Analytics of Three-Dimensional Pathology Imaging Data

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- **3D Liver Vessel Reconstruction**

- **3D GBM Neurosphere Cell Segmentation with Fluorescence Microscopy Images**

- **3D GBM Tissue Reconstruction for Research on Spatial Patterns of Pseudopalisading Cells and Microvascular Hyperplasia**

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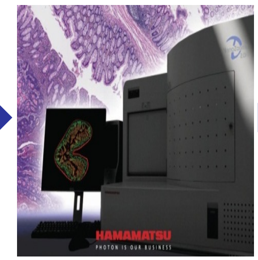
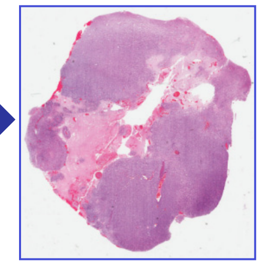
3D Whole Slide Images

- Whole slide image (WSI)
  - Size: 75k x 65k pixels
    ~300 MB/image
  - Millions of objects

Glass Slices

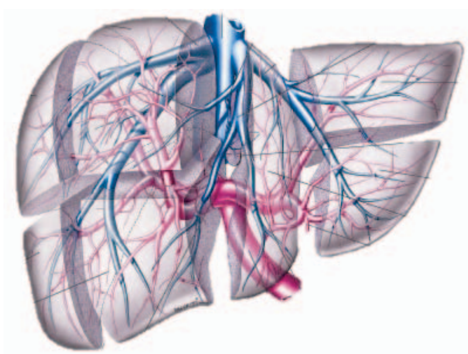


Digital Scan

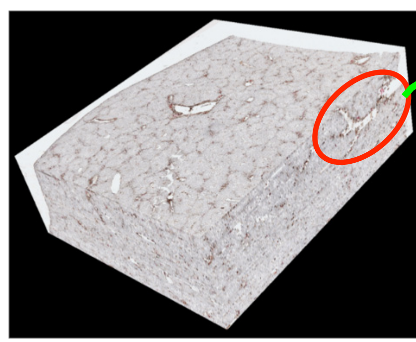


WSI

- 3D micro-anatomic objects in WSI
  - Normal tissue development and disease processes



Human Liver

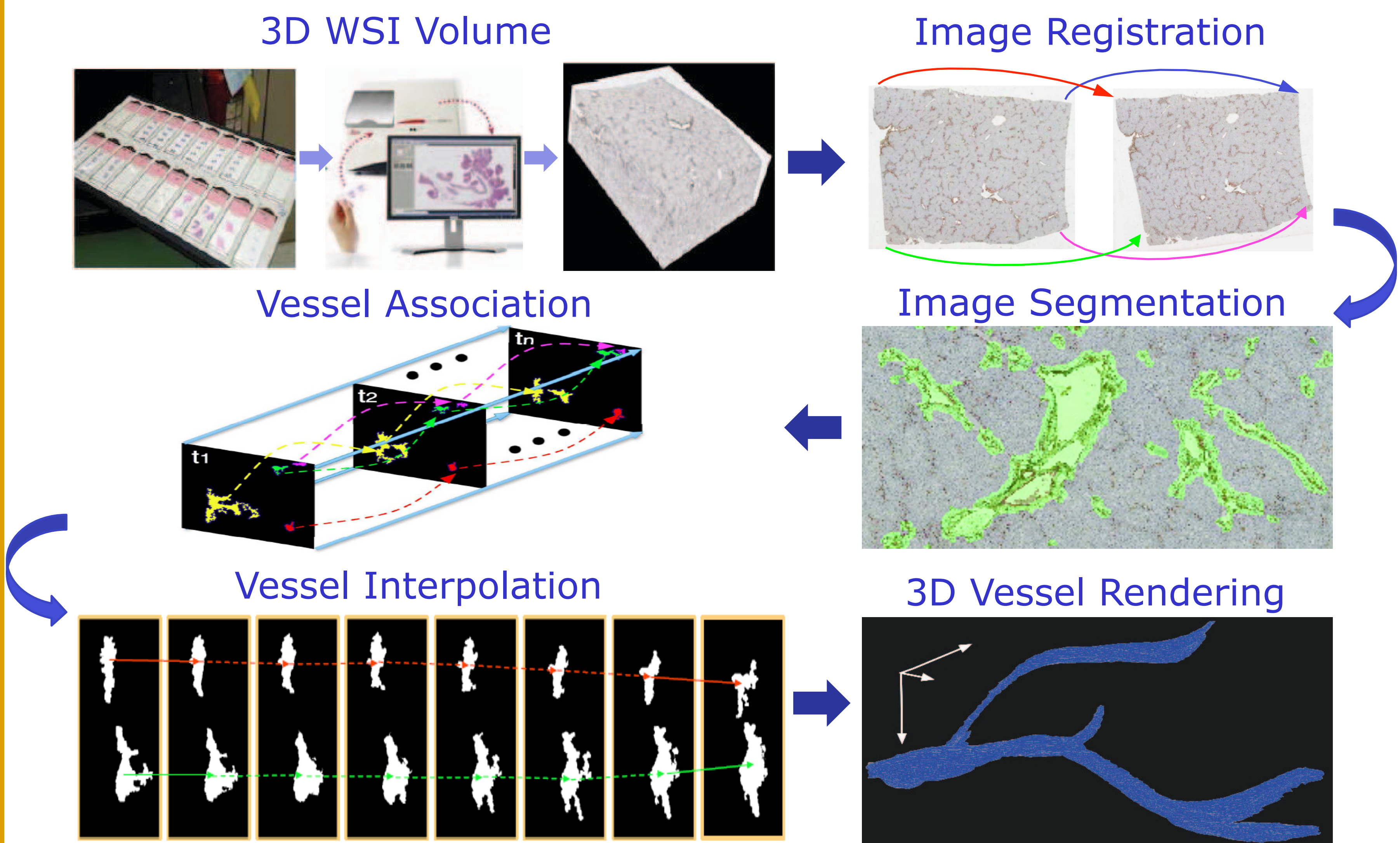


3D WSI Volume

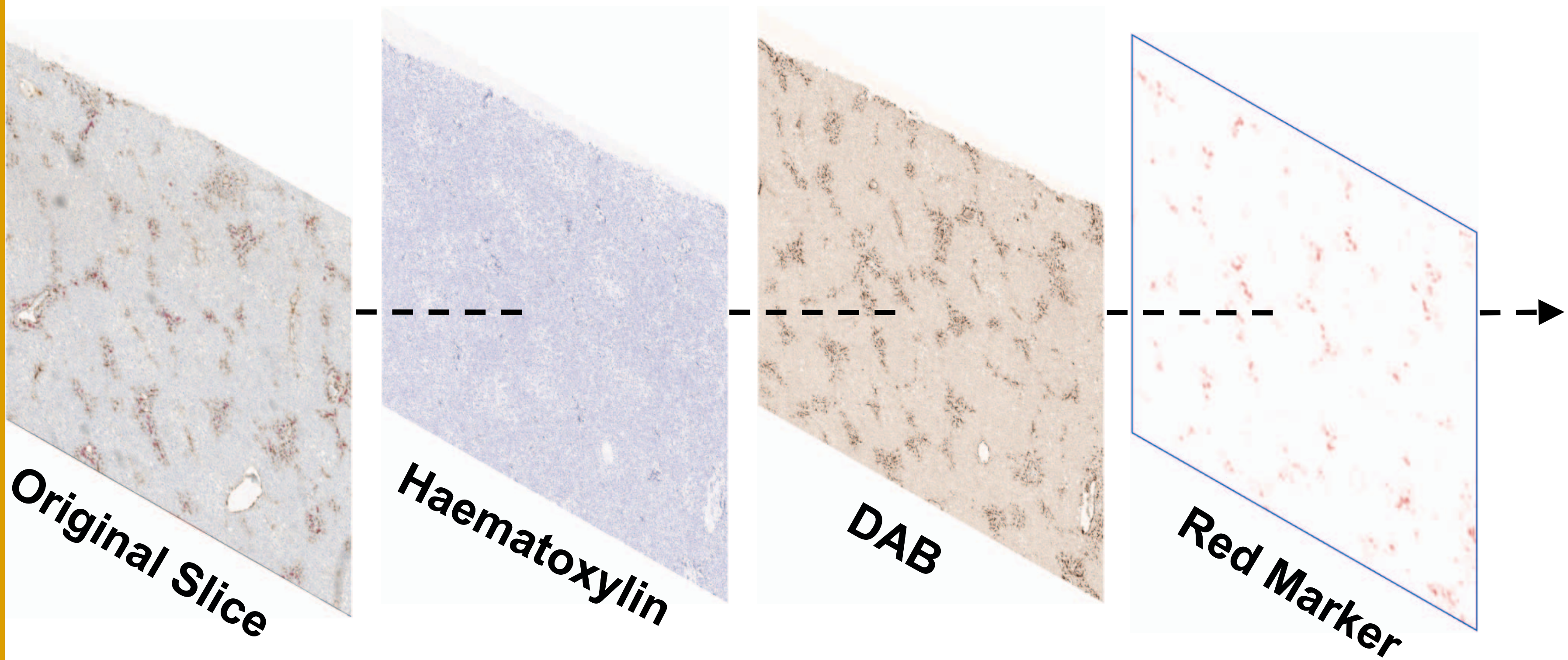
A Reconstructed
3D Vessel Branch

Framework

Quantitative analysis of whole slide images is essential to derive spatial structures and features in 3D

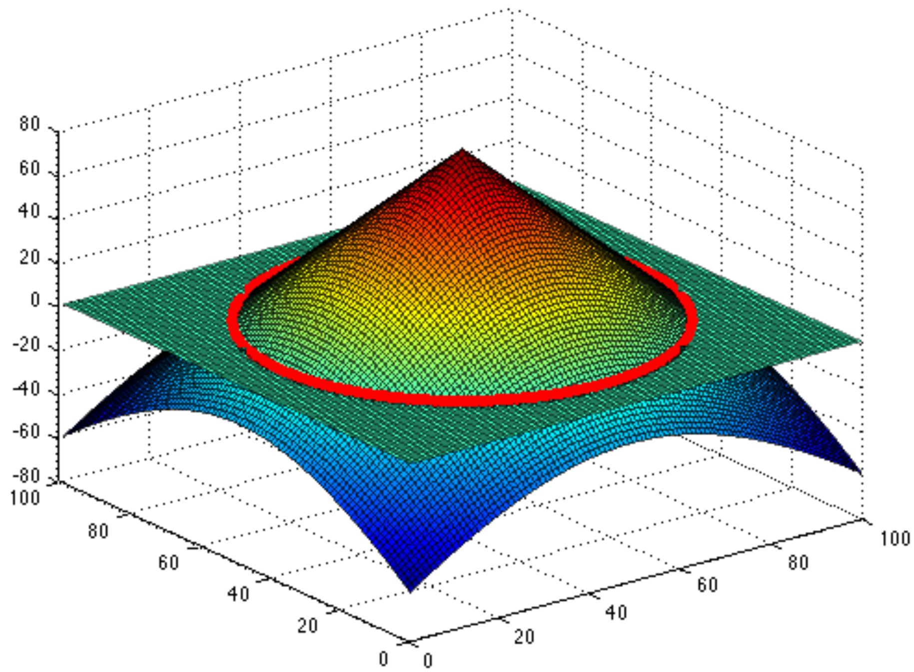


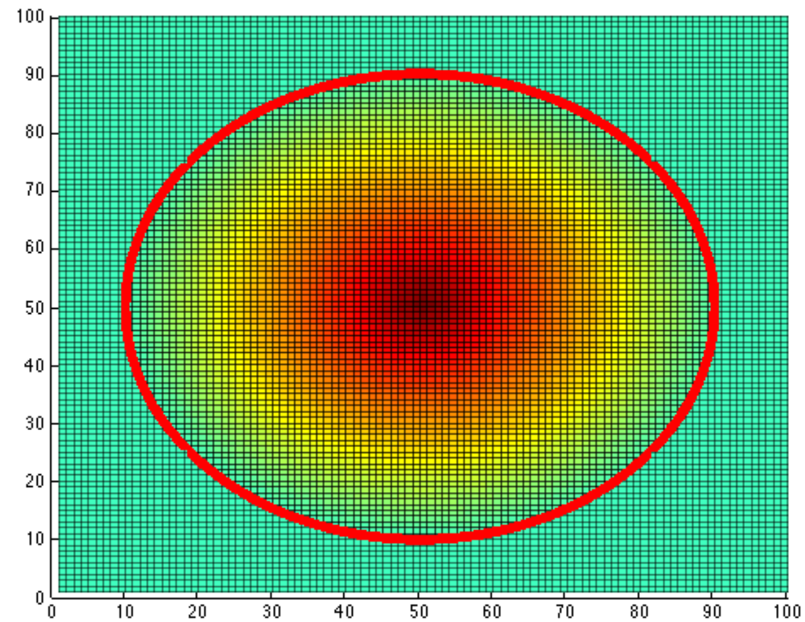
Color Deconvolution



- Find each stain channel
  - Vessels are dyed by DAB stain

A Variational Level Set Method





Curve C is represented via a Lipschitz function *Φ* by $C = \{(x, y) | \phi(x, y) = 0\}$

$$\frac{\partial \phi}{\partial t} = |\nabla \phi| F,\ \phi(0,\ x,\ y) = \phi_0(x,\ y)$$

