THE NATIONAL CENTER FOR BIOMEDICAL ONTOLOGY

Webinar Series

May 21, 2014

RxMix – Enabling complex queries to drug information sources through functional composition

Olivier Bodenreider

Lister Hill National Center for Biomedical Communications
Bethesda, Maryland - USA

LHNCBC

STANFORD SCHOOL OF MEDICINE
Biomedical Informatics

Jonathan Mortensen

Stanford University

NIH U.S. National Library of Medicine

Acknowledgments

- Lee Peters
- Thang Nguyen
- Kelly Zeng
- Ramez Ghazzaoui

- Stuart Nelson, John Kilbourne (RxNorm)
- Kin Wah Fung (RxTerms)
- Mike Lincoln (NDF-RT)

References

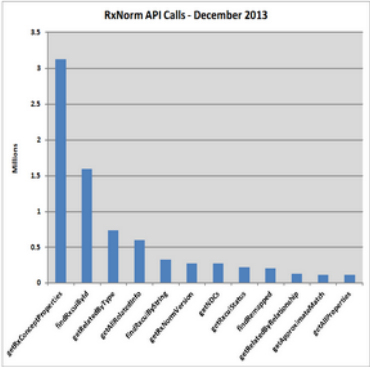
- RxNav, RxMix and drug information sources APIs
  - http://rxnav.nlm.nih.gov/
- Drug information sources
  - RxNorm
    - http://www.nlm.nih.gov/research/umls/rxnorm/index.html
  - RxTerms
    - http://wwwcf.nlm.nih.gov/umlslicense/rxtermApp/rxTerm.cfm
  - NDF-RT
    - http://evs.nci.nih.gov/ftp1/NDF-RT/
  - C3PI RxImageAccess
    - http://rximage.nlm.nih.gov/

Home APIs Applications Documentation Data Sources Terms Of Service Contact Us

APIs

Application Program Interfaces (APIs) are available to users to retrieve data from several drug information sources, including RxNorm, NDF-RT and RxTerms.

Currently there are four APIs available - RxNorm, Prescribable RxNorm, NDF-RT and RxTerms



RxNav APIs RxMix

News Statistics

RxNav brand names

Recent brand names added

4XLA Activator	Alprolix
Averteax Lip Protector	Bentasil
Cyramza	Pediacare Nighttime Multi-Symptom Cold
Purixan	Rompun
Styptstix	

NDF-RT Drug Interactions

Interactions to be removed from NDF-RT
The NDF-RT data provider has announced that the drug interactions will be removed from the data set as early as the June release. There is currently no replacement for this interactions data.

Functions to be deprecated by this change:
findDrugInteractions (REST: /interaction/nui)
findInteractionsFromList (REST: /interaction?nuis)
interactions (REST: /interaction/nui1)

APIs - What's New

Drug Class Members - the RxNorm API function getClassMembers (REST: /members) retrieves the members of a specified drug class from ATC, MeSH or NDF-RT. Read more

Drug Classes. A new function getAllClasses (REST: /classes) allows users to get drug class names from ATC, MeSH or NDF-RT.

http://rxnav.nlm.nih.gov/

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894
National Institutes of Health, Department of Health & Human Services
Copyright, Privacy, Accessibility Viewers & Players, Freedom of Information Act, USA.gov

References

- Peters LB, Mortensen J, Nguyen T, Bodenreider O. Enabling complex queries to drug information sources through functional composition. *Stud Health Technol Inform (Proc Medinfo) 2013;192:692-696.*

http://mor.nlm.nih.gov/pubs/pdf/2013-medinfo-lp.pdf

Outline

- Introduction
  - APIs to drug information sources
  - Complex queries
  - Functional composition
- Interoperability among API functions
  - Definition
  - Implementation
- RxMix demo

Introduction

Olivier Bodenreider

Motivation

- Biomedical vocabularies are used as reference knowledge sources
- They can be used programmatically through Application Programming Interfaces (APIs)
  - Unified Medical Language Server (UMLS)
  - BioPortal
  - RxNorm
- Difficult to compose complex queries across multiple APIs

Drug information sources

- Publicly available
  - RxNorm
  - NDF-RT
  - RxTerms
  - RxImageAccess
- Created/distributed by NLM
  - Datasets
  - Application Programming Interfaces (APIs)

Drug information sources

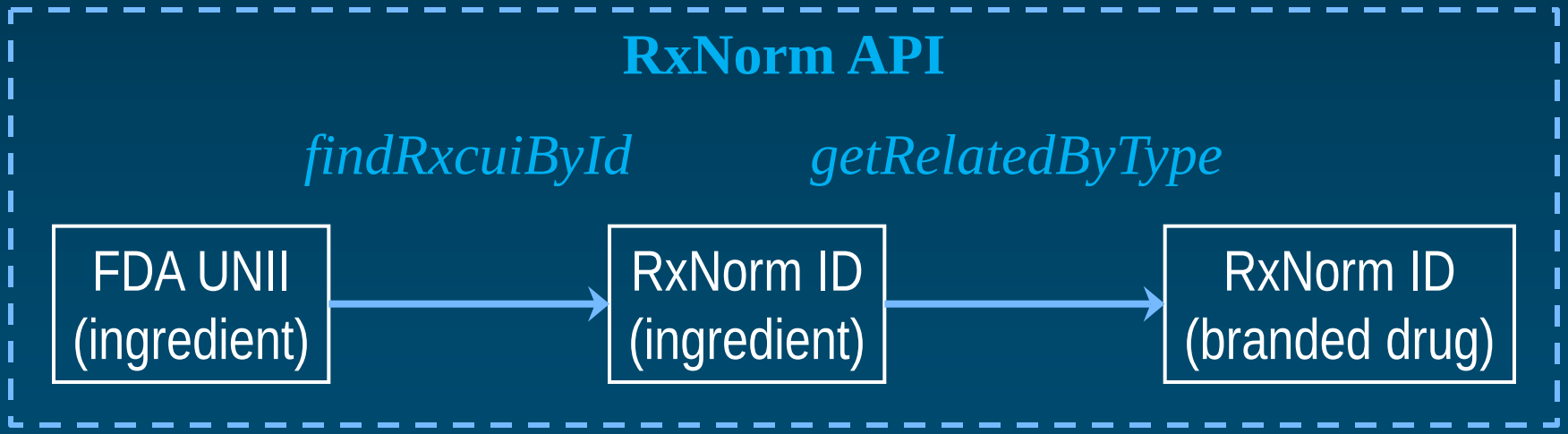
- RxNorm
  - Developed by NLM
  - Normalized names and codes for drug entities
  - Relations among drug entities form a graph
- NDF-RT
  - National Drug File-Reference Terminology
  - Developed by the Veterans Health Administration
  - Generic drugs described in terms of their active ingredients, mechanisms of action, physiologic effects, and therapeutic intent (indications and contraindications)

Drug information sources

- RxTerms
  - Developed at NLM
  - Drug interface terminology derived from RxNorm for prescription writing or medication history recording
- RxImageAccess
  - Developed at NLM
  - High-definition images for oral solid dose forms (“pills”), with additional metadata, for pill identification purposes

Example use case

- Find all the brand name products available for a given generic drug, whose identity is known by the FDA unique ingredient identifier code (UNII)
- Workflow



Interoperability among API functions

Jonathan Mortensen

Objectives

- To enable an end-user to create complex queries to drug information sources through functional composition
- Complex query = workflow
  - Sequence of web service functions
  - Function interoperability driven by an ontology
- Running example: Application to two different web services to drug information sources
  - RxNorm API
  - NDF-RT API – National Drug File-Reference Terminology

Web service annotation

- Several web service annotation and composition frameworks
  - SAWSDL (Semantic Annotations for WSDL and XML Schema) – W3C
  - SSWAP (Simple Semantic Web Architecture and Protocol) – U. Arizona
  - SADI (Semantic Automated Discovery and Integration) – U. British Columbia
  - Taverna – U. Manchester
- Our approach
  - Difficult to retrofit our services to these frameworks
  - Use of an ontology in the background, not in the payload

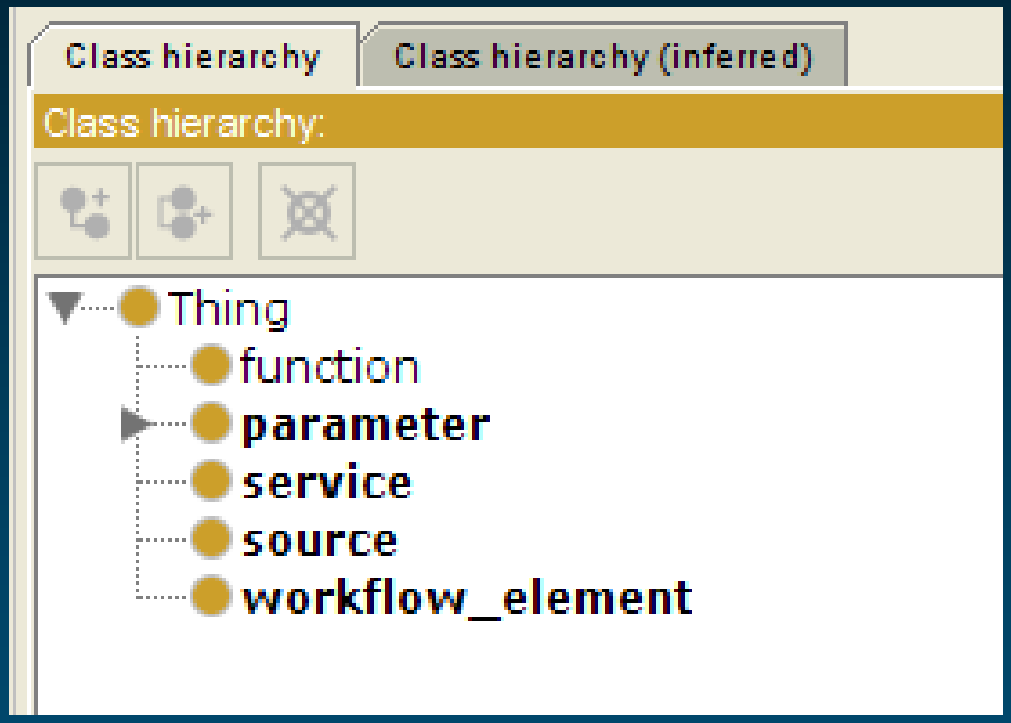
Methods

- Problem: Determine and represent interoperability among RxNorm and NDF-RT API functions based on their input and output
- Semantic representation of input and output
  - Captured in an OWL ontology
- Definition of interoperability between two functions
  - Modeled through rules

