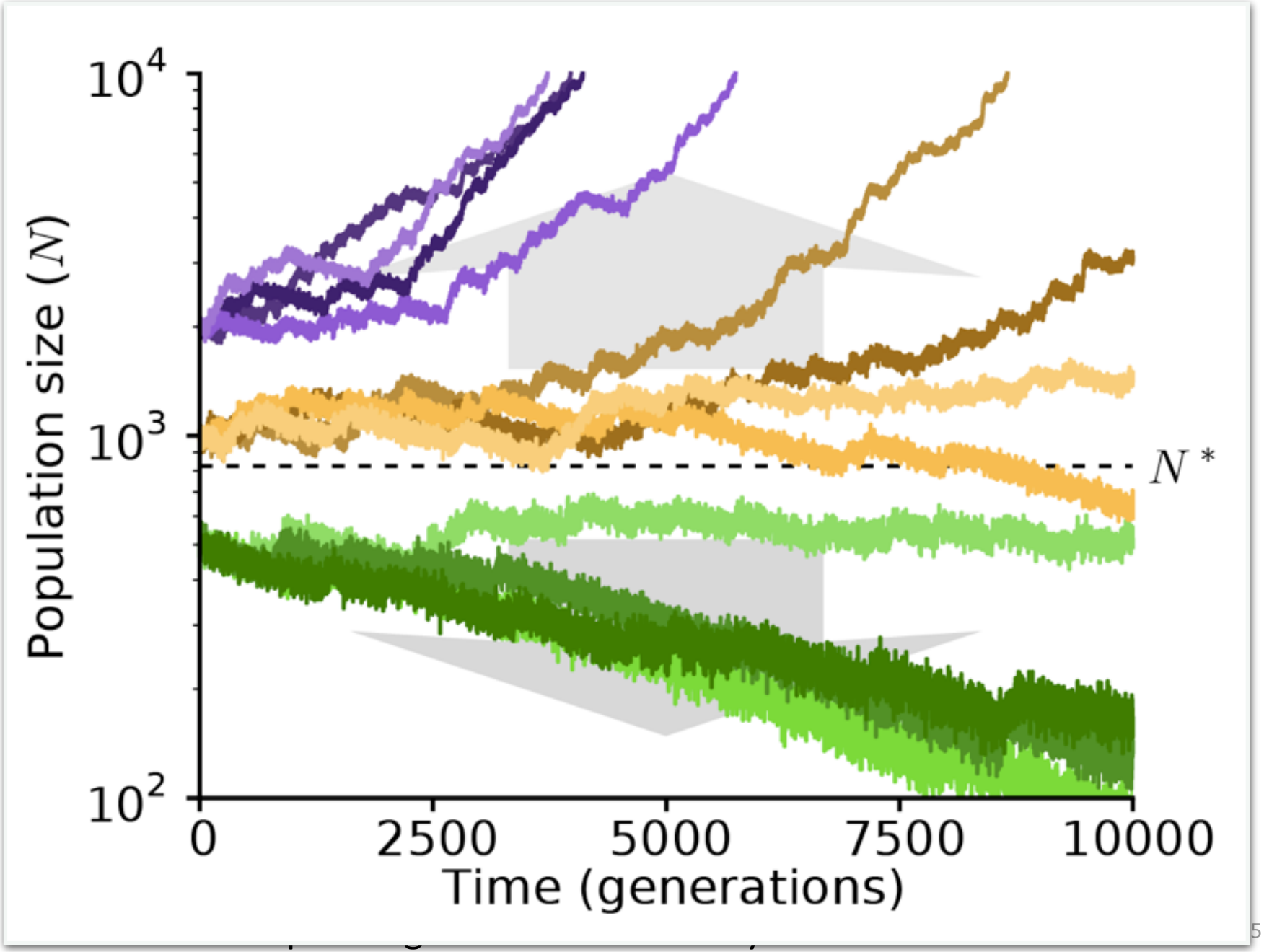
Observed heterogeneity of progression



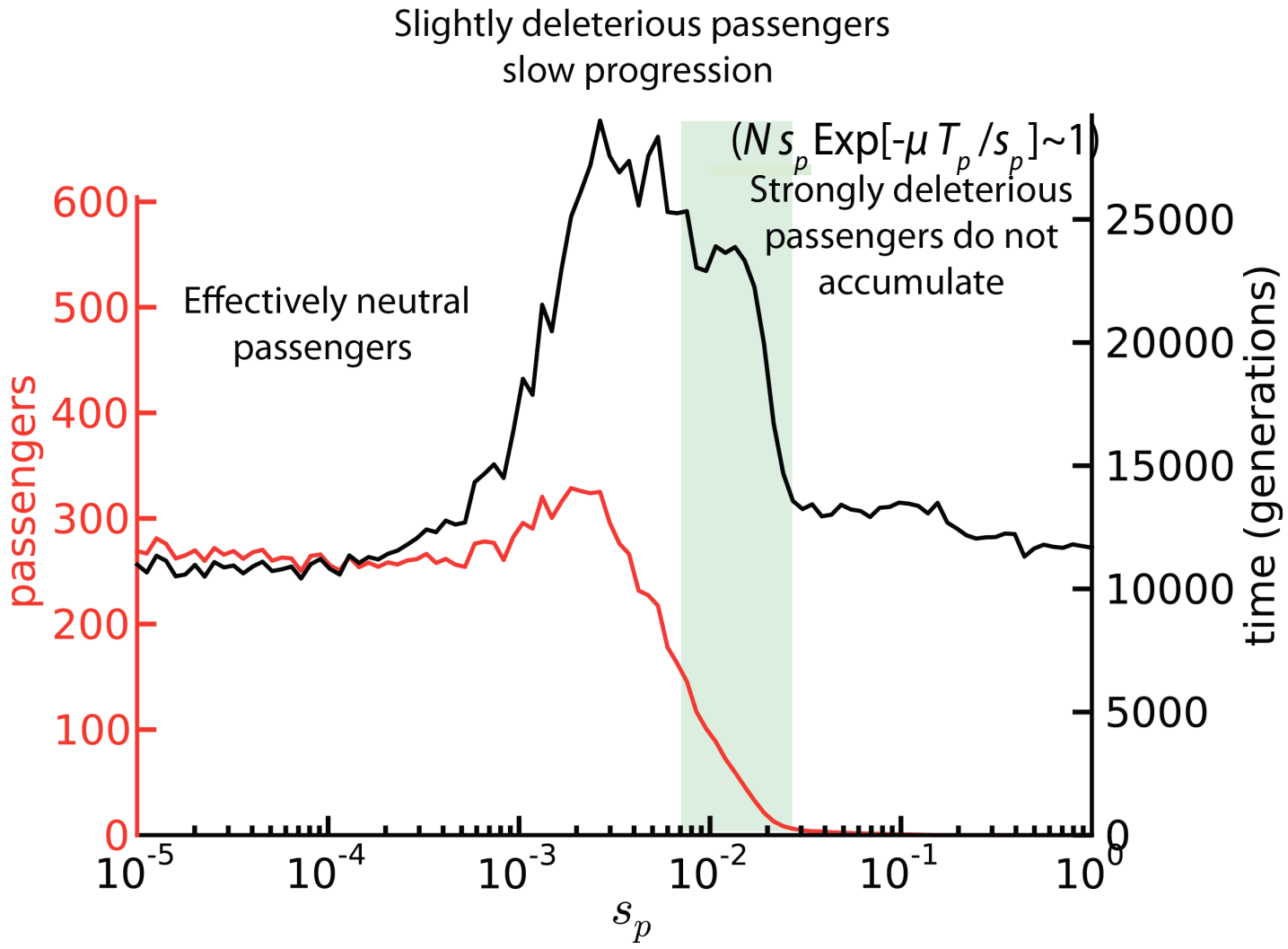
Observed heterogeneity of progression



Effect of hitchhiking passengers



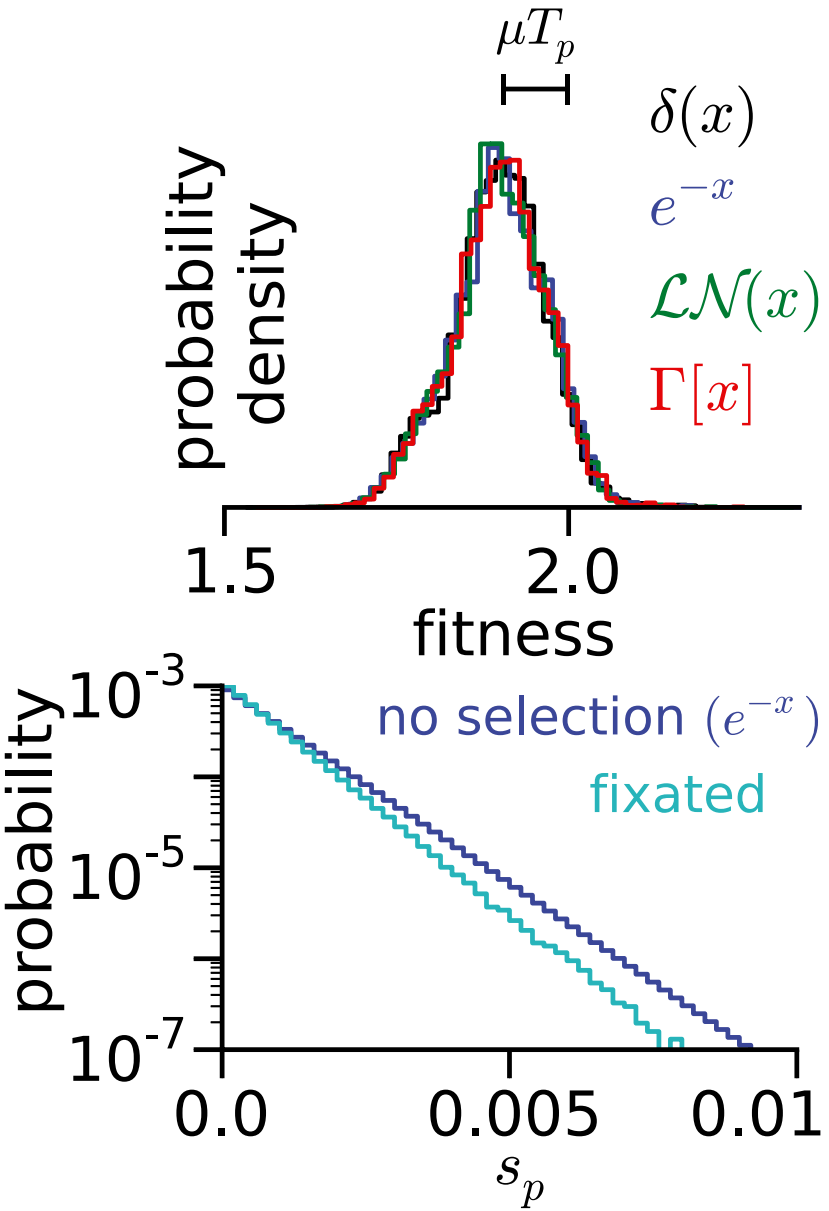
Passenger accumulation slows progression



Proteotoxic mutations

(Geller-Samerotte et. al. 2010)

Passengers evade purifying selection



Questions

1. Can *deleterious* passenger mutations accumulate during cancer development?

2. How deleterious are passenger mutations found in genotyped tumors?

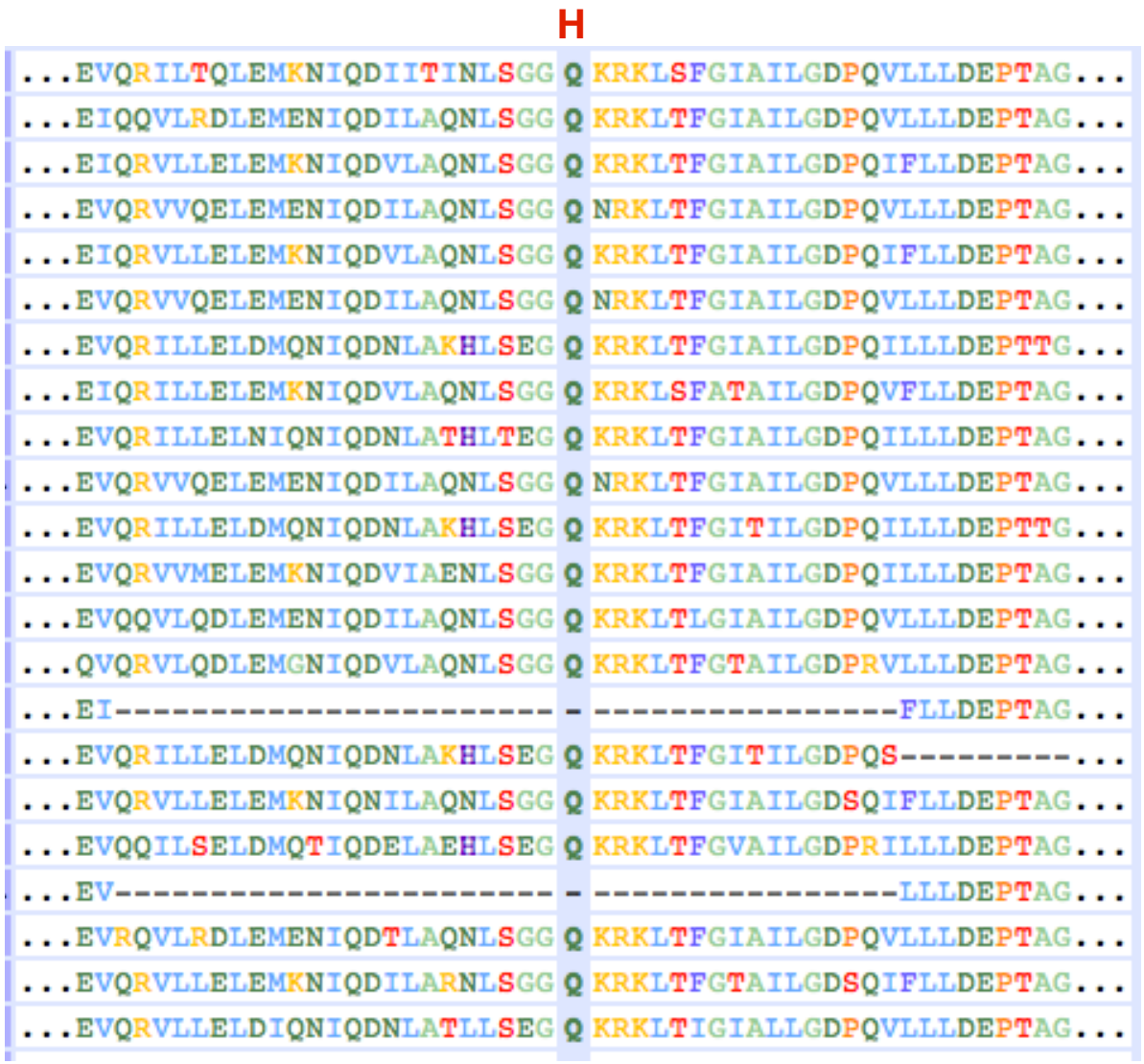
3. How can passenger mutations affect neoplastic progression?