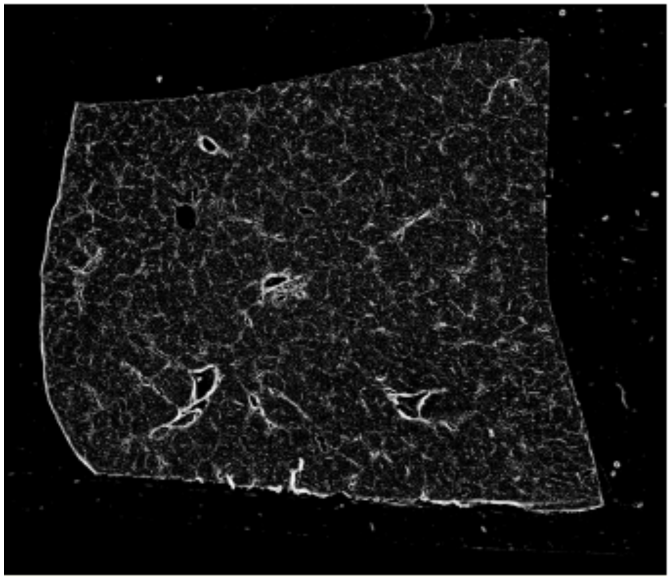
$$\begin{cases} C = \partial\omega = \{(x,\ y) \in \Omega:\ \phi(x,\ y) = 0\}, \\ inside(C) = \omega = \{(x,\ y) \in \Omega:\ \phi(x,\ y) > 0\} \\ outside(C) = \Omega \setminus \overline{\omega} = \{(x,\ y) \in \Omega:\ \phi(x,\ y) < 0\} \end{cases}$$

Vessel Directed Fitting Energy (VDFE)

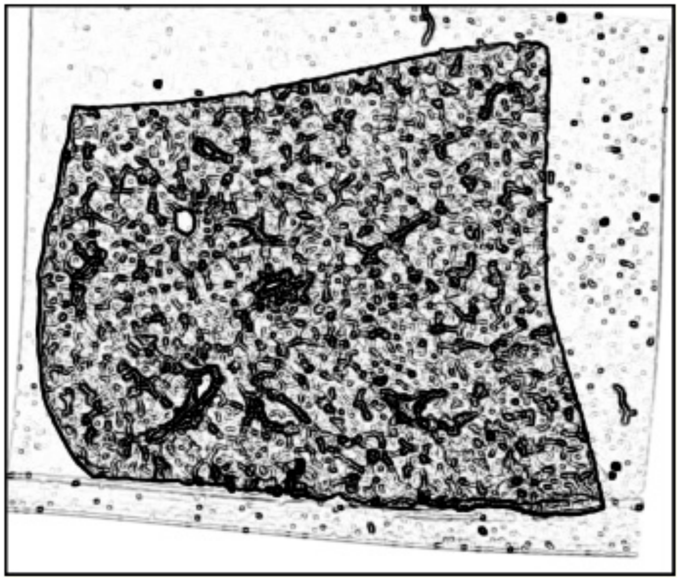
$$E_{\mathrm{VDFE}}(\mathbf{x}, f_1(\mathbf{x}), f_2(\mathbf{x}), \phi) =$$

$$\lambda_1 \int_\Omega G_{\sigma_2}(\|\mathbf{x}-\mathbf{y}\|)\boxed{Q_{\sigma_3}(\mathbf{y})}|I(\mathbf{y}) * G_{\sigma_1}(\mathbf{y}) - f_1(\mathbf{x})|^2 U_1(\phi(\mathbf{y}))d\mathbf{y}$$

$$+ \lambda_2 \int_\Omega G_{\sigma_2}(\|\mathbf{x}-\mathbf{y}\|)\boxed{P(\mathbf{y})}|I(\mathbf{y}) * G_{\sigma_1}(\mathbf{y}) - f_2(\mathbf{x})|^2 U_2(\phi(\mathbf{y}))d\mathbf{y}$$

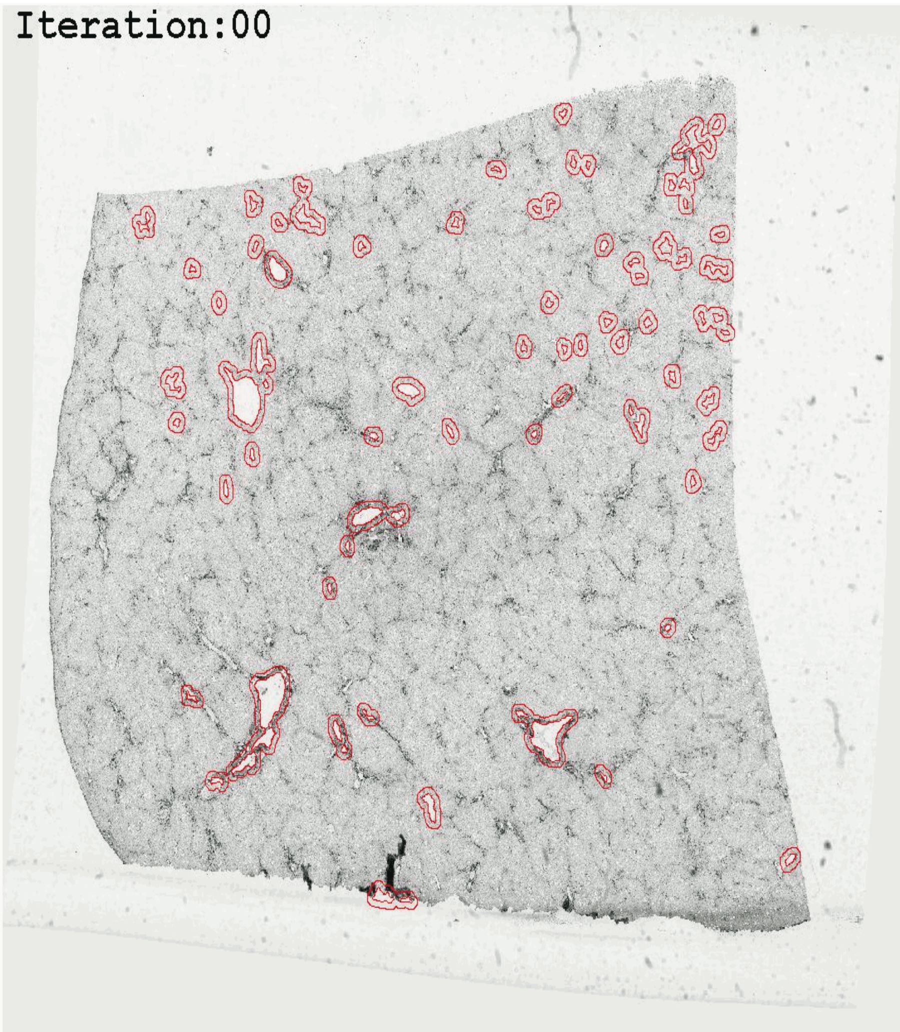


Vessel wall probability map
P(y)

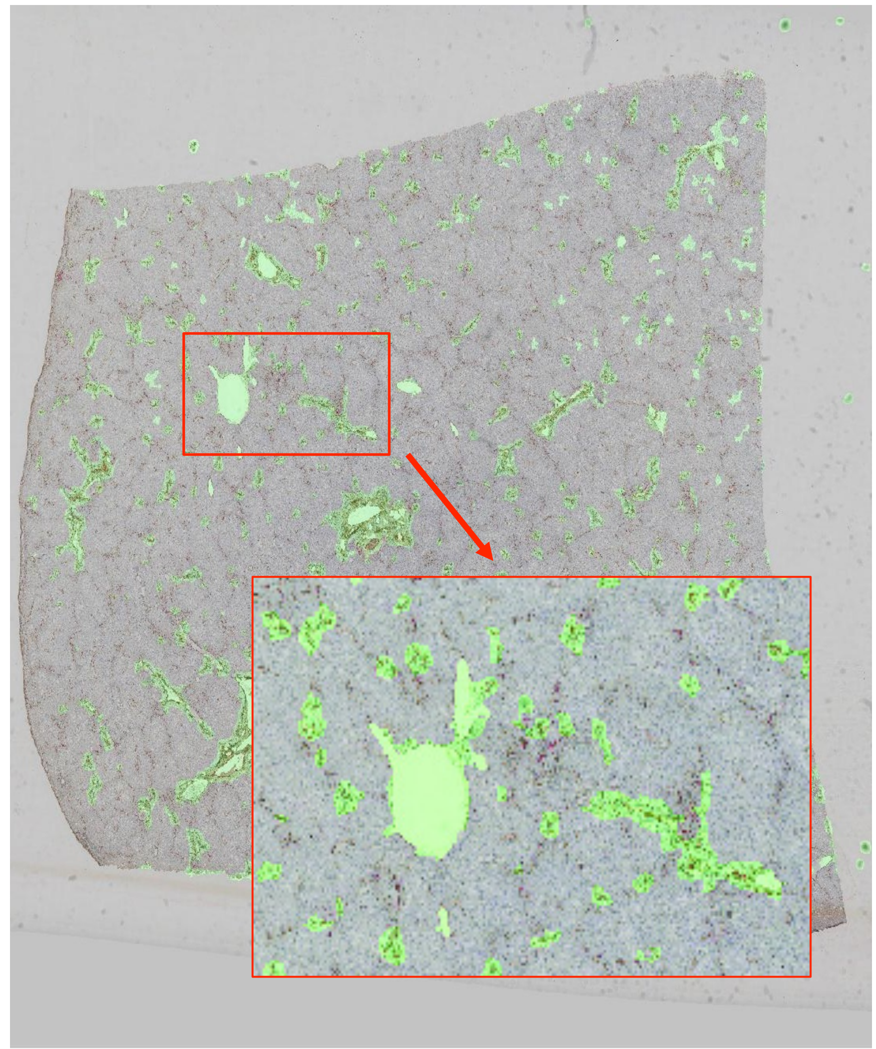


Smooth indicator function
$\boldsymbol{Q_{\sigma 3}}$(y)

VDFE based Level Set Result

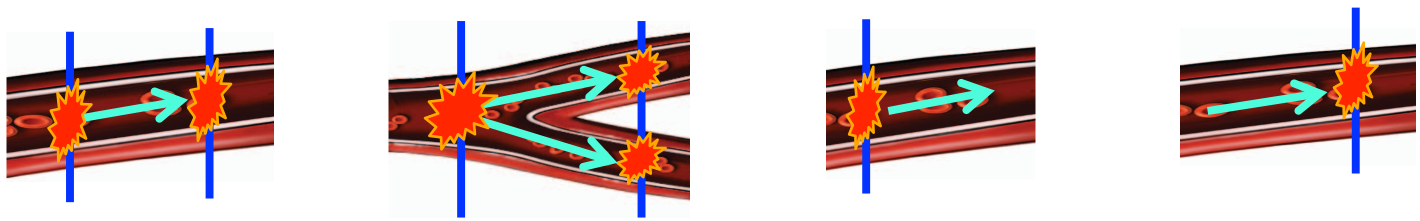


Final Result



Two-stage Vessel Association

- Local bi-slide mapping and global vessel structure association
  - Four vessel association cases



Extension | Bifurcation | Disappearance | Emergence

  - Similarity functions
    - Shape descriptor, spatial relationship, trajectory smoothness

$$\text{One-to-one: } s\left(v_i^t, v_j^{t+1}\right) = \mu_1 \; g\left(v_i^t, v_j^{t+1}\right) + \mu_2 \; d\left(v_i^t, v_j^{t+1}\right)$$

$$\text{One-to-two: } s\left(v_i^t, v_{j_1}^{t+1}, v_{j_2}^{t+1}\right) = \mu_1 \; g\left(v_i^t, v_{j_1}^{t+1} \cup v_{j_2}^{t+1}\right) + \mu_2 \; d\left(v_i^t, v_{j_1}^{t+1} \cup v_{j_2}^{t+1}\right)$$

$$\text{One-to-none: } s\left(v_i^t, v_{\varnothing}^{t+1}\right) = d\left(v_i^t, \Omega_t\right)$$

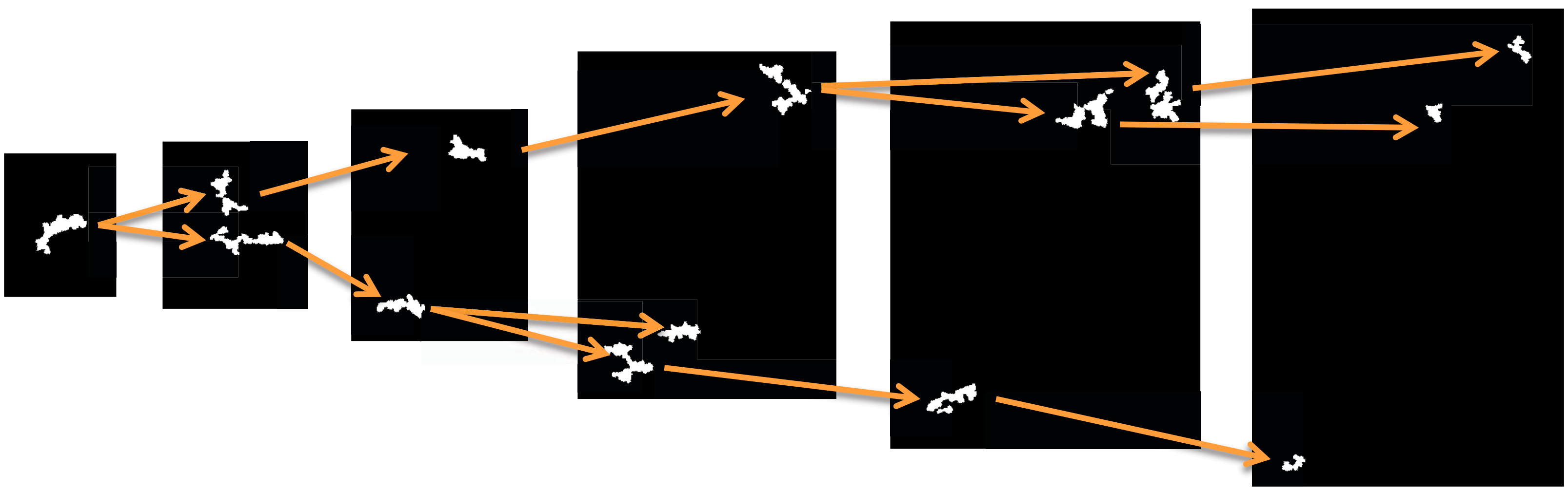
$$\text{None-to-one: } s\left(v_{\varnothing}^{t-1}, v_i^t\right) = d\left(v_i^t, O_t\right)$$

Two-stage Vessel Association

- Global vessel structure association
  - Bayesian Maximum A Posteriori (MAP) framework

$$\mathbf{V}^* = \arg\max_{\mathbf{V}} P(\mathbf{V}|\mathbf{B}) = \arg\max_{\mathbf{V}} \prod_{V_k \in \mathbf{V}} P(V_k|\mathbf{B}) = \underset{B_s^k \in V_k}{P_{\varnothing \to 1}} \left(B_s^k | B_\varnothing\right)$$

