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Viral ecogenomics: exploring viral diversity and virus-host interactions from metagenomes

Simon Roux, Environmental Genomics Group
NASA Workshop without walls: Astrovirology

Outline

- **"Viruses here, viruses there, viruses everywhere"**
  Why and how we study viruses of microbes in the environment

- **"So I got some genomes, now what ?"**
  Strengths and challenges of metagenomics for viral ecology

- **"Should I kill or should I wait ?"**
  Targeted metagenomes reveal new aspects of virus-host dynamics

Mcirobes rule the world

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OUR MICROBIAL PLANET

MICROBES—life forms too tiny to see—play a surprisingly large role in life on Earth. Microbes are everywhere, and they do a lot of good for human health and our planet. In fact, disease-causing microbes make up only a very tiny fraction of the millions of types of microbes. Microbes. . .

Think microbes are bad guys? Think again.

The Microbial Engines That Drive Earth's Biogeochemical Cycles

Paul G. Falkowski,[1*] Tom Fenchel,[2*] Edward F. Delong[3*]

23 MAY 2008 VOL 320 **SCIENCE**

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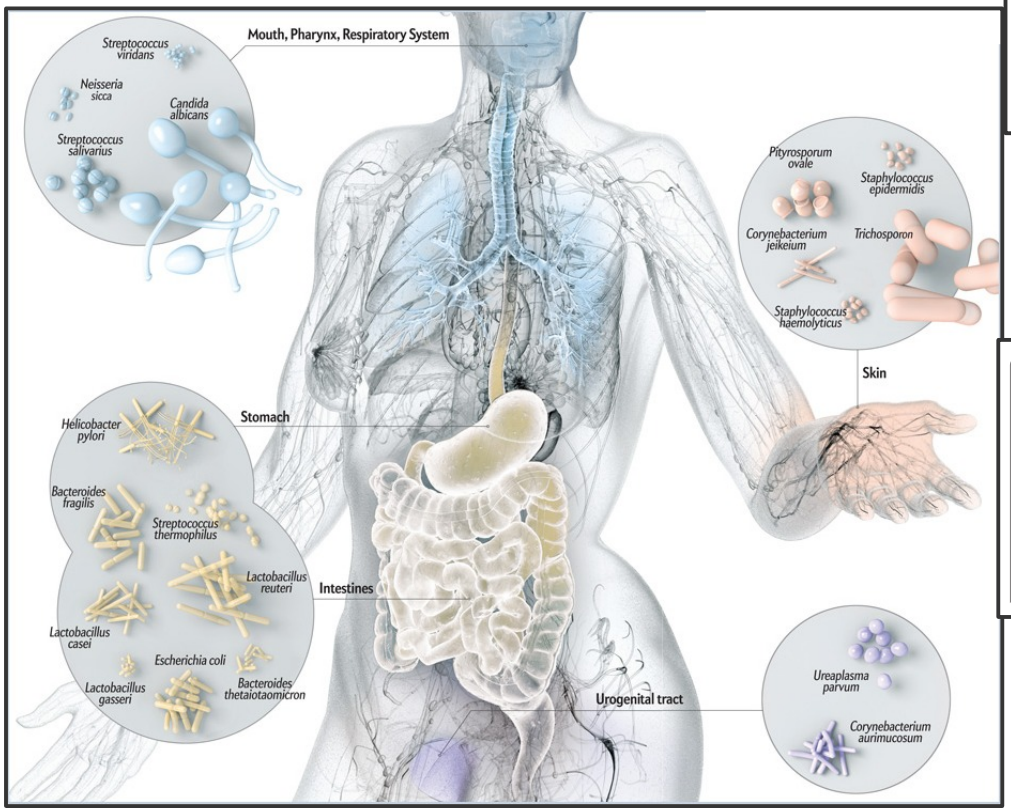

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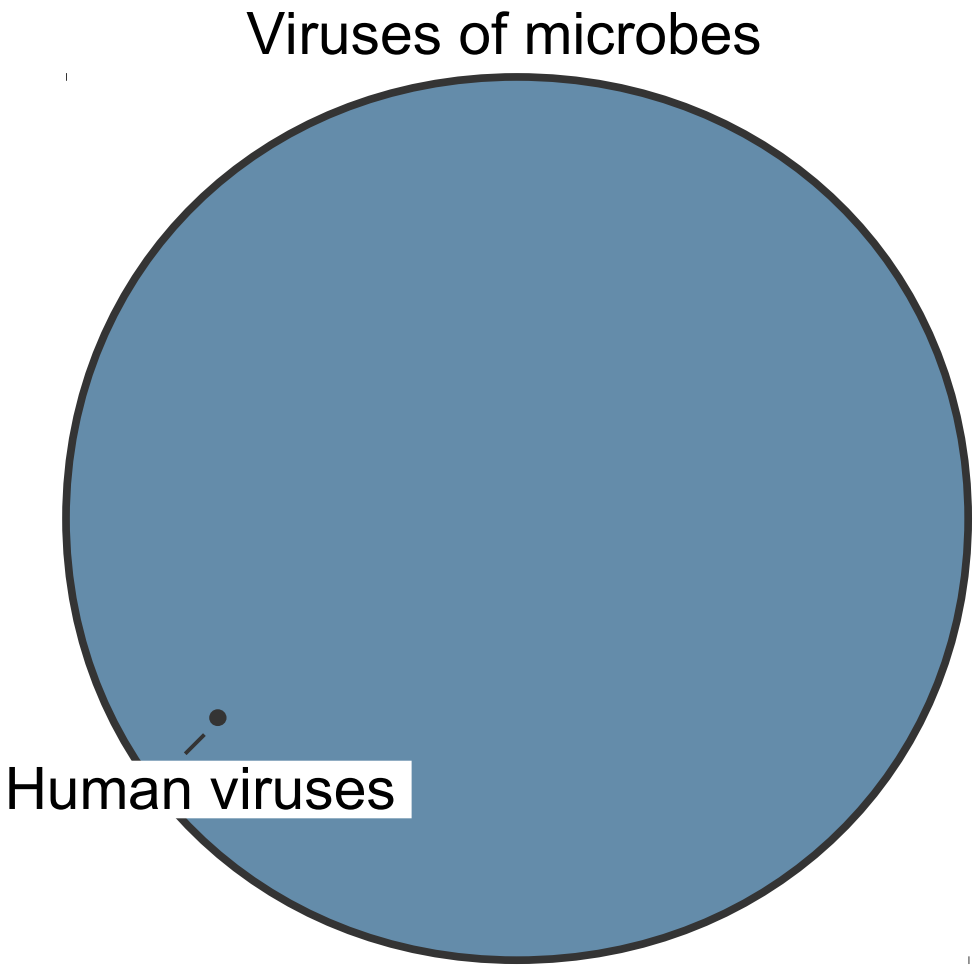
The human microbiome: at the interface of health and disease

Ilseung Cho[1,2] *and Martin J. Blaser*[1,2,3,4]

260 | APRIL 2012 | VOLUME 13 **nature reviews genetics**

Viruses of microbes are everywhere



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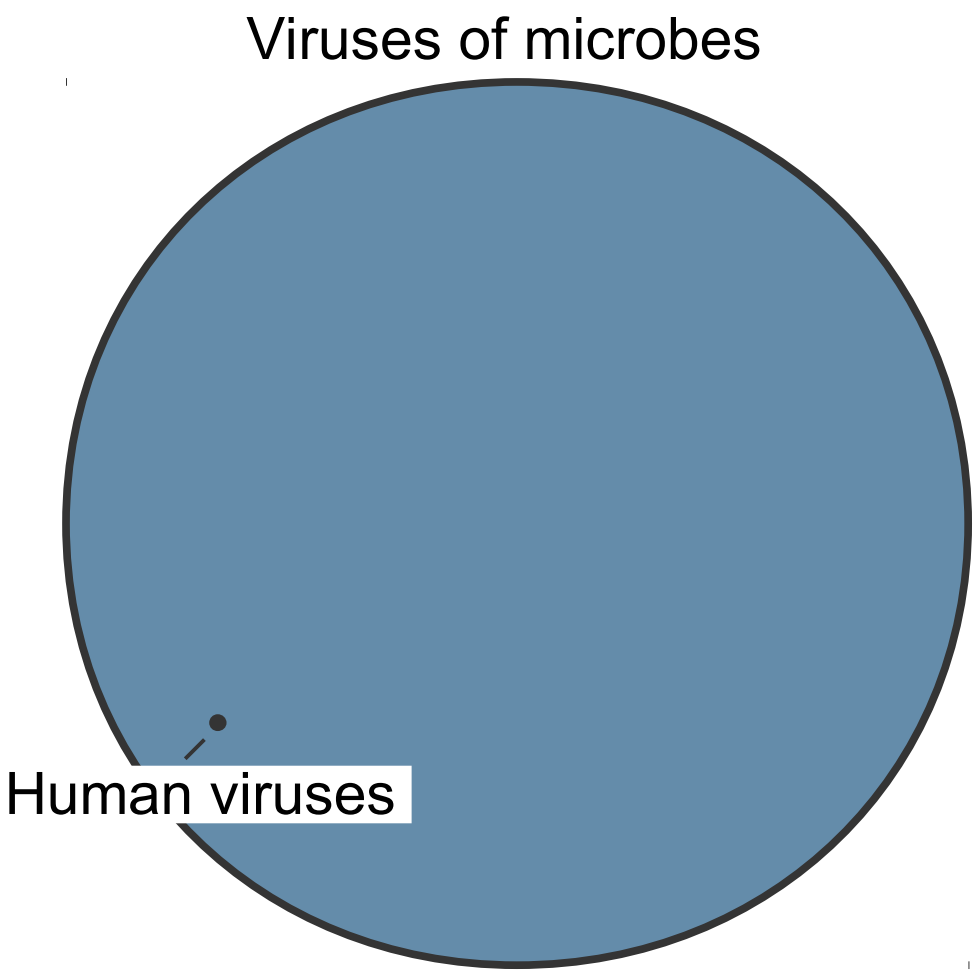

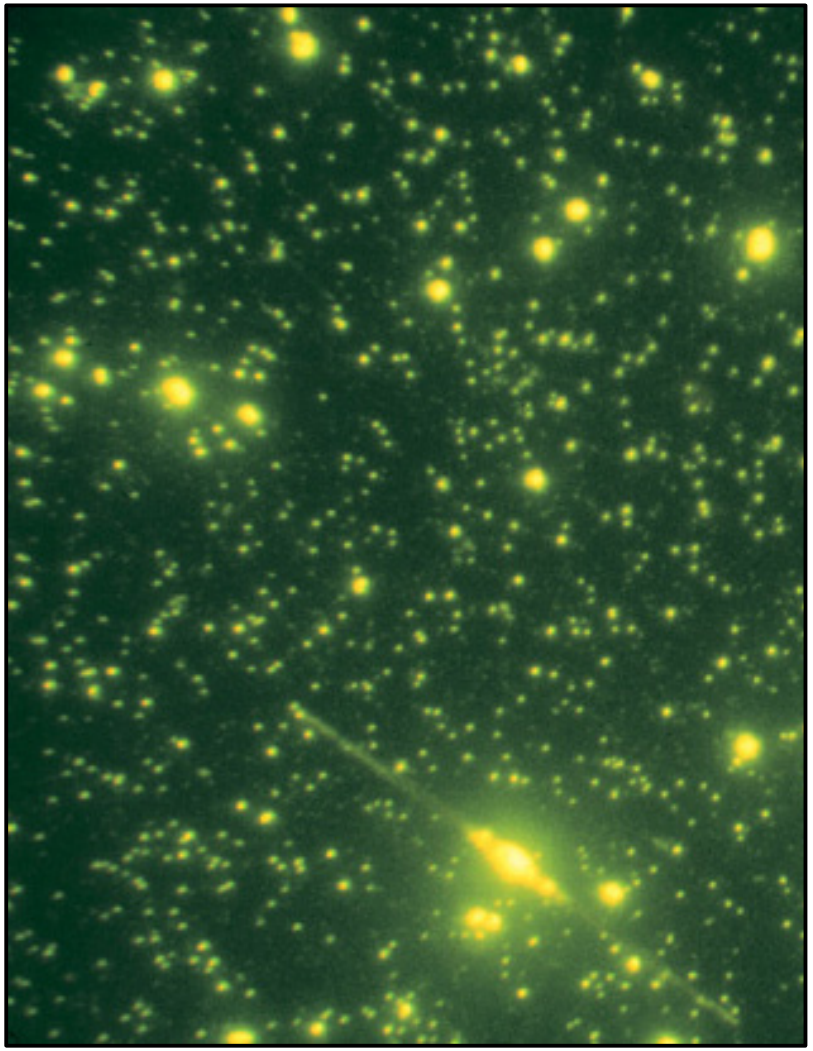

Picture: Fuhrman Lab

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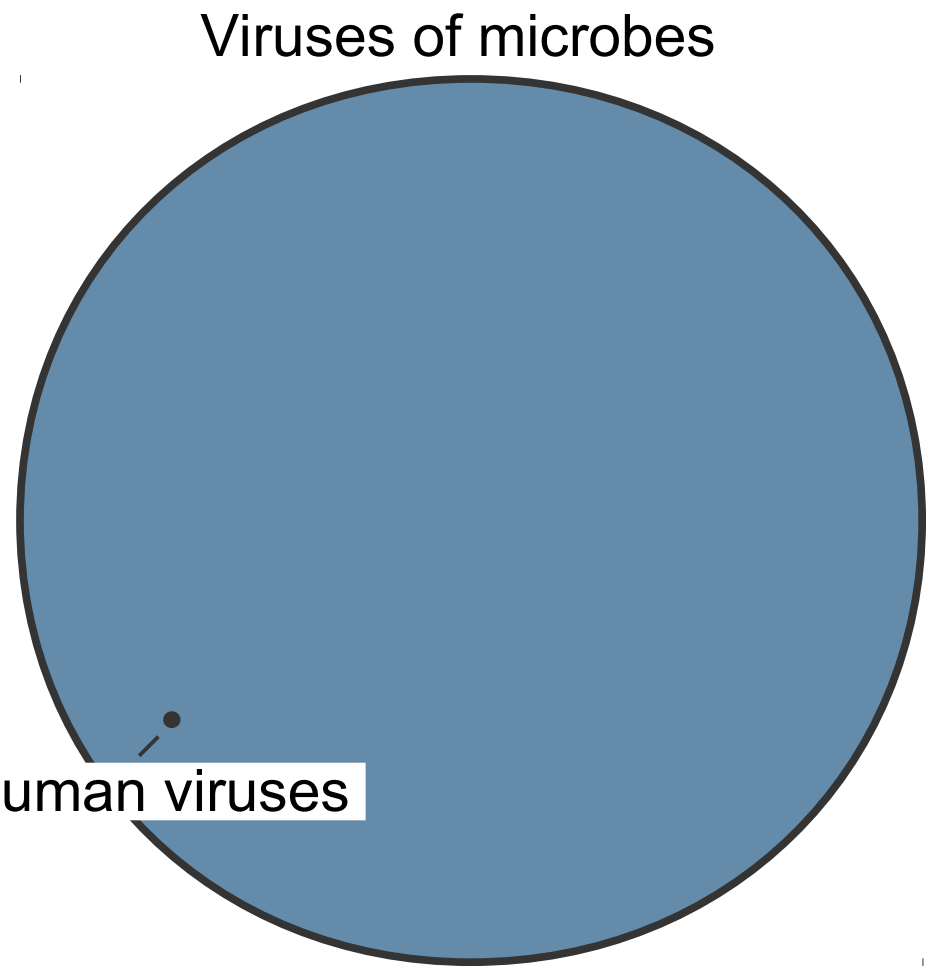

