Multilevel Principal Components Analysis of Three-Dimensional Facial Growth in Adolescents

D.J.J. Farnell , S. Richmond , J Galloway , Al Zhurov ,
P. Pirttiniemi , T. Heikkinen , V. Harila , H. Matthews , P. Claes

PII: S0169-2607(19)31413-0
DOI: <https://doi.org/10.1016/j.cmpb.2019.105272>
Reference: COMM 105272

To appear in: *Computer Methods and Programs in Biomedicine*

Received date: 29 August 2019
Revised date: 19 November 2019
Accepted date: 10 December 2019

Please cite this article as: D.J.J. Farnell , S. Richmond , J Galloway , Al Zhurov , P. Pirttiniemi , T. Heikkinen , V. Harila , H. Matthews , P. Claes , Multilevel Principal Components Analysis of Three-Dimensional Facial Growth in Adolescents, *Computer Methods and Programs in Biomedicine* (2019), doi: <https://doi.org/10.1016/j.cmpb.2019.105272>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Highlights

- mPCA indicated that 20.6% of variation in 3D facial shape was explained by age.
- mPCA results showed strong clustering by ethnicity, sex, and age group.
- Males had larger facial changes and for a longer period of time compared to females.
- Male changes were predominantly in the lower third of the face.
- No obvious differences in facial growth was seen between Finnish and Welsh subjects.

Multilevel Principal Components Analysis of Three-Dimensional Facial Growth in Adolescents

DJJ Farnell^{1*}, S Richmond¹, J Galloway¹, AI Zhurov¹, P Pirttiniemi^{2,3}, T Heikkinen^{2,3}, V Harila^{2,3}, H Matthews^{4,5,6,7,8}, and P Claes^{4,5,9}

¹*School of Dentistry, Cardiff University, Heath Park, Cardiff CF14 4XY, United Kingdom*

²*Research Unit of Oral Health Sciences, Faculty of Medicine, University of Oulu, Oulu, Finland*

³*Medical Research Center Oulu (MRC Oulu), Oulu University Hospital, Oulu, Finland*

⁴*Medical Imaging Research Center, UZ Leuven, 3000 Leuven, Belgium*

⁵*Department of Human Genetics, KU Leuven, 3000 Leuven, Belgium*

⁶*OMFS IMPATH Research Group, Department of Imaging and Pathology, Faculty of Medicine, KU Leuven, Leuven*

⁷*Facial Sciences Research Group, Murdoch Children's Research Institute, Melbourne*

⁸*Department of Paediatrics, University of Melbourne, Melbourne, Australia*

⁹*Department of Electrical Engineering, ESAT/PSI, KU Leuven, 3000 Leuven, Belgium*

Abstract

* Corresponding author: Dr Damian JJ Farnell, farnelld@cardiff.ac.uk

Background and Objectives: The study of age-related facial shape changes across different populations and sexes requires new multivariate tools to disentangle different sources of variations present in 3D facial images. Here we wish to use a multivariate technique called multilevel principal components analysis (mPCA) to study three-dimensional facial growth in adolescents.

Methods: These facial shapes were captured for Welsh and Finnish subjects (both male and female) at multiple ages from 12 to 17 years old (i.e., repeated-measures data). 1000 “dense” 3D points were defined regularly for each shape by using a deformable template via “meshmonk” software. A three-level model was used here, namely: level 1 (sex/ethnicity); level 2, all “subject” variations excluding sex, ethnicity, and age; and level 3, age. The technicalities underpinning the mPCA method are presented in Appendices.

Results: Eigenvalues via mPCA predicted that: level 1 (ethnicity/sex) contained 7.9% of variation; level 2 contained 71.5%; and level 3 (age) contained 20.6%. The results for the eigenvalues via mPCA followed a similar pattern to those results of single-level PCA. Results for modes of variation made sense, where effects due to ethnicity, sex, and age were reflected in modes at appropriate levels of the model. Standardised scores at level 1 via mPCA showed much stronger differentiation between sex and ethnicity groups than results of single-level PCA. Results for standardised scores from both single-level PCA and mPCA at level 3 indicated that females had different average “trajectories” with respect to these scores than males, which suggests that facial shape matures in different ways for males and females. No strong evidence of differences in growth patterns between Finnish and Welsh subjects was observed.

Conclusions: mPCA results agree with existing research relating to the general process of facial changes in adolescents with respect to age quoted in the literature. They support

previous evidence that suggests that males demonstrate larger changes and for a longer period of time compared to females, especially in the lower third of the face. These calculations are therefore an excellent initial test that multivariate multilevel methods such as mPCA can be used to describe such age-related changes for “dense” 3D point data.

Keywords

Multilevel PCA; facial shape changes; adolescence

1 Introduction

Three dimensional (3D) facial imaging is a useful method of exploring and quantifying facial shape. 3D imaging is a valuable tool in understanding surgical outcomes after orthognathic surgery [1], malocclusion [2], associations between facial morphology and cardiometabolic risk [3], lip shape during speech [4], facial asymmetry [5], and sleep apnoea [6]. Foetal alcohol syndrome [7,8], Treacher Collins syndrome [9,10], Downs syndrome [11] are just three examples of disorders that can affect facial shape. Facial simulation is of much interest for human-computer interfaces (see, e.g., [12–14]). Normal facial development (“growth” or “ageing”) begins at conception and can be influenced by genetics with over 50 genes discovered [15–19]. Subtle facial differences can be detected between populations reflecting the differing genetic structures in distinct population groups [20–24]. In addition, environmental factors can influence face shape over the course of life such as maternal smoking or alcohol [25–27], atmospheric toxins which can cross the placenta [28], childhood illnesses [29], and medical conditions [30,31]. 3D (computed tomography) images have also been explored in forensic facial reconstructions [32,33]. A review of the use of 3D facial imaging is given in Ref. [34]. The (statistical) analysis of 3D facial shapes has been carried out in many ways previously. As stated in Ref. [35]: “Two general classes of morphometric methods can be used to analyse landmark coordinate data: coordinate-based methods and coordinate-free methods.” Coordinate-free methods involve finding facial angles, distances between specific landmark points, and ratios of such distances in order to quantify age-related changes [35–40]. Multivariate statistics [41], multilevel univariate methods [42], and multivariate Bayesian-type methods [43] have even been used to analyse such coordinate-free data. An interesting comparison of three different methodologies that predict facial growth relative to incremental and positional changes over short- and long-term time periods is given in Ref. [44]. Multivariate modelling techniques have also been used to analyse coordinate

data directly in order to understand age-related changes in facial size and shape. These methods have included: simple “centering” and / or averaging techniques of facial shape at each age followed by a simple parametric model of growth [45], multivariate or kernel regression [46,47], principal components analysis (PCA) based methods [48–50], clustering and discriminant function analysis [51], and autoregressive moving averaging methods [52]. Another related multivariate technique that employs imputation is given by bootstrapped response-based imputation modelling (BRIM) of facial shape [18]. A recent example is also given by a linear mixed model of optic disk shape [53]. Furthermore, the effects of covariates in images have been explored using variational auto-encoders more generally (see, e.g., [54–56]). Multilinear models [57] have also been used to explore facial shape recently. Although such multilinear models should not be confused with methods presented here, there may well be some methodological overlap with them. For example, the way in which multilinear models “decouples the variation into several modes” [58] is similar in spirit to ideas presented here.

