Personalized Growth Modeling of Brain Tumours

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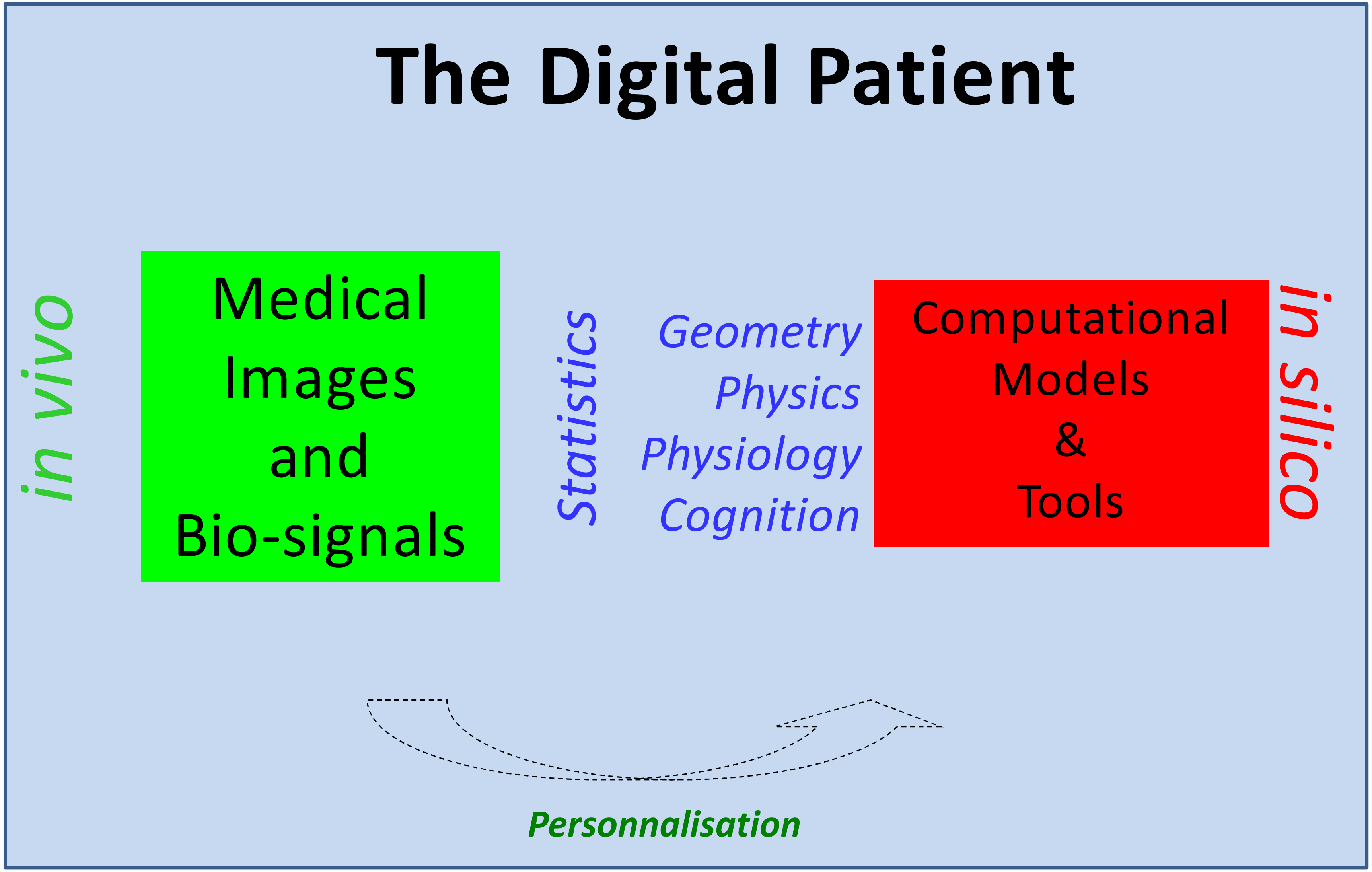
Joint work with E. Konukoglu, E. Stretton, M. Lê,
N. Cordier, E. Geremia, J. Unkelbach, B. Menze, N. Ayache


The Digital Patient
in vivo
Medical Images and Bio-signals
Statistics
Geometry
Physics
Physiology
Cognition
Computational Models & Tools
in silico
Personnalisation

Generic, Patient Specific, Statistical Models

Geometrical/Anatomical

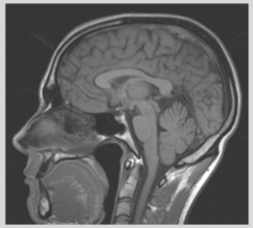
Iconic / Appearance

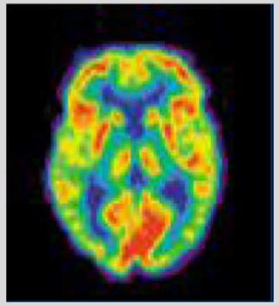
Physical Models

Physiological Models

Cognitive Models

+





Statistical =

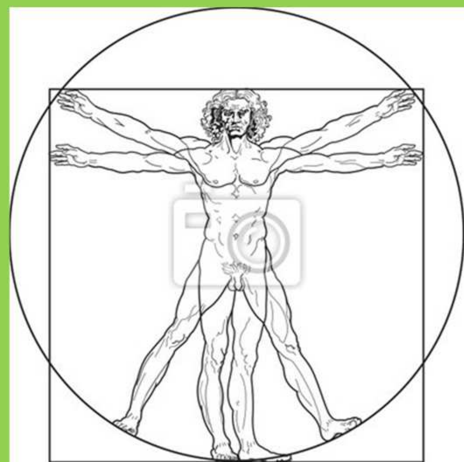
Variability across a population

Personalized =

Specific to a given patient

Generic =

Represent whole population

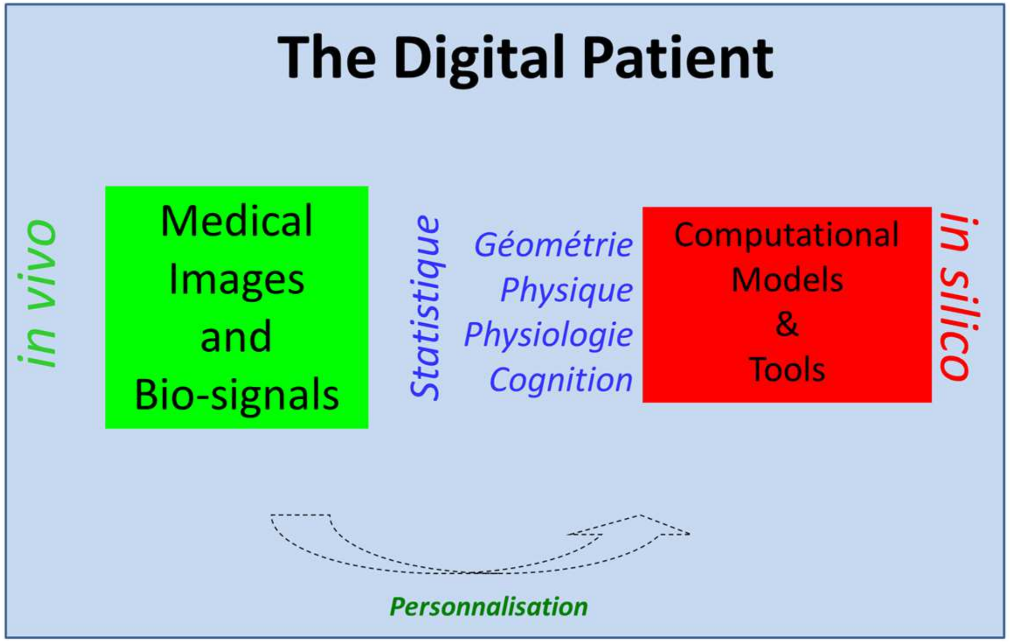


Applications of Digital Patient

Image Fusion

Computer-Aided Diagnosis

Therapy Simulation

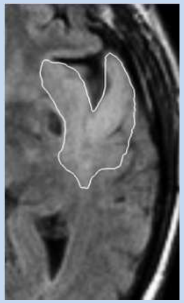


Therapy Planning

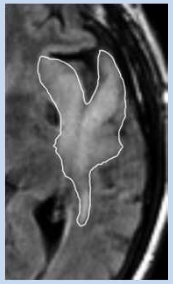
Therapy Guidance

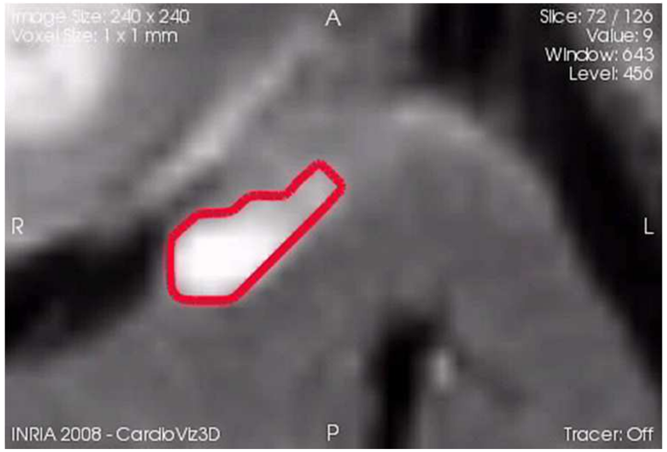
Patient data

Time 1



Time 2





Why is the simulation different from the observation ?

Source of Errors

- Errors from the observation :
  - Noise & Artefacts

Acquisition & Signal Processing Issue

- Errors from the computational model :
  - Computational domain (mesh)
  - Errors in the "parameters" : IC, BC

Personalization Issues

  - Errors in the implementation (bug)
  - Errors in the discretization (grid size)

Verification Issue

  - Errors in the Model (False Hypothesis)

Modeling Issue

Objectives of Model Personalization

- Model Validation (knowledge Building):
  - Model can represent observations ?
    - Yes -> can be tested for model prediction
    - No -> model should be modified
- Model Prediction
- Parameter analysis :
  - Parameter can be used for diagnosis

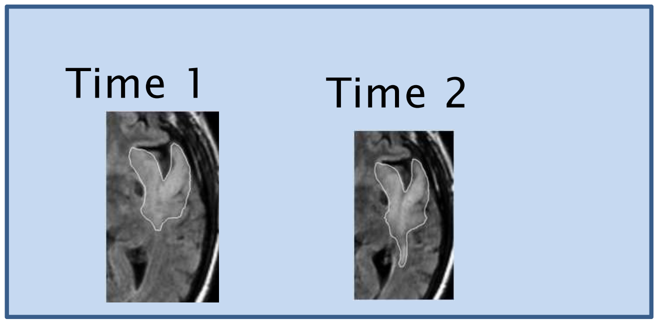
Data Regularization vs Model Personalization

- 2 sources of information :
  - Image Dataset provide observations
    - But may be noisy and partial
  - Biophysical Model based on the law of physics
    - But may not agree with the observation

Medical Images

Tumor Growth Model

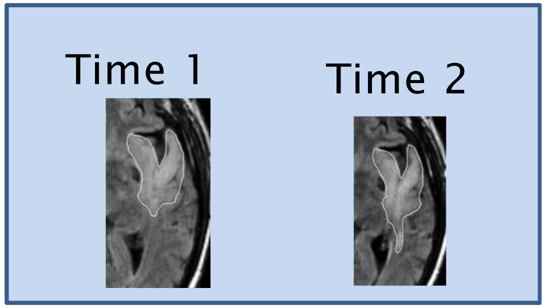
How to combine both information ?



Data Regularization

Data Regularization :
Filter
The data such that its
becomes
Physiologically
plausible

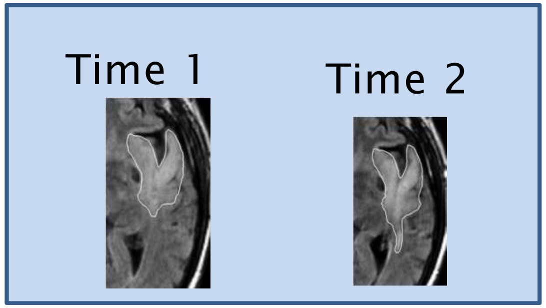
Mostly Trust
The Data



$$\underbrace{\frac{\partial X}{\partial t} = F(X,\theta)}_{\text{Biophysical Model}} + \underbrace{F_{img}}_{\text{Image Force}}$$

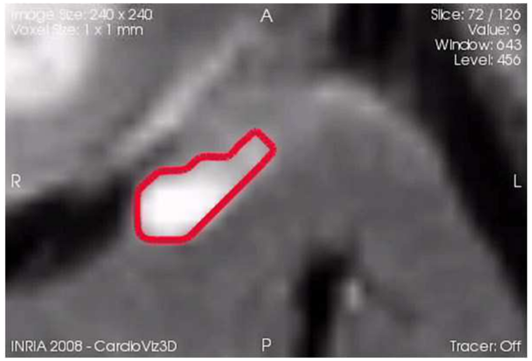
Data Regularization

Model Personalization



Mostly Trust The Model

Model Personalization : Fit Model Parameters, BC, IC from data



Find θ* such that

$$\frac{\partial X}{\partial t} = F(X,\theta^{*}) + F_{img}$$

Agrees with data

Model Personalization

=

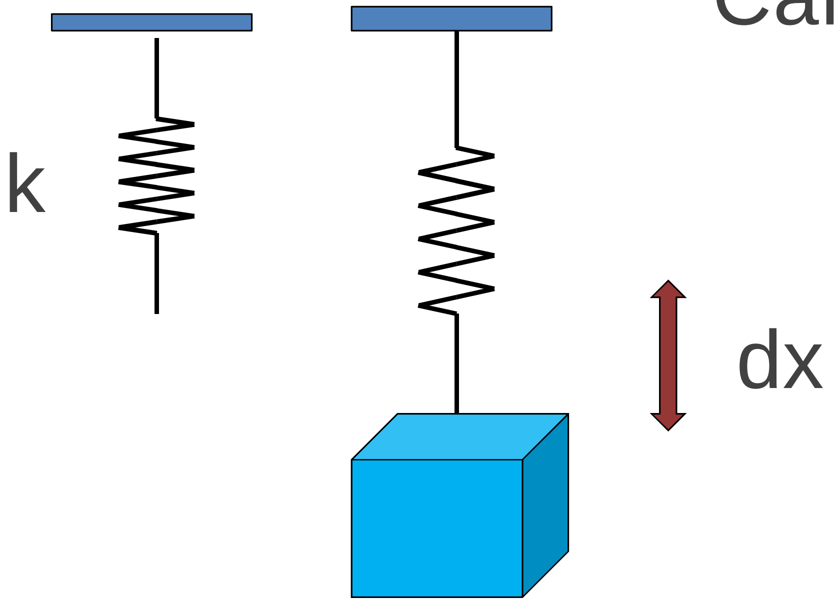
Data Assimilation

Parameter Estimation Issues

- Observability of the parameters
- Dimensionality of the parameters vs Dimension of the observations
- Optimization Techniques

Parameter Observability

- Not all parameters can be estimated from observations

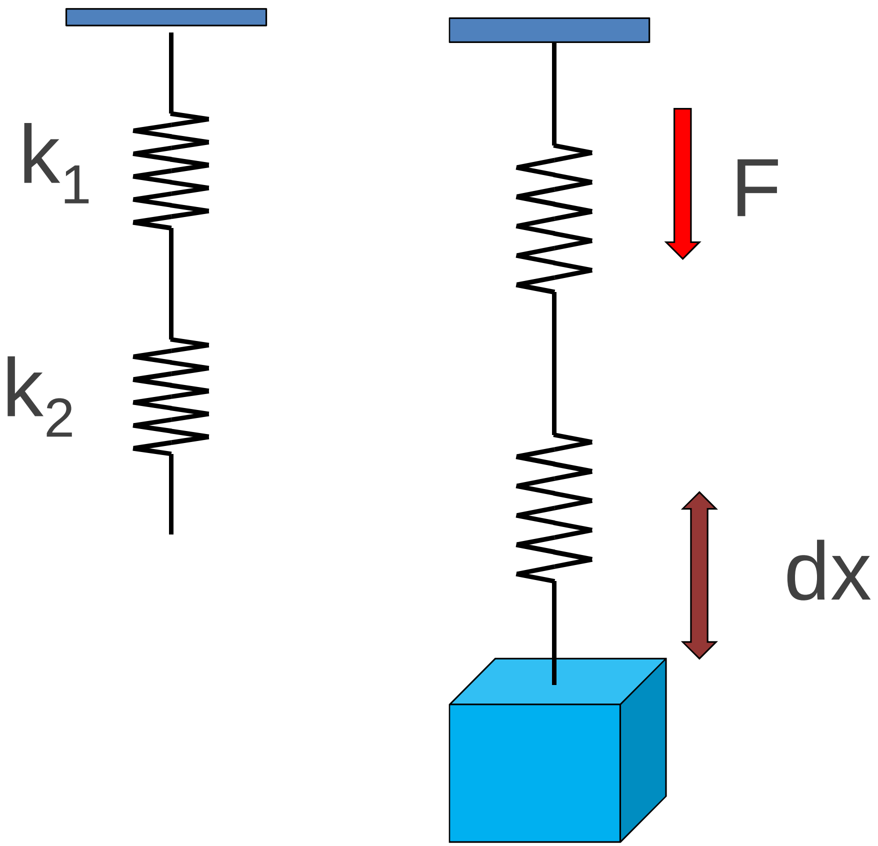


Cannot estimate spring stiffness k from dx!!

$$k = \frac{F}{dx}$$?

Parameter Observability

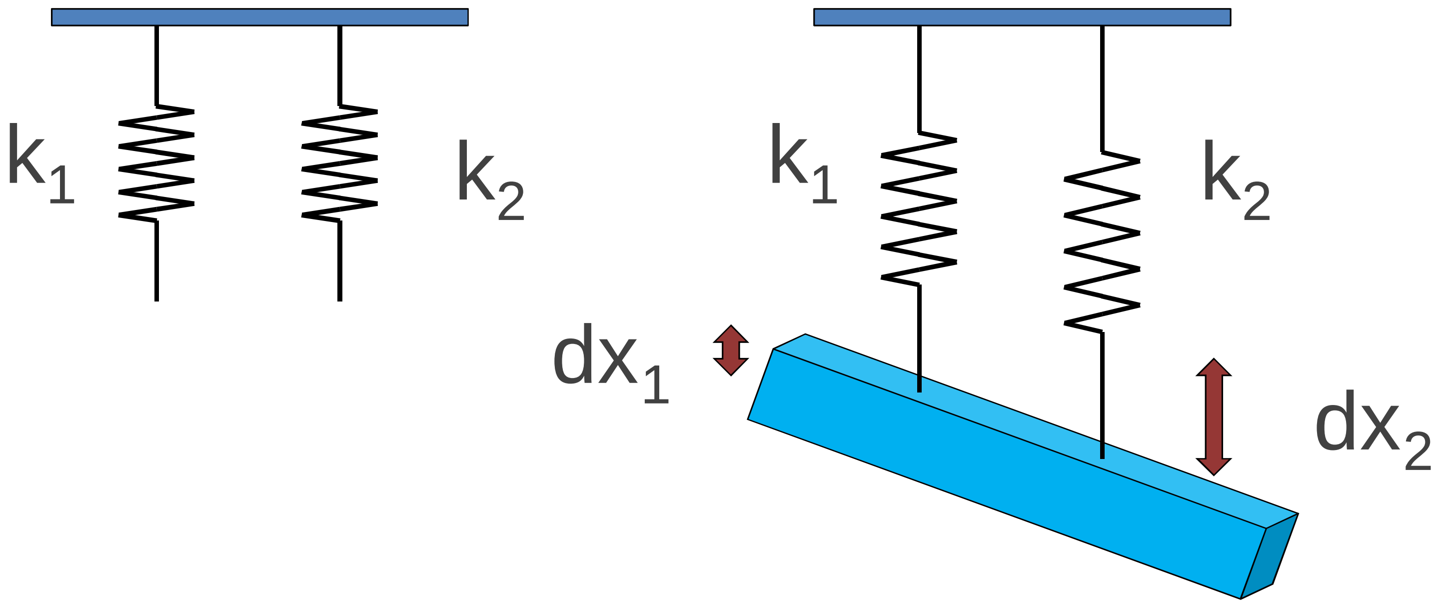
- Can estimate combination of parameters from observation



Only estimate
spring stiffness k_1+k_2
from dx and F!!

Parameter Observability

- Can estimate combination of parameters from observation



Can estimate the ratio of spring stiffness k_1/k_2 from displacements !!

Model as a tool

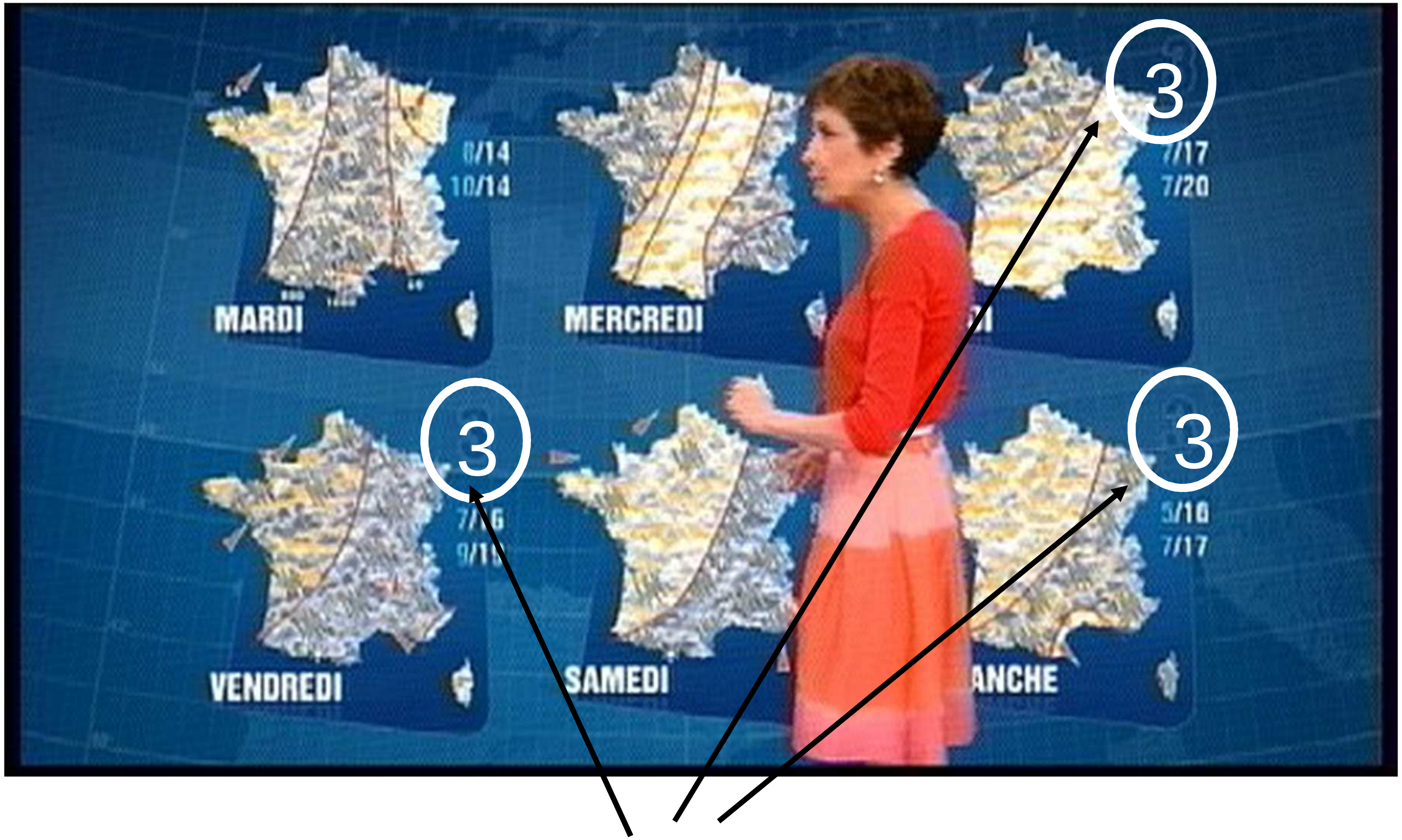
- Models should be designed to answer a given question
- Avoid overfitting of parameters :
  - Adapt model complexity to the complexity of the observations
- Follow Lex Parsimonia (Ockam's razor) : among all suitable models, select the most simple one
  - « The ideal model will be as simple as possible and as complex as necessary for the particular question raised. »

Garny, Noble, Kohl, Dimensionality in cardiac modelling,
Progress in Biophysics and Molecular Biology, Volume 87, Issue1 January 2005, Pages 47-66 Biophysics of Excitable Tissues

Model Selection

- A Model always fails “somewhat”:
  - Should estimate the uncertainty (covariance or posterior distribution) associated with the simulation
  - Estimate all source of errors
- How do I know a model “completely” fails ?:
  - Large discrepancy between observations & simulations after personalization
  - Large variability of parameters for subjects in similar conditions (or same subject)

Handling uncertainties
Example : Weather Forecast



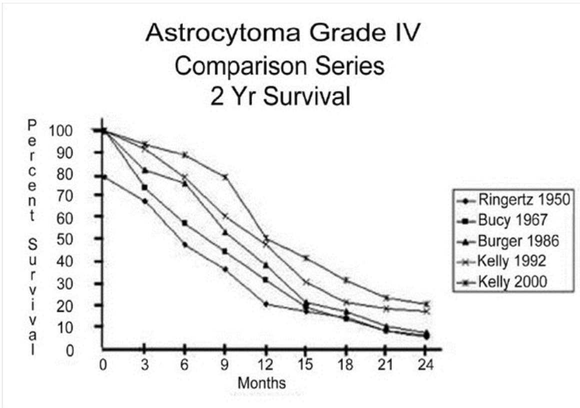
Confidence in
Weather Forecast

Glioma

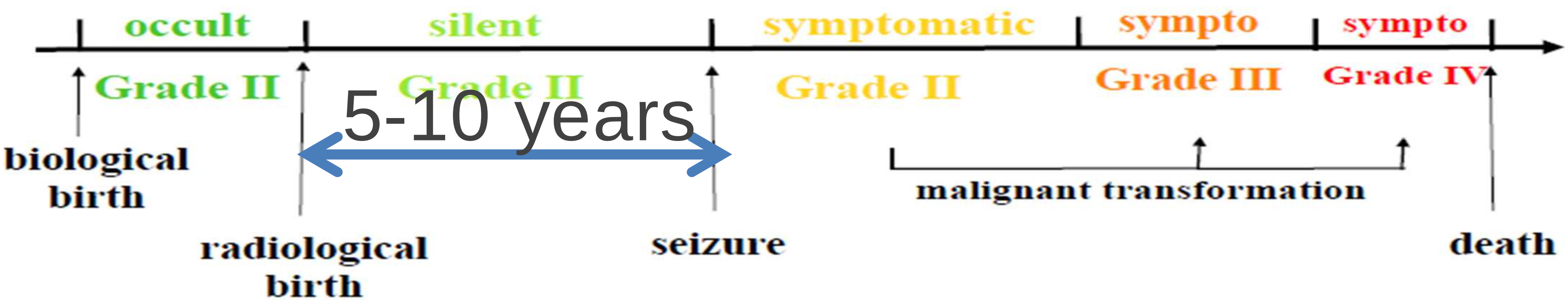
- Incidence: 5-6 cases /100.000 persons/year
  - Young adults: 3rd cause of death
  - Child: 2nd cause of cancer after leukemia
  - Peak for persons between 50-60 year old
- 80% of brain tumors
- Diagnosed with MRI & Clinics

Low Grade & High Grade Glioma

- Low Grade : Astrocytoma & Oligodendroglioma
  - Median survival 10 years
- High grade Glioma : Glioblastoma
  - Median survival : 16 months
  - No major improvement in treatment



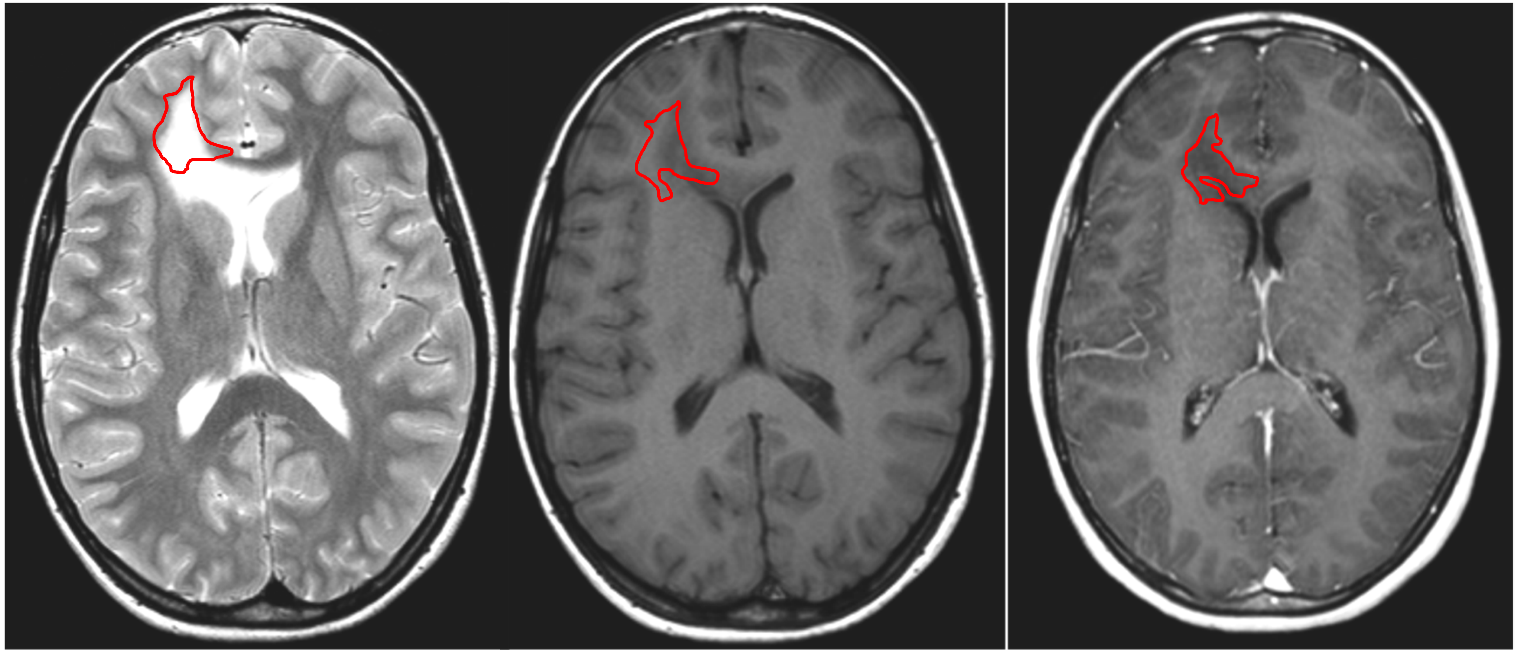
[P. Kelly Surg. Neur. Inter. 2013]



