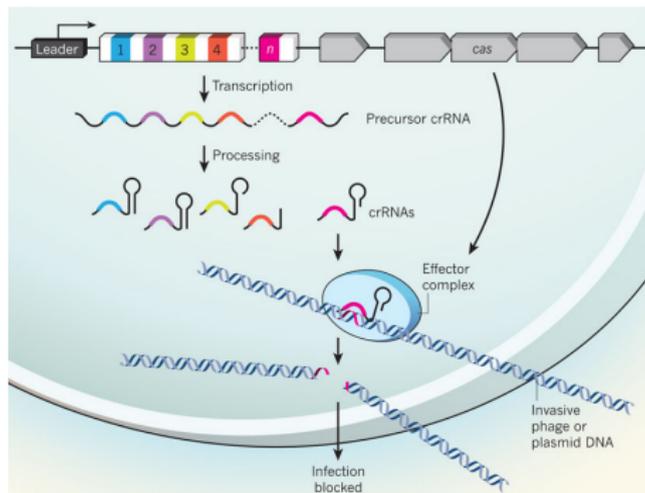


The CRISPR-Cas adaptive immunity system in prokaryotes: Mathematical modeling of virus-host co-evolution

Alexander E. Lobkovsky[†], Jaime Iranzo-Sanz[‡],
Yuri I. Wolf[†], Eugene V. Koonin[†]

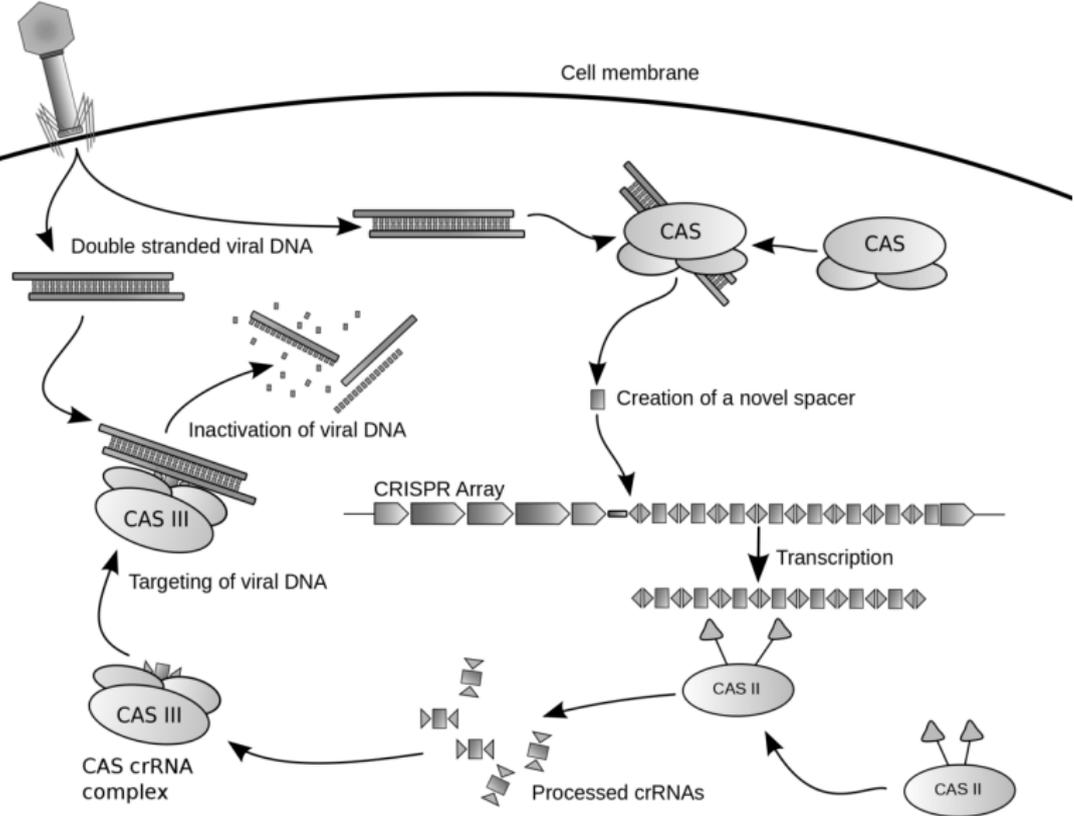
[†] National Center for Biotechnology Information, National Institutes of Health

[‡] Centro de Astrobiología (CSIC/INTA) Instituto Nacional de Técnica Aeroespacial

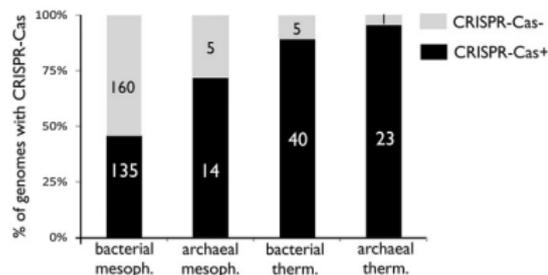


Erik J. Sontheimer & Luciano A. Marraffini, *Nature*. **468**, (2010)

Cells incorporate fragments of foreign DNA and use them later to identify and destroy invading phages or plasmids



Why isn't CRISPR ubiquitous among prokaryotes?



