An Annotated Corpus for Machine Reading of Instructions in Wet Lab Protocols

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Abstract

We describe an effort to annotate a corpus of natural language instructions consisting of 622 wet lab protocols to facilitate automatic or semi-automatic conversion of protocols into a machine-readable format and benefit biological research. Experimental results demonstrate the utility of our corpus for developing machine learning approaches to shallow semantic parsing of instructional texts. We make our annotated Wet Lab Protocol Corpus available to the research community.1

1 Introduction

As the complexity of biological experiments increases, there is a growing need to automate wet laboratory procedures to avoid mistakes due to human error and also to enhance the reproducibility of experimental biological research (King et al., 2009). Several efforts are currently underway to define machine-readable formats for writing wet lab protocols (Ananthanarayanan and Thies, 2010; Soldatova et al., 2014; Vasilev et al., 2011). The vast majority of today’s protocols, however, are written in natural language with jargon and colloquial language constructs that emerge as a byproduct of ad-hoc protocol documentation. This motivates the need for machine reading systems that can interpret the meaning of these natural language instructions, to enhance reproducibility via semantic protocols (e.g. the Aquarium project) and enable robotic automation (Bates et al., 2016) by mapping natural language instructions to executable actions.

In this study we take a first step towards this goal by annotating a database of wet lab protocols with semantic actions and their arguments; and conducting initial experiments to demonstrate its utility for machine learning approaches to shallow semantic parsing of natural language instructions.

Figure 1: An example wet lab protocol. The first seven steps are imperative sentences, and the last sentence describes the end results and their subsequent utilization.

Isolation of temperate phages by plaque agar overlay
1. Melt soft agar overlay tubes in boiling water and place in the 47°C water bath.
2. Remove one tube of soft agar from the water bath.
3. Add 1.0 mL host culture and either 1.0 or 0.1 mL viral concentrate.
4. Mix the contents of the tube well by rolling back and forth between two hands, and immediately empty the tube contents onto an agar plate.
5. Sit RT for 5 min.
6. Gently spread the top agar over the agar surface by sliding the plate on the bench surface using a circular motion.
7. Harden the top agar by not disturbing the plates for 30 min.
8. Incubate the plates (top agar side down) overnight to 48 h.
9. Temperate phage plaques will appear as turbid or cloudy plaques, whereas purely lytic phage will appear as sharply defined, clear plaques.

To the best of our knowledge, this is the first annotated corpus of natural language instructions in the biomedical domain that is large enough to enable machine learning approaches.

There have been many recent data collection and annotation efforts that have initiated natural language processing research in new directions, for example political framing (Card et al., 2015), question answering (Rajpurkar et al., 2016) and cooking recipes (Jermurawong and Habash, 2015). Although mapping natural language instructions to machine readable representations is an important direction with many practical applications, we believe current research in this area is hampered by the lack of available annotated corpora. Our annotated corpus of wet lab protocols could enable further research on interpreting natural language instructions, with practical applications in biology and life sciences.

Prior work has explored the problem of learning to map natural language instructions to actions, often learning through indirect supervision
to address the lack of labeled data in instructional domains. This is done, for example, by interacting with the environment (Branavan et al., 2009, 2010) or observing weakly aligned sequences of instructions and corresponding actions (Chen and Mooney, 2011; Artzi and Zettlemoyer, 2013). In contrast, we present the first steps towards a pragmatic approach based on linguistic annotation (Figure 3). We describe our effort to exhaustively annotate wet lab protocols with actions corresponding to lab procedures and their attributes including materials, instruments and devices used to perform specific actions. As we demonstrate in §6, our corpus can be used to train machine learning models which are capable of automatically annotating lab-protocols with action predicates and their arguments (Gildea and Jurafsky, 2002; Das et al., 2014); this could provide a useful linguistic representation for robotic automation (Bollini et al., 2013) and other downstream applications.

3 Annotation Scheme

In developing our annotation guidelines we had three primary goals: (1) We aim to produce a semantic representation that is well motivated from a biomedical and linguistic perspective; (2) The guidelines should be easily understood by annotators with or without biology background, as evaluated in Table 3; (3) The resulting corpus should be useful for training machine learning models to automatically extract experimental actions for downstream applications, as evaluated in §6.

