Towards Answering Biological Questions with Experimental Evidence: Automatically Identifying Text that Summarize Image Content in Full-Text Articles

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Abstract *Images (i.e., figures) are important experimental evidence that are typically reported in bioscience full-text articles. Biologists need to access images to validate research facts and to formulate or to test novel research hypotheses. We propose to build a biological question answering system that provides experimental evidences as answers in response to biological questions. As a first step, we develop natural language processing techniques to identify sentences that summarize image content.*

1. Introduction

Images (i.e., figures) are important experimental evidence that are typically reported in bioscience full-text articles. Biologists need to access images to validate research facts, and to formulate or to test novel research hypotheses. On the other hand, biologists live in an age of information explosion. As thousands of biomedical articles are published every day, systems that help biologists access efficiently images in literature would greatly facilitate biomedical research. Information retrieval systems (e.g., PubMed) typically return a list of documents in response to a user's query. However, hundreds, thousands or even a larger number of documents can be retrieved; few biologists have time to read all of the retrieved documents. Additionally, many of the retrieved documents might not contain specific information that biologists need. For example, a biologist may specifically want to know the evidence of "X interacting with Y", and he/she might have to navigate a large number of articles to identify the piece of information he/she needs. We are developing question answering techniques to automatically analyze thousands of documents and to extract answers in response to questions[1-3]. In the biology domain, we believe the first step to build a useful question answering system is to identify the text that summarize images that appear in full-text articles.

The motivations of this study come after our manual examination of more than one hundred questions posed by twelve experimental biologists. We found that many biological questions require experimental evidences as answers. In the following we listed five biological questions that require experimental evidences as answers:

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1) Show me the evidences that the phosphatase
   domain and the C2 domain are responsible for
   membrane recruitment of PTEN.
2) Does bysl coexpress with myc?
3) Does ascorbic acid inhibit nitrosamines?
4) Give me all structures of E cahderin.
5) Show me ompa expression.
```

It is well-known that significant amount of experimental evidences are presented in the full-text body as images, including figures or tables, embedded within associated text. Because images are important experimental evidences, a question answering system may provide images as answers in response to biological questions.

However, images alone are frequently meaningless without their associated text (e.g. captions and other associated text). On the other hand, text alone without the images would deprive of the actual supporting experimental evidences.

To answer biological questions that require images as the answers, we propose to provide a short text that summarizes the content of the target images. Biologists can then access the actual images through the text. For example, to answer the question (1), we will provide the textual statement "Subcellular localization studies of PTEN transfected into HEK293T and HeLa cells indicated that targeting of PTEN to the plasma membrane is coupled with rapid degradation and that the phosphatase domain and the C2 domain are both necessary and sufficient for its membrane recruitment." The corresponding image (i.e., image "C" in Figure 1) can be accessed directly from the preceding sentence with a hyperlink. To build such a question answering system, it is essential to develop natural language processing systems that automatically identify text that summarize images. We report natural language processing techniques to achieve such a mapping.

2. Text that Summarize Image Content

We randomly selected a total of ten *Proceedings of the National Academy of Sciences* (PNAS) full-text articles; we manually examined the associated text (e.g., abstract sentences, and image captions and other associated text that appear in the full-text body). As an example, the following shows the associated text of "Table 1" in Figure 1.

Abstract sentences: `Our` *`in vitro`* `surface plasmon resonance measurements using immobilized vesicles showed that both the phosphatase domain and the C2 domain, but not the C-terminal tail, are involved in electrostatic membrane binding of PTEN. Furthermore, the phosphorylation-mimicking mutation on the C-terminal tail of PTEN caused an 80-fold reduction in its membrane affinity, mainly by slowing the membrane-association step.`

Image caption: Binding parameters for PTEN constructs determined from SPR analysis.

Other associated text:

- The sample cell contains the sensor surface coated with the vesicles indicated in Table 1.
- Further measurements using mixed vesicles of POPC/POPS (8:2), which roughly approximate the lipid composition of the inner plasma membrane of mammalian cells to which PTEN is targeted, showed that both the full-length PTEN and the C2 domain had higher affinity (in terms of K_d) for these anionic vesicles (see Table 1).
- The affinity for anionic vesicles was mainly attributed to nonspecific electrostatic interactions, because they did not distinguish POPC/POPS (8:2) from POPC/1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoglycerol (POPG) (8:2) vesicles (Table 1) and the affinity was reduced greatly by 0.5 M KCl [K_d = (2.2 ± 0.4) x 10^{-7} M; k_a = (9.5 ± 1.2) x 10^3 $M^{-1}\cdot s^{-1}$; k_d = (2.1 ± 0.3) x $10^{-3}\cdot s^{-1}$].
