

Validating the use of non-rigid registration methods for tracking tumor growth

by benchmarking methods on synthetic growth cases
with known ground truth displacements



UiO : **Department of Physics**
University of Oslo

Paper #2 in-progress

A Parametric Evaluation of State-of-the-art Image Registration Methods for Assessing Glioblastoma Growth using Synthetic Growth Models.

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Phone: +4790857292

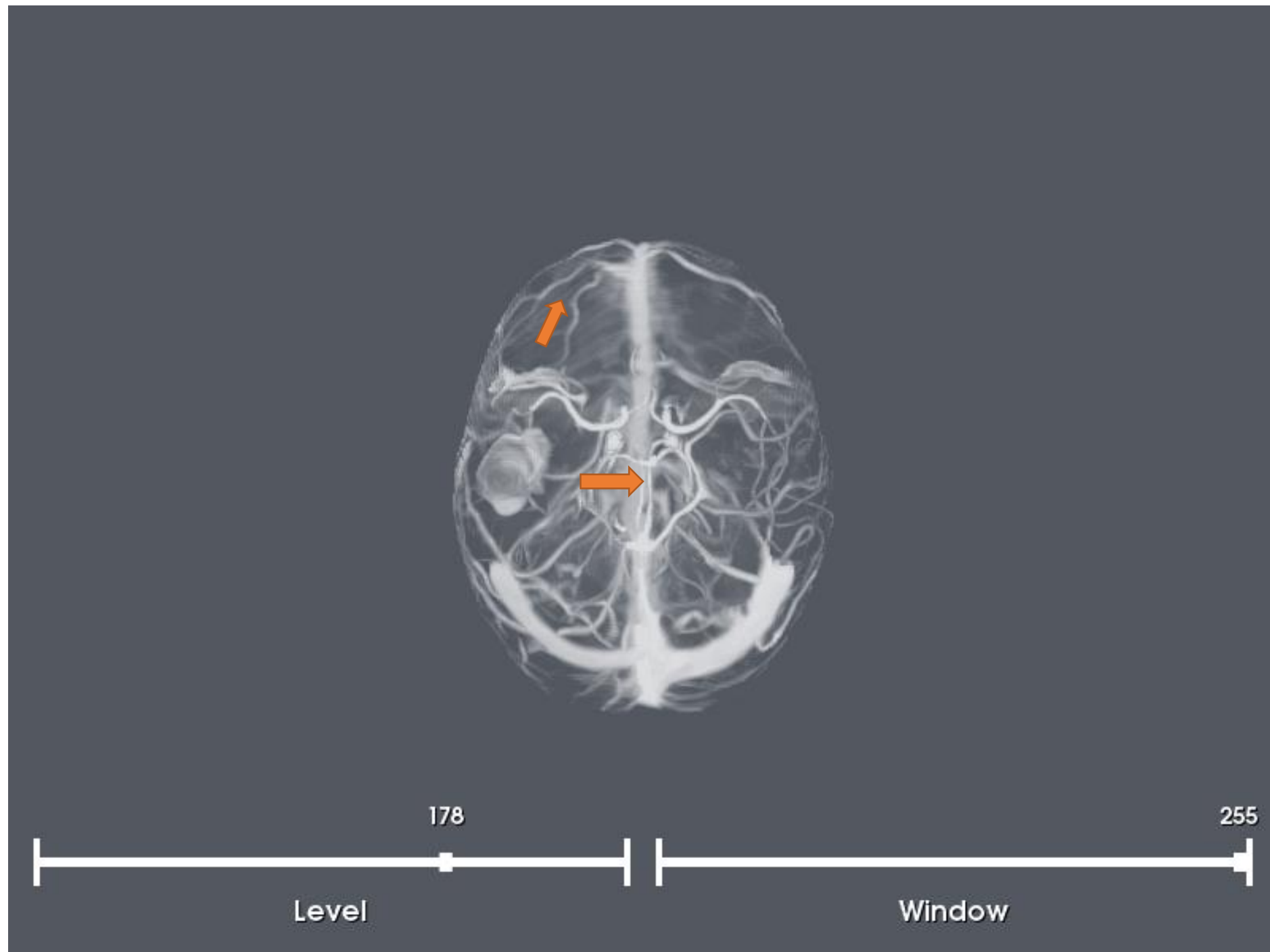
Real growth
case

T1-weighted
post-contrast
~3 years
glioblastoma

Maximum
Intensity
Projection
(MIP)

(SAILOR)

animation



Displacement maps in glioblastoma

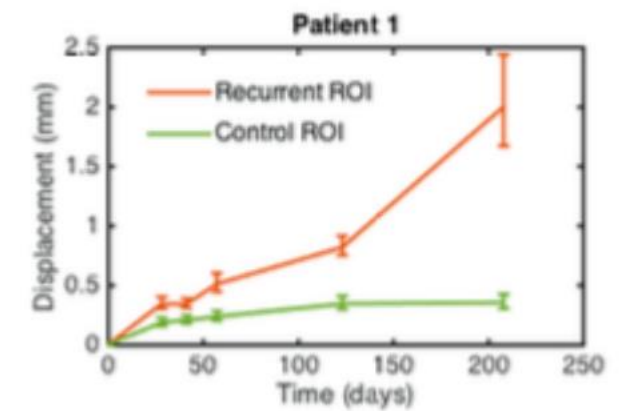
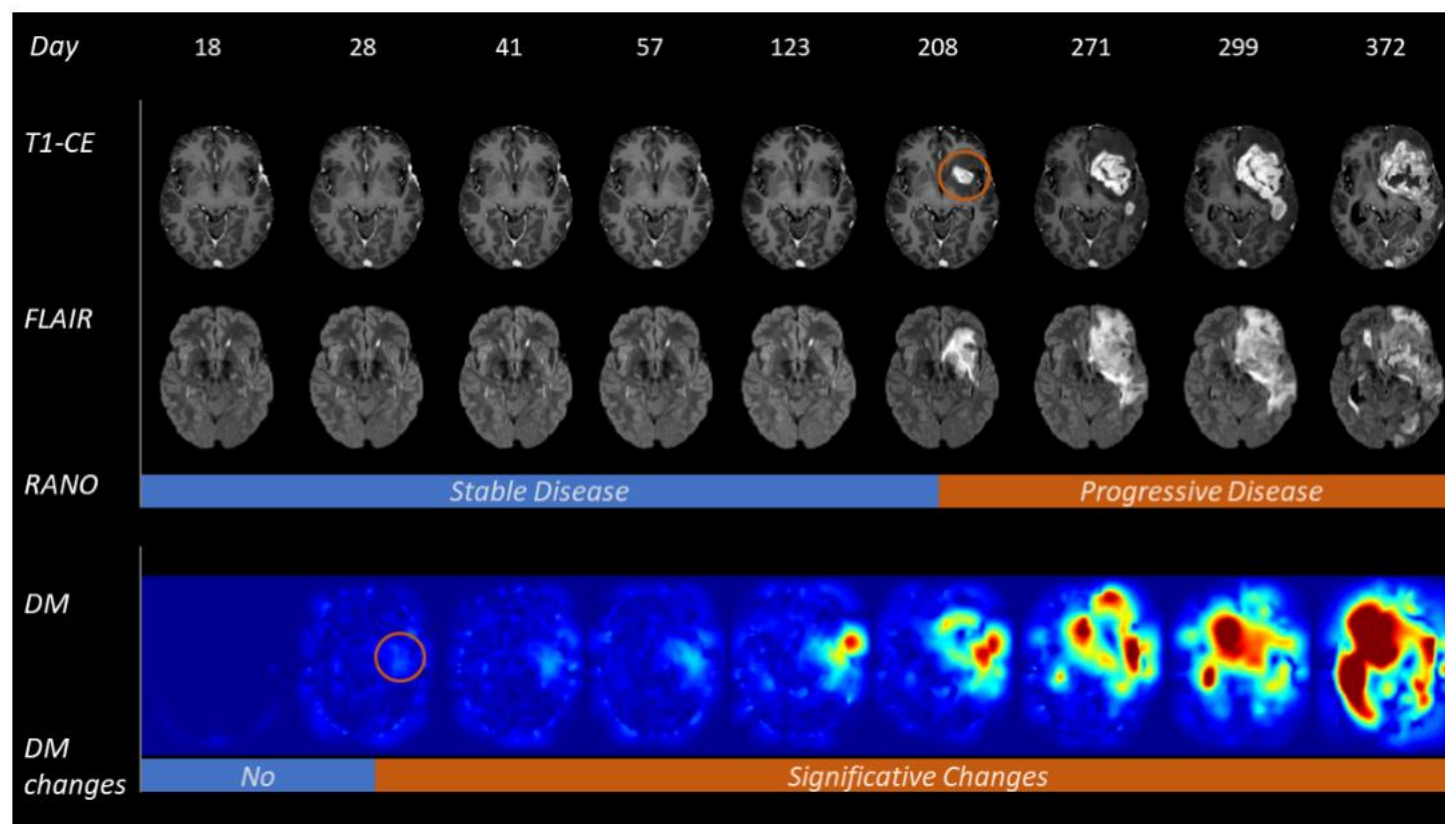


Fig. 2. Longitudinal evolution of Patient 1 from day 18 after starting radiochemotherapy treatment to day 372. According to RANO criteria tumor progression started on day 208, however displacement maps (DM) show significant deformations already at day 28.

Elies Fuster-Garcia 2019/2020

Example: From DICOM to synthetic growth models

- Post-contrast T1-weighted MRI showing tumor
- Tumor mask
- Brain mask

Software used:

dcm2nix

FSL

ITK-SNAP

Aliza

Convert3D

ANTsX

cancer-sim (<https://github.com/ivartz/cancer-sim>) using:

python 3 with libraries:

numpy

nibabel

scipy

perlin_numpy (<https://github.com/pvigier/perlin-numpy>)

Preprocessing

Convert DICOM to NIFTI (first time point DICOM MRI in source/01 folder). dcm2niix v1.0.20171215. The model assumes isotropic voxels, like 1x1x1 *mm*.

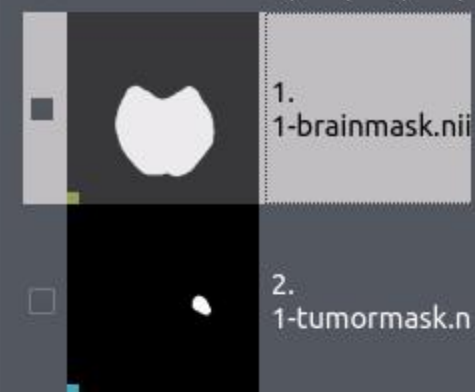
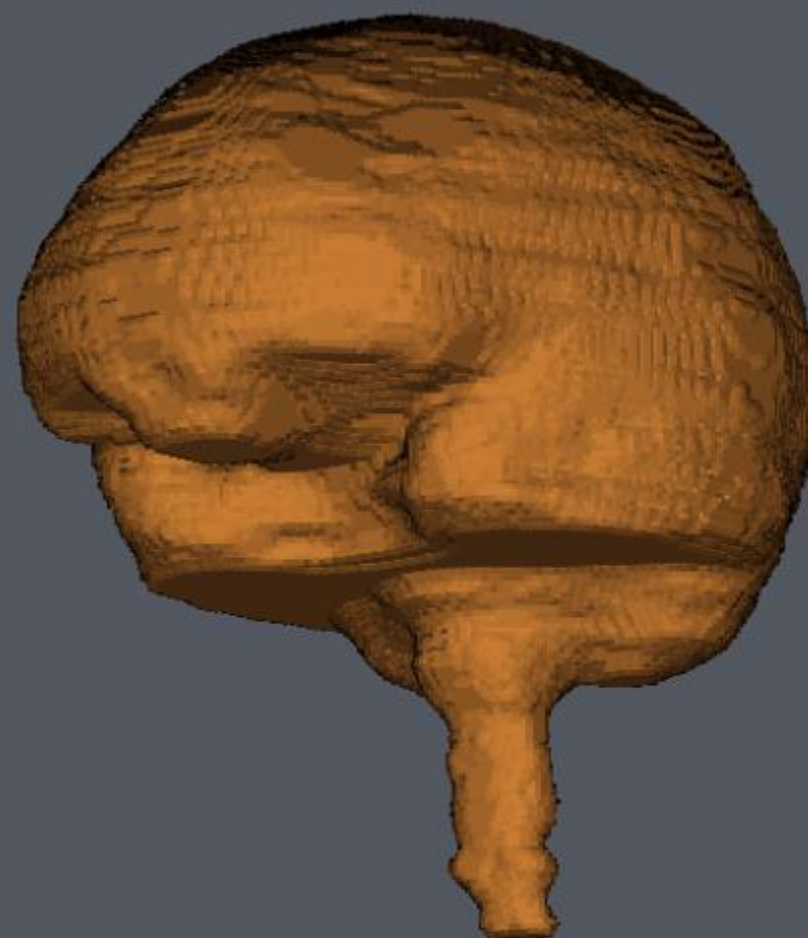
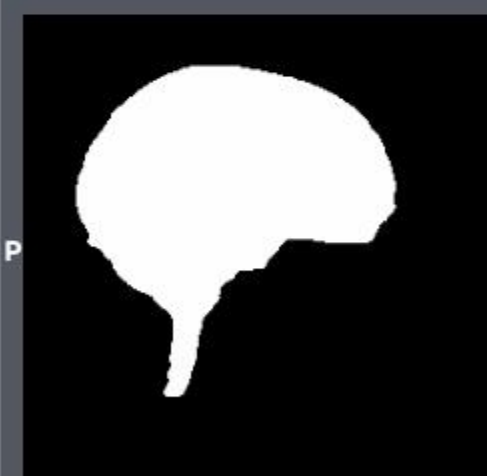
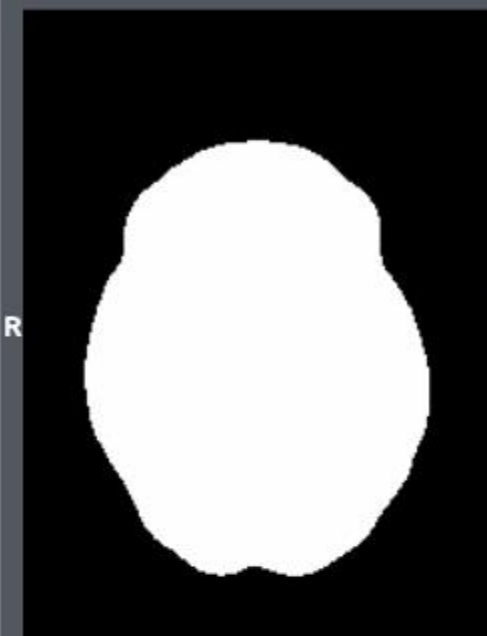
```
$ dcm2niix -z y -b n -o derivatives -f 1-T1c source/01
```

If not isotropic, can be resampled to isotropic units using FSL.

```
$ flirt -in derivatives/1-T1c.nii.gz -ref derivatives/1-T1c.nii.gz -  
  applyisoxfm 1.0 -nosearch -out derivatives/1-T1c-  
  1x1x1.nii.gz
```

Create tumor and brain mask for the isotropic NIFTI MRI.

Here the masks were manually created using ITK-SNAP, then median smoothed (over 2x2x2 px) using Aliza.



1-brainmask.nii.gz

190 x 256 x 256
unsigned short
[0, 1]

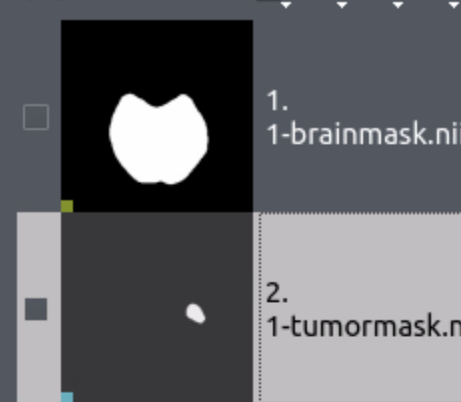
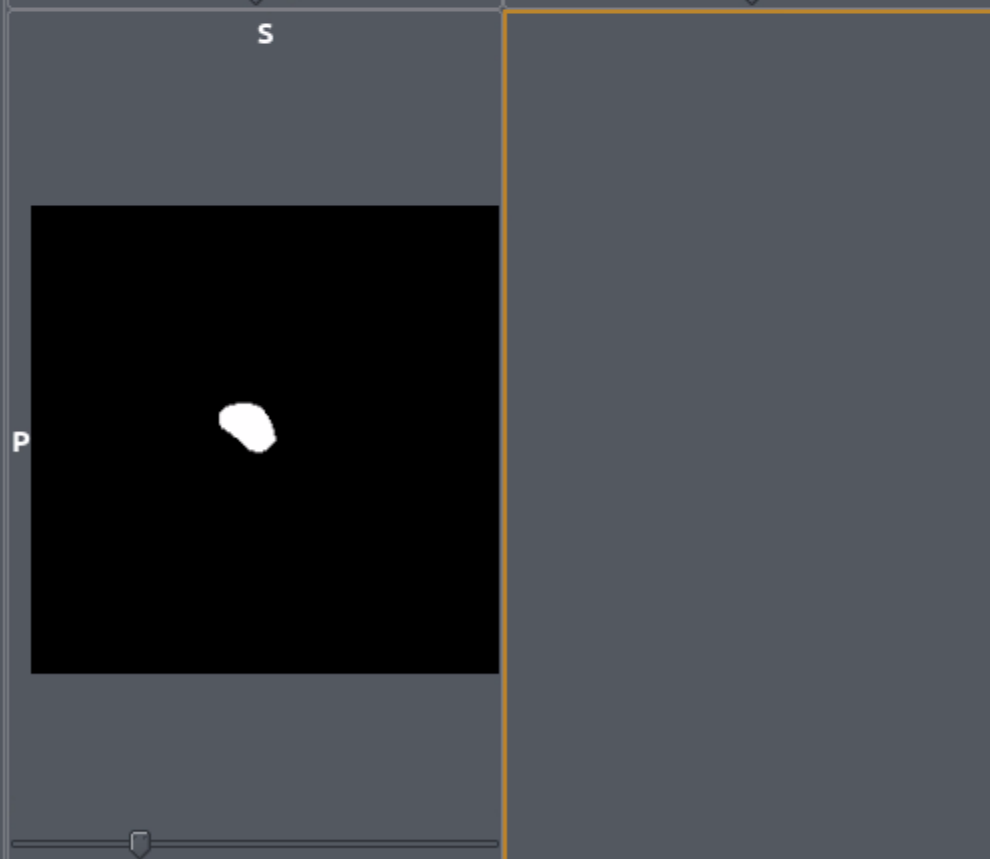
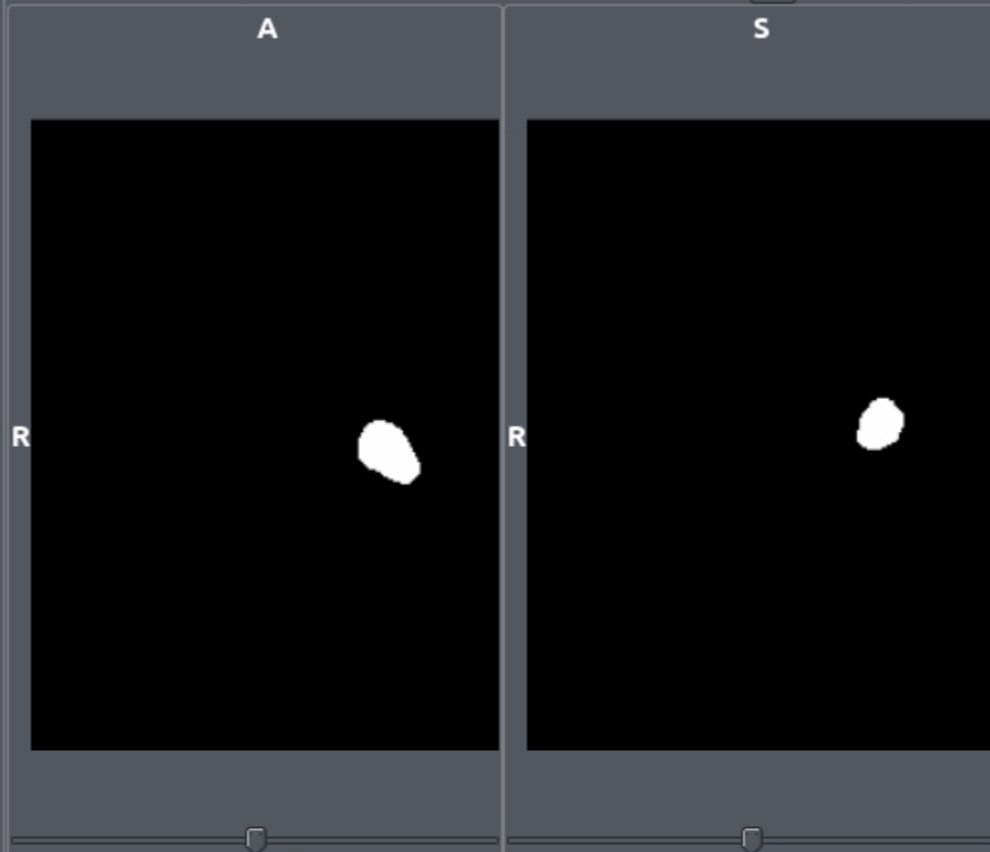
LPI

X left to right

Y posterior to anterior

Z inferior to superior

3D OpenGL views:
GL_R16 190x256x256 (no filtering)



1-tumormask.nii.gz

190 x 256 x 256
unsigned short
[0, 1]

LPI

X left to right

Y posterior to anterior

Z inferior to superior

3D OpenGL views:
GL_R16 190x256x256 (no filtering)

ITK-SNAP Toolbox

Main Toolbar



Cursor Inspector



Cursor position (x,y,z):

