Estimation of evolutionary distance based on K-string composition

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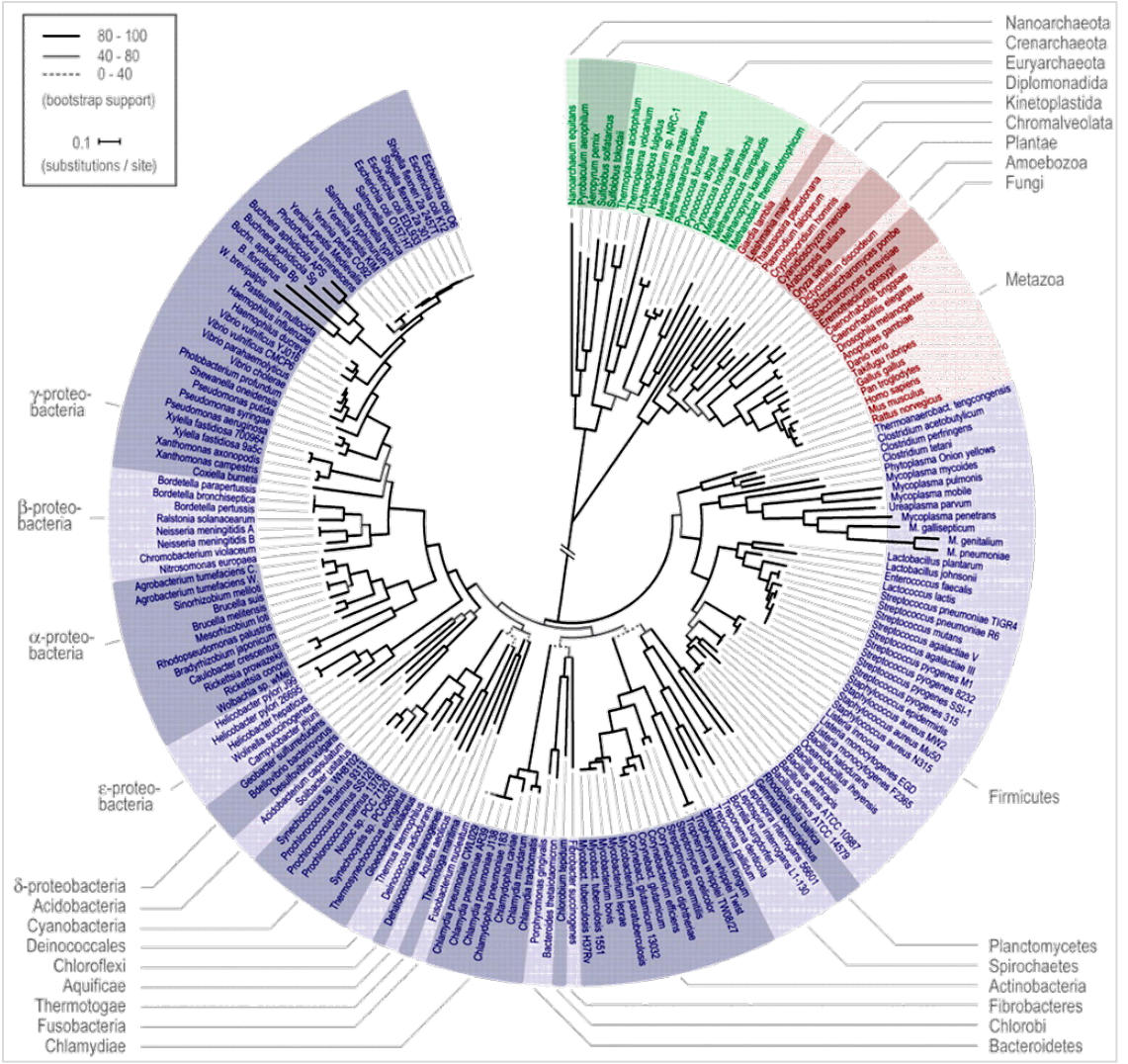
Difficulties in phylogenomics

- Species trees versus gene trees
- Too few common genes
  - "The tree of one percent"
- Model selection
  - A science, or an art?
- Computational complexity
- …



A tree based on 31 genes (Ciccarelli '06)

Phylogenetics above sequence-level

- Rare genomic change
- Gene content & gene order
- *K*-string composition

"In summary, the methods for inferring trees based on whole-genome features are at an early stage of their development, which might be comparable to that of sequence-based methods in the early 1970s. In particular, they generally lack a global probabilistic modeling."

(Philippe 2005)

CVTree: Compositional vector

- "Random background": (K – 2)-order Markov chain

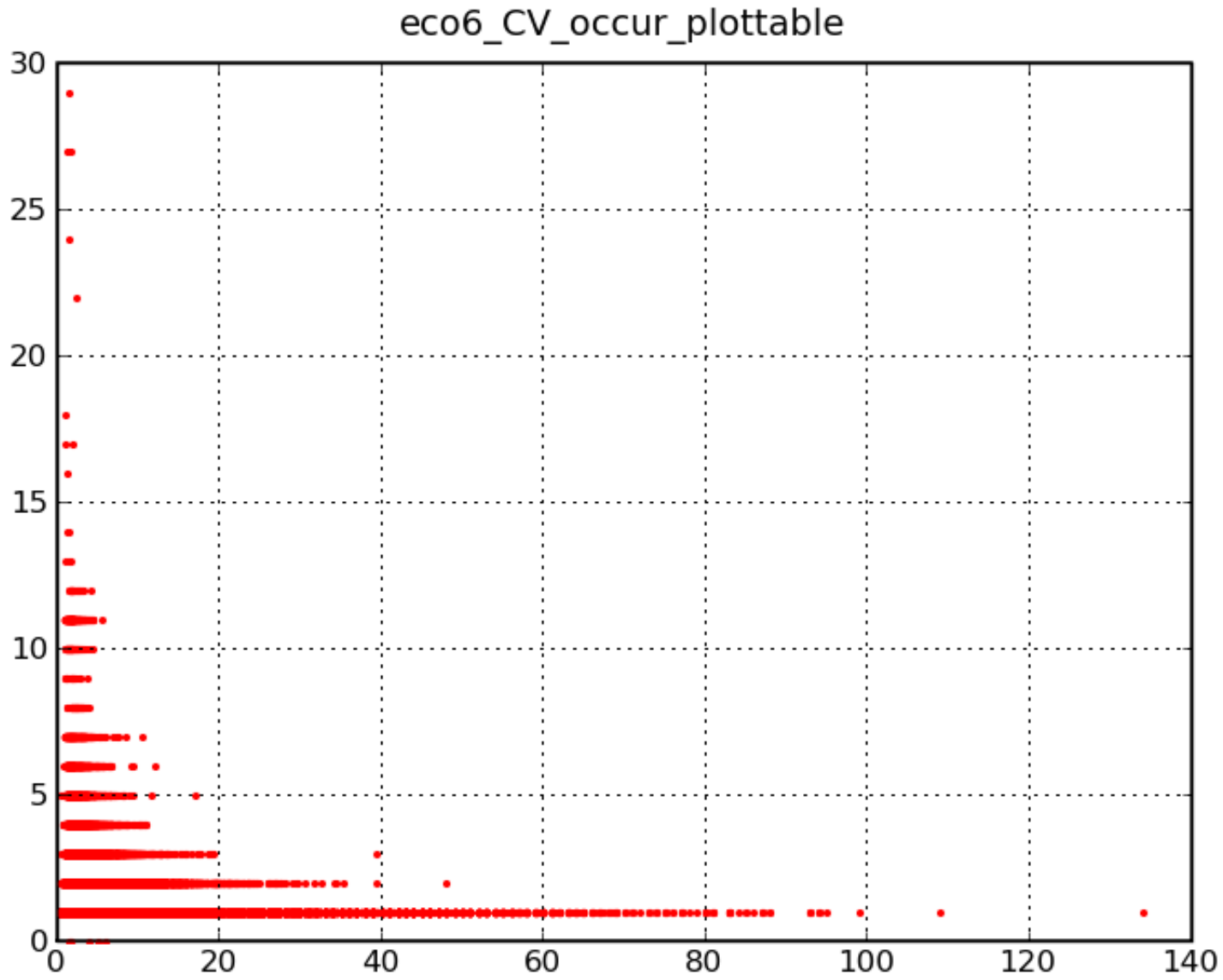
$$f^0(\alpha_1 \cdots \alpha_K) = \frac{f(\alpha_1 \cdots \alpha_{K-1}) f(\alpha_2 \cdots \alpha_K)}{f(\alpha_2 \cdots \alpha_{K-1})}$$

- "Subtraction"

$$a_i = \begin{cases} \dfrac{f(i) - f^0(i)}{f^0(i)}, & f^0(i) \neq 0 \\ 0, & f^0(i) = 0 \end{cases} \qquad i \in \Sigma^K$$

- Distance (dissimilarity)

$$d(\mathbf{a}, \mathbf{b}) = \frac{1 - \cos(\mathbf{a}, \mathbf{b})}{2} \in [0,1]$$



