Recognition of Bio-molecular Events in Text: The BioNLP Shared Task

Lucy Vanderwende Senior Researcher, **NLP** group Microsoft Research

Joint work with Chris Quirk, Pallavi Choudhury, and Michael Gamon

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A CONVERSATION OVERHEARD

Who? SIG-BioMed

Biomedical language processing poses specific technical challenges that make
it of interest to general NLP practitioners and make it of compelling
importance to the larger field of biomedical informatics. The purpose of the
BioMed SIG is to bring together researchers in NLP, bioinformatics, medical
informatics, and computational biology, ...

What? Genia Corpus

- ... a corpus of annotated abstracts taken from National Library of Medicine's MEDLINE database. In GENIA Corpus we annotate a subset of the substances and the biological locations involved in reactions of proteins, based on a data model (GENIA ontology) of the biological domain, in XML format (GPML).
- GENIA Corpus Version 3.0x consists of 2000 abstracts. The base abstracts are selected from the search results with keywords (MeSH terms) *Human*, *Blood Cells*, and *Transcription Factors*.
- annotators who are biologists, in order to get qualified interpretations from a biological perspective. These annotators are not systematically aware of linguistic phenomena.

Why? Information Overload

- Search engines dominate information gathering
 - PubMed
 - Web as corpus
- Search engines today are limited … require a lot of human effort to make sense of the information served up
- Can you find the information you really need to gather?
 - Are key words or key phrases enough?
 - Some spelling, some alternate terms (domain-specific at best only for domain-specific search engines)

Talk Overview

- Goal for this talk
 - Update non-NLP researchers on state of the art for Information Extraction
- The BioNLP shared task
 - http://www-tsujii.is.s.u-tokyo.ac.jp/GENIA/SharedTask
 - Challenges
- Description of the MSR system for BioNLP
- System results
- Translating these results into action
 - Human-machine collaboration
 - Information visualization

Example

In this study we hypothesized that the phosphorylation of TRAF2 inhibits binding to the CD40 cytoplasmic domain.

T1 Protein 57 62 TRAF2 T2 Protein 88 92 CD40



- 1) Phosphorylation of TRAF2
- 2) Binding of TRAF2 to CD40
- 3) Instance of negative regulation
- 4) It's the phosphorylation event that neg-regulates the binding event

Example

In this study we hypothesized that the phosphorylation of TRAF2 inhibits binding to the CD40 cytoplasmic domain.

T1 Protein 57 62 TRAF2 T2 Protein 88 92 CD40



- T4 Phosphorylation 39 54 phosphorylation
- E1 Phosphorylation:T4 Theme:T1
- 15 Binding 73 80 binding
- E2 Binding:T5 Theme1:T1 Theme2:T2
- T6 Negative_regulation 64 72 inhibits
- E3 Negative_regulation:T6 Theme:E2 Cause:E1

Bio-Event: State change of bio-molecules

- Genia Corpus
 - Gene expression
 - Transcription
 - Protein catabolism
 - Localization
 - Phosphorylation
 - Binding
 - Regulation
 - Positive regulation
 - Negative regulation

- Epigenetics and Posttranslational Modifications (EPI)
 - (De)Hydroxylation
 - (De)Phosphorylation
 - (De)Ubiquitination
 - (De) DNA methylation
 - (De)Glycosylation
 - (De)Acetylation
 - (De)Methylation
 - Catalysis

Why is this challenging?

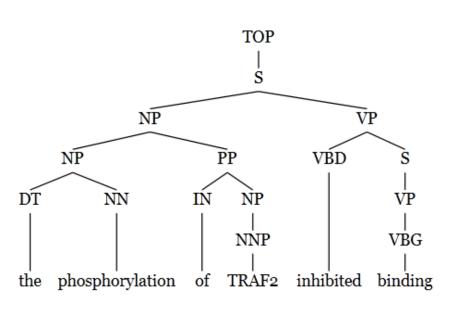
- Many ways to refer to one event
 - Negative_regulation
 - 532 inhibited, 252 inhibition, 218 inhibit, 207 blocked, 175 inhibits, 157 decreased, 156 reduced, 112 suppressed, 108 decrease, 86 inhibitor, 81 Inhibition, 68 inhibitors, 67 abolished, 66 suppress, 65 block, 63 prevented, 48 suppression, 47 blocks, 44 inhibiting, 42 loss, 39 impaired, 38 reduction, 32 down-regulated, 29 abrogated, 27 prevents, 27 attenuated, 26 repression, 26 decreases, ...
- One word can refer to many events
 - "detected"
 - Gene_expression(0.38) Positive_regulation(0.17) Transcription(0.38) Binding(0.03)
 Negative_regulation(0.03)
- Complex nested event-argument structures
 - (phosphorylation of TRAF2) inhibits (binding ...

