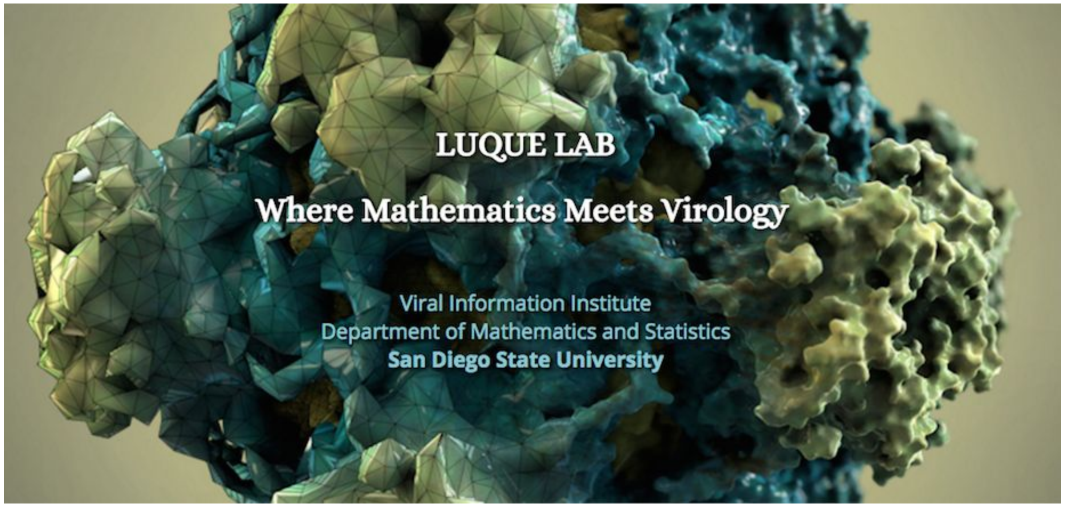
Phage Capsid Structure: Theory, Phage Lifestyle Constraints, And Environmental Diagnostic

Antoni Luque
San Diego State University



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Acknowledgements

http://viralization.org/

From the **Luque Lab**

- Diana Lee
- Antoni Luque

From the **Edwards Lab (SDSU, VII)**

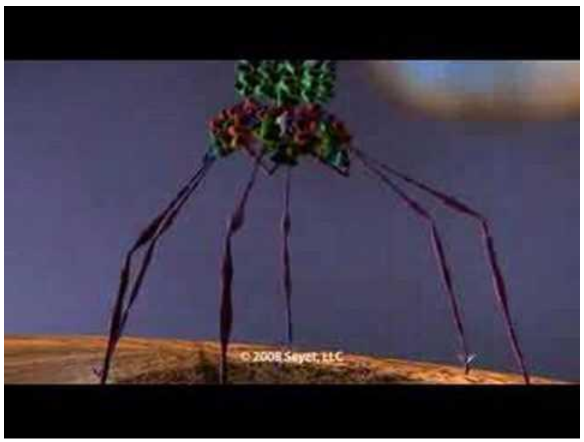
- Kate McNair
- Robert Edwards

Coastal Research and Planning Institute, Lithuania

- Sigitas Sulcius

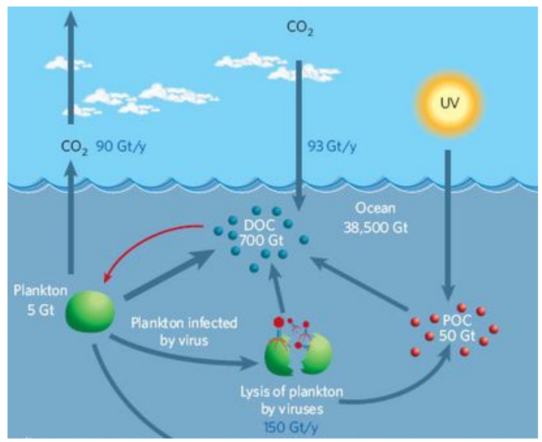
Why study bacteriophages (phages)?

Phages: viruses that infect bacteria



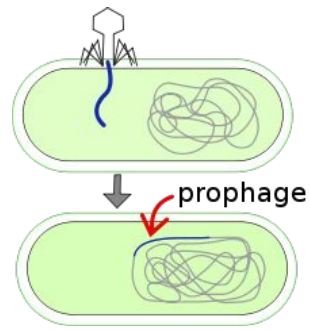
Seyet LLC 2008

Environmental impact



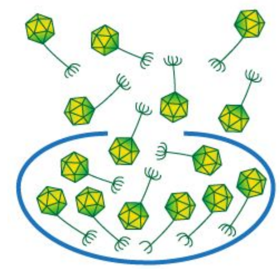
Suttle Nature 2005

Bacterial pathogenicity



Asiela CC 2010

Alternative to antibiotics: phage therapy

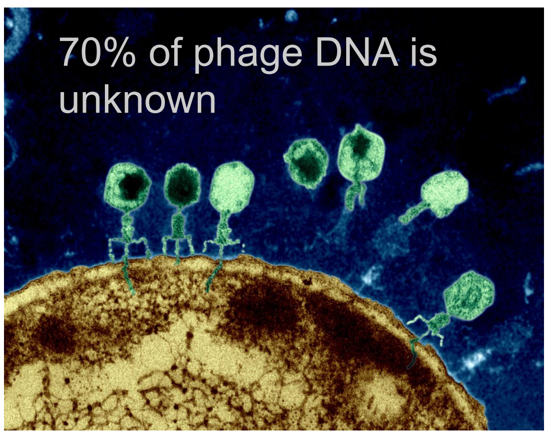


phagesDB.org

Viral Dark Matter: Problem in Phage Environmental Research

THE NEW YORKER

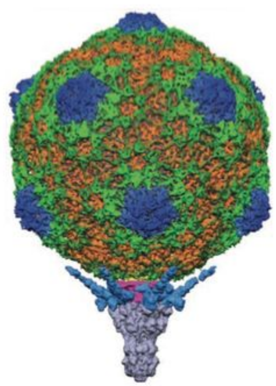
INSIDE THE WORLD OF VIRAL DARK MATTER



Twilley, The New Yorker, 2015
Interview: Forest Rohwer (SDSU, VII)

