Inferring the selective pressures acting on insertions and deletions in the great tit genome

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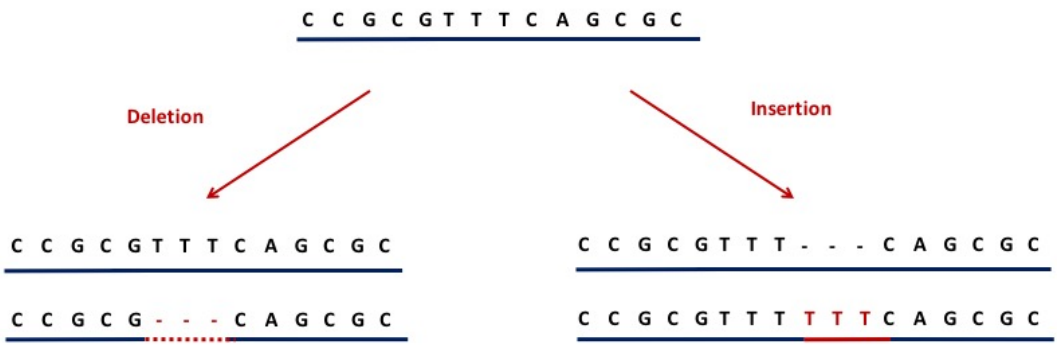
11/10/18

Introduction

Insertions and deletions

- short INDELs: sections of DNA $<$ 50bp that are deleted or inserted in a genome



INDELs often overlooked

- Disproportionately occur in repetitive sequence
- Hard to align
- Often occur in hotspots
- 1/8 as frequent as SNPs in humans

(Earl et al., 2014; Montgomery et al., 2013)

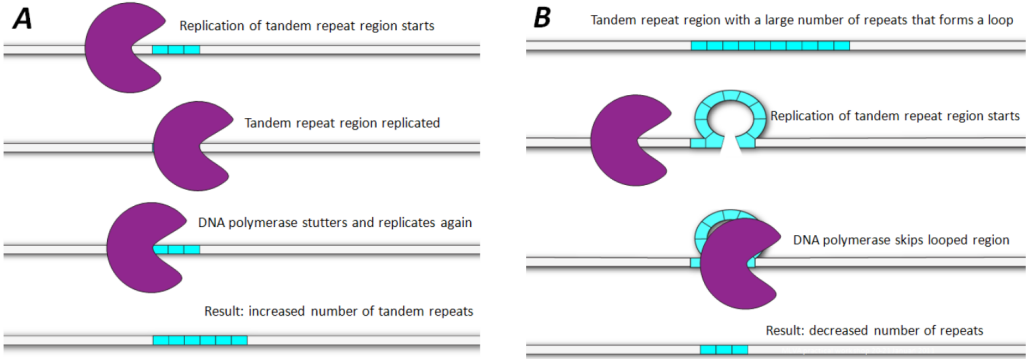
The importance of INDELs in genome evolution

- Contribute more to sequence divergence, in terms of the number of base differences, than SNPs
- Influence genome size:
  - low deletion rate $\rightarrow$ large genomes?
  - high deletion rate $\rightarrow$ compact genomes?

(Britten, 2002; Nam and Ellegren, 2012; Ometto et al., 2005; Sun et al., 2012)

INDEL mutation

- Deletion bias in most organisms
- Polymerase slippage can explain majority of short INDEL events



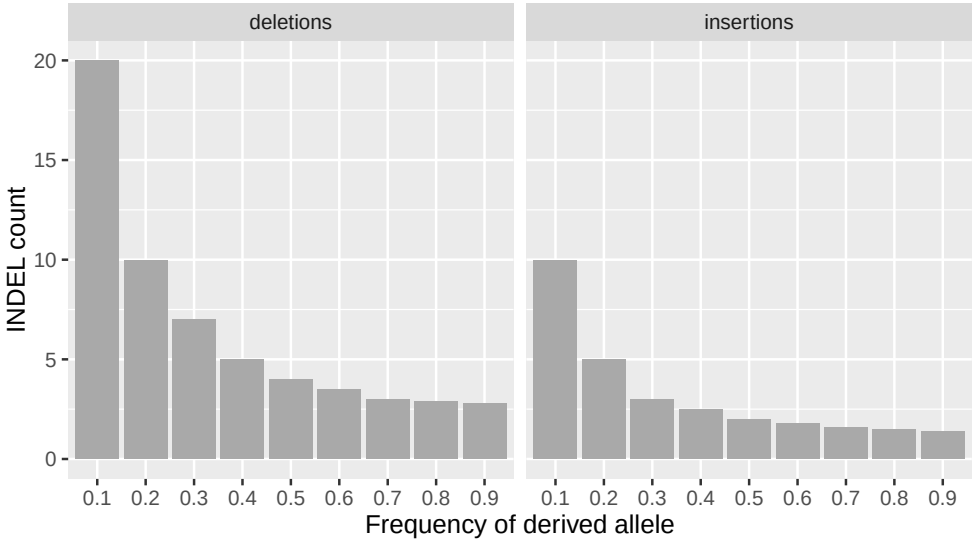
http://www.microtyping.nl/content/2011/11/MLVA

INDEL selection

- Deletions
  - lower mean allele frequency
  - more deleterious
  - two breakpoints
- Insertions may be favoured:
  - elevated fixation probability
  - biased gene conversion
  - minimum intron size
- Polarisation error

(Leushkin and Bazykin, 2013; Ometto et al., 2005)

Importance of polarisation error



(see Hernandez et al., 2007)

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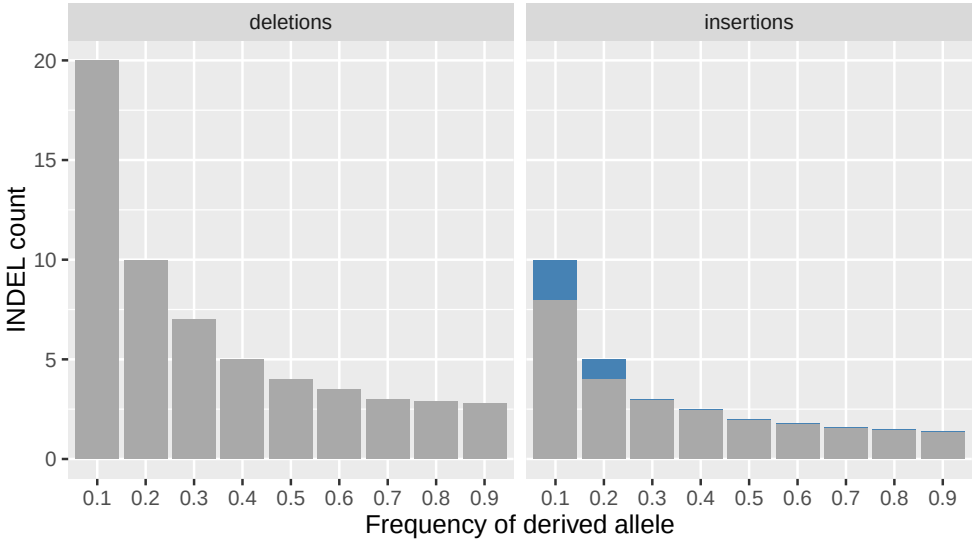

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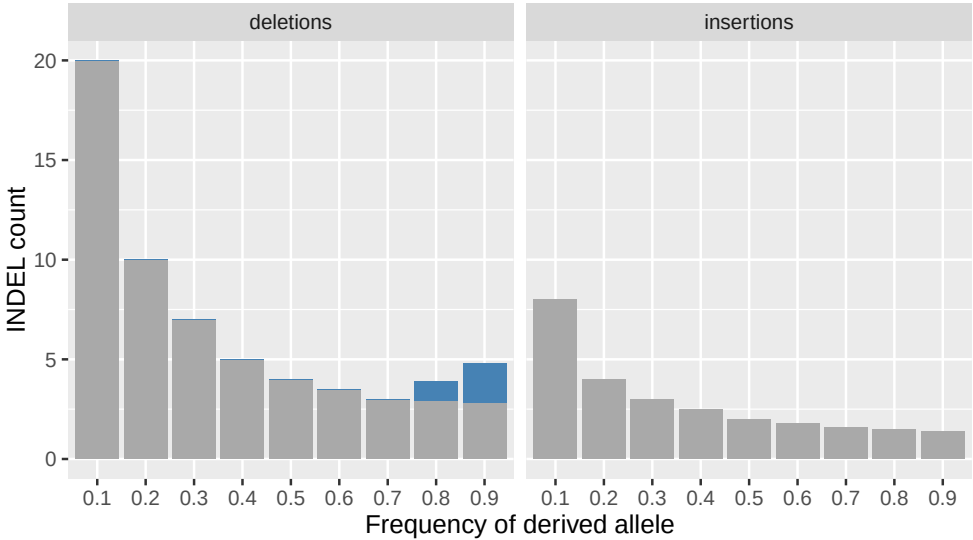