MICROSOFT RESEARCH SYSTEM FOR BIONLP

Parse Input: Split sentences, tokenization, mark tokens as proteins and triggers
Read Data
Obtain constituency parses (50 best or 1 best); McClosky-Charniak 2008, McClosky trained on Genia 2010, ENJU (U Tokyo)
Optionally compute posterior probabilities for all parse edges
•Transform to labeled dependency parses using Stanford Dependency parser
Preparation Optionally apply dependency conversion rules
•Word-based
•Frequency-based
Feature • Dependency parse-based
Extraction •Cluster-based
•Train SVM models
Trigger
Detection
•Train MaxEnt models
Edge
Detection
•Remove Cycles
Post •Remove unwarranted edges
Processing
V

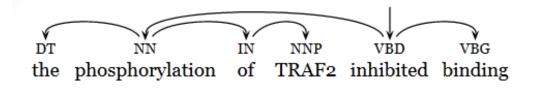
Data preparation - parsing

Constituency parse



- McClosky-Charniak 2008 general
- McClosky 2010 trained on Genia
- EnJu, ...
- One-best or n-best
- Posterior probabilities or none

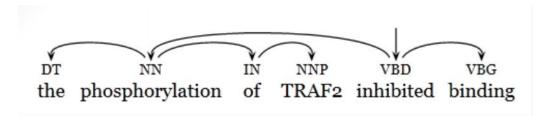
Stanford Dependency parser, labeled



- Additional Conversion Rules
- Posterior probabilities or none

Data preparation

Create features from the following abstraction:

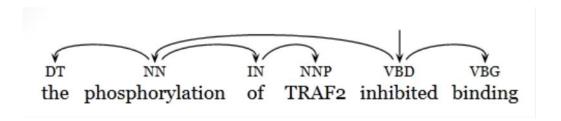


```
det(phosphorylation-2, the-1)
nsubj(inhibited-5, phosphorylation-2)
dobj(inhibited-5, binding-6)
```

```
prep_of(phosphorylation-2, TRAF-2-4)
dobj(phosphorylation-2, TRAF-2-4) -- optional conversion rule
```

Trigger Detection

Is the word a possible trigger?



? The no

? Phosphorylation yes

? Of no

? TRAF-2 protein

? Inhibited yes

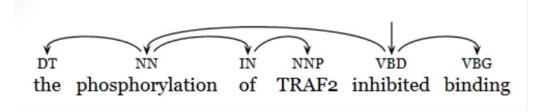
? Binding yes

Trigger Feature Extraction

- For each word, e.g., "phosphorylation"
 - Stem = phosphoryl
 - Bi-/trigrams "ph" "pho" "ho" "hos" "os" "osp" ...
 - Uppercase Y/N, has_number Y/N
 - Was the word a trigger before? Y/N
- Frequency-based features
 - what are co-occurring entities in the sentence?
 - Co-occurring words in the sentence?

Trigger Feature Extraction

- Dependency-based features
 - 1-, 2-, and 3-hop dependency paths types
 - 1-, 2-, and 3-hop dependency paths lexicalized
 - Shortest path from word to protein



- Cluster-based features
 - To which automatically-generated cluster does word belong?
 - {activation, localization, ... lymphoma, malaria}

Edge Detection

 Only 2 possible edge types, trigger-trigger and trigger-protein

	111	pt the phosp	NN horylation	IN of	NNP TRAF2	vBD inhibited	VBG binding	
?	Phosphoryla	tion - TR	AF-2	ye	!S	trigger –	protein	theme
?	Phosphoryla	tion – inł	nibited	ye	!S	trigger –	trigger	cause
?	Phosphoryla	tion – bir	nding	nc)			
?	Inhibited – T	RAF-2		nc)			
?	Inhibited – b	inding		ye	es	trigger –	trigger	theme
?	Binding – TR	AF-2		nc)			

Edge Detection Features

- All of the features for trigger detection, plus
- For a trigger, is the possible edge part of the path to the nearest protein
- For a trigger, what protein/trigger type is the second node
 - Phosph. Theme binding low probability
 - Phosph. Theme PROT high probability