Multilevel principal components analysis (mPCA) [59-64] provides a straightforward method of accounting for covariates or clustering when modelling multivariate data such as shape or image data. It has been shown that specific influences on facial shape can be isolated more effectively by using mPCA (at specific levels of the model) than by using single-level PCA [59-64]. Furthermore, mPCA provides useful information relating to the amount of variability explained by these influences by inspection of eigenvalues. Modes of variation at specific levels also provide insight into how these influences affect facial shape. Previous calculations dealt with: facial shape changes between different “ethnicities” and by sex [61], image shape and texture for two expressions (neutral and smiling) [62,63], and time-series shape data tracked through all phases of a smile [63]. A recent mPCA study [64] considered the effects of age on facial shape in adolescents for Monte Carlo simulated data of 21 3D landmark

points (i.e., coordinate data) and for 12 GPA-scaled 3D landmark points for 195 shapes from 27 white, male school-children aged 11 to 16 years old. Modes of variation via mPCA made sense for both datasets and component scores showed a distinct trend with age in both cases. Conditional probabilities were shown to reflect membership by age group for both datasets and the effects of outliers in the Monte Carlo dataset were reduced by using robust methods [64].

The aim of this work is to explore the effects of ethnicity, sex and age on facial variation. (Environmental and genetic factors will be explored in future research.) We wish to determine the similarities and differences that occur in facial changes in adolescents with respect to age for different groups of subjects by ethnicity and sex. Two groups (Finnish and Welsh) are used here in these initial calculations. The multilevel model presented here allows us to do this by modelling between-group variations at one level of the model and within-group variations at another. We expect that the addition of more ethnic groups would be reflected primarily at the level of the model dealing with ethnicity. However, this statement is somewhat speculative and will be explored in future research. An exploration of age, sex and ethnicity / genotype on facial shape is also presented in Ref. [21]. Thus, here we extend previous mPCA calculations [64] to dense “point clouds” of 3D facial shape for males and female Finnish and Welsh subjects aged 12 to 17 years old. The repeated measures aspect of this data is modelled explicitly by an appropriately constructed mPCA model. We wish to prove the principle that mPCA can be used to study age-related changes of facial shapes for such “dense” point data, as well as to compare and contrast our results to the literature on this subject in the conclusions. Finally, mathematical and practical details related to this work are given in Appendices.

2 Materials and Methods

Figure 1. Schematic of a multilevel model of the effects of sex and age on facial shape.

Our dataset consists of 729 3D facial shapes for subjects aged 12 to 17 years old. Each subject had 5 to 10 shapes at different ages. The number of the subjects presented with respect to ethnicity and sex was: Welsh male = 28, Welsh female = 22, Finnish male = 25, Finnish female = 22.” “Meshmonk” software [65] was used to place 1000 3D points regularly on the face for each subject using a non-rigid template. All shapes were subsequently superimposed and scaled with respect to mean shape using a generalized Procrustes analysis. Ethical approval for this study was obtained from the director of education, head teachers, school committees, and the relevant ethics committees of Bro Taf and Cardiff University (reference 04/WSE/109) and the City of Oulu (reference 7728/2006). As the mathematics is slightly involved, the formalism for mPCA is explored in detail in Appendix A. However, the method can be understood for our dataset by considering Fig. 1, which illustrates the “fully nested” three-level model used in these initial proof-of-principle calculations. Sex and ethnicity are represented by a single level (level 1), variations due to differences between subjects (excepting those of age, ethnicity and sex) are represented at level 2, and age is

represented at level 3. We use this model because this data is “repeated-measures” data, i.e., multiple images from individual subjects at different ages for two ethnicities (Welsh and Finnish) and both sexes. The different types of multilevel model are discussed in detail in Appendix B. We note here though that there are three types: fully nested models (as above) where all subjects and groups belong to just one group in the level above it, which is true (importantly) at all levels; non-nested cases where subjects or groups can belong to more than one groups in the levels above it; or “mixed” cases where some levels are fully nested in the level directly above it and some are not. The associated likelihood function for mPCA is presented in Appendix C and an additional maximum likelihood solution is derived.

3 Results

Figure 2: Eigenvalues from single-level PCA and mPCA.

Results for the eigenvalues are shown in Fig. 2. We see that results of mPCA are of the same magnitude and follow a similar pattern to those results of single-level PCA. As expected, there are only three non-zero eigenvalues for level 1 of the model (sex / ethnicity), which is to be expected as there are only four groups at this level (male and female Finnish and Welsh subjects) and so the rank of the covariance matrix at this level is given by 3. By contrast, there are many non-zero eigenvalues at level 3 of the model (age). As there are many other influences that can affect facial shape other than sex, ethnicity, and age, it is also not surprising that level 2 contains many non-zero eigenvalues of larger magnitude as this level represents “all other variations”. Results of mPCA at the three level indicate that they contribute to: level 1, 7.9% of variation; level 2, 71.5% of variation; and, level 3, 20.6% of variation.

Figure 3: Eigenvectors for level 1 (ethnicity/sex), component 1 via mPCA (ethnicity: Finnish to Welsh from mean - 3SD to mean + 3SD); a) mean + 3SD; b) mean; c) mean - 3SD; d) colour map of the projection of this mode ($\times 3SD$) perpendicular to the surface at each point (blue indicates inward changes and yellow indicates outward changes, where the colour bar is in units of mm).

Figure 4: Eigenvectors for level 1 (ethnicity/sex), component 2 via mPCA (sex: male to female from mean $- 3SD$ to mean $+ 3SD$); a) mean $+ 3SD$; b) mean; c) mean $- 3SD$; d) colour map of the projection of this mode ($\times 3SD$) perpendicular to the surface at each point (blue indicates inward changes and yellow indicates outward changes, where the colour bar is in units of mm).

