A Non-Exchangeable Coalescent Arising in Phylogenetics

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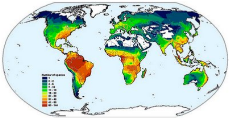
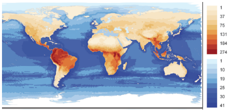
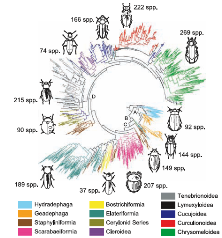
Journées MAS
Grenoble, 30 août 2016

Outline

Pattern & Process

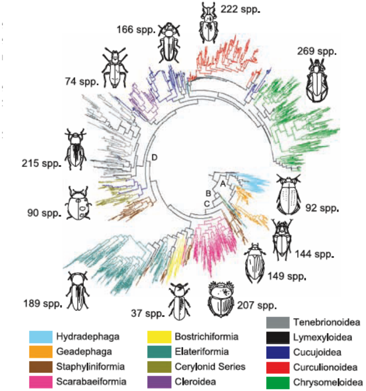


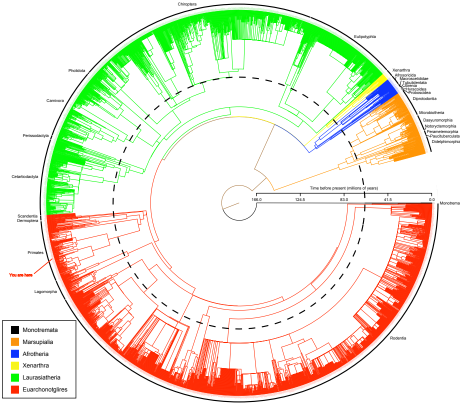




- Design probabilistic models of evolutionary processes...
- ...Generating similar patterns as those observed in nature, and...
- ...Allowing for the inference of these processes from real data...
- ...Assuming the data is a phylogeny (gene tree, species tree,...) already inferred from MSA.

Phylogenetic Trees





Two Questions About Macroevolution

Reconstruct the past of biodiversity : What processes underpin the observed macro-evolutionary patterns ?

- Q1 : "Can we test the possibility that some aspects of the evolutionary record behave as stochastic variables ?" (Raup et al 1973)

  Example of phylogenetic trees = Most basic pattern left by macroevolutionary history

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- Q2 : "Are there mathematically simple or biologically plausible stochastic models for phylogenetic trees whose realizations mimic actual trees ?" (Aldous 2001)

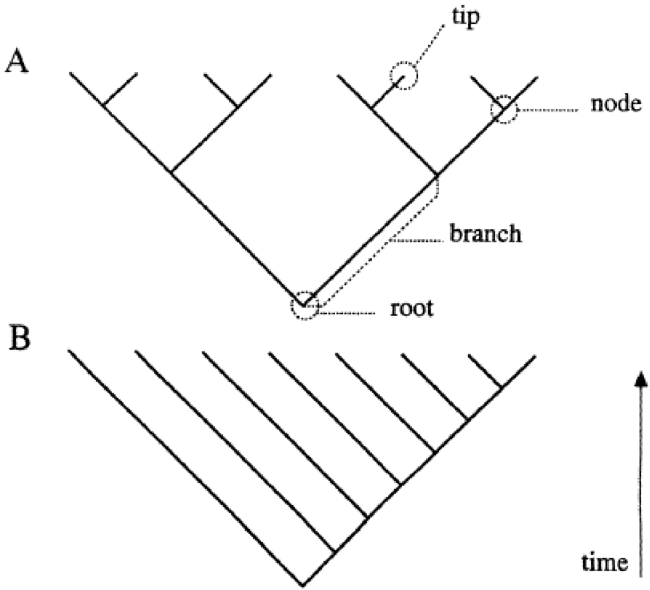
- Alternatively Q2' : Can we infer the most likely evolutionary process to have generated the tree ?

Difficulty of characterizing trees

- Comparing two trees : distance ? Robinson-Foulds, Gromov-Hausdorff, Billera-Holmes-Vogtman...
- Characterizing one tree : distance to some reference tree ?
- A distribution of trees : average tree ?
- Real functions of trees = statistic, likelihood
- Requires stochastic models of trees
  - Compare statistic to its distribution under null model (Q1)
  - Fit a non-null model (Q2)

Outline

Perfectly Balanced Tree (A) vs Caterpillar Tree (B)



Model-free statistics of trees I : Using topology only

See Shao & Sokal (1990), Kirkpatrick & Slatkin (1993), Mooers & Heard (1997)

Local statistics

- $c_i = \#$ nodes on the path from the root to tip i
- $s_{\min}(v) = \#$ tips in smaller daughter clade of node v
- Balance of node $v = s_{\min}(v)/s_{\max}(v)$

