KITP
Eco-evolutionary Dynamics
August 10, 2017

Support:
NSF – Bio Oc; NSF – Physics of Living Systems, Simons Foundation “SCOPE”, Army Research Office, Georgia Tech

SPACE-TIME FRONTIERS OF MARINE VIRAL ECOLOGY

Joshua S. Weitz
School of Biological Sciences and School of Physics
Graduate Program in Quantitative Biosciences
Georgia Institute of Technology

Ashley Coenen
GT Physics

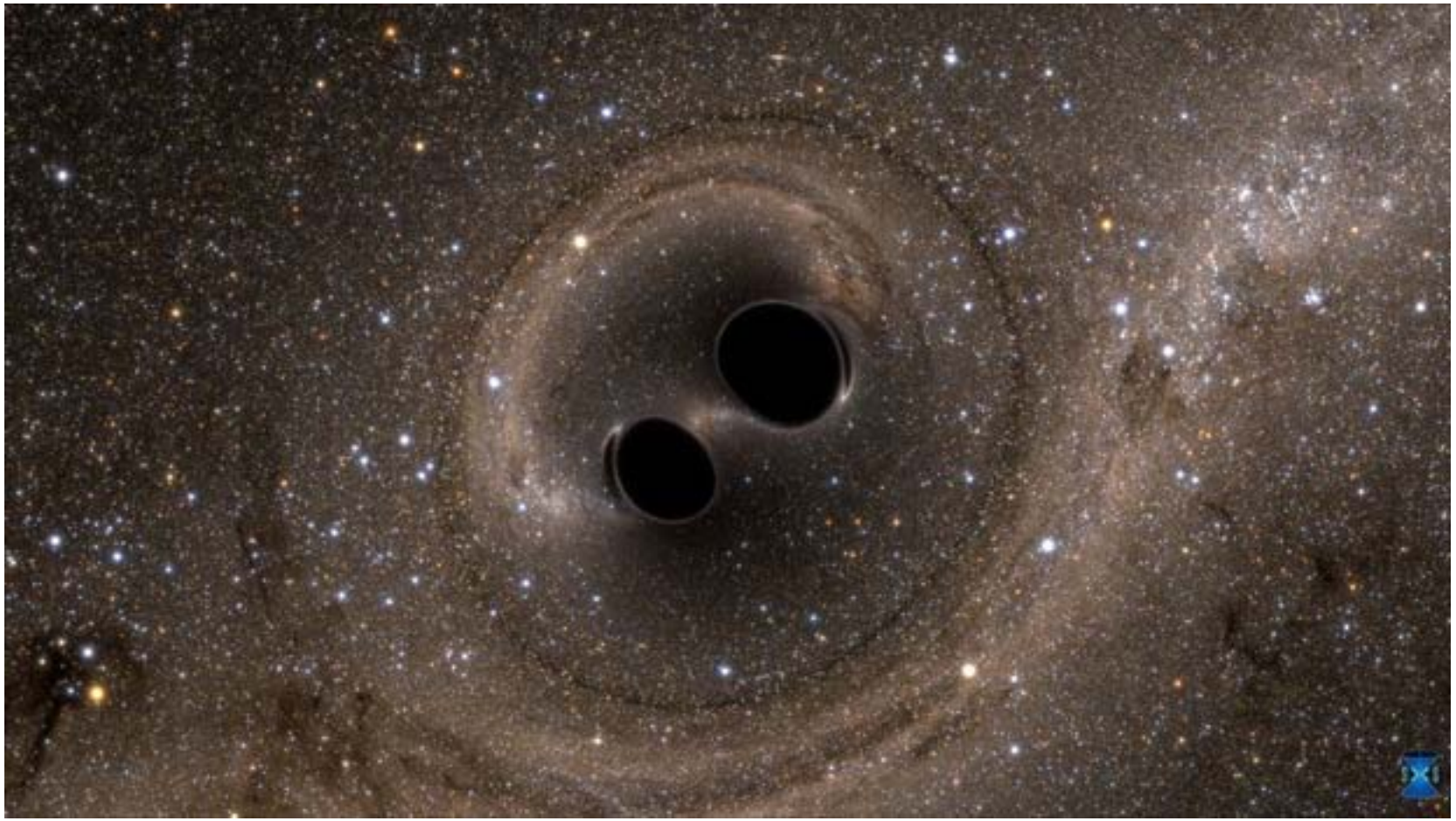
Dr. Luis Jover
GT Physics ‘16

Bradford Taylor
GT, Physics ‘16

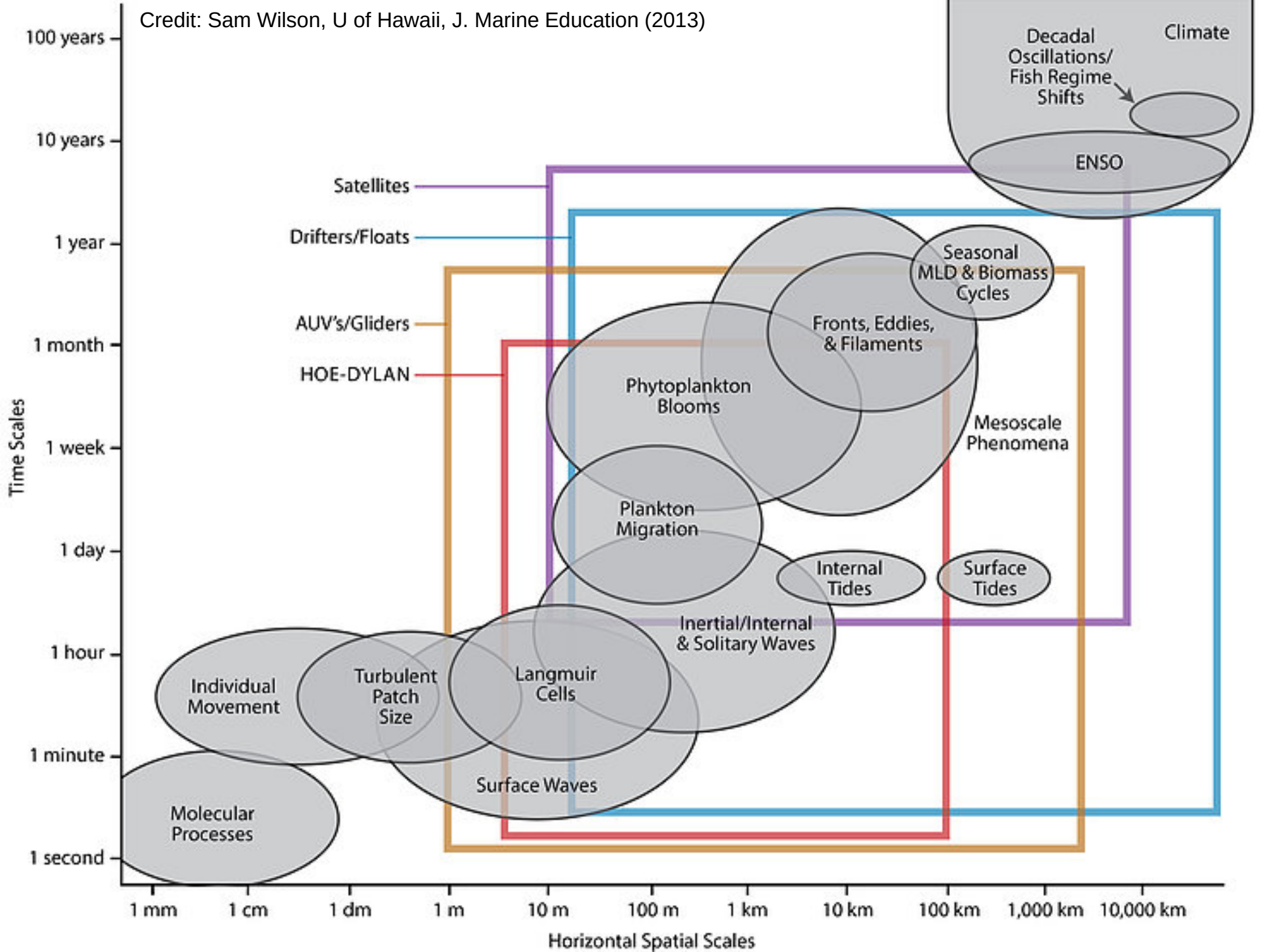
Charles Wigington
GT, Bioinformatics

Dr. Stephen Beckett
GT, Biol. Sci.

Joshua S. Weitz, Georgia Tech, School of Biological Sciences & Physics
Email: jsweitz@gatech.edu, Twitter: @joshuasweitz
Web: http://ecotheory.biology.gatech.edu

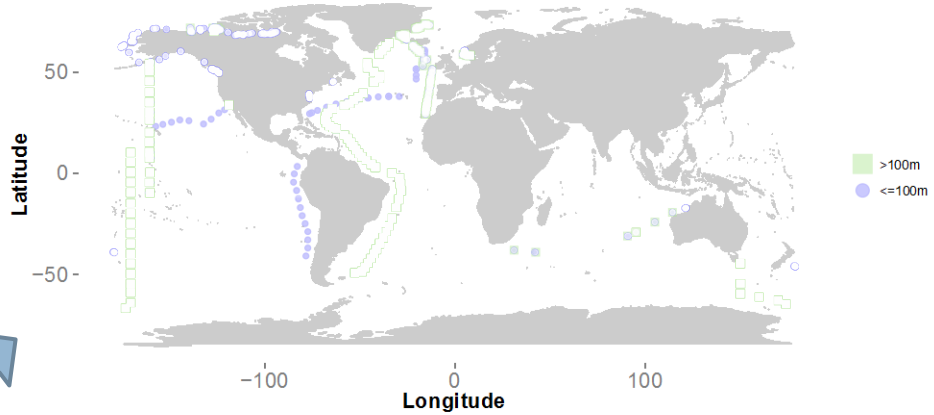


SXS, the Simulating eXtreme Spacetimes (SXS) project (http://www.black-holes.org)

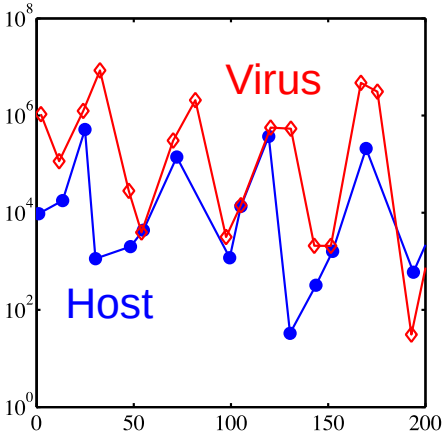

Credit: Sam Wilson, U of Hawaii, J. Marine Education (2013)
100 years
10 years
1 year
1 month
1 week
1 day
1 hour
1 minute
1 second
Time Scales
Climate
Decadal Oscillations/ Fish Regime Shifts
ENSO
Satellites
Drifters/Floats
AUV's/Gliders
HOE-DYLAN
Seasonal MLD & Biomass Cycles
Fronts, Eddies, & Filaments
Phytoplankton Blooms
Mesoscale Phenomena
Plankton Migration
Internal Tides
Surface Tides
Inertial/Internal & Solitary Waves
Individual Movement
Turbulent Patch Size
Langmuir Cells
Surface Waves
Molecular Processes
1 mm
1 cm
1 dm
1 m
10 m
100 m
1 km
10 km
100 km
1,000 km
10,000 km
Horizontal Spatial Scales

The Problem of Scales in Quantitative Viral Ecology:

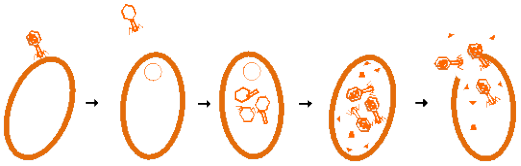
Linking Mechanism to Pattern



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



Infection and lysis leads to Lotka-Volterra like dynamics at the population scale…



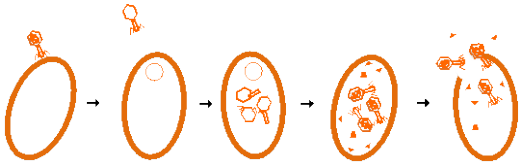
Virus-host interactions modify the fate of cells on time scales similar to division times…

See: "Quantitative Viral Ecology: Dynamics of Viruses and Their Microbial Hosts" (2015). J.S. Weitz,

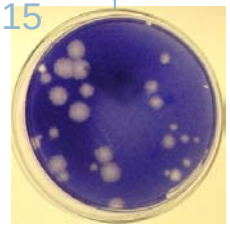
It wasn't always this way…

Frederick Twort

Félix d'Hérelle



1915

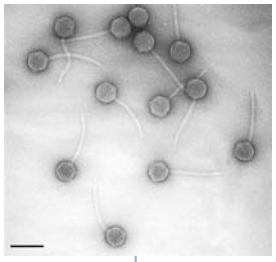


1925

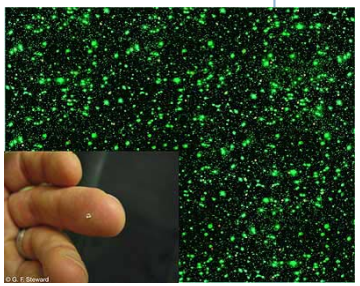
1946

1947

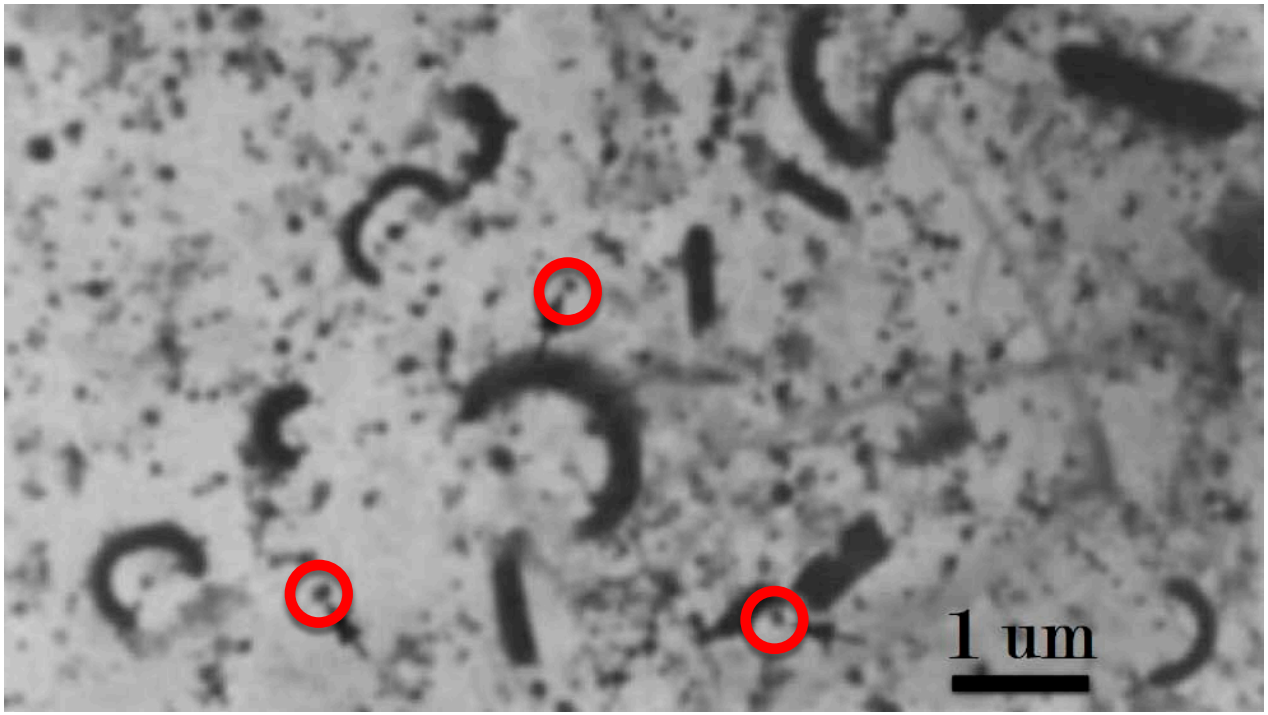
1979



1989



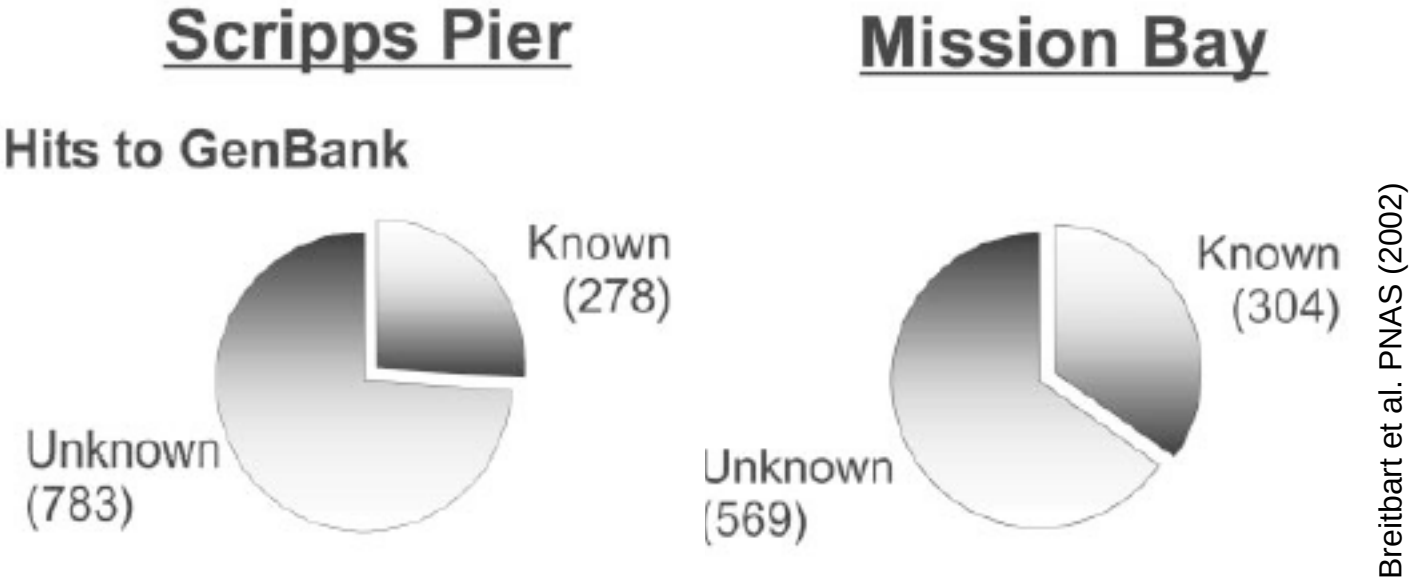
1989 - Numbers



Bergh et al., Nature 1989

“We have found up to 2.5 x 10^8 virus particles per ml in natural waters… 10^3-10^7 times higher than previous reports.”

