EHMN 2026: SBML-Standardised Human Metabolic Network

For Genome-Scale Analysis and QSP Integration

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What Is EHMN 2026?

The Challenge

Legacy genome-scale metabolic models (GEMs) suffer from heterogeneous identifiers, incomplete pathway integration, and limited thermodynamic refinement — constraining reproducibility and translational applicability. MIDD requires tailored metabolic models

The Solution

EHMN 2026 is a rigorously harmonised update of the Edinburgh Human Metabolic Network, featuring systematic identifier reconciliation (MetaNetX, ChEBI), duplicate reaction consolidation, thermodynamic directionality assessment, and structured Reactome pathway annotation — encoded in SBML Level 3 Version 2 with FBC2.

22,642 Reactions

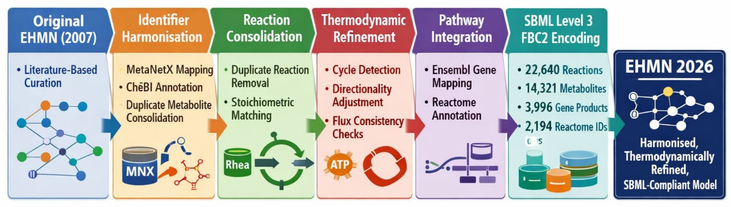
14,321 Metabolites

3,996 Gene Products

2,194 Reactome IDs

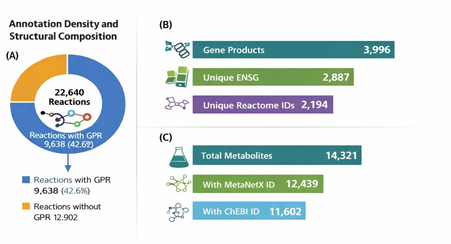
Reconstruction Workflow: From EHMN 2007 to EHMN 2026 using AI-QSP

The workflow proceeds through five sequential stages — from the original literature-curated EHMN (2007) through identifier harmonisation (MetaNetX, ChEBI), reaction consolidation, thermodynamic directionality refinement, and Reactome pathway integration — culminating in SBML Level 3 FBC2 encoding. The emphasis throughout is on refinement and standardisation rather than reaction inflation.



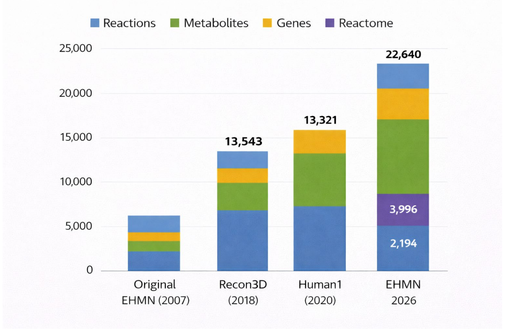
Five-Stage Refinement Pipeline

1. **Original EHMN (2007)** — Literature-based curation; structural foundation for all subsequent stages
2. **Identifier Harmonisation** — MetaNetX mapping, ChEBI annotation, duplicate metabolite consolidation; 612 ambiguous mappings resolved
3. **Reaction Consolidation** — Canonical stoichiometry normalisation; 644 redundant reactions removed (438 reverse pairs + 206 exact duplicates)
4. **Thermodynamic Refinement** — Cycle detection via LP; 37 infeasible ATP-generating cycles eliminated; 1,923 reactions re-constrained
5. **Pathway Integration & SBML Encoding** — Ensembl gene mapping, Reactome annotation, SBML Level 3 FBC2 encoding; fully validated



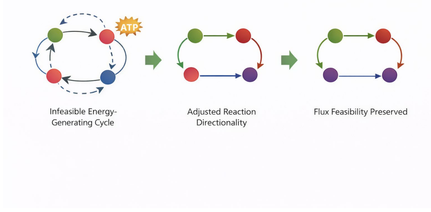
Annotation coverage and structural composition of EHMN 2026. (A) GPR coverage: of 22,642 total reactions, 9,638 (42.6%) carry explicit gene–protein–reaction associations; 13,004 reactions (57.4%) include exchange, sink/demand, transport, and legacy reactions for which no enzymatic gene is expected by design. (B) Gene and pathway integration: EHMN 2026 encodes 3,996 gene products mapped to 2,887 unique Ensembl gene identifiers (ENSG) and 2,194 unique Reactome pathway annotations spanning 642 leaf-level events. (C) Metabolite annotation density: of 14,321 species, 83.1% are matched to MetaNetX MNXref identifiers and 73.0% carry validated ChEBI annotations, reflecting systematic identifier harmonisation across all 11 compartments

A detailed scientific visualization depicting interconnected metabolic networks with gene-protein-reaction associations, pathway integration across biological compartments, and metabolite



Thermodynamic Cycle Detection & Directionality Refinement

Infeasible internal energy-generating cycles (Type-III futile loops) were identified by closing all boundary fluxes and solving a linear programme maximising internal flux magnitude. **37 cycles were fully resolved** across iterative passes. The deposited SBML contains **0 remaining unconstrained ATP-generating loops**, verified by a final boundary-closure LP pass. Global network connectivity and all other reaction fluxes are preserved.



