Three surprising predictions
from modeling evolution experiments

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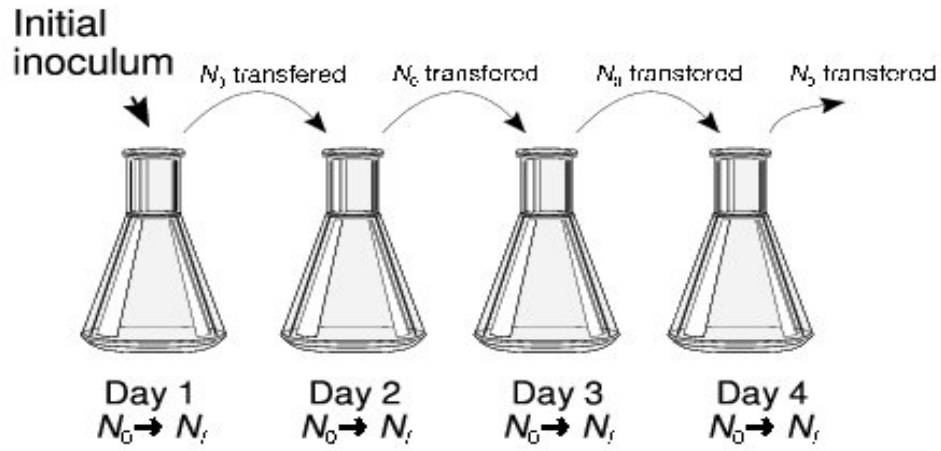
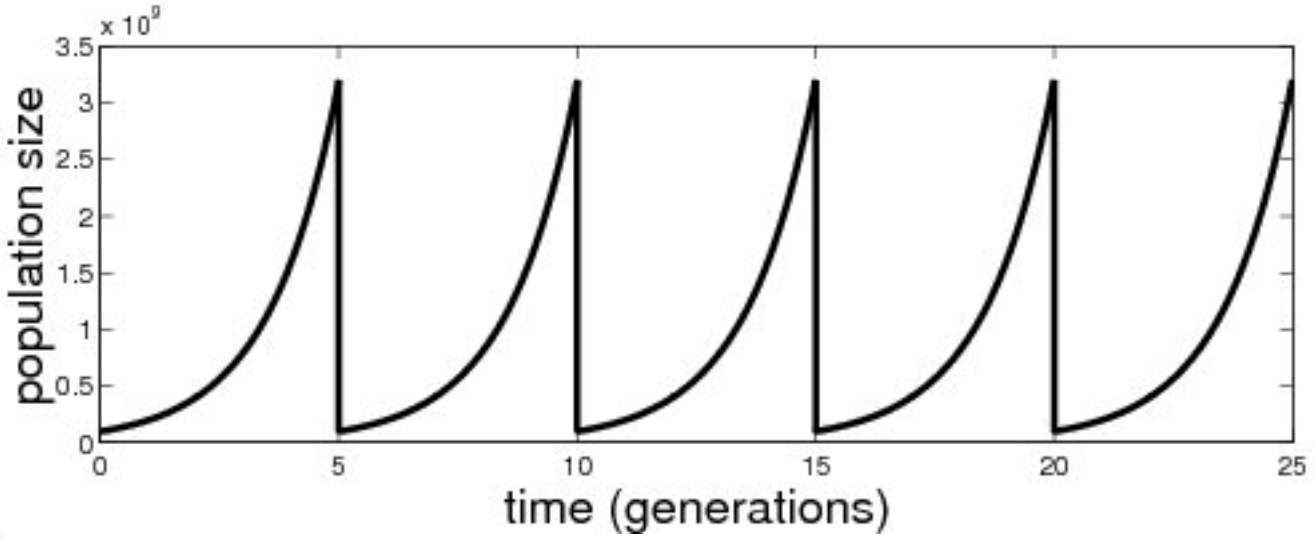

Initial
inoculum
N_0 transfered
N_0 transfered
N_0 transfered
N_0 transfered
Day 1
$N_0 \rightarrow N_f$
Day 2
$N_0 \rightarrow N_f$
Day 3
$N_0 \rightarrow N_f$
Day 4
$N_0 \rightarrow N_f$

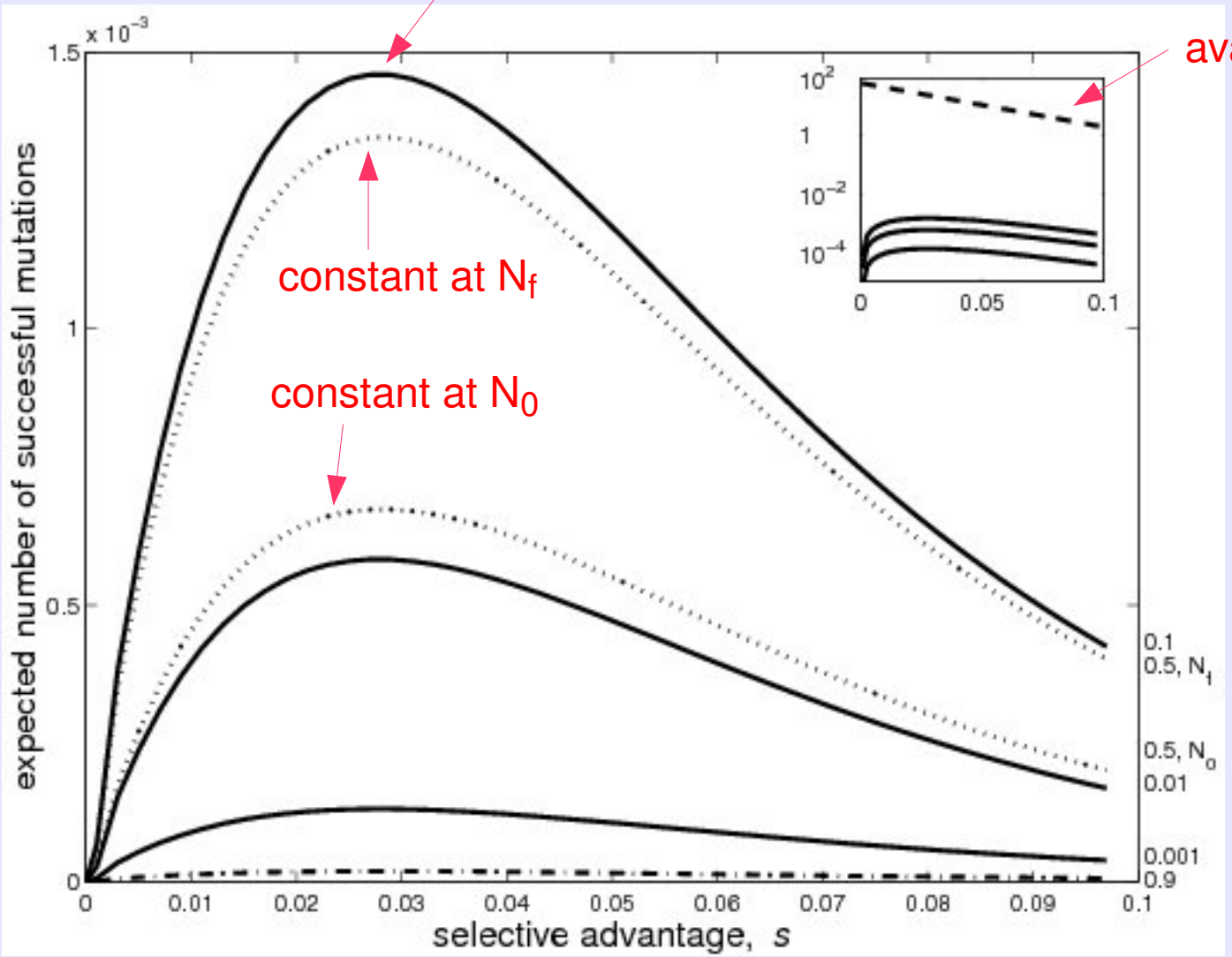

x 10^9
3.5
3
2.5
2
1.5
1
0.5
0
population size
0
5
10
15
20
25
time (generations)

surprise #1: bottlenecks can increase rates of adaptation

- bottlenecks reduce fixation probability for each beneficial mutation (not surprising)
- in classical population genetics, how do we imagine a bacterial population, for *e.g.*, is maintained at a constant size?
  - 2 offspring per individual
  - only one survives, on average
- *i.e.*, a bottleneck of 0.5, **every generation**

