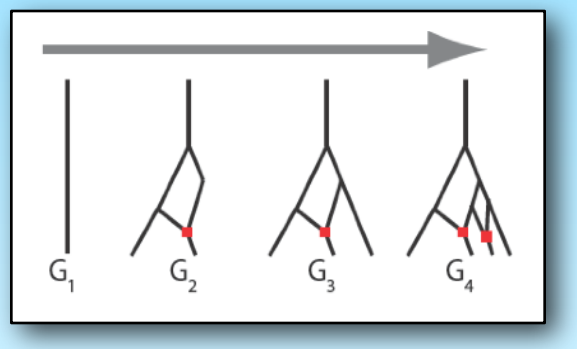
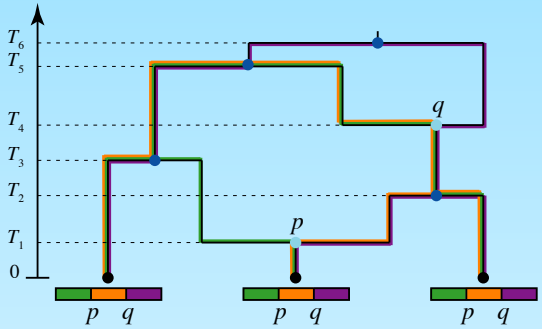
ARGweaver: Genome-wide Inference of Ancestral Recombination Graphs





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Cold Spring Harbor Laboratory

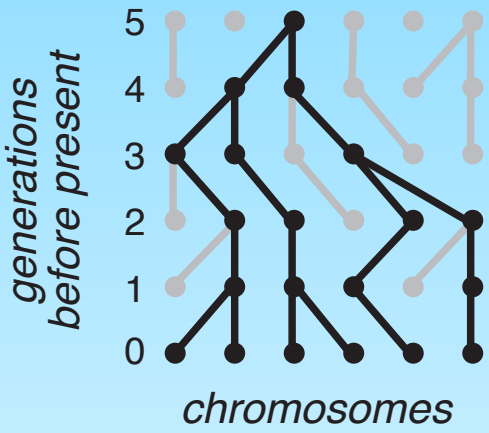
Joint work with Matthew Rasmussen, Melissa Hubisz, and Ilan Gronau

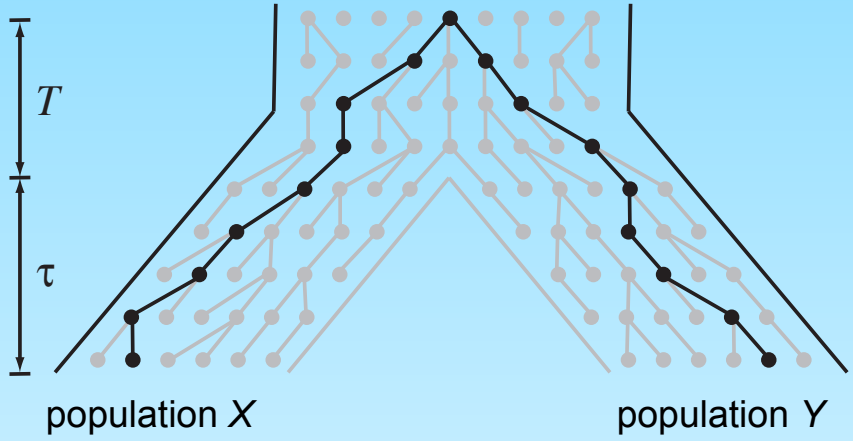
Cold Spring Harbor Laboratory

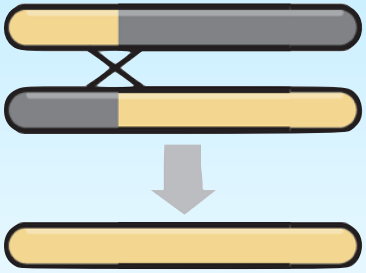
Simons Center for Quantitative Biology

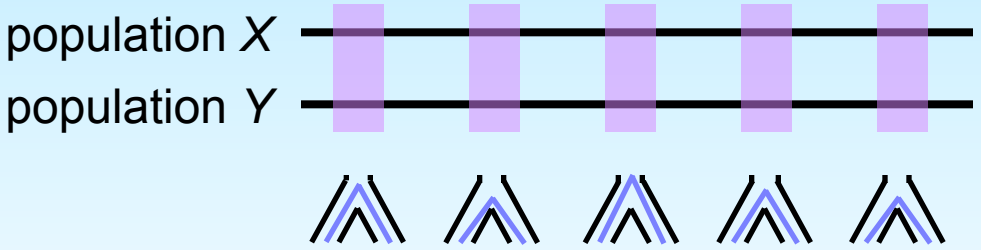
- Broad focus on theoretical and applied quantitative biology, including genomics, evolution, biophysics, cancer and neuroscience
- Founding $50M donation from Simons Foundation plus other gifts
- Ten current faculty members trained in physics, applied mathematics, and computer science
- Positions available at assistant professor, fellow, and postdoc levels

Recombination and Genealogies

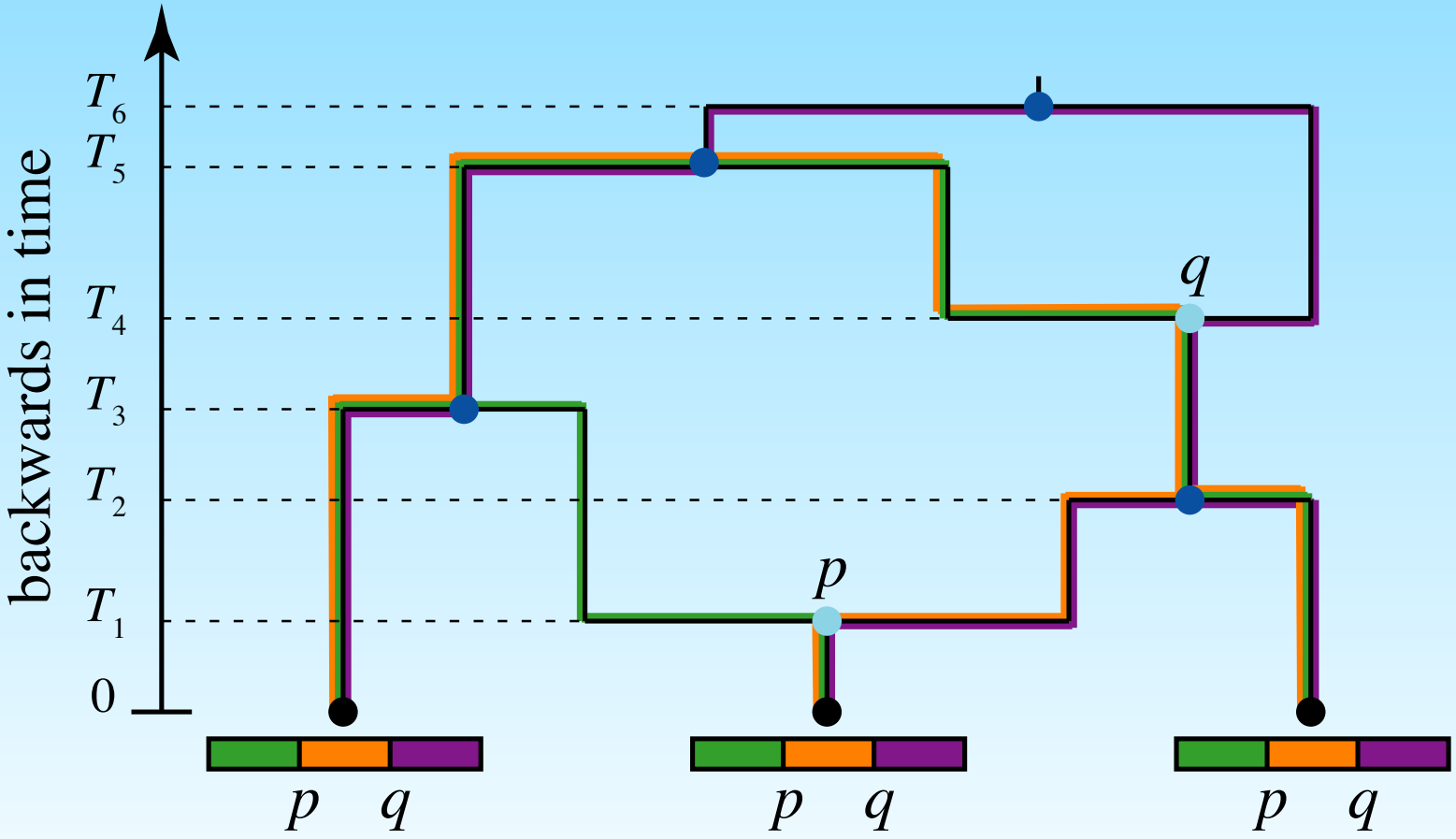








The Ancestral Recombination Graph



Griffiths and Marjoram, *J. Comput. Biol.*, 1996

Alas, if only we knew the ARG…

- Demography inference
- Inference of natural selection
- Recombination rate estimation
- Phasing/imputation
- Association mapping
- …

