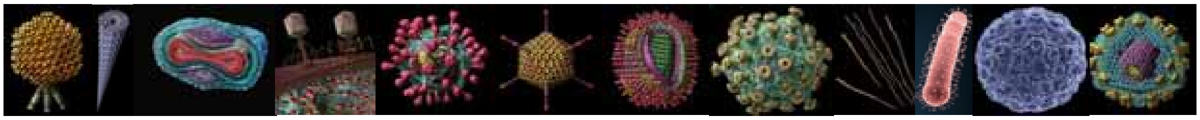
The place of viruses in biology, a metabolism-versus-genes-first debate



- Introduction: discovery, viral diversity and function
- Viruses and origin-of-life theorizing
- Revival of virocentric hypotheses
- The conceptual debate: are viruses alive?
- The phylogenetic debate: can viruses be placed in the tree of life?

The discovery of viruses

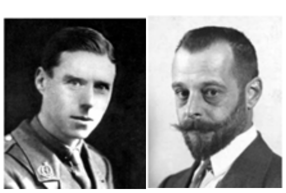
~1900 — 1950 — 2000 — time (years)

Dmitry Ivanovsky (1892)
Suspensions of plant tissues afflicted with mosaic tobacco disease infectious after passage through ceramic filters retaining bacteria – leakage?

Martinus Beijerinck (1898)
Similar observation – interpretation: the infective agent (the **"virus"**) was the liquid

Fiedrich Loeffler & Paul Frosch (1898)
Similar observation (infective filtrates) on the foot-and-mouth disease but retained in filters of smaller grains –the causative agent: "filterable particles".

Viruses identified as extremely small infectious particles

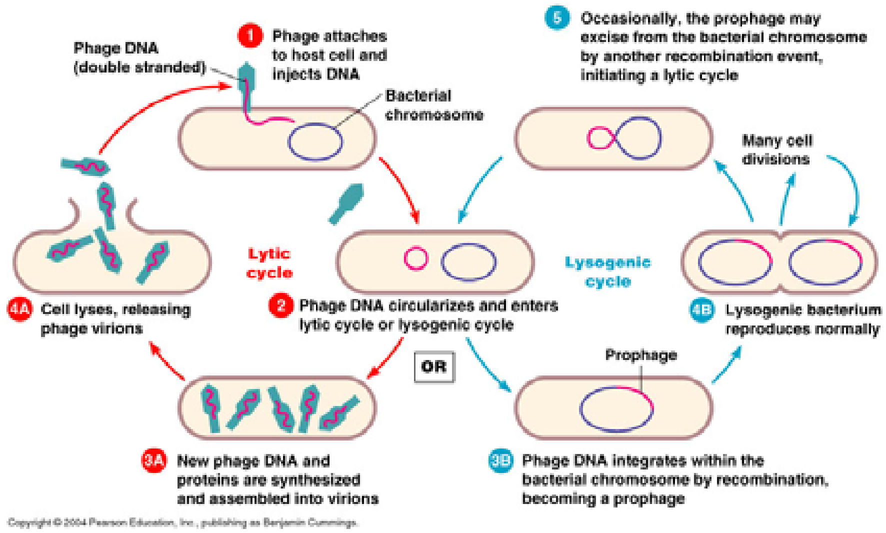


Frederick Twort (1915) and Felix D'Hérelle (1917)
Viruses infecting bacteria: bacteriophages

What do we know about viruses?

Strict molecular parasites - depend on a cell to develop their reproductive cycle

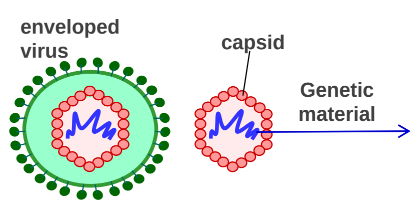
Viral infective/reproductive cycle:



Viruses are extremely diverse

Viral classification according to:

- genetic material



Class
I - ds DNA
II - ssDNA
III - ds RNA
IV - ss RNA (+)
V - ss RNA (-)
VI - ss RNA with DNA intermediate (retroviruses)
VII - ds DNA with RNA intermediate

- shape
- capsid structure
- envelope or not
- additional structures (tail, appendices...)
- hosts

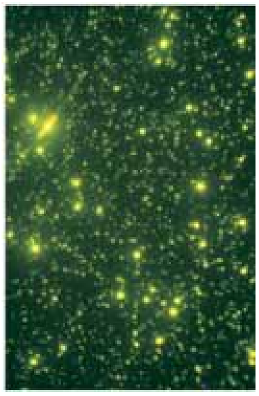
International Committee on Taxonomy of Viruses (ICTV - http://www.ictvonline.org)

Viruses are strict molecular parasites that "possess some of the properties of living systems such as having a genome and being able to adapt to a changing environment"

Virus species is "a polythetic class of viruses that constitute a replicating lineage and occupy a particular ecological niche”

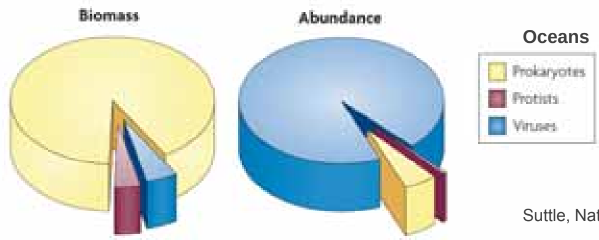
2475 viral species, distributed in 395 genera, 22 subfamilies, 94 families and 6 orders

Viruses are important players in ecology



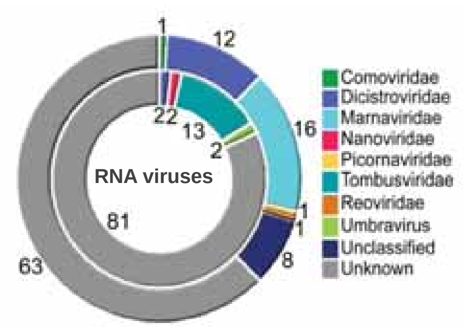
Furhman, Nature (1999)

- Viruses are very abundant in nature (e.g. oceans)

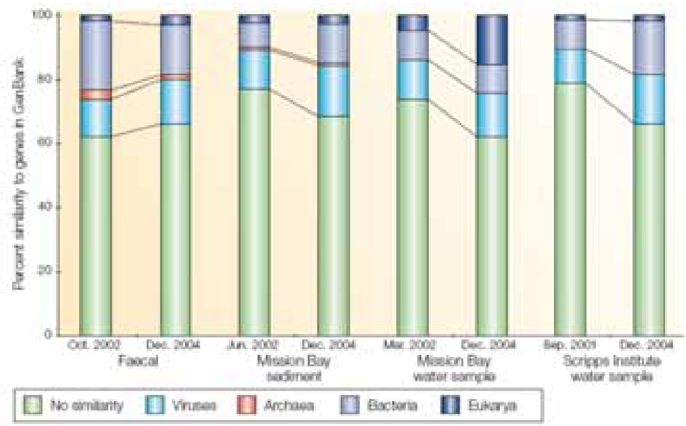


Suttle, Nat Rev Microbiol 2007

- Viruses are extraordinarily diverse: immense genetic reservoir inferred from metagenomic studies (metavirомes – DNA, RNA)



