New evolutionary models for the long range dependencies of loosely linked loci

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Joint work with Paul Fearnhead (Lancaster), Yun Song (Berkeley)

17 June 2015
CONFERENCE on PROBABILITY AND BIOLOGICAL EVOLUTION,
Centre International de Rencontres Mathématiques (CIRM)
Marseille-Luminy.

The basic problem (Computing likelihoods)

For a given population genetics model, what is the probability of observing a sample of DNA sequences randomly drawn from a population?

Haplotype 1 = AACTAGG......CCGTGACC......ACAGCTAT
Haplotype 2 = AACTAGG......CCGTAACC......ACAGCTAT
Haplotype 3 = AACTGGG......CCGTGACC......ACAGCTAT
Haplotype 4 = AACTGGG......CCGTAACC......ACAGTTAT
Haplotype 5 = AACTAGG......CCGTGACC......ACAGTTAT

Applications

- Estimating evolutionary parameters: $L(\theta, \rho) = \mathbb{P}(D \mid \theta, \rho)$
- Ancestral inference
- Disease gene mapping

Closed-form one-locus likelihood functions

- $\boldsymbol{n} = (n_1, \ldots, n_K)$, where n_i = number of samples with allele i.
- $q(\boldsymbol{n})$, probability of an ordered sample with configuration $\boldsymbol{n}$.
- $\theta = 4Nu$, mutation parameter.

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Finite alleles, parent-independent mutation (PIM) model

- Mutation transition matrix satisfies $P_{ij} = P_j$.
- Wright's sampling formula (1949):

$$q_{\mathrm{WSF}}(\boldsymbol{n}) = \frac{\prod_{i=1}^{K} \theta P_i(\theta P_i + 1)\ldots(\theta P_i + n_i - 1)}{\theta(\theta+1)\ldots(\theta+n-1)}$$

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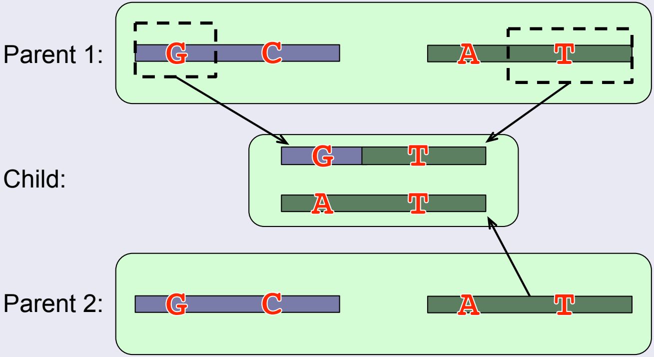
Infinite alleles model

Ewens sampling formula (1972): $$q_{\text{ESF}}(\boldsymbol{n}) = \frac{\theta^K \prod_{i=1}^{K} (n_i - 1)!}{\theta(\theta + 1) \ldots (\theta + n - 1)}$$

Crossover Recombination



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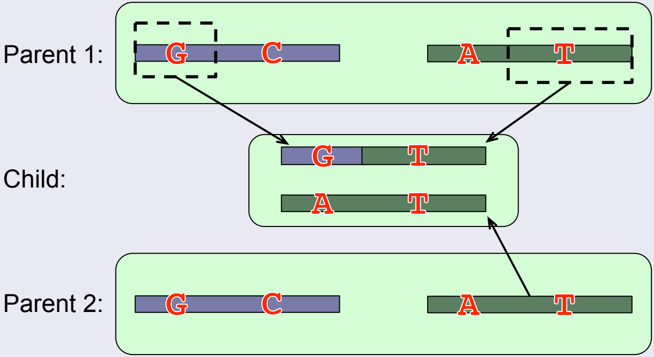

Multi-locus models

- Ancestral recombination graph (ARG)
- Wright-Fisher diffusion with recombination

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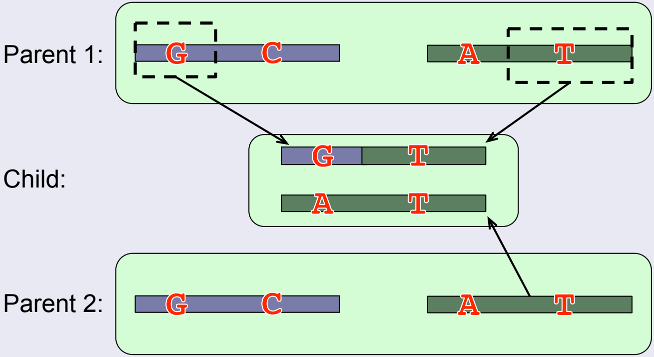
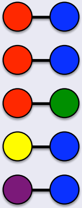


Multi-locus models with recombination

Obtaining an exact, analytic likelihood function under these models has so far remained a challenging open problem, even for just two loci.

Problem setup

A two-locus sample configuration, $\boldsymbol{c} = (c_{ij})$



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Row sums: $\boldsymbol{c}_A = (c_{i\cdot}) = (3, 1, 1)$

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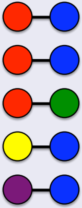

		
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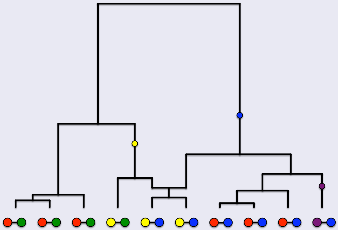
Goal: Compute the sampling distribution, $q(\boldsymbol{c})$.



Previous work

Key Idea: Asymptotic Series (Jenkins & Song, 2009, 2010, 2012)

Write
$$q(\boldsymbol{c};\rho) = q_0(\boldsymbol{c}) + \frac{q_1(\boldsymbol{c})}{\rho} + \frac{q_2(\boldsymbol{c})}{\rho^2} + \ldots,$$
where $q_0, q_1, \ldots$ are independent of the recombination parameter, ρ $(= 4Nr)$ (but implicitly depend on θ_A, θ_B). Now recursively solve for q_0, $q_1, \ldots$.

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- Key property: $q_0(\boldsymbol{c})$ is expressible in terms of the relevant one-locus sampling distributions.

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(Jenkins & Song, 2012)

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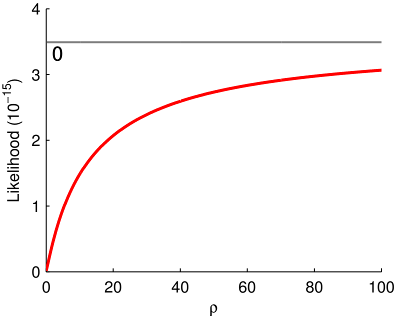
Example

$\boldsymbol{c} = \binom{10\ 7}{2\ \ 1}$, $\theta_A = \theta_B = 0.01$ (symmetric mutation).