Hitchhiking passengers

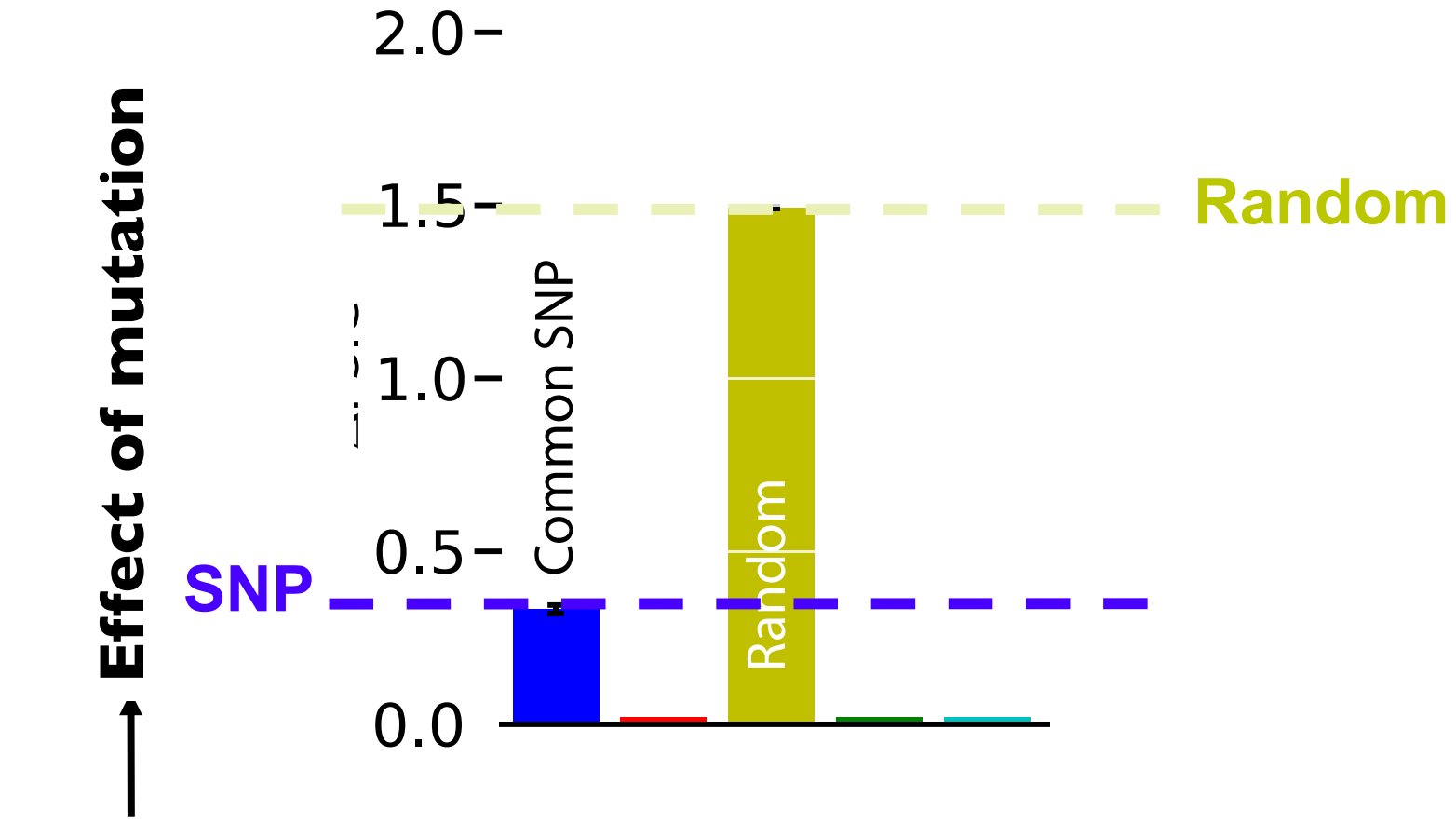
Neutral or deleterious

Deleterious passenger

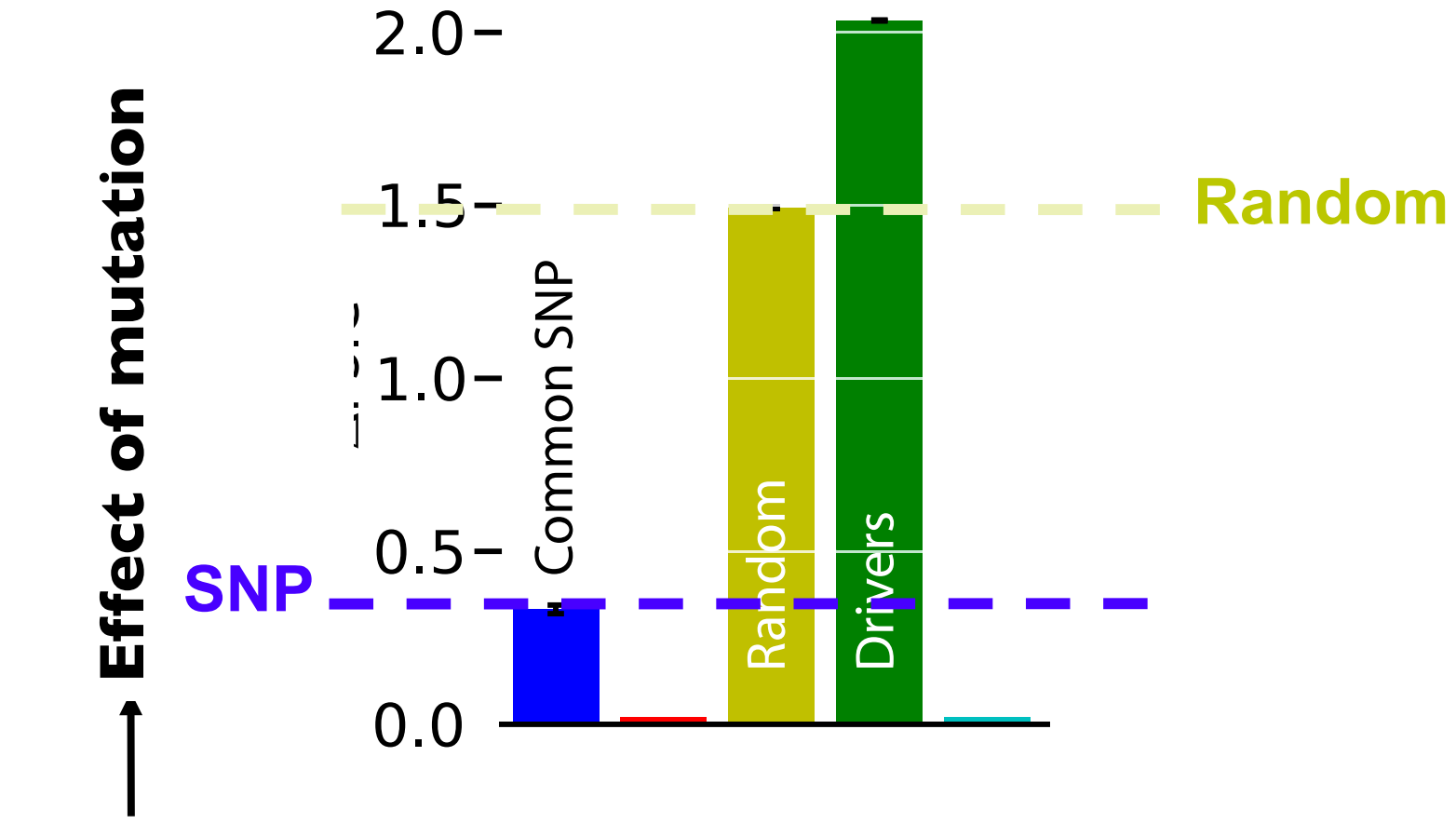
Q532H in ABCA10 of a glioma.



Effect of mutations



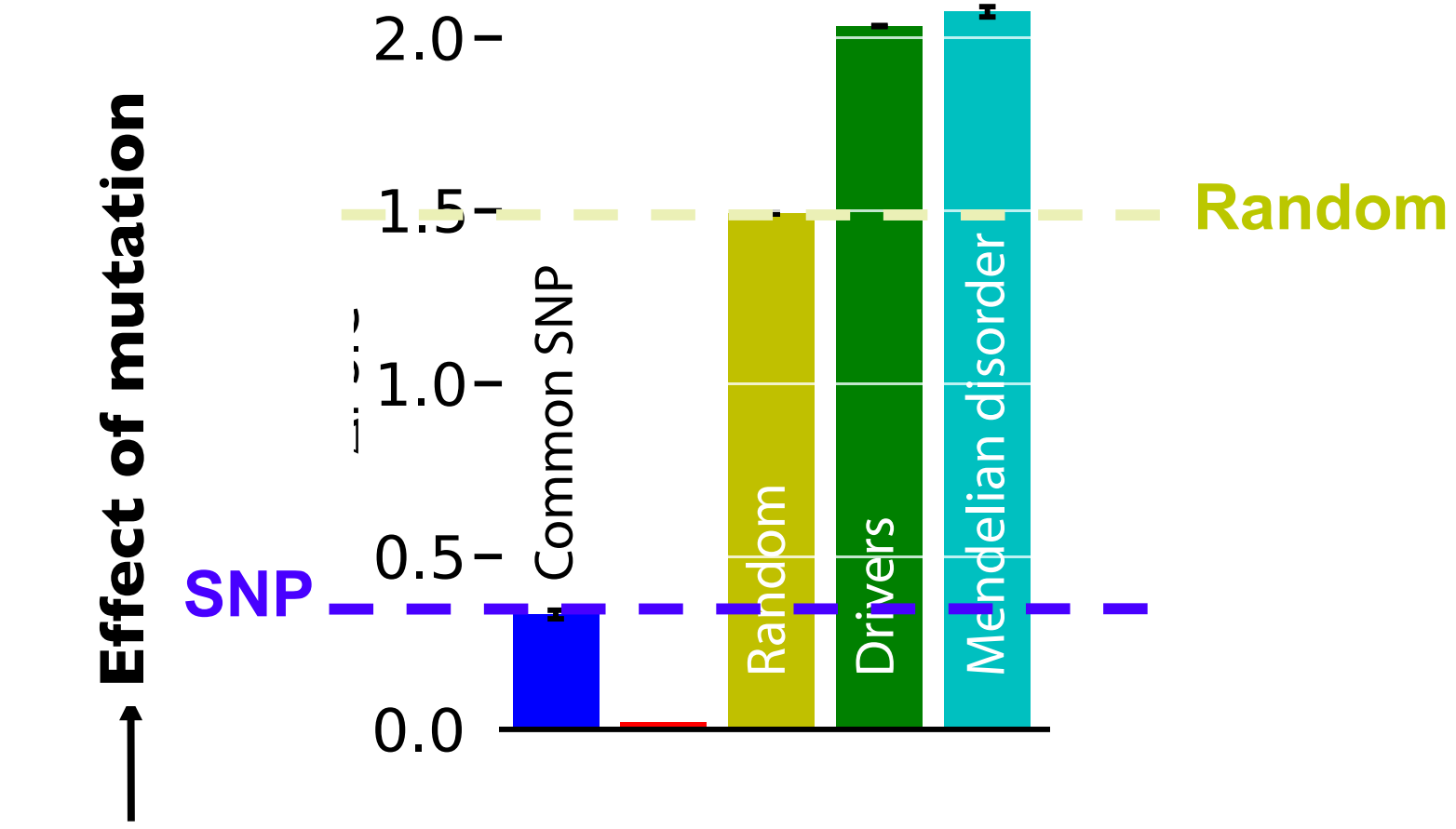
Effect of mutations



PSIC Score Conservation

[**PolyPhen:** Sunyaev et al]

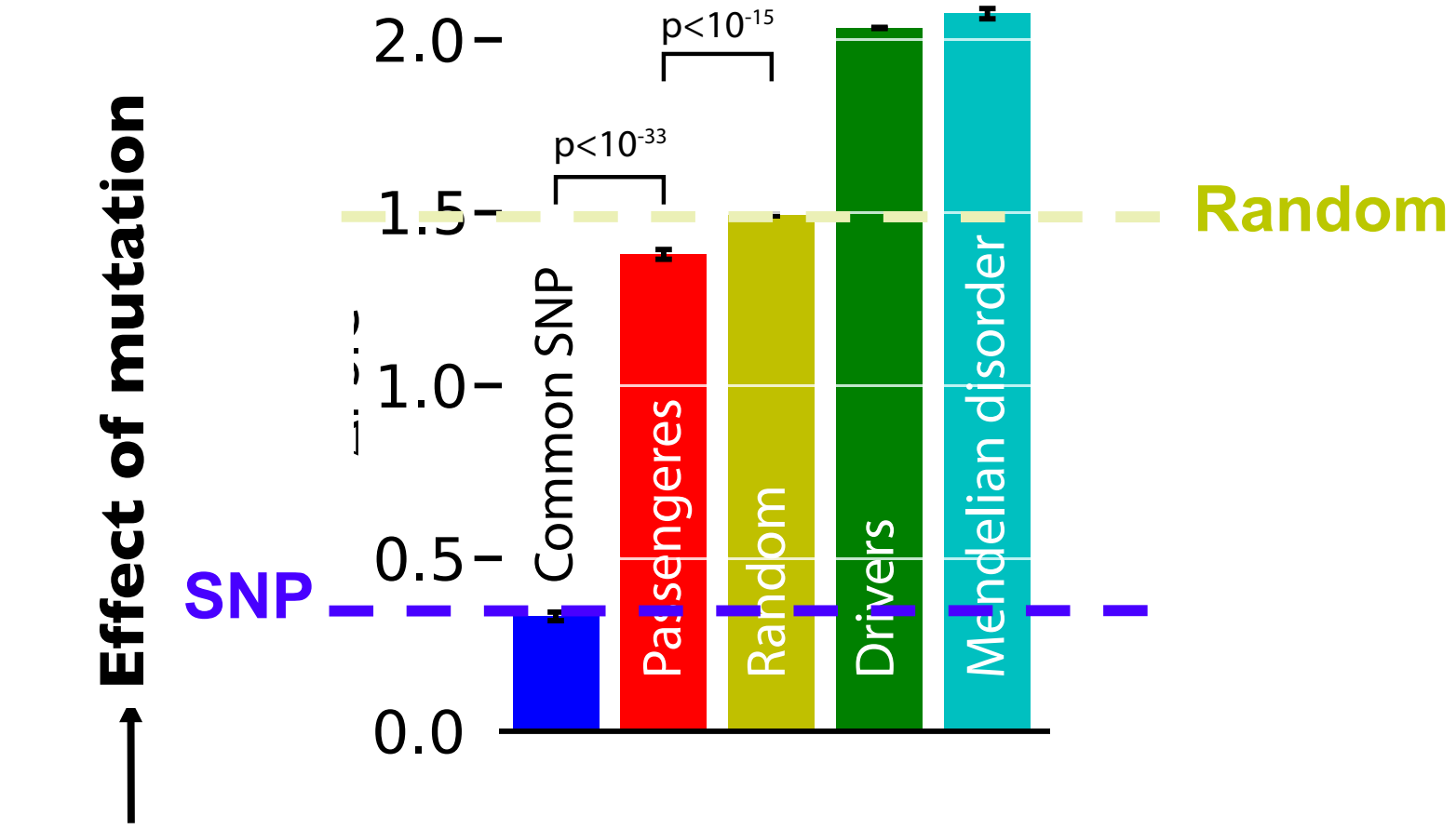
Effect of mutations



PSIC Score Conservation

[**PolyPhen:** Sunyaev et al]

