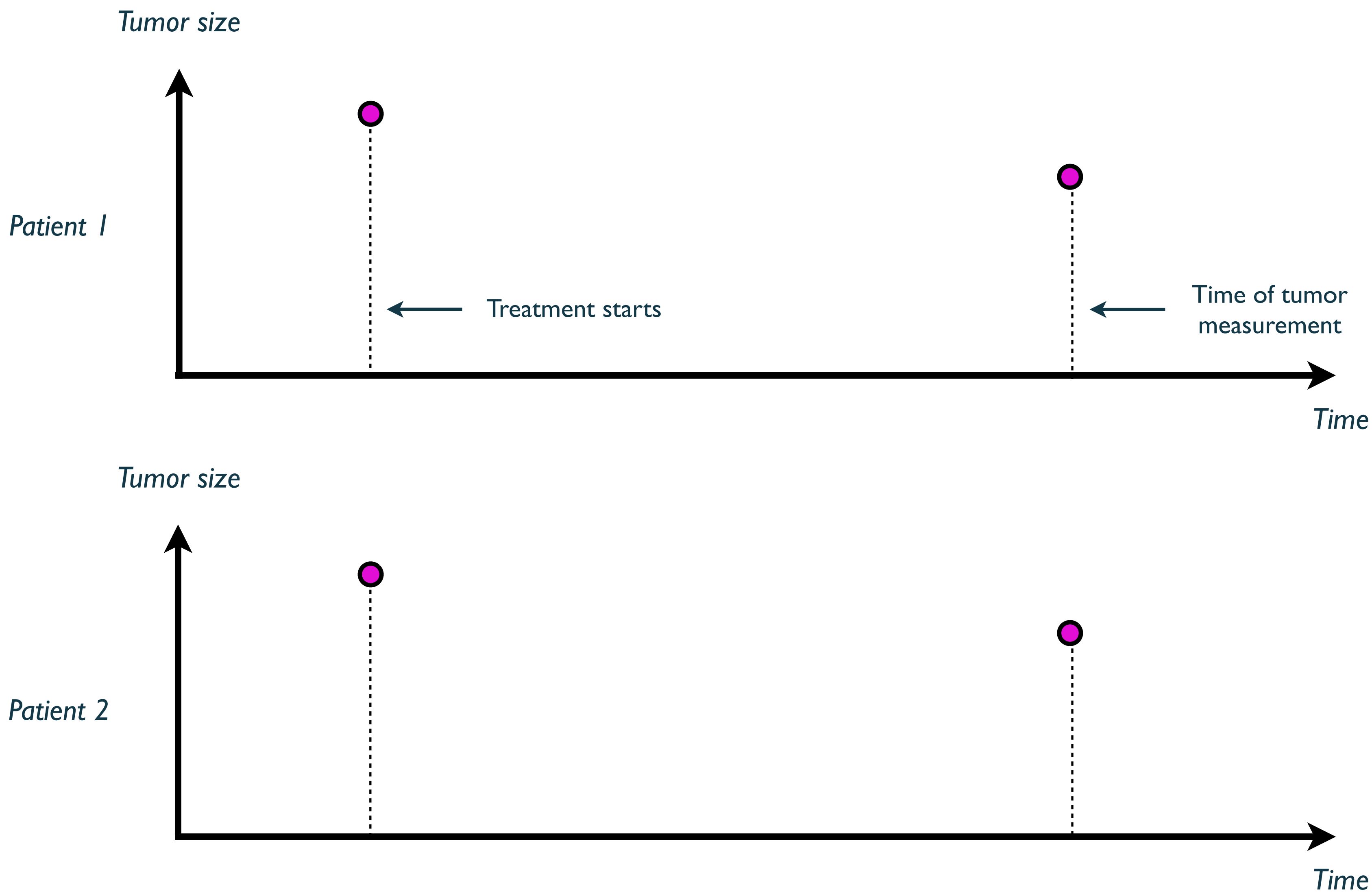
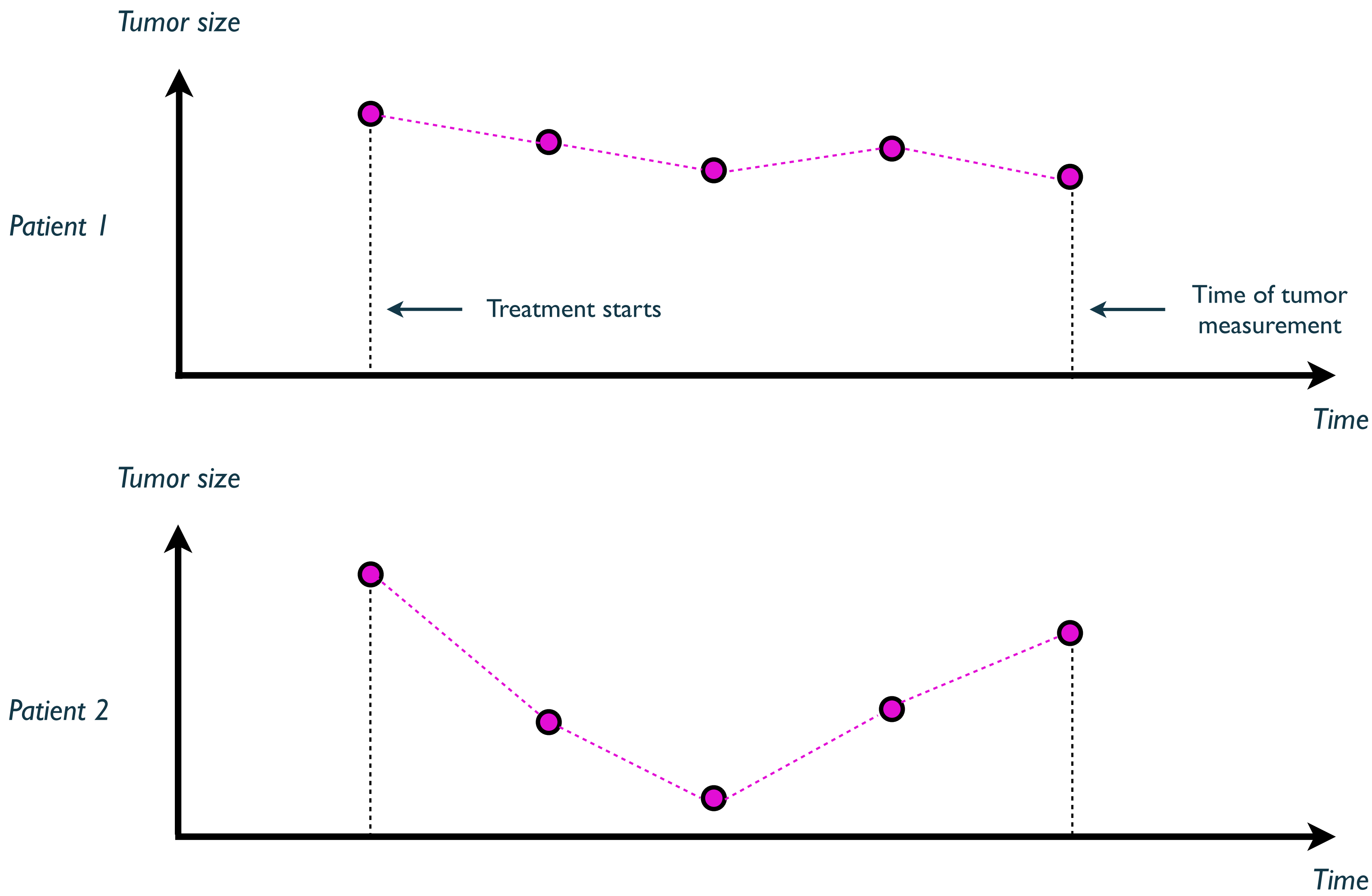
