**AFEP Dictionary for Anaphylaxis**

Sentinel Innovation Center’s Scalable NLP Project

8/28/2023

We implemented the AFEP method described by Yu and colleagues (JAMIA 2015) for creating an NLP dictionary and NLP features for PheNorm modeling. We created the dictionary as follows.

Mine a list of NLP-extracted UMLS (Unified Medical Language System) CUIs (Concept Unique Identifiers) from the following 5 KB articles on anaphylaxis.

1. Wikipedia
2. Medline Plus
3. Medscape
4. Merck Manuals
5. Mayo Clinic

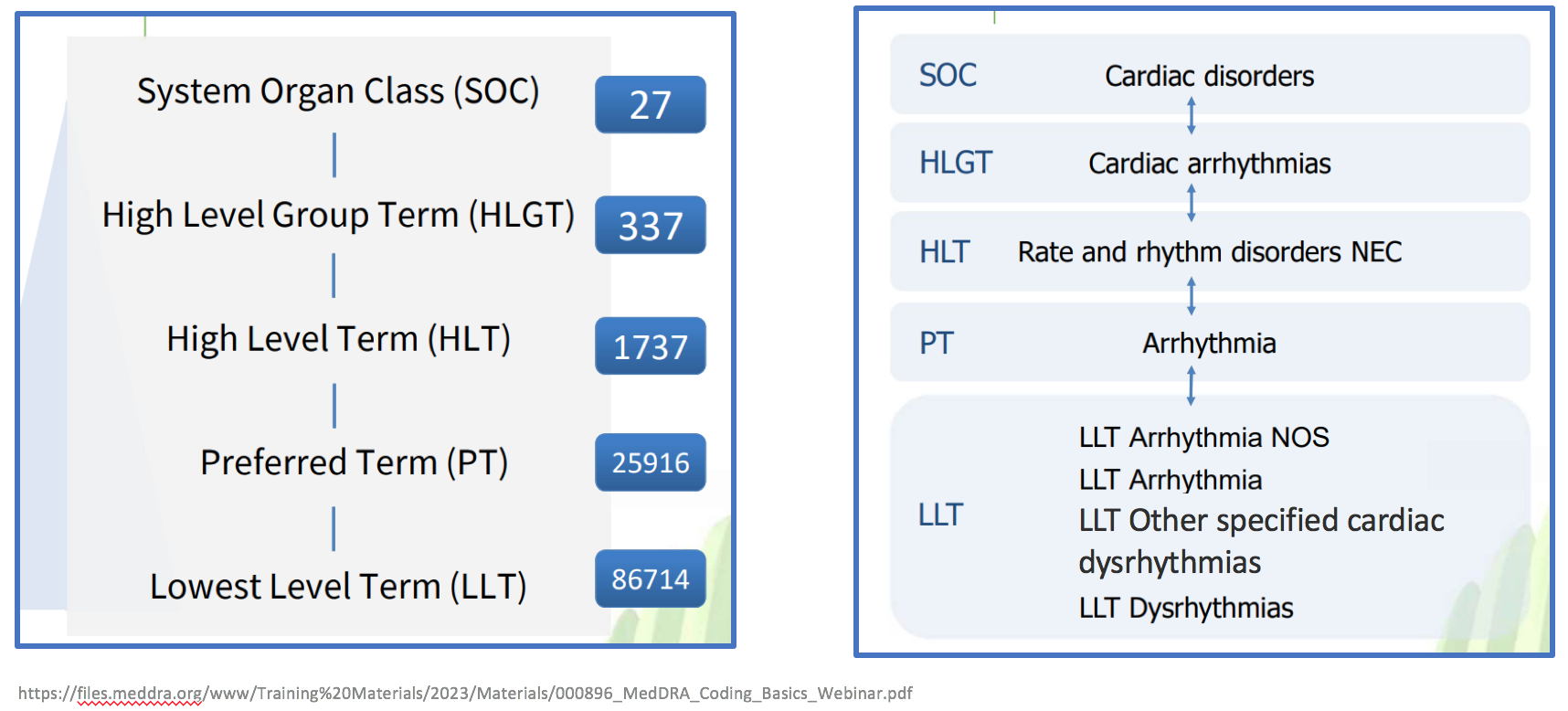
Review results applying the standard AFEP “rule of 3” (i.e., concepts appearing in >=3 KB articles are included in the dictionary), but also prepare summaries of CUIs that appear only in 1 or 2 KB articles. These summaries will be examined by a clinical expert as described later in this section.

