Coupling adaptive molecular evolution to phylodynamics using fitness-dependent birth-death models

Rasmussen and Stadler (*eLife, 2019*)

Seth D. Temple

STAT 591; APMA 990
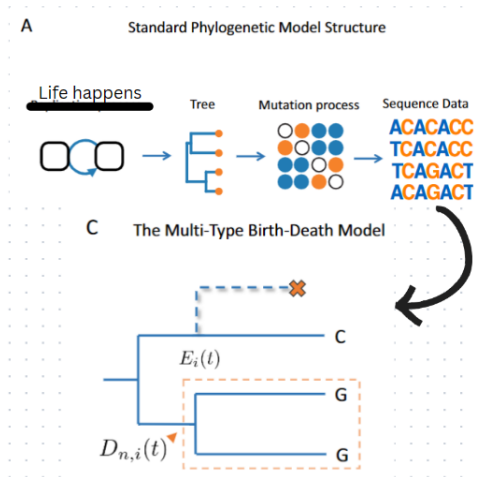Seattle, WA; Vancouver, BC
March 29, 2023

Setting the scene: MTBD

Figure: Doctored version of Fig 1 (Rasmussen, 2019)

Contemporaneous challenges

1. Fitness variation of muts affects tree process for microbes (viruses) → **feedback loop**
   - ▶ Common arg for indep. tree, mut processes in macro speciation is separate time scales
   - ▶ Distr. of fitness effects (DFE) is central ??? in evo bio

2. MTBD model (Stadler, 2013) compute scales $O(2^L)$ for binary char
   - ▶ (Stadler, 2013; Barrido-Sottani, 2018) study three **phenotypes** for HIV transmission

3. Existing methods to study selection in phylogenetics use **dN/dS** w/ codon subs. models
   - ▶ (Harris slides, 2022; Temple, Waples, & Browning, 2023+) indicate other methods required for recent selection

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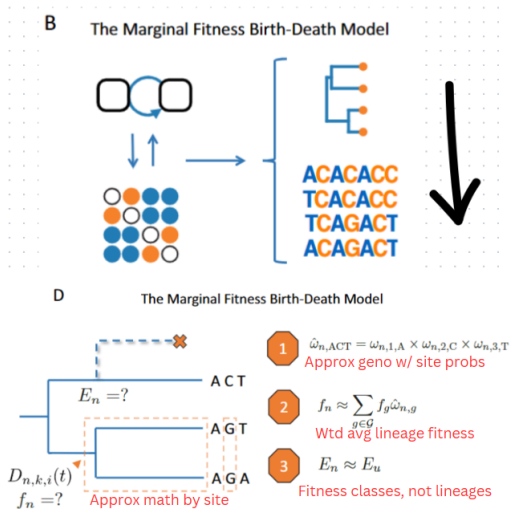
Sneak peak: MFBD

Figure: Doctored version of Fig 1 (Rasmussen, 2019)

Remaining Agenda

1. Mathematical notation
2. MTBD: multi type birth death
   2.1 Two coupled ODEs
   2.2 Computing up tree to root
   2.3 Some equations explained
3. MFBD: marginal fitness birth death
   3.1 Key assumptions
   3.2 Some equations explained
4. Simulation studies
   4.1 Exact MTBD versus approx MFBD
   4.2 Distribution of fitness effects
5. Ebola analysis (epistasis)
6. Takeaways from influenza analysis

Notation

- n, m : lineages
- i, j : state types (genotypes, alleles)
- k, l : sites
- λ, d : birth, death rates
- γ : transition rates
- f, σ : fitness effects (gtype, site-specific)
- s, ρ : sampling rate at (death, $t = 0$)
- $D(t)$: density subtree observations (descending)
- $E(t)$: density state type leaves no observations (extinct)

More definitions at
sdtemple.github.io/misc.html
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MTBD: D descending functions

$$\frac{d}{dt}D_{n,i}(t) = -(\lambda_i + \sum_{j=1}^{M}\gamma_{i,j} + d_i)D_{n,i}(t)$$

(1) No birth, no state transitions, no death

You can develop/motivate this model as a continuous time Markov chain (Temple, 2021)

$$+2\lambda_i E_i(t)D_{n,i}(t)$$

(2) Birth of unsampled

$$+\sum_{j=1}^{M}\gamma_{i,j}D_{n,j}(t)$$

(3) State transition

Here + is separate in a total law sense.
The $\times$ / $\cdot$ is independence in contemporaneous event sense.

