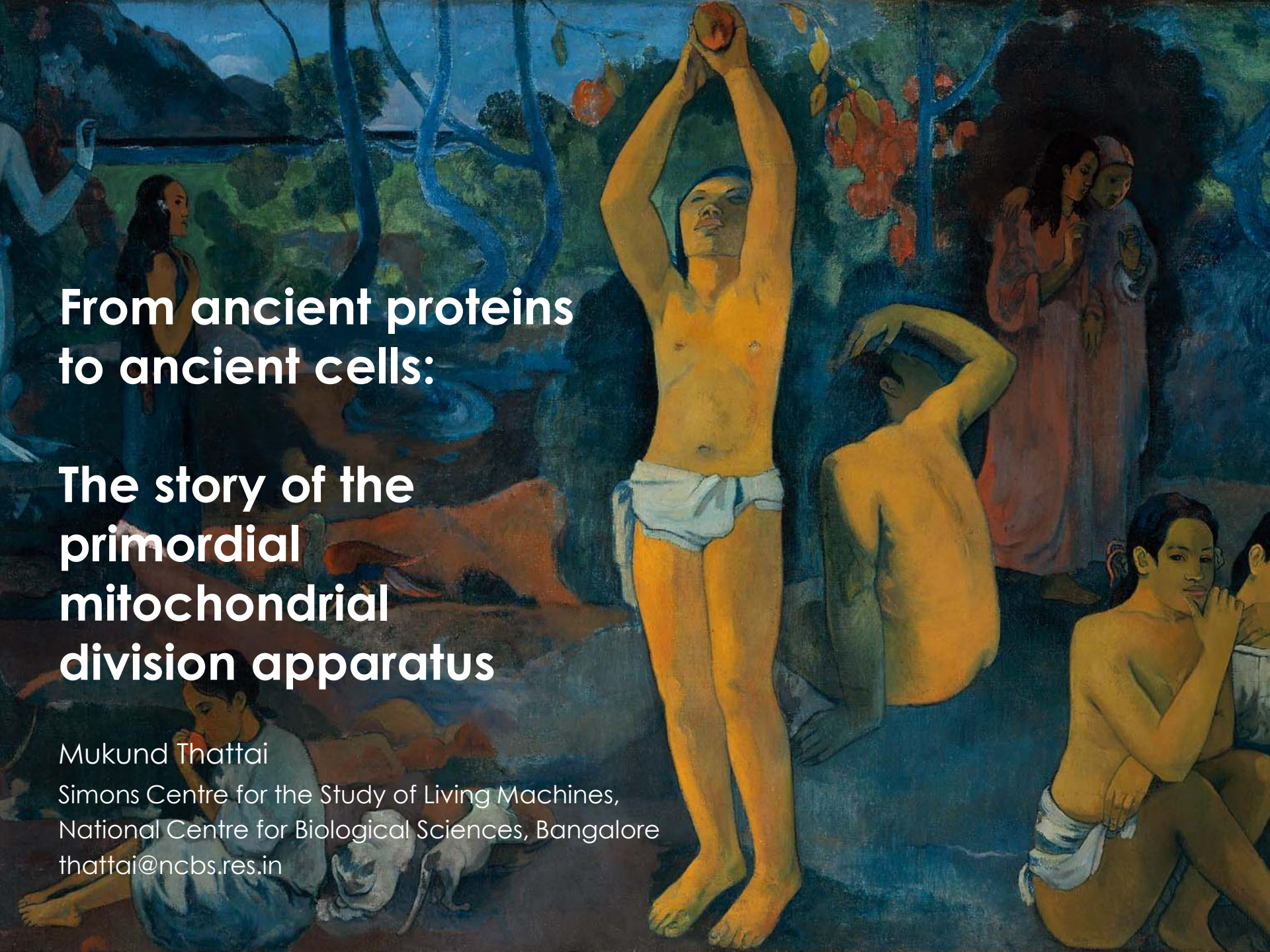
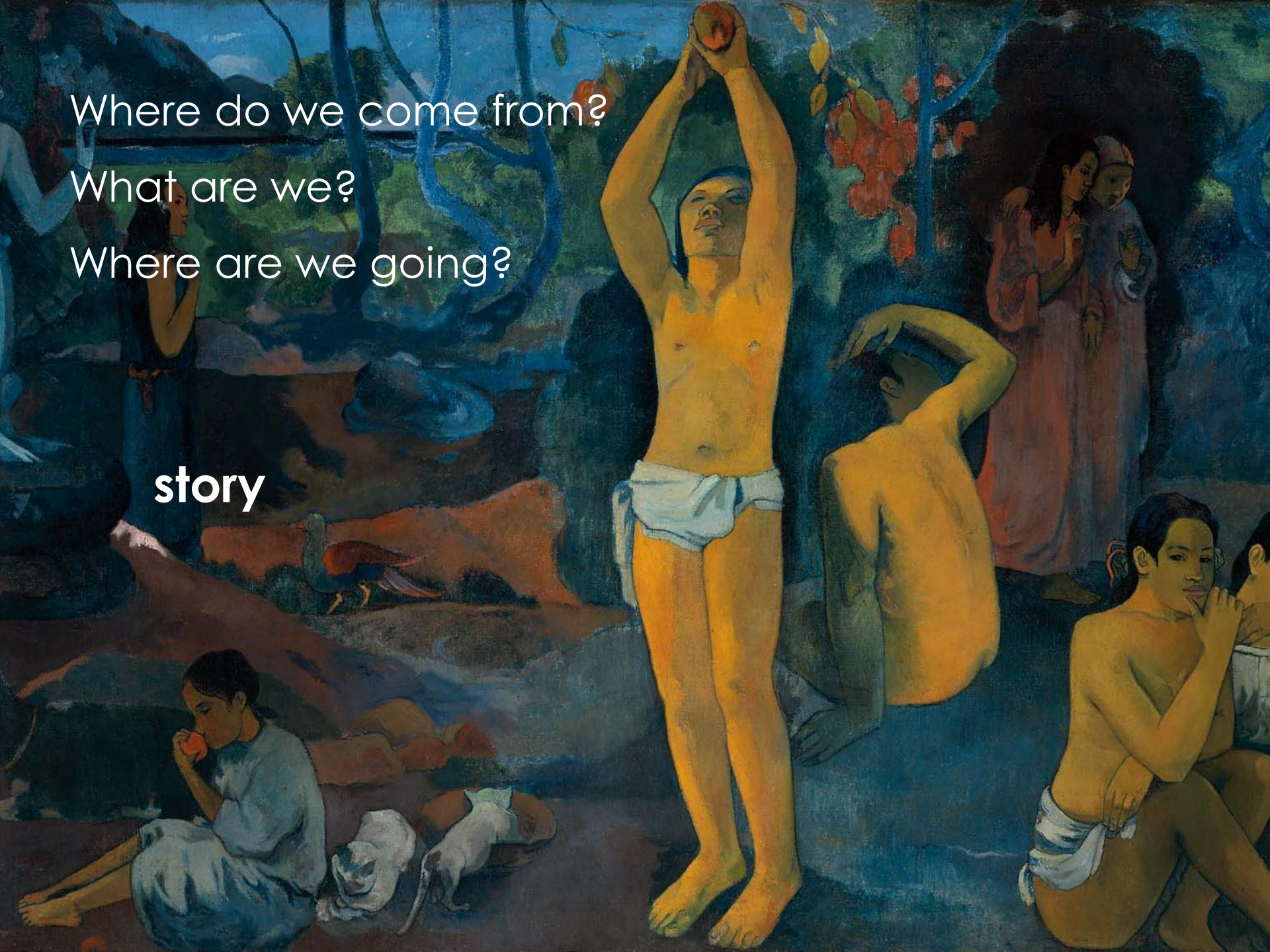


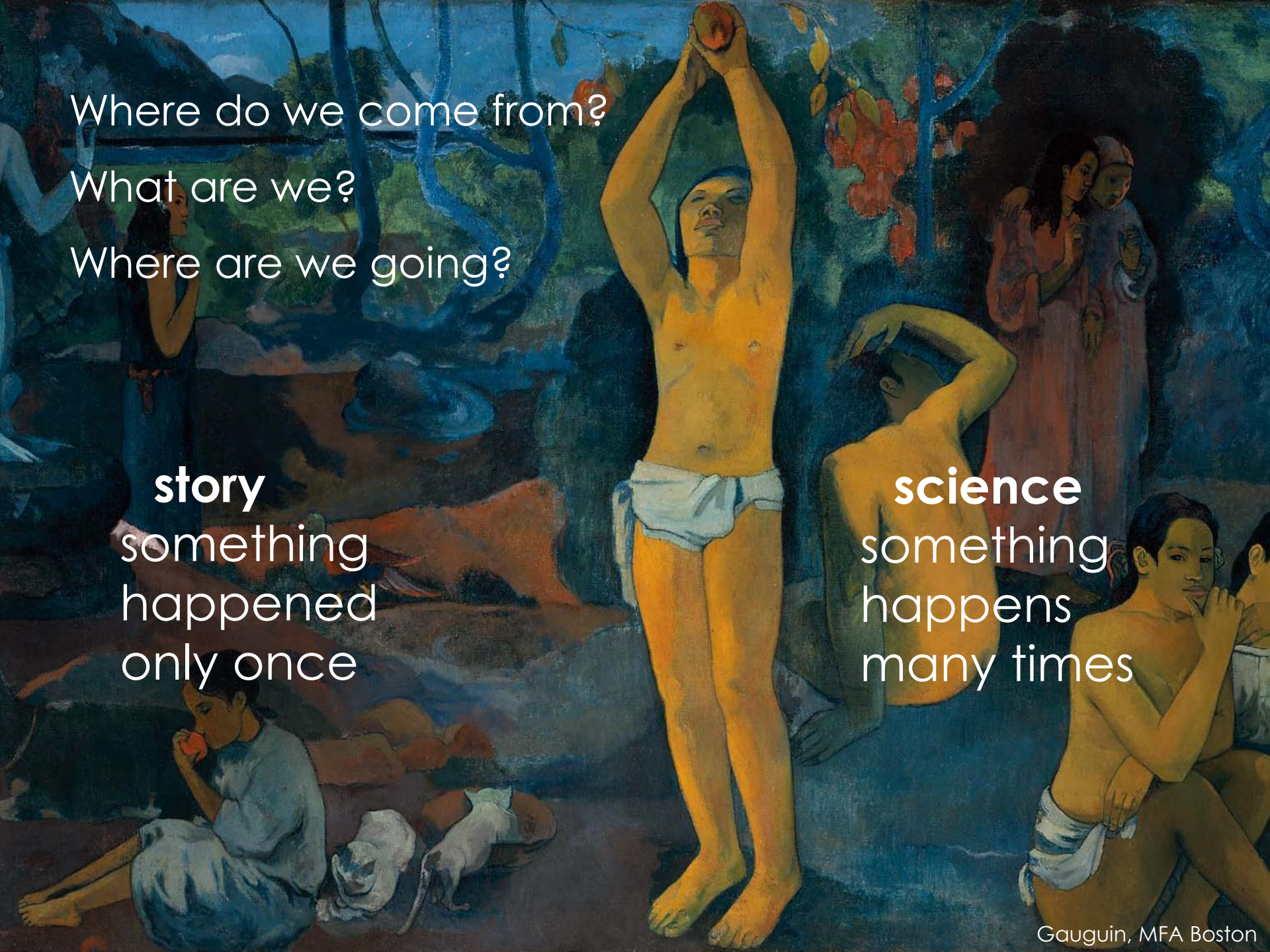
From ancient proteins to ancient cells:

The story of the primordial mitochondrial division apparatus

Mukund Thattai
Simons Centre for the Study of Living Machines,
National Centre for Biological Sciences, Bangalore
thattai@ncbs.res.in

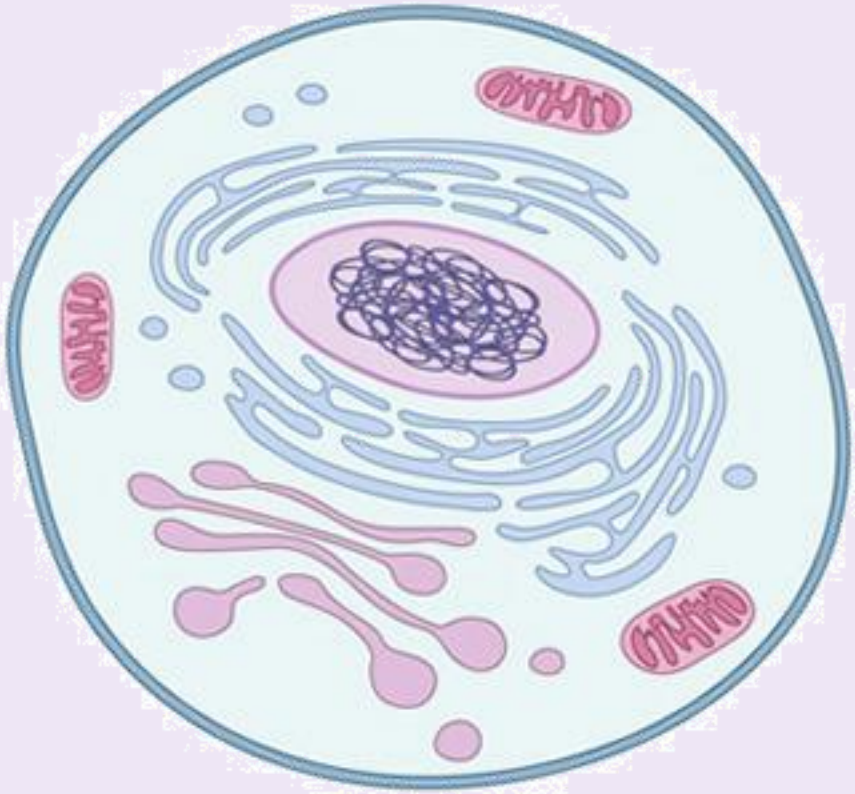

story

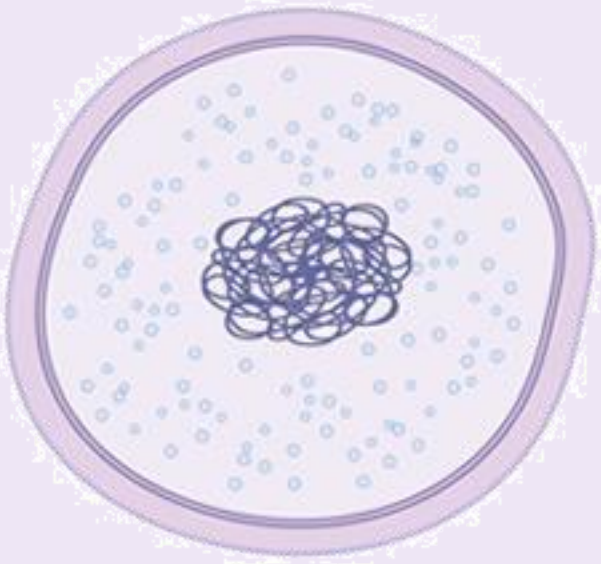

Where do we come from?
What are we?
Where are we going?
story


Where do we come from?
What are we?
Where are we going?
story
something
happened
only once
science
something
happens
many times
Gauguin, MFA Boston

