Quelques approches pour la quantification d'Incertitudes dans le couplage modèle - images

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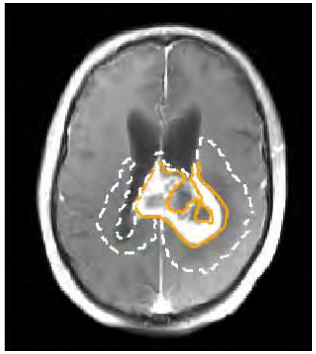
Radiotherapy of Gliomas

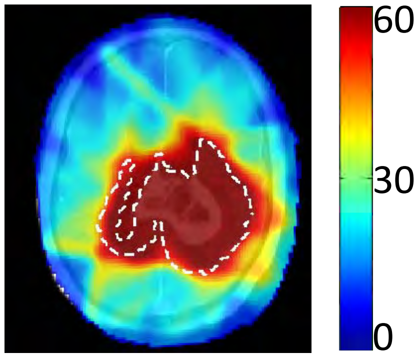
- Image Based planning :
  - GTV : Gross tumor volume
  - CTV : Clinical Target Volume
  - OAR : Organs at risks



Definition of GTV
on T1Gd MRI

Prescription dose

Optimisation



Delivered dose (Gray)

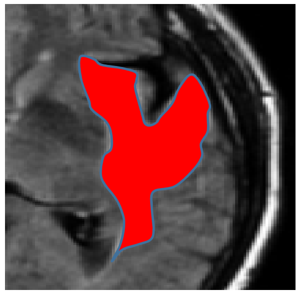
Radiotherapy

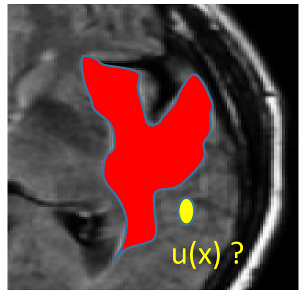
Current Limits of Radiotherapy Planning

1. Do not account for infiltrative tumor cells beyond visible boundary

Use of Biophysical Models to estimate Tumor cell density u(x)

Must account for model parameters uncertainty

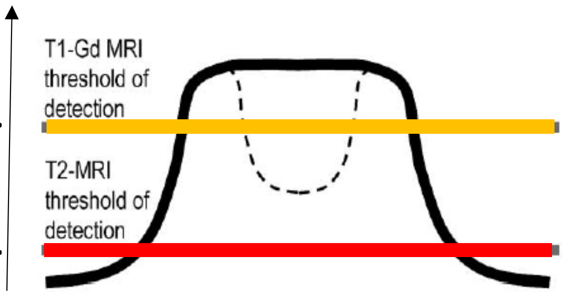


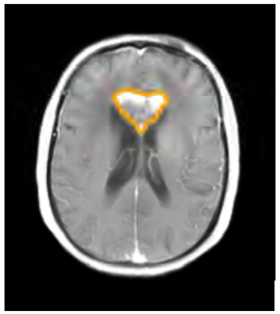


Tumor Cell density

Necrotic Core — U1 Thres.

Edema — U2 Thres.





T1Gd MRI

T2-FLAIR MRI

Current Limits of Radiotherapy Planning

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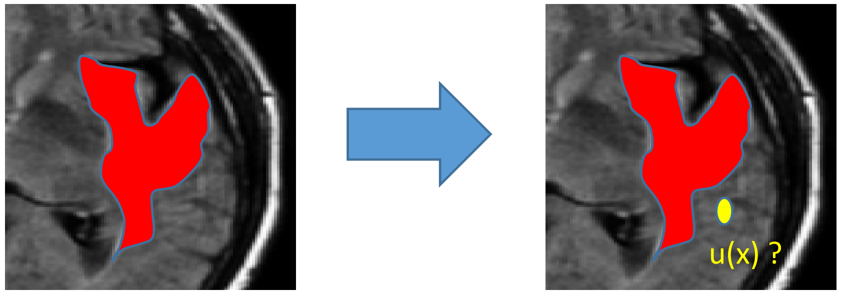
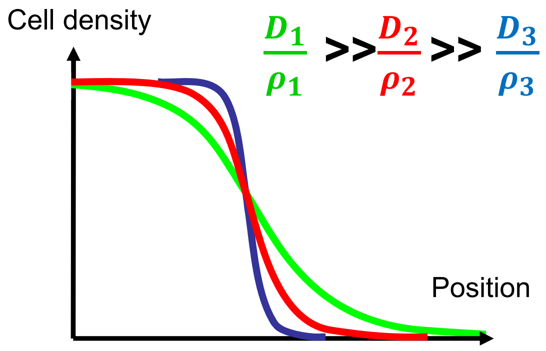


2. Delineation of Tumor volume is often difficult and inaccurate

Account for delineation uncertainty

Tumor Extension & Growth Models

- Tumor Growth Model FKPP:
  - Anisotropic diffusion due to white matter fibers
  - Estimate tumor cell density during 2 time points
  - Depends on speed $\sqrt{\rho D}$ and invisibility index $\sqrt{\frac{D}{\rho}}$



Reaction Diffusion equation:

$$\frac{\partial u}{\partial t} = \underbrace{\nabla(D.\nabla u)}_{\text{Diffusion}} + \underbrace{\rho u(1-u)}_{\text{Proliferation}}$$

u : Tumor cell density

D : Diffusion coefficient

ρ : Proliferation rate

Tumor Growth Model

Reaction Diffusion equation:

$$\frac{\partial \boxed{u}}{\partial t} = \nabla(\boxed{D}.\nabla \boxed{u}) + \boxed{\rho}\boxed{u}(1 - \boxed{u})$$

$\boxed{u}$: Tumor cell density

$\boxed{D}$: Diffusion coefficient

$\boxed{\rho}$: Proliferation rate

Discretization with LBM on multi-core CPUs

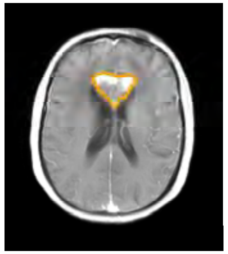
Axial Coronal Sagittal

Harpold, H. et al.: The evolution of mathematical modeling of glioma proliferation and invasion. Journal of Neuropathology & Experimental Neurology (2007)

Estimating Tumor Extension

- C(x) only depends on contour and "invisibility index" $i = \sqrt{\frac{D}{\rho}}$
- Asymptotic analysis of FK leads to solving Eikonal eq.