Global statistics

- Sackin index (Sackin 1972)

$$\frac{1}{n}\sum_i c_i$$

- Colless index (Colless 1982)

$$\frac{2}{(n-1)(n-2)}\sum_v \left(s_{\max}(v) - s_{\min}(v)\right)$$

Model-free statistics of trees II : Using branch lengths also

Local statistics

- 'Distinctiveness' $=$ length of external edge of tip i (Redding et al 2008)
- Local Branching Index (Luksza & Laessig 2014, Neher et al 2014)

$$= \int_{\text{tree}} e^{-d(x,y)/\delta}\, dy$$

Global statistics

- *Phylogenetic Diversity PD* $=$ Total Length of Tree $= \sum_{k=2}^{n} k g_k$ with $g_k =$ internode duration (Vane-Wright et al 1991, Faith 1992)
- Lineage-Through-Time plot
- Gamma (Cox & Lewis 1966, Pybus & Harvey 2000)

$$\gamma = \frac{\frac{1}{n-2}\sum_{i=2}^{n-1}\sum_{k=2}^{i} k g_k - \frac{PD}{2}}{PD/\sqrt{12(n-2)}}$$

Understanding the origin of patterns

- 1960's : Root imbalance = radiation undergone by the larger daughter subclade ?

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- Root balance under the Yule model is uniform !
  "How different, then, is the real world from the stochastic system ? The answer would seem to be 'not very' — the outstanding feature of real and random clades is their basic similarity" (Gould et al 1977, Savage 1983)

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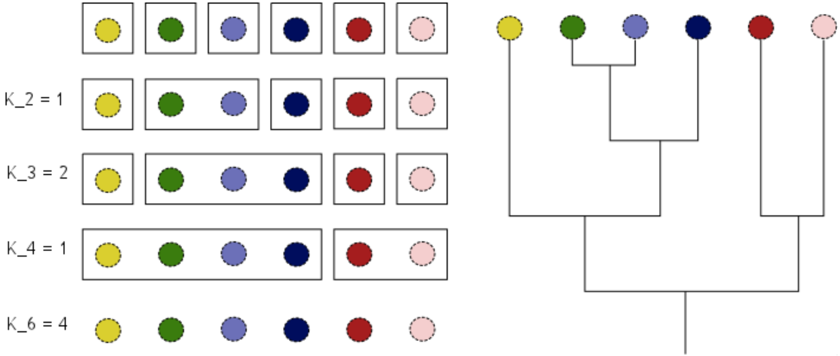
- Empirical root balance $\neq$ uniform (Slowinski 1990, Guyer & Slowinski 1991, 93)

Aldous' Markov branching model on binary tree shapes

Aldous (1996, 2001)

- Assume we are given distributions q_n on $\{1, \ldots, n-1\}$, $n \geq 2$
- Recursively split each subset of n balls according to q_n (r.v.'s K_n below)



- q_n uniform yields the same tree shape as a Yule tree

Sampling consistency

- A tree model is a family of probability distributions (P_n) on (exchangeably labelled) tree shapes with n tips
- Call T_n a random tree with law P_n
- Call T'_n the tree obtained by removing one tip from T_{n+1} (say the tip labelled $n+1$)
- The model is said **sampling consistent** if T_n and T'_n have the same distribution.
- Example : Kingman coalescent.

Aldous' Markov branching model

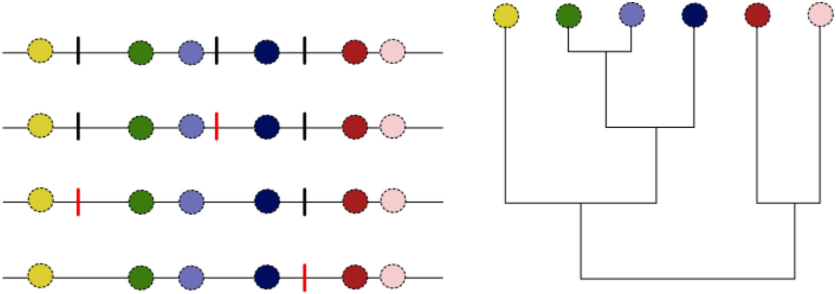
Theorem (Haas et al 2008, Lambert 2016)

A MB tree model is sampling-consistent iff *it there is a function f s.t.*

$$q_n(i) = a_n(f)^{-1} \binom{n}{i} \int_0^1 x^i (1-x)^{n-i} f(x)\, dx$$

Construction

- Color dots are uniformly distributed in the interval
- Intervals are fragmented by r.v. with density $\sim f$