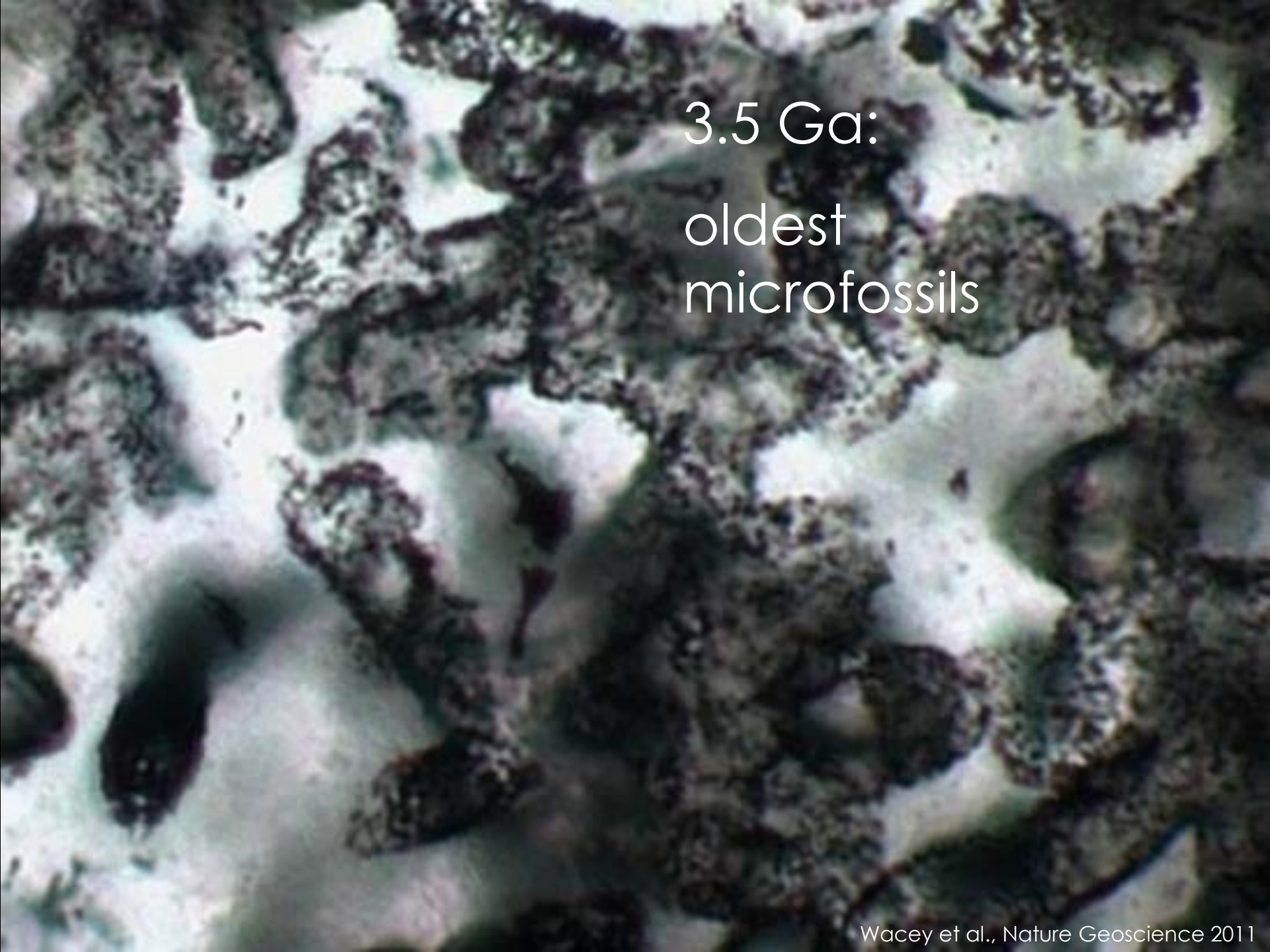
Here's a big fact that requires explanation...

Eukaryotes and prokaryotes



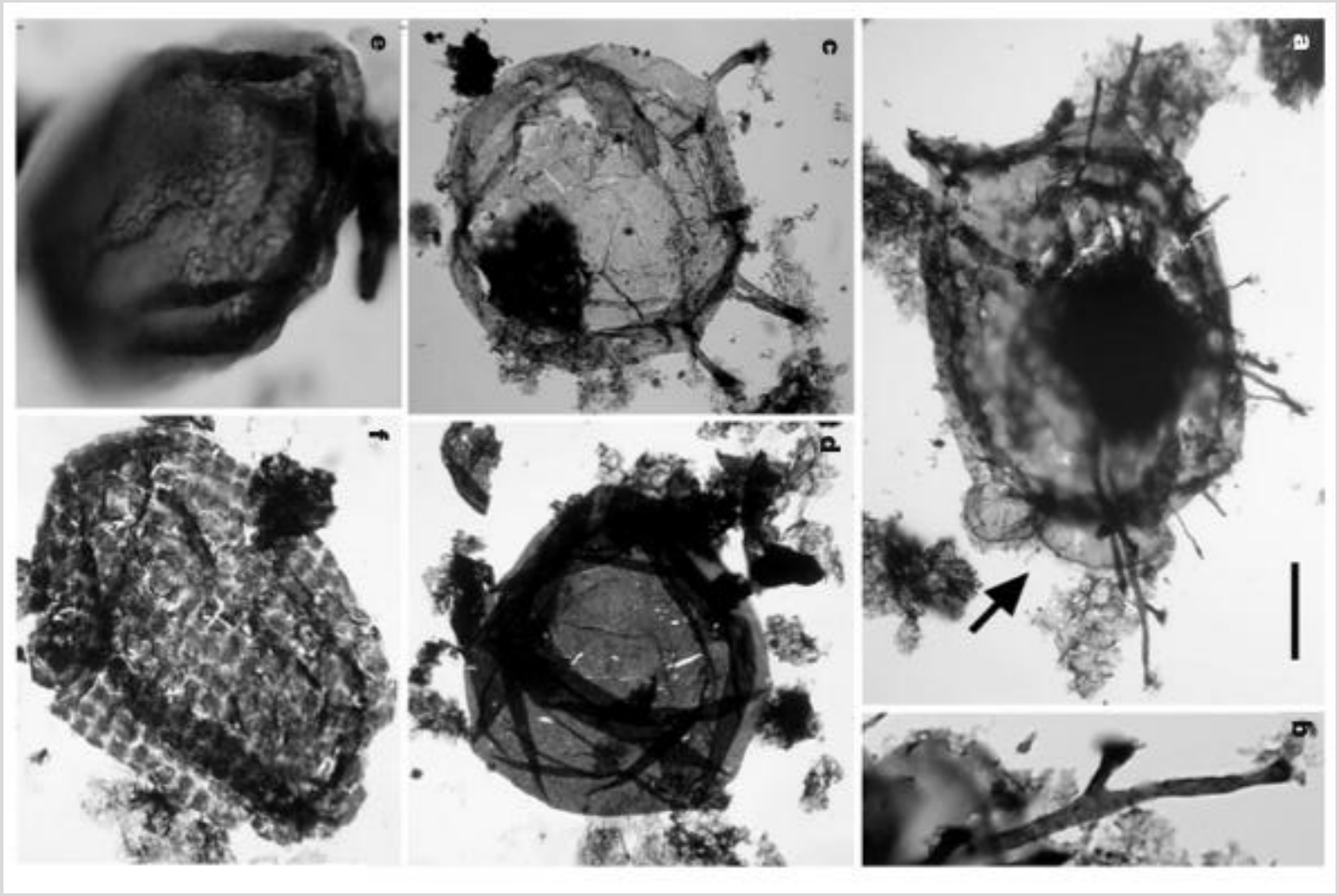


Fuerst, Nature Education, 2010



Wacey et al., Nature Geoscience 2011

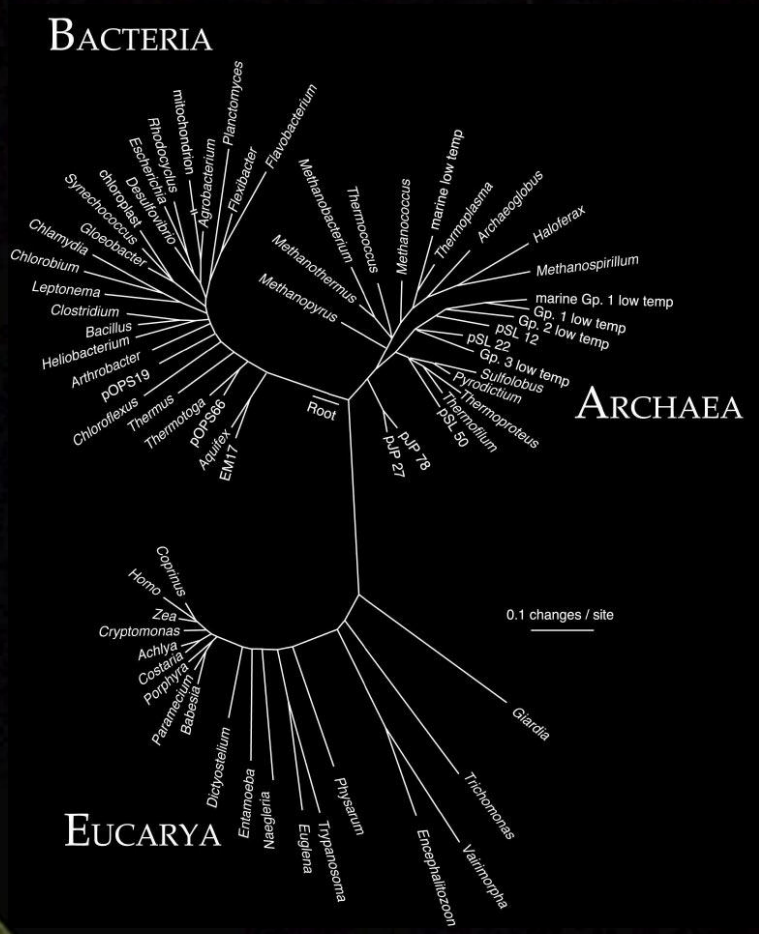
1.5 Ga: complex cellular forms



Javaux, 2001

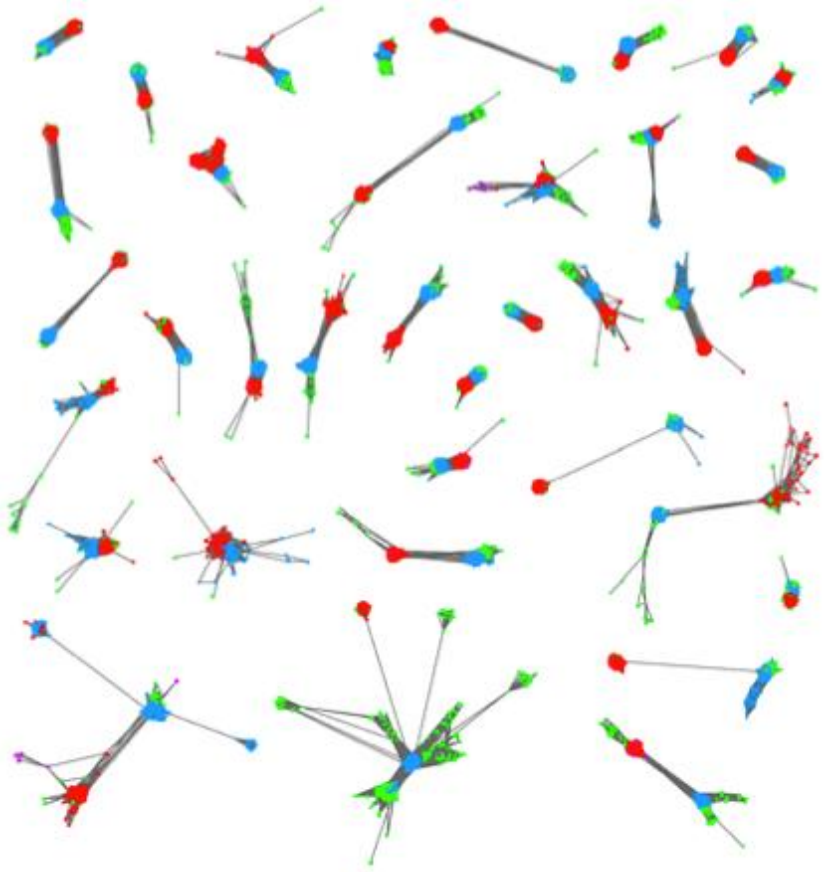
... and here's what we know so far

Carl Woese's "Archaea"