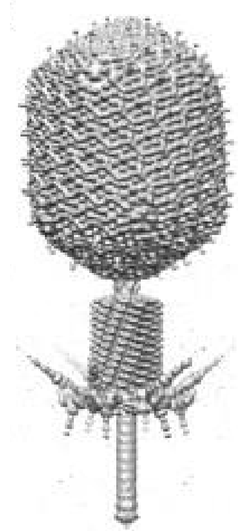
Tailed phages → ~95% of the phage world

Icosahedral capsid (~80%)



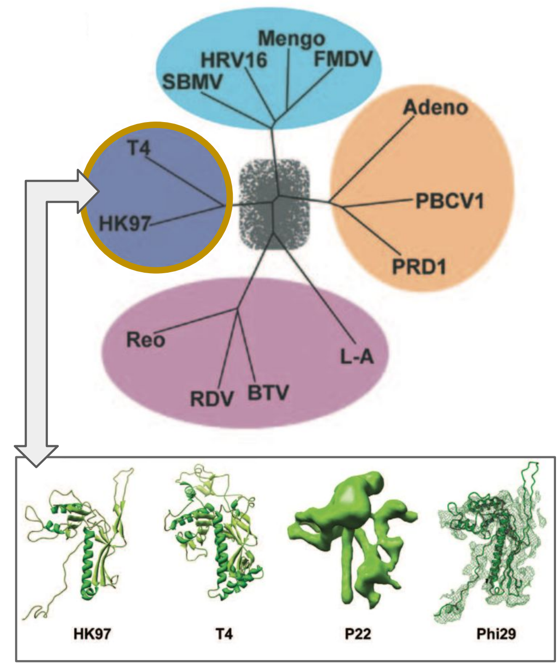
Phage P-SSP7
Liu, Nature SMB, 2010

Elongated capsid (~20%)



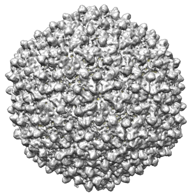
Phage T4
Leiman, Virology J, 2010

Tailed phages → Same protein structural lineage

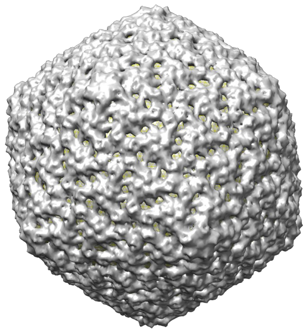


Bamford, *Curr Opin Struct Biol, 2005*

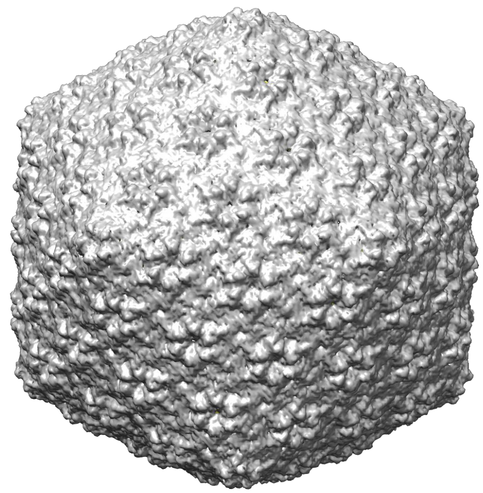
Phage Icosahedral Capsid



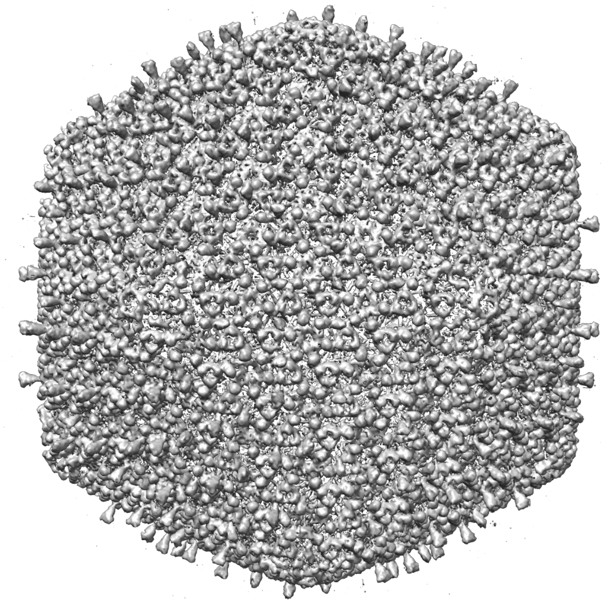
Streptococcus phage C1
D ≈ 39 nm
np = 240