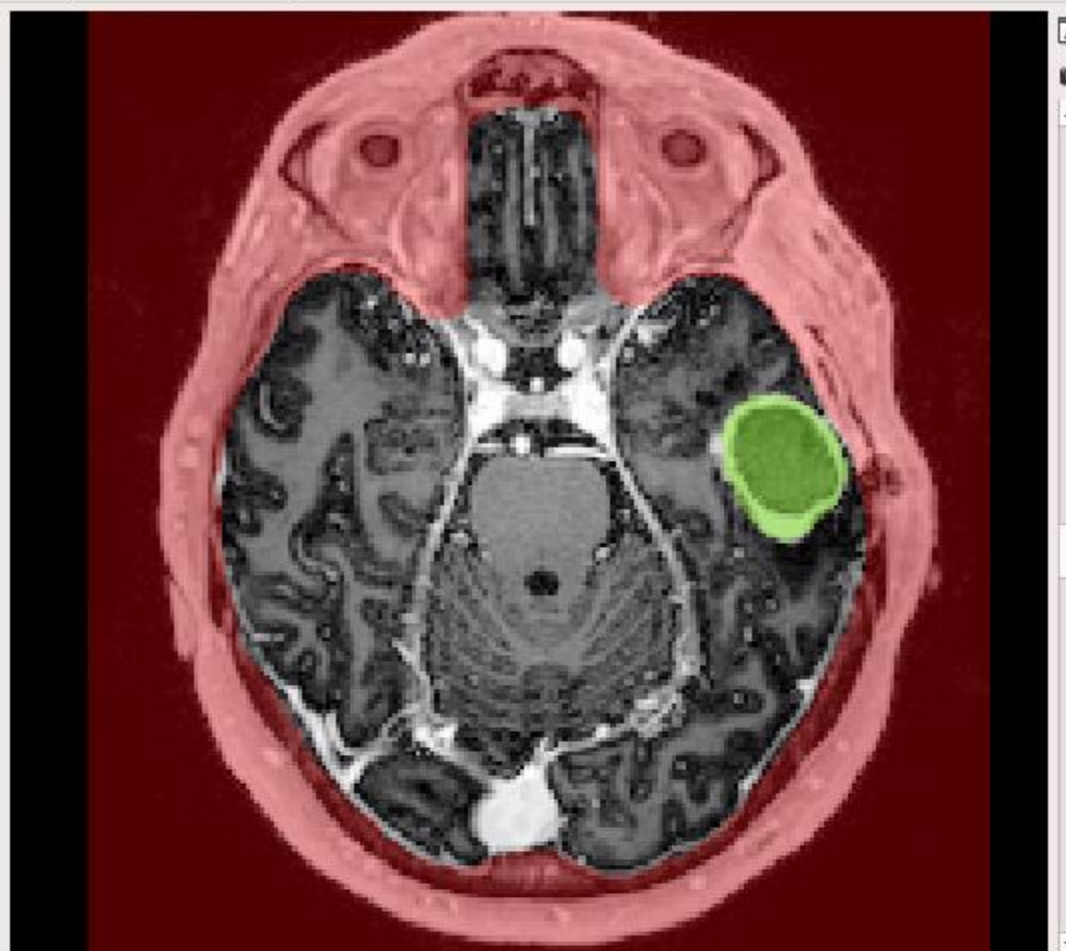
47 121 136

Intensity under cursor:

Layer	Intensity
1-T1c	1.338e...
1-tumormask	1
2-brainmask	1

Label under cursor:

0 Clear Label



zoom to fit 136 of 256



zoom to fit 47 of 190

Image Layer Inspector - ITK-SNAP

General Contrast Color Map Info Metadata

Dimensions

x: 190 y: 256 z: 256

Voxel Spacing

x: 1 y: 1 z: 1

Origin and Orientation

x: 87.29 y: 79.21 z: -157.6

Orientation (RAI) code: Reorient...

3D Cursor Position

Voxel coordinates x: 47 y: 121 z: 136

World (ITK) coordinates x: 45.16 y: -15.94 z: -2.965

World (NIFTI) coordinates x: -45.16 y: 15.94 z: -2.965

Intensity Range

1-T1c

1-tumormask

2-brainmask

Active label: ☒ Label

Paint over: ☒ All labels

Overall label: 50

3D Toolbar



zoom to fit 121 of 256

Example: From DICOM to synthetic growth models

- Post-contrast T1-weighted MRI showing tumor
- Tumor mask
- Brain mask
- Model parameters: params.txt

```
displacement=3 6 9 12  
gaussian_range_one_sided=5  
intensity_decay_fraction=0.1  
num_vecs=32  
angle_thr=7  
spline_order=1  
smoothing_std=4  
perlin_noise_res=0.03  
perlin_noise_abs_max=0.6
```

Example: From DICOM to synthetic growth models

Download and run cancer-sim

```
$ git clone https://github.com/ivartz/cancer-sim
```

```
$ bash cancer-sim/generate-models.sh params.txt  
derivatives/1-T1c.nii.gz derivatives/1-  
tumormask.nii.gz derivatives/1-brainmask.nii.gz  
models
```



Cursor position (x,y,z):

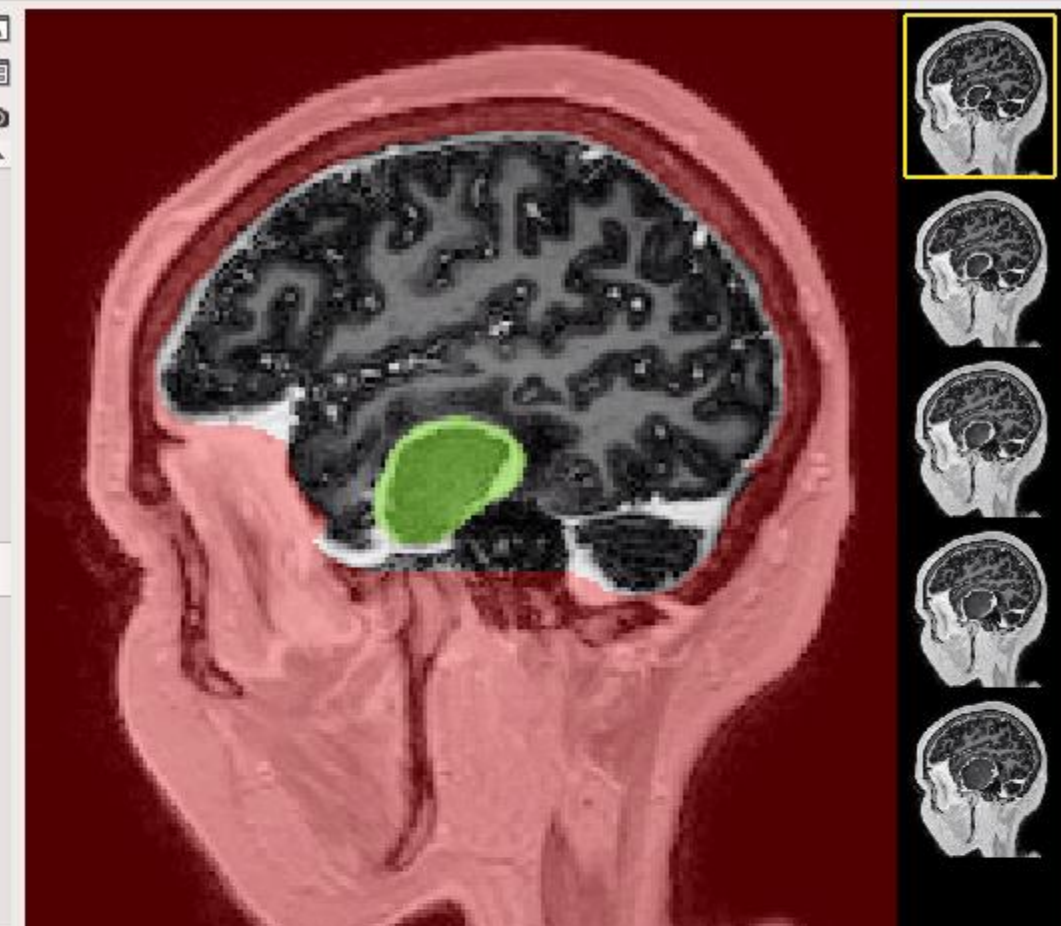
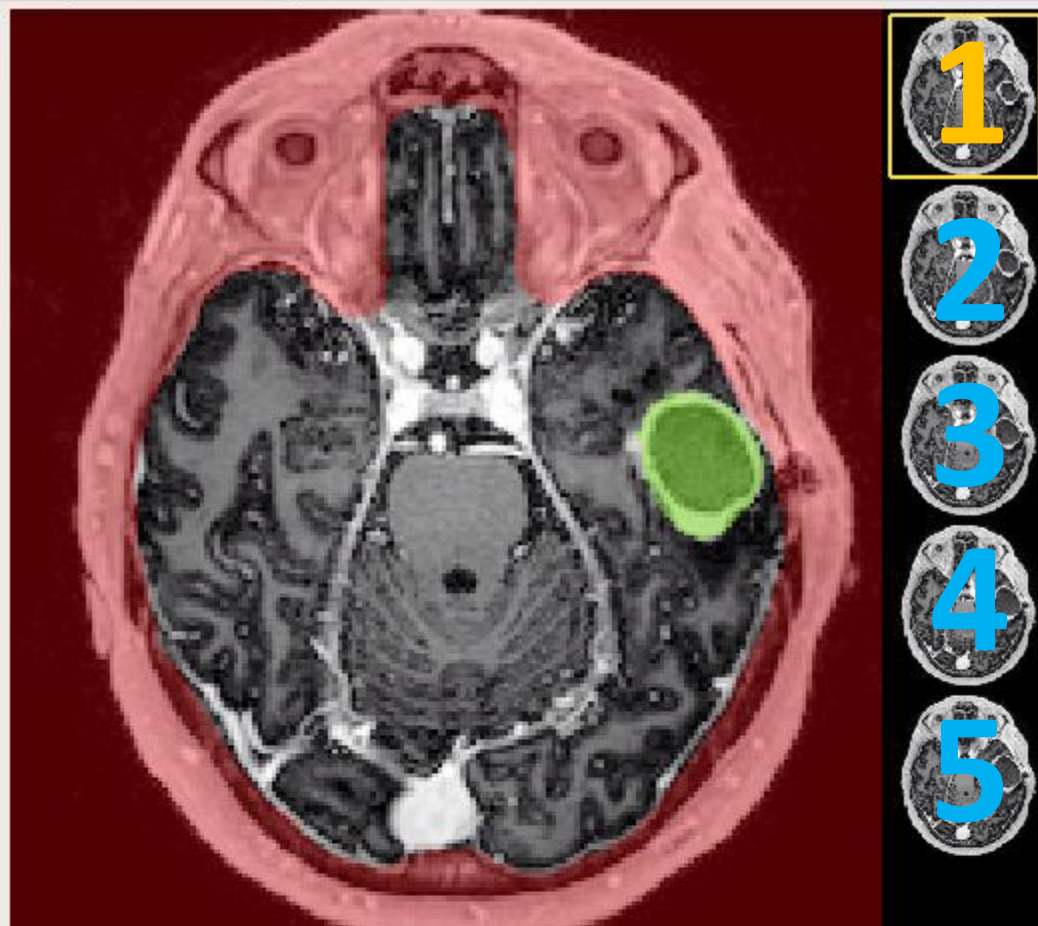
47 121 136

Intensity under cursor:

Layer	Intensity
1-T1c	1.3...
1-tumormask	1
2-brainmask	1
warped	1.4...
warped	1.5...
warped	1.3...

Label under cursor:

0 Clear Label



Simulated radial growth

zoom to fit

47 of 190

Image Layer Inspector - ITK-SNAP

General Contrast Color Map Info Metadata

Linear Contrast Adjustment:

Minimum: 0 Level: 962451 Reset

Maximum: 1924903 Window: 1924903 Auto

Curve-Based Contrast Adjustment:

Selected control point:

Id: 2 x: 359629 y: 0,496

Histogram Display Options:

Main Image: 1-T1c

Additional Images:

- 1-tumormask
- 2-brainmask
- warped
- warped
- warped
- warped
- warped

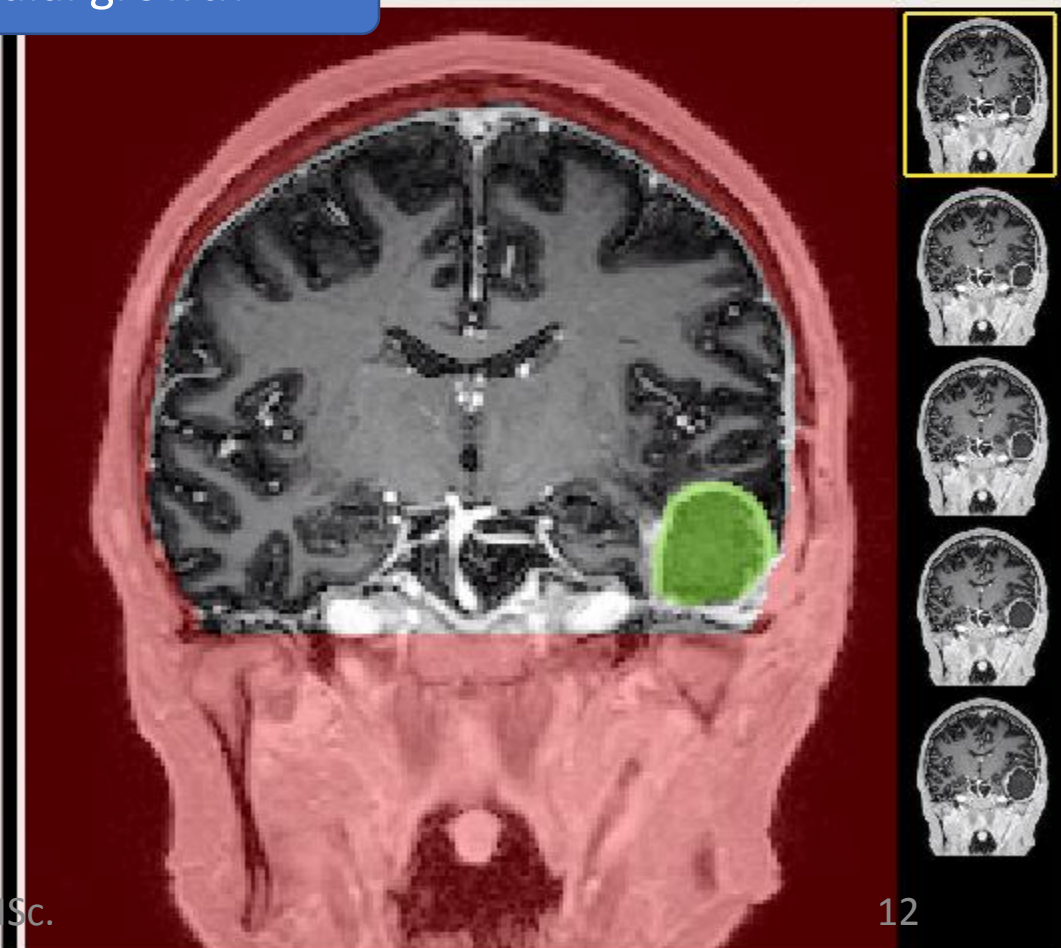
Segmentation:

Active label: Label

Paint over: All labels

Overall label: 50

3D Toolbar



zoom to fit

121 of 256



Cursor position (x,y,z):

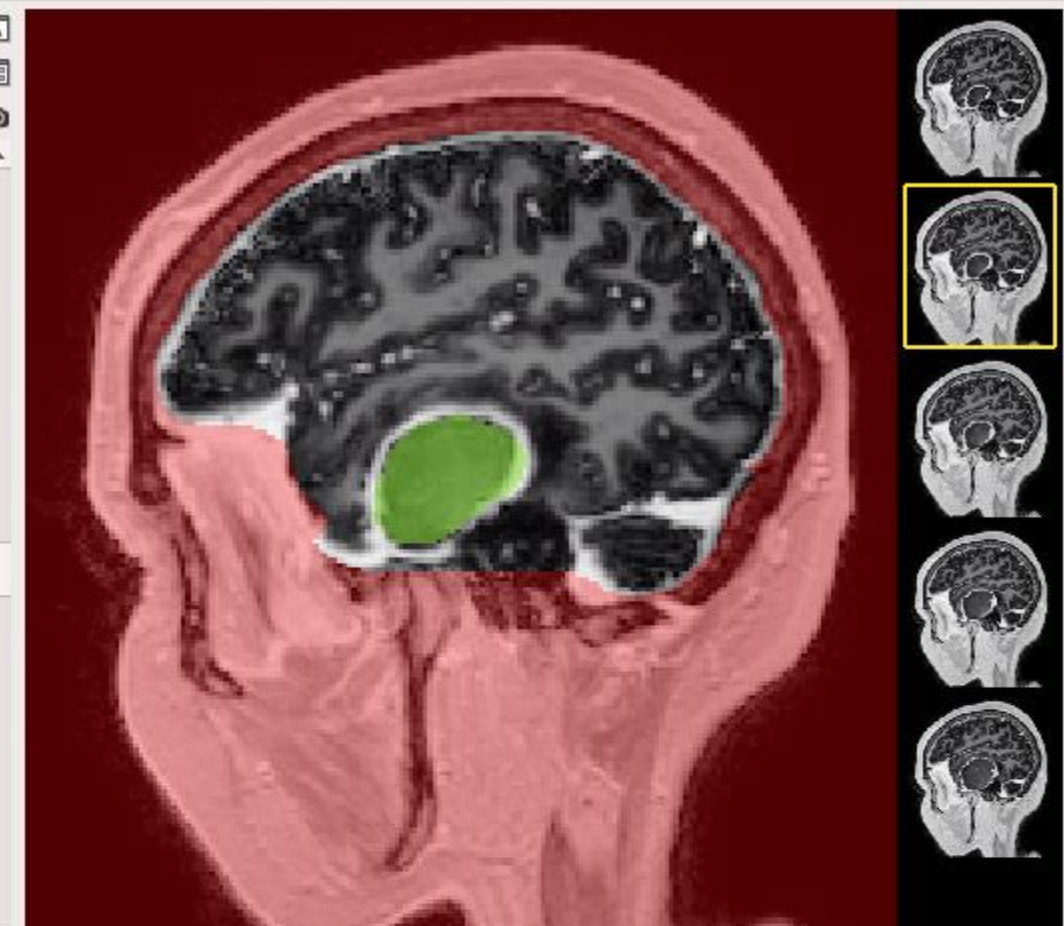
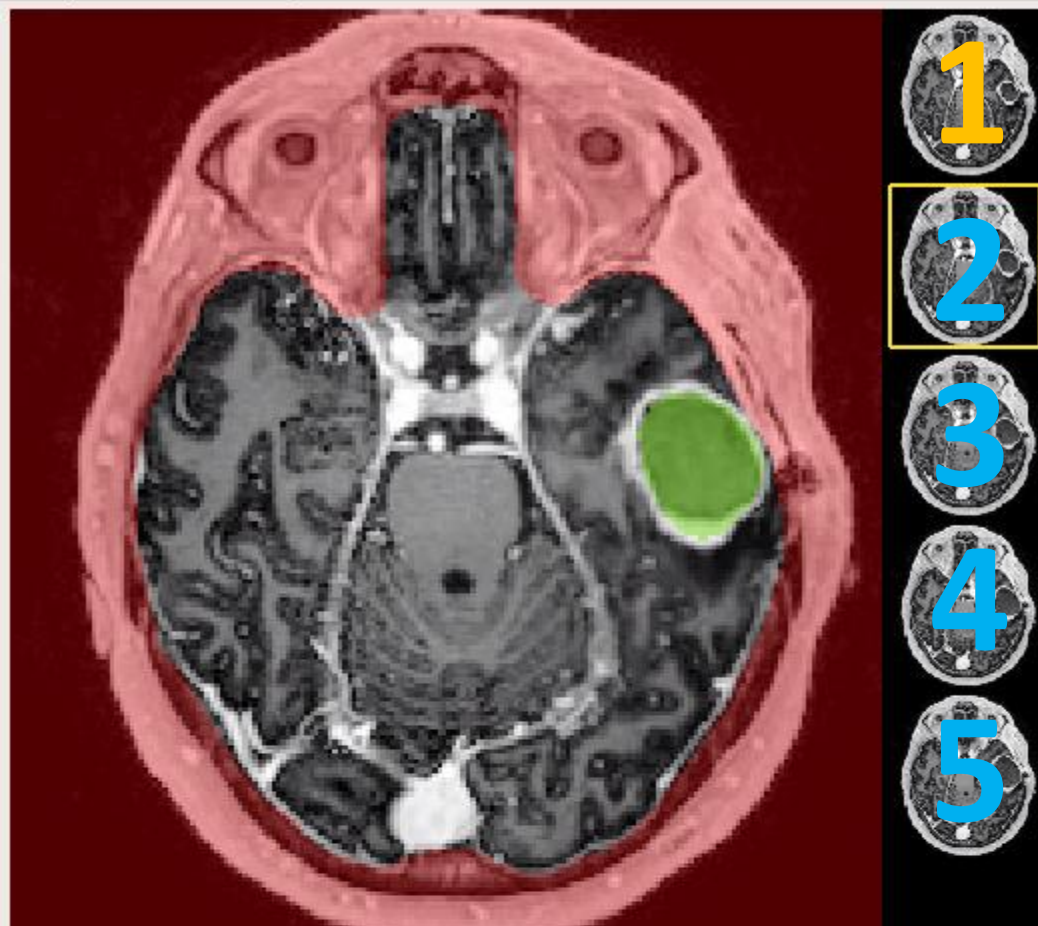
47 121 136

Intensity under cursor:

Layer	Intensity
1-T1c	1.3...
1-tumormask	1
2-brainmask	1
warped	1.4...
warped	1.5...
warped	1.3...