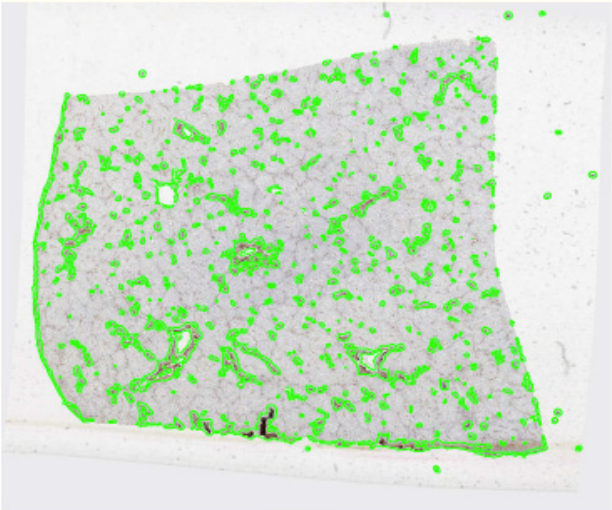
$$\prod_{B_i^k, B_j^k \in V_k} P_{1\to 1}\left(B_j^k | B_i^k\right) \prod_{B_m^k, B_{n_1}^k, B_{n_2}^k \in V_k} P_{1\to 2}\left(B_{n_1}^k, B_{n_2}^k | B_m^k\right) \prod_{B_e^k \in V_k} P_{1\to\varnothing}\left(B_\varnothing | B_e^k\right)$$



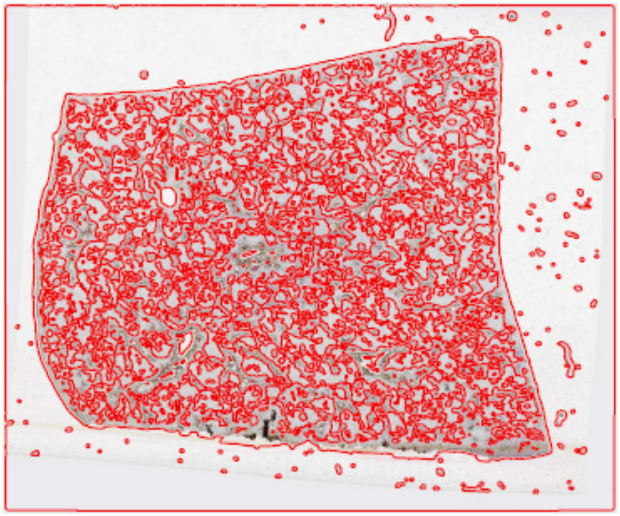
Experiments and Evaluation

- Vessel segmentation

With P Map



Without P Map

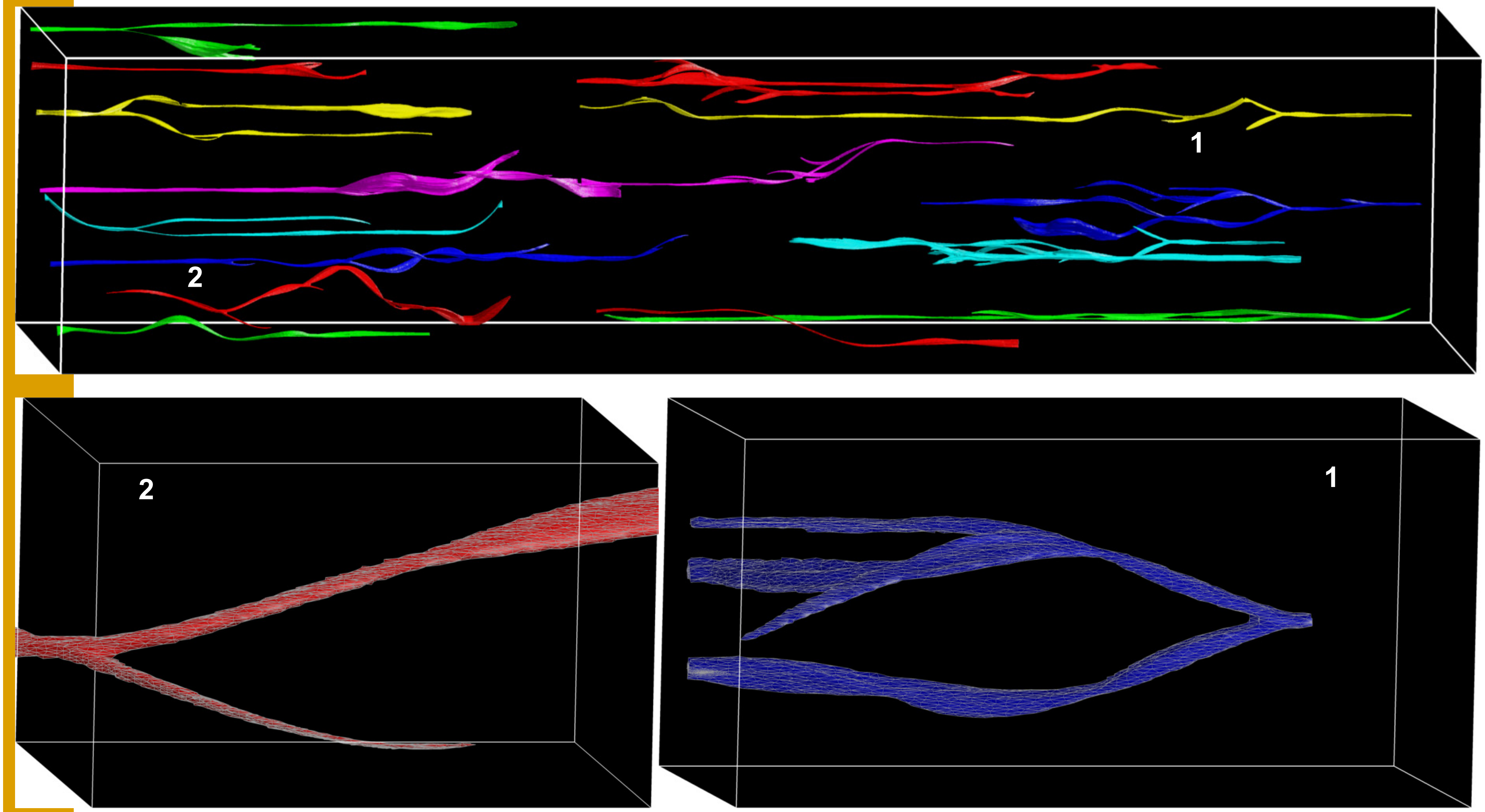


- Segmentation evaluation

Table 1. Evaluation of the segmentation results (Mean ± Standard Deviation).

	Jac	Pre	Rec	F_1	$Haus$
MR	0.45 ± 0.21	0.60 ± 0.27	0.77 ± 0.26	0.59 ± 0.22	34.48 ±75.45
VDLS (our method)	0.84 ± 0.10	0.96 ± 0.06	0.87 ± 0.08	0.91 ± 0.07	6.82 ± 30.99

3D Vessel Rendering



- Investigations on invasive capacity and migration patterns of tumor cells for cancer research
- Lack of platforms and quantitative methods for scalable studies
- Need to be generic to different biological research
- Accommodate large volume of 3D spatial+ temporal data
- 3D cell segmentation, followed by cell tracking

Driving Use Case: Glioblastoma (GBM)

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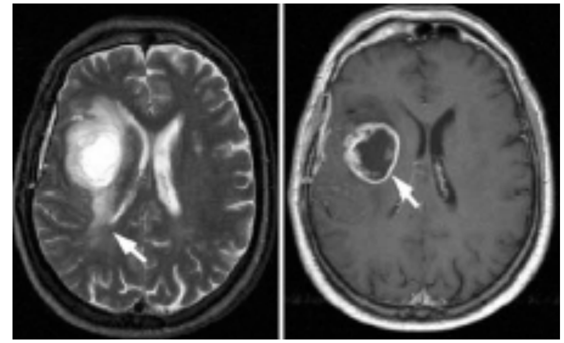
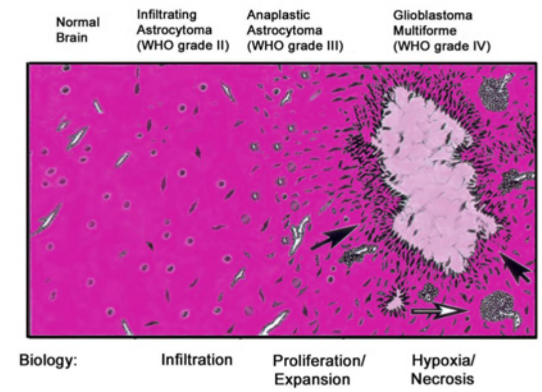
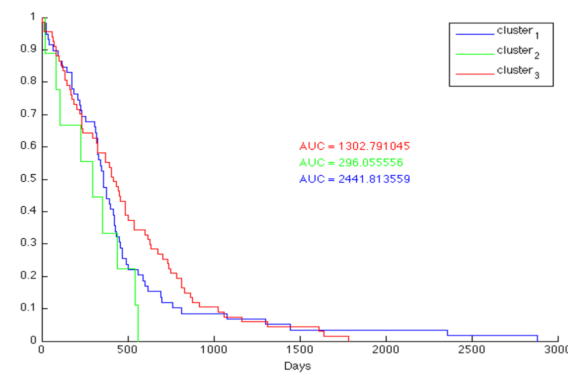
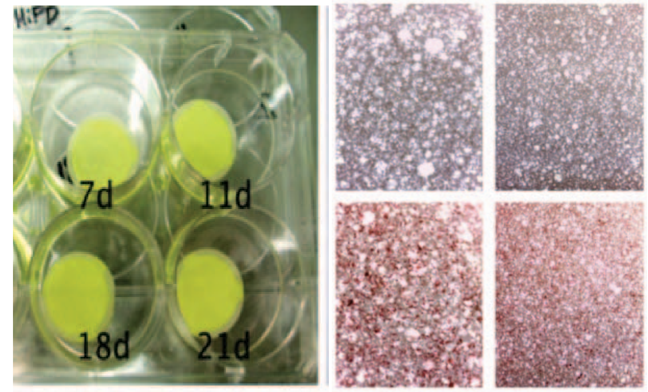
- **Most frequent brain cancers in the central nervous system**
  - **Uniformly fatal**
  - **Infiltrative and inclined to progression**
  - **Resistance to conventional therapies**
  - **Challenge on histological review**
  - **Large inter-reader variability**
- **Heterogeneity**
  - **Grade IV Astrocytoma**
  - **Oligodendroglioma in abundance**
  - **Mixed Oligoastrocytomas**
- **Dismal survival**
  - **14 weeks after resections on average**
  - **De Novo for the majority**



