A Non-Exchangeable Coalescent Arising in Phylogenetics

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CIRM
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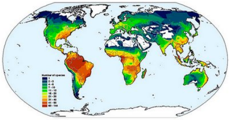
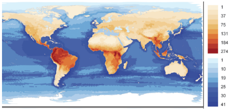
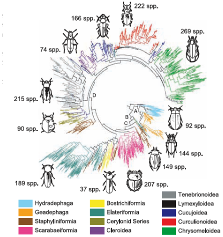
Pattern & Process





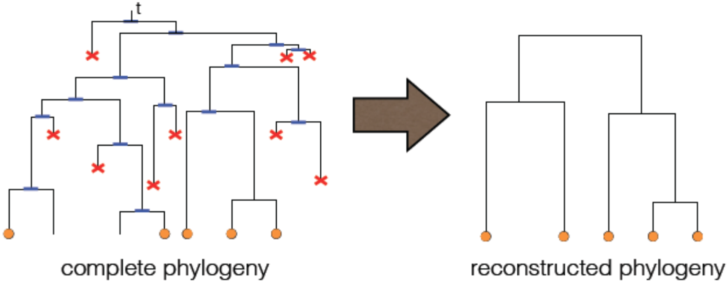


- Design probabilistic models of evolutionary processes...
- ...Generating similar patterns as those observed in nature, and...
- ...Allowing for the inference of these processes from real data...
- ...Assuming the data is a phylogeny (gene tree, species tree,...) already inferred from MSA.

Outline

1. Properties of « Ultrametric Trees »
2. Examples & applications
3. A Non-Exchangeable, Individual-Based Model of Phylogeny
4. Simulations and Inference

Reconstructed tree



- **« Reconstructed tree » or « reduced tree »** at height T = remove all lineages extinct by T (fixed time).

- The reduced tree is one-to-one with...

- ...The **sphere of radius** T $\{x : d(\text{root}, x) = T\}$ = particles alive at time T (yellow dots)

- The sphere is ultrametric : $d(x,z) \leq \max(d(x,y), d(y,z))$.

Comb metric (1)

Let I be a compact interval and $f : I \to \mathbb{R}_+$.

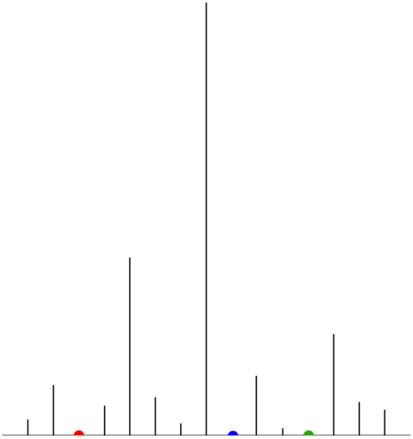
Definition

The mapping f is called a ***comb*** *if for any $\varepsilon > 0$, $\{f \geq \varepsilon\}$ is finite.*
For any $s, t \in I$, define d_f by

$$d_f(s,t) = 2 \sup_{(s \wedge t, s \vee t)} f.$$

Then d_f is an ultrametric distance on $\{f = 0\}$ (properly quotiented) called the comb metric.

Comb metric (2)

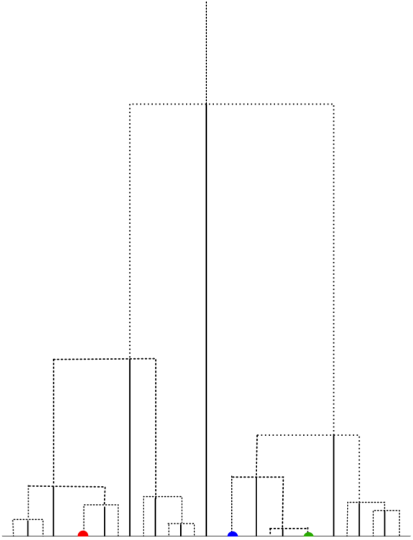


When the comb has finite support,

the comb metric space

is one-to-one with...

Comb metric (3)



When the comb has finite support,

the comb metric space

is one-to-one with...

An « ultrametric tree »

What about the general case ?

A representation theorem

Theorem (L. 2015)

Any compact, ultrametric space with no isolated point is isometric to a (properly completed) comb metric space.

