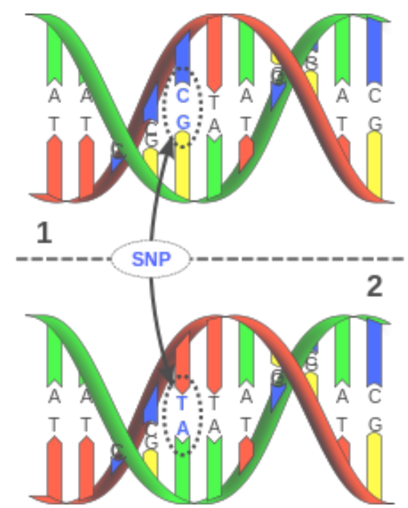
On Genetic Determinants of Facial Shape Variation

Washington Mio

Florida State University

Geometric Topological and Graphical Models
Methods in Statistics – Fields Institute
Spring 2014



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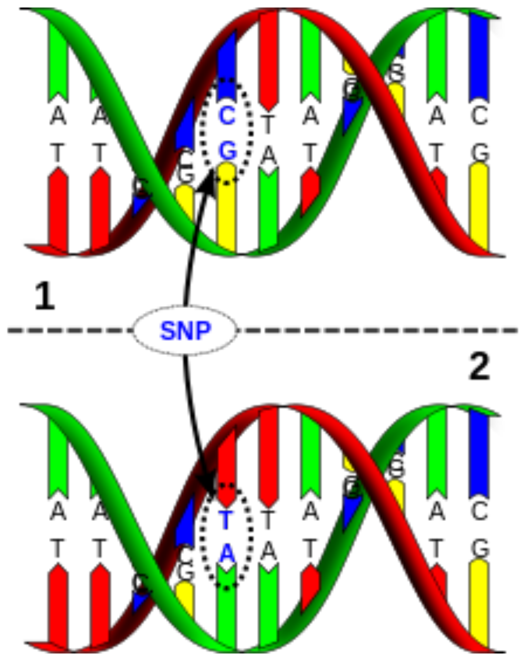
Genetics of Organismal Shape

- Understanding relationships between genetic variation and phenotypic outcomes
- Morphogenesis: biological processes that govern the development of the shape of an organism
- Evolution and inheritance of phenotypic traits
- Personalized and predictive medicine
- Normal and pathological variation: transition to pathological states often occurs at extremes of normality

A March Along the Genome

Single Nucleotide Polymorphisms (SNPs)



Different alleles at a locus

… AACGGATCC …

… AACGAATCC …

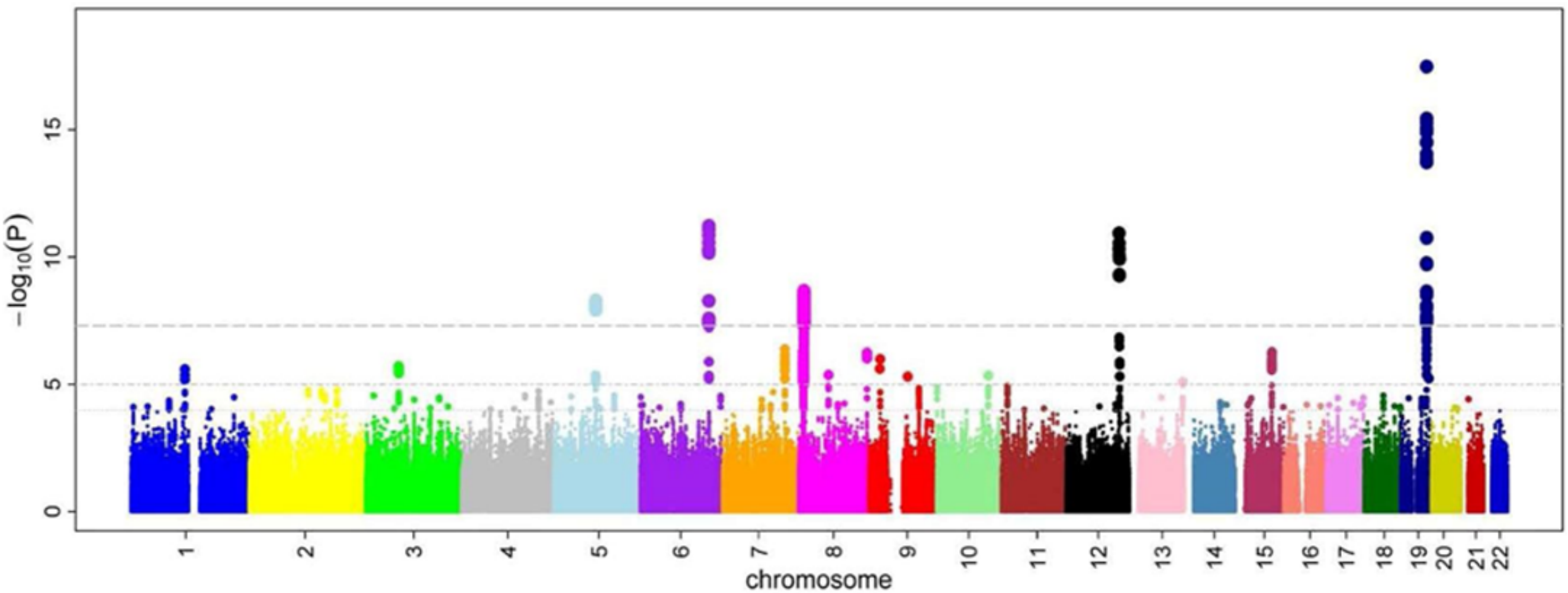
Some Facts

- Most SNPs only have two alleles: A, a
- Pair of chromosomes: AA, Aa, aa
- Three genetic groups at each locus
- Discrete ternary trait
- Kind of continuous if assignment is probabilistic

Genome-Wide Association Studies (GWAS)

- Is a genetic variation associated with a trait?
- SNP by SNP exploratory analysis
- First successful GWAS: age-related macular degeneration (2005) identified two SNPs
- Many traits and diseases analyzed with varying degrees of success

