NASA Astrobiology Institute
Astrovirology Workshop Without Walls
September 18, 2019

Support:
NSF – PoLS; NSF BioOc; NSF Dim of Biodiversity;
Simons Foundation; ARO; NIH

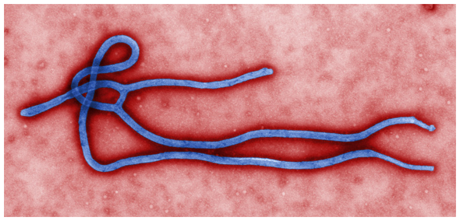
Thanks to Guanlin Li, Michael Cortez, Hend Alrasheed, Rong Jin, Hayriye Gulbudak, Rachel Whitaker, Mark Young, and Charles Wigington

VIRAL INFECTION MODES AND INVASION FITNESS ACROSS A CONTINUUM FROM LYSIS TO LATENCY

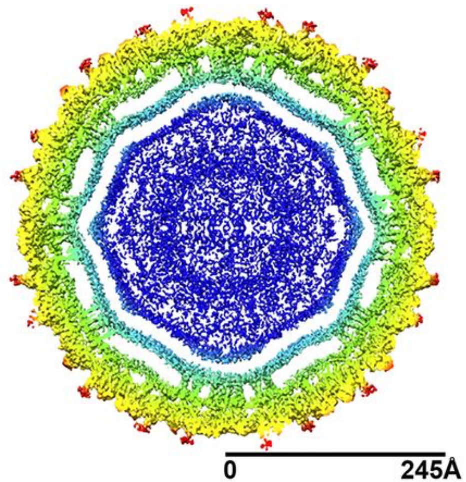
Dr. Joshua S. Weitz
Professor, School of Biological Sciences
Courtesy Professor, School of Physics & ECE
&
Founding Director, Ph.D. in Quantitative Biosciences
Georgia Institute of Technology

http://ecotheory.biology.gatech.edu
jsweitz@gatech.edu

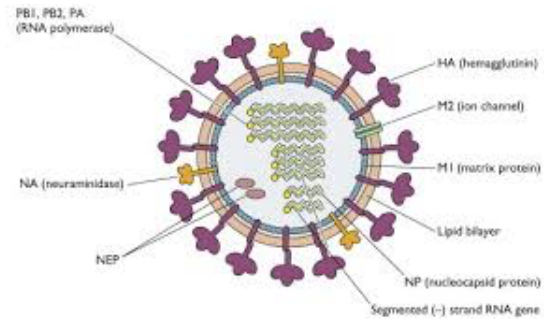
What We Talk About When We Talk About Viruses



Ebola Virus
Image source: CDC



Zika virus core
Sirohi et al. Science, 2016



Influenza virus
virology.ws

John Moore, Getty Images
(Nature, 2014)

Source: CNN

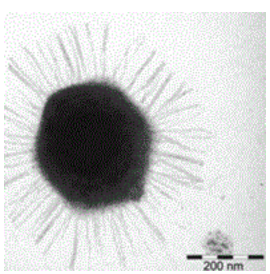
Source: CDC

But viruses infect organisms across the diversity of life

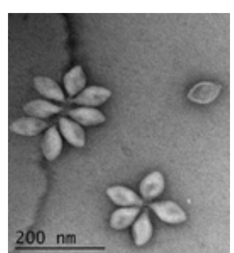
Humans	⟷	HIV, Ebolazaire, Rhinovirus,…
Mammals	⟷	Lentivirus, ...
Birds	⟷	Avian influenza, ...
Insects	⟷	Baculovirus, ...
Plants	⟷	Tobacco mosaic virus, ...

But viruses infect organisms across the diversity of life, including microbes

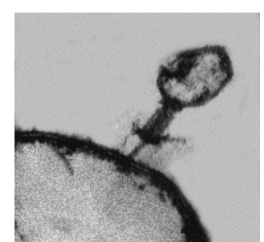
Humans	⟷	HIV, Ebolazaire, Rhinovirus,…
Mammals	⟷	Lentivirus, ...
Birds	⟷	Avian influenza, ...
Insects	⟷	Baculovirus, ...
Plants	⟷	Tobacco mosaic virus, ...
Amoeba	⟷	Giant mimiviruses
Archaea	⟷	Sulfulobus spindle viruses
Bacteria	⟷	Bacteriophages (lambda, T4, ...)



Mimivirus – Raoult et al. CID 2007

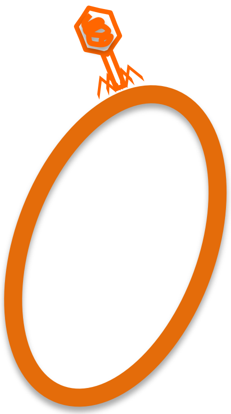


SSV – Quemin et al. J. Vir. 2015

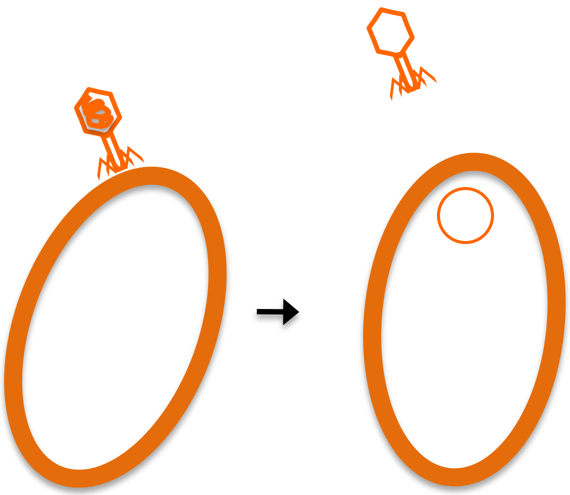


T4 – mbio.ncsu.edu

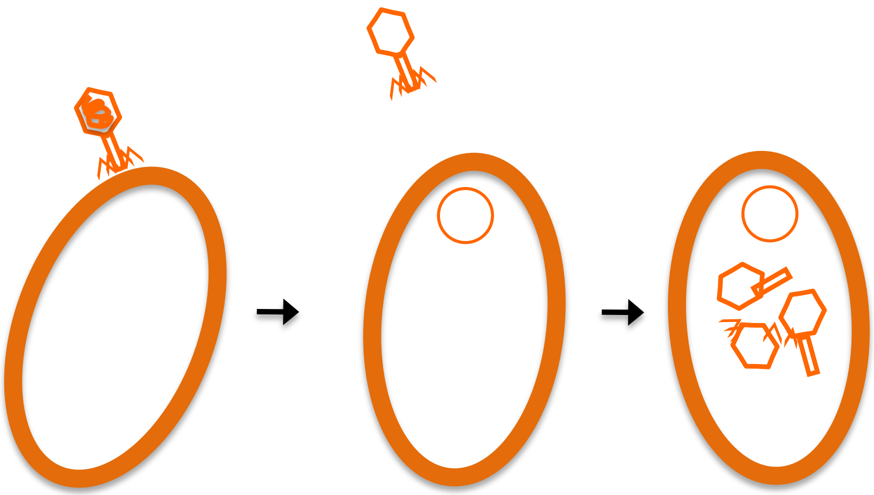
The life of a bacterial virus (phage)



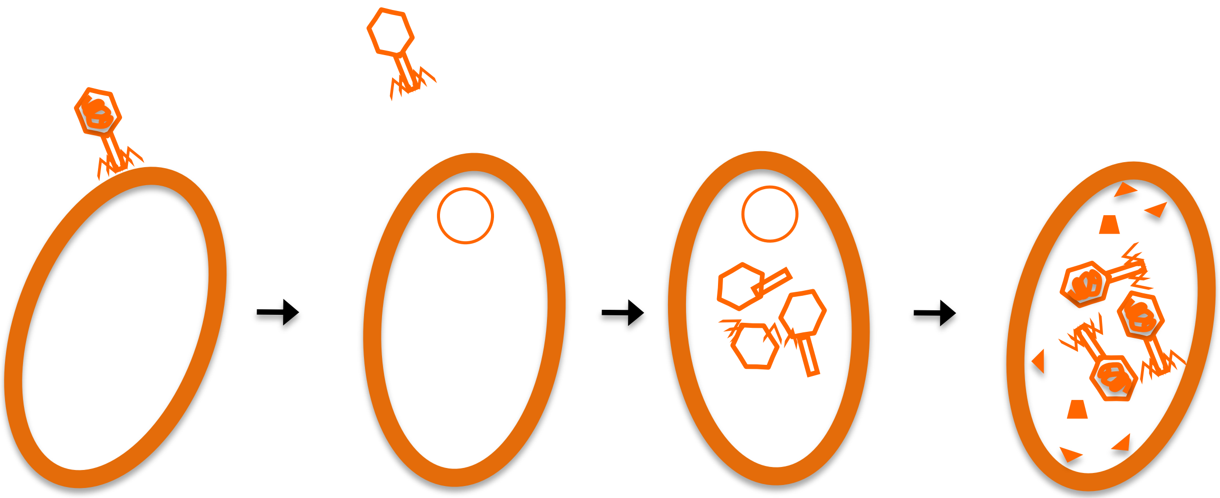
The life of a bacterial virus (phage)



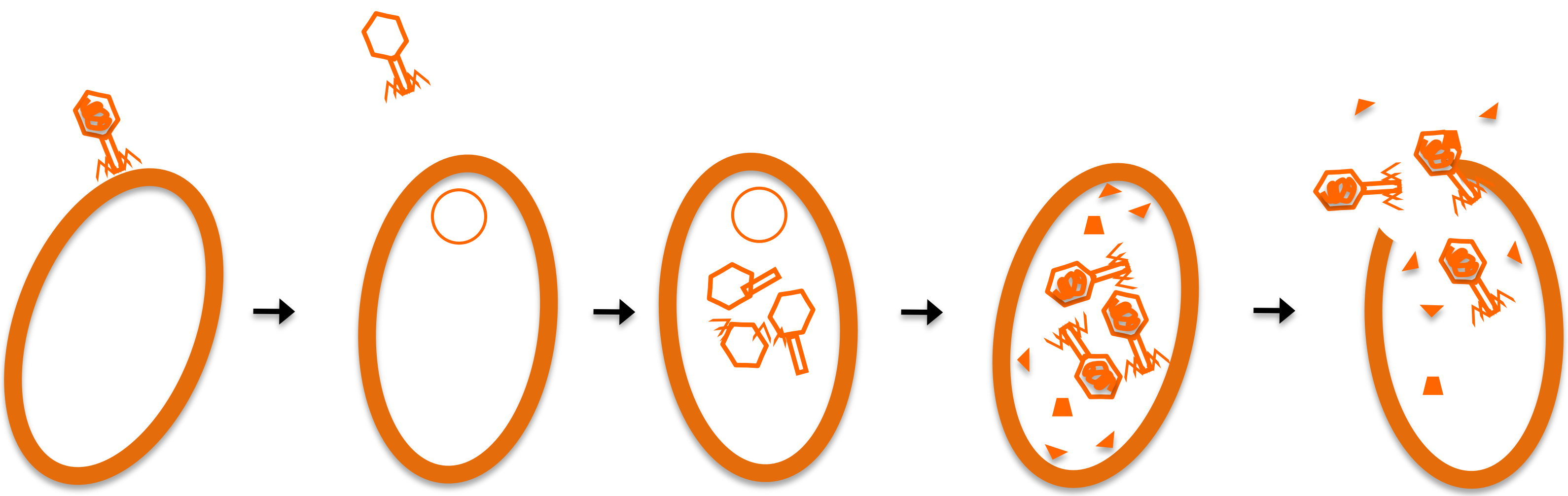
The life of a bacterial virus (phage)



The life of a bacterial virus (phage)



The life of a bacterial virus (phage)



A "predator-prey" model is the basis for studies of **virus-microbe** population dynamics

Dynamic model

$$\frac{dR}{dt} = \overbrace{\omega R_0}^{\text{media inflow}} - \overbrace{f(R)N}^{\text{nutrient consumption}} - \overbrace{\omega R}^{\text{outflow}}$$

$$\frac{dN}{dt} = \overbrace{\epsilon f(R)N}^{\text{cell division}} - \overbrace{\phi NV}^{\text{infection and lysis}} - \overbrace{\omega N}^{\text{outflow}}$$

$$\frac{dV}{dt} = \overbrace{\beta\phi NV}^{\text{lysis}} - \overbrace{\phi NV}^{\text{infection}} - \overbrace{\omega V}^{\text{outflow}}$$

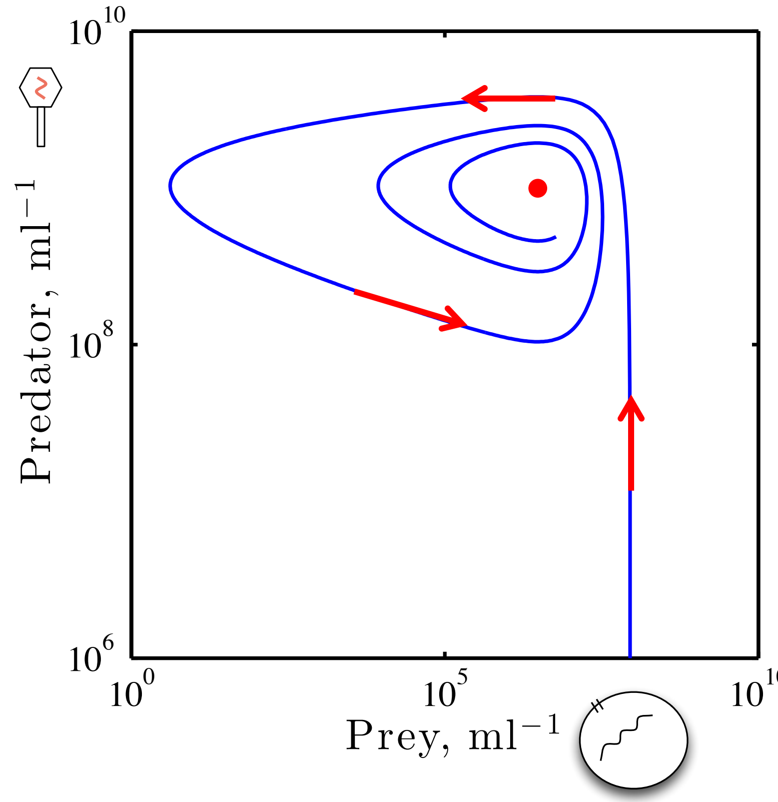
Interactions:

Resource inflow/outflow

Host growth and outflow

Viral lysis and outflow

<u>Result: "Lotka-Volterra" like predator-prey dynamics</u>



Counter-clockwise cycles

Similar model proposed by Campbell (1961) Evolution 15: 153
& adapted to phage-bacteria chemostats by Levin et al. (1977) Am. Nat. 111:3