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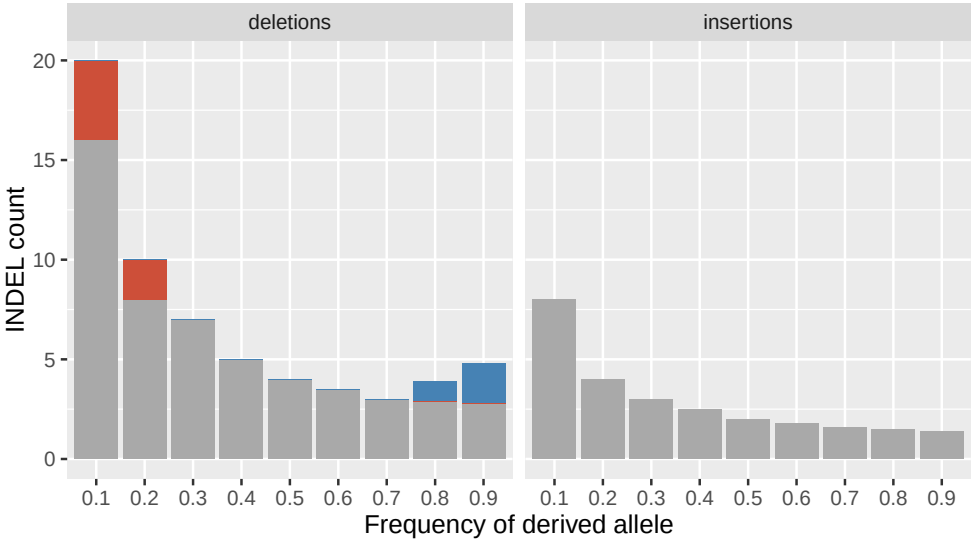

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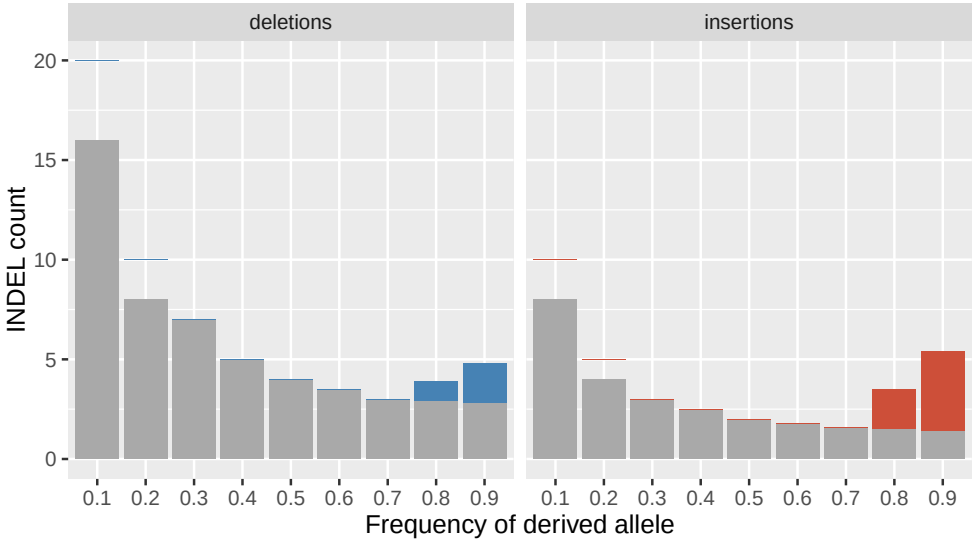

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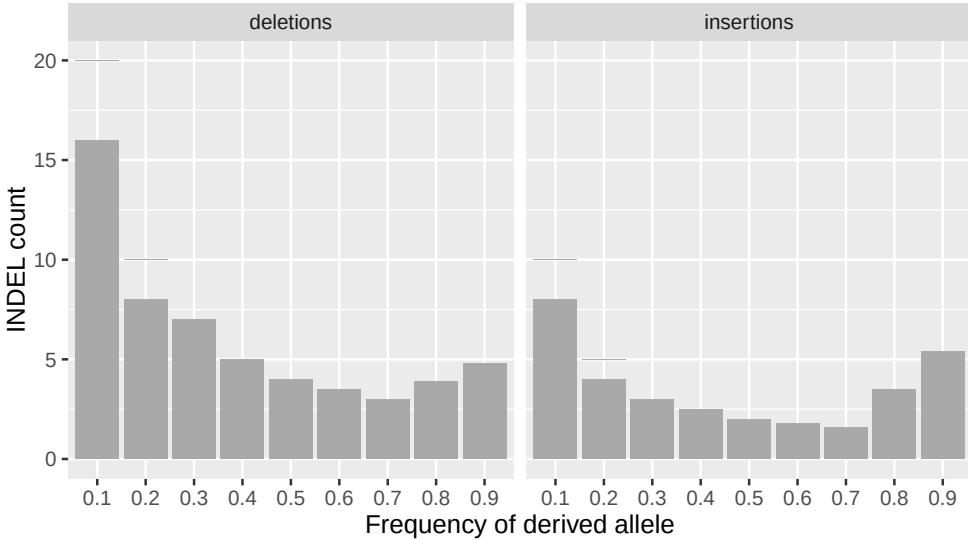


(see Hernandez et al., 2007)

Aims

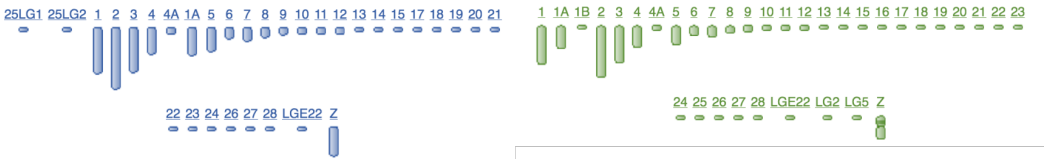
Overcome confounding affect of polarisation error

Quantify how natural selection shapes INDEL diversity in the great tit (*Parus major*)

1. within coding regions
2. in non-coding regions

Advantages of an avian system

- Conserved karyotype and synteny - good for alignments
- Genomes consist of few large macrochromosomes and many small microchromosomes
- Results in a highly dynamic recombination landscape - power to associations with recombination



(van Oers et al., 2014; Stapley et al., 2008)

