Coalescent trees of birth–death models & Applications to phylogenetics

Amaury Lambert
(with H. Alexander, R.S. Etienne, H. Morlon, T. Stadler)

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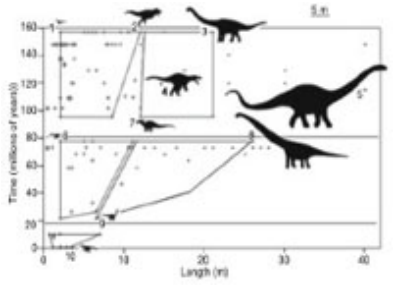
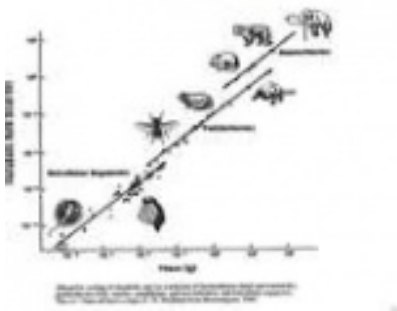
Outline

Evolutionary Biology and Math

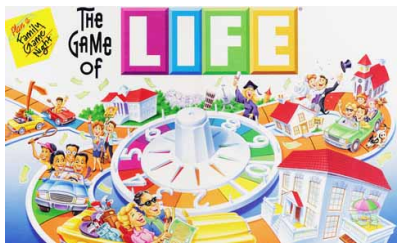
- Evolutionary biologists...
  - collect data : contemporary geno/phenotypes
  - identify patterns
  - postulate evolutionary processes responsible for these patterns.



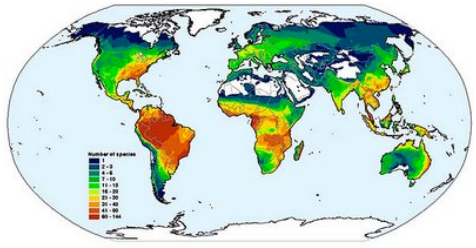


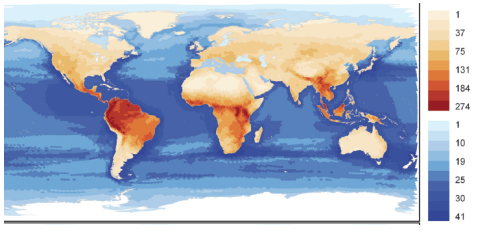
...But since those processes can not be reproduced *in vivo*...

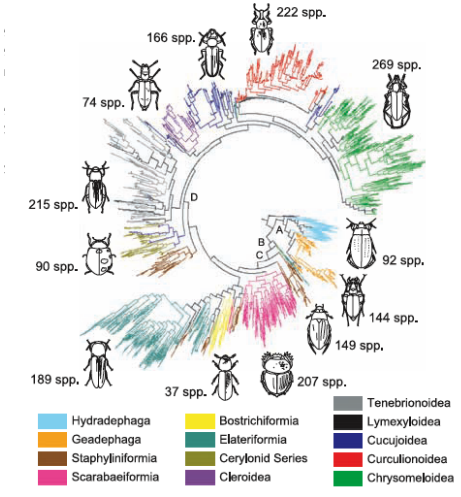
- We (mathematicians)...
  - propose simple models underlying the evolutionary processes
  - predict the patterns generated by these models
  - quantify the ability of competing processes to generate the observed patterns.



Understanding biodiversity patterns



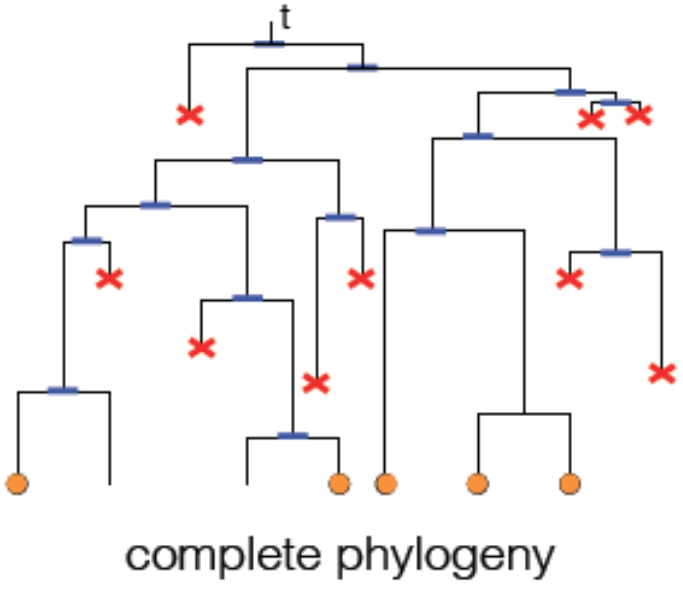




- Why are there so many species in the tropics ?
- Why are there so few species in the oceans ?
- Why are some taxonomic groups so much richer than others ?
- Infer diversification processes to see how these processes depend on time, species traits, current diversity, taxonomic groups, geographic regions, habitats...

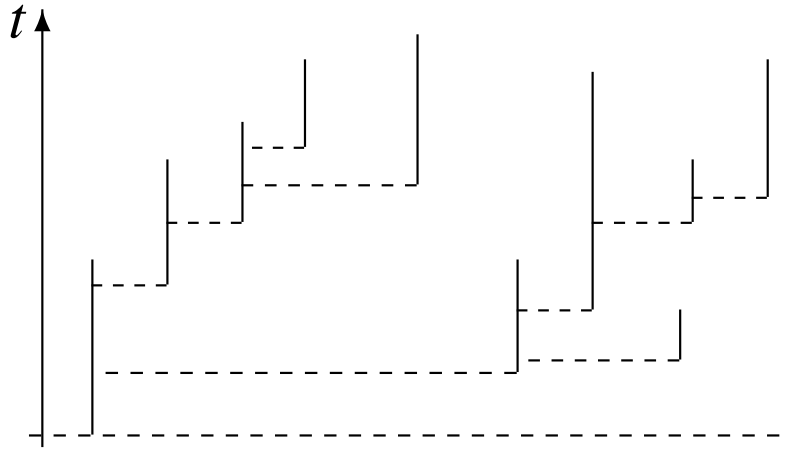
Birth–death models of genealogies/phylogenies

- We use birth–death models of diversification
- Where particles can be individuals or species (Nee et al *PNAS* 1992)
- Particles split into two new particles at rate b = birth (or speciation) rate
- Particles die at rate d = death (or extinction) rate
- $N_t :=$ nb particles at time t
- Particles may bear some trait i, and rates may depend on t, N_t, i,...