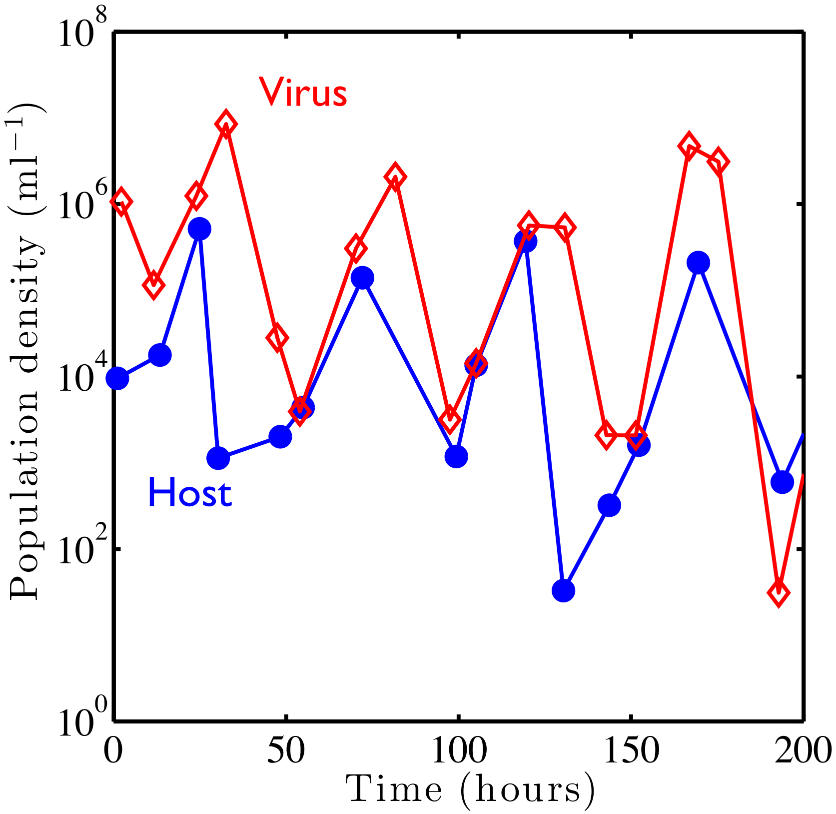
The same types of cycles can be observed in virus-host population dynamics (in the lab)

"Predator-prey" like cycles between phage T4 and *E. coli* B

Data: Bohannan & Lenski, Ecology (1997)

Take-home message:

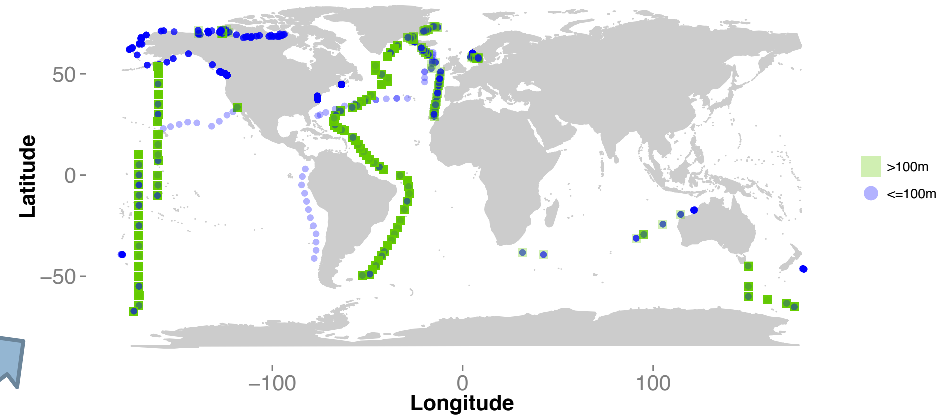
Original models of viral-host dynamics presuppose a "simple" one virus, one host relationship.



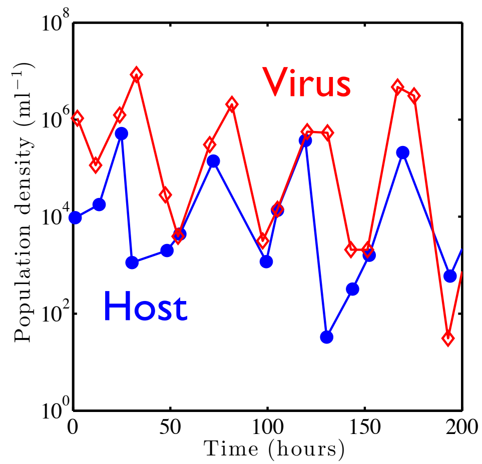
Further analysis of this and other cases in:
Weitz, Quantitative Viral Ecology: Dynamics of Viruses and Their Microbial Hosts, Princeton University Press, 2015.

The Problem of Scales in Quantitative Viral Ecology:

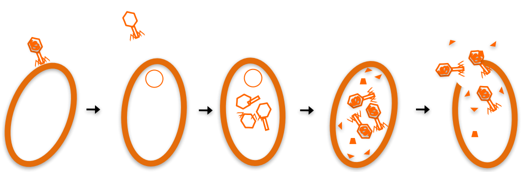
Linking Mechanism to Pattern



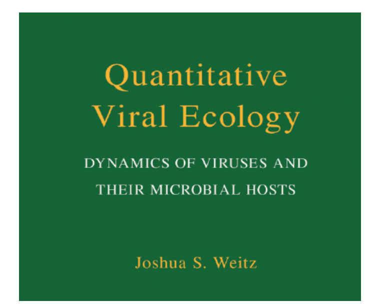
Which scale-up to massive ecosystem effects when integrated over the global oceans.



Infection and lysis leads to oscillatory dynamics at the population scale…



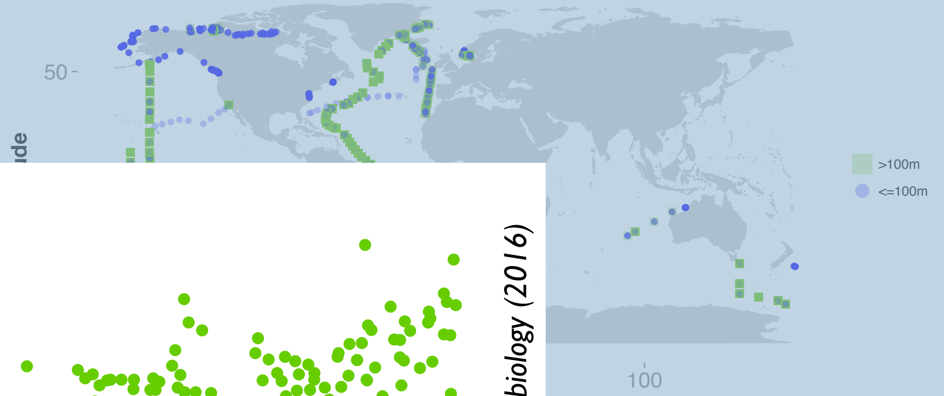
Virus-host interactions modify the fate of cells on time scales similar to division times…

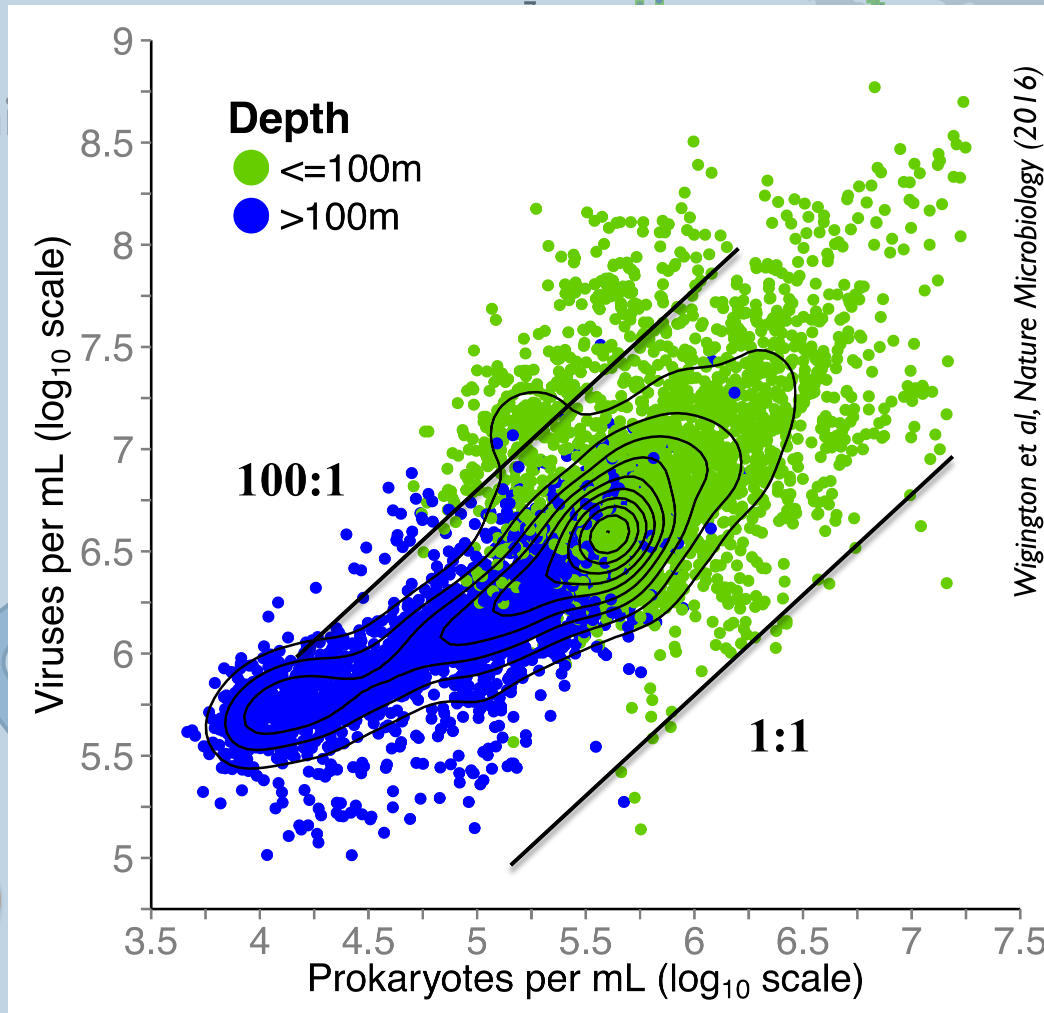


PRINCETON UNIVERSITY PRESS

The Problem of Scales in Quantitative Viral Ecology:

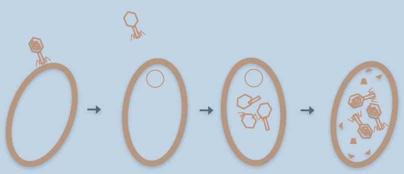
Linking Mechani



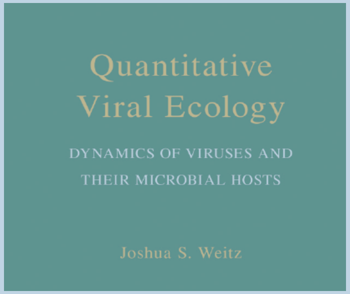


e-up to massive
effects when integrated
obal oceans.

ds to
at the



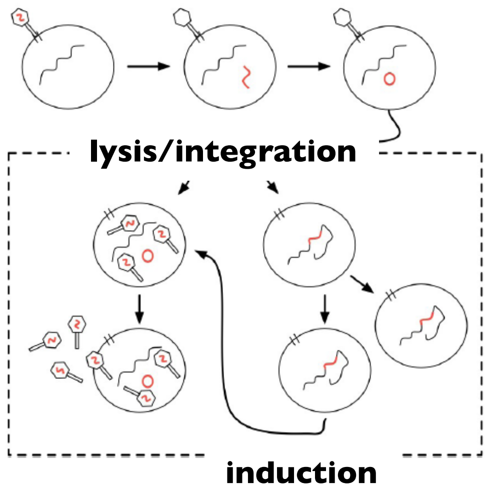
Virus-host interactions modify the fate of cells on time scales similar to division times…



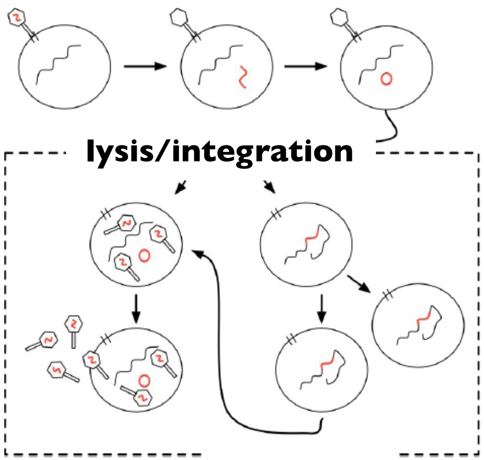
PRINCETON UNIVERSITY PRESS

But do viruses of microbes do more than kill or prepare to kill?

Lysogeny – 'Lessons from a Simple System'



Lysogeny – 'Lessons from a Simple System'



LYSOGENY[1]

ANDRÉ LWOFF

Department of Microbial Physiology, Institut Pasteur, Paris

CONTENTS

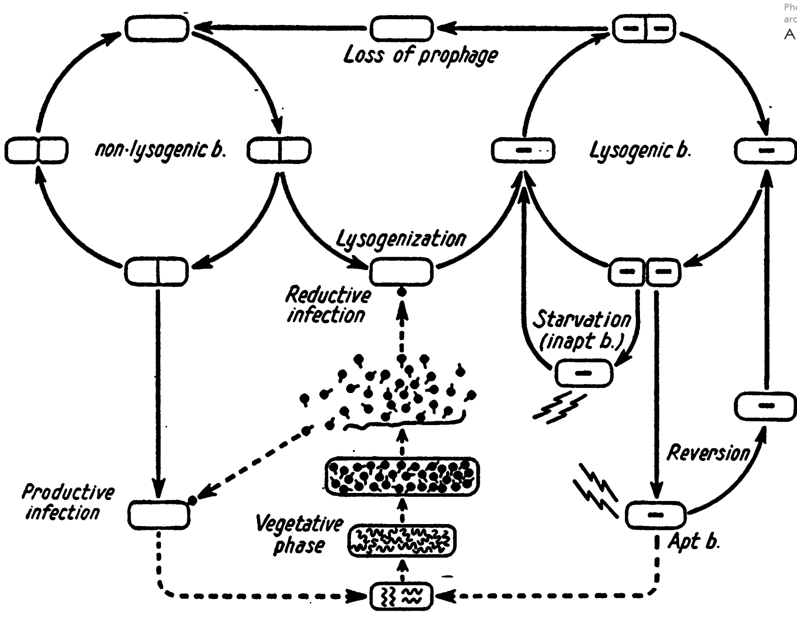


FIG. 1. General view of lysogeny

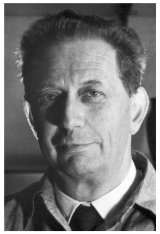
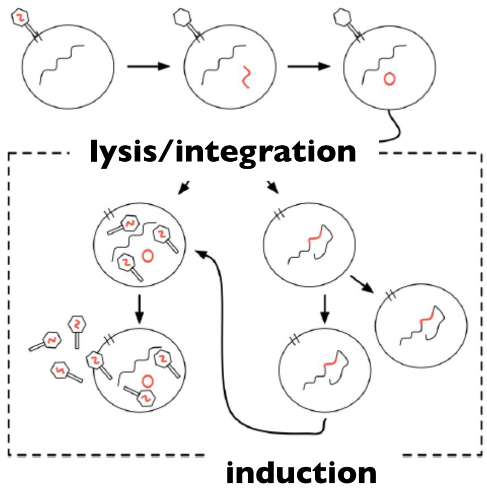


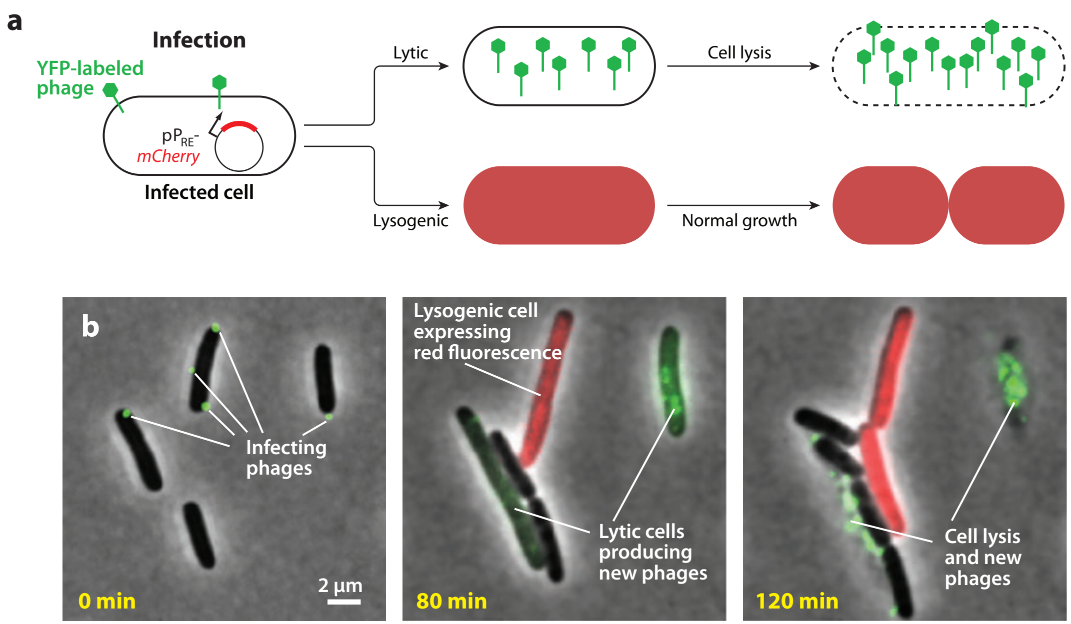
Photo from the Nobel Foundation archive.

