Inferring sex specific selection from gene expression data

Benjamin L. S. Furman[1], Wouter van der Bijl[1], Alison Wright[2], and Judith Mank[1]

[1]Beaty Biodiversity Research Centre, University of British Columbia

[2]Dept. of Animal and Plant Sciences, University of Sheffield

Goal: Find the threshold for sex specific selection using sex specific gene expression regulation, and testing the effect of sex biased selection on rates of sequence evolution.

1. Can we use sex specific expression variation to infer differences in selection between the sexes?

- Phenotypic differences between the sexes are attributed to unequal expression levels of genes.
- Often, arbitrary thresholds of $\log_2$ fold change ($\log_2$FC), P-values (or both) are used to categorize male- vs female- vs un-biased genes.
- Increasing variability among individuals in expression level can indicate selection acting on a gene [1].

Sex specific selection on gene regulation
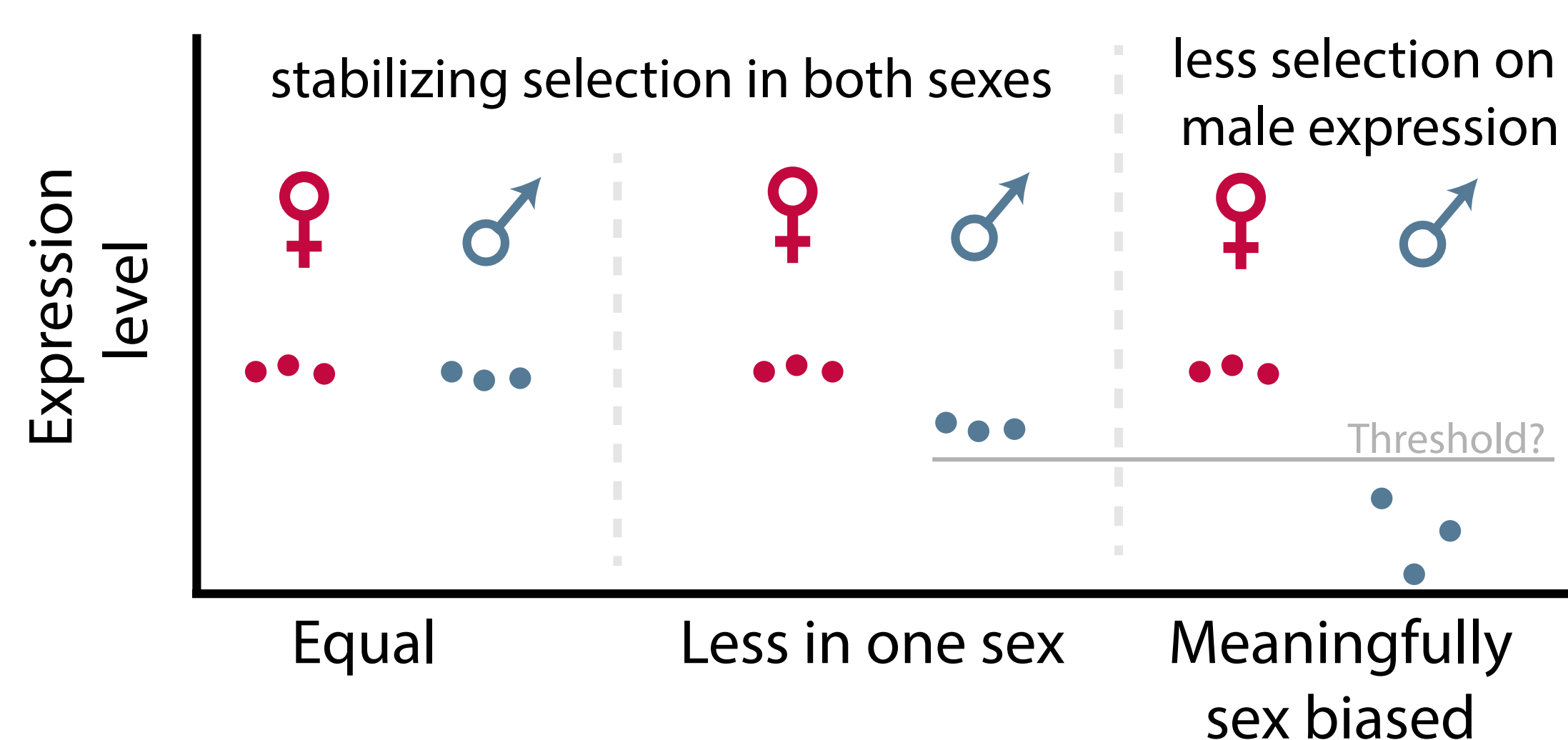
*inspired by [1], who evaluated expression levels and selection across species

We assume that differences between the sexes in expression level variation can indicate the presence of sex biased selection on a gene.

