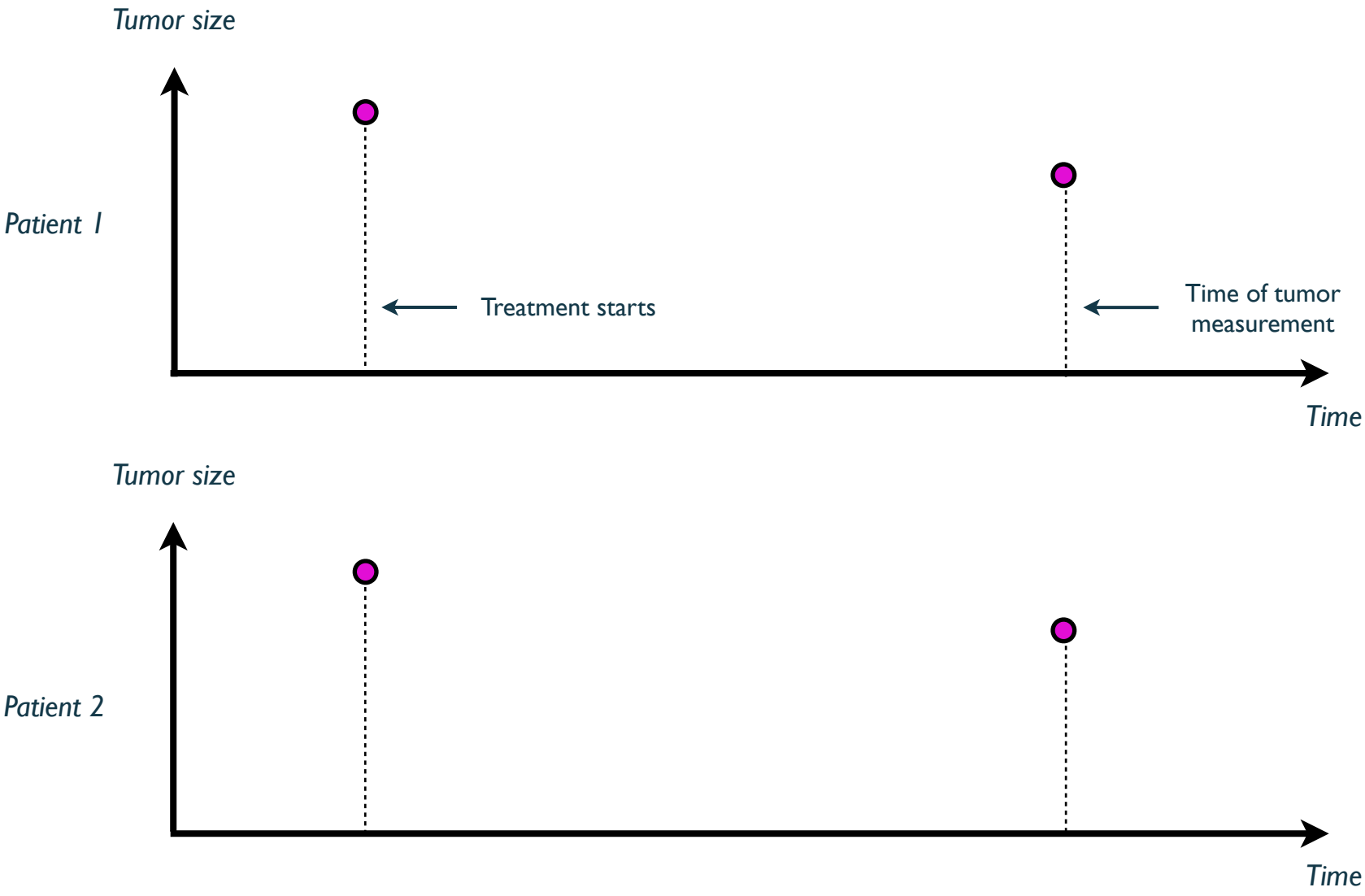
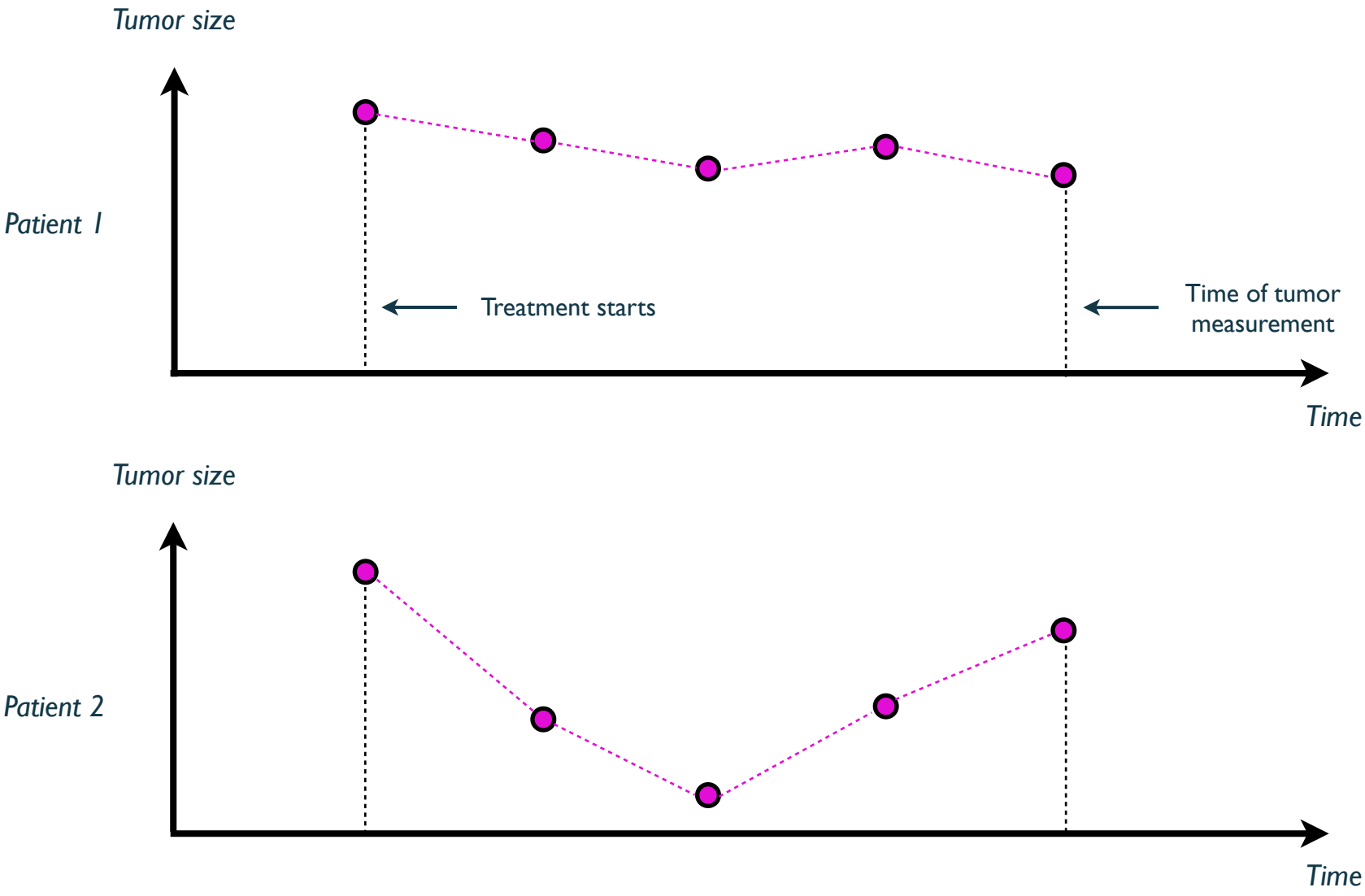
Modeling of efficacy data in clinical oncology