MTBD: E extinct functions

$$\frac{d}{dt}E_i(t) = (1-s_i)d_i \quad \text{(1) not sampled at death}.$$

$$-(\lambda_i + \sum_{j=1}^{M} \gamma_{i,j} + d_i)E_i(t)$$

$$+\lambda_i E_i(t)^2 \quad \text{(2) birth, both went extinct}.$$

$$+\sum_{j=1}^{M} \gamma_{i,j}E_j(t).$$

Those lines not annotated have similar interpretation as last.

Computing from tips to root

Based on pedigree peeling (Cannings, 1976) [Thompson], tree pruning (Felsenstein, 1981)

1. At tip of lineage n, **initalize ODE**
   $D_{n,i}(t) = d_i s_i$ if t at death, else $= \rho_i$
   (Also, initialize for $E(\cdot)$)

2. Solve ODEs

3. Moving up (back in real time), at branch point,
   $D_{a,i} = 2\lambda_i D_{m,i}(t) D_{n,i}(t)$

4. At root, form likelihood | non-extinction
   (akin to cond. sweep in SLiM)

$$D_n = \sum_{i=1}^{l} q_i D_{n,i}(t_{root})/[1 - E_i(t_{root})]$$

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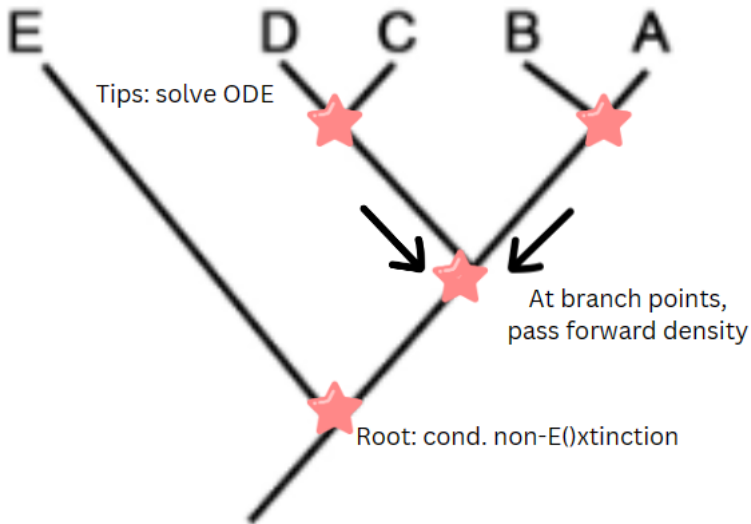Based on pedigree peeling (Cannings, 1976) [Thompson], tree pruning (Felsenstein, 1981)

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Computing from tips to root

MFBD: key assumptions

1. Approx genotype probs with marginal site probs
2. Marginalize over genotype fitness w/ wtd geno probs to get site-specific fitness effects
3. Study discrete space of fitness classes for E densities
4. Trans rates $i \to j$ at site k don't depend on genetic background

Figure: 2.,3. explained next slide.
1. is nearly same as MTBD but w/ fitness-dependent births.

1. Update $D_{n,k,i}$ by numerically integrating (*Equation 19*) over time step Δt.
2. Update the marginal site probabilities $\omega_{n,k,i}$ using (*Equation 20*)
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MFBD: genotype probabilities, fitness

2.

$$\hat{\omega}_{n,g} = \frac{\prod_{k=1}^{L} \omega_{n,k,g_k}}{\sum_{g \in \mathcal{G}} \prod_{k=1}^{L} \omega_{n,k,g_k}}.$$

\prod implies independence

\sum over genotypes is a total law

3.

$$\hat{f}_{n,k,i} = \sum_{\{g \in \mathcal{G} : g_k = i\}} f_g \hat{\omega}_{n,g}.$$

weighted average, infer f's

If fitness multiplicative

$$\hat{f}_{n,k,i} = \sigma_{ki} \prod_{l=1, l \neq k}^{L} \sum_{j=1}^{M} \sigma_{lj} \omega_{n,l,j},$$