André Lwoff

1953 – Lwoff, A., Bacteriology Reviews

Lysogeny – 'Lessons from a Simple System'





Golding et al. Ann Rev. Biophys. 2011
&
Ptashe, A Genetic Switch: Phage Lambda Revisisted, 2004.

Why Be Temperate?
A 40+ year-old question

THEORETICAL POPULATION BIOLOGY 26, 93–117 (1984)

The Population Biology of Bacterial Viruses: Why Be Temperate

FRANK M. STEWART AND BRUCE R. LEVIN

Department of Mathematics, Brown University, Providence, Rhode Island 02912, and Department of Zoology, University of Massachusetts, Amherst, Massachusetts 01003

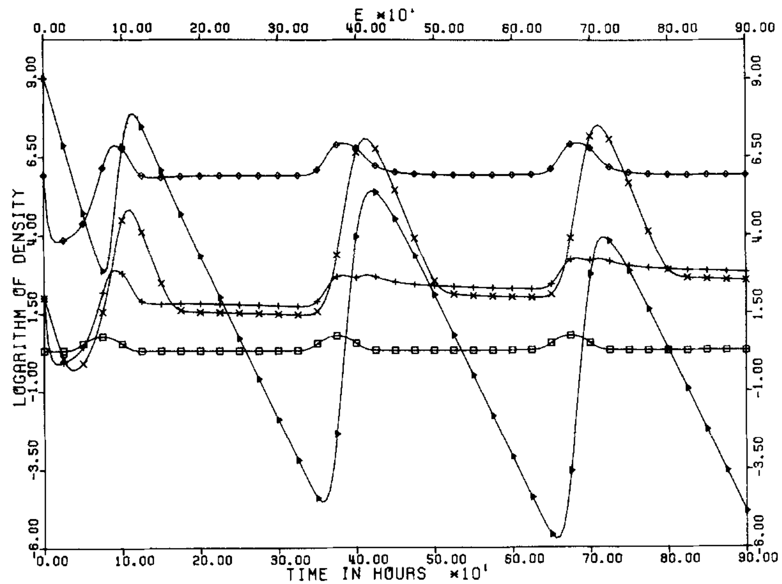
Received May 23, 1983

$$\dot{r} = \rho(C - r) - e\psi(r)(L + (1 - \alpha_S)S),$$

$$\dot{L} = \psi(r)L + \lambda\delta_T ST - (\rho + \xi + \tau)L,$$

$$\dot{S} = (1 - \alpha_S)\,\psi(r)S - \delta_T ST + \tau L - \rho S,$$

$$\dot{T} = \xi\beta_T L + \beta_T(1 - \lambda)\,\delta_T ST - \delta_T LT - \rho T.$$

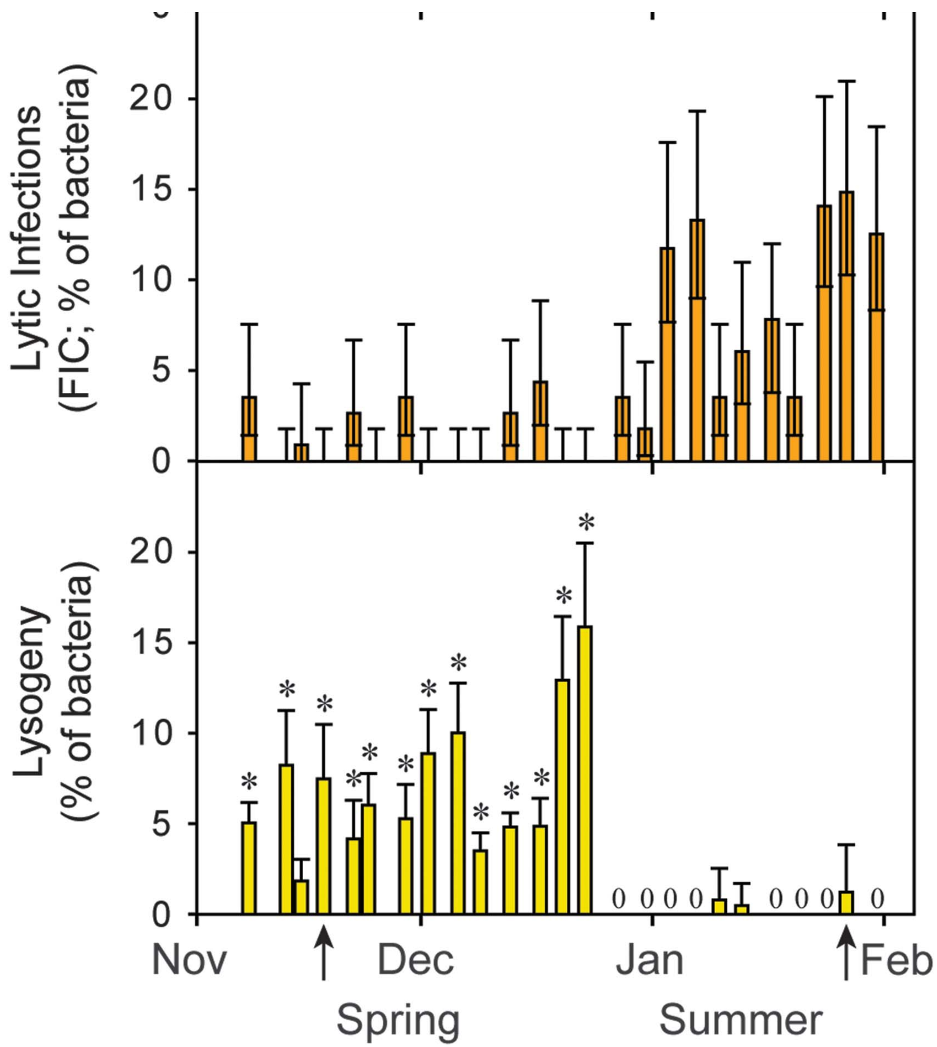


Feast or Famine Hypothesis

Premise: temperate phage do better when few hosts are available and extracellular mortality rate are high.

Caveat: “In spite of the intuitive appeal of this low density hypothesis, we are unable to obtain solutions consistent with it using the model presented here.”

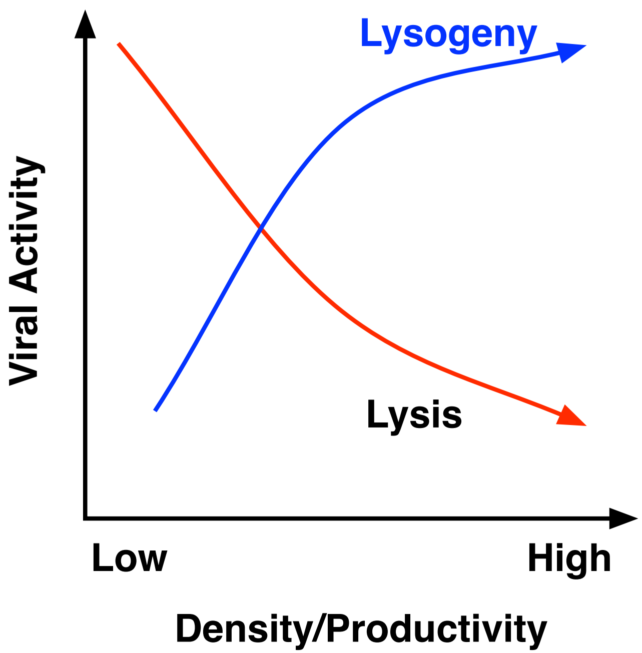
Lysogeny and Plankton Blooms: An Inverse Relationship with Plankton Density



'Seasonal Timebombs': Lysogeny prevalent given low productivity and lysis elevated at high productivity

Brum et al. ISME J. 2015
&
McDaniel et al. Nature 2002

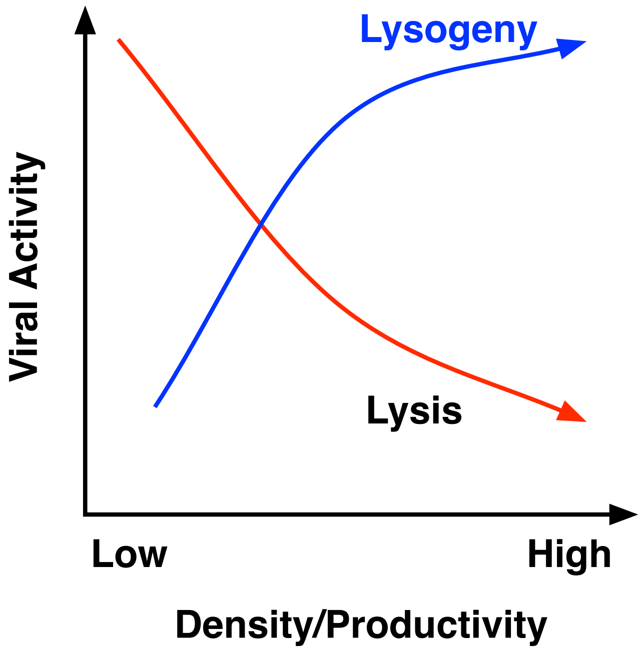
An Alternative Hypothesis: "Piggyback-the-Winner"

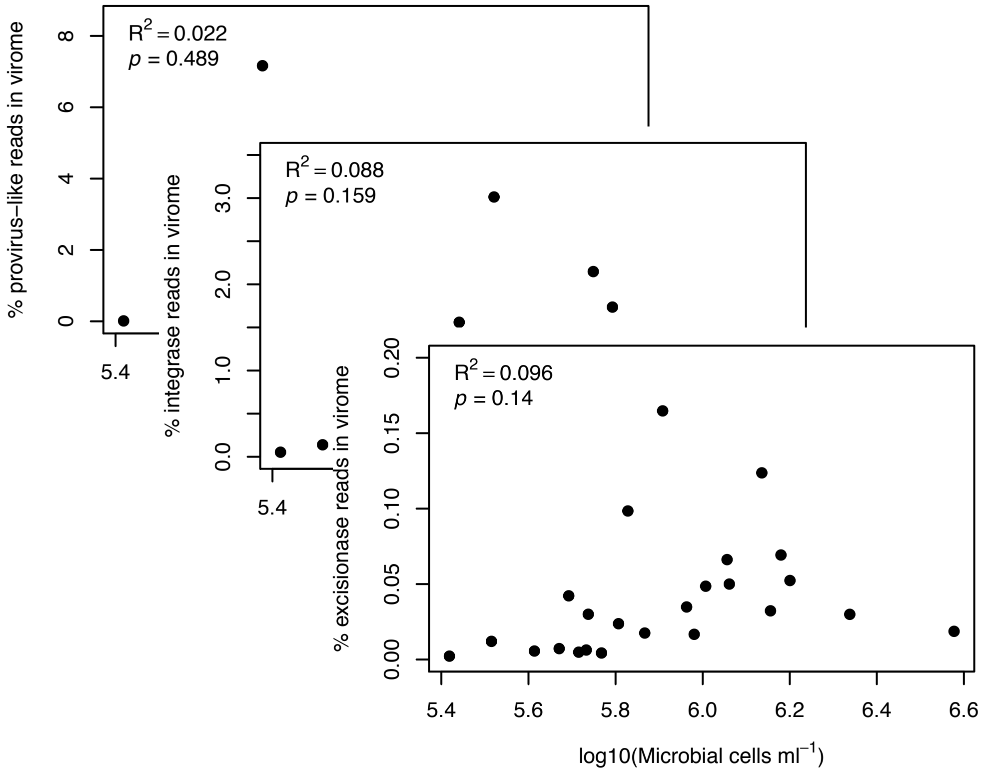


Piggyback-the-winner – lysogeny is positively correlated with increases in host density and productivity.

Knowles et al. Nature 2016

Piggyback-the-Winner: Re-examining the metagenomics evidence

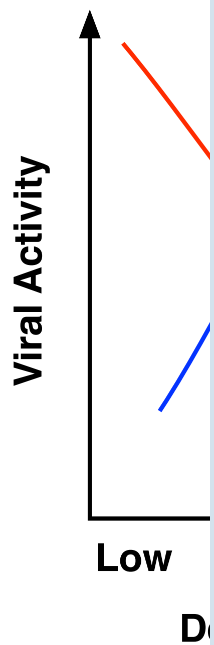




Piggyback-the-winner – lysogeny is positively correlated with increases in host density and productivity.

Knowles et al. Nature 2016

Piggyback-the-Winner: Re-examining the metagenomics evidence



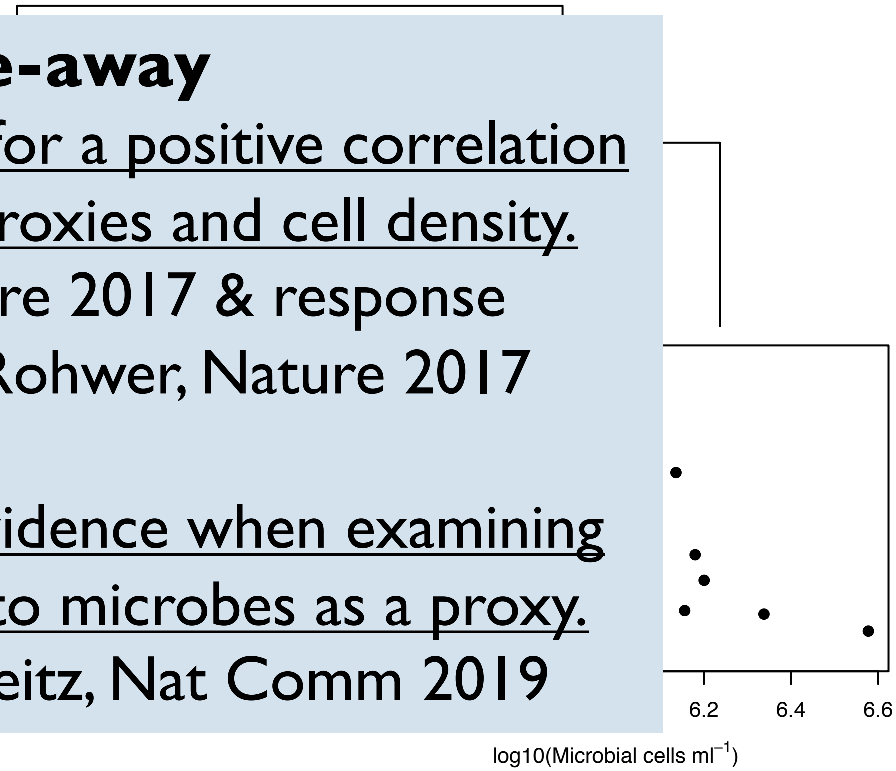
Take-away

<u>Absence of evidence for a positive correlation between lysogeny proxies and cell density.</u>

Weitz et al. Nature 2017 & response from Knowles & Rohwer, Nature 2017

<u>Similar absence of evidence when examining the ratio of viruses to microbes as a proxy.</u>

Alrasheed, Jin & Weitz, Nat Comm 2019



Piggyback-the-winner – lysogeny is <u>positively</u> correlated with increases in host density and productivity.