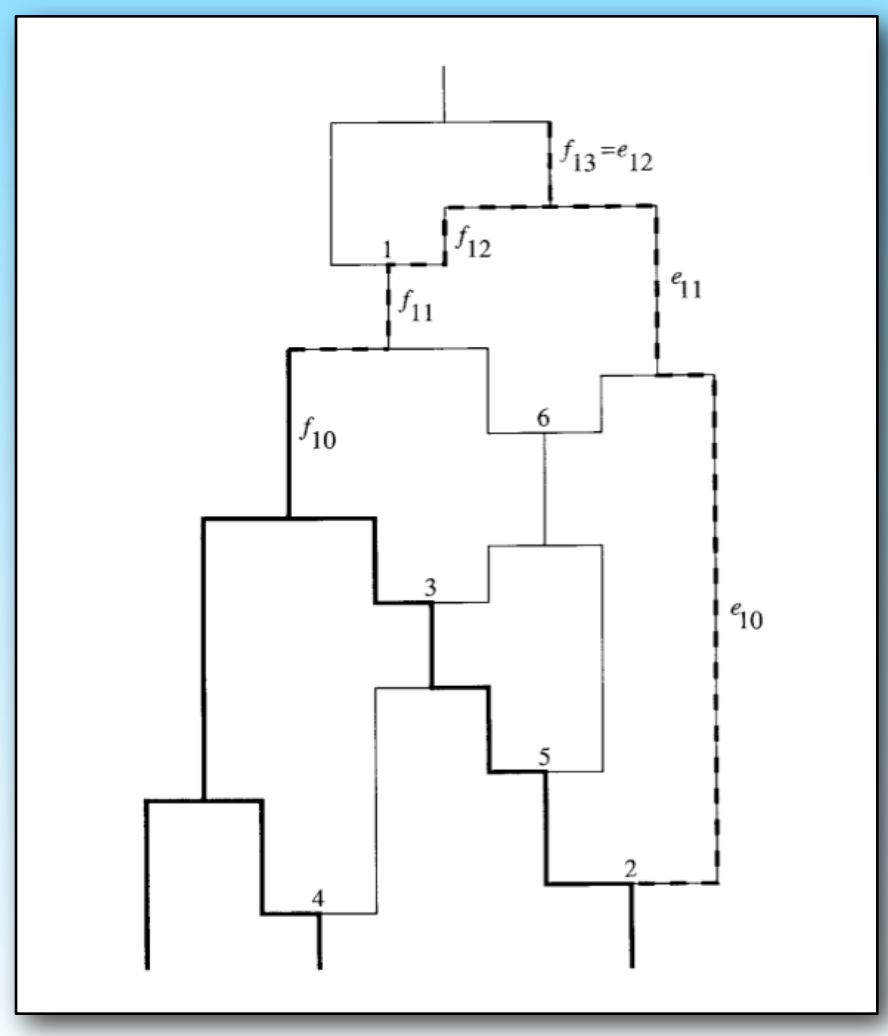
ARG surrogates: IBD, IBS, haplotypes, local ancestry inference, site-frequency spectrum, PCA

Explicit ARG Inference

- **Importance sampling**
  - Griffiths and Marjoram, *J. Comput. Biol.*, 1996
  - Fearnhead and Donnelly, *Genetics*, 2001
- **Markov chain Monte Carlo sampling**
  - Kuhner, Yumato, and Felsenstein, *Genetics*, 2000
  - Nielsen, *Genetics*, 2000
- **Heuristics/Parsimony**
  - Hein, *J. Mol. Evol.*, 1990
  - Kececioglu and Gusfield, *Disc. Appl. Math.*, 1998
  - Song and Hein, *J. Comput. Biol.*, 2005
  - Minichiello and Durbin, *Am. J. Hum. Genet.*, 2006

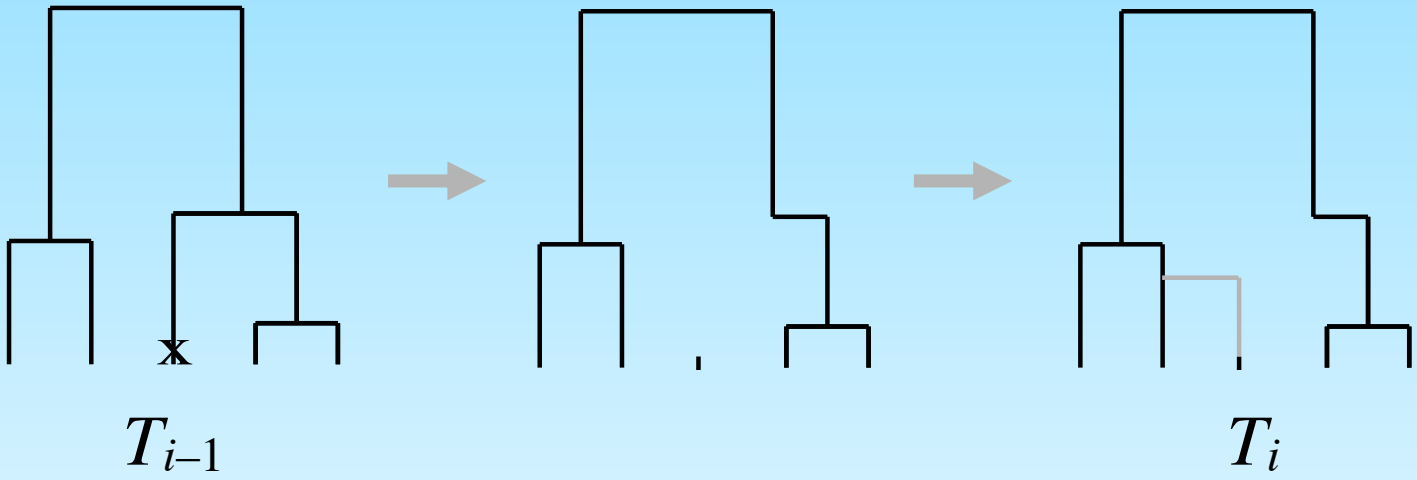
Computationally intensive
Limited to few samples
and/or
Depend on crude approximations

Sequential Coalescent with Recombination



Wiuf and Hein, *Theor. Popul. Biol.*, 1999

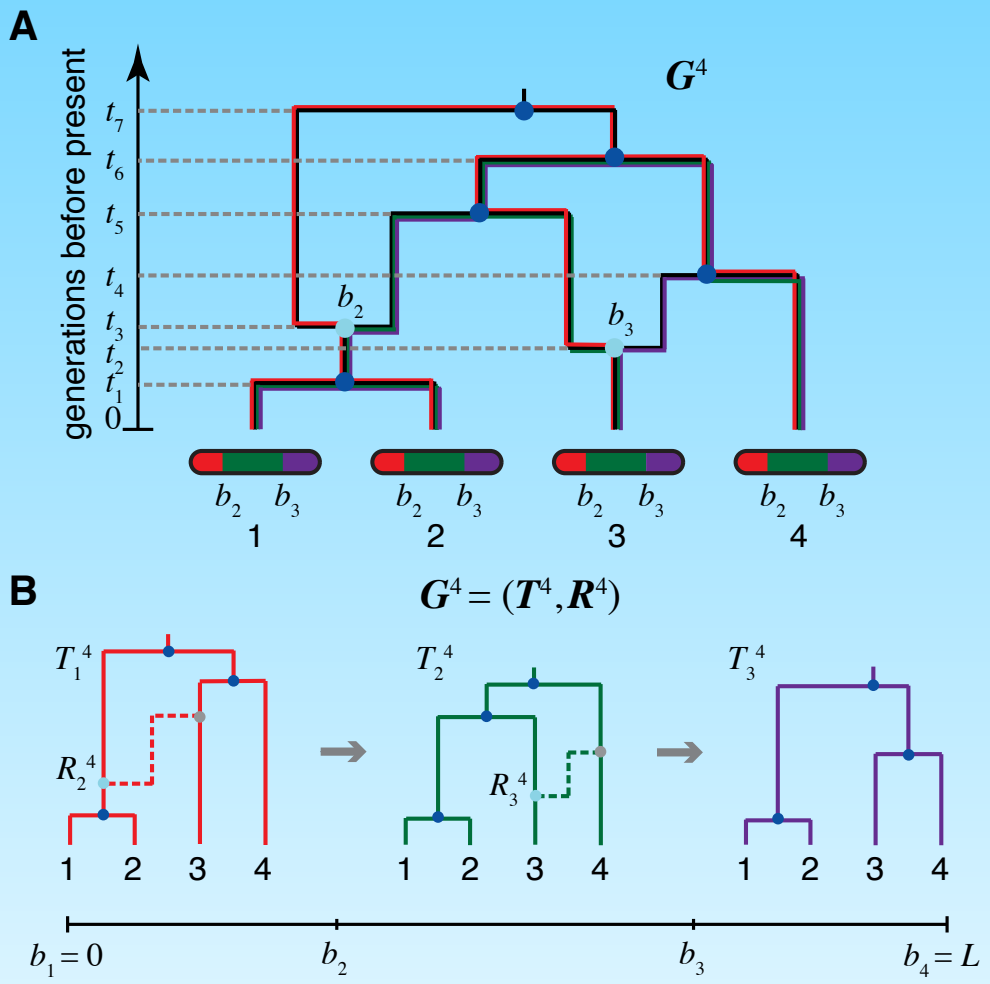
Sequentially Markov Coalescent (SMC)