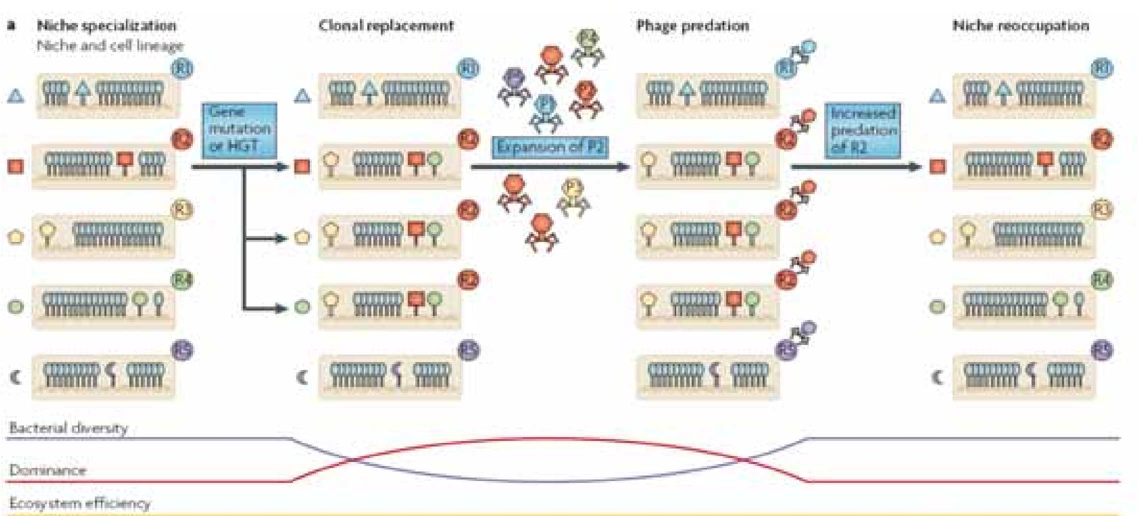
Culley et al, Science 2006



Edwards & Rohwer, 2005

Viruses are important players in ecology

- Abundant and diverse – significant fraction of biomass
- Control population sizes (terminate blooms)
- Biogeochemical cycles: nutrient cycling and sinking rates
- Maintenance of biodiversity via 'kill-the-winner' strategies



Rodriguez-Valera et al, Nat Rev Microbiol 2009

Viruses are important players in evolution

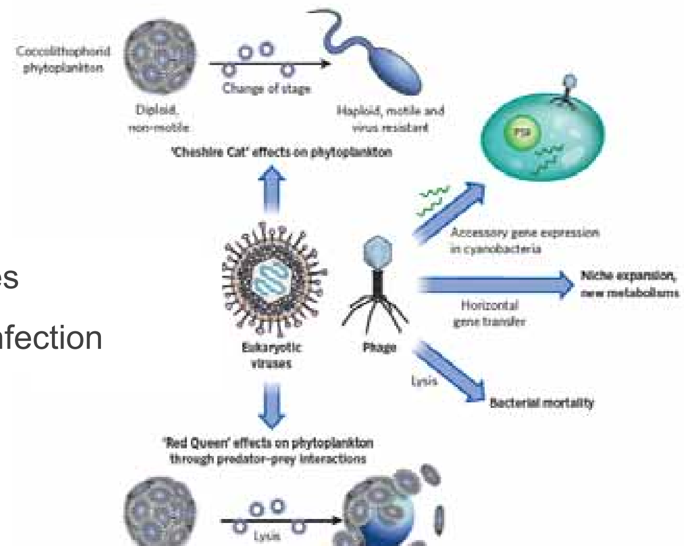
- Models in population genetics to test evolutionary hypotheses

  (high pop size + high number of generations per time unit)
- Foster evolution gene & genomes (high mutation & recombination rate)
- Selective pressure on populations (arms race)
- Horizontal gene transfer

  & innovation in hosts

Viral-mediated HGT

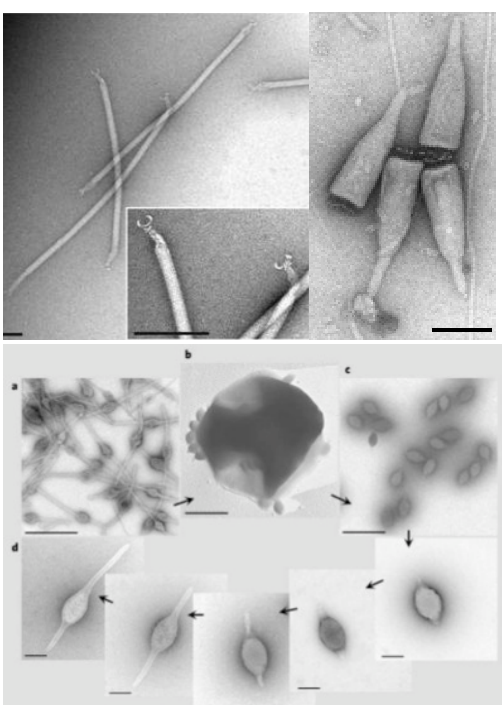
- Through lysogenic cycles
- Recombination during infection
- CRISPR-mediated



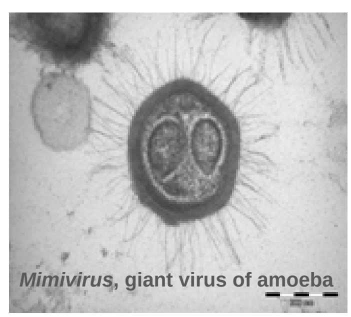
Rohwer & Thurber, 2009

Amazing viruses...

Viruses from hyperthermophilic archaea
(D. Prangishvili)



Mimivirus and other Nucleo-Cytoplasmic
Large DNA Viruses (NCLDV)



dsDNA virus
1.2 Mbp genome
>900 protein coding genes
several translation-related genes
sugar, lipid, aa metabolism

Raoult et al Science 2004

Mamavirus, 1.191 Mbp genome
Megavirus chilensis, 1.259 Mbp genome

... & the revival of an old debate

Viruses & origins of life

~1900 1950 2000

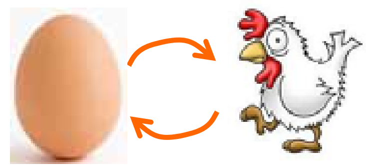
time (years)

Viral discovery simultaneous with conditions for a scientific investigation on the origin of life:

- Louis Pasteur (1860s): refutal of continuous spontaneous generation
- Charles Darwin (Origin of Species, 1859): species continuity to a common ancestor
- Immense progress in organic chemistry, biochemistry and cytology

Two opposed currents of thought – reflecting a chicken-egg dichotomy:

- Nucleocentric – self-replication
- Cytoplasmist – self-maintenance



Viruses:

- Mysterious nature
- Small size and infectivity

⇨ simplest living beings

"smallest = virus, smallest = first, so that virus = first"

Podolsky S. The role of the virus in origin-of-life theorizing. J Hist Biol 1996. 29:79-126.