Label under cursor:

0 Clear Label



Simulated radial growth

zoom to fit

47 of 190

Image Layer Inspector - ITK-SNAP

General Contrast Color Map Info Metadata

Linear Contrast Adjustment:

Minimum: 0 Level: 927089 Reset

Maximum: 1854178 Window: 1854178 Auto

Curve-Based Contrast Adjustment:

Selected control point:

Id: 1 x: 0 y: 0,000

Histogram Display Options:

Main Image: 1-T1c

Additional Images:

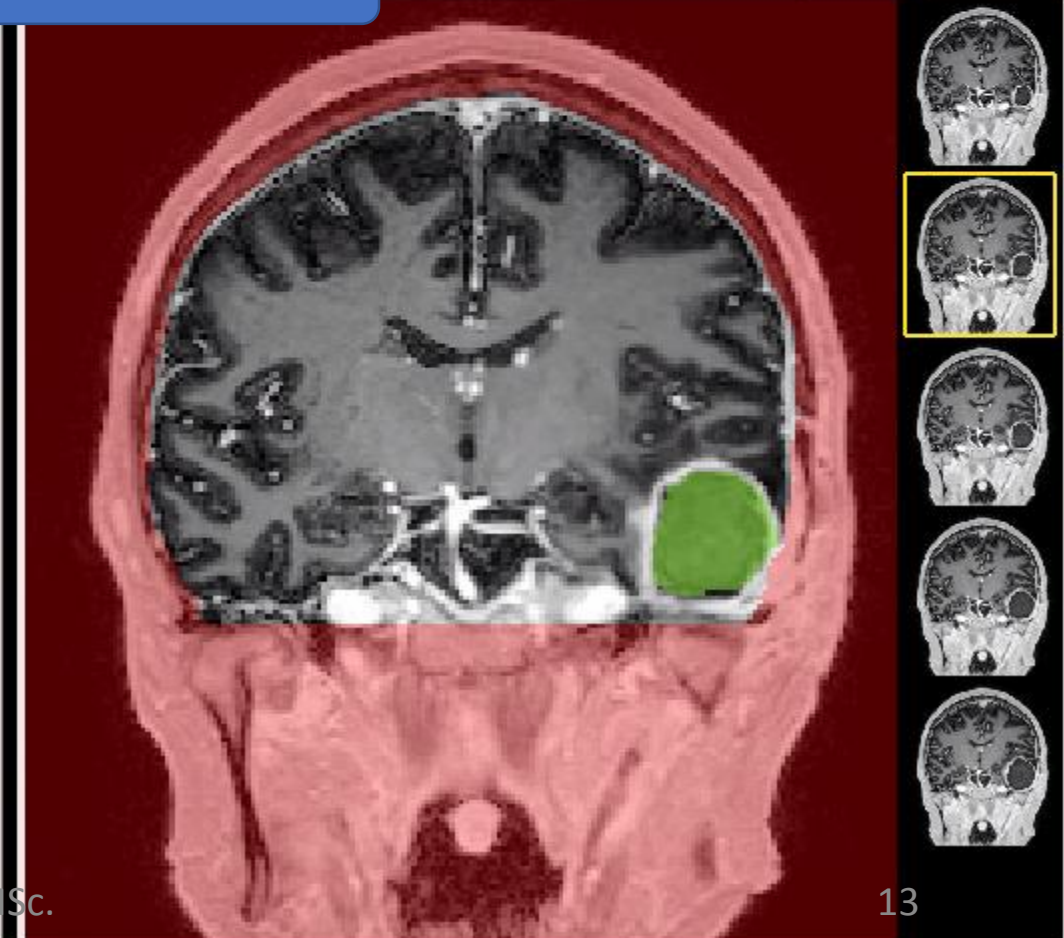
- 1-tumormask
- 2-brainmask
- warped
- warped
- warped
- warped
- warped

Segmentation:

Active label: Label

Paint over: All labels

Overall label: 50



zoom to fit

121 of 256



Cursor position (x,y,z):

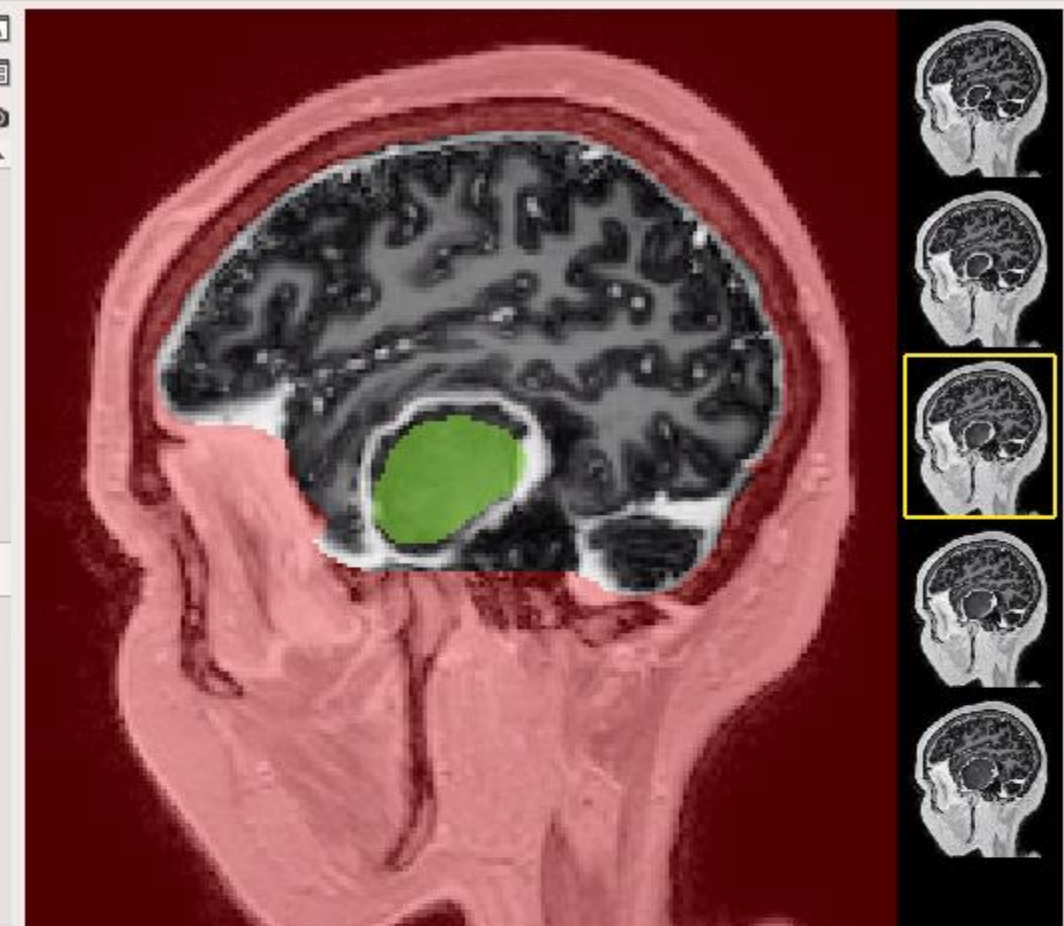
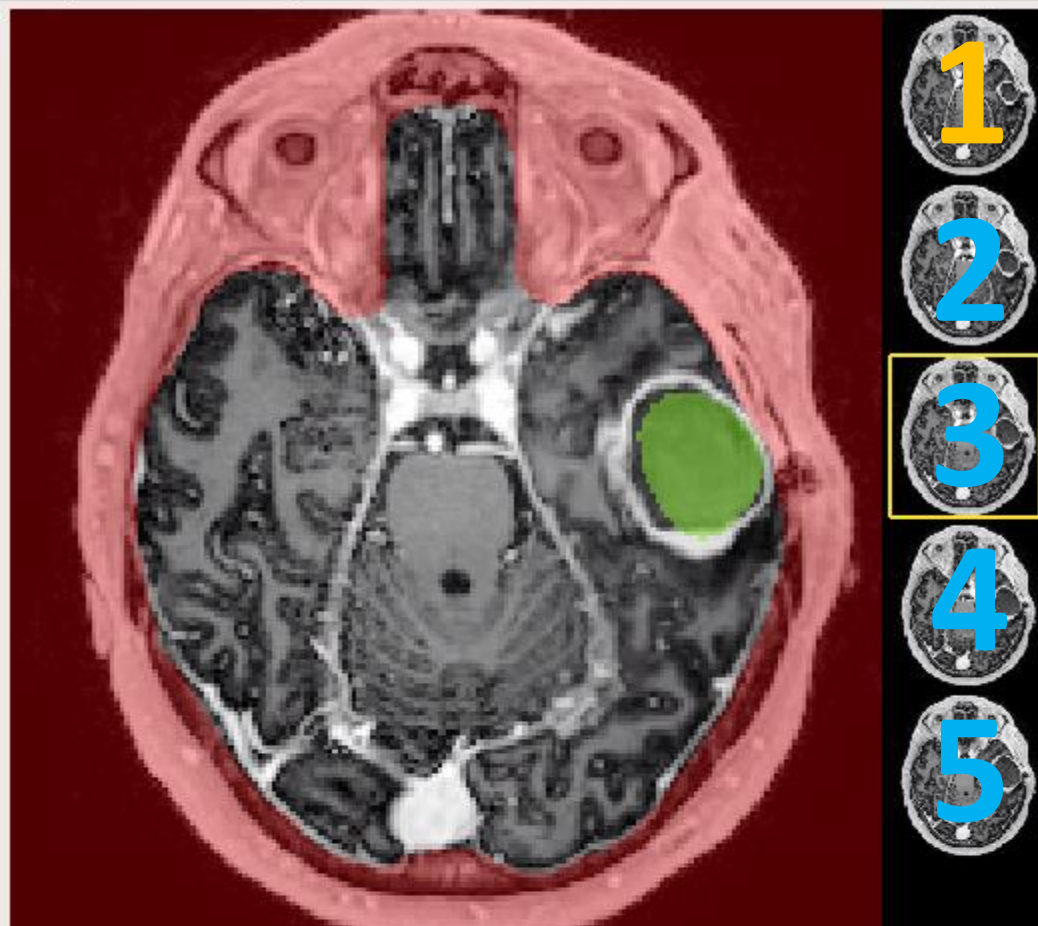
47 121 136

Intensity under cursor:

Layer	Intensity
1-T1c	1.3...
1-tumormask	1
2-brainmask	1
warped	1.4...
warped	1.5...
warped	1.3...

Label under cursor:

0 Clear Label



Simulated radial growth

zoom to fit

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Image Layer Inspector - ITK-SNAP

General Contrast Color Map Info Metadata

Linear Contrast Adjustment:

Minimum: 0 Level: 949802 Reset

Maximum: 1899604 Window: 1899604 Auto

Curve-Based Contrast Adjustment:

Selected control point:

Id: 2 x: 341758 y: 0,513

Histogram Display Options:

Main Image: 1-T1c

Additional Images:

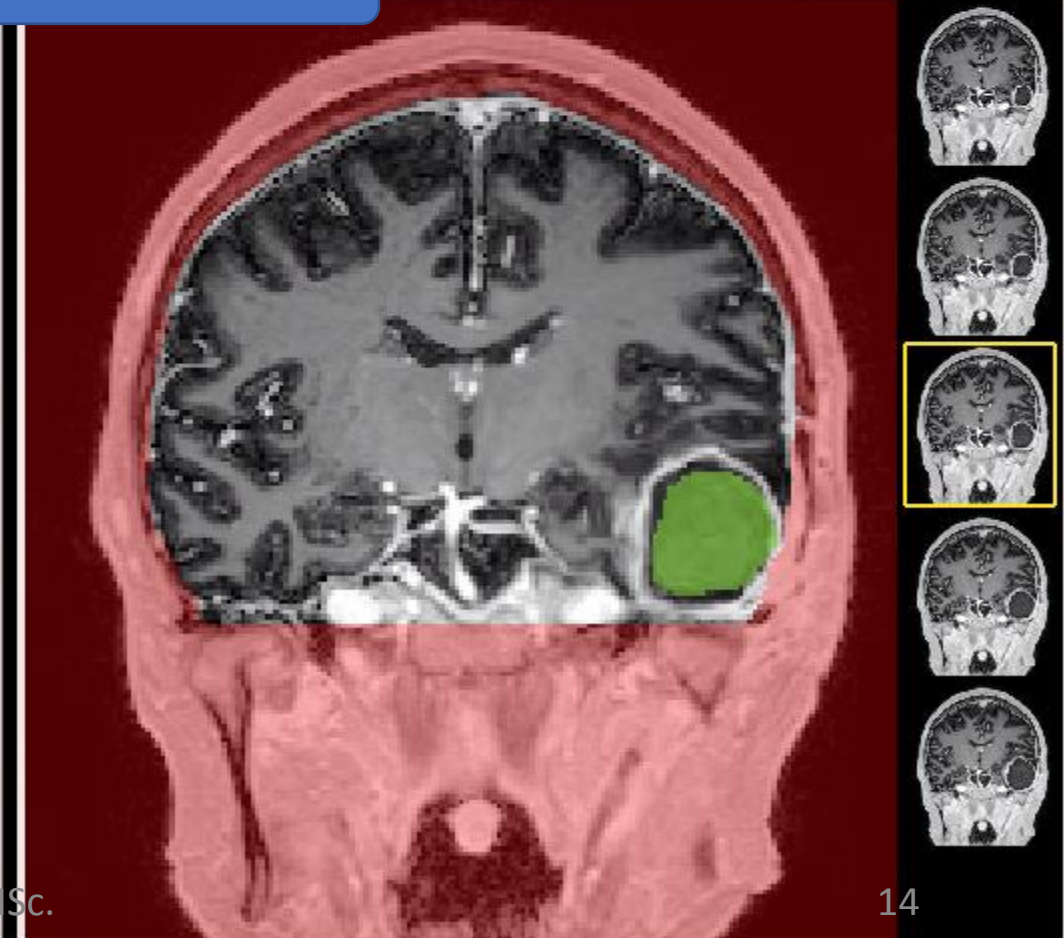
- 1-tumormask
- 2-brainmask
- warped
- warped
- warped
- warped
- warped

Segmentation:

Active label: Label

Paint over: All labels

Overall label: 50



zoom to fit

121 of 256



Cursor position (x,y,z):

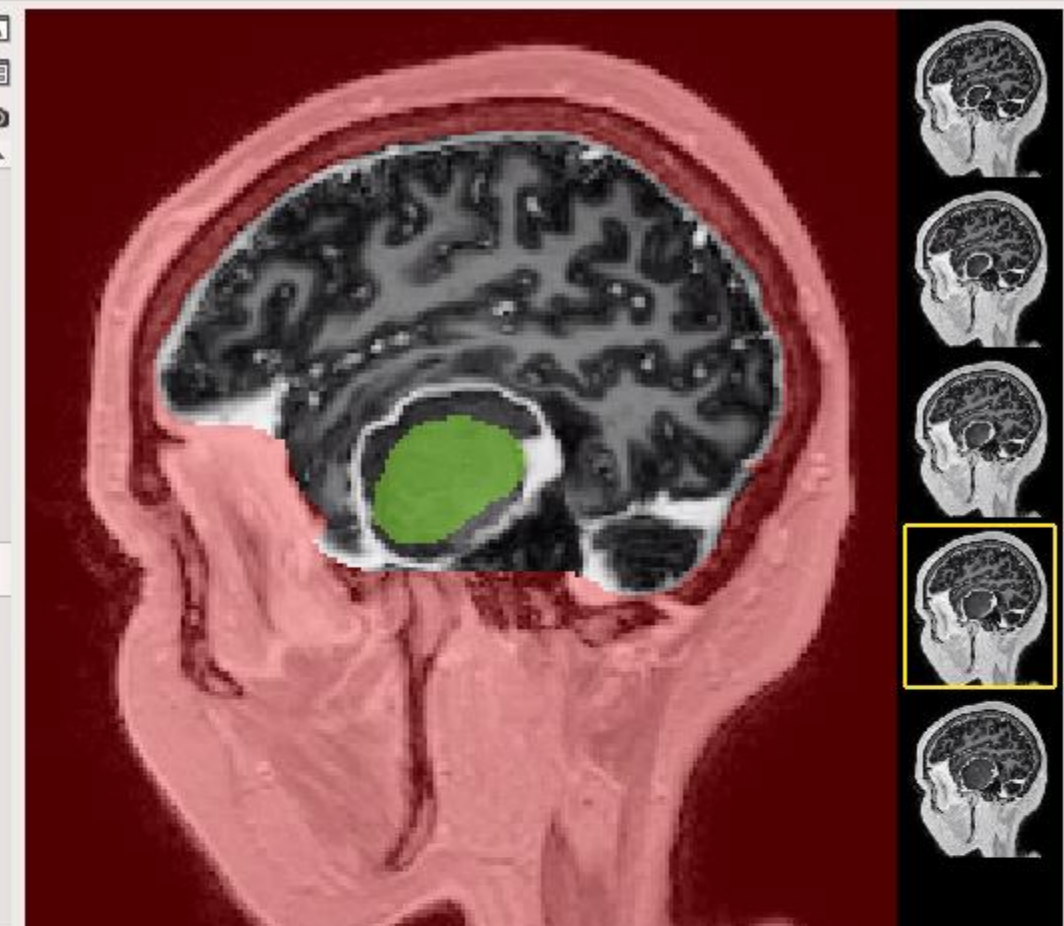
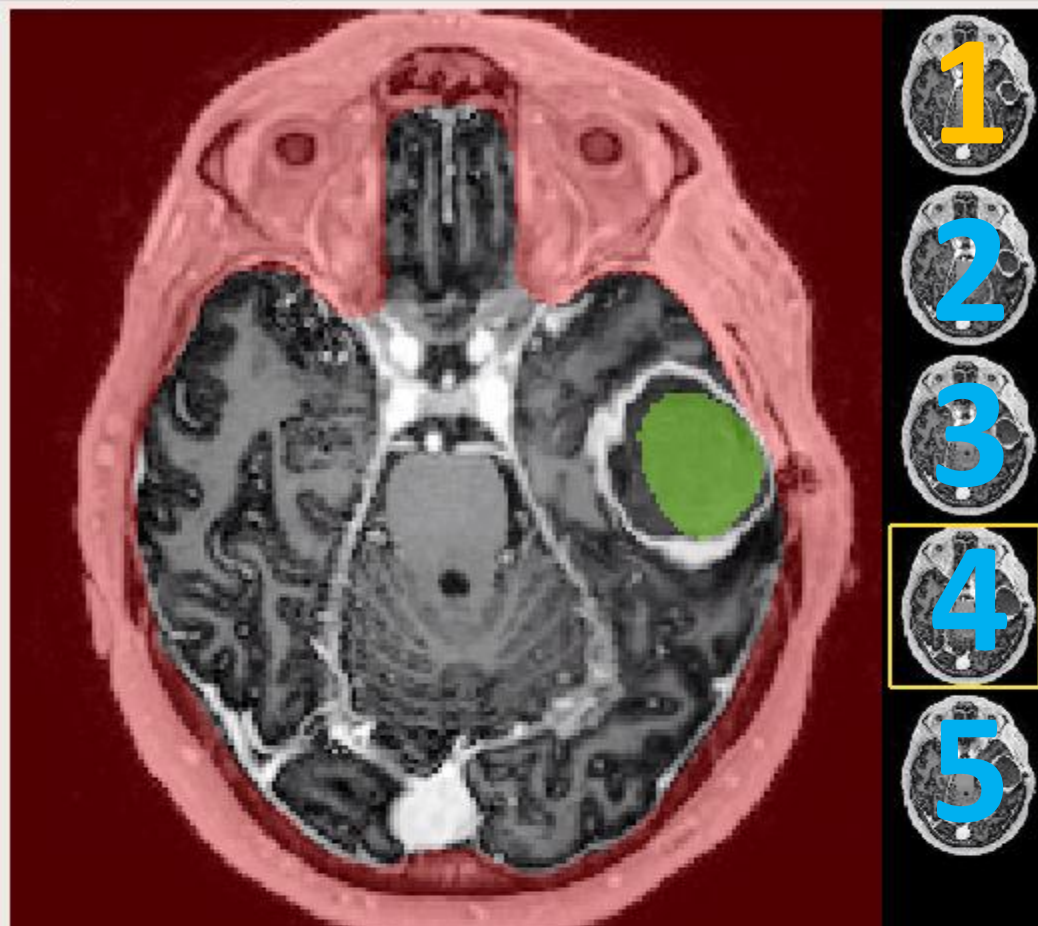
47 121 136

Intensity under cursor:

Layer	Intensity
1-T1c	1.3...
1-tumormask	1
2-brainmask	1
warped	1.4...
warped	1.5...
warped	1.3...

