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MetaNetX: a bridge between metabolic resources for enhanced curation and multi-omics data harmonization

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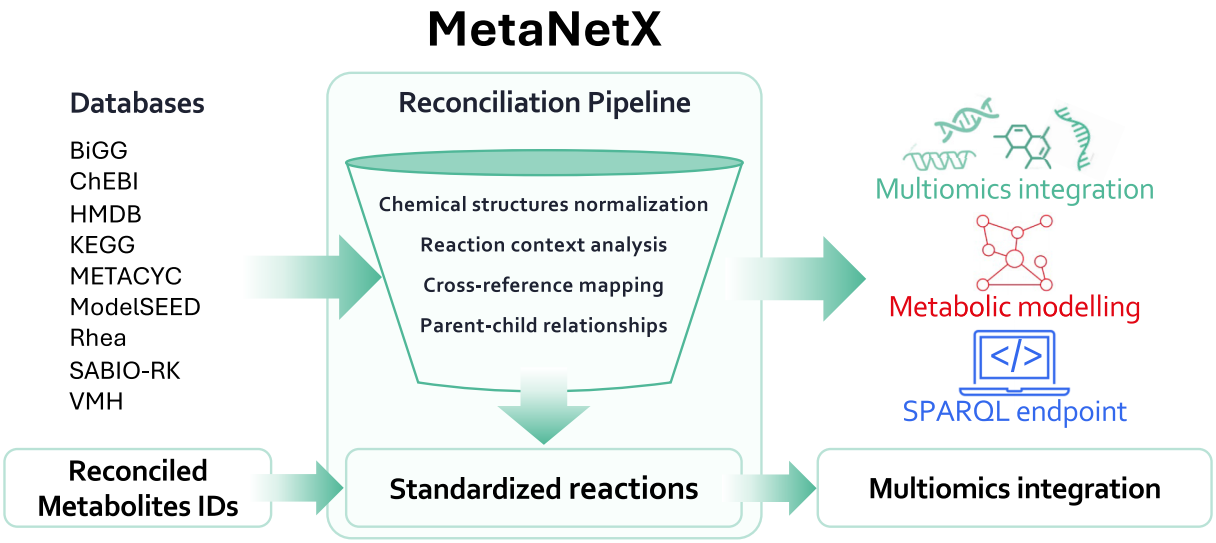
Abstract

MetaNetX (https://www.metanetx.org/) is a comprehensive resource for the reconciliation and integration of metabolic information across diverse biochemical databases. The 2025 update significantly enhances chemical and reaction coverage, incorporating new data and refining chemical structure computation and normalization. These improvements support more accurate reconciliation across sources and enable robust multi-omics integration through standardized identifiers (InChI, SMILES) and curated R-group definitions. The Resource Description Format (RDF) graph has been expanded to capture reconciliation history, and the SPARQL endpoint now includes enriched documentation and example queries, facilitating programmatic access and integration with AI tools. Together, these developments reinforce MetaNetX as a high-quality, open-access platform for systems biology, metabolic modeling, and multi-omics data analysis.

Graphical abstract



Introduction

The integration of biochemical knowledge from diverse databases is essential for systems biology, metabolic modeling, and multi-omics data interpretation. However, many of these resources have been developed in silos, leading to fragmentation and inconsistencies that hinder their combined use. MetaNetX addresses this challenge by providing a unified database that reconciles metabolic information from multiple sources, including reactions, metabolites, proteins, and cellular compartments. Since its inception in 2011 and a major redesign in 2020, MetaNetX has continuously evolved to improve reconciliation accuracy, data accessibility, and support for computational modeling. This paper presents the 2025 update of MetaNetX (MNXref 4.5), focusing on enhanced chemical coverage, improved reconciliation algorithms, and new features supporting multi-omics data harmonization.