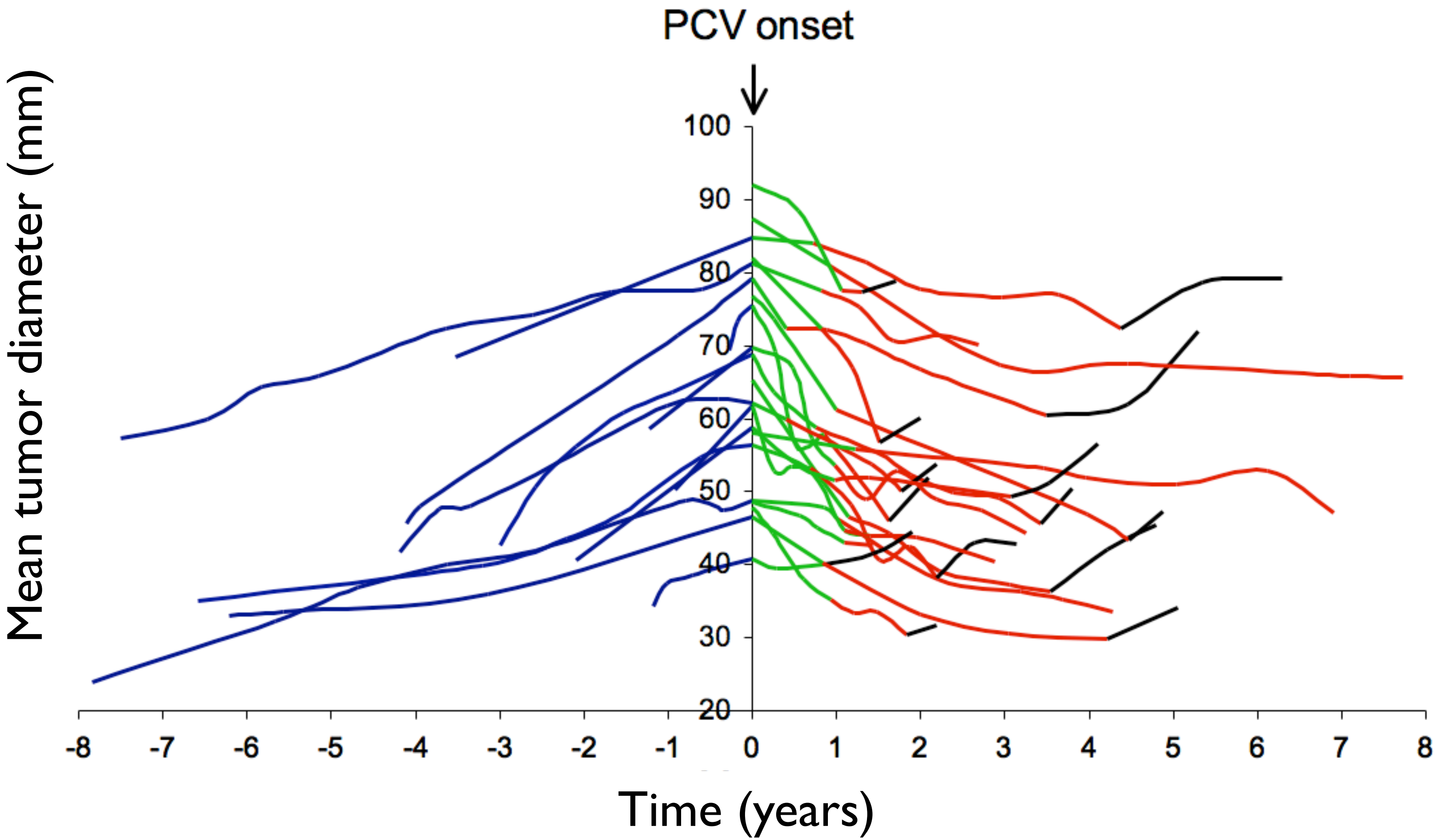
Modeling of efficacy data in clinical oncology

