Combinatorial approaches in phylogenetics

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ALLAN WILSON CENTRE

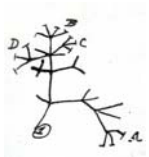
Hamburg, July, 2006

"Unreasonable effectiveness of mathematics" in physics (1960).

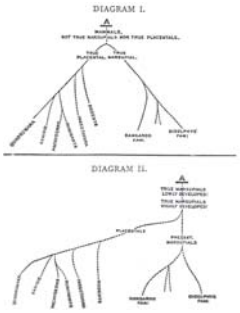
– Eugene Paul Wigner

"The lack of real contact between mathematics and biology is either a tragedy, a scandal or a challenge, it is hard to decide which."

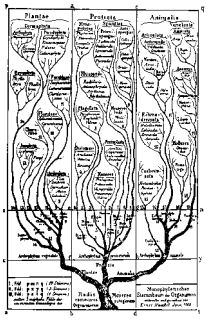
– Gian-Carlo Rota, (1986, in *Discrete thoughts*)



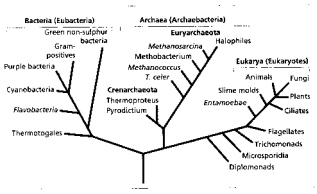
First Notebook on Transmutation of Species, 1837.



Letter from Darwin to Lyell, 1860.



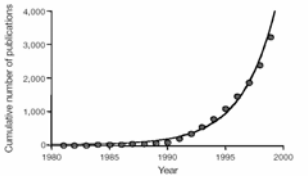
Ernst Haeckel (1866)

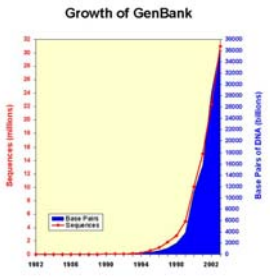


Olsen and Woese (1993)

The genetics era

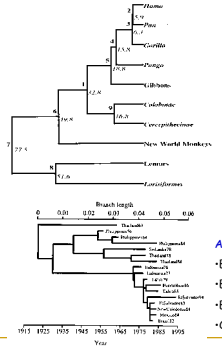
- 1967 Walter Fitch and Emil Margoliash constructed phylogenetic trees from cytochrome c sequences from vertebrates that agreed well with the vertebrate fossil record.





Publications with "molecular" and "phylogenetic" in abstract

Phylogenetic trees

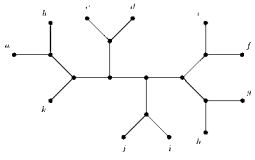


Applications:

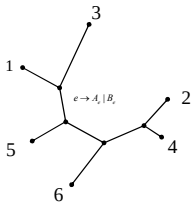
- Evolutionary Biology
- Ecology
- Epidemiology
- Others (language, stemmatology etc)

Phylogenetic trees

- [Definition] A **phylogenetic X-tree** is a tree $T=(V,E)$ with a set X of labelled leaves, and all other vertices unlabelled and of degree ≥ 3.
- If all non-leaf vertices have degree 3 then T is **binary**



Trees and splits



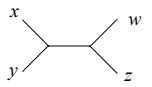
$$\Sigma(T) = \{A_e \mid B_e : e \in E\}$$

Partial order: $(P_X, \leq)$

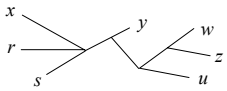
$$T \leq T' \Leftrightarrow \Sigma(T) \subseteq \Sigma(T')$$

Quartet trees

• A **quartet tree** is a binary phylogenetic tree on 4 leaves (say, *x,y,w,z*) written *xy|wz*.



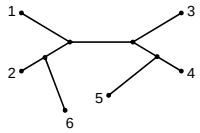
• A phylogenetic X-tree **displays** *xy|wz* if there is an edge in *T* whose deletion separates {*x,y*} from {*w,z*}



Compatibility

A set *Q* of quartets is **compatible** if there is a phylogenetic *X*-tree T that displays each quartet of *Q*

- Example: *Q*={12|34, 13|45, 14|26}



Complexity?

Defining sets

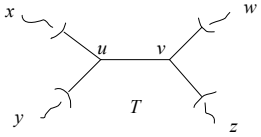
If *T* is the only phylogenetic *X*-tree that displays *Q* (and *X*= L(*Q*)) then we say *Q* **defines** *T* .

- Let *Q*(*T*) be the set of **all** quartets displayed by (any) *T*.