A. D. Weinberger *et al*, mBio (2012)

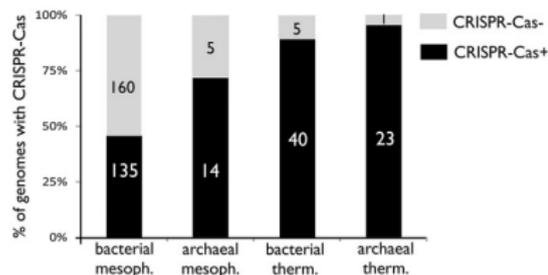
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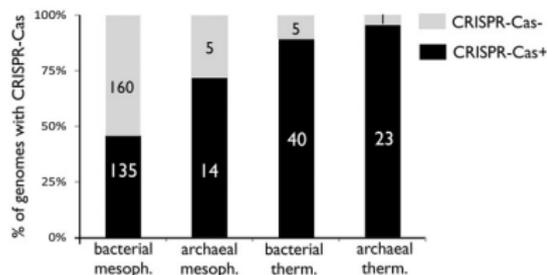
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- ▶ Genomic burden

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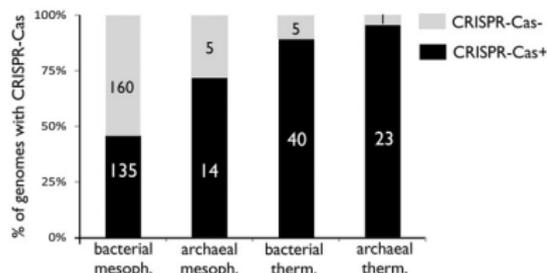
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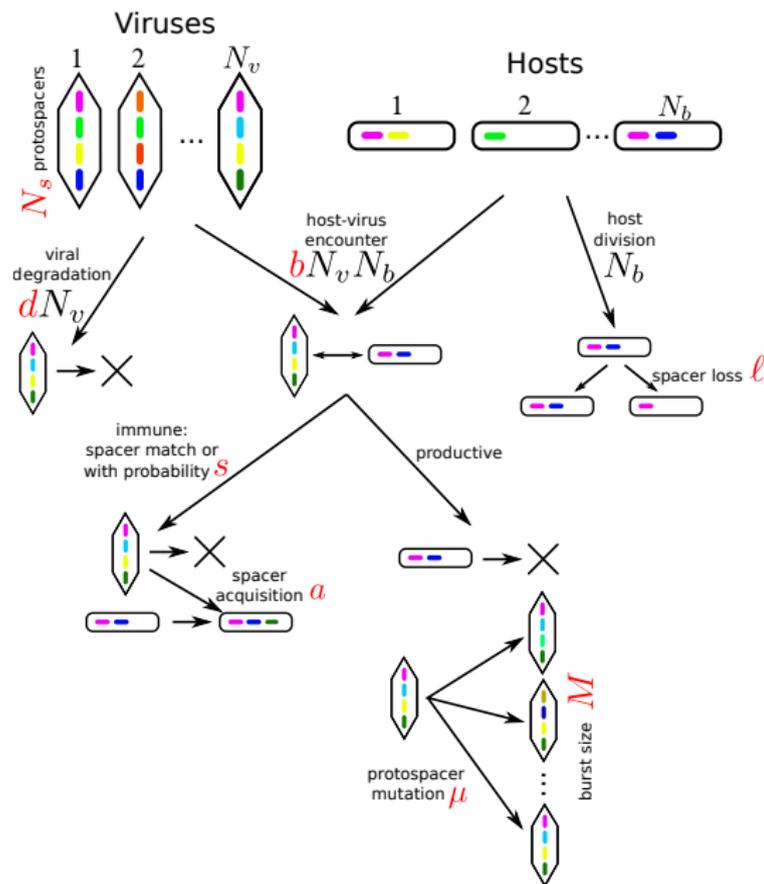
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How does CRISPR survive?