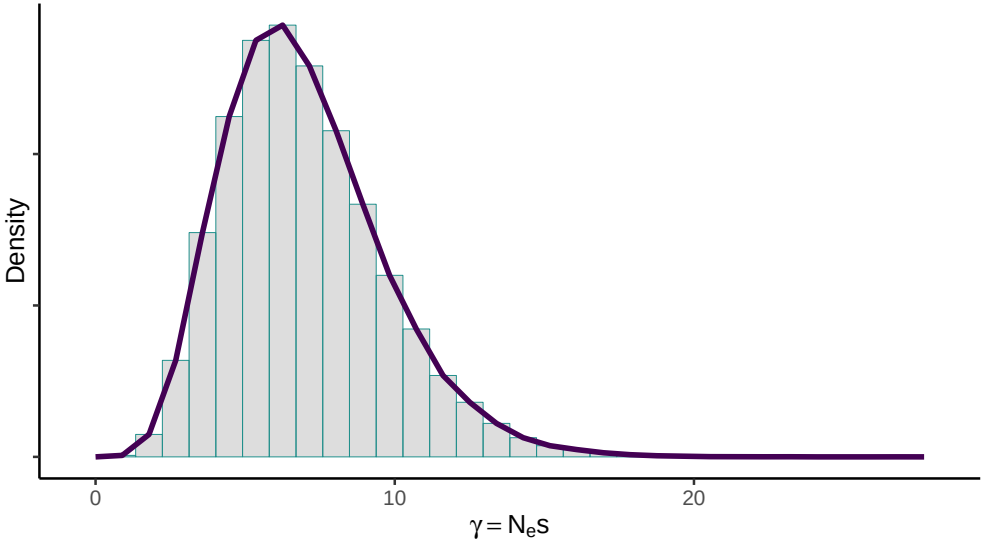
Tackling polarisation error

A novel maximum likelihood approach

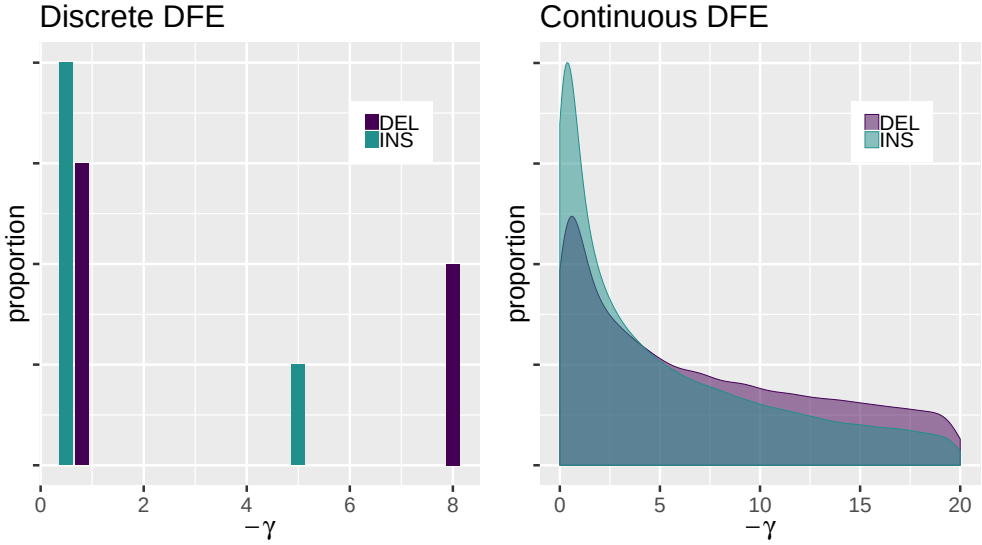
- 'anavar'
- takes the unfolded site frequency spectrum
- estimates for both insertions and deletions:
  - mutation rate ($\theta = 4N_e\mu$)
  - **the distribution of fitness effects (DFE)**
  - polarisation error (ϵ)
- Controls for demography using neutral sites (Eyre-Walker et al., 2006)
- Applicable to both INDELs and SNPs or a combination

(Barton and Zeng, MBE, 2018)

What is the DFE?

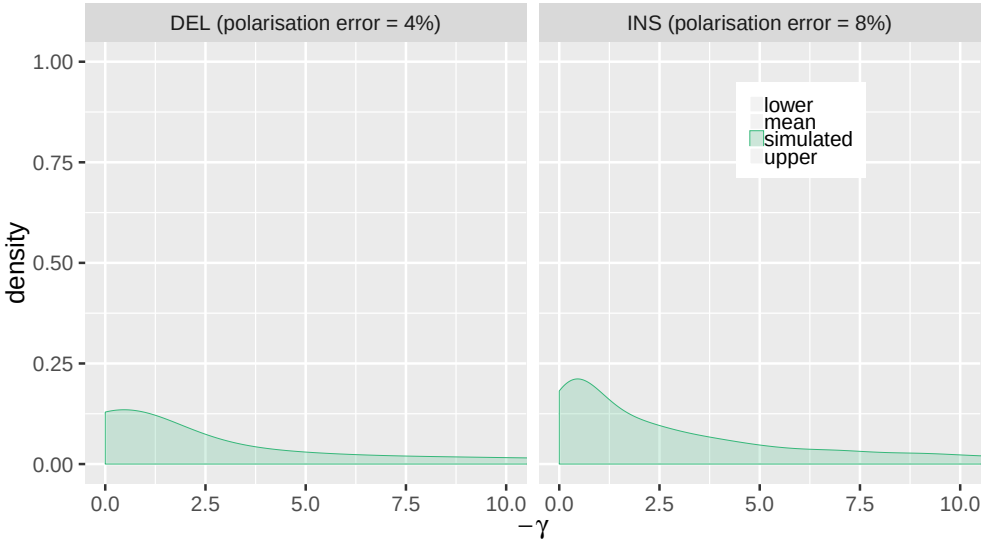


The model can describe the DFE in two ways



(Barton and Zeng, MBE, 2018)

Predicts the DFE well, with polarisation error



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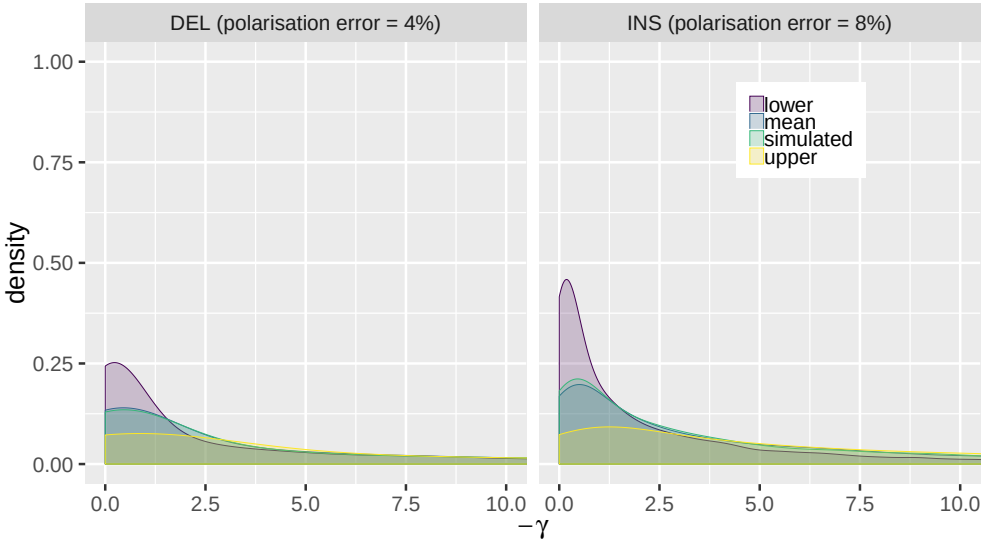
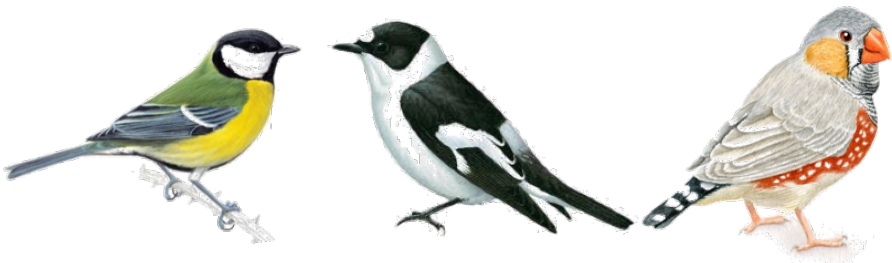


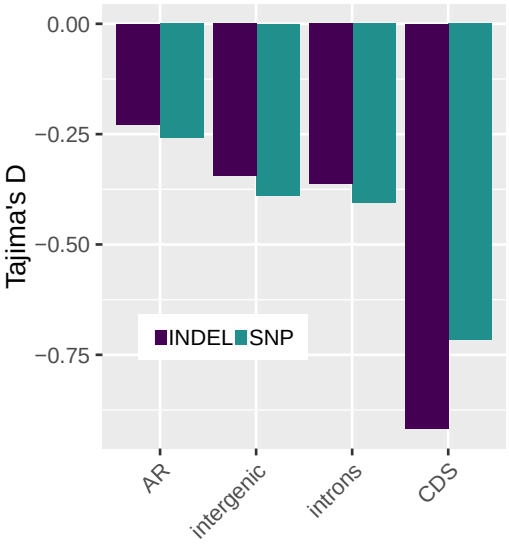
Applying the model to the great tit

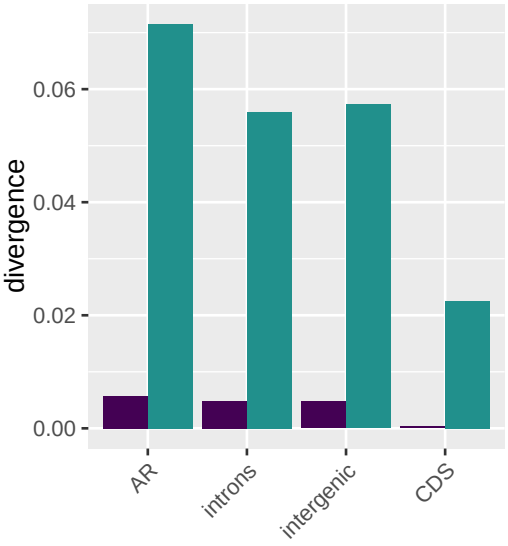
Sample and pipeline

- 10 european great tit males (Corcoran et al., 2017)
- high coverage (44x)
- variant calling with GATK
- multispecies alignment between zebra finch, flycatcher and great tit
- parsimony based polarisation



