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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Context

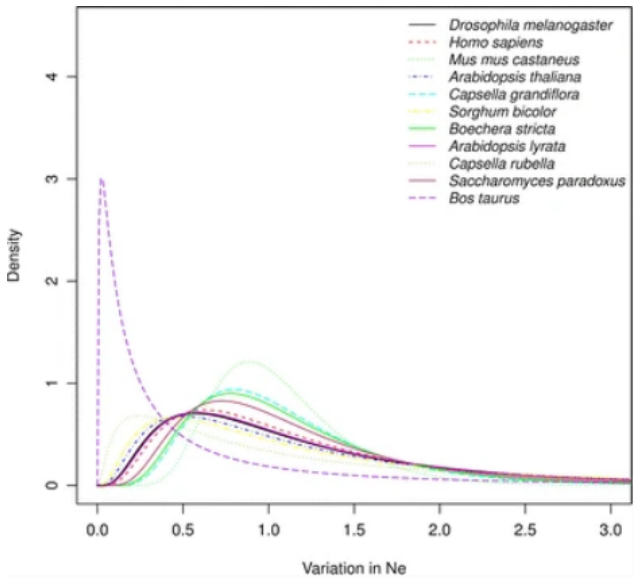
- **Genetic diversity** shaped by
  - Genetic Drift (Kimura, 1968; 1983).
  - Population demography and structure (Nei *et al*, 1974; Wakeley, 1999; Wall *et al*, 2002).
  - **Linked selection** (Hill and Robertson, 1966), **including ...**
  - Selective sweeps (**SW**; Maynard Smith and Haigh, 1974; Gillespie, 1991).
  - Background selection (**BGS**; Charlesworth *et al*, 1993).
  - Balancing selection (**BalS**; 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

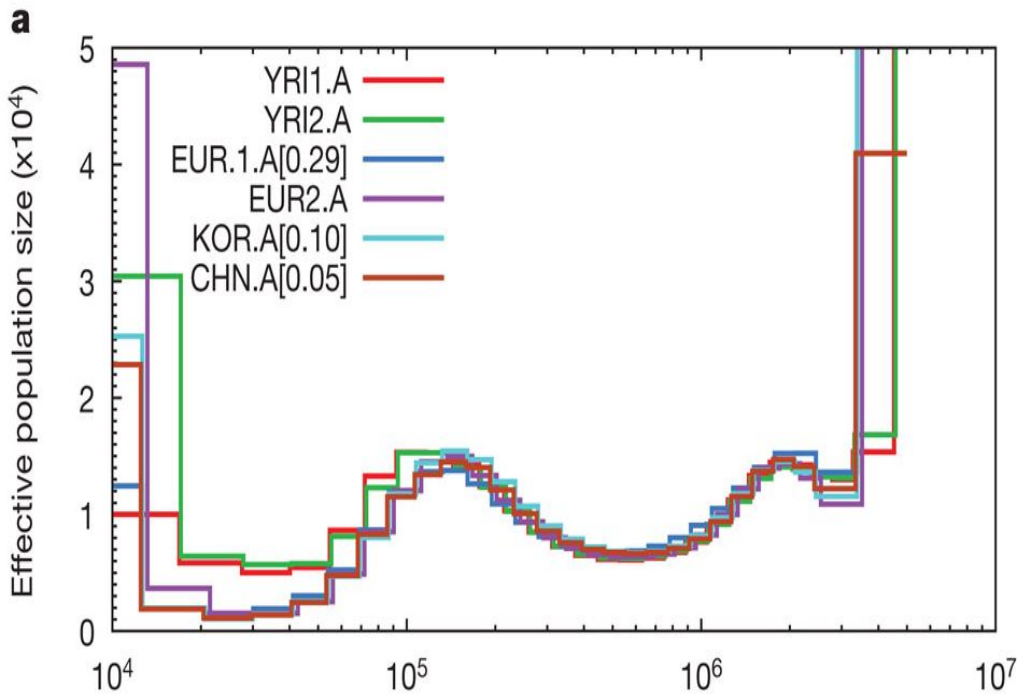
- Linked selection modelled by a change of N_e (Hill and Robertson, 1966; Charlesworth, 2009):
  - decreasing for BGS and SW.
  - increasing for BalS.
- **Variable levels of N_e genome-wide** (Gossmann *et al*, 2011; Jimenez-Mena *et al*, 2016) reflecting variations of selection constraints.



