MRI to Model for TTFields

Semi-Automated MRI Segmentation Workflow for Glioblastoma Treated by Tumor Treating Fields

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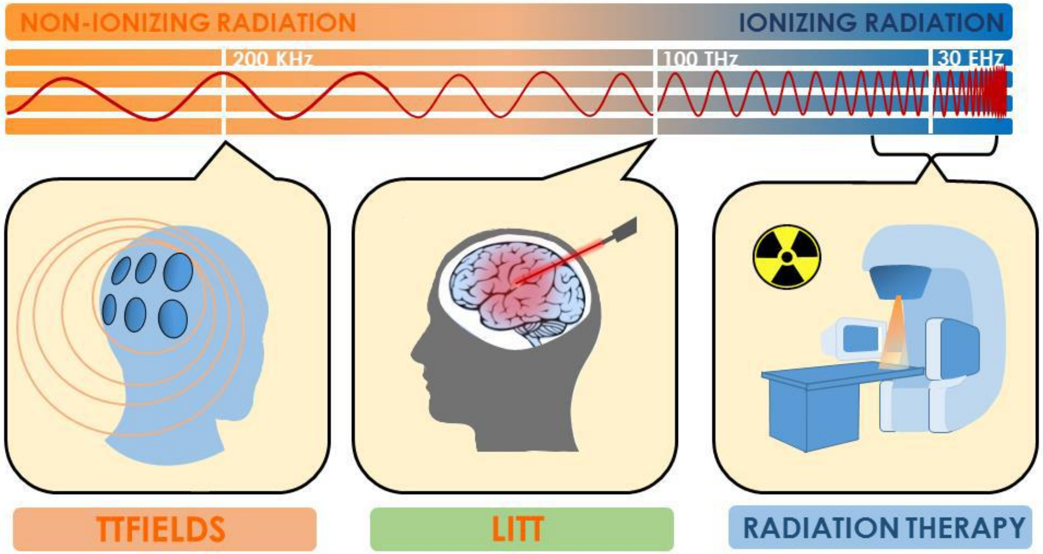
Tumor Treating Fields Improve PFS and OS

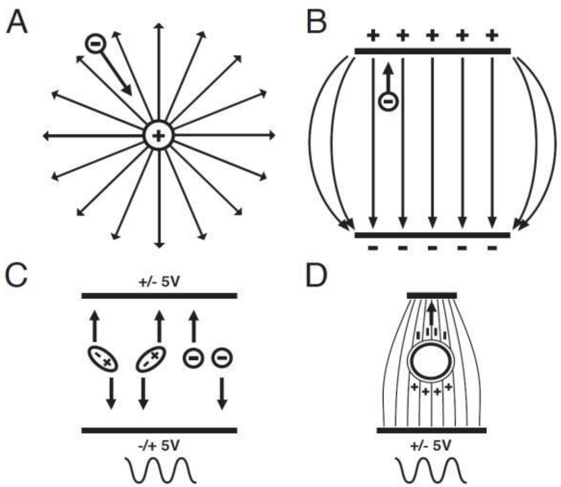
	TMZ alone (n=105)	TMZ + TTFields (n=210)
PFS (months)	4.0 (95% CI, 3.3-5.2)	7.1 (95% CI, 5.9-8.2)
OS (months)	15.6 (95% CI, 13.3-19.1)	20.5 (95% CI, 16.7-25.0)

Stupp R, Taillibert S, Kanner AA, et al. *JAMA,* 314(23):2535–2543. 2015.



Swanson KD, Lok E, Wong ET. *Tumor treating electric fields for glioblastoma*. In Brem S and Abdullah KG (Editors): *Glioblastoma*, Chapter 17, pp. 213-224, 2016.