$$P(T_i \mid T_1, \ldots, T_{i-1}) = P(T_i \mid T_{i-1})$$

$$T_{i-1} \perp T_{i+1} \mid T_i$$

McVean and Cardin, 2005; Marjoram and Wall, 2006

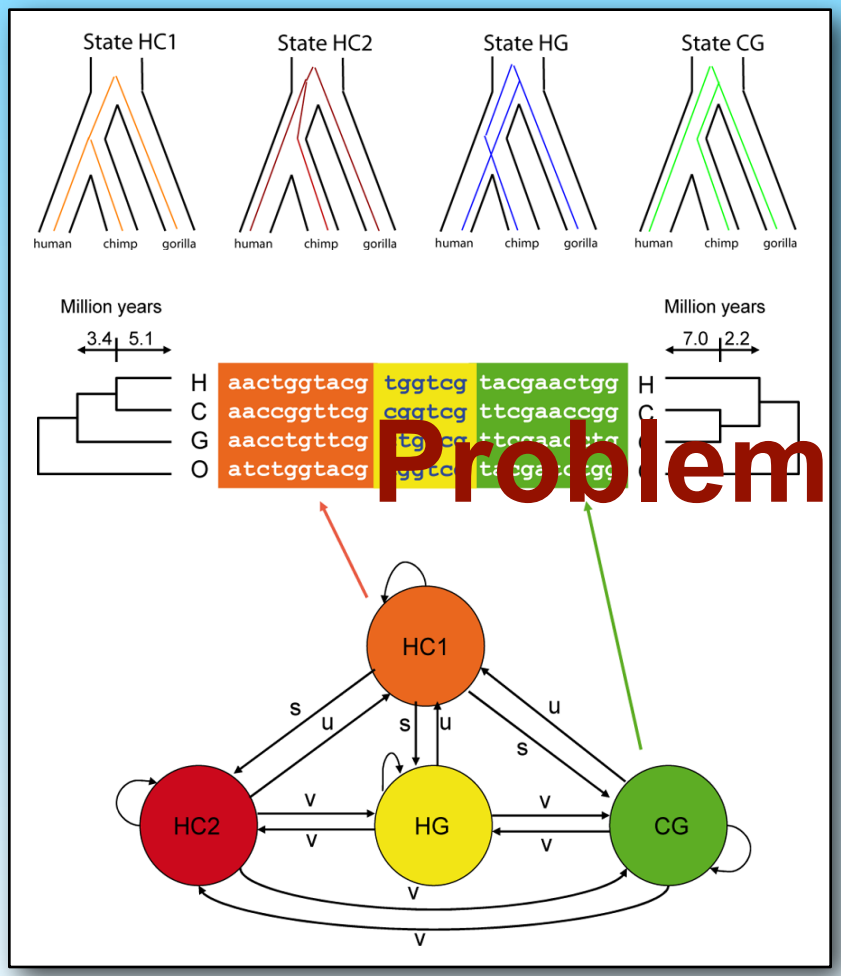


Rasmussen et al., *PLOS Genetics*, 2014

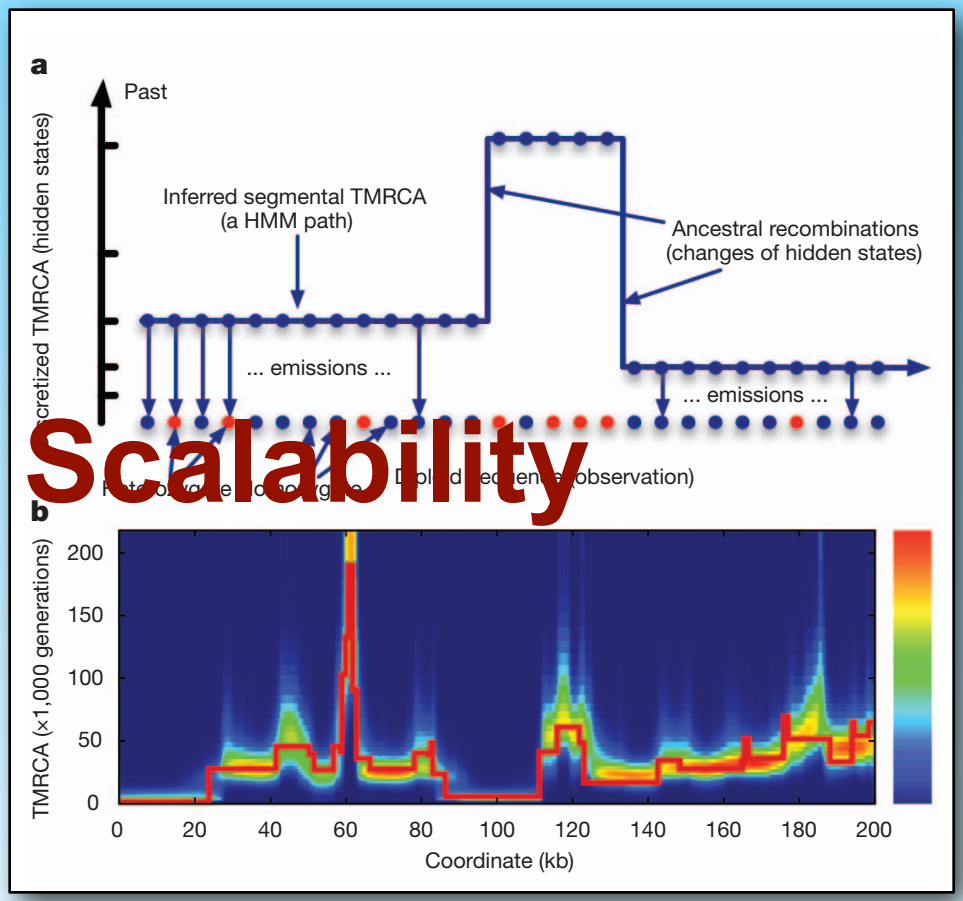
Discretized SMC and Hidden Markov Models

- By ***discretizing*** time and ***enumerating topologies***, the continuous state space of the SMC can be approximated by a finite set
- This opens up the possibility of using ***hidden Markov models*** (HMM) for inference
- Standard dynamic-programming algorithms for HMMs allow for ***exact ARG inference***, up to the SMC and discretization

Hidden Markov Models



Coal-HMM



PSMC

Problem: Scalability

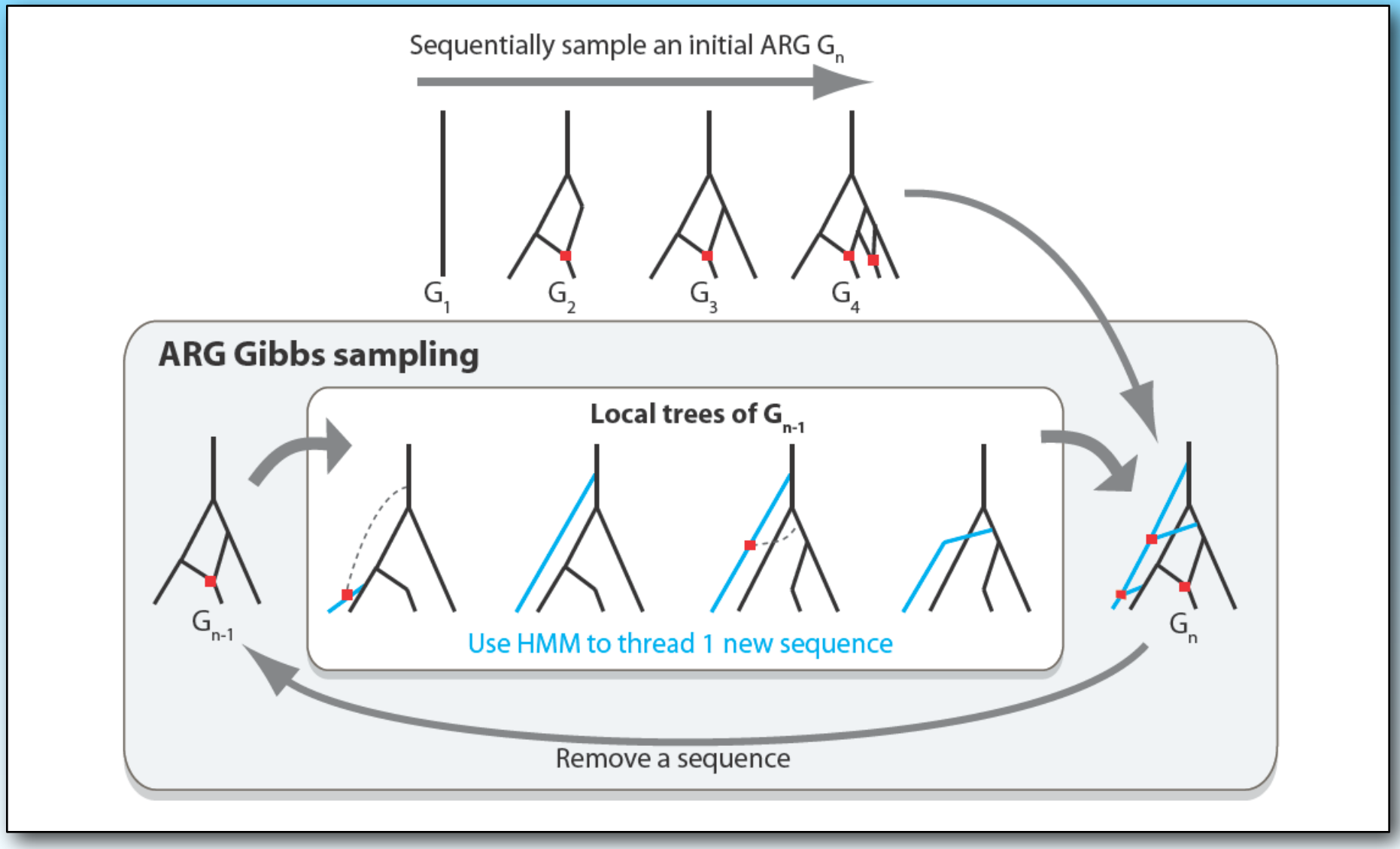
Hobolth et al., *PLOS Genet.*, 2007;
Li and Durbin, *Nature*, 2011