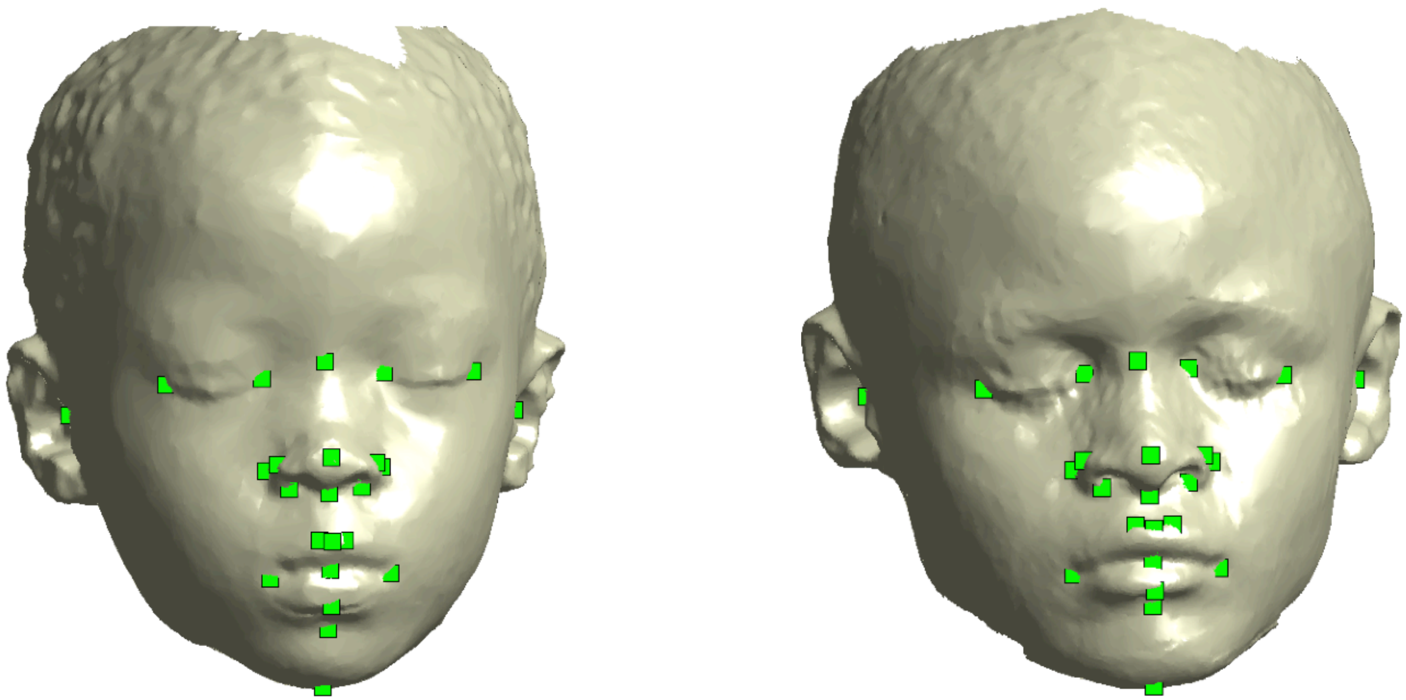
Associations: Manhattan Plots



GWAS of Facial Shape

- Project with Spritz Lab (UC Denver) and Hallgrimsson Lab (Calgary), part of NIH FaceBase consortium
- Study based on 3,700 Tanzanian children
- Data: 3D facial images and saliva samples
- DNA analyses have identified approximately 2,500,000 SNPs
- Replication study with 2,600 subjects
- Task 1: Turn facial shape into a quantitative trait

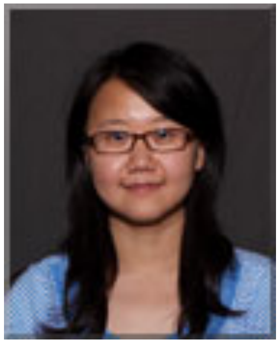
Facial Homology



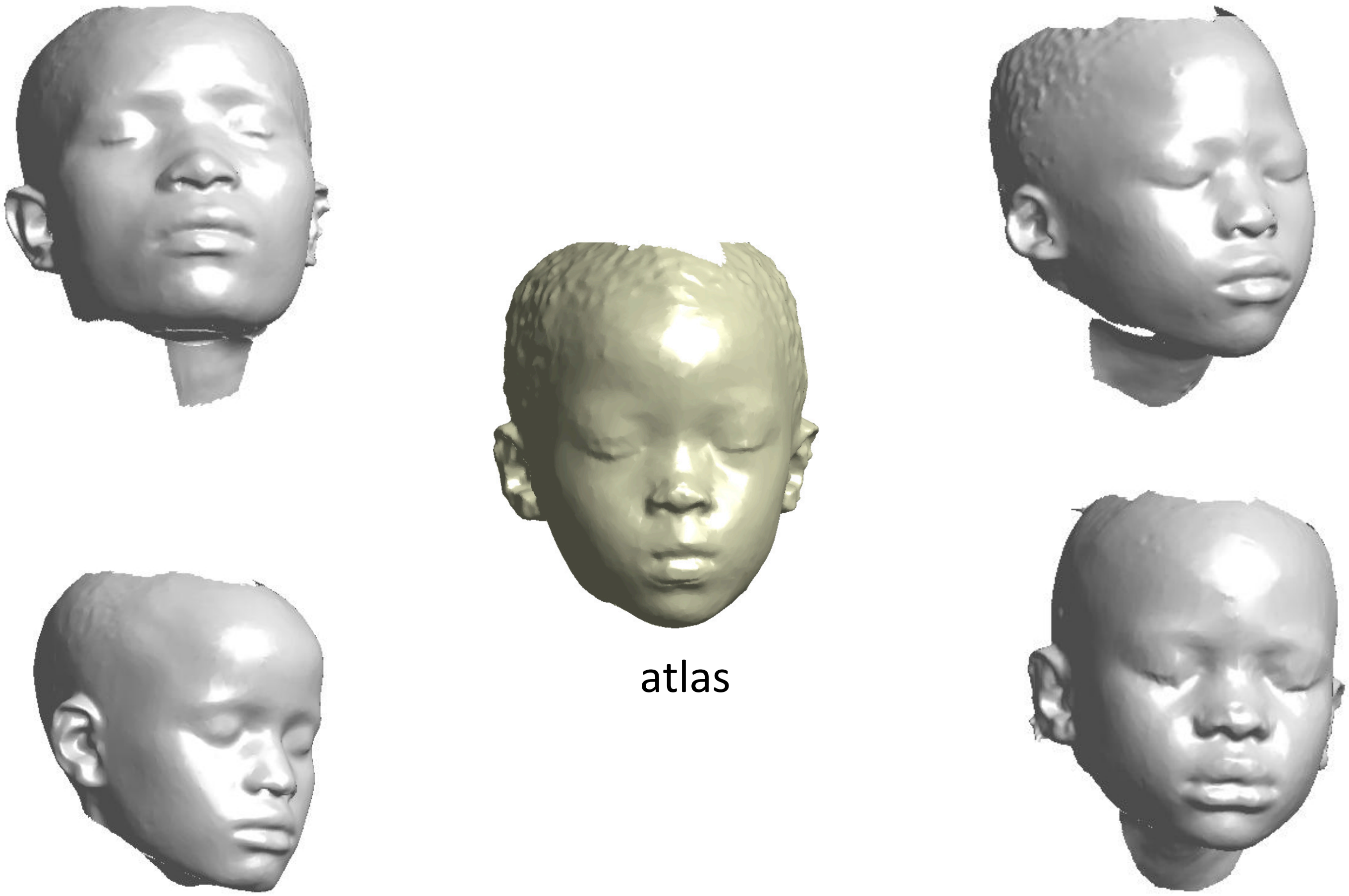
Strategy

- Construction of a landmarked facial atlas from training data
- Coarse spatial alignment of subject and atlas: topological methods
- Fine dense registration and alignment: geometry and optimization
- Morph atlas to subject
- Transfer landmarks