Aldous' Markov β-splitting model on binary tree shapes

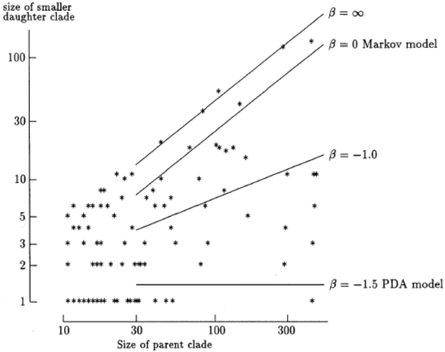
Aldous (1996, 2001), Maliet, Gascuel & Lambert (2016)

- The β-splitting model is for $\beta \in (-2, \infty) : f(x) = cx^{\beta}(1-x)^{\beta}$
- Imbalance decreases with β
- $\beta = 0$ under the Yule model (= Q1)

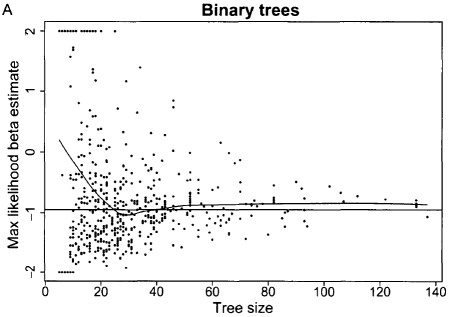
β	Description	Median split
-2	Completely unbalanced	1
-1.5	PDA model	1.5
-1	Unnamed	$\sqrt{m}$
0	Markov model	$m/4$
∞	An almost completely balanced model	$m/2$

Estimating β in real phylogenies

$S_{\min}$ vs $S_{\min} + S_{\max}$ (Aldous 2001)



MLE of β (Blum & François 2006)



$$\Longrightarrow \beta \approx -1$$

Q2 : "Are there mathematically simple/biologically plausible stochastic models for phylogenetic trees whose realizations mimic actual trees ?" (Aldous 2001) or "Why $\beta \approx -1$?"

Outline

1. Introduction

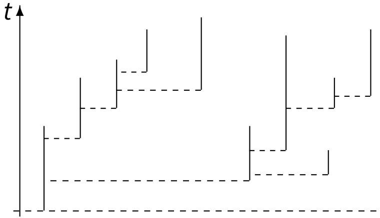
2. Characterizing Trees

3. Lineage-Based Models

4. A Simple Individual-Based Model

Birth-Death Models of Macroevolution (Nee 2006)

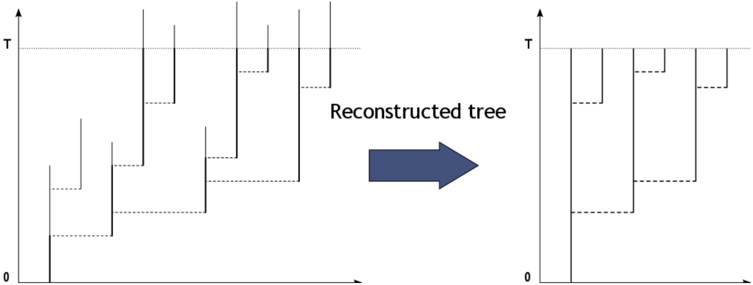
- Species seen as particles that can split (speciation) and die (extinction)
- Rates $b(t, n, a, i)$ and $d(t, n, a, i)$ may depend upon :



- **time** t
- **number** n of standing particles
- a **non-heritable trait** a (e.g., age)
- a **heritable trait** i

Yule model : $b =$ constant, $d = 0$.

Reconstructed Tree



- 'Reconstructed tree' or 'reduced tree' at height T
  = remove all lineages extinct by T (fixed time).

- Q2 : Are there universal conditions on the rates for which the reconstructed tree has $\beta \approx -1$?

- Q2' : What is the law of the reconstructed tree under the model ?
  Can we compute the likelihood of a given ultrametric (clock-like) phylogenetic tree under the model ?

Classifying Lineage-Based Models

Lambert (2010), Lambert & Stadler (2013)

- **A (partial) positive answer to Q2'** :

  The likelihood of reconstructed trees always has an explicit product form IFF $b = b(t)$ and $d = d(t, a)$.

  $\Longrightarrow$ The reconstructed tree is a **'coalescent point process'** [...]