If *T* is binary, then *Q*(*T*) defines *T*.

A necessary condition for *Q* to define *T*

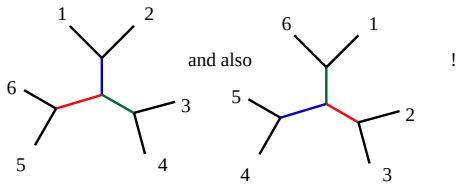
- **Definition:** For a binary phylogenetic tree *T*, a collection *Q* of induced quartet trees *distinguishes* an interior edge {*u,v*} of *T* if there exists a quartet *xy|wz* in *Q* that looks like this:



Observation: If *Q* defines *T* then *T* is binary and *Q* distinguishes every interior edge of *T* (so $|Q| \geq n-3$).

Warning:

Q ={12|45, 56|23, 34|16} distinguishes each interior edge of the tree:



and also

!

Sufficient condition for Q to define T:

- Suppose Q is compatible and distinguishes every interior edge of a binary phylogenetic X-tree T.

Proposition: If there is an element of X that is a leaf of every tree in Q then Q defines T.

Corollary:
There are subsets of $Q(T)$ of size |X|-3 that define T.

Reconstructing trees from characters

Types of "characters"

- Morphology (eg. Wings vs no-Wings)
- DNA sequences (….ACG….)
- Genomic data (gene order, SINEs, RCGs)

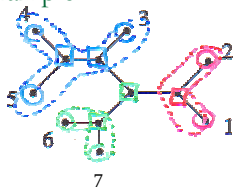
A *character* on X $f : X \to S$

Definitions:

- [Character] A character is any function
  $f : X \to S$
- [Convexity] Given a character $f : X \to S$

and a phylogenetic X-tree $T=(V,E)$, we say f is **convex on *T***
if f extends to $f' : V \to S$
so that $f' | X = f$
and $\{v \in V : f'(v) = s\}$ is connected for all s in S.

Convexity: example



x	1	2	3	4	5	6	7
$f(x)$							

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Biological significance of convexity

- Lemma: A character χ is convex on a phylogenetic tree T if and only if χ could have evolved on T (from any root vertex) without any **reversals** or **convergent evolution.**

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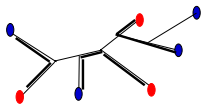
Homoplasy

- $h(f, T)$ = smallest number of reversals/convergent events required to fit f on (rooting of) T.



- $h(f, T)$ easily computed = $l(f, T) - (|f(X)| - 1)$
- For $|f(X)|=2$, h= -1+ max edge-disjoint proper path packing (by Menger's theorem) [S90; extention to $|f(X)|>2$ by ES92]

- $h(f, T)$ = min #SPR operations to transform T into a tree on which f is convex. [Bruen and Bryant 2005]. **Applications**

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Combinatorial aside 1.

- **Theorem** [Bruen and Bryant 2006]
- $h(T, f)$ = min #SPR operations to transform T into a tree on which f is convex.

Let

$$h(f_1, f_2) := \min_T \{h(T, f_1) + h(T, f_2)\}$$

Construct the partition intersection graph.
Theorem [Bruen and Bryant 2006]
$h(f_1, f_2)$ = #edges + #components – r_1 -r_2

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Relevance to molecular biology

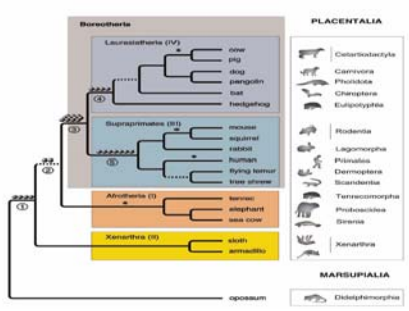
- Large state space
  Example: gene order rearrangements (*n* species, *L* genes, random inversion model)

$$g_1 g_2 \boxed{g_3 g_4 g_5} g_6 g_7 \cdots \Rightarrow g_1 g_2 g_5 g_4 g_3 g_6 g_7 \cdots$$

$$P[h=0] \geq 1 - \frac{2(2n-3)(n-1)}{L(L-1)}$$

- Rare genomic characters (RGC's):
  Examples, Retroposons, SINES, LINES, LTRs, gene content, etc
  (Model, 0->1->?)