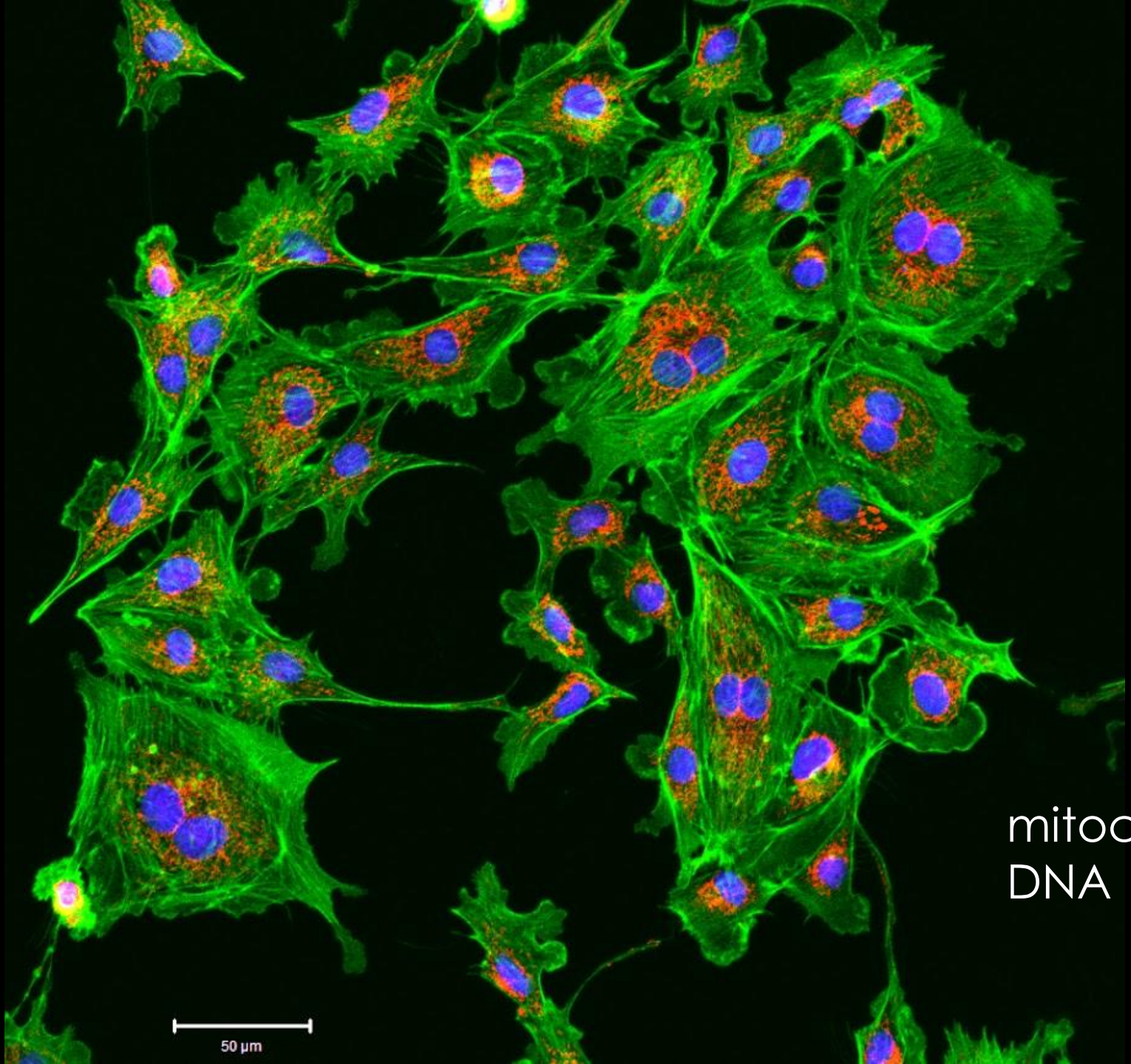


Tree: Norman Pace
Photo: IGB

Eukaryota = Archaea + Bacteria

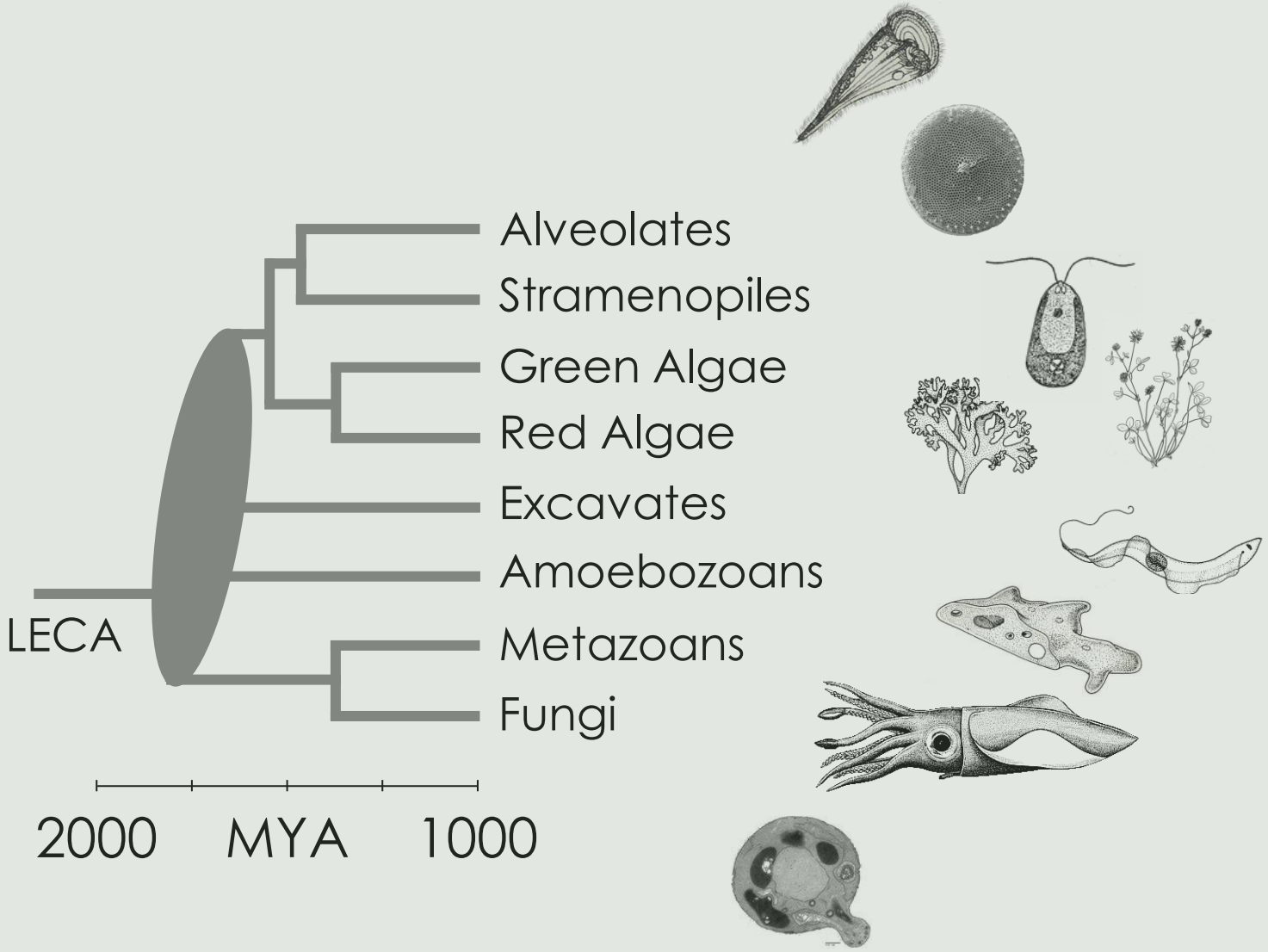


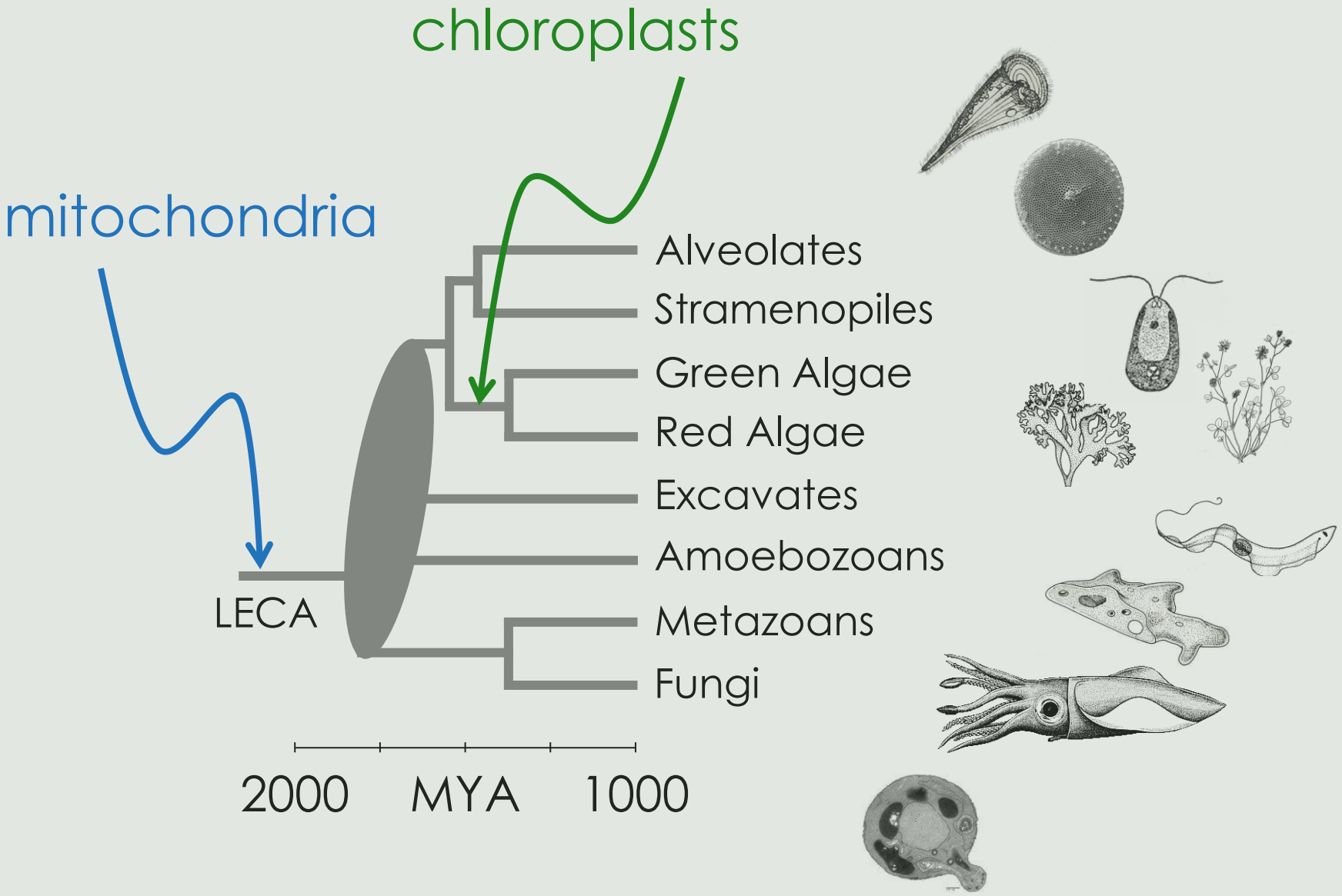
Alvarez-Ponce et al., PNAS 2013

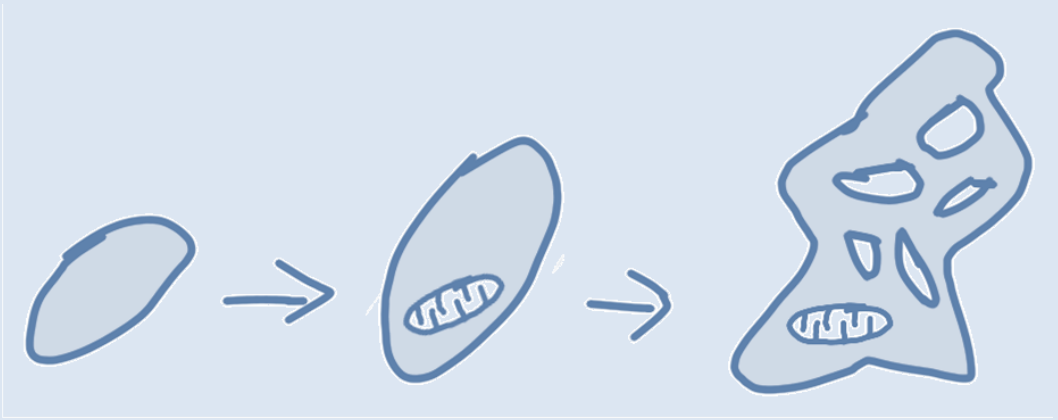


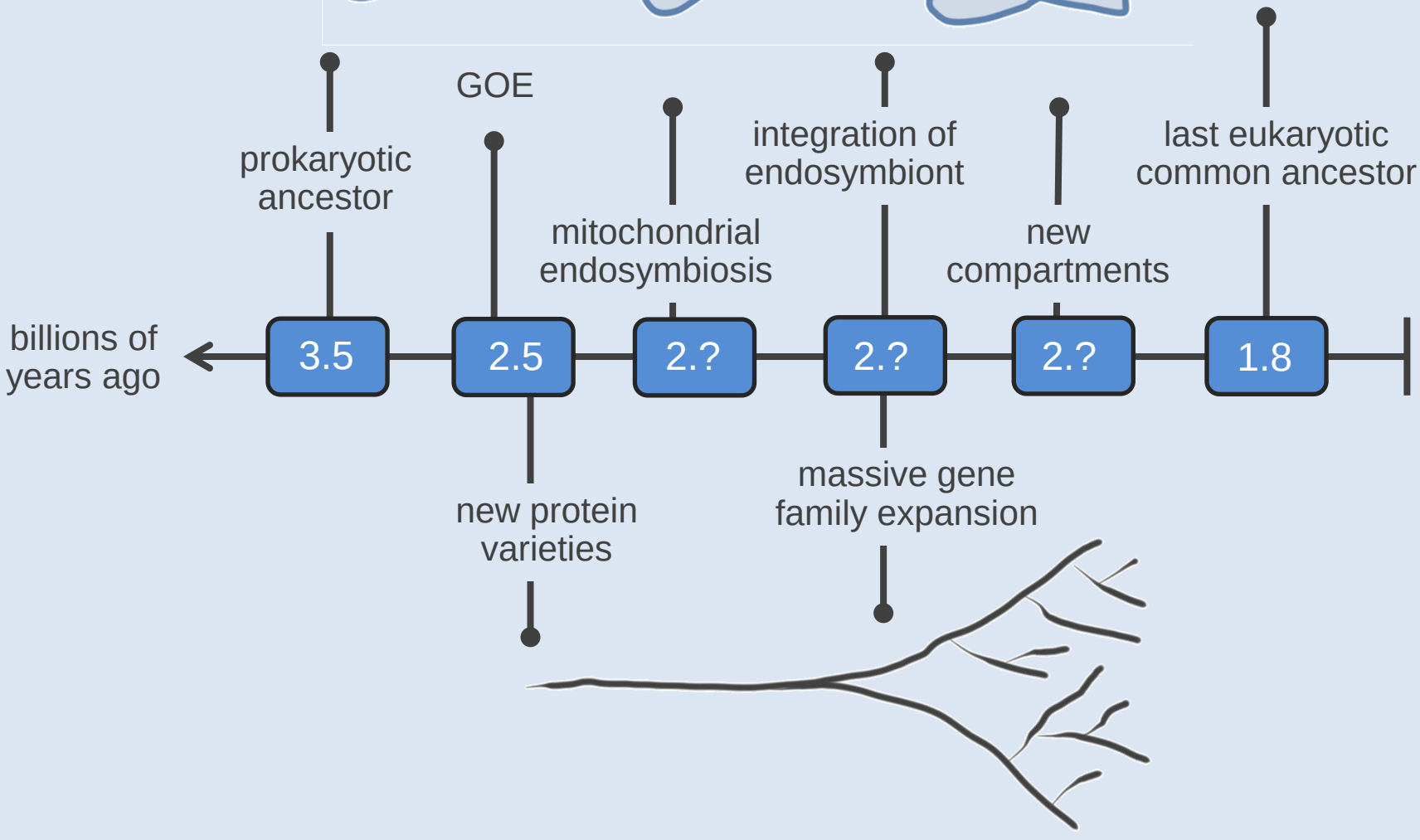
mitochondrial DNA

Lynn Margulis's endosymbiont hypothesis


Alveolates
Stramenopiles
Green Algae
Red Algae
Excavates
Amoebozoans
Metazoans
Fungi
LECA
2000
MYA
1000

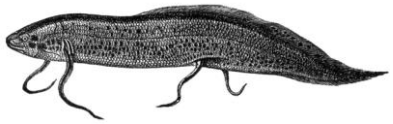

chloroplasts
mitochondria
Alveolates
Stramenopiles
Green Algae
Red Algae
Excavates
Amoebozoans
Metazoans
Fungi
LECA
2000
MYA