MR Sequences & Glial Tumors

- Low Grade Glioma

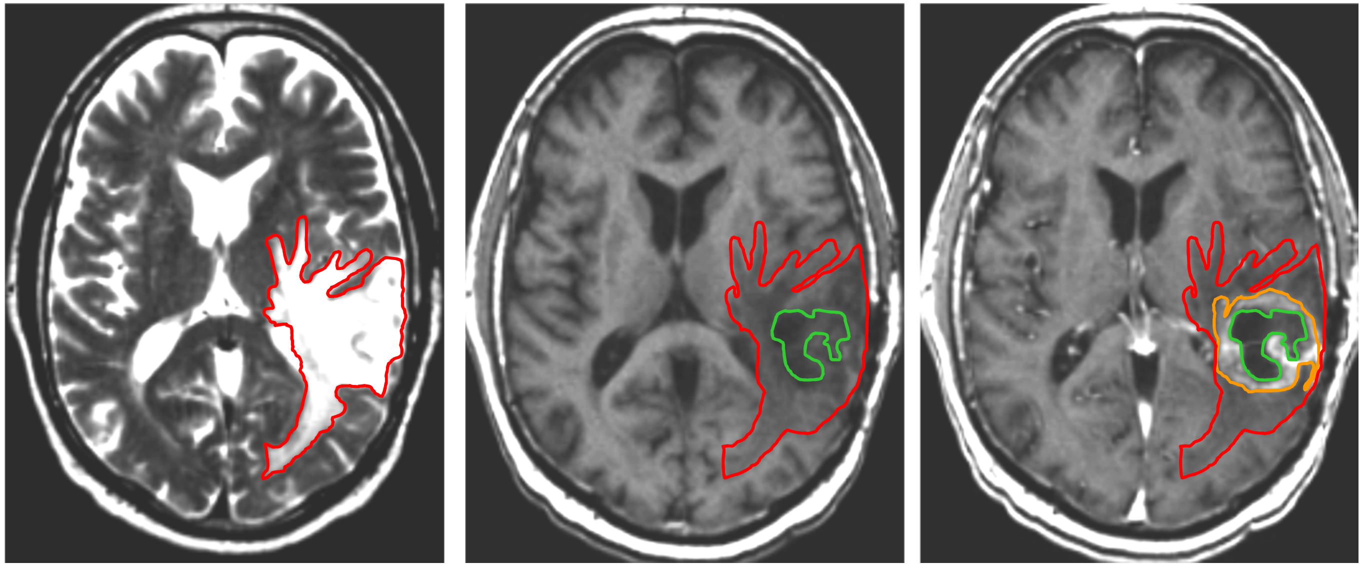
Legend:
+ hyper-intense
- hypo-intense
0 no signal



Pathological structures	T2 / FLAIR	T1	T1+gad
edema	++	-	-

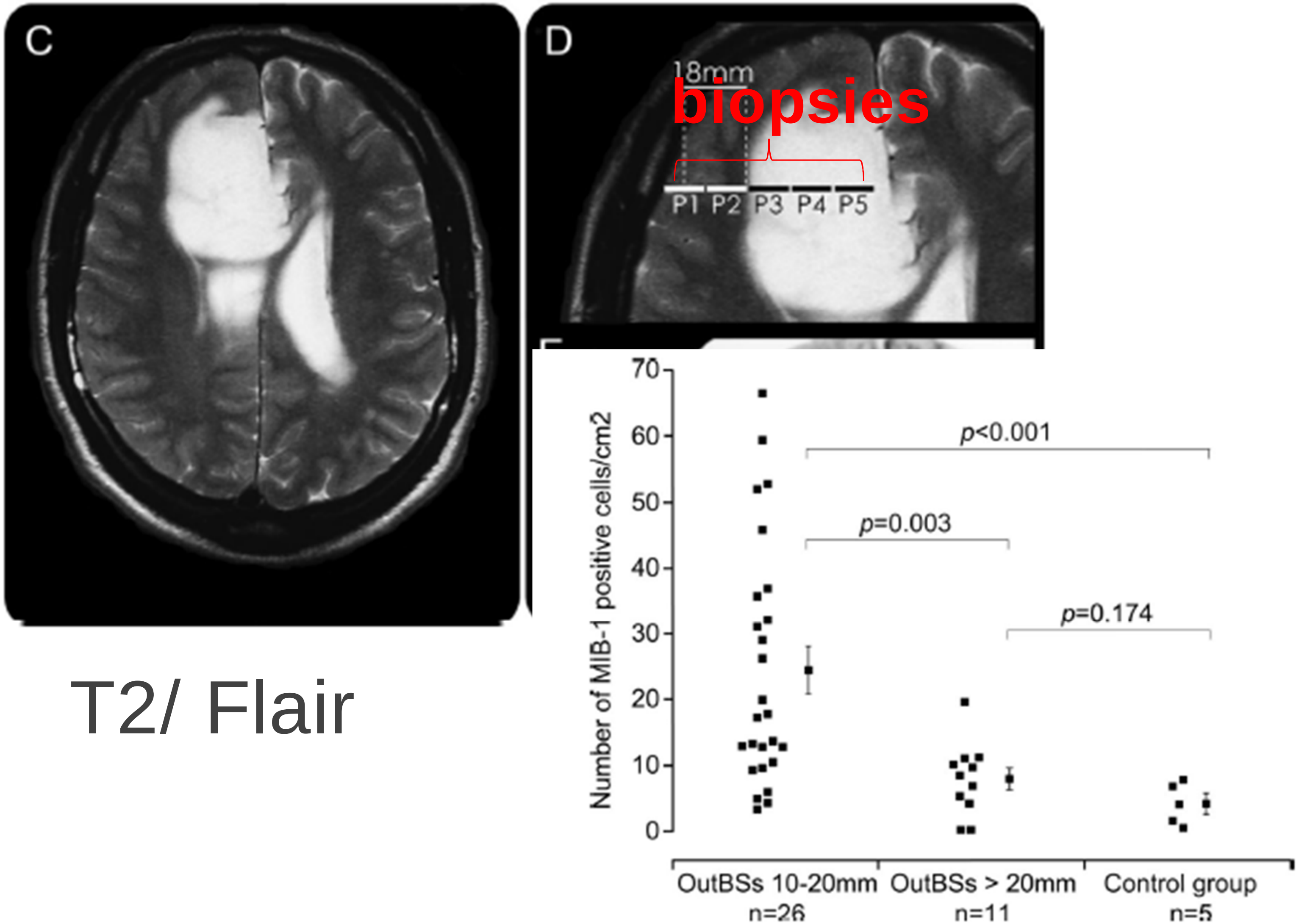
MR Sequences & Glial Tumors

- High Grade Glioma



Pathological structures	T2 / FLAIR	T1	T1+gad
edema / infiltration	++	-	-
active region	++	-	++
necrotic core	++	--	--

Tumor extends beyond visible boundary

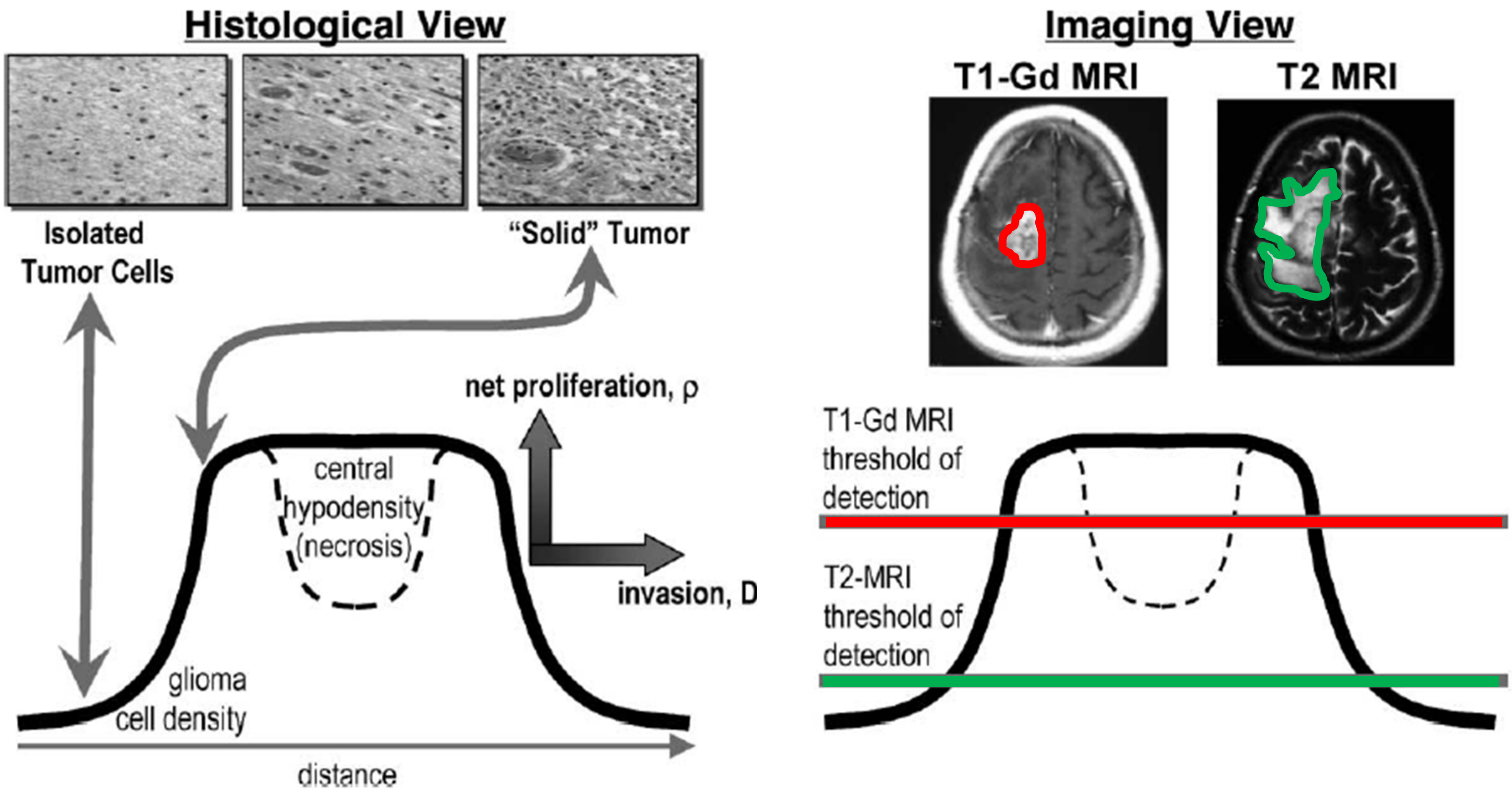


T2/ Flair

Pallud, J et al. "Diffuse Low-Grade Oligodendrogliomas Extend beyond MRI-Defined Abnormalities." *Neurology* 74.21 (2010): 1724–31.

MR Sequences & Glial Tumors

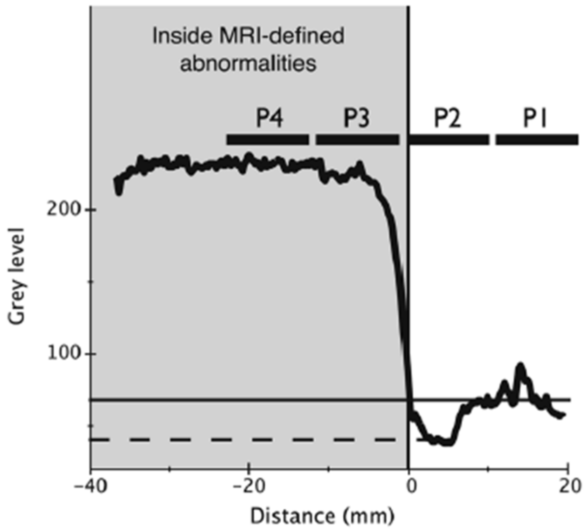
- Main Hypothesis :
  visible contours = isodensity of tumor cells

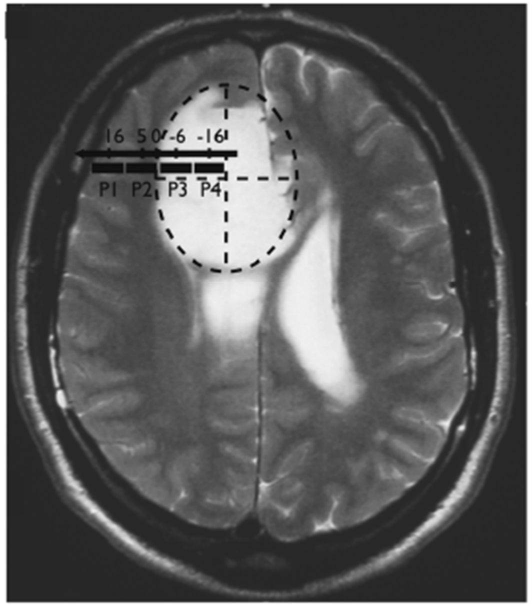


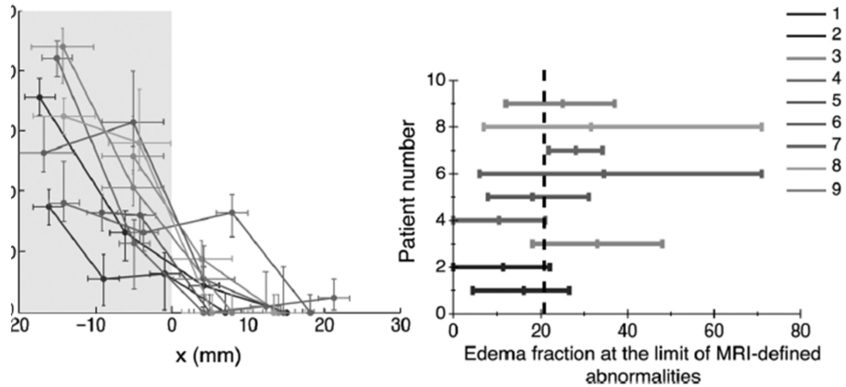
Harpold, Hana L P, Ellsworth C Alvord, and Kristin R Swanson. "The Evolution of Mathematical Modeling of Glioma Proliferation and Invasion." *Journal of neuropathology and experimental neurol* 66.1 (2007): 1–9.

MR Sequences & Glial Tumors

- This hypothesis may not be true !!







Visible Flair abnormality border correlates better with threshold on edema content

Gerin, C, and Johan Pallud. "Quantitative Characterization of the Imaging Limits of Diffuse Low-Grade Oligodendrogliomas." *Neuro-Oncology*(2013): 10–13.

Possible Treatments

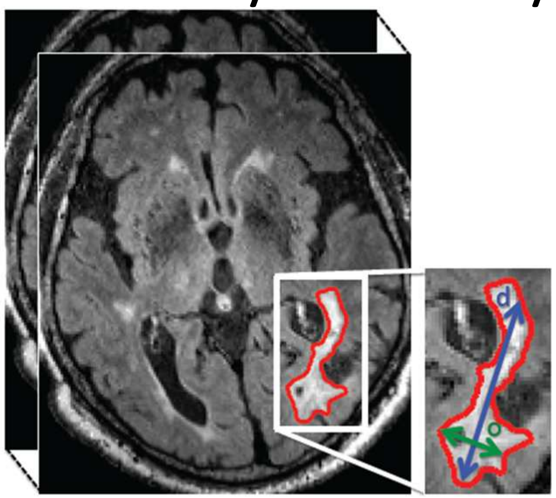
- Upon discovery :
  - Wait & watch (3-6 asymptomatic glioma / 1000 persons)
  - Surgery (awake surgery w functional mapping)
  - Radiotherapy (2cm margin)
  - Chemotherapy (anti-angiogenic drug)

3 Main Problems

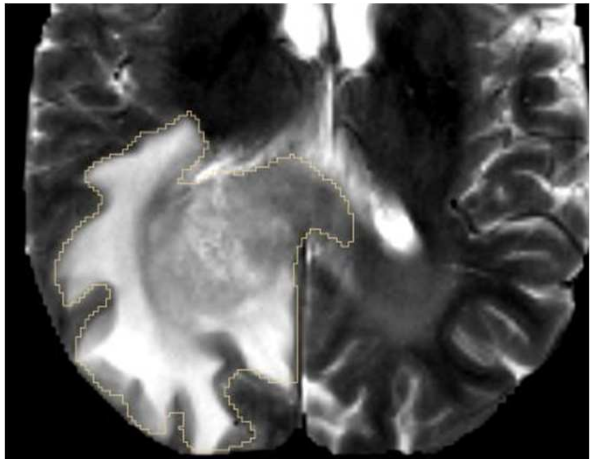
1. Quantify the extent of the tumor
2. Quantify the tumor evolution
3. Improve clinical practice

Quantification of tumor extent

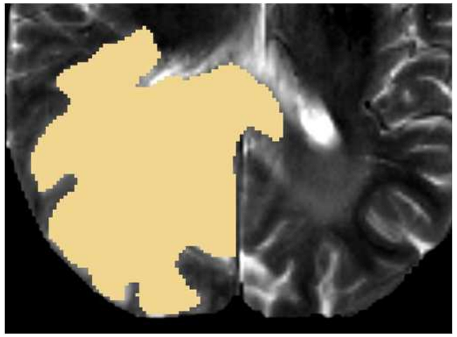
- Current clinical practice :
  - One or two largest diameter (RECIST or RANO criteria)
  - Only 1D or 2D
  - Do not differentiate between tumor compartments (core / edema / white & grey matter)



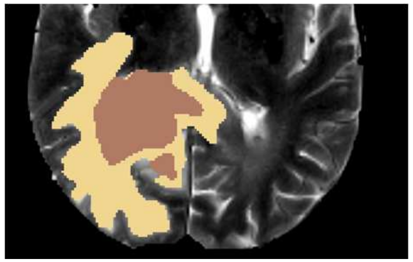
Hierarchy of compartments (Source BRATS)



High grade. T2-w.



tumor + edema
(T_2-w, FLAIR)



core
(abnormal in T_1-w + Gad)

(and T_2-w, for LG
and some HG)

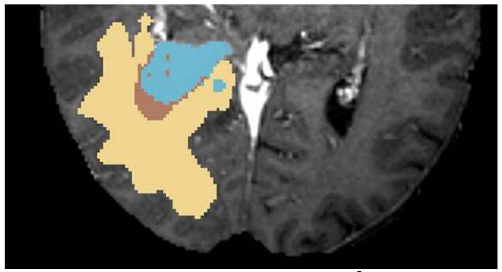
edema

enhancing core
(T_1-w + Gad)

non-enhancing core

necrotic core
(cyst)

the rest
(texture, localisation, etc.)



T1-w + Gad

Automatic Segmentation ?

The Multimodal Brain Tumor
Image Segmentation Benchmark (BRATS)

- Growing at mentation

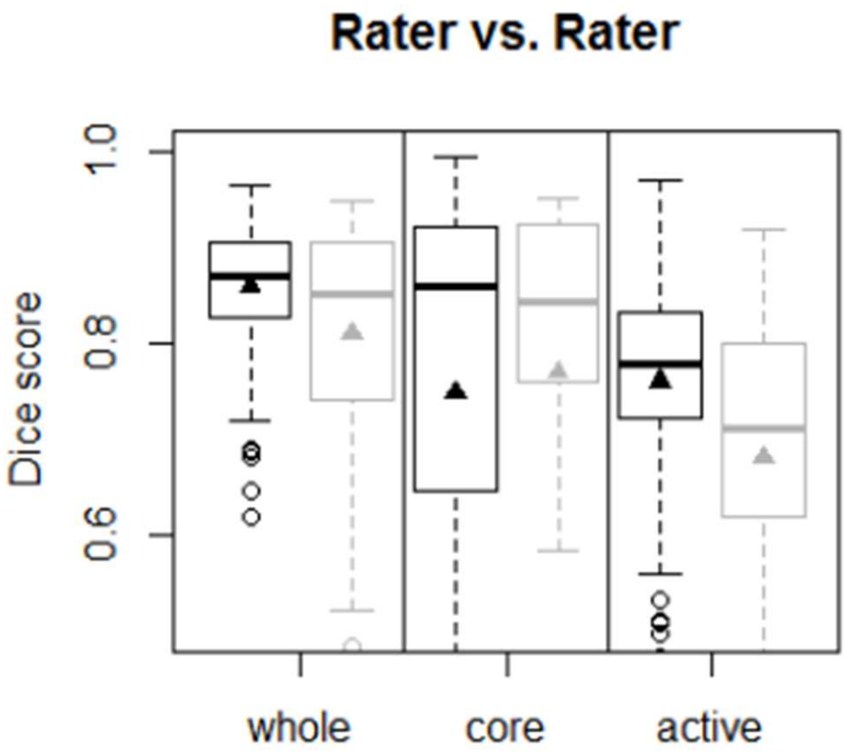
Source : B. Menze et al. *"The Multimo* IEEE TMI 2014

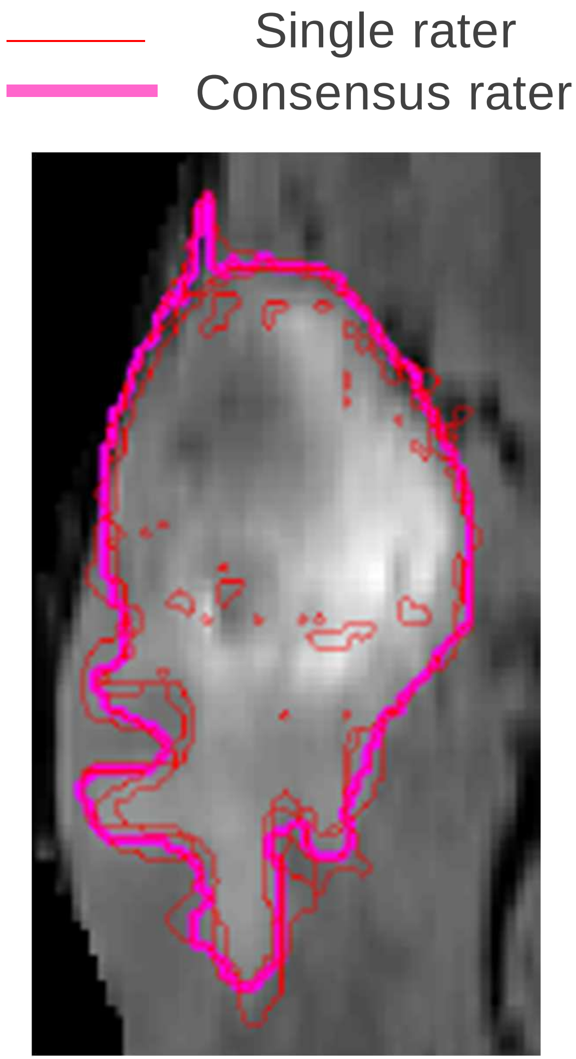
- BRATS Chal lpathy-Cramer,

  K. Farani) runn

A difficult segmentation task

- Fairly large discrepancy between experts





Flair MR

Source : B. Menze et al. “The Multimodal Brain Tumor, Image Segmentation Benchmark (BRATS) », IEEE TMI 2014

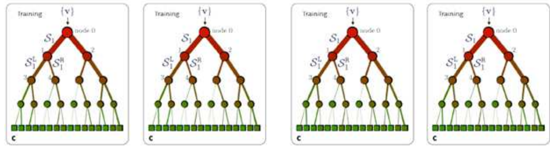
Segmentation approaches

- generative or discriminative
- 2 survey papers

S. Bauer, R. Wiest, L.-P. Nolte, and M. Reyes, “A survey of MRI based medical image analysis for brain tumor studies,” *Phys Med Biol*, vol. 58, no. 13, pp. R97–R129, Jul. 2013.

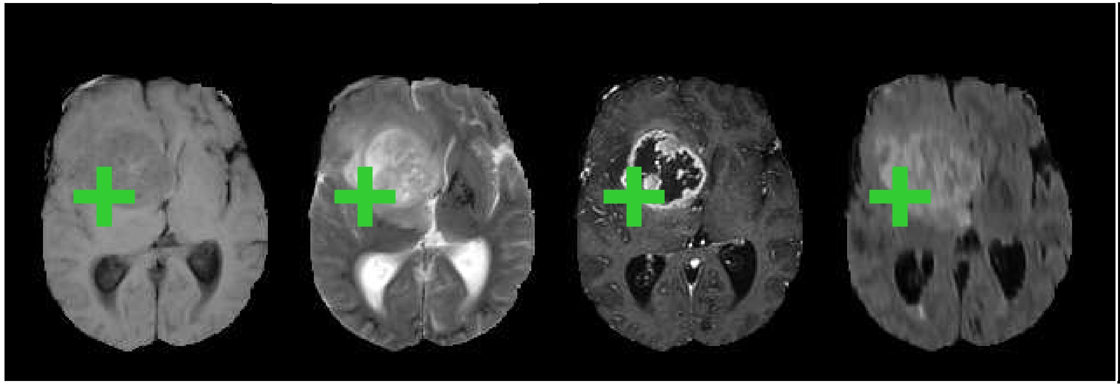
Angelini E., Clatz O., Mandonnet E., Konukoglu E., Capelle L. and Duffau H. , *Glioma Dynamics and Computational Models: A review of Segmentation, Registration and In Silico Growth Algorithms and their Clinical Applications,* Current Medical Imaging Reviews, 2007

Examples of segmentation method

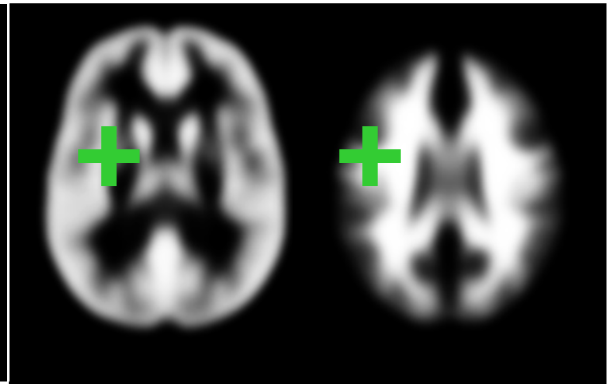


- Random Forest: Features

Local

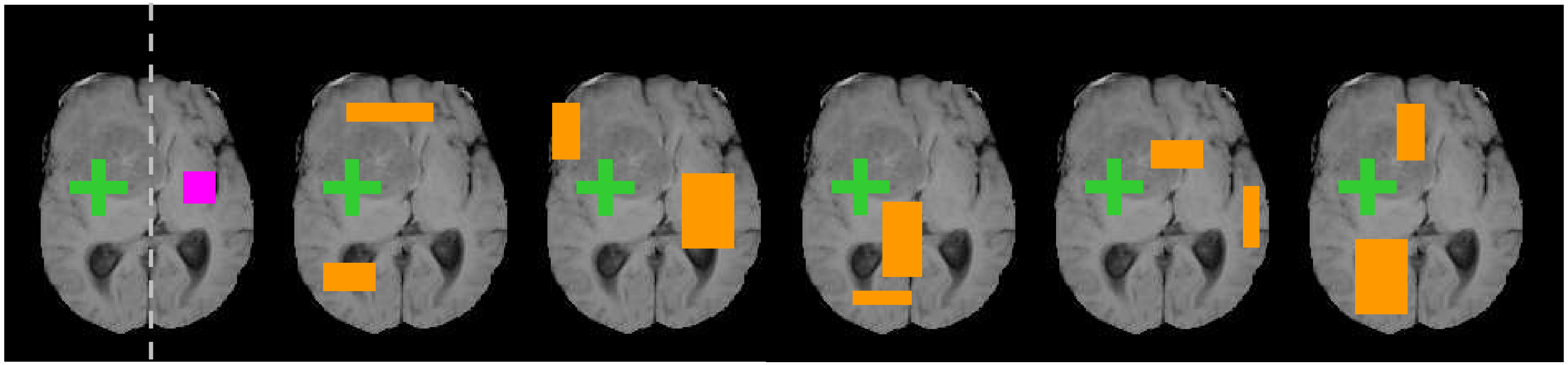


Multi-channel MRIs
T1, T2, T1+Gd, Flair



Spatial priors
GM, WM

Contextual

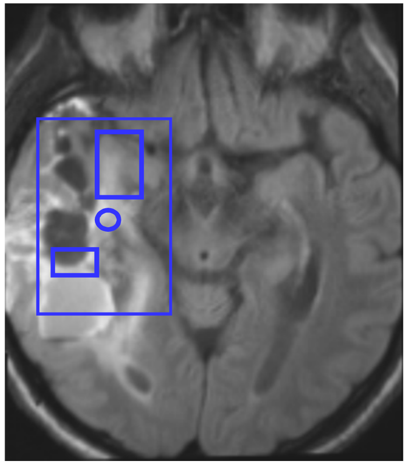


asymmetry

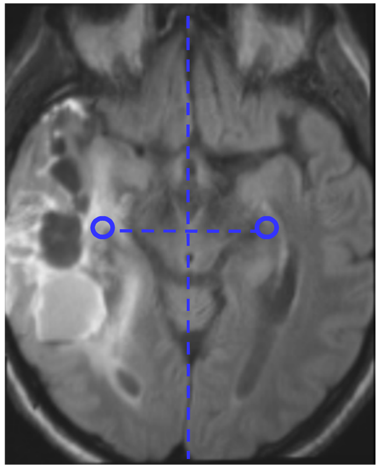
Randomized context-rich features

E. Geremia, D. Zikic, O. Clatz, B.H. Menze, B. Glocker, E. Konukoglu, J. Shotton, O.M. Thomas, S.J. Price, T. Das, R. Jena, N. Ayache, and A. Criminisi, *Classification Forests for Semantic Segmentation of Brain Lesions in Multi-Channel MRI*, in Decision Forests for Computer Vision and Medical Image Analysis, Springer, 2013