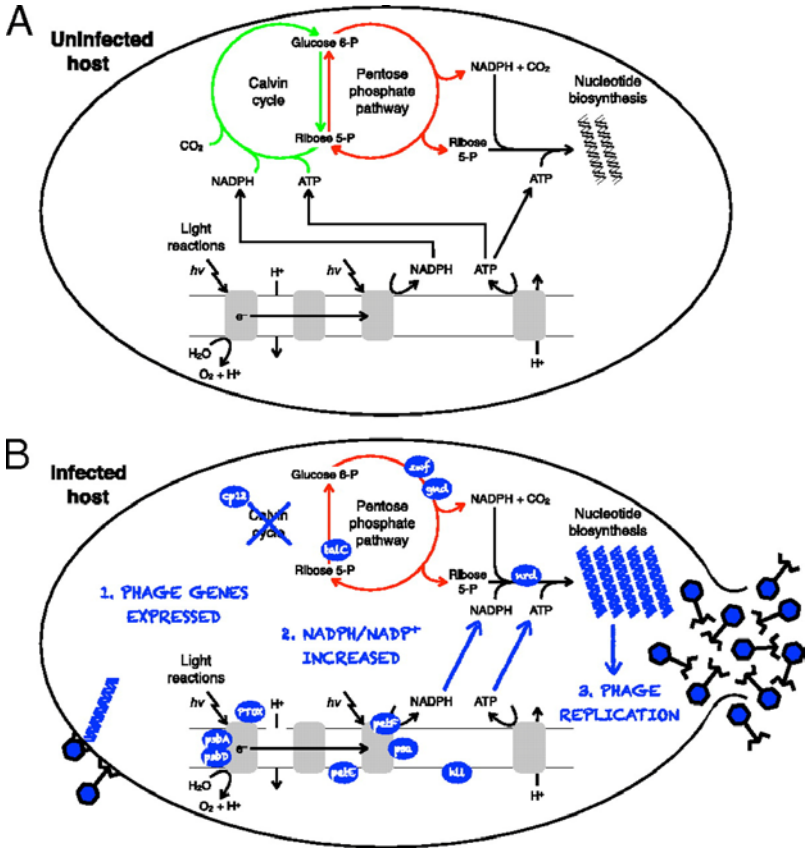
2002 - Diversity



Breitbart et al. PNAS (2002)

“We report a genomic analysis of two uncultured marine viral communities. Over 65% of the sequences were not significantly similar to previously reported sequences, suggesting that much of the diversity is previously uncharacterized.”

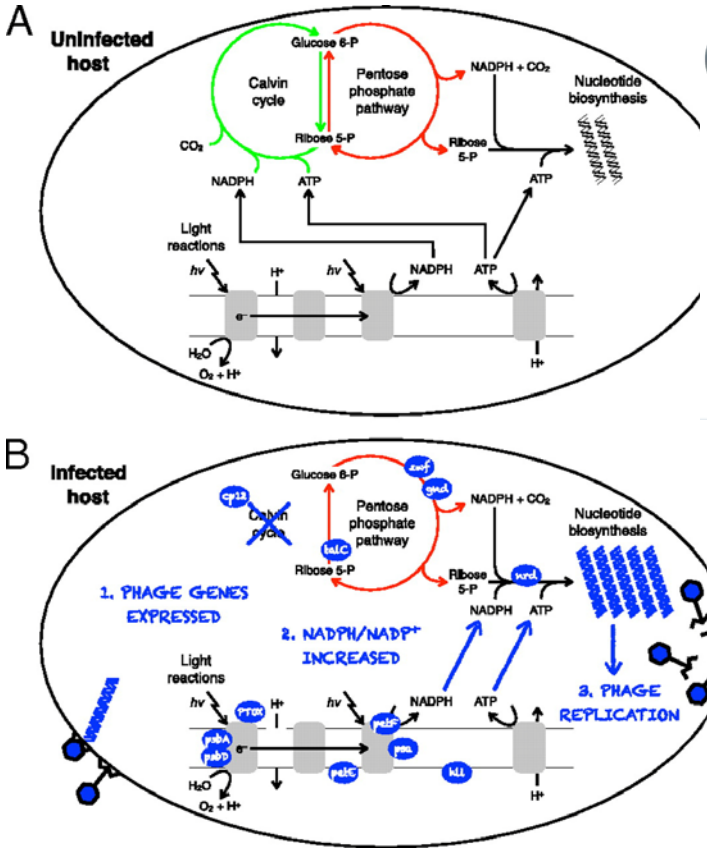
2000s -



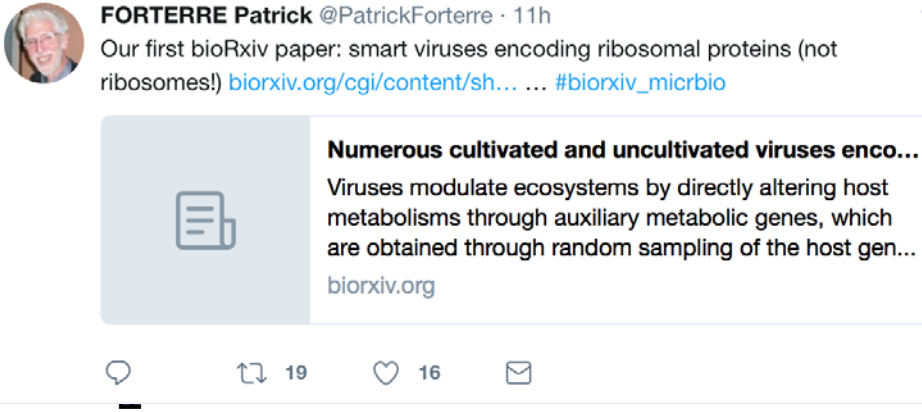
Luke R. Thompson et al. PNAS 2011;108:16147-16148

"An exciting advance in marine virology is the discovery of auxiliary metabolic genes (AMGs), which are phage-encoded metabolic genes that were previously thought to be restricted to cellular genomes" – Breitbart (2012)

2000s -



Luke R. Thompson et al. I
2011;108:16147-16148



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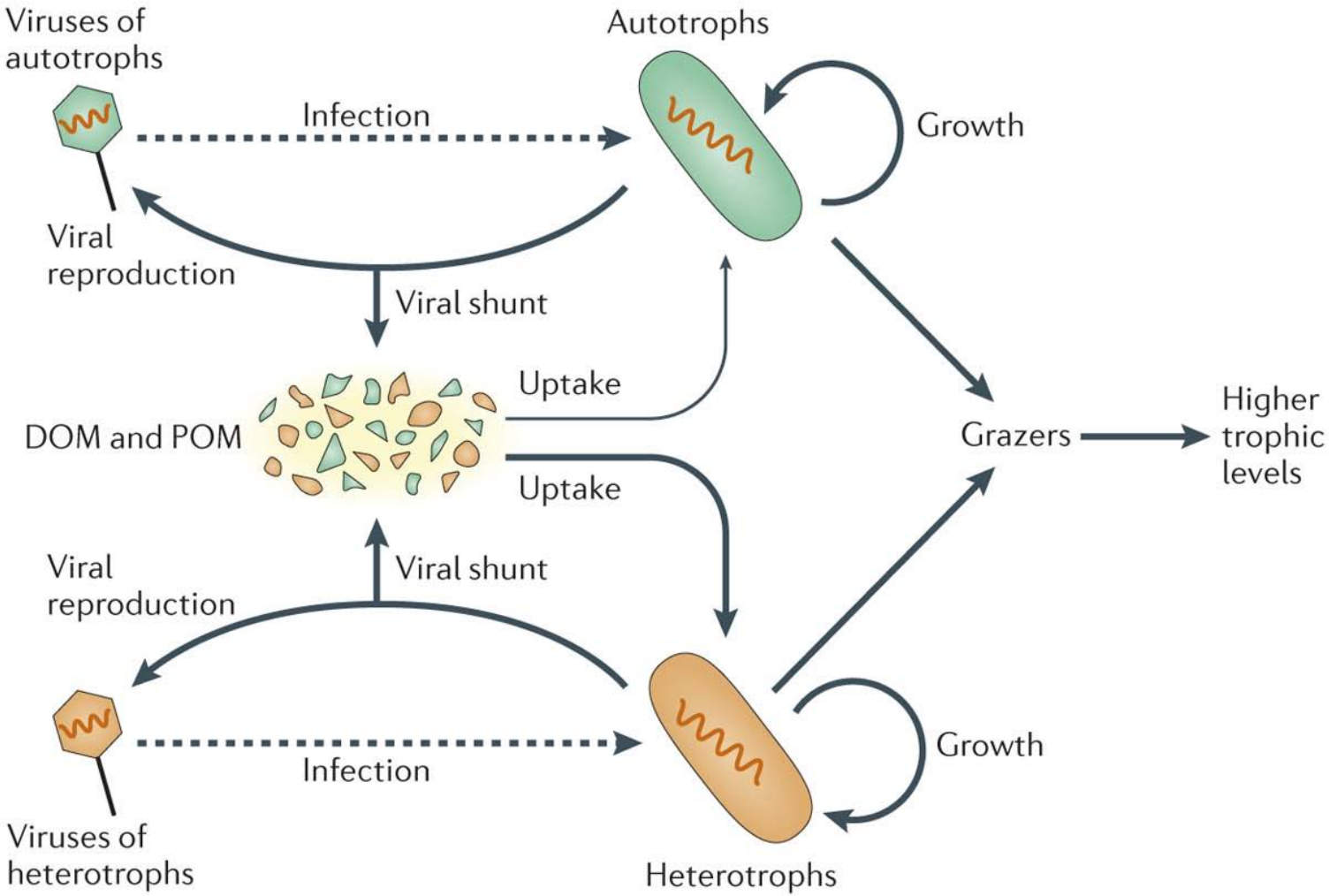


Jover et al., 2014

Today:

What do we know and what can we learn about marine virus effects on community and ecosystem processes over

Time (part 1)

&

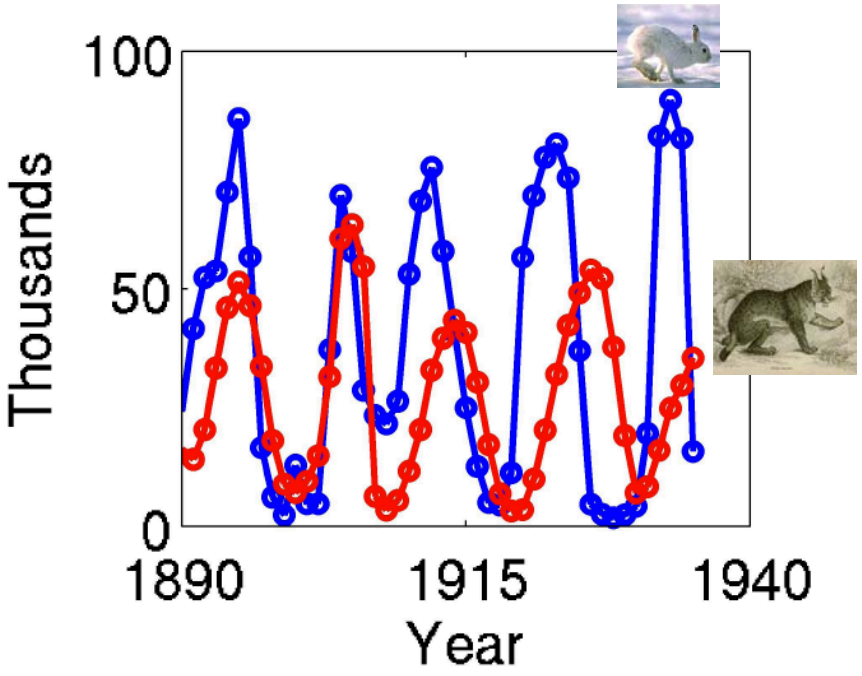
Space (part 2)

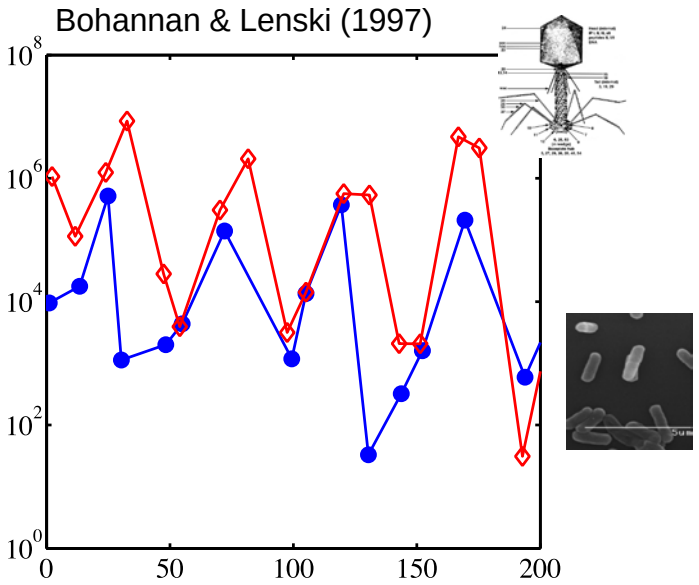
Time (Part 1):

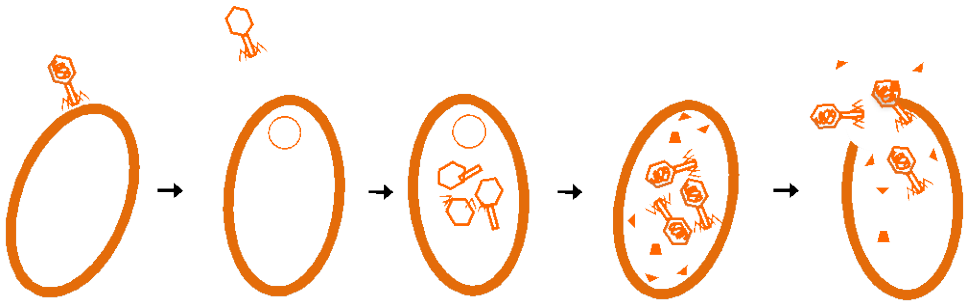
Quantifying the nonlinear dynamics of virus-microbe communities

what we know

Canonical concept: virus-microbe interactions lead to “Lotka-Volterra” dynamics







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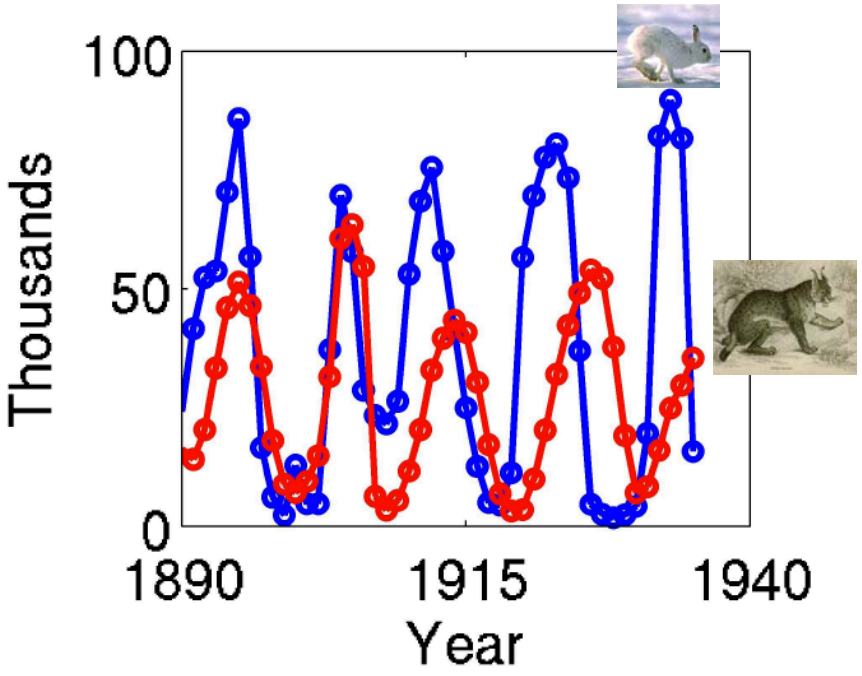
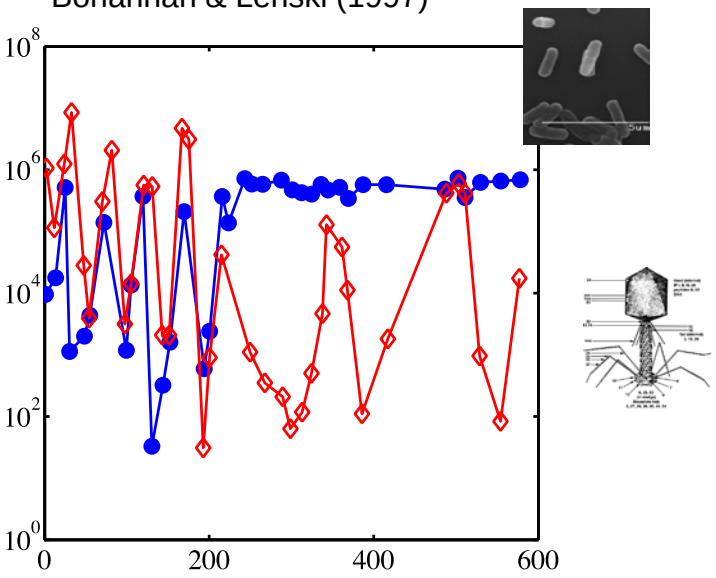
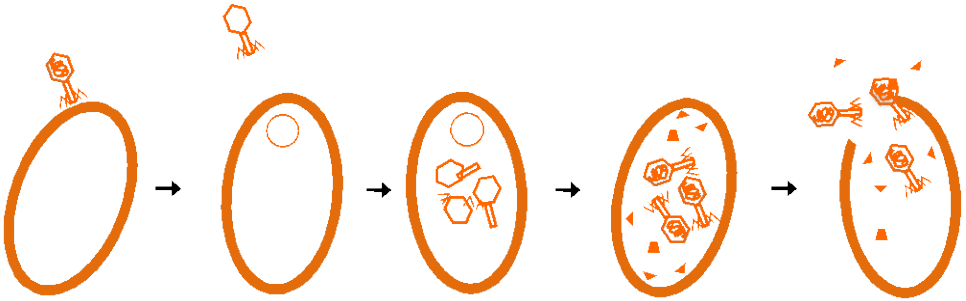
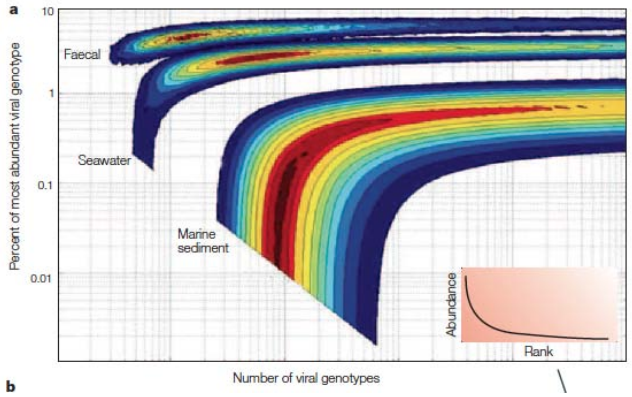


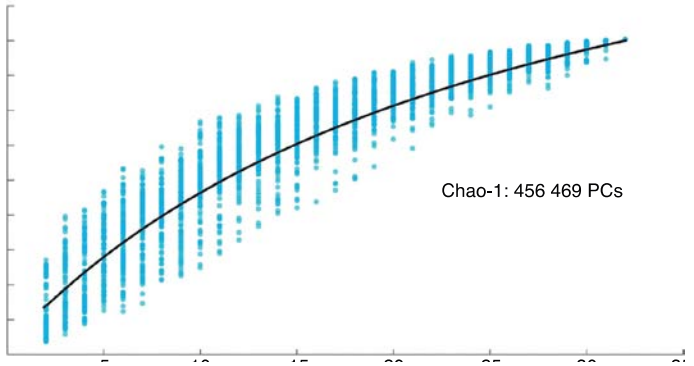
Bohannan & Lenski (1997)





However, natural virus communities are highly diverse





The marine sediment sample contained between 10,000 and 1 million viral genotypes.

- Rohwer and Edwards, Nature 2005.