1000



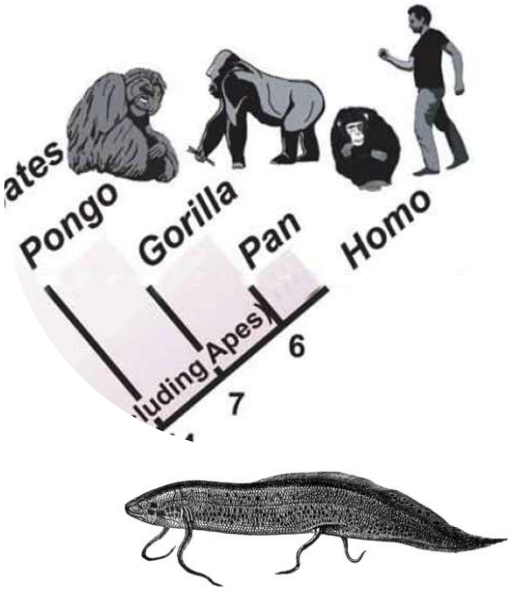

prokaryotic ancestor
GOE
mitochondrial endosymbiosis
integration of endosymbiont
new compartments
last eukaryotic common ancestor
billions of years ago
3.5
2.5
2.?
2.?
2.?
1.8
new protein varieties
massive gene family expansion

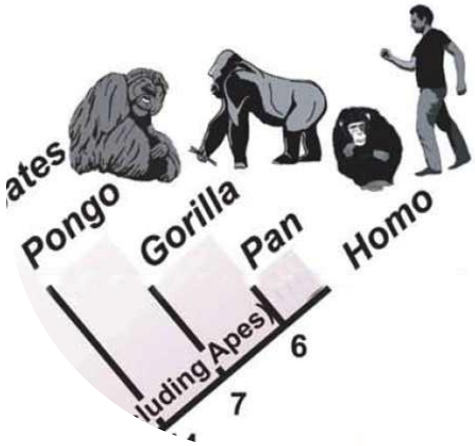
What did the early mitochondrial division appratus look like?

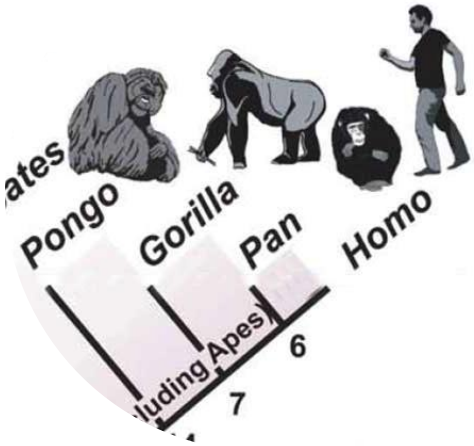
Inferring ancestral states is difficult!



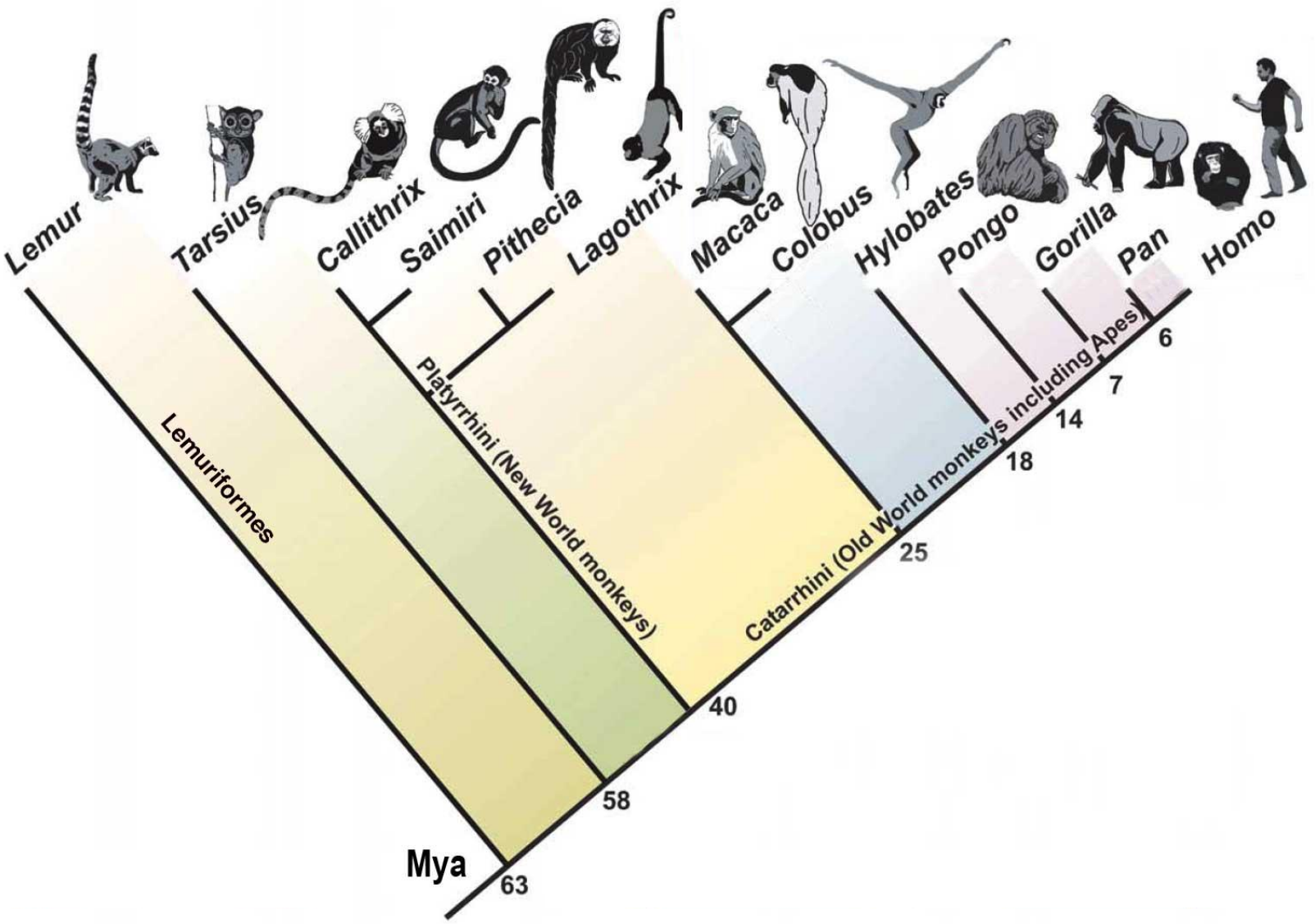
Inferring ancestral states is difficult!





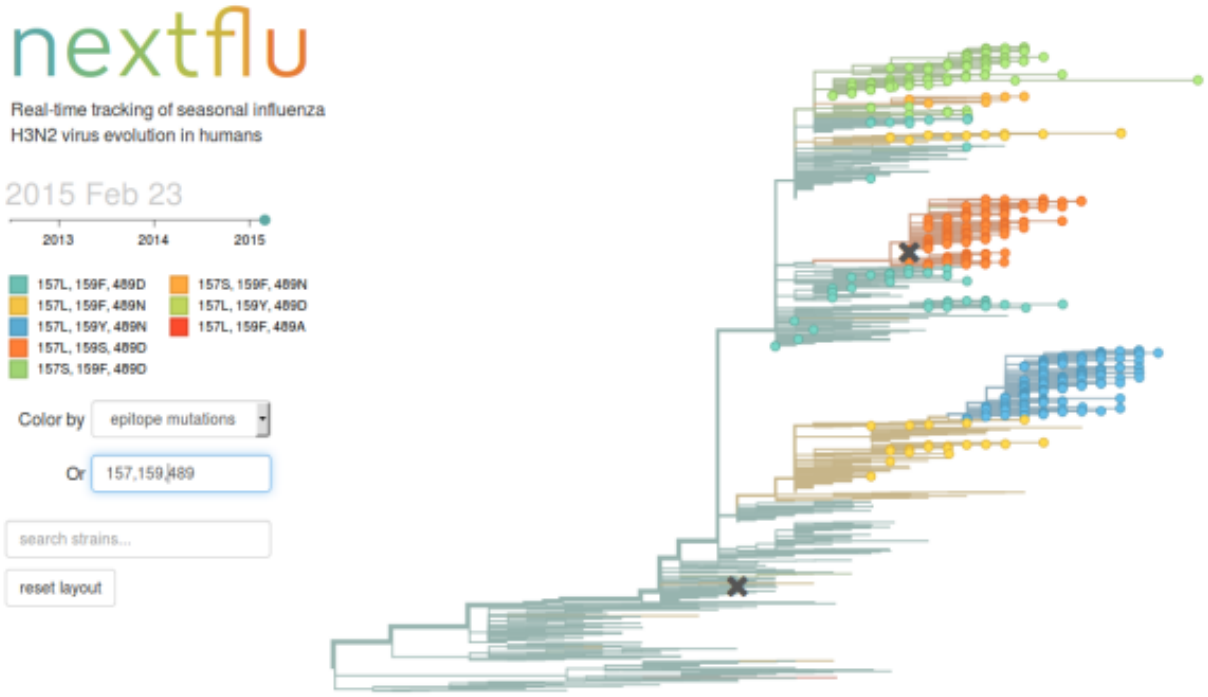


Inferring ancestral states is difficult!



