Day 2 recap

- Check out the videos on SlicerMorph youtube channel for Markups and GPA (for today) http://bit.ly/SM_youtube
- Some segmentation recipes from Slicer Community: https://lassoan.github.io/SlicerSegmentationRecipes/

- **From 10-11**, breakout sessions will be open as self-paced tutorials. Instructors will join back at 11.

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Statistical Shape Analysis – Concepts and Landmarks

A. Murat Maga, PhD
Associate Professor
University of Washington
Division of Craniofacial Medicine
Department of Oral Biology (adjunct)
Department of Anthropology (adjunct)
&
Seattle Children's Research Institute
Center for Developmental Biology and Regenerative Medicine

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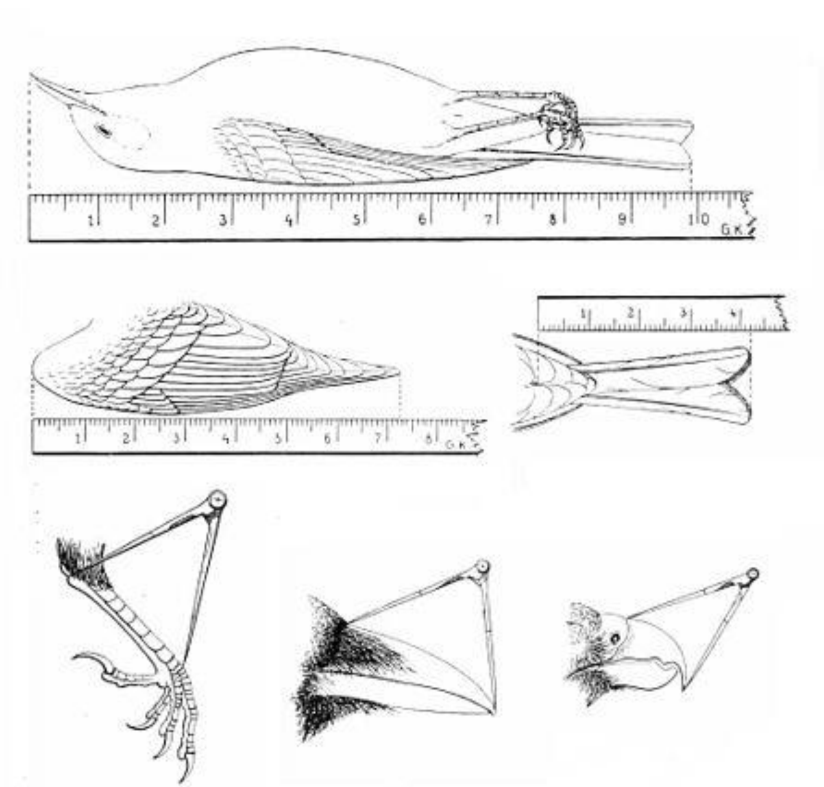
Traditional Morphometrics



Traditional morphometrics analyzes lengths, widths, masses, angles, ratios and areas. These data are also useful when size measurements are of theoretical importance such as body mass and limb cross-sectional area and length in studies of functional morphology. However, these measurements have one important limitation: they contain little information about the spatial distribution of shape changes across the organism.

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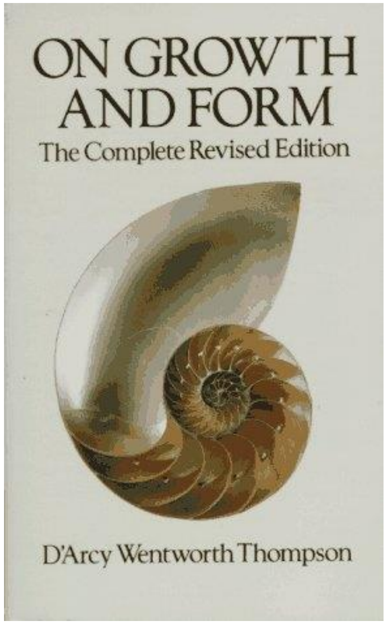
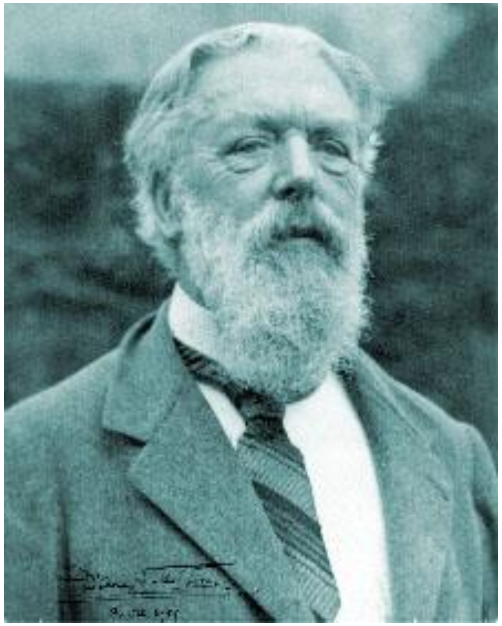
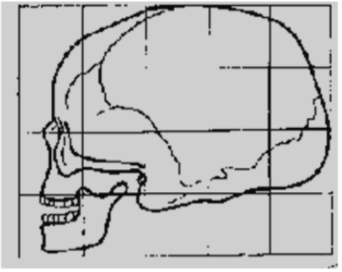
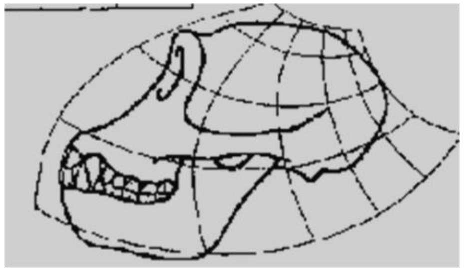
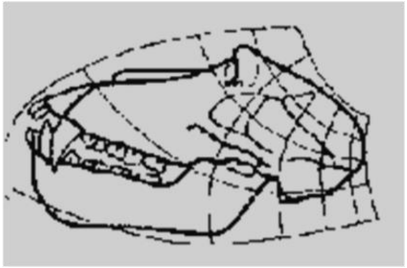
Study of Organismal form (1900s)











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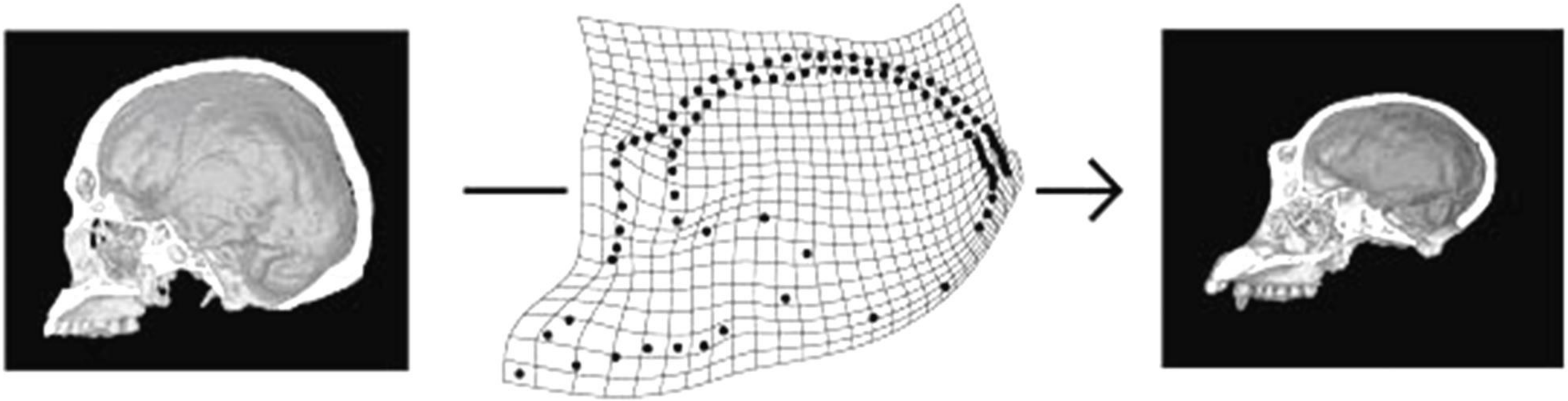
Thin-Plate Spline (TPS) deformations



Bookstein FL. 1989. Principal warps: thin-plate splines and the decomposition of deformations. IEEE Transactions on Pattern Analysis and Machine Intelligence 11:567–585.

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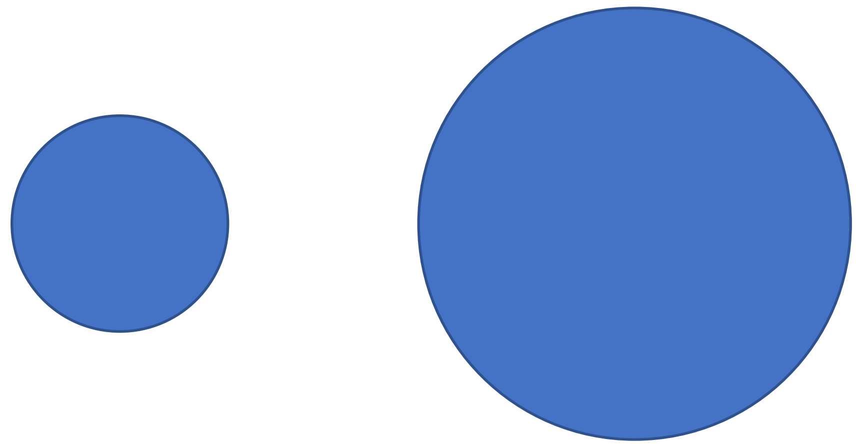
What is biological shape/form?

- **Biological shape** is the residual information left after differences in translation, rotation and **uniform size** is removed from the data.
- **Biological form** is the residual information left after **only** differences in translation and rotation is removed from data. (Size becomes part of the analysis).

Shape vs form



- Same **shape** (circle), but different **forms** (small vs big)**.**

Shape vs form

- What about these?

Shape vs form

- To decide we have to establish some sort of correspondence (or mapping) between these shapes.

Homology and types of landmarks

Type I: juxtaposition of tissue or foramina

Type II: self-evident geometry (tips of prominences or notches)

Type III: geometric construction (e.g., deepest point in the notch)

Semi-landmarks (equidistant along a curve)

Compare this to **pseudo-landmarks** which are not bounded by anatomical LMs

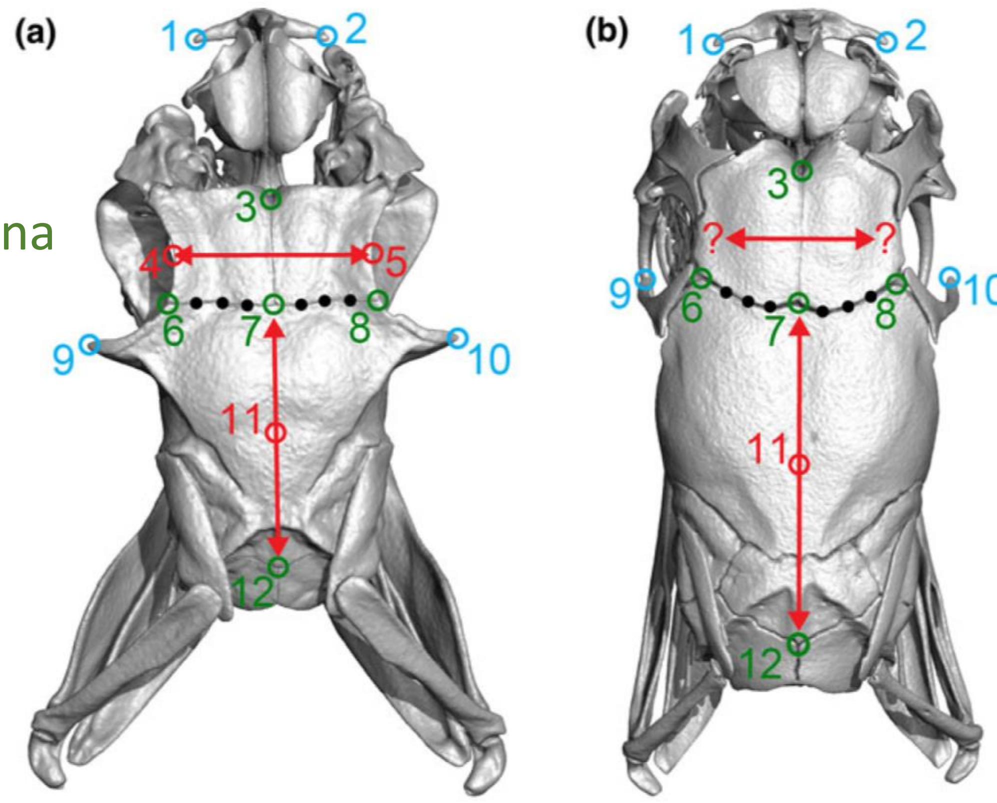


Figure from: Palci, Alessandro, and Michael S. Y. Lee. "Geometric Morphometrics, Homology and Cladistics: Review and Recommendations." *Cladistics* 35, no. 2 (2019): 230–42. https://doi.org/10.1111/cla.12340.

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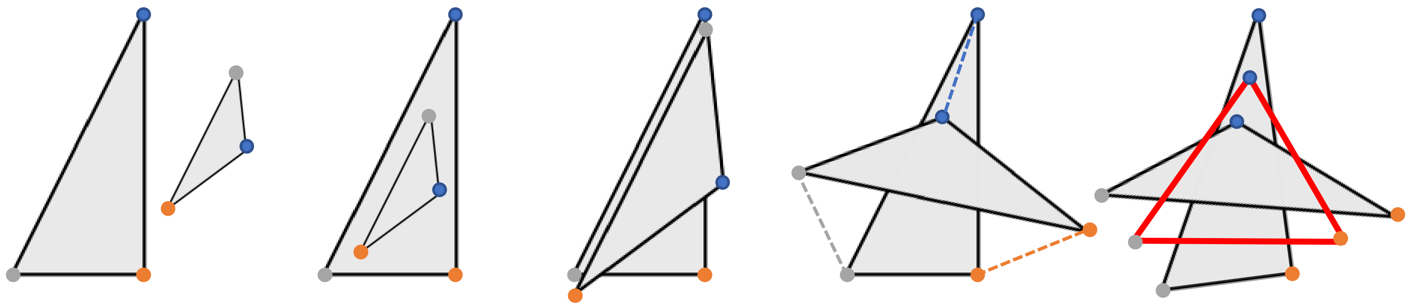
Putting all together



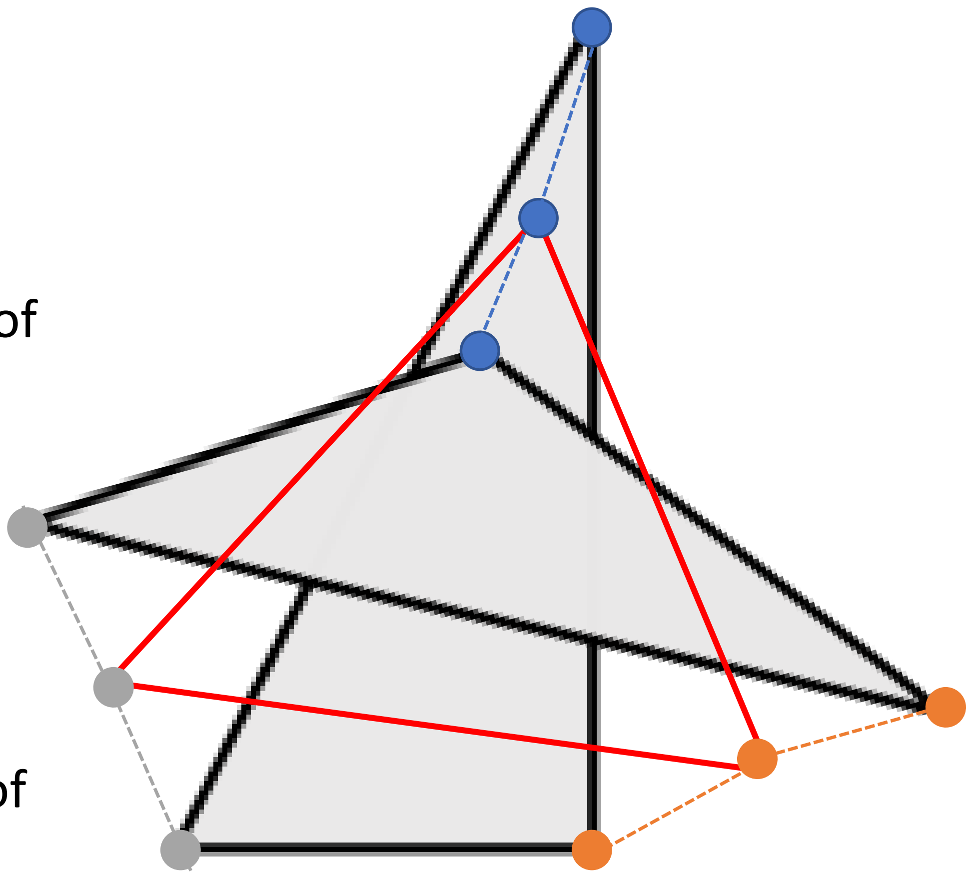
Original Configurations | Superimposition | Scaling | Rotation | Iterations to minimize the difference

Generalized Procrustes Analysis (or GPA)

- Gower JC. 1975. Generalized procrustes analysis. Psychometrika 40:33–51.
- Kendall DG. 1984. Shape Manifolds, Procrustean Metrics, and Complex Projective Spaces. Bull London Math Soc 16:81–121.
- Rohlf FJ, Slice D. 1990. Extensions of the Procrustes Method for the Optimal Superimposition of Landmarks. Systematic Zoology 39:40–59.

