groov^{DB} in 2025: A community-editable database of small molecule biosensors

Joshua D. Love[1], Brady M. Rafferty[2], Michael Thomas[2], Michael Springer[3,4,5], Pamela A. Silver[3,4,5], Simon d'Oelsnitz* [3,5]

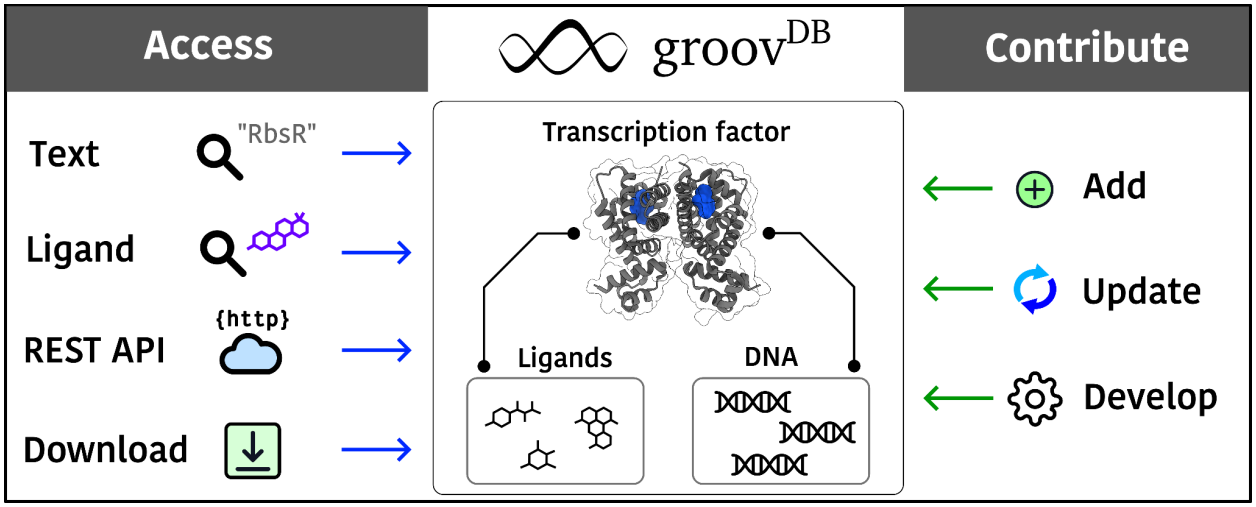
Affiliations

[1] Independent Web Developer. Bentonville, AR, 72712, USA
[2] Harvard University, Cambridge, MA, 02138, USA.
[3] Synthetic Biology HIVE, Department of Systems Biology, Harvard Medical School, Boston, MA, 02115, USA
[4] Wyss Institute for Biologically Inspired Engineering at Harvard University, Boston, MA, 02115, USA.
[5] Department of Systems Biology, Harvard Medical School, Boston, MA, 02115, USA.
* To whom correspondence should be addressed: Simon d'Oelsnitz, simonsnitz@gmail.com

Abstract

The groov^{DB} database (https://groov.bio) was launched in 2022 with the goal of organizing information on prokaryotic ligand-inducible transcription factors (TFs). This class of proteins is important in fundamental areas of microbiology research and for biotechnological applications that develop biosensors for diagnostics, enzyme screening, and real-time metabolite tracking. Uniquely, groov^{DB} contains stringently curated, literature-referenced data on both TF:DNA and TF:ligand interactions. Here, we describe a major update to groov^{DB}, making the database community-editable and adding several advanced features. Users can now add new TF entries and update existing entries using a simple online form. New user interface elements allow viewing of interactive TF protein structures and DNA-binding motifs. Updated query methods enable text-based search, chemical similarity search, and attribute-filtering searches. A new data architecture improves web interface responsiveness by over five-fold. Finally, the number of TF entries has more than doubled and all source code is now open-access.