f versus f^0

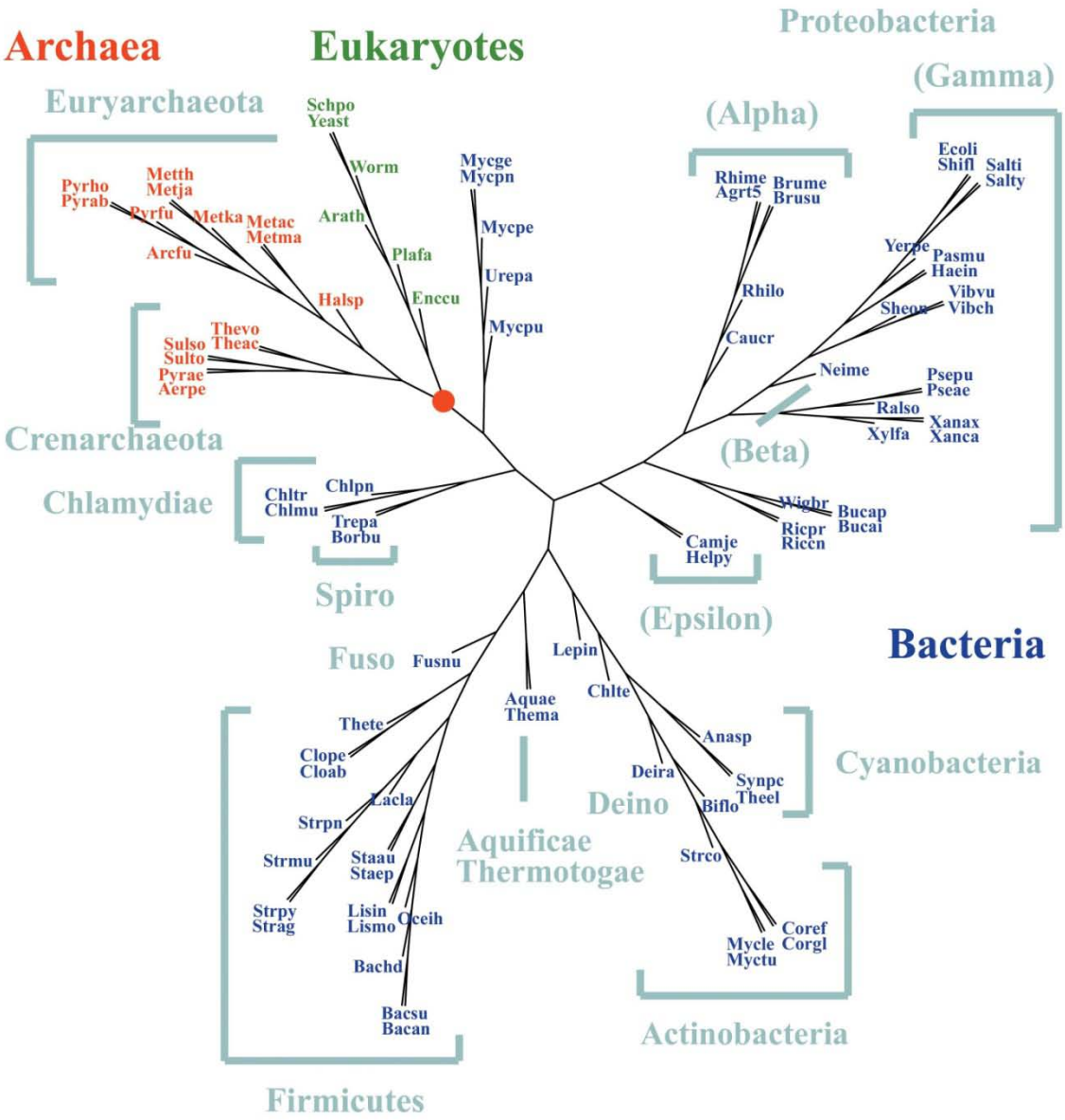
Courtesy of Alexander Grossmann

CVTree

- simple
- efficient
- parameter free
- truly whole genomic

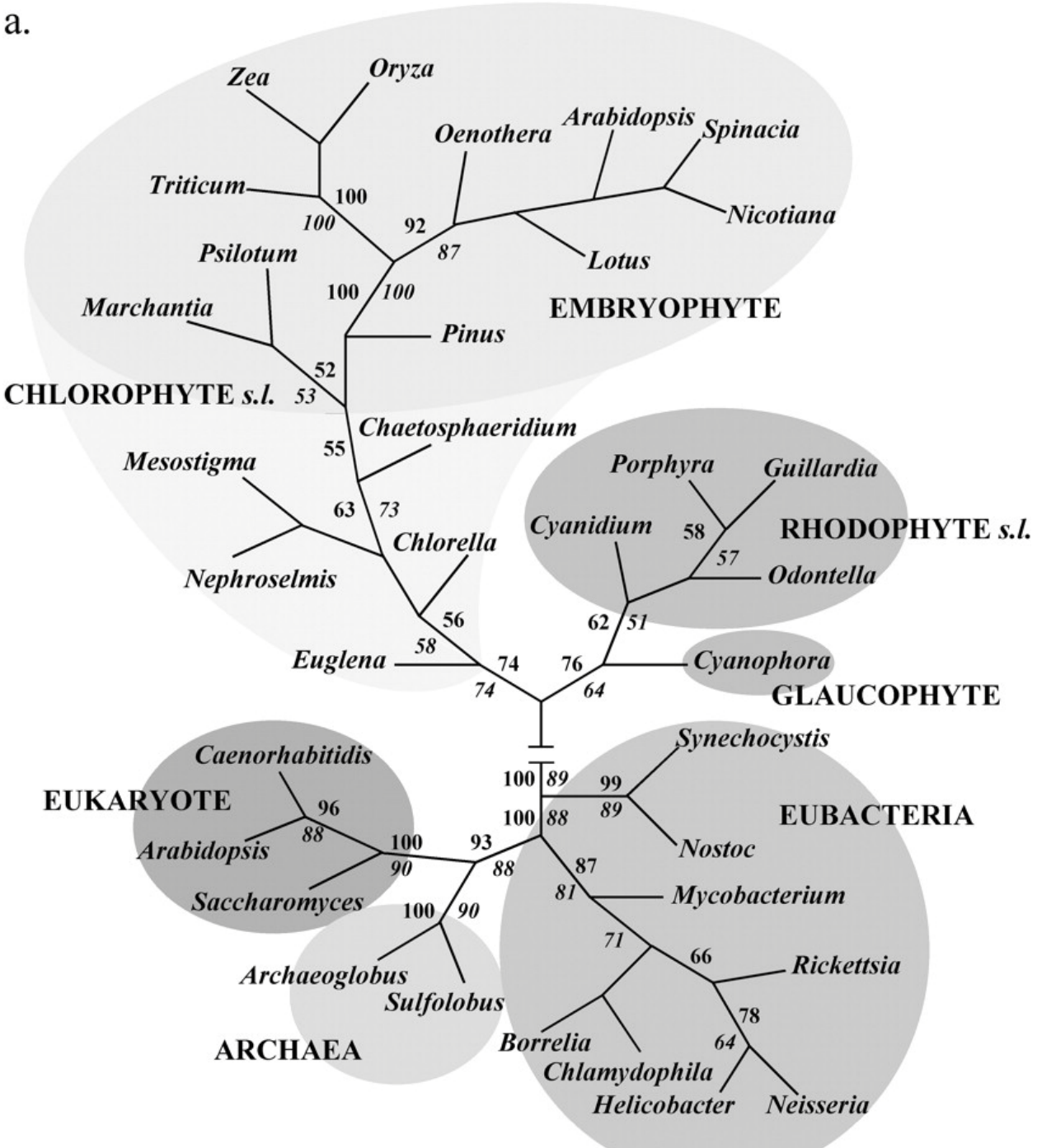
…

- mysterious

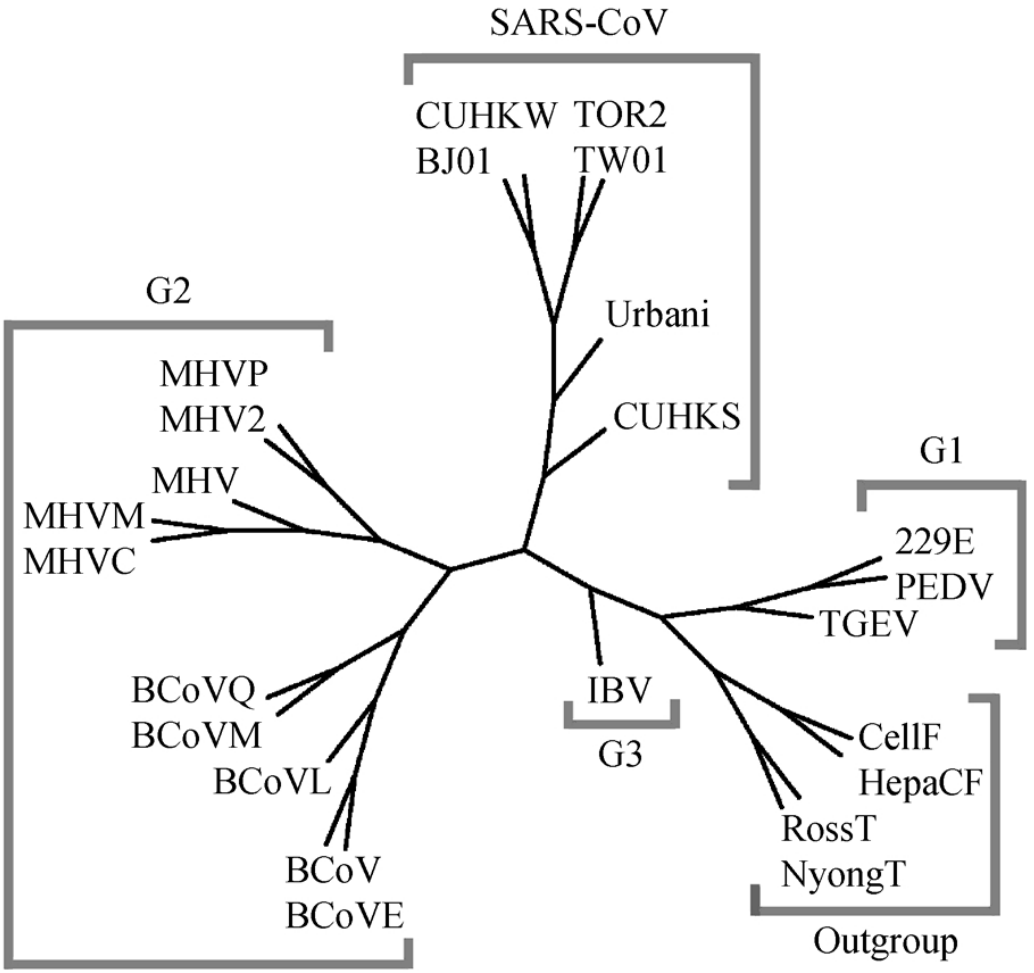


(Qi *et al* ’04)