- As shown in Table 1, Δ^{1-185} and $\Delta^{353-403}$ had 31- and 1.5-fold lower affinity for POPC/POPS (8:2) vesicles than WT, respectively. This suggests that the phosphatase domain is important for the membrane binding of PTEN, whereas the C-terminal tail plays practically no role in membrane binding.
- As shown in Table 1, PTEN had 2-fold higher affinity for the plasma membrane mimic than for POPC/POPS (8:2) vesicles, presumably because the former has a higher anionic lipid content.

As shown in the example above, the abstract sentences are the best to summarize image content. Other associated text typically describe only experimental procedures and do not include indications and conclusions of an experiment. Additionally, image content are typically scattered across other associated text, and therefore, it is difficult to identify a succinct summary from the other associated text.

3. An Annotated Corpus in Which Abstract Sentences Link to Images that Appear in the Full-Text Documents

We hypothesize that images reported in a full-text article can be summarized by sentences in the abstract. To test this hypothesis, we randomly selected a total of 329 biological articles that are recently published in leading biological journals *Cell* (104), *EMBO* (72), *Journal of Biological Chemistry* (92), and *Proceedings of the National Academy of Sciences (PNAS)* (61). For each article, we emailed the corresponding author to ask him or her to identify abstract sentences that summarize the image content in that article.

A total of 119 biologists from 19 countries participated voluntarily the annotation to identify abstract sentences that summarize figures or tables in their 114 articles (39 *Cells*, 29 *EMBO*, 30 *Journal of Biological Chemistry*, and 16 *PNAS*), a collection that is 34.7% of the total articles we requested. The responding biologists included the corresponding authors to whom we had sent emails, as well as the first authors of the articles to whom the corresponding authors had forwarded our emails. None of the biologists were compensated.

This collection of 114 full-text articles incorporates 742 images and 826 abstract sentences. The average number of images per document is 6.5±1.5 and the average number of sentences per abstract is 7.2±1.9. Our data show that 87.9% images correspond to abstract sentences and 66.5% abstract sentences correspond to images; those statistics have empirically validated our hypothesis that image content can be summarized by abstract sentences. This collection of 114 annotated articles was then used as the corpus to evaluate our natural language processing approaches that automatically identify abstract sentences that summarize image content in the full-text articles.

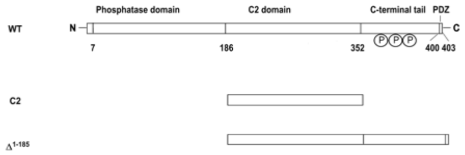
4. NLP Approaches that Link Abstract Sentences to Images

Linking abstract sentences to images is a task of linking the abstract sentences to other associated text of the images. Our study is built upon two assumptions. The first is that image content consistently corresponds to its associated text. The second is that there are strong lexical similarities between the text associated with each image and the corresponding sentence(s) in the abstract. We empirically evaluated both assumptions.

We deployed hierarchical clustering techniques[4] to cluster abstract sentences and images based on the lexical similarities. The details of the study are reported elsewhere[5]. In the following sections, we describe a few systems we explored including the clustering algorithms and feature selections.

4.1. Clustering Algorithms

Hierarchical clustering algorithms are widely used in many other areas including biological sequence alignment[6], gene expression analysis[7], and topic detection[8]. The algorithm starts with the set of text that includes abstract sentences or image captions. Each sentence or image caption represents a document that needs to be clustered. The algorithm identifies pair-wise document similarities based on the TF*IDF weighted cosine similarity. It then merges the two documents with the highest similarity into one cluster. It then re-evaluates pairs of documents/clusters; two clusters can be merged if the average similarity across all pairs of documents within the two clusters exceeds a predefined threshold. When multiple clusters can be merged at any time, the pair of clusters with the highest similarity is always preferred.



(A) “Schematic representation of structures of PTEN and its mutants. PTEN has a N-terminal phosphatase domain, a C2 domain, and a C-terminal tail that contains multiple phosphorylation sites and a PDZ domain-binding sequence. Numbering is based on the X-ray structure of PTEN.”