Objectives

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)

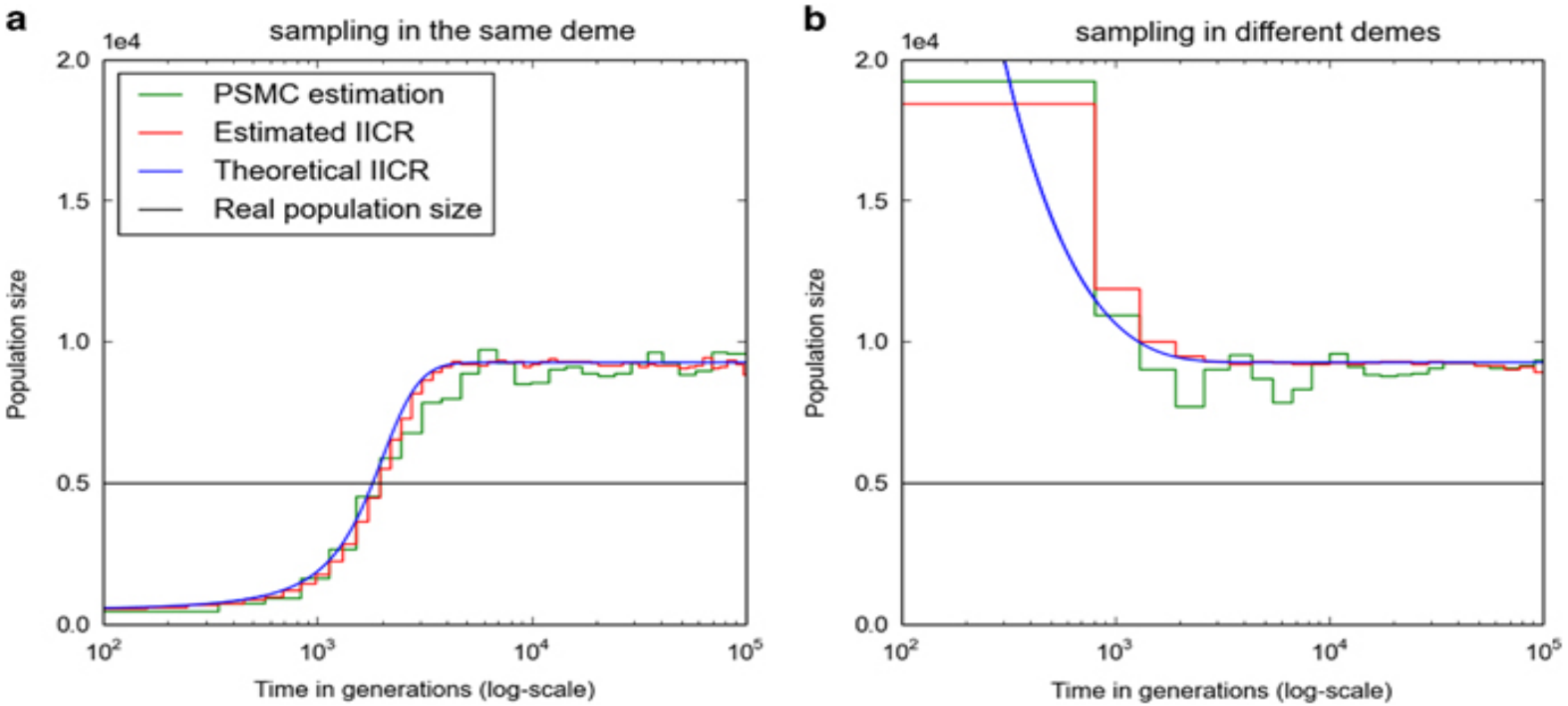
- Arbitrary evolution model.
- T_2 coalescence time between two haploid sequences, in units of $2N$ generations.
- Let $F(t) = \mathbb{P}(T_2 \leq t)$, and $F'(t) = f(t)$.
- $$IICR(t) = \frac{1 - F(t)}{f(t)} \quad \text{(Mazet } \textit{et al}\text{, 2016)}$$

IICR properties

- 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 λ_iN diploids.

