Contour processes, Coalescent point processes and applications

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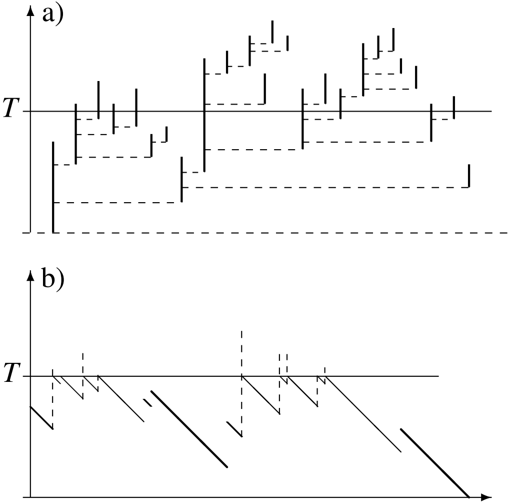
Outline

1. Contour
2. Coalescent
3. Bottlenecks
4. Mutations
5. Epidemics
6. Phylogenies

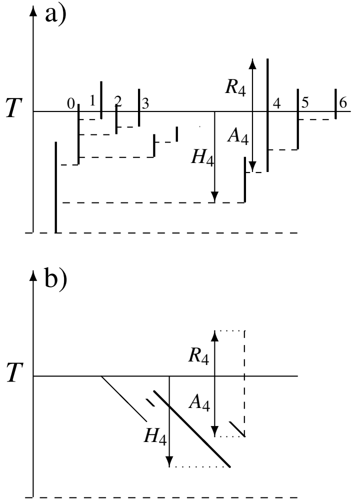
Jumping contour of a tree

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



Retrieving information from the contour

The depths of the excursions of the JCP away from T are the coalescence times of consecutive extant individuals at time T.



- H_i = coalescence time between individuals $i-1$ and i = depth of i-th excursion of the contour process

- A_i = age of individual i = undershoot of last jump of...

- R_i = residual lifetime of individual i = overshoot of last jump of...

Splitting trees

A (time-inhomogeneous) splitting tree (Geiger & Kersting 97) is a random tree model (genealogy, epidemic, phylogeny,...), where :

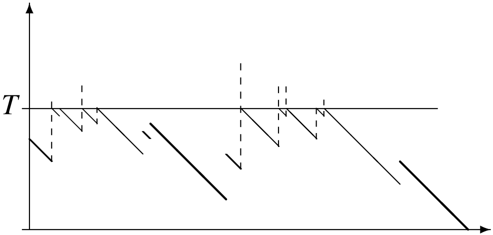
- particles reproduce singly and independently
- the birth rate $\lambda(t)$ may depend on absolute time t (only)
- lifetime distributions can be general and may also depend on birth time : example of a death rate $\mu(t,a)$ depending on absolute time t and age a of particles.

The population size process $(N_t;t \geq 0)$ is a binary Crump–Mode–Jagers process (with age-independent birth point process).

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 has the same law as a compound Poisson process X with Lévy measure $\lambda P(V \in \cdot)$, without negative jumps and drift -1, reflected below T and killed upon hitting 0.



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Coalescent point process

$H^T :=$ depth of an excursion of the JCP away from T.

Corollary

The coalescent tree (or reconstructed tree) seen from T of a splitting tree, is a coalescent point process : the coalescence times form a sequence of i.i.d. r.v. distributed as H^T, killed at its first value larger than T.

⇒ Notation :

$$F_T(s) := \frac{1}{P(H^T \geq s)}.$$

Coalescent point processes : Popovic (2004), Aldous & Popovic (2005), L. & Popovic (2012).

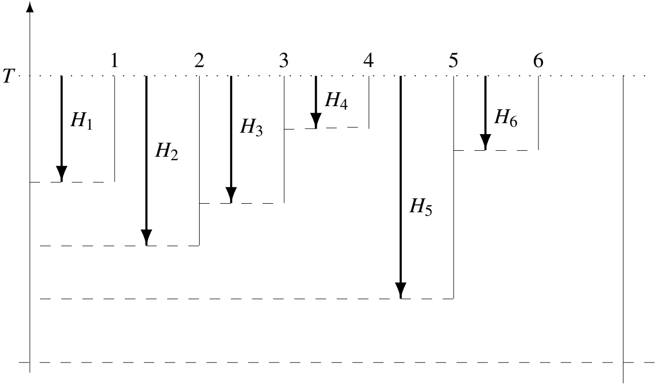

FIGURE: Illustration of a coalescent point process showing the coalescence depths $H_1, \ldots, H_6$ for each of the 6 consecutive pairs of tips. The depth H_7 is the first one larger than T.