Results for modes of variations from mPCA at levels 1, 2 and 3 are shown in Figs. 3 to 8, respectively. Fig. 3 shows that level 1, component 1 via mPCA corresponds (broadly) to differences between Finnish and Welsh subjects, i.e., from (Finnish) slightly upturned nose and prominent cheeks to (Welsh) a straighter nose, less prominent cheeks, and a generally “squarer” face. By contrast, level 1, component 2 via mPCA in Fig. 4 corresponds (broadly) to differences between males and females, i.e., from (males) prominent chin and brow to (females) more prominent cheeks, reduced chin, nose, and forehead, and rounder face. However, we cannot preclude that some mixing of the effects of ethnicity (Wales versus Finland) and sex has occurred as we have coded these factors together within this specific level via mPCA. Results of single-level PCA for component 4 are quite similar to results for level 1, component 1 via mPCA and results of single-level PCA for component 6 are similar to results for level 1, component 2 via mPCA, and so these results of single-level PCA are not presented here.

Figure 5: Eigenvectors for level 2 (all other "subject" variations), component 1 via mPCA; a) mean + 3SD; b) mean; c) mean - 3SD; d) colour map of the projection of this mode ($\times 3SD$) perpendicular to the surface at each point (blue indicates inward changes and yellow indicates outward changes, where the colour bar is in units of mm).

Figure 6 Eigenvectors for level 2 (all other “subject” variations), component 2 via mPCA; a) mean + 3SD; b) mean; c) mean – 3SD; d) colour map of the projection of this mode ($\times 3SD$) perpendicular to the surface at each point (blue indicates inward changes and yellow indicates outward changes, where the colour bar is in units of mm).

Fig. 5 shows that level 2, component 1 via mPCA corresponds to changes in the overall width of the face, and (strongly) the prominence of the jaw and mouth/cheeks. The eigenvalue for this component was the largest overall via mPCA and strong changes can be seen in Fig. 5. Note that mPCA, level 2, component 2 in Fig. 6 corresponds to changes going from a thinner to a rounder (flatter) face. Arguably, these changes in Figs. 5 and 6 are not due to ethnicity, sex, or age. Although this is what we would expect, some caution is warranted as these components can be subtle to interpret. Inspection of components for single-level PCA (not shown here) indicate that single-level PCA, component 1 corresponds to mPCA, level 2, component 1 and single-level PCA, component 2 probably corresponds to mPCA, level 2, component 2.

Figure 7: Eigenvectors, level 3 (age), component 1 via mPCA (increasing age from: mean – 3SD to mean + 3SD); a) mean + 3SD; b) mean; c) mean – 3SD; d) colour map of the projection of this mode ($\times 3SD$) perpendicular to the surface at each point (blue indicates inward changes and yellow indicates outward changes, where the colour bar is in units of mm).

Figure 8: Eigenvectors level 3 (age), component 2 via mPCA (decreasing age from: mean – 3SD to mean + 3SD); a) mean + 3SD; b) mean; c) mean – 3SD; d) colour map of the projection of this mode ($\times 3SD$) perpendicular to the surface at each point (blue indicates inward changes and yellow indicates outward changes, where the colour bar is in units of mm).

Results for major modes of variation at level 3 via mPCA in Figs. 7 and 8 are consistent with changes in facial shape due to age. For example, level 3, component 1 in Fig. 7 indicates an increase in the prominence of the chin and the size of the nose with increasing age, such that features become more strongly defined. Furthermore, the forehead also becomes less prominent with increasing age and cheeks also become less rounded. The second component via mPCA at level 3 in Fig. 8 also corresponds to an increase in prominence of the chin again, so features become slightly more defined, although the face also becomes slightly wider. It is much harder to identify specific modes associated with age for single-level PCA compared to mPCA. Again, it is likely that different “effects” are strongly mixed together for single-level PCA.

Figure 9: Standardised component scores via: top left, mPCA, level 1, components 1 and 2; top right, mPCA, level 3, components 1 and 2; bottom left, single-level PCA, components 4 and 6; bottom right, single-level PCA, components 1 and 2. Centroids for the four groups by ethnicity and sex are shown in the left-hand figures and centroids for the six age groups (12 years old to 17 years old) are shown in the right-hand figures.

Results for standardised component scores are shown in Fig. 9 for mPCA and single-level PCA. We see that strong differentiation between groups by ethnicity and sex is seen at level 1 via mPCA, as expected. No strong difference between these ethnicity and sex groups is seen at the other levels. This figure also clearly shows that level 1, component 1 via mPCA relates to ethnicity and level 1, component 2 via mPCA relates to sex. As can be seen from Fig. 9, single-level PCA also shows similar differences between these groups for components 4 and 6, although there is much more overlap in these scores when compared to those results of mPCA. Figure 9 demonstrates also that a strong progression in the positions of the centroids of standardised component scores with age group occurs at level 3 via mPCA. (No strong differentiation in centroids with age is observed in scores at either levels 1 or 2 via mPCA.) Single-level PCA results also shows a progression in terms of the centroids of the component scores with age in both components 1 and 2. We see also from Fig. 9 that (average / centroid)

standardised scores for males (i.e., lines with blue upward diamonds for Welsh males and with green downward diamonds for Finnish males) and females (i.e., lines with red “right” diamonds for Welsh females and with pink “left” diamonds for Finnish females) appear to follow different paths or “trajectories” for both single-level PCA and mPCA. Indeed, males appear to have a larger “trajectory” than females with respect to these centroids of standardised scores for level 3, component 1 via mPCA. Similarly, the trajectory of centroids for component 2 via single-level PCA is also shorter for females compared to males. However, sample sizes for each ethnicity / sex group are small and so any such statements are somewhat speculative. The issue of the length of these trajectories is also complicated (slightly) by the fact that we have standardised components so that scores for different components are on a similar scale. There was no obvious evidence of a difference in growth patterns for Welsh females versus Finnish females and for Welsh males versus Finnish males, i.e., it is hard to say if the “trajectories” of their centroids at level 3 via mPCA are different, although we remark again that such analyses are hampered by small sample sizes.

4 Discussion

The effect of age on 3D facial shape data in adolescents has been explored in this work. The formalism for mPCA has been described and it was seen that mPCA allows us to model variations at different levels of structure in the data, namely: level 1 (ethnicity / sex); level 2 (all “other” variations, i.e., excepting ethnicity / sex /age); and, level 3 (age). Eigenvalues appeared to make sense for our dataset. In particular, examination of eigenvalues suggested that age contributed approximately 20.6% to the total variation in the shapes. Modes of variation via mPCA also appeared to make sense, where changes in facial shape due to ethnicity and sex were observed (correctly) at level 1 and changes due to age were seen (also correctly) at level 3. Evidence of clustering by ethnicity and sex and (separately) by age group was seen in the standardised component scores at levels 1 and 3, respectively, of the mPCA model (and also in scores for single-level PCA). These results are good tests that mPCA provides reasonable results. It was also noted that “trajectories” of centroids of standardised component scores for males and females appeared to be different at level 3 of the mPCA model and via single-level PCA. Indeed, trajectories of these scores for females appeared to be shorter than for males for level 3, component 1 via mPCA and also (separately) in component scores via single-level PCA. However, this was hard to ascertain definitively due to small sample sizes. No obvious evidence of differences in trajectories between Welsh and Finnish subjects (for males and females separately) with age was observed, although again sample sizes were small. An initial exploration of the associated multivariate probability distribution for such multilevel architectures was presented in appendices and the different types of multilevel models via mPCA were described. The likelihood function for mPCA was presented in appendices and an additional maximum likelihood solution was presented.

