

- ✓ We propose a model to describe tumor size dynamics and time-to-progression in patients with low-grade glioma treated with temozolomide.
- ✓ We analyze mean tumor diameters in a population approach using data from 120 patients treated with temozolomide. 60 patients were used to estimate parameters and we performed external validation with the other 60 patients. The outcomes of this analysis are then used to predict time-to-progression considered as a long-term clinical outcome.
- ✓ The TGI model with a resistance term and biomolecular covariates well describes individual tumor dynamics. Natural tumor growth rate and relative change in tumor size at 8 weeks were found as best predictors for the time-to-progression.

Context

- ✓ Modeling a tumor's dynamic response to antitumor treatment is a promising approach towards predicting long term outcomes such as time-to-progression and optimizing individual therapeutic protocol.
- ✓ Low-grade gliomas (LGGs) are progressive brain tumors characterized by slow and continuous growth preceding anaplastic transformation.
- ✓ LGGs remain incurable. Currently most of LGGs are treated with temozolomide (TMZ) which is a chemotherapy treatment.

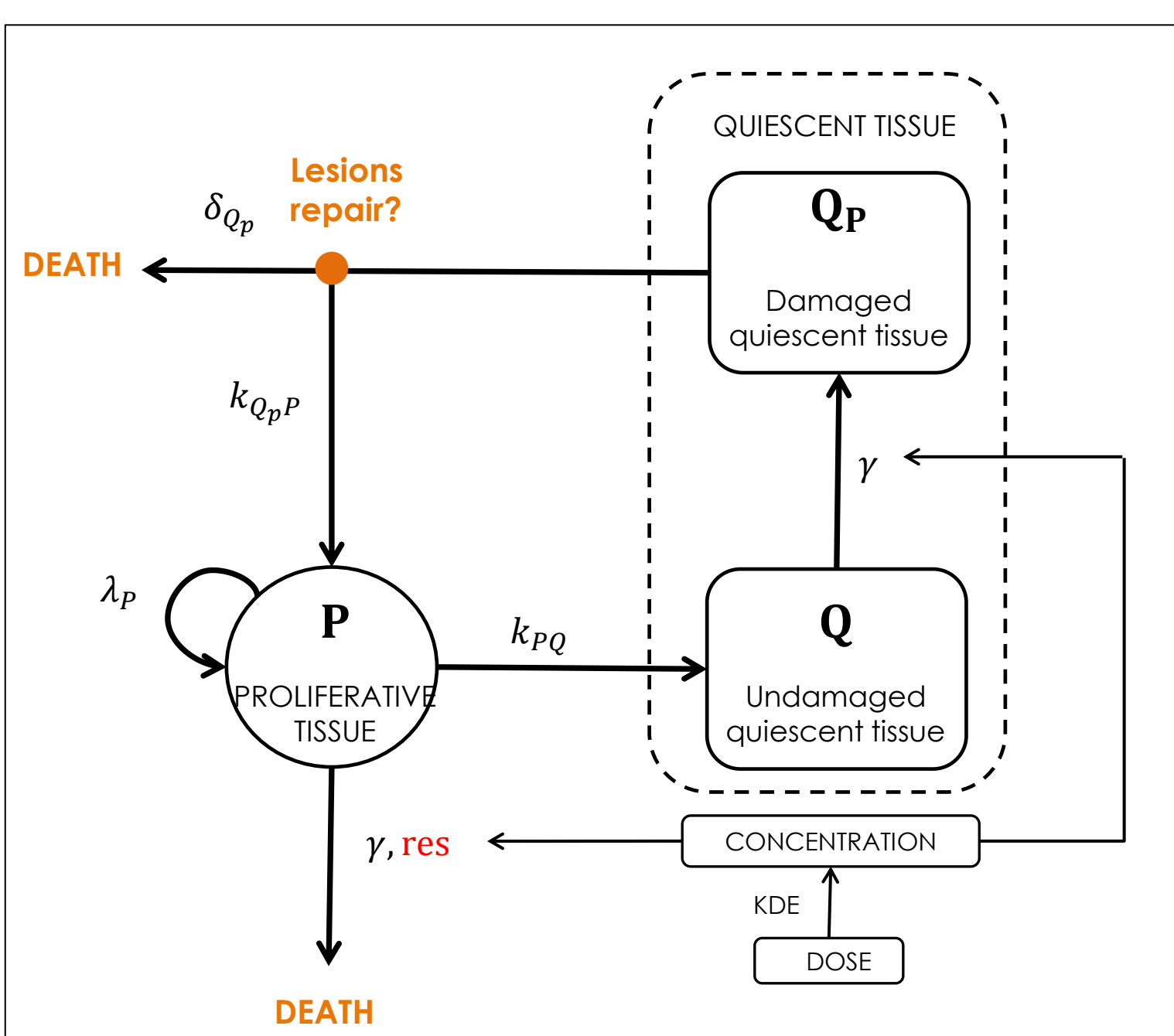
Tumor dynamic modeling

Data collection

- ✓ In our study, tumor size measurements were expressed as mean tumor diameters (MTDs) in mm and were estimated manually from MRI images.
- ✓ The patients received between 2 and 30 cycles. TMZ was administered from days 1 through 5, repeated every month.
- ✓ Data for **120 patients**, including time-to-progression, were available. **Tumor regrowth during the treatment (resistance) was observed in 45 patients (38%).**

