A longitudinal tumor growth inhibition model for low-grade glioma

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Introduction

- Rate of successful development in oncology: 5%
- For compounds entering phase III: only 40%
- FDA recommends the use of quantitative methods for leveraging knowledge from clinical data
- Objective: to be able to predict long-term clinical outcome from early clinical evaluation
- Means: through modeling time-course of tumor shrinkage (tumor-growth inhibition model)

Existing models / relevance

- Wang et al. CPT 2009 for NSCLC
  - Link time of death to change in tumor size observed 8 weeks after therapy starts, thus providing a method for early screening of candidate drugs
- Claret el al. JCO 2010 for CRC
  - Predict survival in phase III trial based on the modeling of tumor size dynamic in phase II

Low grade gliomas

- WHO grade II gliomas (LGG) are diffusely infiltrative brain tumors affecting young adults
- Tumor grows slowly: 1-2 mm/year ($\approx$10 times less than high grade gliomas)
- Patients mainly asymptomatic for years
- Tumor size is monitored with periodic MRIs
- Treatment starts when tumor size gets too high

Treatments

- None of them is curative
- Surgery, radiotherapy and chemotherapy (Temodal®, and PCV)
- PCV chemotherapy induce prolonged response:
  - Tumor size can decrease in patients for a prolonged period (> 2 years) after treatment stops
- Could the characterization of this prolonged response help to suggest improvements of the therapeutic protocol?

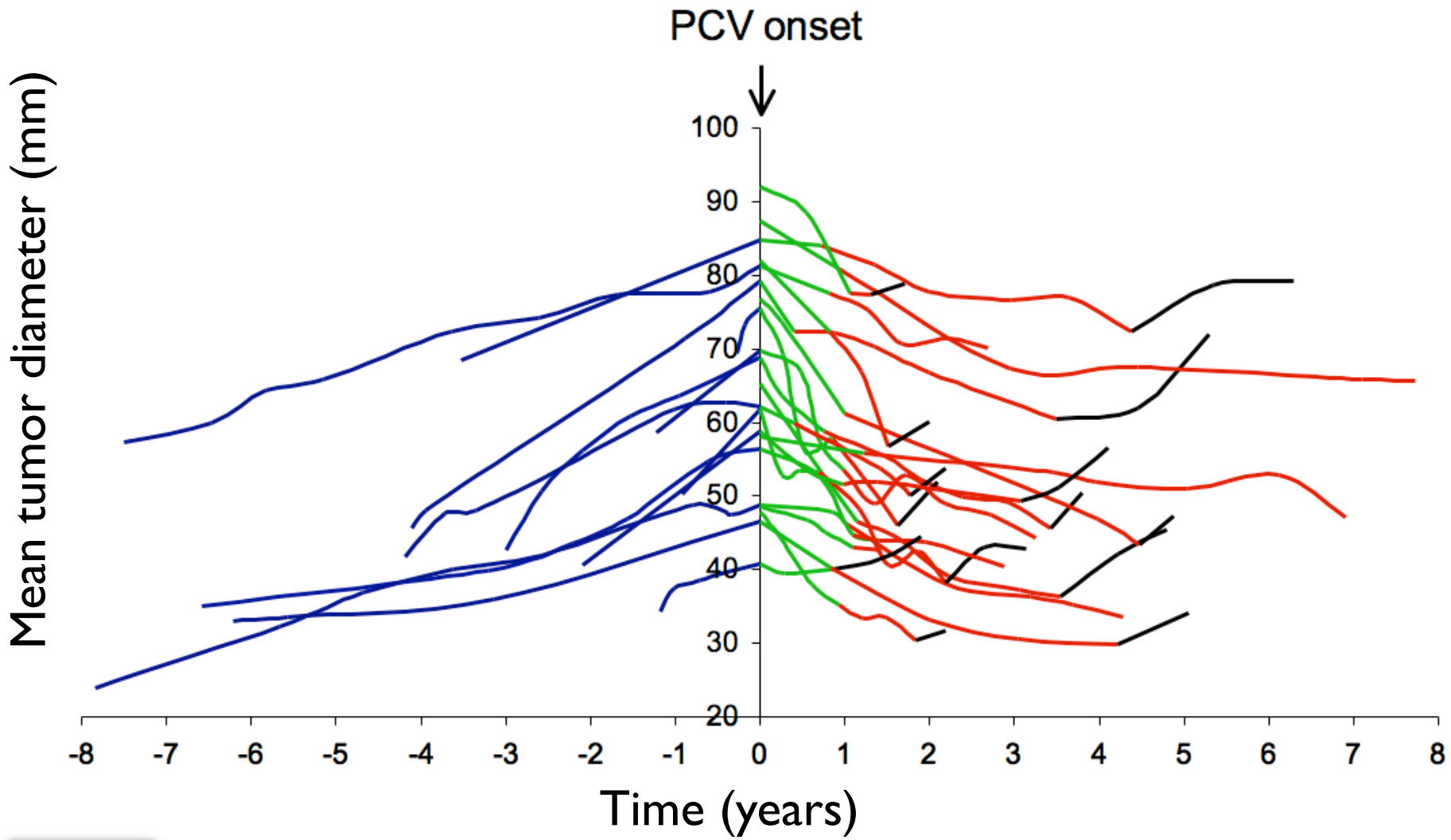
Data description

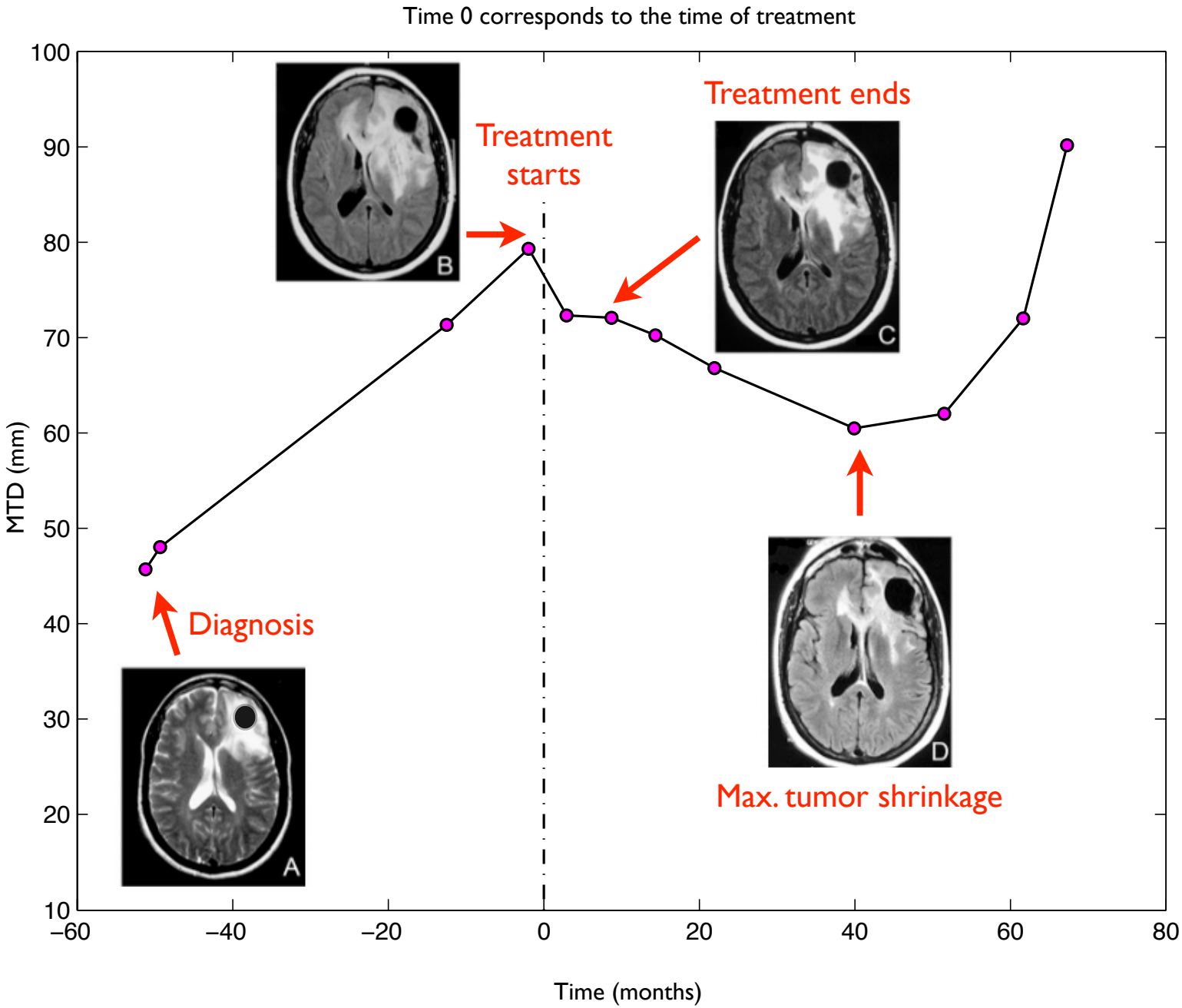
- Tumor size from 21 patients
- PCV treatment protocol : a maximum of 6 cycles (high toxicity) with a 6-weeks interval
  - **Procarbazine** (alkylating agent - phase nonspecific): 60 mg/m2 on days 8-21
  - **Lomustine** (alkylating agent - phase nonspecific): 110 mg/m2 on day 1
  - **Vincristine** (S-phase specific) : 1.4 mg/m2, maximum 2mg/m2 on day 8 and 29