Benjamin Ribba

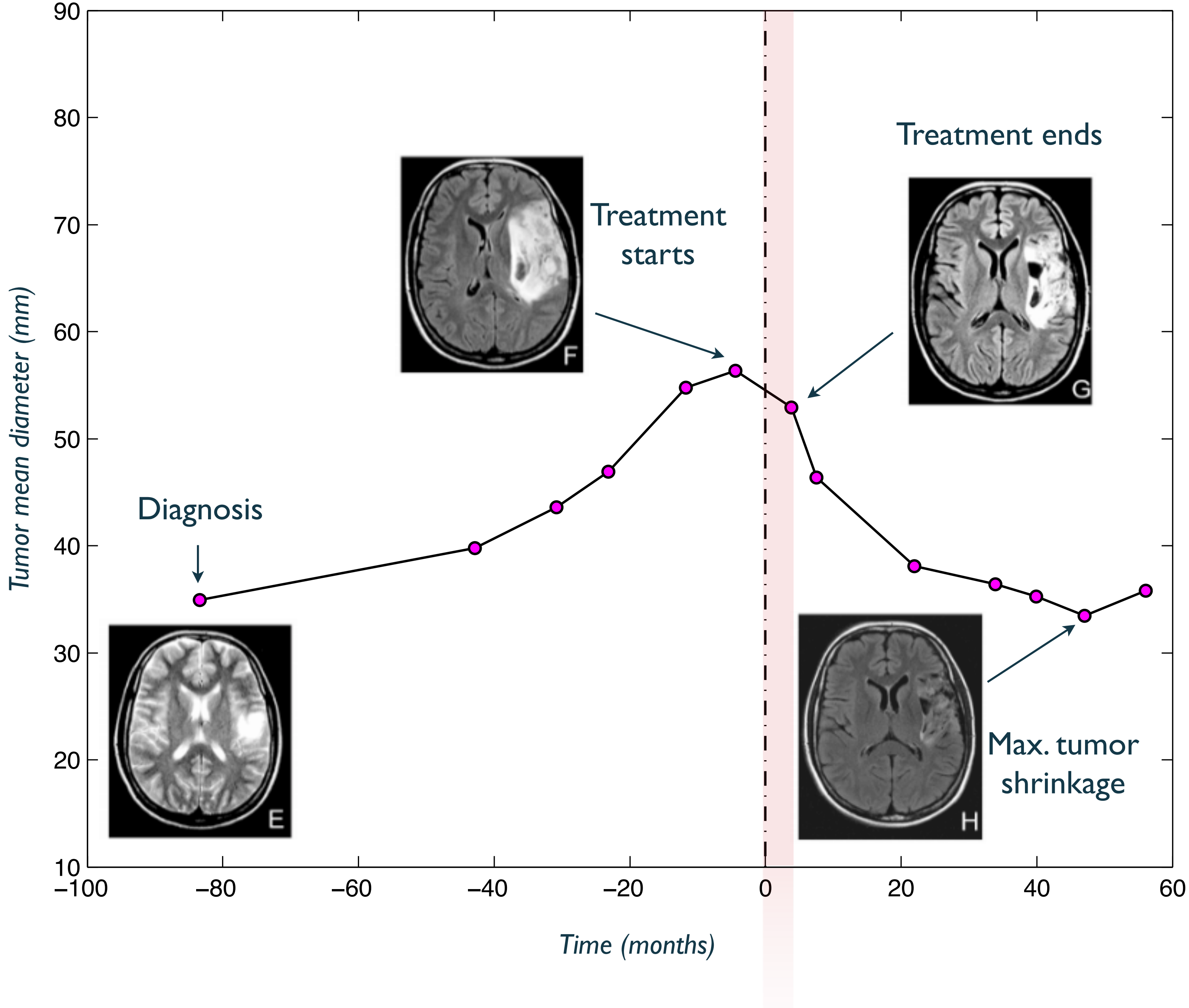

Tumor size
Patient 1
Treatment starts
Time of tumor
measurement
Time
Tumor size
Patient 2
Time


Tumor size
Patient 1
Treatment starts
Time of tumor measurement
Time
Tumor size
Patient 2
Time

Models and tools to analyze such type of data?



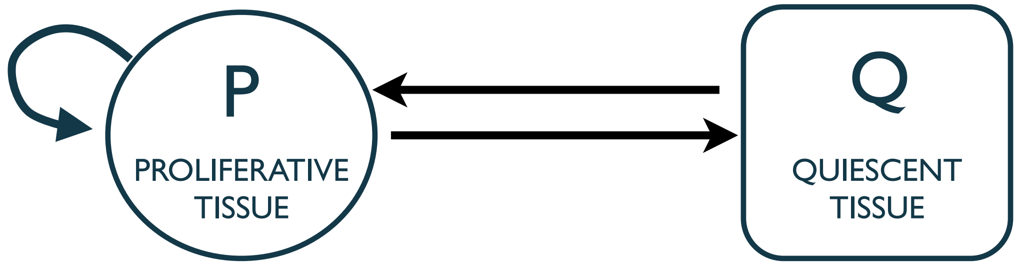
PCV onset
Mean tumor diameter (mm)
100
90
80
70
60
50
40
30
20
-8
-7
-6
-5
-4
-3
-2
-1
0
1
2
3
4
5
6
7
8
Time (years)