Assumptions on rates

Rates $b(t,n,a,i)$ and $d(t,n,a,i)$ may depend upon :

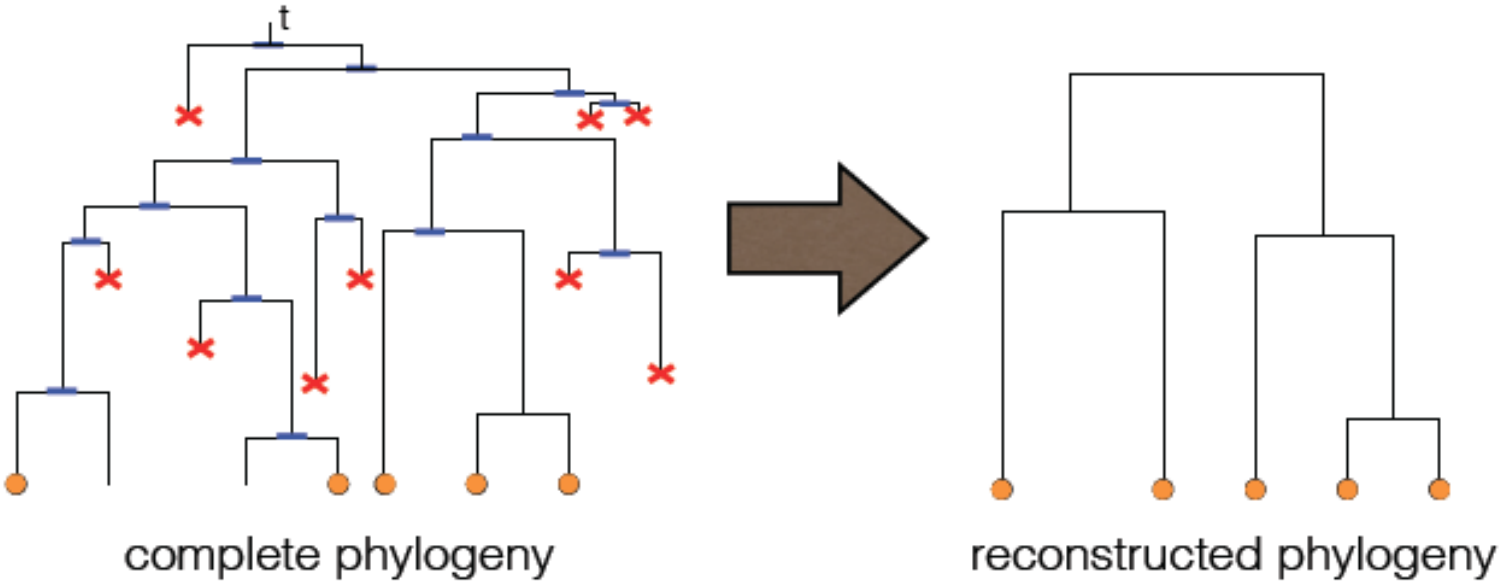


- **time** t
- **number** n of standing particles
- a **non-heritable trait** a (e.g., age)
- a **heritable trait** i
- Traits behave as iid Markov processes on each lineage
- Asymmetric birth = Mother keeps her trait
- Orientation = Daughter sprouts to the right

Outline

Reconstructed (or reduced) tree

- **Goal.** Use time-calibrated phylogenies to infer div processes
- By computing the likelihood of phylogenies (ML, MCMC) and estimating rates



Reconstructed tree = start with one particle at time 0, stop at time T, remove all lineages extinct by T.

Q1 : Can we characterize the distribution of the reconstructed tree under a generalized birth–death model of diversification ?

The CPP distribution (Popovic 2004, Aldous & Popovic 2005)

A reference distribution on ultrametric, oriented trees with edge lengths

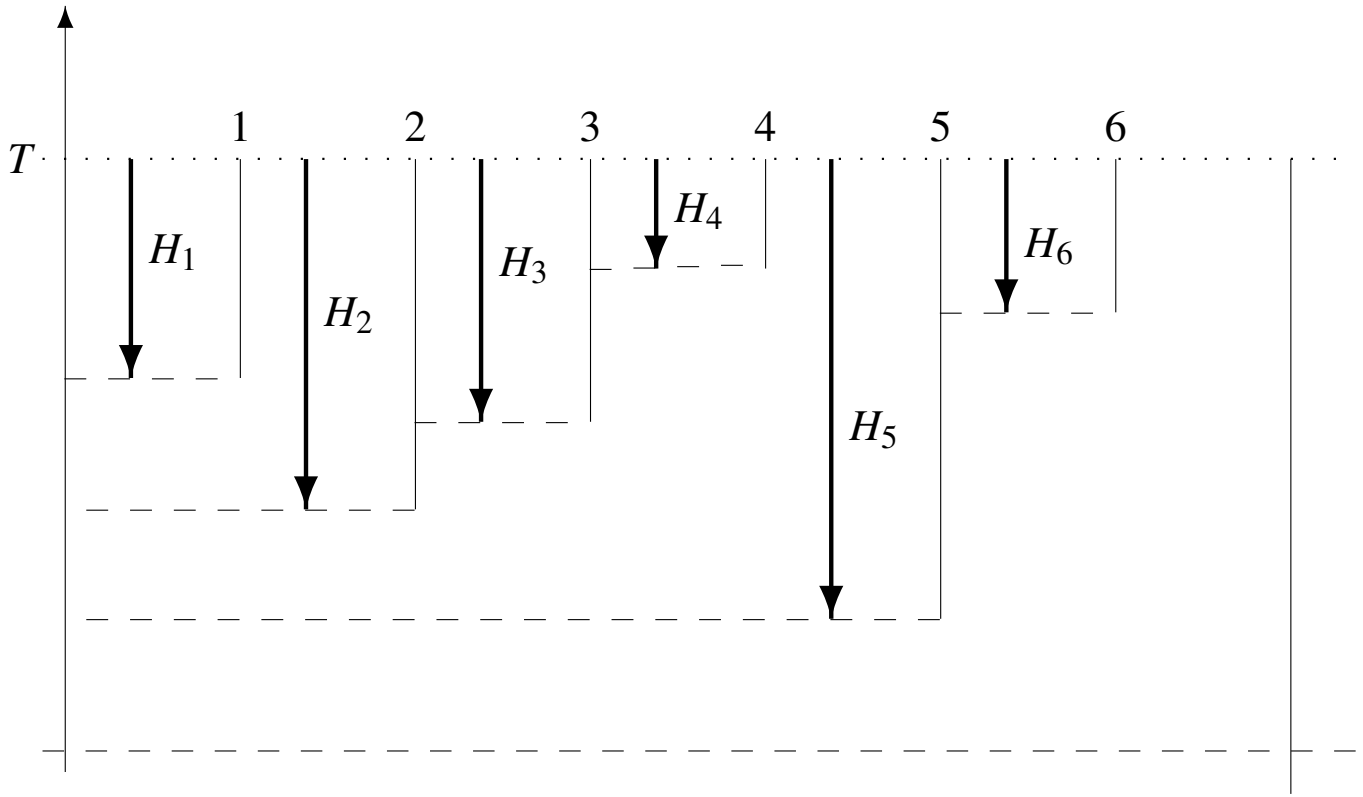
CPP = Coalescent Point Process = Oriented tree whose node depths $H_1, H_2, \ldots,$ form a sequence of **iid random variables** killed at its first value larger than T.

The likelihood of a tree with node depths $h_1, \ldots, h_{n-1}$ can be factorized as a product

$$L(h_1, \ldots, h_{n-1}) = P(H > T) \prod_{i=1}^{n-1} f(h_i),$$

where f is the density of H.

Simulating CPPs



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

Recall that t is time and a is any non-heritable trait.