MetaNetX has evolved substantially since its inception. The 2015 release (MNXref 2.0) introduced a unified database for metabolites, reactions, proteins, and compartments, enabling structure-based reconciliation across major biochemical resources (KEGG [1], MetaCyc [2], Rhea [3], BiGG [4], the SEED [5]) and introducing distinct proton identifiers [6]. The

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2020 update (MNXref 4.0) featured a redesigned pipeline with enhanced automation, improved reconciliation quality, manual curation for ambiguous mappings, diagnostic tools for genome scale metabolic models, and a SPARQL endpoint for RDF data access [7].

The 2025 update incorporates the Virtual Metabolic Human (VMH) database [8], expands chemical and reaction coverage, enhances chemical structure computation and reconciliation, and improves RDF graph storage and SPARQL documentation. Support for multi-omics data harmonization and mapping and curated R-group definitions further strengthen MetaNetX as a comprehensive metabolic resource.

Materials and methods

Tools and software

The computation of the reconciliation was performed using different software components glued together by Bash (https://www.gnu.org/software/bash/), Perl 5.32.1 (https://www.perl.org/), Python 3.9 (https://www.python.org/), and R 4.1.0 (https://www.R-project.org) scripts. These components include InChI 1.06 [9], RDKit 2024.9.6 (https://www.rdkit.org/), Gurobi 11.0.2 (https://www.gurobi.com/), Blast 2.7.1+ [10], COBRA Toolbox 2.0.0 [11], and libSBML 5.19.0 [12].

The MetaNetX website backend is written in Perl with the help of Apache (https://httpd.apache.org/) and Virtuoso (https://virtuoso.openlinksw.com/). The frontend uses jQuery (https://jquery.com/) and DataTables (https://datatables.net/) with some of their plugins to ease browsing. The MetaNetX pipeline code and data are managed with git (https://git-scm.com/) and dvc (https://dvc.org/). The RDF structures are checked with Apache Jena 4.10.0 (https://jena.apache.org/).

Results

Data sources and integration

MetaNetX integrates biochemical data from a broad range of resources, including ChEBI [13], KEGG [1], Rhea [3], BiGG [4], The SEED [5], and the recently added VHM [8] (Tables 1 and 2). Each source is parsed, standardized, and mapped to MetaNetX identifiers through a combination of automated pipelines and manual curation.

Chemical structure computation and reconciliation

Metabolic networks databases consist of metabolites that act as substrates and products of biochemical reactions. However, there exists numerous inconsistencies in name or chemical structures within the different databases, and through their cross-references. The MetaNetX algorithm reconciles chemical-entity identifiers according to structural information, reaction context, and, to a lesser extent, cross-references and names from source databases. In MetaNetX, metabolites are defined as sets of chemical-entity identifiers that are considered equivalent. Within a set, chemical entities may interconvert via spontaneous reactions—such as acid–base reaction or tautomerism (e.g. MNXM733981 in Fig. 1)—which spontaneously takes place in aqueous solution (as in cellular metabolism). In addition, entities participating in enzymatically catalyzed reactions [e.g. the conversion of D-alanine (MNXM1105731) to L-alanine (MNXM1105732)] are systematically assigned to distinct sets and considered distinct metabolites.

To enable this reconciliation, chemical structures obtained from source databases are recomputed and standardized. Canonical InChI and SMILES strings are generated using two levels of normalization:

- Weak normalization, which reflects at best the original description. Isotopes are removed, and R groups are systematically replaced with star atoms.
- Strong normalization, which fully protonates molecules and resolves some tautomers, and re-encodes R groups with ^{13}C, among others.

As for MetaNetX 4.5, this dual normalization strategy permits reconciliation among resources, better preserving original structural variability. Generic metabolites, those containing undefined atoms or chains (e.g. R-groups), are also normalized (via the strong normalization described above) and canonicalized (meaning that there is a unique representation for each chemical entity), allowing internal representation via SMILES and InChI for reconciliation. Chemical entities that are not structurally defined are referred to as chemical symbols.

