Imaging-enabled Therapy:

New Horizons of Translational Molecular Radiology towards Patient-individualized Medicine

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Some work done under an
Indo-Dutch collaboration program between:

Indian side:

National Neuroimaging Facility, NBRC, Manesar *(Subha, Ralla, Suhela)*
&
NBRC Clinical Centre, Government Hospital, at Gurgaon *(Prasun)*

Dutch side:

Utrecht University/Centre for Translational Molecular Medicine *(Peter)*
&
Philips Medical Systems, Best *(Arindam)*

Part - A

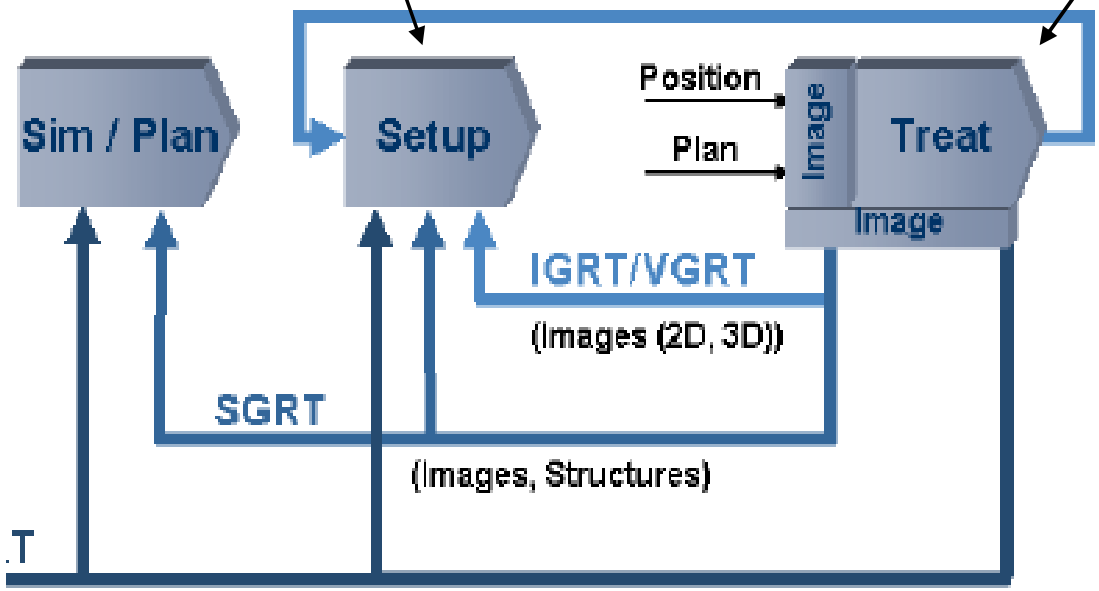
MR Imaging-Enabled Radiotherapy Planning System for Brain Tumour as Glioma

Neuroimaging Based Radiotherapy Planning

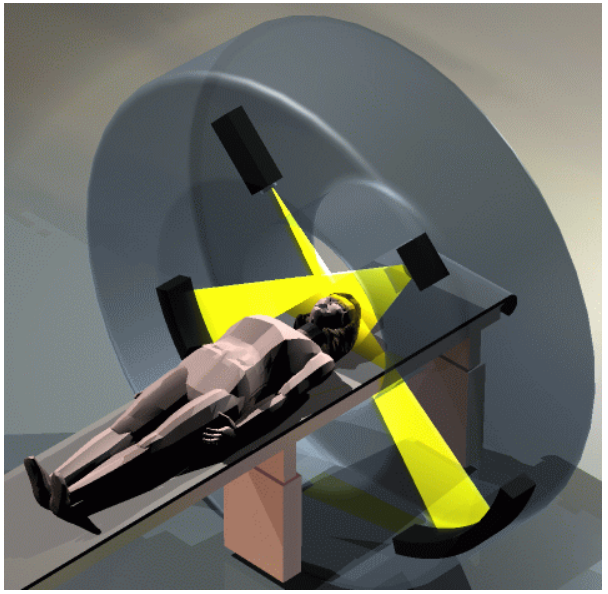
2 Components:

MR Imaging – Demarcating glioma spread:
4th Order Glioma Permeation Tensor Imaging
and Tractography

Image-based Radiotherapy Planning & Enhancement



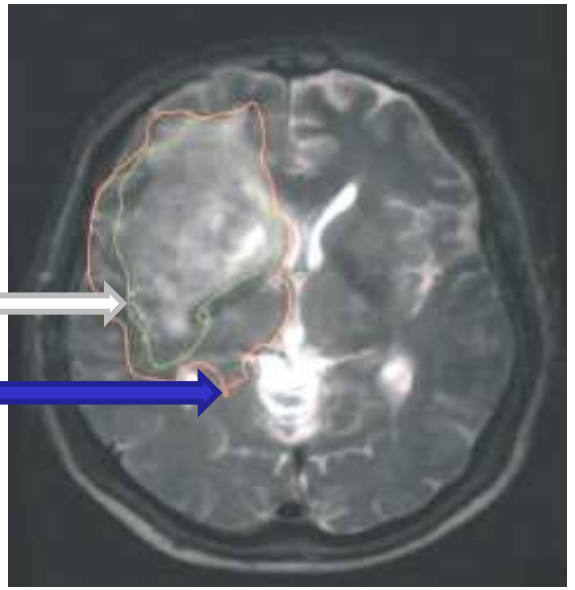
Linear Accelerator



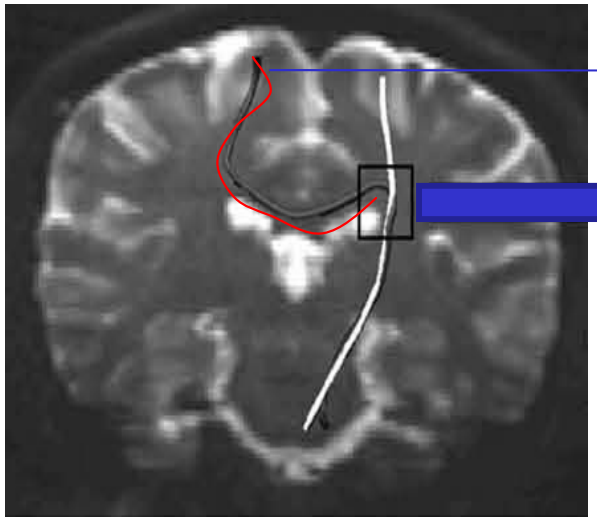
Diffusion tensor imaging (DTI): Better Demarcation

T1 based margin

2nd rank DTI based margin: More extension



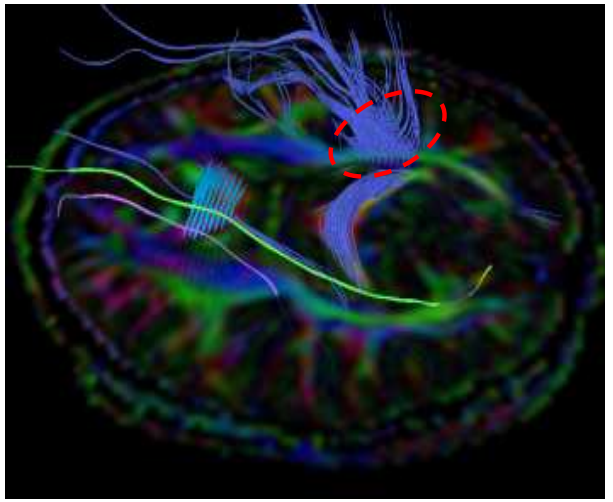
2nd rank DTI errors in low SNR area & in Cortex
Higher rank DTI reduces error



2nd order track (wrong)

4th order DTI track

Crossing Tracts not accesible



Higher Order Diffusion Tensor Imaging

2nd Order DTI

$$D_{ij} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix}$$

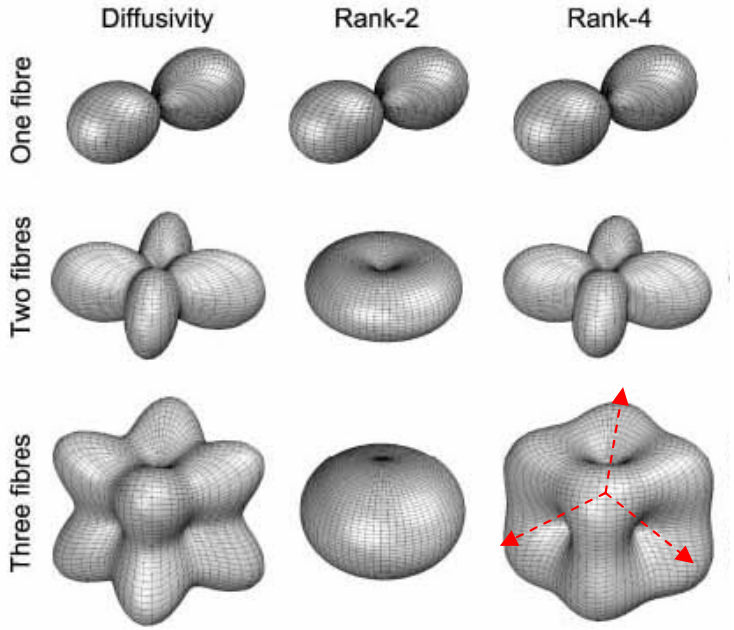
Minimum 6 diffusion gradient directions reqd.

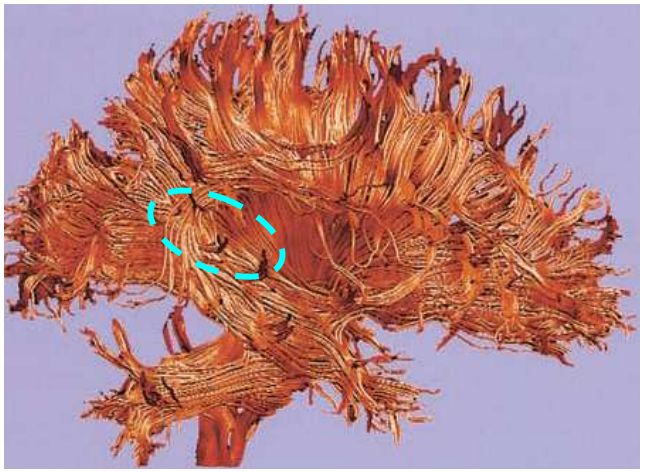
4th Order DTI

$$D_{ijkl} = \begin{bmatrix} D_{xxxx} & D_{xxxy} & D_{xxxz} & D_{xxxy} & D_{xxyy} & D_{xxyz} & D_{xxxz} & D_{xxyz} & D_{xxzz} \\ D_{xxxy} & D_{xxyy} & D_{xxyz} & D_{xxyy} & D_{xyyy} & D_{xyyz} & D_{xxyz} & D_{xyyz} & D_{xyzz} \\ D_{xxxz} & D_{xxyz} & D_{xxzz} & D_{xxyz} & D_{xyyz} & D_{xyzz} & D_{xxzz} & D_{xyzz} & D_{xzzz} \\ D_{xxxy} & D_{xxyy} & D_{xxyz} & D_{xxyy} & D_{xyyy} & D_{xyyz} & D_{xxyz} & D_{xyyz} & D_{xyzz} \\ D_{xxyy} & D_{xyyy} & D_{xyyz} & D_{xyyy} & D_{yyyy} & D_{yyyz} & D_{xyyz} & D_{yyyz} & D_{yyzz} \\ D_{xxyz} & D_{xyyz} & D_{xyzz} & D_{xyyz} & D_{yyyz} & D_{yyzz} & D_{xyzz} & D_{yyzz} & D_{yzzz} \\ D_{xxxz} & D_{xxyz} & D_{xxzz} & D_{xxyz} & D_{xyyz} & D_{xyzz} & D_{xxzz} & D_{xyzz} & D_{xzzz} \\ D_{xxyz} & D_{xyyz} & D_{xyzz} & D_{xyyz} & D_{yyyz} & D_{yyzz} & D_{xyzz} & D_{yyzz} & D_{yzzz} \\ D_{xxzz} & D_{xyzz} & D_{xzzz} & D_{xyzz} & D_{yyzz} & D_{yzzz} & D_{xzzz} & D_{yzzz} & D_{zzzz} \end{bmatrix}$$

Minimum 15 diffusion gradient directions reqd.