We utilized the EXACT2 framework (Soldatova et al., 2014) as a basis for our annotation scheme. We borrowed and renamed 9 object-based entities from EXACT2, in addition, we created 5 measure-based (NUMERICAL, GENERIC-MEASURE, SIZE, PH, MEASURE-TYPE) and 3 other (MENTION, MODIFIER, SEAL) entity types. EXACT2 connects the entities directly to the action without describing the type of relations, whereas we de-
### Table 1: Statistics of our Wet Lab Protocol Corpus by protocol category.

| Protocol Category       | Count | avg #Sentences | avg #Words | avg #Entities | avg #Relations | avg #Actions |
|-------------------------|-------|----------------|-----------|--------------|---------------|-------------|
| molecular biology       | 186   | 27.42          | 338.06    | 85.25        | 84.20         | 35.77       |
| microbiology            | 105   | 22.07          | 328.94    | 74.46        | 71.71         | 27.89       |
| cell biology            | 94    | 19.23          | 236.74    | 61.09        | 60.95         | 23.93       |
| Plant biology           | 48    | 17.17          | 219.96    | 44.67        | 43.85         | 20.44       |
| Immunology              | 79    | 25.92          | 339.58    | 83.17        | 78.24         | 32.68       |
| chemical biology        | 110   | 14.37          | 188.30    | 46.40        | 47.45         | 19.01       |

### Table 2: Statistics of the Wet Lab Protocol Corpus.

|                         | Total | per Protocol | per Sentence |
|-------------------------|-------|--------------|--------------|
| # of sentences          | 13679 | 21.99        | –            |
| # of words              | 177770| 285.80       | 12.99        |
| # of entities           | 43236 | 69.51        | 3.16         |
| # of relations          | 42425 | 68.21        | 3.10         |
| # of actions            | 17485 | 28.11        | 1.28         |

### Table 3: Inter-annotator agreement (Krippendorff’s $\alpha$) between annotators with biology, linguistics and other backgrounds.

| Annotators               | Entities+Actions | Relations   |
|--------------------------|------------------|-------------|
| Biologist-Linguist       | 0.7600           | 0.6084      |
| Biologist-Other          | 0.7621           | 0.6619      |
| Linguist-Other           | 0.7574           | 0.6753      |
| all 4 coders             | 0.7599           | 0.6625      |

### 4 Annotation Process

Our final corpus consists of 622 protocols annotated by a team of 10 annotators. Corpus statistics are provided in Table 1 and 2. In the first phase of annotation, we worked with a subset of 4 annotators including one linguist and one biologist to develop the annotation guideline for 6 iterations. For each iteration, we asked all 4 annotators to annotate the same 10 protocols and measured their inter-annotator agreement, which in turn helped in determining the validity of the refined guidelines. The average time to annotate a single protocol of 40 sentences was approximately 33 minutes, across all annotators.

#### 4.1 Inter-Annotator Agreement

We used Krippendorff’s $\alpha$ for nominal data (Krippendorff, 2004) to measure the inter-rater agreement for entities, actions and relations. For entities, we measured agreement at the word-level by tagging each word in a span with the span’s label. To evaluate inter-rater agreement for relations between annotated spans, we consider every pair of spans within a step and then test for matches between annotators (partial entity matches are allowed). We then compute Krippendorff’s $\alpha$ over relations between matching pairs of spans. Interrater agreement for entities, actions and relations is presented in Figure 3.

### 5 Methods

To demonstrate the utility of our annotated corpus, we explore two machine learning approaches for extracting actions and entities: a maximum entropy model and a neural network tagging model. We also present experiments for relation classification. We use the standard precision, recall and $F_1$ metrics to evaluate and compare the performance.
5.1 Maximum Entropy (MaxEnt) Tagger

In the maximum entropy model for action and entity extraction (Borthwick and Grishman, 1999), we used three types of features based on the current word and context words within a window of size 2:

- **Parts of speech features** which were generated by the GENIA POS Tagger (Tsuruoka and Tsujii, 2005), which is specifically tuned for biomedical texts;
- **Lexical features** which include unigrams, bigrams as well as their lemmas and synonyms from WordNet (Miller, 1995) are used;
- **Dependency parse features** which include dependent and governor words as well as the dependency type to capture syntactic information related to actions, entities and their contexts. We used the Stanford dependency parser (Chen and Manning, 2014).

5.2 Neural Sequence Tagger

We utilized the state-of-the-art Bidirectional LSTM with a Conditional Random Fields (CRF) layer (Ma and Hovy, 2016; Lample et al., 2016; Plank et al., 2016), initialized with 200-dimentional word vectors pretrained on 5.5 billion words from PubMed and PMC biomedical texts (Moen and Ananiadou, 2013). Words unseen in the pretrained vocabulary were randomly initialized using a uniform distribution in the range (-0.01, 0.01). We used Adadelta (Zeiler, 2012) optimization with a mini-batch of 16 sentences and trained each network with 5 different random seeds, in order to avoid any outlier results due to randomness in the model initialization.