Process

1. Obtain each of the 5 KB articles listed above, and prepare each for processing by MetaMap.
   1. *Note that this requires manually adding an end-of-line character as the last character in each KB article so that MetaMap will process the entire article. In June 2023 David Cronkite discovered that MetaMap may omit some parts of a text file that does not end with an end-of-line character*.
2. Obtain MetaMap version 2020.
3. Obtain the UMLS dataset, release 2022AB, from the National Library of Medicine (NLM) web site, including both the “Common” and the “Strict” datasets. These UMLS datasets will be the sources of the MedDRA and RxNORM vocabularies we will use to create an NLP dictionary and NLP-derived covariates usd in modeling.
4. Process each KB article using MetaMap using the **MedDRA and RxNORM** vocabulary.
   1. MetaMap settings used will be:
      1. -R MDR,RXNORM (for MedDRA and RxNORM)
      2. -Z 2022AB (UMLS version number)
      3. -V NLM (for UMLS subset version of NLM)
      4. -N (field MM output: mmi)
      5. -b (compute all mappings)
      6. Note: the command line to specify these settings is:  
         -R MDR,RXNORM -Z 2022AB -V NLM -N -b
5. Assemble a list of **CUIs appearing in 3+ KB articles**; all of these CUIs will be used to operationalize NLP-derived covariates.
6. Add to the above list of CUIs appearing in 3+ KB articles any additional CUIs appearing in only 1 or 2 KB articles that a clinical expert recommends based on manual review.
   1. The resulting list of CUIs includes all CUIs appearing in 3+ KB articles and expert-recommended CUIs appearing in 1 or 2 KB articles.
   2. Some (likely most) of these CUIs will be MedDRA “preferred terms.”
7. For each MedDRA preferred term (PT) in the above list, assemble a list of MedDRA “lower level” terms (LLTs) that should be counted as instances of their associated PT using the **normalization process** described below.
   1. Ask a clinical expert to manually review these lists for face validity. Retain the LLTs as recommended by the clinical expert.
8. Assemble a final list of all CUIs, including the CUI-specific lists of LLTs added in the above step to create the AFEP dictionary.

**Normalization Process**

Concepts in the AFEP dictionary are from MedDRA (Medical Dictionary for Regulatory Activities) and RxNorm. RxNorm contains only medication concepts. MedDRA, a standardized terminology used for pre- and post-marketing surveillance, contains concepts for diseases, diagnoses, findings, signs, symptoms, etc. Importantly, MedDRA also includes a robust hierarchy describing relationships between its concepts at varying levels of granularity.



Since we are limiting our list to the specific concepts found in 3+ knowledgebase articles, we may miss some synonymous concepts that were not included through that AFEP process. Feature normalization can help us recognize when two distinct concepts identified by NLP are actually the same or similar. We can achieve feature normalization by taking advantage of the aforementioned MedDRA hierarchy.

The level of the MedDRA hierarchy to which we would like to normalize is the Preferred Term (PT) level. Each PT has one or more associated lower-level terms (LLTs). By counting instances of each LLT as an instance of its associated PT, we can achieve better coverage of the relevant PTs.

To do this, we can utilize the UMLS Source/Concept table (MRCONSO) and the UMLS relationships table (MRREL). We must first identify which of our AFEP concepts are of type PT from MRCONSO. This can be achieved as follows:

*1. Using all UMLS CUIs in the AFEP dictionary, query MRCONSO to identify which are preferred terms (PTs):*

select CUI

from MRCONSO

where SAB='MDR' and TTY='PT'

and CUI in ( #list of UMLS CUIs from AFEP dictionary )

group by CUI;

Next, we must identify which LLTs are associated with each of those PTs in the AFEP dictionary. This can be achieved as follows:

*2. Using all CUIs returned from the query #1, select associated concepts from MRREL which are of the appropriate type (LLT or OL) and which have the appropriately specified relationship type:*

select b.cui1, b.rela, b.cui2 from mrconso a, mrrel b, mrconso c

where a.cui=b.cui1 and c.cui=b.cui2

and a.SAB='MDR' and b.SAB='MDR' and c.SAB='MDR'

and b.rela='classified\_as'

and (c.TTY='LLT' or c.TTY='OL')

and a.cui !=c.cui

and a.cui in ( #list of CUIs from the first query )

group by b.cui1, b.rela, b.cui2;

The results of query #2 is the mapping from LLTs to their associated PTs. When processing our corpus, we simply count any instance of the normalization LLTs as instances of the associated PTs.

Full query text and results is available at the end of this document.

**Completed AFEP Dictionary and Associated LLTs**

All code utilized by this project and required to achieve the resultant AFEP dictionary as described above is included in this repository.

