Phylogeny of Mixture Models

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Outline

Introduction (phylogeny, molecular phylogeny)

Mathematical models (CFN, JC, K2, K3)

Maximum likelihood (ML) methods

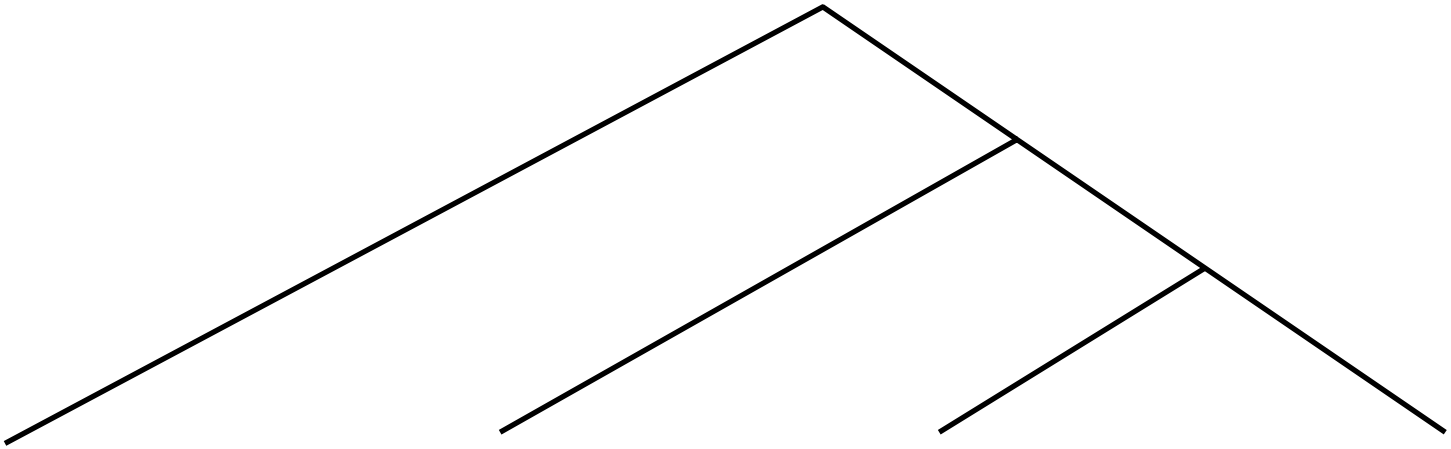
Our setting: mixtures of distributions
ML, MCMC for ML fails for mixtures

Duality theorem: tests/ambiguous mixtures

Proofs (strictly separating hyperplanes,
non-constructive ambiguous mixtures)

Phylogeny

development of a group: the development over time of a species, genus, or group, as contrasted with the development of an individual (ontogeny)



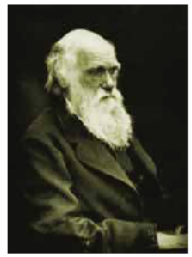
orangutan gorilla chimpanzee human

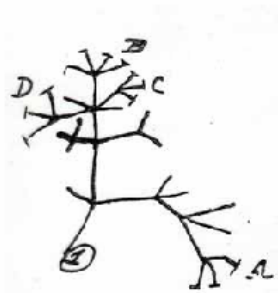
Phylogeny – how?

development of a group: the development over time of a species, genus, or group, as contrasted with the development of an individual (ontogeny)

past – morphologic data
(beak length, bones, etc.)

present – molecular data
(DNA, protein sequences)





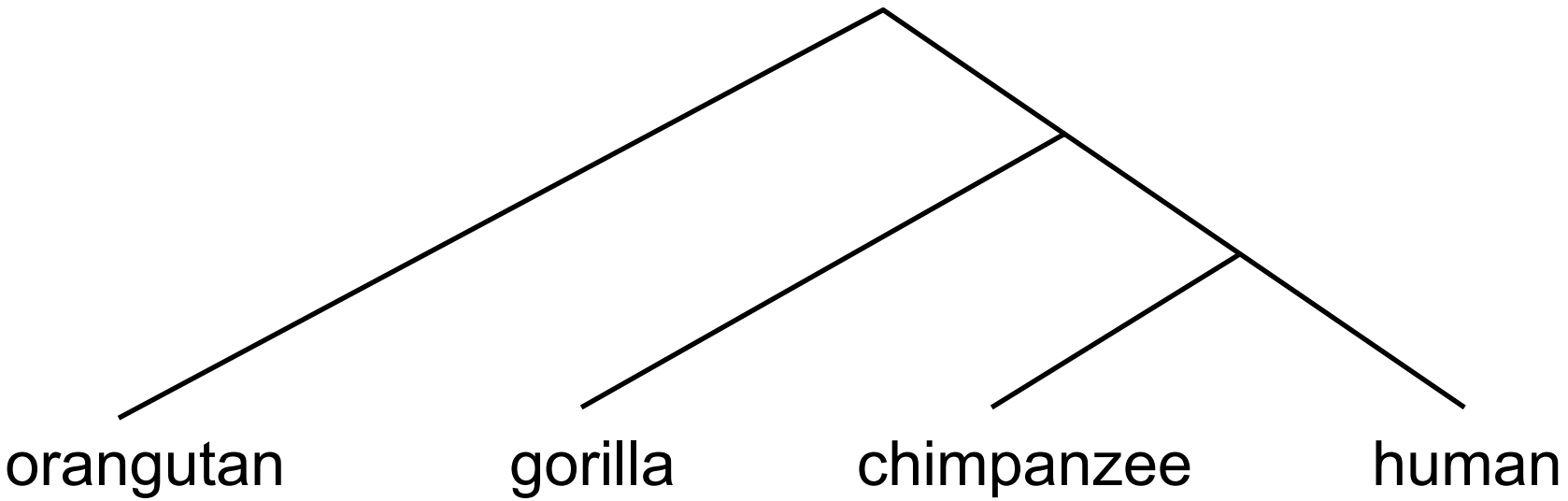
First Notebook on Transmutation of Species, 1837.

Molecular phylogeny

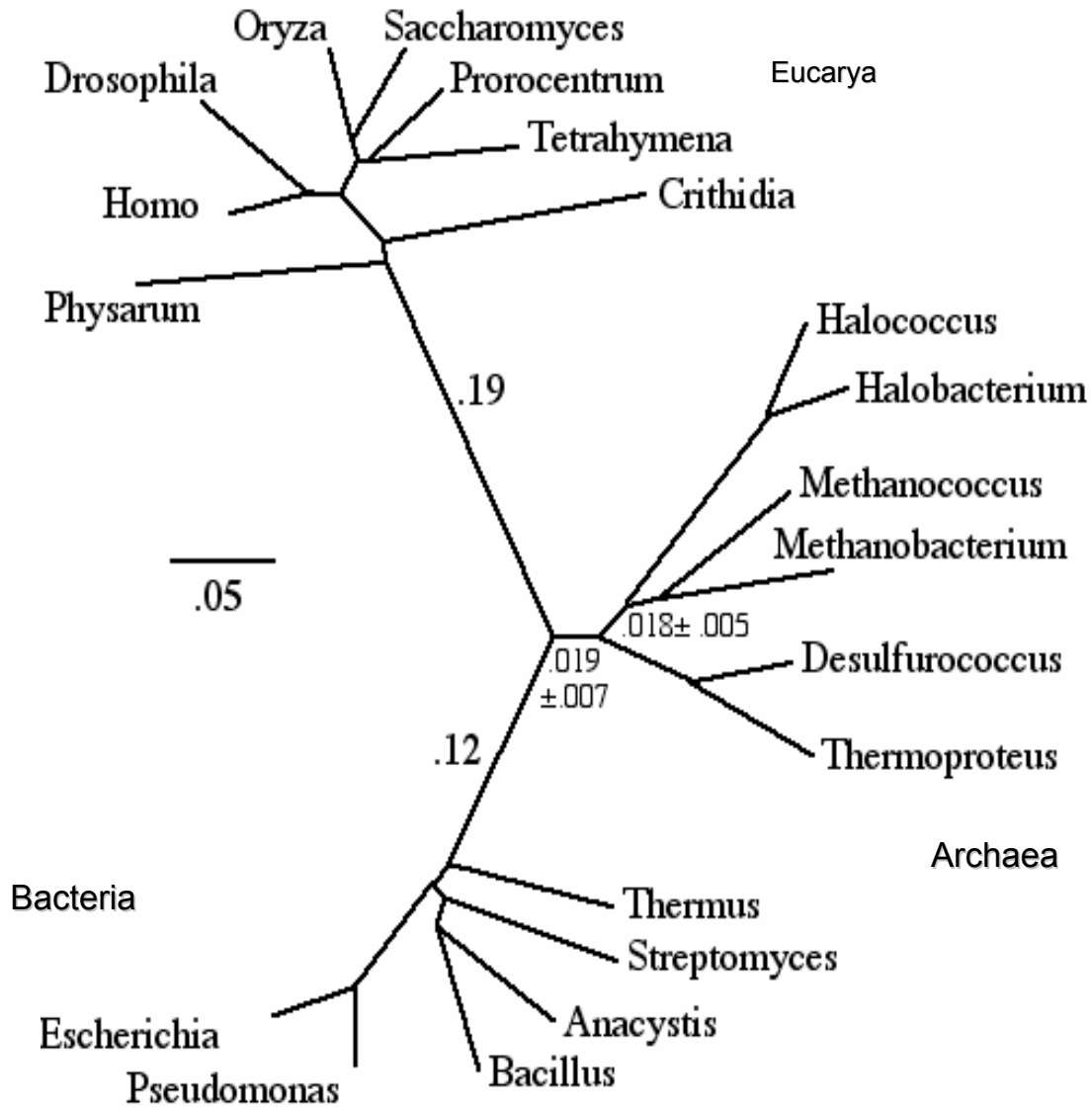
INPUT: aligned DNA sequences

Human:	**ATCGGTAAGTACGTGCGAA**
Chimpanzee:	**TTCGGTAAGTAAGTGGGAT**
Gorilla:	**TTAGGTCAGTAAGTGCGTT**
Orangutan:	**TTGAGTCAGTAAGAGAGTT**

OUTPUT: phylogenetic tree



Example of a real phylogenetic tree



Universal phylogeny

deduced from comparison of SSU and LSU rRNA sequences (2508 homologous sites) using Kimura's 2-parameter distance and the NJ method.

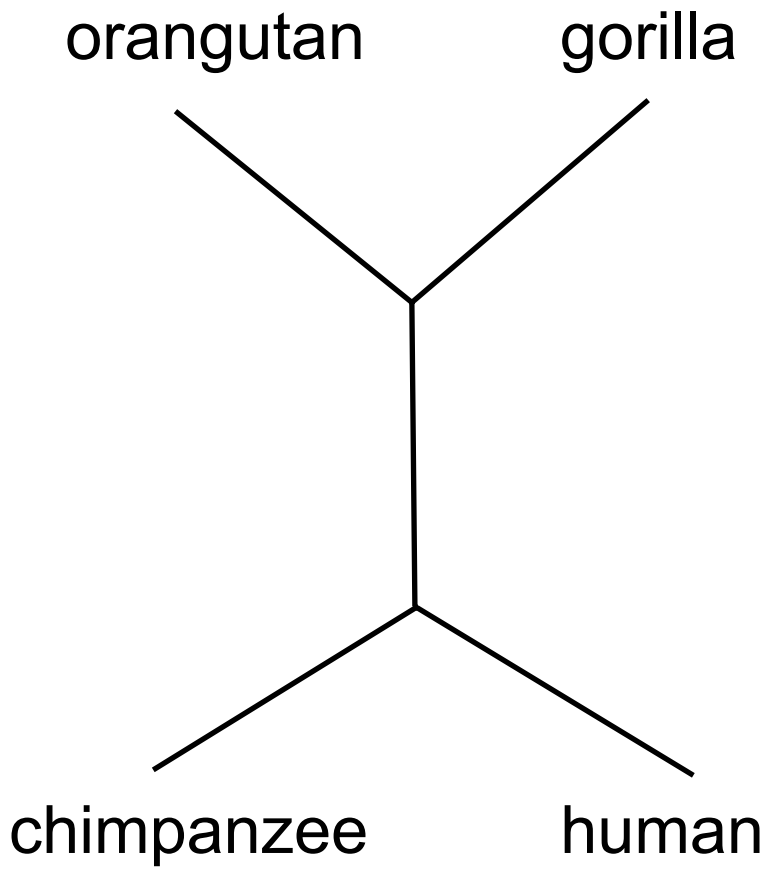
The absence of root in this tree is expressed using a circular design.