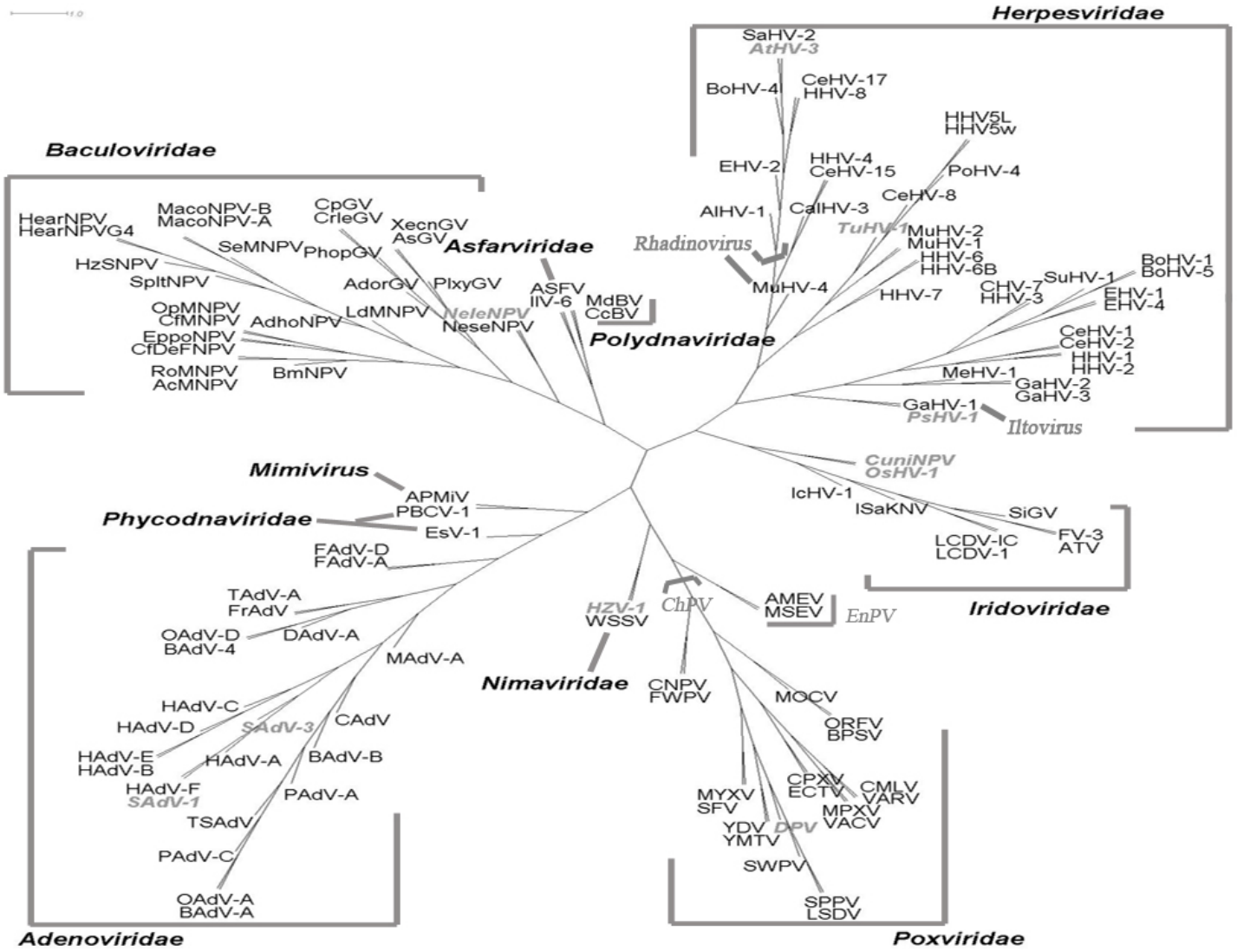
CVTree of chloroplasts



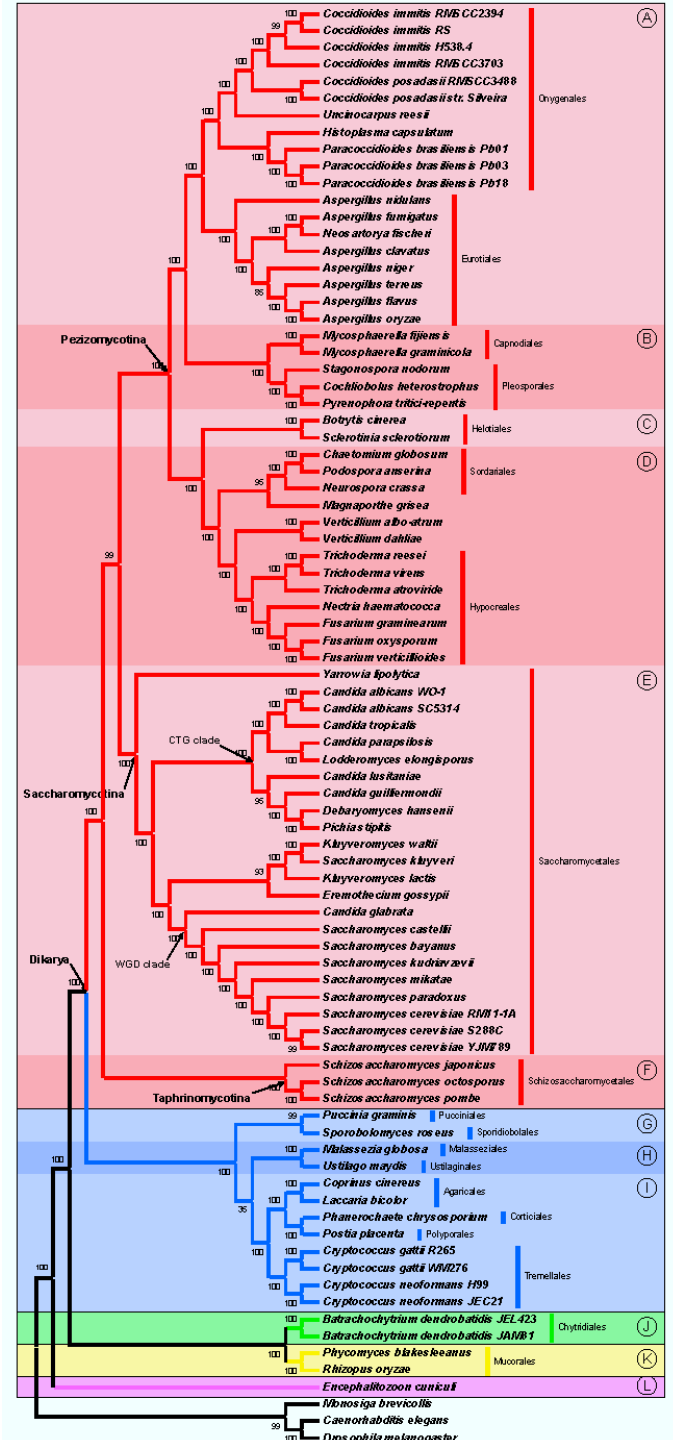
CVTree of coronavirus

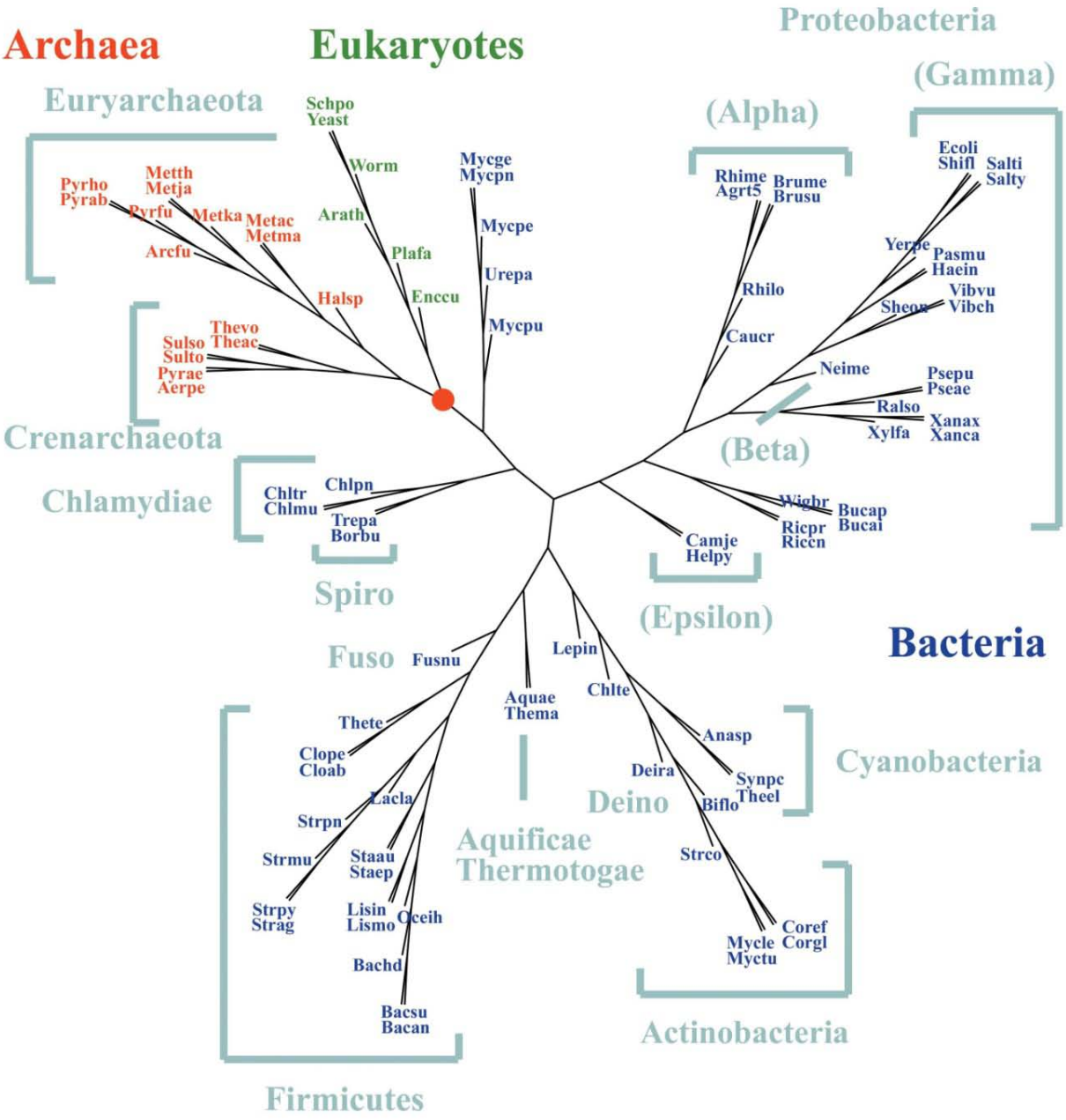


CVTree of dsDNA viruses



CVTree of fungi

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Eukaryotes
Proteobacteria
(Gamma)
(Alpha)
Euryarchaeota
Schpo
Yeast
Worm
Arath
Plafa
Enccu
Mycge
Mycpn
Mycpe
Urepa
Mycpu
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Pyrab
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Metma
Arcfu
Halsp
Thevo
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Theac
Sulto
Pyrae
Aerpe
Crenarchaeota
Rhime
Agrt5
Brume
Brusu
Rhilo
Caucr
Ecoli
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Yerpe
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Haein
Vibvu
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Xylfa
Xanax
Xanca
(Beta)
Chlamydiae
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Chlmu
Chlpn
Trepa
Borbu
Spiro
Wigbr
Ricpr
Riccn
Bucap
Bucai
Camje
Helpy
(Epsilon)
Bacteria
Fuso
Fusnu
Lepin
Aquae
Thema
Chlte
Thete
Clope
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Lacla
Strpn
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Bacan
Firmicutes
Aquificae
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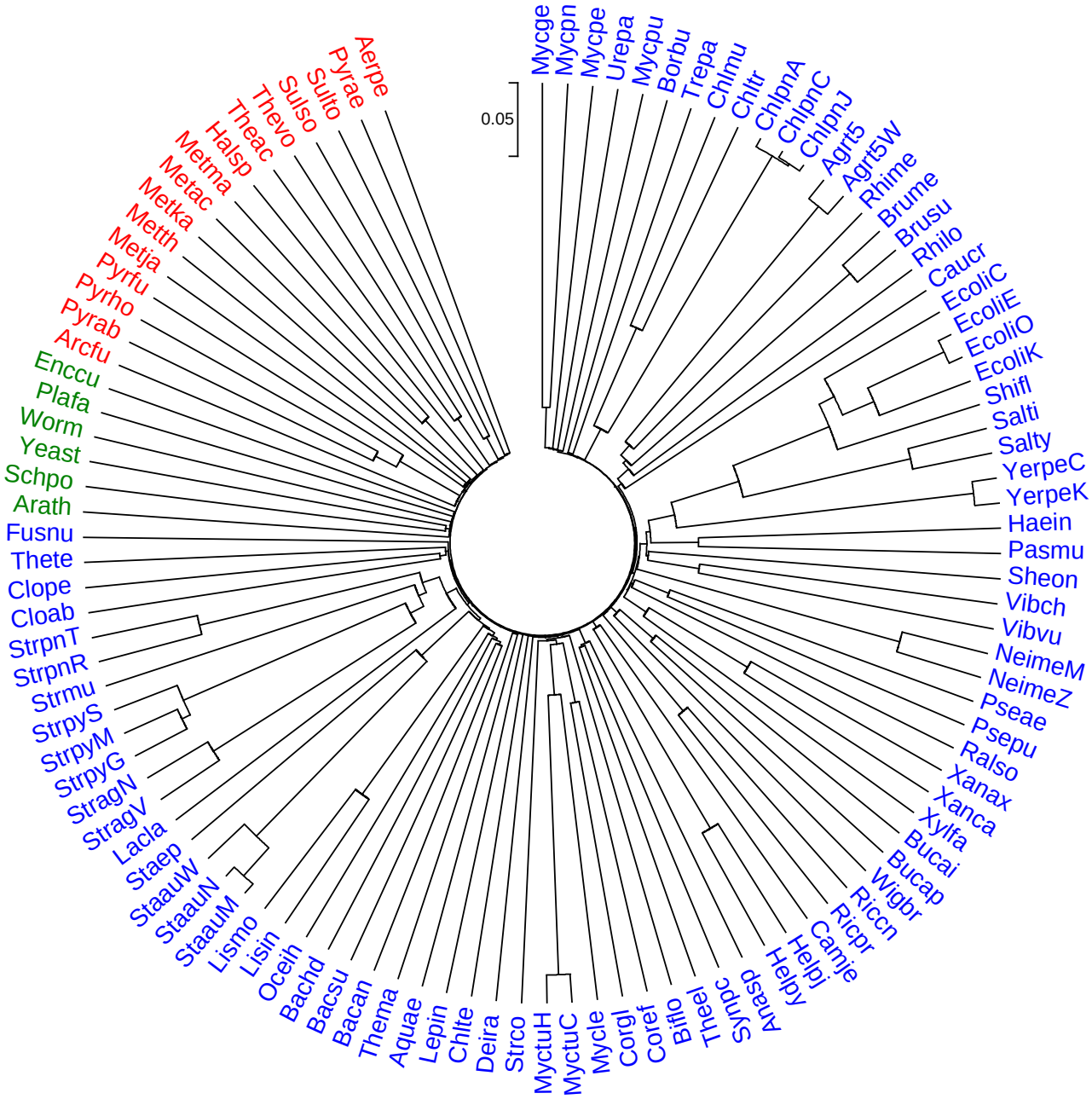
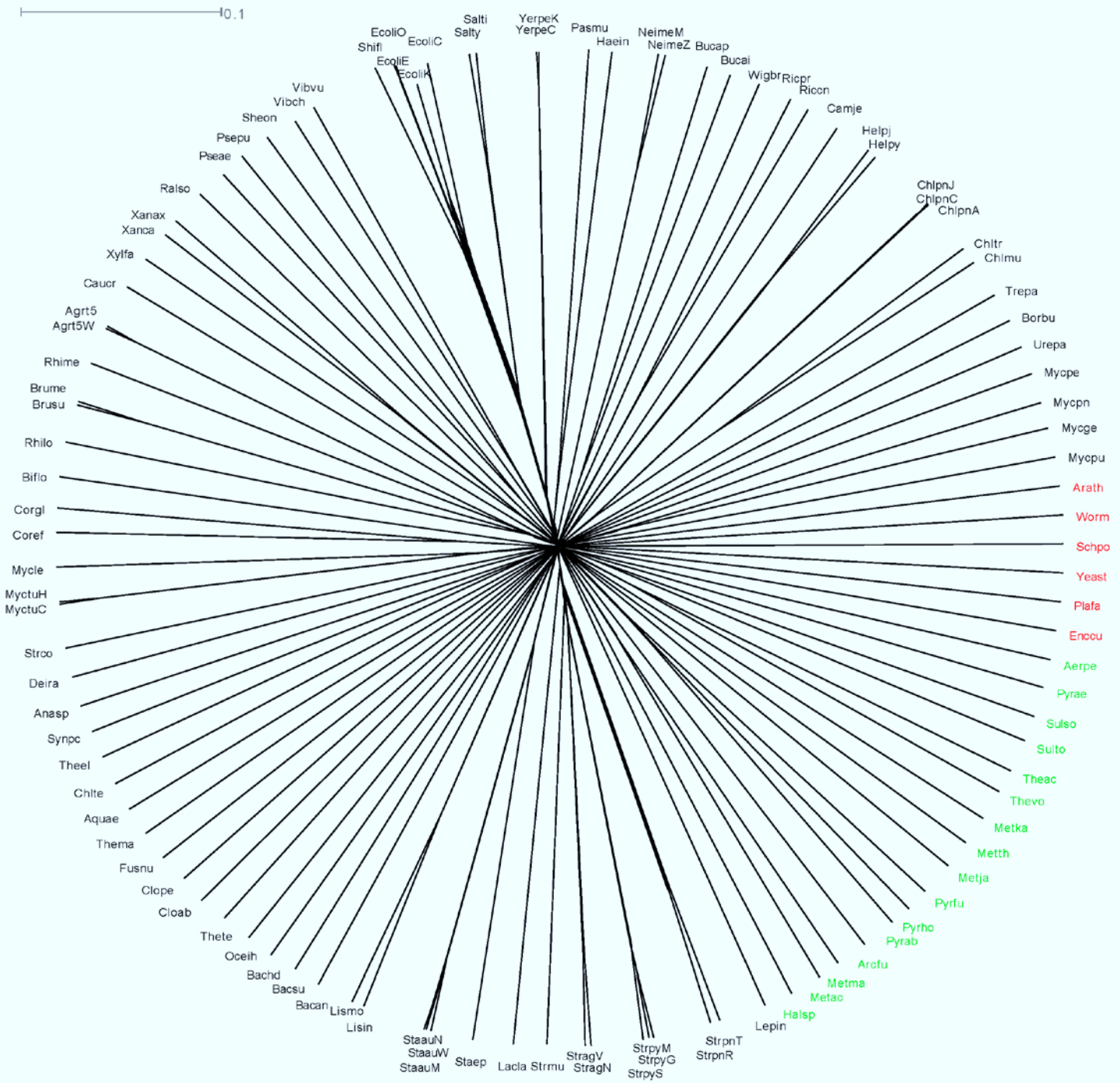
Actinobacteria



The tree plotted to scale

"Concentrating on the topology of the trees in the first place, we did not scale the branch lengths on the tree. However, these lengths should reflect evolution rates in terms of *K*-string composition changes. The calibration of branch lengths is further complicated by the overlapping nature of the *K*-strings when $K \geq 2$."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NeimeM
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Aquae
Chlte
Theel
Synpc
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Coref
Corgl
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Brume
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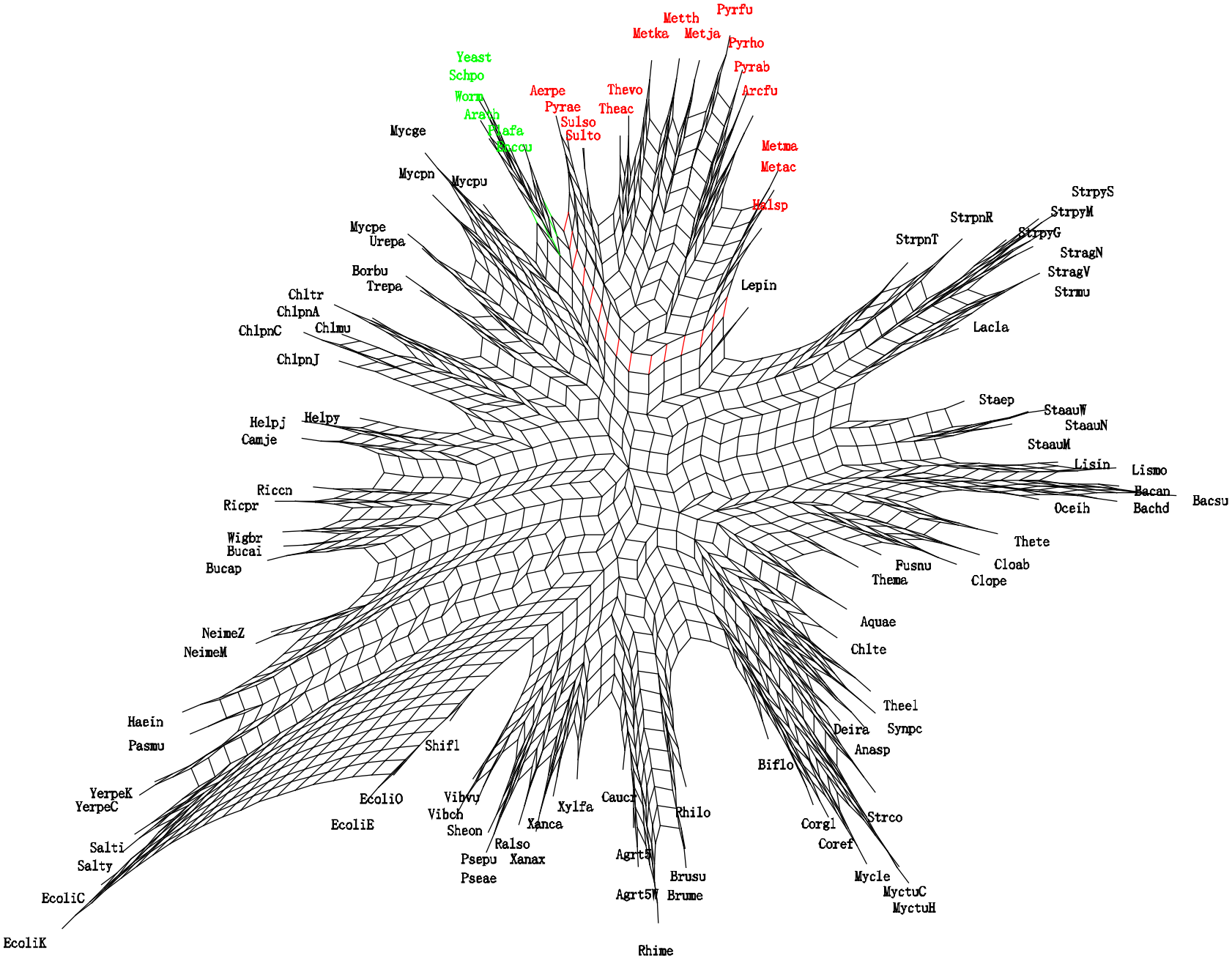
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Schpo
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Worm
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Plafa
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Sulto
Saccu
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Oceih
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Wigbr
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Bucap
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Aquae
NeimeZ
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Vibch
Rhilo
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Salti
Ralso
Coref
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Xanax
Agrt5W
Salty
Brusu
Mycle
Pseae
MyctuC
EcoliC
Agrt5W
Brume
MyctuH
EcoliK
Rhime

- “However, the methods proposed so far are extremely crude. Oligonucleotide or oligopeptide frequencies are transformed into distances without any underlying model of evolution. It is nevertheless remarkable that something considered as a bias in standard sequence-based methods (Lockhart *et al*. 1994) contains a phylogenetic signal, but it is not yet clear whether accurate methods can be developed to extract it.”