Graphic abstract



Introduction

Prokaryotes adapt to their environment by triggering the expression of genes in response to chemical stimuli using ligand-inducible transcription factors (TFs). Upon binding to their small molecule ligand, TFs undergo a conformational change that alters their ability to bind to DNA, which either promotes transcription, by recruiting an RNA polymerase, or represses transcription, by occluding the RNA polymerase from initiating transcription[1]. TFs largely define how a prokaryote's chemical environment influences its transcriptional program, and therefore mapping the ligand and DNA targets of TFs is crucial to understand and predict microbial behavior.

For decades, prokaryotic TFs have also played a pivotal role in biotechnology. Initially employed as inducible gene expression systems in organisms such as yeasts, mammalian cells, insects, and plants, TFs became core to the field of Synthetic Biology in the early 2000s, where they were used to build logic circuits[2,3]. Shortly afterwards, TFs found use as high-throughput screening tools for strain and enzyme engineering; by using a TF responsive to an enzyme product to control GFP expression, millions of enzyme variants expressed within cells could be screened using fluorescence-activated cell sorting[4–7]. More elaborate genetic schemes used TFs to stabilize production phenotypes within engineered strains, dynamically regulate pathways to minimize cellular toxicity, and autonomously induce gene expression based on cellular density to obviate the need for inducers[8–11]. Beyond metabolic engineering applications, TFs have served as central components for diagnostics and live cell imaging. Cell-free systems controlled by TFs have been used to monitor water pollution and build responsive textiles[12,13]. TFs have been linked to bioelectronic and acoustic readouts to report on disease states within the gut of live animals[14–16]. And TFs fused to split GFP proteins have been used to record real-time abundance of compounds such as hydrogen peroxide, cyclic di-GMP, itaconate, and fructose 1,6-bisphosphate in mammalian cells[17–20].

Despite these exciting applications, identifying a ligand-inducible TF appropriate for a given project remains challenging. Few existing resources document experimentally validated TF binding interactions, and in particular, ligand binding interactions. Several databases, such as MIST, P2CS, KEGG, and iModulonDB, describe signal transduction pathways or transcriptomic datasets in prokaryotes, but lack specific DNA or ligand binding information[21–24]. Other databases, such as RegulonDB, DBTBS, CoryneRegNet, and RhizoRegNet, report on the DNA binding interactions of TFs, but information is only available for specific organisms[25–28]. Finally, some databases provide some information on TF-ligand interactions, such as RegPrecise and PRODORIC, but these interactions are often not supported by experimental evidence[29,30].

groovDB is a manually curated database of experimentally validated prokaryotic ligand-inducible transcription factor interactions initially launched in 2022[31]. In this release of groov^{DB}, new features and updated content are incorporated to make the database easier to query, more responsive, more intuitive, and open to community contribution. Overall, groov^{DB} is positioned to facilitate the identification of TFs broadly useful for microbiology and biotechnology research.

System overview and database content

Since its launch in 2022, groov^{DB} has been a leading resource for ligand-inducible transcription factors commonly used in synthetic biology, microbiology, and broader biotechnology research. groov^{DB} has consistently been improved in each update, which offers a more intuitive user interface, new ways to contribute to and query the database, improved responsiveness, greater documentation, and expanded content. These improvements translate to facilitating the study and utility of transcription factor biosensors for applications relevant to health and sustainability.

In this latest update, we have made groov^{DB} a community-editable and open-source application. Users can now add their own transcription factors or update existing entries using a simple online form. In addition, the open-sourced codebase for both the frontend and backend, alongside detailed documentation, now enables software contributions from the community. Together, these updates greatly facilitate both internal and external contributions to this growing database. Finding TF entries is now easier with the ability to perform advanced searches based on TF property filters, text-based queries, and via a new chemical similarity search feature. We also offer new methods to access data within groov^{DB}, including programmatic access via a REST API and downloading the entire database as a static file. Improved user interface elements support the display of interactive Alphafold structures when crystal structures are not available, as well as DNA motif visualization that summarizes interactions with multiple DNA sequences. Finally, we have more than doubled the size of groov^{DB}, which now contains >215 unique transcription factors, >260 unique operator sequences, and >320 unique ligands from 112 unique organisms.

