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Accumulation of passenger mutations in cancer

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Somatic evolution of cancer

1. Drivers: mutations in tumor suppressors and oncogenes
   advantageous to cancer
   same genes affected in different tumors
2. Passengers: randomly occurring mutations
   neutral or deleterious
   different genes in different tumors

Tumor(s)	Genes sequenced	protein coding mutations	putative driver mutations†	Reference
11 Breast Cancers	55%	115.4 ± 53.2	5.1 ± 3.3	(11)
10 Colon Cancers	55%	75.0 ± 11.7	4.0 ± 0.9	(11)
4 astrocytomas, grade IV	81%	206 ± 343	5.5 ± 7.0	(12)
acute myeloid leukemia	85%	10	2	(6)
malignant melanoma	85%	239	7	(7)
small-cell lung cancer	86%	100	4	(8)

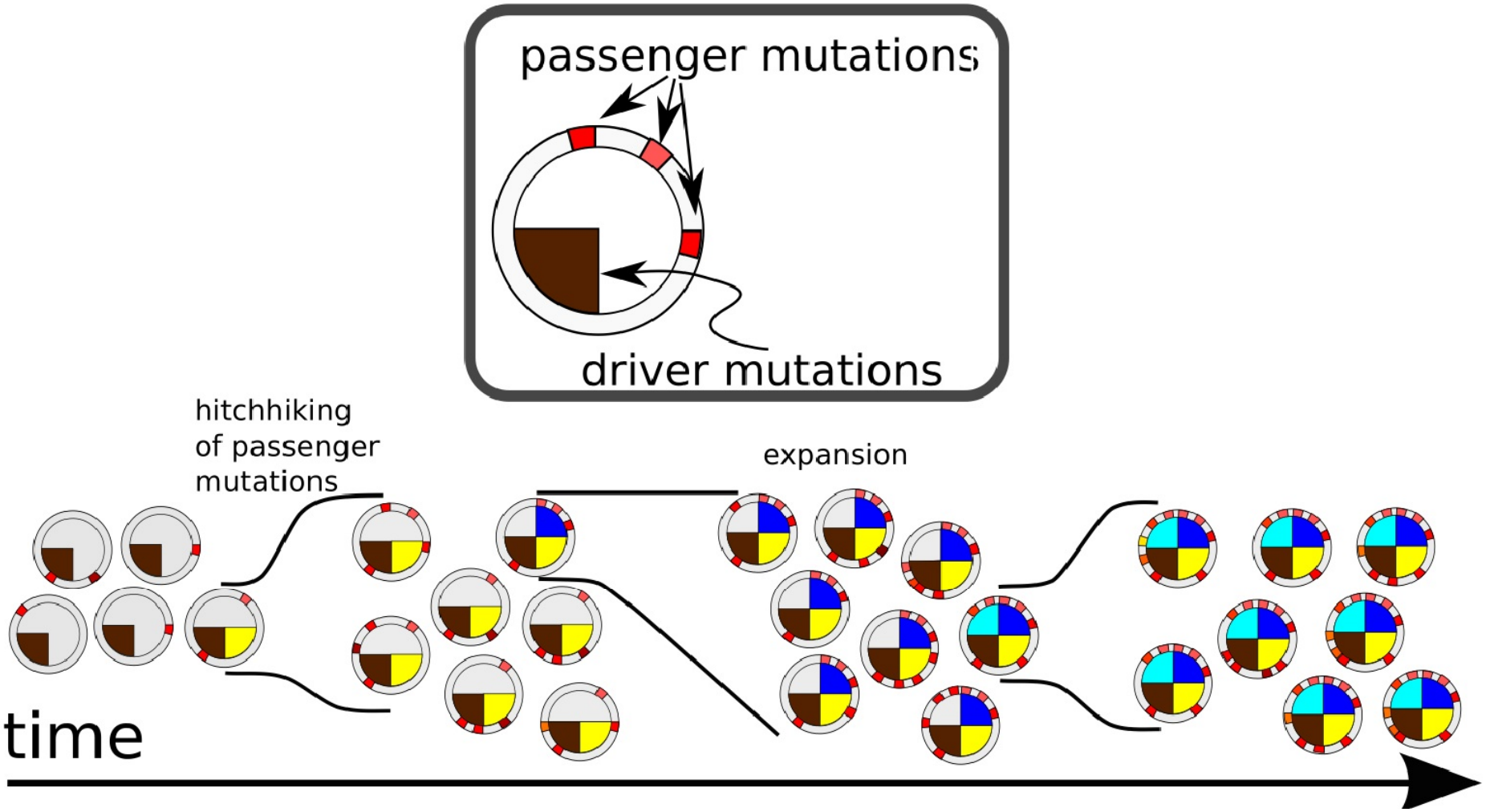
*Based on fraction of protein coding genome sequenced assuming a complete human genome of 22,287 genes (13). These estimates, in all likelihood, underestimate the number of passengers as many are misread as sequencing errors. Approximately 76%(8) to 88%(7) of all substitutions are detected (False negative rate), while only an estimated 25% of indels are detected. Approximately, 97% of identified mutations are genuine (True positive rate).

Outline

Two ideas

1. Cancer is experiencing a heavy genetic load of passenger mutations.
2. Therapy could be aimed at elevating deleterious effect of passenger mutations.

Somatic evolution of cancer



Genetic load and population meltdown

Accumulation of deleterious mutations in asexual population gradually leads to **population extinction**

- **Genetic load** = fraction of the population to die

$$L = \frac{w_{\max} - \bar{w}}{w_{\max}}$$

- In steady state (mut/sel balance) the **mean fitness** Muller-Lynch

$$\bar{w} = \exp(-U) = \exp(-\mu T)$$

Number of new deleterious mutations per generation per individual

Population meltdown/Ratchet

Accumulation of mutations

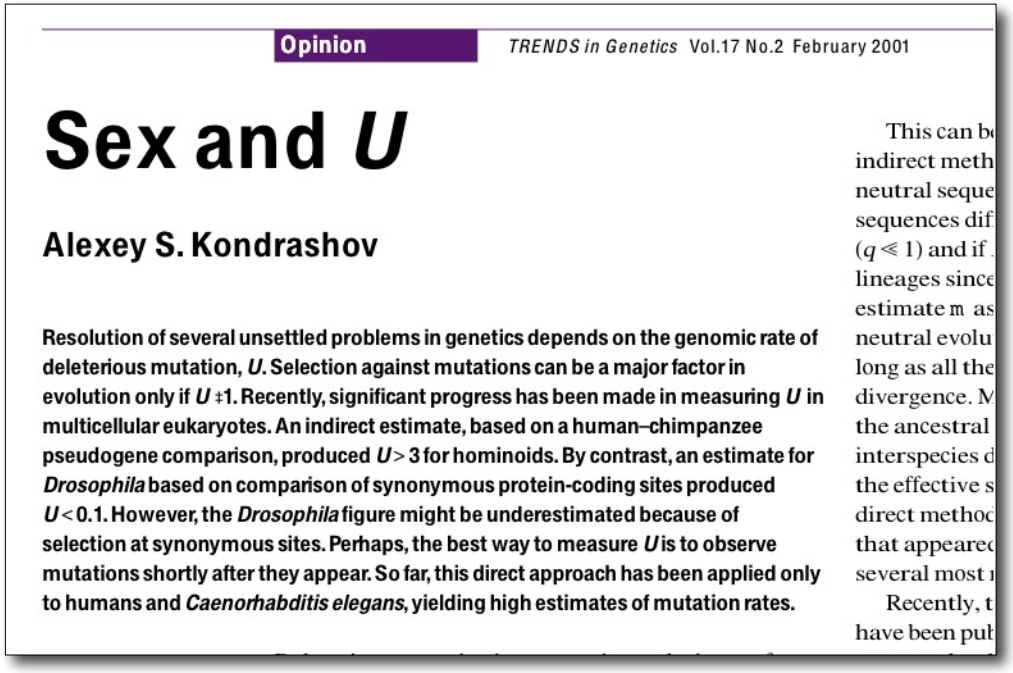
↓

Loss of most fit class (ratcheting)

↓

Drop in population size

Asexual populations are at risk of meltdown



Opinion TRENDS in Genetics Vol.17 No.2 February 2001

Sex and *U*

Alexey S. Kondrashov

Resolution of several unsettled problems in genetics depends on the genomic rate of deleterious mutation, *U*. Selection against mutations can be a major factor in evolution only if $U \ddagger 1$. Recently, significant progress has been made in measuring *U* in multicellular eukaryotes. An indirect estimate, based on a human–chimpanzee pseudogene comparison, produced $U > 3$ for hominoids. By contrast, an estimate for *Drosophila* based on comparison of synonymous protein-coding sites produced $U < 0.1$. However, the *Drosophila* figure might be underestimated because of selection at synonymous sites. Perhaps, the best way to measure *U* is to observe mutations shortly after they appear. So far, this direct approach has been applied only to humans and *Caenorhabditis elegans*, yielding high estimates of mutation rates.

This can b
indirect meth
neutral seque
sequences dif
($q \ll 1$) and if
lineages since
estimate m as
neutral evolu
long as all the
divergence. M
the ancestral
interspecies d
the effective s
direct metho
that appeared
several most
Recently, t
have been pub

Idea #1

Can accumulation of deleterious passenger mutations lead to cancer meltdown ?

1. Asexual population
2. High rate of mutations
   x100 normal, genomic instability, epigenetic alterations, …
3. Accumulation of passenger mutations via hitchhiking/bottlenecks

How fast is this process ?