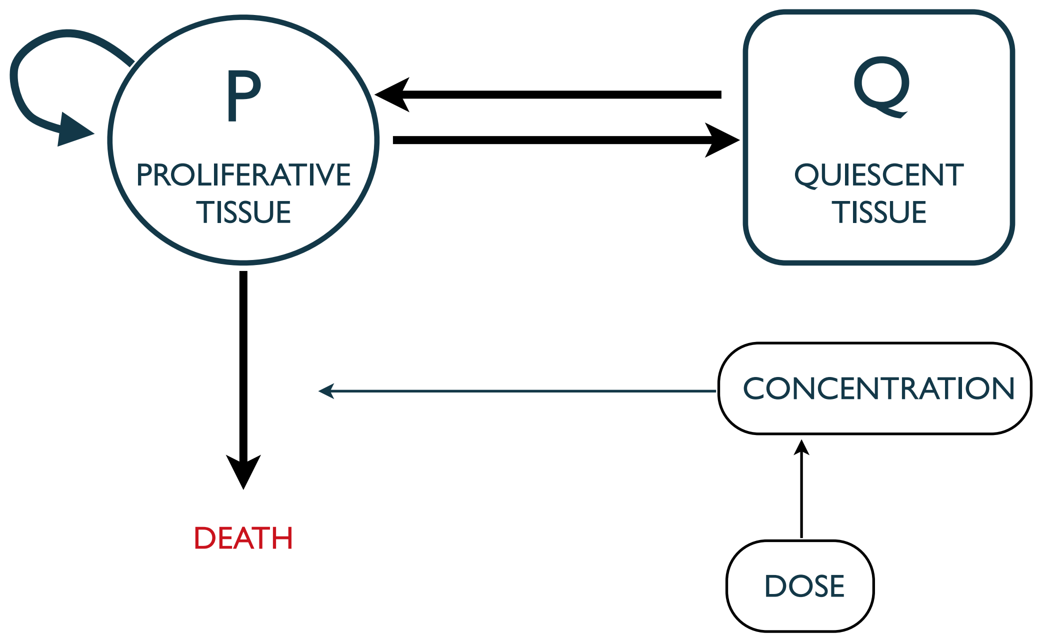


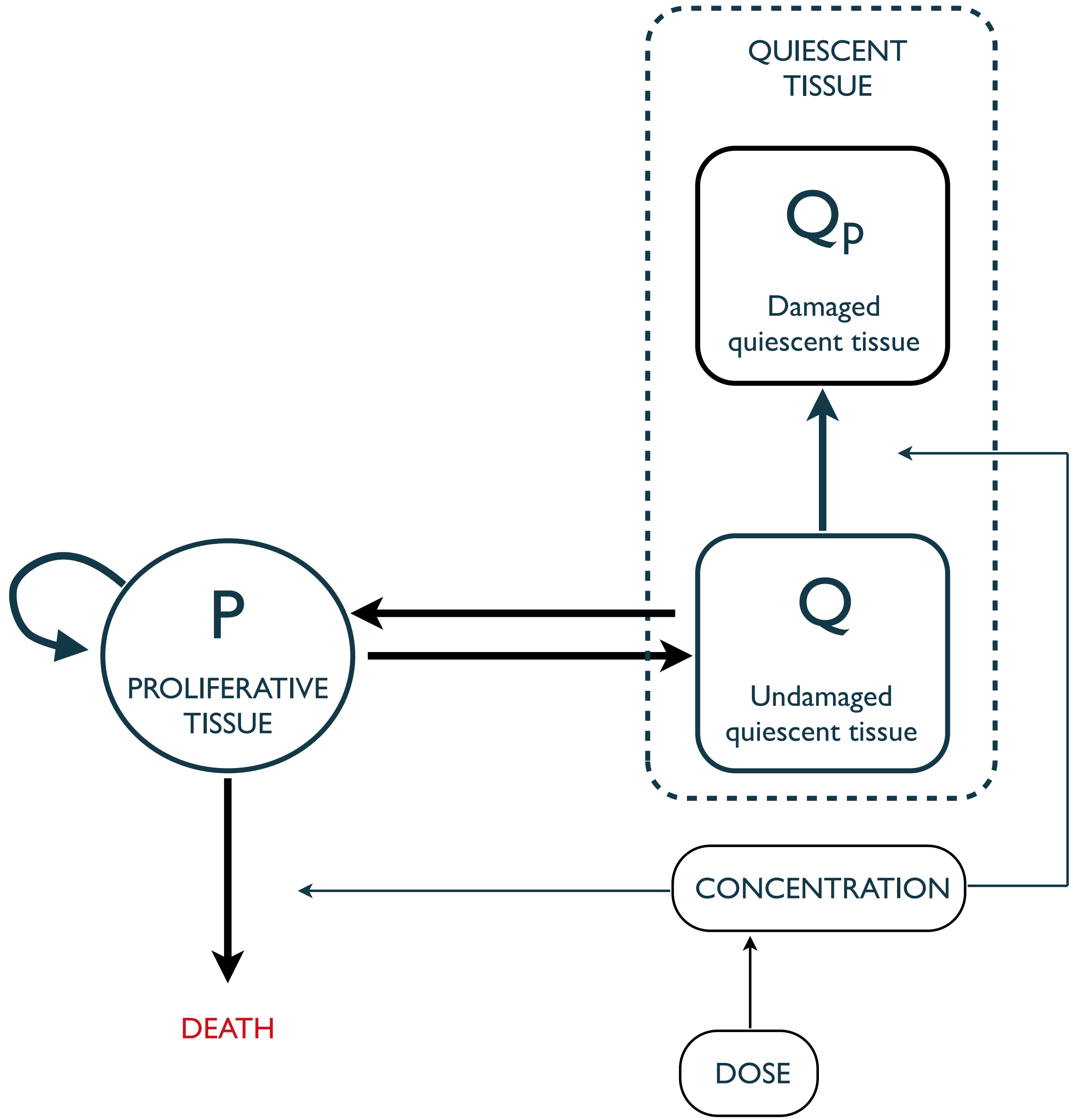
Treatment ends
Treatment starts
Diagnosis
Max. tumor shrinkage
Tumor mean diameter (mm)
Time (months)
F
G
E
H
90
80
70
60
50
40
30
20
10
−100
−80
−60
−40
−20
0
20
40
60