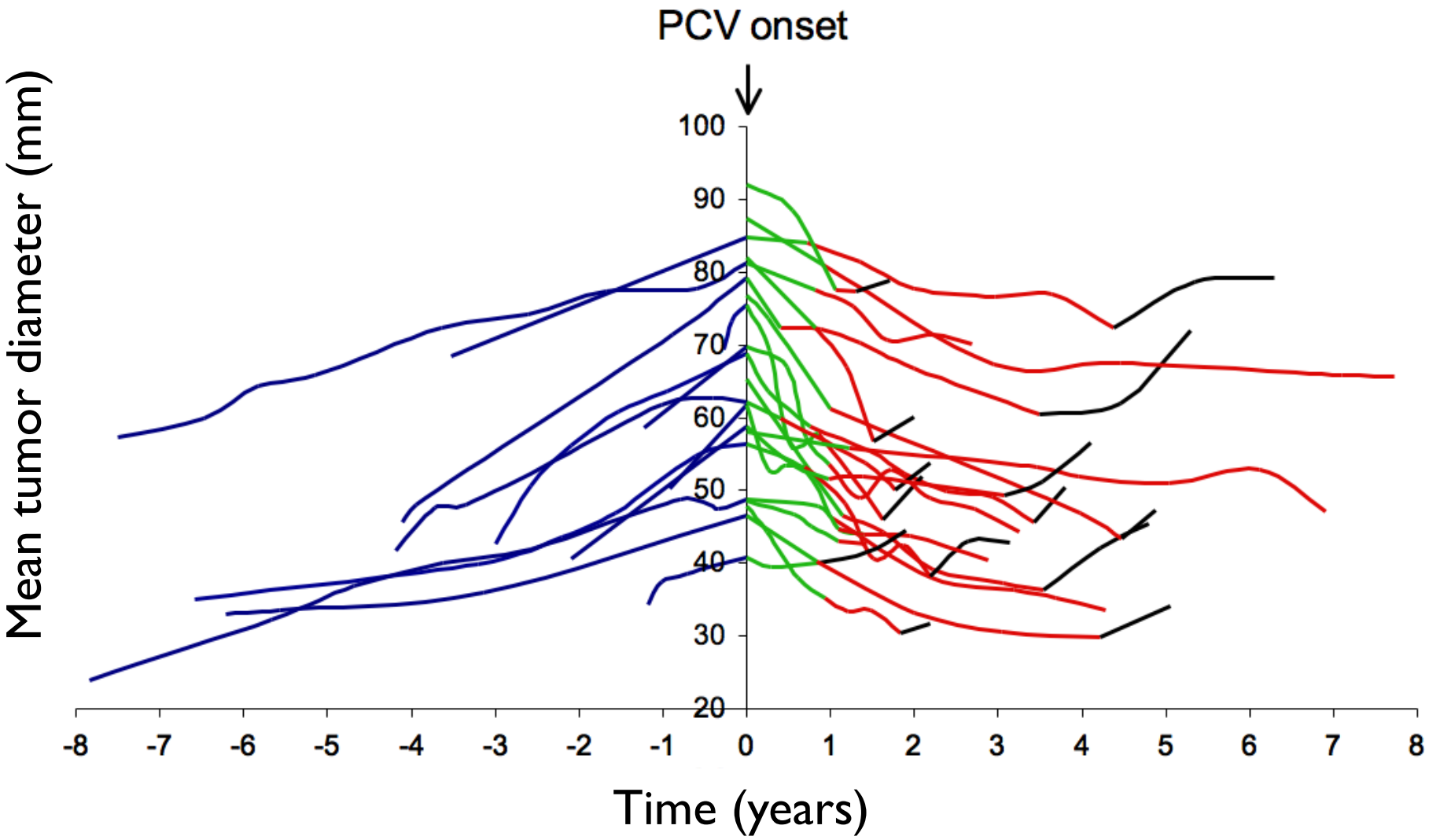
Benjamin Ribba

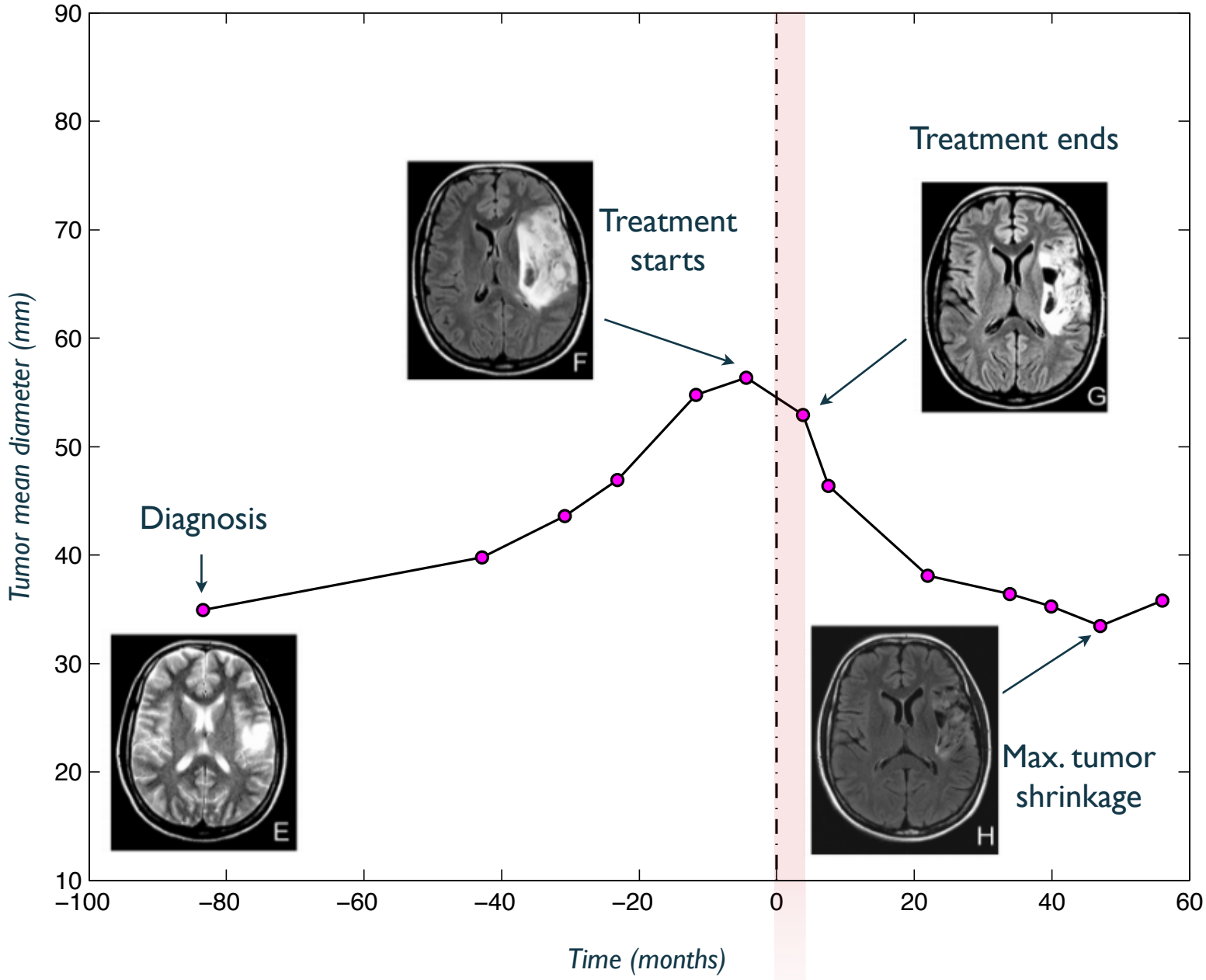

Le Petit Prince


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

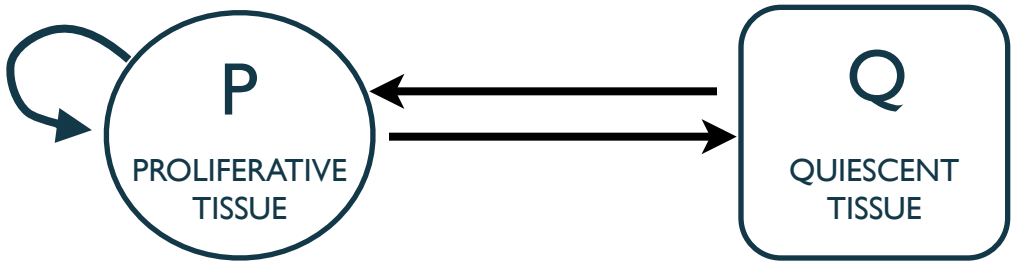