Thermodynamic Refinement: Pathway-Level Results

OXPHOS / ETC
80% irreversible — consistent with proton-motive-force directionality (ΔΨ ~−180 mV in vivo)

Fatty Acid β-Oxidation
59.1% irreversible — net ΔG'° ~−69 kJ/mol per cycle; energetic commitment correctly captured

Amino Acid Metabolism
51.2% irreversible — near-equal split reflecting reversible transamination equilibria

MAR Enzymatic Core
54.0% irreversible — 12,969 core enzymatic reactions; 65 blocked after thermodynamic curation

Overall, **43.2% of all reactions are irreversible** (vs. ~40% Human1, ~35% Recon3D), eliminating ~9,792 backward flux solutions and yielding more constrained, biologically realistic flux distributions.

EHMN 2026 as an Interoperable Metabolic Backbone

EHMN 2026 sits at the centre of a multi-layer modelling ecosystem. Upstream annotation resources (MetaNetX, ChEBI, Reactome, KEGG, BRENDA) populate the model; downstream integration targets include CYTOCON DB for immune calibration, SABIO-RK/BRENDA for selective kinetic augmentation, TRANSFAC/TRANSPATH for regulatory coupling, and COBRA/COBRAPy/Tellurium for constraint-based analysis. The uniform Meta

Reactome Pathway Integration

Coverage at a Glance

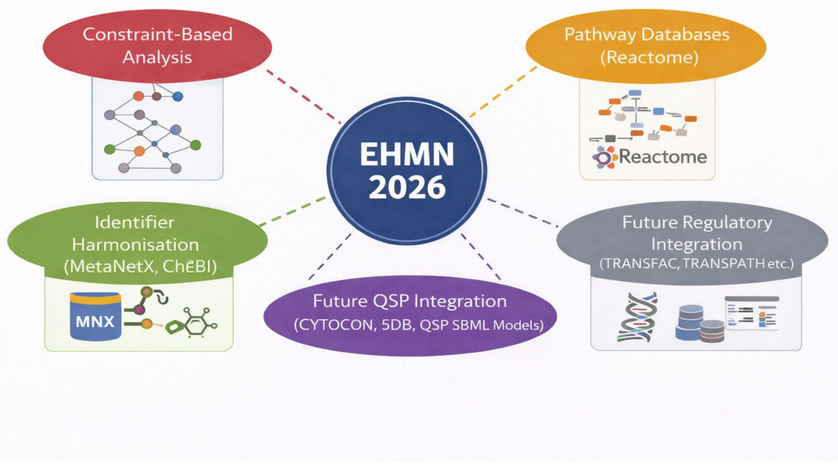
EHMN 2026 integrates Reactome pathway identifiers for **7,910 reactions (34.9%)** spanning **2,194 unique Reactome IDs**. Restricting to the 12,969 MAR enzymatic core yields **61% Reactome coverage** — the highest among current human GEMs (Human1: ~31%; Recon3D: ~15%).
No published version of Recon3D or Human1 includes a systematic genome-wide Reactome annotation layer natively embedded in SBML.

What This Enables

Subsystem Flux Queries
Direct pathway-level flux summation without external mapping tables

Drug Target Impact
Gene → Reactome pathway IDs per reaction; intersect with ChEMBL/DrugBank directly

Modular Disease Modelling
Prune or perturb specific pathway modules for disease-context analysis



Unique Architectural Advantages for QSP

MetaNetX Harmonisation
80.6% of metabolites carry MNXref IDs — uniform namespace prevents ID conflicts across coupled PBPK/PD modules

Native Reactome Annotation
2,194 Reactome IDs embedded in SBML — 61% enzymatic-core coverage; highest among current human GEMs

Thermodynamic Completeness
37 futile cycles eliminated; 0 remaining infeasible loops; 43.2% irreversible reactions — stricter than any comparator

11-Compartment Architecture
Explicit inner mitochondrial space (20 species), lysosome (640), peroxisome (844) — enables organelle-specific perturbation modelling

Modelling Tasks: Where EHMN 2026 Excels

Modelling Task	EHMN 2026 Advantage	Best-Suited Model
Standard FBA	43.2% irreversibility reduces artefactual reverse-flux predictions	All three suitable
Gene essentiality screening	3,996 confirmed genes; conservative GPR avoids false-positive essentiality calls	EHMN 2026 preferred
Pathway-level flux aggregation	Only model with native Reactome event IDs per reaction in SBML	EHMN 2026 uniquely
Organelle-specific perturbation	11 compartments with explicit lysosome, peroxisome, inner mito space	EHMN 2026 uniquely
QSP / PBPK + signalling coupling	Uniform MetaNetX namespace; Reactome IDs link to TRANSFAC/TRANSPATH	EHMN 2026 uniquely
Lipid subclass / FA chain-length	C6–C26 chain-length variants as distinct reactions; LCAD/MCAD/SCAD modelling	EHMN 2026 preferred

EHMN2026 was created using AI-QSP platform. Quarterly upgrades are available on request

Harmonised MetaNetX + ChEBI identifier reconciliation across 14,321 species	**Thermodynamically Refined** 37 futile cycles eliminated; 0 remaining infeasible loops in deposited SBML
Pathway-Annotated 2,194 Reactome IDs; 61% enzymatic-core coverage — highest among human GEMs	**QSP-Ready** Designed as interoperable scaffold for CYTOCON, TRANSFAC, TRANSPATH, SABIO-RK integration

SBML Model available (96MB) at www.iqanova.org · SBML Level 3 Version 2 Compatible with COBRA Toolbox, COBRAPy, Tellurium ·

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Goryanin, I.; Slovianov, L.; Checkley, S.; Goryanin, I. EHMN 2026: A Thermodynamically Refined, SBML-Standardised Human Metabolic Network for Genome-Scale Analysis and QSP Integration. *Metabolites* **2026**, *16*, 236. https://doi.org/10.3390/metabo16040236