# Seminar:
# Refined Dose-Toxicity Analysis: Computational Methods and Applications

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# Project Summary

Design, implement, and evaluate an algorithm that creates spatially dependent dose features at the inter-organ level to identify specific areas of the head and neck that are more or less critical and sensitive to radiation damage.

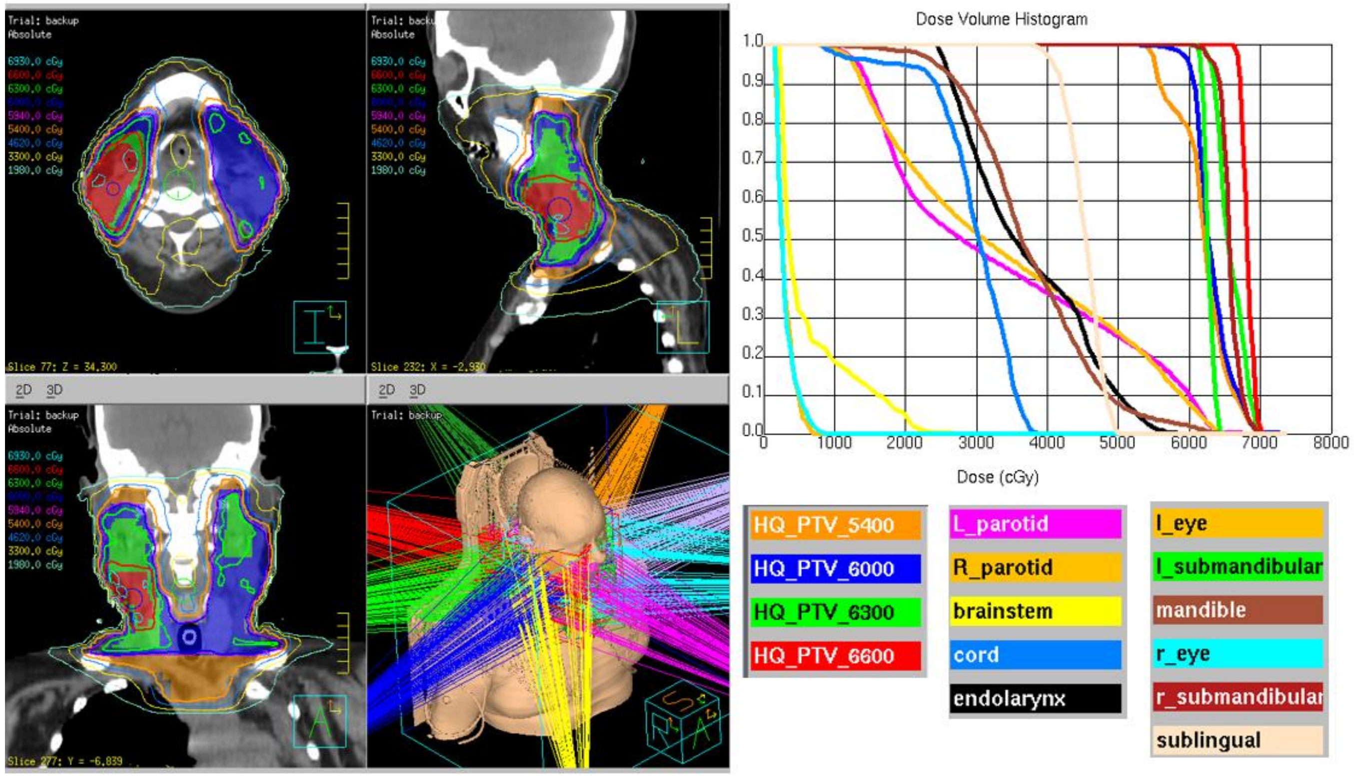


*Fig. 1*: View of sample radiotherapy treatment plan and the associated dose volume histograms for affected anatomical structures

# Paper Selection

**Paper:** Deformable Registration of Organic Shapes via Surface Intrinsic Integrals: Application to Outer Ear Surfaces [1]

**Authors:** Sajjad Baloch, Alexander Zouhar, and Tong Fang

**Why?** Presents challenges involved in deformable registration of organic shapes

Proposes a more robust method for deformable registration (may be useful in solving problems we could encounter)