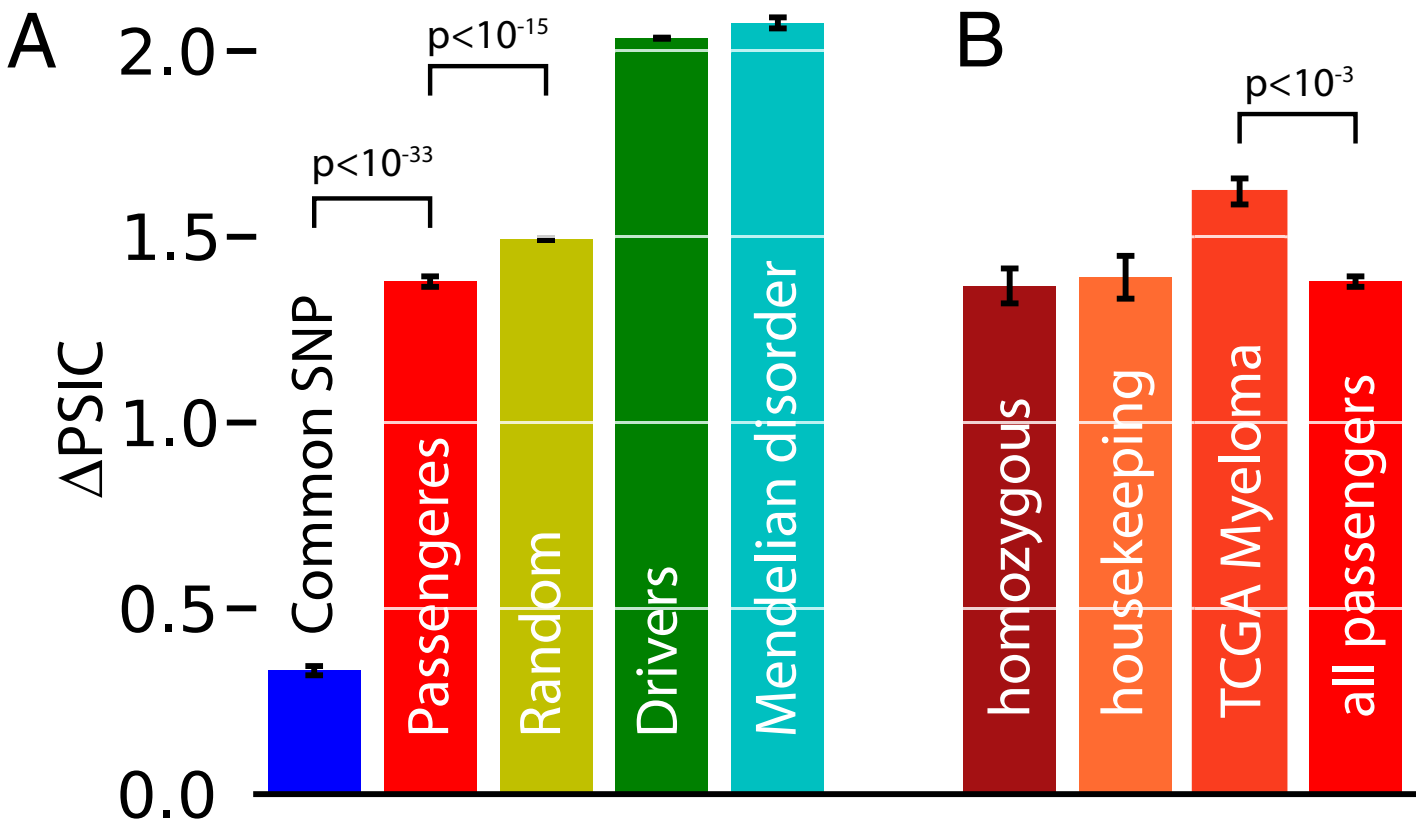
Effect of mutations



PSIC Score Conservation

[**PolyPhen:** Sunyaev et al]

Effect of mutations



PolyPhen

Questions

1. Can *deleterious* passenger mutations accumulate during cancer development?

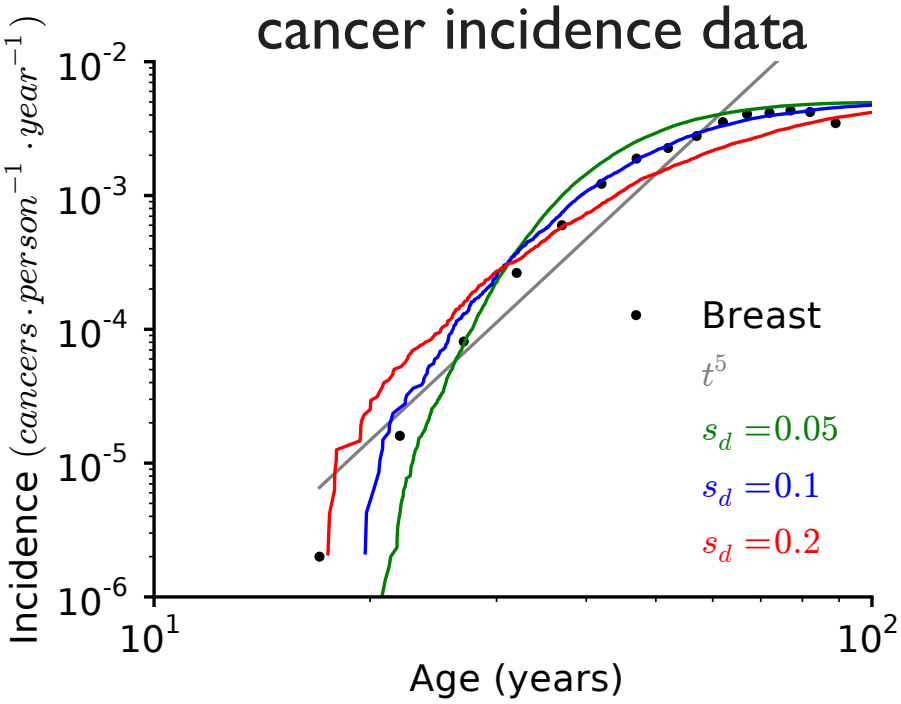
2. How deleterious are passenger mutations found in genotyped tumors?

3. How can passenger mutations affect neoplastic progression?

Model - Experiment

Model vs data

Model agrees with cancer incidence data



$S_d \sim 0.2$

$(r \sim 10\ \mathrm{y}^{-1})$

$I_{\max} \sim 10^{-2}$

$$I_{\max} = r \int_0^\infty P(\tau) d\tau = r P_\infty$$

occur

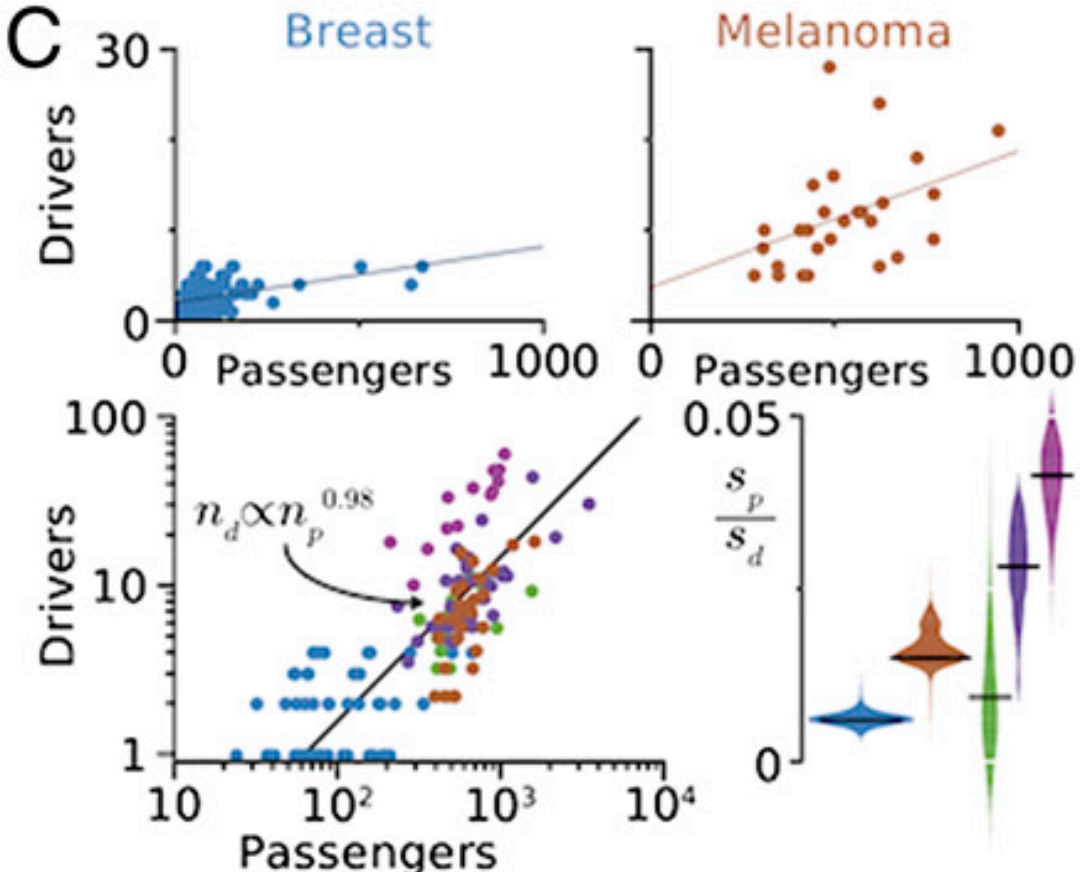
prob to progress in time τ
(from simulations)

$P_\infty \sim 10^{-3}$

0.1% of lesions ever progress!

Model agrees with cancer genomics data

Cancer genomics

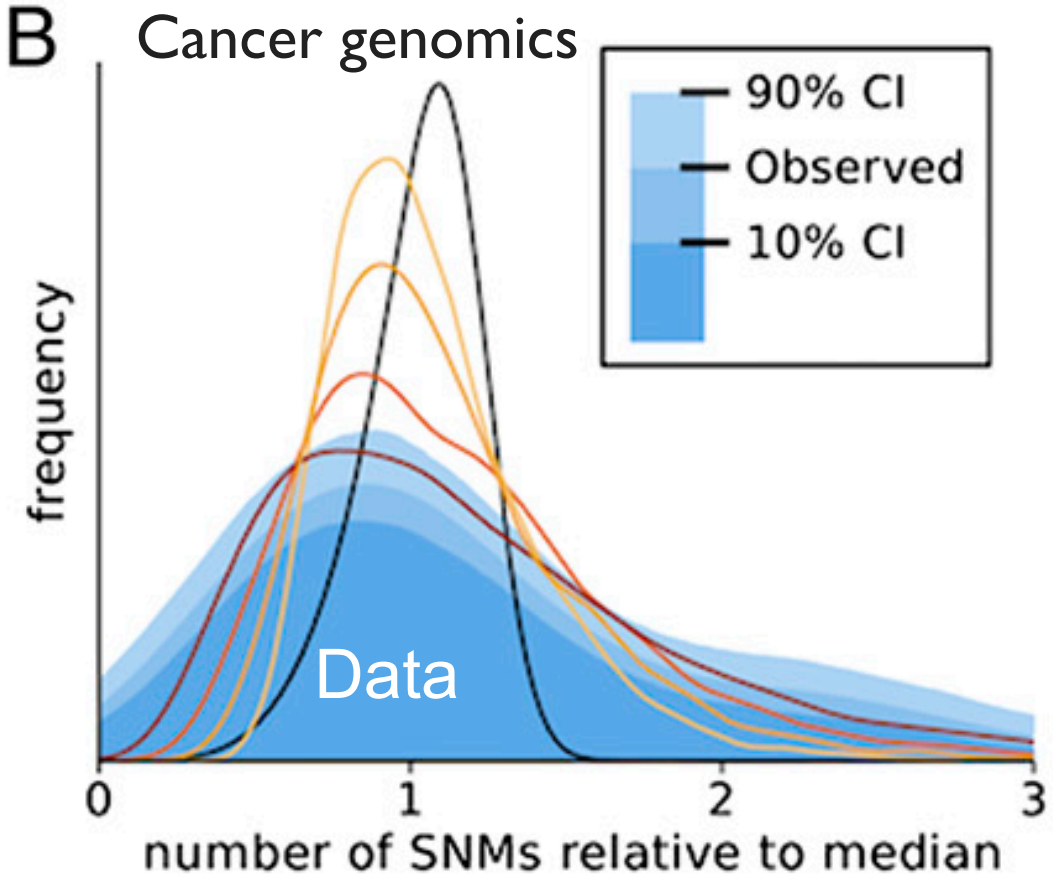


Theory

$$n_d = s_p/s_d \cdot n_p + \text{constant}$$

$$s_p/s_d \sim 0.005\text{–}0.05$$

Estimating parameters from cancer genomics data



$s_d = 0.05$

$s_d = 0.1$

$s_d = 0.2$

$s_d = 0.4$

$S_d \sim 0.4$

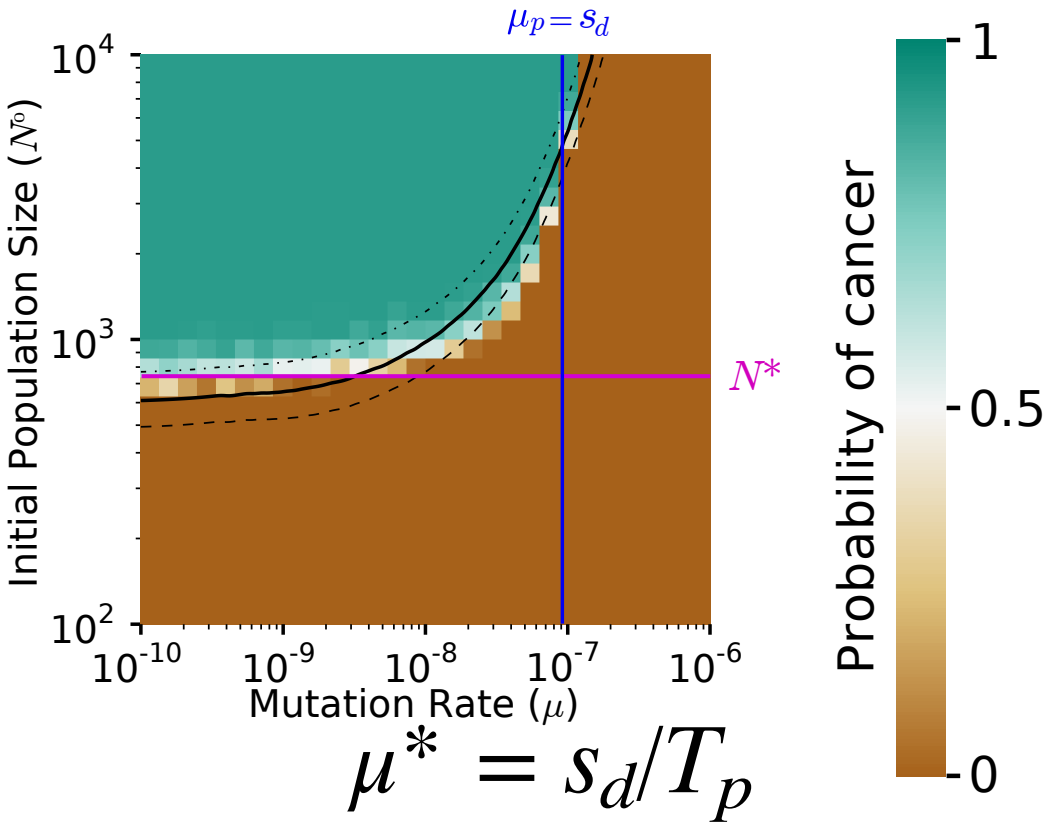
Defining Stem Cell Dynamics in Models of Intestinal Tumor Initiation

Louis Vermeulen,[1,2*†] Edward Morrissey,[1*] Maartje van der Heijden,[1,2] Anna M. Nicholson,[1] Andrea Sottoriva,[3] Simon Buczacki,[1] Richard Kemp,[1] Simon Tavaré,[1,4] Douglas J. Winton[1]