Mao Li

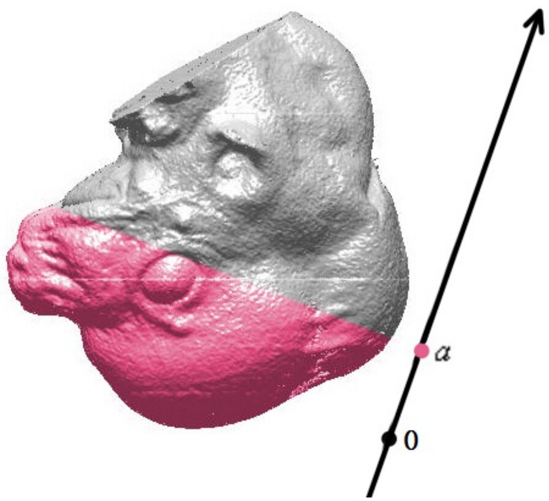


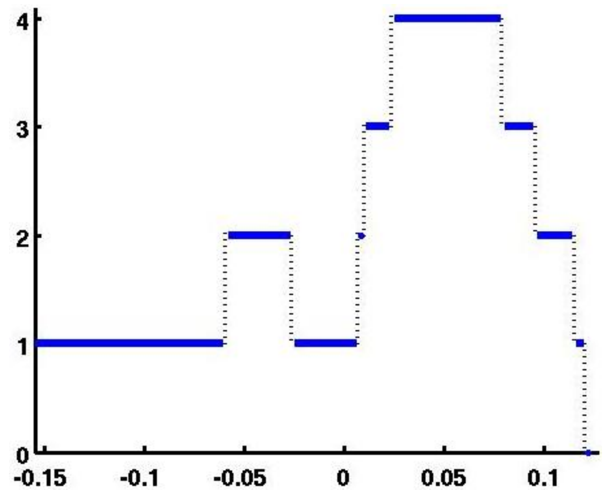
Coarse Spatial Alignment



All centered and size normalized

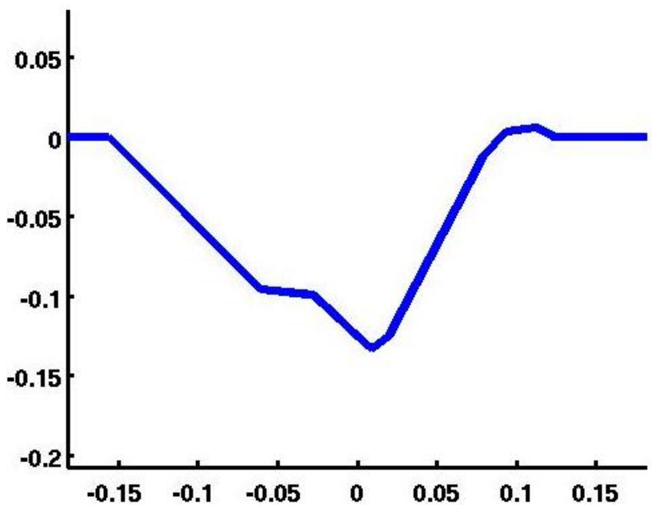
Euler Characteristic Curves





$$\chi_v : I \to \mathbb{Z}$$

Cumulant EC-Curve



$$\chi_v : I \to \mathbb{Z}$$

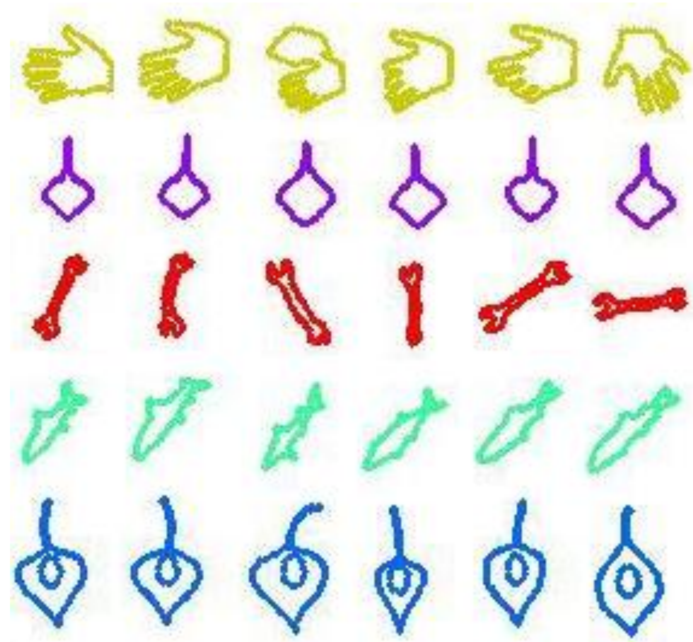
$$\bar{\chi}_v = \chi_v - \mu_v$$

$$F_v(x) = \int_{-\infty}^{x} \bar{\chi}_v(y)\,dy$$

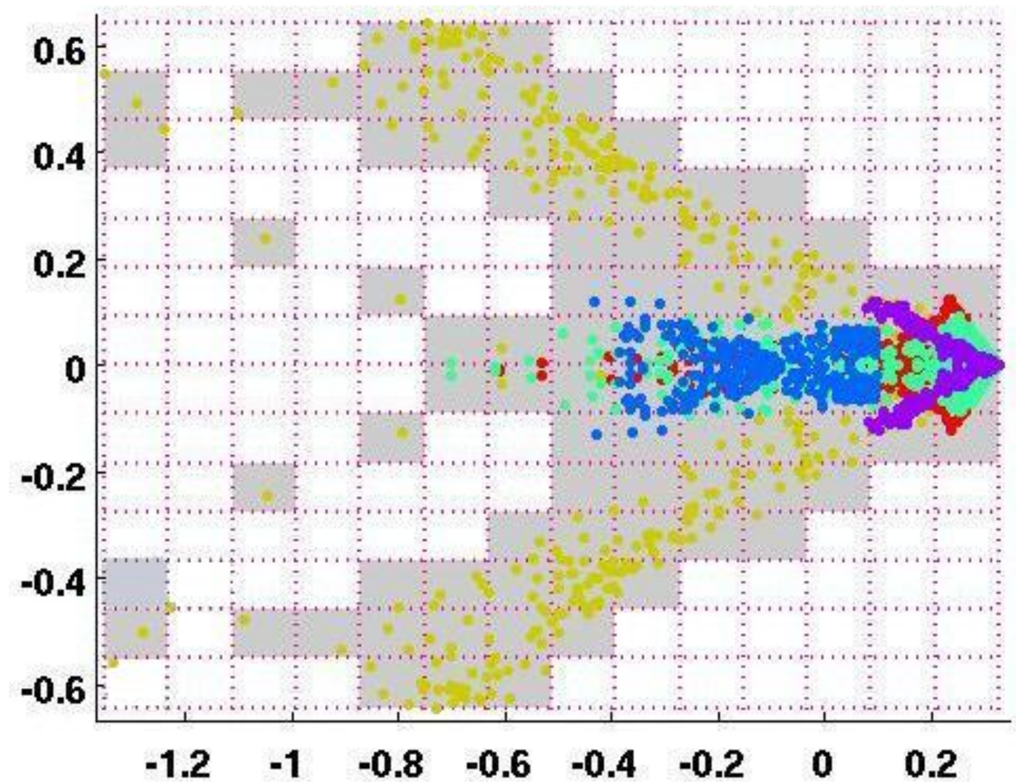
EC-Signatures

$$\Gamma_v = (\mu_v, F_v) \qquad \Gamma_v \in \mathbb{R} \times \mathbb{L}^2$$