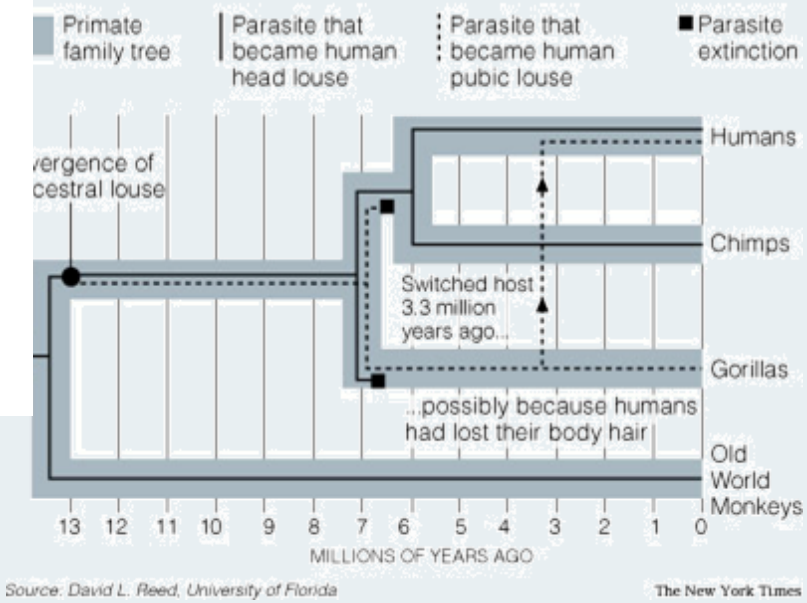
Wikipedia, copyright unknown

Proteins and DNA are digital: phylogenetics is relatively easy



Neher & Bedford, 2015

Try to use the easy question to answer the difficult question



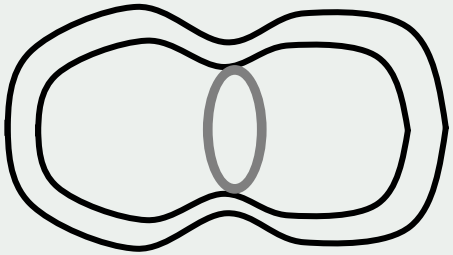
Toups et al., 2011

What did the early mitochondrial division appratus look like?

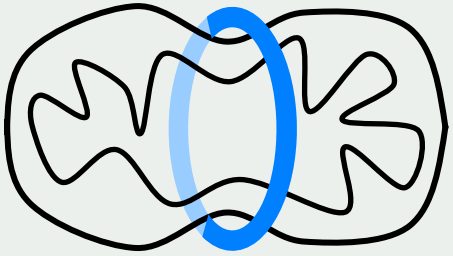
What did the early mitochondrial division appratus look like?

Can we use a protein as a probe to figure this out?

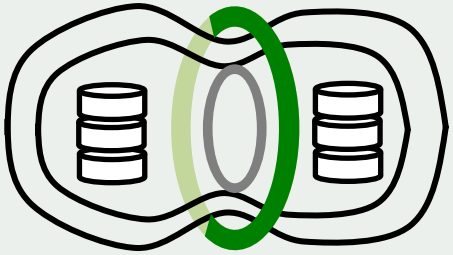
Eukaryote endosymbiont division is coordinated by dynamin



Bacteria: FtsZ

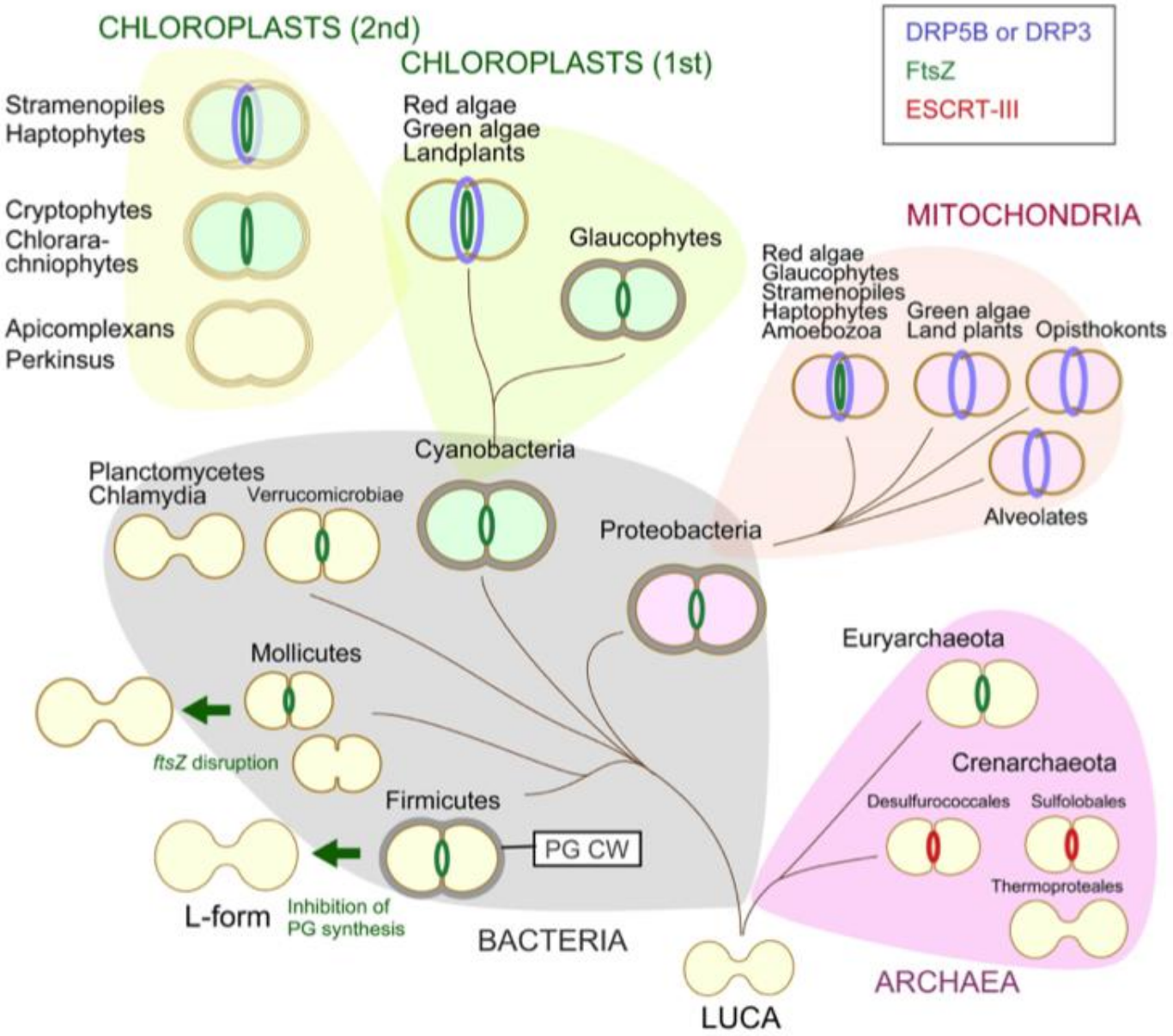


Mitochondria: Dynamin



Chloroplasts: Dynamin + FtsZ

Division across the domains of life



Miyagishima et al., Frontiers Plant Sci 2014

Three dynamin superclasses group according to function

chloroplast division

C

protist cytokinesis

Mx-like anti-viral dynamins

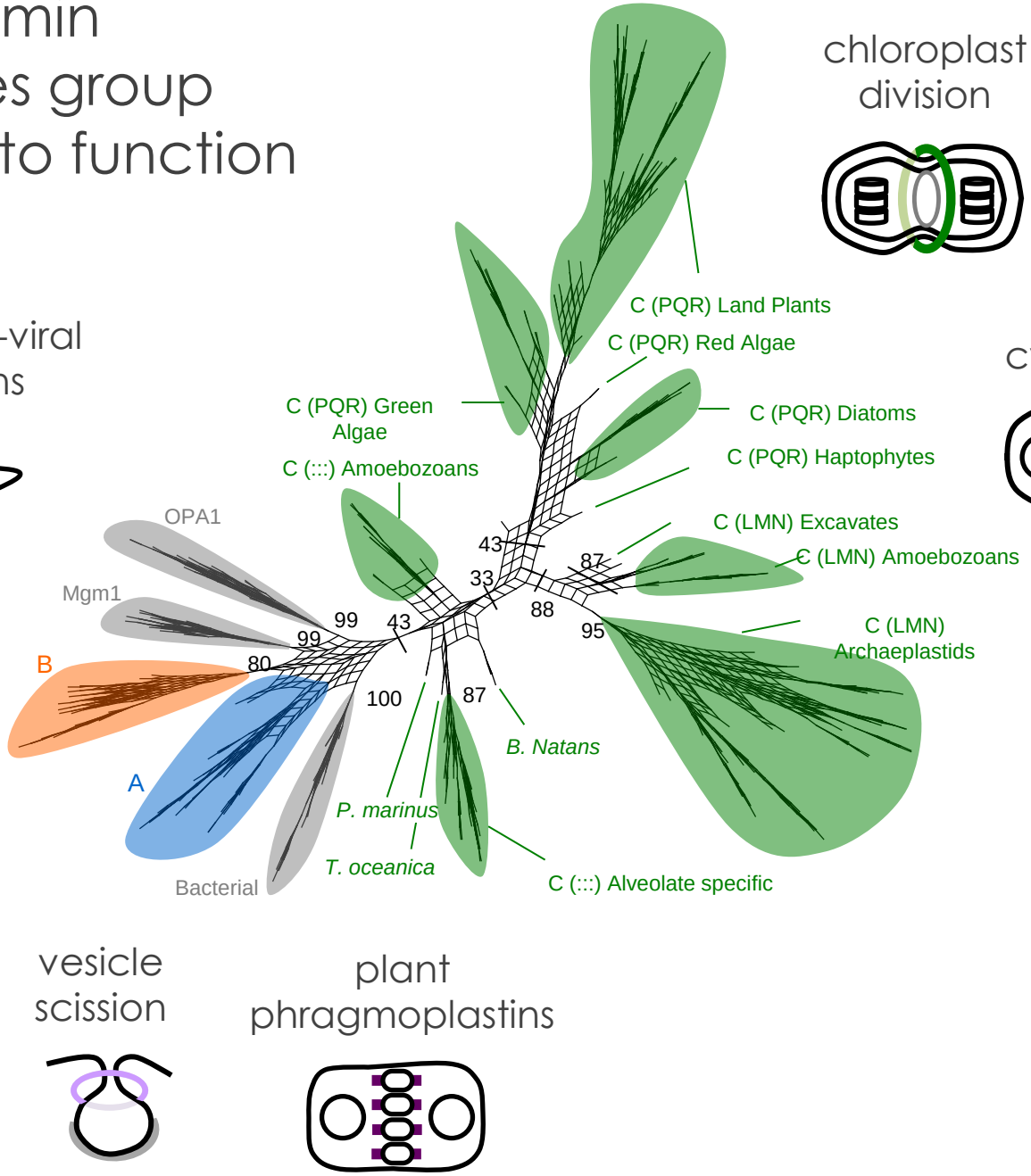
B

mitochondrial division

A

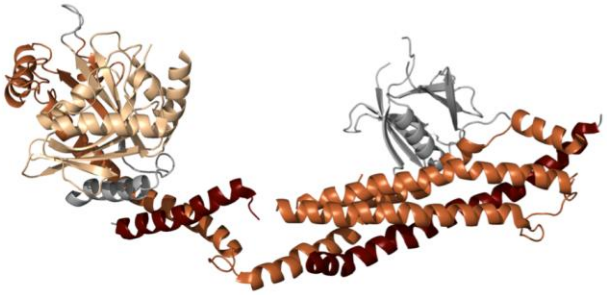
vesicle scission

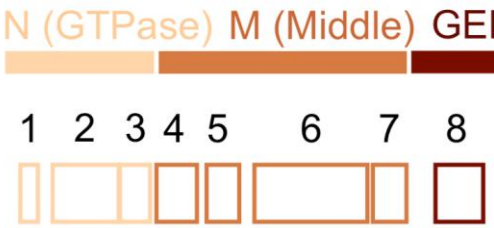
plant phragmoplastins

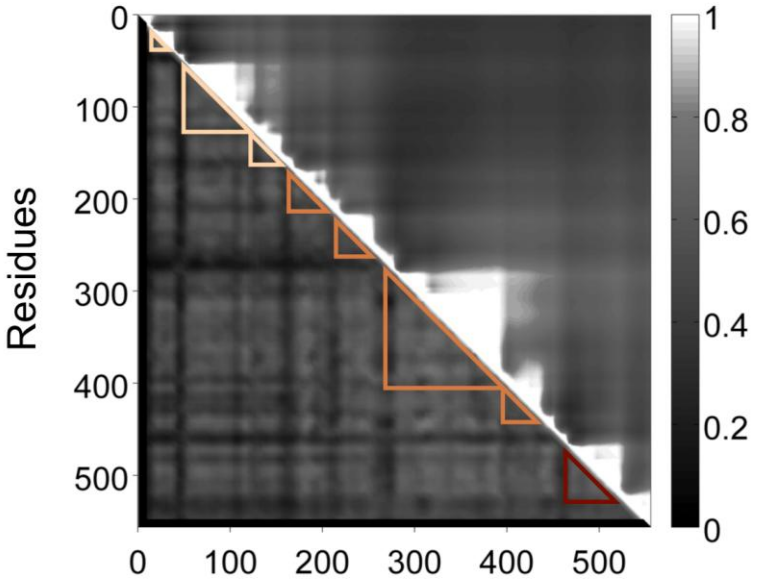


Problem:
protein evolution is messy,
especially over 2 billion years

Dynamin breaks into discrete evolutionary segments







Class A

```
1A2A3A4A5A6A7A8A
:::4S:6X::
::::::7Y8Z
:2V::::::
::::::::
::::::::
::::::::
::::::::
 :::::::
 :::::::
 :::::::
2E::::::
 :::::::
2U::::::
2T :: ::
 : :: ::
2W :: :
   :
```

Class B

```
1B2B3B4B?6B??
::::::7J8K
::::::::
::::::::
:2F::::::
:2G::::::
:::::::
:::::::
:::::::
:2H:::::
::: :::
 :: :::
  : :::
  : :::
  : ::
  :  :
     :
     :
     :
     :
     :
     :
```

Protein signatures:
"Fake amino acids"