1900 1950 2000

time (years)

1900 –1930

Nucleocentric (and virocentric!) models on the rise

• Leonard Troland

1914 – first life form was an "enzyme or organic catalyst"

1917 – "genetic enzyme"

• Hermann Müller

1922 – gene (Troland's "genetic enzyme") → gene = virus

1929 – first living organism was a primitive gene

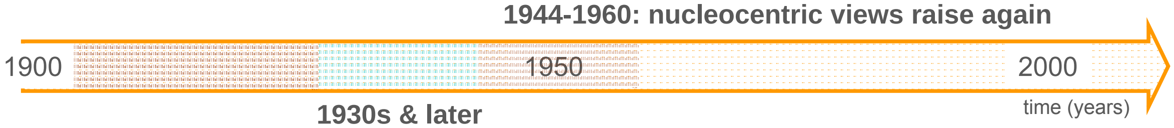
• John B.S. Haldane (1929, The origin of life)

"life may have remained in the virus stage for many millions of years before a suitable assemblage of elementary units was brought together in the first cell"

• Alexander & Bridges (1928) – living organisms divided in:

- Cytobionta (cells)
- Ultrabionta (viruses)

1944-1960: nucleocentric views raise again



1930s & later
Cytoplasmist models on the rise

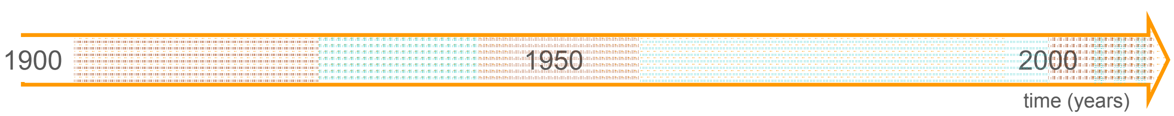
- Alexander I. Oparin (1938, The origin of life – and later work)

  life as a self-regulating system of catalytic reactions (metabolism first)

But also criticisms to the idea that simple = primitive

- Robert G. Green (1932)
- André Lwoff (1943, 1957): viruses as products of regressive evolution
- John B.S. Haldane (1932):
  - "most evolutionary change has been degenerative"
  - self-reproduction first but in a living system interdependence of genes & other components

- Avery et al. (1944): DNA as genetic material
- Herschey & Chase (1952): nucleic acid component of viruses is the infective element
- Watson & Crick (1953): DNA structure – self-copying mechanism



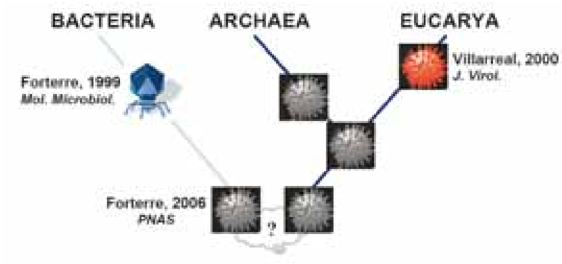
1960s to 2000s virocentric views abandoned

- Alexander I. Oparin (1961): viruses as products of cells
- Advances in biochemistry and molecular biology demonstrated that viruses are strict molecular parasites – selfish genetic elements with an extracellular phase
- A better model for the origin of life: ribozymes and the "RNA world"

21st century: renaissance of old virocentric ideas

- Very heterogeneous proposals with viruses being central:
  - at operational level: seen functionally as living beings
  - at phylogenetic level: viruses as descendants of viruses predating cells

Viruses as "inventors" of DNA and donors of the DNA replication system in the 3 domains



Viruses as integral domain of life

CEOs

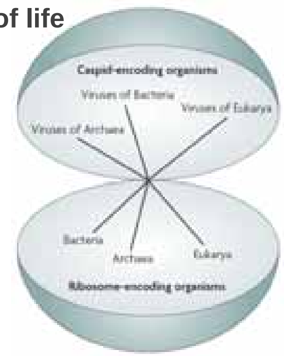
Raoult & Forterre NRM 2008

REOs

Ultrabionta (viruses)

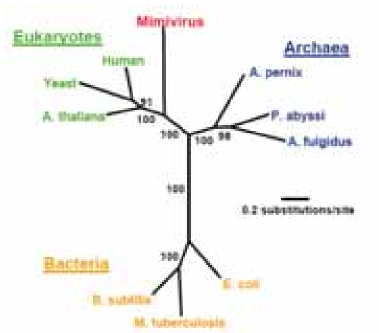
Cytobionta (cells)

Alexander & Bridges 1928



Giant viruses as 4th domain of life

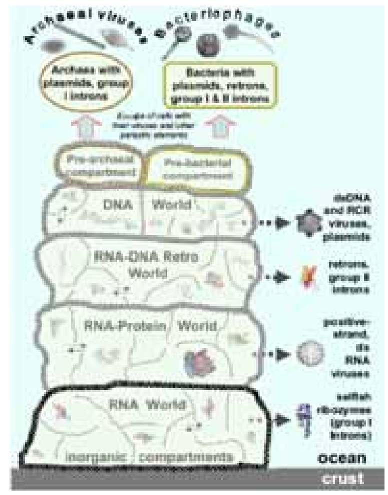
(NCPLDV) Raoult et al Science 2004



"Ancient virus world" and related models

"Viruses" predate cellular life

Koonin et al. Biol Direct 2006



The conceptual debate: are viruses alive?

Defining life, a difficult task

"Metabolist" view

"Energy"

Self-maintenance

"Geneticist" view

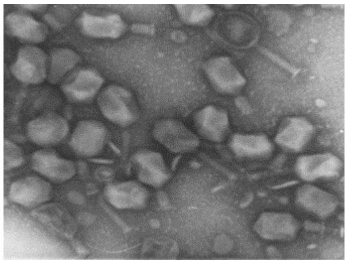
"Information"

Self-replication and (darwinian) evolution

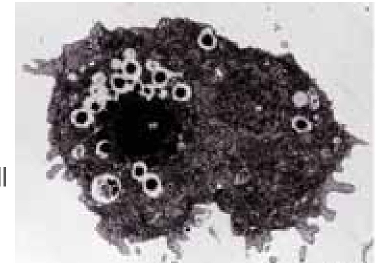
For metabolist views:

Viruses lack metabolism → viruses **NOT** alive ('borrowed life')

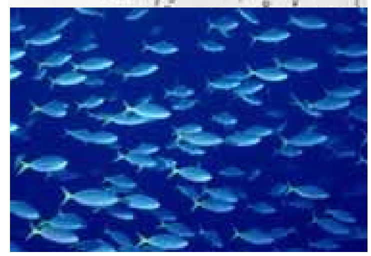
A conceptual trick: the virocell concept



virions ⟳ "virocell"
virus infecting a cell



fish eggs ⟳ fish



Artifice to transfer the properties intrinsic to cells (which viruses actually lack) to viruses

Epistemological "cheating"

Lopez-Garcia, Hist Phil Life Sci 2012
Lopez-Garcia & Moreira, Education, Evolution and Outreach 2012

The conceptual debate: are viruses alive?