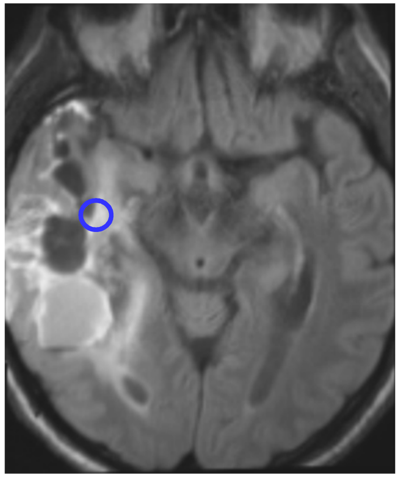
Selected Features



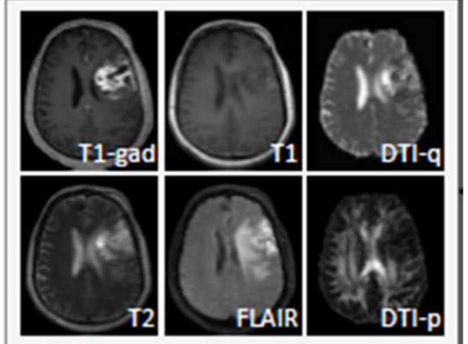
41 %
Contextual features



36 %
Asymetry

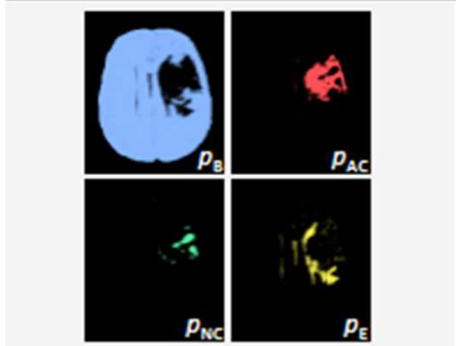


23 %
Local Features

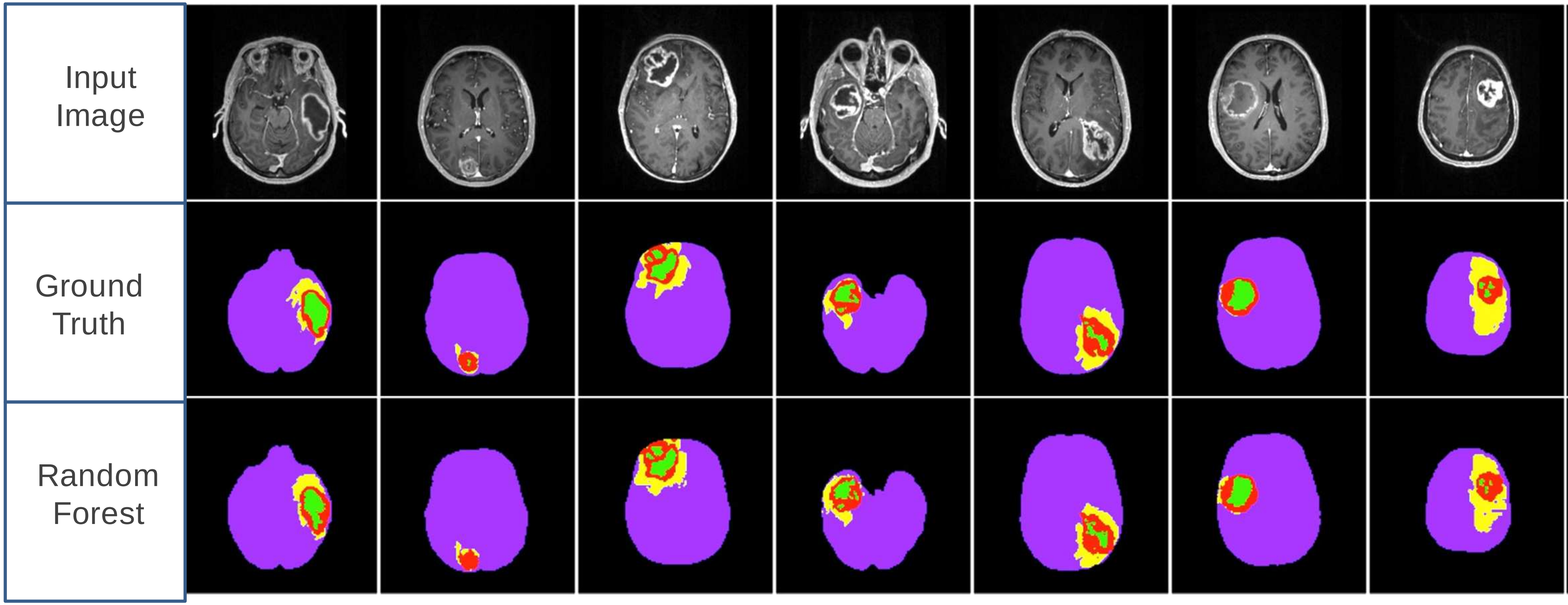


(A) input data: MRI + DTI

Typical Results



(B) initial tissue probabilities



Necrotic Core   Proliferating Cells   Edema   Parenchyma

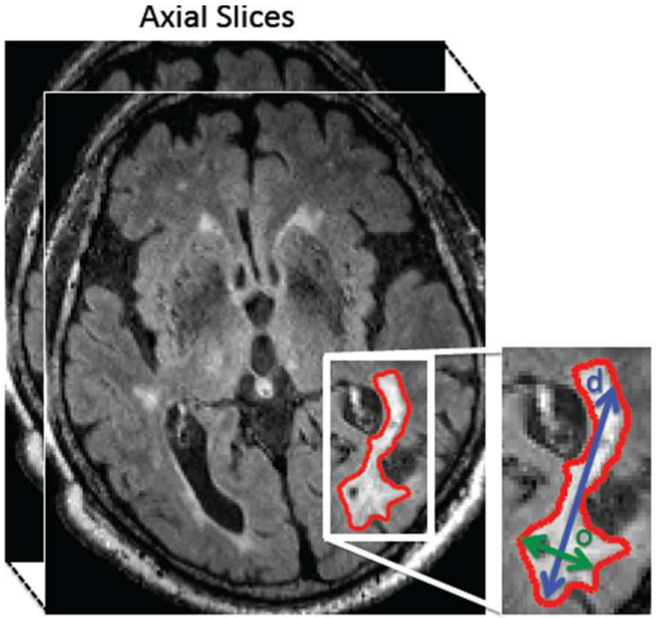
E. Geremia, D. Zikic, O. Clatz, B.H. Menze, B. Glocker, E. Konukoglu, J. Shotton, O.M. Thomas, S.J. Price, T. Das, R. Jena, N. Ayache, and A. Criminisi, *Classification Forests for Semantic Segmentation of Brain Lesions in Multi-Channel MRI*, in Decision Forests for Computer Vision and Medical Image Analysis, Springer, 2013

3 Main Questions

1. Quantify the extent of the tumor
2. Quantify the tumor evolution
3. Improve clinical practice

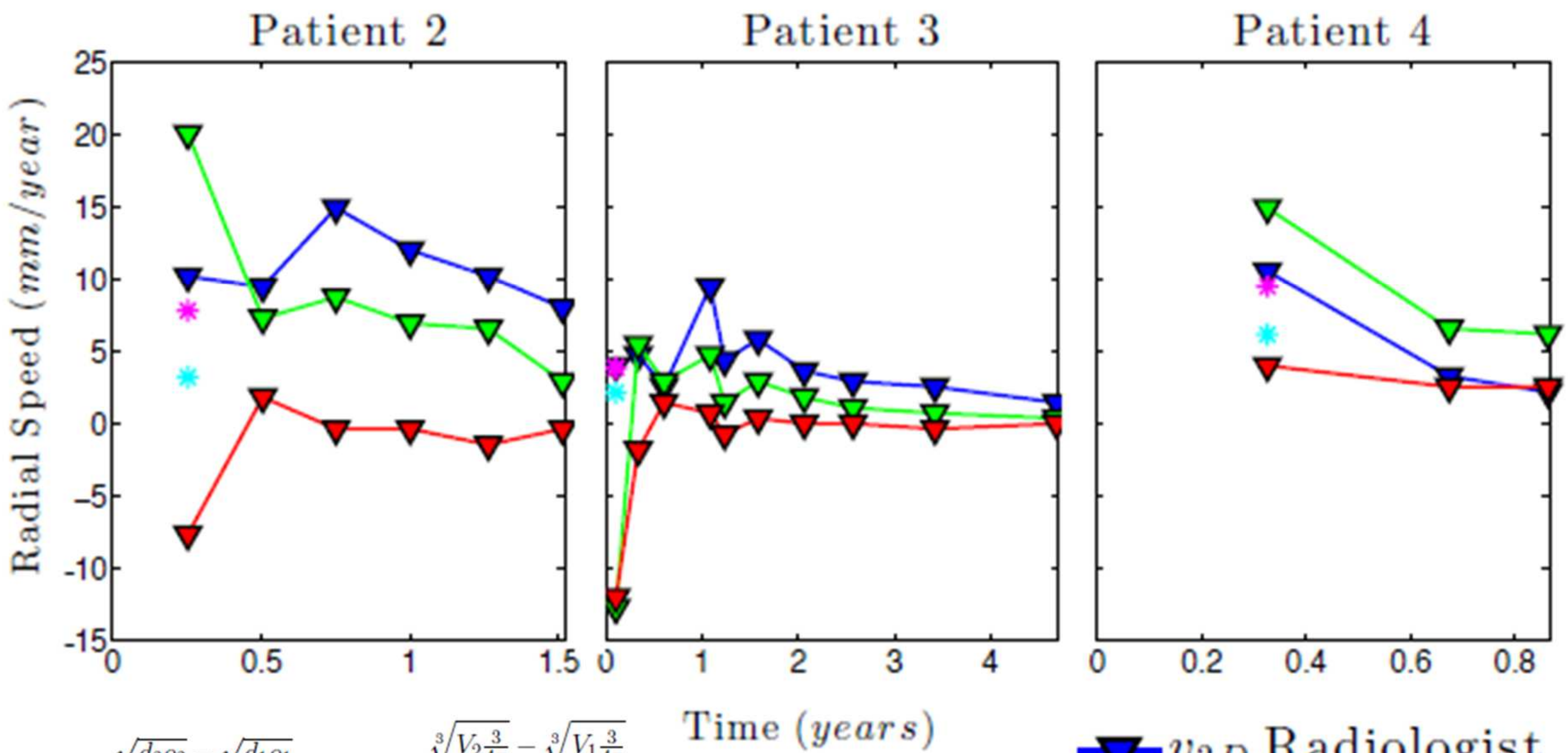
Quantification of tumor growth

Imaging Modality	*RECIST* (1D)	*Macdonald* (2D)	*RANO* (2D)
T1-gad	$\geq$ 20% increase in sum of maximal diameters; confirm at 4 weeks	$\geq$ 25% increase in product of orthogonal diameters; confirm at 4 weeks	$\geq$ 25% increase in product of orthogonal diameters; confirm at 4 weeks
T2/FLAIR	$\geq$ 20% increase in sum of maximal diameters; confirm at 4 weeks	N/A	Significant increase

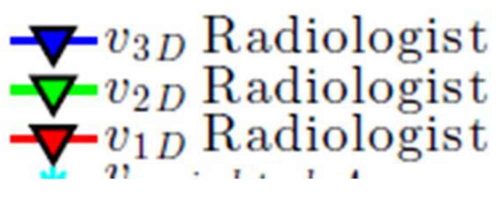


Discrepancy between growth speed

- Growth rate based on 1D, 2D or 3D measurements from the same images



$$v_{1D} = \frac{d_2 - d_1}{2\delta t}, \qquad v_{2D} = \frac{\sqrt{d_2 o_2} - \sqrt{d_1 o_1}}{2\delta t}. \qquad v_{3D} = \frac{\sqrt[3]{V_2 \frac{3}{4\pi}} - \sqrt[3]{V_1 \frac{3}{4\pi}}}{\delta t},$$



[Stretton 2014]

Can we do better ?

Maybe using a personalized tumor growth model

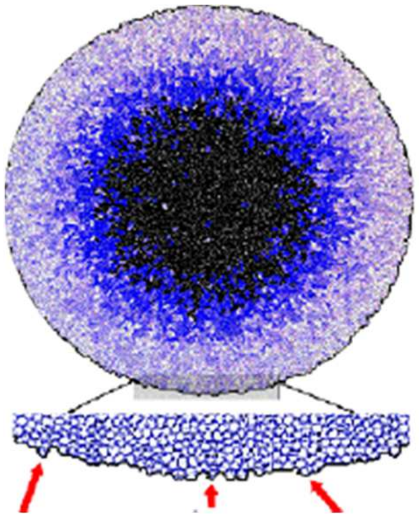
- Estimate glioma growth speed in grey and white matter
- Take into account anatomical barriers
- Can extrapolate future evolution

Tumor Growth Modeling

Extremely complex phenomena

genes↔proteins↔ enzymes↔ cells↔tissus↔ organs

AVascular Growth



Drasdo et al., Phys. Biol. 2005

Angiogenesis

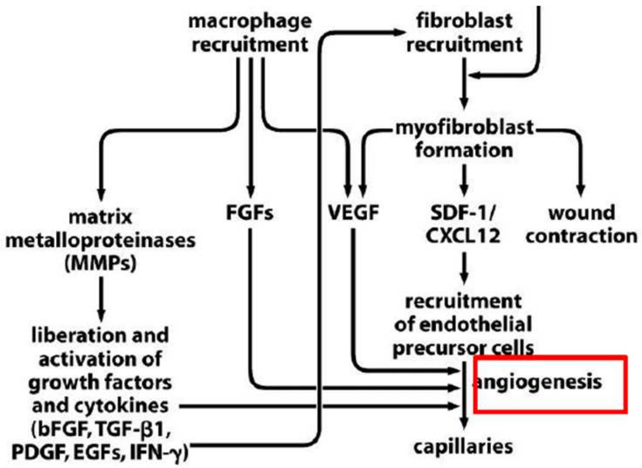
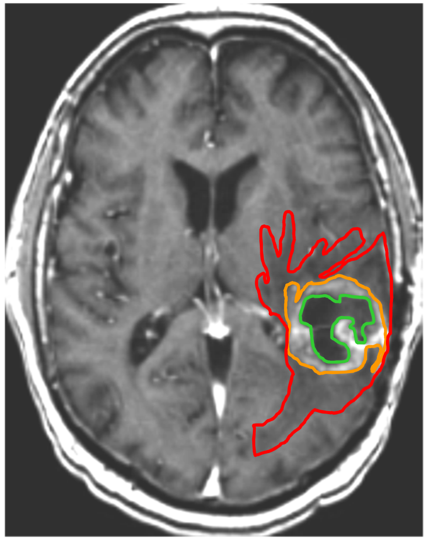


Figure 13-10 The Biology of Cancer (© Garland Science 2007)

M. Brady, IHP, 2012

Vascular Growth



T1+ gad

T S Deisboeck and G Stamatakos, editors, *Multiscale Cancer Modeling*, CRC Press, 2010.

Mathematical Tumor Growth Models

Microscopic Models

Alarcon [Prog. Biophys. Mol. Biol. 2004]

Araujo [Bull. Math. Biol. 2004]

Athale-Deisboeck [JTB 2006]

Byrne [Math Med Bio 2003, MMMAS 2006]

Breward [Bull. Math. Biol. 2004]

Chaplain [NeuroOncology 2000]

Drasdo [Phys. Biol. 2005]

Frieboes-Cristini [NeuroImage 2007]

Maini [Tissue Eng. 2004]

Mantzaris [J Math. Biol. 2004]

Lloyd-Szekely [MICCAI 2007]

Plank [Bull. Math. Biol. 2004]

Zhang [J Th. Biol. 2007]

- *in-vivo* and *in-vitro* experiments
- Cellular level dynamics: interactions between different cells, different chemicals secreted, nutrition/oxygen sources,…
- Large variety of mathematical methods: PDEs, cellular automata, statistical methods
- Stochastic nature of the tumor growth
- Complex models, large number of parameters

Macroscopic Models

Mathematical Tumor Growth Models

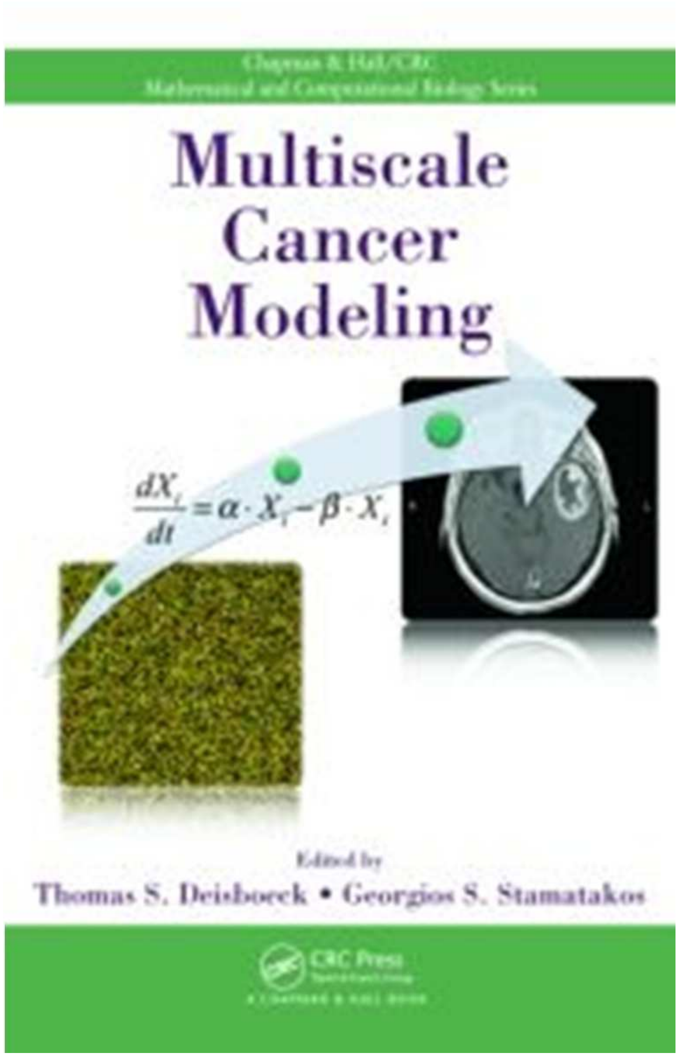
Microscopic Models

Macroscopic Models

- Observations at the macroscopic scale e.g. medical images
- Average behavior of tumor cells and their interactions with the tissues (white matter, gray matter, …)
- simpler formulations, smaller number of variables
- Identification through manual fitting with observations

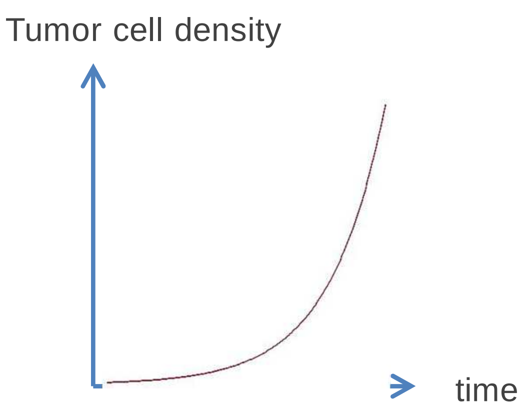
Ashraf-Davatzikos [Media 2006]
Clatz [IEEE TMI 2005]
Hogea [MICCAI 2006, 2007]
Jbadbi-Benali [MRM 2005]
Garg-Miga [SPIE 2008]
Mohamed [MedIA 2006]
Murray [Mathematical Biology 2002]
Prastawa-Gerig [MICCAI 2005, MedIA 2008]
Sierra-Szekely [MedIA 2005]
Stamatakos [Brit. J. Rad. 2006]
Stein [J Biophys. 2007]
Swanson [Br. J. Cancer 2002, 2008]
Tracqui [Cell Proliferation 1995]

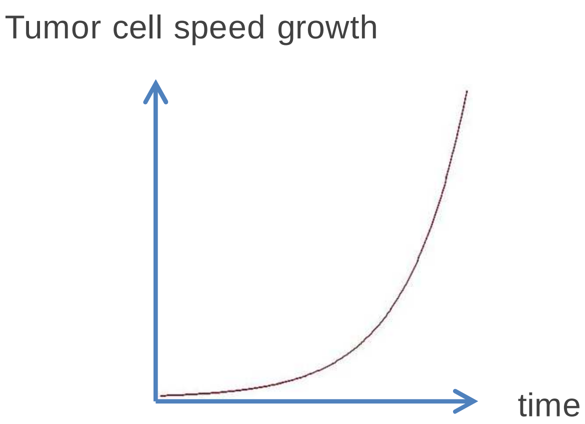
Multiscale Cancer Modeling



T S Deisboeck and G Stamatakos, editors, *Multiscale Cancer Modeling*, CRC Press, 2010.

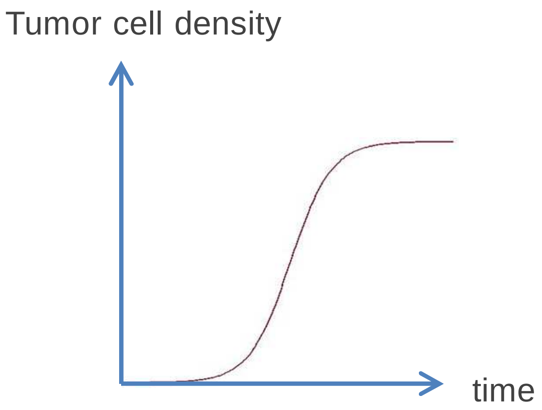
Simple Global Growth models

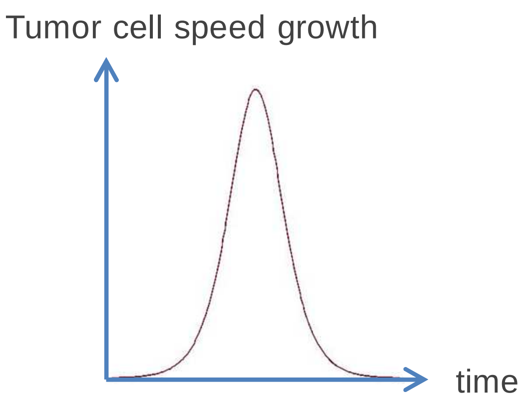




Exponential

$$\frac{dc}{dt} = \rho c$$

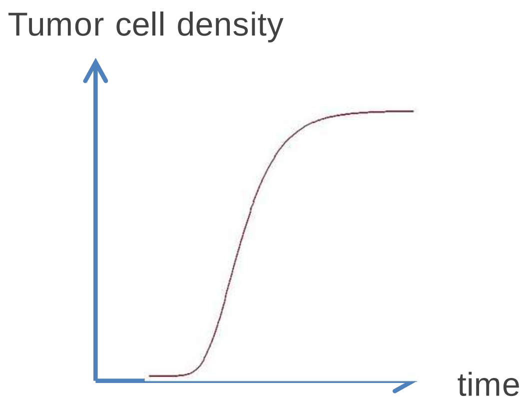


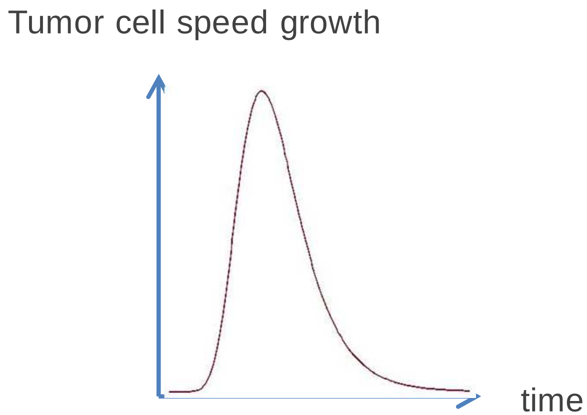


Logistic

$$\frac{dc}{dt} = \rho c(1 - c)$$

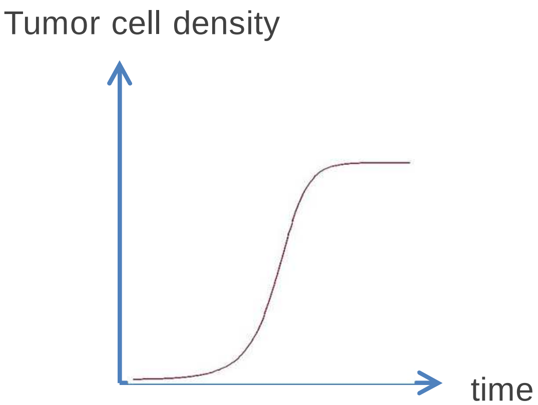
Simple Global Growth models

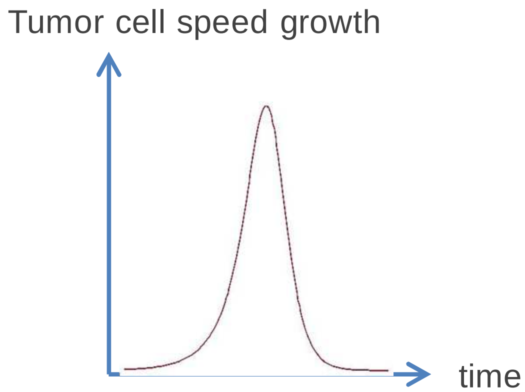




Gompertz

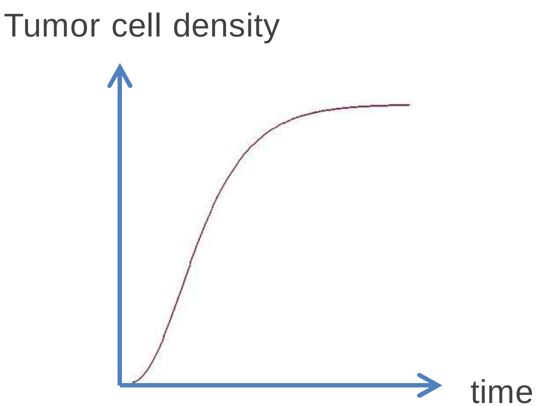
$$\frac{dc}{dt} = \rho c \log(K/c)$$

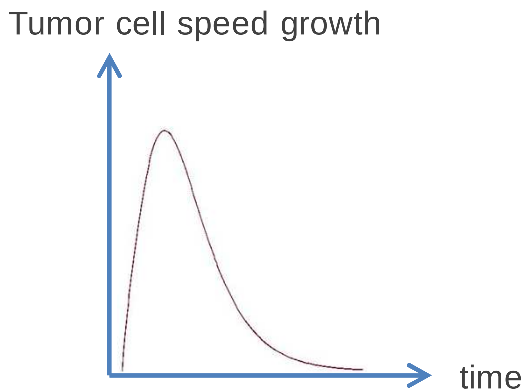




Generalized Logistic

$$\frac{dc}{dt} = \frac{\rho}{\nu} c(1 - c^{\nu})$$





Universal Growth

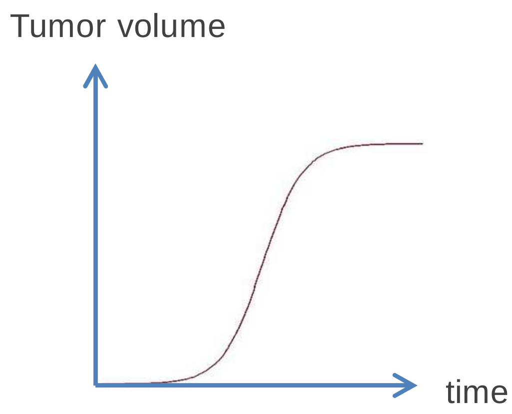
[West et al. 2001]

$$\frac{dc}{dt} = \frac{\rho}{\nu} c^{\frac{3}{4}}(1 - c^{1/4})$$

Limitation of Global Models

- Model evolution of global volume

$$\frac{dc}{dt} = \rho c(1 - c)$$



- Limitations :
  - heterogeneity of image
  - Anisotropy of phenomena
  - Natural barriers

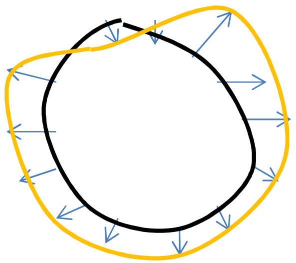
- Adding spatial information

From Global to Local Models

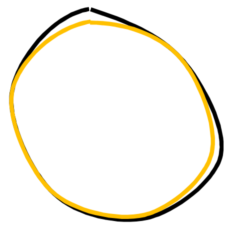
$$\frac{dc}{dt} = \underbrace{v \cdot \nabla c}_{\text{Advection / Transport}} + \underbrace{\rho c(1-c)}_{\text{reaction}}$$

$$\frac{dc}{dt} = \underbrace{\mathrm{d}\nabla \cdot \nabla c}_{\text{Diffusion}} + \underbrace{\rho c(1-c)}_{\text{reaction}}$$

$$\frac{\partial}{\partial t}\int_{\Omega} c \, dV = \int_{\Omega} \rho c(1-c) dV$$



Velocity Field



Laplacian Smoothing

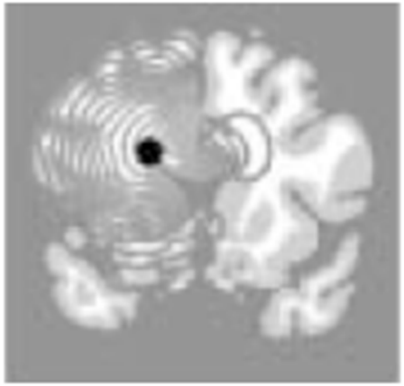
[Hogea et al. 2006]
[T. Colin, O. Saut et al.]

