# Efficient querying of genomic databases for single-cell RNA-seq with *gget*

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## Abstract

**Motivation:** A recurring challenge in interpreting single-cell RNA-seq data is the assessment of results in the context of existing genomic databases. Currently, there is no tool implementing automated, easy programmatic access to information stored in a diverse collection of large, public genomic databases.
**Results:** *gget* is a free and open-source command-line tool and Python package that enables efficient querying of genomic databases. *gget* consists of a collection of separate but interoperable modules, each designed to facilitate one type of database querying required for single-cell RNA-seq data analysis in a single line of code.
**Availability:** The manual and source code are available at https://github.com/pachterlab/gget.

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## Introduction

The increasingly common use of single-cell RNA-seq to provide transcriptomic characterization of cells is dependent on quick and easy access to reference information stored in large genomic databases such as Ensembl, NCBI, and UniProt (Cunningham *et al.*, 2022; NCBI Resource Coordinators, 2013; UniProt Consortium, 2021). A majority of researchers currently access genomic databases to annotate and functionally characterize putative marker genes through web access (Stalker *et al.*, 2004; Birney *et al.*, 2004). This process is time-consuming and error-prone, as it requires manually copying and pasting data, such as gene IDs.

To facilitate and automate functional annotation for single-cell RNA-seq analyses, we developed *gget:* a free and open-source software package that rapidly queries information stored in several large, public databases directly from a command line or Python environment. *gget* consists of a collection of tools designed to perform the database querying required for single-cell RNA-seq data analysis in a single line of code. In addition to providing access to genomic databases, *gget* can also leverage sequence analysis tools, such as BLAST (Altschul *et al.*, 1990, 1997), thus simplifying complex annotation workflows.

While there are some web-based Application Programming Interface (API) data mining systems, such as BioMart (Durinck *et al.*, 2005; Kasprzyk *et al.*, 2004), we identified several limitations in such tools, including limits to query types and to utilizing databases in tandem. Moreover, large-scale single-cell RNA-seq analysis is better served by command line or packaged APIs that can fetch data directly into programming environments.

The *gget* modules combine MySQL (Oracle Corporation, 1995), API, and web data extraction queries to rapidly and reliably request comprehensive information from different databases (Figure 1). This approach allows *gget* to perform tasks unsupported by existing tools built around standard API queries (de Ruiter, 2016). For instance, searching for genes and transcripts using free-form search terms. Each *gget* tool requires minimal arguments, provides clear output, and operates from both the command line and Python environments, such as JupyterLab, maximizing ease of use and accommodating novice programmers.