In particular, any sphere $\{x \in t : d(root, x) = T\}$ *of a locally compact real tree* (t, d) *having no isolated point, is isometric to a comb metric space.*

The spheres of the Brownian tree can be represented by a comb whose graph is a Poisson point process with intensity $dx\, y^{-2}\, dy$ (properly stopped).

For Lévy trees, see L. & Popovic, *Ann. Appl. Prob.* (2013).

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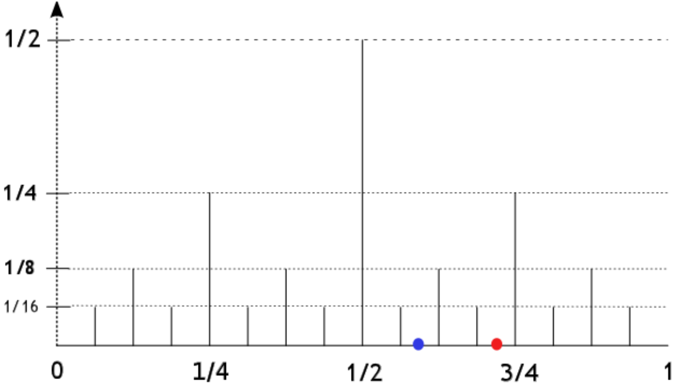
Expl1. The $p-$adic comb

- $U :=$ Non stationary sequences of 0's and 1's with Hamming distance
$$d_H(x,y) = 2^{-\min\{n: x_n \neq y_n\}}$$
- $(x_n) \mapsto \sum x_n 2^{-n}$ maps (U, d_H) to the dyadic comb (see fig)
- Blue dot $= (1,0,0,1,\ldots)$ Red dot $= (1,0,1,1,\ldots)$



Expl 2. Exchangeable coalescents

...and Aldous' construction

Let f be a comb on $[0,1]$ and (V_i) i.i.d. random variables uniform in $(0,1)$. Define the partition $R_f(t)$ on $\mathbb{N}$ induced by the equivalence relation $\sim_t$

$$i \sim_t j \Leftrightarrow d_f(V_i, V_j) \leq t.$$

The process $(R_f(t); t > 0)$ is an exchangeable coalescent process.

For example, take

$$f = \sum_{j \geq 1} \tau_j \mathbb{1}_{U_j},$$

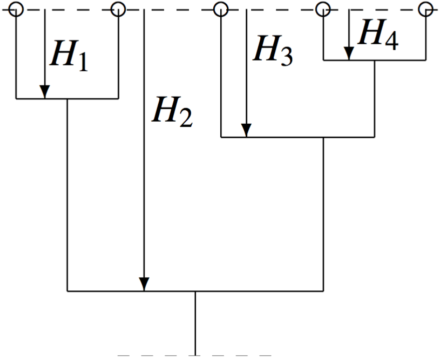
where the (U_j) are i.i.d. uniform on $(0,1)$ and $\tau_j = \sum_{k \geq j+1} e_k$, where e_k are independent exponential r.v. with parameter $k(k-1)/2$, then the process $(R_f(2t); t \geq 0)$ has the same law as the Kingman coalescent.

Expl3. The coalescent point process

(Popovic 2004, Aldous & Popovic 2005)

- **Coalescent Point Process** = CPP = Depths $H_1, H_2, \ldots,$ form a sequence of iid random variables killed at its first value larger than T.

- More general definition via Poisson point processes (cf Brownian tree)



$b = b(t)$ and $d = d(t,a)$ always produce CPP

L.& Stadler, *TPB*, 2013

Consider a birth–death process started at time 0 with 1 particle and

- Birth rate $b = b(t)$, where t is time
- Death rate $d = d(t,a)$, where a is any non-heritable trait (e.g. age).

Theorem (L. & Stadler 2013)

The reconstructed tree at time T is a CPP with typical node depth H, where the function $F = 1/P(H > \cdot)$ is the unique solution to a linear integro-differential equation with initial condition $F(0) = 1$.

If b and d are time-homogeneous, F can also be obtained by inverting an explicit Laplace transform.

The result still holds with bottlenecks/partially sampled tips.

$\Rightarrow$ Likelihoods in product form $\Rightarrow$ Applications...

