Multiscale *EGFR* mutated NSCLC Tumor Heterogeneity Knowledge-Based Model predicts Tumor Growth under Gefitinib: an avenue to *in silico* clinical trial

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Background

Treatment for lung adenocarcinoma (LUAD) patients is complex: mechanistic modeling based on knowledge could help clinicians testing biological assumptions, and comparing and combining treatments, if tumor evolution in size and genetic heterogeneity can be represented. We therefore present a knowledge-based mathematical mechanistic model that could complement clinical decision.

Project Formulation

LUAD: most common lung cancer subtype [1]. About ⅛ of LUAD harbor a tumor driver mutation in **Epidermal Growth Factor Receptor (EGFR+)** [2]. SoC for advanced EGFR+ LUAD is EGFR tyrosine kinase inhibitor, *e.g.* gefitinib[3].

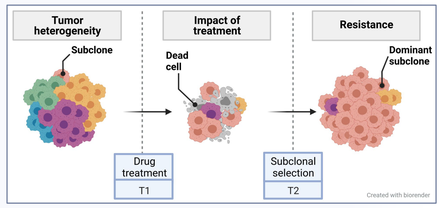

Illustration of the phenomena that drive tumor growth. Cell colors represent tumor subclones: different genotype but similar phenotype

Aim of the study: produce a mechanistic model of lung cancer to predict tumor size evolution over time in EGFR+LUAD patients, and **compare it** to an **already published model**[4].

Model Benchmark

Protocol

We ran an *in silico* trial following **4000** EGFR+ LUAD patients, treated with **gefitinib** 250mg once daily, and monitored their tumor size, as reported in Nagase *et al.*'s [4] model.

- Overlap: model's ability to reproduce real life variability

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O = (Obs. interval ∩ Pred. interval)/Obs. interval
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- Precision: model's ability to provide results with reasonable variability

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P = (Obs. interval ∩ Pred. interval)/Pred. interval
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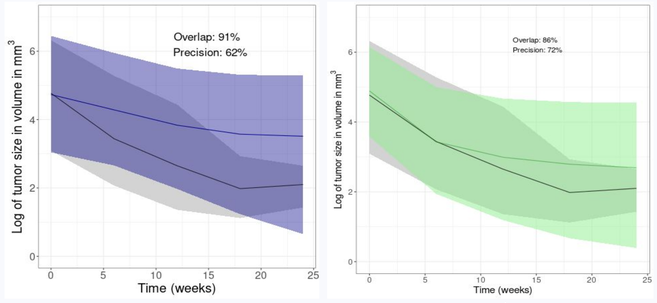


ISELA and Bayesian models against raw data are plotted. For each distribution (raw data ; ISELA model ; Bayesian model), the median and 25-75% interval is provided and used for computation of overlap and precision. Grey: raw data reported by Nagase *et al* ; Blue: ISELA model ; Green: Bayesian model.

Results

Both models efficiently reproduce experimental data, indicating that ISELA model is able to reproduce the evolution of tumor size of a database not used to build or calibrate it.

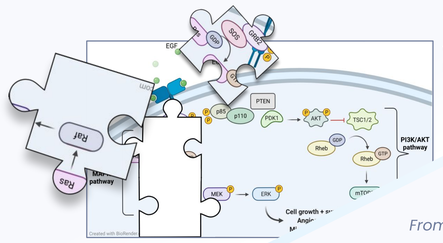
Next steps?

- Challenge the model in reproducing clinical data not used for its construction nor calibration
- Extend the ISELA model to increase its context of use beyond EGFR+ LUAD patients

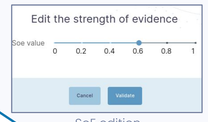
Systemic Knowledge Review

300+ scientific papers

- Identify the relevant **biological entities** and their **relationship**
- Define a **Strength of evidence** (SoE) scoring for every piece of knowledge
- Manual **collection**, **selection**, **evaluation** of pieces of knowledge

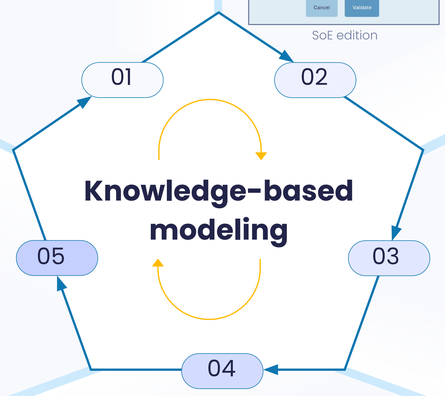


We have assembled pieces of knowledge



SoE edition

Realized on the **jinkō platform**, a state-of-the-art clinical trial simulation cloud-based SaaS solution.

