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

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Abstract

Introduction

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.

Methods

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=41) with 19 manually-placed landmarks was superimposed onto the reference in a leave-one-out approach to identify the closest barycentric coordinate on the mask. These coordinates were then projected back onto the training faces and the manual and automatic landmark placements were compared.

Results and Conclusion

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.

# Introduction

# Materials and Methods

## MeshMonk Overview

### Explanation of process

### Parameters and tuning

## Spatially dense facial quasi-landmarking of 3D facial scans

### Spatially dense facial quasi-landmarking.

3D images in wavefront.obj file format are imported into an in-house 3D image-cleaning program for cropping and trimming, removing hair, ears, and any dissociated polygons. Five crude positioning landmarks are placed on the face to establish a rough facial orientation, but not to guide the eventual landmark mask to the face. An anthropometric mask (Claes et al., 2012) is non-rigidly mapped (Snyders et al., 2014) onto all 3D images and their reflections, constructed by changing the sign of the *x* coordinate (Claes et al., 2011), using the MeshMonk software and the parameters described above. This establishes homologous spatially dense (~10,000) quasi-landmark (QL) configuration for all 3D images and their reflections. Facial shape can be symmetrized using generalized Procrustes alignment (Rohlf and Slice, 1990) to eliminate differences in position, orientation and size of both original and reflected quasi-landmark configurations. The average of an original and its reflected quasi-landmark configuration constitutes the symmetric component, while the difference between the two configurations constitutes the asymmetric component.

### Facial quality control.

Outlier faces, due to quasi-landmark mapping errors, are detected by measuring the Mahalanobis distance for each face to the overall average face in the symmetrized shape space spanned by an orthogonal basis of principal components that captures 98% of the total variation in face shape. From the distribution of Mahalanobis distances, a *z* score for each facial shape is established, and each face with a *z* score equal to or larger than 2 is manually inspected for quasi-landmark errors. Identified erroneous faces are removed, and the whole process starting from the generalized Procrustes superimposition of original and reflected quasi-landmark configurations is repeated.

## Validation

### Sample and data curation

Over many years, our collaborative group has recruited study participants through several studies at the Pennsylvania State University and sampled in the following locations: State College, PA (IRB 44929 and 4320); New York, NY (IRB 45727); Urbana-Champaign, IL (IRB 13103); Dublin, Ireland; Rome, Italy; Warsaw, Poland; and Porto, Portugal (IRB 32341).

Digital facial stereophotogrammetry has been used to capture 3D facial surfaces of N~6,000 participants using the 3dMD Face 2-pod and 3-pod systems (3dMD, Atlanta, GA). This well-established method uses digital photography to generate a dense 3D point cloud representing the surface geometry of the face from multiple 2D images with overlapping fields of view. During photo capture, participant volunteers were asked to adopt a neutral facial expression with their mouth closed and gaze forward, following standard facial image acquisition protocols (Heike et al., 2010). 3D images were immediately stitched together by the camera system and visually checked to make sure that no major holes or artifacts existed.

### Manual placement of validation landmarks

Of the larger sample, N=50 images were chosen at random for validation. This number was then reduced by excluding images from participants that reported major facial injury or surgery and excluding images which did not pass the quality control measures reported above. This resulted in N=41 images for validation. Images were diverse with respect to sex (F=29, M=12), age (18-79, µ=32.7), height (149.86-184.00 cm, µ=167.13 cm), weight (43.00-103.80 kg, µ=67.62 kg), and 3D camera system used (SI Table 1). Most participants reported being of European descent. 3dMDpatient was used to record the 3D coordinates of 19 standard landmarks (7 midline and 12 bilateral) from each unaltered image in wavefront.obj format (Fig. X; Table X). Two independent observers placed these landmarks three times each, with at least 24 hours in-between landmarking sessions, resulting in 6 total landmark iterations for each facial scan. For each individual, we checked for gross landmark coordinate errors (e.g. mislabeling right and left side landmarks) before analysis.