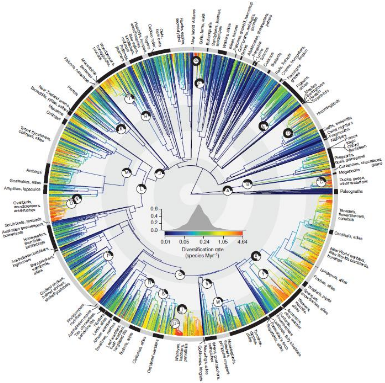
Appl. 1 « Do species age ? »

Alexander, L., Stadler, *Systematic Biology* (2015 ?)

Gamma distributed lifetime $(k, s > 0)$, with mean $m := ks$

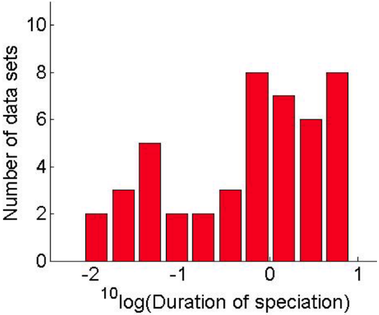
$$g(a) = \Gamma(k)^{-1} s^{-k} a^{k-1} e^{-a/s}$$

- Test on simulations : accurate MLEs of b and m
- MLE on *Aves* phylogeny = 9993 extant bird sp (Jetz et al *Nature* 2012)
- Exponential model rejected $(p = 10^{-15})$
- Shape parameter $k \gg 1$: extinction rate increases with age
- Average lifetime $m = 15.26\ My$
- Speciation rate $b = 0.108\ My^{-1}$



Appl.2 *« How long does speciation take ? »*

Etienne, Morlon, L., *Evolution* (2014)



- Speciation takes time

  = new populations take time to diverge from mother pop until total reproductive isolation

- Test on simulations : efficient inference of duration of speciation

- Left : duration of speciation inferred in 46 bird clades (in My)

Other models of reconstructed trees ?

- Advantages of CPP as models of phylogenies :
  - Process-based
  - Mathematically tractable
  - Likelihood-based methods available Stadler (2011), Morlon, Parsons & Plotkin (2011), L. & Stadler (2013), Etienne, Morlon & L. (2014), L., Morlon & Etienne (2015), Alexander, L. & Stadler (2015)...
- Shortcomings :
  - Lineage-based : No insight at the ind level, no predictions at the population level
  - Topology always equivalent to Yule tree = Uniform over trees with ranked node depths

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Goal

In this second part, our goal is to propose :

- A biologically reasonable model of phylogeny
  - Individual-based
  - Where species play different roles
- Mathematically tractable
- Fitting empirical patterns

The Red Queen Hypothesis

- “Old species are continually replaced by younger, fitter species”
- Examples
  - Key innovations, niche invasions
  - Evolutionary arms races
- No parameterization of fitness = fitness mediated by order of appearance

Asymmetric multispecies model

Let $\lambda > \mu > 0$, $c > d > 0$, and $K =$ scaling parameter.

- Individual-based model with n species = multitype logistic branching process (Ethier & Kurtz 1980, L. 2005)
- *Per capita* birth rate λ, death rate μ
- Death by competition at **rate** c_{ij} **felt by** each ind of sp i, **from** each ind of sp j, where **sp i is *younger* than sp j** and

$$\begin{cases} c_{ij} & = & 0 \\ c_{ii} & = & c/K \\ c_{ji} & = & d/K \end{cases}$$

Large population limit

Now species have **levels** :
Species at level 1 = youngest species,
Species at level 2 = 2nd youngest species,...

If $K^{-1}X_i(0)$ converge as $K \to \infty$, then $K^{-1}(X_i) \Rightarrow (x_i)$ (Kurtz 1981)

$$\dot{x}_i = \left(\lambda - \mu - cx_i - d\sum_{j<i} x_j\right) x_i$$

which, letting $\kappa := \frac{\lambda-\mu}{c}$ and $\alpha := 1 - \frac{d}{c}$ has equilibrium state

$$\lim_{t\to\infty} x_i(t) =: \bar{x}_i = \kappa\alpha^{i-1}.$$

⇒ Younger species are more abundant.