**Our project:**

# Paper Selection

**Paper:** Sparing the region of the salivary gland containing stem cells preserves saliva production after radiotherapy for head and neck cancer [2]

**Authors:** Peter van Luijk, et. al.

**Why?** Presents an example of a clinically relevant question that could be answered using our framework

**Our project:**

# **Problem:** Registration of Complex Organic Shapes is Hard

**Anatomical correspondence ≠ geometric correspondence**

Limitations of currently used methods:

- Clamp histograms: Depend on surface normal- bad for flat surfaces
- Intrinsic shape contexts: Don't differentiate concave, convex, saddle regions, not good
- 3D shape contexts: nothing about topology of surface

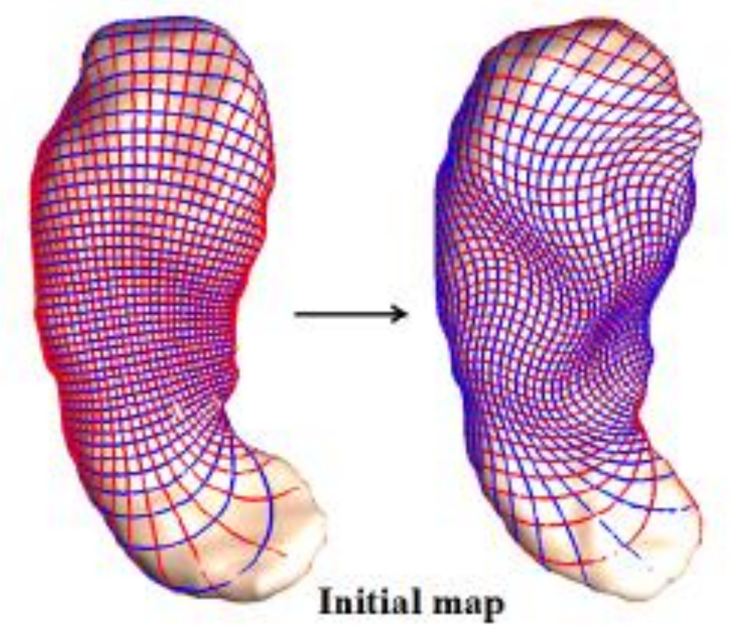


*Fig. 2*: Two different hippocampal surfaces and a surface diffeomorphism between them [3]

# **Solution:** Combine Coupled Global and Local Information with Anatomical Information

| Maxima and Minima of Mean Curvature | Minima of Minimum Principal Curvature | Maxima of Maximum Principal Curvature | Minima of Gauss Curvature | |
|---|---|---|---|---|
| Geodesic Distance Integrals (GDI) | | | | Prior Anatomical Information |
| Deformable Registration Method | | | | |

**Goal:** Given a surface $\mathrm{M}_S$ representing source anatomy and another surface $\mathrm{M}_T$ representing the target anatomy, find a diffeomorphic transformation h such that $\mathrm{M}_S \rightarrow \mathrm{h}(\mathrm{M}_T)$ that warps $\mathrm{M}_S$ to $\mathrm{M}_T$ while by minimizing the bending energy, $\mathrm{E}(\mathrm{h}) = \omega_e \mathrm{E}_e(\mathrm{h}) + \omega_i \mathrm{E}_i(\mathrm{h})$ where $\mathrm{E}_e(\mathrm{h})$ represents the external energy and $\mathrm{E}_i(\mathrm{h})$ represents the internal energy.