Image-based Glioma Growth Models

2D, Isotropic, homogeneous

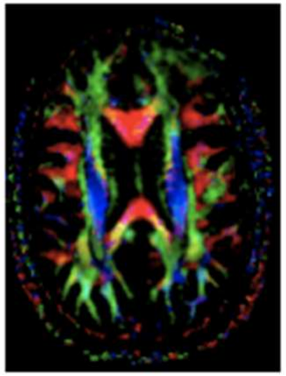
1995
P. Tracqui et al.

3D, Isotropic, Non-homogeneous

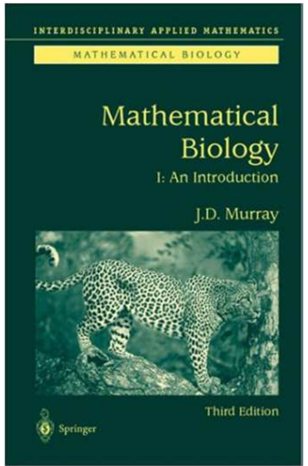


2002
K. Swanson et al.

3D, anisotropic, Non-homogeneous



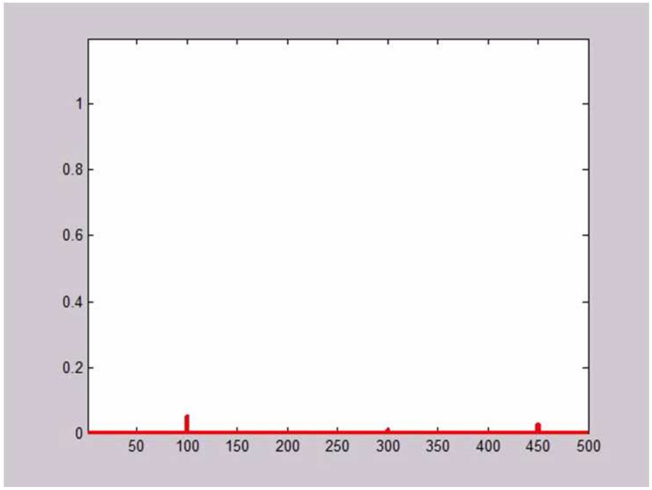
2005
O. Clatz et al.
Jbabdi et al.



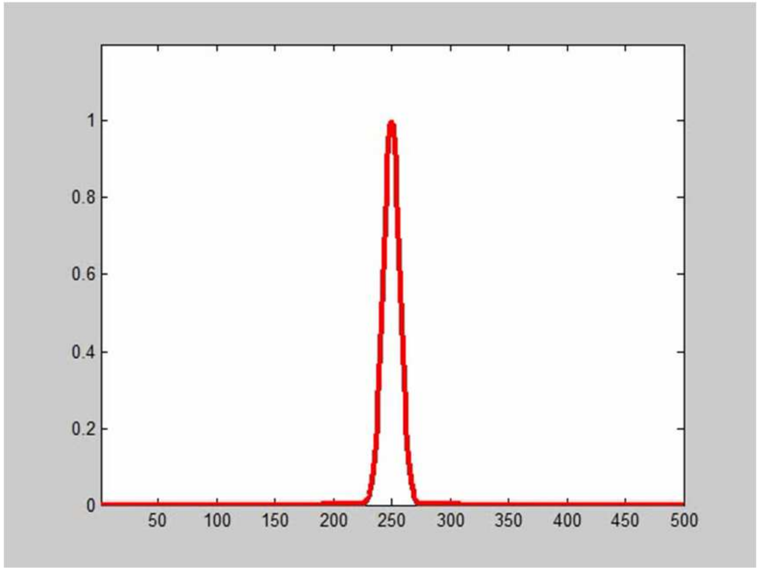
James Murray
Univ. Of Washington

Giese, Alf M. et al., " Migration of Human Glioma Cells on Myelin", Neurosurgery:, April 1996 - Volume 38 - Issue 4 - pp 755-764

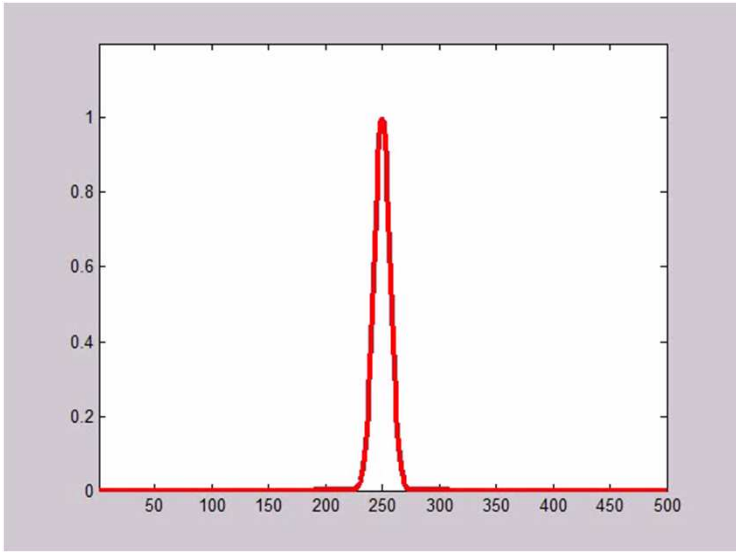
Understanding Reaction diffusion



Reaction Only



Diffusion Only



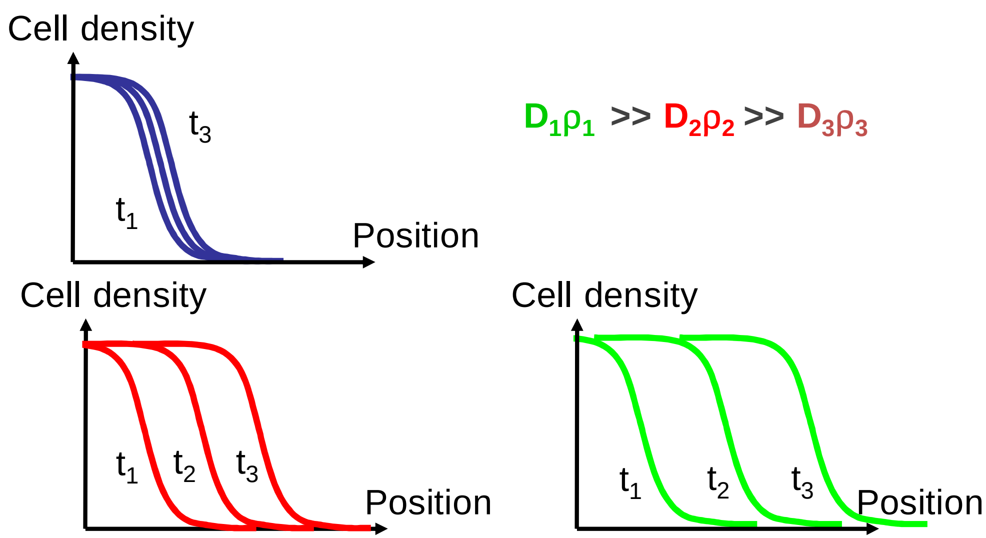
Reaction-Diffusion

Fisher Equation

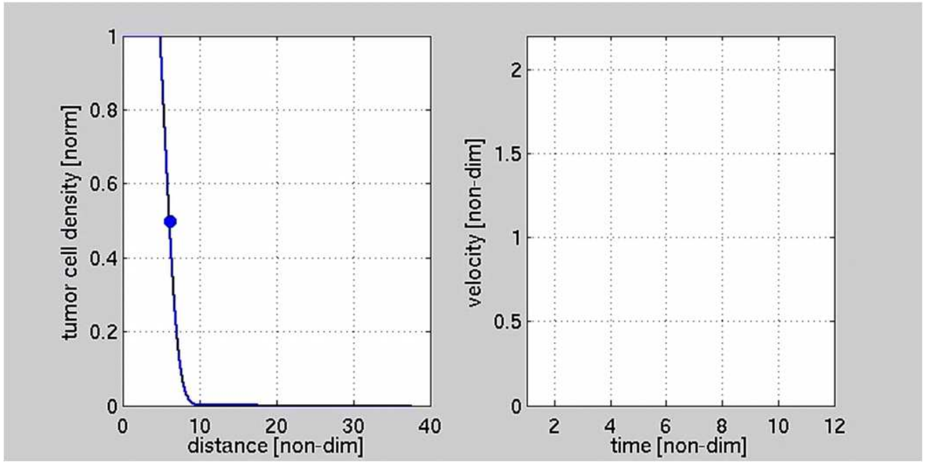
$$\frac{\partial c}{\partial t} = \nabla.(D\nabla c) + \rho c(1-c)$$

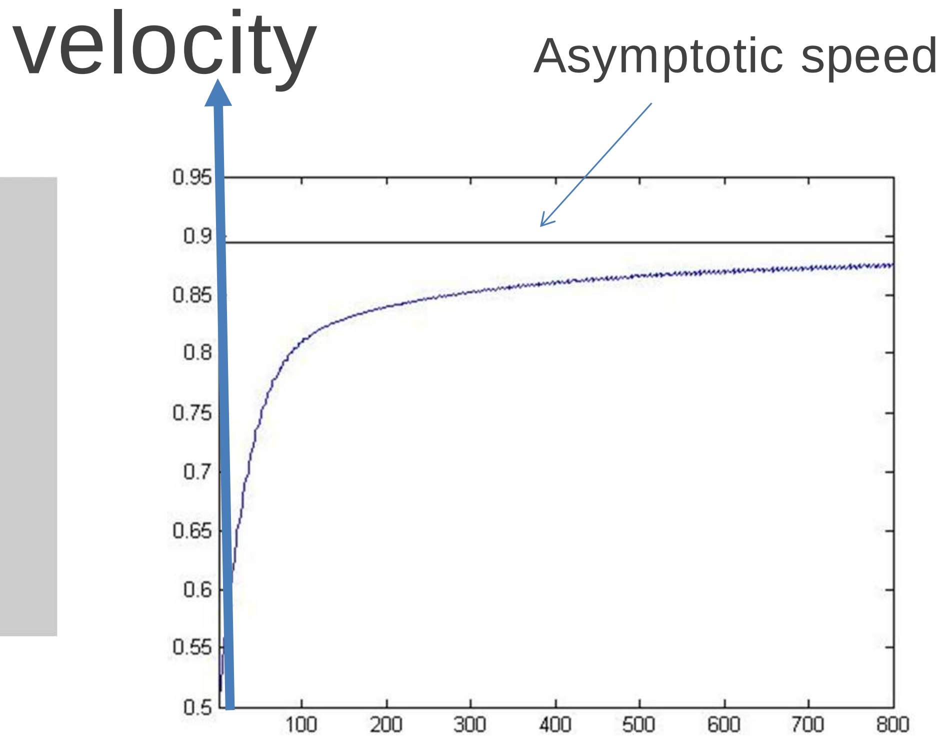
Product controls growth speed $\boxed{D\rho}$

Velocity index$=2\sqrt{D\rho}$



Speed of moving front



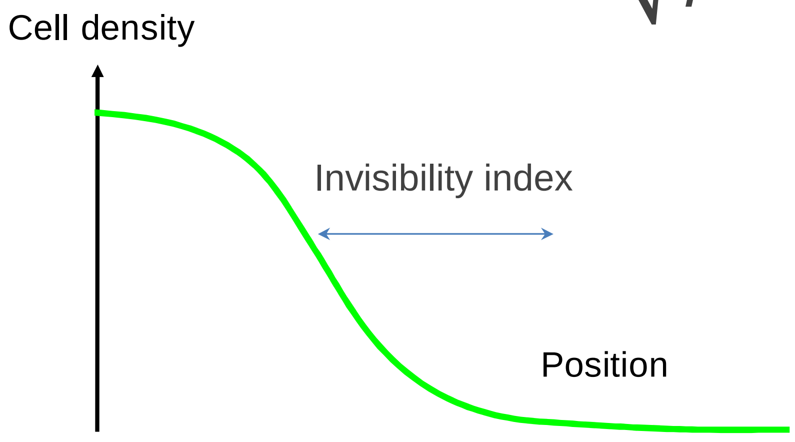


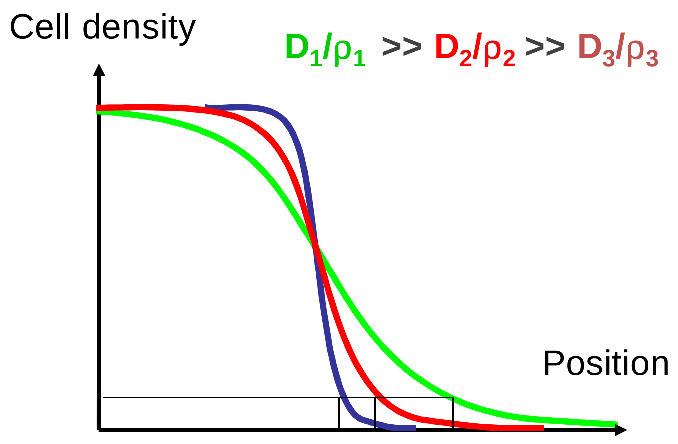
Fisher Equation

$$\frac{\partial c}{\partial t} = \nabla.\left(D\nabla c\right) + \rho c(1-c)$$

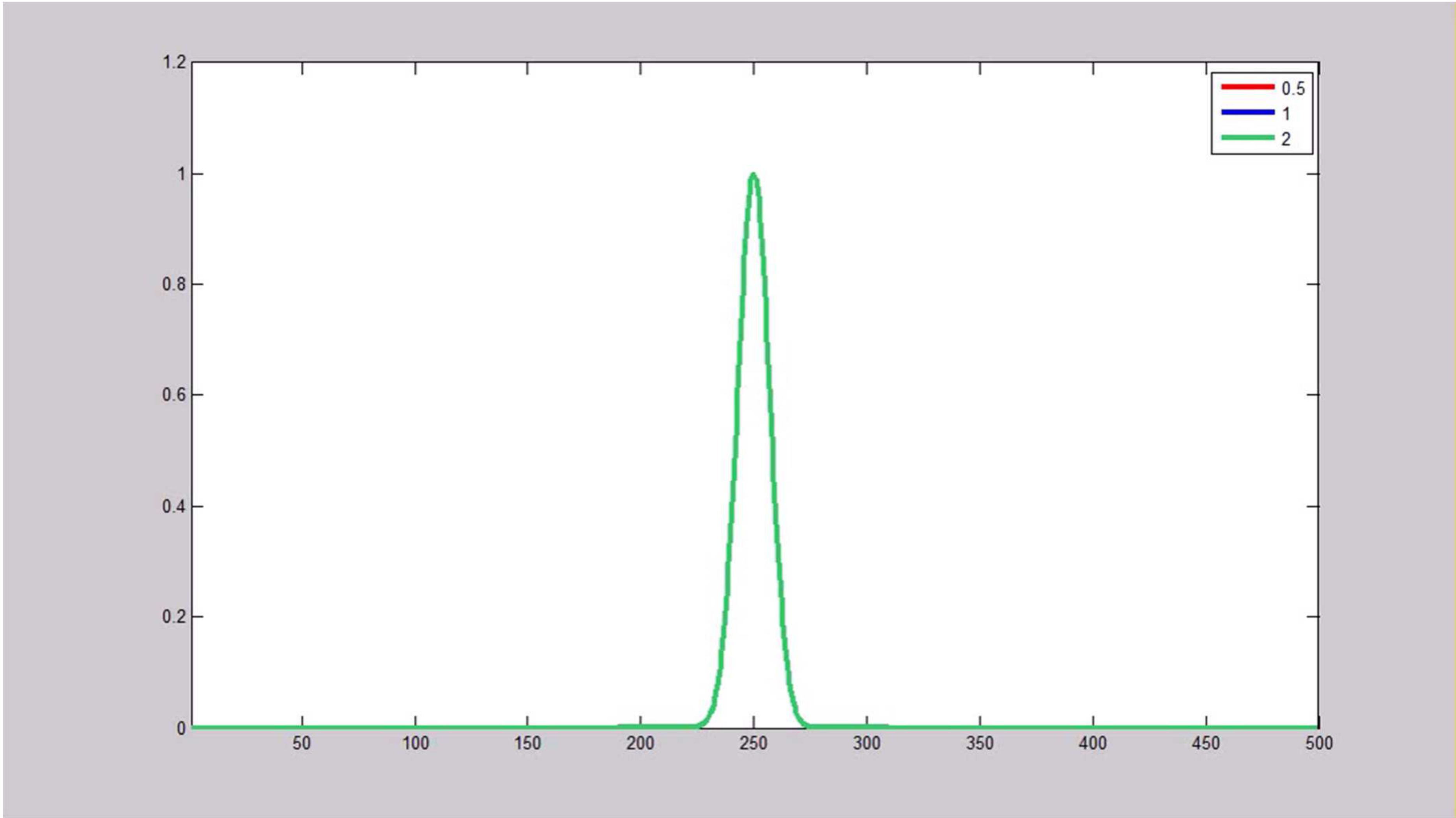
Ratio controls the extent of infiltration $\boxed{\frac{D}{\rho}}$

Invisibility index= $\sqrt{\frac{D}{\rho}}$



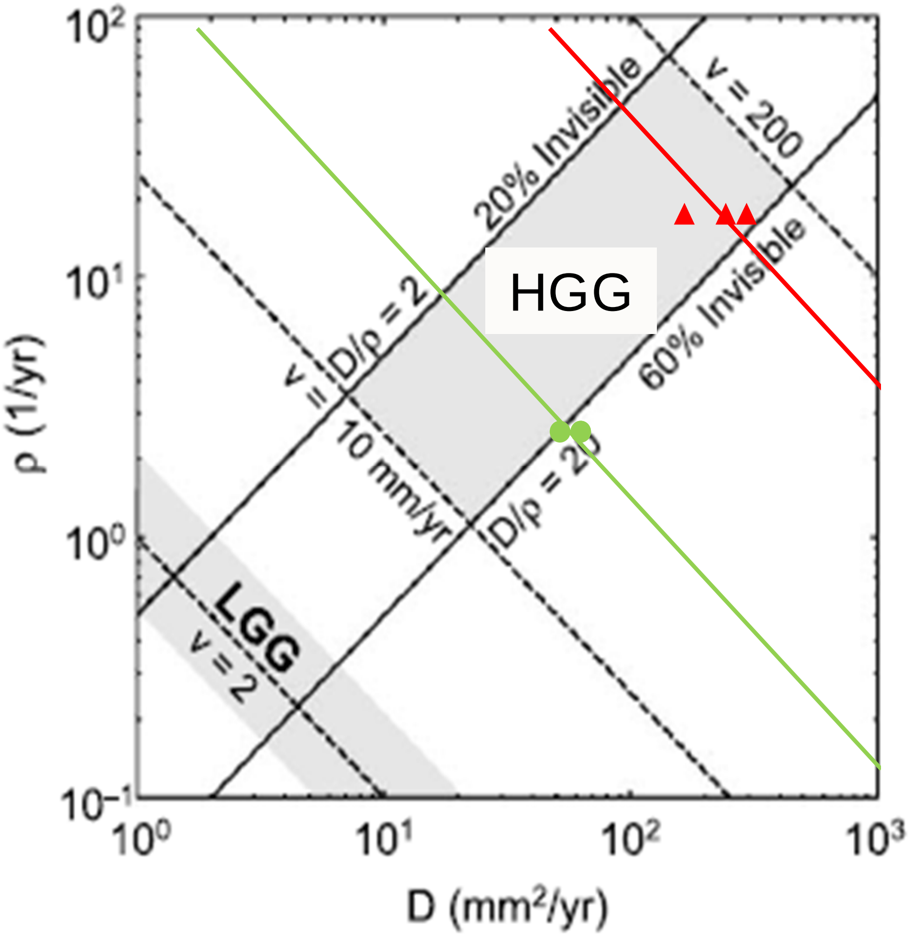


Understanding the Fisher Equation



Infiltration vs. propagation

$v = 2(D\rho)^{1/2}$



High grade,
v_w = 110mm/yr

Low grade,
v_w = 2-4mm/yr

$i = D/\rho$

From Swanson et al.

State space Fisher equation

A Multilevel Model of Tumor Growth

March

- Proposed by Clatz et al. (2005)
- Includes
  - Geometry
  - Statistics (Atlas)
  - Biomechanics
  - Physiopathology

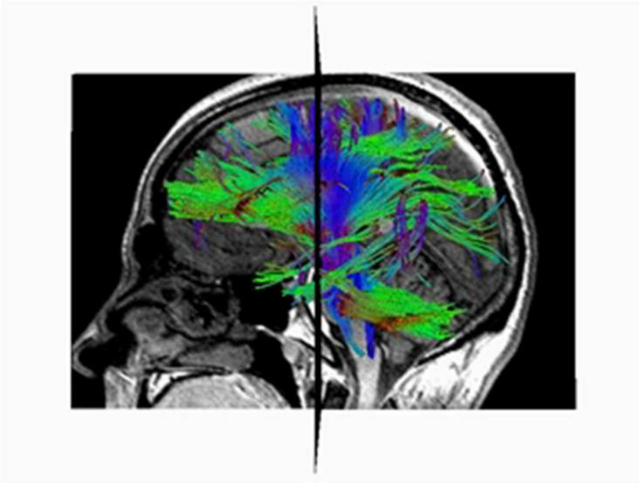
September

Coll. CAL-CHU (Nice) & SPL BWH (Harvard)

O. Clatz, M. Sermesant, P.-Y. Bondiau, H. Delingette, S. Warfield, G. Malandain, N. Ayache. Realistic Simulation of the 3D Growth of Brain Tumors in MR Images Including Diffusion and Mass Effect. *IEEE Transactions on Medical Imaging.* 24(10):1334-1346, Oct. 2005.

Anisotropic Diffusion

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



Different Cell Motility depending on tissue

- White matter -> High diffusion
- Grey Matter -> Low diffusion

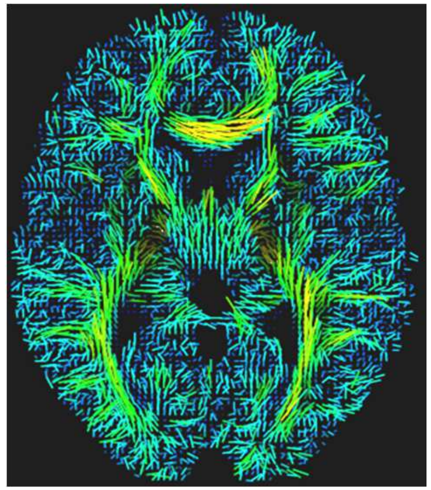
D= Tumor Diffusion Tensor

In grey matter $D = d_g \, Id$

DTI Image

In white matter $D = d_w \frac{D_{water}}{d_0}$

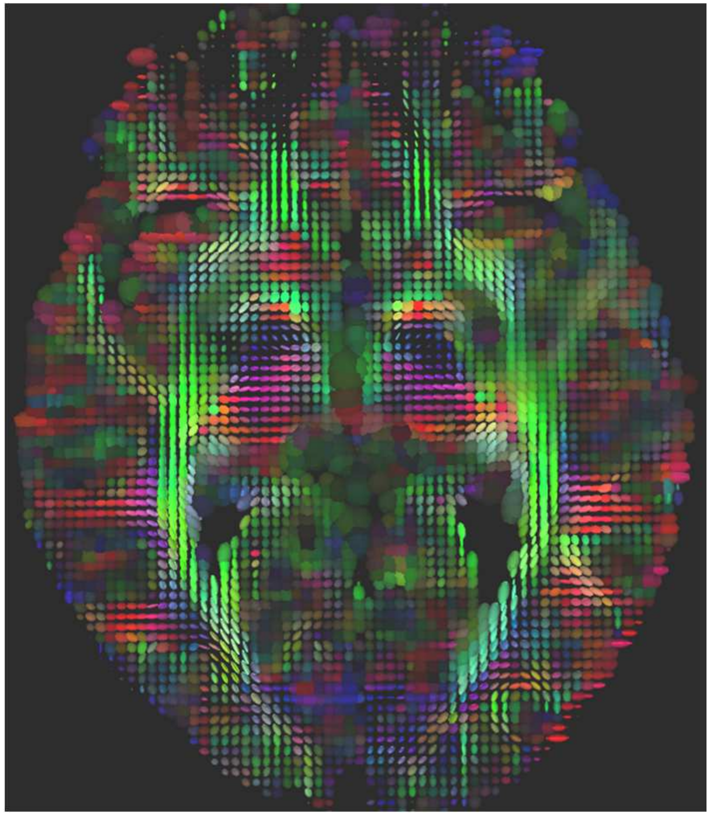
Normalization factor



Other methods for TDT : [Jbabdi 2005], [Swanson et al.]

1. Geometrical Model

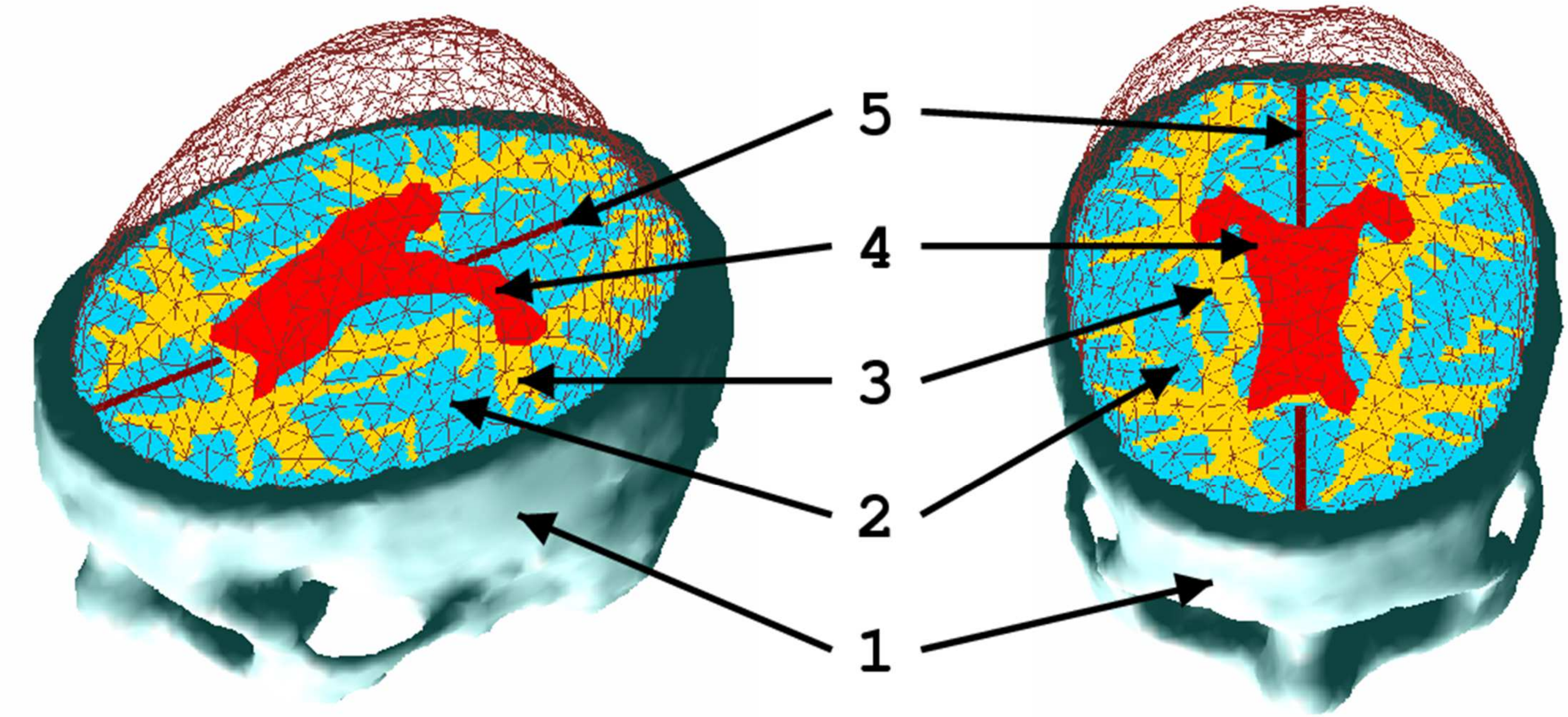
Segmented T1 MRI
(Brainweb)
GM,WM,CSF, Skull, etc.