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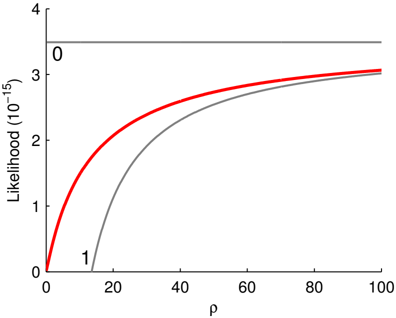

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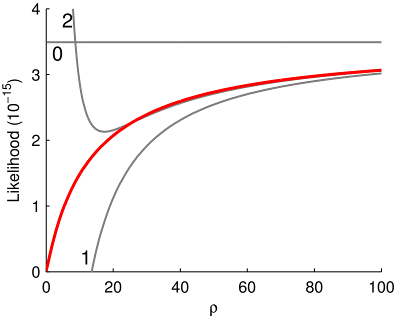

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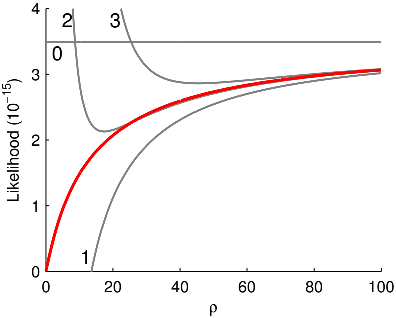

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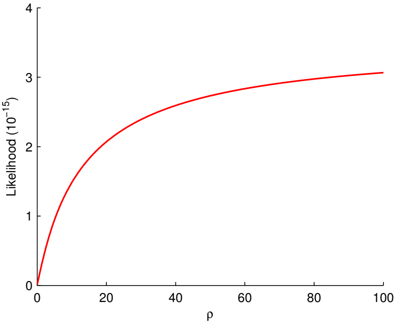

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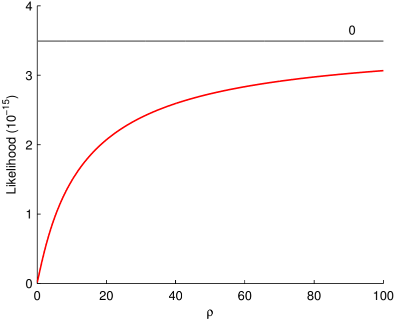

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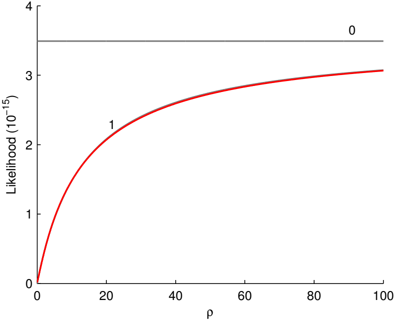

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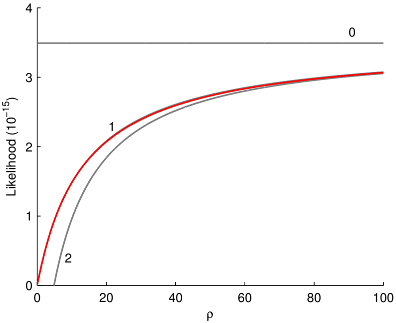

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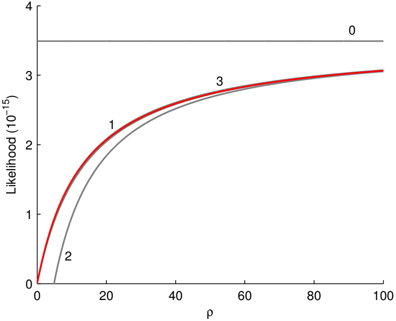

Intriguing observation

Reminder: Asymptotic expansion

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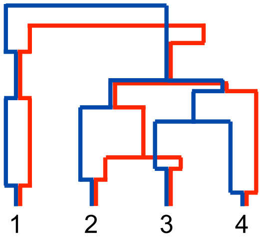
Observation: The same is true of $q_1(\boldsymbol{c})$.

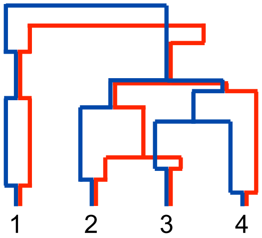
$$q_1(\boldsymbol{c}) = \binom{c}{2} q^A(\boldsymbol{c}_A)q^B(\boldsymbol{c}_B) + \sum_{i,j} \binom{c_{ij}}{2} q^A(\boldsymbol{c}_A - \boldsymbol{e}_i)q^B(\boldsymbol{c}_B - \boldsymbol{e}_j)$$
$$- q^B(\boldsymbol{c}_B)\sum_i \binom{c_{i\cdot}}{2} q^A(\boldsymbol{c}_A - \boldsymbol{e}_i) - q^A(\boldsymbol{c}_A)\sum_j \binom{c_{\cdot j}}{2} q^B(\boldsymbol{c}_B - \boldsymbol{e}_j).$$

[$\boldsymbol{e}_i = (0\dots,0,1,0,\dots,0)^T$, a unit vector with a 1 in the ith position.]



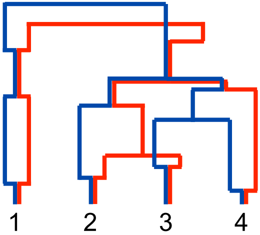
The standard coalescent with recombination

For large recombination rates, ARGs are typically very complicated, containing many recombination events.



Counterintuitive

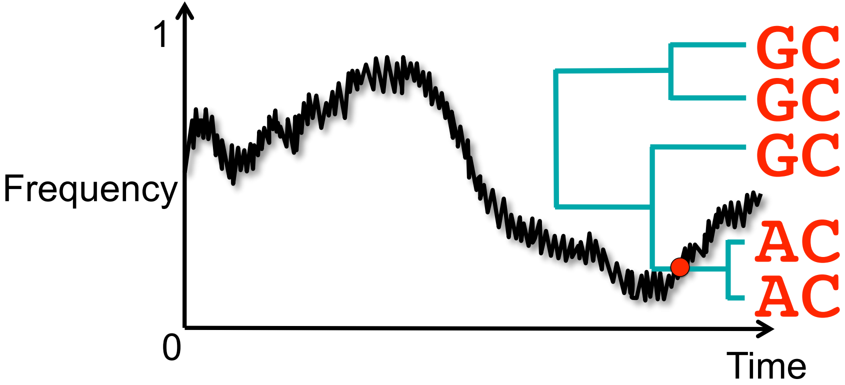
However, we in fact expect the dynamics to be easier to study for large recombination rates, since the loci under consideration would then be less dependent.