There has been much previous research relating to the process of facial changes in adolescents with respect to age (see, e.g., Refs. [36-52,66-70]). In particular, a review of age-related facial changes [40] points out the difficulty of predicting changes in specific subjects, noting, for example, that: “the adolescent growth spurt in the mandible occurs in less than 25% of the cases, but the presence, onset, duration, and magnitude of the pubertal growth spurt in facial dimensions cannot be accurately predicted for any single individual.” mPCA provides a possible method of resolving this problem by representing individual variations at one level and group-level and / or age-related changes at other levels. However, more research (and larger sample sizes) are necessary to establish if this will work in practice at an “individual level”.

Our results for the first two components at level 3 via mPCA appear to support statements relating to “aging” in adolescents in Ref. [52], which states (generally) that: “a chubby face turns into an elongated and more distinct face during the growth” and that “facial features, such as the nose and the eyes, become more prominent and evolve to the main characteristics of a face.” However, we believe that our results via mPCA and single-level PCA also demonstrate differences in age-related changes in facial shape between the sexes. No obvious differences in growth patterns between Welsh and Finnish subjects was evident. An analysis of differences in changes in facial shape during adolescence between the sexes is given in Ref. [49] and the interested is referred to this reference for more information. It is stated in the abstract of Ref. [67] that “a large part of male facial volume preponderance occurred in the lower third of the face,” which (speculatively) is reminiscent of changes due to level 3, component 1 via mPCA. Furthermore, we remark again that trajectories of centroids of standardised component scores with age group for level 3 via mPCA and via single-level PCA were different for males compared to females. A recent study [49] used PCA of “landmark” 3D facial shape data in order to study facial changes in male and female

populations aged 12 to 15 years old. The authors of this study also found that males had larger trajectories with age with respect to PC components than females [49], which agrees with initial results presented here. These results for a “larger trajectory” for males in this age range correspond with empirical evidence given in Ref. [70], which states that “surface changes are greater in boys than girls” with “boys exhibiting more changes later.” (Some caution should be exercised here though as some members of both sexes are probably still changing between the ages of 12 and 17 years old.) We therefore conclude that our work supports existing evidence in the literature relating to facial changes in adolescents with respect to age.

An important advantage of such multilevel methods as presented here is that our model can reflect explicitly the design of the experiment or structure of the population of shapes. We can view the model in Fig. 1 for our study as an idealisation of the structure of the population of our shapes, namely: individual shapes at level 3 nested within subjects at level 2 (i.e., multiple shapes from each subject) and individual subjects at level 2 nested within the different ethnicity / sex groups at level 1. We expect that models that follow the structure of the experiment or population should perform better than those (e.g., single-level) models that do not. Indeed, this has been shown to be the case here. Again, we wished to “prove the principle” that multivariate multilevel models can be used to explore facial variation with age only; an exploration of alternative potential (e.g., 3- or 4-level) models will be carried out in future research. Another important advantage of mPCA is that eigenvectors within each level are orthogonal, although eigenvectors do not necessarily need to be orthogonal between levels. mPCA should therefore demonstrate less “mixing” between effects in modes of variation (for those influences represented at different levels of the model) than in modes of variation via single-level PCA. Indeed, the evidence presented in this article strongly supports this supposition. Finally, the importance of multivariate techniques, including PCA, is

becoming recognised more generally in engineering and computer science (see, e.g. Refs. [71,72]).

Understanding the normal variation of the growth of facial shape in adolescents is crucial in ascertaining how human adolescents age. The results presented here have been shown to be a useful first step in establishing multivariate multilevel statistical approaches as a viable method of modelling the effects of age in adolescents across multiple populations. By comparing new shapes to the model, it should be possible in future to identify those subjects that are outlying to normal variation encapsulated in the model and therefore at risk of disease. However, larger sample sizes are necessary in this case. Our results therefore have the potential to be very important clinically in assessing normal facial variation in adolescents in future. The significance of this article is also that it presents important methodological advances for the mPCA method in appendices, including a full maximum-likelihood solution.

5 Conclusions

We have shown in this article that mPCA can be applied to “dense” 3D point data representing facial shape. Changes in facial shape due to ethnicity, sex, and age were represented correctly at appropriate levels of the mPCA model. Results of mPCA compared well to those results of single-level PCA, although we expect that less “mixing” of different effects should occur in modes of variations for mPCA compared to single-level PCA. We found suggestive differences in age-related changes in facial shape between the sexes. Our results relating to age-related changes in adolescents appeared to agree with previous results cited in the literature. No strong evidence of differences in age-related changes in facial shape was observed by ethnicity. Our results yielded insight into facial changes in adolescents with

respect to age and they are an encouraging and successful initial exploration of the use of mPCA to study age-related changes in facial shape during adolescence for “dense” 3D point data.

Acknowledgments

This investigation was supported by the KU Leuven, BOF (C14/15/081), NIH (1-RO1-DE027023) and the FWO Flanders (G078518N).

Appendix A: mPCA Mathematical Formalism

3D landmark points are represented by a vector z for each shape. Single-level PCA is carried out by finding the mean shape vector μ over all shapes and a covariance matrix

$$\Sigma_{k_1, k_2} = \frac{1}{N-1} \sum_{i=1}^n (z_{ik_1} - \mu_{ik_1})(z_{ik_2} - \mu_{ik_2}) . \quad (A1)$$

k_1 and k_2 indicate elements of this covariance matrix and i refers to a given subject. The eigenvalues λ_l and (orthonormal) eigenvectors u_l of this matrix are found readily. For PCA, one ranks all the eigenvalues into descending order and one retains the first p_1 components in the model. The shape z is modeled by

$$z^{model} = \mu + \sum_{l=1}^{p_1} a_l u_l , \quad (A2)$$

The coefficients $\{a_l\}$ (also referred to as “component scores” here) are found readily by using a scalar product with respect to the set of orthonormal eigenvectors, i.e., $a_l = u_l \cdot (z - \bar{z})$, for a fit of the model to a new shape vector z . The component score a_l is standardized by dividing by the square root of the eigenvalue λ_l .