"Metabolist" view ⟷ **"Geneticist" view**

"Energy" — "Information"

Self-maintenance — Self-replication and (darwinian) evolution

For geneticist views:

Viruses not able to self-replicate → **NOT** alive

Viruses do evolve but…

Two possibilities to consider viruses alive according to geneticist views:

1) Everything that evolves or is evolved is alive (includes **viruses & "memes")**

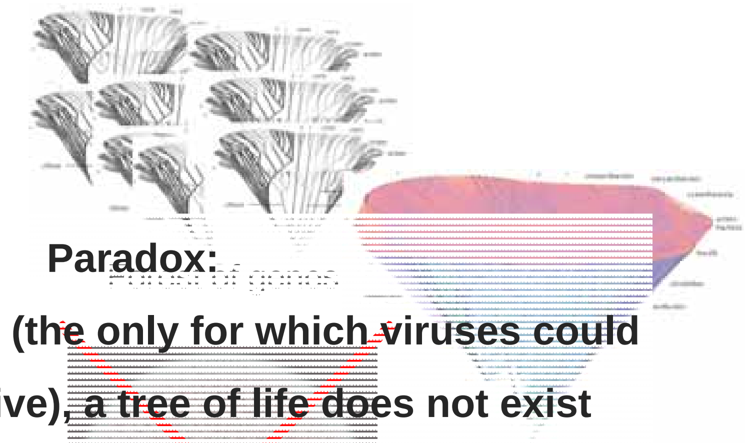
2) **Extend** the definition of virus to include a **self-replicating capacity**:
the virus world option, where virus has a dual meaning:
- contemporary viruses unable to self-replicate
- virus-like self-replicating entities (those that precede cellular life in this model)

CONFUSING, but acceptable

The phylogenetic debate:
can viruses be placed in the tree of life?

What is a tree of life?

Trees of organisms
versus
trees of genes



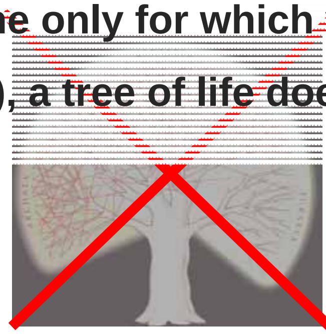
Forest of genes

network of genes

Paradox:

for geneticist views (the only for which viruses could be considered alive), a tree of life does not exist

"core" gene trees



no tree of life

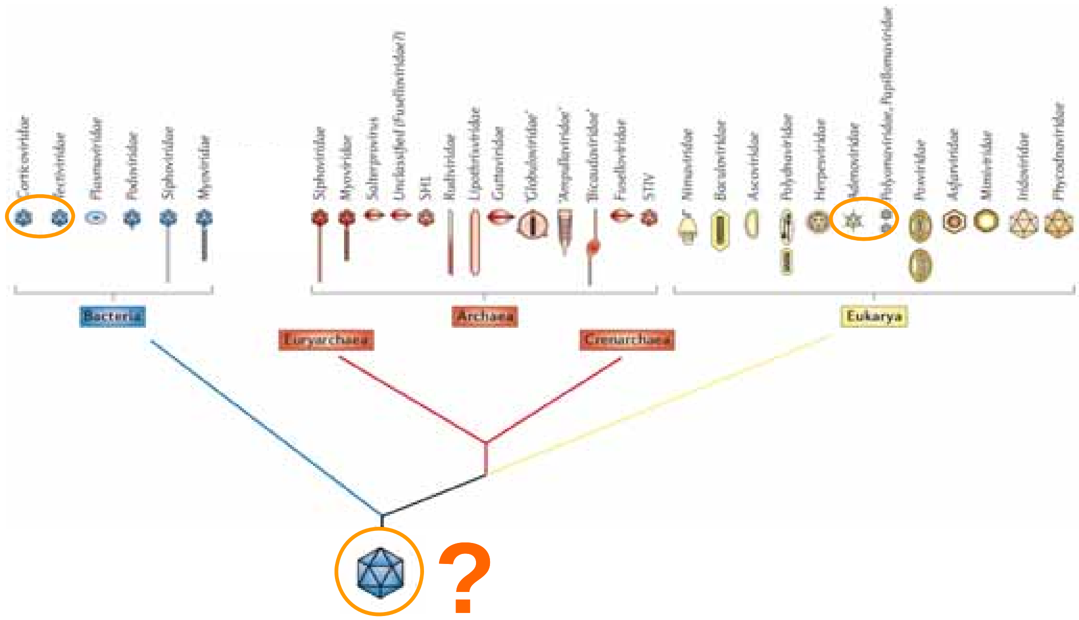
The phylogenetic debate:
can viruses be placed in the tree of life?

1) The virus world & related models

- Recognize the impossibility to place viruses in a tree of life
    - No single gene shared by ALL viral families
    - Lack structural continuity
    - Genome volatility
- "Hallmark viral genes" largely distributed and/or protein folds absent from cells
- Structural motifs shared by capsid proteins from distant viral lineages & infection of distant host by viruses of the same family: evidence for a common origin predating cells?

Koonin et al 2006

Are some shared motifs proof of common & ancient origin?



(e.g. jelly-roll capsid protein)