Conjecture

There exists a simpler stochastic process that describes the important dynamics of the ARG for large recombination rates, with $q_1(\boldsymbol{c})$ capturing its sampling distribution.

Duality



Conjecture

Furthermore, we should be able to make a similar statement about the Wright-Fisher diffusion, via duality.

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Outline of approach

1. Start with a two-locus Moran model.

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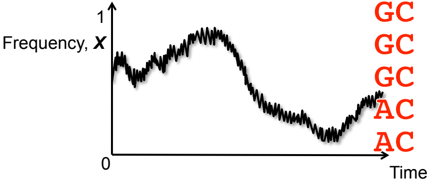
4. Take the diffusion limit of the fluctuations of the coordinates about the deterministic limit.

The Wright-Fisher diffusion

$$d\boldsymbol{X} = \mu(\boldsymbol{X})dt + \sigma(\boldsymbol{X})d\boldsymbol{W},$$
$$\boldsymbol{X} = (X_{ij}), \qquad i, j, \in \{A, C, G, T\}.$$



The (two-locus) Wright-Fisher diffusion

- State space: $\Delta = \left\{ \boldsymbol{x} = (x_{ij}) \in [0,1]^{K \times L} \mid \sum_{i,j} x_{ij} = 1 \right\}.$

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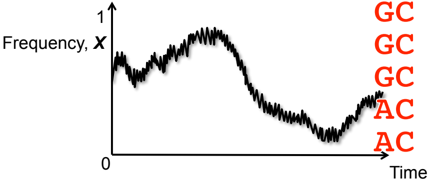

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- Drift coefficient

$$\mu_{ij}(\boldsymbol{x}) = -\frac{\rho}{2}(x_{ij} - x_{i \cdot} x_{\cdot j}) + (\text{mutation terms}; \theta_A, \theta_B)$$

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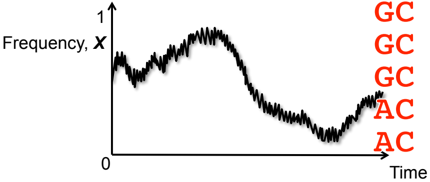


The (two-locus) Wright-Fisher diffusion

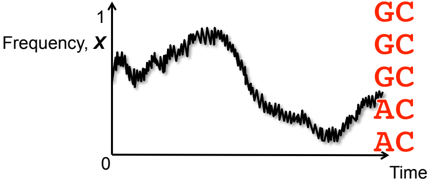
- State space: $\Delta = \left\{ \mathbf{x} = (x_{ij}) \in [0,1]^{K \times L} \mid \sum_{i,j} x_{ij} = 1 \right\}.$
- Drift coefficient

$$\mu_{ij}(\mathbf{x}) = -\frac{\rho}{2}(x_{ij} - x_{i\cdot}x_{\cdot j}) + (\text{mutation terms}; \theta_A, \theta_B)$$

- Diffusion coefficient: $\sigma^2_{ij,kl}(\mathbf{x}) = x_{ij}(\delta_{ij,kl} - x_{kl}).$

The Wright-Fisher diffusion

$$d\boldsymbol{X} = \mu(\boldsymbol{X})dt + \sigma(\boldsymbol{X})d\boldsymbol{W},$$
$$\boldsymbol{X} = (X_{ij}), \qquad i, j, \in \{A, C, G, T\}.$$



Sampling distribution

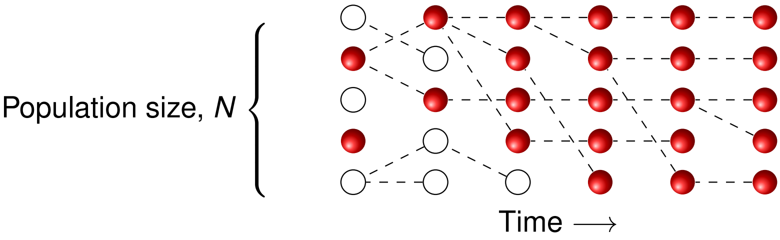
$$q(\boldsymbol{c}) = \mathbb{E}\left[\prod_{i,j} X_{ij}^{c_{ij}}\right].$$

- Using a standard result: $\mathbb{E}[\mathcal{L}f(\boldsymbol{X})] = 0$, we get a linear system of equation for the moments of $\boldsymbol{X}$.
- But this system grows exponentially in the sample size.
- So we need an approximation.

How to derive this diffusion?

Classical approach

- Start from a finite population model of size N.
- Let $N \to \infty$ (possibly after a rescaling of time).
- Rates of mutation and recombination are assumed to be such that they occur at $O(1)$ in the diffusion limit.



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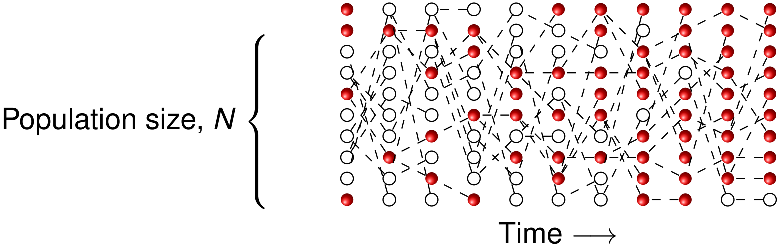

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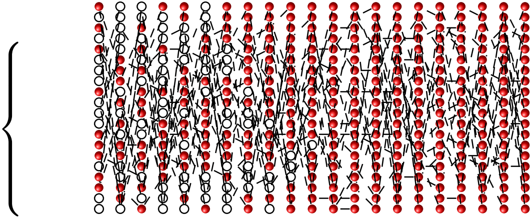
Population size, N



Time $\longrightarrow$

How to derive this diffusion?