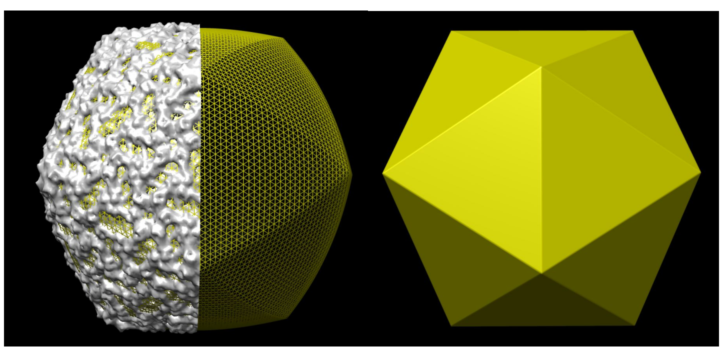
Staph. aureus phage 80α
D ≈ 68 nm
np = 420



E. coli phage T5
D ≈ 95 nm
np = 780



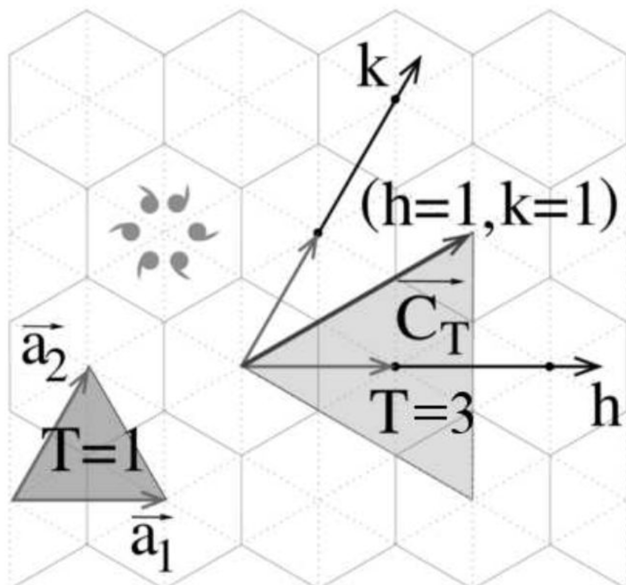
Rastonia solacanearum phage ϕRSL1
D ≈ 122 nm
np = 1620



Geometrical Theory of Viral Capsids

Icosahedron

One triangle to rule them all



T-number

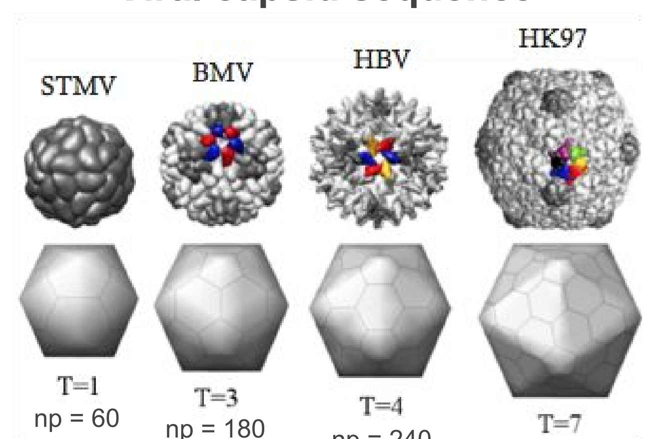
$$T = h^2 + hk + k^2$$

$$T = 1,\ 3,\ 4,\ 7,\ 9,\ 12\ldots$$

Number of proteins

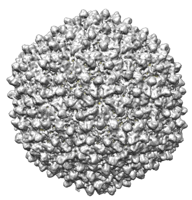
$$np = 60T$$

Viral capsid sequence

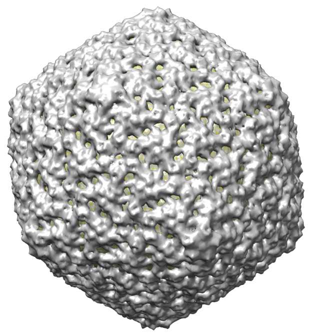


Caspar and Klug, Cold Spring Harbor Symp. Quant. Biol., 1962
Luque and Reguera, Biophysical Journal, 2010
Twarock, J. Theor. Biol., 2004 (Tiling approach)

Phage Icosahedral Capsid: T-number



Streptococcus phage C1
D ≈ 39 nm
np = 240
T = 4



Staph. aureus phage 80α
D ≈ 68 nm
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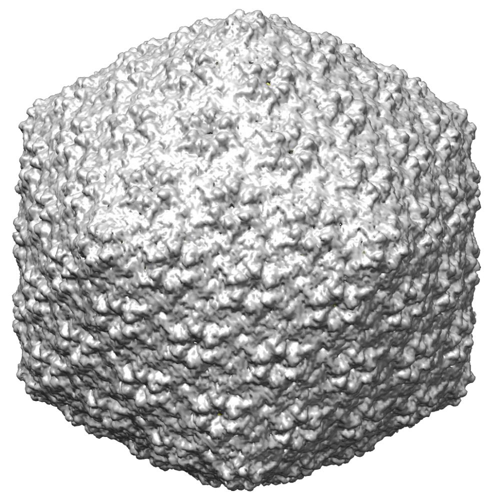
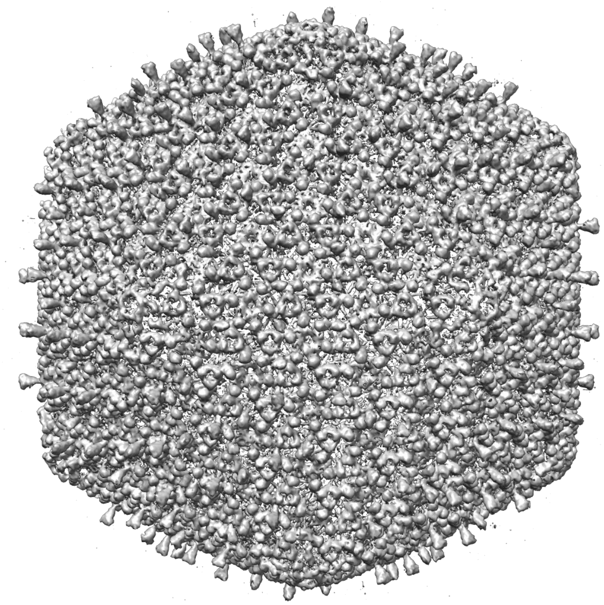
T = 7