Bamford et al 2005

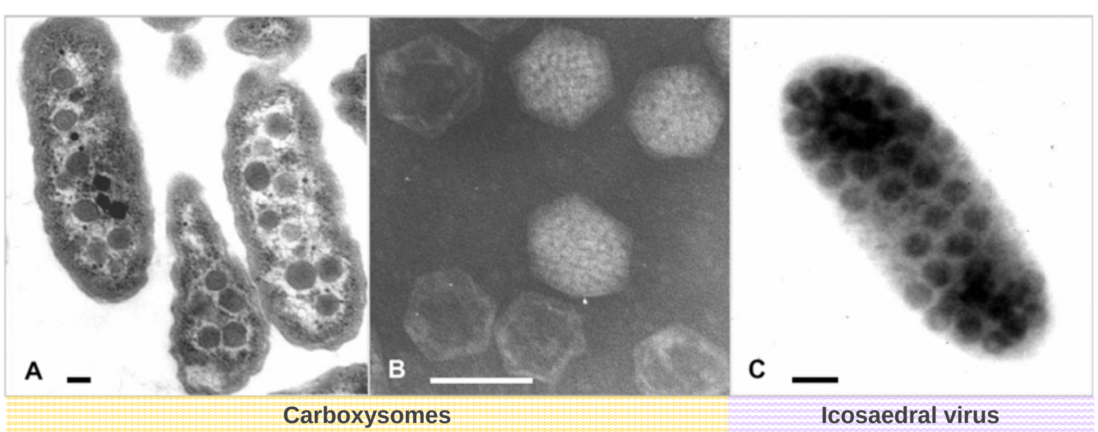
Koonin et al 2006

Pranghishvili, Forterre & Garrett 2006

Alternative explanation 1: convergence

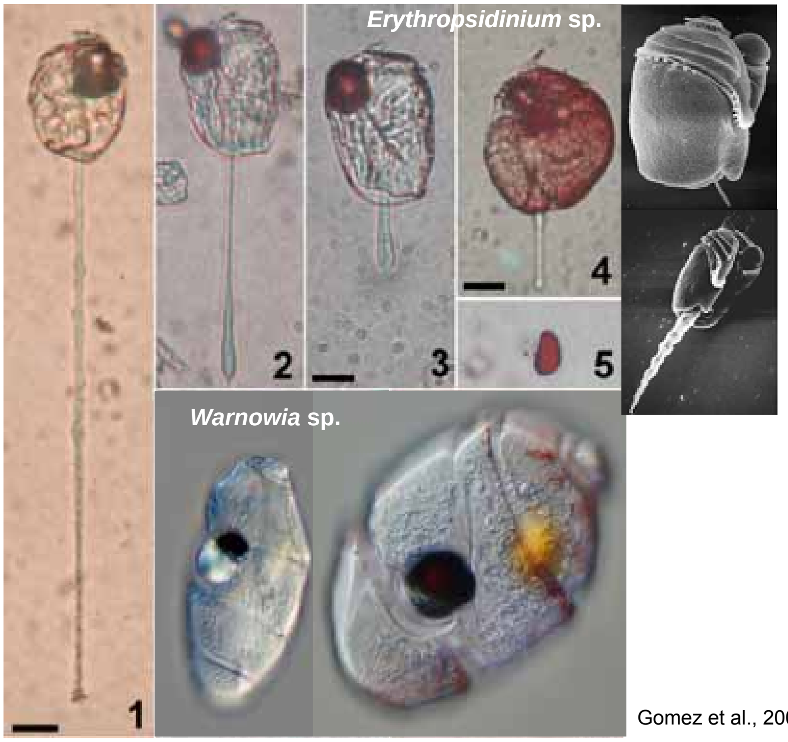
Simple geometrical protein structures → strong 3D constraints

Strong selection (imposed by structural or functional constraints)
→ high probability to converge to similar folds



Alternative explanation 1: convergence

Convergence of complex structures: "eye"-bearing dinoflagellates



Gomez et al., 2009

Family Warnowiaceae:

Phagotrophic unarmored dinoflagellates with an ocelloid

- Ocelloid:
Photoreceptor system with cornea, lens and pigment cup-like structures (an "eye"). "Ontogenetically", it derives from ancient chloroplast.

- *Erythropsidinium*:
Also possesses a **piston**, an extensible appendage (fragile)

- Nematocysts
Extrusive organelles for prey capture. Shared by some warnowiids and some *Polykrikos*

Alternative explanation 2: Horizontal gene transfer (HGT)

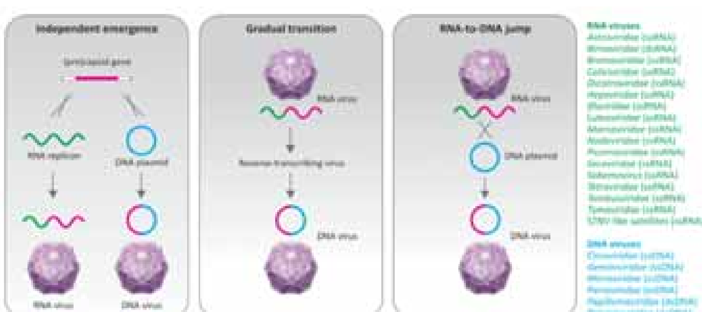
HGT is extensive among viral lineages (likely cell mediated)

Some recent examples:

- Multiple HGT events have occurred among dsRNA viruses from different families

Liu et al. BMC Evol Biol 2012

- Recombination events between RNA and DNA viruses (HGT)



Diemer & Stedman, Biol Direct 2012

Krupovic, BioEssays 2012

→ "Network-like rather than tree-like mode of viral evolution"

Koonin & Dolja, BMC Evol Biol 2012

Alternative explanation 3: host shifts

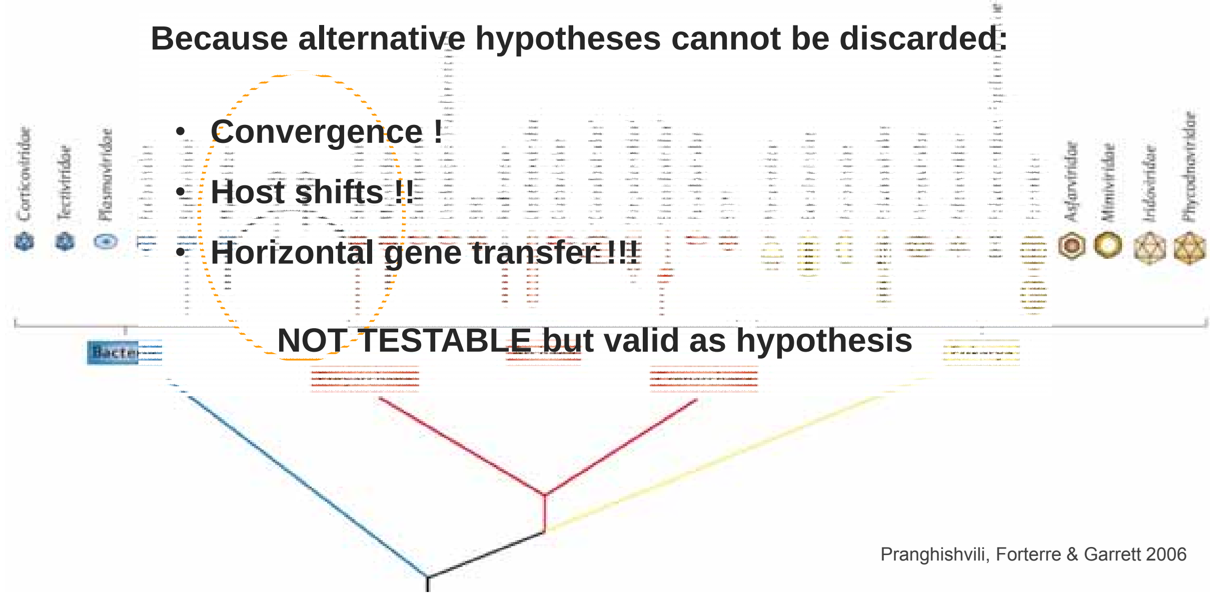
Can structural motifs shared by capsid proteins from distant viral lineages & infection of distant host by viruses of the same family be taken as proof of common and ancient origin?

NO!

