Combiner démographie et génétique en biologie des populations

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- **GOAL:** parameter inference in biology of conservation
- 2 research communities: **demographic** data VS **genetic** data
- demography: find the **census size** $N(t)$ =number of individuals
- genetics: capacity of a population to maintain its genetic diversity, measured through **effective population size** $N_e(t)$
- our approach: **joint model** for demography and genetics

Genetic data

locus	1	2	3	4
individual 1	1	0	0	1
individual 2	0	1	1	1
individual 3	0	1	1	0

- sample of n_{gen} individuals
- genotype at L loci
- two possible alleles $0/1$ at every locus
- data $N^{A_1 \dots A_L}$ = number of individuals with genome $A_1 \dots A_L$

typically: ≈ 20 loci, ≈ 5 alleles, $n_{gen} \approx 50$

Demographic data

date	01/03	02/03	01/06	02/06	01/09	02/09
individu 1	1	0	0	0	0	0
individu 2	0	0	1	1	0	1
individu 3	1	1	0	1	1	0

- at times t_i, $i = 1, ..., 6$, every individual alive is captured with probability p_i (**unknown**) and marked.
- **capture history** of an individual $\omega = \{1001\}$: $\omega_i = 1 \iff$ individual captured at i
- data $N_\omega =$ number of individuals with given capture history

typically: 5 years, 5 sessions per year

Figure: Bulbul de Cabanis, Kenya

The computation-intensive approach

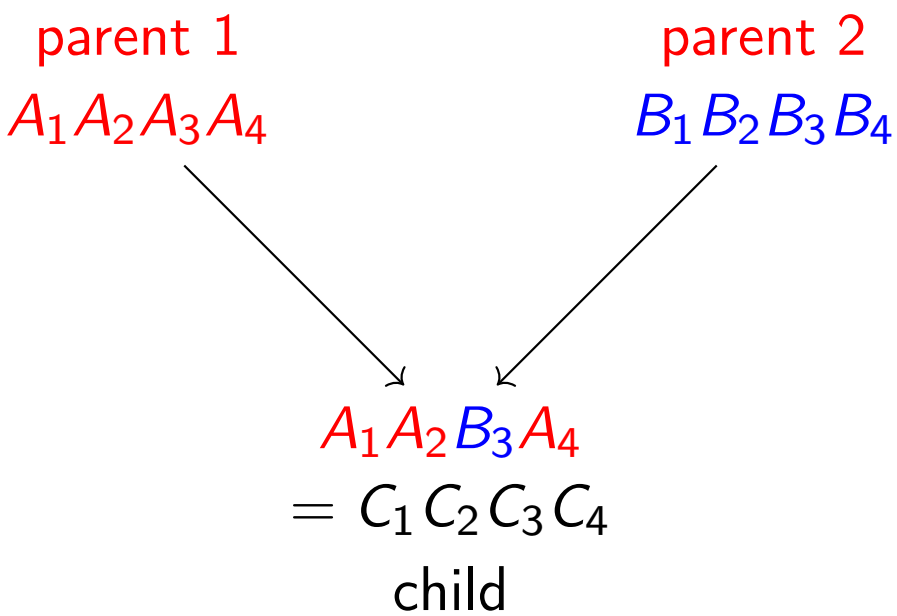
Algorithm (Approximate Bayesian Computing, Tavaré et al., 1997; Beaumont et al., 2002)

- *compute summary statistics* $\mathcal{D} = (\mathcal{D}_{gen}, \mathcal{D}_{dem})$ *from the data*
- *sample* θ_k *according to a prior* $\pi(\theta)$
- *simulate* $\mathcal{D}_k$ *from the model with parameter* θ_k
- *keep* θ_k *iff* $|\mathcal{D}_k - \mathcal{D}| < \varepsilon$

- approach of our collaborators (Miguel de Navascués and Raphaël Leblois): use SLIM to simulate and apply ABC
- our (complementary) approach: understand better the properties of the model; maybe later combine ABC with likelihood-based approaches

