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Heterogeneity in effective size across the genome: effects on the Inverse Instantaneous Coalescence Rate (IICR) and implications for demographic inference under linked selection

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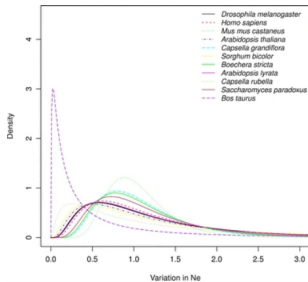
- **Genetic diversity** shaped by
 - Genetic Drift (Kimura, 1968; 1983).
 - Population demography and structure (Nei *et al*, 1974; Wakeley, 1999; Wall *et al*, 2002).
 - **Linked selection** (Hill and Robertson, 1966), **including ...**
 - Selective sweeps (**SW**; Maynard Smith and Haigh, 1974; Gillespie, 1991).
 - Background selection (**BGS**; Charlesworth *et al*, 1993).
 - Balancing selection (**BaIS**; Ford 1975).
- **Respective role of these forces?** (Kern and Hahn 2018; Jensen *et al* 2019).

Linked selection and demographic inference

- Linked selection **pervasive** (Elyashiv *et al*, 2016; Pouyet *et al*, 2018).
- Linked selection **biases demographic inference** (Ewing and Jensen, 2016; Schrider *et al*, 2016; Pouyet *et al*, 2018; Johri *et al* 2021)

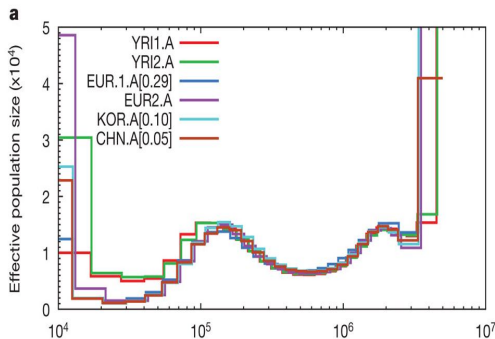
The variable N_e hypothesis

- Linked selection modelled by a change of N_e (Hill and Robertson, 1966; Charlesworth, 2009):
 - decreasing for BGS and SW.
 - increasing for BalS.
- **Variable levels of N_e genome-wide** (Gossmann *et al*, 2011; Jimenez-Mena *et al*, 2016) reflecting variations of selection constraints.



Characterize the effects of linked selection on genome-wide patterns of genetic diversity.

- Model linked selection through several classes of N_e .
- Study the genome-wide distribution of coalescence times (T_2).
- Consequences for demographic inference with PSMC (Li and Durbin, 2011) or MSMC (Schiffels and Durbin, 2014).



Inverse Instantaneous Coalescence Rate (IICR)

- Arbitrary evolution model.
- T_2 coalescence time between two haploid sequences, in units of $2N$ generations.
- Let $F(t) = \mathbb{P}(T_2 \leq t)$, and $F'(t) = f(t)$.

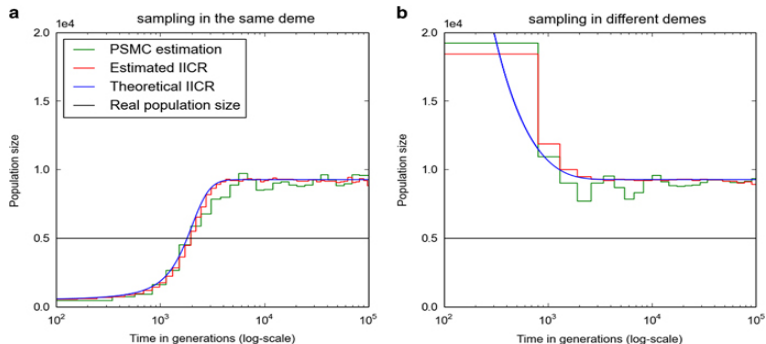
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$$IICR(t) = \frac{1 - F(t)}{f(t)} \quad (\text{Mazet } et al, 2016)$$

- IICR $\Leftrightarrow T_2$ distribution.
- Can be obtained numerically (Rodriguez *et al*, 2018) for a given evolution model.
- Convenient because :
 - inferred from genomic data by PSMC or MSMC.
 - direct interpretation **under panmixia and neutrality** : population size history.

Population structure

- PSMC does estimate the IICR but ...
- ... the IICR does not reflect population size history.



Mazet *et al* (2016), Chikhi *et al* (2018).