# Minimization of External Energy

$$E_e(h) := \gamma_G E_e^G(h) + \gamma_F E_e^F(h)$$

$\gamma_G, \gamma_F$ are weights

$E_e^G, E_e^F$ are energies of geometric and anatomical components

$E_e^G$ has 2 components: global shape $E_e^S(h)$ and local/regional geometry $E_e^F(h)$

# Minimization of External Energy: $E_e^G$

**Geodesic Distance Integrals:** Define global shape/topology

$$\mathcal{S}(u) := \int_{x \in \mathcal{M}} g(u, x) d\mathcal{M}.$$

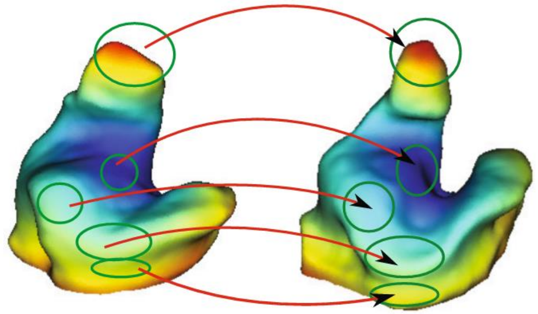

*Fig 4:* Normalized GDI maps; mapped circles indicate similar regions. [1]

**Local Information:** Feature vector at a point $\mathrm{u} \in M$: $\boldsymbol{\alpha}_l(u)$: $(\kappa_\mu(u), \kappa_G(u), \kappa_{pc1}(u), \kappa_{pc2}(u))$

- $\kappa_\mu$ = extrema of mean curvature
- $\kappa_{pc1}$ = minima of minimum principal curvature
- $\kappa_{pc2}$ = maxima of maximum principal curvature
- $\kappa_G$ = minima of Gauss curvature

Computed at various scales, $s_k$, to resolve ambiguity:

$$A(u) = [\boldsymbol{\alpha}_r(u; s_1), \ldots, \boldsymbol{\alpha}_r(u; s_k), S(u)]$$

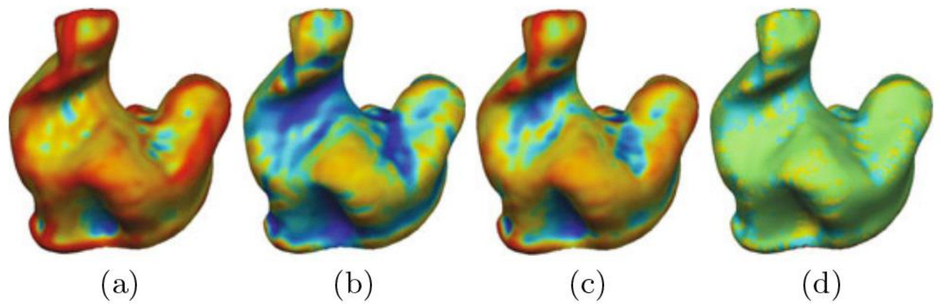


*Fig 5:* Normalized curvature maps (low (blue) to high (red)): (a) Mean curvature; (b) Minimum principal curvature; (c) Maximum principal curvature; (d) Gauss curvature. Note that extrema correspond with landmarks. [1]

# Landmark Definition

**Geometric Landmark:** point exhibiting local extrema

1. Select landmarks via thresholding: pick a set of points, $D \in M$, with most "curvedness" compared to neighboring points, gradually relax thresholds to possibly select less "interesting" points

2. Find correspondences between "geometrically interesting" points (landmarks) on source and target surface

**Anatomical Landmark:** From canonical ear surface (CES) description of ear

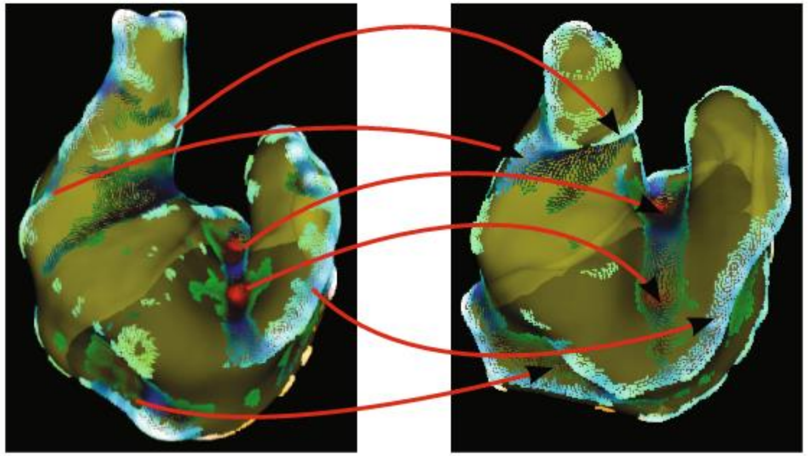

*Fig 6:* Geometric landmarks on ear surfaces. Arrows indicate correspondences between source and target. [1]