Ontology of functions

- Developed in OWL using Protégé
- Main classes
  - Service (e.g., RxNorm, NDF-RT)
  - Function: input and output parameters
  - Function parameter: semantics of identifiers
- Examples
  - *RxNorm API has_function findRxcuiByID*
  - *findRxcuiById has_input id_type*
  - *findRxcuiById has_input id*
  - *findRxcuiById has_output RxCUI*
  - *RxNorm API has_function getRelatedByType*
  - *getRelatedByType has_input RxCUI*

Main class hierarchy



Class “Service”

Description: service

Members

- NDF-RT_API
- RxImageAccess_API
- RxNorm_API
- RxTerms_API

Target for Key

Disjoint With

- workflow_element
- type
- user_defined
- source, parameter, workflow_element
- int
- source
- parameter

The 4 APIs are instances of the class Service

Class “Function”

Description: function

Members

- approxMatch
- findConceptsByID
- findConceptsByName
- findDrugInteractions
- findInteractionsFromList
- findRemapped
- findRxcuiById
- findRxcuiByString
- getAllConcepts
- getAllConceptsByKind
- getAllConceptsByTTY
- getAllInfo
- getAllProperties
- getAllRelatedInfo
- getAllRxTermInfo

All API functions are instances of the class Function

Function “findRxcuiById”

input 2

input 1

RxNorm SOAP API

source

findRxcuiById(*idType, id, allSourcesFlag*)

input 3

Search for an identifier from another vocabulary and return the RxCUIs of any con[illegible] which have an RxNorm term as a synonym or have that identifier as an attribute.

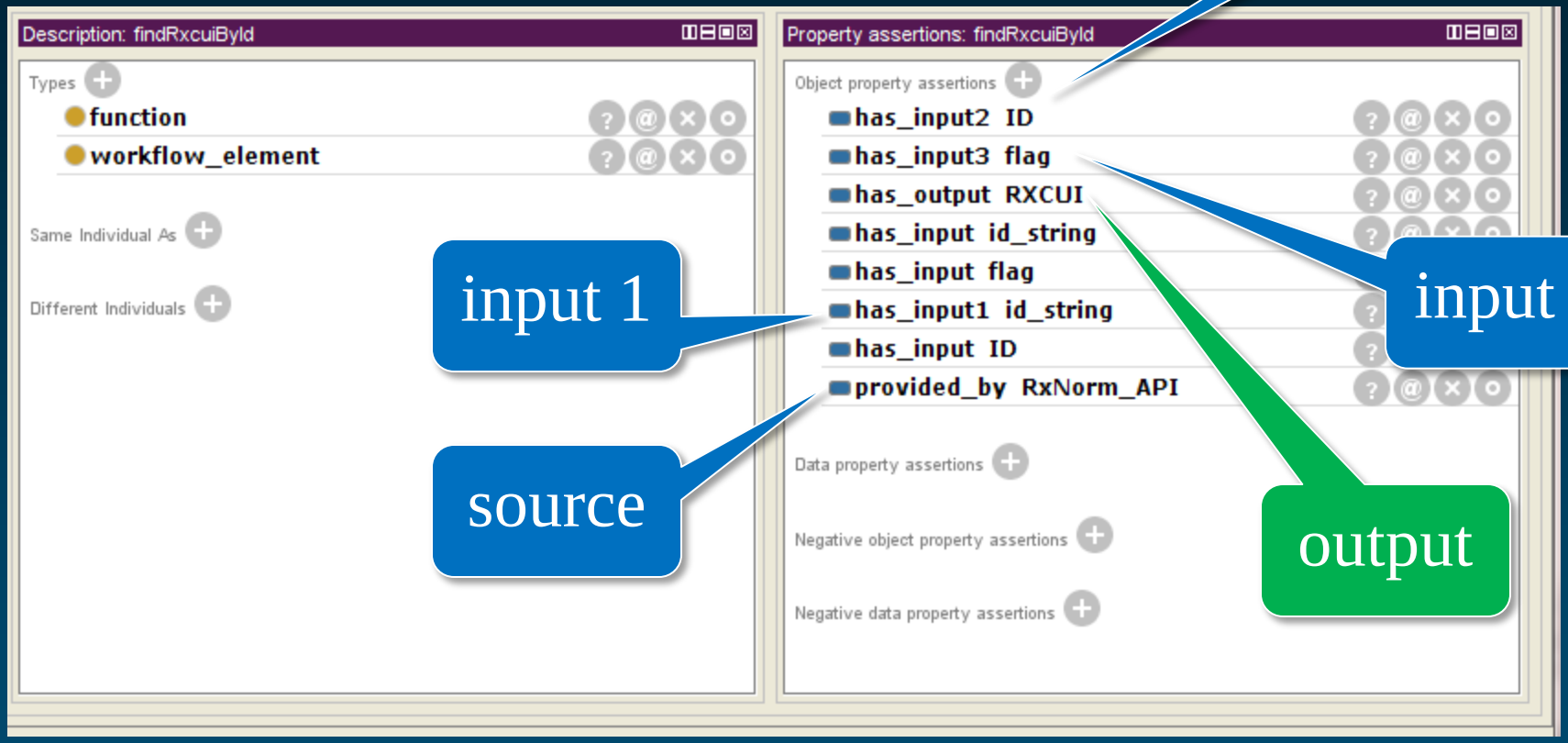
Input:

idType - the identifier type. See the getIdTypes example for the valid types. T[illegible]es the types:

output

idType	Example Id	Details
AMPID	2050	the Gold Standard Drug Identifier from Gold Standard Drug Database (SAB:GS)
ANDA	ANDA007581	the FDA Abbreviated New Drug Application identifier
ATC	M02AA01	the Anatomical Therapeutic Chemical (ATC) identifier
GCN_SEQNO	009172	the Generic Code Sequence Number from First Databank Inc (SAB:NDDF)
GFC	108077	the Generic Formula Code (GFC) from Micromedex RED BOOK (SAB:MMX)
[illegible]	[illegible]	the first five characters of the Generic Product Packaging Code from Master [illegible]

Function “findRxcuiById”



Function “getRelatedByType”

input 1

input 2

RxNorm SOAP API

getRelatedByType(*rxcui, type-list*)

Get the related RxNorm identifiers of an RxNorm concept specified one or more term types. See default paths for the paths traveled to get concepts for each term type.

Input:

rxcui - the RxNorm identifier

type-list - an array of one or more RxNorm term types. Valid RxNorm term types are list in the getTermTypes example.

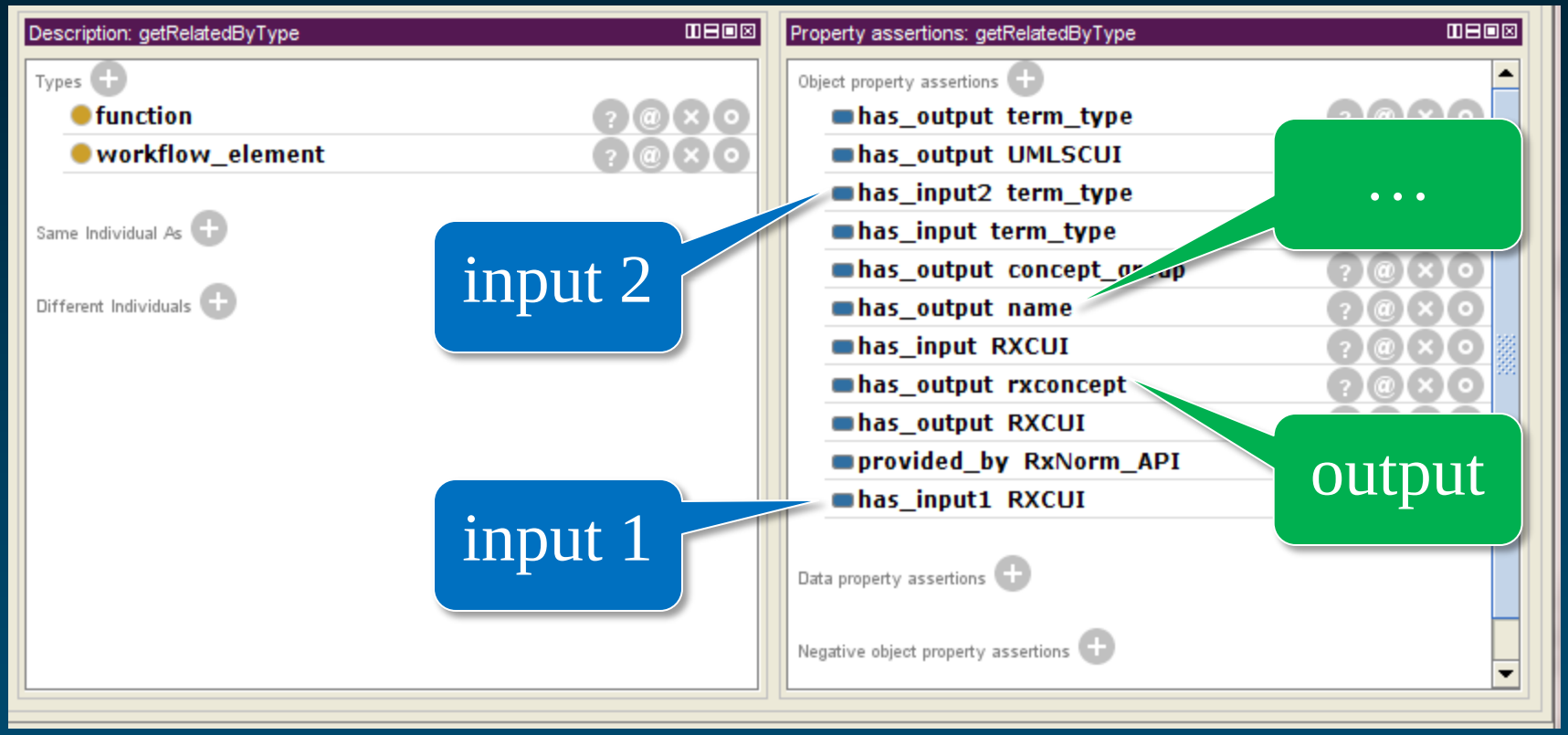
Output:

an array of RxNorm concept group structures. An RxNorm concept group structure has the following fields:

- Type - the RxNorm term type
- Array of RxNorm concept structures. See getRxConceptProperties for the description of the RxNorm concept structure.

output

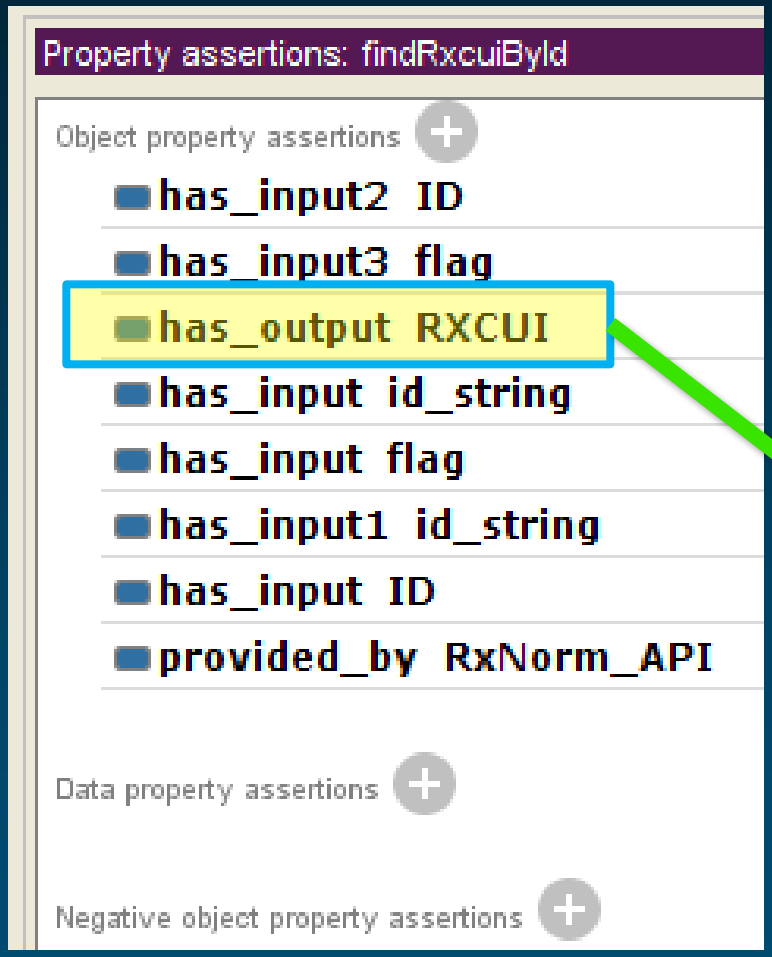
Function “getRelatedByType”

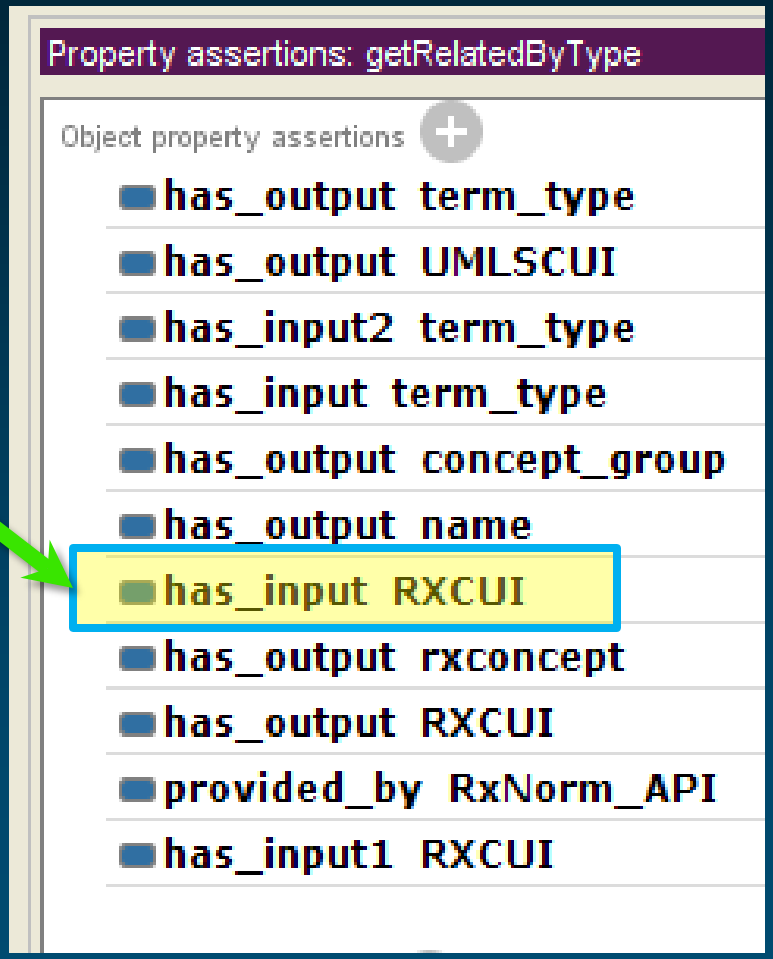


Rules of interoperability

- Main rule – If the input of *B* matches the output of *A*, then *A* is potentially interoperable with *B*
- Additional rules
  - Interoperability between generic IDs and specific IDs in the input or output of functions
- Example
  - A: *rxnorm:findRxcuiById has_output RxCUI*
  - B: *rxnorm:getRelatedByType has_input RxCUI*
  - input of *B* matches the output of *A* => *rxnorm:getRelatedByType interoperable_with rxnorm:findRxcuiById*

findRxcuiById → getRelatedByType





Implementation

- The OWL ontology supports the interoperability rules
- Interoperability relations inferred from the rules support the determination of interoperability for a given pair of functions
- The ontology and the interoperability relations drive
  - The validation of workflows
  - The graphical interface for creating workflows
    - Only allowable functions are proposed in the menu

Production rules (SWRL)

Rules:

Rules

```
has_input(?c, ?b), has_output(?a, ?b) -> interoperable_with(?a, ?c)
has_id(?d, ?c), has_input(?b, ?c), has_output(?a, ID), provided_by(?a, ?d) -> interoperable_with(?a, ?b)
has_member(?b, ?c), has_output(?a, ?b) -> has_output(?a, ?c)
has_id(?e, ?c), has_input(?b, ID), has_output(?a, ?c), has_source(?d, ?e), provided_by(?b, ?d) -> interoperable_with(?a, ?b)
```

Composer

```
has_input(?c, ?b), has_output(?a, ?b) -> interoperable_with(?a, ?c)
```

If the input of c matches the output of a

Then c interoperable with a (i.e., c can follow a)

Implementation

- Rules applied through a reasoner in Protégé
  - HermIT
- Inferred properties added to the knowledge base
  - Interoperable_with properties

Properties before/after applying rules

Property assertions: findRxcuiById

Object property assertions

- has_input2 ID
- has_input3 flag
- has_output RXCUI
- has_input id_string
- has_input flag
- has_input1 id_string
- has_input ID
- provided_by RxNorm_API

Data property assertions

Negative object property assertions

Property assertions: findRxcuiById

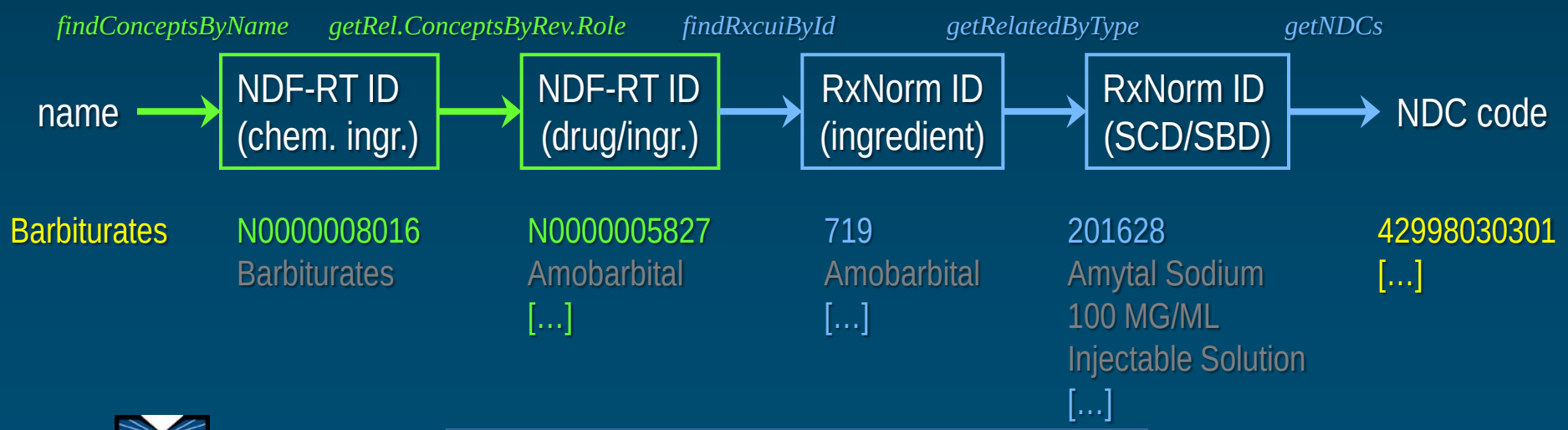
- interoperable_with getUNII
- interoperable_with getQuantity
- has_input2 ID
- interoperable_with getRxTermDisplayName
- interoperable_with getSplSetId
- interoperable_with findConceptsByID
- has_input3 flag
- interoperable_with getAllProperties
- interoperable_with getRxConceptProperties
- interoperable_with getRelatedByRelationship
- interoperable_with getRxcuiStatus
- interoperable_with getNDCs
- interoperable_with getRelatedByType
- has_output RXCUI

