Module 7: Programmatic Access to Public Chemical Databases

Learning Objectives

- Know how to formulate a PUG-REST request URL.
- Know how to access PubChem data from a spread sheet (in Google Sheet)
- Know how to access PubChem data from a python script.

1. Useful resources for students with no programming background

In this module, we will learn how to "programmatically" access PubChem and other public databases. Cheminformaticians often write computer programs to process a large amount of chemical data and to automate some tasks that are routinely performed. Therefore, computer programming is an essential skill for future cheminformaticians. While this module does not require prior knowledge of computer programming, it is highly recommended that students with no or little programming background build some basic computer programming skills. There are many online resources that help you learn computer programming and below are some of them.

- w3schools.com (https://www.w3schools.com)
- Tutorialspoint.com (https://www.tutorialspoint.com/index.htm)
- Code.org (https://code.org)
- Code Academy (https://www.codecademy.com)
- Exercism (http://exercism.io)
- Cloud9 (https://c9.io)
- Ideone (https://ideone.com)
- LearnPython.org (https://www.learnpython.org)
- Python Challenge (http://www.pythonchallenge.com)

In addition, an introductory material about Web APIs (Application Programming Interfaces) is available at the OLCC web site (as a Special Topic Module).

- **Programmatic Access to Data (by Jordi Cuadros)** (http://olcc.ccce.divched.org/Spring2017OLCCSpecialTopic-Programmatic%20Access%20to%20Data)

The present module focuses on accessing PubChem data, but many other public chemical information resources also provide programmatic access to their data. Some examples complied by the OLCC Cheminformatics Faculty are available at this URL:

- Programmatic Access to Web-Based Chemical Information – Examples (http://olcc.ccce.divched.org/content/prog-access)

2. Overview of Programmatic Access to PubChem

Currently PubChem[1-3] contains more than 235 million depositor-provided substance descriptions, 94 million unique chemical structures and 232 million biological test results from one million assays, covering more than 10 thousand unique protein target sequences. Many researchers in the biomedical science community have a great interest in programmatic access to this vast amount of data because it presents new opportunities for data-driven research in a "big data" era. PubChem provides several ways for programmatic access to its data, including:

- Entrez Utilities (also called E-Utilities or E-Utils)
- Power User Gateway (PUG)
- PUG-SOAP
- PUG-REST

E-Utilities, used for programmatic access to information contained in the Entrez system, are suited for accessing text or numeric-fielded data, they cannot deal with more complex types of data specific to PubChem, such as chemical structures and tabular bioactivity data. Thus, PubChem provides additional programmatic access routes specialized for PubChem data and analysis services: PUG, PUG-SOAP, and PUG-REST. While suitable for low-level programmatic access to PubChem, PUG exchanges data through a complex eXtended Markup Langauge (XML) schema that requires some expertise to use. For the sake of user-friendliness and for integration with a

variety of third party tools, PubChem provides two easier-to-use web service access methods: PUG-SOAP, which uses the simple object access protocol (SOAP) and PUG-REST, which is a Representational State Transfer (REST)-style interface. An overview of these programmatic access routes to PubChem is given in the following paper:[4]

- **PUG-SOAP and PUG-REST:**
  Web Services for Programmatic Access to Chemical Information in PubChem
  Kim *et al.*, *Nucleic Acids Res.* **2015**, 43(W1), W605-W611.
  (http://dx.doi.org/10.1093/nar/gkv396).