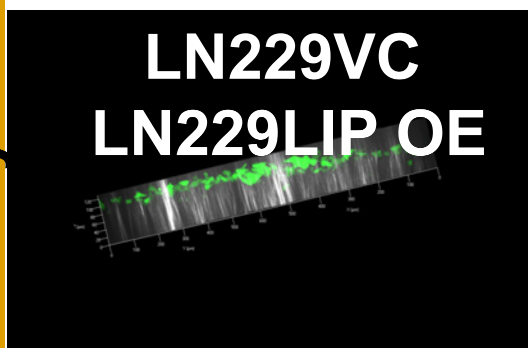


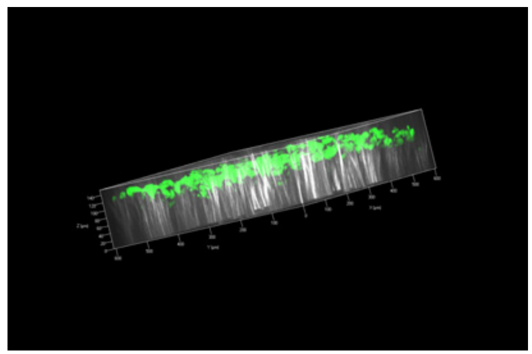


Data Preparation

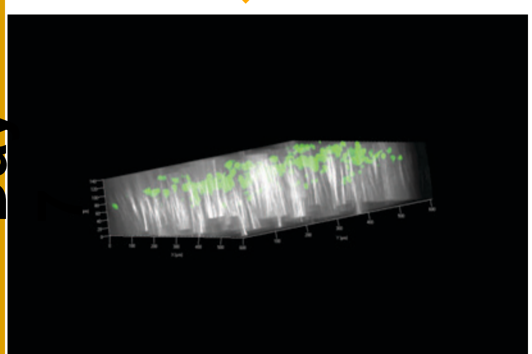


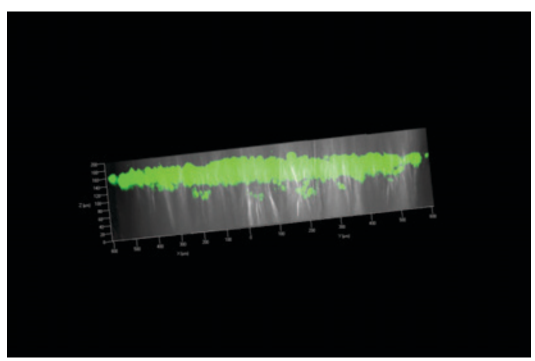
Day

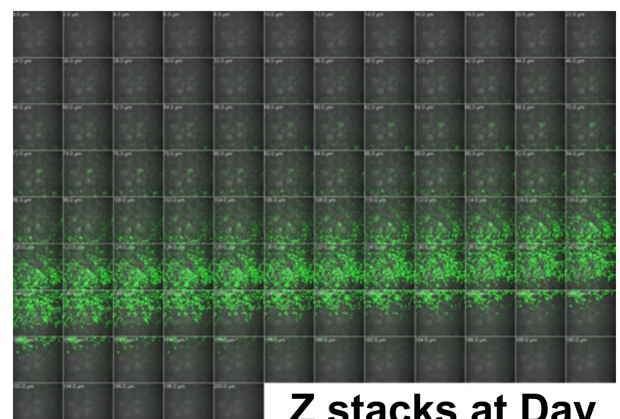




Day

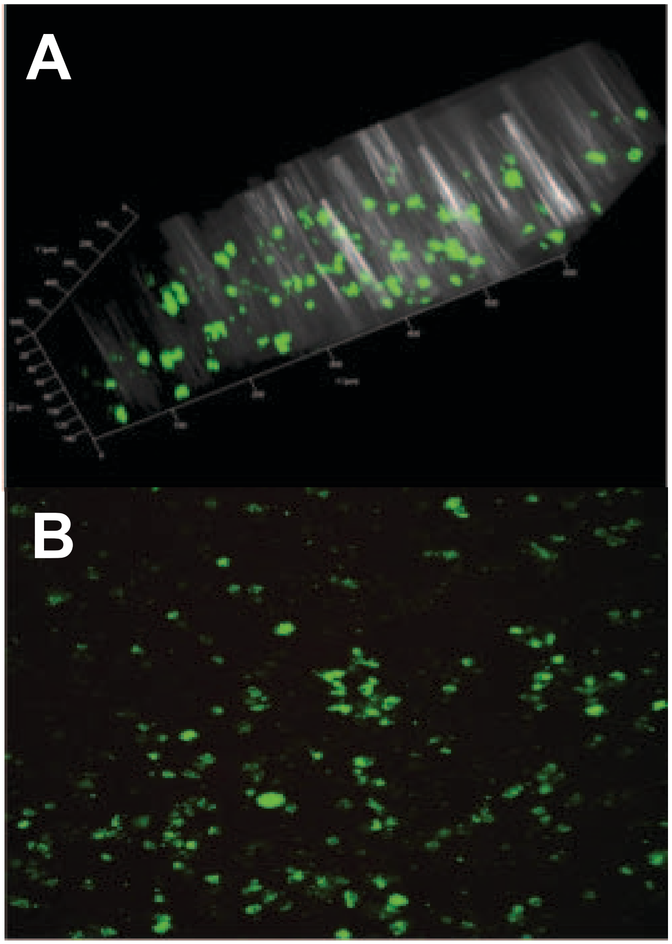


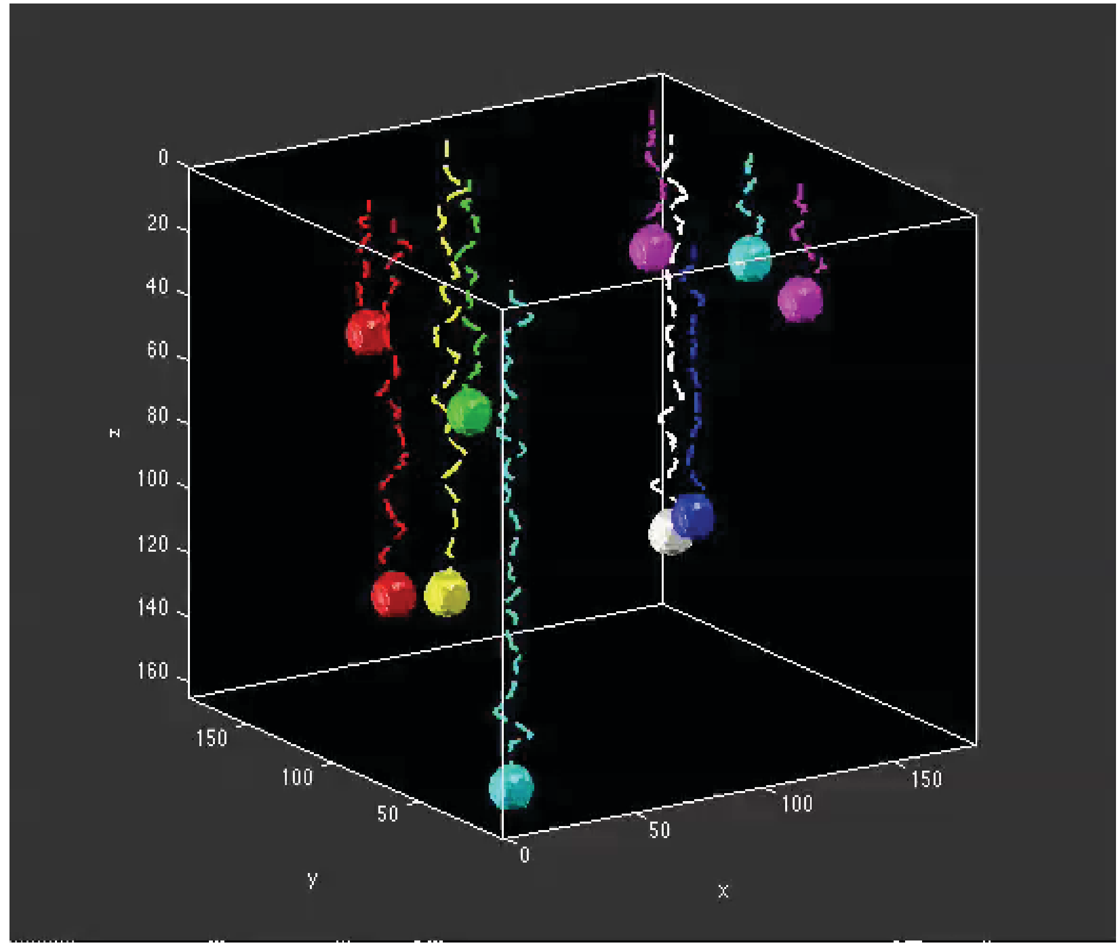


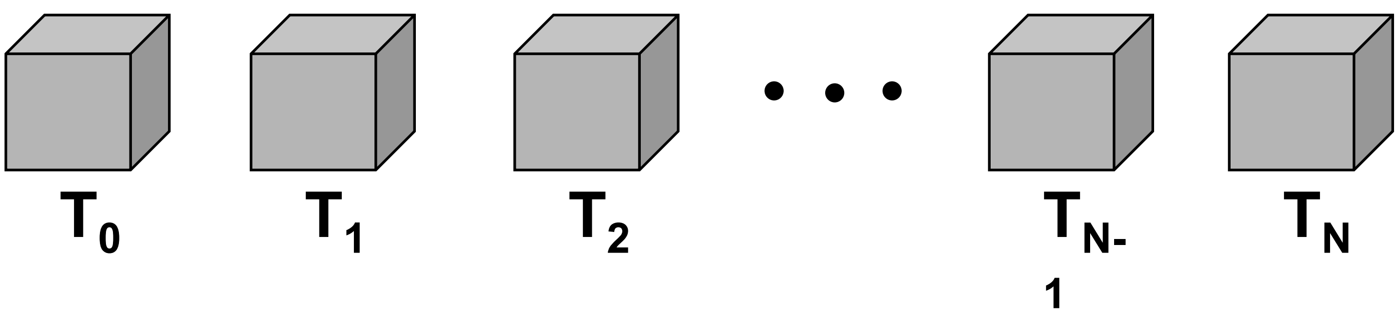


Z stacks at Day 7

Data Preparation

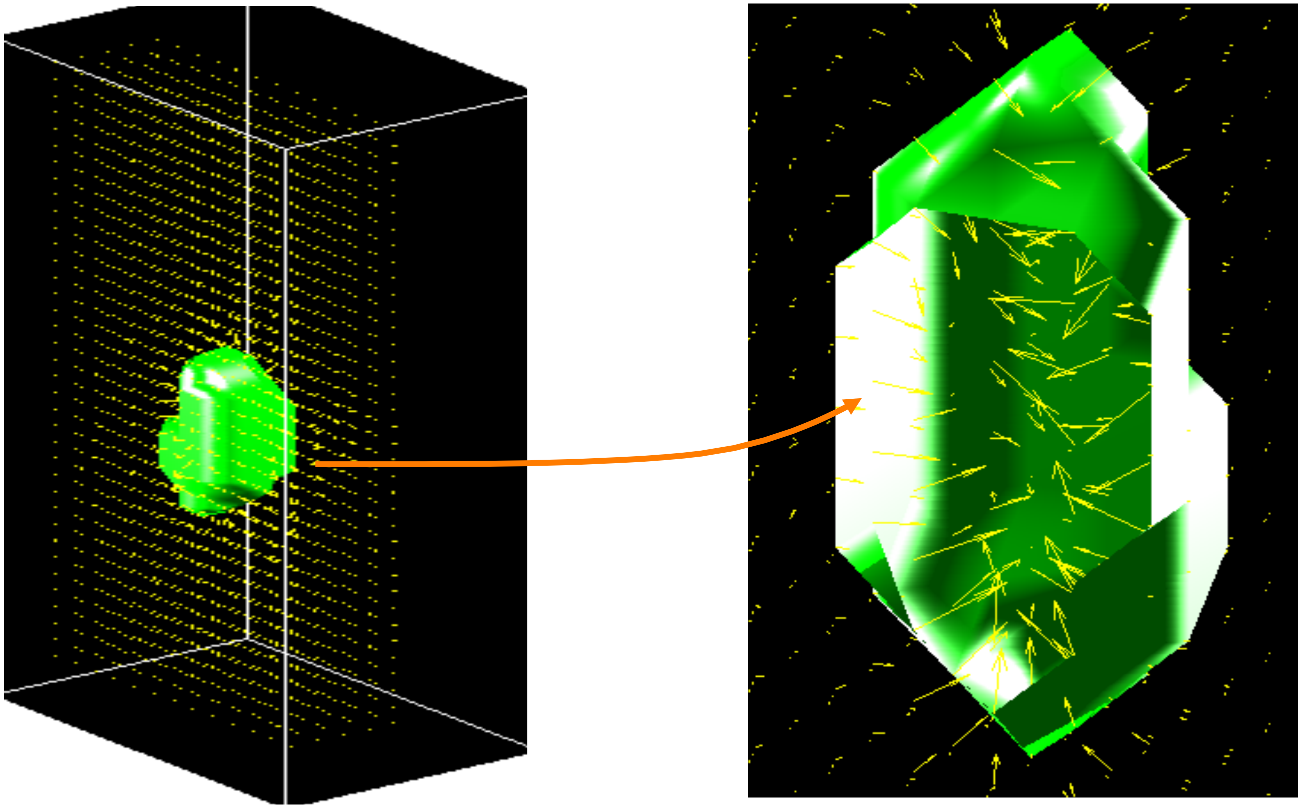


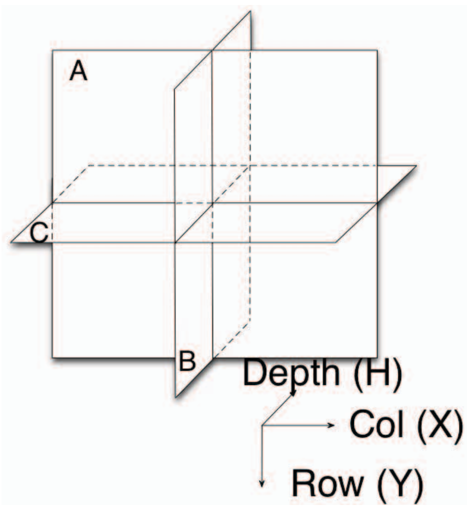


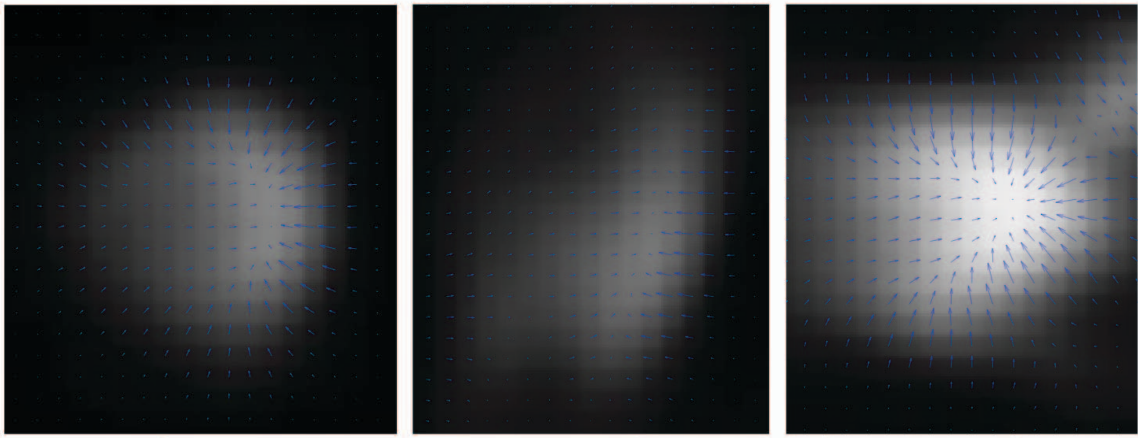


= 24 GBs/ 24 hours !!