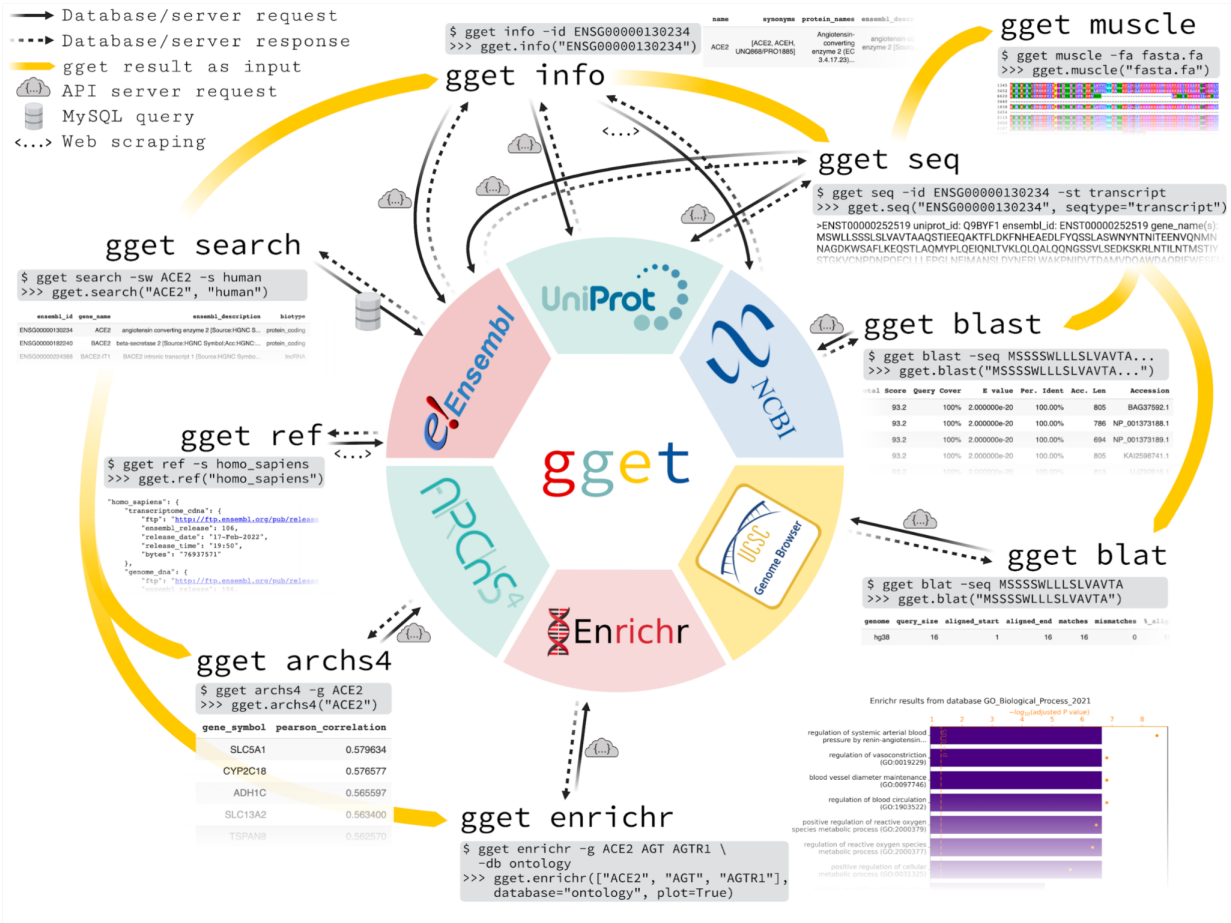


**Figure 1** Overview of the nine *gget* tools and the public databases they access. One simple command line ($) example and its Python (>>>) equivalent are shown for each tool with the corresponding output.

## Description

*gget* consists of nine tools:

- *gget ref:* Fetch File Transfer Protocols (FTPs) and metadata for reference genomes or annotations from Ensembl by species.
- *gget search:* Fetch genes or transcripts from Ensembl using free-form search terms.
- *gget info*: Fetch extensive gene or transcript metadata from Ensembl, UniProt, and NCBI by Ensembl ID.
- *gget seq:* Fetch nucleotide or amino acid sequences of genes or transcripts from Ensembl or UniProt by Ensembl ID.
- *gget blast:* BLAST (Altschul *et al.*, 1990, 1997) a nucleotide or amino acid sequence to any BLAST database.
- *gget blat:* Find the genomic location of a nucleotide or amino acid sequence using BLAT (James Kent, 2002).
- *gget muscle:* Align multiple nucleotide or amino acid sequences to each other using the Muscle5 algorithm (Edgar, 2021).
- *gget enrichr:* Perform an enrichment analysis on a list of genes using Enrichr (Chen *et al.*, 2013; Xie *et al.*, 2021; Kuleshov *et al.*, 2016) and an extensive collection of gene set libraries, including KEGG (Kanehisa and Goto, 2000; Kanehisa, 2019; Kanehisa *et al.*, 2021) and Gene Ontology (Ashburner *et al.*, 2000; Gene Ontology Consortium, 2021).

- *gget archs4:* Find the most correlated genes to a gene of interest or find the gene's tissue expression atlas using ARCHS4 (Lachmann *et al.*, 2018).

Each *gget* tool accesses data stored in one or several public databases, as depicted in Figure 1. *gget* fetches the requested data in real-time, guaranteeing that each query will return the latest information. One exception is *gget muscle*, which locally compiles the Muscle5 algorithm (Edgar, 2021) and therefore does not require an internet connection.

*gget info* combines information from Ensembl, NCBI, and UniProt (Cunningham *et al.*, 2022; NCBI Resource Coordinators, 2013; UniProt Consortium, 2021) to provide the user with a comprehensive executive summary of the available information about a gene or transcript. This also enables users to assert whether data from different sources are consistent.

By accessing the NCBI server (NCBI Resource Coordinators, 2013) through HTTP requests, *gget blast* does not require the download of a reference BLAST database, as is the case with existing BLAST tools (Buchfink *et al.*, 2021; Camacho *et al.*, 2009). The whole self-contained *gget* package is approximately 3 MB after installation.

The package dependencies were carefully chosen and kept to a minimum. *gget* depends on the HTML parser *beautifulsoup4* (Richardson, 2022), the Python MySQL-connector (Oracle, 2022), and the HTTP library *requests* (Reitz, 2022). All of these are well-established packages for server interaction in Python. *gget* has been tested on Linux/Unix, Mac OS (Darwin), and Windows.

## Usage and documentation

*gget* can be installed from the command line by running ‘pip install gget’. Figure 1 depicts one use case for each *gget* tool with the corresponding output.

Each *gget* tool features an extensive manual available as function documentation in a Python environment or as standard output using the help flag [-h] in the command line. The complete manual with examples can be viewed in the *gget* repository, available at https://github.com/pachterlab/gget. A separate *gget examples* repository is accessible at https://github.com/pachterlab/gget_examples and includes exemplary workflows immediately executable in Google Colaboratory (Bisong, 2019).

## Discussion

Our open-source Python and command-line program *gget* enables efficient and easy programmatic access to information stored in a diverse collection of large, public genomic databases. The *gget* modules were motivated by experience with tedious single-cell RNA-seq data analysis tasks (Supplementary Figure 1), however, we anticipate their utility for a wide range of bioinformatics tasks.

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