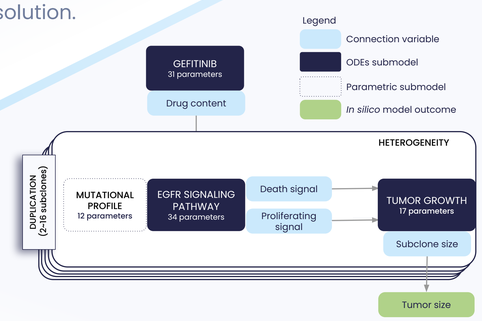


Computational Model Development

From knowledge to mathematical equations, embedded in computer code

Mathematical modeling

5 biological **models** implemented in parallel & integrated with connecting variables. The ***i**n **s**ilico* **E**GFR+ **L**ung **A**denocarcinoma (ISELA) model is composed of up to **83 ordinary differential equations (ODEs), 43 variables, and 170 parameters** reflecting intra-tumor heterogeneity.



Graphical representation of the ISELA model. It includes 6 interconnected submodels of distinct granularity levels: from molecular reactions to tissue level:

- mutational profile,
- EGFR signaling pathways
- tumor growth
- gefitinib pharmacometrics
- tumor heterogeneity and duplication

Focus on the clonal heterogeneity

Tumor subclone: Group of tumor cells that might harbor genotype differences but that share the same phenotype. In the model, we consider:

- **Coexistence of 2 to 15 subclones** [5]
- Preserved **EGFR mutation** across subclones
- Subclones with **similar behavior** in response to biological signals
- Subclones with **distinct properties** derived from sub-clonal mutations
  - Inter-subclonal variability due to mutations, or epigenetic alterations
  - Some yield a new tumor subclone

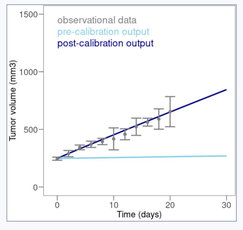
Relevant model endpoint

Tumor radius: Radius in centimeter of the primary tumor, under the assumption that the tumor is a spheroid.

Calibration & Virtual population

Calibration process

1. **Experimental data** gathering
   - **From 26** published experiments: spheroids, xenografts, clinical results, with relevant mutational profiles
2. Ensuring **model adequation to experimental data**
3. Step-by-step calibration protocol definition, composed of **blocks with increasingly broad objectives**
4. **Fitness functions *f*** creation representative of the experimental data
   - Iterative optimization until *f*-minimization is deemed satisfying



Example of simulation outputs before and after calibration (in this case tumor radius over time)

Virtual population for benchmark purposes

Virtual patients creation: vectors of values of parameters to respect the characteristics of the population used to build Nagase *et al.*'s model (2020)[4].

Characteristics	Nagase *et al*'s model	ISELA model
Age, years (range)	59 (27 - 82)	58.8 (27.5 - 81.9)
Gender, % (n)		
- Women	81.8	82.8 (3312)
- Men	18.2	17.2 (688)
Asian, % (n)	99.7	100 (4000)
Common EGFR mutations % (n)	96.2	100 (400)

References

[1] Siegel *et al.*, CA CANCER, 2020
[2] Vallee *et al.*, Int J Oncol, 2013
[3] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206995s003lbl.pdf
[4] Nagase *et al.*, CPT Pharmacometrics Syst Pharmacol, 2020
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Acknowledgments

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Conclusion

The results obtained from the benchmark analysis ensure that the ISELA mechanistic model can reproduce tumor growth variability in advanced EGFR+ LUAD patients. The ISELA model is currently being expanded to clinical endpoints evaluation such as time to progression, in order to provide a tool for cost-effective research and development, to eventually overcome:

- **reproducibility crisis**, as we would be able to simulate an **unlimited number of patients**
- ethical and practical difficulties for control arms: modeling **digital twins** for each patient to effectively creates a synthetic control arm.

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