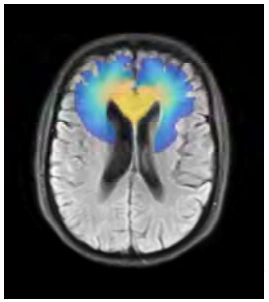
$$\boxed{\frac{\sqrt{\nabla\tilde{u}\cdot\left(\mathbf{D}\nabla\tilde{u}\right)}}{\sqrt{\rho\tilde{u}}\left(1-\sqrt{\tilde{u}}\right)}=1,\ \tilde{u}\left(\Gamma\right)=u_0}$$



or

U=0.8

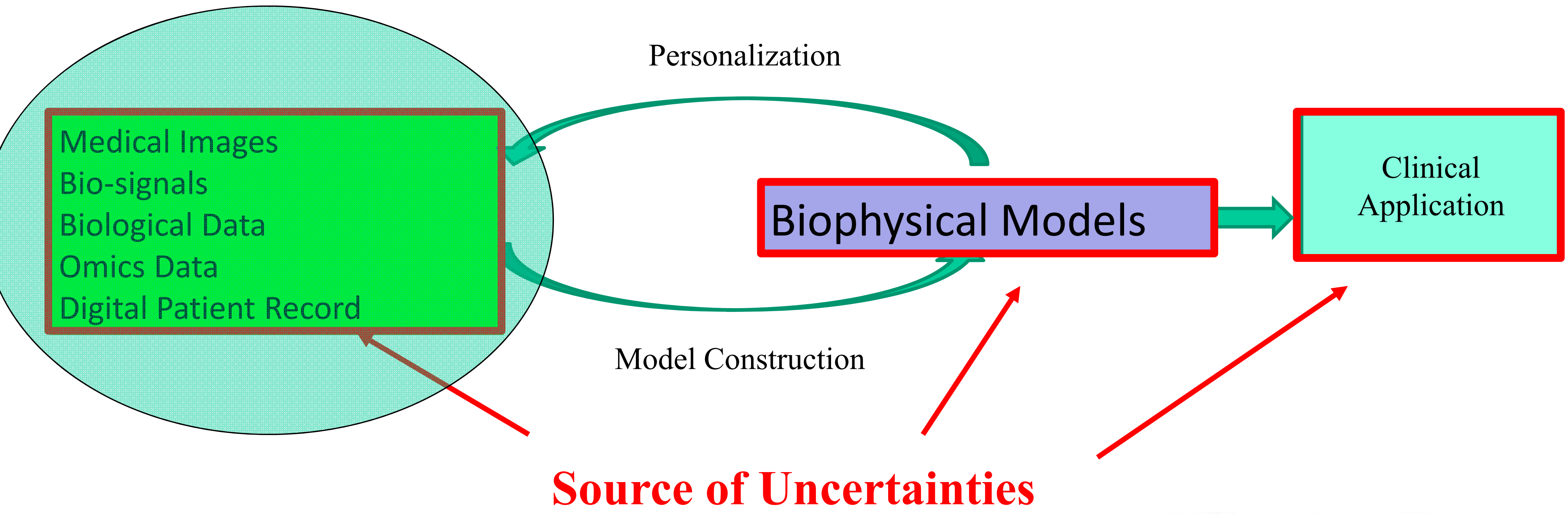
U=0.2



- Solved with Anisotropic Fast Marching Algorithm

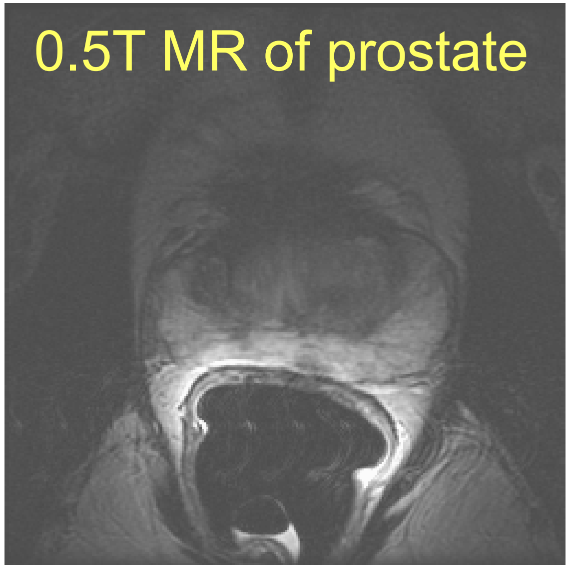
E. Konukoglu, O. Clatz, P.Y. Bondiau, H. Delingette, N. Ayache. *Extrapolating Glioma Invasion Margin in Brain MRI: Suggesting New Irradiation Margins.* Medical Image Analysis 2010.

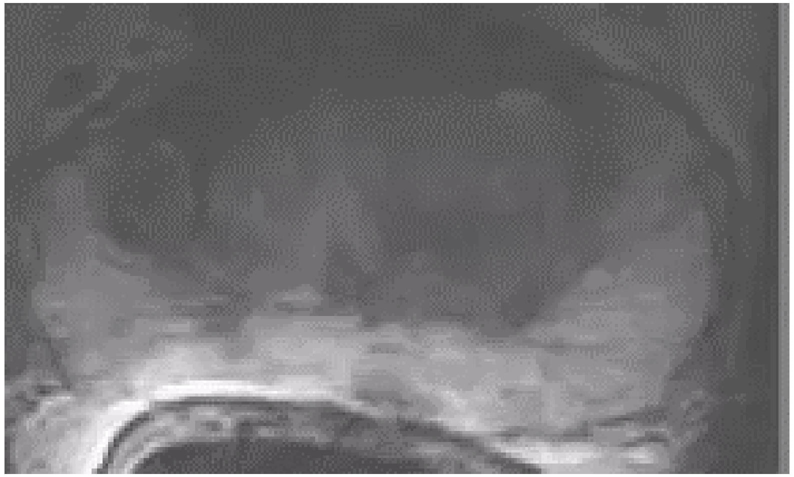
Coupling between Biophysical Models and Medical Imaging



