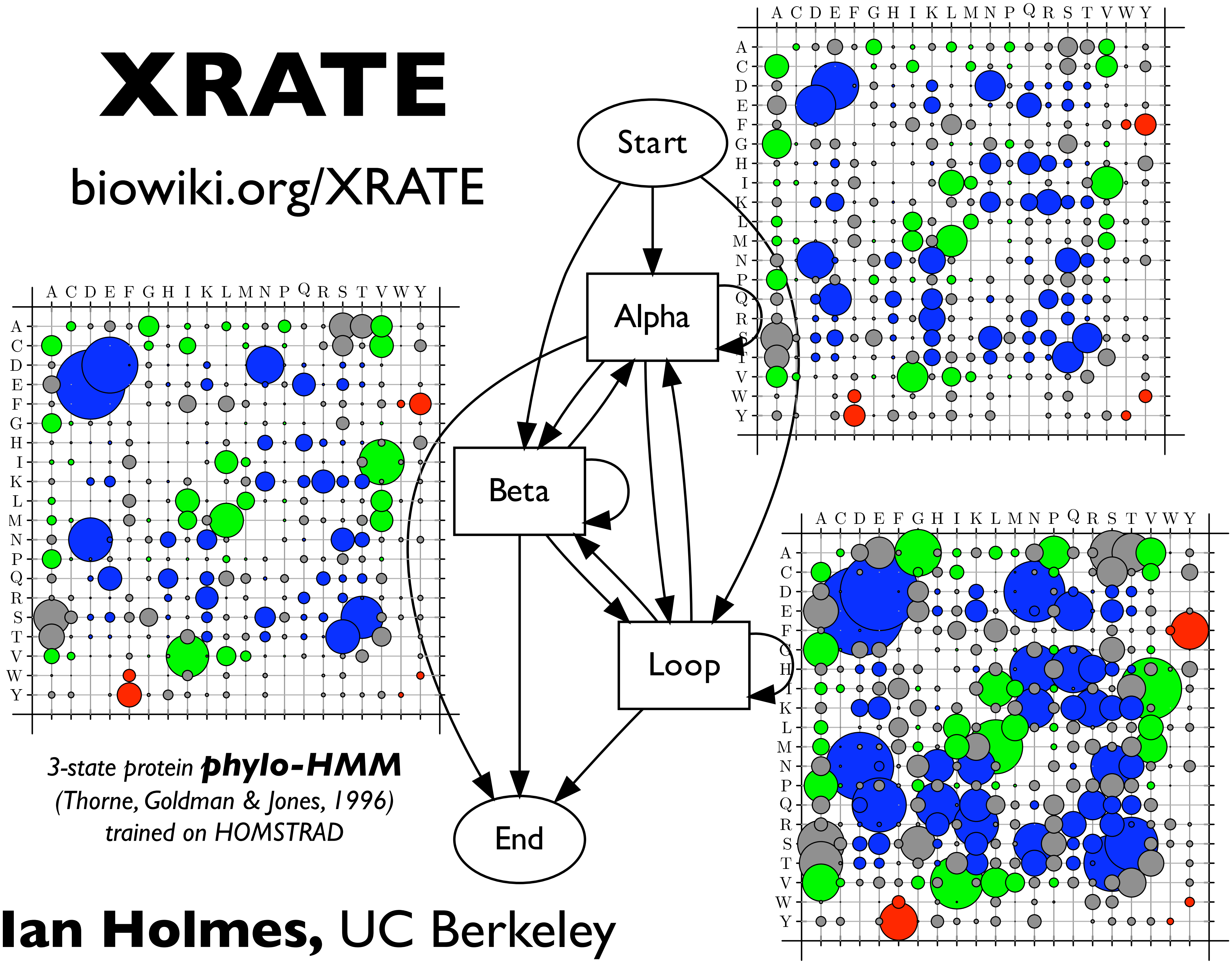
XRATE

biowiki.org/XRATE

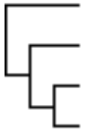

Start
Alpha
Beta
Loop
End
A C D E F G H I K L M N P Q R S T V W Y
A C D E F G H I K L M N P Q R S T V W Y

3-state protein ***phylo-HMM***
(Thorne, Goldman & Jones, 1996)
trained on HOMSTRAD