Knowing the threshold for sex biased selection, we can infer when a gene has less phenotypic influence on a sex.

2. The point where expression variation begins to increase is different for female and male biased genes.
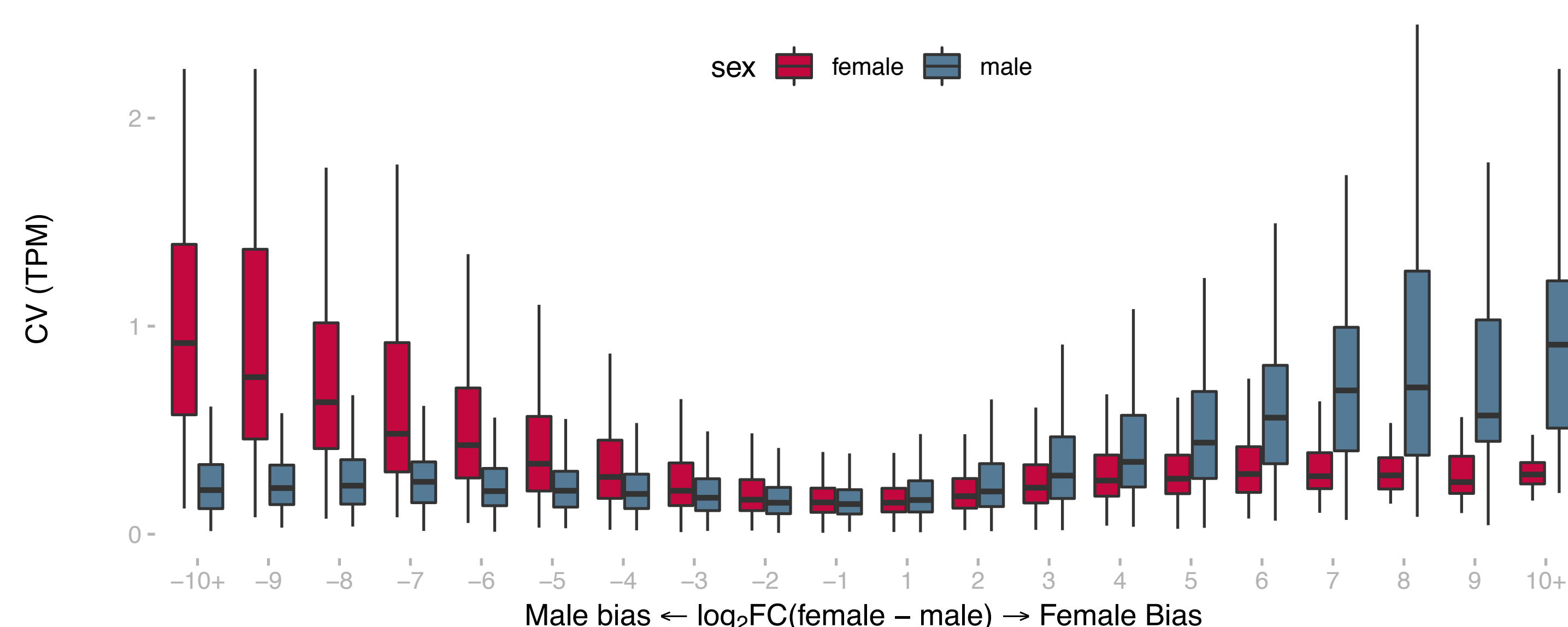