RxMix demo

Olivier Bodenreider

“Real-life” use case

- Find all the NDC codes for a given allergy class (e.g., barbiturates)
  - Input: [NDF-RT] Barbiturates (N0000008016)
  - Output: [RxNorm] list of NDC codes
- Complex workflow



http://mor.nlm.nih.gov/RxMix/

RxMix

Create applications from RxNorm, RxTerms, NDF-RT, and RxImageAccess APIs

WORKFLOW

No Workflow Defined

BUILD

Select Function

No function selected

LOAD

From workflow library

From my workflows

INPUT

Input:

Interactive

Batch

Basic Instructions

1. BUILD workflow using Select Function, then Add to Workflow (or select a button in LOAD section to load a workflow)
2. Enter INPUT value for interactive mode (or input file name for batch mode)
3. Select OUTPUT fields and output format
4. EXECUTE by pressing Run/Submit button

OUTPUT

Output Format

TABLE XML JSON TEXT

http://mor.nlm.nih.gov/RxMix/

Documentation

Introduction

RxMix is an interface for building applications that allows users to combine functions of the RxNorm, RxTerms, NDF-RT, and RxImageAccess APIs. It allows users to run either interactively or in batch mode.

Sample RxMix configurations

Find drug interaction brands for Morphine (RXCUI = 7052)

Find allergy drugs for Proton Pump Inhibitors (NUI = N0000000147)

APIs

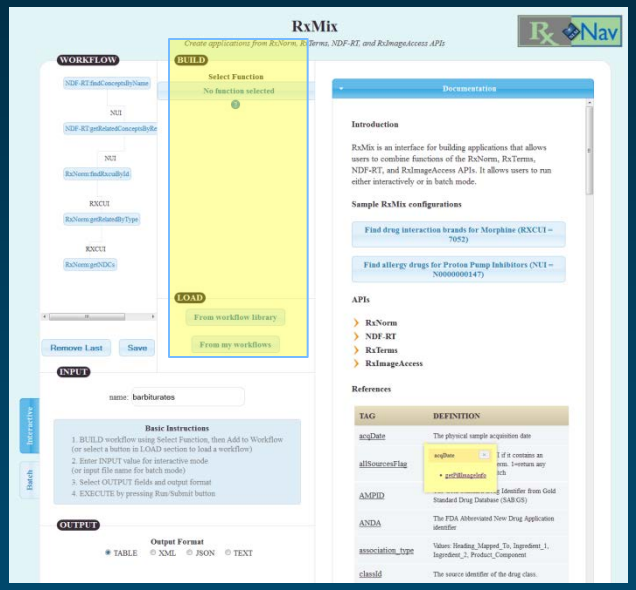
- RxNorm
- NDF-RT
- RxTerms
- RxImageAccess

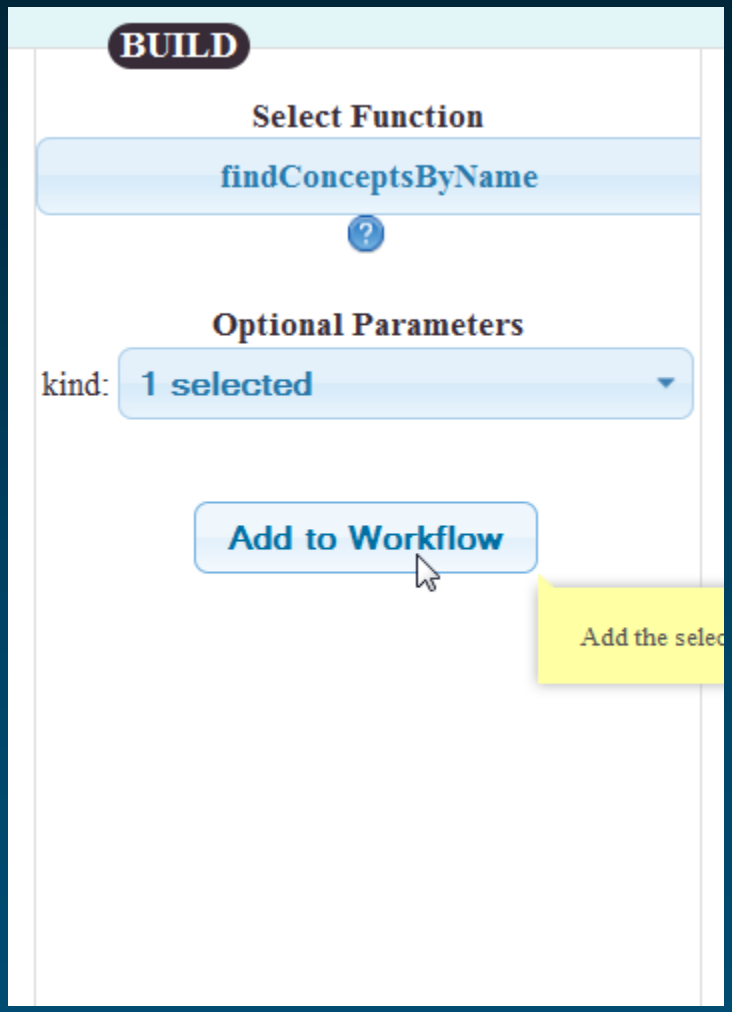
References

TAG	DEFINITION
acqDate	The physical sample acquisition date
allSourcesFlag	0=only return an RXCUI if it contains an RXNORM vocabulary term. 1=return any RXCUI which has a match
AMPID	The Gold Standard Drug Identifier from Gold Standard Drug Database (SAB:GS)
ANDA	The FDA Abbreviated New Drug Application identifier
association_type	Values: Heading_Mapped_To, Ingredient_1, Ingredient_2, Product_Component
classId	The source identifier of the drug class.

findConceptsByName *getRel.ConceptsByRev.Role* *findRxcuiById* *getRelatedByType* *getNDCs*

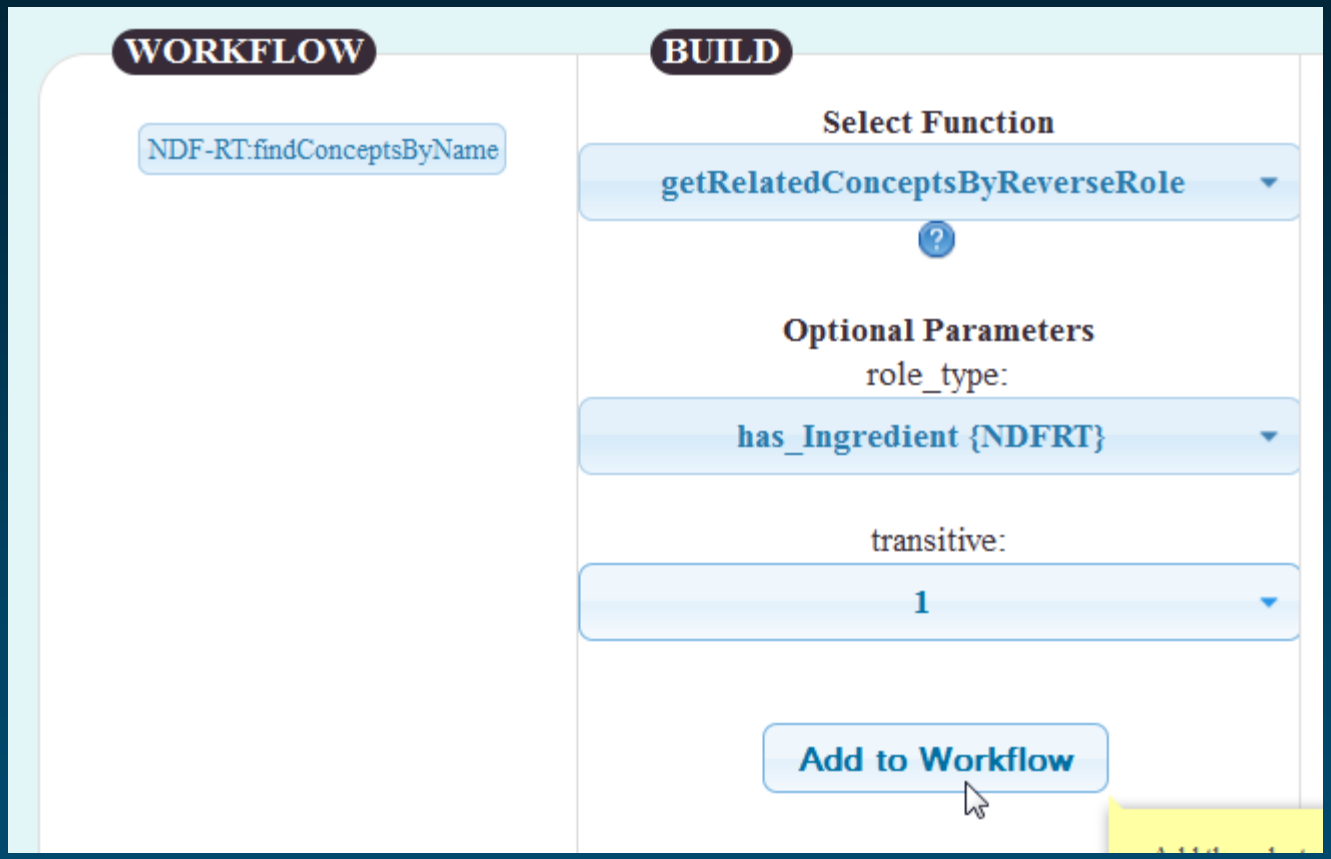
name → NDF-RT ID (chem. ingr.) → NDF-RT ID (drug/ingr.) → RxNorm ID (ingredient) → RxNorm ID (SCD/SBD) → NDC code





