Combining a Quantitative Systemic Pharmacology (QSP) model of NSCLC with an existing KPD model of Gemcitabine: a first step towards a new paradigm in clinical trials simulation

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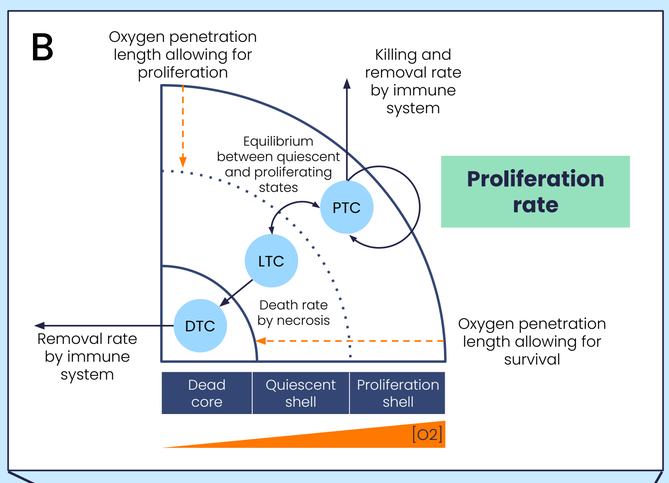
BACKGROUND

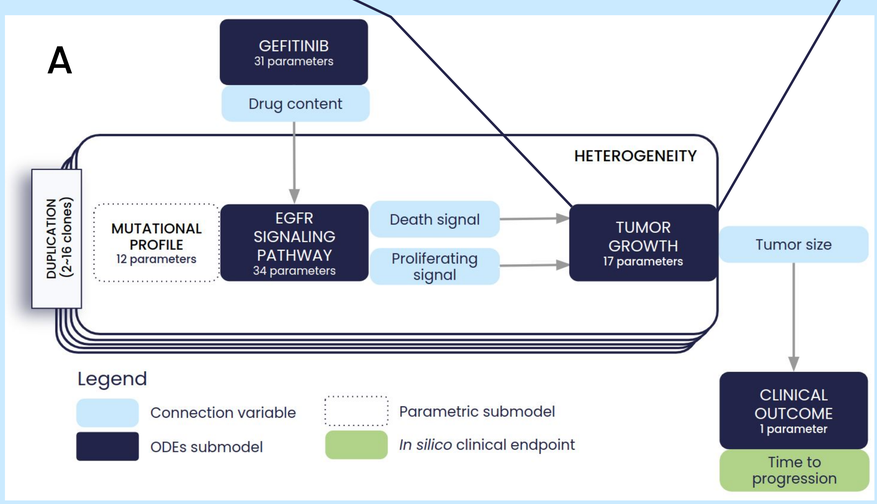
Developing a **quantitative systems pharmacology (QSP) disease model** often requires extensive knowledge investigation, complex development and calibration phases. It is important for researchers to be able to leverage this modeling effort by easily combining a disease model with other treatment models. Here, we propose an approach that **combines a in-depth QSP disease model of non-small cell lung cancer** (NSCLC) [1] with an existing **drug pharmacodynamics (KPD) model of gemcitabine** [2]. Through a **minimal calibration step** involving **only 2 parameters, introduced for the connection,** and based on **limited clinical data extracted from the KPD model publication**, this integrative framework seeks to bridge the gap between understanding disease progression mechanisms and drug actions, paving the way for a new paradigm in simulating and optimizing clinical trials.

NSCLC QSP platform allows for **streamlined integration** of **literature KPD drug models**

NSCLC QSP model

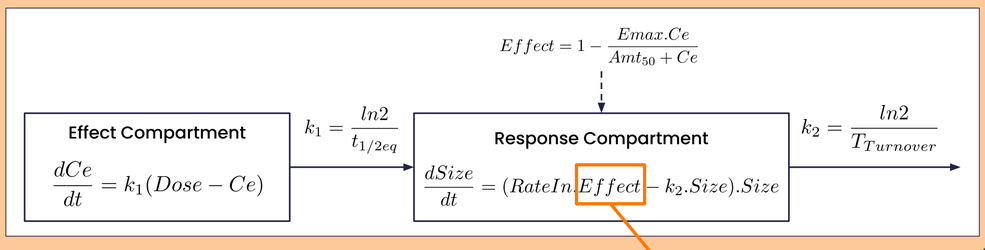
Fig 1. A) Overall structure of the epidermal growth factor receptor (EGFR)-mutated NSCLC QSP model from [1]. This mechanistic model links patients' descriptors, such as the mutational profile, to tumor size evolution and time to progression in agreement with the RECIST (Response Evaluation Criteria In Solid Tumors) criteria. **B)** Tumor growth submodel scheme. DTC: dead tumoral cell, LTC: latent tumoral cell, PTC: proliferating tumoral cell.