- **A (partial) negative answer to Q2** :

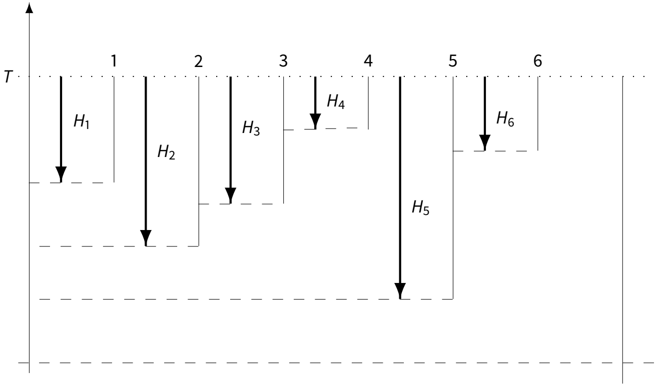
  Reconstructed trees always have the same topology in distribution as Yule trees ($\beta = 0$) IFF $b = b(t, n)$ and $d = d(t, n, a)$

  $\Longrightarrow$ As soon as $b = b(t, n)$ and $d = d(t, n, a)$, estimate $\beta \approx \mathbf{0}$

The CPP distribution

Rannala (1997), Popovic (2004), Aldous & Popovic (2005)

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



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

Assume that $b = b(t)$ **and** $d = d(t, a)$.
Set $g(t, s)$ the density at time s of the extinction time of a species born at time t.

Theorem (Lambert & Stadler 2013)

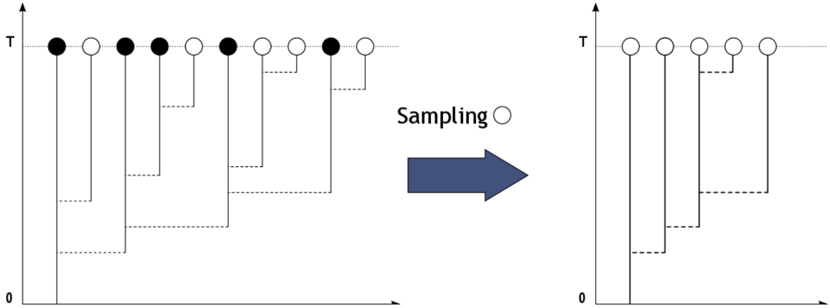
The ***reconstructed (oriented) tree is a CPP*** *with typical node depth H, where the function $F = 1/P(H > \cdot)$ is the unique solution to the following linear integro-differential equation*

$$F'(t) = b(t) \left(F(t) - \int_{T-t}^{T} ds\, F(s)\, g(t, s) \right) \qquad t \geq 0,$$

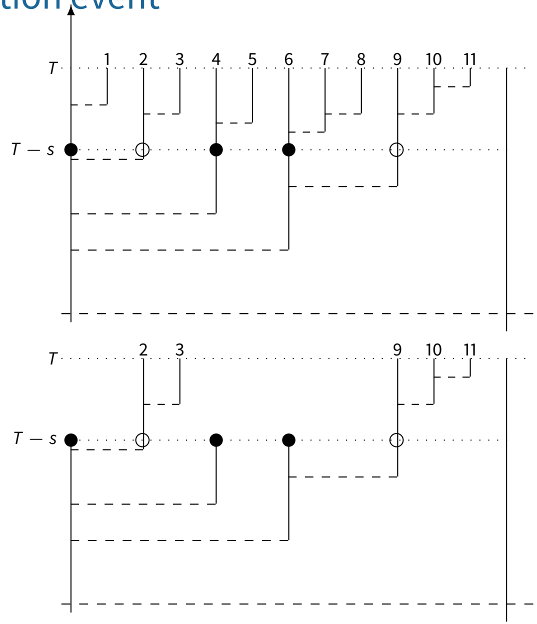
with initial condition $F(0) = 1$.

The result still holds with missing species/mass extinction events : each species is removed independently with the same probability p.

Missing species



Mass extinction event



Special cases

- If $b = b(t)$ and $d = d(t)$ (Kendall 1948, Nee et al 1994)

$$F(t) = 1 + \int_{T-t}^{T} ds\, b(s)\, e^{\int_s^T du\, (b-d)(u)}$$

- If b is constant and $d = d(a)$, then $g(s,t) = g(t-s)$ [if a the age $g(a) = d(a)\, e^{-\int_0^a ds\, d(s)}$] (Lambert 2010)

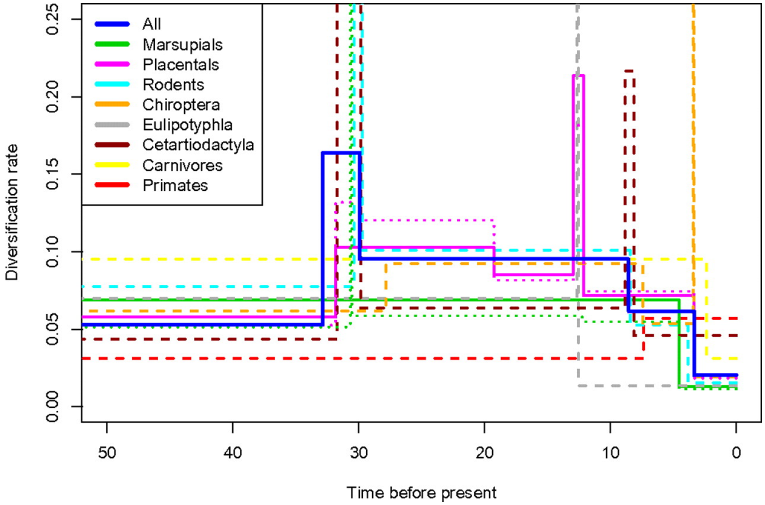
$$F' = b\, \left(F - F \star g\right),$$