Label under cursor:

0 Clear Label



Simulated radial growth

zoom to fit

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Image Layer Inspector - ITK-SNAP

General Contrast Color Map Info Metadata

Linear Contrast Adjustment:

Minimum: 0 Level: 939196 Reset

Maximum: 1878392 Window: 1878392 Auto

Curve-Based Contrast Adjustment:

Selected control point:

Id: 2 x: 363953 y: 0,530

Histogram Display Options:

Main Image: 1-T1c

Additional Images:

- 1-tumormask
- 2-brainmask
- warped
- warped
- warped
- warped

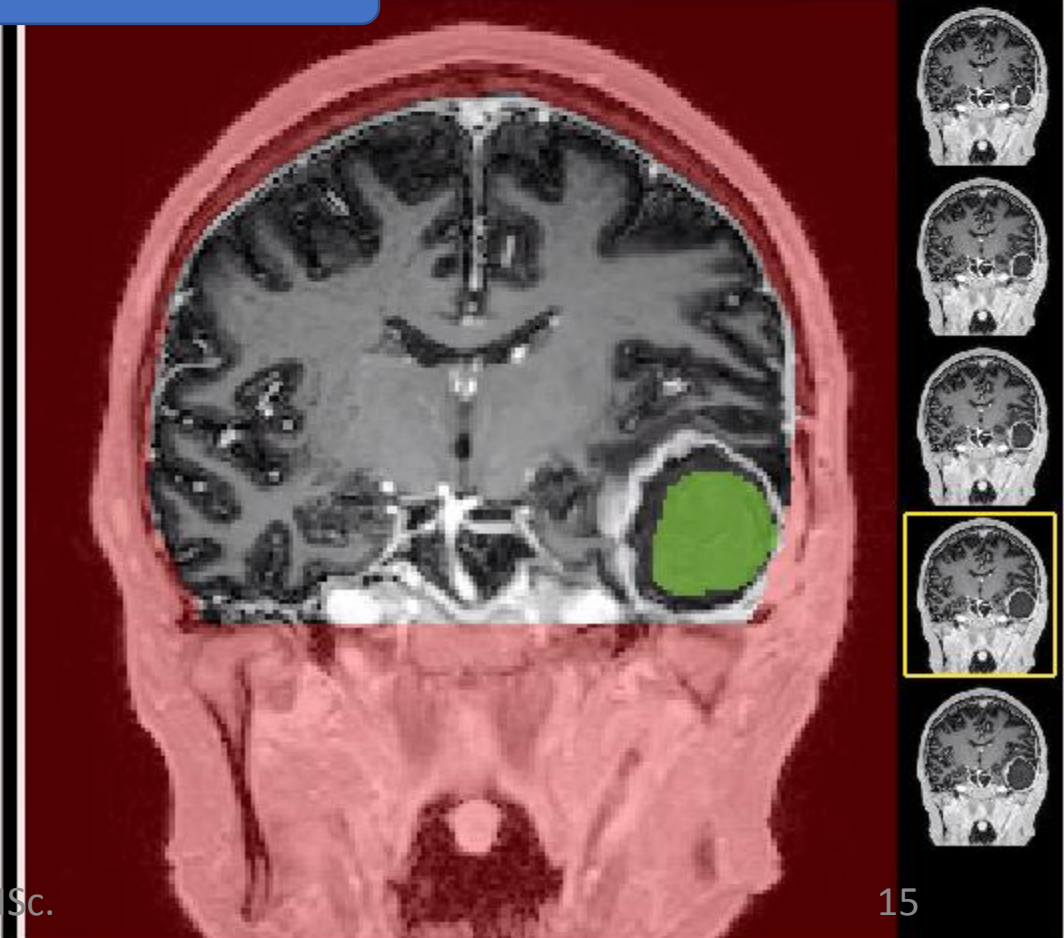
Segmentation:

Active label: Label

Paint over: All labels

Overall label: 50

3D Toolbar



zoom to fit

121 of 256



Cursor position (x,y,z):

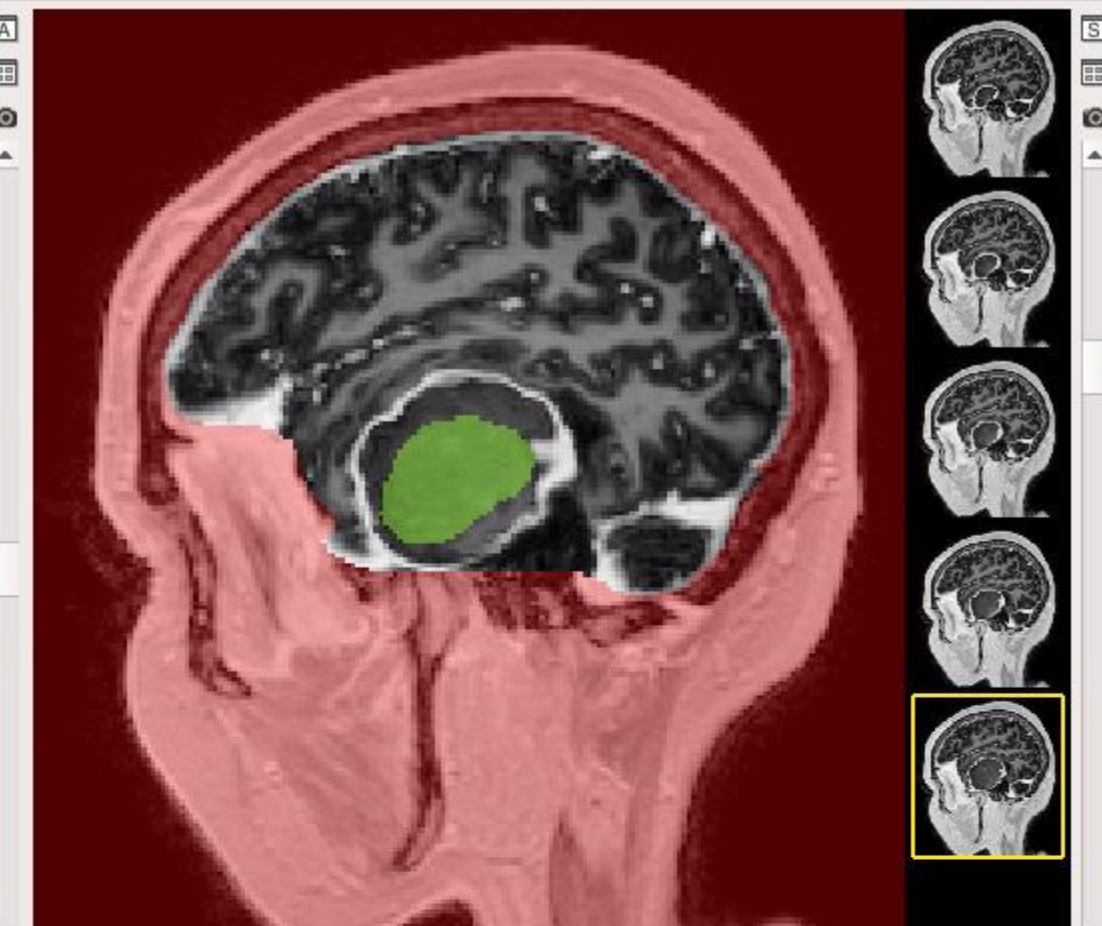
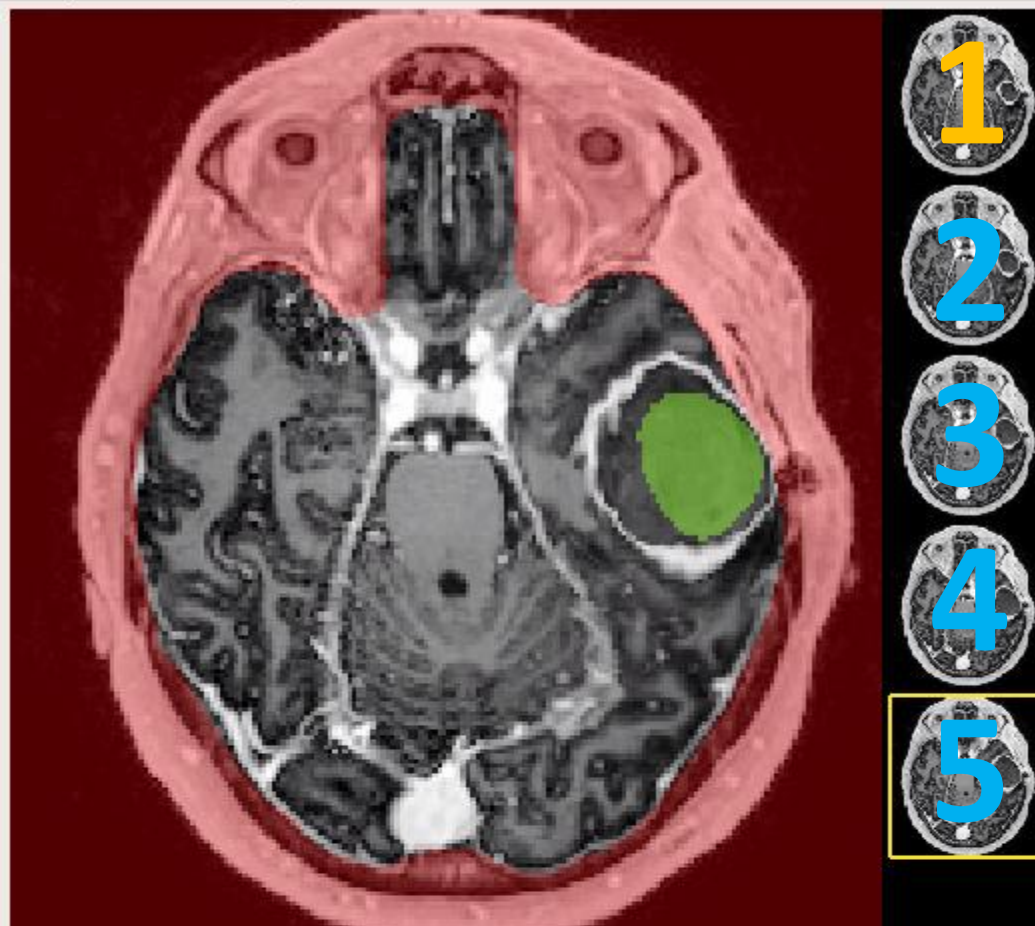
47 121 136

Intensity under cursor:

Layer	Intensity
1-T1c	1.3...
1-tumormask	1
2-brainmask	1
warped	1.4...
warped	1.5...
warped	1.3...

Label under cursor:

0 Clear Label



Simulated radial growth

zoom to fit

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Image Layer Inspector - ITK-SNAP

General Contrast Color Map Info Metadata

Linear Contrast Adjustment:

Minimum: 0 Level: 936980 Reset

Maximum: 1873961 Window: 1873961 Auto

Curve-Based Contrast Adjustment:

Selected control point:

Id: 2 x: 371744 y: 0,530

Histogram Display Options:

Main Image: 1-T1c

Additional Images:

- 1-tumormask
- 2-brainmask
- warped
- warped
- warped
- warped
- warped

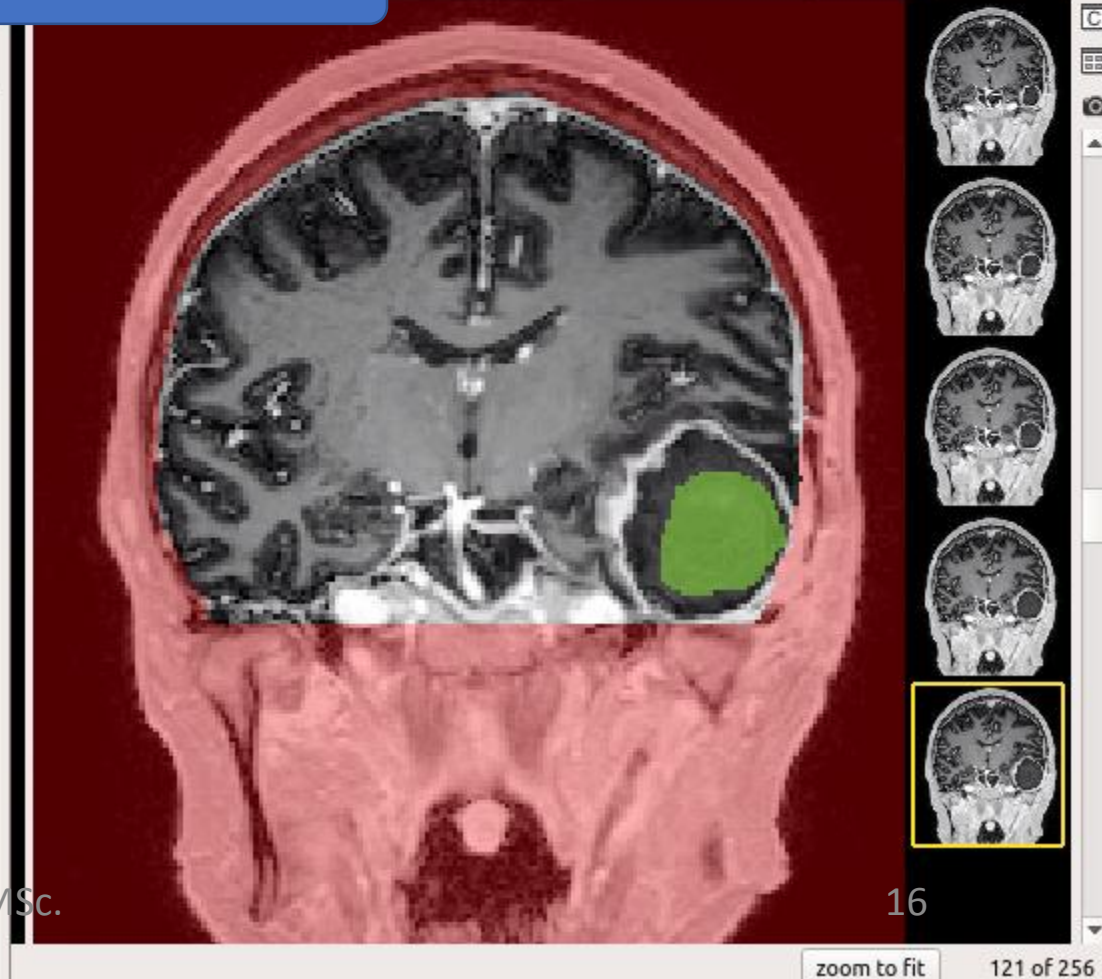
Segmentation:

Active label: Label

Paint over: All labels

Overall label: 50

3D Toolbar



zoom to fit

121 of 256



Cursor position (x,y,z):

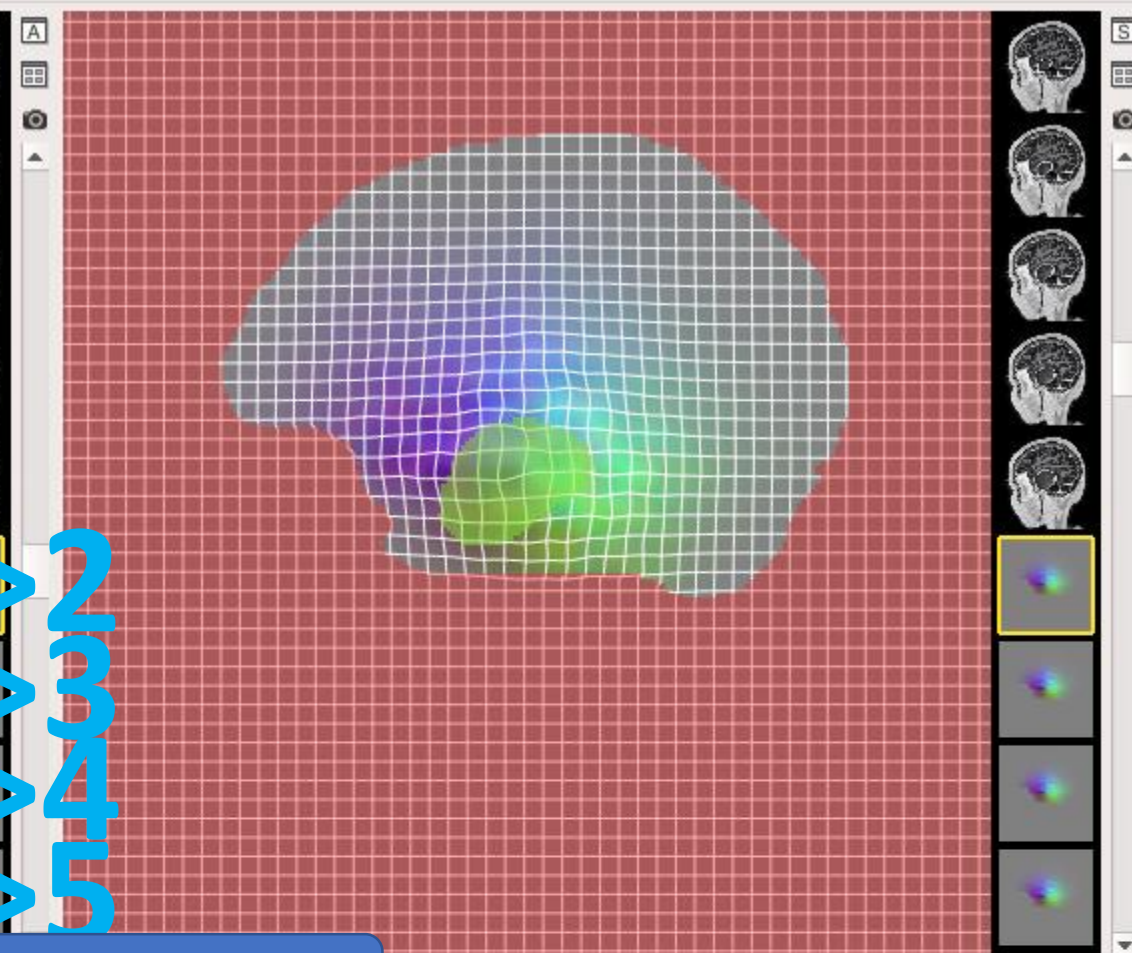
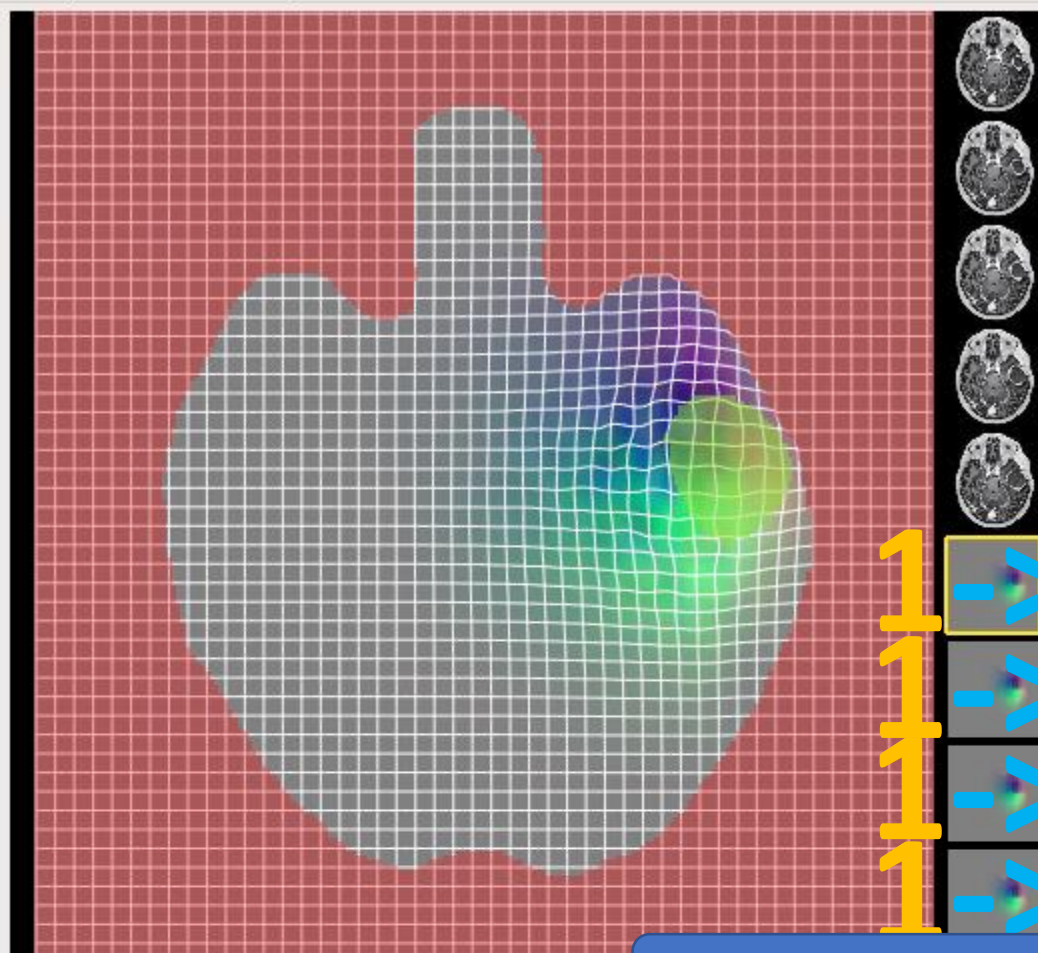
47 121 136

Intensity under cursor:

Layer	Intensity
1-T1c	1.3...
1-tumormask	1
2-brainmask	1
warped	1.4...
warped	1.5...
warped	1.3...