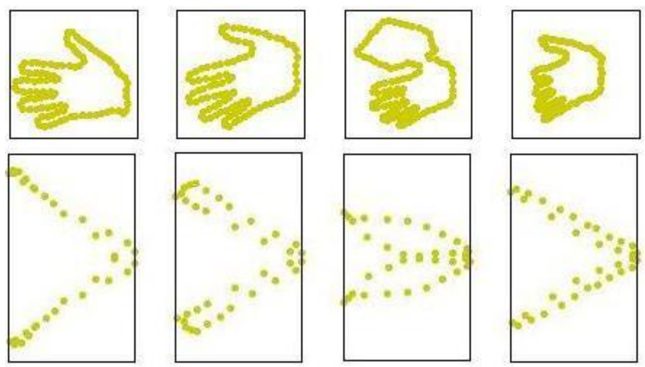
Toy Example

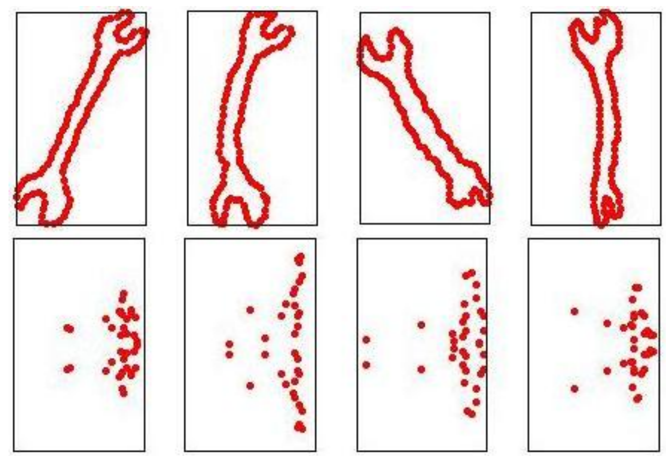


Reduced EC-Signatures

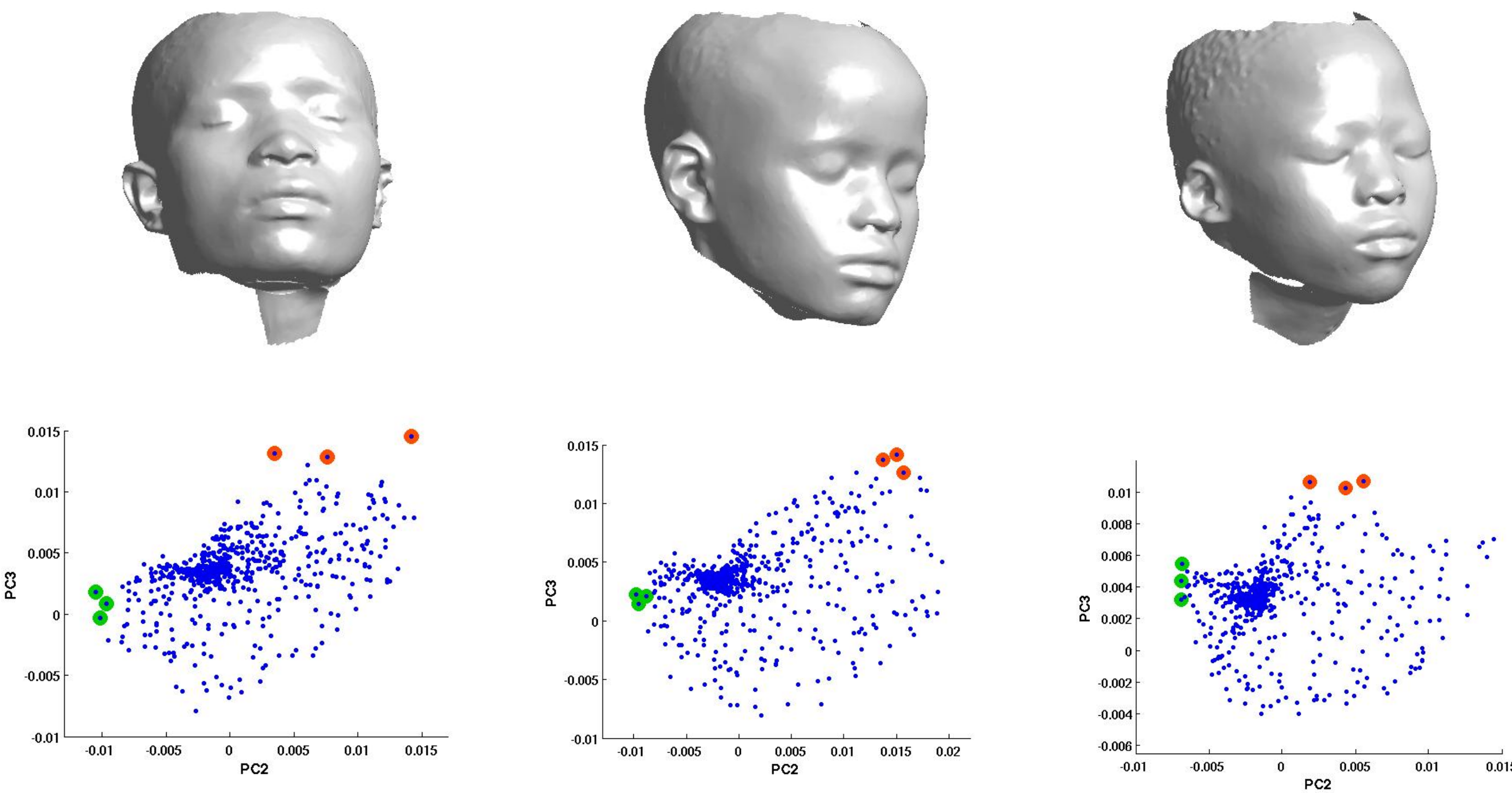


Point Cloud Representation

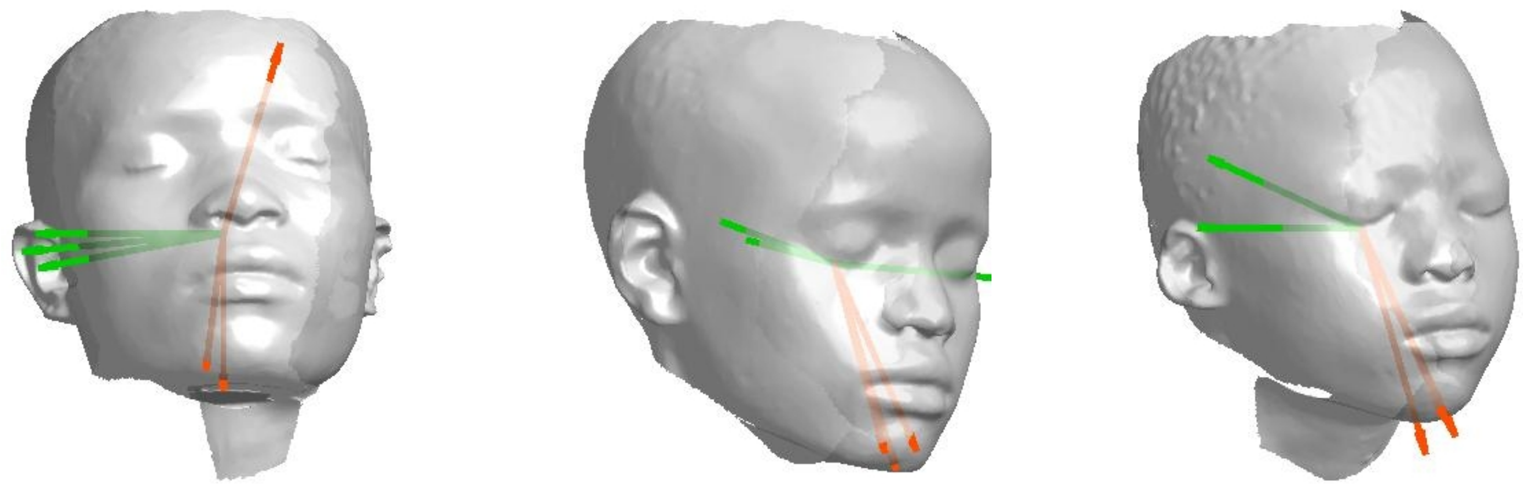




Face Representation

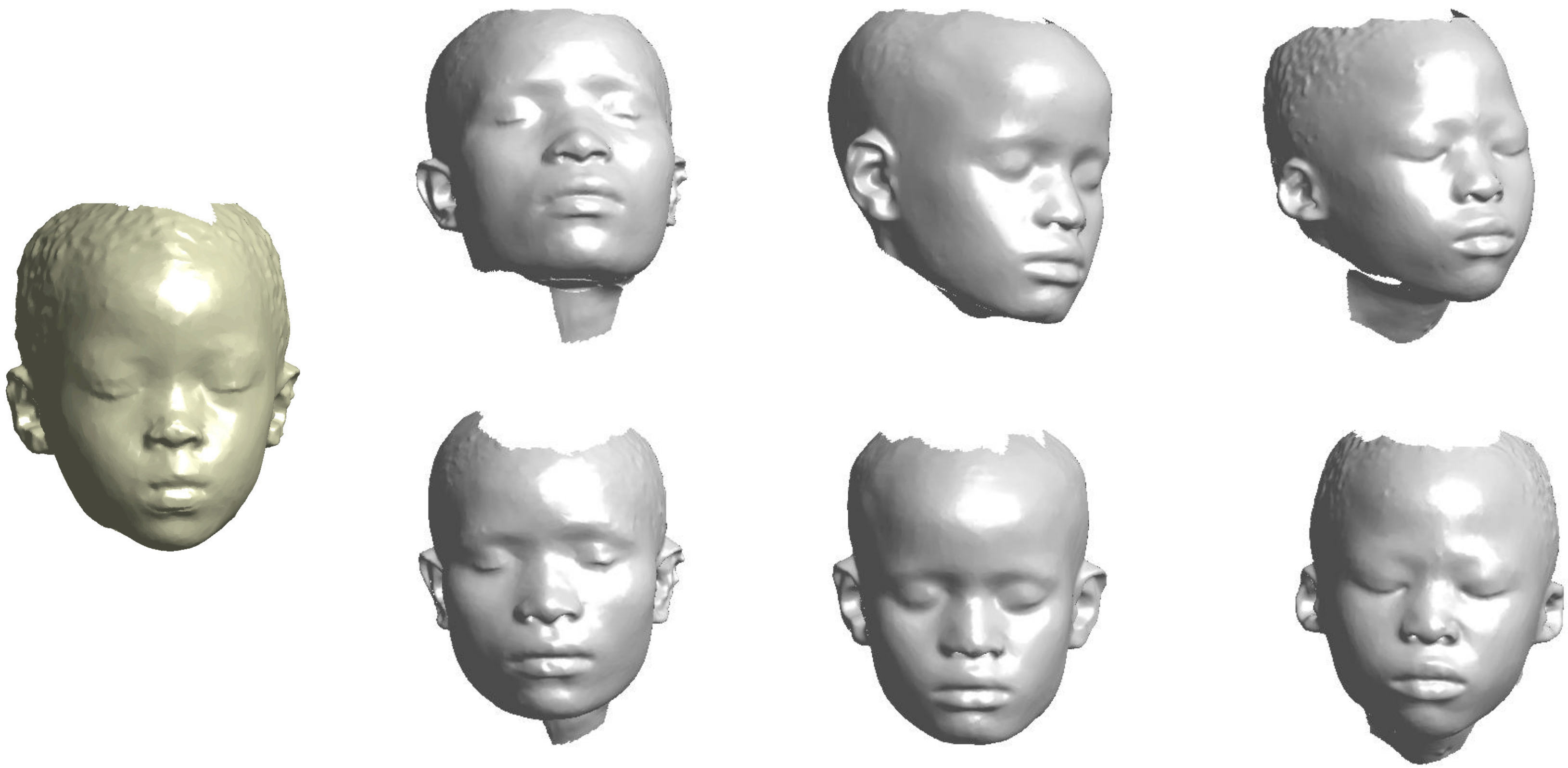


Red and Green



3 x 3 = 9

Before and After



Automated Landmarking

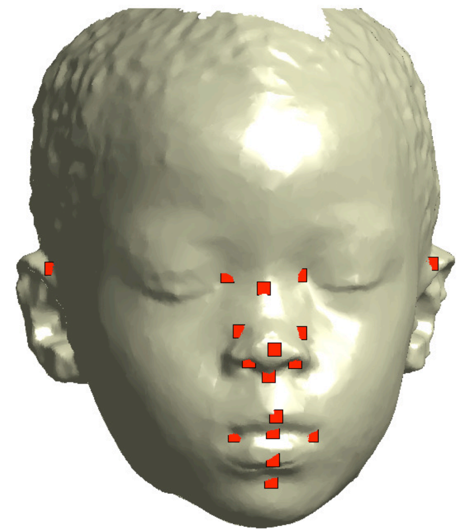
Face mesh

Mean curvature map

High mean curvature

Geometric Control Points

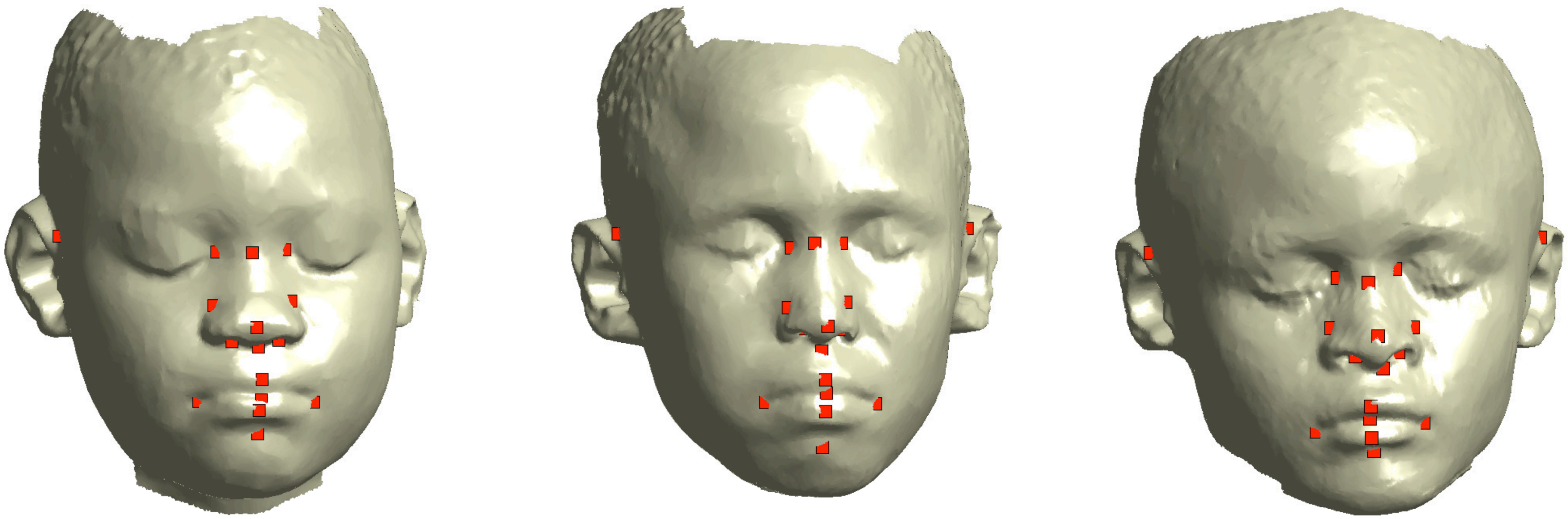
