BIOS: An Algorithmically Generated Biomedical Knowledge Graph

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ABSTRACT

Biomedical knowledge graphs (BioMedKGs) are essential infrastructures for biomedical and healthcare big data and artificial intelligence (AI), facilitating natural language processing, model development, and data exchange. For many decades, these knowledge graphs have been built via expert curation, which can no longer catch up with the speed of today’s AI development, and a transition to algorithmically generated BioMedKGs is necessary. In this work, we introduce the Biomedical Informatics Ontology System (BIOS), the first large scale publicly available BioMedKG that is fully generated by machine learning algorithms. BIOS currently contains 4.1 million concepts, 7.4 million terms in two languages, and 7.3 million relation triplets. We introduce the methodology for developing BIOS, which covers curation of raw biomedical terms, computationally identifying synonymous terms and aggregating them to create concept nodes, semantic type classification of the concepts, relation identification, and biomedical machine translation. We provide statistics about the current content of BIOS and perform preliminary assessment for term quality, synonym grouping, and relation extraction. Results suggest that machine learning-based BioMedKG development is a totally viable solution for replacing traditional expert curation.
1. INTRODUCTION

Biomedical knowledge graphs (BioMedKGs) are specialized databases for formal representation of biomedical data and knowledge, where biomedical concepts are represented as graph nodes, and the relationships between concepts are represented as graph edges. Three essential components in BioMedKGs make them the most important informatic infrastructure for biomedical big data and artificial intelligence (AI). The first component are the terms (names) of each concept, which are synonymous to each other and are considered part of the node properties. The terms can be formal or informal and are intended to include as many variations as possible. For example, type 2 diabetes, type II diabetes, type 2 diabetes mellitus, T2DM, non-insulin-dependent diabetes, NIDDM, and so on, all refer to the same concept and are all the terms of the same node. The terms are critical information for natural language processing (NLP), which is used for processing free text, such as electronic health records (EHRs), research papers, and conversations between doctors and patients, to identify mentions of biomedical concepts via any of their names\textsuperscript{1,2}. The second component are the relations (the graph edges). The relations are typed and directed (some can be bidirectional). By connecting two concepts, the relations form a triplet, such as $\{\text{Acetaminophen, may treat, Fever}\}$, where “may treat” is the relation, and Acetaminophen and Fever are the connected concepts and are referred to as the head entity and the tail entity, respectively. Relations are critical information for numerous AI tasks, such as automatic diagnosis\textsuperscript{3}, question answering\textsuperscript{4}, and drug discovery\textsuperscript{5,6}. The third essential component of BioMedKGs is the ID system used for standardized representation. For example, a concept ID represents the same concept, no matter which term is used, or in which language, which facilitates interoperability and data exchange between systems, institutions, and countries.

Building BioMedKGs requires tremendous amount of expert input and is extremely costly\textsuperscript{7}. As a result, BioMedKGs developed from scratch are usually limited in size and are commonly built over decades. Some BioMedKGs choose to build on top of existing ones to unify them for focused domains. For example, the Human Phenotype Ontology is built on top of OMIM, Orphanet, and DECIPHER and focuses on phenotype-driven differential diagnostics, genomic diagnostics, and translational research\textsuperscript{8}. Some projects focus on aggregation to create a gigantic BioMedKG. The largest one is the Unified Medical Language System (UMLS)\textsuperscript{9,10}, which is a long term project started in 1986. Aggregated over 200 vocabularies and BioMedKGs, UMLS contains 4.5 million concepts’ 14 million terms in 25 languages as of Release 2021AB. It also contains 21 million relation triplets labeled with 974 different types of relations. However, despite such a gigantic size, users often find that UMLS does not cover enough concepts, terms, or relation triplets to meet the growing demand for NLP and AI development. With its decades-long development integrating vocabularies that have even longer histories, it is hard to imagine any expert-curated BioMedKG to be larger than the UMLS, which might have reached the limit.
for human expert curation. Recently, deep learning-based NLP models are becoming increasingly accurate, to the extent that they can be deployed for real-world services. As NLP technology evolves to approach human parity for many tasks, we believe that the transition from expert-curated BioMedKGs to algorithmically generated BioMedKGs will be feasible.