Study a stochastic virus-host co-evolution model with explicit CRISPR dynamics

Stochastic model of CRISPR/virus co-evolution



Fix:

- ▶ $N_s = 10$
- ▶ $M = 10$
- ▶ $s = 0.1$
- ▶ $l = 0.05$
- ▶ $d = 0.5$

Vary:

- ▶ Encounter rate b
- ▶ Spacer addition probability a
- ▶ Viral mutation rate μ

Without the CRISPR adaptive immunity: Lotka-Volterra

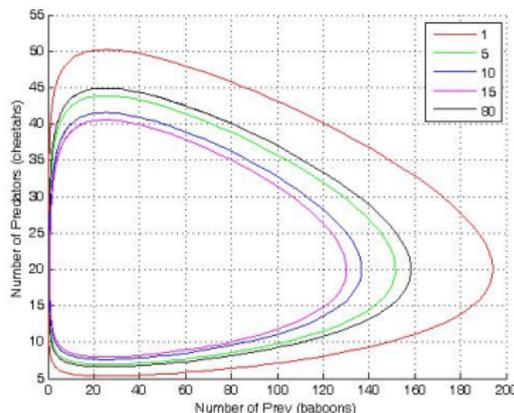
$$\begin{aligned}\dot{N}_b &= N_b - bN_bN_v(1-s) \\ \dot{N}_v &= -dN_v + bN_bN_v(M - Ms - 1)\end{aligned}$$

Marginally stable fixed point:

$$\begin{aligned}N_b &= \frac{d}{b(M - Ms - 1)} \\ N_v &= \frac{1}{b(1 - s)}\end{aligned}$$

Critical immunity: $s_{\text{crit}} = 1 - M^{-1}$

Family of orbits around the fixed points with period $\frac{2\pi}{\sqrt{d}}$



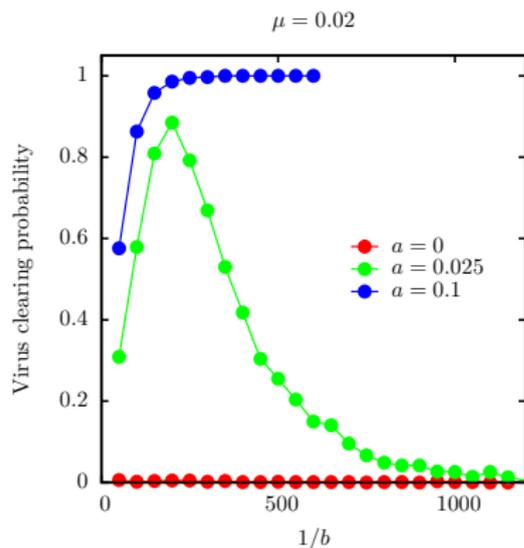
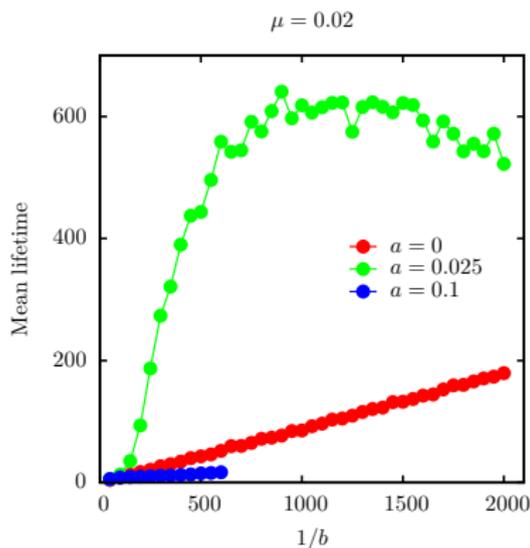
Constant of the motion:

$$V = -b(M - Ms - 1)N_b + d \log N_b - b(1 - s)N_v + \log N_v$$

Finite population \rightarrow stochastic extinction

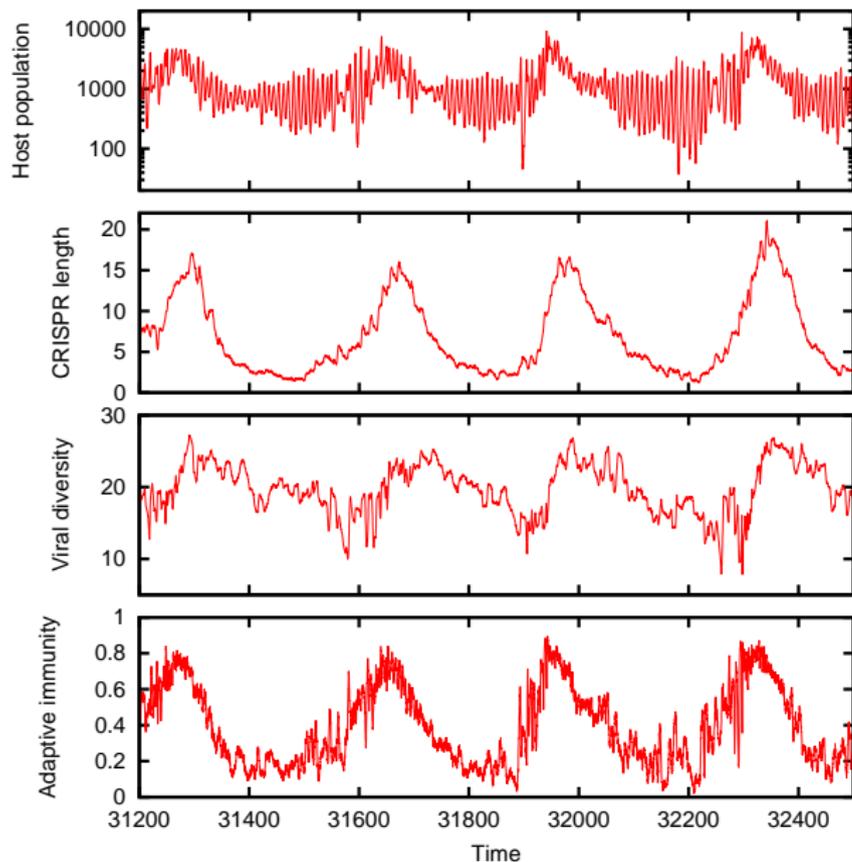
(De)stabilization of LV by CRISPR

- ▶ Dynamics of the system are **not** canonical LV
- ▶ Critical spacer addition probability $a_{\text{crit}}(\mu)$ above which virus is cleared in large populations