In this module, we will learn how to access PubChem using PUG-REST, because it is the simplest to use and learn. More in-depth information on programmatic access to PubChem is described in these documents:

- **E-Utilities**
  - Entrez Programming Utilities Help (http://www.ncbi.nlm.nih.gov/books/NBK25501/)
  - E-Utilities Quick Start (http://www.ncbi.nlm.nih.gov/books/NBK25500/)
- **PUG**
  - PUG Help (https://pubchem.ncbi.nlm.nih.gov/pug/pughelp.html)
- **PUG-SOAP**
  - PUG-SOAP Help (http://pubchem.ncbi.nlm.nih.gov/pug_soap/pug_soap_help.html)
  - PUG-SOAP Client Help (http://pubchem.ncbi.nlm.nih.gov/pug_soap/client_help.html)
  - PUG-SOAP Web Service Reference (http://pubchem.ncbi.nlm.nih.gov/pug_soap/PUG_SOAP.html)
- **PUG-REST**
  - PUG-REST Help (http://pubchem.ncbi.nlm.nih.gov/pug_rest/PUG_REST.html**)**
  - PUG-REST Tutorial (http://pubchem.ncbi.nlm.nih.gov/pug_rest/PUG_REST_Tutorial.html**)**
  - Programmatic Retrieval of Small Molecule Information from PubChem Using PUG-REST (in press). [Available to logged-in students at bottom of this module.]

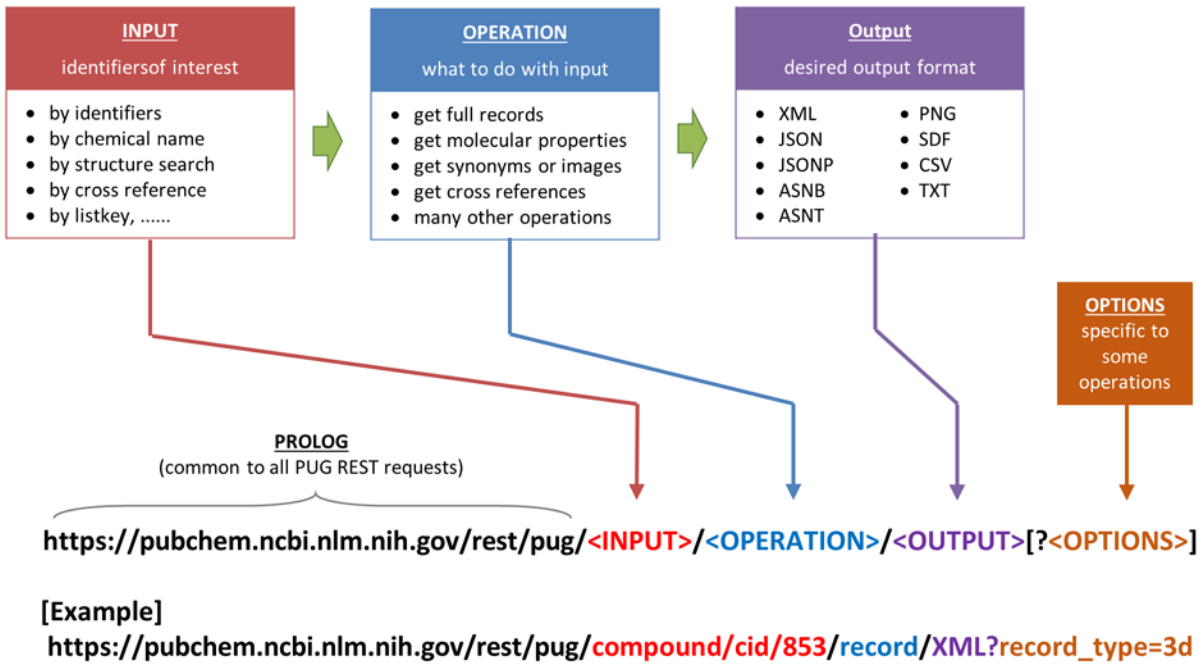
3. PUG-REST

3.1. Concepts and Syntax of PUG-REST requests

PUG-REST is the simplest to use and learn among the existing programmatic access methods to PubChem. Importantly, because information necessary for a PUG-REST request can be encoded into a single Uniform Resource Locator (URL) that can be written by hand without programming expertise. Conceptually, a web service request from the user to PubChem requires three pieces of information:

- **input**: a list of PubChem identifiers of interest (e.g., CID, AID, SID).
- **operation**: what to do with the input identifiers.
- **output**: the format of the output from the operation.