processing



High curvature points

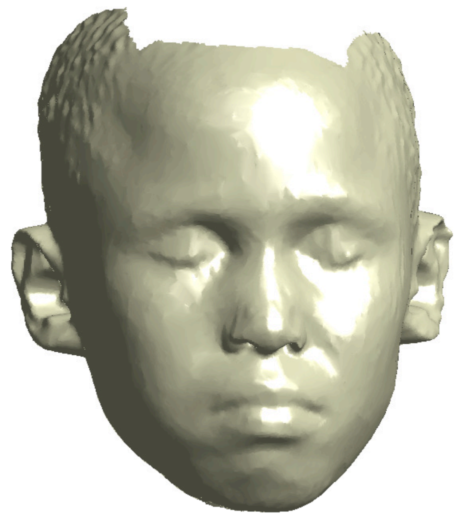
17 control points

Consistency Across Subjects



Morphing Faces

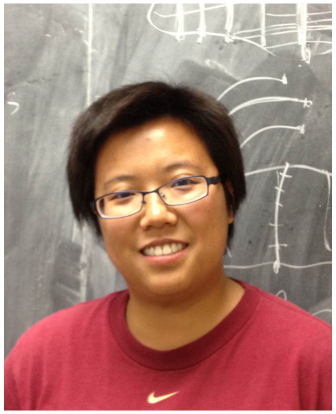
Subject 1



Subject 2

Morphing 1 to 2

Qiuping Xu



Morphing Guided by Control Points

M = compact Riemannian manifold
$p_1, \ldots, p_n$: control points
$a_1, \ldots, a_n$: real numbers

Construct $f : M \rightarrow R$

that minimizes

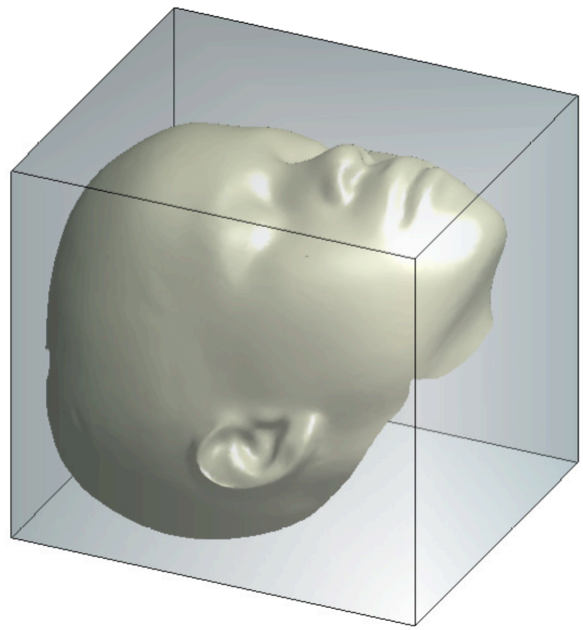
$$E(f) = \frac{1}{n}\sum_i (f(p_i) - a_i)^2 + \lambda \int_M (\Delta f(p))^2 dV(p)$$