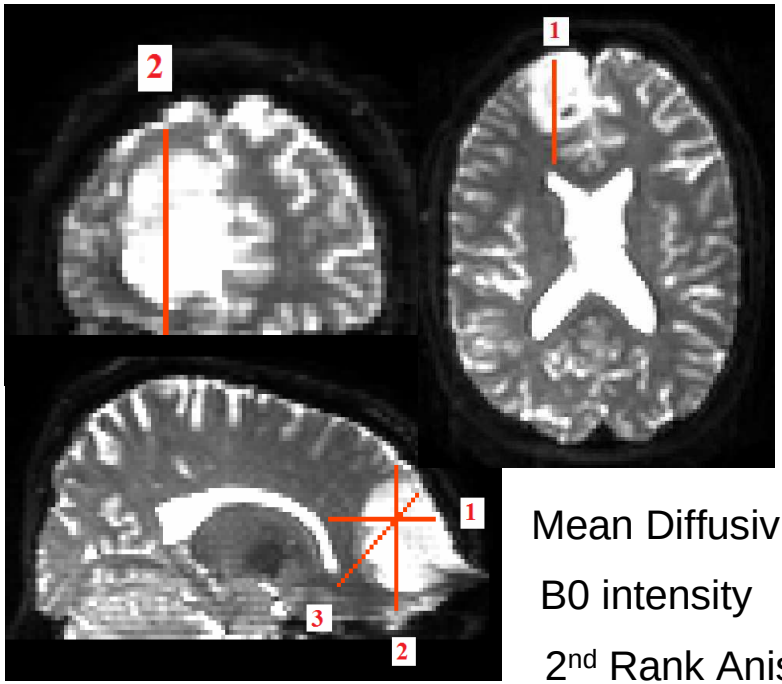
Higher-rank DTI reqd. for multiple crossing tracts across which glioma infiltrates



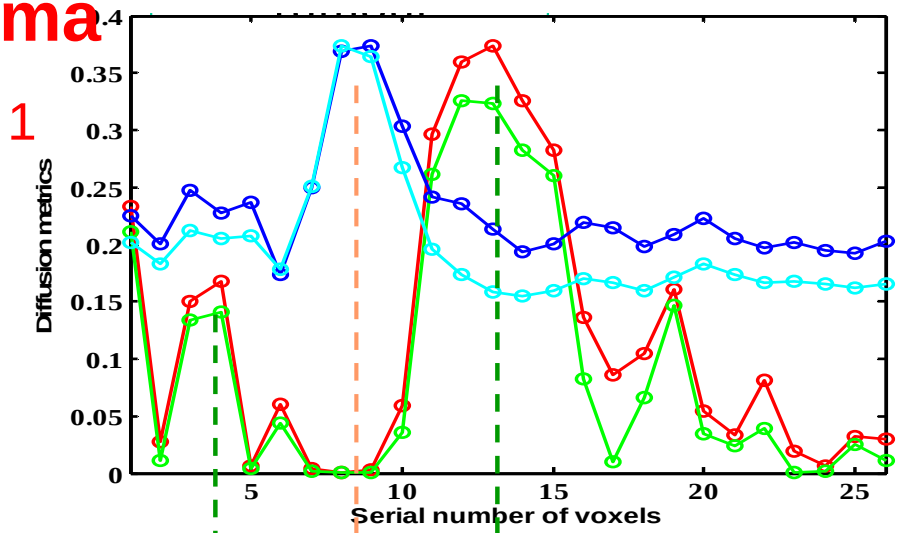


3 crossing tracts: Directions by D (ijkl) tensor

4th Rank Tensor's Benefit: Glioma



b0 Maps



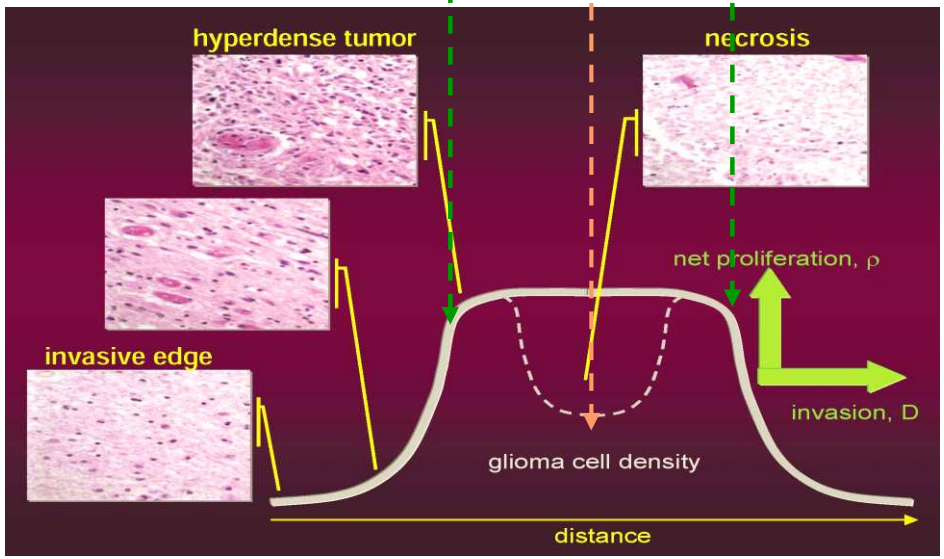
Mean Diffusivity

B0 intensity

2nd Rank Anisotropy

4th Rank Anisotropy

Tumour



Benefit of 4th rank Tensor:

Linear Sensitivity Factor = 0.38/0.31 = 1.23

Volume Sensitivity Factor = 1.23^3 = 1.86

Hence radiotherapy dose resolution approx. doubles

W.I.P.: Demarcating & Predicting subclinical invasion of CA:

'Glioma Diffusion Tensor' Vs. Water Diffusion Tensor (DTI):

Tumour Growth Simulation for Therapy Planning

Water Diffusion Tensor

$$\mathrm{D} = \lambda_1 e_1 e_1^{\mathrm{T}} + \lambda_2 e_2 e_2^{\mathrm{T}} + \lambda_3 e_3 e_3^{\mathrm{T}}$$

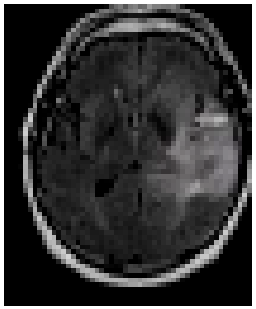
Transformation

Cellular Diffusion Tensor for Glioma

:

$$\bar{\mathrm{D}} = a_1(r)\lambda_1 e_1 e_1^{\mathrm{T}} + a_2(r)\lambda_2 e_2 e_2^{\mathrm{T}} + a_3(r)\lambda_3 e_3 e_3^{\mathrm{T}}$$

where the vector $(a_i)_i$ is defined by



Microarray Samples

GBM

Normal Brain

$$\begin{pmatrix} a_1 \\ a_2 \\ a_3 \end{pmatrix} = \begin{pmatrix} r & r & 1 \\ 1 & r & 1 \\ 1 & 1 & 1 \end{pmatrix} \begin{pmatrix} c_1 \\ c_p \\ c_s \end{pmatrix}$$

Adjustable parameter

Infiltrative Index:

T_2 : Gd Ratio

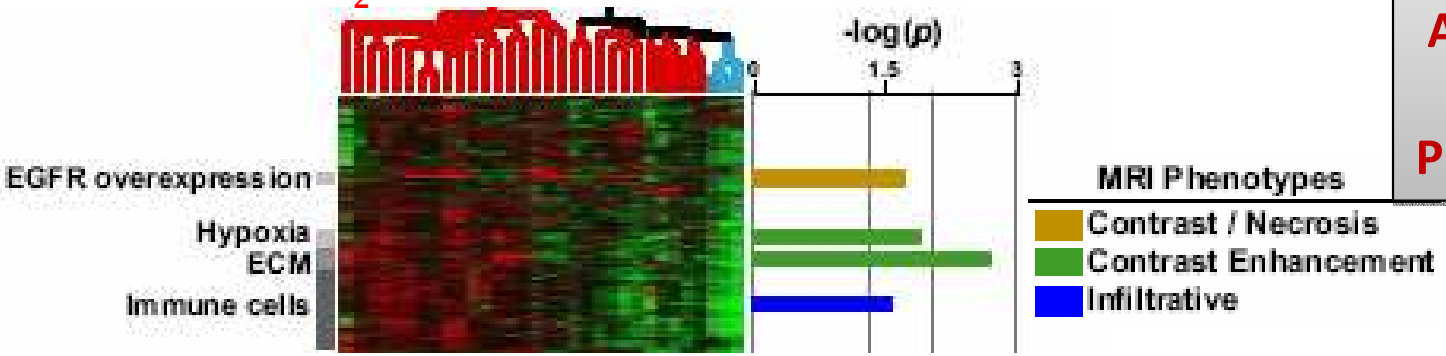
4^{th} Rank Glioma Tensor

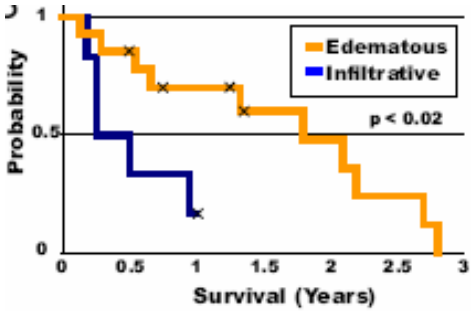
↓

Accurate Prediction of Spread

↓

Precise radiotherpy Planning





Part-B

MRI Image-Enabled Therapeutics for Regenerative Medicine in Stroke & Vascular Dementia