Community editing

To facilitate the continuous expansion of content in groov^{DB}, we have introduced a feature allowing users to add or update TF entry pages after creating an account. Users can create or sign into their account simply using their Google credentials, via the secure OAuth 2.0 protocol, or by manually entering their account details. User authentication and authorization is securely managed by the AWS Cognito service. After sign-in, users can create a TF entry by completing a form that includes necessary metadata, ligand binding information, and DNA binding information for their new entry. Criteria for ligand and DNA interaction evidence are thoroughly

described in documentation pages, helping guide the contributor while maintaining the rigorous integrity of the database. Inputs are validated in real time to prevent downstream integration issues. Upon submission, the TF entry is moved to a queue that must be reviewed and approved by an administrator, which further strengthens the accuracy of the database content. After approval, a bioinformatic pipeline is run to fetch additional metadata, such as PDB structure codes, the Alphafold structure code, host organism name and taxonomy ID, the protein sequence, genome context, additional references, and links to the external databases such as KEGG[23]. Following a second round of administrator approval to validate the newly generated content, the TF entry is added to the publicly-facing database. Users can also update existing TF entries to ensure database content is current and up-to-date as new literature results are published. To update a TF entry, users edit the entry's populated submission form. The updated TF form is then passed through the same administrator review process as for TF entry creation to ensure consistency. Finally, beyond content contributions, users can now support the development of the open-source groov^{DB} software, which is freely available on GitHub as frontend and backend repositories.

New query tools

GroovDB provides three methods to query the database: browsing, text search, and chemical similarity search. Users can browse for TFs based on several features, such as their structural family, their host organism, Uniprot ID, or RefSeq ID through a new interactive data table on the "Browse" page. Advanced searches can be performed in the same data table by filtering entries based on TF attributes or via a comprehensive full text-based search. From the Home page, the database can be queried using text-based and chemical-similarity search. Text searches return entries that have TF aliases or ligands that match the text input. Chemical similarity search accepts an input chemical in SMILES notation and returns TF entries with corresponding ligands that are similar to the input chemical, based on tanimoto similarity scores. Only ligands that meet a similarity threshold are returned, and this threshold can be adjusted by the user. The chemical similarity search method is particularly useful when users are looking for a template TF biosensor for evolution that responds to a ligand similar to a user-defined target, as several directed evolution methodologies exist for altering TF ligand specificity[32,33]. As the database content continues to grow, these query features will greatly simplify finding relevant TF entries.

Programmatic access

New methods are provided for programmatic access to all data in groov^{DB}, which is particularly valuable for bioinformatics or machine learning projects that need high-quality, manually curated data. A new REST API allows users to fetch subsets of the database, including defined TF entries, sets of entries from particular families, or all entries. Detailed documentation on query structures with examples and the expected data format to be returned is provided in a dedicated

Swagger page. The full database in JSON format is also available via a download link, which is continuously updated as TF entries are added or updated.