DTI
Main fiber bundles of WM

2. Biomechanical Model

Inhomogeneous Anisotropic Linear Elastic



1 Skull. 2 Grey matter 3 White matter.
4 Ventricles. 5 Falx cerebri

3. Physiopathological Model

Evolution of tumor density c

Fisher Kolmogorov

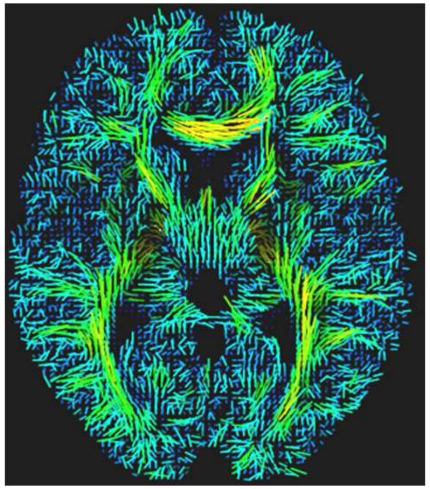
$$\boxed{\frac{\partial c}{\partial t} = \underbrace{\nabla.(D\nabla c)}_{\text{Anisotropic migration}} + \underbrace{\rho c(1-c)}_{\text{Logistic proliferation}}}$$

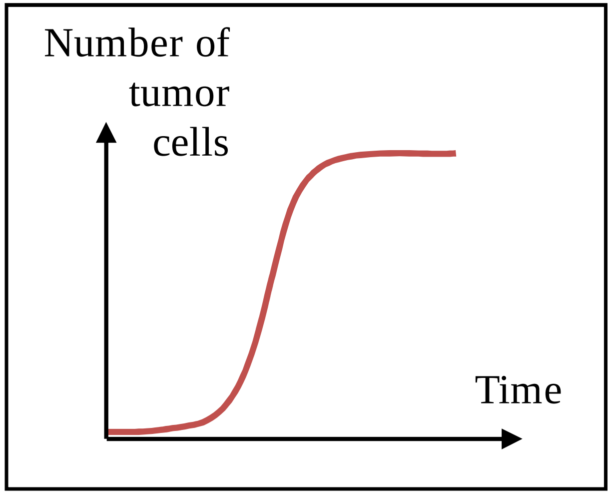
+CL

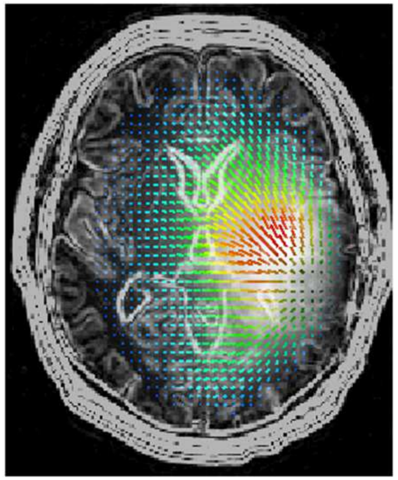
Biomechanical coupling

$$\boxed{\mathrm{div}(\sigma - \alpha c\, I_3) + Fe = 0}$$

Mass effect



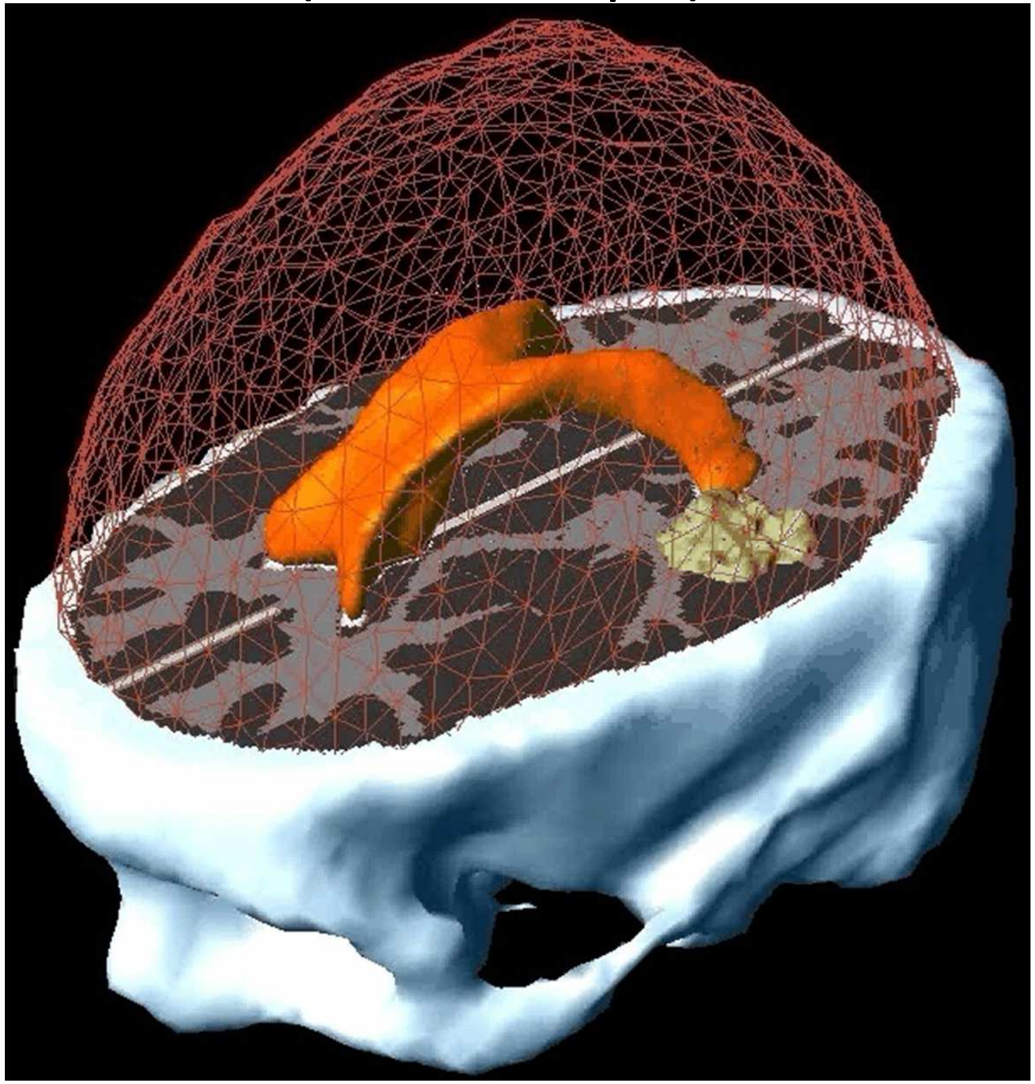




Collaboration Centre Antoine Lacassagne & Harvard

Simulated Growth

(Mars – Sept.)



O Clatz,,PY Bondiau, H Delingette, M Sermesant, SK Warfield, G. Malandain, N.A.. *Brain Tumor Growth Simulation.* IEEE-TMI 2005

Solving the Fisher equation :

- Several schemes :
  - Explicit schemes
  - Lattice-Boltzman Method
  - Semi-implicit scheme : “smooth and grow”

Easily parallelizable

- Parameters :
  - Diffusivity in grey matter d_g+ white matter d_w
  - Proliferation factor : ρ

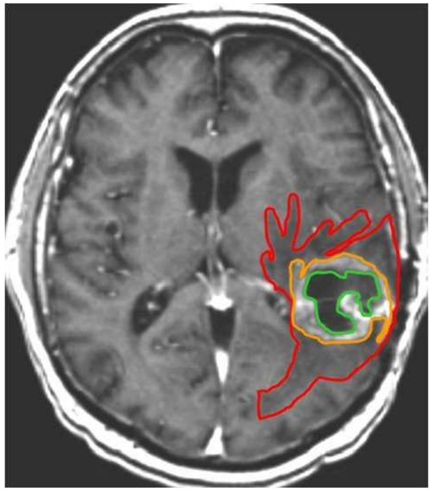
Necrosis and vascularisation

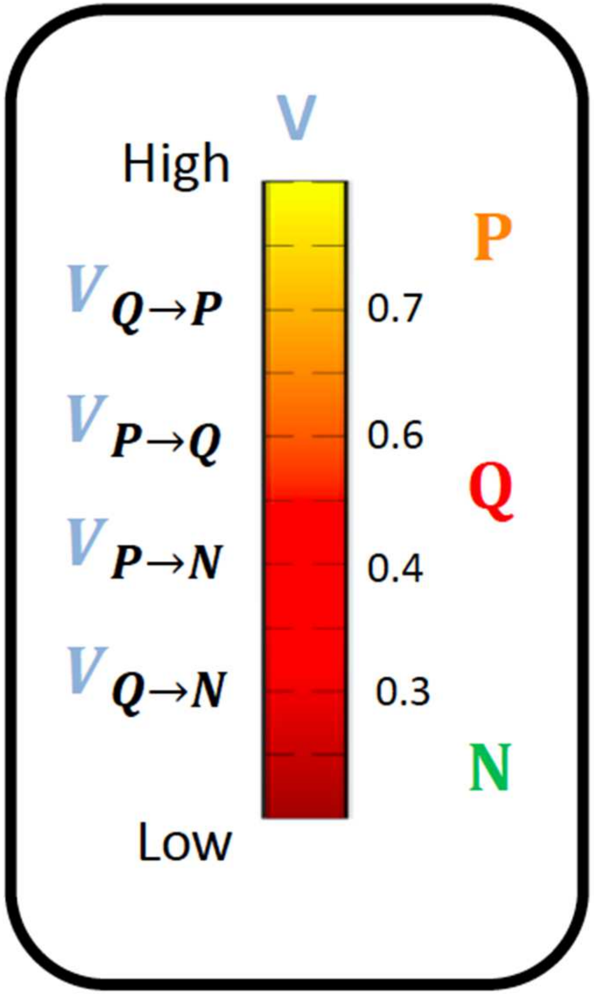
- **3 types** of tumor cells

Proliferating : multiplication and diffusion

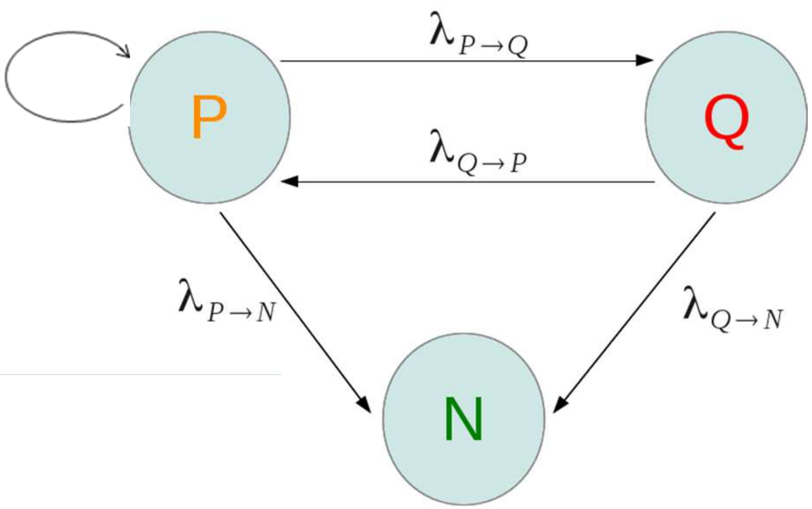
Quiescent : strong diffusion

Necrosed : static





- ***Transitions** : depend on vascularisation*



- ***Vascularisation** : function of P & N*

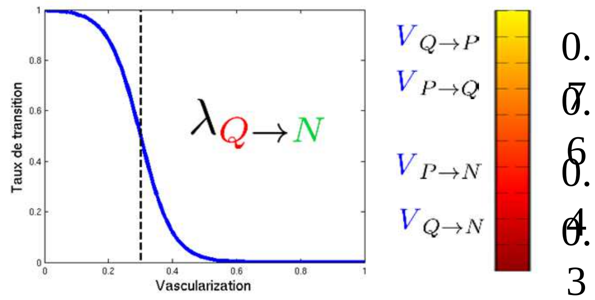
T. Colin, O. Saut et al., 2012, M. Le 2012

Necrosis and vascularisation

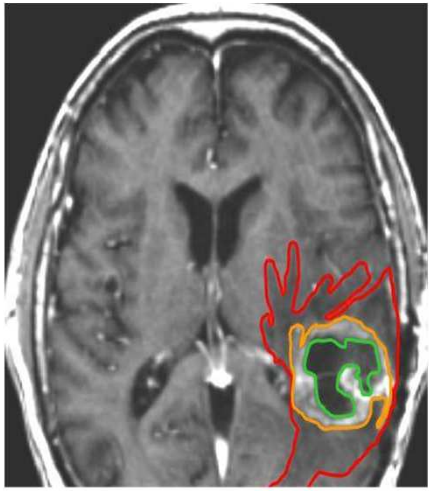
	DIFFUSION	PROLIFERATION	TRANSITIONS
$\frac{\partial P}{\partial t} =$	$\nabla.(D_P(1-T)\nabla P)$	$+\rho P(1-T)$	$-\lambda_{P\to Q}P - \lambda_{P\to N}P + \lambda_{Q\to P}Q$
$\frac{\partial Q}{\partial t} =$	$\nabla.(D_Q(1-T)\nabla Q)$		$-\lambda_{Q\to P}Q - \lambda_{Q\to N}Q + \lambda_{P\to Q}P$
$\frac{\partial N}{\partial t} =$			$+\lambda_{P\to N}P + \lambda_{Q\to N}Q$

$$T = P + Q + N$$

	ANGIOGENESIS	DEGRADATION
$\frac{\partial V}{\partial t} =$	$\alpha P(1-V)$	$-\beta NV$

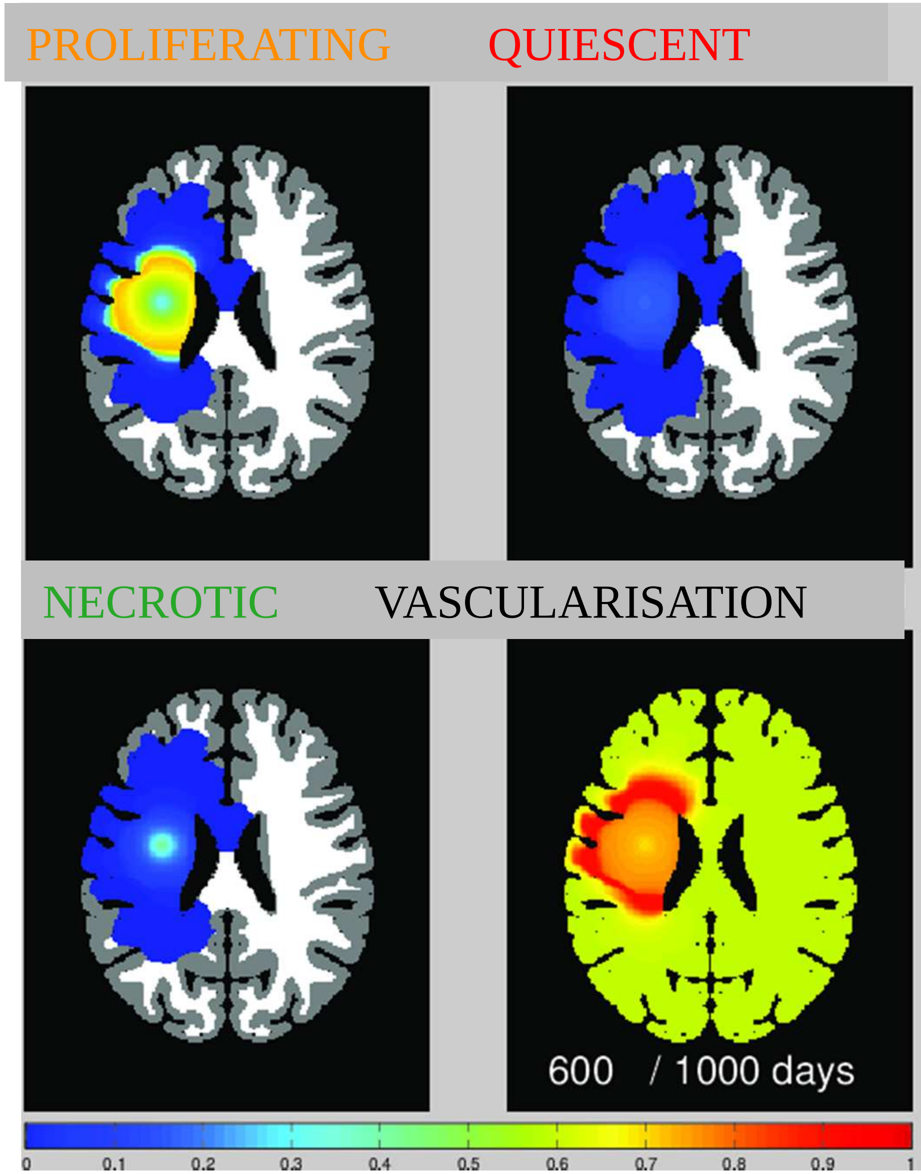


Necrosis and vascularisation



3 types of cells

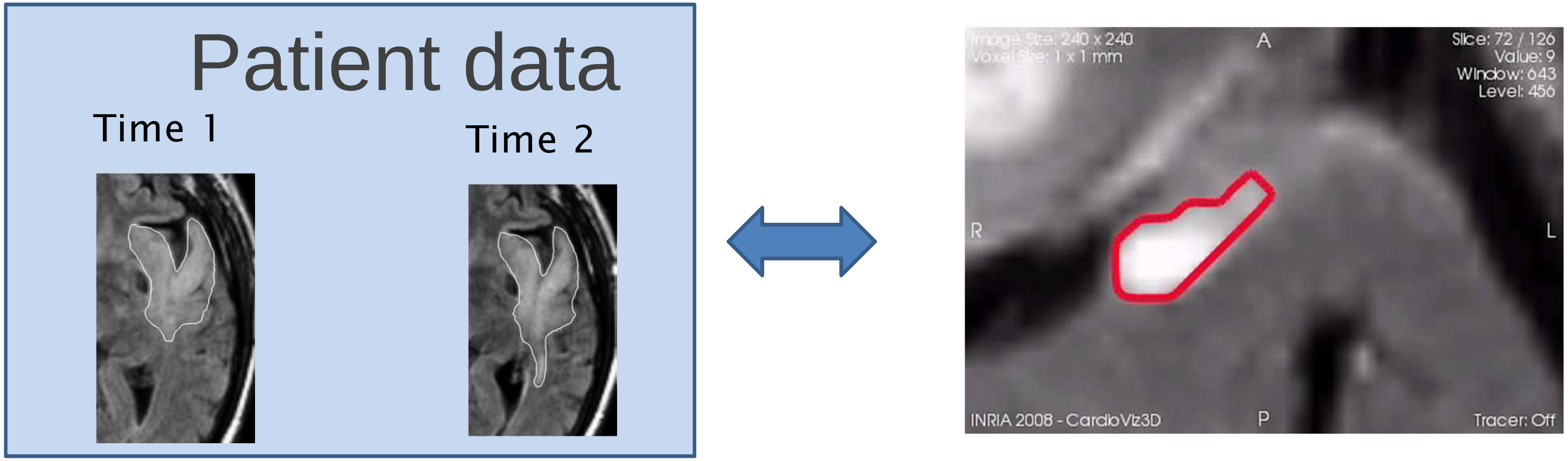
Proliferating
Quiescent
Nécrotic



T. Colin, O. Saut et al., M. Le 2012

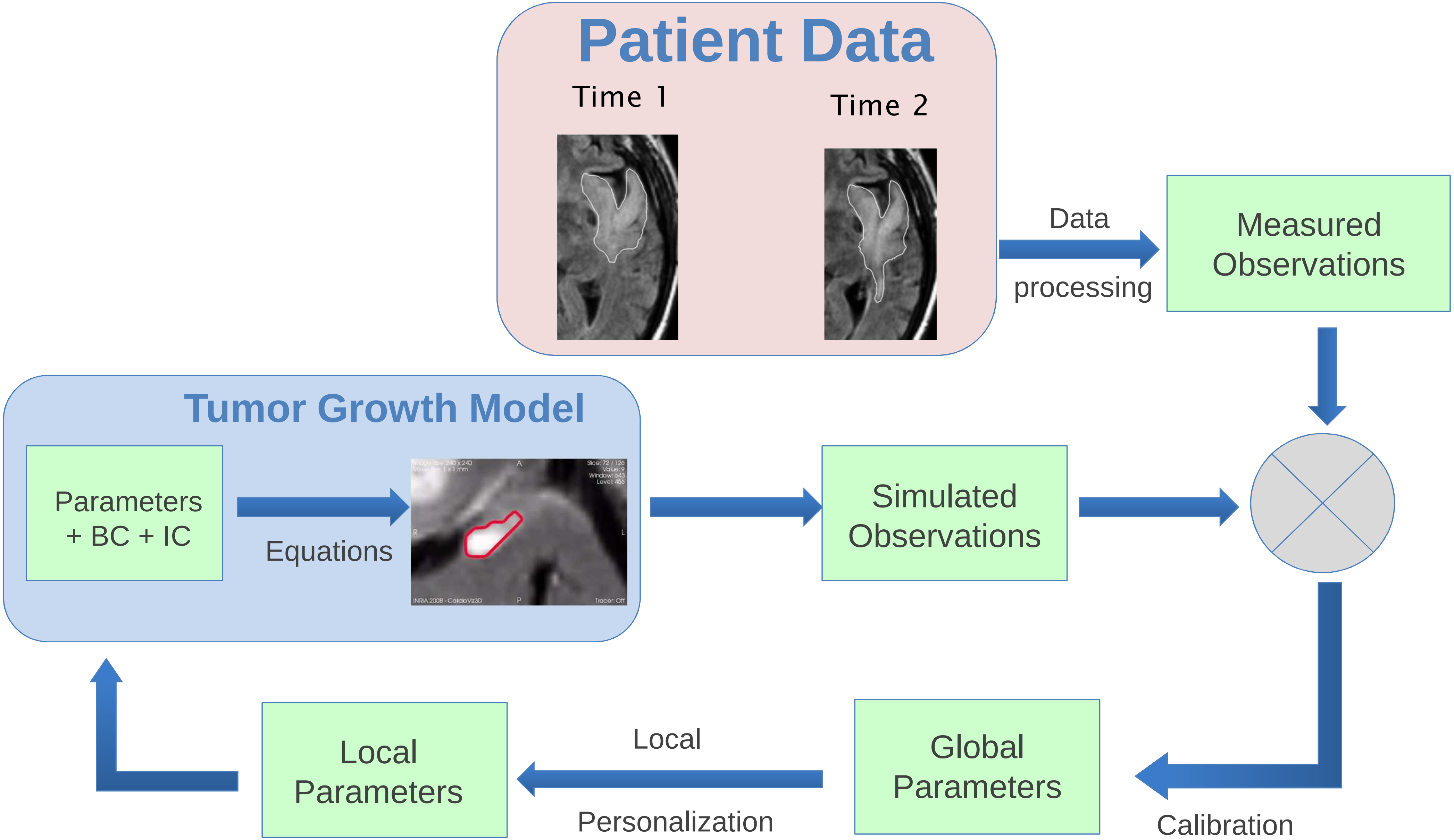
- ***Vascularisation*** *: function of P and N*

Personnalization of Glioma Growth Models



- Why Personalization of Models ?
  - Understanding the limits of models
  - Quantification of tumor growth
  - Therapy planning

Model Personalization



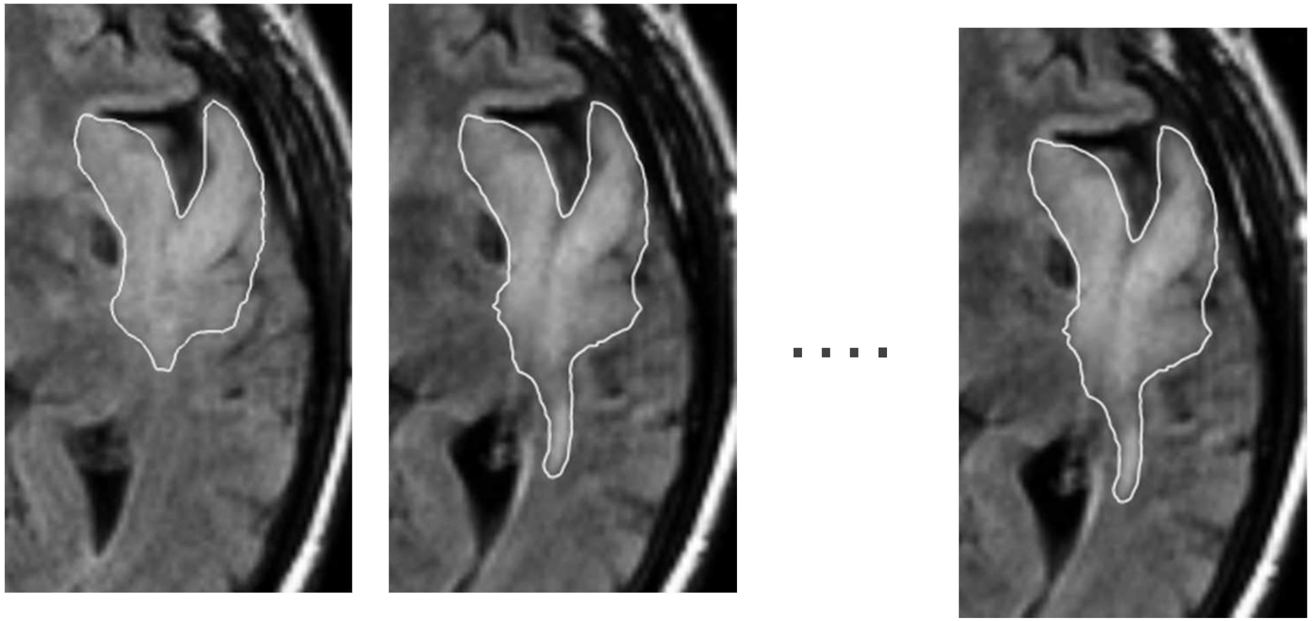
Personnalization

- 1. Growth speed
- 2. Invisibility Index

A simpler problem

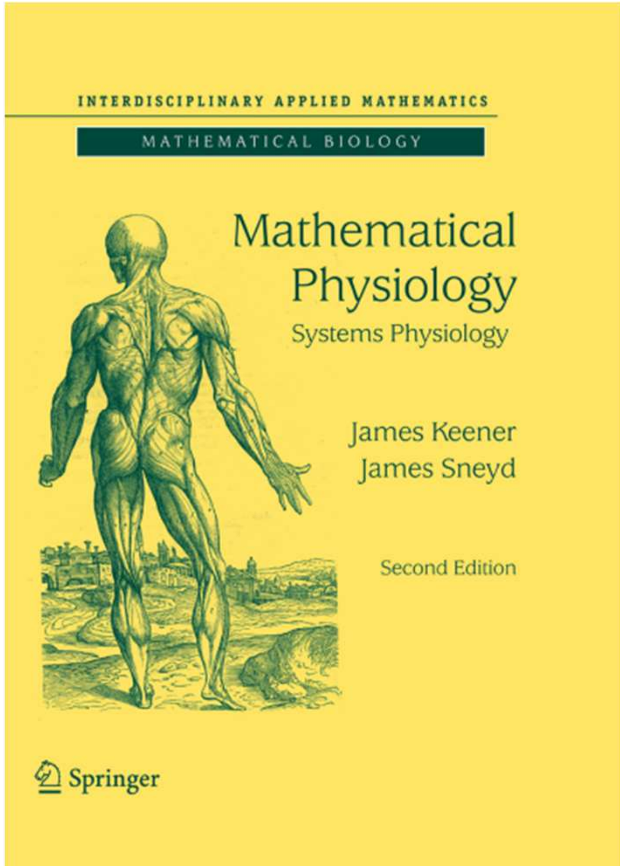
- Only observe the evolution of 2 contours

Estimate only the speed of front



A simpler Model

- Approximate the RD equation for an isodensity surface ⇨ Asymptotic analysis



Search solution as $c(x - vt)$

Leads to Eikonal equation

Isotropic propagation $F\nabla T = 1$

Anisotropic propagation

$$2\sqrt{\rho}\,\sqrt{\nabla T^{\mathrm{T}} D \nabla T} = 1$$

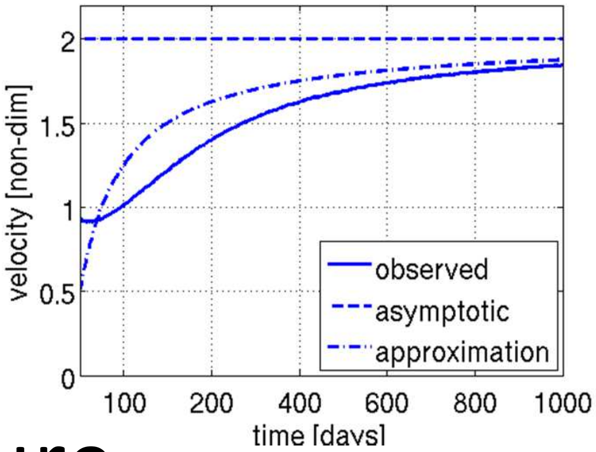
Solved with (Anisotropic) Fast Marching

“Mathematical physiology”, Keener & Sneyd, Springer

Advanced Asymptotic Model of Tumor Growth

- Include dependence on time

$$\left(\frac{4\rho T-3}{2T\sqrt{\rho}}\right)\sqrt{\nabla T'\mathbf{D}\nabla T}=1$$