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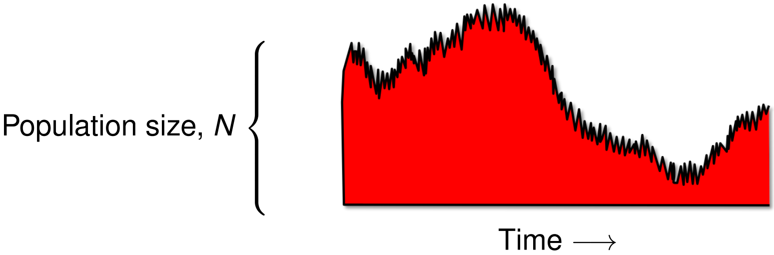
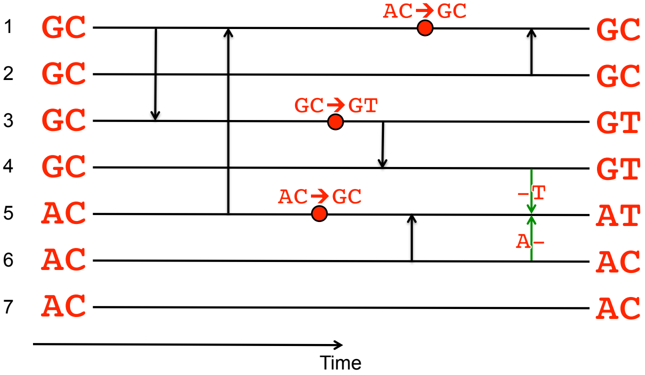


1. Moran model



Rates

Resampling	$N^2/2$
Mutation (locus A)	$\theta_A/2$
Mutation (locus B)	$\theta_B/2$
Recombination	$\rho/2$

2. Change coordinates (Ohta & Kimura, 1969)

Old system $\left(X_{ij}^{(N)}\right)$, $i \in \{1, 2, \ldots, K\}, j \in \{1, 2, \ldots, L\}$

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Diffusion limit

$$\mathbb{E}[\Delta X_{i\cdot}^{(N)} \mid \boldsymbol{X}] = \left[\frac{\theta_A}{2}\sum_{k=1}^{K} P_{ki}^{A} X_{k\cdot}^{(N)} - \frac{\theta_A}{2} X_{i\cdot}^{(N)}\right] dt + o(dt),$$

$$\mathbb{E}[\Delta X_{\cdot j}^{(N)} \mid \boldsymbol{X}] = \left[\frac{\theta_B}{2}\sum_{l=1}^{L} P_{lj}^{B} X_{\cdot l}^{(N)} - \frac{\theta_B}{2} X_{\cdot j}^{(N)}\right] dt + o(dt),$$

$$\mathbb{E}[\Delta D_{ij}^{(N)} \mid \boldsymbol{X}] = \left[-\frac{\rho}{2} D_{ij}^{(N)} - D_{ij}^{(N)} + \frac{\theta_A}{2}\sum_{k=1}^{K} P_{ki}^{A} D_{kj}^{(N)} - \frac{\theta_A}{2} D_{ij}^{(N)} \right.$$
$$\left. + \frac{\theta_B}{2}\sum_{l=1}^{L} P_{lj}^{B} D_{il}^{(N)} - \frac{\theta_B}{2} D_{ij}^{(N)} + O(N^{-1})\right] dt + o(dt)$$

3. Rescale recombination, ρ

Suppose $\rho_\beta = \rho N^{\beta-1} = 4N^\beta r$ is fixed as $N \to \infty$, where $0 < \beta < 1$.
Rescale time to capture this fast behaviour: $t_{\text{new}} = N^{1-\beta} t_{\text{old}}$.

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4. Seek a diffusion limit

Diffusion limit

$$\mathbb{E}[\Delta X_{i\cdot}^{(N)} \mid \boldsymbol{X}] = O\left(\frac{1}{N^{1-\beta}}\right) dt + o(dt),$$

$$\mathbb{E}[\Delta X_{\cdot j}^{(N)} \mid \boldsymbol{X}] = O\left(\frac{1}{N^{1-\beta}}\right) dt + o(dt),$$

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after $N \to \infty$.

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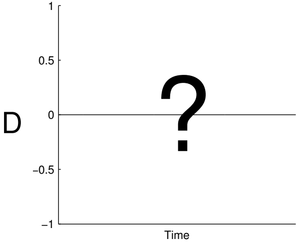
after $N \to \infty$.

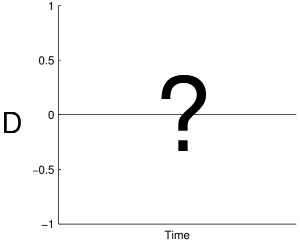
- The description is completed by finding the limiting covariance matrix.
- But—on this timescale it is **0**!

Diffusion limits



Wright-Fisher
diffusion

Diffusion limits



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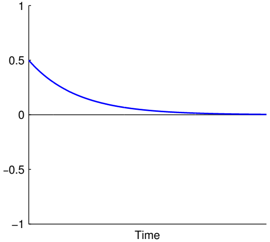
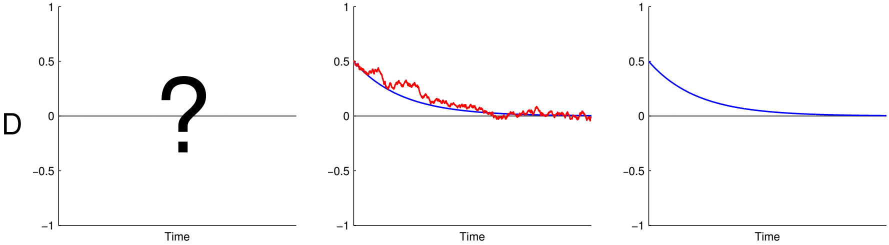


∞-population

Diffusion limits



Wright-Fisher diffusion

Intermediate limit?

∞-population

Summary so far

If

$$\mathbf{M}^{(N)} = \Big((X_{i\cdot}^{(N)}), (X_{\cdot j}^{(N)}), (D_{ij}^{(N)} = X_{ij} - X_{i\cdot}^{(N)} X_{\cdot j}^{(N)}) \Big)$$

then

$$\mathbf{M}^{(N)} \xrightarrow{d} \mathbf{M} := \Big\{ ((X_{i\cdot}(0)), (X_{\cdot j}(0)), (D_{ij}(0) e^{-\rho_\beta t/2})' : t \geq 0 \Big\},$$

as $N \to \infty$.

- This is a law-of-large-numbers result. (Baake & Herms, 2008)

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- This is a law-of-large-numbers result. (Baake & Herms, 2008)
- We really want a central limit theorem.
- So we should be asking: what is the diffusion limit of

$$\boldsymbol{U}^{(N)}(t) := N^{(1-\beta)/2} [\boldsymbol{M}^{(N)}(t) - \boldsymbol{M}(t)]?$$

CLTs for density-dependent population processes

Theorem [Ethier & Kurtz, 1986, Ch. 11; Kang *et al.*, 2014]

Suppose that $\boldsymbol{U}^{(N)}(0) \to \boldsymbol{U}(0)$ as $N \to \infty$, and $\boldsymbol{M}(t)$ the solution to

$$\frac{\mathrm{d}\boldsymbol{M}(t)}{\mathrm{d}t} = \boldsymbol{w}(\boldsymbol{M}(t))$$

exists, for some $\boldsymbol{w}$.