Three special cases

1. Time-homogeneous case (L. 2010) $\equiv \lambda$ and $\mu(a)$ do NOT depend on t ...And then F_T does not depend on T...
2. Markovian case (Nee, May & Harvey 1994) $\equiv \mu(t)$ does NOT depend on a

$$F_T(t) = 1 + \int_{T-t}^{T} dx\,\lambda(x)\,e^{\int_x^T dy\,r(y)},$$

where $r(t) := \lambda(t) - \mu(t)$ (instantaneous growth rate).

3. Time-homogeneous + Markov (Rannala, 1997) $\equiv \lambda$ and μ are constant $\equiv$ linear birth–death process

$$F_T(t) = 1 + \frac{\lambda}{r}(e^{rt} - 1).$$

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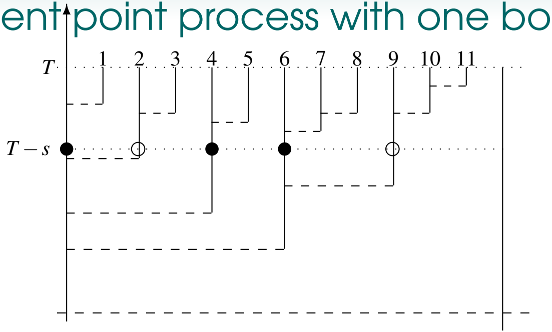
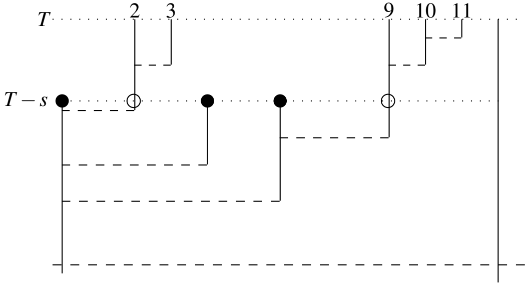
Bottleneck : definition

- Start with a coalescent point process
- add a bottleneck with survival probability ε at time s backwards, i.e., all lineages crossing this time section are independently deleted with probability $1-\varepsilon$
- Set $B_\varepsilon^T :=$ coalescence time between two consecutive survivors,
- so that $s=0$ corresponds to sampling.

Coalescent point process with one bottleneck





Bottleneck : result

- With probability $P(H^T < s)$, B_ε^T is distributed as H^T conditional on $H^T < s$
- With probability $P(H^T \geq s)$,

$$B_\varepsilon^T \overset{(d)}{=} \max\{A_1, \dots, A_K\},$$

where the A_i's are i.i.d. distributed as H^T conditional on $H^T \geq s$ and

$$\mathbb{P}(K = j) = \varepsilon(1-\varepsilon)^{j-1}.$$

- This yields

$$F_\varepsilon(t) := \frac{1}{P(B_\varepsilon^T \geq t)} = \begin{cases} F_T(t) & \text{if} \quad t < s \\ \varepsilon F_T(t) + (1-\varepsilon) F_T(s) & \text{if} \quad t \geq s \end{cases}$$

More bottlenecks

Start with a coalescent point process and add extra bottlenecks with survival probabilities $\varepsilon_1, \dots, \varepsilon_k$ at times $T - s_1 > \dots > T - s_k$ (where $s_1 \geq 0$ and $s_k < T$).

Proposition (L. (2012))

Conditional on survival, the new reconstructed tree is again a coalescent point process with inverse tail distribution F_ε given by

$$F_\varepsilon(t) = \varepsilon_1 \cdots \varepsilon_m F_T(t) + \sum_{j=1}^{m} (1 - \varepsilon_j)\, \varepsilon_1 \cdots \varepsilon_{j-1} F_T(s_j) \qquad t \in [s_m, s_{m+1}],$$

for each $m \in \{0, 1, \dots, k\}$, with $s_0 := 0$ and $s_{k+1} := T$.

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Neutral, Poissonian mutations

- Supercritical, time-homogeneous, splitting tree
- $N_t :=$ population size at time t
- $\alpha :=$ Malthusian parameter $= \lim_{t\to\infty} \frac{1}{t} \log N_t$
- $\theta :=$ mutation rate on lineages.