  (Philippe *et al*. 2005)

- “Why, for example, does the *K*-string complement of a proteome yield a tree that is similar to sequence-based trees?” (Snel *et al*. 2005)

A heuristic probabilistic model

- Transition of frequency distribution:

  Assume that the evolution process is stationary, and the average mutation rate per site is 1 – α. Let

  $L = |\mathrm{S}| - K + 1$, then the conditional distribution

$$f\left(\mathrm{S}^{(t+1)}(\mathbf{i}) \middle| \mathrm{S}^{(t)}(\mathbf{i}) = n\right) = \mathrm{binomial}(n, \alpha^K)$$

$$* \mathrm{binomial}\left(L, (1-\alpha^K)\frac{\mathrm{E}\,\mathrm{S}(\mathbf{i})}{L}\right)$$

- Time evolution of expectation

$$\mathrm{E}\left(\mathrm{S}^{(t')}(\mathbf{i})\middle|\mathrm{S}^{(t)}(\mathbf{i})=n\right)=\mathrm{E}\,\mathrm{S}(\mathbf{i})+\alpha^{K(t'-t)}(n-\mathrm{E}\,\mathrm{S}(\mathbf{i}))$$

Calibration of CVTree

- Generalized CV

$$w(\mathrm{S}, \mathbf{i}) = (\mathrm{S}(\mathbf{i}) - \mathrm{S}^0(\mathbf{i}))c(\mathbf{i})$$

where $\mathrm{S}^0(\mathbf{i})$ is an unbiased estimator of $\mathrm{S}(\mathbf{i})$, and $c(\mathbf{i})$ is arbitrary "normalization" factor.

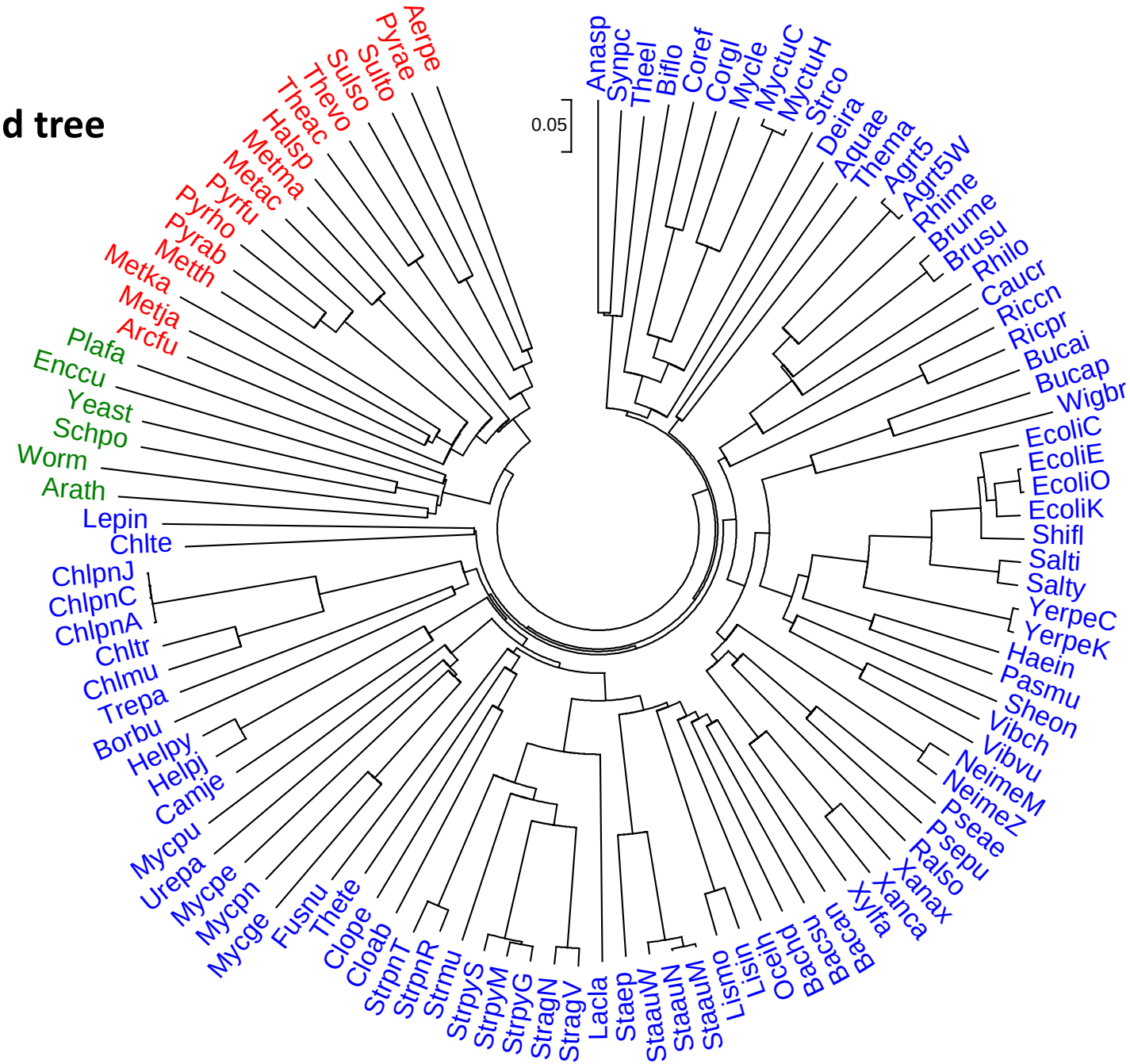
- Angle between vectors vs. sequence identity

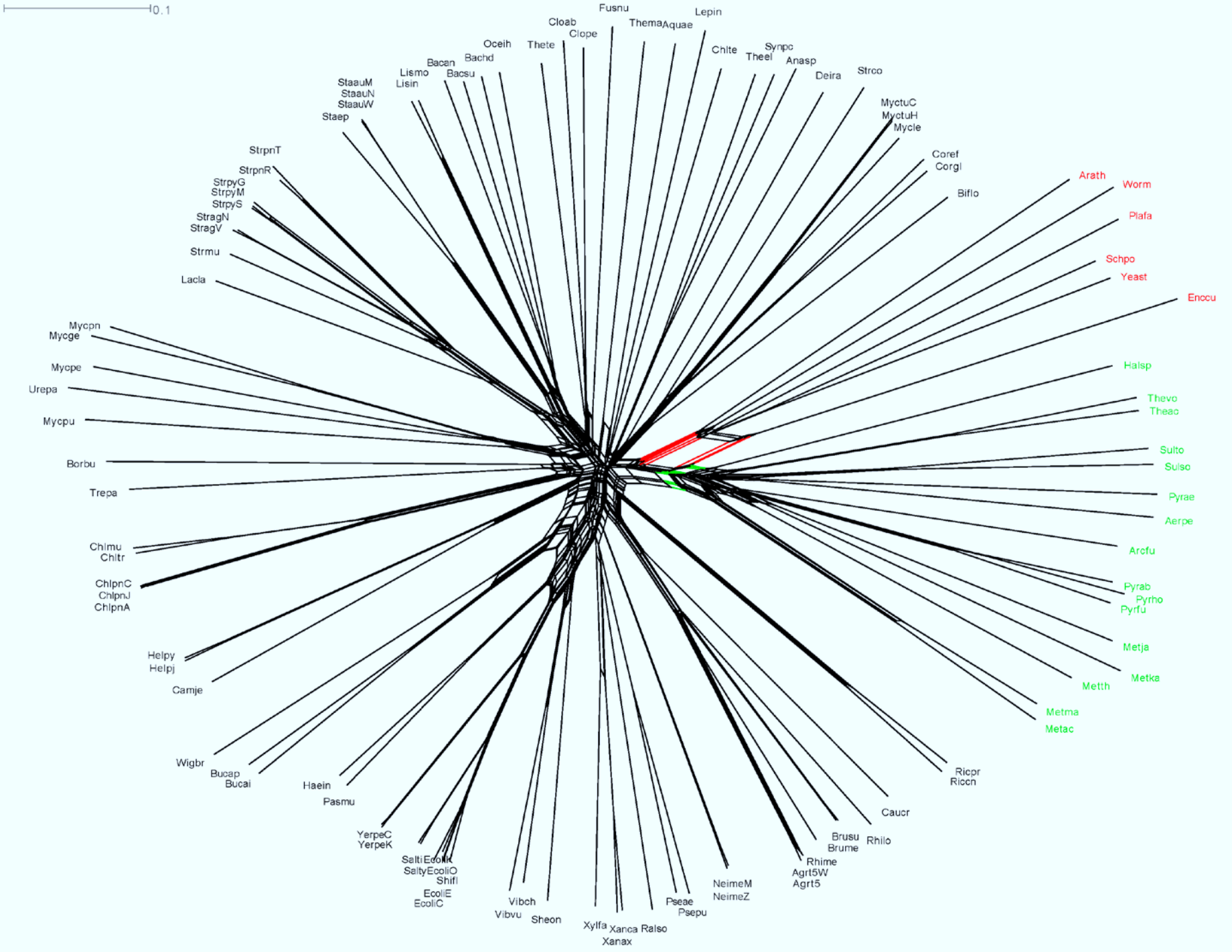
$$\mathrm{E}\cos(w(\mathrm{S}), w(\mathrm{S}')) = q^K$$

- Calibration

$$\hat{p}(\mathrm{S},\mathrm{S}') = 1 - \cos^{1/K}\left(w(\mathrm{S}), w(\mathrm{S}')\right)$$

The calibrated tree

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Lepin
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Pyrfu
Helpy
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Metma
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Wigbr
Bucap
Bucai
Ricpr
Riccn
Haein
Pasmu
Caucr
YerpeC
YerpeK
Brusu
Brume
Rhilo
SaltiEcoliK
SaltyEcoliO
ShifI
Rhime
Agrt5W
Agrt5
EcoliE
EcoliC
NeimeM
NeimeZ
Vibch
Vibvu
Pseae
Psepu
Sheon
Xylfa
Xanca
Ralso
Xanax

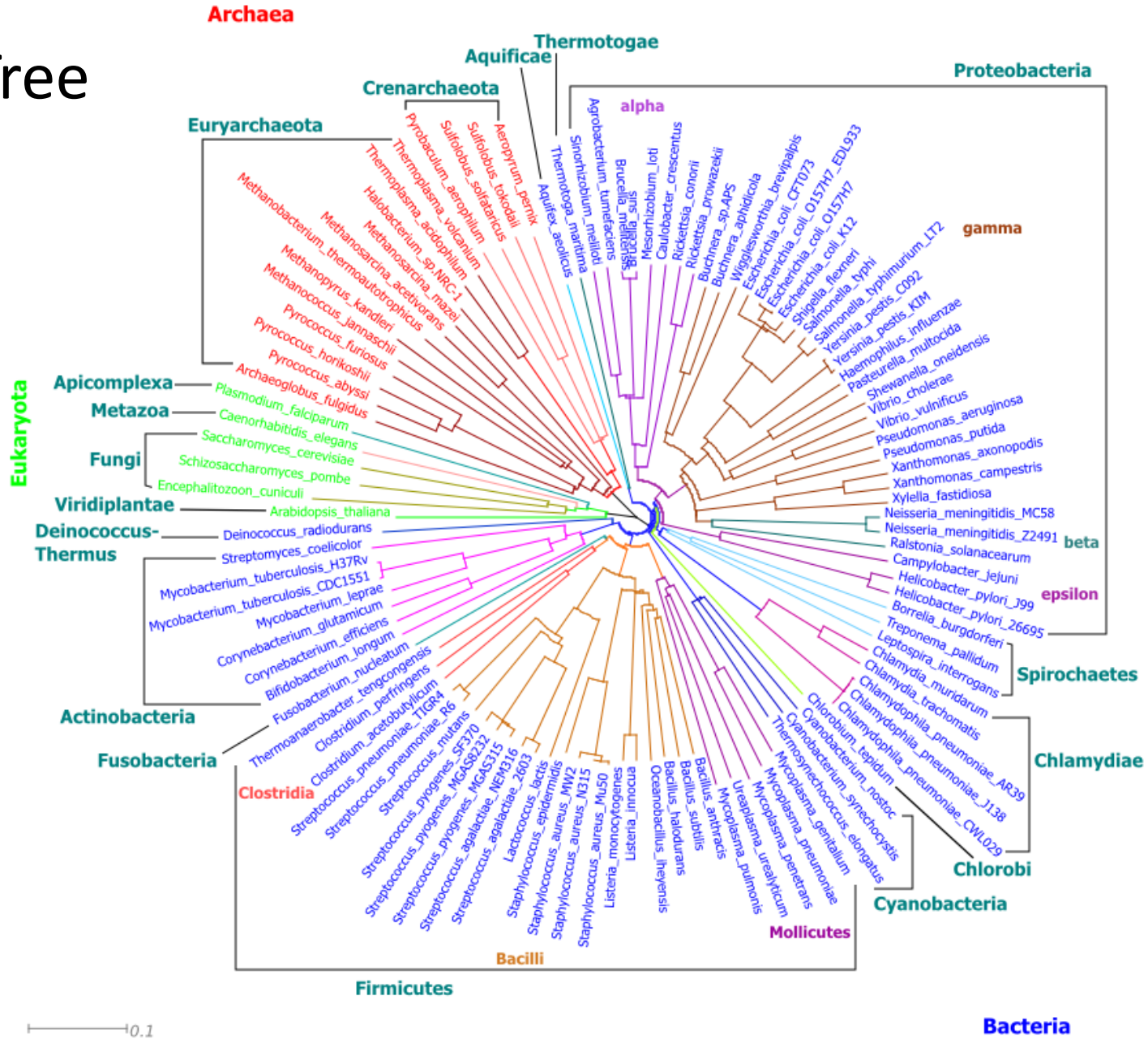
Using pre-/absence of words

- Any sequence S as above can be represented also by just the set $X(\mathrm{S})$ of its K-strings. In a "gedanken alignment", ignoring repeats and collisions, we may put