mPCA allows us to isolate the effects of various influences on shape at different levels of the model and this is illustrated as a schematic in Fig. 1 given above. The covariance matrix at level 3 is formed with respect to all “repeated measurements” of 3D facial shape for each subject individually (at different ages) and then these covariance matrices are averaged over all subjects to give the level 3 covariance matrix, Σ^3 . The average shape over all ages for each subject l_2 in each sex / ethnicity group l_1 is denoted by $\mu_{l_1 l_2}^3$. Each subject “forms their own group” at level 2. Note that the “repeated measures” aspect of the data is therefore modelled

explicitly at level 3 by using this approach. The covariance matrix Σ^2 at level 2 is formed with respect to the shapes $\mu_{l_1 l_2}^3$ and then these covariance matrices are averaged over l_1 (i.e., the four sex / ethnicity groups here) to give the level 2 covariance matrix, Σ^2 . The average shape for each sex / ethnicity group l_1 is denoted by $\mu_{l_1}^2$. Finally, the covariance matrix Σ^1 at level 1 is formed with respect to these shapes $\mu_{l_1}^2$ and the overall “grand mean” shape is denoted by μ^1 . Again, these relationships are illustrated in Fig. 1 for the multilevel model used here. mPCA diagonalizes the covariance matrices at the three levels separately. The l -th eigenvalue at level 1 is denoted by λ_l^1 , with associated eigenvector u_l^1 , the l -th eigenvalue at level 2 is denoted by λ_l^2 , with associated eigenvector u_l^2 , and the l -th eigenvalue at level 3 is denoted by λ_l^3 , with associated eigenvector u_l^3 . We rank the eigenvalues into descending order at each level of the model separately, and then we retain the first p_1 , p_2 and p_3 eigenvectors of largest magnitude at the three levels, respectively. Note that eigenvectors within each level are orthogonal, although eigenvectors do not necessarily need to be orthogonal between levels. We expect that mPCA should demonstrate less “mixing” between effects in modes of variation (for those influences represented at different levels of the model) than in modes of variation via single-level PCA. The shape z is modeled via mPCA by

$$z^{model} = \mu^1 + \sum_{l=1}^{p_1} a_l^1 u_l^1 + \sum_{l=1}^{p_2} a_l^2 u_l^2 + \sum_{l=1}^{p_3} a_l^3 u_l^3, \quad (A3)$$

where μ^1 is the “grand mean” at level 1, as described above. The coefficients $\{a_l^1\}$, $\{a_l^2\}$ and $\{a_l^3\}$ (again referred to as “component scores” here) are determined for any new shape z by using a global optimization procedure in MATLAB R2017 with respect to an appropriate cost function. The mPCA component scores a_l^1 , a_l^2 and a_l^3 may again be standardized by dividing by the square roots of λ_l^1 , λ_l^2 , and λ_l^3 respectively.

Appendix B: Fully Nested, Non-Nested, and “Mixed” Cases

Before going on to define the associated likelihood function via mPCA, it is useful firstly to define what types of model are possible via this multilevel approach. We define these as:

- Fully “nested” cases are those where shapes, subjects, or groups belong to exactly and only one group in the above it and (importantly) at all levels. A classic example here are clusters by school or class for some arbitrary “outcome” (e.g., exam results or here, facial shape). Each child belongs to one class only and each class belongs to only one school. Thus, this design is “fully nested” at all levels.
- Fully “non-nested” cases have groups at a given level than can belong to more than one group in the levels above it. An example here would be to represent sex and ethnicity at different levels (e.g., 1 and 2) of the model and subjects at the bottom level. Note that one can have males and females for multiple types of ethnicity (e.g., Finnish or Welsh, as given here). This design is “non-nested” at all levels (excepting the bottom level). Note also that there is no actual order as such for the ethnicity and sex levels (1 and 2) as such in this example.
- Some multilevel cases contain both fully nested and non-nested elements, which we shall refer to here as “mixed.” An example might be to set sex and ethnicity at separate levels (1 and 2) for a given set of subjects but with repeated measures at level 4 for each subject at level 3 (e.g., exam results at different time points). Again, there is no actual order as such for the ethnicity and sex levels, although there definitely is an order for repeated measures as they belong to only one subject in the level above them. (Note that each subject “forms their own group” at level 3 in this model.)

Appendix C: Likelihood function for a fully nested 3-level model

Note that we consider a three-level fully nested model (as used here), although the extension to more levels follows on analogously. Firstly, we define two sets of weights or probabilities at levels 1 (π_{l_1}) and 2 ($\pi_{l_1 l_2}$), where l_1 refers to a specific sex /ethnicity group at level 1 and l_2 refers to a specific subject in group l_1 . We remember again that the average shape over all shapes at different ages for each subject (here) is denoted by $\mu_{l_1 l_2}^3$. The average shape for group l_1 is denoted by $\mu_{l_1}^2$ and the overall grand mean is denoted by μ^1 . The number of sex / ethnicity groups at level 1 is $m_1(=4)$ and the number of subjects in each group l_1 is m_{l_1} . Note that $\sum_{l_1} m_{l_1}$ is the total number of subjects (and not the total number of shapes), i.e., 118 subjects in total. Finally, sample sizes at the lowest level are given by $n_{l_1 l_2}$. For our dataset, $n_{l_1 l_2}$ refers to the number of repeated measurements for each subject l_2 in each group l_1 . A general expression for the likelihood function of a fully nested three-level model is given by

$$L = \prod_{l_1}^{m_1} \prod_{l_2}^{m_{l_1}} \prod_i^{n_{l_1 l_2}} \pi_{l_1} \pi_{l_1 l_2} P(z_i | l_1 l_2) \quad , \quad (C1)$$

The associated log-likelihood is given by,

$$LL = \sum_{l_1}^{m_1} n_{l_1} \ln \pi_{l_1} + \sum_{l_1}^{m_1} \sum_{l_2}^{m_{l_1}} n_{l_1 l_2} \ln \pi_{l_1 l_2} + \sum_{l_1}^{m_1} \sum_{l_2}^{m_{l_1}} \sum_i^{n_{l_1 l_2}} \ln P(z_i | l_1 l_2) \quad , \quad (C2)$$

where

$$n_{l_1} = \sum_{l_2}^{m_{l_1}} n_{l_1 l_2} \quad . \quad (C3)$$

Note that n_{l_1} is the total number of shapes within group l_1 and that the total number of shapes overall is given by: $n = \sum_{l_1} n_{l_1}$. For mPCA, we model different sources of variation at different levels of the model and (common) covariance matrices are diagonalized at each level, as explained above. Hence, a natural assumption is to use multivariate Gaussians at the lowest level to represent the distribution of data within a group. A general expression for the multivariate Gaussian distributions at level 3 is given by

$$P(z_i | l_1 l_2) = N(z_i | \mu_{l_1 l_2}^3, \Sigma_{l_1 l_2}^3) \quad , \quad (C4)$$

where $\Sigma_{l_1 l_2}^3$ is the covariance matrix for subject $l_1 l_2$ in in sex / ethnicity group l_1 . (Note again that mPCA uses a common covariance matrix at level 3 and so the expression above is slightly more general.) A further natural assumption (see also Ref. [52]) for mPCA is that the probabilities at levels 1 (π_{l_1}) and 2 ($\pi_{l_1 l_2}$) are also proportional to Gaussians, where

$$\pi_{l_1 l_2} \propto N(\mu_{l_1 l_2}^3 | \mu_{l_1}^2, \Sigma_{l_1}^2) \quad \& \quad \pi_{l_1} \propto N(\mu_{l_1}^2 | \mu^1, \Sigma^1) \quad . \quad (C5)$$