Label under cursor:

0 Clear Label



Ground truth displacement fields

Image Layer Inspector - ITK-SNAP

General Contrast Color Map Info Metadata

Linear Contrast Adjustment:

Minimum: -3,392 Level: -0,067 Reset

Maximum: 3,257 Window: 6,649 Auto

Curve-Based Contrast Adjustment:

Selected control point:

Id: 1 x: -3,392 y: 0,000

Histogram Display Options:

1-T1c

Additional Images

1-tumormask

2-brainmask

warped

warped

warped

warped

warped

warped

Active label

Label

Paint over:

All labels

Overall label

50

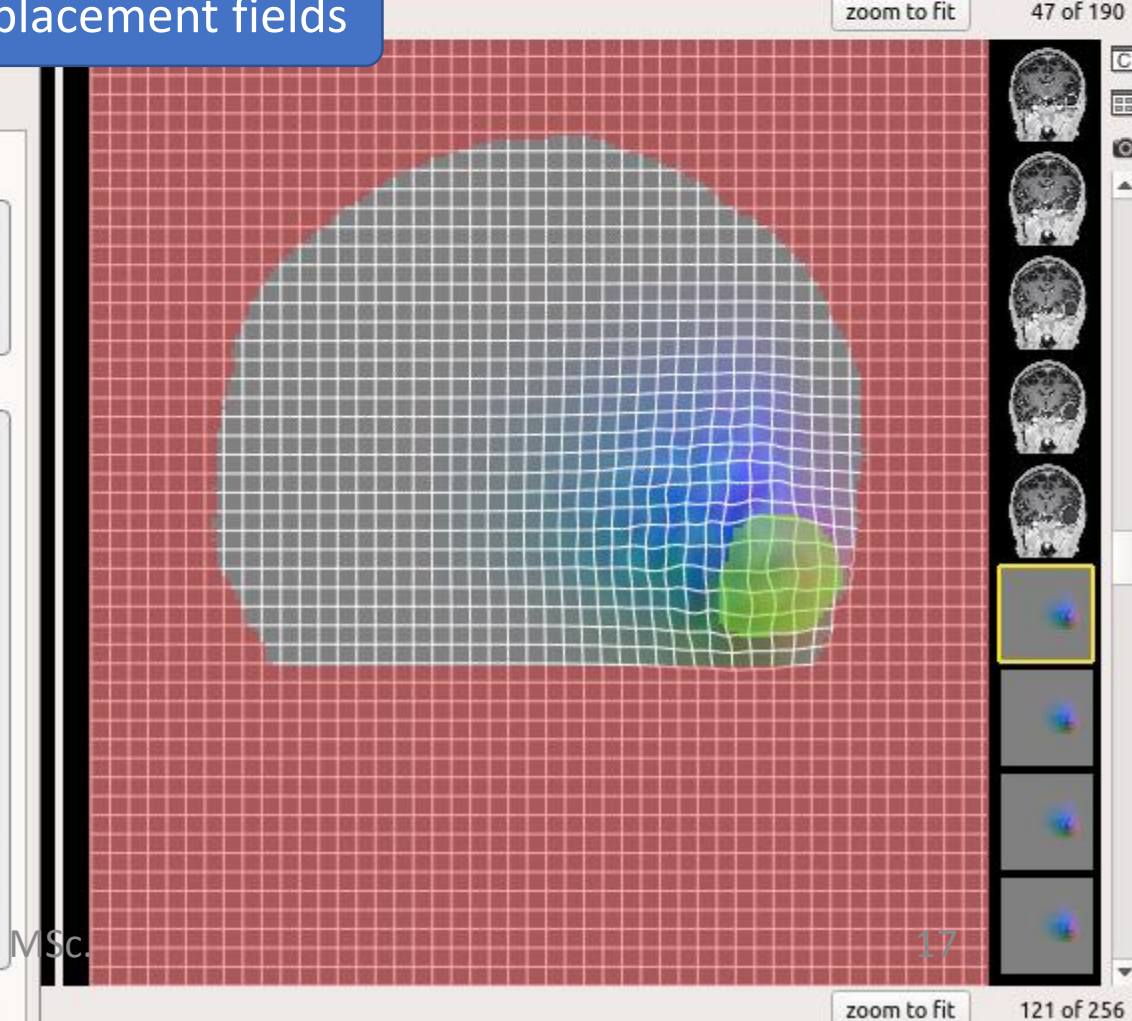
3D Toolbar

inter-neg-field-3

inter-neg-field-6

inter-neg-field-9

inter-neg-field-12





Cursor position (x,y,z):

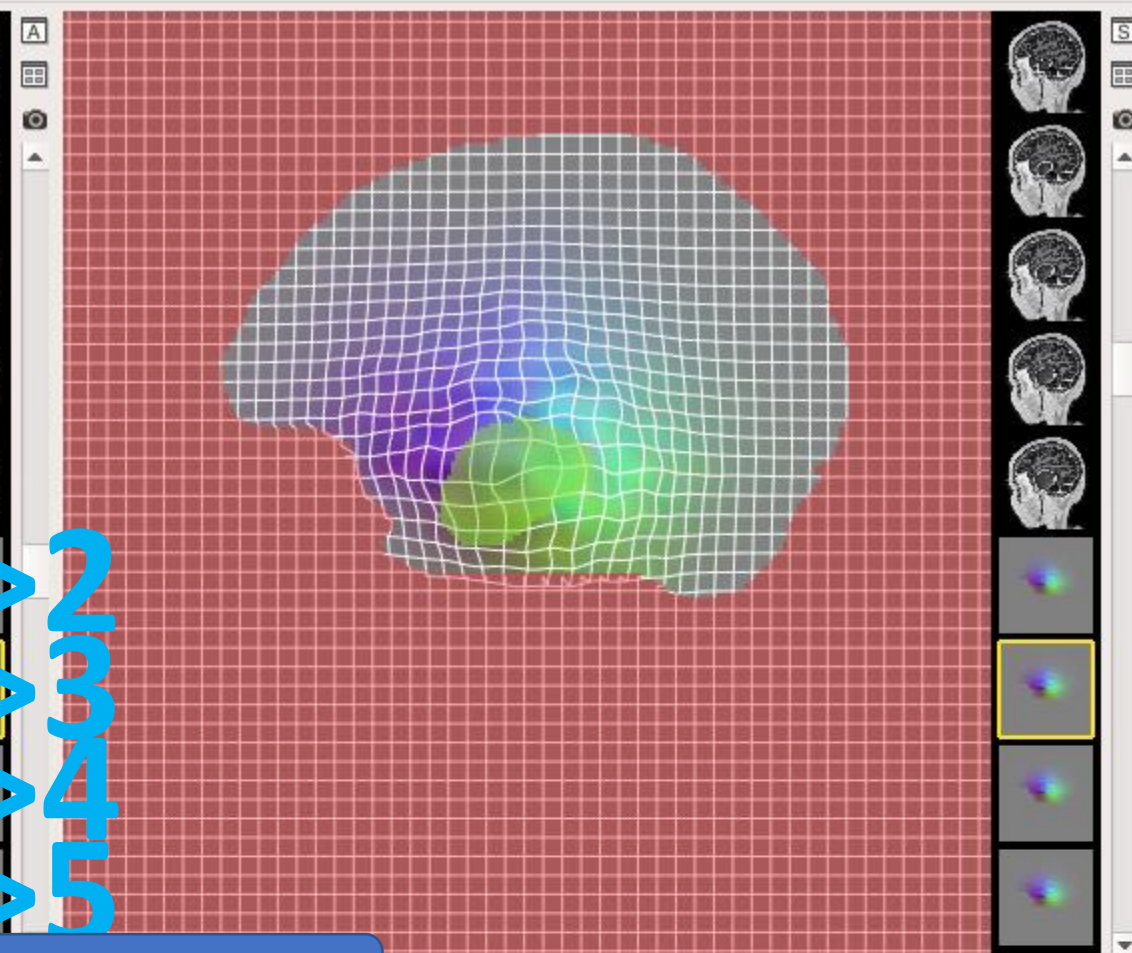
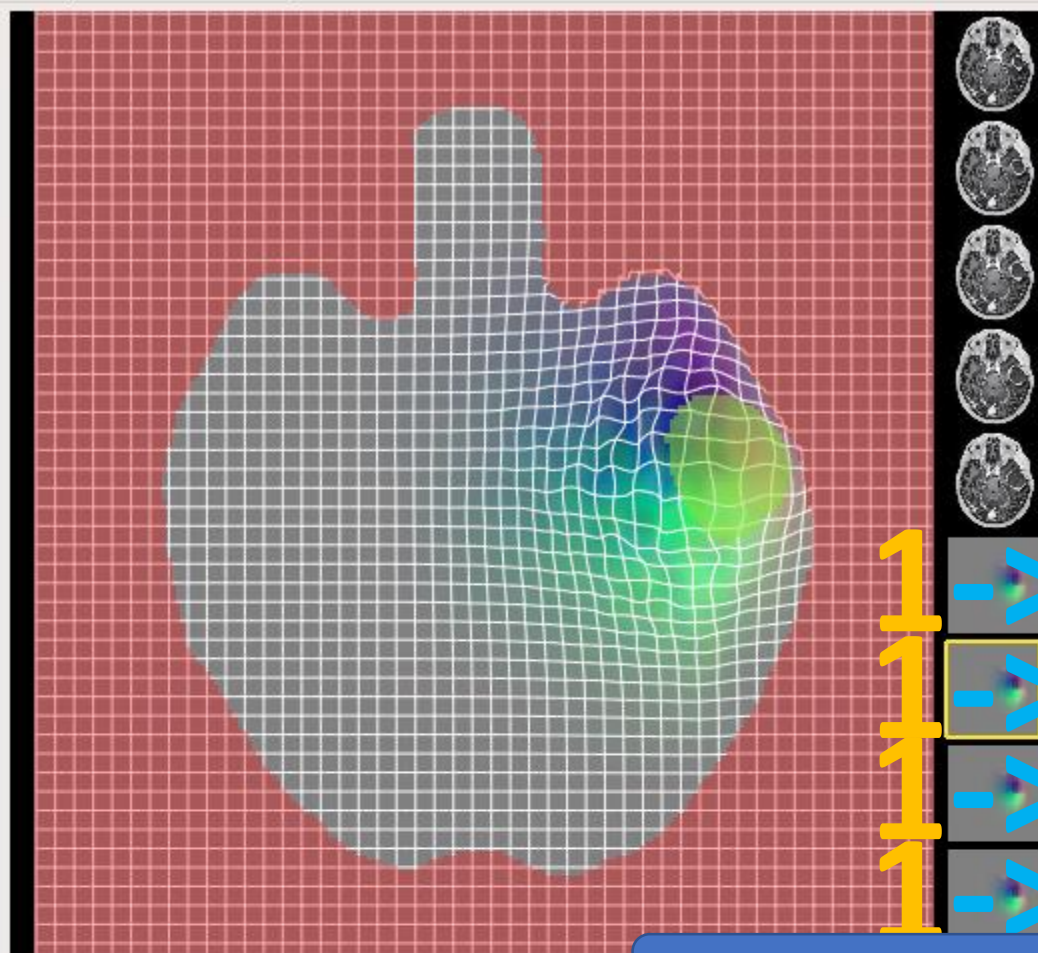
47 121 136

Intensity under cursor:

Layer	Intensity
1-T1c	1.3...
1-tumormask	1
2-brainmask	1
warped	1.4...
warped	1.5...
warped	1.3...

Label under cursor:

0 Clear Label



Ground truth displacement fields

Image Layer Inspector - ITK-SNAP

General Contrast Color Map Info Metadata

Linear Contrast Adjustment:

Minimum: -6,784 Level: -0,135 Reset

Maximum: 6,514 Window: 13,298 Auto

Curve-Based Contrast Adjustment:

Index into Color Map

Image Intensity

Selected control point:

Id: 1 x: -6,784 y: 0,000

Histogram Display Options:

1-T1c

Additional Images

1-tumormask

2-brainmask

warped

warped

warped

warped

warped

warped

Active label

Label

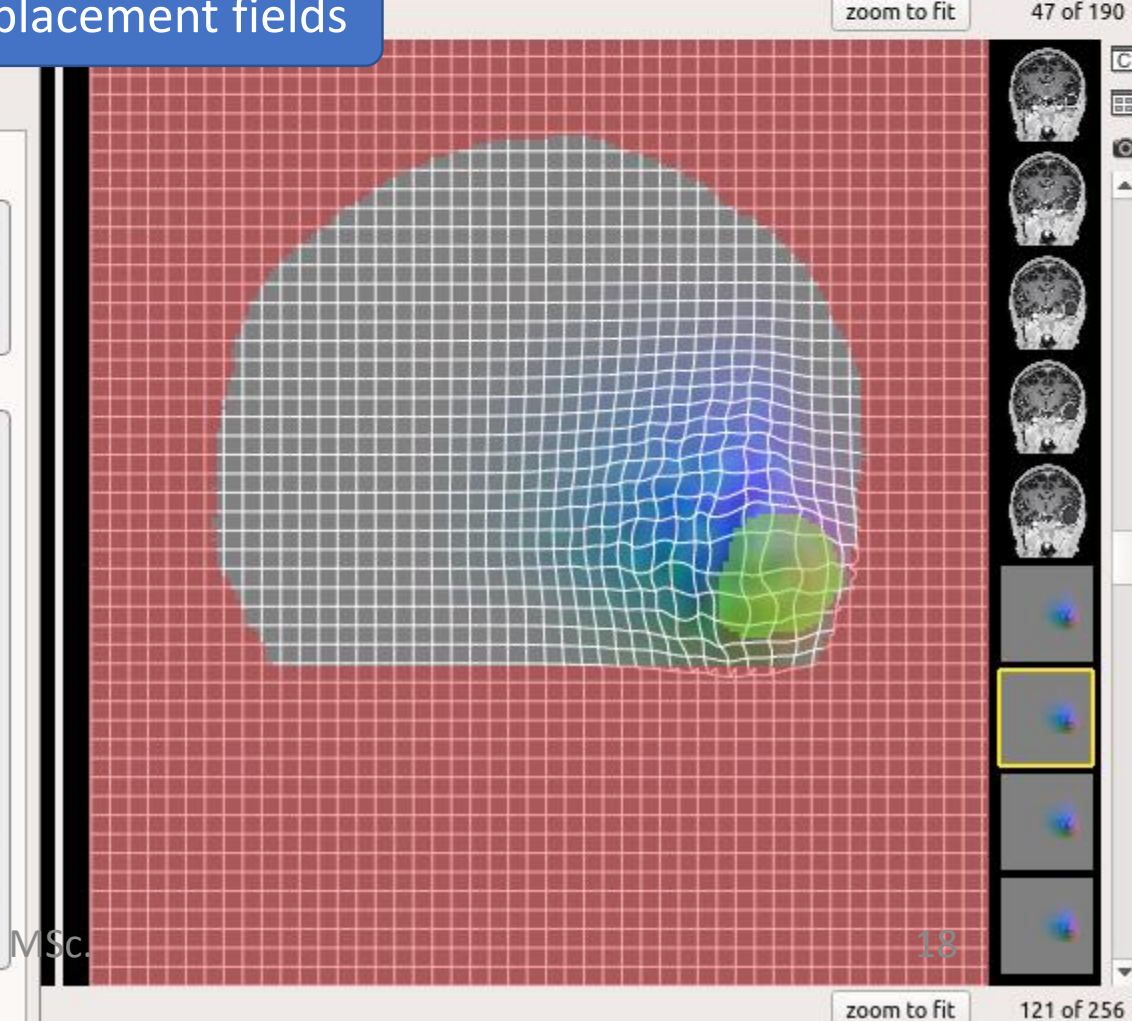
Paint over:

All labels

Overall label

50

3D Toolbar





Cursor position (x,y,z):

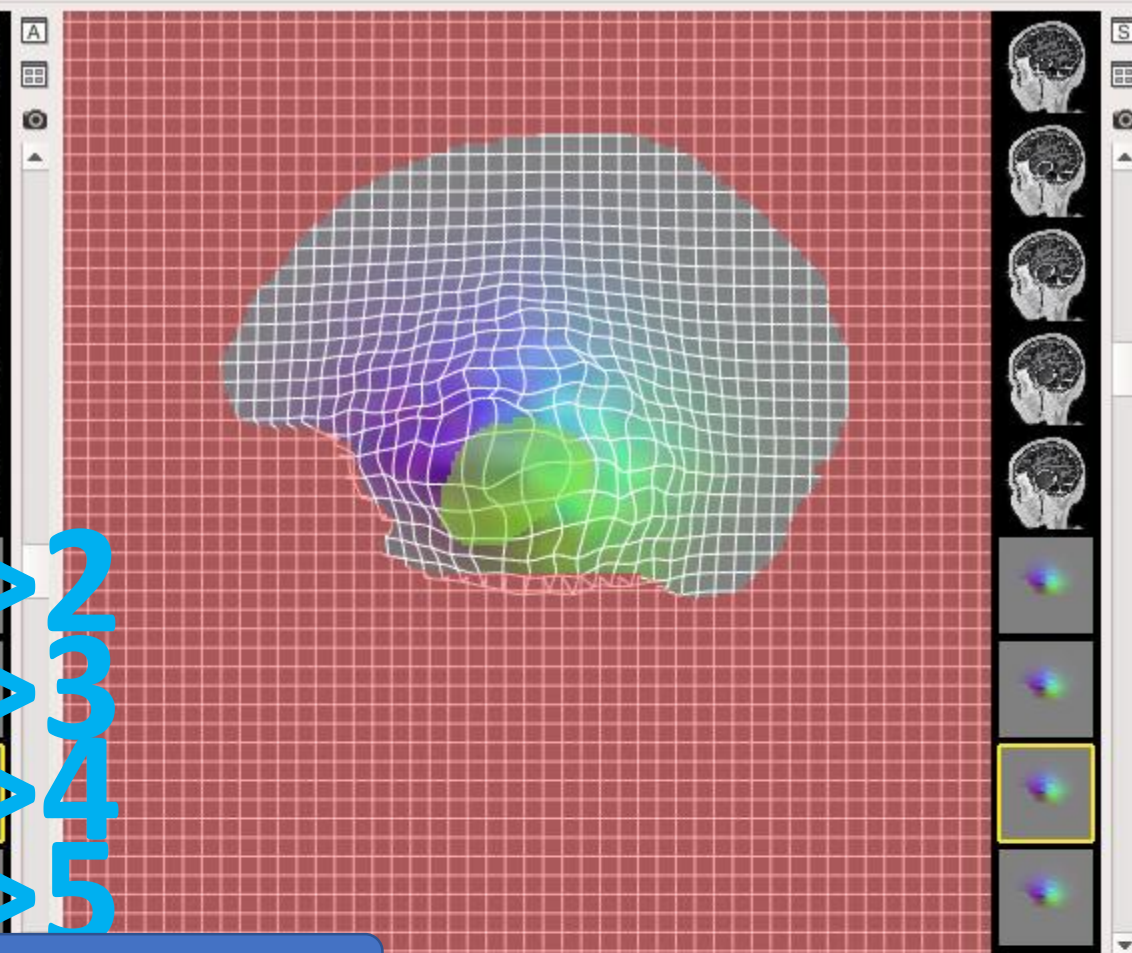
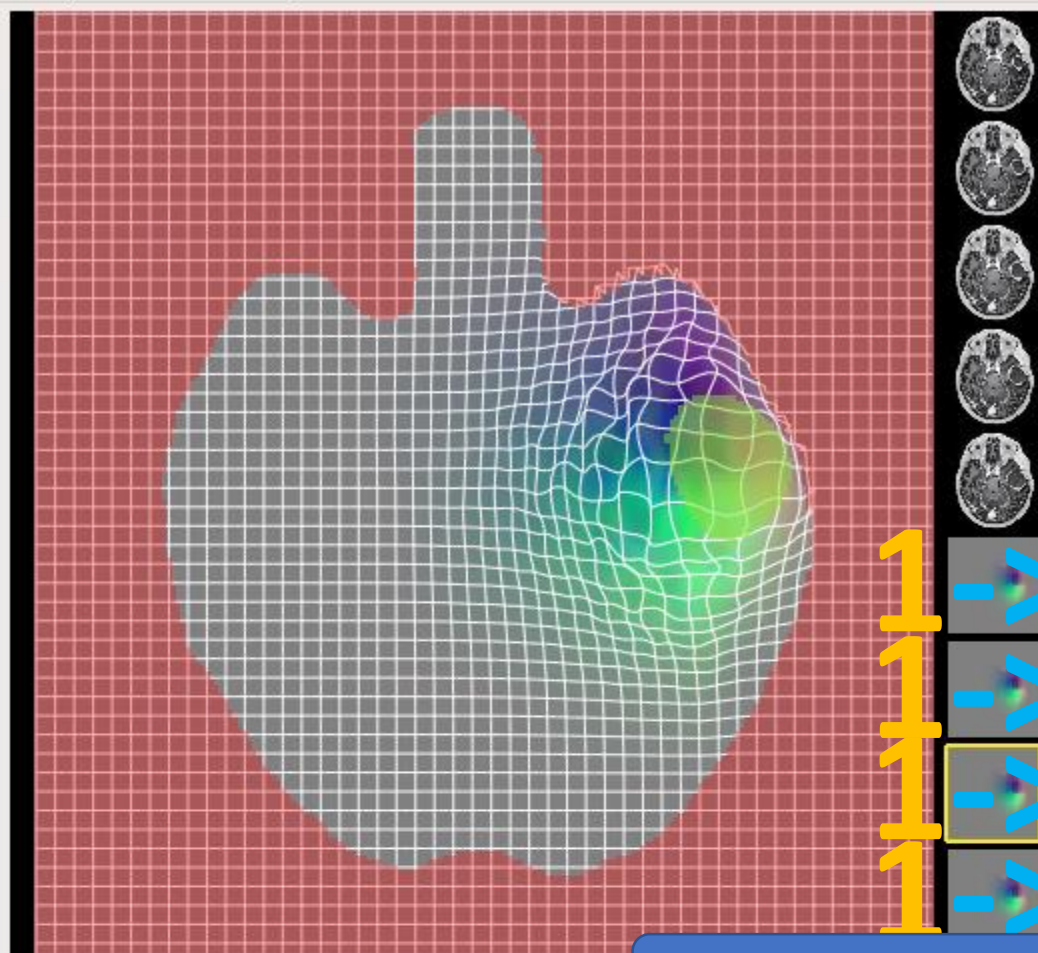
47 121 136

Intensity under cursor:

Layer	Intensity
1-T1c	1.3...
1-tumormask	1
2-brainmask	1
warped	1.4...
warped	1.5...
warped	1.3...