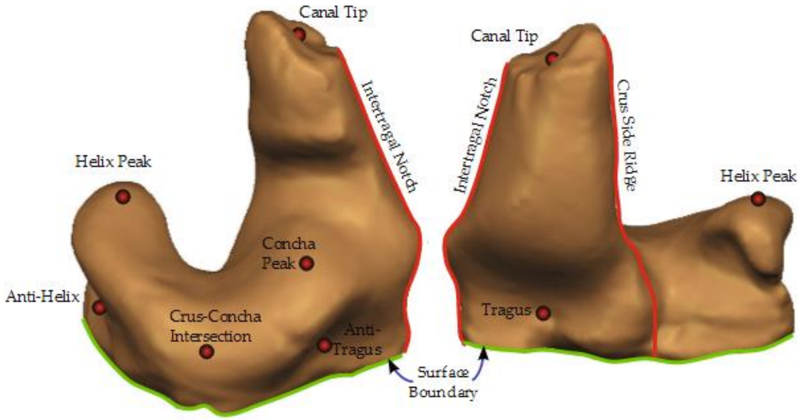


*Fig 7:* Anatomical landmarks on the human ear. [1]

# Minimization of Bending Energy

Carried out in blocks with components $\sum\|h(l_S^i) - l_T^i\|$, initial guess h is output of previous block, *l* is landmark of interest:

1. Landmarks on source surface are identified
2. Each landmark $u_s \in D$ on the source surface is mapped to landmark $u_t \in M$ on the target surface.
   - $D_s$ deformed under $h^k$ to yield new point set $h^k(D_s)$, each point $h^k(u_s)$ mapped to points $u_t \in M$ through closest point projection
   - Neighborhood defined around $u_t$, find point in neighborhood which minimizes $v^* = argmin(\|A_s(u_s) - A_T(v)\|$
3. Corresponding points define displacements: $d^k = M_T(v^*) - M_S(u)$
4. Find differential displacement with small δ: $\delta d^k$
5. Deform surface points by corresponding differential displacement: $h^{k+1}(u) = h^k + \delta d^k(u)$

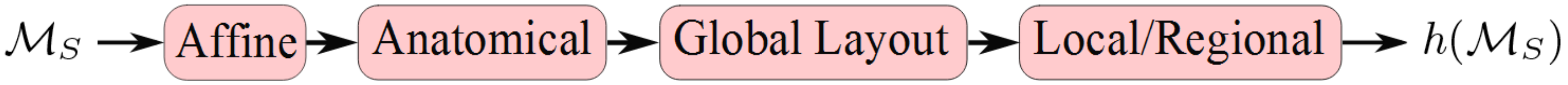


*Fig. 3*: Optimization Strategy: Rigid registration, then anatomical, global, and local/regional geometric deformations [1]

