

Mgr. Lenka Kožejová Jaklová: Impact of therapy on facial development in patients with orofacial cleft: data modelling using the methods of virtual anthropology

The main aim of submitted PhD. thesis is to provide a comprehensive evaluation of the effect of early neonatal cheiloplasty on the morphology and growth of the palate and face in patients with different types of orofacial clefts in comparison with normal growth patterns and symmetry in healthy probands. The thesis is divided to two parts:

1. The first part focuses on palatal and facial development in children with orofacial clefts after early neonatal cheiloplasty.
2. The second part deals with the normal development of the palate in healthy individuals and the development of directional asymmetry in relation to age and sex in a healthy population.

The aim is achieved by summarizing six papers published in international journals, namely Jaklová et al. (2020), Kožejová Jaklová et al. (2021), Kožejová Jaklová et al. (2023), Kožejová Jaklová et al. (2024), Harnádková et al. (2023) a Jana Velemínská et al. (2022). The latter was shared with me on the top of those mentioned in the thesis. To publish 6 papers during Ph.D. study covering main topics of the thesis is really a great success. Well done. What is expected for this topic to be presented during the defense, see Section *Main topics for presentation during the defense*.

The research has been supported by three projects from the Grant Agency of Charles University, projects GA UK No. 266522, 304221, and 372221. It is not clear if the author of the thesis is a principal investigator or a member of the team. This should be explained during the defense.

The submitted PhD. thesis is divided to 11 chapters including Introduction, Bibliography and Appendices totaling 151 pages. The Sections 2 to 4 comprise the theoretical parts of the thesis, namely, the treatment of orofacial cleft, then the growth and development of the face and palate in patients with orofacial cleft, and the growth and development of the palate and facial symmetry in healthy individuals. In Section 5, the objectives of the research are described. In Section 6, the material and methods are briefly summarized. Finally, in Sections 7 to 9, the results, future directions and conclusions are discussed.

The Bibliography in Section 10 consist of approx. 250 references mainly related to extensive theoretical parts and discussion. Despite the fact that the thesis concentrates on 3D geometrical morphometrics, I would expect at lease to cite some publications using 2D approaches related to the research of student supervisor related to cleft, e.g., J. Velemínská et al. (2006) and Velemínská, Smahel, and Katina (2007). The Section 6 is very brief, lacking necessary details needed to understand methodological choices, and doesn't include any references (these should be there).

Since my scientific research include shape data acquisition, methodological development, software implementation and applications of geometrical morphometrics (of statistical shape and image analysis), I will concentrate on these topics in this review.

1. **Populations and data.** It is stated in the thesis, that 3D palatal models ($n = 400$) and 3D facial scans ($n = 509$) have been obtained longitudinally and transversely. This sounds impressive, but this is rather collection of independently obtained palatal models and faces for several studies/purposes. How the controls had been obtained? (Kožejová Jaklová et al. (2024), see, "and their healthy peers"). Are these matched controls? What is expected for this topic to be presented during the defense, see Section *Main topics for presentation during the defense*.

2. **Landmark placement and registration.** The landmarks were placed manually on the 3D models using the [Morphome3cs software](#) (Computer Graphics Group, Faculty of Mathematics and Physics, Charles University, Prague, Czech Republic). It is not clear neither from the thesis nor from the papers if *coherent point drift-dense correspondence analysis* (CPD-DCA, Hutton, Buxton, and Hammond (2001), Dupej, Krajíček, and Pelikán (2015) or the poster information from [Eurographics Symposium on Geometry Processing](#)) was performed in this software or somewhere else. Pls explain. For recent challenges in the topic see, e.g., Yuan and Maharjan (2023).

3. Measurements used

- Selected “classical” distances.
- Procrustes distances.
- Selected landmark coordinates. Why only landmarks were used?
- Corresponding mesh point coordinates.
- Centroid size. How was the centroid size calculated? See, e.g., Jana Velemínská et al. (2022).
- Are there any other measurements used?