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

- Genome-wide distribution of T_2

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

- IICR

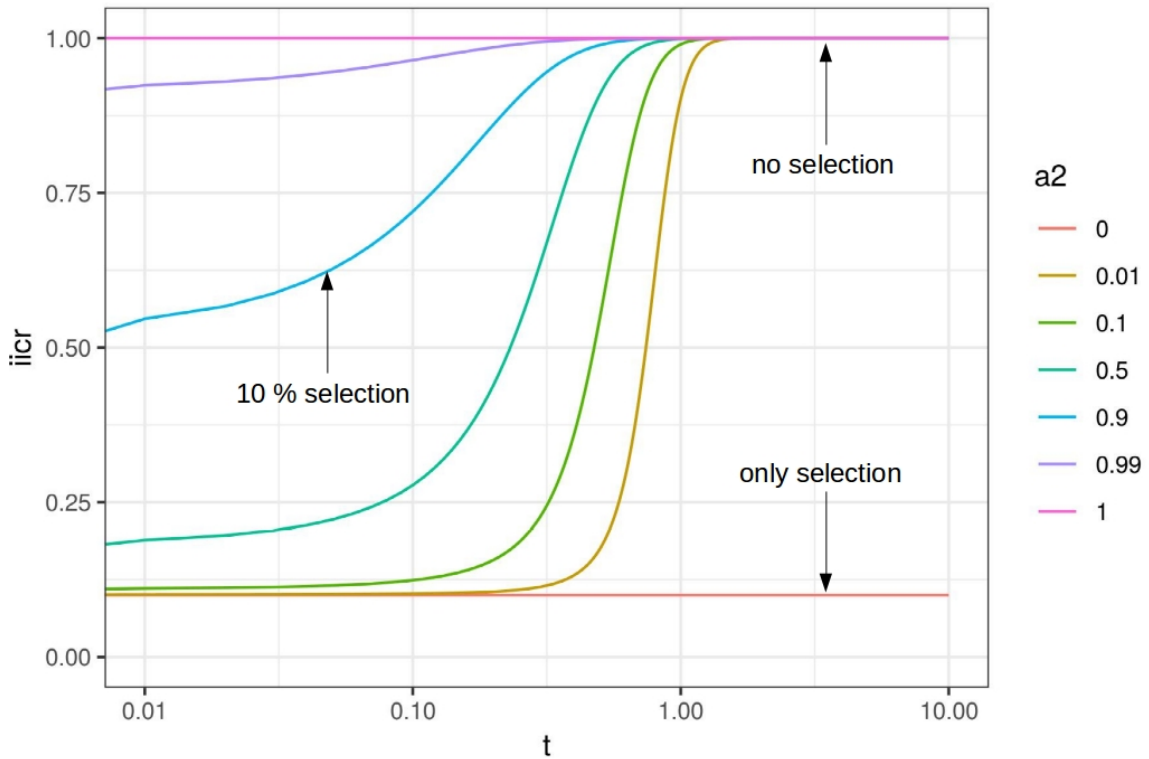
$$IICR(t) = -\frac{1 - F(t)}{f(t)} = \frac{\sum_{i=1}^{K} a_i e^{-\mu_i t}}{\sum_{i=1}^{K} a_i \mu_i e^{-\mu_i t}}.$$

Mathematical properties

- $IICR(t)$ increasing (backward in time)
  $\rightarrow$ 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