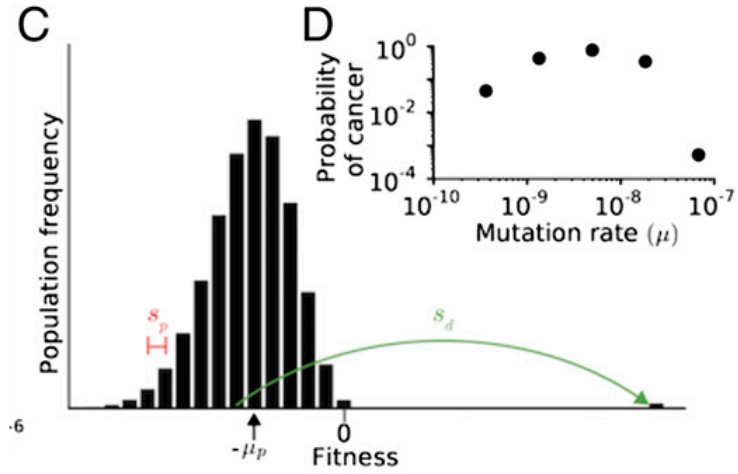
$S_d(p53,APC,Kras)=0.2\text{-}0.5$

Back to the model

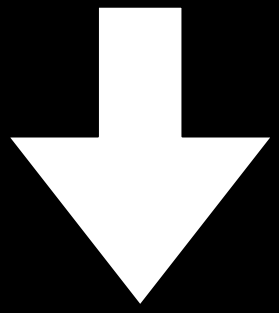
Critical mutation rate



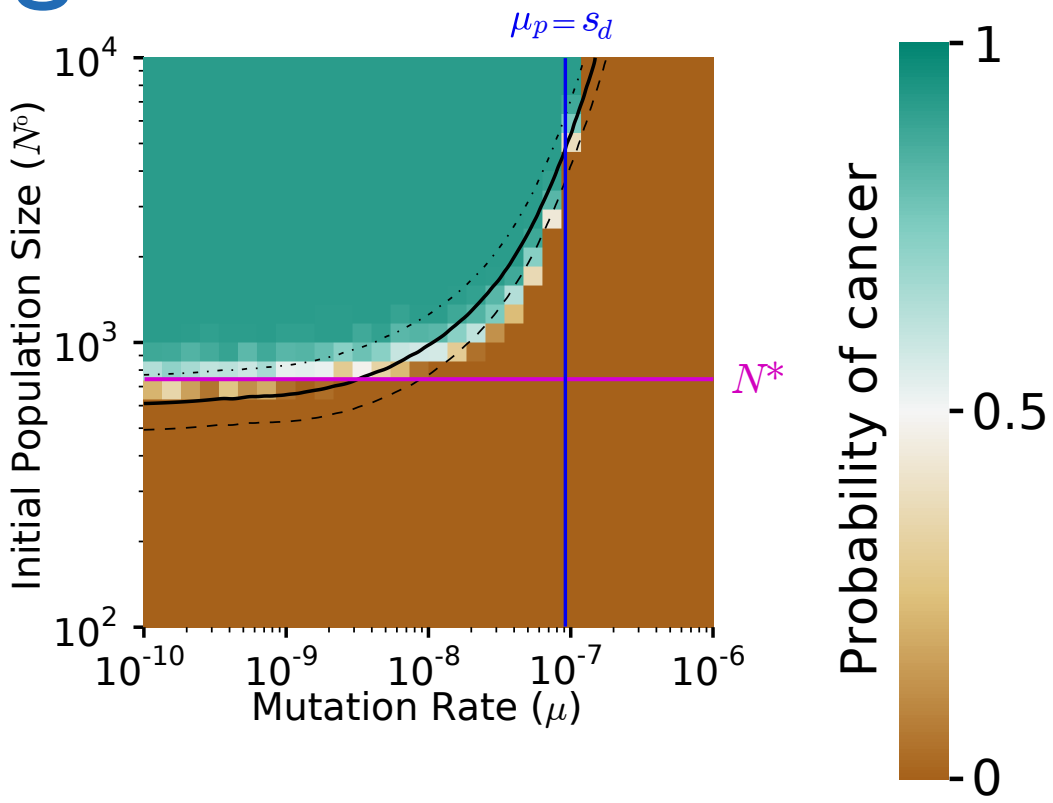
$$\mu^* = s_d / T_p$$



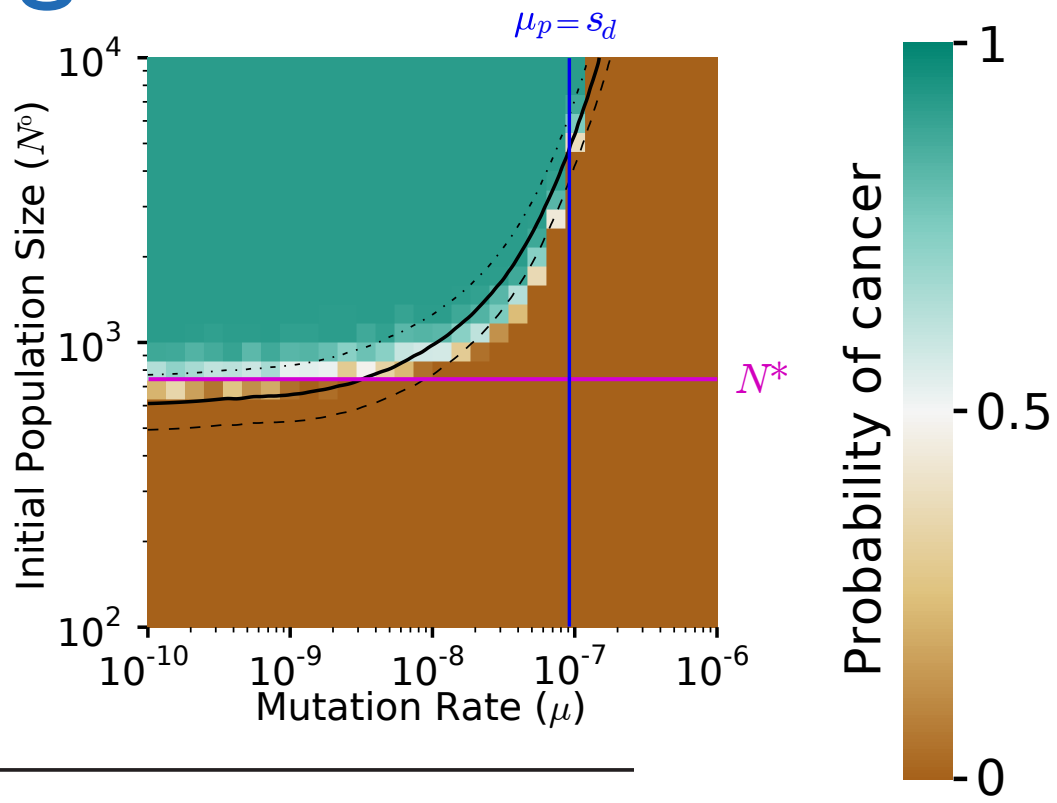
Critical mutation rate



Higher load => better response



Higher load => better response



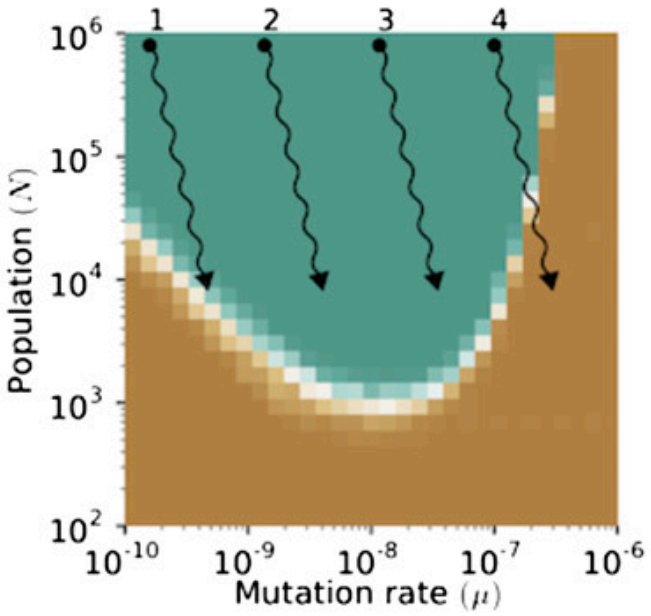
Priority Report

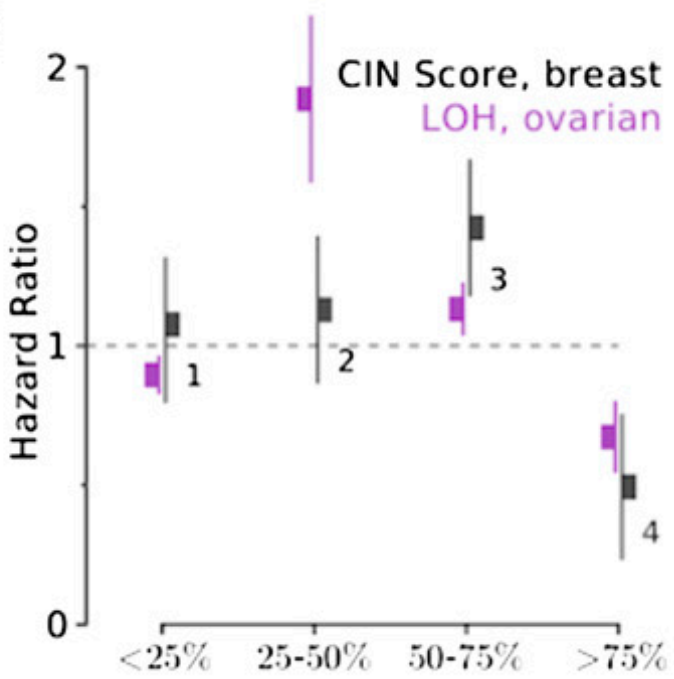
Paradoxical Relationship between Chromosomal Ir and Survival Outcome in Cancer

Nicolai J. Birkbak[1,2], Aron C. Eklund[1], Qiyuan Li[1,2], Sarah E. McClelland[5], David Endesfelder[5], Patrick Tan[7,8], Iain B. Tan[9,10], Andrea L. Richardson[2,4], Zoltan Szallasi[1,3], and Charles Swanton[5,6]

"We also observed this paradoxical relationship between CIN and prognosis in ovarian, gastric, and non–small cell lung cancer, with poorest outcome in tumors with intermediate, rather than extreme, CIN70 scores."

Higher load => better response





Priority Report

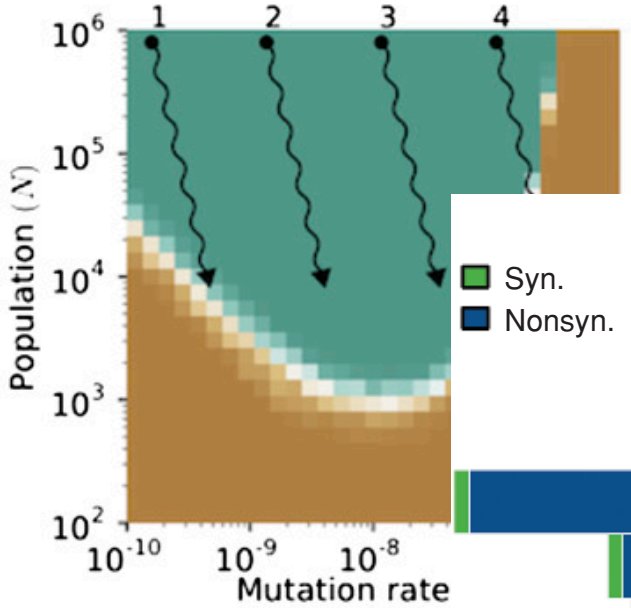
Cancer Research

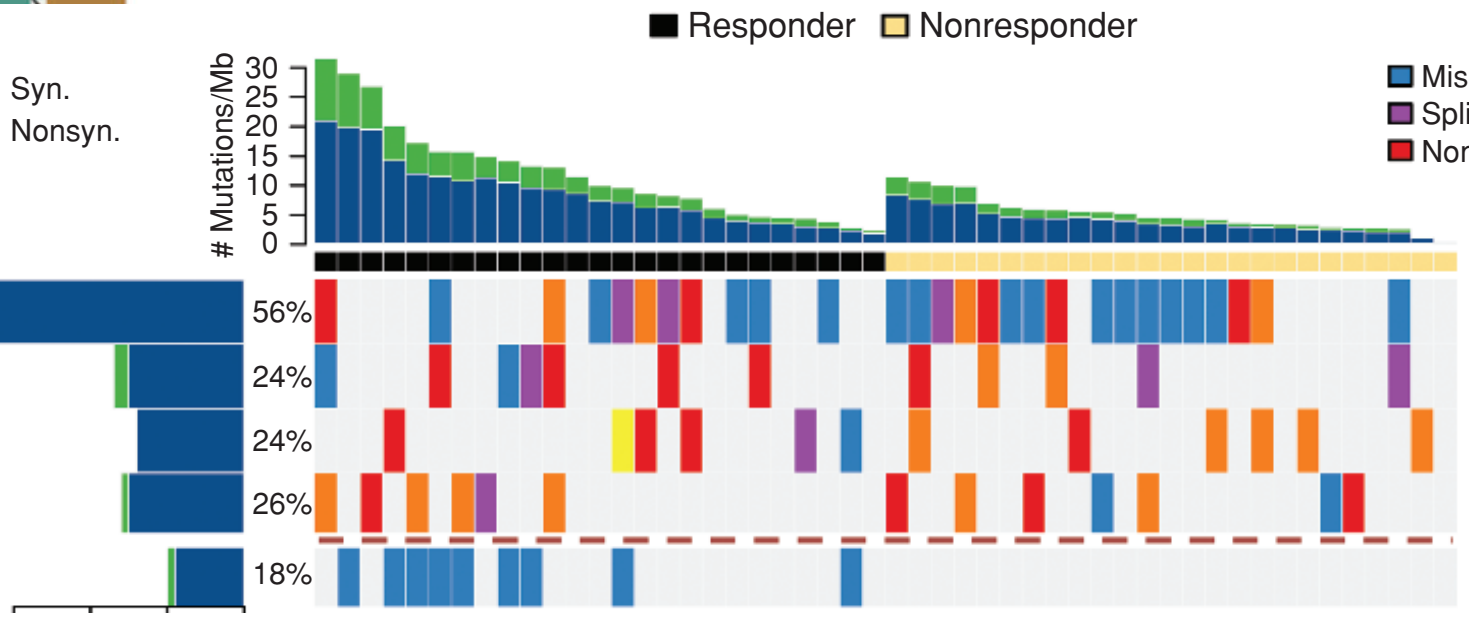
Paradoxical Relationship between Chromosomal Instability and Survival Outcome in Cancer

Nicolai J. Birkbak[1,2], Aron C. Eklund[1], Qiyuan Li[1,2], Sarah E. McClelland[5], David Endesfelder[5], Patrick Tan[7,8], Iain B. Tan[9,10], Andrea L. Richardson[2,4], Zoltan Szallasi[1,3], and Charles Swanton[5,6]

"We also observed this paradoxical relationship between CIN and prognosis in ovarian, gastric, and non–small cell lung cancer, with poorest outcome in tumors with intermediate, rather than extreme, CIN70 scores."