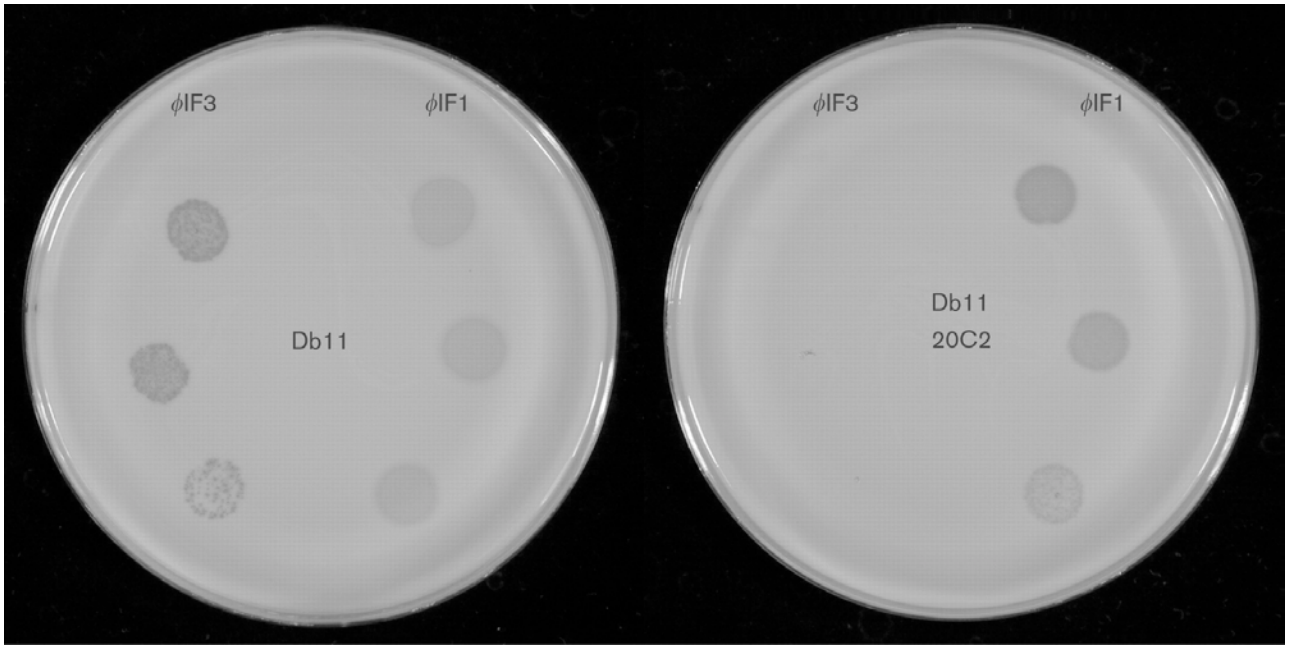
On estimation problems see:
Haegeman, et al. ISME J 2013

It seems likely that viral sequence space, while large, is unlikely to approach the two billion genes estimated from 14 genomes a decade ago.

- Ignacio-Espinoza, Solonenko & Sullivan, Curr Opp Virology, 2013

How to characterize who infects whom…

- Collect bacteria and phages for host-phage typing studies, from the environment, or from an experiment.
- Use spot assays to see “who infects whom”



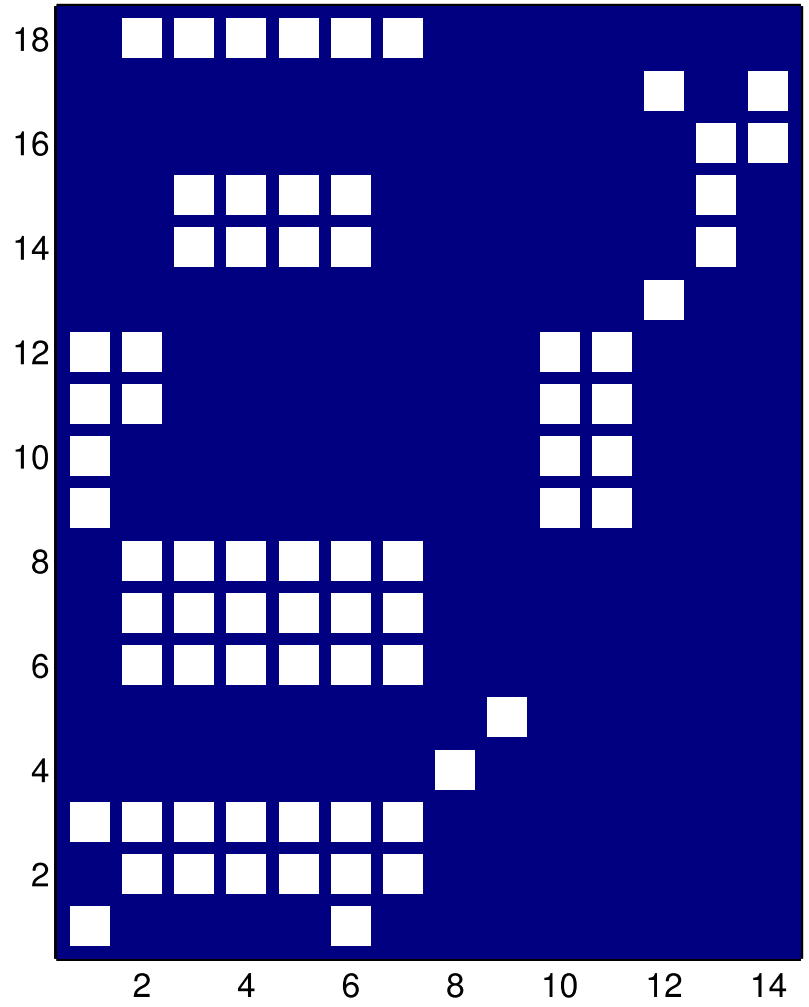
Petty et al. (Microbiology, 2006)

An example dataset: Miklic A. and Rogelj I. (2003)

Table 1 Host specificity of phages for eighteen isolated Lactococcus lactis strains

Phages	Host bacterium																	
	MB18	MB20	KR3	KR7	KR8	KR36	KR43	PT2	PT4	PT9	PT13	PT18	PT19	PT27	PT28	PT67	PT70	CAa120
Prolate																		
UMB18	+	-	+	-	-	-	-	-	+	+	+	+	-	-	-	-	-	-
UMB20	-	+	+	-	-	+	+	+	-	-	+	+	-	-	-	-	+	-
UKR36	-	+	+	-	-	+	+	+	-	-	-	-	-	+	+	-	+	+
UKR43	-	+	+	-	-	+	+	+	-	-	-	-	-	+	+	-	+	+
UPT2	-	+	+	-	-	+	+	+	-	-	-	-	-	+	+	-	+	+
CHL92	+	+	+	-	-	+	+	+	-	-	-	-	-	+	+	-	+	+
Isometric																		
UKR3	-	+	+	-	-	+	+	+	-	-	-	-	-	-	-	-	+	-
UKR7	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
UKR8	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-
UPT4	-	-	-	-	-	-	-	-	+	+	+	+	-	-	-	-	-	-
UPT9	-	-	-	-	-	-	-	-	+	+	+	+	-	-	-	-	-	-
UPT19	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-
UPT28	-	-	-	-	-	-	-	-	-	-	-	-	-	+	+	-	-	-
UPT67	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-

+, Spot formation; -, no spot formation.



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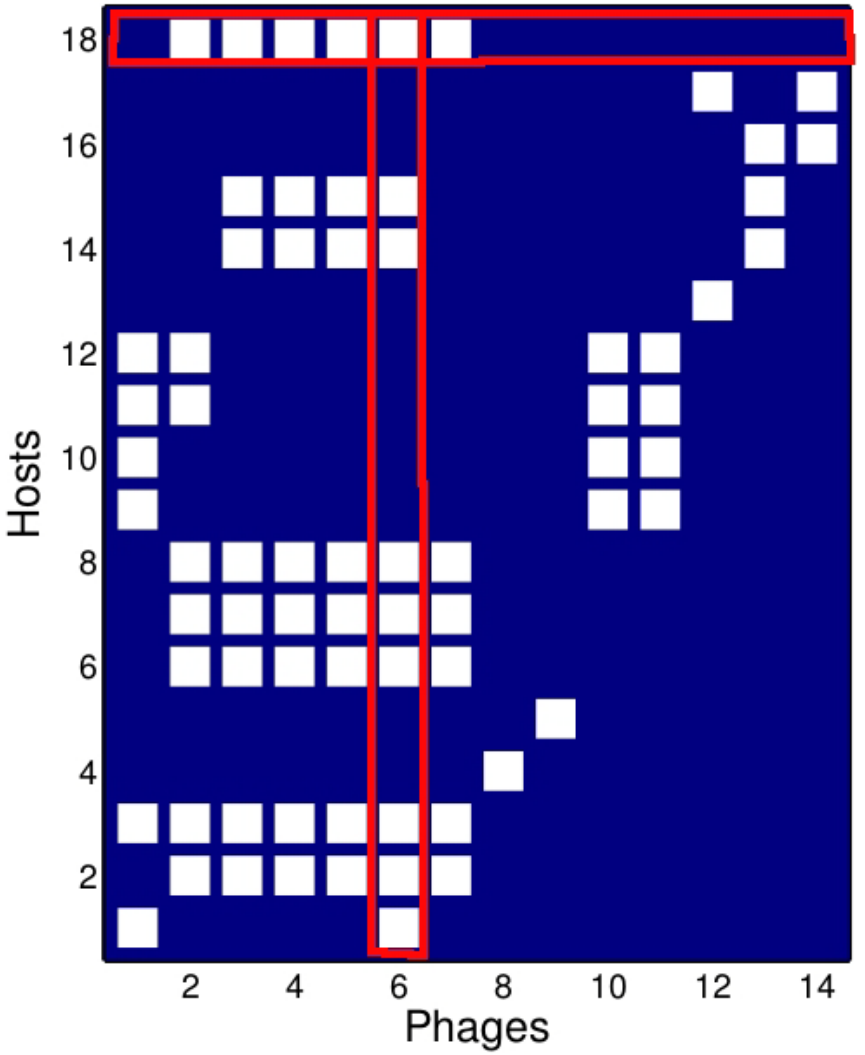
UKR36	-	+	+	-	-	+	+	+	-	-	-	-	-	+	+	-	+	+
UKR43	-	+	+	-	-	+	+	+	-	-	-	-	-	+	+	-	+	+
UPT2	-	+	+	-	-	+	+	+	-	-	-	-	-	+	+	-	+	+
CHL92	+	+	+	-	-	+	+	+	-	-	-	-	-	+	+	-	+	-
Isometric																		
UKR3	-	+	+	-	-	+	+	+	-	-	-	-	-	-	-	-	+	-
UKR7	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
UKR8	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-
UPT4	-	-	-	-	-	-	-	-	+	+	+	+	-	-	-	-	-	-
UPT9	-	-	-	-	-	-	-	-	+	+	+	+	-	-	-	-	-	-
UPT19	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	+	-	-
UPT28	-	-	-	-	-	-	-	-	-	-	-	-	-	+	+	-	-	-
UPT67	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	+	-

+, Spot formation; -, no spot formation.



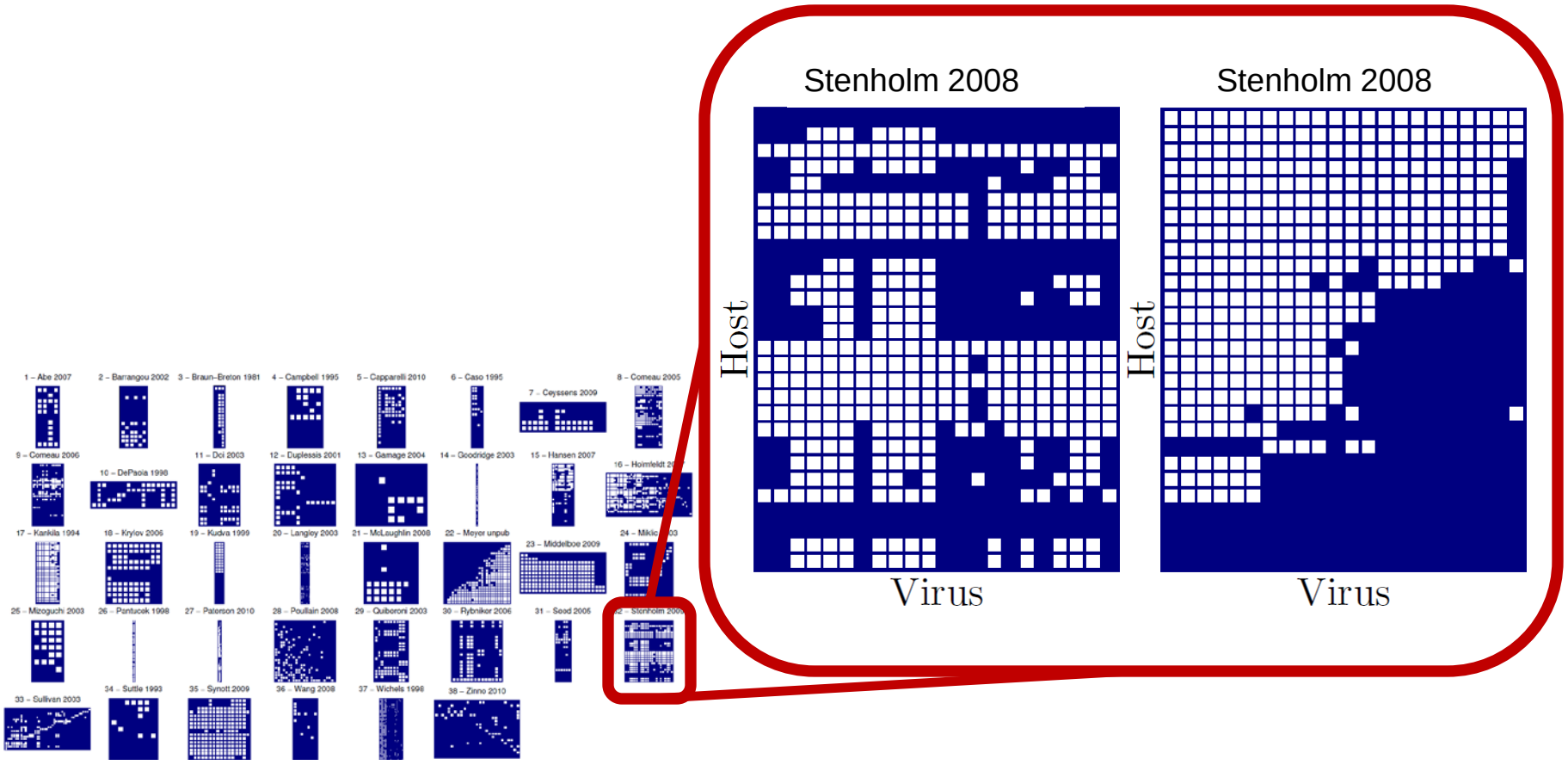
Examine patterns at a large scale

Metaanalysis

- 38 studies
- >12,000 infections
- Diversity of taxa, habitats
- Spans host-phage typing, ecological sampling and experimental evolution
- Each matrix hand-curated

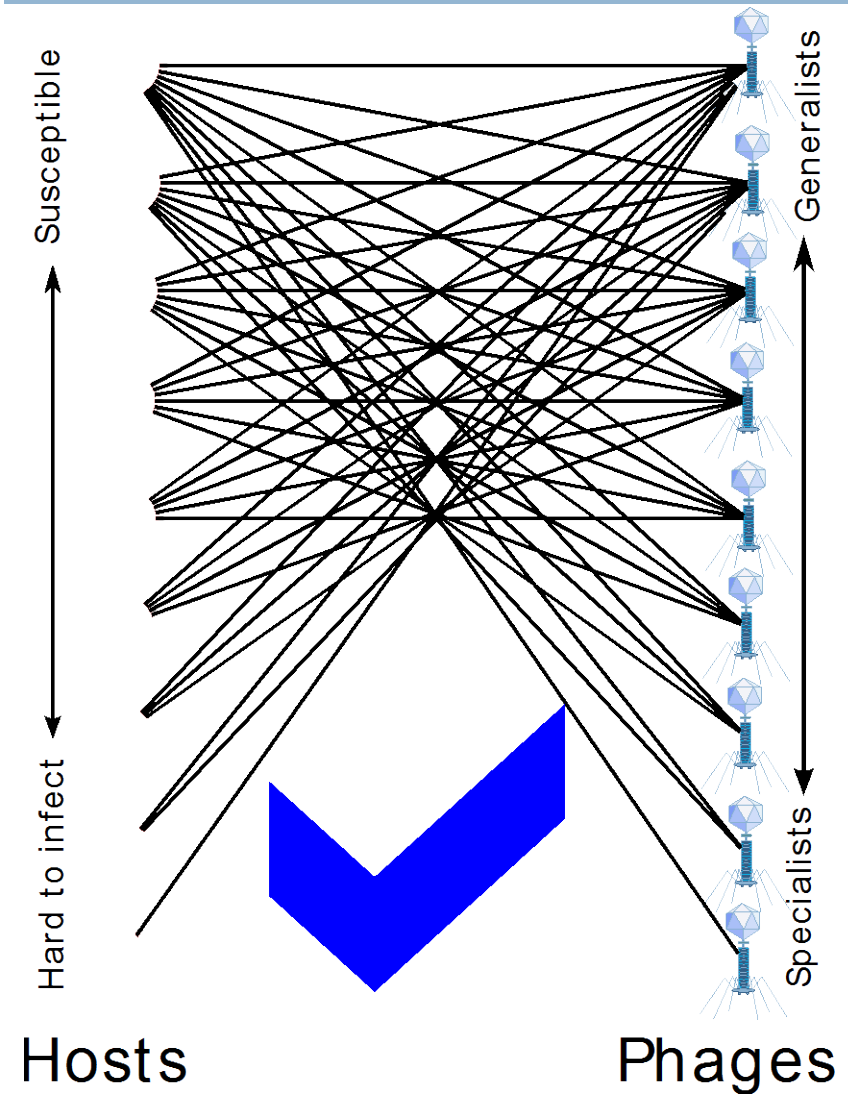
Dr. Cesar Flores

Nestedness found to be enriched in many cases, even when original format does not appear to be so.



Flores, Meyer, Valverde, Farr & Weitz (2011) Statistical structure of host-phage interactions. PNAS 108 :E288-E297

Phage-bacteria infection networks are typically nested (on microevolutionary scales)



Broadening host-range of infection appears common in both ecological and evolutionary studies.