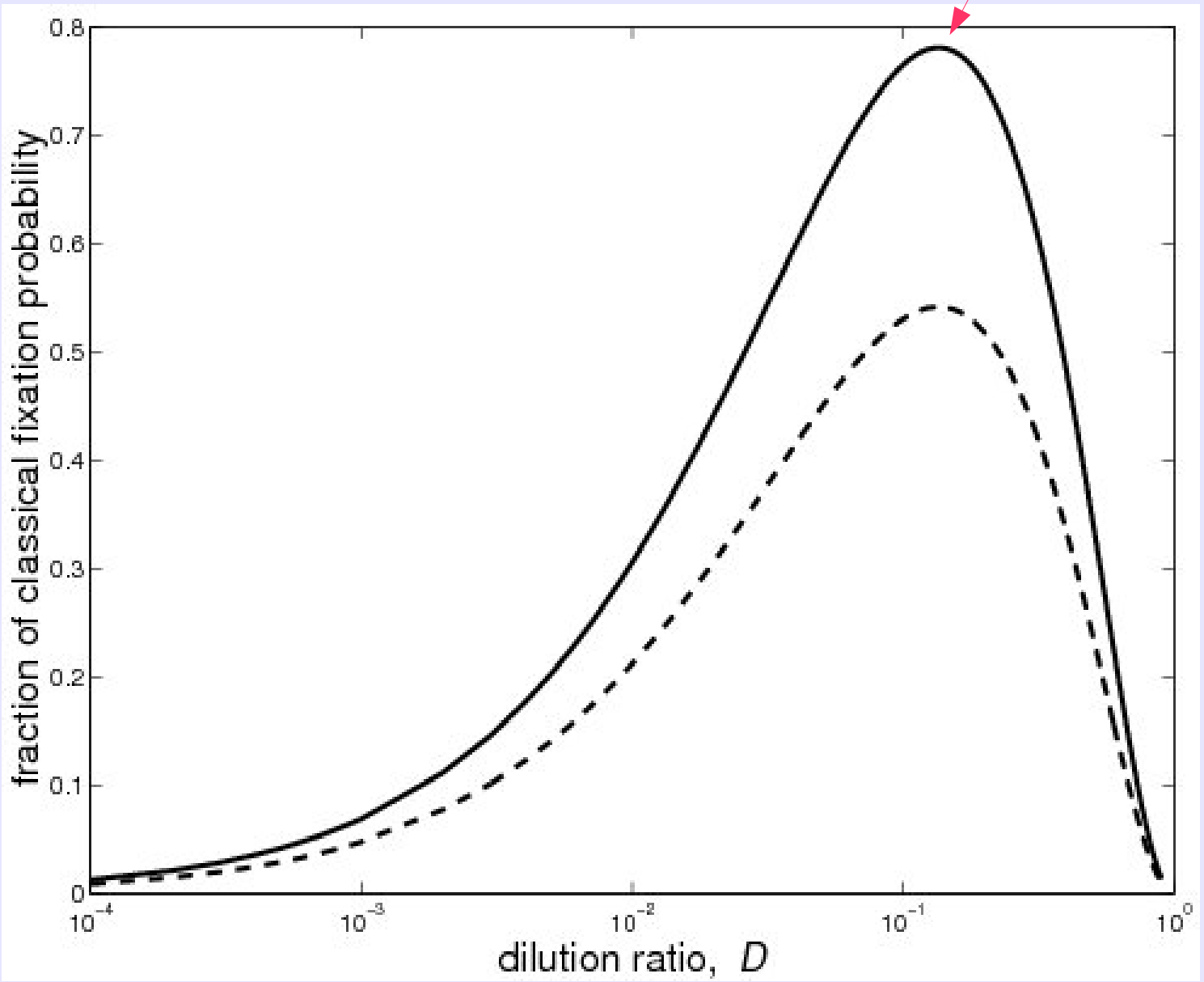
bottlenecks at 0.1

available mutations



Wahl, Gerrish, Saika-Voivod, *Genetics,* 2002

peak at $e^{-2} \simeq 0.135$

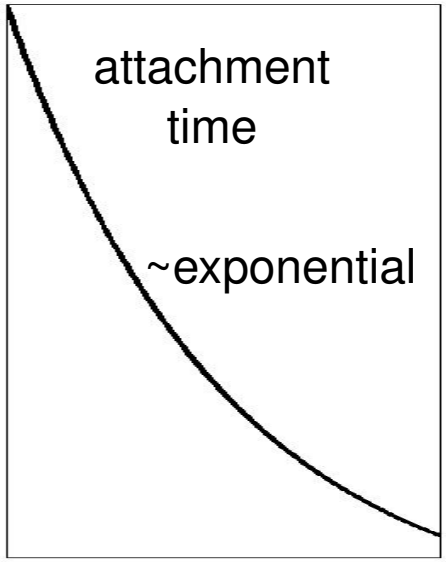


Wahl, Gerrish, Saika-Voivod, *Genetics,* 2002

#1b: bottlenecks reduce stochasticity

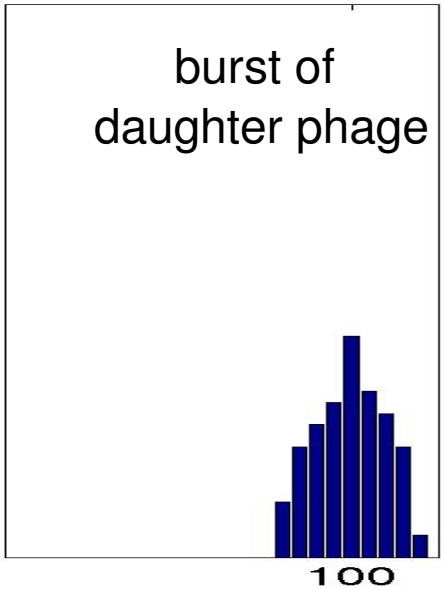
- it is the periods of sustained **growth**, with almost no culling of new offspring, which most distinguish growth-bottleneck protocols
- we can expect **higher** adaptation rates in these populations (if bottleneck is neither too severe nor too frequent)
- if this is true, bottlenecks will **reduce** the stochasticity of the evolutionary trajectory