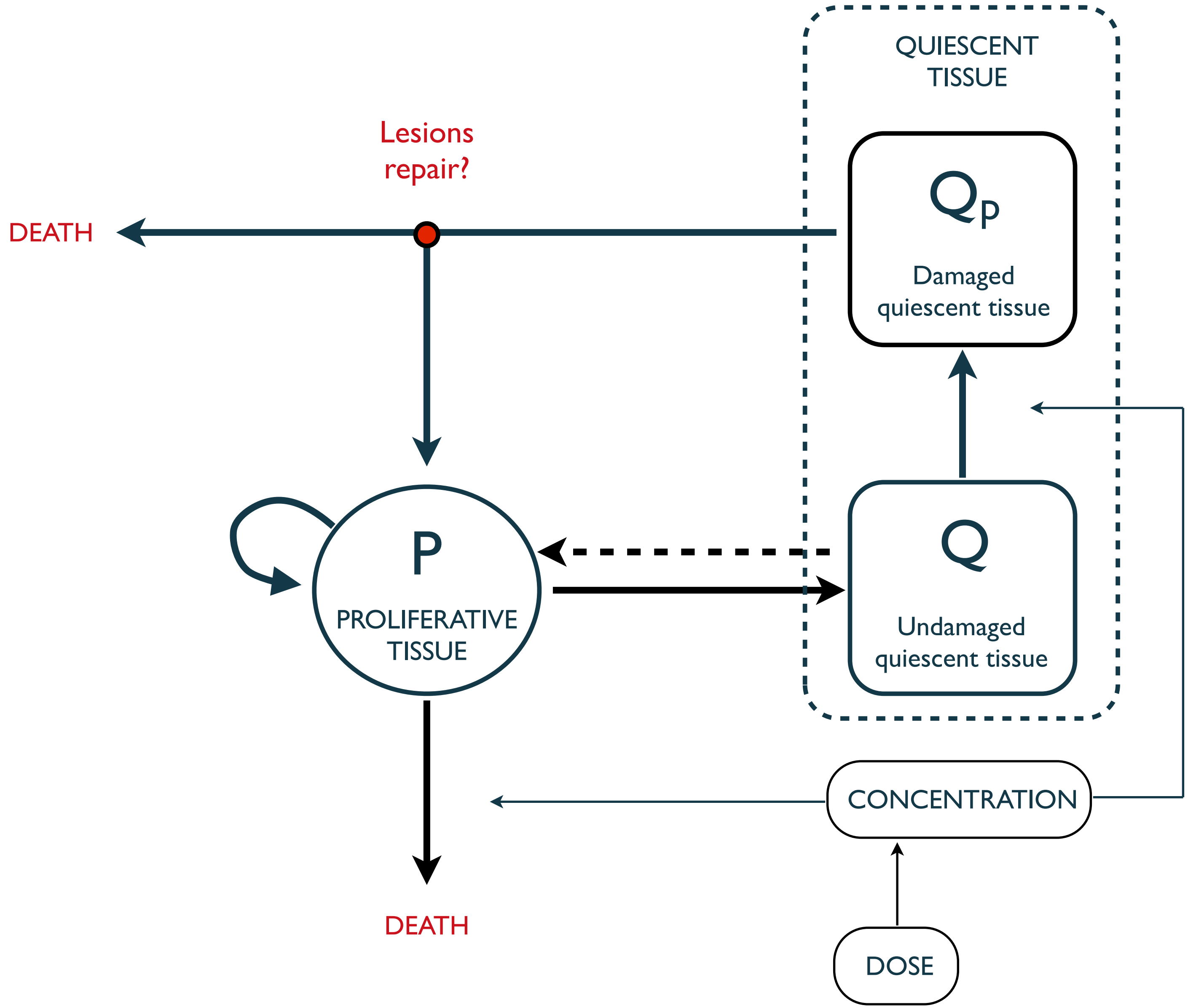
What we know from biology

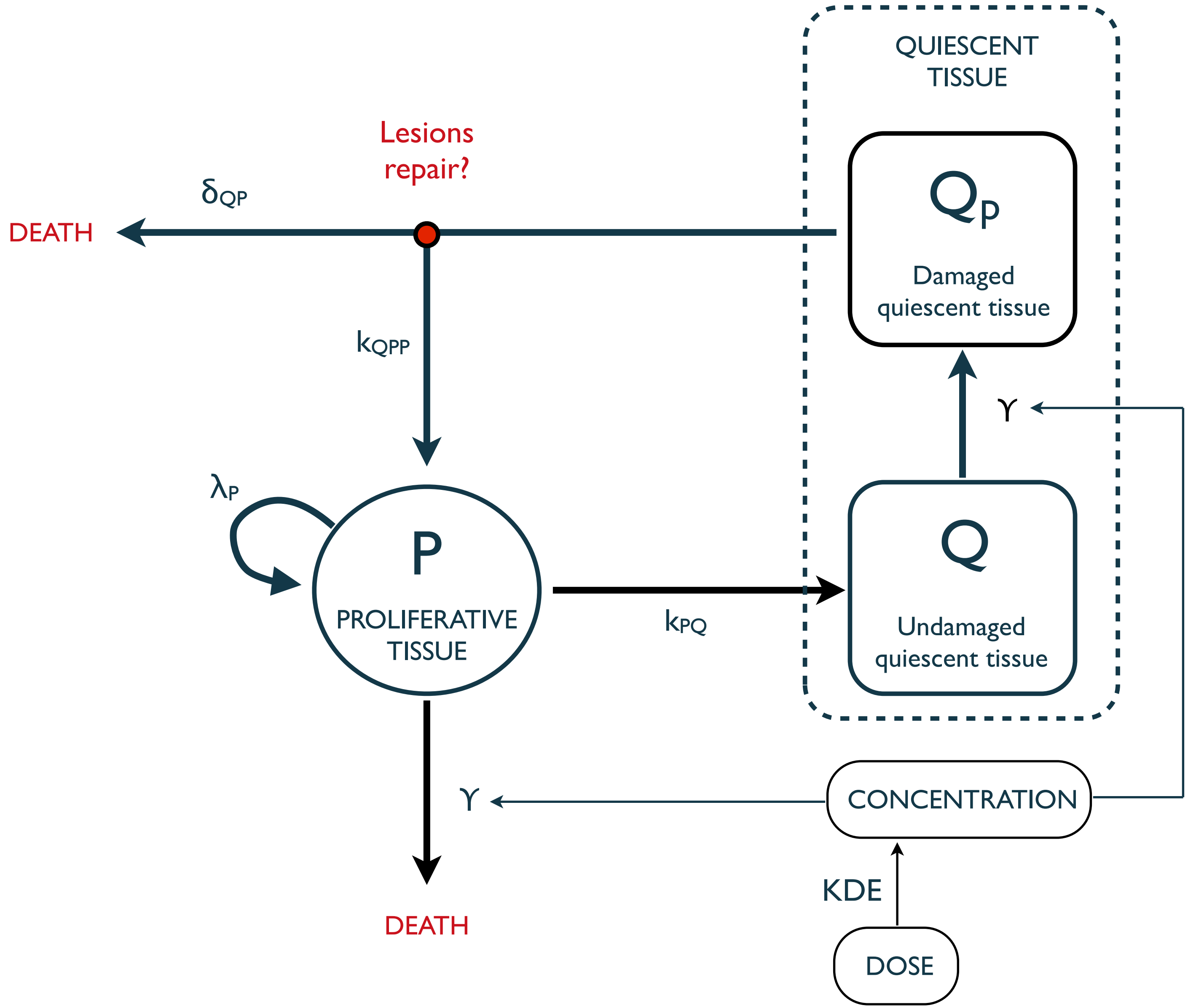
- The tumor is composed by two main types of tissues: proliferative and quiescent
- Drugs induce direct kill of proliferating cells
- Quiescent cells that have sustained DNA damages die when re-entering the cell cycle


P
PROLIFERATIVE
TISSUE
Q
QUIESCENT
TISSUE


P
PROLIFERATIVE TISSUE
Q
QUIESCENT TISSUE
CONCENTRATION
DEATH
DOSE


QUIESCENT
TISSUE
Q_P
Damaged
quiescent tissue
P
PROLIFERATIVE
TISSUE
Q
Undamaged
quiescent tissue
CONCENTRATION
DEATH
DOSE


QUIESCENT
TISSUE
Lesions
repair?
DEATH
Q_P
Damaged
quiescent tissue
P
PROLIFERATIVE
TISSUE
Q
Undamaged
quiescent tissue
CONCENTRATION
DEATH
DOSE


QUIESCENT
TISSUE
Lesions
repair?
δQP
DEATH
Qp
Damaged
quiescent tissue
kQPP
ϒ
λP
P
PROLIFERATIVE
TISSUE
Q
Undamaged
quiescent tissue
kPQ
ϒ
CONCENTRATION
KDE
DOSE
DEATH