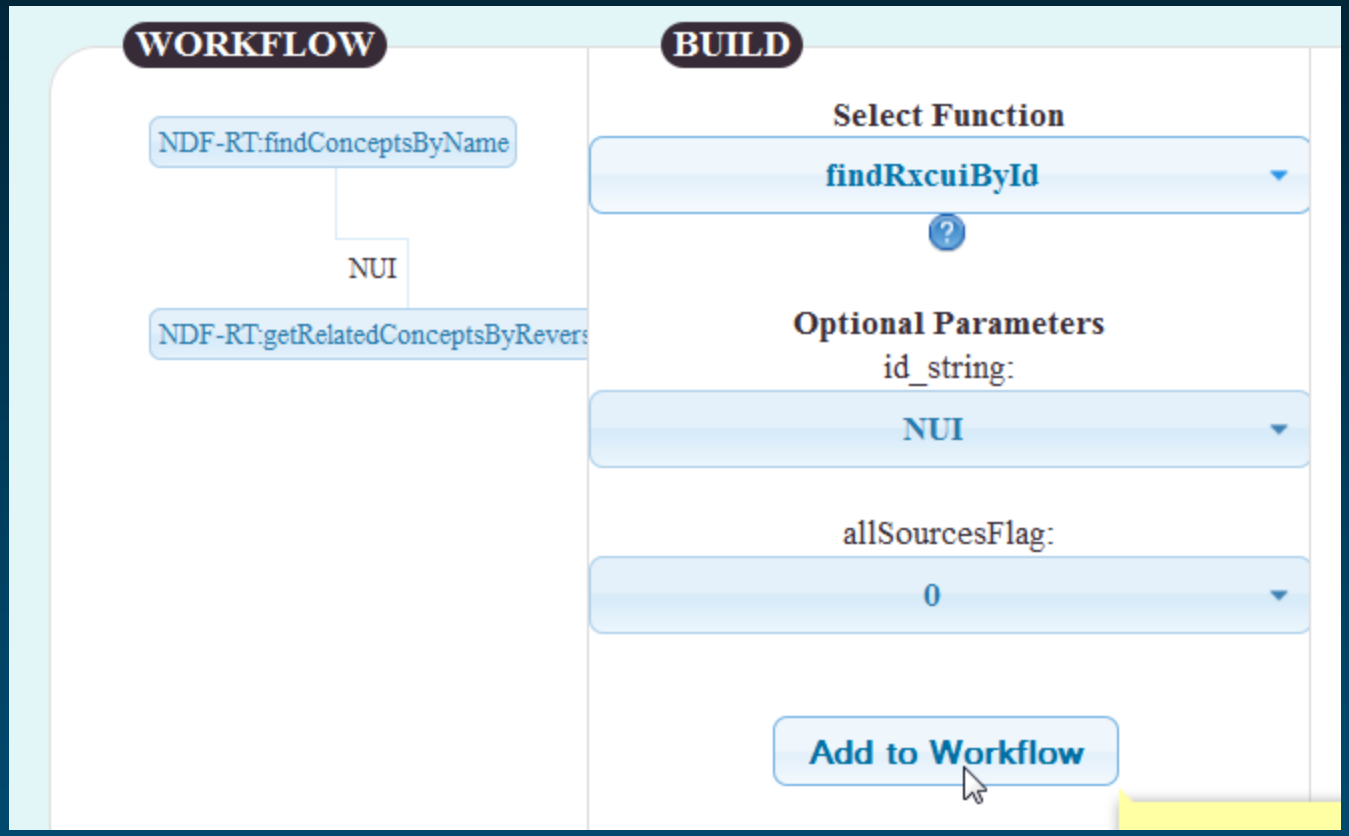
findConceptsByName *getRel.ConceptsByRev.Role* *findRxcuiById* *getRelatedByType* *getNDCs*

name → NDF-RT ID (chem. ingr.) → NDF-RT ID (drug/ingr.) → RxNorm ID (ingredient) → RxNorm ID (SCD/SBD) → NDC code



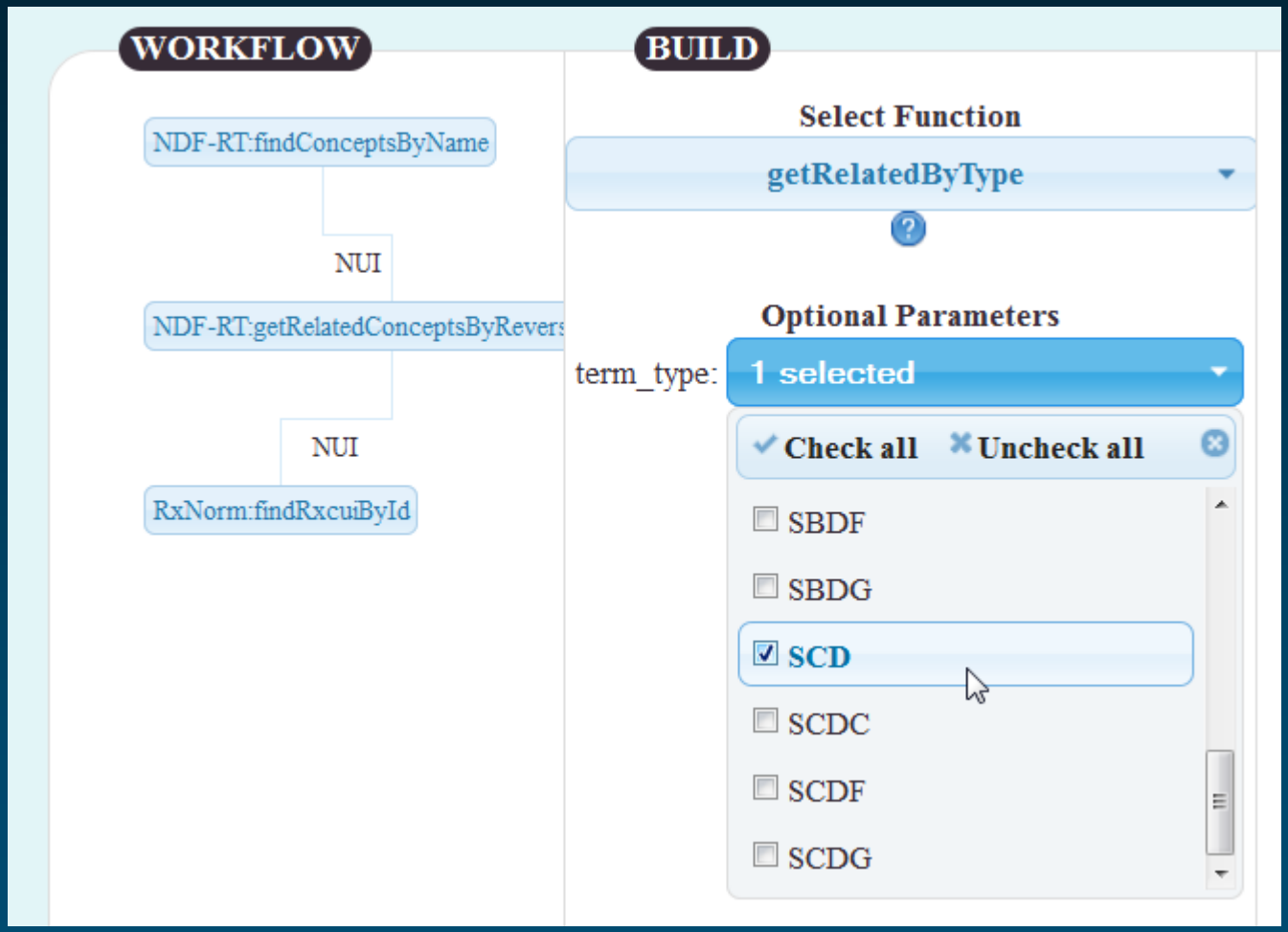
findConceptsByName *getRel.ConceptsByRev.Role* *findRxcuiById* *getRelatedByType* *getNDCs*

name → NDF-RT ID (chem. ingr.) → NDF-RT ID (drug/ingr.) → RxNorm ID (ingredient) → RxNorm ID (SCD/SBD) → NDC code