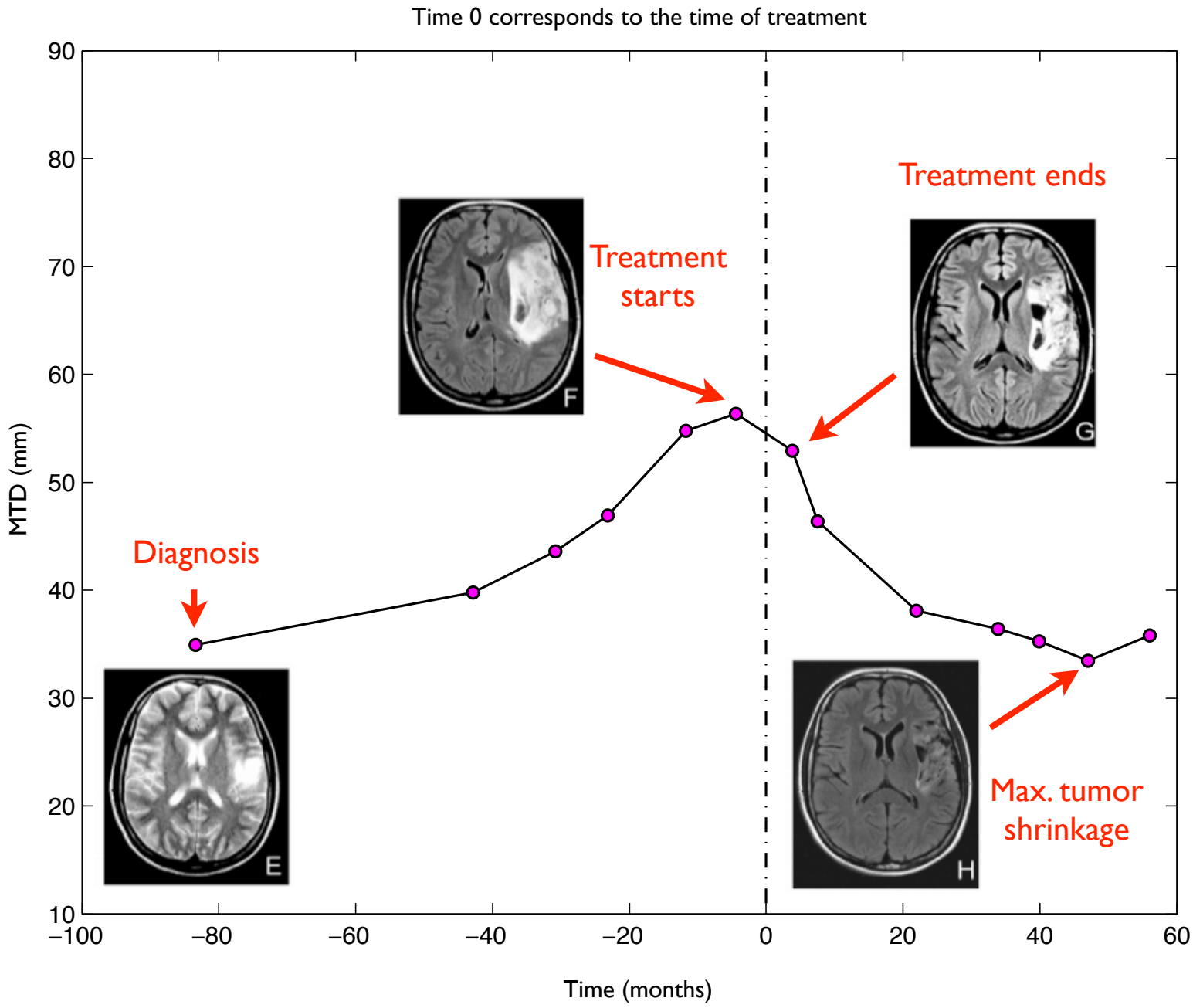
Tumor size measurements

- Printed images were available
- Tumor volumes were estimated manually using three diameters (D1×D2×D3/2)
- Tumor volume were converted into a mean tumor diameter MTD ($2\times V^{1/3}$)
- Conventional method to assess LGG growth dynamic

21 low-grade glioma patients treated with PCV chemotherapy (Procarbazine, CCNU, Vincristine)




Time 0 corresponds to the time of treatment
Treatment starts
Treatment ends
Diagnosis
Max. tumor shrinkage
A
B
C
D
MTD (mm)
Time (months)
100
90
80
70
60
50
40
30
20
10
–60
–40
–20
0
20
40
60
80