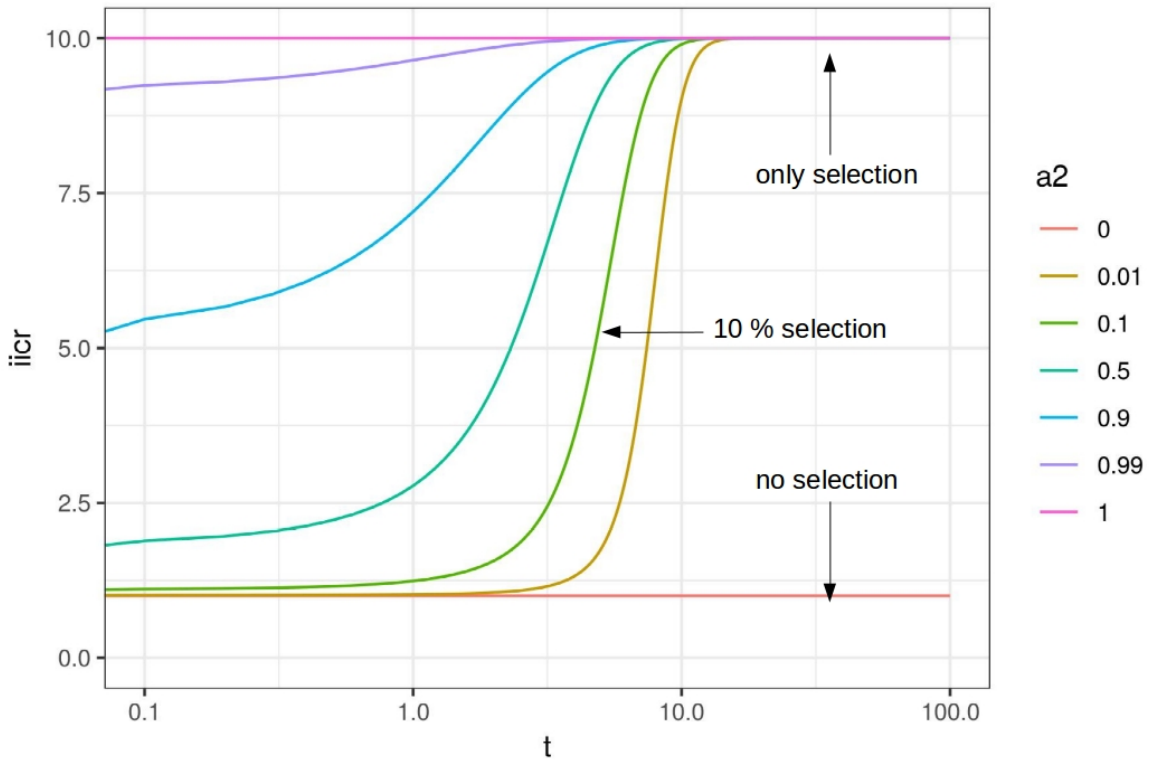
- $\lambda_1 = 0.1$ (BGS/SW), $\lambda_2 = 1$ (neutral).



$\rightarrow$ **BGS/SW** impact **recent past** IICR.

Two classes of N_e

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



$\rightarrow$ **BalS** impacts intermediate to **ancient past** IICR, even if in **small proportion**.