Models and tools to analyze such type of data?

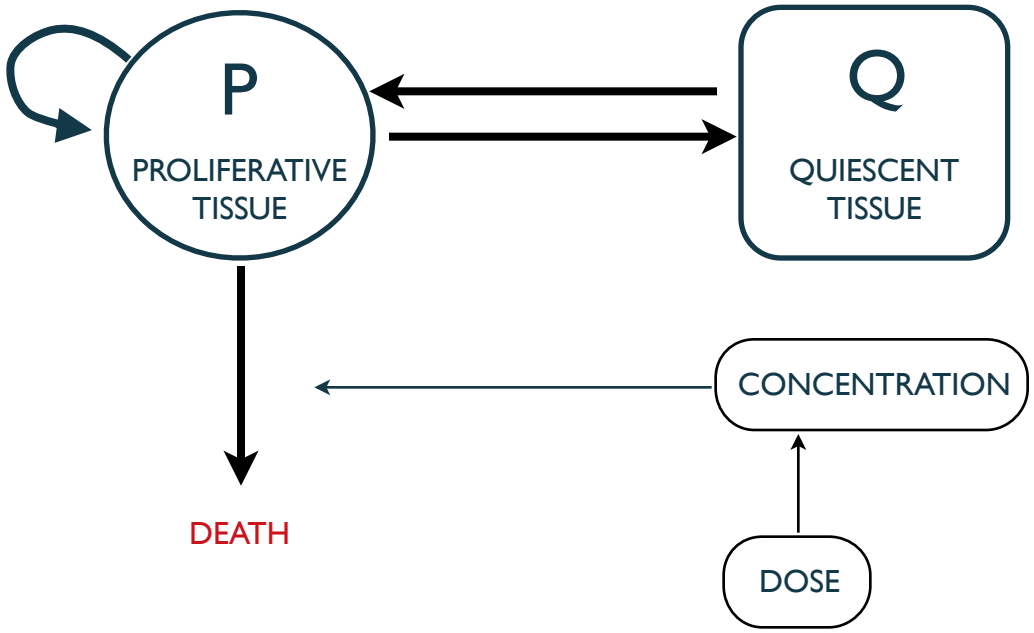

PCV onset
Mean tumor diameter (mm)
100
90
80
70
60
50
40
30
20
-8
-7
-6
-5
-4
-3
-2
-1
0
1
2
3
4
5
6
7
8
Time (years)