Source: Manolo Gouy, Introduction to Molecular Phylogeny

Dictionary

Leaves = Taxa = {chimp, human, ...}
Vertices = Nodes
Edges = Branches
Tree = Tree

Unrooted/Rooted trees



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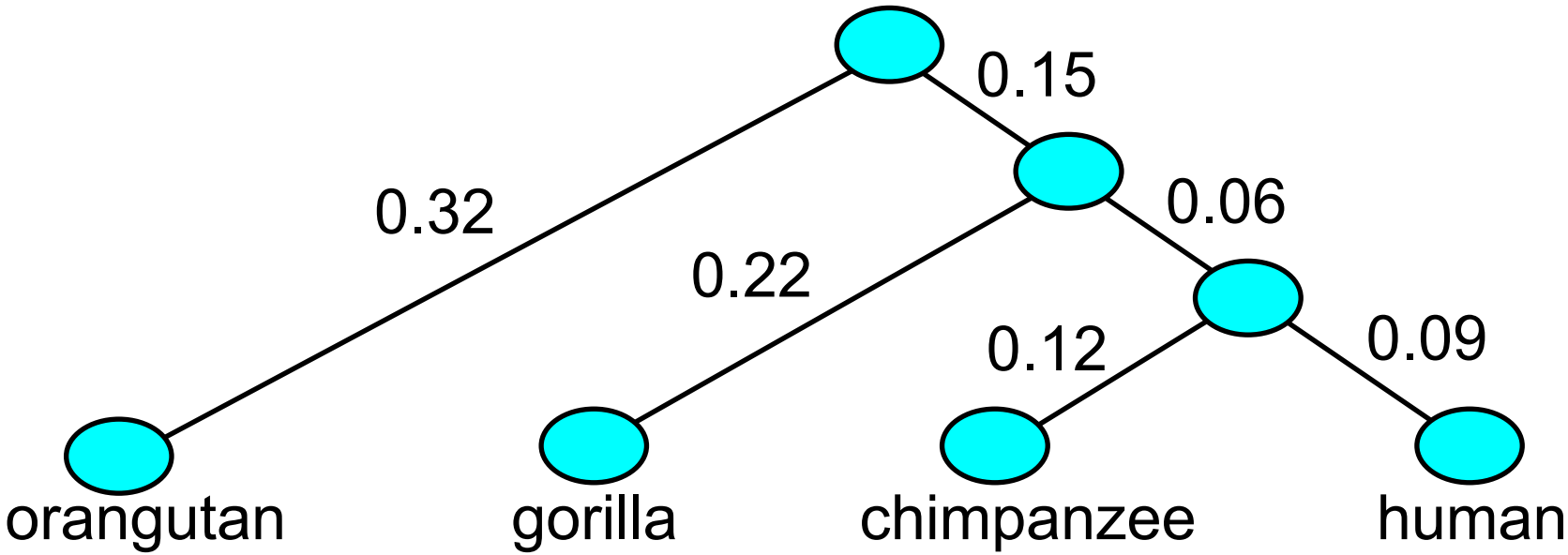
Cavender-Farris-Neyman (CFN) model

Weight of an edge = probability that 0 and 1 get flipped



CFN model

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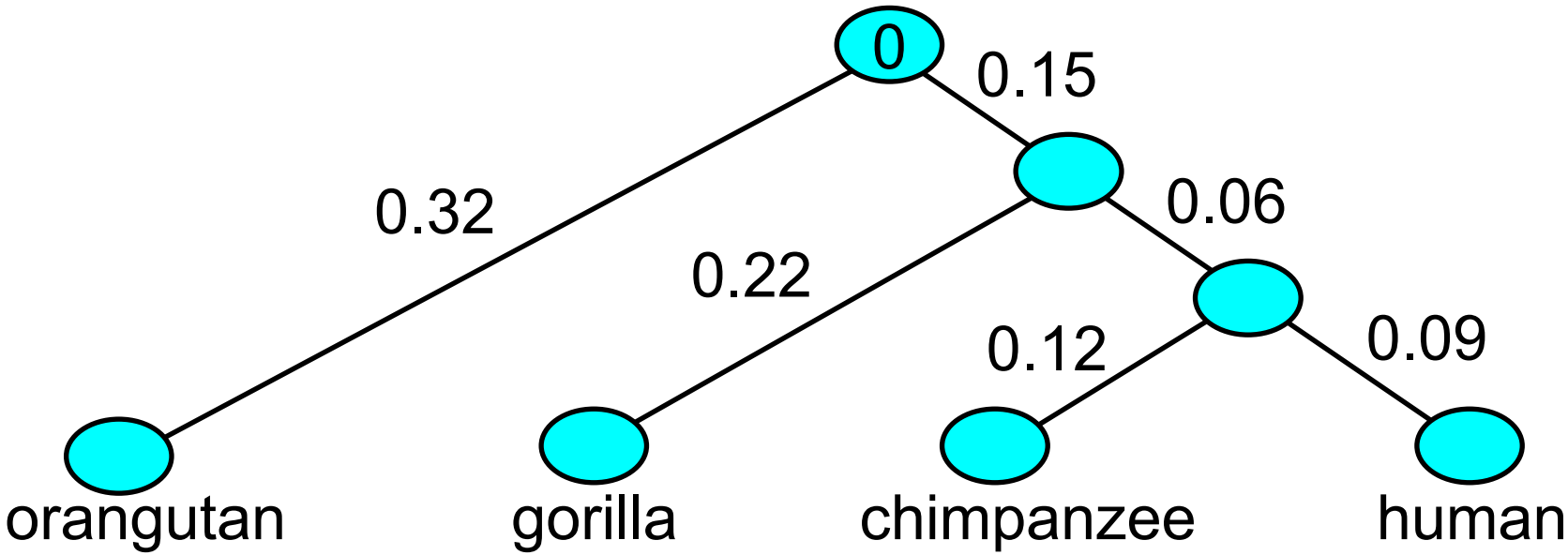

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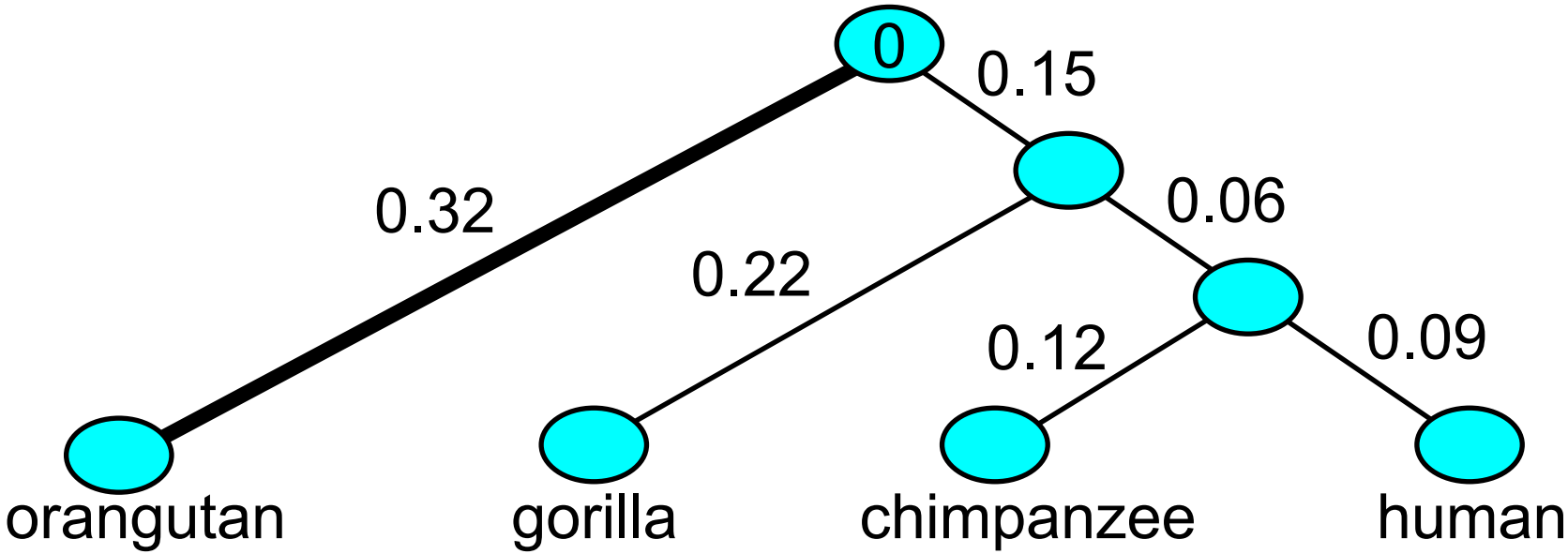