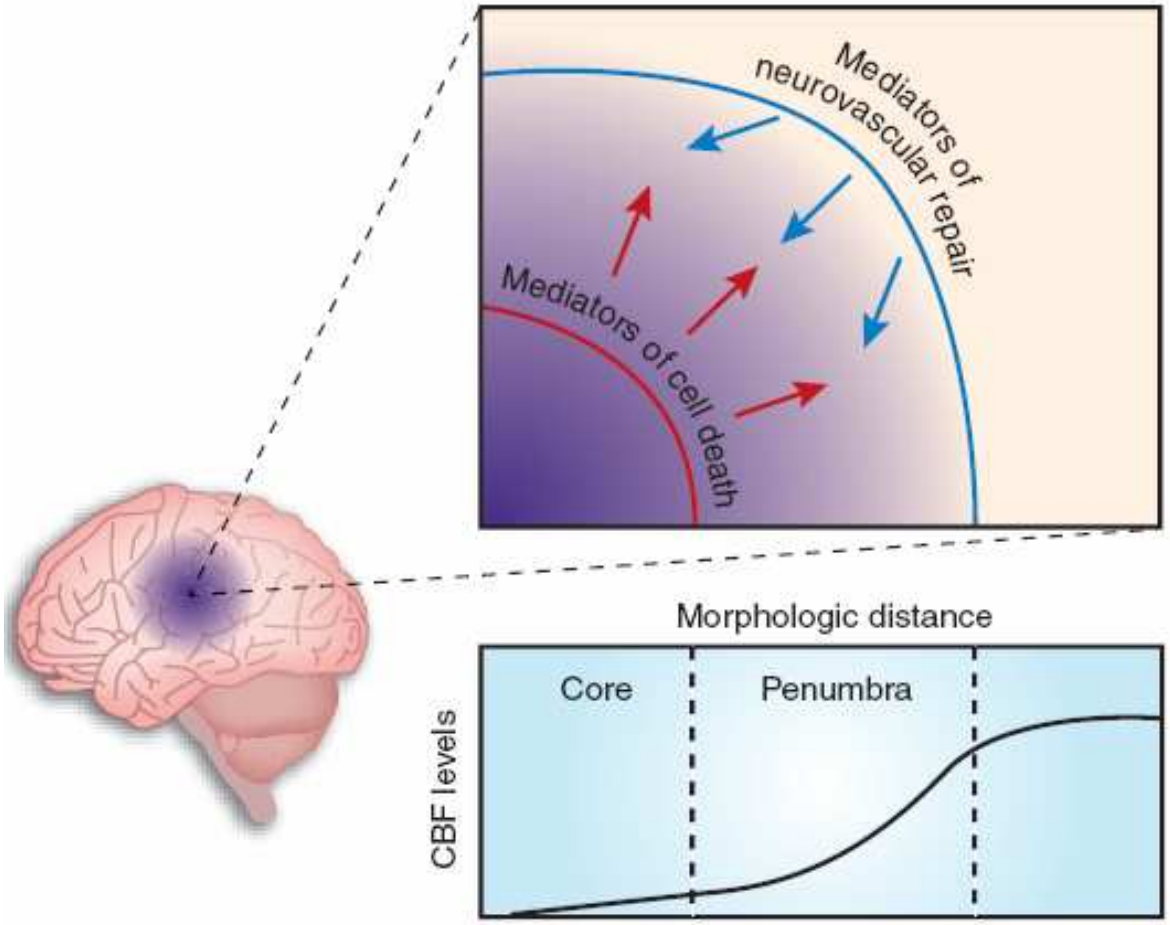
Scope of Therapy for Vascular dementia

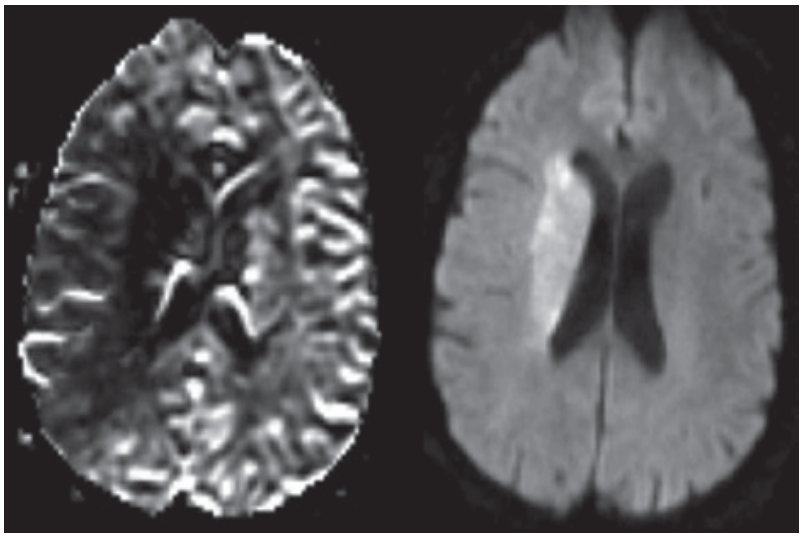
Aim: Restore the Ischaemic Tissue/Penumbra having viability

Collateral Measures: Aspirin, Thrombolytics, Plasmin

Causal Measures: New Neuron formation (Neurogenesis) by

Drugs: Angiogenesis Agents, Erythopoetin EPO *(proteins)*



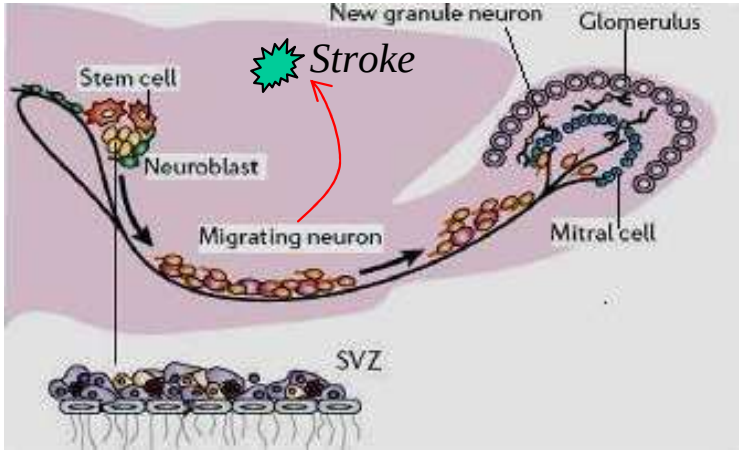


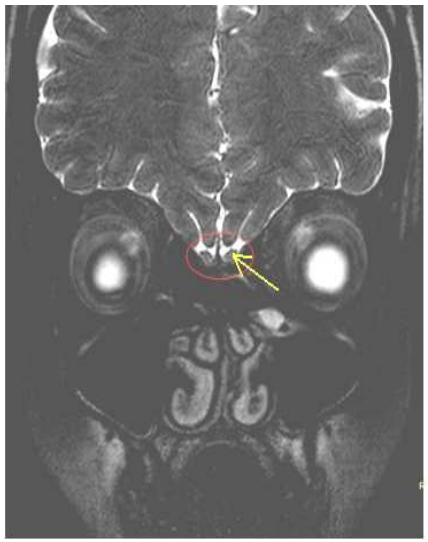
One lacks a quantitative approach to the dynamics and optimization of therapy, and this is dealt here

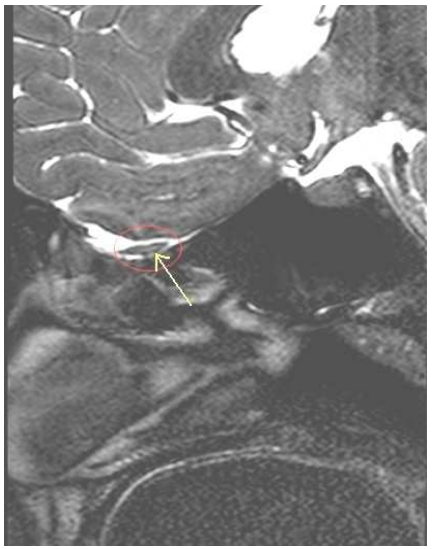
Adult Neurogenesis (Neuron Formation)

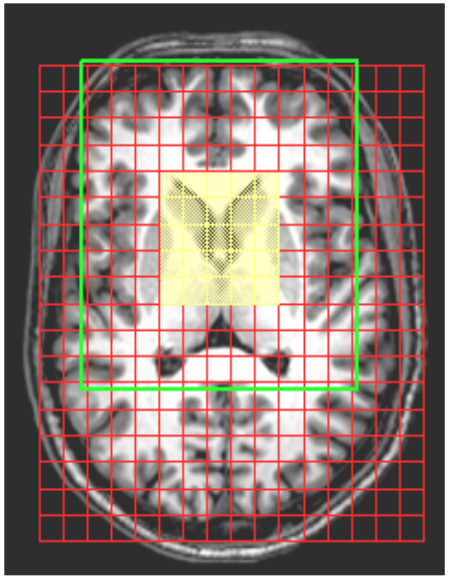
Adult neurogenesis: Subventricular zone (SVZ) of ventricles

Human Neural Migratory Stream by CSF Flow Imaging (collateral channel)





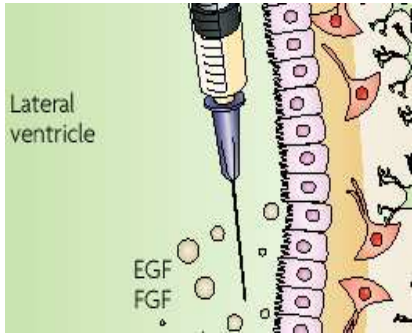


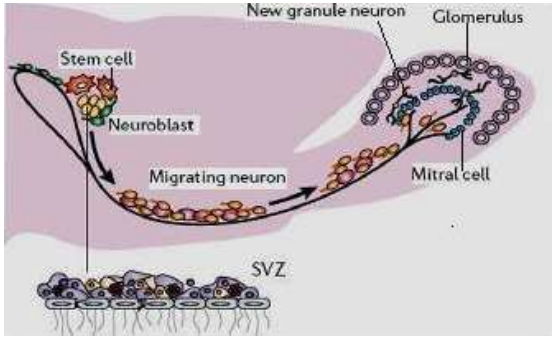


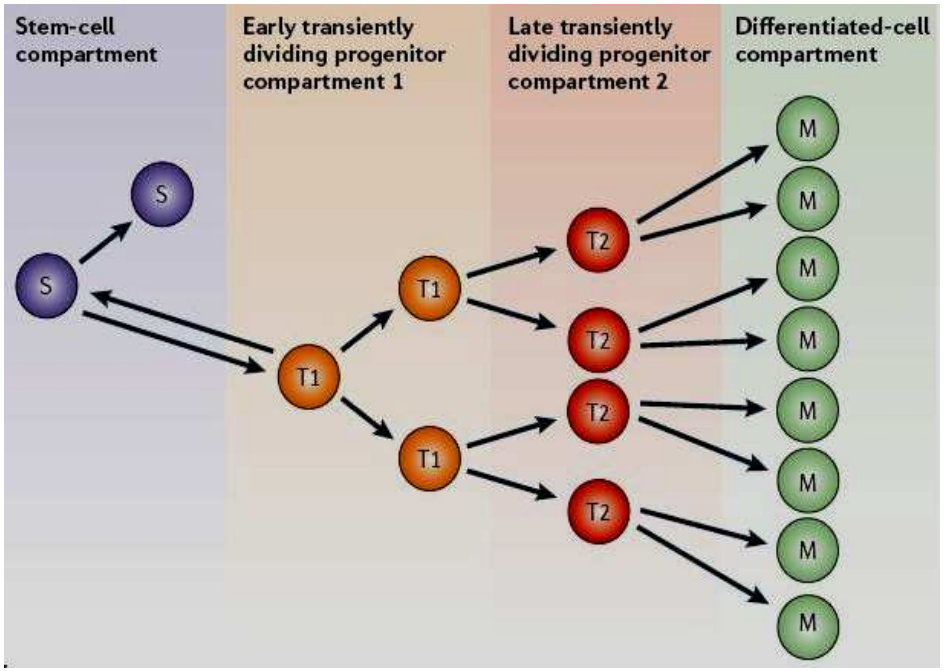
Neurogenesis by Erythropoetin : Compartmental Analysis