More complex models

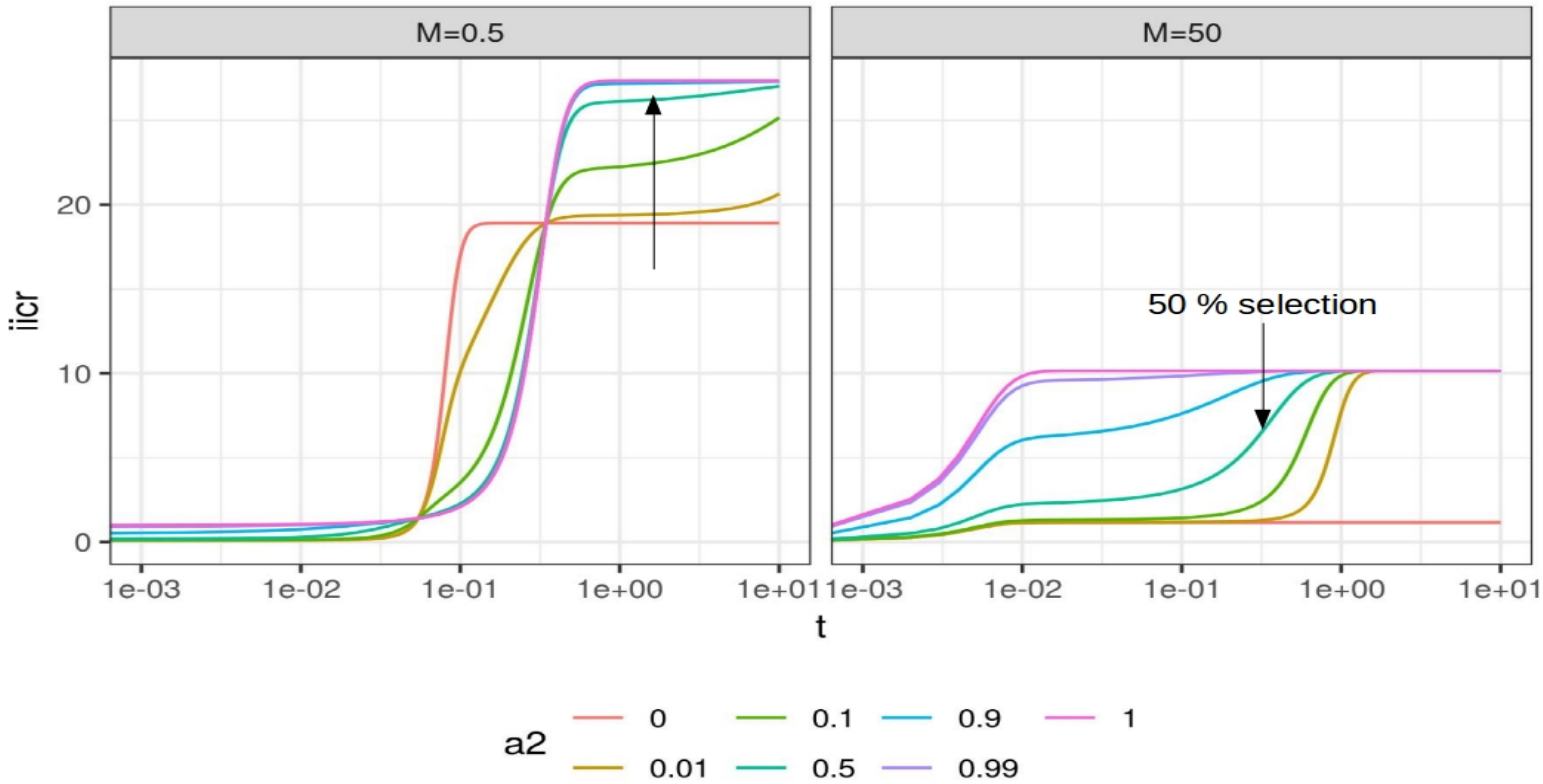
$$IICR(t) = \frac{\sum_{i=1}^{K} a_i(1 - F_i(t))}{\sum_{i=1}^{K} a_i f_i(t)}$$

$f_i()$ pdf of T_2.