Mechanisms of Action are Under Study



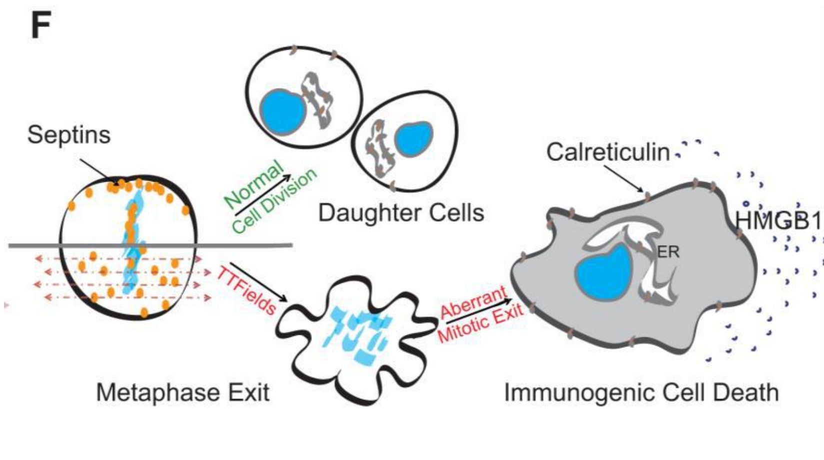
Gutin P, Wong ET. Presented at 2012 ASCO Annual Meeting Education Session; June 1-5, 2012; Chicago, IL. ASCO University website.

- Tubulin and/or Septin delocalization
- Modulation of voltage-sensing ion channels
- Ionic currents in the cytoplasm
- Microtubule alignment
- Kinesin transport disruption via tubulin C-termini effects

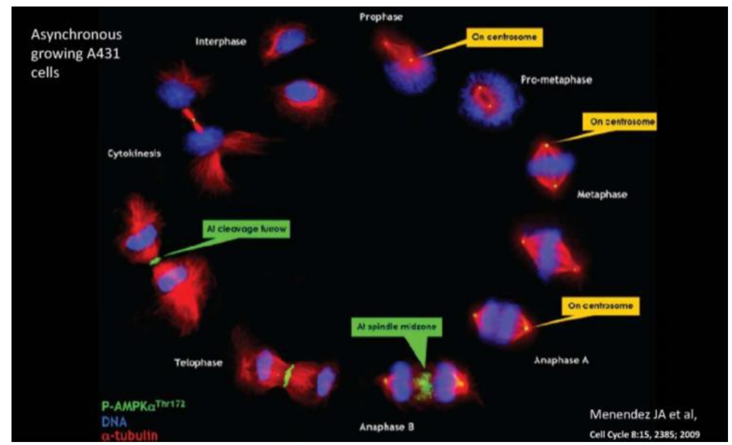
Gera N, Yang A, Holtzman TS, Lee SX, Wong ET, Swanson KD (2015) Tumor Treating Fields Perturb the Localization of Septins and Cause Aberrant Mitotic Exit. PLoS ONE 10(5): e0125269.

Tuszynski JA, Wenger C, Friesen DE, Preto J. An Overview of Sub-Cellular Mechanisms Involved in the Action of TTFields. Mattsson M-O, ed. *International Journal of Environmental Research and Public Health*. 2016;13(11):1128.

There are Cellular Effects

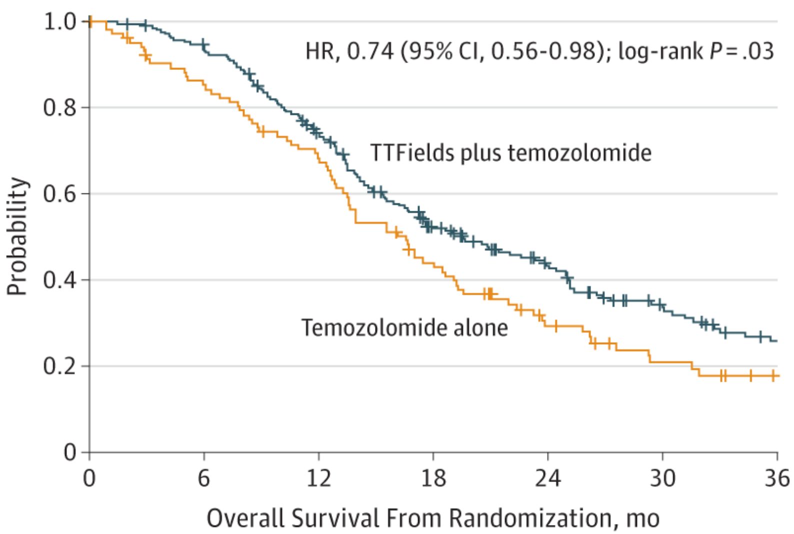


Wong ET, Lok E, Swanson KD.
Curr Treat Options Oncol
2015;16:40



Vazquez-Martin A, Oliveras-Ferraros C, Menendez JA, et al.
Cell Cycle 2009;8(15):2385-2398.