Enhanced web interface

The web interface of groov^{DB} has been significantly revised to provide a more intuitive and data-rich user experience. Several improvements have been made to the TF entry pages. Interactive Alphafold structures fetched from the Alphafold Protein Structure Database are now supported for all TF entries, which aids the molecular exploration of DNA and ligand binding interfaces[34]. DNA motif visualization has also been improved. In the previous version, only one DNA sequence could be associated with each TF entry, which limited accuracy. The current release now supports the integration of multiple DNA sequences, which are used to create a position-weighed sequence motif using the React LogoJS component[35]. This change is particularly important for accurately reporting the DNA binding specificity of global TF regulators, which often promiscuously bind to many DNA sequences bearing a small specificity motif[1]. Additional display modifications further improve the readability of data in each TF entry page, including a new protein sequence viewer that indicates the protein length as well as new Uniprot-like display formats for metadata, such as the organism name and KEGG ID. On the Home page, a continuously updated panel with database content statistics, including the number of unique TFs and ligands, is now displayed. Finally, documentation on the About page has been significantly revised. Criteria for accepted TF:ligand and TF:DNA interaction evidence is detailed, a new Frequently Asked Questions page is added, and a new contact form with CAPTCHA validation was incorporated.

Expanded content and statistics

The current release of groov^{DB} has more than doubled in size compared to its original release (**Table 1**). This version documents 588 manually curated binding interactions from 441 literature articles, which includes 320 unique ligand interactions and 268 unique DNA interactions. Data is distributed across 216 ligand-inducible TFs, which belong to over 8 major structural families, marking a substantial increase in database quality and quantity. The TetR family is most represented, with over 100 members, likely due to not only their abundance in microbial genomes, but also their relative ease of characterization since they are small, generally soluble, and often bind to short specific sequences (**Figure 1A**)[36]. A wide range of structurally diverse ligands are represented, with two distinct clusters around sugars and coenzyme A ligated molecules (**Figure 1B**). Certain transcription factor families tend to bind to structurally similar ligands, such as the LacI family's preference for sugars and the LuxR family's preference for homoserine lactone quorum molecules. However, other families bind to many structurally unrelated molecules, including the TetR and MarR families. Transcription factors within groov^{DB} belong to a total of 112 unique organisms. Interestingly, although well-studied model organisms

like *Escherichia coli* and *Pseudomonas aeruginosa* have greater representation, two thirds of all regulators come from organisms with four or fewer transcription factors, highlighting the rich diversity of organisms represented in groov^{DB} that would be missed in the more common organism-specific databases (**Figure 1C**).