Higher load => better response





Somatic *ERCC2* Mutations Correlate with Cisplatin Sensitivity in Muscle-Invasive Urothelial Carcinoma

Eliezer M. Van Allen[1,2], Kent W. Mouw[3,4], Philip Kim[5], Gopa Iyer[6,7], Nikhil Wagle[1,2], Hikmat Al-Ahmadie[6,8], Cong Zhu[2], Irina Ostrovnaya[9], Gregory V. Kryukov[2], Kevin W. O'Connor[3], John Sfakianos[5], Ilana Garcia-Grossman[7], Jaegil Kim[2], Elizabeth A. Guancial[10], Richard Bambury[7], Samira Bahl[2], Namrata Gupta[2], Deborah Farlow[2], Angela Qu[1], Sabina Signoretti[11], Justine A. Barletta[11], Victor Reuter[6,8], Jesse Boehm[2], Michael Lawrence[2], Gad Getz[2,12], Philip Kantoff[1], Bernard H. Bochner[5,6], Toni K. Choueiri[1], Dean F. Bajorin[6,7], David B. Solit[6,7,13], Stacey Gabriel[1], Alan D'Andrea[3,4], Levi A. Garraway[1,2], and Jonathan E. Rosenberg[6,7]

Questions

1. Can *deleterious* passenger mutations accumulate during cancer development?

2. How deleterious are passenger mutations found in genotyped tumors?

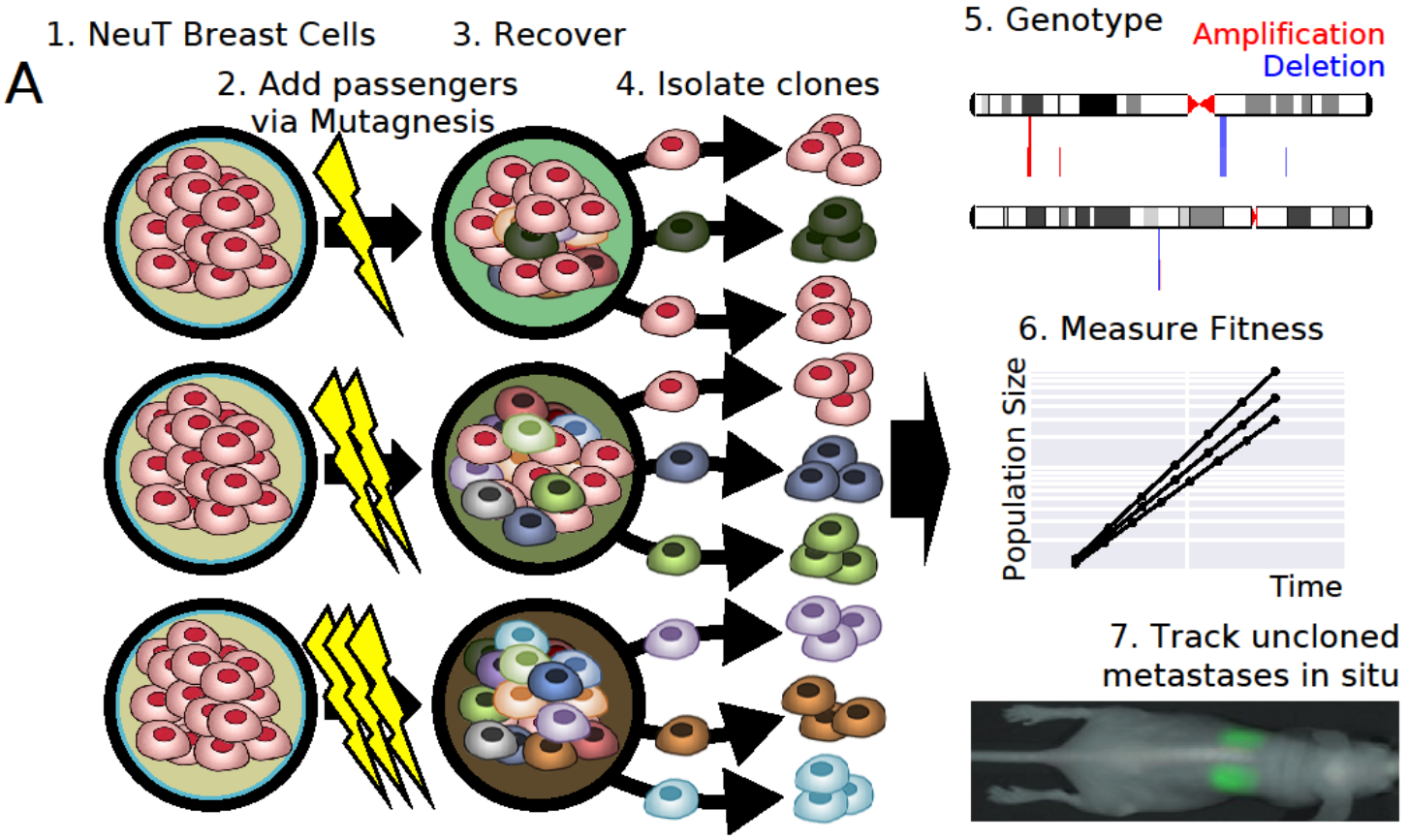
3. How can passenger mutations affect neoplastic progression?

Effect of passenger mutations

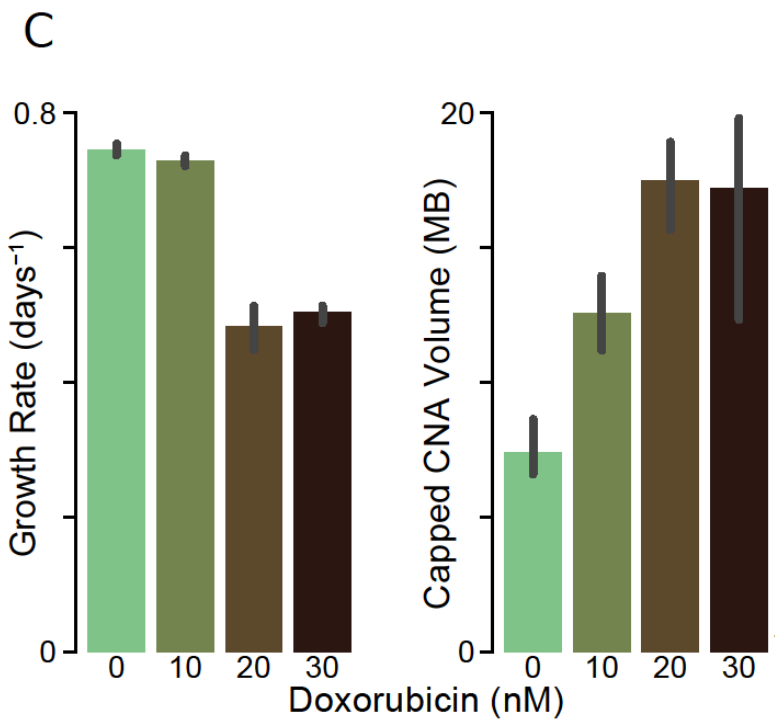
Experiment

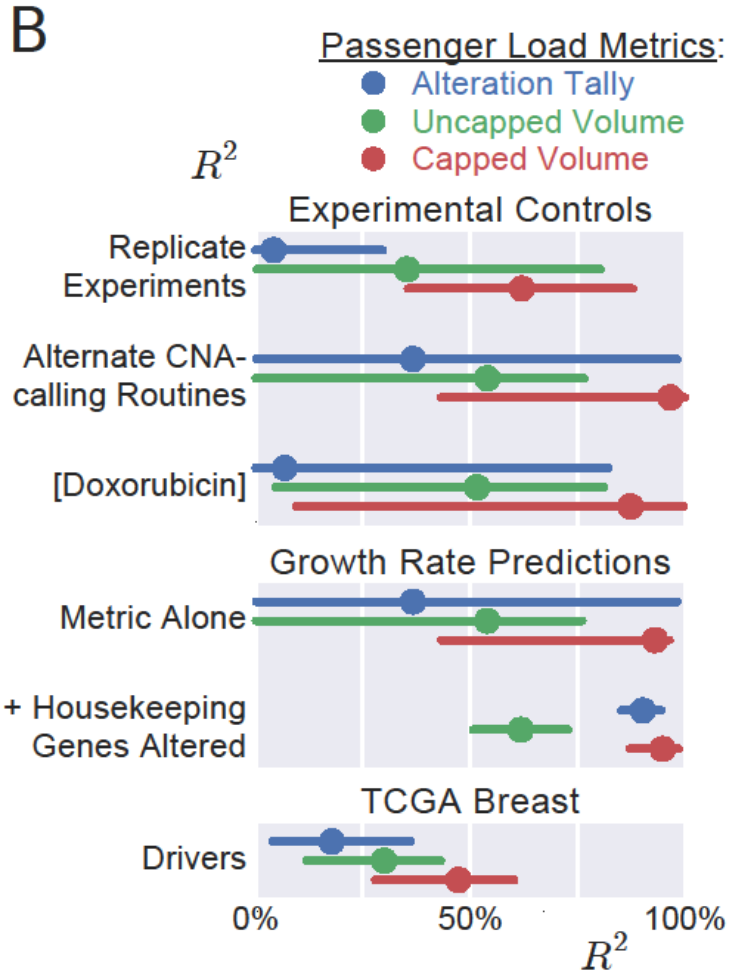
1. Develop cell lines with the same drivers and a different number of passengers
2. Measure effect of passengers on fitness
3. Measure genetic load of passengers by genotyping

Proliferative and metastatic fitness



Passenger load reduces proliferative fitness

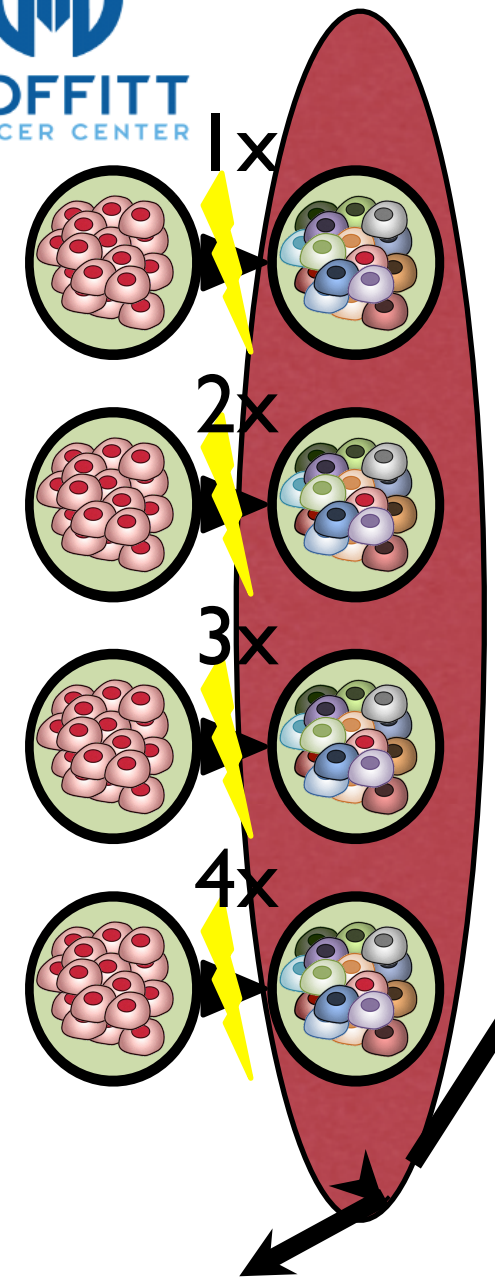


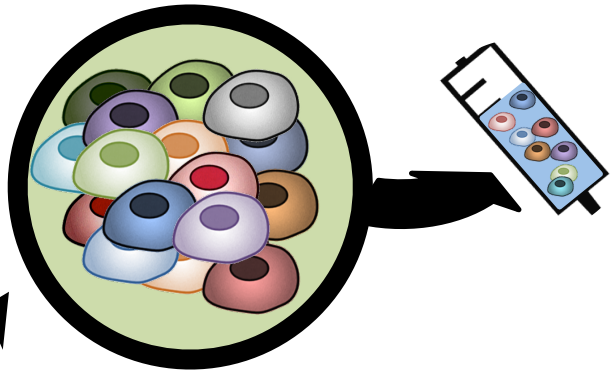


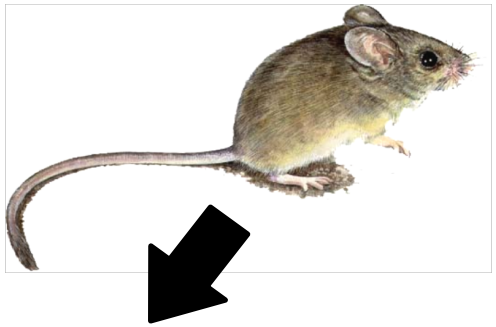
Metastatic potential

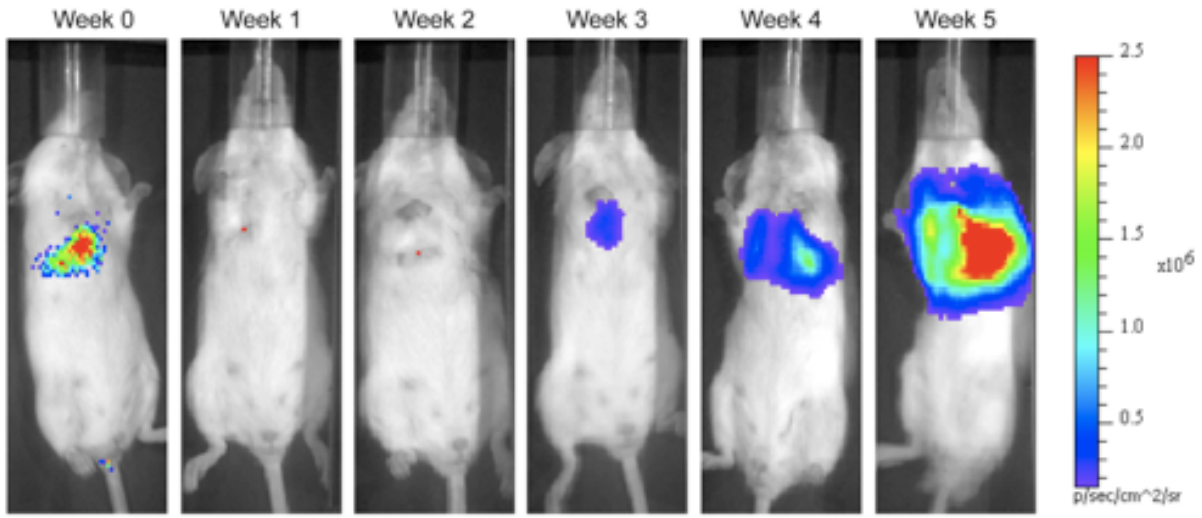
MCF-10A/Her2/Luciferase cells

- Transformed = same driver mutations
- Dox = different load of passenger mutations