Some Definitions

Procrustes coordinates: New set of coordinates after GPA
Consensus (mean) shape: The average of individual landmarks (red triangle)
Procrustes residuals: [Procrustes coordinate – consensus shape]; i.e. description of how each individual different from the consensus. (vector defined by the dashed line)
Procrustes distance: The squared sum of these differences, i.e., measure of how far the individual is from the mean (dashed lines).



https://life.bio.sunysb.edu/morph/glossary/gloss1.html
https://life.bio.sunysb.edu/morph/glossary/gloss2.html

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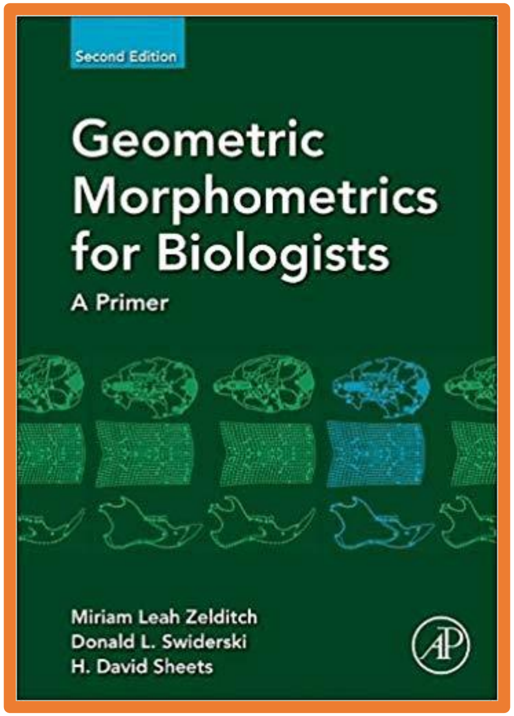
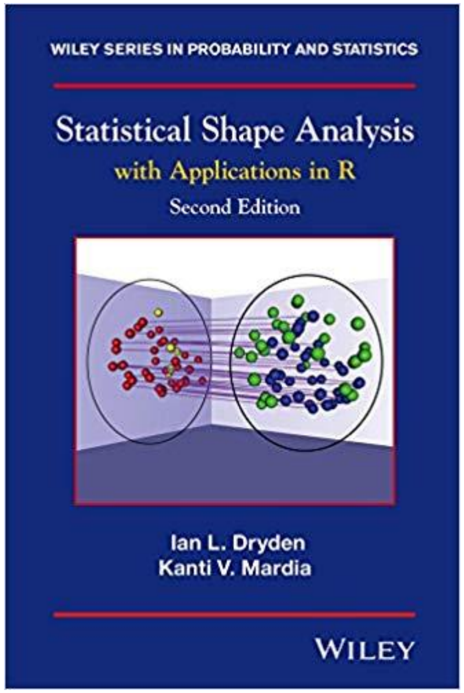
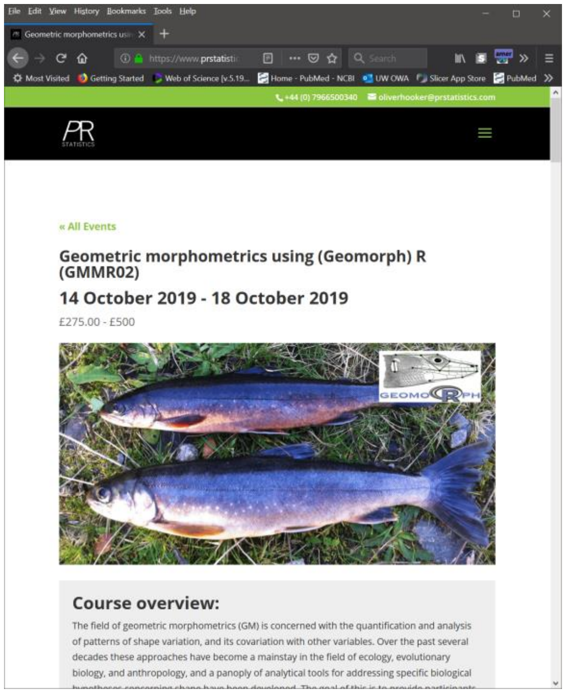
Textbooks



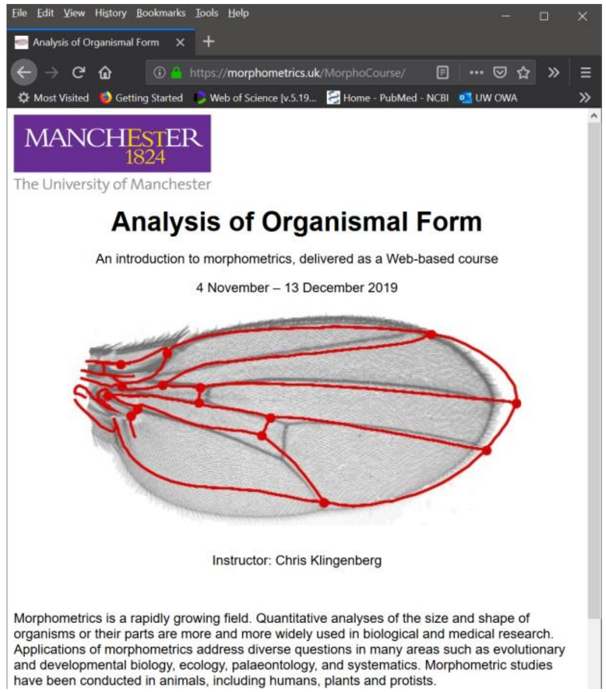


Also a short online paper https://geosci.uchicago.edu/~mwebster/Webster_and_Sheets_2010.pdf
A Practical Introduction to Landmark-based Geometric Morphometrics

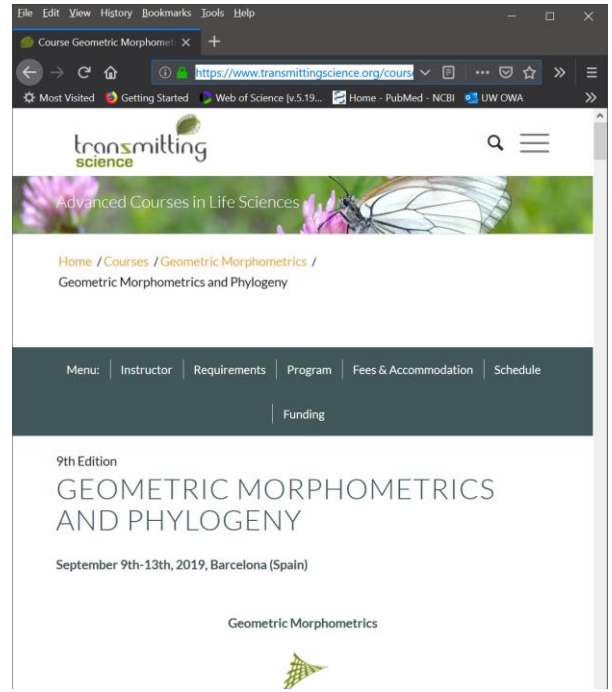
Geometric morphometrics specific short courses



https://www.prstatistics.com/course/geometric-morphometrics-using-r-gmmr02/ (Dean Adams)



https://morphometrics.uk/MorphoCourse/ (Chris Klingenberg)



https://www.transmittingscience.org/courses/geometric-morphometrics/geometric-morphometrics-phylogeny/

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GPA Gotchas

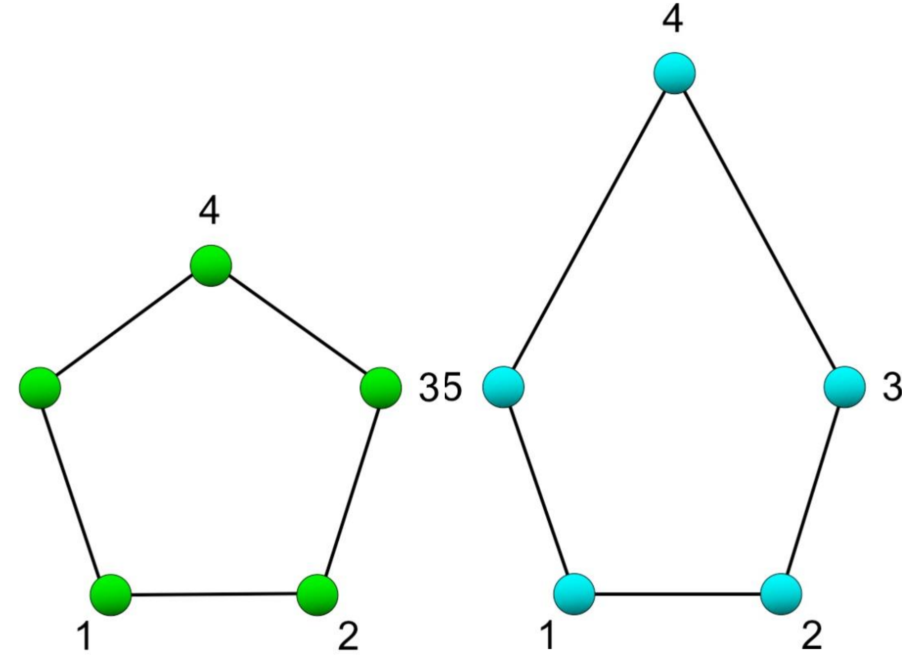
- In Generalized Least Squares (GLS) method of optimization variance will be distributed across landmarks.

Warning about Procrustes

Procrustes-based analyses tell you about variation of the entire shape.

Procrustes analysis does not (easily) tell you how much variation occurs at a particular landmark.

With the removal of size and coordinate system, shape is being measured as displacement in each landmark relative to all the other landmarks.



Variations on a theme of Procrustes

Procrustes (Generalized Least Squares, GLS)
- minimizes sum-of-squares among homologous landmarks
- best method for minimizing difference in shape
- distributes differences equally among landmarks

Generalized Resistant Fit (GRF)
- uses median rather than mean for the fitting algorithms
- allows some landmarks to be more variable than others
- does not find smallest possible difference between shapes

Bookstein Shape Coordinates
- uses two landmarks as baseline
- common in early "geometric morphometric" studies

GPA implementation of **SlicerMorph** (with the option of skipping scaling step).

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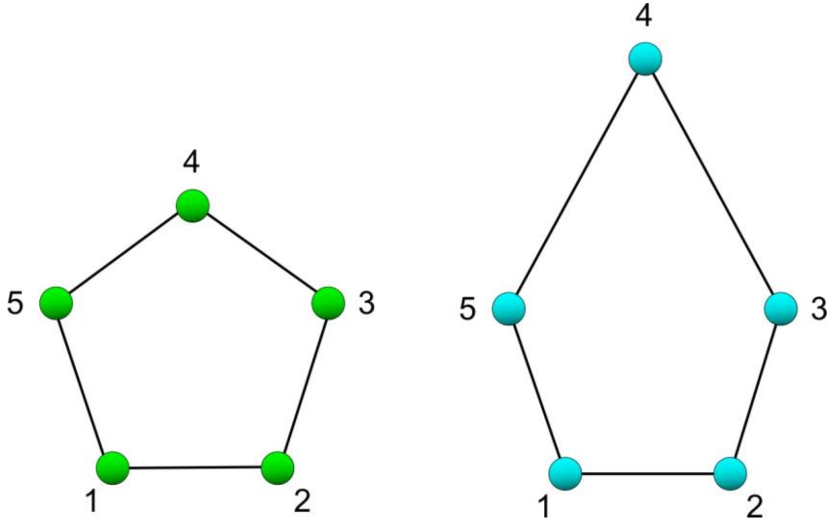
Euclidean Distance Matrix Analysis (EDMA)

- Can be useful in case/control study designs.
- Exploratory Method to identify significantly different differences between groups.
- All possible pairwise landmark distances are calculated. For N landmarks there are [Nx(N-1)]/2 pairwise distance.

5 LMs=20 pairwise distances



'Pinocchio Effect'

Lele S, Richtsmeier J. 1991. Euclidean Distance Matrix Analysis - a Coordinate-Free Approach for Comparing Biological Shapes Using Landmark Data. Am J Phys Anthropol 86:415–427.

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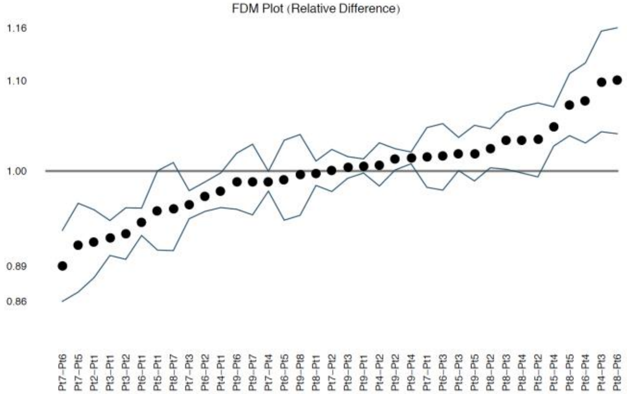
Euclidean Distance Matrix Analysis

EDMA: example results

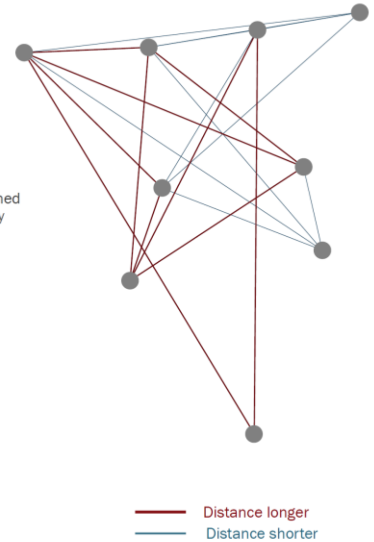
In this example the faces of left facing people and right facing people have been landmarked (landmarks at the corners of each eye, the edges of the nose, the corners of the mouth, and the chin). There were nine landmarks total, which gives 36 interlandmark distances.

The FDM plot shows the ratio of each interlandmark distance between the two samples (left facing over right facing), with those landmarks that got farther apart having ratios greater than 1.0, those that got closer having ratios less than 1.0. 95% confidence intervals were found with 1000 bootstrap replicates.



EDMA: example results

The consensus of the second sample is shown here with those interlandmark distances that got significantly longer in red and those that got significantly shorter in blue. For people who turned their heads from left to right, the nose and chin got significantly farther from the left eye and left corner of the mouth, whereas those same landmarks got closer to the right eye and the right corner of the mouth.



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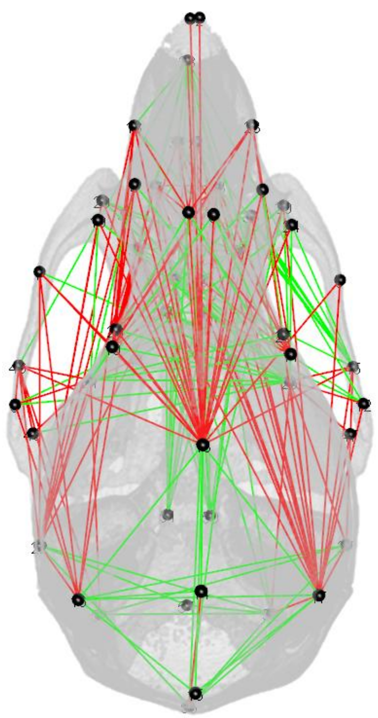
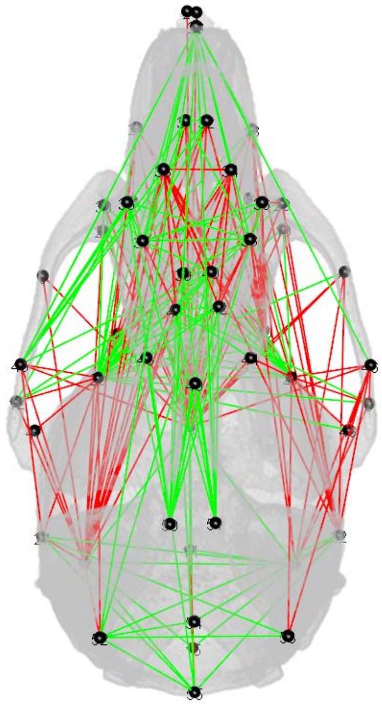
Effect of gestational (E0-E8) chronic alcohol exposure on skull development

Distances significantly smaller in EtOH group

Distances significantly larger in EtOH group



Superior / Dorsal view



Inferior / Ventral view

Student Project: EDMA is NOT available in SlicerMorph, but we have a prototype implementation that a student can take over. Any takers?

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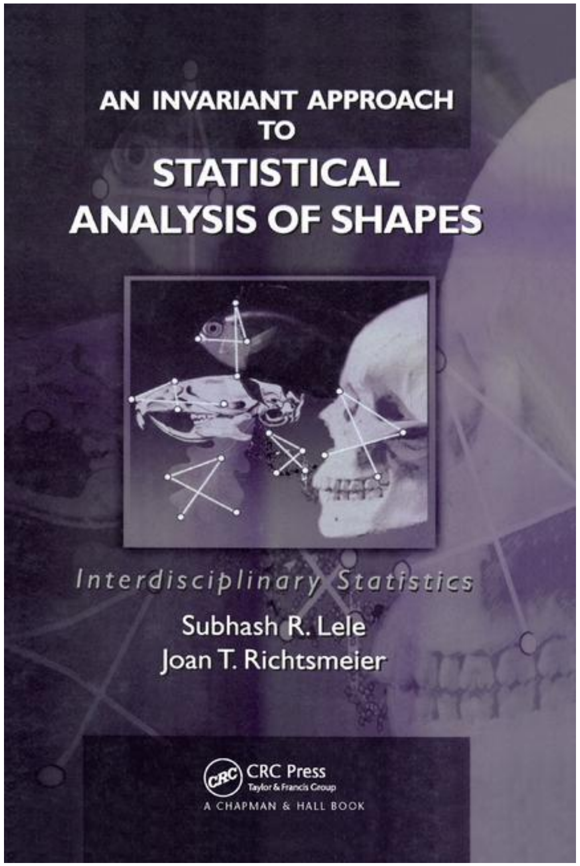
EDMA References:



- Lele, Subhash, and Joan T. Richtsmeier. "Statistical Models in Morphometrics: Are They Realistic?" *Systematic Zoology* 39, no. 1 (March 1, 1990): 60–69. https://doi.org/10.2307/2992208.
- Lele, S., and Jt Richtsmeier. "Euclidean Distance Matrix Analysis - a Coordinate-Free Approach for Comparing Biological Shapes Using Landmark Data." *American Journal of Physical Anthropology* 86, no. 3 (November 1991): 415–27. https://doi.org/10.1002/ajpa.1330860307.
- Lele, S., and T. M. Cole III. "A New Test for Shape Differences When Variance–Covariance Matrices Are Unequal." *Journal of Human Evolution* 31, no. 3 (September 1996): 193–212. https://doi.org/10.1006/jhev.1996.0057.
- Lele, Subhash R, and Charles E McCulloch. "Invariance, Identifiability, and Morphometrics." *Journal of the American Statistical Association* 97, no. 459 (September 1, 2002): 796–806. https://doi.org/10.1198/016214502388618609.

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What does PCA do?

- 1. Rotates data to its major axes for easier visualization
- 2. Preserves original distances between data points (in other words, PCA does not **distort the variation data**, but **only if the covariance method** is used, which is standard in geometric morphometrics)
- 3. Removes correlations between variables to make further statistical analysis simpler
- 4. Can be a tool for 'noise' removal.