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

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

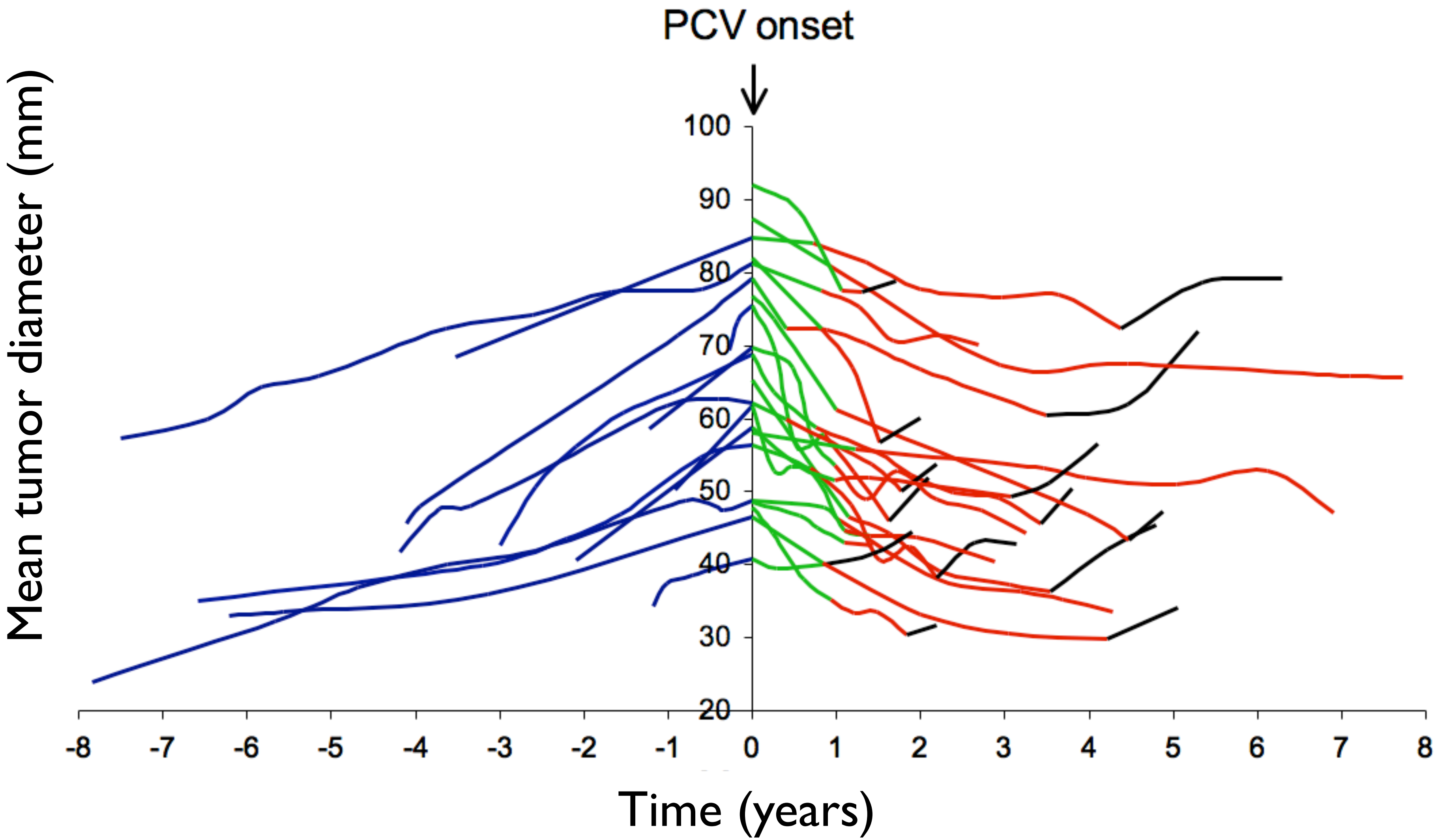
QUIESCENT TISSUE

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

QUIESCENT TISSUE

$$P^\star = P + Q + Q_P$$

TUMOR SIZE


PCV onset
Mean tumor diameter (mm)
100
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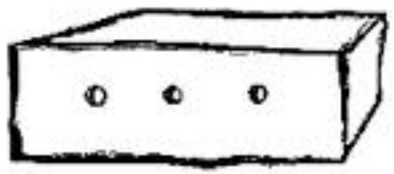
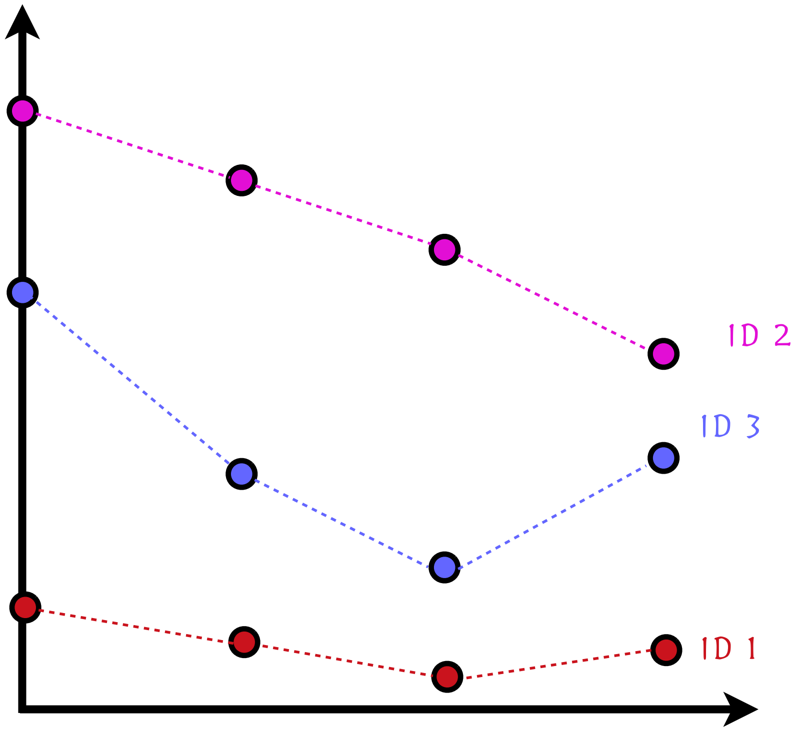
40
30
20
-8
-7
-6
-5
-4
-3
-2
-1
0
1
2
3
4
5
6
7
8
Time (years)

If you, please, draw me a sheep



Mixed-effect models



$$y_{ij} = f\left(t_{ij}, \boldsymbol{\psi_i}\right) + e_{ij} \quad 1 \leq i \leq N \quad 1 \leq j \leq n_i$$