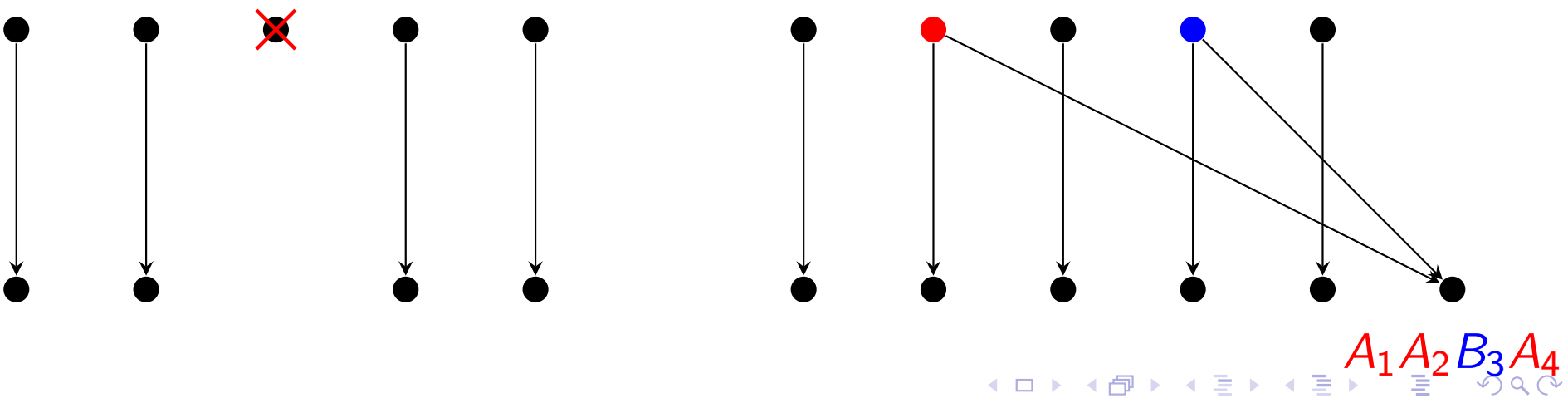
Genetic transmission

- genotype: $A_1 \dots A_L$
- loci are assumed **independant** (e.g. on different chromosomes)
- when two parents $A_1A_2A_3A_4$ and $B_1B_2B_3B_4$ have a child: for every allele, child takes an allele at random

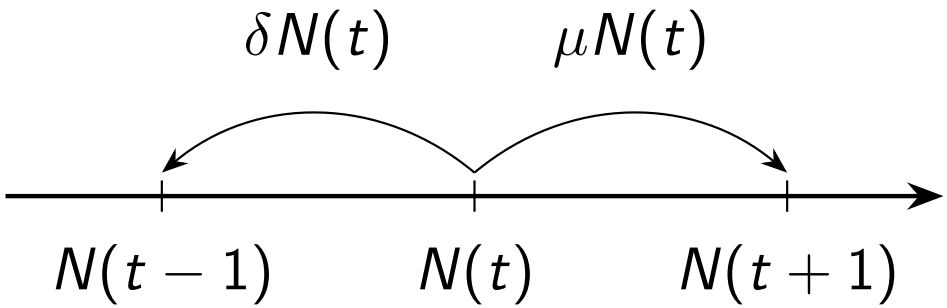


Joint model

- parameters: $N(0), \mu, \delta$
- $N(t) =$ number of individuals at time t
- with rate $\delta N(t)$, an individual is chosen at random and dies
- with rate $\mu N(t)$, two individuals are chosen at random and reproduce



- $N(t)$ = number of individuals is a **birth and death process**



- $(N(t), (X^{A_1 \dots A_L})_{A_1 \dots A_L})$ = continuous time Markov chain
- genetics resembles a **Wright-Fisher** or **Moran** model with recombination, but with varying population size

Remark

We loose some information by forgetting the pedigree and the life history of individuals

Diffusion limit

When $N(0)$ is large, time scale of $\asymp 1$ generation: **diffusion approximation**

Proposition

- $N(t+h) \approx N(t) + h(\mu - \delta)N(t) + h(\mu + \delta)N(t)\mathcal{N}(0,1)$
- *at a given locus and alele* $X(t) = X^{A_i}(t)$ *is approximately a Wright-Fisher diffusion*

$$X(t+h) \approx X(t) + \sqrt{\frac{\mu+\delta}{N(t)} X(t)(1-X(t))\mathcal{N}(0,h)}$$

- *correlation between loci vanish*

$$D^{A_iA_j}(t) = X^{A_iA_j}(t) - X^{A_i}(t)X^{A_j}(t) \approx 1/N(t)$$

$N_e(t) = \frac{\mu+\delta}{N(t)}$ is called the **effective population size**

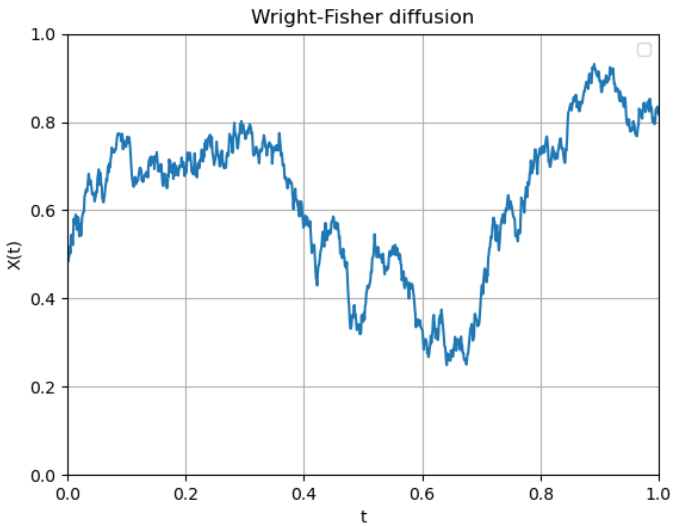
Wright-Fisher diffusion

If $N(t) = N$ was constant, in the diffusion limit $N = N(0) \to \infty$, the reparameterized process $\tilde{X}(t) = X(Nt)$ converges