In PUG-REST, these three pieces of information are encoded into an URL in the following format:



Some tasks require additional pieces of information that do not fit into the three-part PUG-REST URL. They should be provided as a list of '&'-separated option name and option value pairs, following the question mark ("?") appended at the end of the request URL. Some examples are presented in next section, but there are much more things that users can do through PUG-REST. To get more detailed information on PUG-REST, read the following four articles:

- **PUG-SOAP and PUG-REST:**
  Web Services for Programmatic Access to Chemical Information in PubChem
  Kim *et al.*, *Nucleic Acids Res.* **2015**, 43(W1), W605-W611.
  (http://dx.doi.org/10.1093/nar/gkv396).
- **Programmatic Retrieval of Small Molecule Information from PubChem Using PUG-REST** (in press). [Available to logged-in students at bottom of this module.]
- **PUG-REST Help** (http://pubchem.ncbi.nlm.nih.gov/pug_rest/PUG_REST.html**)**
- **PUG-REST Tutorial**
  (http://pubchem.ncbi.nlm.nih.gov/pug_rest/PUG_REST_Tutorial.html**)**

3.2. PUG-REST examples

(1) Getting the full record of a compound record.

One of the most common tasks requested through PUG-REST is to retrieve all computed properties for a given chemical or chemicals. The following example URLs retrieve the full record of acetone in an XML format.

(a) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/cid/180/record/XML

(b) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/name/acetone/record/XML

(c) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/inchikey/CSCPPACGZOOCGX-UHFFFAOYSA-N/record/XML

(d) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/inchikey/CSCPPACGZOOCGX-UHFFFAOYSA-N/record/XML?record_type=2d

(e) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/inchikey/CSCPPACGZOOCGX-UHFFFAOYSA-N/record/XML?record_type=3d

In the above examples, the input compound is specified by CID (CID 180), name (acetone), and InChiKey (CSCPPACGZOOCGX-UHFFFAOYSA-N). The input identifiers can also be specified by SMILES or InChI strings, although special care needs to be taken because these identifiers contain special characters (such as "/") that cause conflicts with the URL syntax.[4] In addition, the hits returned from a structure search (e.g., identity/similarity search or sub/superstructure search) can be used as the input identifiers for a PUG-REST request. [It is highly recommended to use the synchronous "fast" inputs for structure searches (e.g., fastidentity, fastsimilarity_2d,

fastsimilarity_3d, fastsubstructure, fastsuperstructure, and fastformula). Read the "Asynchronous operations in PUG-REST" section of this paper.]

The keyword "record", followed by the input identifier, invokes the full record retrieval of the input compound. By default, the "record_type" option is set to "2d", meaning that the information derived from the 2-D structure of the input compound will be returned. By setting this option to "3d", one can get the information derived from the 3-D structure. Therefore, examples (a) through (d) returns 2-D information, and example (e) returns 3-D information.

(2) Getting the 2-D and 3-D structure image of a compound

Below are examples of the molecular structure image retrieval through PUG-REST.

(a) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/cid/180/record/PNG

(b) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/cid/180/record/PNG?record_type=2d

(c) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/cid/180/record/PNG?record_type=3d

When the output file format for full record retrieval is set to "PNG", the image of the input compound is retrieved. The 3-D image of the input compound can be retrieved by setting the "record_type" option to "3d". When a list of compounds are specified as the input, the image of only the first compound on the list will be returned.