In this work, we introduce the development of the Biomedical Informatics Ontology System (BIOS), which, to our knowledge, is the first large scale publicly available BioMedKG that is fully generated by machine learning algorithms. The content of the current release of BIOS is learned from PubMed abstracts and PubMed Central articles. It contains 4.1 million concepts, 7.4 million terms, and 7.3 million relation triplets. Unlike previous work that uses machine learning to address a particular part of BioMedKG construction, BIOS uses machine learning in the entire process of BioMedKG development, namely: (1) curation of biomedical terms, (2) aggregating synonyms to create concept nodes, (3) semantic type classification of the concepts, and (4) relation identification, as illustrated in Figure 1. BIOS also aims to be a multi-language BioMedKG. At this initial stage, we translate the English terms to Chinese, a low resource language, using biomedical machine translation. BIOS can be accessed and downloaded at https://bios.idea.edu.cn. The focus for the design and development of BIOS will be on healthcare (e.g., diagnosis and treatment) instead of drug development or biochemistry. We hope this release of BIOS and its future updates will serve as a useful infrastructure of AI and big data for healthcare industry and research community.
Figure 1: Development of BIOS involves full process of BioMedKG construction. Steps are introduced in the Methods section. Specifically, a-c: Section 3.1, d-g: Section 3.2, h: Section 3.3, i: Section 3.4, j: Section 3.5, k-n: Section 3.6.

2. RELATED WORK

2.1 Related work in building BioMedKGs

We review general BioMedKGs (instead of those for specific domains, such as cancer) developed using machine learning and NLP. Previous work on machine learning-based integration, inference, or refinement of existing BioMedKGs will not be reviewed, as they do not generate new concepts or terms and are less effective on inferring new relations.

A number of existing approaches are based on EHR data. An early work from Finlayson et al. identified mentions of biomedical concepts based on existing ontologies and applied a series of statistical NLP techniques for data cleaning; they reported cooccurrence data of the identified concepts, which forms a graph, but not in the sense of a BioMedKG that requires directed and typed relations\(^1\). Rotmensch et al. constructed a knowledge graph with EHR data by using the manually curated Google Health Knowledge Graph and the UMLS as dictionaries to identify disease and symptom concepts from EHR free text, and learned their associations using logistic regression, naïve Bayes, and Bayesian network classification models\(^2\). Li et al. applied the
BiLSTM-CRF model to discover symptoms from the clinical notes (other entities were extracted from structured data). However, they reported that the model had problems in generalizability, which is a common phenomenon and we will address it in this paper. Additionally, synonym grouping was achieved by using a mapping dictionary, i.e., the concepts were in fact predefined instead of learned. Their relation extraction was also based on cooccurrence instead of sentence meaning.

Similar to our approach, SemMedDB and KGen use PubMed as the corpus for knowledge graph construction. Because SemMedDB identifies UMLS concepts and relations with statistical NLP, it cannot generate concepts and terms that are not in the UMLS. KGen applies a different set of statistical NLP methods. Similar to SemMedDB, the identified terms are linked to UMLS concepts, i.e., no new concepts are generated. Different from SemMedDB, the verbs of the sentences are used as the relations in KGen, i.e., the relations are in the free text form instead of being controlled. In comparison, BIOS does not rely on existing ontologies and learns its own terms and concepts, which in spirit is similar to the work of Never-ending Language Learner (NELL). However, BIOS does not reuse predictions as new training samples, which is a hallmark of NELL. BIOS puts an emphasis on grouping synonyms to form concepts, which is not only novel but also important for NLP in biomedicine.

2.2 Related NLP technologies

We also briefly review recent NLP technologies relevant to the construction of BIOS.

Named entity recognition (NER): NER is a sequential tagging task and is used for identifying biomedical terms. Tokens in an input sentence are classified to be the beginning token of a term (tagged as B), a non-beginning token of a term (tagged as I), or a token not in a term (tagged as O). By extending the tags with semantic types (a coarse classification of the concept), such as B-diseases, we can achieve NER and semantic type classification simultaneously. The NER model employed in BIOS is the standard BERT sequential classifier, which replaces BiLSTM-CRF as the new standard deep learning NER model. Our approach of using automated annotation to generate training data belongs to the distant supervision (DS-NER) category, where recent studies mainly focus on sample cleaning techniques. Recent novel developments in discontinuous NER, nested NER, and Seq2Seq NER are not employed in the BIOS project currently due to concerns of engineering maturity.

Biomedical term embedding (BTE): Like word embedding, BTE aims to embed terms with real-valued vectors that should be similar (e.g., by the cosine similarity) when the terms are related or close in meaning. Yet different from word embedding, BTE should be able to embed any given term, including incorrectly spelled ones, and should not have the out-of-vocabulary problem. BTE is a critical tool in BIOS for grouping synonyms to form concepts. BTE is also
used in relation extraction and in evaluating machine translation. SapBERT\textsuperscript{32} and CODER\textsuperscript{33} are two recent state-of-the-art BTE models that are both based on contrastive learning, where the former is trained from the synonym structure of the UMLS and the latter is trained from both the UMLS synonym and relations. However, neither of the two is capable of embedding terms meaningfully to the levels that synonymous terms can be grouped to concepts by clustering techniques. Therefore, for biomedical terms embedding in BIOS, we further developed CODER++, which will be introduced in the methods section. Classification is another potential approach for synonym clustering\textsuperscript{34}, but BTE was adopted due to the flexibility of embedding vectors.