# Application to Outer Ear Surfaces

**Set-up:** Ear surfaces from scans of 17 patients, 1 randomly selected as template

**Experiment:** Register all scans to template with

1. Rigid registration from [4]
2. Proposed registration method

**Qualitative Analysis:** Comparison via error maps

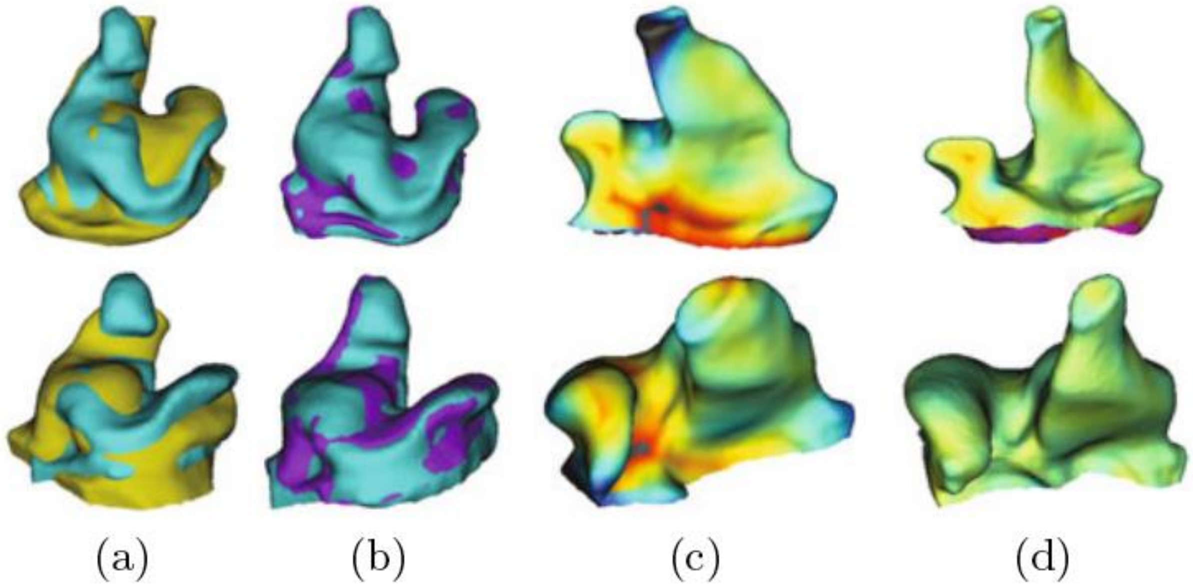

*Fig 8:* Deformable registration: (a) subject registered with rigid method (gold, template (cyan); (b) registered by proposed method (purple); (c) error map before registration; (d) error map after registration

# Application to Outer Ear Surfaces

**Quantitative Analysis (Anatomical Correspondence):**

expert manual labeling of ear anatomy on template and source --> registration --> quantitative analysis of label overlap:

$$\frac{(Area_{label} \cap Area_{GT})}{(Area_{label} \cup Area_{GT})}$$

where $Area_{GT}$ is the area of the segmented source surface after registration and $Area_{label}$ is the area of the labeled region on the target

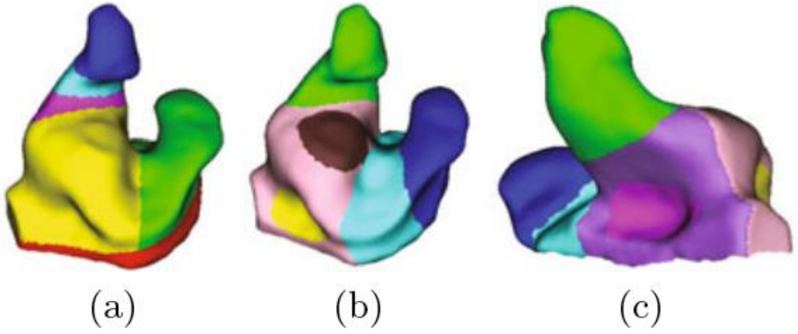


*Fig 9:* Expert manual segmentation of the template [1]

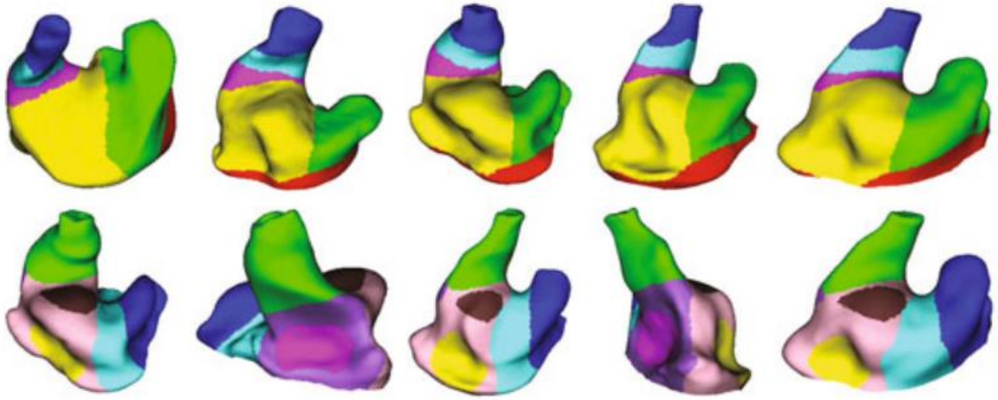

*Fig 10:* Label transfer from the template based on estimated diffeomorphism: (top row) coarse segmentation; (bottom row) detailed segmentation