Goal. Characterize the allelic partition under the infinitely-many alleles model.
See also Griffiths & Pakes (1988), Taïb (1992), Abraham & Delmas (2007), Bertoin (2009, 2010, 2011), Sagitov & Serra (2009, 2011).

Expected frequency spectrum

In (L. 2009) and (Champagnat & L. 2012a), we have characterized the clonal coalescent point process to give an explicit expression for the expectation, conditional on N_t, of

$A(k,t,y) :=$ number of alleles of age in $(y, y+dy)$ and carried by k alive individuals at time t.

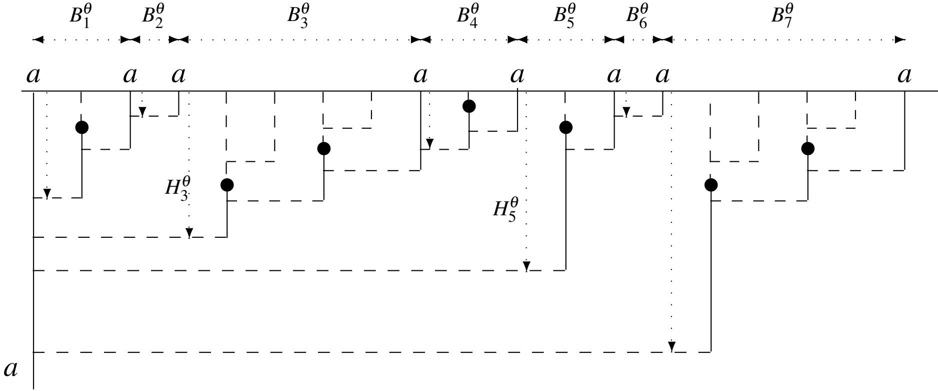
= expected allele frequency spectrum for small families.

Clonal coalescent point process

B_i^θ = distances between consecutive virgin lineages

H_i^θ = max of branch lengths between consecutive virgin lineages

$\Longrightarrow (B_i^\theta, H_i^\theta)$ are i.i.d.



Largest or oldest families at time t

Proposition (Champagnat & L. 2012b)

Assume $\alpha \leq \theta$. The following results hold in expectation.

- *If $\alpha < \theta$, there are explicit constants b and $\beta := \theta/(\theta - \alpha)$. such that largest families have sizes $b(\alpha t - \beta \log(t)) + c$ and they all have age $\sim \dfrac{\log(t)}{\theta - \alpha}$.*
  Oldest families have ages $\gamma t + a$ and tight sizes, where $\gamma := \alpha/\theta$.
- *If $\alpha = \theta$, there are explicit constants b and $\beta := 1/(2\alpha)$, such that largest families have sizes $b(\alpha t - \beta \log(t) + c)^2$ and they all have age $\sim t/2$.*
  Oldest families have ages $t - \gamma \log(t) + a$ and tight sizes, where $\gamma := 1/\alpha$.

If $\alpha > \theta$, largest families have sizes $ce^{(\alpha-\theta)t}$ and are also the oldest ones (born at times $O(1)$).

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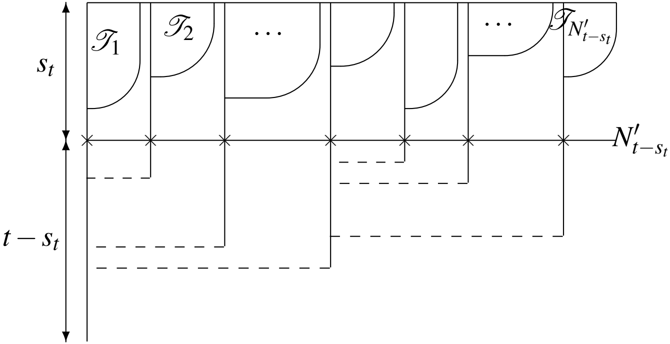
Convergence in distribution (1)

ASSUME $\alpha < \theta$.