- Mass extinction event with survival probability p at time $T - s$

$$F_p(t) = \begin{cases} F(t) & \text{if } 0 \le t \le s \\ (1-p)F(s) + pF(t) & \text{if } s \le t \le T, \end{cases}$$

Appl.1 Diversification of Mammals

Stadler "Mammalian Phylogeny Reveals Recent Diversification Rate Shifts" *PNAS* (2011)



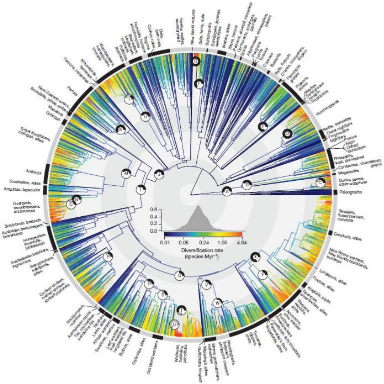
Appl.2 Do species age ?

Alexander, Lambert & Stadler "Quantifying Age-dependent Extinction from Species Phylogenies"
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 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 $b = 0.108\ My^{-1}$

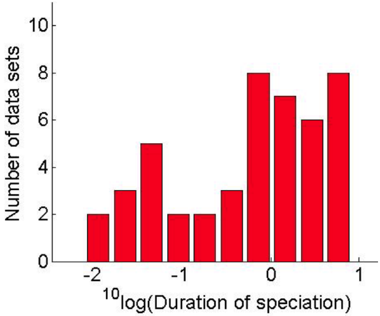


Appl.3 How long does speciation take ?

Etienne, Morlon, Lambert "Estimating the Duration of Speciation from Phylogenies" *Evolution* (2014)

Model of **Protracted Speciation** (Rosindell et al 2010, Etienne & Rosindell 2012)

- Species are ensembles of populations, each population gradually diverges from mother species
- Newborn populations are incipient, become good after some random time = new species
- Speciation stage = non-heritable trait



- Duration of speciation = Time before a good sp appears in the pop genealogy
- Test on simulations : efficient inference of duration of speciation
- Left : duration of speciation inferred in 46 bird clades (in My)

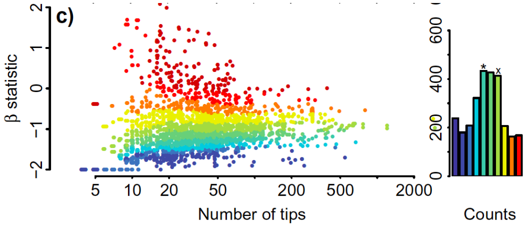
A positive answer to Q2 ?

Hagen, Hartmann, Steel, Stadler "Age-Dependent Speciation Can Explain the Shape of Empirical Phylogenies" *Systematic Biology (2015)*

- $b = b(a)$ parameterized by

$$b(a) = ca^{\phi-1}$$

- Estimates of ϕ lie in $(0, 1)$: speciation rate decreases with age



For $\phi = 0.6$, the reconstructed tree has $\beta \approx -1$.

Q2 : "Why $\beta \approx -1$?"

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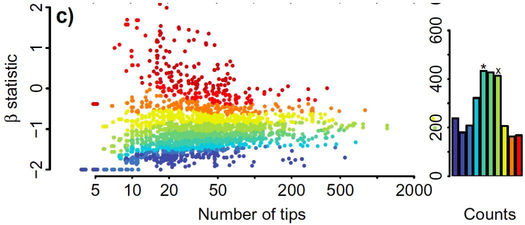

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— "Because $\phi \approx 0.6$" ;-)

Outline

Goal

In this section, 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"
- Key innovations, niche invasions, co-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, Lambert 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)

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

  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 (Champagnat 2006) as $K \to \infty$ each new mutant arises

- after the populations have reached their deterministic equilibrium
- before macroscopic departure from this equilibrium.

In the mutation timescale, i.e., when time is accelerated by a factor $1/K\varepsilon_K$,

- The descendance of a mutant reaches macroscopic abundance with probability $1 - \mu/\lambda$
- $X_i \approx K\overline{x}_i$
- Species i produces a mutant at rate $\varepsilon_K(K\overline{x}_i)/K\varepsilon_K = \overline{x}_i$

Statement

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*

$$\rho_n = \lambda \left(1 - \frac{\mu}{\lambda}\right) \sum_{i=1}^{n} \overline{x}_i$$

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* $(\overline{x}_1, \overline{x}_2, \ldots, \overline{x}_{N_t - 1}, 0, \ldots, 0)$.