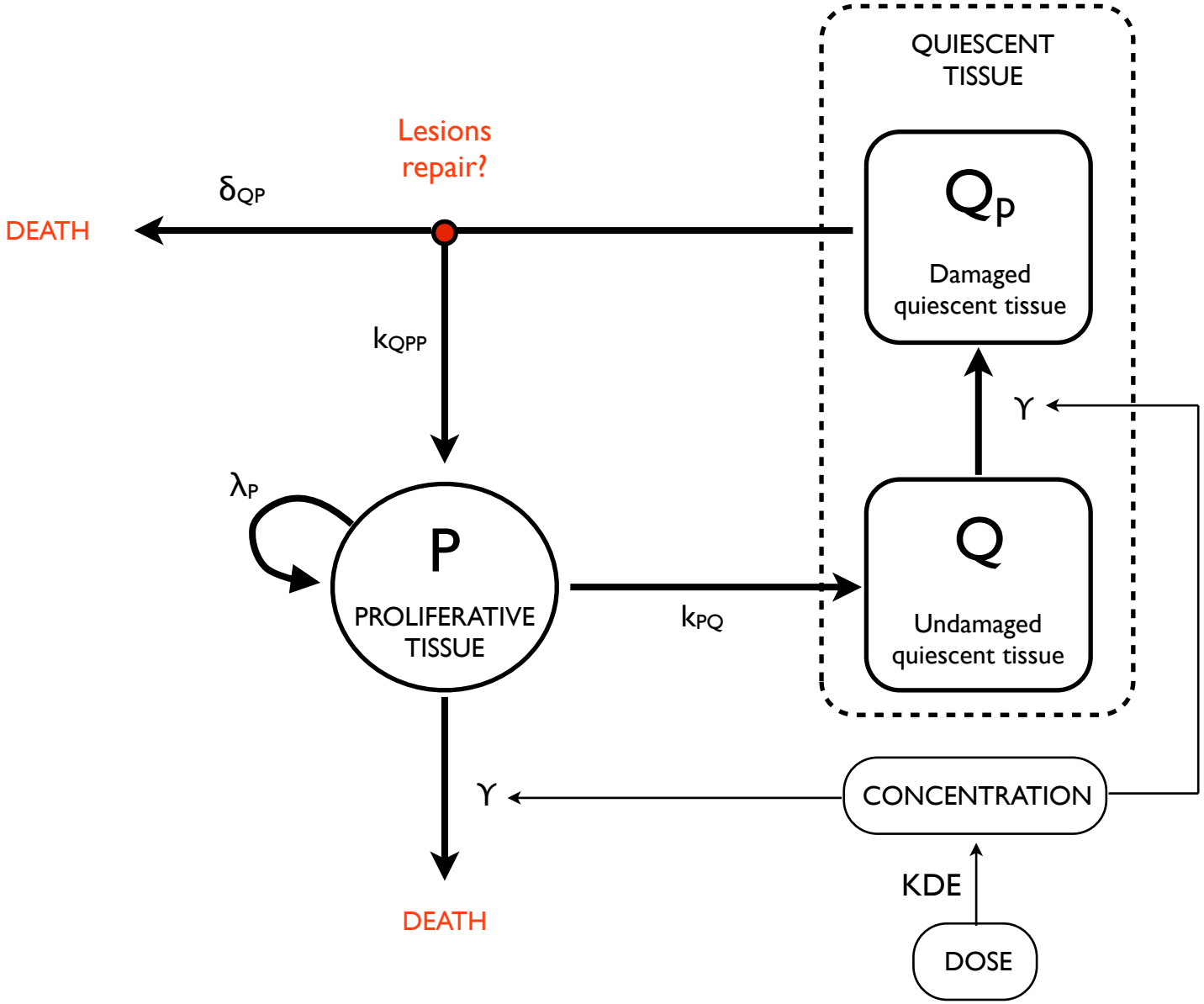

Time 0 corresponds to the time of treatment
MTD (mm)
Time (months)
90
80
70
60
50
40
30
20
10
−100
−80
−60
−40
−20
0
20
40
60
Diagnosis
Treatment starts
Treatment ends
Max. tumor shrinkage
E
F
G
H

Underlying hypothesis

- LGG is composed by proliferative and quiescent cell tissues
- Cytotoxics induce direct kill of proliferating cells
- Quiescent cells that have sustained DNA damages due to treatment subsequently die when re-entering the cell cycle

Modeling treatment

- Treatment is represented as a whole by a unique variable (C), virtual drug concentration encompassing the three agents
- We assume this concentration to exponentially decay through the parameter KDE that we estimate
- At the time of treatments (t = Ttreat), we set C = 1 (arbitrary unit)


QUIESCENT TISSUE
Lesions repair?
δ_{QP}
DEATH
Q_P
Damaged quiescent tissue
k_{QPP}
γ
λ_P
P
PROLIFERATIVE TISSUE
k_{PQ}
Q
Undamaged quiescent tissue
γ
CONCENTRATION
KDE
DOSE
DEATH

Mathematical equations

$$\frac{dC}{dt} = -KDE \times C$$

$$\frac{dP}{dt} = \lambda_P \times P\left(1 - \frac{P^*}{K}\right) + k_{Q_P P} \times Q_P - k_{PQ} \times P - \gamma_P \times C \times P$$

$$\frac{dQ}{dt} = k_{PQ} P - \gamma_Q \times C \times Q$$

$$\frac{dQ_P}{dt} = \gamma_Q \times C \times Q - k_{Q_P P} Q_P - \delta_{Q_P} \times Q_P$$