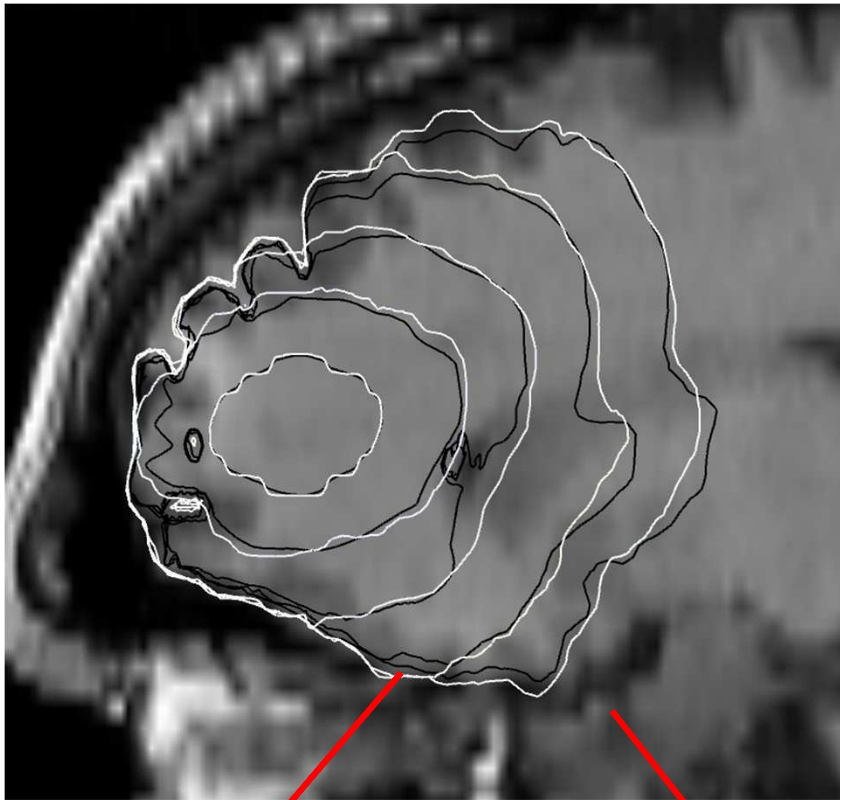
- Include dependence on curvature

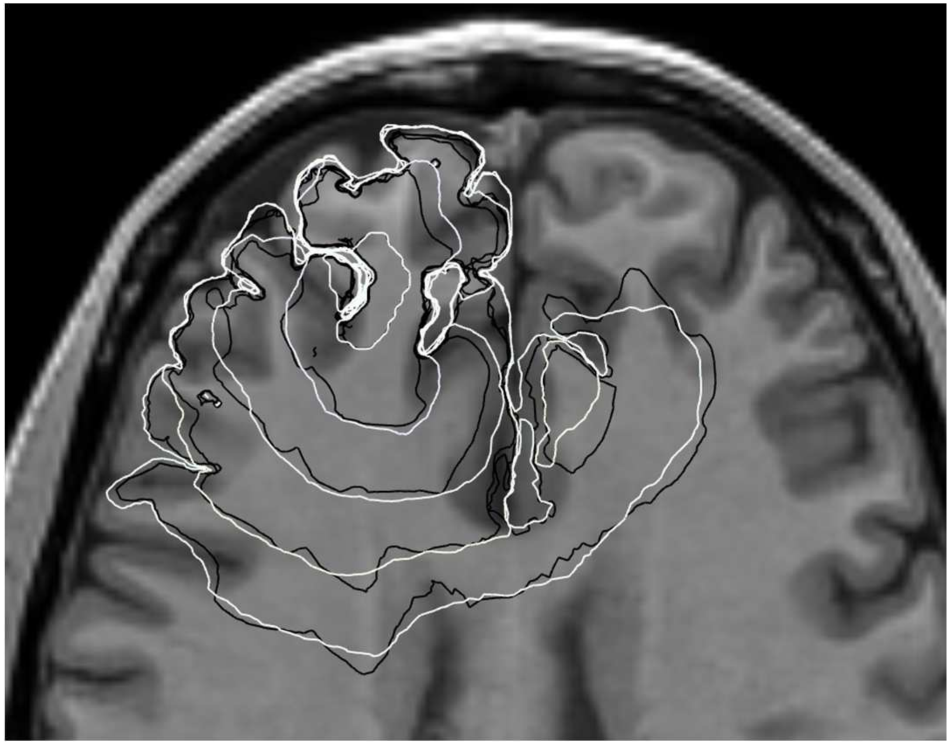
$$\left\{\frac{4\rho T-3}{2T\sqrt{\rho}}-0.3\sqrt{\rho}\left(1-e^{-\left|\kappa_{eff}\right|/\left(0.3\sqrt{\rho}\right)}\right)\right\}\sqrt{\nabla T'\mathbf{D}\nabla T}=1,\ \kappa_{eff}=\nabla\cdot\frac{\mathbf{D}\nabla T}{\sqrt{\nabla T'\mathbf{D}\nabla T}}$$

Eikonal-Curvature equation

Solved by iterative anisotropic fast-marching

Comparing Reaction-Diffusion with Traveling Time Formulation

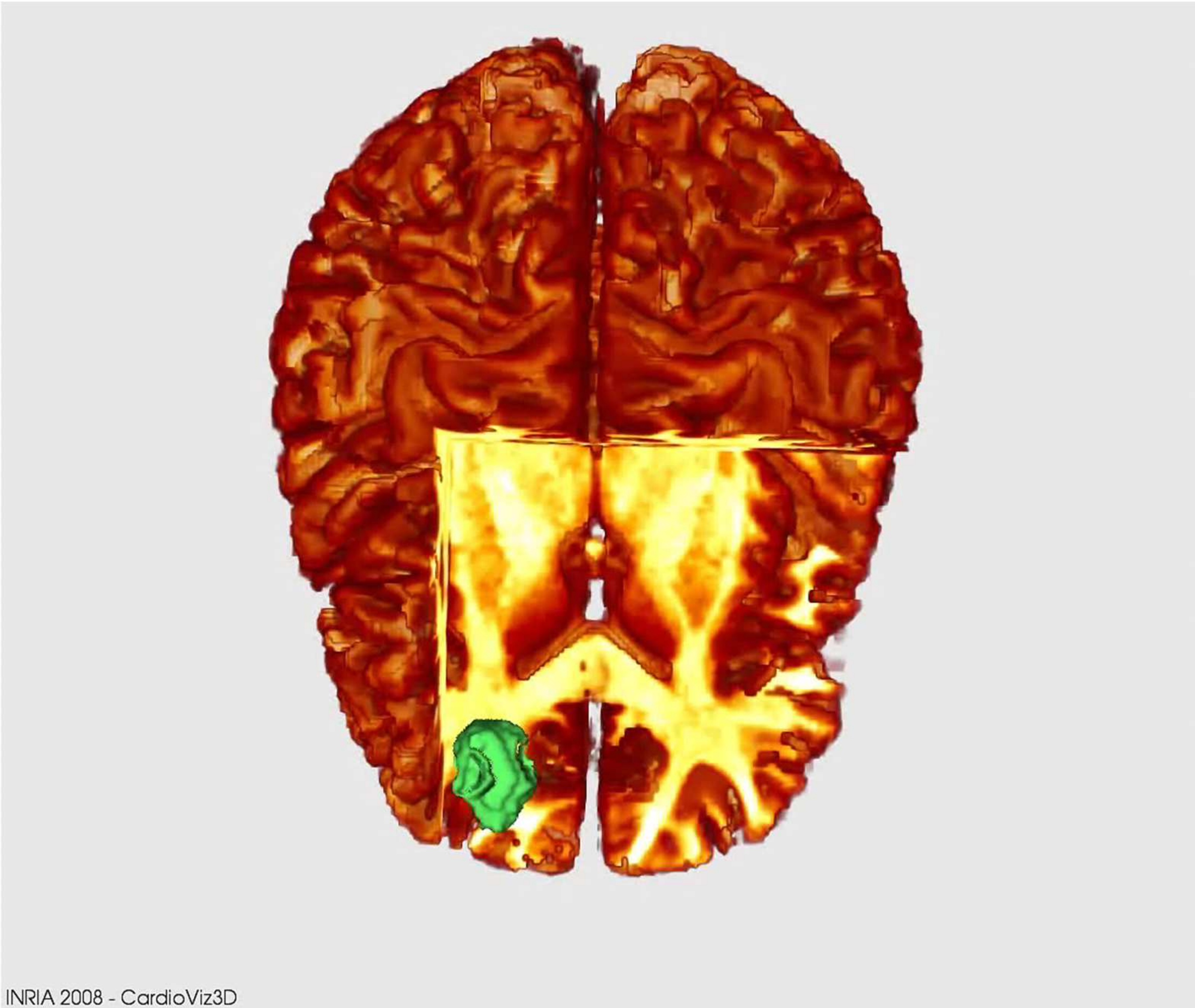




u=0.4 iso-density contour at days 400,600,800,1000 and 1200

Black: Traveling Time

White Fisher PDE


INRIA 2008 - CardioViz3D

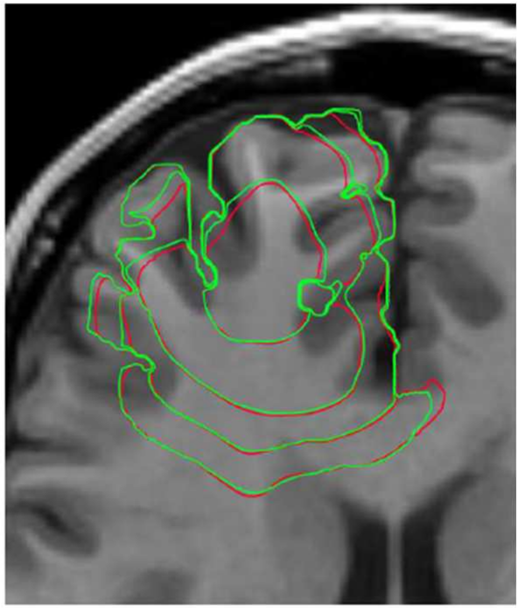
Parameters of tumor growth model

- Diffusion of tumor cells in
  - White matter : d_w
  - Grey matter : d_g
- ~~Proliferation rate~~ : ρ
- Time of initial appearance of the tumor : T_0

Observability issue
Cannot estimate both ρ and D

Set value of ρ

	Red	Green
d_w	0.273	0.153
d_g	0.024	0.014
ρ	0.012	0.0185



But speed $v \approx 2\sqrt{\rho D}$ depends On both ρ and D

Personalization

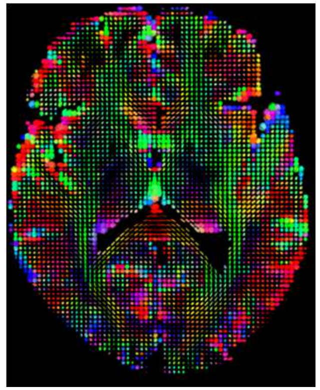
- Input

Tumor segmentation

Time between exams

$$\Delta t_1, \Delta t_2, \ldots, \Delta t_{N-1}$$

DTI



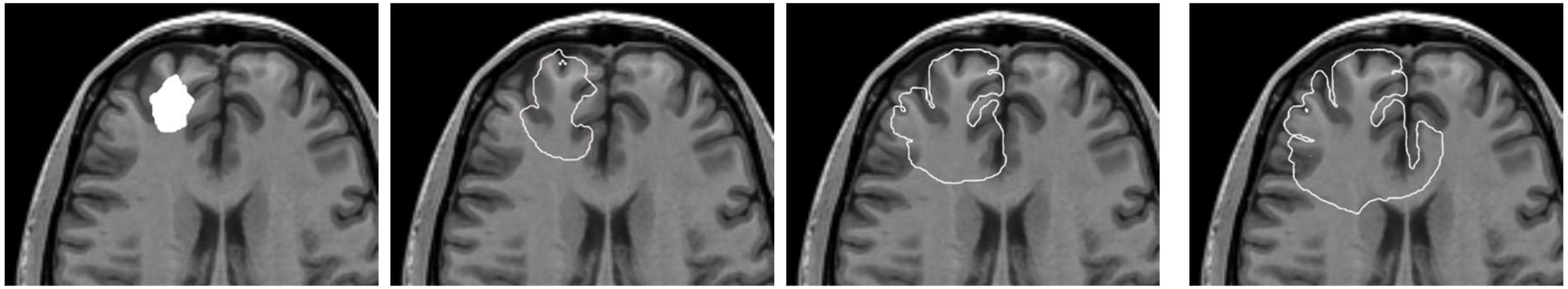
$\mathbf{D}_{\text{water}}$

- Ouput : $\boxed{\left(\rho d_w, \rho d_g, T_0\right)}$
  - Speed GM and WM,
  - Time T0

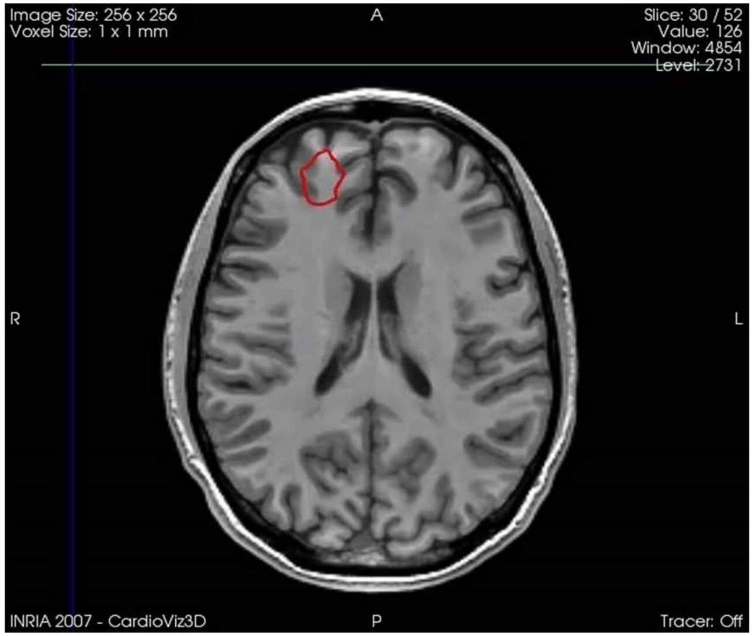
$$\mathbf{D} = \begin{cases} \alpha d_w \mathbf{D}_{\text{water}}, \text{ white matter} \\ d_g \mathbf{I}_3, \text{ gray matter} \end{cases}$$

Forward & Backward Simulation

For a set of parameters $\left(\rho d_w, \rho d_g, T_0\right)$



+ 200 days + 400 days + 600 days



Forward Simulation

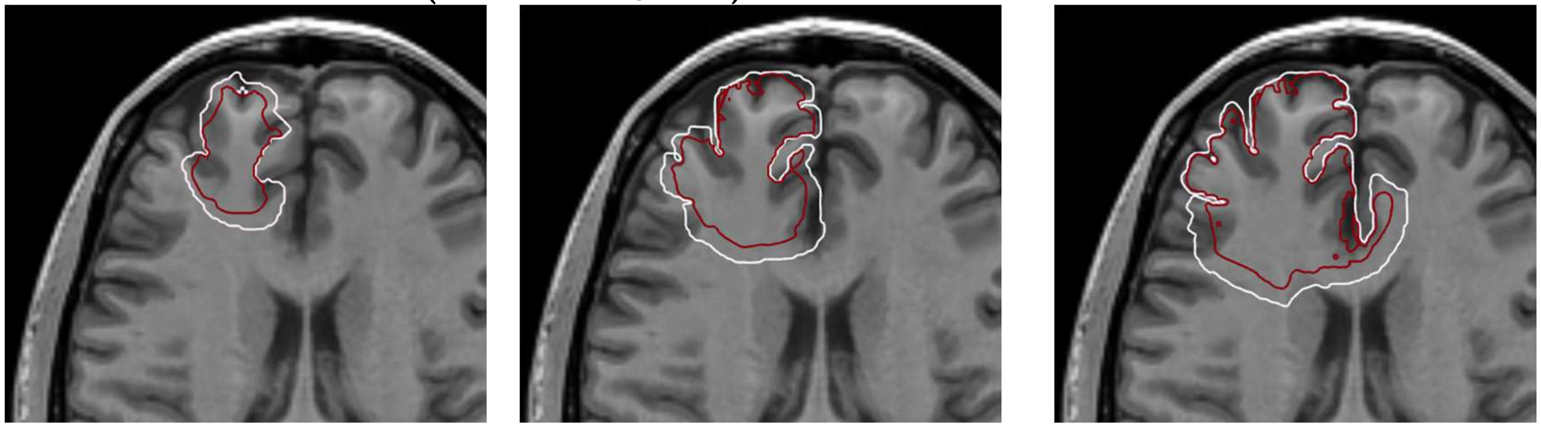
Estimation of $\left(\rho d_w, \rho d_g\right)$

Backward Simulation

Estimation of T_0

Error Criterion

For a set of parameters $\left(\rho d_w, \rho d_g, T_0\right)$



Difference between real and simulated contours

$$C_1 = \sum_{i=1,..,N-1} dist\left(\Gamma_i, \hat{\Gamma}_i\right)^2$$

Difference between estimated and simulated time to shrink to a single voxel

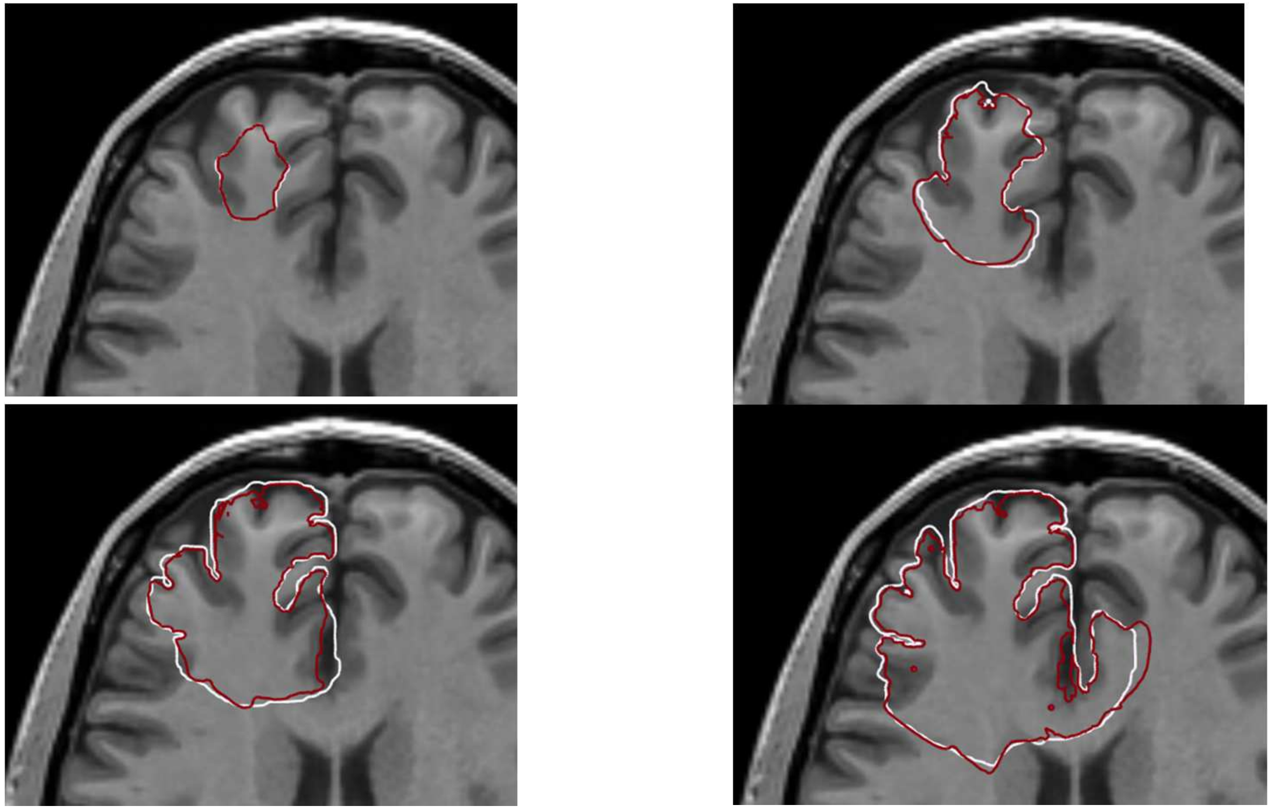
$$C_2 = \left(v_{\min}\left|T_{\min} - T_0\right|\right)^2$$

Optimisation

$$\boxed{C = C_1 + C_2}$$

- Minimisation of criterion
  - Gradient-Free Algorithm Powell UoByQa

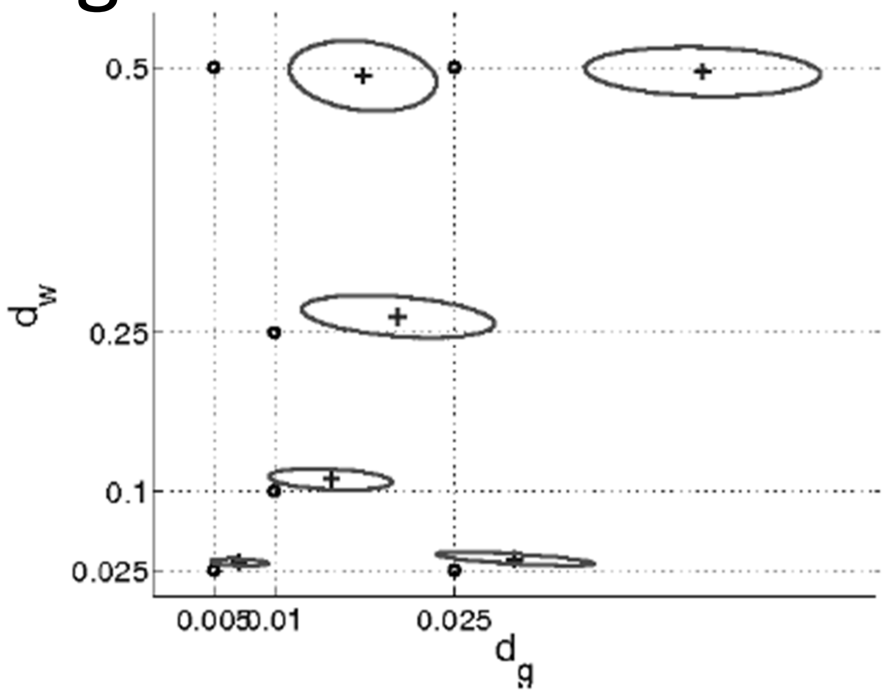
$$\left(\rho d_w^*, \rho d_g^*, T_0^*\right)$$

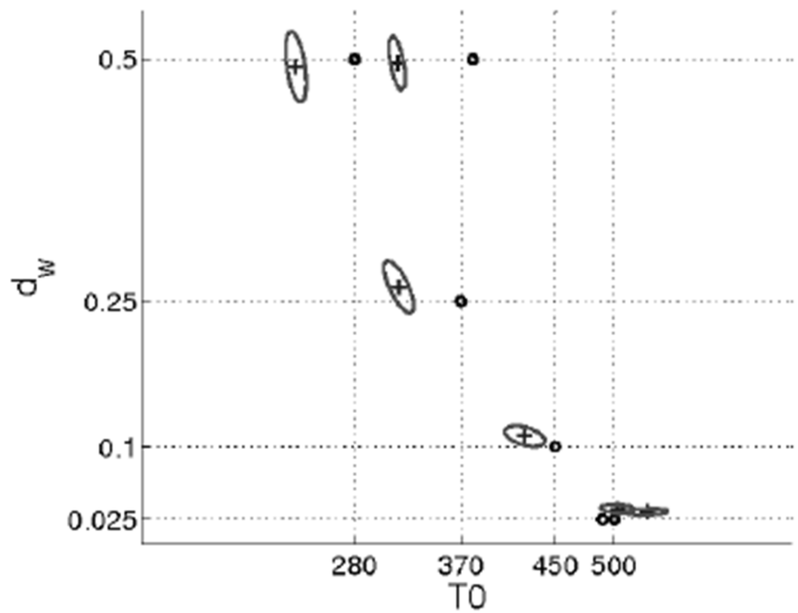


Powell, Mathematical Programming, vol. 92, no. 3, 2002

Test on synthetic cases

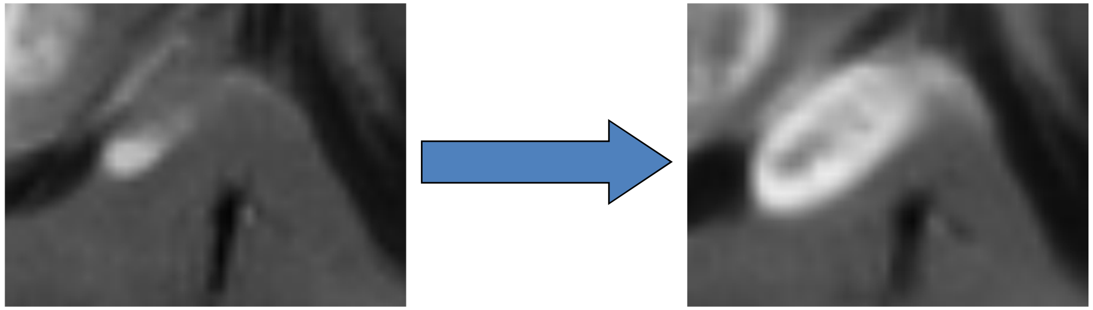
- Recover well d_w (constant relative error)
- Bias + large uncertainty for d_g
- Estimate parameter uncertainty due to segmentation uncertainty



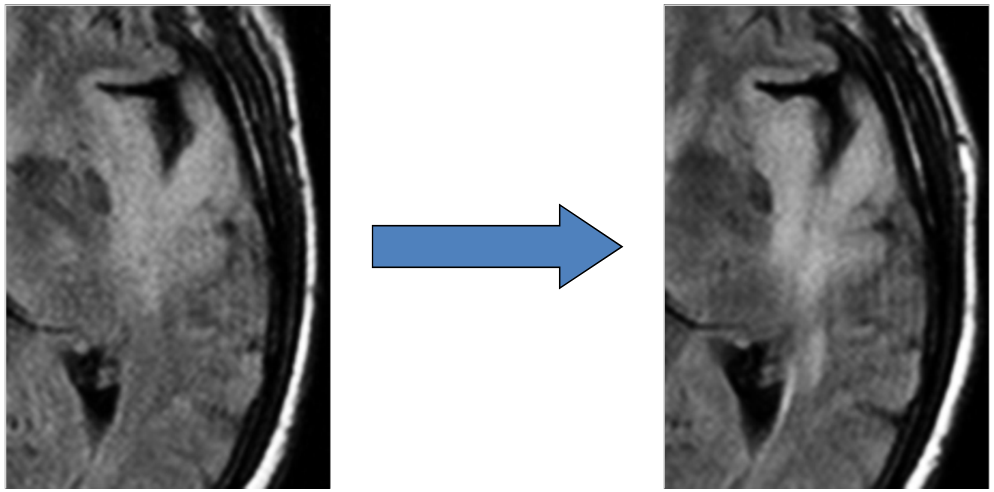


Two real cases

Time 1 Time 2

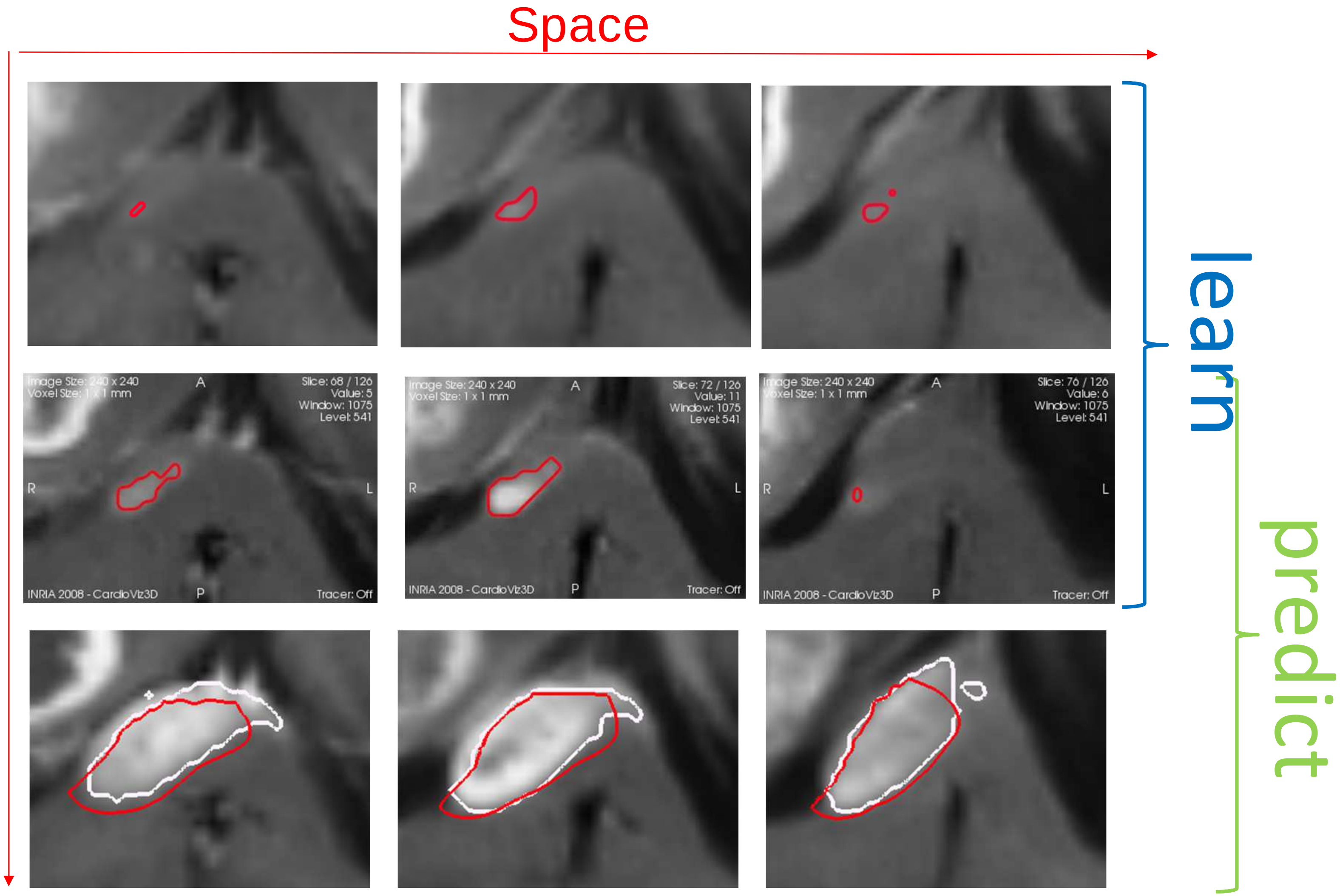


High grade glioma evolution



Low grade glioma evolution

High Grade Glioma

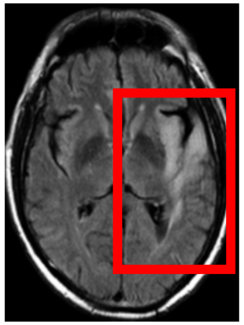


*MRI T1 Gd, 0.5*0.5*6.5mm*
3 time points

MR DTI : 2.5mm (time 2)