Knowles et al. Nature 2016

What environmental conditions should favor lysogeny rather than lysis?

What environmental conditions should favor lysogeny rather than lysis?

On old lesson:

A bird in the hand is worth two in the bush.

What environmental conditions should favor lysogeny rather than lysis?

On old lesson:

A bird in the hand is worth two in the bush.

A new puzzle:

*A virus in the cell is worth **N** in the bloom.*

What environmental conditions should favor lysogeny rather than lysis?

On old lesson:

A bird in the hand is worth two in the bush.

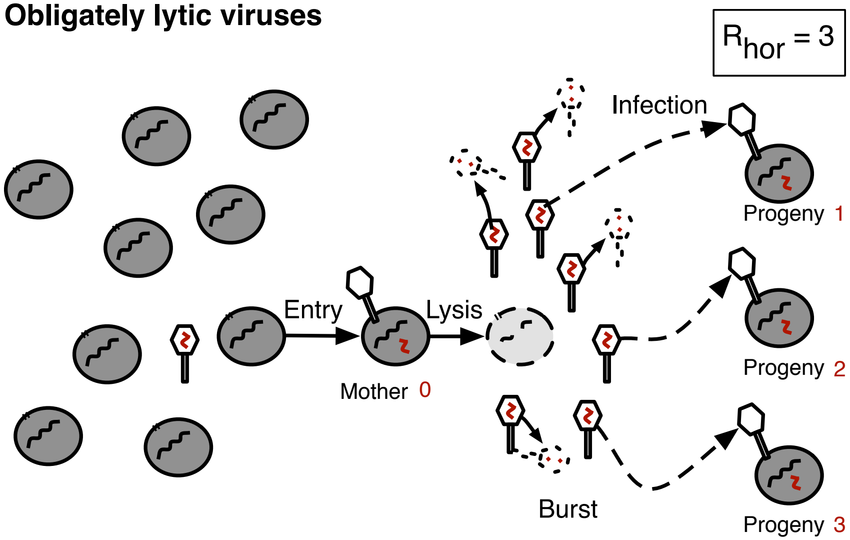
A new puzzle:

*A virus in the cell is worth **N** in the bloom.*

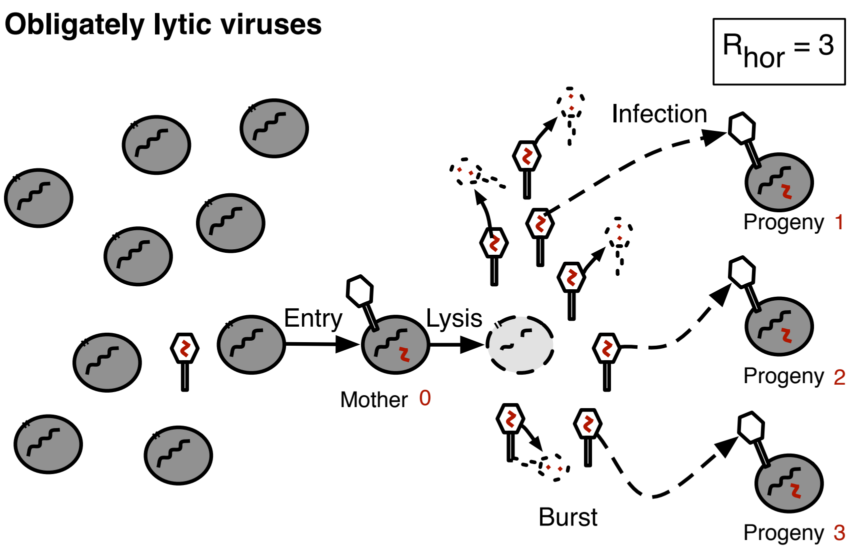
But, what is ***N***?

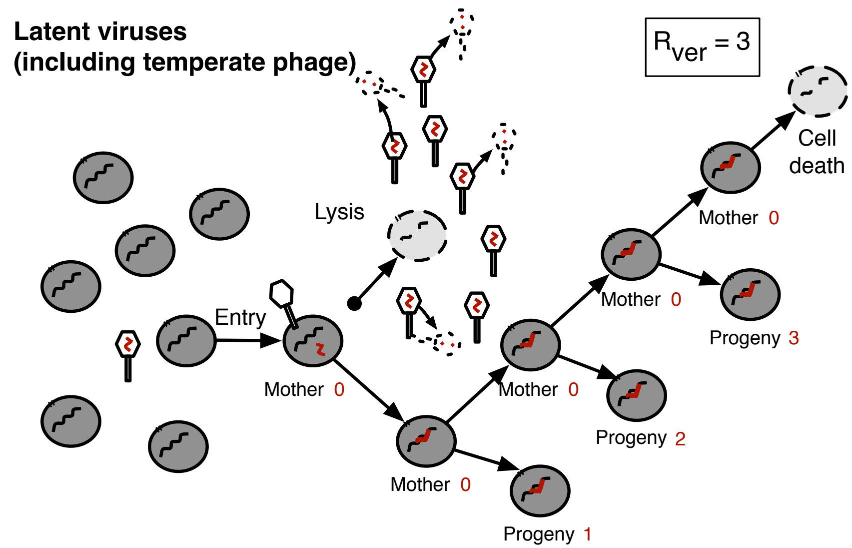
Viral proliferation at the individual level for *lytic strategies*

Obligately lytic viruses

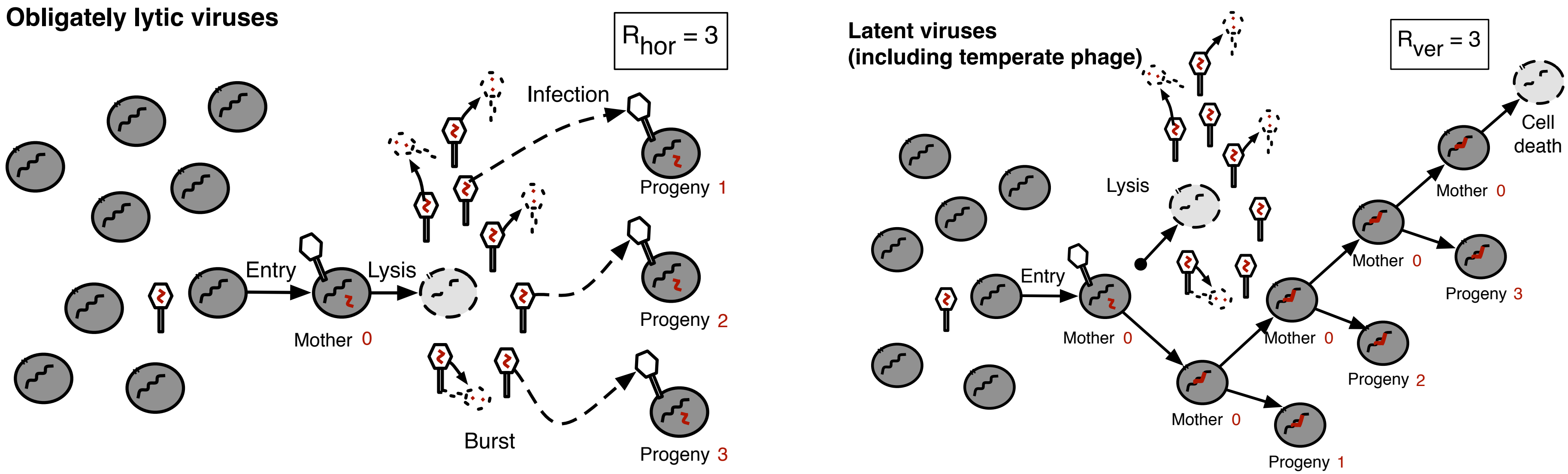


Viral proliferation at the individual level for *lytic strategies* and *latent strategies*





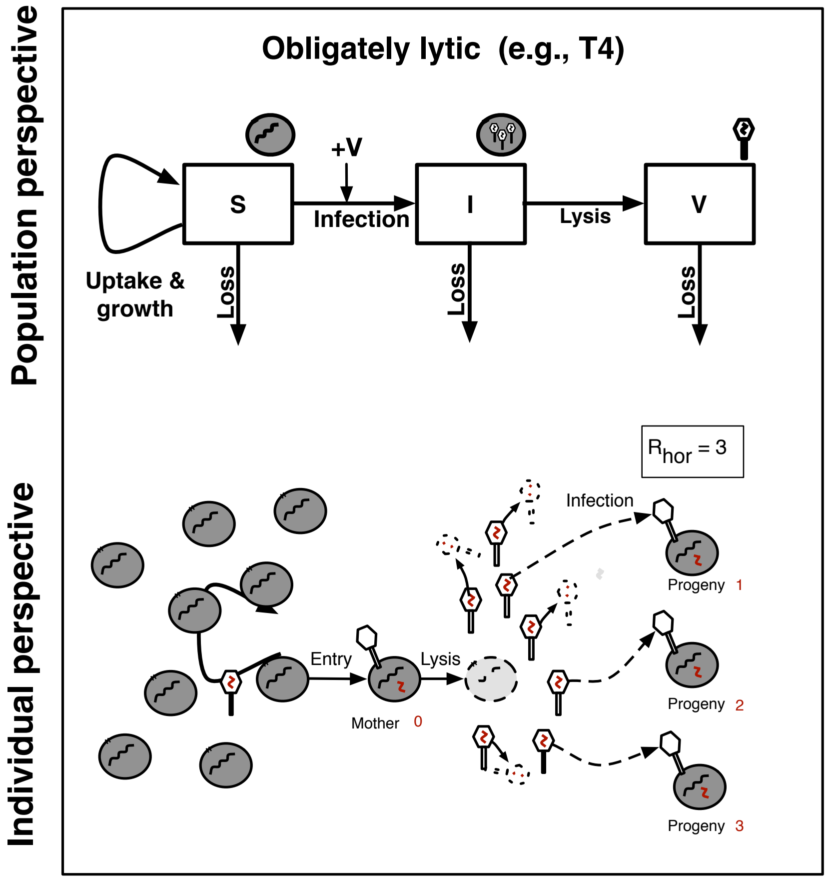
Viral proliferation at the individual level for *lytic strategies* and *latent strategies*



Two vastly different strategies can lead to the same 'fitness' at the individual level.

How does this depend on cell densities?

Population dynamics of lytic viruses

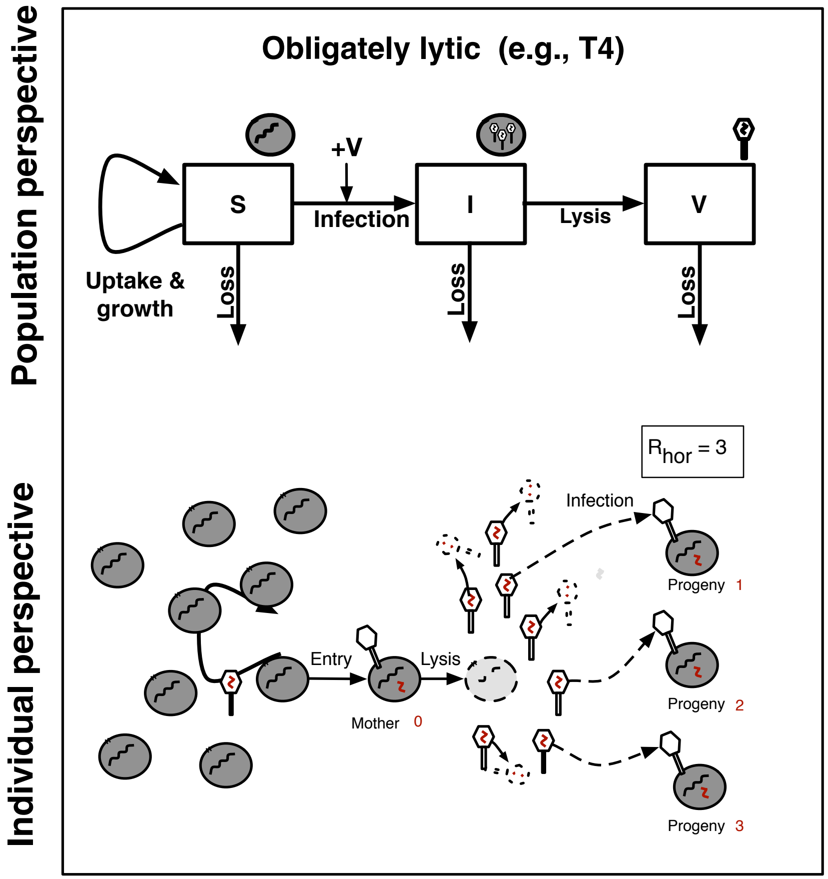


$$\frac{\mathrm{d}S}{\mathrm{d}t} = \overbrace{bS\,(1 - N/K)}^{\text{logistic growth}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{dS}^{\text{cell death}}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \overbrace{\phi SV}^{\text{infection}} - \overbrace{\eta I}^{\text{lysis}} - \overbrace{d' I}^{\text{cell death}}$$

$$\frac{\mathrm{d}V}{\mathrm{d}t} = \overbrace{\beta\eta I}^{\text{lysis}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{mV}^{\text{viral decay}}$$

Population dynamics of lytic viruses



$$\frac{dS}{dt} = \overbrace{bS\,(1 - N/K)}^{\text{logistic growth}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{dS}^{\text{cell death}}$$

$$\frac{dI}{dt} = \overbrace{\phi SV}^{\text{infection}} - \overbrace{\eta I}^{\text{lysis}} - \overbrace{d' I}^{\text{cell death}}$$