(3) Getting molecular properties of a set of compounds

One may download molecular properties for a set of compounds, as in the following example:

(a) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/cid/887,702,1031,263/property/MolecularFormula,MolecularWeight,CanonicalSMILES,HeavyAtomCount,XLOGP/CSV

In this example, the molecular formula, molecular weight, canonical SMILES, Heavy Atom Count, and XLOGP value for 4 compounds are retrieved in a CSV format, which can be read in a spread sheet program like Excel and Google Sheet. A list of the molecular properties available through PUG-REST can be found in the PUG-REST specification document:

https://pubchem.ncbi.nlm.nih.gov/pug_rest/PUG_REST.html#_Toc458584223

(4) Getting a list of CIDs whose synonym is or contains "atorvastatin"

Through PUG-REST, one can perform a search by synonym.

(a) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/name/atorvastatin/cids/txt

(b) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/name/atorvastatin/cids/txt?name_type=complete

(c) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/name/atorvastatin/cids/txt?name_type=word

By default, the "name_type" option is set to "complete", meaning that only those whose synonym completely matches the input chemical name will be returned. One can perform partial synonym matching, by setting this option to "word". These search options are conceptually equivalent to an Entrez search with Entrez indices "[completesynonym]" and "[synonym]".

(5) Getting a list of CIDs for compounds identical to a query compound

Below are examples of PUG-REST request URLs for identity search.

(a) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/fastidentity/cid/4594/cids/TXT

(b) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/fastidentity/cid/4594/cids/TXT?identity_type=same_stereo_isotope

(c) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/fastidentity/cid/4594/cids/TXT?identity_type=same_connectivity

(d) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/fastidentity/cid/4594/cids/TXT?identity_type=same_isotope

(e) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/fastidentity/cid/4594/cids/TXT?identity_type=same_stereo

Note that various "contexts" of identity can be selected using the "identity_type" option. By default, this option is set to "same_stereo_isotope", which returns compounds identical to the query compound in both stereochemistry and isotopism. When it is set to "same_connectivity",

the identity search will returns molecules with the same connectivity (ignoring stereochemistry and isotopism).

(6) Getting a list of CIDs for compounds with a given substructure

The following examples perform substructure searches through PUG-REST.

(a) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/fastsubstructure/cid/6857523/cids/TXT

(b) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/fastsubstructure/cid/6857523/cids/TXT?StripHydrogen=false

(c) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/fastsubstructure/cid/6857523/cids/TXT?StripHydrogen=true

By default, the substructure search will keep explicit hydrogen atoms in the query substructure. By setting the StripHydrogen parameter to "true", one can strip off hydrogen atoms from the query substructure before performing a substructure search.

(7) Getting a list of CIDs for compounds with a given molecular formula

The following examples show how to perform a molecular formula search through PUG-REST.

(a) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/fastformula/C6H12O6/cids/TXT

(b) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/fastformula/C6H12O6/cids/TXT?AllowOtherElements=true

By default, the search results from a molecular formula search will exactly match the entered stoichiometry. One may allow other elements in the returned results by using the "AllowOtherElements=true" option.

(8) Getting a list of AIDs for assays that target a given protein.

One can retrieve assays that are performed against a particular target, which can be specified by gene symbol, NCBI's Gene ID, or NCBI's global identifier (gi) (for protein sequences).

(a) https://pubchem.ncbi.nlm.nih.gov/rest/pug/assay/target/genesymbol/HMGCR/aids/TXT

(b) https://pubchem.ncbi.nlm.nih.gov/rest/pug/assay/target/geneid/3156/aids/TXT

(c) https://pubchem.ncbi.nlm.nih.gov/rest/pug/assay/target/gi/118573791/aids/TXT

(9) Getting a list of compounds tested in an assay.

The following examples show how to get a list of compounds tested in a given assay.

(a) https://pubchem.ncbi.nlm.nih.gov/rest/pug/assay/aid/1053202/cids/XML

(b) https://pubchem.ncbi.nlm.nih.gov/rest/pug/assay/aid/1053202/cids/XML?cids_type=all

(c) https://pubchem.ncbi.nlm.nih.gov/rest/pug/assay/aid/1053202/cids/XML?cids_type=active

(d) https://pubchem.ncbi.nlm.nih.gov/rest/pug/assay/aid/1053202/cids/XML?cids_type=inactive

Using the "cids_type" option, one can download all compounds tested in an assay or only those compounds tested to be active (or inactive).