Tumor Growth Inhibition model

- ✓ In the model, the tumor is composed by proliferative (P) and non-proliferative quiescent tissue (Q), expressed in millimeters.
- ✓ A resistance term is added on the proliferative compartment to account for tumor size increase during treatment.



$$\begin{aligned}\frac{dC}{dt} &= -KDE \times C \\ \frac{dP}{dt} &= \lambda_P \times P \left(1 - \frac{P^*}{K}\right) + k_{QP} \times Q_p - k_{PQ} \times P - \gamma e^{-res.t} \times C \times KDE \times P \\ \frac{dQ}{dt} &= k_{PQ} \times P - \gamma \times C \times KDE \times P \\ \frac{dQ_p}{dt} &= \gamma \times C \times KDE \times Q - k_{QP} \times Q_p - \delta_{QP} \times Q_p \\ P^* &= P + Q + Q_p\end{aligned}$$

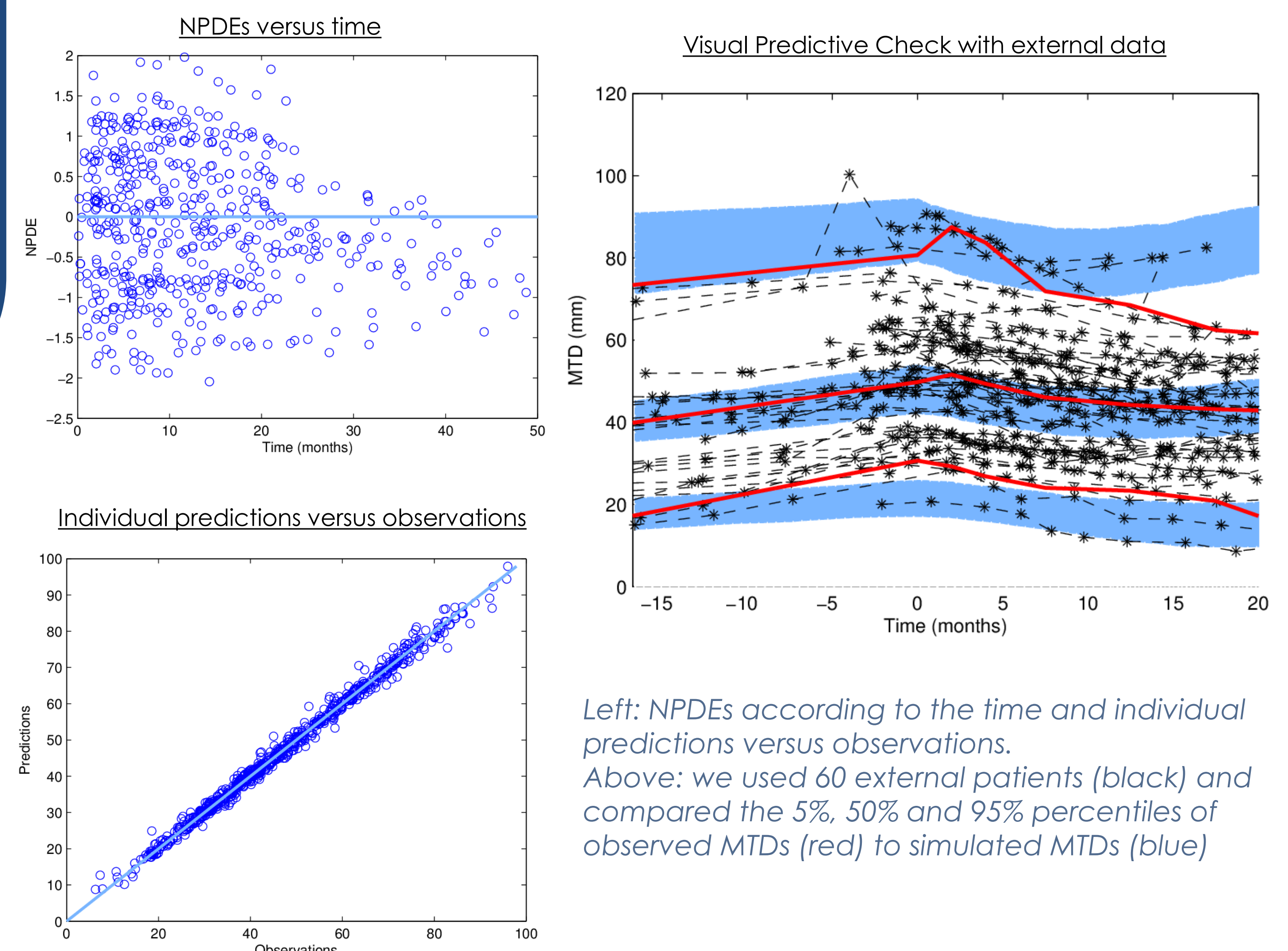
Parameter estimations

- ✓ The model contains 9 parameters to estimate including 2 initial conditions: $P_0 = P(t=0)$ and $Q_0 = Q(t=0)$.

Basic doubling time for the proliferative tissue	9 months
Ratio proliferation rate versus quiescent rate	3
Ratio death rate versus resistance for proliferative tissue	2.6