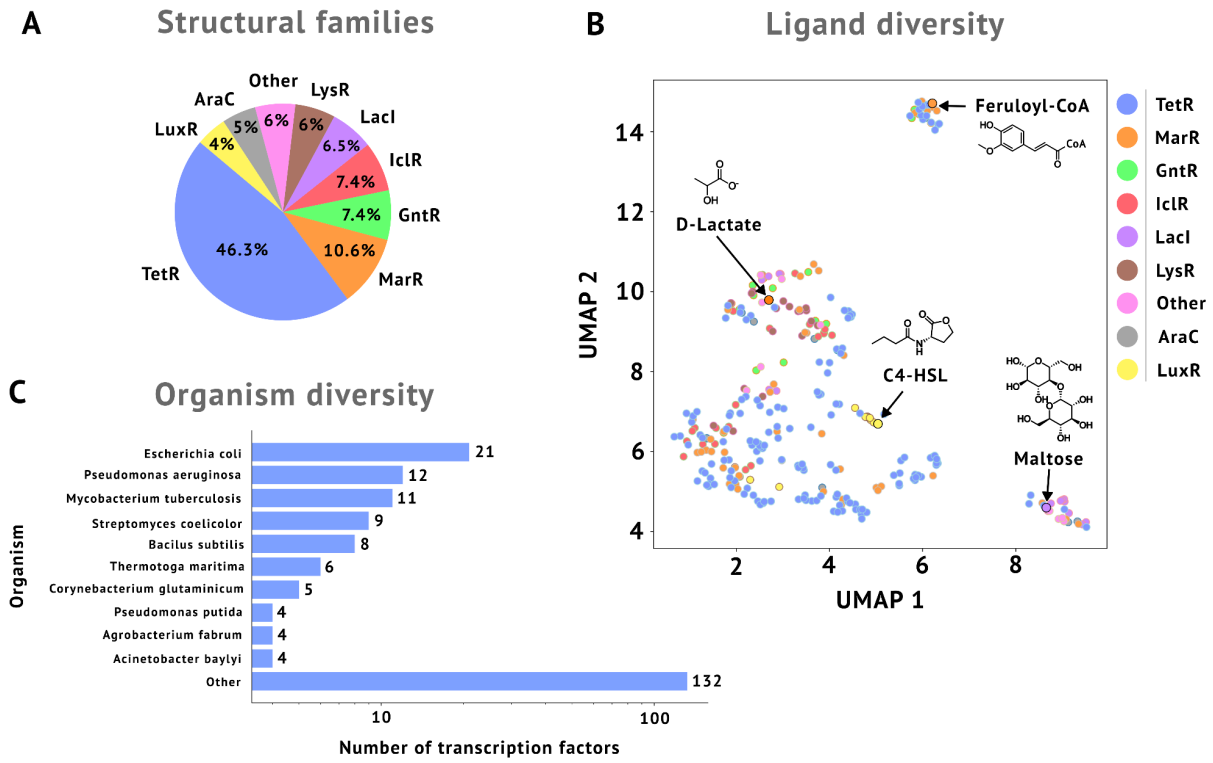


Figure 1: Content of groov^{DB} in 2025. (A) Relative abundance of major structural families. (B) UMAP projection of ligand chemical fingerprints colored by transcription factor family. Each point represents a unique ligand and selected ligands are highlighted and labeled. (C) Diversity of organisms represented in groov^{DB}. Transcription factors belonging to the ten most represented organisms are highlighted.

Table 1: Comparison of the past and current versions of groov^{DB}

Content	groov^{DB} 2022	groov^{DB} 2025
Total sensors	101	216
Total unique ligands	131	320
Total unique organisms	62	112
Total DNA interactions	101	268
Entries with structures available	34	216

Improved data infrastructure

To provide a more rapid and robust infrastructure to host content in groov^{DB}, we made several significant changes to the architecture of the application. All database content is stored in two locations: a static JSON file for rapid access and a flexible NoSQL database for managing entry additions and updates. By fetching content from a static server, page loading is over five-fold more responsive compared to the previous version. Both databases are always kept in sync with each other, which enables this hybrid database approach to strike a balance between speed and flexibility. To further improve responsiveness, we integrated the global React state manager, Zustand, which caches web page content. To provide a secure administration portal for supporting the integrity and accuracy of database content, we have deployed authentication endpoints using the Infrastructure as Code model. To provide a robust framework that can scale with variable traffic, groov^{DB} was built using a serverless architecture that is able to expand and contract on demand. Finally, the frontend interface is deployed with AWS Amplify, which allows for a flexible continuous integration / continuous deployment workflow.

Summary and future directions

The goal of groov^{DB} has been to organize the world's knowledge of genetically-encoded small molecule biosensors. The release of groov^{DB} presented herein represents a significant advance towards this goal by adding community-editing, enhanced visualizations, new query methods, and expanded content to its previous version. In the past couple of years we have directed our efforts towards making database contribution easier to promote the expansion of content. In the future, we aim to make groov^{DB} more actionable by tailoring it for practical use cases. We envision this involving the addition of more complex sequences, such as TF-regulated promoters and experimentally validated inducible expression plasmids, which can be directly used in defined experimental workflows. Furthermore, we aim to incorporate non-natural TFs, such as TF variants that have been engineered for improved sensitivity, that might be more practical for various bioengineering applications.

Data availability

All original data containing experimental evidence displayed in groov^{DB} transcription factor entry pages are listed under the "References" section, with links to the source articles. All source code of groov^{DB} is open-sourced on GitHub under an MIT license. The GitHub repository for the frontend code is available here: https://github.com/groov-bio/groov-db-ui. The GitHub repository for the backend code is available here: https://github.com/groov-bio/groov-db-api.