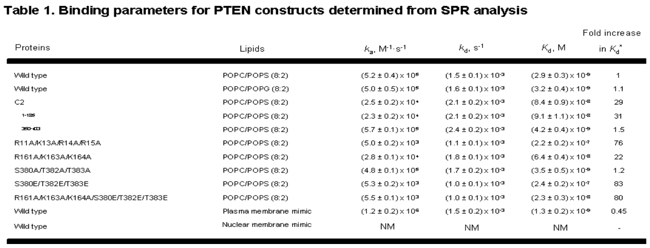


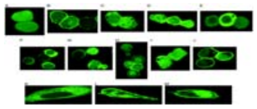
Table 1. Binding parameters for PTEN constructs determined from SPR analysis

Proteins	Lipids	k_a, $M^{-1} \cdot s^{-1}$	k_d, s^{-1}	K_d, M	Fold increase in K_d*
Wild type	POPC/POPS (8:2)	$(5.2 \pm 0.4) \times 10^5$	$(1.5 \pm 0.1) \times 10^{-3}$	$(2.9 \pm 0.3) \times 10^{-9}$	1
Wild type	POPC/POPG (8:2)	$(5.0 \pm 0.5) \times 10^5$	$(1.6 \pm 0.1) \times 10^{-3}$	$(3.2 \pm 0.4) \times 10^{-9}$	1.1
C2	POPC/POPS (8:2)	$(2.5 \pm 0.2) \times 10^4$	$(2.1 \pm 0.2) \times 10^{-3}$	$(8.4 \pm 0.9) \times 10^{-8}$	29
1-185	POPC/POPS (8:2)	$(2.3 \pm 0.2) \times 10^4$	$(2.1 \pm 0.2) \times 10^{-3}$	$(9.1 \pm 1.1) \times 10^{-8}$	31
350-403	POPC/POPS (8:2)	$(5.7 \pm 0.1) \times 10^5$	$(2.4 \pm 0.2) \times 10^{-3}$	$(4.2 \pm 0.4) \times 10^{-9}$	1.5
R11A/K13A/R14A/R15A	POPC/POPS (8:2)	$(5.0 \pm 0.2) \times 10^3$	$(1.1 \pm 0.1) \times 10^{-3}$	$(2.2 \pm 0.2) \times 10^{-7}$	76
R161A/K163A/K164A	POPC/POPS (8:2)	$(2.8 \pm 0.1) \times 10^4$	$(1.8 \pm 0.1) \times 10^{-3}$	$(6.4 \pm 0.4) \times 10^{-8}$	22
S380A/T382A/T383A	POPC/POPS (8:2)	$(4.8 \pm 0.1) \times 10^5$	$(1.7 \pm 0.2) \times 10^{-3}$	$(3.5 \pm 0.5) \times 10^{-9}$	1.2
S380E/T382E/T383E	POPC/POPS (8:2)	$(5.3 \pm 0.2) \times 10^3$	$(1.0 \pm 0.1) \times 10^{-3}$	$(2.4 \pm 0.2) \times 10^{-7}$	83
R161A/K163A/K164A/S380E/T382E/T383E	POPC/POPS (8:2)	$(5.5 \pm 0.1) \times 10^3$	$(1.0 \pm 0.1) \times 10^{-3}$	$(2.3 \pm 0.3) \times 10^{-8}$	80
Wild type	Plasma membrane mimic	$(1.2 \pm 0.2) \times 10^6$	$(1.5 \pm 0.2) \times 10^{-3}$	$(1.3 \pm 0.2) \times 10^{-9}$	0.45
Wild type	Nuclear membrane mimic	NM	NM	NM	-

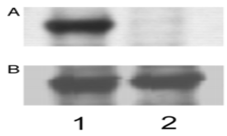
(B) **“**Binding parameters for PTEN constructs determined from SPR analysis**”**

Das S, Dixon JE, Cho W. 2003. Membrane-binding and activation mechanism of PTEN. *Proc Natl Acad Sci 100(13): 7491-6.*

PTEN is a tumor suppressor that reverses the action of phosphoinositide 3-kinase by catalyzing the removal of the 3' phosphate of phosphoinositides. Despite the critical role of PTEN in cell signaling and regulation, the mechanisms of its membrane recruitment and activation is still poorly understood. **PTEN is composed of an N-terminal phosphatase domain, a C2 domain, and a C-terminal tail region that contains the PSD-95/Dlg/ZO-1 homology (PDZ) domain-binding sequence and multiple phosphorylation sites. Our *in vitro* surface plasmon resonance measurements using immobilized vesicles showed that both the phosphatase domain and the C2 domain, but not the C-terminal tail, are involved in electrostatic membrane binding of PTEN. Furthermore, the phosphorylation-mimicking mutation on the C-terminal tail of PTEN caused an 80-fold reduction in its membrane affinity, mainly by slowing the membrane-association step. Subcellular localization studies of PTEN transfected into HEK293T and HeLa cells indicated that targeting of PTEN to the plasma membrane is coupled with rapid degradation and that the phosphatase domain and the C2 domain are both necessary and sufficient for its membrane recruitment. Results also indicated that the phosphorylation regulates the targeting of PTEN to the plasma membrane not by blocking the PDZ domain-binding site but by interfering with electrostatic membrane binding of PTEN**. On the basis of these results, we propose a membrane-binding and activation mechanism for PTEN, in which the phosphorylation/dephosphorylation of the C-terminal region serves as an electrostatic switch that controls the membrane translocation of the protein.