Relation extraction (RE): RE is an NLP classification task that predicts whether a sentence expresses a particular relationship between two identified named entities. Lots of RE models have been proposed for a few available expert annotated datasets\textsuperscript{35–37}. However, the size of the annotated samples, the number of annotated relation types, and the annotated document formats are far from enough for training contemporary deep learning models for large scale RE for the construction of BioMedKGs. Like DS-NER, distantly supervised RE (DS-RE)\textsuperscript{38} becomes popular to address the training sample problem in order to achieve high-throughput relation extraction. Current research of DS-RE focuses on improving label quality by filtering noisy samples, adjusting sample weights, or generating realistic samples\textsuperscript{39–45}. For engineering robustness and modularization, models that jointly detect named entities and relations\textsuperscript{46–48} are not considered currently for constructing BIOS.

Biomedical machine translation (BMT): Contemporary deep learning-based machine translation (MT), especially the Transformer architecture\textsuperscript{49}, can offer satisfying translation quality. However, the training set of tens of millions of parallel sentences required is prohibitive for the biomedical domain and for low resource languages. The BMT model adopted in BIOS was trained with samples acquired by a novel sentence alignment model using parallel documents\textsuperscript{50}. While research on unsupervised MT is promising \textsuperscript{51–53}, so far it is still experimental and lacking in engineering maturity.

3. METHODS

3.1 Annotation for NER
To achieve term discovery via DS-NER, we need to use automatic methods to annotate a corpus with existing ontologies, i.e., tagging each token with B, I, or O along with the term’s semantic type classification, to provide a training sample. From the UMLS (release 2020AB), we manually selected 8 vocabulary sources that we deem to provide an adequate coverage of biomedical terms. At this initial stage, we only included 64 semantic types from the UMLS,
with some important semantic types, such as genes, to be added in the next release.

The UMLS contains a huge number of terms that are not really biomedical terms by common standards, as will be illustrated by example in the results section. Since the main annotation method is string matching using the forward maximum matching algorithm (FMM), to reduce the possibility of matching strings that have identical spelling with recorded terms but have other meaning, for each vocabulary source, we filtered its terms with manually selected term types that are specific to that source. For instance, permutations and acronyms were not included. Finally substantial filtering rules based on dictionaries, regular expressions, and sentence parsing were applied to remove common words and problematic terms that may cause errors in FMM.

The remaining terms, referred to as “seed terms”, can still be ambiguous. Particularly, a term can have multiple biomedical meanings with different semantic types. Therefore, we trained a dedicated semantic type annotator (STA) to predict the semantic type of a term using the term itself as well as its surrounding text as input. Training samples were multi-word terms from the UMLS, as they generally do not have ambiguous daily meaning. The semantic types of these terms were used as the label, and in case a term has multiple semantic types in the UMLS, a random one is used, leveraging the fact that a large sample size can overcome moderate noise in the data. The classification model was trained on PubMedBERT, a BERT model pretrained on PubMed abstracts.

With the STA, we performed automatic annotation as follows: We used the seed terms as the dictionary to perform FMM on PubMed abstracts and half of PubMed Central full texts (referred to as the PubMed corpus hereinafter). For each matched term, we applied the STA to predict its semantic type. If the predicted type was from the same semantic group (a UMLS hierarchy for semantic types) as any of the recorded semantic types of that term in the UMLS, the term would be annotated with that recorded semantic type with probability $1 - DF$, where $DF$ is the fraction of documents that contain the term; otherwise, the matched term would be considered as a wrong match and would not be annotated.

### 3.2 Term discovery and cleaning

We used PubMedBERT to train a B-I-O sequential tagging model for NER. As reported in Lin et al., machine learning-based NER models tend to memorize annotated terms in the training data and have limited generalizability to identify terms that they have not seen. This phenomenon is even more prominent for deep learning models, because they have a much larger parameter space for memorizing than do conventional models. With the ability to automatically annotate very large datasets, we could address this issue by using a different sampling strategy. Specifically, instead of annotating a corpus that may contain repeated mentions of only part of
the seed terms, we chose to sample only one sentence per term from the entire PubMed corpus. This sampling strategy covered more terms than the traditional method. More importantly, the model was shown only one occurrence per term. In other words, what the model saw repeatedly was the surrounding patterns around the terms, and it would try to memorize those surrounding patterns, instead of the terms. This allowed the model to gain generalizability to discover new terms.