$1/b \sim$ population size

Slow oscillations on top of the LV oscillations



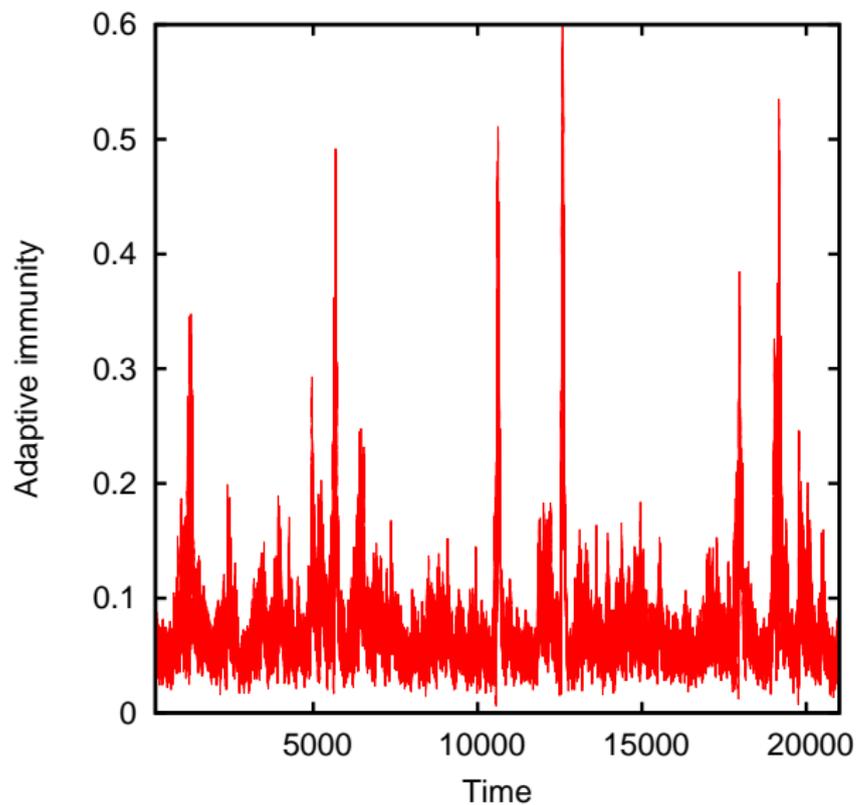
$$b = 0.0001$$

$$\mu = 0.001$$

$$a = 0.005$$

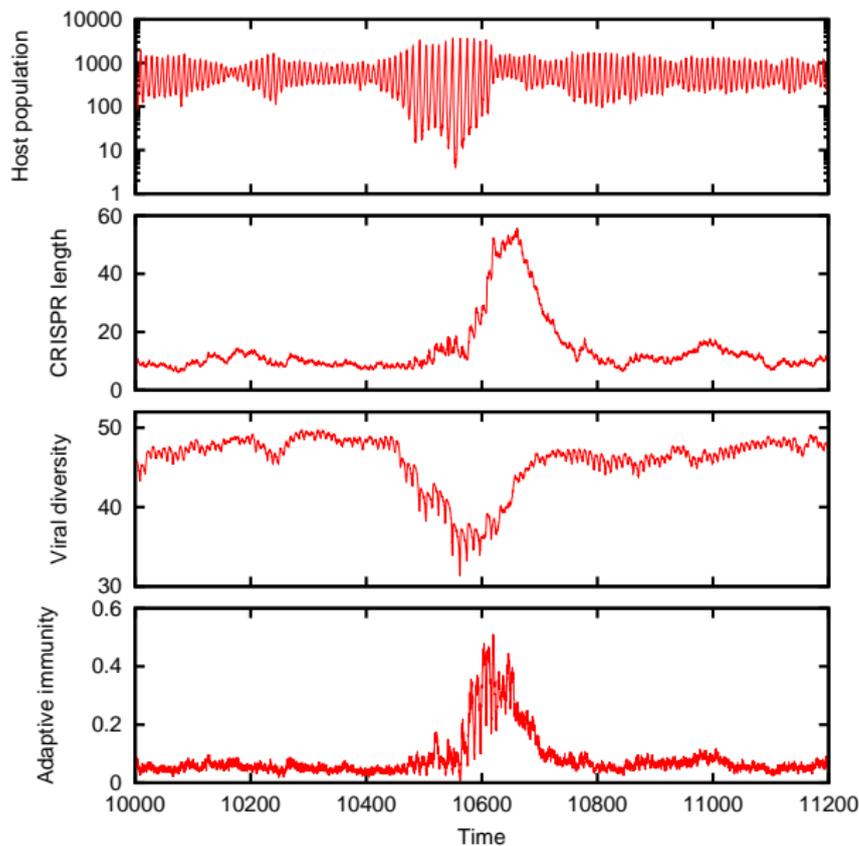
Excitable medium-like behavior

$b = 0.0001$, $\mu = 0.03$, $a = 0.2$



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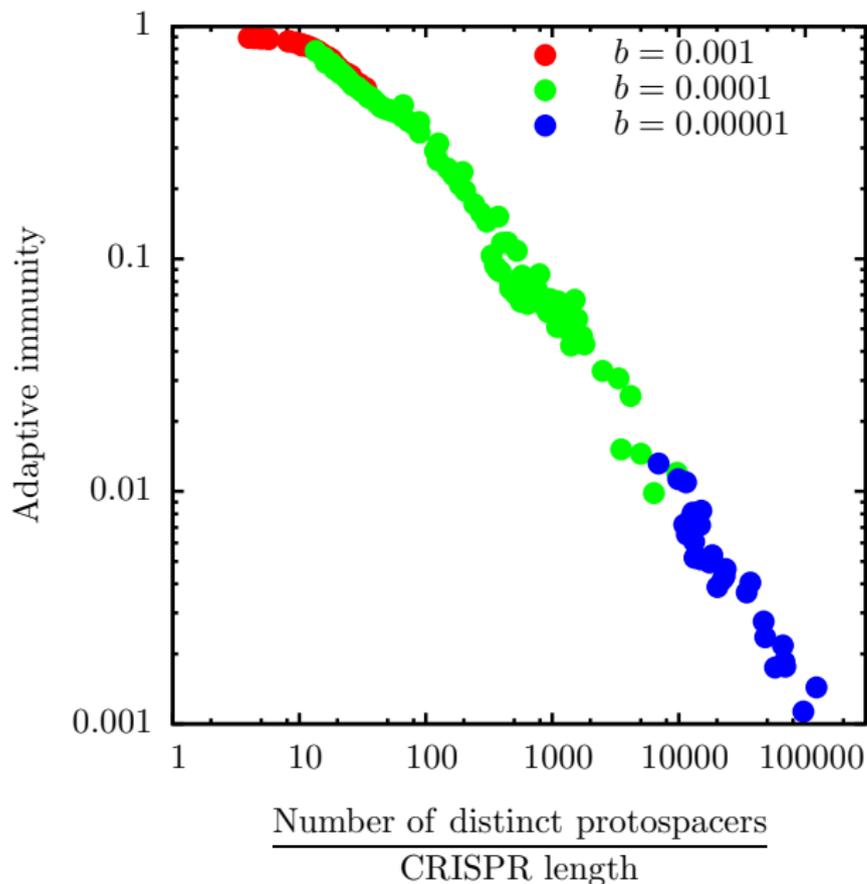
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FitzHugh-Nagumo
description?