Speciation by point mutation

Each newborn is a mutant with probability ε_K, where for all $V > 0$,

$$e^{-VK} \ll \varepsilon_K \ll \frac{1}{K \ln K}$$

Separation of timescales as $K \to \infty$:

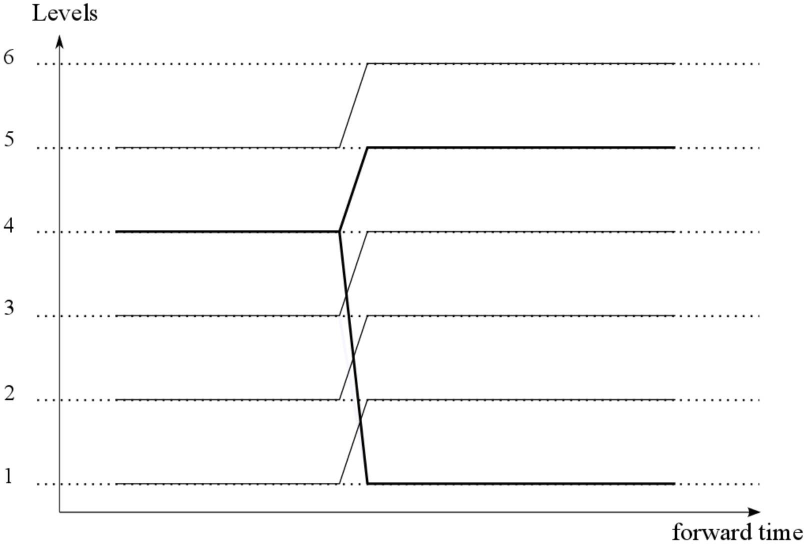
Theorem

Set $T_N :=$ first time when the number of species exceeds N.

Let $(N_t; t \geq 0)$ be a pure-birth process with birth rate $\rho_n = \lambda \left(1 - \frac{\mu}{\lambda}\right) \sum_{i=1}^{n} \bar{x}_i$.

Then, as $K \to \infty$, the process $K^{-1}(X_i)\left(\frac{1}{K\varepsilon_K}(t \wedge T_N)\right)$ converges (fdd) to the process $(\bar{x}_1, \bar{x}_2, \ldots, \bar{x}_{N_t - 1}, 0, \ldots, 0)$.

Speciation in forward time...



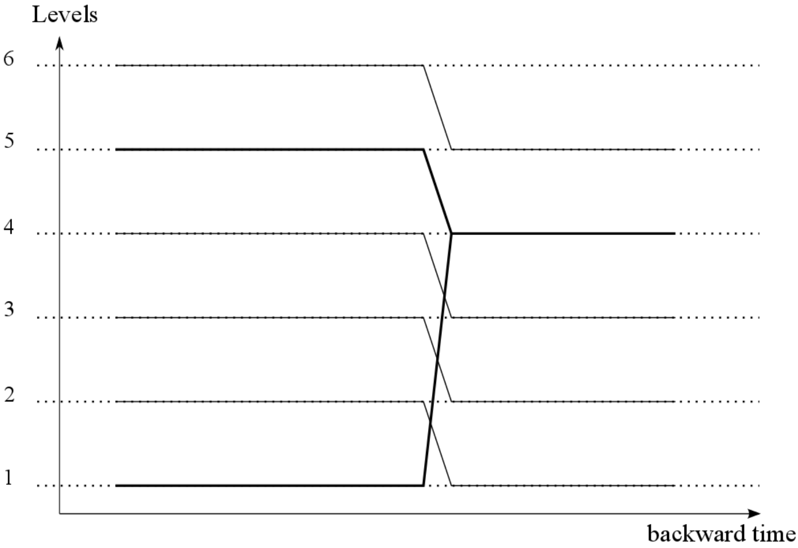
A non-exchangeable coalescent process

In the new timescale, at constant rate

$$\rho = \frac{\kappa}{1-\alpha}\left(1-\frac{\mu}{\lambda}\right)$$

- Speciation occurs from the sp at level i, with proba $(1-\alpha)\,\alpha^{i-1}$
- All species simultaneously “shift up” their level by $+1$
- The new species occupies the newly vacated bottom level = youngest species.
- Backwards-in-time picture = Shift-Down/Look-Up Coalescent