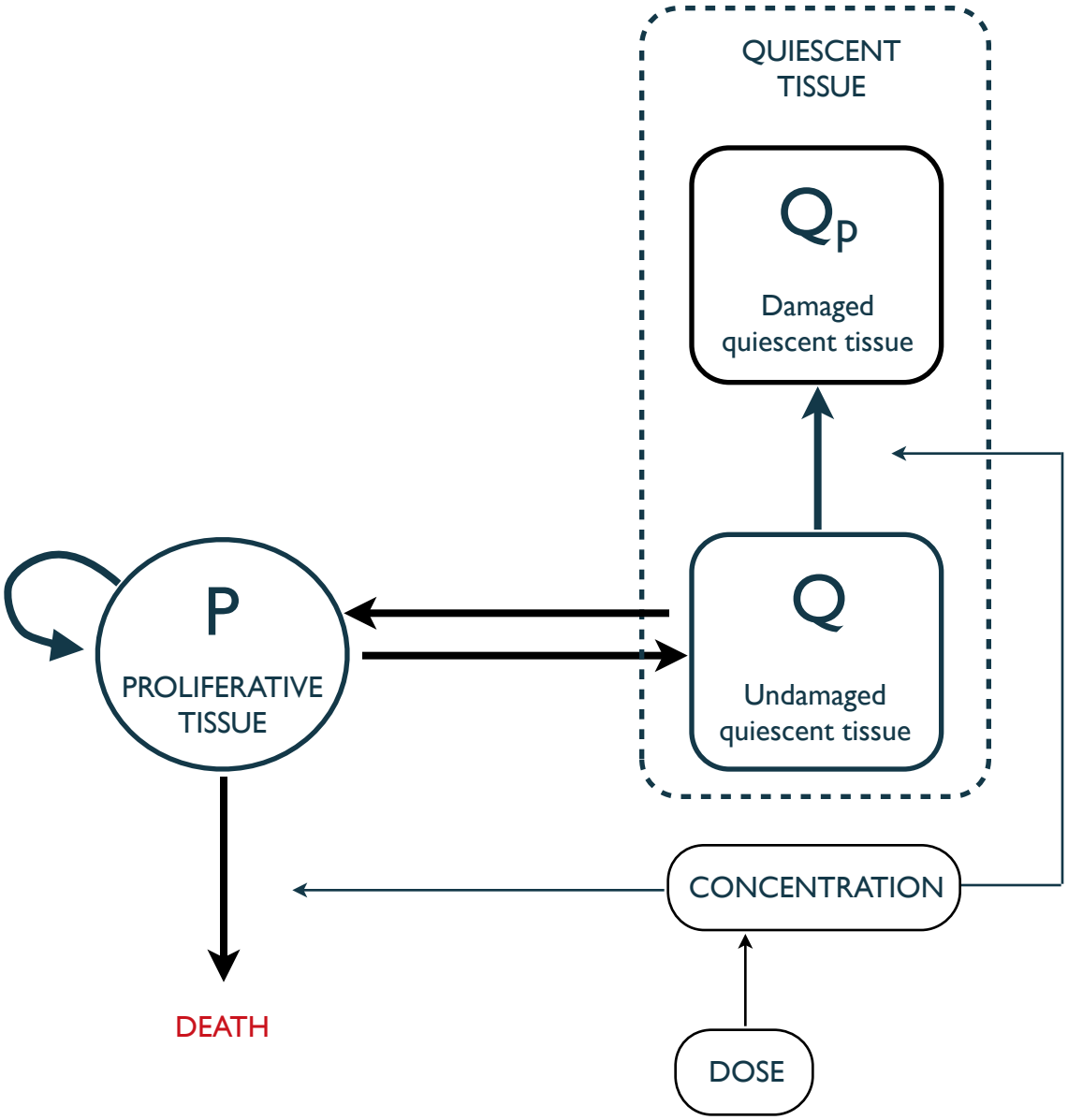

Tumor mean diameter (mm)
90
80
70
60
50
40
30
20
10
−100
−80
−60
−40
−20
0
20
40
60
Time (months)
Diagnosis
Treatment starts
Treatment ends
Max. tumor shrinkage
E
F
G
H