4. Statistical methods

- “Classical” Principal component (PC) analysis to reduce the dimension, PC scores, shapes as extremes of chosen PCs. “Asymmetry” PC analysis, see, e.g., Kožejová Jaklová et al. (2023), Kožejová Jaklová et al. (2021), Harnádková et al. (2023). Are these analyses done on inter-landmark distances or corresponding mesh points? It is not clear, pls explain. What is “Asymmetry” PC analysis? Add a reference. How did you calculate and separate “asymmetry” and “symmetry” PCs? When modelling a change from a state before operation to the state after operation, what would be the best choice of type of the PC analysis?
- Per-vertex *t*-tests (I guess that these are two-sample *t*-tests) results on color-coded mesh point maps showing shell/point distances and *p*-values of see, e.g. Kožejová Jaklová et al. (2023), Jaklová et al. (2020) etc. Is this *t*-test with Welch or other approximation of degrees of freedom to reflect the heterogeneity of variances? Were there any post-hoc multiplicity correction applied?
- Normality tests, see, e.g., Harnádková et al. (2023), Kožejová Jaklová et al. (2021). Henze-Zirkler test, Shapiro–Wilk and multivariate Box *M*-test. Were these tests applied on landmark or corresponding mesh point coordinates? Pls explain. Are there any assumptions needed before using these tests? Why we use normality tests? What are the consequences of using wrong statistical methods after testing normality? What are we testing with Wilcoxon’s paired signed-rank test? See, e.g., Kožejová Jaklová et al. (2021). Is there any assumption needed before using this test? Which characteristic should we present in connection with this test?
- Procrustes ANOVA using multi-sample Goodall *F*-test. What is the hypothesis here? Was this method used on Procrustes distances and directional asymmetry scores? Were there any post-hoc multiplicity correction applied?
- Two-way ANOVA, see, e.g., Harnádková et al. (2023). Were there any post-hoc multiplicity correction applied?
- MANOVA and Hotelling T^2 tests, see, e.g., Harnádková et al. (2023). Is this done on PC scores? Were there any post-hoc multiplicity correction applied?
- In some of the papers I spotted mixed-effect model. Pls explain how this was used.
- Which statistical model was used to present non-linear development of a healthy palate? Add a reference.

- What is expected for this topic to be presented during the defense, see Section *Main topics for presentation during the defense*.

Main topics for presentation during the defense

1. Present a graphical overview of age, sex, group (cleft type and healthy), before and after surgery, controls if needed etc. per paper to see all data overview related to the design and aims.
2. Present a tabulated overview of the statistical methods/tests used always clearly describing
 - Clear name of the statistical method/test used and attach a reference (see section *Statistical methods* above).
 - Measurement values being tested (see section *Measurements* above).
 - Null and alternative hypothesis.
 - Graphical representations used in a connection with this method, e.g., color-coded mesh point maps, PC scores etc.
3. For each data collection from (1) and statistical methods (2) above add a list of your papers where it was used.
4. For each of 5 (or 6) papers, summarize your contribution, and add your part in percentages. This should be clear especially distinguishing your contribution from the contribution of the other Ph.D. students.

Future directions

This thesis could not be written without team effort in data acquisition (help of fellow anthropology students), implementation of 3D mesh related methodology (computer science colleagues), and above all, great leadership of a supervisor mentoring students towards outputs in international journals. This is really a great step forward. But then the future directions should not only include wishes for better design choices (e.g., repeated measurements of an individual across time) but also wishes to be able to choose and describe the statistical methods used more clearly and then wishes to be able to use state-of-the art and modern statistical approaches. These could include *using curves instead of landmarks* (see, e.g., Vittert, Bowman, and Katina (2019)) or *functional data analysis* instead of classical statistical approaches (see, e.g., Katina, Vittert, and Bowman (2021)).

Summary

The thesis addresses interesting and relevant topics. The thesis research generates significant new knowledge in anthropology, and it demonstrates a solid understanding of the state-of-the-art in the research area of facial development in patients with orofacial cleft. The theoretical part, conclusions and discussion are presented clearly, but the description of statistical methods is brief, lacking necessary details needed to understand methodological choices, and doesn't include any references. Future directions should include the cooperation with a statistician to avoid wrong choices of statistical methods and to use state-of-the art and modern statistical approaches to analyze and present the

The thesis meets the requirements imposed on a PhD. dissertation. Therefore, I recommend it for defense and its acceptance, and I agree with the award of a PhD. academic degree after successful defense.

Brno, 2024-09-20

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Assoc. Prof. PaedDr. RNDr. Stanislav Katina, Ph.D.
Institute of Mathematics and Statistics
Masaryk University

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