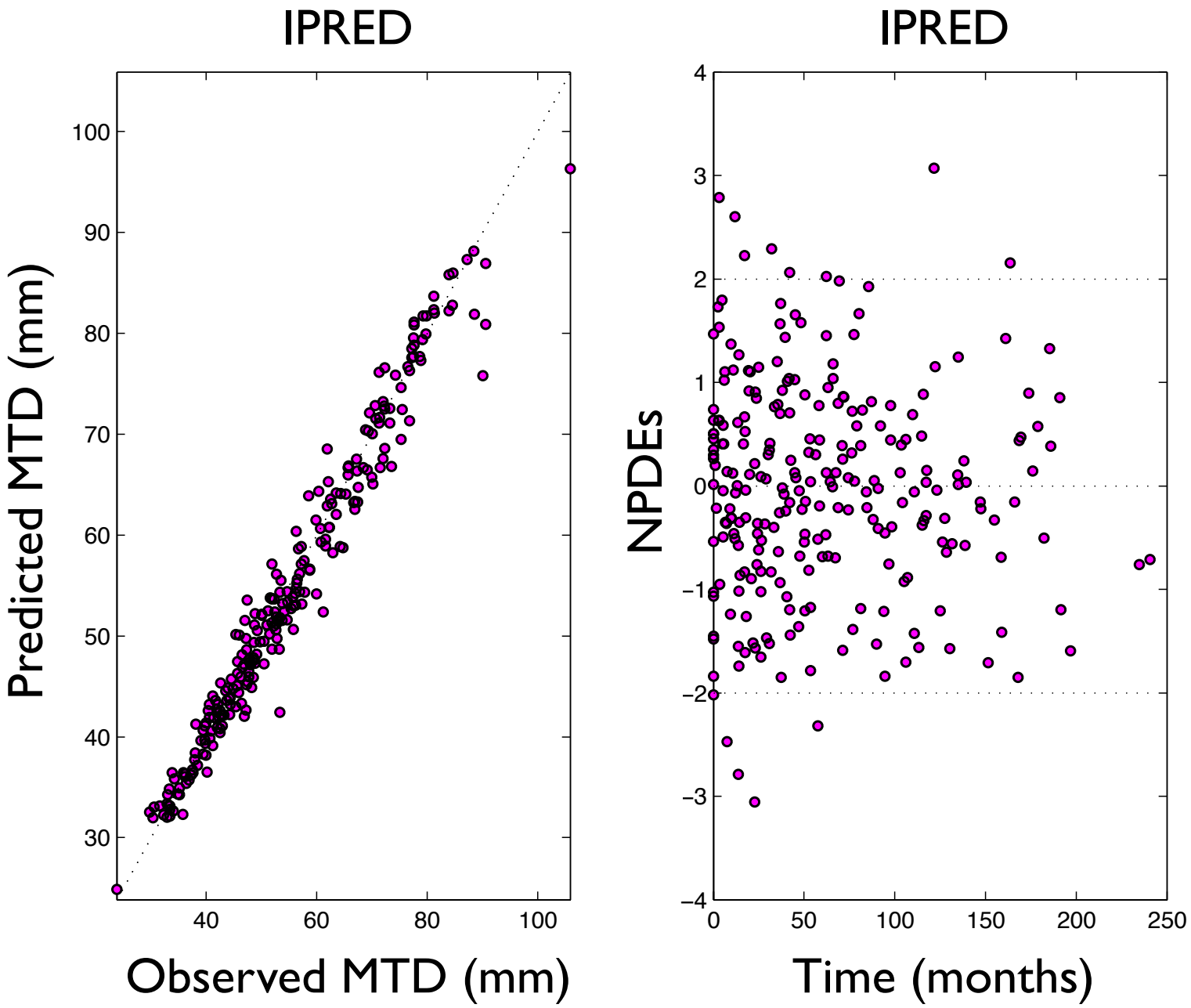
$$P^* = P + Q + Q_P$$

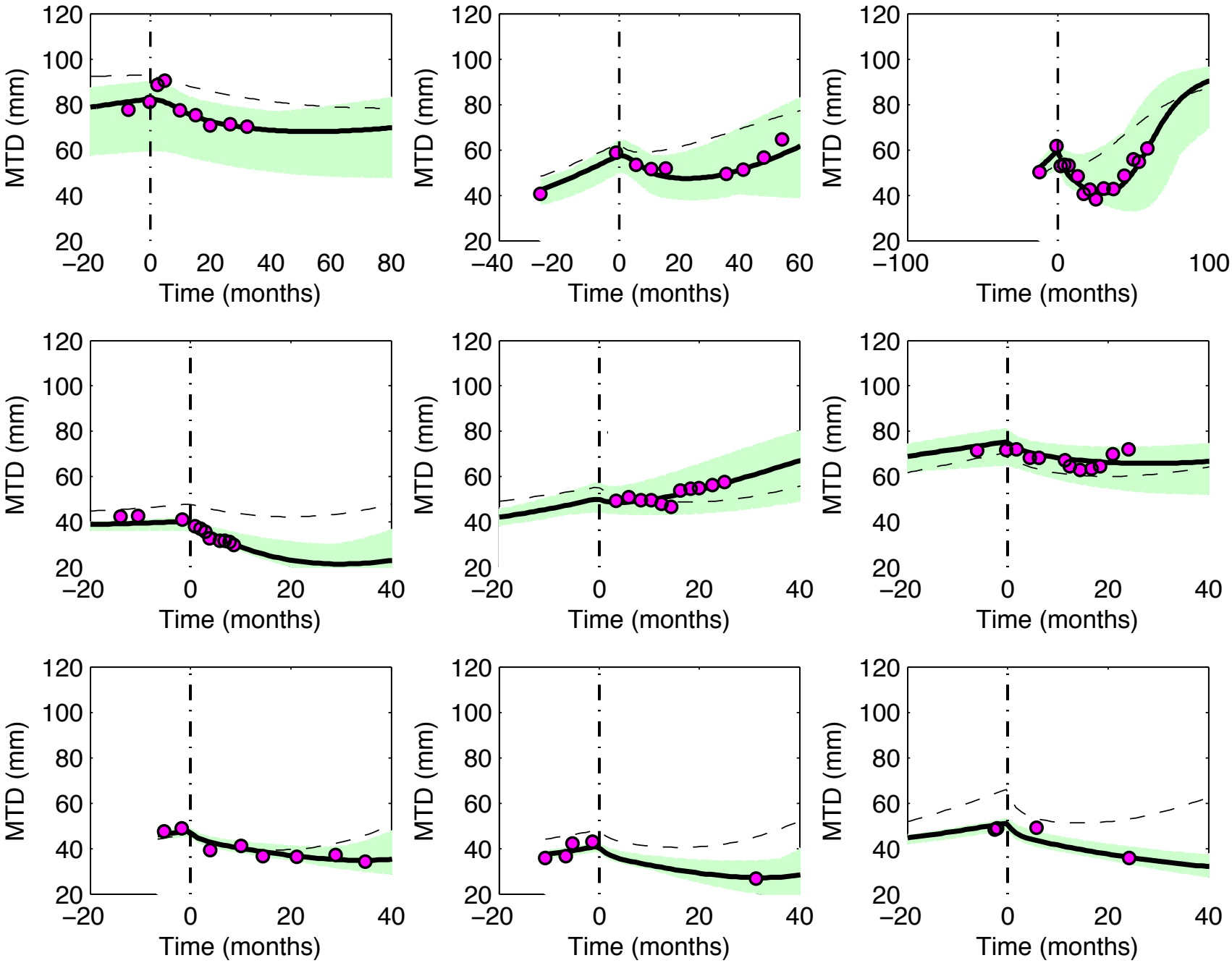
Parameters

- System of 4 compartments written as ordinary differential equations
- 6 parameters and 2 initial conditions (P_0 and Q_0)
- λ_P (growth rate) and k_{PQ} (quiescence rate) only regulates tumor growth in the absence of treatment

Statistical framework

- The model was developed within a mixed-effect (population) context where structural parameters are associated with inter-individual variability
  - 8 fixed parameters and 7 inter-individual variability parameters
- The software Monolix was used to estimate parameters

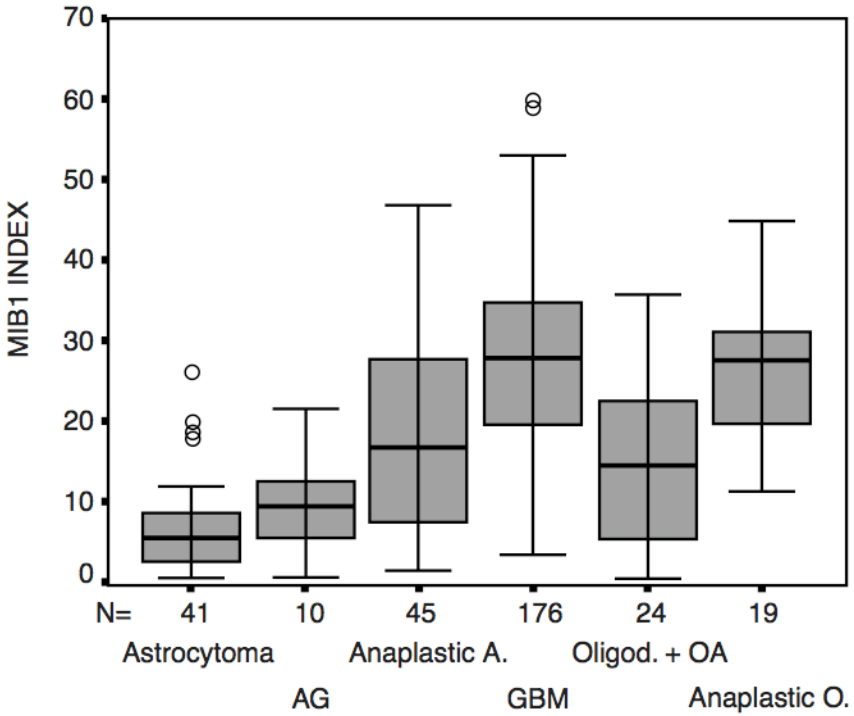

IPRED
Predicted MTD (mm)
Observed MTD (mm)
100
90
80
70
60
50
40
30
40
60
80
100
IPRED
NPDEs
Time (months)
4
3
2
1
0
−1
−2
−3
−4
0
50
100
150
200
250


MTD (mm)
Time (months)
120
100
80
60
40
20
−20
0
20
40
60
80
−40
−100
100

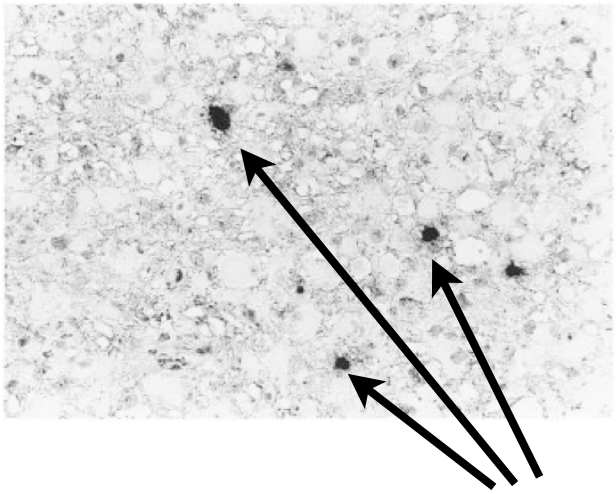
Parameter estimates PCV

Parameter (unit)	Description	Mean value (SE%)	IIV (SE%)
P_0 (mm)	Baseline on P	7.13 (25)	94% (23)
Q_0 (mm)	Baseline on Q	41.2 (7)	54% (10)
λ_P (month^{-1})	Growth rate	0.121 (16)	72% (9)
k_{PQ} (month^{-1})	Quiescence rate	0.030 (21)	76% (12)
k_{QPP} (month^{-1})	Feedback to proliferation	0.003 (35)	97% (31)
δ_{Q^*} (month^{-1})	Elimination rate	0.009 (21)	75% (12)
γ	Treatment efficacy	0.729 (37)	115% (9)
KDE (month^{-1})	Drug elimination rate	0.240 (33)	70% (-)