Method





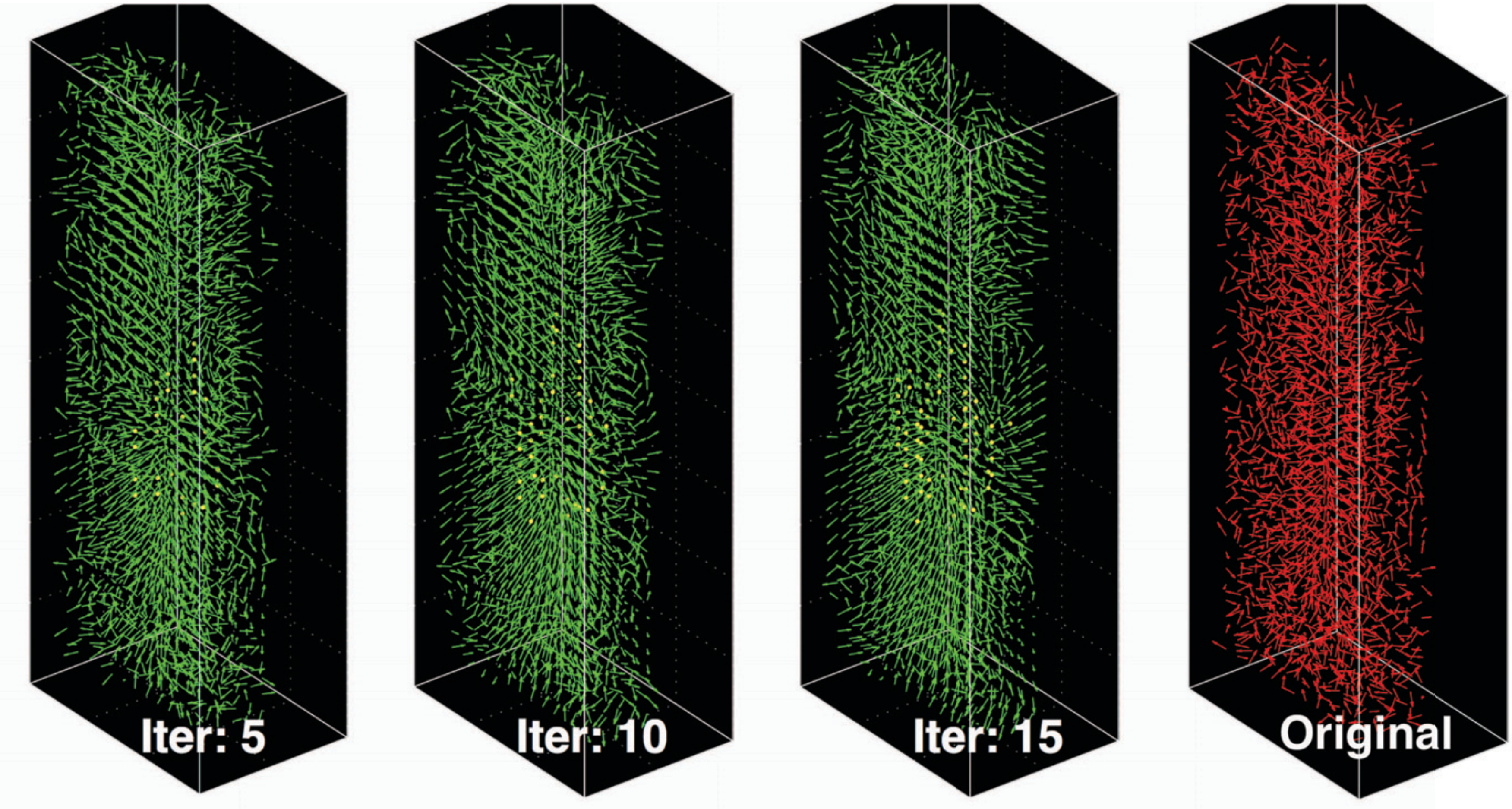


A: Row-Col-Depth=30

B: Row-Depth-Col=108

C: Depth-Row-Col=380

Method: Regulate Gradient Field



Method: Find Gradient Mode

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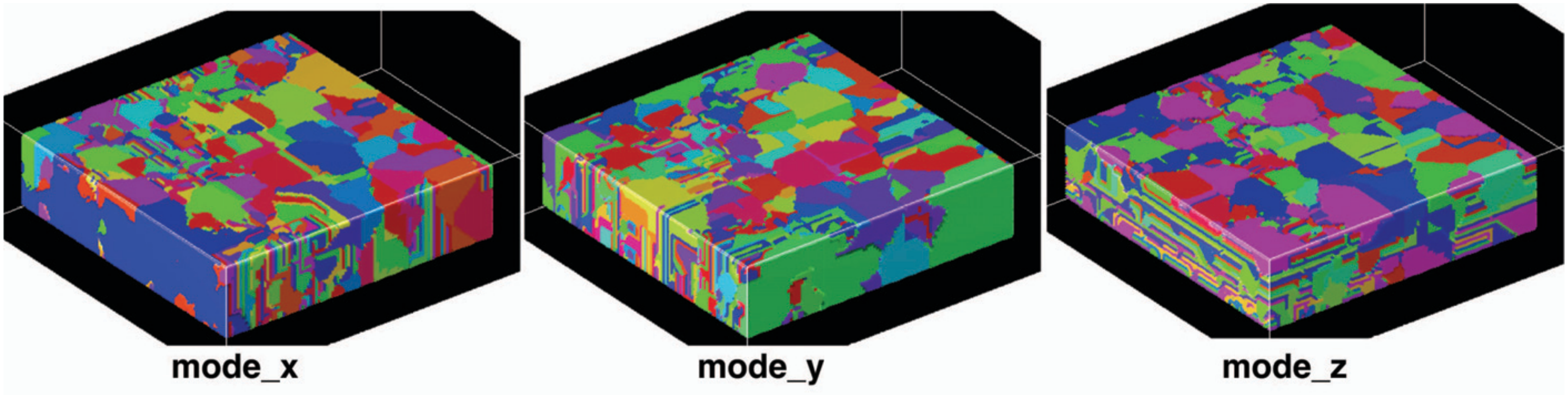
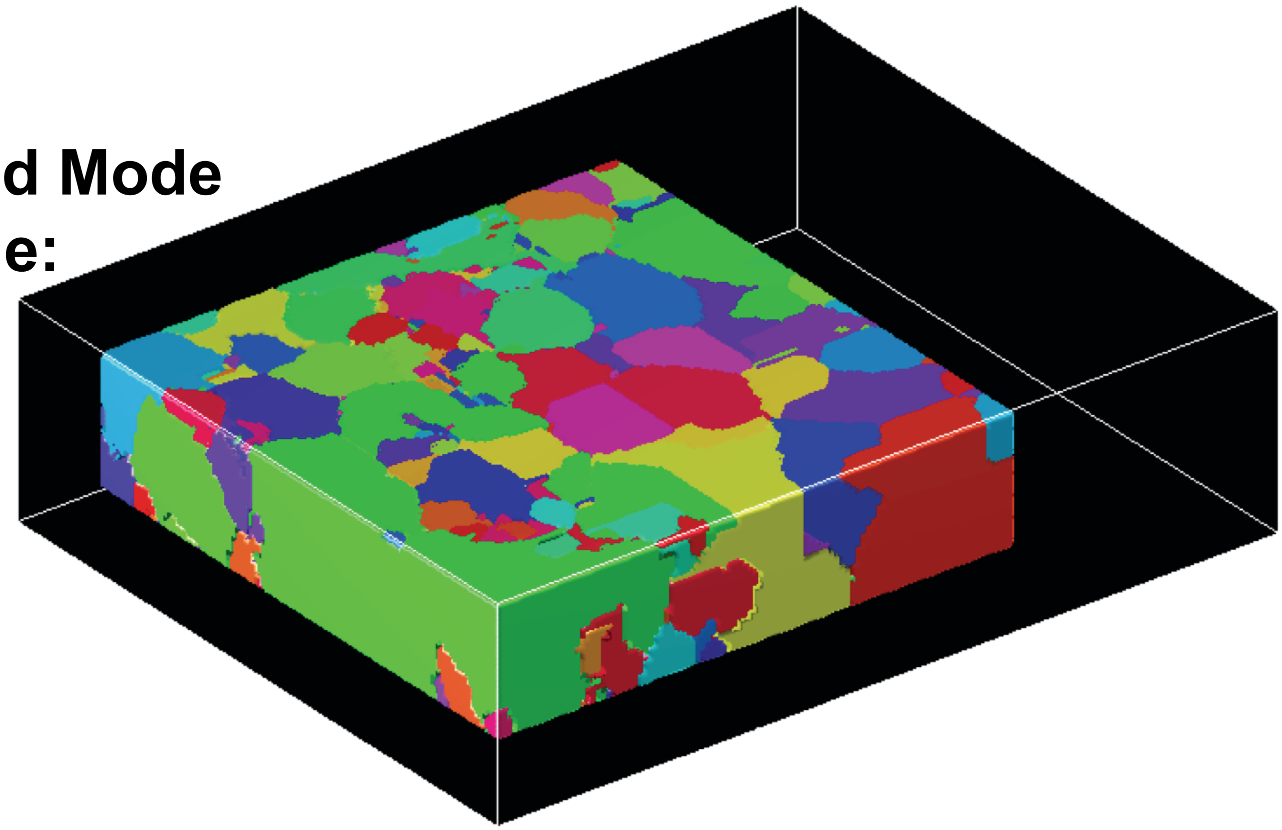


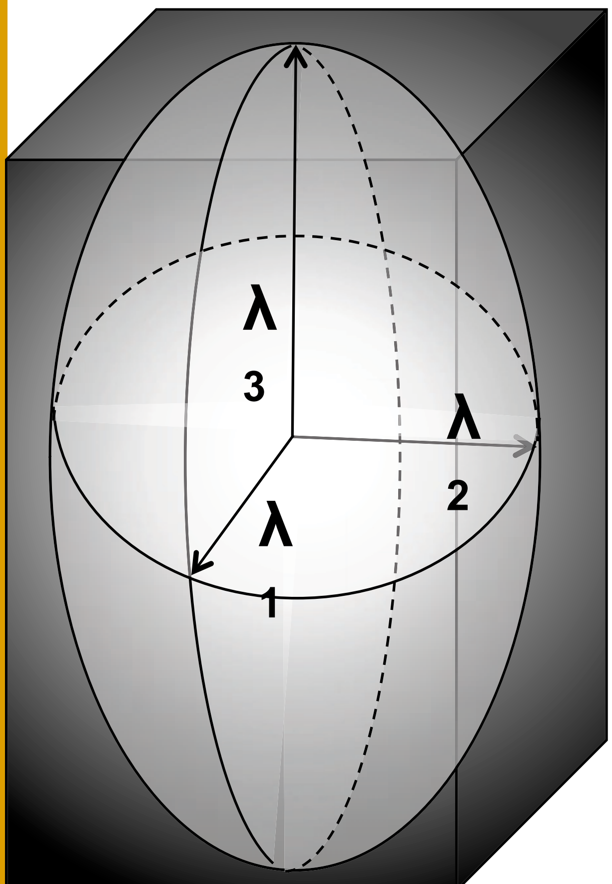
Merged Mode Volume:



Method: Enhance Bimodality

$$\widehat{V}(\mathbf{x}) = \widehat{V}(\mathbf{x}_0) + (\mathbf{x}-\mathbf{x}_0)^T \nabla \widehat{V}(\mathbf{x}_0) + \frac{1}{2!}(\mathbf{x}-\mathbf{x}_0)^T \mathcal{H}\{\widehat{V}(\mathbf{x}_0)\}(\mathbf{x}-\mathbf{x}_0) + \mathcal{O}(\mathbf{x}^3)$$

where $\mathcal{H}(\widehat{V}(\mathbf{x}))$ is a 3×3 Hessian matrix with its entry $H(i,j) = \partial^2 \widehat{V} / (\partial x_i \partial x_j)\big|_{\mathbf{x}}$.



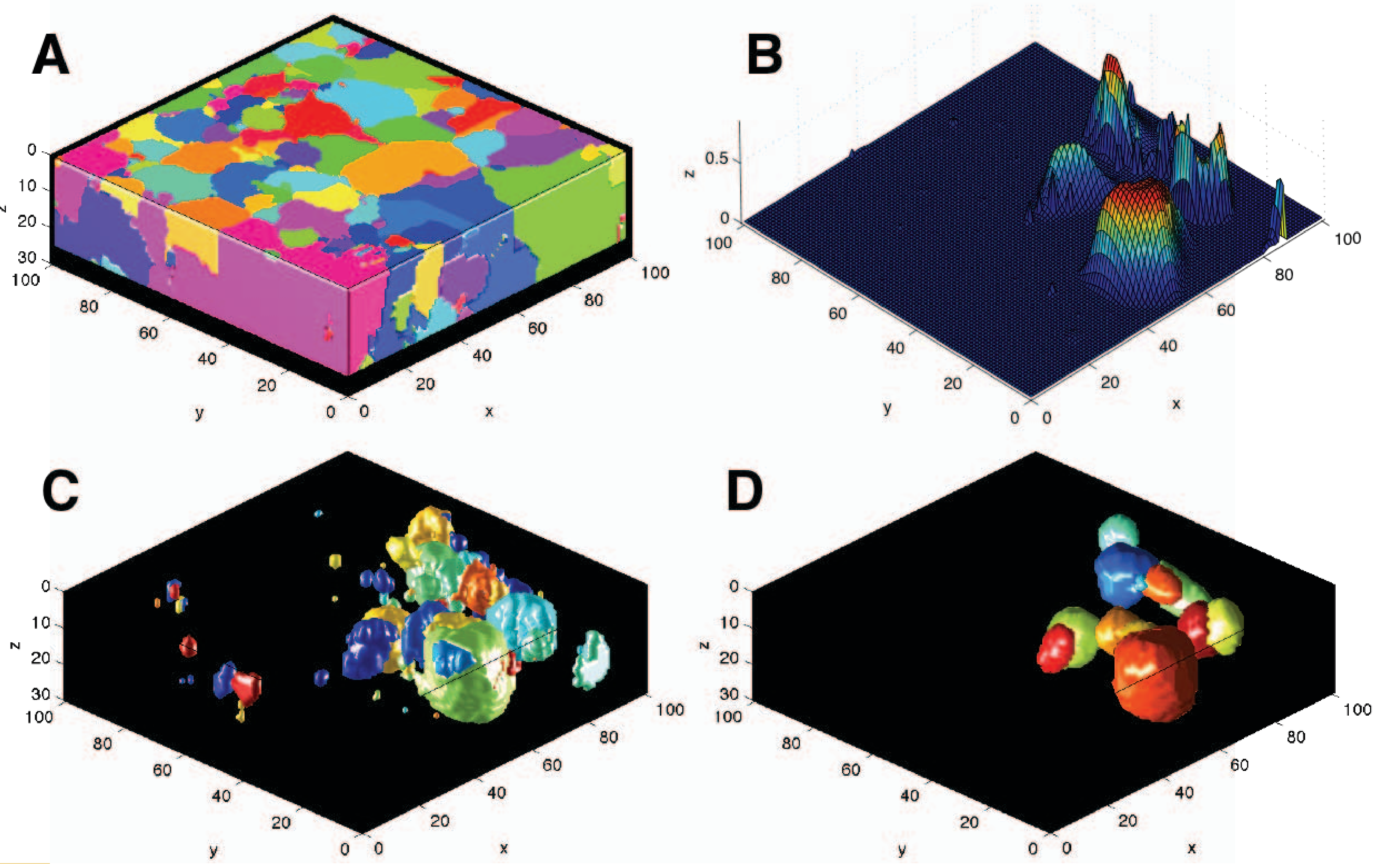
$$\mathcal{H}\{\widehat{V}(\mathbf{x}) * G(\mathbf{x}, s^*)\}Y = Y\Lambda^*, \; \Lambda^* = \begin{pmatrix} \lambda_1^* & 0 & 0 \\ 0 & \lambda_2^* & 0 \\ 0 & 0 & \lambda_3^* \end{pmatrix}$$

$$\begin{cases} \lambda_3 \le \lambda_2 \le \lambda_1 \ll 0 \\ |\lambda_1| \approx |\lambda_2| \approx |\lambda_3| \end{cases}$$