# Evaluation of Novel Surface Descriptor

Goal: Evaluate components of surface descriptor

1. Registration based only on anatomical information
2. Combined anatomy and GDIs
3. Combined anatomy and complete surface descriptor

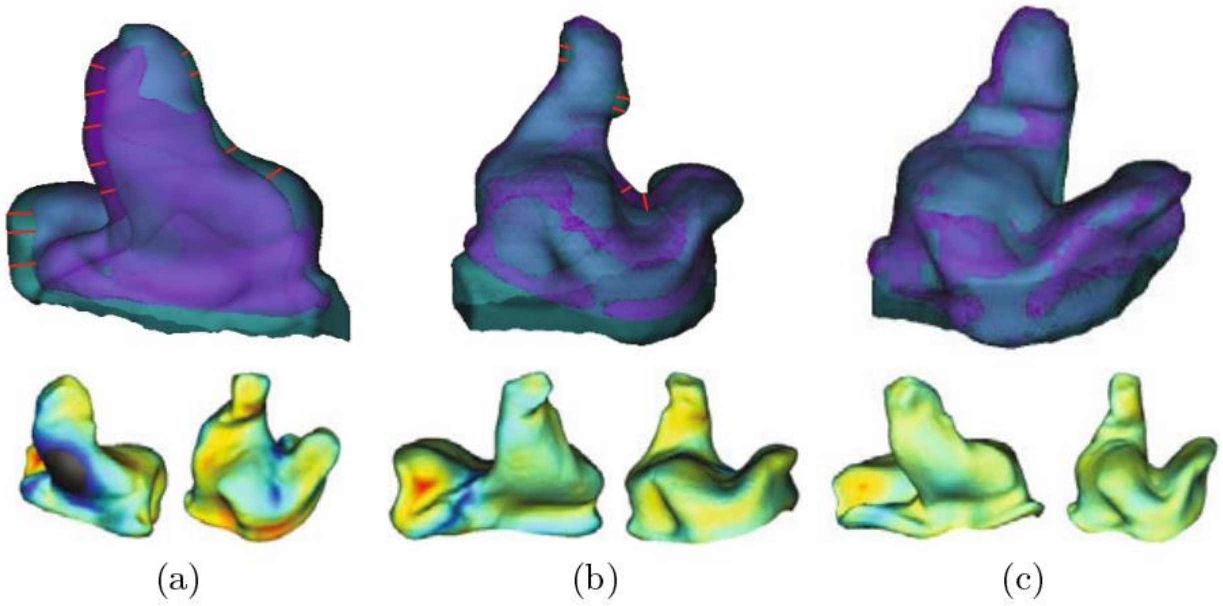


*Fig 11:* valuation of various features: (a) Anatomical features; (b) Anatomy + GDI; (c) Complete descriptor. (Top) Warped surfaces; Red lines indicate regions, where the registration does not perform well. (Bottom) Error map. Complete descriptor yields almost uniform error map [1]

# Next Steps

Development of digital atlas of ear anatomy using this registration method

# Assessment: Positives

- Method "appears" to solve several issues associated with deformable registration of organic surfaces
- Fairly detailed description of mathematical steps- would be easy to implement if had anatomical information
- *Also, method does not actually require anatomical information*
- Incorporation of multiple types of surface landmarks at several different scales qualitatively appears to lead to a better registration
- *Proposes a new feature vector that the authors claim is more distinguishing*
- Includes many figures with qualitative information (and a small amount of quantitative) about registration accuracy