Uncertainty Quantification in Medical Image Analysis

- Widely Ignored issue
- Example : Image Segmentation



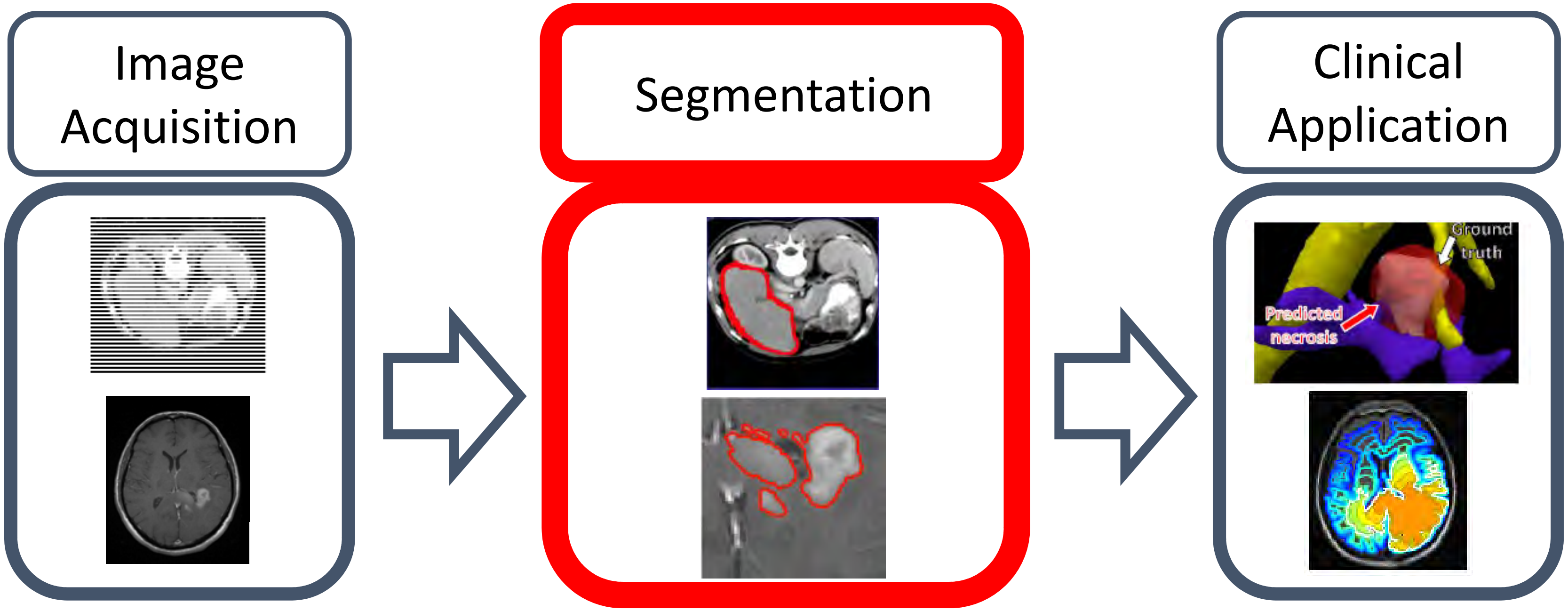


Potentially Large Inter Expert Variability

State of the art : Uncertainty in segmentation

- Generative probabilistic models:
  - Maximum a Posteriori or Maximum Likelihood
- Seeked Uncertainty p(Z):
  - Joint posterior probability of shape and Image parameters $p(\theta_S, \theta_I | Data) \rightarrow p(Z|I) = \int p(Z|\theta_S, \theta_I) p(\theta_S, \theta_I | Data) d\theta_S \, d\theta_I$
- Current approach :
  - Stochastic Sampling (MCMC) for small problems
  - Often use "Mean Field Approximation" or "Variational Bayes" for large problems $p(\theta_I, \theta_S | Data\ ) \approx \prod_I p(\theta_i | Data)$

Common Problem



Source of uncertainty !

Common Problem

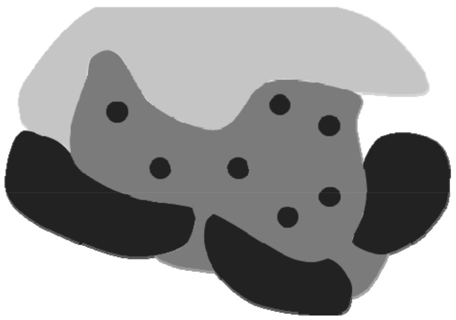
Solution: Use many segmentations to evaluate the uncertainty

- Multiple clinicians segmentations

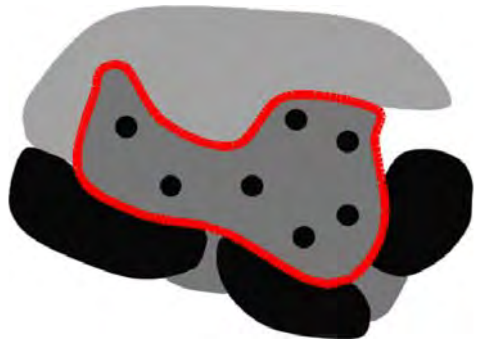
Time & Resource consuming !

- Automatically create numerous plausible segmentations from a single expert one

State-of-the-Art : Sampling Probabilistic Generative Image Models



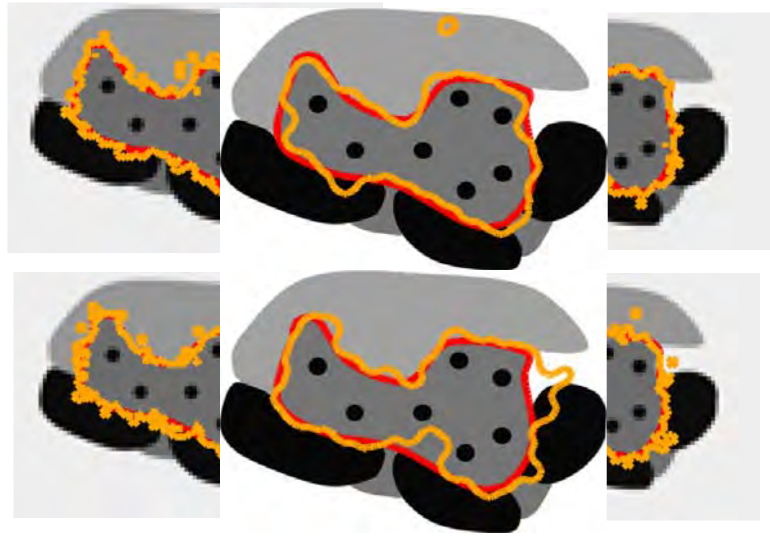
Input Image



Manually / Automatically Segmented Image

Samples from Log Odds Level Sets

Samples from Markov Random Field



Lack of spatial coherence and plausibility

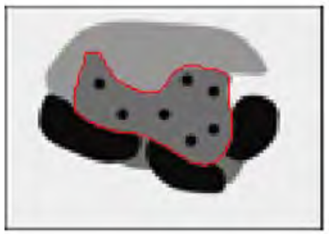
Warfield, S.K. et al.: Simultaneous truth and performance level estimation (STAPLE): an algorithm for the validation of image segmentation. IEEE TMI (2004)

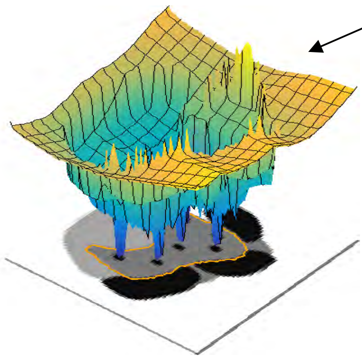
Pohl, K.M. et al.: Using the logarithm of odds to define a vector space on probabilistic atlases. Medical Image Analysis (2007)