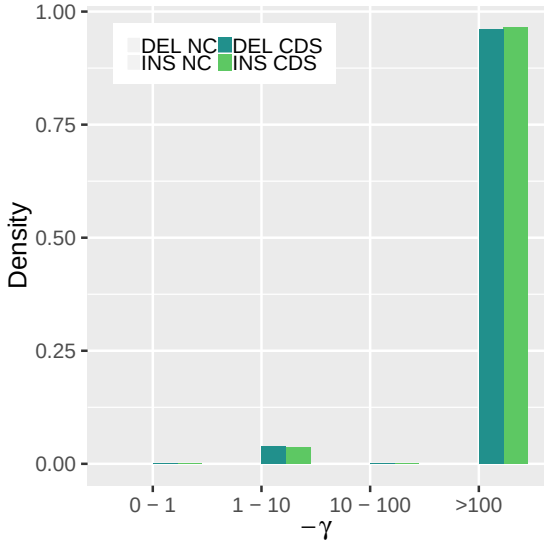
Summarising the data set





INDELs genome wide

Polymorphic INDELs predominantly strongly deleterious



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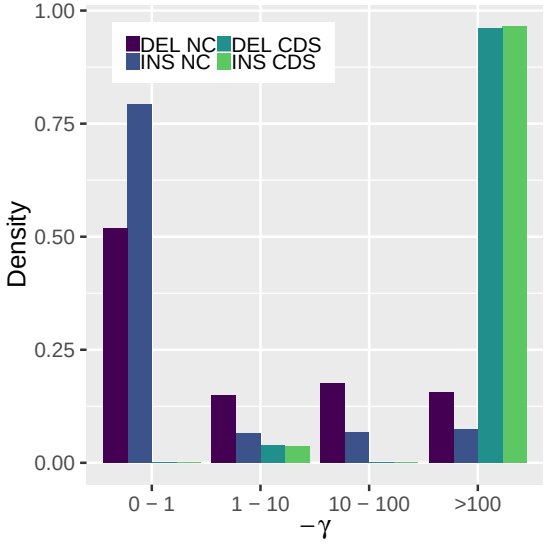
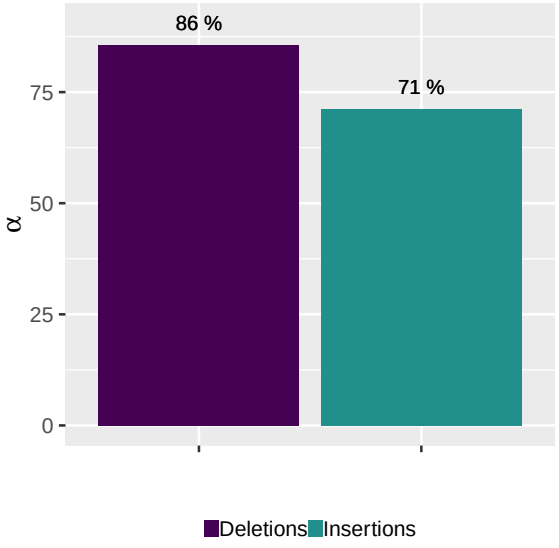
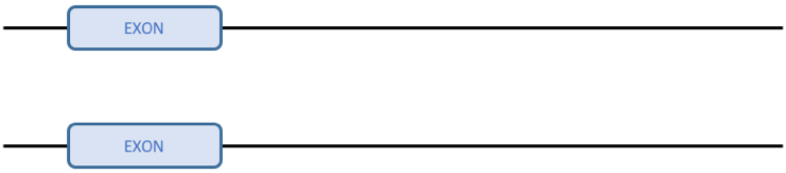


Coding INDEL fixations largely beneficial



Moving away from coding regions

Approach



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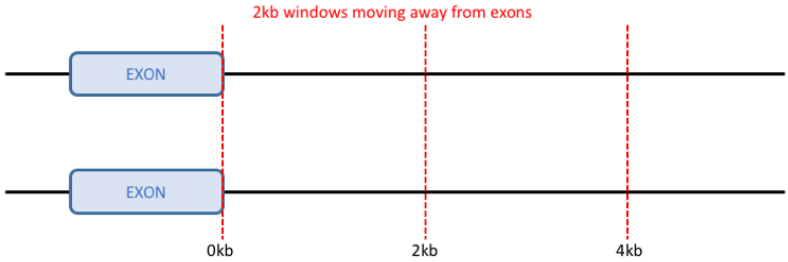

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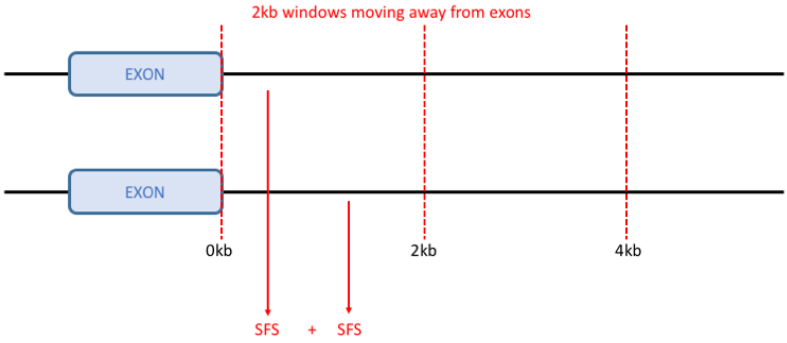
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EXON
EXON
0kb
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+
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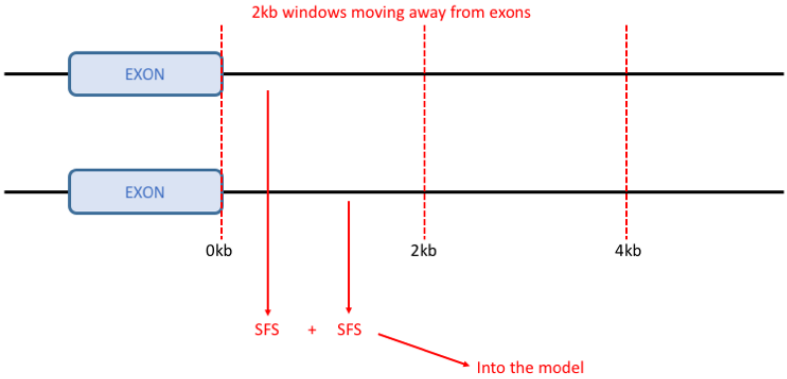
Approach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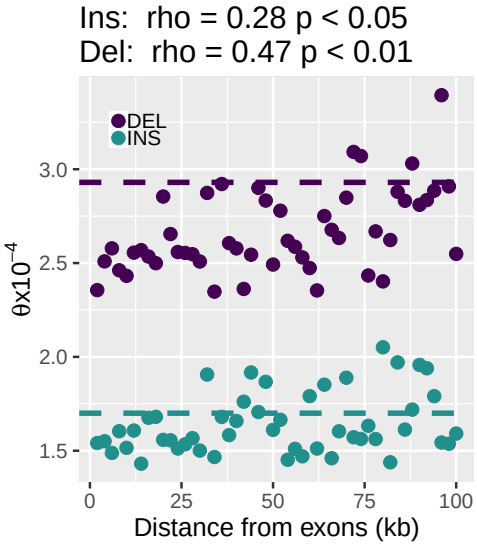
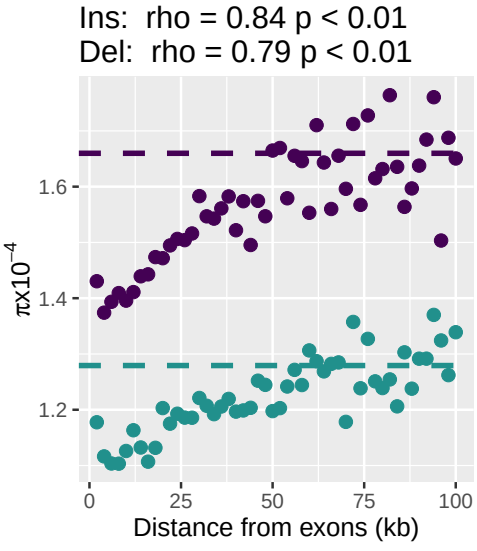
Into the model

Diversity increases with distance





Linked selection?