ρ(set)	d_w	d_g
$0.05\ 1/day$	$0.66\ mm^2/day$	$0.0013\ mm^2/$

Simulation/Reality



Low Grade Glioma

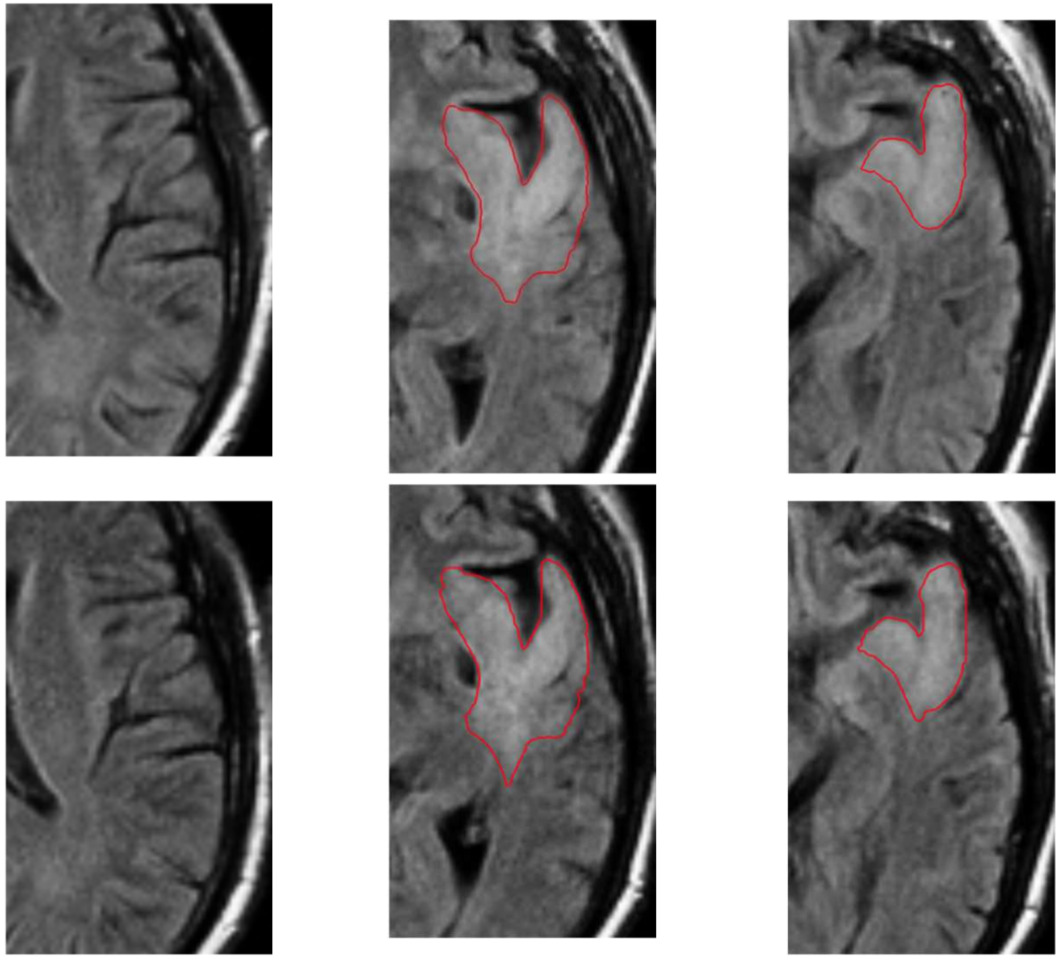
Space

Learn

on

4 months

time



$\rho(\text{set})$	d_w	d_g
$0.008\ 1/day$	$0.20\ mm^2/day$	$0.0007\ mm^2/day$

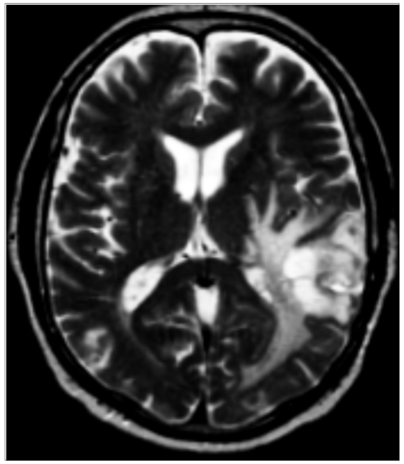
IRM T2 Flair
*0.5*0.5*6.5mm*
5 time points
MR DTI : 2.5mm (T0)

Personnalisation

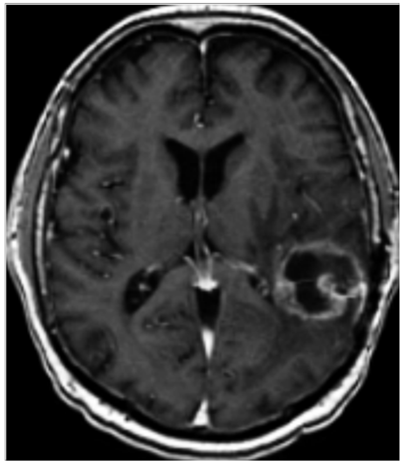
- 1. Growth speed

- 2. Invisibility Index

T2 and T1 Gd Images

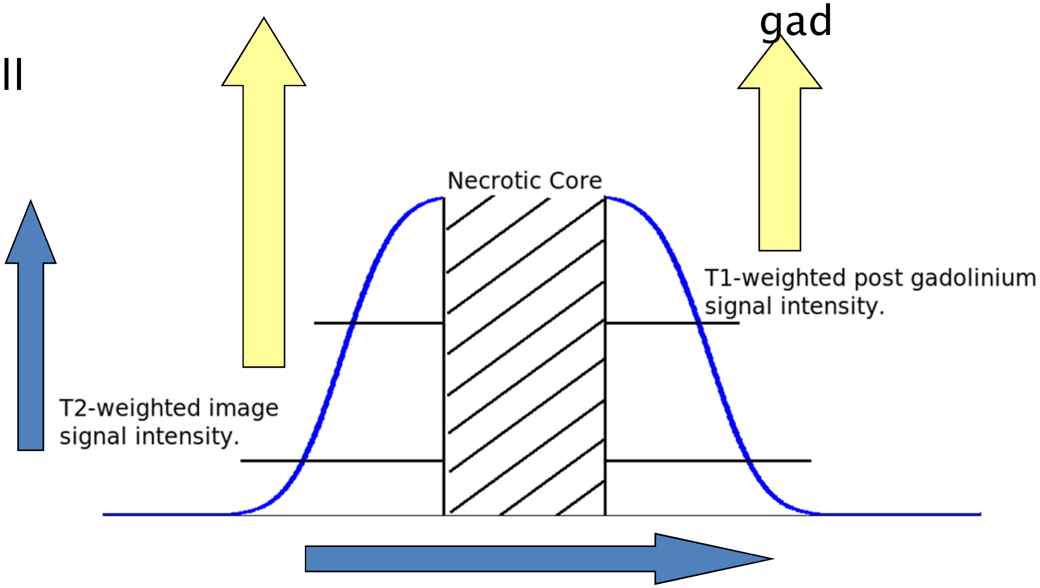


T2w



T1w post-gad

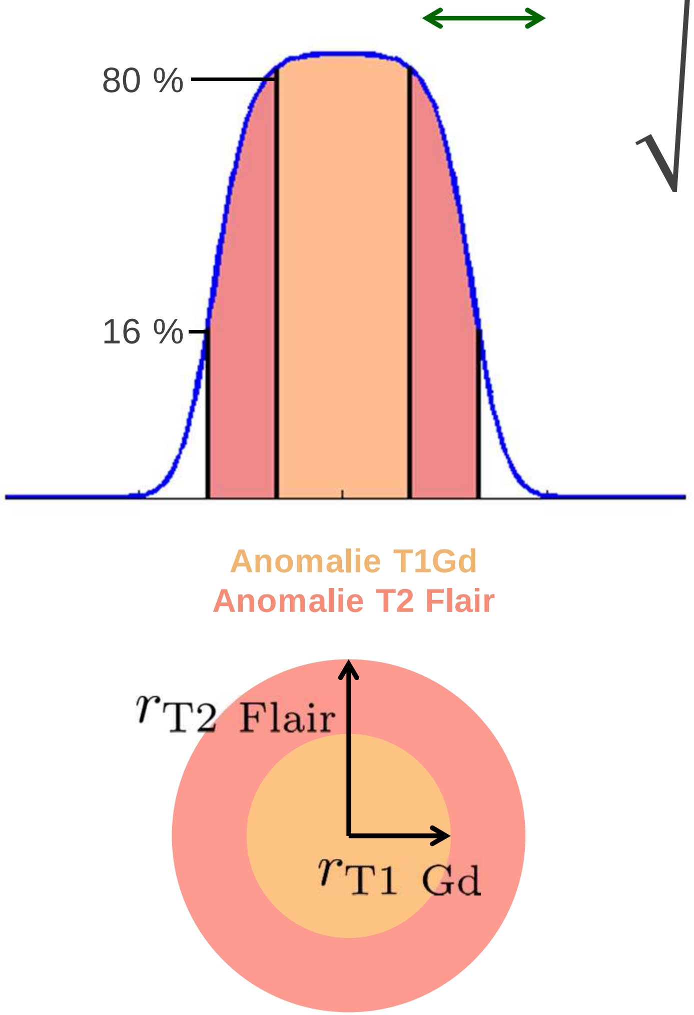
Tumor cell density



Invisibility Index

$$\sqrt{\frac{D}{\rho}}$$

- Empirical formula to estimate
  Invisibility index
  from 2 radii of T1Gd & Flair images



Swanson et al.

Predict Infiltration

- Given invisibility index
- Solve an Eikonal equation

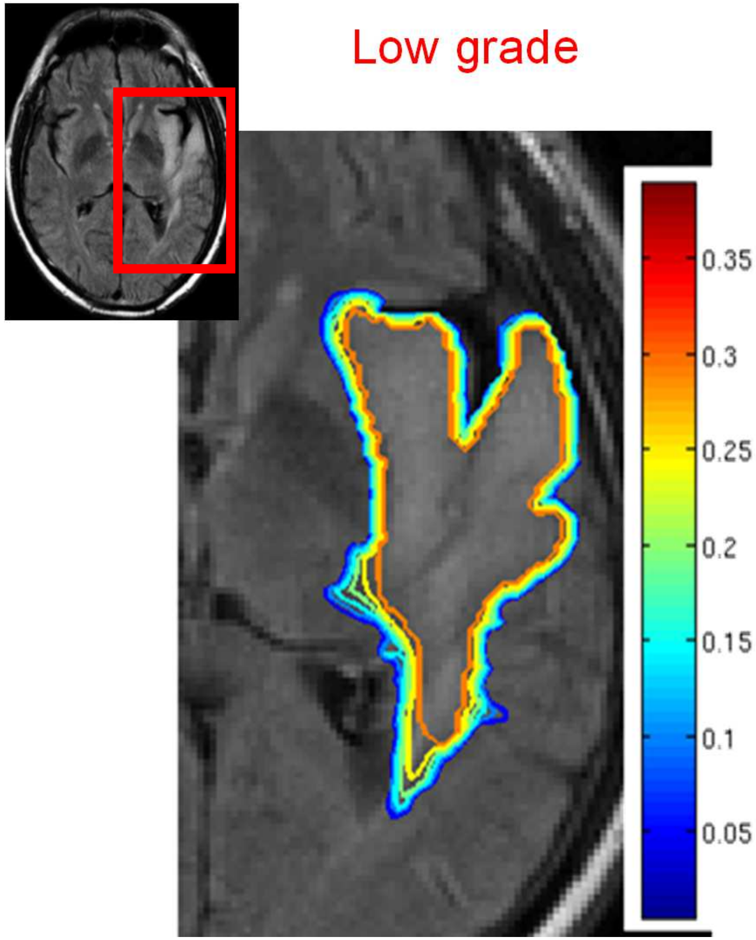
$$\boxed{\frac{\sqrt{\nabla\tilde{u}\cdot\left(\mathbf{D}\nabla\tilde{u}\right)}}{\sqrt{\rho\tilde{u}\left(1-\sqrt{\tilde{u}}\right)}}=1,\ \tilde{u}\left(\Gamma\right)=u_0}$$

- Anisotropic Fast Marching Algorithm

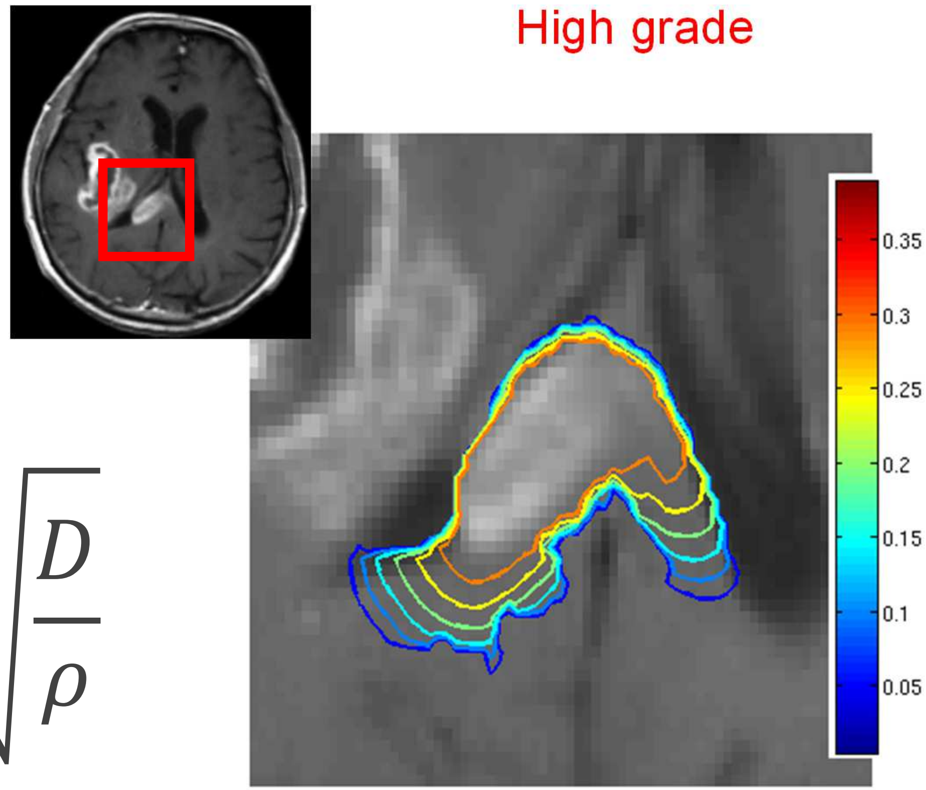
E. Konukoglu, O. Clatz, P.Y. Bondiau, H. Delingette, N. Ayache. *Extrapolating Glioma Invasion Margin in Brain MRI: Suggesting New Irradiation Margins.* Medical Image Analysis 2010.

Predict Invisible infiltration

Predicted Isodensities between 40% and 1%



$$\sqrt{\frac{D}{\rho}}$$



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.

Limitations

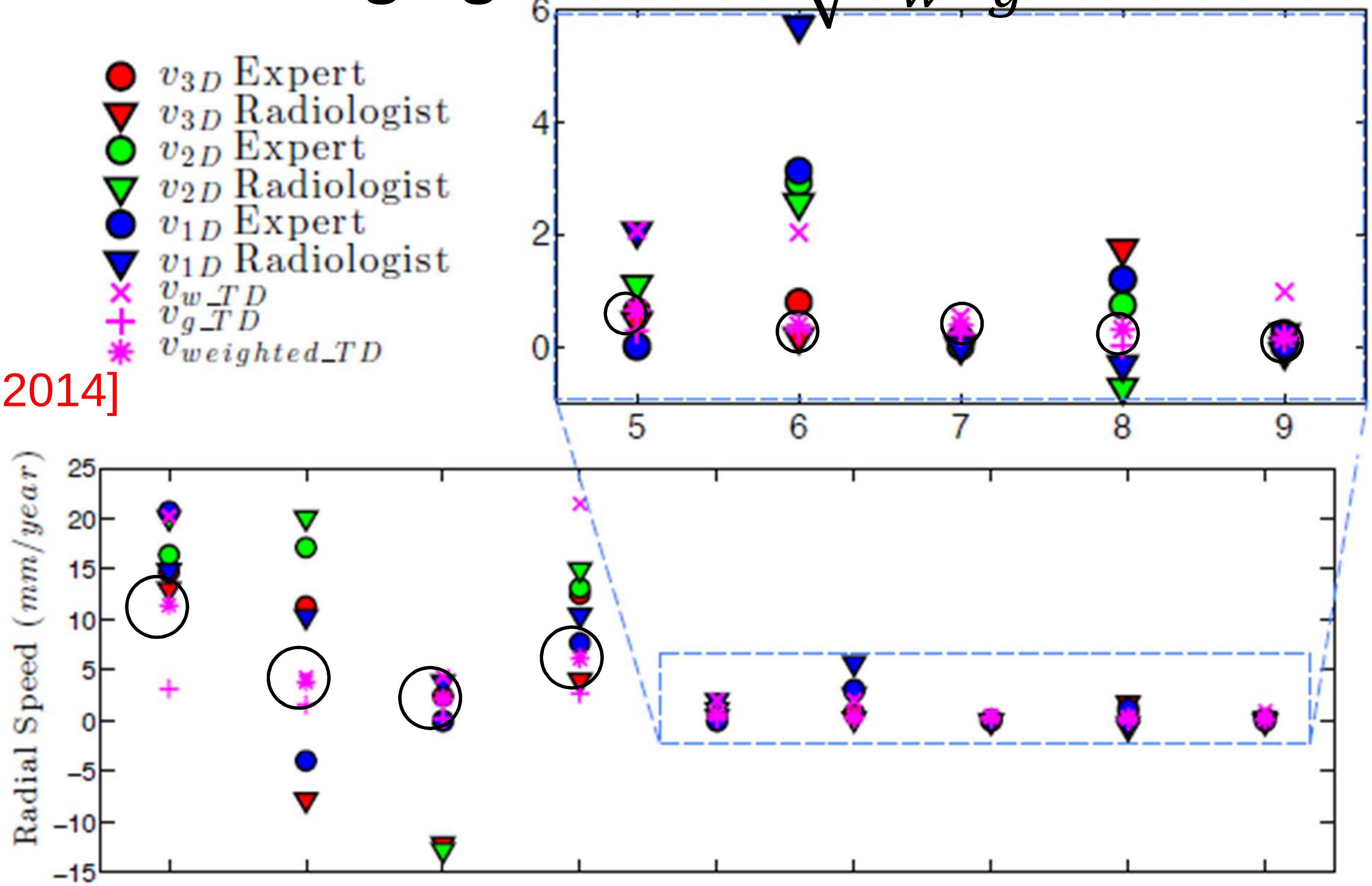
- Difficult to have patient DT-MRI
- Assume DT-MRI undisturbed during tumor growth
- Uncertainty in the tumor delineation
- Only model growth no shrinkage
- No mass effect
- Prediction : assumes no effect of therapy

3 Main Problems

1. Quantify the extent of the tumor
2. Quantify the tumor evolution
3. Improve clinical practice
    - Diagnosis
    - Surgery
    - Radiotherapy

Quantification of tumor growth

- Stable Average growth as $\sqrt{v_w v_g}$



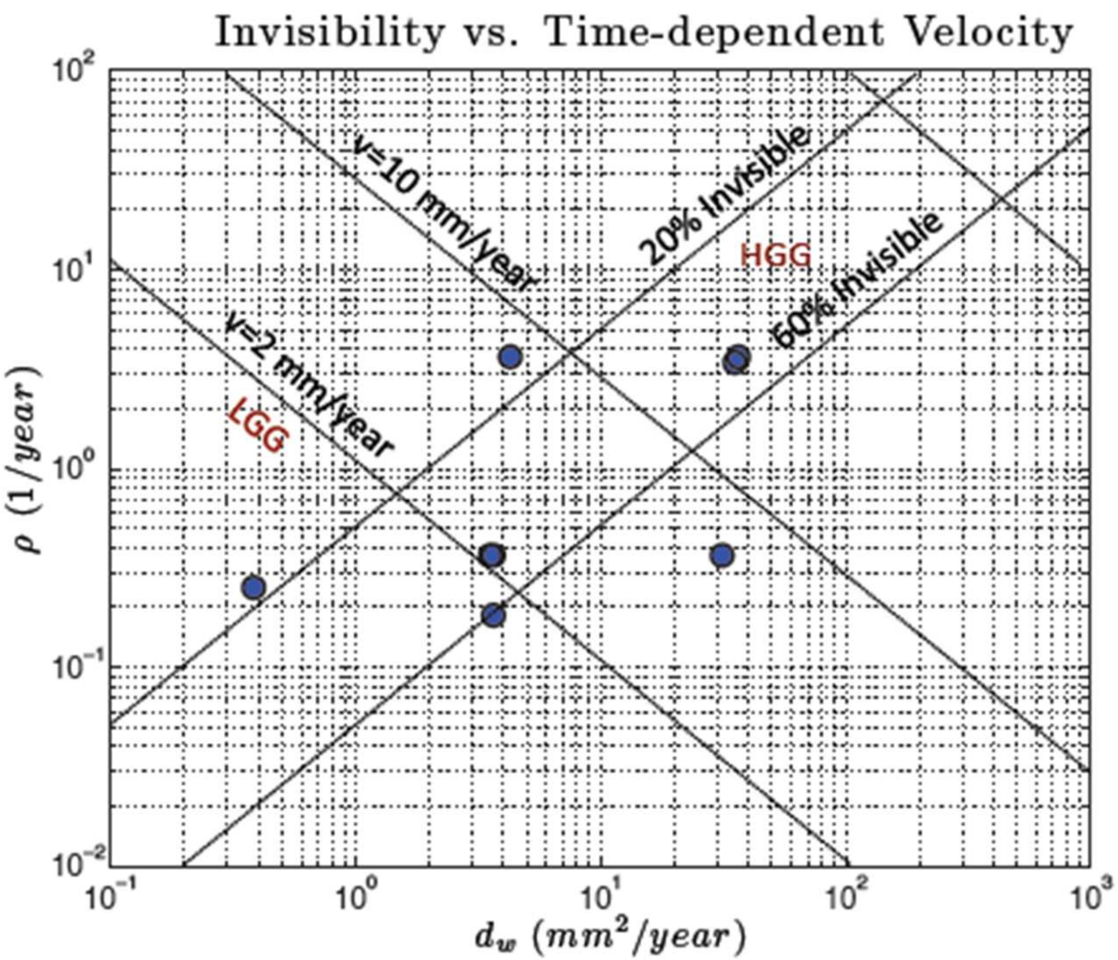
[Stretton 2014]

Quantification of tumor growth

- Grading Tumor growth

[Stretton 2014]

Collaboration with DKFZ



Quantification of tumor growth

- Better prediction of Time-To-Progression than current practice (Recist)

[Stretton 2014]

Collaboration with DKFZ

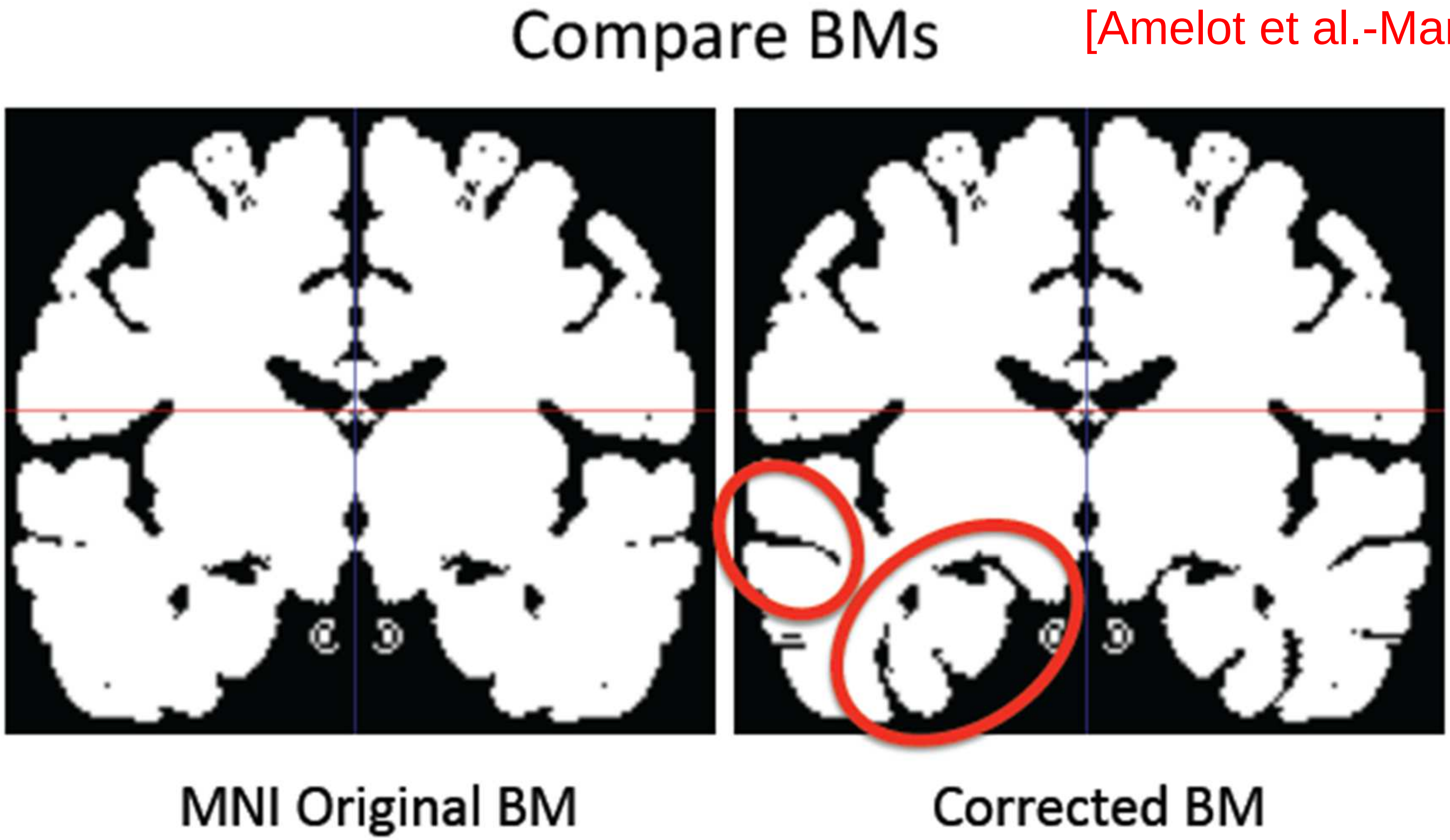
Manual and Model TTP Predictions in 1D

Patient No.	Retrospectively Calculated *TTP* Interval in 1D *(days)*	Radiologist Predicted $TTP_{v_{1D}}$ *(days)*	Model Predicted $TTP_{v_{weighted\_A}}$ *(days)*
1	[1 92]	58	47
2	[92 184]	~~60~~	149
3	[221 396]	328	260
4	[315)	~~174~~	~~188~~
5	[1154)	~~961~~	~~704~~
6	[189)	~~78~~	637
7	[724)	~~undefined~~	1171
8	[112)	~~1046~~	159
9	[915)	2428	1248