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exists, for some $\boldsymbol{w}$. Then [under some regularity conditions]

$$\sup_{s \le t} |\boldsymbol{M}^{(N)}(s) - \boldsymbol{M}(s)| \xrightarrow{d} 0,$$

and $\boldsymbol{U}^{(N)} \xrightarrow{d} \boldsymbol{U}$, where

$$\boldsymbol{U}(t) = \boldsymbol{U}(0) + \int_0^t [\nabla \boldsymbol{w}(\boldsymbol{M}(s))]\boldsymbol{U}(s)\mathrm{d}s + \int_0^t \boldsymbol{\sigma}(\boldsymbol{M}(s))\mathrm{d}\boldsymbol{W}(s),$$

and $\boldsymbol{\sigma}$ is such that

$$N^{1-\beta}[\boldsymbol{M}^{(N)}]_t - \int_0^t \boldsymbol{\sigma}(\boldsymbol{M}^{(N)}(s))\boldsymbol{\sigma}(\boldsymbol{M}^{(N)}(s))' ds \xrightarrow{d} \boldsymbol{0}.$$

Main aim

Find the diffusion limit of $\boldsymbol{U}^{(N)}(t) = N^{(1-\beta)/2}[\boldsymbol{M}^{(N)}(t) - \boldsymbol{M}(t)]$.

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1. Identify $\boldsymbol{w}$, which supplies the drift part of $\boldsymbol{U}$.
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3. [Check regularity requirements.]

Sketch proof.

Recall:

$$\mathbb{E}[\Delta X_{i\cdot} \mid \boldsymbol{X}] = o(dt),$$
$$\mathbb{E}[\Delta X_{\cdot j} \mid \boldsymbol{X}] = o(dt),$$
$$\mathbb{E}[\Delta D_{ij} \mid \boldsymbol{X}] = \left[-\frac{\rho_\beta}{2} D_{ij}\right] dt + o(dt)$$

So: Drift of $\boldsymbol{M}$:

$$\boldsymbol{w}(\boldsymbol{M}) = \left(\boldsymbol{0}, \boldsymbol{0}, -\frac{\rho_\beta}{2}\boldsymbol{D}\right)'$$

Drift of $\boldsymbol{M}^{(N)}$:

$$\boldsymbol{w}^{(N)}(\boldsymbol{M}) = \left(\boldsymbol{0}, \boldsymbol{0}, -\frac{\rho_\beta}{2}\boldsymbol{D}\right)' + O(N^{\beta-1})$$

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Find the diffusion limit of $\boldsymbol{U}^{(N)}(t) = N^{(1-\beta)/2}[\boldsymbol{M}^{(N)}(t) - \boldsymbol{M}(t)]$.

Sketch proof (*cont.*).

Consider: $\boldsymbol{U}^{(N)}(t) = N^{(1-\beta)/2} \Big[\qquad \Big],$

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Sketch proof (*cont.*).

Consider: $\boldsymbol{U}^{(N)}(t) = N^{(1-\beta)/2} \Big[[\boldsymbol{M}^{(N)}(0) - \boldsymbol{M}(0)] \qquad \Big],$

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Sketch proof (*cont.*).

Consider:
$$\boldsymbol{U}^{(N)}(t) = N^{(1-\beta)/2}\Big[[\boldsymbol{M}^{(N)}(0) - \boldsymbol{M}(0)] + \int_0^t [\boldsymbol{w}^{(N)}(\boldsymbol{M}^{(N)}(s)) - \boldsymbol{w}(\boldsymbol{M}(s))]ds\Big],$$

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1st term

We assumed $\boldsymbol{U}^{(N)}(0) \to \boldsymbol{U}(0)$ as $N \to \infty$.

Main aim

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2nd term

$$\begin{aligned} N^{(1-\beta)/2} \int_0^t [\boldsymbol{w}_3^{(N)}(\boldsymbol{M}^{(N)}(s)) - \boldsymbol{w}_3(\boldsymbol{M}(s))]ds &= N^{(1-\beta)/2} \int_0^t \Big[-\frac{\rho_\beta}{2}[\boldsymbol{D}^{(N)}(s) - \boldsymbol{D}(s)] + O(N^{\beta-1})\Big] ds \\ &= \int_0^t \Big[-\frac{\rho_\beta}{2}\boldsymbol{U}_3^{(N)}(s) + O(N^{(\beta-1)/2})\Big] ds \\ &\xrightarrow{d} -\frac{\rho_\beta}{2}\int_0^t \boldsymbol{U}_3(s)ds, \qquad N \to \infty. \end{aligned}$$

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Find the diffusion limit of $\boldsymbol{U}^{(N)}(t) = N^{(1-\beta)/2}[\boldsymbol{M}^{(N)}(t) - \boldsymbol{M}(t)]$.

Sketch proof (*cont.*).

Consider: $$\boldsymbol{U}^{(N)}(t) = N^{(1-\beta)/2}\left[[\boldsymbol{M}^{(N)}(0) - \boldsymbol{M}(0)] + \int_0^t [\boldsymbol{w}^{(N)}(\boldsymbol{M}^{(N)}(s)) - \boldsymbol{w}(\boldsymbol{M}(s))]ds + \boldsymbol{R}^{(N)}(t)\right],$$

where $$\boldsymbol{R}^{(N)}(t) := \boldsymbol{M}^{(N)}(t) - \boldsymbol{M}^{(N)}(0) - \int_0^t \boldsymbol{w}^{(N)}(\boldsymbol{M}^{(N)}(s))ds.$$

3rd term

- “The difference between the evolution of the Moran process and its expectation.” Key observation: $\boldsymbol{R}^{(N)}(t)$ is a martingale.
- Appeal to the martingale CLT to characterise its limit.
- In other words: we know $\boldsymbol{\sigma}(\boldsymbol{M}(t))$. □

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Putting all this together:

$$\boldsymbol{U}^{(N)}(t) \to \left[\boldsymbol{U}(0) - \frac{\rho_\beta}{2}\int_0^t (\mathbf{0},\mathbf{0},\mathbf{1})' \circ \boldsymbol{U}(s)ds + \int_0^t \boldsymbol{\sigma}(\boldsymbol{M}(s))d\boldsymbol{W}(s)\right].$$

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Apart from a (complicated, time-evolving) covariance term, $D_{ij}(t)$ follows an Ornstein-Uhlenbeck process!

Main aim

Find the diffusion limit of $\boldsymbol{U}^{(N)}(t) = N^{(1-\beta)/2}[\boldsymbol{M}^{(N)}(t) - \boldsymbol{M}(t)]$.

