Dear Editorial Board,

We would like to submit a manuscript entitled “The relationship between *dN/dS* and scaled selection coefficients” for your consideration for publication in *Molecular Biology and Evolution.*

Probabilistic models of coding-sequence evolution represent some of the most valuable and powerful tools to discern the effects of natural selection in phylogenetic data. While a wide variety of such models exist, these models have largely been developed independently. As a consequence, there is an unfortunate and large gap in our understanding of how distinct modeling frameworks relate to each other. Researchers interested in applying these methods to their study system of choice thus find that they have a bewildering array of different methods at their disposal. Which specific method to choose is often not obvious, and frequently researchers simply pick the methods they believe will work best on their data, without having any solid evidence to support this belief. The problem of model choice is further compounded by a lack of understanding of how different modeling frameworks perform on the same data, in particular whether inferences made with distinct model frameworks will yield comparable or conflicting information about the evolutionary process.

The study we present establishes a formal mathematical relationship between two competing models: *dN/dS* models and mutation-selection balance models, which estimate selection coefficients from phylogenetic data. By deriving a link between these distinct frameworks, we are able to uncover previously unknown properties inherent to each of these modeling approaches. We use this theoretical relationship to precisely elucidate the circumstances in which each modeling approach is justified, and we identify methodological biases inherent to the *dN/dS* inference framework.

We believe that results from our research have broad applicability to both the molecular evolution community and to the ever-growing community of researchers engaging in comparative sequence analysis. To our knowledge, our study is the first of its kind to probe the relationship among distinct modeling frameworks in order to achieve a deeper understanding of the models’ capabilities, limitations, and unique behaviors. We hope that our work will help researchers in selecting inference methods and will also pave the way for increased robustness in model development, such that models are not developed and tested in a vacuum but rather in concert with their modeling counterparts. We look forward to your decision.

Sincerely,

Stephanie J. Spielman and Claus O. Wilke