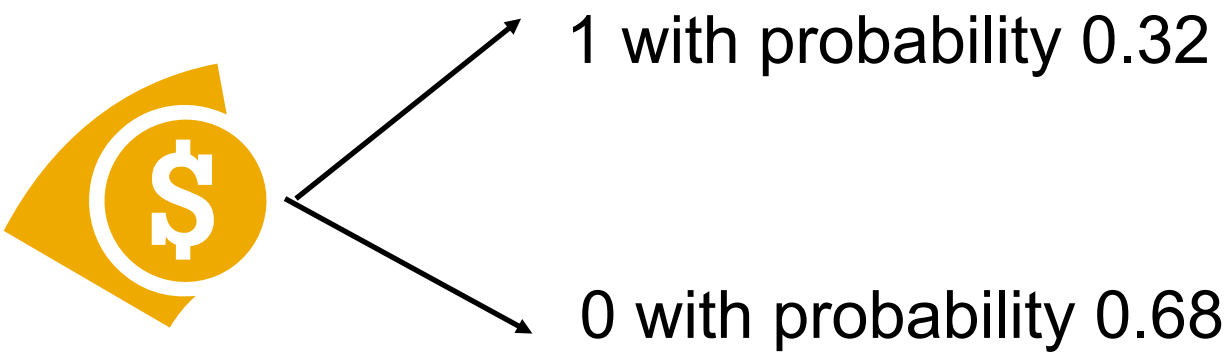

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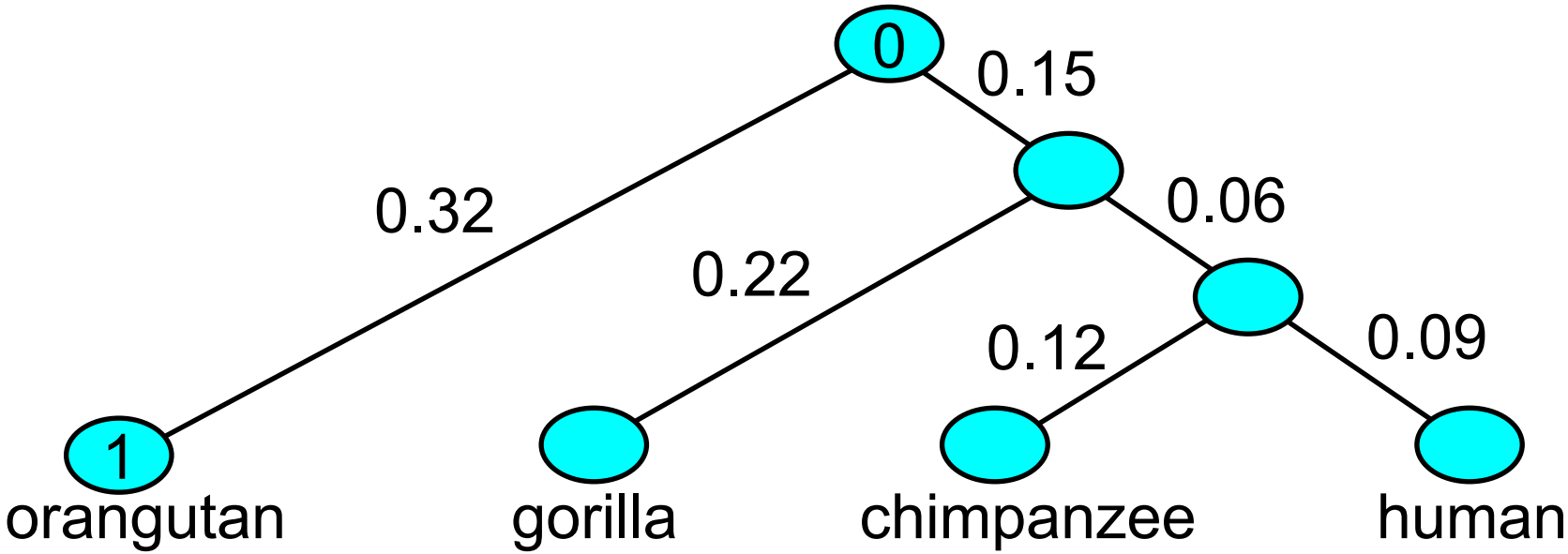

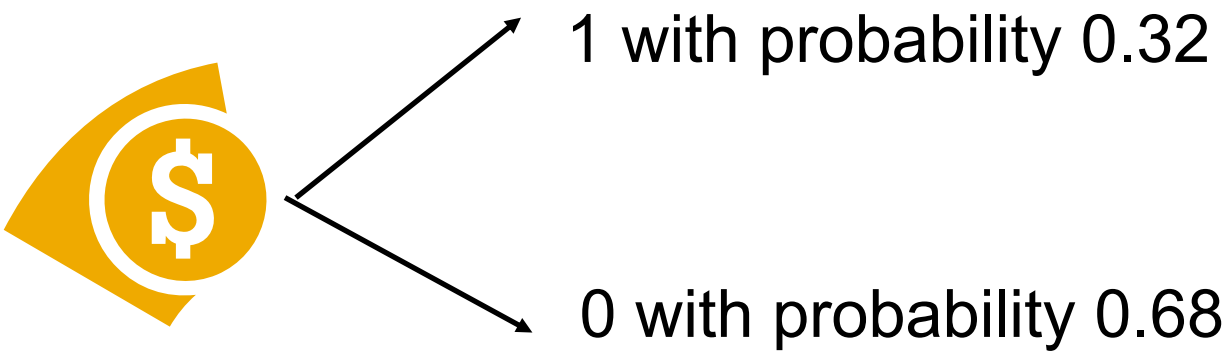

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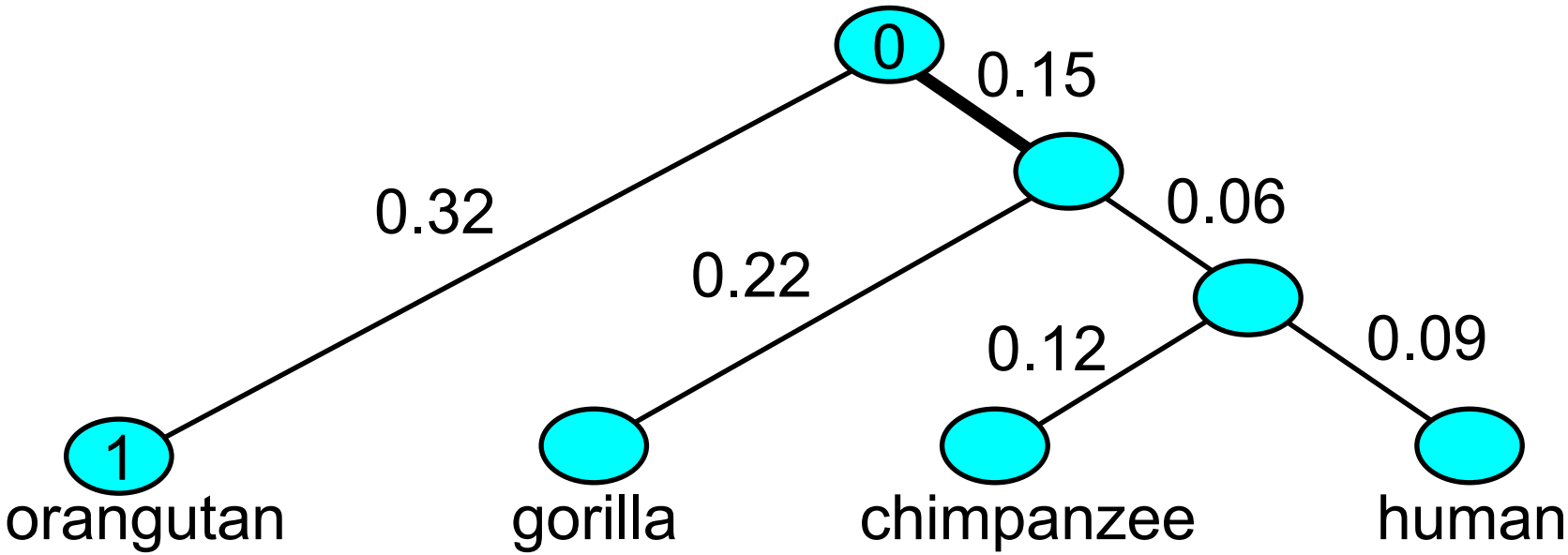

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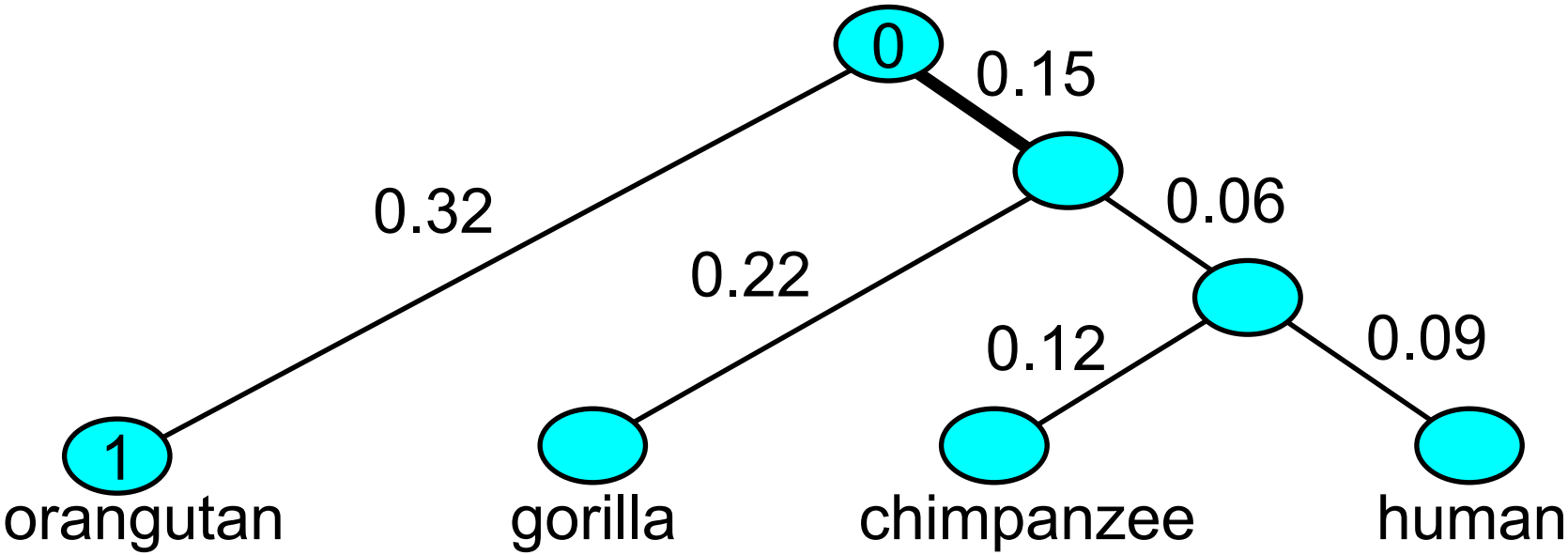

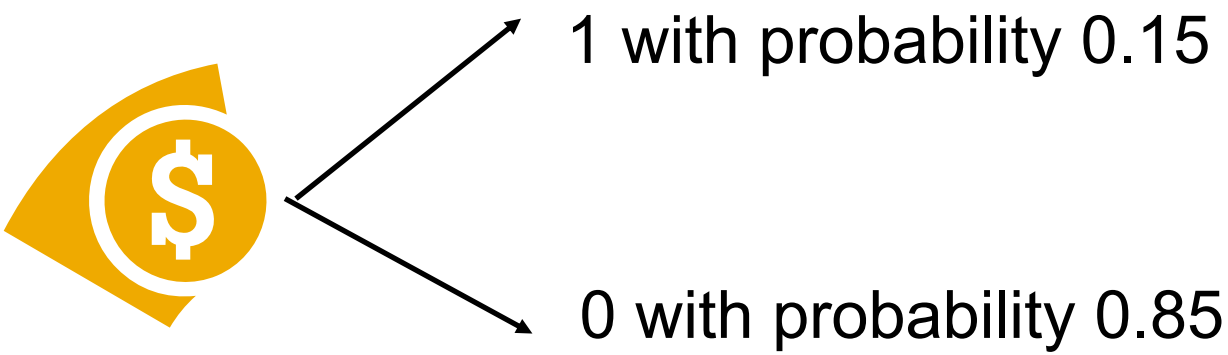

CFN model

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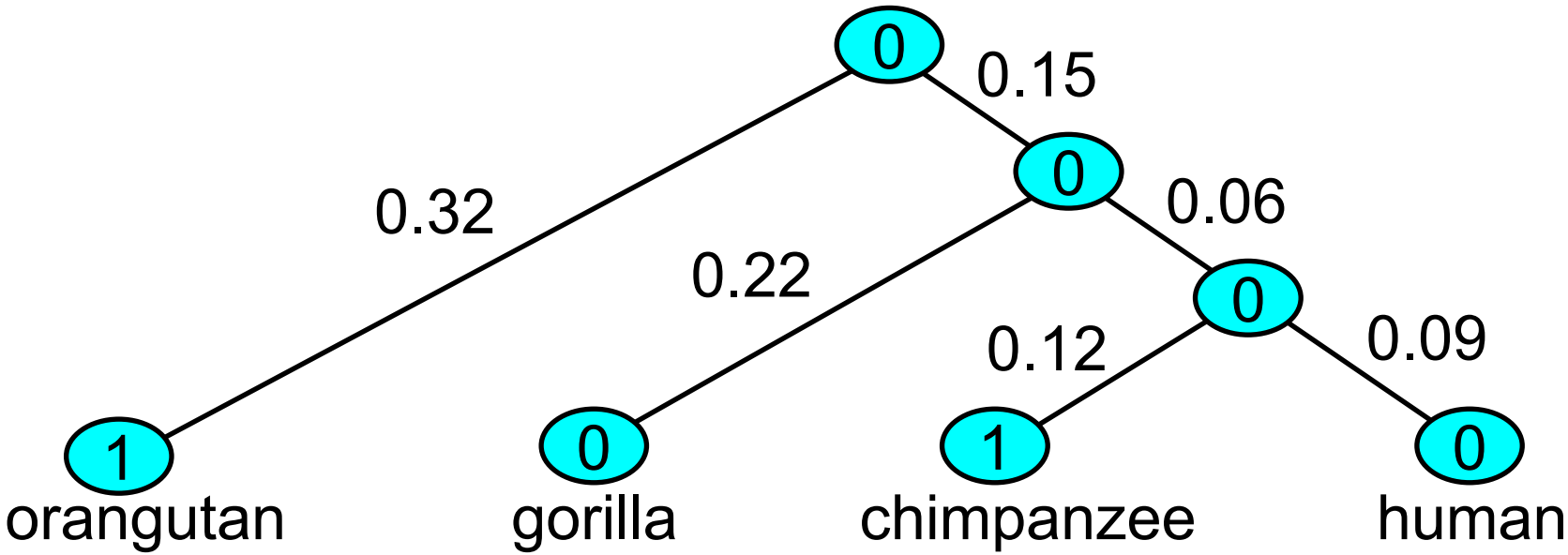

