**MeshMonk: open-source large-scale intensive 3D facial phenotyping**

**Keywords:** automatic landmarking; automated phenotyping; non-rigid registration; phenomics; morphometrics; 3D; face

In the post-genomics era, an emphasis has been placed on understanding ‘genotype-phenotype’ connections so that the biological basis of complex phenotypes can be explained. However, our ability to intensively and comprehensively characterize phenotypes is limited. Anthropometric studies of morphology have traditionally relied on a sparse set of landmarks manually placed on images, then the analysis of these landmarks or distances in candidate gene or genome-wide association studies. This requires the tedious placement of landmarks on many images and is error prone and sensitive to individual differences based on observer. Here, we report a toolbox for fast and repeatable dense phenotyping of 3D images. We have validated this method using 3D facial images, although the procedure can also be applied to 3D scans capturing different morphological structures such as the human brain and skeletal bones.

Given a facial image (target) with five crude positioning landmarks, a rigid registration is first used to orient an anthropometric mask (reference) to the target scan. Then, using a weighted k-nearest neighbors and a visco-elastic transformation model, the reference is transformed to fit the specific shape of the target. For facial scans, this results in homologous spatially dense (N=7,160) quasi-landmark configurations for all 3D images. As validation, a dataset (N=40) with 19 manually-placed landmarks was superimposed onto the reference to identify the closest barycentric coordinate on the mask. These coordinates were then projected back onto the training faces, as well as a new set of 20 faces, and the manual and automatic landmark placements compared.

We demonstrate that this method is highly accurate, with an average Euclidean distance between the manual and automatic placements of ~1.2 mm. The process is robust, even for varying scan quality, camera systems, and ancestries. Though validated using 19 landmarks, the true contribution of this method is that it allows for automated dense phenotyping, freeing the researcher from the use of a limited number of landmarks and allowing them to comprehensively explore variations in surface shape. This expansion opens up an exciting avenue of study in assessing genomic and phenomic data to better understand the genetic contributions to complex morphological traits.