Modeling evolution of transcription factor binding sites

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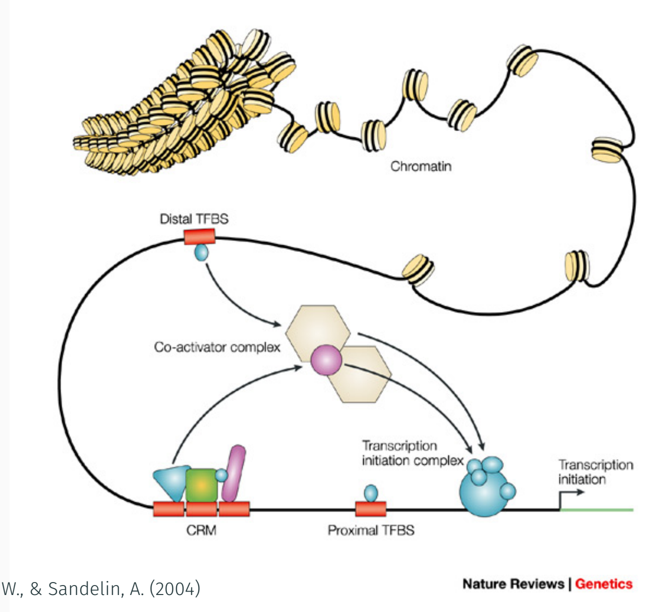
Introduction

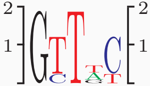
TFs bind to specific sets of short sequences



Wasserman, W. W., & Sandelin, A. (2004)

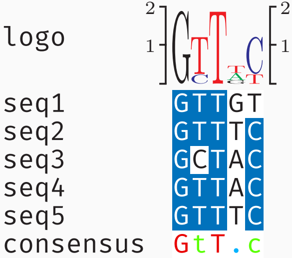
TFBS: Properties

- Short sequences (5-25bp)

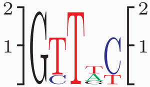
logo	
seq1	GTTGT
seq2	GTTTC
seq3	GCTAC
seq4	GTTAC
seq5	GTTTC
consensus	GtT.c

TFBS: Properties

- Short sequences (5-25bp)
- Proximity to TSS (100-1000bp)



- Short sequences (5-25bp)
- Proximity to TSS (100-1000bp)
- Degeneracy

logo 

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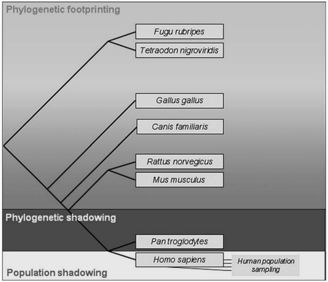
Separation of mutability and selection

Phylogenetic footprinting for identifying regulatory elements



- Selective pressure causes slower evolution of regulatory elements
- Phylogenetic footprinting – Identifying highly consered sequences in evolutionary diverse species
- Need to explicitly model phylogenetic relationship over simple conservation based approaches

Tagle et al. (1988)

Substitution Models

- Evolution can be modeled as a continuous time markov chain. Transition Matrix $P(t) = \{P_{\alpha\beta}\}$
- Rate matrix $Q = \begin{pmatrix} * & \mu_{AC} & \mu_{AG} & \mu_{AT} \\ & & \dots & \end{pmatrix}$
- $p_\alpha(t + \delta t) = p_\alpha(t) + \sum_{\beta \neq \alpha} \mu_{\beta\alpha} p_\beta(t) - \sum_{\beta \neq \alpha} \mu_{\alpha\beta} p_\alpha(t)$
- $P(t) = \exp(Qt)$
- Simple models
    - Jukes Cantor (JC69): Equal base frequencies and equal mutation rates
    - Kimura (K80): Distinguishes between transition and transversion ratios
    - Felenstein (F81): Allows different base frequencies
    - HKY: Kimura+Felenstein