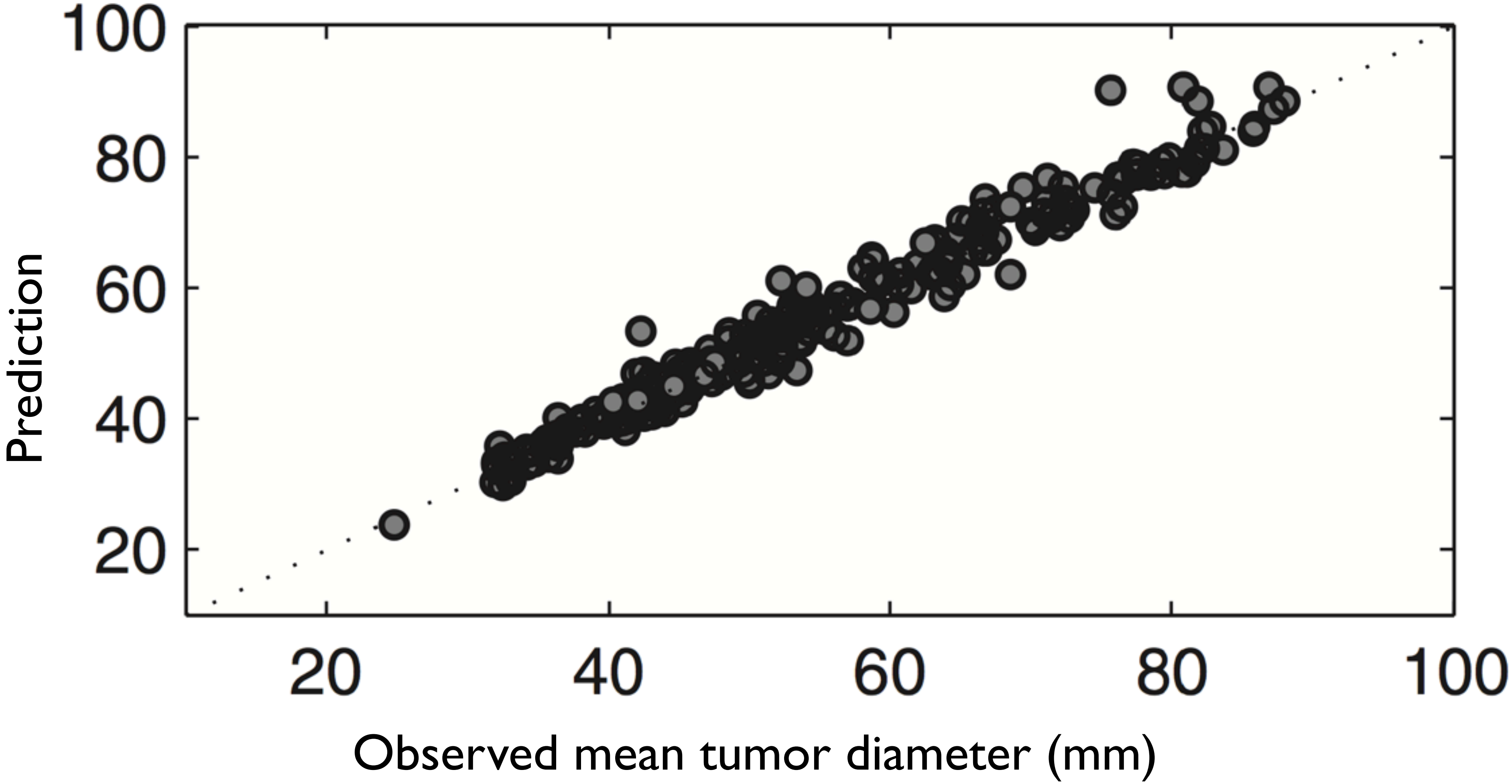
$$\boldsymbol{\psi_i} \sim \mathcal{N}\left(\theta_m, \theta_\sigma\right) \qquad e_{ij} \sim \mathcal{N}\left(0, a^2\right)$$

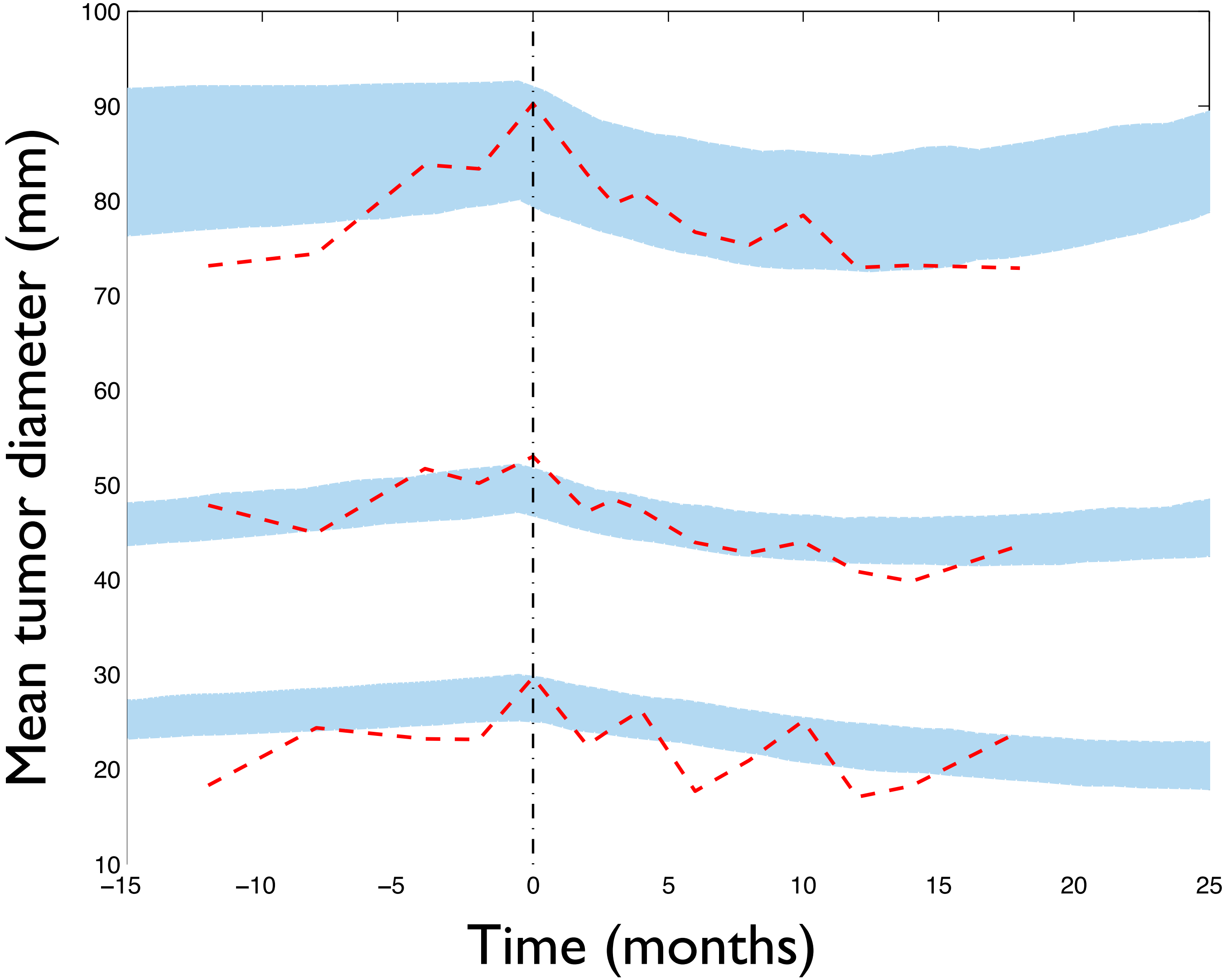
$$p\left(\psi_i\right) = \frac{1}{\sqrt{2\pi}\sqrt{det(\theta_\sigma)}} e^{-\frac{1}{2}\left(\psi_i - \theta_m\right)' \theta_\sigma^{-1}\left(\psi_i - \theta_m\right)}$$

