Dear Madam/Sir,

We are writing to submit a manuscript entitled "OSPREY 3.0: Open-Source Protein Redesign for You, with Powerful New Features" to the *Journal of Computational Chemistry*.

Protein and drug design algorithms enable the development of new therapeutics that might be impossible or too expensive to discover using experimental methods. For over a decade, my lab has been working on the OSPREY software package, which implements unique and powerful algorithms for this problem. OSPREY is distinguished by its combination of algorithms with provable guarantees of accuracy, modeling of continuous flexibility and free energy using Boltzmann-weighted conformational ensembles, and ability to search very large sequence spaces efficiently.

In this paper, we present the third major release of OSPREY. OSPREY 3.0 offers substantial improvements in three areas: performance, new algorithms, and ease of use. We believe the new algorithms significantly improve both efficiency and the realism of the biophysical model. The performance and ease-of-use improvements will greatly facilitate the use of both the new and old algorithms in empirical designs. Like previous versions of OSPREY, OSPREY 3.0 is available as open-source, and unlike previous releases it is already available on Github. This paper also presents benchmark results, which provide significant new evidence for the accuracy of the software and the algorithms and models from which it was built.

What is new entails a vastly more efficient implementation of the algorithms, together with a Python front end for ease of use. Finally, we have implemented GPU acceleration, which compares favorably in empirical tests to the previous landmark biophysics application of GPUs, molecular dynamics.

This work, therefore, is immediately applicable for both users and developers of protein design algorithms, and is also of interest to scientists interested in the biophysical modeling of proteins and in conformational search algorithms. Its focus on improved computational modeling will be of interest to the computational chemistry community, and indeed several of the algorithms in OSPREY were first published in the *Journal of Computational Chemistry*.

We believe that the following scientists would be well qualified to review this work:

Bruce Tidor
Department of Biological Engineering, Massachusetts Institute of Technology
Department of Electrical Engineering & Computer Science, Massachusetts Institute of Technology
Computer Science and Artificial Intelligence Laboratory, Massachusetts Institute of Technology
Room 32-212
Cambridge, MA 02139-4307 USA

Email: tidor@mit.edu

Ivet Bahar
Department of Computational & Systems Biology
School of Medicine, University of Pittsburgh
3064 Biomedical Science Tower 3
3501 Fifth Avenue, Pittsburgh, PA 15213
Email: bahar@pitt.edu

Ron Elber
Department of Chemistry and Biochemistry, University of Texas
Institute of Computational Sciences and Engineering, University of Texas
1 University Station, ICES, C0200
The University of Texas at Austin
Austin, TX 78712
Email: ron@ices.utexas.edu

Gevorg Grigoryan
Department of Computer Science, Dartmouth College
6211 Sudikoff Lab, Hanover, NH 03755
Email: gevorg.grigoryan@dartmouth.edu

Ivelin Georgiev
Department of Pathology, Microbiology, and Immunology
Vanderbilt University Medical Center
1211 Medical Center Drive, Nashville, TN 37232
Email: ivelin.georgiev@vanderbilt.edu

Chris Bailey-Kellogg
Department of Computer Science, Dartmouth College
6211 Sudikoff Lab, Hanover, NH 03755
Email: cbk@cs.dartmouth.edu

Due to competing interests, we request excluding the following people as potential reviewers: David Baker (University of Washington), Brian Kuhlman (University of North Carolina), and Tanja Kortemme (University of California, San Francisco).

The corresponding author for this work is:

Professor Bruce R. Donald

Department of Computer Science, Duke University
Department of Biochemistry, Duke University Medical Center
Department of Chemistry, Duke University
Room D106, Levine Science Research Center
Research Drive
Durham, NC 27708 USA
Phone: 919-660-6583
Fax: 919-660-6519
Email: brd+jcc18@cs.duke.edu