It is not unexpected that site-level positive results can occur when a gene-level test does not yield a positive result

- **Lack of power for the global test**: if the proportion of sites under selection is very small, a mixture-model test, like BUSTED, will miss it.
- **Model violations:** MEME supplies much more flexible distributions of **`dN/dS`** over sites; compared to alignment-wide 3-bit BUSTED distribution.
- **False positives at site-level**: our site-level tests have good statistical properties, but each positive site result could be a false positive; FWER correction would make site-level tests too conservative.
- **Summary**: gene-level selection tests need a minimal proportion of sites to be under selection to be powered; site-level tests should not be used to make inferences about gene-level selection.

However, we caution that despite obvious interest in identifying specific branch-site combinations subject to diversifying selection, such inference is based on very limited data (the evolution of one codon along one branch), and cannot be recommended for purposes other than data exploration and result visualization. This observation could be codified as the "***selection inference uncertainty principle***" — one cannot simultaneously infer both the site and the branch subject to diversifying selection. In this manuscript [MEME], we describe how to infer the location of sites, pooling information over branches; previously [aBSREL] we have outlined a complementary approach to find selected branches by pooling information over sites.

Murrell et al 2012