(10) Getting bioactivity data determined in an assay.

It is possible to download the bioactivity data for a given assay through PUG-REST.

(a) https://pubchem.ncbi.nlm.nih.gov/rest/pug/assay/aid/1053202/record/CSV

(b) https://pubchem.ncbi.nlm.nih.gov/rest/pug/assay/aid/1053202/record/CSV?cid=823611,1270560,2104765

It is also possible to download the bioactivity data for a particular compound or compounds tested in the input assay by providing the comma-separated list of CIDs of interest after the question mark.

(11) Getting a list of assays in which a compound was tested.

Through PUG-REST, one can get a list of assays in which a given compound was tested. Below are some examples.

(a) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/cid/5329102/aids/XML

(b) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/cid/5329102/aids/XML?aids_type=all

(c) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/cid/5329102/aids/XML?aids_type=active

(d) https://pubchem.ncbi.nlm.nih.gov/rest/pug/compound/cid/5329102/aids/XML?aids_type=inactive

By adjusting the "aids_type" parameter to "active" (or "inactive), one can retrieve assays in which the compound is tested to be active (or inactive). By default, any assays in which the input compound is tested are retrieved.

3.3. Accessing PubChem data from a spread sheet program

Through PUG-REST, one can access PubChem data from a spread sheet software, such as Google Sheet or MicroSoft Excel. Below is an example Google Sheet file that shows how to auto-populate data from PubChem into the spread sheet.

https://docs.google.com/spreadsheets/d/12-UkxgCxNVp2Ceim47TRffhqquLi2TFPKj3PJpii7bY/edit?usp=sharing

In this example, the function **IMAGE()** is used to retrieve the molecular images in the PNG format, and **IMPORTXML()** is used to get the record name and some molecular properties. While

the **IMPORTXML()** function is used to get data in an XML format, the **IMPORTDATA()** function should be used to get PubChem data in CSV or TXT format. Note that the PUG-REST request URL used in the **IMPORTXML()** contains a comma-separated list of the input CIDs to retrieve data for all CIDs at a single request. While it is possible to make ten PUG-REST requests (one for each CID) to get the same data, it is highly recommended that users should minimize the number of requests. On the other hand, the image retrieval through PUG-REST supports only one input CID at a time, and therefore ten PUG-REST requests are made to get the images for all CIDs.

It is also possible to use MicroSoft Excel to do the same task as done in the above Google Sheet example. The **WEBSERVICE()** function in MicroSoft Excel 2013/2016 is equivalent to **IMPORTXML()** and **IMPORTDATA()** in Google Sheet. It returns the data retrieved from a web service request (in both XML and CSV/TXT). However, MicroSoft Excel does not have a built-in function equivalent to **IMAGE()** in Google Sheet, one needs to write a script for the image retrieval in VBA (Visual Basic for Applications), which is beyond the scope of this module.

3.4. Accessing PubChem data from a script

This section introduces how to make a PUG-REST request from a script, with example Python scripts. These examples are simple and short enough for students with no programming background to understand. You can modify and run these scripts on your web browser. While the examples are written in Python, it is possible to do the same tasks using other programming languages.

Example 1: Search by chemical name (https://trinket.io/library/trinkets/f009cf46ee)

<iframe src="https://trinket.io/embed/python/f009cf46ee" width="100%" height="600" frameborder="0" marginwidth="0" marginheight="0" allowfullscreen></iframe>

This example searches PubChem for compounds whose name is “atorvastatin” and retrieve their full record. All lines beginning with the “#” characters are comments, which are ignored during the execution of a script. These comments are usually used to provide human-readable explanations about the script.