Life Cycle of a Lytic Virus

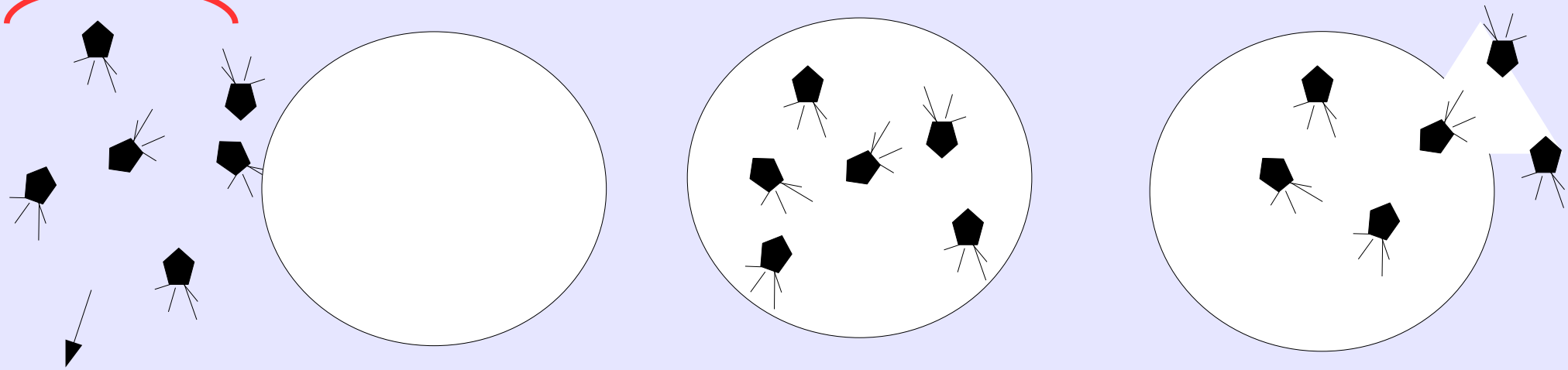


lysis time

~ fixed



“free” phage



clearance

In classical population genetics,
a beneficial mutation almost always increases the expected number of offspring.

In lytic viruses, a beneficial mutation could:

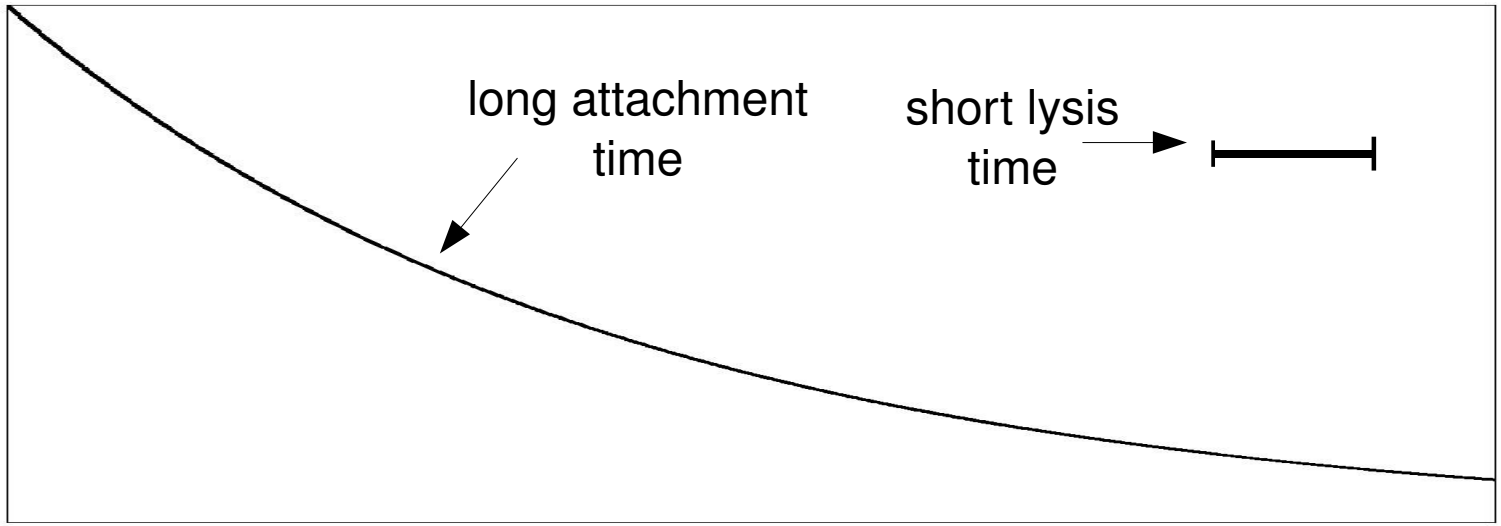
- increase the attachment rate
- reduce the lysis time
- increase the burst size
- reduce the clearance rate

(or some combination of all four)

genotype ID	attachment rate (kN) "A"	lysis time "T"	burst size "B"
37f-41	1.89E-2	62.20	83.89
C12A-9	2.45E-2	77.41	74.41
C12B-29	1.71E-2	59.68	82.80
C12F-6	2.42E-2	62.15	18.34
C12G-6	8.71E-3	68.80	47.44
C12I-11	1.67E-2	61.72	48.05
C12J-9	1.40E-2	80.61	72.09
P5G-13	5.34E-3	73.37	92.41
P5H-15	1.67E-2	71.83	124.60
P5L-2	8.76E-3	66.85	24.17
P5O-11	1.40E-2	66.86	116.39
P5S-5	1.25E-2	75.42	26.81
P5T-5	2.03E-2	58.97	91.22

Φ6 data from Christina Burch

Case 1: the burst-death model



- generation times are exponentially distributed
- a classic birth-death model can be used... except for the burst of ~100 offspring

Burst-death model: in time interval δt,
constant probability of attaching, $\alpha\delta$t
constant probability of clearing, $\mu\delta$t
When attached, burst of B offspring released

$$g(x,t+\delta t)=g(x,t)+p_1\alpha\delta t\,x^B-p_1\alpha\delta t\,x^1+p_2 2\alpha\delta t\,x^{B+1}-p_2 2\alpha\delta t\,x^2+\ldots$$