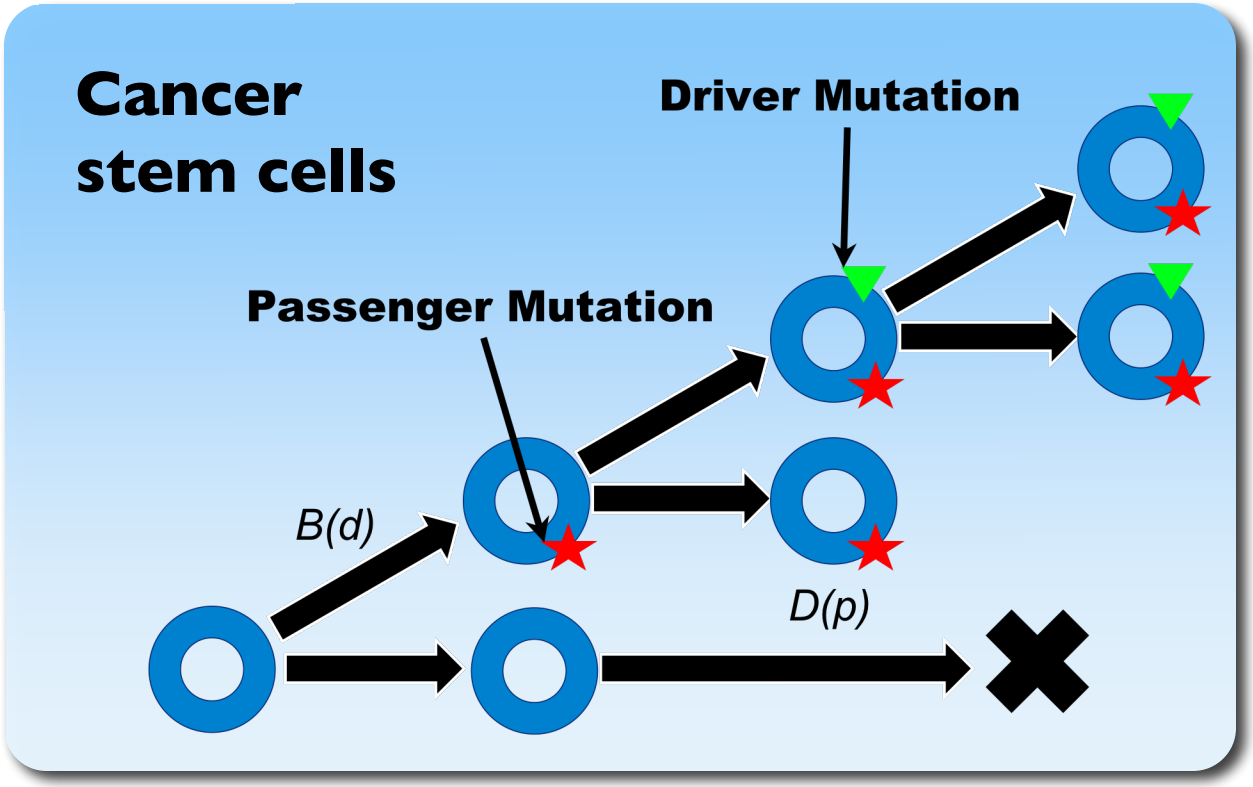
Cancer and U

1. Can deleterious passenger mutations accumulate during cancer development?
2. How strong is the phenotype of passenger mutations?
3. How can this vulnerability of cancer be exploited by therapeutics?

Simulations

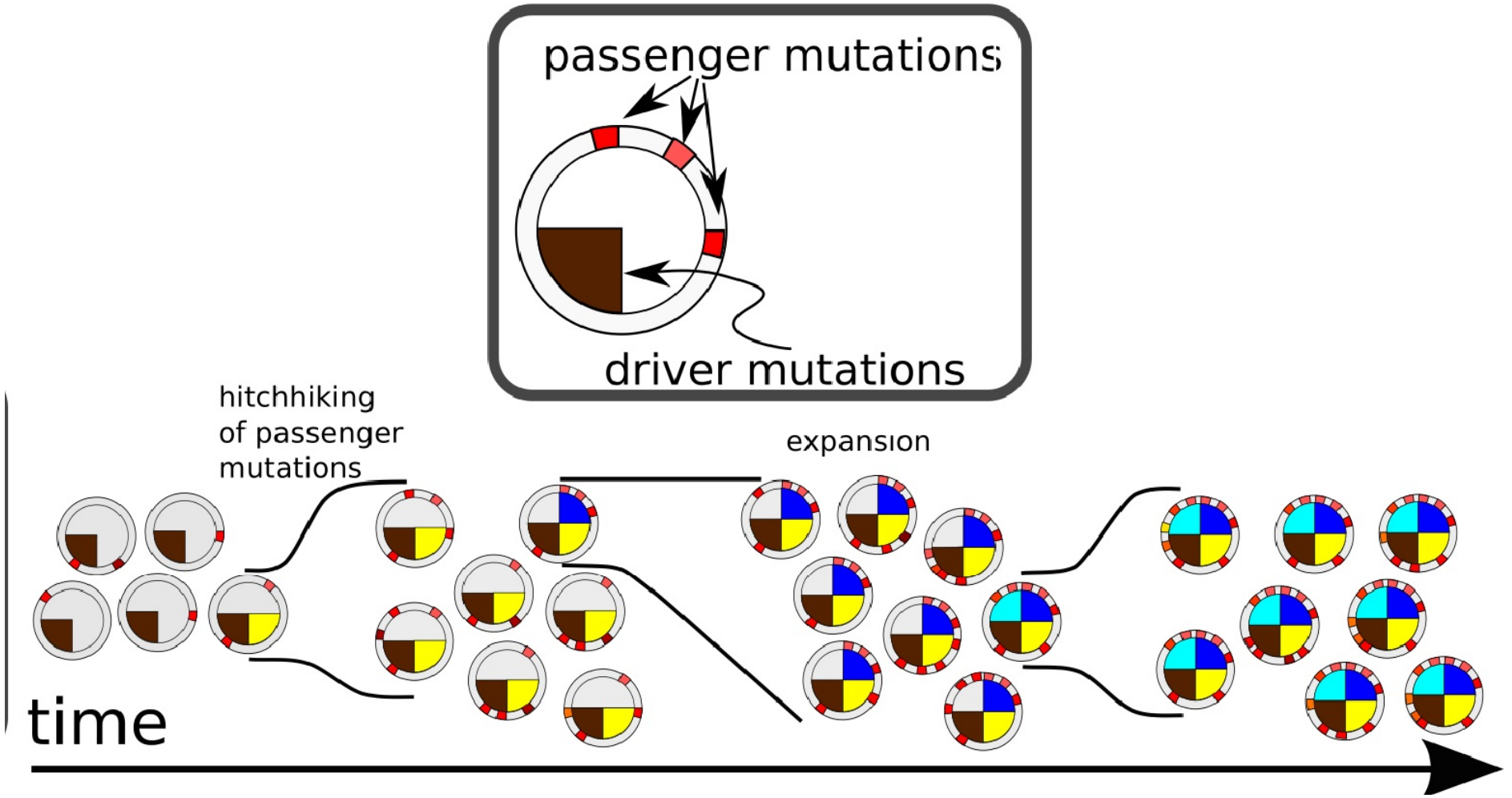
$$D(p,N) = \frac{N}{K}$$

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



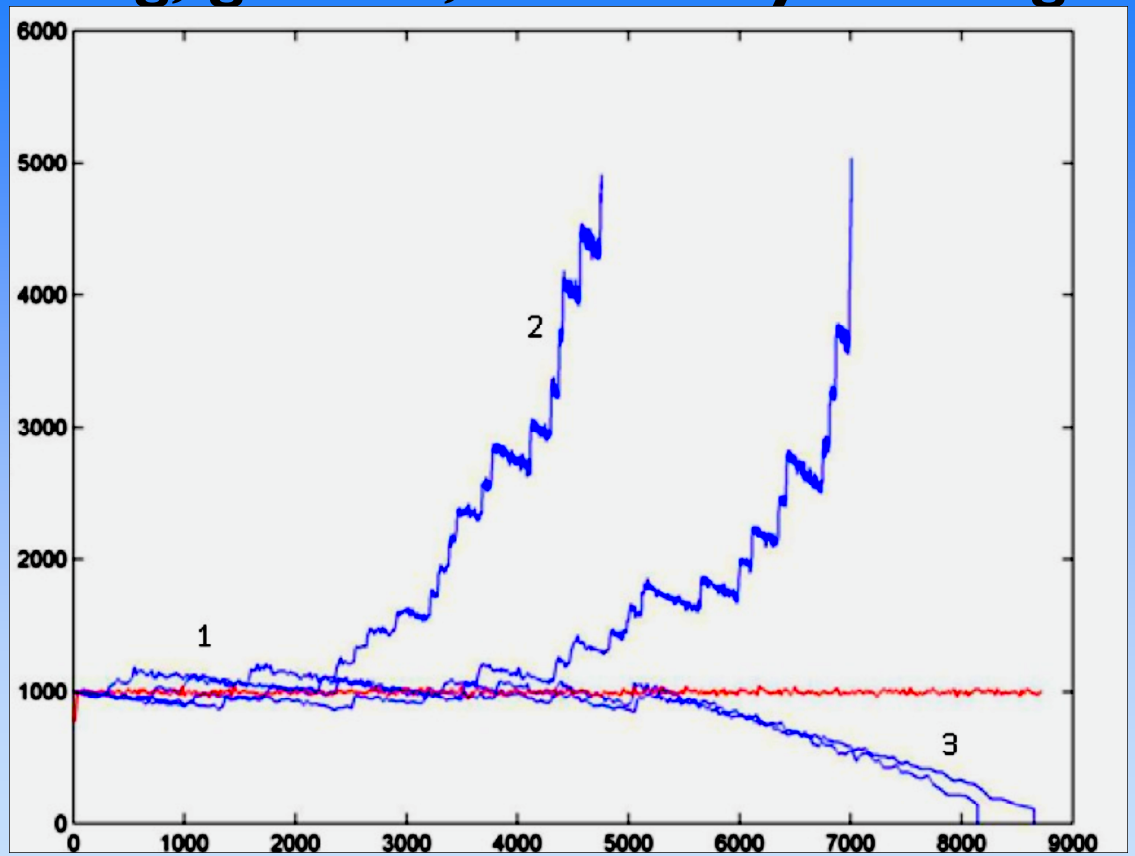
- Drivers - large advantageous effect 0.1
- Passenger - small deleterious effect 0.001
- Population size can change