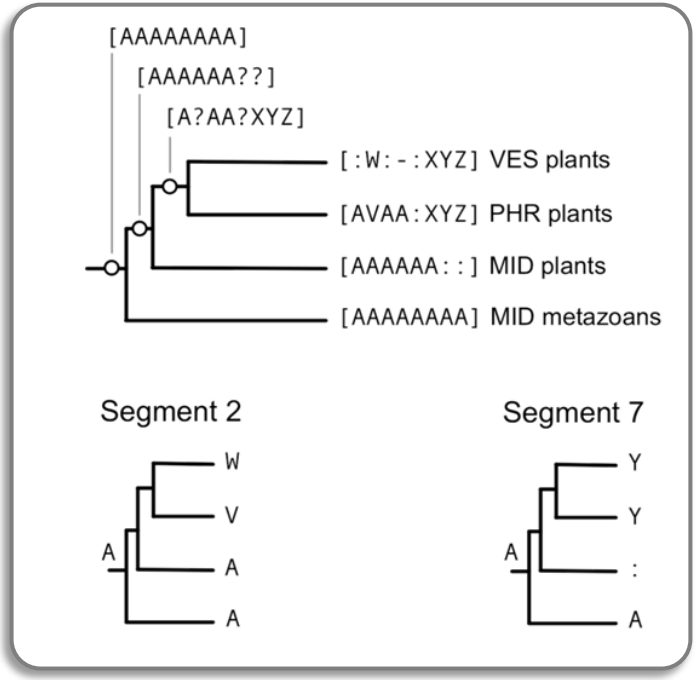
`[:W:-:XYZ]` VES plants

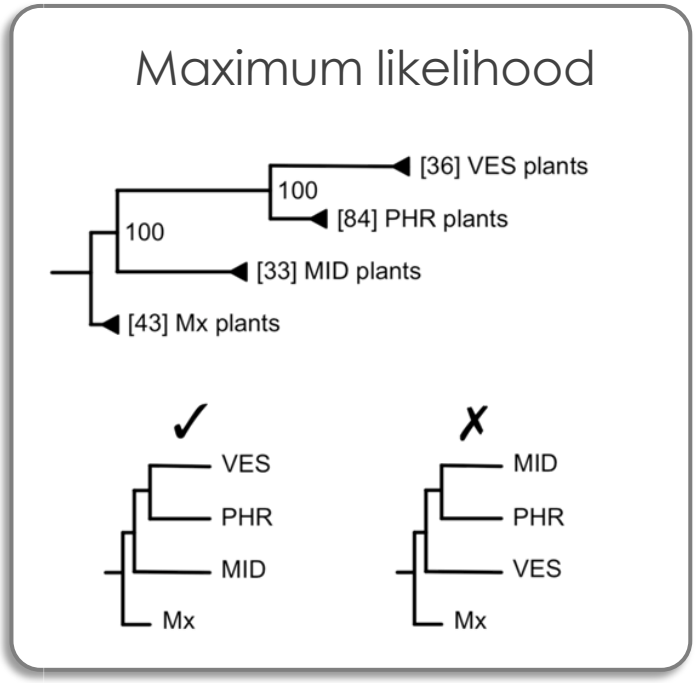
`[AVAA:XYZ]` PHR plants

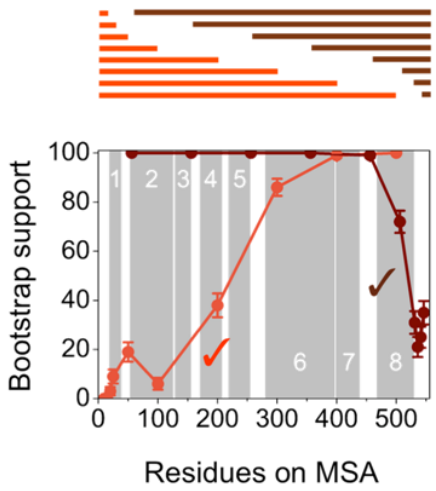
`[AAAAAA::]` MID plants

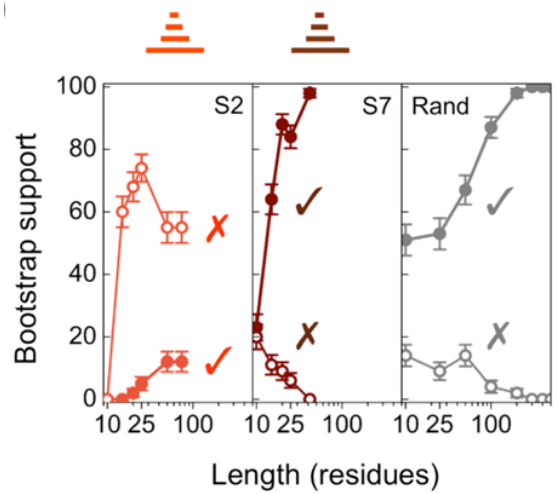
`[AAAAAAAA]` MID metazoans

Evolution is heterogeneous across time and sequence

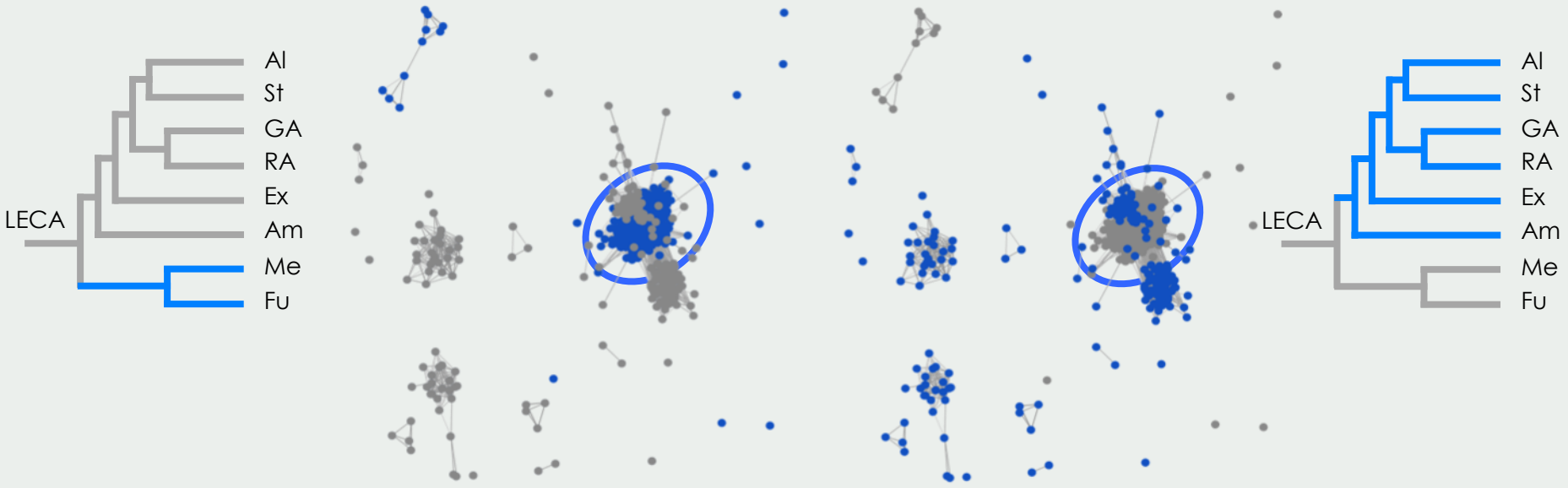




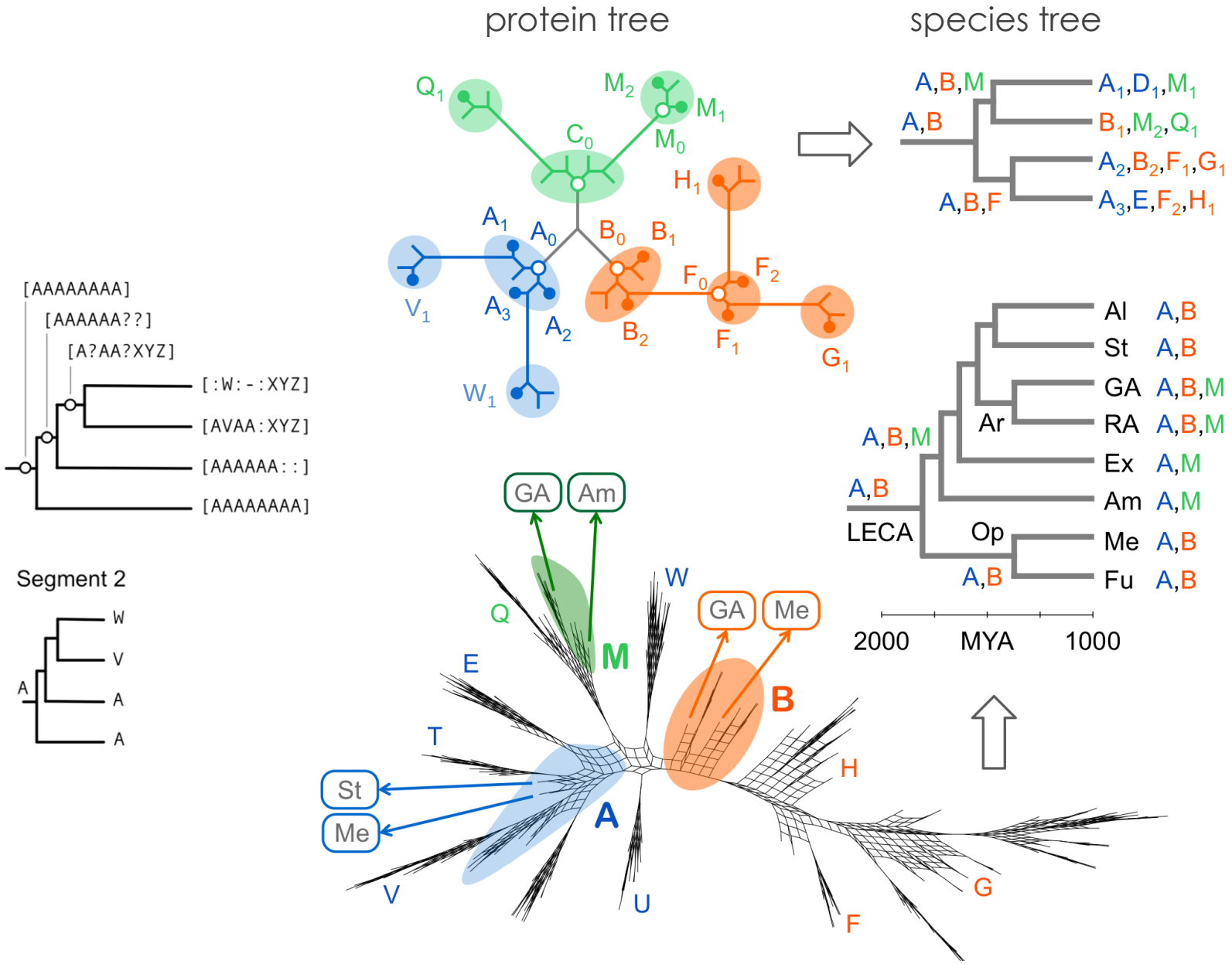




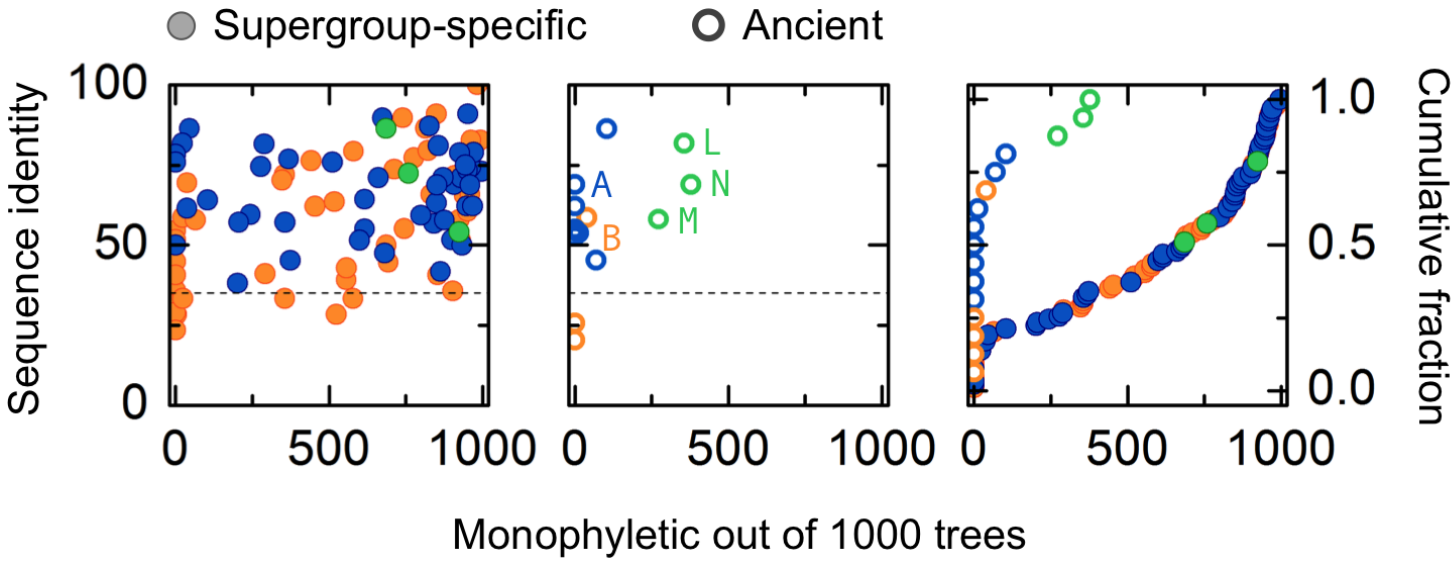
No problem:
Heterogeneous evolution means that ancestral variants might still be around!