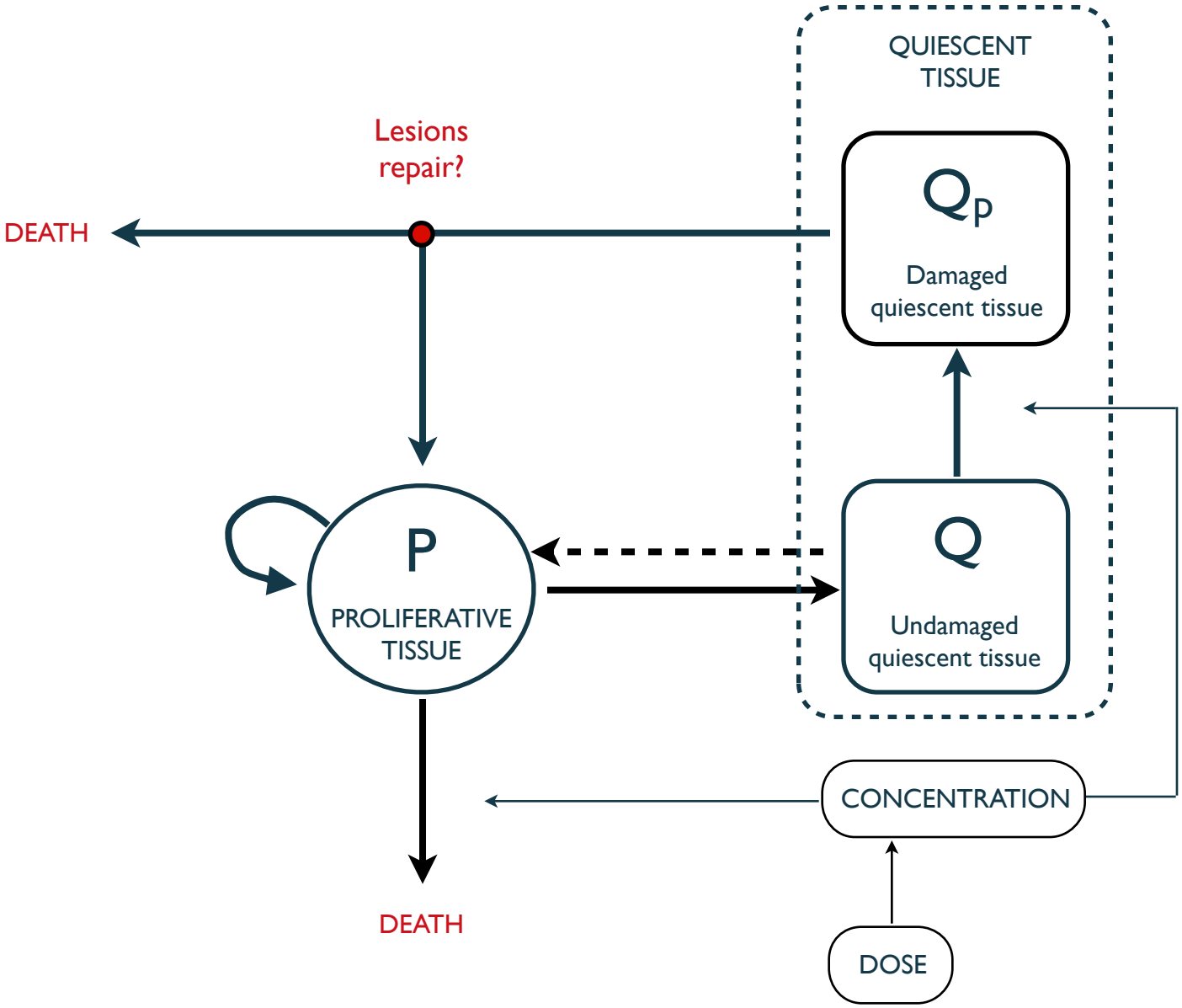
What we know from biology

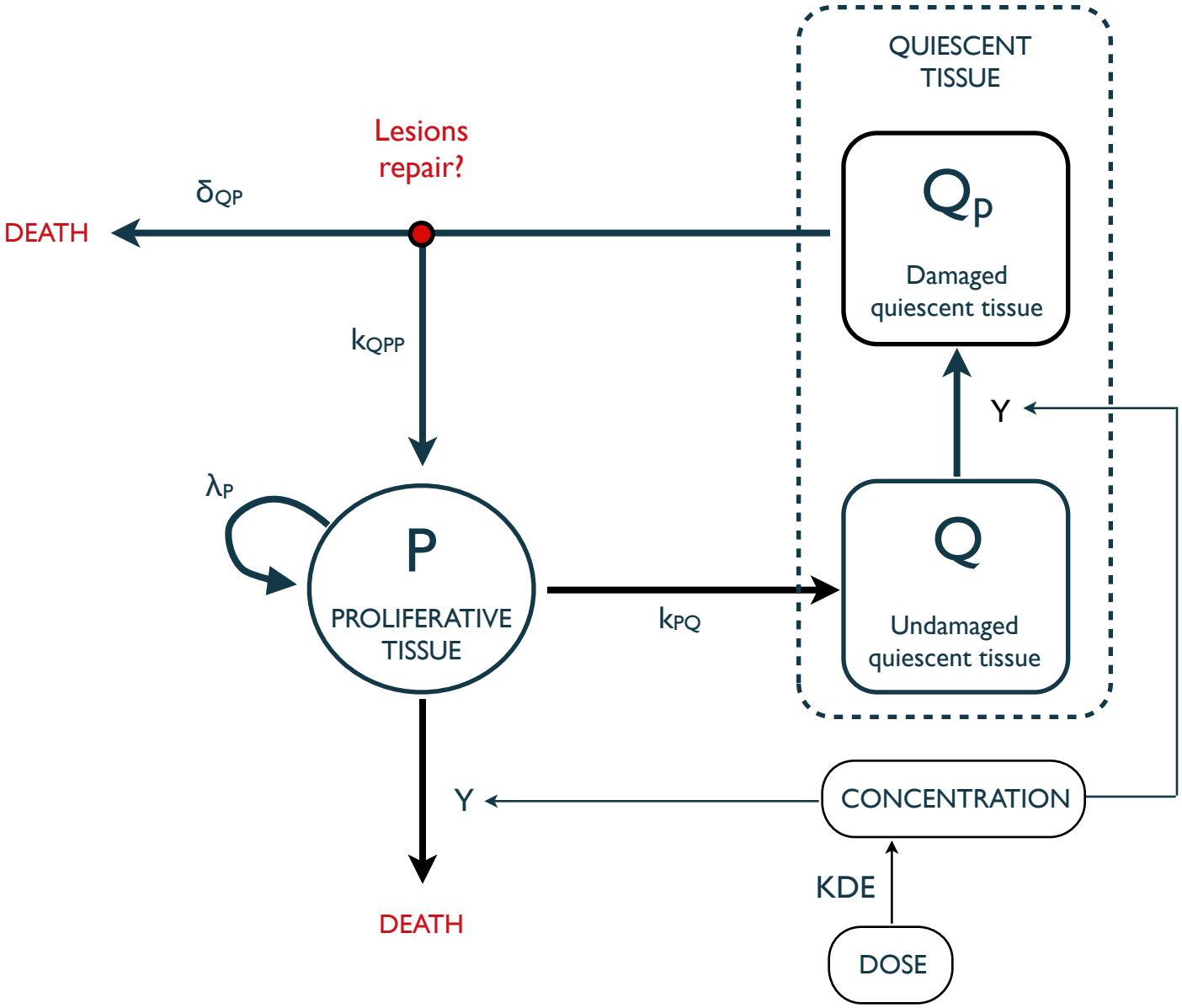
- The tumor is composed by two main types of tissues: proliferative and quiescent
- Drugs induce direct kill of proliferating cells
- Quiescent cells that have sustained DNA damages die when re-entering the cell cycle