Recent example (Kreigs *et al.* PLoS biology, April 2006. Tree of placental mammals)



Character compatibility

- [Compatibility] Characters $f_1, f_2, \ldots, f_k$ are ***compatible*** if there exists a phylogenetic X-tree (a 'perfect phylogeny') on which they are all convex.

- Complexity: NP-hard, but special cases are solvable in polynomial time.

A link to graph theory…

G is **chordal** if every cycle of length four or more has a chord

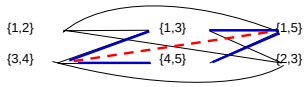
Example

Definition:

- Given $G = (V,E)$ and a partition $V = V_1 \cup V_2 \cup \cdots \cup V_k$ a **restricted chordal completion** of G is any chordal graph $H = (V, E'), E \subseteq E'$
  satisfying $x, y \in V_i \Rightarrow \{x, y\} \notin E' - E$

Characterising compatability

Species	1	2	3	4	5
Characters					
f_1	A	A	B	B	X
f_2	C	E	C	B	B
f_3	U	R	R	S	U

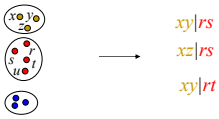


Theorem

- F is compatible if and only if int(F) has a restricted chordal completion.
- If F is compatible, then int(F) has tree-width at most k=|F|.

Equivalence of character and quartet compatibility

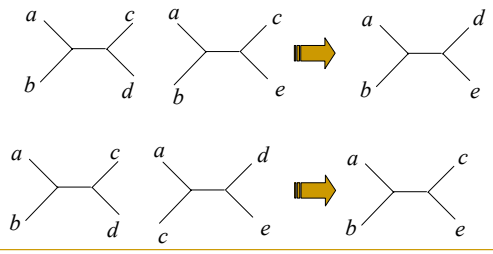
$$C \rightarrow Q(C)$$



Lemma: Each character in C is convex on T if and only if T displays all the quartets in $Q(C)$.

[C is "compatible", C "defines" T iff $Q(C)$ does]

New quartet trees from old ones



Dyadic rules for quartet trees

(Colonius and Schulze; Dekker)

(**Q1**): $\{ab|cd, ab|ce\} \vdash ab|de$

(**Q2**): $\{ab|cd, ac|de\} \vdash ab|ce, ab|de, bc|de.$

Any phylogenetic X–tree that displays the quartet trees on the left of (**Q1**) or (**Q2**) also displays the corresponding quartet tree(s) on the right.

Dyadic quartet closure

$$\mathcal{Q} = \mathcal{Q}_1 \subseteq \mathcal{Q}_2 \subseteq \cdots \subseteq \mathcal{Q}_m = \mathrm{qcl}_\theta(\mathcal{Q})$$

where $\mathcal{Q}_{i+1}$ consists of $\mathcal{Q}_i$ together with all additional quartets that can be obtained from a pair of quartets in $\mathcal{Q}_i$ by applying the rule(s) allowed by θ.

For $\theta \subseteq \{1, 2\}$, let the dyadic quartet closure under rule θ, $\mathrm{qcl}_\theta(\mathcal{Q})$, denote the minimal set of quartet trees that contains $\mathcal{Q}$ and is closed under rule (**Qi**) for each $i \in \theta$.
We denote these closures with: $\mathrm{qcl}_1(\mathcal{Q}), \mathrm{qcl}_2(\mathcal{Q}), \mathrm{qcl}_{1,2}(\mathcal{Q})$.

The closure of a set of quartets

For a compatible set $\mathcal{Q}$ of quartet trees, the *closure* $\mathrm{cl}(\mathcal{Q})$ is defined as

$$\mathrm{cl}(\mathcal{Q}) = \bigcap_{\mathcal{T} \in \mathrm{co}(\mathcal{Q})} \mathcal{Q}(\mathcal{T})$$

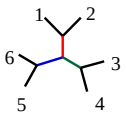
where $\mathrm{co}(\mathcal{Q})$ is the set of phylogenetic trees that display each of the trees in $\mathcal{Q}$.
Thus $\mathrm{cl}(\mathcal{Q})$ consists of precisely those quartet trees that are displayed by every phylogenetic tree that displays $\mathcal{Q}$.

- Rules of order $<p$ (for any fixed p) do not suffice compute $\mathrm{cl}(Q)$.
- There is a set Q that is incompatible but every strict subset Q' is compatible and satisfies $\mathrm{cl}(Q')=Q'$

Example 1: qcl_2

Definition: If Q distinguishes every interior edge of a binary phylogenetic tree T and we can order Q so that each quartet tree in the ordering introduces precisely one new leaf label, we say Q has a **tight ordering** for T.