Label under cursor:

0 Clear Label



Ground truth displacement fields

Image Layer Inspector - ITK-SNAP

General Contrast Color Map Info Metadata

Linear Contrast Adjustment:

Minimum: -10,176 Level: -0,202 Reset

Maximum: 9,771 Window: 19,947 Auto

Curve-Based Contrast Adjustment:

Index into Color Map

Image Intensity

Selected control point:

Id: 1 x: -10,176 y: 0,000

Histogram Display Options:

1-T1c

Additional Images

1-tumormask

2-brainmask

warped

warped

warped

warped

warped

Active label

Label

Paint over:

All labels

Overall label

50

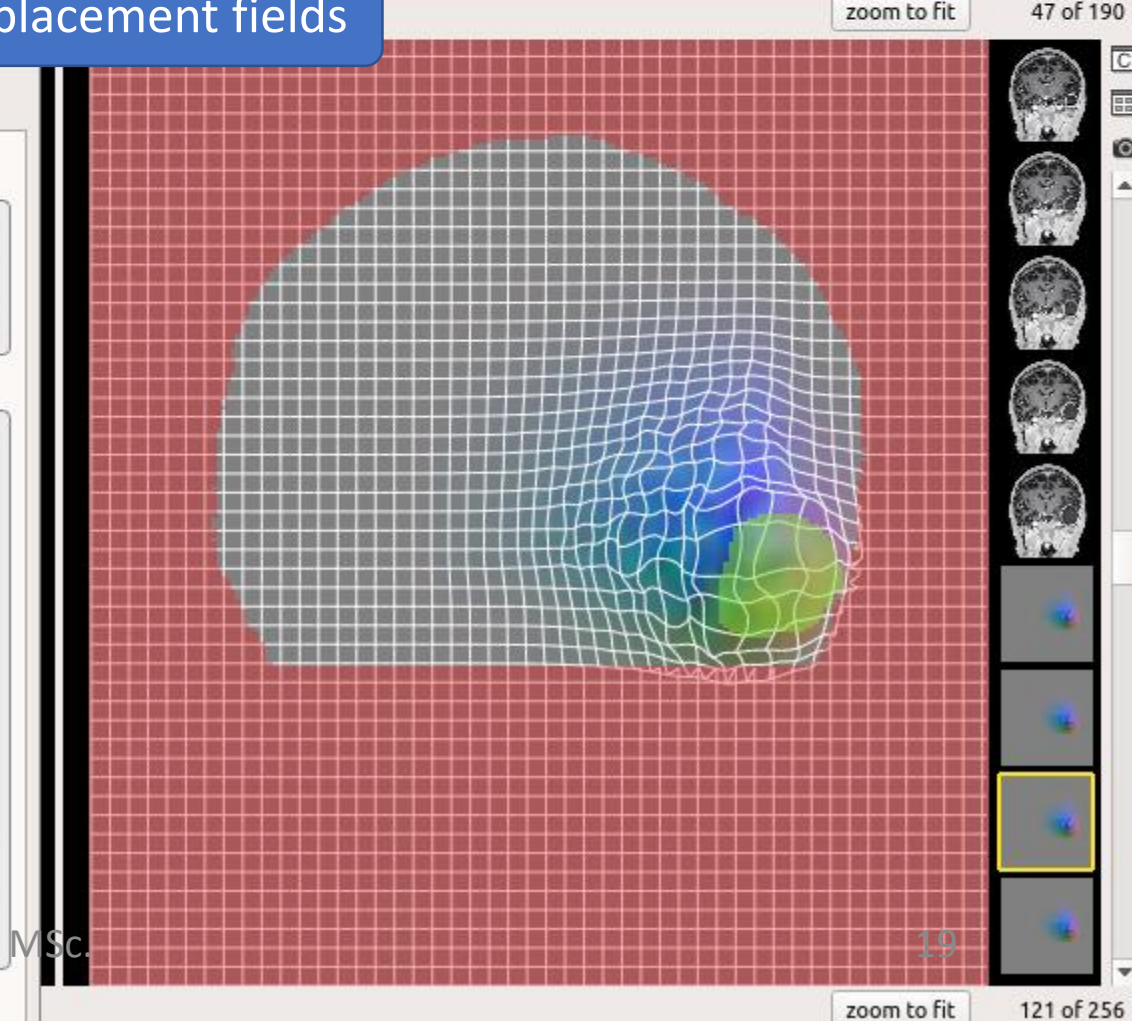
3D Toolbar

inter-neg-field-3

inter-neg-field-6

inter-neg-field-9

inter-neg-field-12





Cursor position (x,y,z):

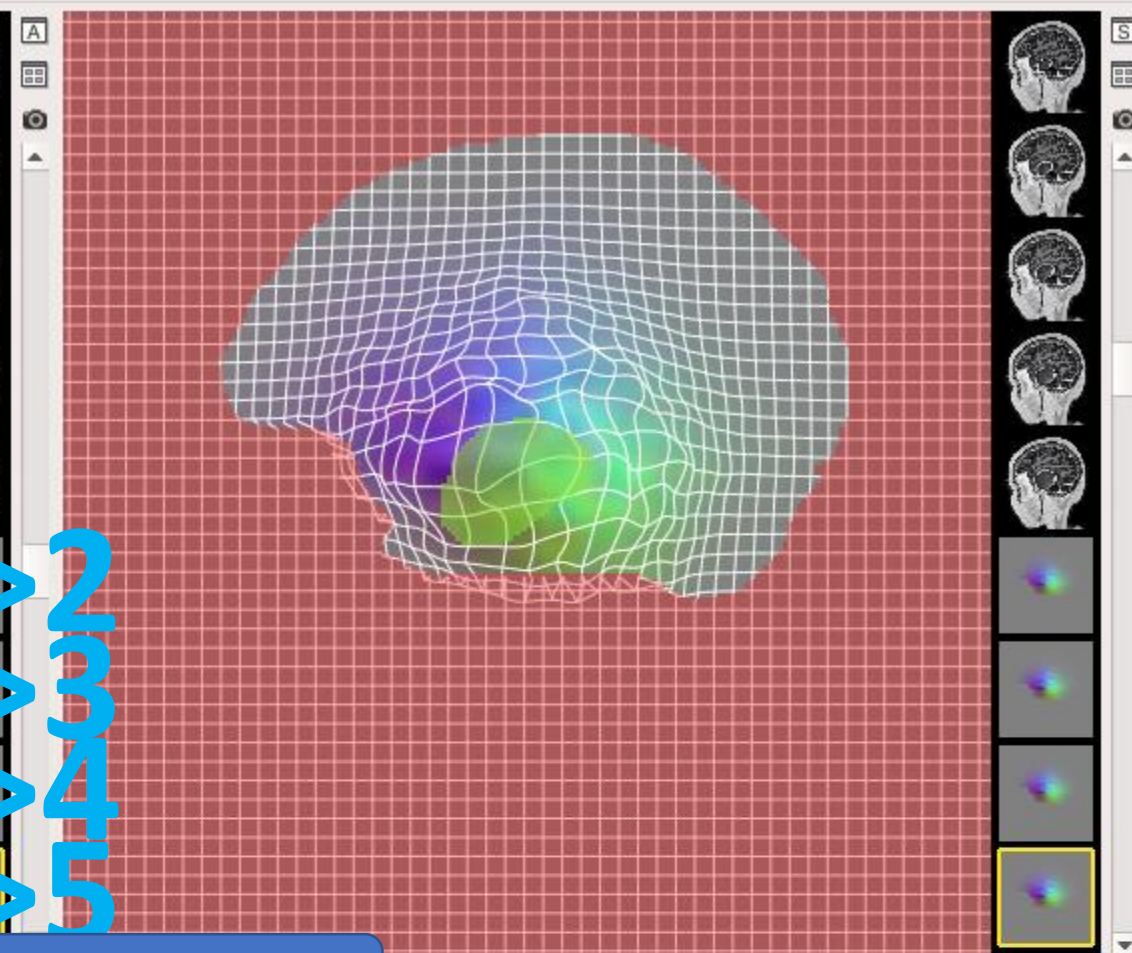
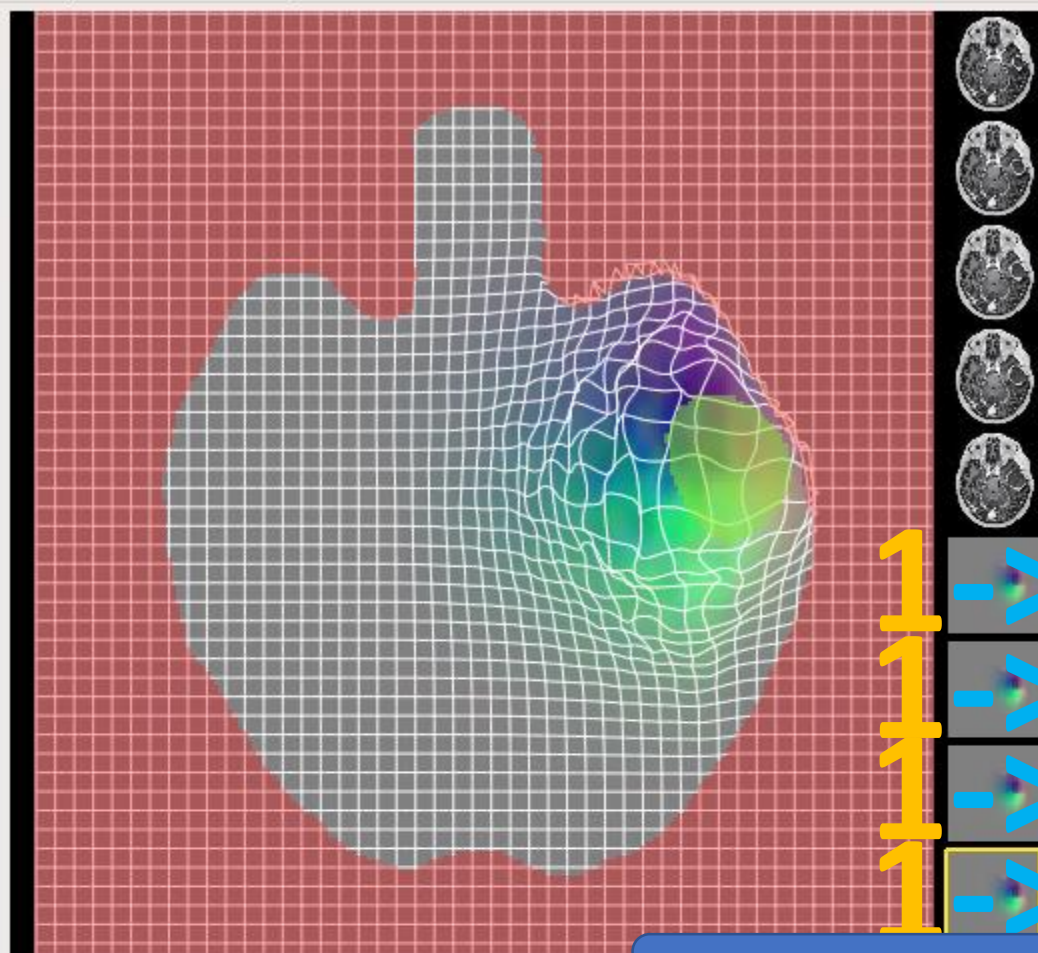
47 121 136

Intensity under cursor:

Layer	Intensity
1-T1c	1.3...
1-tumormask	1
2-brainmask	1
warped	1.4...
warped	1.5...
warped	1.3...

Label under cursor:

0 Clear Label



Ground truth displacement fields

Image Layer Inspector - ITK-SNAP

General Contrast Color Map Info Metadata

Linear Contrast Adjustment:

Minimum: -13,568 Level: -0,270 Reset

Maximum: 13,028 Window: 26,597 Auto

Curve-Based Contrast Adjustment:

Index into Color Map

Image Intensity

Selected control point:

Id: 1 x: -13,568 y: 0,000

Histogram Display Options:

1-T1c

Additional Images

1-tumormask

2-brainmask

warped

warped

warped

warped

warped

warped

Active label

Label

Paint over:

All labels

Overall label

50

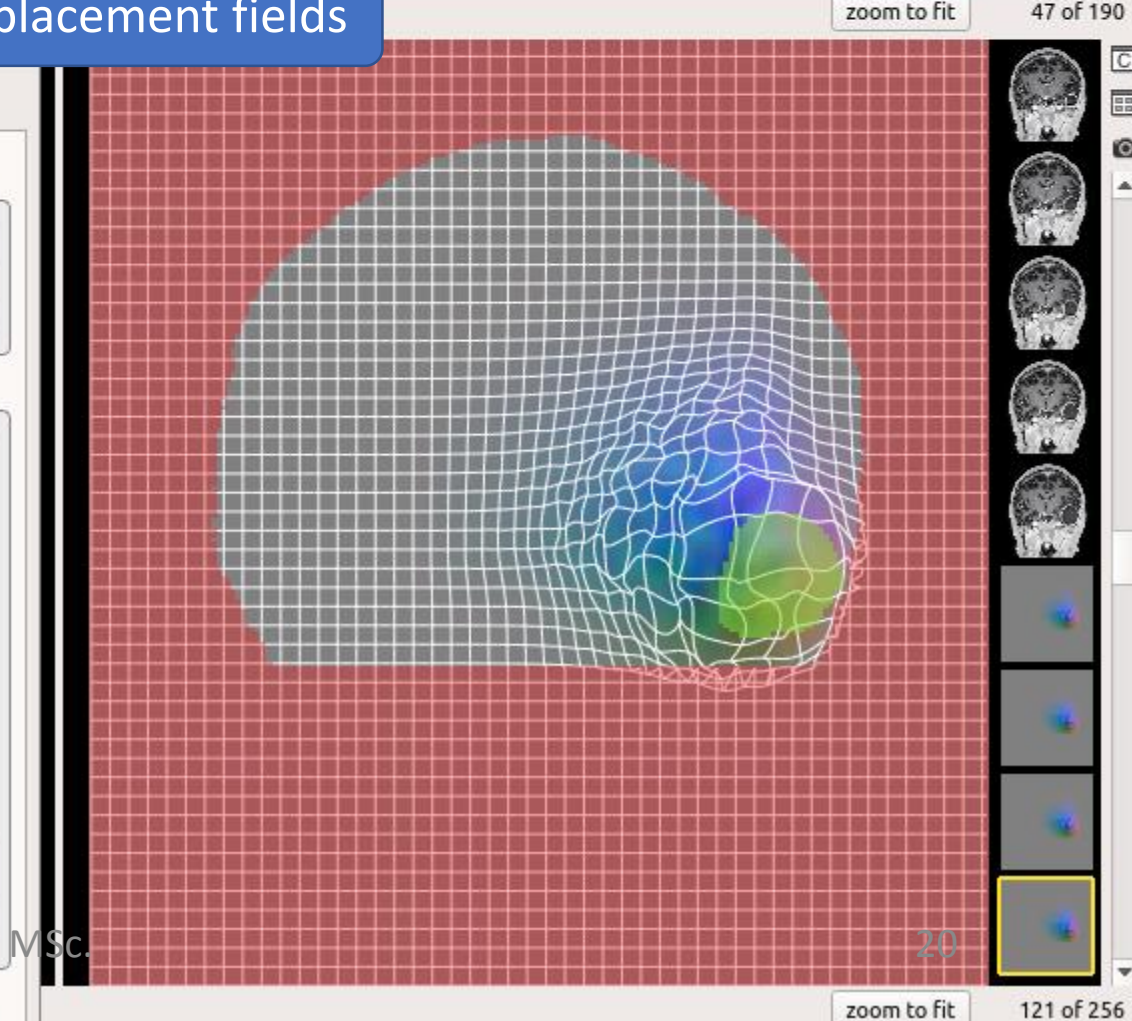
3D Toolbar

inter-neg-field-3

inter-neg-field-6

inter-neg-field-9

inter-neg-field-12



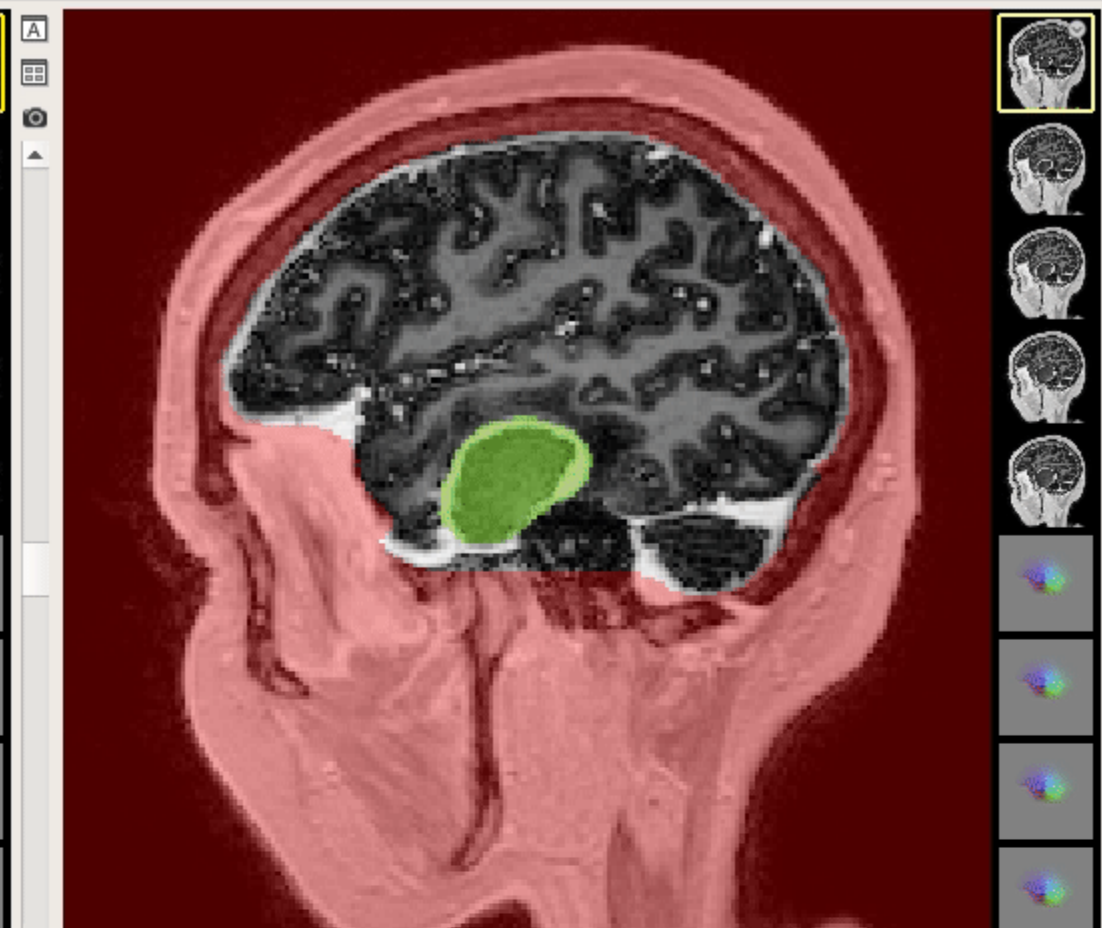


Cursor position (x,y,z):

47	121	136
----	-----	-----

Label under cursor:

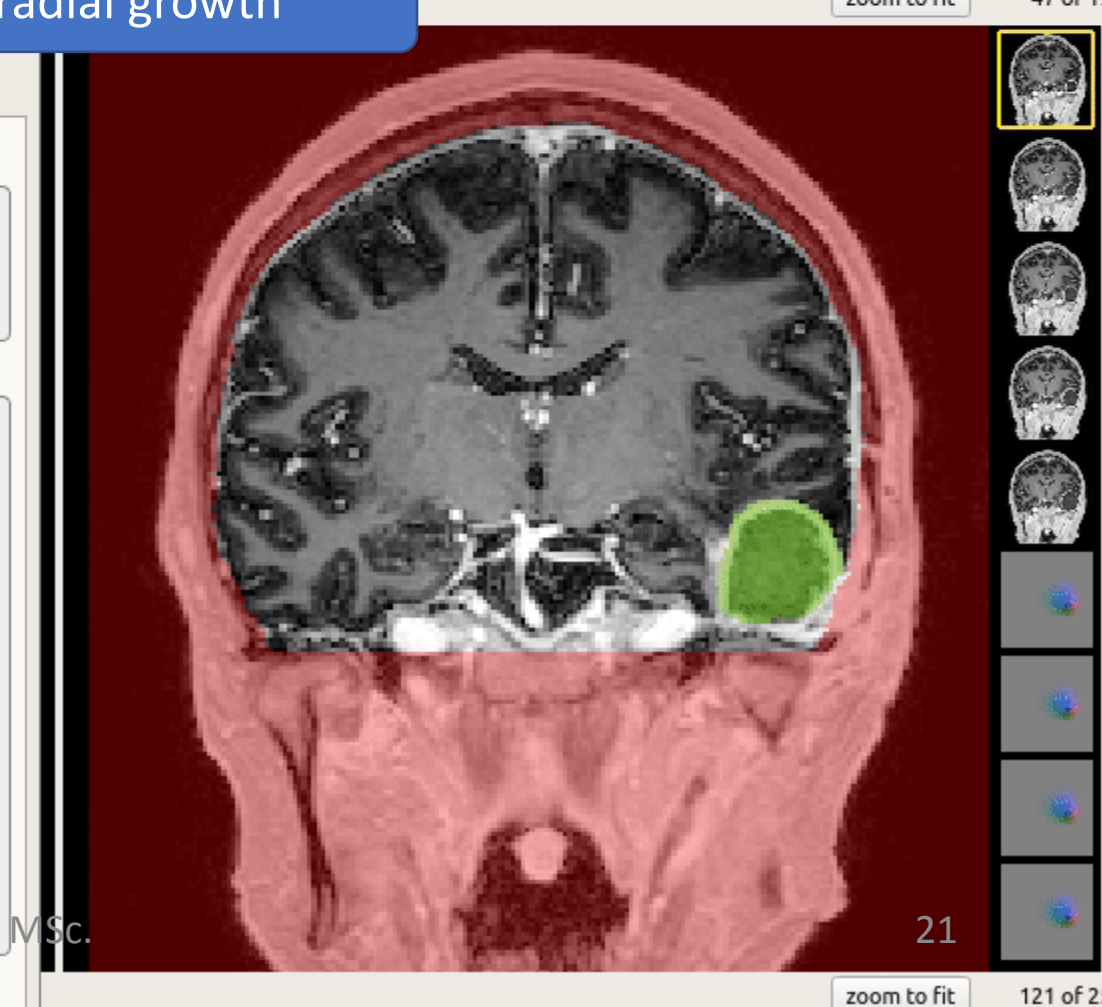
0 Clear Label



Simulated radial growth

zoom to fit

47 of 190



zoom to fit

121 of 256



Cursor position (x,y,z):