Theorem (L. & Stadler 2013)

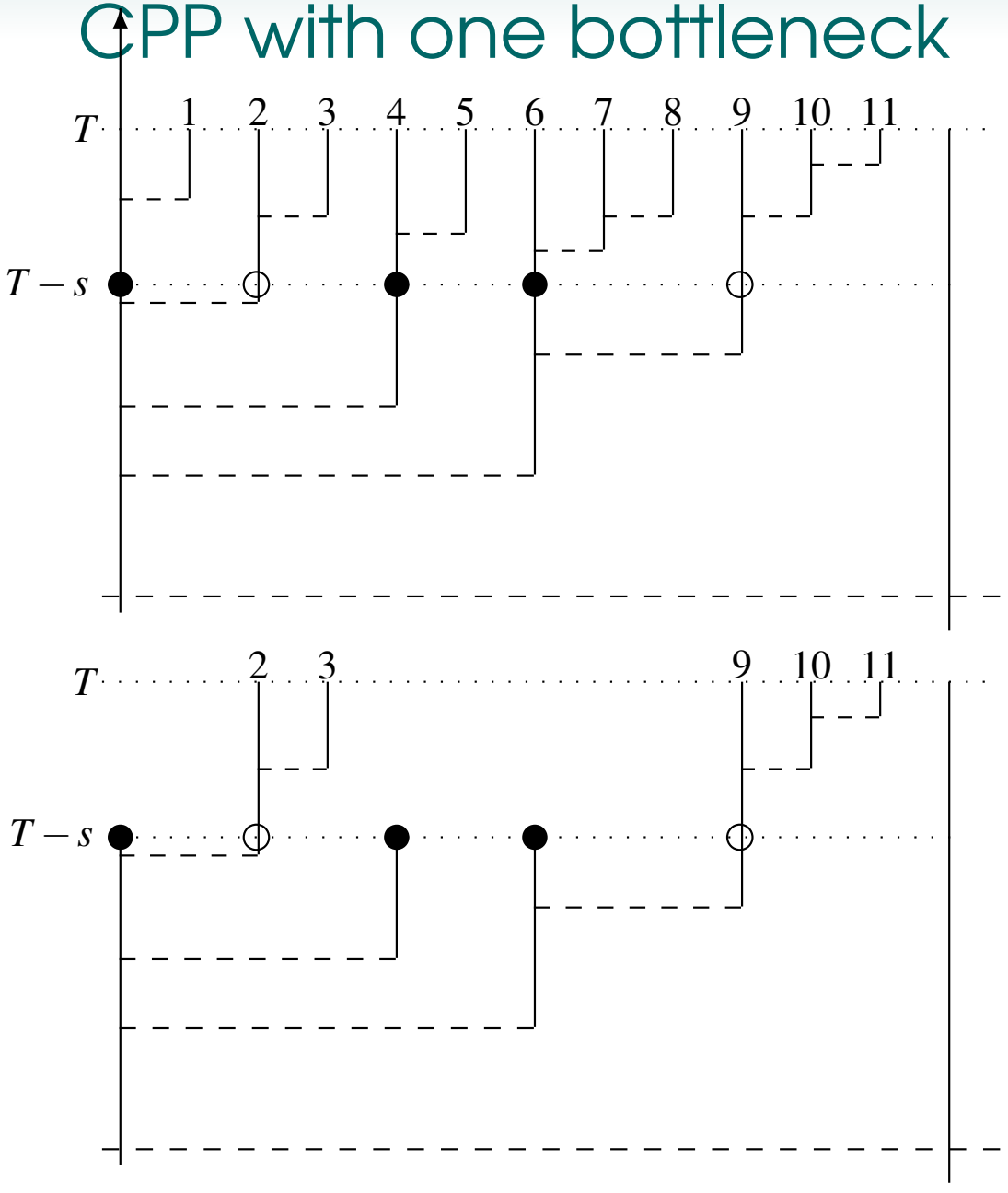
If $b = b(t)$ ***and*** $d = d(t,a)$, *then* ***the reconstructed oriented tree is a CPP*** *with typical node depth* H *whose distribution is given by*

$$P(H > t) = \exp\left(-\int_{T-t}^{T} b(s)\,p(s)\,ds\right) \qquad t \in [0,T],$$

where $p(t)$ *denotes the probability that a particle born at time* t *has extant descendance by time* T.

This still holds in the presence of ***bottlenecks*** = *mass extinction events (fixed times, fixed probabilities).*

CPP with one bottleneck



Law of H from model parameters (1)

Set $g(t,s)$ **be the density at time s of the extinction time of a species born at time t.**

Proposition (L. & Stadler 2013)

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 $F(0) = 1$.

Law of H from model parameters (2)

If $\mathbb{E}_{t,x}$ denote the expectation associated to the trait X started at time t in state x, then

$$g(t,s) = \int_{\mathbb{R}} \nu_t(dx)\; u_s(t,x) \qquad s \geq t,$$

where ν_t is the initial trait ditribution for sp born at t and

$$u_s(t,x) := \mathbb{E}_{t,x}\left(d(s,X_s)\; e^{-\int_t^s dr\, d(r,X_r)}\right) \qquad s \geq t.$$

If X is a Markov process with generator L_t at time t, then by Feynman–Kac formula, u_s is the unique solution to

$$\frac{\partial u_s}{\partial t}(t,x) + L_t u_s(t,x) = d(t,x)\; u_s(t,x),$$

with terminal condition $u_s(s,x) = d(s,x)$.

Two special cases

- If $b = b(t)$ and $d = d(t)$, then

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

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

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

with $F(0) = 1$. Equivalently, F is the unique non-negative function with Laplace transform

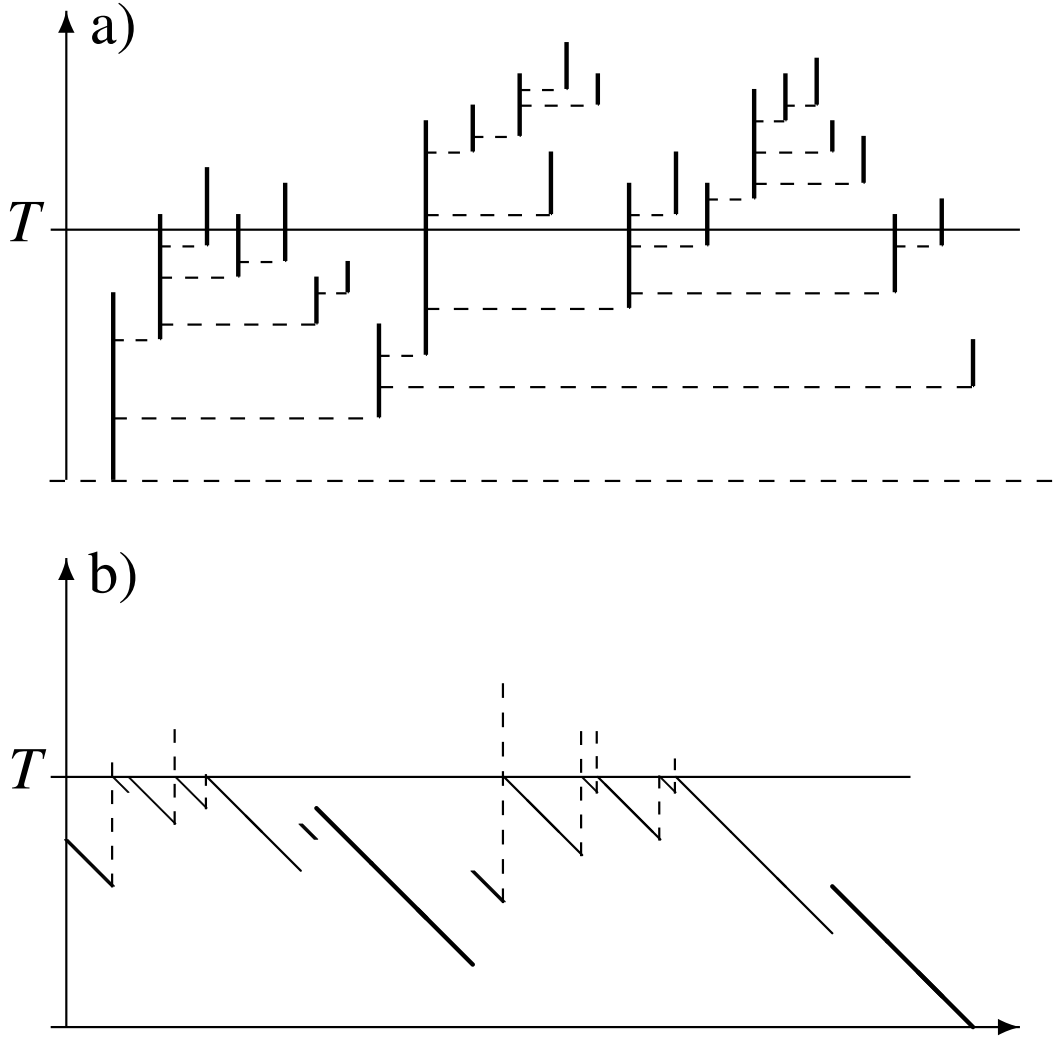
$$\int_0^\infty F(t)\, e^{-tx}\, dt = \frac{1}{\psi(x)},$$