Training

- In conjunction with previously published data on c-Raf-induced phosphorylation of GABP factors ...
- dt ti:1 bow .:1 t1HOut JJ:1 dist 1POS NN:1 dep dist dist 2nn:1 dist 2POS NN:1 dist 2isName:1 dist 2annType Protein:1 dist 2txt NAMED ENT:1 dist 3POS JJ:1 POS NN:1 linear -1 POS JJ:1 linear 2 POS NN:1 dep dist dist 2dep:1 dist 2POS JJ:1 dt at:1 linear -2 POS JJ:1 linear -3 POS JJ:1 dep dist dist 2amod:1 nonstem ation:1 tt ati:1 tt tio:1 tt ion:1 dt io:1 dt on:1 linear 1 POS IN:1 t1HOut amod:1 t1HOut amod JJ:1 dep dist dist 3amod:1 chain dist dist 3-rev amod:1 dt or:1 linear -3_isName:1 linear_-3_annType_Protein:1 linear_-3_txt_NAMED_ENT:1 dt_ph:1 bow_previously:1 bow_of:1 bow (:1 dist 1POS IN:1 dep dist dist 1advmod:1 dist 1txt previously:1 dist 1POS RB:1 dep dist dist 1appos:1 linear 1 txt of:1 t1HOut prep of:1 t1HOut NNS:1 t1HOut prep of NNS:1 dep dist dist 3prep of:1 dist 3POS NNS:1 chain dist dist 3-rev prep of:1 chain dist dist 2-rev prep of-rev nn:1 linear 3 POS NNS:1 t1HIn NNS:1 dt la:1 tt ory:1 dt ry:1 dt sp:1 dt ho:1 bow ,:1 dist 2POS VBN:1 tt pho:1 tt lat:1 bow with:1 bow -: 1 linear -2 txt -: 1 dep dist dist 2hyphen: 1 chain dist dist 2-rev amod-rev hyphen: 1 bow In: 1 bow on: 1 t1HIn prep on:1 dep dist 3prep on:1 chain dist dist 3-frw prep on:1 dt os:1 nameCount 1:1 tt hor:1 dep dist 2prep with:1 bow induced:1 dist 3txt induced:1 linear -1 txt induced:1 bow factors:1 t1HOut factors:1 dist 3txt factors:1 linear 3 txt factors:1 stem_phosphoryl:1 tt hos:1 tt osp:1 tt sph:1 tt ryl:1 tt yla:1 dt yl:1 stem gaz Phosphorylation:1 bow phosphorylation:1 t1HOut induced:1 t1HOut amod induced:1 txt phosphorylation:1 t1HOut prep of factors:1 t1HIn prep on NNS:1 chain dist dist 2-frw prep onrev amod:1 bow data:1 t1HIn data:1 dist 3txt data:1 dep dist 1pobj:1 dist 1txt In:1 bow A:1 dist 1txt A:1 dist 2POS NNP:1 chain dist dist 2-frw prep on-rev dep:1 chain dist dist 2-frw prep on-frw prep with:1 bow conjunction:1 dist 2txt conjunction:1 bow published:1 dist 2txt published:1 chain dist dist 1frw prep on-rev amod-rev advmod:1 bow GABP:1 dist 2txt GABP:1 t1HIn_prep_on_data:1 chain dist dist 1frw prep on-rev dep-rev appos:1 # phosphorylation

Testing

 In conjunction with previously published data on c-Raf-induced phosphorylation of GABP factors ...

stem_gaz_Phosphorylation	(0.41)
dt_or	(0.35)
dt_os	(0.33)
stem_phosphoryl	(0.33)
tt_sph	(0.30)
tt_osp	(0.30)
tt_hos	(0.30)
tt_pho	(0.29)
tt_ryl	(0.29)
tt_hor	(0.29)

Class Scores: Phosphorylation:0.602 None:0.150 Binding:0.005 Regulation:0.004 Transcription:0.003 Localization:0.002 Phosphorylation/Positive_regulation:0.002 Negative_regulation:0.001 Positive_regulation/Negative_regulation:0.001