This assumption is reasonable when the sample sizes per group are large. (Note again that mPCA uses a common covariance matrix also at level 2 and so the expression above is slightly more general.) When sample sizes are low however, the following “flat” expression for these probabilities [52] might be more appropriate,

$$\pi_{l_1 l_2} = \frac{1}{m_{l_1}} \quad \forall \quad l_2 \quad \& \quad \pi_{l_1} = \frac{1}{m_1} \quad \forall \quad l_1 \quad . \quad (C6)$$

Finally, let us now assume that π_{l_1} and $\pi_{l_1 l_2}$ are completely “free” parameters. The maximum likelihood (ML) solution for Eq. (C2) with respect to π_{l_1} and $\pi_{l_1 l_2}$ (with additional Lagrange multipliers to ensure that probabilities sum correctly to 1) is given by,

$$\pi_{l_1 l_2} = \frac{n_{l_1 l_2}}{n_{l_1}} \quad \& \quad \pi_{l_1} = \frac{n_{l_1}}{n} . \quad (C7)$$

Hence, we see that Eq. (C6) for mPCA is a limiting case of the ML solution, i.e., when all sample sizes per group are equal (at each level appropriately). The analysis of the likelihood function has therefore yielded valuable insight into the mPCA method. Note also that (biased) population estimates of covariance matrices are obtained via the ML solution rather than sample estimates used in mPCA. This result means that one uses denominators of “ n ” rather than “ $n - 1$ ” when evaluating these matrices. In principle, a maximum likelihood solution could be found for distributions other than multivariate Gaussians of Eq. (C4) used at level 3, including non-parametric multivariate distributions.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

References

1. C.H. Cau, A. Cronin, P. Durning, A.I. Zhurov, A. Sandham, S. Richmond, A new method for the 3D measurement of postoperative swelling following orthognathic surgery. *Orthodontic Craniofacial Research* **9** (2006) 31–37.
2. B. Krneta, J. Primožič, A.I. Zhurov, S. Richmond, M. Ovsenik, Three-dimensional evaluation of facial morphology in children aged 5–6 years with a Class III malocclusion. *European Journal of Orthodontics* **36** (2012) 133–139.
3. J. Djordjevic, D.A. Lawlor, A.I. Zhurov, A.M. Toma, R. Playle, S. Richmond, A population-based cross-sectional study of the association between facial morphology and cardiometabolic risk factors in adolescence. *BMJ Open* **3** (2013) e002910.
4. H. Popat, A.I. Zhurov, A.M. Toma, S. Richmond, D. Marshall, P.L. Rosin, Statistical modeling of lip movement in the clinical context. *Orthodontic Craniofacial Research* **15** (2015) 92–102.
5. M. Alqattan, J. Djordjevic, A.I. Zhurov, S. Richmond, Comparison between landmark and surface-based three-dimensional analyses of facial asymmetry in adults. *European Journal of Orthodontics* **37** (2013) 1–2.
6. A. Al Ali, S. Richmond, H. Popat, R. Playle, T. Pickles, A.I. Zhurov, D. Marshall, P.L. Rosin, J. Henderson, K. Bonuck, The influence of snoring, mouth breathing and apnoea on facial morphology in late childhood: A three-dimensional study. *BMJ Open* **5** (2015) e009027.
7. K. Jones and D. Smith, Recognition of the fetal alcohol syndrome in early infancy. *The Lancet* **302** (1973) 999–1001.
8. A.P. Streissguth, J.M. Aase, S.K. Clarren, S.P. Randels, R.A. LaDue, and D.F. Smith, Fetal alcohol syndrome in adolescents and adults. *Journal of the American Medical Association* **265** (1991) 1961–1967.

9. J. McKenzie and J. Craig, Mandibulo-facial dysostosis (Treacher Collins syndrome). *Archives of Disease in Childhood* **30** (1955) 391.
10. D. Poswillo, The pathogenesis of the Treacher Collins syndrome (mandibulofacial dysostosis). *British Journal of Oral Surgery* **13** (1975) 1–26.
11. J.E. Allanson, P. O'Hara, L.G. Farkas, and R.C. Nair, R.C., Anthropometric craniofacial pattern profiles in Down syndrome. *American Journal of Medical Genetics* **47** (1993) 748–752.
12. J. Vandeventer, 4D (3D Dynamic) Statistical Models of Conversational Expressions and the Synthesis of Highly-Realistic 4D Facial Expression Sequences. Ph.D. Thesis, Cardiff University, Cardiff, UK, 2015.
13. J. Vandeventer, L. Graser, M. Rychlowska, P.L. Rosin, D. Marshall, Towards 4D coupled models of conversational facial expression interactions. In *Proceedings of the British Machine Vision Conference*; BMVA Press: Durham, United Kingdom (2015) 142–141.
14. K. Al-Meyah, D. Marshall, P. Rosin, 4D Analysis of Facial Ageing Using Dynamic Features. *Procedia Computer Science* **112** (2017) 790–799.
15. L. Paternoster, A.I. Zhurov, A.M. Toma, J.P. Kemp, B. St. Pourcain, N.J. Timpson, G. McMahon, W. McArdle, S.M. Ring, G. Davey Smith, Genome-wide Association Study of Three-Dimensional Facial Morphology Identifies a Variant in PAX3 Associated with Nasion Position. *American Journal of Human Genetics* **90** (2012) 478–485.
16. G. Fatemifar, C.J. Hoggart, L. Paternoster, J.P. Kemp, I. Prokopenko, M. Horikoshi, V.J. Wright, J.H. Tobias, S. Richmond, A.I. Zhurov, Genome-wide association study of primary tooth eruption identifies pleiotropic loci associated with height and craniofacial distances. *Human Molecular Genetics* **22** (2013) 3807–3817.