E. coli phage T5
D ≈ 95 nm
np = 780
T = 13



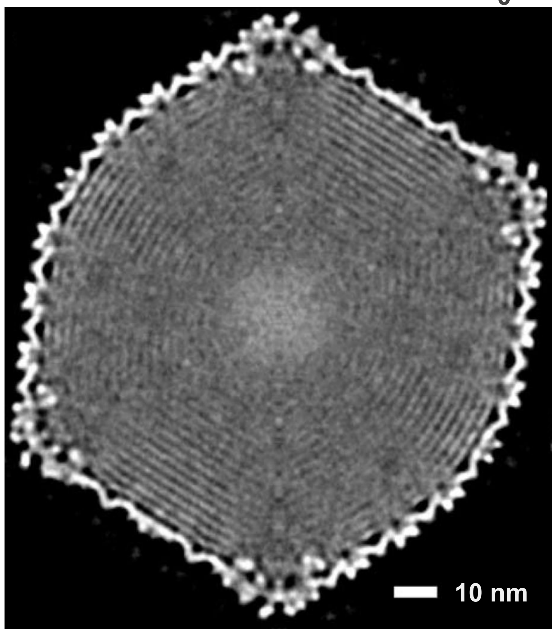
Rastonia solacanearum phage ϕRSL1
D ≈ 122 nm
np = 1620
T = 27

Can we analyze the phage structure environmentally?

- Phage DNA → T-number
- Capsid size → T-number

T-number as a Function of DNA and Capsid Size

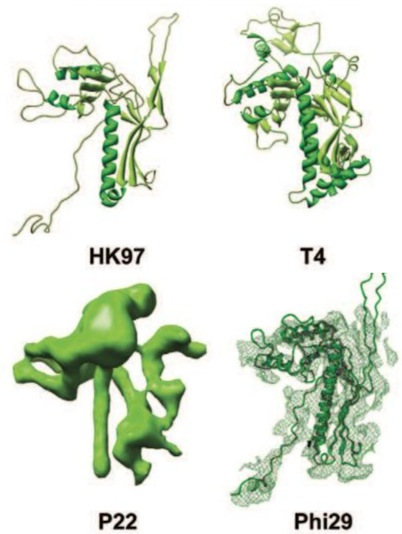
Constant DNA density (ϱ_0)



Pseudomonas aeruginosa phage ϕKZ
Fokine JMB 2005

$\langle\varrho_0\rangle = 0.48 \pm 0.06$ bp/nm^3

Constant capsid interior protein surface (s_0)



Bamford, Curr Opin Struct Biol 2005

$\langle s_0\rangle = 23 \pm 2$ nm^2

DNA → volume → surface → number of proteins → T-number

$$T(DNA) = \frac{a}{s_0 \rho_0^{2/3}} DNA^{2/3}$$

$$a = \frac{2}{\sqrt{3}\,(5+\sqrt{5})} \left(\frac{3\left(\sqrt{10+2\sqrt{5}}\right)^3}{80\,(3+\sqrt{5})} \right) \approx 0.51$$