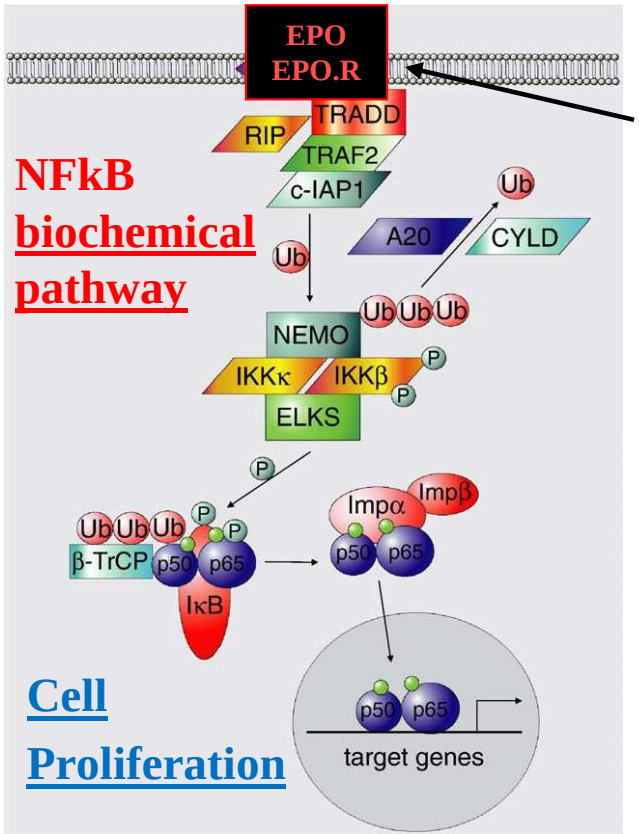
Each neural cell type is considered as a separate compartment.

Analysis using biochemical kinetics for each compartment





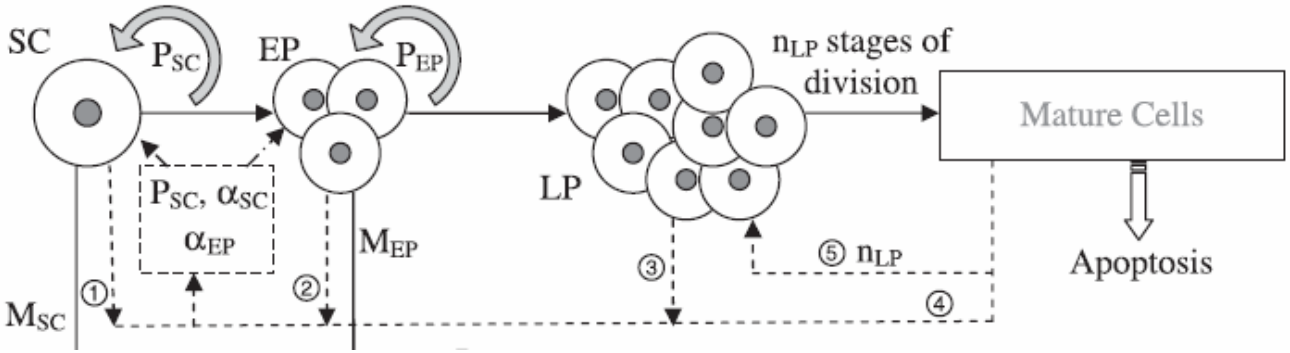




NFkB biochemical pathway

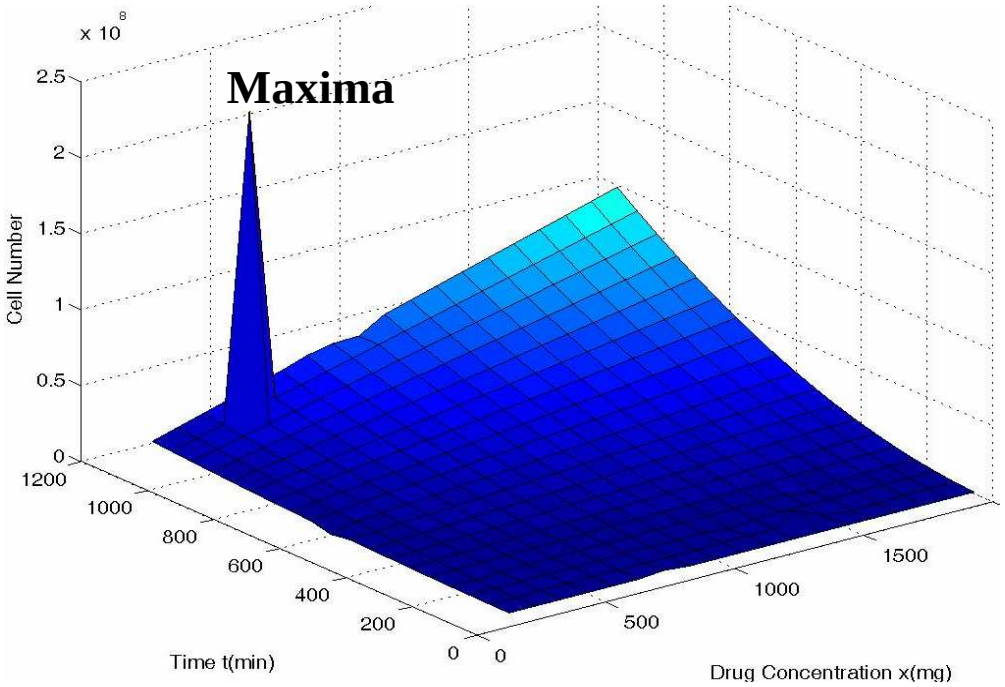
Cell Proliferation

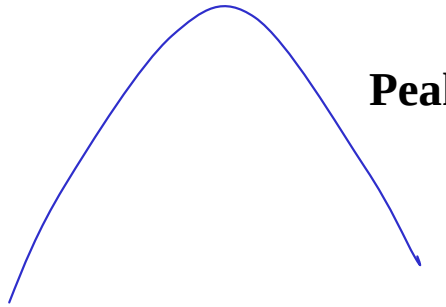
Erythropoetin



$$\frac{dN_{SC}}{dt} = \gamma\left(\frac{\alpha}{\tau}\right)\ln(2)\, f(x(t))\, \frac{N_{SC}}{\Theta}\left(1 - \frac{N_{SC}}{\Theta}\right) - \mu N_{SC}$$

Neurogenesis: Regenerating optimal No. of neurons (Erythropoetin)

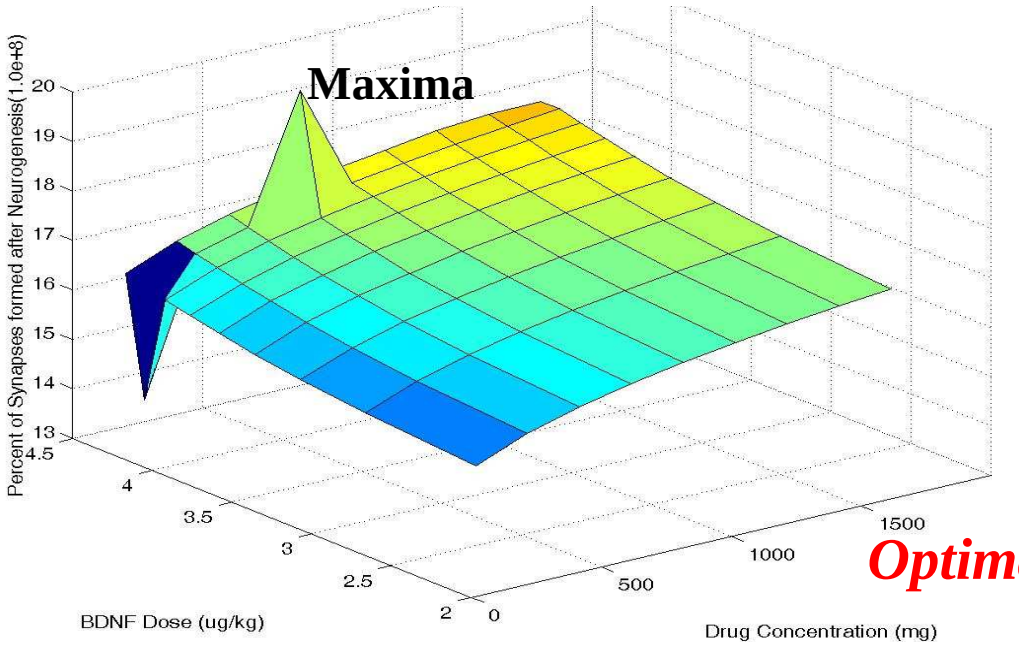


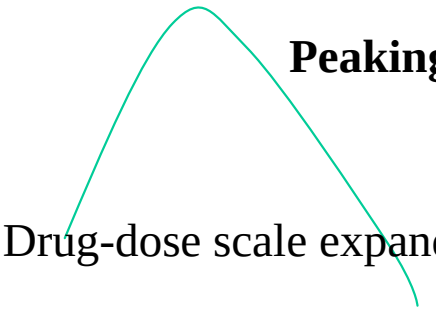


← Time scale expanded →

Neurogenesis peak:
Erythopoetin dose conc. 500 mg at 20 hrs.

