Integration of Genome-Scale Metabolism and Quantitative Immune Databases Enables AI-Driven QSP Modeling: An Asthma Case Study Using EHMN 2026

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Introduction

Quantitative Systems Pharmacology (QSP) models increasingly aim to incorporate mechanistic biology at scale; however, integration of genome-scale metabolic networks with pharmacometric workflows remains limited by incomplete baseline information, high-dimensional parameter spaces, and computational constraints. Genome-scale reconstructions provide mechanistic coverage but lack quantitative population priors, whereas immune datasets provide quantitative measurements without mechanistic context. EHMN 2026, a recently upgraded human metabolicnetwork (EHMN 2026 [1]), provides an opportunity to bridge this gap. Here, we present an AI-enabled QSP (AI-QSP) framework integrating EHMN 2026 with the data extracted from CYTOCON database [2] to enable immune–metabolic pharmacodynamic simulation and scalable virtual population generation, demonstrated using asthma as a representative disease.

Methods

AI-QSP framework: The AI-QSP framework integrates two complementary capabilities within a shared SBML-based modelling infrastructure (Figure 1). Both arms produce SBML Level 3 Version 2 models distributed as COMBINE archives, share the same simulation infrastructure (Tellurium, libSBML, libroadrunner/CVODE), and follow the same ASME V&V 40 / ICH M15 credibility assessment structure.

- **Arm 1 — LLM-assisted model evolution** (companion poster [3]): OpenAI GPT-based LLMs interpret biological text and propose structural model extensions. Applied to a compact CAR-T QSP model (21 reactions, 19 calibrated parameters). Delivers: model reconstruction, structural extension, automated parameter optimisation, Sobol' GSA (N = 1,024), profile-likelihood identifiability.
- **Arm 2 — Deterministic ontology-driven assembly** (this paper): rule-based pipeline using SBO/GO/EC/ChEMBL ontology matching assembles near-genome-scale SBML models from structured databases. Applied to asthma (41,918 reactions, 4 compartments, 6 PD hooks, mepolizumab PK). Delivers: automated SBML generation, multicompartment physiology, EHMN 2026 metabolic integration, PK/PD simulation, validated surrogate.

Arm 2: Ontology-Driven Genome-Scale Assembly Pipeline: The genome-scale assembly module automates model construction through a six-step deterministic pipeline (Table 1). All assembly decisions are auditable and reproducible from the same database inputs via rule-based ontology matching.

Step	Input	Operation	Output
1	Disease annotation + therapy list	Species retrieval from CYTOCON DB: query by tissue tag, compartment, and disease annotation	Species list with baseline concentrations and compartment assignments
2	Species list + EHMN 2026 [11]	Graph matching to EHMN 2026 metabolic nodes via shared GO biological process terms and MetaNetX metabolite identifiers (NetworkX bipartite matching)	Candidate reaction set with metabolic bridge pool connections
3	Candidate reactions + SBO library	Reaction classification: each reaction assigned SBO mechanistic class (e.g., SBO:0000179 degradation, SBO:0000176 transcription activation) via EC/GO/SBO cross-reference tables	Annotated reaction catalogue with SBO class tags
4	Annotated reactions + compartment volumes	Multicompartment SBML assembly: species-to-compartment assignment; volume-explicit transport reactions generated for cross-compartment species in CYTOCON DB	Draft SBML model (libSBML 5.20, SBML Level 3 Version 2 [13])
5	Drug target list + SBO classes	PD hook assignment: drug targets matched to SBO reaction classes via ChEMBL target annotation; Emax modifier variables inserted into kinetic laws of matched reactions	SBML model with six PD hook assignment rules
6	Final SBML + simulation protocols	COMBINE archive export [22]: SBML L3V2, SED-ML simulation definitions, VP parameter files, OMEX manifest	Distributable COMBINE archive; BioModels deposit

CYTOCON DB: provides baseline species concentrations, tissue/compartment annotations, and literature references for cytokines, chemokines, and immune cell populations across human physiological fluids and tissues.

EHMN 2026 is the published Edinburgh Human Metabolic Network 2026 [1], a thermodynamically refined, SBML-standardised human metabolic reconstruction comprising 22,642 reactions, 14,321 metabolites, and 3,996 gene products across 11 compartments.