...Coalescence in backward time



Intertwining (Rogers & Pitman 1981)

Let $((X_t, Y_t), t \geq 0)$ a Markov process with state-space $E \times F$ with generator $\hat{G}$ and K a probability kernel from E to F with associated operator

$$Kf(x) = \int_F K(x, dy) f(x, y).$$

Theorem (Rogers & Pitman 1981)

If there exists a generator G of a Markov process in E such that for each $f : E \times F \to \mathbb{R}$ in the domain of $\hat{G}$,

$$K\hat{G}(f)(x) = GK(f)(x) \quad x \in E,$$

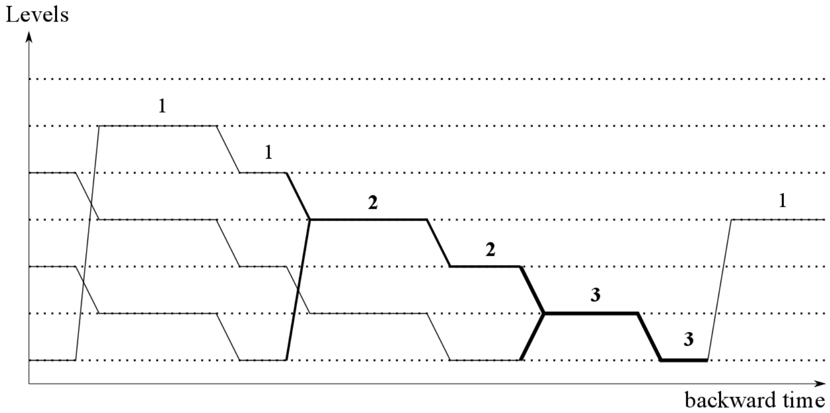
then

1. $\mathbb{P}(Y_0 \in dy | X_0) = K(X_0, dy)$ *a.s. implies that for each $t > 0$,*

$$P(Y_t \in dy | (X_s, 0 \leq s \leq t)) = K(X_t, dy) \quad a.s.$$

2. $(X_t, t \geq 0)$ *is a Markov process.*

The weight measure (1)



Weight = 1 + Number of coalescences ‘from below’ since last visit of level 1

= Number of ‘delayed’ lineages (i.e., coal. only when leaving level 1)

Intertwining (1)

$W_t(\ell) =$ weight of level ℓ = number of 'delayed' lineages at level ℓ

$N_t := W_t(\mathbb{N}) =$ number of 'delayed' lineages.

Theorem

$(N_t; t \geq 0)$ is a $\delta_{1-\alpha}$ coalescent process and conditional on $(N_s; 0 \leq s \leq t)$,

$$W_t = \sum_{i=1}^{N_t} \delta_{G_i},$$

where the G_i's are i.i.d. Geom(α) random variables.

Intertwining (2)

$W_t(\ell) =$ weight of level ℓ = number of 'delayed' lineages at level ℓ

$B_t(w) =$ number of lineages with weight w.

Theorem

$(B_t;t \geq 0)$ is a Markov process and conditional on $(B_s;0 \leq s \leq t)$,

$$W_t = \sum_{w \geq 1} \sum_{i=1}^{B_t(w)} \delta_{Y_{wi}},$$

where the Y_{wi}'s are independent Geom(α^w) random variables, conditioned to be pairwise distinct.

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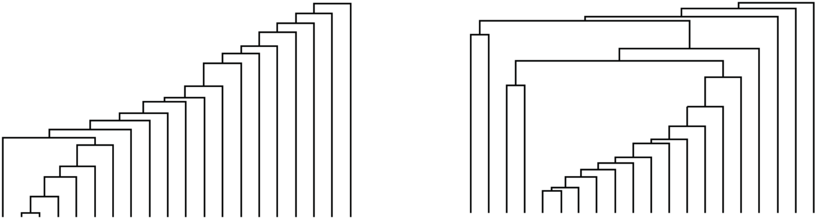
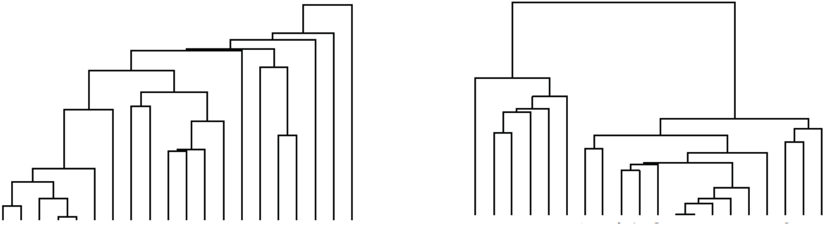
Simulated trees with 20 tips