Reaction context is provided by where a metabolite appears in a chemical equation, possibly considering its enzyme catalyzer. Reaction context may suggest structure attribution to a chemical symbol.

Chemical entities from different resources may have varying levels of annotation detail, particularly regarding chemical structure and stereochemistry. These similar chemical entities may be reconciled as one or several metabolites, depending on their reaction context and cross-references.

Because chemical entities within a set may have slightly different structures (weak normalization) and names, a specific one is selected as representative, prioritizing entries from resources with expert curation and stable cross-references. In particular, ChEBI identifiers curated and used by Rhea are preferred, given their consistent maintenance and well-documented structural validation [3].

Reconciliation workflow

The reconciliation process follows six iterative steps:

1. Namespace initialization: Chemical entities are retrieved, normalized, and stored.
2. Identical structures: Entities with identical strong normalized structures are merged.
3. Similar structures in reactions: Entities with similar structures are reconciled based on reaction context across resources [20].
4. Similar structures without reactions: Entities lacking structural data but sharing trusted cross-references are merged.
5. Chemical symbol assignment via reactions: chemical symbols are assigned based on reaction participation.
6. Final set naming: Sets names are assigned and propagated from previous versions.

If no structure is provided, the algorithm uses primarily the reaction context, then the cross-references to cluster this chemical-entity in the right set. If the chemical entities in the pair do not appear in any other reaction, they cannot be reconciled with chemical entities with structures, and one cannot determine that they interconnect. Names and cross-references only are not used to enforce reconciliation. Fortunately, chem-