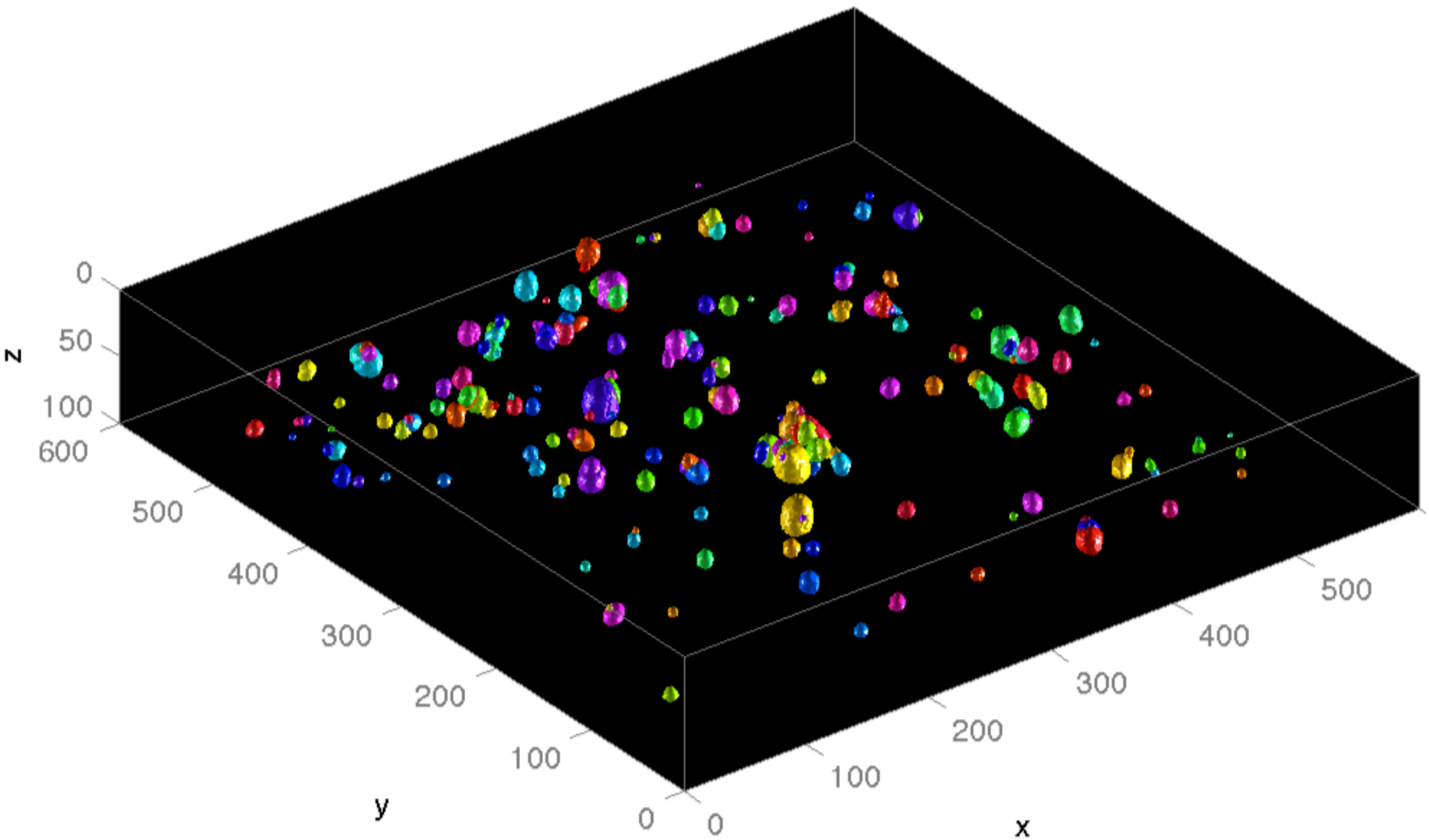
$$C(\mathbf{x}, s) = \begin{cases} 0, & \text{if } \lambda_i > 0, \; \exists\, i \in \{1,2,3\} \\ \left[1 - e^{-\frac{\lambda_1^2}{2\sigma_1^2 |\lambda_2||\lambda_3|}}\right]\left[1 - e^{-\frac{s^2 \sum_{i=1}^{3} \lambda_i^2}{2\sigma_2^2}}\right], & \text{otherwise} \end{cases}$$

$$\boxed{C(\mathbf{x}) = \max C(\mathbf{x}, s_i) \quad \forall i}$$

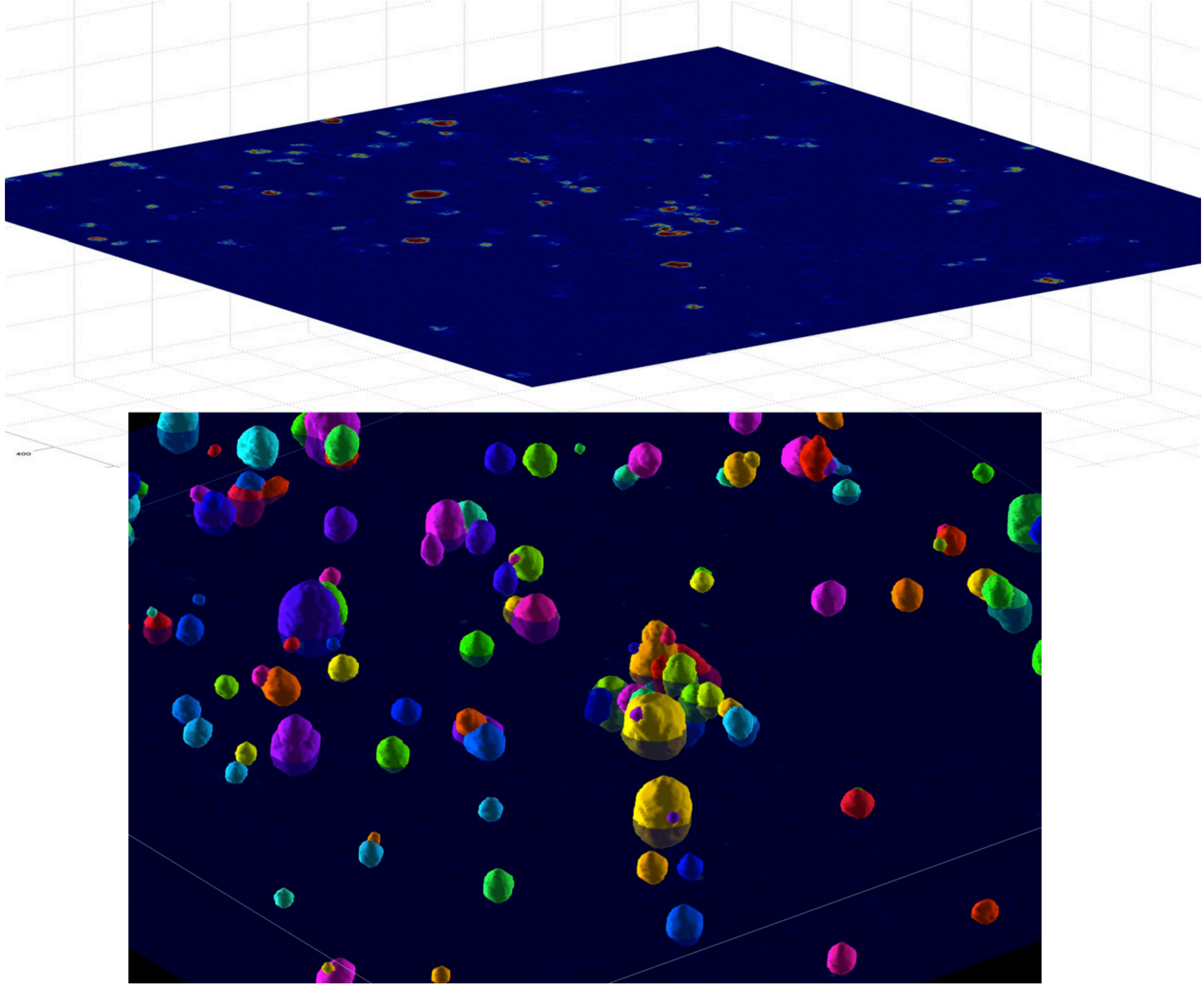
Result



Result



Validation



Validation

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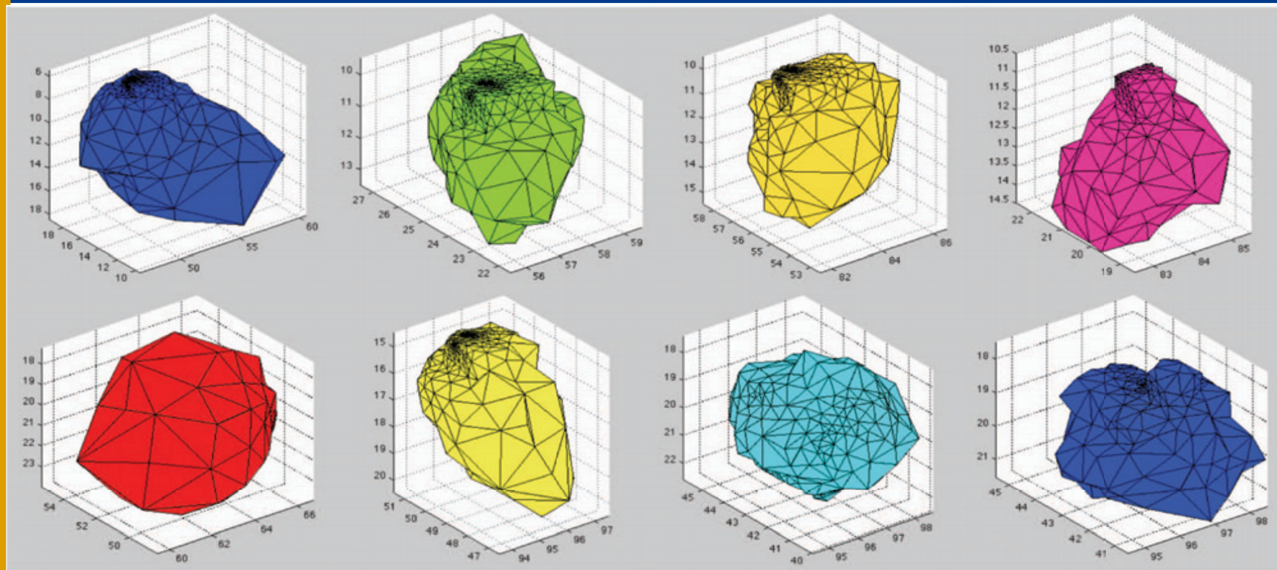

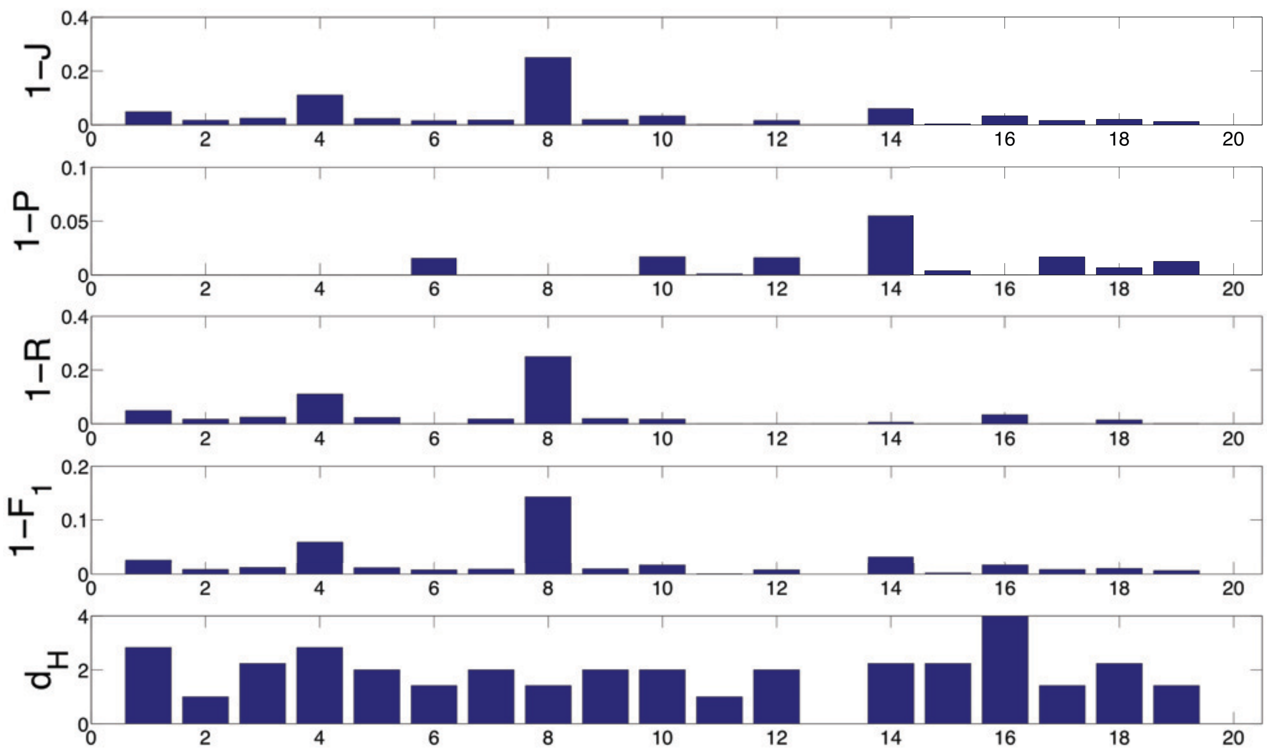

We randomly selected 20 cells and compared the cell structure similarity by volume- and distance-based measures.