Freeze

Genotyping

Passenger load reduces metastatic potential

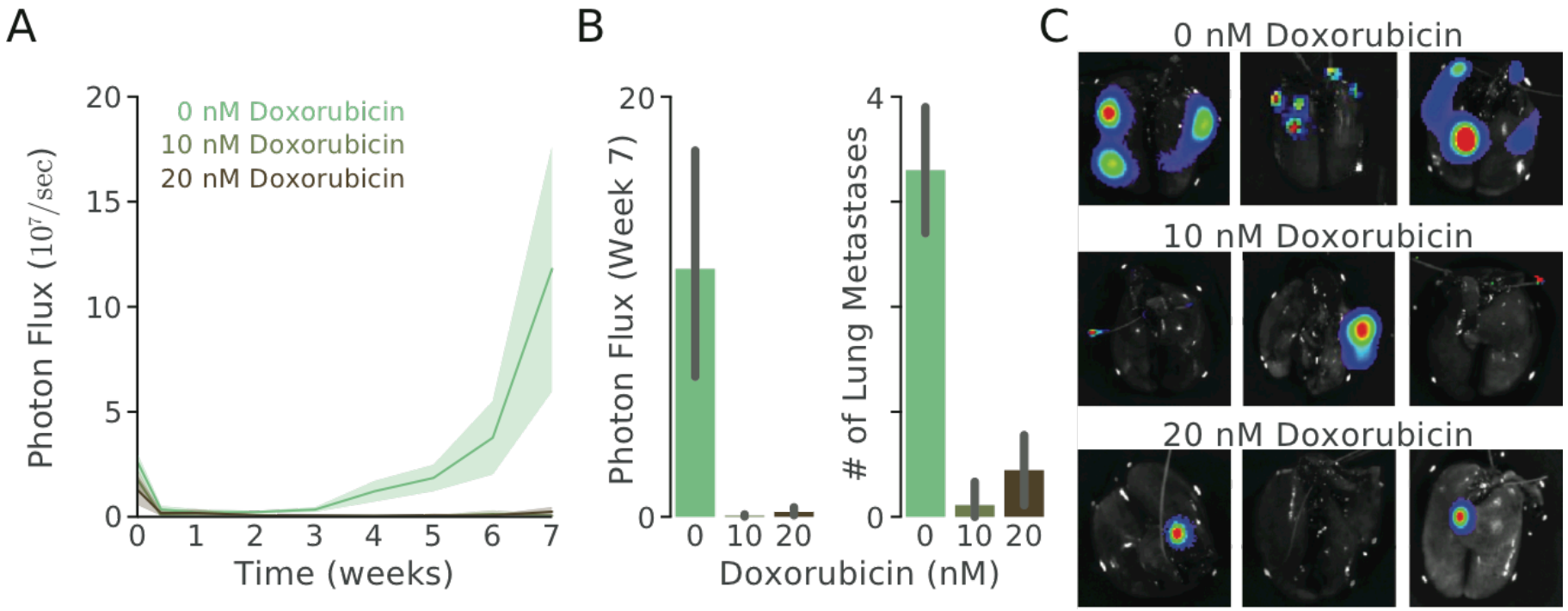
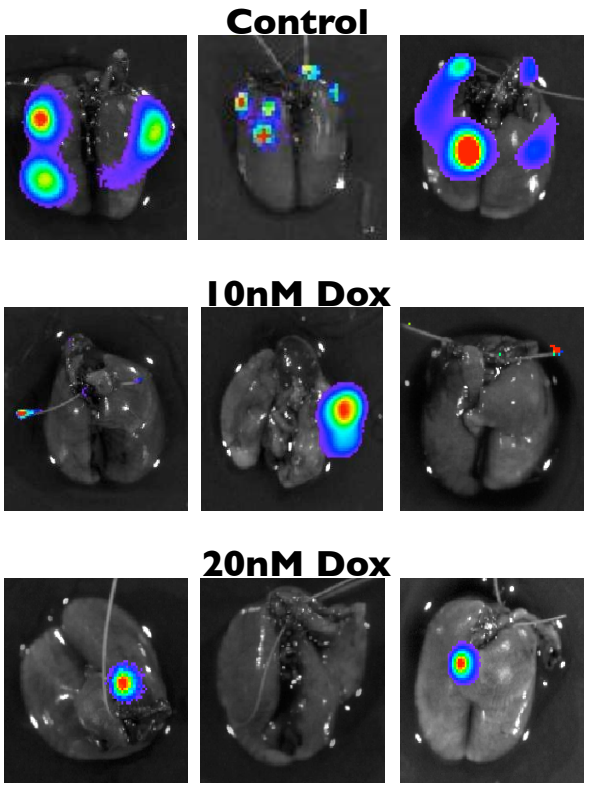
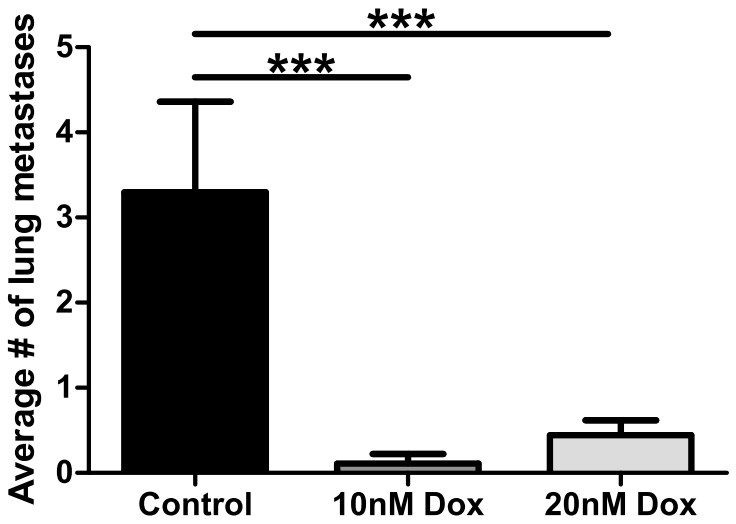
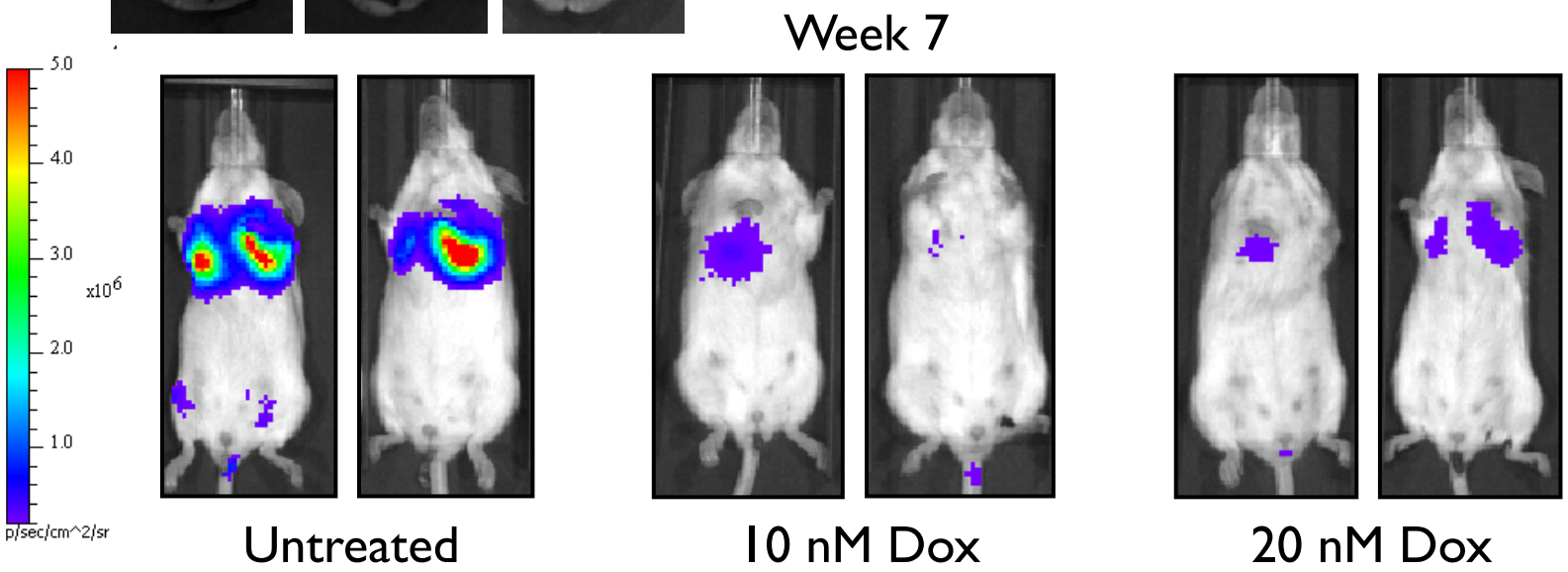


Figure 4. Higher passenger load reduces metastatic potential of cancer cells.

Mutational load negatively correlates with metastasis





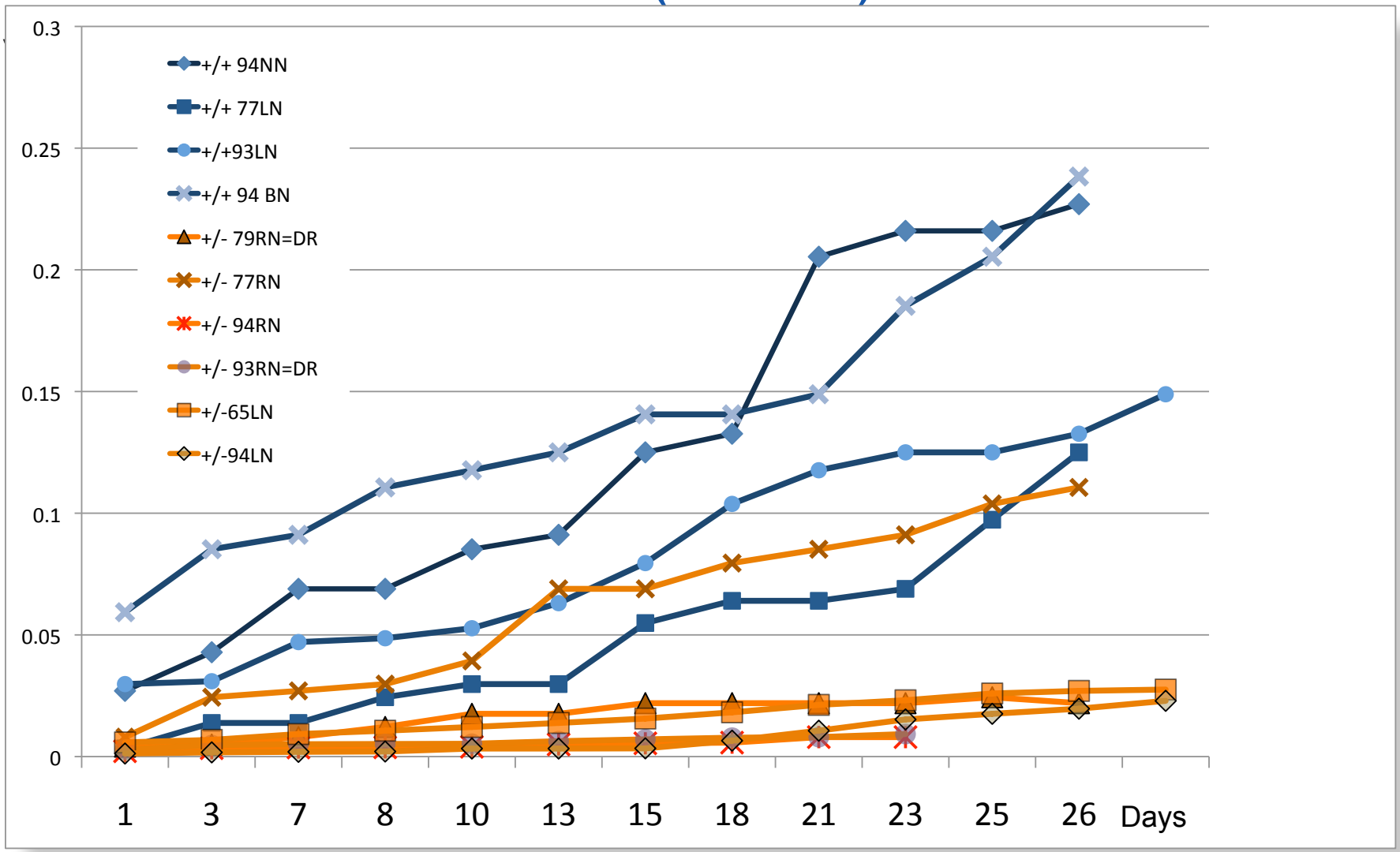


Effect of passenger mutations

New Experiment: Her2+ breast cancer mouse model:

mildly elevated mutation rate (H2AX+/-)

normal mutation rate (control)



Questions

1. Can *deleterious* passenger mutations accumulate during cancer development?

2. How deleterious are passenger mutations found in genotyped tumors?

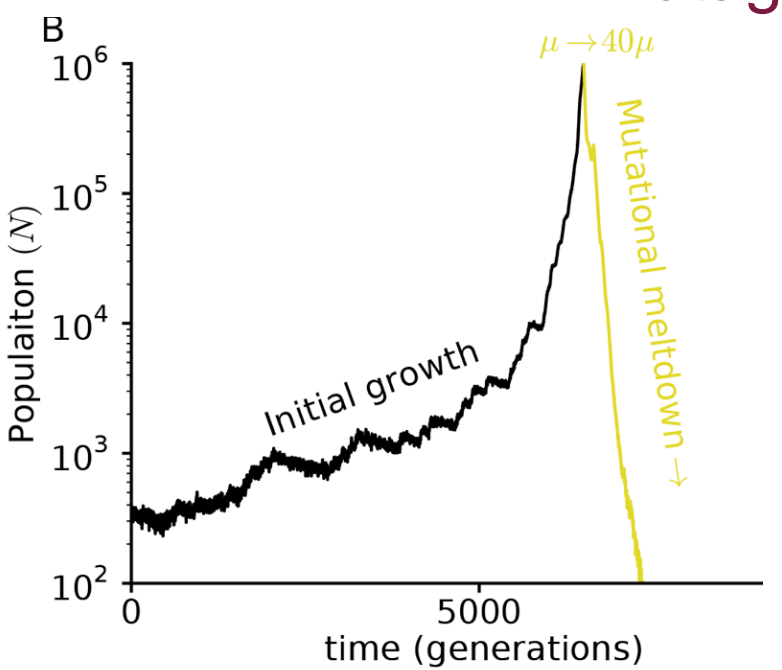
3. How can passenger mutations affect neoplastic progression?

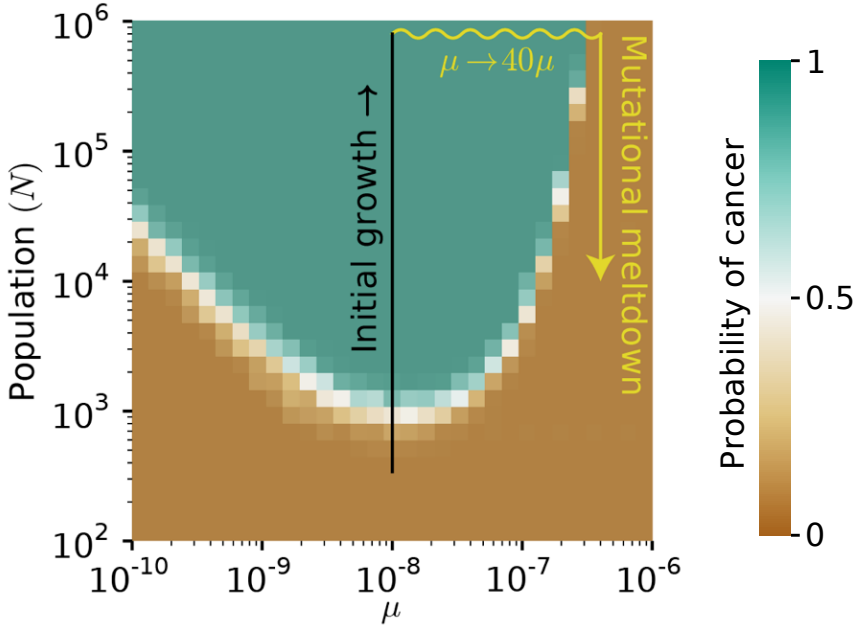
4. Can passenger load be used therapeutically?