System Results on Genia

	D	evelopment Set			Test Set	
Event Class	Recall	Precision	F1	Recall	Precision	F1
Gene_expression	76.37	81.46	78.83	73.95	73.22	73.58
Transcription	49.37	73.58	59.09	41.95	65.18	51.05
Protein_catabolism	69.57	80.00	74.42	46.67	87.50	60.87
Phosphorylation	73.87	84.54	78.85	87.57	81.41	84.37
Localization	74.63	75.76	75.19	51.31	79.03	62.22
=[SVT-TOTAL]=	72.02	80.51	76.03	68.99	74.03	71.54
Binding	47.99	50.85	49.38	42.36	40.47	41.39
=[EVT-TOTAL]=	65.97	72.73	69.18	62.63	65.46	64.02
Regulation	32.53	47.05	38.62	24.42	42.92	31.13
Positive_Regulation	38.74	51.67	44.28	37.98	44.92	41.16
Negative_Regulation	35.88	54.87	43.39	41.51	42.70	42.10
=[REG-TOTAL]=	36.95	51.79	43.13	36.64	44.08	40.02
MSR-Total	50.20	62.60	55.72	48.64	54.71	51.50
FAUST-Total				49.41	64.75	56.04
UMass-Total				48.49	64.08	55.20
Uturku-Total				49.56	57.65	53.30
Oturku-Total				49.50	57.65	53.30

System Results on Epigenetics

	D	evelopment Set	:		Test Set	
Event Class	Recall	Precision	F1	Recall	Precision	F1
Hydroxylation	25.81	61.54	36.36	30.43	84.00	44.68
Dehydroxylation	100.00	100.00	100.00	100.00	100.00	100.00
Phosphorylation	71.88	85.19	77.97	72.31	85.45	78.33
Dephosphorylation	0.00	0.00	0.00	0.00	0.00	0.00
Ubiquitination	63.16	75.00	68.57	67.78	81.88	74.16
Deubiquitination	0.00	0.00	0.00	0.00	0.00	0.00
DNA_methylation	72.73	72.18	72.45	71.43	73.86	72.63
DNA_demethylation	0.00	0.00	0.00	0.00	0.00	0.00
Glycosylation	61.43	67.19	64.18	39.05	69.47	50.00
Deglycosylation	0.00	0.00	0.00	0.00	0.00	0.00
Acetylation	89.23	75.32	81.69	87.42	85.28	86.34
Deacetylation	68.42	92.86	78.79	62.50	93.75	75.00
Methylation	64.62	75.00	69.42	62.18	73.62	67.42
Demethylation	0.00	0.00	0.00	0.00	0.00	0.00
Catalysis	3.33	15.38	5.48	4.50	33.33	7.94
====[MSR TOTAL]====	57.22	72.23	63.85	55.70	77.60	64.85
UTurku Total				68.51	69.208	68.86
FAUST Total				59.88	80.25	68.59
UMASS Total				57.04	73.30	64.15

A CONVERSATION JOINED QUESTIONS ASKED

Translating these results into ...

Given input text:

 The B cells were found to express BMP type I and type II receptors and BMP-6 rapidly induced phosphorylation of Smad1/5/8.

```
    T6 Protein 561 566 BMP-6
    T7 Protein 602 607 Smad1
    T8 Protein 608 609 Smad5
    T9 Protein 610 611 Smad8
```

System Output

```
- T31
        Positive regulation 575 582
                                  induced
- T32
        Phosphorylation 583 598
                                   phosphorylation
- E2
        Positive regulation:T31
                                 Theme:E3
                                            Cause:T6
- E4
        Positive regulation:T31
                                 Theme:E5
                                            Cause:T6
- E6
        Positive regulation:T31
                                 Theme:E7
                                            Cause:T6
        Phosphorylation:T32
                                 Theme:T7
- E3
        Phosphorylation:T32
                                 Theme:T8
- E5
– E7
        Phosphorylation:T32
                                 Theme:T9
```

Translating these results into ...

Given input text:

 The B cells were found to express BMP type I and type II receptors and BMP-6 rapidly induced phosphorylation of Smad1/5/8.

```
    T6 Protein 561 566 BMP-6
    T7 Protein 602 607 Smad1
    T8 Protein 608 609 Smad5
    T9 Protein 610 611 Smad8
```

"Friendly facts"

- Positive_regulation(BMP-6, phosphorylation of Smad1)
- Positive_regulation(BMP-6, phosphorylation of Smad5)
- Positive_regulation(BMP-6, phosphorylation of Smad8)
- Phosphorylation(Smad1)
- Phosphorylation(Smad5)
- Phosphorylation(Smad8)

"friendly facts"

- A better search engine
 - Solves the time-consuming nature of search
 - Solves the memory recall problem
 - Solves the problem of not knowing where to look, if all categories can be anticipated
- Entity focused ... who is? What is?
- You have to know what you're looking for