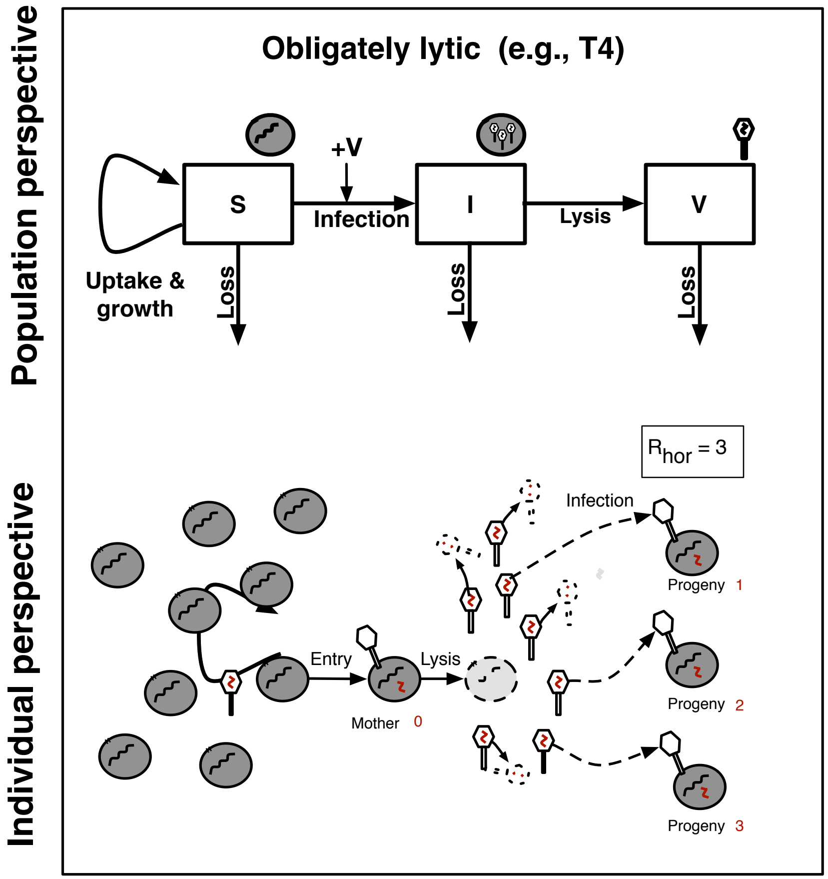
$$\frac{dV}{dt} = \boxed{\overbrace{\beta\eta I}^{\text{lysis}}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{mV}^{\text{viral decay}}$$

Viruses increase in population, within infected cells given exclusively <u>horizontal transmission</u> when

$$\mathcal{R}_{hor} = \beta\left(\frac{\phi S^*}{\phi S^* + m}\right)\left(\frac{\eta}{\eta + d'}\right)$$

is greater than 1

Population dynamics of lytic viruses



$$\frac{\mathrm{d}S}{\mathrm{d}t} = \overbrace{bS\,(1 - N/K)}^{\text{logistic growth}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{dS}^{\text{cell death}}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \overbrace{\phi SV}^{\text{infection}} - \overbrace{\eta I}^{\text{lysis}} - \overbrace{d' I}^{\text{cell death}}$$

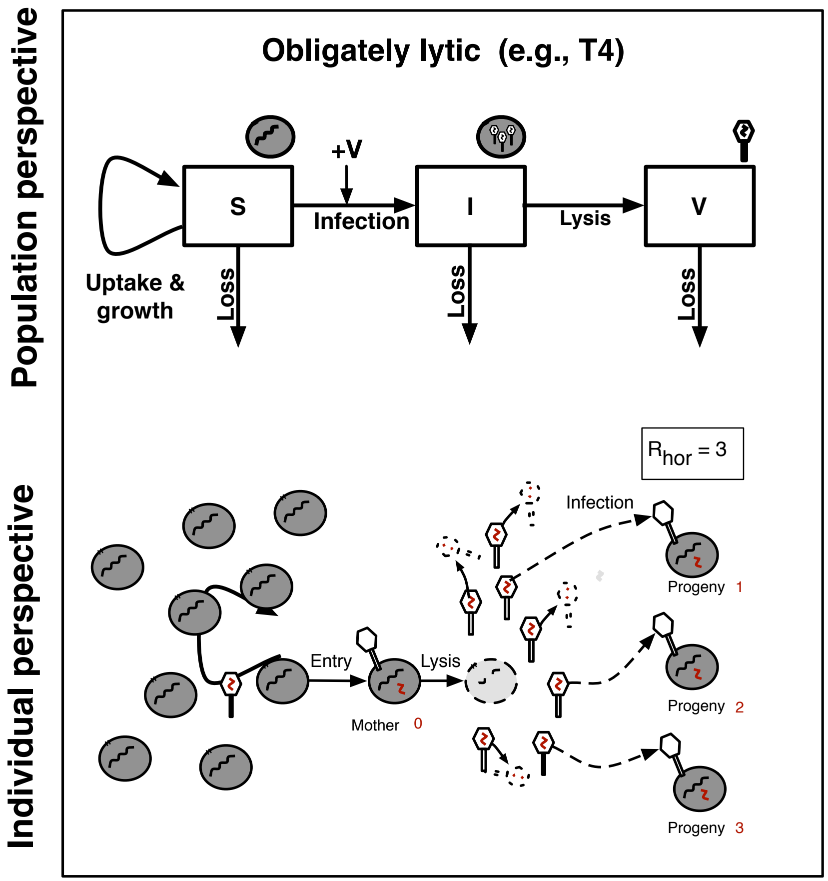
$$\frac{\mathrm{d}V}{\mathrm{d}t} = \boxed{\overbrace{\beta\eta I}^{\text{lysis}}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{mV}^{\text{viral decay}}$$

Viruses increase in population, within infected cells given exclusively <u>horizontal transmission</u> when

$$\mathcal{R}_{hor} = \begin{matrix}\textbf{Burst}\\\textbf{size}\end{matrix} \left(\begin{matrix}\textbf{Probability of}\\\textbf{viral adsorption}\\\textbf{to host}\\\textbf{before decay}\end{matrix}\right) \left(\begin{matrix}\textbf{Probability}\\\textbf{of lysis}\\\textbf{before}\\\textbf{washout}\end{matrix}\right)$$

is greater than 1

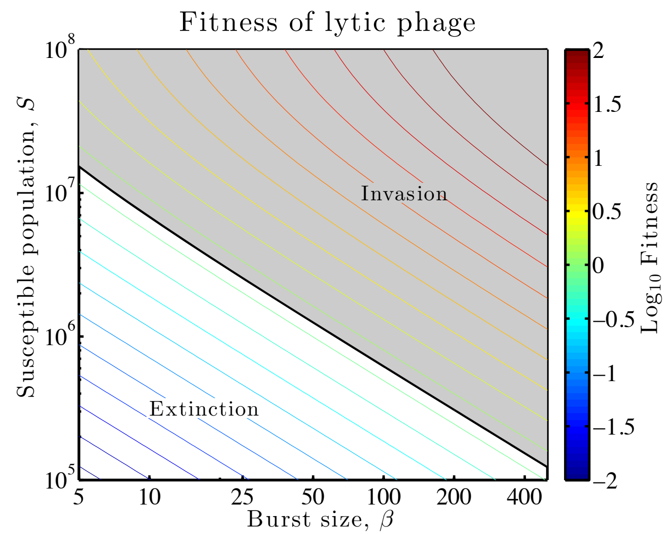
Population dynamics of lytic viruses



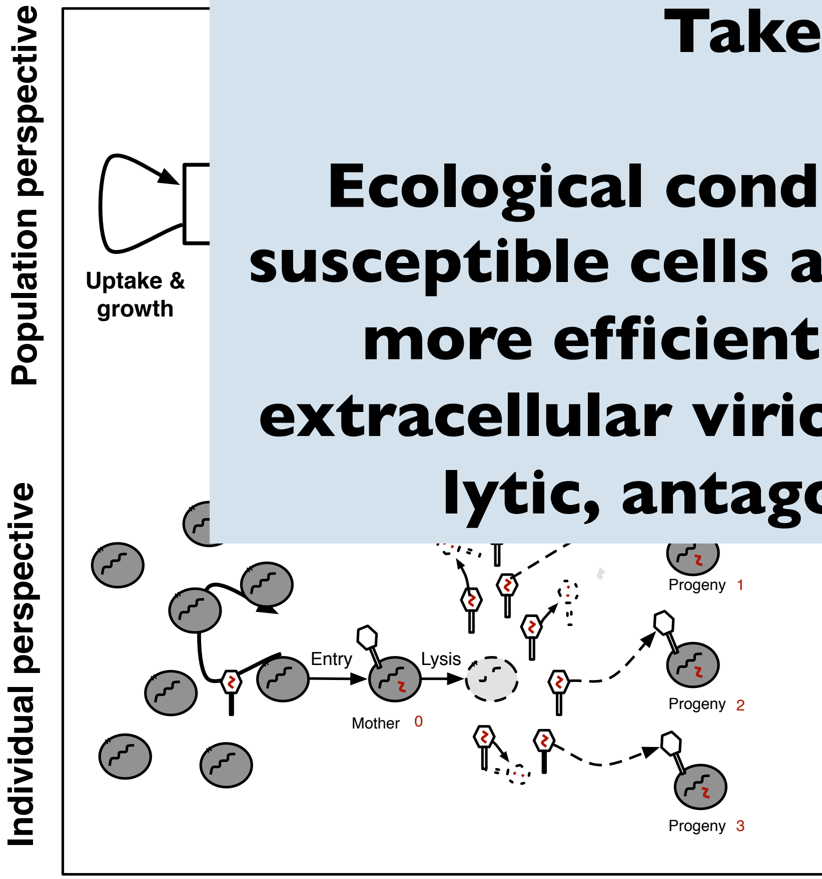
$$\frac{dS}{dt} = \overbrace{bS\left(1 - N/K\right)}^{\text{logistic growth}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{dS}^{\text{cell death}}$$

$$\frac{dI}{dt} = \overbrace{\phi SV}^{\text{infection}} - \overbrace{\eta I}^{\text{lysis}} - \overbrace{d' I}^{\text{cell death}}$$

$$\frac{dV}{dt} = \overbrace{\beta \eta I}^{\text{lysis}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{mV}^{\text{viral decay}}$$

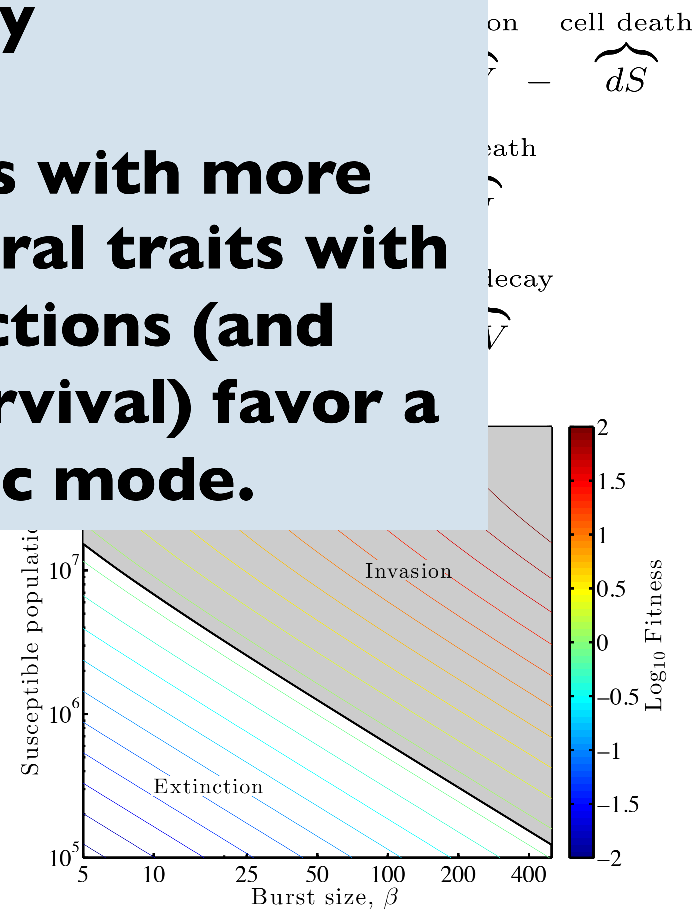


Population dynamics of lytic viruses

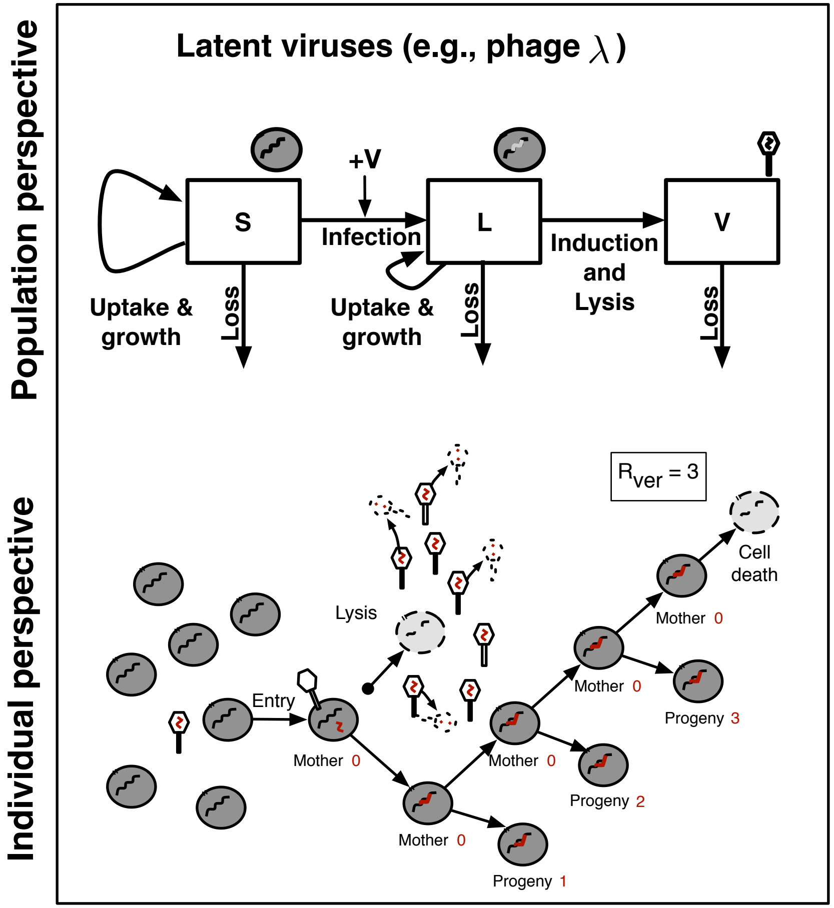


Take-away

Ecological conditions with more susceptible cells and viral traits with more efficient infections (and extracellular virion survival) favor a lytic, antagonistic mode.