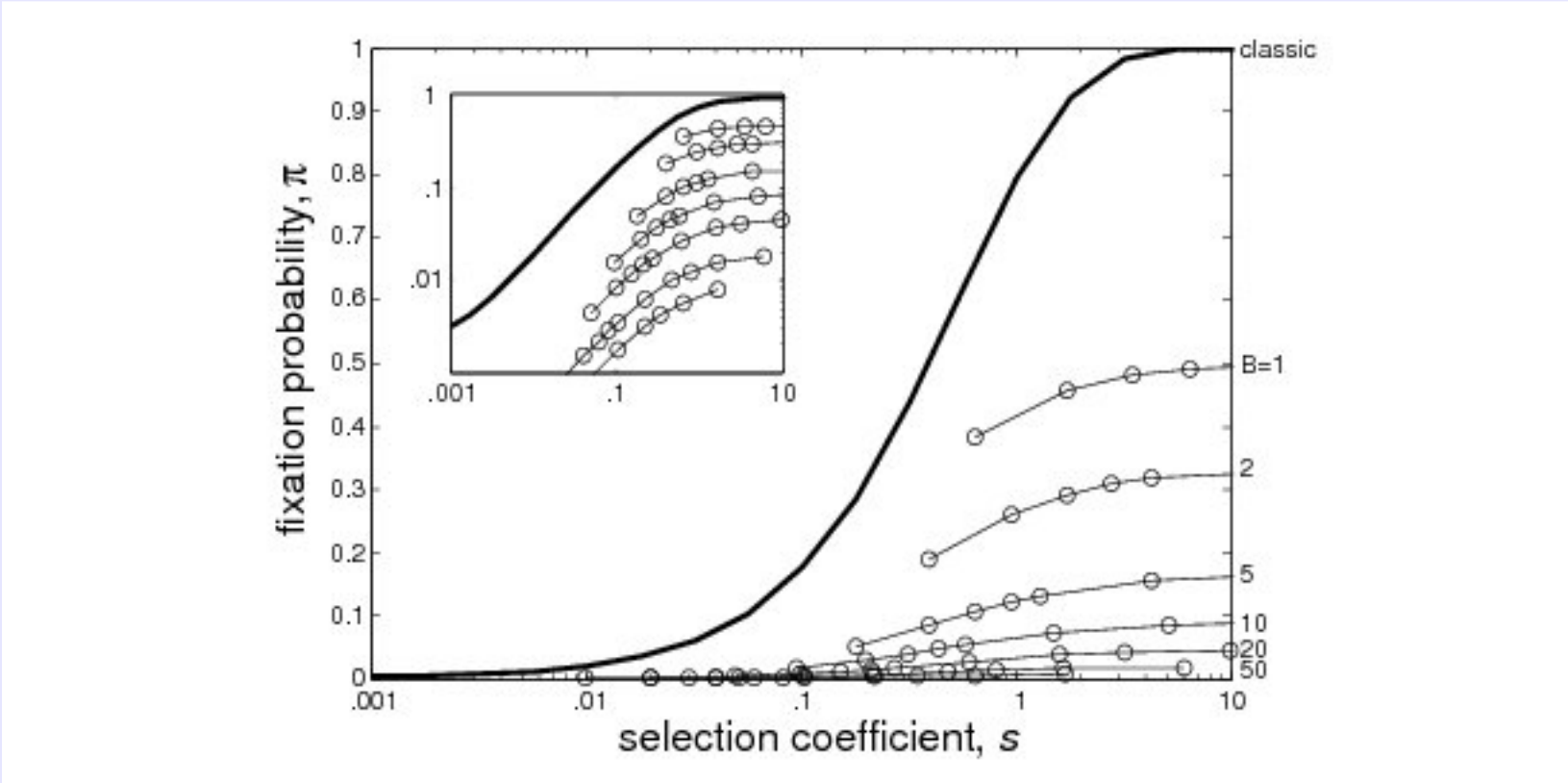
$$\ldots+p_1\mu\delta t\,x^0-p_1\mu\delta t\,x^1+p_2 2\mu\delta t\,x^1-p_2 2\mu\delta t\,x^2+\ldots$$

$$\frac{\partial g}{\partial t}=\alpha\sum i\,p_i(x^{B+i-1}-x^i)+\mu\sum i\,p_i(x^{i-1}-x^i)$$

$$\frac{\partial g}{\partial t}=\frac{\partial g}{\partial x}(\alpha x^B-(\alpha+\mu)x+\mu)$$

$$g(x,t)=p_0+p_1x+p_2x^2+\ldots$$
$$\frac{\partial g}{\partial x}=p_1+2p_2x+3p_3x^2+\ldots$$

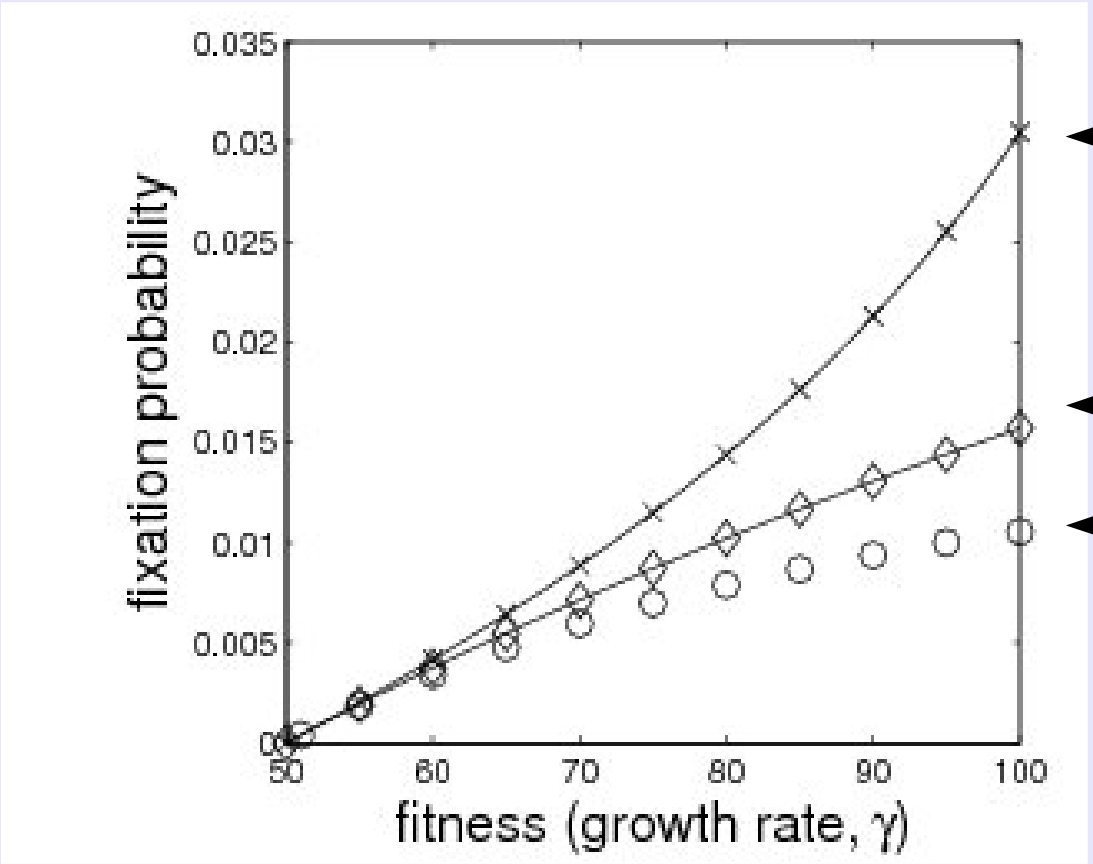
Results: the burst-death model



In a population of constant size,
π is **much** smaller than classically predicted.