Using graphs

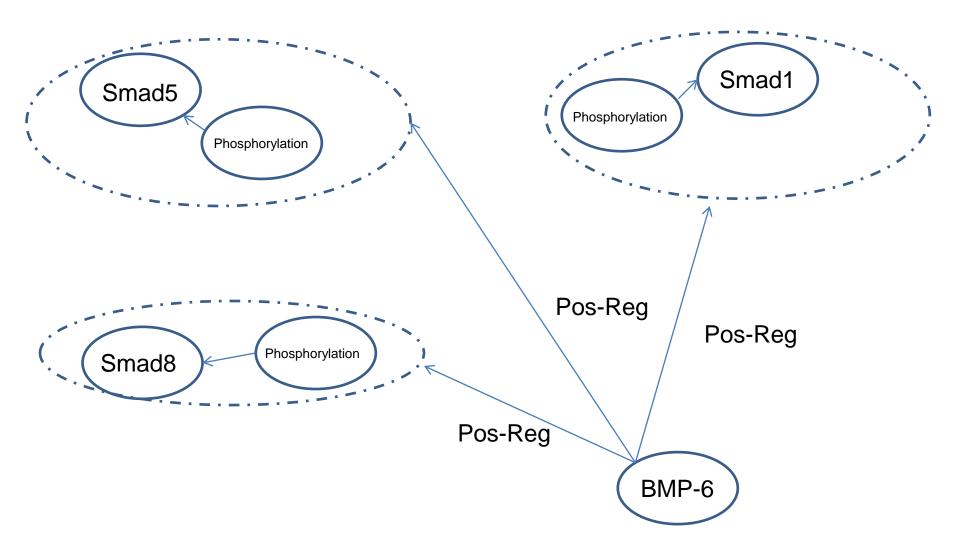
Natarajan, J. D. Berrar, W. Dubitzky, C. Hack, Y. Zhang, C. DeSesa, J. Van Brocklyn, E. Bremer.

Text mining of full-text journal articles combined with gene expression analysis reveals a relationship between sphingosine-1-phosphate and invasiveness of a glioblastoma cell line.

In BMC Bioinformatics, 2006, 7:373.

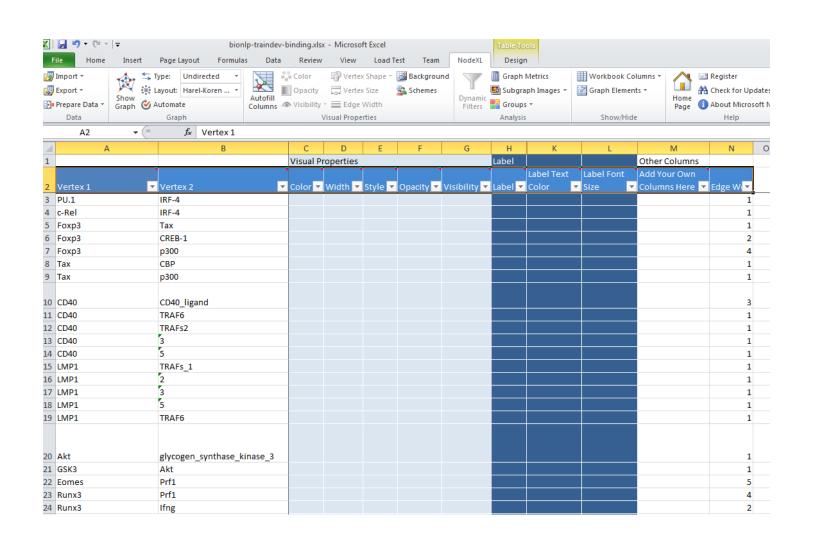
- They mined full-text articles and inferred gene-gene interaction networks for these 72 genes, from which they identified at least one interesting network which they further pursued.
- The paper shows success in applying information extraction to improve the workflow of biomedical researchers by adding improved search tools for literature review.