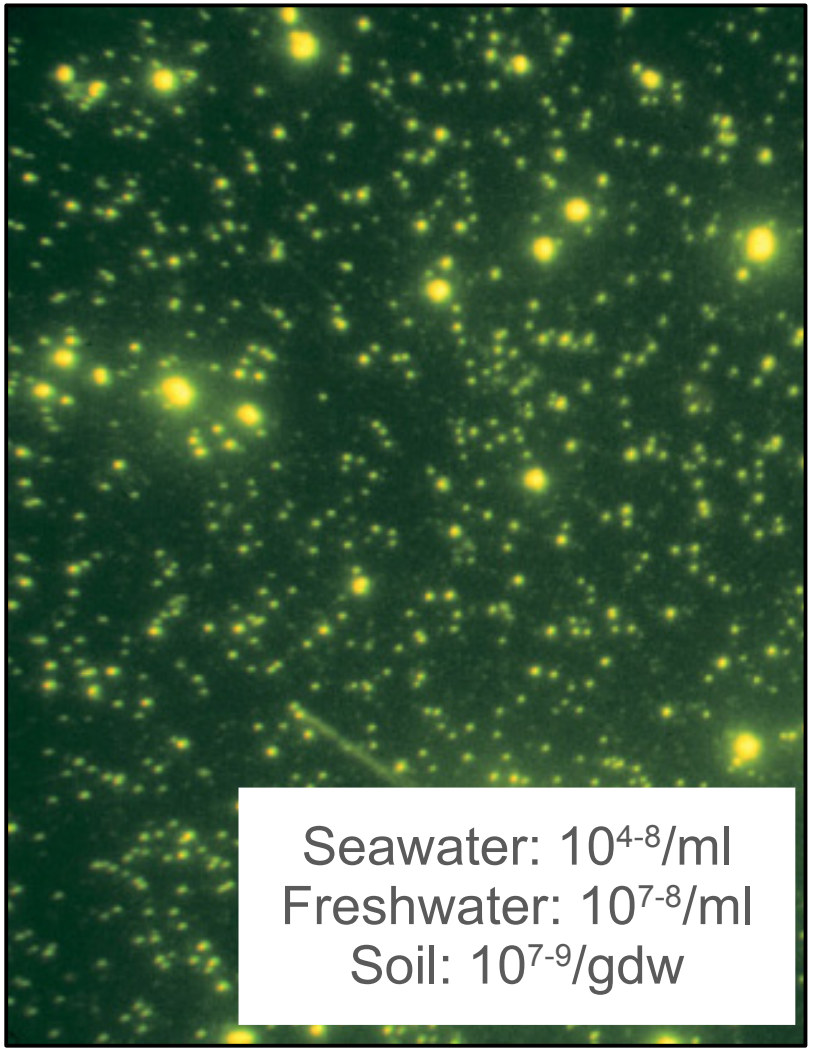

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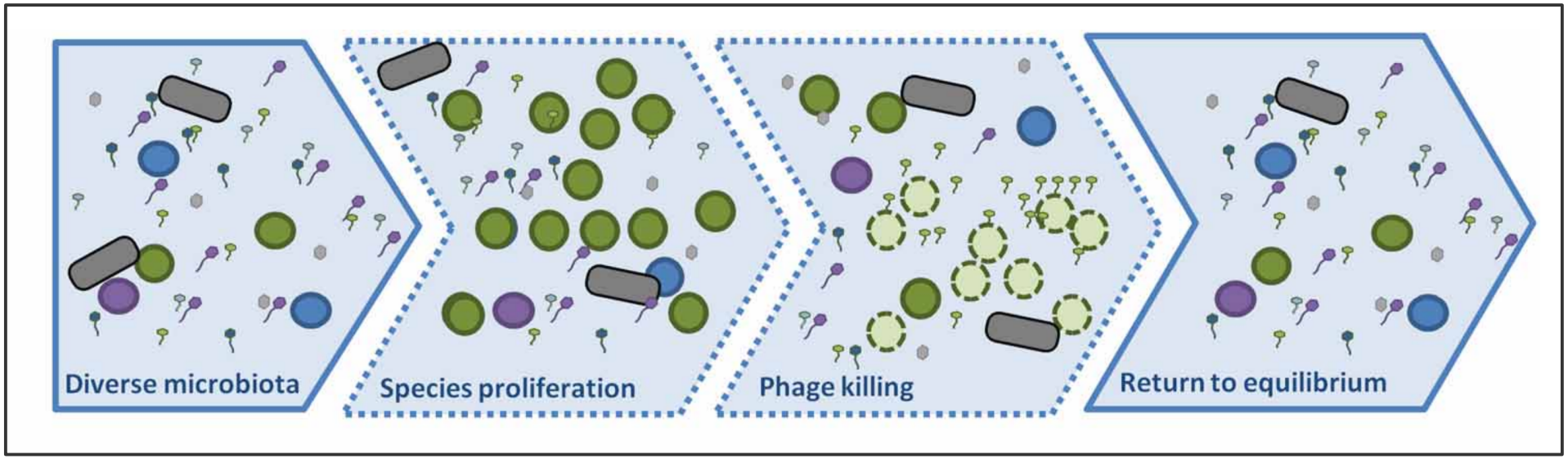
Virus impacts on ecosystems

- **Viruses influence microbial community structure & diversity**
  - "Kill the winner" hypothesis



Frede Thingstad, 2000, De Paepe *et al.*, 2014

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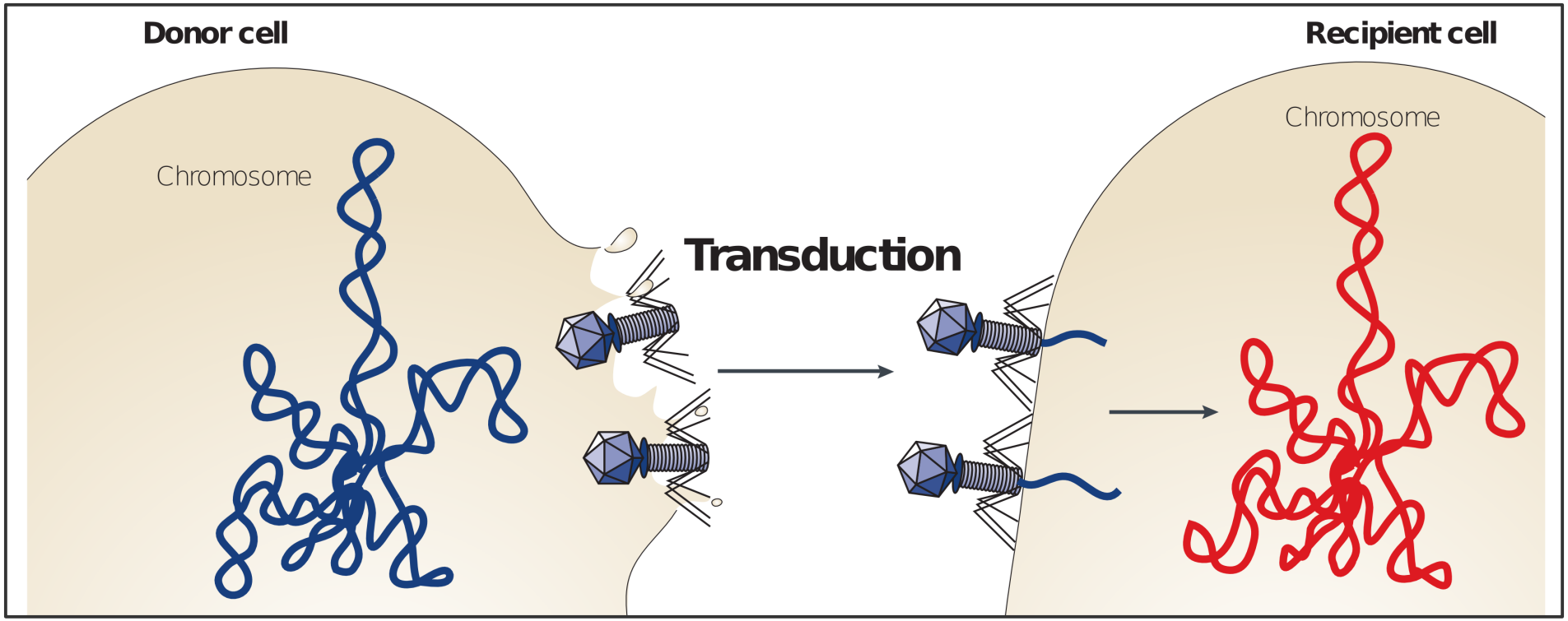
  - Transduction(s), but also free DNA release, Gene Transfer Agent (GTA)



Frost *et al.*, 2005

Virus impacts on ecosystems

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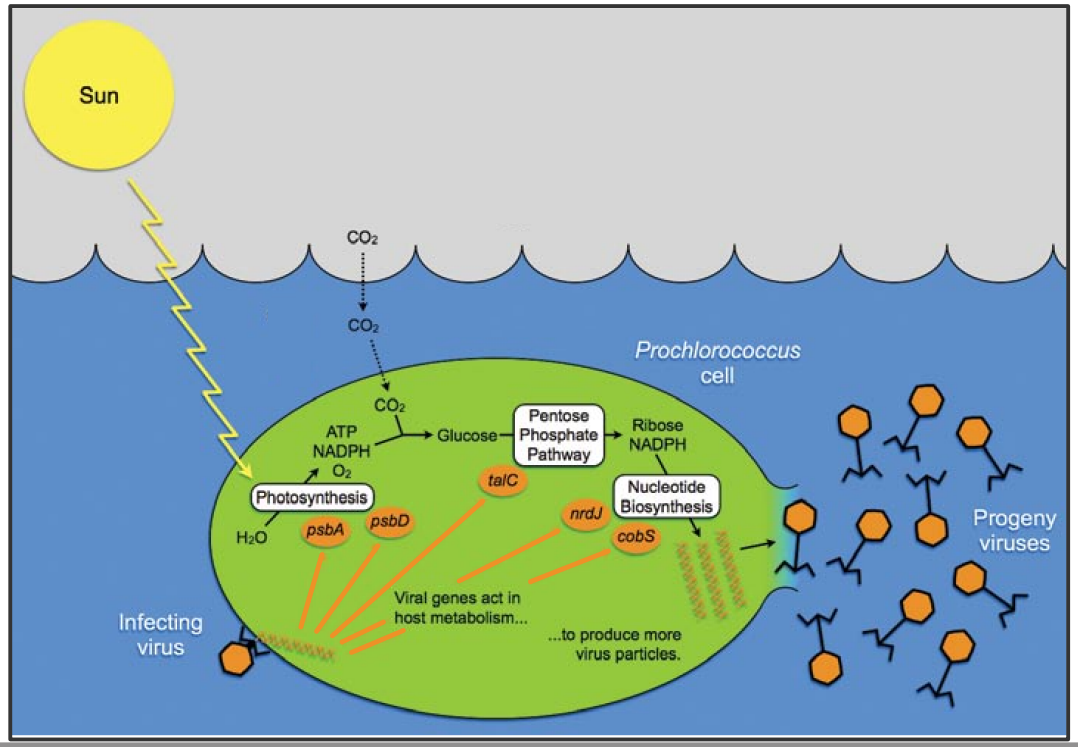
- **Viruses act as lateral gene transfer agents**
  - Transduction(s), but also free DNA release, Gene Transfer Agent (GTA)
- **Virus alter host cell phenotype**
  - Integrated phages encoding toxins: lysogenic conversion
  - Auxiliary metabolic genes (AMGs)

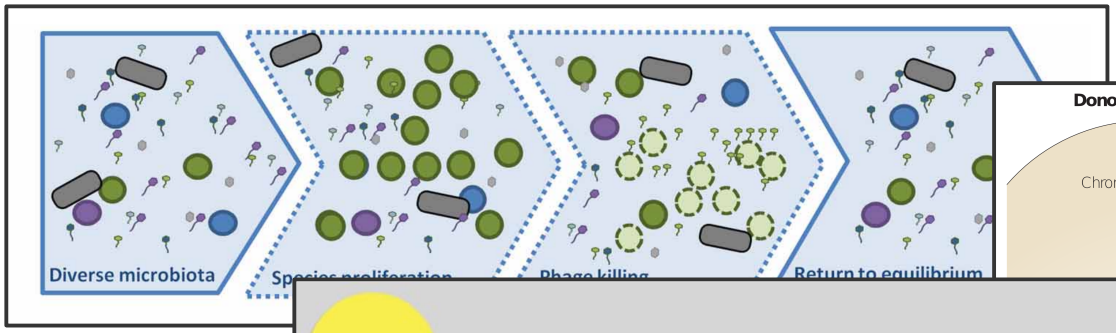


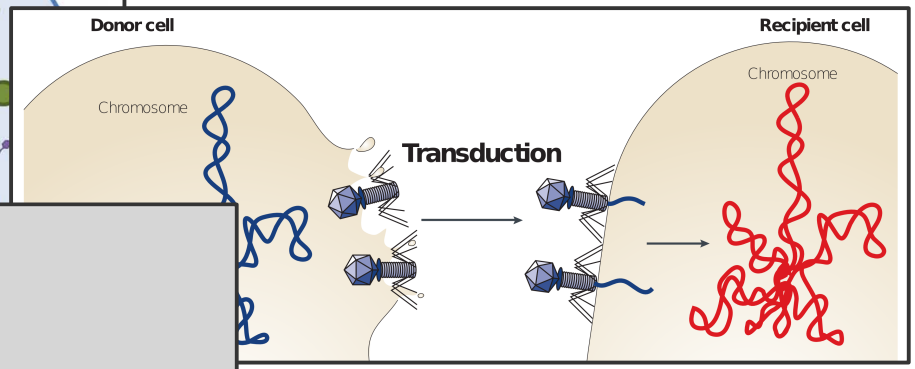
- AMG examples:
  - Photosystem
  - Central C
  - N/P/S metabolism
  - Fermentation (giant virus)
  - ...

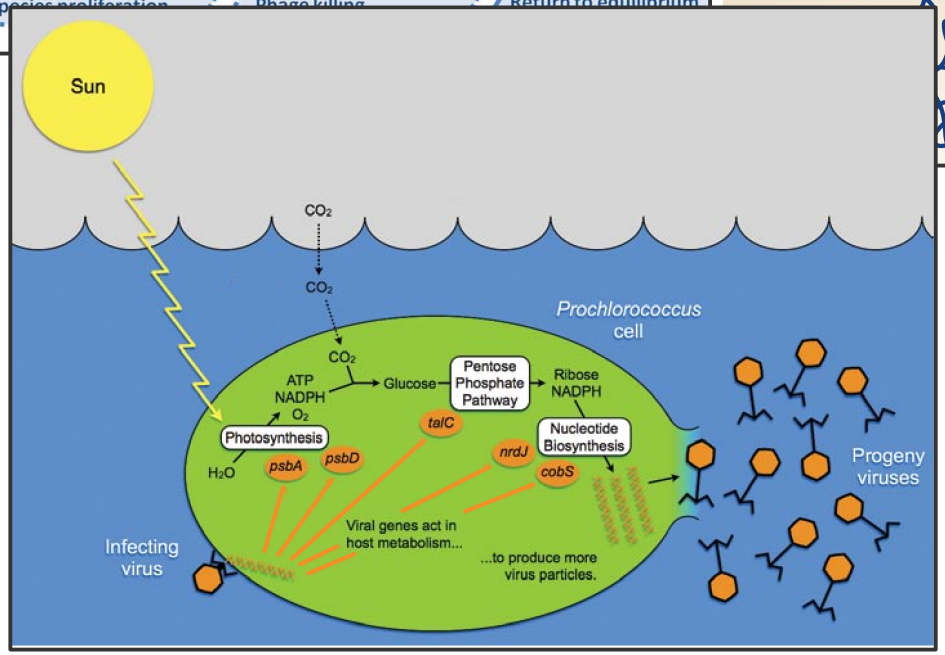
Breitbart *et al.*, 2007

Why study viral ecology ?

- **Viruses of microbes are important**
  - Virus-like particles are (highly) abundant ✓
  - Viral infections can strongly impact microbial communities ✓







Challenges of viral ecology

- **How can we study environmental viruses ?**
  - No universal marker gene (no 16S or 18S)
  - Challenging to cultivate
  - Needs cultivation-free “no-prior-knowledge required” approaches

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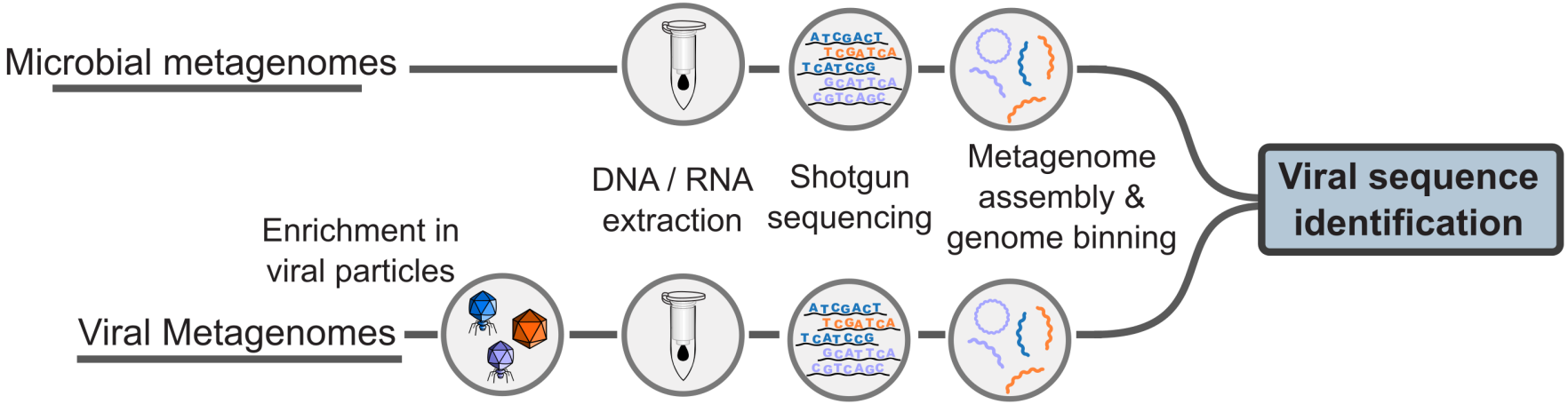
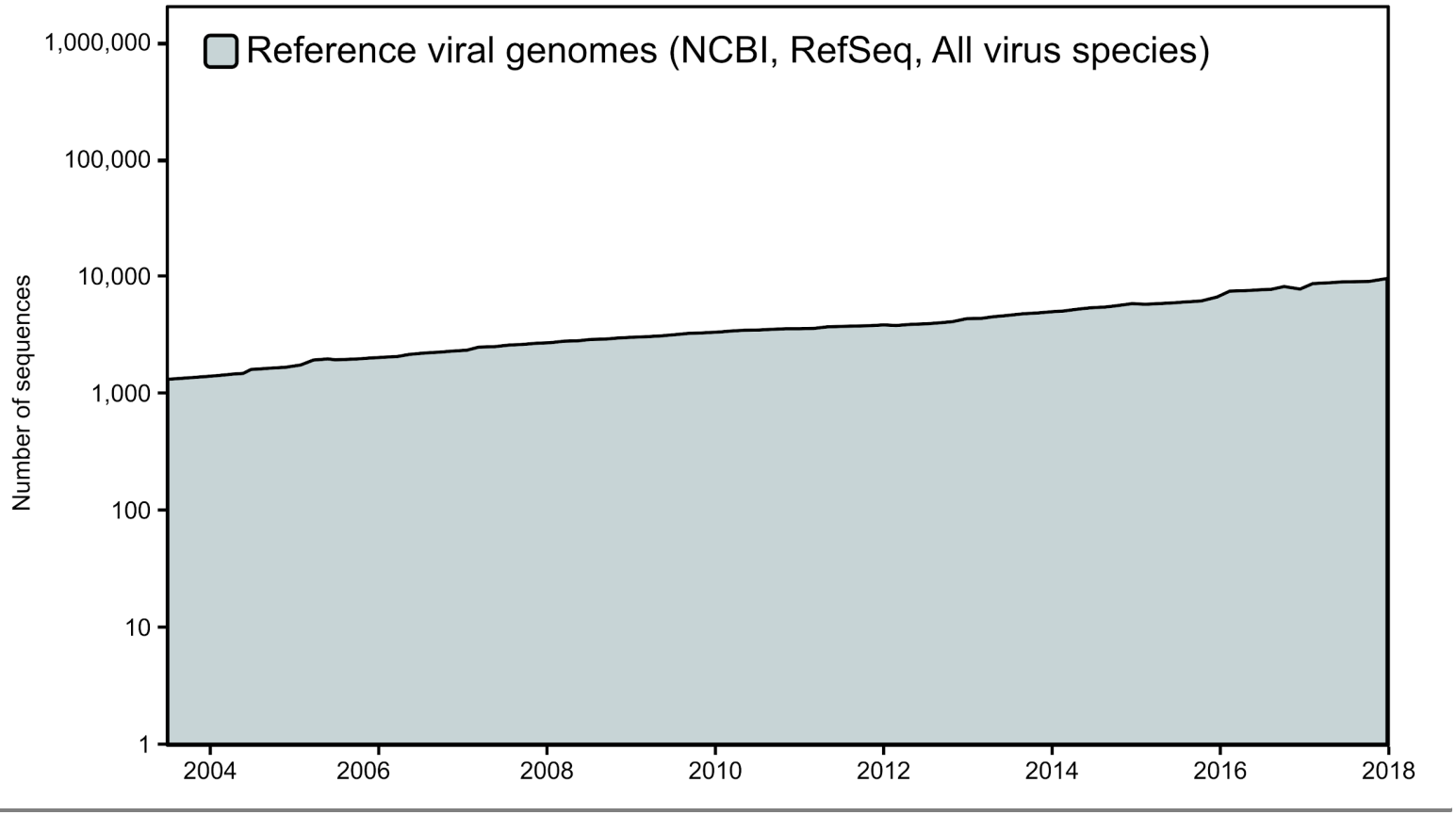
- **Assemble viral genomes from (viral) metagenomes**