Example: {12|35, 13|56, 15|34}.



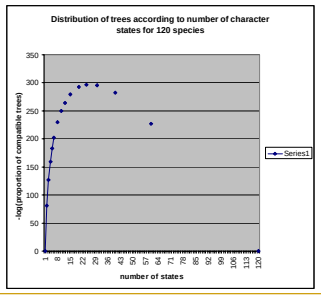
Proposition:
If Q has a tight ordering for T, then $\mathrm{qcl}_2(Q) = Q(T)$
In particular Q defines T.

Application: How many characters are needed to define a binary phylogenetic X-tree?

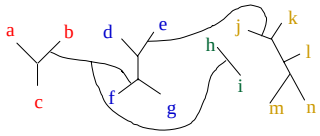
- For binary characters we need n-3 (n=|X|).
- For r-state characters (r fixed) we need at least (n-3)/(r-1)
- What if r is not fixed?

(it is not useful to make r too large!)

I(χ) := - log(Pr[χ is convex on random T])



Where do these numbers come from?

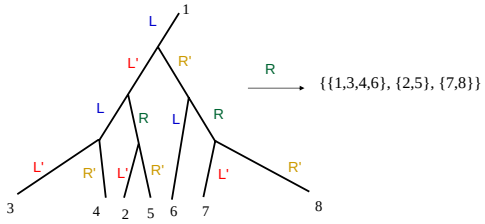


Carter *et al.* (1990); Erdös & Székely (1993).

binary phylogenetic trees with n leaves, $b(n) = 1 \times 3 \times \cdots \times (2n-5)$

of these on which χ is convex = $b(n)\prod_{i=1}^{r} b(a_i+1) \,/\, b(n-r+2)$

Edge-colouring a tree by $Z_2 \times Z_2$



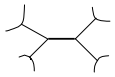
Theorem (Huber, Moulton, S, 2003)

For any tree these ***four*** characters defines T.

Proof: show $Q(C)$ contains a subset with a tight ordering for T.

Application 2: "Short" quartets

- $Q_{short}(T)$



- **Theorem** (Erdös *et al.* 1997)

$Q_{short}(T)$ contains a subset that has a tight ordering for T (and so $qcl_2(Q_{short}(T)) = Q(T)$).

- Application to show that trees can be reconstructed from 'short' sequences evolved under finite-state Markov process

A further application involving qcl_2:

We say Q is **excess-free** if $|L(Q)|-3-|Q| = 0$.
(note: If Q defines a tree, then $exc(Q) \leq 0$).

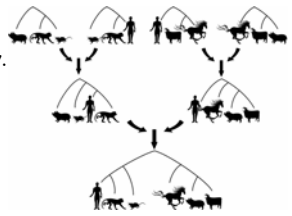
- **Proposition:** Suppose a subset Q of $Q(T)$ contains an excess-free subset Q_0 that defines T. Then $qcl_2(Q)=Q(T)$.

- Why? Let us say a set Q of quartet trees is "good" if (i) Q defines a phylogenetic tree, and (ii) $exc(Q)=0$.

  Theorem [Bocker, Dress 1999] Any good set of ($\geq$2) quartets is the disjoint union of precisely two good sets.

Aside: Phylogenetic patchworks

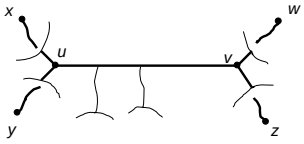
- If Q is 'good' then its good subsets for a 'patchwork', and it contains a maximal hierarchy.



New Theorem (2006; S. Grunewald).
Say Q is 'thin' if $exc(Q')\geq 0$ for all subsets of Q' of Q. Then any thin set is compatible.

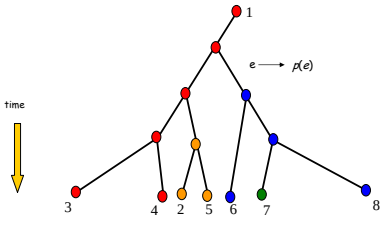
Example 2: qcl_1

- **Definition:** For a binary phylogenetic tree T, a collection Q of displayed quartet trees is a *generous cover* for T if for all pairs u,v of interior vertices of T, we have a quartet $xy|wz$ in Q that looks like this:



Theorem (Dezulian + S, 2003): If Q is a generous cover for T, then $qcl_1(T) = Q(T)$. Thus Q defines T.