Synaptogenesis: Optimizing Synapse formation (Benzamide drug)





← Drug-dose scale expanded →

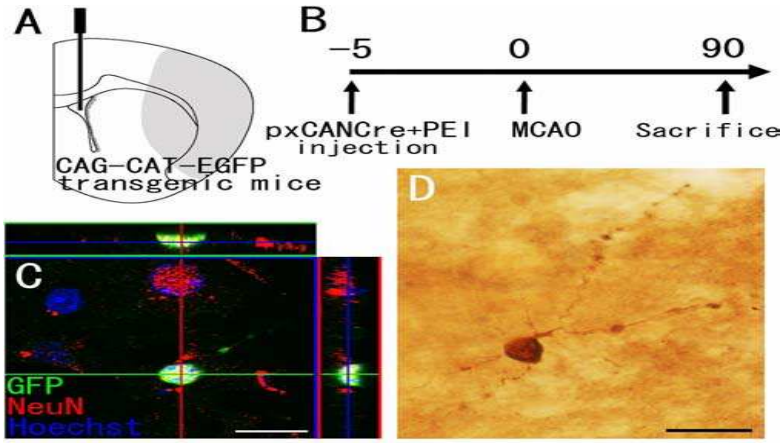
Optimal Synaptogenesis: Benzamide dose 3.5-4 µg/kg after 20 hrs of insult

Optimal synapse forming efficiency:19% neurons

Validation of Optimization process

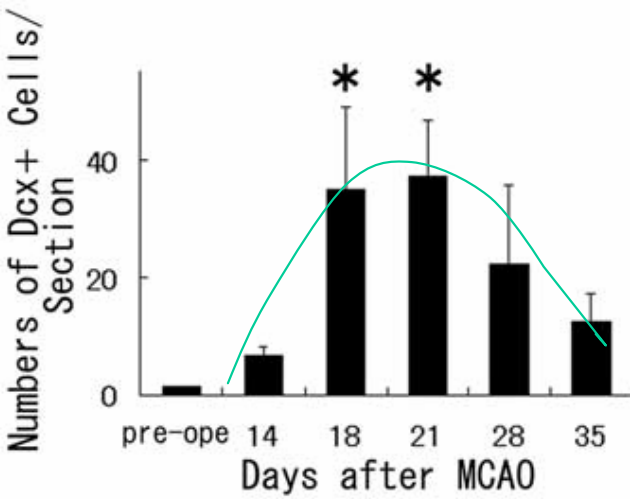
Experimental Stroke:

Neuroblasts of SVZ → Neurons → Synapses in Striatum

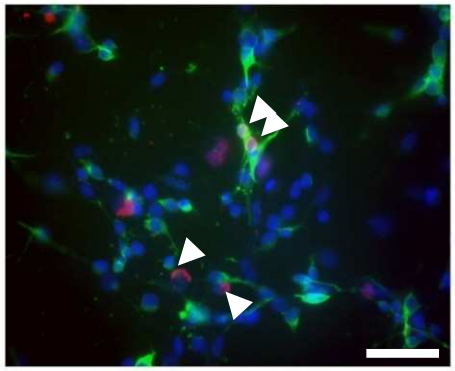


(Expt. Data from collaborator. Sawamoto Lab)

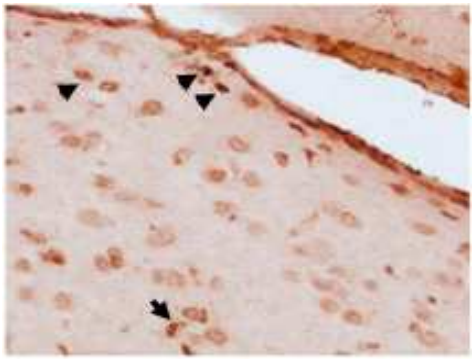
Temporal Peaking



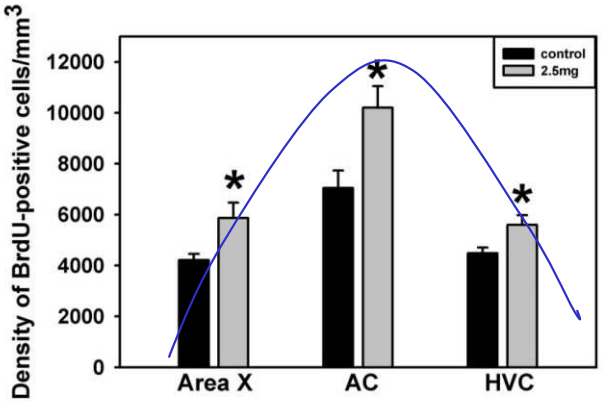
Drug-induced Neurogenesis : Naloxone



Neuronal Marker, Tuj 1



Subventricular Zone



Distance from SVZ →

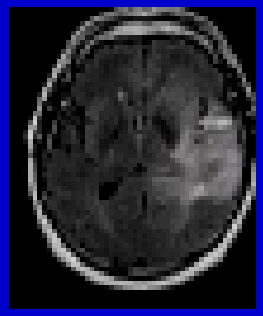
(NBRC Data, Iyengar Lab, 2009)

Method also usable in Glioma : *Radiogenomics → Pharmacogenomics*

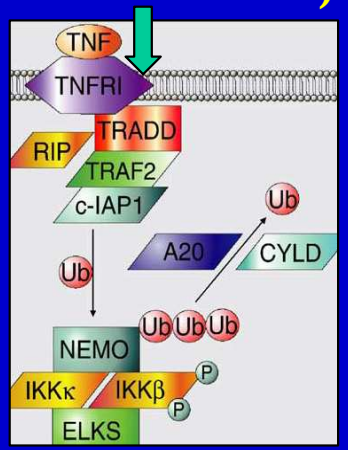
Predicting Efficiency of Bortezomib Drug in Glioma

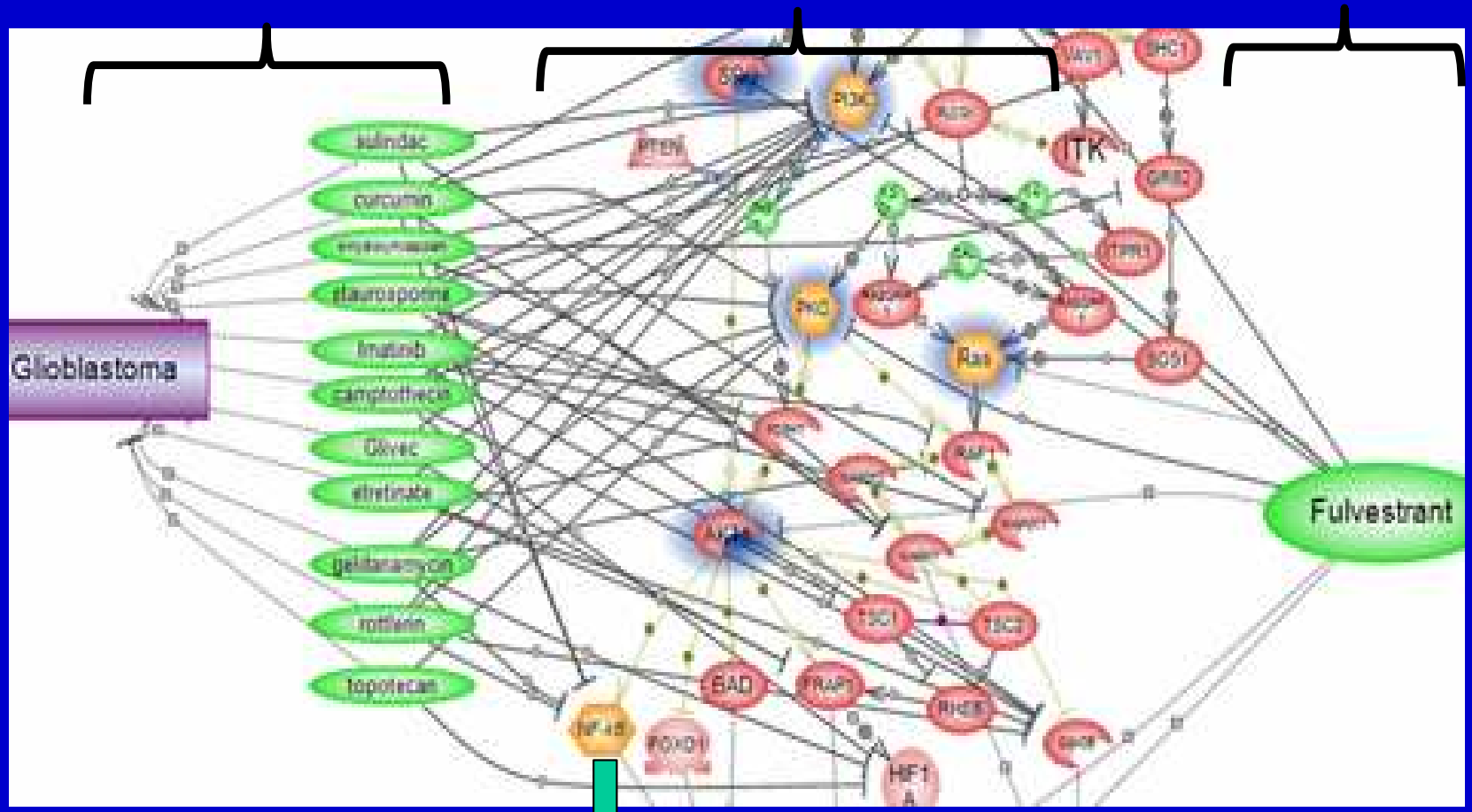
MRI Gentiic Modules → Growth Factor Pathways → Multi-target Drugs → Optimization

INPUT→ *Factors/Inhibitors (Drugs)* *Modulatory (Growth) Factors* *Hormones*



Bortezomib (NFkB Inhibitor)





OUTPUT→ Apoptosis Cell-growth Angiogenesis Cell-cycling

World Neuroepiodemiology Clock:

1 person to Dementia every 5 seconds

1 person to Glioma every 5 minutes

"For Whom the Bells Toll…. It Tolls for Thee"

Acknowledgements:

Utrecht University Asian Program
Philips Medical Electronics Ltd
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Subha

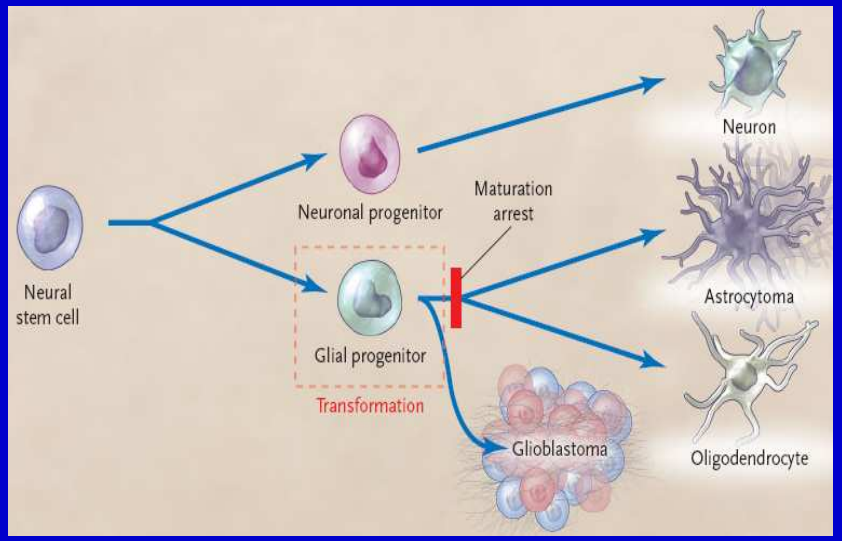
Ralla

Suhela

Lab Members
(Projects Awarded by Utrecht University / Philips)