Somatic evolution of cancer



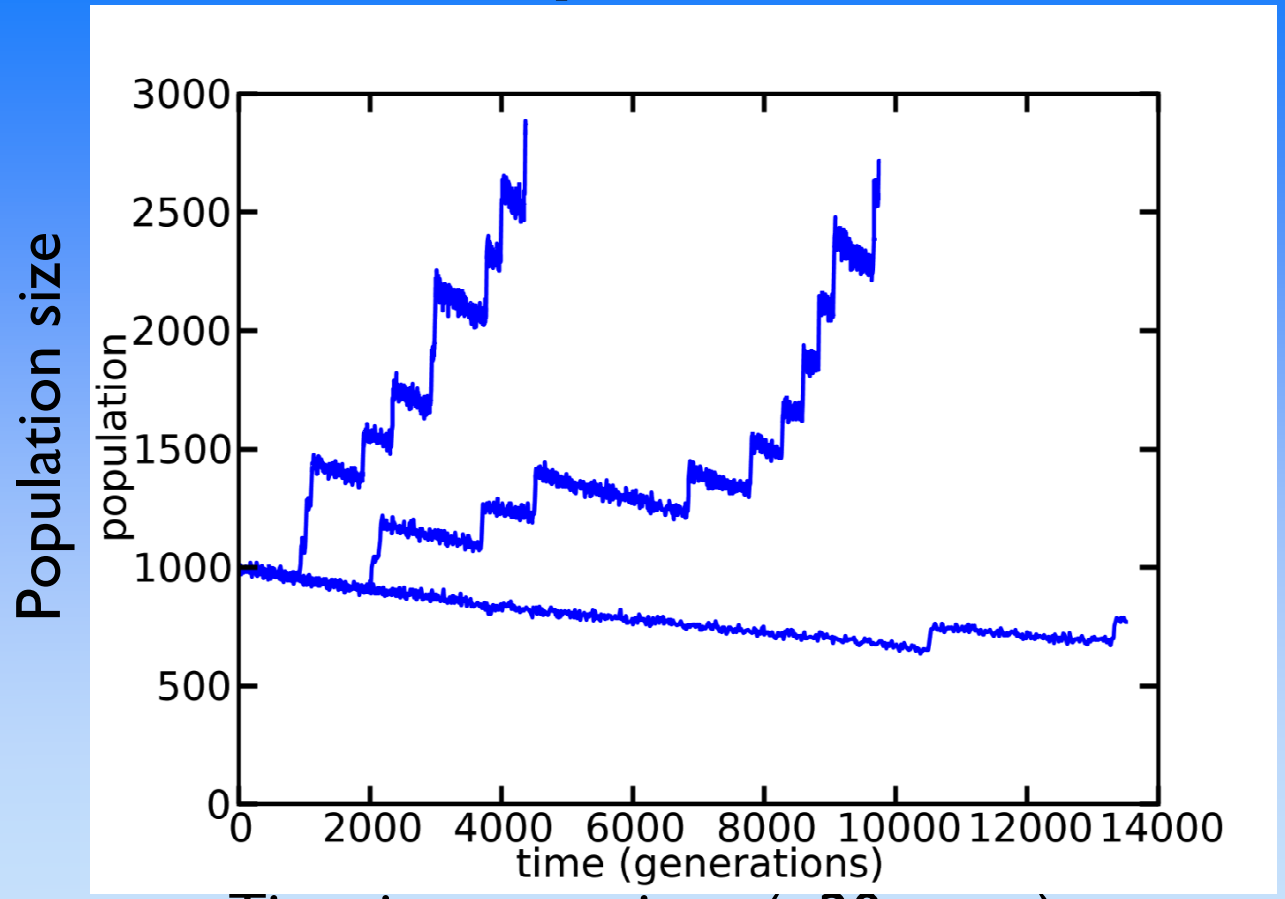
Simulations

Hitchhiking, growth, dormancy and regression



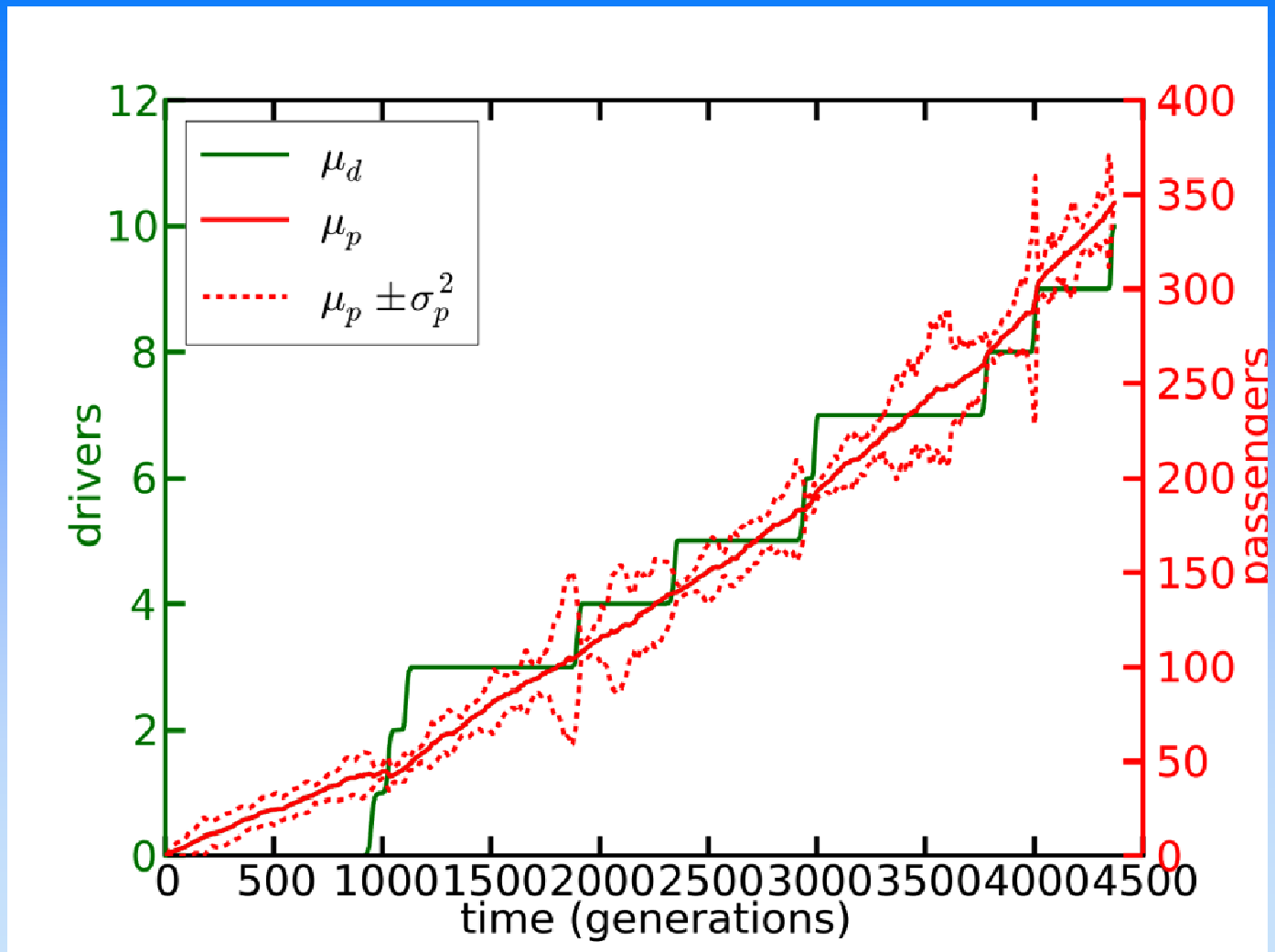
Simulations

Identical parameters

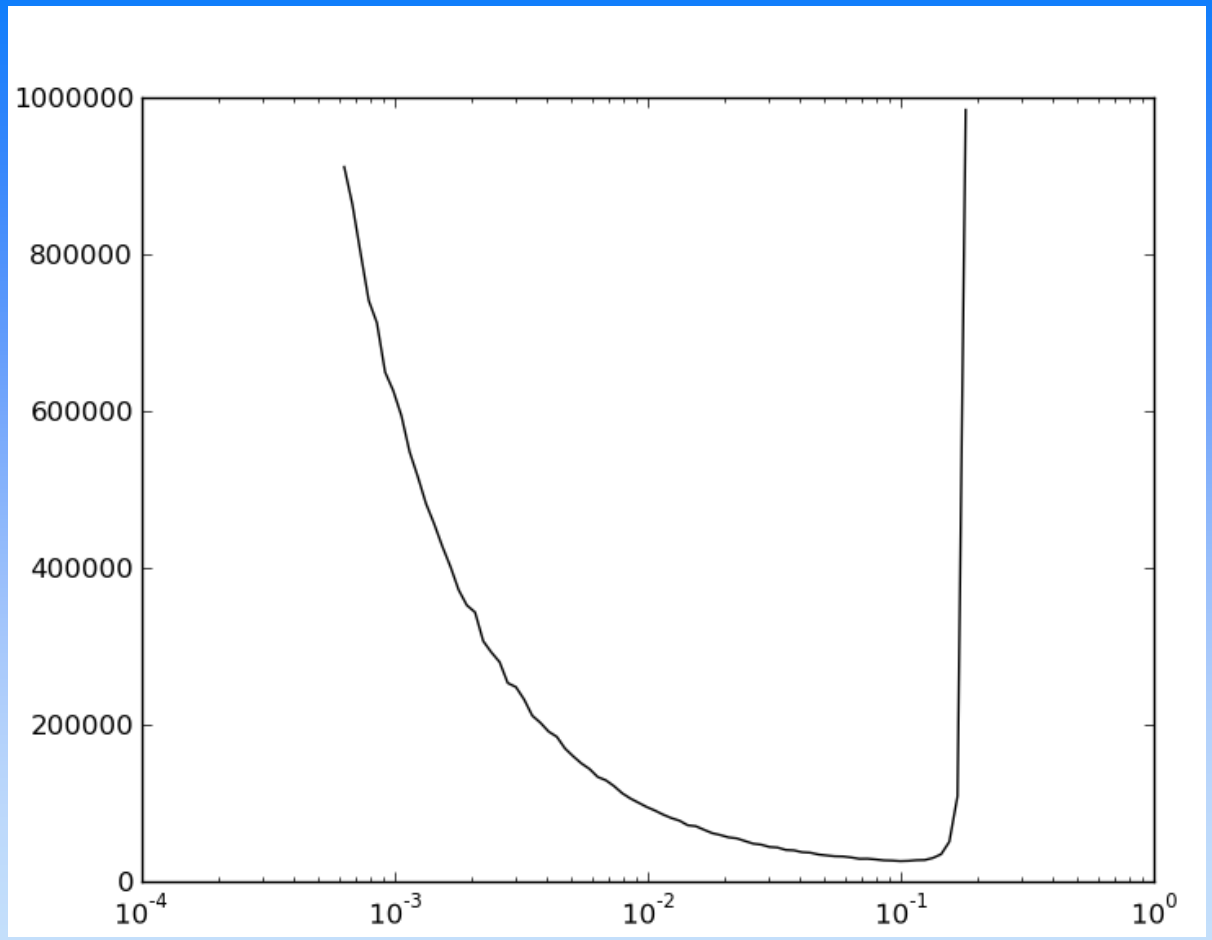


Time in generations (~20 years)