Capsid size → surface → number of proteins → T-number

$$T(R) = \frac{b}{s_0}(2R)^2$$

$$b = \frac{2}{\sqrt{3}\,(5+\sqrt{5})}$$

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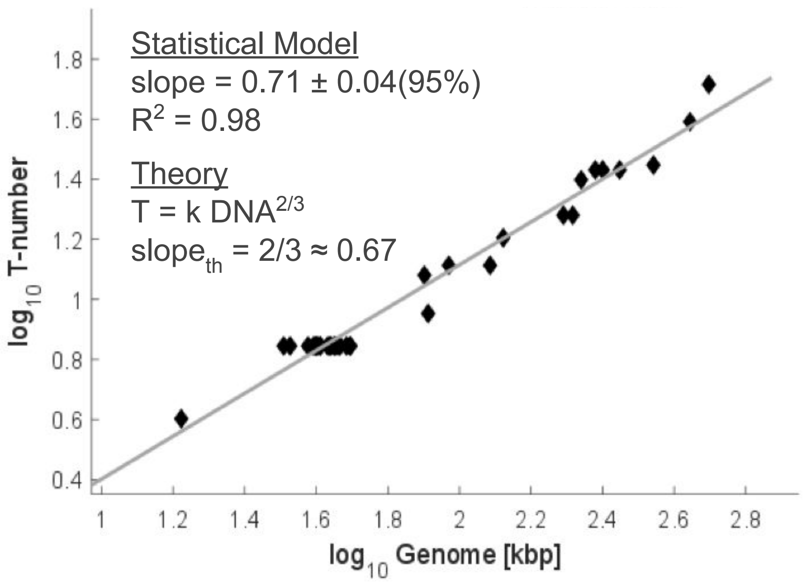
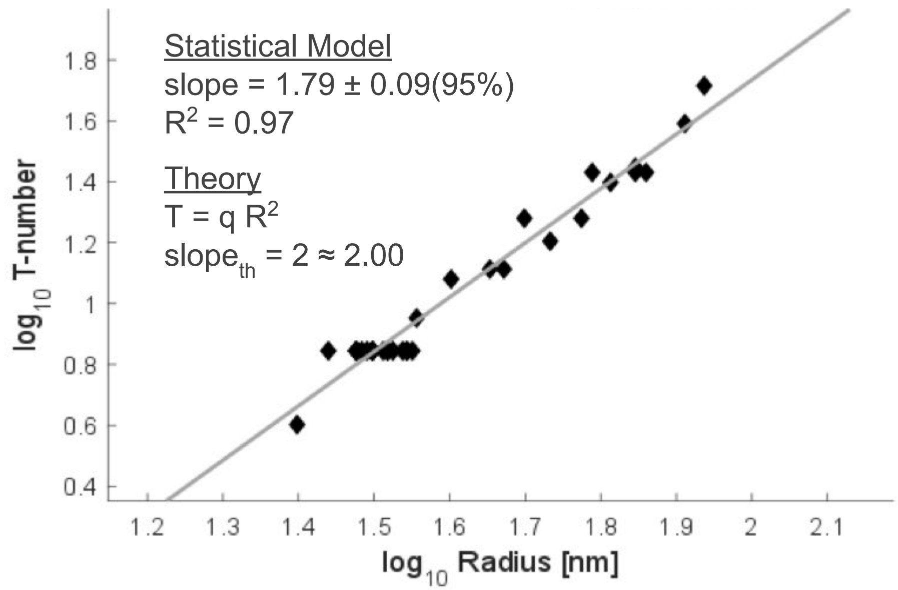
Theoretical Validation and Statistical Models

T(DNA): T-number versus phage genome size



- Linear model: excellent agreement (log-log)
- Scaling exponent is in agreement with theory
- Geometrical prefactor: validated

T(R): T-number versus capsid radius



- Linear model: excellent agreement (log-log)
- Scaling exponent is slightly smaller than theory
- Correction: Shell thickness depends on capsid size?

Initial phage structural data: *Suhanovsky and Teschke, Virology, 2015*
Structural data refinement using Chimera

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Theoretical Correction for T(R)

Assumption: T versus internal radius

$$T(R_{in}) = \frac{b}{\sigma_0^2} R_{in}^2 = q R_{in}^2$$

Revised equation for T(R)

$$T(R) = \frac{b}{\sigma_0^2}(R - h(R))^2$$

$$T(R) = kR^\alpha$$

⟹ Taylor expansion (R_0) + Perturbation analysis ($\epsilon = h_0/R_0$)

New scaling exponent

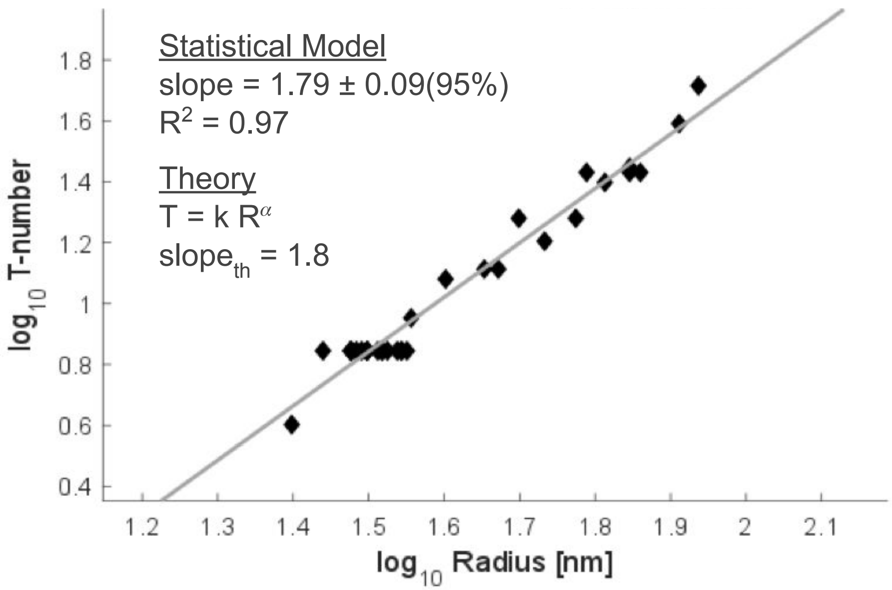
$$\alpha \approx 2(1 - h') + O(\epsilon)$$

Capsid thickness: Thin shell elastic theory

$$h(R) \approx \left(\frac{1-\nu}{Y}\frac{\sigma_0}{\delta s} p_0\right) R$$

$$h' \approx 0.1$$

T(R): T-number versus capsid radius



- Linear model: excellent agreement (log-log)
- Scaling exponent is in agreement with theory
- Geometrical prefactor: validated (logarithmic agreement)

Initial phage structural data: *Suhanovsky and Teschke, Virology, 2015*
Structural data refinement using Chimera