The rules for cleaning the seed terms were again applied to clean the discovered terms. In addition, we conducted further cleaning by performing FMM using the newly discovered terms as the dictionary on the PubMed corpus and would filter a term if the ratio between its FMM count in the corpus and the number of times it was predicted by the NER model was over a threshold, which meant the term was only predicted occasionally and was likely an error. Finally, we filtered terms that were not a noun phrase or did not end with a noun in the sentence where it was predicted, based on the Stanford Parser.

3.3 Synonym grouping to form concepts

So far, we have only identified individual terms, which still needed to be linked to corresponding concepts. Intuitively, one might think that this should be achieved by mapping terms to concepts as a classification task. However, as BIOS is built entirely from scratch, there is not a predefined concept set. In other words, concepts need to be computationally defined by what terms are discovered. Our strategy was to rely on similarity of BTE vectors to identify synonyms, and then each synonym group would be defined as a concept. This would require the BTE model to meaningfully understand any given biomedical term and to embed synonymous terms much closer than do those nonsynonymous ones, and no existing BTE model could satisfy this requirement. In our experiments, we observed that CODER and SapBERT were weak at understanding tiny differences, such as the differences between 1 and 2 or between \( \alpha \) and \( \beta \). To reinforce the model to distinguish close terms, we continued training CODER with hard samples: each sample was a UMLS term accompanied by 30 terms closest in embedding that were retrieved by Faiss, and the labels were whether they were synonyms in the UMLS. Faiss’s indexing was periodically updated to reflex the latest state of the BTE model. We referred to the new model as CODER++. The output of CODER++ were 768-dimensional vectors. We manually selected a conservative similarity threshold 0.8 for identifying synonyms, which would give very high precision and moderate recall.

We then clustered all the identified terms as follows. First, we considered all the terms as nodes of an undirected graph and edge weights were the BTE cosine similarity of the connected terms. Next, edges whose weights were below 0.8 were removed, and the whole graph became a collection of connected subgraphs. Intuitively, terms in the same subgraph were synonymous, but some subgraphs could contain hundreds of terms. Therefore, for subgraphs with more than
50 terms, we performed recursive graph bipartition with Ratio Cut, until the subgraph had fewer than 50 nodes, or the cosine similarity of the mean BTEs of the two obtained subgraphs from a ratio cut was greater than 0.6. This concluded the term clustering, and each subgraph was treated as a biomedical concept.

### 3.4 Biomedical machine translation

BIOS adopted Luo et al.’s BMT model, which reported a remarkable BLEU score of 35.04 for English-Chinese translation and 40.13 for Chinese-English. According to our experiments, the model could translate common terms accurately, because it might have memorized them from the training data. However, it could translate uncommon terms, such as complicated chemical names, very arbitrarily. We used a back-translation method to automatically determine which translations were unreliable: We used BMT to translate every term from English to Chinese, then back to English, and the Chinese translation would be considered unreliable and would be deleted if the original and the back-translated English terms’ CODER++ similarity was less than 0.55 (chemicals require a higher threshold of 0.8), which is based on the intuition that if the Chinese was generated arbitrarily, there would be no way that the back-translated English could be similar to the original term. The thresholds were selected empirically.

### 3.5 Semantic type classification

The semantic type schema of BIOS was modified from that of the UMLS according to our understanding of relevance and ease of use for healthcare big data and AI. For example, we merged all the 26 subclasses of chemicals of the UMLS as a single semantic type *Chemical or Drug*.

To determine the semantic types of the concepts, we aggregated the NER model’s predictions. The original predictions included 64 UMLS types, which were mapped to 18 BIOS types. Each concept could have multiple terms; each term could be predicted multiple times in the PubMed corpus by the NER model, and each time had an individual type prediction. Therefore, we counted the type distribution by aggregating all the type predictions of all the terms belonging to the same concept, and we kept the semantic types that reached 1/3 of the total counts. Therefore, theoretically a concept could have at most 3 semantic types, but most would have a single type.