Hubbarde et al., *Genetics*, 2007

Results: the burst-death model

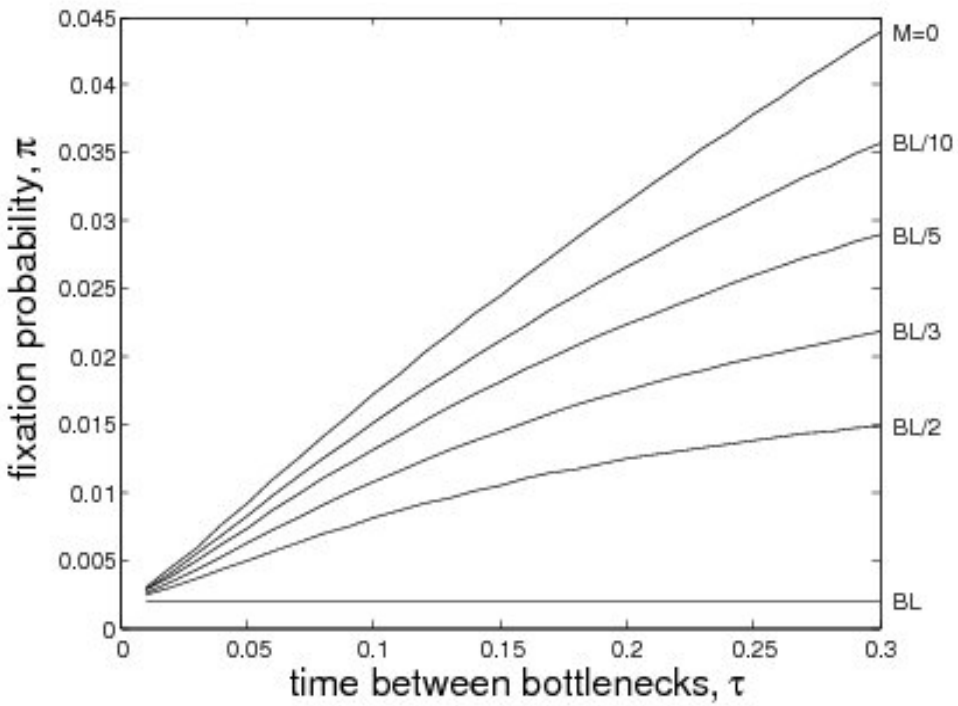


Alexander and Wahl, *Evolution*, 2008

surprise #2: “not all beneficial mutations are created equal”

- for mutations with the same fitness
  - mutations that reduce clearance *always* have a higher chance of fixation
  - mutations that increase burst size *always* have the lowest chance of fixation
  - mutations that increase burst rate (attachment rate) are in between
- this holds in all parameter regimes *for the burst-death model*

Results: the burst-death model



low clearance rate

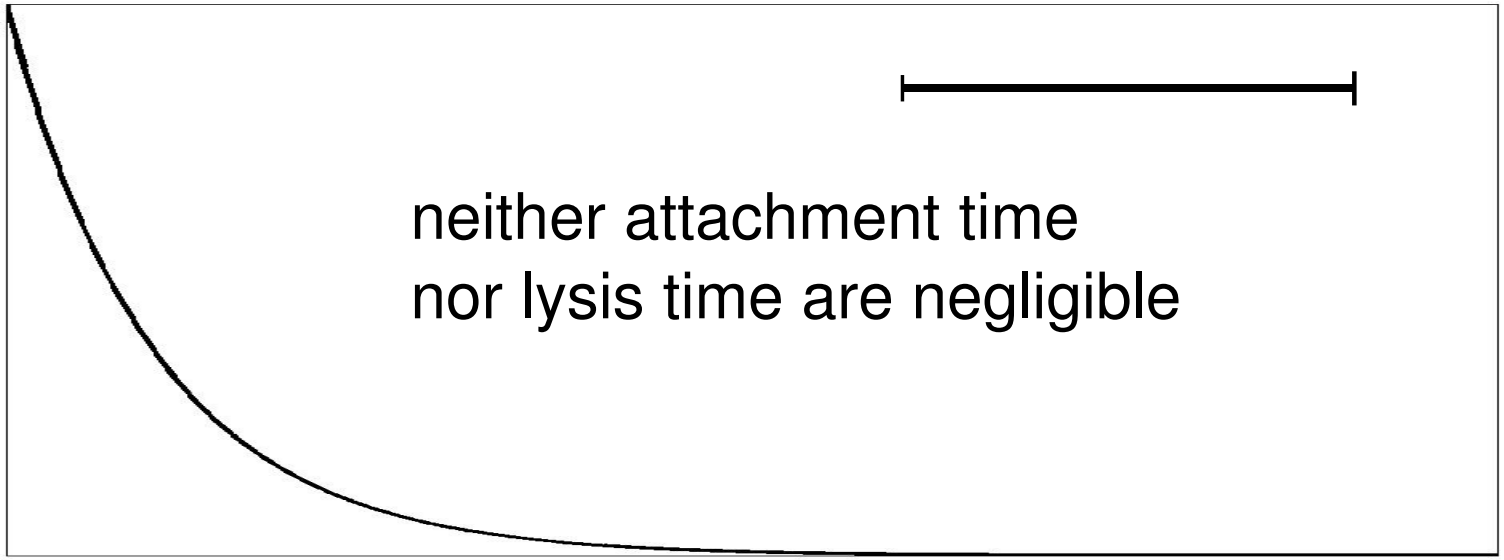
moderate clearance

high clearance
(constant size)

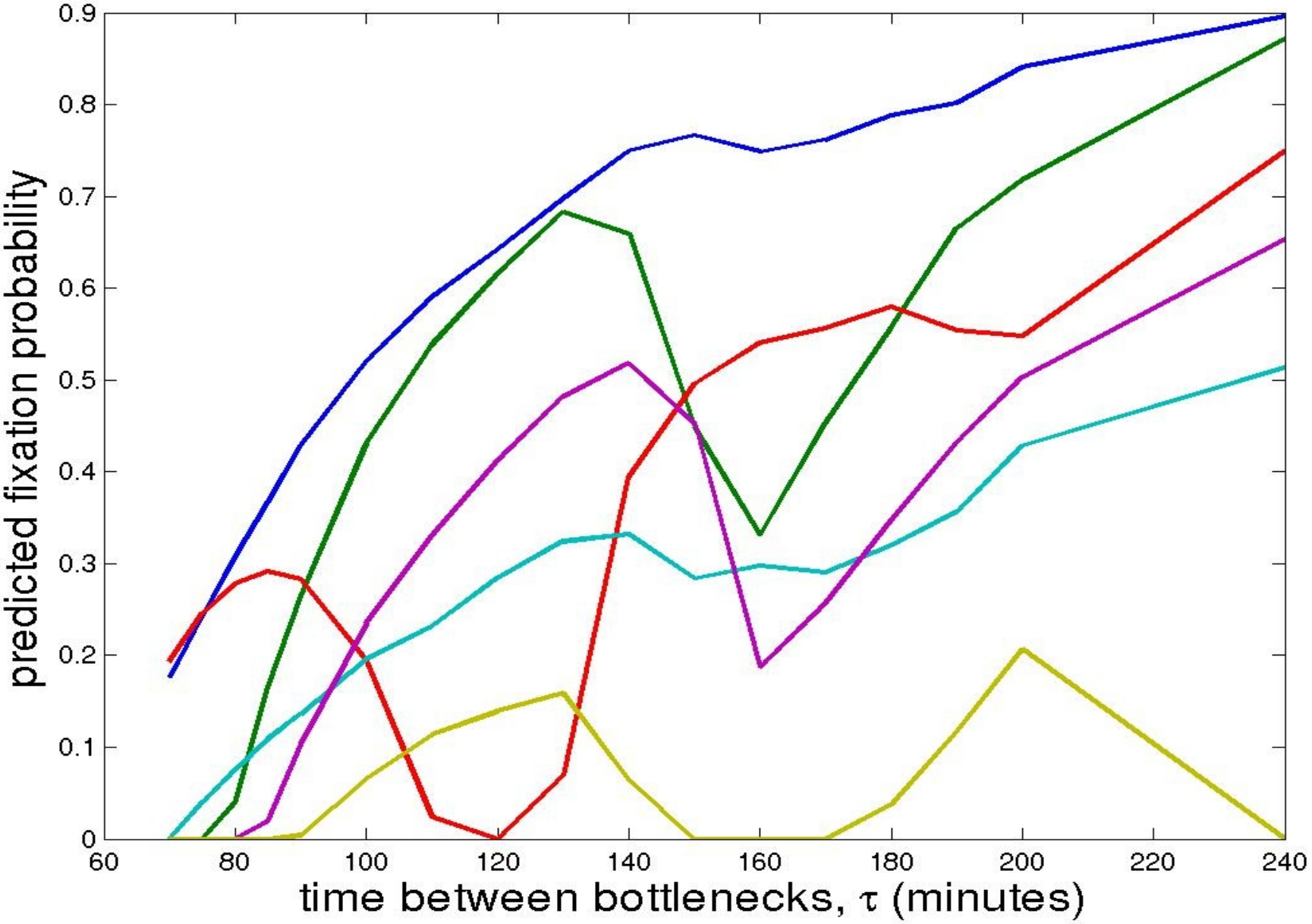
Note: fixation increases smoothly with the length of the growth period between bottlenecks
(this will become more interesting later)

Hubbarde et al., *Genetics*, 2007

Case 2: the attachment-lysis model



First, we tried simulating...