5.3 Relation Classification

To demonstrate the utility of the relation annotations, we also experimented with a maximum entropy model for relation classification using features shown to be effective in prior work (Li and Ji, 2014; GuoDong et al., 2005; Kambhatla, 2004). The features are divided into five groups:

- **Word features** which include the words contained in both arguments, all words in between, and context words surrounding the arguments;
- **Entity type features** which include action and entity types associated with both arguments;
- **Overlapping features** which are the number of words, as well as actions or entities, in between the candidate entity pair;
- **Chunk features** which are the chunk tags of both arguments predicted by the GENIA tagger;
- **Dependency features** which are context words related to the arguments in the dependency tree according to the Stanford Dependency Parser.

Also included are features indicating whether the two spans are in the same noun phrase, prepositional phrase, or verb phrase.

6 Results

The full annotated dataset of 622 protocols are randomly split into training, dev and test sets using a 6:2:2 ratio. The training set contains 374 protocols of 8207 sentences, development set contains
### 6.1 Entity Identification and Classification

Table 4 shows the performance of various methods for entity tagging. We found that the BiLSTM-CRF model consistently outperforms other methods, achieving an overall F1 score of 86.89 at identifying action triggers and 72.61 at identifying and classifying entities.

Table 6 shows the system performance of the MaxEnt tagger using various features. Dependency based features have the highest impact on the detection of entities, as illustrated by the absolute drop of 7.84% in F-score when removed. Parts of speech features alone are the most effective in capturing action words. This is largely due to action words appearing as verbs or nouns in the majority of the sentences as shown in Table 7. We also notice that the GENIA POS tagger, which is trained on Wall Street Journal and biomedical abstracts in the GENIA and PennBioIE corpora, under-identifies verbs in wet lab protocols. We suspect this is due to fewer imperative sentences in the training data. We leave further investigation for future work, and hope the release of our dataset can help draw more attention to NLP research on instructional languages.

### 7 Conclusions

In this paper, we described our effort to annotate wet lab protocols with actions and their semantic arguments. We presented an annotation scheme that is both biologically and linguistically motivated and demonstrated that non-experts can effectively annotate lab protocols. Additionally, we empirically demonstrated the utility of our corpus for developing machine learning approaches to shallow semantic parsing of instructions. Our annotated corpus of protocols is available for use by the research community.

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A Annotation Guidelines

The wet lab protocol dataset annotation guidelines were designed primarily to provide a simple description of the various actions and their arguments in protocols so that it could be more accessible and be effectively used by non-biologists who may want to use this dataset for various natural language processing tasks such as action trigger detection or relation extraction. In the following sub-sections we summarize the guidelines that were used in annotating the 622 protocols as we explore the actions, entities and relations that were chosen to be labelled in this dataset.

A.1 Actions

Under a broad categorization, Action is a process of doing something, typically to achieve an aim. In the context of wet lab protocols, action mentions in a sentence or a step are deliberate but short descriptions of a task tying together various entities in a meaningful way. Some examples of action words, (categorized using GENIA POS tagger), are present in Table 7 along with their frequencies.

A.2 Entities

We broadly classify entities commonly seen in protocols under 17 tags. Each of the entity tags were designed to encourage short span length, with the average number of words per entity tag being 1.6. For example, Concentration tags are often very short: 60% 10x, 10M, 1 g/ml, while the Method tag has the longest average span of 2.232 words with examples such as rolling back and forth between two hands (as seen in Figure 4). The methods in wet lab protocols tend to be descriptive, which pose distinct challenges from existing named entity extraction research in the medical and other domains.

A.2.1 Object Based Entities

Reagent: A substance or mixture for use in any kind of reaction in preparing a product because of its chemical or biological activity.

Location: Containers for reagents or other physical entities. They lack any operation capabilities other than acting as a container. These could be laboratory glassware or plastic tubing meant to hold chemicals or biological substances.

Device: A machine capable of acting as a container as well as performing a specific task on the objects that it holds. A device and a location are similar in all aspects except that a device performs a specific set of operations on its contents, usually illustrated in the sentence itself, or sometimes implied.

Seal: Any kind of lid or enclosure for the location or device. It could be a cap, or a membrane that actively participates in the protocol action, and hence is essential to capture this type of entity.

A.2.2 Measure Based Entities

Amount: The amount of any reagent being used in a given step, in terms of weight or volume.