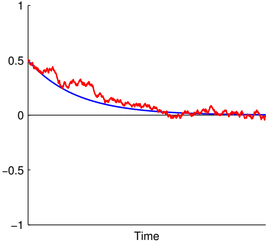
Putting all this together:

$$\boldsymbol{U}^{(N)}(t) \rightarrow \left[\boldsymbol{U}(0) - \frac{\rho_\beta}{2}\int_0^t (\mathbf{0},\mathbf{0},\mathbf{1})' \circ \boldsymbol{U}(s)ds + \int_0^t \boldsymbol{\sigma}(\boldsymbol{M}(s))d\boldsymbol{W}(s)\right].$$

Apart from a (complicated, time-evolving) covariance term, $D_{ij}(t)$ follows an Ornstein-Uhlenbeck process!

Retracing our steps…

$$\boldsymbol{D}^{(N)}(t) \approx \boldsymbol{D}(0)e^{-\rho_\beta t/2} + N^{(\beta-1)/2}\boldsymbol{U}_{\boldsymbol{D}}(t).$$



Stationary distribution

Tracing our steps backwards, we can derive an approximate stationary distribution:

$$\boldsymbol{D} \sim \text{Normal}\left(\mathbf{0}, \frac{1}{\rho}[X_{i\cdot}(0)X_{\cdot j}(0)(\delta_{ik} - X_{k\cdot}(0))(\delta_{jl} - X_{\cdot l}(0))]_{ij,kl}\right).$$

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$$q_{\text{Gaussian}}(\boldsymbol{c}) = \mathbb{E}\left[\prod_{i,j} X_{ij}^{c_{ij}}\right] = \mathbb{E}\left[\prod_{i,j}(D_{ij} + X_{i\cdot}X_{\cdot j})^{c_{ij}}\right] = \ldots.$$

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Accuracy

"Truth": $$q(\boldsymbol{c}) \approx q_0(\boldsymbol{c}) + \frac{q_1(\boldsymbol{c})}{\rho} + \frac{q_2(\boldsymbol{c})}{\rho^2} + \ldots + \frac{q_\lambda(\boldsymbol{x})}{\rho^\lambda},$$

Gaussian model: $$q^{(G)}(\boldsymbol{c}) \approx q_0(\boldsymbol{c}) + \frac{q_1(\boldsymbol{c})}{\rho} + \frac{q_2^{(G)}(\boldsymbol{c})}{\rho^2} + \ldots + \frac{q_\lambda^{(G)}(\boldsymbol{x})}{\rho^\lambda}.$$

		$\rho = 100$			$\rho = 200$		
λ	Type of sum	$\Phi(1)$	$\Phi(10)$	$\Phi(100)$	$\Phi(1)$	$\Phi(10)$	$\Phi(100)$
0	True	0.50	0.72	1.00	0.54	0.95	1.00
	Gaussian	0.50	0.72	1.00	0.54	0.95	1.00
1	True	0.74	0.95	1.00	0.90	0.99	1.00
	Gaussian	0.74	0.95	1.00	0.90	0.99	1.00
2	True	0.95	1.00	1.00	1.00	1.00	1.00
	Gaussian	0.64	0.99	1.00	0.85	1.00	1.00
4	True	1.00	1.00	1.00	1.00	1.00	1.00
	Gaussian	0.64	0.99	1.00	0.83	1.00	1.00
6	True	1.00	1.00	1.00	1.00	1.00	1.00
	Gaussian	0.64	0.99	1.00	0.83	1.00	1.00

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		$\rho = 25$			$\rho = 50$		
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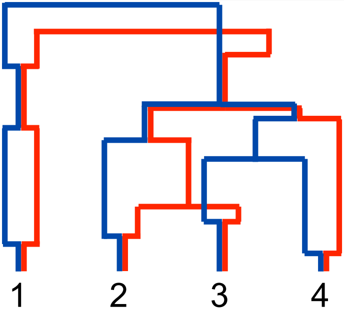
- Q: Are there simple, general CLTs for non-Markovian density-dependent population processes?

A new coalescent model

Question

Can we give a similar treatment to the ancestral recombination graph?



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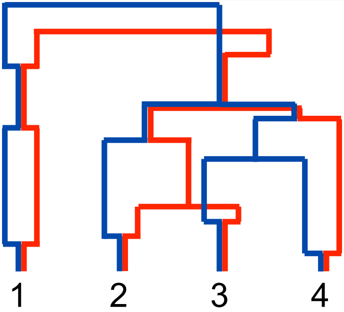

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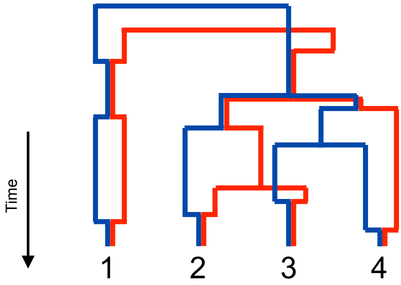

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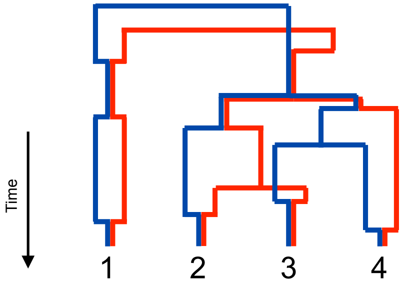

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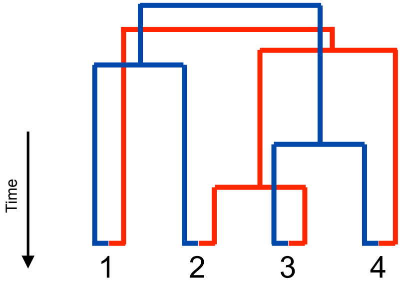

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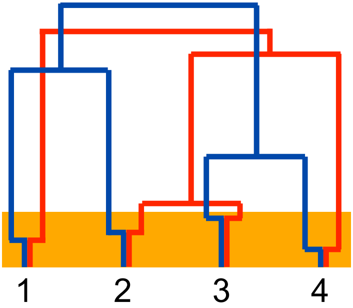

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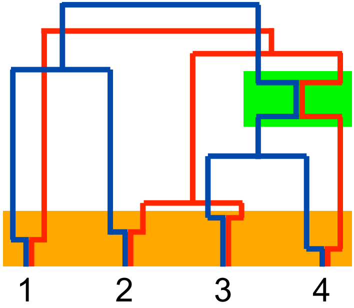

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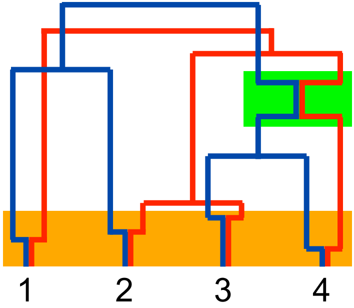
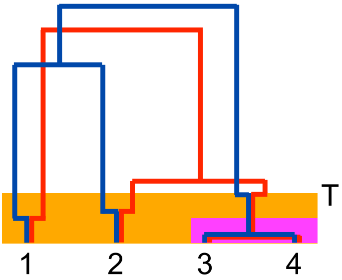
$q_1(\boldsymbol{c})$ represents the effects of any single nontrivial event in the ARG that could distinguish its sampling distribution from that of two independent coalescent trees.