Ian Holmes, UC Berkeley

HMM emitting columns of amino acids

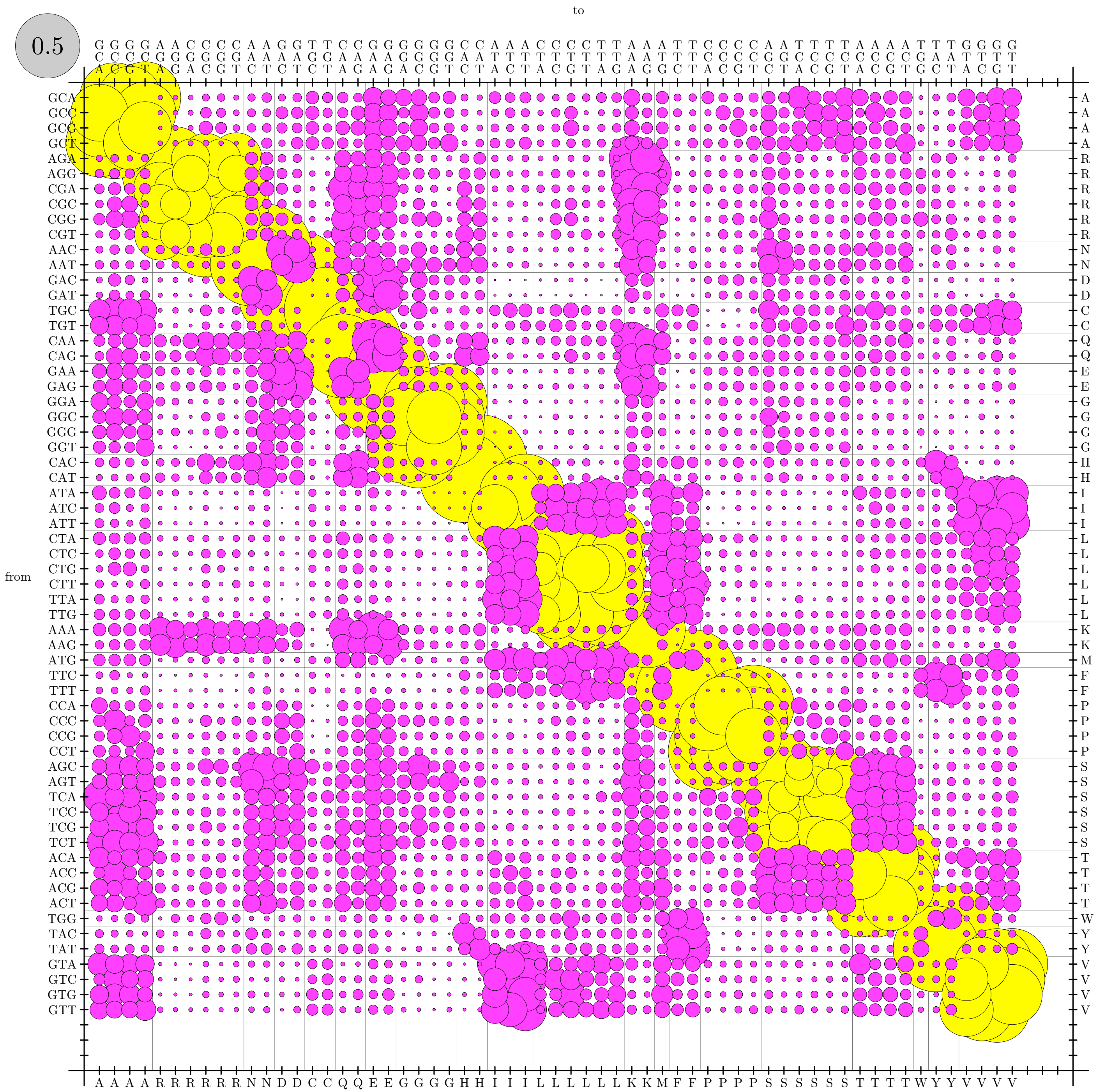
Ricin alignment;
colors denote secondary structure



*Finite continuous-time Markov chain +
tree + HMM = Felsenstein + Viterbi*

Thorne, Goldman, Jones; MBE, 1996

Codons



Empirical 61x61 matrix trained on PANDIT (7738 protein families)