Without the comments and blank lines, only the remaining three lines are actually executed. In line 8, the “urllib.request” module is imported, which contains the definition of the function “urllib.request.urlopen()” in line 11. This function makes a web service request to the URL

provided within the parentheses. The returned result is stored in the "request" object. In line 14, the returned data are read from the object and printed out.

Example 2: Molecular property retrieval (https://trinket.io/library/trinkets/a42e5b43e8)

<iframe src="https://trinket.io/embed/python/a42e5b43e8" width="100%" height="600" frameborder="0" marginwidth="0" marginheight="0" allowfullscreen></iframe>

This example illustrates how to retrieve molecular properties of a list of CIDs. In this example, the three pieces of information required for a PUG-REST request (that is, the input, operation, and output) are stored in respective variables (Lines 12-14). These variables are used to construct a PUG-REST request URL, which is stored in a variable called "url" (Line 17). In Line 20, this "url" variable is used as an argument in the function "urllib.request.urlopen()", which makes the PUG-REST request.

Note that Example 2 uses additional variables to store different parts of the PUG-REST request URL, making it longer than Example 1. It is possible to reduce Example 2 into a three-line script without using these additional variables, by directly specifying the PUG-REST URL in the parentheses after "urllib.request.urlopen" as shown in Example 1.

Example 3: 2-D similarity search using CID queries (https://trinket.io/library/trinkets/490a1841a3)

<iframe src="https://trinket.io/embed/python/490a1841a3" width="100%" height="600" frameborder="0" marginwidth="0" marginheight="0" allowfullscreen></iframe>

In this example, 2-D similarity search is repeatedly performed using a list of CIDs as queries. The query compounds are defined in Line 17. Because 2-D similarity search can take only one query compound at a time, it should be repeated using a "for" loop as shown in Lines 20 through 28. In this "for" loop, each CID in "queries" (defined in Line 17) is assigned to the variable "mycid", which is used to construct a PUG-REST request URL in Lines 24-25.

Note that the input CID is converted into a string [using the str() function at line 24] before it is concatenated with the other parts of the URL. This conversion is necessary because the input identifiers are provided as numbers at Line 17. If they are provided as strings (with each of them enclosed in quotes), they could be directly used in the URL.

Example 4: 2-D similarity search using isomeric SMILES queries (https://trinket.io/library/trinkets/3437cdefb0)

<iframe src="https://trinket.io/embed/python/3437cdefb0" width="100%" height="600" frameborder="0" marginwidth="0" marginheight="0" allowfullscreen></iframe>

This example also performs 2-D similarity search using a list of SMILES strings as queries. An important difference between Examples 3 and 4 is the way in which the input identifiers are encoded in the PUG-REST request URL. Some special characters used as input identifiers are also reserved for the URL syntax, causing issues when directly encoded in an URL path. An example is the "/" (forward slash) character used in isomeric SMILES and InChI strings. To avoid conflicts with URL syntax, these line notations need to be included in the options part of the URL (after the "?" mark) (as in Lines 27-28).

References

(1) Kim, S.; Thiessen, P. A.; Bolton, E. E.; Chen, J.; Fu, G.; Gindulyte, A.; Han, L. Y.; He, J. E.; He, S. Q.; Shoemaker, B. A.; Wang, J. Y.; Yu, B.; Zhang, J.; Bryant, S. H. *Nucleic Acids Res.* **2016**, *44*, D1202.

(2) Wang, Y.; Bryant, S. H.; Cheng, T.; Wang, J.; Gindulyte, A.; Shoemaker, B. A.; Thiessen, P. A.; He, S.; Zhang, J. *Nucleic Acids Res.* **2017**, *45*, D955.

(3) Kim, S. *Expert Opinion on Drug Discovery* **2016**, *11*, 843.

(4) Kim, S.; Thiessen, P. A.; Bolton, E. E.; Bryant, S. H. *Nucleic Acids Res.* **2015**, *43*, W605.