Figure 1: The coefficient of variation (CV) of transcripts per million (TPM) for gonad expression data of four bird species, with 5+ individuals per sex.
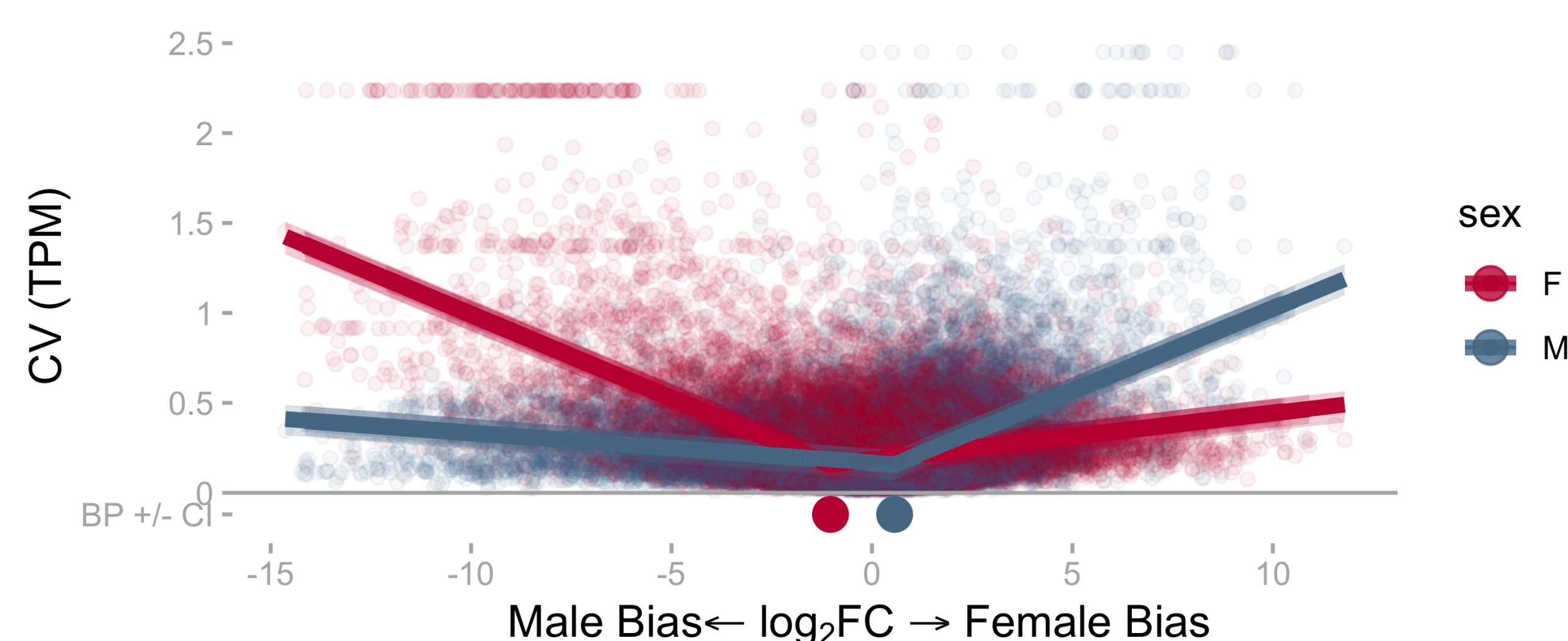

Figure 2: Mixed segmented regression models fit to the CV of gene expression. Female breakpoint at -1.03 $\log_2$FC (red line). Male breakpoint at 0.57 (blue line).

- Breakpoints only represent the start of the increase in CV. But the CV of one sex does not exceed the other until $|\log_2$FC$| > 1.5$.

References

[1] Romero et al. 2012 *Nat Rev Genet*
[2] Schrader et al. 2017 *MBE*
[3] Meisel 2011 *MBE*
[4] Harrison et al. 200X *PNAS*
[5] Van Dyken & Wade 2010 *Genetics*
[6] Dapper & Wade 2016 *Evolution*
[7] Connallon & Knowles 2005 *Trends in Genet*