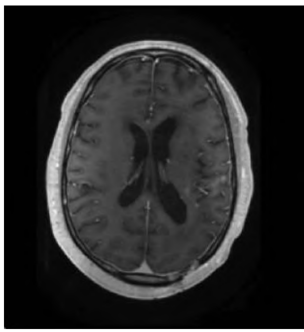
Unanswered Macroscopic Questions



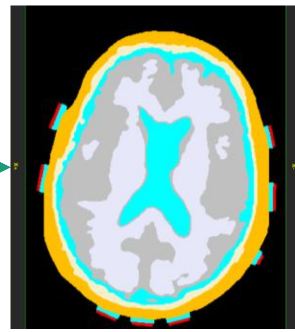
Stupp R, Taillibert S, Kanner AA, et al. (2015). *JAMA,* 314(23):2535–2543. 2015.

- Does electric field strength at the tumor correlate with improved outcomes?
- Predicting patient response beforehand
- Optimizing array placement to improve "dosage"
- Modulating CSF salinity and/or volume to improve patient outcome

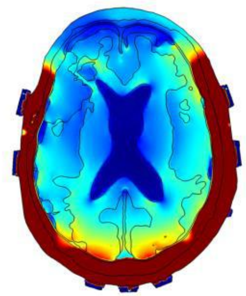
A Method for Answering Questions



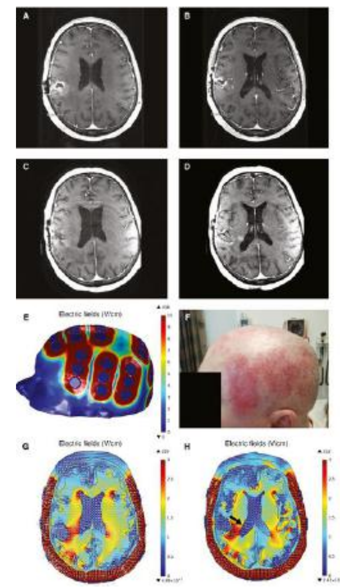
NIFTI MRI



White Matter
Gray Matter
Cerebellum/Brainstem
Cerebrospinal Fluid
Orbits
Skull
Scalp
Gel
Electrodes

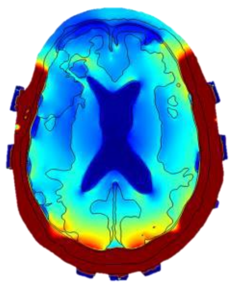


Physics model

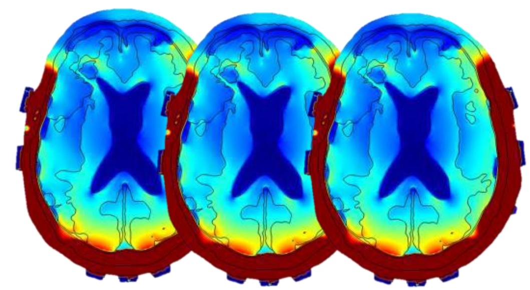


Lok, Edwin, Van Hua, and Eric T. Wong. "Computed modeling of alternating electric fields therapy for recurrent glioblastoma." *Cancer medicine* 4.11 (2015): 1697-1699.

More Models for More Significant Questions

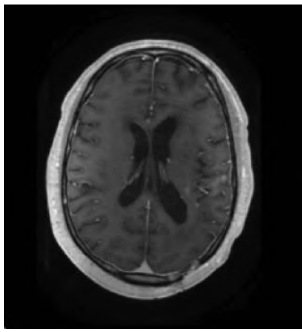


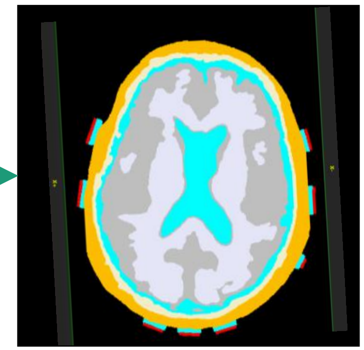
- What is the range of field strengths in patients?
- How does altering electrical conductivity, relative permittivity, CSF salinity, and tumor positioning affect the field strength in the tumor/GTV?