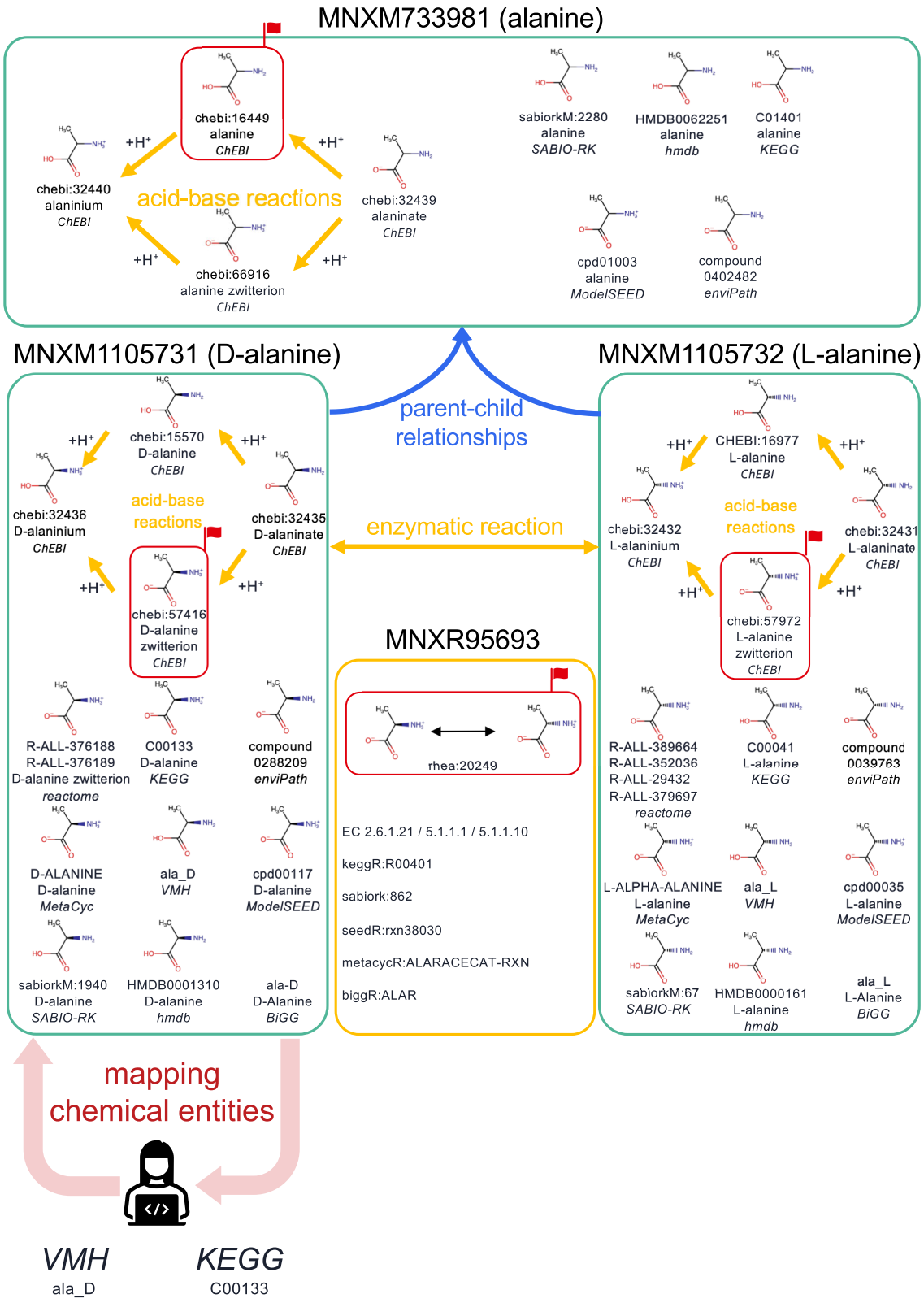

Figure 1. Internal structure of data for the reconciliation of chemical-entity identifiers. Example: alanine.

Table 1. Summary table comparing releases, showing total counts of chemicals, for MetaNetX versions 2.0 [6], 3.2, 4.0 [7], and the new 4.5

	2.0 [6]	3.2	4.0 [7]	4.5
BiGG [4]	4039	10 348	18 217	18 217
ChEBI [13]	75 507	123 835	134 607	223 004
enviPath [14]		12 306	12 306	253 521
HMDB [15]	42 542	43 179	195 008	298 876
KEGG [1]	28 429	40 256	83 452	86 138
LIPID MAPS [16]	40 719	40 772	43 085	49 190
MetaCyc [2]	15 472	17 159	20 296	27 164
Reactome [17]	4576	5344	5526	77 710
SABIO-RK [18]		7683	8944	9806
SwissLipids [19]		505 004	777 657	779 249
The SEED [5]	16 280	27 693	67 990	67 990
VMH [8]				15 872
MetaNetX	**132 812**	**691 484**	**1 045 320**	**1 495 668**

Empty fields show the data source was not included in this MetaNetX version.

ical entities appearing in metabolic models usually appear in many reactions.

A large-scale curation effort has aligned MetaNetX chemical structures with those from major providers. Manual corrections continue to be applied when automated reconciliation is insufficient. Identified errors are systematically reported to the originating resources, many of which have since been corrected thanks to the responsiveness of their curators.

Data distribution and access

The RDF scheme has been completed to store detailed relationships between entities. It now captures the reconciliation history for each metabolite and reaction, enabling traceability of each reconciliation step. The SPARQL endpoint has been updated with improved documentation and integrated example queries, enhancing usability for researchers. Documentation is automatically generated using WIDOCO (https://github.com/dgarijo/Widoco), and example queries are embedded within the endpoint interface, allowing integration with Large Language Model-based (LLM-based) tools such as ExpasyGPT [21]. The RDF is downloadable as Turtle (ttl) files. The legacy TSV format is still available for backward compatibility.

Improved reconciliation accuracy

The updated structure computation pipeline has led to a substantial increase in the number of reconciled compounds (here defined as sets) across sources (rows "MetaNetX" in Tables 1 and 2). This reduces redundancy and improves the consistency of metabolic models derived from MetaNetX.