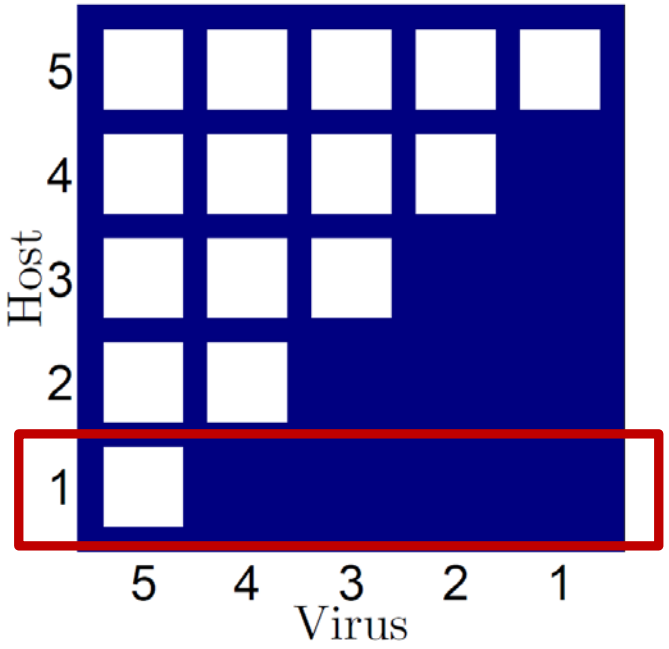
Data:
Weitz et al., Trends in Micro (2013)

Models:
Jover, Cortez & Weitz, JTB (2013)
Thingstad et al., PNAS (2014)
Haerter, Mitarai and Sneppen, ISME J (2014)
Korytowski and Smith, Theor Ecol (2015)
Leung & Weitz, Phys Rev E (2016)

How can strains coexist given nested networks?

aka – the problem of overlapping niches

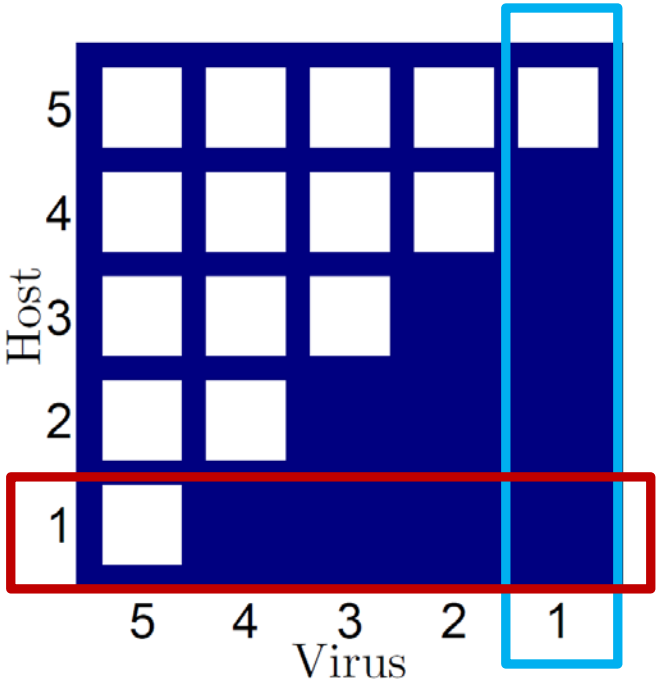
Why doesn't the most resistant host outcompete the rest ?



How can strains coexist given nested networks? *aka – the problem of overlapping niches*

Why doesn't the most resistant host outcompete the rest ?

Why isn't the most specialist virus outcompeted by the rest ?



Approach: use dynamic models of phage-bacteria communities to predict potential modes of coexistence

$$\overbrace{\frac{dH_i}{dt}}^{\text{Change of density of host } i} = \overbrace{r_i H_i \left(1 - \frac{\sum_j H_j}{K}\right)}^{\text{Host growth and competition}} - \overbrace{\sum_j M_{ij}\phi_j H_i V_j}^{\text{Viral lysis}},$$

$$\overbrace{\frac{dV_j}{dt}}^{\text{Change of density of virus j}} = \overbrace{\sum_i M_{ij}\phi_j \beta_j H_i V_j}^{\text{Virion release}} - \overbrace{m_j V_j}^{\text{Viral decay}},$$

Dr. Luis Jover

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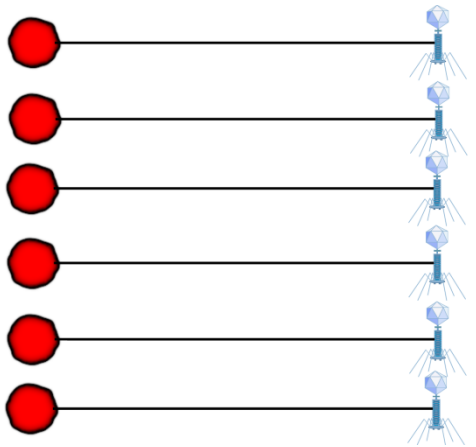
Similar to "Kill-the-Winner" models…

Elements of a theory for the mechanisms controlling abundance, diversity, and biogeochemical role of lytic bacterial viruses in aquatic systems

T. Frede Thingstad
Department of Microbiology, University of Bergen, Jahnebakken 5, N-5020 Bergen, Norway



Host Viru

Approach: use dynamic models of phage-bacteria communities to predict potential modes of coexistence

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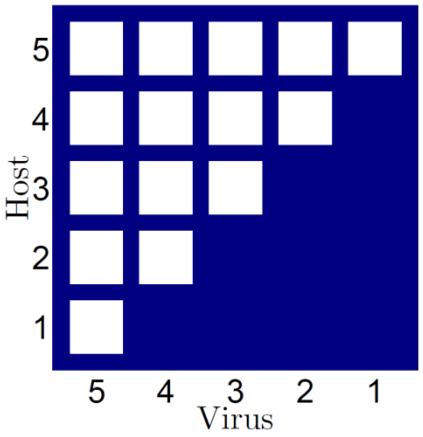
Similar, except that cross-infection is structured…

Infection Network

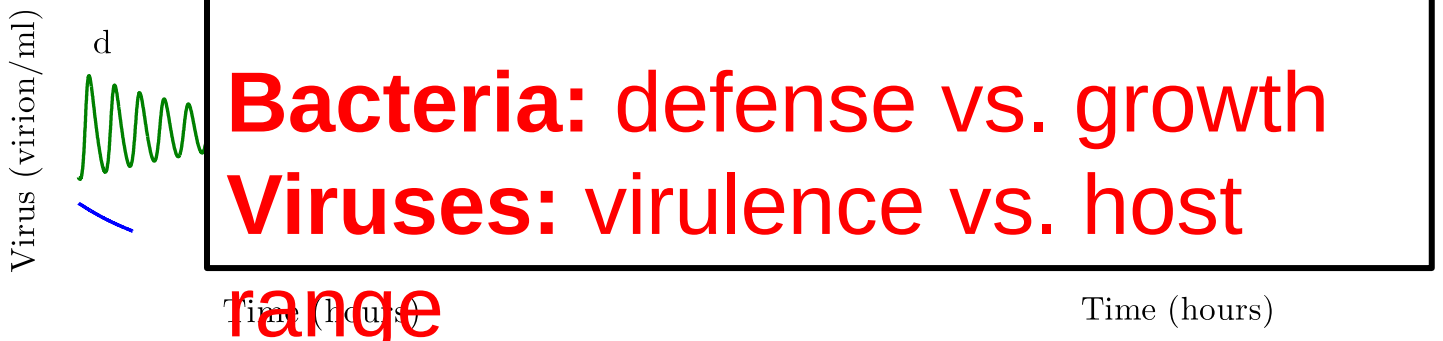
$$M = \begin{pmatrix} 1 & 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 & 0 \\ 1 & 1 & 1 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 \end{pmatrix} =$$



Initial results:
dynamics can differ given the same infection network

Community A:
1 virus and 1 host coexist

Community B:
2 viruses and 2 hosts coexist

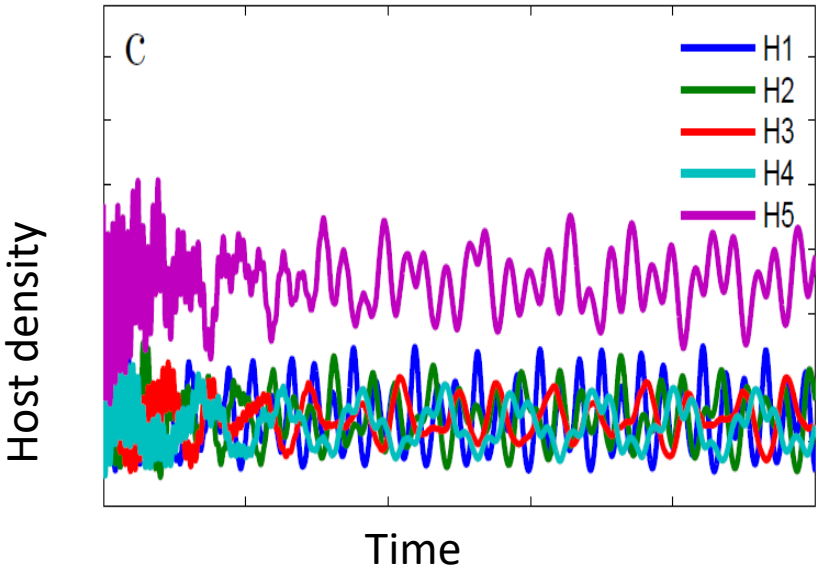


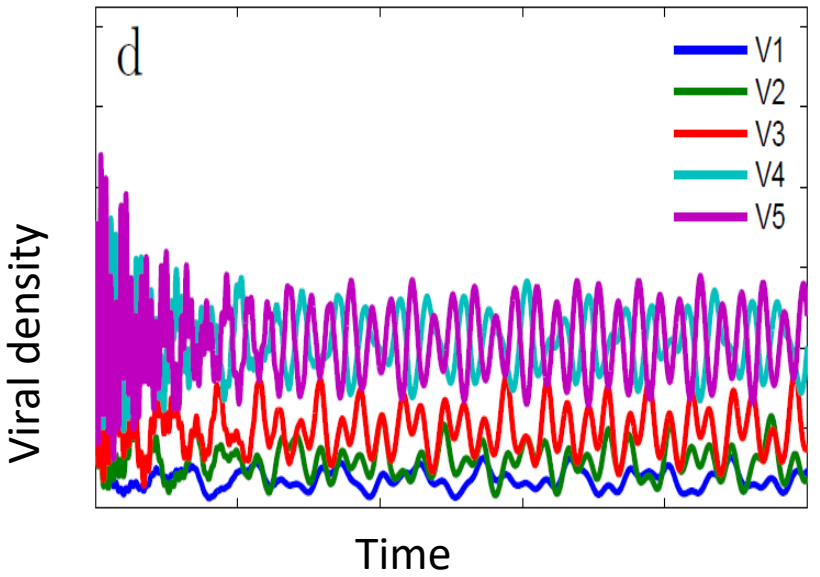
The strains trade-off in life history traits

Bacteria: defense vs. growth
Viruses: virulence vs. host range

Both communities have 2 viruses, 2 hosts, and a nested network…

Coexistence occurs via a stable fixed point or oscillations when trade-offs are satisfied



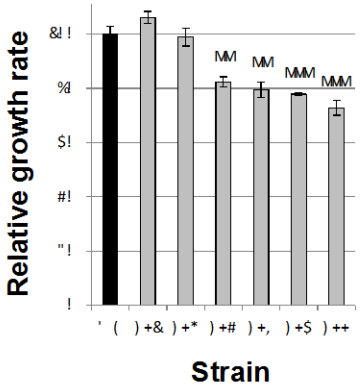


Is there evidence for such trade-offs?

Trade-offs linking life history rates and infection ranges

Genomic island variability facilitates Prochlorococcus–virus coexistence

Sarit Avrani[1], Omri Wurtzel[2], Itai Sharon[1†], Rotem Sorek[2] & Debbie Lindell[1] doi:10.1038/nature10172



Virus:
T4-like
podoviruses

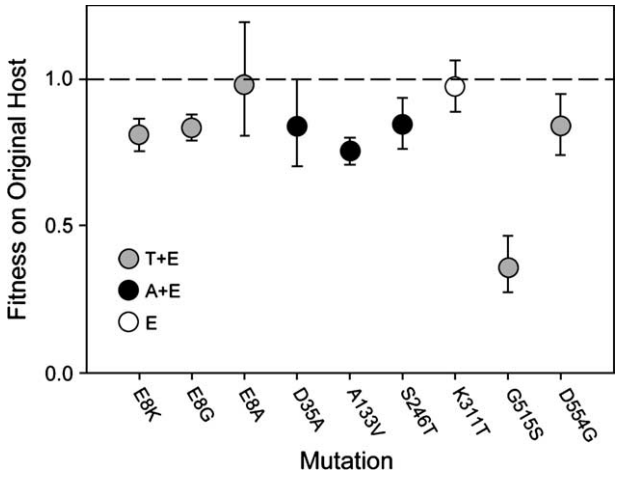
Host:
Cyanobacteria -
Prochlorococcus

http://proportal.mit.edu

Pleiotropic Costs of Niche Expansion in the RNA Bacteriophage Φ6

Siobain Duffy,*,†,1 Paul E. Turner* and Christina L. Burch†

DOI: 10.1534/genetics.105.051136



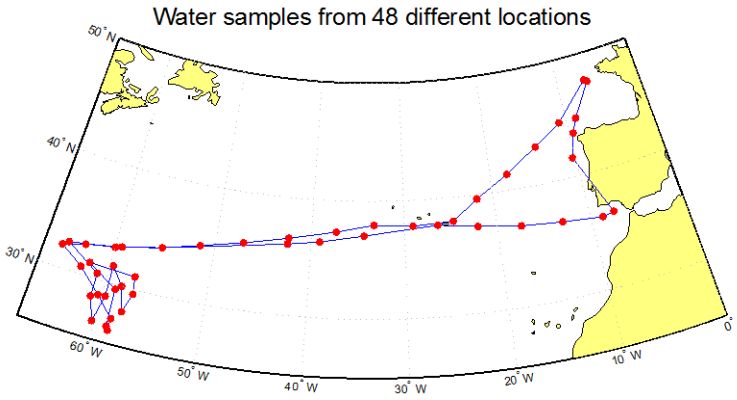
Host tradeoff:
growth rate vs. resistance
(sometimes)

Viral tradeoff:
fitness vs. host range
(sometimes)

But are nested infection networks common at larger, marine scales?

Moebus and Nattkemper (Helgol Meeresunters, 1981)

- Bacteria and phages collected at 48 different stations in the Atlantic Ocean.



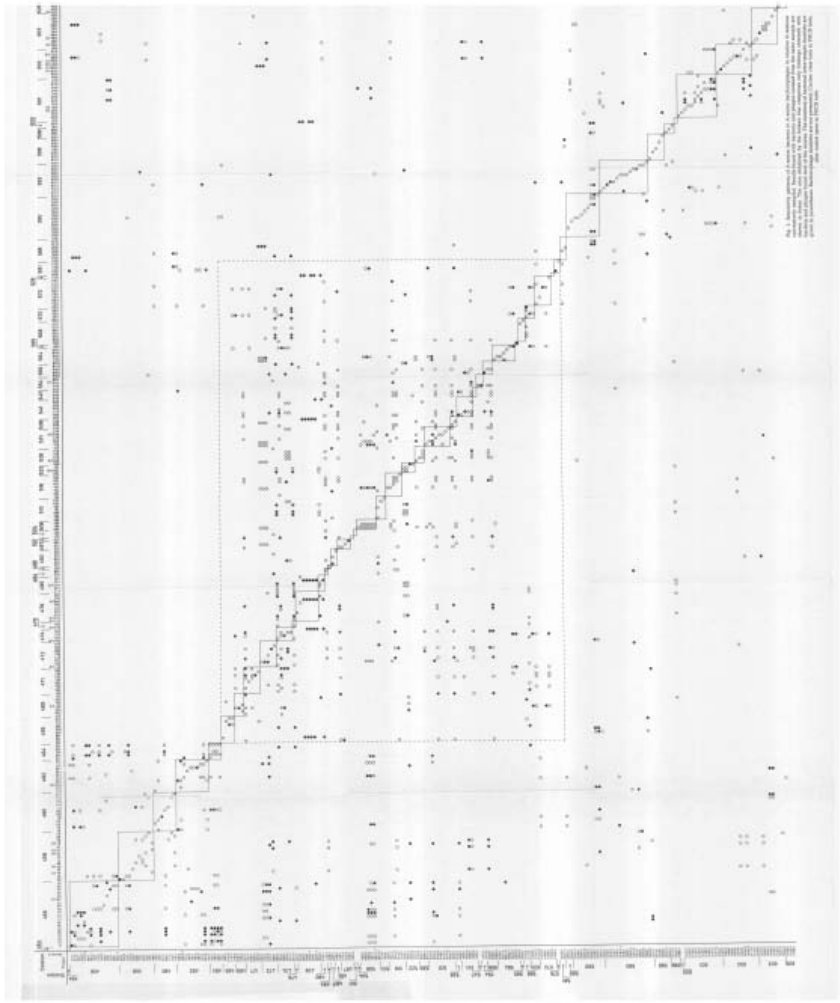
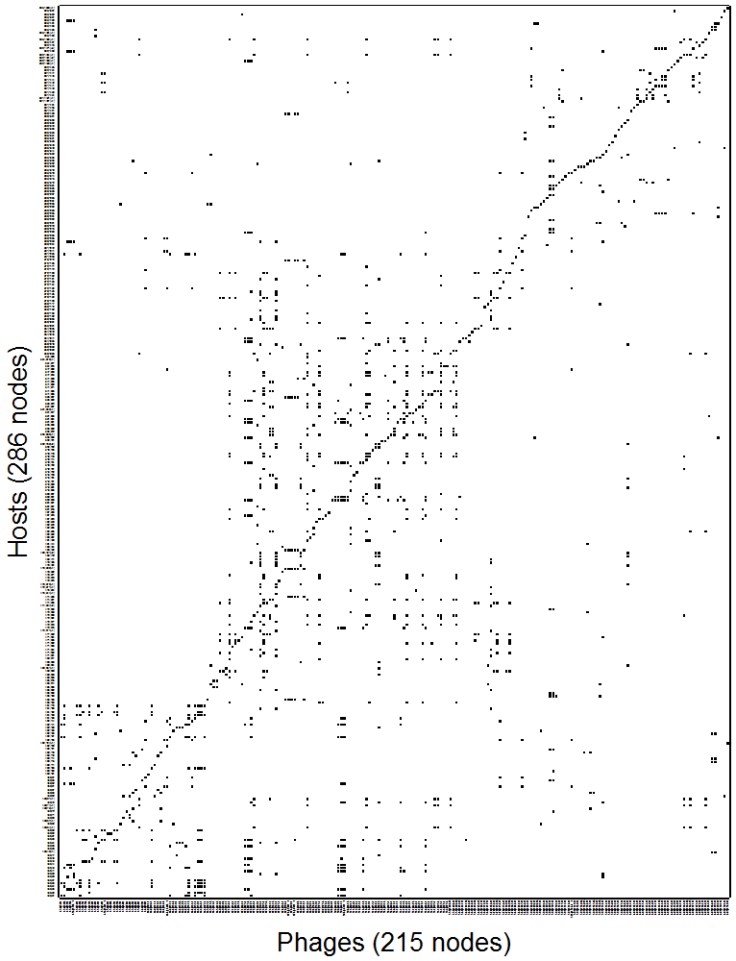
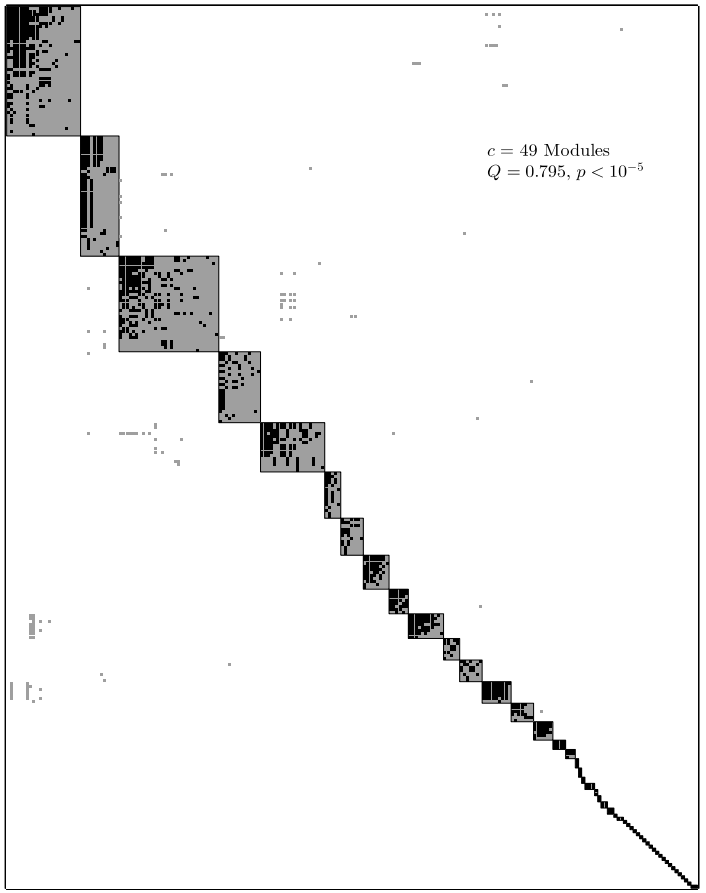


Fig. 1: *Source:* (7900 × 6618 pixels) We scanned the original source of the study. Rows represents bacteria and columns phage. A filled circle represents a strong interaction while an unfilled circle a weak interaction.