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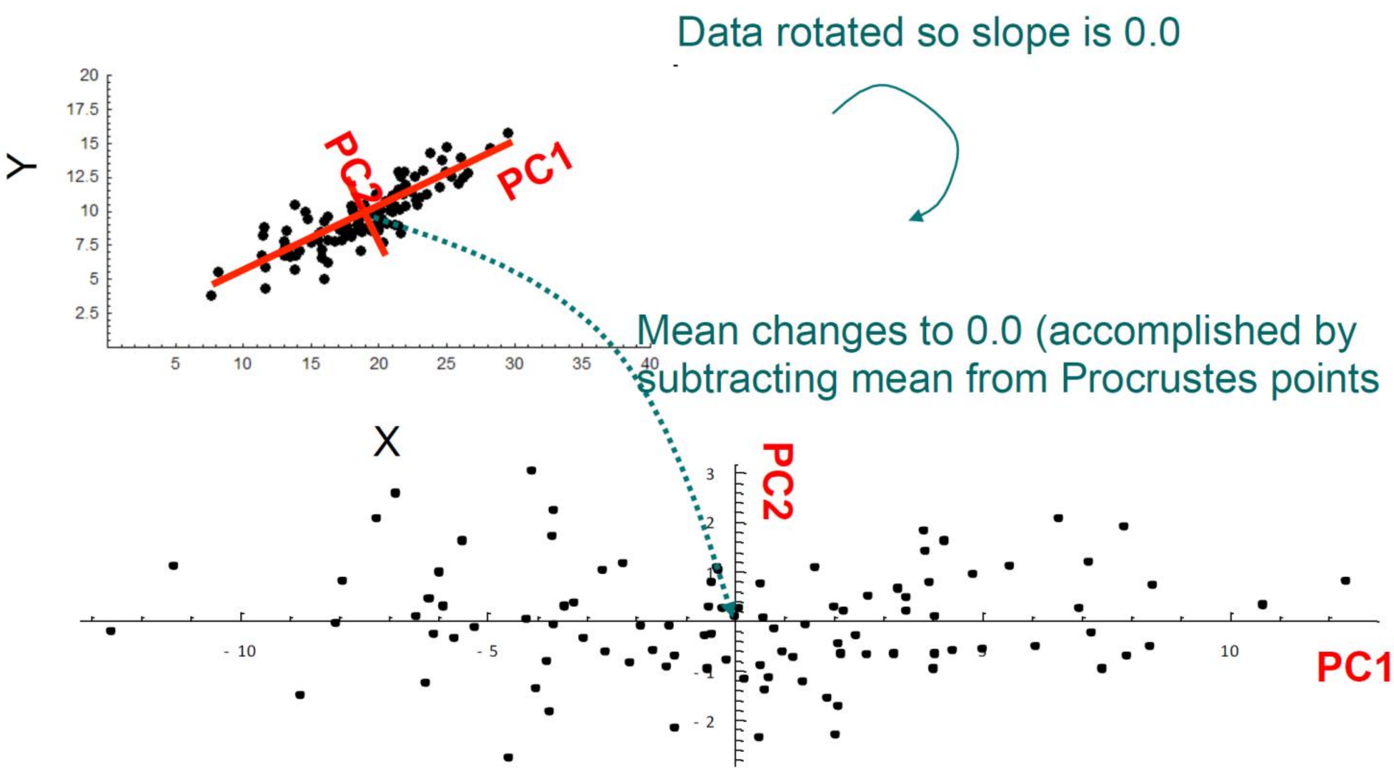
Principal components are a 'rigid rotation' of the original data



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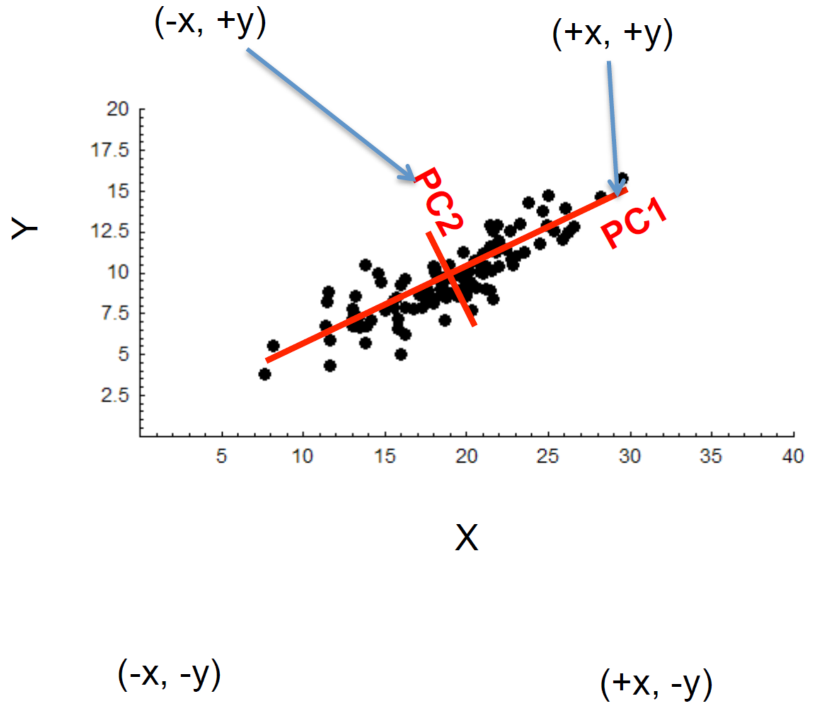
Eigenvector 'loadings' tell how each original variable contributes to the PC



Eigenvector Matrix

	PC1	PC2
X	0.89	-0.44
Y	0.44	0.89

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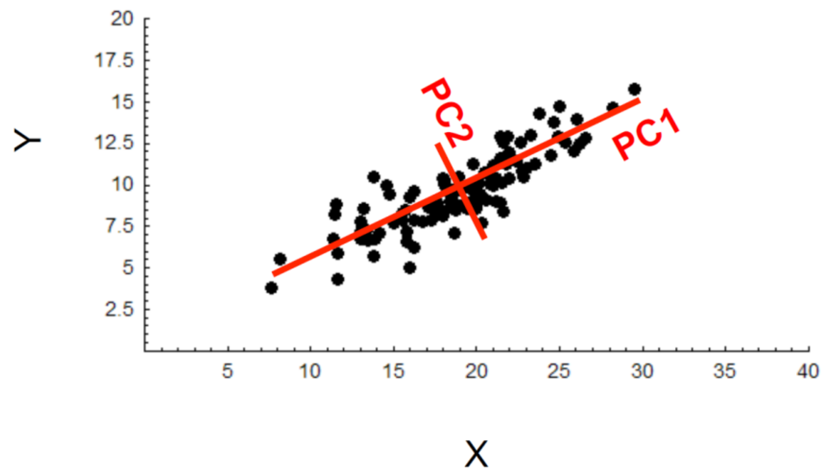
Eigenvectors also describe how to transform data from original coordinate system to PCs and back

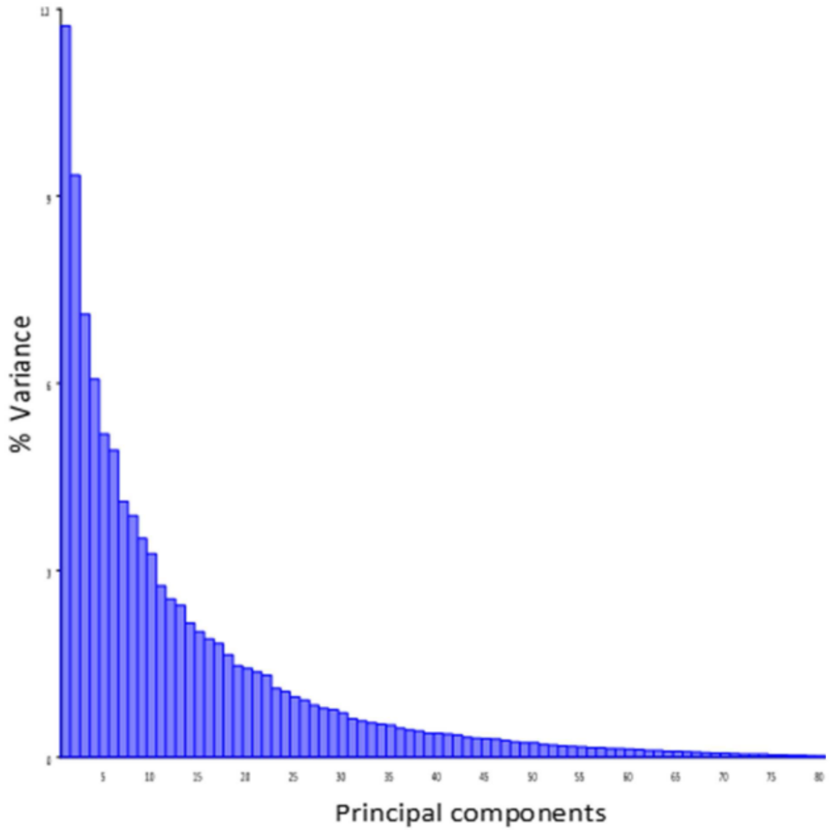


Eigenvector Matrix

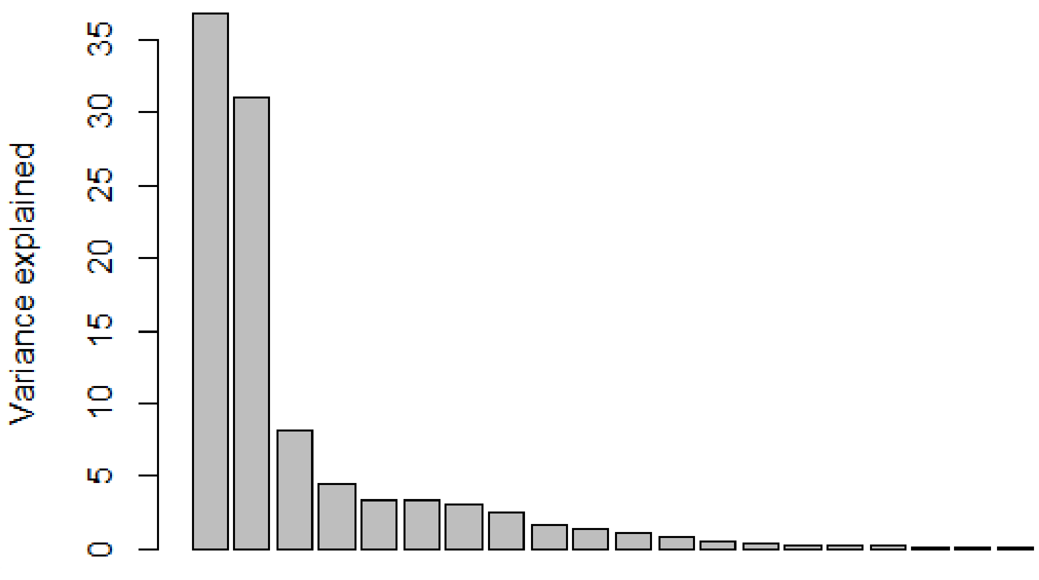
	PC1	PC2
X	0.89	-0.44
Y	0.44	0.89

(multiply PC1 X score by 0.89 and PC1 Y score by -0.44 and add back X,Y meanto get real X,Y)

Principle Components are ranked by variance



Mouse skulls from Maga et al. 2015



Plethodon Dataset from Geomorph

PCA is important in Geometric Morphometrics because....

1. PCA scores are used as shape variables
2. Eigenvectors are convenient axes for shape space
3. Eigenvectors and their scores are uncorrelated as variables
4. Variance (eigenvalues) is partitioned across eigenvectors and scores in descending order
5. Scores can be safely used for all other statistical analyses, including tree building
6. Eigenvectors can be used to build shape models

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6. Eigenvectors can be used to build shape models

PCs themselves have 0 (zero) inherent biological meaning. They are NOT traits.

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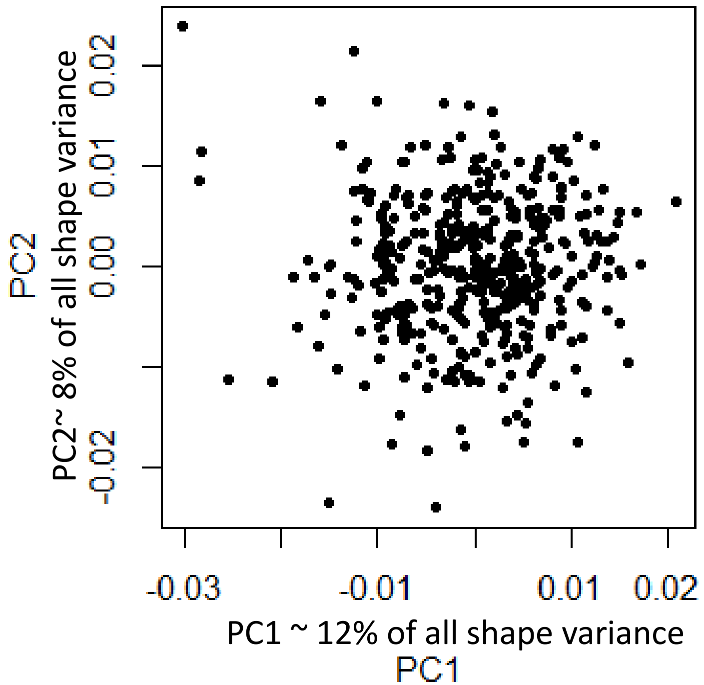
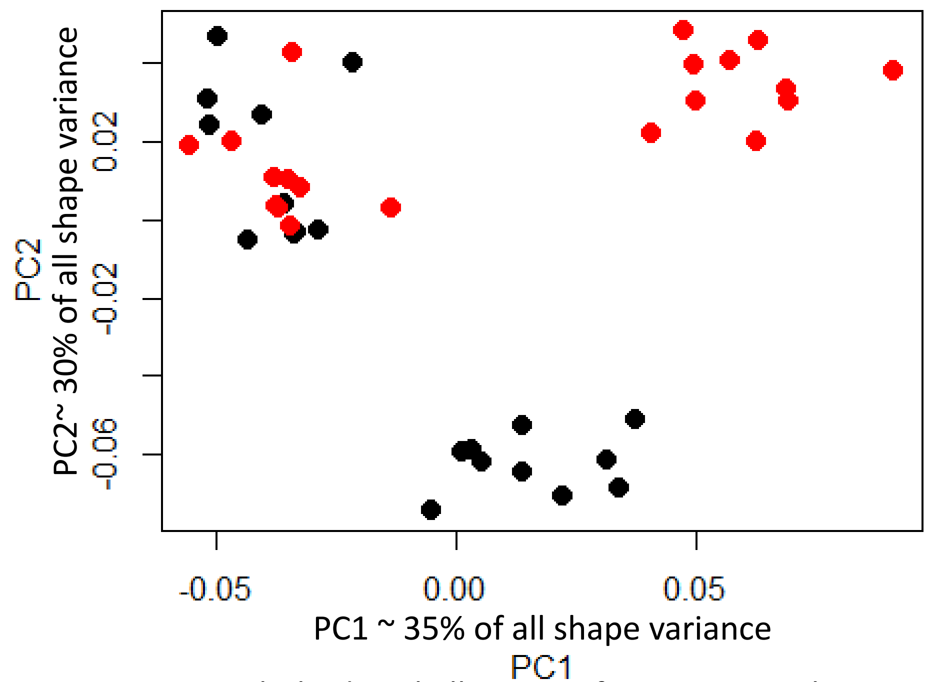
…but some PCA results are more interpretable than others



Mouse skulls from Maga et al. 2015. Frontiers in Physiology



Plethodon skull Dataset from Geomorph
Adams 2004, *Ecology* 85, no. 10:2664–70.

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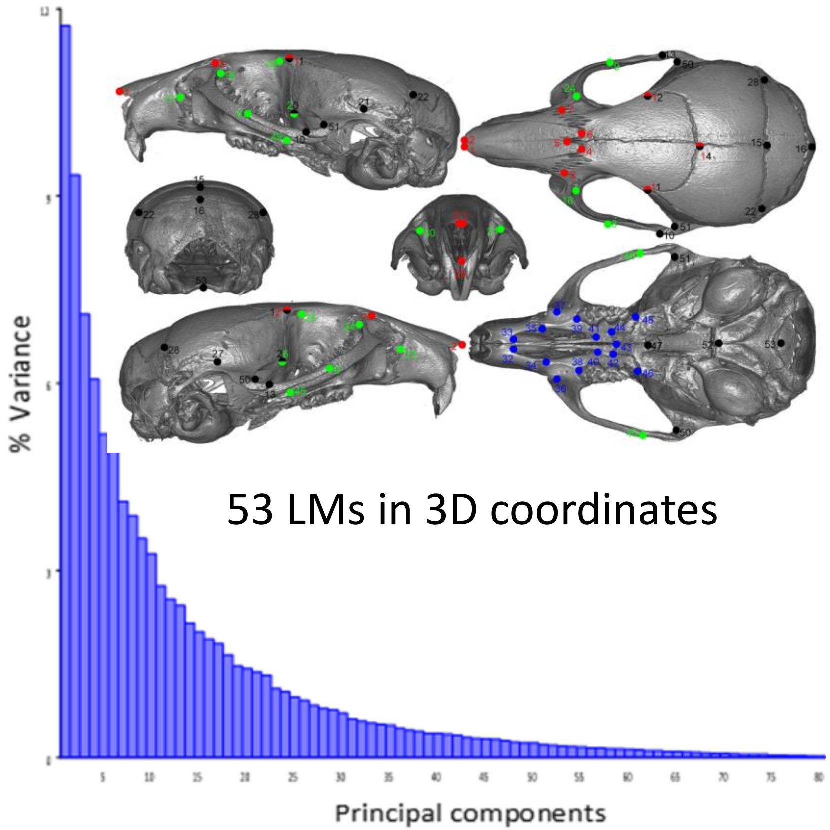
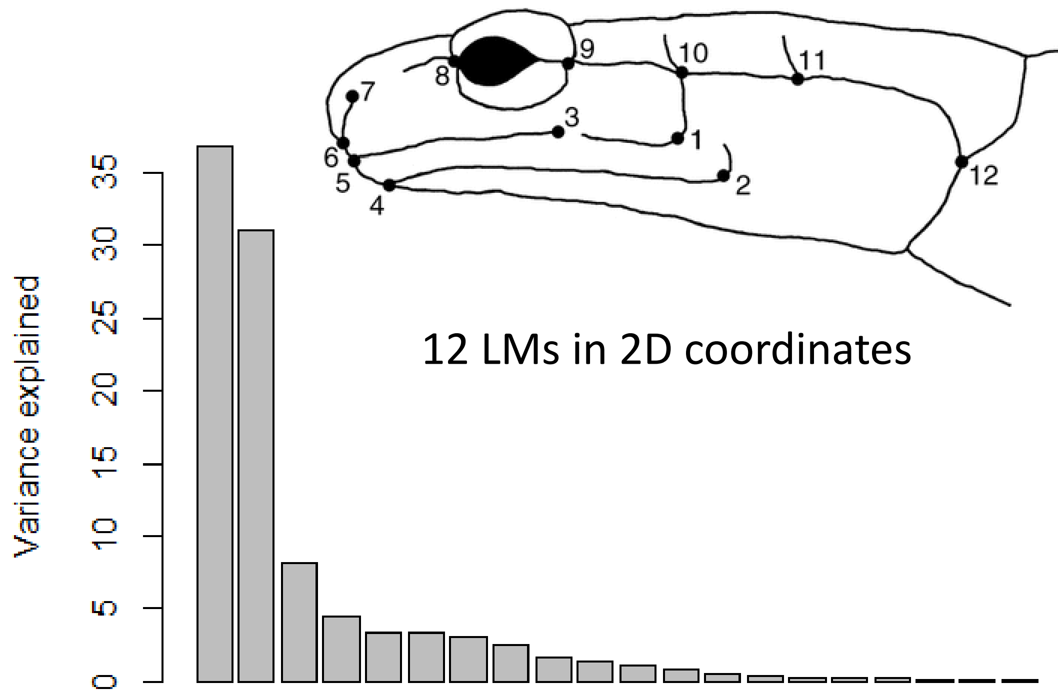
How many landmarks to use?



53 LMs in 3D coordinates

Mouse skulls from Maga et al. 2015



12 LMs in 2D coordinates

Plethodon skull Dataset from Geomorph
Adams 2004, *Ecology* 85, no. 10:2664–70.