Because alternative hypotheses cannot be discarded:

- **Convergence !**
- **Host shifts !!**
- **Horizontal gene transfer !!!**

NOT TESTABLE but valid as hypothesis



D. Moreira & P. López-García (2009) Ten reasons to exclude viruses from the tree of life. Nat Rev Microbiol

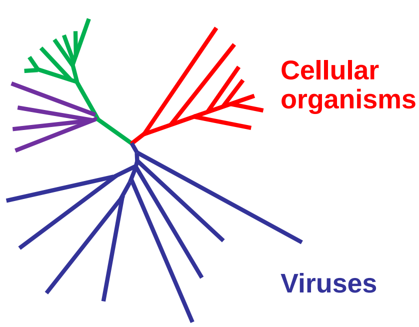
Can viruses be placed in the tree of life?

2) Viruses (or some viral families) form a fourth domain in the tree of life

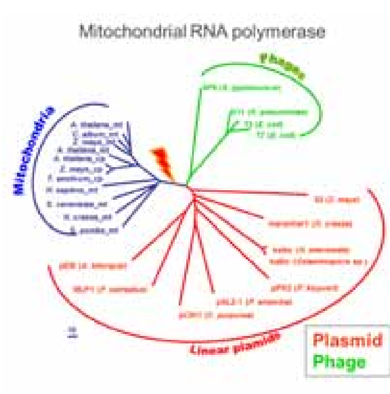
Genes shared by viruses and cells

Molecular phylogeny: need to compare homologous genes/proteins

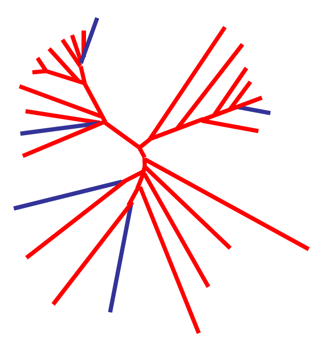
TESTABLE



Common origin

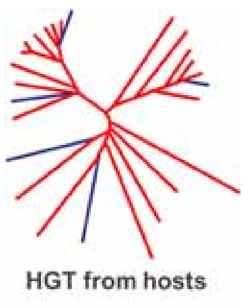


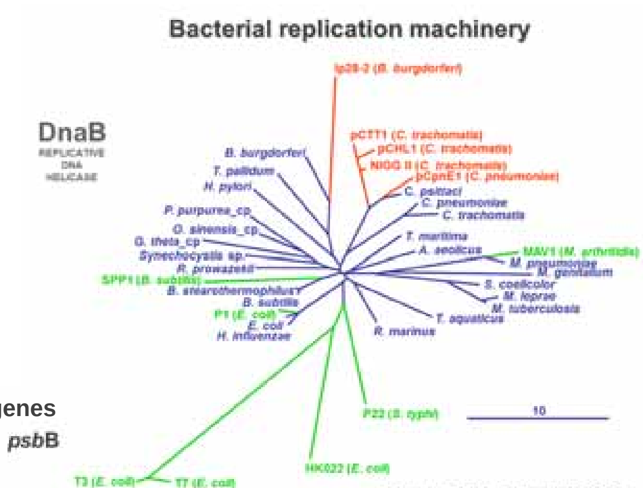
Viral origin



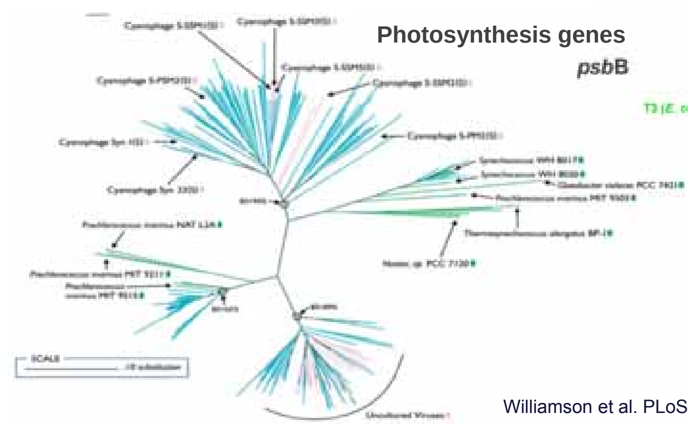
HGT from hosts

Genes shared by viruses and cells: mostly cellular origin



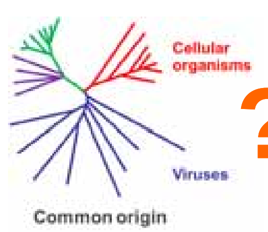


Moreira, Mol. Microbiol. 2000



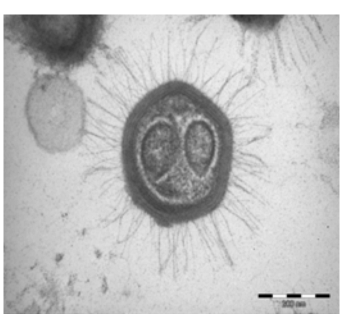
Williamson et al. PLoS ONE 2008

Do giant viruses form a fourth domain of life?



?