Heester et al. Journal of Neurology 1999



Staining MIB-1
antibody for Ki-67

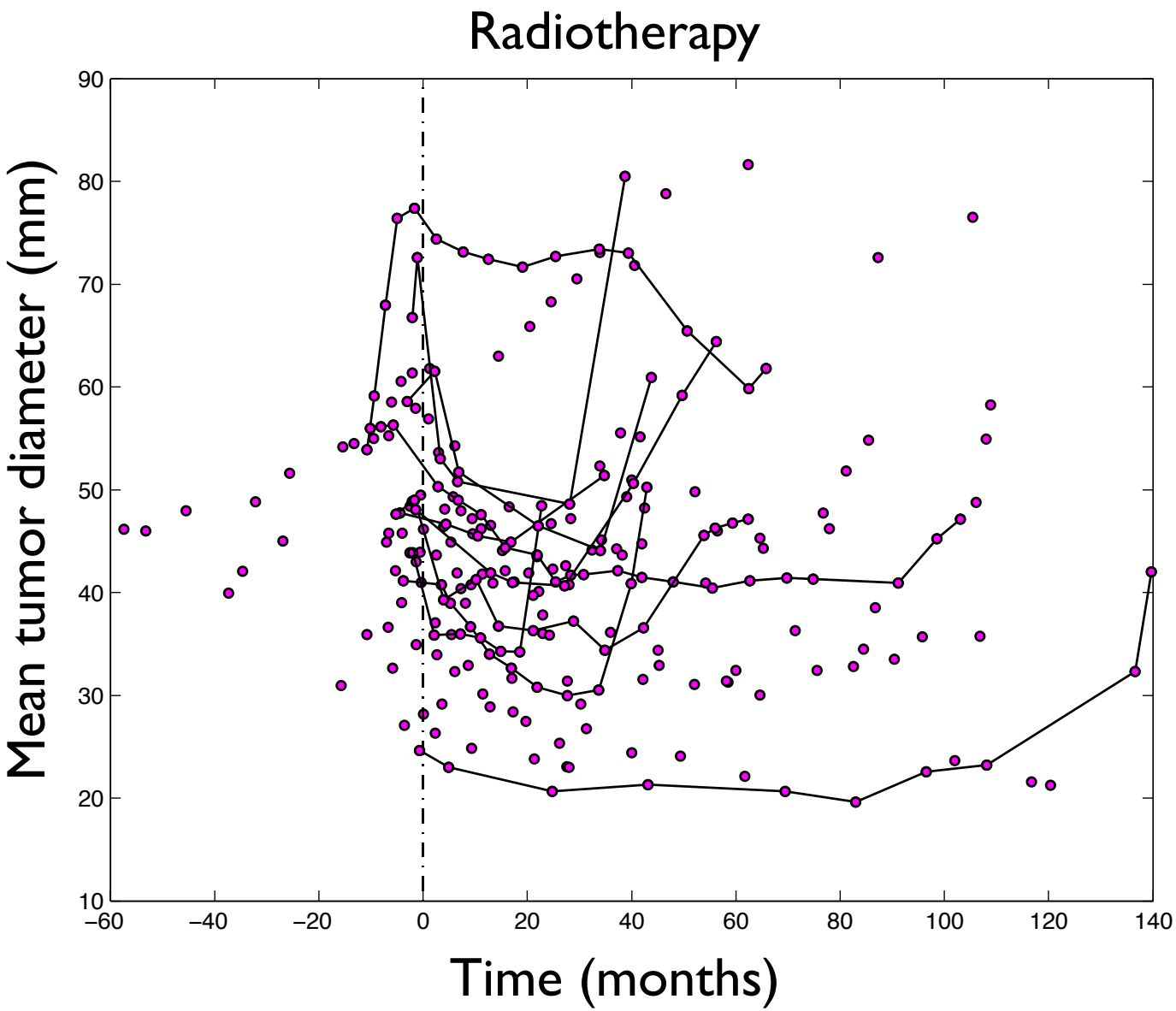


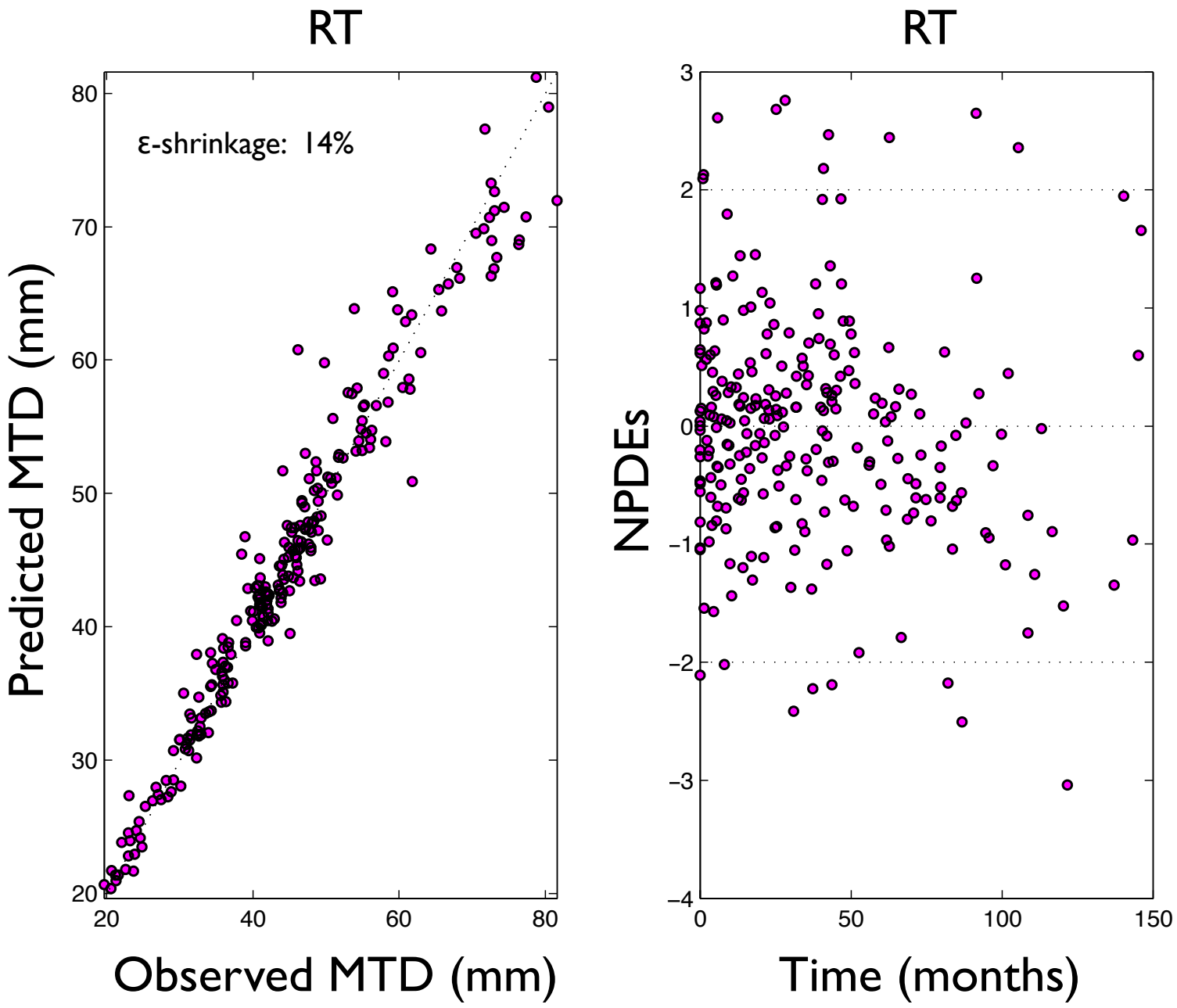
Positive staining nuclei

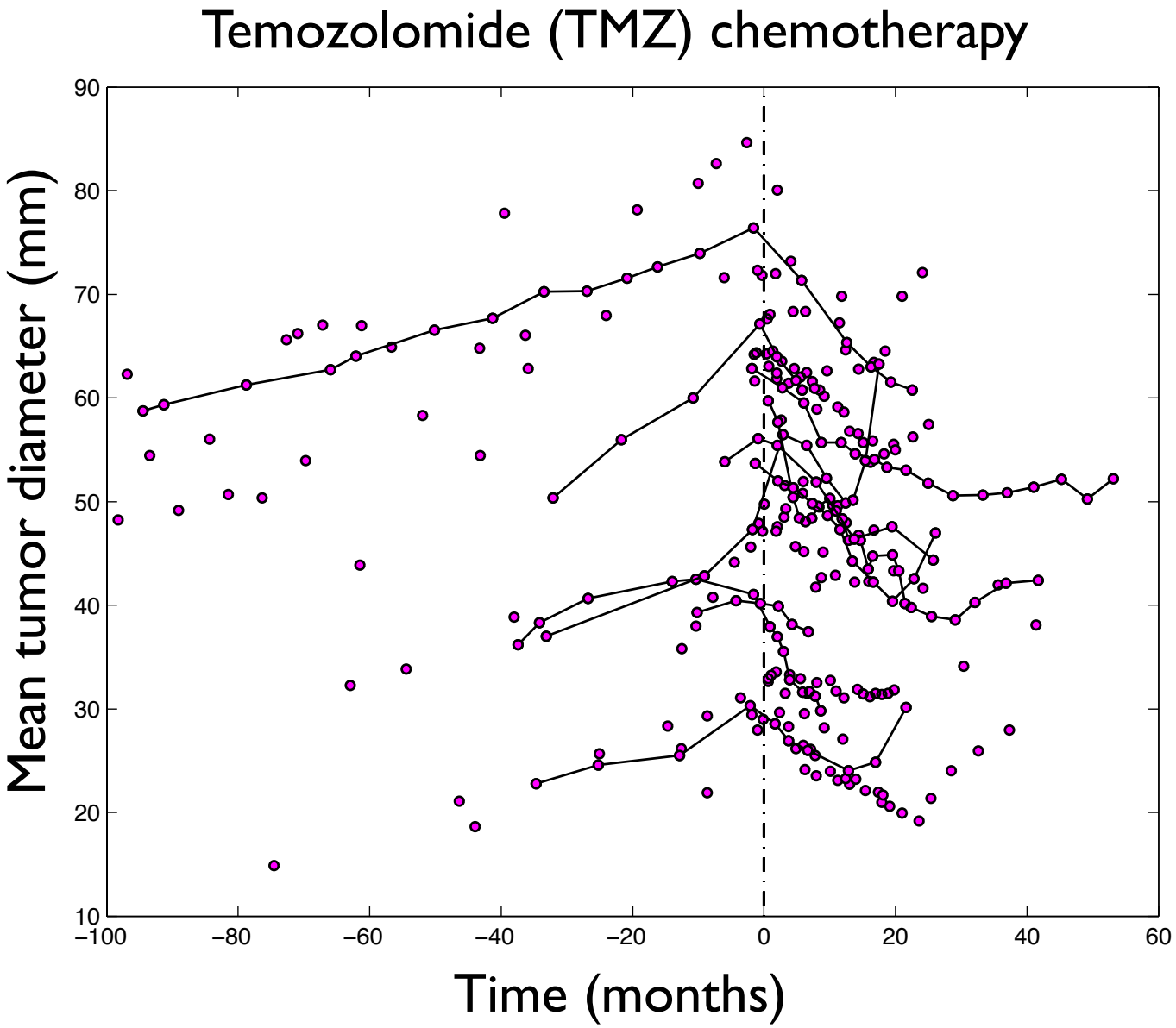
	Observed (n=24)	Predicted (n=21)
Oligodendrogliomas	15% (SD=10%)	14% (SD=10%)

