Application of an AI Framework to Update a Quantitative Systems Pharmacology Model of CAR-T Therapy

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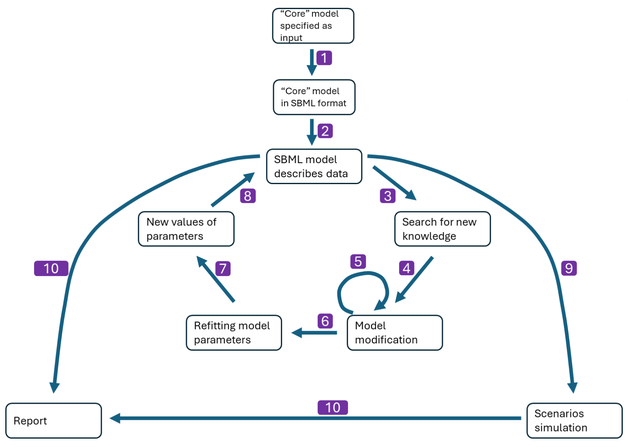
Introduction

Quantitative systems pharmacology (QSP) models provide mechanistic insight into drug action and disease dynamics but are typically constructed through labour-intensive, expert-dependent workflows that limit scalability. To address these challenges, we developed an AI-QSP (Artificial Intelligence–QSP) prototype that extends conventional QSP workflows by embedding automated model updating, parameter optimization, scenario generation, and verification within an AI-assisted modelling framework [1]. The present study applies this prototype to update a published CAR-T QSP model [2], with the objective of evaluating the feasibility, strengths, and limitations of AI-assisted automated model evolution.

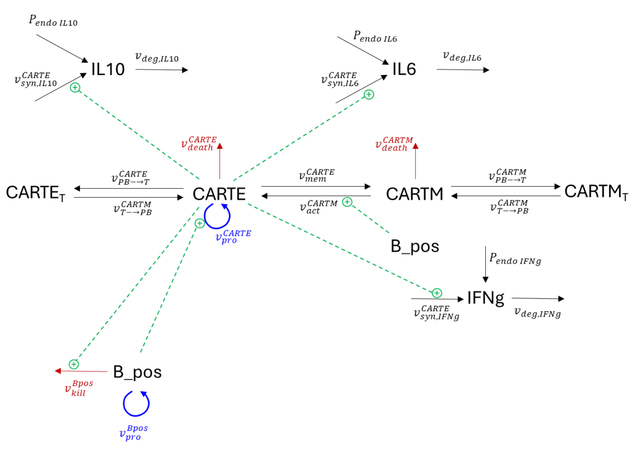
Methods

AI-QSP framework: The AI-QSP prototype consists of multiple Large Language Models (LLMs) interconnected through structured prompt workflows and integrated with Python-based modelling tools executed locally. The overall architecture of the AI-assisted quantitative systems pharmacology (AI-QSP) framework is illustrated below.



The framework implements an iterative workflow that integrates artificial intelligence–based knowledge interpretation, mechanistic modeling in Systems Biology Markup Language (SBML), and automated parameter optimization.

Description of core model (AIcore): The reference model used for validation of the AI-QSP prototype was a previously published quantitative systems pharmacology (QSP) model describing the dynamics of chimeric antigen receptor T-cell (CAR-T) therapy. The model captures key interactions between tumor cells, CAR-T cell populations, and cytokine signaling processes that regulate therapeutic response, immune activation, and treatment resistance mechanisms [2] (see scheme below):



The model describes the dynamics of antigen-positive tumor cells (Bpos), effector CAR-T cells (CARTE), and memory CAR-T cells (CARTM). CARTE proliferation is driven by antigen stimulation from Bpos. CARTE cells can differentiate into memory CAR-T cells (CARTM). Effector CAR-T cells mediate tumor killing of Bpos. Both CARTE and CARTM undergo natural death processes. Tumor cells proliferate logistically.

