# Gene duplication and loss
# Part III

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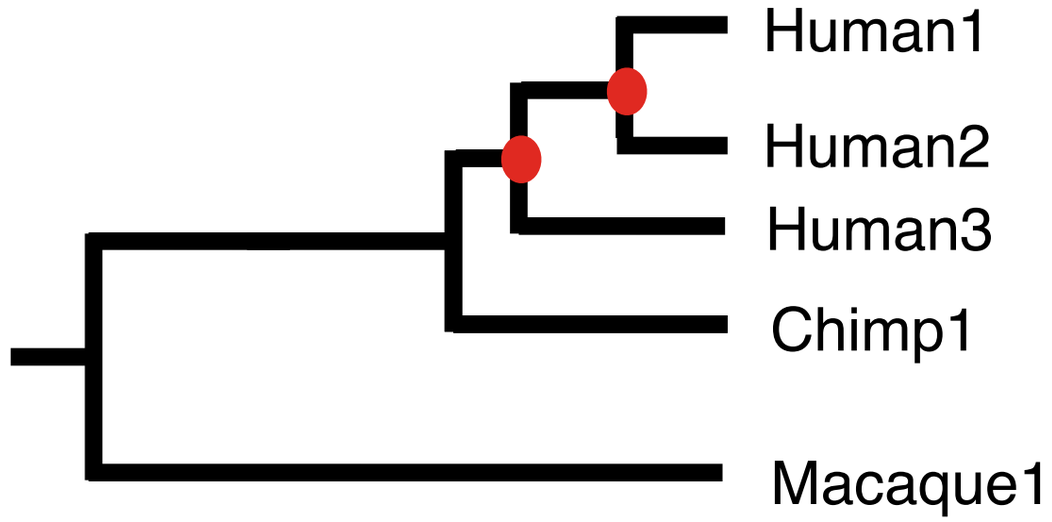
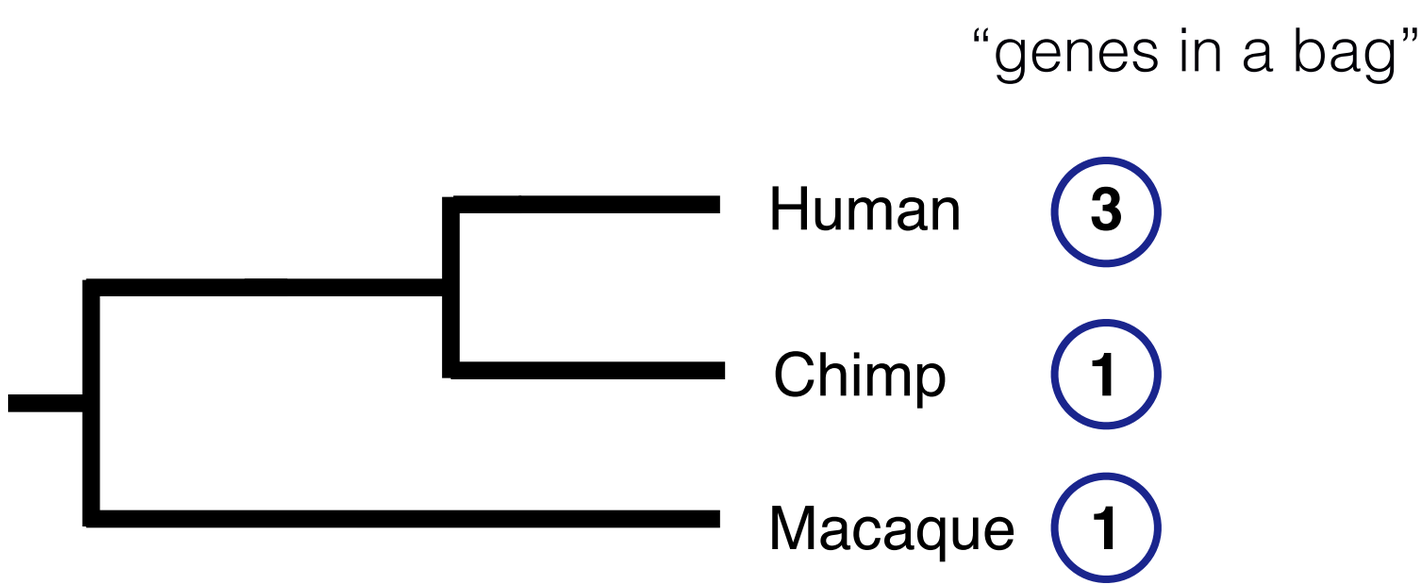
# Inferring duplications and losses using gene trees



# An alternative approach

"Count" methods



# An alternative approach

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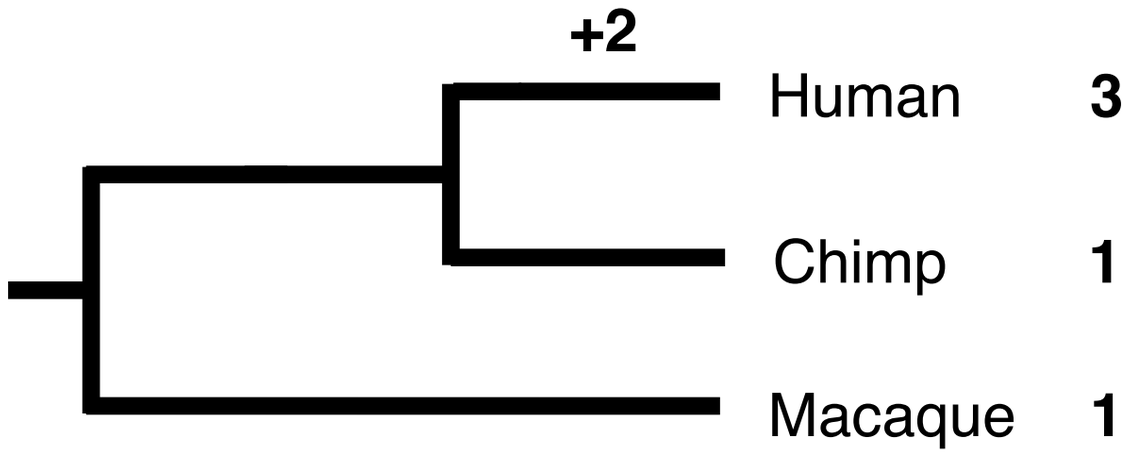

# An alternative approach

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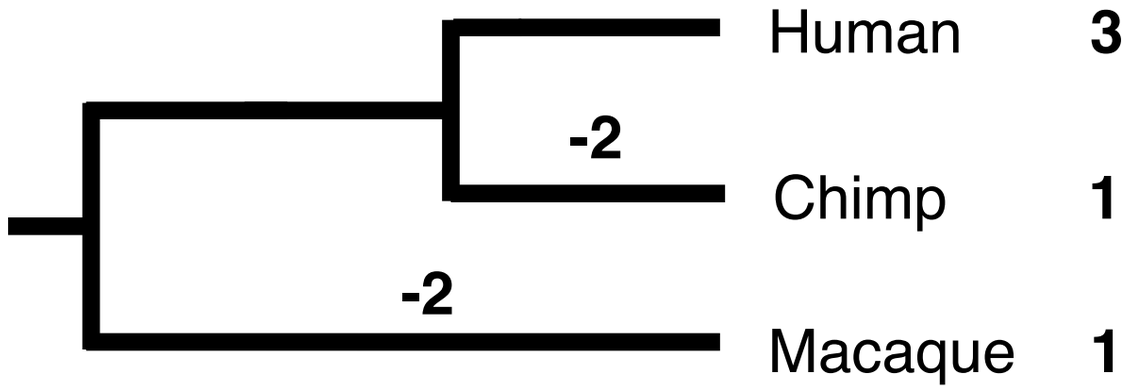
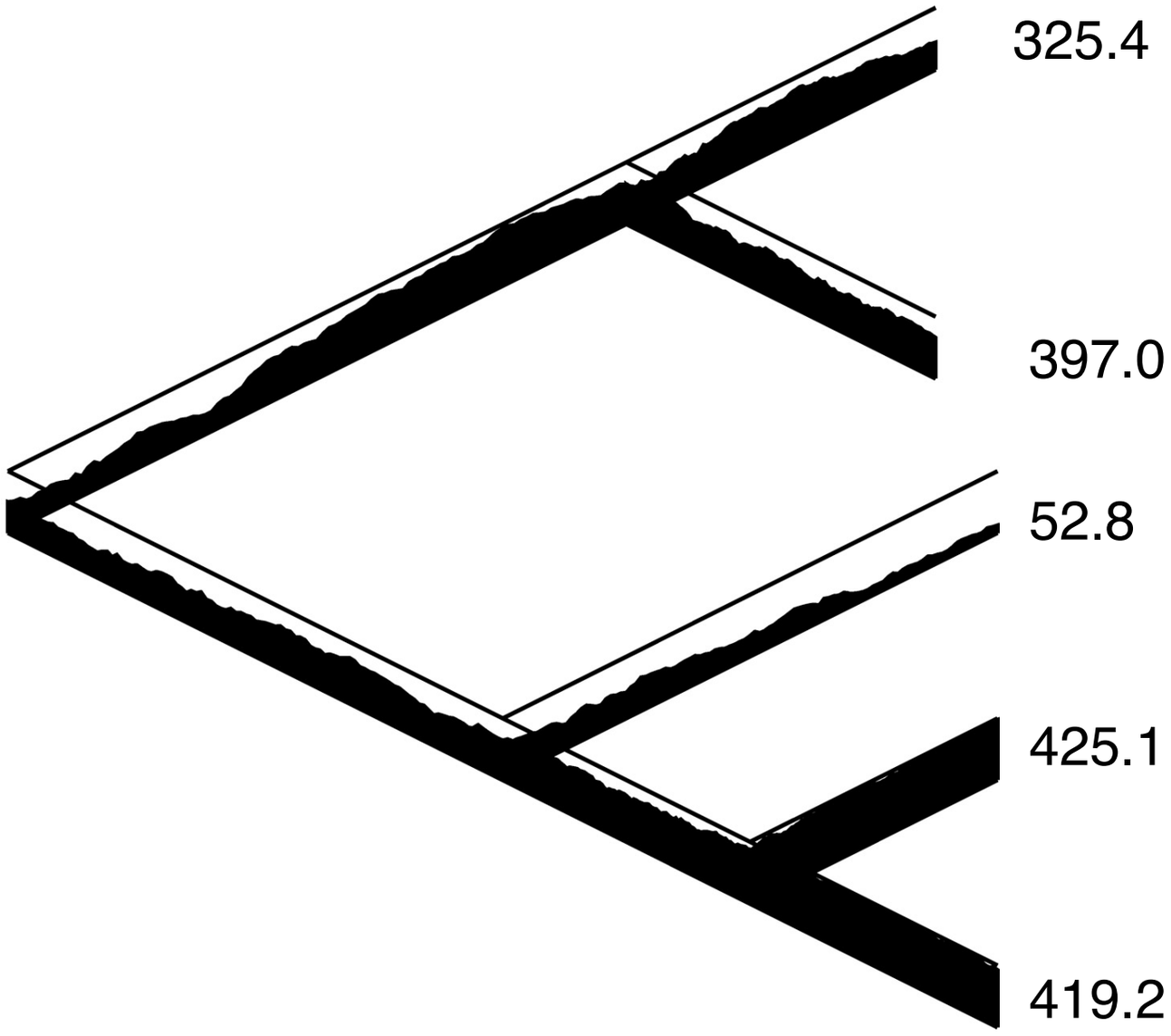


# Quantitative trait models on trees




Felsenstein (2005)

# A model for gene family evolution

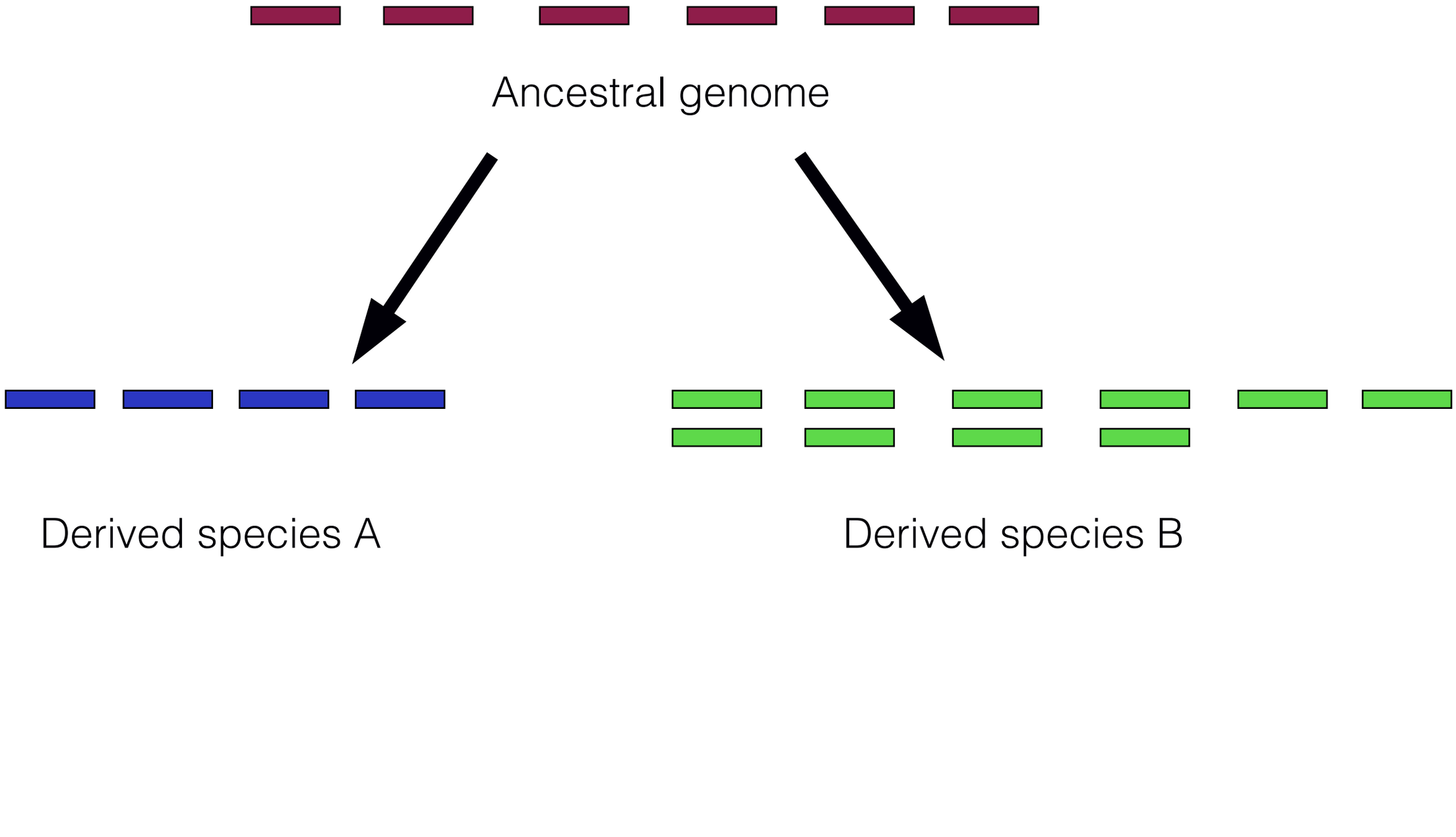
Homogeneous birth and death process

Birth = duplication

Death = loss

Hahn et al. (2005)

# A model for gene family evolution



There are no true models, only helpful ones.

--G.E.P. Box

No model, no inference.

--J. Felsenstein

# A model for gene family evolution

Birth-Death transition probability (Bailey 1964):

$$P(X(t) = c \mid X(0) = s) = \sum_{j=0}^{\min(s,c)} \binom{s}{j} \binom{s+c-j-1}{s-1} \alpha^{s-j} \beta^{c-j} (1-\alpha-\beta)^j$$

$$\alpha = \frac{\mu(e^{(\lambda-\mu)t} - 1)}{\lambda e^{(\lambda-\mu)t} - \mu}, \quad \beta = \frac{\lambda(e^{(\lambda-\mu)t} - 1)}{\lambda e^{(\lambda-\mu)t} - \mu}$$

The necessary parameters:

-Current family size

-Ancestral family size

-Time since divergence

-Birth and death rates per gene

# A model for gene family evolution

Assuming birth and death rates are equal (Hahn et al. 2005):

$$P(X(t) = c | X(0) = s) = \sum_{j=0}^{\min(s,c)} \binom{s}{j}\binom{s+c-j-1}{s-1}\alpha^{s+c-2j}(1-2\alpha)^j,$$

$$\alpha = \frac{\lambda t}{1+\lambda t}$$

The necessary parameters:

-Current family size

-Ancestral family size

-Time since divergence

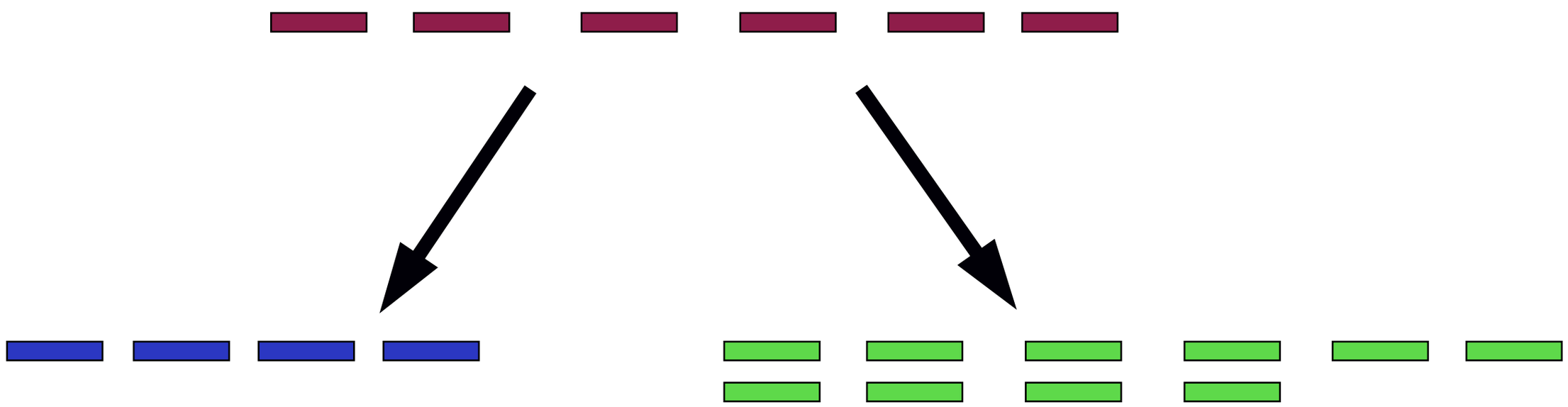
-Birth and death rates per gene

# A model for gene family evolution

Assuming birth and death rates are equal:

$$\mathrm{Mean}(X(t)|X(0)=s)=s,$$

$$\mathrm{Var}(X(t)|X(0)=s)=2s\lambda t.$$



# A model for gene family evolution

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The necessary parameters:

-Current family size

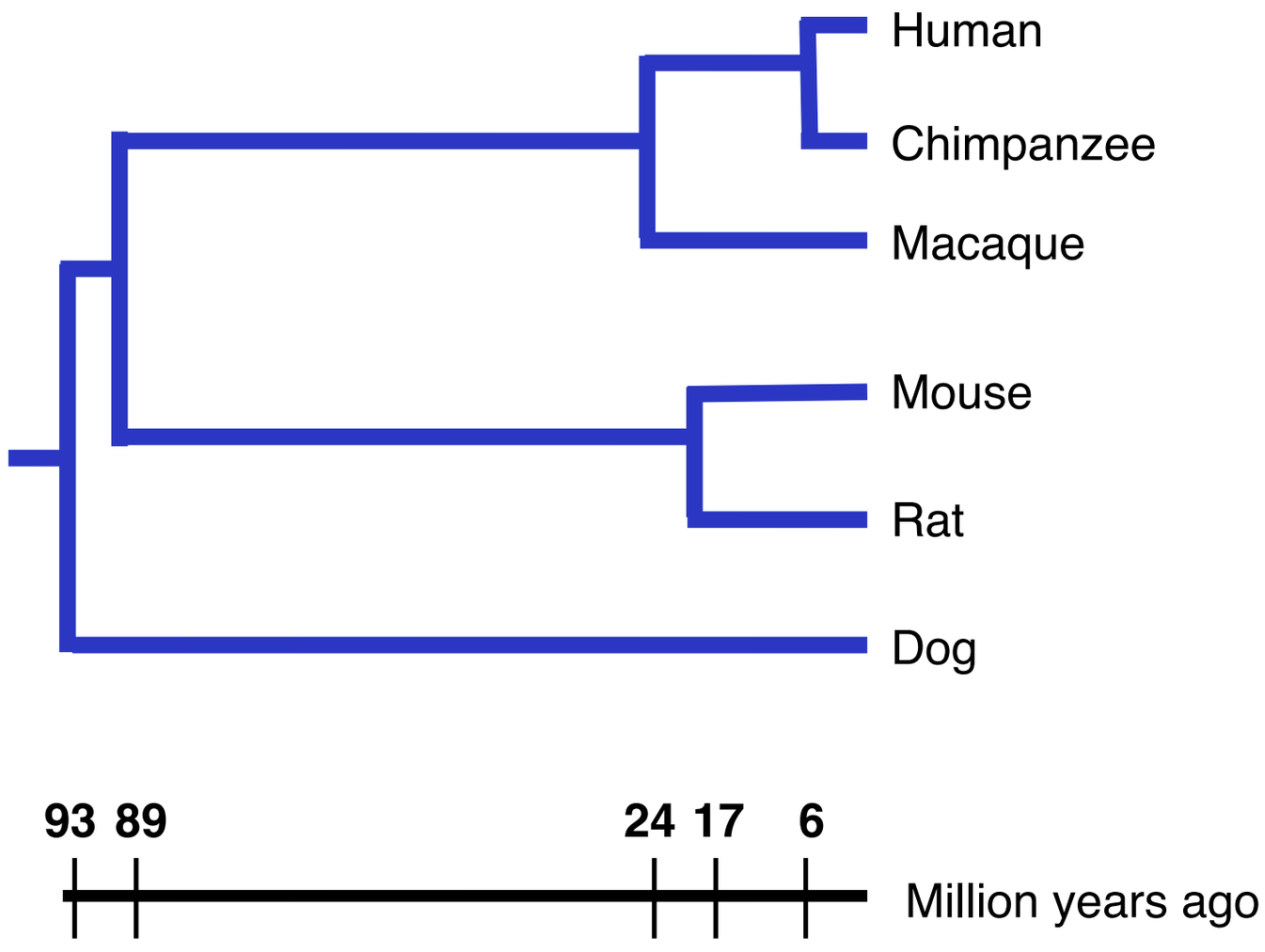
-Ancestral family size

-Time since divergence

-Birth and death rates per gene

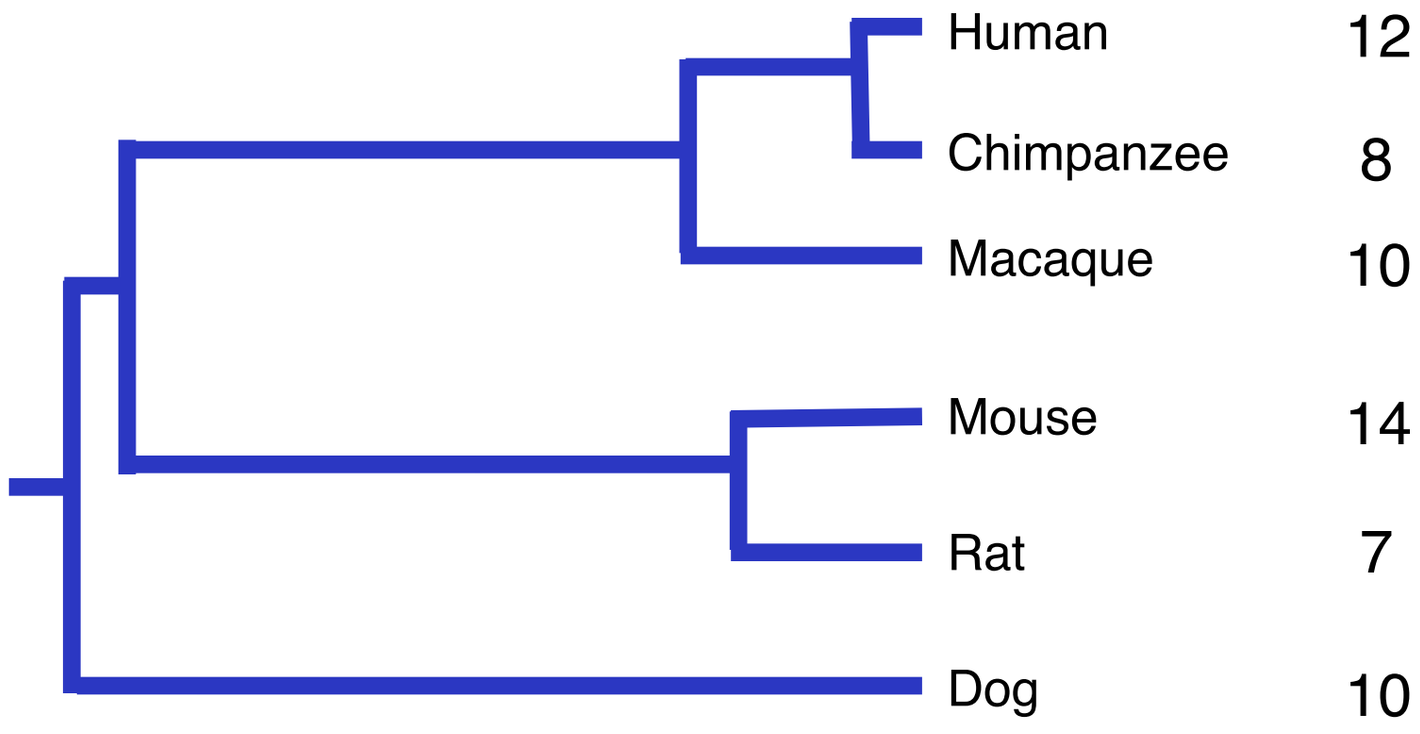
# A model for gene family evolution

Time since divergence
(ultrametric tree)



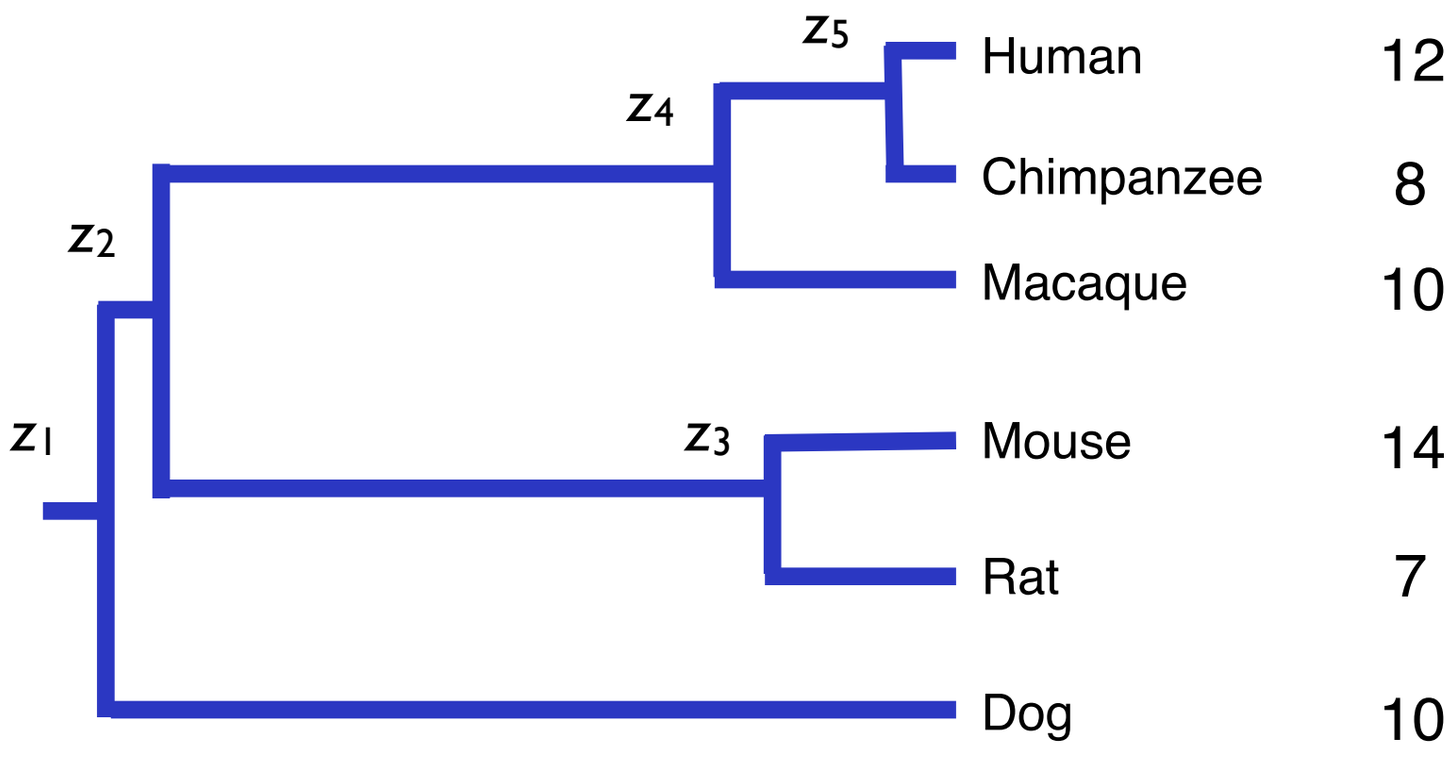
# A model for gene family evolution

Current family sizes



# A model for gene family evolution

Ancestral family sizes and birth and death rates (λ, μ) can be inferred using likelihood!



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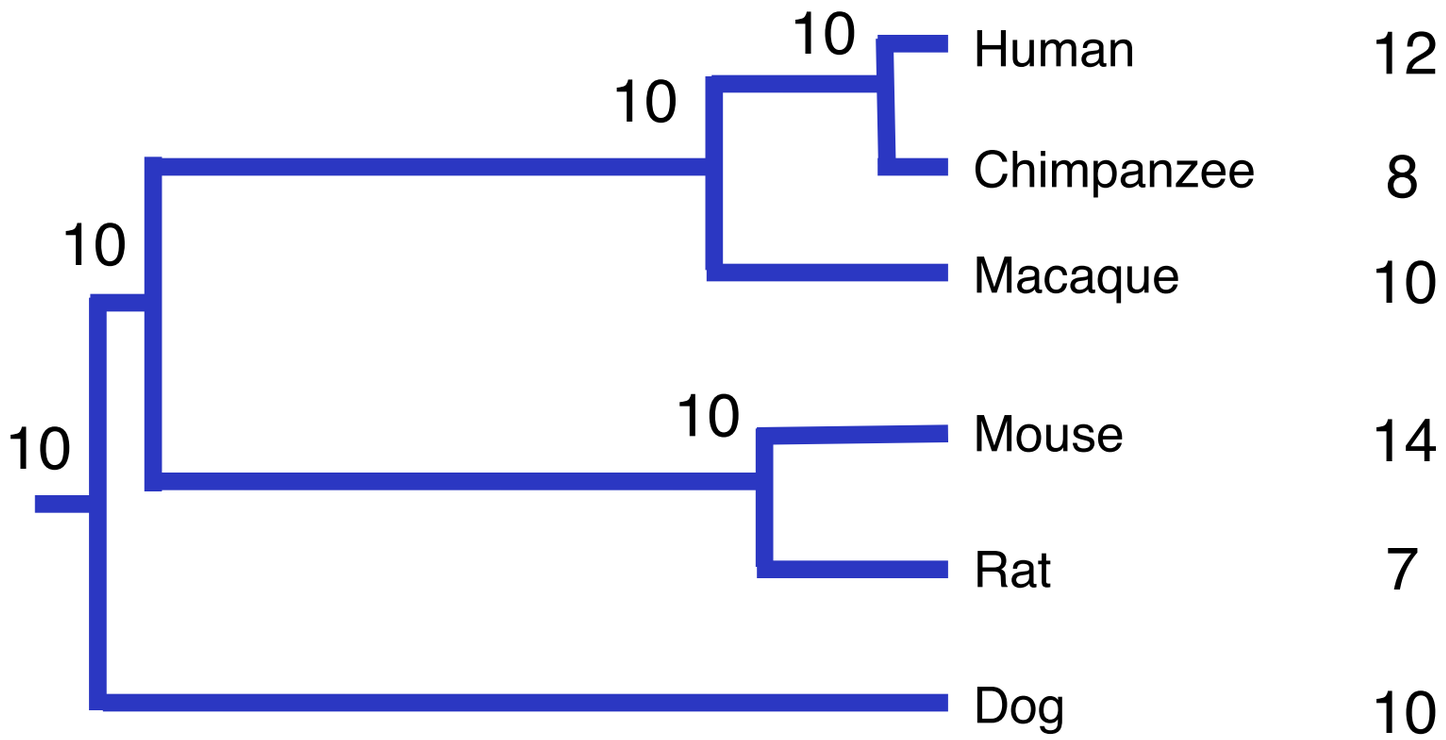
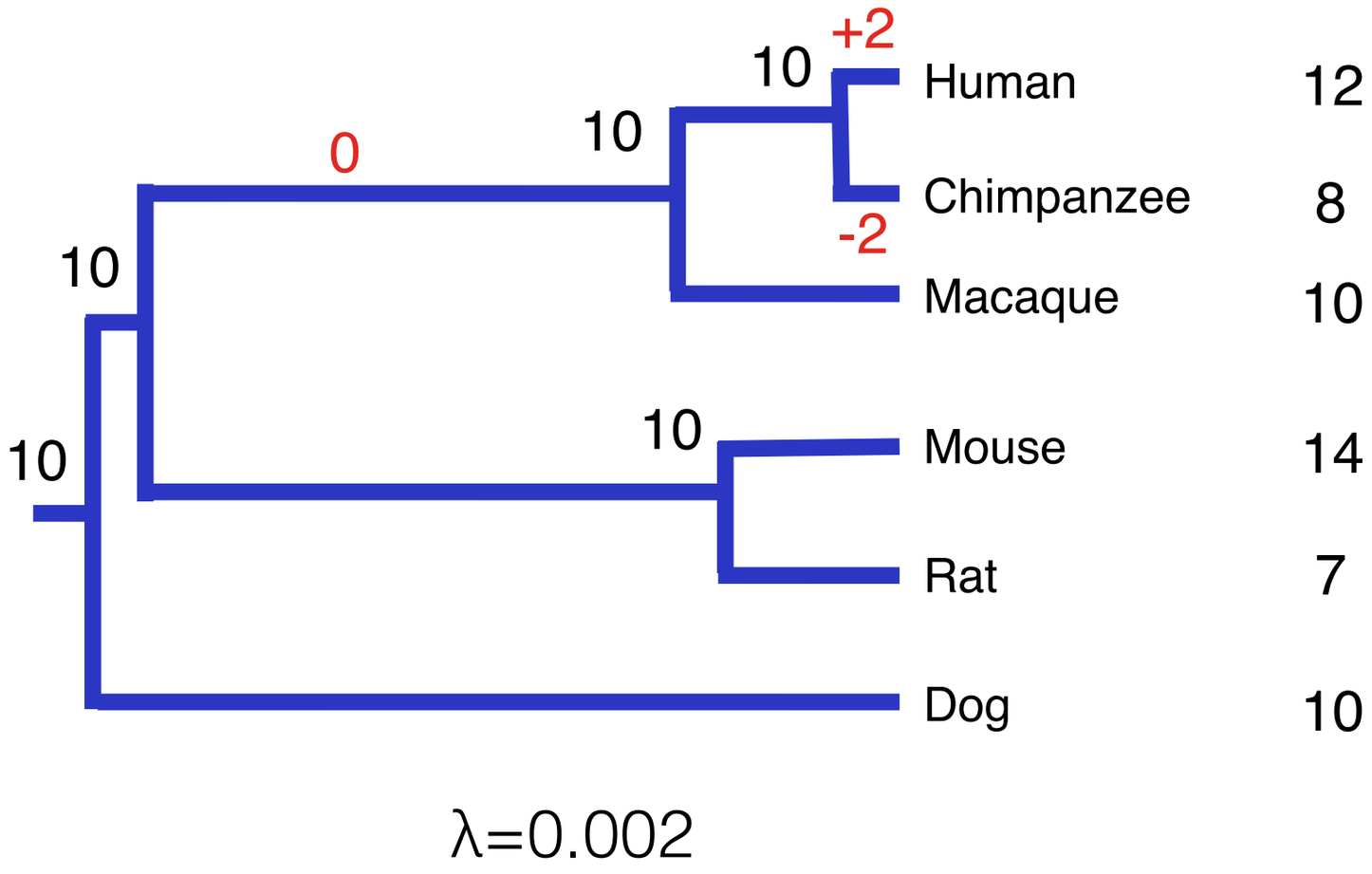



λ=0.002

(assuming birth=death)

# A model for gene family evolution

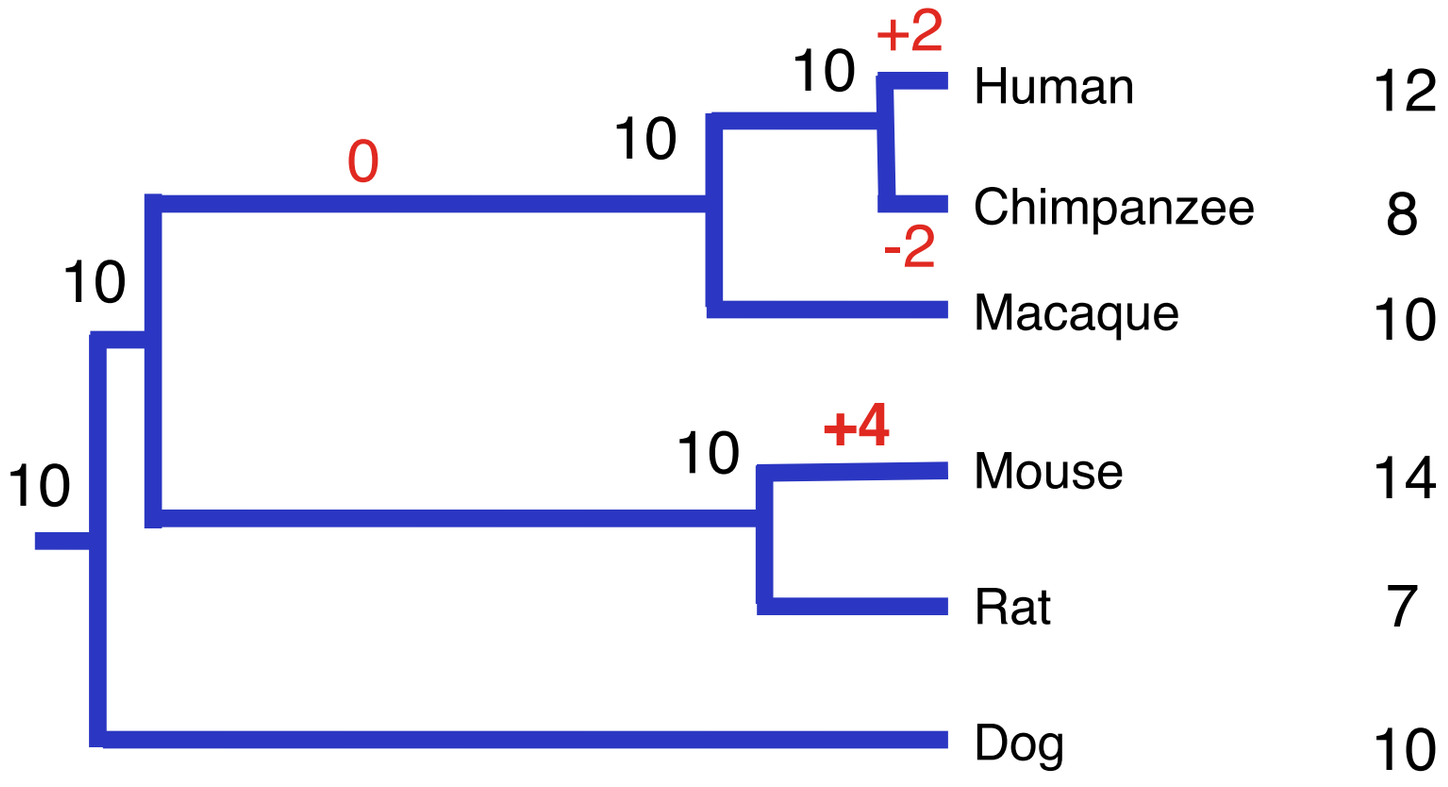
With this information we can infer changes in gene family size…




λ=0.002

# A model for gene family evolution

…and identify rapidly evolving families/lineages




λ=0.002

We use Monte Carlo simulations to find families with low *P*-values and branches with large numbers of changes

# A model for gene family evolution

Assumptions:

-Single-gene changes at a time*

-All families have a representative at the root*

-birth=death**

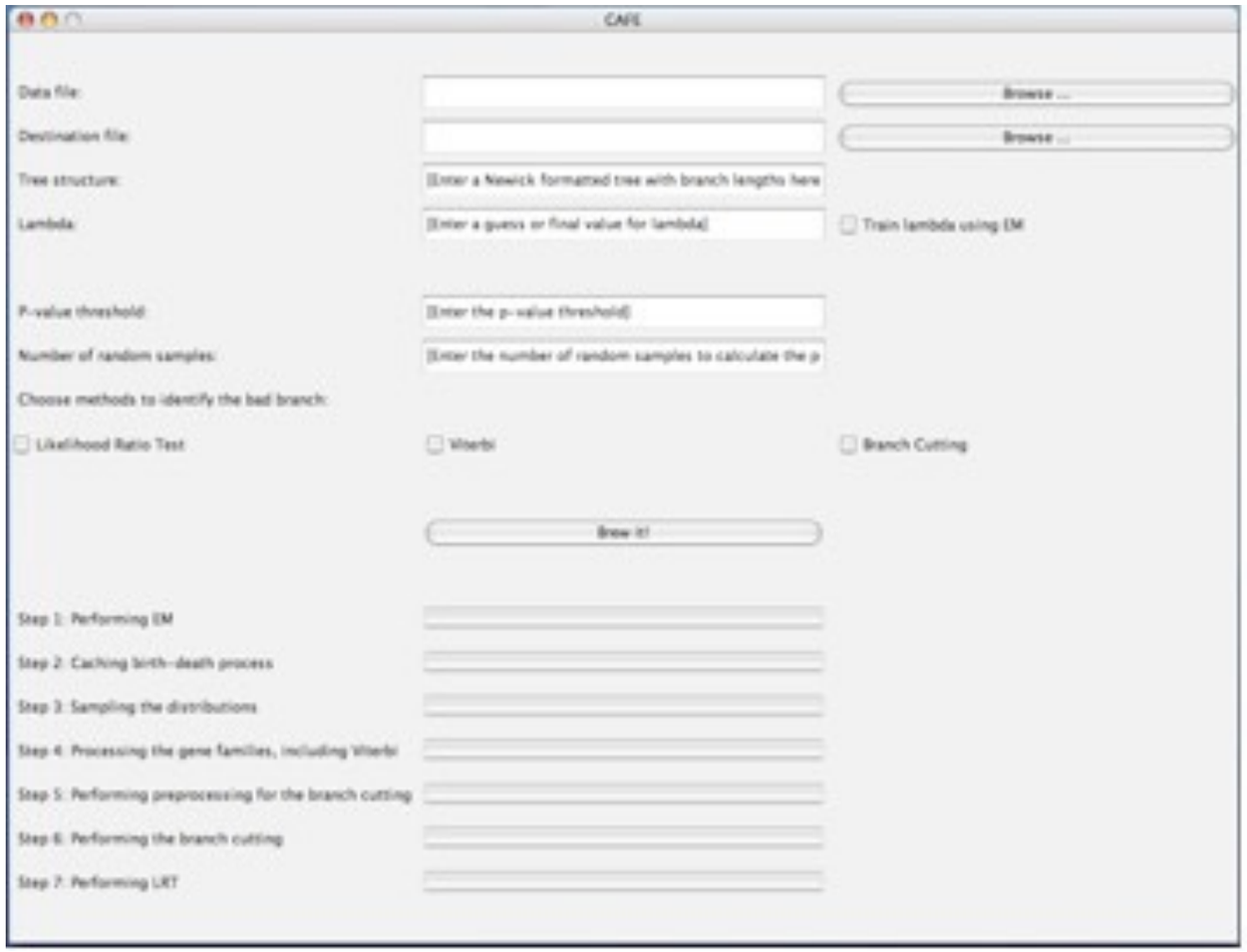
-All lineages have same rate**

-No error in our observations**

-All families have equal per-gene transition probabilities***

# CAFE

## (Computational Analysis of gene Family Evolution)

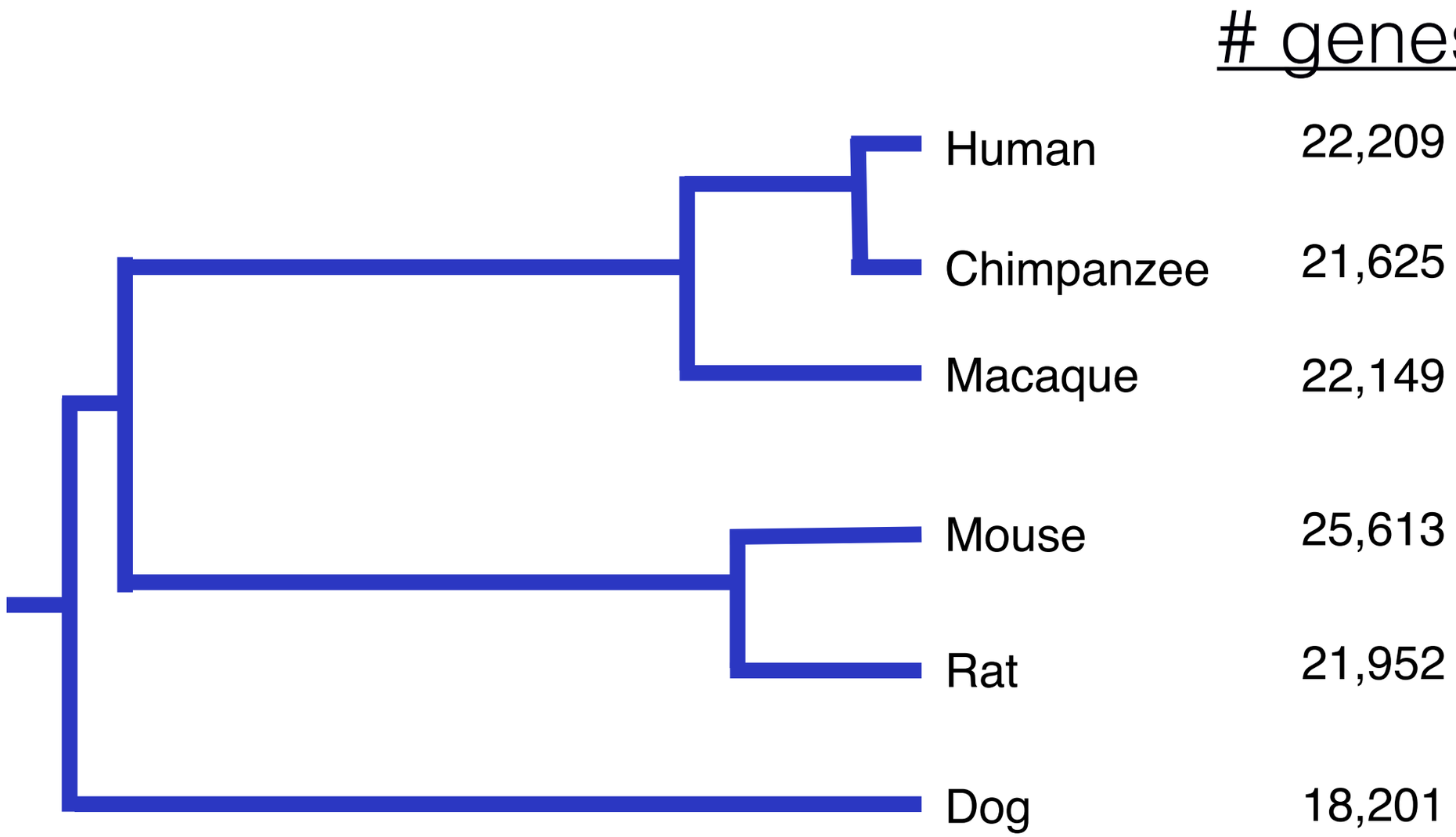



De Bie et al. (2006)

# Using CAFE

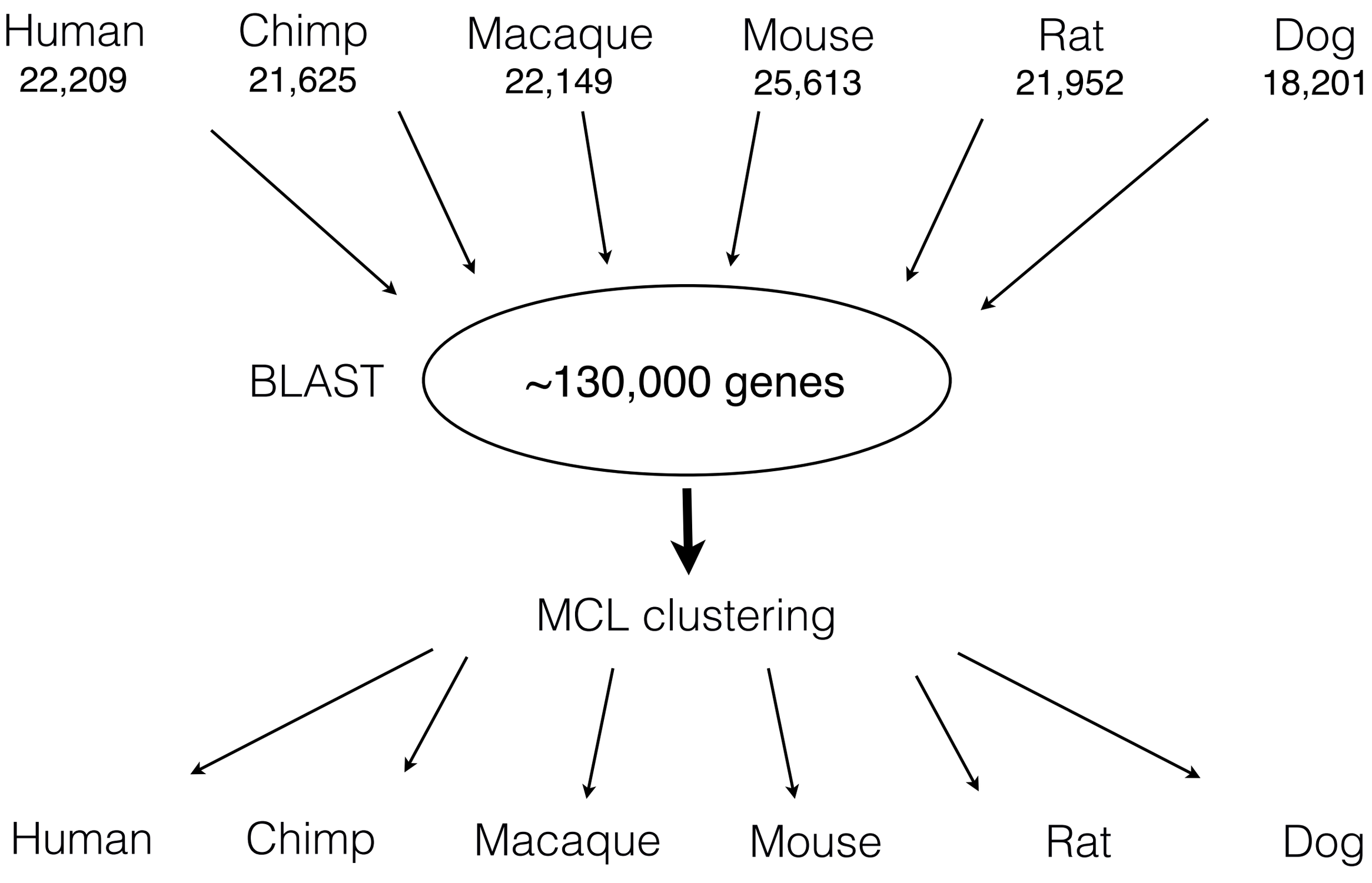
Now let's work through a dataset and elaborations on the basic model…

# Genome size in mammals

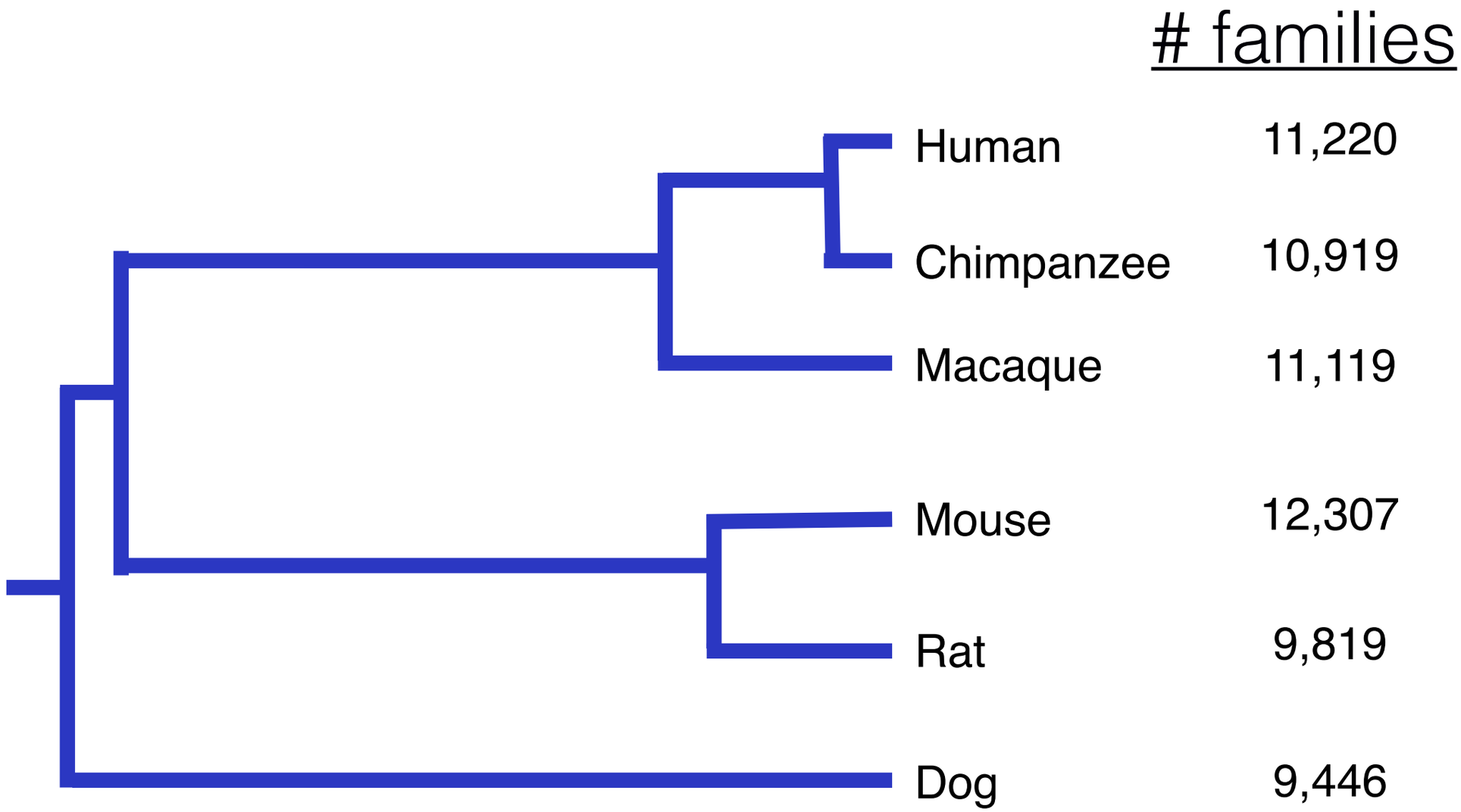



All data from Ensembl

# Constructing gene families



# Gene families in mammals



# Annotation artifacts

Some gene families are present in only one copy, in only one species.

| Human | Chimp | Mouse | Rat | Dog |
|---|---|---|---|---|
| 476 | 549 | 2,673 | 620 | 240 |

We remove these from further analyses.

# Present at the root?

9,990 gene families were inferred to have been present in the mammalian most recent common ancestor (MRCA).

# Genome evolution in mammals

- 5,285 of 9,990 gene families have changed in size
- We estimate that the MRCA contained 19,523 genes in these families

Demuth et al. (2006)

# The rate of gene gain and loss

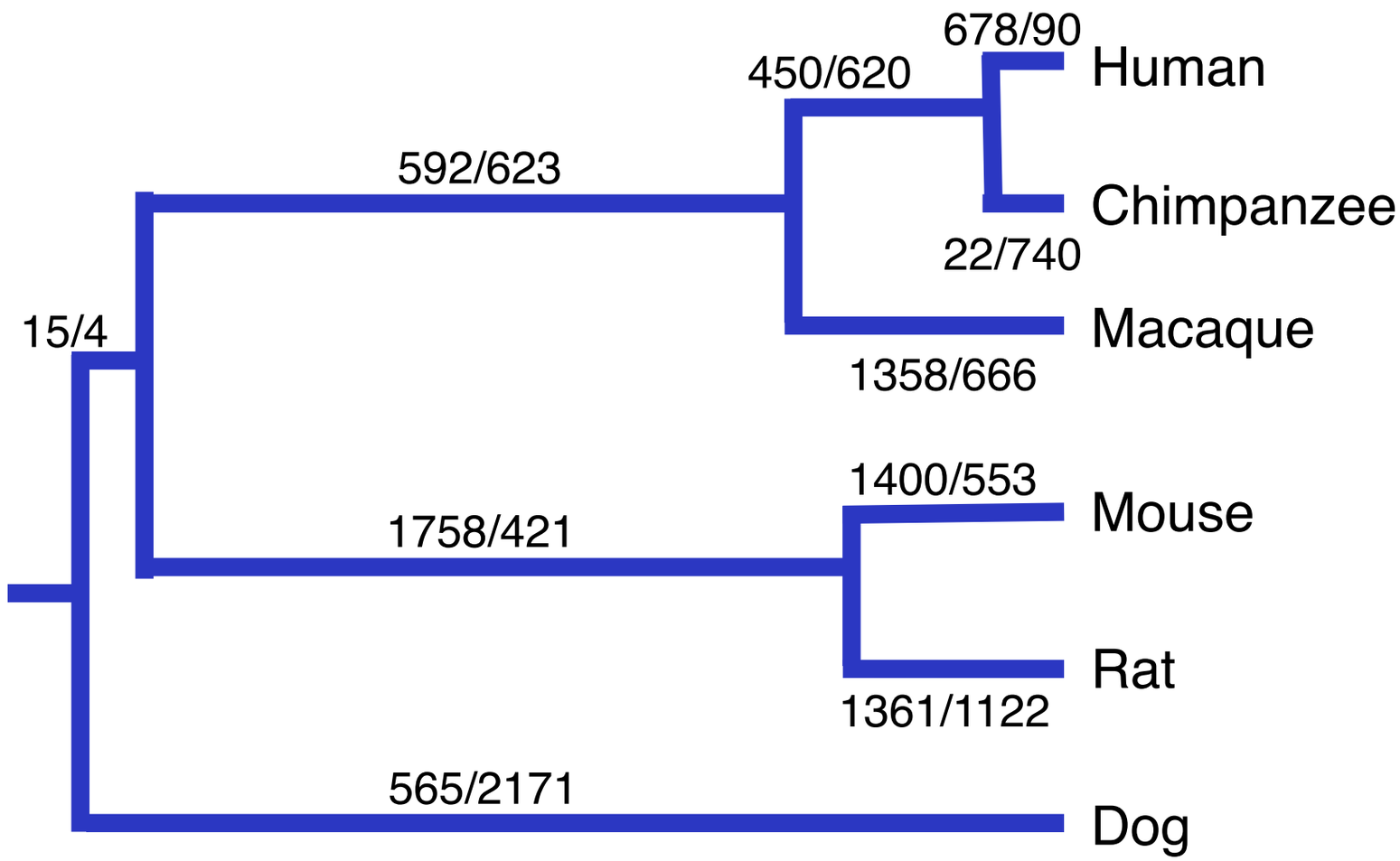
We estimate λ=0.0017 /gene/my
across the whole tree

This number is very similar to estimates by other groups for just the rate of gene duplication.

mouse and rat:  0.0013-0.0026 (Lynch and Conery 2003; Gibbs et al. 2004)

human: 0.009 (Lynch and Conery 2003)

# Gene gain and loss in the great apes



# Gene gain and loss in the great apes

In humans:

- 675 genes have been gained

In chimpanzees:

- 740 genes have been lost

$$\begin{array}{r} + \\ \hline 1415 \end{array}$$

1,415 human genes not found in chimps!

# Reality check

Do these numbers make sense?

# Back-of-the-envelope calculations

Lynch and Conery (2000, 2003):

rate of gene duplication in humans is 0.009/gene/my

22,000 x 0.009 dupes/gene/my x 5 million years

= 990 new gene duplicates

If genomes are not constantly expanding, expect approximately equal number of gene losses (990).

= 1,980 human genes not shared with chimps [1,415]

# Differences between human and chimp

There are a large number of differences between humans and chimps (6% at the gene level).