$$J = 0.96 \pm 0.06$$
$$J_{low} = 0.75$$

$$P = 0.99 \pm 0.01$$
$$P_{low} = 0.95$$

$$R = 0.97 \pm 0.06$$
$$R_{low} = 0.75$$

$$F_1 = 0.98 \pm 0.03$$
$$F_{1low} = 0.86$$

$$d_H = 1.81 \pm 0.93$$
$$d_{H_{high}} = 4$$

3D GBM Imaging Analytics

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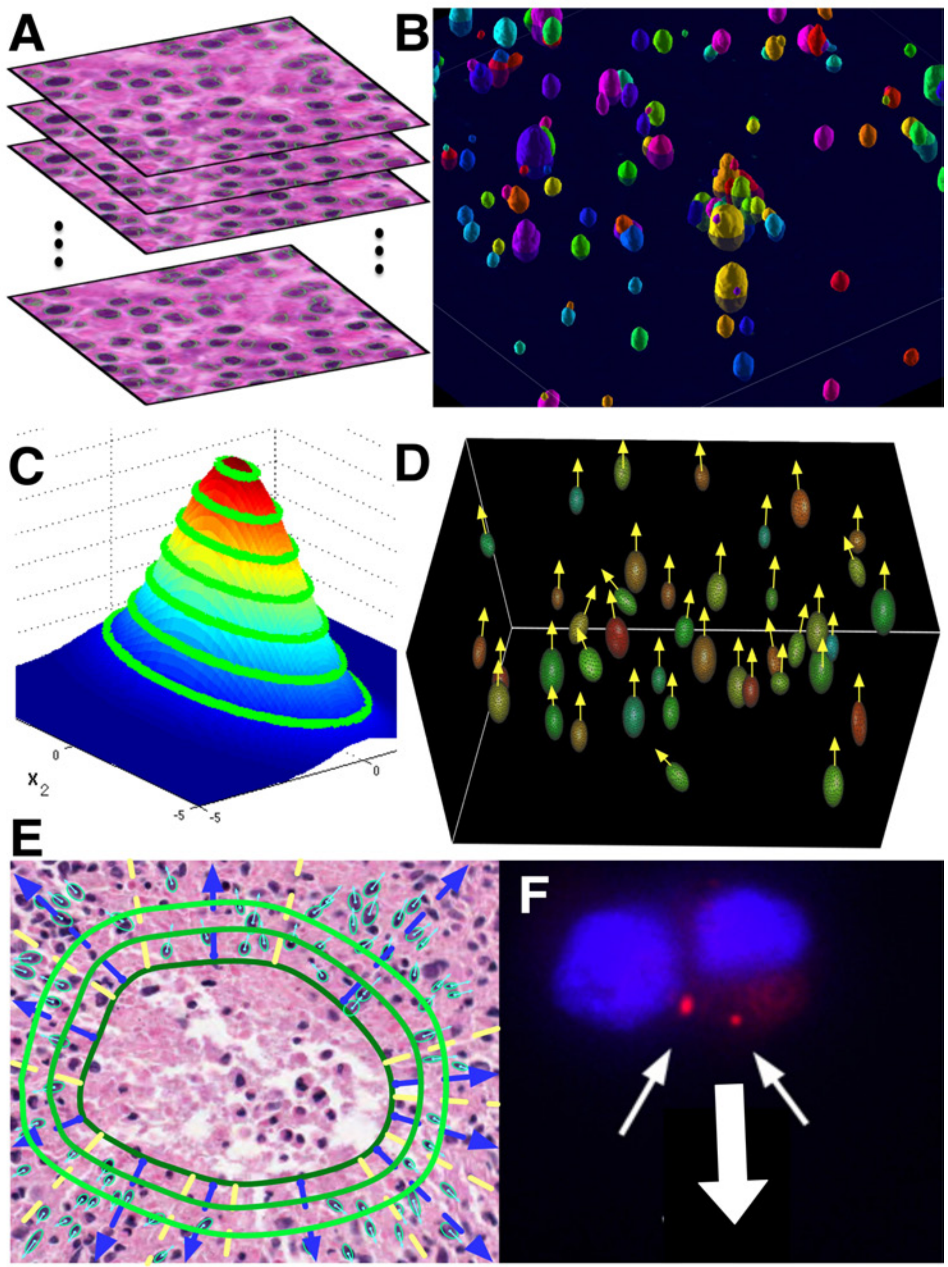
Scientific Aim on PCs



1) Image Registration
2) 2D/3D Cell Segmentation
3) Cell Cross-section Tracklet
4) Cell Reconstruction
5) Degree of Cell Directionality Measure
6) Statistical Test on Significance
7) Spatial Patterns of PC and Vessel Distribution

Step 1: Tissue Level Registration

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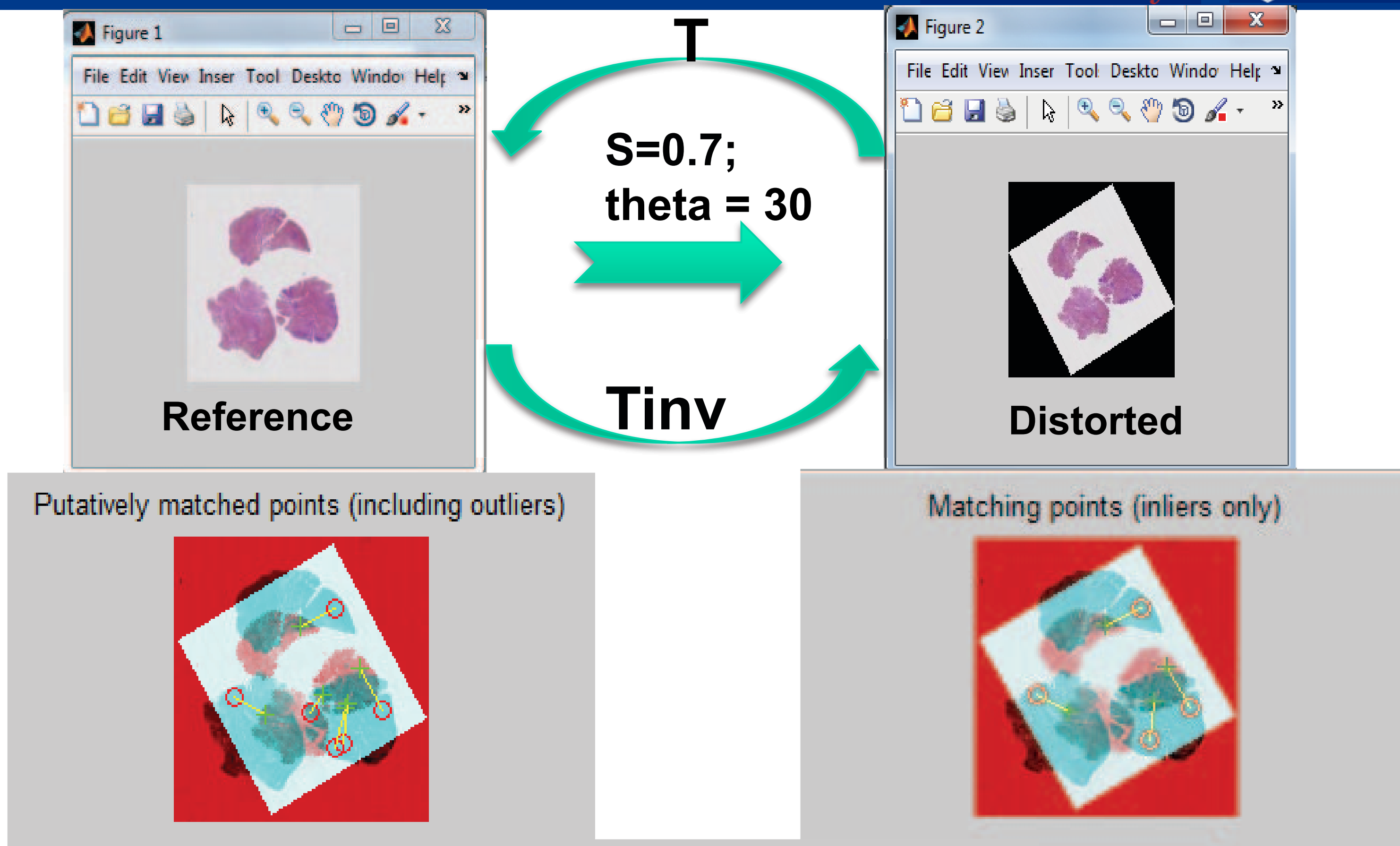
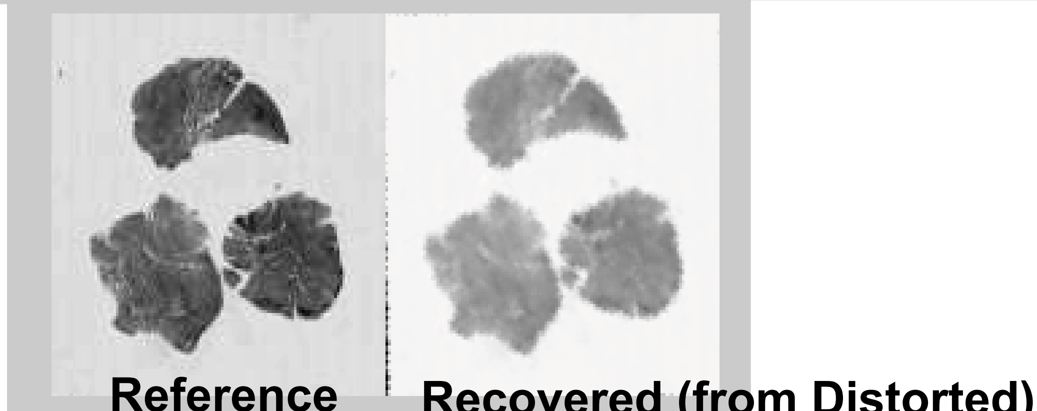


Step 1: Registration (Tissue/Coarse Level)



Step 2: 2D Nuclei Segmeantion

Seed Detection
(determine the number of cells)

↓

Active Contour Model
(deform contours)

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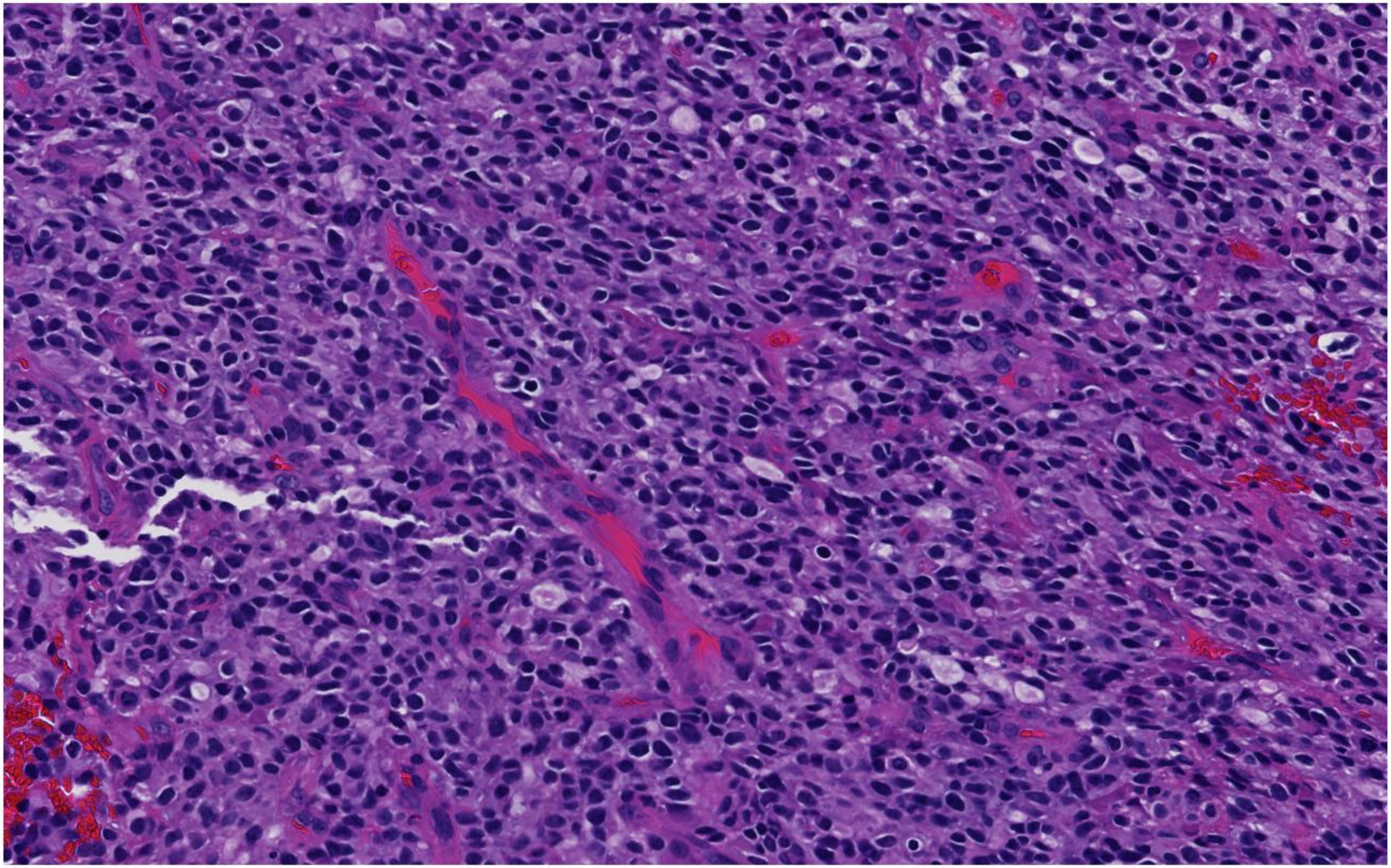
Original GBM Image