Definition of anatomical barriers

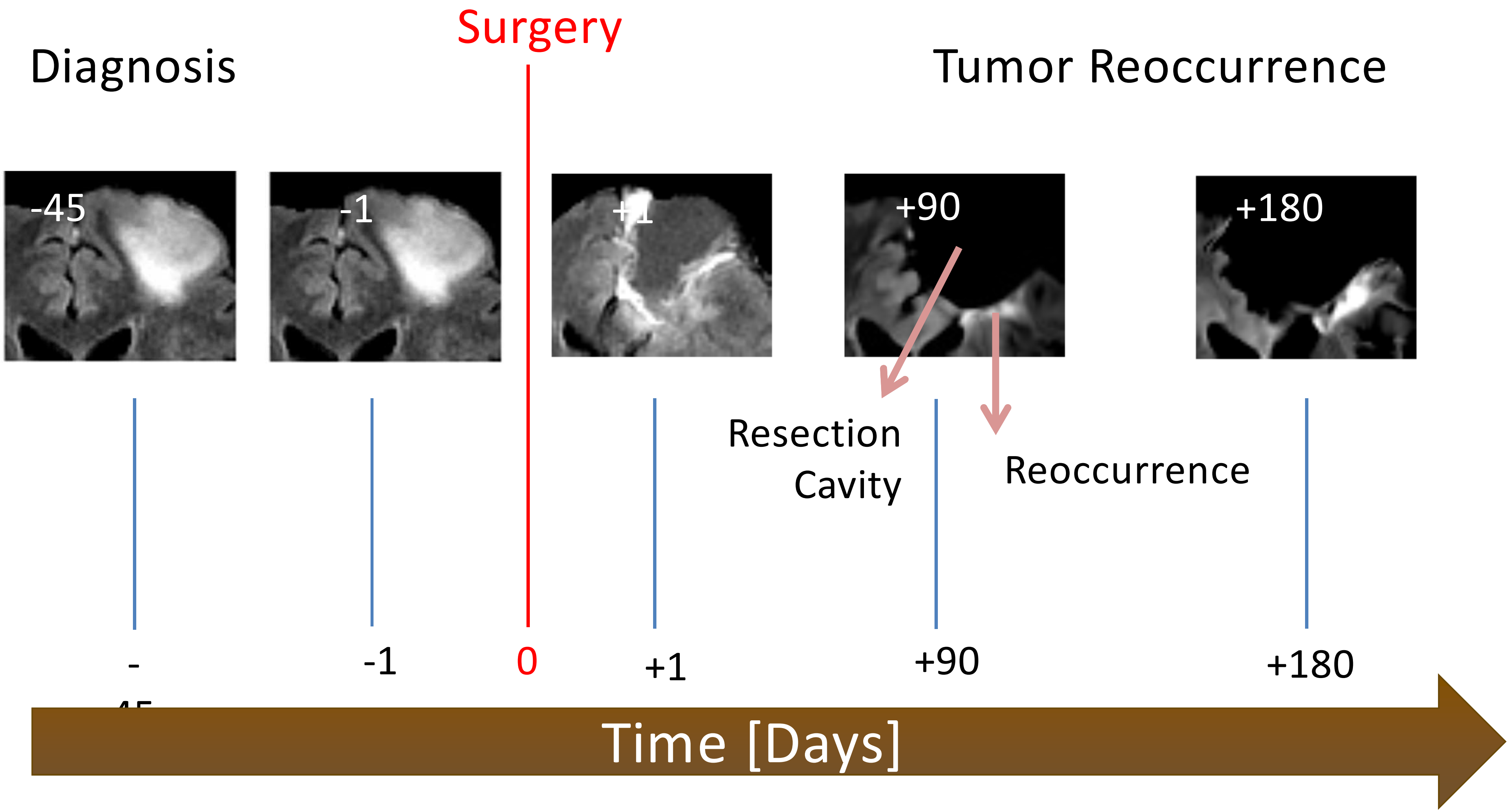
- Atlas with well defined anatomical barrier

[Amelot et al.-Mandonnet 2014]



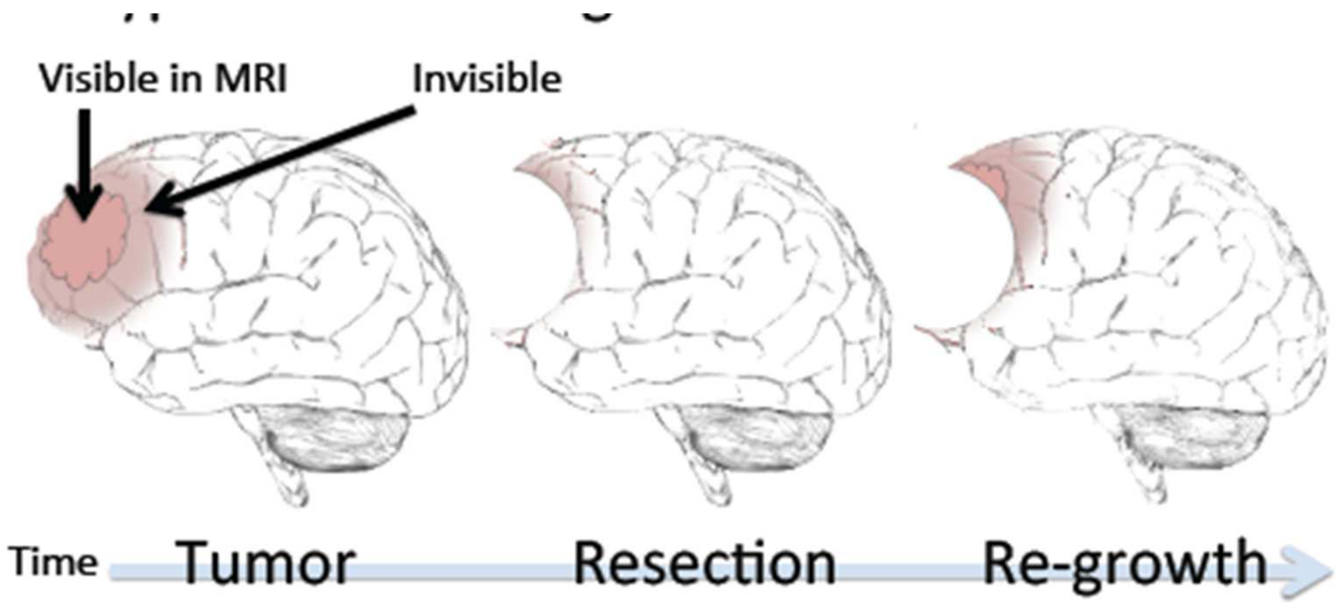
Based on MNI 152

Recurrence after surgery



Recurrence after surgery

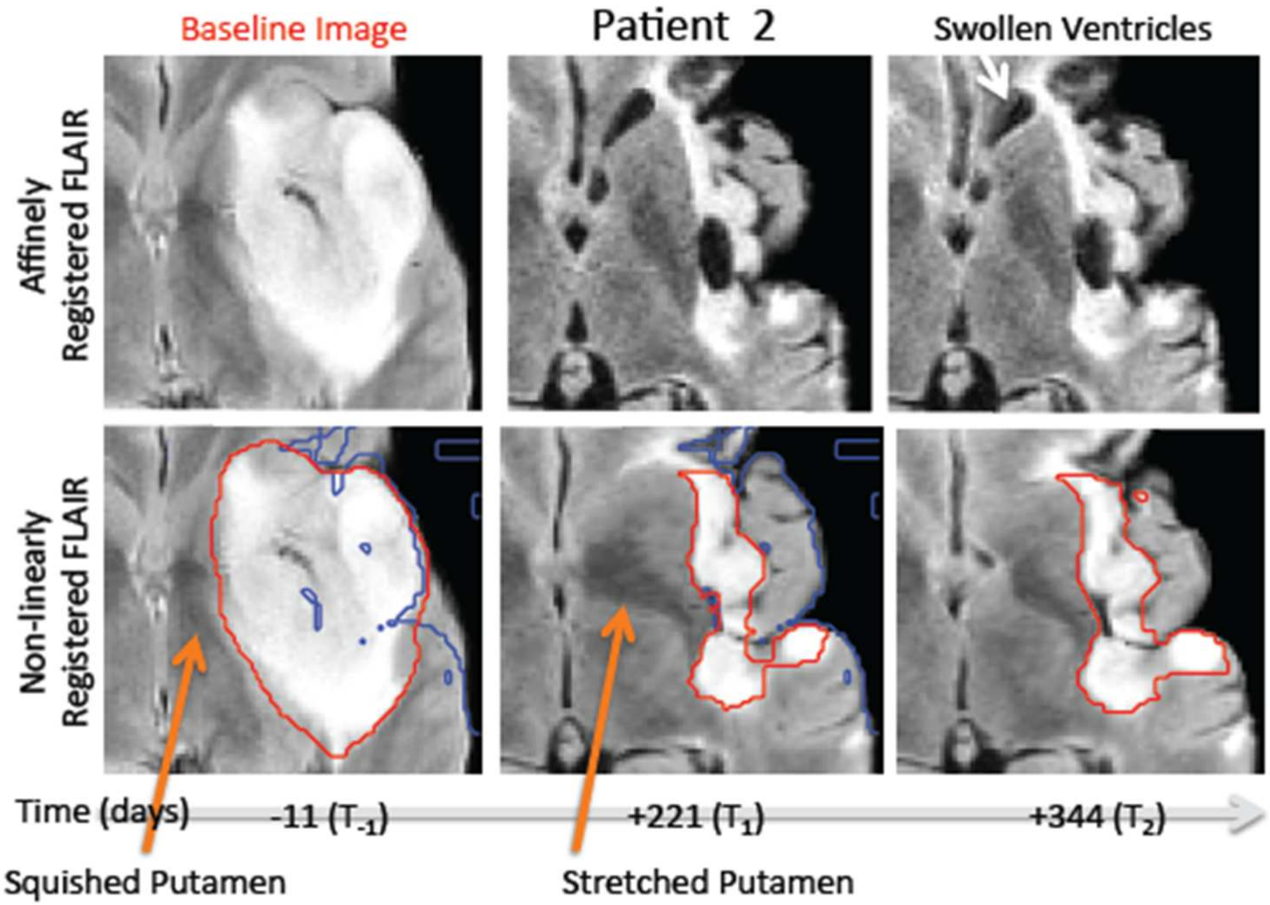
- Is it possible to :
  - Predict the location of recurrence ?
  - Predict the time of recurrence ?
  - Predict the extent of infiltration ?



Recurrence after surgery

- Difficulty due to large deformation after surgery
- Effect of therapy

[Stretton 2014]



Qualitative Results

[Stretton 2014]

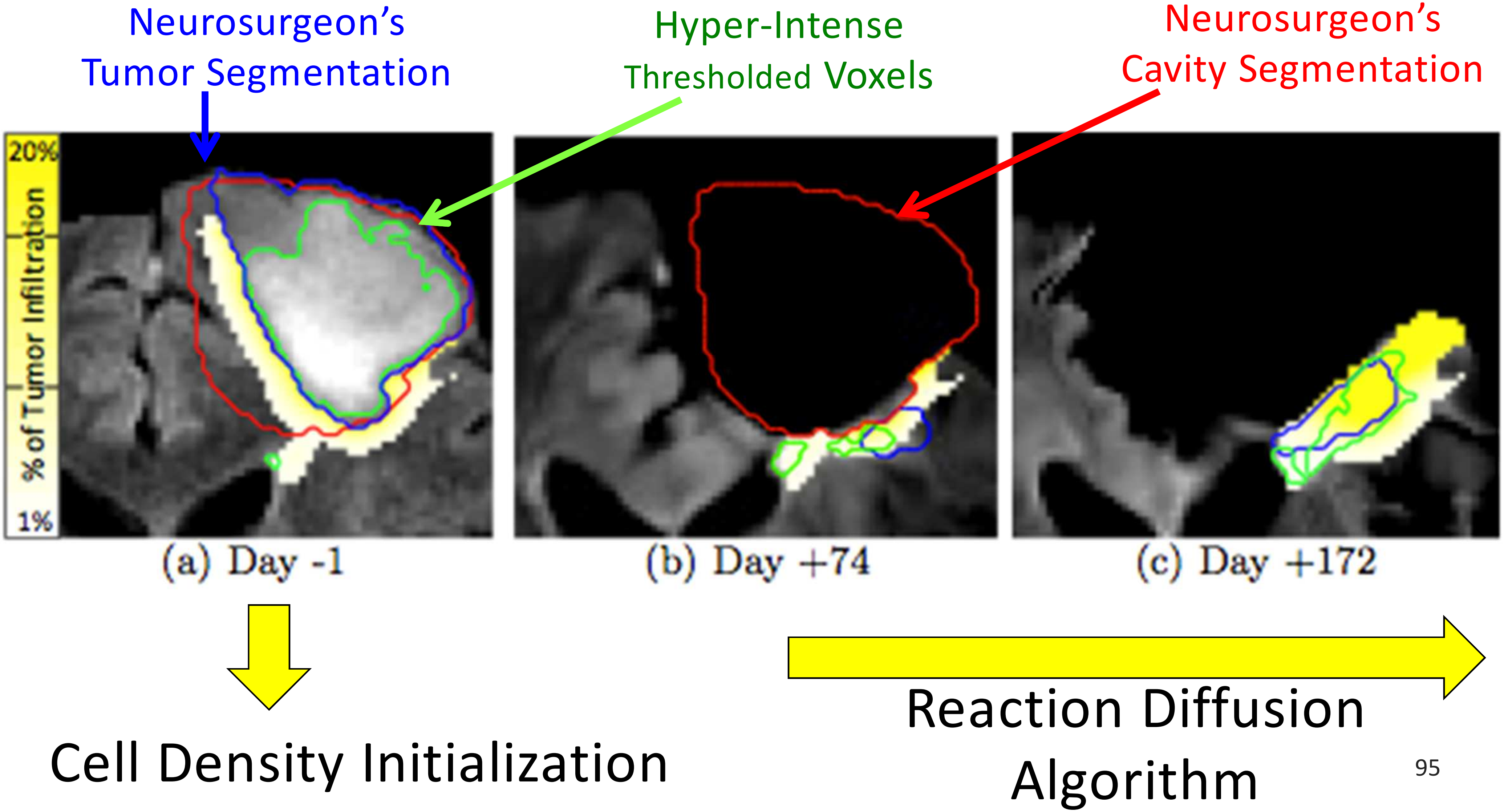
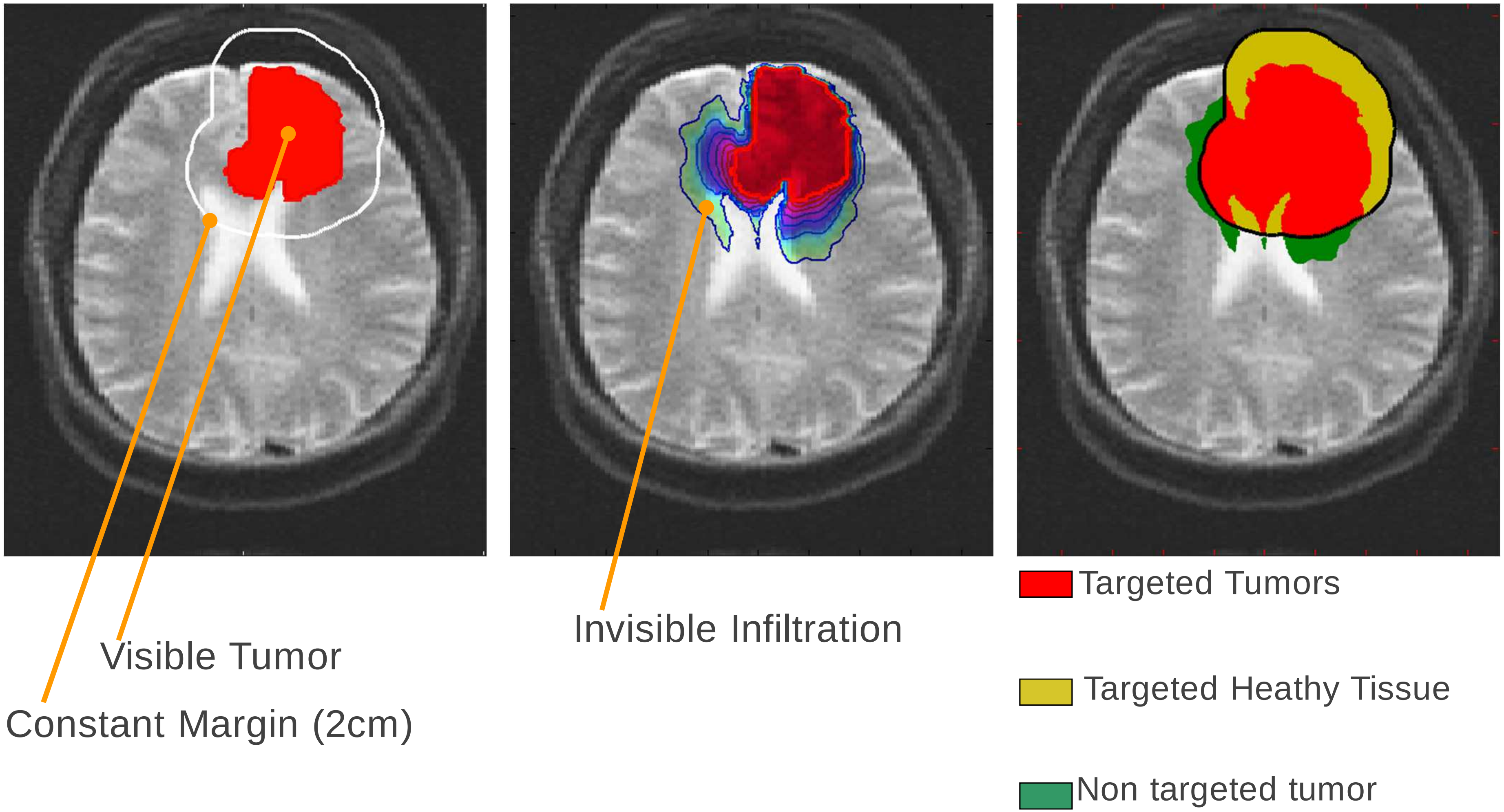


Image guided therapy

Cyberknife au CAL, Nice

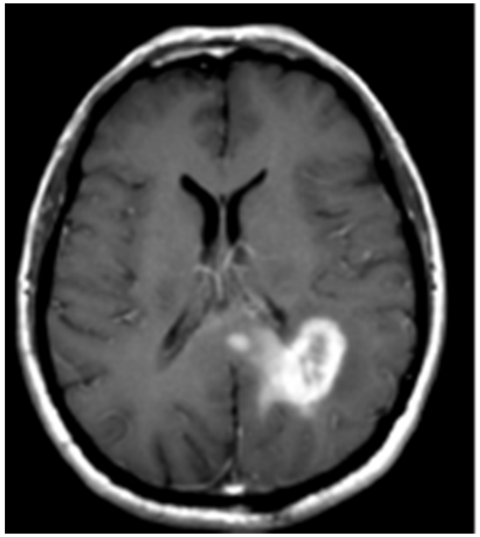
MGH
Boston

Dosimetry planning

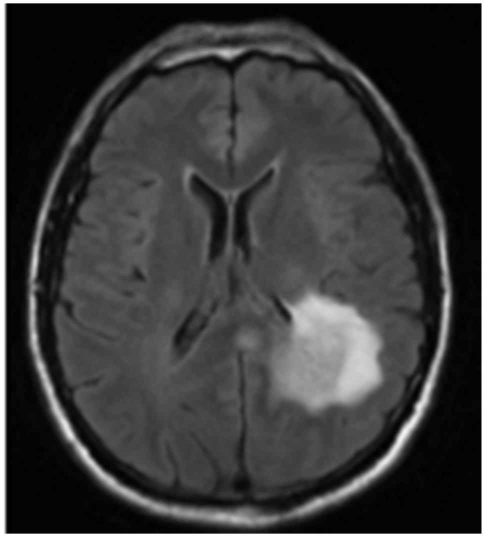


Predicting infiltration

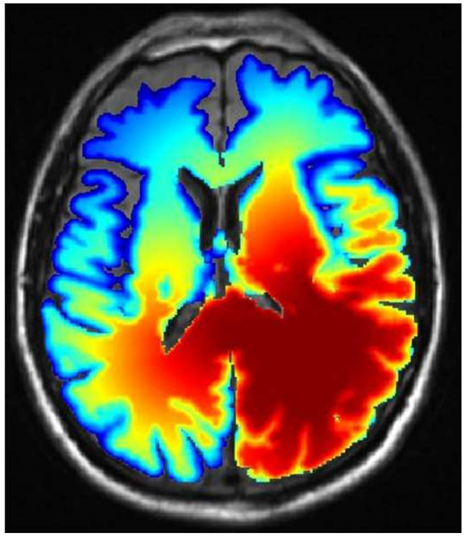
$$\frac{\partial u}{\partial t} = \nabla.(D\nabla u) + \rho u(1-u)$$



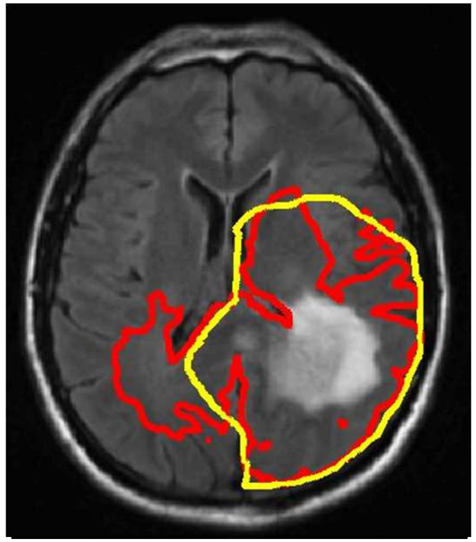
T1 Gd



T2 Flair



Log-density
Of predicted
tumor cells



Simulated
Target Volume

Standard
Target Volume

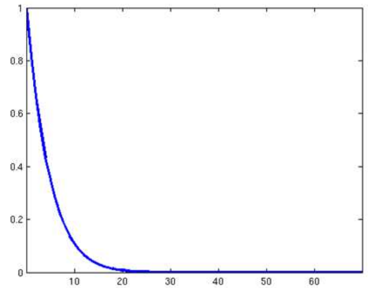
J Unkelbach B Menze, E Konukoglu, F Dittmann, N Ayache, H Shi, *Radiotherapy planning for glioblastoma based on a tumor growth model: implications for spatial dose redistribution.* Physics in Medicine and Biology, December 2013.

Same
Volume

Radiotherapy Dose Planning

- Linear Quadratic Model

P(cell survival| Dose d, Fractions N_f) $\approx \exp(-d\left(\alpha + \frac{\beta}{N_f} d\right))$



Survival Probability

Optimize d_i at each voxel to minimise surviving tumoral cells

$$\min_{d} \sum_{i \in T} \boxed{c_i} \exp(-d_i(\alpha + \frac{\beta}{\alpha N_f} d_i))$$

$$\text{subject to } \frac{1}{N_T} \sum_{i \in T} d_i \leq \boxed{d^p}$$

$$d_i \geq 0$$

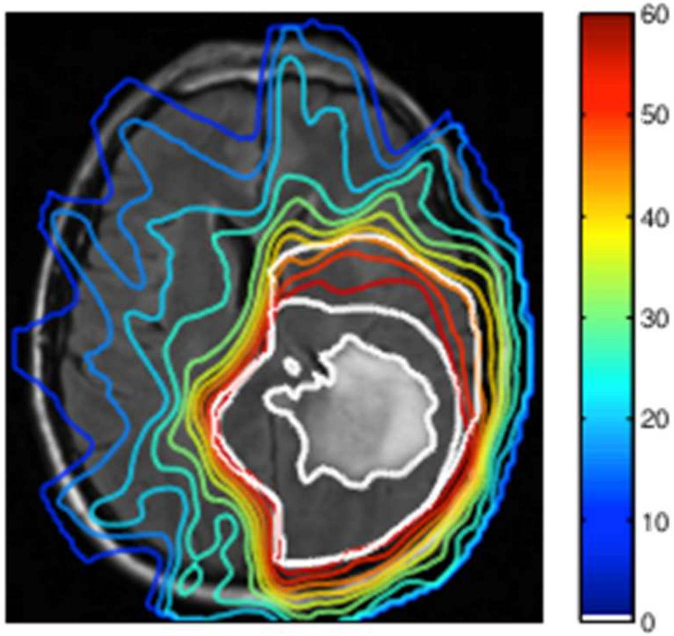
Tumor model

Maximum Allowed Dose

Solve Analytically

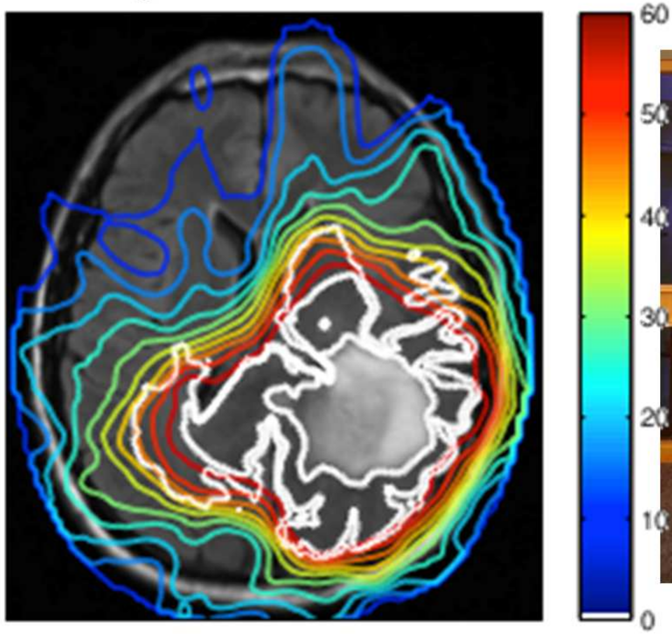
Radiotherapy

Standard Dosimetry
Tumor Contours
+ margin



GTV : 60 Gy - *T1Gd + 2cm*
CTV 46 Gy - *T2Flair + 1.5cm*

Optimized Dosimetry
For the personalized growth model



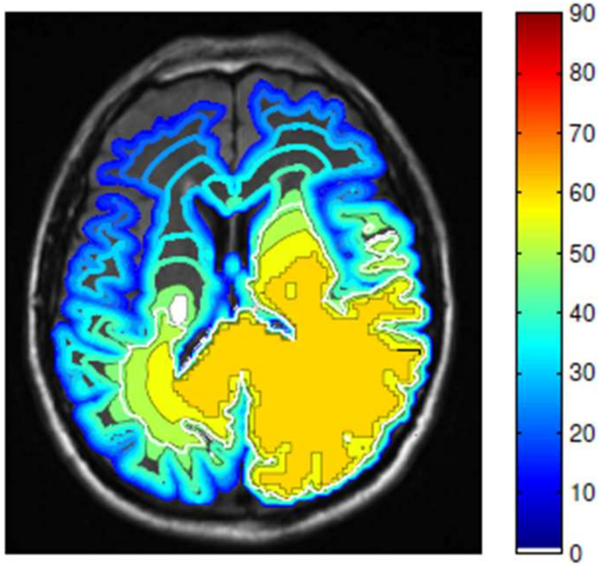
Same total dose

MGH
Boston

J Unkelbach, B Menze, E Konukoglu, F Dittmann, M Le, N Ayache, H Shi. *Radiotherapy planning for glioblastoma based on a tumor growth model: improving target volume delineation.*
Physics in Medicine and Biology, December 2013.

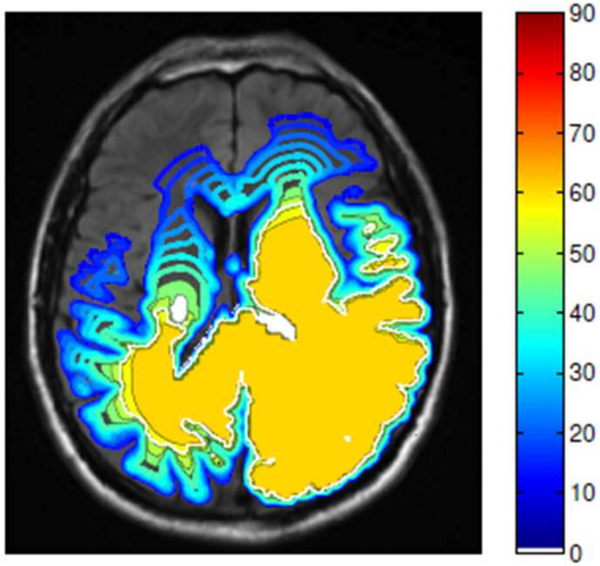
Impact of invisibility index

$\sqrt{\frac{D}{\rho}} = 4,2 \text{ mm}$

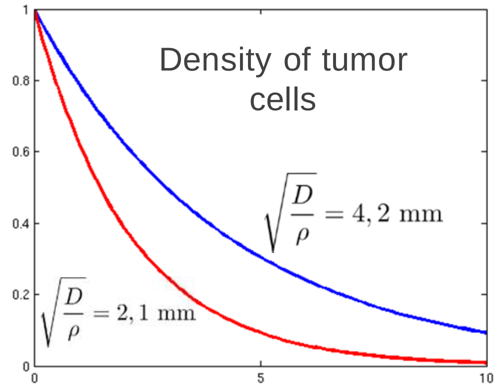


Computed Dose (Gray)

$\sqrt{\frac{D}{\rho}} = 2,1 \text{ mm}$



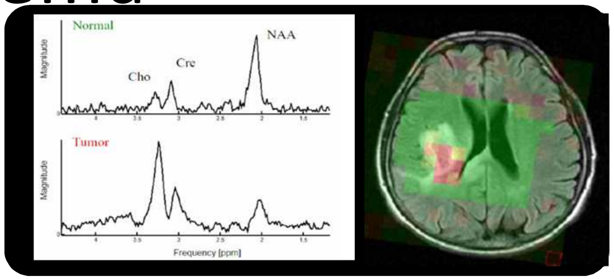
Compute dose(Gray)



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

Challenges

- Understanding Imaging of brain tumor :
  - vasogenic edema vs infiltrated edema
  - Imaging tumor cell density



MR Spectroscopy

- Multiple compartment tumor growth models & more imaging (PET, perfusion)
- Better account of anisotropic diffusion
- Apply on Large cohort of patients

Take Home Messages

- Objectives of Model Personalization
- Data Assimilation vs Data Regularization
- Notion of parameter Observability
- Model as a tool
- Glioma growth models
- Personalization of speed and invisibility index
- Clinical applications for radiotherapy

Acknowledgments

- Colleagues : B. Ribba, J. Unkelbach, O. Clatz, B. Menze, N. Ayache
- Phd Students : E. Konukoglu, M. Lê, N. Cordier, E. Stretton
- Medical Collaborators : E. Mandonnet,
- Funding : Inria, ERC

Take Home Messages

- Geometric & Biophysical Personalization
- Notion of parameter Observability
- Sensitivity Analysis
- Calibration & Parameter Optimization techniques
- Model as a tool
- Uncertainty estimation