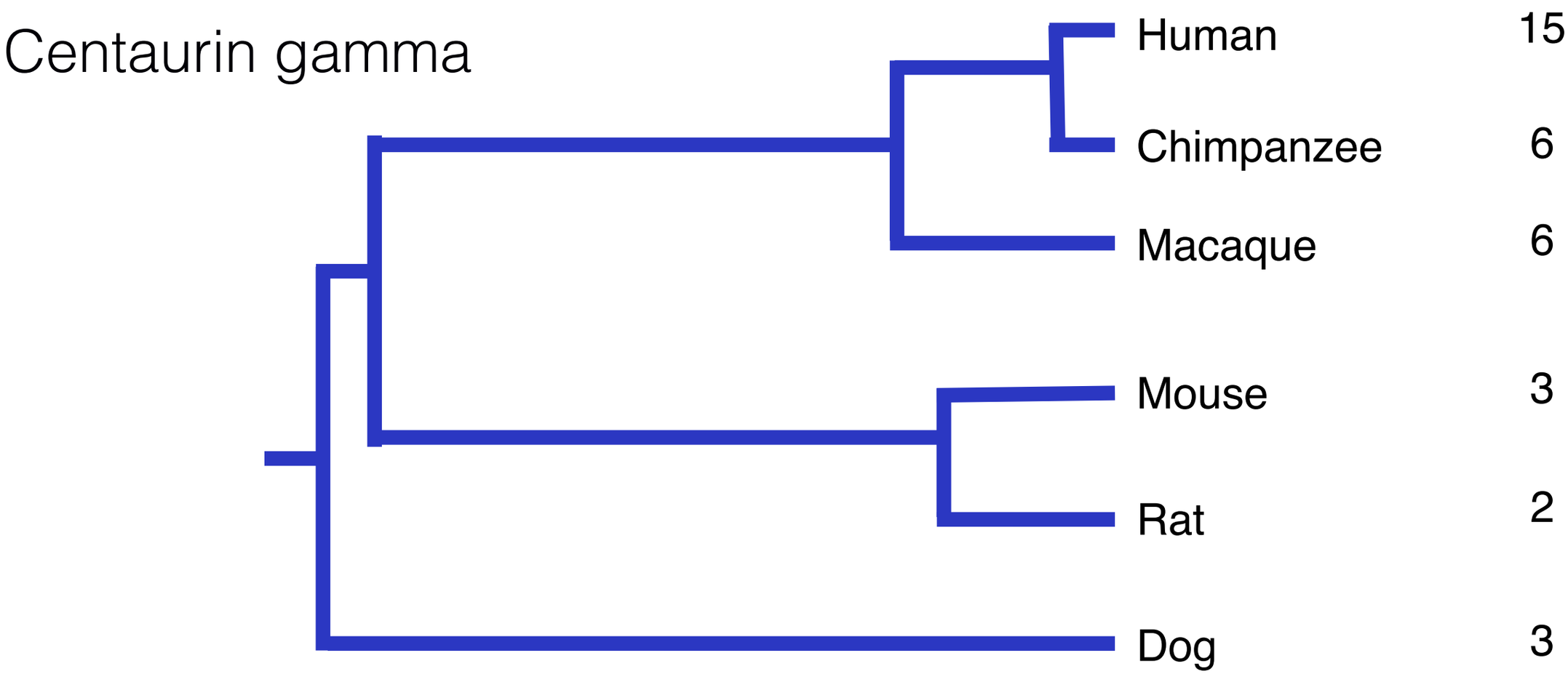
Losses and gains of genes are occurring in the primates at high rates.

The genomic revolving door

# Accelerated evolution of gene families

Of the 9,990 families inferred to be present  in the mammalian MRCA, we found 180 with $P<0.0001$.

# Accelerated evolution of gene families



# Accelerated evolution of gene families

The most common biological functions assigned to the significant families include:

immune defense

brain and neuronal development

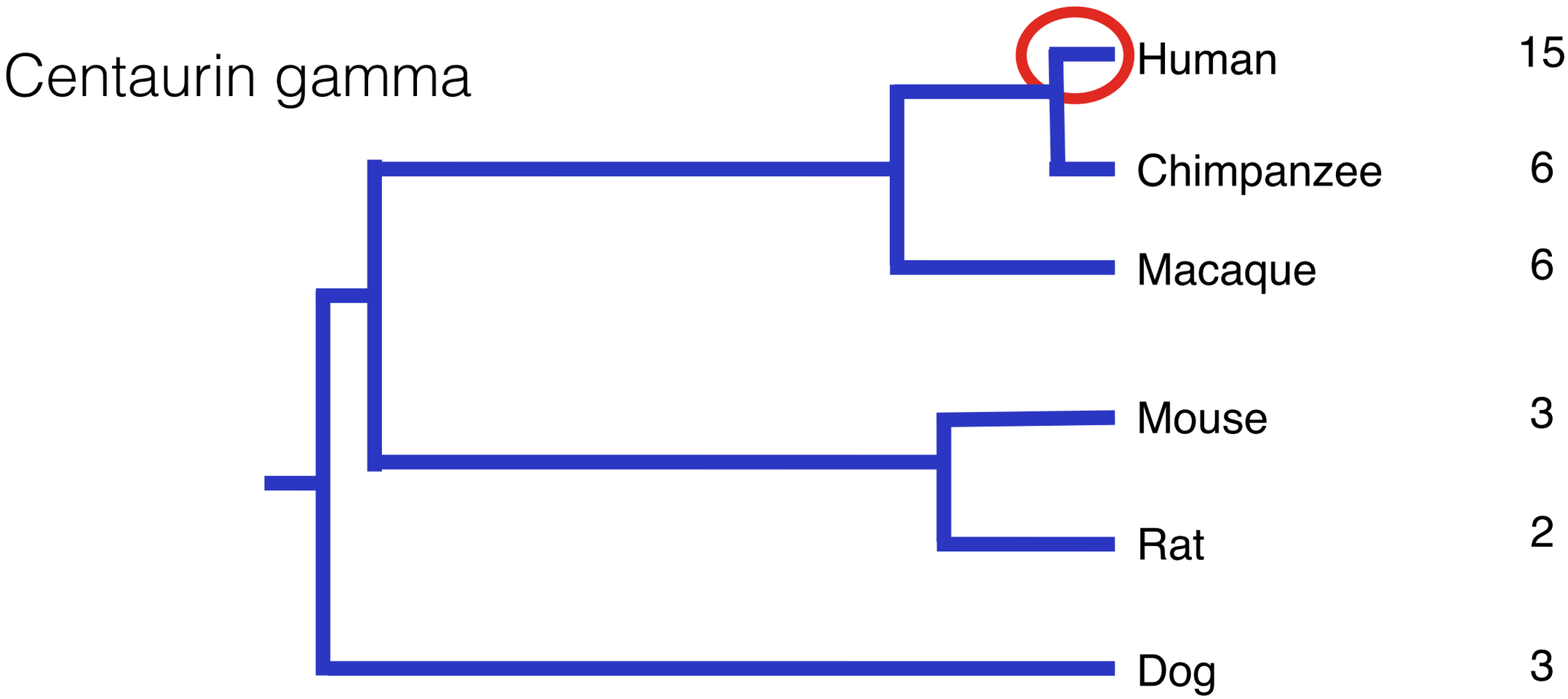
intercellular transport

Interestingly, these are the same functions that evolve rapidly at the nucleotide level in primates.

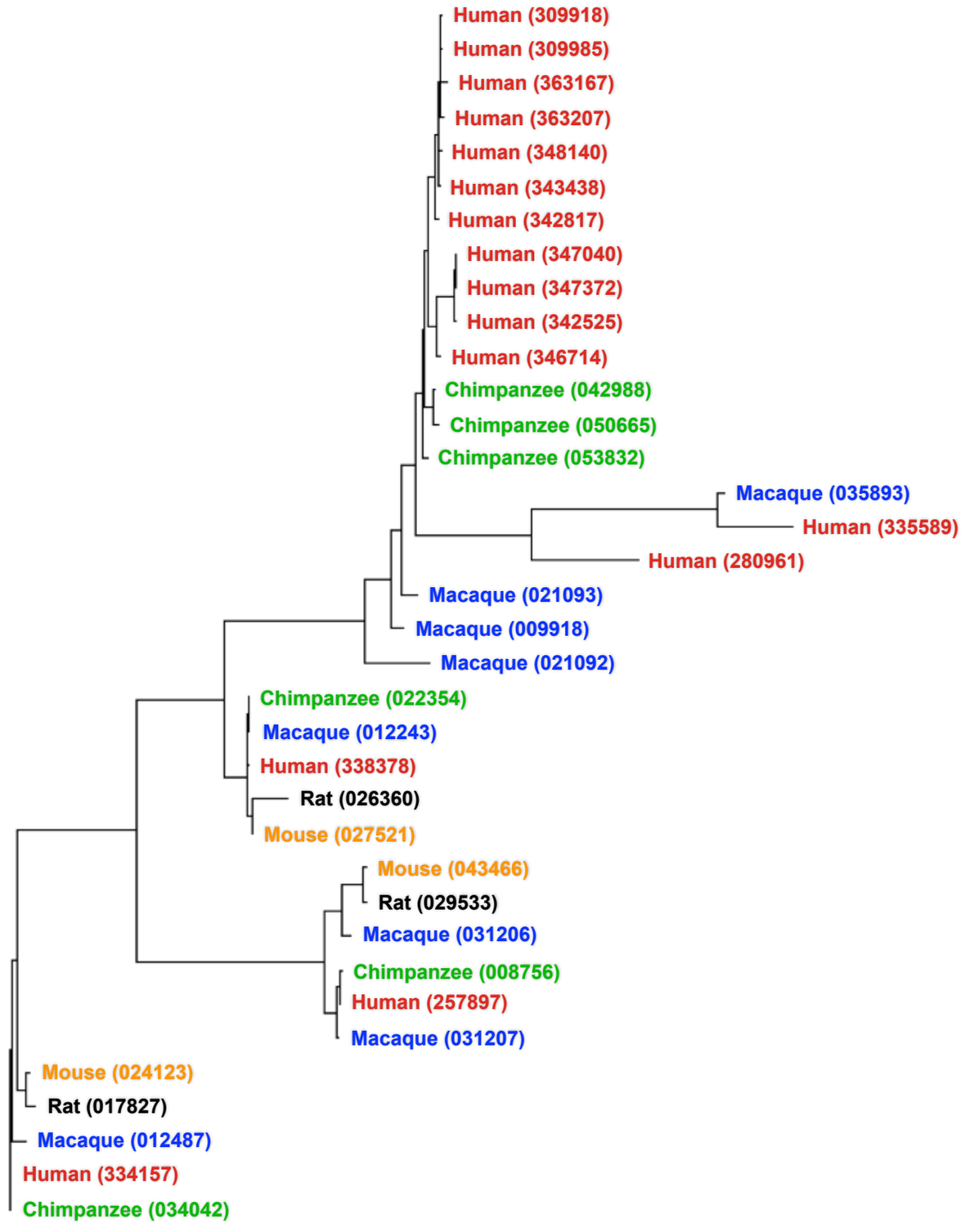
# Accelerated evolution of gene families

Using CAFE, one can identify which branches of the tree show the most unlikely changes in family size.

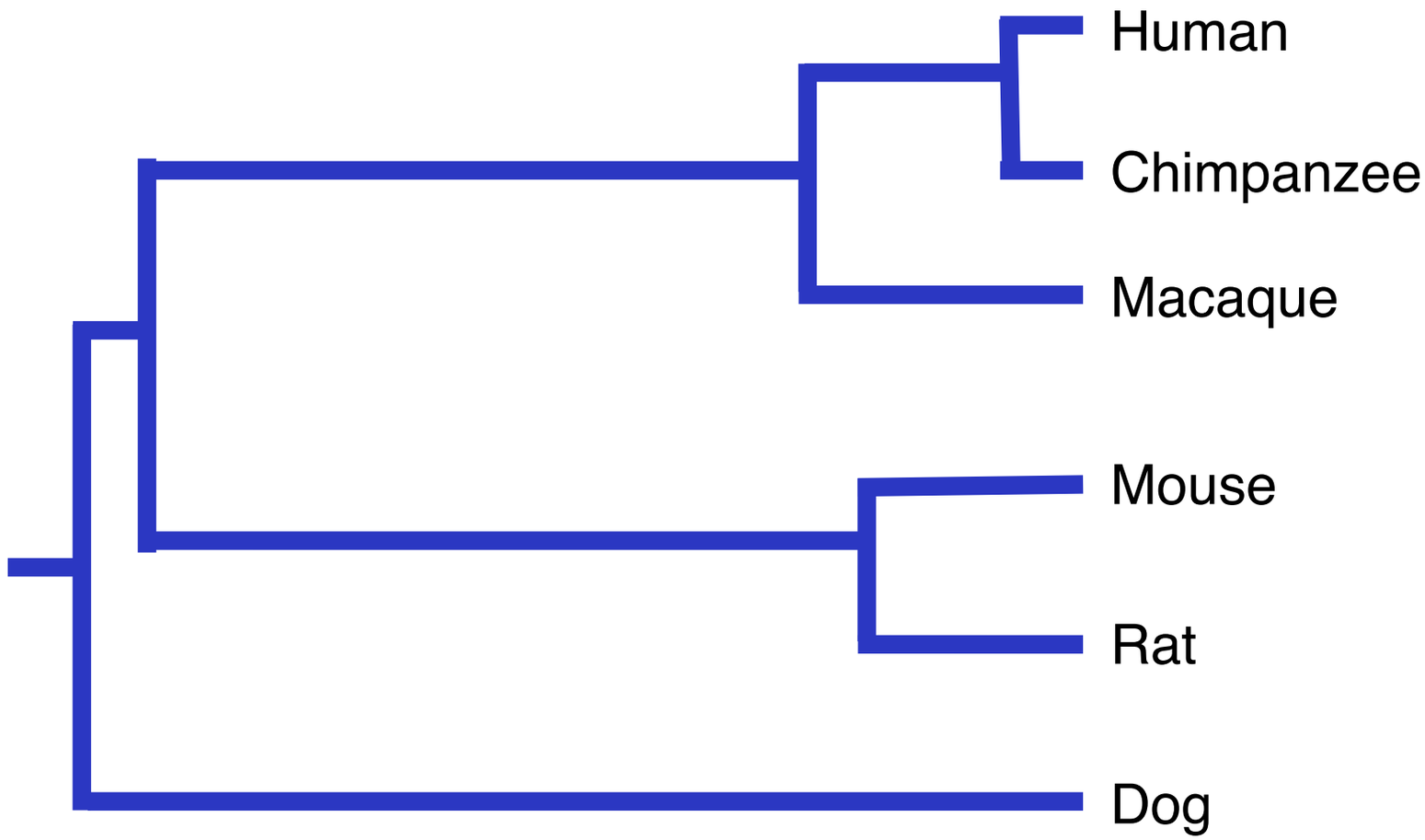
# Accelerated evolution of gene families



# Large expansion of Centaurin gamma in humans



# The rate of gene gain and loss



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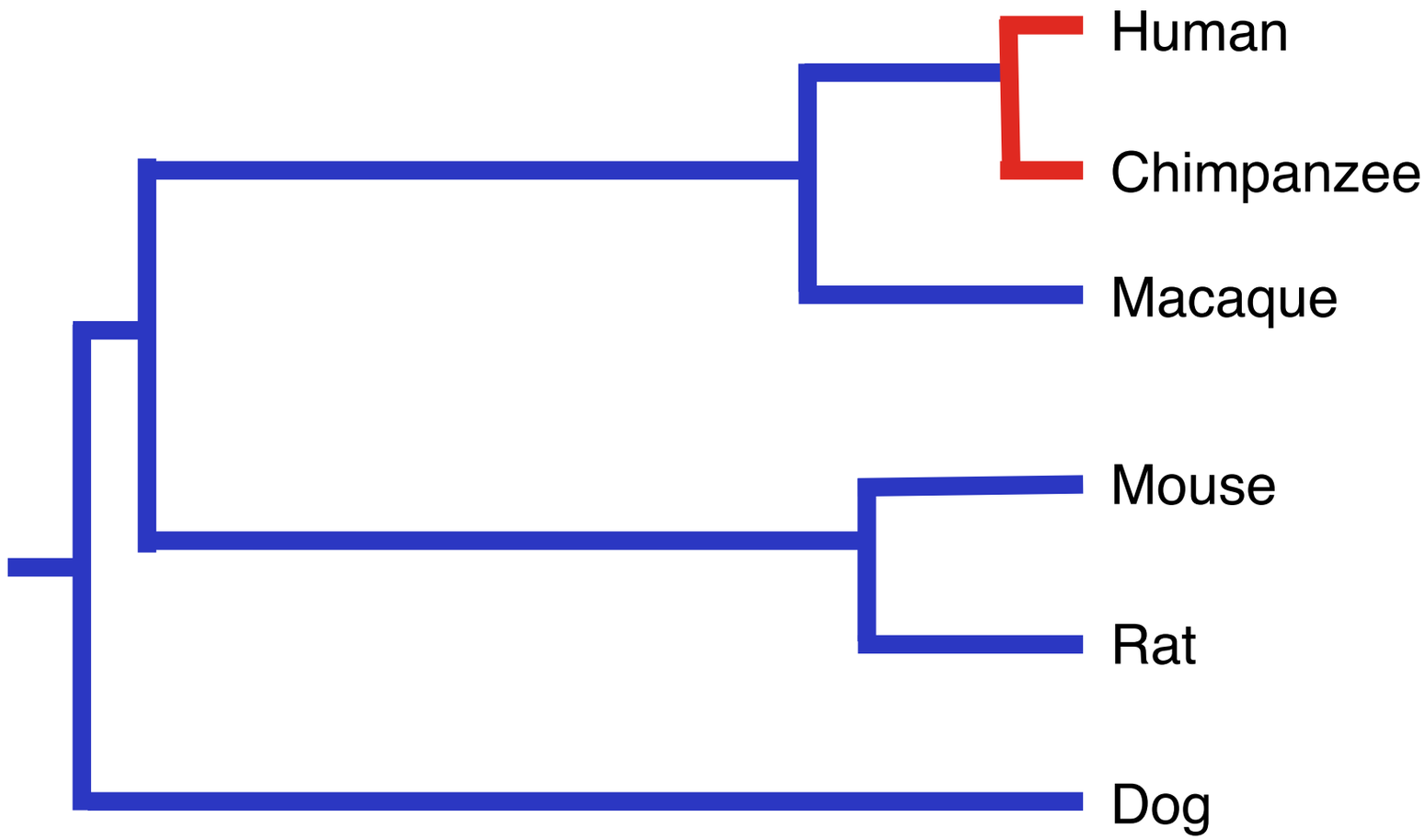
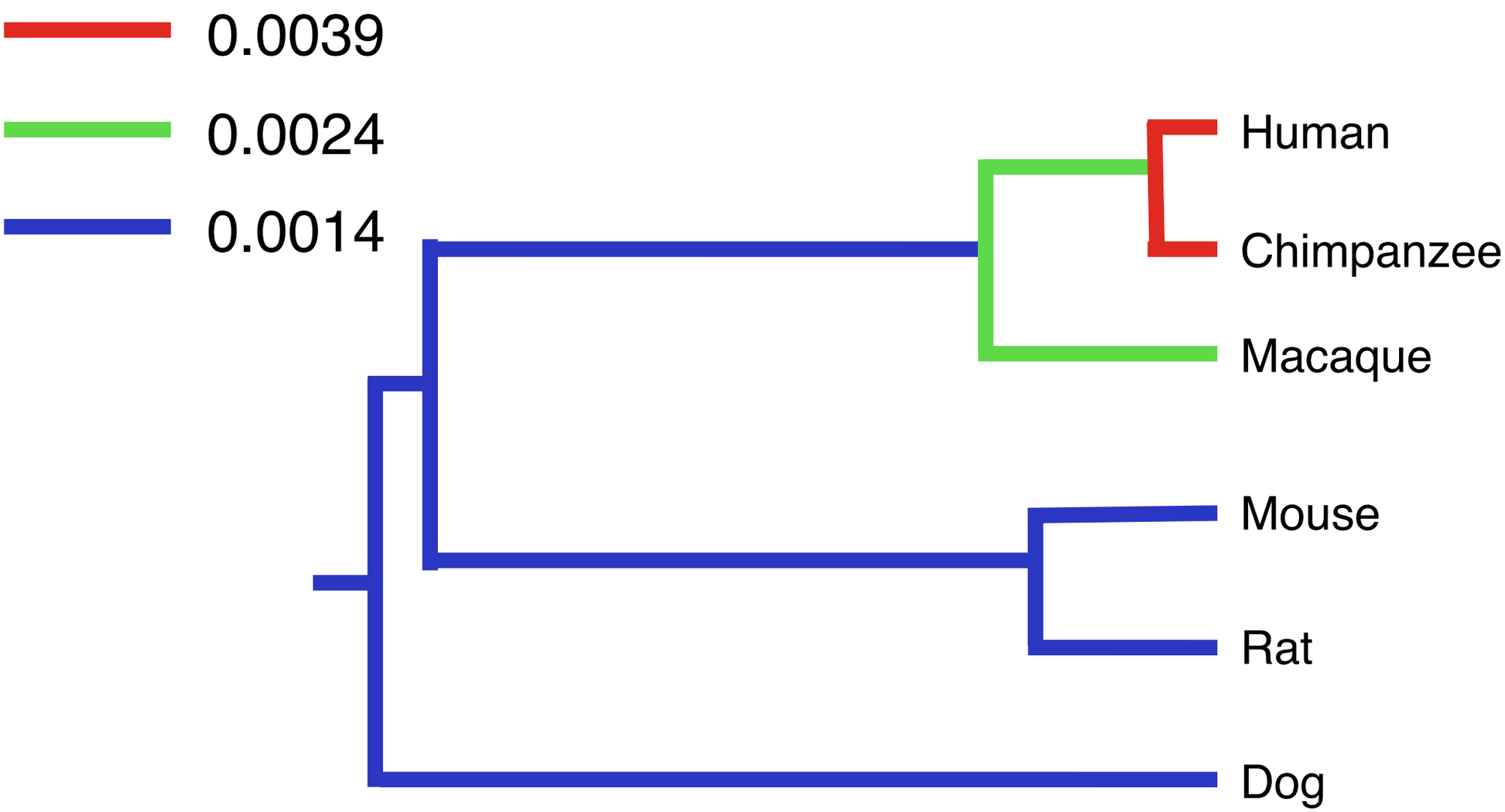