Take the coalescent point process at time t,

choose s_t such that $s_t \to \infty$, and set

$$N'_{t-s_t} := \text{number of subtrees } (\mathscr{T}_i) \text{ grafted on branch lengths} \geq s_t$$



Convergence in distribution (2)

Set

$$X_t^{(k)} := \text{ size of the } k\text{-th largest family in the whole population}$$

$$Y_i := \text{ size of the largest family in subtree } \mathscr{T}_i.$$

With $s_t := \log(t) \ / \ (\theta - \alpha)$, we have

- $N'_{t-s_t} \to \infty$
- $(X_t^{(1)}, \dots, X_t^{(k)})$= first k order statistics of $\{Y_1, \dots, Y_{N'_{t-s_t}}\}$ W.H.P.
- With $L_t(x) :=$ number of families larger than x at time t,

$$\mathbb{P}(Y \geq x_t + c) = \mathbb{P}(L_{s_t}(x_t + c) \geq 1) \sim \mathbb{E}(L_{s_t}(x_t + c)).$$

Convergence in distribution (3)

$X_t^{(k)} :=$ size of the k-th largest family in the whole population

Theorem (Champagnat & L. 2012b)

There is an explicit constant $c \in (0,1)$, such that $(X_t^{(k)} - b(\alpha t - \beta \log(t)); k \geq 1)$ converge (fdd) to the (ranked) atoms of a mixed Poisson point measure with intensity

$$\mathscr{E} \sum_{j \in \mathbb{Z}} c^j \delta_j,$$

where $\mathscr{E}$ is some exponential r.v.

Convergence in distribution (4)

$A_t^{(k)} :=$ age of the k-th oldest family in the whole population

Theorem (Champagnat & L. 2012b)

The sequence $(A_t^{(k)} - (\alpha t \,/\, \theta); k \geq 1)$ *converges (fdd) to the (ranked) atoms of a mixed Poisson point measure with intensity*

$$\mathscr{E}\, e^{-\theta a}\, da,$$

where $\mathscr{E}$ *is some exponential r.v.*

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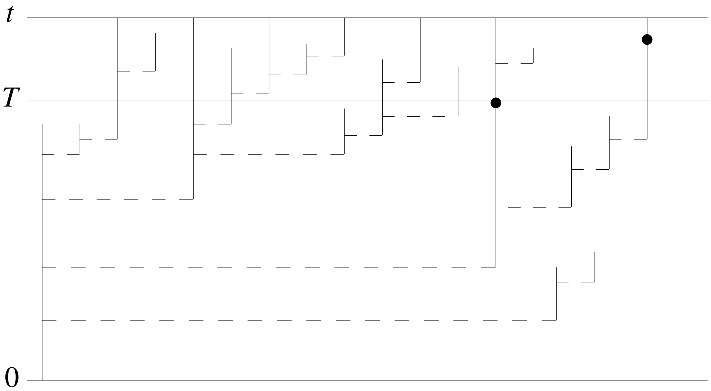
Epidemic model

- Epidemics modelled by a splitting tree, where birth = transmission (rate λ) and lifetime = period of infectiousness
- each patient can be detected to be a carrier only after an independent exponential clock with parameter δ running from the beginning of her infection (medical exam or symptoms) ;
- $T :=$ detection time = first time when one these clocks rings.

Splitting tree with exponential clocks

$\Rightarrow$ Each individual is equipped with an exponential clock with parameter δ initialized at birth.

$T :=$ first time when one of these clocks rings.



Vervaat transform

Let $X^{(T)}$ be the JCP of the splitting tree truncated below the detection time T.

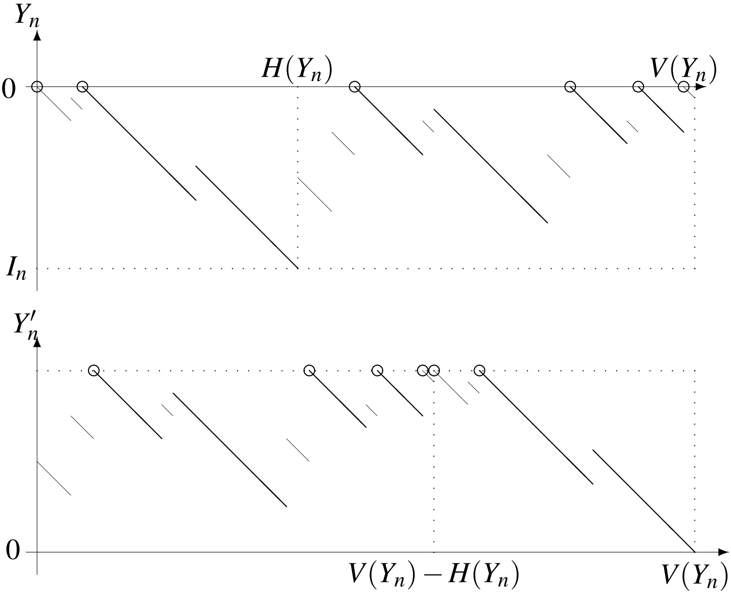
Theorem (L. & Trapman 2012)

For any $n \geq 1$, for any $t > 0$, for any càdlàg path e,

$$\mathbb{P}\left(N_T = n, T \in dt, X^{(T)} \in de\right) = \frac{\delta}{b}\, e^{-\delta V(e)}\, P\left(-I_n \in dt, Y_n' \in de\right),$$

where $V(e)$ denotes the total lifetime of a path e, Y_n is the concatenation of n i.i.d. excursions of a Lévy process, I_n is its infimum and Y_n' is its Vervaat transform.