Importance of metagenomics

- **Unprecedented exploration of viral diversity**
  - Now the primary source of new viral genomes



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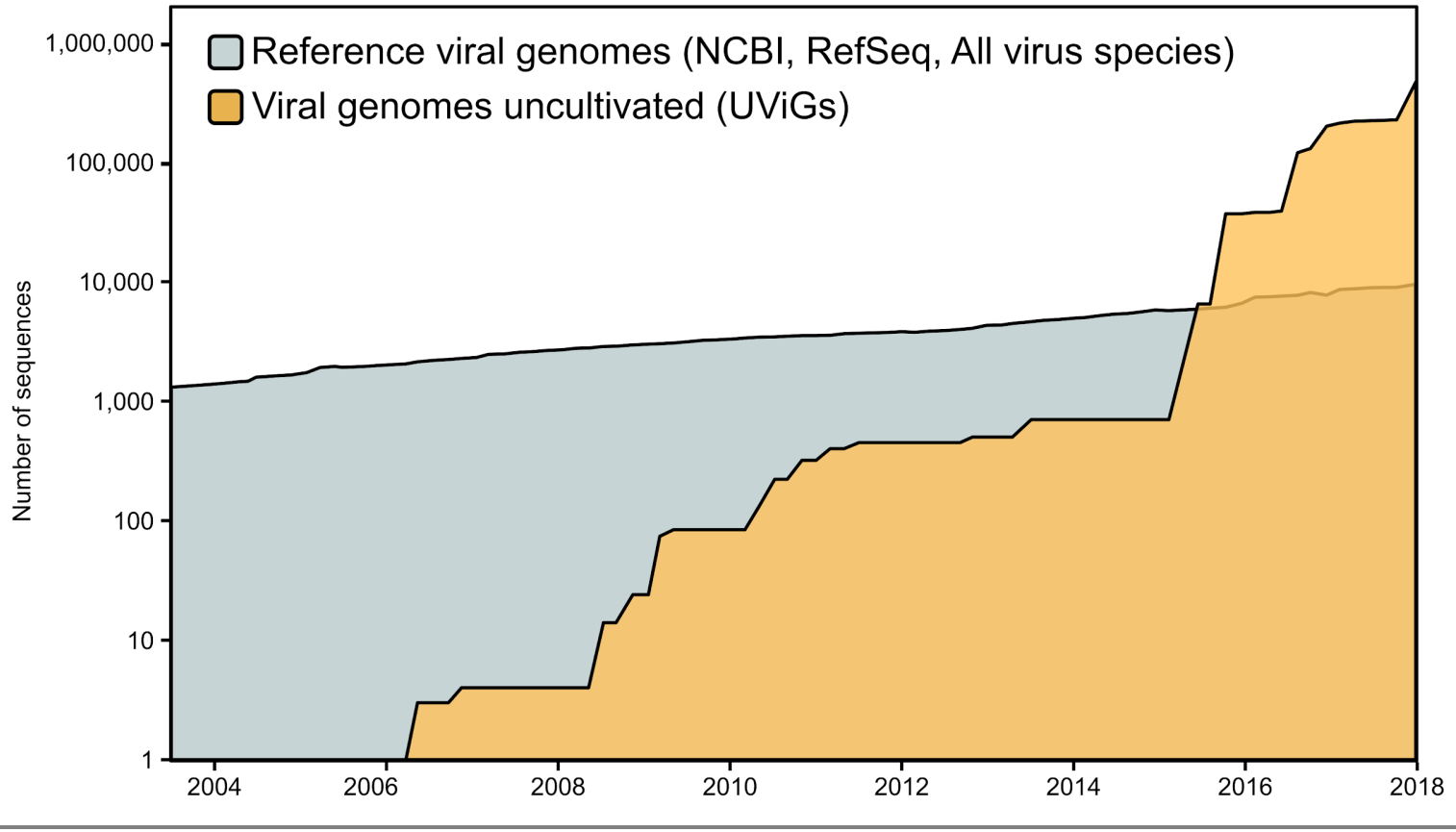

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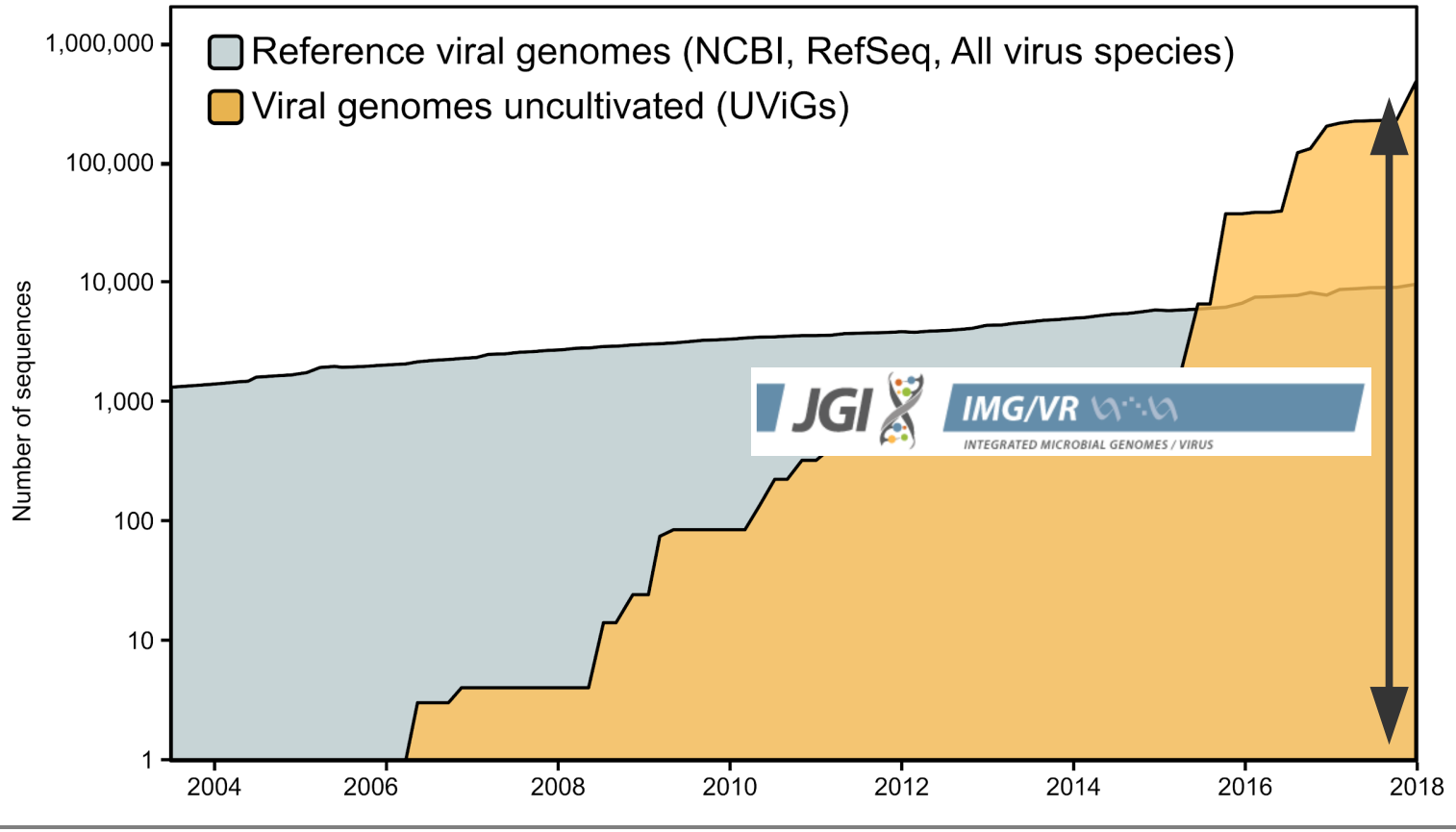

https://img.jgi.doe.gov/cgi-bin/vr

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Viral metagenome possibilities

- Standards to analyze, describe, and report UViGs

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PERSPECTIVE

Minimum Information about an Uncultivated Virus Genome (MIUViG)

Simon Roux[1], Evelien M Adriaenssens[2], Bas E Dutilh[3,4], Eugene V Koonin[5], Andrew M Kropinski[6], Mart Krupovic[7], Jens H Kuhn[8], Rob Lavigne[9], J Rodney Brister[5], Arvind Varsani[10,11], Clara Amid[12], Ramy K Aziz[13], Seth R Bordenstein[14], Peer Bork[15], Mya Breitbart[16], Guy R Cochrane[12], Rebecca A Daly[17]

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Free online platforms with virus-dedicated tools

https://ivirus.readthedocs.io
https://www.cyverse.org

https://kbase.us

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But it's not that simple (of course...)

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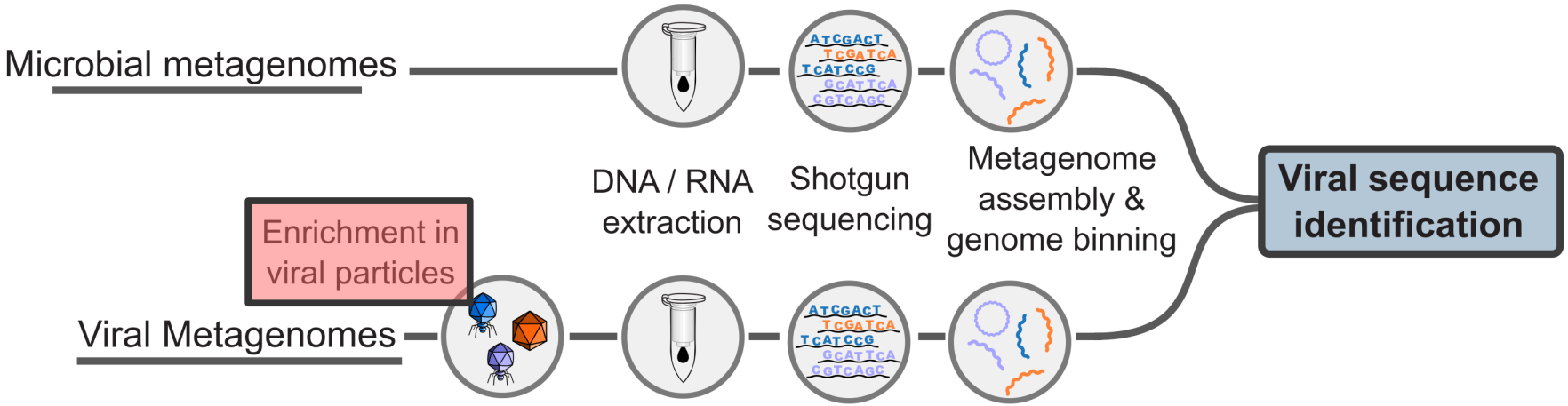
Major challenges in viral ecogenomics

- **Sample-to-viral-sequence pipeline**
  - Methods still in development for many environments, e.g. soil

PeerJ

Towards optimized viral metagenomes for double-stranded and single-stranded DNA viruses from challenging soils

Gareth Trubl[1,4], Simon Roux[2], Natalie Solonenko[1], Yueh-Fen Li[1], Benjamin Bolduc[1], Josué Rodríguez-Ramos[1,5], Emiley A. Eloe-Fadrosh[2], Virginia I. Rich[1] and Matthew B. Sullivan[1,3]



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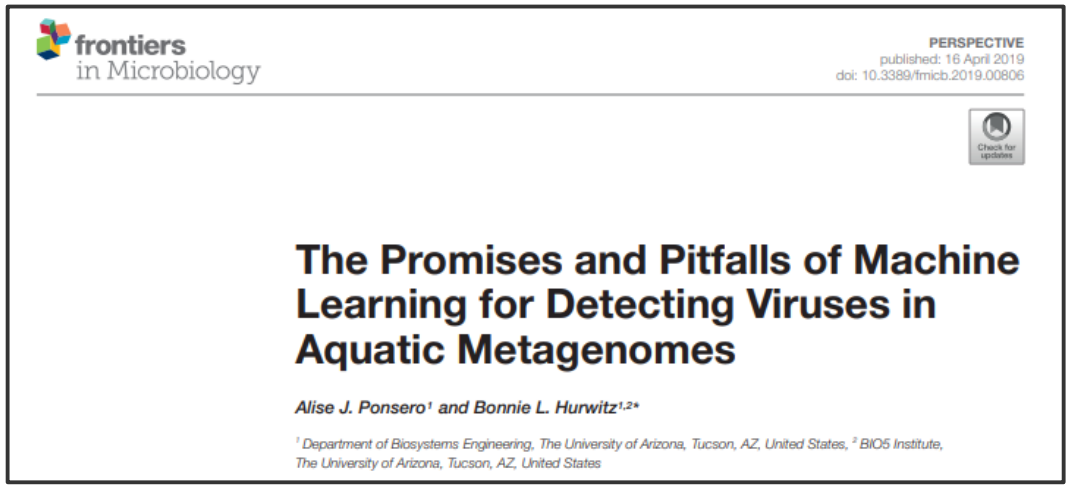