Population dynamics of latent viruses

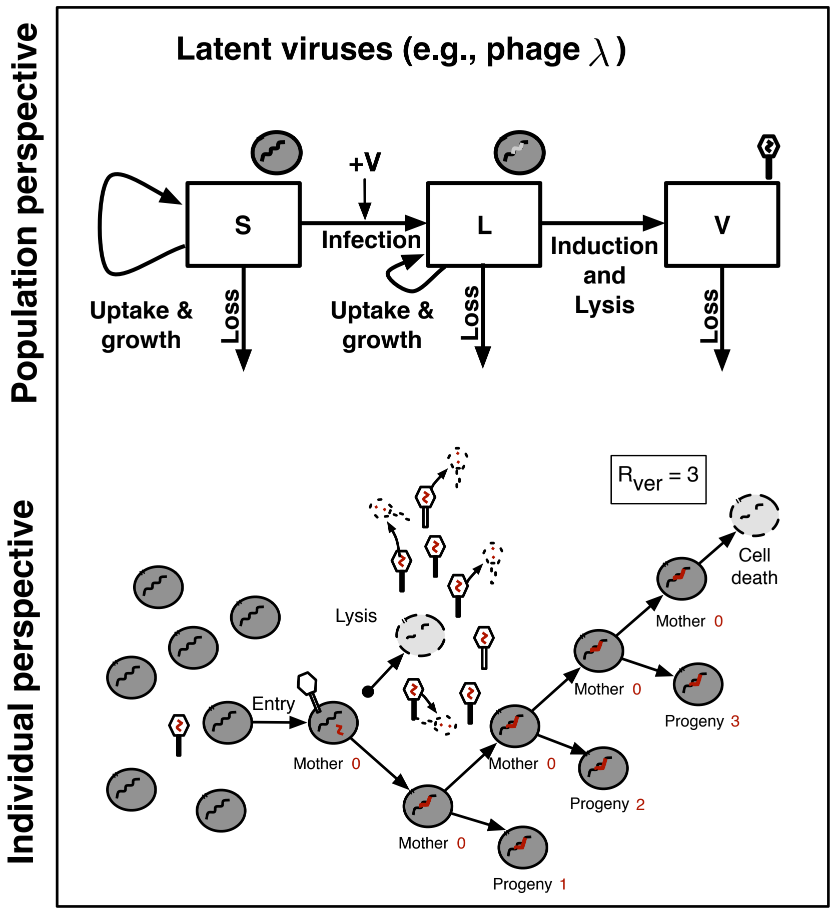


$$\frac{dS}{dt} = \overbrace{bS\,(1 - N/K)}^{\text{logistic growth}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{dS}^{\text{cell death}}$$

$$\frac{dL}{dt} = \overbrace{qb'L\,(1 - N/K)}^{\text{lysogen growth}} + \overbrace{\phi SV}^{\text{infection}} - \overbrace{p\eta L}^{\text{lysis}} - \overbrace{d'L}^{\text{cell death}}$$

$$\frac{dV}{dt} = \overbrace{\beta p\eta L}^{\text{lysis}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{mV}^{\text{viral decay}}$$

Population dynamics of latent viruses



$$\frac{dS}{dt} = \overbrace{bS\left(1 - N/K\right)}^{\text{logistic growth}} - \overbrace{\phi S V}^{\text{infection}} - \overbrace{dS}^{\text{cell death}}$$

$$\frac{dL}{dt} = \boxed{\overbrace{qb'L\left(1 - N/K\right)}^{\text{lysogen growth}}} + \overbrace{\phi S V}^{\text{infection}} - \overbrace{p\eta L}^{\text{lysis}} - \overbrace{d'L}^{\text{cell death}}$$

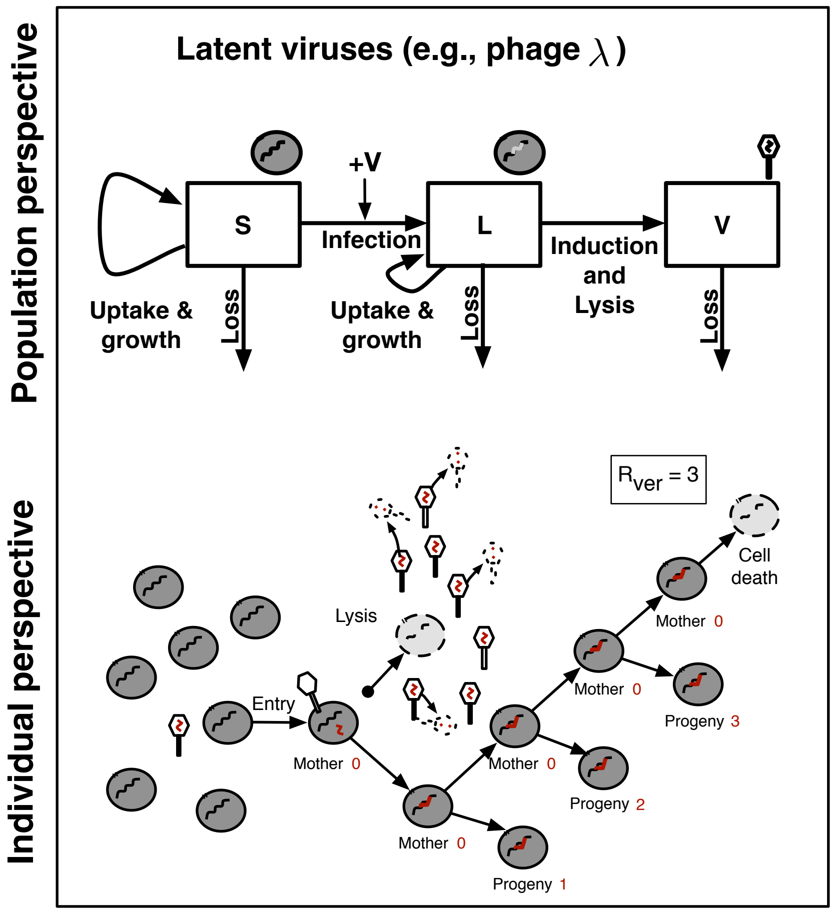
$$\frac{dV}{dt} = \overbrace{\beta p \eta L}^{\text{lysis}} - \overbrace{\phi S V}^{\text{infection}} - \overbrace{mV}^{\text{viral decay}}$$

Viruses increase in population, within infected cells given exclusively <u>vertical transmission</u> when

$$\mathcal{R}_{ver} = \frac{b'\left(1 - \frac{S^*}{K}\right)}{d'}$$

is greater than 1

Population dynamics of latent viruses



$$\frac{\mathrm{d}S}{\mathrm{d}t} = \overbrace{bS\left(1 - N/K\right)}^{\text{logistic growth}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{dS}^{\text{cell death}}$$

$$\frac{\mathrm{d}L}{\mathrm{d}t} = \boxed{\overbrace{qb'L\left(1 - N/K\right)}^{\text{lysogen growth}}} + \overbrace{\phi SV}^{\text{infection}} - \overbrace{p\eta L}^{\text{lysis}} - \overbrace{d'L}^{\text{cell death}}$$

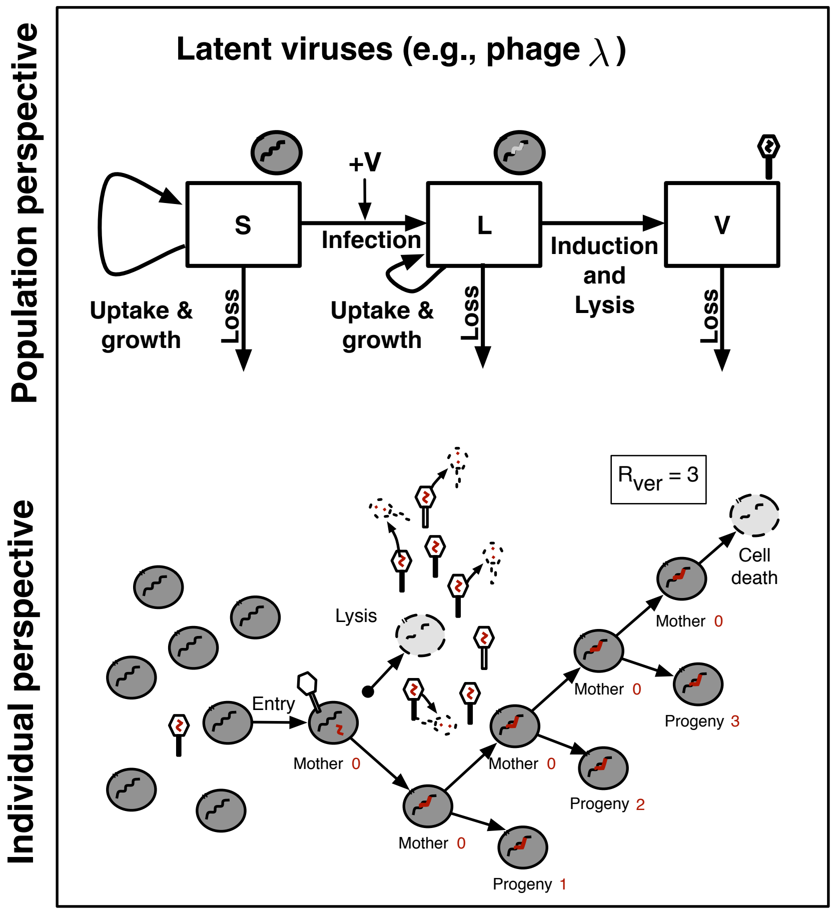
$$\frac{\mathrm{d}V}{\mathrm{d}t} = \overbrace{\beta p\eta L}^{\text{lysis}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{mV}^{\text{viral decay}}$$

Viruses increase in population, within infected cells given exclusively <u>vertical transmission</u> when

$$\mathcal{R}_{ver} = \text{Division rate} \times \text{Cell lifespan}$$

is greater than 1

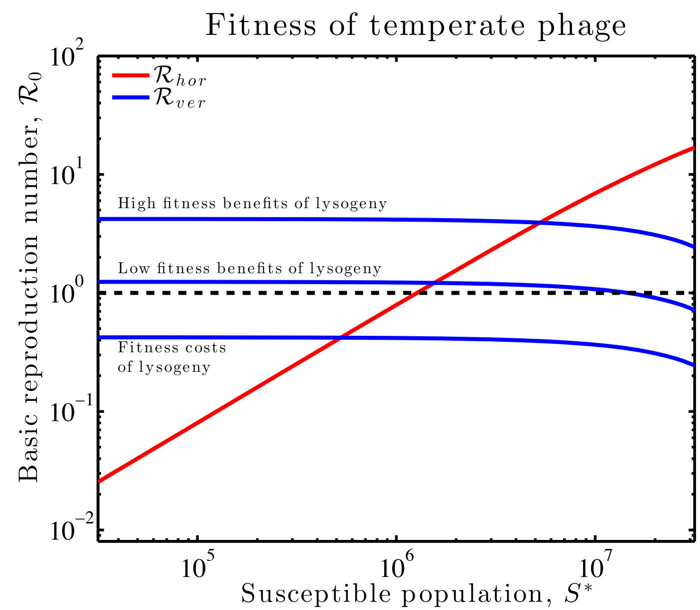
Population dynamics of latent viruses



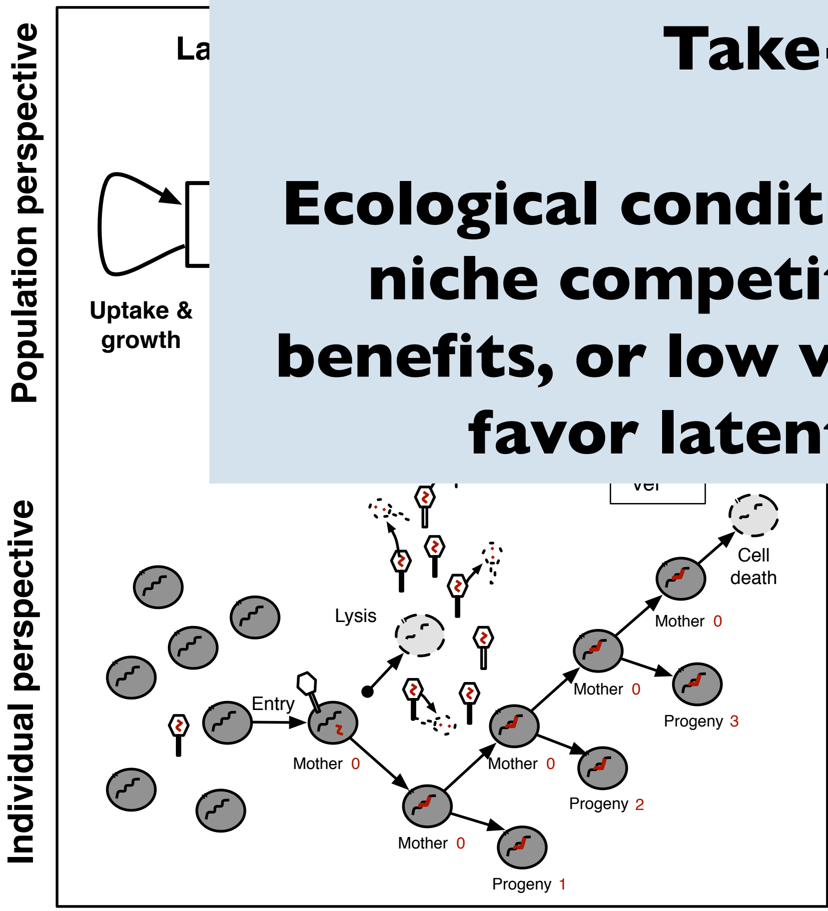
$$\frac{\mathrm{d}S}{\mathrm{d}t} = \overbrace{bS\left(1 - N/K\right)}^{\text{logistic growth}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{dS}^{\text{cell death}}$$

$$\frac{\mathrm{d}L}{\mathrm{d}t} = \overbrace{qb'L\left(1 - N/K\right)}^{\text{lysogen growth}} + \overbrace{\phi SV}^{\text{infection}} - \overbrace{p\eta L}^{\text{lysis}} - \overbrace{d'L}^{\text{cell death}}$$

$$\frac{\mathrm{d}V}{\mathrm{d}t} = \overbrace{\beta p\eta L}^{\text{lysis}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{mV}^{\text{viral decay}}$$

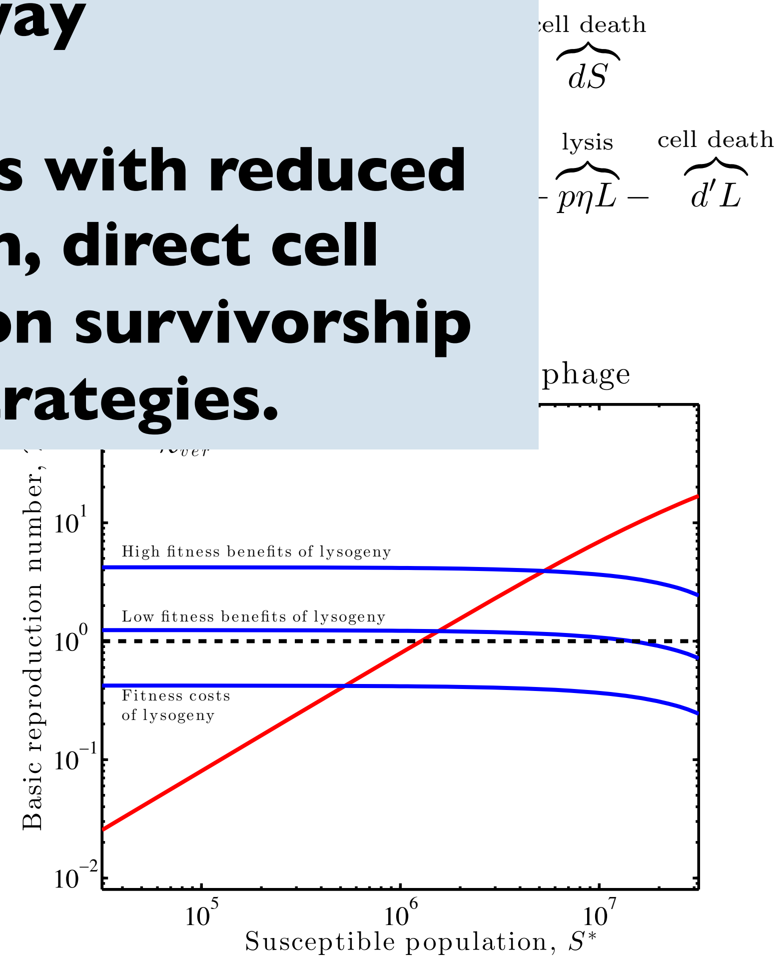


Population dynamics of latent viruses

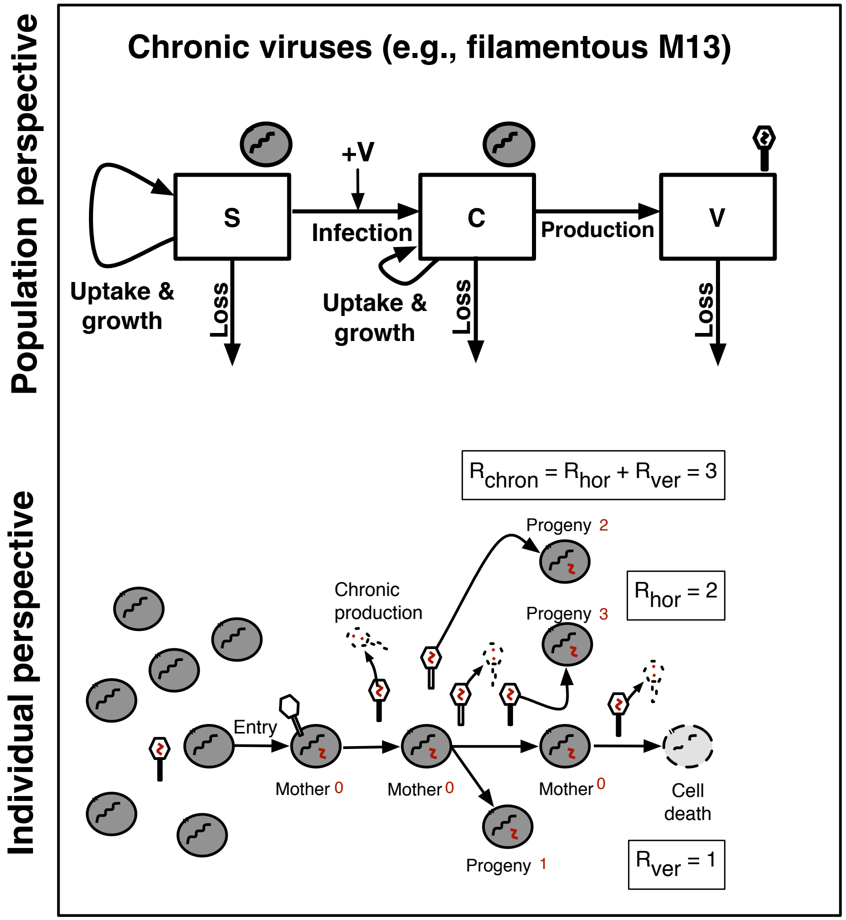


Take-away

Ecological conditions with reduced niche competition, direct cell benefits, or low virion survivorship favor latent strategies.