Assume: while free, constant clearance rate, μ
while free, constant attachment rate, α
fixed lysis time, T
constant burst size, B

We want the pgf for a single lineage, beginning with one free virion at time t=0.

Clearance and attachment are competing exponentially-distributed processes.

Let $\theta = \mu + \alpha$.

"Lifetime" of free virion has probability density function: $\theta e^{-\theta u}$

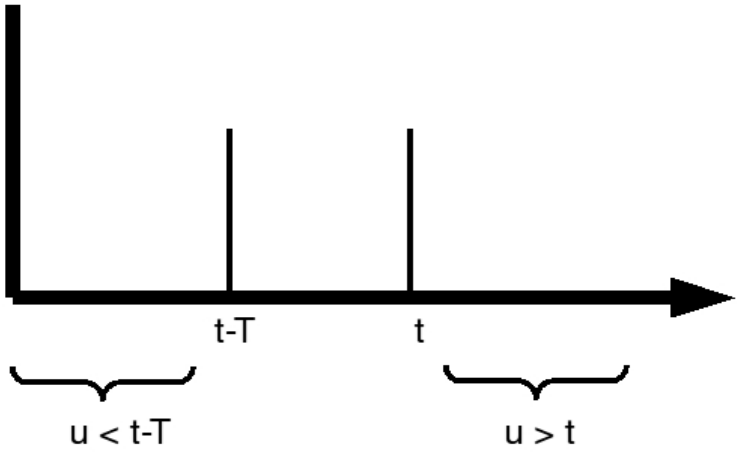
And the probability of clearing before attaching: $\frac{\mu}{\alpha+\mu}$

We now take a different approach,
conditioning on when the initial virion either attaches or clears.

$$g(x,t) = \int_{u=0}^{u=t-T} \theta e^{-\theta u}$$ [pgf at t, if clear/attach at u in *(0, t-T)*] *du*

$$+ \int_{u=t-T}^{u=t} \theta e^{-\theta u}$$ [pgf at t, if clear/attach at *u* in *(t-T, t)*] *du*

$$+ \int_{u=t}^{u=\infty} \theta e^{-\theta u}$$ [pgf if nothing has happened yet] *du*



time at which virion attaches/clears, u

[pgf at t, if nothing happened yet] = x

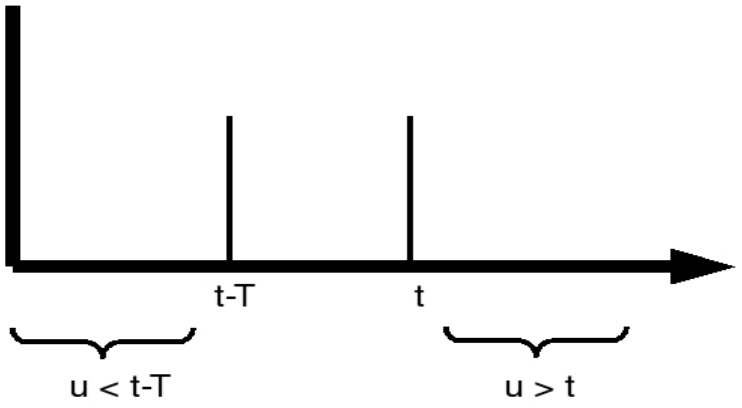
(with probability one, there is one free phage at t)

[pgf at t, if cleared/attached at $u \in (t\text{-}T, t)$] = 1

(with probability one, there are no free phage at t)

[pgf at t, if cleared/attached at $u \in (0, t\text{-}T)$] = ?

with probability $\frac{\mu}{\alpha+\mu}$, the virus was cleared → pgf = 1



with probability $\frac{\alpha}{\alpha+\mu}$, the initial virion attached...

If it attached at *u*, it produces B identical copies of itself at time *u+T.*

Each of these grows according to the same pgf,
until time *t.*

Thus, [pgf at t, if cleared/attached at $u \in (0, t-T)$] is:

$$\frac{\mu}{\alpha+\mu}(1)+\frac{\alpha}{\alpha+\mu}\, g\left(x, t-(u+T)\right)^{B}$$

So overall we have the following implicit equation for g:

$$g(x,t)=\int_{u=0}^{u=t-T}\theta e^{-\theta u}\left[\frac{\mu}{\alpha+\mu}(1)+\frac{\alpha}{\alpha+\mu}g(x,t-(u+T))^{B}\right]du$$

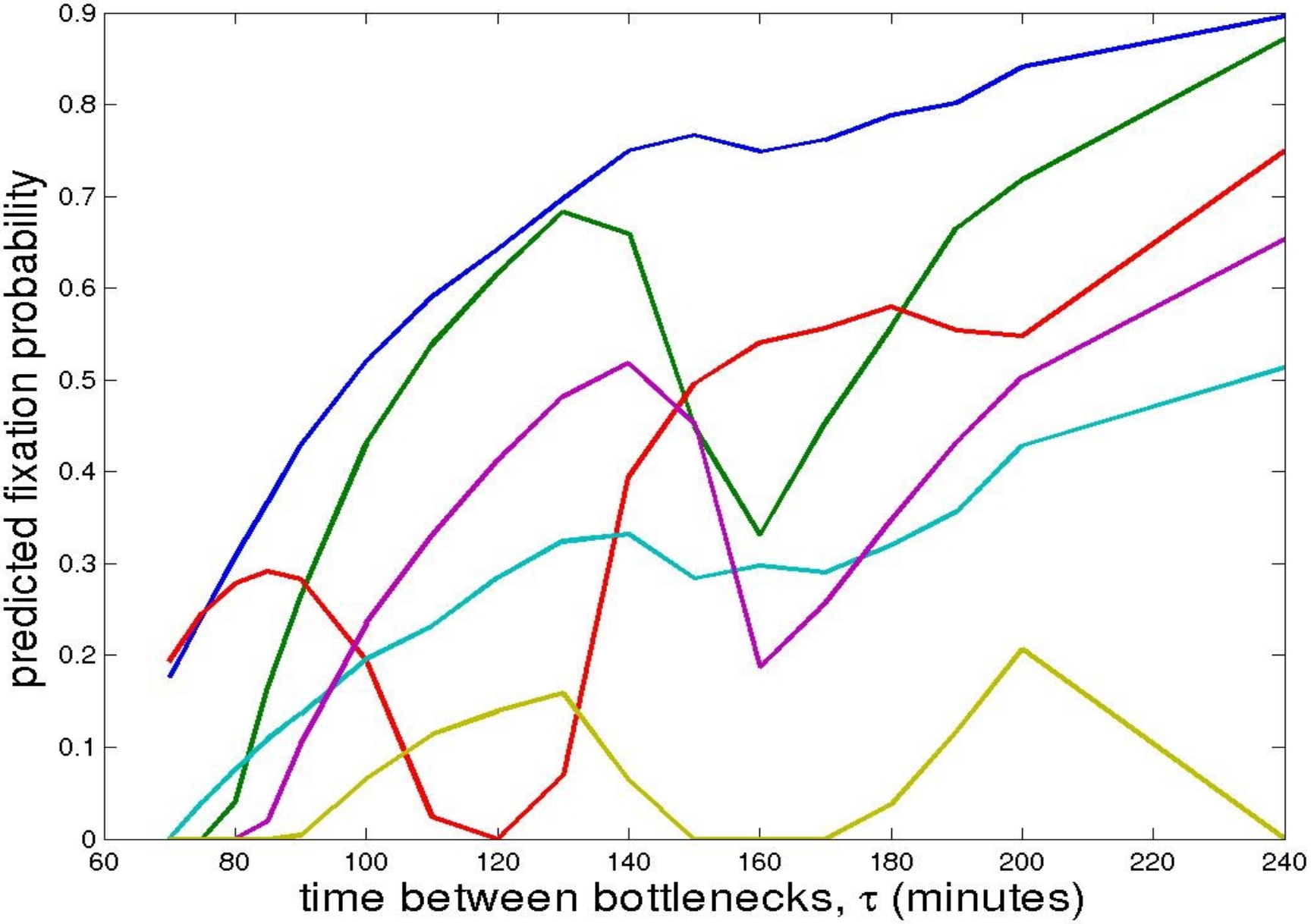
$$+\int_{u=t-T}^{u=t}\theta e^{-\theta u}(1)\,du$$