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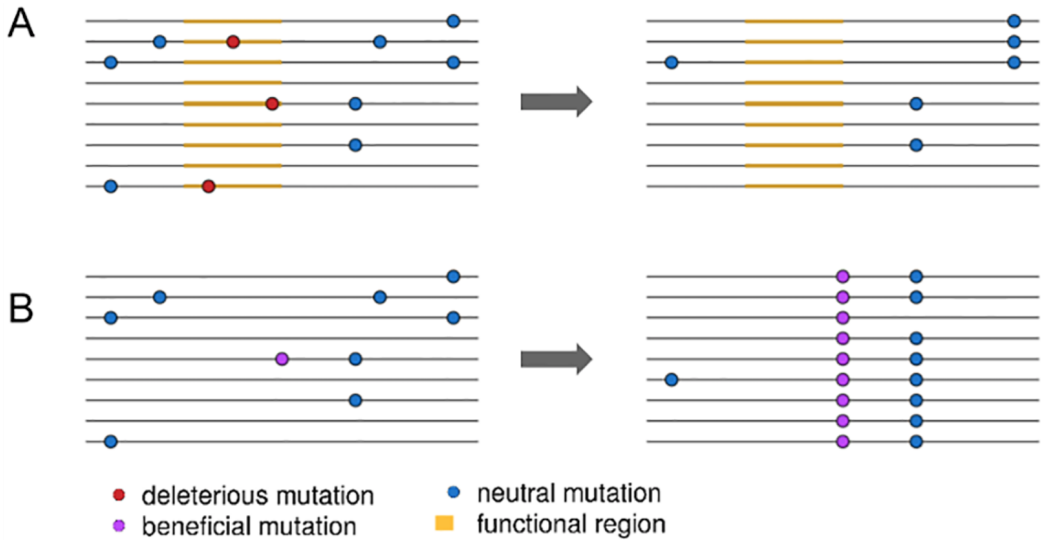
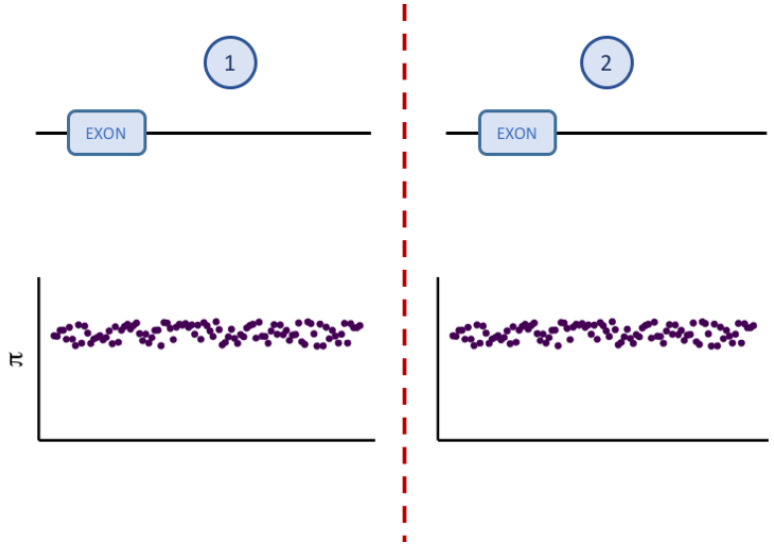


(Cropped from fig 1. Josephs and Wright, 2016)

Two possible explanations



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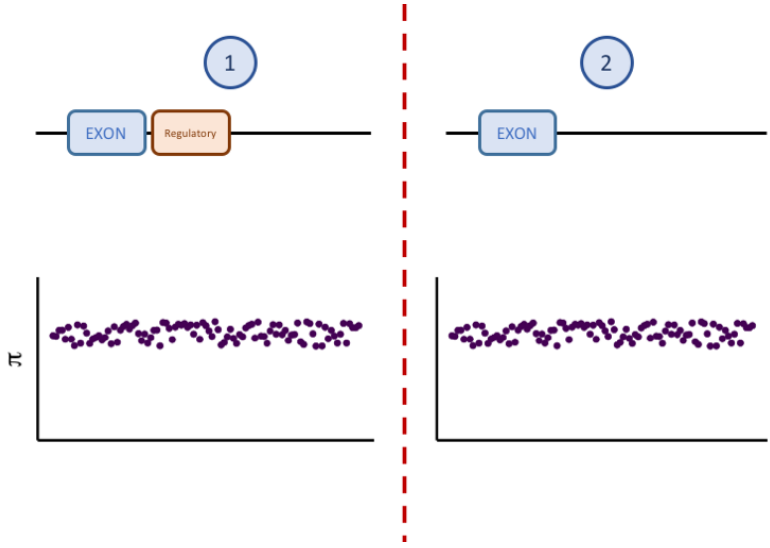

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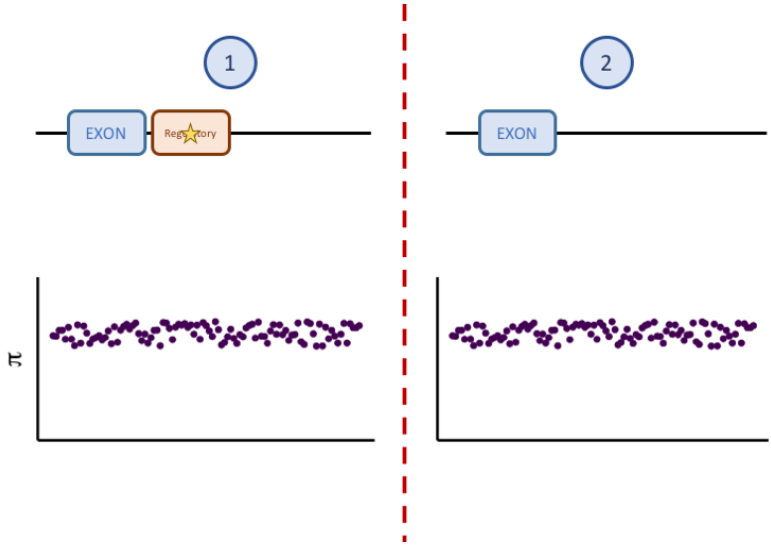

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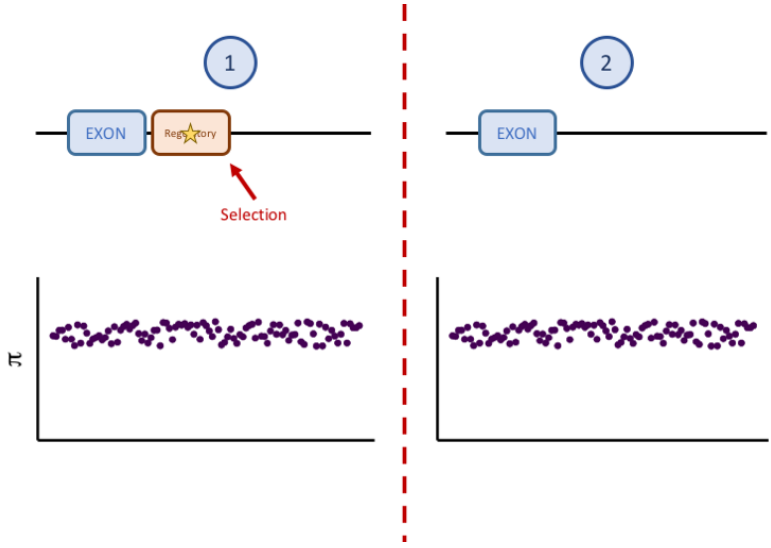

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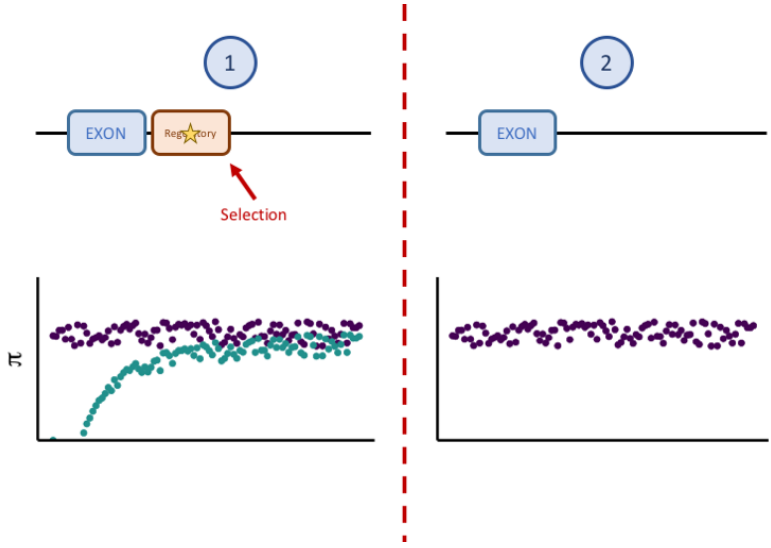