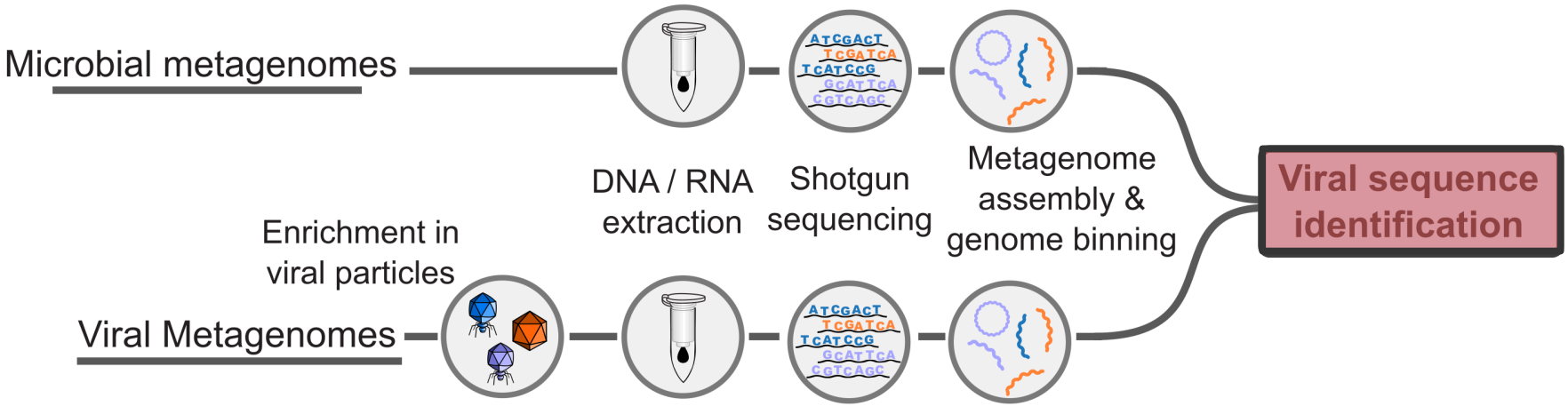

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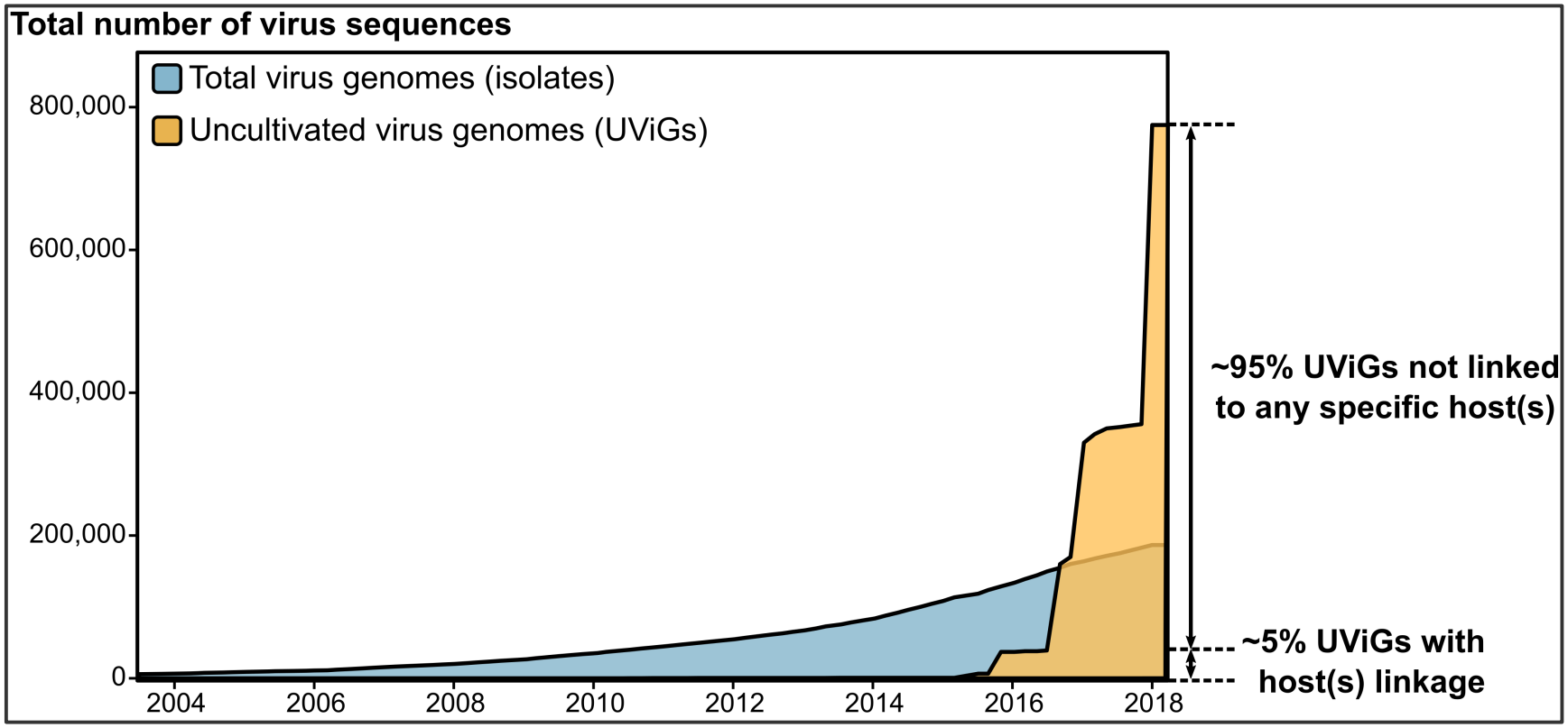

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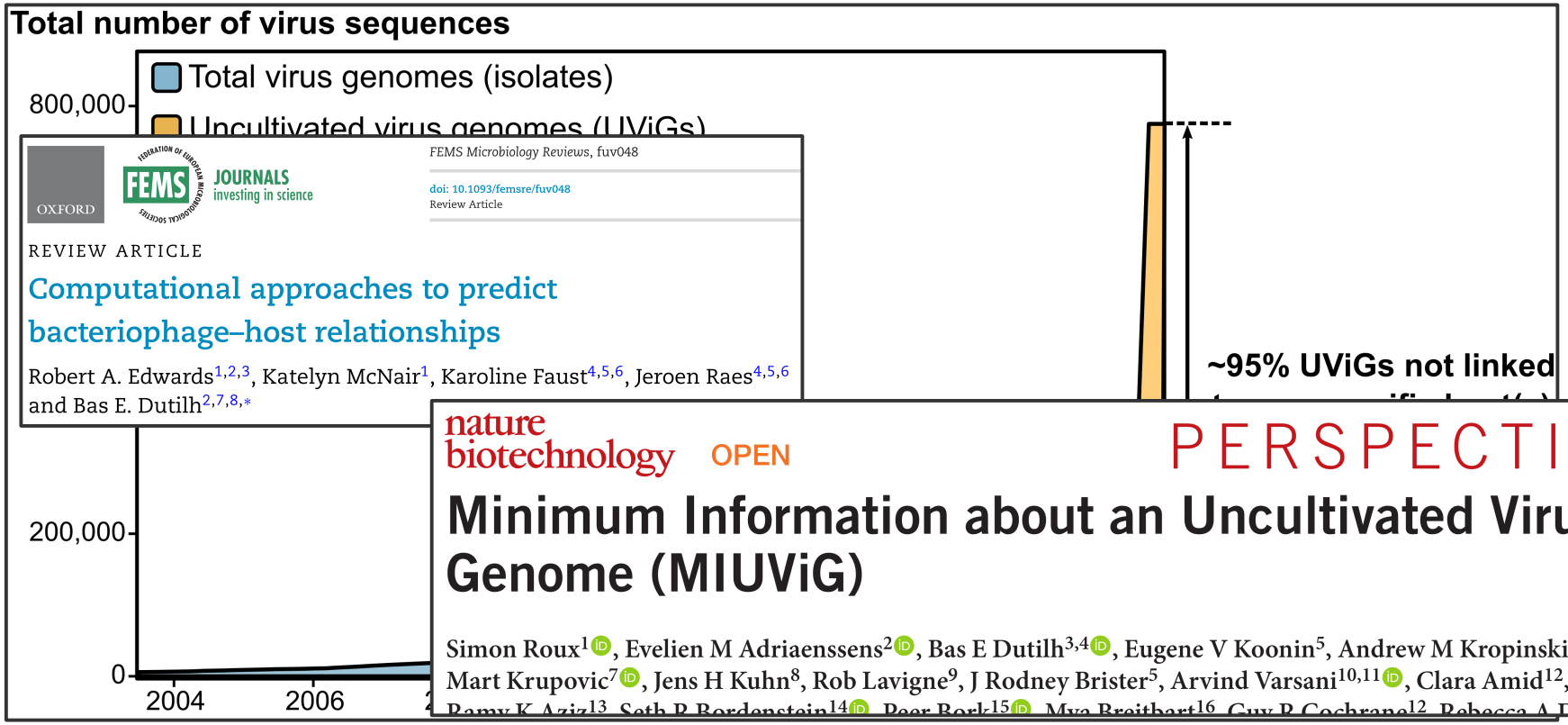

OXFORD
FEMS JOURNALS investing in science
FEMS Microbiology Reviews, fuv048
doi: 10.1093/femsre/fuv048
Review Article

REVIEW ARTICLE

Computational approaches to predict bacteriophage–host relationships

Robert A. Edwards[1,2,3], Katelyn McNair[1], Karoline Faust[4,5,6], Jeroen Raes[4,5,6] and Bas E. Dutilh[2,7,8,*]

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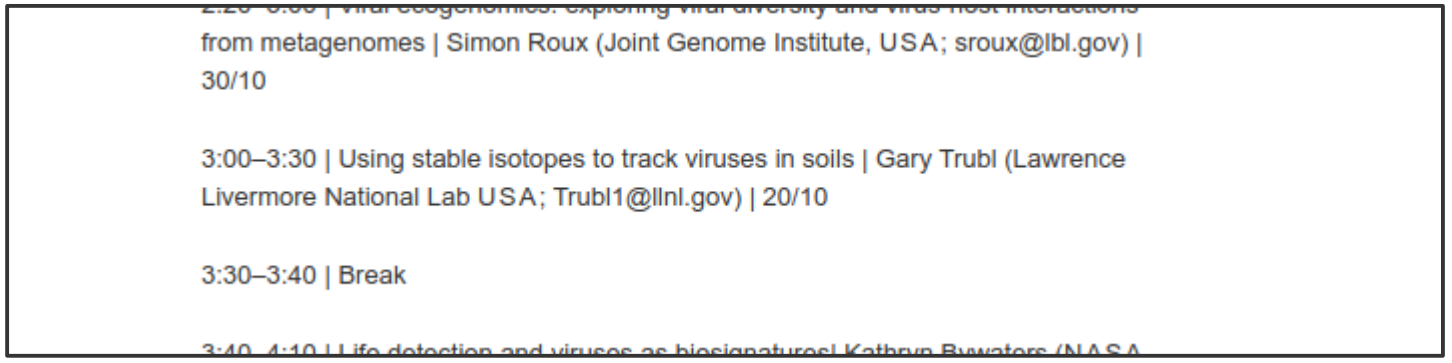
- **Virus activity / infectivity**
  - Virus sequence in metagenome ≠ active ("infectious") virus
  - Stay for next talk !



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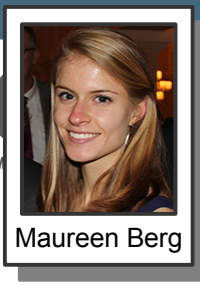
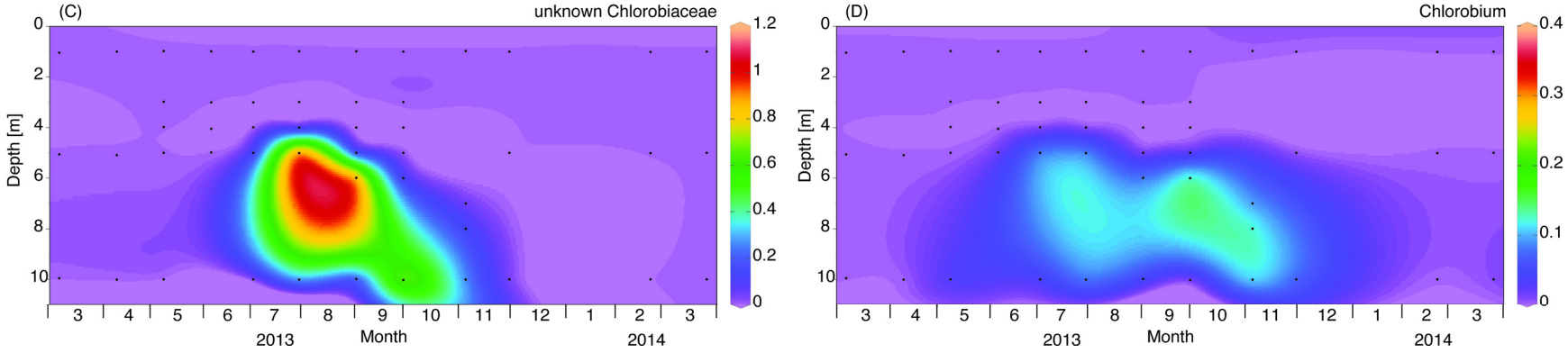
Viruses of Green Sulfur Bacteria


Maureen Berg

- **Green Sulfur Bacteria**
  - Seasonal bloom in stratified lake
  - example: 16S profile in Lake Vechten



Bloom in anoxic layer, i.e. late summer when lake is stratified

Diao, Huisman, & Muyzer, 2018

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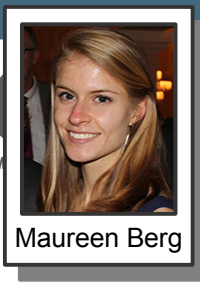

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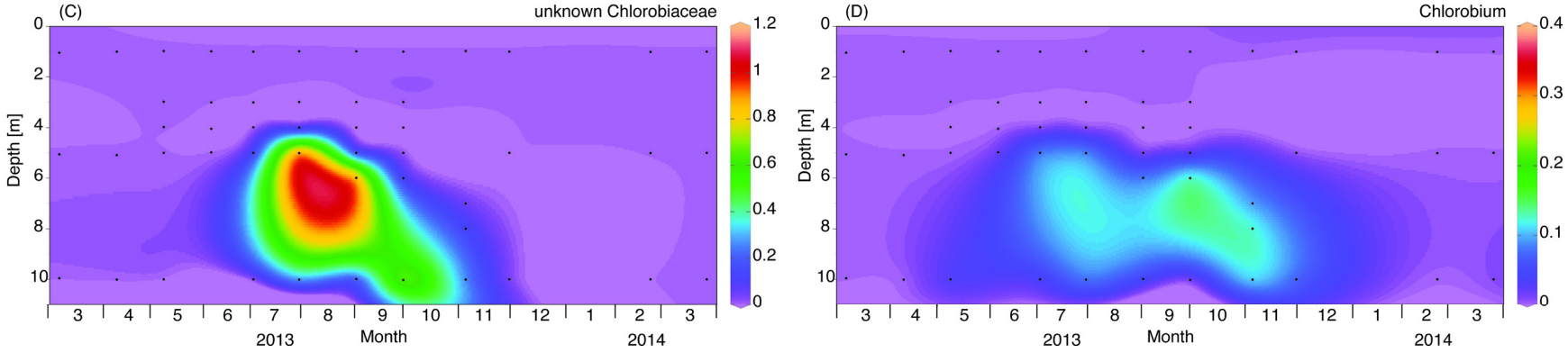

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Which viruses infect GSB ?

Diao, Huisman, & Muyzer, 2018

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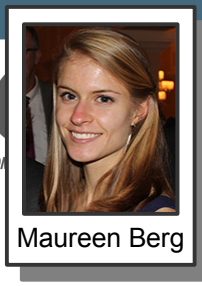

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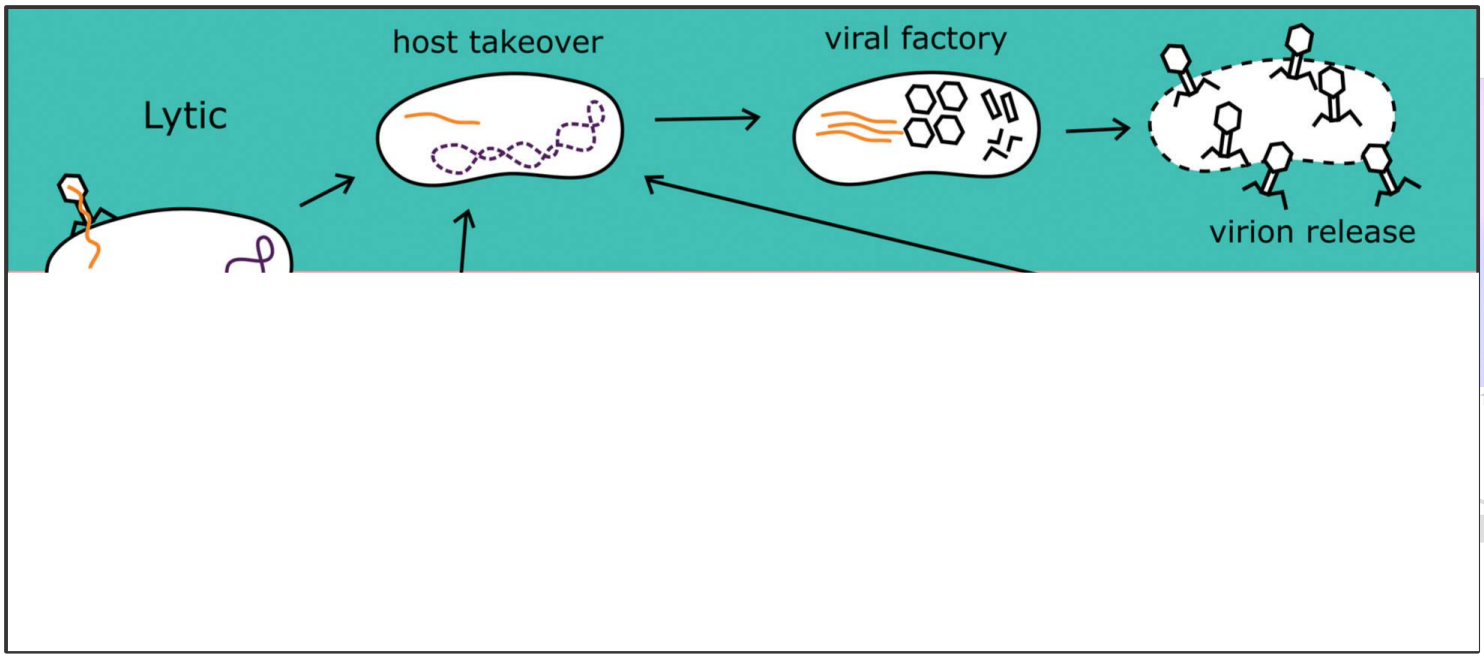

Yes because abundant host

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Active arms race ?