Panmictic model with “selection”

- K genomic classes with relative proportion a_i .
- Class i evolves under the WF model with $\lambda_i N$ diploids.

$$T_2^i \sim \mathcal{E}(\mu_i), \quad \mu_i = 1/\lambda_i$$

- Genome-wide distribution of T_2

$$f(t) = \sum_{i=1}^K a_i \mu_i e^{-\mu_i t}$$

- IICR

$$IICR(t) = -\frac{1 - F(t)}{f(t)} = \frac{\sum_{i=1}^K a_i e^{-\mu_i t}}{\sum_{i=1}^K a_i \mu_i e^{-\mu_i t}}.$$

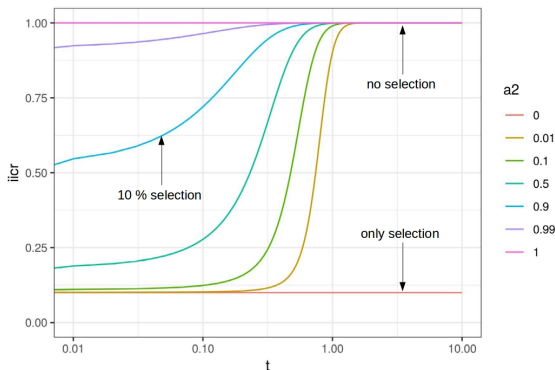
- $IICR(t)$ increasing (backward in time)
→ spurious signal of **population size decline**.
- Starting value:

$$IICR(0) = \frac{1}{\sum_{i=1}^K \frac{a_i}{\lambda_i}}$$

- $IICR(t) \rightarrow \lambda_{max}$ as $t \rightarrow +\infty$

Two classes of N_e

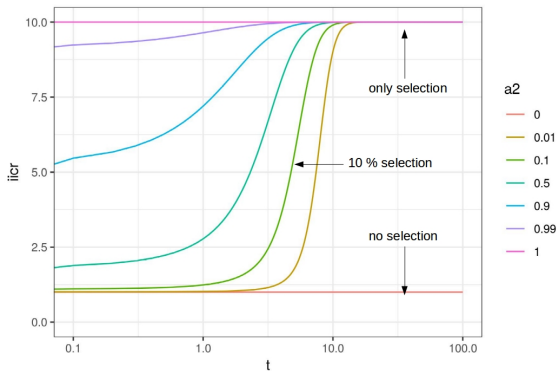
- $\lambda_1 = 0.1$ (BGS/SW), $\lambda_2 = 1$ (neutral).



→ **BGS/SW** impact **recent past** IICR.

Two classes of N_e

- $\lambda_1 = 1$ (neutral), $\lambda_2 = 10$ (BaIS).



→ **BaIS** impacts intermediate to **ancient past** IICR, even if in **small proportion**.

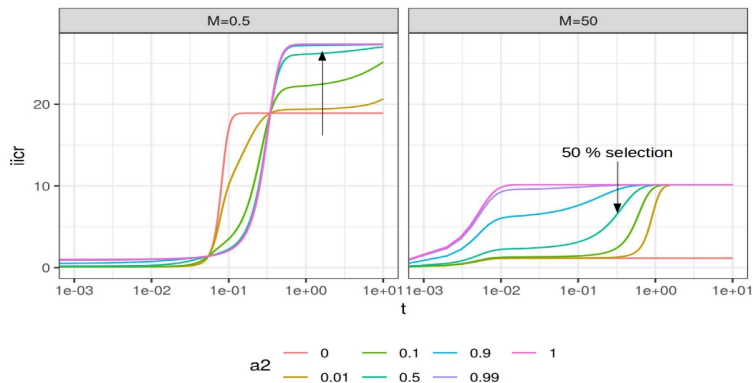
$$IICR(t) = \frac{\sum_{i=1}^K a_i(1 - F_i(t))}{\sum_{i=1}^K a_i f_i(t)}$$

$f_i()$ pdf of T_2 .

- Genuine population size changes.
- Population structure (stationary or non stationary).
- Transient (rather than recurrent) selection.

Example 1: stationary n island model

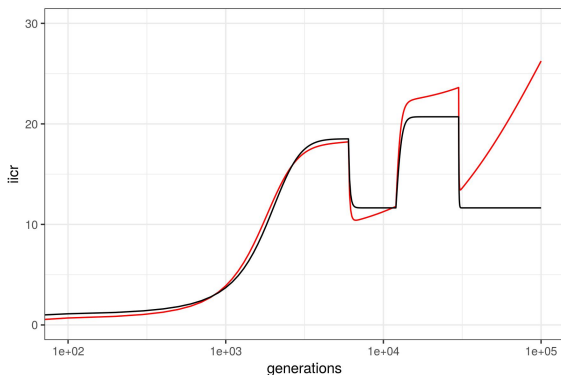
- $n = 10$ islands, two classes: $\lambda_1 = 0.1$, $\lambda_2 = 1$.