where ψ is the Lévy exponent

$$\psi(\lambda) = \lambda - \int_0^\infty b\, g(t)\left(1 - e^{-\lambda t}\right) dt \qquad x \geq 0.$$

Jumping contour of a tree

a) Binary tree with edge lengths and b) Jumping contour process of its truncation below time T.

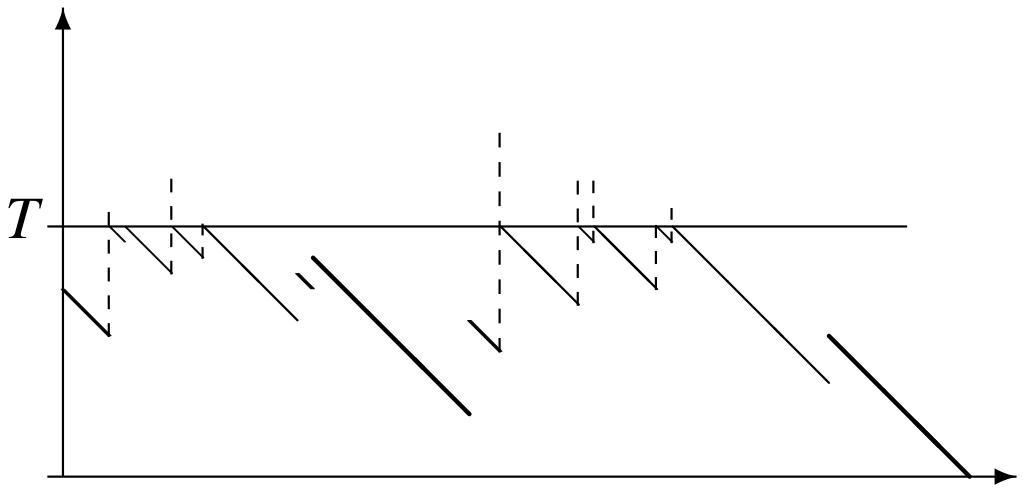


Contour of a splitting tree

Theorem (L. (2010))

The jumping contour process of a splitting tree truncated below T is a strong Markov process.

In the time-homogeneous case, it is a ***Lévy process with Lévy density*** $bg(\cdot)$***, without negative jumps and drift*** -1*, reflected below T and killed upon hitting 0.*



Application to the bird phylogeny

With T. Stadler and H.K. Alexander

- Gamma distributed lifetime ($k, \theta > 0$)

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

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

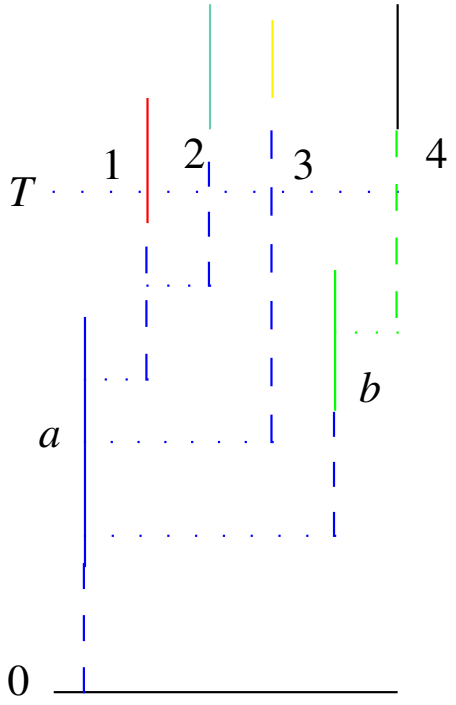
Outline

Protracted speciation (Rosindell et al 2010, Etienne & Rosindell 2012)

With R.S. Etienne and H. Morlon

- Particles = Populations
- **Speciation stage** = non-heritable trait = Each population gradually diverges from mother species
  - Newborn populations are **incipient** = same species as mother population
  - Become **good** after some random time = new species
- Each species is represented by a single population

Protracted speciation (2)



- 4 extant populations at time T
- 3 extant species
- Species b is represented by Population 4
- Species a is represented by Population 2.

Protracted speciation (3)

Assume that the birth rate b does not depend on speciation stage.

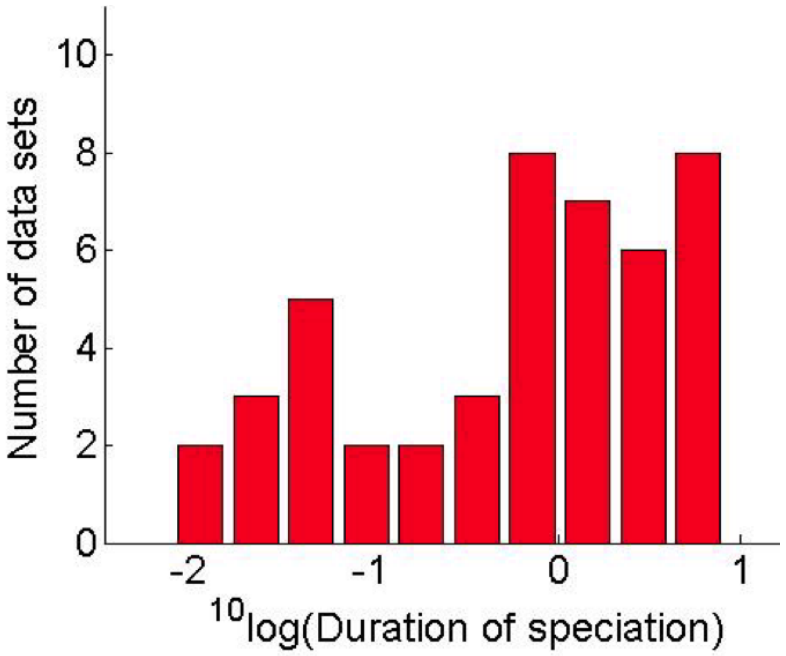
Theorem (Etienne, L. & Morlon 2013)

The reconstructed tree spanned by extant ***representative*** *populations at T is a* ***coalescent point process*** *with node depth H^r, where*

$$P(H^r > t) = \exp\left(-\int_{T-t}^{T} b(s)\,(1-p_1^r(s))\,ds\right)$$

and $p_1^r(t)$ is the probability that a species born at time t does not have any good descending species that has extant descendance at time T.