Howard-Varona et al., 2018

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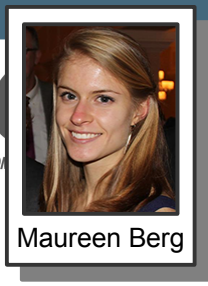

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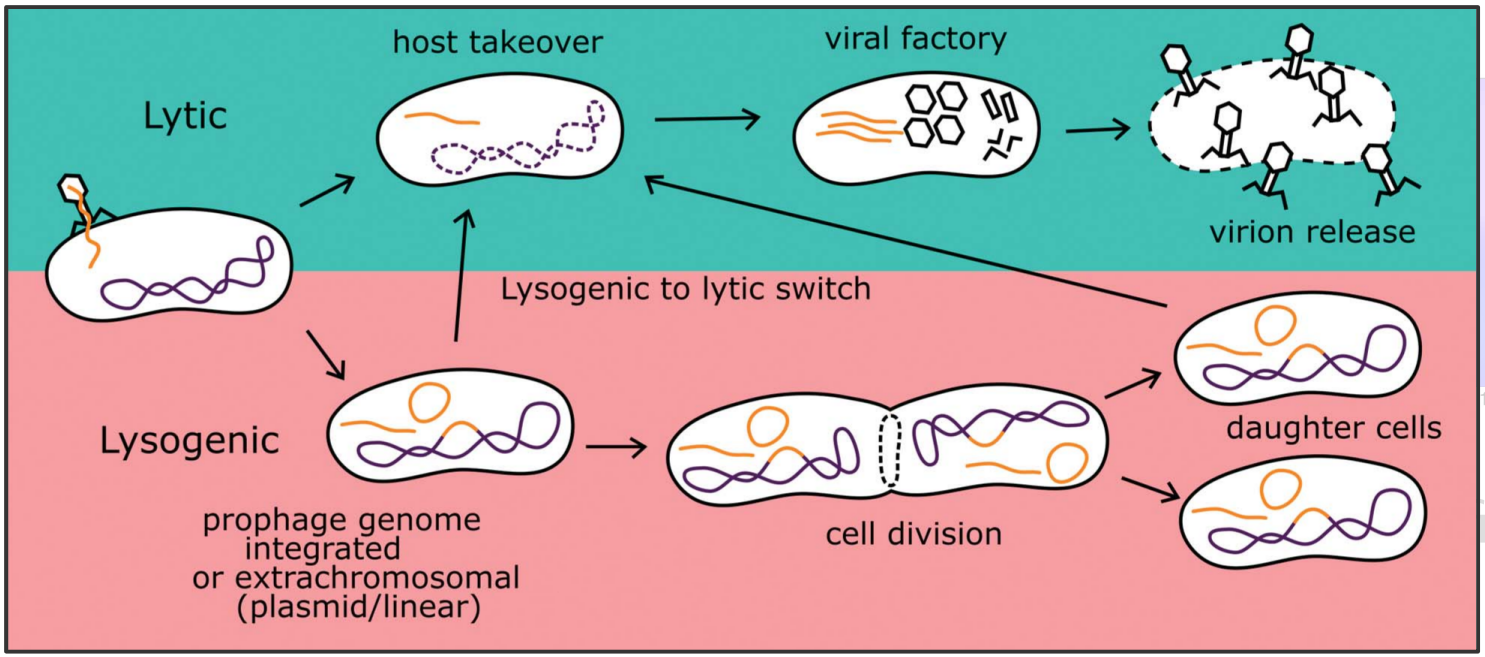

Yes because abundant host

Yes because strong seasonal variation

Which viruses infect GSB ?
Active arms race or temperate infections/latency ?

Howard-Varona et al., 2018

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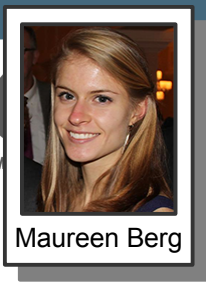

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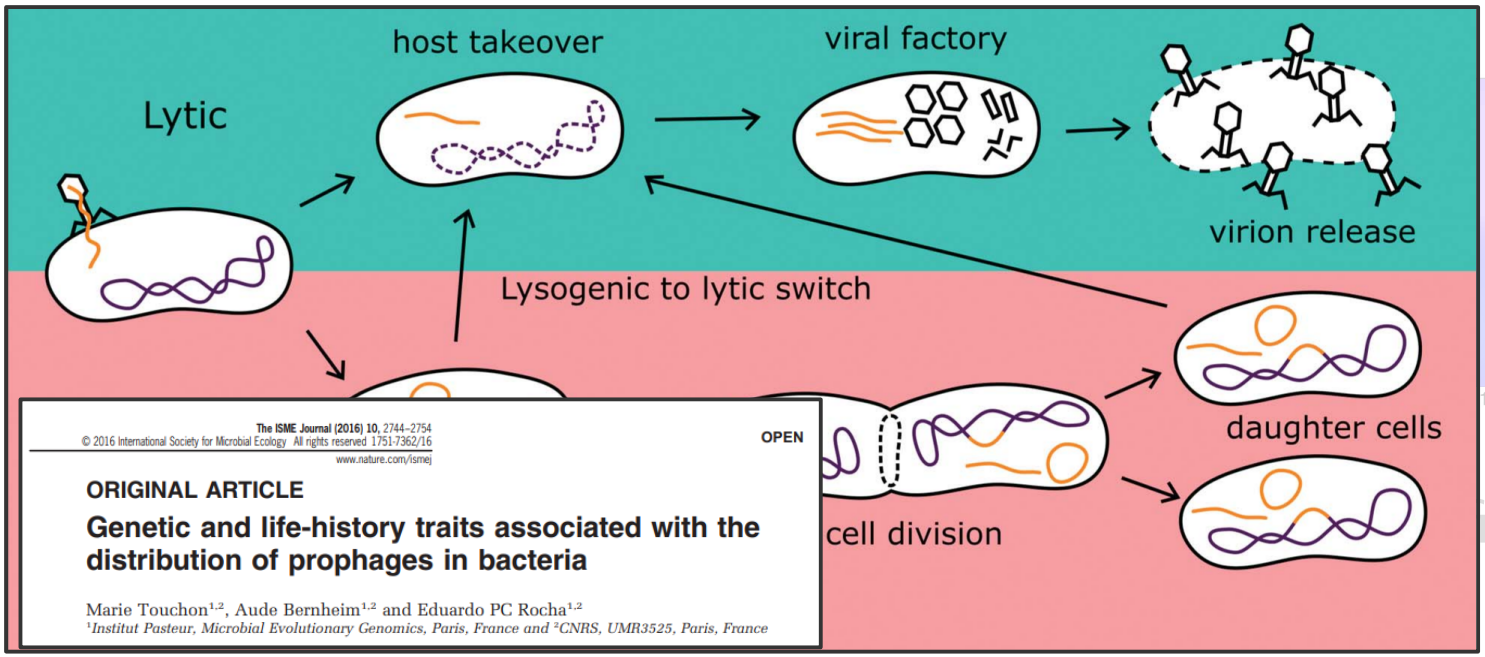


The ISME Journal (2016) 10, 2744–2754

www.nature.com/ismej

OPEN

ORIGINAL ARTICLE

Genetic and life-history traits associated with the distribution of prophages in bacteria

Marie Touchon[1,2], Aude Bernheim[1,2] and Eduardo PC Rocha[1,2]
[1]Institut Pasteur, Microbial Evolutionary Genomics, Paris, France and [2]CNRS, UMR3525, Paris, France

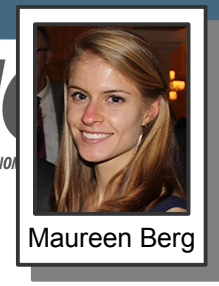
Yes because abundant host

Yes because strong seasonal variation

Which viruses infect GSB ?
Active arms race or temperate infections/latency ?

Howard-Varona et al., 2018

Viruses of Green Sulfur Bacteria



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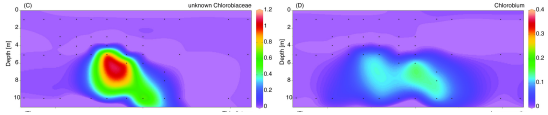

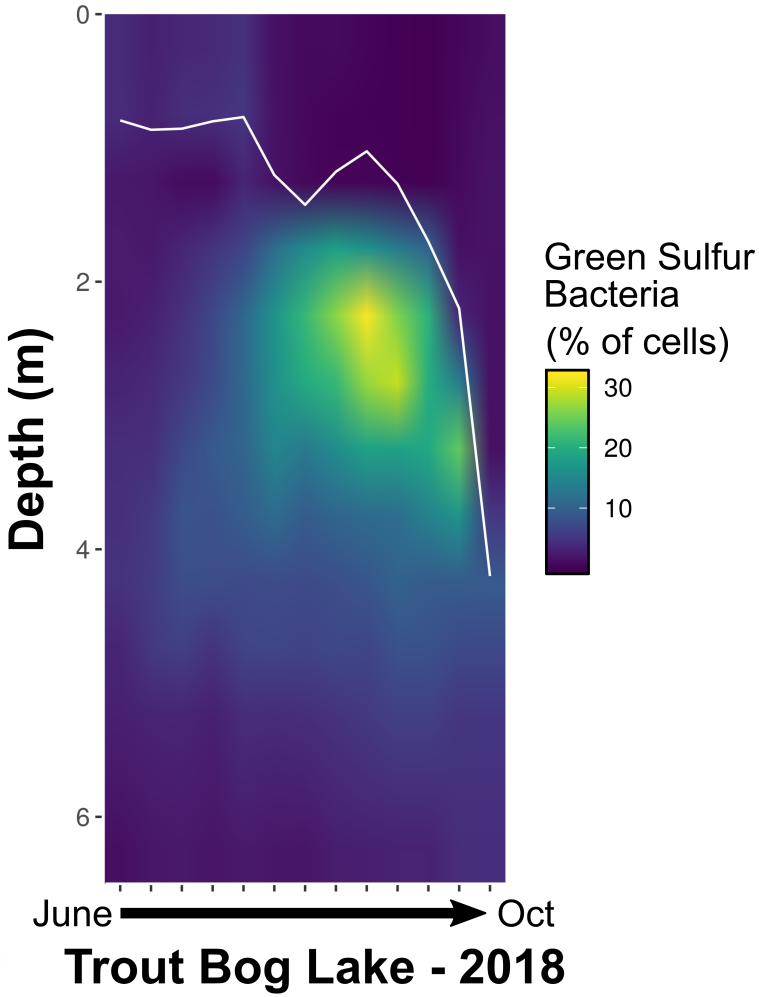

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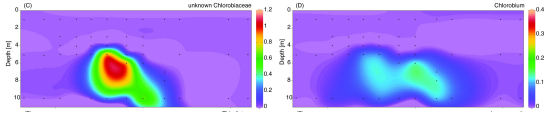

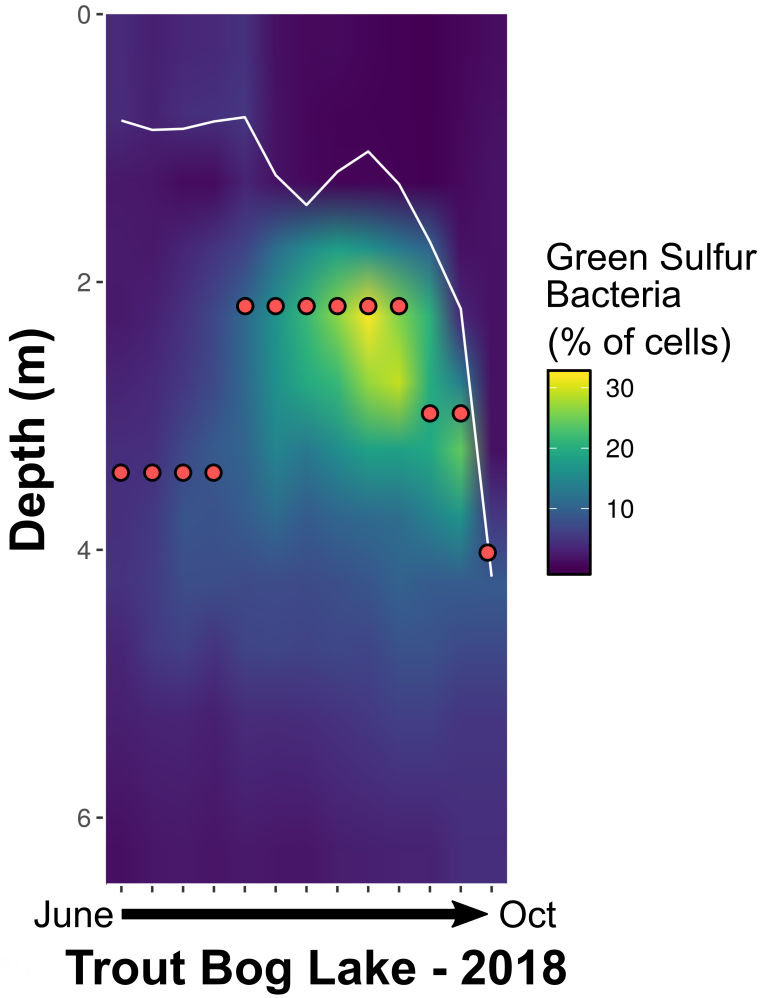

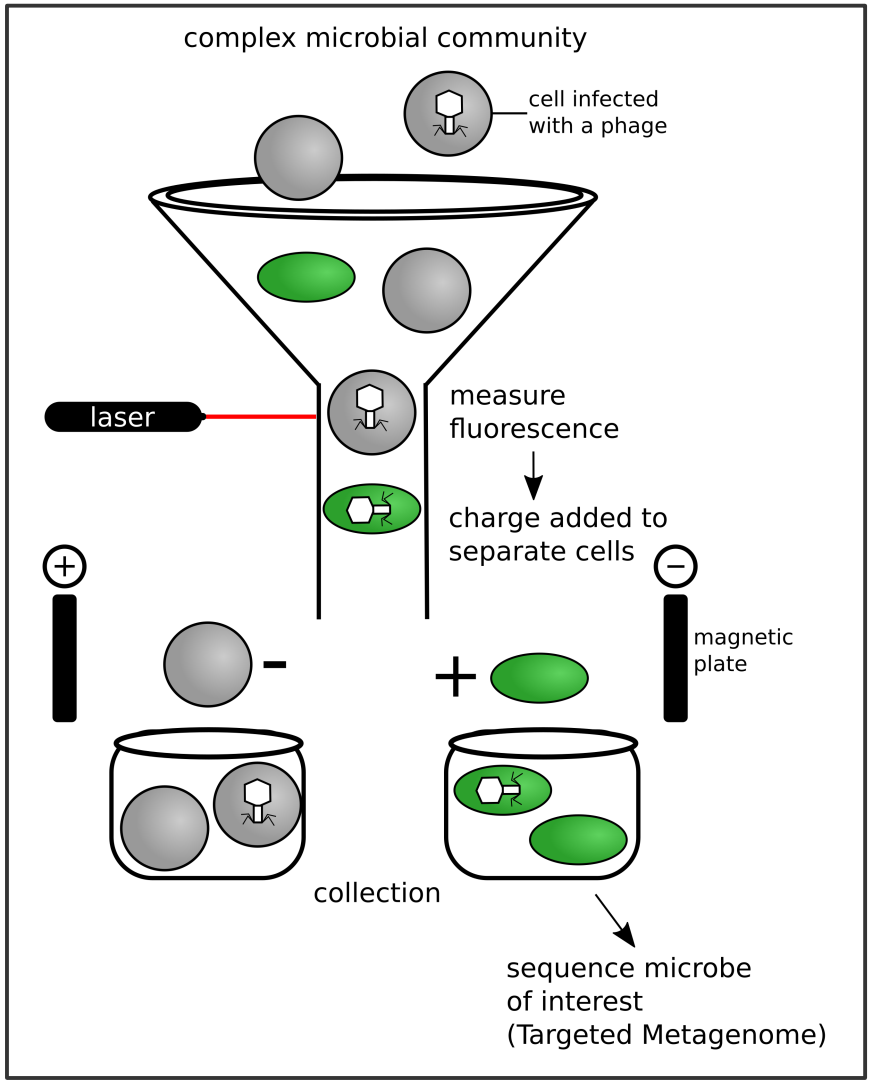

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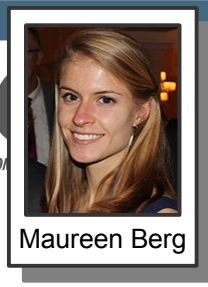

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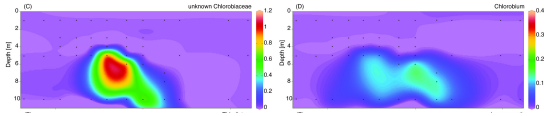
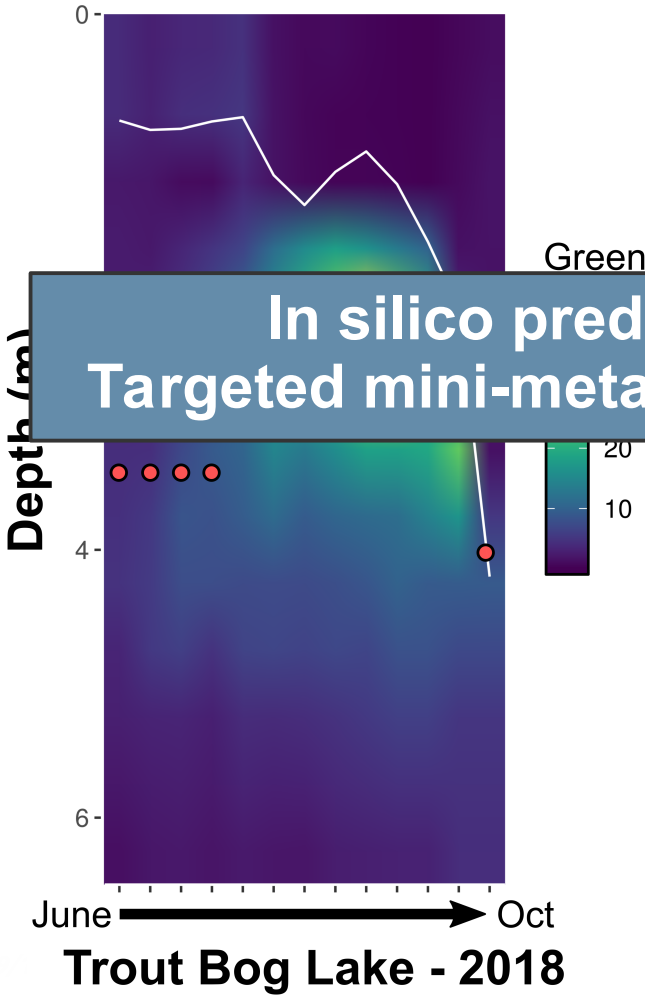
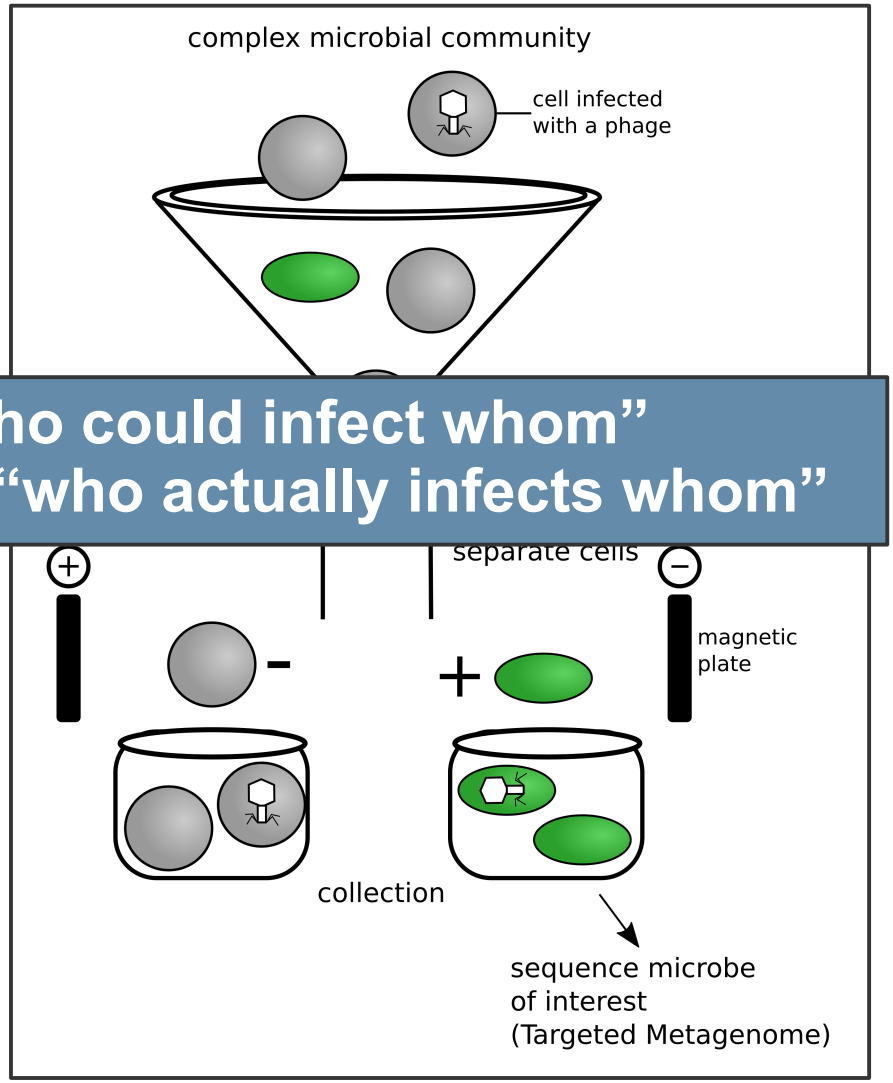