The full version of the AFEP dictionary, as well as relevant LLTs that should be counted as instances of a PT from the AFEP dictionary, are included in the associated repository in **ANA\_AFEP\_All\_PTs\_and\_LLTs\_2023\_08\_28.xlsx**. The workbook includes three worksheets which contain:

1. The full AFEP dictionary, including LLT normalization terms
2. The AFEP dictionary without LLT normalization terms
3. The LLT normalization terms only

**Addendum**

The exact queries and results used to define the normalization (PT to LLT) mappings:

select CUI

from MRCONSO

where SAB='MDR' and TTY='PT'

and CUI in

('C0000729','C0000737','C0740651','C0413234','C0857035','C0041755','C0877248','C0559546','C0231848','C4055482','C2939065','C0001883','C0155877','C0850569','C1527304','C0199747','C0577620','C0854051','C0002792','C4316895','C0685898','C0340865','C0854649','C0002994','C1504374','C0003467','C0700198','C3853540','C0554804','C0004096','C0347950','C0947961','C0392707','C0413120','C0005658','C0020649','C1328414','C0006266','C0018790','C0751535','C0036980','C0600228','C0007203','C0235710','C0008031','C0232292','C0009443','C0009676','C0010200','C1306577','C0549249','C0011991','C0011992','C0012833','C0013182','C1527344','C0013404','C0559469','C0014236','C0220787','C0021932','C0014563','C4047193','C0349790','C0344183','C0238614','C0015376','C0743747','C0542571','C0015663','C0856904','C0016382','C0016470','C0016462','C0232070','C4728126','C0426576','C0476207','C0744425','C0039231','C0019825','C0020517','C0442856','C0857353','C0546884','C0020683','C0242184','C0020523','C0079603','C0021368','C1533685','C1261392','C0021564','C4510560','C0021925','C0022885','C0023052','C0577628','C0220870','C1304200','C0240211','C0041657','C0024899','C0199470','C1861783','C0027627','C0079840','C0026821','C0027497','C0027498','C0028778','C0013604','C0521481','C0030193','C0030252','C0559470','C0199176','C0202202','C0033774','C0242073','C1260922','C4324659','C0162297','C5208132','C0476273','C1145670','C0037090','C0035273','C1260880','C0036974','C0586407','C0037296','C0149783','C0038340','C0677500','C0038450','C0543467','C0038999','C0151602','C0236068','C0039070','C0231835','C0087111','C0700184','C0236071','C0151610','C0040533','C1504322','C0740852','C0042109','C0042196','C0042420','C0595862','C1275515','C1096052','C0859897','C0042963','C0413119','C0221232','C0043144')

group by CUI;

+----------+

| CUI |

+----------+

| C0000737 |

| C0002792 |

| C0002994 |

| C0003467 |

| C0004096 |

| C0005658 |

| C0006266 |

| C0008031 |

| C0009676 |

| C0010200 |

| C0011991 |

| C0012833 |

| C0013182 |

| C0013404 |

| C0013604 |

| C0014236 |

| C0015376 |

| C0015663 |

| C0016382 |

| C0016462 |

| C0016470 |

| C0018790 |

| C0020517 |

| C0020523 |

| C0020649 |

| C0020683 |

| C0021368 |

| C0021932 |

| C0022885 |

| C0023052 |

| C0024899 |

| C0027497 |

| C0027627 |

| C0028778 |

| C0030193 |

| C0030252 |

| C0033774 |

| C0035273 |

| C0036974 |

| C0036980 |

| C0037090 |

| C0037296 |

| C0038450 |

| C0038999 |

| C0039070 |

| C0039231 |

| C0040533 |

| C0041657 |

| C0041755 |

| C0042109 |

| C0042963 |

| C0043144 |

| C0079840 |

| C0087111 |

| C0149783 |

| C0151602 |

| C0151610 |

| C0162297 |

| C0199176 |

| C0199470 |

| C0199747 |

| C0231835 |

| C0232070 |

| C0235710 |

| C0236068 |

| C0236071 |

| C0238614 |

| C0240211 |

| C0242073 |

| C0242184 |

| C0340865 |

| C0392707 |

| C0442856 |

| C0476273 |

| C0521481 |

| C0542571 |

| C0543467 |

| C0546884 |

| C0549249 |

| C0559546 |

| C0586407 |

| C0595862 |

| C0600228 |

| C0700184 |

| C0700198 |

| C0740651 |

| C0740852 |

| C0854051 |

| C0854649 |

| C0859897 |

| C0877248 |

| C1096052 |

| C1145670 |

| C1260880 |

| C1260922 |

| C1275515 |

| C1306577 |

| C1504322 |

| C1527344 |

| C1533685 |

| C1861783 |

| C3853540 |

| C4316895 |

| C4510560 |

+----------+

104 rows in set (0.85 sec)

select b.cui1, b.rela, b.cui2 from mrconso a, mrrel b, mrconso c

where a.cui=b.cui1 and c.cui=b.cui2

and a.SAB='MDR' and b.SAB='MDR' and c.SAB='MDR'

and b.rela='classified\_as'

