

Phylodynamics: how Genetics and Mathematics are changing our understanding of infectious diseases.

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Plan for today



- A brief overview of how we came to using phylogenetic trees and mathematical models;
- The awesome things we can do with them;
- An interesting combinatorics problem on how to build better trees.

In the beginning there were hierarchies...



Linnaean system of classification (~ 1735)

I've never done anything useful...



Geoffrey Harold Hardy (1877-1947)

- "I have never done anything 'useful'. No discovery of mine has made, or is likely to make, directly or indirectly, for good or ill, the least difference to the amenity of the world." ^a
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$$p + q = 1$$

$$p^2 + 2pq + q^2 = 1$$

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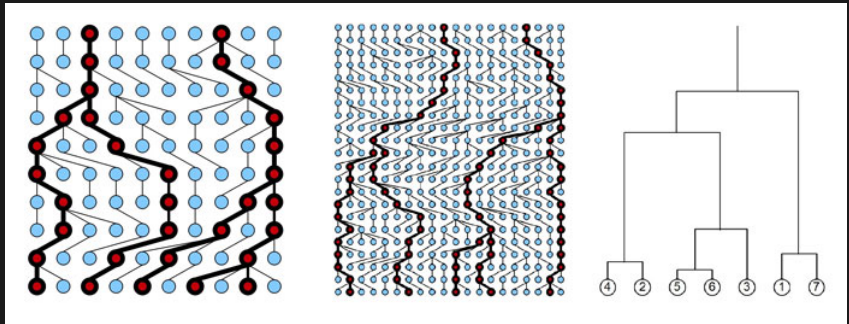
$$p^2 + 2pq + q^2 = 1$$

- Stability!

^aTitchmarsh (1950)

Population Genetics

- Hardy-Weinberg is nice and useful, but describes an ideal setting with no mutation, selection or population structure.
- In the 1980s, John Kingman starts a revolution...



Kingman's coalescent (1982)¹

¹Figure from <http://culturemath.ens.fr/content/genealogie-de-populations-le-coalescent-de-kingman-2101>
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Population Genetics

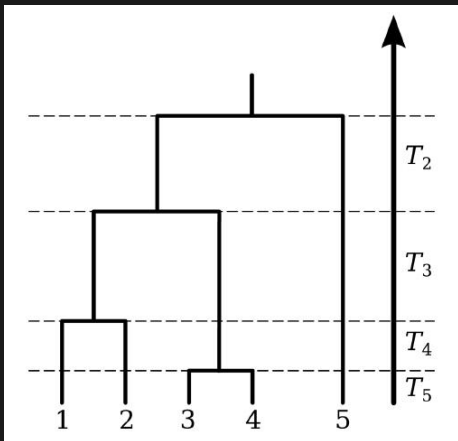


Figure 4 from Volz et al. (2013)

Let T_n denote the time for n lineages to *coalesce*, i.e., merge into one ancestral lineage, in a population of size N . Then:

$$Pr(T_n = t) = \lambda_n e^{-\lambda_n t}$$

$$\lambda_n = \binom{n}{2} \frac{1}{N} = \binom{n}{2} \frac{1}{N_e \tau}$$

where N_e is the effective population size and τ is the generation time. Let T_{mrca} denote the age of the most recent common ancestor:

$$\begin{aligned} \mathbb{E}[T_{\text{mrca}}] &= \mathbb{E}[T_n] + \mathbb{E}[T_{n-1}] + \dots + \mathbb{E}[T_2] \\ &= 1/\lambda_n + 1/\lambda_{n-1} + \dots + 1/\lambda_2 \\ &= 2N(1 - \frac{1}{n}) \end{aligned}$$



Bridging Disease Ecology and Genetics

if the tree is a reasonable representation of ancestry, then we can use it as proxy to hidden/unobservable population processes. One such process is infection:

$$\begin{aligned}\frac{dS}{dt} &= -\beta IS \\ \frac{dI}{dt} &= \beta IS - \gamma I \\ \frac{dR}{dt} &= \gamma I.\end{aligned}$$

Here is an idea²:

$$\lambda_n(t) = \binom{n}{2} \frac{2\beta S(t)}{I(t)}$$

Some more glossing over the details yields:

$$\lambda_n = \binom{n}{2} \frac{2\gamma}{I}$$

²Equations and ideas taken from Volz et al. (2013)