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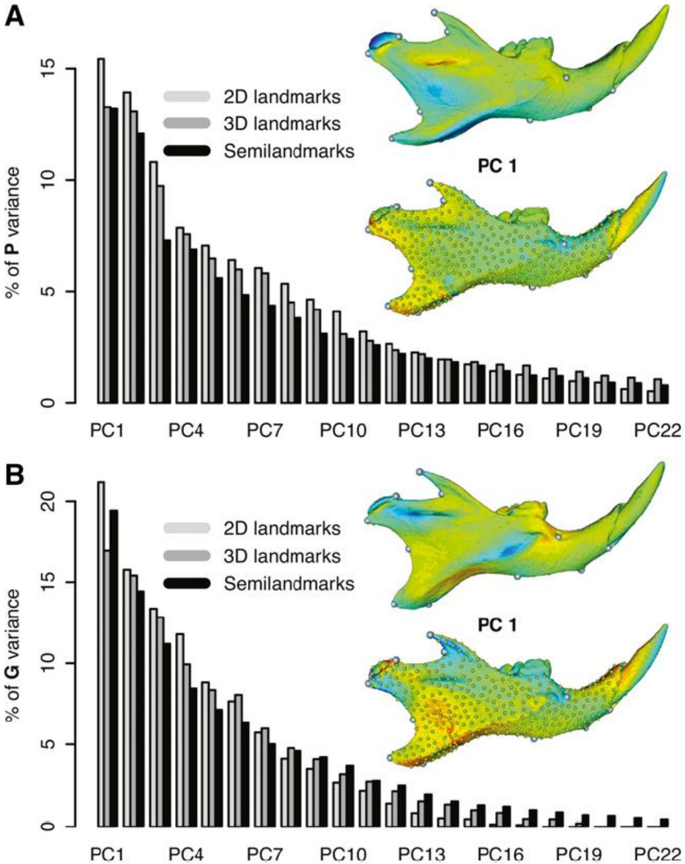
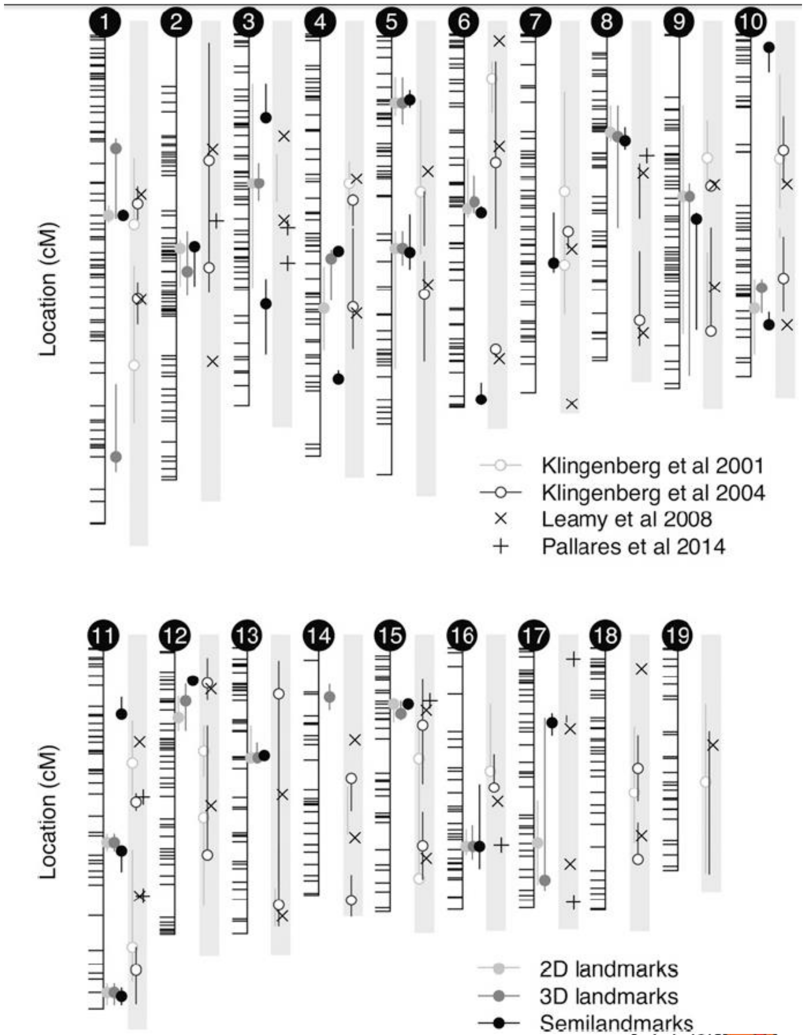
2D vs 3D?





Navarro, Nicolas, and A. Murat Maga. "Does 3D Phenotyping Yield Substantial Insights in the Genetics of the Mouse Mandible Shape?" *G3: Genes, Genomes, Genetics* 6, no. 5 (May 1, 2016): 1153–63. https://doi.org/10.1534/g3.115.024372.

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Curse of dimensionality

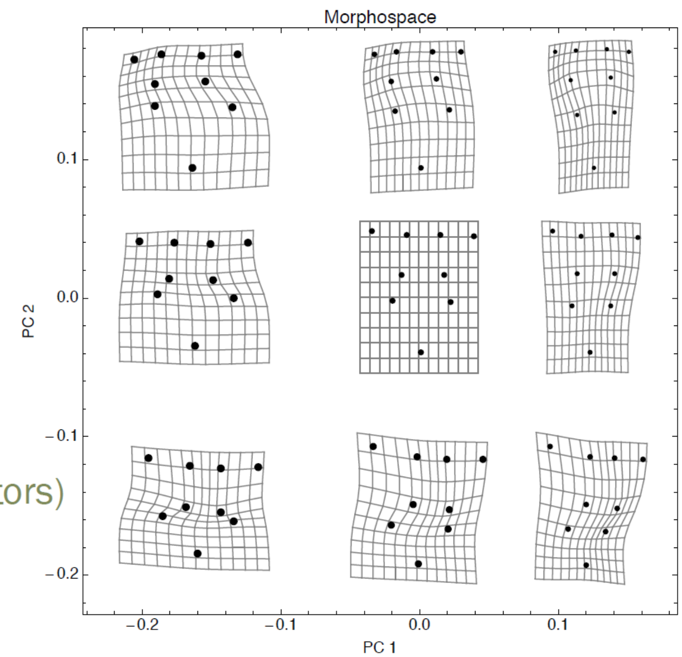
- **The curse of dimensionality:** When the dimensionality increases, the volume of the space increases so fast that the available data become sparse.

12 LMs in 2D = 20 dimensional space (24 variables - 4 DOF lost due to superimposition, scaling and rotation)
53 LMs in 3D = 152 dimensional space (159 variable - 7 DOF lost due to superimposition, scaling and rotation)

As a rule of thumb, you need at least sample size > your variable space
(in practice you often need sample size >>> your variable space, e.g., in mouse crosses)

Shape modelling…

How to construct models of shapes in morphospace

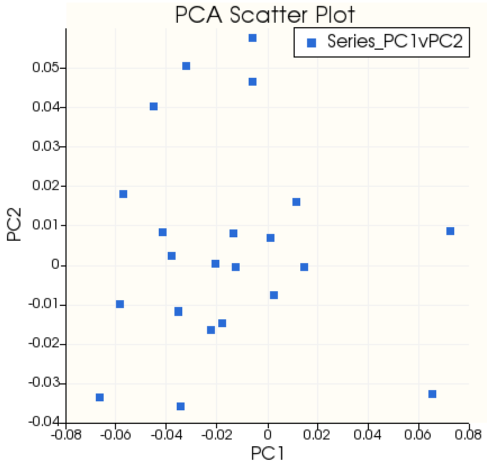


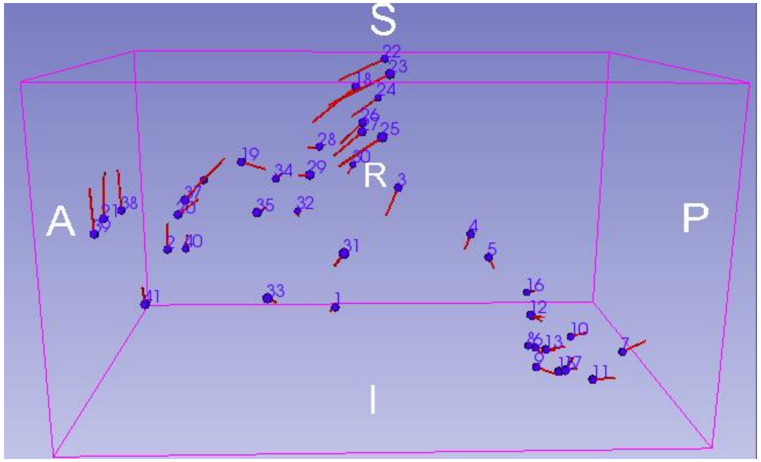
Ingredients:

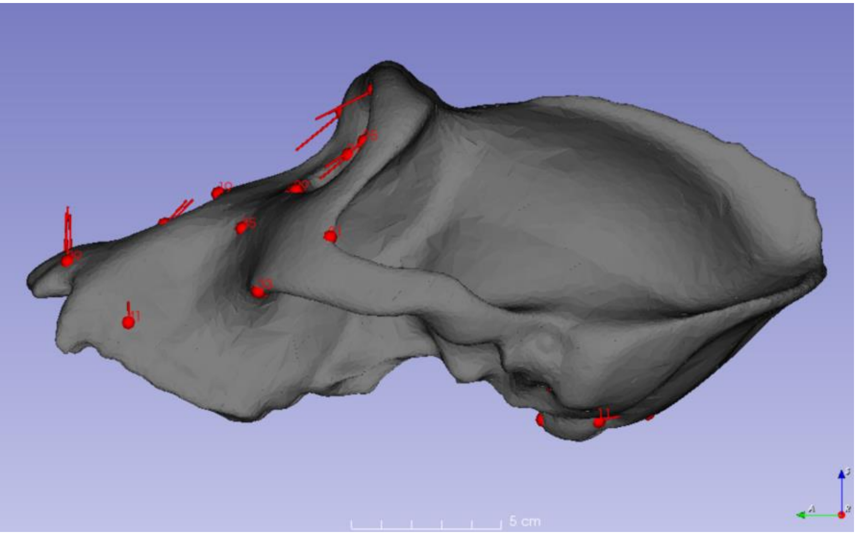
1. mean shape (consensus)
2. eigenvectors
3. the score (address) of the point to be modelled

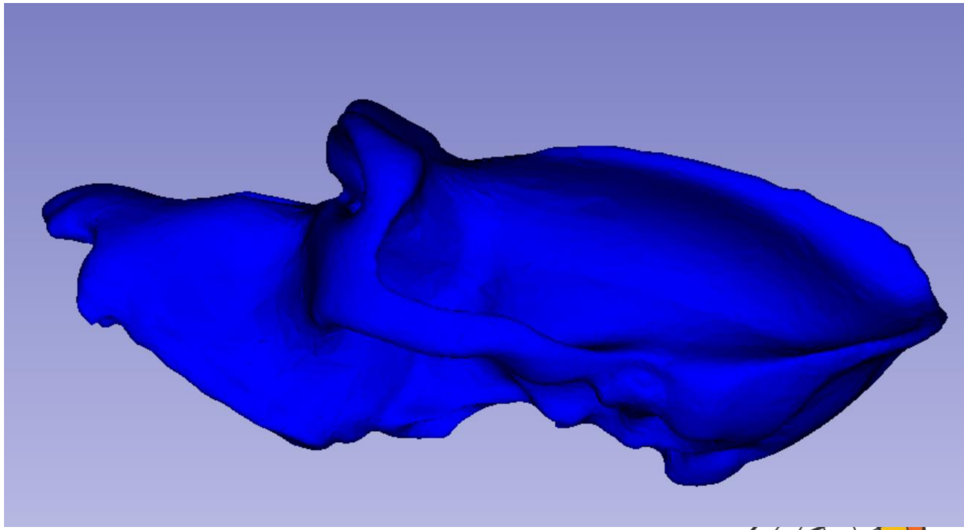
Model = consensus + ∑ (scores * eigenvectors)

Visualizing PCA results









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Some other analyses on GM data

- Study of variability (Procrustes anova)
- Study of symmetry
- Study of allometry
- Study of modularity and integration
- Study of covariance through partial-least squares

(SlicerMorph does not provide inferential statistics analysis on shape coordinates –yet. Take your data into R)

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Procrustes ANOVA

Statistical assessment of the terms in the model using Procrustes distances among specimens. **Sum-of-squared Procrustes distances** are used as a measure of SS. The observed SS are evaluated through permutation. In morphometrics this approach is known as a **Procrustes ANOVA**

Example from geomorph

#conduct GPA-alignment

Y.gpa <- gpagen(plethodon$land)

 # construct a geomorph data frame

gdf <- geomorph.data.frame(Y.gpa, site = plethodon$site, species = plethodon$species)

procD.lm(coords ~ species, data = gdf, iter = 999)

Output of the code

Analysis of Variance, using Residual Randomization
Permutation procedure: Randomization of null model residuals
Number of permutations: 1000
Estimation method: Ordinary Least Squares
Sums of Squares and Cross-products: Type I
Effect sizes (Z) based on SS distributions

	Df	SS	MS	Rsq	F	Z	Pr(>SS)	
species	1	0.029258	0.0292578	0.14856	6.6304	3.1637	0.001	**
Residuals	38	0.167682	0.0044127	0.85144				
Total	39	0.196940						

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Call: procD.lm(f1 = coords ~ species, iter = 999, data = gdf)

Goodall C. 1991. Procrustes Methods in the Statistical Analysis of Shape. Journal of the Royal Statistical Society Series B (Methodological) 53:285–339.

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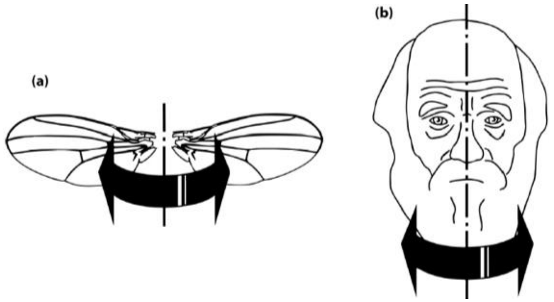
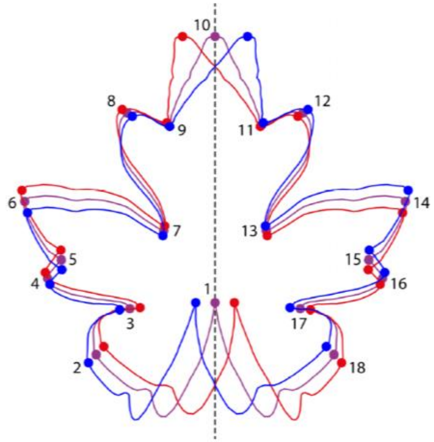
Analysis of symmetry with geometric morphometrics

Types of symmetry

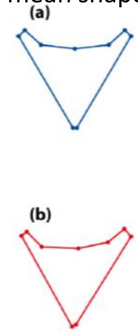


Matching Object



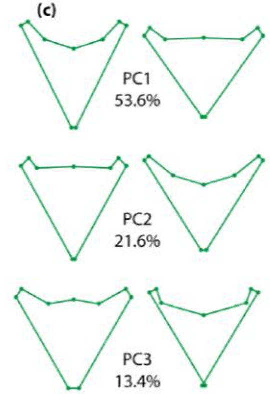
Original configuration
Reflected and relabed
Symmetrized

Symmetrized mean shape

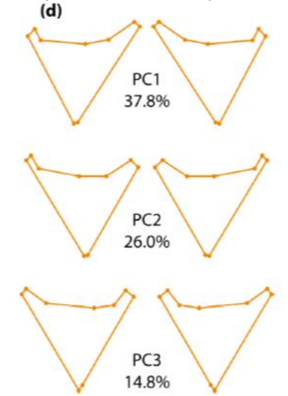


Mean asymmetry (DA)

PCA on Symmetric component



PCA on Asymmetric component



Directional asymmetry (DA) is the mean asymmetry in the population, and therefore can be estimated as the average of individual left–right shape differences over all the individual. Or equivalently, as the difference between the average of all left configurations and the average of all right configurations.

Fluctuating asymmetry (FA) is the variation of individual asymmetries around the average of directional asymmetry, and thus can be computed as each individual's left–right shape difference minus the overall average of the left–right shape differences.

FA Score: Sqrt of sum of an individual's FA^2 (akin to Procrustes distance), is a metric used in studies of asymmetry and developmental instability.

- Klingenberg CP. 2015. Analyzing Fluctuating Asymmetry with Geometric Morphometrics: Concepts, Methods, and Applications. Symmetry 7:843–934.
- Klingenberg CP, Barluenga M, Meyer A. 2002. Shape Analysis of Symmetric Structures: Quantifying Variation Among Individuals and Asymmetry. Evolution 56:1909–1920.

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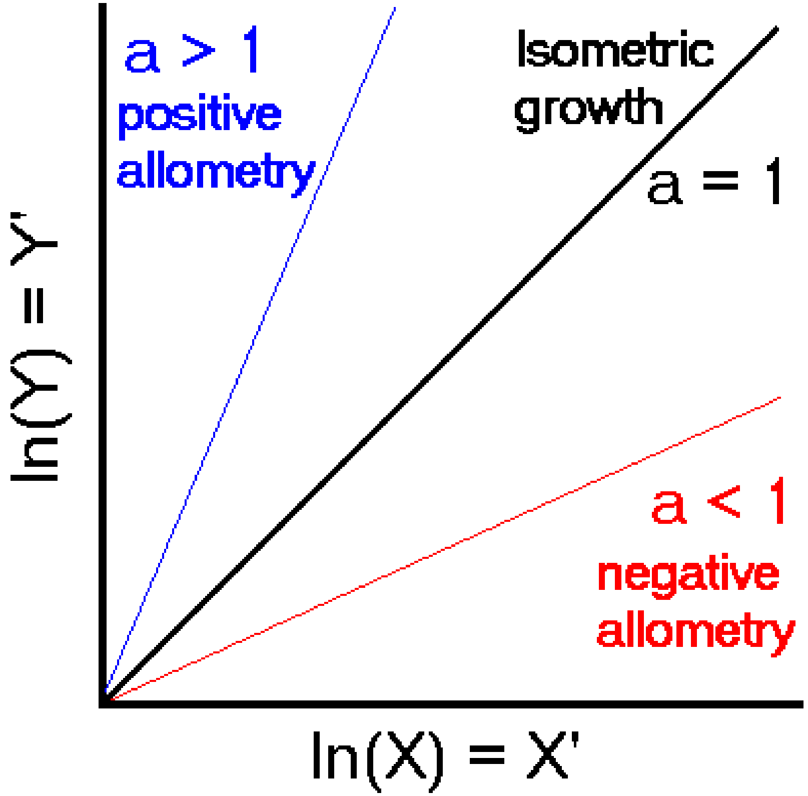
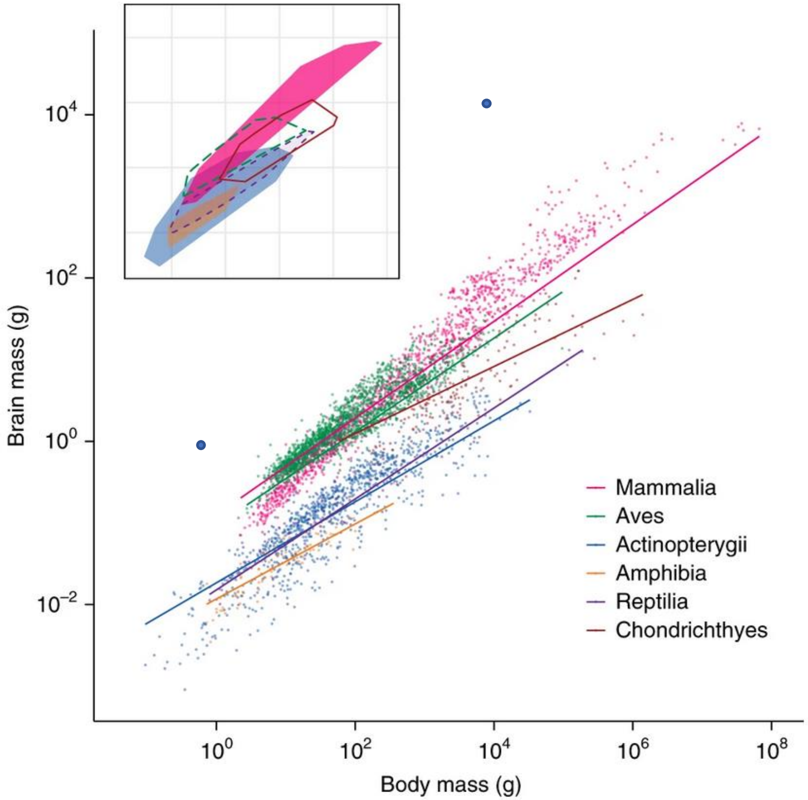
Allometry