A 2-parameter model fits the data significantly better

# The rate of gene gain and loss

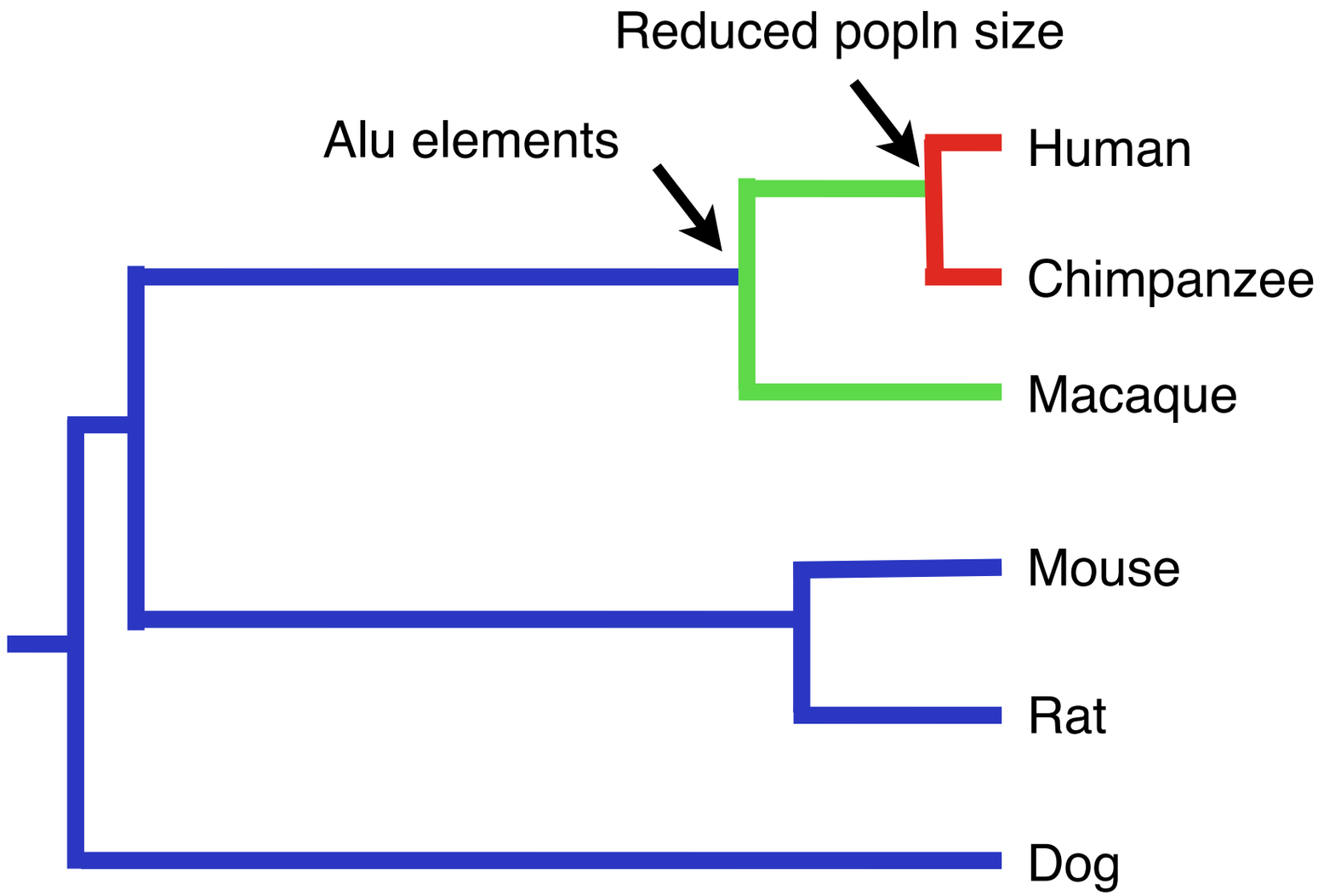



The rate of gain and loss in primates is 2-3 times higher than the rest of the mammals

# Accelerated rate of gene gain and loss in primates

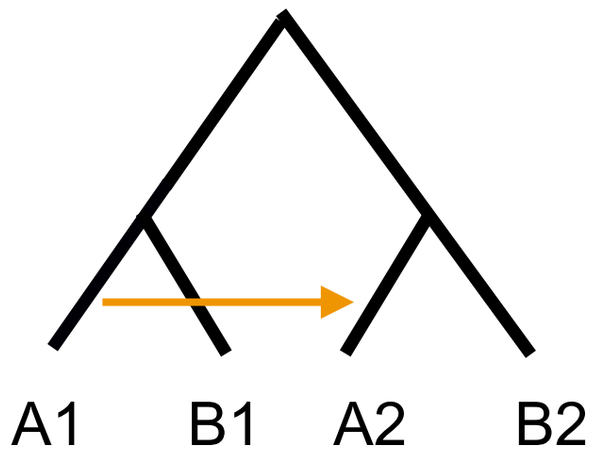
Why?

# Accelerated rate of gene gain and loss in primates

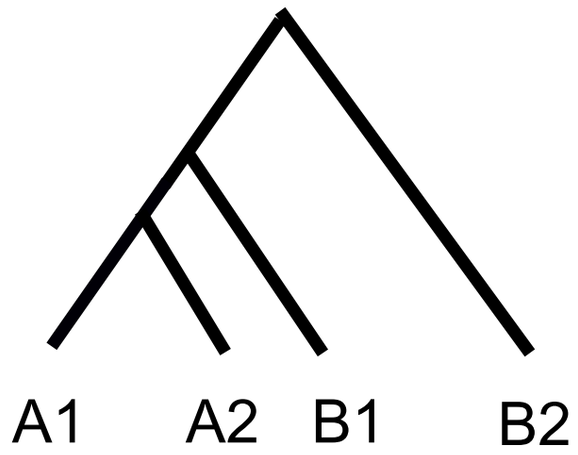


# Gene conversion

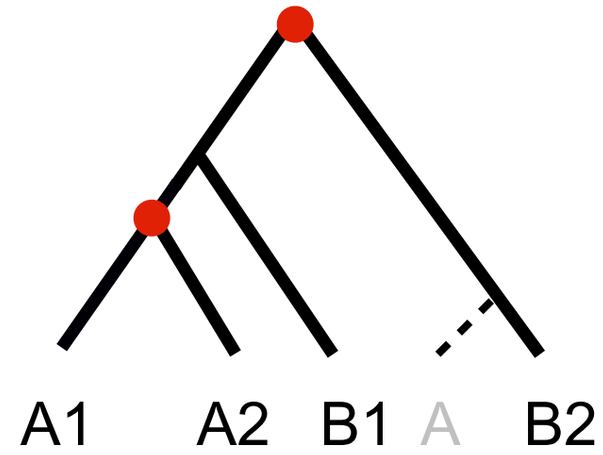
If there is gene conversion, reconciliation can result in extra duplications and losses




gene tree
(before conversion)



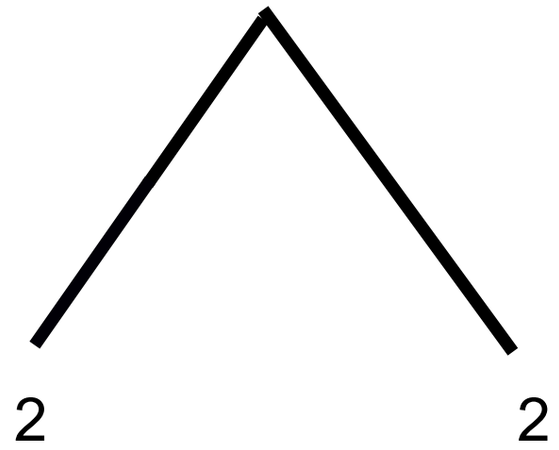

gene tree
(after conversion)



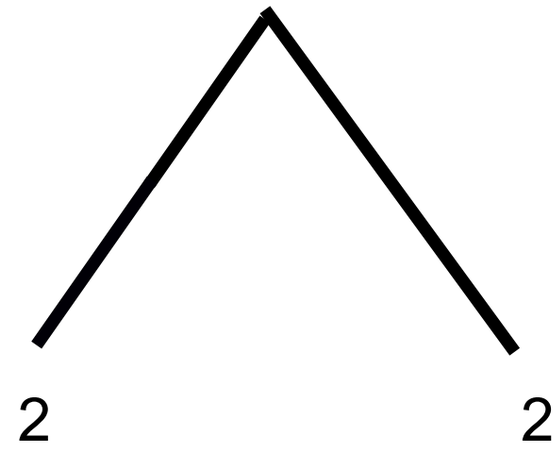

reconciled gene tree

# Gene conversion

But with “count” models, there is no change due to conversion:

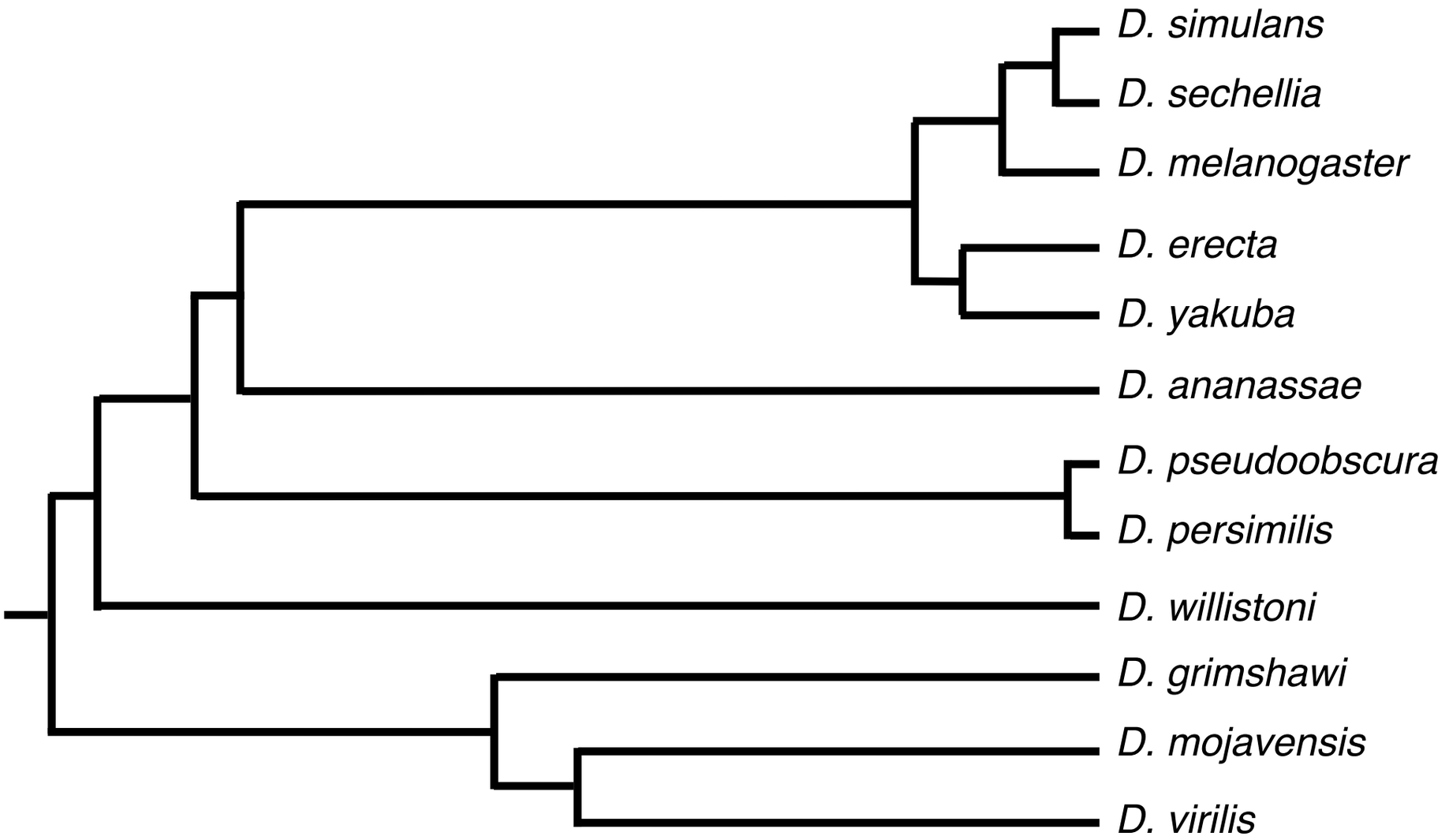



data
(before conversion)

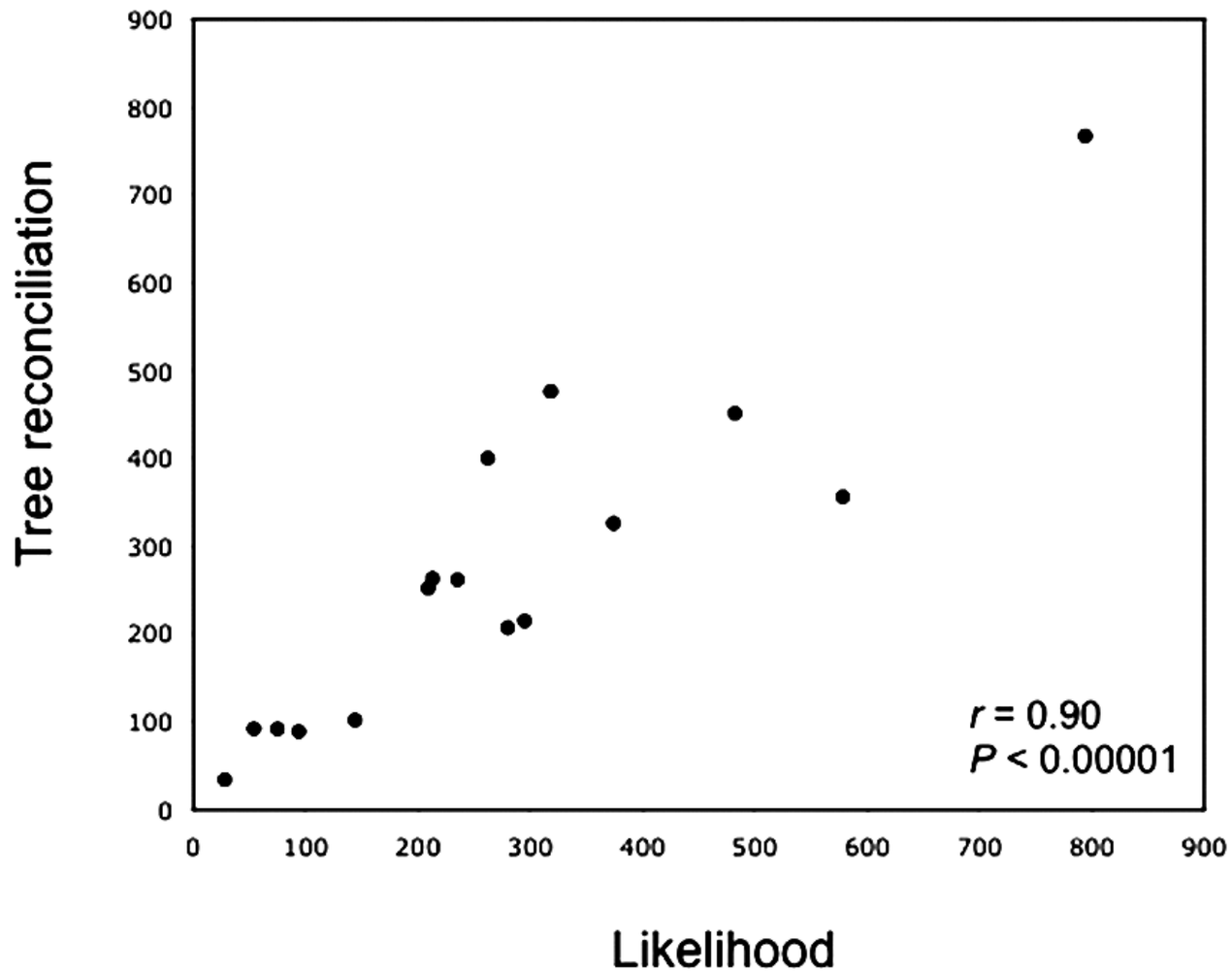



data
(after conversion)

# 12 *Drosophila* genomes

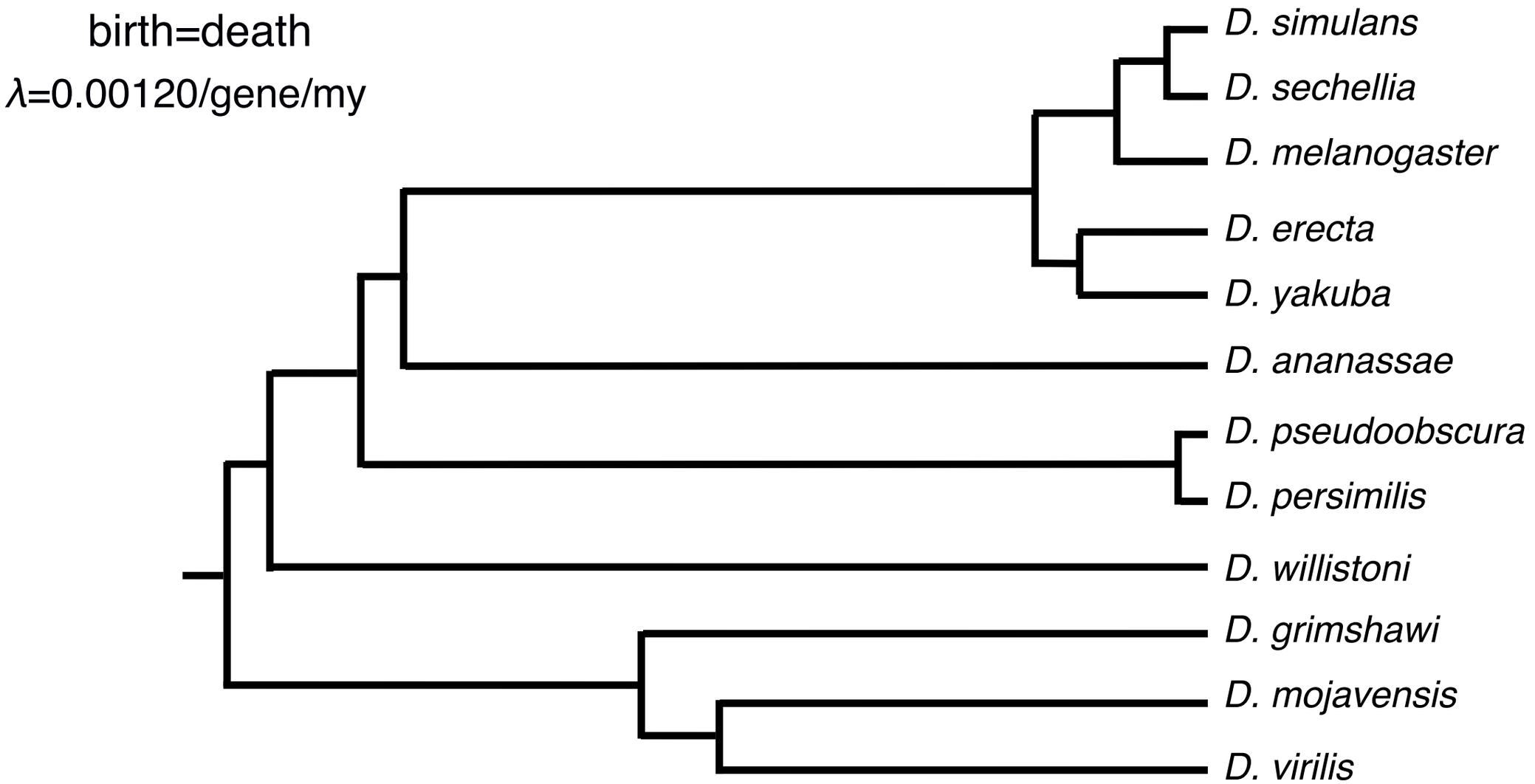


# Gene conversion




Hahn et al. (2007)