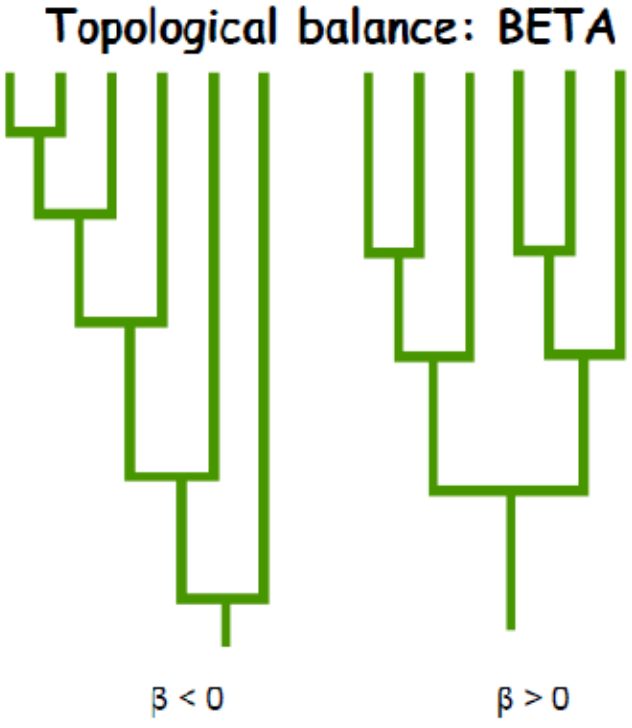
Protracted speciation (4)

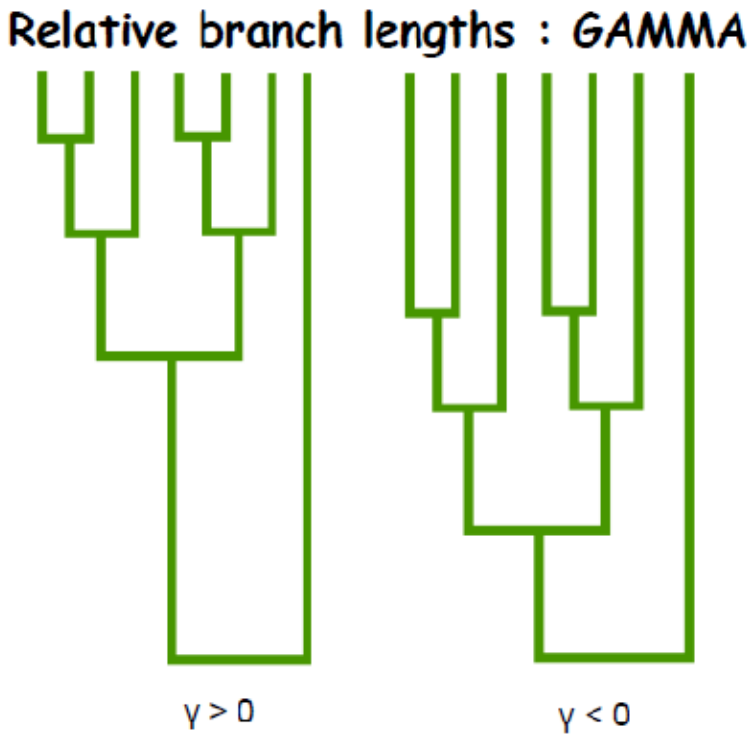


- Test on simulations : poor ML inference for each individual parameter
- Efficient inference of **duration of speciation** = waiting time before **first descending good** population
- Left : duration of speciation inferred in 46 bird clades (in My)

Outline

More real data : Two statistics





- MLE of Beta-splitting (Aldous 1996)
- Pure birth model : $\beta = 0$
- Real trees are imbalanced : $\beta < 0$ (Blum & François 2006)

- Pure birth model : $\gamma = 0$
- Kingman coalescent has nodes closer to tips : $\gamma > 0$
- Real trees have nodes closer to the root : $\gamma < 0$ (McPeek 2008)

The URT distribution

- Protracted speciation models produce $\gamma < 0$, BUT $\beta \approx 0$
- CPP = Fast simulation + fast inference, BUT always $\beta \approx 0$
- All CPPs have the same topology in distribution
- This topology is called **URT = uniform distribution** on ranked **oriented** trees after ignoring the orientation
  (The Kingman coalescent tree follows URT but not CPP)
- **Q2 :** What conditions on rates are necessary and sufficient to produce CPP trees ? URT trees ?

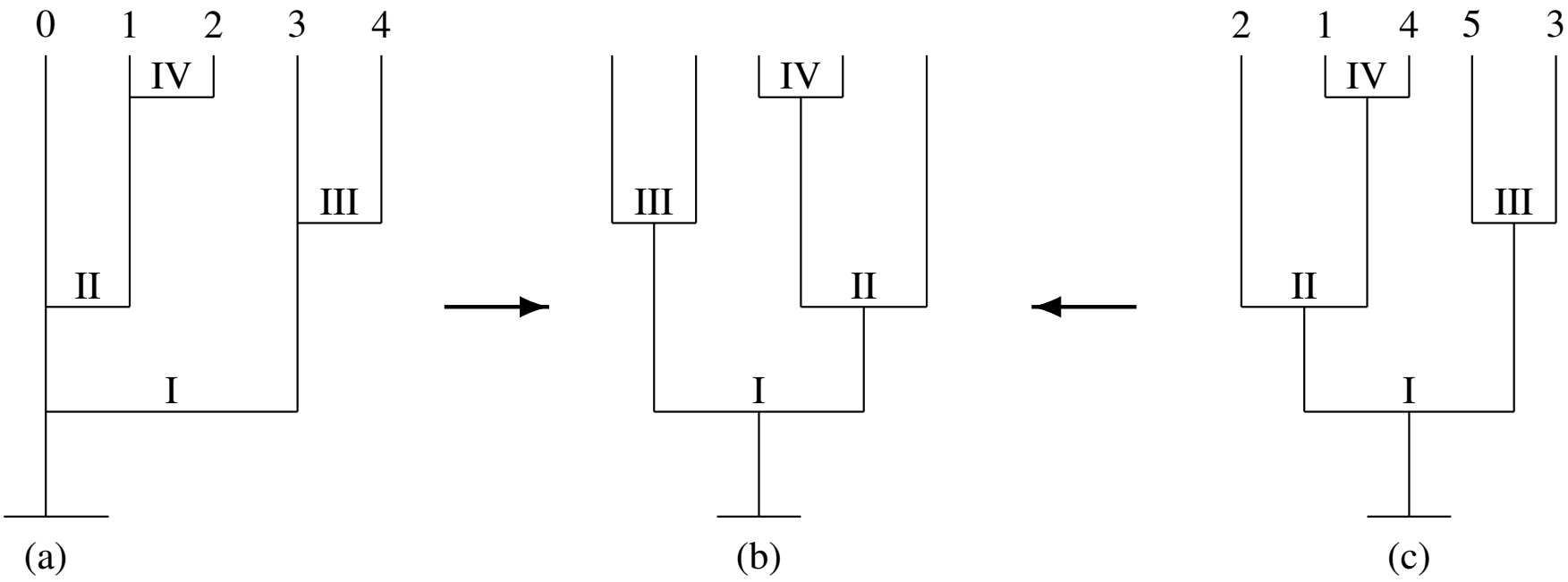


FIGURE : Under the uniform distribution on ranked oriented trees, the probability of the tree in (a) is $1/(n-1)! = 1/24$; under the uniform distribution on ranked labelled trees, the probability of the tree in (c) is $2^{n-1}/n!(n-1)! = 1/180$; under URT, the probability of the tree τ in (b) is $2^{n-1-c}/(n-1)! = 1/6$.