In silico prediction: "who could infect whom"
Targeted mini-metagenome: "who actually infects whom"



Virus-GSB dynamics in Trout Bog Lake

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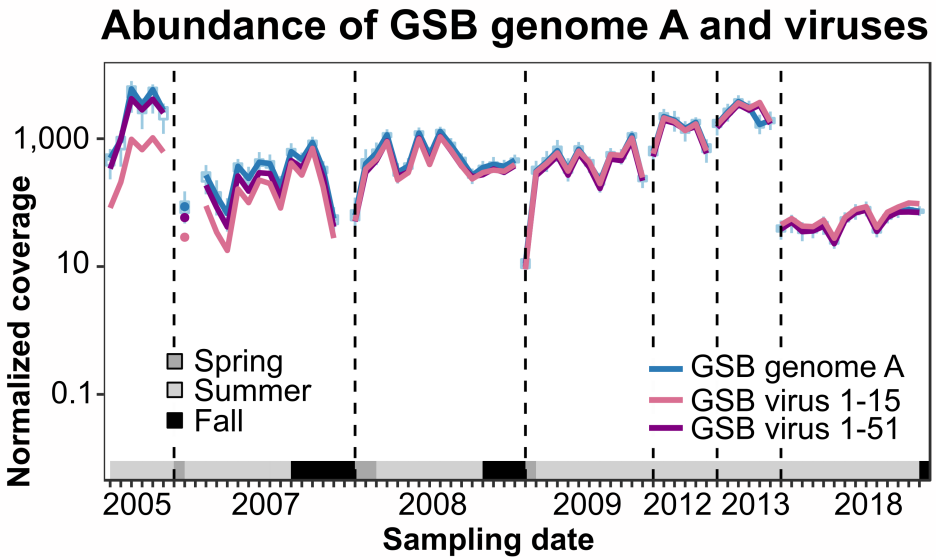

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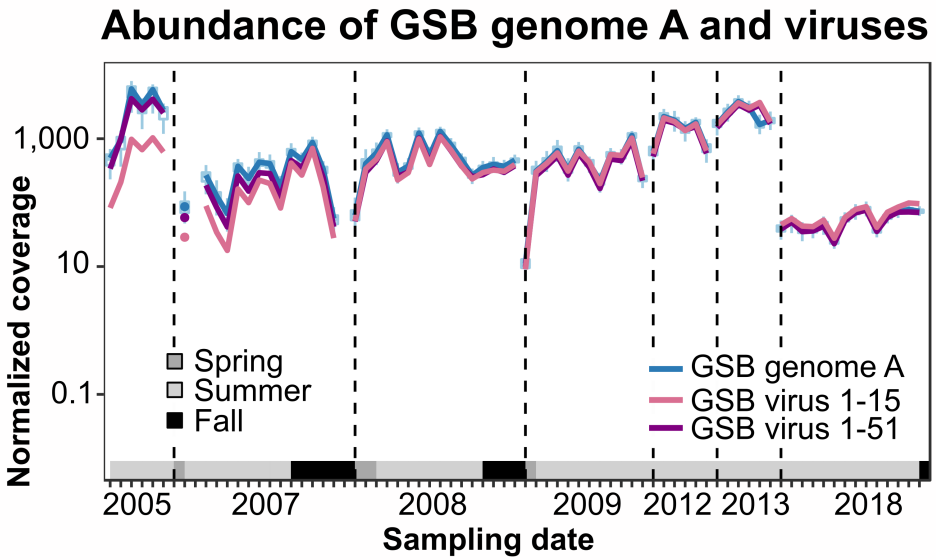

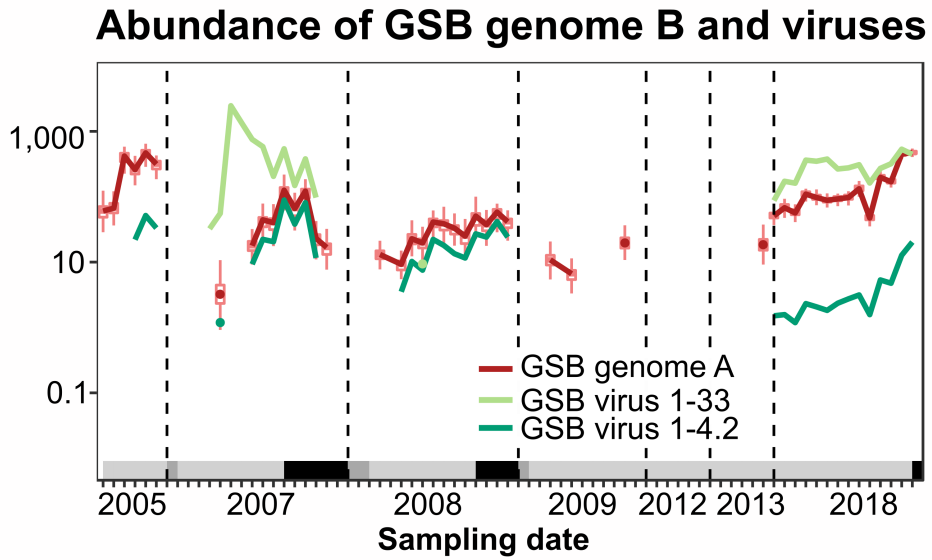

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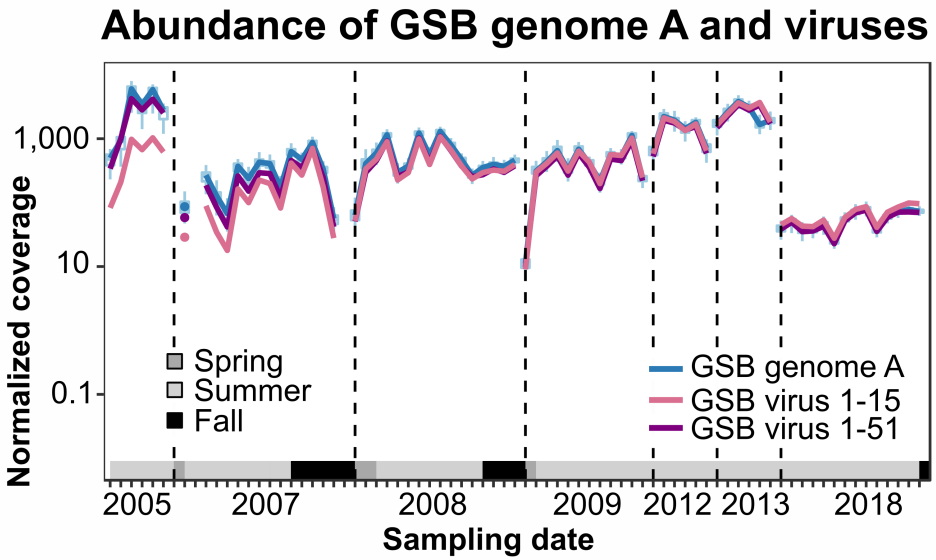

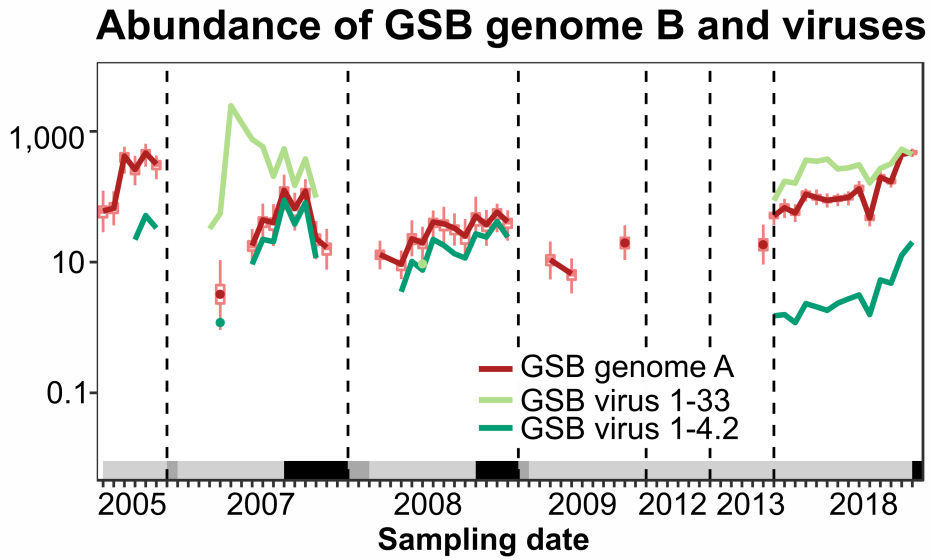

Stable association ?

Arms race ?

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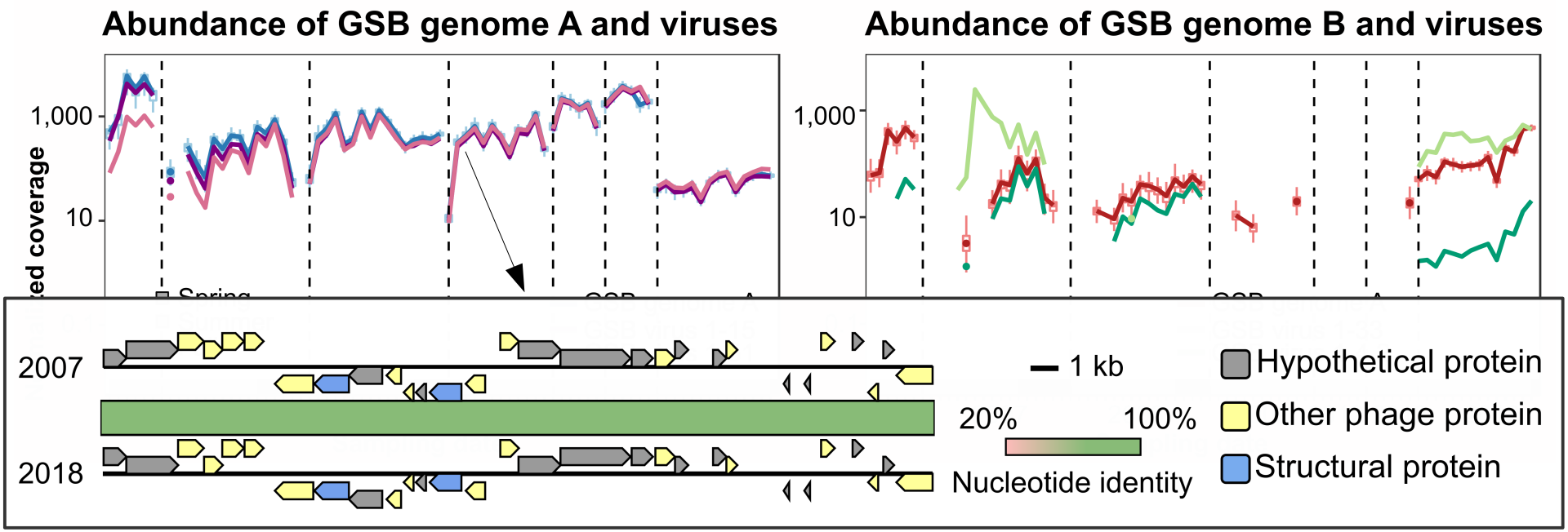

GSB virus 1-51 and 1-15: virtually unchanged between 2005 and 2018

Stable association ✓ **Arms race ?**

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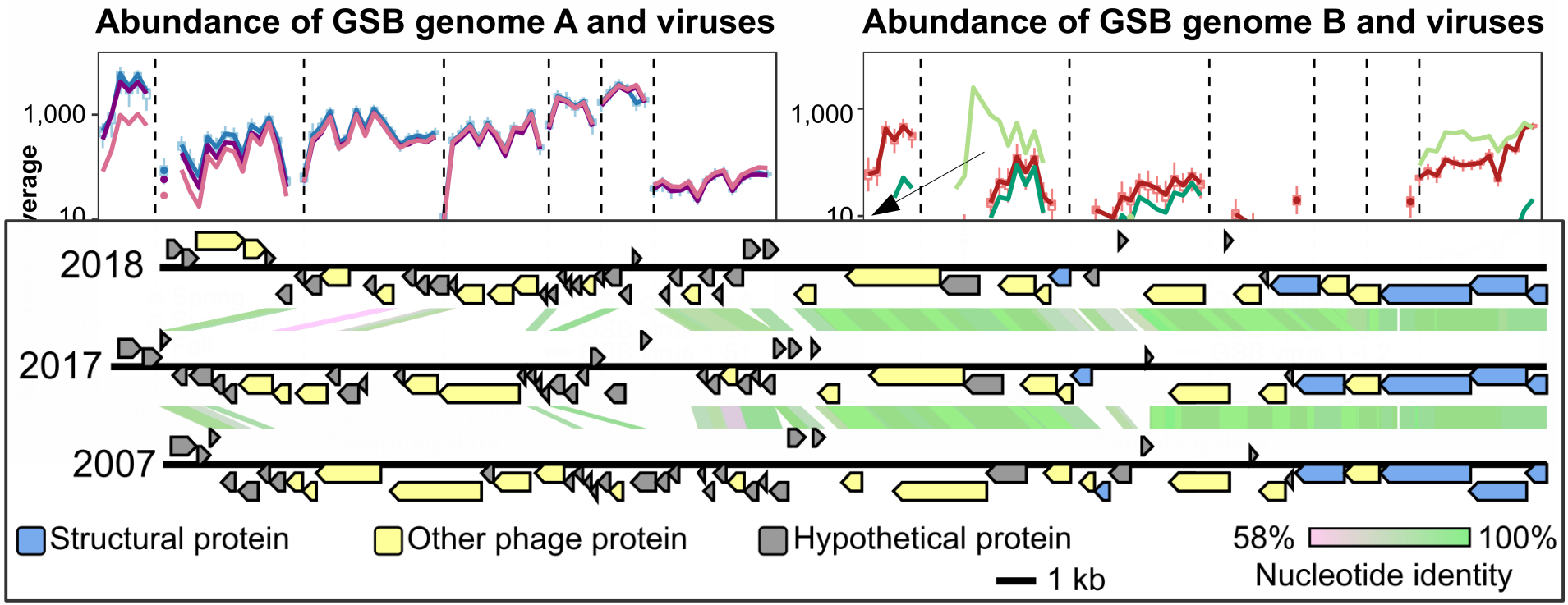