# Differences in rates of gain and loss

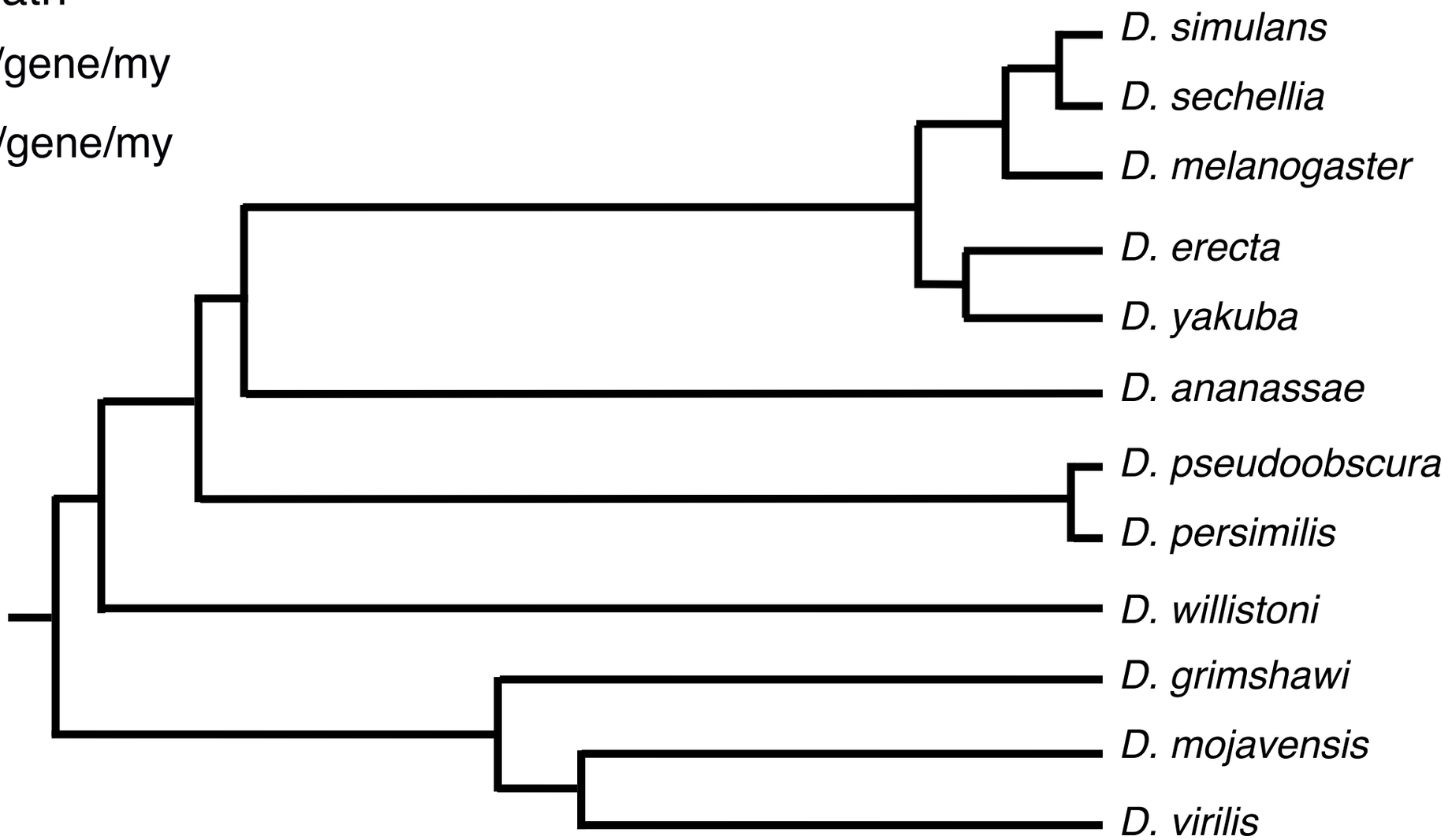


# Differences in rates of gain and loss

birth≠death

$\lambda$=0.00108/gene/my

$\mu$=0.00134/gene/my



# When genomes go bad

-2X Sanger: **very bad**, vastly undercounts genes

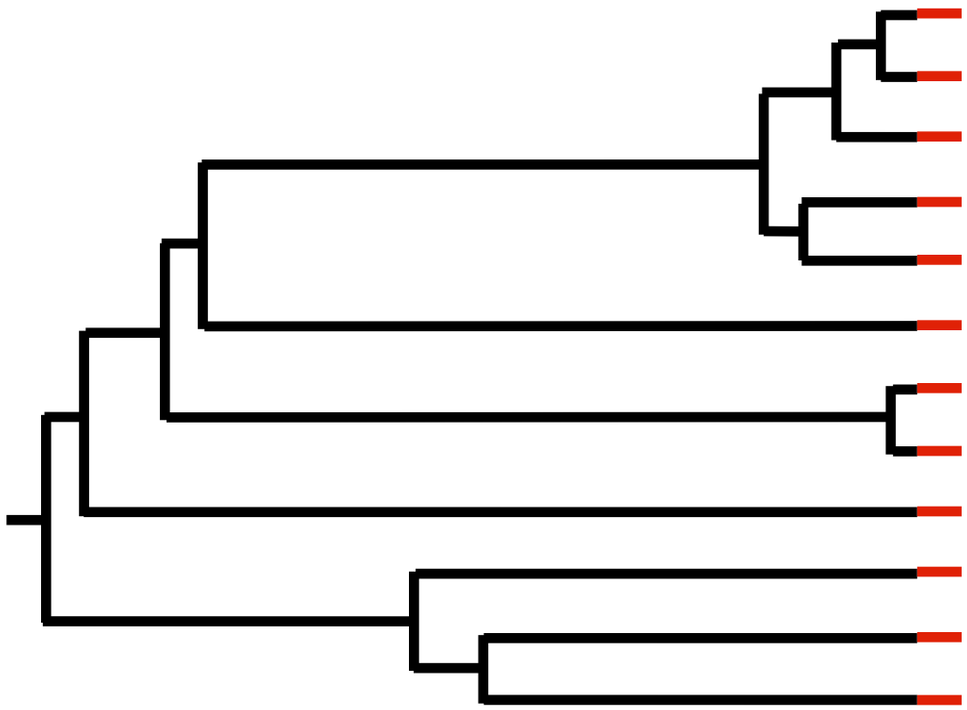
-12X 454: **pretty bad**, slightly overcounts

-82X Illumina: **bad**, but equally over- and undercounts

The best of these (Illumina) still has ~40% of families with errors

(and don’t think your transcriptome assembly is any better!)