Our Approach: GPSSI for segmentation sampling

Gaussian Process:
Segmentation as a level set

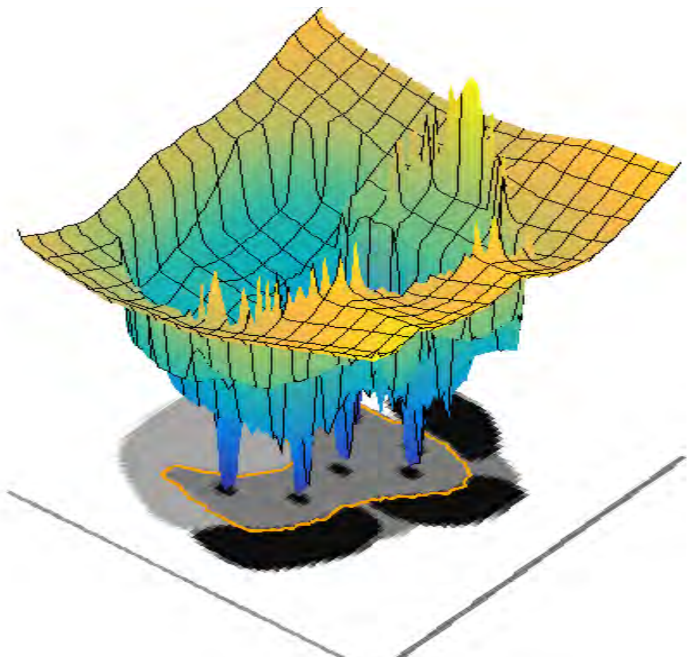
$$\text{Segmentation} \sim \mathcal{N}(\mu, \Sigma)$$





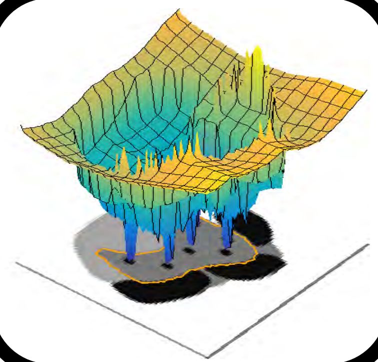
Geodesic Distance Map :

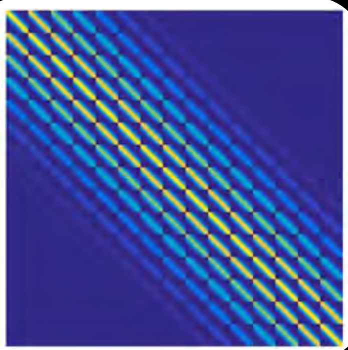
- Zero Level Set ->Input Segmentation
- Slope depends on Intensity Variation



GPSSI

Gaussian Process:
Segmentation as a level set





Mean:
Geodesic
distance

+

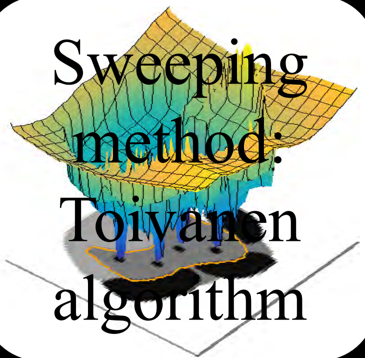
Covariance:
Squared
exponential

=

Samples

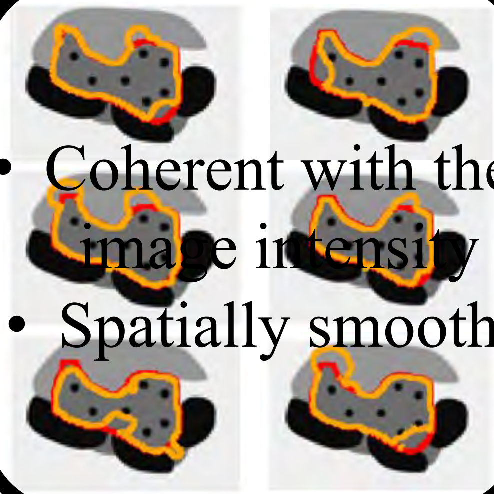
Our Solution: GPSSI

Gaussian Process:
Segmentation as a level set



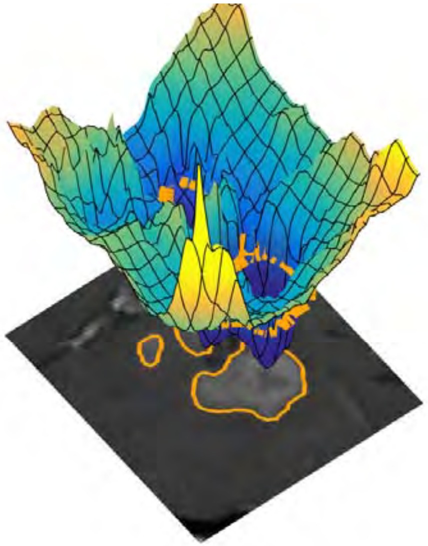
Sweeping method: Toivanen algorithm

Circulant matrix: Efficient factorization

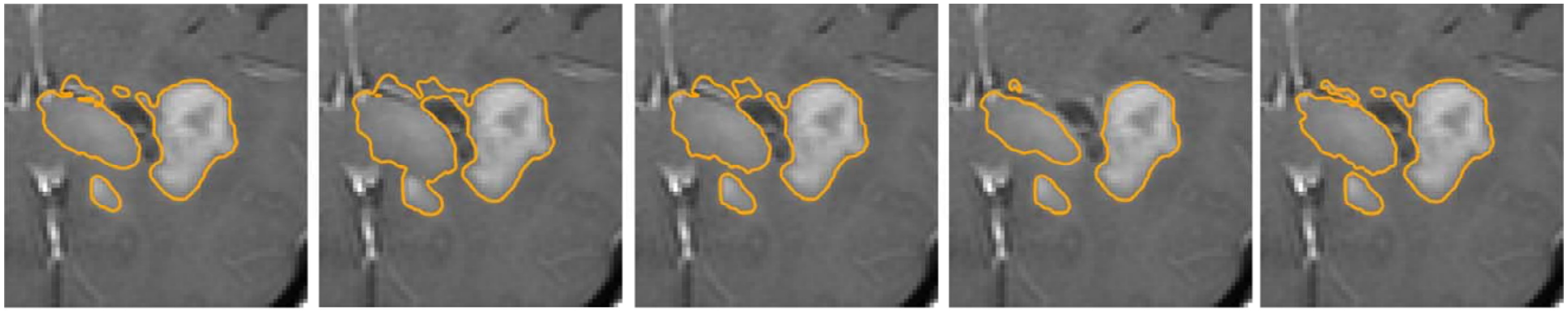


- Coherent with the image intensity
- Spatially smooth

Mean: Geodesic distance + Covariance: Squared exponential = Samples

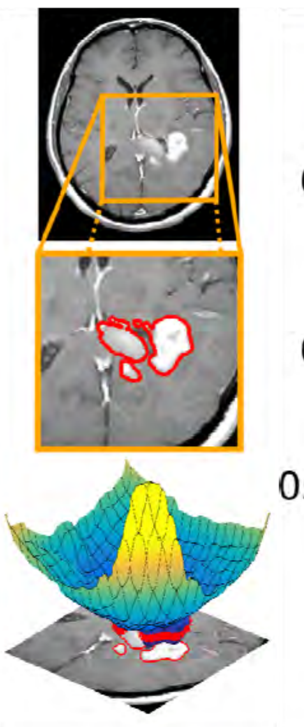


Segmentation samples of brain tumor (T1Gd MRI)