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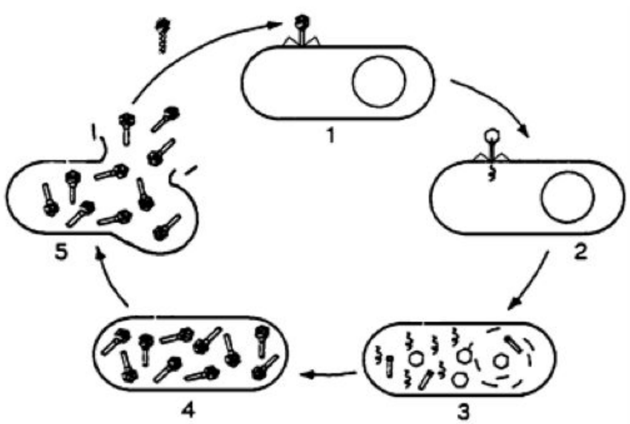
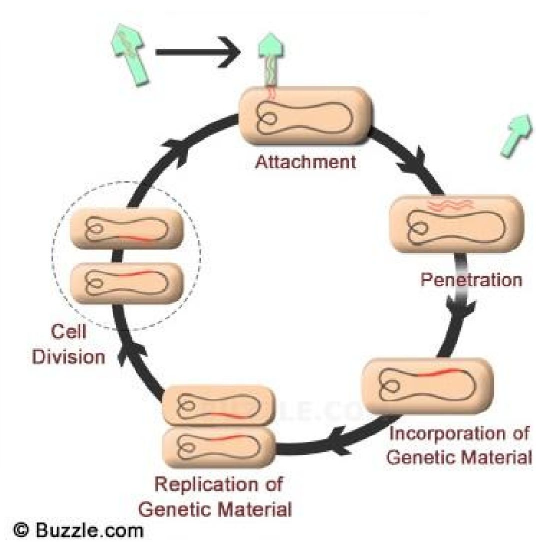
Phage Lifestyles

Lytic lifestyle



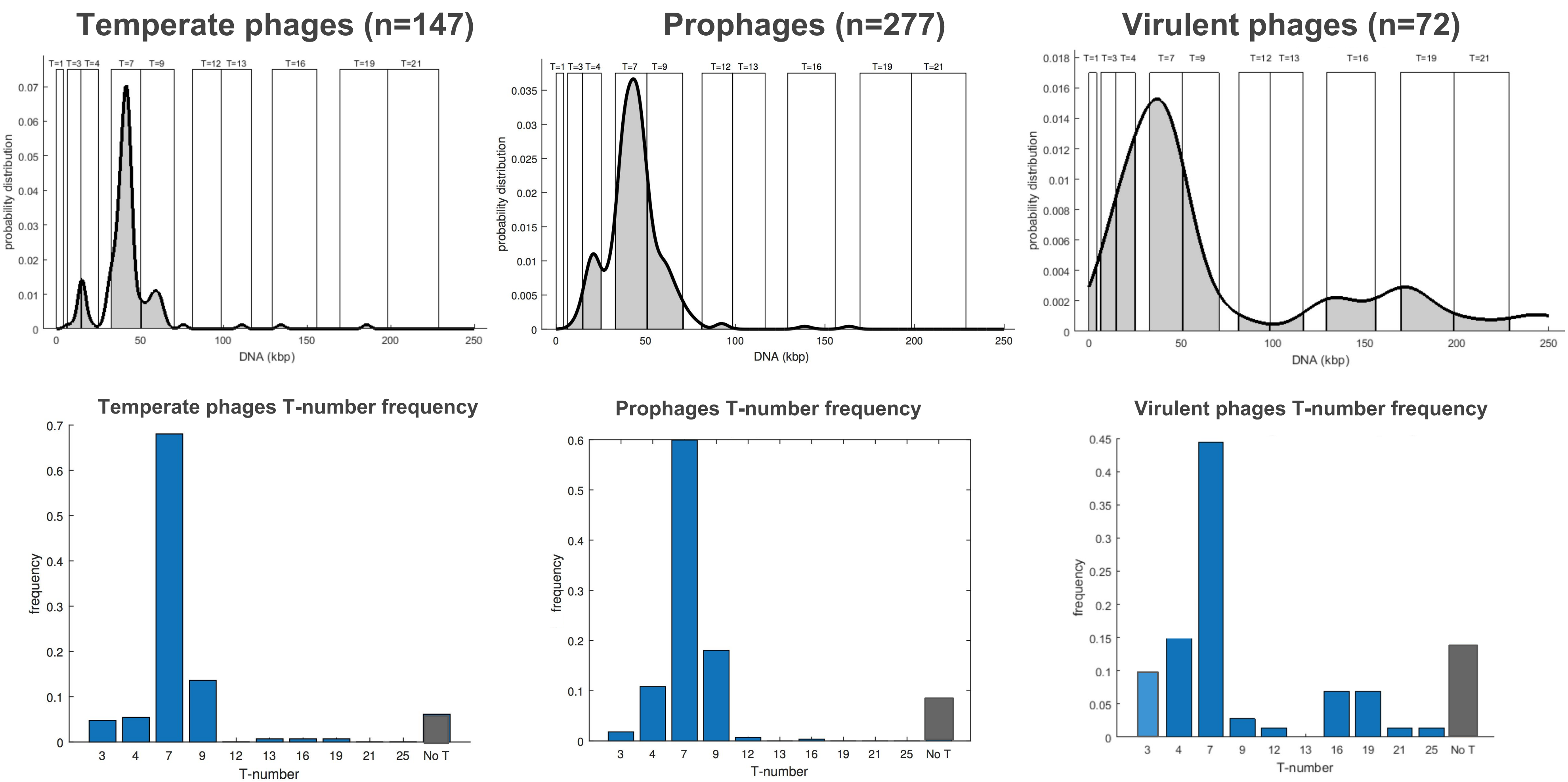
Lysogenic lifestyle



Type of Phages

- **Virulent** phages → Always lytic
- **Temperate** phages → Lytic / Lysogenic
- **Prophages** → lysogenic (dormant)