$$+\int_{u=t}^{u=\infty}\theta e^{-\theta u}x\,du$$

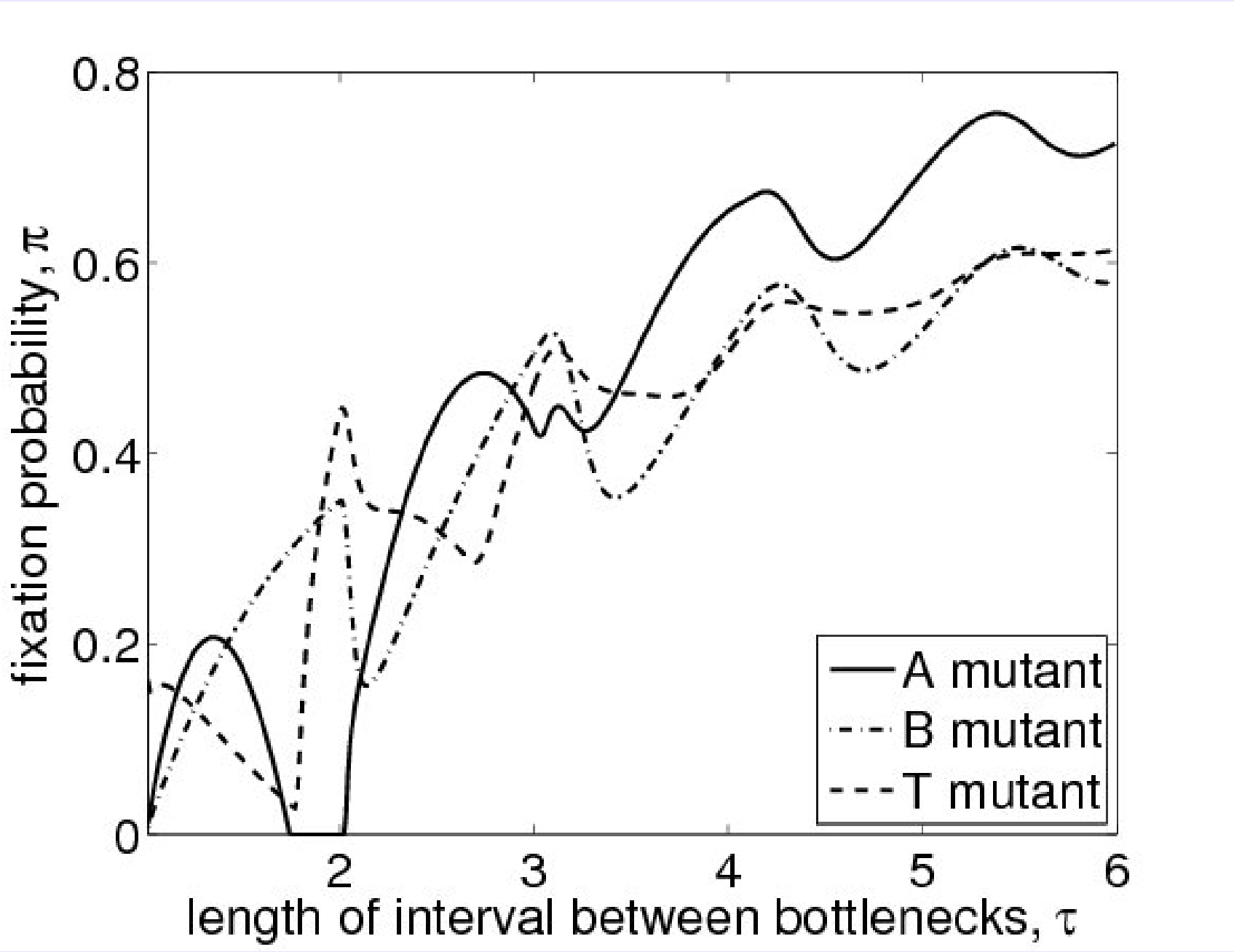
We can integrate, make a change of variables, differentiate:

$$\frac{\partial g}{\partial t}=\alpha g(x,t-T)^{B}-(\alpha+\mu)g(x,t)+\mu$$

Recall: simulation results for real phage mutants...