Back to the model

Understanding treatment

Mutagenic chemo

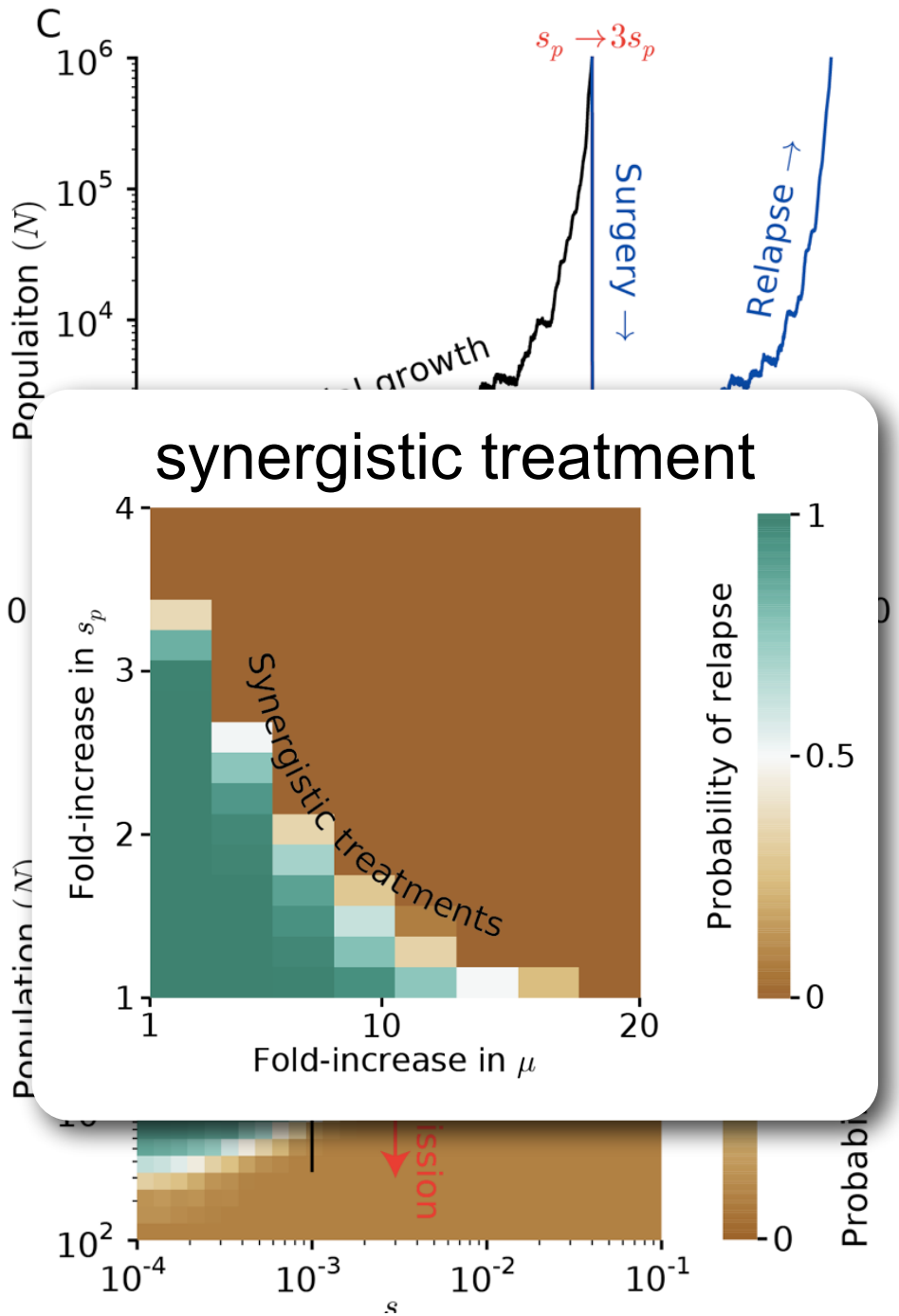




- requires very high mutation rate

- likely relapse

Understanding treatment



Increasing effects of passengers

- small effects are sufficient
- reduction of cancer size
- kills most mutated cells, i.e. cells with biggest potential for resistance
- makes cancer less evolvable

Potential approaches

- HSP90/HSP70 inhibitors
- higher temperature
- immunotherapy

Can passenger mutations
trigger an immune response?

Response to immunotherapy is associated with mutational load

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma

Alexandra Snyder, M.D., Vladimir Makarov, M.D., Taha Merghoub, Ph.D., Jianda Yuan, M.D., Ph.D., Jesse M. Zaretsky, B.S., Alexis Desrichard, Ph.D., Logan A. Walsh, Ph.D., Michael A. Postow, M.D., Phillip Wong, Ph.D., Teresa S. Ho, B.S., Travis J. Hollmann, M.D., Ph.D., Cameron Bruggeman, M.A., Kasthuri Kannan, Ph.D., Yanyun Li, M.D., Ph.D., Ceyhan Elipenahli, B.S., Cailian Liu, M.D., Christopher T. Harbison, Ph.D., Lisu Wang, M.D., Antoni Ribas, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., and Timothy A. Chan, M.D., Ph.D.

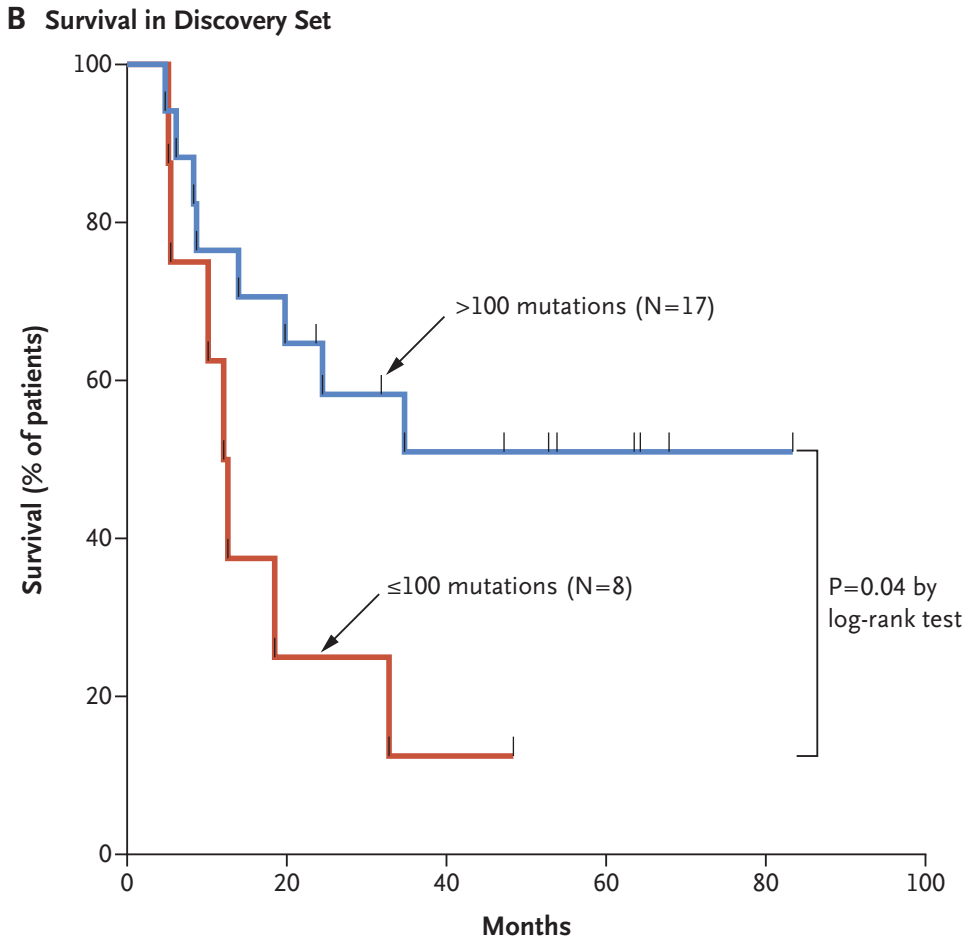


Figure 2. Mutational Landscape of Tumors According to Clinical Benefit from Ipilimumab Treatment.

Response to immunotherapy is associated with mutational load

SCIENCE sciencemag.org
9 OCTOBER 2015

ONCOLOGY

Genomic correlates of response to CTLA-4 blockade in metastatic melanoma

Eliezer M. Van Allen,[1,2,3*] Diana Miao,[1,2*] Bastian Schilling,[4,5*] Sachet A. Shukla,[1,2] Christian Blank,[6] Lisa Zimmer,[4,5] Antje Sucker,[4,5] Uwe Hillen,[4,5] Marnix H. Geukes Foppen,[6] Simone M. Goldinger,[7] Jochen Utikal,[5,8,9] Jessica C. Hassel,[10] Benjamin Weide,[11] Katharina C. Kaehler,[12] Carmen Loquai,[13] Peter Mohr,[14] Ralf Gutzmer,[15] Reinhard Dummer,[7] Stacey Gabriel,[2] Catherine J. Wu,[1,2] Dirk Schadendorf,[4,5†] Levi A. Garraway[1,2,3†]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma

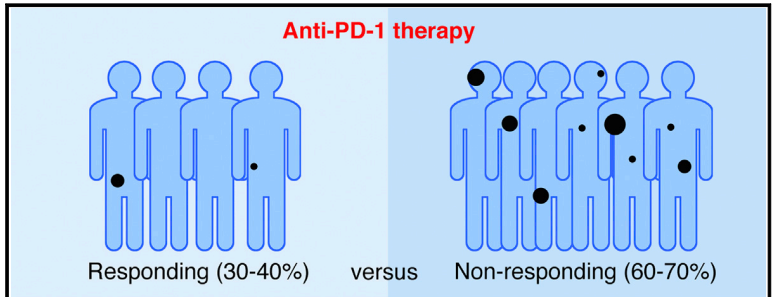
Alexandra Snyder, M.D., Vladimir Makarov, M.D., Taha Merghoub, Ph.D., Jianda Yuan, M.D., Ph.D., Jesse M. Zaretsky, B.S., Alexis Desrichard, Ph.D., Logan A. Walsh, Ph.D., Michael A. Postow, M.D., Phillip Wong, Ph.D., Teresa S. Ho, B.S., Travis J. Hollmann, M.D., Ph.D., Cameron Bruggeman, M.A., Kasthuri Kannan, Ph.D., Yanyun Li, M.D., Ph.D., Ceyhan Elipenahli, B.S., Cailian Liu, M.D., Christopher T. Harbison, Ph.D., Lisu Wang, M.D., Antoni Ribas, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., and Timothy A. Chan, M.D., Ph.D.

Article

Cell
Hugo et al., 2016, Cell *165*, 35–44
March 24, 2016 ©2016 Elsevier Inc.

Genomic and Transcriptomic Features of Response to Anti-PD-1 Therapy in Metastatic Melanoma

Graphical Abstract



Authors

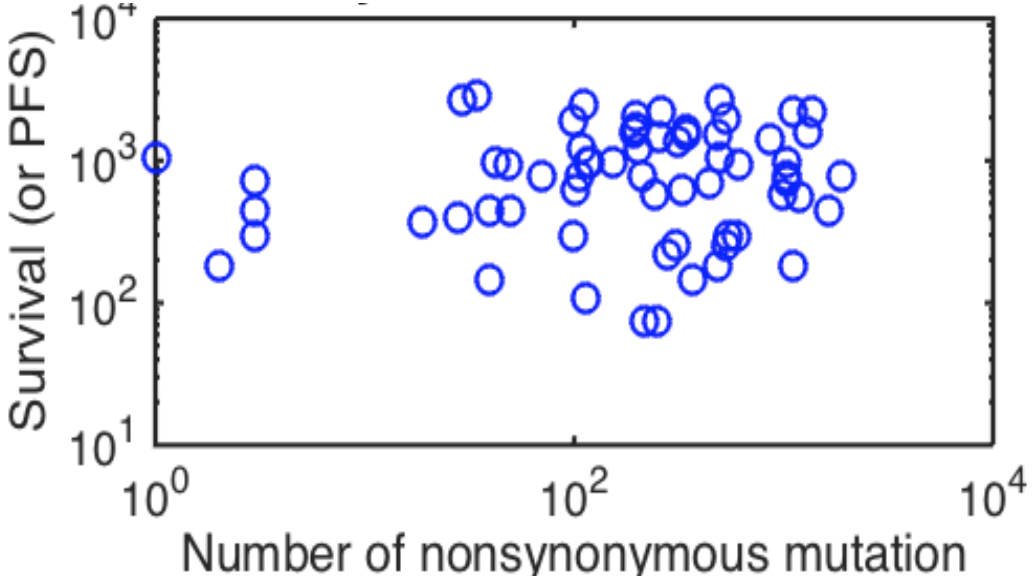
Willy Hugo, Jesse M. Zaretsky, Lu Sun, ..., Douglas B. Johnson, Antoni Ribas, Roger S. Lo