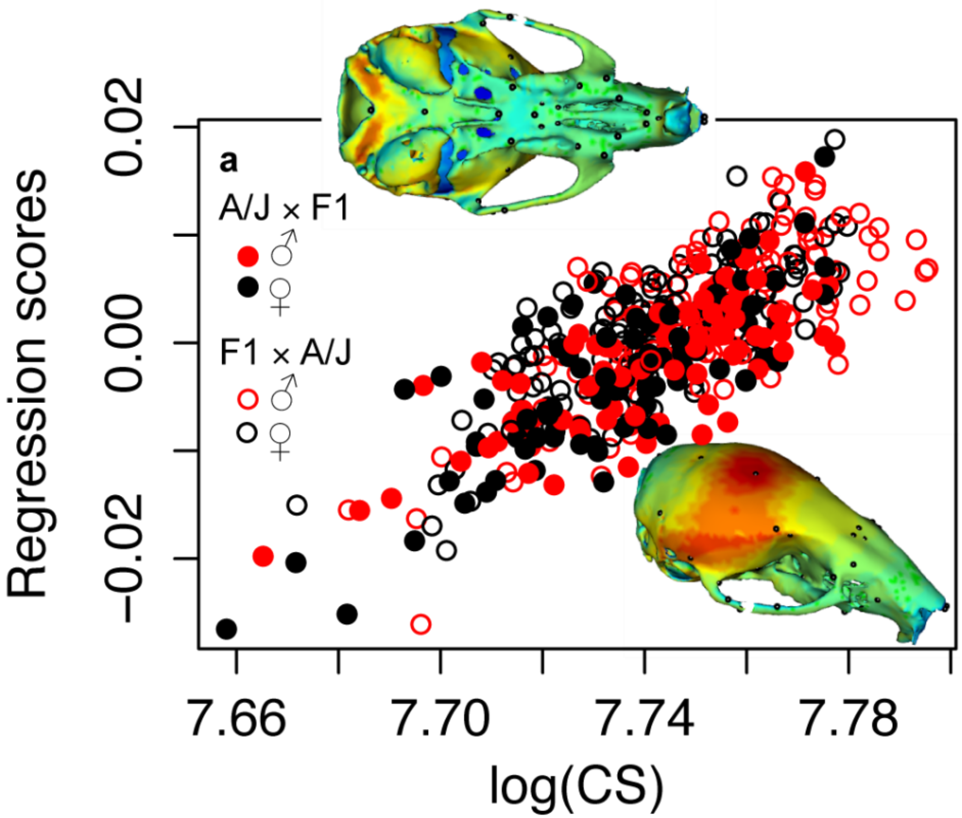


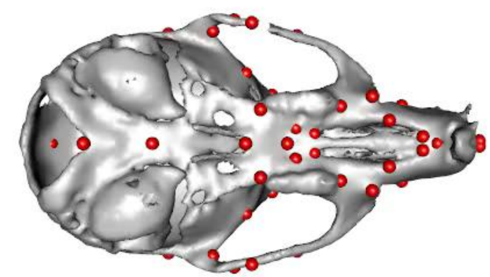
a > 1
positive allometry
Isometric growth
a = 1
a < 1
negative allometry
ln(Y) = Y'
ln(X) = X'

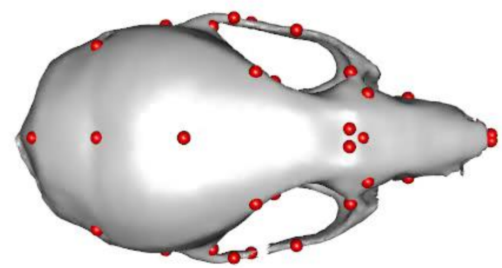


Brain mass (g)
Body mass (g)
10^4
10^2
10^0
10^{-2}
10^0
10^2
10^4
10^6
10^8
Mammalia
Aves
Actinopterygii
Amphibia
Reptilia
Chondrichthyes

Effect of skull size on the skull shape



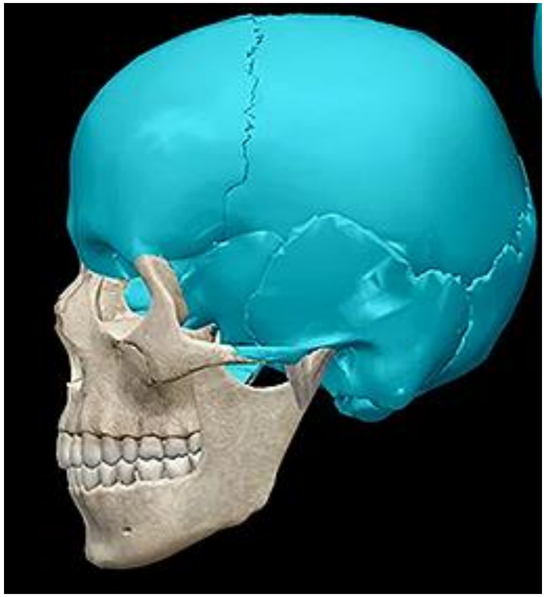


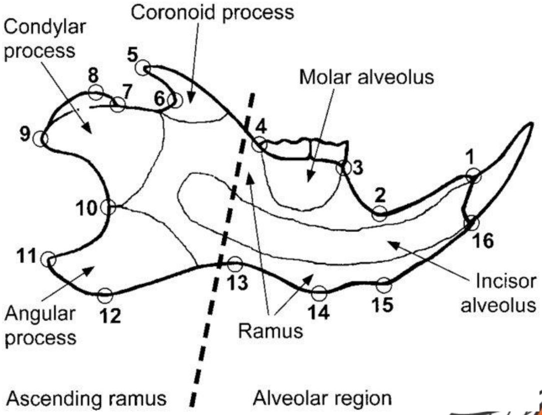


Maga AM, Navarro N, Cunningham ML, Cox TC. 2015. Quantitative trait loci affecting the 3D skull shape and size in mouse and prioritization of candidate genes in-silico. Frontiers in Physiology | Craniofacial Biology 6:92.

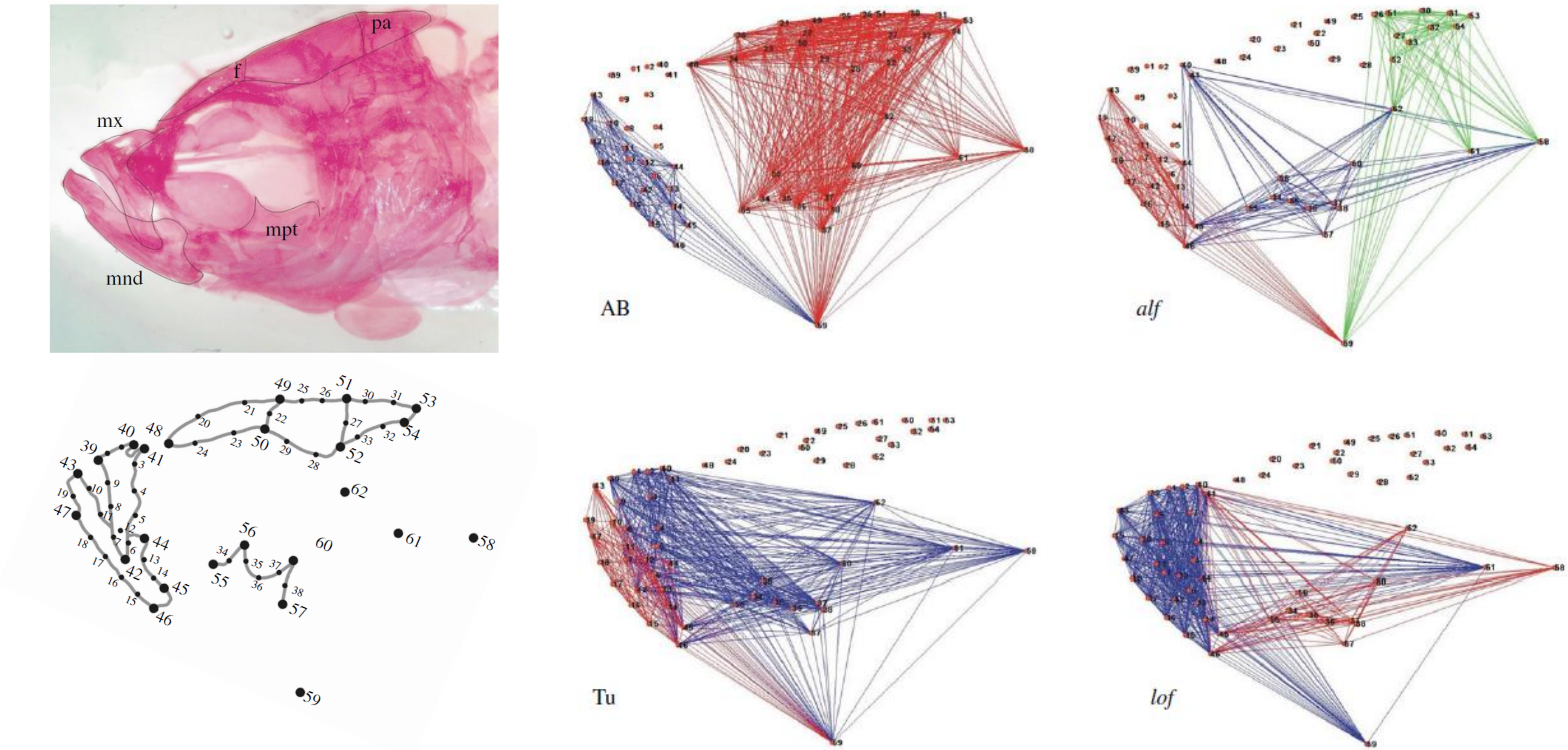
Modularity and integration

- A system is modular, if it can be divided into multiple sets of strongly interacting parts that are relatively autonomous with respect to each other.
- Typical examples:
  - splanchnocranium (face) vs neurocranium
  - Ascending ramus vs body of mandible





Modularity in zebrafish skull



Parsons Kevin J., Son Young H., Crespel Amelie, Thambithurai Davide, Killen Shaun, Harris Matthew P., and Albertson R. Craig. “Conserved but Flexible Modularity in the Zebrafish Skull: Implications for Craniofacial Evolvability.” *Proceedings of the Royal Society B: Biological Sciences* 285, no. 1877 (April 25, 2018): 20172671. https://doi.org/10.1098/rspb.2017.2671.

What can you do with SlicerMorph GPA module?

- **GPA in SlicerMorph will provide**
  - Procrustes distances
  - Aligned Procrustes coordinates
  - Centroid sizes
  - 2D/3D plot of mean shapes
  - Visualization of individual landmark variances

  (**not for analysis, but for QC!!!**)
  - PCA and PC scores
  - 2D/3D eigenvectors (lollipop plots)
  - Visualization along PCA axes
  - Deformation of a reference shape model along PC axes using TPS
  - 3D animations of PCA results

- **SlicerMorph won't currently do:**
  - Procrustes anova
  - Multivariate regression of shape coordinates on CS
  - Symmetry analysis
  - Modularity/Integration
  - Essentially any sort of statistics based on analysis of coordinate data
  - For these, import the output from GPA into R and do all these analyses in geomorph/Morpho/shapes packages. (Exercise for day 4)

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To Slide or Not to Slide: Considerations for semi-landmarks

What is wrong with equidistant samples?

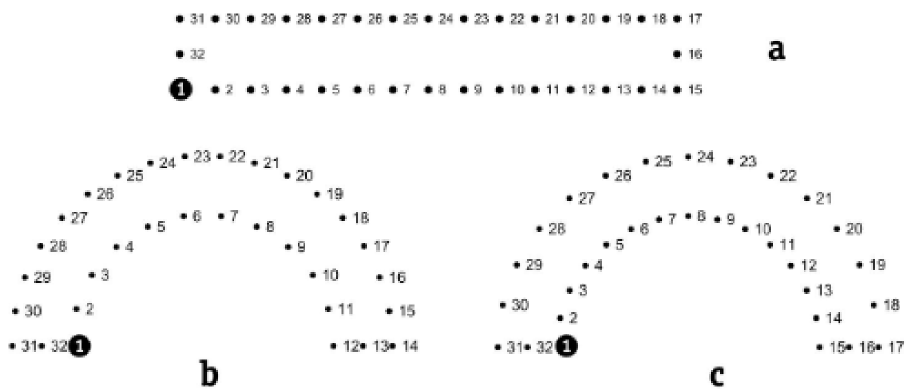

Figure 3. (a) Form with one true landmark in the lower left corner and 31 other points equally spaced along the outline. (b) Bent form with one true landmark (1) and 31 other points in equal spacing. (c) The position of the points now optimizes bending energy.

Produce spacing as a by-product of the analysis since the analysis is ignorant of the actual spacing.

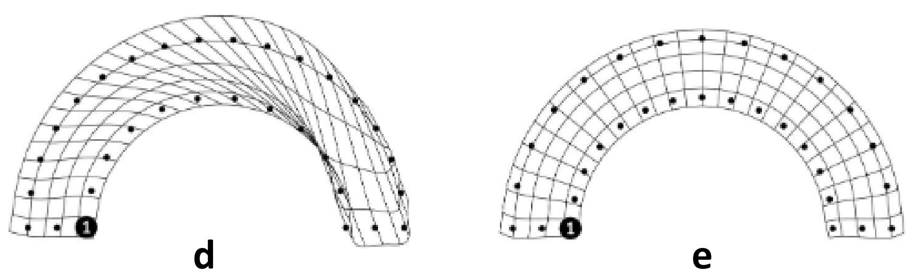

Figure 4. Splines corresponding to Figure 3. (a) Deformation grid from the form in Figures 3a and 3b. (b) Deformation grid from the form in Figures 3a and 3c.

Gunz, Philipp, Philipp Mitteroecker, and Fred L. Bookstein. "Semilandmarks in three dimensions." *Modern morphometrics in physical anthropology*. Springer, Boston, MA, 2005. 73-98.

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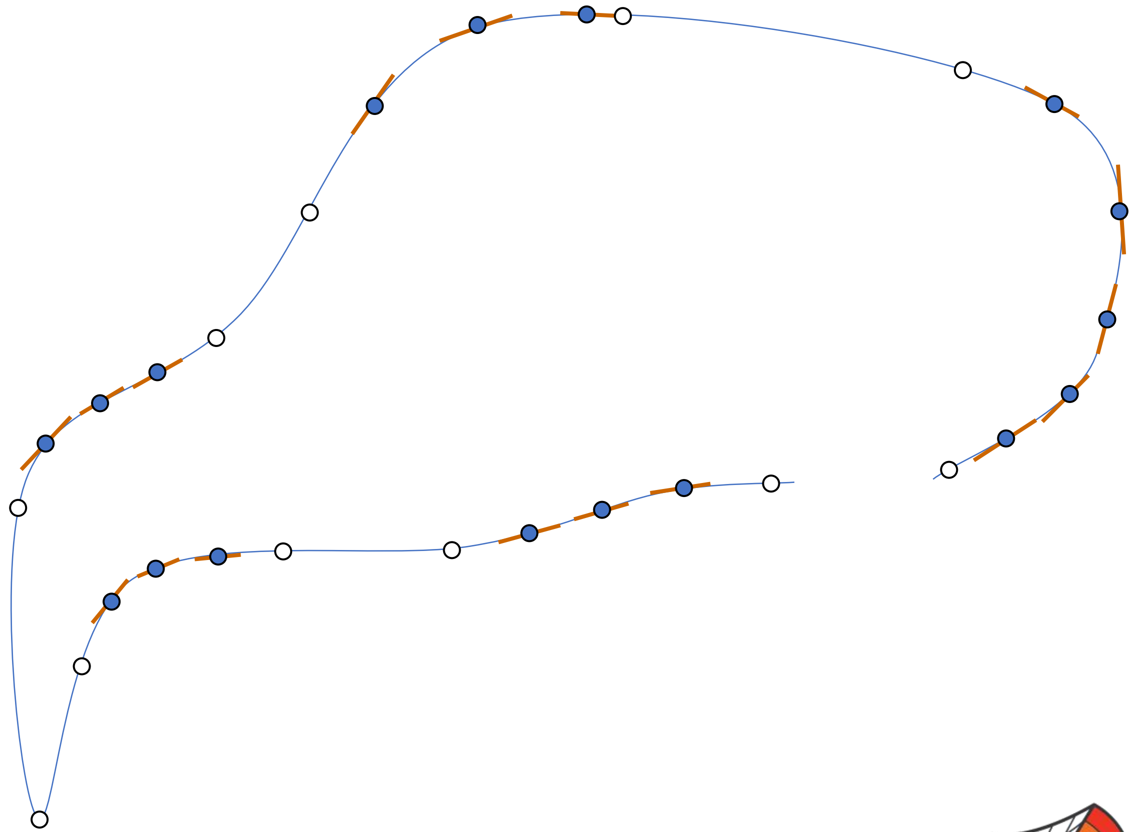
Sliding semi-landmark method

1) Slide semi-landmark points along the surface until they satisfy matching criteria with a single reference specimen
2) Calculate Procrustes average shape
3) Slide semi-landmark points along the surface until they satisfy matching criteria with the Procrustes average
4) Repeat steps 3 and 4 until convergence



Bookstein, Fred L. "Landmark methods for forms without landmarks: morphometrics of group differences in outline shape." *Medical image analysis* 1.3 (1997): 225-243.