$$Q^{(K)}(\mathrm{S},\mathrm{S}') := \frac{1}{2}\left(\frac{\left|X(\mathrm{S}) \bigcap X(\mathrm{S}')\right|}{\left|X(\mathrm{S})\right|} + \frac{\left|X(\mathrm{S}) \bigcap X(\mathrm{S}')\right|}{\left|X(\mathrm{S}')\right|} \right)$$

and $$q^{(K)}(\mathrm{S},\mathrm{S}') := Q^{(K)}(\mathrm{S},\mathrm{S}')^{1/K}$$

$K = 9$ Tree


Archaea
Thermotogae
Aquificae
Crenarchaeota
Euryarchaeota
Proteobacteria
alpha
gamma
beta
epsilon
Eukaryota
Apicomplexa
Metazoa
Fungi
Viridiplantae
Deinococcus-Thermus
Actinobacteria
Fusobacteria
Clostridia
Bacilli
Firmicutes
Mollicutes
Spirochaetes
Chlamydiae
Chlorobi
Cyanobacteria
Bacteria
Aeropyrum_pernix
Sulfolobus_solfataricus
Sulfolobus_tokodaii
Pyrobaculum_aerophilum
Thermoplasma_volcanium
Thermoplasma_acidophilum
Halobacterium_sp.NRC-1
Methanosarcina_acetivorans
Methanosarcina_mazei
Methanobacterium_thermoautotrophicus
Methanopyrus_kandleri
Methanococcus_jannaschii
Pyrococcus_furiosus
Pyrococcus_horikoshii
Pyrococcus_abyssi
Archaeoglobus_fulgidus
Aquifex_aeolicus
Thermotoga_maritima
Sinorhizobium_meliloti
Agrobacterium_tumefaciens
Brucella_melitensis
Brucella_suis
Mesorhizobium_loti
Caulobacter_crescentus
Rickettsia_conorii
Rickettsia_prowazekii
Buchnera_sp.APS
Buchnera_aphidicola
Wigglesworthia_brevipalpis
Escherichia_coli_CFT073
Escherichia_coli_O157H7_EDL933
Escherichia_coli_O157H7
Escherichia_coli_K12
Shigella_flexneri
Salmonella_typhi
Salmonella_typhimurium_LT2
Yersinia_pestis_C092
Yersinia_pestis_KIM
Haemophilus_influenzae
Haemophilus_multocida
Pasteurella_multocida
Shewanella_oneidensis
Vibrio_cholerae
Vibrio_vulnificus
Pseudomonas_aeruginosa
Pseudomonas_putida
Xanthomonas_axonopodis
Xanthomonas_campestris
Xylella_fastidiosa
Neisseria_meningitidis_MC58
Neisseria_meningitidis_Z2491
Ralstonia_solanacearum
Campylobacter_jejuni
Helicobacter_pylori_J99
Helicobacter_pylori_26695
Borrelia_burgdorferi
Treponema_pallidum
Leptospira_interrogans
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Chlamydia_trachomatis
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Chlorobium_tepidum
Cyanobacterium_nostoc
Thermosynechococcus_elongatus
Mycoplasma_genitalium
Mycoplasma_pneumoniae
Mycoplasma_penetrans
Ureaplasma_urealyticum
Mycoplasma_pulmonis
Bacillus_anthracis
Bacillus_subtilis
Bacillus_halodurans
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Staphylococcus_epidermidis
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Streptococcus_pyogenes_MGAS315
Streptococcus_pyogenes_SF370
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Streptococcus_mutans
Clostridium_perfringens
Clostridium_acetobutylicum
Thermoanaerobacter_tengcongensis
Fusobacterium_nucleatum
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Corynebacterium_efficiens
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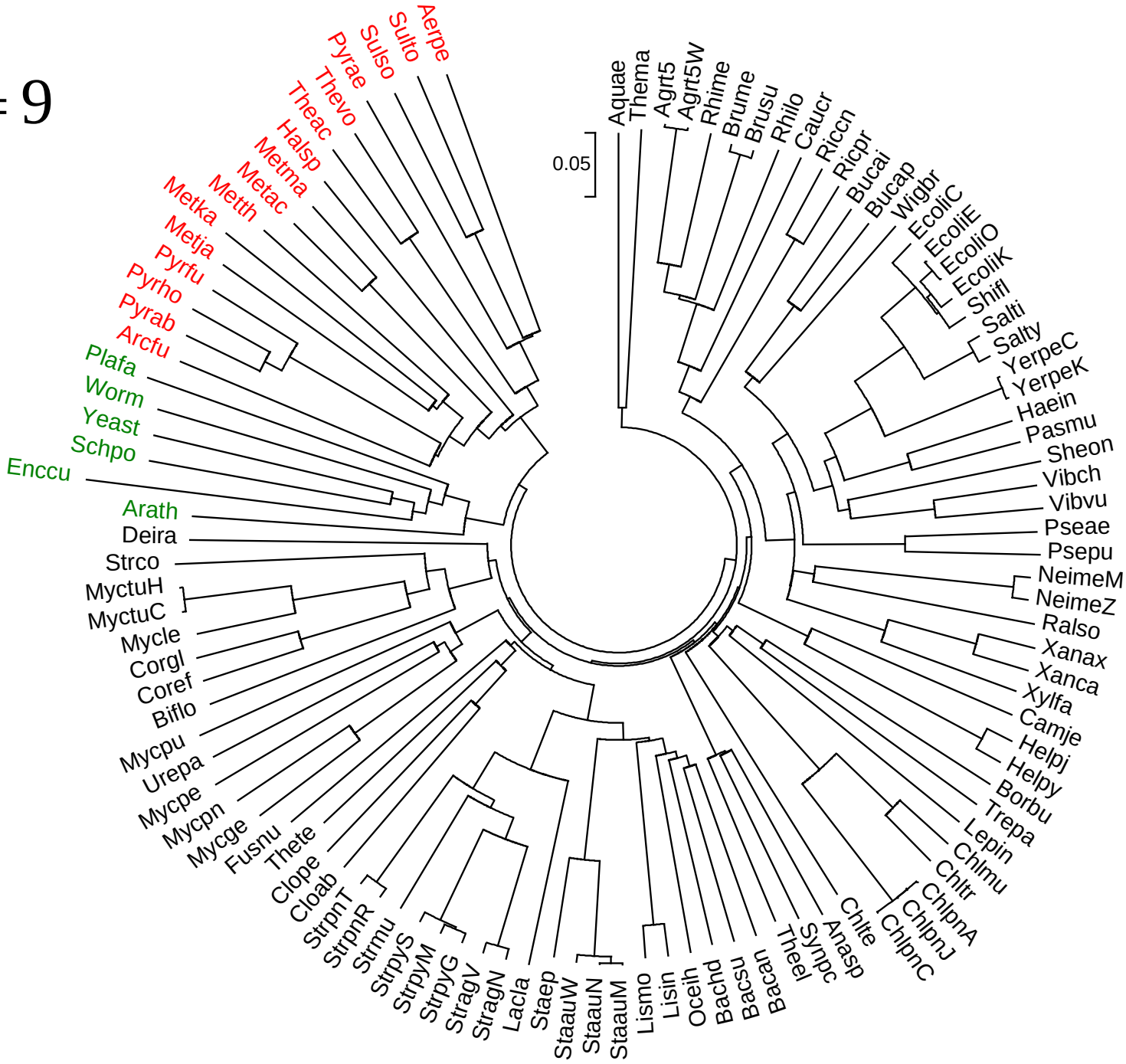
$K = 9$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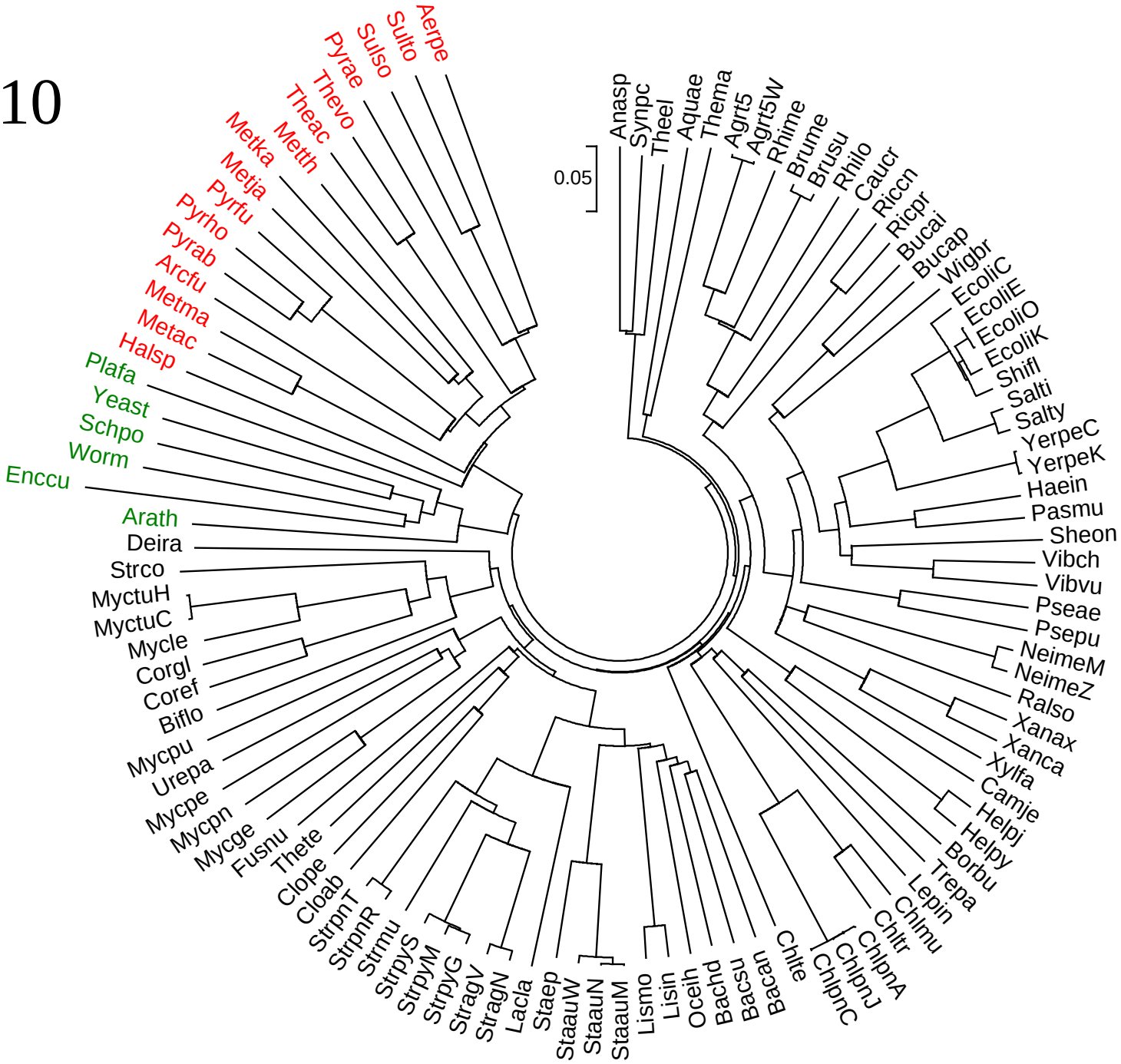
Agrt5
Thema
Aquae

$K = 10$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Yeast
Schpo
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Xanax
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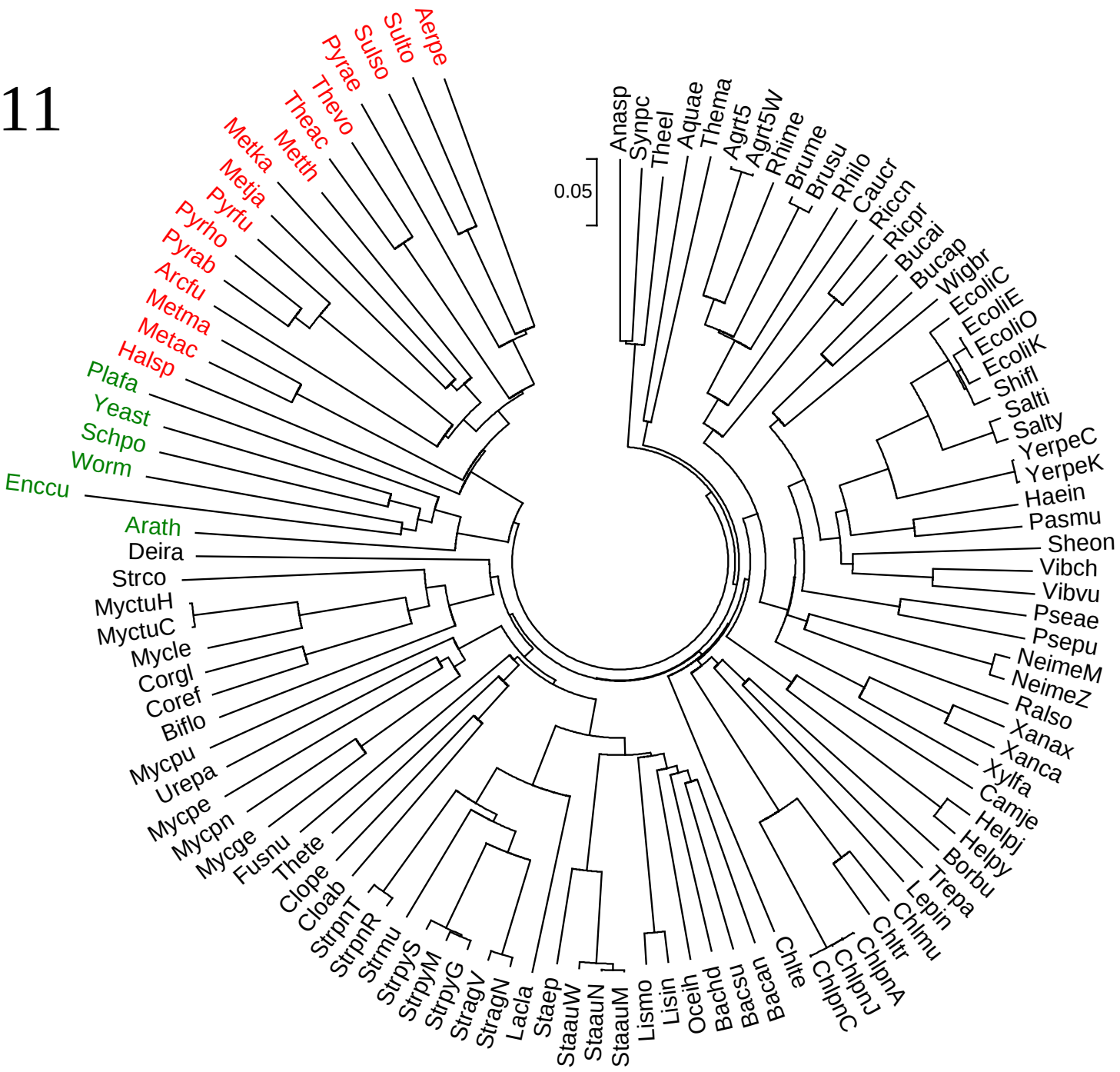
$K = 11$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StaauN
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Lismo
Lisin
Oceih
Bachd
Bacsu
Bacan
Chlte
ChlpnC
ChlpnJ
ChlpnA
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Lepin
Trepa
Borbu
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Helpj
Camje
Xylfa
Xanca
Xanax
Ralso
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NeimeM
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Pseae
Vibvu
Vibch
Sheon
Pasmu
Haein
YerpeK
YerpeC
Salty
Salti
Shifl
EcoliK
EcoliO
EcoliE
EcoliC
Wigbr
Bucap
Bucai
Ricpr
Riccn
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Brume
Rhime
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Agrt5
Thema
Aquae
Theel
Synpc
Anasp