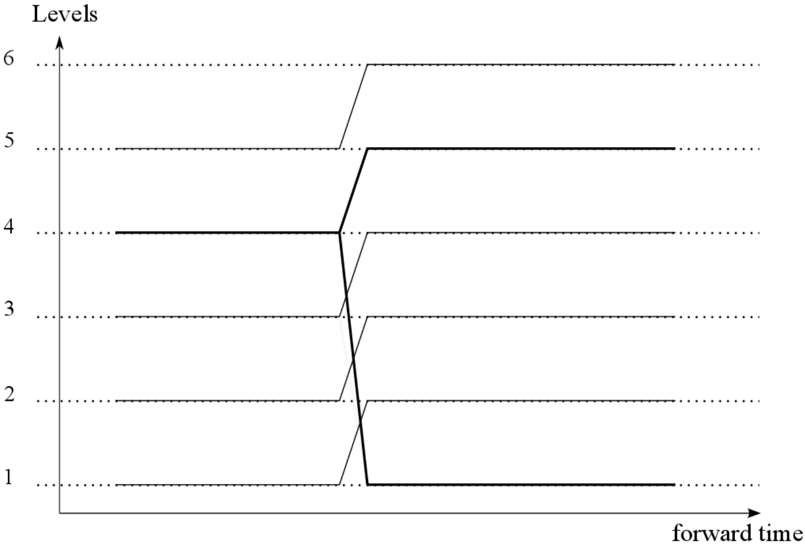
A Non-Exchangeable Coalescent Process

In the new timescale at stationarity, at constant rate

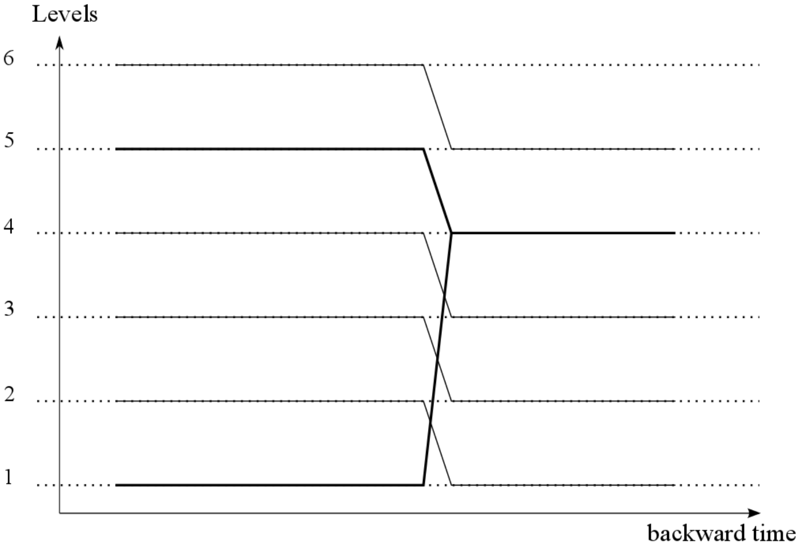
$$\rho = \frac{\kappa}{1-\alpha}\left(1 - \frac{\mu}{\lambda}\right)$$

- 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

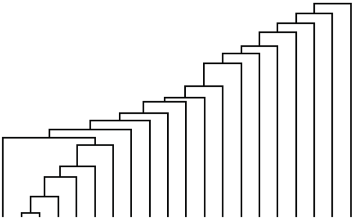
Speciation in forward time...

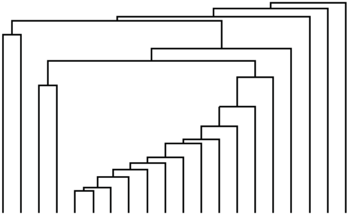


...Coalescence in backward time



Simulated trees with 20 tips





$$\alpha = 0.1$$

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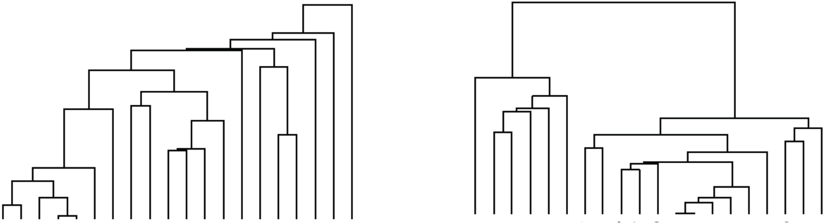
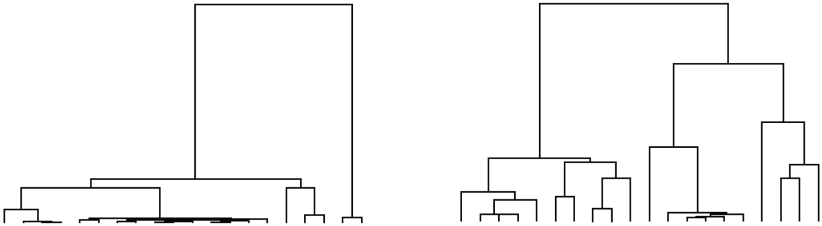


