Dear sir/madam

Please find attached a paper entitled "Decomposing structural response due to sequence changes in protein domains with machine learning." by Bryant et al. We do believe this paper to be suitable for publication in JMB as it enables assessing deviations in relative structural response, and thus prediction of evolutionary trajectories, in protein domains across evolution. How protein domain structure changes in response to mutations is not well understood. Some mutations change the structure drastically, while most only result in small changes. Here we decompose the relationship between changes in domain sequence and structure using machine learning. We train a random forest regressor that predicts the structural similarity between pairs with an average accuracy of 0.029 lDDT score, and a correlation coefficient of 0.92. Decomposing the feature importance shows that the domain length, or analogously, size is by far the most important feature for the prediction of evolutionary trajectories.

We do recommend the following reviewers as they are experts in this area:

- Christine Orengo <c.orengo@ucl.ac.uk>
- Nick Grishin <grishin@chop.swmed.edu>
- Dave Ardell <dardell@ucmerced.edu>
- Charlotte Deane <deane@stats.ox.ac.uk>
- Thornton Janet <thornton@ebi.ac.uk>
- Sheena E. Radford

We do believe that **Sheena Radford <s.e.radford@leeds.ac.uk>** or Michael J.E. Sternberg would be a suitable editor for this paper.

 Yours

 Arne Elofsson - on behalf of all the authors.