Answer to Q2

Proposition (L. & Stadler 2013)

1. *Reconstructed trees always follow CPP*
   IFF $b = b(t)$ *and* $d = d(t,a)$

2. *Reconstructed tree shapes always follow URT*
   IFF $b = b(t,n)$ *and* $d = d(t,n,a)$

Remark. As soon as $b = b(t,n)$ and $d = d(t,n,a)$, we will estimate $\beta \approx 0$.

$b = b(a)$ fails to produce URT

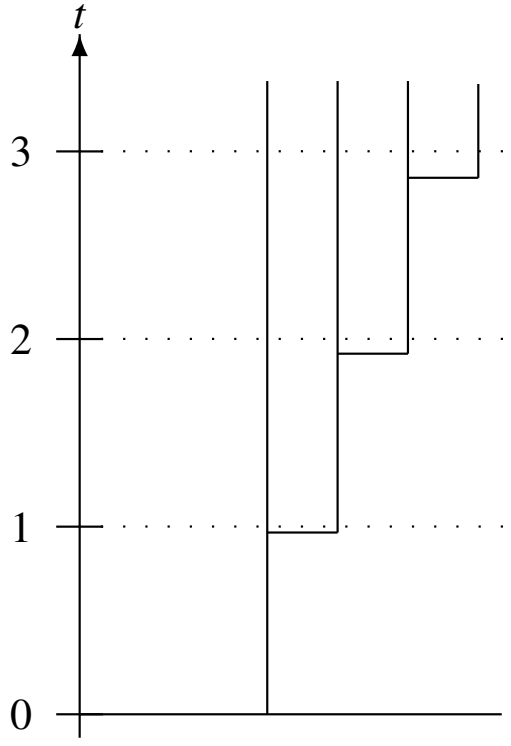


FIGURE : Here, $d = 0$ and $b(a) = \mathbb{1}_{[1-\varepsilon,1]}(a)$, where a is the age.

$\Longrightarrow$ **Age-dependent speciation rates** can produce caterpillar trees w.h.p., and so **do NOT produce URT** trees in general.

$d = d(i,a)$ fails to produce URT

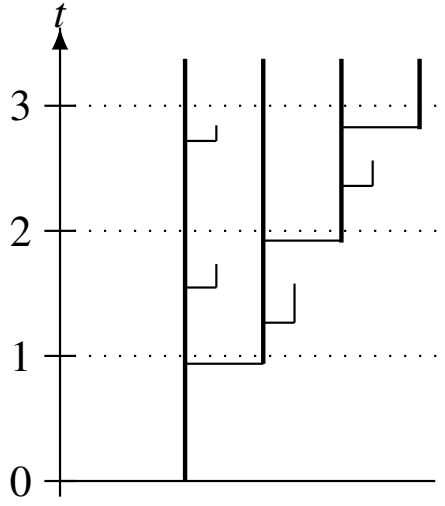


FIGURE : Species can bear the heritable trait $i = 0$ or 1. *All sp bear trait 0 except (the anc and) when born from a sp with trait 1 and age a in* $[1-\varepsilon, 1]$. Here $b = 1$, $d(1) = 0$ and $d(0) \gg -\log(\varepsilon)/\varepsilon$.

$\Longrightarrow$ **Heritable trait-dependent extinction rates** can produce caterpillar trees w.h.p. and so **do NOT produce URT** trees in general.

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

- If $b = b(t,n)$ and $d = d(t,n,a)$, then the law of the oriented tree is invariant under regrafting of subtrees (same time, different edge)
- The law of the oriented reconstructed tree is invariant under permutation of edges
- **The reconstructed tree shape always follows URT**.

$b = b(n)$ or $d = d(n)$ fail to produce CPP

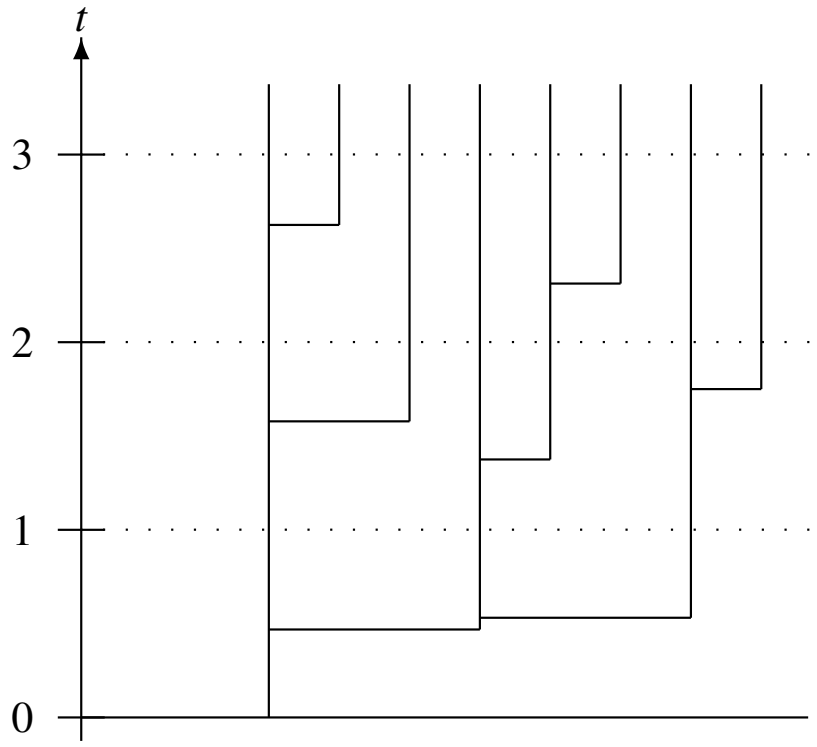


FIGURE : Here, $d = 0$ and $b = 1 + B\mathbb{1}_{n=2}$ with $B \gg 1$.
Alternatively $b = 1$ and $d(n) = D\mathbb{1}_{n=2}$, with $D \gg 1$.

$\Longrightarrow$ **Rates dependent on the nb of species** can produce trees where the 1st and 2nd speciations are arbitrarily close w.h.p., and so do **NOT produce CPP** trees in general.

Answer to Q2

Proposition (L. & Stadler 2013)

1. *Reconstructed trees always follow CPP*
   IFF $b = b(t)$ *and* $d = d(t,a)$

2. *Reconstructed tree shapes always follow URT*
   IFF $b = b(t,n)$ *and* $d = d(t,n,a)$

Q3 : Can we design tractable models of diversification with both $\beta < 0$ and $\gamma < 0$?