Halpern Bruno Model : Accounting for position specific selection

- Substitution v/s Mutation : Different things
- JC/K80/F81: Do not explicitly differentiate mutation from selection
- HB Model:

$$\underbrace{r^i_{\alpha\beta}}_{\text{Substitution rate}} = \underbrace{\mu_{\alpha\beta}}_{\text{Probability of mutation(inst.)}} \times \overbrace{f^i_{\alpha\beta}}^{\text{Probability of fixation}}$$

  - 'Position-specific selection aware' substitution model, originally formulated for amino acids
  - All positions in the binding site evolve independently at equal rates
  - Covariation structure between different species are ignored

Halpern Bruno Model : Estimating fixation probability

$$r^i_{\alpha\beta} = \mu_{\alpha\beta} \times f^i_{\alpha\beta}$$

- Selection coefficient(s) – Relative reduction in contribution of β over α to fitness

$$F(\alpha) = 1; F(\beta) = 1 + s$$

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- Reversibility condition: $\pi_\alpha \mu_{\alpha\beta} f_{\alpha\beta} = \pi_\beta \mu_{\beta\alpha} f_{\beta\alpha} \implies \frac{\pi_\beta \mu_{\beta\alpha}}{\pi_\alpha \mu_{\alpha\beta}} = \frac{f_{\alpha\beta}}{f_{\beta\alpha}} = e^{2Ns}$

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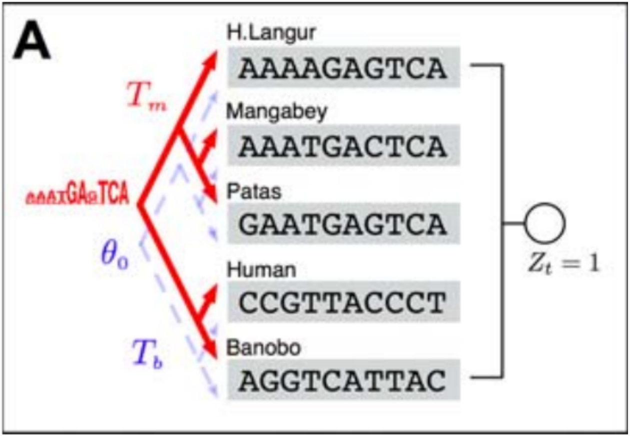
- $f_{\alpha\beta} \propto \frac{ln \frac{\pi_\beta \mu_{\beta\alpha}}{\pi_\alpha \mu_{\alpha\beta}}}{1-\frac{\pi_\alpha \mu_{\alpha\beta}}{\pi_\beta \mu_{\beta\alpha}}} \implies r_{\alpha\beta} = \mu_{\alpha\beta} \frac{\ln \frac{\pi_\beta \mu_{\beta\alpha}}{\pi_\alpha \mu_{\alpha\beta}}}{1-\frac{\pi_\alpha \mu_{\alpha\beta}}{\pi_\beta \mu_{\beta\alpha}}}$

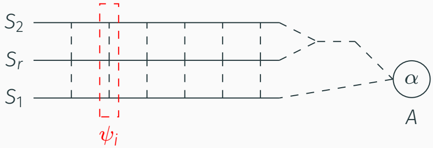
TFBS Prediction: Using HB Model over background



Modeling full phylogeny as one component: HB or JC/F81/HKY.

$F(x|\theta) = \frac{\log P(S|HB)}{\log P(S|JC)}$

HB model: Example with aligned sequences



MSA of Orthologous Sequences

$$
\begin{aligned}
P(\psi_i) &= \sum_{\alpha} P(\psi_i, A_i = \alpha|\theta) \\
&= \sum_{\alpha} P(A_i = \alpha) P(\psi_i|A_i = \alpha, \theta) \\
&= \sum_{\alpha} P(A_i = \alpha) \prod_{s_i} P(s_i|A_i = \alpha, \theta)
\end{aligned}
$$

$$S = \{\psi_1, \psi_2, \ldots, \psi_L\};$$

$$\psi_i = \{s_1^i, s_2^i, \ldots, s_N^i\}$$

$A =$ Unobserved ancestral sequence

Site Level Selection

Selection acting on whole TFBS as a unit

- Substitution rates are position specific in TFBS but independence assumption does not necessarily hold