→ Selection effect weaker than under panmixia for $M \leq 1$.

Example 2: human evolution model (Mazet *et al*, 2016)

- $n = 10$, **non stationary** M (4 epochs).
- + λ distribution estimated by Gossmann *et al* (2011) (red).



→ **Main effect** of selection in the **ancient past**.

- Under panmixia, **linked selection** leaves a **signature of population decline** from the largest genomic N_e (with PSMC or MSMC).
- **BGS/SW impact recent past IICR, BalS ancient past.**
- **Larger effect of BalS**, even if in much lower proportions.
- Linked selection partly **masked by population structure**.
- Ref: Genetics, 220(3), iyac008.

- **Joint inference of demography and linked selection** parameters?
- Approximate model of linked selection, but :
 - **fast** IICR evaluation.
 - **flexible** modelling: several forms of selection, population structure, demographic changes, transient or fluctuating selection ...
- Model genomic variations of mutation rate, gene flow ...

PhD positions in population genomics available in september 2022.

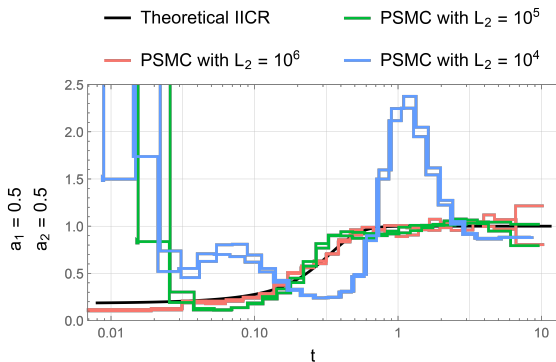
- Inference in spatial models.
- Inference from genomic time series.
- Genomic offset.

Why BGS does not leave a signal of expansion?

- The **decline signature** comes for the **variability of N_e along the genome**, not considered by
 - single locus models (Zeng and Charlesworth, 2011; Walczak *et al*, 2012).
 - models with **regular and short scale** alternance of neutral and selected loci (Johri *et al*, 2021).
- **Variable N_e hypothesis** less appropriate for samples properties like the **Site Frequency Spectrum** (Ewing and Jensen, 2016).
 - excess of singletons in BGS vs neutral models (Charlesworth *et al*, 1993).

IICR prediction and PSMC estimation

- Panmictic model with $\lambda_1 = 0.1$, $\lambda_2 = 1$.
- PSMC applied to genomes, simulated with variable N_e (class 1, class 2, class 1 ...).

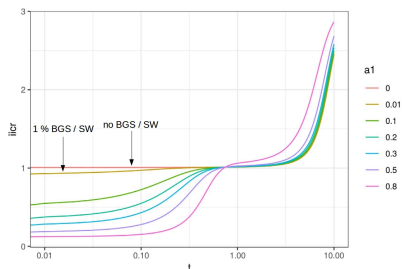


→ consistent for **large scale N_e variations.**

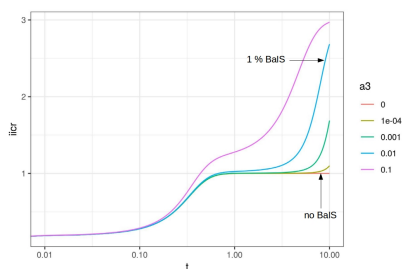
Three classes of N_e

$\lambda_1 = 0.1$ (BGS/SW), $\lambda_2 = 1$ (neutral), $\lambda_3 = 3$ (BaIS).

$a_3 = 0.01$



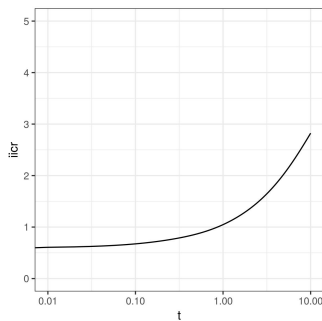
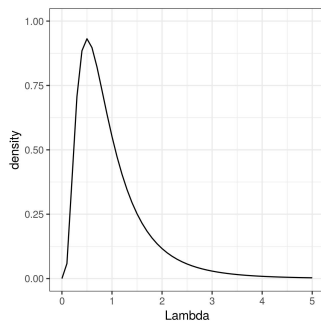
$a_1 = 0.5$



- stronger effect of BaIS vs BGS/sweeps for the same proportion.
- intermediate plateau depending on a_1 and a_3

Realistic N_e distributions: *humans*

Gossmann *et al* (2011): N_e distribution assumed log-normal and estimated from polymorphism and divergence data.



→ long term 6-fold decline from $t = 10$.