# Assessment: Negatives

- Don’t state qualifications of “expert” who labeled anatomy
- Comparison of accuracy of this method/other methods is only presented qualitatively
- Comparison is only against a *rigid* registration method developed by the same authors
- Essentially no quantitative data included
- *No data/error metrics to show that this method improves on existing methods in any way*
- *No information about efficiency (qualitative or quantitative)*
- *No comparison of efficiency with previously developed methods*
- Method may be hard to generalize for less well-characterized anatomical structures since it relies on a list of anatomical landmarks (CES)
- No test on more/less complex or larger organ structures

# Applications

- More robust surface descriptor may be useful to improve surface-surface deformable registration of organic surfaces
- May be too inefficient for larger structures than the ear or for multiple structures at once (no data included)
- Would possibly need to consider anatomical landmark definitions
- **Most significant:** Gives us ideas of challenges and solutions to consider when deformably registering anatomical structures in the head and neck

# Paper 2 Overview

Luijk, P. V., et.al (2015). Sparing the region of the salivary gland containing stem cells preserves saliva production after radiotherapy for head and neck cancer.

**Background:**

- Decrease in saliva production = common with head/neck radiation (40%)
- Parotid (salivary) gland sparing radiation -> partial recovery over time
- *Spare parotid stem cells = allow regeneration?*

**Key Results:**

- Certain areas of the parotid (salivary) gland contain more stem cells
- Damage to rat parotid gland (decrease in saliva production) depends on dose given to this stem-cell containing area
- Radiation dose to corresponding region of human parotid gland is most predictive of change in saliva production

# Technical Approach

**Determine location of stem cells in rat/mouse/human with immunohistochemistry**

**Determine critical region of rat parotid gland**

1. Irradiate subsections of rat parotid gland
2. Measure change in saliva production over time
3. Determine which (if any) regions are most critical to avoid

**Find corresponding region in human parotid gland**

Analyze 74 patients- determine sub volume of parotid most predictive of decreased saliva production 1 year after radiation via 10-fold cross validation analysis