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

Example 1: stationary n island model

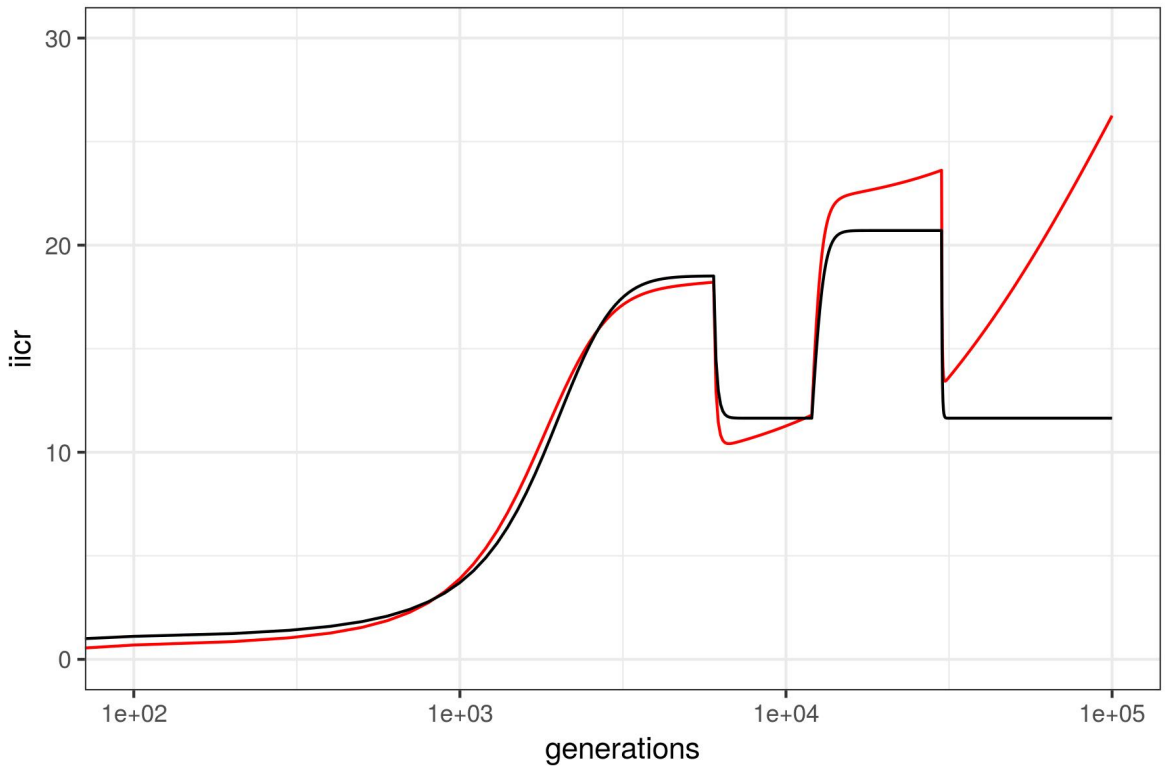
- $n = 10$ islands, two classes: $\lambda_1 = 0.1$, $\lambda_2 = 1$.



→ **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).
- $+ \lambda$ distribution estimated by Gossmann *et al* (2011) (red).



$\rightarrow$ **Main effect** of selection in the **ancient past**.

Main conclusions

- 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 strucure**.
- Ref: Genetics, 220(3), iyac008.

Perspectives

- **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 ...

Advertizing

PhD positions in population genomics available in september 2022.