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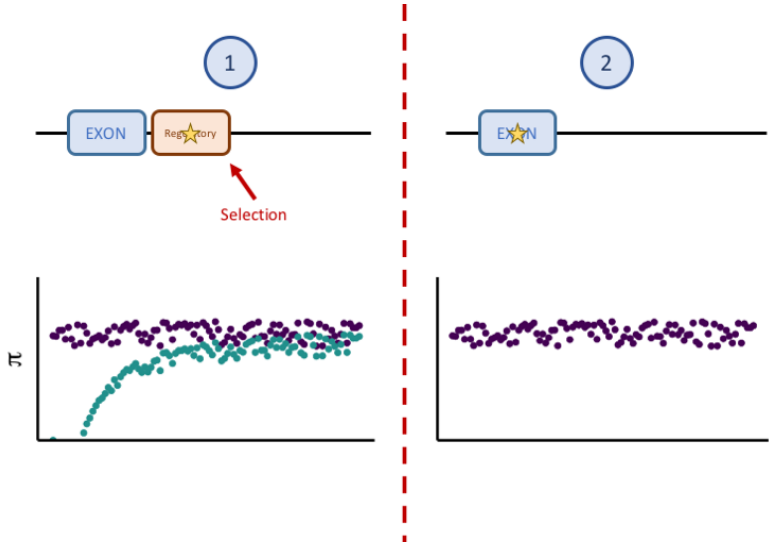

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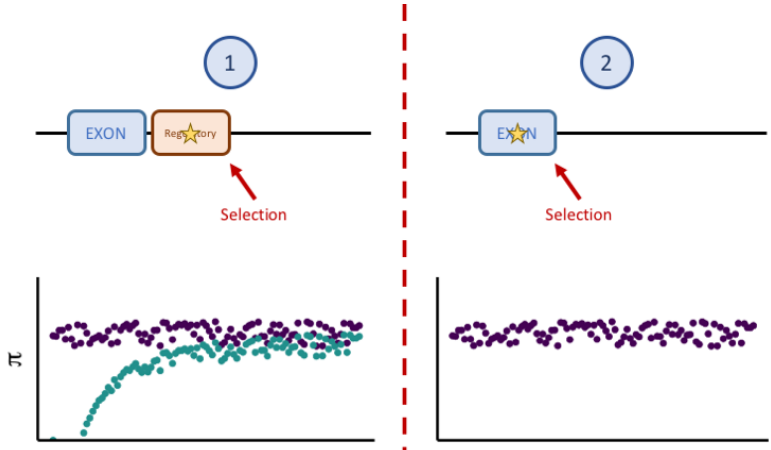

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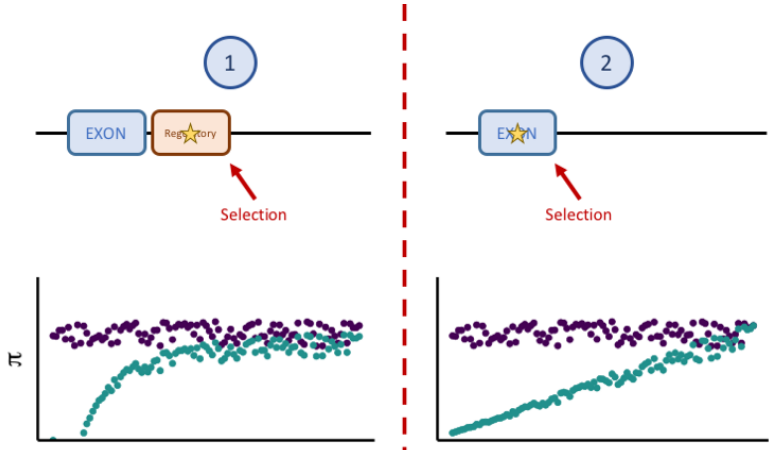
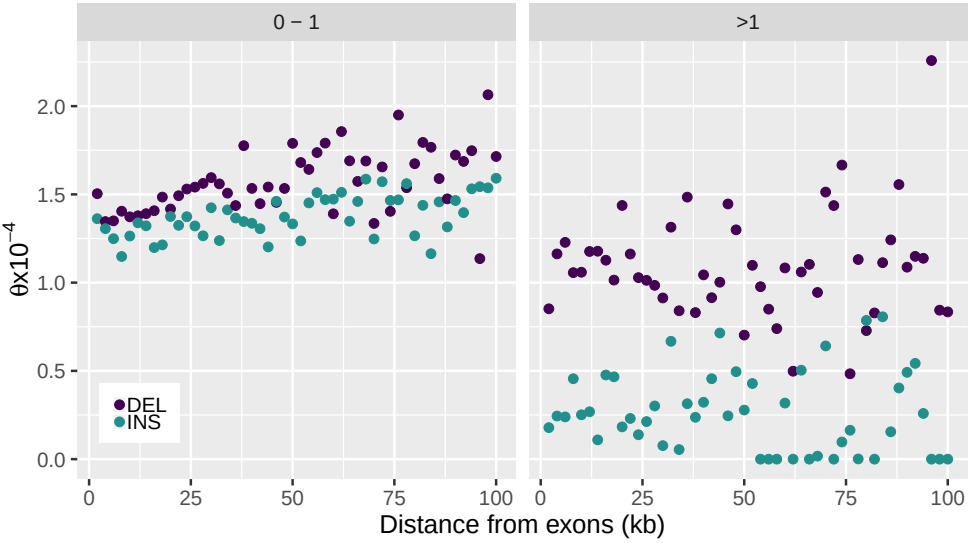
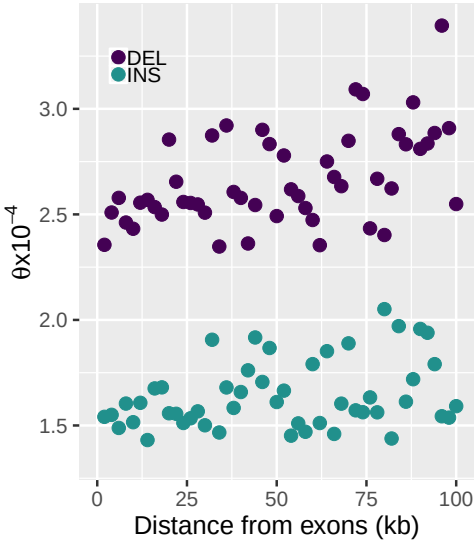
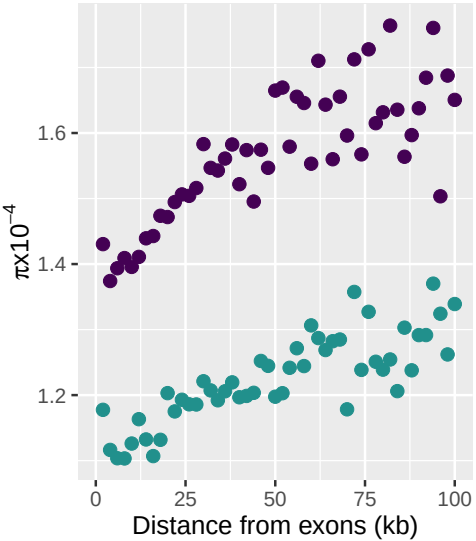


Driven by neutral variation



How far does the correlation persist?