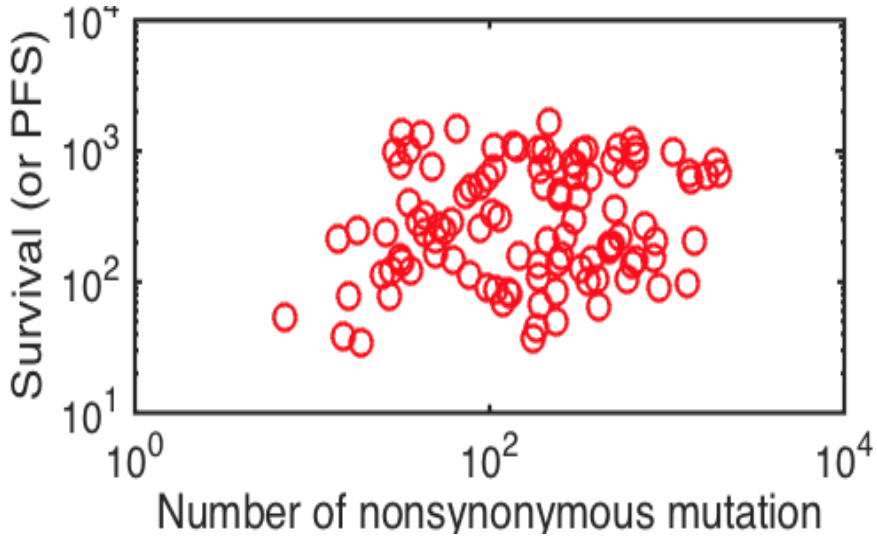
Correspondence

rlo@mednet.ucla.edu

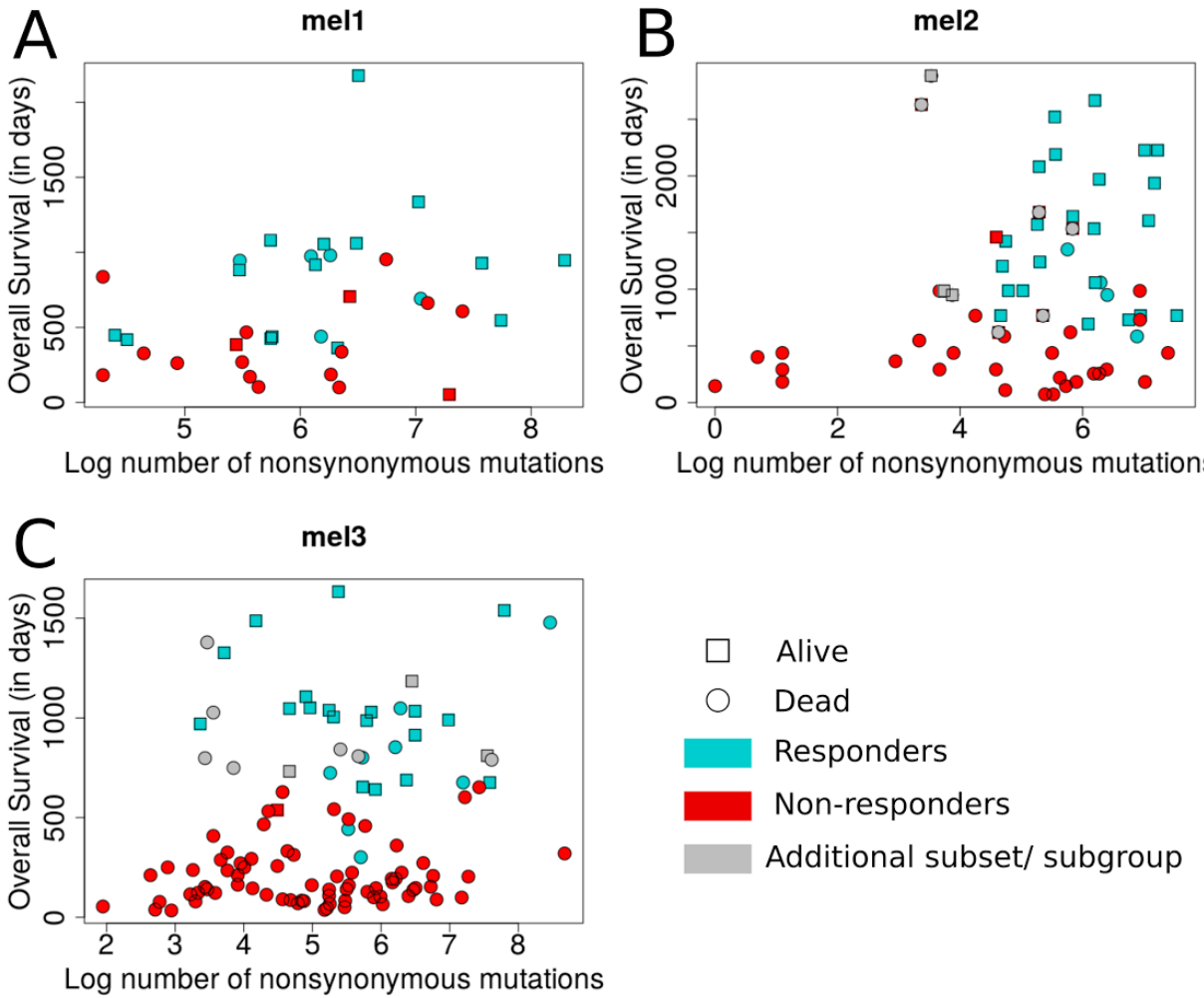
In Brief

Response to immunotherapy is associated with mutational load, ***really?***





Response to immunotherapy is associated with mutational load, ***really?***



Summary

1. Deleterious passengers can accumulate during cancer progression

2. Accumulated passengers show signatures of non-neutral mutations

3. Load of passengers reduces fitness (proliferative and metastatic) of cancer cells

   immunological effect is *questionable….*

Chris McFarland

Stanford University

Kirill Korolev,

Boston University

Carino Gurjao,

École Normale Supérieure de Lyon

Experiments

Julia Yaglom

Michael Sherman

BU Medical School

Metastatic potential

MOFFITT CANCER CENTER

David Morse,

Jacob Scott

Jonathan Wojtkowiak

David Basanta

Genomics

Gregory Kryukov

Broad Institute

Shamil Sunyaev

BWH Genetics

NIH Physical Sciences in Oncology

MIT-France Program

Impact of deleterious passenger mutations on cancer progression

Christopher D. McFarland[a], Kirill S. Korolev[b], Gregory V. Kryukov[c,d], Shamil R. Sunyaev[a,c,d], and Leonid A. Mirny[a,b,c,e,1]

[a]Graduate Program in Biophysics, Harvard University, Boston, MA 02115; [b]Department of Physics, Massachusetts Institute of Technology, Cambridge, MA 02129; [c]Broad Institute of MIT and Harvard, Cambridge, MA 02139; [d]Division of Genetics, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115; and [e]Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA 02139

Edited* by Robert H. Austin, Princeton University, Princeton, NJ, and approved January 4, 2013 (received for review August 23, 2012)

Tug-of-war between driver and passenger mutations in cancer and other adaptive processes

Christopher D. McFarland[a], Leonid A. Mirny[a,b,c,1], and Kirill S. Korolev[b,d,1]

Cold Spring Harbor Laboratory

bioRxiv beta

THE PREPRINT SERVER FOR BIOLOGY

HOME |

Search

New Results

Passenger DNA alterations reduce cancer fitness in cell culture and mouse models

Christopher D McFarland, Julia A Yaglom, Jonathan W Wojtkowiak, Jacob G Scott, David L Morse, Michael Y Sherman, Leonid A Mirny

doi: http://dx.doi.org/10.1101/026302

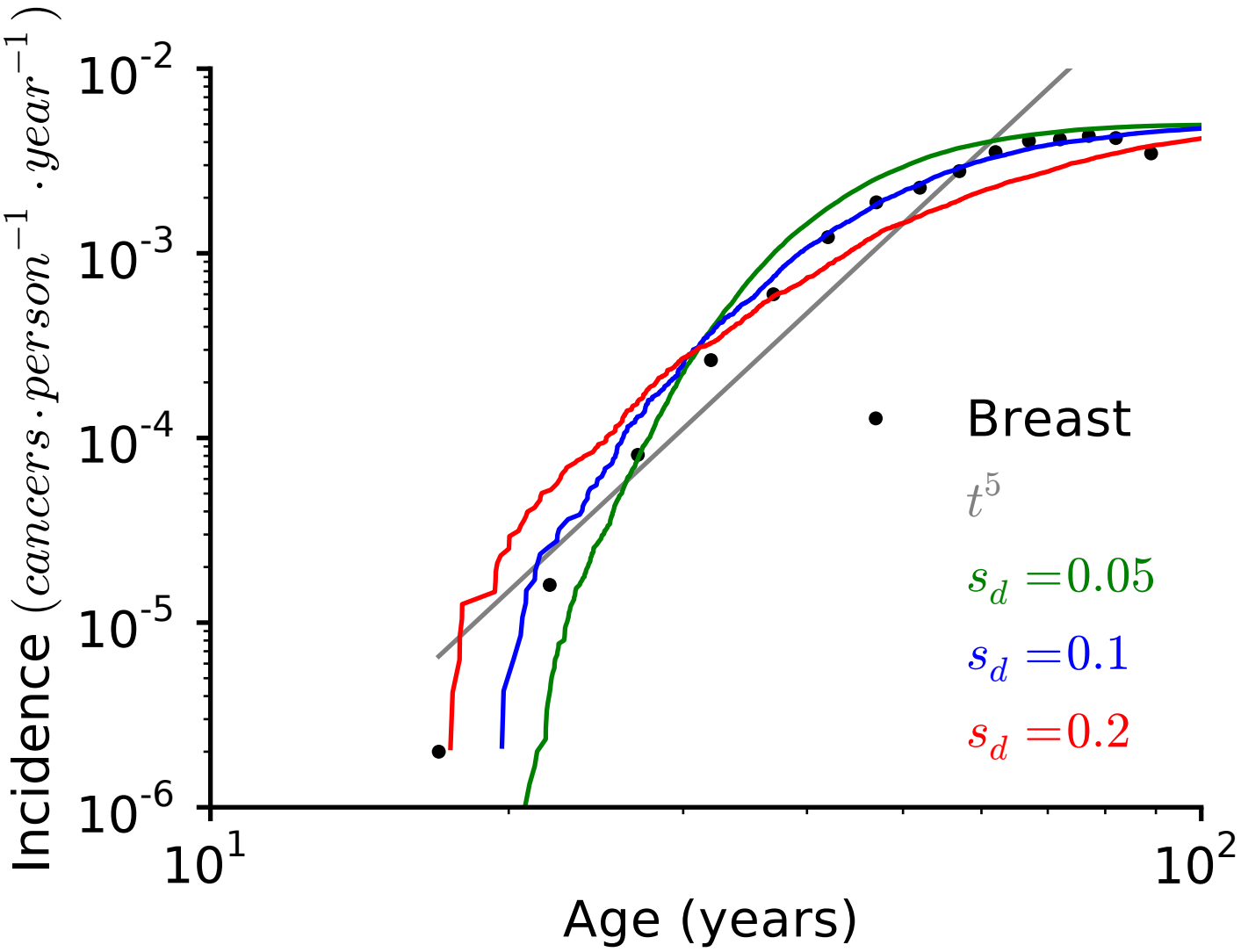
Weighted down by passengers?

The Stock Solution

Nature Reviews Cancer | AOP, published online 7 March 2013; doi:10.1038/nrc3488

Weighed down by passengers?

Estimating model parameters

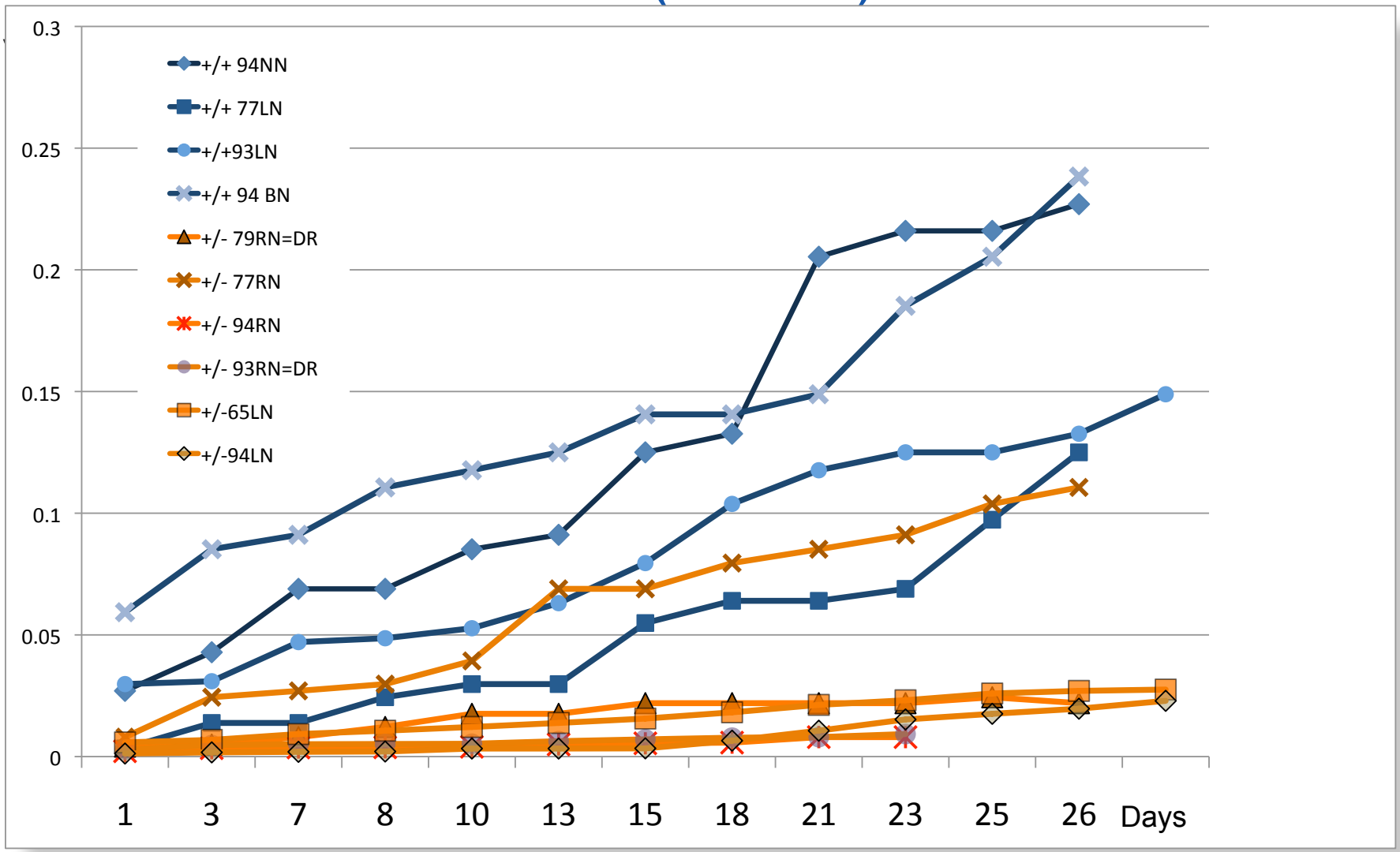


Effect of passenger mutations

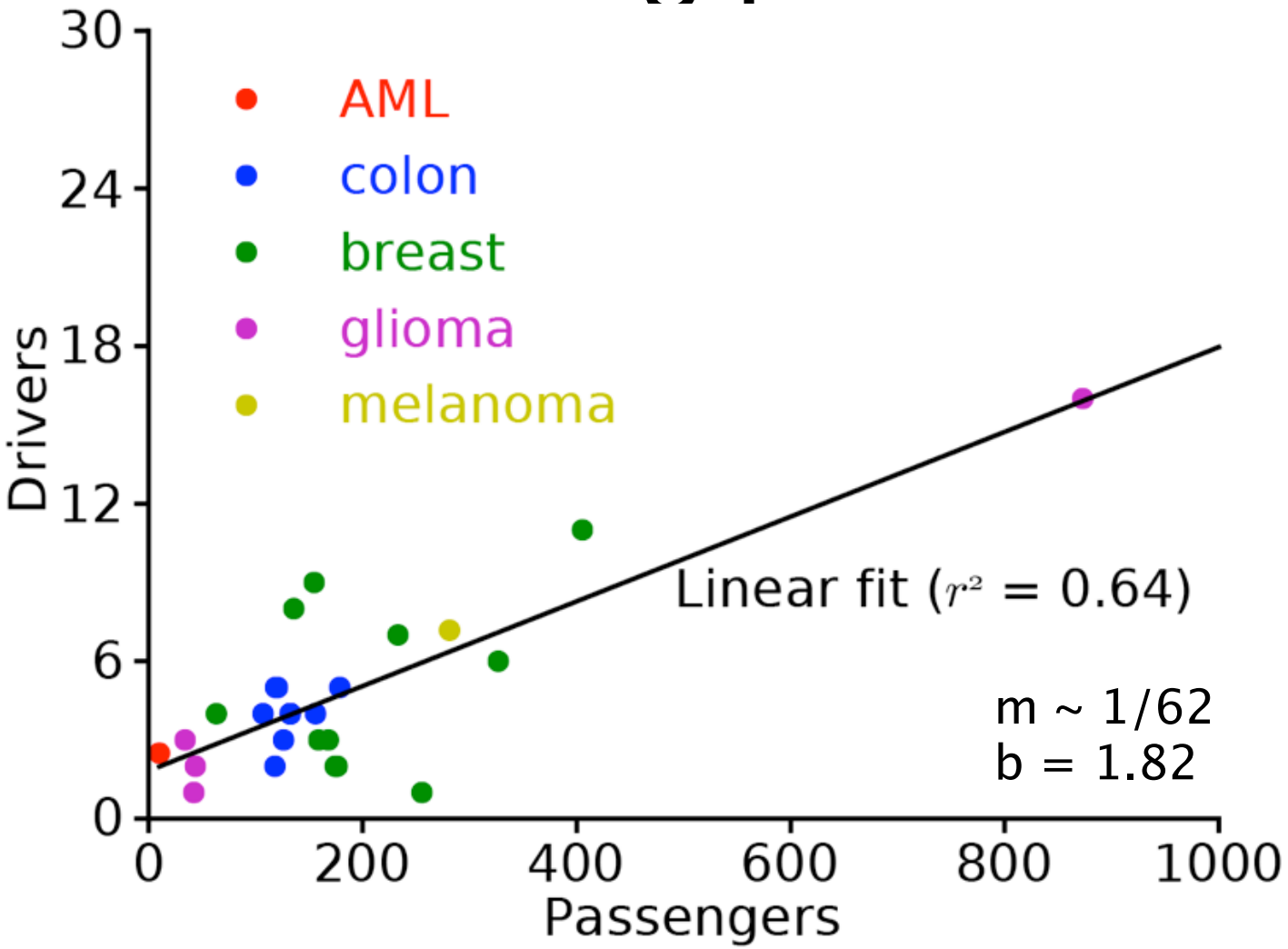
New Experiment: Her2+ breast cancer mouse model:

mildly elevated mutation rate (H2AX+/-)

normal mutation rate (control)



estimating parameters



$n_d = m*n_p + b$, where $m = s_p/s_d$ and $b = \log(D(\ N\_final\ )/s_d$