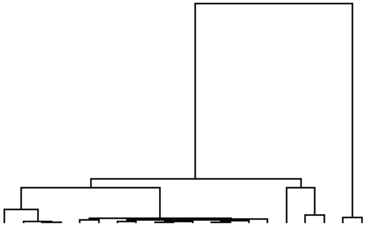
$$\alpha = 0.1$$

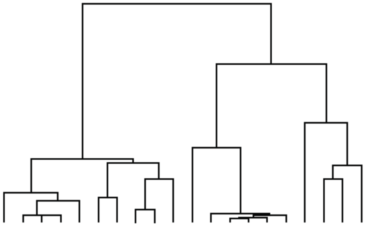
Simulated trees with 20 tips



$$\alpha = 0.7$$

Simulated trees with 20 tips





$$\alpha = 0.99$$

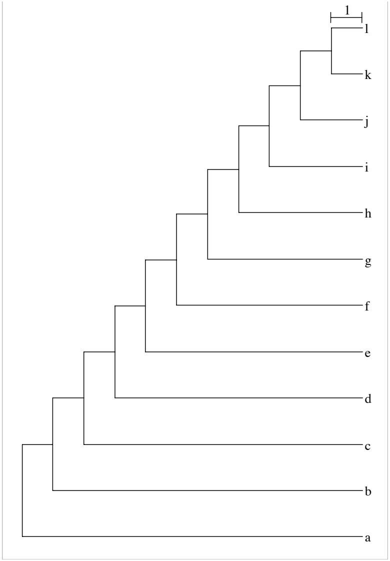
Convergence to the Kingman coalescent

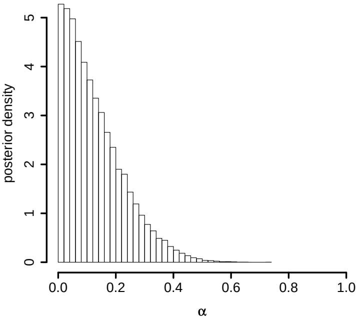
Recall $\alpha = 1 - d/c$ and $\kappa = (\lambda - \mu)/c$ = abundance of youngest species.

Theorem

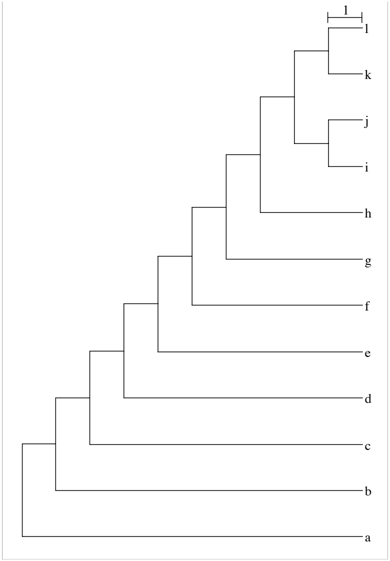
As $\alpha \to 1$, the process $(B_{t/(1-\alpha)}; t \geq 0)$ converges (fdd) to $N_t \delta_1$, where $(N_t; t \geq 0)$ is a pure-death process with death rate $Cn(n-1)/2$, where $C = (1 - \mu/\lambda)\kappa$ (replacement rate).