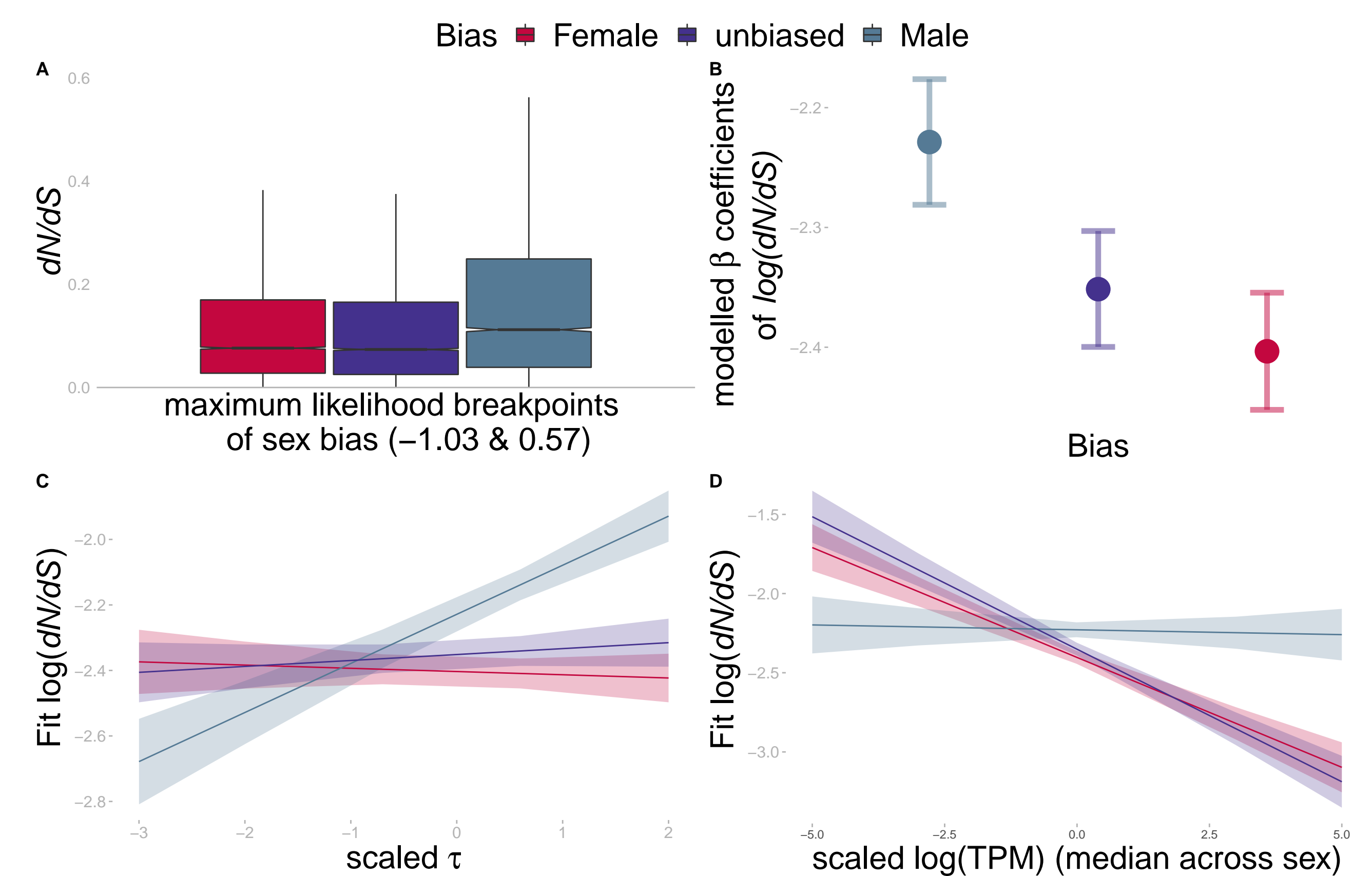## 3. τ and expression level affect *dN/dS* differently for male vs female/unbiased genes.

Figure 3: Data (A) and a mixed model fit (B–D) to rates of molecular evolution (*dN/dS*; B, rate $\pm$95%CI) for gene expression categories inferred from the breakpoint analysis (Fig. 2). This model accounts for expression evenness (τ) measured across 8 tissues (C), and median expression level across individuals (TPM) (D), as both parameters can influence *dN/dS* [3].