Application: How many `evolved' characters are needed to reconstruct a tree?



1 2 3 4 5 6 7 8

Theorem (Mossel +S, 2004)

Elchanan Mossel

[Assume probability of state change on each edge for each character Bounded between (a,b), $0<a<b<1/2$]

The number k of indep. characters required to reconstruct T (correctly with probability>1-ε) is

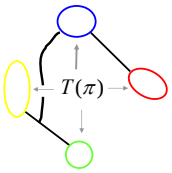
$$k = c \cdot \frac{\log(n)}{p}$$

- n = #species, p =smallest substitution probability, $c=c(\varepsilon,b)$
- The tree reconstruction algorithm is polynomial time (in n,k)

Proof relies on generous cover result.

Combinatorial aside: computing P(σ)

- Recursively
- Mobius-inversion (Evans *et al.* 2004)

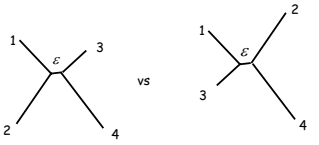


$$\prod_{e \in T(\pi)} (1 - p(e)) = \sum_{\pi \le \sigma} P(\sigma)$$

$$Q(\pi)$$

$$P(\pi) = \sum_{\pi \le \sigma} \mu(\pi, \sigma) Q(\sigma)$$

Topological aside: tree space under Markov models



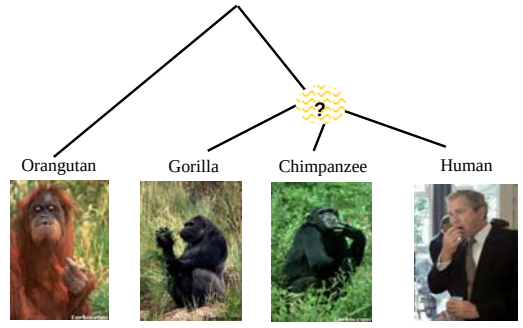
Infinite state Markov process

$$k \propto \frac{1}{\varepsilon}$$

Finite state Markov process

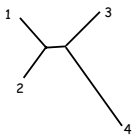
$$k \propto \frac{1}{\varepsilon^2}$$

Example



Adapted From the Tree of the Life Website, University of Arizona

Markov models (II)



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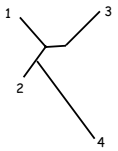
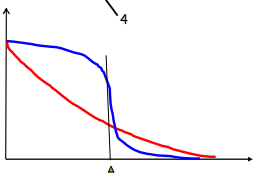


- "site saturation"

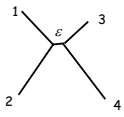
Persi Diaconis

Distance from uniform distribution

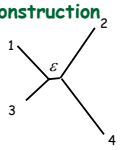


Number of moves

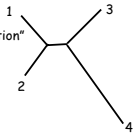
Markov models and tree reconstruction



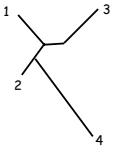
vs



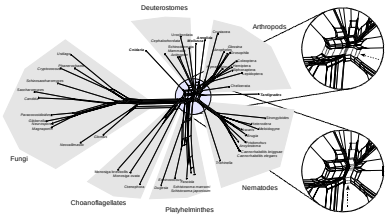
- "site saturation"



vs

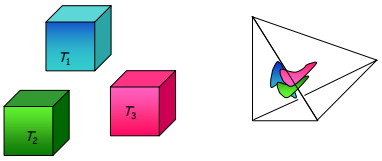


Example: Deep divergence in the Metazoan phylogeny



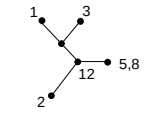
From Huson and Bryant, 2006

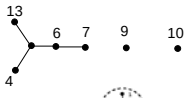
The space of 'phylogenetic oranges'



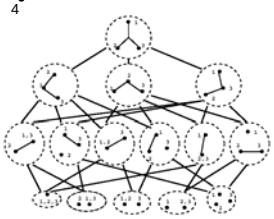
$$TS(X) = \coprod_{T} [0,1]^{e(T)} / \sim$$

Combinatorial aside (II) the Tuffley poset





Chris Tuffley



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Theorem (2005)

$TS(X)$ is a compact regular cell complex which is

- contractible
- homeomorphic to the geometric realization of the Tuffley poset on X