Treated in the setting of reproducing kernel Hilbert spaces

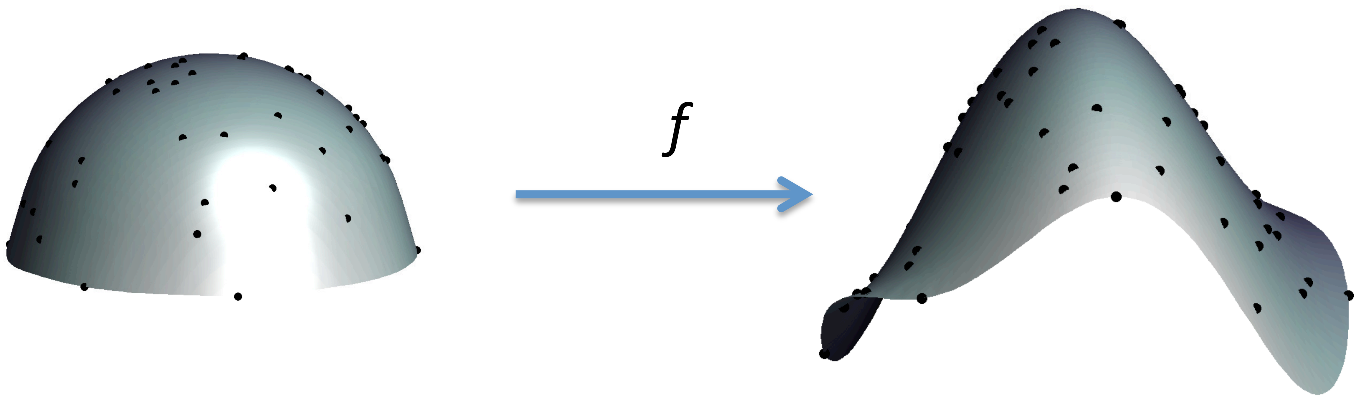
Remarks

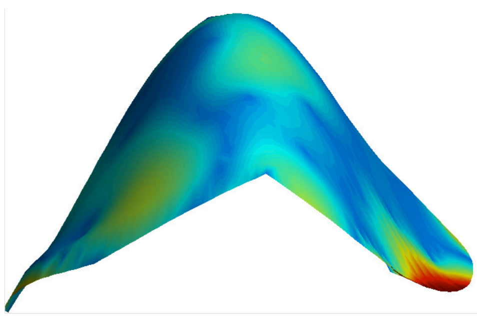
- M = Euclidean space, thin-plate spline model (Duchon, Meinguet, Wahba, Bookstein, …)
- Closed Riemannian manifolds (P. Kim)
- Prior work on manifold domains mostly theoretical
- Fast empirical approximations

Bounding Box

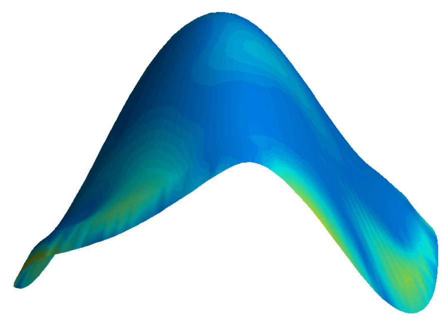


Box Spline





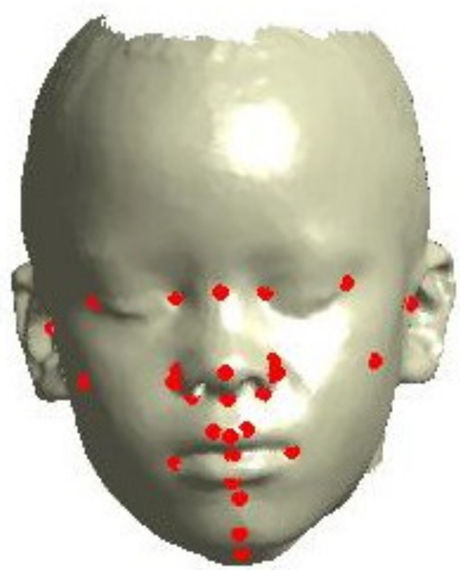
TPS



Box spline

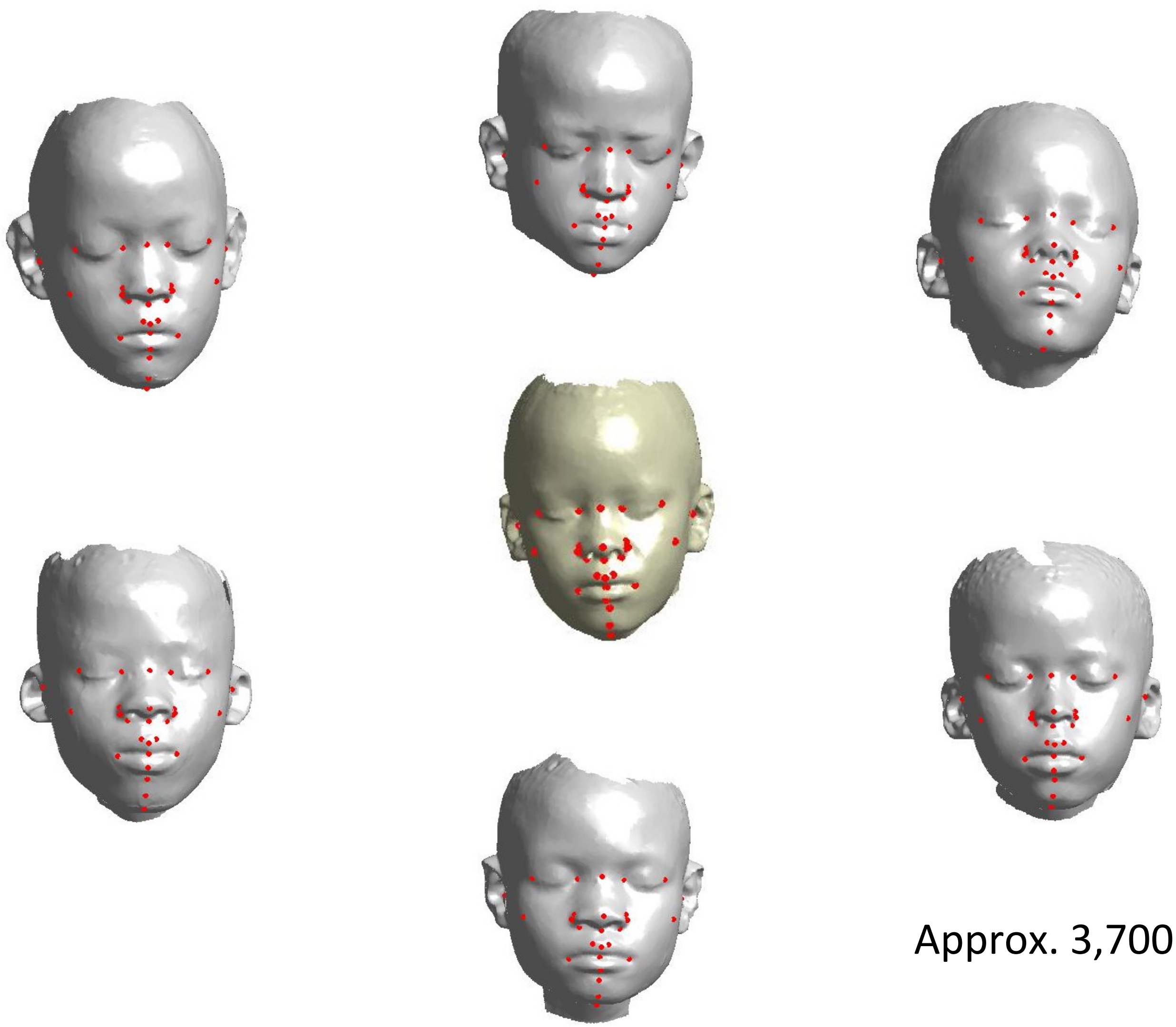
Back to Automated Landmarking

- Training set: a collection of manually landmarked shapes
- Use the morphing model to construct a landmarked consensus (mean) shape