Gemcitabine KPD model

Fig 2. Schematic representation of gemcitabine KPD model from [2]. The drug is administered in the Effect compartment and reduces tumor size in the Response compartment by decreasing ***RateIn***, the rate of tumor growth at baseline.



Combined model with minimal interface

$$proliferationRate = \frac{EGFRProlifSignal^{\gamma}}{EGFRProlifSignal^{\gamma} + K^{\gamma}_{prolifSignal}} \cdot k_{basalProlif} \cdot (1 - cellOccupancy) \cdot Effect \cdot N_{prolifCells}$$

Direct results reproduction failed due to **different modeling hypothesis**: tumor size is stable before treatment in KPD model vs growing in the disease model.

Clinical Data

Clinical observations of tumor size used to build the KPD model [2], with very few data points after 20 weeks.

2 Adjustment Parameters

Addition of 2 parameters to compensate the different modeling hypothesis: one modulates the proliferation reduction and the other the additional effect on apoptosis.

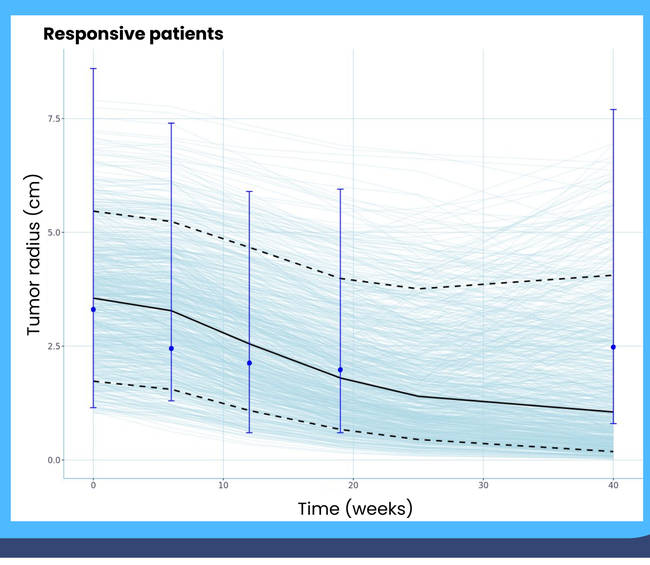
Minimal calibration

Calibration of only the 2 additional parameters

Calibration solely based on clinical data used to build the KPD model, without external data involved.

Calibrated combined model reproducing clinical data

Fig 3. Calibration results for tumor radius evolution. The median and 90% observation intervals are shown in cyan. Simulated traces for individual patients using the combined model are displayed in light blue, with the median shown as a solid black line and the 90% prediction interval as a dotted black line. Based on the statement from [2] that 'there was no evidence of relapse during treatment,' only virtual patients with tumor shrinkage during treatment, labeled as 'responsive patients,' were included in this plot.



Extended capabilities for both models

Additional clinical outcomes for gemcitabine treatment such as Time to Progression

Comparison of gemcitabine effect on disease vs other treatments, such as gefitinib, already implemented in the disease model

METHODS

The combined model is built by integrating the NSCLC disease model, which accounts for tumor growth and other relevant phenomena, with the segment of the gemcitabine KPD model representing treatment time-course and magnitude. The logical connection between both models is established based on gemcitabine inhibition of tumor growth, as outlined in the KPD model.

Due to a significant difference in modeling hypotheses—specifically, the assumption of tumor steady state in the KPD model, which differs from the dynamic nature of the disease progression model—two additional parameters are introduced in the combined model. These parameters are calibrated to reproduce the median patient behavior observed in the clinical data used to build the KPD model.

RESULTS

A virtual population is created based on the patient characteristics and the estimated variability of PD parameters provided by Tham et al. [2].

The clinical results provided in the previous publication are successfully reproduced through simulations of gemcitabine treatment on this virtual population.

CONCLUSION

- Developing and validating a comprehensive mechanistic disease model can be complex and time-consuming, but once established, connecting it with treatment models is relatively straightforward.
- The combination of disease and treatment models, coupled with minimal calibration, offers significant enhancements to both models' capabilities. This approach holds promise for the future of QSP modeling.

REFERENCES

- [1] L'Hostis, A. et al. Knowledge-based mechanistic modeling accurately predicts disease progression with gefitinib in EGFR-mutant lung adenocarcinoma. npj Systems Biology and Applications vol. 9 (2023).
- [2] Tham, L.-S. et al. A Pharmacodynamic Model for the Time Course of Tumor Shrinkage by Gemcitabine + Carboplatin in Non–Small Cell Lung Cancer Patients. Clinical Cancer Research vol. 14 4213–4218 (2008).