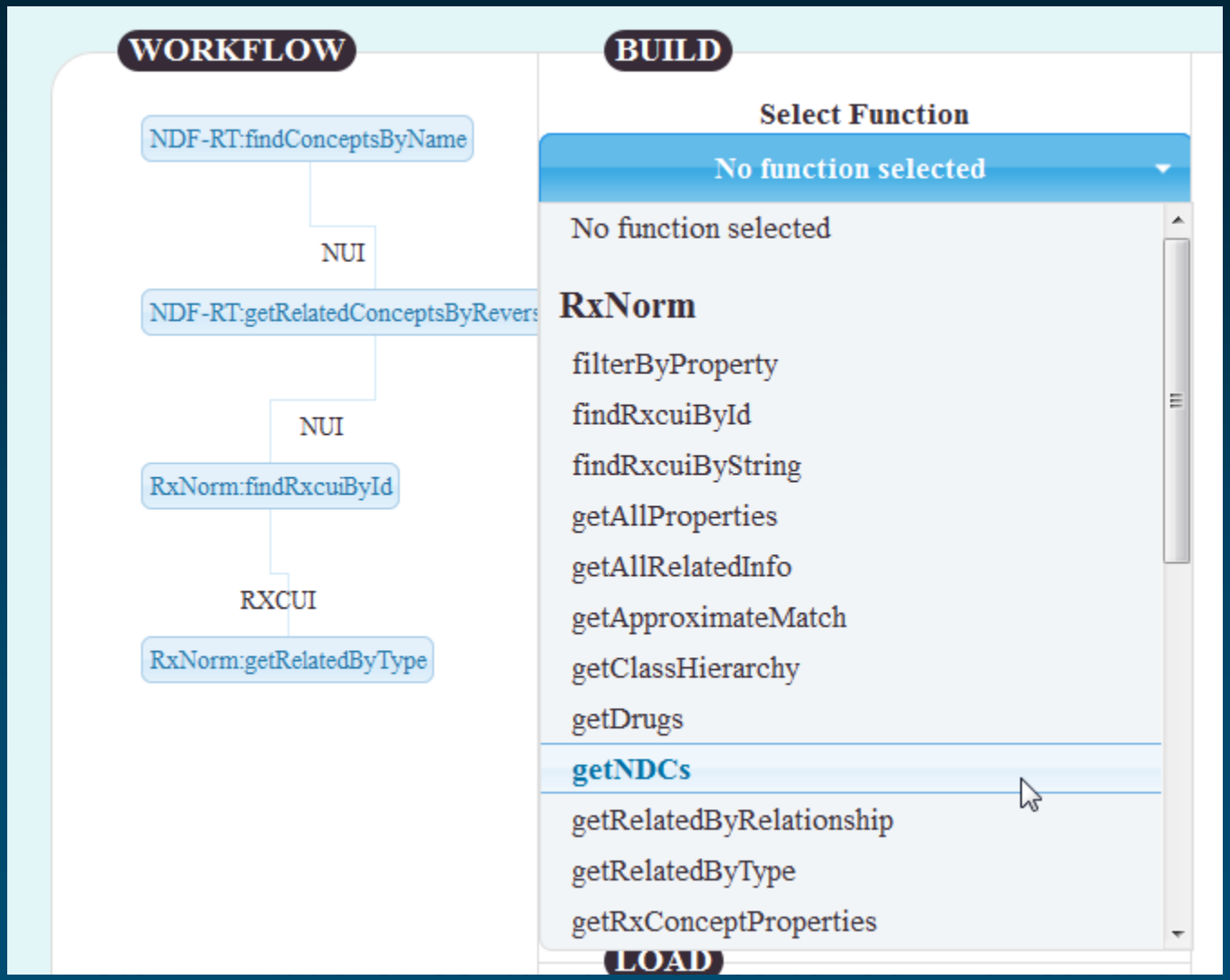
findConceptsByName *getRel.ConceptsByRev.Role* *findRxcuiById* *getRelatedByType* *getNDCs*

name → NDF-RT ID (chem. ingr.) → NDF-RT ID (drug/ingr.) → RxNorm ID (ingredient) → RxNorm ID (SCD/SBD) → NDC code



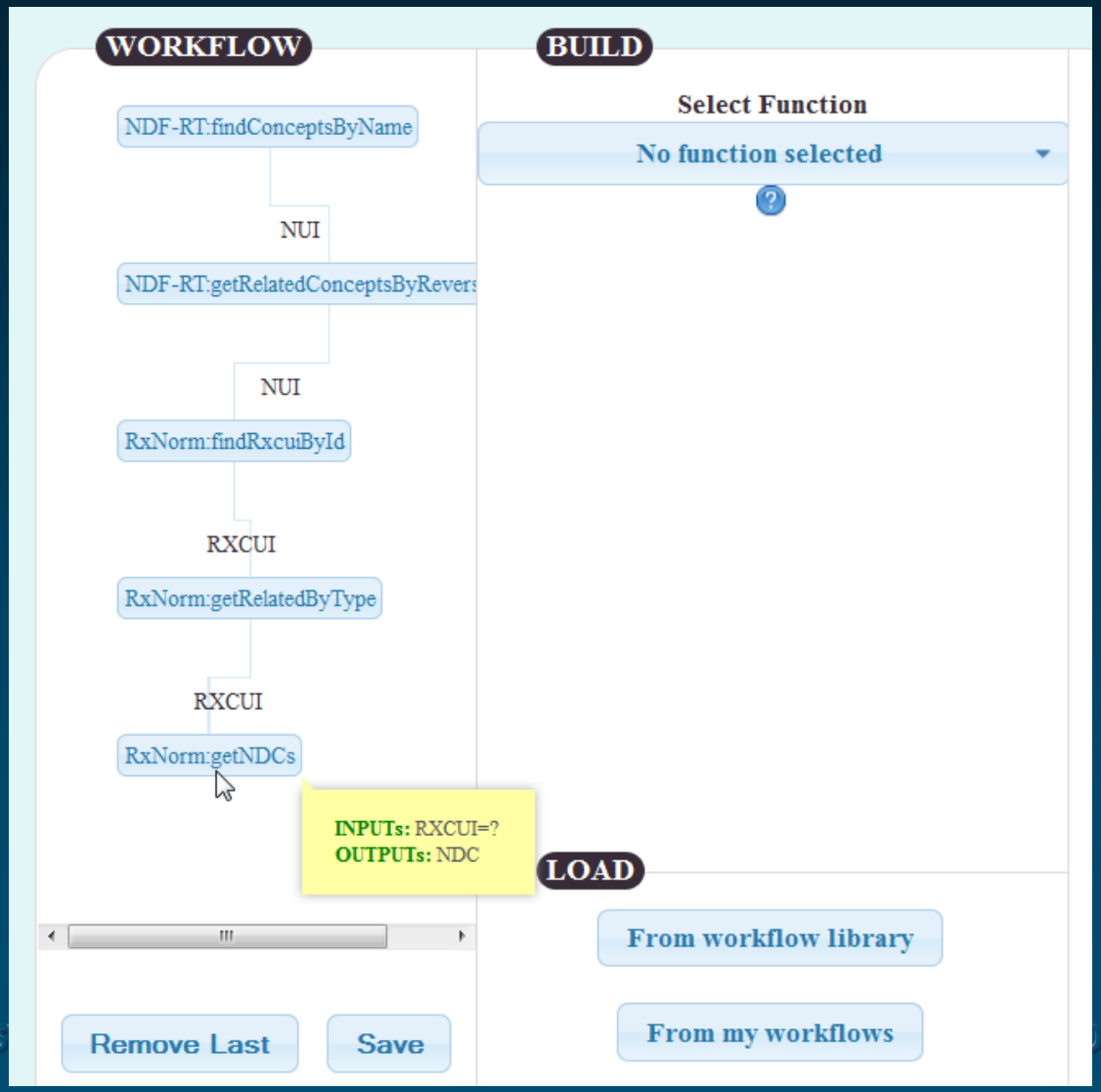
findConceptsByName *getRel.ConceptsByRev.Role* *findRxcuiById* *getRelatedByType* *getNDCs*

name → NDF-RT ID (chem. ingr.) → NDF-RT ID (drug/ingr.) → RxNorm ID (ingredient) → RxNorm ID (SCD/SBD) → NDC code