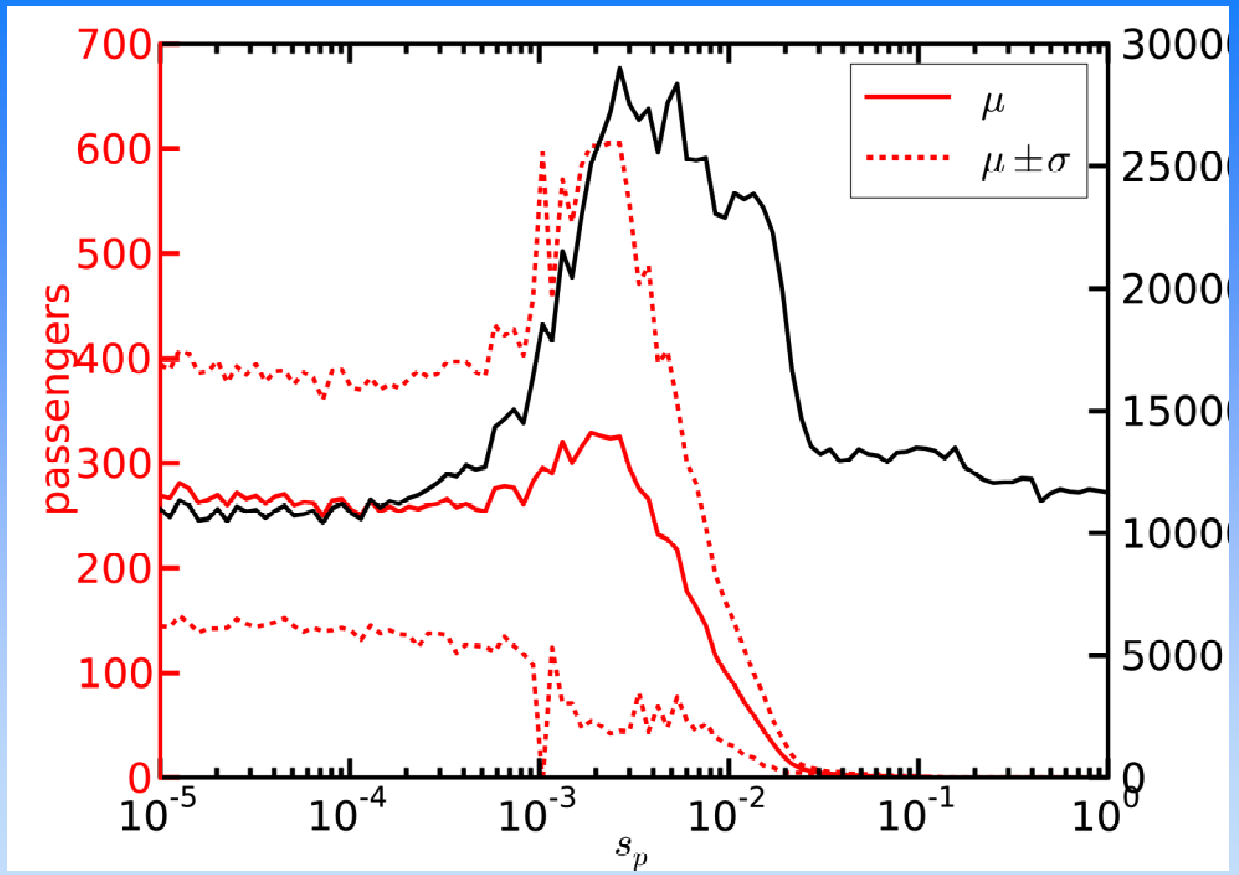
Simulations



Extinction time



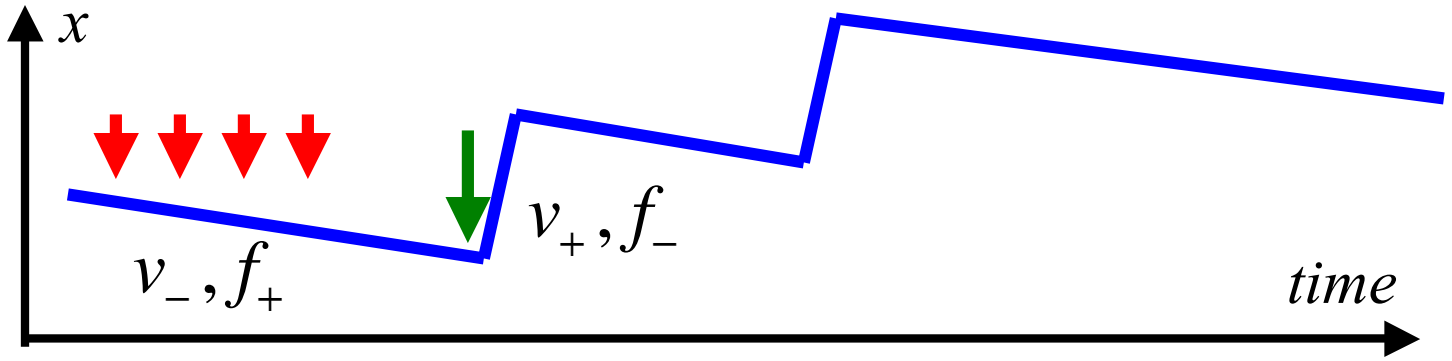
Waiting time
and accumulation of passengers



Effect of passenger a mutation, s_p

Analytical model

Two state process, x - population size



v: Velocities

f : frequencies of switching

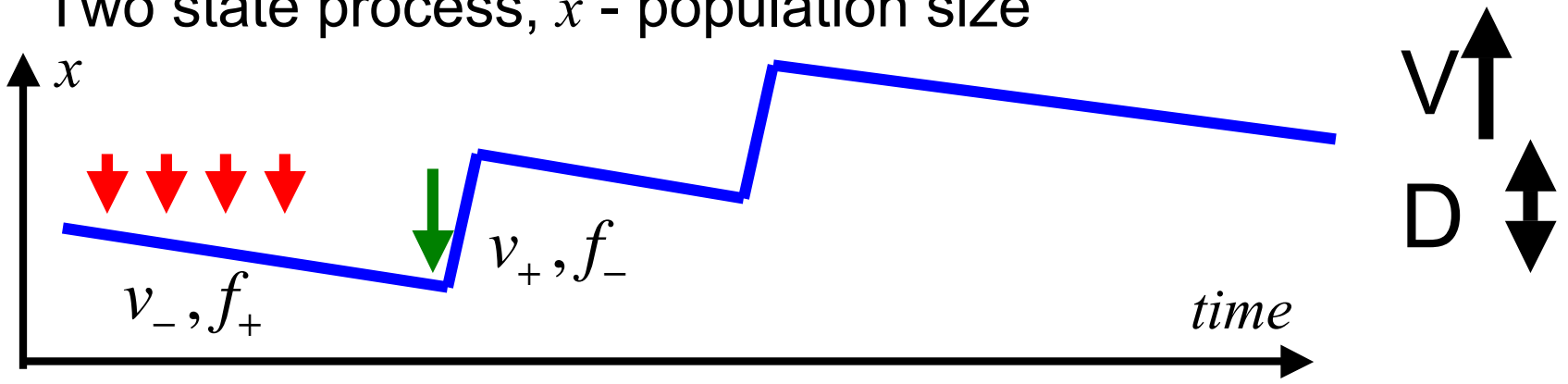
$$\frac{\partial p_+(x,t)}{\partial t} = f_+ p_-(x,t) - f_- p_+(x,t) - v_+ \frac{\partial p_+(x,t)}{\partial x}$$

$$\frac{\partial p_-(x,t)}{\partial t} = f_- p_+(x,t) - f_+ p_-(x,t) - v_- \frac{\partial p_-(x,t)}{\partial x}$$

(Dogterom Leibler: Dynamics of microtubules PRL 1993)

Analytical model

Two state process, x - population size



On long time scales: diffusion with drift

$$f_- \gg f_+$$

$$V = \frac{f_+ v_+ - f_- v_-}{f_+ + f_-} \approx f_+ \Delta_+ - v_-$$

$$D = \frac{v_+ v_-}{f_+ + f_-}$$

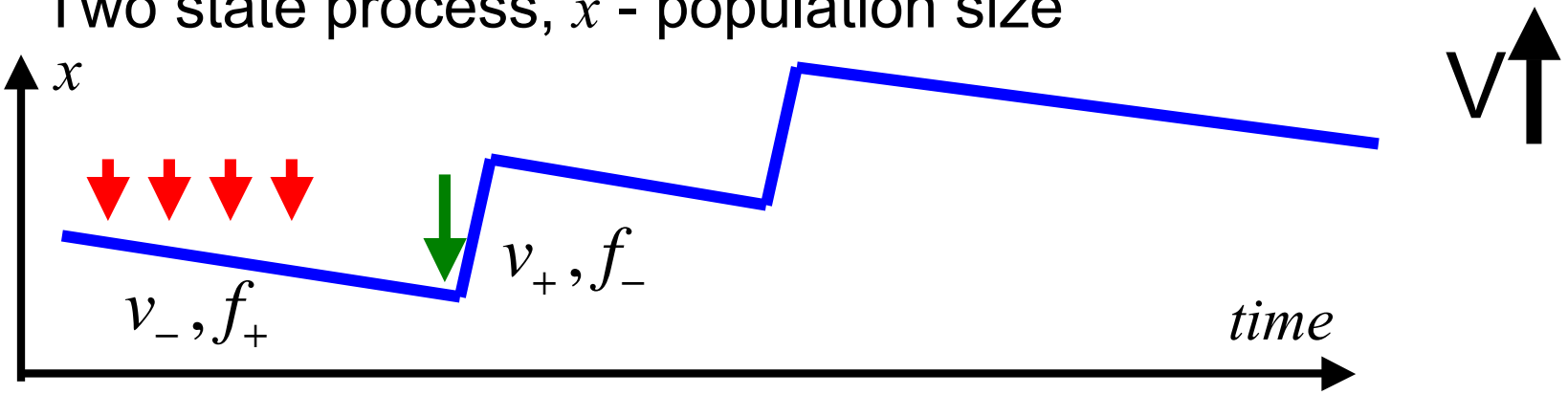
$$f_+ = \Pr\{fix.driver\}[mut.rate\ drivers] = \frac{s_d}{1+s_d} x T_d \mu$$

$$\Delta_+ = x s_d$$

$$v_- \approx \Pr\{fix.pass\}[mut.rate\ \ pass] \times \Delta_- = T_p \mu x s_p$$