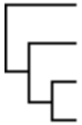
Kosiol, Holmes & **Goldman,** MBE 2007

Parametric d_N/d_S models correctly reproduce PAML

Heger, Ponting & Holmes, *in prep*

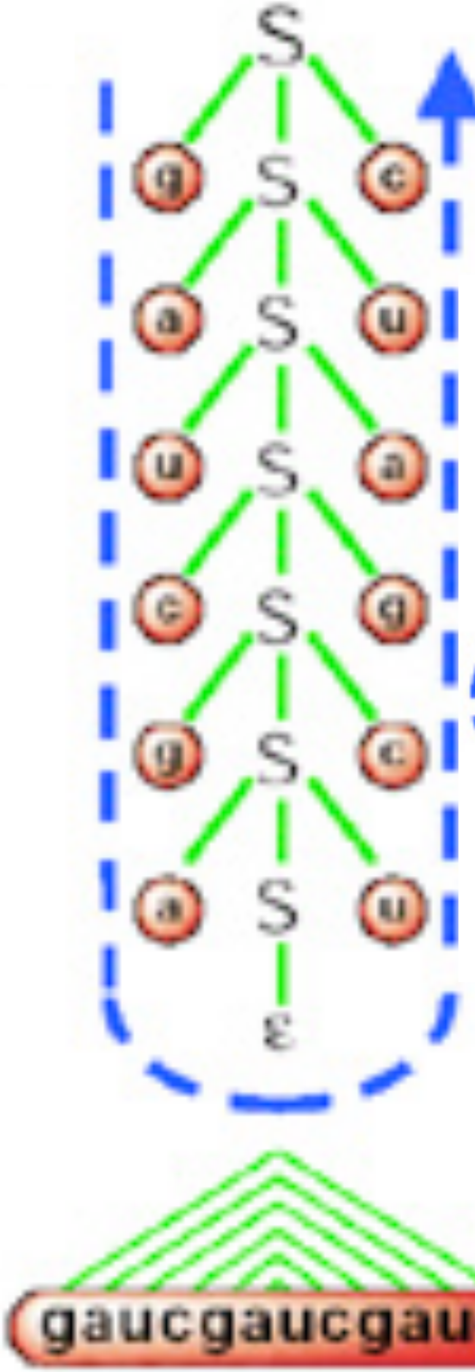
HMM emitting exons and introns

Intron flanked by two exons (simple example)

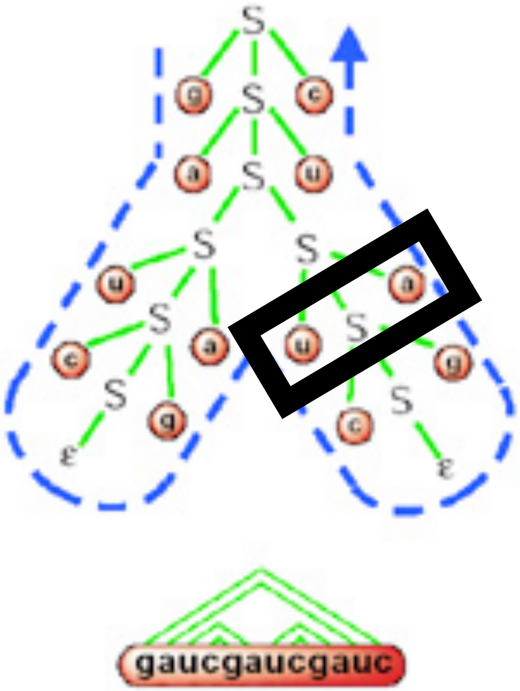


e.g. Pedersen & Hein, Bioinf., 2003
Siepel & Haussler, 2004

RNA



Context-free RNA parse tree
Searls, 2002



Phylo-SCFGs:

PFOLD

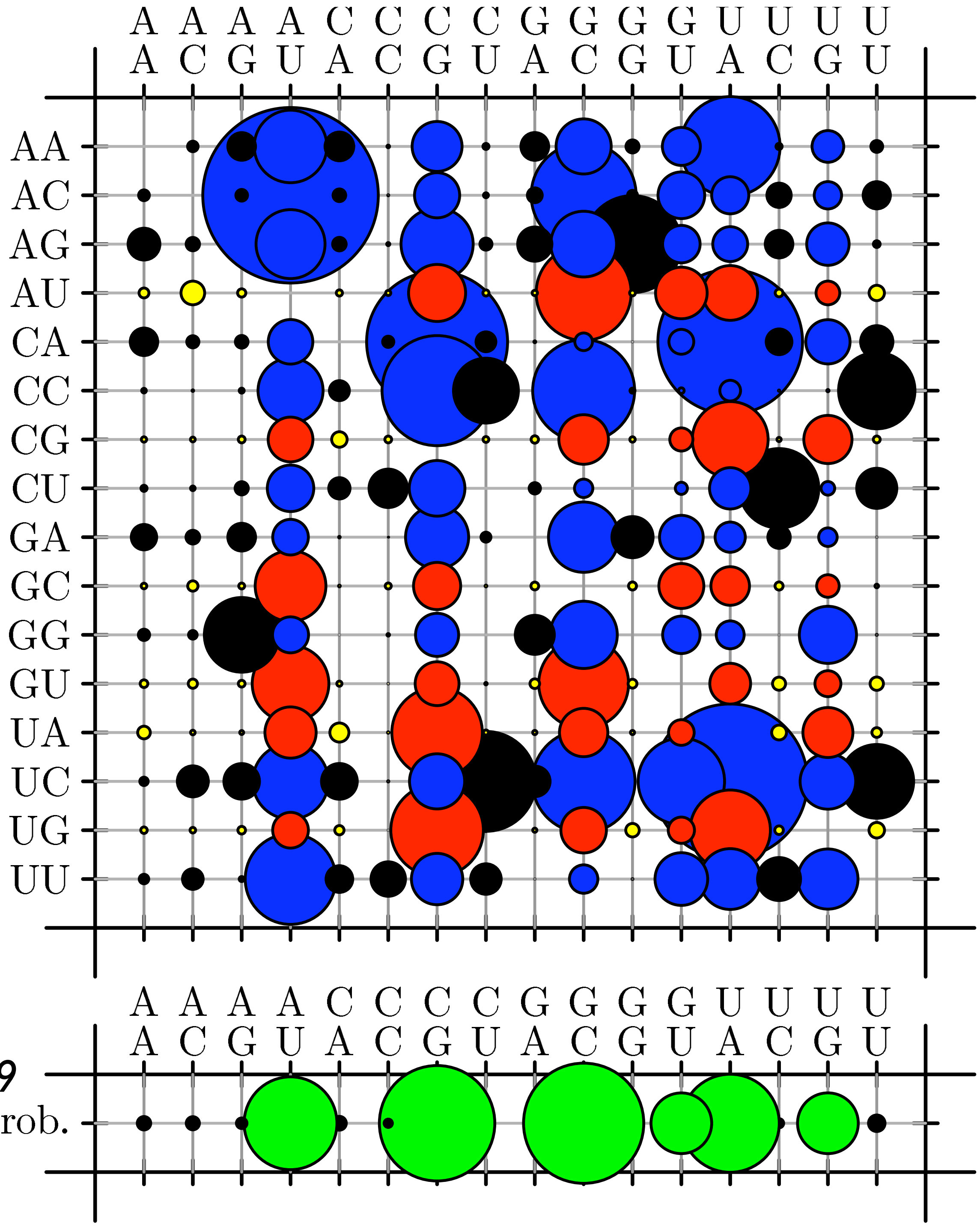
Knudsen & Hein, 1999

EVOFOLD

Pedersen et al, 2004

ClosingBp

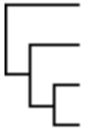
Bradley et al, 2008



Trained on rRNA (Dowell & Eddy, 2006)