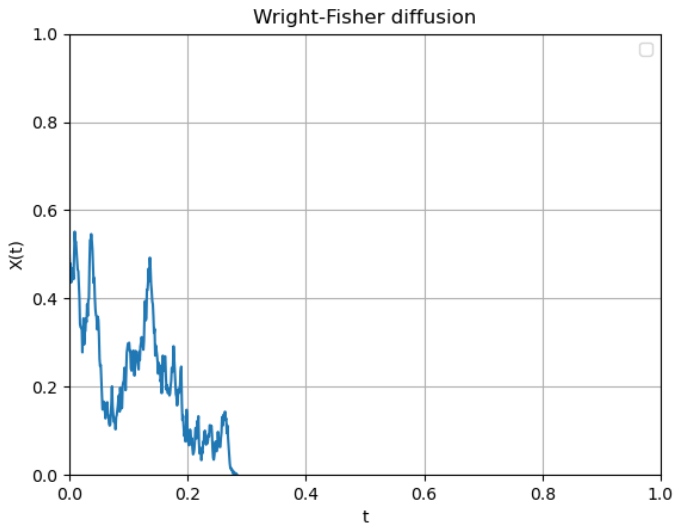
Definition (Wright-Fisher diffusion)

$$d\tilde{X}(t) = \sqrt{(\mu + \delta)\tilde{X}(t)(1 - \tilde{X}(t))}dB_t$$

$\mu + \delta = 1$



$\mu + \delta = 10$



Some remarks

- to obtain the limit of $X(t) = X^{A_i}(t)$, one just looks at

$$\mathbb{E}[X(t+h) - X(t)] \approx 0$$

$$\mathrm{Var}[X(t+h) - X(t)] \approx \frac{\mu + \delta}{N(t)} X(t)(1 - X(t))$$

- to obtain joint frequencies $X^{A_i A_j}$, one proves that the **linkage disequilibrium**

$$D^{A_i A_j}(t) = X^{A_i A_j}(t) - X^{A_i}(t) X^{A_j}(t) \approx 1/N(t)$$

remains small

- slow-fast analysis in the spirit of Ethier-Nagylaki (1989)

$$\mathbb{E}[D(t+h) - D(t)] \approx -\frac{h}{4} dt \; ; \; \mathrm{Var}[D(t+h) - D(t)] = o(h)$$

Model for genetic sampling:

- at time 0 and 1, sample n_{gen} individuals, $\tilde{X}^{A_i}$ = observed frequency
- **summary statistics**: $\mathcal{D}_{gen} = (\tilde{\Delta}^{A_i}, \tilde{D}^{A_i A_j})$

$$\tilde{\Delta}^{A_i} = \tilde{X}^{A_i}(1) - \tilde{X}^{A_i}(0) \text{ frequency variation}$$
$$\tilde{D}^{A_i A_j} = \tilde{X}^{A_i A_j}(0) - \tilde{X}^{A_i}(0)\tilde{X}^{A_j}(0) \text{ linkage disequilibrium}$$

Proposition

$$\tilde{\Delta}^{A_i} \approx \mathcal{N}\left(0, \left(\frac{1}{n_{gen}} + \frac{\mu+\delta}{N(0)}\right) X^{A_1}(0)(1 - X^{A_1}(0))\right)$$

are independent between loci thus a maximum likelihood estimator gives an estimator $N_e^{dem} = \hat{N}_e(\mathcal{D}_{gen})$

Model for demographic sampling:

- capture occasions at times $t_1 = 0, t_2, \ldots, t_6 = 1$
- at time t_i, an individual is captured with proba p_i (= nuisance parameter)
- every capture history ω is seen N_ω times
- summary statistics $\mathcal{D}_{dem} = (N_\omega)_{\omega \in \{0,1\}^6}$

Remark

From $\mathcal{D}_{dem}$ one obtains $\hat{\mu}, \hat{\delta}, \hat{N}(0), \hat{p}_i$ thus $\hat{N}_e^{dem} = \frac{\hat{\mu}+\hat{\delta}}{\hat{N}}$

demographic sampling has an explicit likelihood, but details of estimation are still to be worked out, $N(t_i)$ are latent variables

Our roadmap:

Conjecture

The demographic and genetic estimator are approximately independant $\hat{N^e}_{dem} \perp \hat{N^e}_{gen}$

- find the best combined estimator $\hat{N}^e_{opt} = \lambda \hat{N}^e_{dem} + (1-\lambda)\hat{N^e}_{gen}$
- need to estimate the variances, either from computation or data (bootstrap)

Merci !