P
PROLIFERATIVE
TISSUE
Q
QUIESCENT
TISSUE


P
PROLIFERATIVE TISSUE
Q
QUIESCENT TISSUE
CONCENTRATION
DEATH
DOSE


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


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


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

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

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

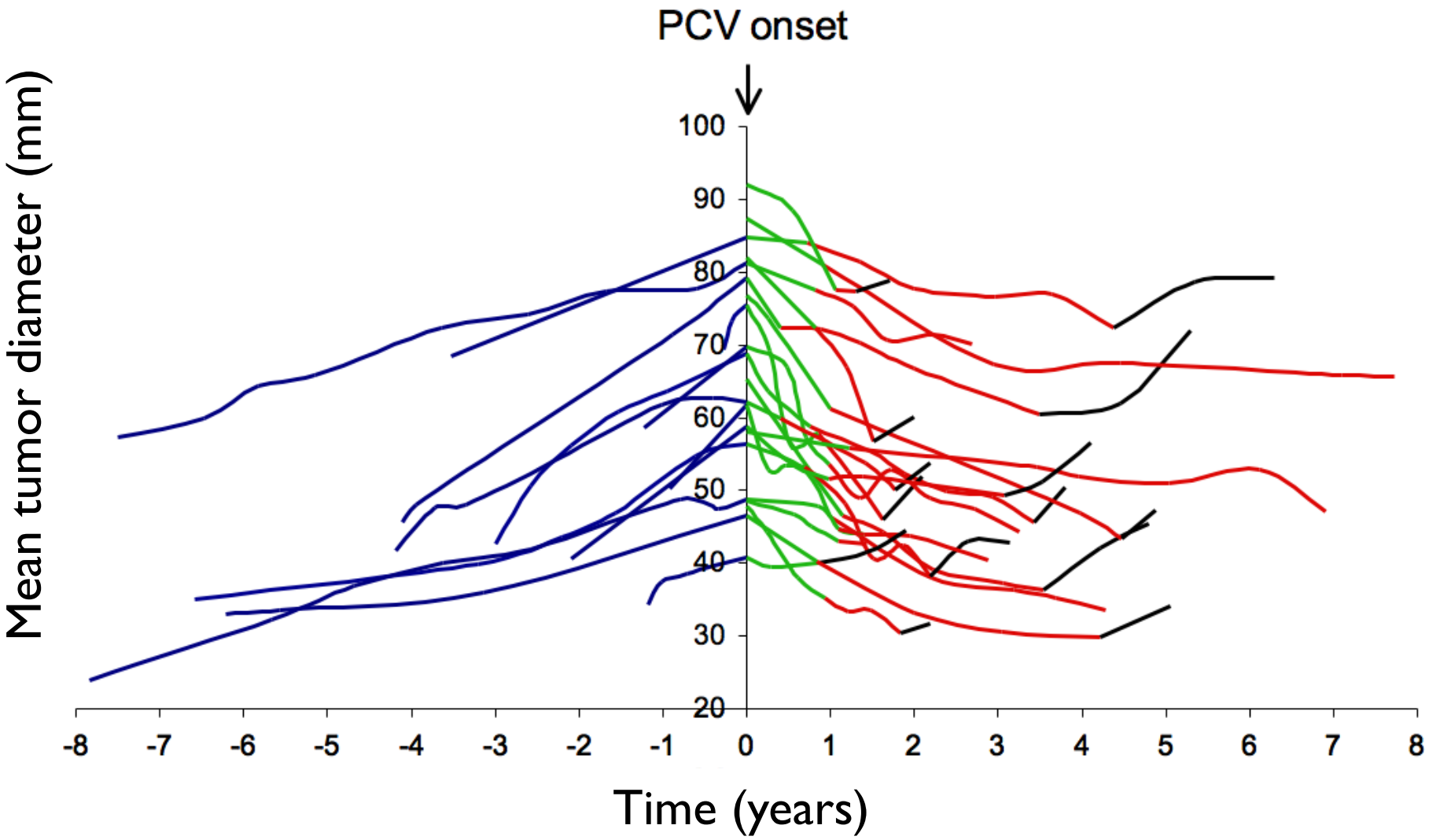
Quiescent tissue

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

Quiescent tissue

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

Tumor size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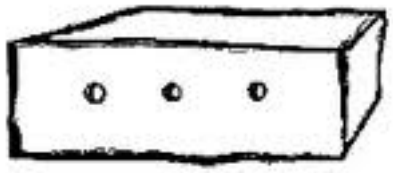
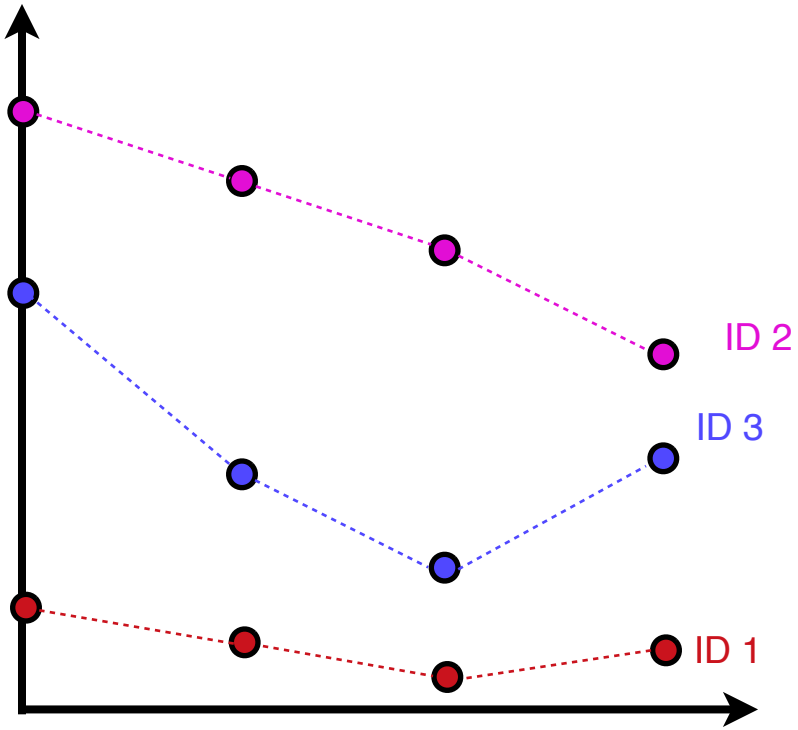
-7
-6
-5
-4
-3
-2
-1
0
1
2
3
4
5
6
7
8
Time (years)


Le Petit Prince

If you, please, draw me a sheep



Mixed-effect models



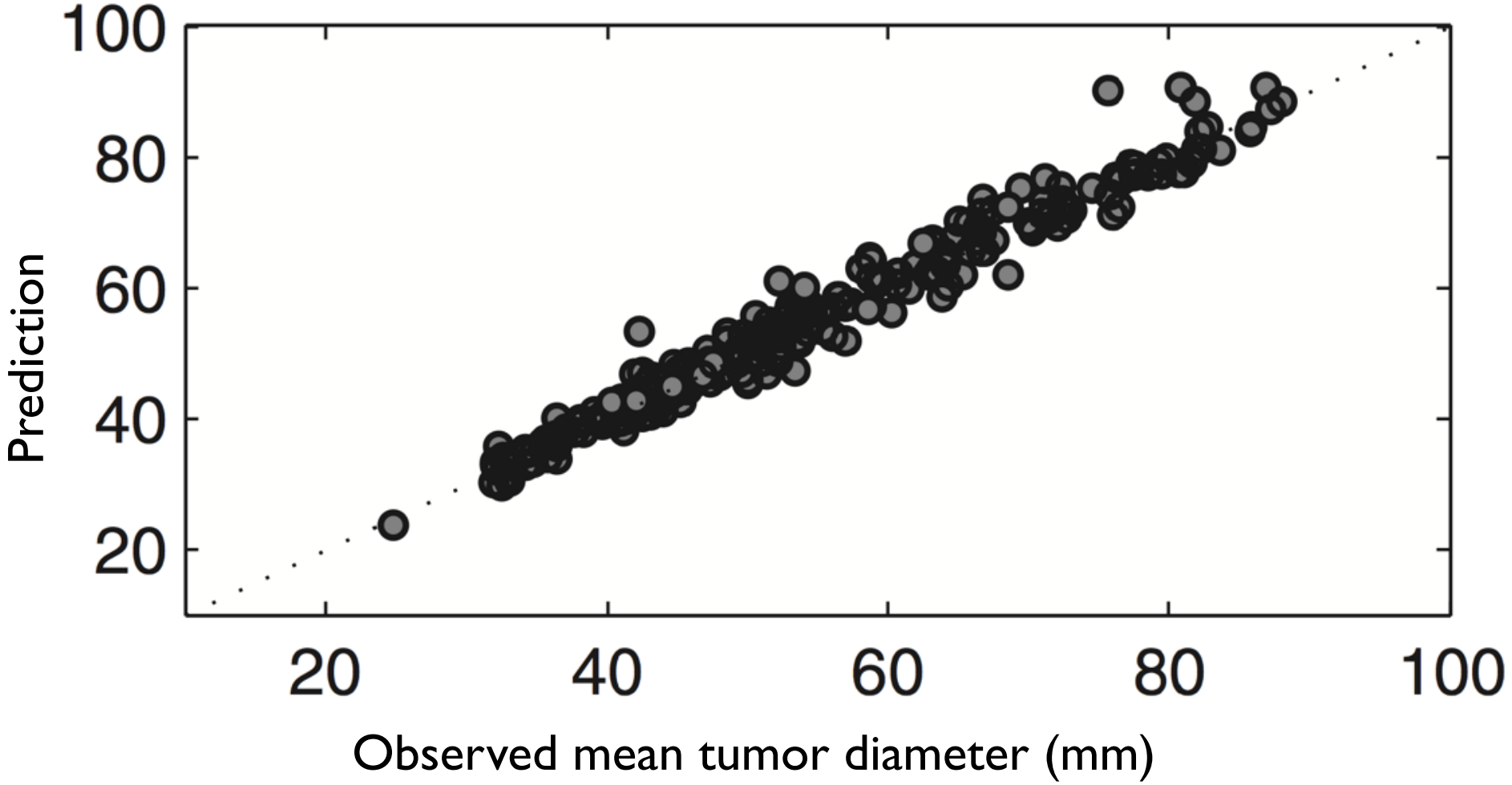
$$y_{ij} = f\left(t_{ij}, \boldsymbol{\psi_i}\right) + e_{ij} \quad 1 \leq i \leq N \quad 1 \leq j \leq n_i$$