Analytical model

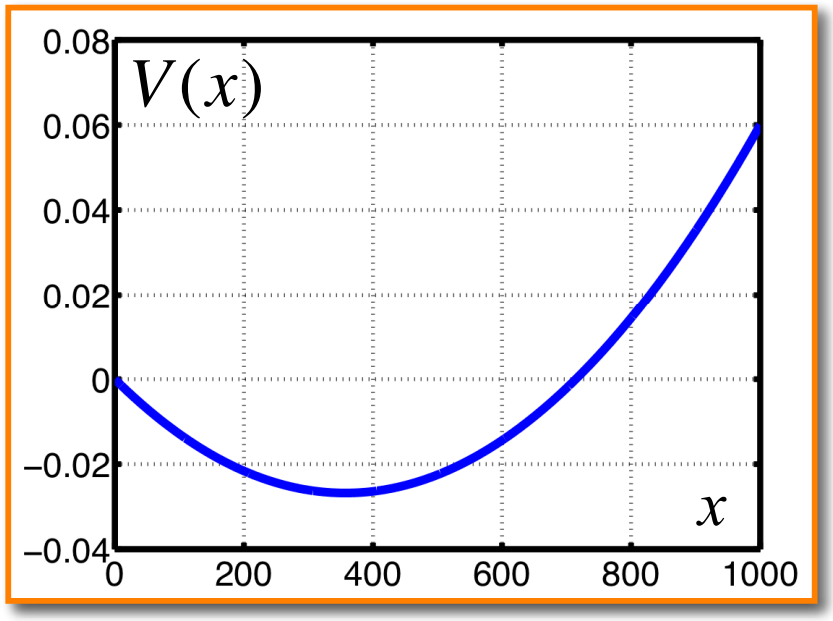
Two state process, x - population size



On long time scales: diffusion with drift

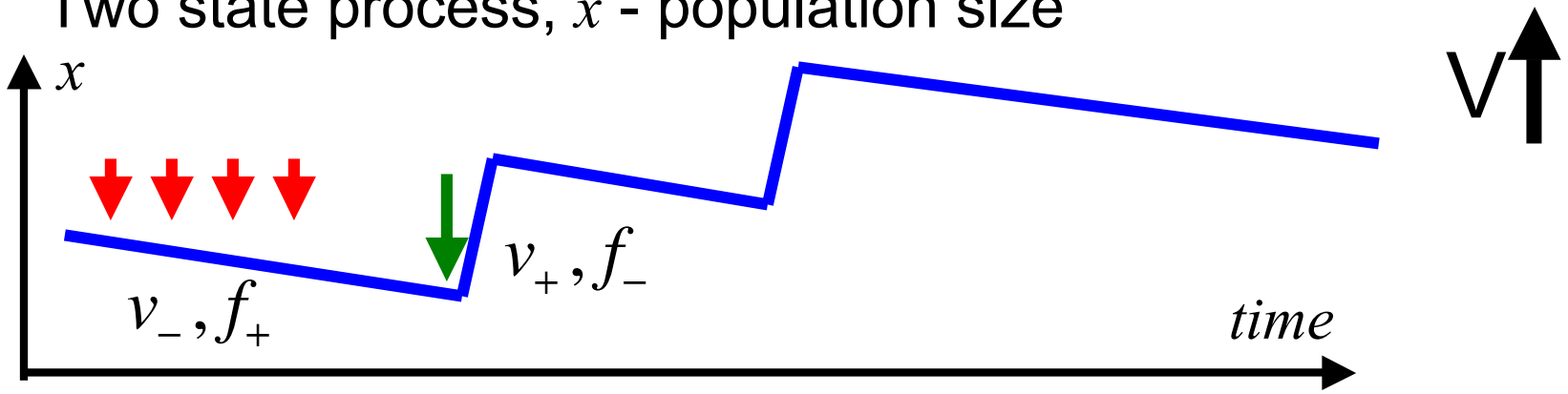
$$V(x) \approx \mu\left[x^2 T_d s_d^2 - x T_p s_p \right]$$

$$x^{crit} \approx \frac{T_p}{T_d} \frac{s_p}{s_d^2}$$



Analytical model

Two state process, x - population size



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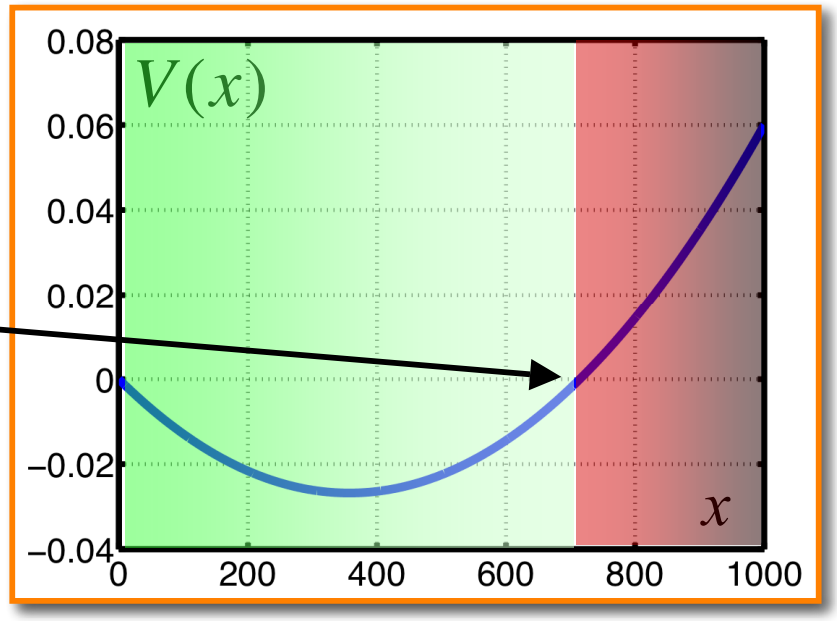
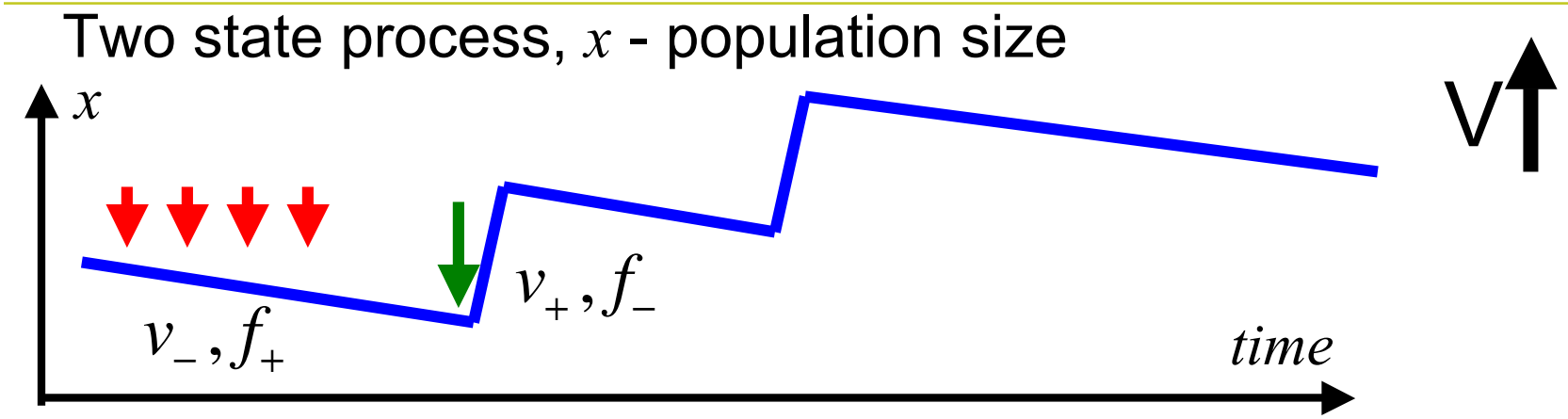
Critical cancer size



Analytical model



Another critical point:

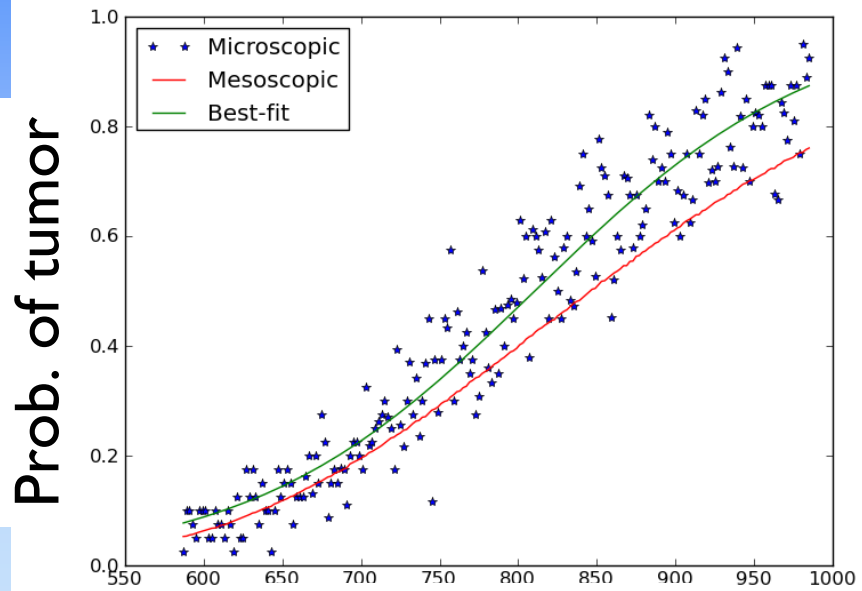
gain in fitness by a driver = loss of fitness due to passengers