New Approach: Chromosome "Threading"

- Start with a data set of n sequences, D, and an ARG for n–1 of them, G_{n-1}
- Extend G_{n-1} to represent evolutionary history of n th sequence, obtaining G_n
- Sample this extension in a manner consistent with the conditional distribution, $P(G_n \mid G_{n-1}, D, \Theta)$, under the DSMC
- In repeated applications this operation is the basis of an ***ARG sampling*** algorithm

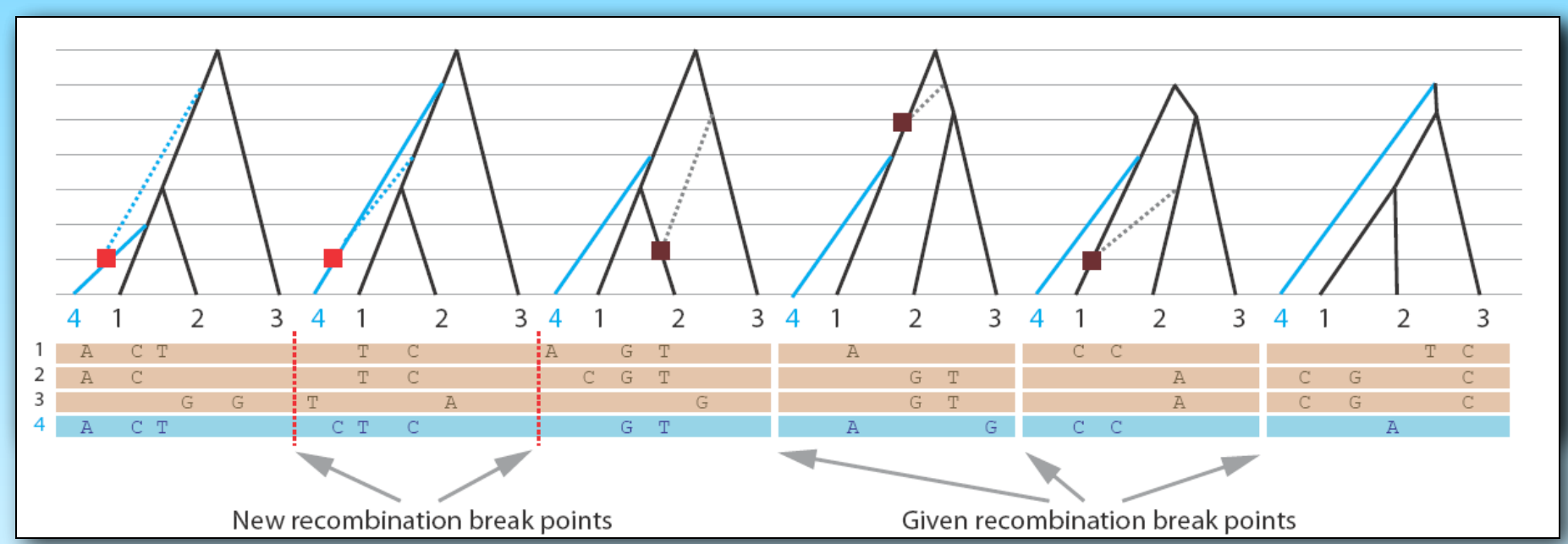
Rasmussen et al., *PLOS Genetics*, 2014

ARGweaver Sampling



Rasmussen et al., *PLOS Genetics,* 2014

Threading



Solution: stochastic traceback with HMM

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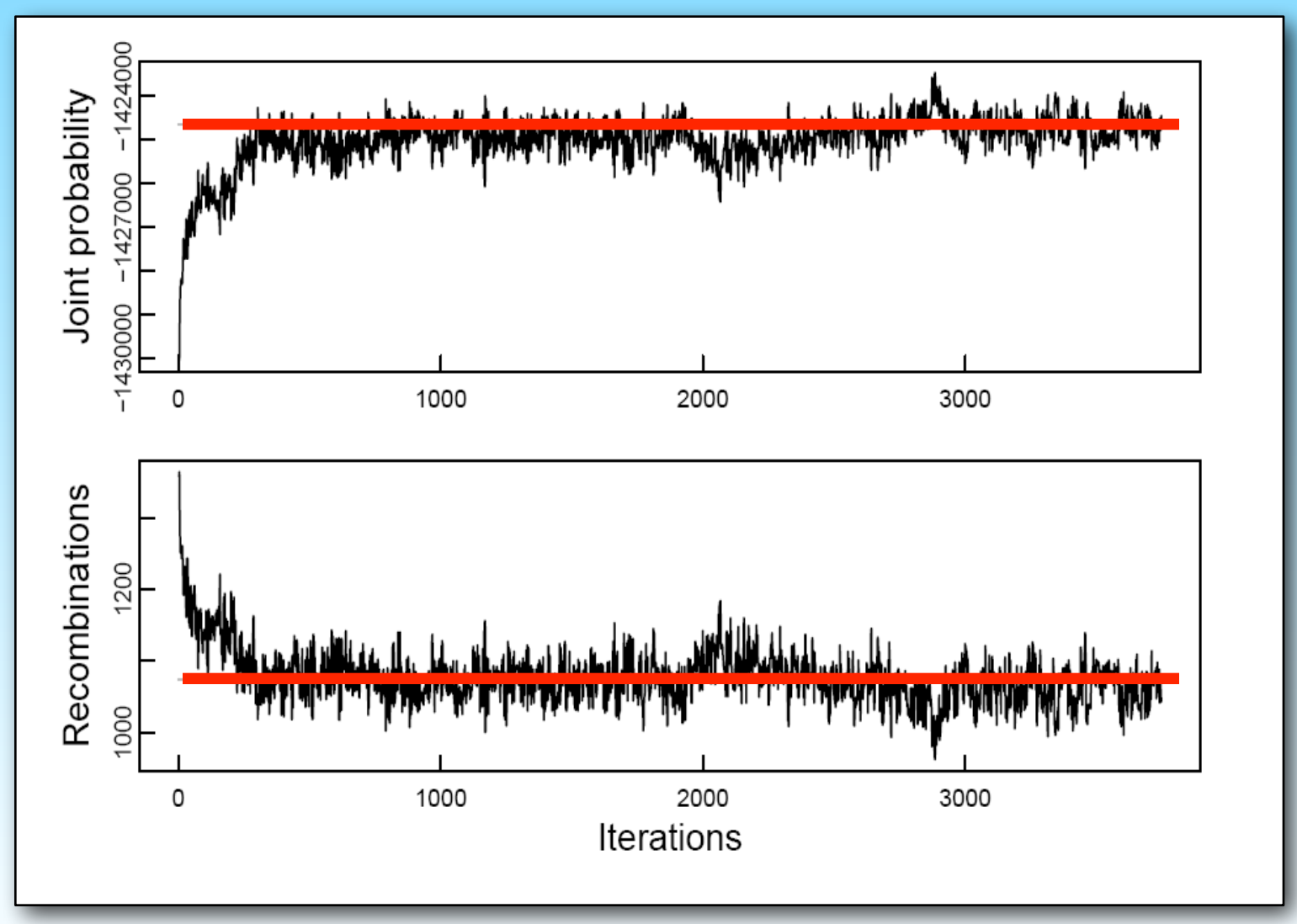
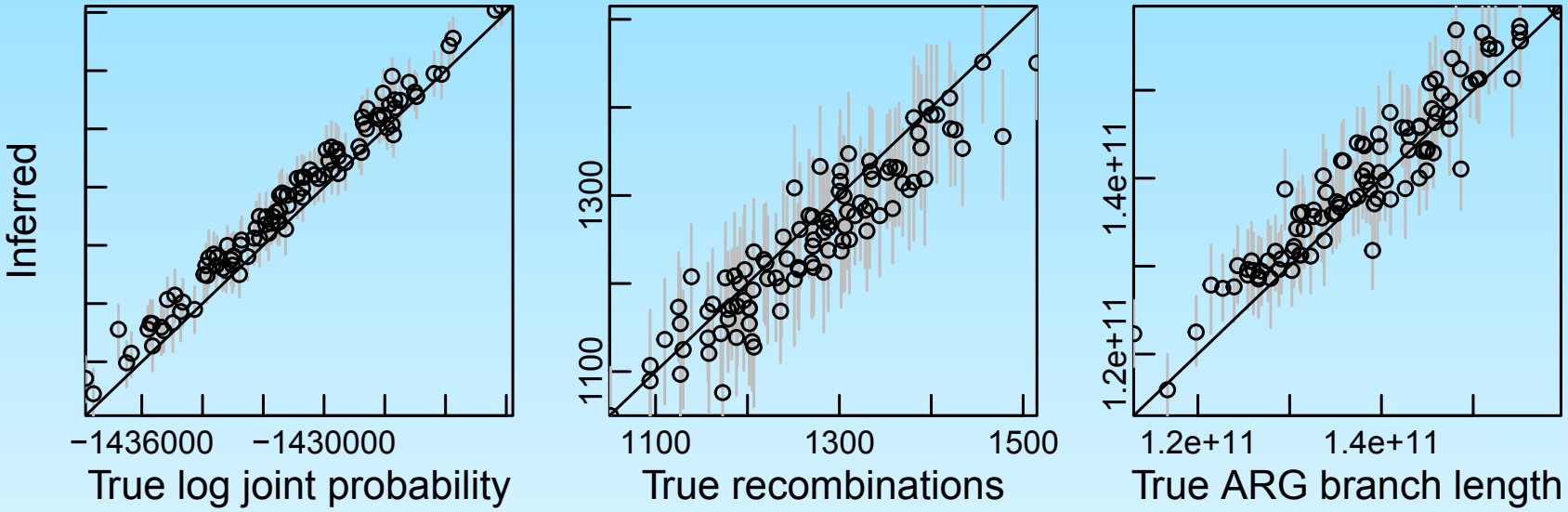
Rasmussen et al., *PLOS Genetics,* 2014