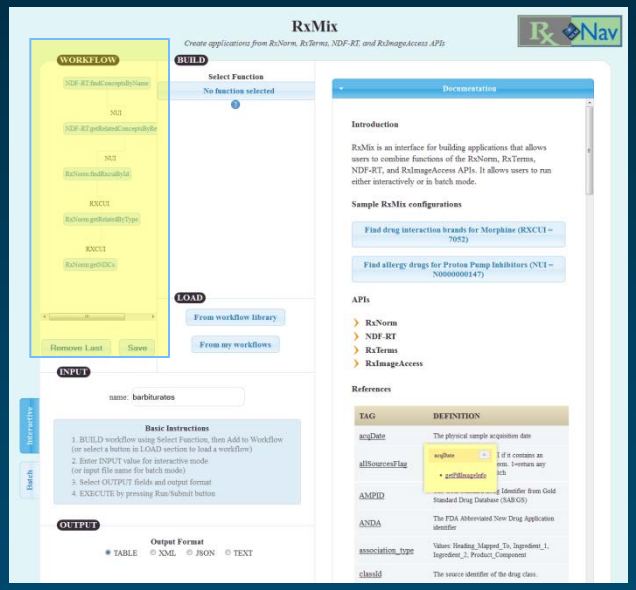


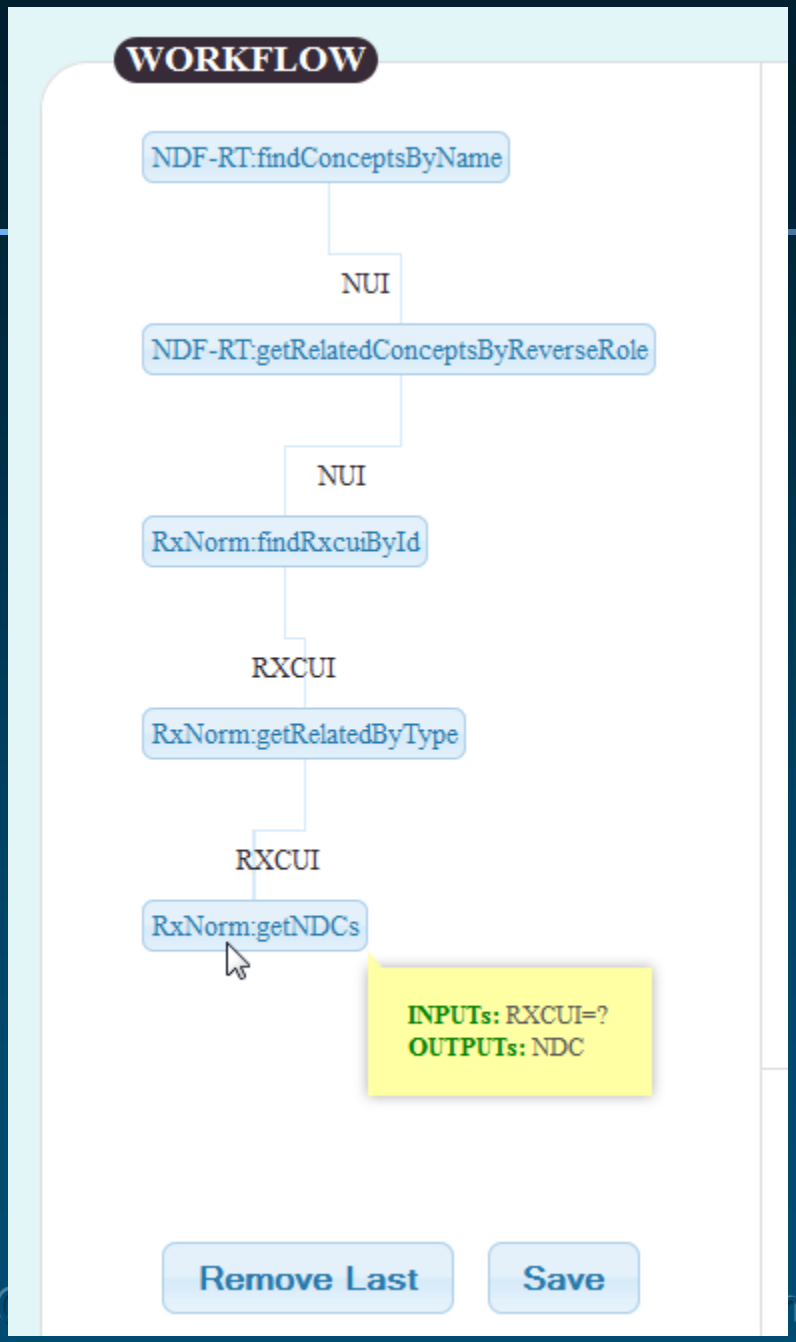
findConceptsByName *getRel.ConceptsByRev.Role* *findRxcuiById* *getRelatedByType* *getNDCs*

name → NDF-RT ID (chem. ingr.) → NDF-RT ID (drug/ingr.) → RxNorm ID (ingredient) → RxNorm ID (SCD/SBD) → NDC code

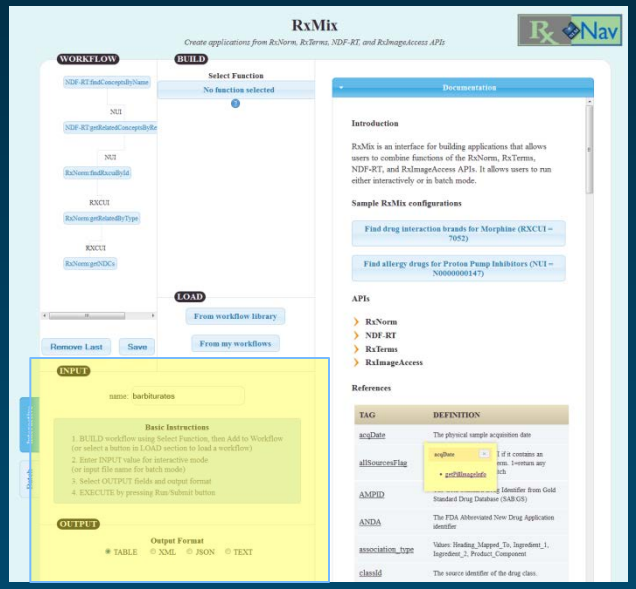


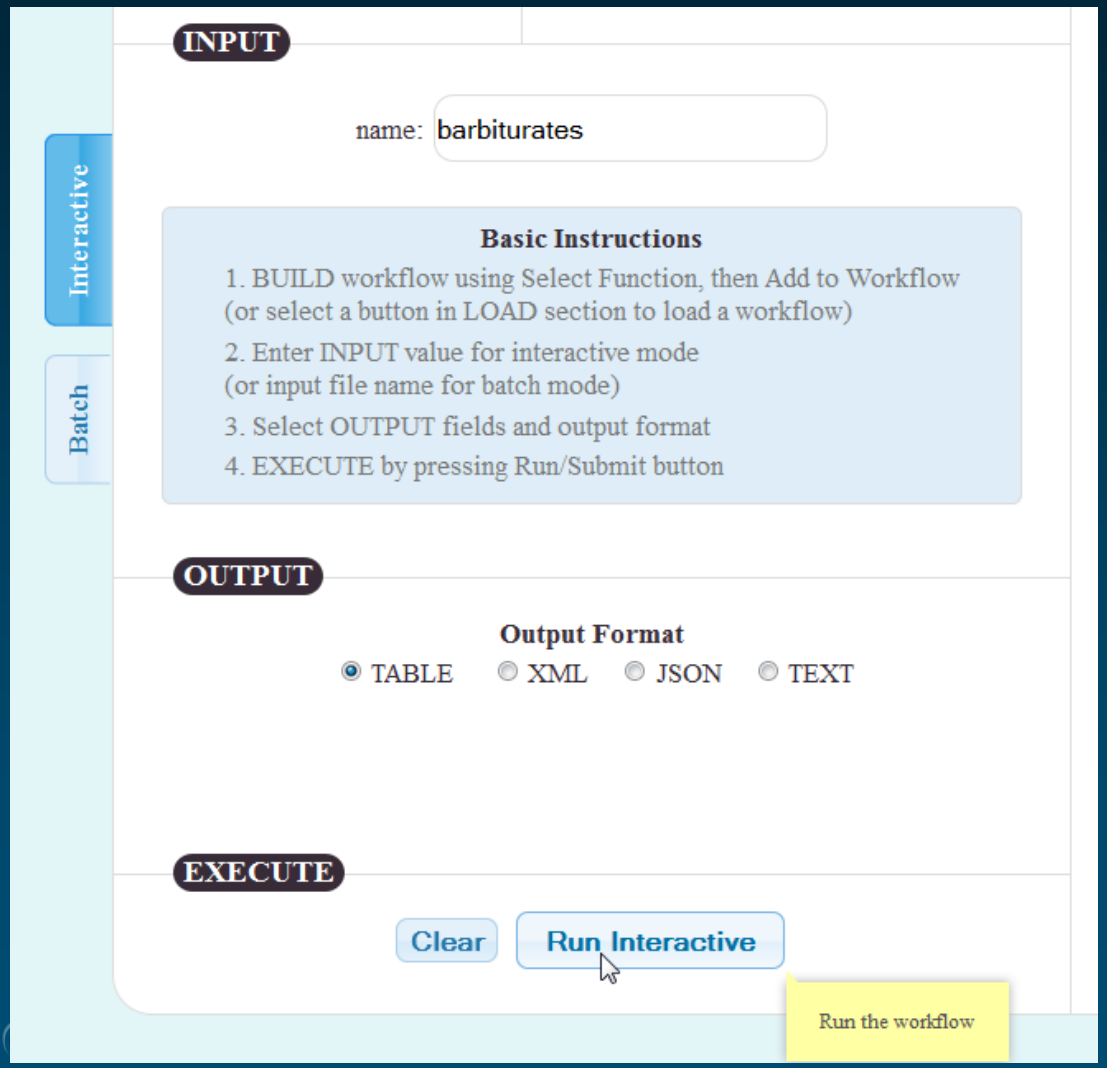
Complete workflow



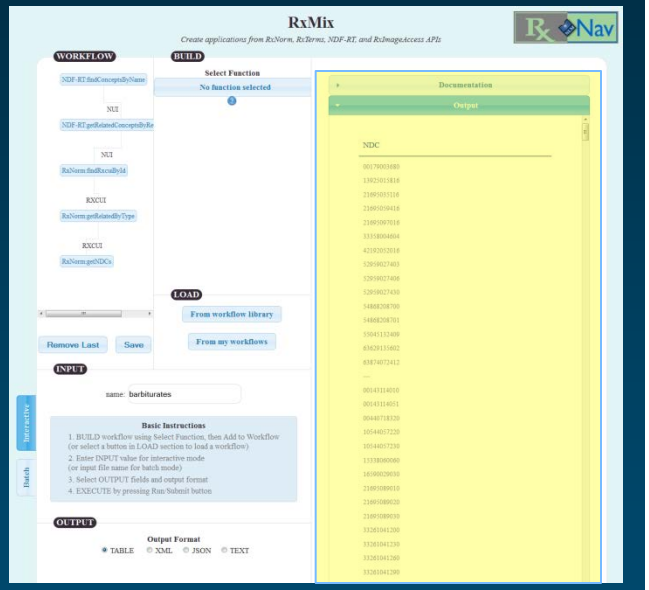


Add input and run (interactively)





Output



Documentation

Output

NDC

00179003680
13925015816
21695035116
21695059416
21695097016
33358004604
42192052016
52959027403
52959027406
52959027430
54868208700
54868208701
55045132409
63629135602
63874072412

00143114010
00143114051
00440718320
10544057220
10544057230
15338060060
16590029030
21695089010