AI-QSP based automatic update of AIcore QSP model: AI-QSP was instructed to incorporate biological knowledge related to the following phenomena: T-cell exhaustion, PD-1/PD-L1 checkpoint signaling, Tumor antigen escape

The following simplified prompt illustrates the instructions used to guide the AI-assisted model update process:

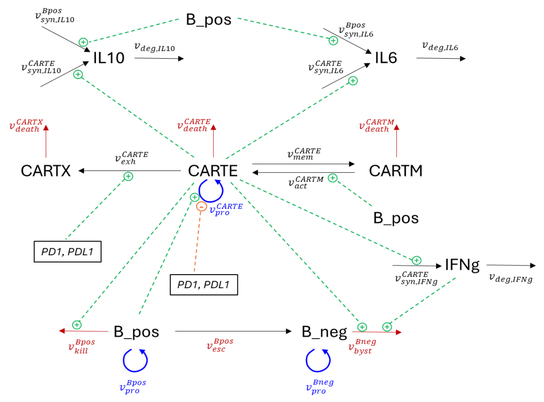
Given an SBML model describing CAR-T therapy dynamics with the species CARTE, CARTM, B_pos, cytokines, and tumor growth processes:
1. Identify important biological mechanisms in CAR-T therapy that are not currently represented in the model.
2. Focus on the following mechanisms:
- T-cell exhaustion
- PD-1 / PD-L1 checkpoint regulation
- tumor antigen escape
3. Propose model extensions by:
- introducing new state variables if required
- defining new reactions or transitions
- modifying rate laws if necessary
4. Describe the proposed model updates in SBML-compatible form includig species, parameters, and kinetic expressions.

Synthetic data and model calibration: a synthetic dataset was generated using simulations of the reconstructed AIcore QSP model. Model calibration was performed by the AI-QSP framework's optimization engine. The objective was to minimize the log-transformed root mean square error (log-RMSE) between the model simulations and the synthetic benchmark data.

A random-restart global search strategy, implemented in Python with Tellurium and NumPy, was used to sample 200 candidate parameter vectors within plausible biological bounds. The full calibration comprised 19 parameters: seven kinetic parameters governing CAR-T and tumor dynamics, plus six cytokine production and stimulation parameters, three cytokine degradation rate constants, two antigen-recognition parameters, and one baseline degradation constant.

Results

Generation of updated QSP model and analysis of its structure*:* Applying several cycles described in AI-QSP workflow updated version of CART QSP model (**AIupdate2**) was generated on the basis of Aicore QSP model



Key Process-Level Differences

Process	AIcore	AIupdate2
Tissue migration (CARTE, CARTM)	✓ Present	✗ Absent
Exhaustion transition (CARTE → CARTE_EX)	✗ Absent	✓ Rxn_CARTE_Exhaustion
Antigen-negative tumour growth	✗ Absent	✓ Rxn_Bneg_growth
Bystander killing of B_neg	✗ Absent	✓ Rxn_Bneg_Bystander_Killing
Antigen escape (B_pos → B_neg)	✗ Absent	✓ Rxn_Antigen_Escape
CAR-T proliferation (antigen-driven)	✓ k_prolif_eff × CARTE × B_pos/(K_prolif + B_pos)	✓ V × same expression
Tumour killing (saturable)	✓ k_kill × CARTE × B_pos/(K_kill + B_pos)	✓ V × same expression
Cytokine synthesis (IL-6, IL-10, IFN-γ)	✓ Present	✓ Present (volume-scaled)

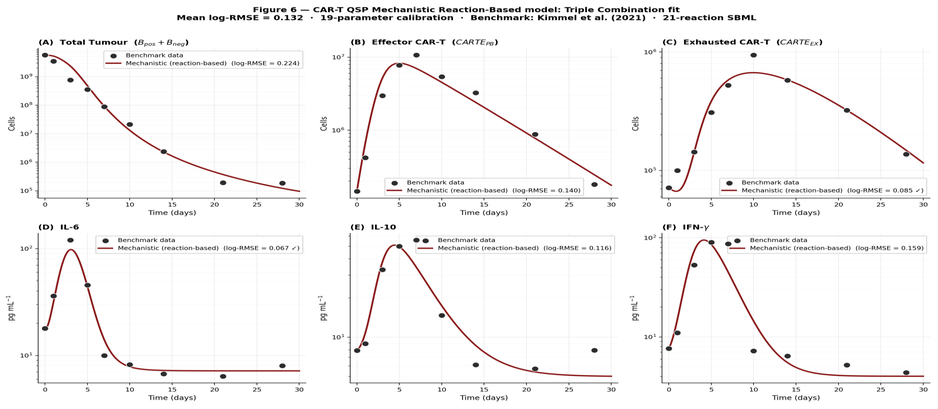
The AIupdate2 model differs from the AIcore model in both **state variables** and **biological processes**. Indeed, there are 3 groups of variables/processes in these model versions:

- Group 1: Included in AIcore version only
- Group 2: Included in "AIupdate2" version only
- Group 3: Included in both versions

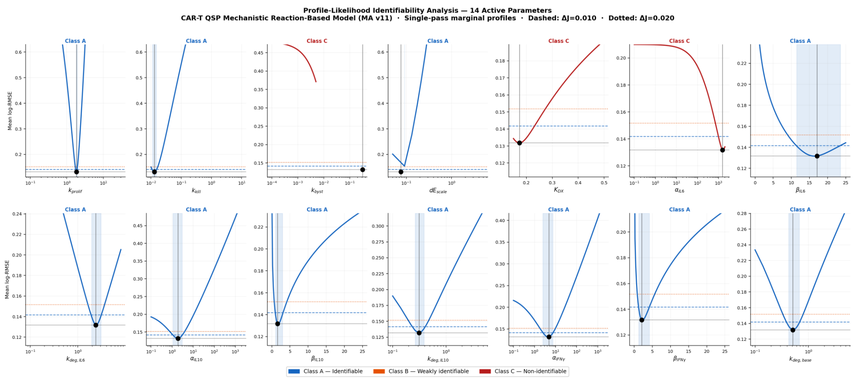
AI-QSP based automatic calibration of AIupdate2 *:* Initially, AIupdate2 was applied for calibration against the synthetic dataset. Calibration converged to poor solutions, likely due to structural limitations in the right-hand side rate expressions introduced during the AI-guided extension step.
This failure is itself an informative outcome: it demonstrates that AI-generated structural extensions, even when technically correct at the SBML level, may not be immediately calibratable and require further adaptive refinement.

> In response, the AI-QSP framework was re-engaged to adaptively modify the rate expressions of the problematic processes, producing **AIupdate3** — with revised kinetic formulations for the exhaustion and bystander killing pathways that improve the conditioning of the optimisation landscape

Calibration of AIupdate3 *:* AI-QSP framework was applied to successfully calibrate AIupdate3 model version



Global Sensitivity and identifiability analysis of AIupdate3 *:* A Sobol' variance-based GSA was performed on all 19 calibrated parameters using a Saltelli quasi-random sample of N = 1024 base vectors (40,960 total model evaluations). First-order (S_1) and total-order (S_T) Sobol' indices were computed. Following GSA analysis, profile-likelihood identifiability was assessed for the 14 active parameters using single-pass marginal profiles evaluated across each parameter's full bound range:



Ten of 14 parameters were classified as identifiable, with finite bounded confidence intervals; four parameters were non-identifiable

Conclusions

An AI-based framework for automated updating of QSP models was developed and evaluated in the context of CAR-T therapy modelling. The results demonstrate that AI-assisted workflows can accelerate model extension while maintaining mechanistic interpretability and expert oversight. The AI-QSP framework provides a scalable approach for iterative QSP model development and supports integration of diverse biological and clinical data sources. This work establishes a generalizable paradigm for transparent, data-driven evolution of mechanistic pharmacology models. Model credibility was assessed using ASME V&V 40 and ICH M15 principles, including global sensitivity and profile-likelihood analyses

References

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3. Goryanin I, Demin O., Checkley S., Goryanin I. An AI-Assisted Workflow for Reconstruction, Extension, and Calibration of Quantitative Systems Pharmacology Models. , Submitted to CPT and BioRxiv, available on request goryanin@iqanova.org, www.iqanova.org