Compared to MNXref 4.0, version 4.5 introduces dual-level normalization, automatic SPARQL query documentation, and the integration of the VHM database [8], collectively enhancing usability, reproducibility, and biochemical completeness. The software stack was also updated, favoring open-source software.

Support for multi-omics data harmonization and mapping

Accurate and consistent metabolite mapping is an essential first step toward multi-omics data harmonization. MetaNetX facilitates this process by providing a coherent biochemical namespace that enables proteomic, metabolomic, and fluxomic datasets to be mapped onto standardized chemical and reaction entities. While MetaNetX does not perform integrative analyses itself, it supplies the unified identifiers and RDF framework necessary for downstream cross-omics correlation and model contextualization.

Table 2. Summary table comparing releases, showing total counts of reactions, for MetaNetX versions 2.0 [6], 3.2, 4.0 [7], and the new 4.5

	2.0 [6]	3.2	4.0 [7]	4.5
BiGG [4]	11 458	30 574	56 340	56 342
KEGG [1]	9925	10 503	11 161	11 863
MetaCyc [2]	13 783	15 162	17 208	20 242
Rhea [3]	32 256	39 692	50 042	69 008
SABIO-RK [18]		6994	8118	8953
The SEED [5]	13 260	13 244	43 855	43 843
VMH [8]				28 794
MetaNetX	**31 527**	**42 182**	**74 638**	**83 796**

Empty fields show the data source was not included in this MetaNetX version.
Numbers of reactions are not straightforward to compare as some reactions sources use compartmentalized reactions (e.g. BiGG), and some do not (e.g. Rhea).

Compared with other resources offering identifier cross-mapping, MetaNetX focuses specifically on chemical structure and reaction-aware reconciliation. In contrast, BridgeDb [22] primarily provides programmatic access for generic identifier translation and does not consider metabolic reactions, and PMhub [23] and BioCyc [2] include cross-references but do not provide mapping tools. MetaNetX addresses these limitations by combining structural normalization (InChI, SMILES), reaction context, and curated R-group definitions within an RDF graph.

Through its interactive web interface, users can query molecules by name or identifier, visualize standardized chemical structures, and inspect parent–child relationships and tabular cross-resource comparisons. The integrated ID-mapper tool (https://www.metanetx.org/cgi-bin/mnxweb/id-mapper) supports precise translation of metabolites, reactions, and compartments between reference databases, while the SPARQL endpoint (https://rdf.metanetx.org/) provides advanced, federated query capabilities. By leveraging chemically coherent entity groupings and reaction-context-aware mapping, MetaNetX ensures robust and reproducible data harmonization, thereby empowering metabolic modeling and multi-omics workflows. Examples are available on the ID mapper and on the SPARQL query editor pages, with the mapping examples and the SPARQL query examples respectively.

A typical use case is the mapping of a list of identifiers from one resource to another, e.g. from HMDB [15] identifiers to ChEBI [13] or KEGG [1] identifiers. The mapping to multi-

ple resources enables interpretations in different contexts, e.g. a metabolomic analytical platform could provide well suited identifiers depending on the context of the study: organism, biofluid or tissue, preferred database. The mapping will also highlight duplications, i.e. several identifiers mapped on the same MetaNetX set.