Capsid Structure as a Function of Phage Type



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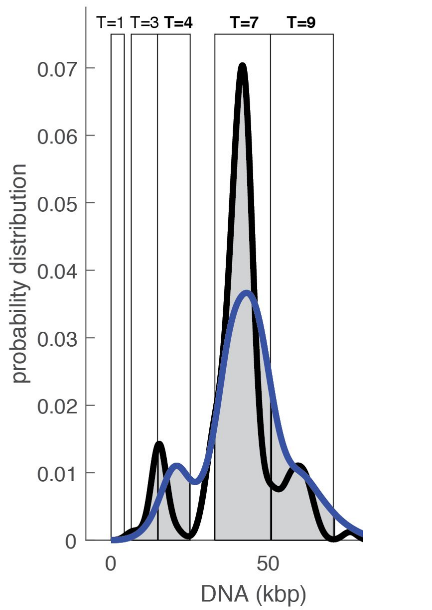
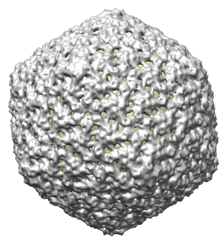
Lysogenic Lifestyle Constraints Phage Structure

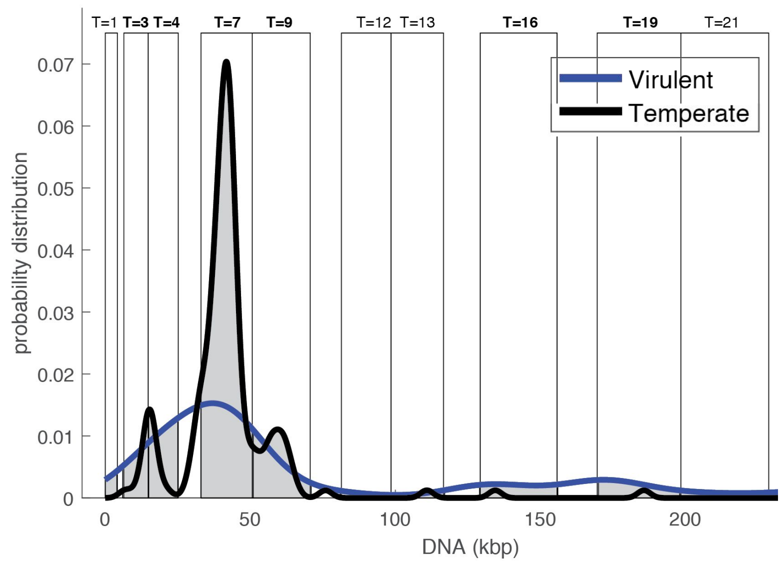
Phage structure and lysogenic lifestyle

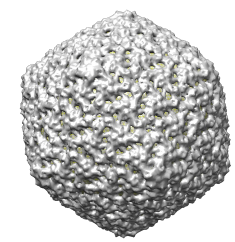




D ≈ 60-70 nm
np = 420
T = 7

Phage structure and lytic lifestyle





D ≈ 60-70 nm
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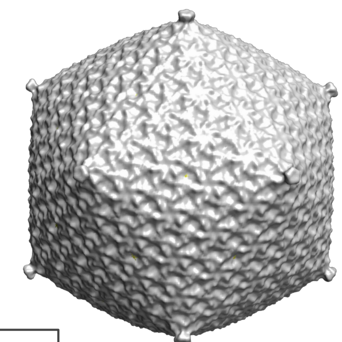
T = 7



D ≈ 110-120 nm
np = 1140
T = 19

- Selection pressure on icosahedral capsids.
- T = 7 dominates and constraints selection.
- Prophage structural selection pressure is lower.
- Why does lysogeny impose such structural constraint?

- Lytic lifestyle promotes structure variability
- Less restrictive selection on T-numbers.
- Valley in medium-large T numbers
- What is the advantage of adopting large T-number capsids for virulent phages?

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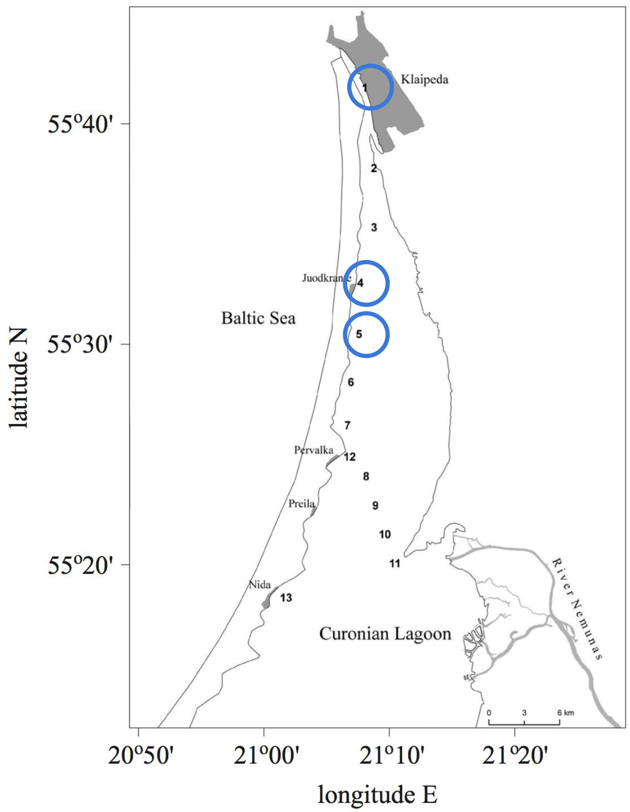
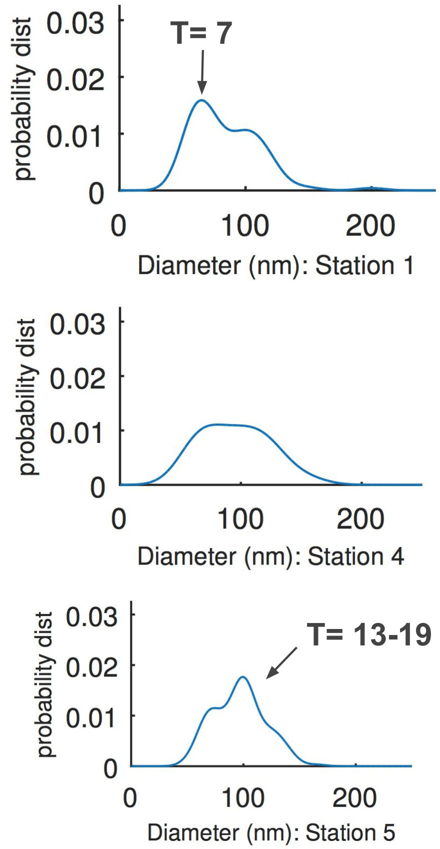
Lysogenic-to-Lytic Transition in the Environment