Translation & other informational genes

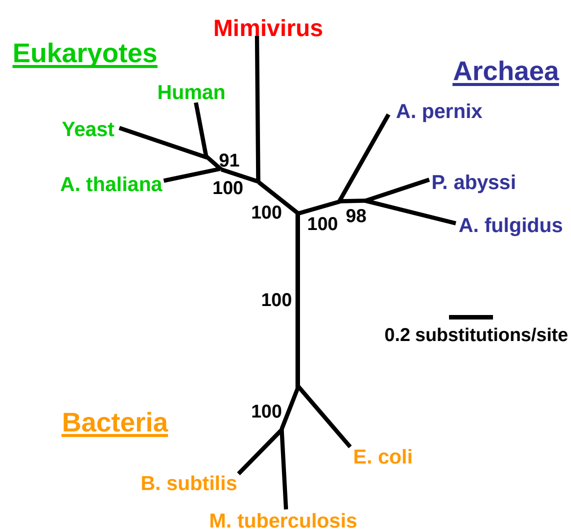


Mimivirus, giant virus of amoeba

Raoult et al Science 2004

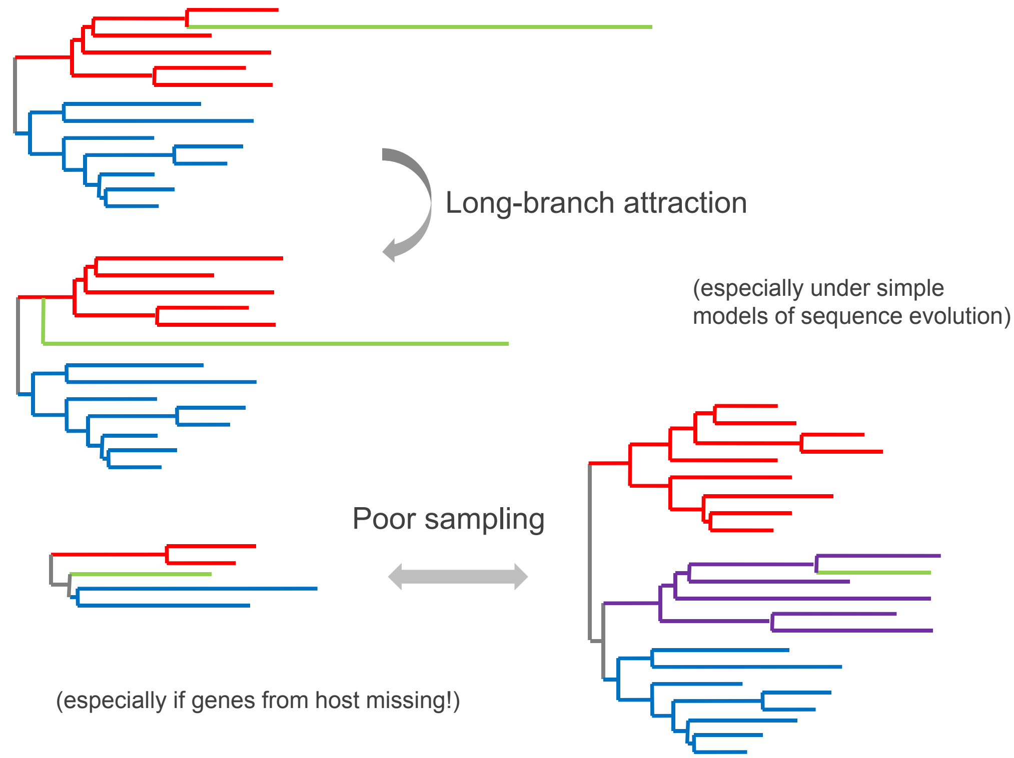
Concatenation of 7 proteins

(arg-tRNA-synthetase, met-tRNA-synthetase, tyr-tRNA-synthetase, RNA-pol-II large subunit, RNA-pol-II second large subunit, PCNA, 5 '-3 ' exonuclease)



H_0: Giant DNA viruses (NCLDV) constitute a fourth domain of life

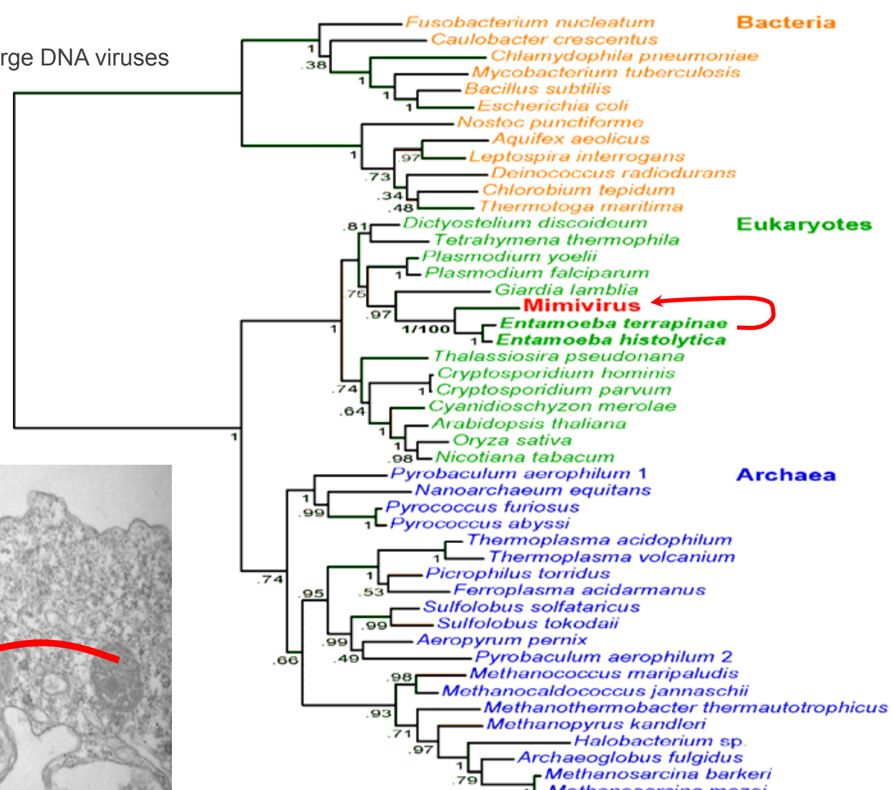
Potential problems of phylogenetic reconstruction

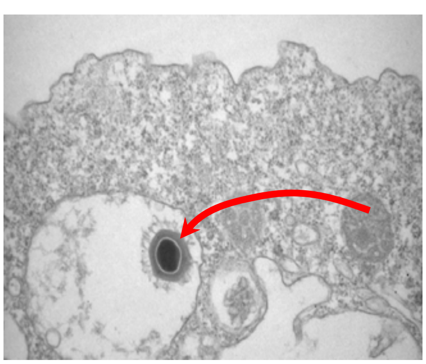


Do giant DNA viruses constitute a fourth domain of life?

NCLDV
nucleocytoplasmic large DNA viruses

Tyr-RS

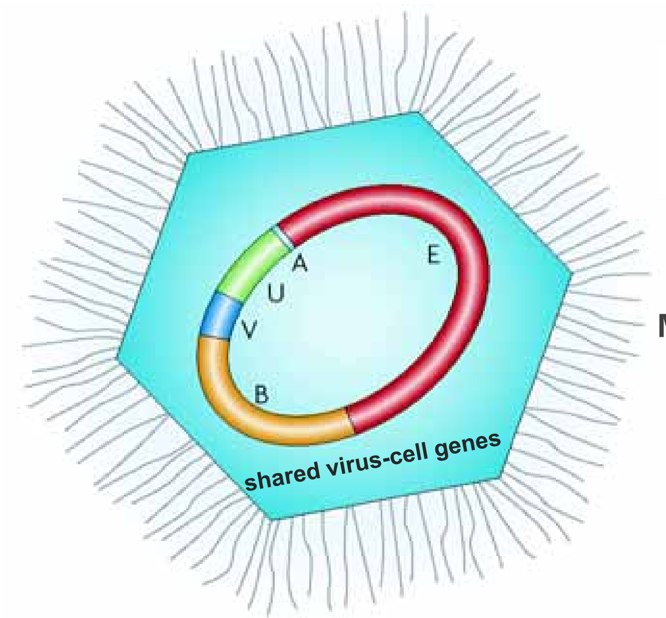




Moreira & López-García 2005, Science

What about the rest of Mimivirus cell-like genes?