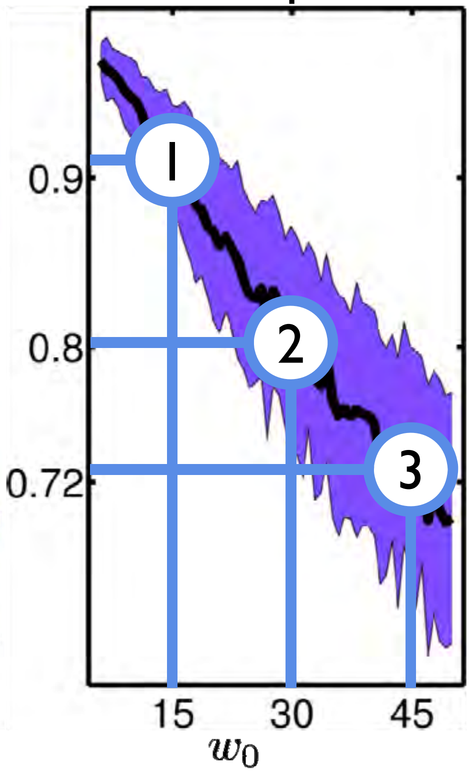


Control Variability

Segmentation samples of brain tumor (T1Gd MRI)

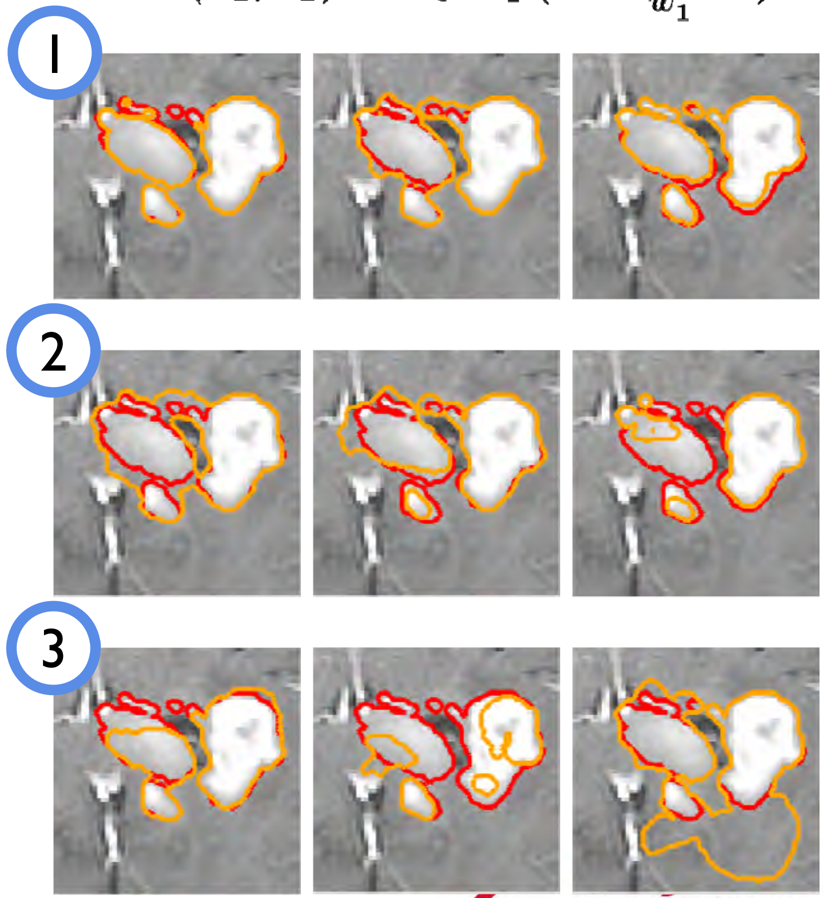


Inter-Sample Dice



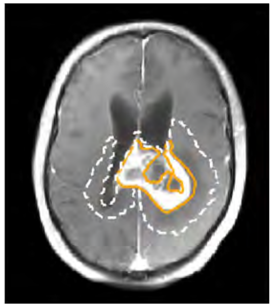
Squared exponential covariance

$$\Sigma(x_1, x_2) = w_0 \exp\left(-\frac{d(x_1, x_2)^2}{w_1^2}\right)$$



Towards Probabilistic Radiotherapy Planning

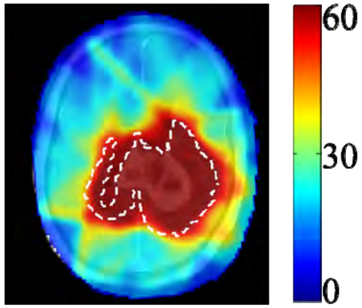
- Old Workflow



Definition of GTV on T1Gd MRI

Prescription dose

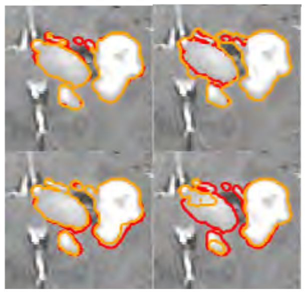
Optimisation



Delivered dose (Gray)

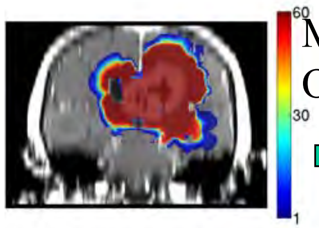
Radiothérapie

- New Workflow 1 (Without Any Tumor Model)



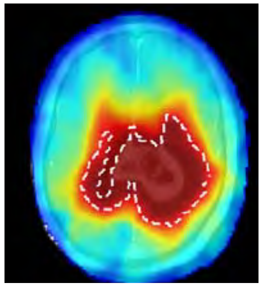
Segmentation Samples

MCMC



Probabilistic Prescription Dose

Multiple Optimisation

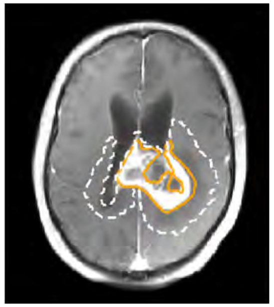


Expected Delivered Dose

Actual Delivered Dose

Towards Probabilistic Radiotherapy Planning

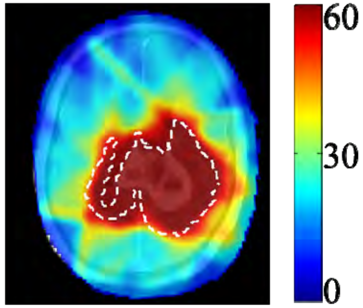
- Old Workflow



Definition of GTV on T1Gd MRI

Prescription dose

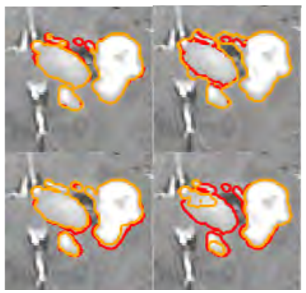
Optimisation



Delivered dose (Gray)

