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

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In the post-genomics era, emphasis has been placed on disentangling ‘genotype-phenotype’ connections so that the biological basis of complex phenotypes can be understood. However, our ability to efficiently and comprehensively characterize phenotypes lags behind our ability to characterize genomes. Anthropometric studies of morphology have traditionally relied on sparse sets of landmarks manually placed on images, from which linear distances and angles are calculated to be used in genetic association studies. This requires the tedious placement of landmarks on many images and is error prone and sensitive to individual differences among observers. Here, we report a toolbox for fast and reproducible high-throughput phenotyping of 3D images. While we demonstrate the utility of this method using 3D facial images, the procedure can also be applied to 3D scans of other complex 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 using a leave-one-out approach and the manual and automatic landmark placements were 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 to variation due to scan quality, camera systems, and ancestries. Though validated using 19 landmarks, for comparison with traditional methods, this method allows for automated dense phenotyping, freeing the researcher from the use of a limited number of landmarks and allowing for more comprehensive investigations of facial shape variation. 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.