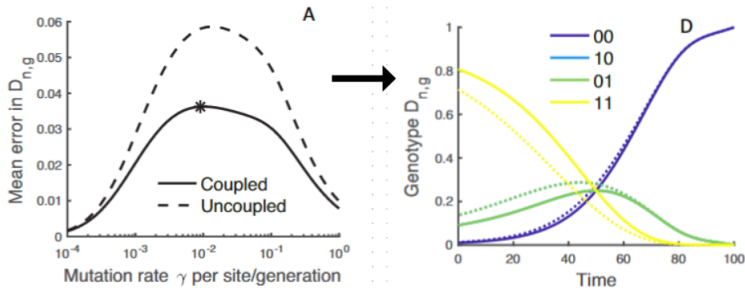# Sim study: exact MTBD or approx MFBD

Figure: Comparing MFBD versus MTBD truth, where mean is over genotypes and time-integrated. Genotypes with favored allele 1, i.e., 01, 10, 11, more frequent as $t \to 0$
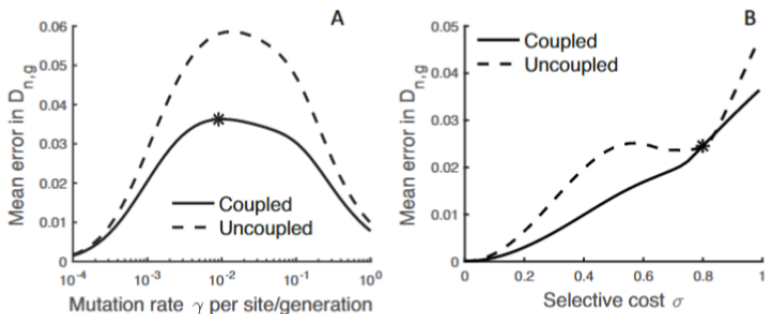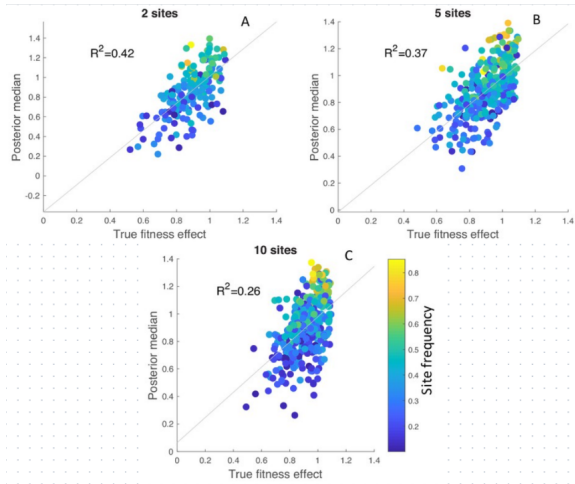
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Figure: Comparing MFBD versus MTBD truth, where mean is over genotypes and time-integrated. Uncoupled (dashed) is naive method and not of interest. Qualitatively similar finding when study epistatis.
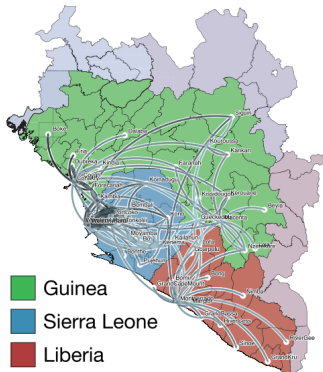
Sim study: site-specific fitness

Figure: Site-specific fitness estimates and true fitness decreasing with num sites

Ebola data analysis

- Outbreak in West Africa 2014-2016
- 1610 viral samples

Guinea
Sierra Leone
Liberia

Figure: Epi dynamics from (Suchard, 2018).
Also studied by (Stockdale, 2021), (Temple, 2021), others.