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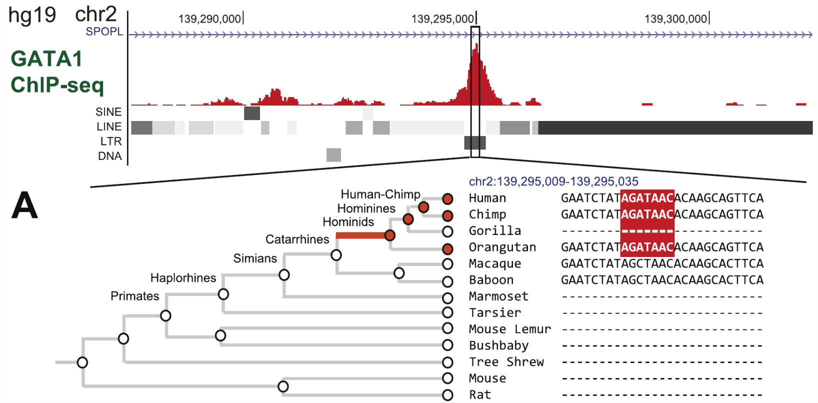
- The same substitution in a far less optimal site might lead to a functional loss
- A better model would be to account for substitution of entire site i.e. site-level selection treating binding sites as evolutionary units
- How: Reformulate the previous problem for two sites a, b instead of bases

Functional Turnover

TFBS Turnover



Functional turnover: TFBS can be gained or lost during evolution

Functional turnover: Birth & Death Process

Aim: Detect lineage-specific rates of TFBS evolution and the branch of origin of individual TFBS

- Binding sites are known to show turnover: TFBS can be gained/lost during speciation events
- Estimate rate of birth α and death β from orthologous sequences
- Infer ancestral states; branch of origin

Functional turnover: Birth & Death Process

$$
\begin{aligned}
w(t) &= \text{Probability that TFBS exists at time } t \\
\alpha, \beta &= \text{Birth, death rate respectively} \\
w(t+1) &= \alpha(1 - w(t)) + (1 - \beta)w(t) \\
w'(t) &= \alpha - (\alpha + \beta)w(t)
\end{aligned}
$$

We formulate two type of solutions, $u(t), v(t)$ such that: $u(t)$ represents those class of motifs present at $t = 0$ and $v(t)$ represents class of motifs that did not exist at $t = 0$.

Functional turnover: Birth & Death Process

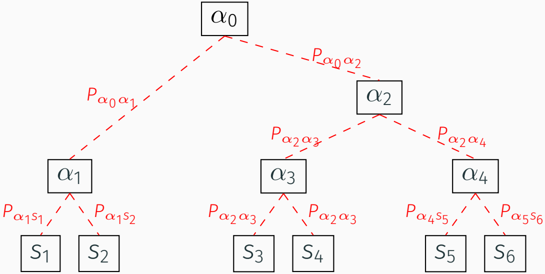
Let $p_{ij}(t)$ represent the probability of observing j motif occurrences after t , initial i

$$u(t) = \frac{1}{\alpha + \beta}(\alpha + \beta e^{-(\alpha+\beta)t})$$
$$v(t) = \frac{\alpha}{\alpha + \beta}(1 - e^{-(\alpha+\beta)t})$$

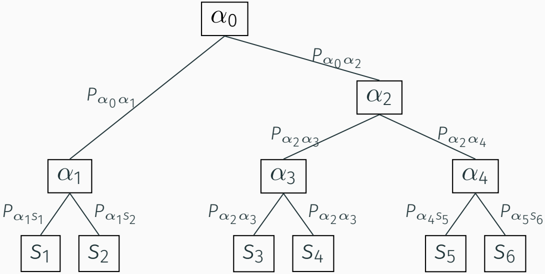
- At each node calculate the likelihood of observing daughter nodes given α, β
- Determine most likely ancestral state using MLE
- Infer branch of origin