ARGweaver Converges Quickly



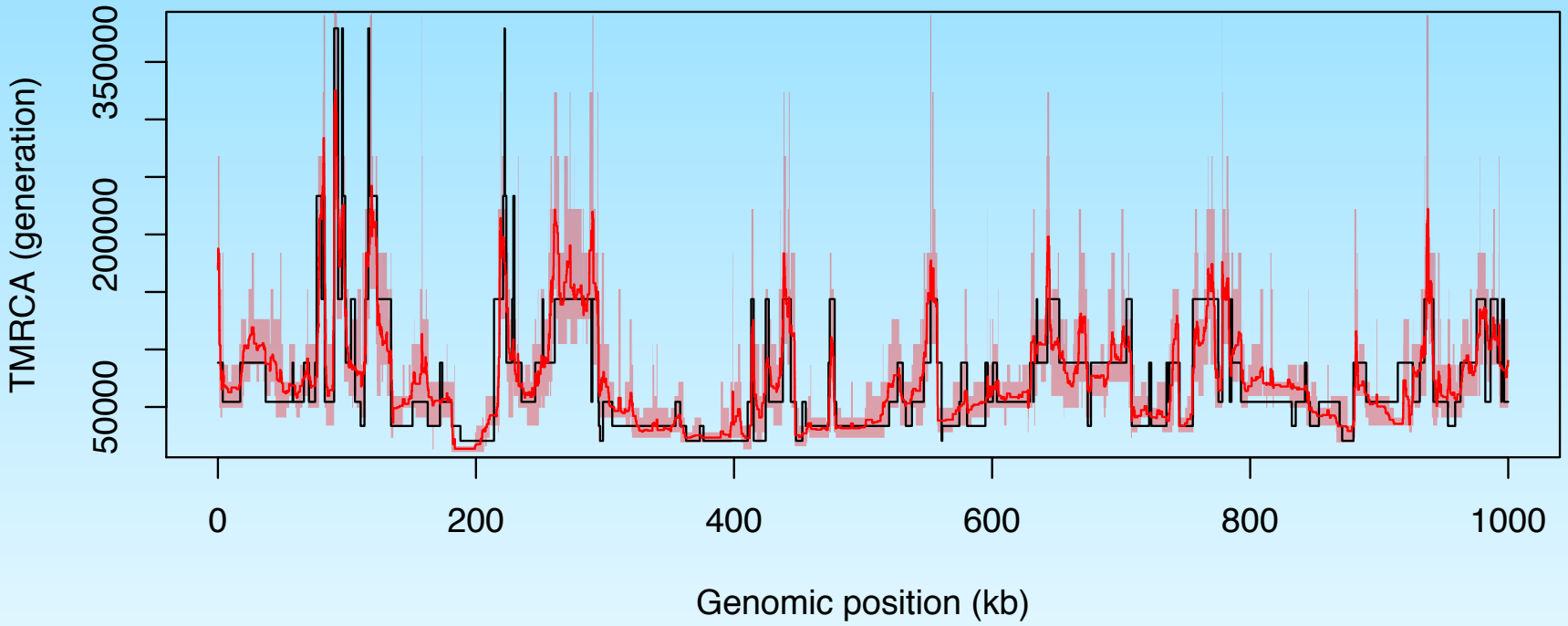
Rasmussen et al., *PLOS Genetics,* 2014

Recovery of Features of Simulated ARGs



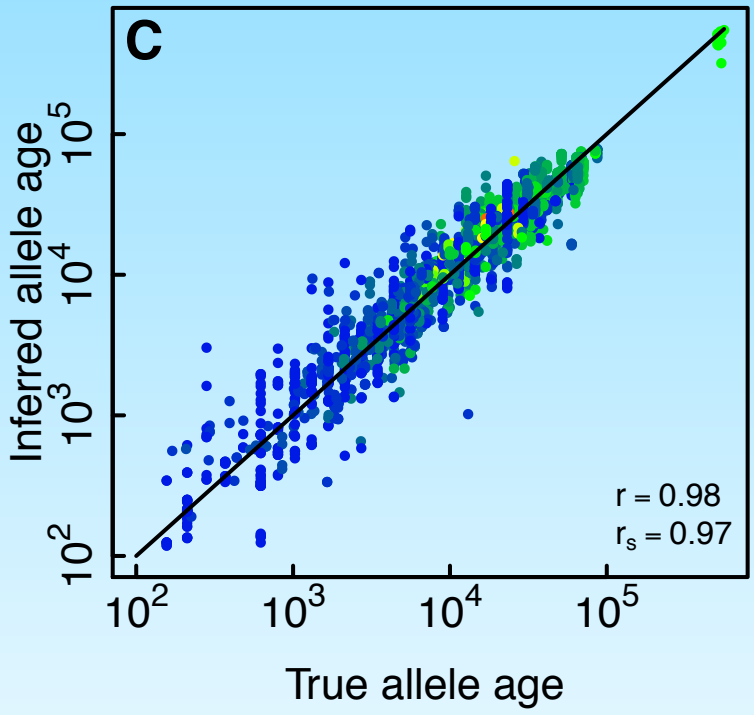
Rasmussen et al., *PLOS Genetics,* 2014

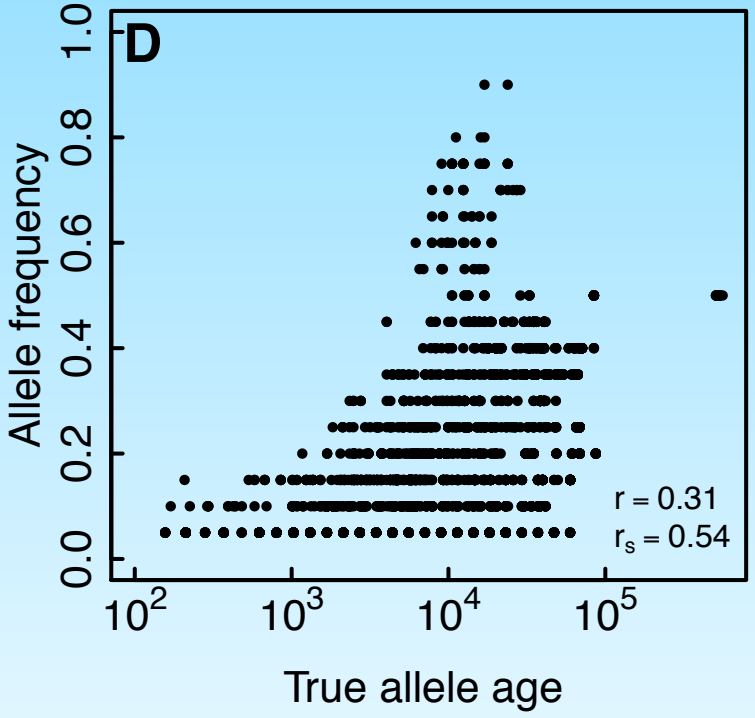
Recovery of Times to Most Recent Common Ancestry