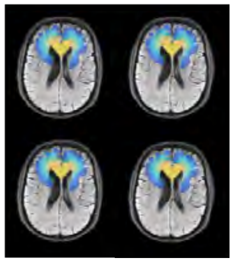
Radiothérapie

- New Workflow 2 (with tumor model)



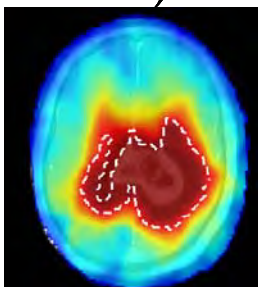
Segmentation Samples

MCMC



Samples of tumor Cell density u(x)

Multiple Optimisation



Expected Delivered Dose

Actual Delivered Dose

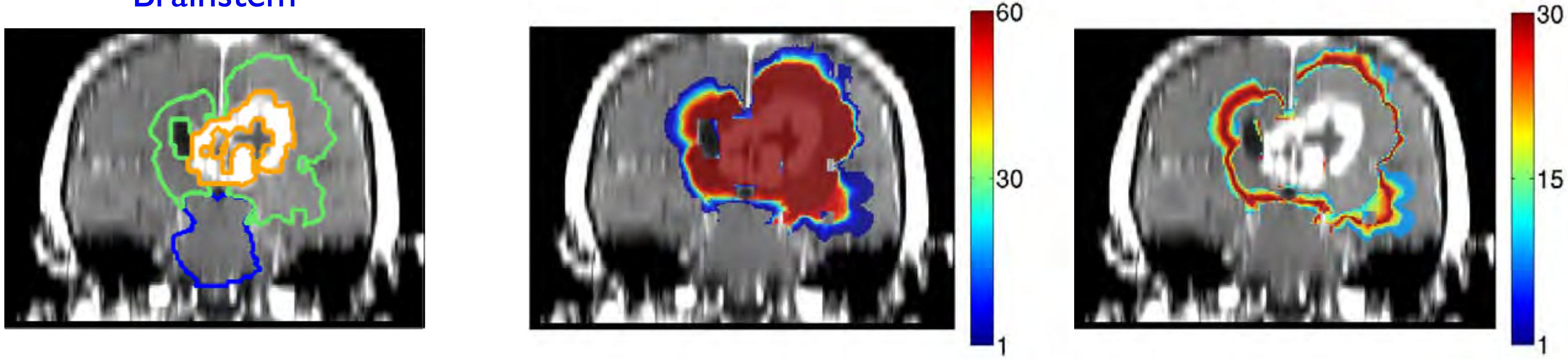
Probabilistic Prescription Dose

Brain tumor on T1Gd MRI:

Gross Tumor Volume
Clinical Target Volume
Brainstem

Prescription dose:
Mean dose

Standard deviation
of the dose



Sample 40 GTV and brainstems, Compute 40 CTV

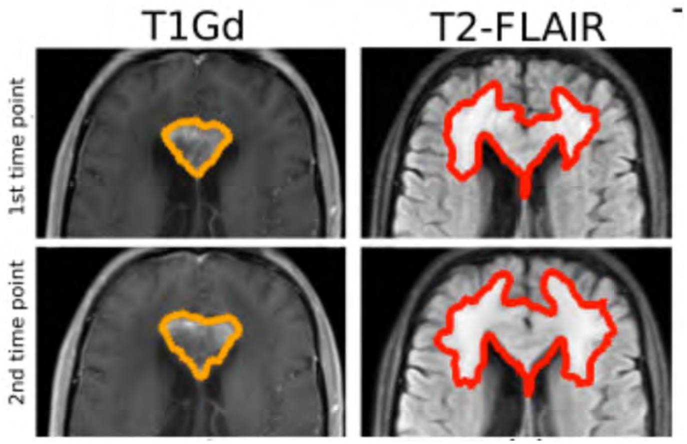
Planning: 60 Gy inside the CTV, 0 Gy outside

Bayesian Personalization of Tumor Models

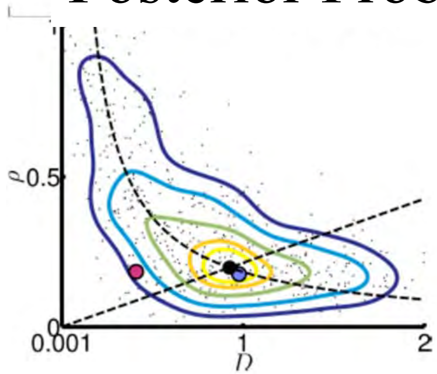
- Estimate posterior distribution $P(D, \rho | Segmentation)$ from :
  - Edema and Tumor core contours at 2 time points

1[st] Time

2[nd] Time



Posterior Probability



Posterior

Probability that D, ρ match the segmentations Seg?

Posterior: $P(D, \rho \mid Seg) \propto$ $\boldsymbol{P(Seg|D, \rho)}$ $\boldsymbol{P(D, \rho)}$

Likelihood

$$\mathrm{P}(Seg|D, \rho) = \exp\left(-\frac{HD^2}{\sigma^2}\right)$$

HD: Hausdorff Distance

Prior

Log-uniform

Gaussian Process Hamiltonian Monte Carlo (GPHMC):

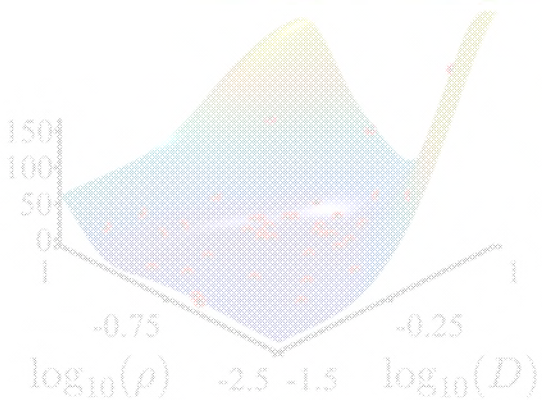
- High acceptance rate
- Reasonable number of model evaluations

GPHMC

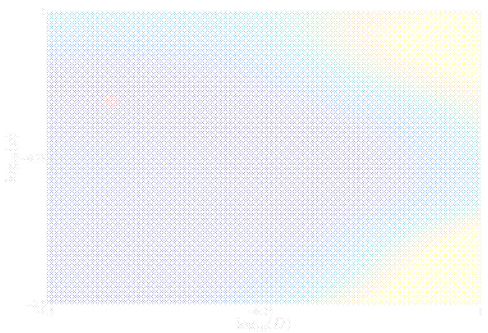
Interpolate the potential energy with a GP based on random points

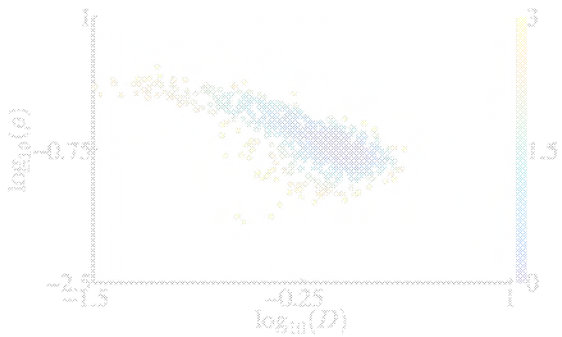
Sampling strategy: Hamiltonian dynamics using the GP interpolation