$\alpha = 0.7$

Simulated trees with 20 tips



$\alpha = 0.99$

Intertwining (Rogers & Pitman 1981)

Let $((X_t, Y_t), t \geq 0)$ be 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)

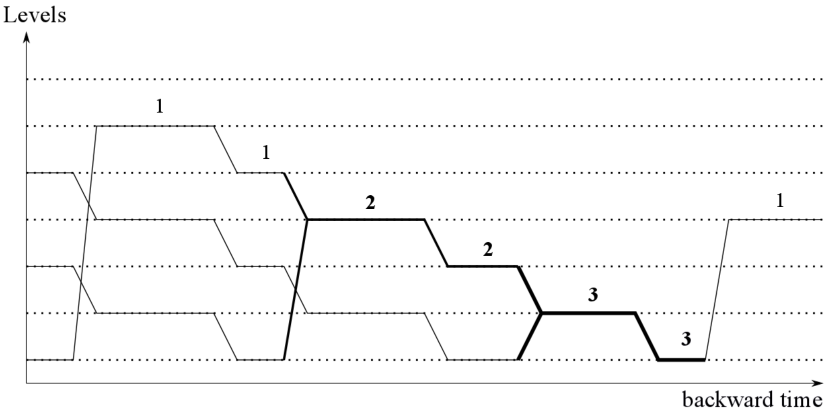
If there exists a generator G of a Markov process in E such that for each $f : E \times F \to \mathbb{R}$ in the domain of $\hat{G}$,

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

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 with generator G.*

The weight measure



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 levels 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.*

Convergence to the Kingman coalescent

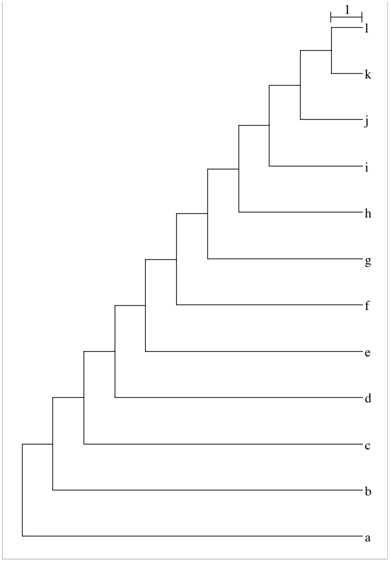
Recall $\alpha = 1 - d/c$ and $\kappa = (\lambda - \mu)/c =$ abundance of youngest species.

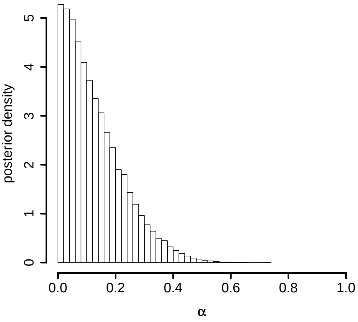
Theorem

As $\alpha \to 1$, the process $(B_{t/(1-\alpha)}; t \geq 0)$ converges (fdd) to $Z_t \delta_1$, where

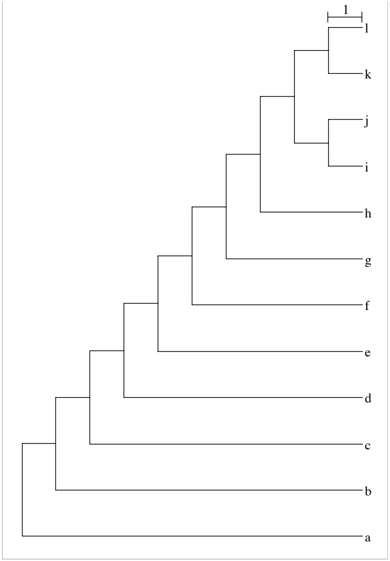
- *$(Z_t; t \geq 0)$ is a pure-death process with death rate $Cn(n-1)/2$*
- *$C = (1 - \mu/\lambda)\kappa$ (replacement rate).*