(Lineage/Specie) specific models

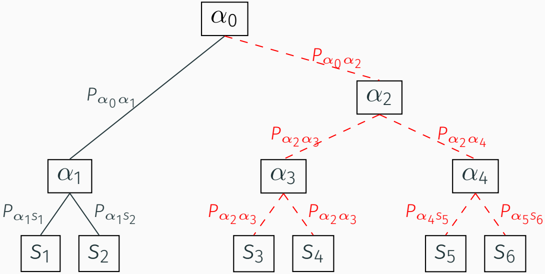
Full phylogeny evolving following motif model



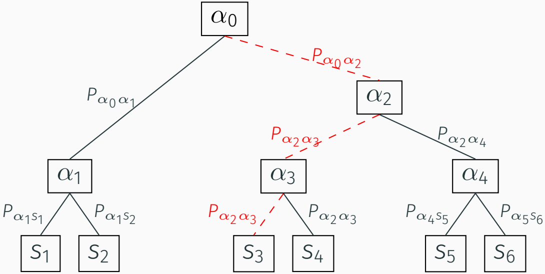
Full phylogeny evolving following background model

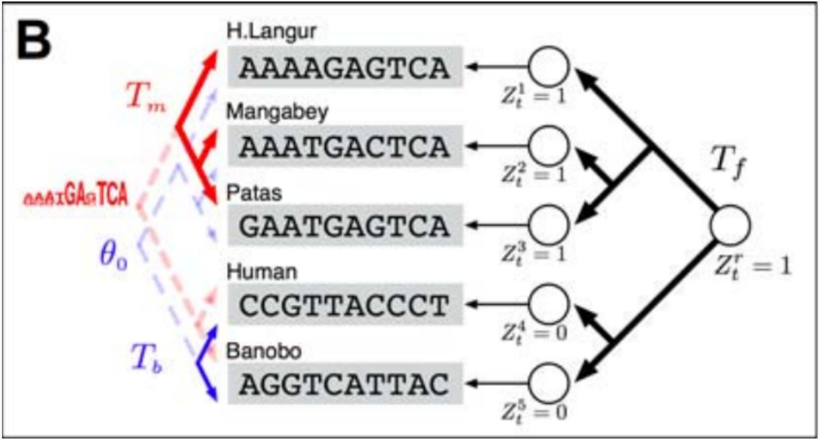


Lineage Specific Evolution



Specie Specific Evolution





Lineage specific model

Lineage Specific Evolution: Model

- Explicitly model functional turnover long T_f as a JC substitution process

$$P_f = \begin{pmatrix} \frac{1}{2} + \frac{1}{2}e^{-2\beta} & \frac{1}{2} - \frac{1}{2}e^{-2\beta} \\ \frac{1}{2} - \frac{1}{2}e^{-2\beta} & \frac{1}{2} + \frac{1}{2}e^{-2\beta} \end{pmatrix}$$

  $\beta =$ branch length

- Conditioning on TFBS functionality to model nucleotide substitution
- Capture function-specific evolution in every lineage

Summary

- HB model accounts for selection in TFBS evolution
- HB model can be extended to allow TFBS as a unit of evolution
- Turnovers can be treated in birth-death framework
- More general models can account for turnover and functional dependency across lineages

Questions?

Ornstein-Uhlenbeck Model I

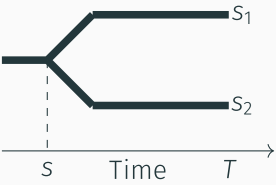
- HB models neglects lineage or specie specific selection
- OU models this gap by accounting for lineage/specie specific selection by requiring regime specific optima to be obtained
- OU models can model evolution by defining a quantitative trait as a score attached to the TFBS: $X(t)$
- Motivation: Account for the optima in the phylogeny regime assuming the change in optima coincide with phylogenetic branch points
- $X(t)$ evolves by two components one deterministic(selection), other stochastic (mutation)

Ornstein-Uhlenbeck Model II

$$
\begin{aligned}
dX(t) &= \alpha(\theta - X(t)) + \sigma dB(t) \\
\alpha &= \text{Strength of selection} \\
\theta - X(t) &= \text{Distance from optimum value} \\
\sigma &= \text{strength of random drift} \\
dB(t) &= \text{random white noise}
\end{aligned}
$$