Vervaat transformation



Methicillin–resistant *Staphylococcus aureus*

- patients have i.i.d lengths of stay in the hospital, all distributed as some r.v. K (such that $E(K) < \infty$) ;
- Conditional on infection, the length of stay of a patient is a size-biased version of K ;
- At detection time T, all patients in the hospital are screened and identified.

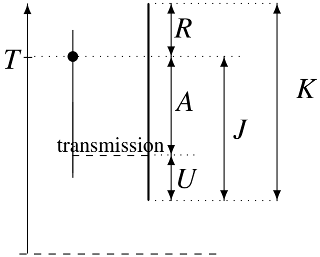
Notation

For individual i, set

- $U_i :=$ time elapsed from entrance of the hospital up to infection
- $A_i :=$ time elapsed from infection up to T
- $R_i :=$ residual lifetime in the hospital after T.

Set $m := \mathbb{E}(K)$ and let ϕ denote the inverse of the convex function

$$x \mapsto x - \frac{\lambda}{m} \int_{(0,\infty]} (1 - e^{-xy}) \mathbb{P}(K > y)\, dy.$$



Inference from hospital data

Proposition (L. & Trapman 2012)

Conditional on $N_T = n$, the triples (U_i, A_i, R_i) of the n (randomly labelled) carriers at time T are i.i.d., distributed as the r.v. (U, A, R) (independent of n), where

$$\mathbb{E}(f(U,A,R)) =$$

$$\frac{\lambda}{m}\,\frac{\phi(\delta)}{\phi(\delta)-\delta}\int_{u=0}^{\infty} du \int_{a=0}^{\infty} da \int_{z=u+a}^{\infty} \mathbb{P}(K \in dz)\, e^{-\phi(\delta)a} f(u,a,z-u-a),$$

In particular, the times $J_i = U_i + A_i$ spent in the hospital up to time T are i.i.d., distributed as the r.v. J

$$\mathbb{P}(J \in dy) = \frac{\lambda/m}{\phi(\delta)-\delta}\, \mathbb{P}(K > y)\left(1 - e^{-\phi(\delta)y}\right) dy.$$

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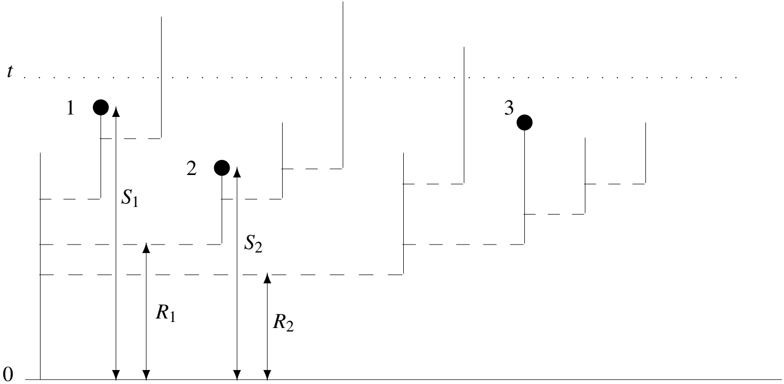
Temporally-spaced epidemiological data (with Tanja Stadler)

- A sampled individual immediately leaves the infective population.
- $S_i :=$ sampling time of individual i
- $R_i :=$ coalescence time between individuals $i-1$ and i.

By the contour technique, the (S_i, R_i) is a Markov chain with explicit transitions.
$\Rightarrow$ inference of model parameters from viral phylogenies (HIV, flu).

Splitting tree with exponential clocks (2)

Black dots = sampling/detecting



Phylogenetic tree models (with H. Morlon, R.S. Etienne, B. Haegeman)

...(statistical) work in progress...

1. Protracted speciation (Etienne & Rosindell 2011) : New born species are incipient, and turn good after a random time
2. Speciation by genetic differentiation and point mutation : two individuals are in the same species if their MRCA belongs to a geodesic without mutation.

⇒ Infer parameters of diversification dynamics from real phylogenetic tree shapes.

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