- Does electric field strength in the GTV/tumor even correlate with patient outcome?
- What is the hazard ratio of a 1V/cm difference in the necrotic core?
- Can differences in response be explained by tumor positioning, CSF volume, etc?

Steps to Generate a Model





Pre-processing

1. Convert DICOM to NIFTI
2. Register to MNI space

Segmentation

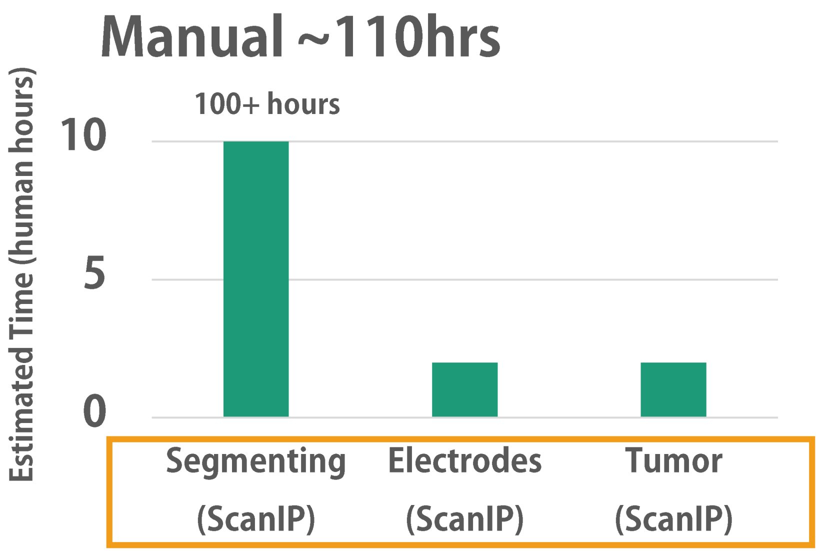
3. Segment White Matter, Gray Matter, Cerebellum/Brainstem, Cerebrospinal Fluid, Orbits, Skull, and Scalp

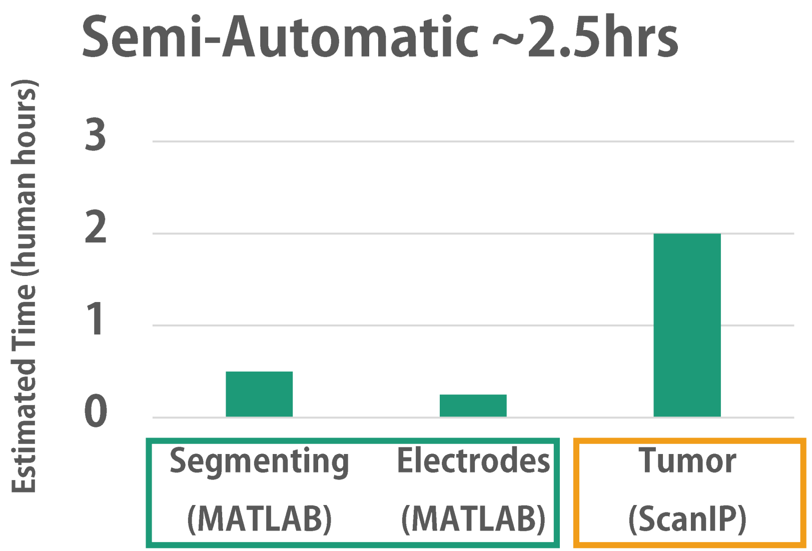
Post-processing

4. Add Tumor and GTV
5. Place Gel and Electrodes on Scalp's surface
6. Smooth masks in preparation for finite element analysis