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Determining position of sliding semi-landmarks

1) **Minimum bending energy criterion:** select semi-landmark positions that result in the smoothest possible transformation to the mean shape

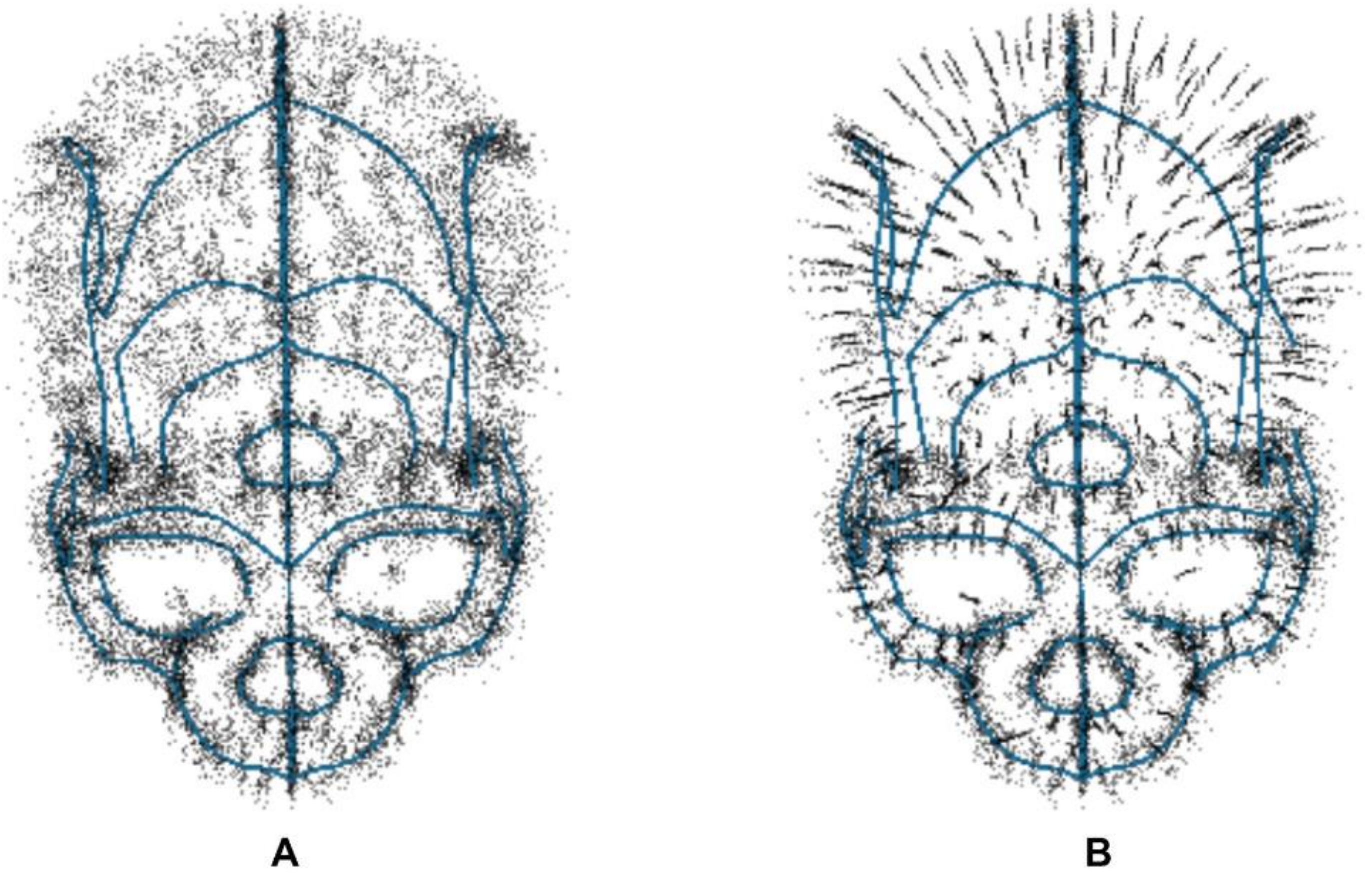
2) **Procrustes distance criterion:** estimate the tangent to the mean surface for each semi-landmark point and remove the component of the difference between the mean and each specimen that lies along this tangent.

Minimum bending energy or Procrustes distance?

- Use different background assumptions
- The difference between the criteria can alter the results when morphological variation in the sample is low
- More noticeable with smaller numbers of semi-landmarks

Perez, S. Ivan, Valeria Bernal, and Paula N. Gonzalez. "Differences between sliding semi-landmark methods in geometric morphometrics, with an application to human craniofacial and dental variation." *Journal of anatomy* 208.6 (2006): 769-784.

Choice of what to minimize impacts the outcome



Gunz and Mitteroecker 2013

Limitations of semi-landmarks

- Limits to homology
- The method of handling semi-landmarks can influence the results
- The number of semi-landmarks may also influence the results
- Sliding semi-landmark positions are dependent on the dataset. Not possible to compare new shapes without recalculating

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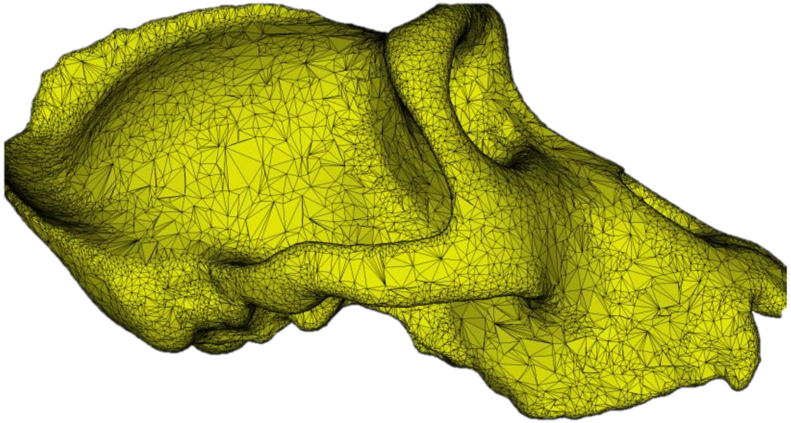
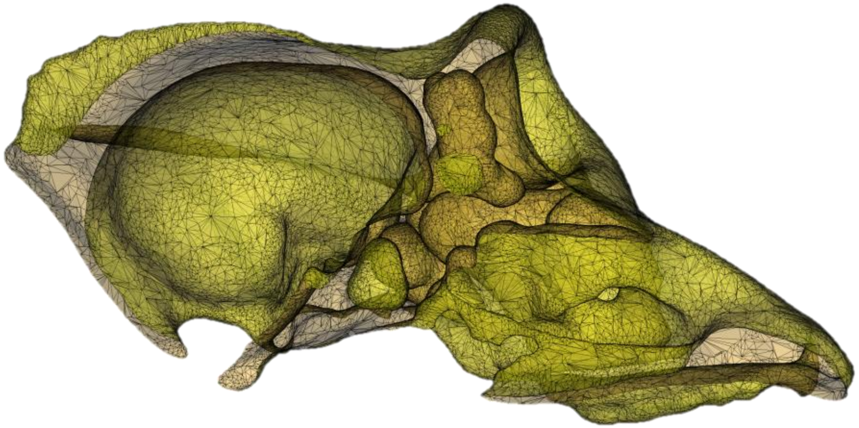
Working with semi and pseudo landmarks in SlicerMorph

Initial semi-landmark placement

- Generating equally spaced samples on a surface can be surprisingly complex
- SlicerMorph provides flexible tools for generating semi-landmarks and pseudo-landmarks for different data types



Exterior of mesh



Complex internal structures

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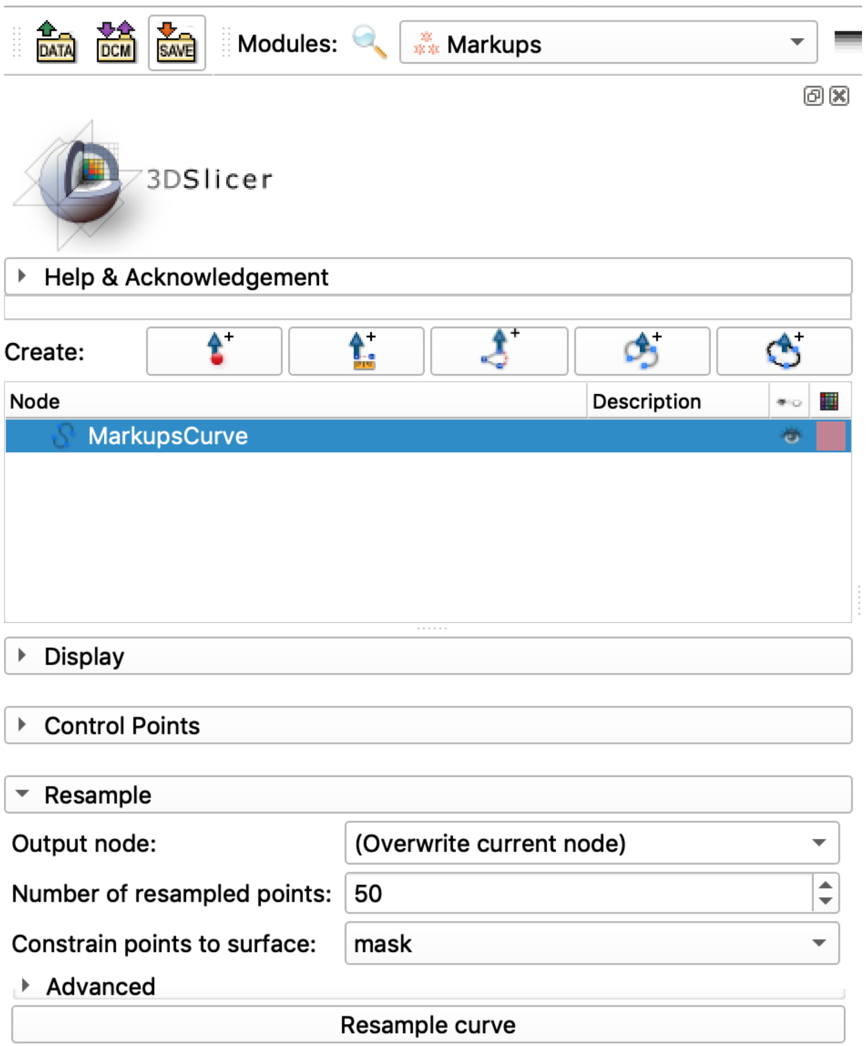
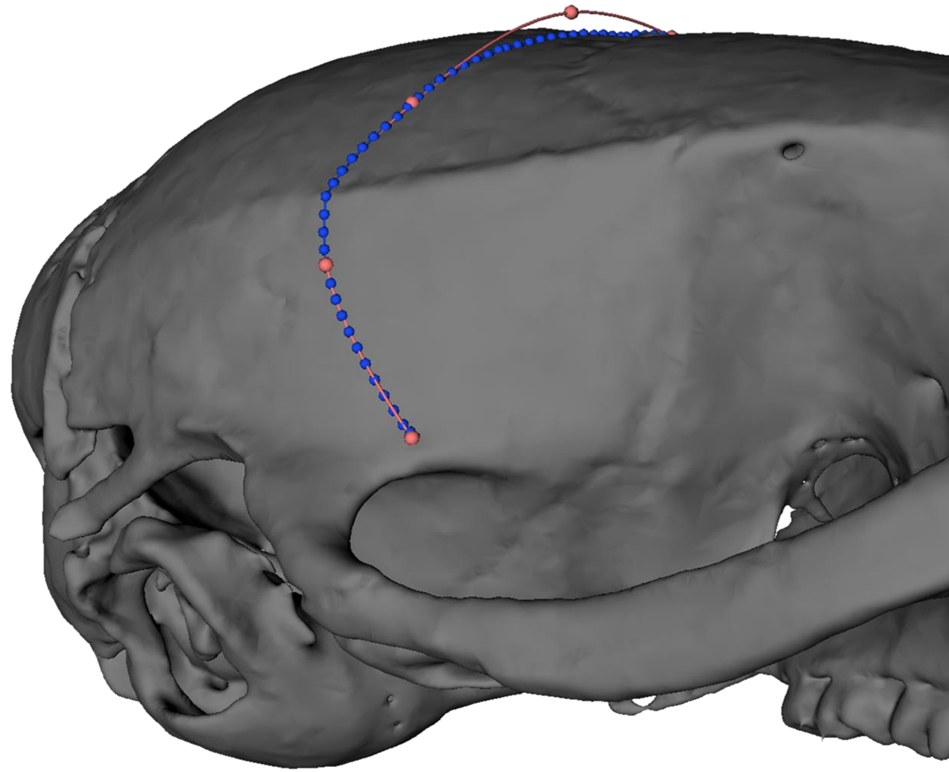
Semi-landmarking: Curves





First and last point considered fixed.

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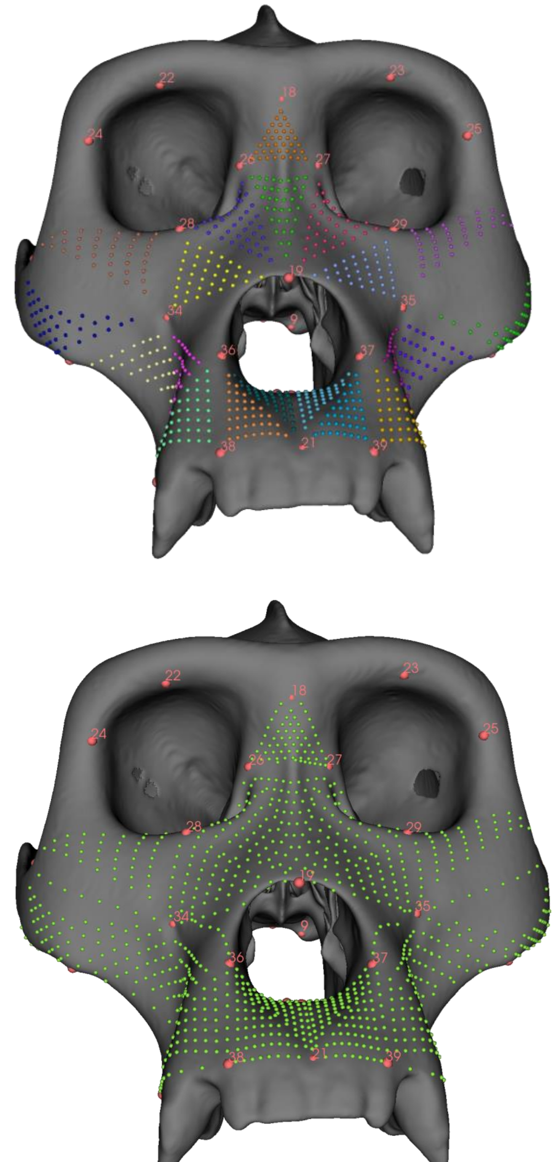
Place Semi-LM Patches



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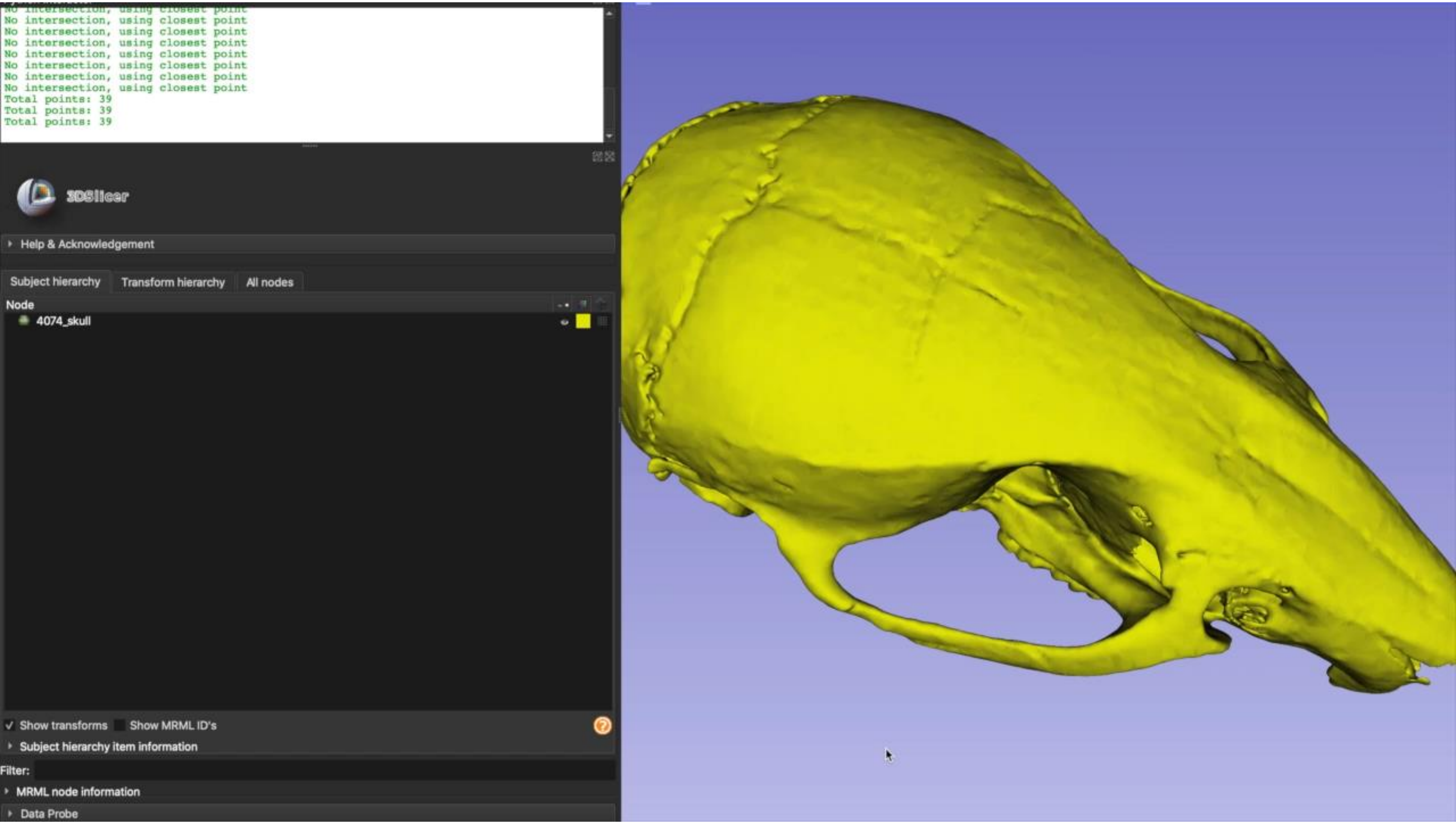
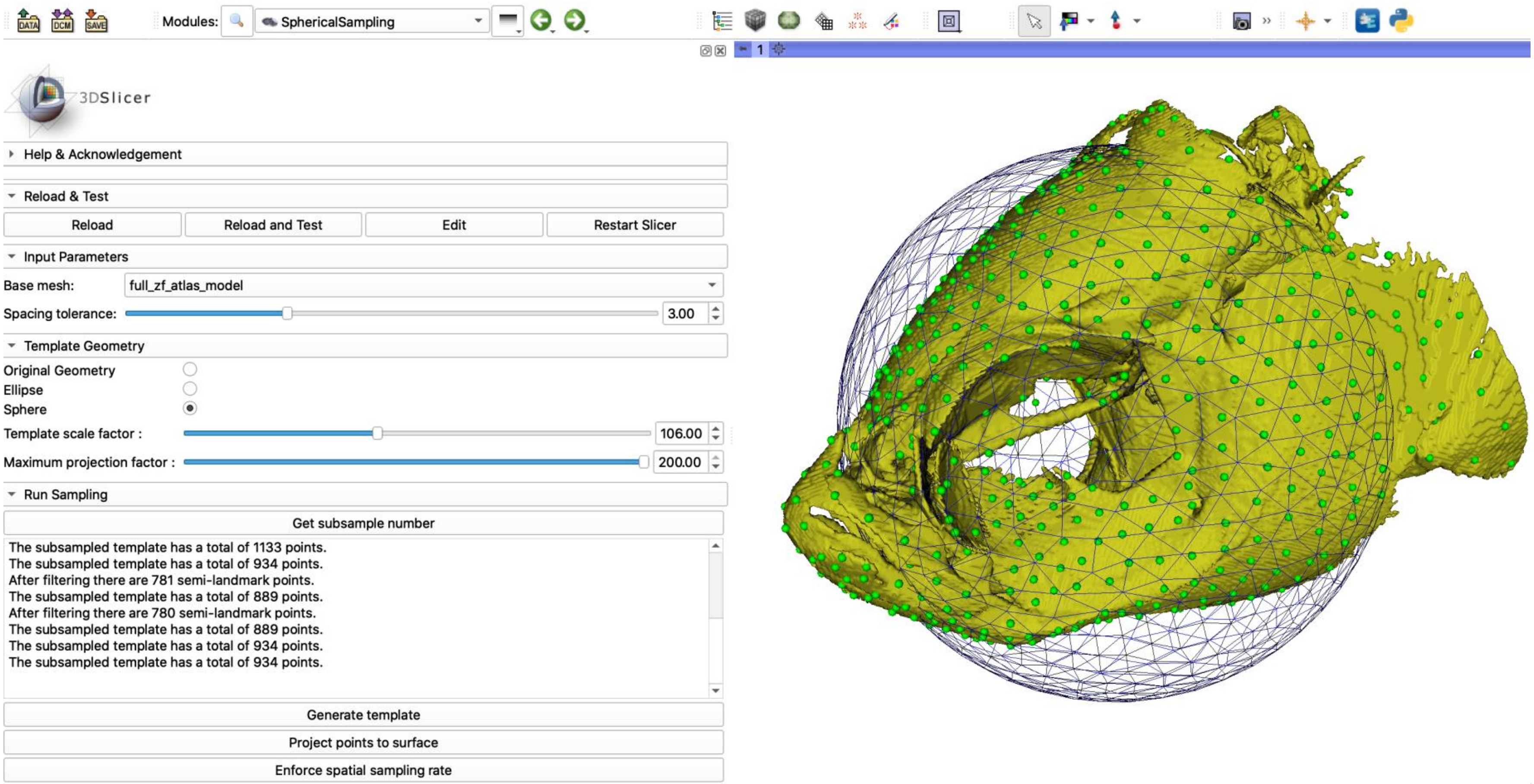
Patch Placement Video