Phage-host networks are modular at large-scales (and nested within a “module”)

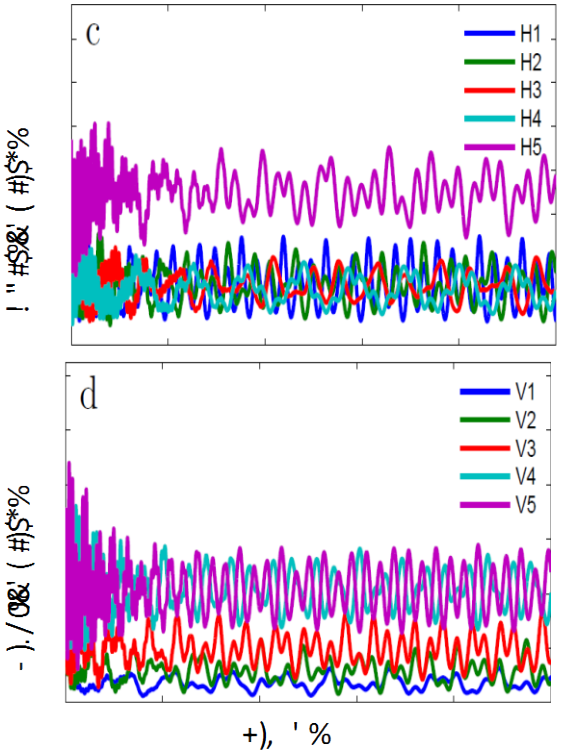




Flores, Valverde & Weitz, ISME J, 2013

Summary thus far…

- Tradeoffs facilitate coexistence of viruses and their hosts.
- Abundance and resistance are not necessarily correlated.
- Nestedness and tradeoffs do not need to be “perfect” for coexistence
- Modular networks can also give rise to persistent diversity.



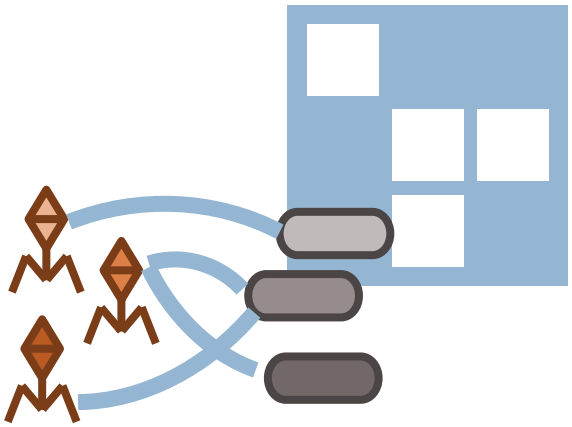
Further reading:
Jover, Cortez & Weitz, J. Theor. Biol., 332: 65-77 (2013); Thingstad et al., PNAS (2014); Jover, Flores, Cortez & Weitz, Scientific Reports (2015)

Time (Part 1):

Quantifying the nonlinear dynamics of virus-microbe communities

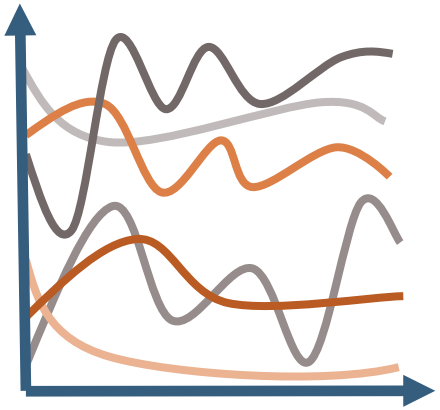
what can we learn?

Inferring network interactions from time-series



"forward problem"

"inverse problem"



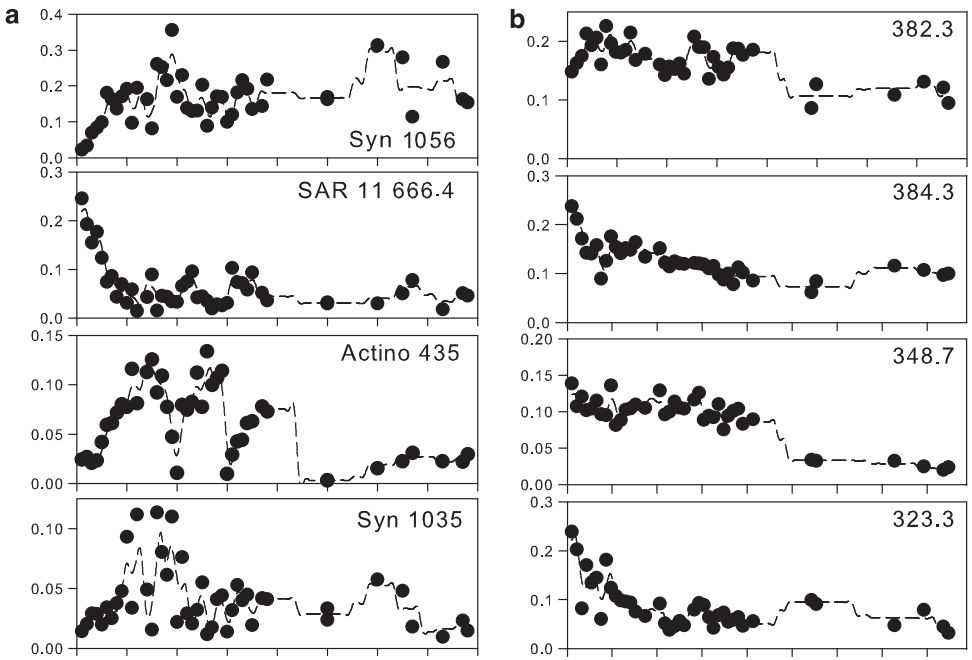
interaction network (cannot directly observe *in situ*)

host + virus time-series via metagenomic sampling

Existing, widespread approaches: **correlation-based**

More recently: **model-based (regression)**

Inferring network interactions from time-series in practice



4–1285
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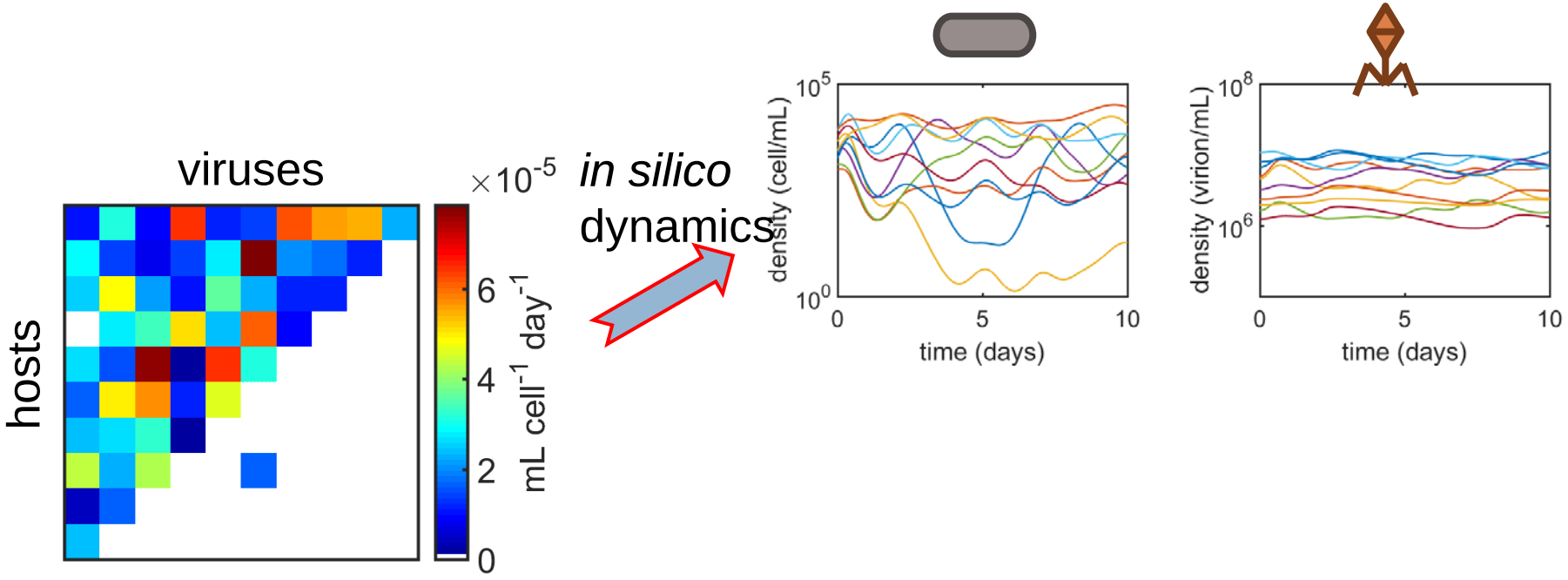
www.nature.com/ismej

ORIGINAL ARTICLE

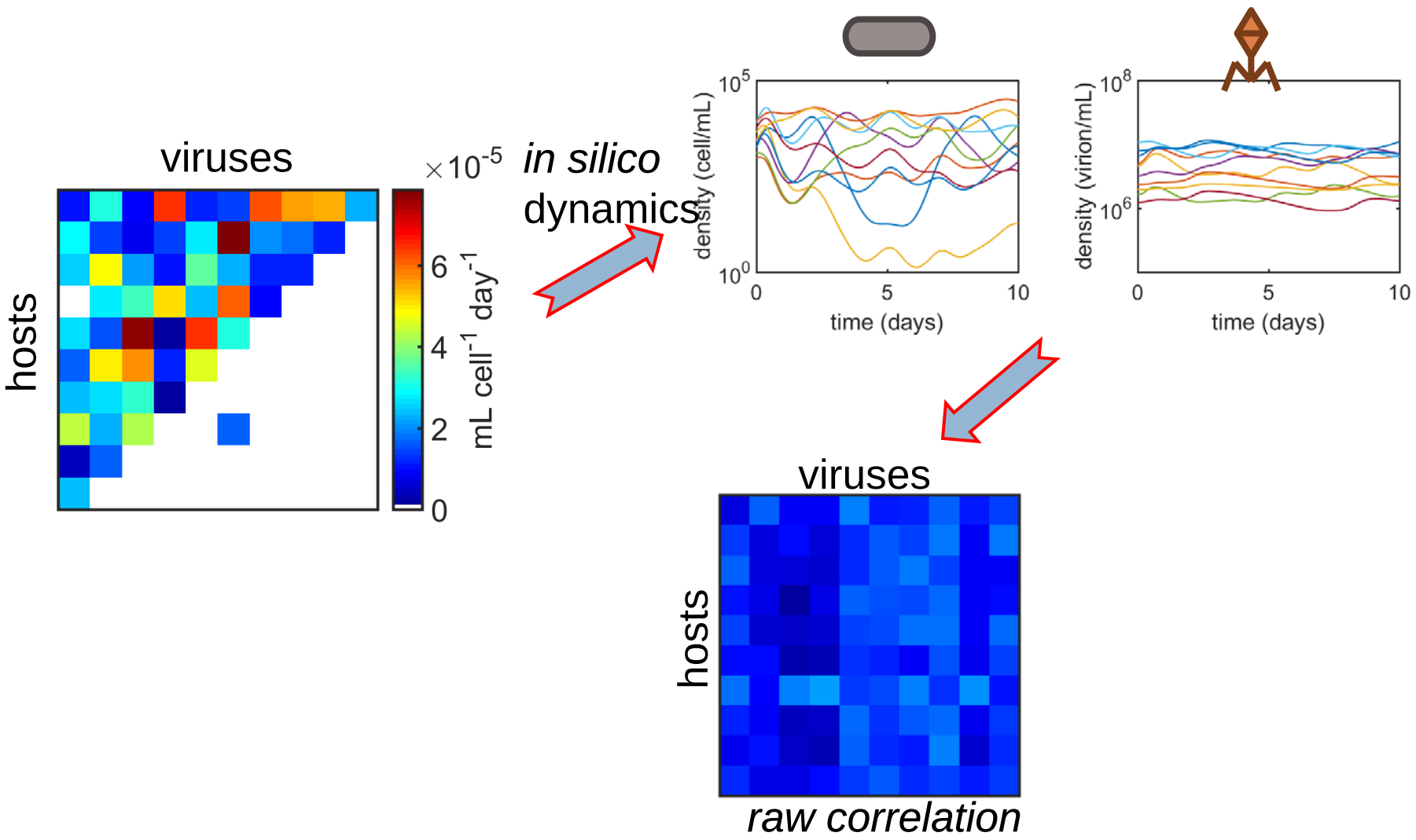
Short-term observations of marine bacterial and viral communities: patterns, connections and resilience

David M Needham, Cheryl-Emiliane T Chow, Jacob A Cram, Rohan Sachdeva, Alma Parada and Jed A Fuhrman
University of Southern California, Department of Biological Sciences, Los Angeles, CA, USA

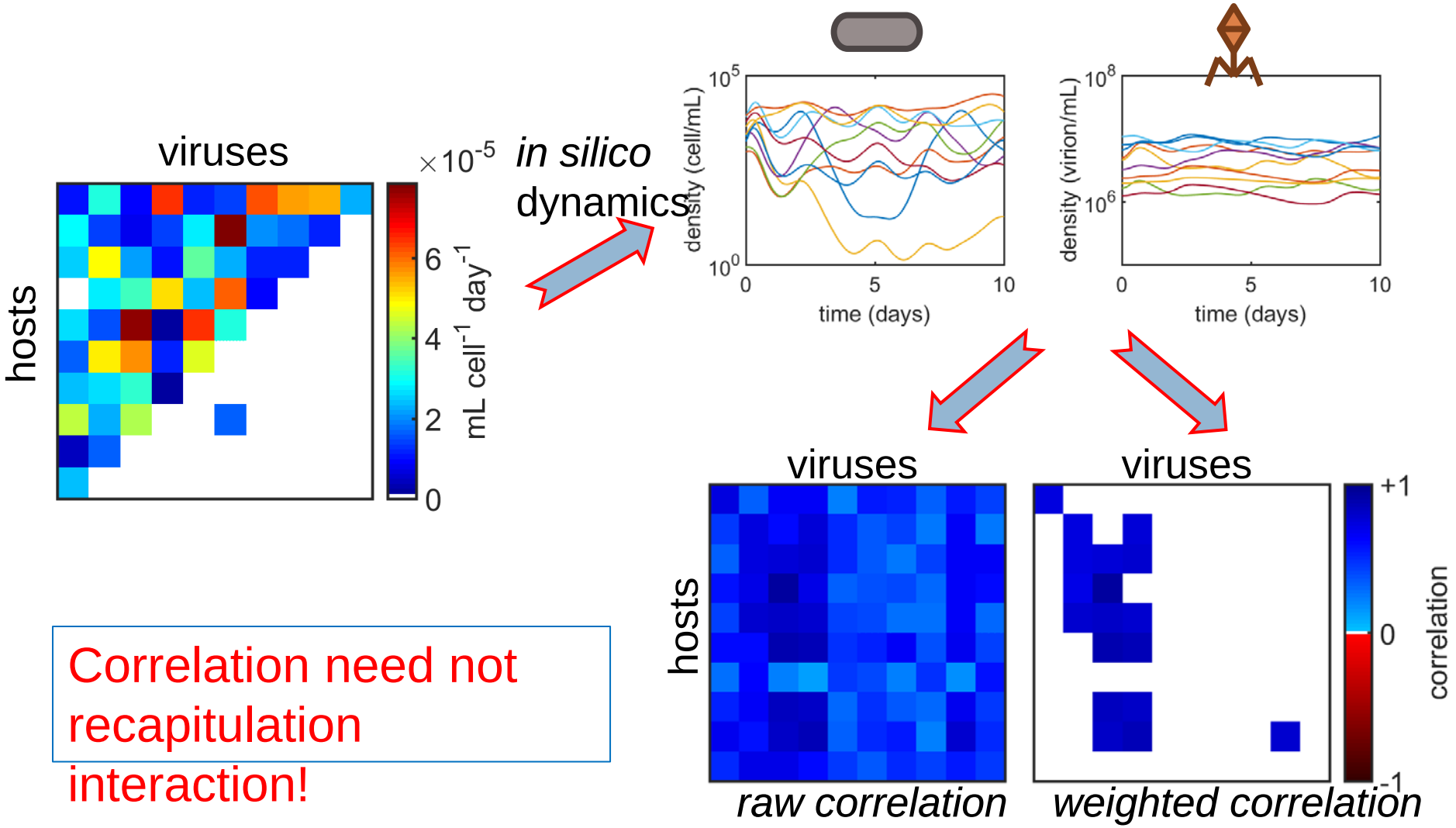
The (underappreciated) problem with correlation-based inference



The (underappreciated) problem with correlation-based inference

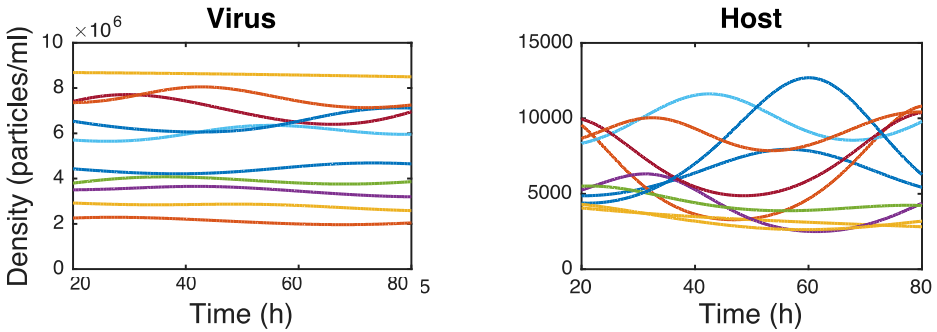


The (underappreciated) problem with correlation-based inference

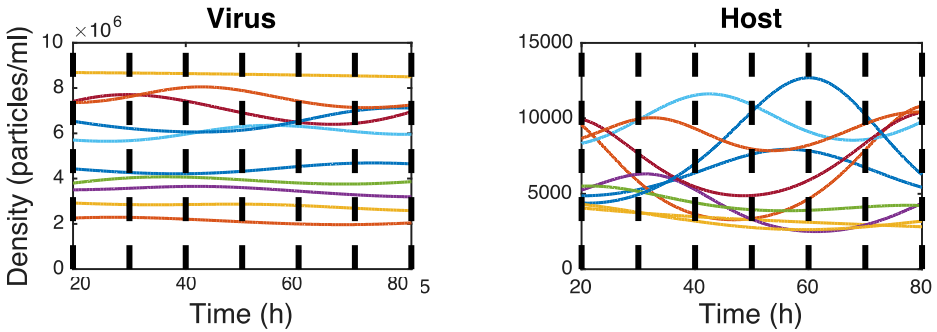


Correlation need not recapitulation interaction!