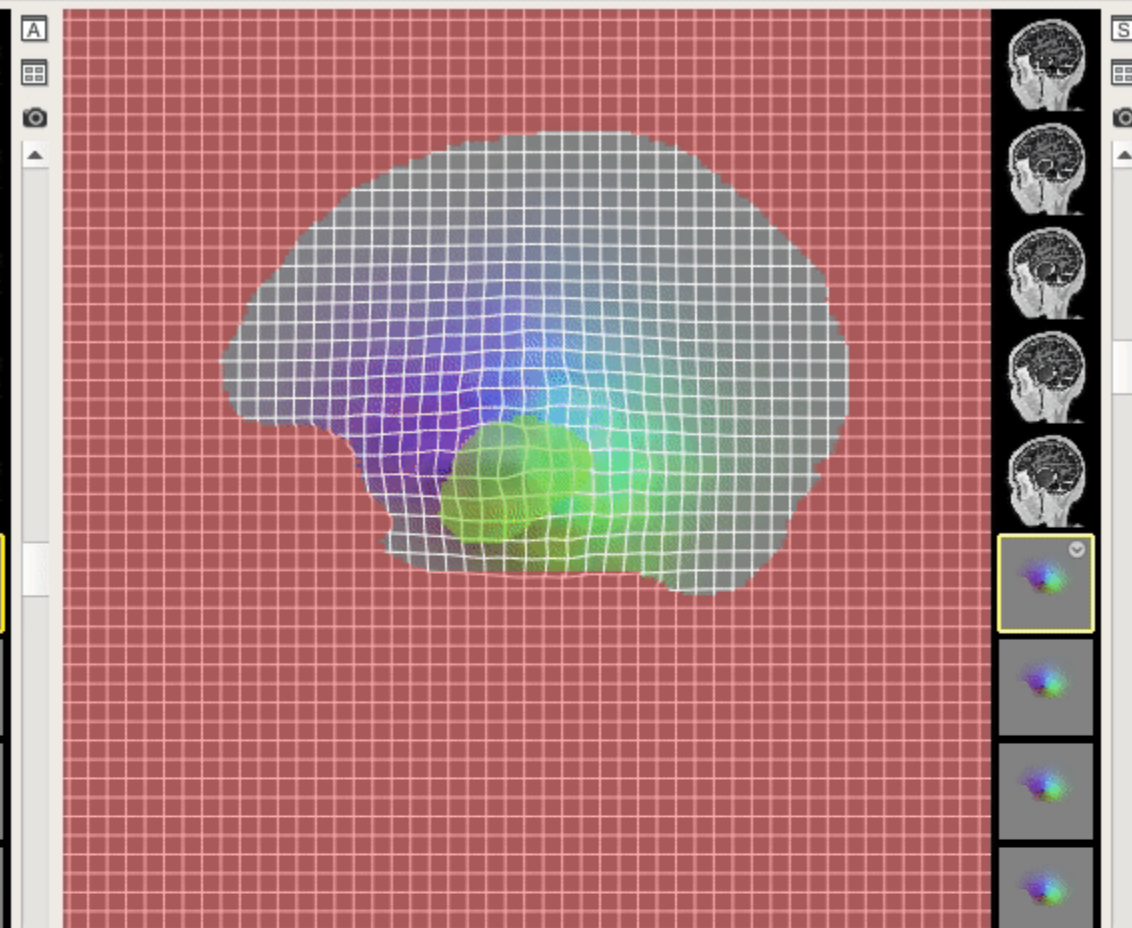
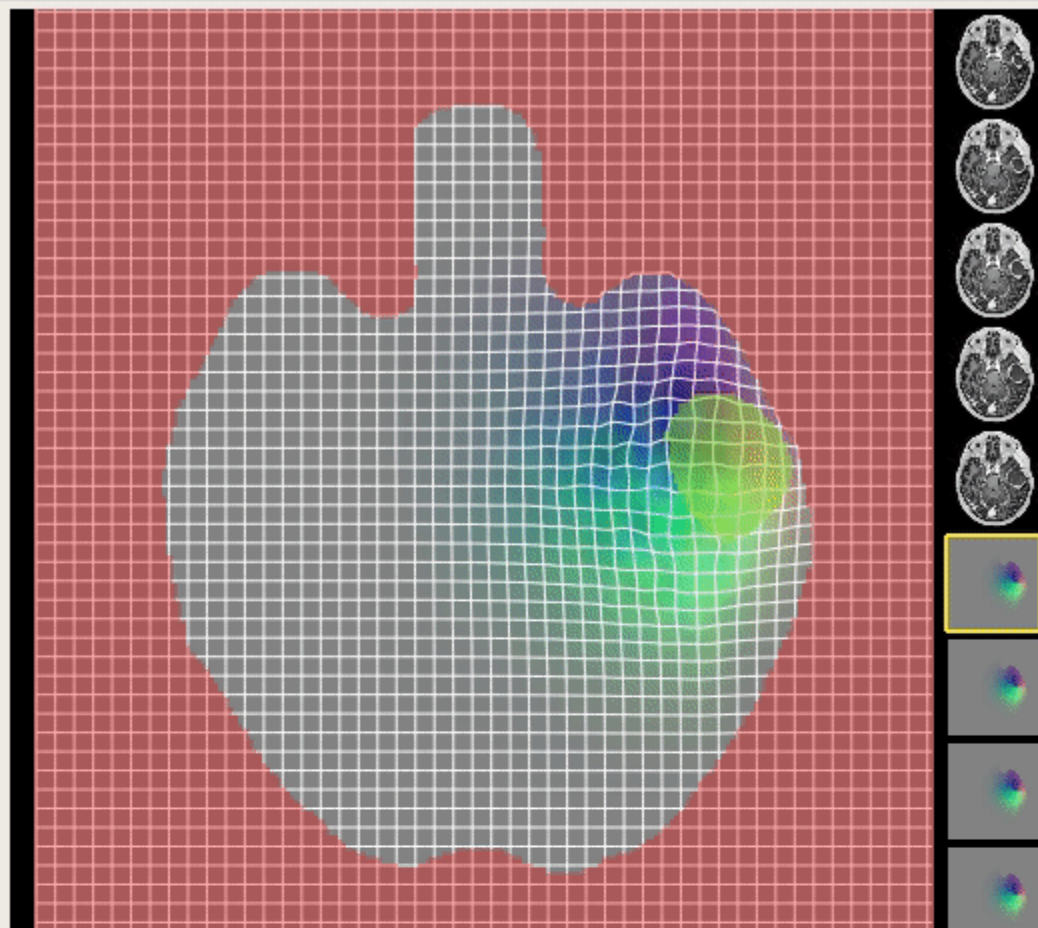
47 121 136

Intensity under cursor:

Layer	Intensity
1-T1c	1.3...
1-tumormask	1
2-brainmask	1
warped	1.4...
warped	1.5...
warped	1.3...

Label under cursor:

0 Clear Label



Ground truth displacement fields

zoom to fit

47 of 190

Image Layer Inspector - ITK-SNAP

General Contrast Color Map Info Metadata

Linear Contrast Adjustment:

Minimum: -3,392 Level: -0,067 Reset

Maximum: 3,257 Window: 6,649 Auto

Curve-Based Contrast Adjustment:

Index into Color Map

Image Intensity

Selected control point:

Id: 1 x: -3,392 y: 0,000

Histogram Display Options:

1-T1c

Additional Images

1-tumormask

2-brainmask

warped

warped

warped

warped

warped

warped

Active label

Label

Paint over:

All labels

Overall label

50

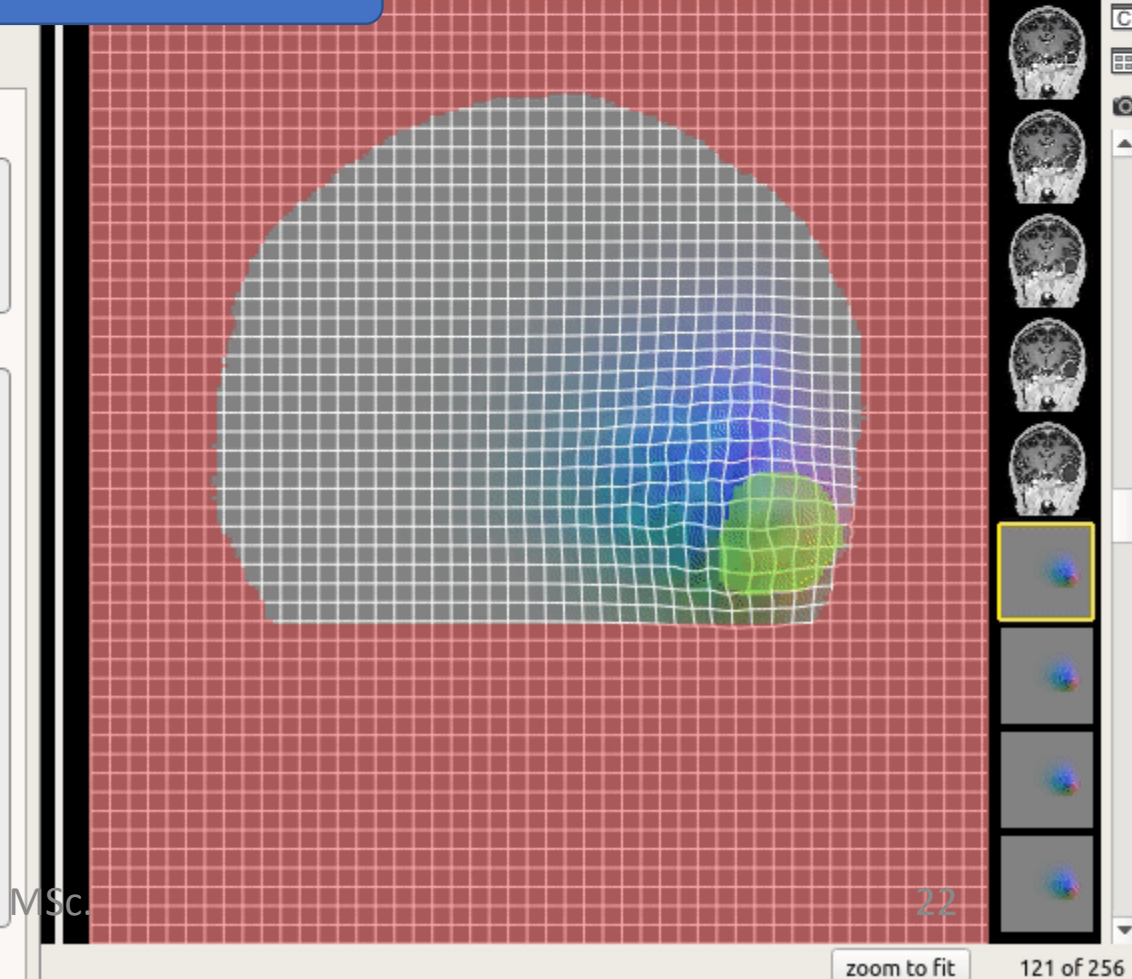
3D Toolbar

inter-neg-field-3

inter-neg-field-6

inter-neg-field-9

inter-neg-field-12



zoom to fit

121 of 256

ITK-SNAP Toolbox

Main Toolbar



Cursor Inspector



Cursor position (x,y,z):

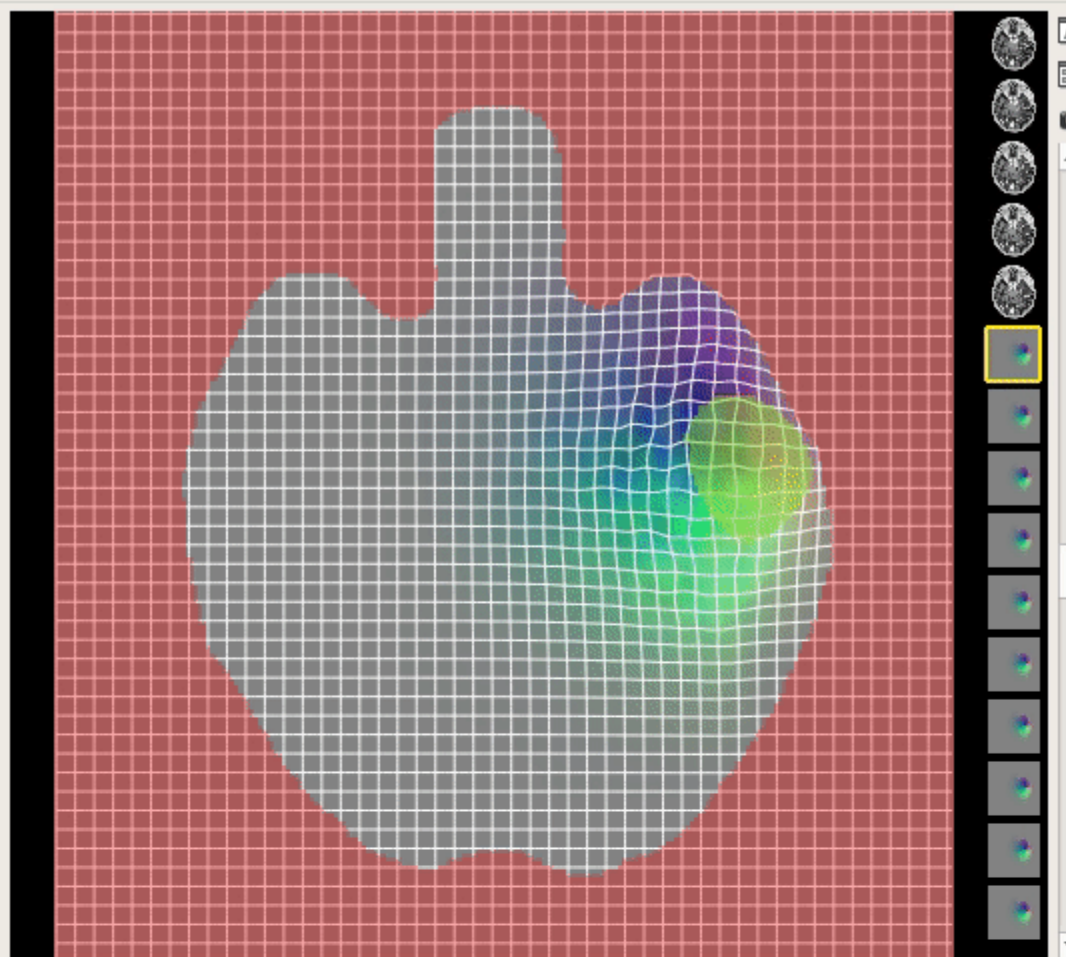
47 121 136

Intensity under cursor:

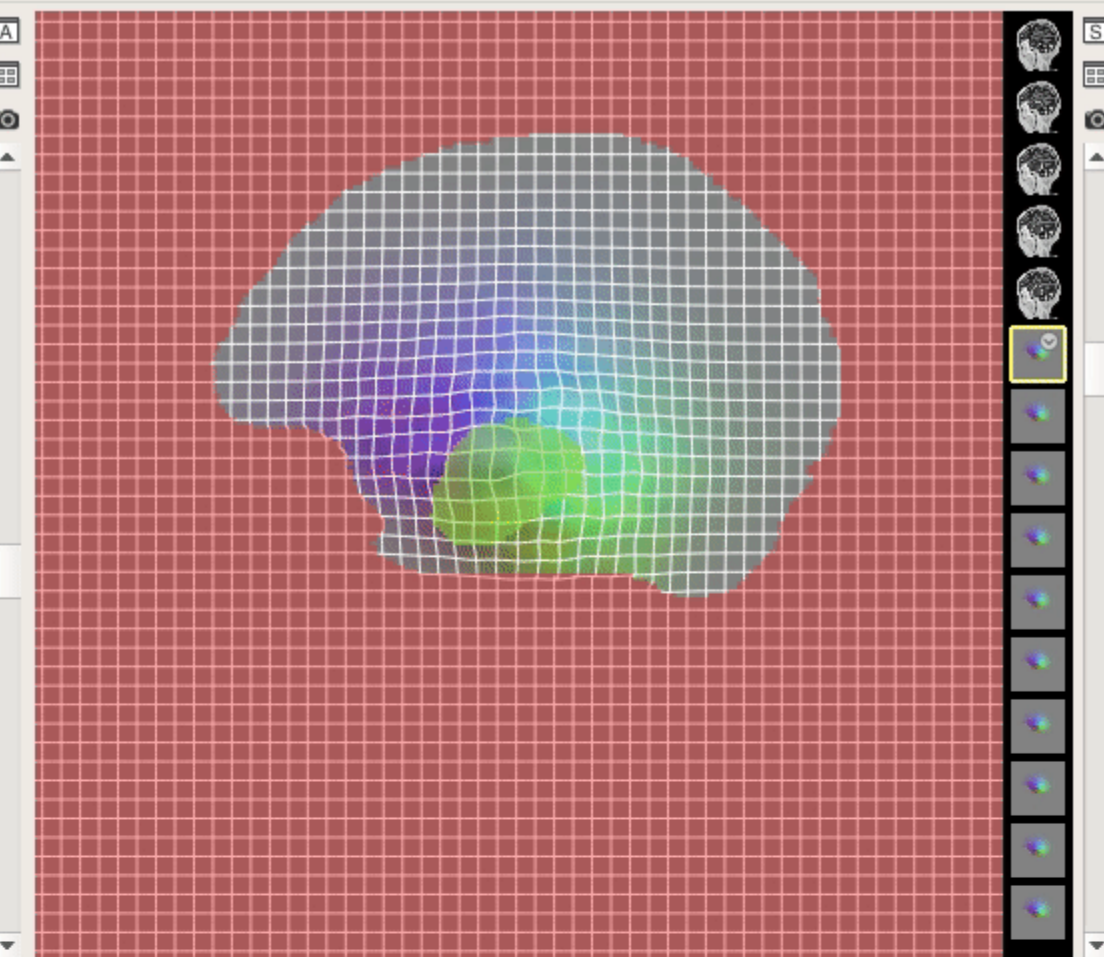
Layer	Intensity
1-T1c	1.3...
1-tumormask	1
2-brainmask	1
warped	1.4...
warped	1.5...
warped	1.3...

Label under cursor:

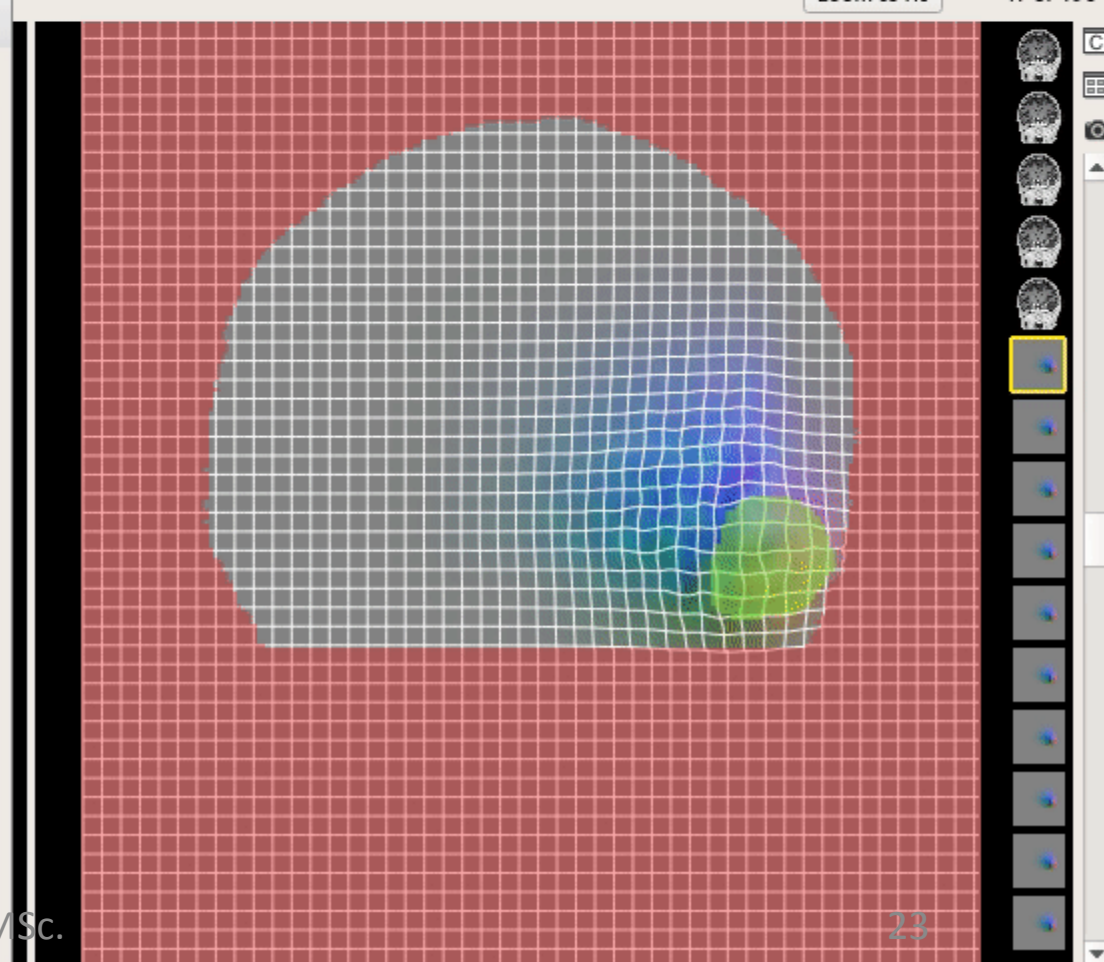
0 Clear Label



zoom to fit 136 of 256



zoom to fit 47 of 190



zoom to fit 121 of 256

Image Layer Inspector - ITK-SNAP

General Contrast Color Map Info Metadata

General Image Layer Properties:

Filename: sim-example/models/0001/interp-neg-field-3.0mm.nii.gz

Nickname:

How to Display this Image Layer:

Display as: ☒ Separate image ☐ Semi-transparent overlay

Overlay opacity:

Display order:

How to Visualize Multiple Image Components:

Display mode: Deformation Grid Display

Component:

Segmentation

Active label: ☒ Label

Paint over: ☒ All labels

Overall label: 50

3D Toolbar

warped

interp-neg-field-3 Grid

interp-neg-field-6 Grid

interp-neg-field-9 Grid

interp-neg-field-12 Grid

interp-neg-field-15 Grid

interp-neg-field-18 Grid

interp-neg-field-21 Grid

interp-neg-field-24 Grid

interp-neg-field-27 Grid

interp-neg-field-30 Grid



Cursor position (x,y,z):

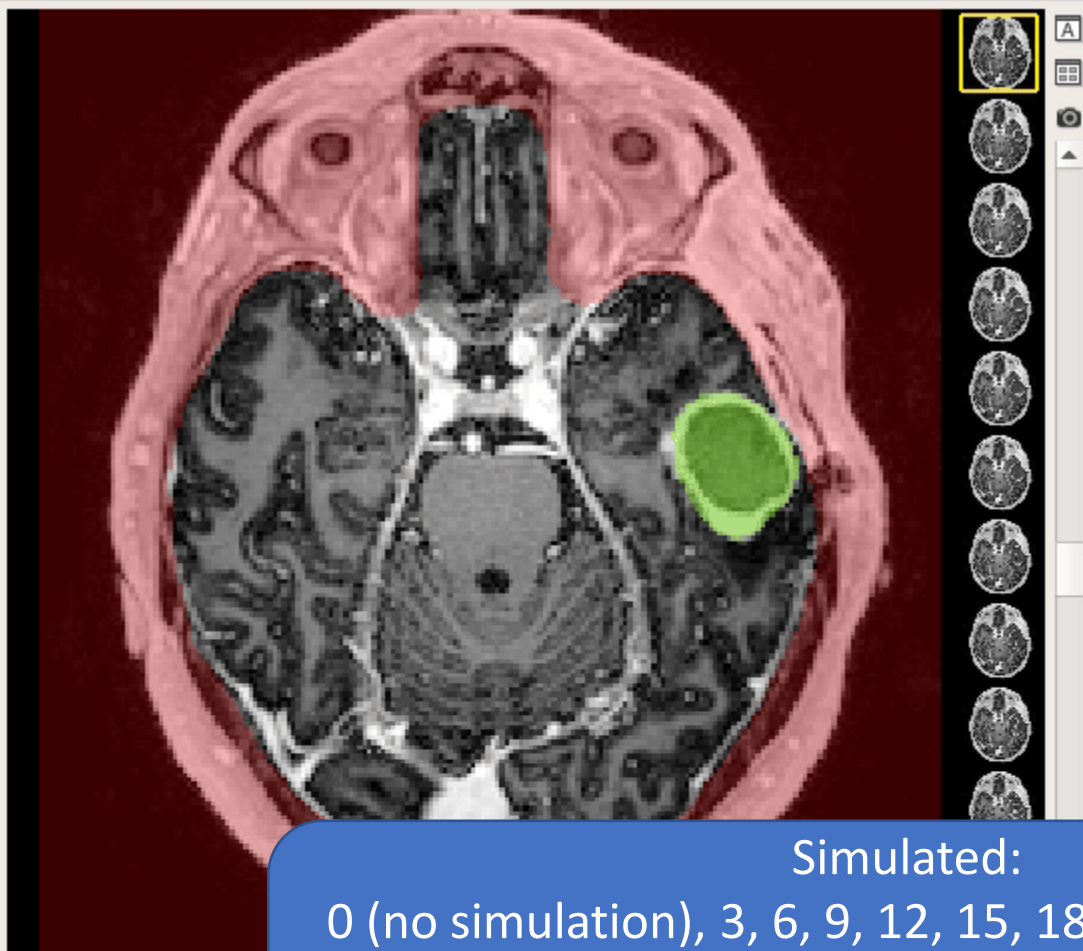
47 121 136

Intensity under cursor:

Layer	Intensity
1-T1c	1.3...
1-tumormask	1
2-brainmask	1
warped	1.4...
warped	1.5...
warped	1.3...