PseudoLMGenerator



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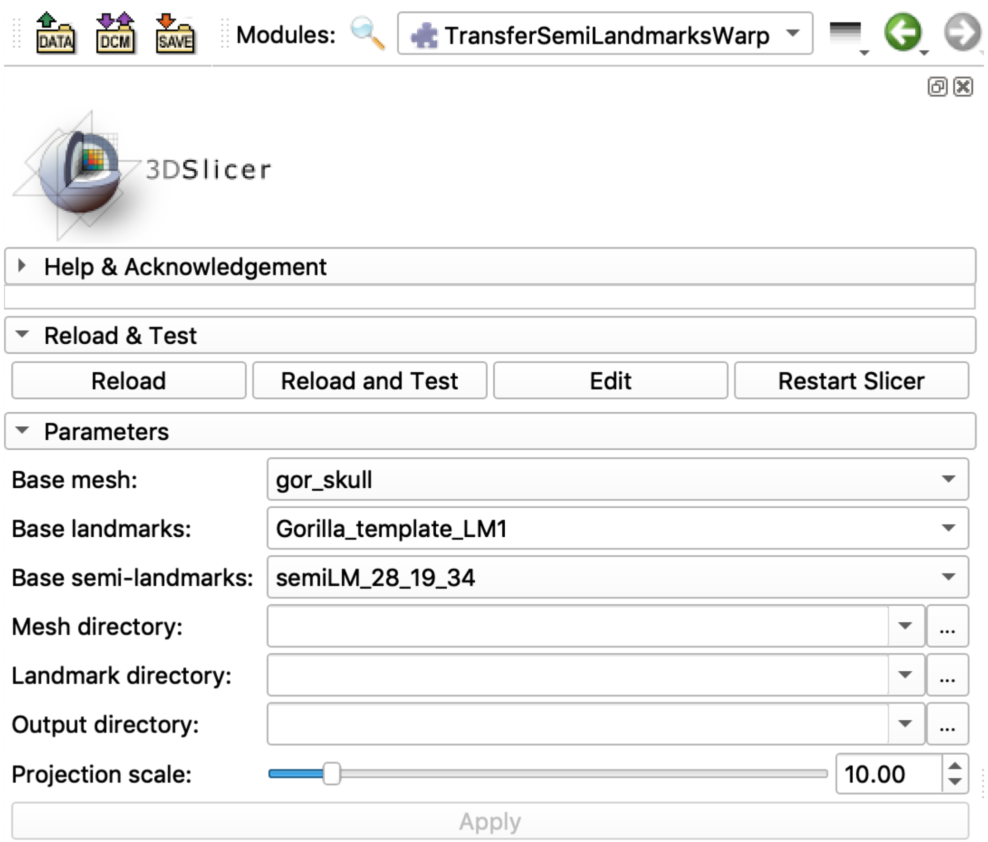
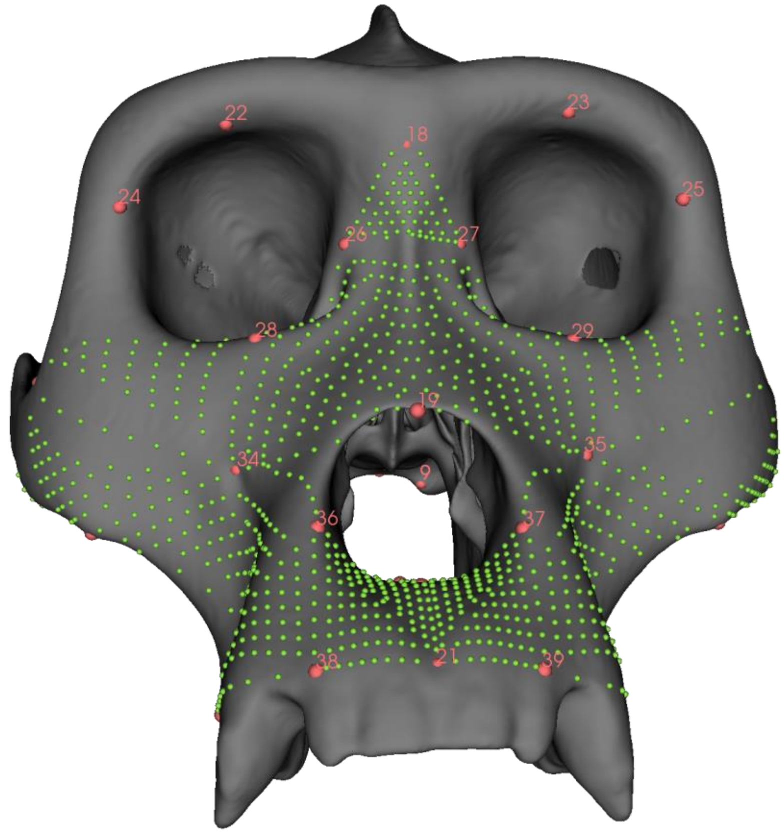
Transferring Semi-landmarks-TPS





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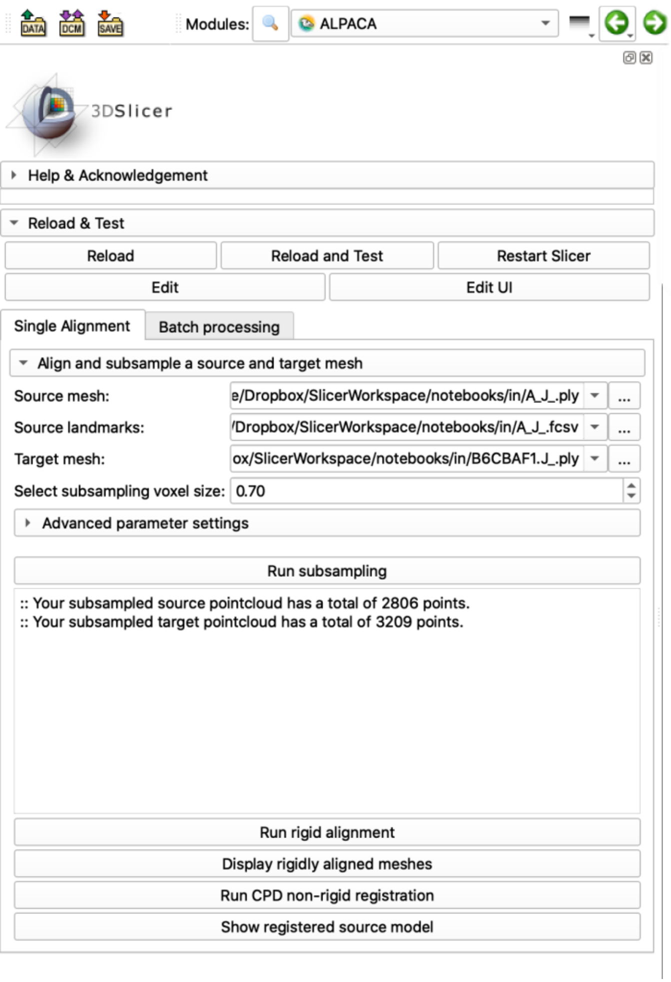
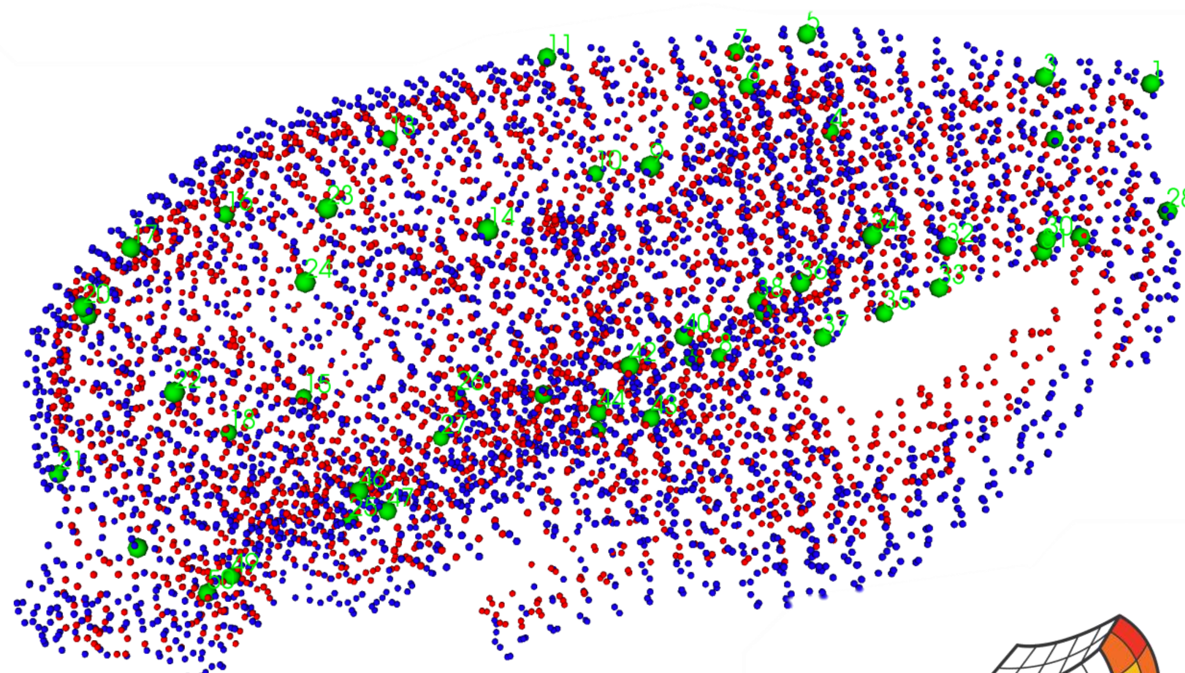
Transferring Landmarks - ALPACA





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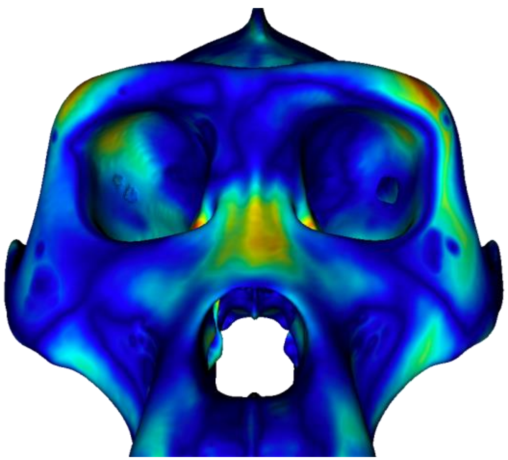
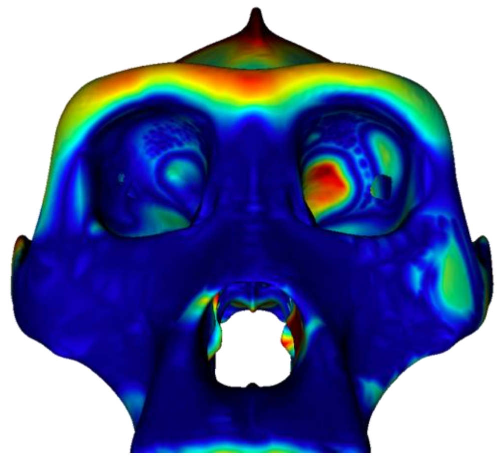
Comparing Semi-landmark methods

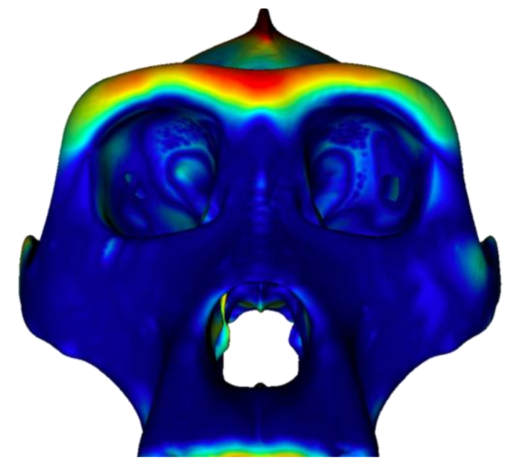
Species	N	Manual landmarks (mm)	Individually placed patch semi-landmarks (mm)	TPS-placed patch semi-landmarks (mm)	Spherical surface sampling (mm)
Gorilla	22	1.267 (SD=0.177)	1.177 (SD=0.162)	1.076 (SD=0.521)	1.124 (SD=0.120)



Manual landmarks only



Individually placed patch semi-landmarks

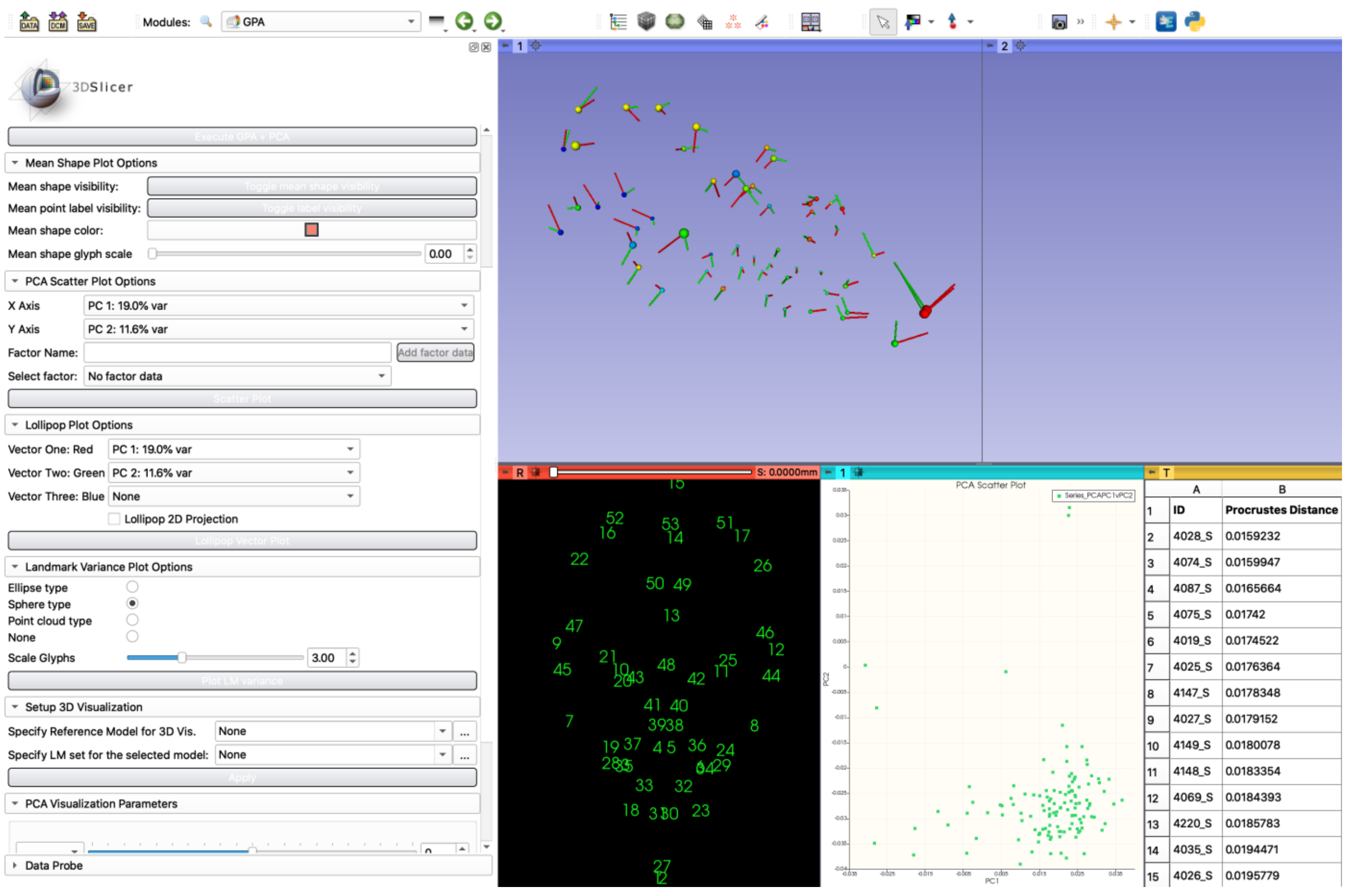


TPS-placed patch semi-landmarks

Rolfe, S., Davis, C., & Maga, A. M. (2021). Comparing semi-landmarking approaches for analyzing three-dimensional cranial morphology. *American Journal of Physical Anthropology*, *175*(1), 227–237. https://doi.org/10.1002/ajpa.24214

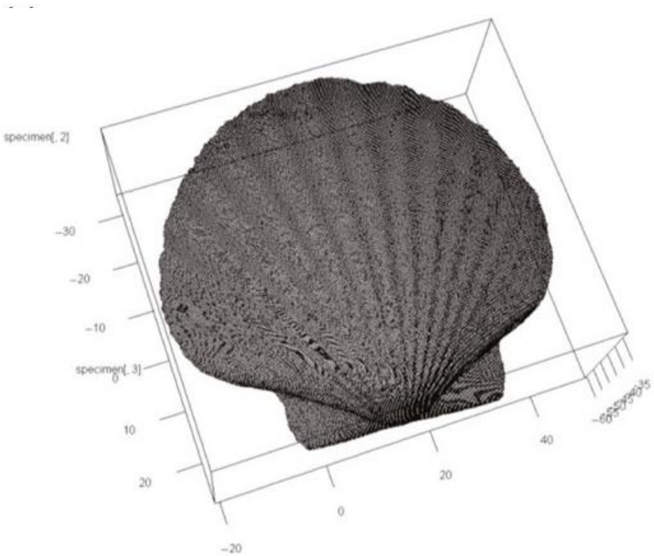
Semi-landmark analysis in SlicerMorph: GPA

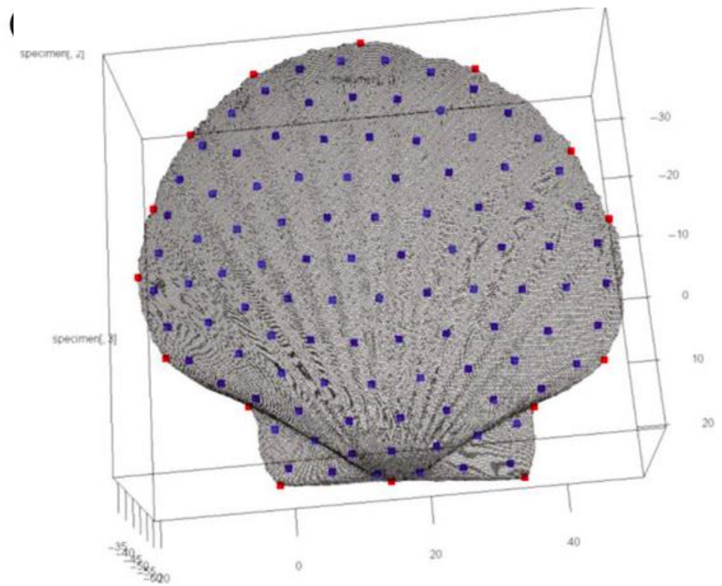
SlicerMorph does not allow sliding of the semiLMs, use R instead.