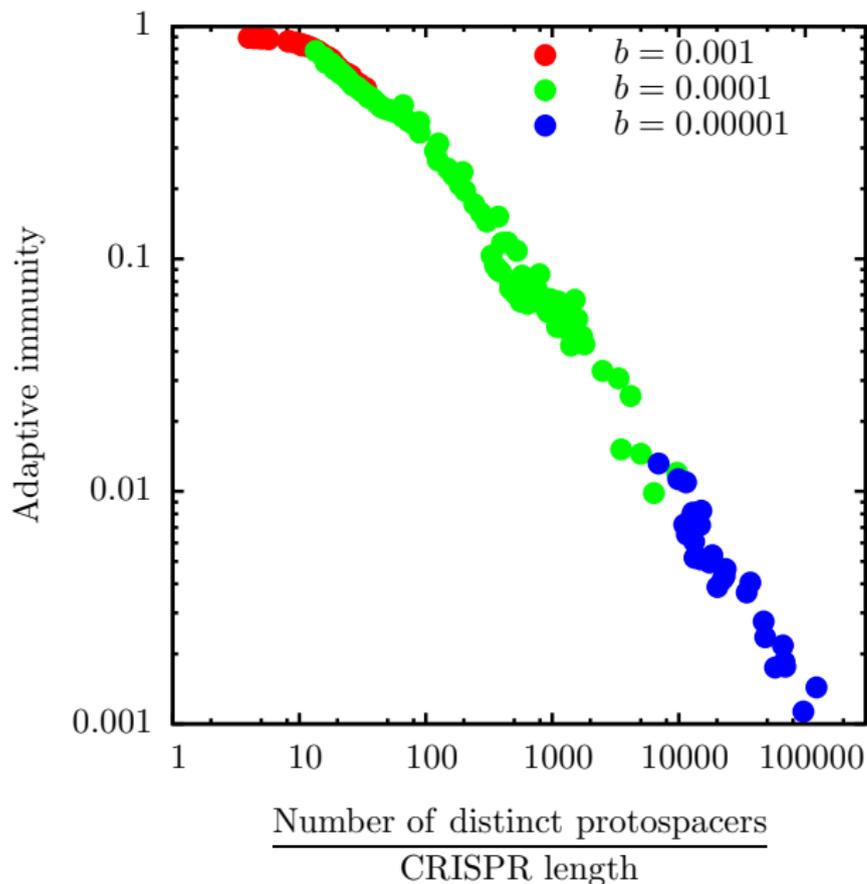
Slow variable?

Small parameter?