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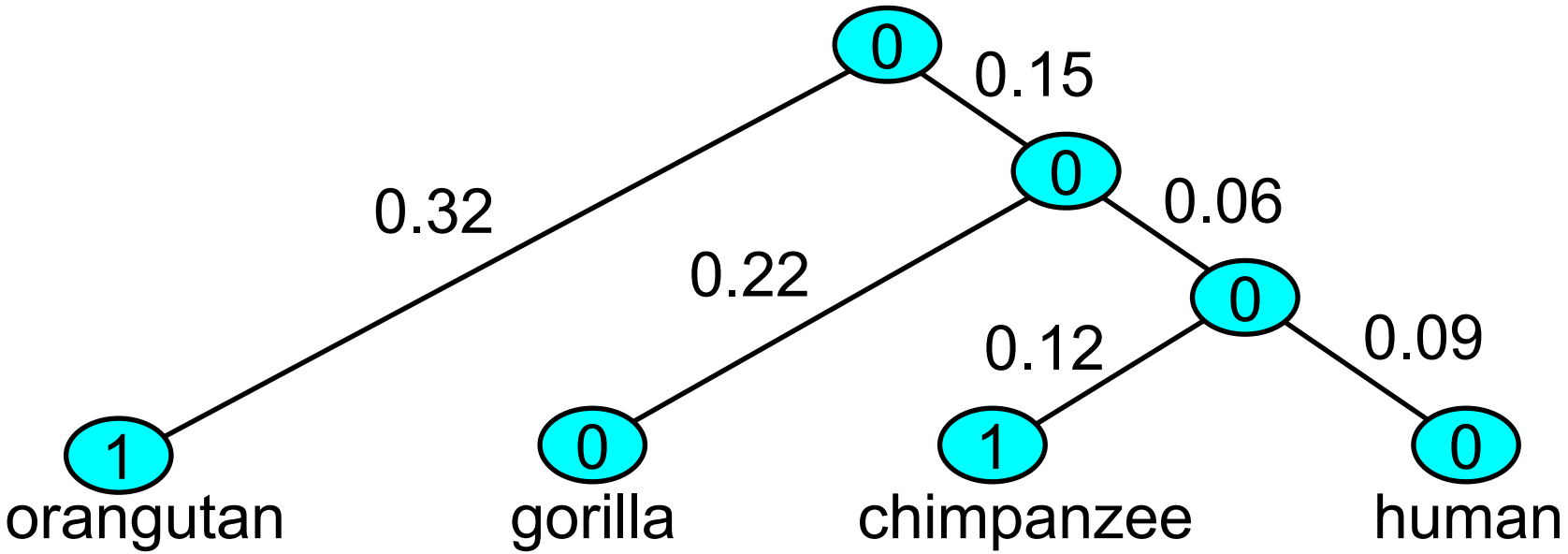
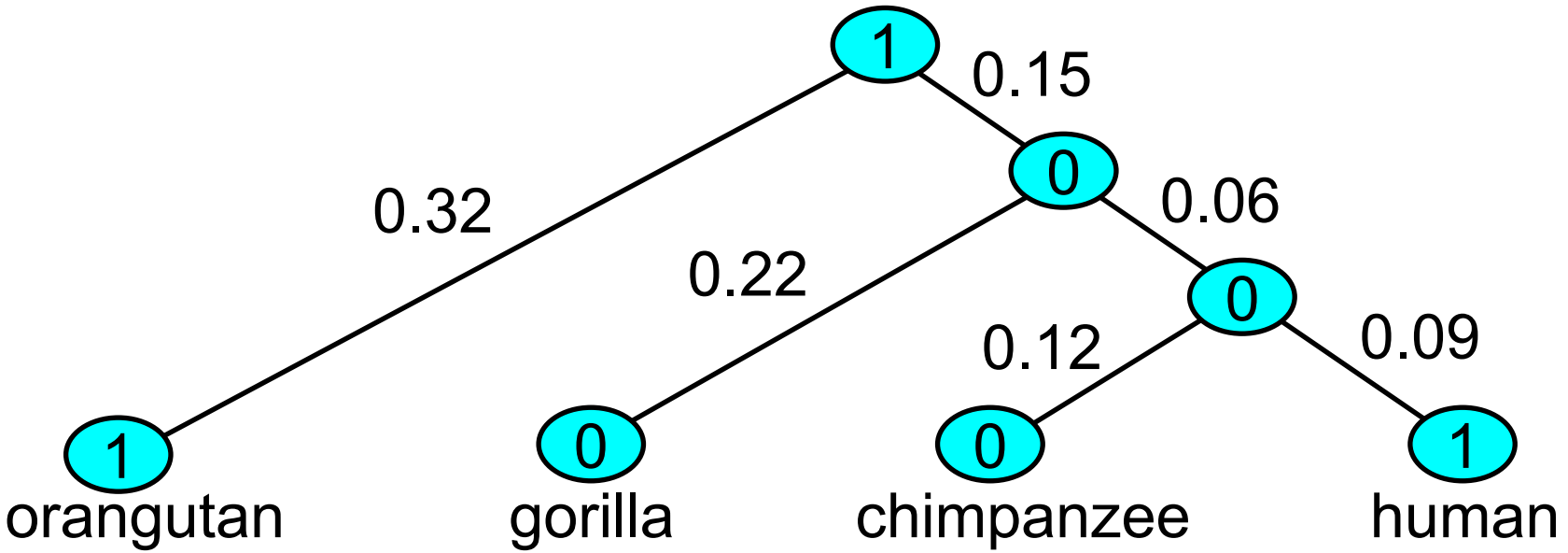


1…….. 0…….. 1…….. 0…….

CFN model

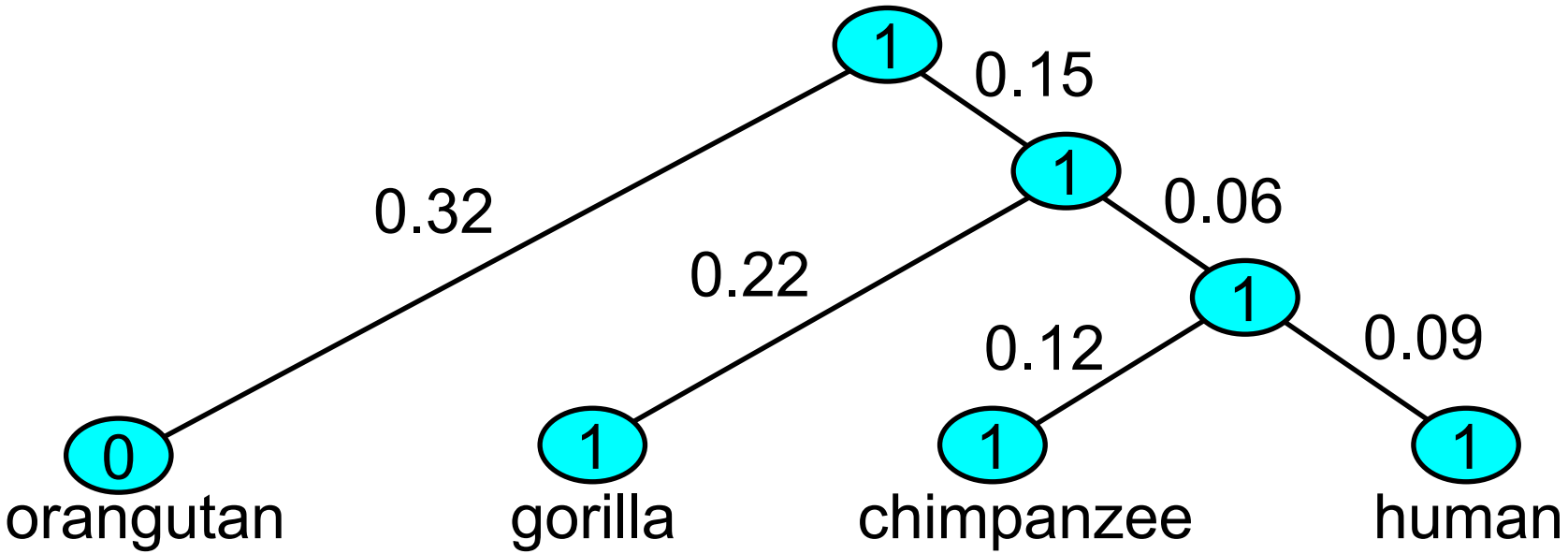
Weight of an edge = probability that 0 and 1 get flipped



11…….. 00…….. 10…….. 01……..

CFN model

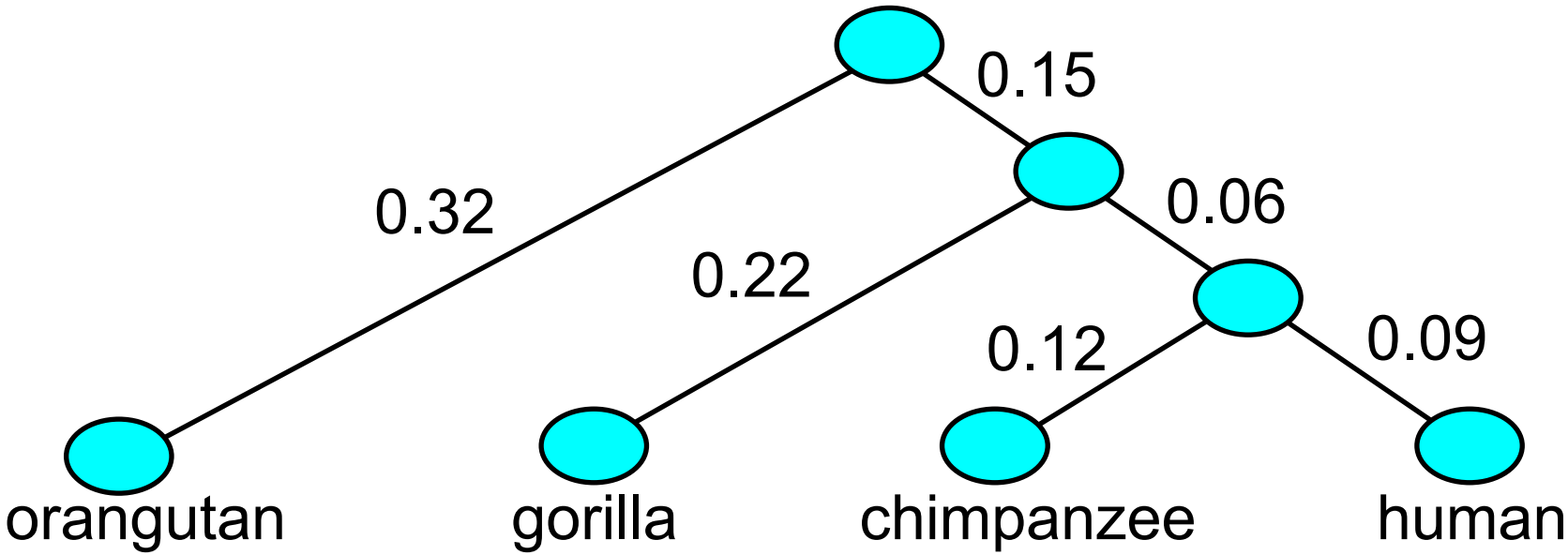
Weight of an edge = probability that 0 and 1 get flipped



110…….. 001…….. 101…….. 011……..