Bridging Disease Ecology and Genetics

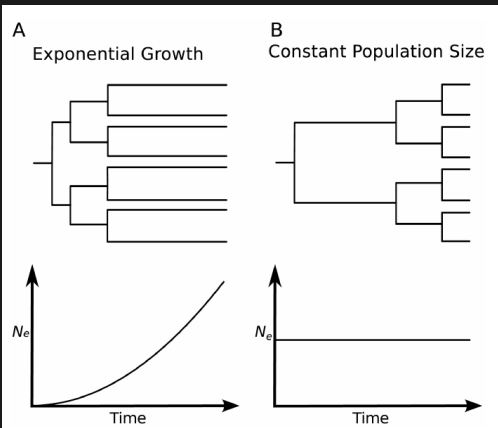
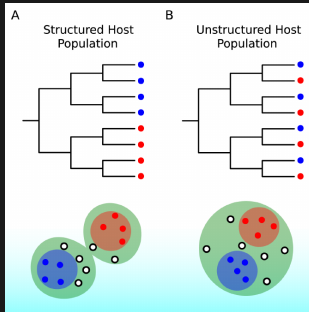


Table 1. Estimated annual growth rates of N_e for early HIV sub-epidemics.

Growth Rate	Group	Subtype	Risk Group
0.17 [83]	M	NA	Central Africa
0.27 [84]	M	C	Central Africa
0.48 [67]–0.83 [65]	M	B	North America/Eur/Aust, MSM
0.068 [63]	O	NA	Cameroon

Taken from Volz et al. (2013)

Bridging Disease Ecology and Genetics II

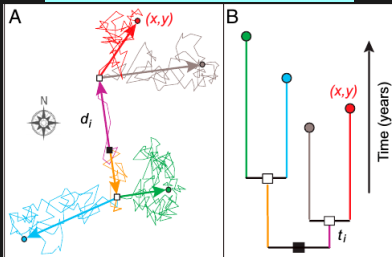


Let $\mathbf{X}(t)$ be the state at the t . We are interested in the likelihood of ending up in $\mathbf{X}(t)$ if we started at $\mathbf{X}(s)$. Here's an idea (Lemey et al., 2010):

$$p(\mathbf{X}(t)|\mathbf{X}(s)) \sim \text{MVN}(\mathbf{X}(s), \mathbf{P}^{-1} \times (t - s))$$

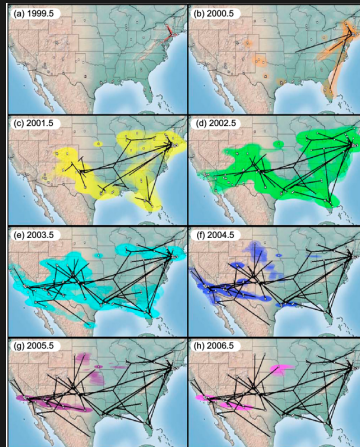
where \mathbf{P} is the infinitesimal precision matrix of the diffusion process. Note that:

- (i) the diffusion matrix depends only on time differences and;
- (ii) analytical solutions are available through clever traversing of the tree (Pybus et al., 2012).



Bridging Disease Ecology and Genetics II

“...phylogenies reconstructed from spatial epidemics are branching structures that record the correlated histories of transmission among sampled infections...” (Pybus et al., 2012)





Summary so far...

- By conditioning on the inferred ancestry of DNA/RNA sequences, we can use phylogenetic trees as correlation structures;
- It is possible to obtain insight into temporal (dynamic) and spatial features of populations from genetic data;
- **Phylogenies** are the centre of it all: almost everything we do is **conditional** on the tree.

Summary so far...

- By conditioning on the inferred ancestry of DNA/RNA sequences, we can use phylogenetic trees as correlation structures;
- It is possible to obtain insight into temporal (dynamic) and spatial features of populations from genetic data;
- **Phylogenies** are the centre of it all: almost everything we do is **conditional** on the tree.
- This suggests we should also pay close attention to tree estimation... Bayesian and maximum likelihood phylogenetic methods rely on stochastic tree search. There is great interest in making the **traversal** of tree-space more **efficient**.

An open problem – preliminaries

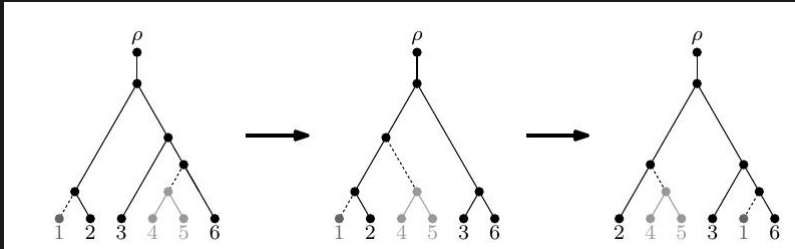
Defn. 1: An (unrooted) phylogenetic X -tree is a tree T on a tip (leaf) set X with all internal nodes of degree of at least 3. If the degree of all internal nodes is exactly 3 then we say we have a *binary* X -tree.

- Every unrooted (rooted) binary X -tree has $2n - 3$ ($2n - 2$) edges (also called branches), with $n = |X|$;
- There exist $\frac{(2n-3)!}{2^{n-2}(n-2)!} = (2n-3)!!$ rooted X -trees on n tips/leafs. For $n = 53$, there are roughly as many trees as there are particles in the observable universe!