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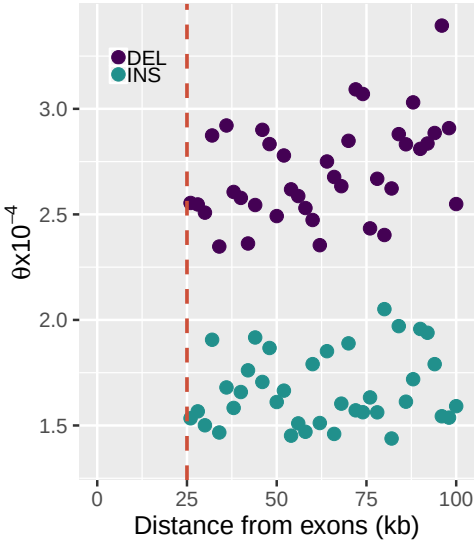

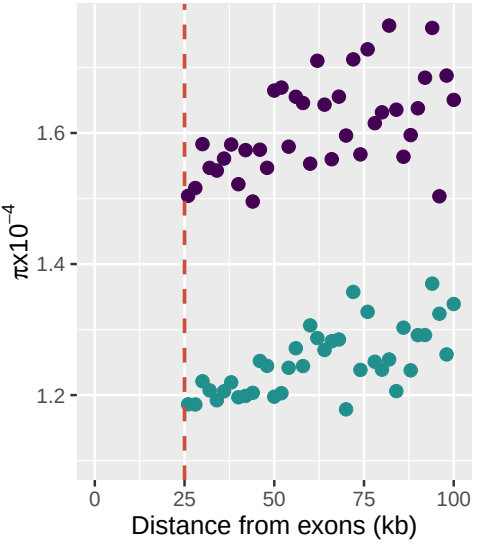

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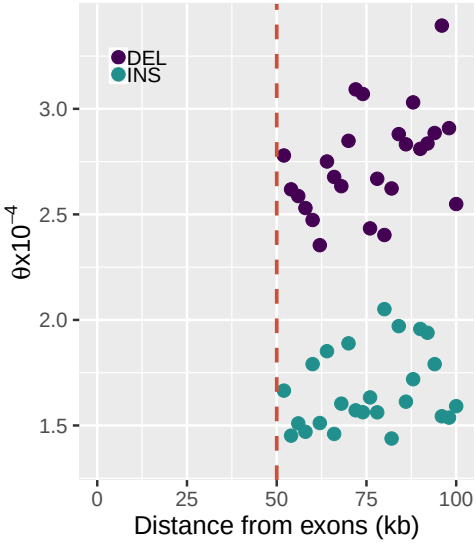

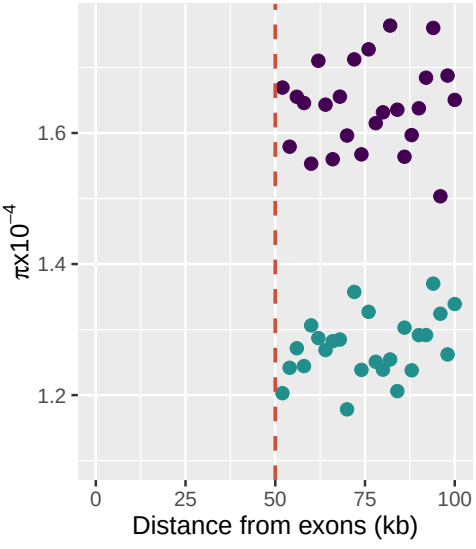

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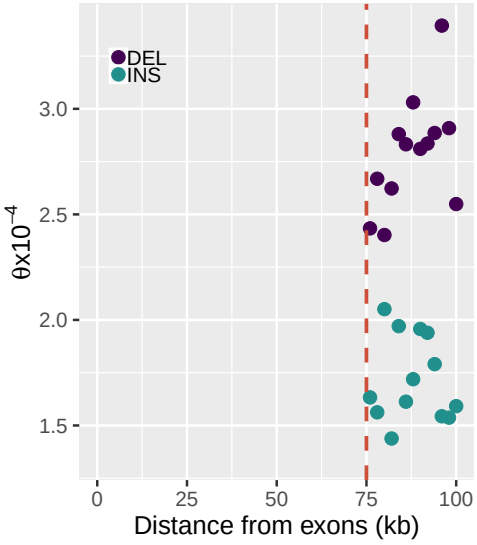

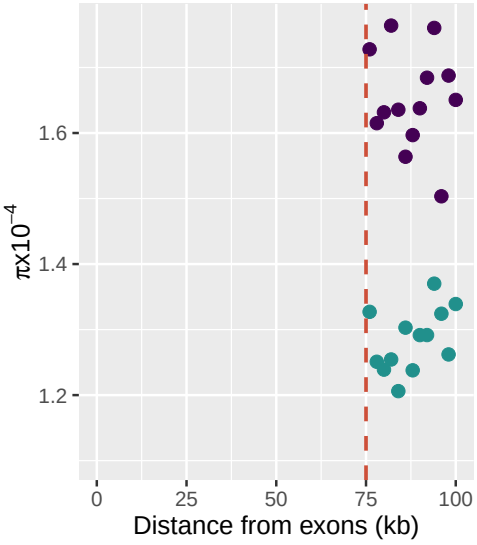

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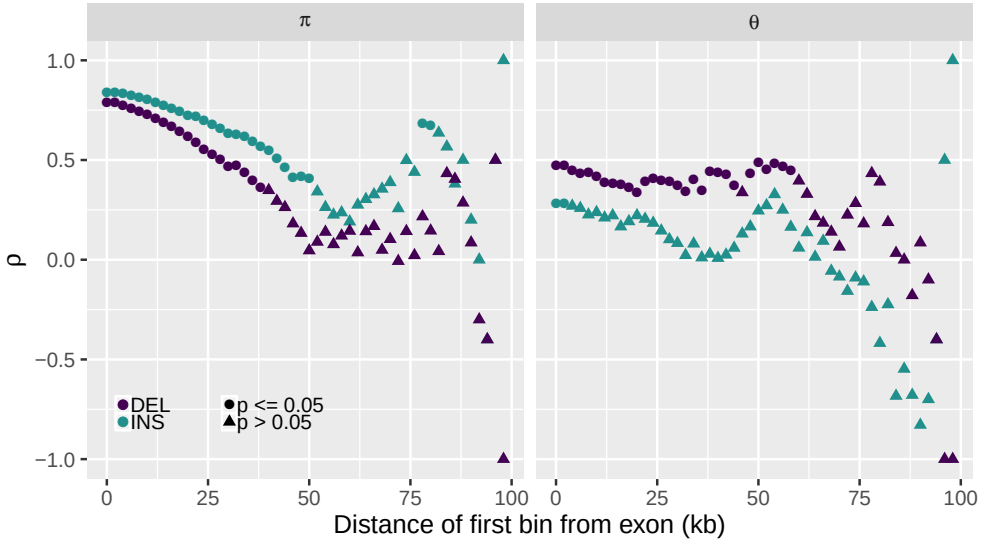


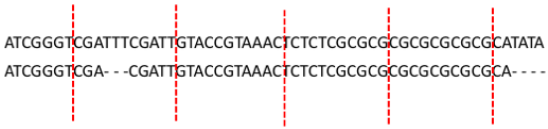
Recombination Analyses

Getting the data

ATCGGGTCGATTTCGATTGTACCGTAAACTCTCTCGCGCGCGCGCGCGCGCATATA

ATCGGGTCGA- - -CGATTGTACCGTAAACTCTCTCGCGCGCGCGCGCGCGCA- - - -

Getting the data



Getting the data

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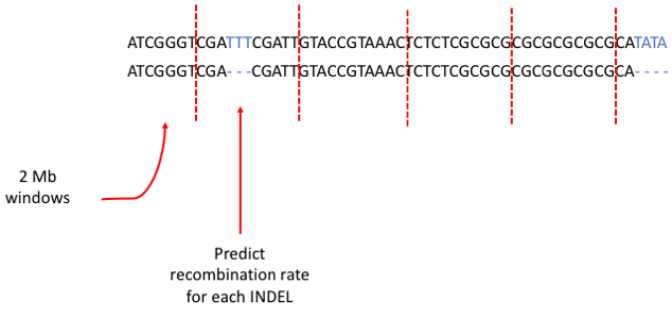
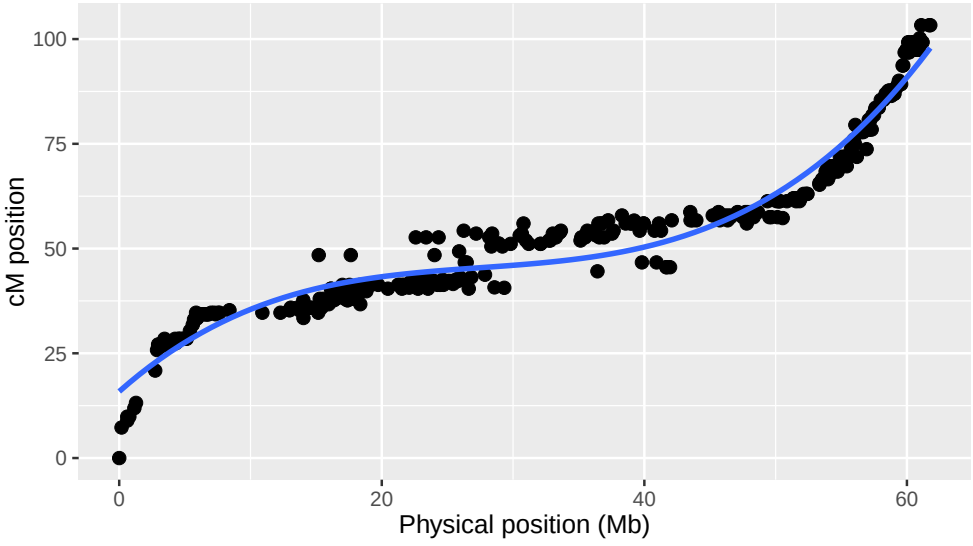