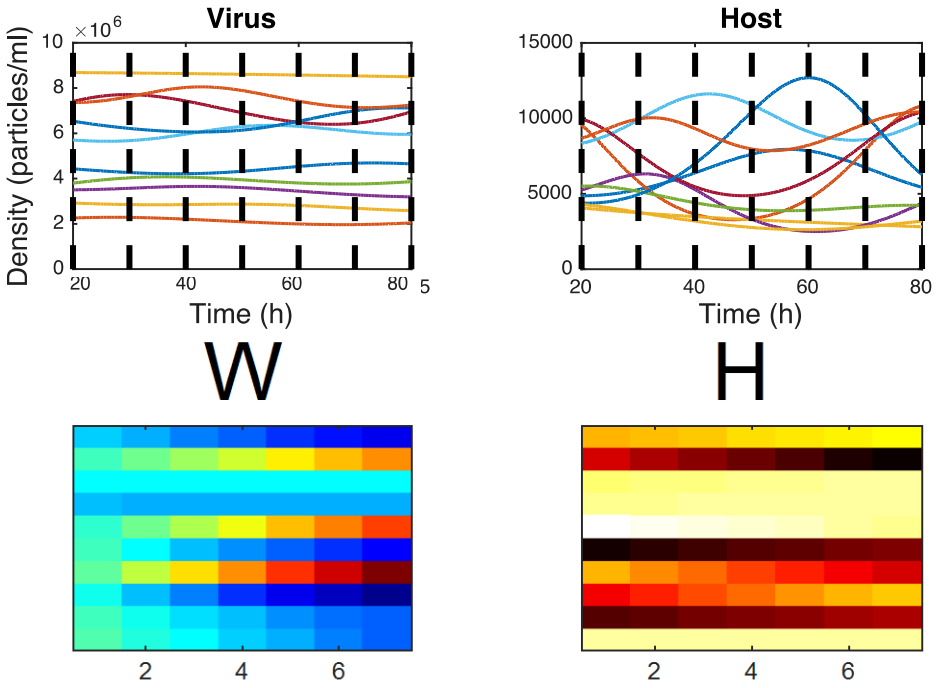
Model-based inference: a principled alternative



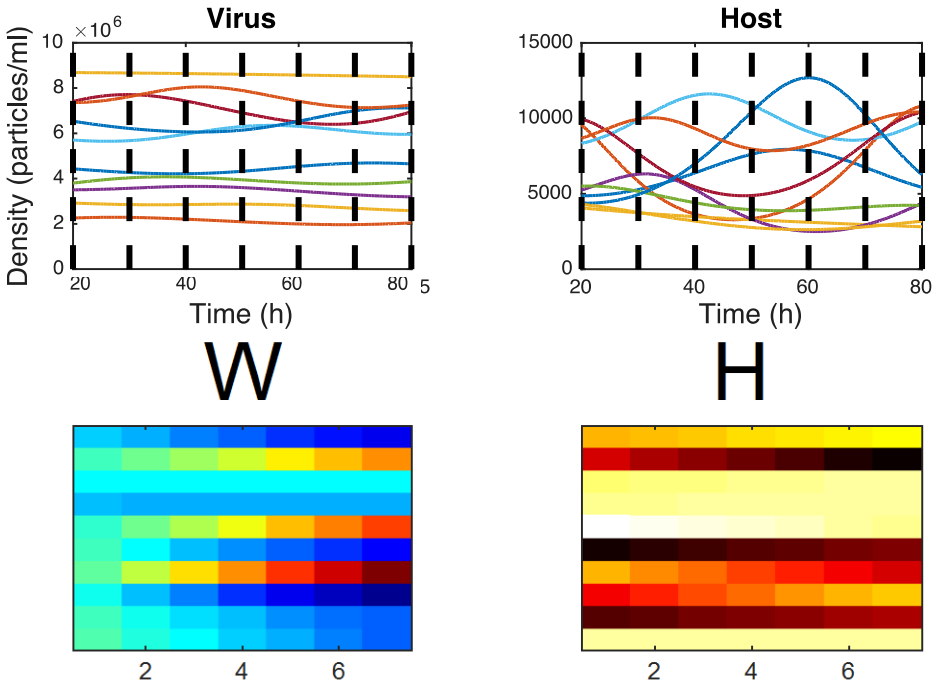
Model-based inference: a principled alternative



Model-based inference: a principled alternative



Model-based inference: a principled alternative



Measured per-capita changes in viral densities

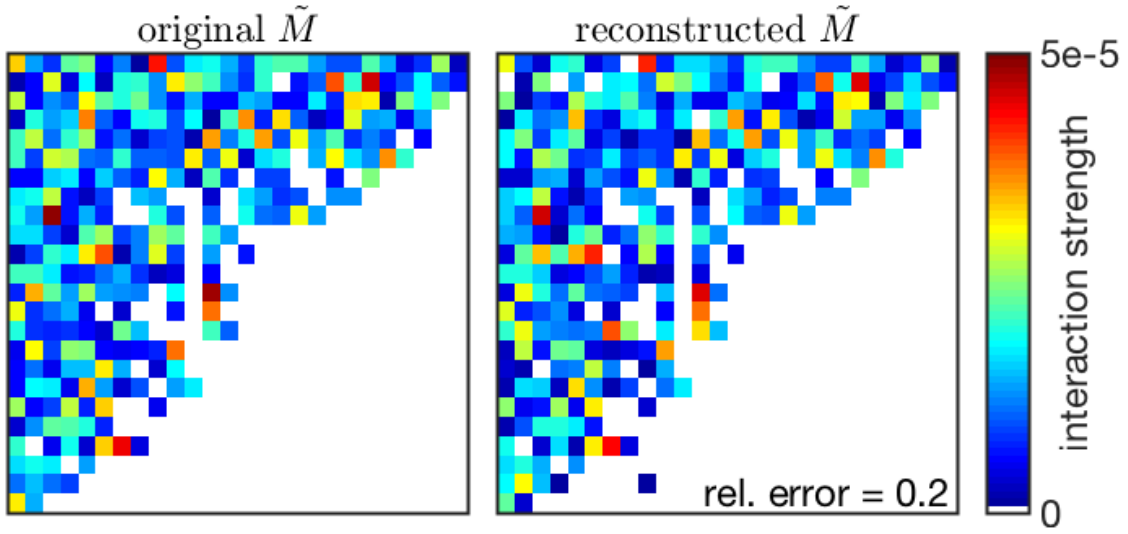
$$W \approx \left(\tilde{M}^{\intercal}\,\vec{m}\right)\begin{pmatrix} H \\ \vec{1} \end{pmatrix}$$

Measured per-capita changes in host densities

Cross-infection network (unknown)

Viral decay rates (unknown)

Inference as an “optimization” problem, i.e., finding the best network & traits to fit the observed dynamics.



Measured per-capita changes in viral densities

$$W \approx \left(\tilde{M}^{\intercal}\ \vec{m}\right)\begin{pmatrix} H \\ \vec{1} \end{pmatrix}$$

Measured per-capita changes in host densities

Cross-infection network (unknown)

Viral decay rates (unknown)

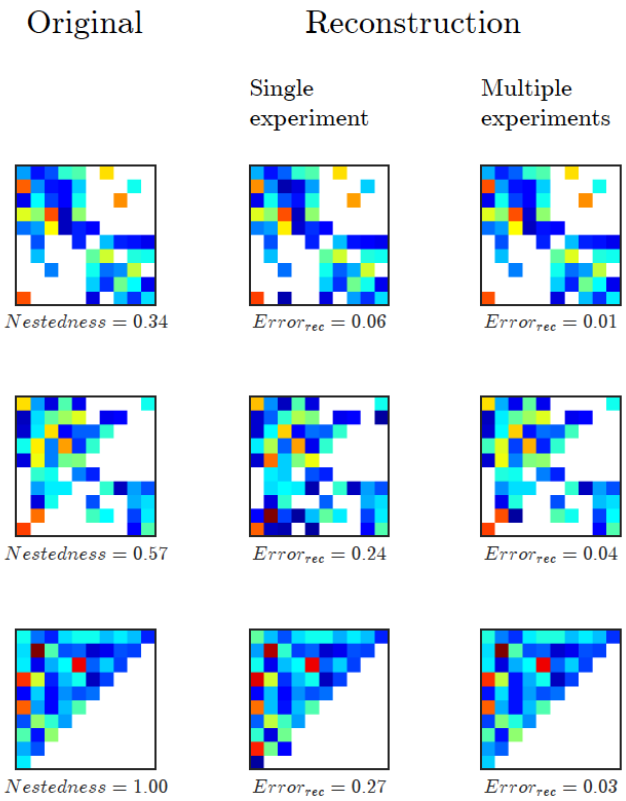
Convex optimization (cvx)

$$\frac{\Delta \ln\left(V_j(t_k)\right)}{\Delta t_k} \approx \sum_{i=1}^{N_h} \tilde{M}_{ij} H_i(t_k) - m_j$$

$$\underset{\left(\tilde{M}^T,\, \vec{m}\right)}{\text{minimize}} \quad \left\| W - \left(\tilde{M}^T\ -\vec{m}\right)\begin{pmatrix} H \\ \vec{1} \end{pmatrix} \right\|_2$$

$$\text{subject to} \quad \tilde{M}_{ij} \geq 0,$$
$$m_i \geq 0.$$

Model-based inference a step towards including theory in the pipeline of discovery of environmental cross-infection



Jover, Romberg & Weitz (2016) *Roy. Soc. Open Science.* Inferring phage-bacteria infection networks from time-series data

Coenen & Weitz (in prep) The limits to infection inference given correlation-based approaches

Features

- Uses model, rather than correlation, based approach for inference
- Leverages densities from metagenomes.
- Multiple experiments can be combined.

Challenges

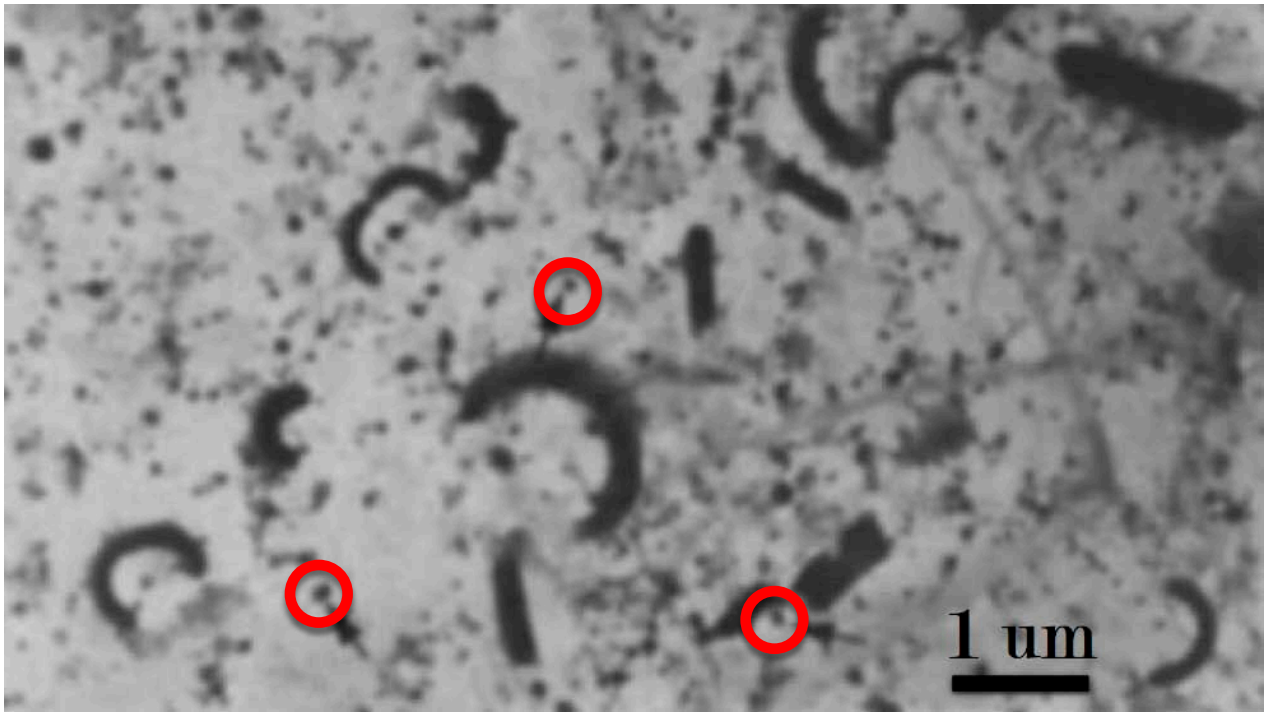
- Diversity
- Spatiotemporal scale
- Other modes of infection
- Experimental tests ongoing

Space (Part 2):

Quantifying the large-scale properties of virus-microbe communities

what we know

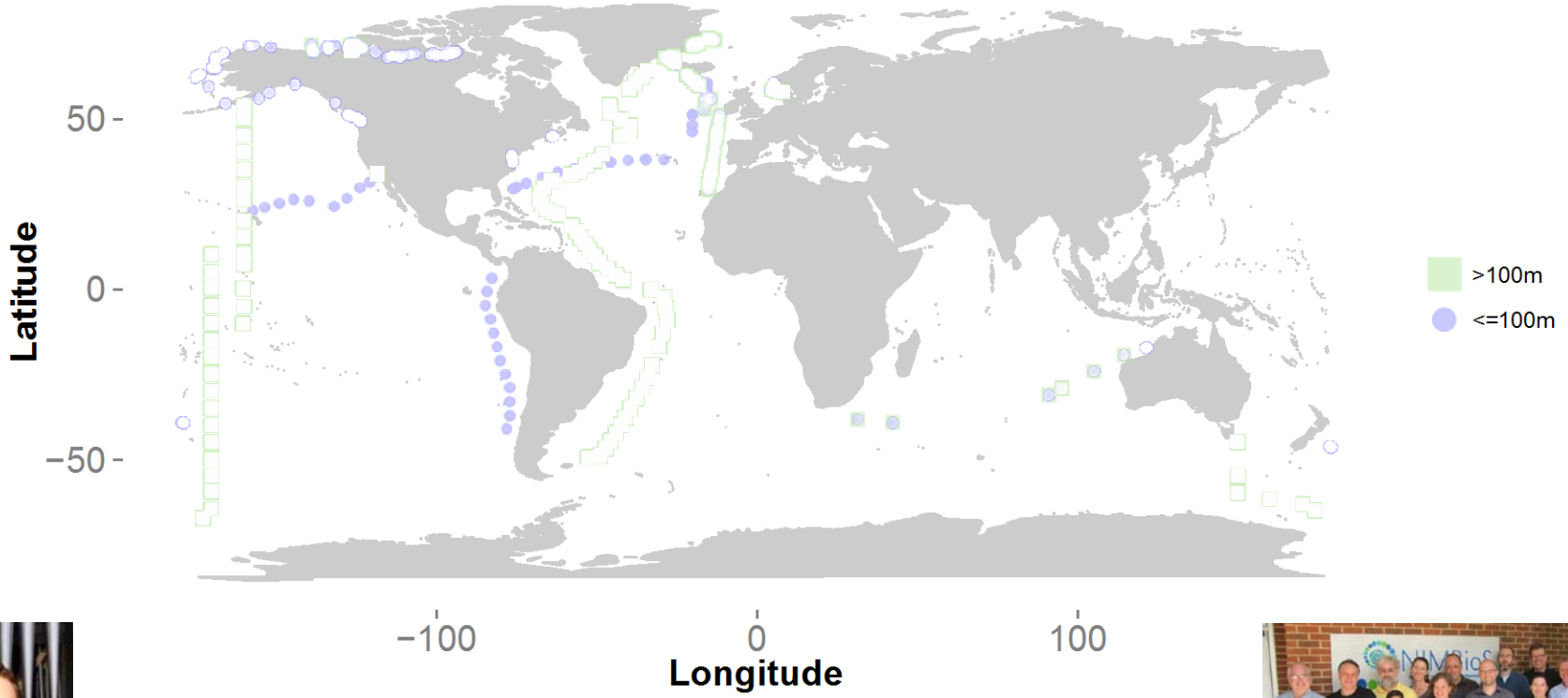
1989 - Numbers



Bergh et al., Nature 1989

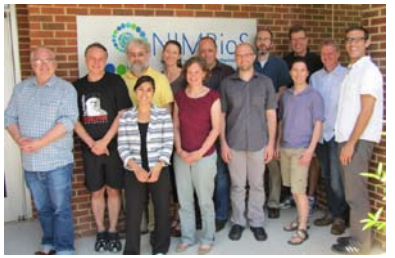
“We have found up to 2.5 x 10^8 virus particles per ml in natural waters… 10^3-10^7 times higher than previous reports.”