# Error increases estimated rate of gain and loss



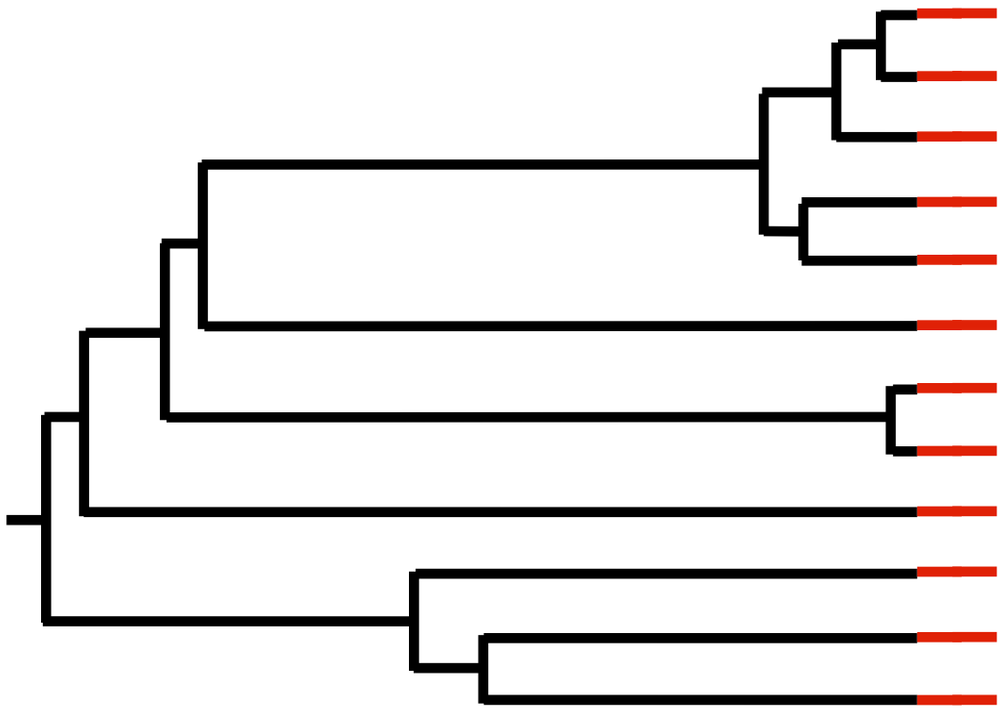
simulated rate: **λ=0.0012**

add **10%** error to data →



after adding error: **λ=0.0027**

# Error increases estimated rate of gain and loss

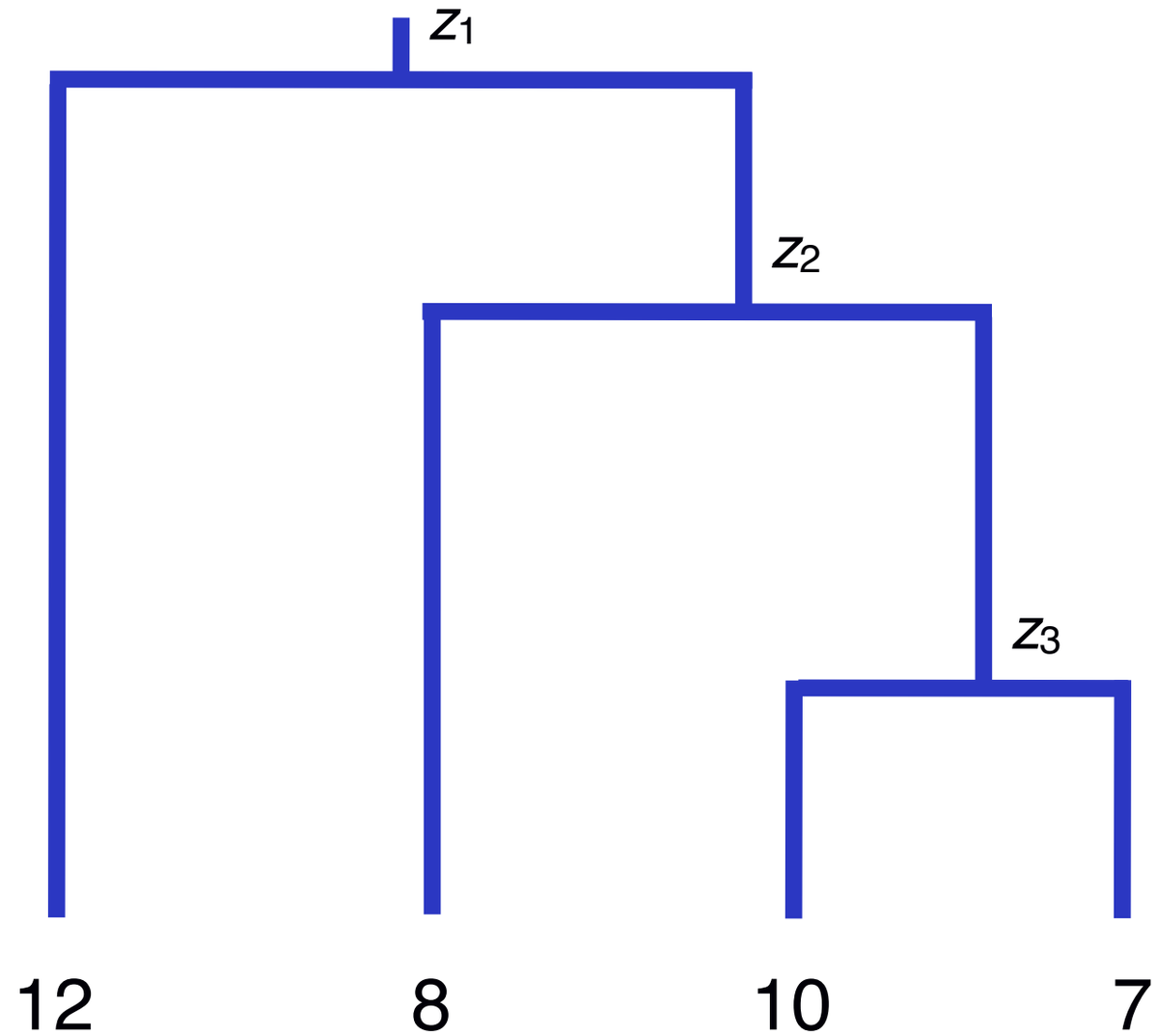


simulated rate: **λ=0.0012**

add **40%** error to data →

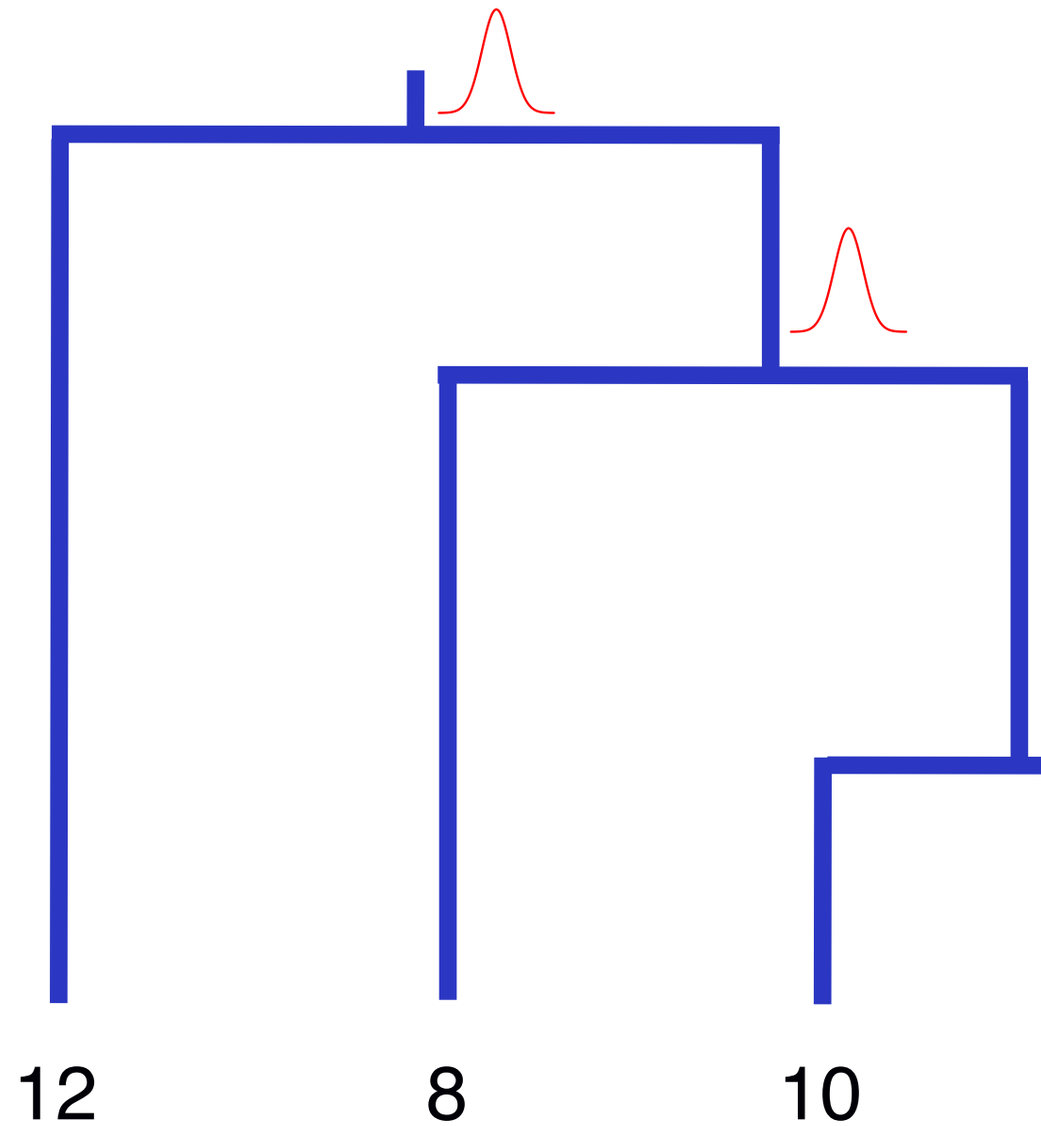
after adding error: **λ=0.0085**

# A model for gene gain and loss



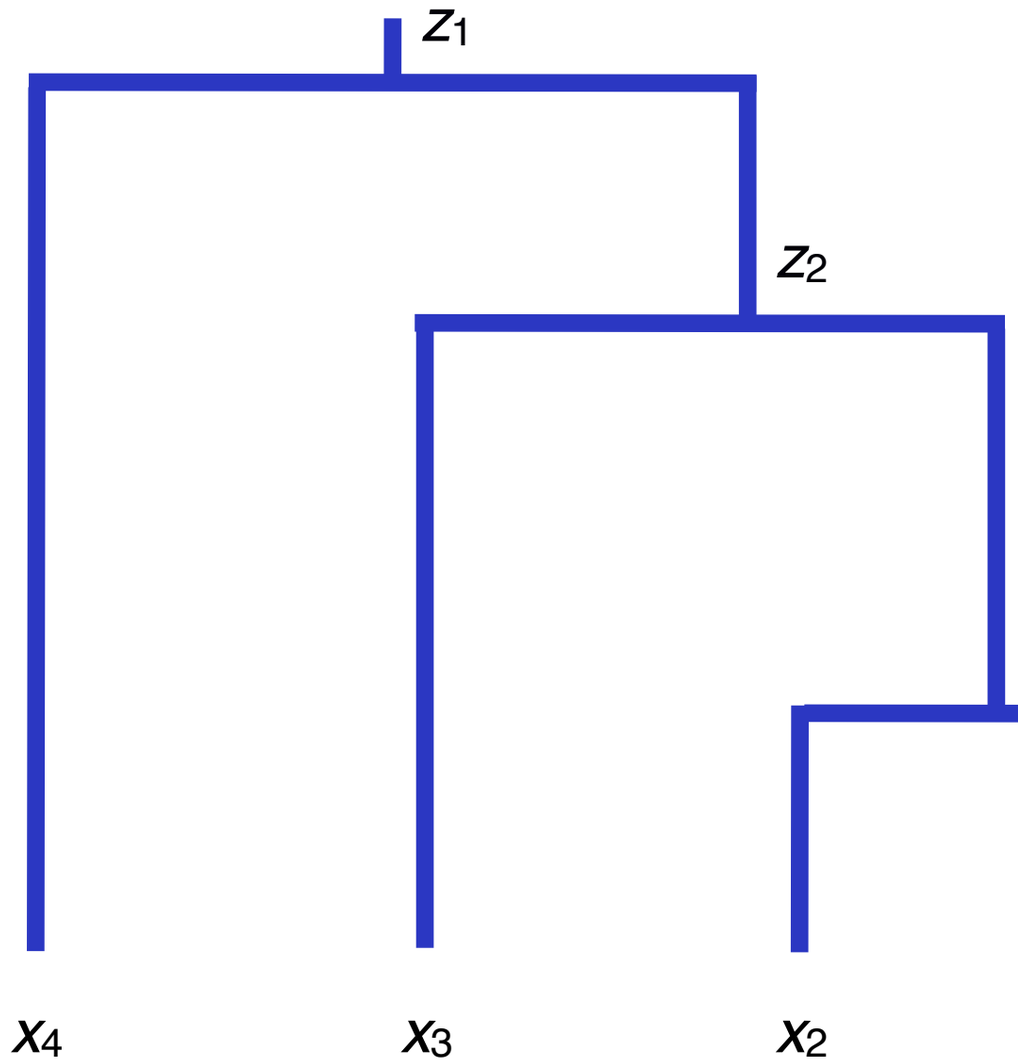

*Z*: hidden variables

# A model for gene gain and loss



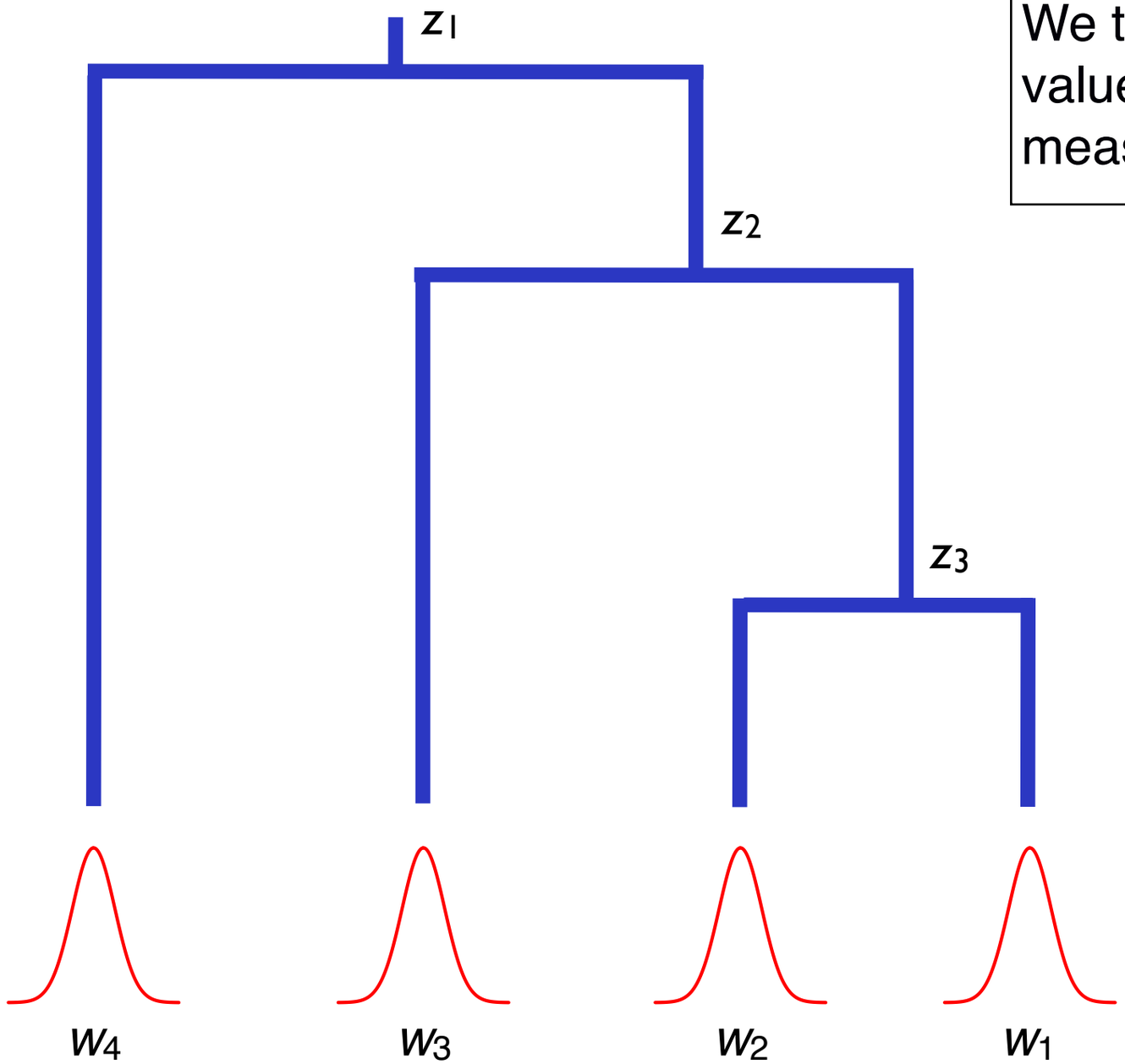

*Z*: hidden variables

# Modeling genome error



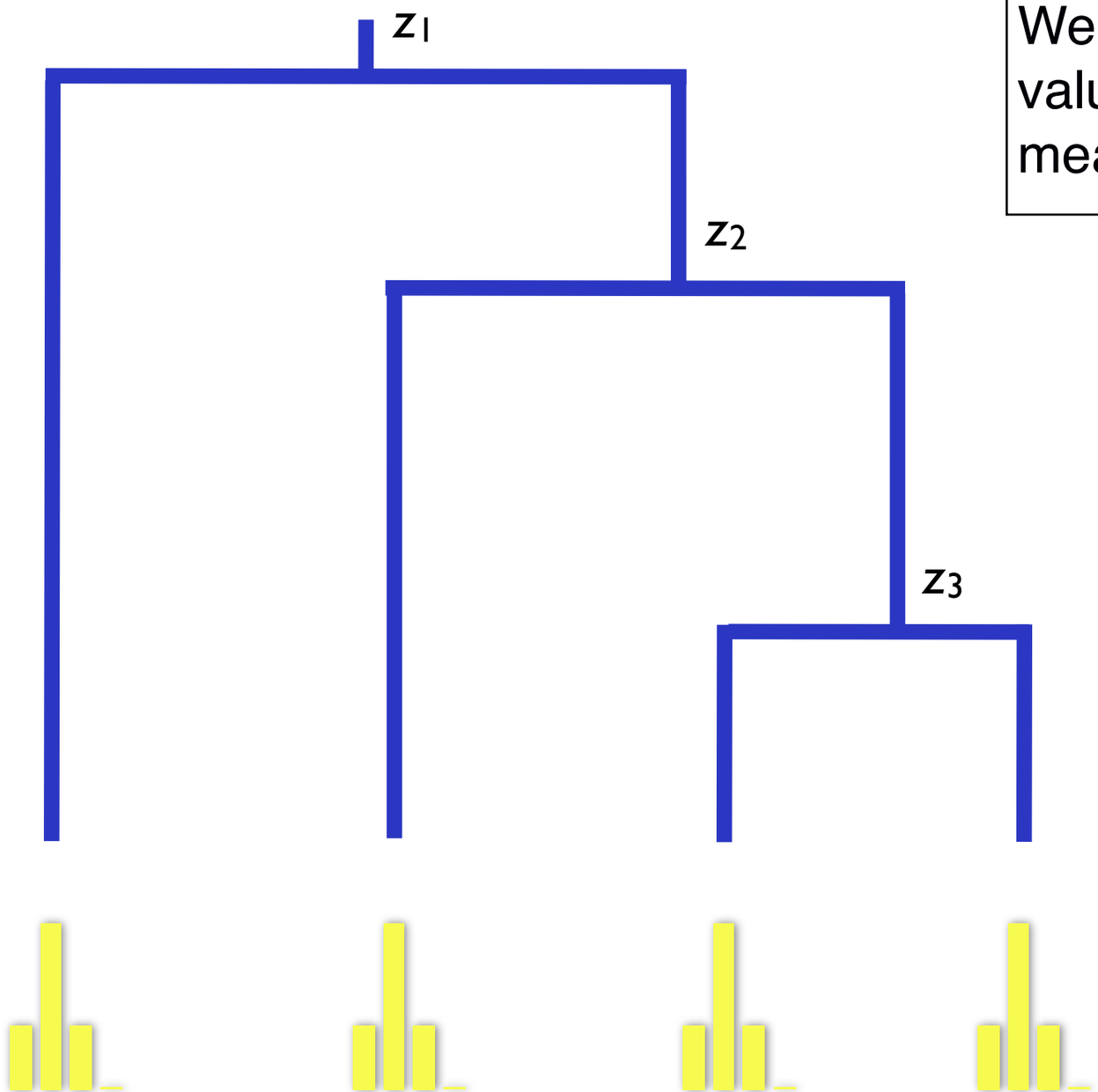

*Z*: hidden variables
*X*: observed variables

# Modeling genome error




We treat the observed values as error-prone measures

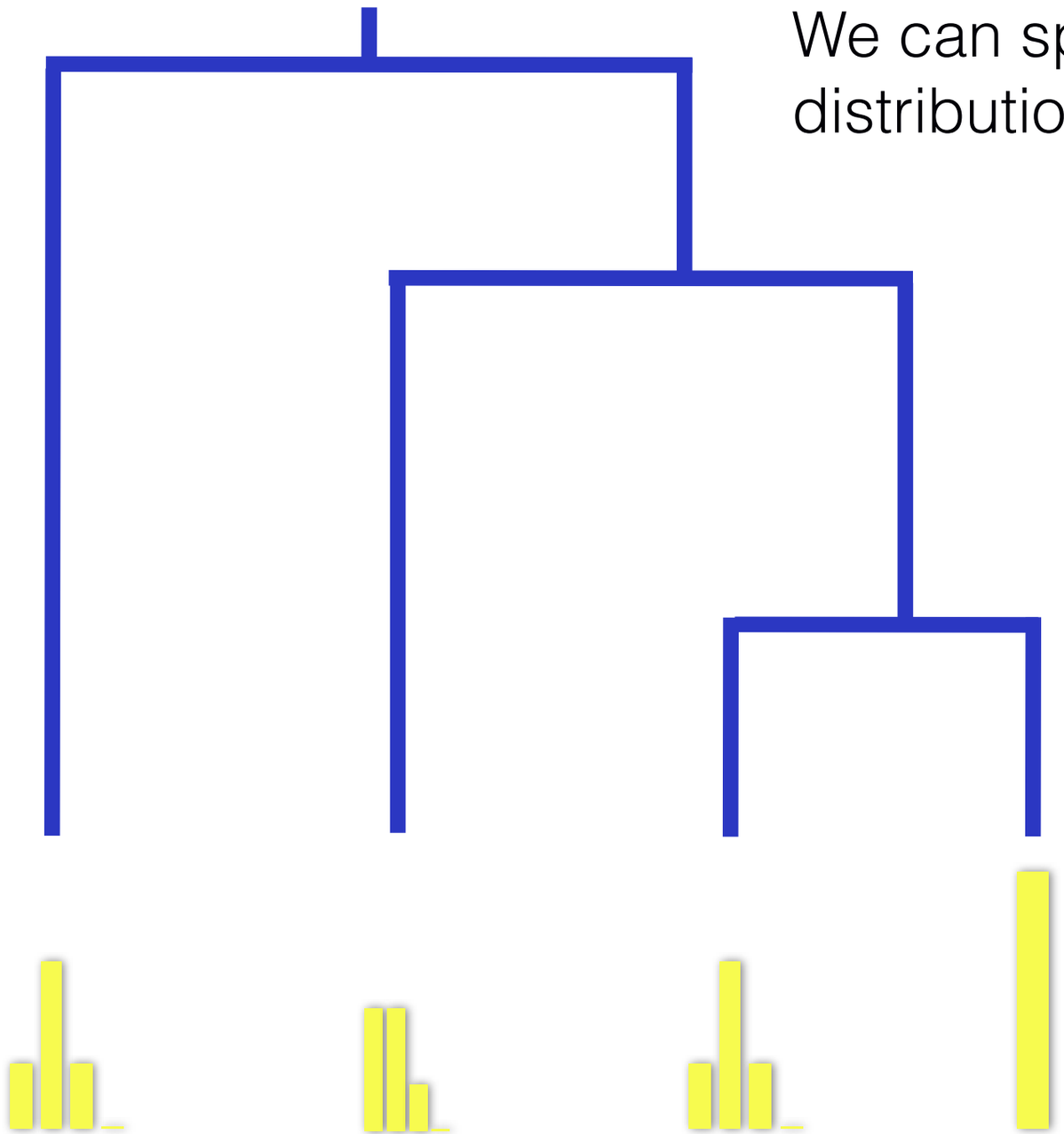
# Modeling genome error




We treat the observed values as error-prone measures

# Modeling genome error

CAFE 3.0



We can specify different error distributions for different species

# Modeling genome error

## Original model

$$\lambda, \mu = \text{argmax}_{\lambda,\mu}\left(\prod_{n=1}^{N} P(X_n \mid \lambda, \mu, T)\right)$$

$$= \text{argmax}_{\lambda,\mu}\left(\prod_{n=1}^{N} P(X_n \mid Z_n, \lambda, \mu, T) P(Z_n \mid \lambda, \mu, T)\right)$$

$$= \text{argmax}_{\lambda,\mu}\left(\prod_{n=1}^{N}\left\{\begin{array}{l}\sum_{z_{n1}=0}^{M}\sum_{z_{n2}=0}^{M}\cdots\sum_{z_{nu}=0}^{M} P(X_n \mid Z_n \\ = (z_{n1}, z_{n2} \ldots z_{nu}), \lambda, \mu, T) \\ \times P(Z_n = (z_{n1}, z_{n2} \ldots z_{nu}) \mid \lambda, \mu, T)\end{array}\right\}\right).$$

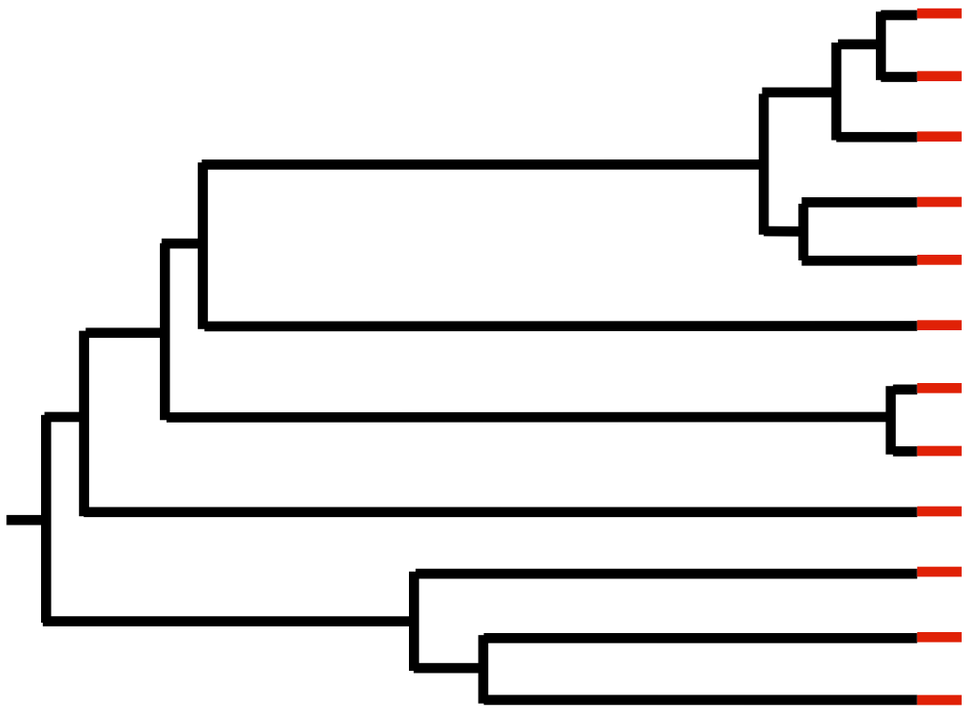
## Model with error

$$\lambda, \mu = \text{argmax}_{\lambda,\mu}\left(\prod_{n=1}^{N}\left\{\begin{array}{l}\sum_{x_{n1}=0}^{M}\sum_{x_{n2}=0}^{M}\cdots\sum_{x_{ns}=0}^{M} P(W_n \mid X_n \\ = (x_{n1}, x_{n2}, \ldots x_{ns})) \\ \times P(X_n, \lambda, \mu, T)\end{array}\right\}\right)$$

$$= \text{argmax}_{\lambda,\mu}\left(\prod_{n=1}^{N}\left\{\begin{array}{l}\sum_{x_{n1}=0}^{M}\sum_{x_{n2}=0}^{M}\cdots\sum_{x_{ns}=0}^{M} P(W_{n1} \mid X_{n1} \\ = x_{n1}) P(W_{n2} \mid X_{n2} = x_{n2}) \\ \times \ldots P(W_{ns} \mid X_{ns} = x_{ns}) \\ \times P(X_n, \lambda, \mu, T)\end{array}\right\}\right).$$