A new coalescent model

Possible "nontrivial events"

1. A coalescence prior to the first time all lineages have recombined (T).



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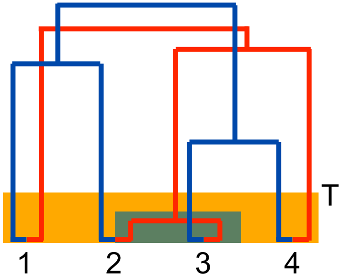

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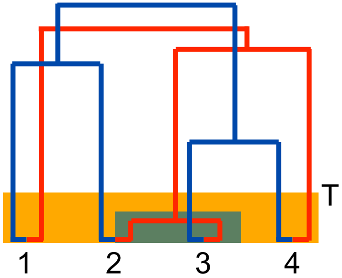
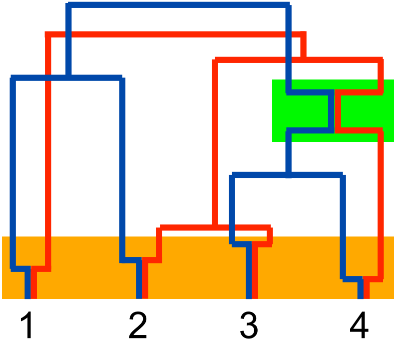


- In fact, these are the only events (or nonevents) of relevance.

Trivial event

Another "nontrivial" event?

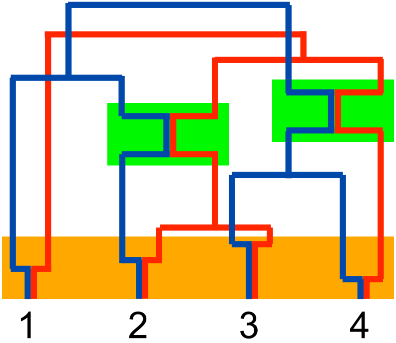
1. First coalescence: $O(1)$.



Trivial event

Another "nontrivial" event?

1. First coalescence: $O(1)$.
2. Second coalescence: $O(\rho^{-1})$.



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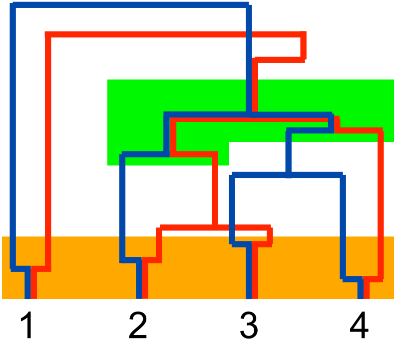

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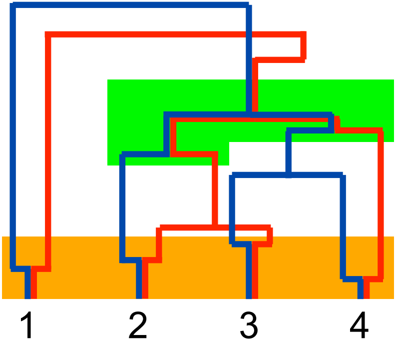
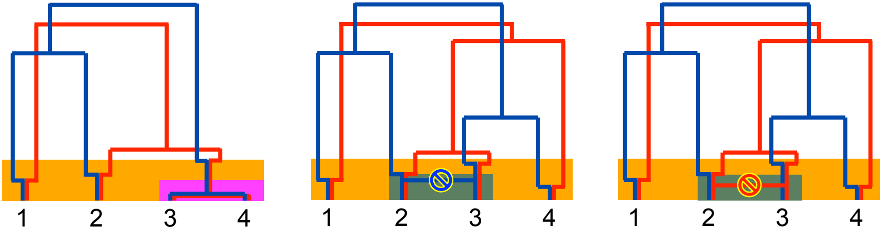
Overall probability of this event is $O(\rho^{-2})$—i.e. negligible.



- A coupling between the ARG and a pair of independent coalescent trees can make these arguments rigorous.

Coupling argument (outline)



F_1: Type 1 failure F_2: Type 2 failure F_3: Type 3 failure

Outline of argument

Show that:

- $\mathbb{P}(F_1) = \frac{1}{\rho}\binom{c}{2} + O\left(\frac{1}{\rho^2}\right)$,

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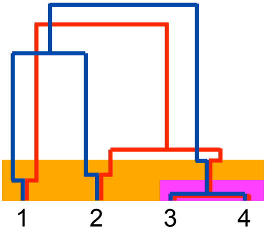

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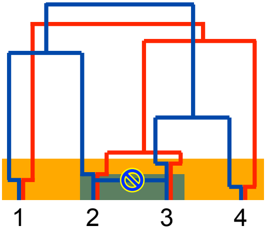
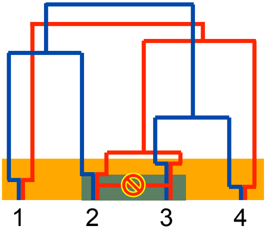


F_2: Type 2 failure



F_3: Type 3 failure

Outline of argument

Show that:

- $\mathbb{P}(F_1) = \frac{1}{\rho}\binom{c}{2} + O\left(\frac{1}{\rho^2}\right)$,
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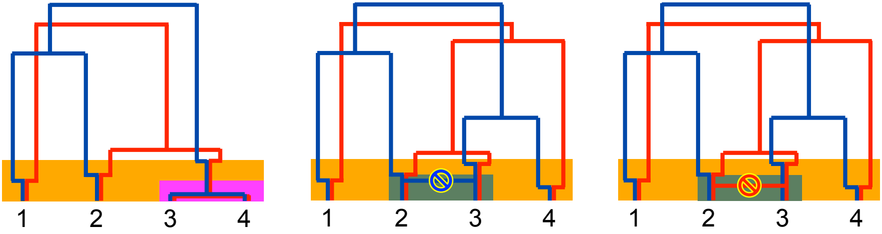

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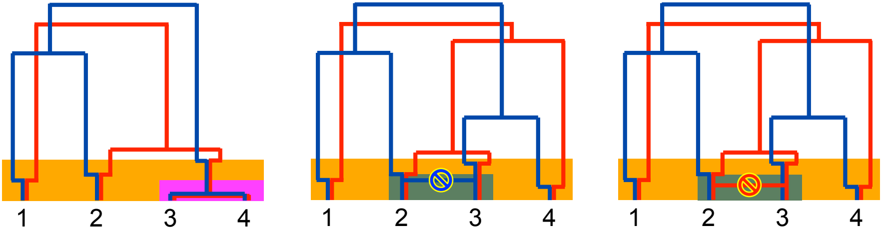