Posterior probability samples



$E_{pot} = -\log P(D, \rho | Seg)$





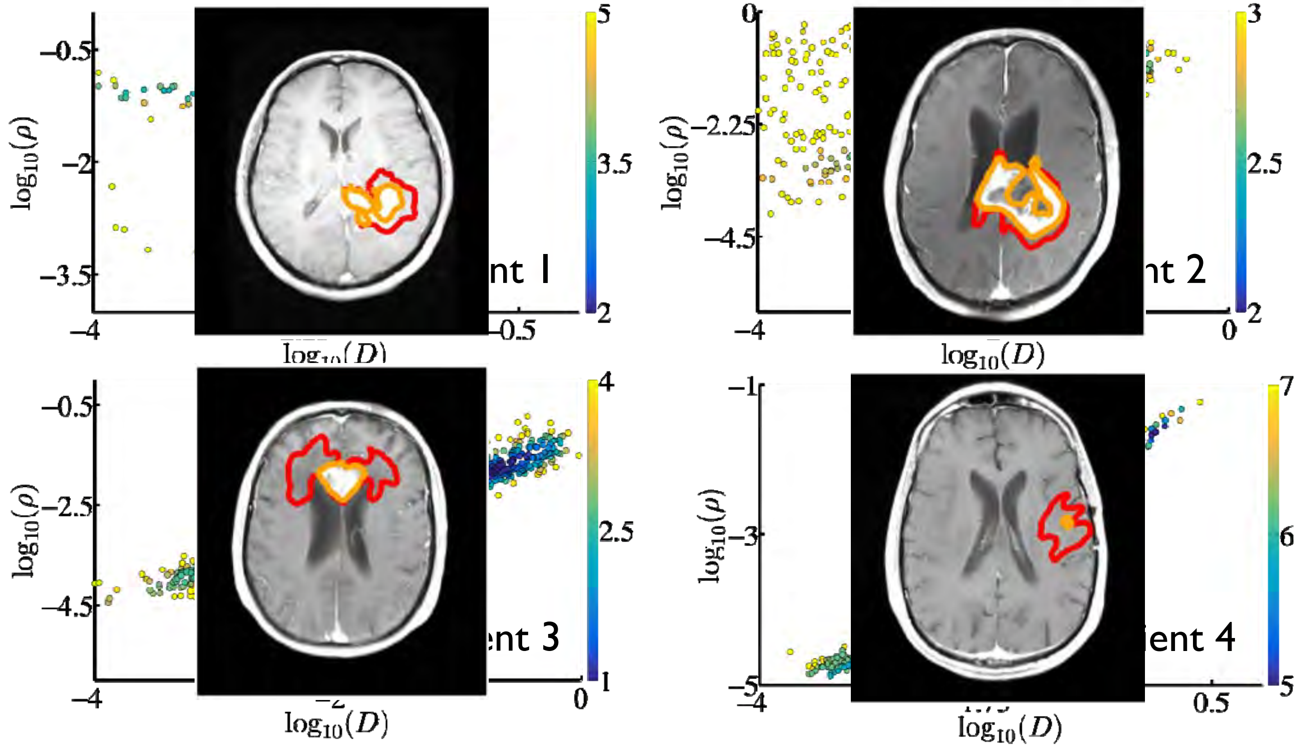
Rasmussen, C. E.: Gaussian processes to speed up hybrid Monte Carlo for expensive Bayesian integrals. Bayesian Statistics (2003)

Patients

7 patients studied

Details for 4 patients

Posterior Samples

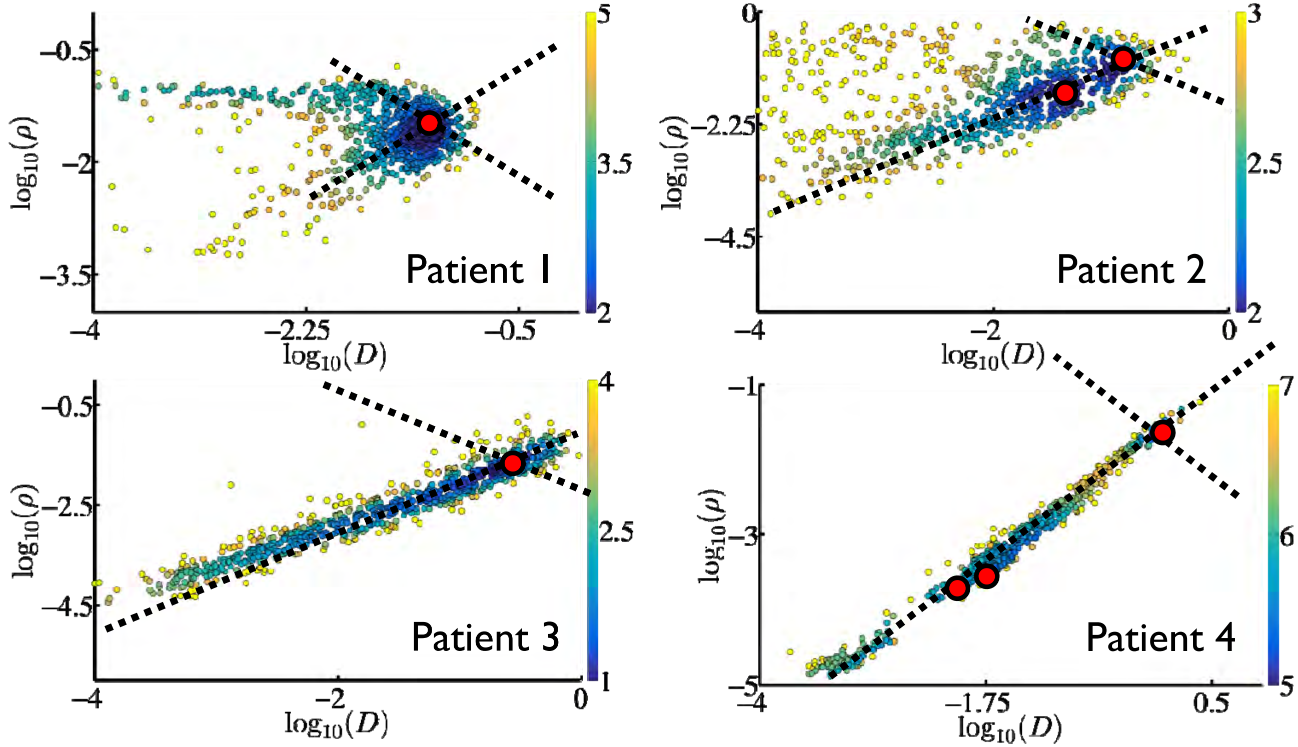


Posterior Samples

Direct optimization (multiple initialization)

$v = 2\sqrt{D\rho}$ = cstant

$\lambda = \sqrt{\frac{D}{\rho}}$ = cstant



1. Samples from the posterior density of the parameters
2. Comparison with the direct optimization results
3. The personalization captures well the infiltration λ