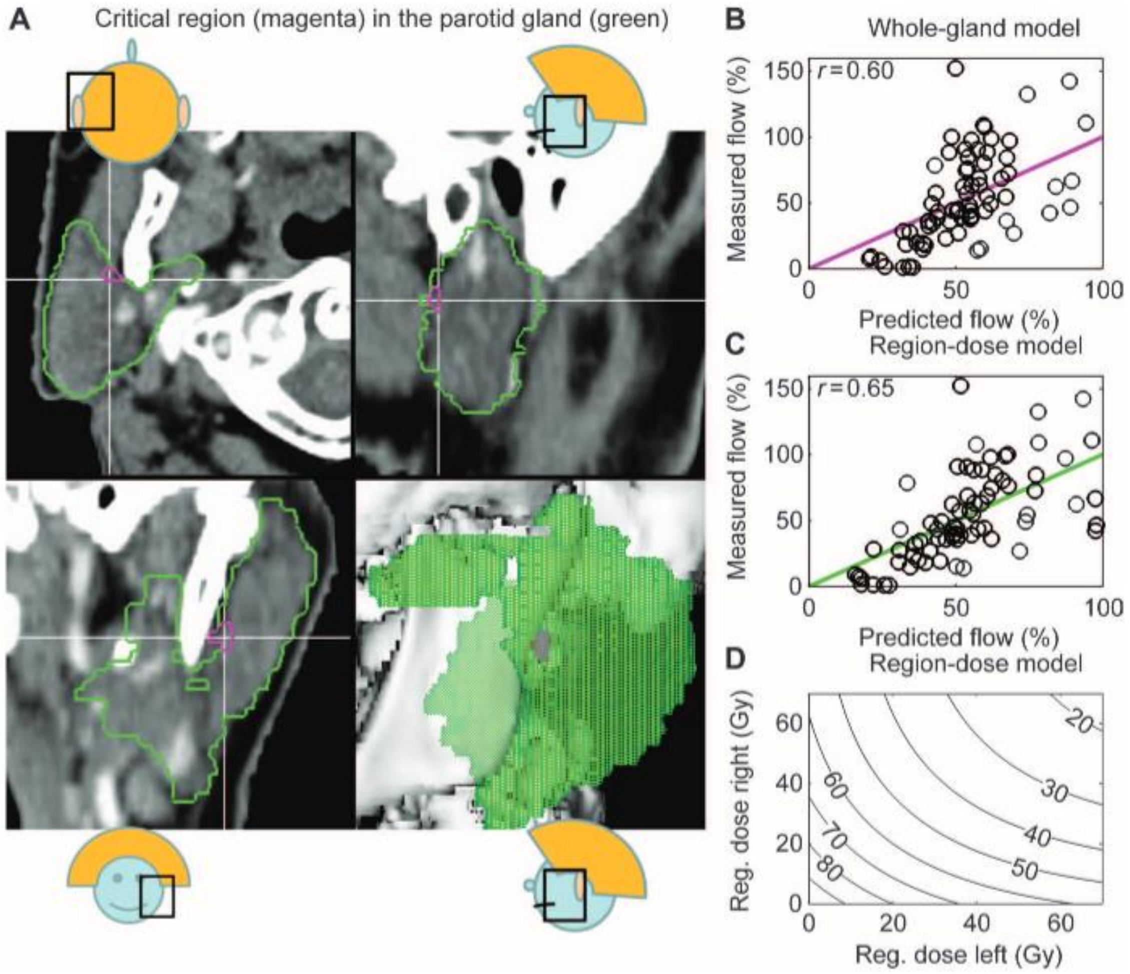


*Fig. 12.* The radiation dose to human parotid gland substructures predicted loss of saliva production. Saliva production 1 year after radiotherapy was related to the radiation dose administered to specific subvolumes of the gland. (A) Critical subvolume (magenta) within the parotid gland (green). (B and C) Dose to this subvolume most strongly correlated with post-treatment saliva production. (D) Prediction of total saliva production at 1 year after radiotherapy based on the dose to the critical subvolumes of both parotid glands. [2]

# Assessment

**Positives**

- Rat studies show causation
- Human studies imply some predictive power
- Detailed methods/statistical analysis of results

**Negatives**

- No causation in humans between dose to region -> decreased saliva production (but would be unethical)
- Also shows correlation with whole-parotid dose in humans
- Does not investigate other regions of parotid in humans
- Human experiments do not control for age, other possible confounders
- r=.65 for stem cell region dose predictive power of saliva flow change, .60 for whole parotid- is this a significant difference?

# Next Steps/Conclusions

**This group:**

- Find stem-cell containing regions in other organs
- Determine adverse-reaction correlation with dose to these regions
- Radiotherapy planning to avoid stem-cell containing parotid region- improved outcome?

**Our group:**

- Manually segment parotid region and analyze predictive power of dose to this region for xerostomia
- Compare to whole-parotid dose and dose to only non-stem cell containing regions

**Our project:**

- Automatic identification of locations in the head and neck that are more/less critical to avoid to prevent adverse reactions (Could these be stem cell containing regions?)

# References


1. Baloch, S., Zouhar, A., & Fang, T. (2011). Deformable Registration of Organic Shapes via Surface Intrinsic Integrals: Application to Outer Ear Surfaces. *Medical Computer Vision. Recognition Techniques and Applications in Medical Imaging Lecture Notes in Computer Science,* 11-20. doi:10.1007/978-3-642-18421-5_2

2. Luijk, P. V., Pringle, S., Deasy, J. O., Moiseenko, V. V., Faber, H., Hovan, A., . . . Coppes, R. P. (2015). Sparing the region of the salivary gland containing stem cells preserves saliva production after radiotherapy for head and neck cancer. *Science Translational Medicine, 7*(305). doi:10.1126/scitranslmed.aac4441

3. Lui, L. M., Wong, T. W., Thompson, P., Chan, T., Gu, X., & Yau, S. (2010). Compression of surface registrations using Beltrami coefficients. *2010 IEEE Computer Society Conference on Computer Vision and Pattern Recognition*. doi:10.1109/cvpr.2010.5540017

4. Zouhar, A., Fang, T., Unal, G., Slabaugh, G., Xie, H., & Mcbagonluri, F. (2006). Anatomically-Aware, Automatic, and Fast Registration of 3D Ear Impression Models. *Third International Symposium on 3D Data Processing, Visualization, and Transmission (3DPVT'06)*. doi:10.1109/3dpvt.2006.29

# Questions?