17. P. Claes, H. Hill, M.D. Shriver, Toward DNA-based facial composites: Preliminary results and validation. *Forensic Science International: Genetics* **13** (2014) 208–216.
18. P. Claes, D.K. Liberton, K. Daniels, K.M. Rosana, E.E. Quillen, L.N. Pearson, B. McEvoy, M. Bauchet, A.A. Zaidi, W. Yao, and H. Tang, Modeling 3D facial shape from DNA. *PLoS Genetics* **10** (2014) e1004224.
19. P. Claes, J. Roosenboom, J.D. White, T. Swigut, D. Sero, J. Li, M.K. Lee, A. Zaidi, B.C. Mattern, C. Liebowitz, and L. Pearson, Genome-wide mapping of global-to-local genetic effects on human facial shape. *Nature Genetics* **50** (2018) 414–423.
20. S. Richmond, L.J. Howe, S. Lewis, E. Stergiakouli, A. Zhurov, Facial Genetics: A Brief Overview. *Frontiers in Genetics* **9** (2018) 462.
21. S.M. Hopman, J.H. Merks, M. Suttie, R.C. Hennekam, and P. Hammond, Face shape differs in phylogenetically related populations. *European Journal of Human Genetics* **22** (2014) 1268–1271.
22. S. Leslie, B. Winney, G. Hellenthal, D. Davison, A. Boumertit, T. Day, K. Hutnik, E.C. Royrvik, B. Cunliffe, D.J. Lawson, and D. Falush, D., 2015. The fine-scale genetic structure of the British population. *Nature* **519** (2015) 309.
23. M. Nelis, T. Esko, R. Mägi, F. Zimprich, A. Zimprich, D. Toncheva, S. Karachanak, T. Piskáčková, I. Balašćák, L. Peltonen, and E. Jakkula, Genetic structure of Europeans: a view from the North–East. *PloS One* **4** (2009) e5472.
24. E. Persyn, R. Redon, L. Bellanger, and C. Dina, The impact of a fine-scale population stratification on rare variant association test results. *PLoS One* **13** (2018) e0207677.
25. S. Richmond, A.I. Zhurov, A.S.M. Ali, P. Pirttiniemi, T. Heikkinen, V. Harila, S. Silinevica, G. Jakobsone, I. Urtane, Exploring the midline soft tissue surface changes from 12 to 15 years of age in three distinct country population cohorts. *European Journal of Orthodontics* (2019) – in press.

26. L. Mamluk, H.B. Edwards, J. Savović, V. Leach, T. Jones, T.H. Moore, S. Ijaz, S.J. Lewis, J.L. Donovan, D. Lawlor, and G.D. Smith, G.D., Low alcohol consumption and pregnancy and childhood outcomes: time to change guidelines indicating apparently 'safe' levels of alcohol during pregnancy? A systematic review and meta-analyses. *BMJ Open* **7** (2017) e015410.
27. E. Muggli, H. Matthews, A. Penington, P. Claes, C. O'Leary, D. Forster, S. Donath, P.J. Anderson, S. Lewis, C. Nagle, and J.M. Craig, Association between prenatal alcohol exposure and craniofacial shape of children at 12 months of age. *JAMA Pediatrics* **171** (2017) 771–780.
28. L.J. Howe, G.C. Sharp, G. Hemani, L. Zuccolo, S. Richmond, and S.J. Lewis, Prenatal alcohol exposure and facial morphology in a UK cohort. *Drug and Alcohol Dependence* **197** (2019) 42–47.
29. H. Mirghani, N. Osman, S. Dhanasekaran, H.M. Elbiss, and G. Bekdache, Transplacental transfer of 2-naphthol in human placenta. *Toxicology Reports* **2** (2015) 957–960.
30. N. Pound, D.W. Lawson, A.M. Toma, S. Richmond, A.I. Zhurov, I.S. Penton-Voak, Facial fluctuating asymmetry is not associated with childhood ill-health in a large British cohort study. *Proceedings of the Royal Society B: Biological Sciences* **281**, no. **1792** (2014) 20141639.
31. J. Djordjevic, A.I. Zhurov, S. Richmond, Visigen Consortium. Genetic and Environmental Contributions to Facial Morphological Variation: A 3D Population-Based Twin Study. *PLoS ONE* **11** (2016) e0162250.
32. S.D.S. Rocha, D.L.D.P. Ramos, and M.D.G.P. Cavalcanti, Applicability of 3D-CT facial reconstruction for forensic individual identification. *Pesquisa Odontológica Brasileira* **17** (2003) 24–28.

33. W.J. Lee, C.M. Wilkinson, and H.S. Hwang, An accuracy assessment of forensic computerized facial reconstruction employing cone-beam computed tomography from live subjects. *Journal of Forensic Sciences* **57** (2012) 318–327.
34. A.R. Al-Khatib, Facial three dimensional surface imaging: An overview. *Archives of Orofacial Sciences* **5** (2010) 1–8.
35. J.T. Richtsmeier, J.M. Cheverud, and S. Lele, S., Advances in anthropological morphometrics. *Annual Review of Anthropology* **21** (1992) 283–305.
36. R.M. Ricketts, The influence of orthodontic treatment on facial growth and development. *The Angle Orthodontist* **30** (1960) 103–133.
37. E.O. Bergersen, The male adolescent facial growth spurt: its prediction and relation to skeletal maturation. *The Angle Orthodontist* **42** (1972) 319–338.
38. S.J. Chaconas, and J.D. Bartroff, Prediction of normal soft tissue facial changes. *The Angle Orthodontist* **45** (1975) 12–25.
39. A. Verdonck, M. Gaethofs, C. Carels, and F. de Zegher, Effect of low-dose testosterone treatment on craniofacial growth in boys with delayed puberty. *The European Journal of Orthodontics* **21** (1999) 137–143.
40. S.E. Bishara, Facial and dental changes in adolescents and their clinical implications. *The Angle Orthodontist* **70** (2000) 471–483.
41. S.N. Bhatia, G.W. Wright, and B.C. Leighton, A proposed multivariate model for prediction of facial growth. *American Journal of Orthodontics* **75** (1979) 264–281.
42. B.A. Chvatal, R.G. Behrents, R.F. Ceen, and P.H. Buschang, Development and testing of multilevel models for longitudinal craniofacial growth prediction. *American Journal of Orthodontics and Dentofacial Orthopedics* **128** (2005) 45–56.