Getting the data - recombination rate



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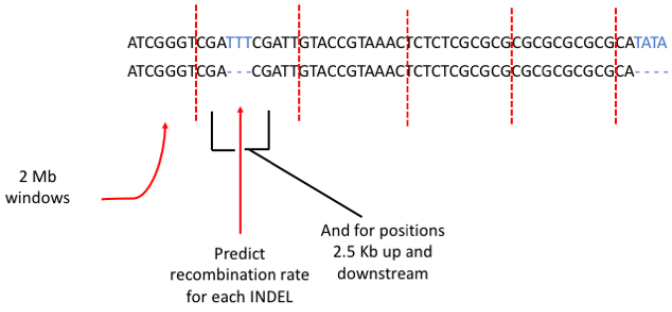
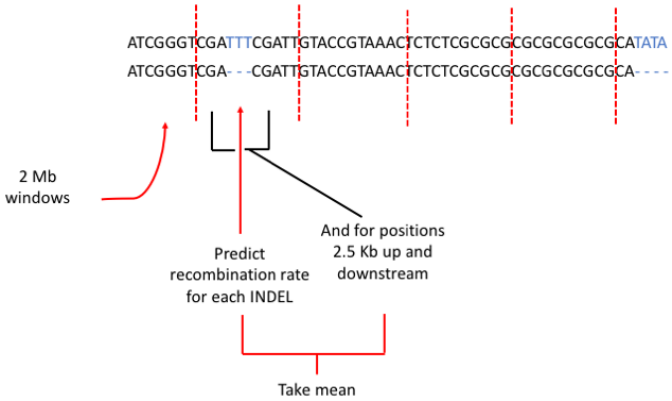


Getting the data



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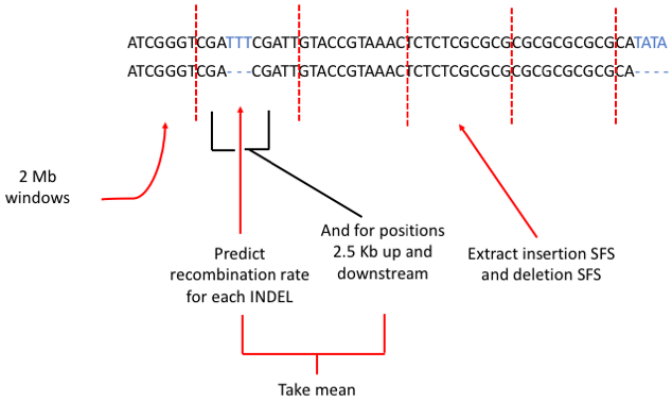
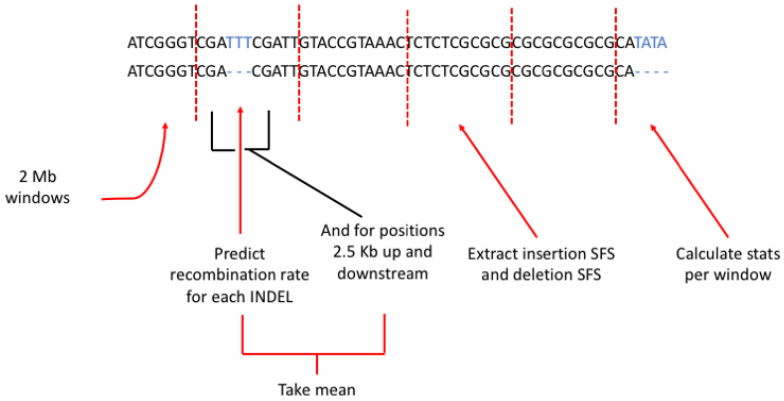
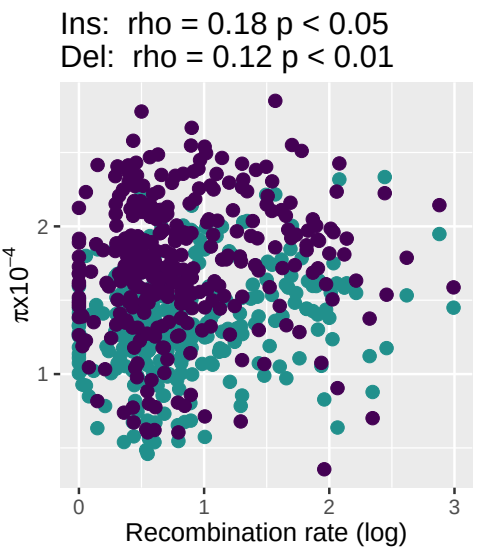
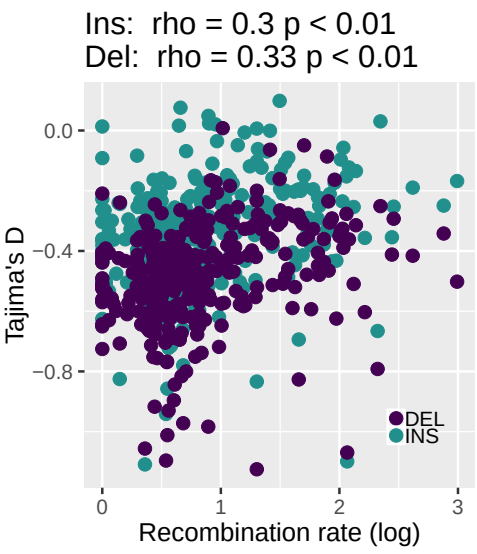


Getting the data



Association between diversity and recombination





Round up

Conclusion

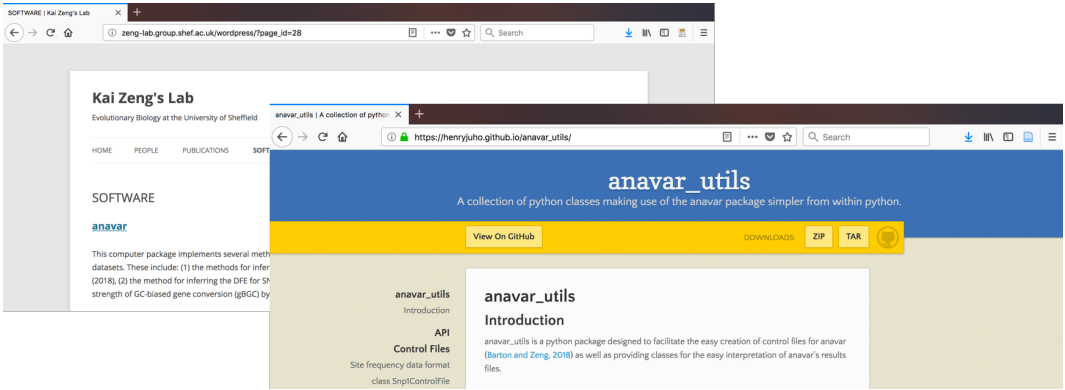
- INDELs in genes mostly extremely deleterious - 96%
- Remainder are weakly deleterious - deletions more so
- α estimate at 71% and 86% for insertions and deletions
- Regions adjacent to exons, and areas of low recombination, have reduced INDEL diversity - genetic hitch-hiking
- Extends over relatively large distance 0-100kb

Next steps

- Interesting to investigate if reduced diversity is due to positive selection or purifying selection
- Look at whether efficacy of selection on INDELs is higher in regions with higher N_e

Plug for the model

- User friendly computer package - anavar - `http://zeng-lab.group.shef.ac.uk`
- Methods are applicable to both INDELs and SNPs or a combination
- Code for integration with python - `https://henryjuho.github.io/anavar_utils/`



Questions?