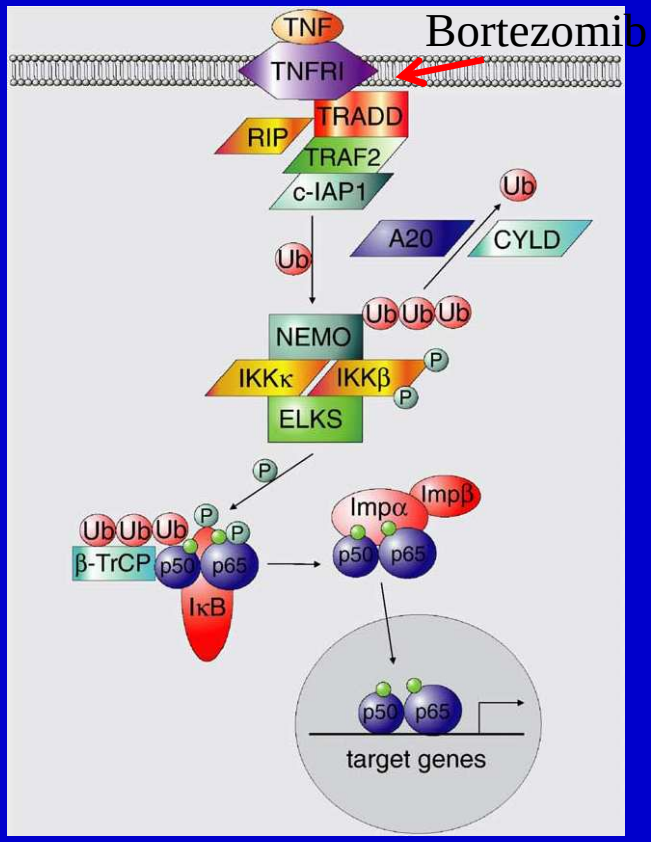
Clinical Trial *in-silico*:
Bortezomib as NFkB Inhibitor in Glioma

Kinetic Compartmental Analysis

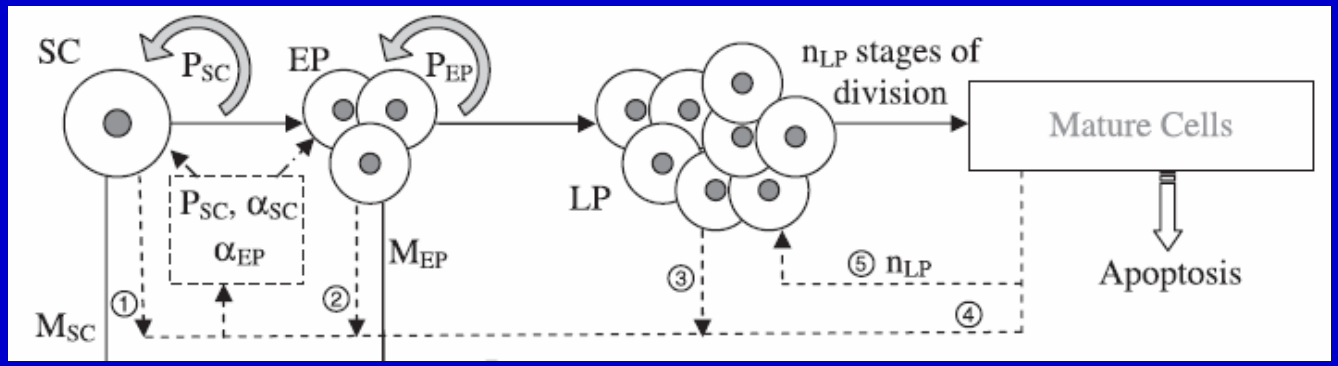


Cell Proliferation: NFκB Pathway

Inhibitor: Bortezomib, BRT



Cell Cycling: Dynamics



World Dementia Clock:
1 person converts every 5 sec

"For Whom the Bells Toll…. It Tolls for Thee"

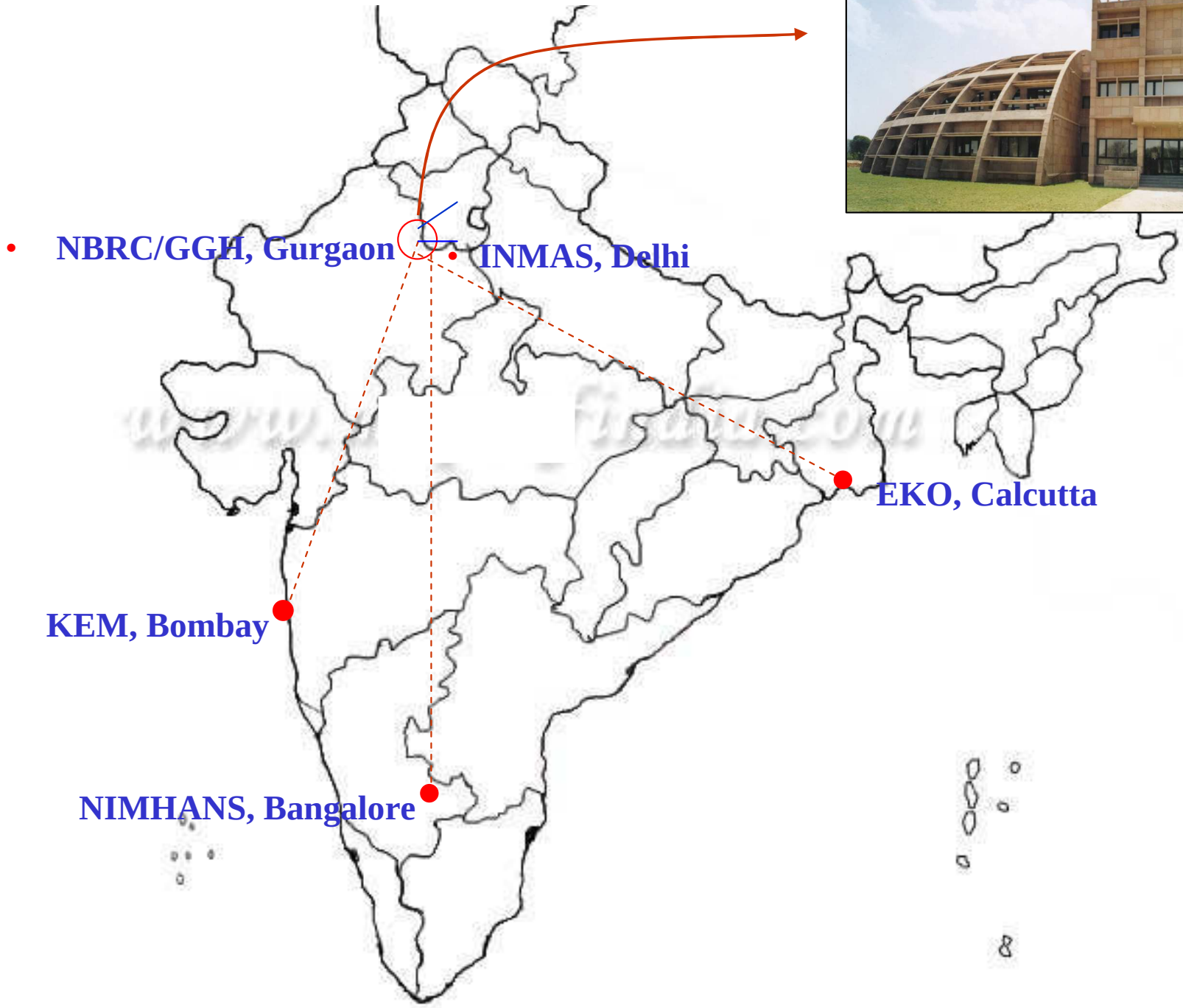
Acknowledgements:

Utrecht University Asian Program
Philips Medical Electronics Ltd
Dept of Biotechnology (DBT), Govt. of India

Lab Members
(Projects Awarded by Utrecht University/Philips)

Imaging's advantage: Brain dynamics by MRI

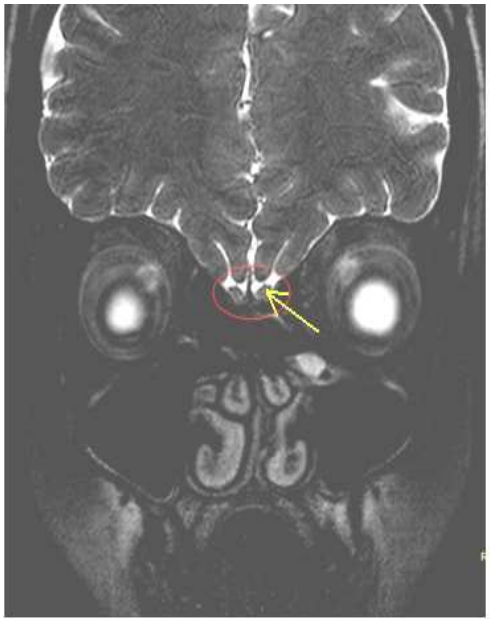
Standardiation Testing of settings: Philips, Siemens, GE scans

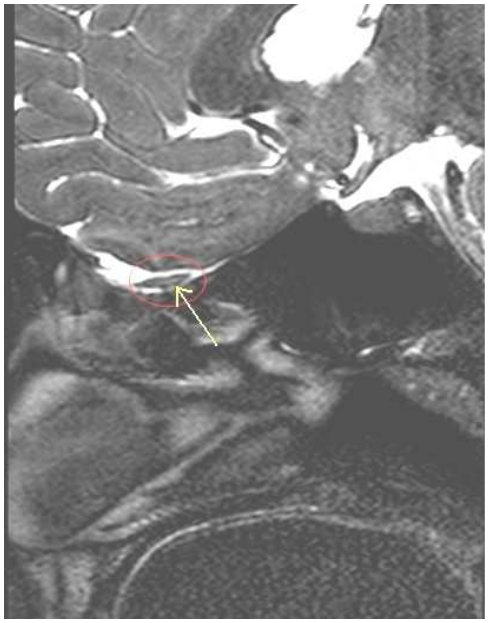


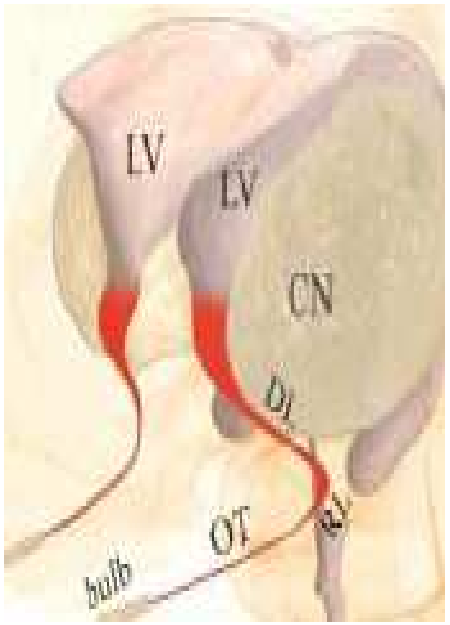
Human Rostral Migratory Stream by CSF Flow Imaging:

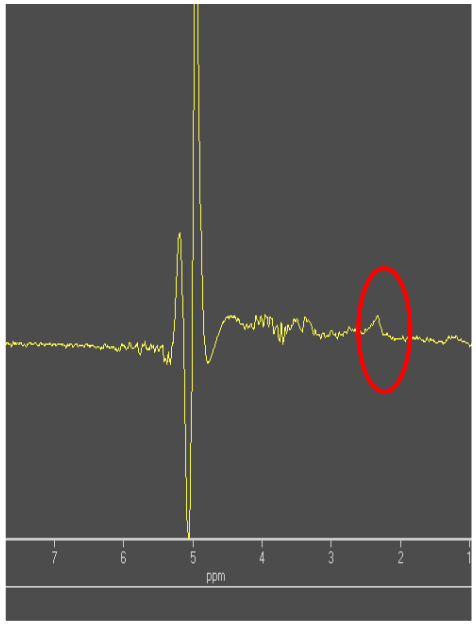
MRI

MRS: NPC Cell marker









Philips 3 Tesla scanner

T2 weighted image, maps spin-lattice relaxation

Pulse Sequence: Fast Gradient Echo, and then PRESS

Part – A : MRI Delineation of Tumour Invasion

Predicting subclinical spread of glioma : Margin demarcation

- **Therapy Failure: Relapse**

  Occurs at glioma margin or at target radiotherapy volume

- **Reason:**

  Sublethal radiotherapy dose enhances migration of glioma cells

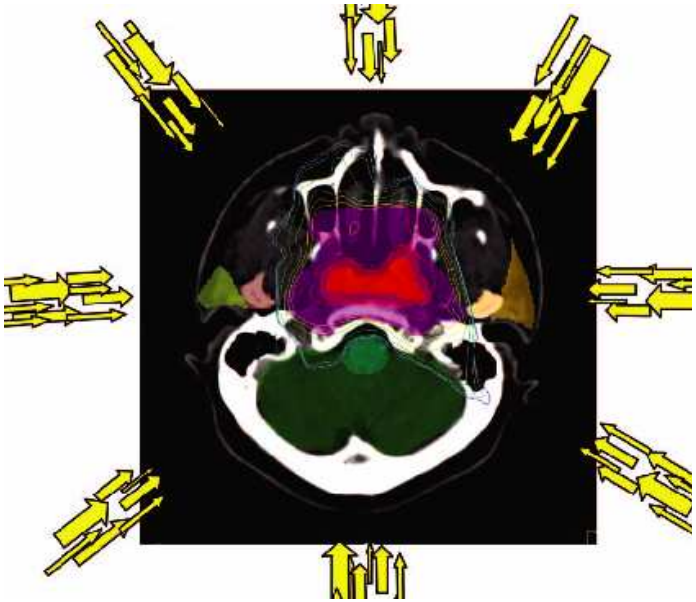
- **Technique Needed:**

  Neuroimaging-guided Conformational radiation dosing

- **Aims:**

  Defining Infiltrative volume for radiotherapy dosing/planning
  Enhancing Radiobiological Efficiency of the therapy

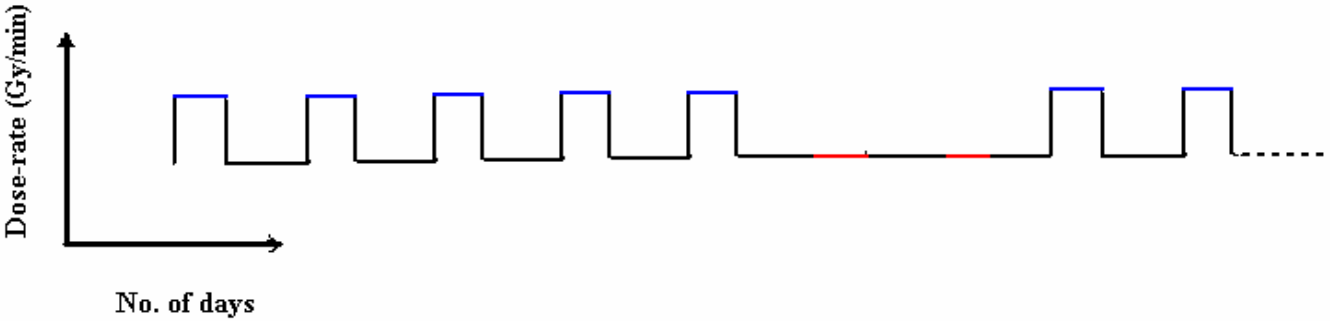
Part – B : Image-Guided Therapy Planning : Radiotherapy Enhancement



Conventional radiation therapy protocol – Dose :

2 Grays/day, 5 days/wk. For 6 weeks

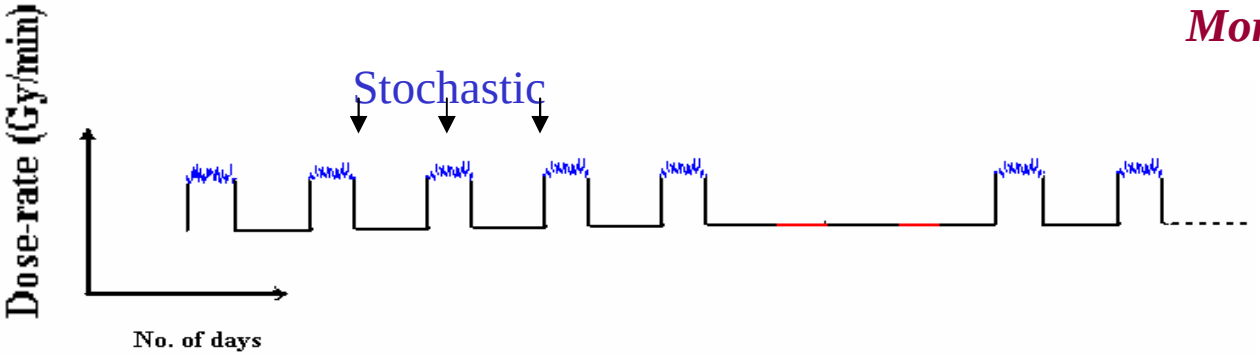
Duration of the protocol – 1 ½ months



Linear Accelerator Beam Planning System

OBJECTIVE

More efficient ?

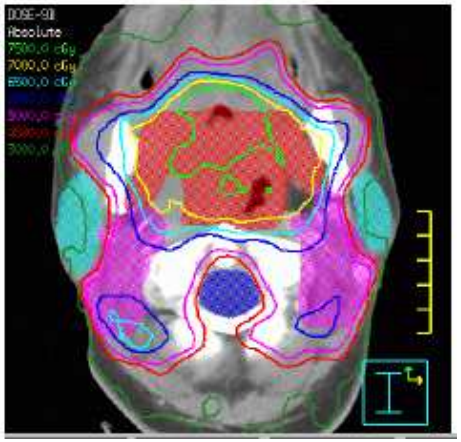


Q : Can stochastic perturbation increase cell kill without increasing total dose ?

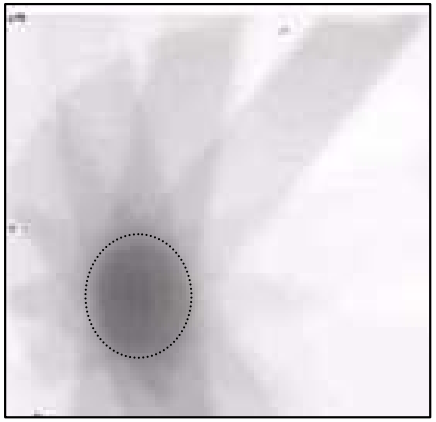
Use of the Algorithms developed for Treatment Planning in MR Imaging-Guided Radiotherapy (IGRT)

(in coopn. with Philips Therapy Planning System)

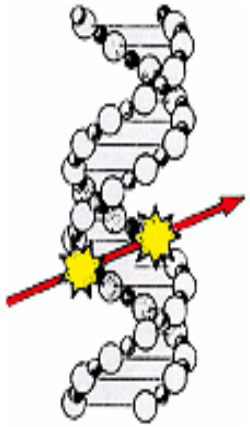
Image-Guided Radiotherapy Plan



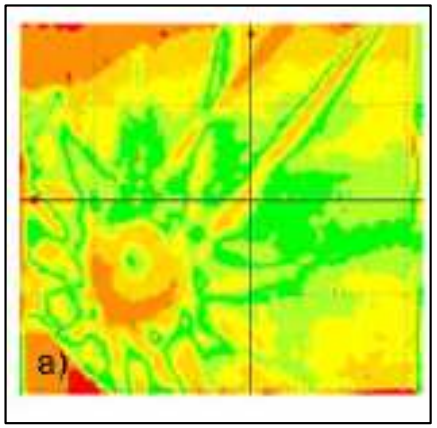
Nth Confocal Beaming spares Normal Tisue



Radiobiological Platform

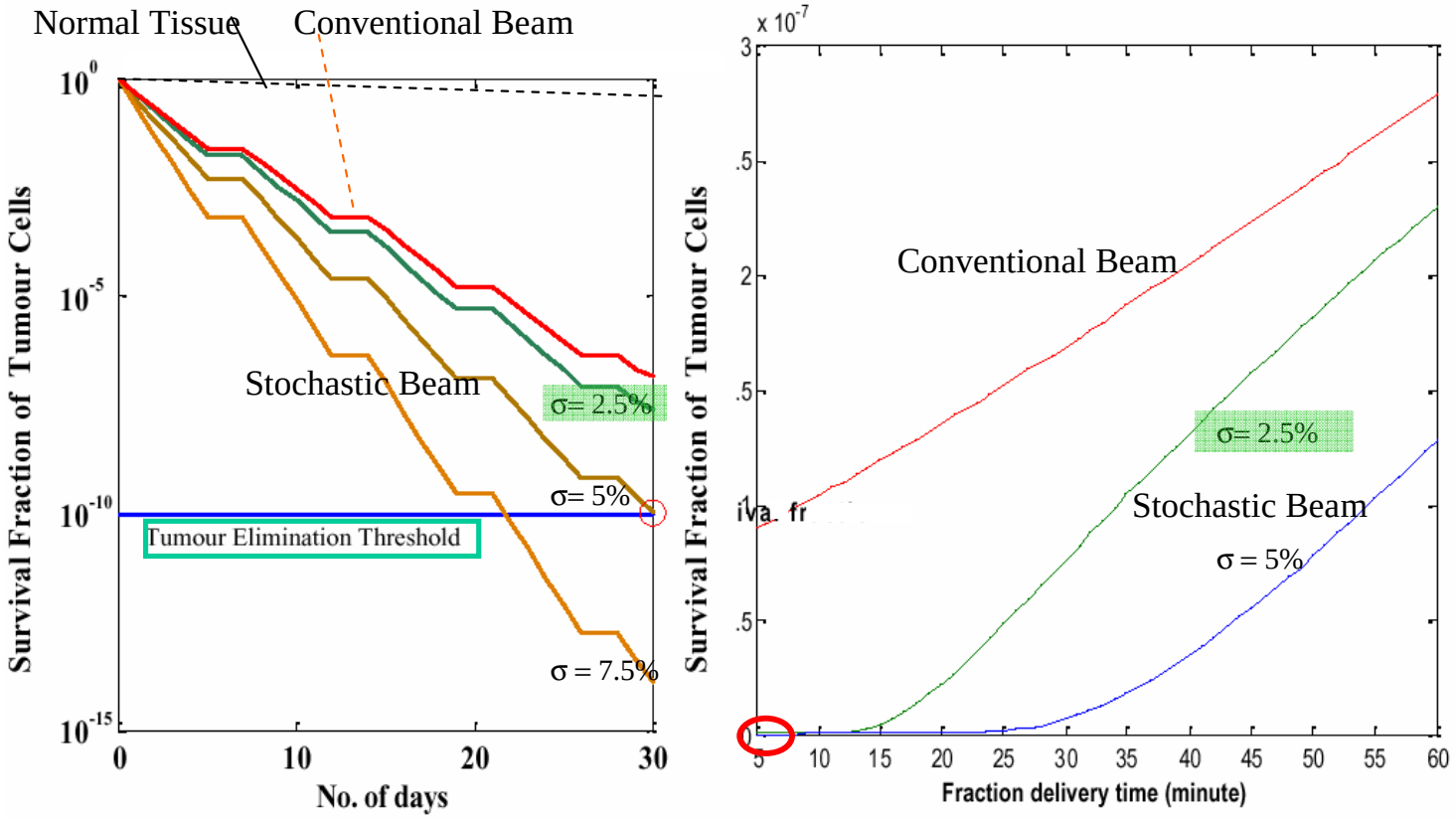


Monte Carlo Therapy Platform (cell-photon)