43. D.J. Rudolph, S.E. White, and P.M. Sinclair, Multivariate prediction of skeletal Class II growth. *American Journal of Orthodontics and Dentofacial Orthopedics* **114** (1998) 283–291.
44. B.J. Turchetta, L.S. Fishman, and J.D. Subtelny, Facial growth prediction: a comparison of methodologies. *American Journal of Orthodontics and Dentofacial Orthopedics* **132** (2007) 439–449.
45. M.L. Moss, R. Skalak, M. Shinozuka, H. Patel, L. Moss-Salentijn, H. Vilmann, and P. Mehta, Statistical testing of an allometric centered model of craniofacial growth. *American Journal of Orthodontics* **83** (1983) 5–18.
46. H.Y. Suh, S.J. Lee, Y.S. Lee, R.E. Donatelli, T.T. Wheeler, S.H. Kim, S.H. Eo, and B.M. Seo, A more accurate method of predicting soft tissue changes after mandibular setback surgery. *Journal of Oral and Maxillofacial Surgery* **70** (2012) e553–e562.
47. H.S. Matthews, A.J. Penington, R. Hardiman, Y. Fan, J.G. Clement, N.M. Kilpatrick, and P. Claes, P.D., Modelling 3D craniofacial growth trajectories for population comparison and classification illustrated using sex-differences. *Scientific Reports* **8** (2018) 4771.
48. E.D. Schneiderman, S.M. Willis, C.J. Kowalski, and T.R. Ten Have, T.R., A PC program for growth prediction in the context of Rao's polynomial growth curve model. *Computers in Biology and Medicine* **22** (1992) 181–188.
49. J. Koudelová, J. Dupej, J. Brůžek, P. Sedlak, and J. Velemínská, Modelling of facial growth in Czech children based on longitudinal data: Age progression from 12 to 15 years using 3D surface models. *Forensic Science International* **248** (2015) 33–40.
50. R.J. Hennessy and J.P. Moss, Facial growth: separating shape from size. *The European Journal of Orthodontics* **23** (2001) 275–285.

51. E.S.J. Abu Alhaija and A. Richardson, Growth prediction in Class III patients using cluster and discriminant function analysis. *The European Journal of Orthodontics* **25** (2003) 599–608.
52. A.J. Lin, S. Lai. and F. Cheng, Growth simulation of facial/head model from childhood to adulthood. *Computer-Aided Design and Applications* **7** (2010) 777–786.
53. I.J. MacCormick, B.M. Williams, Y. Zheng, K. Li, B. Al-Bander, S. Czanner, R. Cheeseman, C.E. Willoughby, E.N. Brown, G.L. Spaeth, G. Czanner, Accurate, fast, data efficient and interpretable glaucoma diagnosis with automated spatial analysis of the whole cup to disc profile. *PloS One* **10** (2019) e0209409.
54. C. Doersch, Tutorial on variational autoencoders, (2016) arXiv:1606.05908.
55. Y. Pu, Z. Gan, R. Henao, X. Yuan, C. Li, A. Stevens, and L. Carin, Variational autoencoder for deep learning of images, labels and captions. In *Advances in Neural Information Processing Systems*, Curran Associates, Inc., Red Hook, USA. (2016) 2352–2360.
56. S.J. Wetzel. Unsupervised learning of phase transitions: From principal component analysis to variational autoencoders. *Physical Review E* **96** (2017) 022140.
57. D. Vlastic, M. Brand, H. Pfister, and J. Popović, J., 2005, Face transfer with multilinear models. *ACM Transactions on Graphics (TOG)* **24** (2005) 426–433.
58. C. Cao, Y. Weng, S. Zhou, Y. Tong, and K. Zhou, Facewarehouse: A 3d facial expression database for visual computing. *IEEE Transactions on Visualization and Computer Graphics* **20** (2013) 413–425.
59. F. Lecron, J. Boisvert, M. Benjelloun, H. Labelle, and S. Mahmoudi, Multilevel statistical shape models: A new framework for modeling hierarchical structures, *9th IEEE International Symposium on Biomedical Imaging (ISBI)* (2012) 1284–1287.

60. D.J.J. Farnell, H. Popat, and S. Richmond, Multilevel principal component analysis (mPCA) in shape analysis: A feasibility study in medical and dental imaging, *Computer Methods and Programs in Biomedicine* **129** (2016) 149–159.
61. D.J.J. Farnell, J. Galloway, A.I. Zhurov, S. Richmond, P. Perttiniemi, and V. Katic, Initial Results of Multilevel Principal Components Analysis of Facial Shape, *Annual Conference on Medical Image Understanding and Analysis*. Springer, Cham. (2017) 674–685.
62. D.J.J. Farnell, J. Galloway, A.I. Zhurov, S. Richmond, P. Perttiniemi, and R. Lähdesmäki, What's in a Smile? Initial Results of Multilevel Principal Components Analysis of Facial Shape and Image Texture. In *Medical Image Understanding and Analysis*, Springer, Cham. **894** (2018) 177–188.
63. D.J.J. Farnell, J. Galloway, A.I. Zhurov, S. Richmond, D. Marshall, P.L. Rosin, K. Al-Meyah, P. Perttiniemi, and R. Lähdesmäki, What's in a Smile? Initial Analyses of Dynamic Changes in Facial Shape and Appearance, *Journal of Imaging* **5** (2019) 2.
64. D.J.J. Farnell, J. Galloway, A.I. Zhurov, S. Richmond, Multilevel Models of Age-Related Changes in Facial Shape in Adolescents. *Annual Conference on Medical Image Understanding and Analysis*. Springer, Cham. (2019) – In Press.
65. J.D. White, A. Ortega-Castrillon, H. Matthews, A.A. Zaidi, O. Ekrami, J. Snyders, Y. Fan, T. Penington, S. Van Dongen, M.D. Shriver, and P. Claes, MeshMonk: Open-source large-scale intensive 3D phenotyping. *Scientific Reports* **9** (2019) 6085.
66. S.N. Bhatia and B.C. Leighton, Manual of facial growth: A computer analysis of longitudinal cephalometric growth data (Oxford University Press, 1993).
67. V.F. Ferrario, C. Sforza, C.E. Poggio, and J.H. Schmitz, Facial volume changes during normal human growth and development. *The Anatomical Record: An Official Publication of the American Association of Anatomists* **250** (1998) 480–487.

68. K.S. West and J.A. McNamara Jr, Changes in the craniofacial complex from adolescence to midadulthood: a cephalometric study. *American Journal of Orthodontics and Dentofacial Orthopedics* **115** (1999) 521–532.
69. V.F. Ferrario, C. Sforza, G. Serrao, V. Ciusa, and C. Dellavia, Growth and aging of facial soft tissues: a computerized three-dimensional mesh diagram analysis. *Clinical Anatomy: The Official Journal of the American Association of Clinical Anatomists and the British Association of Clinical Anatomists* **16** (2003) 420–433.
70. C.H. Kau and S. Richmond, Three-dimensional analysis of facial morphology surface changes in untreated children from 12 to 14 years of age. *American Journal of Orthodontics and Dentofacial Orthopedics* **134** (2008) 751–760.
71. Y. Wang, Y. Si, B. Huang, and Z. Lou, Survey on the theoretical research and engineering applications of multivariate statistics process monitoring algorithms: 2008–2017. *The Canadian Journal of Chemical Engineering* **96(10)** (2018) 2073–2085.
72. Y. Ding, X. Ma, and Y. Wang, Health status monitoring for ICU patients based on locally weighted principal component analysis. *Computer Methods and Programs in Biomedicine* **156** (2018) 61–71.