4. Male and female-biased genes are under different constraints, as indicated by the different responses to sex limited expression.
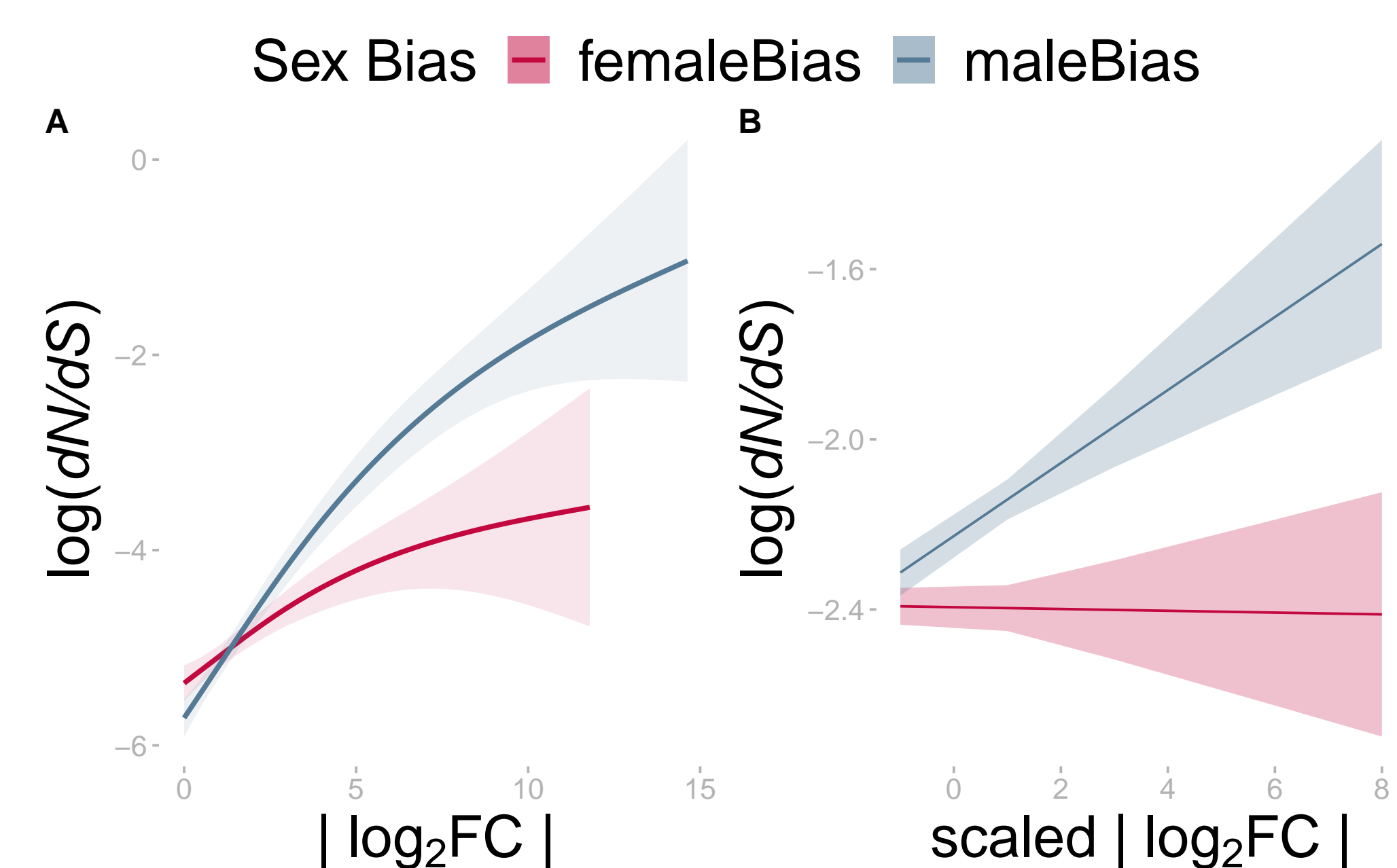

Figure 4: Sex biased expression is a continuous variable, and expression is increasingly sex limited in expression as bias increases. In the data (A), *dN/dS* increases for male and female biased genes. But, with a mixed model fit to *dN/dS* (B), including τ and median TPM, the slope is positive only for male biased genes. GAMs reveal a slight, but not significant, increase for female biased genes (not shown).

5. Discussion

The connection between the magnitude of expression level differences between the sexes and phenotypic dimorphism is unclear. However, we can use expression data itself to infer when differences in expression level between the sexes also have differences in expression variance. Expression variability reflects the amount of purifying selection acting on the regulation of a gene [1], and here we used sex specific expression variation to determine when a gene is likely experiencing sex biased selection.

These breakpoints suggest meaningful fold-change thresholds for studying sex biased expression. Given that most expression bias in these taxa is due to reduced expression in one sex [4], these thresholds indicate the points at which sexual conflict over optimal expression level has been resolved. As sex biased expression increases, the reduction in expression level in one sex means that regulatory selection on that gene is less effective in that sex. This leads to a shift in mutation–selection balance due to a reduction in the proportion of individuals under selection in a population [5,6]. Male biased genes show this expected increase in *dN/dS*, but female biased genes do not (Fig. 4). This supports the idea that these two categories of genes exhibit different underlying characteristics and constraints [4,7].