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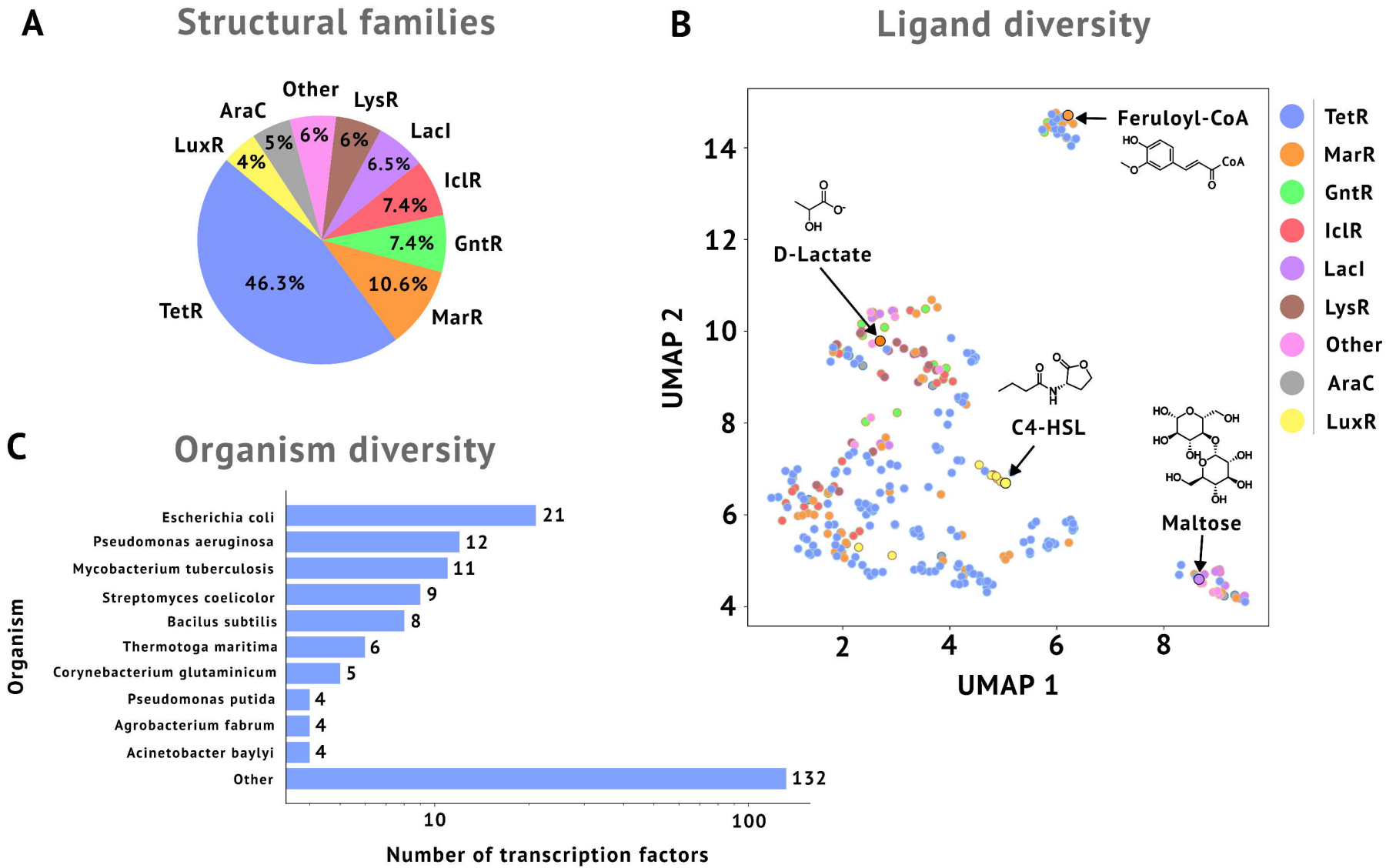
A
Structural families
Other
LysR
AraC
LacI
LuxR
IclR
GntR
MarR
TetR
6%
6%
5%
4%
6.5%
7.4%
7.4%
10.6%
46.3%
B
Ligand diversity
Feruloyl-CoA
D-Lactate
C4-HSL
Maltose
UMAP 2
UMAP 1
TetR
MarR
GntR
IclR
LacI
LysR