CFN model

Weight of an edge = probability that 0 and 1 get flipped



0000,0001,0010,0011,0100,0101,0110,0111,…

Denote the distribution on leaves $\mu(T,w)$

T = tree topology

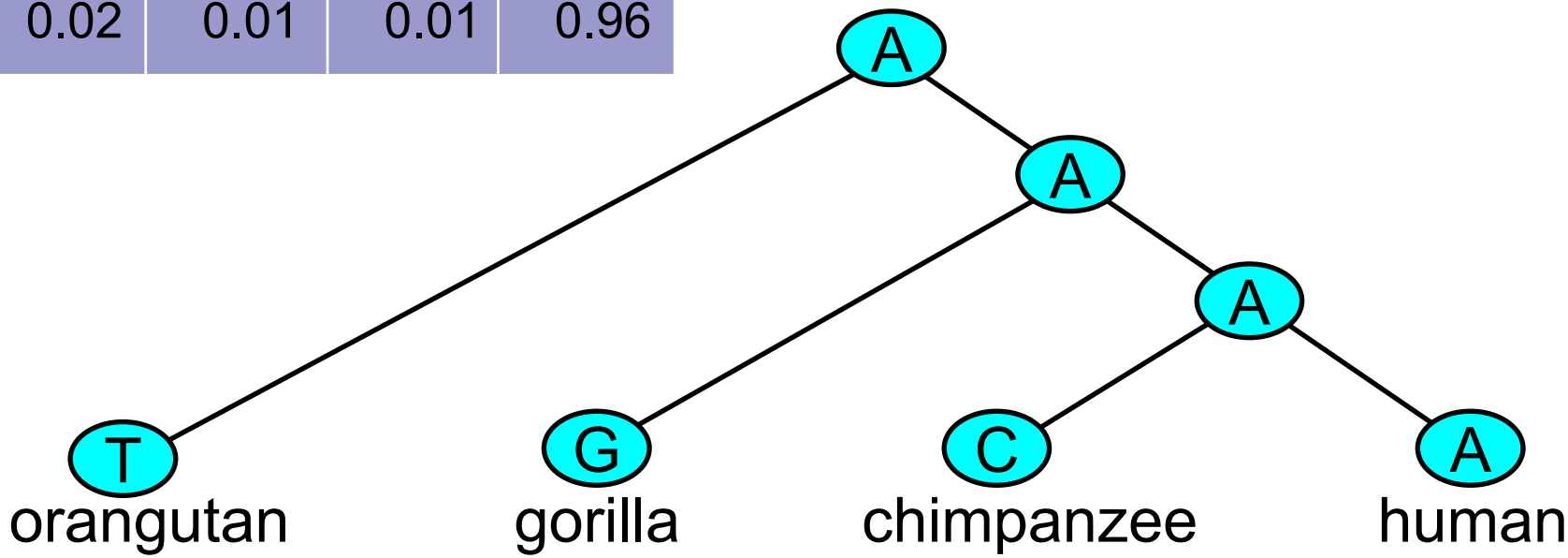
w = set of weights on edges

Generalization to more states

Weight of an edge = ~~probability that 0 and 1 get flipped~~

transition matrix

	A	G	C	T
A	0.9	0.05	0.03	0.02
G	0.05	0.87	0.07	0.01
C	0.03	0.07	0.89	0.01
T	0.02	0.01	0.01	0.96



Models: Jukes-Cantor (JC)

Rate matrix

$$\begin{array}{c|cccc} & A & G & C & T \\ A & -3\alpha & \alpha & \alpha & \alpha \\ G & \alpha & -3\alpha & \alpha & \alpha \\ C & \alpha & \alpha & -3\alpha & \alpha \\ T & \alpha & \alpha & \alpha & -3\alpha \end{array}$$

exp(t.R)

	A	G	C	T
A	0.9	0.05	0.03	0.02
G	0.05	0.87	0.07	0.01
C	0.03	0.07	0.89	0.01
T	0.02	0.01	0.01	0.96

there are 4 states

Models: Kimura's 2 parameter (K2)

Rate matrix

$$\begin{array}{c|cccc} & A & G & C & T \\ A & -\alpha-2\beta & \alpha & \beta & \beta \\ G & \alpha & -\alpha-2\beta & \beta & \beta \\ C & \beta & \beta & -\alpha-2\beta & \alpha \\ T & \beta & \beta & \alpha & -\alpha-2\beta \end{array}$$

exp(t.R)

	A	G	C	T
A	0.9	0.05	0.03	0.02
G	0.05	0.87	0.07	0.01
C	0.03	0.07	0.89	0.01
T	0.02	0.01	0.01	0.96

purine/pyrimidine mutations less likely

Models: Kimura's 3 parameter (K3)

Rate matrix

	A	G	C	T
A	$-\alpha-\beta-\gamma$	α	β	γ
G	α	$-\alpha-\beta-\gamma$	γ	β
C	γ	β	$-\alpha-\beta-\gamma$	α
T	β	γ	α	$-\alpha-\beta-\gamma$

exp(t.R)

take hydrogen bonds into account

	A	G	C	T
A	0.9	0.05	0.03	0.02
G	0.05	0.87	0.07	0.01
C	0.03	0.07	0.89	0.01
T	0.02	0.01	0.01	0.96

Reconstructing the tree?

Let D be samples from $\mu(T,w)$.
Can we reconstruct T (and w) ?

- parsimony
- distance based methods
- maximum likelihood methods (using MCMC)
- invariants
- ?

Main obstacle for all methods:

too many leaf-labeled trees

$(2n-3)!!=(2n-3)(2n-5)\ldots 3.1$

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Maximum likelihood method

Let D be samples from $\mu(T,w)$.

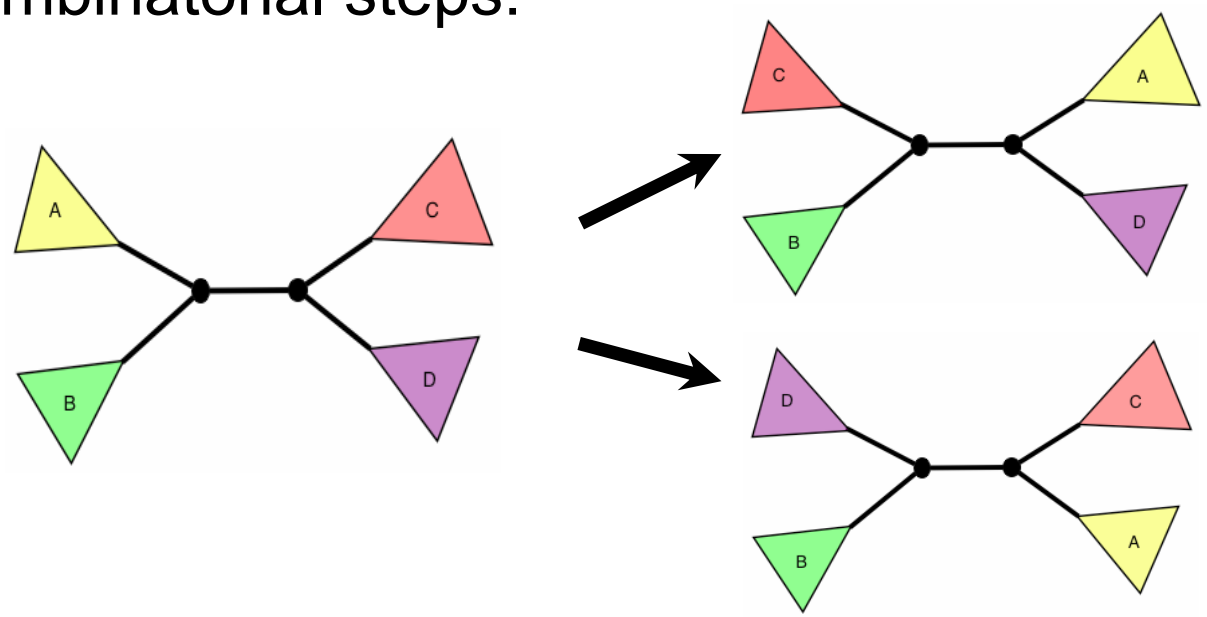
Likelihood of tree S is

$L(S) = \max_w \Pr(D \mid S,w)$

For $|D| \to \infty$ then the maximum likelihood tree is T

MCMC Algorithms for max-likelihood

Combinatorial steps:



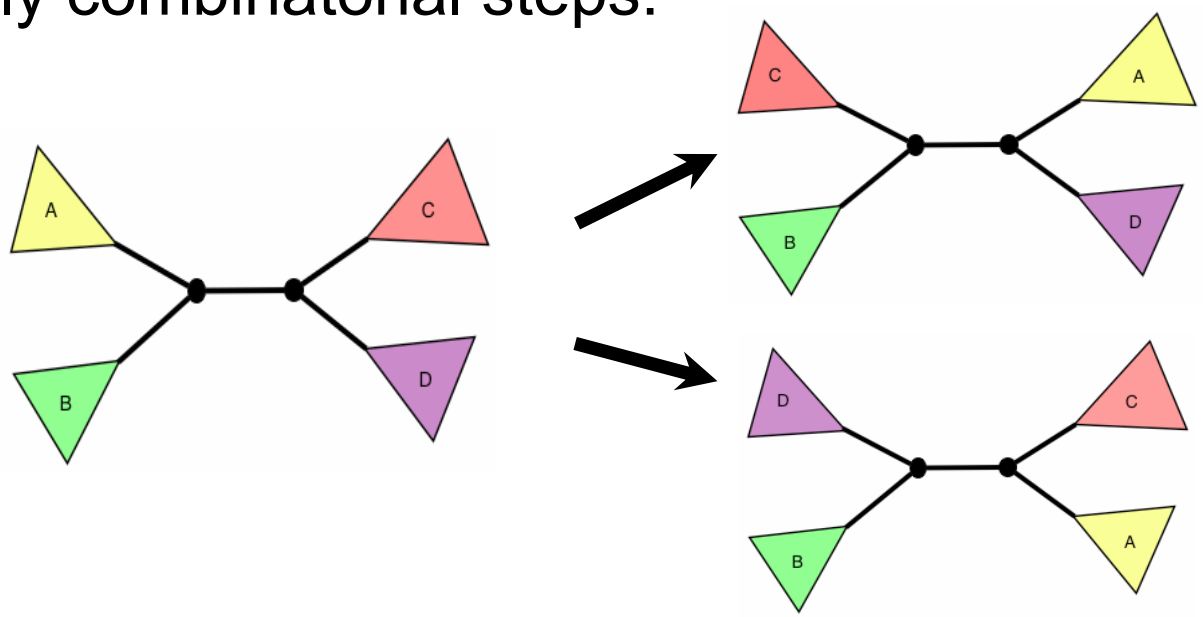
NNI moves (Nearest Neighbor Interchange)

Numerical steps (i.e., changing the weights)

Move with probability $min\{1, L(T_{new})/L(T_{old})\}$

MCMC Algorithms for max-likelihood

Only combinatorial steps:



NNI moves (Nearest Neighbor Interchange)

Does this Markov Chain mix rapidly?