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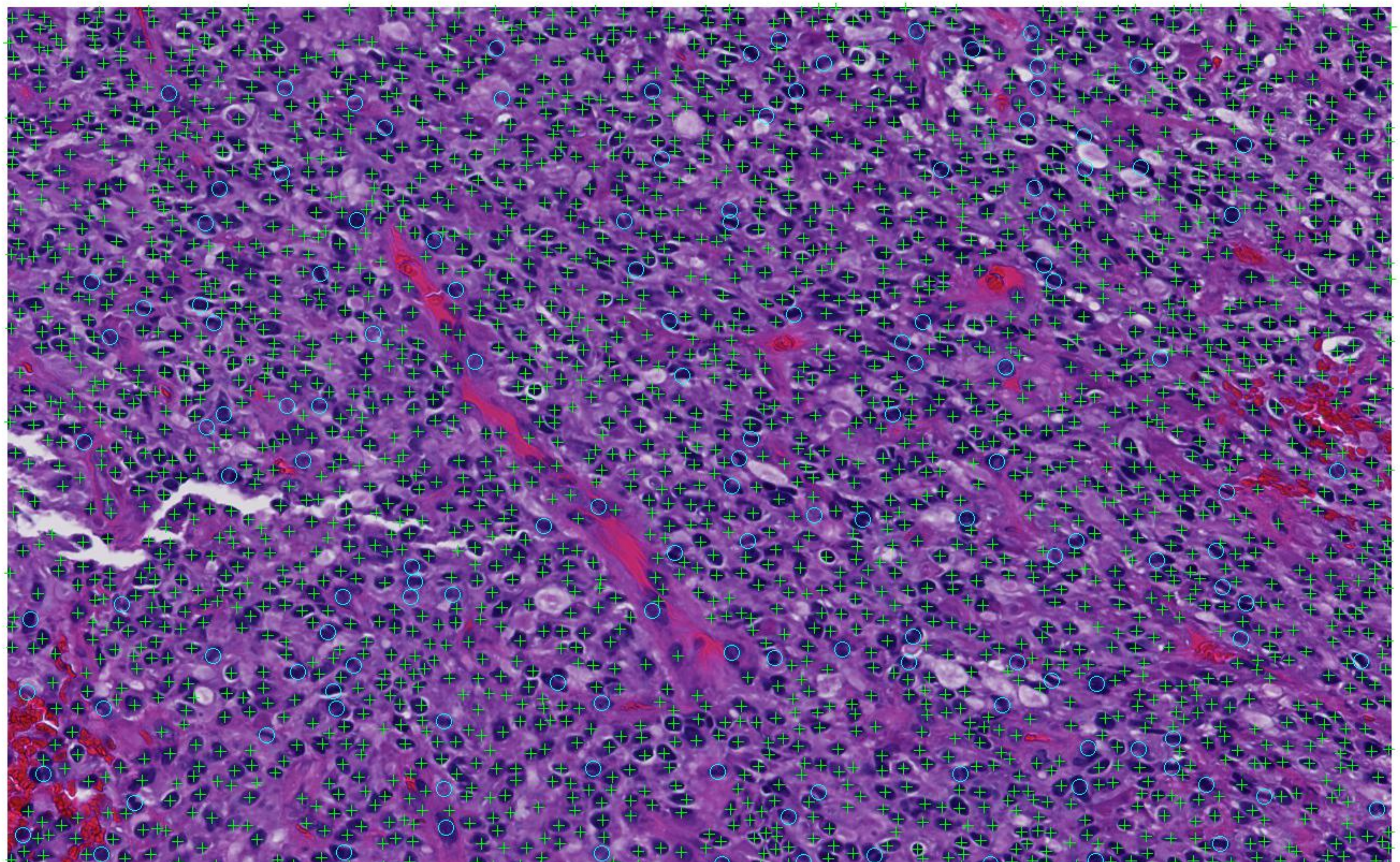
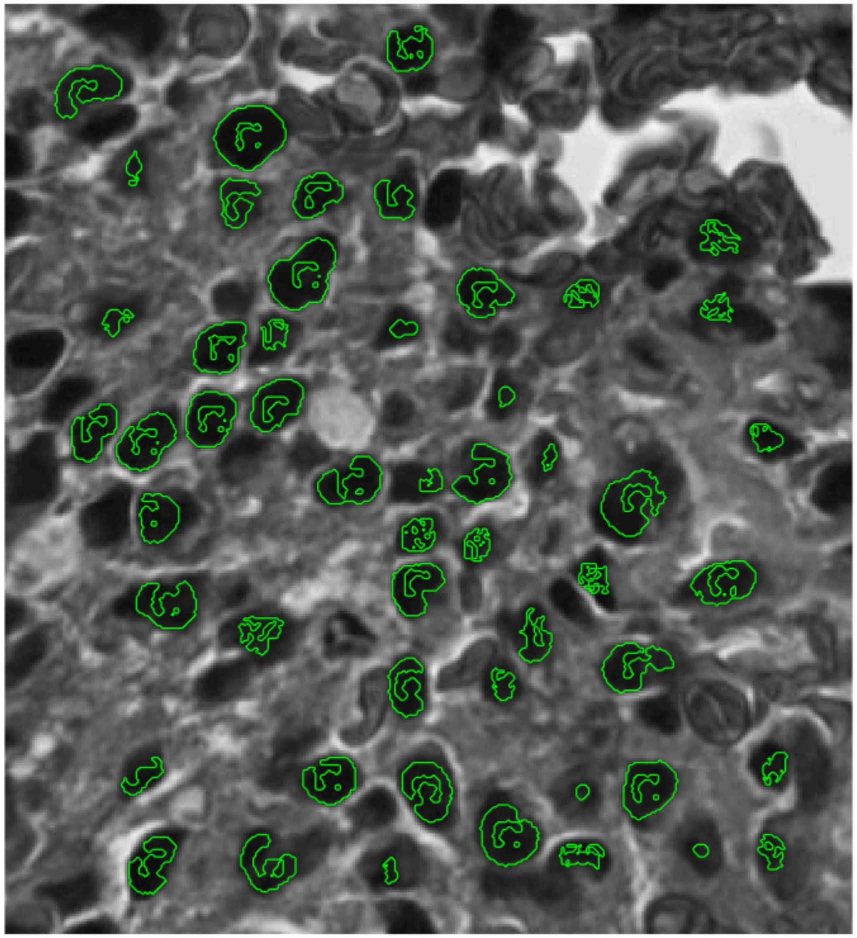
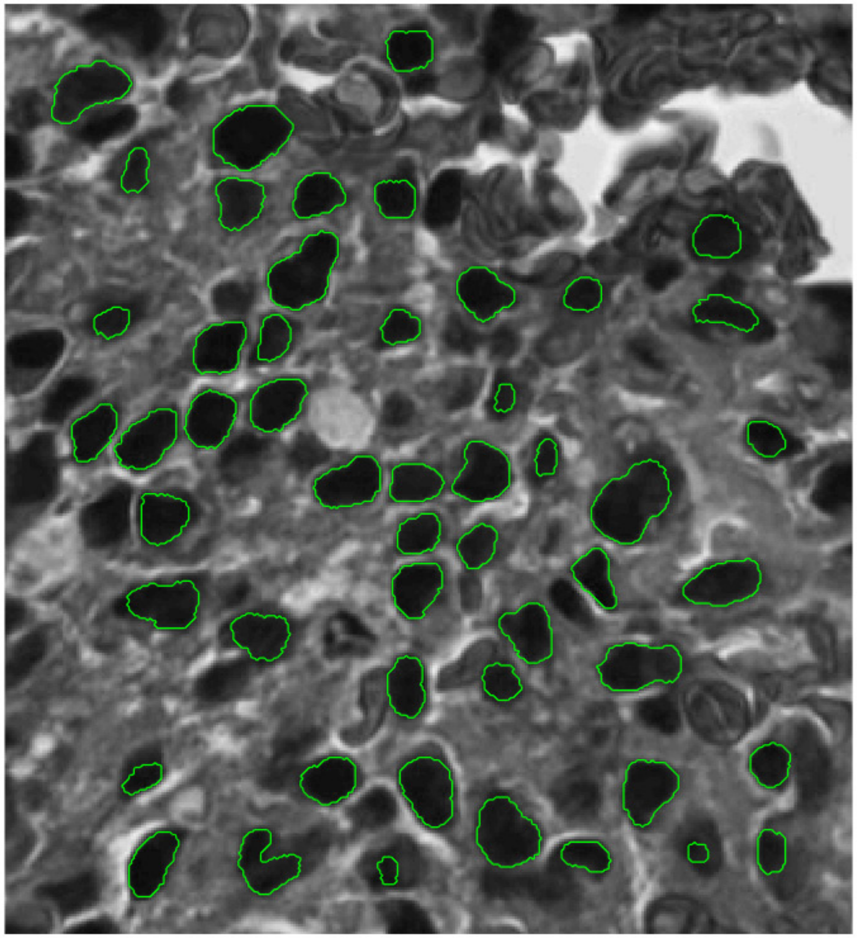
Final Result



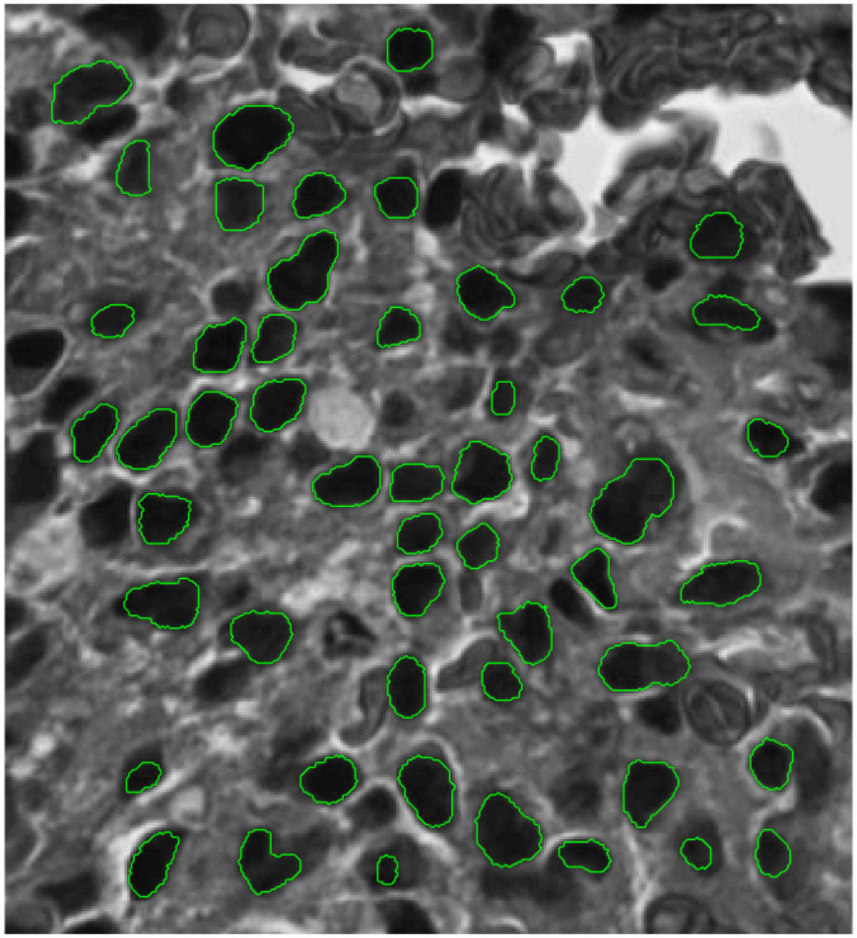
1 iterations



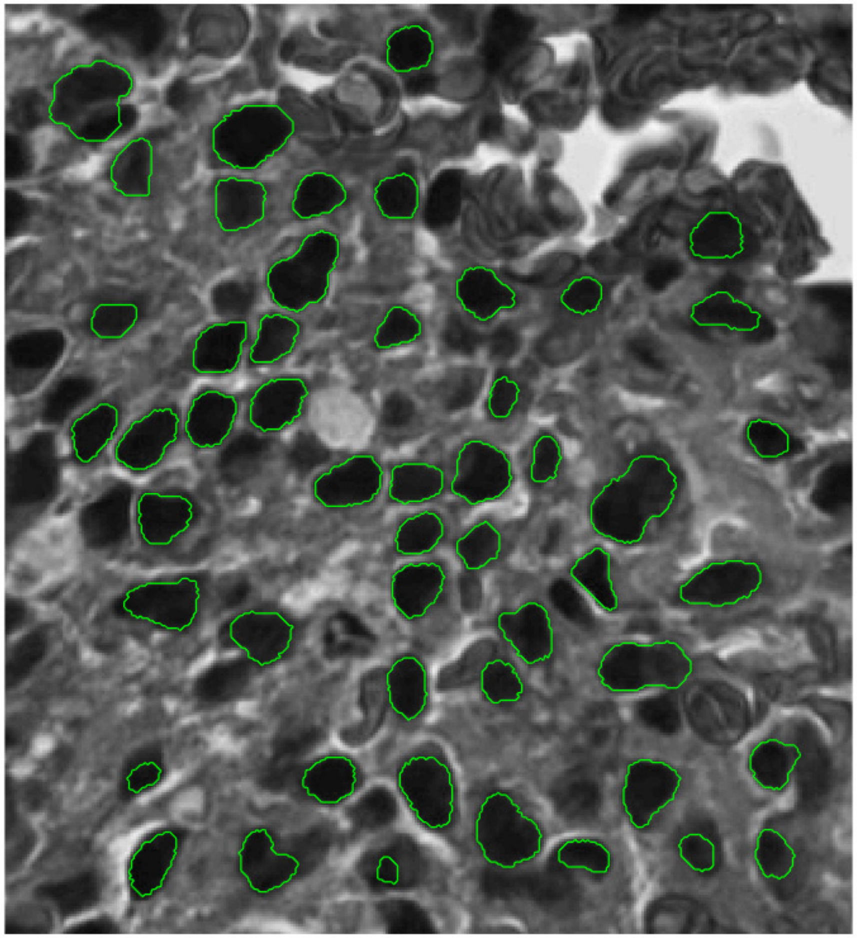
4 iterations



7 iterations



10 iterations



Thank you!

NIH National Institutes of Health

NSF

National Cancer Institute

University of Leeds