Rasmussen et al., *PLOS Genetics,* 2014

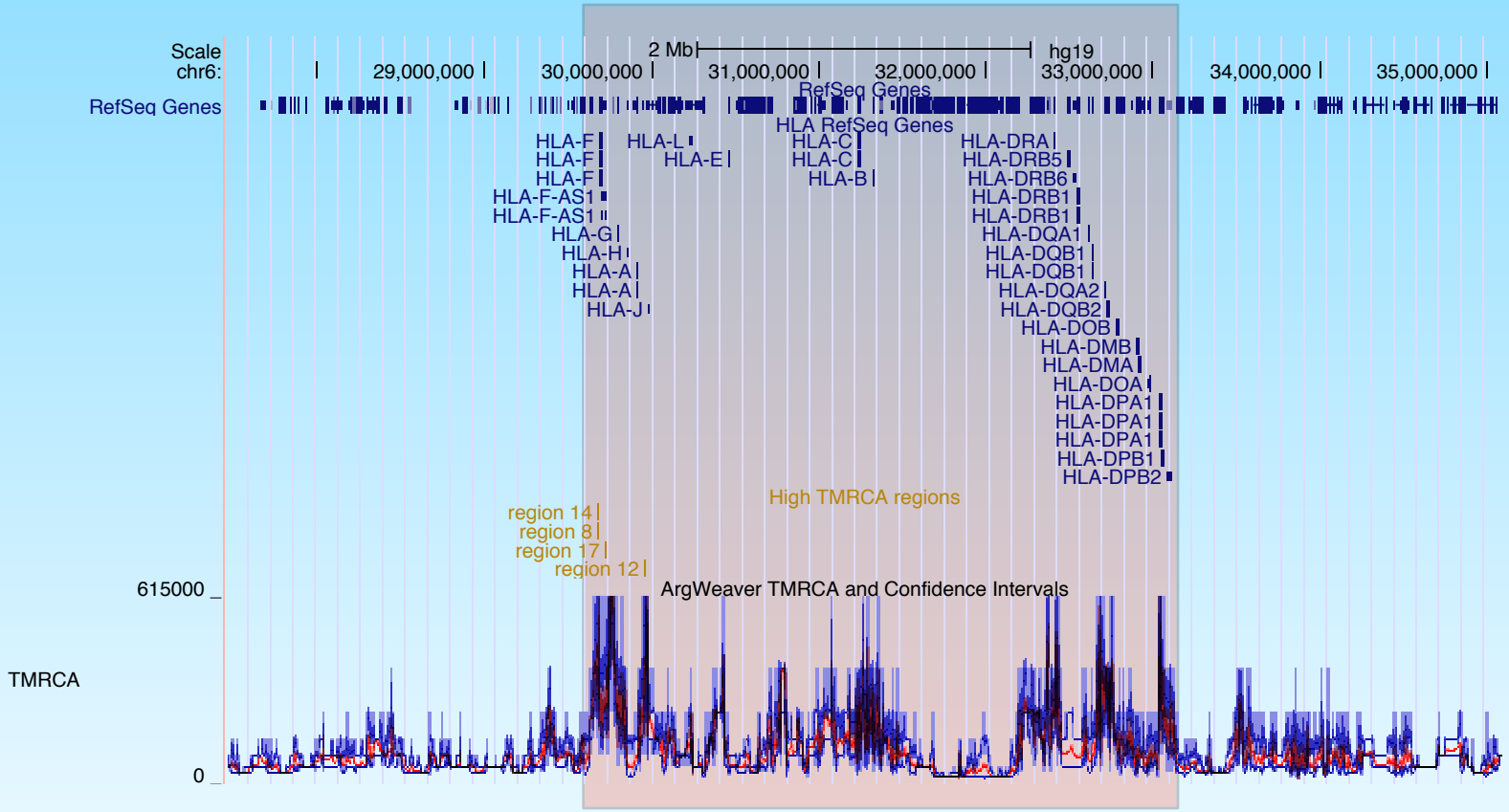
Recovery of Allele Age





Rasmussen et al., *PLOS Genetics,* 2014

Real Data: Regions of High TMRCA

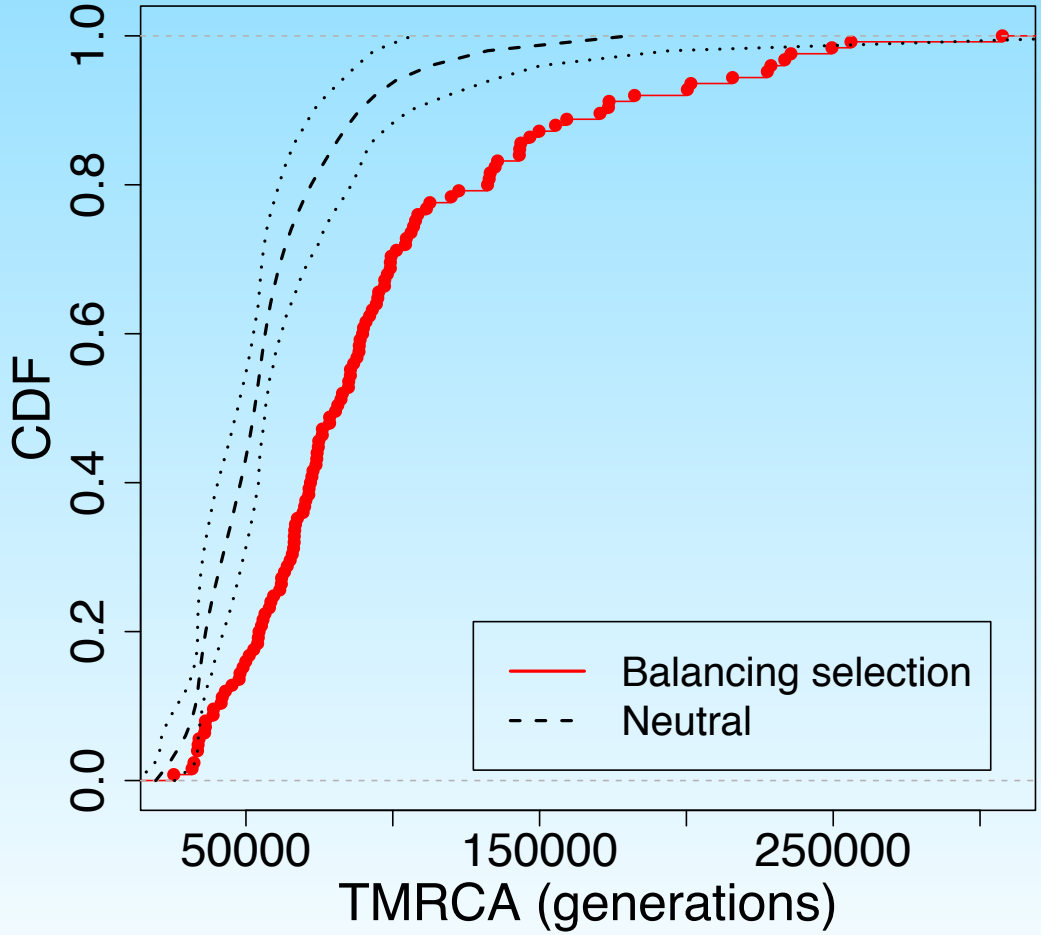


HLA Region

Cold Spring Harbor Laboratory

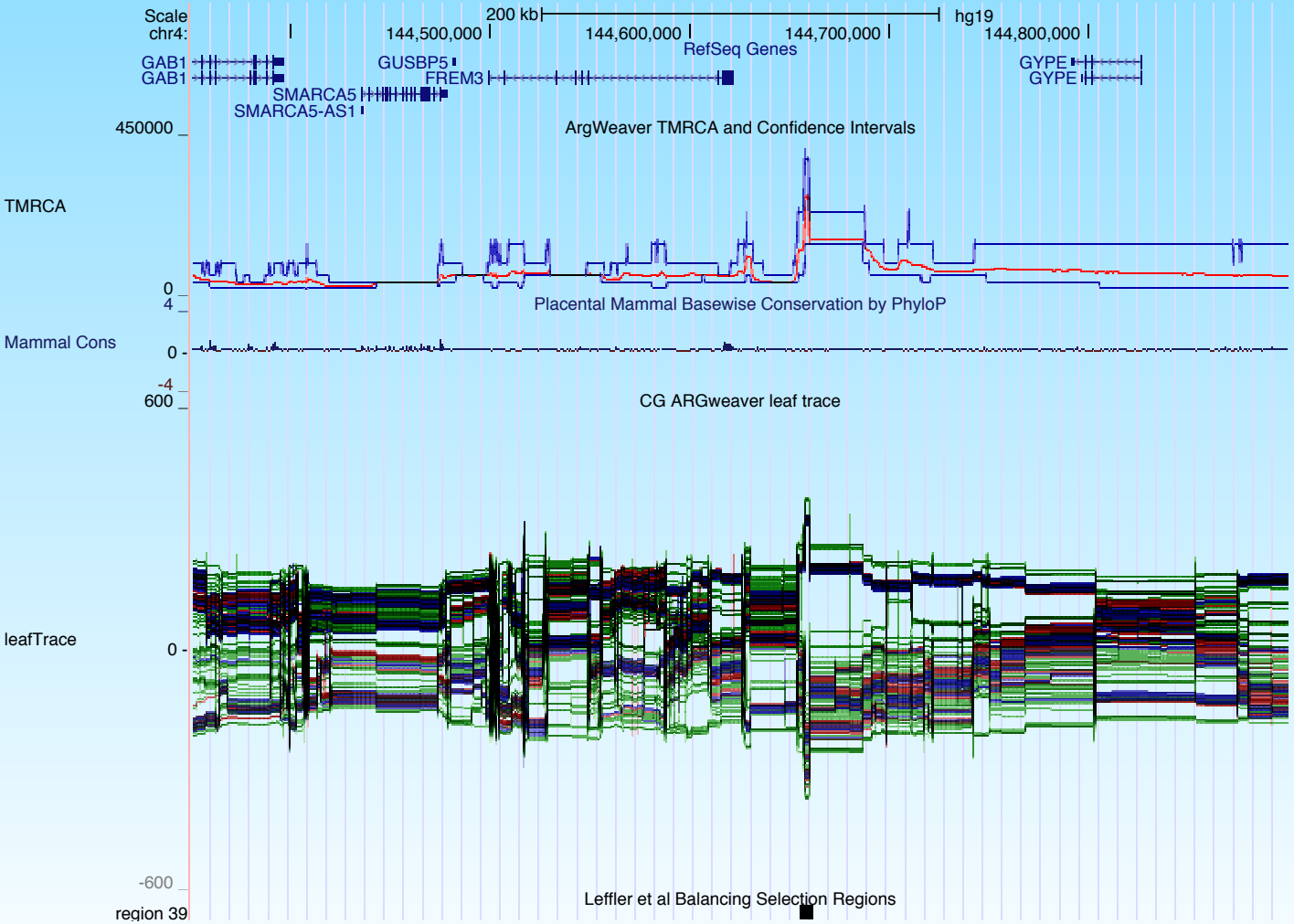