Not known!

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Mixtures

For a tree topology T, set of weights $w_1, \ldots, w_\ell$ and probabilities $p_1, \ldots, p_\ell$ where $\sum_i p_i = 1$, consider the mixture distribution:

$$\mu = \sum_i p_i \mu(T, w_i)$$

one tree topology
multiple mixtures

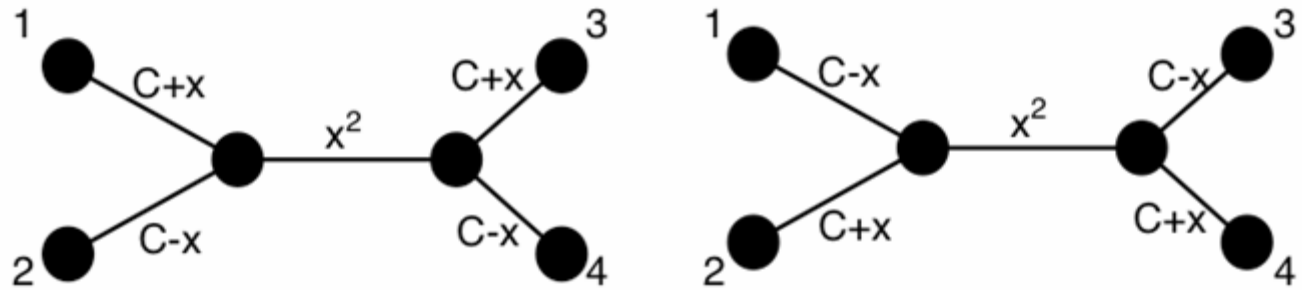
Can we reconstruct the tree T?

The mutation rates differ for positions in DNA

Reconstruction from mixtures - ML

Theorem 1:

maximum likelihood: fails to for CFN, JC, K2, K3



For every $0 < C < 1/2$, all x sufficiently small,

(i) maximum likelihood tree ≠ true tree

(ii) 5-leaf version: MCMC torpidly mixing

Similarly for JC, K2, and K3 models

Reconstruction from mixtures - ML

Related results:

[Kolaczkowski,Thornton] Nature, 2004.

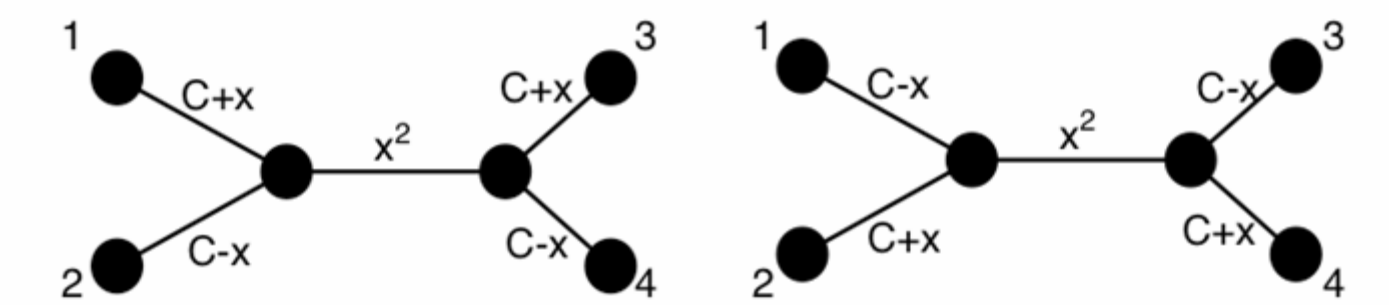
Experimental results for JC model

[Chang] Math. Biosci., 1996.

Different example for CFN model.

Reconstruction from mixtures - ML

Proof:



Difficulty: finding edge weights that maximize likelihood.

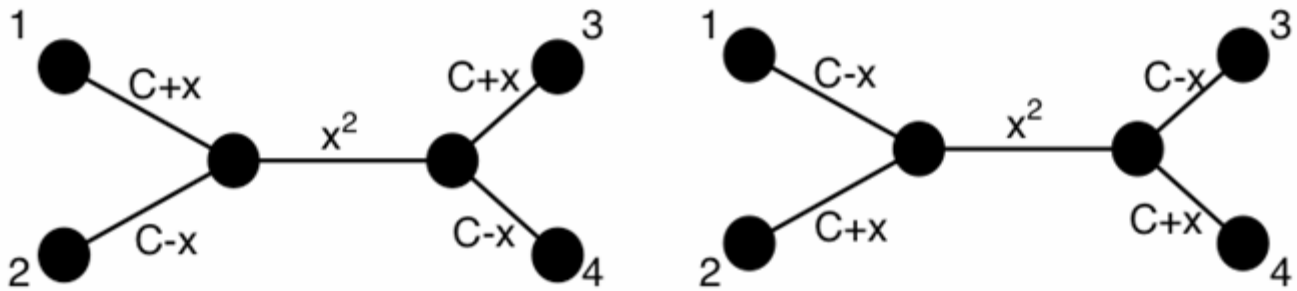
For x=0, trees are the same -- pure distribution, tree achievable on all topologies. So know max likelihood weights for every topology.

$$(\text{observed})^T \log \mu(T,w)$$

If observed comes from \mu(S,v) then it is optimal to take T=S and w=v (basic property of log-likelihood)

Reconstruction from mixtures - ML

Proof:



Difficulty: finding edge weights that maximize likelihood.

For x=0, trees are the same -- pure distribution, tree achievable on all topologies. So know max likelihood weights for every topology.

For x small, look at Taylor expansion bound max likelihood in terms of x=0 case and functions of Jacobian and Hessian.

$$L_{T,v+\Delta v}(\mu + x\Delta\mu) =$$

$$\mu^T \ln \mu + \mu^T \left(\frac{1}{2}(\Delta v)^T H_f(v)(\Delta v)\right) + x(\Delta\mu)^T \left(f(v) + J_f(v)(\Delta v)\right)$$
$$+O\left(||\Delta v||^3 + x||\Delta v||^2\right),$$

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Reconstruction – other algorithms?

GOAL: Determine tree topology

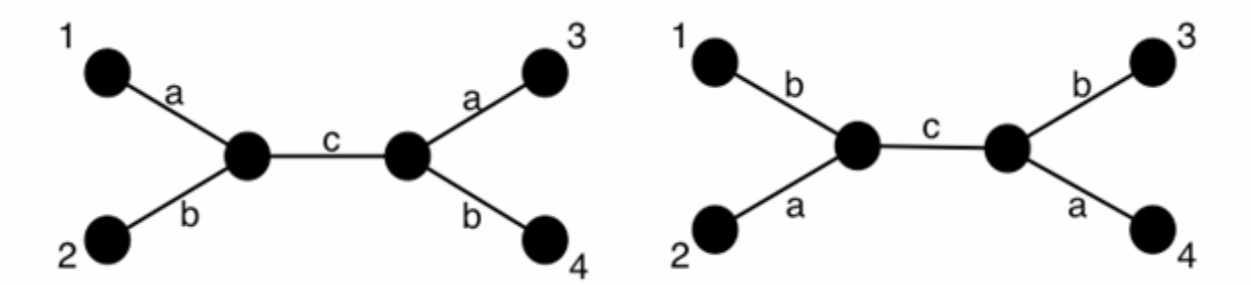
Duality theorem: Every model has either:

A) ambiguous mixture distributions on 4 leaf trees (reconstruction impossible)
B) linear tests (reconstruction easy)

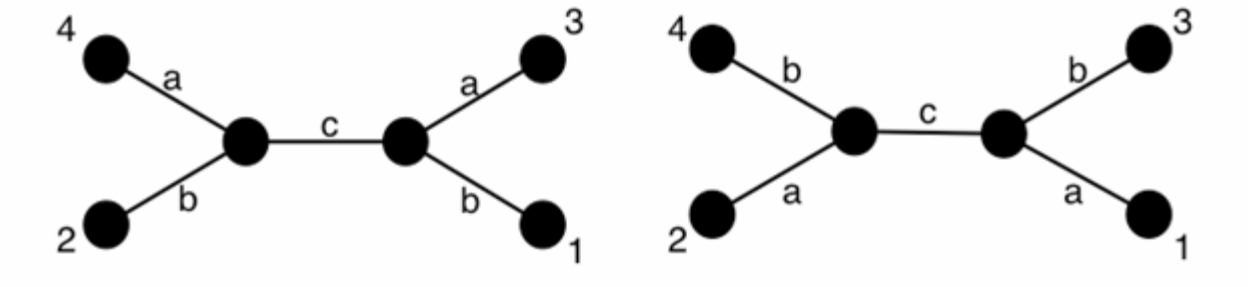
The dimension of the space of possible linear tests:

CFN = 2, JC = 2, K2 = 5, K3 = 9

Ambiguity in CFN model



For all $0<a,b<1/2$, there is $c=c(a,b)$ where:
above mixture distribution on tree T is identical to below mixture distribution on tree S.

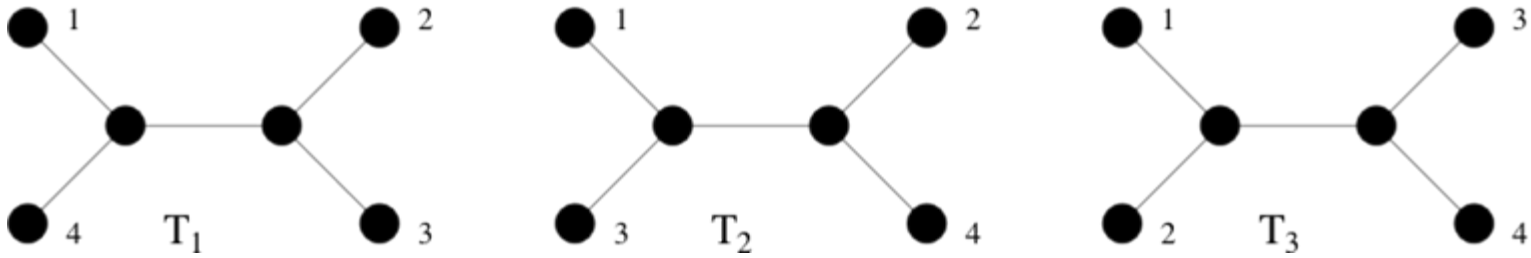


Previously: non-constructive proof of nicer ambiguity in CFN model [Steel,Szekely,Hendy,1996]

What about JC?

What about JC?

Reconstruction of the topology from mixture **possible.**



Linear test = linear function which is

>0 for mixture from T_2

<0 for mixture from T_3

There exists a linear test for JC model.

Follows immediately from Lake'1987 – linear invariants.