and (c.TTY='LLT' or c.TTY='OL')

and a.cui !=c.cui

and a.cui in

('C0000737','C0002792','C0002994','C0003467','C0004096','C0005658','C0006266','C0008031','C0009676','C0010200','C0011991','C0012833','C0013182','C0013404','C0013604','C0014236','C0015376','C0015663','C0016382','C0016462','C0016470','C0018790','C0020517','C0020523','C0020649','C0020683','C0021368','C0021932','C0022885','C0023052','C0024899','C0027497','C0027627','C0028778','C0030193','C0030252','C0033774','C0035273','C0036974','C0036980','C0037090','C0037296','C0038450','C0038999','C0039070','C0039231','C0040533','C0041657','C0041755','C0042109','C0042963','C0043144','C0079840','C0087111','C0149783','C0151602','C0151610','C0162297','C0199176','C0199470','C0199747','C0231835','C0232070','C0235710','C0236068','C0236071','C0238614','C0240211','C0242073','C0242184','C0340865','C0392707','C0442856','C0476273','C0521481','C0542571','C0543467','C0546884','C0549249','C0559546','C0586407','C0595862','C0600228','C0700184','C0700198','C0740651','C0740852','C0854051','C0854649','C0859897','C0877248','C1096052','C1145670','C1260880','C1260922','C1275515','C1306577','C1504322','C1527344','C1533685','C1861783','C3853540','C4316895','C4510560')

group by b.cui1, b.rela, b.cui2;

+----------+---------------+----------+

| cui1 | rela | cui2 |

+----------+---------------+----------+

| C0000737 | classified\_as | C0000729 |

| C0000737 | classified\_as | C0221512 |

| C0000737 | classified\_as | C0232488 |

| C0000737 | classified\_as | C0232491 |

| C0000737 | classified\_as | C0344304 |

| C0000737 | classified\_as | C0423644 |

| C0000737 | classified\_as | C0522061 |

| C0000737 | classified\_as | C0549273 |

| C0000737 | classified\_as | C0857092 |

| C0000737 | classified\_as | C0857334 |

| C0000737 | classified\_as | C0920154 |

| C0000737 | classified\_as | C1096624 |

| C0000737 | classified\_as | C1609533 |

| C0000737 | classified\_as | C1662979 |

| C0000737 | classified\_as | C1698089 |

| C0000737 | classified\_as | C3805159 |

| C0002792 | classified\_as | C0340865 |

| C0002792 | classified\_as | C0344159 |

| C0002792 | classified\_as | C0344183 |

| C0002792 | classified\_as | C0685898 |

| C0002792 | classified\_as | C0857035 |

| C0002792 | classified\_as | C1096621 |

| C0002792 | classified\_as | C1536101 |

| C0002792 | classified\_as | C5441893 |

| C0002792 | classified\_as | C5442289 |

| C0002792 | classified\_as | C5577808 |

| C0002994 | classified\_as | C0549440 |

| C0002994 | classified\_as | C0743747 |

| C0002994 | classified\_as | C0857036 |

| C0002994 | classified\_as | C0857323 |

| C0002994 | classified\_as | C0859055 |

| C0002994 | classified\_as | C0863128 |

| C0002994 | classified\_as | C0877772 |

| C0002994 | classified\_as | C0920175 |

| C0002994 | classified\_as | C1304200 |

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| C0003467 | classified\_as | C0233481 |

| C0003467 | classified\_as | C0233485 |

| C0003467 | classified\_as | C0235107 |

| C0003467 | classified\_as | C0235111 |

| C0003467 | classified\_as | C0262377 |

| C0003467 | classified\_as | C0349231 |

| C0003467 | classified\_as | C0542180 |

| C0003467 | classified\_as | C0549258 |

| C0003467 | classified\_as | C0549259 |

| C0003467 | classified\_as | C0581386 |

| C0003467 | classified\_as | C0683278 |

| C0003467 | classified\_as | C0700031 |

| C0003467 | classified\_as | C0700613 |

| C0003467 | classified\_as | C0853074 |

| C0003467 | classified\_as | C0853241 |

| C0003467 | classified\_as | C0857102 |

| C0003467 | classified\_as | C0857126 |

| C0003467 | classified\_as | C0857480 |

| C0003467 | classified\_as | C0859031 |

| C0003467 | classified\_as | C0860603 |

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| C0008031 | classified\_as | C0740396 |

| C0008031 | classified\_as | C0856134 |

| C0008031 | classified\_as | C0856578 |

| C0008031 | classified\_as | C0857030 |

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| C0011991 | classified\_as | C0857184 |

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| C0013604 | classified\_as | C0238094 |

| C0013604 | classified\_as | C0333241 |

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| C0016470 | classified\_as | C0577620 |

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