SCFG emitting basepaired columns

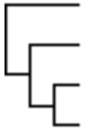
Hammerhead ribozyme



PFOLD
Knudsen & Hein, Bioinformatics, 1999

SCFG emitting basepaired columns

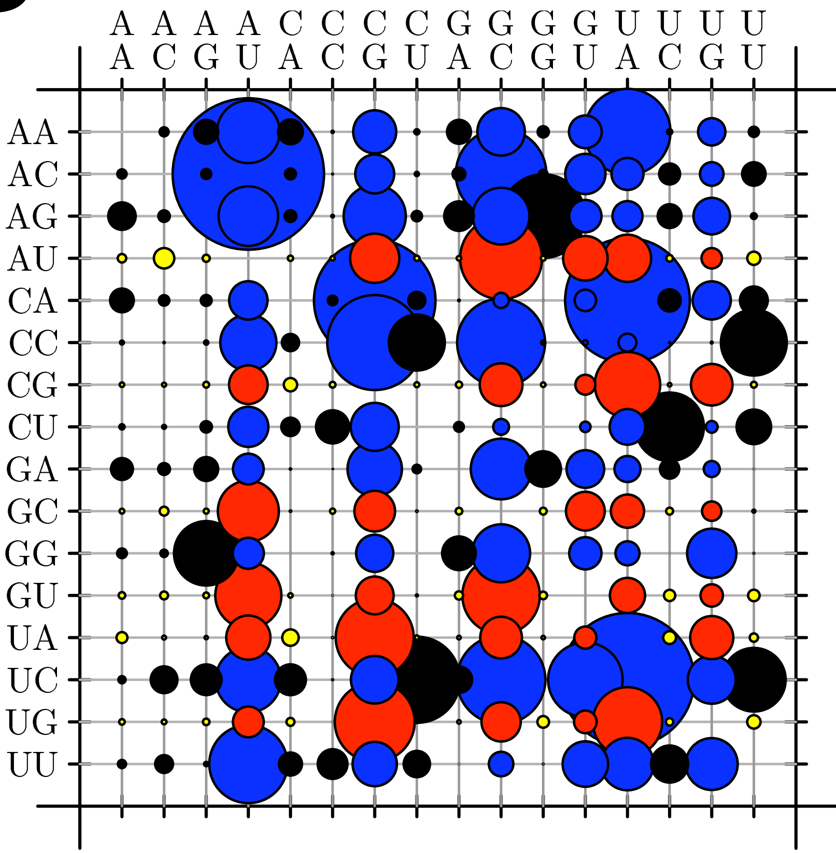
Hammerhead ribozyme

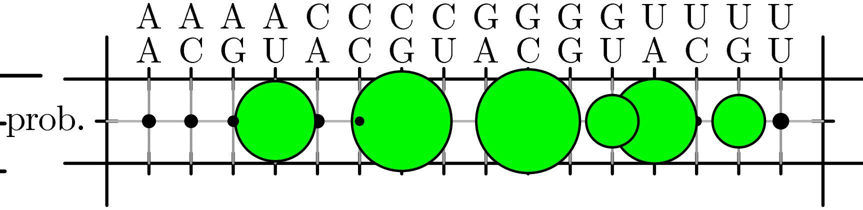


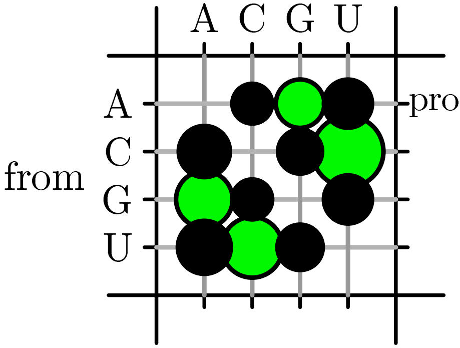
PFOLD
Knudsen & Hein, Bioinformatics, 1999

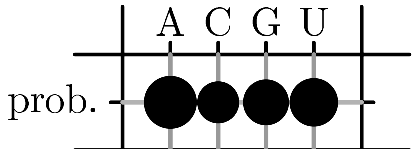
PFOLD phylo-grammar

```
S   →  L (0.131)
     | B (0.869)

F   →  lnuc F* rnuc
F*  →  F (0.788)
     | B (0.212)

L   →  F (0.105)
     | U (0.895)

B   →  L S

U   →  nuc U*
U*  →  End
```









PFOLD in xrate format

```
S   → L (0.131)
    | B (0.869)

F   → lnuc F* rnuc
F*  → F (0.788)
    | B (0.212)

L   → F (0.105)
    | U (0.895)

B   → L S

U   → nuc U*
U*  → End
```

```
;; state S: the initial state. Goes to L or B
(transform (from (S)) (to (L)) (prob 0.131))
(transform (from (S)) (to (B)) (prob 0.869))

;; state F: emits a covarying base pair
(transform (from (F)) (to (LNUC F* RNUC)))
(transform (from (F*)) (to (F)) (prob 0.788))
(transform (from (F*)) (to (B)) (prob 0.212))

;; state L: goes to U (unpaired) or F (paired)
(transform (from (L)) (to (F)) (prob 0.105))
(transform (from (L)) (to (U)) (prob 0.895))

;; state B: generates a bifurcation
(transform (from (B)) (to (L S)))

;; state U: emits a single unpaired base
(transform (from (U)) (to (NUC U*)))
(transform (from (U*)) (to ()) (prob 1))
```

Bioinformatics motivation

- **Analyze multiple sequence alignments**
  - **measure** evolutionary rates in various contexts
  - **annotate** ncRNAs, CDS's, motifs, pseudogenes, ...