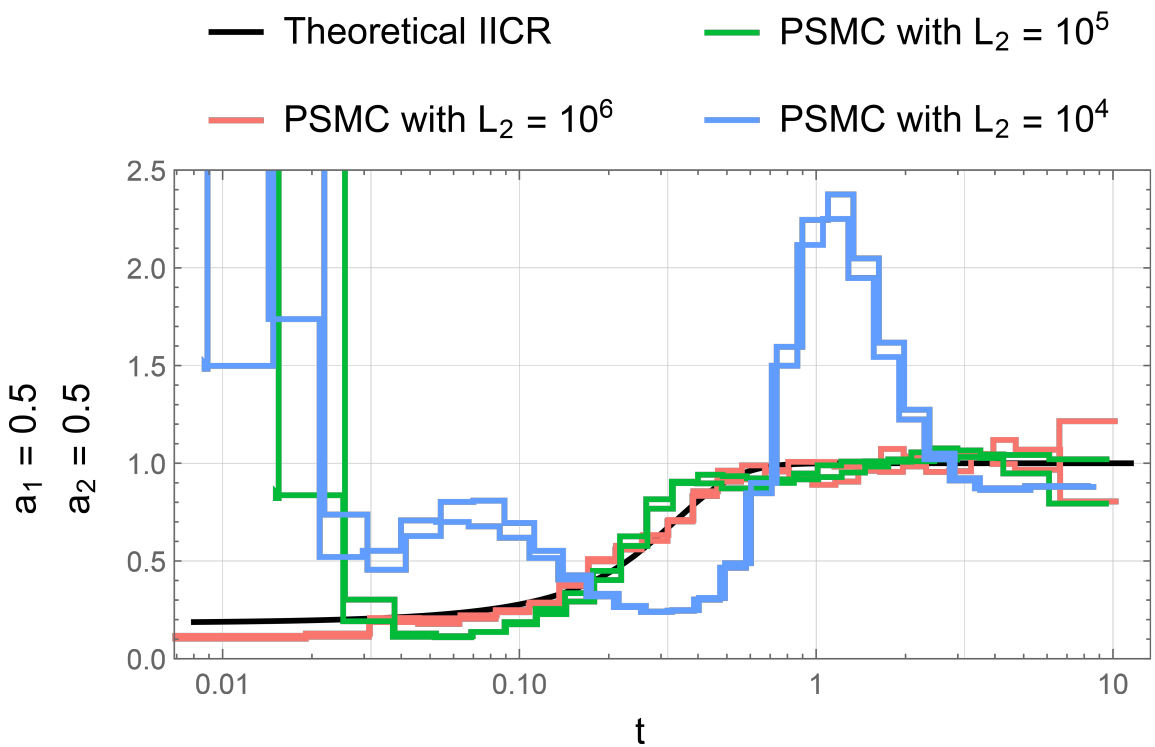
- Inference in spatial models.
- Inference from genomic time series.
- Genomic offset.

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 . . .).

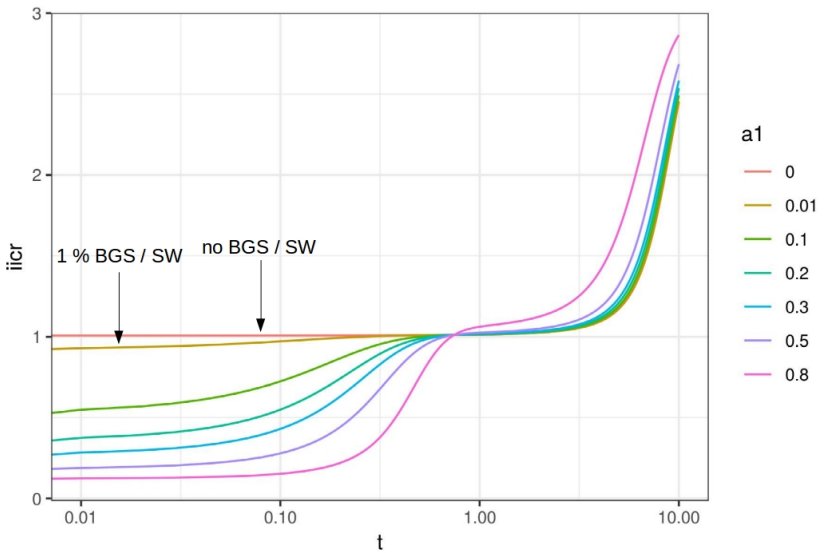


$\rightarrow$ consistent for **large scale N_e variartions**.