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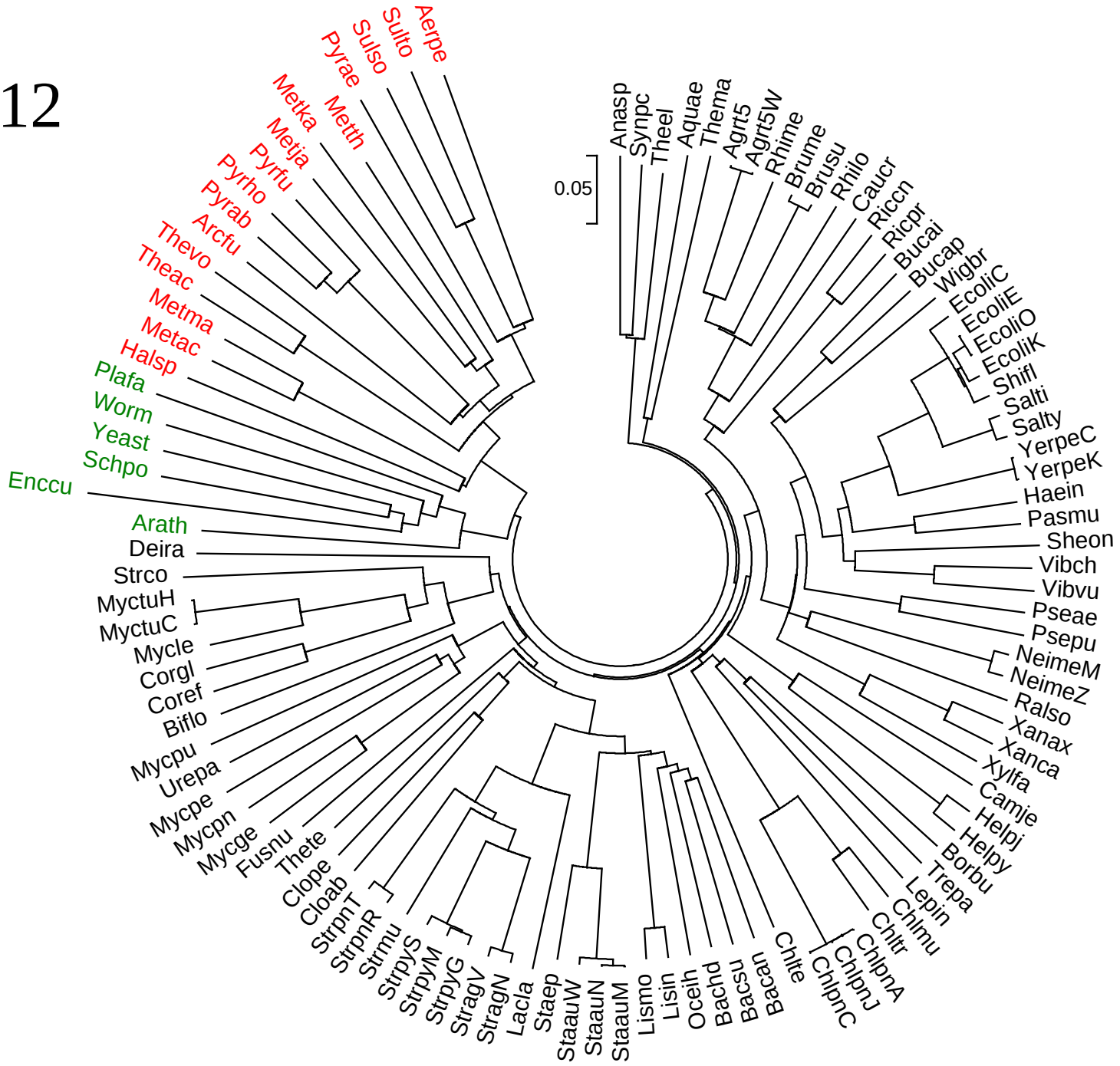
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Fusnu
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StrpnR
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Synpc
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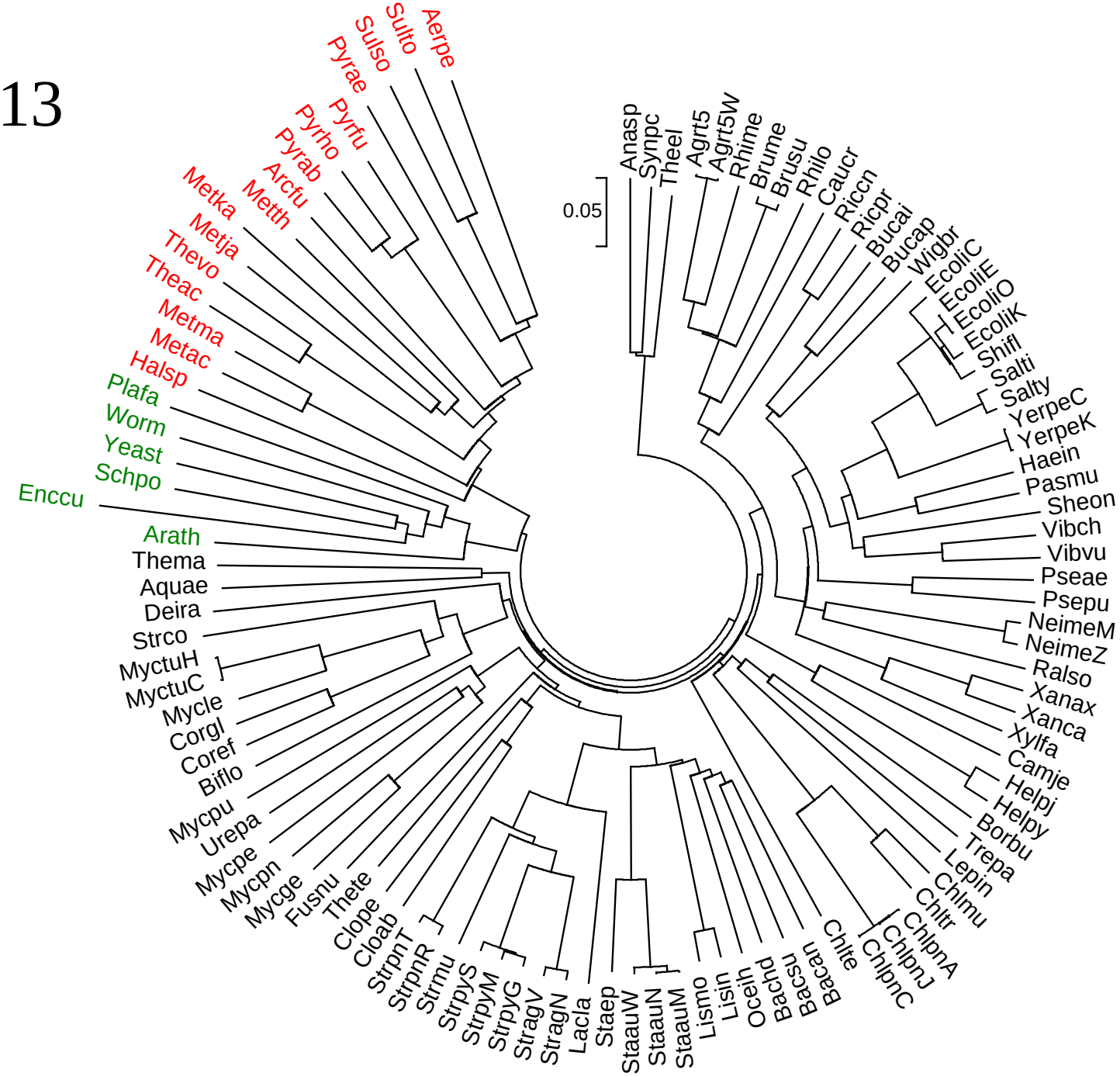
$K = 13$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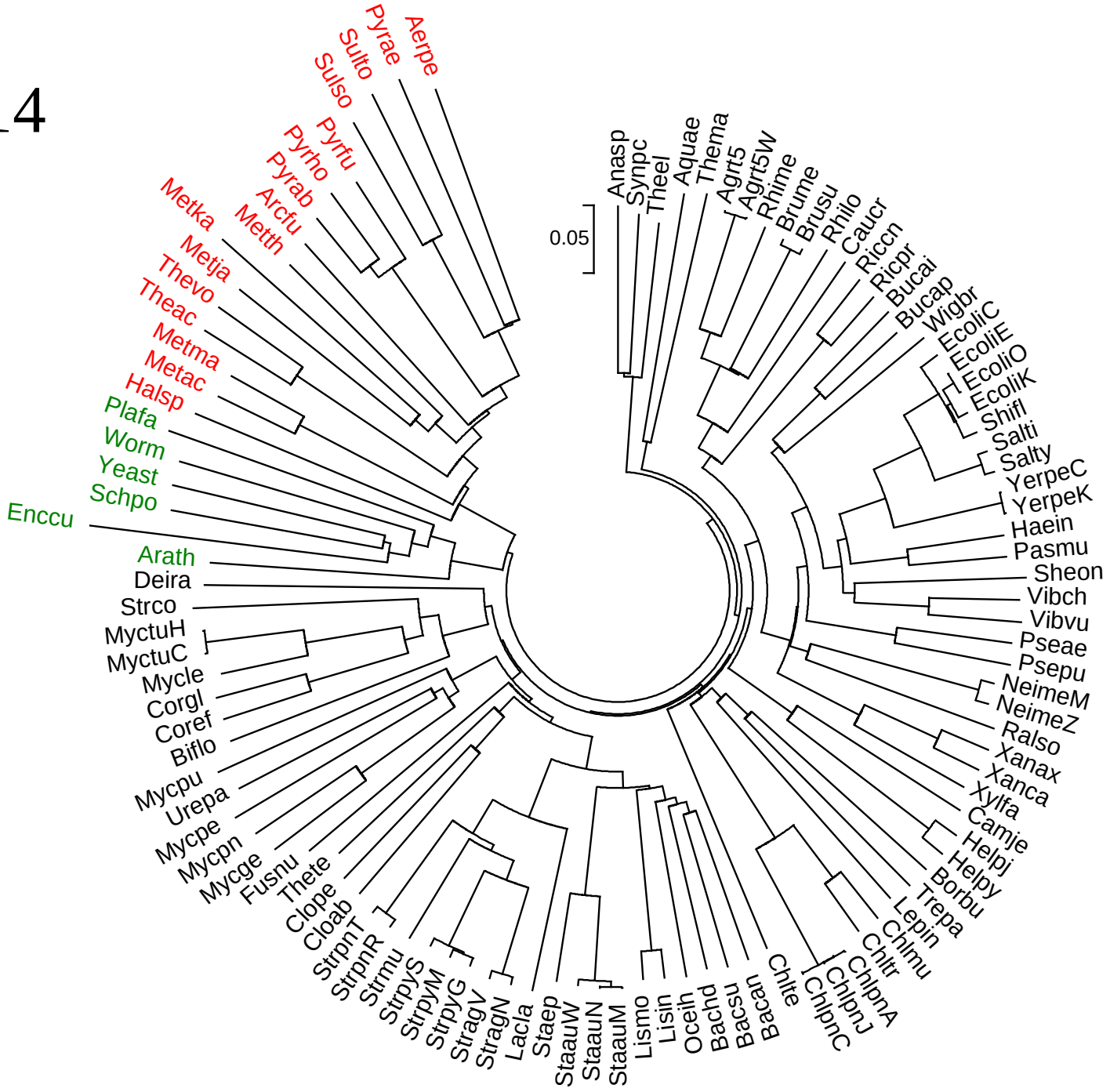
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Thema
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Bucap
Wigbr
EcoliC
EcoliE
EcoliO
EcoliK
Shifl
Salti
Salty
YerpeC
YerpeK
Haein
Pasmu
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Vibch
Vibvu
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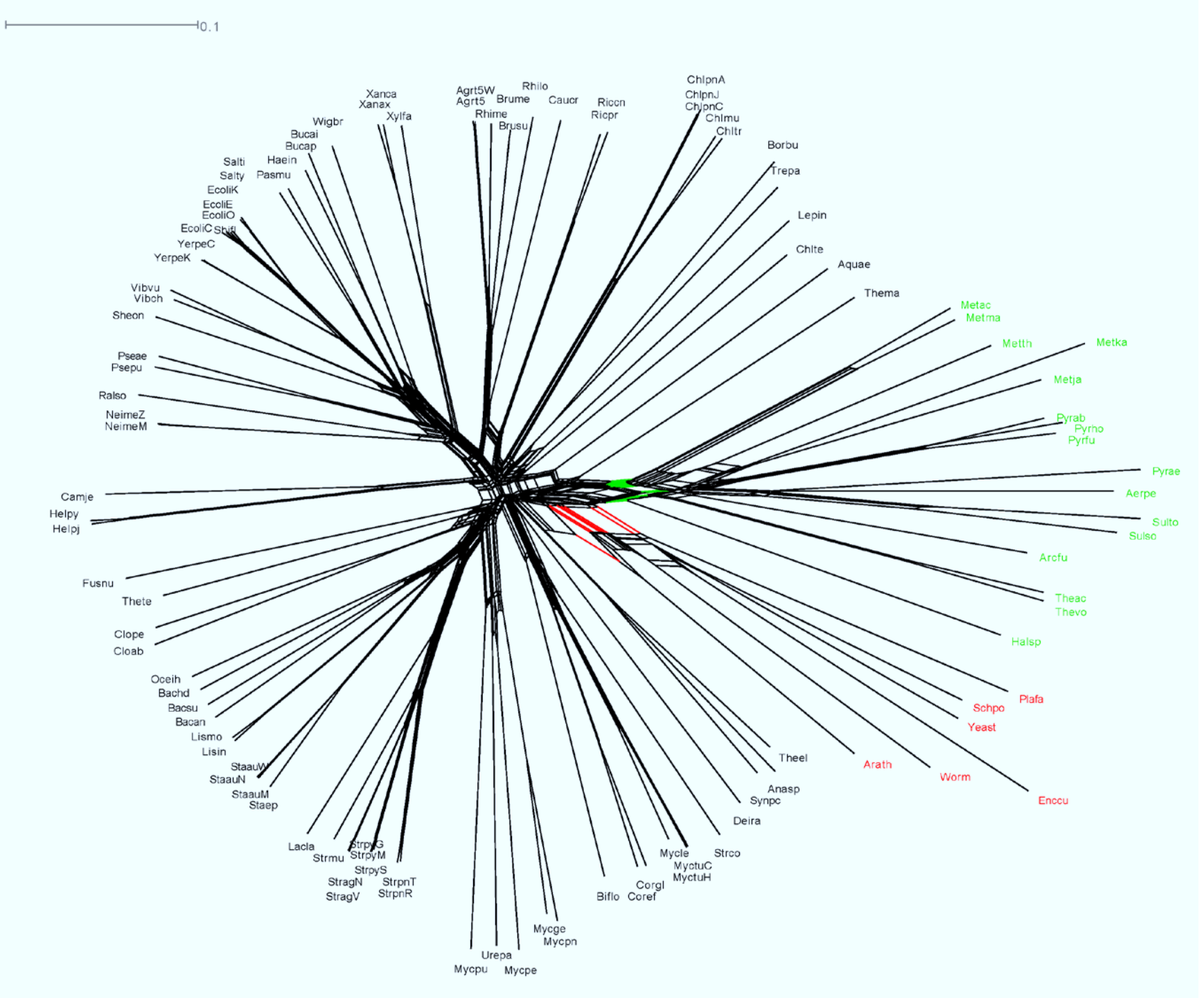
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Ricen
Ricpr
Xanca
Xanax
Xylfa
Wigbr
Bucai
Bucap
Haein
Pasmu
Salti
Salty
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EcoliO
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Pyrae
Aerpe
Sulso
Sulto
Arcfu
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Halsp
Plafa
Schpo
Yeast
Arath
Worm
Enccu