- **Develop versatile models, algorithms, tools**
  - *"phylo-grammars"*
  - Expectation Maximization, "phylo-EM"
  - Extensible: gap characters, lineage-specific rates, arbitrary grammars/models, parametric (c.f. HyPhy), ...

Phylo-Grammar literature

- Felsenstein & Churchill. 1996.
  Three-state phylo-HMM (rates .3, 2, 10).
- Thorne, Goldman & Jones. 1996.
  Protein secondary structure phylo-HMM.
- Knudsen & Hein. 1999.
  Phylo-SCFG for RNA structure prediction.
- Pedersen & Hein. 2003.
  Phylo-HMM for gene prediction.
- Siepel & Haussler. 2004.
  Dinucleotide (CpG) null model.

The Expectation Maximization algorithm for estimating substitution rate matrices from multiple alignments with phylogenetic trees

a.k.a.

“Phylo-EM”

Phylo-EM (definitions)

$$\theta = \{\pi, \mathbf{R}\}$$

Parameters

$$p_i(t) = P(x(t) = i)$$

x(t) = state at time t

$$\begin{aligned} \frac{d}{dt}\mathbf{p}(t) &= \mathbf{R}\mathbf{p} \\ \mathbf{p}(0) &= \pi \end{aligned}$$

Equation of state

$$\begin{aligned} \mathbf{p}(t) &= \pi\mathbf{M}(t) \\ \mathbf{M}(t) &= \exp(\mathbf{R}t) \end{aligned}$$

Matrix exponential

$$= \mathbf{U}\exp(\mathbf{D}t)\mathbf{U}^{-1}$$

Diagonal form

$$\mathbf{R} = \mathbf{U}^{-1}\mathbf{D}\mathbf{U}$$

Phylo-EM (derivation)

$$\begin{aligned}
\theta^{(n+1)} &= \text{argmax}_\theta \; \mathcal{E}(\theta|\theta^{(n)}) \\
\mathcal{E}(\theta|\theta^{(n)}) &= \sum_x P(x|y,\theta^{(n)}) \log P(x,y|\theta)
\end{aligned}$$

(general form of EM algorithm)

$$\begin{aligned}
y &= \text{present-day sequences (observed)} \\
x &= \text{ancestral sequences (unobserved)}
\end{aligned}$$

$$\mathcal{E}(\theta|\theta^{(n)}) = \sum_i \left(S_i \log \pi_i + D_i R_{ii} + \sum_{j \neq i} C_{ij} \log R_{ij} \right)$$

$$\begin{aligned}
S_i &= E\left[\#\text{ of ancestral residues in state } i\right] \\
D_i &= E\left[\#\text{ of residues} \times \text{time spent in state } i\right] \\
C_{ij} &= E\left[\#\text{ of mutations } i \rightarrow j\right]
\end{aligned}$$

Phylo-EM (algorithm)

$$R_{ij} \quad \leftarrow \quad \frac{C_{ij}}{D_i}$$

(iterate to convergence)

$$R_{ij} \quad = \quad \text{Rate of substitution } i \to j$$

(continuous-time Markov chain)

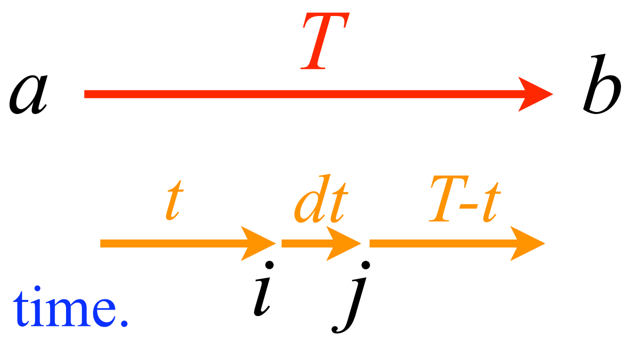
$$C_{ij} \quad = \quad E[\text{number of } i \to j \text{ substitutions}]$$

$$D_i \quad = \quad E[\text{dwell time in state } i]$$

posterior expectations: $E[x] \equiv \langle x \rangle_{P(\text{history}|\text{data},\mathbf{R})}$