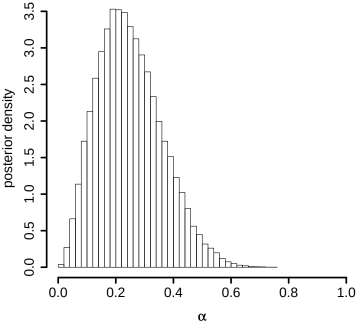
MCMC inference (1) : Caterpillar tree



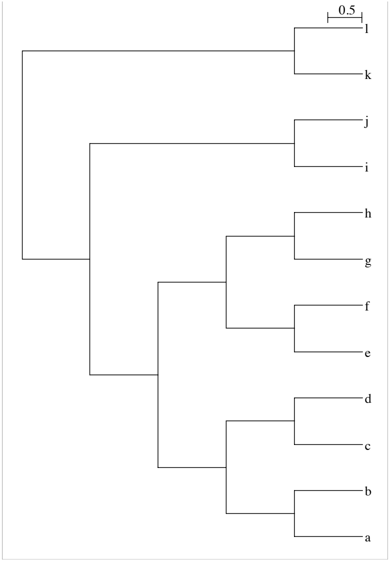


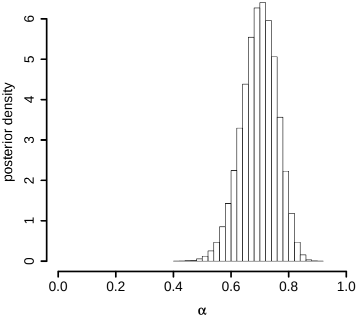
MCMC inference (2) : Very imbalanced tree



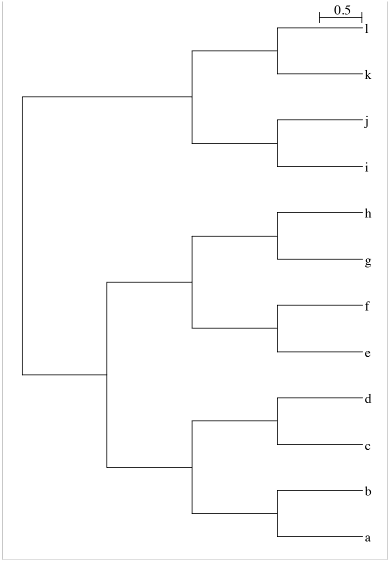


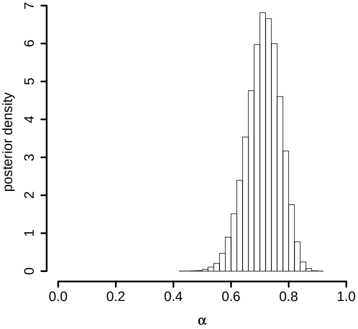
MCMC inference (3) : Balanced tree





MCMC inference (4) : Very balanced tree





Conclusion and perspectives

- A simple model of phylogeny based on an individual-based model of evolution under the Red Queen hypothesis see also Chisholm & O'Dwyer (2014)
- Reduction of state-space for fast simulation of the phylogeny of a sample of species
- Convergence to Kingman coalescent as $\alpha \to 1$
- Likelihood computation after data augmentation : MCMC inference algorithm
- WIP : Distributions of β and γ vs α
- WIP : Inference in the transient phase, inference under models of niche colonisation (Verónica Miró Pina)

Institutions

- ***Stochastic Models for the Inference of Life Evolution*** **(SMILE)**
  $\subset$ Center for Interdisciplinary Research in Biology
  $\subset$ Collège de France

- ***Stochastics & Biology group***
  $\subset$ Laboratoire de Probabilités et Modèles Aléatoires
  $\subset$ UPMC University Paris 06

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  - T.L. Parsons (CNRS & SMILE, Paris)
- Thanks to the members of the SMILE group

SMILE group in May 2015

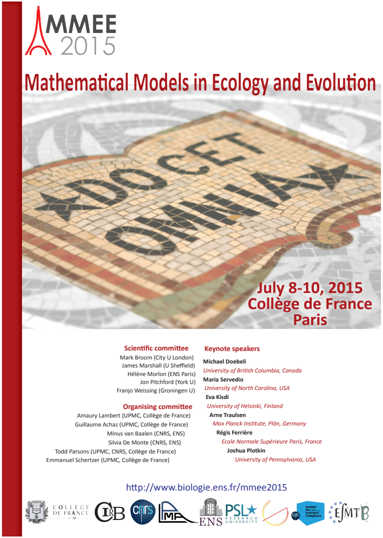
Conference announcement

Mathematical Models in Ecology & Evolution

Collège de France, Paris, France

July 8–10, 2015

`http://www.biologie.ens.fr/mmee2015/`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