Table X. Description of landmarks used in validation. Landmark descriptions from the Richtsmeier Lab (http://www.getahead.la.psu.edu/).

|  |  |  |  |
| --- | --- | --- | --- |
| Landmark | Abvn. | Location | Definition |
| Glabella | g | Midline | The most prominent midline point between the eyebrows. |
| Nasion | n | Midline | The point in the midline of both the nasal root and the nasofrontal suture. This point is always above the line that connects the two inner canthi. |
| Pronasale | prn | Midline | The most protruded point of the apex nasi. |
| Subnasale | sn | Midline | The midpoint of the angle at the columella base where the lower border of the nasal septum and the surface of the upper lip meet. |
| Labiale superius | ls | Midline | The midpoint of the upper vermillion line. |
| Labiale inferius | li | Midline | The midpoint of the lower vermillion line. |
| Pogonion | SPg | Midline | The most anterior point of the chin. |
| Endocanthion | en | Bilateral | The point at the inner commissure of the eye fissure. |
| Exocanthion | ex | Bilateral | The point at the outer commissure of the eye fissure. |
| Alar curvature | ac | Bilateral | The most lateral point in the curved base of each ala. Indicating the facial insertion of the nasal wingbase. |
| Subalare | sbal | Bilateral | The point at the lower limit of each alar base, where the alar base disappears into the skin of the upper lip. The landmarks indicate the labial insertion of the alar base |
| Crista philtri | cph | Bilateral | The lower point on each elevated margin of the philtrum just above the vermillion line. |
| Chelion | ch | Bilateral | Point located at each labial commissure at the most lateral intersection of upper and lower lip. |

### Automatic placement of validation landmarks (Need some sort of image flow chart for this)

To obtain automatic indications of the 19 validation landmarks, a leave-one-out approach was used to identify the placement of the landmark on the anthropometric mask, then the landmarks were projected back on to the left-out face. Specifically, the average manual landmark configurations of 39 faces were aligned to the anthropometric mask and forced to lie on the surface of the mask, if the landmark and the mask differed in the *z-*dimension. The nearest barycentric coordinate (Hille, 1982) on the anthropometric mask was identified using the average manual landmark coordinates and the barycentric coordinates were then placed on the left-out face. This resulted in the automatic placement of the validation landmarks using a “training” set that did not include the test face.

### Statistical analysis

To validate the placement of automatic landmarks resulting from the MeshMonk anthropometric mask registration, we compared the placement of 19 automatically placed landmarks to those placed manually by two independent observers, while considering the manually placed landmarks to be the “gold standard.” Measurement errors were calculated as the standard deviation between the automatic and manual *x*, *y*, and *z* coordinates as well as the Euclidean distance between landmark placements. In validation, we considered the automatic placements to be a third observer, with the goal of determining if including the automatic placements resulted in errors that were within or below the range of those produced by human observers.

#### Precision of manual landmarks

Precision has been previously defined as the absolute difference between repeated measures of the same estimates and can be calculated local to each landmark without superimposition (Aldridge et al., 2005). Precision was calculated for each landmark as the standard deviation between the *x*, *y*, and *z* coordinates of each rater’s landmarking iterations independently. Measures are averaged across landmarks, images, and subjects (Table X). The average standard deviation along the *x*, *y*, and *z* coordinates for each landmark, averaged across images and subjects is described in SI Table X.

**Table X. Precision of manual landmarks, averaged across all landmarks and subjects.** AZ and JW correspond to the average precision for rater AZ and rater JW, respectively. µ stands for the precision averaged across AZ and JW, or the average precision for both raters.

|  |  |  |  |
| --- | --- | --- | --- |
| Standard deviation | Rater | Average (mm) | SD (mm) |
| X coordinates | AZ | 0.5879967 | 0.477457 |
| JW | 0.4491878 | 0.369121 |
| **µ** | **0.5185923** | **0.423289** |
| Y coordinates | AZ | 0.6512371 | 0.454689 |
| JW | 0.4934764 | 0.440956 |
| **µ** | **0.5723568** | **0.447822** |
| Z coordinates | AZ | 0.4967871 | 0.459968 |
| JW | 0.3674858 | 0.376654 |
| **µ** | **0.4321365** | **0.418311** |