Phage sampling in the Curonian Lagoon



Sulcius, Oceanologia, 2011

Lysogeny → Lytic transition?



Connection with phage lifestyle framework

Lytic to temperate switching of viral communities

B. Knowles[1]*, C. B. Silveira[1,2]*, B. A. Bailey[3], K. Barott[4], V. A. Cantu[5], A. G. Cobián-Güemes[1], F. H. Coutinho[2,6], E. A. Dinsdale[1,7], B. Felts[3], K. A. Furby[8], E. E. George[1], K. T. Green[1], G. B. Gregoracci[9], A. F. Haas[1], J. M. Haggerty[1], E. R. Hester[1], N. Hisakawa[1], L. W. Kelly[1], Y. W. Lim[1], M. Little[1], A. Luque[3,5,7], T. McDole-Somera[8], K. McNair[5], L. S. de Oliveira[2], S. D. Quistad[1], N. L. Robinett[1], E. Sala[10], P. Salamon[3,7], S. E. Sanchez[1], S. Sandin[8], G. G. Z. Silva[5], J. Smith[8], C. Sullivan[11], C. Thompson[2], M. J. A. Vermeij[12,13], M. Youle[14], C. Young[15], B. Zgliczynski[8], R. Brainard[15], R. A. Edwards[5,7,16], J. Nulton[3], F. Thompson[2] & F. Rohwer[1,7]

Viral Information Institute
Knowles,... Luque, et al, Nature 2016

- Piggy-back-the-winner framework: More resources → more lysogeny
- Our new structural approach provides an independent approach to analyze phage lifestyle
- Hypothesis: Lysogenic transition near Klaipeda
- What is the ecological impact of this transition in the Curonian Lagoon?

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Conclusions

- Validation for the theory of phage capsids → It provides mechanistic understanding
- Lysogenic lifestyle constraints the phage capsid structure (T~7)
- Lytic lifestyle promotes phage structure variability
- Gap on medium-large T-structures
- Environmental analysis of lysogenic to lytic transitions and new hypothesis on phage lifestyle

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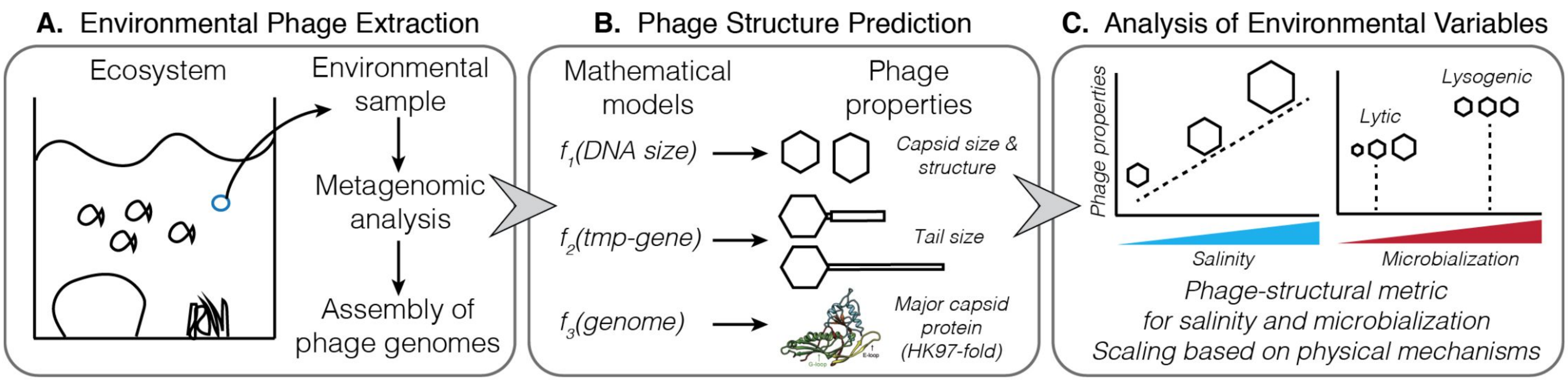
Perspectives

Environmental analysis of phage structure: Proxy for environmental and ecological changes



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