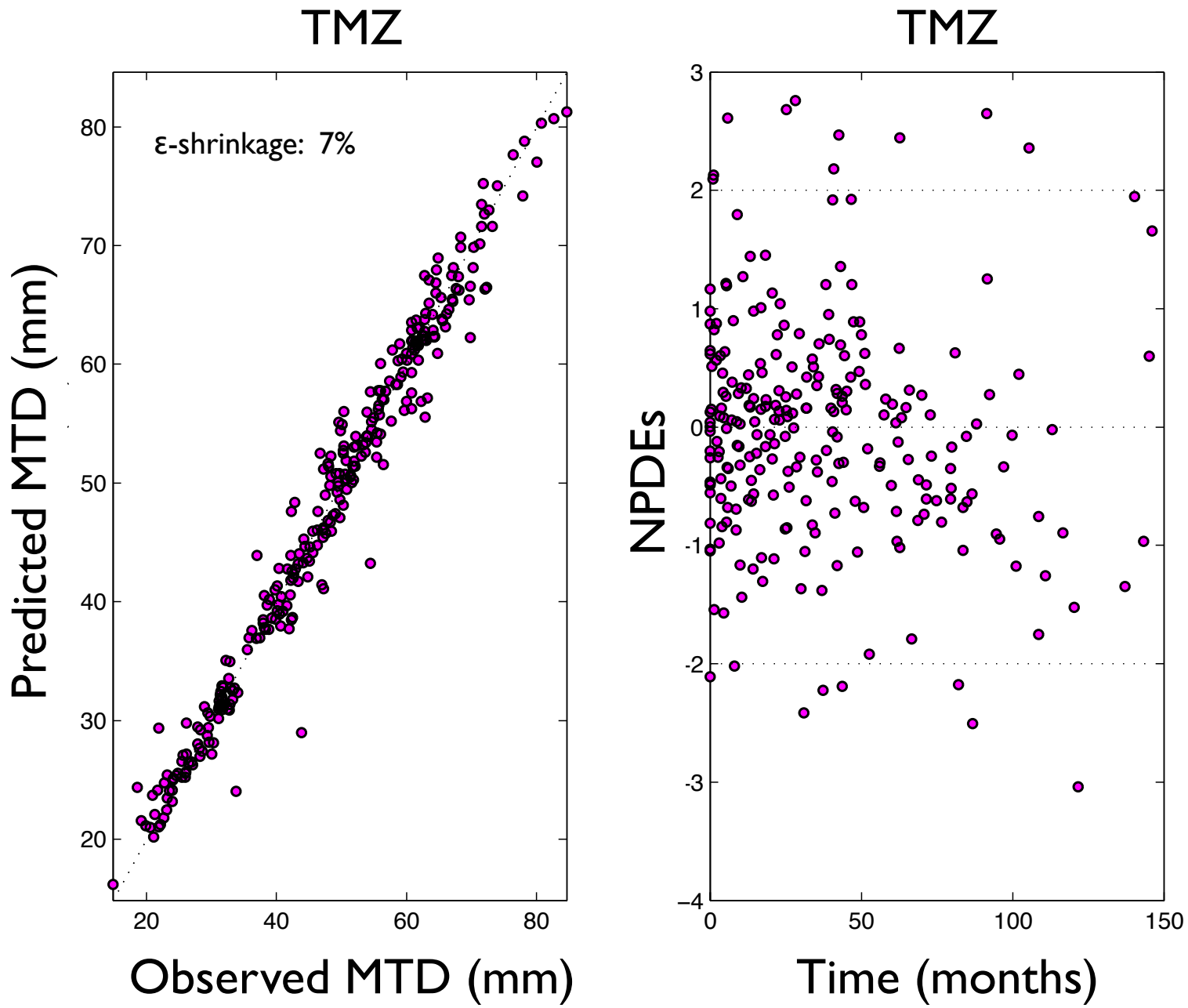
Additional datasets

- Radiotherapy (n=25 patients) - Salpêtrière hospital
- Temozolomide (TMZ) chemotherapy: (n=24 patients randomly selected) - Salpêtrière hospital


Radiotherapy
Mean tumor diameter (mm)
Time (months)
90
80
70
60
50
40
30
20
10
−60
−40
−20
0
20
40
60
80
100
120
140


RT
ε-shrinkage: 14%
Predicted MTD (mm)
Observed MTD (mm)
20
30
40
50
60
70
80
20
40
60
80
RT
NPDEs
Time (months)
−4
−3
−2
−1
0
1
2
3
0
50
100
150

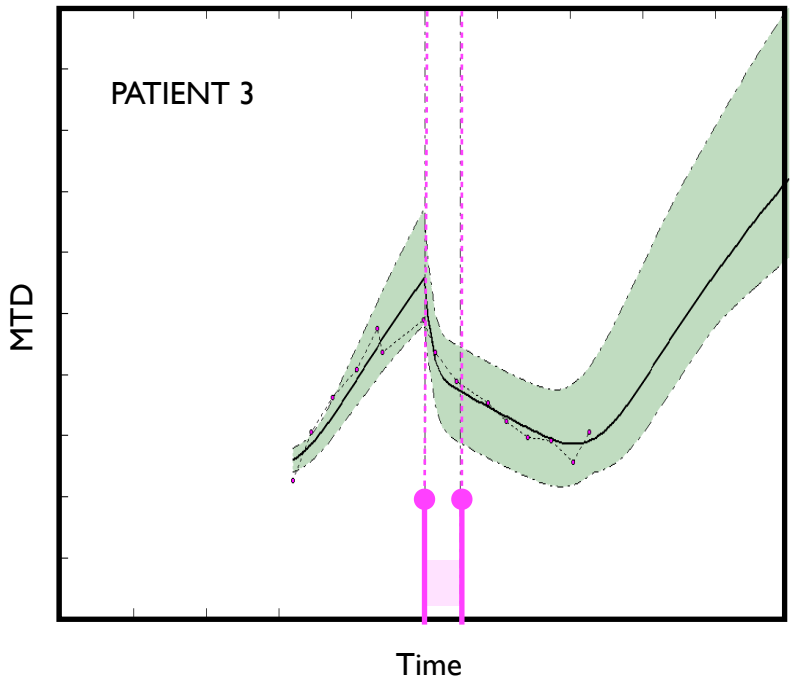

Temozolomide (TMZ) chemotherapy
Mean tumor diameter (mm)
Time (months)
90
80
70
60
50
40
30
20
10
−100
−80
−60
−40
−20
0
20
40
60