Label under cursor:

0 Clear Label



Simulated:
 0 (no simulation), 3, 6, 9, 12, 15, 18, 21, 24, 27 and 30
mm maximum displacement magnitude
 = 10 synthetic growth models
 Artefacts appear from 18 *mm* and larger

Image I

Gener

Linear Contrast Adjustment:

Minimum: 0 Level: 962451 Reset

Maximum: 1924903 Window: 1924903 Auto

Curve-Based Contrast Adjustment:

Selected control point:

Id: 2 x: 359629 y: 0,496

Histogram Display Options:

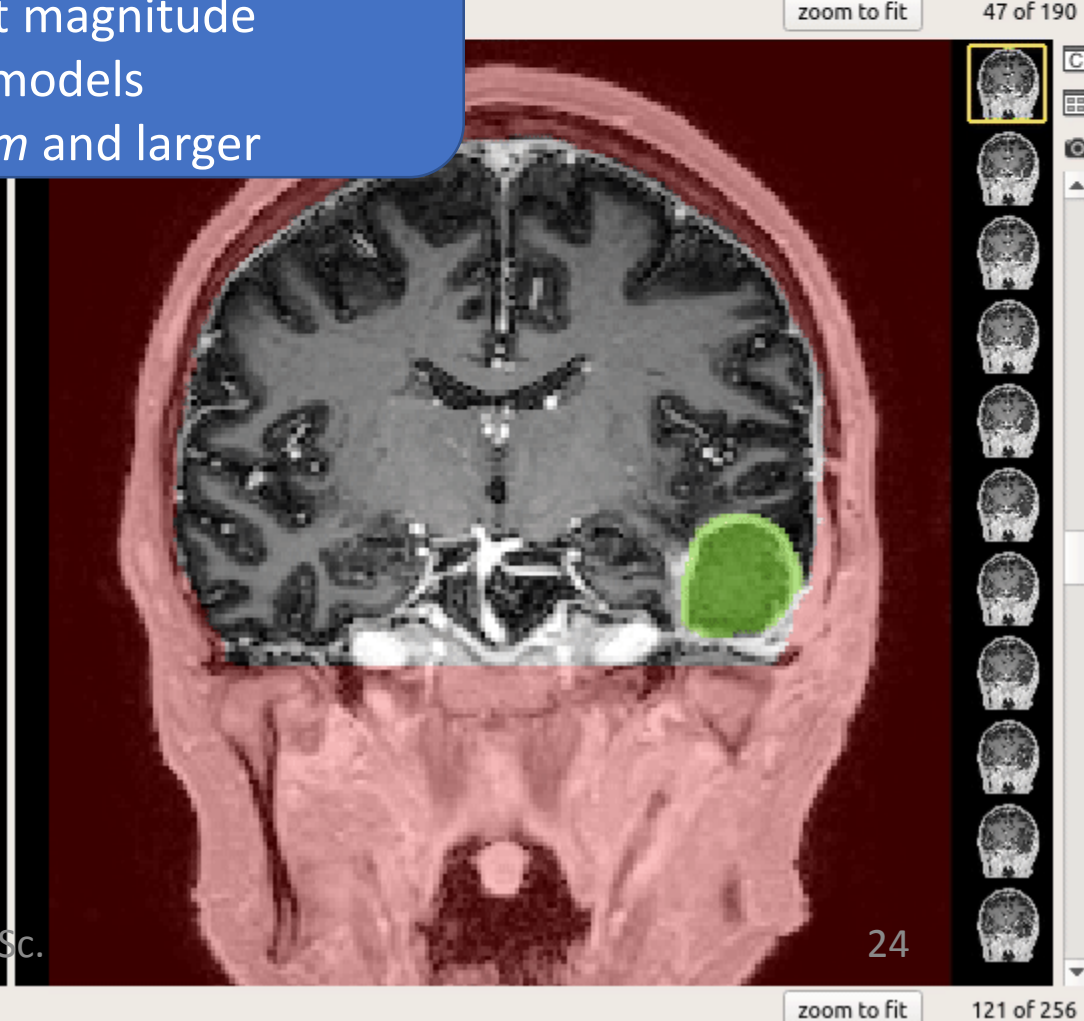
Segmentation

Active label: Label

Paint over: All lab

Overall label: 50

3D Toolbar



Example: From DICOM to synthetic growth models + cross-correlation assessment using second examination

Download and run cancer-sim

```
$ git clone https://github.com/ivartz/cancer-sim
```

```
$ bash cancer-sim/generate-models.sh params.txt derivatives/1-T1c.nii.gz derivatives/1-tumormask.nii.gz derivatives/1-brainmask.nii.gz models
```

Co-register real second time point MRI to real first time point MRI

```
$ bash cancer-sim/antsRigidRegister.sh derivatives/1-T1c.nii.gz derivatives/2-T1c.nii.gz derivatives/1-brainmask.nii.gz derivatives/reg
```

Compute and save cross-correlation similarities between (co-registered) real second time point MRI and model MRIs

```
$ bash cancer-sim/compute-cc-models.sh derivatives/reg/2-T1c-reg.nii.gz derivatives/1-brainmask.nii.gz models > models/correlations.txt
```

Five non-rigid registration methods estimating displacement fields

- Optical flow: Gunnar-Farneback¹, Iterative Lucas-Kanade² and TV-L1³ versions
- ANTs: Symmetric image Normalization (SyN)^{4,5}, cross-correlation⁴ and mutual information versions

- 1) Farnebäck, Gunnar. "Two-frame motion estimation based on polynomial expansion." *Scandinavian conference on Image analysis*. Springer, Berlin, Heidelberg, 2003.
- 2) Le Besnerais, Guy, and Frédéric Champagnat. "Dense optical flow by iterative local window registration." *IEEE International Conference on Image Processing 2005*. Vol. 1. IEEE, 2005.
- 3) Zach, Christopher, Thomas Pock, and Horst Bischof. "A duality based approach for realtime tv-l1 optical flow." *Joint pattern recognition symposium*. Springer, Berlin, Heidelberg, 2007.
- 4) Avants, Brian B., et al. "Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain." *Medical image analysis* 12.1 (2008): 26-41.
- 5) Avants, Brian, C. L. Epstein, and James C. Gee. "Geodesic image normalization in the space of diffeomorphisms." 2006.

Benchmarking

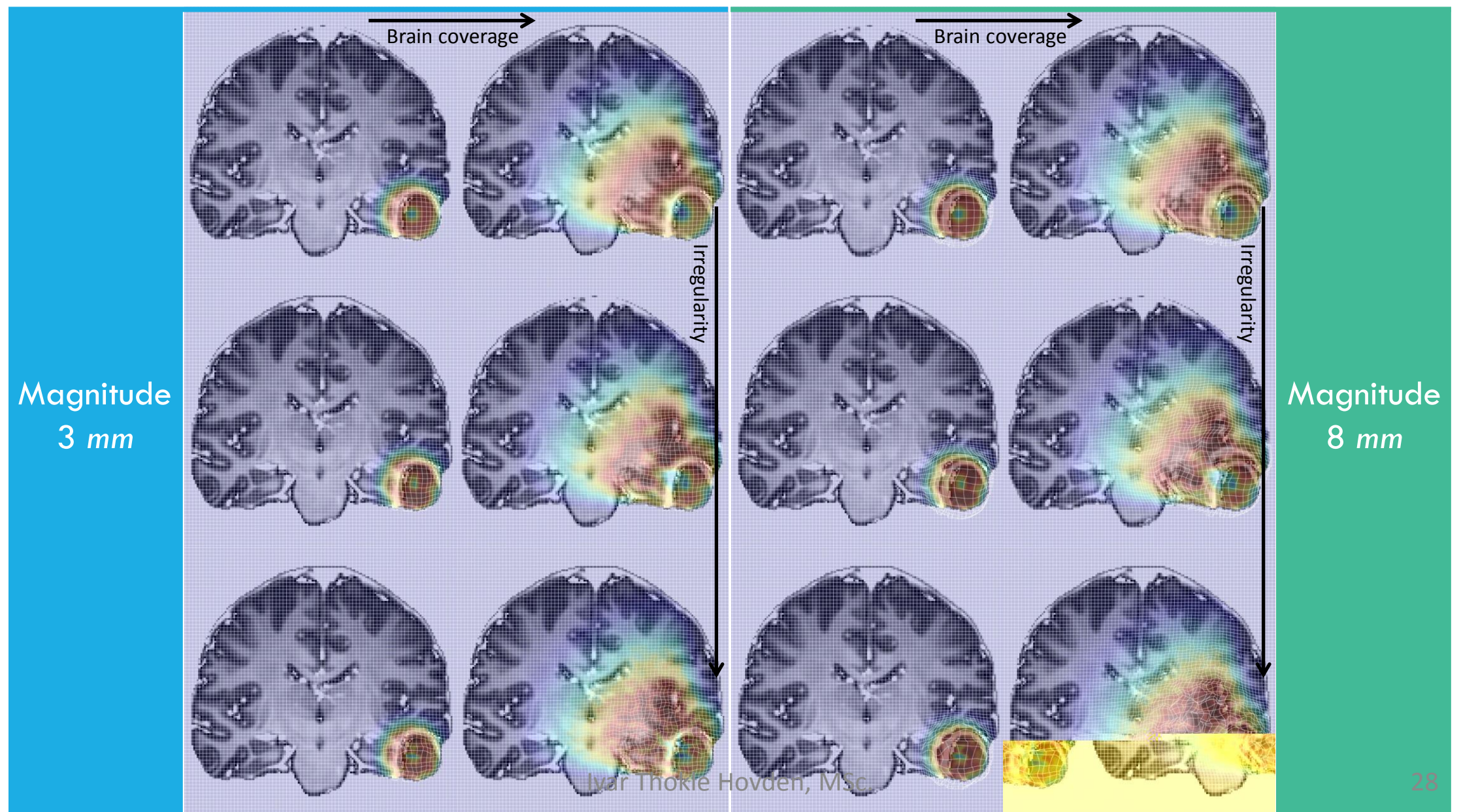
- Created dataset of 27 (patients) * 12 (models) = 324 models

Models
patient

Model	Magnitude [<i>mm</i>]	Brain coverage	Irregularity
1	3	High	No
2	3	High	High
3	3	High	Intermediate
4	3	Low	No
5	3	Low	High
6	3	Low	Intermediate
7	8	High	No
8	8	High	High
9	8	High	Intermediate
10	8	Low	No
11	8	Low	High
12	8	Low	Intermediate

Benchmarking

- Created dataset of 27 (patients) * 12 (models) = 324 models



Benchmarking

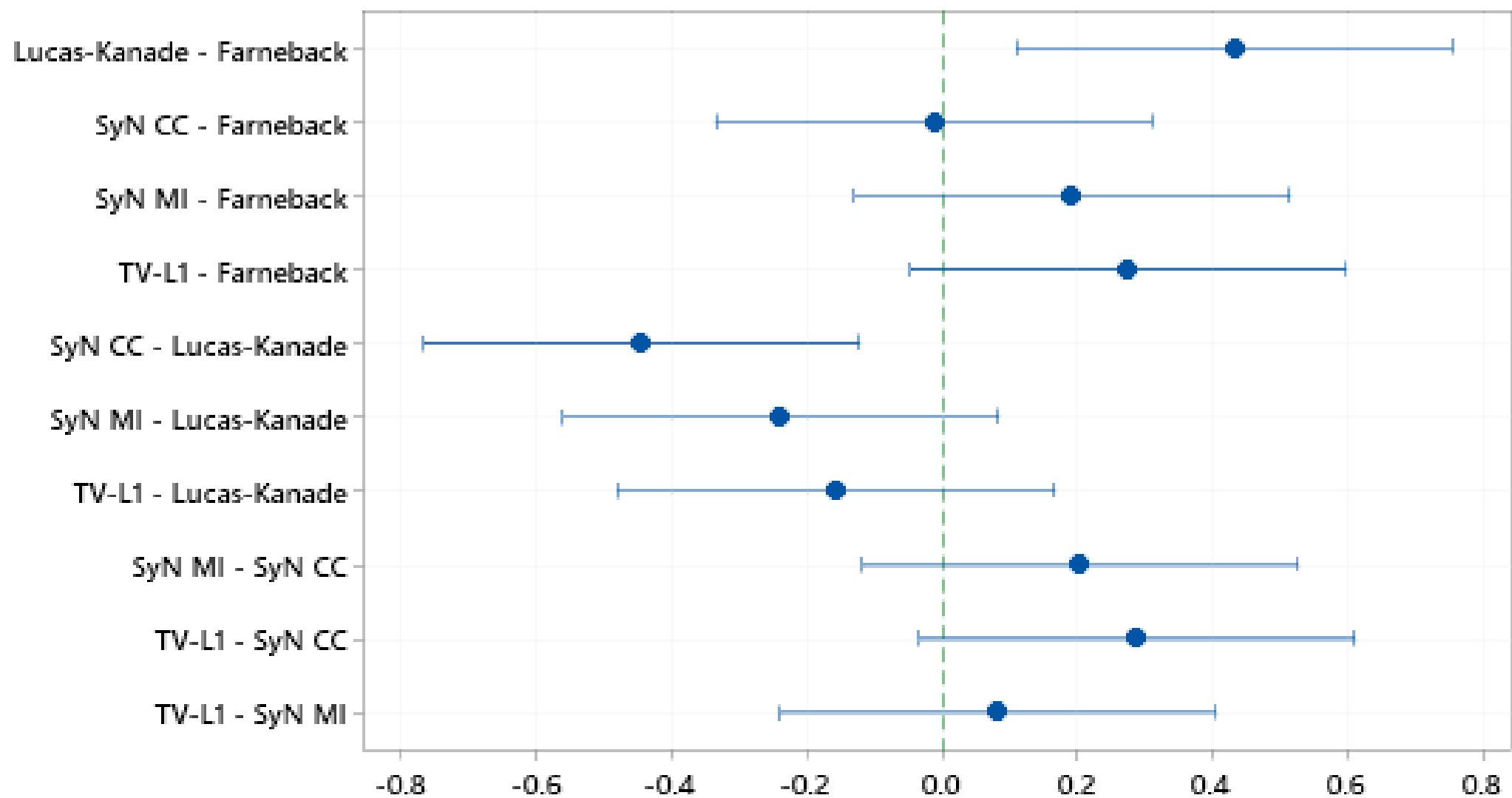
- Created dataset of 27 (patients) * 12 (models) = 324 models
- Ran the five registration methods on 324 real-synthetic pairs to estimated displacement fields
- Computed voxel-wise absolute and relative displacement error in necrotic, edema and enhancing tumor regions
- Kruskal-Wallis (K-W) and One-way ANOVA analysis on absolute and relative errors to investigate differences in registration performance as function of model parameters, registration method and lesion tissue type

Results

- Difference in method performances (relative errors) for low and high brain coverage (K-W, $p=0.02$). Best performance for high brain coverage.
- SyN CC and Farneback methods had best performances with lowest absolute and relative errors (K-W, ANOVA; $p<0.037$).

Tukey Simultaneous 95% CIs

Differences of Means for ln (Relative error)



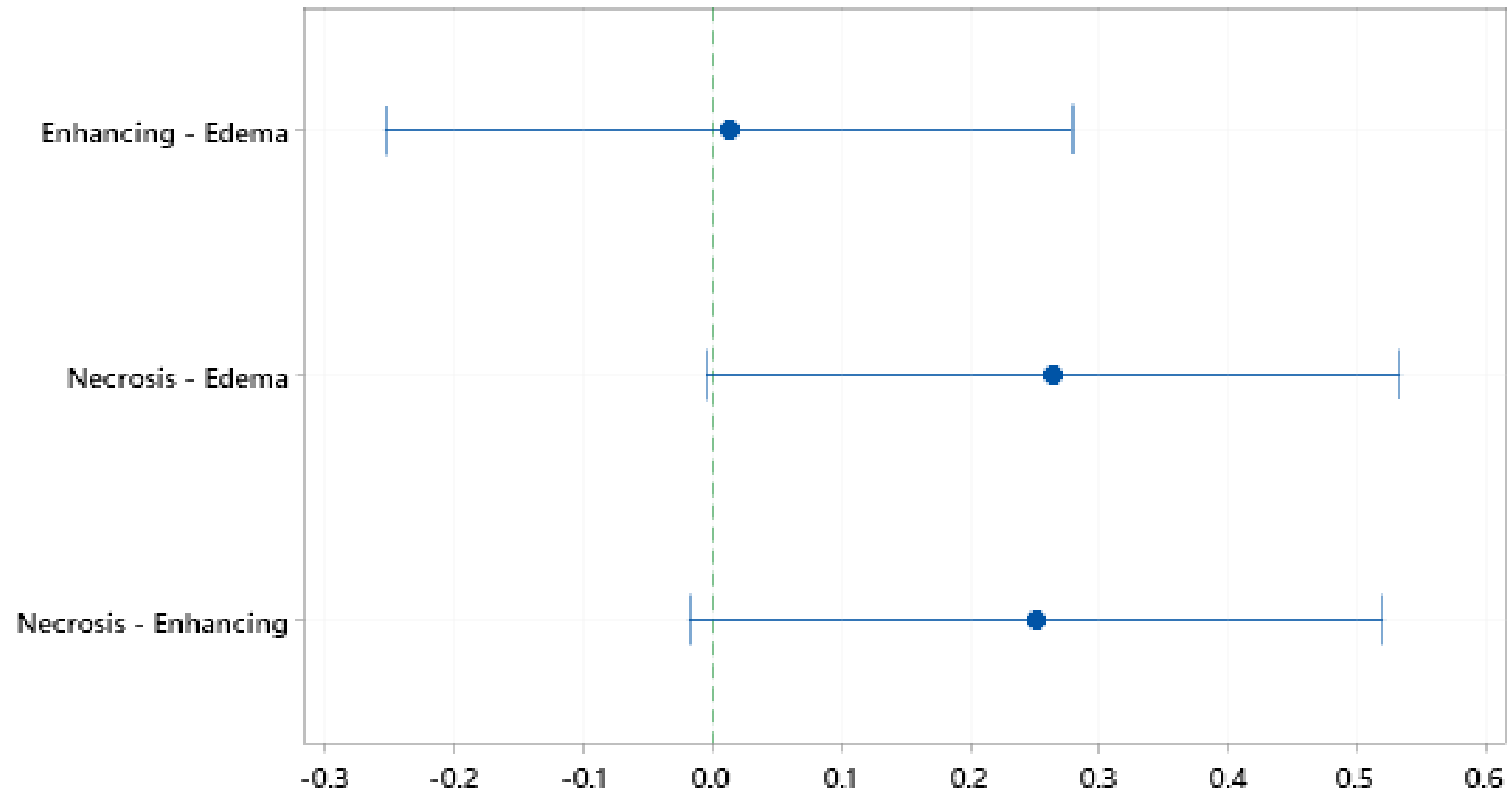
If an interval does not contain zero, the corresponding means are significantly different.

Results

- Difference in method performances (relative errors) for low and high brain coverage (K-W, $p=0.02$). Best performance for high brain coverage.
- SyN CC and Farneback methods had best performances with lowest absolute and relative errors (K-W, ANOVA; $p<0.037$).
- Different performances as a function of tissue type (K-W; $p=0.019$, absolute error, ANOVA; $p\leq 0.035$, relative error). Best performance in enhancing tissue.

Tukey Simultaneous 95% CIs

Differences of Means for ln (Relative error)



If an interval does not contain zero, the corresponding means are significantly different.