$$s_p = [steady\ state\ loss\ of\ \ fitness]$$

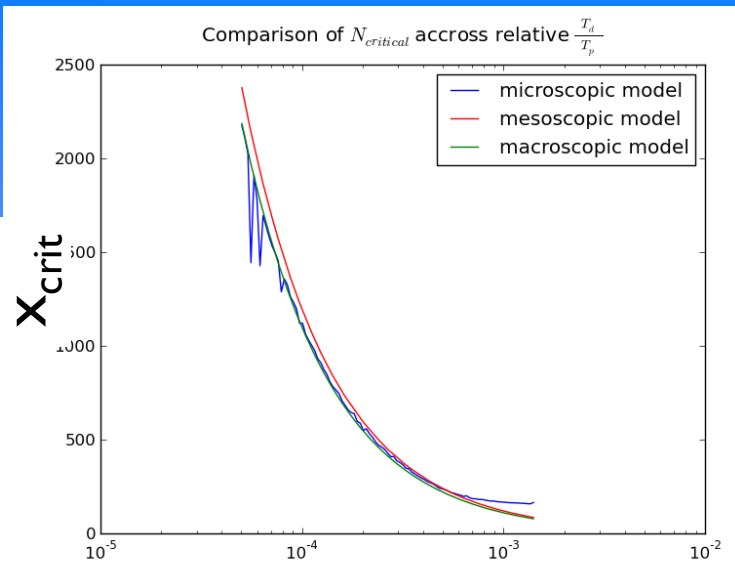
$$s_p = \mu T_p$$

Critical mutation rate

Theory

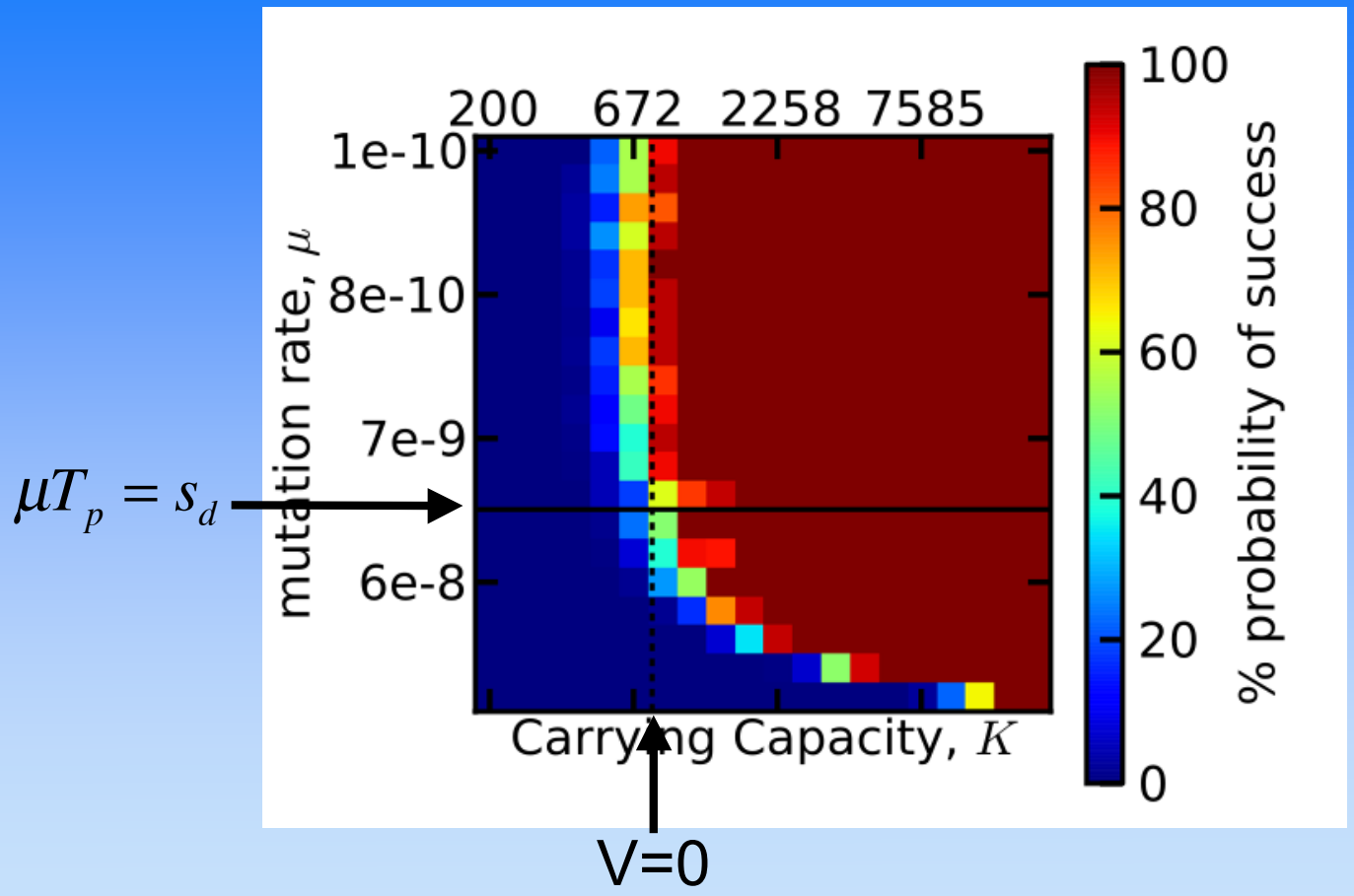


Population size, x



Td/Tp

Theory


200
672
2258
7585
1e-10
8e-10
7e-9
6e-8
mutation rate, μ
Carrying Capacity, K
100
80
60
40
20
0
% probability of success
$\mu T_p = s_d$
V=0

Questions

1. Can deleterious passenger mutations accumulate during cancer development?
2. How strong is the phenotype of passenger mutations?
3. How can this vulnerability of cancer be exploited by therapeutics?

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Cancer genomics

~30,000 single nucl. mutations per sample

~10^2 non-synonymous mutations

Drivers

~5-10 driver genes affected

Passengers

~10^2 of "random" genes involved

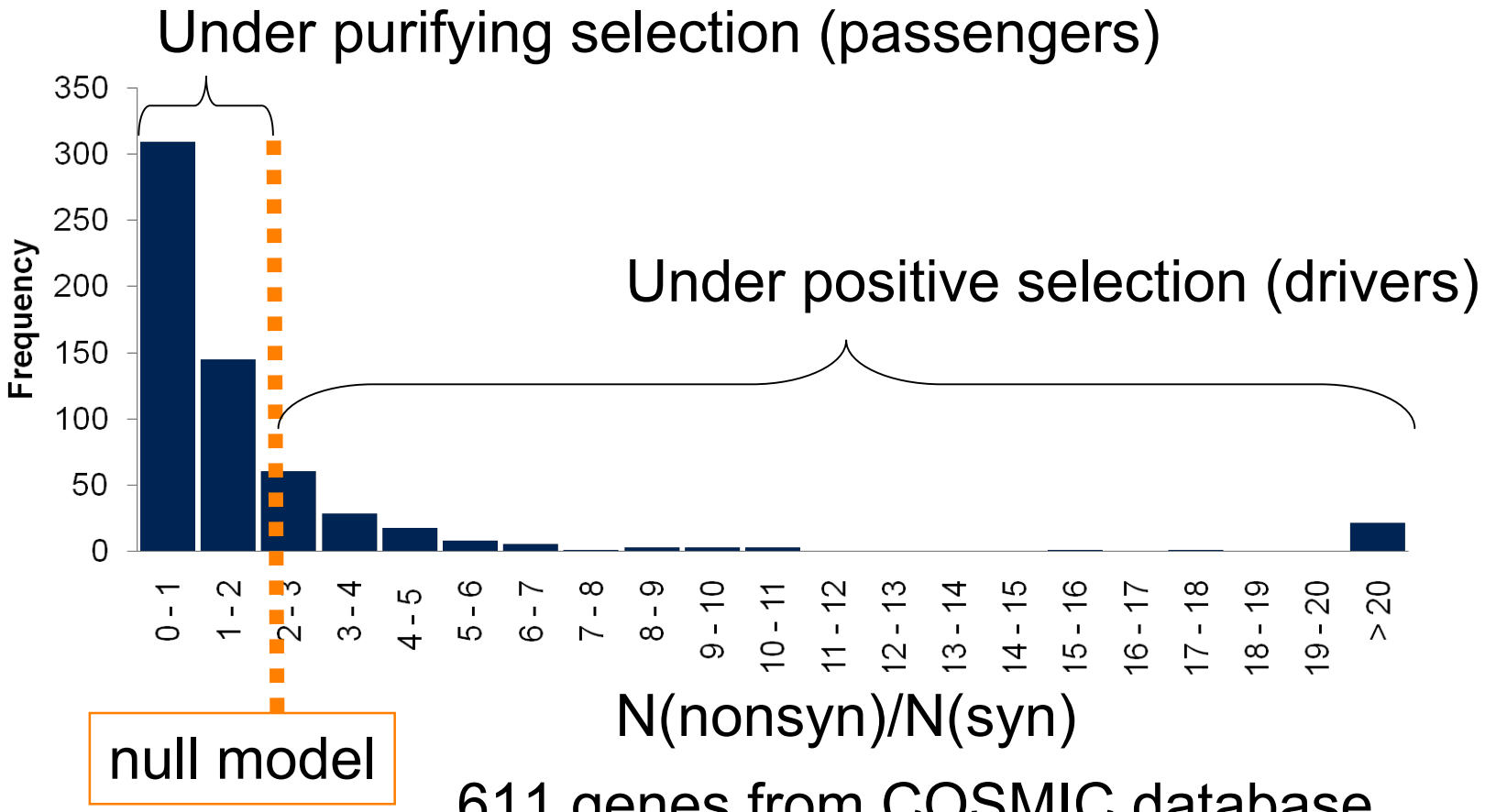
Cancer genomics

Passenger are commonly assumed to be neutral

If they are deleterious

- experience purifying selection;
- evade strong purifying selection by hitchhiking/bottlenecks