Spacers are distributed at random among viruses and hosts

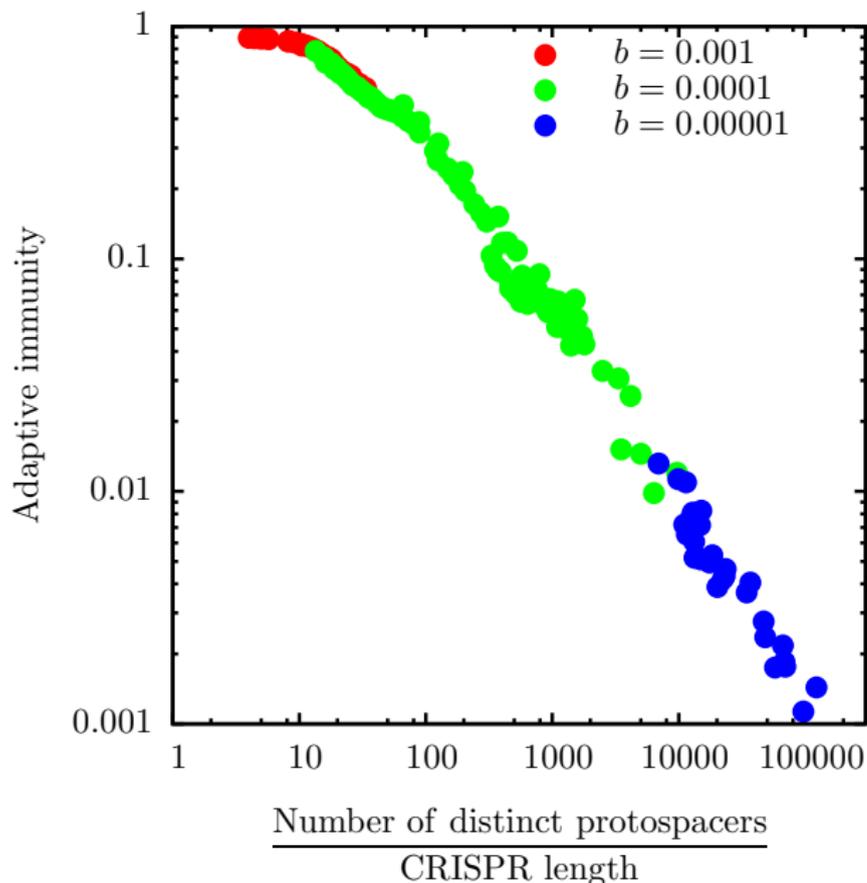


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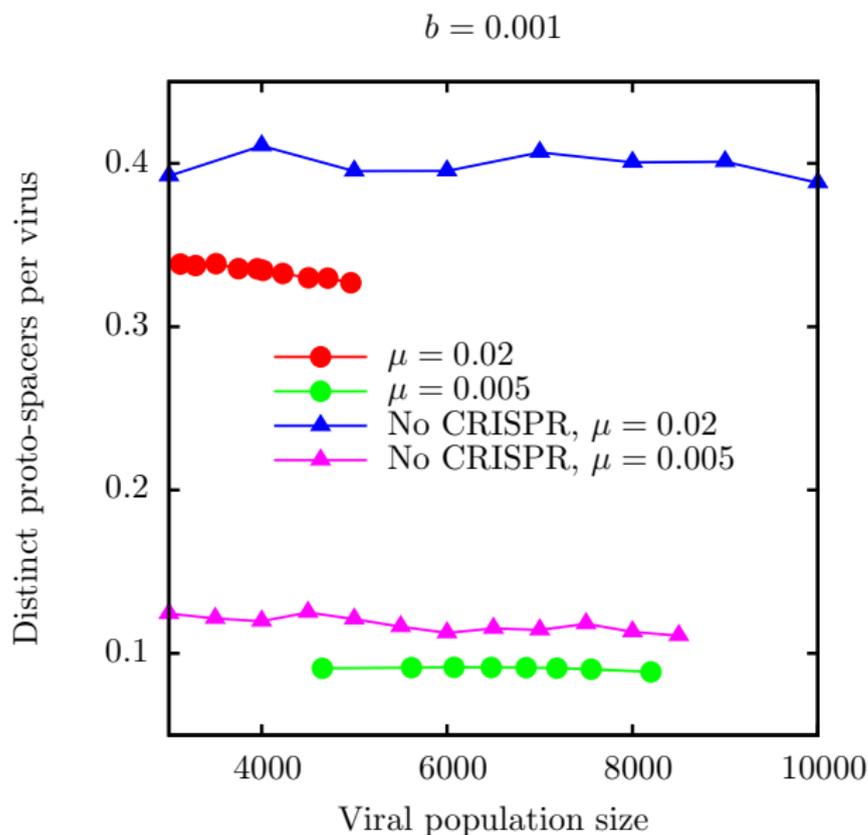
- ▶ What model parameters does the shape of the master curve depend on?

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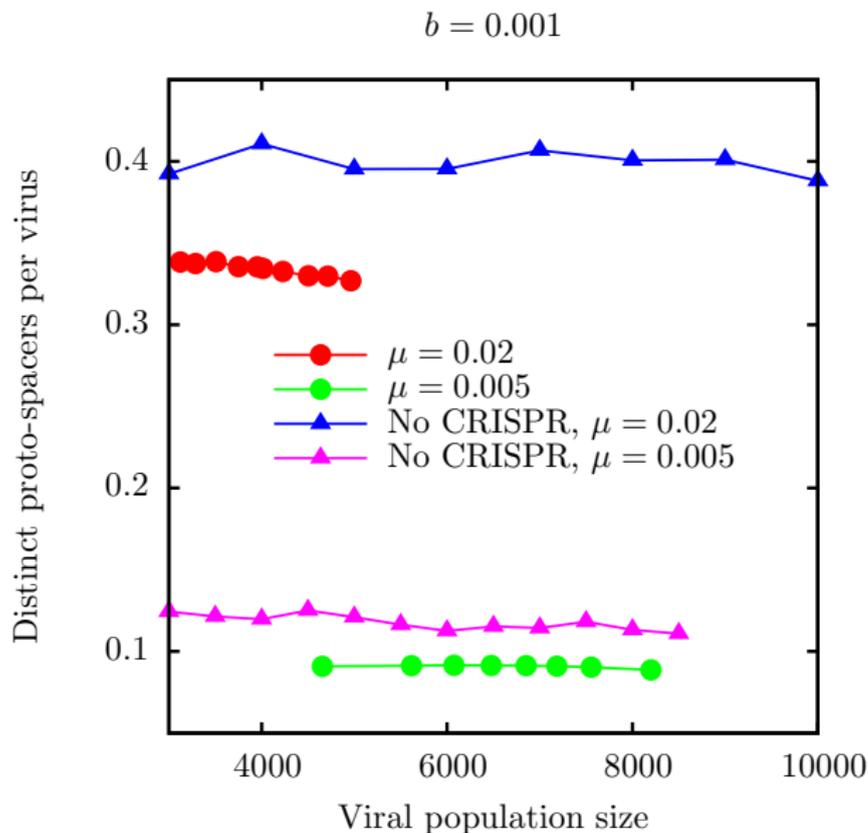
- ▶ What model parameters does the shape of the master curve depend on?
- ▶ How do the number of proto-spacers and CRISPR length L depend on model parameters?