Other
AraC
LuxR
C
Organism diversity
Escherichia coli 21
Pseudomonas aeruginosa 12
Mycobacterium tuberculosis 11
Streptomyces coelicolor 9
Bacilus subtilis 8
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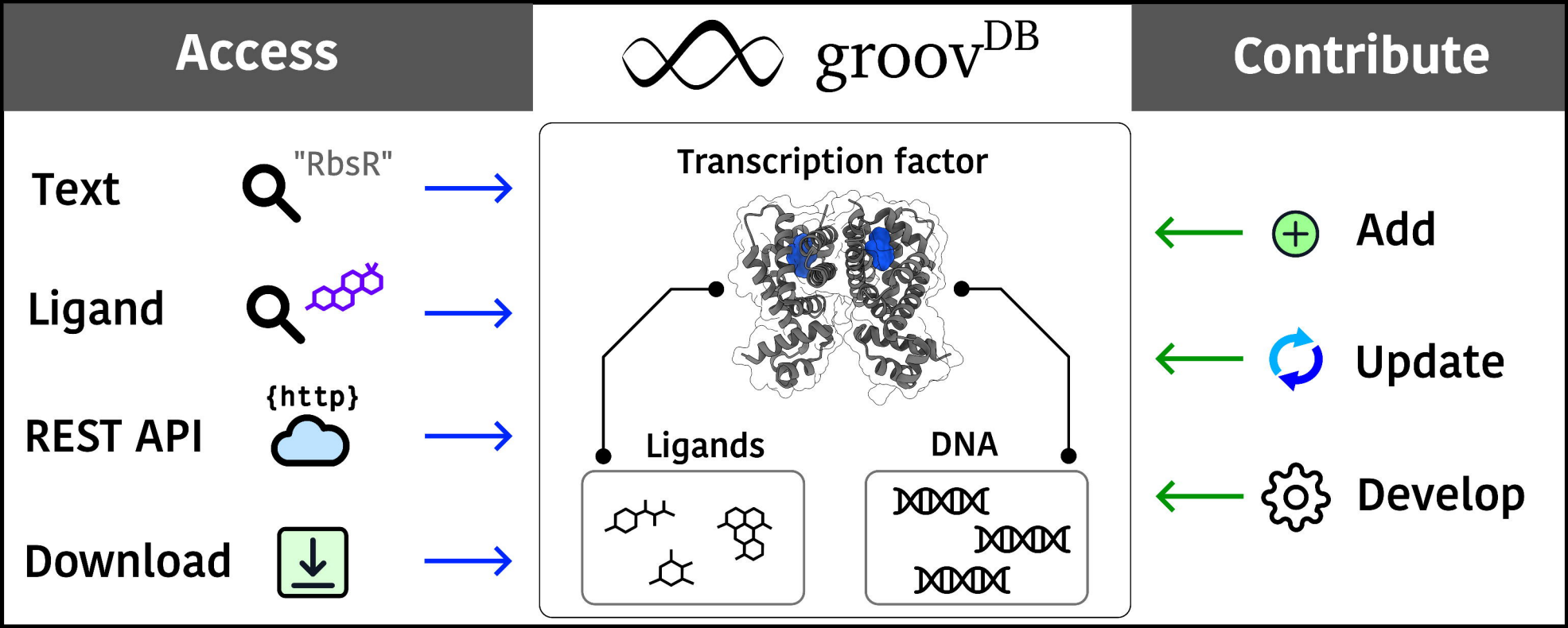
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