Bayesian Model Selection

- Use posterior distribution to compare 2 hypothesis :
  - M1 : T2-FLAIR abnormality frontier is c= 16 %
  - M2 : c=2%
- Compute Model Evidence (Chib's method)

$$P(Segmentation \mid M) = \frac{P(Segmentation \mid M, D, \rho) P(D, \rho \mid M)}{P(D, \rho \mid M, Segmentation)}$$

- Compute Bayes factor, $B = \frac{P(Segmentation \mid M_1)}{P(Segmentation \mid M_2)}$
- Results slightly leans towards the 16 % threshold

Probabilistic Delivered Dose

- Model tries to minimize tumor cell survival and maximize survival of organs at risk

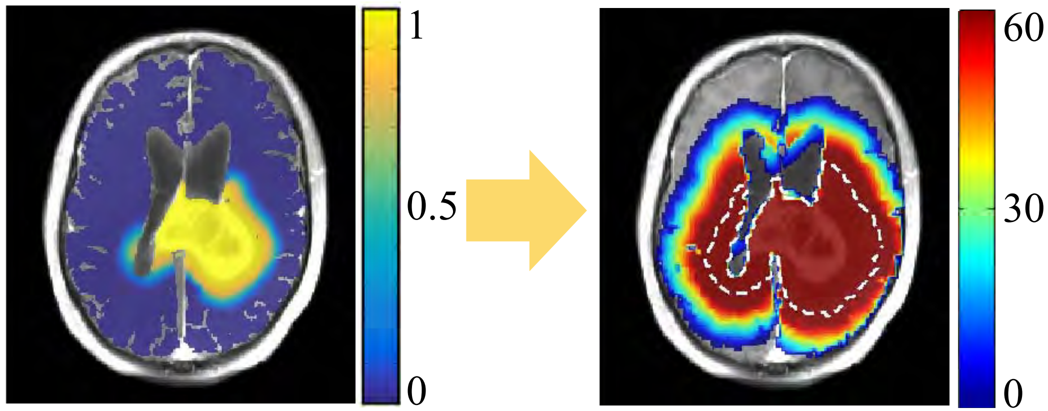
Prescription Dose

- Maximum A Posteriori

$$d = \text{argmin}_d \sum_i u_i^{\text{MAP}} \exp(-\alpha d_i)$$

- Probabilistic

$$d = \text{argmin}_d E[\sum_i u_i \exp(-\alpha d_i)]$$



Tumor cell density: u

Delivered dose d

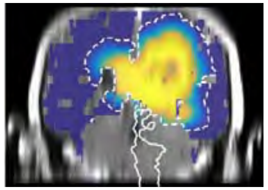
Effect of Segmentation Sampling & Tumor extension Modeling

Scenario 1
Clinical routine,
1 time point
only

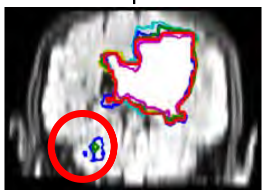
Scenario 2
2 time points

Scenario 3
2 time points +
segmentation
samples

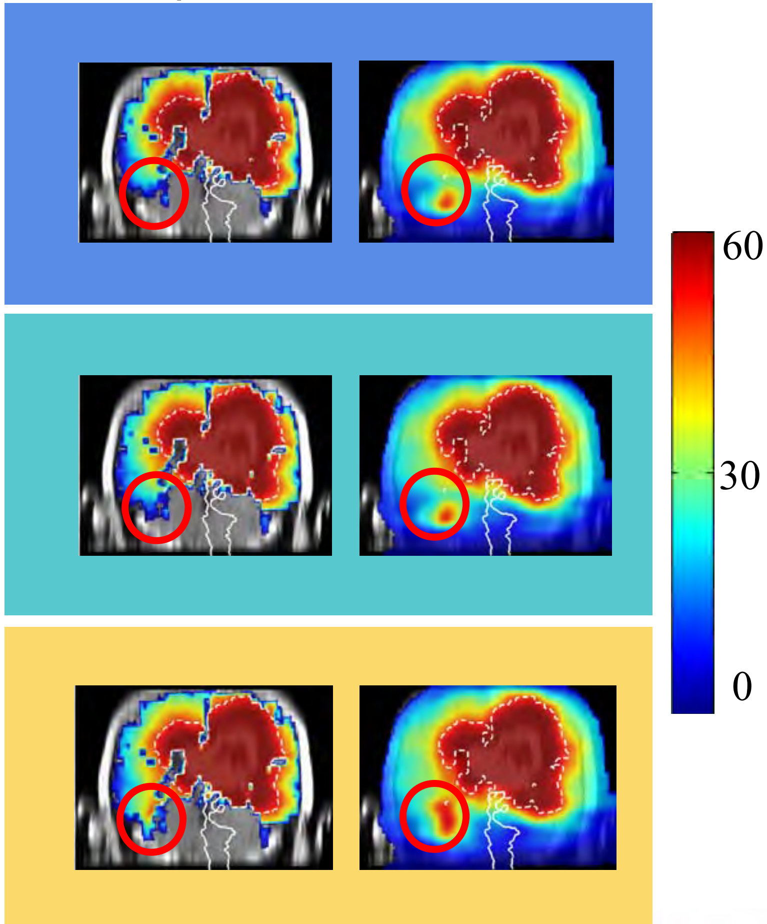
Scenario 3:
Mean tumor cell density



Segmentation
samples



Prescription dose IMRT



Summary of Uncertainty in Radiotherapy Planning

- Without tumor model :
  - Probabilistic CTV by averaging plausible CTV
- With Tumor model
  - Probabilistic CTV by including estimation of tumor cell density
- Dose Delivery planning can account for effect of segmentation and model parameters uncertainty
- Full Posterior with GPHMC for small number of parameters
- First steps towards Bayesian model selection

Related publications

- Matthieu Lê, Hervé Delingette, Jayashree Kalpathy-Cramer, Elizabeth R Gerstner, Tracy Batchelor, Jan Unkelbach, and Nicholas Ayache. MRI Based Bayesian Personalization of a Tumor Growth Model. IEEE Transactions on Medical Imaging, 35(10):2329-2339, April 2016

- Matthieu Lê, Hervé Delingette, Jayashree Kalpathy-Cramer, Elizabeth R Gerstner, Tracy Batchelor, Jan Unkelbach, and Nicholas Ayache. Personalized Radiotherapy Planning Based on a Computational Tumor Growth Model. IEEE Transactions on Medical Imaging, pp 11, 2016.

- Matthieu Lê, Jan Unkelbach, Nicholas Ayache, and Hervé Delingette. Sampling Image Segmentations for Uncertainty Quantification. Medical Image Analysis, 34:42-51, December 2016..

Perspectives

- Develop image segmentation and registration methods with “meaningful” uncertainty quantification
- Need for reduced biophysical models for Bayesian personalization and model selection
- Adapt clinical decision process indices to uncertain measurements