### 3.6 Relation extraction

Similar to NER, we used distant supervision to train the RE model, and we used Wikidata as the source of labels. Wikidata is a general domain knowledge graph. We performed exact matching using the BIOS terms as dictionary on Wikidata page titles (not aliases) to identify biomedical concepts, and we also required the page to contain at least one manually selected biomedical relation for disambiguation. We mapped selected relations from Wikidata to
BIOS relations for building the model, which included 9 pairs of unidirectional relations (e.g., “is a” and “reverse is a”) and 1 bidirectional relation (“significant drug interaction”). We then retrieved sentences from the PubMed corpus that contained both head and tail entities of Wikidata triplets to form a DS-RE dataset. Entity matching in sentences was based on FMM using all the BIOS terms, and the two terms were required to be no more than 10 tokens away from each other. Each sample was a bag of sentences that contained the same pair of head and tail entities, and the label was a $K$-dimensional binary vector $(y_1, ..., y_K)$ to indicate which relations were true (multi-label classification). Artificial negative samples ($y_k = 0$, for $k = 1, ..., K$) were generated by identifying sentences that contained entities whose semantic types were compatible with any of the $K$ relations, but the corresponding triplets were not recorded in Wikidata.

The RE model was trained by sentence bags. Each sentence input $x = (x_0, ..., x_l)$ was a sequence of tokens. Depending on the relative positions of the head and tail entities, it could be one of two forms:

$$(x_0, ..., [H\_ST], x_{hs}, ..., x_{he}[H\_ED], ..., [T\_ST], x_{ts}, ..., x_{te}[T\_ED], ..., x_l),$$

$$(x_0, ..., [T\_ST], x_{ts}, ..., x_{te}[T\_ED], ..., [H\_ST], x_{hs}, ..., x_{he}[H\_ED], ..., x_l),$$

where $x_{hs}, ..., x_{he}$ and $x_{ts}, ..., x_{te}$ are the tokens of the head and tail entity terms, and they are surrounded by special tokens to indicate their starts and ends. The sentence would be encoded by the PubMedBERT PLM:

$$h_0, ..., h_l = PLM(x),$$

$$h_{PLM}^x = concat(h_{[H\_ST]}, h_{[T\_ST]}).$$

Additionally, we used CODER to provide context independent encoding for the head and tail entities:

$$h_{CODER} = concat(CODER(x_{hs}, ..., x_{he}), CODER(x_{ts}, ..., x_{te})).$$

CODER was trained by UMLS relations, which only had a tiny overlap with Wikidata relations. Therefore, by using CODER we could transfer basic knowledge from the UMLS to improve the model accuracy, with minimal risk of information leakage. The final feature for a sentence was represented as:

$$h_x = concat(h_{PLM}^x, h_{CODER}).$$

To be able to track which relation was predicted by which sentence, we used the max operation instead of attention\(^4\) to aggregate sentences in a bag. For sentences $\{x^1, ..., x^q\}$, we obtained their representations $h_{x^1}, ..., h_{x^q}$. Probability of sentence $x^j$ expressing relation $r_k$ was predicted as

$$p_{x^j, r_k} = \sigma(W_k h_{x^j} + b_{r_k}), j = 1, ..., q, \text{ and } k = 1, ..., K,$$

where $\sigma(x)$ is the logistic function. For each relation, the sentence giving the highest probability was taken for calculating the cross-entropy loss for back-propagation:
\[ m_k = \arg \max_{1 \leq j \leq q} p_{x^j, r_k} \]

\[ Loss = \sum_{k=1}^{K} \left( -y_k \log p_{x^{m_k}, r_k} - (1 - y_k) \log (1 - p_{x^{m_k}, r_k}) \right) \]

In prediction, sentences were given to the RE model individually rather than in bags. A relation \( r_k \) would be predicted for a pair of head and tail entities if the corresponding probability exceeded 0.5.

4. RESULTS

The dictionary of seed terms obtained from cleaning 8 selected source vocabularies contained 1.10 million terms. Only 450 thousand seed terms appeared in the PubMed corpus according to the automatic annotation rule, which could be covered by 440 thousand sentences, following the sampling strategy of 1 sentence per term. Applying the NER model trained with these sentences to predict new terms in the PubMed corpus yielded a total of 6.10 million unique terms. Among which, only 635 thousand (10.4%) were covered in the UMLS, reflecting the limitation of coverage of this largest expert-curated BioMedKG. After applying further term cleaning, we eventually kept 5.20 million English terms, which were further clustered into 4.14 million concepts using CODER++ embedding. Table 1 shows the composition of the concepts by semantic types. Table 2 shows the distribution of the number of terms per concept. By using FMM, the discovered term appeared 612 million times in the PubMed corpus. Those term appeared the most was “cells”, which appeared 10.2 million times. However, 35.5% of the terms appeared only once. Table 3 shows the cumulative coverage by the most frequent terms.