Discussion

The 2025 release of MetaNetX (MNXref 4.5) represents a significant advancement in the integration, standardization, and reconciliation of metabolic data, building on major milestones since its inception in 2015 [6] and enhancements in 2020 [7]. This update delivers improved reconciliation accuracy, broader coverage of metabolites and biochemical reactions, and enhanced support for multi-omics applications. Metabolic data resources use different identifiers and nomenclature, are often not in sync for the same metabolites, and may contain duplicates. So, the reconciliation of metabolic data is a major concern. Several attempts have been made to achieve identifier cross mapping between resources. Some databases reconcile only based on cross-references (BridgeDb [22], PMhub [23] or BioCyc/MetaCyc [2]), but cross-references may be contradictory, outdated or missing. Some reconcile based on standard InChI (UniChem [24]), but standard InChI does not deal with R-groups and have issues with some tautomers. Some databases reconcile specifically for some clades (plants for PMhub [23]), or for the genomes of their collection (BioCyc/MetaCyc [2]). MetaNetX reconciles with advanced structural information, taking into account R-groups and stereochemistry relationships, with cross-references and a ranking on resource reliability, and with the reaction context in different metabolic models. MetaNetX reconciliation is clade and genome agnostic, and wants to be as generic as possible. StructRecon [25] uses a process close to the one of MetaNetX, but includes MetaNetX. Their identifier cross mapping interface provides similar input, but we think MetaNetX output is easier for biologists. Also, MetaNetX reconciles biochemical reactions and cellular compartments. By applying refined structural reconciliation methods, but specifically optimized for genome-scale metabolic models and taking into account the reaction context of chemical entities, MetaNetX achieves seamless alignment across diverse biochemical databases and experimental standards—including those evaluated by StructRecon [25]—ensuring both computational interoperability and experimental relevance.

With the integration of new resources such as the VHM database [8] and the MetaNetX participation in the Recon4IMD project (https://www.recon4imd.org/), MetaNetX significantly expands its capacity to support organism-specific metabolic reconstructions. The platform now incorporates hundreds of new enzyme and reaction entries relevant to inborn errors of metabolism (IMDs), facilitating comprehensive harmonization of chemical entities, reactions, genes, and enzymatic functions. The ongoing curation process identifies and resolves inconsistencies in identifiers, molecular structures, nomenclature, and cross-references, both within MetaNetX and in collaboration with primary data providers, reinforcing data integrity and consistency across platforms [26].

These harmonized datasets underpin sophisticated computational tools like BioRetro [27] and GSETransformer [28], which utilize MetaNetX's standardized data to perform advanced biosynthetic pathway planning and predict natural product biosynthesis with high precision.

Another key innovation in this release is the enhanced incorporation of standardized chemical structure representations (InChI, SMILES) into the RDF framework and SPARQL endpoint, accompanied by thorough documentation and example queries to support interoperability with artificial intelligence and large language models [21].

MetaNetX carefully manages biochemical nuances—such as tautomeric forms and radical species—that challenge simplified one-to-one mappings between metabolites and molecular identifiers, addressing these edge cases to maintain biological fidelity. The integration pipeline prioritizes data sources containing reaction context, preserving critical functional information while gracefully handling databases lacking such data.

In the context of increasing restrictions on open biochemical data access [29], MetaNetX reaffirms its commitment to open science principles, promoting transparent, accessible resources to support reproducibility and data sharing in the metabolic modeling community.

This release thus substantially strengthens MetaNetX as a comprehensive and open platform vital for systems biology, synthetic biology, and multi-omics data integration efforts.

Future work will extend MetaNetX to additional plant organisms and natural products, for example from the Plant Metabolic Network [30] and LOTUS [31]. Planned user interface upgrades include website refurbishment, and programmatic APIs for omics data ingestion. The pipeline will integrate COBRApy [32] or COBRA.jl [33] and extend the normalization process to polymers and for accurate tautomer handling. SPARQL endpoint improvements will focus on federated query support, and expansion of LLM-assisted query generation (ExpasyGPT [21]) to support interactive model debugging.

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Conflict of interest

None declared.

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Data availability

All data integrated into MetaNetX are available through the MetaNetX website (https://www.metanetx.org) and its SPARQL endpoint (https://rdf.metanetx.org/sparql) under a Creative Commons Attribution 4.0 International License (CC BY 4.0). The RDF graph and reconciliation mappings can be downloaded from the MetaNetX FTP server.

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