CRISPR only slightly suppresses viral diversity



Weak selection
pressure
proto-spacer
content

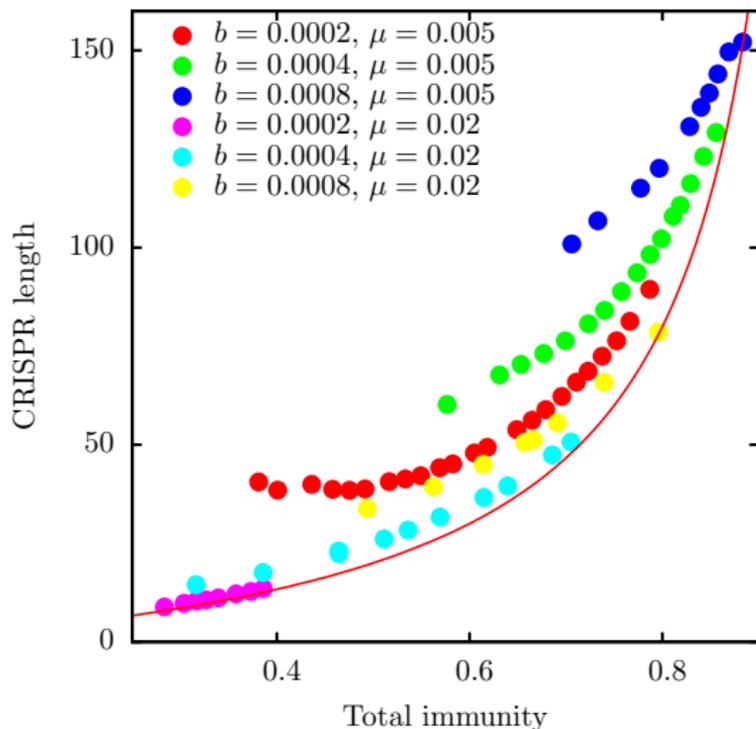
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Weak selection pressure
proto-spacer content

Number of distinct
proto-spacers in
absence of
CRISPR
depends on
 N_V, N_S, M, μ
(computable
analytically)

Virus evolution is unconstrained in large populations at high mutation rates



p : total immunity

$$\dot{L} = -\frac{1}{2}L\ell + bN_v p a N_s$$

In steady state

$$N_v = \frac{1}{b(1-p)}$$

Hence

$$\frac{L\ell}{a} = \frac{2N_s p}{1-p}$$

Solid red line

Assumption: CRISPR length and immunity are uncorrelated among individuals in a population

Three species dynamics

- ▶ CRISPR– hosts grow with rate $1 + c$

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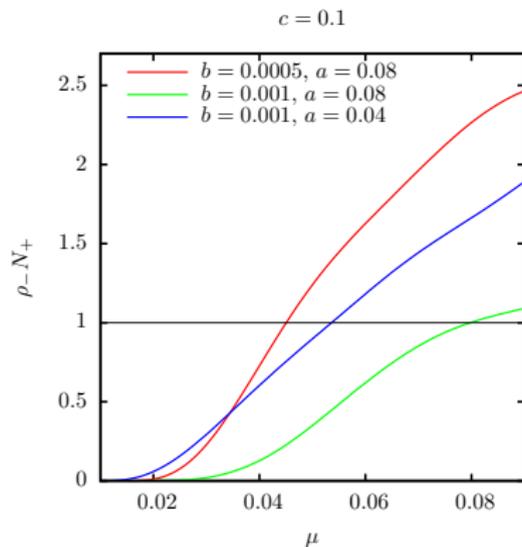
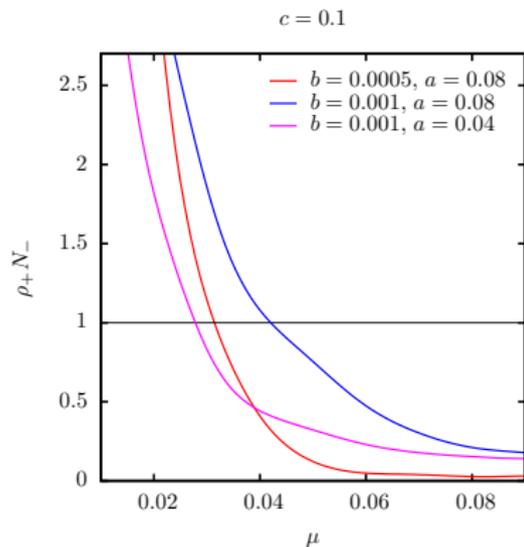
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 - ▶ Repeat for CRISPR+ introductions (initially without spacers)

Spacer-less CRISPR+ hosts can be favored by selection



Invasion threshold:

	$a \uparrow$	population size \uparrow
μ_+	\uparrow	\downarrow
μ_-	\uparrow	\downarrow

Discussion

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