On branch of length T, transition $a \to b$ is observed. Expected number of $i \to j$ substitution events: $C_{ij}(a,b,T)$

$$\begin{aligned}\mathbf{R} &= \mathbf{U}\Lambda\mathbf{U}^{-1}\\ \exp(\mathbf{R}t) &= \mathbf{U}\exp(\Lambda t)\mathbf{U}^{-1}\end{aligned}$$



Diagonalize rate matrix. Integrate over substitution event time.

$$\begin{aligned}C_{ij}(a,b,T) &= \frac{1}{\exp(\mathbf{R}T)_{ab}}\int_0^T \exp(\mathbf{R}t)_{ai}\ (R_{ij}dt)\ \exp(\mathbf{R}(T-t))_{jb}\\ &= \frac{R_{ij}}{\exp(\mathbf{R}T)_{ab}}\sum_{k=1}^{N} U_{ak}U^{-1}_{ki}\sum_{l=1}^{N} U_{jl}U^{-1}_{lb}\mathcal{J}_{kl}(T)\end{aligned}$$

Integral for dwell time $D_i(a,b,T)$ can similarly be expressed in terms of...

$$\mathcal{J}_{kl}(T) = \begin{cases} T\exp(\lambda_k T) & \text{if } \lambda_k = \lambda_l \\ (\exp(\lambda_k T) - \exp(\lambda_l T))/(\lambda_k - \lambda_l) & \text{if } \lambda_k \neq \lambda_l \end{cases}$$

Loop & stem rates

- Can formulate evolutionary questions as phylo-grammar parameterization problems

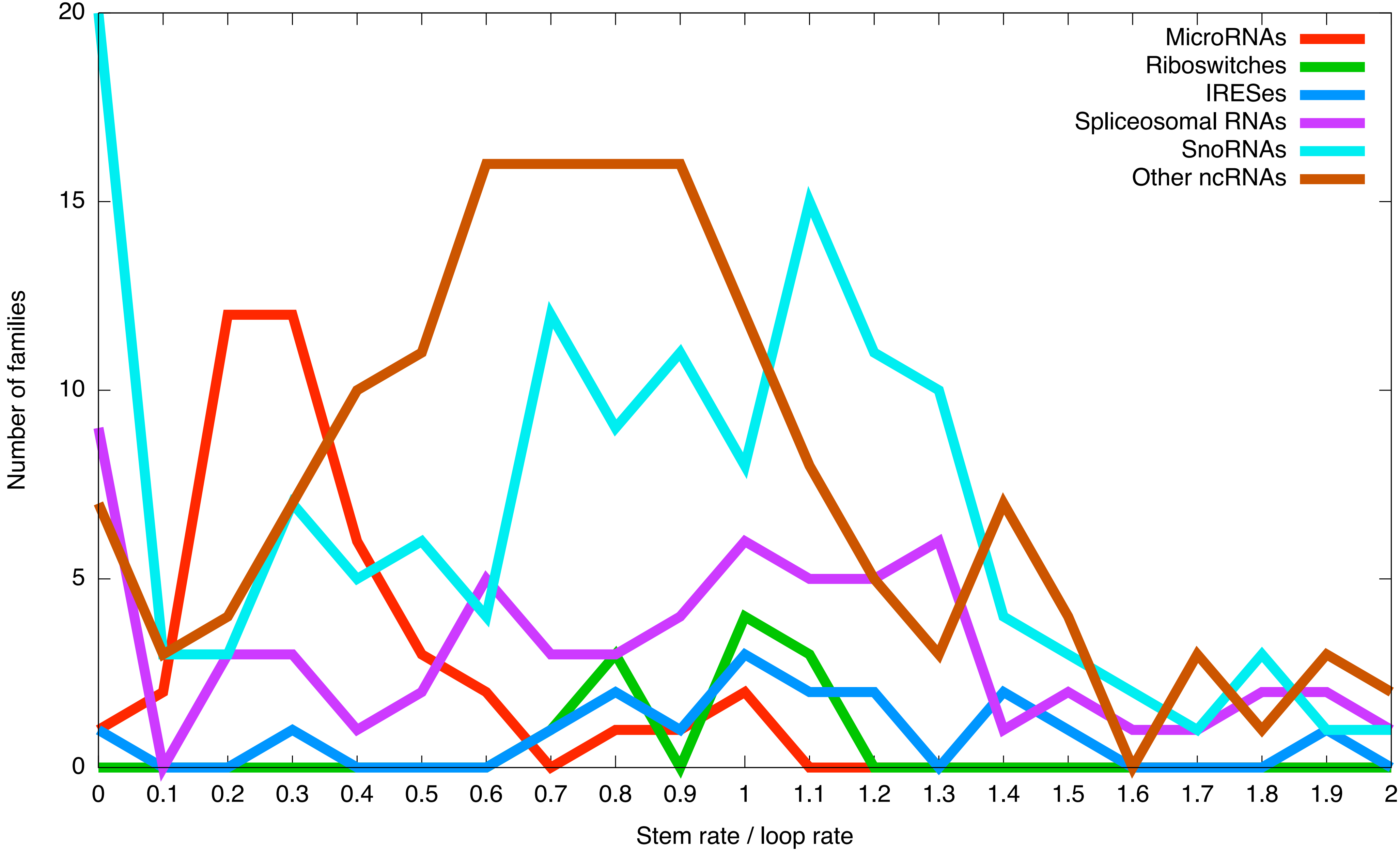
  e.g. "what is the ratio of substitution rates in loops compared to stems?"