Using pre-/absence of words

- Any sequence S as above can be represented also by just the set $X(\mathrm{S})$ of its K-strings. In a "gedanken alignment", ignoring repeats and collisions, we may put

$$Q^{(K)}(\mathrm{S},\mathrm{S}') := \frac{1}{2}\left(\frac{\left|X(\mathrm{S}) \bigcap X(\mathrm{S}')\right|}{\left|X(\mathrm{S})\right|} + \frac{\left|X(\mathrm{S}) \bigcap X(\mathrm{S}')\right|}{\left|X(\mathrm{S}')\right|} \right)$$

and $$q^{(K)}(\mathrm{S},\mathrm{S}') := Q^{(K)}(\mathrm{S},\mathrm{S}')^{1/K}$$

or $$:= Q^{(K+1)}(\mathrm{S},\mathrm{S}') / Q^{(K)}(\mathrm{S},\mathrm{S}')$$

Making up alignments

- Pattern:

  1: key, must match

  0: space, to watch

- "Align" pairwise:

  For keys occur in both sequences, concatenate letters in spaces.

- Sequence-based distance

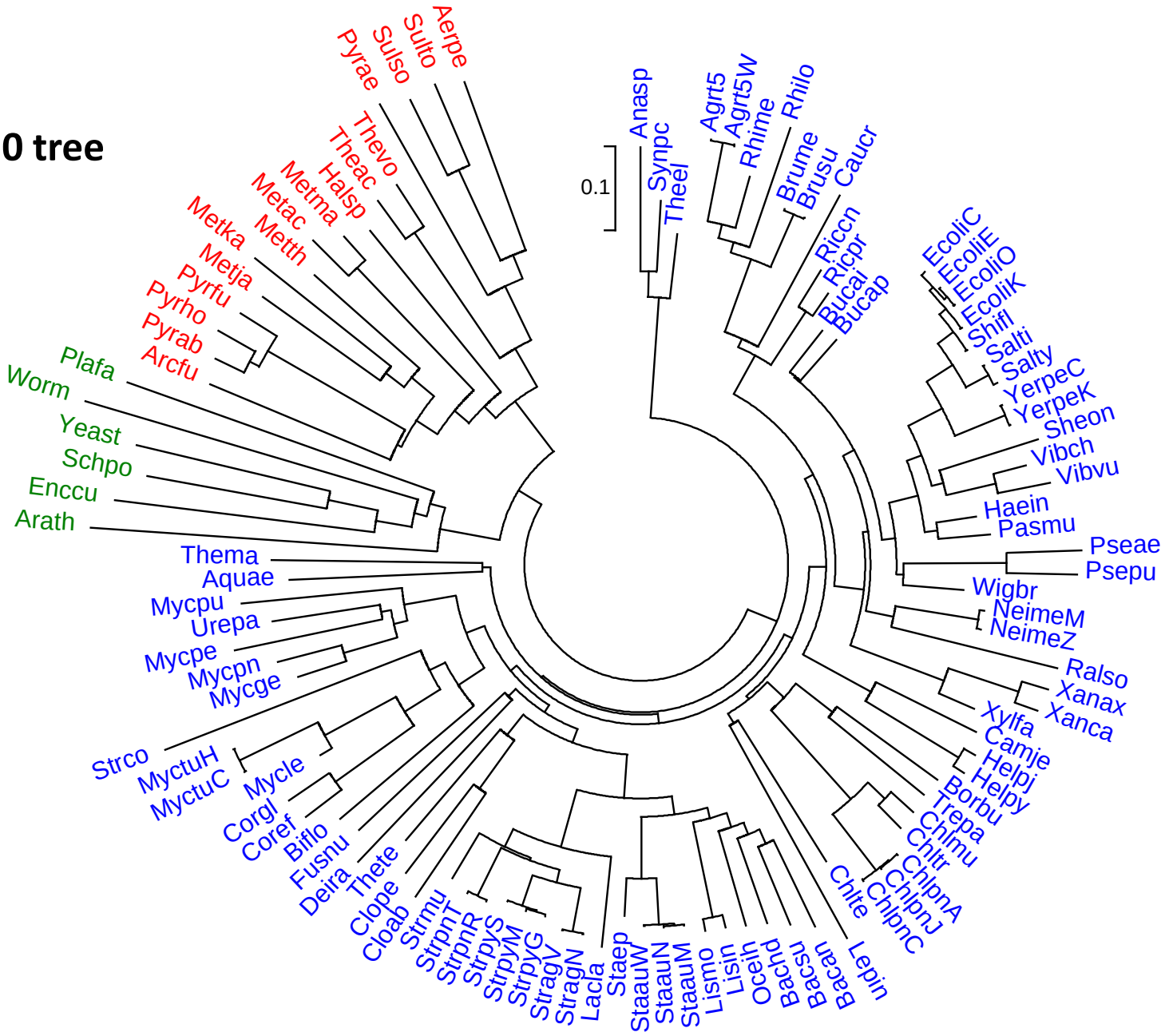
111110

X: VKAAWG,HAGEYG…
Y: VKAAWS,HAGEYG…

GG…
SG…

$$\hat{p} = n_d / n$$

011111110 tree



The missing words approach

- Probabilities of double- vs. single-missing

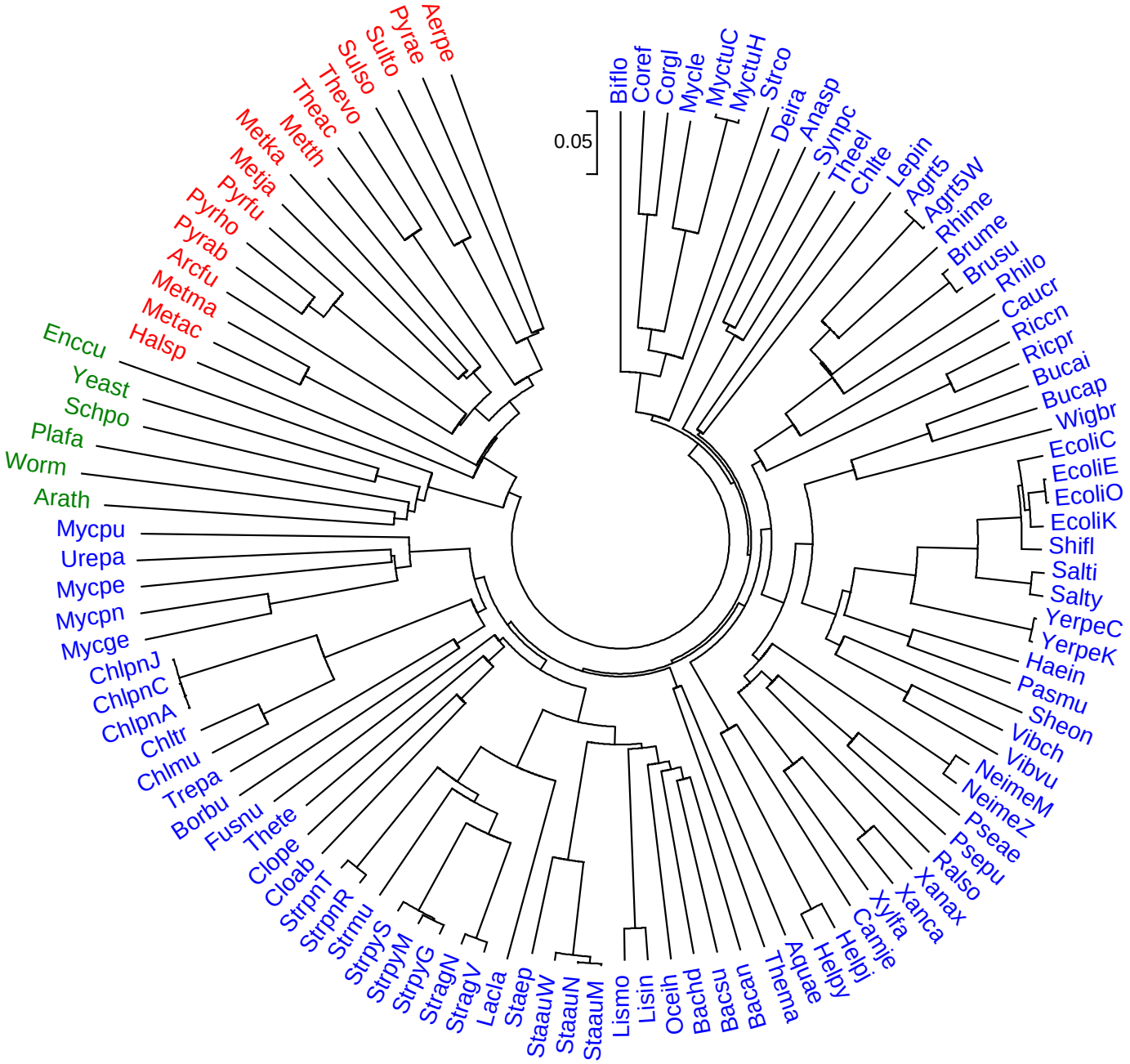
$$p_0 = u^{2-q^K} \Rightarrow \hat{q} = \left(2 - \frac{\ln p_0}{\ln u}\right)^{1/K}$$

- Estimation of probabilities

$$\hat{p}_0 = \frac{n_0}{|\Sigma|^K}$$

$$\hat{u} = \sqrt{\frac{n_0 + n_{\bar{B}}}{|\Sigma|^K} \cdot \frac{n_0 + n_{\bar{A}}}{|\Sigma|^K}}$$