Population dynamics of chronic viruses

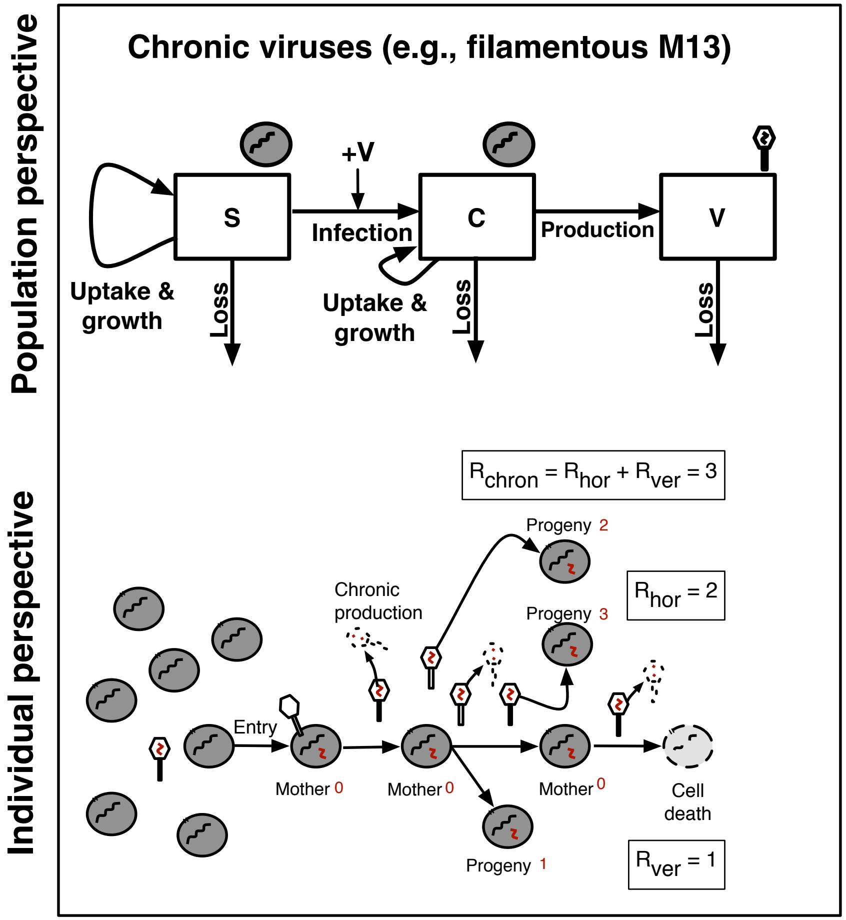


$$\frac{\mathrm{d}S}{\mathrm{d}t} = \overbrace{bS\,(1 - N/K)}^{\text{logistic growth}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{dS}^{\text{cell death}}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \overbrace{b'I\,(1 - N/K)}^{\text{logistic growth}} + \overbrace{\phi SV}^{\text{infection}} - \overbrace{d'I}^{\text{cell death}}$$

$$\frac{\mathrm{d}V}{\mathrm{d}t} = \overbrace{\alpha I}^{\text{virion production}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{mV}^{\text{viral decay}}$$

Population dynamics of chronic viruses



$$\frac{\mathrm{d}S}{\mathrm{d}t} = \overbrace{bS\left(1 - N/K\right)}^{\text{logistic growth}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{dS}^{\text{cell death}}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \boxed{\overbrace{b'I\left(1 - N/K\right)}^{\text{logistic growth}}} + \overbrace{\phi SV}^{\text{infection}} - \overbrace{d'I}^{\text{cell death}}$$

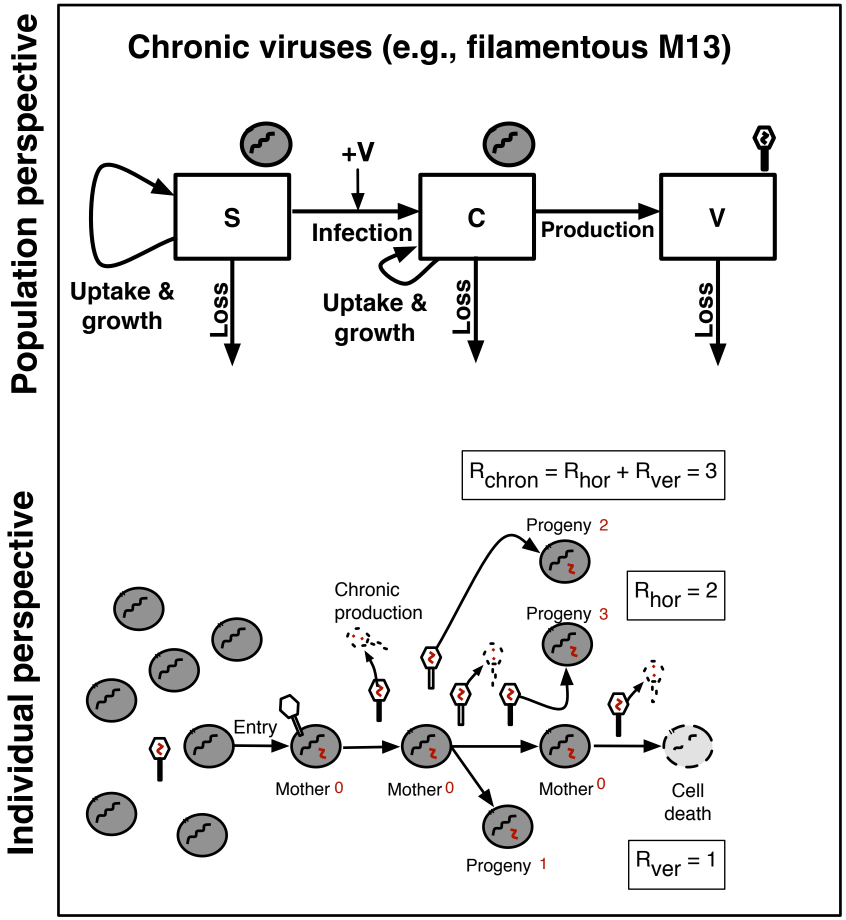
$$\frac{\mathrm{d}V}{\mathrm{d}t} = \boxed{\overbrace{\alpha I}^{\text{virion production}}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{mV}^{\text{viral decay}}$$

Viruses increase in population, within infected cells given <u>mixed transmission</u> when

$$\mathcal{R}_{chron} \equiv \overbrace{\frac{\alpha}{d'}\left(\frac{\phi S^*}{\phi S^* + m}\right)}^{\text{horizontal}} + \overbrace{\frac{b'(1 - S^*/K)}{d'}}^{\text{vertical}}$$

is greater than 1

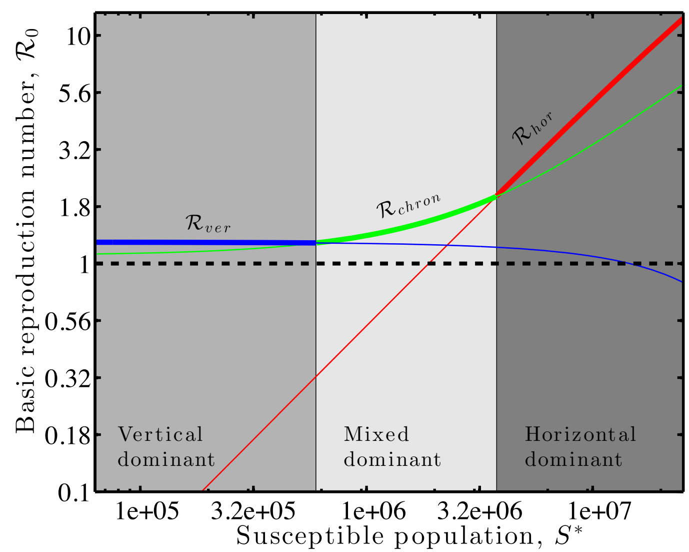
Population dynamics of chronic viruses



$$\frac{dS}{dt} = \overbrace{bS\,(1 - N/K)}^{\text{logistic growth}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{dS}^{\text{cell death}}$$

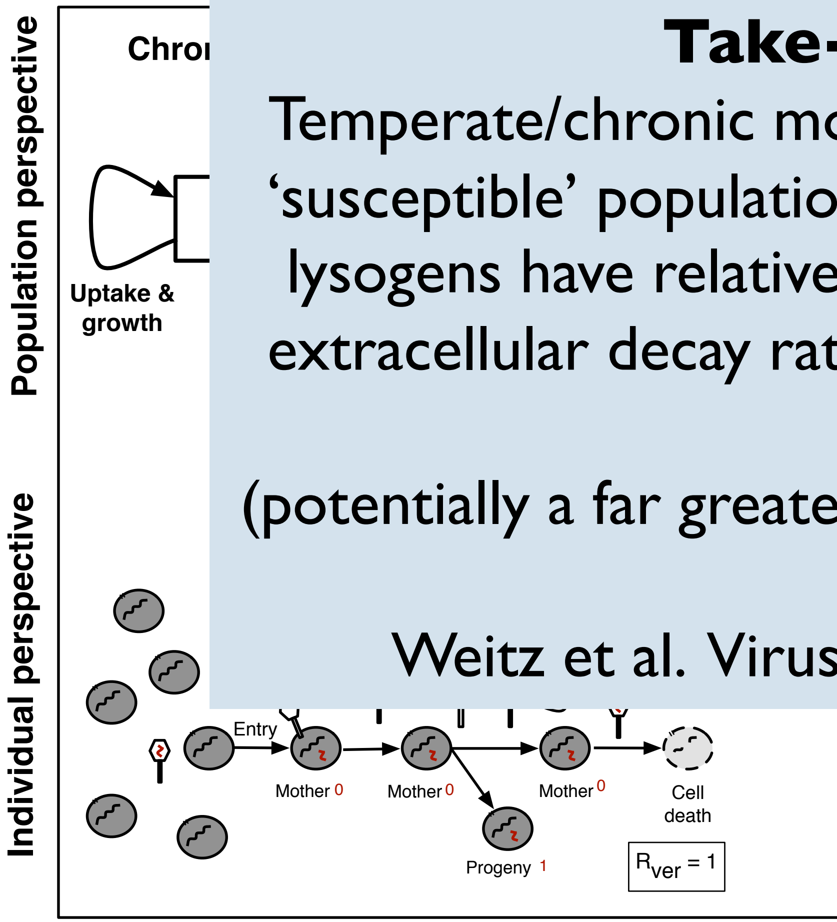
$$\frac{dI}{dt} = \overbrace{b'I\,(1 - N/K)}^{\text{logistic growth}} + \overbrace{\phi SV}^{\text{infection}} - \overbrace{d'I}^{\text{cell death}}$$

$$\frac{dV}{dt} = \overbrace{\alpha I}^{\text{virion production}} - \overbrace{\phi SV}^{\text{infection}} - \overbrace{mV}^{\text{viral decay}}$$



Weitz et al. "Viral fitness across a continuum from lysis to latency". Virus Evolution, 2019

Population dynamics of chronic viruses

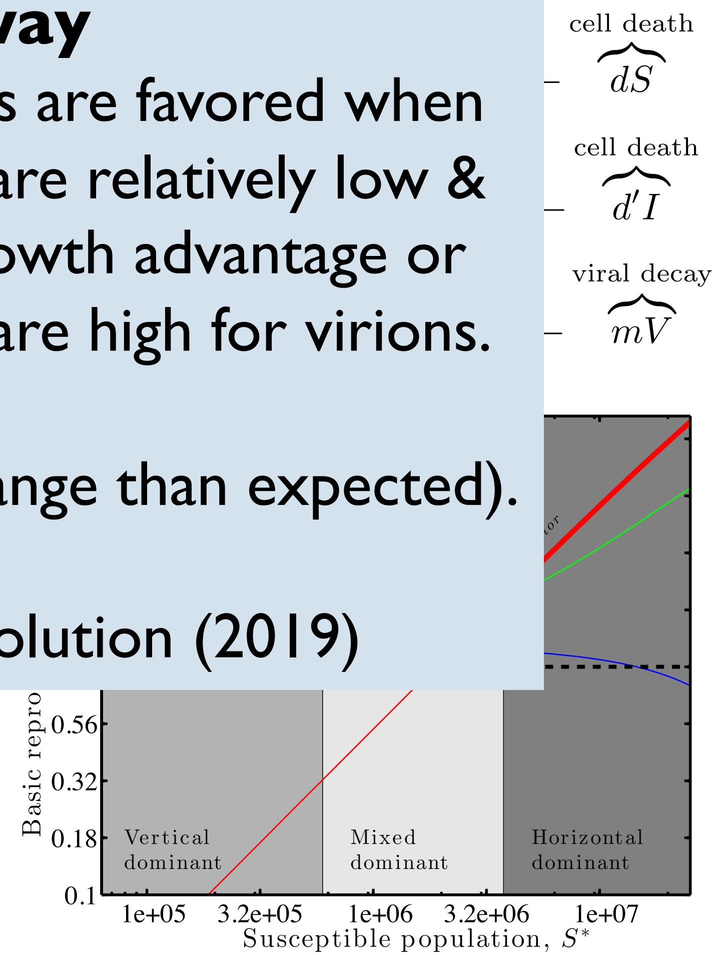


Take-away

Temperate/chronic modes are favored when 'susceptible' populations are relatively low & lysogens have relative growth advantage or extracellular decay rates are high for virions.

(potentially a far greater range than expected).