Semi-landmark analysis in R: Morpho and Geomorph

R Toolboxes Morpho and Geomorph for morphometric analysis provide support for transferring, sliding, and analyzing semi-landmarks





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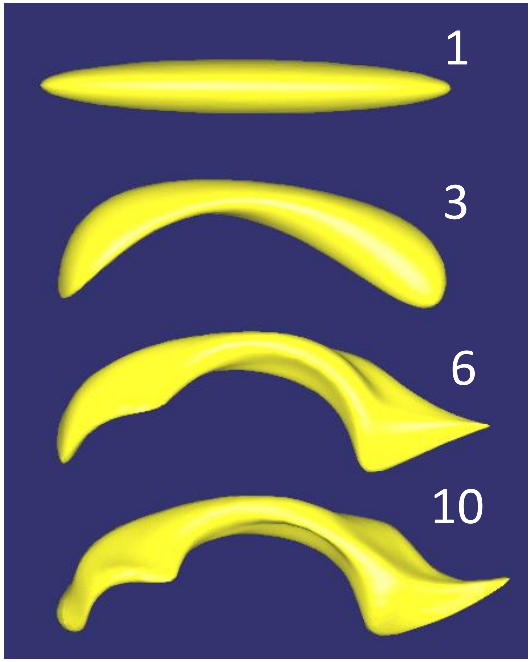
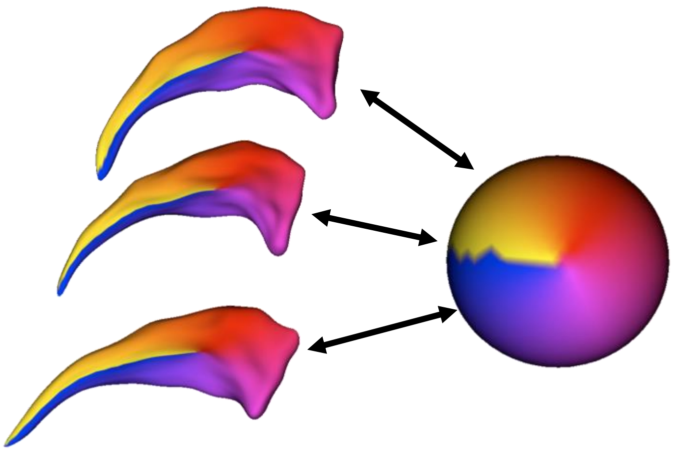
Other Shape Analysis Tools within 3D Slicer Ecosystem

Spherical harmonic representation and point distributed models (SPHARM-PDM)





SPHARM description is computed from the mesh and its spherical parameterization

Styner, Lieberman, Pantazis, Gerig: Boundary and Medial Shape Analysis of the Hippocampus in Schizophrenia, Medical Image Analysis, 2004, pp 197-203

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Limitations of SPHARM methods

- Requirement for spherical topology of meshes
- Challenging for complicated or noisy data sets
- Developed for high N of shapes with similar morphology – should preform a quality assessment to check for correspondence issues

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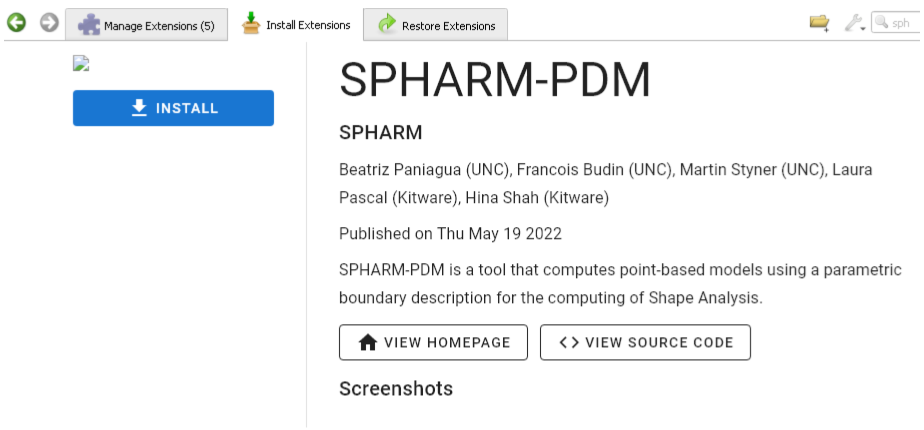
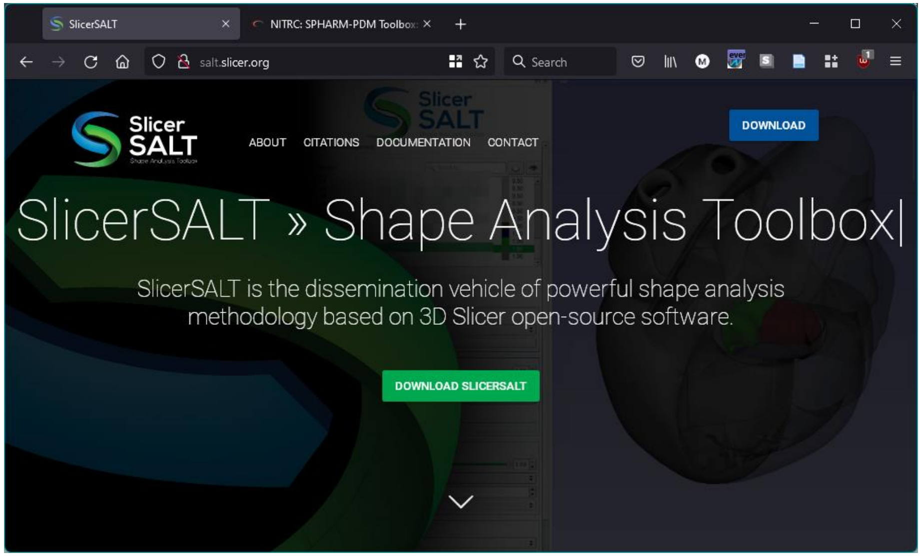
Spharm is available through:





As an extension…

And also part of SlicerSALT, a custom application based on Slicer (free).

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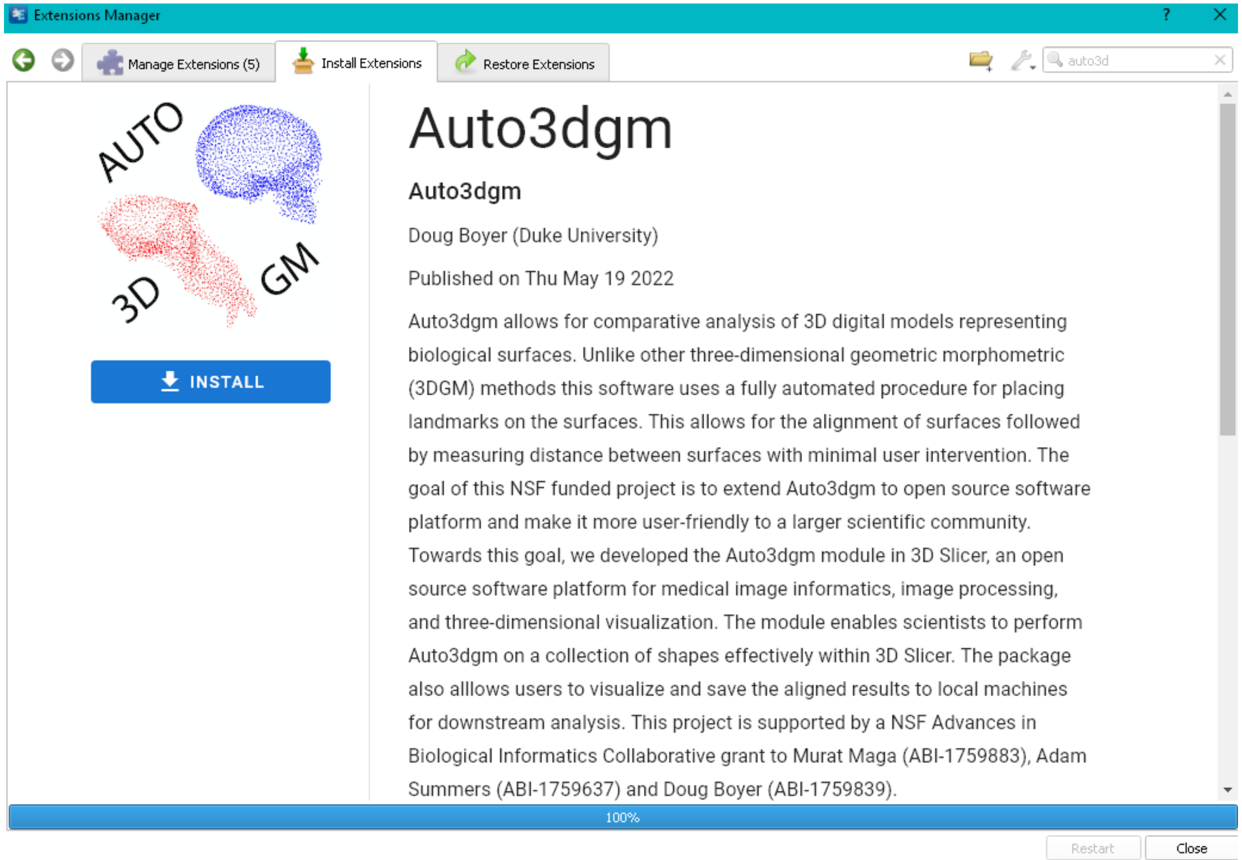
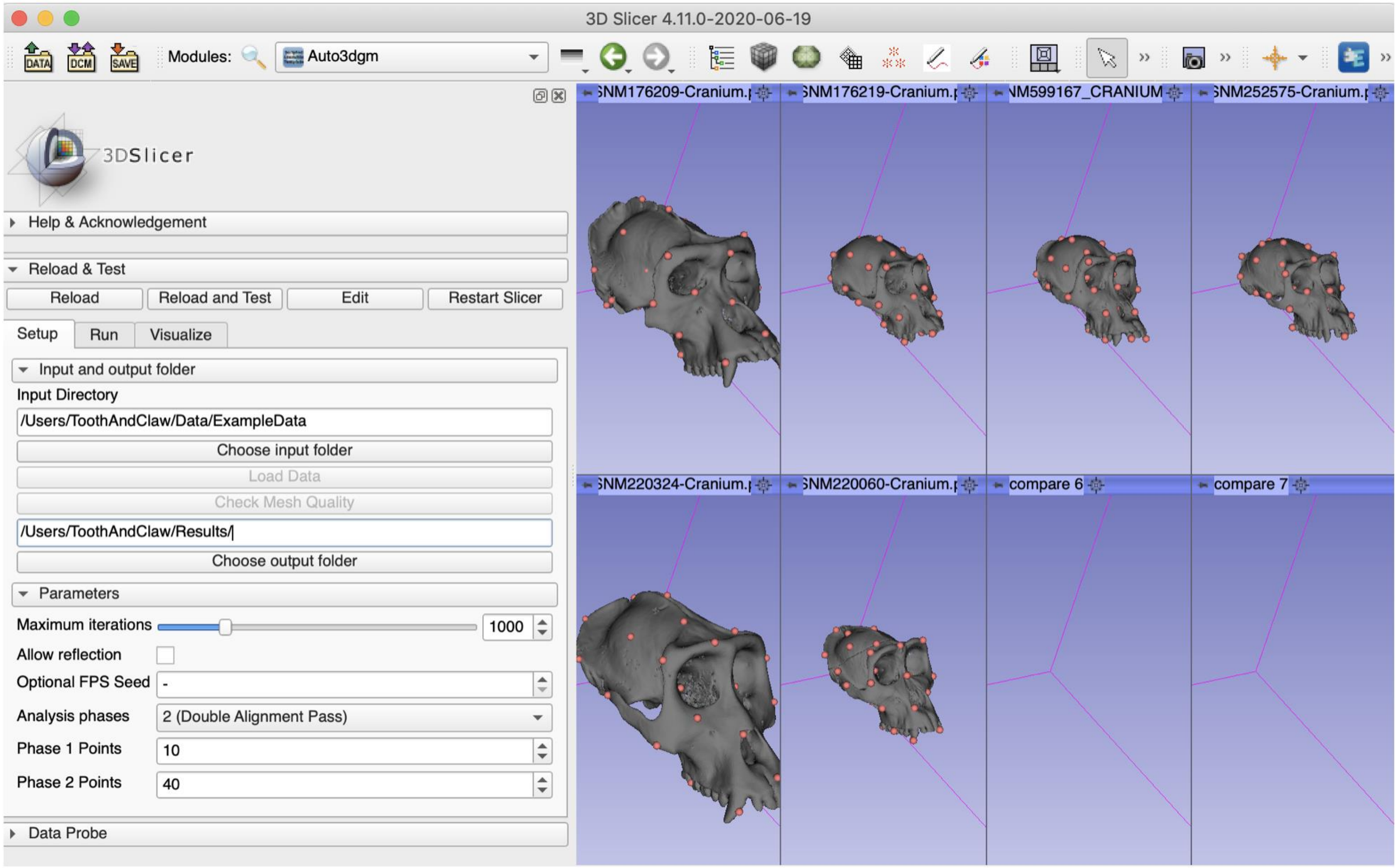
Auto3Dgm


Extensions Manager
Manage Extensions (5)
Install Extensions
Restore Extensions
auto3d
AUTO
3D
GM
INSTALL
Auto3dgm
Auto3dgm
Doug Boyer (Duke University)
Published on Thu May 19 2022
Auto3dgm allows for comparative analysis of 3D digital models representing biological surfaces. Unlike other three-dimensional geometric morphometric (3DGM) methods this software uses a fully automated procedure for placing landmarks on the surfaces. This allows for the alignment of surfaces followed by measuring distance between surfaces with minimal user intervention. The goal of this NSF funded project is to extend Auto3dgm to open source software platform and make it more user-friendly to a larger scientific community. Towards this goal, we developed the Auto3dgm module in 3D Slicer, an open source software platform for medical image informatics, image processing, and three-dimensional visualization. The module enables scientists to perform Auto3dgm on a collection of shapes effectively within 3D Slicer. The package also alllows users to visualize and save the aligned results to local machines for downstream analysis. This project is supported by a NSF Advances in Biological Informatics Collaborative grant to Murat Maga (ABI-1759883), Adam Summers (ABI-1759637) and Doug Boyer (ABI-1759839).
100%
Restart
Close

Auto3DGM



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Resources

Gunz, Philipp, Philipp Mitteroecker, and Fred L. Bookstein. "Semilandmarks in three dimensions." *Modern morphometrics in physical anthropology*. Springer, Boston, MA, 2005. 73-98.

Watanabe, Akinobu. "How many landmarks are enough to characterize shape and size variation?." PloS one 13.6 (2018): e0198341.

Bardua, C., Felice, R. N., Watanabe, A., Fabre, A. C., & Goswami, A. (2019). A practical guide to sliding and surface semilandmarks in morphometric analyses. *Integrative Organismal Biology*, *1*(1), obz016.

Perez, S. Ivan, Valeria Bernal, and Paula N. Gonzalez. "Differences between sliding semi-landmark methods in geometric morphometrics, with an application to human craniofacial and dental variation." *Journal of anatomy* 208.6 (2006): 769-784.

Bookstein, Fred L., and William DK Green. "A feature space for edgels in images with landmarks." *Journal of Mathematical imaging and vision* 3.3 (1993): 231-261.

Cutting, Court, et al. "A three-dimensional smooth surface analysis of untreated Crouzon's syndrome in the adult." *The Journal of craniofacial surgery* 6.6 (1995): 444-453.

Andresen, Per Rønsholt, and Mads Nielsen. "Non-rigid registration by geometry-constrained diffusion." *Medical Image Analysis* 5.2 (2001): 81-88.

Ekrami, Omid, et al. "Measuring asymmetry from high-density 3D surface scans: An application to human faces." *PloS one*13.12 (2018): e0207895.

Darvann, Tron A., et al. "Automated quantification and analysis of facial asymmetry in children with arthritis in the temporomandibular joint." *2011 IEEE International Symposium on Biomedical Imaging: From Nano to Macro*. IEEE, 2011.

Styner, Lieberman, Pantazis, Gerig: Boundary and Medial Shape Analysis of the Hippocampus in Schizophrenia, Medical Image Analysis, 2004, pp 197-203

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Some key literature on landmark based statistical shape analysis

- Adams DC, Rohlf FJ, Slice DE. 2013. A field comes of age: geometric morphometrics in the 21st century. Hystrix 24:7–14.
- Adams, Dean C. "Evaluating Modularity in Morphometric Data: Challenges with the RV Coefficient and a New Test Measure." *Methods in Ecology and Evolution*, January 1, 2016, n/a-n/a. https://doi.org/10.1111/2041-210X.12511.
- Bookstein FL. 1989. Principal warps: thin-plate splines and the decomposition of deformations. IEEE Transactions on Pattern Analysis and Machine Intelligence 11:567–585.
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- Drake AG, Klingenberg CP. 2008. The pace of morphological change: historical transformation of skull shape in St Bernard dogs. Proc Biol Sci 275:71–76.
- Klingenberg CP, Barluenga M, Meyer A. 2002. Shape Analysis of Symmetric Structures: Quantifying Variation Among Individuals and Asymmetry. Evolution 56:1909–1920.
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- Klingenberg CP. 2009. Morphometric integration and modularity in configurations of landmarks: tools for evaluating a priori hypotheses. Evol Dev 11:405–421.
- Klingenberg CP. 2010. Evolution and development of shape: integrating quantitative approaches. Nat Rev Genet 11:623–635.
- Klingenberg CP. 2016. Size, shape, and form: concepts of allometry in geometric morphometrics. Dev Genes Evol 226:113–137.
- Lele S, Richtsmeier J. 1991. Euclidean Distance Matrix Analysis - a Coordinate-Free Approach for Comparing Biological Shapes Using Landmark Data. Am J Phys Anthropol 86:415–427.
- Lele S, Richtsmeier JT. 1995. Euclidean distance matrix analysis: confidence intervals for form and growth differences. Am J Phys Anthropol 98:73–86.
- Rohlf FJ, Corti M. 2000. Use of two-block partial least-squares to study covariation in shape. Syst Biol 49:740–753.
- Rohlf FJ, Slice D. 1990. Extensions of the Procrustes Method for the Optimal Superimposition of Landmarks. Systematic Zoology 39:40–59.
- Rohlf FJ. 2000. On the use of shape spaces to compare morphometric methods. Hystrix-Italian Journal of Mammalogy 11:9–25.

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