Genomics

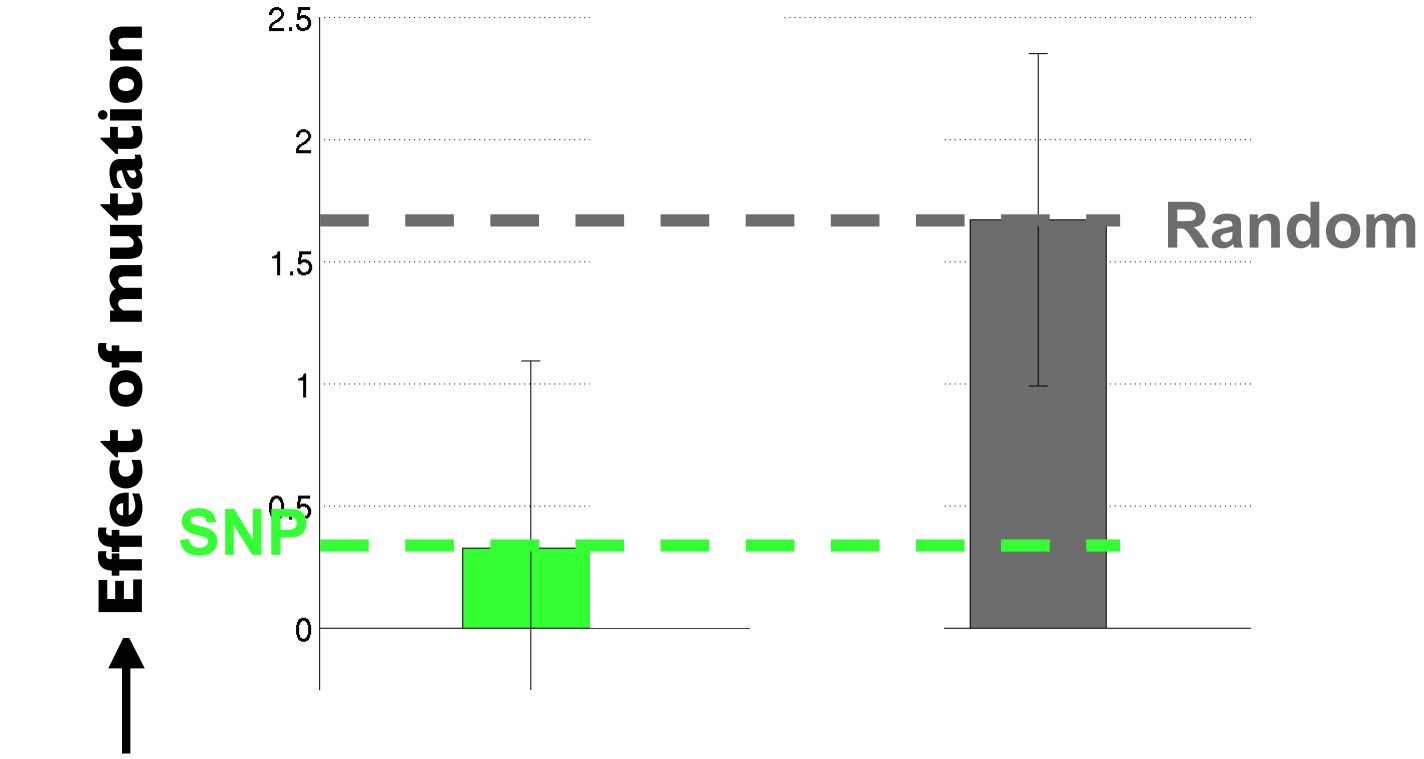


611 genes from COSMIC database

Hitchhiking passengers

Neutral or deleterious

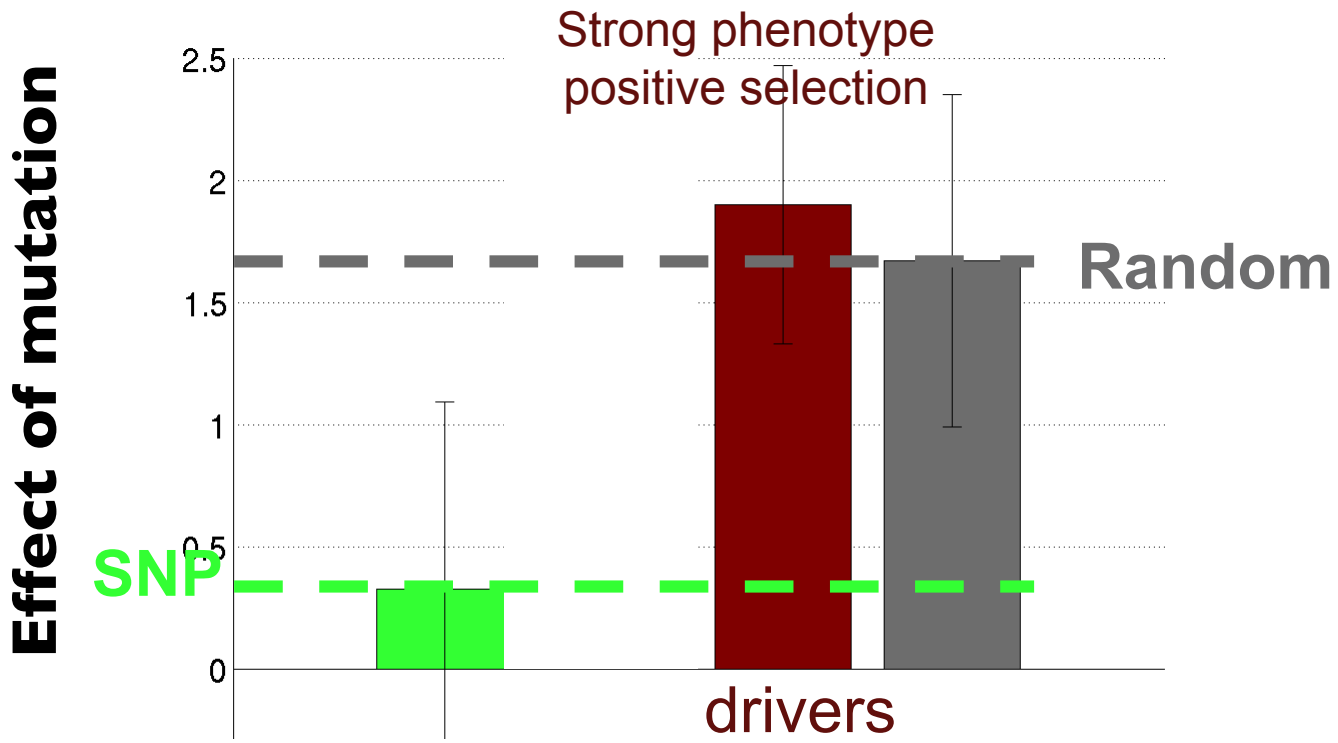
Effect of mutations



PSIC Score Conservation

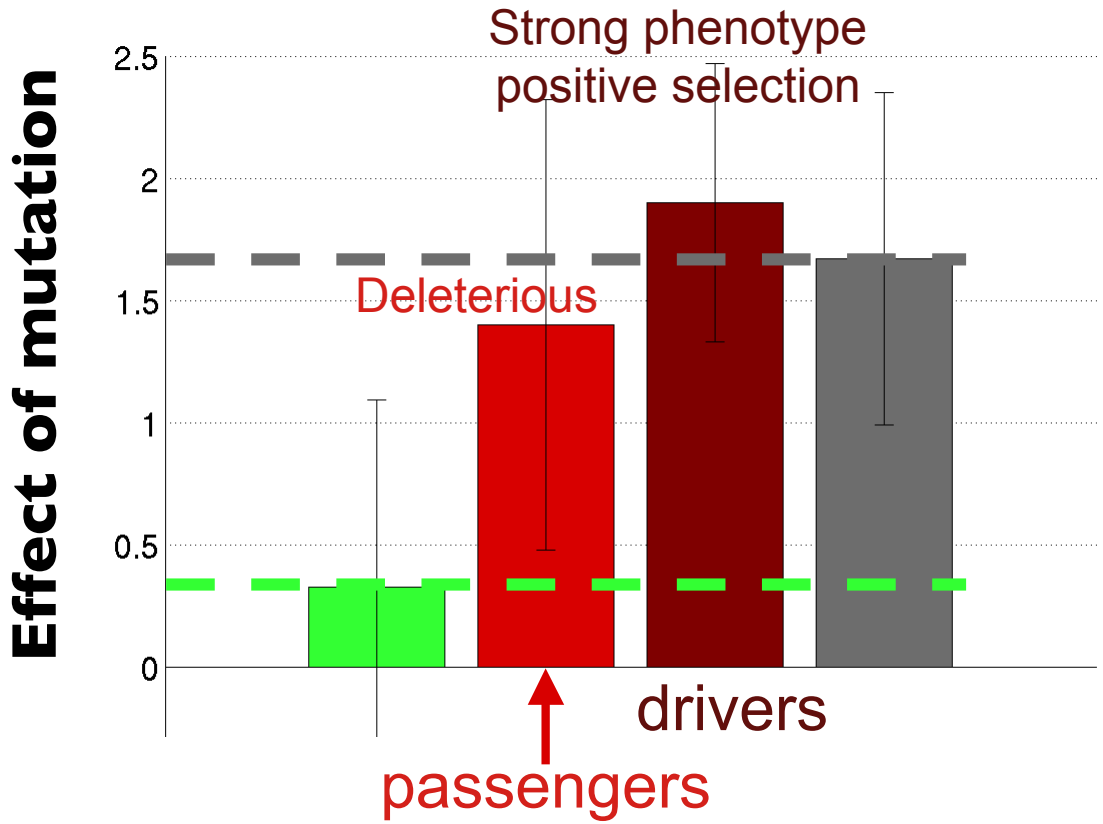
Structural info [**PolyPhen**, Sunyaev]

Effect of mutations



PolyPhen

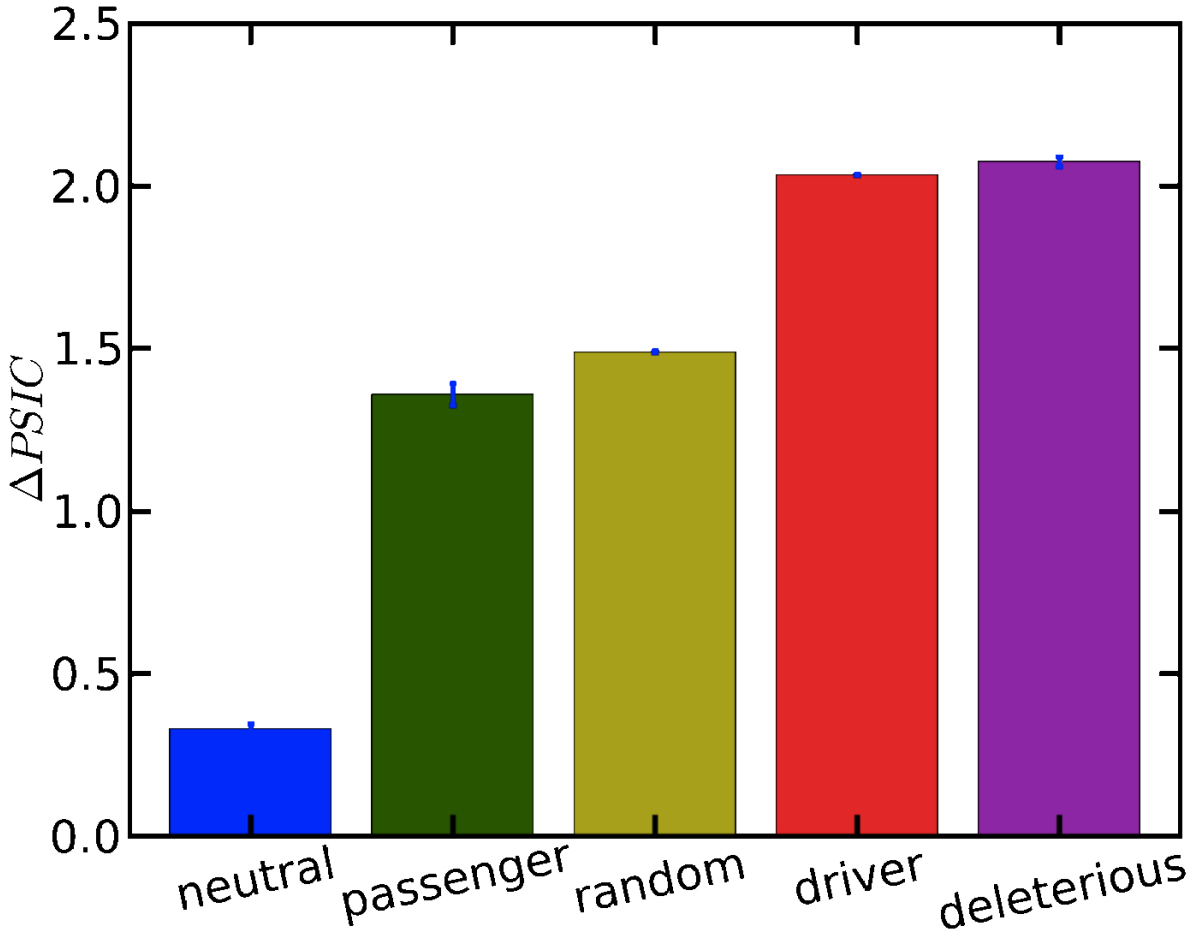
Effect of mutations



Passenger mutations evade purifying selection and deleterious.

PolyPhen

Most recent data



Passenger mutations evade purifying selection and deleterious.