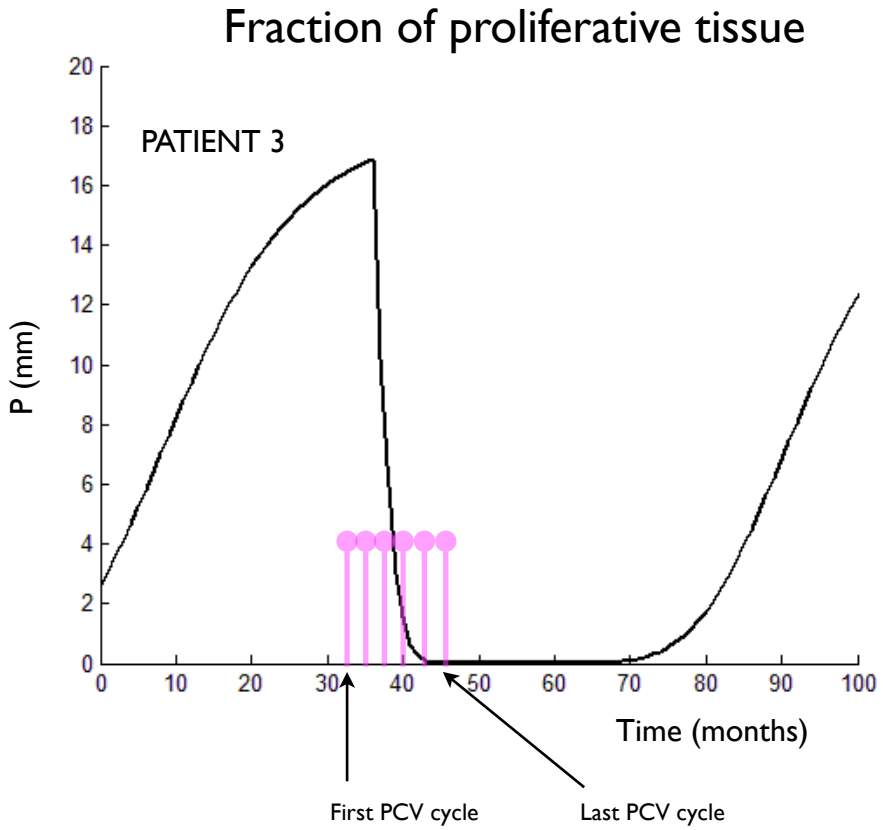

TMZ
ε-shrinkage: 7%
Predicted MTD (mm)
Observed MTD (mm)
20
30
40
50
60
70
80
20
40
60
80
TMZ
NPDEs
Time (months)
3
2
1
0
-1
-2
-3
−4
0
50
100
150

Parameter consistency

Parameter (unit)	PCV	RT	TMZ
Tumor baseline	48.3 mm	44.2 mm	43.2 mm
Basic doubling time for the proliferative tissue	8.3 months	7.3 months	8.8 months
Ratio proliferation rate versus quiescence rate	4.0	5.5	5.2
Ratio death rate versus proliferation rate for DNA-damaged quiescent tissue	3.0	No feedback to proliferation	4.2