= Automated

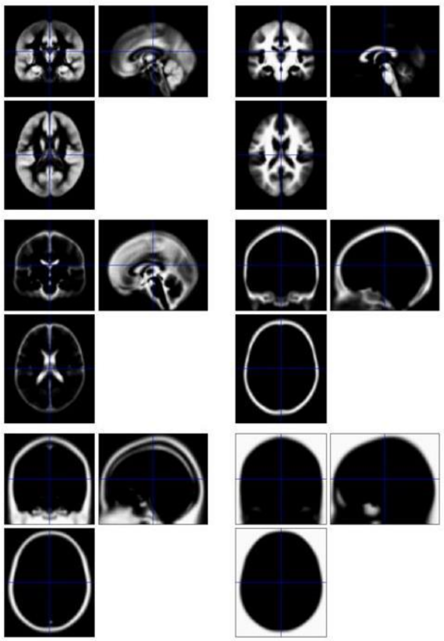
Existing Segmentation Tools are a Partial Solution





Ashburner, John, et al. "SPM8 manual." *Functional Imaging Laboratory, Institute of Neurology* 41 (2008).

We Also Segment on Brainstem and Orbits

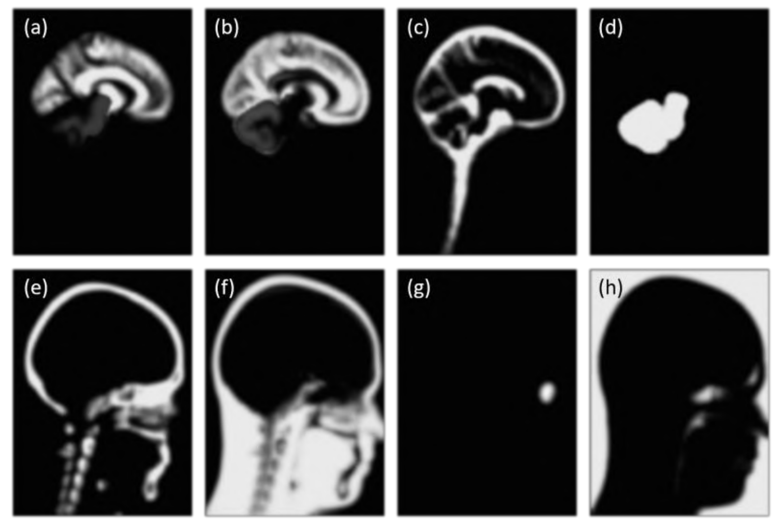


SPM

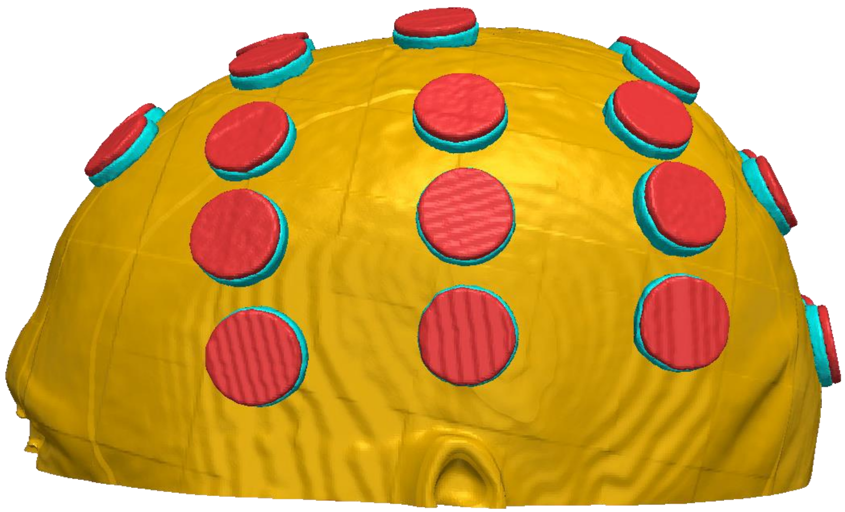
White Matter
Gray Matter
Cerebrospinal Fluid
Skull
Scalp

Diedrichsen, J. (2006). A spatially unbiased atlas template of the human cerebellum. *Neuroimage, 33, 1,* p. 127-138.