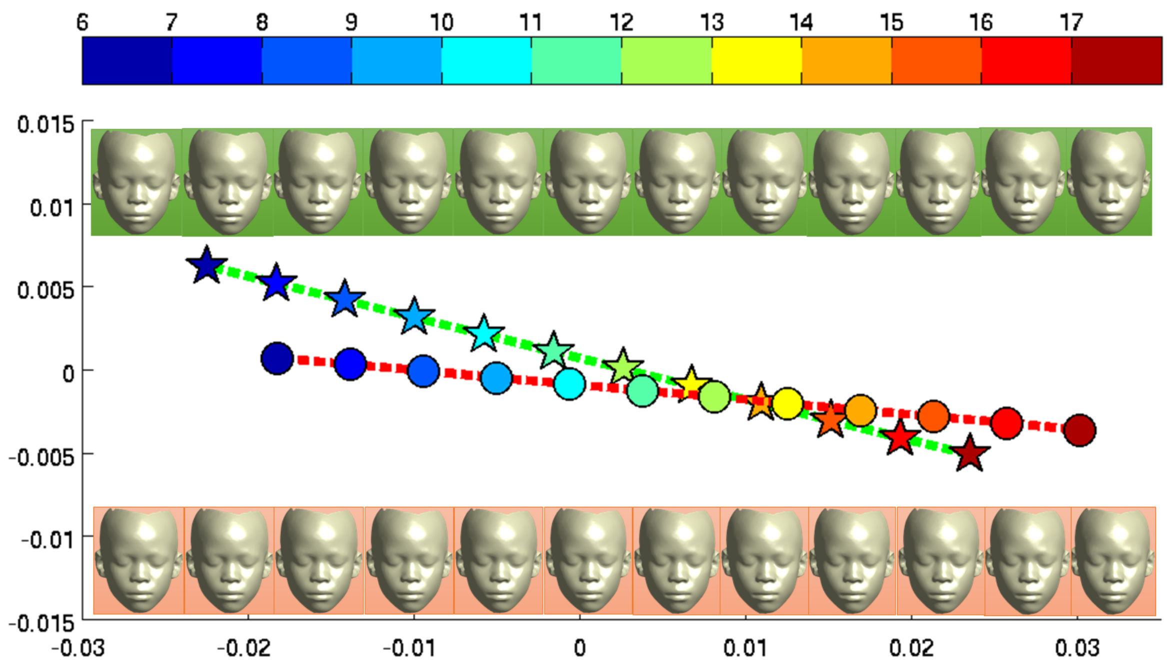
Facial atlas with 29 landmarks

More on Landmarking

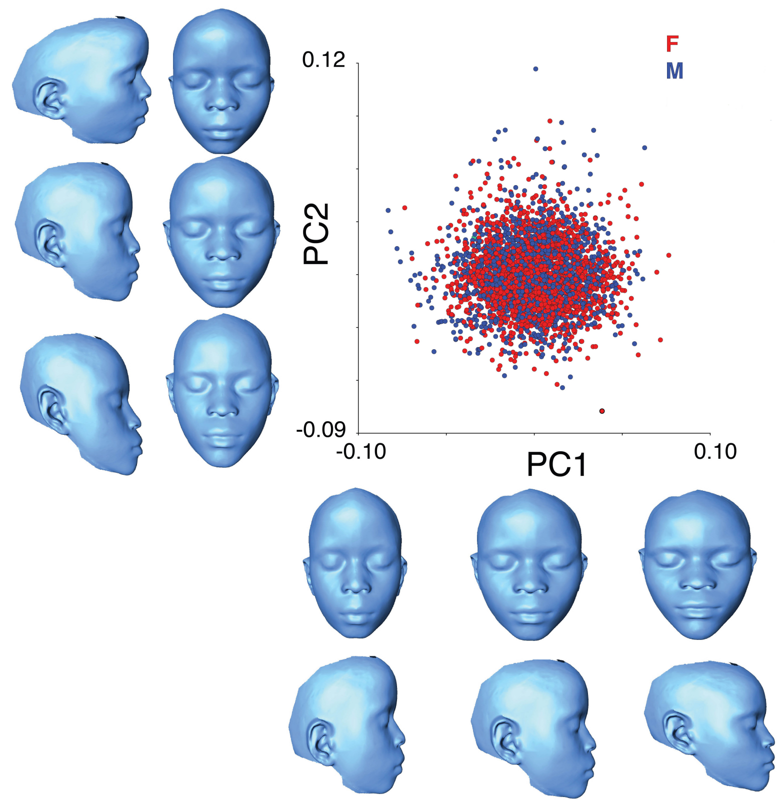


Approx. 3,700 faces

Morphometric Analysis



Morphometric Analysis



Principal modes of variation

Back to SNPs

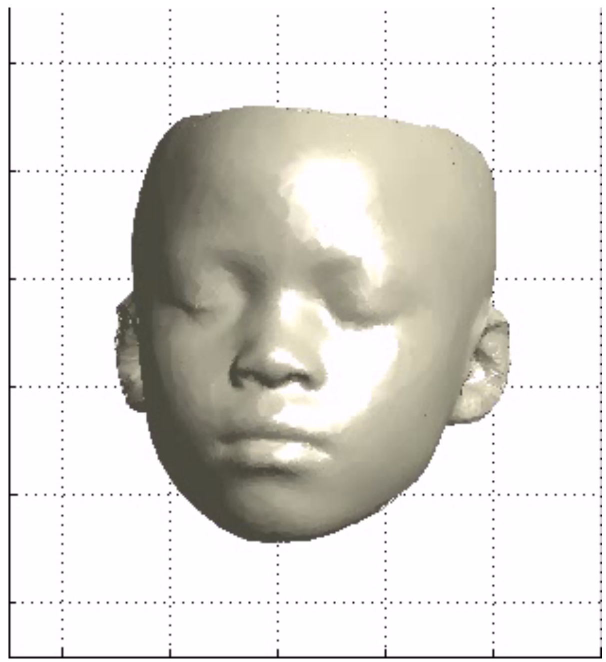
What SNPs send strong signals of association with facial shape?

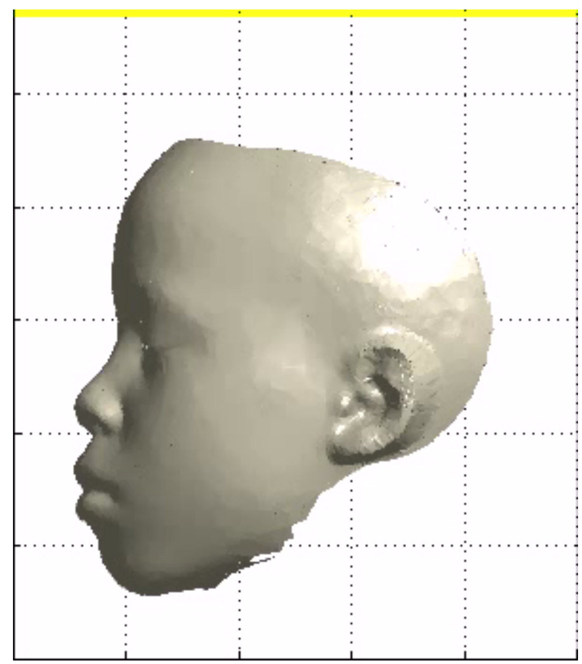
Gene	Trait
xxxx	phyltrum width
……..	upper facial height
……..	upper facial depth
……..	nasal ala length
……..	nasal width

In situ hybridization in the face of developing mice at E9.5 and E10.5 indicate expression of some top hits