Rasmussen et al., *PLOS Genetics,* 2014

Regions of Shared Human/Chimp Polymorphism Have Old TMRCAs



Leffler et al., *Science*, 2013

Putative Balancing Selection at FREM3



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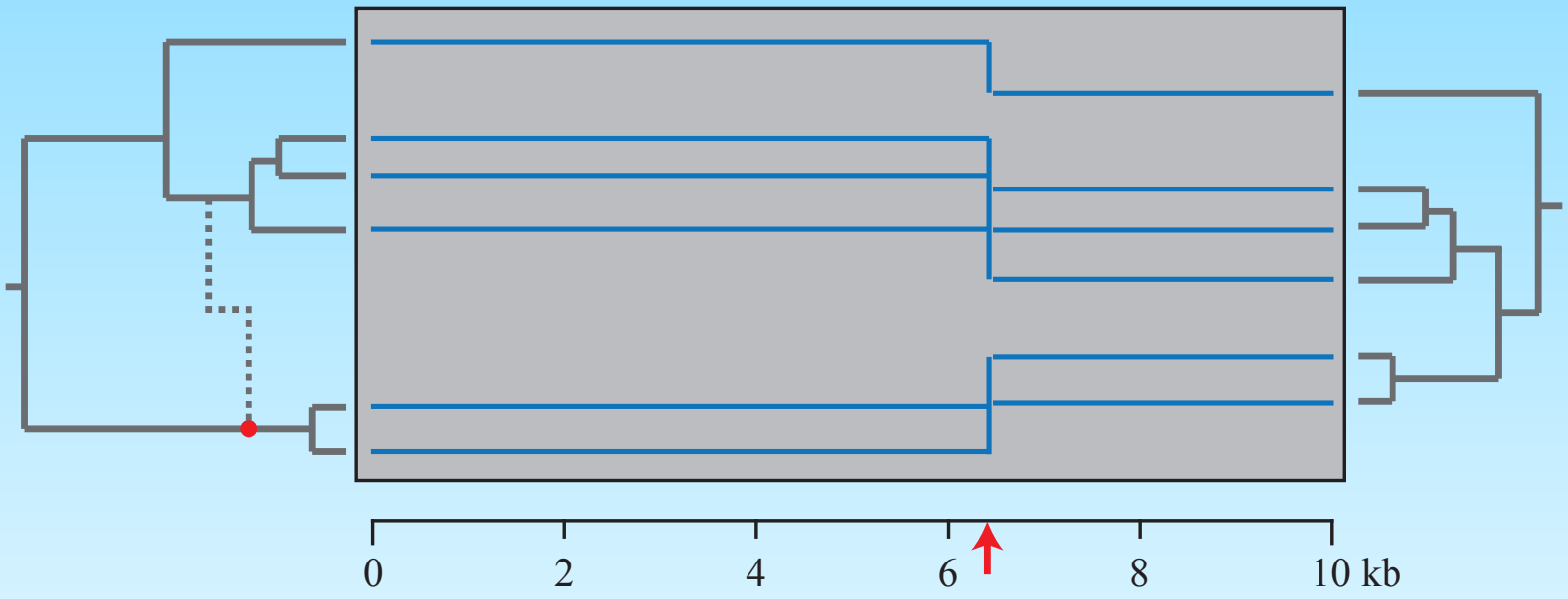
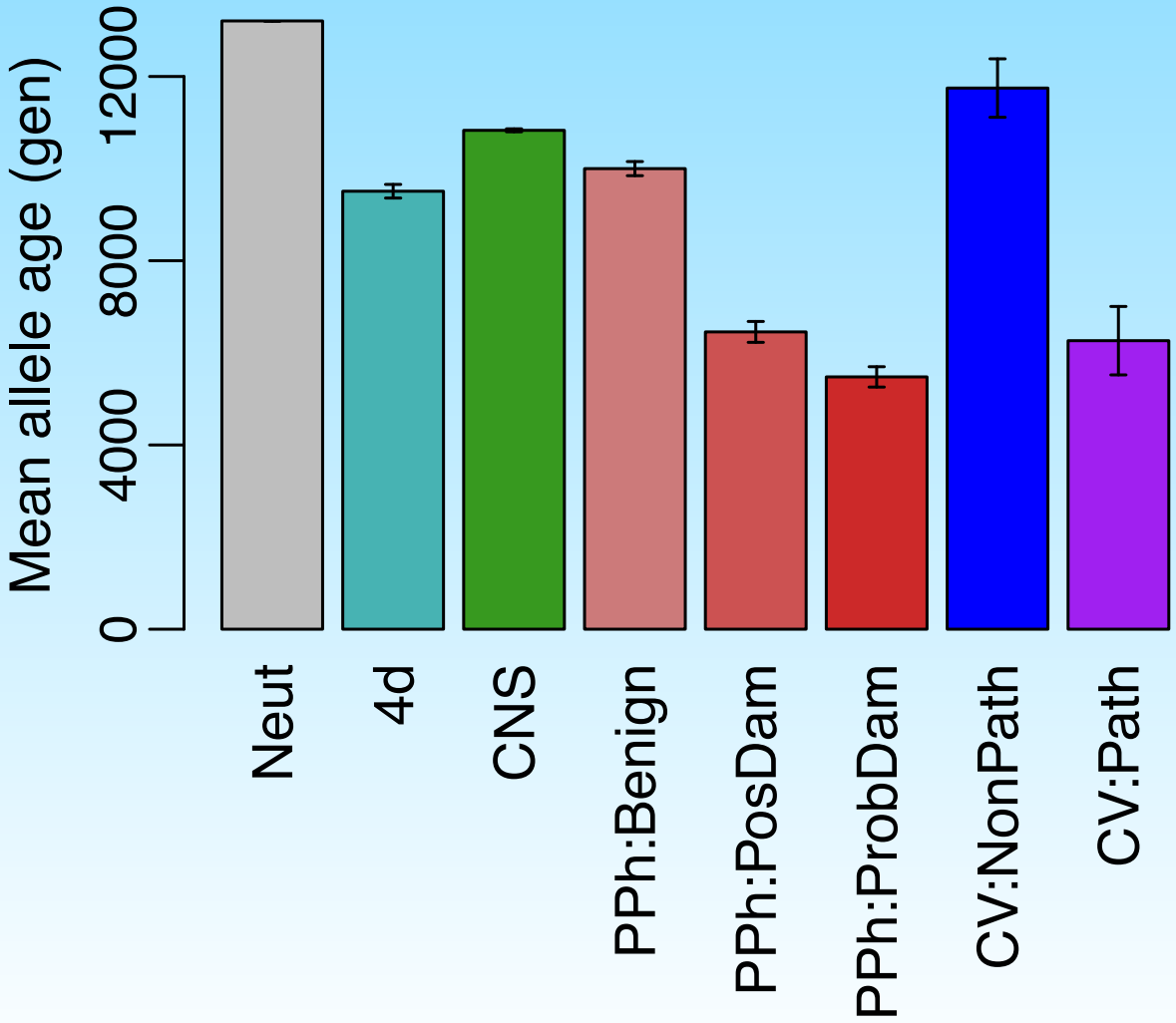
Leffler et al., *Science*, 2013