PolyPhen

Deleterious passenger

Q532H in ABCA10 (ATP-binding transporter) **in glioma**

H

```
...EVQRILTQLEMKNIQDIITINLSGGQKRKLSFGIAILGDPQVLLLDEPTAG...
...EIQQVLRDLEMENIQDILAQNLSGGQKRKLTFGIAILGDPQVLLLDEPTAG...
...EIQRVLLELEMKNIQDVLAQNLSGGQKRKLTFGIAILGDPQIFLLDEPTAG...
...EVQRVVQELEMENIQDILAQNLSGGQNRKLTFGIAILGDPQVLLLDEPTAG...
...EIQRVLLELEMKNIQDVLAQNLSGGQKRKLTFGIAILGDPQIFLLDEPTAG...
...EVQRVVQELEMENIQDILAQNLSGGQNRKLTFGIAILGDPQVLLLDEPTAG...
...EVQRILLELDMQNIQDNLAKHLSEGQKRKLTFGIAILGDPQILLLDEPTTG...
...EIQRILLELEMKNIQDVLAQNLSGGQKRKLSFATAILGDPQVFLLDEPTAG...
...EVQRILLELNIQNIQDNLATHLTEGQKRKLTFGIAILGDPQILLLDEPTAG...
...EVQRVVQELEMENIQDILAQNLSGGQNRKLTFGIAILGDPQVLLLDEPTAG...
...EVQRILLELDMQNIQDNLAKHLSEGQKRKLTFGITILGDPQILLLDEPTTG...
...EVQRVVMELEMKNIQDVIAENLSGGQKRKLTFGIAILGDPQILLLDEPTAG...
...EVQQVLQDLEMENIQDILAQNLSGGQKRKLTLGIAILGDPQVLLLDEPTAG...
...QVQRVLQDLEMGNIQDVLAQNLSGGQKRKLTFGTAILGDPRVLLLDEPTAG...
...EI----------------------------------------FLLDEPTAG...
...EVQRILLELDMQNIQDNLAKHLSEGQKRKLTFGITILGDPQS---------...
...EVQRVLLELEMKNIQNILAQNLSGGQKRKLTFGIAILGDSQIFLLDEPTAG...
...EVQQILSELDMQTIQDELAEHLSEGQKRKLTFGVAILGDPRILLLDEPTAG...
...EV----------------------------------------LLLDEPTAG...
...EVRQVLRDLEMENIQDTLAQNLSGGQKRKLTFGIAILGDPQVLLLDEPTAG...
...EVQRVLLELEMKNIQDILARNLSGGQKRKLTFGTAILGDSQIFLLDEPTAG...
...EVQRVLLELDIQNIQDNLATLLSEGQKRKLTIGIALLGDPQVLLLDEPTAG...
```

PolyPhen

Cancer Genomics

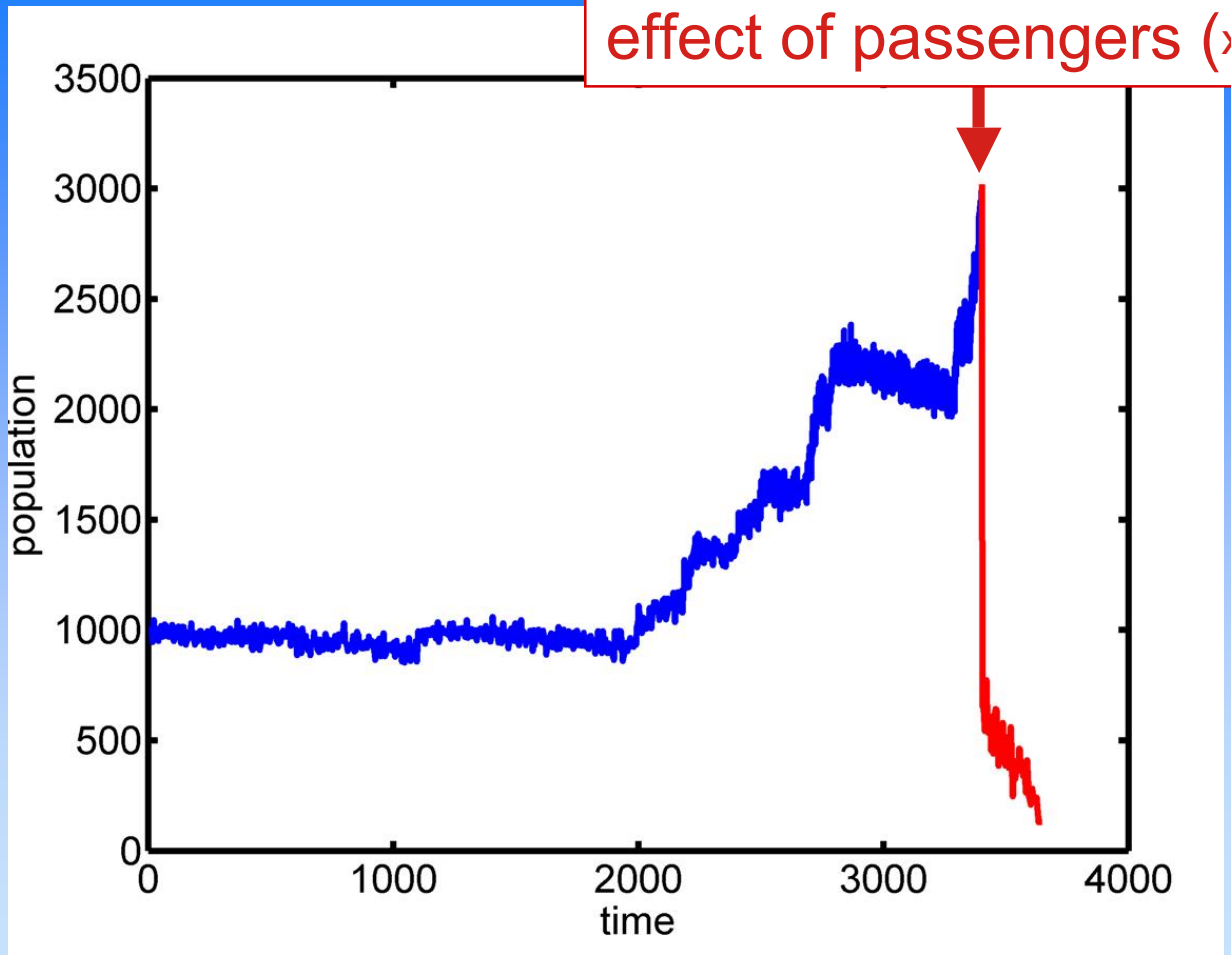
Conclusions

1. Signatures of positive and purifying selection among genes mutated in cancer.
2. Passengers show signatures of deleterious mutations

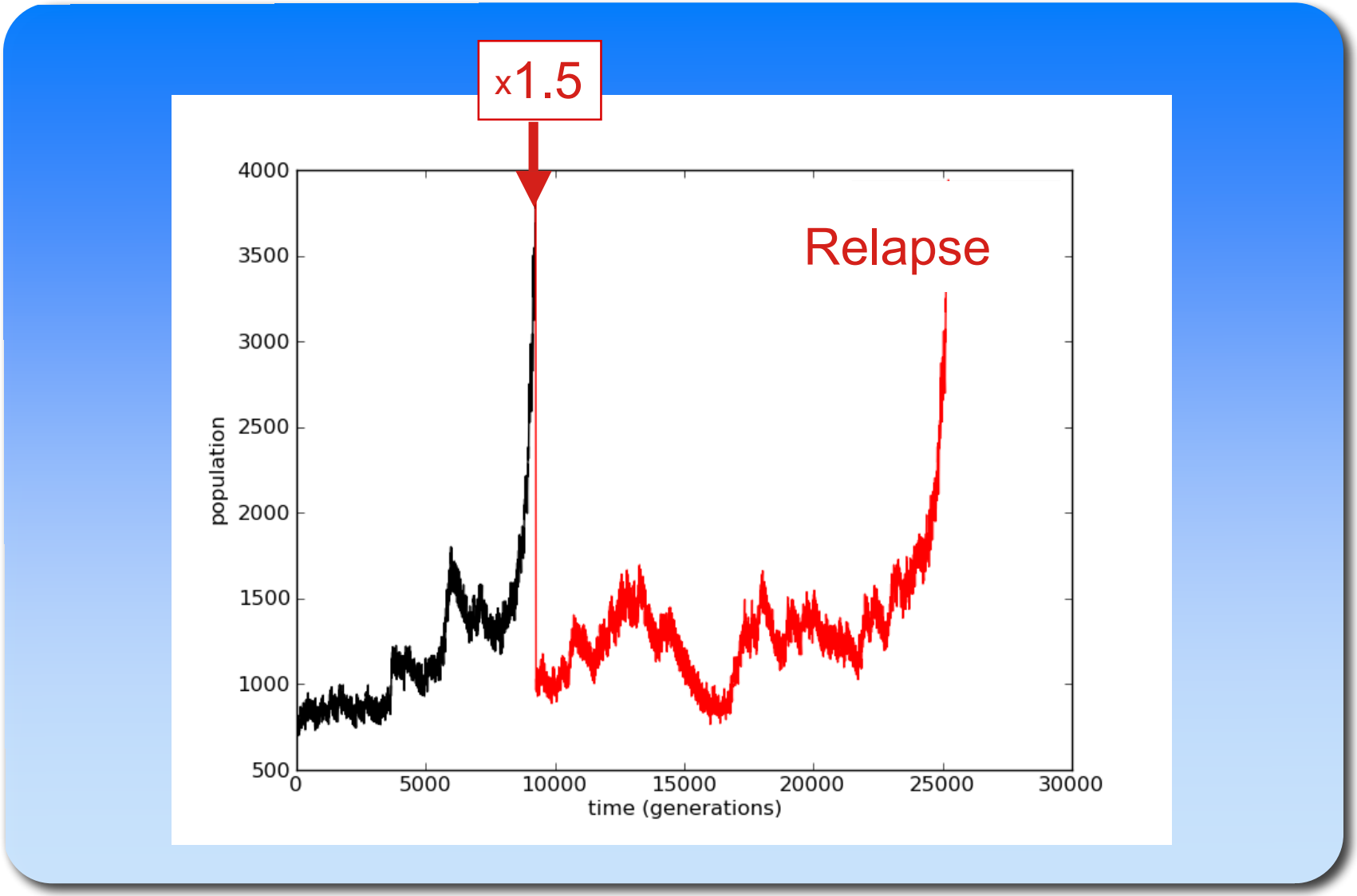
Questions

1. Can deleterious passenger mutations accumulate during cancer development?
2. How strong is the phenotype of passenger mutations?
3. How can this vulnerability of cancer be exploited by therapeutics?

Simulations



Simulations



Idea #2

Random mutations affect protein's ability to fold and can lead to aggregation.

This effect is buffered by chaperons and unfolding protein response (UPR) system.

<u>Effect of passenger mutations can be amplified</u>

1. chaperon inhibition
2. proteasome inhibition
3. high temperature (hyperthermia)

and their combination

Experimental evidences

1. Cancers need chaperons.
   Elimination of HSF1 protects from cancer, inhibition stops cancer growth (S. Lindquist 2008)
2. Cl… …er
   c…
   H… …ect
   (M…
3. Proteasome inhibitors are potent antitumor agents. Bortezomib
4. Cancer is sensitive to hyperthermia.

Can this selective antitumor activity be mediated by passenger mutations?

what about viruses?

Can chaperon inhibition suppress mutator phenotype in viruses?

Summary

Passenger mutations can play an important role in tumor development:

- accumulate despite deleterious effect
- evade purifying selection
- can make cancer cells vulnerable to population meltdown

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