Table 1: Composition of concepts in BIOS by semantic type.

| Semantic type                  | Count     | Proportion |
|-------------------------------|-----------|------------|
| Chemical or Drug              | 2,193,599 | 0.507      |
| Disease or Syndrome           | 434,196   | 0.100      |
| Therapeutic or Preventive Procedure | 308,836 | 0.071      |
| Anatomy                       | 198,322   | 0.046      |
| Medical Device                | 154,911   | 0.036      |
| Sign, Symptom or Finding      | 123,477   | 0.029      |
| Microorganism                 | 119,015   | 0.028      |
| Neoplastic Process            | 120,562   | 0.028      |
| Diagnostic Procedure          | 113,385   | 0.026      |
| Laboratory Procedure          | 88,709    | 0.021      |
| Physiology                    | 88,977    | 0.021      |
| Eukaryote                     | 86,232    | 0.020      |
| Pathology                     | 86,619    | 0.020      |
| Anatomical Abnormality        | 76,633    | 0.018      |
| Mental or Behavioral Dysfunction | 68,191 | 0.016 |
| Injuries or Poisoning             | 51,226 | 0.012 |
| Research Activity or Technique    | 9,556  | 0.002 |
| Research Device                   | 1,531  | 0.000 |

Table 2: Distribution of number of terms per concept.

| Terms per concept | Proportion |
|-------------------|------------|
| 1                 | 0.8874     |
| 2-5               | 0.1028     |
| 6-10              | 0.0063     |
| 11-20             | 0.0023     |
| 21-30             | 0.0007     |
| >30               | 0.0005     |

Table 3: Term occurrence coverage by the most frequent terms.

| Number of most frequent terms | Coverage of total occurrences |
|-------------------------------|------------------------------|
| 1,000                         | 0.460                        |
| 10,000                        | 0.711                        |
| 100,000                       | 0.884                        |
| 1,000,000                     | 0.978                        |

Though BIOS (the current release) has 5.2 million English terms and the UMLS (Release 2020AB) has 9.5 million English terms, these two BioMedKGs cannot be compared just by numbers. Besides knowing that both sizes are “inflated” (BIOS contains many typos that appeared in the PubMed corpus and the UMLS contains many non-natural language terms like permutations), the two vocabularies also have drastically different term quality. Figure 2 is a case study that compares the FMM string matching results using BIOS and UMLS respectively on the same piece of PubMed abstract. It shows that matched strings using UMLS covered more than half of the text and included many words and numbers that are not biomedical terms in common sense. Some of these “terms” were spelling collisions, e.g. “but” was a term of ‘butting’, a mental/behavioral dysfunction, and “be” was a term of ‘bacterial endocarditis’; however, most were simply due to over curation. For inexperienced UMLS users, using all the terms will lead to uninformative results. However, trying to control term quality using term types and sources risks harming the recall. For example, our NER identified 635 thousand UMLS terms in the PubMed corpus, but by filtering term types and sources, our seed terms covered only 450 thousand of them. On the other hand, the strings matched by the BIOS dictionary were all nontrivial biomedical terms, including terms that were not included in the UMLS. There were also missed terms in the result of BIOS. For example, BIOS only contained “ige-mediated allergic disease”, but not its plural form.
We evaluated the accuracy of using CODER++ embedding for identifying synonymous terms, using the UMLS as a silver standard. Terms from the intersection of BIOS and the UMLS vocabularies were tested in pairs, and the labels were determined by if their concept codes were identical. Using whether the embeddings’ cosine similarity was greater than 0.8 as the classification rule, the classification achieved 0.309 for recall and 0.953 for precision. We further manually examined those predictions ruled as false positive (similarity > 0.8 but had different concept codes in the UMLS), and found that among 200 randomly sampled “false positives”, 193 were manually found synonymous (20 of them are shown in Table 4). Therefore, the corrected estimation of precision was 0.998. Using the UMLS as the silver standard may favor the metrics as CODER++ was trained using UMLS data. However, being able to correct the UMLS suggests that the model was generalizable.

Table 4: Examples of manually reviewed pairs of terms that have different concept IDs in the UMLS but have CODER++ embedding similarity above 0.8 and were classified as synonyms. Note that many of these terms have multiple UMLS concept IDs, and it is possible that the pair of terms have a common one. Evaluation of synonymy consulted examples from the UMLS. For example, because “cell” and “cell structure” are synonyms in the UMLS, so should “hepatocyte” and “hepatocyte structure”.