Living fossils: present-day remnants of ancient proteins



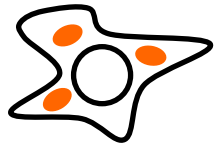
Living fossils can be seen in the statistics

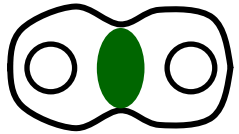


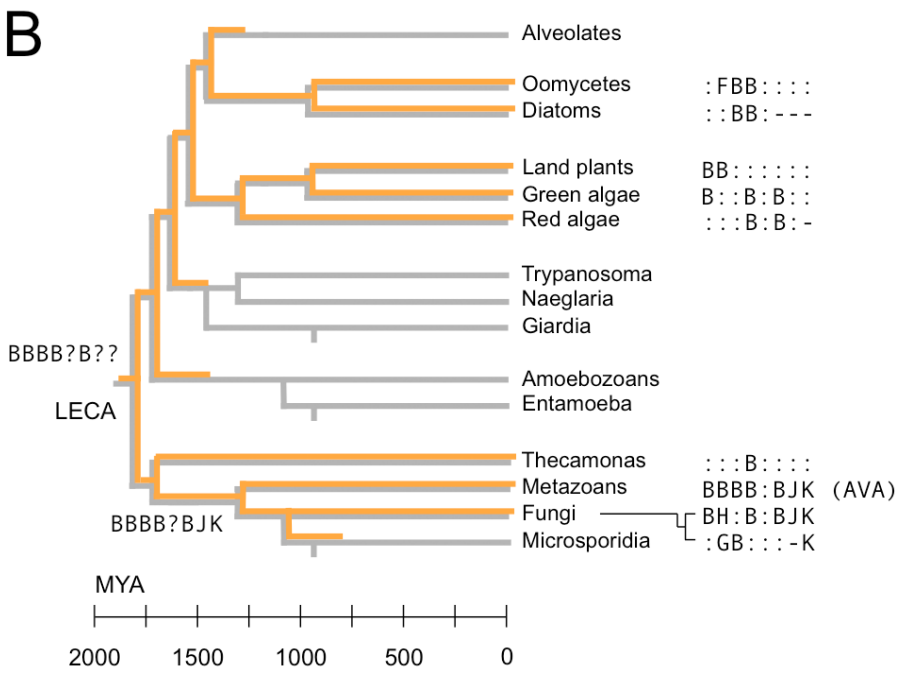
Living fossils	Tight: > 35% sequence identity Ancient: Present in multiple supergroups Paraphyletic: Ancestral to other clusters

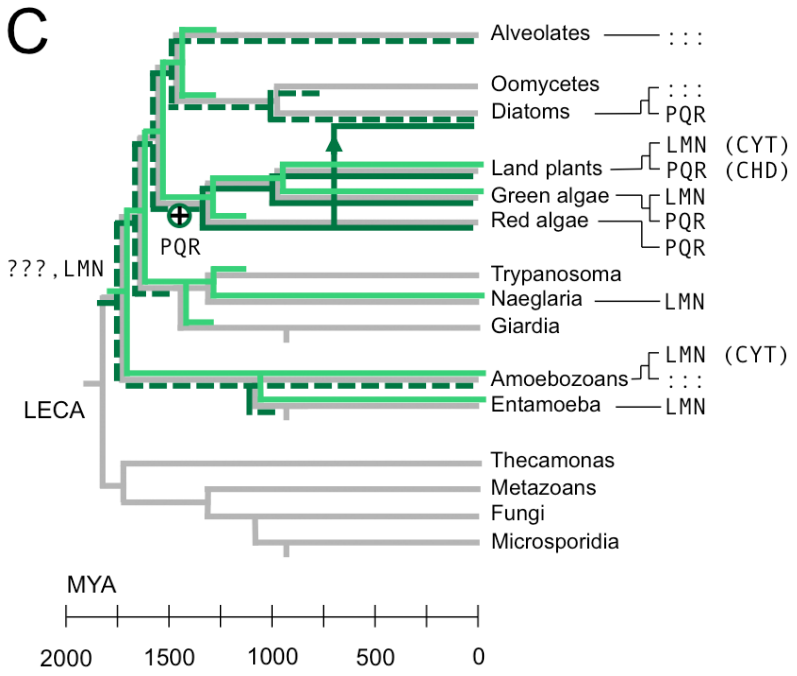
Living fossil segments allow us to reconstruct ancient dynamins

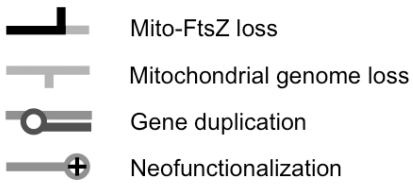
Punctuated evolution of dynamins across 1.8 billion years

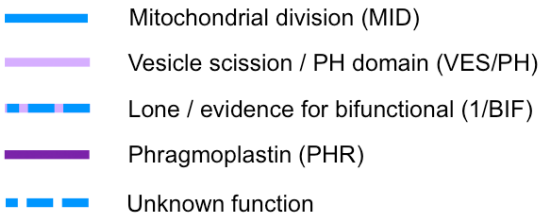


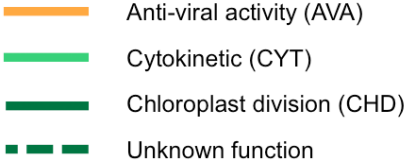




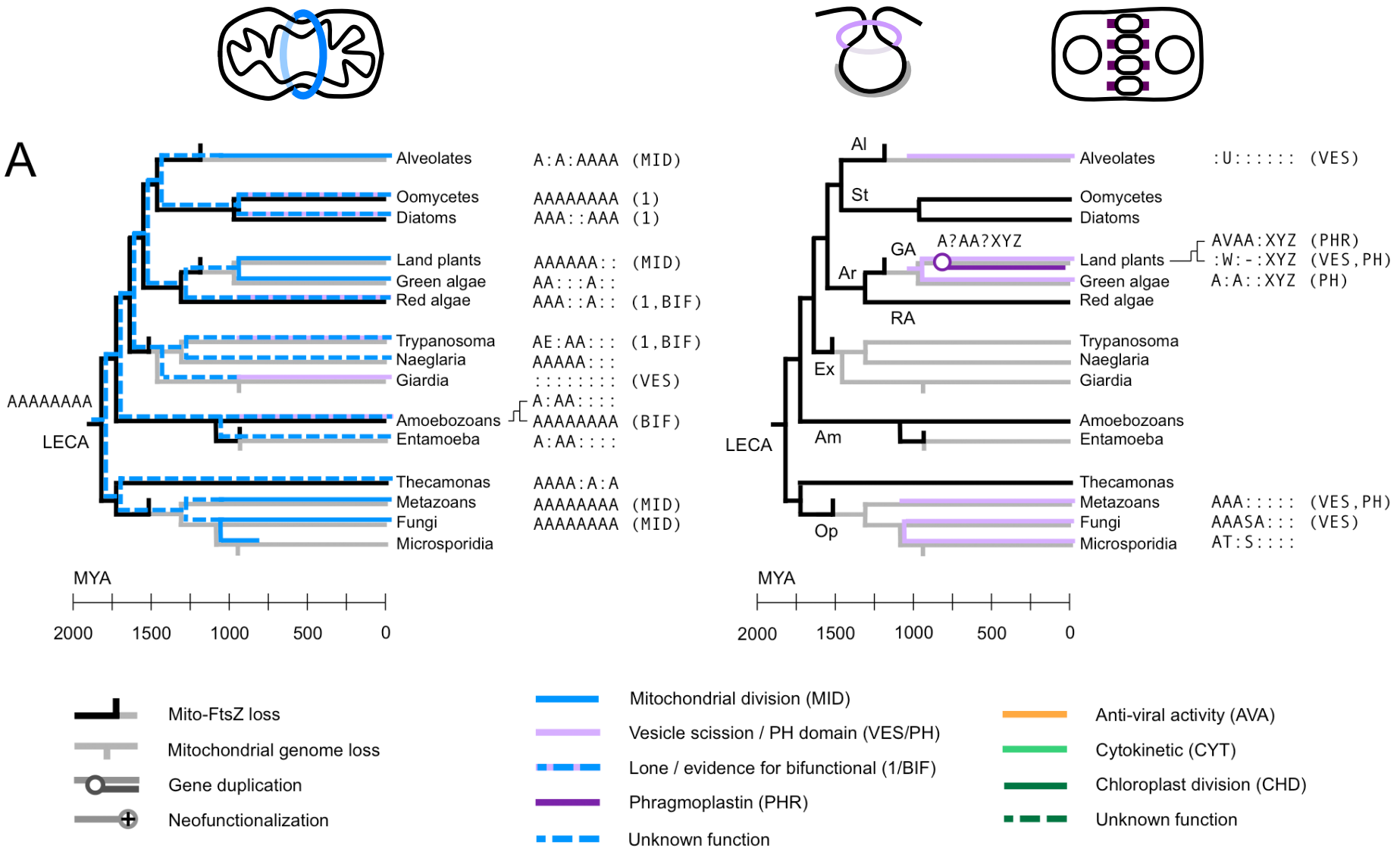








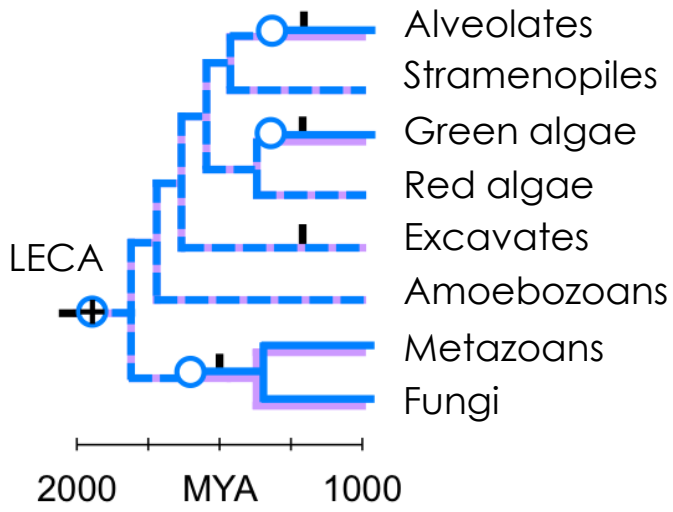
Punctuated evolution of dynamins across 1.8 billion years

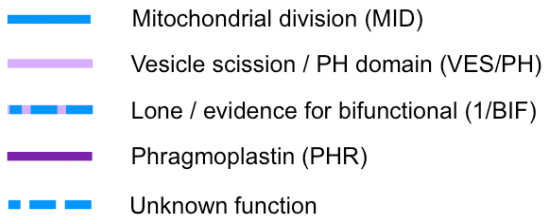


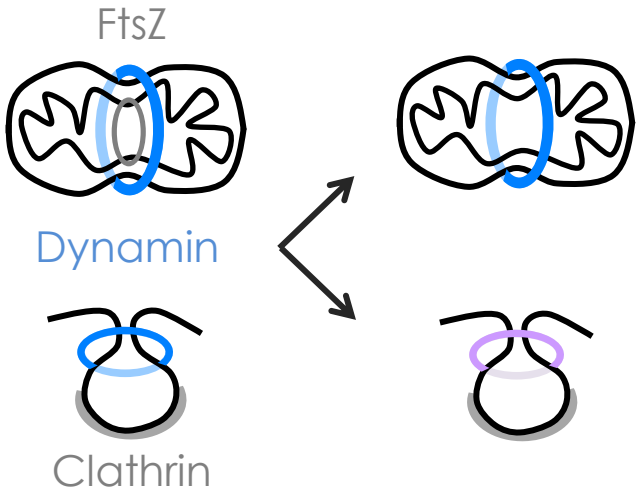
Not "just" a story:

The same evolutionary pattern occurs many times independently

An ancient bifunctional dynamin pulled off the same duplication trick in multiple eukaryotic lineages







An ancient bifunctional dynamin pulled off the same duplication trick in multiple eukaryotic lineages

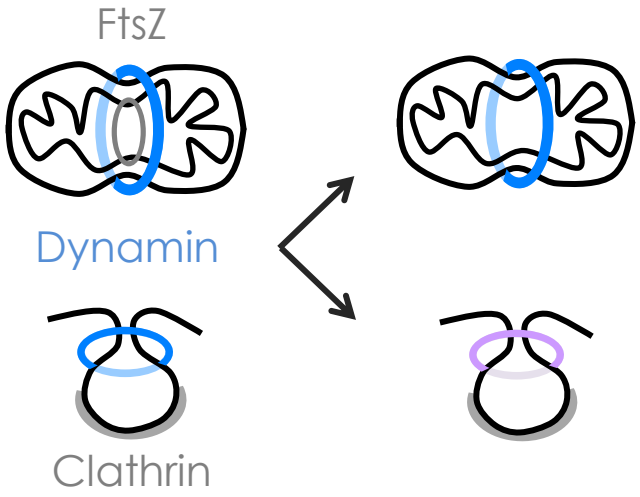
Bifunctional

$$XO + OY \underset{\gamma/2}{\leftarrow} XY \underset{\delta}{\overset{\gamma/2}{\rightarrow}} XY + OO \underset{\alpha}{\overset{\alpha}{\rightarrow}} XO + OY$$

Specialized $\uparrow \alpha$ $\alpha \uparrow$

$$XO \underset{\delta}{\overset{\gamma}{\rightarrow}} XO + OO \overset{\alpha}{\rightarrow} XO + OY$$