Lake's invariants $\rightarrow$ Test

f=μ(AGCC) + μ(ACAC) + μ(AACT) +μ(ACGT)
- μ(ACGC) - μ(AACC) - μ(ACAT) - μ(AGCT)

For μ=μ(T_1,w), $f=0$
For μ=μ(T_2,w), $f<0$
For μ=μ(T_3,w), $f>0$

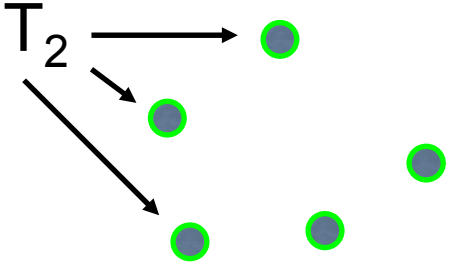
Linear invariants v. Tests

The set of points defined by $\mu(T_2, w)$ for all valid w defines a set describing all distributions generated by T_2.

The convex hull (i.e., linear combinations in that set) are the set of mixture distributions

Linear invariant = hyperplane containing mixtures from T_1

Test = hyperplane **strictly** separating mixtures from T_2 from mixtures from T_3

pure distributions from T_2 

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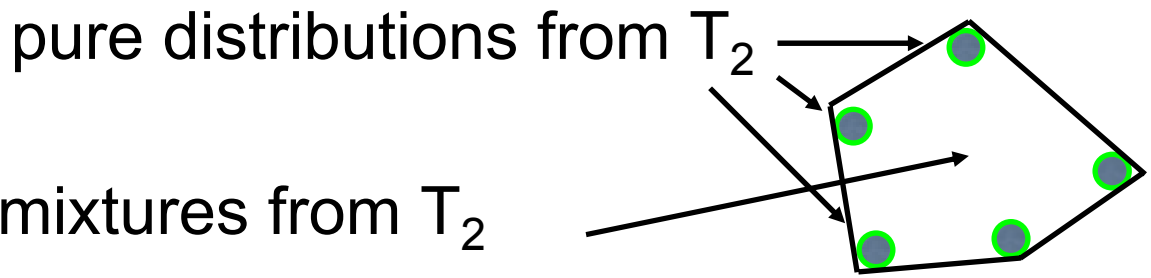

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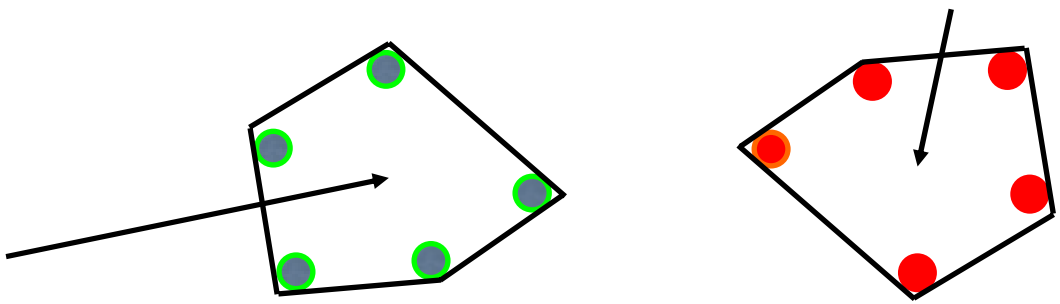
mixtures from T_3

mixtures from T_2



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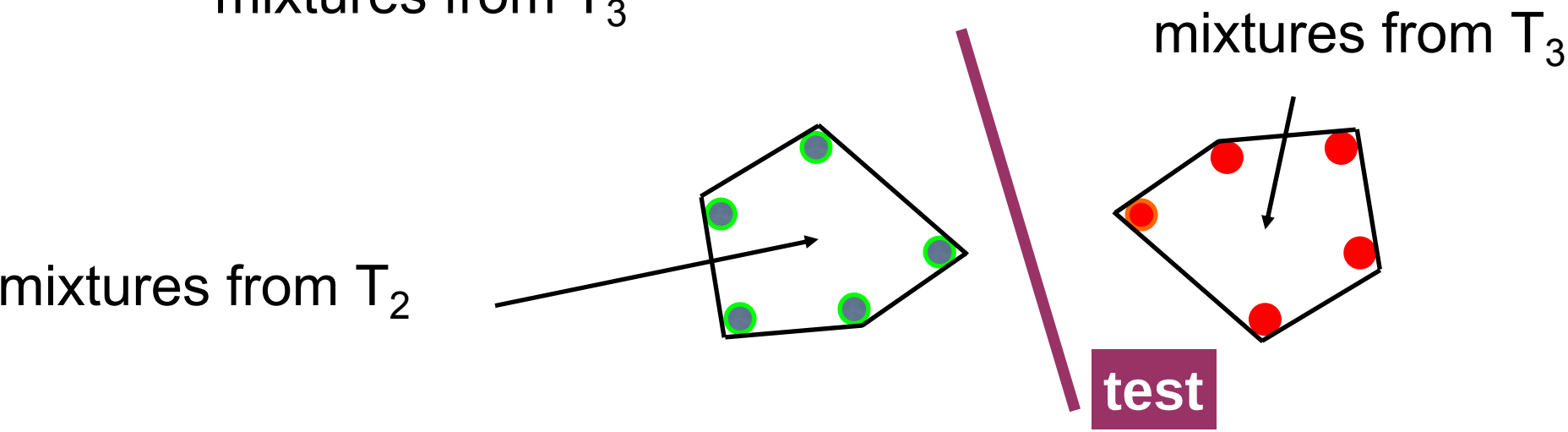

Separating hyperplanes

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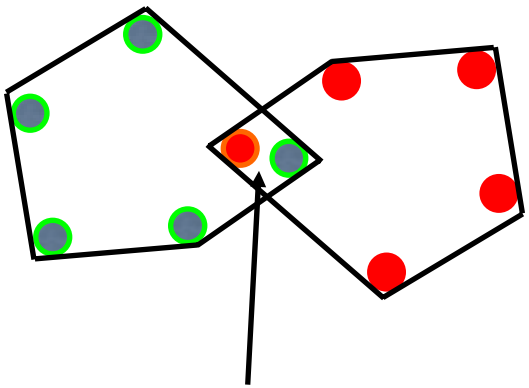
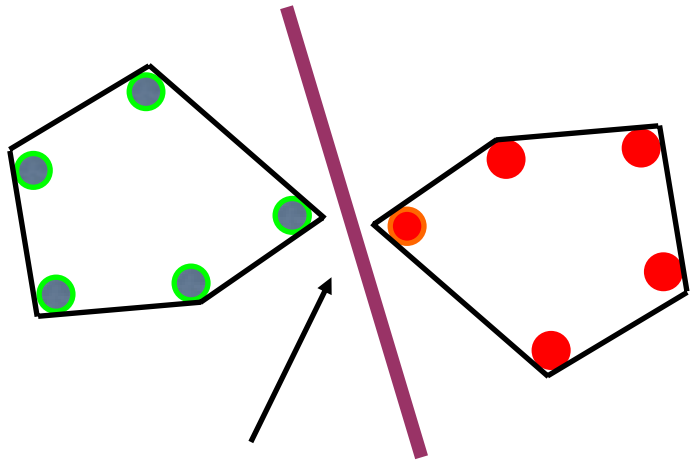
Separating hyperplane theorem:



ambiguous mixture



separating hyperplane

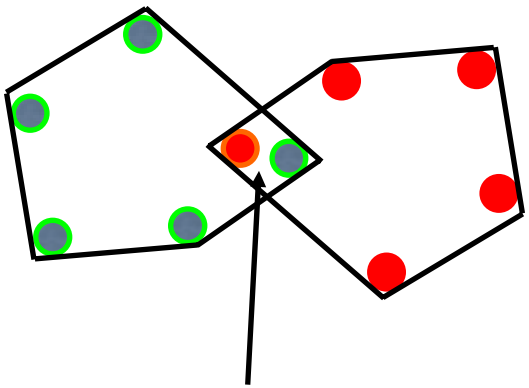
Strictly separating hyperplanes ???

Duality theorem: Every model has either:

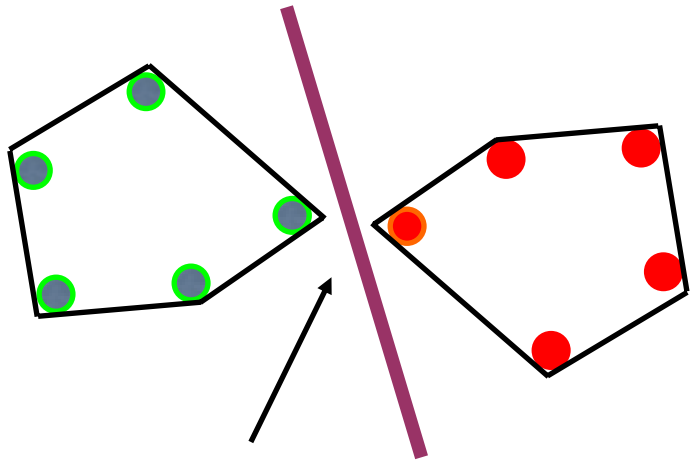
A) ambiguous mixture distributions on 4 leaf trees (reconstruction impossible)

B) linear tests (reconstruction easy)

Separating hyperplane theorem ?:



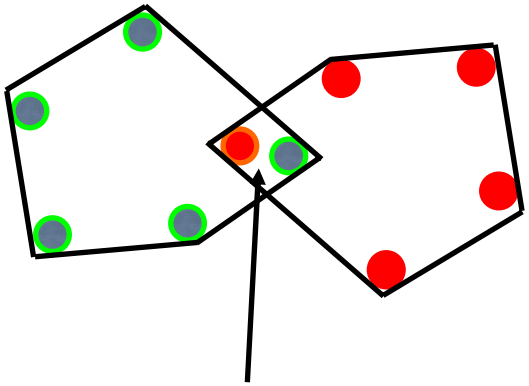
ambiguous mixture



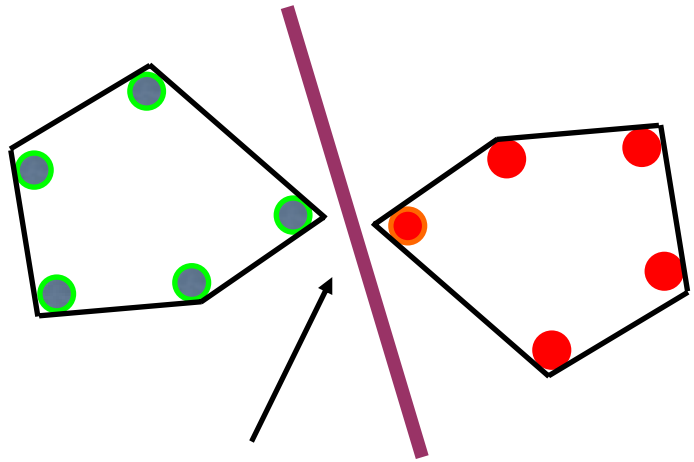
strictly separating hyperplane?

Strictly separating not always possible

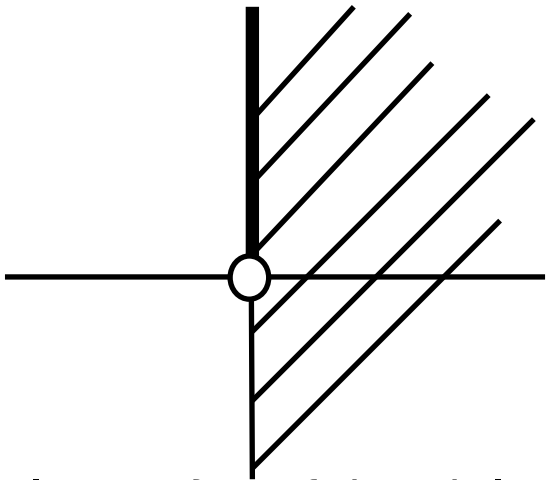
Separating hyperplane theorem ?:



ambiguous mixture



strictly separating hyperplane?