1996 – 2012 – More Numbers



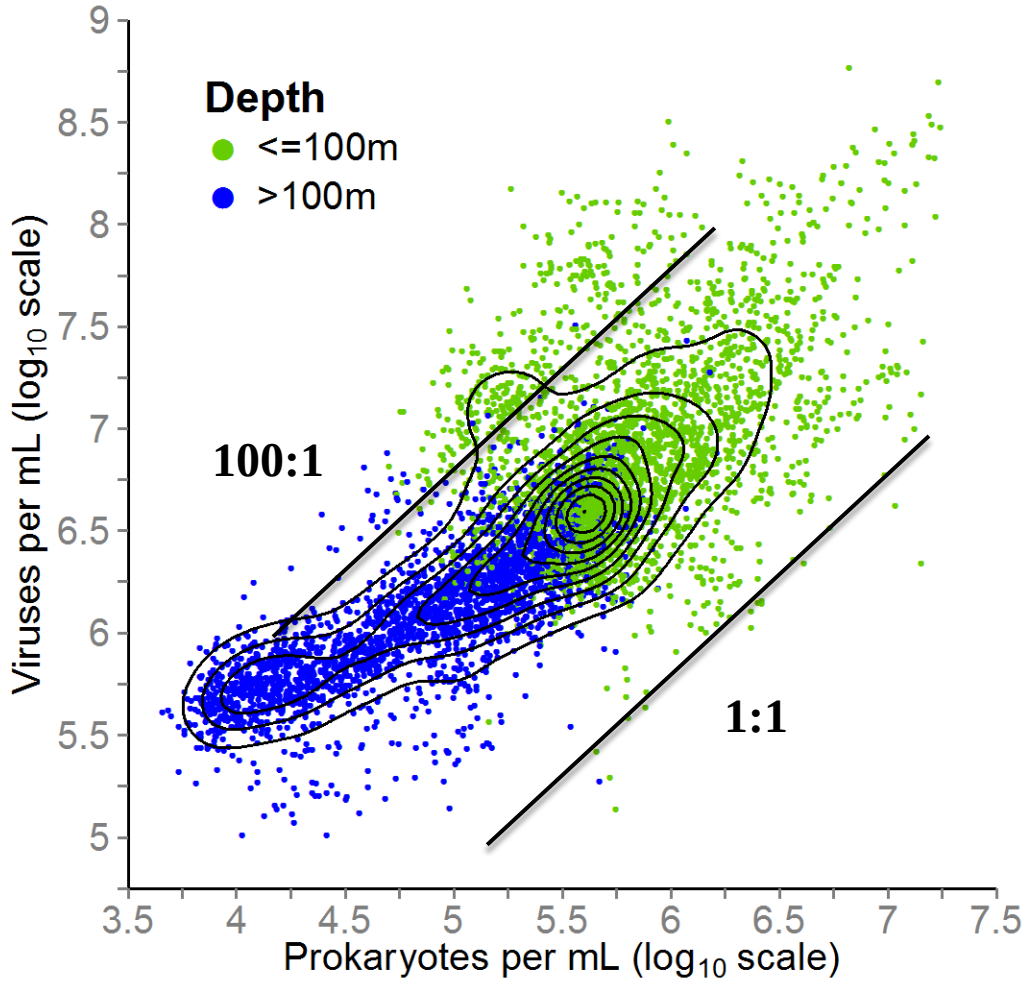
Wigington et al, Nature Microbiology (2016) & available at bioRxiv

C. Wigington



NIMBioS Working Group, Corina Brussaard, Jan Finke

1996 – 2012 – More Numbers



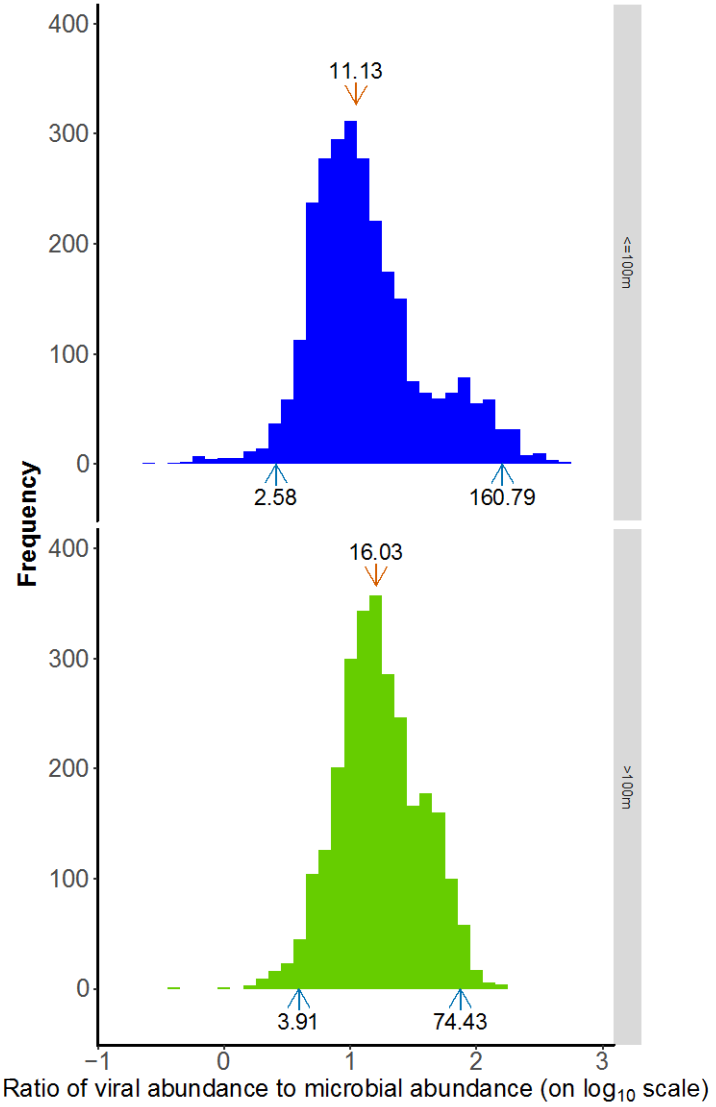
Wigington et al, Nature Microbiology (2016) & available at bioRxiv

Viruses and large-scale patterns in the global oceans

We find substantial variation in the virus to microbial cell ratio, approximately 2-orders of magnitude.

The variation in virus-to-microbe abundances is poorly described by a 10:1 model.

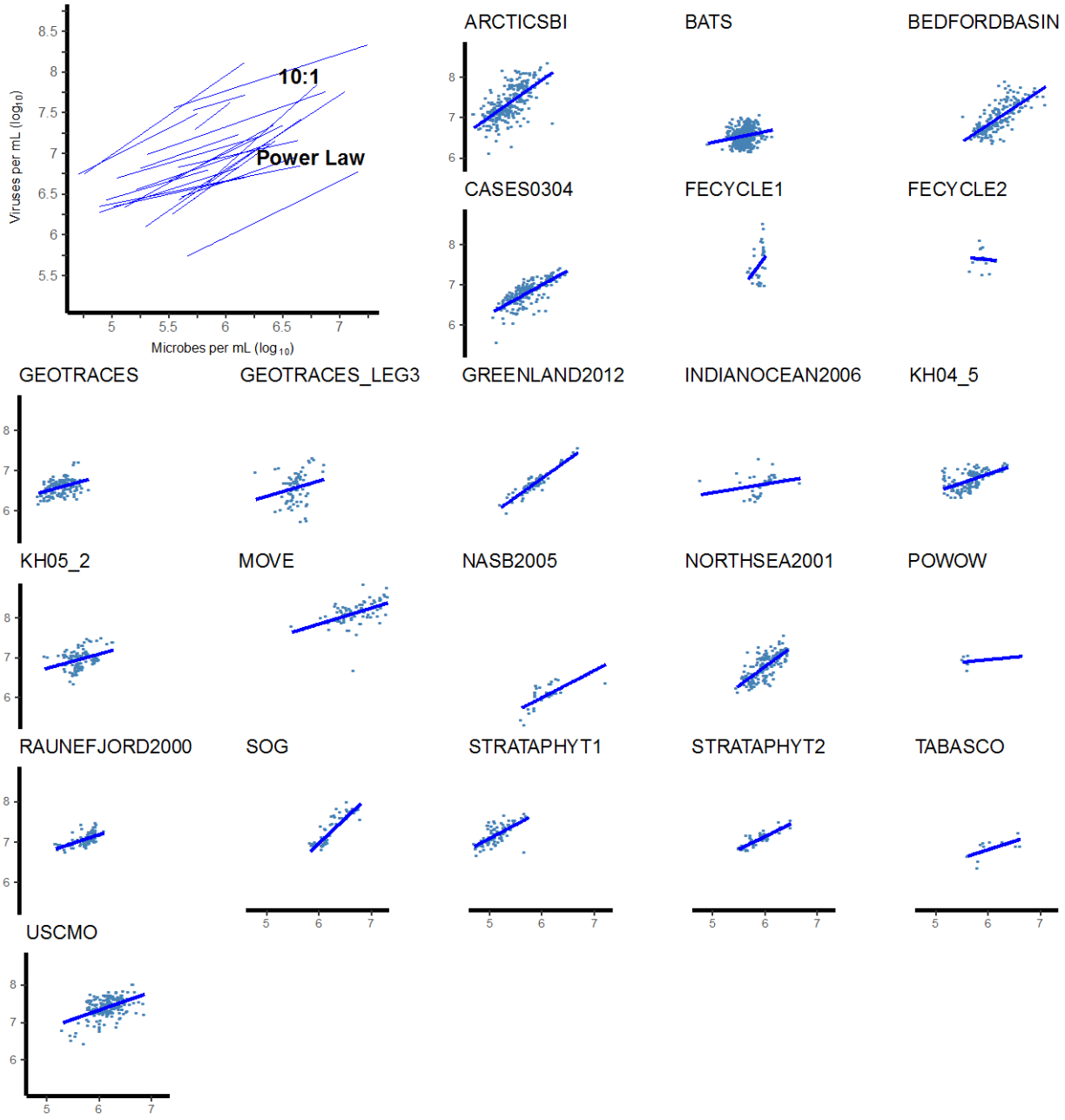
<u>Instead, large variations are typical!</u>



How do emergent virus-to-microbe relationships vary in distinct ocean sampling regimes?

1. Analyze each marine survey separately.

2. Assess the relationship between virus and microbial cell abundances.



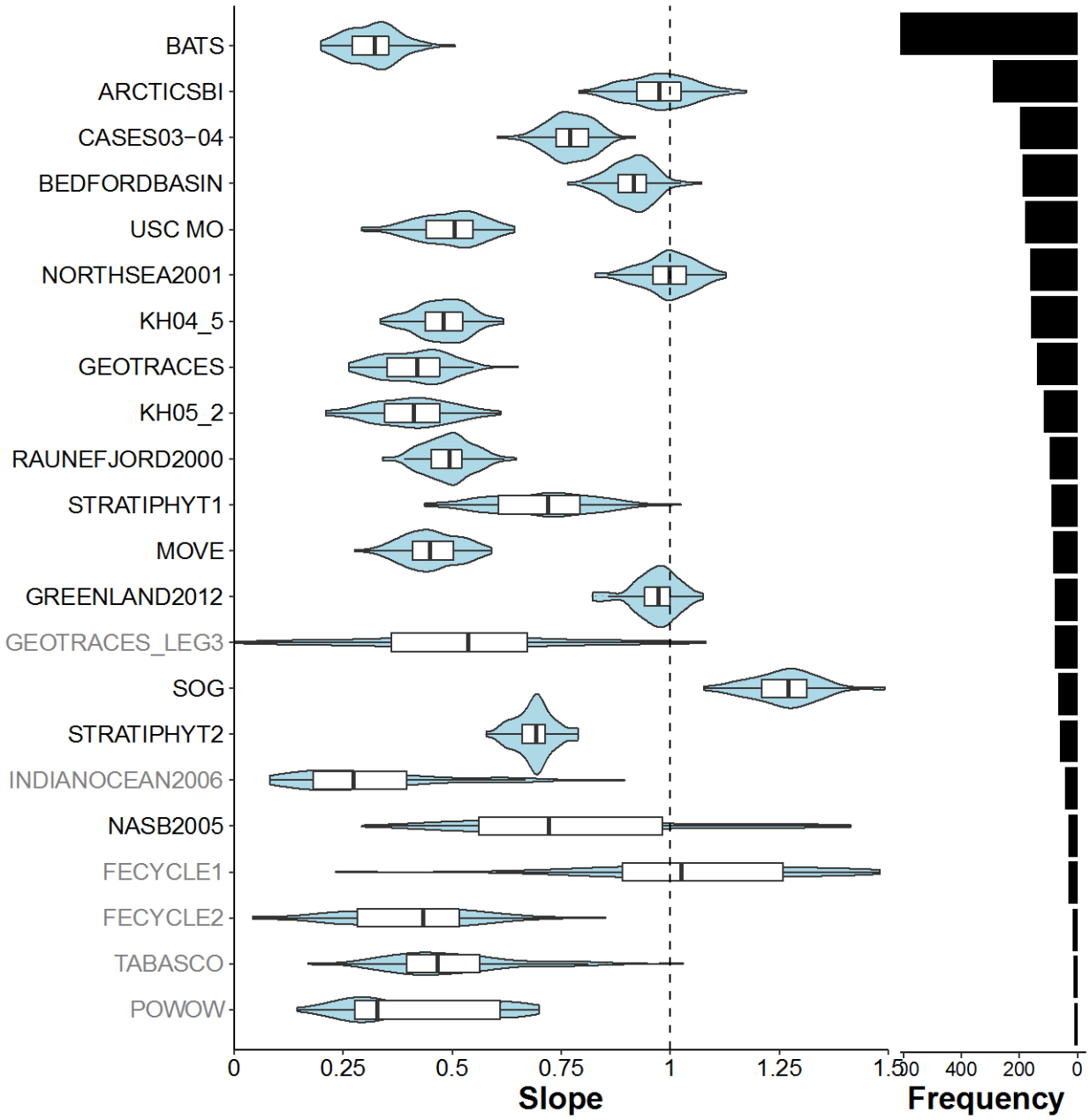
How do emergent virus-to-microbe relationships vary in distinct ocean sampling regimes?

1. Analyze each marine survey separately.

2. Assess the relationship between virus and microbial cell abundances.

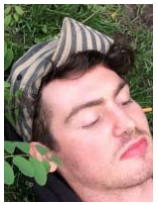
3. Power-law relationships tend to have scaling exponents <1

4. In general, the virus-to-microbe ratio *decreases* with increasing microbial cell, rather than remaining fixed.



See related work in Knowles et al. Nature (2016) & Parikka et al. Biol. Reviews (2016)

A maximum likelihood approach: applied to the global oceans virus-microbe dataset

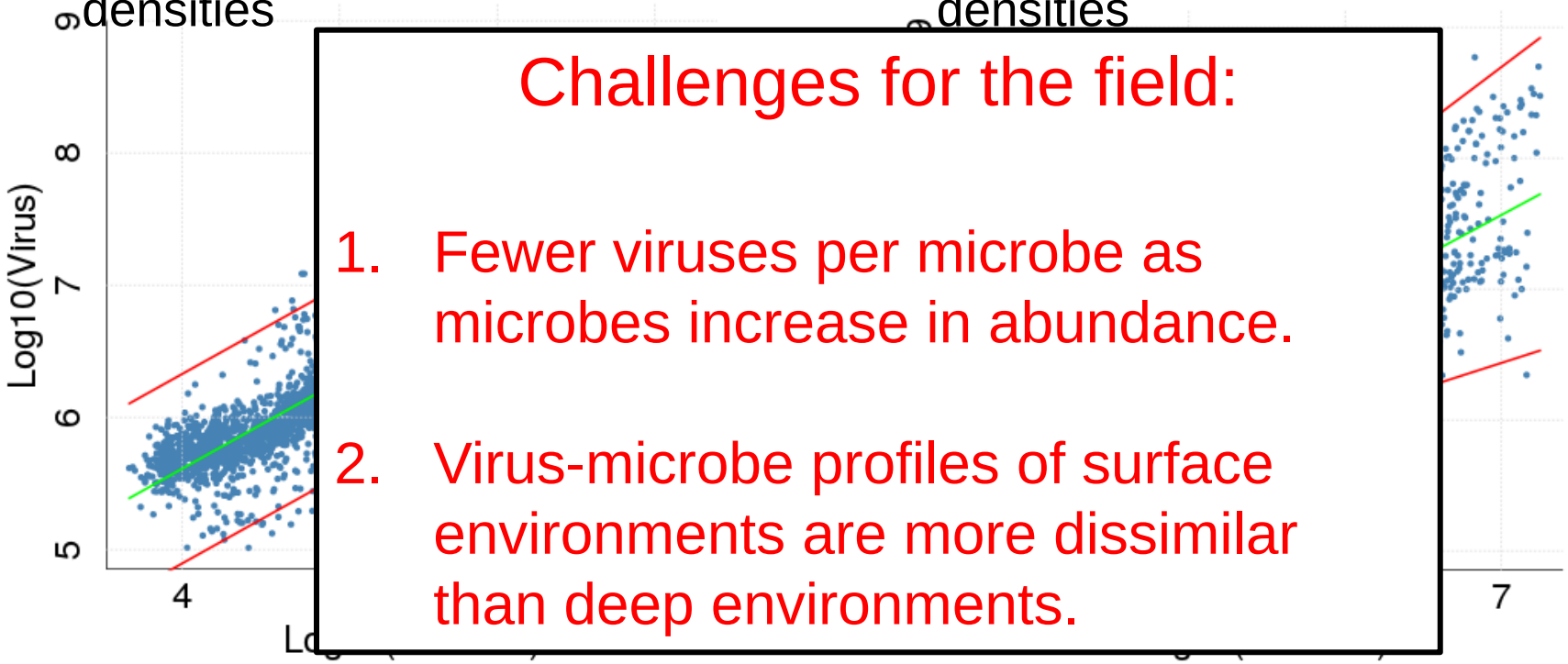


B. Cael Barry

Stephen Becket

Constant variance model – the spread in virus densities is independent of microbial densities

Variable variance model – the spread in virus densities increases with microbial densities



Challenges for the field:

1. Fewer viruses per microbe as microbes increase in abundance.
2. Virus-microbe profiles of surface environments are more dissimilar than deep environments.

AIC = 4682

AIC = 4130 (better support)

Space (Part 2):

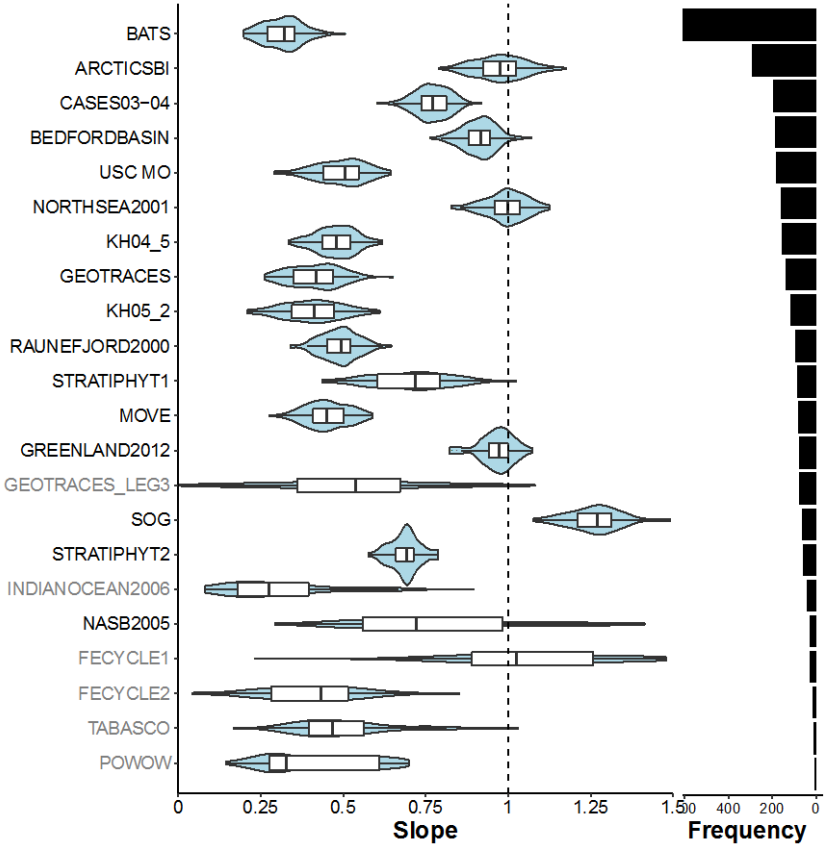
Quantifying the large-scale properties of virus-microbe communities

what can we learn?

What Mechanisms Can Explain the Nonlinear Relationship between Virus and Microbial Cell Abundances?