| Term 1, Concept ID          | Term 2, Concept ID          | Similarity | Synonym |
|-----------------------------|-----------------------------|------------|---------|
| tumor cell, C0431085        | neoplastic cell, C0597032   | 0.807      | Yes     |
| hepatocyte, C0227525        | hepatocyte structure, C0682613 | 0.868     | Yes     |
As an example of synonym grouping in BIOS, Table 5 lists all the terms of Concept CN00016530 *Congenital Melanocytic Nevus*. The concept has 14 distinct English terms, and the variations mainly come from the combinations of “melanocytic”, “pigmented”, or “nevocytic”, and “nevus”, “nevus”, or “naevus”. The plural form “congenital melanocytic nevi” was automatically labeled as preferred term because it had the highest frequency in the PubMed corpus. Another example is Concept CN00016533 *Systemic Lupus Erythematosus*, which contains 60 distinct English terms, but a lot of the variations come from the many ways to spell “erythematous” wrongly, such as “erithematosus”, “erythmatosus”, or “erythmathosus”. These typos were not removed, because we did not have an automatic way to robustly identify typos, and also because we thought keeping the typos could potentially be useful.
A total of 877 thousand relation triplets were identified from Wikidata and directly imported into BIOS. From these triplets, 240 thousand matched sentences from the PubMed corpus, which formed the DS-RE dataset. Table 6 shows the sample size (number of triplets) for each relation type. Each sample was a bag of sentences; the average number of sentences was 42, and we used at most 16 of them to fit in the GPU memory. The dataset was partitioned by 100:1:1 for training, validation, and testing, respectively. Precision, recall, and F1-score on the test set are reported in Table 6. The RE model was applied on part of the PubMed corpus to mine relation triplets, and so far, 1.10 million triplets have been predicted.

Table 6: Sample size and test set precision, recall, and F1 of relation extraction.

| Sample size | Precision | Recall | F1-score |
|-------------|-----------|--------|----------|
| All (micro-average) | 877K | 97.25 | 94.59 | 95.9 |
| is a | 170K | 98.82 | 95.57 | 97.17 |
| part of | 78K | 97.04 | 88.34 | 92.49 |
| may treat | 6K | 90.63 | 93.55 | 92.06 |
| involved in | 47K | 91.04 | 98.39 | 94.57 |
| found in taxon | 90K | 92.92 | 94.59 | 93.75 |
| active ingredient in | 2K | 75 | 60 | 66.67 |
| expressed in | 36K | 100 | 95.24 | 97.56 |
| may cause | 3K | 78.57 | 91.67 | 84.62 |
| encoded by | 5K | 66.67 | 100 | 80 |
| significant drug interaction | 2K | 75 | 93.75 | 83.33 |
| inverse is a | 170K | 98.06 | 95.88 | 96.96 |
| reverse part of | 78K | 96.1 | 90.24 | 93.82 |
| reverse may treat | 6K | 97.06 | 98.51 | 97.78 |
| reverse involved in | 47K | 96.08 | 87.5 | 91.59 |
| reverse found in taxon | 90K | 98.34 | 97.8 | 98.07 |
| reverse active ingredient in | 2K | 92.31 | 100 | 96 |
| reverse expressed in | 36K | 100 | 99.16 | 99.58 |
| reverse may cause | 3K | 100 | 70.37 | 82.61 |
| reverse encoded by | 5K | 98.21 | 98.21 | 98.21 |

Finally, besides the relations predicted by the RE model and those imported from Wikidata, another source of “is a” relations was the NER model. The NER model’s prediction included
67 possible UMLS semantic types that were simplified to 18 BIOS types. For example, the predicted semantic type for the concept *Tumor Cell* was the UMLS type *Cell*, but it was simplified to the BIOS type *Anatomy*. However, the original information was not lost and was converted to corresponding relation triplets, e.g. [*Tumor Cell, is a, Cell*]. We obtained 2.86 million “is a” relations and equally many “reverse is a” relations in this way.

BMT was used to translate English terms to Chinese. Overall, 58.5% of English terms could be reliably translated to Chinese according to the back-translation rule (including when the Chinese terms appear the same as in English), and 56.3% concepts had Chinese translations. Table 7 shows the translation rate by semantic type. Microorganisms and eukaryotes have the lowest translation rates, because the BMT had never seen those words from the training data. In total, we obtained 2.31 million distinct Chinese terms.

| Semantic type                      | Concept | Term |
|------------------------------------|---------|------|
| Anatomical Abnormality             | 0.675   | 0.698|
| Anatomy                            | 0.676   | 0.691|
| Chemical or Drug                   | 0.462   | 0.479|
| Diagnostic Procedure               | 0.716   | 0.730|
| Disease or Syndrome                | 0.798   | 0.814|
| Eukaryote                          | 0.114   | 0.114|
| Injury or Poisoning                | 0.692   | 0.734|
| Laboratory Procedure               | 0.771   | 0.780|
| Medical Device                     | 0.553   | 0.561|
| Mental or Behavioral Dysfunction   | 0.546   | 0.580|
| Microorganism                      | 0.383   | 0.396|
| Neoplastic Process                 | 0.849   | 0.861|
| Pathology                          | 0.805   | 0.820|
| Physiology                         | 0.697   | 0.708|
| Research Activity or Technique     | 0.753   | 0.772|
| Research Device                    | 0.680   | 0.676|
| Sign, Symptom, or Finding          | 0.676   | 0.695|
| Therapeutic or Preventive Procedure| 0.686   | 0.695|