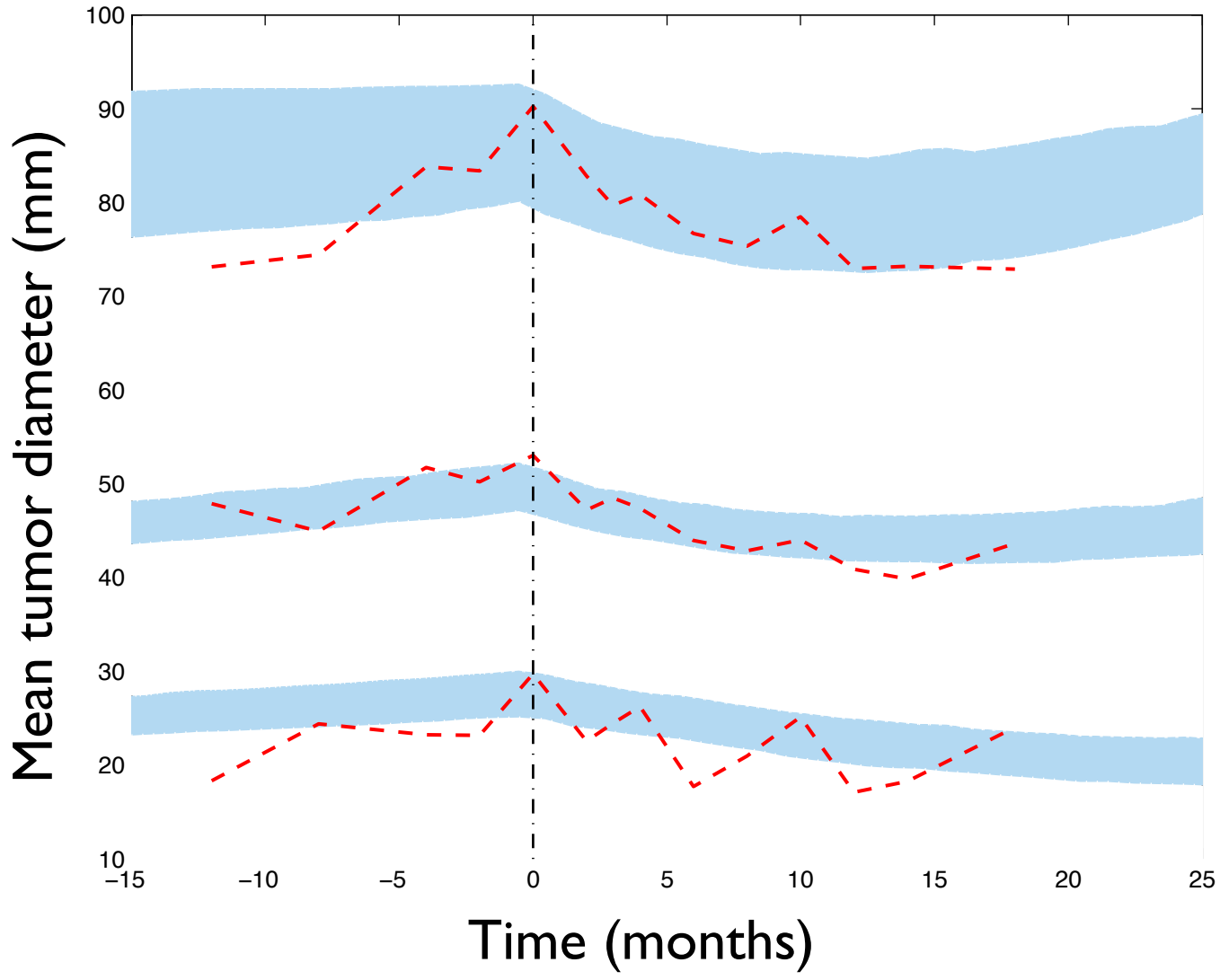
$$\boldsymbol{\psi_i} \sim \mathcal{N}\left(\theta_m, \theta_\sigma\right) \qquad e_{ij} \sim \mathcal{N}\left(0, a^2\right)$$