Monofunctional



$$P_{M\to M}(t) = e^{-\alpha t}$$

$$P_{M\to S}(t) = (1 - e^{-\alpha t}) - \frac{\alpha}{\alpha+\omega}\left(1 - e^{-(\alpha+\omega)t}\right)$$

$$P_{M\to B}(t) = \frac{\alpha}{\alpha+\omega}\left(1 - e^{-(\alpha+\omega)t}\right)$$

$$P_{S\to S}(t) = 1 - \frac{\alpha}{\alpha+\omega}\left(1 - e^{-(\alpha+\omega)t}\right)$$

$$P_{S\to B}(t) = \frac{\alpha}{\alpha+\omega}\left(1 - e^{-(\alpha+\omega)t}\right)$$

$$P_{B\to S}(t) = \frac{\omega}{\alpha+\omega}\left(1 - e^{-(\alpha+\omega)t}\right)$$

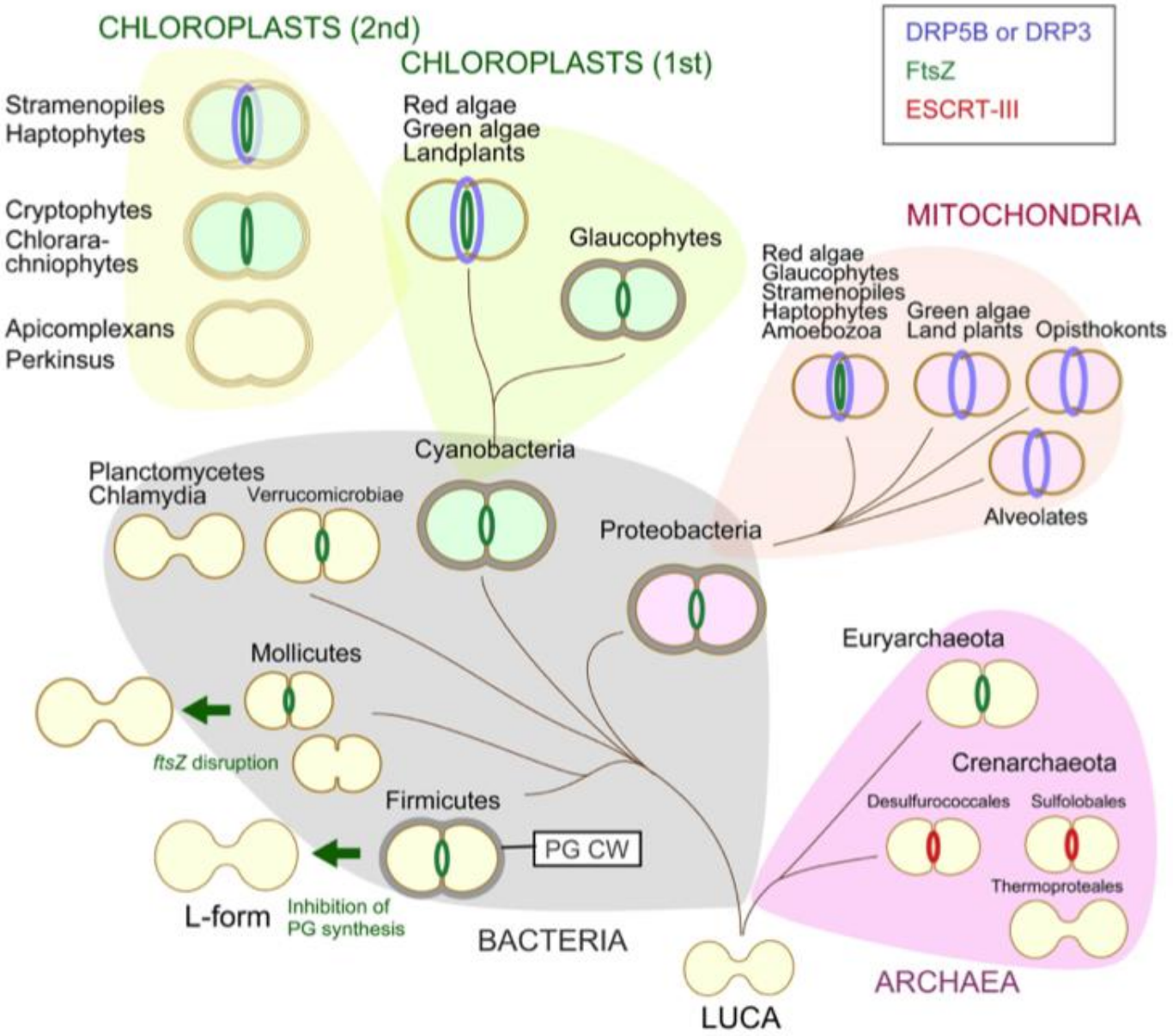
$$P_{B\to B}(t) = 1 - \frac{\omega}{\alpha+\omega}\left(1 - e^{-(\alpha+\omega)t}\right)$$

What does all this have to do with the primordial mitochondrial division appratus?

or

How does
evolutionary protein biology
become
evolutionay cell biology?

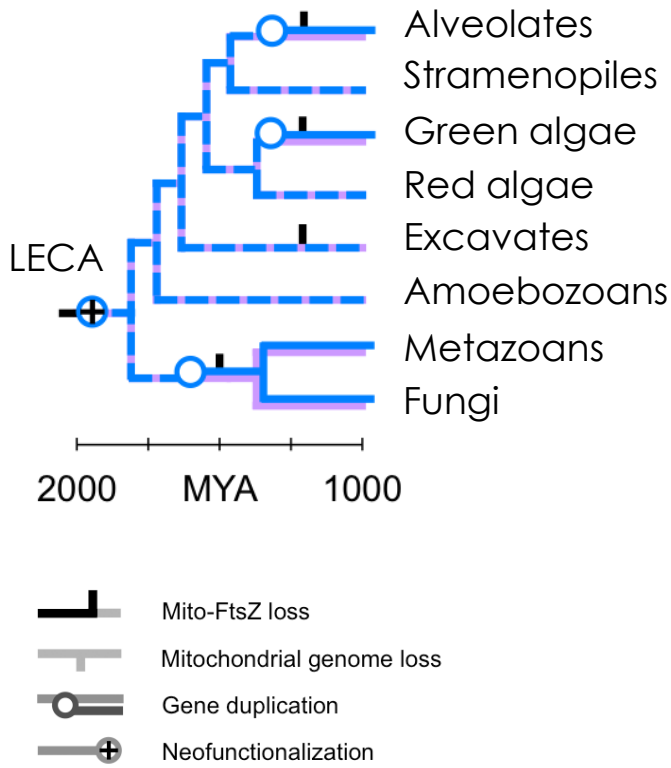
Division across the domains of life

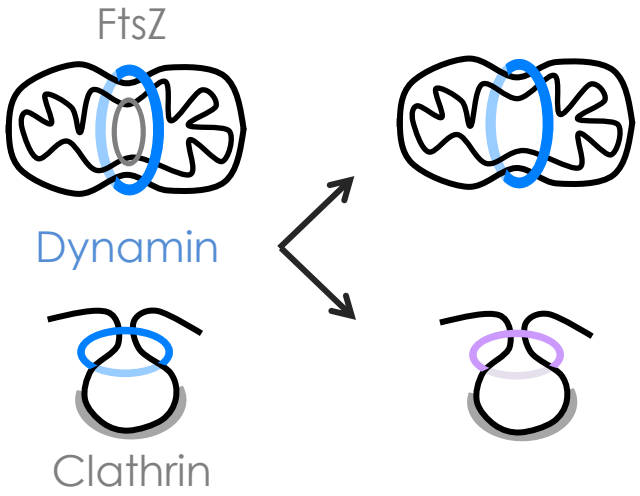


Miyagishima et al., Frontiers Plant Sci 2014

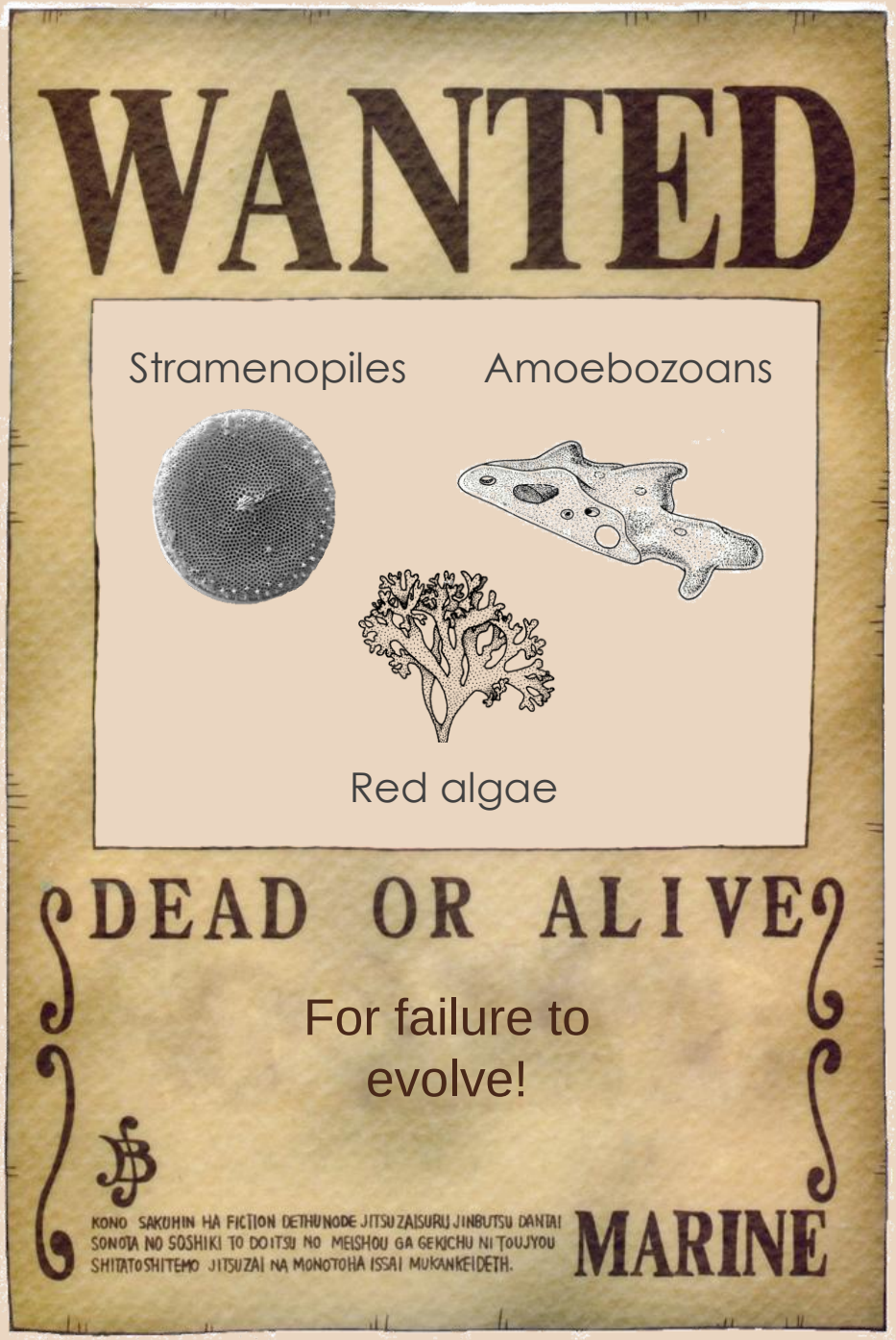
Surprise!

All Mito-FtsZ lineages still use the ancient dynamin



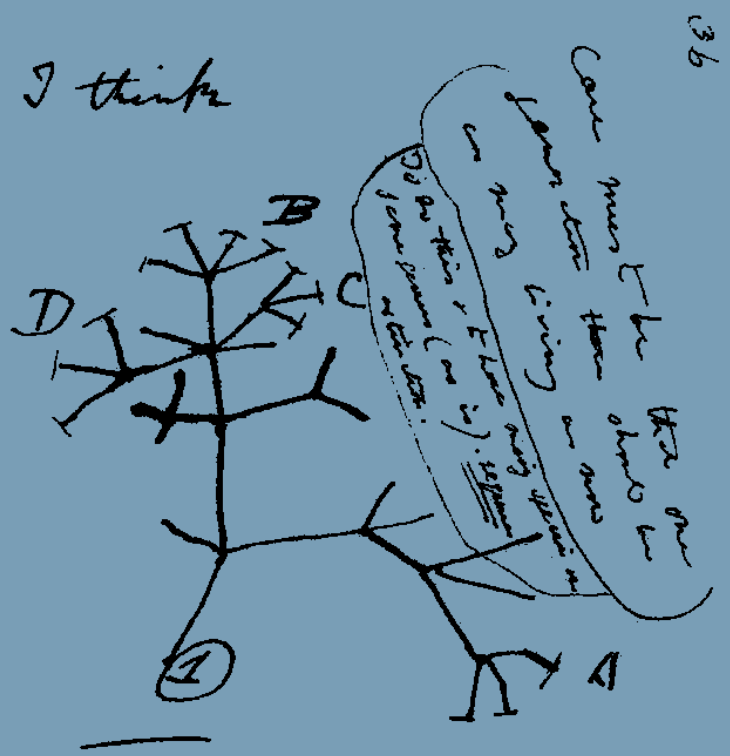


If you really want to measure what the mitochondrial division apparatus was doing 2 billion years ago, go study one of <u>these</u> guys



Nishida et al., PNAS 2002;
Gilson et al., Eukaryotic Cell 2002;
Leger et al., PNAS 2015

What did Darwin think?



"In looking for the gradations by which an organ has been perfected, we ought to look exclusively to its lineal ancestors; but this is scarcely ever possible, and we are forced in each case to look to the collateral descendants from the same original parent-form. … These anomalous forms may almost be called living fossils; they have endured to the present day"

On the Origin of Species

Ramya Purkanti

K. S. Krishnan

Purkanti, R., & Thattai, M. Ancient dynamin segments reveal early stages of host-mitochondrial integration. Proc Natl Acad Sci USA (2015).

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