Leaf Trace

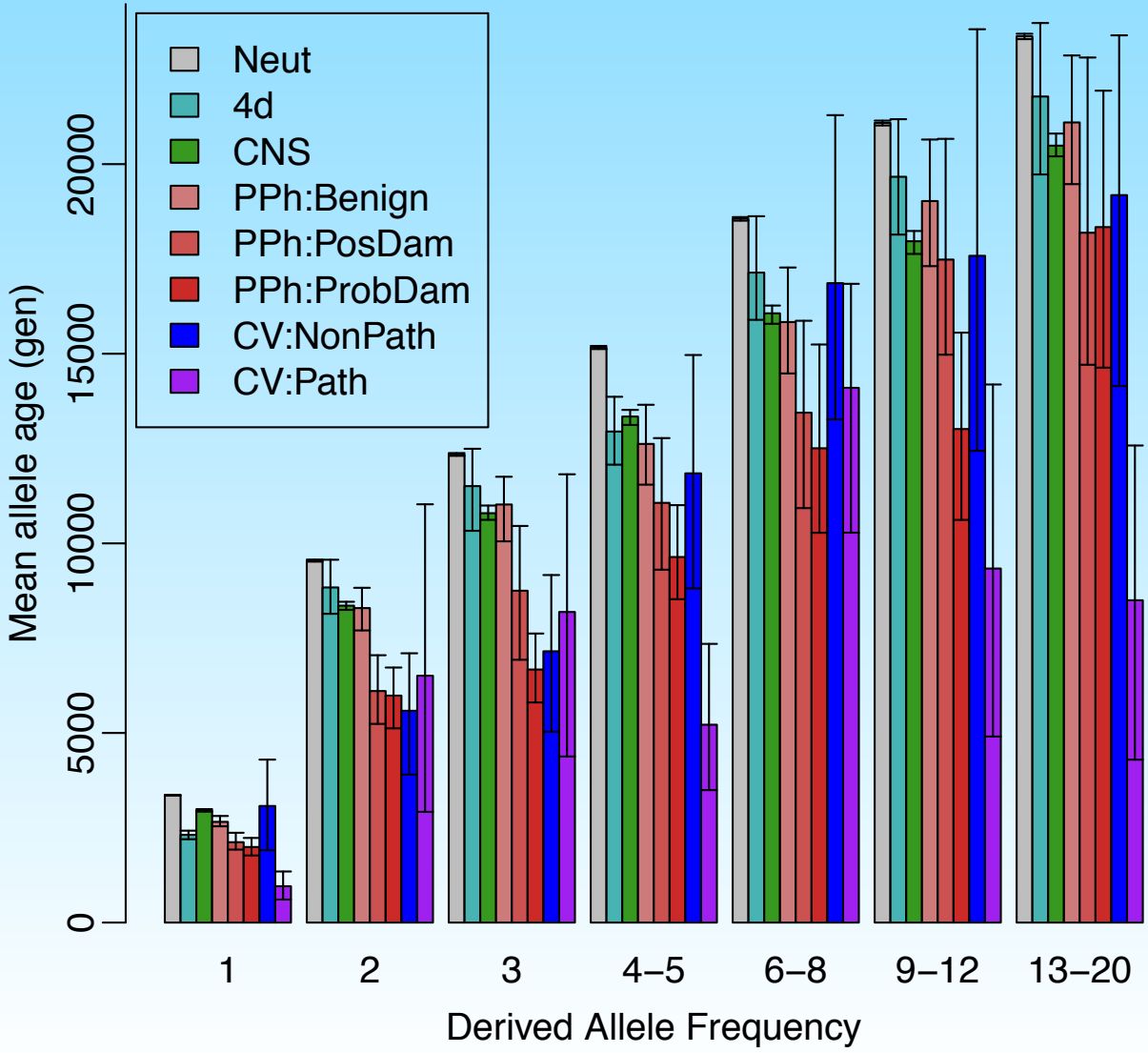


Rasmussen et al., *PLOS Genetics,* 2014

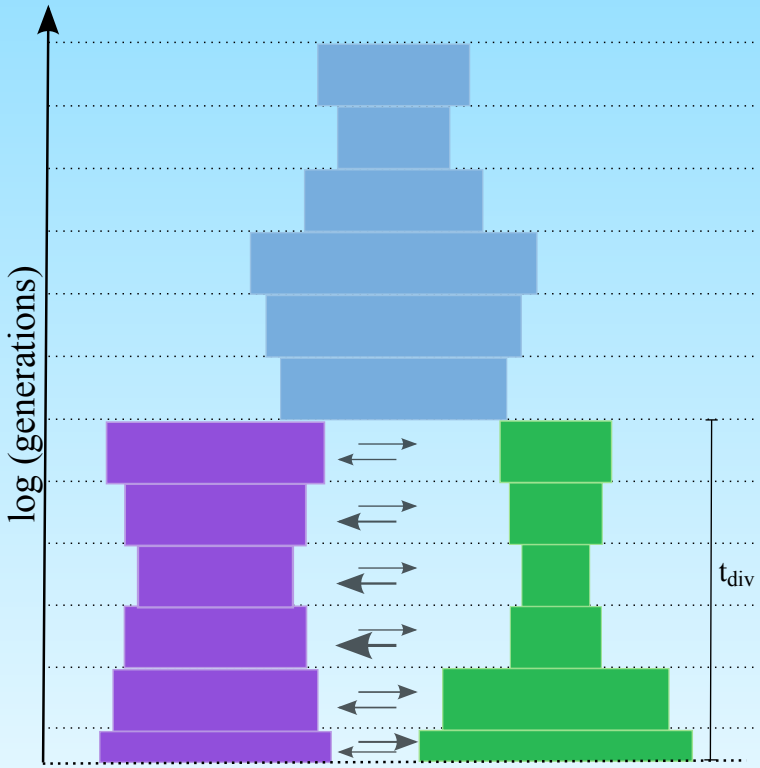
Sites Under Selection Have Decreased Allele Age

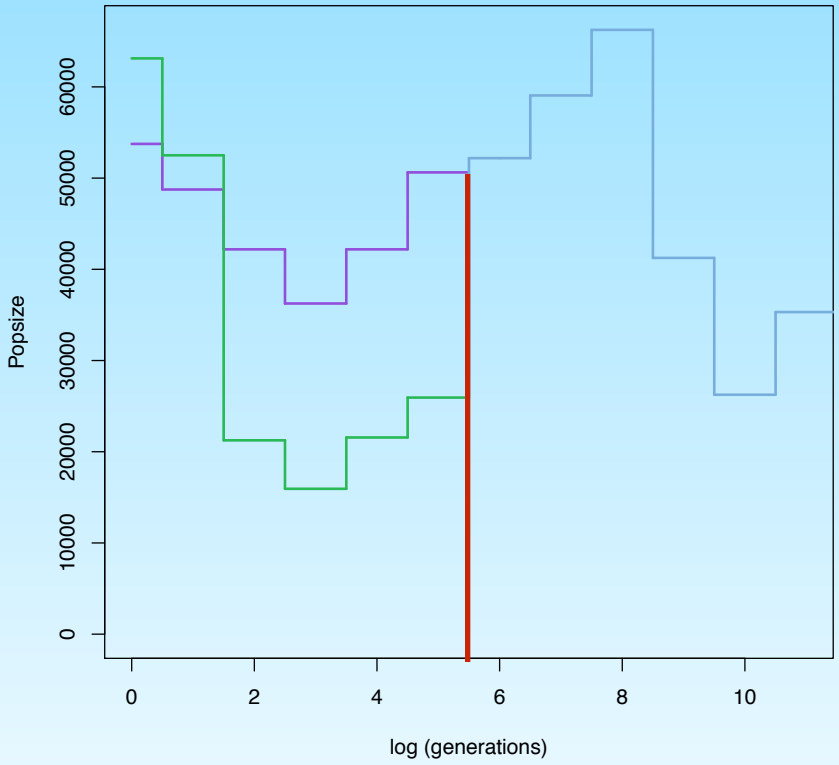


…Even After Accounting for Derived Allele Frequency



Current Work: IM + *ARGweaver*





Other Advances

- Joint phasing and threading—allows analysis of unphased genomes
- Clean-up of theory: rounding issues, “active branches”, etc.
- Watch for new paper from Melissa Hubisz

Acknowledgments

Contributors:, Matthew Rasmussen, Melissa Hubisz, Ilan Gronau

Other Group Members: Charles Danko, Andre Martins, Lenore Pipes, Brad Gulko, Jaaved Mohammed

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