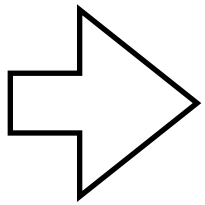
Prolonged response



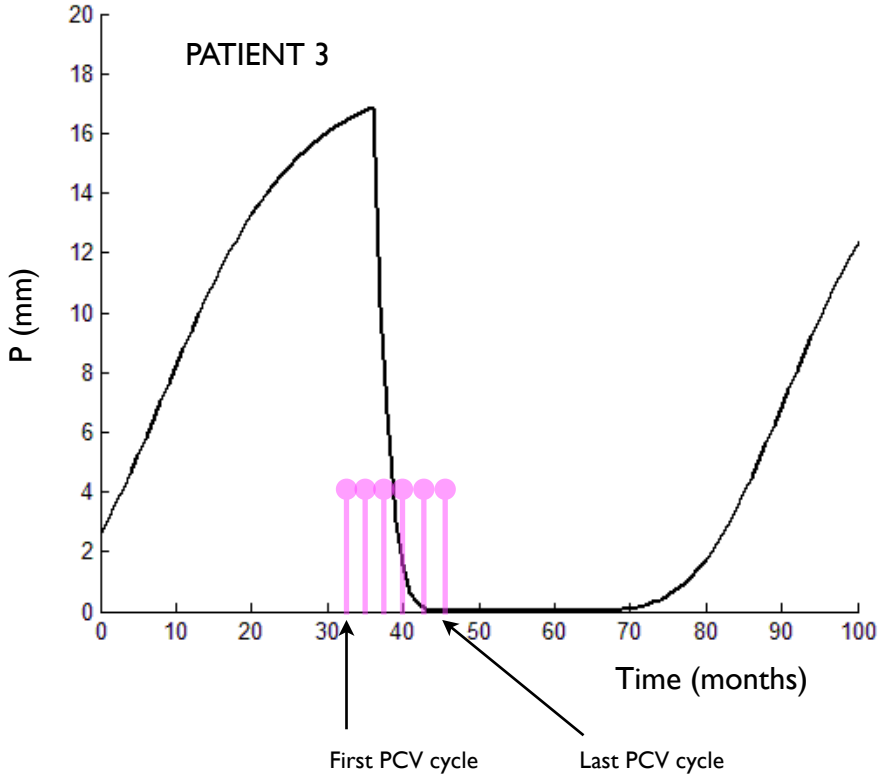


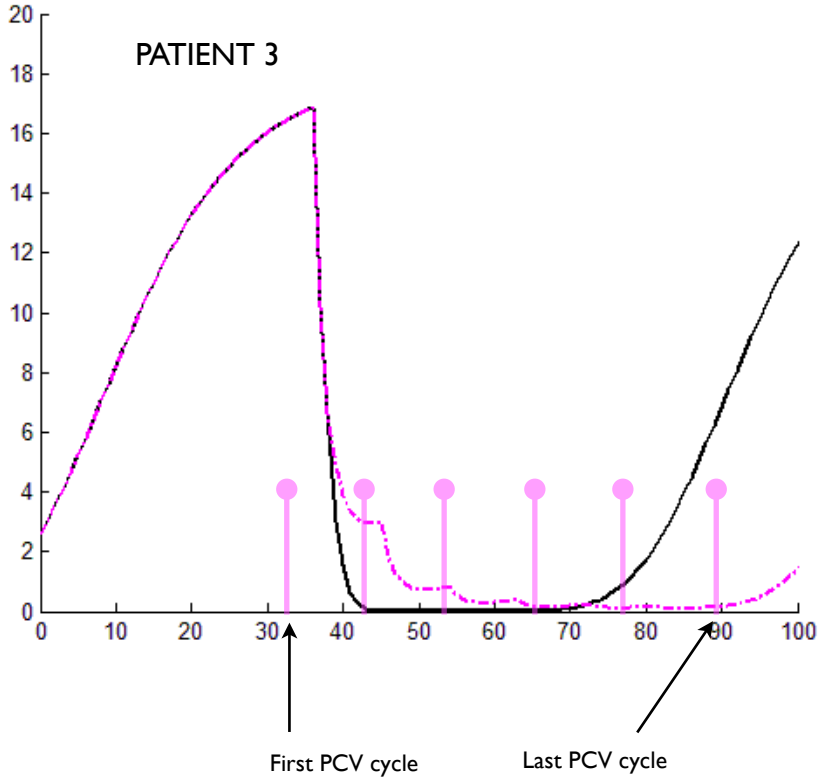
Lengthening time interval

1 cycle every 6 weeks

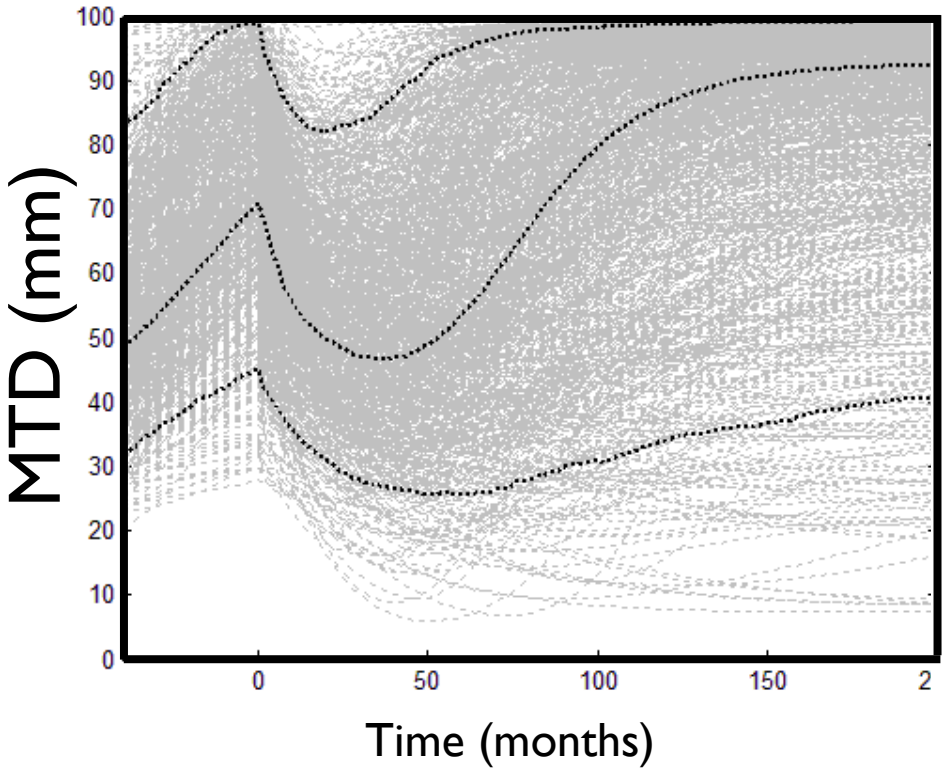


1 cycle every 9 months

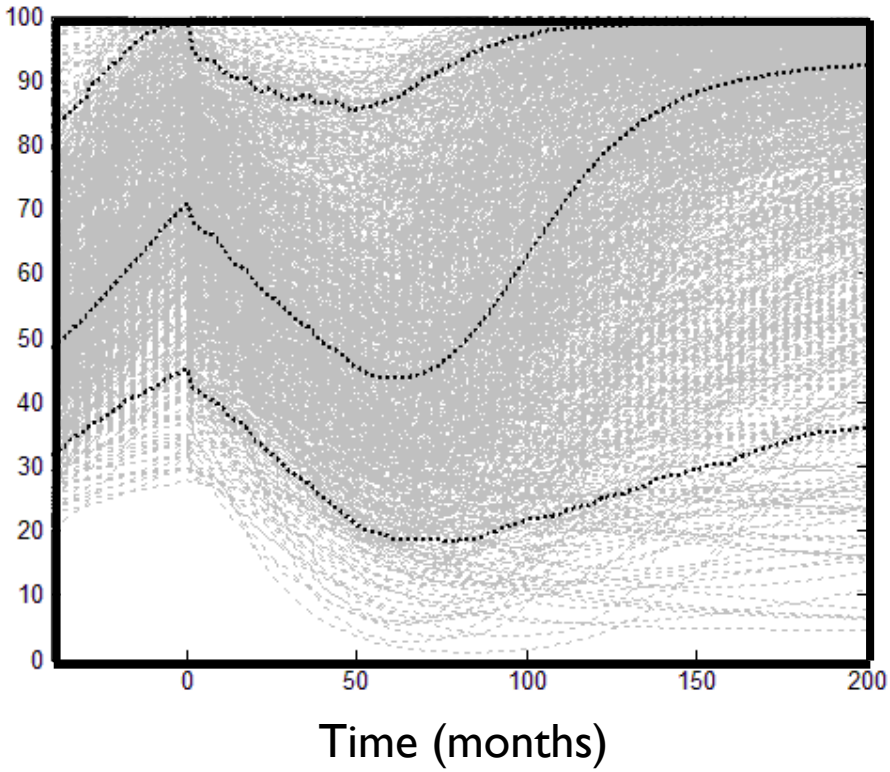




PCV 6 weeks



PCV 9 months

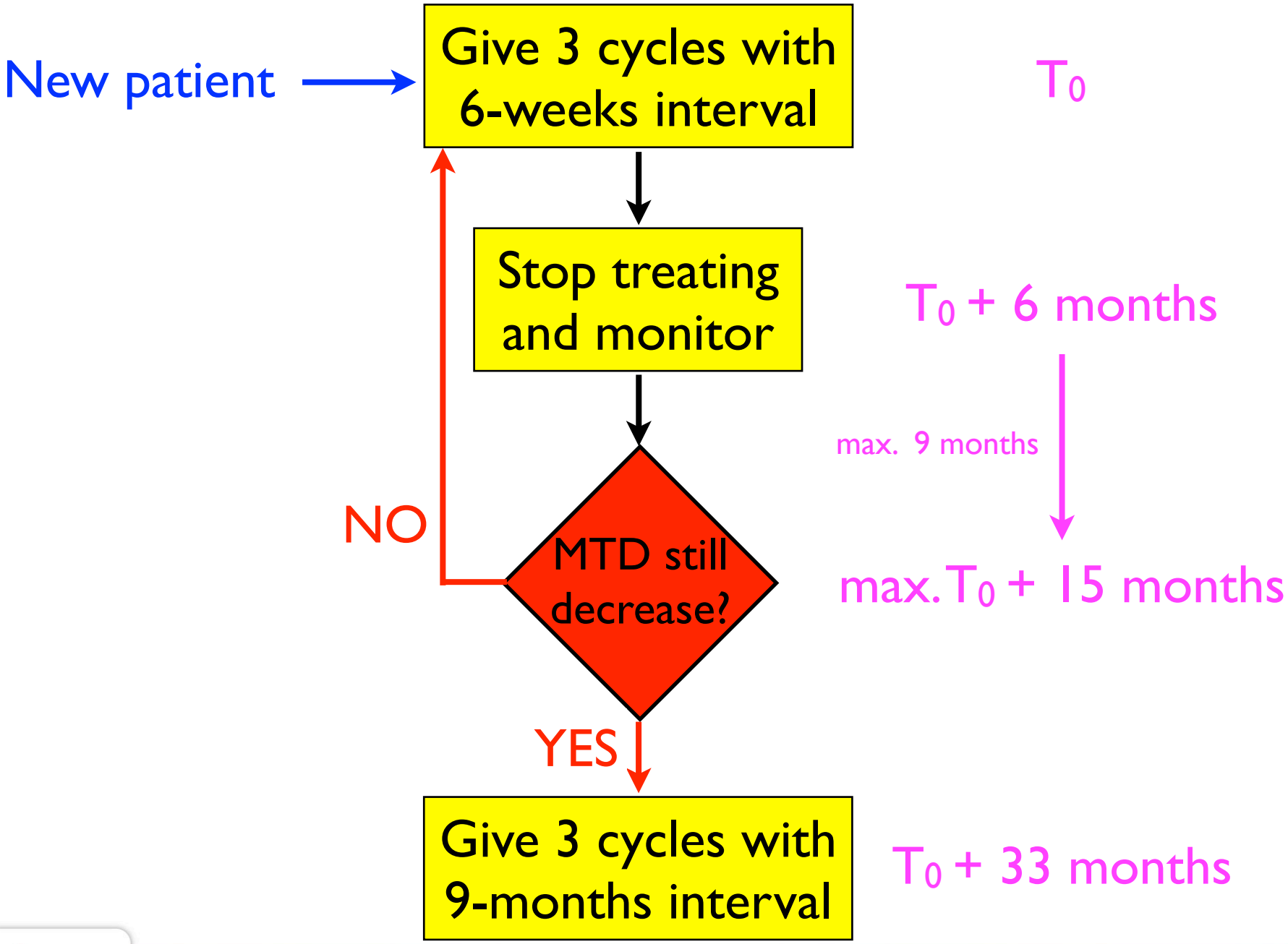


PCV 6 weeks	
MTD shrink	-34%
Prolonged response	36 months

PCV 9 months	
MTD shrink	-40%
Prolonged response	64 months

Clinical translation

- Give only 3 cycles according to the classical protocol (every 2 months) and then monitor the tumor size for 9 months with periodic MRI
  - If the tumor resumes its growth (or remain stable) within the 9 months, start again treatment following the classical protocol
  - If the tumor size continues decreasing after 9 months, increase the treatment interval


New patient
Give 3 cycles with 6-weeks interval
T0
Stop treating and monitor
T0 + 6 months
max. 9 months
NO
MTD still decrease?
max. T0 + 15 months
YES
Give 3 cycles with 9-months interval
T0 + 33 months

Conclusions

- We propose a semi-mechanistic TGI model for low-grade glioma patients
- Parameters can be classified into:
  - system-specific parameters
  - treatment related parameters
- Consistency of system-specific parameters across different treatments including radiotherapy
- Future work includes link with long-term clinical outcome