MW9 Tree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Bucai
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Riccn
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Brusu
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Rhime
Agrt5W
Agrt5
Lepin
Chlte
Theel
Synpc
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Deira
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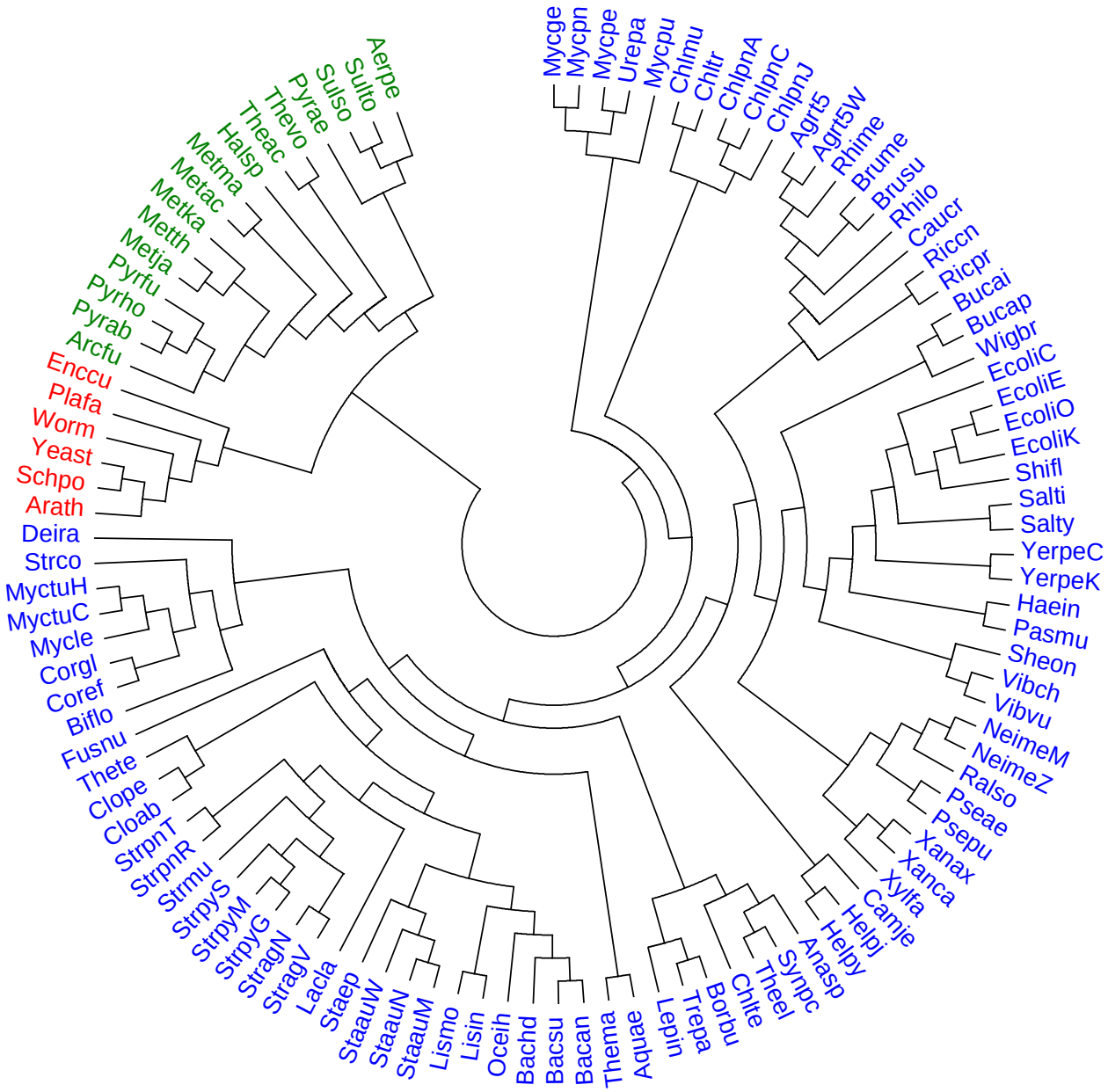
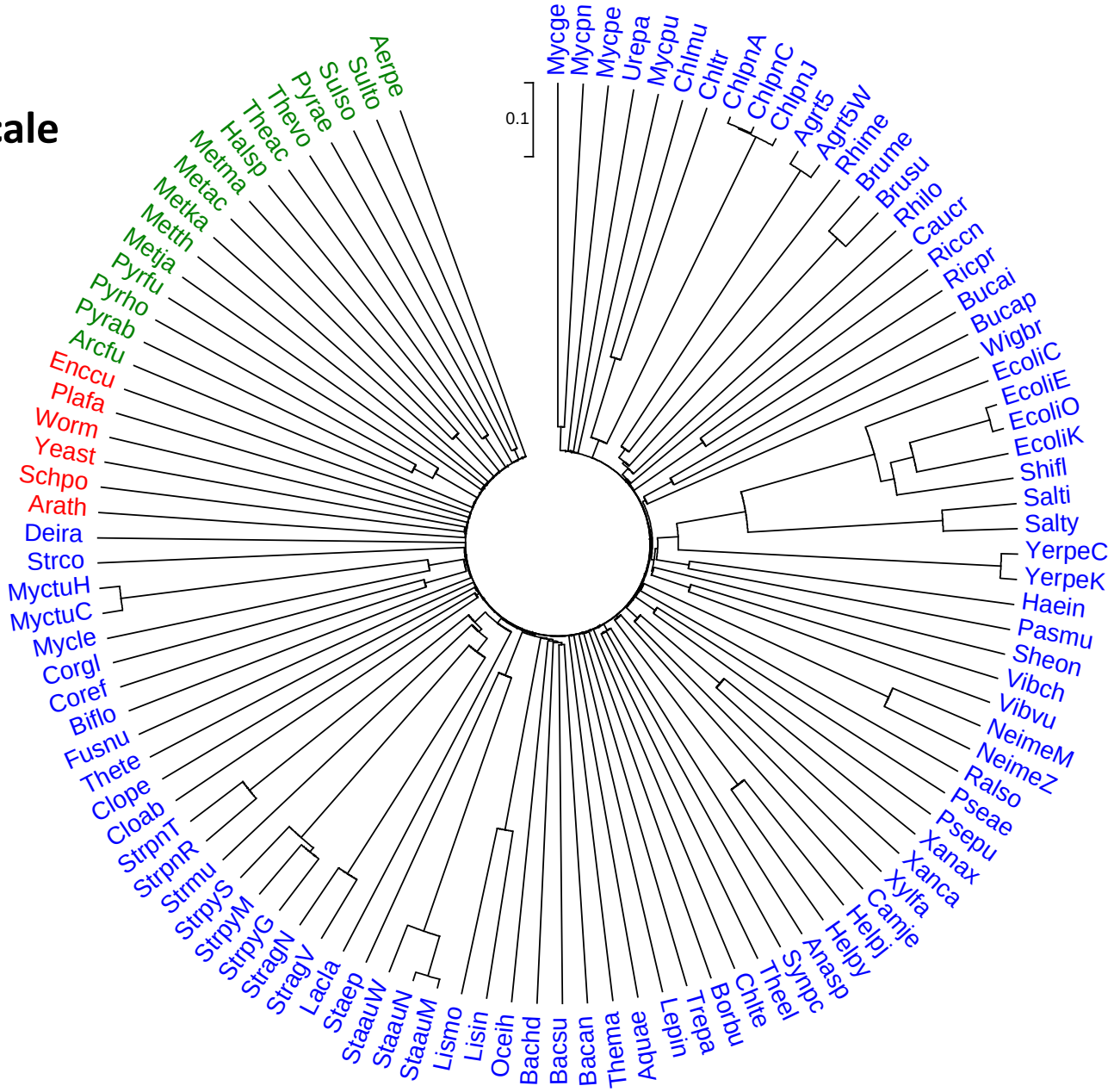
MyctuH
MyctuC
Mycle
Corgl
Coref
Biflo

A tree based on "Jensen-Shannon" distance $JSh(S, S')$, the "symmetrized" Kullback-Leibler distance between the "induced K-string probabilities"

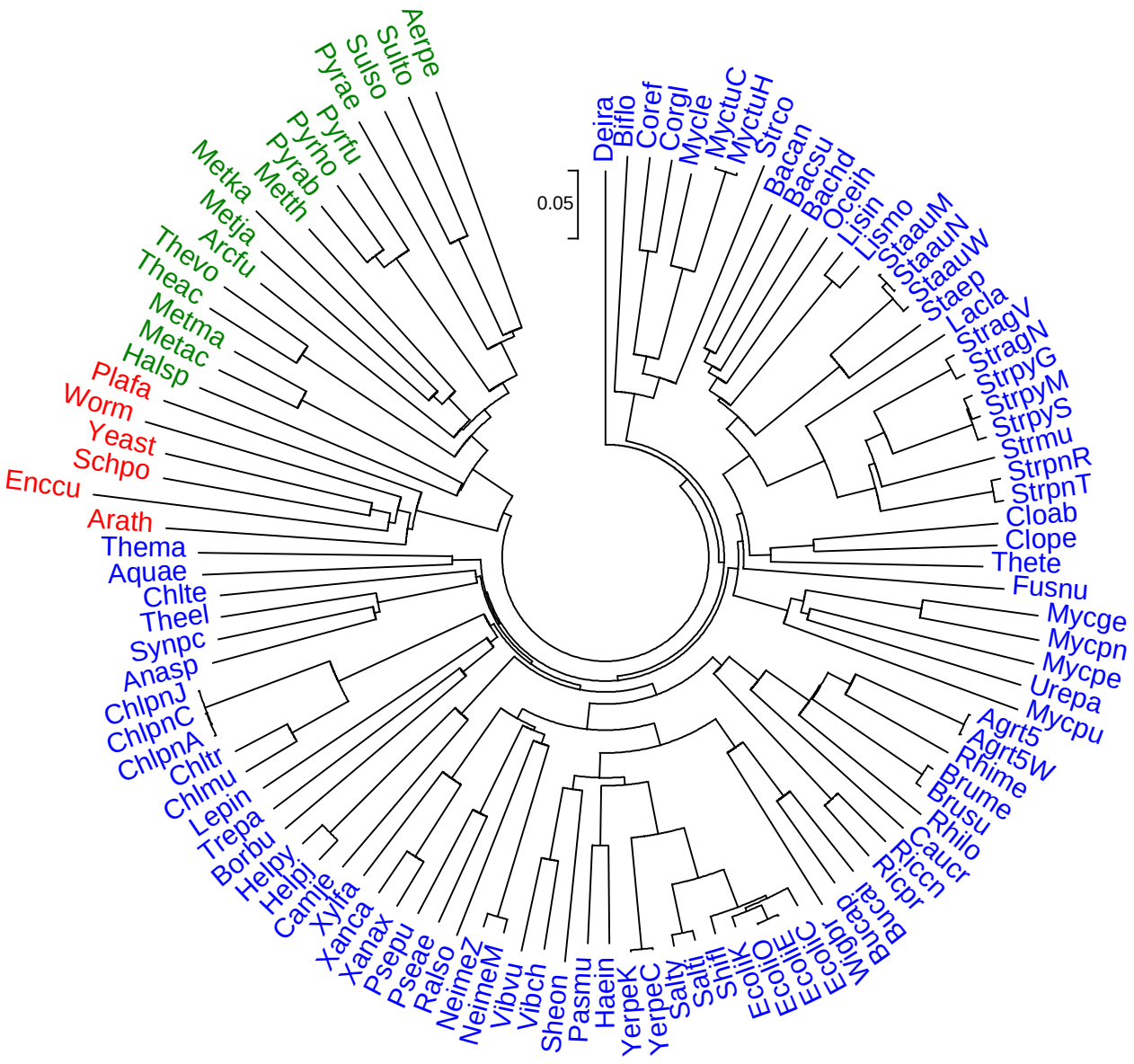


The tree drawn to scale

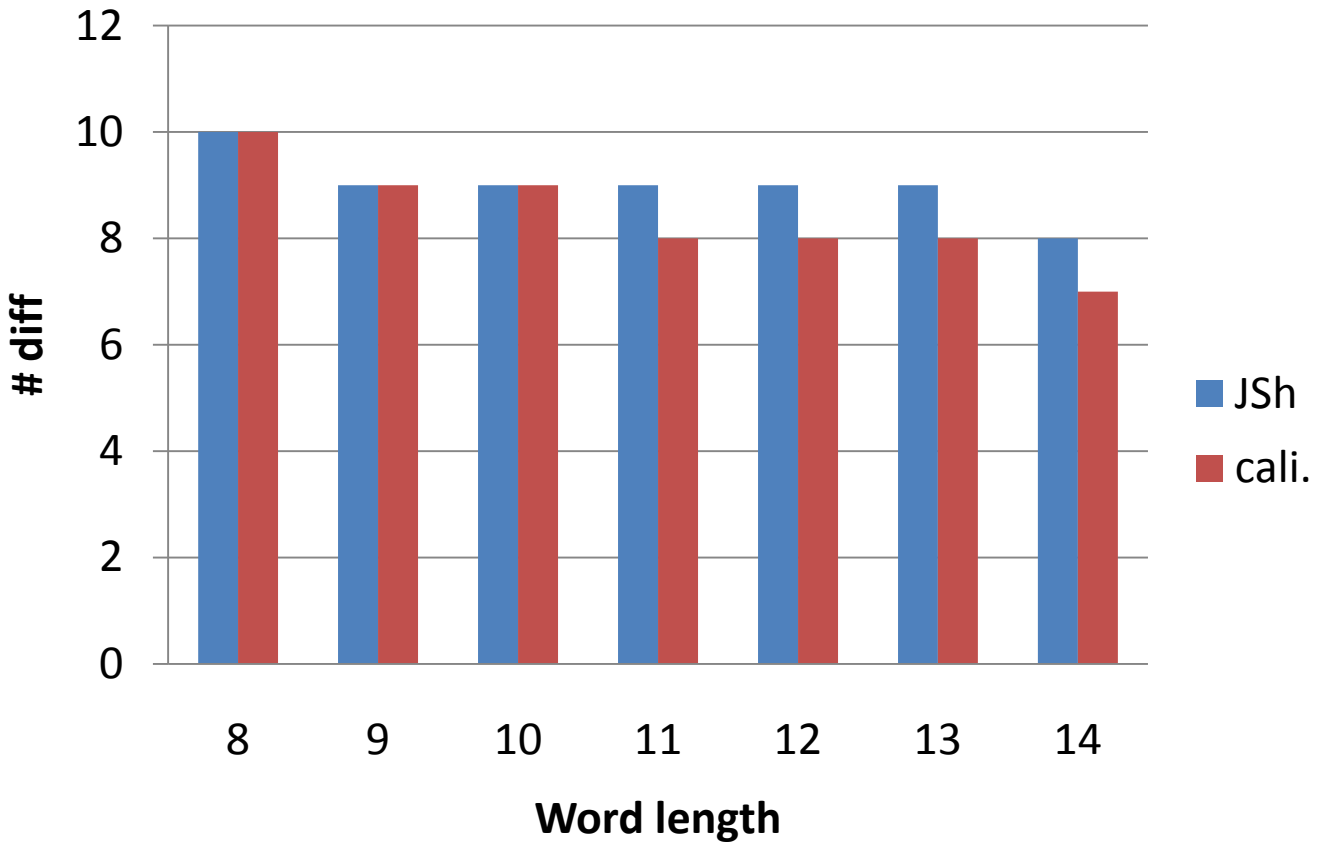


The tree using the calibrated distance

$$1-\left(1-JSh(\mathrm{S},\mathrm{S}')\right)^{1/K}$$



Comparison with “standard” taxonomy



Outlook

- More realistic evolutionary dynamics
- Taking account of the variance of the frequency distribution
  - Better construction of composition vector
  - Optimal value of K

Acknowledgement

- Bailin Hao
- Andreas Dress
- Zhao Xu

Thank You!