(C) “Subcellular localization of PTEN and its mutants in HEK293T and HeLa cells. PTEN and its mutants tagged with EGFP at their C termini were transiently transfected into HEK293T (*A*–*G*) and HeLa (*H*–*J*) cells, and their subcellular localization was monitored by confocal microscopy. (*A*) C2 domain. (*B*) $\Delta^{353–403}$/C124A. (*C*) $\Delta^{1–185}$. (*D*) $\Delta^{353–403}$/C124A/R161A/K163A/R164A. (*E*) Phosphatase domain (C124A). (*F*) C124A–PTEN. (*G*) C124A/S380E/T382E/T383E. (*H*) C124A/S380A/T382A/T382A. (*I*) C124A/$\Delta^{400–403}$. (*J*) C124A/S380A/T382A/T383A/$\Delta^{400–403}$. (*K*) C124A (HeLa). (*L*) C124A/S380A/T382A/T382A (HeLa). (*M*) $\Delta^{400–403}$/C124A/S380A/T382A/T383A (HeLa).”



(D) “Phosphorylation of PTEN and mutants in HEK293T cells. (*A*) Immunostaining of PTEN-transfected cell extracts with the S380/T382/T383-phospho-specific antibody. Lane 1, cells transfected with PTEN–EGFP; lane 2, cells transfected with S380A/T382A/T383A–EGFP. (*B*) Immunostaining of the same cell extracts with the anti-PTEN antibody shows that total PTEN amounts are comparable for the two lanes.”

Figure 1: An example of a full-text biological article (pmid=12808147) in which the abstract sentences summarize the corresponding images (Arrows indicate the correspondences).

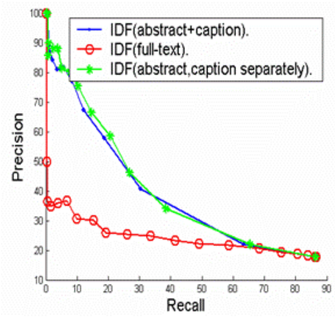


Figure 2

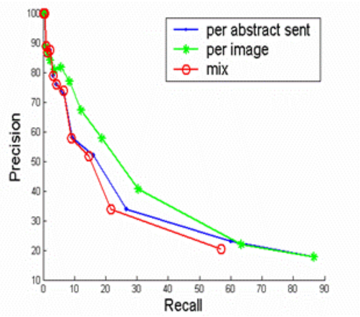


Figure 3

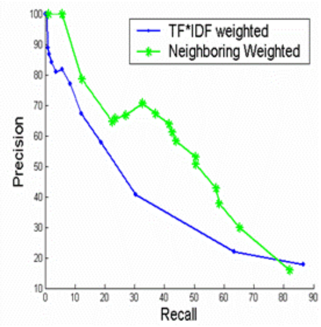


Figure 4

4.2. Features, Weights, Clustering Strategies

We explored bag-of-words as the learning features. We explored three different methods to obtain the IDF value for each word feature: 1) ***IDF(abstract+caption):*** the IDF values were calculated from the pool of abstract sentences and image captions; 2) ***IDF(full-text):*** the IDF values were calculated from all sentences in the full-text article; and 3) ***IDF(abstract)::IDF(caption):*** we obtained two sets of IDF values. For word features that appear in abstracts, the IDF values were calculated from the abstract sentences; for words that appear in image captions, the IDF values were calculated from the image captions.

We also explored the position features. The positions of abstract sentences that correspond to images seem to have a "neighboring effect". The chance that two abstract sentences link to an image decreases when the distance between two abstract sentences increases.