GSB virus 1-33: Yearly replacement of ~ 1/3rd of the genome

Stable association

Arms race ✓

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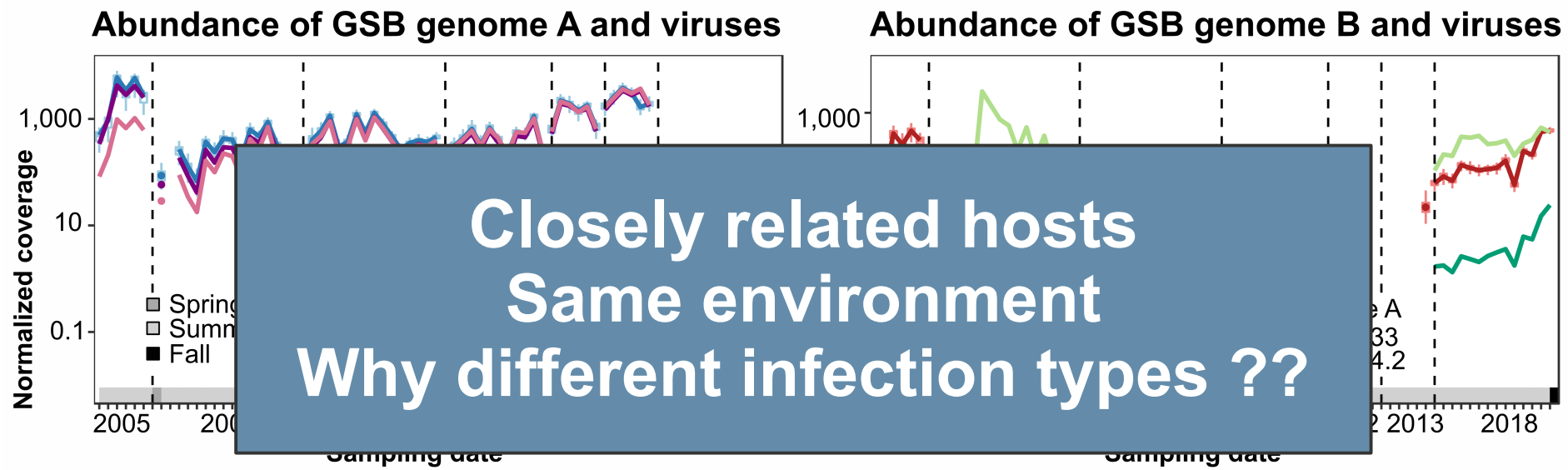

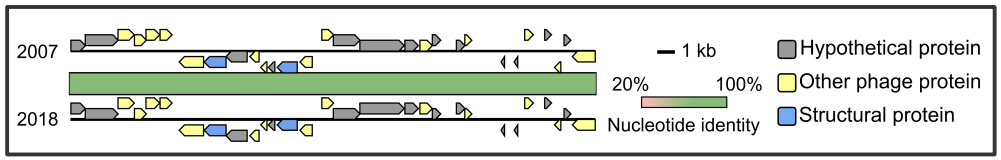

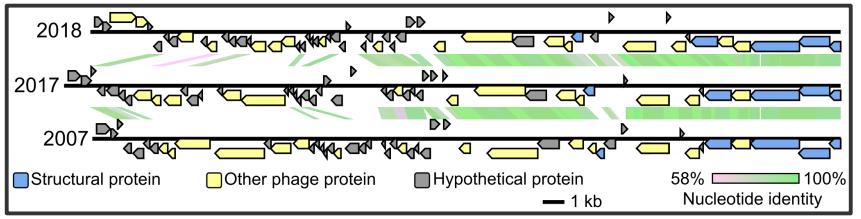

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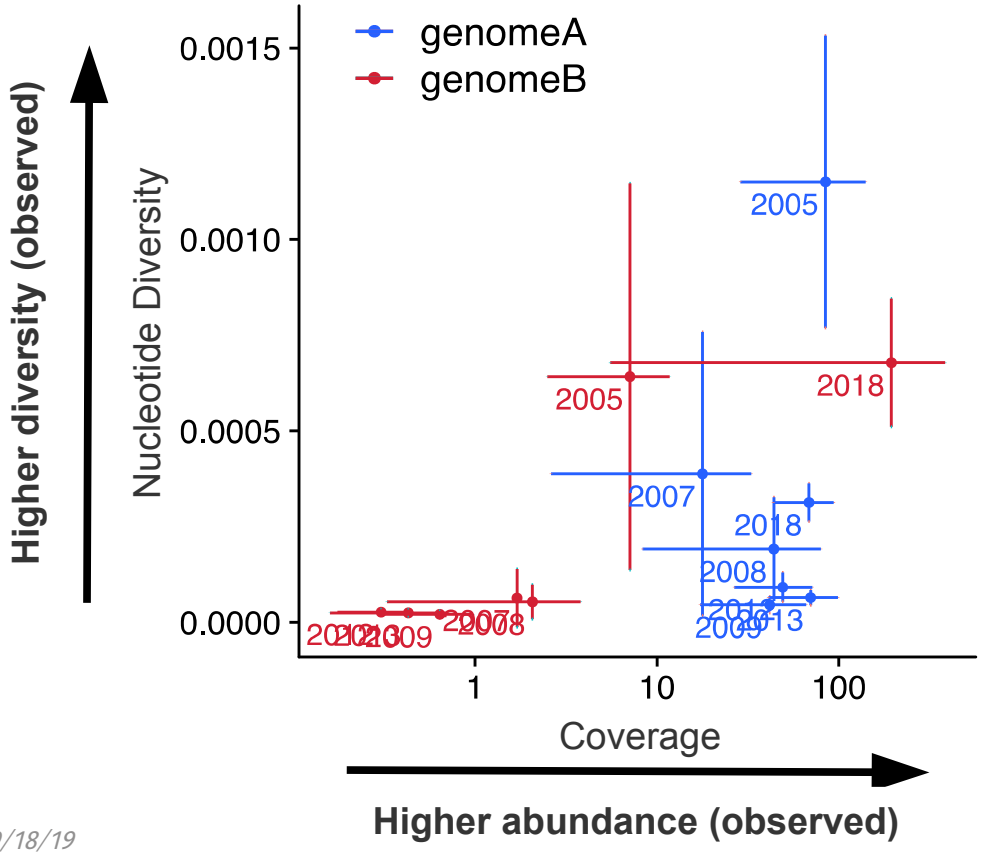

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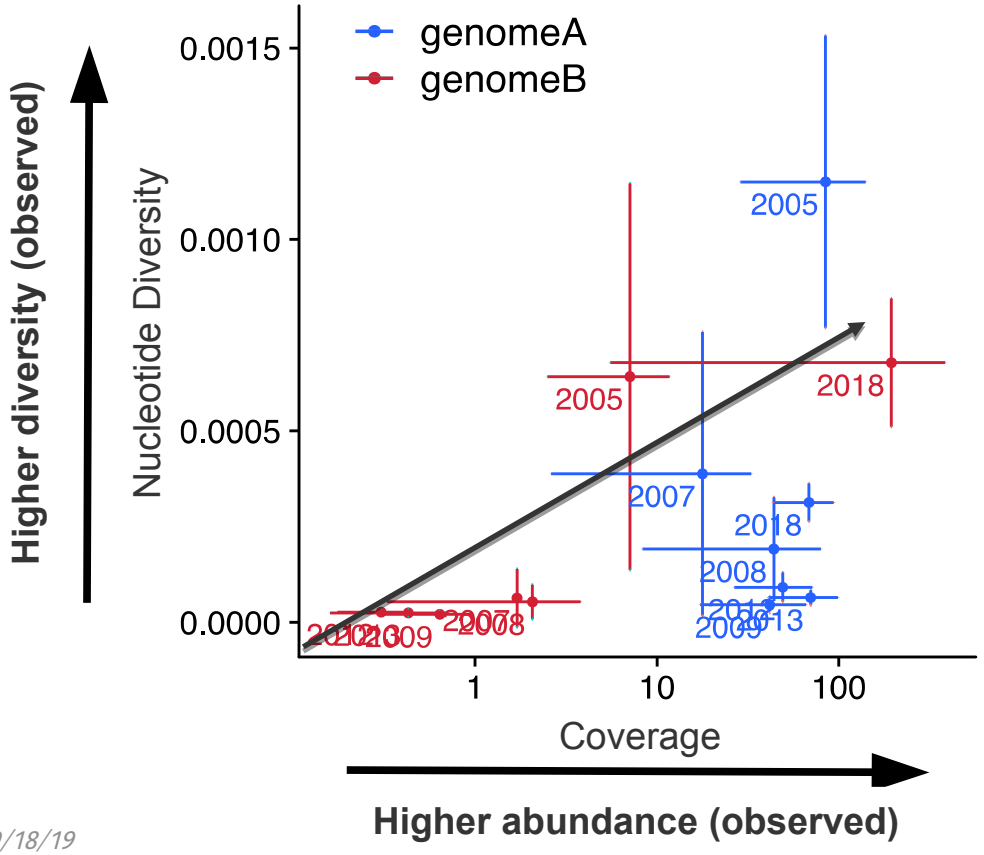

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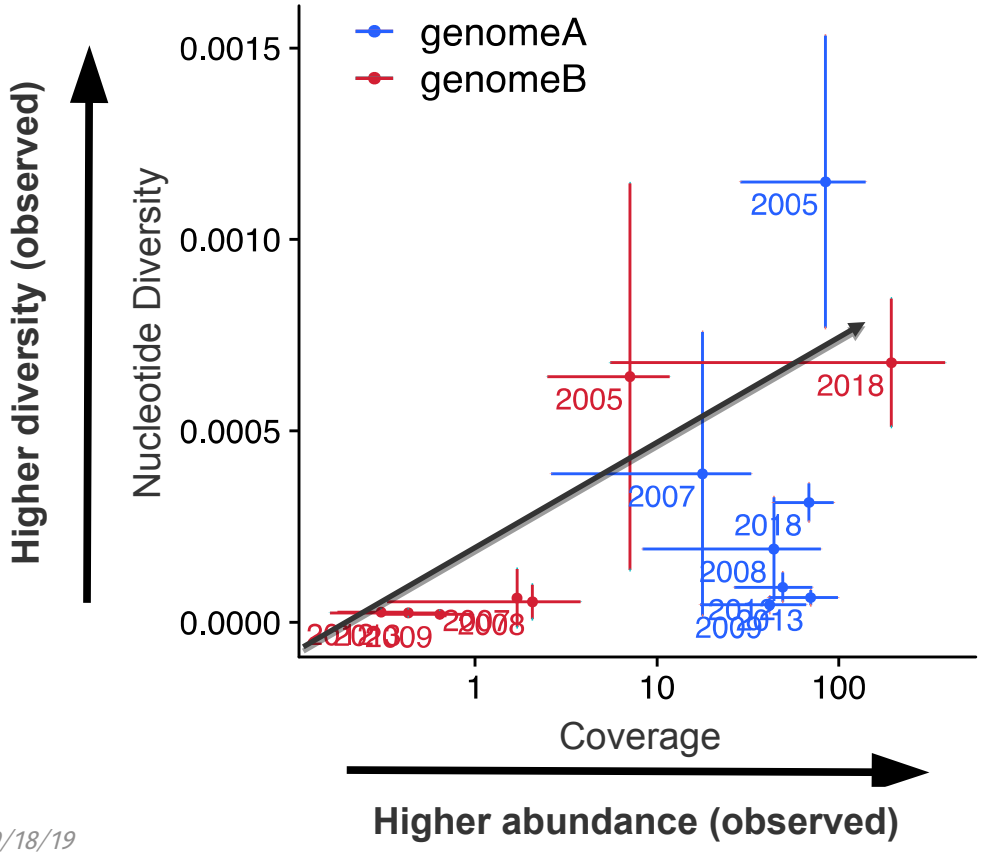

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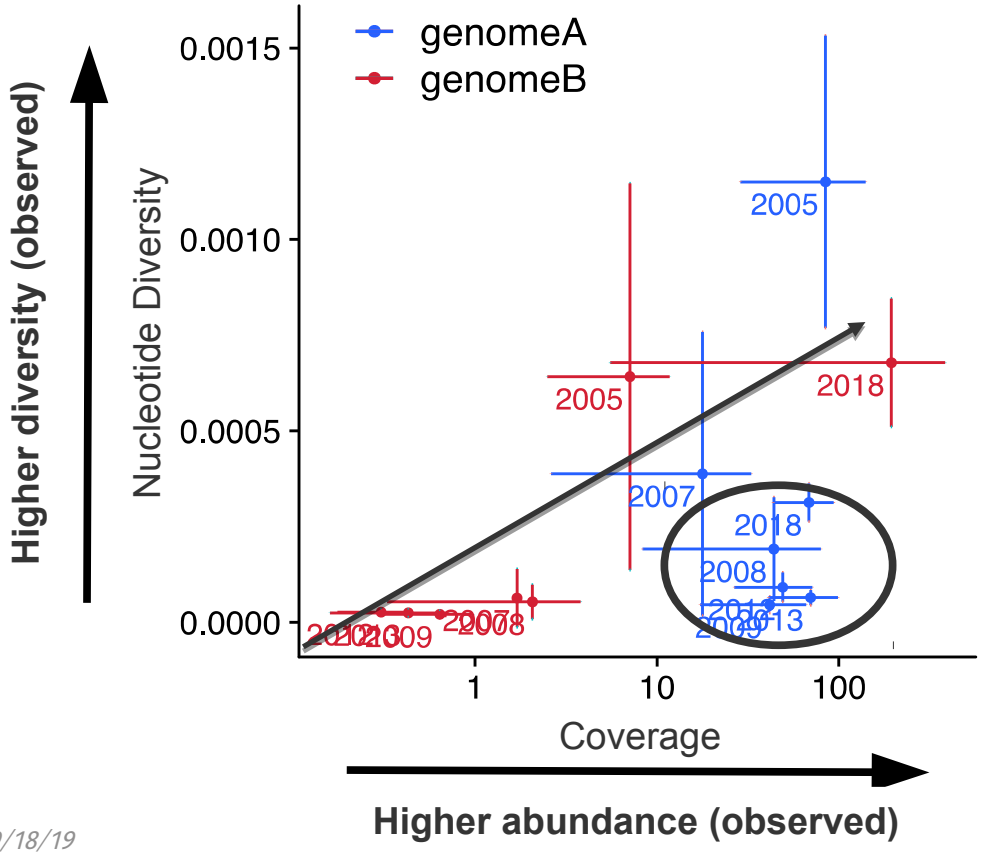

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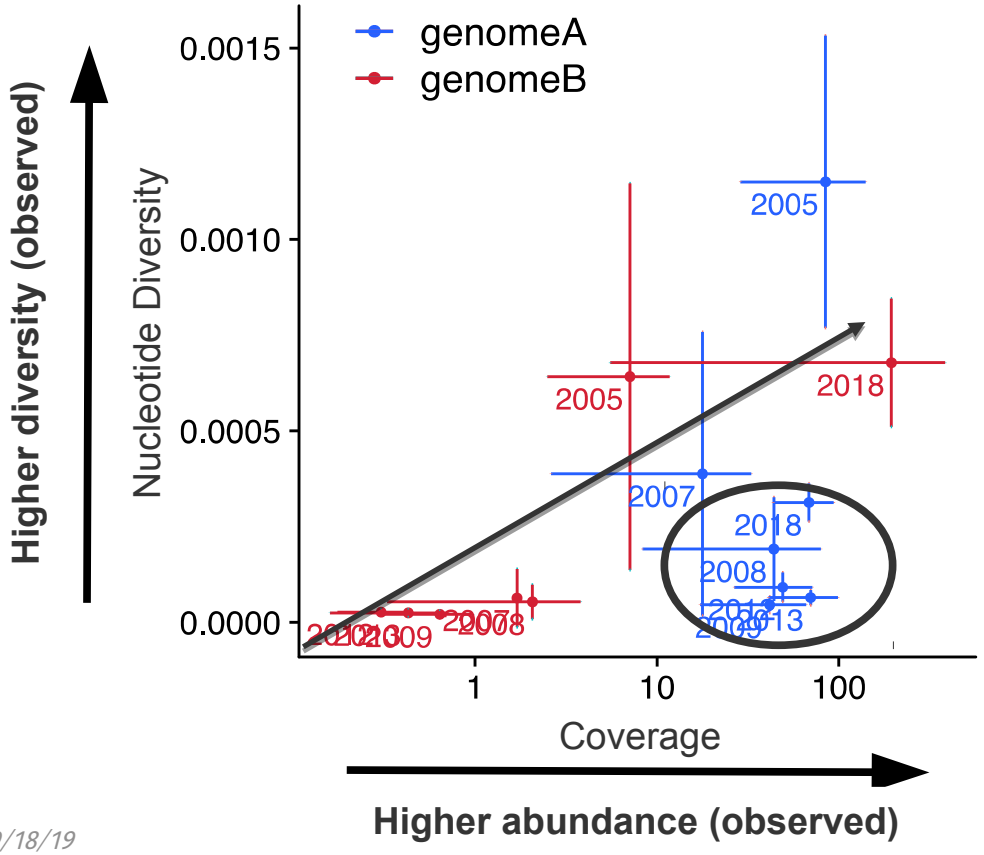


- Observed diversity should scale with coverage
- Ok for genome B (arms race)
- Exception for genome A
  - high coverage – low diversity
  - genome-wide sweep already reported
    - → host population ~ clonal
    - → latent infections