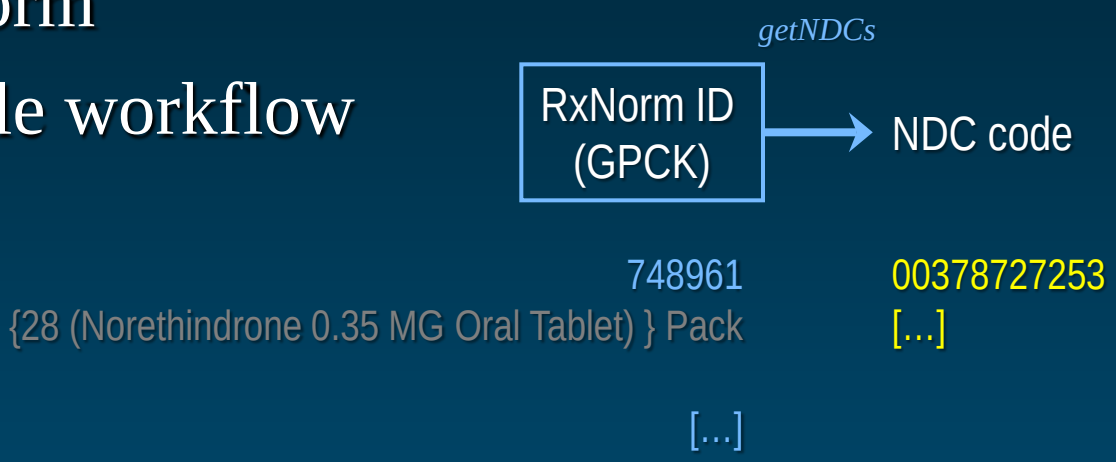
Over 1000 NDCs retrieved

Script of the demo

- RxMix overview
  - documentation is integrated
- Objective:
- Build a workflow
  - Find all the NDC codes for a given allergy class (e.g., barbiturates)
- Steps
  - [at first, all functions are available]
  - 1) NDF-RT:findConceptsByName
    - select INGREDIENT_KIND
  - [show output in mouse over]
  - [show that only the functions compatible with the output are listed]
  - 2) NDF-RT:getRelatedConceptsByReverseRole
    - role_type = has_ingredient
    - transitive = 1
    - [show access to the documentation]
  - [show that the parameter passed between functions is listed]
  - [cross over to RxNorm]
  - 3) RxNorm:findRxcuiById
    - [NUI is already preselected -- only element from the output to match the input]
  - 4) RxNorm:getRelatedByType
    - click SCD
    - ctrl-click SBD
  - 5) RxNorm:getNDCs
- [look at the complete workflow]
- Input value: barbiturates
- Execute workflow: Run
  - takes about 10 seconds
- Output
  - over 1000 NDCs
- Can save the workflow for reuse
- Can run any workflow on a list of input values (batch mode)
- Library of workflows
  - Find the National Drug Codes (NDCs) for clinical drugs of an ingredient
  - fairly close to what we did

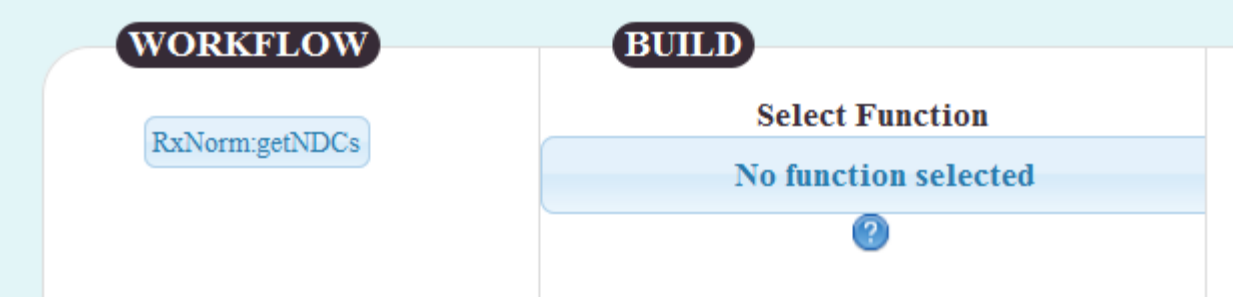
Batch mode

- Find all the NDC codes for generic packs in RxNorm
- Simple workflow

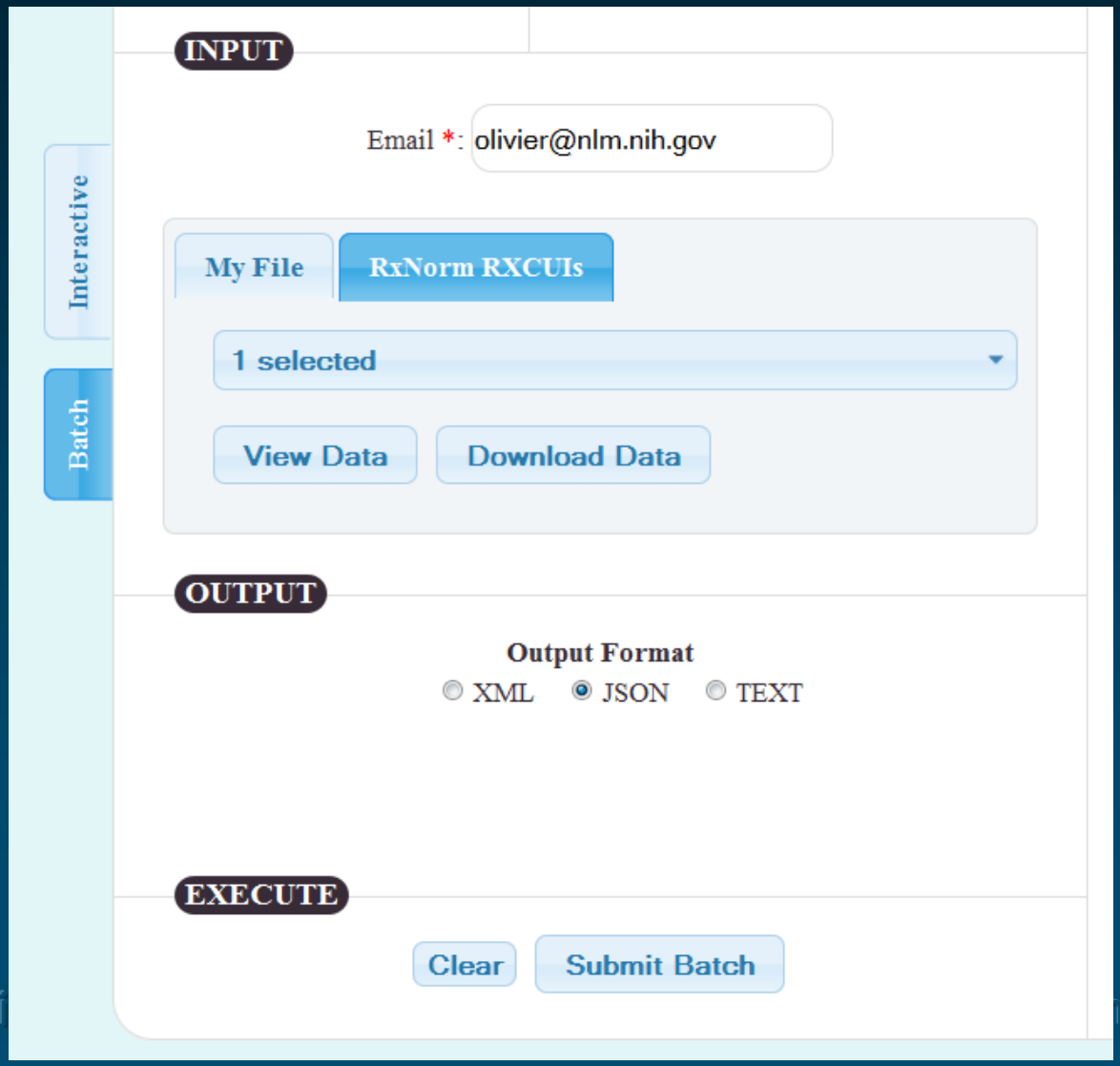


- Batch mode
  - Iterate over all the generic packs in RxNorm (GPCK)

Create workflow



Select input and output



JSON output


```
  - {
      name: "getNDCs",
      level: "0",
      input: "1246586",
    - outputs: {
      - output: [
          - {
              NDC: "42192011807"
            },
          - {
              NDC: "42192013101"
            },
          - {
              NDC: "45802034664"
            }
        ]
      }
    },
  - {
      name: "getNDCs",
      level: "0",
      input: "866813",
    - outputs: {
      - output: {
          NDC: "42192070918"
        }
      }
    },
  - {
      name: "getNDCs",
      level: "0",
      input: "1431253",
    - outputs: {
      - output: {
          NDC: "41250059702"
        }
      }
    },
```

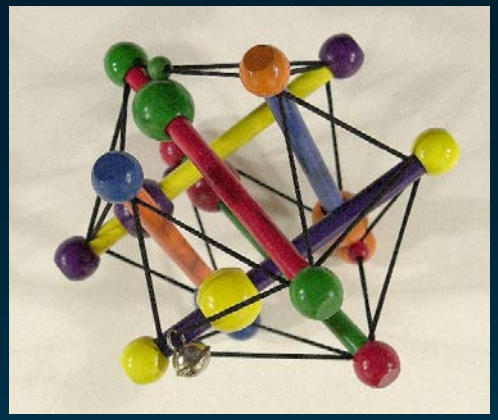
Examples of use cases

- Finding clinical drugs which may cause allergic reactions
- Finding interactions to RxNorm clinical drugs
- Finding NDF-RT ingredients from RxNorm clinical drugs
- Finding VA classes for RxNorm clinical dose forms
- Finding brand names from clinical drug strings

Library of common use cases integrated in RxMix

Summary

- Web service composition model for the RxNorm and NDF-RT APIs
- Enables an end-user to create complex queries to drug information sources ("workflows")
- Our model supports common use cases, including checking interactions for RxNorm drugs and deploying allergy lists defined in reference to drug properties in NDF-RT
- RxMix: http://mor.nlm.nih.gov/RxMix/



Medical Ontology Research

Contact: olivier@nlm.nih.gov
Web: mor.nlm.nih.gov

Olivier Bodenreider

Lister Hill National Center
for Biomedical Communications
Bethesda, Maryland - USA