June 27, 2018

Dear Editor,

We are pleased to submit our manuscript entitled “MeshMonk: open-source large-scale intensive 3D phenotyping” for consideration for publication as a Technology Report in Frontiers in Genetics, as part of *The Genes and Mechanisms Underlying Normal-Range Craniofacial Variation* article collection in Applied Genetic Epidemiology. This work is original and has not been published nor is it being considered for publication elsewhere.

In this manuscript, we introduce the MeshMonk toolbox for fast and reproducible high-throughput phenotyping of 3D images. This represents a step forward in our ability to describe complex structures, like the human face, in terms of large sets of homologous landmarks (N=7,160 for the face) that finely characterize minute details of the structure and are homologous across samples. Using the MeshMonk registration toolbox, researchers are no longer limited to a few homologous points, chosen because they can be reliability indicated over many hours of work, and can easily incorporate 3D images from different sources and taken using different cameras. Indeed, our recent work using the MeshMonk software utilized two datasets and identified 15 genomic regions associated with normal-range facial variation, containing more loci than had previously been reported in a single GWAS of facial variation, even those with a much larger sample size than our own. Though we were limited by samples, the increase in phenotyping afforded by using MeshMonk provided a valuable and powerful phenotype for the GWAS. Also, in this manuscript, we illustrate the ability of the MeshMonk registration to map onto anatomical surfaces by comparing the placements of 19 sparse landmarks indicated manually and automatically utilizing MeshMonk. We show that MeshMonk is accurate, with an average root mean squared error between manual and automatic indications of 0.68 mm. Additionally, analyses of variance in landmark placements and centroid sizes showed that no significant level of variation could be attributed to the use of the toolbox.

With MeshMonk, we can advance our ability to integrate genomic and phenomic data to explore variation in complex morphological traits and answer evolutionary and clinical questions about normal range variation, growth and development, dysmorphology, and taxonomic classification. For these reasons, our manuscript will be of general interest to the readership of this Frontiers in Genetics and scientists in the field of evolutionary biology, anthropology, genetics, and clinical morphology. The toolbox and tutorials are free to access and download and are available at <https://github.com/TheWebMonks/meshmonk>, aligning with the open-access model of Frontiers in Genetics.

The manuscript has been reviewed and approved by all authors. We believe that the following reviewers would provide valuable feedback on the manuscript: Peter Hammond ([peter.hammond@wrh.ox.ac.uk](mailto:peter.hammond@wrh.ox.ac.uk)), Christoph Zollikofer ([zolli@aim.uzh.ch](mailto:zolli@aim.uzh.ch)), and Carl Stephan ([c.stephan@uq.edu.au](mailto:c.stephan@uq.edu.au)). We appreciate your time and consideration in reviewing our manuscript and look forward to hearing from you soon.

On behalf of the authors,

Yours sincerely,

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