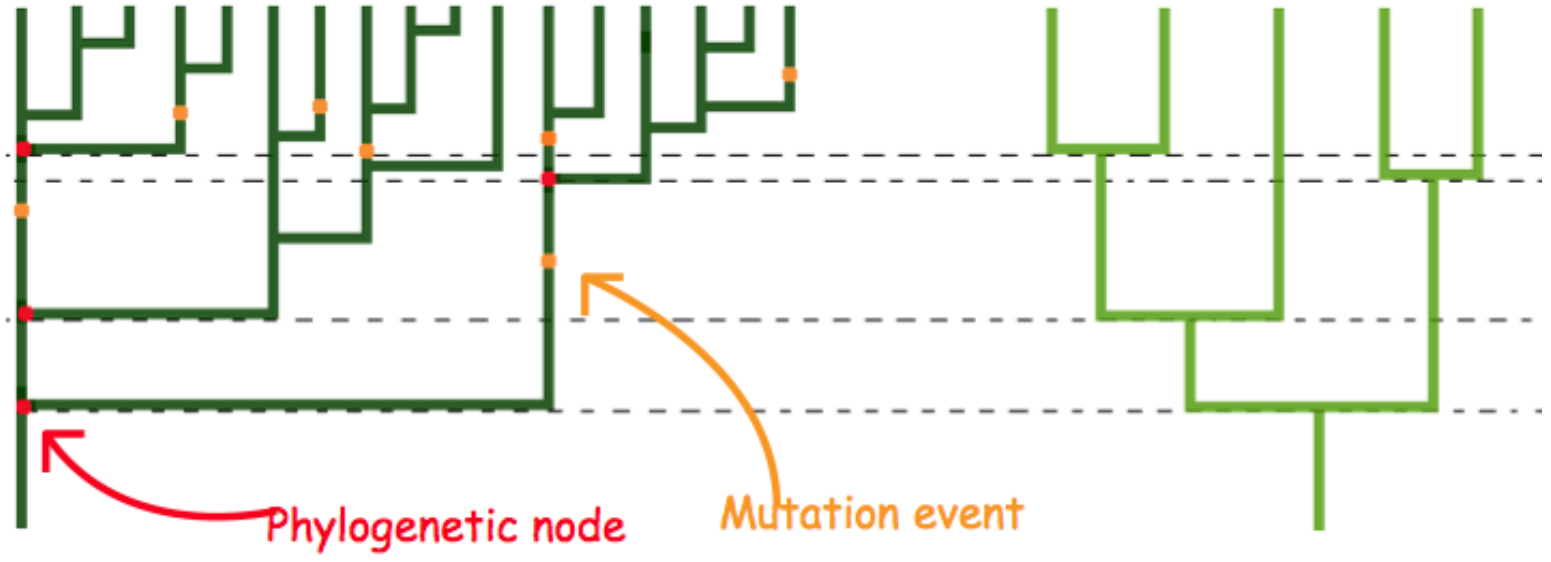
Outline

Speciation by genetic differentiation (1)

Work in progress with M. Manceau and H. Morlon

- Start with a birth–death tree (constant rates b and d, but...)
- Add Poissonian mutations rate θ, infinite-allele model
- **Species = minimal monophyletic taxon** such that any 2 tips with the same allele belong to the same species
- SGD = Speciation by genetic differentiation = individual-based version of protracted speciation

Speciation by genetic differentiation (2)

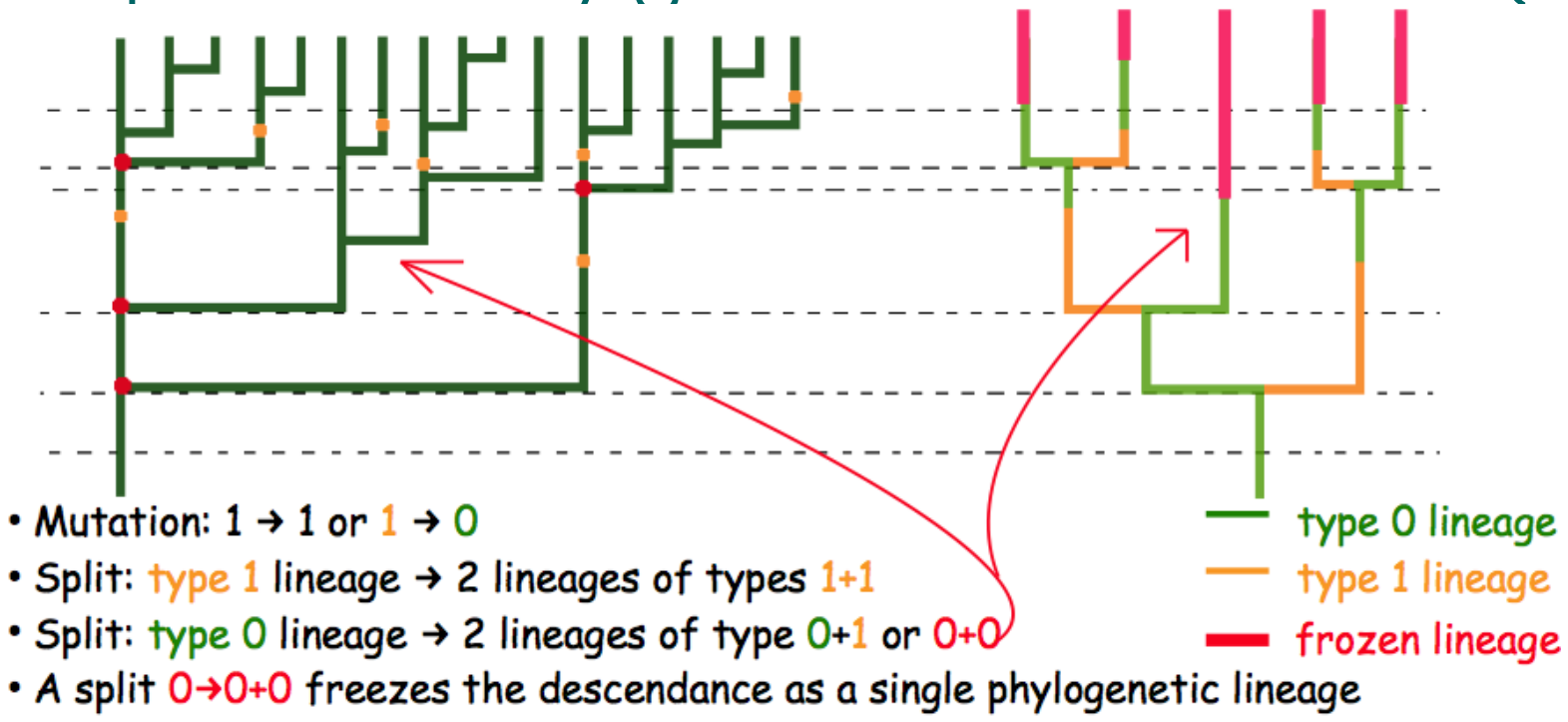


- A node on the genealogy is phylogenetic (= appears on the phylogeny) if

  (i) The previous node is phylogenetic
  (ii) All tips separated by this node carry different alleles

- The first node is phylogenetic if it satisfies (ii)

Speciation by genetic differentiation (3)