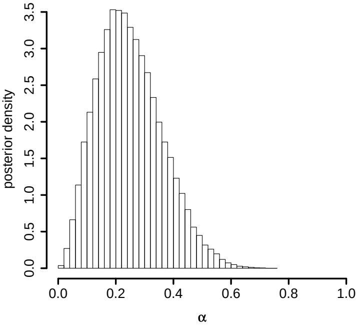
MCMC inference (1) : Caterpillar tree



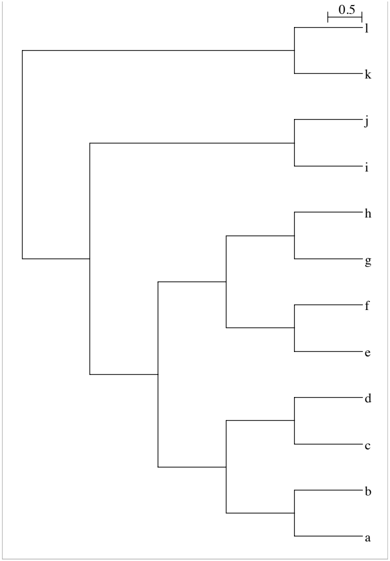


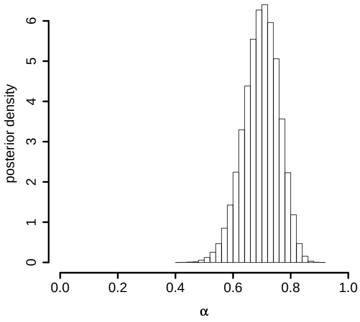
MCMC inference (2) : Very imbalanced tree





MCMC inference (3) : Balanced tree

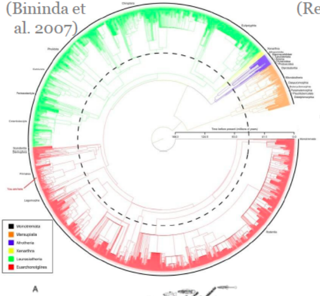




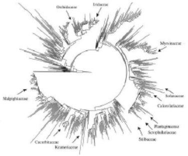
Conclusions

- One-parameter model of phylogeny based on a non-neutral, individual-based model of evolution see also Chisholm & O'Dwyer (2014)
- Relaxing neutrality fails to reproduce universal pattern
- So why $\beta = -1$?
- $\exists$ numerical methods for likelihood computation for general diversification processes
- But all mathematical methods known only work for $\beta = 0$ trees

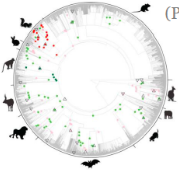
(Bininda et al. 2007)



(Renner & Schaefer 2010)

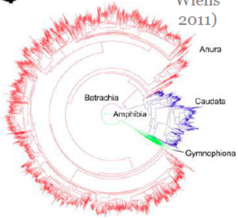


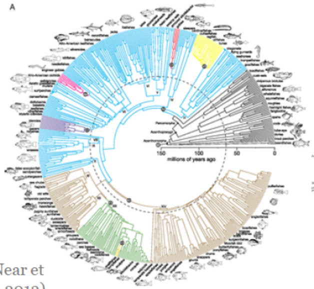
(Purvis et al. 2011)



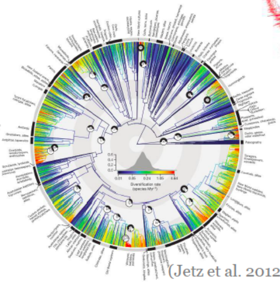
Thank you !

(Pyron & Wiens 2011)

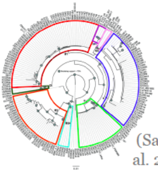




(Near et al. 2013)



(Jetz et al. 2012)



(Sahl et al. 2012)

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S.M.I.L.E

Stochastic Models for the Inference of Life Evolution

SMILE = Stochastic Models for the Inference of Life Evolution

Other lineage-based models of macro-evolution

- Diversity-dependent diversification (Etienne et al *Proc B* 2012)

- Trait-dependent diversification : BiSSE, QuaSSE, GeoSSE... (Maddison et al *Syst Biol* 2007, FitzJohn *MEE* 2012...)

  But pb with false positives...

- Reviews...
  - Ricklefs *TREE* (2007)
  - Pyron & Burbrink *TREE* (2013)
  - Stadler *JEB* (2013)
  - Morlon *Eco Lett* (2014)

Alternative Answers to Q2

- Phylogenetic reconstruction artifact ? (Huelsenbeck & Kirkpatrick *Evolution* 1996)
- Protracted/age-dependent speciation ? (Rosindell et al *Eco Lett* 2010, Hagen et al *Syst Biol* 2015)
- Neutral Biodiversity Theory ? (Jabot & Chave *Eco Lett* 2009, Davies et al *Evolution* 2012, Manceau, Lambert & Morlon *Eco Lett* 2015)