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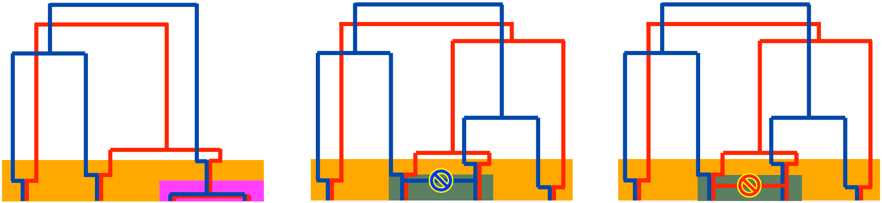

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- $\mathbb{P}(\text{any other type of failure}) = O\left(\frac{1}{\rho^2}\right)$.

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$$q(\boldsymbol{c} \mid (F_2 \cup F_3)^{\complement};\infty) = \left[\frac{1}{1 - \mathbb{P}(F_2) - \mathbb{P}(F_3)}\right][q(\boldsymbol{c};\infty)$$
$$- \mathbb{P}(F_2)q(\boldsymbol{c} \mid F_2;\infty) - \mathbb{P}(F_3)q(\boldsymbol{c} \mid F_3;\infty)].$$

Theorem.

The sampling distribution of the loose linkage coalescent is

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$$\underbrace{- q^B(\boldsymbol{c}_B)\sum_i \binom{c_{i\cdot}}{2} q^A(\boldsymbol{c}_A - \boldsymbol{e}_i) - q^A(\boldsymbol{c}_A)\sum_j \binom{c_{\cdot j}}{2} q^B(\boldsymbol{c}_B - \boldsymbol{e}_j)}_{\text{...with the restriction that no "prohibited coalescences" occur before time } T}.$$

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2. Otherwise:
   - Simulate from two independent coalescent trees conditioned not to have any prohibited coalescences before time T, as described earlier.

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  - More than two loci
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Future work

- Further generalizations:
    - More than two loci
    - Natural selection
- Better tools:
    - Duality between the two models?
    - “Separation of timescales” (cf. Möhle, 1998)

References

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Acknowledgements

- Discussions with Song lab, Bob Griffiths, Charles Langley, Ben Peter, John Pool, Nadia Singh
- Simons Institute for the Theory of Computing
- Isaac Newton Institute

Research supported in part by EPSRC (PAJ, PF), NIH (PAJ, YSS), Alfred P. Sloan Research Fellowship (YSS), and a Packard Fellowship for Science and Engineering (YSS).

Covariances of the Moran model

$$\lim_{\mathrm{d}t\to 0}(\mathrm{d}t)^{-1}\mathbb{E}[\Delta \boldsymbol{M}^{(N)}(\tau) \mid \boldsymbol{M}^{(N)}(\tau)=\boldsymbol{m}]$$
$$= N^{\beta-1}\lim_{\mathrm{d}\tau\to 0}(\mathrm{d}\tau)^{-1}\mathbb{E}[\Delta \boldsymbol{M}^{(N)}(\tau) \mid \boldsymbol{M}^{(N)}(\tau)=\boldsymbol{m}] =: \boldsymbol{w}^{(N)}(\boldsymbol{m}),$$

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Thus, with $\boldsymbol{m}=(x_1,\ldots,x_K,y_1,\ldots,y_L,d_{11},\ldots,d_{KL})$, we have

$$\boldsymbol{w}^{(N)}(\boldsymbol{m}) = \boldsymbol{w}(\boldsymbol{m}) + O(N^{\beta-1}),$$

where
$$\boldsymbol{w}(\boldsymbol{m}) = \Big(\underbrace{0,\ldots 0}_{K},\underbrace{0,\ldots 0}_{L},\underbrace{-\frac{\rho_\beta}{2}d_{11},\ldots,-\frac{\rho_\beta}{2}d_{KL}}_{K\times L}\Big)',$$

Covariances of the Moran model (II)

$\boldsymbol{s}^{(N)}(\boldsymbol{m}) = \boldsymbol{s}(\boldsymbol{m}) + O(N^{-\beta})$ is determined in a similar fashion:

$$\boldsymbol{s}(\boldsymbol{m}) = \begin{bmatrix} \boldsymbol{s}_{\mathbf{XX}}(\boldsymbol{m}) & \boldsymbol{s}_{\mathbf{XY}}(\boldsymbol{m}) & \boldsymbol{s}_{\mathbf{XD}}(\boldsymbol{m}) \\ \boldsymbol{s}_{\mathbf{XY}}(\boldsymbol{m}) & \boldsymbol{s}_{\mathbf{YY}}(\boldsymbol{m}) & \boldsymbol{s}_{\mathbf{YD}}(\boldsymbol{m}) \\ \boldsymbol{s}_{\mathbf{XD}}(\boldsymbol{m}) & \boldsymbol{s}_{\mathbf{YD}}(\boldsymbol{m}) & \boldsymbol{s}_{\mathbf{DD}}(\boldsymbol{m}) \end{bmatrix},$$

where

$$\begin{aligned} [\boldsymbol{s}_{\mathbf{XX}}(\boldsymbol{m})]_{ik} &= x_i(\delta_{ik} - x_k), \\ [\boldsymbol{s}_{\mathbf{YY}}(\boldsymbol{m})]_{jl} &= y_j(\delta_{jl} - y_l), \\ [\boldsymbol{s}_{\mathbf{XY}}(\boldsymbol{m})]_{ij} &= d_{ij}, \\ [\boldsymbol{s}_{\mathbf{XD}}(\boldsymbol{m})]_{i,kl} &= d_{kl}(\delta_{ik} - x_i) - x_k d_{il}, \\ [\boldsymbol{s}_{\mathbf{YD}}(\boldsymbol{m})]_{j,kl} &= d_{kl}(\delta_{jl} - y_j) - y_l d_{kj}, \\ [\boldsymbol{s}_{\mathbf{DD}}(\boldsymbol{m})]_{ij,kl} &= x_i y_j(\delta_{ik} - x_k)(\delta_{jl} - y_l) + d_{kj} x_i y_l + d_{il} x_k y_j \\ &\quad + d_{ij}(x_k y_l - \delta_{ik} y_l - \delta_{jl} x_k) \\ &\quad + d_{kl}(x_i y_j - \delta_{ik} y_j - \delta_{jl} x_i) + d_{ij}(\delta_{ik}\delta_{jl} - d_{kl}). \end{aligned}$$