Cerebellum/Brainstem



To Generate Electrode and Gel Masks

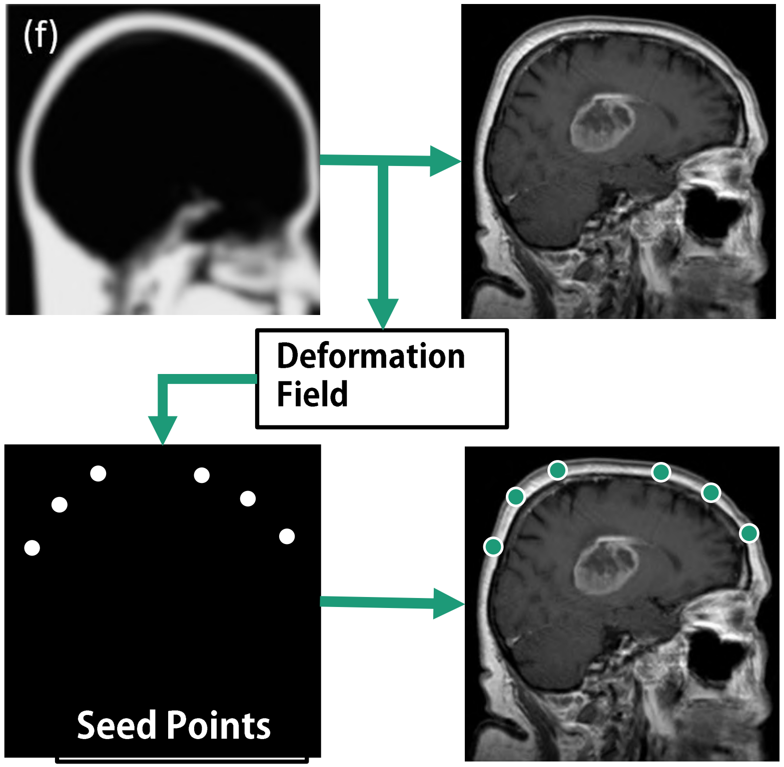


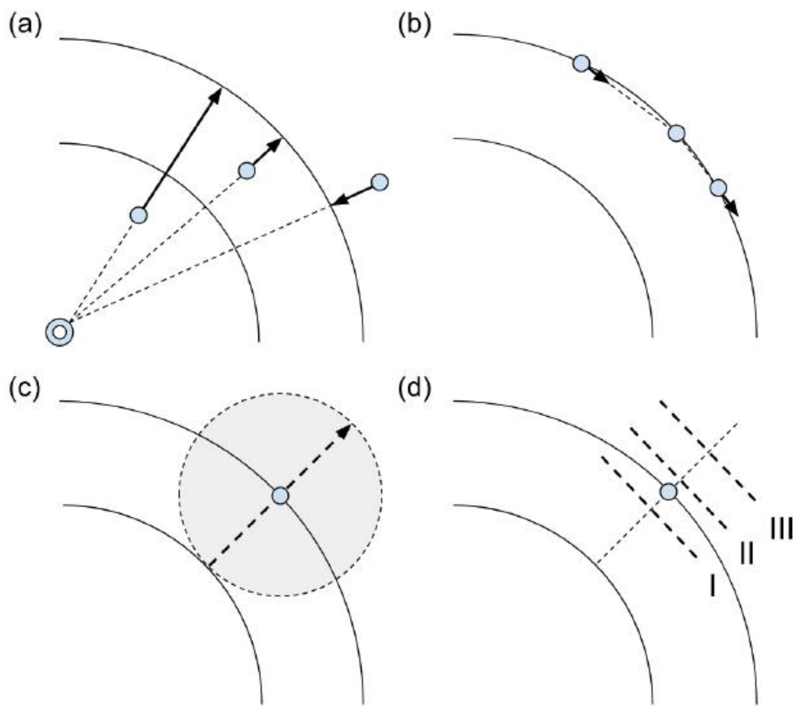
- 36 electrodes
- 36 corresponding gel layers

Two problems:

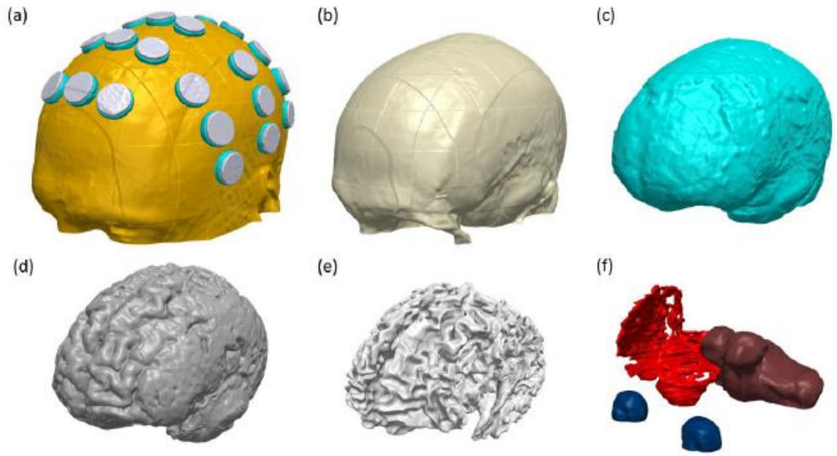
1. Finding electrode locations on the scalp
2. Creating cylinders normal to the scalp's surface at that point

Moving Seed Points and Generating Masks

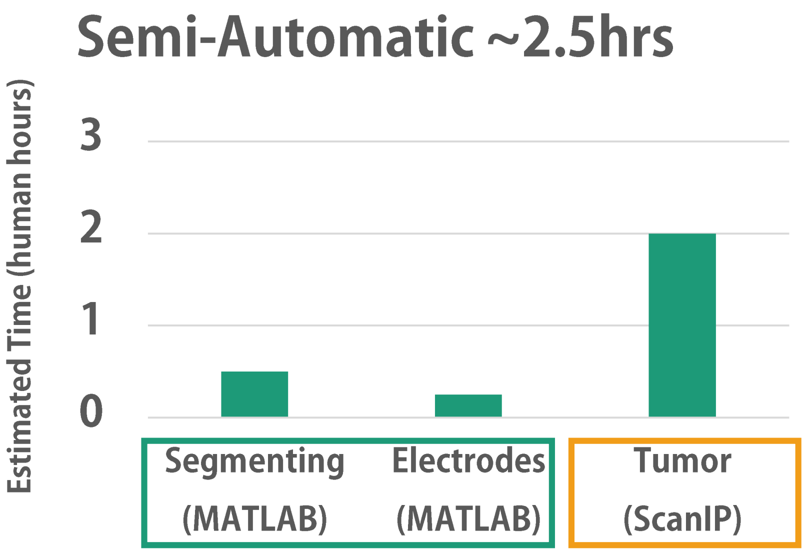




Output of the Semi-Automatic Workflow



Timmons, J.J., Lok, E., San, P., Bui, K., & Wong, E.T. (2017). End-to-End Workflow for Finite Element Analysis of Tumor Treating Fields in Glioblastomas. In press—Physics in Medicine & Biology



Using the Code

github.com/JJTimmons/TTFields-Workflow

Installation and use

1. Download the repo (Clone or download > Download ZIP) and unzip into SPM8/toolbox (or elsewhere)
2. In MATLAB, add the SPM8 path
3. Add the path and subpaths of TTFields-Workflow
4. Type and enter "TTFs" in the MATLAB console
5. Within the prompt, navigate to a DICOM directory for segmentation and select all images; ctrl-A then Enter then click "Done"

```
addpath('C:\spm8')

addpath(genpath('C:\spm8\toolbox\TTfields-Workflow-master'))

TTFs
```

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Adding Tumor + Meshing

ScanIP (Synopsys, Mountain View, CA)
MeshLab (Christophe Geuzaine, C. & Remacle, J.F.)
iso2Mesh (Qianqian Fang, Q. & Boas, D.)

Finite Element Analysis

COMSOL Multiphysics (COMSOL, Burlington, MA)
Abaqus FEA (Dassault Systèmes, Vélizy-Villacoublay, France)

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Phina Le

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