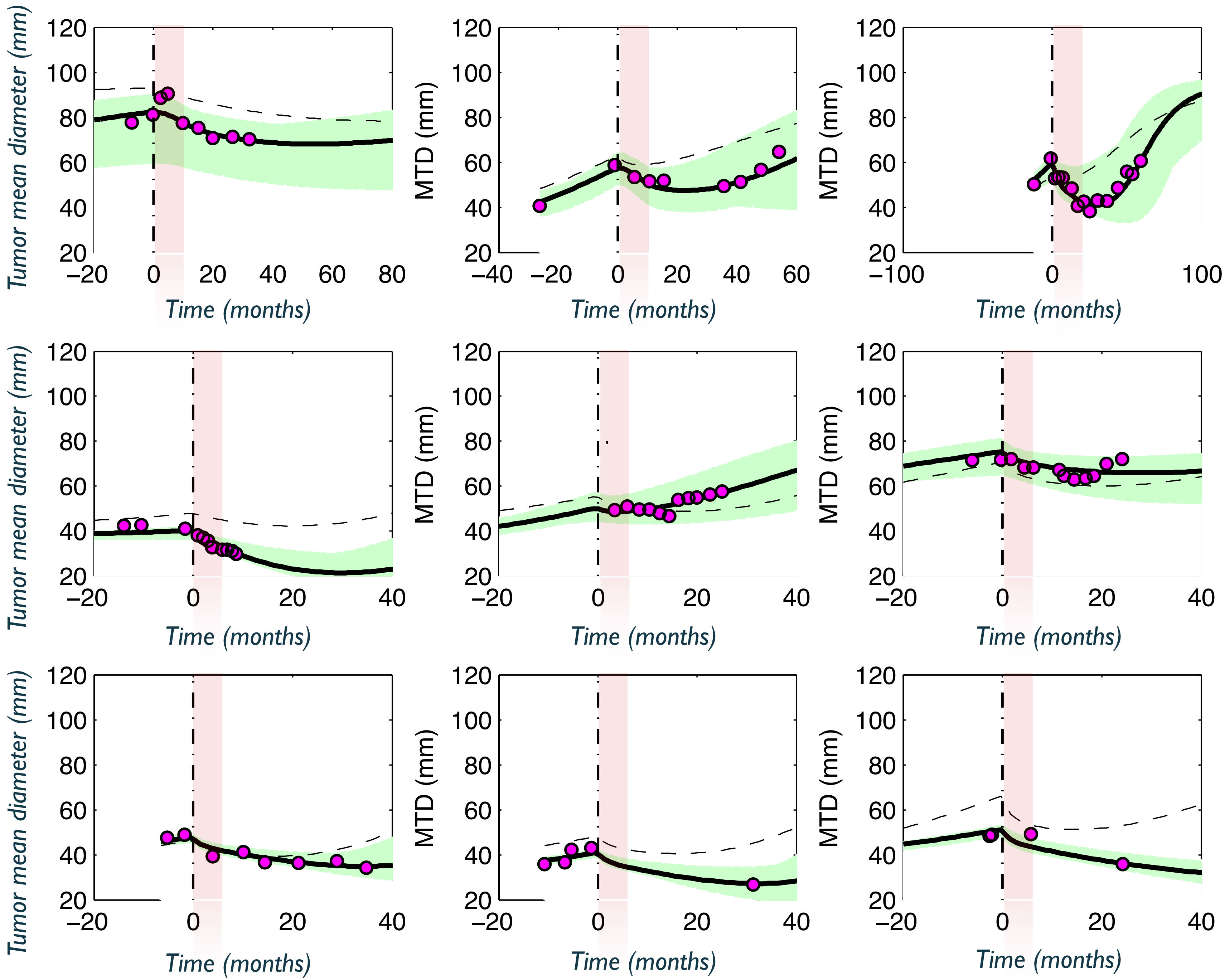
$$p_{y_i|\psi_i} = \prod_{j=1}^{n_i} p_{y_{ij}|\psi_i}$$

$$\Downarrow$$

$$p\left(y_i, \psi_i\right) = p\left(y_i \mid \psi_i\right) \times p\left(\psi_i\right)$$


100
80
60
40
20
Prediction
20
40
60
80
100
Observed mean tumor diameter (mm)


Mean tumor diameter (mm)
Time (months)
100
90
80
70
60
50
40
30
20
10
–15
–10
–5
0
5
10
15
20
25


Tumor mean diameter (mm)
MTD (mm)
Time (months)
120
100
80
60
40
20
–20
0
20
40
60
80
–40
100
–100

Conclusions

- Importance of repeated measurements in oncology
- ODE model to correctly reproduce tumor size dynamic in brain tumor patients
- Mixed-effect regression techniques for population analysis
- Model simulation to suggest clinicians with new therapeutic hypothesis

Ribba et al. *A tumor growth inhibition model for low-grade glioma treated with chemotherapy or radiotherapy*. Clinical Cancer Research, 2012