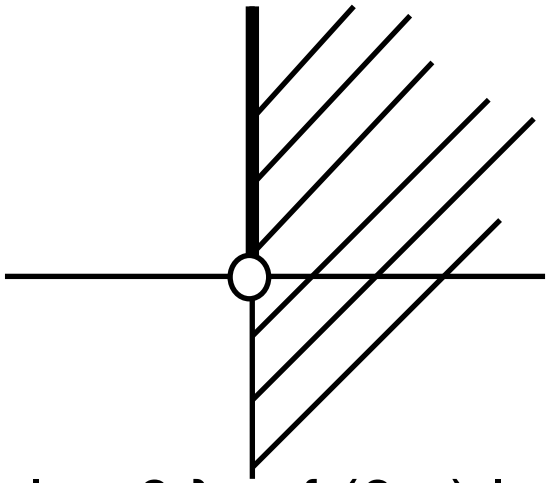


$\{ (x,y) \mid x>0 \} \cup \{ (0,y) \mid y>0 \}$

NO strictly separating hyperplane

$\{(0,0)\}$

When strictly separating possible?



NO strictly separating hyperplane

$\{ (x,y) \mid x>0 \} \cup \{ (0,y) \mid y>0 \}$

$(x, y^2 - xz) \qquad x \geq 0,\ y>0$

$\{(0,0)\}$

Lemma:
Sets which are convex hulls of images of open sets under a multi-linear polynomial map have a **strictly** separating hyperplane.

standard phylogeny models satisfy the assumption

Outline

Introduction (phylogeny, molecular phylogeny)

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Our setting: mixtures of distributions
ML, MCMC for ML fails for mixtures

Duality theorem: tests/ambiguous mixtures

Proofs (**strictly separating hyperplanes**,
non-constructive ambiguous mixtures)

Proof

Lemma:
For sets which are convex hulls of images of open sets under a multi-linear polynomial map – **strictly** separating hyperplane.

Proof:

$P_1(x_1,\ldots,x_m),\ldots,P_n(x_1,\ldots,x_m), \qquad x=(x_1,\ldots,x_m) \in O$

WLOG linearly independent

Proof

Lemma:
For sets which are convex hulls of images of open sets under a multi-linear polynomial map – **strictly** separating hyperplane.

Proof:

$P_1(x_1,\ldots,x_m),\ldots,P_n(x_1,\ldots,x_m), \qquad x=(x_1,\ldots,x_m) \in O$

Have $s_1,\ldots,s_n$ such that
$s_1 P_1(x) + \ldots + s_n P_n(x) \geq 0$ for all $x \in O$

Proof

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Goal: show
$s_1 P_1(x) + \ldots + s_n P_n(x) > 0$ for all $x \in O$

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Proof:

$P_1(x_1,\ldots,x_m),\ldots,P_n(x_1,\ldots,x_m), \qquad x=(x_1,\ldots,x_m) \in O$

Have $s_1,\ldots,s_n$ such that
$s_1 P_1(x) + \ldots + s_n P_n(x) \geq 0$ for all $x \in O$

Goal: show
$s_1 P_1(x) + \ldots + s_n P_n(x) > 0$ for all $x \in O$

Suppose: $s_1 P_1(a) + \ldots + s_n P_n(a) = 0$ for some $a \in O$

Proof

Lemma:
For sets which are convex hulls of images of open sets under a multi-linear polynomial map – **strictly** separating hyperplane.

Proof:

$P_1(x_1,\ldots,x_m),\ldots,P_n(x_1,\ldots,x_m), \qquad x=(x_1,\ldots,x_m) \in O$

linearly independent
$s_1 P_1(x) + \ldots + s_n P_n(x) \geq 0$ for all $x \in O$

$s_1 P_1(0) + \ldots + s_n P_n(0) = 0$
Let $R(x)=s_1 P_1(x) + \ldots + s_n P(x)$ - non-zero polynomial

Proof

Lemma:
For sets which are convex hulls of images of open sets under a multi-linear polynomial map – **strictly** separating hyperplane.

Proof:

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$s_1 P_1(0) + \ldots + s_n P_n(0) = 0$
Let $R(x)=s_1 P_1(x) + \ldots + s_n P(x)$ - non-zero polynomial

$R(0)=0 \Rightarrow$ no constant monomial

Proof

Lemma:
For sets which are convex hulls of images of open sets under a multi-linear polynomial map – **strictly** separating hyperplane.

Proof:

$P_1(x_1,\ldots,x_m),\ldots,P_n(x_1,\ldots,x_m), \qquad x=(x_1,\ldots,x_m) \in O$

linearly independent
$s_1 P_1(x) + \ldots + s_n P_n(x) \geq 0$ for all $x \in O$

$s_1 P_1(0) + \ldots + s_n P_n(0) = 0$
Let $R(x)=s_1 P_1(x) + \ldots + s_n P(x)$ - non-zero polynomial

$R(0,\ldots,0,x_i,0\ldots,0) \geq 0 \Rightarrow$ no monomial x_i

Proof

Lemma:
For sets which are convex hulls of images of open sets under a multi-linear polynomial map – **strictly** separating hyperplane.

Proof:

$P_1(x_1,\ldots,x_m),\ldots,P_n(x_1,\ldots,x_m), \qquad x=(x_1,\ldots,x_m) \in O$

linearly independent
$s_1 P_1(x) + \ldots + s_n P_n(x) \geq 0$ for all $x \in O$

$s_1 P_1(0) + \ldots + s_n P_n(0) = 0$
Let $R(x)=s_1 P_1(x) + \ldots + s_n P(x)$ - non-zero polynomial

$R(0,\ldots,0,x_i,0\ldots,0) \geq 0 \Rightarrow$ no monomial x_i
$\ldots. \Rightarrow$ no monomials at all, a contradiction

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Duality application:

non-constructive proof of mixtures

Duality theorem: Every model has either:

A) ambiguous mixture distributions on 4 leaf trees (reconstruction impossible)

B) linear tests (reconstruction easy)

For K3 model the space of possible tests has dimension 9

$$T = \sigma_1 T_1 + \ldots + \sigma_9 T_9$$

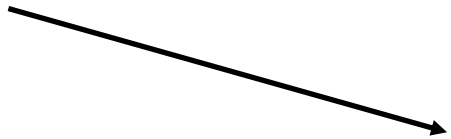
Goal: show that there exists no test

Duality application:

non-constructive proof of mixtures

rate matrix

	A	G	C	T
A	$-\alpha-\beta-\gamma$	α	β	γ
G	α	$-\alpha-\beta-\gamma$	γ	β
C	γ	β	$-\alpha-\beta-\gamma$	α
T	β	γ	α	$-\alpha-\beta-\gamma$



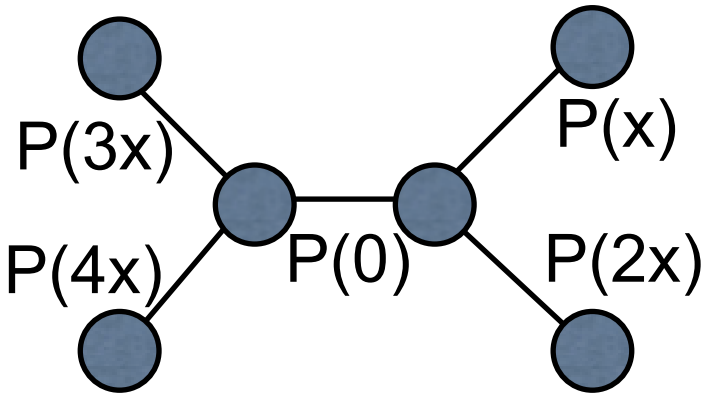
transition matrix P = exp(x.R)

entries in P = generalized polynomials

$\sum$ poly(α,β,γ,x) exp(lin(α,β,γ,x))

LEM: The set of roots of a non-zero generalized polynomial has measure 0.

Non-constructive proof of mixtures



transition matrix $P(x) = \exp(x.R)$

Test should be 0 by continuity.

$T_1,\ldots,T_9$ are generalized polynomials in α,β,γ,x

Wronskian $\det W_x(T_1,\ldots,T_9)$ is a generalized polynomial α,β,γ,x

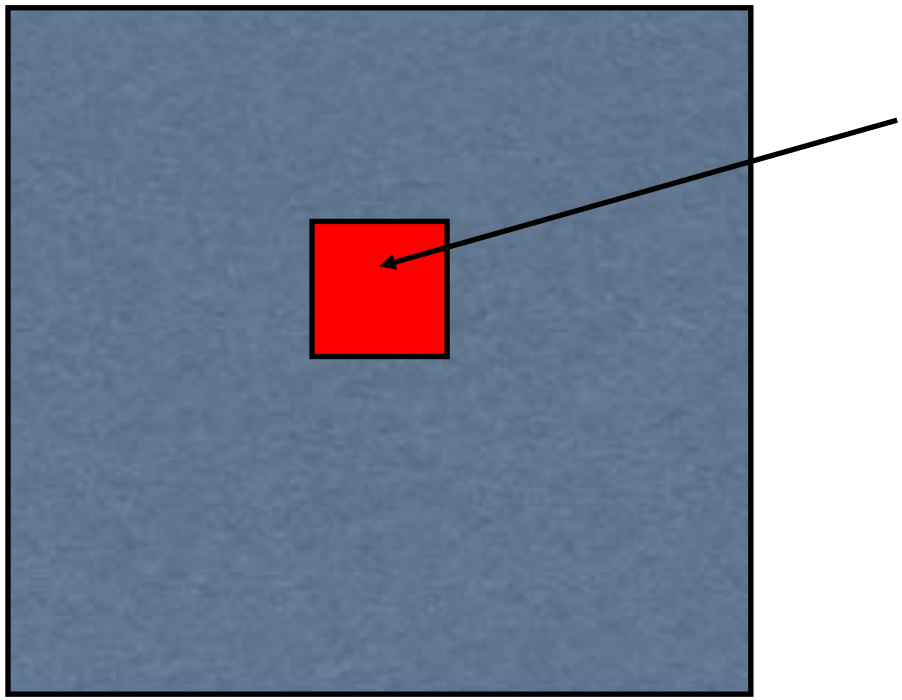
$\det W_x(T_1,\ldots,T_9) \neq 0$

$W_x(T_1,\ldots T_9)\,[\sigma_1,\ldots\sigma_9]=0$

$\Rightarrow$**NO TEST !**

Non-constructive proof of mixtures

The last obstacle: Wronskian W(T1,…,T9) is **non-zero**



Horrendous generalized polynomials, even for e.g., $\alpha=1,\beta=2,\gamma=4$

plug-in complex numbers

LEM: The set of roots of a **non-zero** generalized polynomial has measure 0.

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Open questions

M a semigroup of doubly stochasic matrices (with multiplication). Under what conditions on M can you reconstruct the tree topology?

*	x	x	x
x	*	x	x
x	x	*	x
x	x	x	*

$0<x<1/4$

yes

$0<x<1/2$

no

*	x
x	*

*	x	y	y
x	*	y	y
y	y	*	x
y	y	x	*

$0<y\cdot x<1/4$

yes

$0<z\cdot y\cdot x<1/2$

no

*	x	y	z
x	*	z	y
y	z	*	x
z	y	x	*

Open questions

Idealized setting: For data generated from a pure distribution (i.e., a single tree, no mixture):

Are MCMC algorithms *rapidly* or *torpidly mixing?*

How many characters (samples) needed until maximum likelihood tree is true tree?