Translating these results into ... a graph

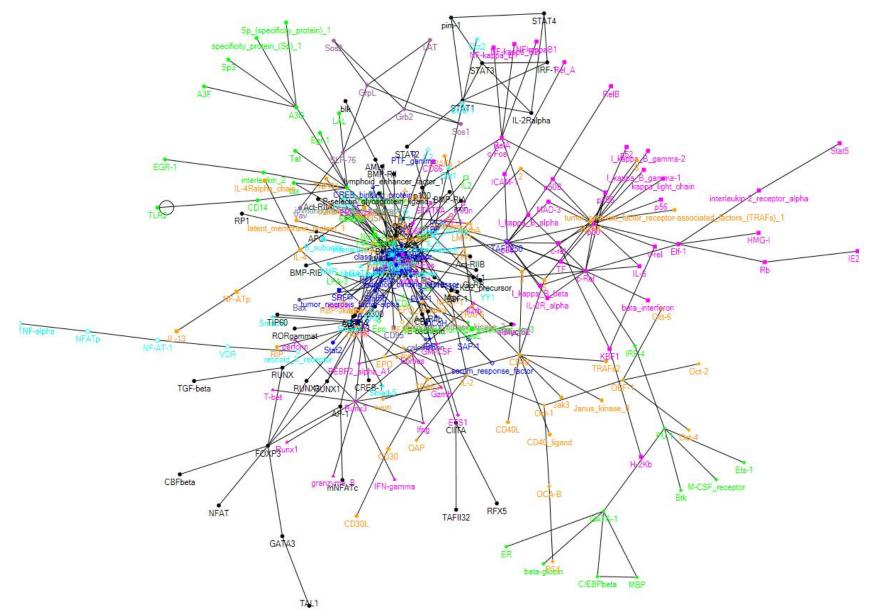


NodeXL, an Excel template

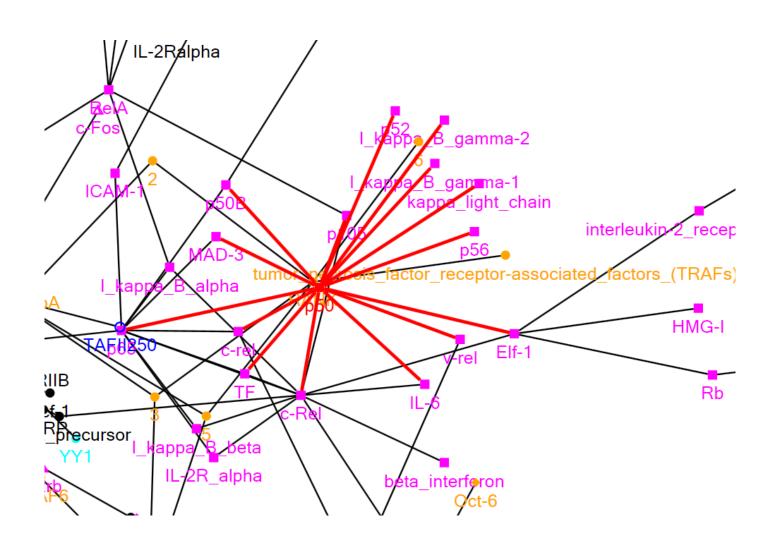
http://nodexl.codeplex.com



A different view of Binding

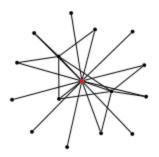


Focus on binding relations for P50

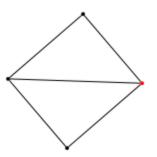


An abstract view of binding properties using relations up to 2 edges away

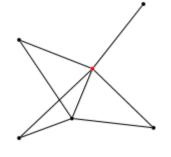
• P50



P300

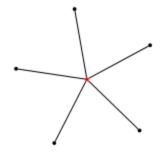


• STAT1



• C/EBPbeta

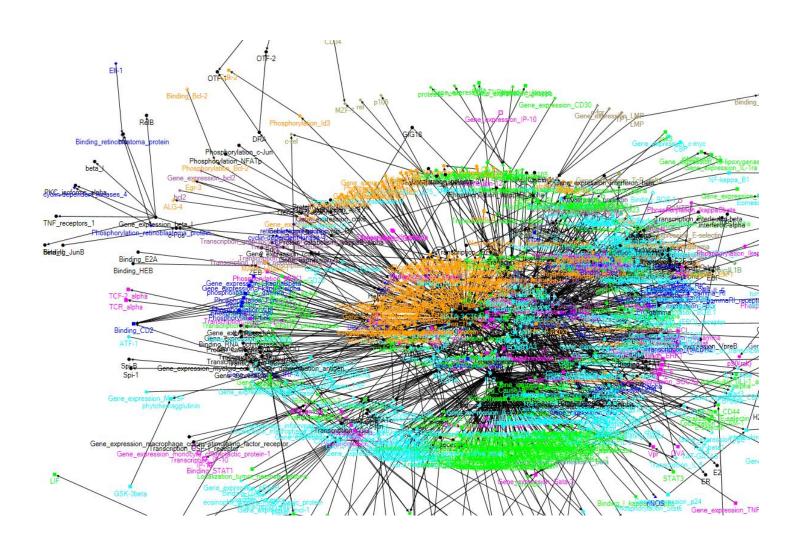
• PU.1



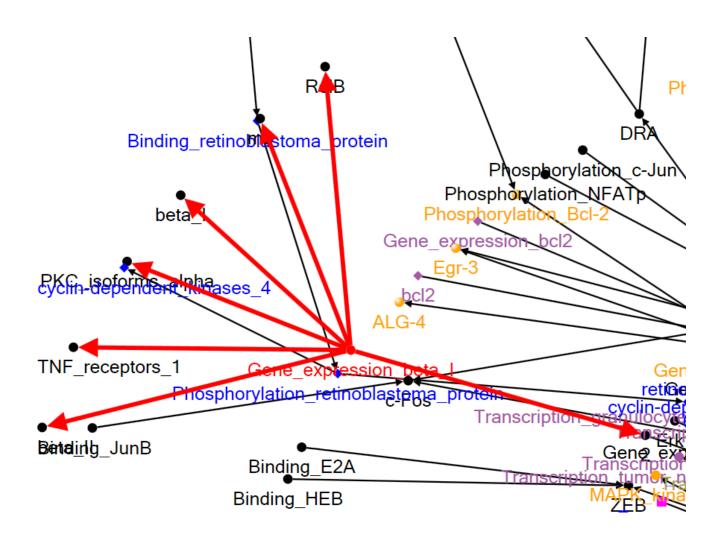
TRAF6



A different view of Regulation

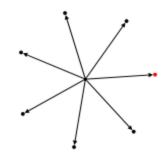


Focus on regulations



An abstract view of regulation properties using relations up to 2 edges away

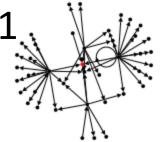




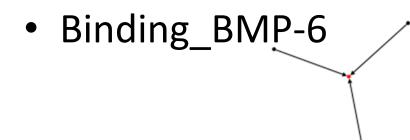
Binding_CD10



Binding_AP1



Gene_exp_Foxp3



Interleukin-6



ActiveText, Microsoft External Research project

Document Information

Title: Phenotypic characterization of a glucose transporter null mutant in Leishmania mexicana

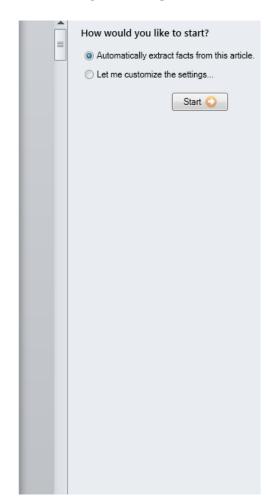
Authors: Dayana Rodriguez-Contreras; Xiuhong Feng; Kristie M. Keeney; H. G. Archie Bouwer; Scott M.

Landfear

Year: 2007

Abstract

Glucose is a major source of energy and carbon in promastigotes of Leishmania mexicana, and its uptake is mediated by three glucose transporters whose genes are encoded within a single cluster. A null mutant in which the glucose transporter gene cluster was deleted by homologous gene replacement was generated previously and shown to grow more slowly than wild type promastigotes but not to be viable as amastigotes in primary tissue culture macrophages or in axenic culture. Further phenotypic characterization demonstrates that the null mutant is unable to import glucose, mannose, fructose, or galactose and that each of the three glucose transporter isoforms, LmGT1, LmGT2, and LmGT3, is capable of transporting each of these hexoses. Complementation of the null mutant with each isoform is able to restore growth in each of the four hexoses to wild type parasites. Null mutant promastigotes are reduced in size to about 2/3 the volume of wild type parasites. In addition, the null mutants are significantly more sensitive to oxidative stress than their wild type counterparts. These results underscore the importance of glucose transporters in the parasite life cycle and suggest reasons for their non-viability in the disease-causing amastigote stage.