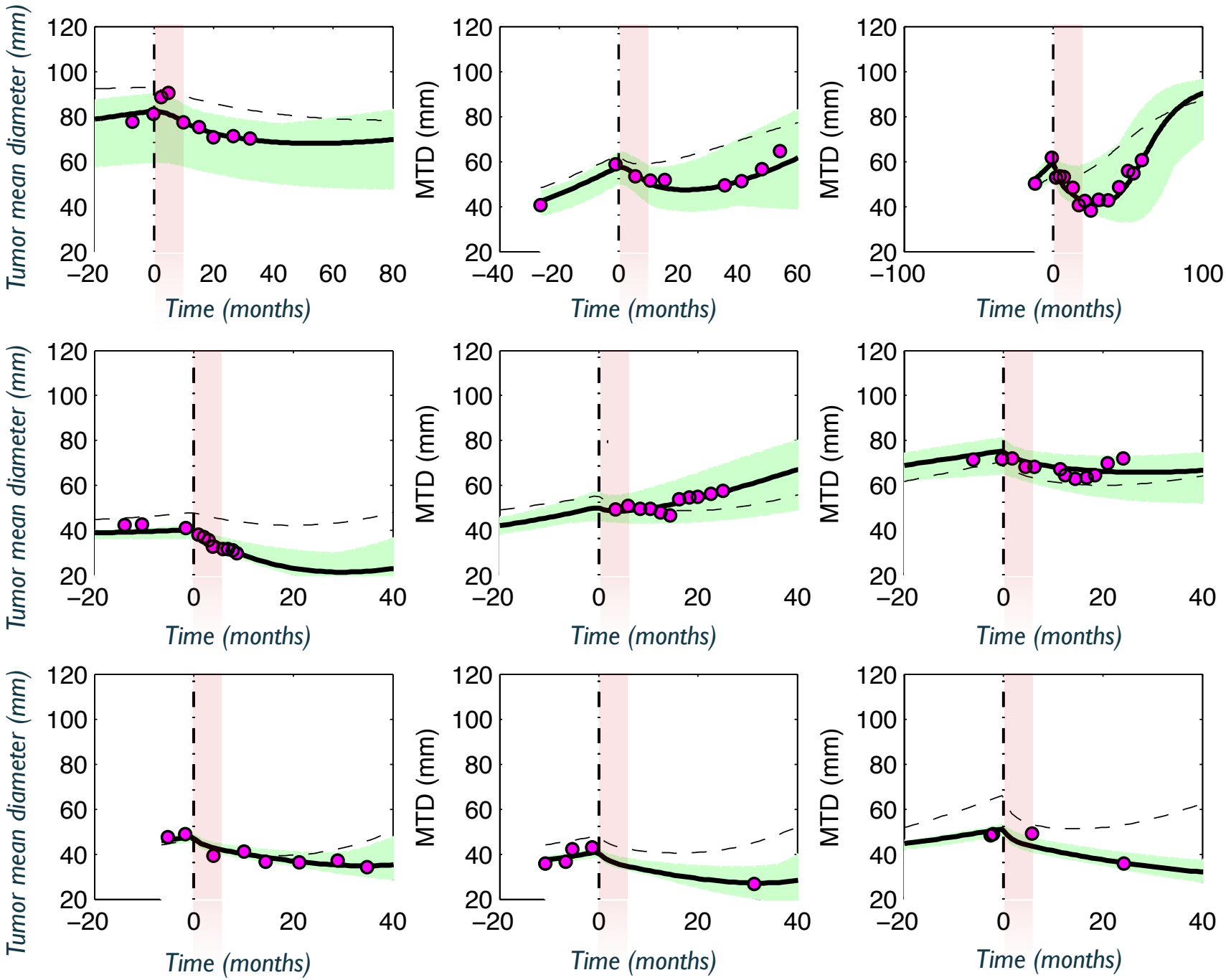
$$p\left(\psi_i\right) = \frac{1}{\sqrt{2\pi}\sqrt{det(\theta_\sigma)}} e^{-\frac{1}{2}(\psi_i - \theta_m)' \theta_\sigma^{-1} (\psi_i - \theta_m)}$$

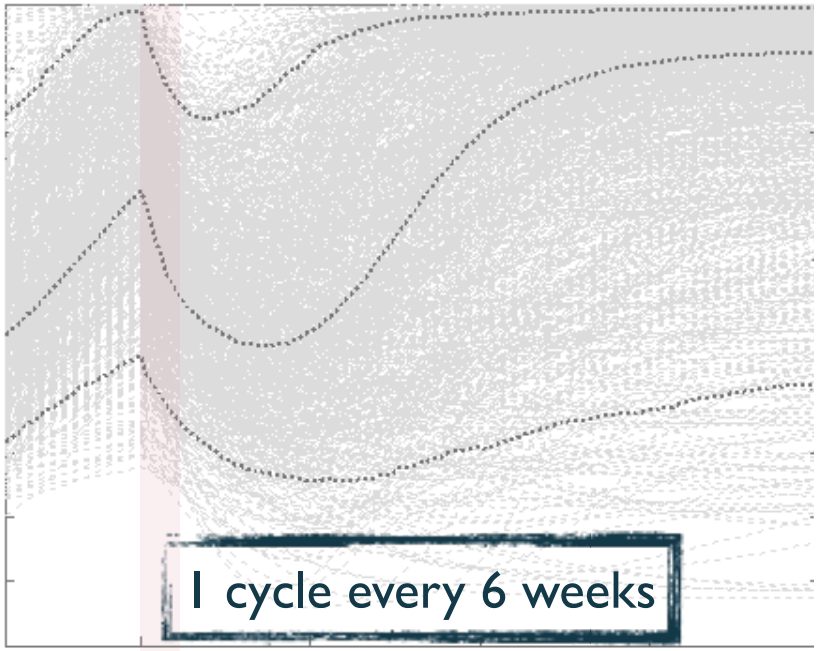
$$p_{y_i|\psi_i} = \prod_{j=1}^{n_i} p_{y_{ij}|\psi_i}$$

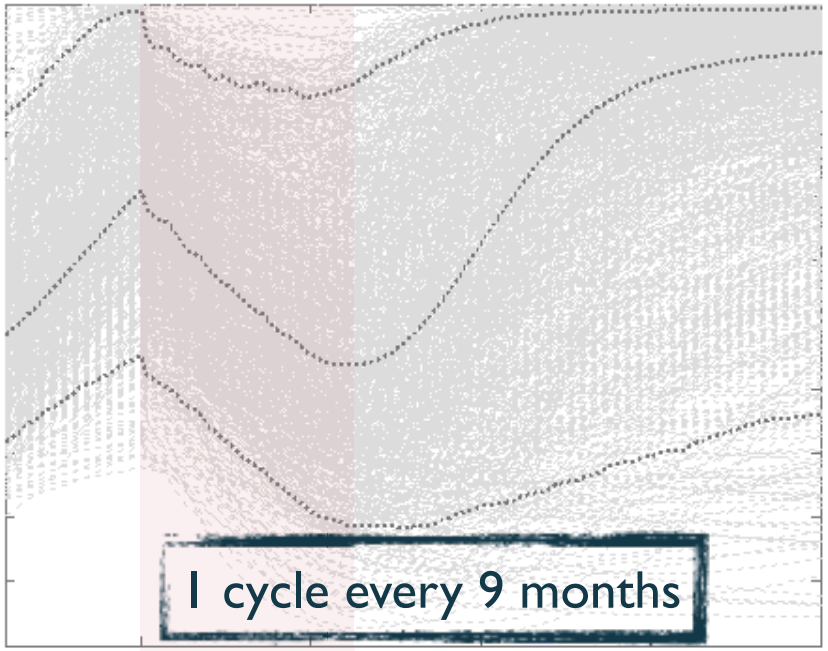
$$p\left(y_i, \psi_i\right) = p\left(y_i \mid \psi_i\right) \times p\left(\psi_i\right)$$


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


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


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





MTD shrink	-34 %
Prolonged response	36 months

MTD shrink	-40 %
Prolonged response	64 months

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