Immune cell dynamics, metabolic Integration, and PD Hooks*:*

The immune signaling layer integrates cytokines, chemokines, immune cell populations, and inflammatory mediators derived from curated biological knowledge. Species dynamics follow the general system of ordinary differential equations. Metabolic state modulates immune reaction rates through the E_META modifier:

E_META = [1/(1 + alpha*[Lactate])] * [[O2]/(K_O2 + [O2])]

Six modular PD hooks use an Emax inhibitory formulation (E = 1 − Emax*D/(EC50+D)), matched to biologically annotated reaction classes via SBO/ChEMBL:

Hook	Biological target	Drug class (example agent)	SBO class matched
E_ALRM	Epithelial alarmin signalling (TSLP)	Anti-TSLP (tezepelumab [19])	SBO:0000245 (enhancer)
E_T2	IL-4/IL-5/IL-13 type-2 pathway	Anti-IL-4Rα (dupilumab [18])	SBO:0000170 (stimulator)
E_EOS	Eosinophil survival/production	Anti-IL-5 (mepolizumab [12])	SBO:0000179 (inhibitor of degradation)
E_NEUT_REC	Immune cell trafficking	Unassigned (E = 1.0)	SBO:0000185 (transport)
E_META_STRESS	Metabolic stress regulation	Metabolic microenvironment (aliases E_META)	Metabolic bridge pool reactions
E_STEROID_SENS	Steroid responsiveness	Corticosteroids (aliases E_META)	Inflammatory effector reactions

Results

***Automated Model Assembly and Structural Verification*:**

Property	Value
Total reactions	41,918 (immune signalling and EHMN 2026 metabolic bridge pool reactions combined; near genome-scale structural coverage; all with valid MathML kinetic laws)
Immune signalling species	3,738 across 4 physiological ODE compartments (distinct from EHMN 2026's 14,321 metabolite-compartment species [11])
Global parameters	42,280 (globally scoped SBML parameters; subset nominally set — see Supplementary Table S4)
ODE compartments	4 (Blood 5 L; Serum 3 L; Lung Tissue 0.5 L; Other 10 L)
EHMN 2026 bridge pools	6 metabolites (glucose, O_2, lactate, glutamine, arginine, ATP) from cytosol/mitochondria [11]
PD hooks	6 (E_ALRM, E_T2, E_EOS, E_NEUT_REC, E_META_STRESS, E_STEROID_SENS)
PK module	Mepolizumab 2-compartment (published population PK [12]); C_drug(t) drives E_EOS
SBML validation (libSBML 5.20)	0 errors, 0 warnings
Cross-platform reproducibility	<0.01% relative difference (COPASI, Tellurium, Python)
Model assembly time (Steps 1–6)	<3 min (Intel Core i7, 16 GB RAM)

Structural verification confirmed zero SBML schema errors, complete kinetic law definitions for all 41,918 reactions, no orphan species, mass balance for all transport reactions, and 0% cross-pathway PD hook misassignment.

Illustrative Decision-Support Demonstrations:

Scenario 1: Dose-Response Ranking

Five mepolizumab dose levels produced blood eosinophil reductions at day 28 with correct monotonic ordering across all 1,000 constrained virtual patients (100% ranking consistency). Quantitative results (median and 95% constrained VP interval):

Dose level	Median reduction (%)	95% VP interval
100% (100 mg q28d, nominal)	−41.8%	−70.4% to −5.1%
50% (50 mg q28d)	−31.2%	−58.6% to −4.0%
20% (20 mg q28d)	−19.7%	−42.1% to −2.4%
10% (10 mg q28d)	−9.4%	−23.5% to −1.1%
5% (5 mg q28d)	−4.8%	−13.1% to −0.5%

Scenario 2: Biomarker Stratification

High-eosinophil VPs (>0.5 × 10^9/L baseline; n = 342) showed greater predicted eosinophil reduction at day 28 than low-eosinophil VPs (<0.3 × 10^9/L; n = 289): −52.3% vs. −28.4% median (Mann-Whitney U $p < 0.001$; non-overlapping interquartile ranges). This stratification emerges mechanistically from the IL-5–eosinophil survival coupling in the assembled reaction network: virtual patients with higher baseline eosinophil counts have a larger IL-5-driven survival flux available for E_EOS to suppress. The pattern is directionally consistent with the stratification rationale underlying mepolizumab's regulatory approval (DREAM trial: greater response at blood eosinophils ≥150/µL) — arising from assembly logic, not statistical fitting.

Metabolic Perturbation

Metabolic microenvironment normalisation (E_META_STRESS → 1.0, representing resolution of tissue hypoxia and lactate accumulation) produced illustrative downstream cytokine reductions: IL-13 −47.1% (median; 95% VP interval −86.1% to +28.4%) and IL-5 −49.2% (median; −89.3% to +15.0%) at day 28. The wide VP intervals include some positive values, reflecting indirect immunometabolic feedback pathways in the assembled network where metabolic improvement can transiently increase signalling before stabilising. These illustrative results confirm structural coupling between the EHMN 2026 metabolic bridge layer and cytokine endpoints, though the wide intervals indicate this pathway requires tighter VP constraints in Stage 2 calibration

Conclusions

Integration of CYTOCON-derived immune baselines with EHMN 2026 enabled dynamic coupling between inflammatory activity, reproducing expected qualitative relationships between cytokine suppression and normalization of metabolic flux proxies during corticosteroid treatment. AI-constrained baseline initialization reduced the occurrence of non-physiological virtual individuals compared with independent sampling approaches.

References

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