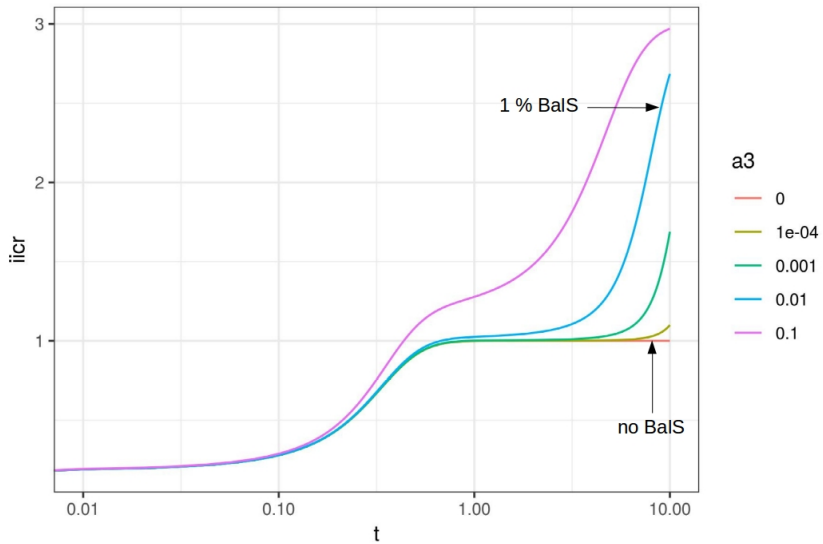
Three classes of N_e

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

$a_3 = 0.01$



$a_1 = 0.5$

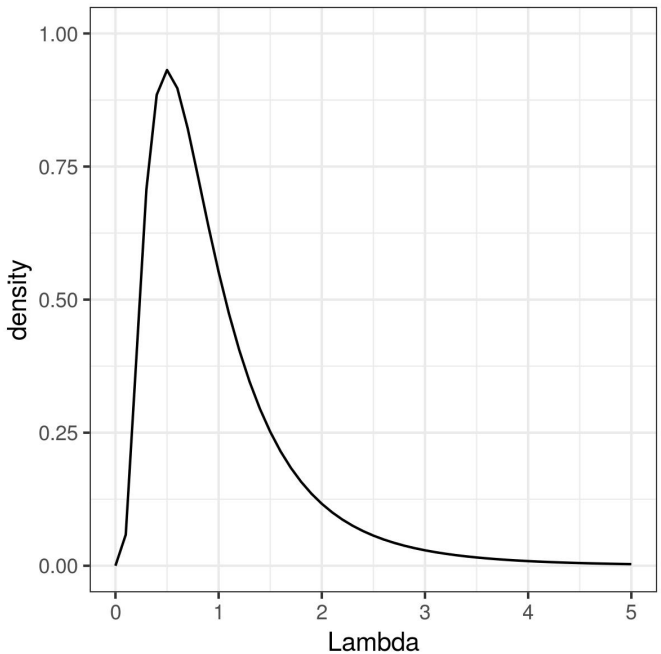


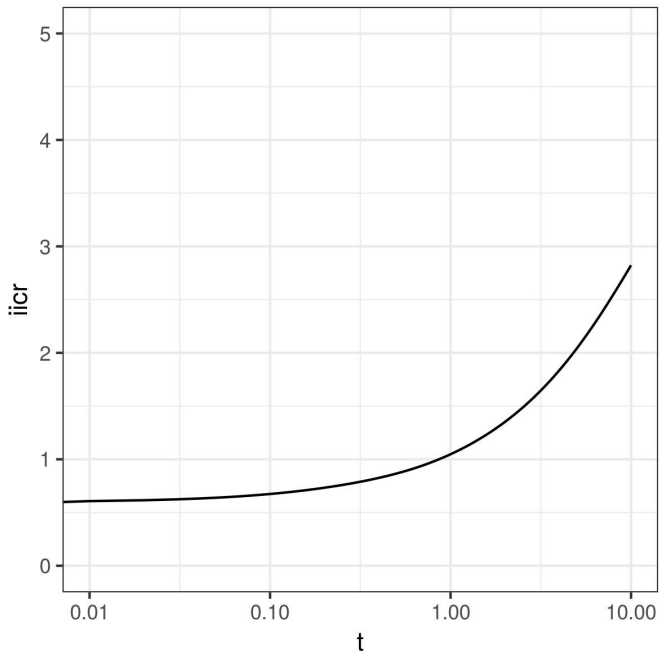
$\rightarrow$ stronger effect of BalS vs BGS/sweeps for the same proportion.

$\rightarrow$ 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.





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