Weitz et al. Virus Evolution (2019)

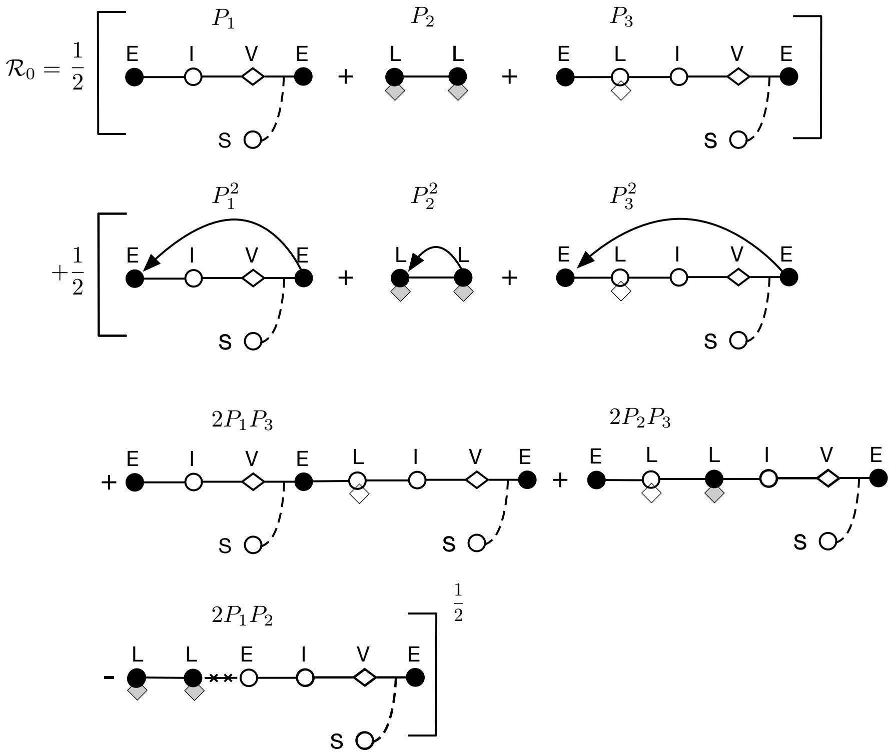


Weitz et al. "Viral fitness across a continuum from lysis to latency". Virus Evolution, 2019

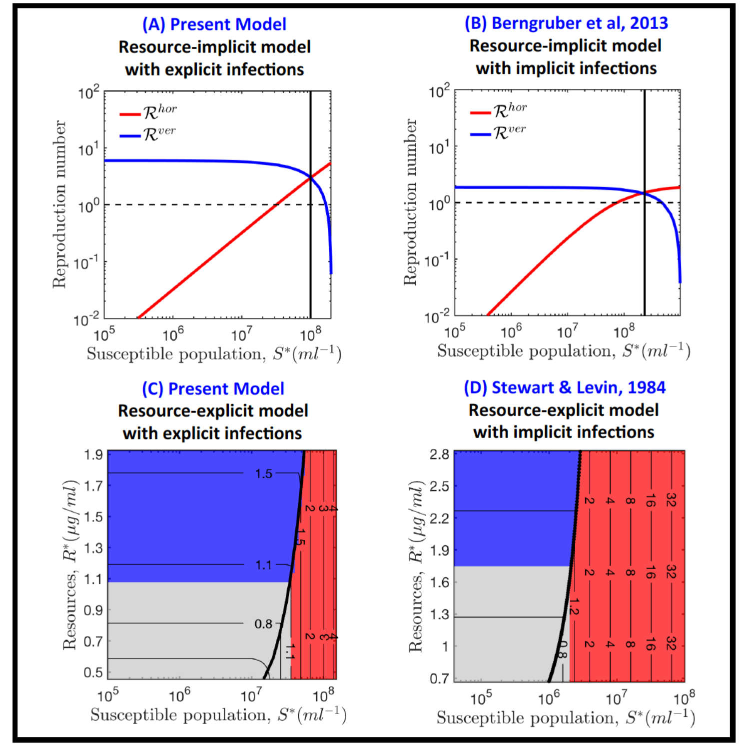
What environmental conditions should favor lysogeny rather than lysis?

Answering this question requires a unified metric, e.g.,:

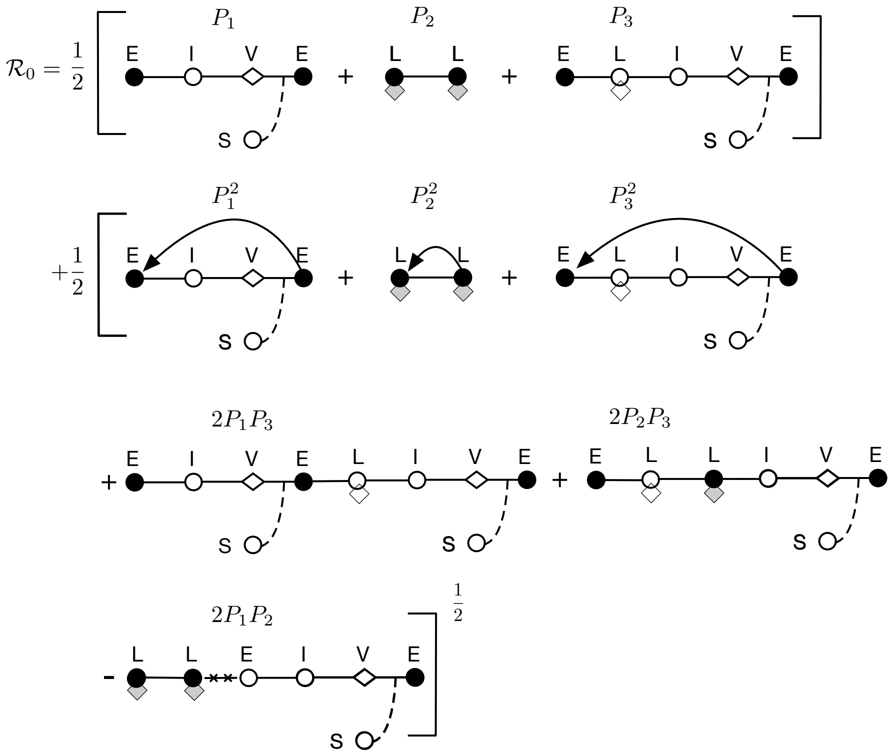
$\mathcal{R}_0$: *the average number of new infected cells produced by a single (typical) infected cell and its progeny virions in an otherwise susceptible population.*

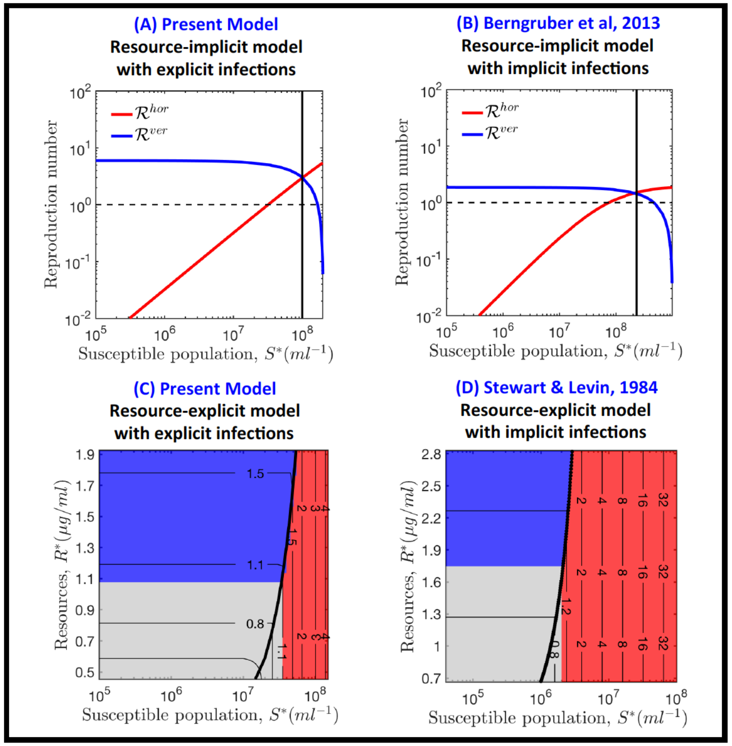


$\mathcal{R}_0 = \frac{1}{2}$
P_1
P_2
P_3
P_1^2
P_2^2
P_3^2
$+\frac{1}{2}$
$2P_1P_3$
$2P_2P_3$
$2P_1P_2$
$\frac{1}{2}$
E
I
V
L
S



(A) Present Model
Resource-implicit model
with explicit infections
(B) Berngruber et al, 2013
Resource-implicit model
with implicit infections
$\mathcal{R}^{hor}$
$\mathcal{R}^{ver}$
Reproduction number
Susceptible population, $S^*(ml^{-1})$
(C) Present Model
Resource-explicit model
with explicit infections
(D) Stewart & Levin, 1984
Resource-explicit model
with implicit infections
Resources, $R^*(\mu g/ml)$



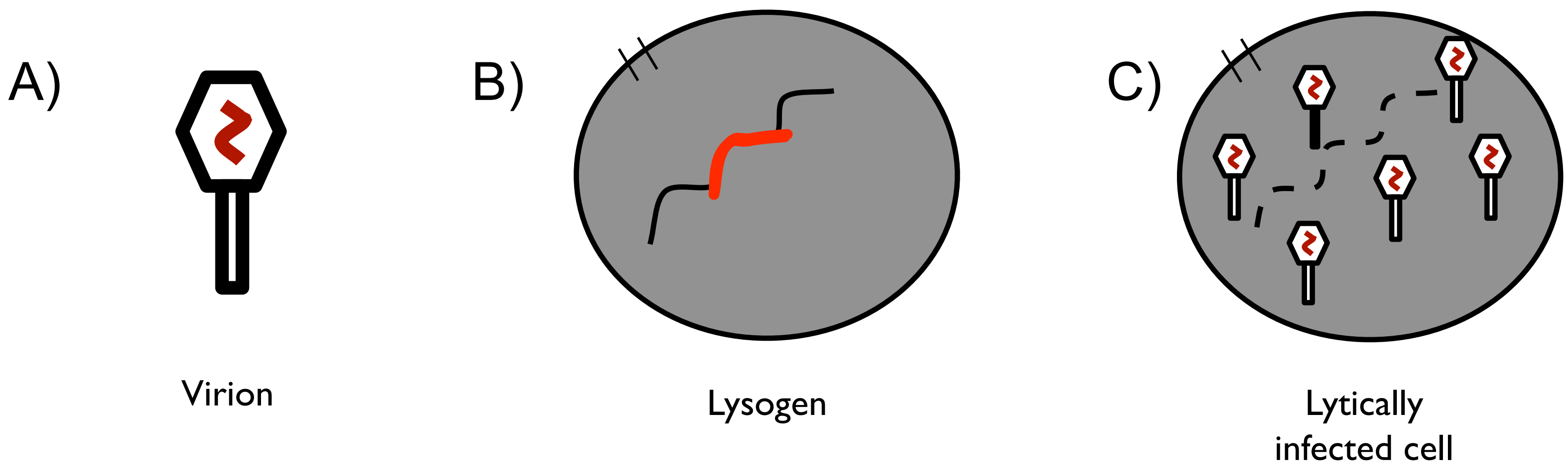


Take-away

Loop-based approach decomposes viral fitness into lytic, lysogenic, and lyso-lytic loops, transcends model details & reveals generic mechanisms for the benefits of latency.

Li, Cortez & Weitz, biorxiv: 709758

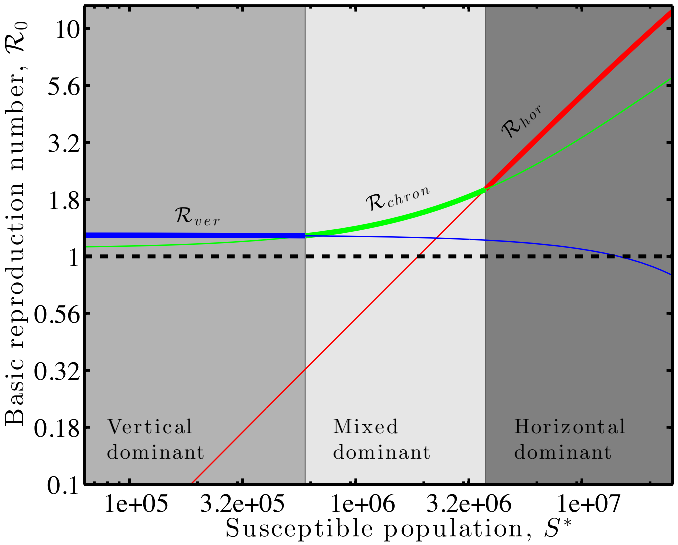
Q: What is a Virus?

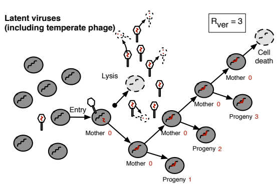


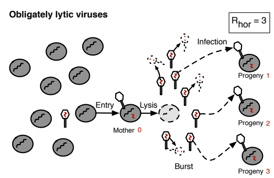
D: All of the above.

Viral fitness in the environment depends on measuring the present and long-term value of infection across the entire viral life cycle, whether inside or outside hosts.

A new challenge for **theory, experiments, and field-work.**







More details:

Re-examination of the relationship between marine virus and microbial cell abundances. Wigington et al., Nat. Micro 2016

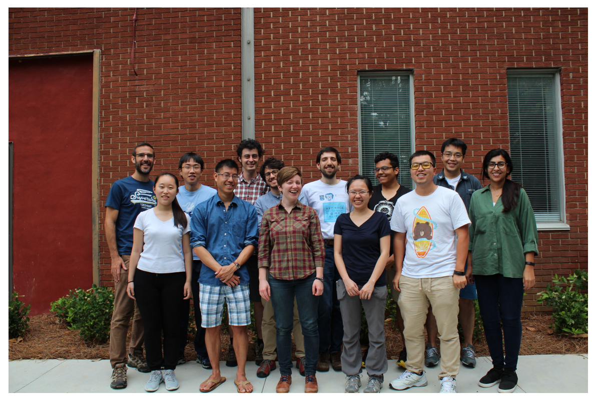
Lysis, lysogeny, and virus-microbe ratios, Weitz et al. Nature 2017

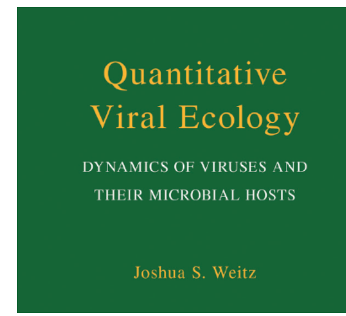
Heterogeneous viral strategies promote coexistence in virus-microbe systems, Gulbudak & Weitz, J. Theor. Biol. 2019;

Alrasheed, Jin, & Weitz, Caution in inferring viral strategies from abundance correlations in marine metagenomes. Nat. Comm, 2019

Viral invasion fitness across a continuum from lysis to latency, Weitz, Li, Gulbudak, Cortez, and Whitaker., Virus Evolution 2019

Why be temperate: a synthesis, Li, Cortez & Weitz, biorxiv & in review https://doi.org/10.1101/709758





PRINCETON UNIVERSITY PRESS

Acknowledgements

GT: Chad Wigington, Stephen Beckett, Guanlin Li, Hend Alrasheed, Rong Jin
Florida State: Michael Cortez
MSU: Mark Young
UIUC: Rachel Whitaker
UL-Lafayette: Hayriye Gulbudak

Thank you!

Follow us:

http://ecotheory.biology.gatech.edu (web)

@joshuasweitz & @weitz_group (twitter)

weitzgroup.github.io (code, data, and information)

biorxiv.org & arxiv.org (preprints)