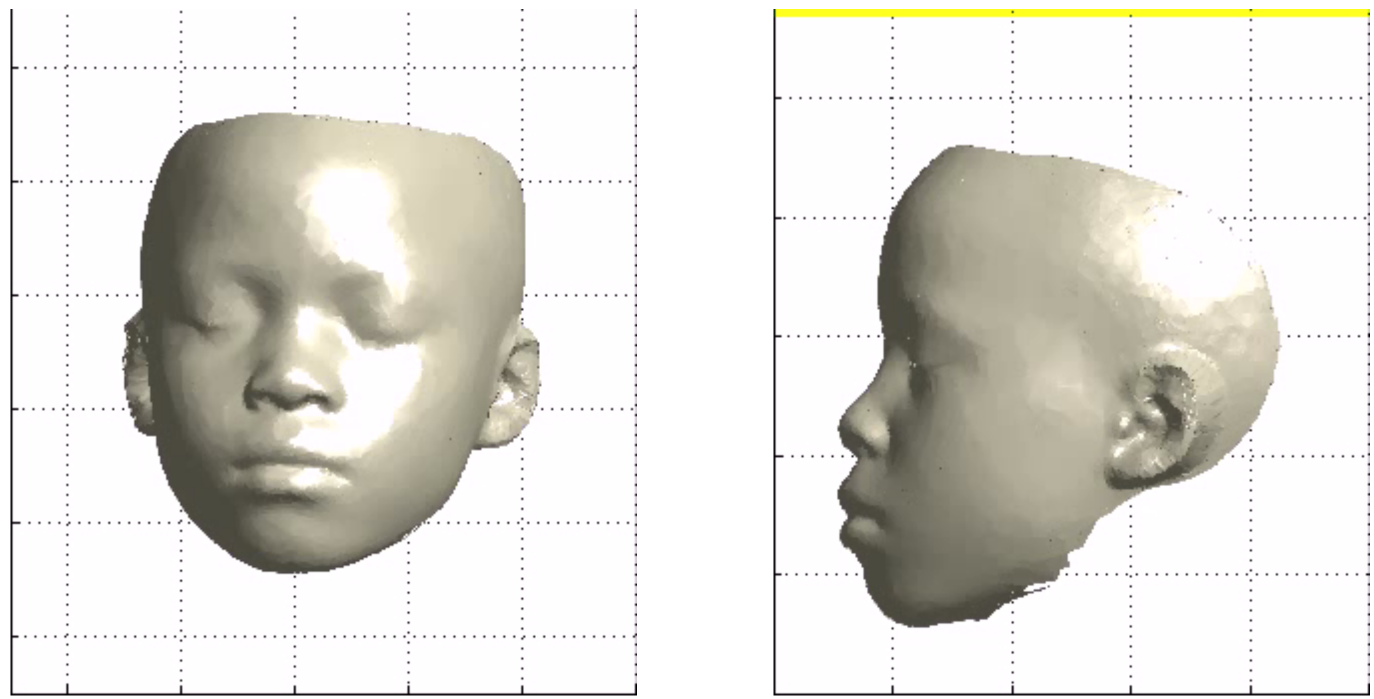
Dense Modeling

Main Mode of Variation

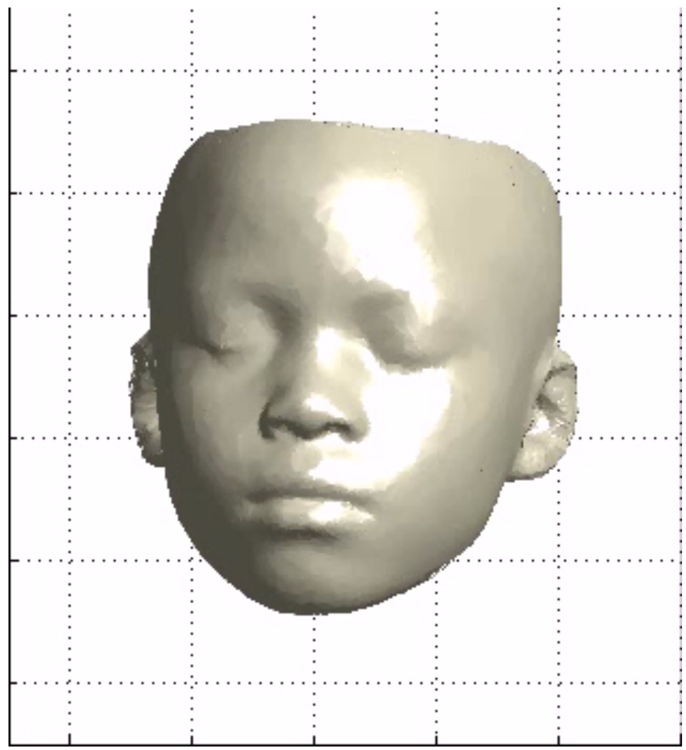




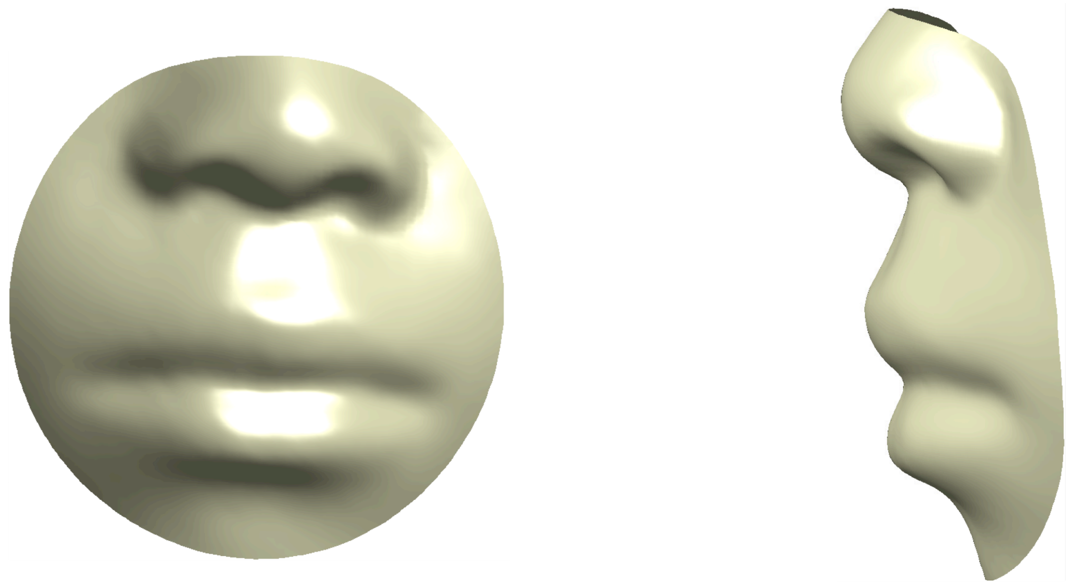
Second Mode



Third Mode



Modular Analysis



Two views of the midface

Summary

- GWAS identified several SNPs (genes) strongly associated with normal facial shape variation
- Topological and geometric methods used to model shape variation
- Replication study and Caucasian GWAS ongoing
- Future analyses: dense representation of full face, face modules, and interactions amongst modules
- FaceBase2: study of a large number of dysmorphic syndromes, both common and rare
- Examples: Down, fetal alcohol, Noonan, Williams, …

People

Collaborators	**Postdocs & Students**
R. Spritz, Medicine, Colorado-Denver	Mao Li, FSU
B. Hallgrimsson, Medicine, Calgary	Qiuping Xu, FSU
S. Santorico, Statistics, Colorado-Denver	Joanne Cole, Colorado
M. Manyama, Bugando, Tanzania	Jacinda Larson, Calgary
O. Klein, Medicine, UC San Francisco	Denise Liberton, Calgary

- NIH, 3U01DE020054, *Genetic Determinants of Orofacial Shape and Relationship to Cleft Lip/Palate*, 09/21/09 - 04/30/15
- NSF, DBI-1052942, *Collaborative Research: Biological Shape Spaces, Transforming Shape Into Knowledge*, 09/15/10 - 08/31/14

The End

Thank You!