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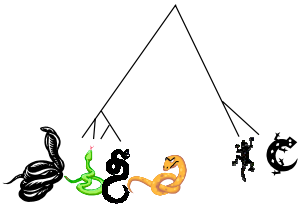
Part 3: phylogenetic diversity and trees from distance data



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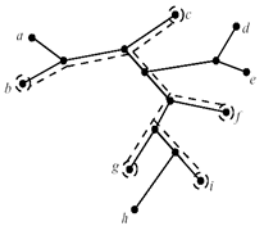
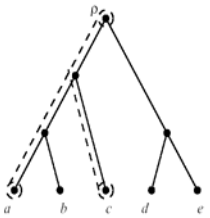
Modifications (I)

- Unrooted trees (with arbitary branch lengths)

$$PD'(W) = \sum_{e \in T(W)} l(e)$$

$$PD(W) = PD'(W \cup \{\rho\})$$





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Optimisation problem

- **Problem:** Given a phylogenetic tree T on X with edge weights.
- Find a subset Y_{max} of X given size k to maximise *PD*.

Nee and May (Science 1997)

For rooted trees with a clock, and standard PD, the greedy algorithm solves this problem

General case?

A combinatorial property

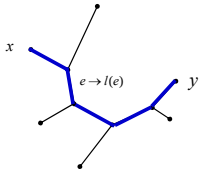
- Proposition: For any two subsets A, B of X with $2 \leq |B| < |A|$ there exists x in A - B so that

$$PD(A-\{x\}) + PD(B \cup \{x\}) \geq PD(A) + PD(B)$$

- Corollary: Y_{max} can always be found by using the 'greedy algorithm' [Why?]

[The sets of maximal PD-score for their cardinality form a (strong) greedoid]

Calculating PD



$$d(x,y) := \sum_{e \in p(T;x,y)} l(e)$$

$$l = l(T,w) := \sum_{e} l(e)$$

Theorem [Yves Pauplin 2000 *Molecular Biology and Evolution*]

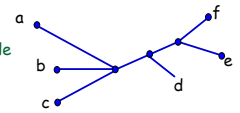
$$l = \sum_{\{x,y\} \subseteq X} \left(\frac{1}{2}\right)^{\Delta(x,y)} d(x,y) \qquad (= \tfrac{1}{16} d(x_1,x_2) + \ldots.)$$

Theorem (Semple+S 2004)

For any phylogenetic tree T

$$l = \sum_{\{x,y\}} \frac{1}{\prod_{v \in I(x,y)} (d(v)-1)} d(x,y)$$

Example



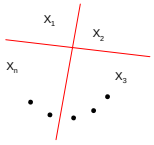
$$l = \frac{1}{3} d(a,b) + \frac{1}{6} d(a,d) + \ldots$$

CHICKEN SCRATCHINGS

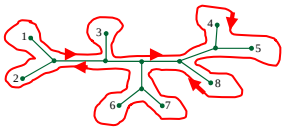
Cyclic Permutation on X

$\pi = (x_1, x_2, ..., x_n)$

$\Sigma^o(\pi) :=$ the splits (bipartitions of X) induced by planar 'cuts'.



[Definition] π is a cyclic ordering for T if $\Sigma(T) \subseteq \Sigma^o(\pi)$



$$l = \frac{1}{2}\sum_{i=1}^{n} d(x_i, x_{i+1})$$

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PD for tree reconstruction

$$l = \sum_{\{x,y\}} \frac{1}{\prod_{v \in I(x,y)} (d(v)-1)} d(x,y)$$

- Can be used as with δ in place of d as a tree reconstruction method (BME)
  - This method is consistent (Desper and Gascuel, 2004)
  - NJ selects the pair of leaves (at each step) to minimize the increase in BME score (Desper and Gascuel, 2004)

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The end

Further details

•E. Mossel and M. Steel, A phase transition for a random cluster model on phylogenetic trees. *Mathematical Biosciences*, 187 (2004), 189-203.

•C. Semple and M. Steel (2004) Cyclic permutations and evolutionary trees. *Advances in Applied Mathematics* 32(4): 669-680.

• V. Moulton and M. Steel (2004). Peeling phylogenetic 'oranges'. *Advances in Applied Mathematics* 33(4): 710-727.

•K. Huber, V. Moulton and M. Steel (2005). Four characters suffice to convexly define a phylogenetic tree. *SIAM Journal on Discrete Mathematics* 18(4): 835-843.

•M. Steel (2005). Phylogenetic diversity and the greedy algorithm. *Systematic Biology* 54(4): 527--529.

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