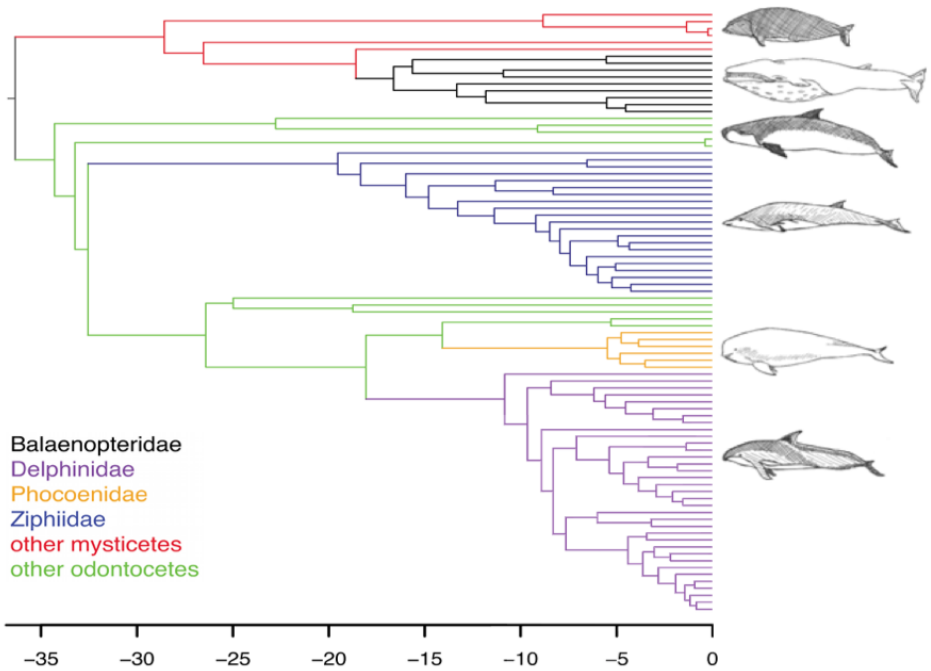


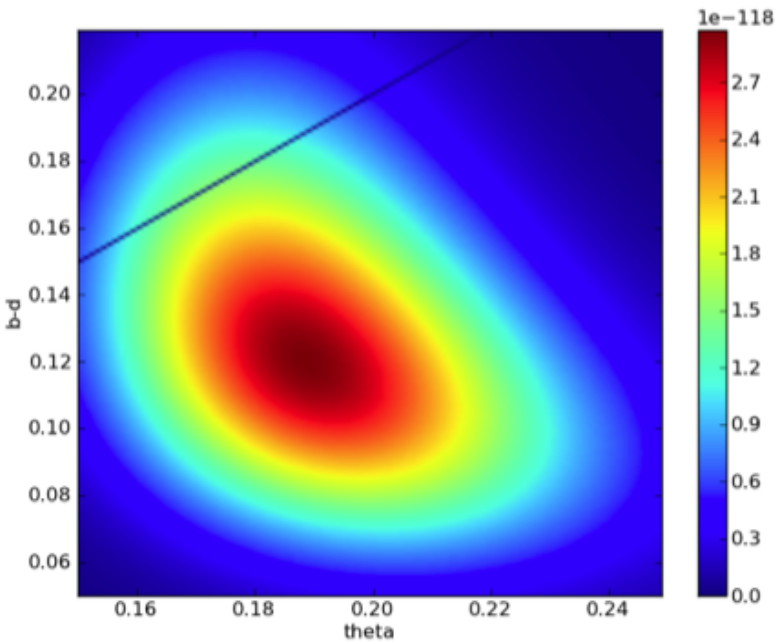
The phylogeny is generated by a 3-type time-inhomogeneous branching process

- a lineage is in state 1 if the allele it is carrying is NOT represented at T
- a lineage is in state 0 if the allele it is carrying is represented at T
- a lineage in state 0 gets frozen into one single phylogenetic lineage when it splits into two 0-lineages

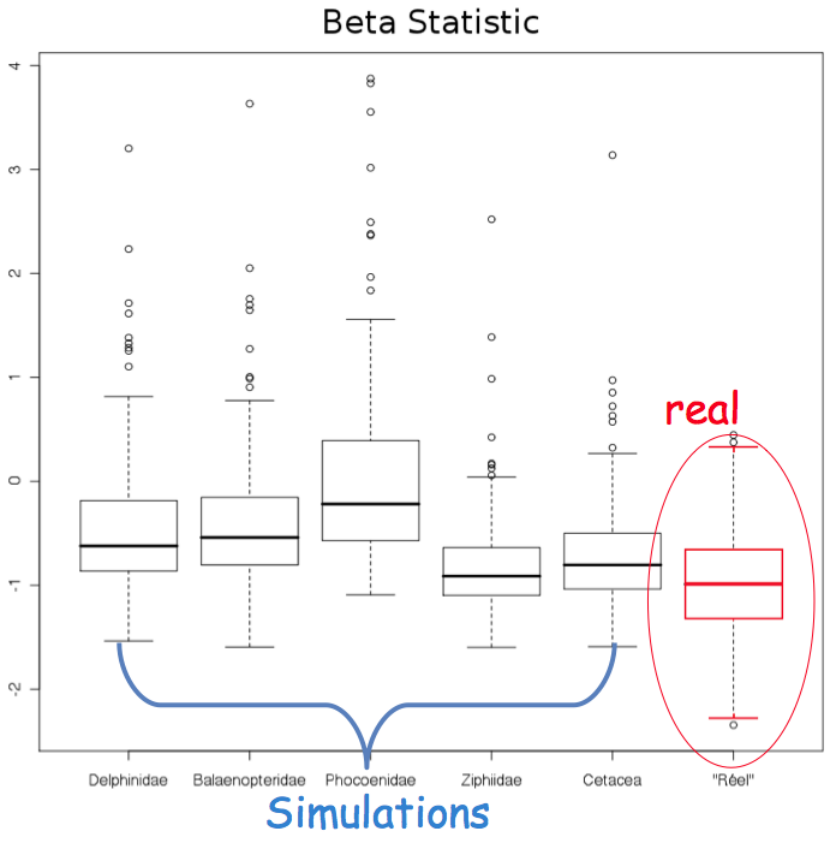
Speciation by genetic differentiation (4)

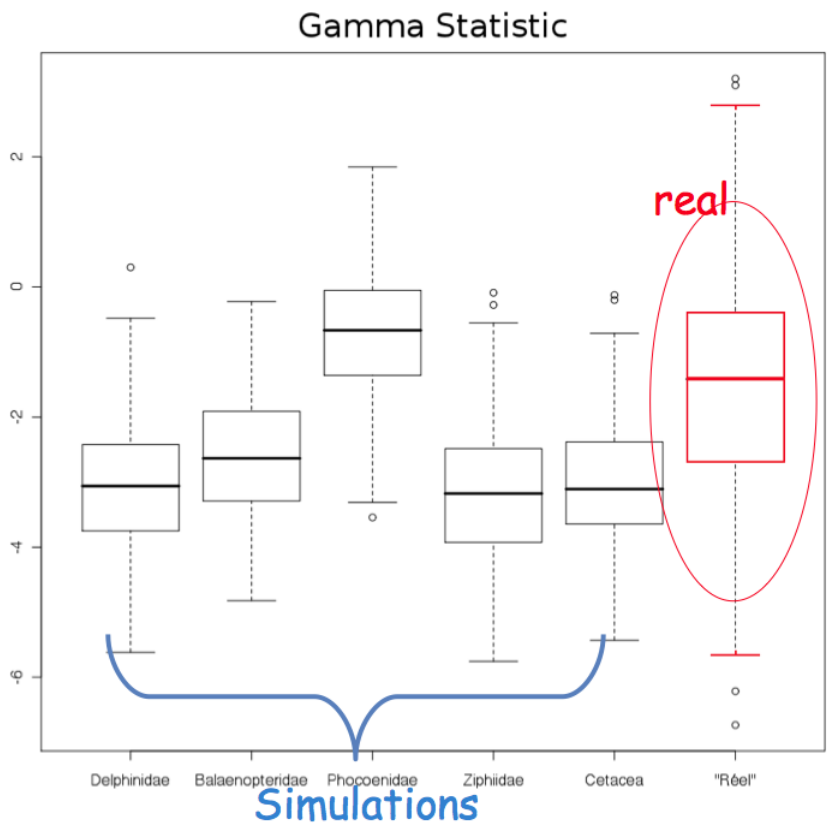
- Branching process representation : fast simulation
- Likelihood computation by peeling algorithm
- Tests by simulations : accurate ML estimates of θ and $b-d$
- Inference from Cetaceans (Steeman et al *Syst Biol* 2009) generates realistic values of β, γ





Speciation by genetic differentiation (5)





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

- **ANR** ***Modèles Aléatoires eN Écologie, Génétique, Évolution*** **(MANEGE)**

SMILE : A cross-disciplinary group in CIRB

- CIRB = Center for Interdisciplinary Research in Biology (Collège de France)
- SMILE = Stochastic Models for the Inference of Life Evolution