Ebola results: superimposed phylo tree
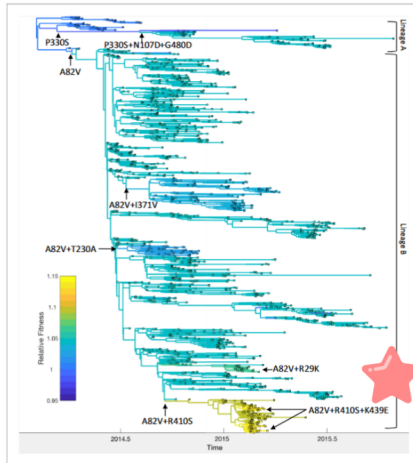
Figure: Inferred tree and MFBD params for Ebola 2014-2016.
Red star highlights recent triple mutation of highest fitness,
evidencing epistasis.

Ebola results: genotypes table

Table 1. Estimated posterior median fitness and 95% CI for the Ebola GP mut...

Genotype	Sample freq	Base model
Makona	0.036	1.00
A82V	0.720	1.05 (1.04–1.07)
P330S	0.002	0.98 (0.82–1.14)
P330S+N107D+G480D	0.037	1.04 (0.98–1.12)
A82V+R410S	0.044	1.09 (1.00–1.18)
A82V+R410S+K439E	0.035	1.14 (1.01–1.26)
A82V+R29K	0.019	1.06 (0.93–1.19)
A82V+T230A	0.026	1.03 (0.93–1.11)
A82V+I371V	0.067	1.03 (0.98–1.09)

Figure: Doctored Table 1 from (Rasmussen, 2019). Used genotype instead of site MFBD model b/c other study suggested epistasis. Genotype ranks preserved when geography incorporated.
Fitness between hosts in pop **attenuated** compared to Urbanowski cell culture infectivity

Influenza data analysis → takeaways

- BEAST2 MCMC never converged → caution

- Pop level fitness est *in vivo* did not correlate well with deep mutational scanning *in vitro* (yeast?)
  - ▶ But, ad hoc effort to incorporate DMS outside info improved likelihood substantially

- Rapid turnover in flu viruses (we all get sick) (Volz, 2013)
  - ▶ Phylogeography may be important

- Many muts occur once in phylogeny, same background as other muts in HA protein
  - ▶ "identifiability ... akin to ... collinearity in ... regression"

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Concluding remarks

- Marginal fitness birth death model is **approx, scalable** way to study fitness effects in rapidly evolving microbes
  - ► Builds upon multi type birth death model by approximating multi site genotypes with site-specific contributions

- Real data analysis **teaches that** epidemiological fitness *in vivo* population $\neq$ cellular infectivity *in vitro*

- Class: build up likelihoods w/ coupled ODEs, model correlated phylogenetic obs with trees

- Stats lesson: take a simplifying assumption, and test how well things work

- (Opinion: baking MFBD into tree explore in BEAST2 still does not fully study HUGE tree space. Know from coalescent theory how unwieldy trees are.)

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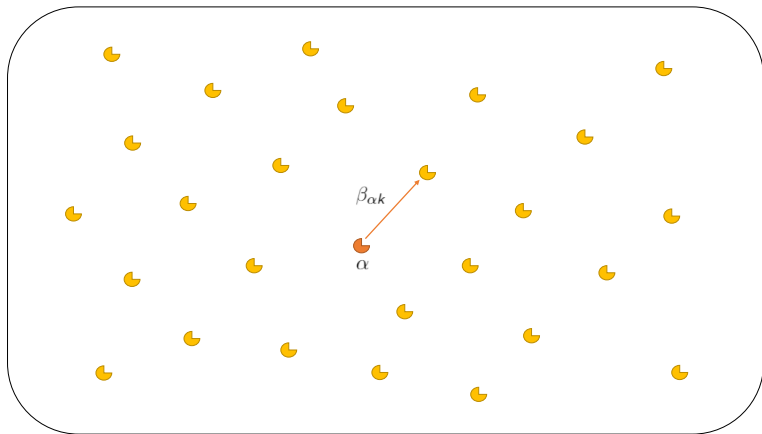
Pause: Q & A

Appendices and references following

More relevant materials at sdtemple.github.io, including:

- Commentary on unifying BDS and SIR (MacPherson et al., 2021)
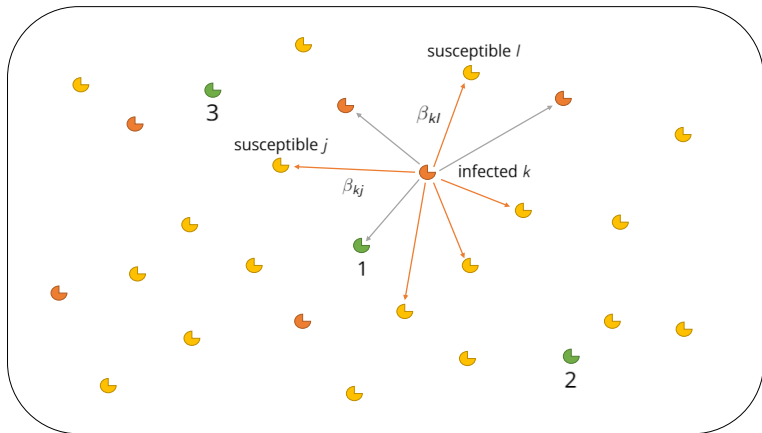- Report on PBLA (Stockdale et al., 2021): https://github.com/sdtemple/pblas

Stochastic epidemic (Stockdale, 2021; Temple, 2021)

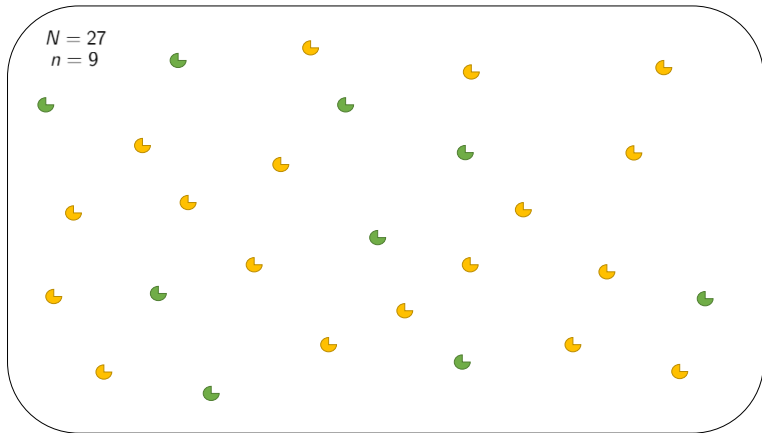Infection rates β_{kj} and removals after $r_j - i_j \sim \text{Gamma}(m_j, \gamma_j)$

Stochastic epidemic

At time t, $S(t)$ susceptibles, $I(t)$ infecteds, and $R(t)$ removeds, with $N = S(t) + I(t) + R(t)$.

Stochastic epidemic

Epidemic ends when $I(t) = 0$.

$N = 27$
$n = 9$

Stochastic epidemic

To simulate an epidemic, we exploit **Poisson processes (PPs)**. Define a *race* as the minimum of (exponential) rvs.

Algorithm (Epidemic Simulator)

1. $S(0) = N - 1, I(0) = 1$
2. Until $I(t) = 0$:
   1. **Race $S(t)I(t)$ PPs with rate β and $I(t)$ PPs with rate γ,** where t_1 is the winning race time.
   2. If a γ-PP wins, $I(t_1) = I(t) - 1$ and $R(t_1) = R(t) + 1$.
   3. If a β-PP wins, $S(t_1) = S(t) - 1$ and $I(t_1) = I(t) + 1$.
   4. Update $t = t_1$.

This is way to frame (Gillespie, 1977) for SIR model

Stochastic epidemic model

$\{S(t), I(t)\}$ is a continuous-time Markov chain (CTMC) with "jumps" based on an underlying Poisson process.

- $\tau_{kj} := r_k \wedge i_j - i_k \wedge i_j$
  - ▶ Time k tries to infect j

- $\psi_j = \exp(-\sum_{k \neq j}^n \beta_{kj} \tau_{kj})$
  - ▶ Probability j not infected before i_j
  - ▶ $\psi_{kj} = \exp(-\beta_{kj} \tau_{kj})$ is marginal term

- $\chi_j = \sum_{k \neq j}^n \beta_{kj} 1_{\{i_k < i_j < r_k\}}$
  - ▶ Probability j infected at i_j

- $\phi_j = \exp(-\sum_{k=n+1}^N \beta_{jk}(r_j - i_j))$
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References I

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