Potential Co-variates

Nutrients
Diversity
Relative importance of grazing
Resistance & specificity
Non-specific viruses (e.g., of eukaryotes)
Vesicles
Spatial structure
Lysogeny



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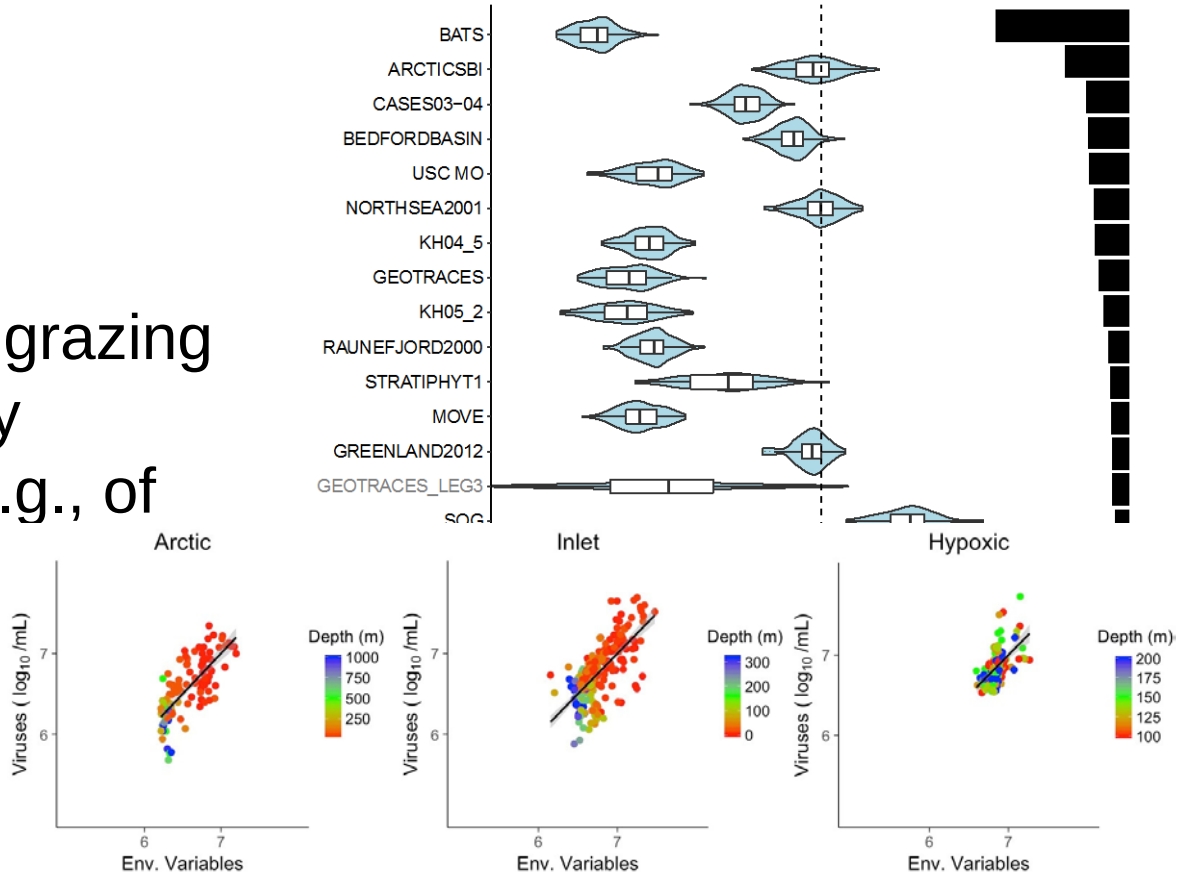

Finke et al. Viruses, 2017

What Mechanisms Can Explain the Nonlinear Relationship between Virus and Microbial Cell Abundances?

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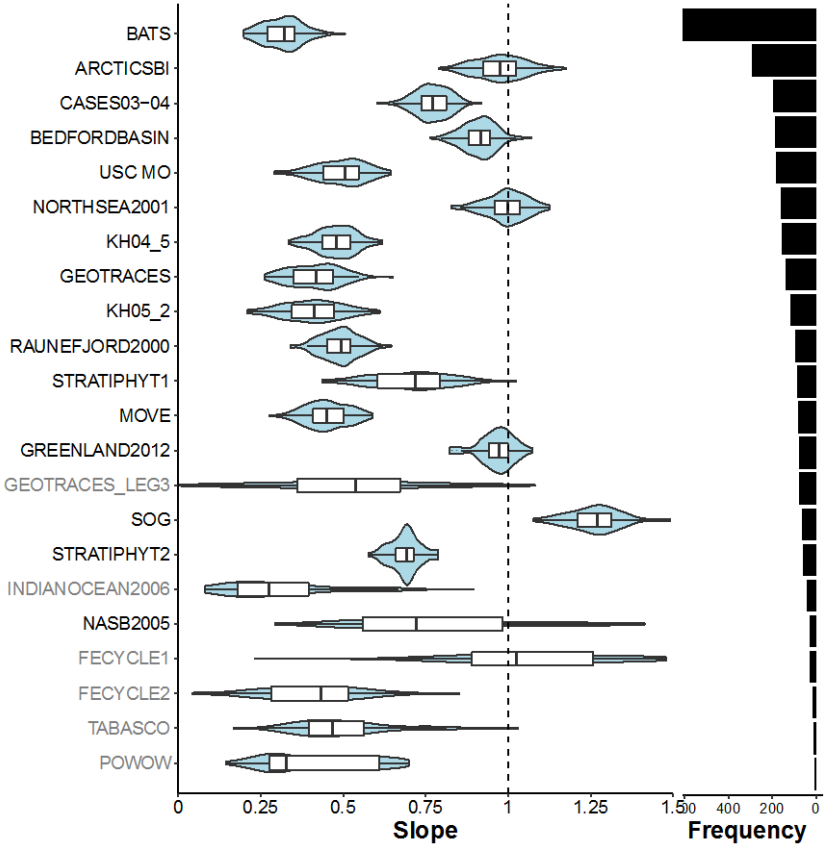
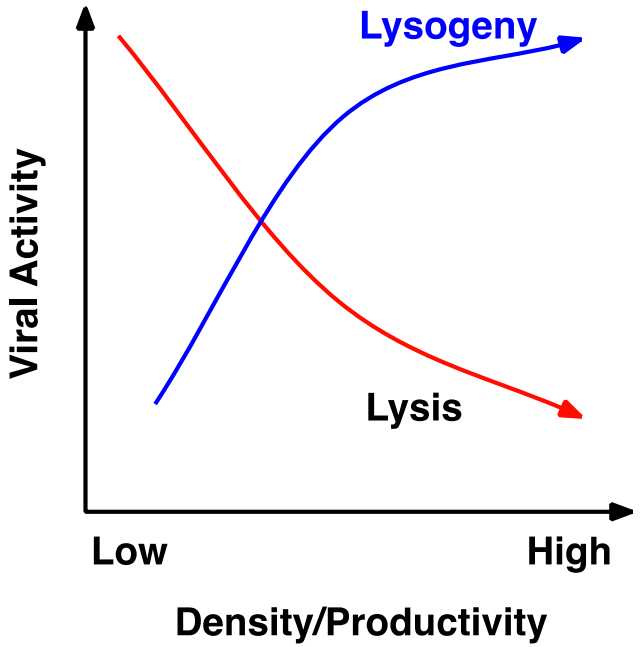


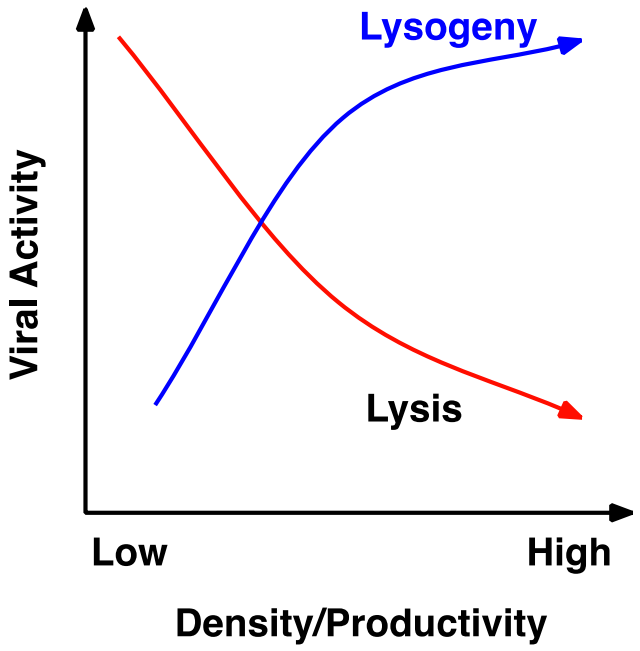
“Piggyback the Winner (PtW)”
Knowles et al., Nature, 2016

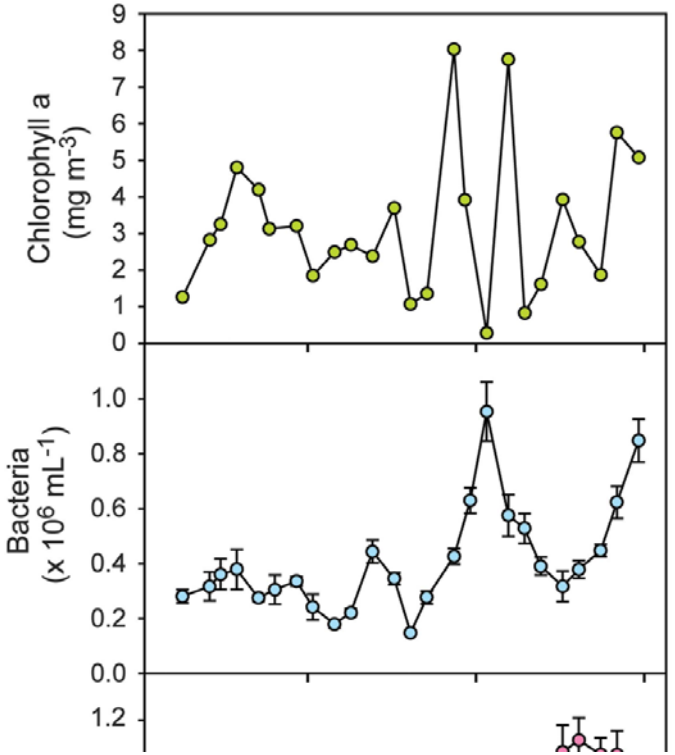
Piggyback-the-Winner: Concepts and Critiques



Piggyback-the-winner: Lysis suppressed and lysogeny enhanced at high productivity/densities, thereby causing decreases in VMR.

Piggyback-the-Winner: Concepts and Critiques



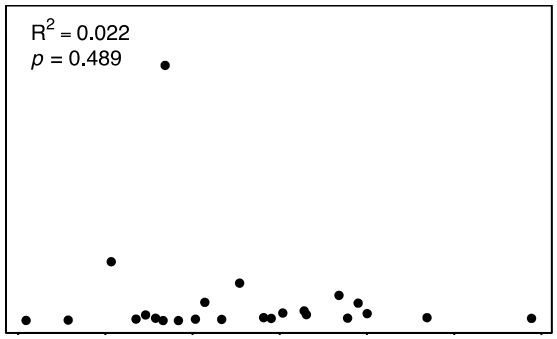


Piggyback-the-winner: Lysis suppressed and lysogeny enhanced at high productivity/densities, thereby causing decreases in VMR.

Contrasting Concept: Lysogeny prevalent given low productivity and lysis elevated at high productivity, e.g., Arctic ocean study by Brum et

PtW Claim 1 – In coral reef environments, systems with high microbial abundance have increasing relevance of lysogeny.

However, increasing "temperate-like" genes in the virome could indicate high induction and decreasing relevance of lysogeny (to the extent that weak relationships are present, many of which are not).



Microbes	Provirus-like reads	Method	Bootstrap 95% CI
Log	Linear	Pearson	(-0.37,0.36)
Linear/Log	Linear/Log	Kendall	(-0.13,0.46)
Linear/Log	Linear/Log	Spearman	(-0.15,0.64)
Log	Linear	Robust - Bisquare	(-0.41,0.58)
Log	Linear	Robust - Hampel	(-0.78,0.57)
Log	Linear	Robust - Huber	(-0.95,0.49)

Additional details and methods in:
Weitz, Beckett, Brum, Cael & Dushoff.
Lysis, lysogeny, and virus-microbe ratios, *biorXiv: 051085*

PtW Claim 2 – When increasing relevance of lysogeny is integrated into a dynamic model, then the virus-to-microbe ratio decreases with increasing microbial abundance.

However, there is no lysogeny in the PtW model. Rather, the PtW model is a lytic model where the lysis and viral release increases with increasing cell abundance.

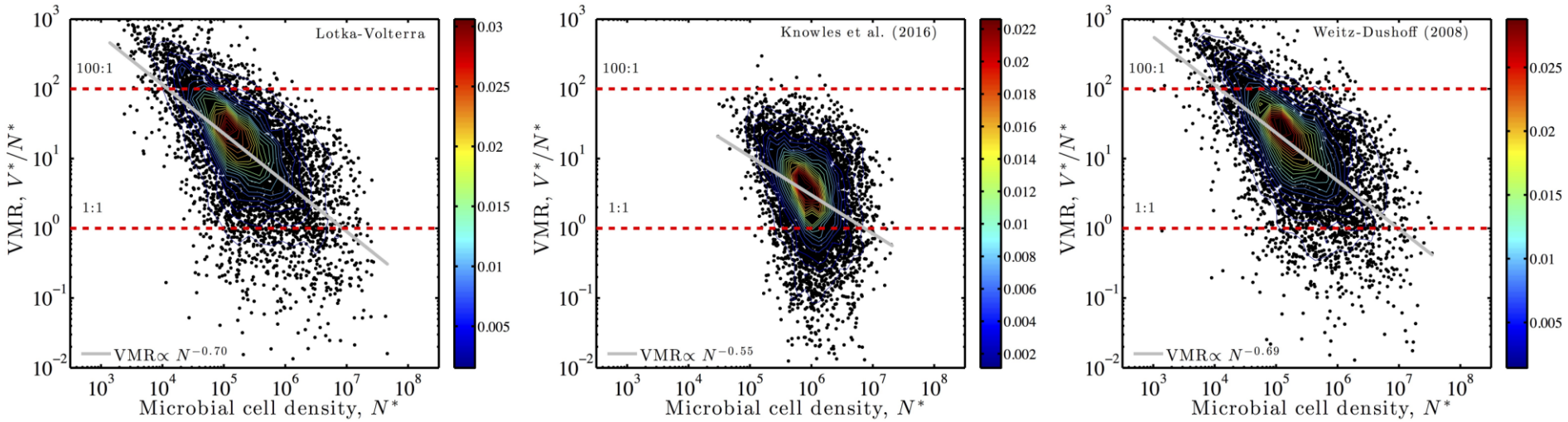
$$\overbrace{\frac{dN}{dt}}^{\text{mcirobial cell change}} = \overbrace{rN(1-N/K)}^{\text{microbial growth}} - \overbrace{\phi NP}^{\text{lysis}} - \overbrace{dN}^{\text{microbial mortality}}$$

$$\overbrace{\frac{dV}{dt}}^{\text{viral particle change}} = \overbrace{\beta\phi NV\frac{N}{K}}^{\text{viral release}} - \overbrace{mV}^{\text{viral decay}}$$

Additional details and methods in:
Weitz, Beckett, Brum, Cael & Dushoff.
Lysis, lysogeny, and virus-microbe ratios, *biorXiv: 051085*

PtW Claim 3 - Other models cannot explain this result, hence PTW is the likely mechanism underlying nonlinear VMRs in coral reefs and the global oceans.

However, multiple models – including "Lotka-Volterra" models – can exhibit a declining VMR with increasing microbial cell

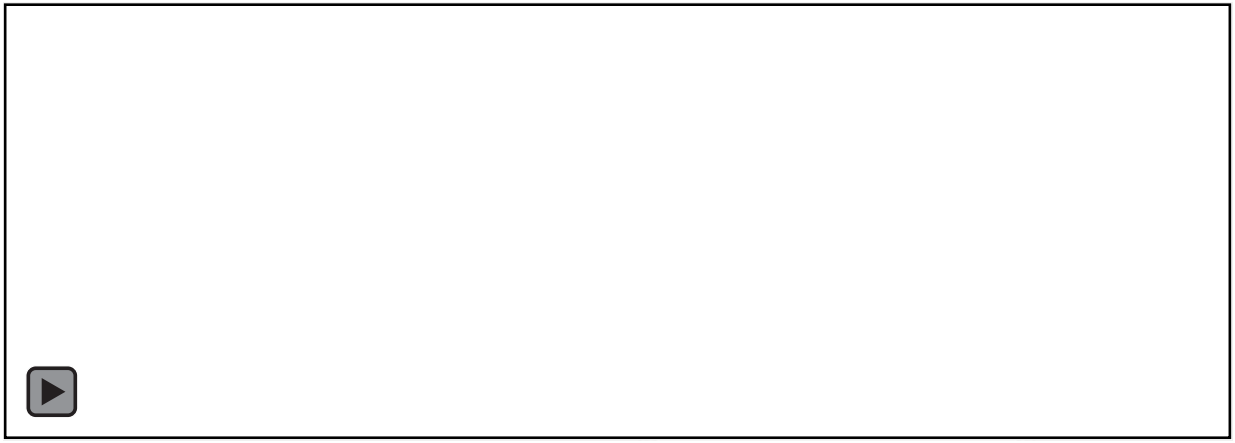


Additional details and methods in:
Weitz, Beckett, Brum, Cael & Dushoff.
Lysis, lysogeny, and virus-microbe ratios, *biorXiv: 051085*

My view:

We need better measurements and models of viral and microbial dynamics that can directly test mechanisms based on core principles of virus biology.

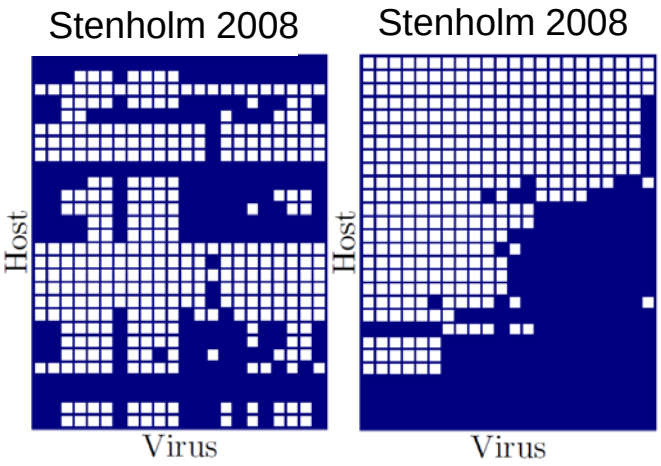
In doing so, we may find that not all mechanisms and patterns are universal. Different laws may emerge at different scales and in different oceanic



Taylor, Penington, and Weitz, Phys Biol (2016)

Questions ?

Weitz Group
http://ecotheory.biology.gatech.edu
http://qbios.gatech.edu



Flores et al., PNAS, 2011
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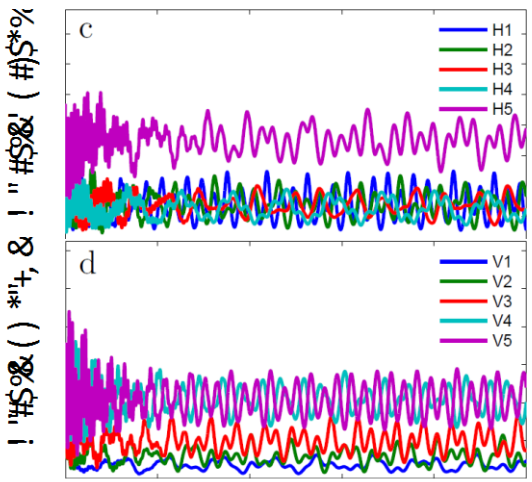

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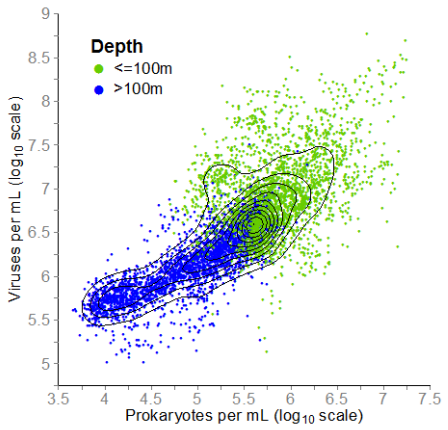

Wigington et al. Nature Micro 201
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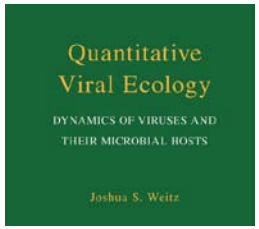

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