5. DISCUSSION

We started the BIOS project in January, 2021, and released the first version for download in January, 2022. In a year, BIOS has grown to a size comparable to the largest expert-curated BioMedKGs in the world that have been developed for many decades, and at this rate, BIOS will soon surpass all of them. While existing BioMedKGs provided key training materials, proper measures were taken in model training to make sure that BIOS did not simply memorize
the training data. As a result, only a small fraction of BIOS overlaps with the UMLS. The data of BIOS and UMLS also have significantly different qualities. For example, the terms in BIOS are based on what people use in writing, including typos, and BIOS can have better performance than UMLS when used as dictionaries for matching biomedical terms. During the development, when we tried to use existing BioMedKGs as training or test data, we have also found that expert-curated data are less accurate than what we have expected. All of these strengthen our belief in the viability of data-driven and algorithmically generated BioMedKGs.

The development of BIOS has many unsolved problems. DS-NER and DS-RE are still immature techniques that are being actively researched by the NLP community. For DS-NER, the main difficulties come from incorrectly labeling terms as non-terms due to the incompleteness of the dictionary, and only labeling part of a long term, such as only labeling “sclerosing cholangitis” in “chronic sclerosing cholangitis” because the dictionary does not contain the long term. From our experiments, we have found that the former case does not appear as a serious problem when the training dataset is large, but the latter case strongly affects what kind of terms the model will seek. Ideally, one would want to tag the complete term. However, in practice, a term usually appears as multiple layers of nested noun phrases, and by each bigger layer, the essentiality of the term becomes lower, and it is up to subjectivity to tell where the term should end. The tagging strategy strongly affects the NER result. For example, when we expanded the tagged term to the longest possible noun phrase containing it, the trained NER model would identify 33 million terms instead of 6 million. Thus, defining the “right” boundary remains a key problem. For DS-RE, identifying incomplete entities poses an even greater problem than it does to NER, as it can affect the correctness of the relations. Additionally, for certain relations, the low proportion of sentences (like 1 out of 10) actually expressing the tagged relation can make the training data too noisy to learn the right sentence patterns.

Ambiguity in evaluation is another difficulty. For the aforementioned nested term boundary problem in NER, instead of being either right or wrong, the boundaries can also be confidently right or less confidently right, which affects all the conventional metrics, such as recall and precision. Ambiguity also affects synonym classification. For example, “cortex” and “cerebral cortex” are strictly speaking different, but in actual use, “cortex” refers to “cerebral cortex” most of the times, and they are also labeled as synonymous in the UMLS (Concept C0007776). For another example, “coronary artery disease”, “coronary heart disease” and “ischemic heart disease” are considered the same by many, but they are distinct concepts in the UMLS (Concepts C1956346, C0010068, and C0151744). This ambiguity makes a universal classification criterion and objective evaluation almost impossible.

While we have confidence in our approach of generating BioMedKGs algorithmically, we are not against human intervention. In fact, we are aware that there are many problems in BIOS
that can be hard to solve by models and algorithms alone in the near future, and we will develop a platform to actively interact with users and ask for their contribution. For example, we may detect a pair of terms that have very high similarity according to CODER++ embedding, say 0.75, and we may ask the users to judge if they are synonymous. In addition, we will also actively explore other sources for knowledge extraction. For example, the EHR will be a good source for identifying nonstandard terms used by the doctors in real clinical settings. Extracting certain relations, such as disease-and-drugs and disease-and-laboratory tests, can also be easier and more accurate from the EHR.

6. SUMMARY

In this paper, we introduced the methodology for building BIOS, including term discovery, computationally forming concepts, semantic type classification, relation extraction, and machine translation. We also conducted preliminary assessment for the content of BIOS. As a BioMedKG built by machine learning from the ground up, BIOS lights the path to future knowledge graph development: not only does it easily reach a gigantic size with very acceptable quality, but also it exhibits significant difference from expert-curated BioMedKGs, such as in term coverage. With machine learning techniques continuing to advance and more and more people contributing to the project, we are certain that BIOS will be increasingly accurate and will eventually be larger and more up-to-date than all expert-curated BioMedKGs.

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