Giant viruses, giant chimeras — Moreira & Brochier-Armanet, BMC Evol Biol 2008



- Eukaryotic origin 56%
- Bacterial origin 29%
- Archaeal origin 1%
- Viral origin 5%
- Unresolved 9%

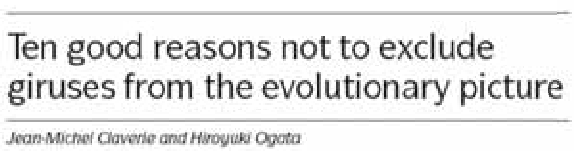
Most viral cell-like genes have been acquired by HGT from host or bacteria (possibly intracellular symbionts)

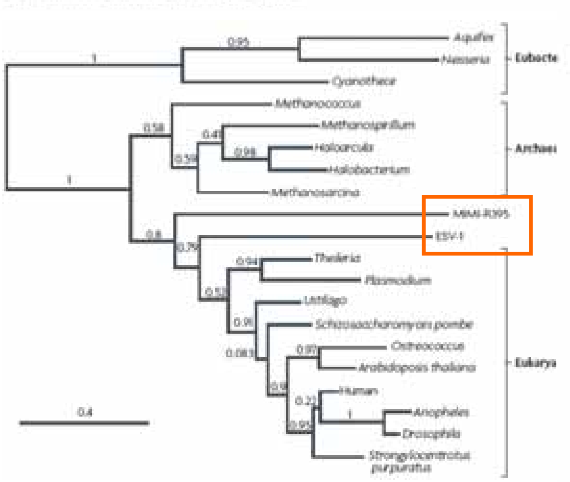
See also: Williams TA, Embley TM,Heinz E. Informational gene phylogenies do not support a fourth domain of life for nucleocytoplasmic large DNA viruses. PLoS ONE 2011

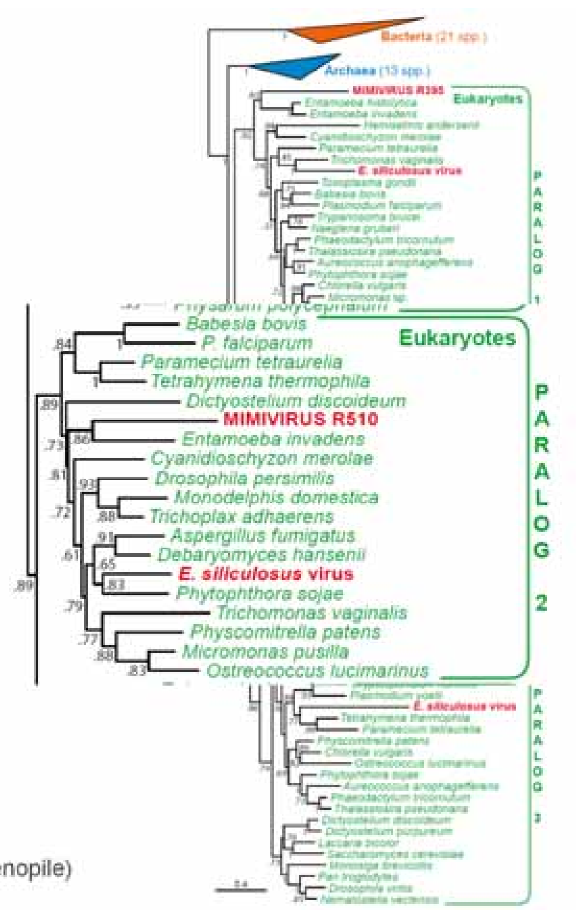
Illustrative anecdotes…

Ten reasons to exclude viruses from the tree of life

Moreira & López-García Nat Rev Microbiol 2009





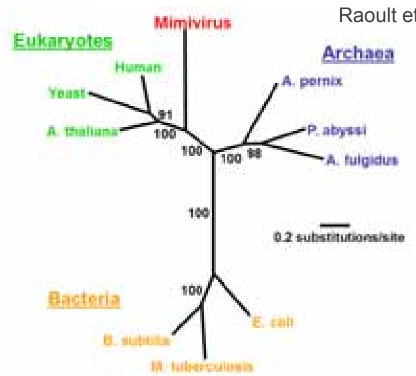


Clamp loader protein from Mimivirus (infecting amoeba) and *Ectocarpus silicosus* ESV-1 (host: brown alga/Stramenopile)

Illustrative anecdotes…

Mimivirus forms a 4th domain of life

Raoult et al. 2004

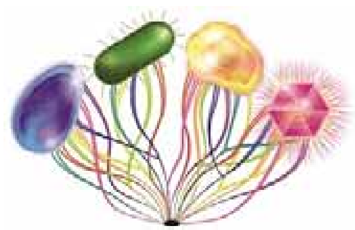


There is no such thing as a tree of life (and of course viruses are out!)

Didier Raoult 2009

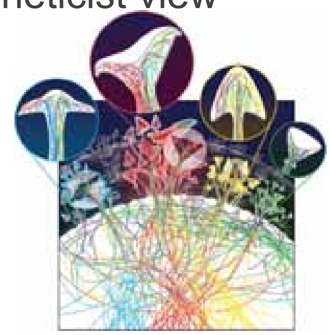
From a metabolist view…

…to a geneticist view



… to something fuzzy ("rhizome" of life)

Raoult 2010



In conclusion

- The epistemological discussion about whether viruses are alive or not and whether some virus-like forms (using "virus" as a metaphor for self-replicating entities) precede the first cells is a matter of debate that can be understood within the metabolism-versus-genes dialectics
- Viruses **cannot** be included in the tree of life

  For geneticists views a tree of life does not exist

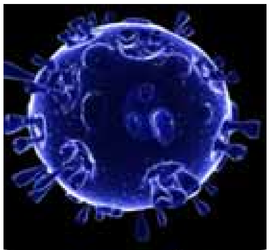
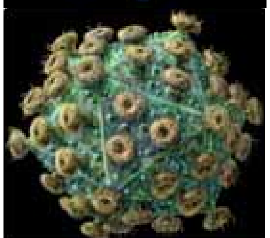
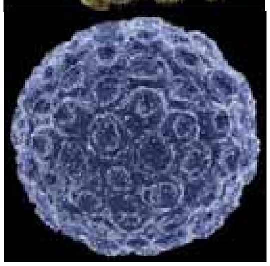
  For metabolist views – a tree of life exists but attempts to incorporate viruses are artificial and alien to proper phylogenetic practice:

  - Viruses do not share a common ancestry
  - Viral recognizable cell-like genes have overwhelmingly been acquired from hosts by horizontal gene transfer (HGT)

→ Consequently, the claim that viruses form a fourth domain in the tree of life can be solidly refuted by proper molecular phylogenetic analyses and needs to be removed from this debate

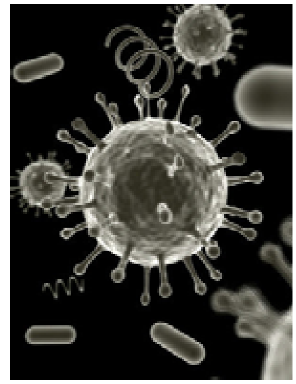
Lopez-Garcia, Hist Phil Life Sci 2012

Lopez-Garcia & Moreira, Education, Evolution and Outreach 2012

Thanks!

спасибо



David Moreira