Concentration: Measure of the relative proportions of two or more quantities in a mixture. Usually in terms of their percentages by weight or volume.

Time: Duration of a specific action described in a single step or steps, typically in secs, min, days, or weeks.

Temperature: Any temperature mentioned in degree Celsius, Fahrenheit, or Kelvin.

Method: A word or phrase used to concisely define the procedure to be performed in association with the chosen action verb. Its usually a noun, but could also be a passive verb.

Speed: Typically a measure that represents rotation per min for centrifuges.

Numerical: A generic tag for a number that numerically participates in the protocol action, and hence usually in terms of their percentages by weight or volume.

Figure 4: Examples, Frequency and Avg-Word for actions and entities.
| Label          | Syntax/Rules                                                                 | Example                                                                                                                                 |
|----------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Acts-on        | Action ⇒ Reagent | Location | Mention | Device | Seal                                           | ![Acts-on Diagram](image) |
| Creates        | Action ⇒ Reagent | Mention                                           | ![Creates Diagram](image) |
| Site           | Action ⇒ Location | Device | Mention | Reagent                                      | ![Site Diagram](image) |
| Using          | Action ⇒ Method | Action | Seal | Device | Mention | Reagent | Location | ![Using Diagram](image) |
| Setting        | Action | Device | Modifier ⇒ Method | Action | Seal | Device | Mention | Reagent | Location | ![Setting Diagram](image) |
| Count          | Action ⇒ Numerical                                                        | ![Count Diagram](image) |
| Measure-Type-Link | Action ⇒ Measure-Type                                                    | ![Measure-Type-Link Diagram](image) |
| Coreference    | Mention ⇒ [Every other entity]                                             | ![Coreference Diagram](image) |
| Mod-Link       | [Every Entity or Action] ⇒ Modifier                                        | ![Mod-Link Diagram](image) |
| Measure        | Reagent | Location | Device | Mention | Seal ⇒ Amount | Numerical | Size | Concentration | Generic-Measure | pH | ![Measure Diagram](image) |
| Meronym        | Reagent | Location | Device | Mention | Seal ⇒ Reagent | Location | Device | Mention | Seal | ![Meronym Diagram](image) |
| Or             | [All Entities or Action] ⇒ [All Entities or Action]                        | ![Or Diagram](image) |
| Of-Type        | Generic-Measure | Numerical ⇒ Measure-Type | ![Of-Type Diagram](image) |

Table 8: Relations along with their rules and examples
doesn’t fit time, temp, etc and which isn’t accompanied by its unit of measure.

**Generic-Measure:** Any measures that don’t fit the list of defined measures in this list.

**Size** A measure of the dimension of an object. For example: length, area or thickness.

**Measure-Type** A generic tag to mark the type of measurement associated with a number.

**pH:** measure of acidity or alkalinity of a solution.

### A.2.3 Parts of Speech based Entities

**Modifier** A word or a phrase that acts as an additional description of the entity it is modifying. For example, *quickly mix vs slowly mix* are clearly two different actions, informed by their modifiers “quickly” or “slowly” respectively.

**Mention** Words that can refer to an object mentioned earlier in the sentence.

### A.3 Relations

#### A.3.1 Action Relations (Action - Entity)

**Acts-On** Links the reagent, or location that the action acts on, typically linking the direct objects in the sentence to the action.

**Creates** This relation marks the physical entity that the action creates.

**Site** A link that associates a Location or Device to an action. It indicates that the Device or Location is the site where the action is performed. It is also used as a way to indicate which entity will finally hold/contain the result of the action.

**Using** Any entity that the action verb makes use of is linked with this relation.

**Setting** Any measure type entity that is being used to set a device is linked to the action that is attempting to use that numerical.

**Count** A Numerical entity that represents the number of times the action should take place.

**Measure Type Link** Associates an action to a Measure Type entity that the Action is instructing to measure.

#### A.3.2 Binary Relations (Entity - Entity)

**Coreference** A link that associates two phrases when those two phrases refer to the same entity.

**Mod Link** A Modifier entity is linked to any entity that it is attempting to modify using this relation.

**Settings** Links devices to their settings directly, only if there is no Action associated with those settings.

**Measure** A link that associates the various numerical measures to the entity its trying to measure directly.

**Meronym** Links reagents, locations or devices with materials contained in the reagent, location or device.

**Or** Allows chaining multiple entities where either of them can be used for a given link.

**Of-Type** used to specify the Measure-Type of a Generic-Measure or a Numerical, if the sentence contains this information.