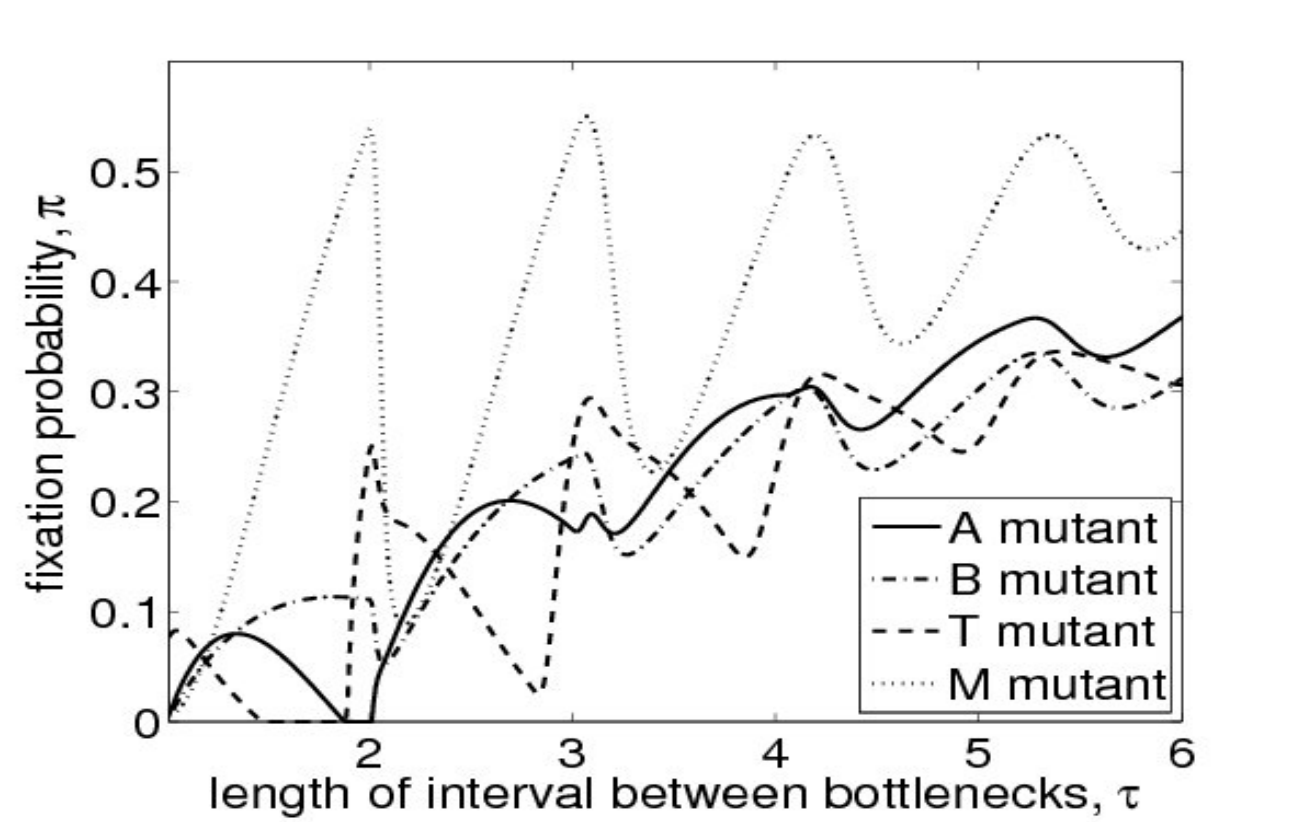


Analytical results:



Patwa and Wahl, *Genetics*, 2008

The effect is even stronger when we allow mutations which reduce clearance:



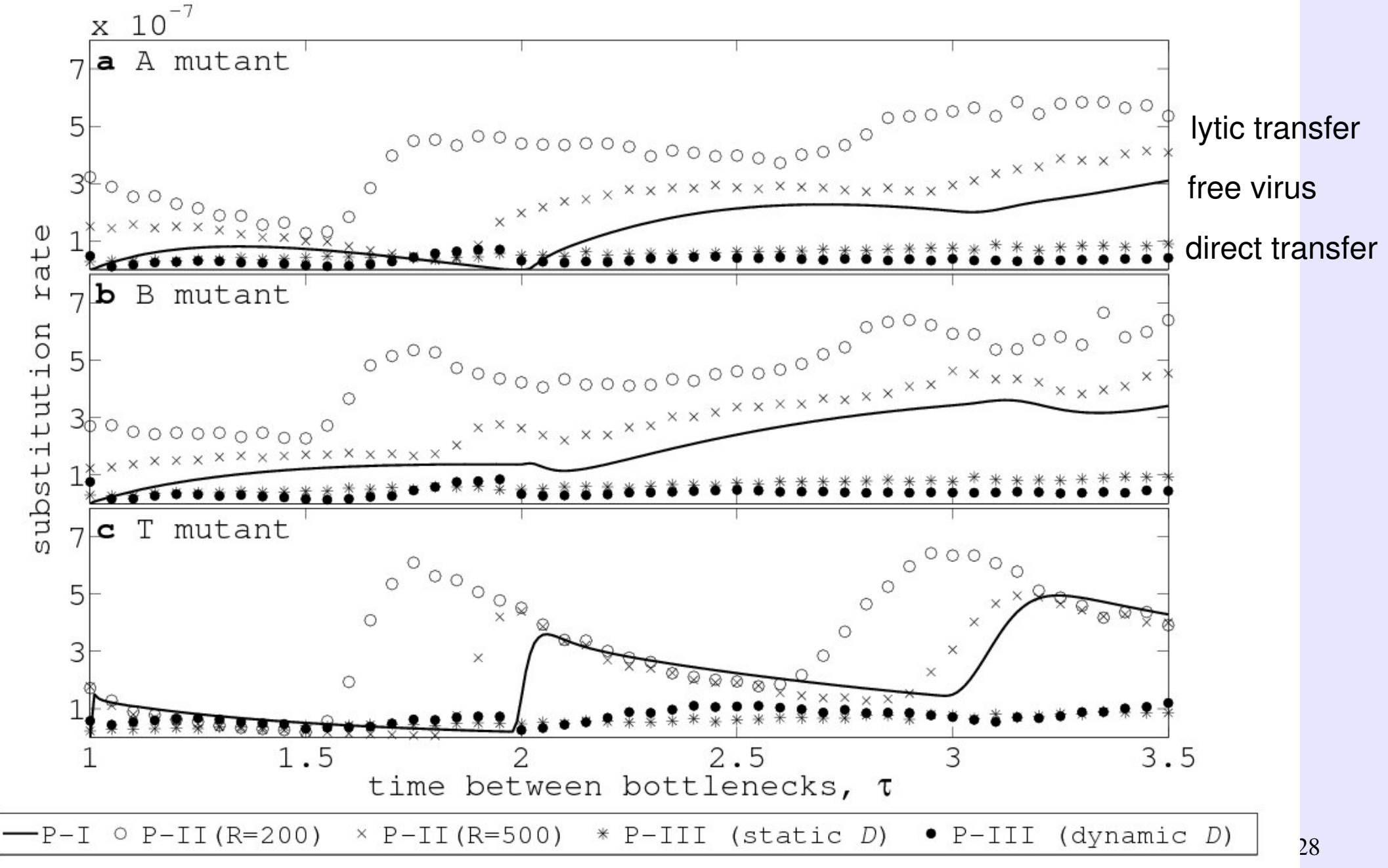
Small changes in bottleneck timing can have huge effects on fixation.

surprise #2b: the most fit mutations are not the most likely to fix

- the length of time between bottlenecks strongly selects for mutations with certain effects
- the most fit mutations are **not** the most likely to reach fixation; fixation isn't proportional to *s*
- mutations which can reduce clearance (sticking to vessel walls, infecting dead cells) will be strongly selected
- many of these qualitative conclusions probably hold for other experimental preps

surprise #3: not all bottlenecks are created equal

- these results were for transfer of free virions only at the bottleneck
- transfer of free virions is like transfer of pathogenic virus to a new host
- but what about
  - direct transfer (environment for both host and virus periodically reduced, eg. drought) ?
  - lytic transfer (experimental) ?



lytic transfer

free virus

direct transfer

surprise #3: not all bottlenecks are created equal

- direct transfer has the slowest adaptation rate, slower by as much as an order of magnitude
- transfer of free virus allows for faster adaptation (pathogenic microbes)
- lytic transfer has the fastest adaptation rates
- this ordering holds for all types of mutations

Acknowledgments

- Chris DeHaan, Ivan Saika-Voivod, Jennifer Hubbarde, Geoff Wild, Helen Alexander, Zaheerabbas Patwa
- Phil Gerrish, Christina Burch
- NSERC, Canada Research Chairs program
- SHARCNET computing facility