To integrate "neighboring effect" into our existing hierarchical clustering algorithms, we modified the TF*IDF weighted cosine similarity with neighboring weights. Assuming that we consider an abstract sentence or an image caption as a document, the TF*IDF weighted cosine similarity for a pair of document *i* and *j* is *Sim(i,j)*, we integrated the "neighboring effect" and the final similarity *W(i,j)* is:

$$W(i,j)=Sim(i,j)*(1-abs(P_i/T_i-P_j/T_j))$$

1) If *i* and *j* are both abstract sentences, T_i=T_j=*total number of abstract sentences;* and P_i and P_j represents the positions of sentences *i* and *j* in the abstract.

2) If *i* and *j* are both image captions, T_i=T_j=*total number of images that appear in a full-text article;* and P_i and P_j represents the positions of images *i* and *j* in the full-text article.

3) If *i* and *j* are an abstract sentence and an image caption, respectively, T_i=*total number of abstract sentences* and T_j=*total number of images that appear in a full-text article;* and P_i and P_j represent the positions of abstract sentence *i* and image *j*.

Finally, we have explored three clustering strategies; namely, *per-image*, *per-abstract sentence*, and *mix.*

Per-image clusters each image caption with all abstract sentences. The image is assigned to (an) abstract sentence(s) if they belong to the same cluster. This method values features in abstract sentences more than image captions because the decision that an image belongs to (a) sentence(s) depends upon the features from all abstract sentences and the examined image caption. The features from other image captions will not play a role for the clustering.

Per-abstract-sentence takes each abstract sentence and clusters it with all image captions that appear in a full-text article. Images are assigned to the sentence if they belong to the same cluster. This method values features in image captions higher than the features in abstract sentences because the decision that an abstract sentence belongs to image(s) depends upon the features from the image captions and the examined abstract sentence. The features from other abstract sentences will not play a role for the clustering.

Mix clusters all image captions with all abstract sentences. This method treats features in abstract sentences and image captions equally.

5. Results and Discussion

Figure 2 shows that the "local" IDFs, or the IDFs calculated from the abstract sentences and image captions yield much better performance than the "global" IDFs, or the IDFs that are calculated from the full-text article. The results are not surprising because "local" IDFs reflect more on the characteristics of the full-text article in study than the "global" IDFs. Figure 3 show that *Per-image* out-performs the other two strategies. The results suggest that features in abstract sentences are more useful than features in caption for the task of clustering. Figure 4 shows that "neighboring weighted" approach has a significant enhancement over the TF*IDF weighted approach. The recall ranges from 0% to 88%, while precision ranges from 100% to 8%. When the recall is 33%, the precision of "neighboring weighted" approach increases to 72% from the original 38%, which corresponds to a 34% absolute increase. The results strongly indicate the importance of "neighboring effect" or positions as additional features. When the precision is 100%, the recall is 4.6%. A high precision is the key to success for this application. Many successful natural language processing systems achieved high precisions with a cost of lower recall[9].

6. Future Work

Our long term goal is to integrate the body of this work into our larger question answering system[3]. Additionally, we believe that we have room to enhance the performance for linking abstract sentences to images. We believe that "orderly effect", which is that the position order of image pairs (i.e., one image appears ahead of the other image) reflects the position order of abstract sentences, may be a useful feature to further enhance the task for linking abstract sentences to images. To test this hypothesis, we examined the statistics in our data set. Excluding images that have not been annotated to any sentences, we found a total of 1,640 image pairs. Of those only 433 pairs are reversed, and therefore a total of 1,207 or 73.6% image pairs appear with the same order of their corresponding sentences. To integrate "ordering effect" into existing algorithm, we may apply first a high-precision clustering algorithm to identify the first match between abstract sentences to images, and then cluster the preceding sentences with preceding abstracts and the following sentences with following abstracts to capture the next matches.

7. Related Work

Research and systems have been developed in experimental data retrieval. Tulipano and colleagues[10] defined an image taxonomy (e.g., "imaging instruments" and "imageable probes" are two children concepts of "imaging entity") and linked the image taxonomy to the Gene Ontology[11]. BioImage is a web-based object-oriented image database[12]. The SLIP system identifies images that depict protein subcellular locations[13]. PDB is a database for biological macromolecules and their relationships to sequence, function and disease[14]. Captions were explored for image classification in newswire images[15]. However, none of the existing systems incorporates the natural language processing techniques (e.g., summarization and question answering) to map images to text.

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