See Steel (2014) for a gentle introduction to phylogenetic trees, specially targeted at mathematicians.

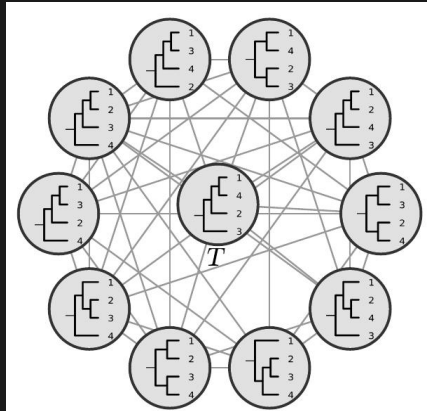
Tree surgery...

Let $Y \subset X$. Then call X' the Y -tree that has internal nodes compatible with those in T , i.e., X' is a *subtree* of X . An subtree-prune and re-graft (SPR) operation on a tree T detaches X' and re-grafts it onto another node in the tree.



Two consecutive (rooted) SPR operations on a 6-leaf tree (Whidden and Matsen, 2015)

Graphs about graphs...



The neighbourhood of T in the SPR graph ($G(n)$) (Whidden and Matsen, 2015)

The diameter is $n - \Theta(\sqrt{n})$ and the average degree is $2(n - 3)(2n - 7)$.

Ricci-Ollivier curvature (Whidden and Matsen, 2015)

With a random-walk in a metric space, we can define “curvature”, that is, how “difficult” it is to go from x to y (Ollivier, 2009) as follows: let m_x and m_y be the probability masses of the positions x and y on $G(n)$ after some (finite) time. Then:

$$W_1(m_x, m_y) := \min_{\xi \in \Pi(m_x, m_y)} \sum_{\{z, w\} \subset V} d(z, w) \xi(z, w) \quad (1)$$

The so-called coarse Ricci-Ollivier curvature of x and y is then:

$$\kappa(m; x, y) := 1 - \frac{W_1(m_x, m_y)}{d(x, y)}. \quad (2)$$

Here, for two trees T and S , $d(T, S)$ is how many SPR operations are needed to transform T in S (vice-versa).

A conjecture

Whidden and Matsen (2015) prove a bunch of useful results about the SPR graph. For instance, they show that for two trees T and S :

$$\frac{-2}{d(T, S)} \leq \kappa(T, S) \leq \frac{2}{d(T, S)} \quad (3)$$

Moreover, if T and S are adjacent (with $|T| = |S| = n$), the the maximum curvature of the uniform random-walk is

$$\frac{6n - 17}{3n^2 - 13n + 14} \quad (4)$$

Conjecture (Whidden and Matsen, 2015): Let k_n be the maximum curvature between two trees with n -leaves. Then:

$$k_n \leq \frac{2}{D(n) - 1} \quad (5)$$

where $D(n)$ is the diameter of the SPR graph on n -leaves trees.

My two pence

- It is important to prove not only this conjecture, but also to study variants on different spaces resulting from other transformations;
- In the context of phylodynamics, height-restricted SPRs are arguably a more important transformation;
- Recursive application of the techniques used to prove the curvature for adjacent trees could be extended to k -radius neighbourhoods;
- A more productive approach could be to relate what we know for the graph (e.g. average degree, diameter, etc) to its local properties, taking advantage of more heavy graph-theoretic methods/results.

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- There is a lot of cool maths to be done in:
 - ◊ Lie algebras of Markov models of DNA evolution;
 - ◊ Further merging ODE-based models and phylogenetics;
 - Combinatorics on the space of phylogenetics trees ~~and networks!~~

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- There is a lot of cool maths to be done in:
 - ◊ Lie algebras of Markov models of DNA evolution;
 - ◊ Further merging ODE-based models and phylogenetics;
 - Combinatorics on the space of phylogenetics trees ~~and networks!~~
- Maths rocks! Q.E.D

Thank you!



- Thanks a bunch for watching!
- I am grateful to the organising committee for the invitation;
- Special thanks to Andrew Rambaut (Edinburgh), Mike Steel (Cantenbury, NZ), Patrice Showers Corneli (Utah), Erick Matsen (Hutchson) and Felipe Figueiredo (PROCC)³.

³Mathematicians are underlined.
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Useful links

<http://i.imgur.com/T5XLPLB.jpg>
http://www.math.canterbury.ac.nz/~m.steel/files/presentations/winthrop1_to_4.pdf
http://www.math.canterbury.ac.nz/~m.steel/files/presentations/winthrop5_to_10.pdf
<http://www.phylobabble.org/t/the-interface-between-mathematics-statistics-and-phylogenetics-topics-for-a-talk/537>