Host diversity as key for virus-host dynamics

- Diverse host population

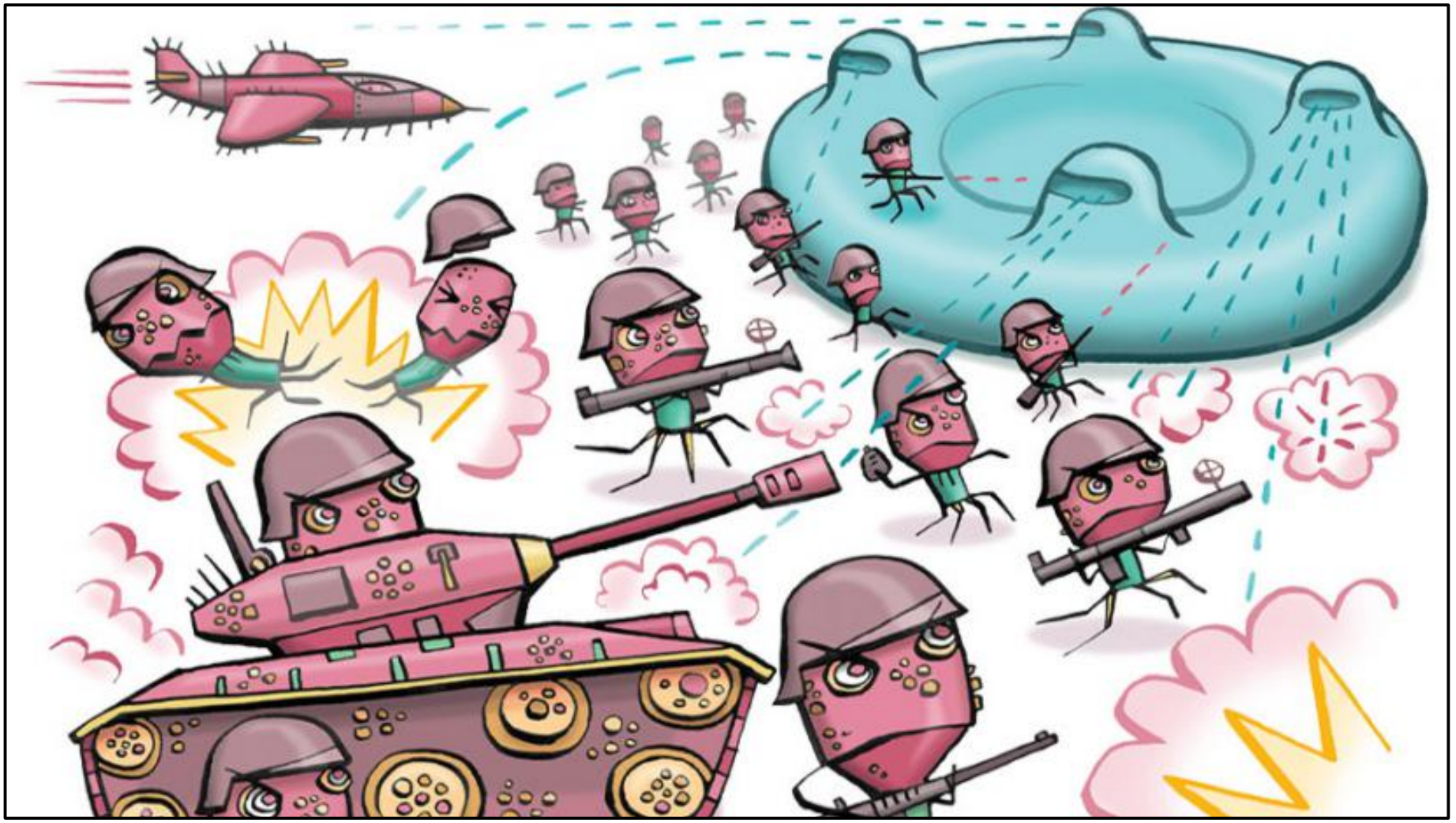


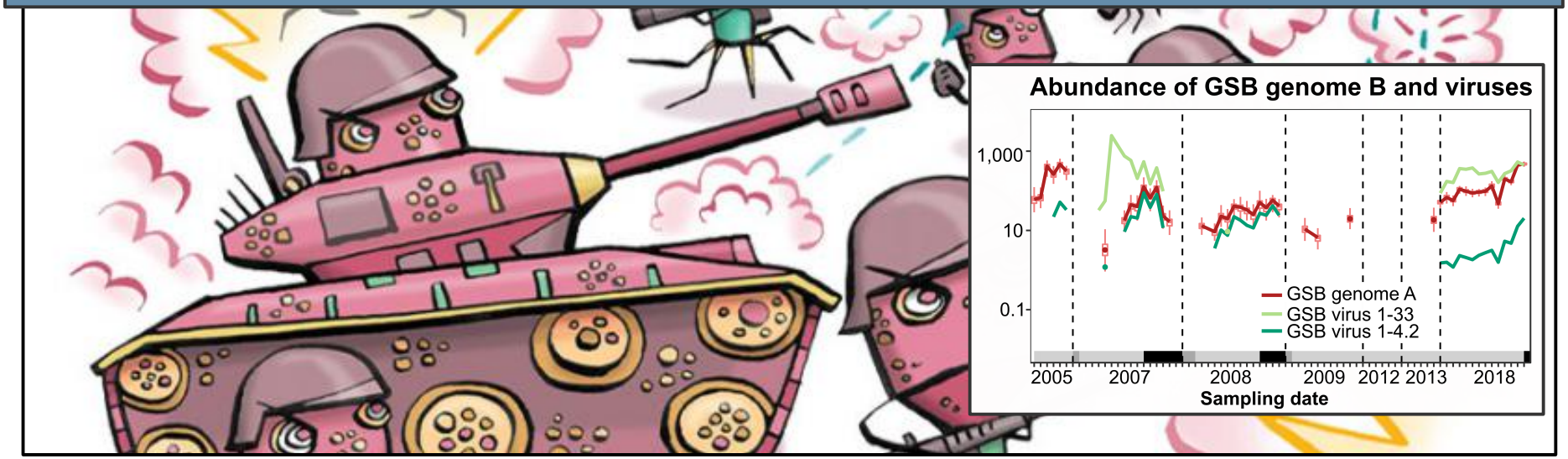
Illustration adapted from https://bigpictureeducation.com/fight-finish, © Glen McBeth

Host diversity as key for virus-host dynamics

- Diverse host population

Diverse host population:

- Variation in phage susceptibility between population members
- Phage-resistant mutants can arise in natural populations
- Selection for new phage variants, co-diversification, arms race
- Dynamics associated with lytic phages or short latency



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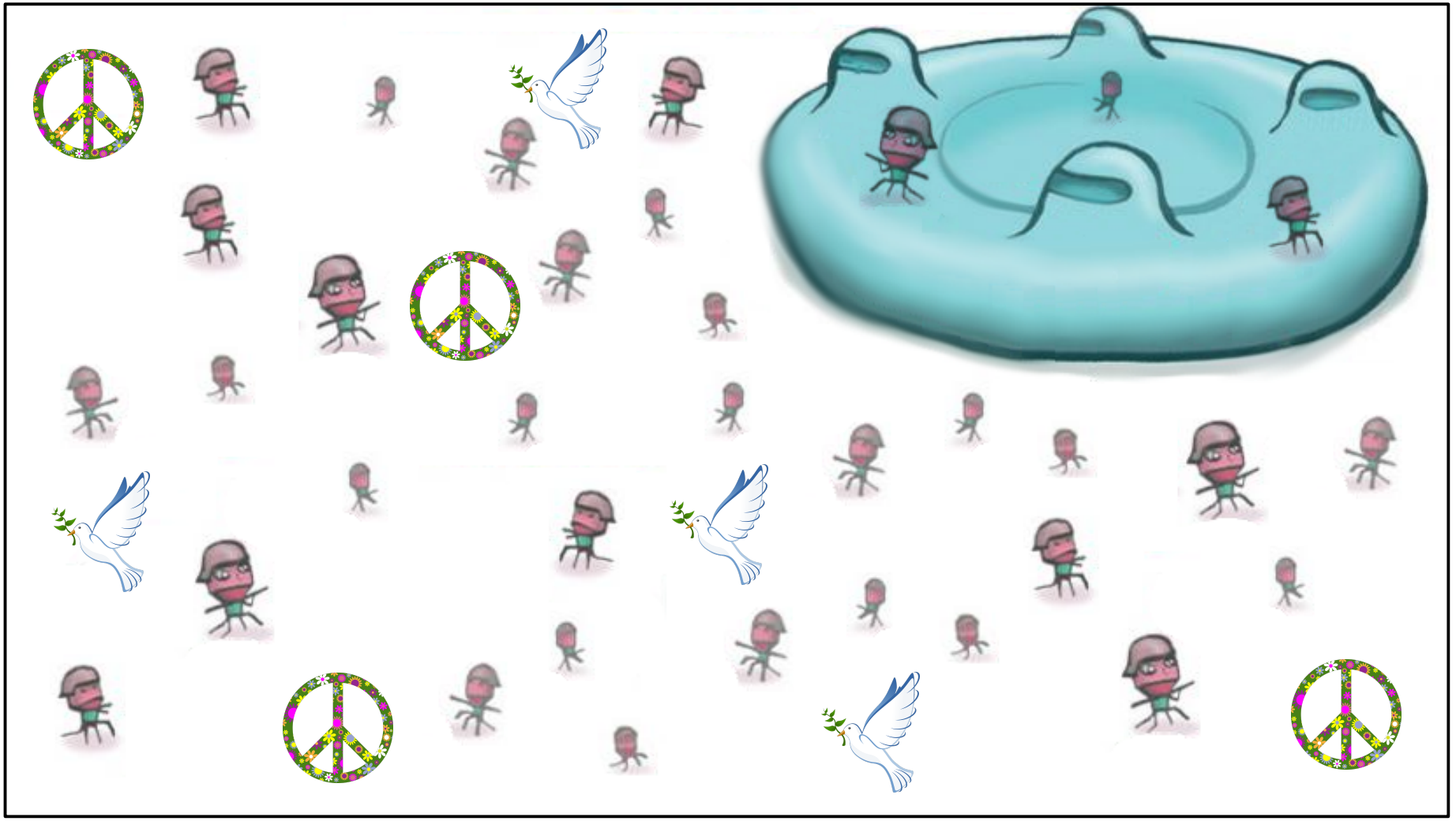
Virus-host interactions: how we see it

- Low diversity host population



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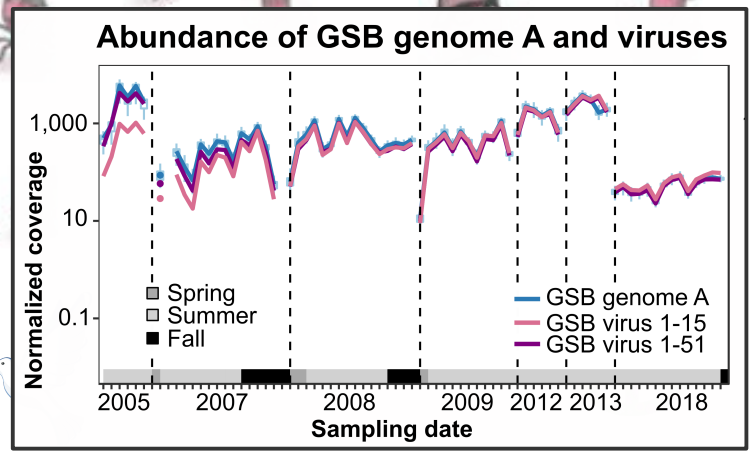
Low diversity host population:

- Most population members have similar susceptibility
- Resistant mutants less likely to arise before ~100% infection rate
- Selection for temperate / long latency period phages



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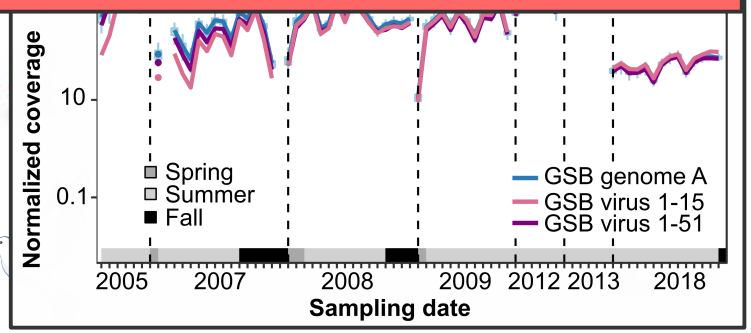
(i.e. is this even plausible ?)



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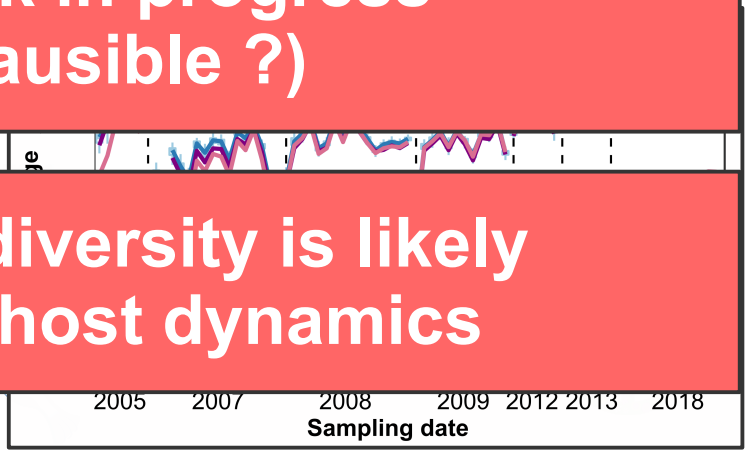
Host population genetic diversity is likely
a critical driver of virus-host dynamics



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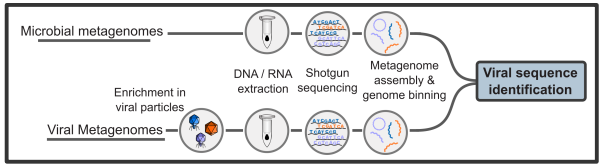
Conclusion



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  - We (start to) understand how to find them
  - Metagenomics is foundational for virus ecogenomics
  - Standards for virus discovery, analysis, and report

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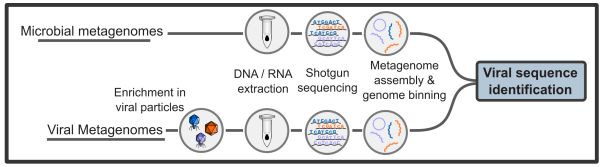

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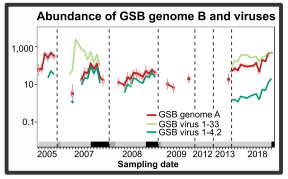

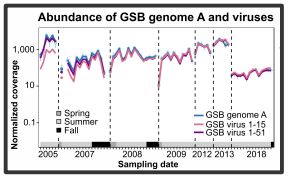

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  - Host linkage is the #1 challenge
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  - Will require large integrative approaches (multi ‘omics + modeling + …)

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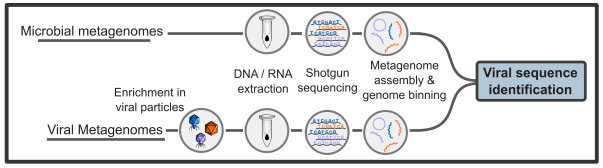

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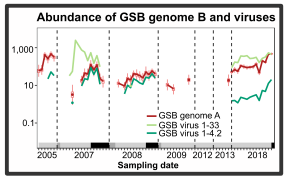

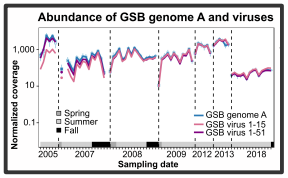

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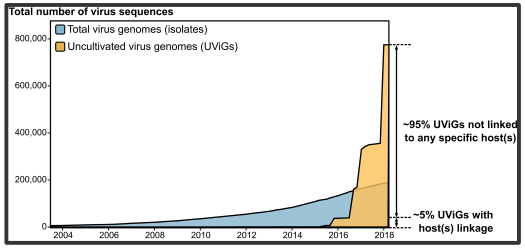
- **Lots of discovery to be made !!!**
  - Completely new type of viruses ?
  - New mechanisms for host cell reprogramming ?
  - New defense/counter-defense mechanism(s) ?



Join Us in Oakland in 2020

Registration opens October 1, 2019

VEGA Viral EcoGenomics & Applications
Symposium hosted by the DOE Joint Genome Institute

Keynote Speakers:

Jennifer Doudna

Eddy Rubin

Mart Krupovic

Workshops:

KBase PREDICTIVE BIOLOGY
DOE Systems Biology Knowledgebase

MycoCosm
THE FUNGAL GENOMICS RESOURCE

PhycoCosm
THE ALGAL GENOMICS RESOURCE

Tools to Explore Microbial Genomes & Microbiomes: MGM Workshop @JGI

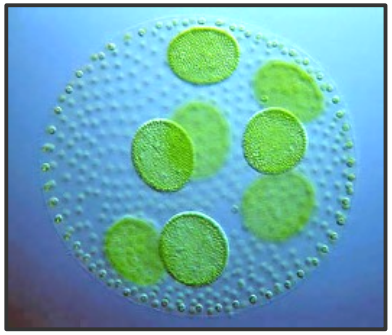
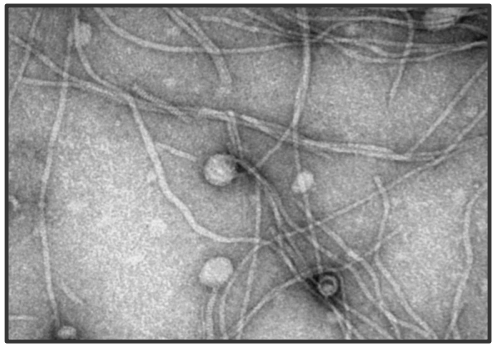
- Five-day hands-on workshop includes seminars and extensive tutorials on how to use the Integrated Microbial Genomes & Microbiomes (IMG/M) system for comparative analysis of isolate genomes and metagenomes.
- **November 4 – 8, 2019 in Berkeley, California**
- **Limited to 40 participants**
- **Register now!**

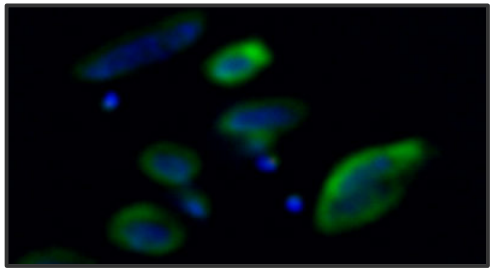
mgm.jgi.doe.gov

Community Science Program (CSP)
New Investigator Call for Proposals

- **CSP New Investigator Call** emphasizes the generation of pilot data to assess the feasibility of a large-scale CSP proposal submission

Deadline
September 26
bit.ly/NewPI2020



Contact:
Susannah Tringe
SGTringe@lbl.gov

Thanks !

- Prokaryote Super Program & JGI
  - **Maureen Berg**
  - Emiley Eloe-Fadrosh
  - Axel Visel
  - Nikos Kyrpides
  - Natalia N. Ivanova
  - David Paez-Espino
  - Rex Malmstrom
  - **Danielle Goudeau**

- MacMahon Lab @ UW-M
  - Charles Olmsted
  - Trina Mac Mahon

- Bryant lab @ Penn State
  - Jennifer Thweatt
  - Don Bryant