Han et al. (2013) *Molecular Biology and Evolution*

# Error increases estimated rate of gain and loss



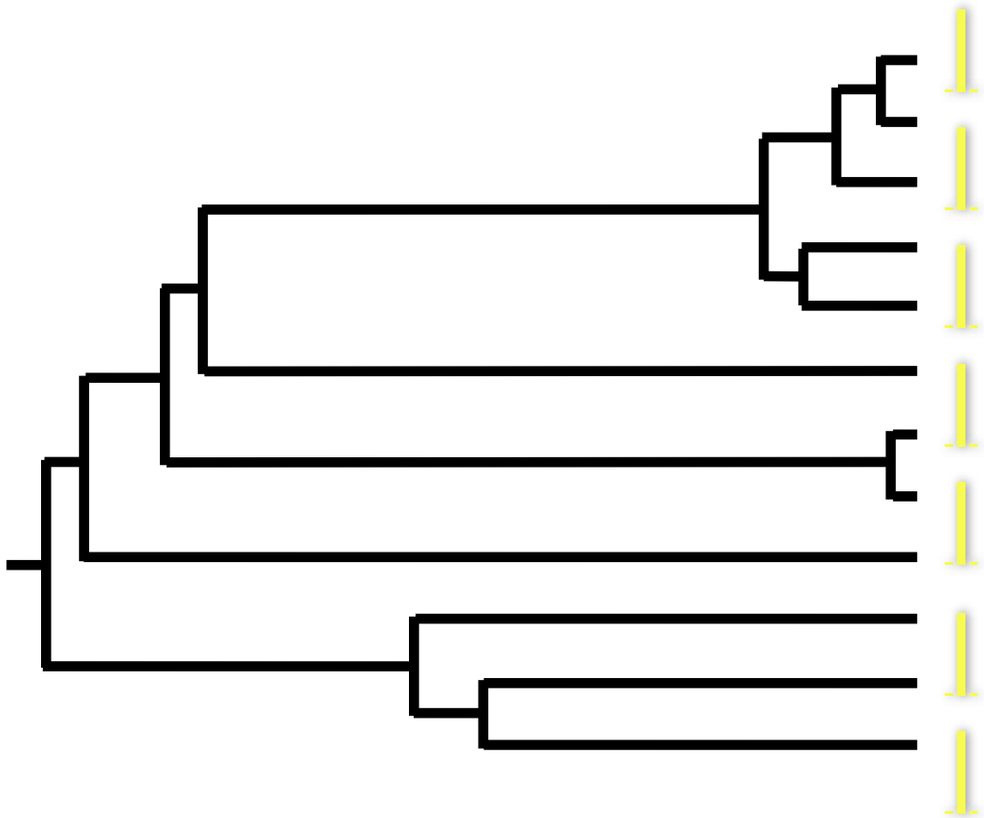
simulated rate: **λ=0.0012**

add **10%** error to data →



after adding error: **λ=0.0027**

# Accounting for error corrects rate estimate



simulated rate: **λ=0.0012**

add **10%** error to data →

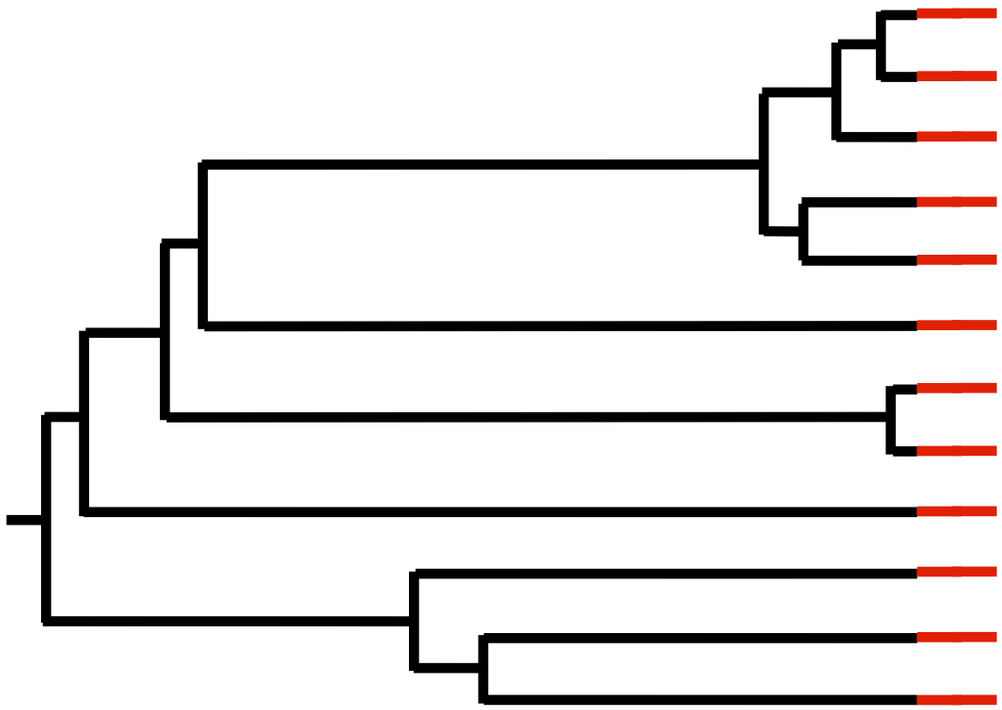


after adding error: **λ=0.0027**

↓

using correct error model: λ=0.0012

# Error increases estimated rate of gain and loss

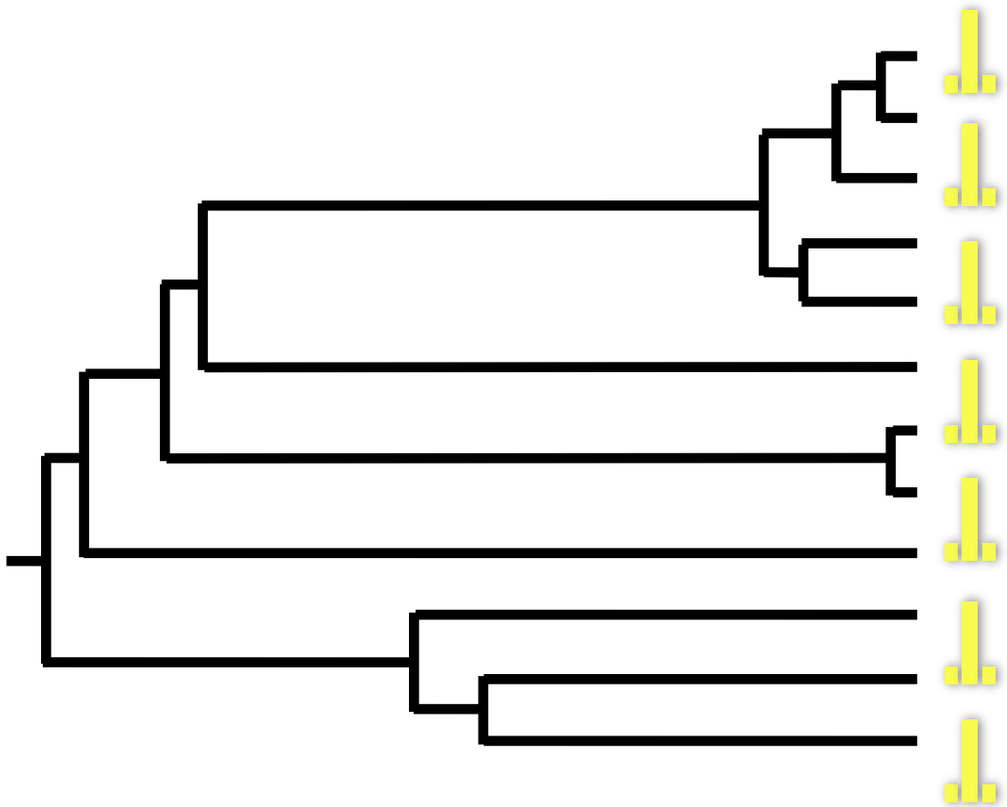


simulated rate: **λ=0.0012**

add **40%** error to data →

after adding error: **λ=0.0085**

# Accounting for error corrects rate estimate



simulated rate: **λ=0.0012**

add **40%** error to data → 

after adding error: **λ=0.0085**

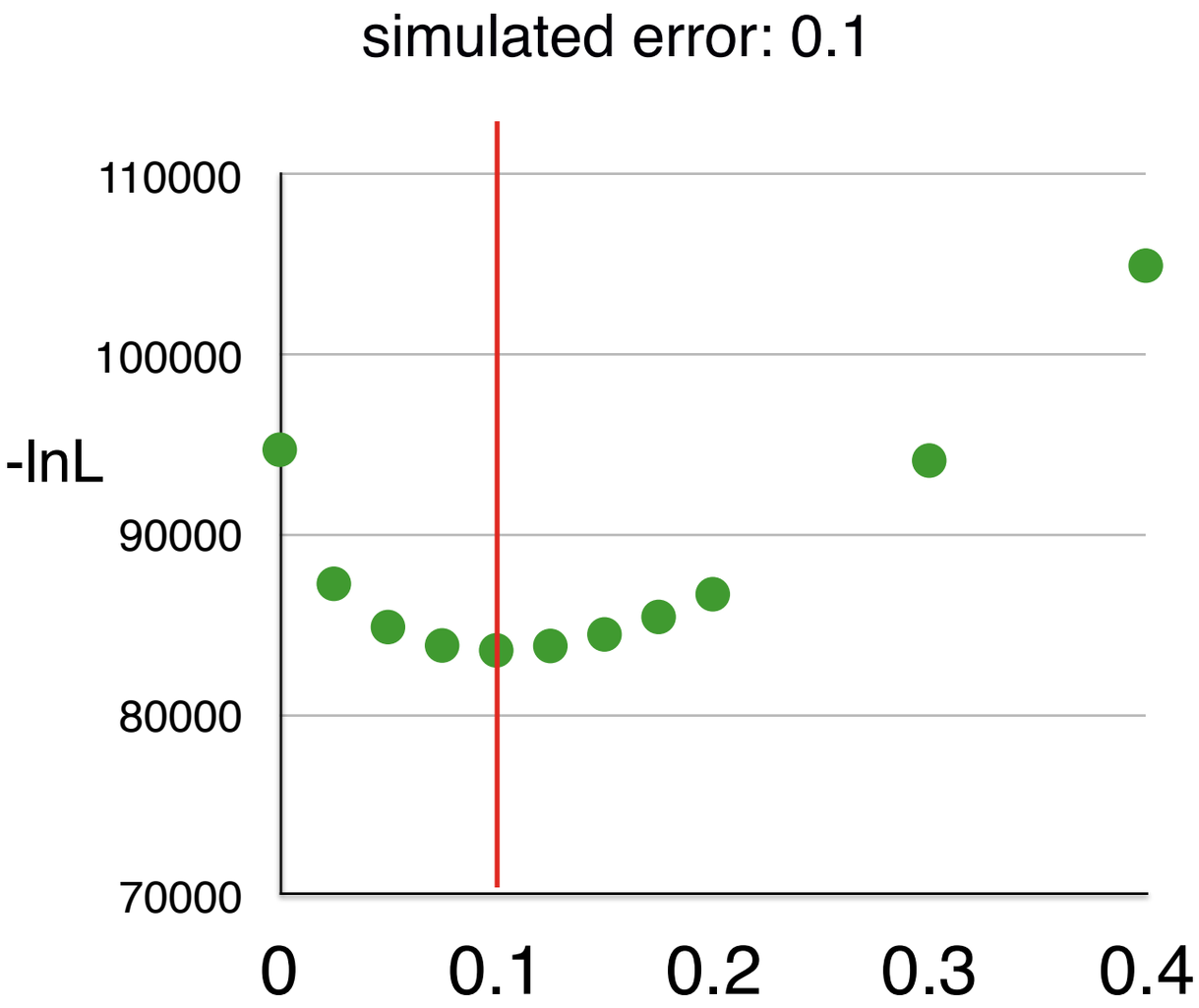
using correct error model: λ=0.00124

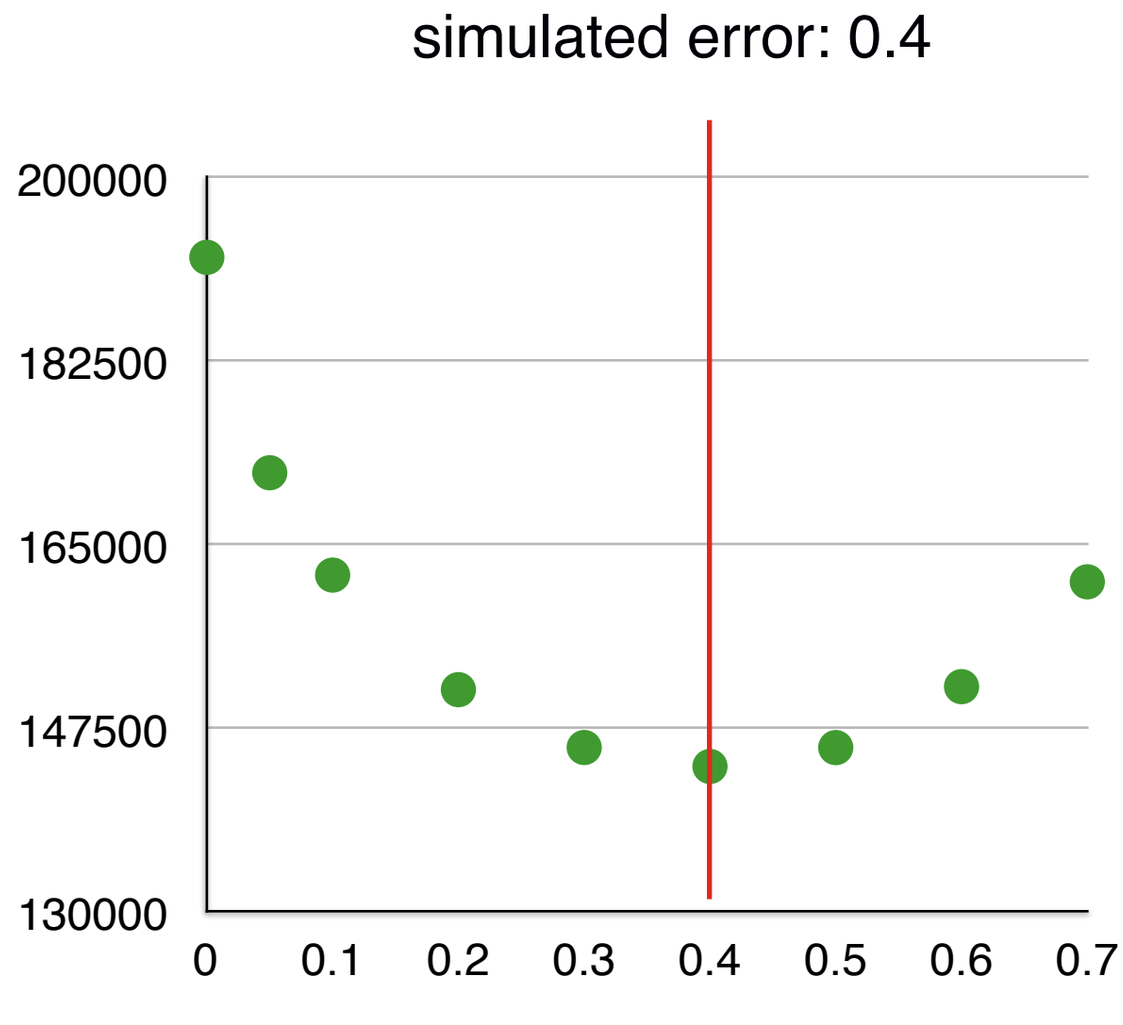
# Estimating the correct error model

Thus far, we have assumed the correct error model is known.

Can we estimate it when it is not known?

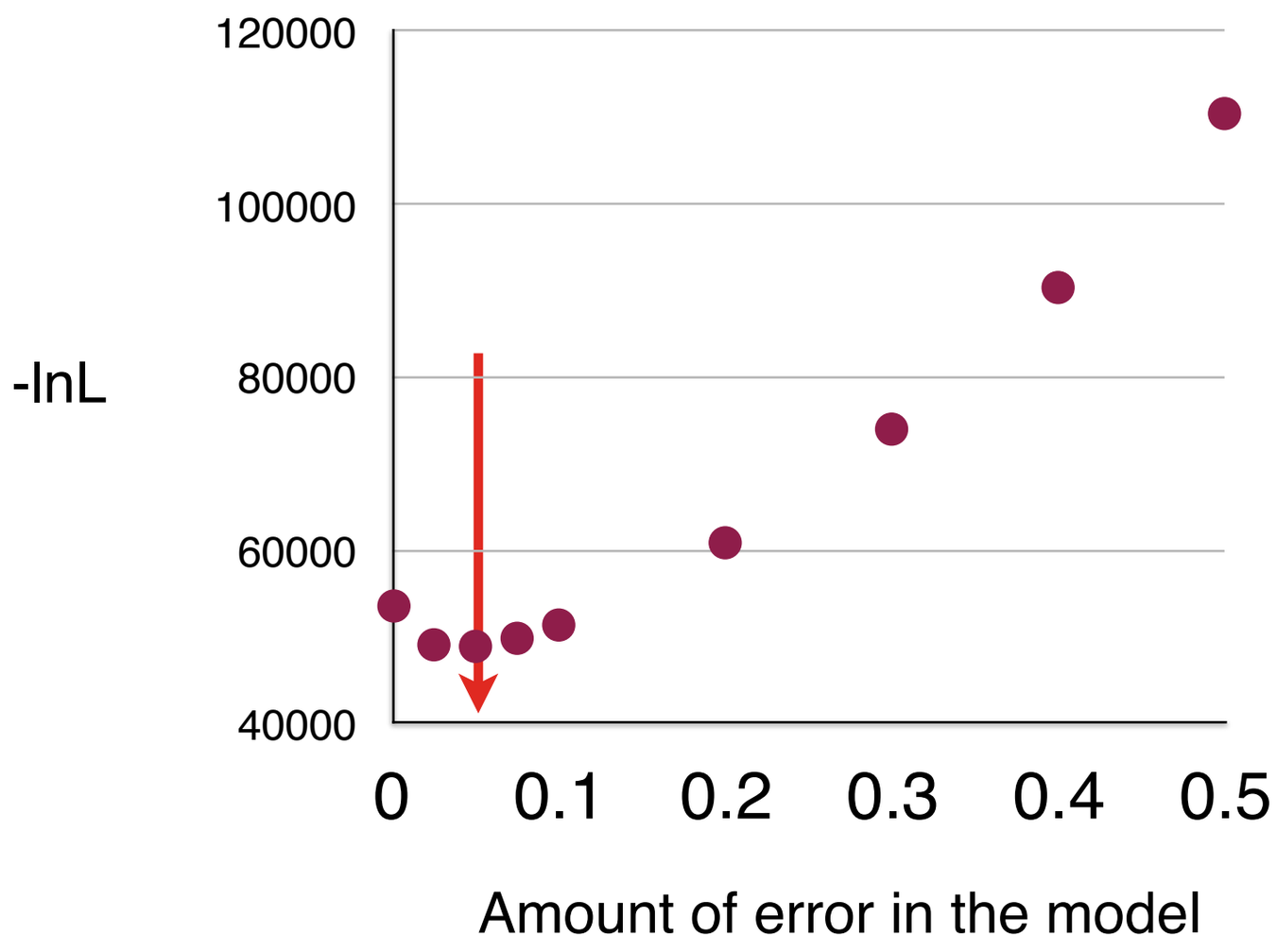
# Estimating the correct error model



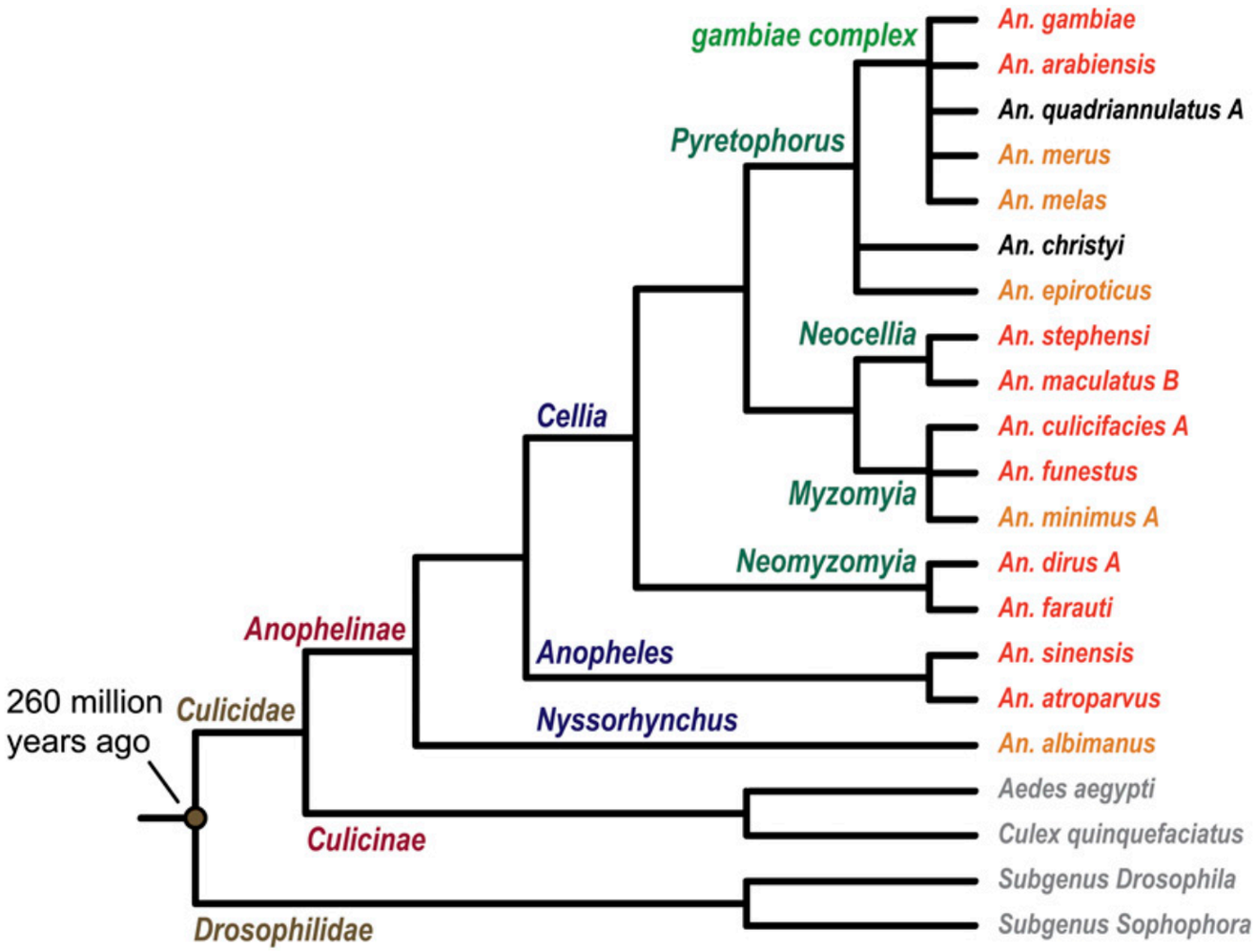



# Estimating the error model from data

Using the real 12 Drosophila genomes



# Accounting for error corrects rate estimate



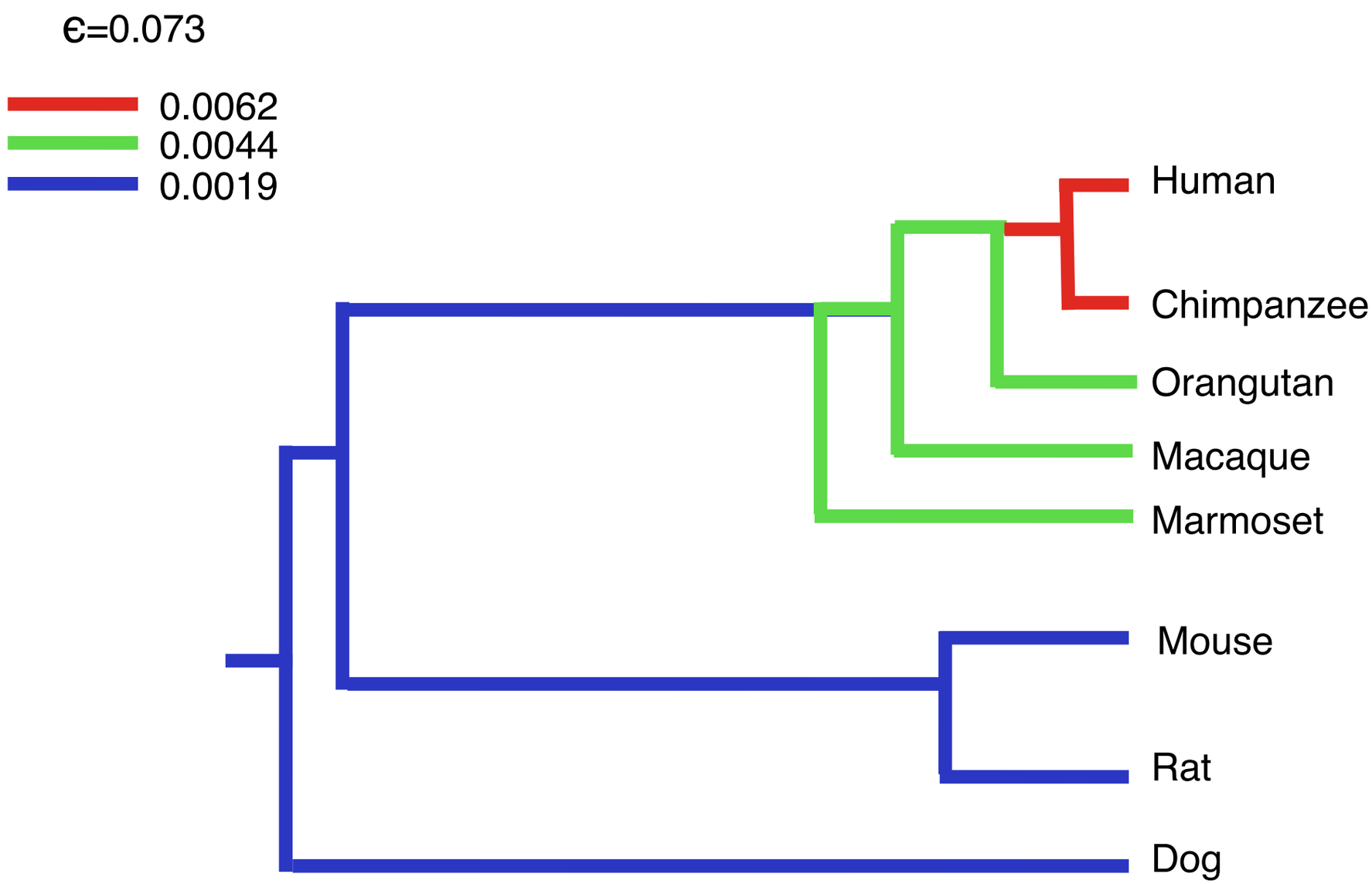

uncorrected λ=0.0032

ϵ=0.104

corrected λ=0.0018

Neafsey et al. (2015) *Science*

# Is there really a hominoid rate acceleration?




Han et al. (2013) *Molecular Biology and Evolution*