Farther the TFBS from 'optimum' $\implies$ higher the selection force

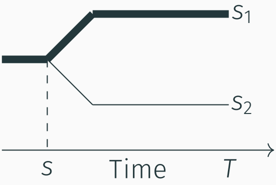
Ornstein-Uhlenbeck Model: Multivariate normal



$$E[\mathrm{X}(t)] = \begin{pmatrix} \theta_0 \\ \theta_1 \end{pmatrix}$$

$$\Sigma = \sigma^2 \begin{pmatrix} T & s \\ s & T \end{pmatrix}$$

s_1, s_2 – BM



$$\begin{aligned} E[X_1(T)] &= \theta_0 e^{-\alpha T} + \theta_1(1 - e^{-\alpha T}) \\ E[X_2(T)] &= \theta_0 e^{-\alpha T} + \theta_1 e^{-\alpha(T-s)}(1 - e^{-\alpha s}) \\ &\quad + \theta_2(1 - e^{-\alpha(T-s)}) \end{aligned}$$

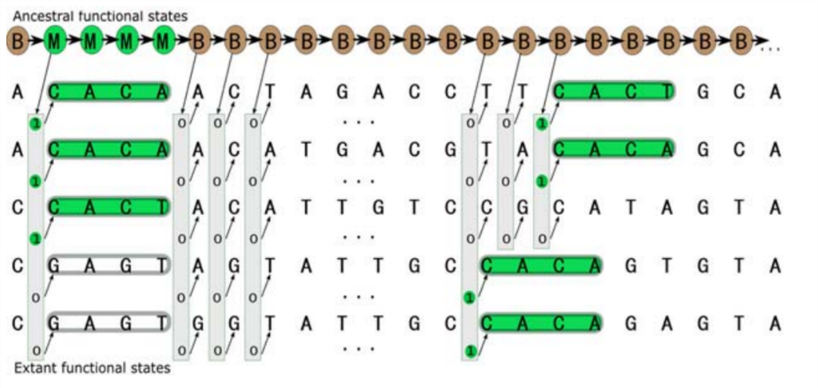
s_2 – new optimum regime, s_1 – ancestral

Jukes Cantor

$$Q = \begin{pmatrix} -\frac{3\mu}{4} & \frac{\mu}{4} & \frac{\mu}{4} & \frac{\mu}{4} \\ \frac{\mu}{4} & -\frac{3\mu}{4} & \frac{\mu}{4} & \frac{\mu}{4} \\ \frac{\mu}{4} & \frac{\mu}{4} & -\frac{3\mu}{4} & \frac{\mu}{4} \\ \frac{\mu}{4} & \frac{\mu}{4} & \frac{\mu}{4} & -\frac{3\mu}{4} \end{pmatrix}$$

$$P = \begin{pmatrix} \frac{1}{4} + \frac{3}{4}e^{-t\mu} & \frac{1}{4} - \frac{3}{4}e^{-t\mu} & \frac{1}{4} - \frac{3}{4}e^{-t\mu} & \frac{1}{4} - \frac{3}{4}e^{-t\mu} \\ \frac{1}{4} - \frac{1}{4}e^{-t\mu} & \frac{1}{4} + \frac{3}{4}e^{-t\mu} & \frac{1}{4} - \frac{1}{4}e^{-t\mu} & \frac{1}{4} - \frac{1}{4}e^{-t\mu} \\ \frac{1}{4} - \frac{1}{4}e^{-t\mu} & \frac{1}{4} - \frac{1}{4}e^{-t\mu} & \frac{1}{4} + \frac{3}{4}e^{-t\mu} & \frac{1}{4} - \frac{1}{4}e^{-t\mu} \\ \frac{1}{4} - \frac{1}{4}e^{-t\mu} & \frac{1}{4} - \frac{1}{4}e^{-t\mu} & \frac{1}{4} - \frac{1}{4}e^{-t\mu} & \frac{1}{4} + \frac{3}{4}e^{-t\mu} \end{pmatrix}$$

Lineage Specific Evolution



Ancestor = background $\implies$ evolution independent

Ancestor = motif $\implies$ TFBS evolves as unit