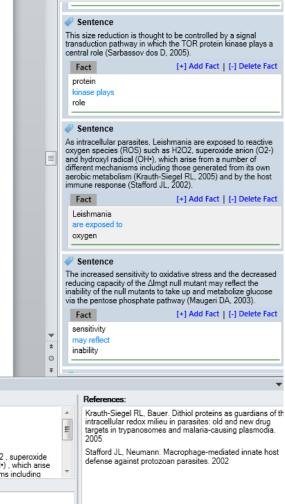
ActiveText, Microsoft External Research project

Microscopic examination of \underline{Almgt} null mutant $\underline{promastigates}$ suggests that they are smaller than either wild type parasites or null mutants that have been complemented with the LmGT2 glucose transporter gene on an $\underline{episomal}$ expression vector ($\underline{Almgt}[pGT2]$) (Fig. 6). To quantify this reduction in size, we measured \underline{cell} volume by monitoring partitioning of 3H2O and [14C] carboxyl-inulin into the three cell lines, and we determined the protein content per cell. The ratio for wild type/ \underline{Almgt} cells was 1.57 \pm 0.10 (n=7) for the cell volume and 1.53 \pm 0.10 (n=13) for the protein content measurement, confirming that the \underline{Almgt} null mutants are significantly smaller than wild type $\underline{promastigates}$. $\underline{Episomal}$ complementation with LmGT2 was able to restore the size of \underline{Almgt} parasites, as the ratio for wild type/ \underline{Almgt} [pGT2] cells was 1.01 \pm 0.07 (n=3) for the cell volume and 1.00 \pm 0.02 (n=3) for protein content. \underline{Trhese} results complement the previous observation that \underline{Almgt} promastigates grow slowly and to a lower cell density compared to wild type parasites (Burchmore RJ, 2003).

It is notable that restriction of nutrients such as glucose and amino acids leads to a pronounced reduction in cell size in many eukaryotes. This size reduction is thought to be controlled by a signal transduction pathway in which the TOR protein kinase plays a central role (Sarbassov dos D, 2005). This TOR pathway is highly conserved among eukaryotes, and potential homologs of the TOR, raptor, and GBL proteins, that constitute the functional protein kinase, are encoded within the L. major genome (systematic names LmjF36.6320 and LmjF34.4530 for TOR, LmjF25.0610 for raptor, and LmjF10.0780 for GBL proteins). These observations suggest that the reduced size of Almgt null mutants might be mediated by a TOR-raptor-GBL complex.

3.5 Increased susceptibility of Almgt promastigates to oxidative stress

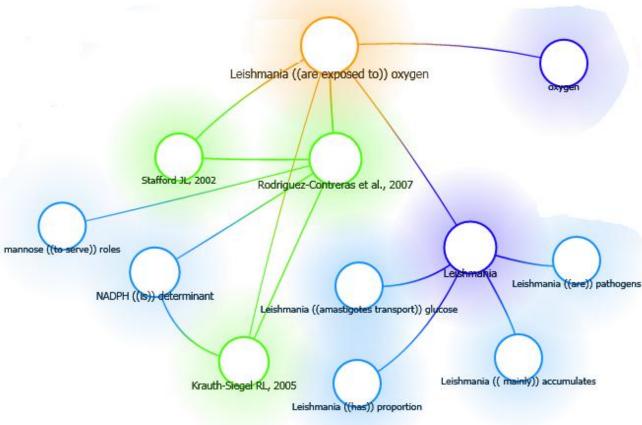
As intracellular parasites, Leishmania are exposed to reactive oxygen species (ROS) such as H2O2, superoxide anion (O2-) and hydroxyl radical (OH•), which arise from a number of different mechanisms including those generated from its own aerobic metabolism (Krauth-Siegel RL, 2005) and by the host immune response (Stafford JL, 2002). To evaluate whether Almgt parasites are more sensitive to oxidative stress, we exposed both wild type and Almgt promastigates to increasing concentrations of a



ActiveText :: Edit Fact			
Subject:	Verb:	Object:	Ref
Leishmania	are exposed to	oxygen reactive oxygen reactive oxygen species reactive oxygen (ROS) such as H2O2, superoxide anion (O2-) and hydroxyl radical (OH+), which arise from a number of different mechanisms including	Kra intr targ 200 Sta def
Write your own:	Write your own:	○ Write your own:	

Visualizing the ActiveText data

Our hypothesis is that you might discover information you wouldn't have necessarily known to go looking for, so "not your old search engine"



ActiveText

- Annotator can be either a reader or the author
- Annotator can accept/modify/reject the facts extracted
- Annotator can "write your own", which hopefully will lead to high-level relation annotations, similar to "regulation" or "binding"

A CONVERSATION CONTINUING

Summary

- The BioNLP shared task
- Machine Learning architecture with rich features derived from NLP (lexical, syntactic, semantic)
- Demonstrated feasibility of the task through system results
- Translating these results into action
 - Information visualization
 - Human-machine collaboration
- More communication between CS/NLP and Bioinformatics is essential to plan next steps