#### Euclidean distance of manual landmarks

An additional measure of intra-observer calculated was the Euclidean distance between landmarking iterations of each rater. Importantly, by calculating distance between placements, instead of distance to the centroid of placements, we create values that are not biased by a change in the centroid when placements are added or removed. This does, however, result in values that are roughly double than the distance to the centroid. This is a mathematical artifact, and not reflective of increased error.

**Table X. Euclidean distance between manual landmarking iterations, averaged across all landmarks and subjects.** AZ and JW correspond to the average distance for rater AZ and rater JW, respectively. µ stands for the distance averaged across AZ and JW, or the average distance for both raters.

|  |  |  |  |
| --- | --- | --- | --- |
| Euclidean distance for iteration: | Rater | Average (mm) | SD (mm) |
| 1 to 2 | AZ | 1.458172 | 1.040034 |
| JW | 1.242497 | 1.015184 |
| **µ** | **1.3503345** | **1.027609** |
| 1 to 3 | AZ | 1.571938 | 1.082158 |
| JW | 1.211532 | 0.928953 |
| **µ** | **1.391735** | **1.005555** |
| 2 to 3 | AZ | 1.451603 | 1.001641 |
| JW | 0.932768 | 0.735655 |
| **µ** | **1.1921855** | **0.868648** |

# Results

## Intra-observer error of manual landmarks

The quantitative study of morphology using 3D coordinates requires specific attention to measurement error and has a robust presence in the literature. For each independent observer, we calculated the intra-observer error of the manual landmarks as the standard deviation between the *x*, *y*, and *z* coordinates of each landmark iteration and the Euclidean distance between the iterations. Table X reports the standard deviation of the *x*, *y* and *z* coordinates averaged across all landmarks for both raters as well as the mean error of the two raters. The average standard deviation of both raters across x, y, and z coordinates was 0.507 mm (0.518 mm along the *x*-dimension, 0.572 mm in the *y*-dimension, and 0.432 mm in the *z*-dimension). This range of deviation is considered highly precise and is similar to previously reported measures of landmark error (Aldridge et al., 2005). The Euclidean distance between each rater’s iterations, as well as the average of the two raters, is given in Table X. The average Euclidean distance was 1.31 mm (1.35 mm for iteration 1 to 2, 1.391 mm for iteration 1 to 3, and 1.19 mm for iteration 2 to 3).

## Distance between points

## Centroid sizes

1. **Discussion**

Manual landmarks were considered the gold standard and have long been used and validated in morphological studies (Aldridge paper).

# Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

# Author Contributions

JW performed validation analyses and landmarked the 3D scans used for validation with AZ. JW and AOC and wrote the first draft of the manuscript under supervision of PC. PC conceptualized the design of the study. HM, OE, SVD, and MS provided input throughout the analyses and writing process. JS developed the MeshMonk code.

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# Ethics statement

Institutional review board (IRB) approval was obtained at all locations and all participants signed a written consent form before participation. The Pennsylvania State University IRB board approved the collection of the participants recruited at the following locations: State College, PA (IRB 44929 and 4320); New York, NY (IRB 45727); Urbana-Champaign, IL (IRB 13103); Dublin, Ireland; Rome, Italy; Warsaw, Poland; and Porto, Portugal (IRB 32341).

# References

# Data Availability Statement

The informed consent with which the data were collected does not allow for dissemination of identifiable data to persons not listed as researchers on the IRB protocol. Thus, the full surface 3D images cannot be made publicly available. In the interest of reproducibility, we have provided the 19 manual and automatic landmarks used for validation as well as the code used to analyze them. These data are available in the following GitHub repository: https://github.com/juliedwhite/RemappingValidation/. The MeshMonk code and tutorials are available at https://github.com/TheWebMonks/meshmonk.