- 323 RFAM families in 5 classes (miRNA, U*, sno*, IRES, riboswitch)

- Use XRate to estimate trees (Jukes-Cantor)

- Fit scaling factors to loop & stem matrices

miRNA stems evolve slower than other ncRNAs



Trained on RFAM

Limitations of phylo-EM

- **Advantages of phylo-EM**
  - Converges very quickly
  - Counts are useful in themselves
- **Disadvantages**
  - Gets stuck in local maxima
  - Sensitive to initial seed
  - Point estimate; no “error bars”
- **An MCMC equivalent would be nice**

EM-flavored MCMC

1. Sample θ from $g(\theta|\theta^{(n)})$:

$$\begin{aligned} g(\theta|\theta^{(n)}) &= \frac{\exp\left(\mathcal{E}(\theta|\theta^{(n)})\right)}{Z} \\ Z &= \int \exp\left(\mathcal{E}(\theta'|\theta^{(n)})\right) d\theta' \end{aligned}$$

2. Accept new θ with Hastings probability

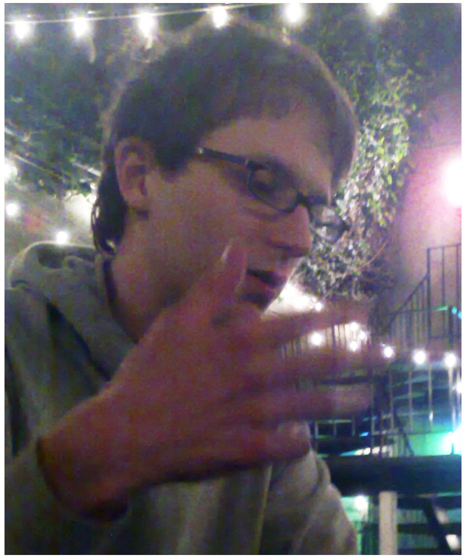
$$h(\theta,\theta^{(n)}) = \frac{P(y|\theta)}{P(y|\theta^{(n)})}\frac{g(\theta^{(n)}|\theta)}{g(\theta|\theta^{(n)})} = \frac{P(y|\theta)}{P(y|\theta^{(n)})}\exp\left(\mathcal{E}(\theta^{(n)}|\theta) - \mathcal{E}(\theta|\theta^{(n)})\right)$$

3. If accept, set $\theta^{(n+1)} \leftarrow \theta$
   If reject, set $\theta^{(n+1)} \leftarrow \theta^{(n)}$

Code's at **biowiki.org**, thanks to...

Robert Bradley

Andrew Uzilov



Lars Barquist

Collaborators

Marc Suchard
Nick Goldman
Carolin Kosiol
Chris Ponting
Andreas Heger
Sue Celniker
Mike Eisen

Mitchell Skinner

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