Estimations of meaningful constants derived from the model parameters

Model evaluation

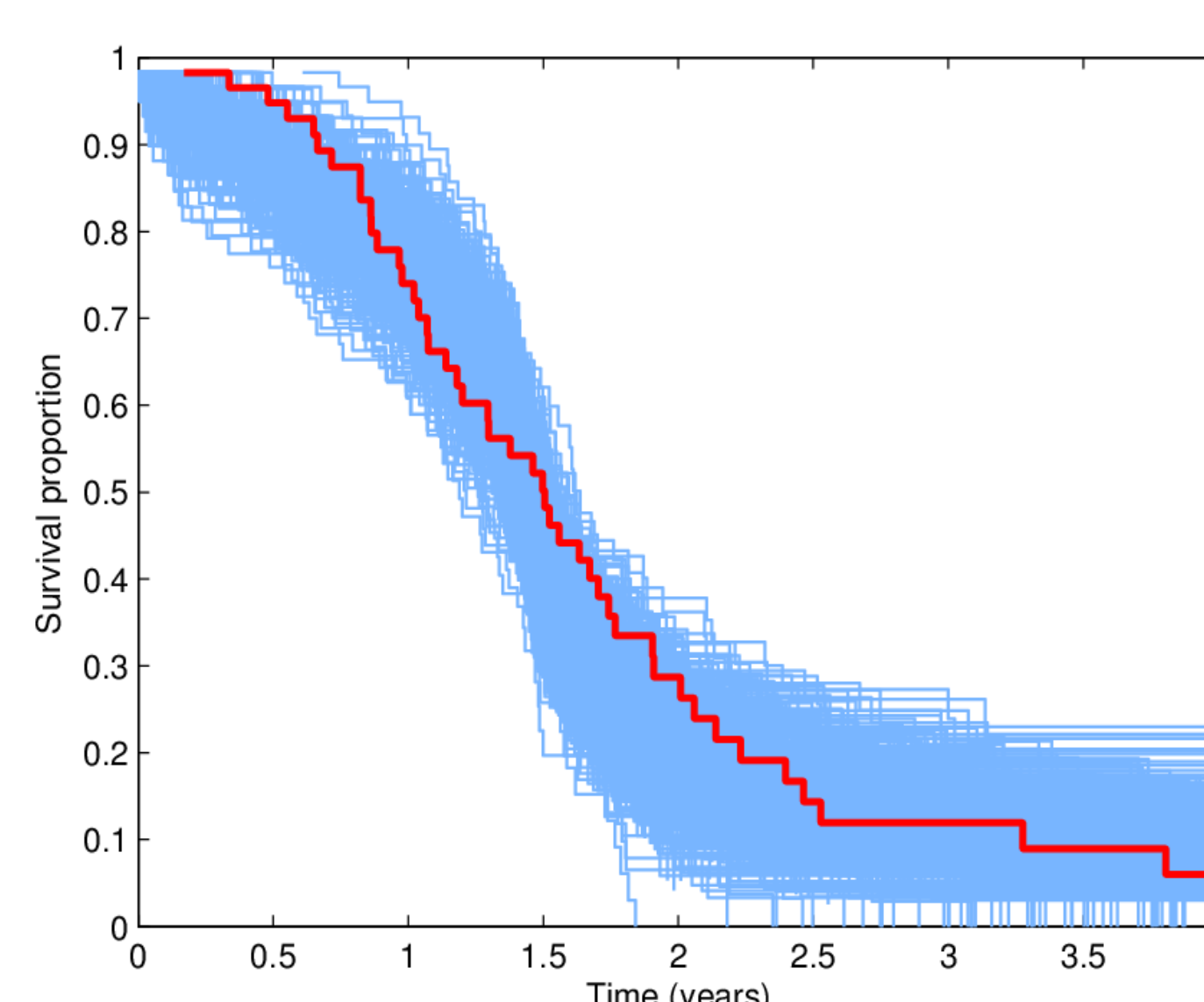
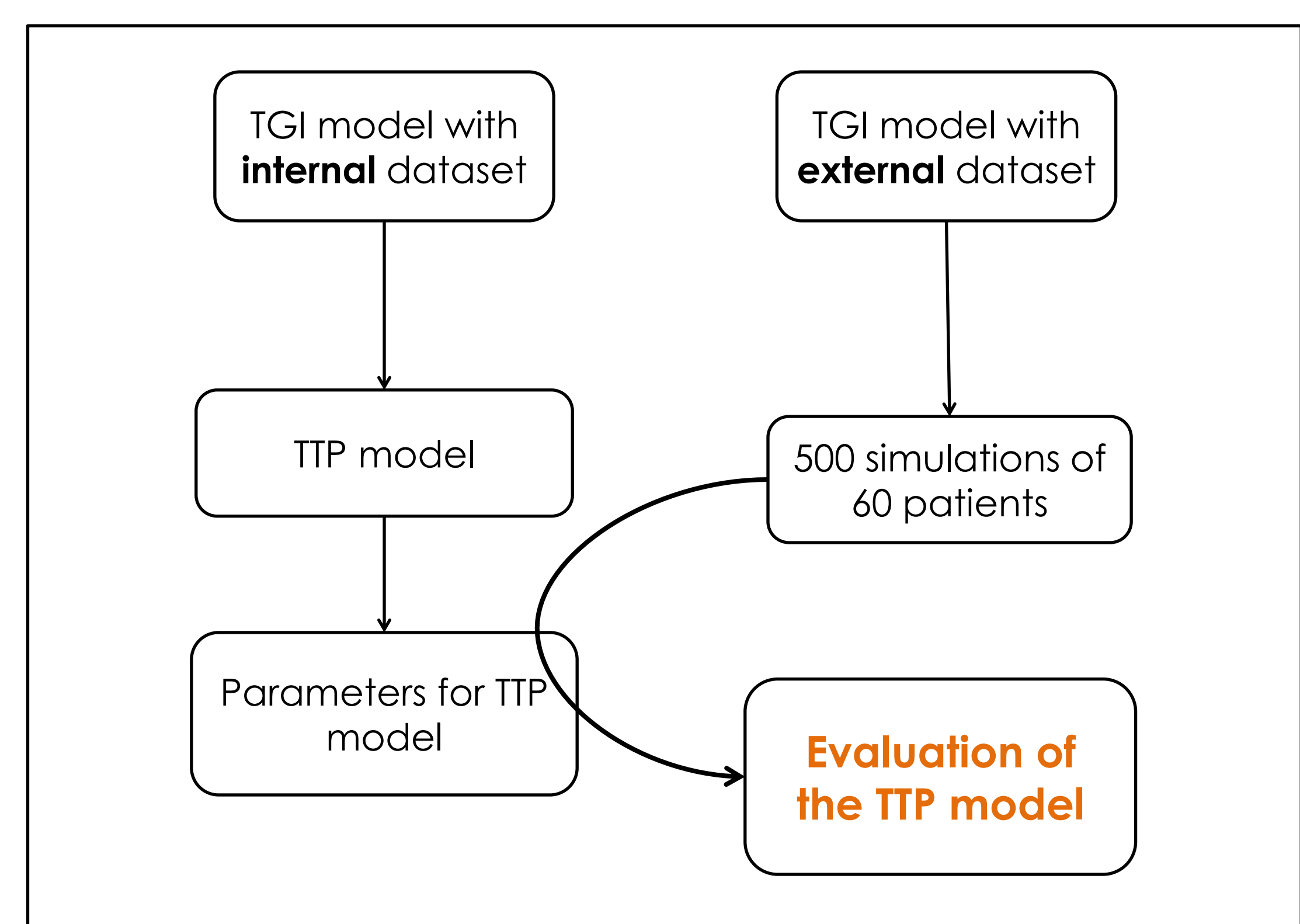


Left: NPDEs according to the time and individual predictions versus observations.
Above: we used 60 external patients (black) and compared the 5%, 50% and 95% percentiles of observed MTDs (red) to simulated MTDs (blue)

Model with covariates

- ✓ Additional data: biomolecular statuses (1p19q, p53, IDH) are available for 41 patients.
- ✓ A mutation in p53 induces an increase in tumor proliferation as found in the literature.
- ✓ IDH mutation decreases the recruitment of quiescent cells into proliferation.

Time-to-progression (TTP) modeling



Predictors	Estimates (rse)
Natural speed	-1.58 (20%)
Rel change 8 wks	12.6 (53%)

Model validation: time-to-progression data with external dataset (red) and 500 simulated curves (blue)