### S4 Text. Estimation of proportion parameters

The estimation of these proportion parameters required in can be easily implemented with methods that were well-established in the FDR literature [1-10]. Here, we estimate them with a simple non-parametric manner using in the calculation of q-values [6,8,9]. Let *κ*0+ be the null proportion of  and *κ*+0 be the null proportion of ; then *κ*0+ and *κ*+0 can be conservatively estimated by



where *m* is the total number of analyzed genes, and λα and λβ are tuning parameters to determine whether an observed *P* value comes from the null case. In addition, *κ*00 is similarly estimated as



It needs to highlight that a value of λα or λβ that is much closer to one could lead to a higher confidence to guarantee the null of  or . However, a larger λα or λβ would miss many  and  which actually come from the null distribution; in contrast, a smaller value of λα or λβ that is closer to zero has the risk of incorporating non-null  or . Investigating the optimal value for λα or λβ is beyond the scope of our study. In the present study, for simplicity we employ λα = λβ = 0.5 following prior work [11]. Ultimately, it has



Once the estimates of these proportions are obtained, the estimated mixture null distribution for *P*max can be built to control FWER or FDR [11]. A comprehensive theoretical derivation with regards to the control of FWER or FDR can be conferred in [11]

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