Fast-growing glioma (Grade III): Effect at 4 weeks

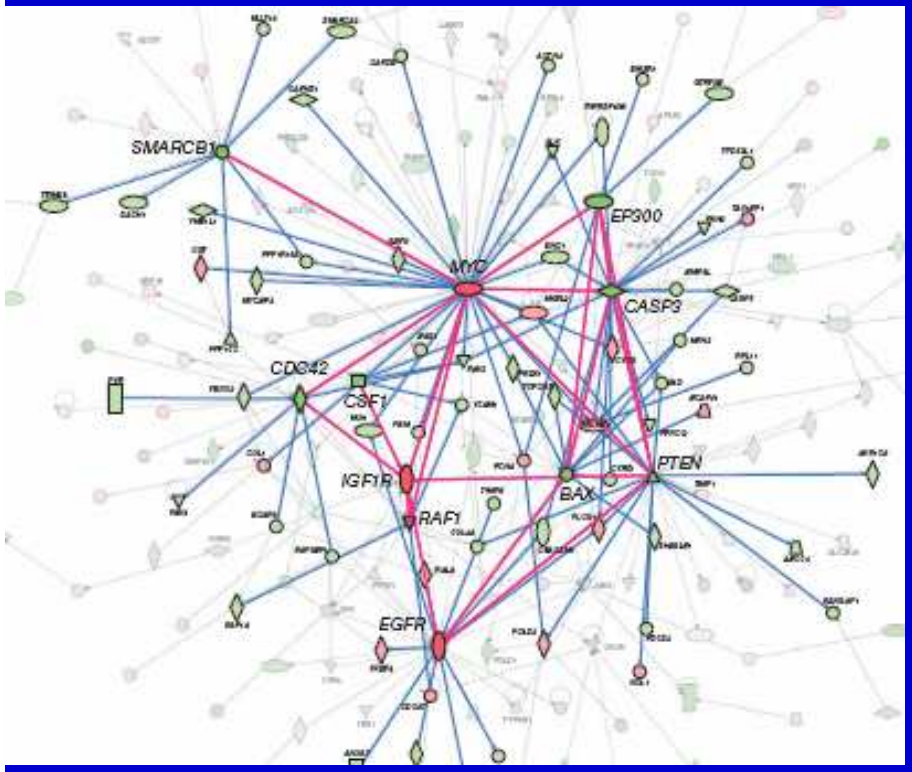
[Dose = 2 Grays/day; Confocal beams on tumour, sparing normal tissue]

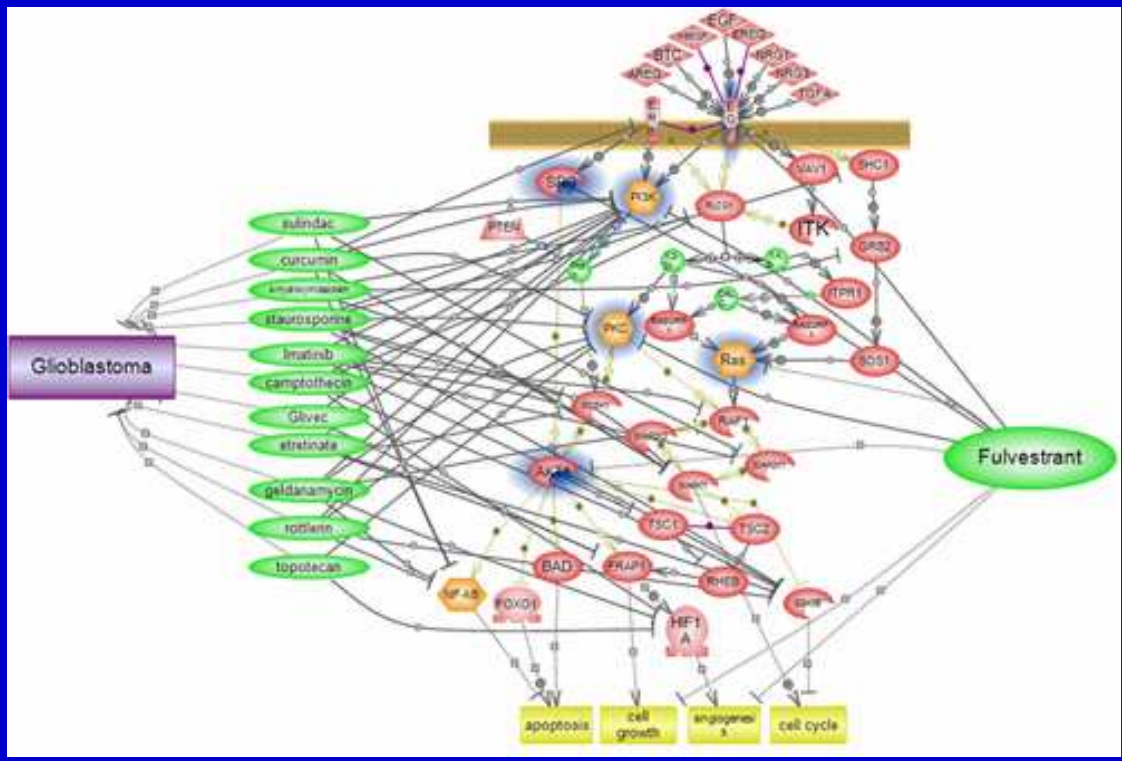


Scope of Work: MRI-based Spatio-temporal Glioma Landscape

Tensor Radiogenomics - MRI

Major Genic Modules → Major Growth Factor Agonists →
Dynamic Pathways → Multi-targetted Drugs → Therapy Optimization

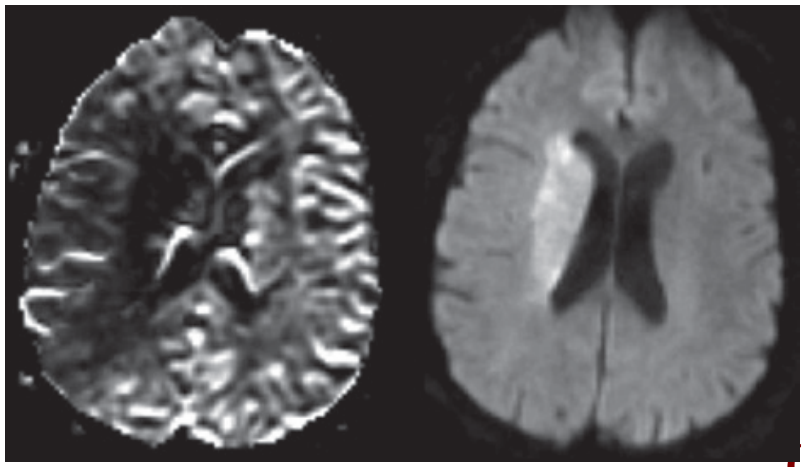




Exploring Clinical Application: Work in progress

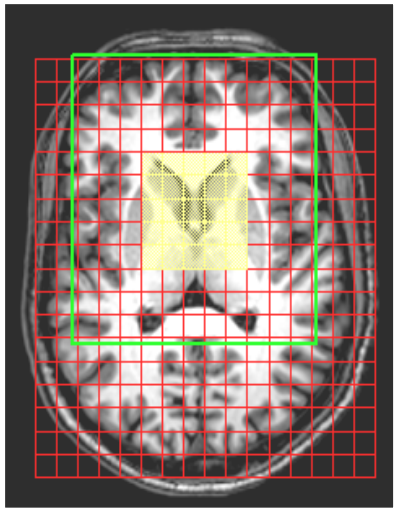
In Cooperation with Artemis Hospital-Gurgaon, AIIMS-Delhi

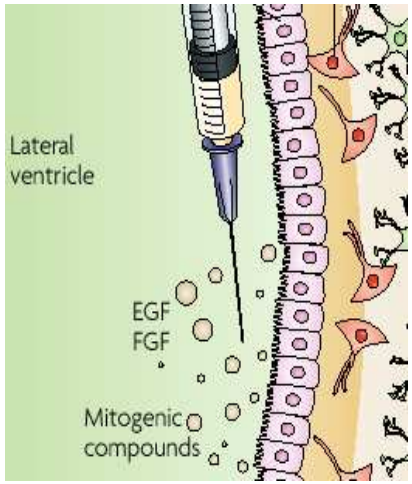
In Brain….Perfusion-Diffusion Mismatch : Ischaemic Area/Penumbra Area to rescued

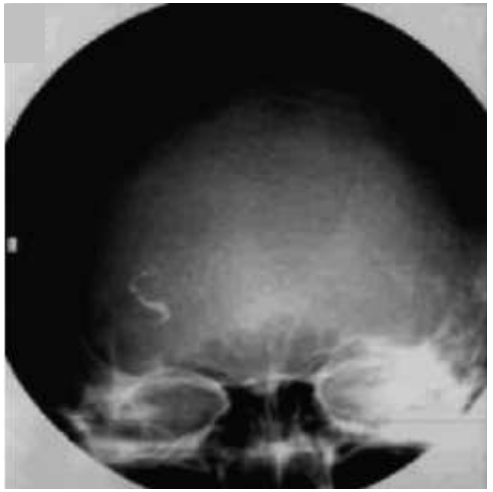


Drugs given I.V./orally

(Crosses Blood Brain Barrier)

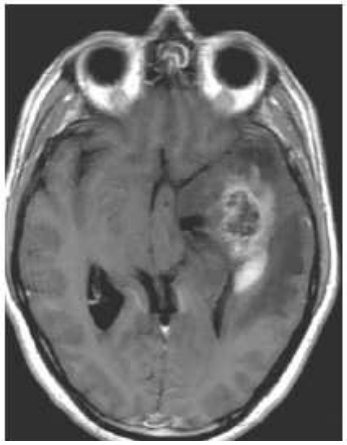




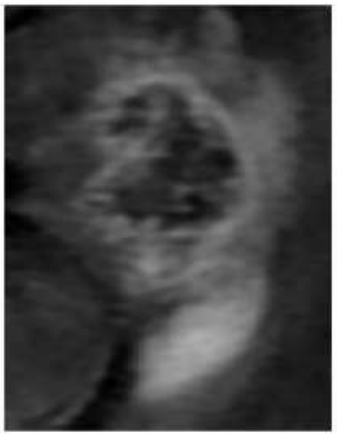


Imaging-based Radiotherapy: Treatment Planning system

Computed planning of 4th Order Tensorial Radiotherapy
Earlier Radiobiological Response of Tumour,
Less Radio-necrosis of Normal Tissue



Original Tumour



ROI: Day 1

Day 7

Day 15

Day 21

Day 30