Natural Language Processing for Health (HLP)

September 2018

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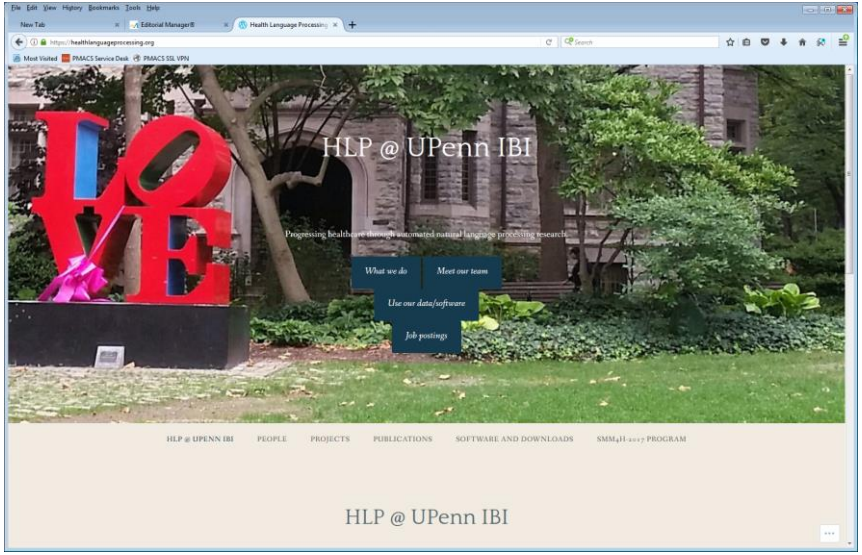


https://healthlanguageprocessing.org

Graciela Gonzalez-Hernandez

Contact: gragon@upenn.edu

Twitter: @gracielagon

Institute for Biomedical Informatics

Perelman School of Medicine
University of Pennsylvania

Program & Speaker List

- **Welcome/Introduction –** Graciela Gonzalez-Hernandez, Ph.D.

- **KEYNOTES** ***(15 minutes + 15 minutes for questions each)***

Deep neural networks and distant supervision for geographic location mention extraction

Arjun Magee
Dept. of Biomedical Informatics
Arizona State University

Social Media Mining for Pharmacovigilance: challenges and opportunities: Case Control Studies from Twitter?

Graciela Gonzalez-Hernandez, Ph.D
Health Language Processing Lab – Penn IBI
University of Pennsylvania

Deep neural networks and distant supervision for geographic location mention extraction

Arjun Magge [1,2], Davy Weissenbacher [3], Abeed Sarkar [3], Matthew Scotch [1,2], and Graciela Gonzalez [3]

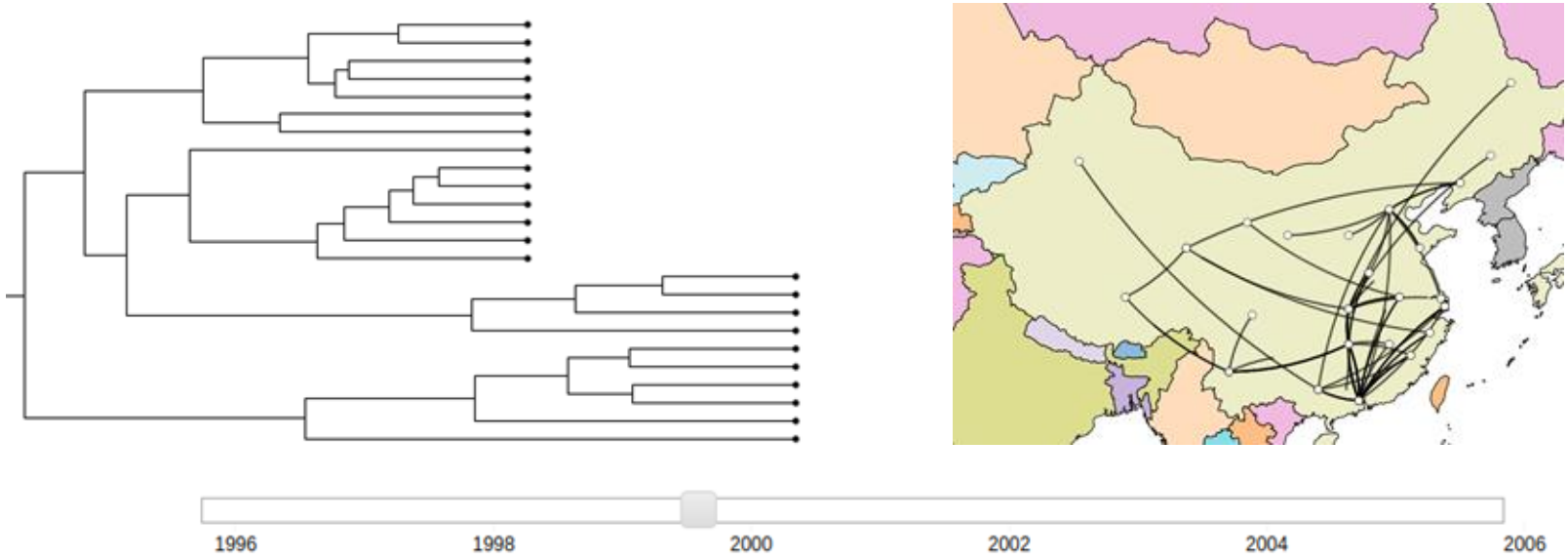
[1] Department of Biomedical Informatics, Arizona State University
[2] Biodesign Center for Environmental Health Engineering, Biodesign Institute, Arizona State University
[3] Department of Biostatistics, Epidemiology and Informatics, The Perelman School of Medicine, University of Pennsylvania

Sept 6, 2018

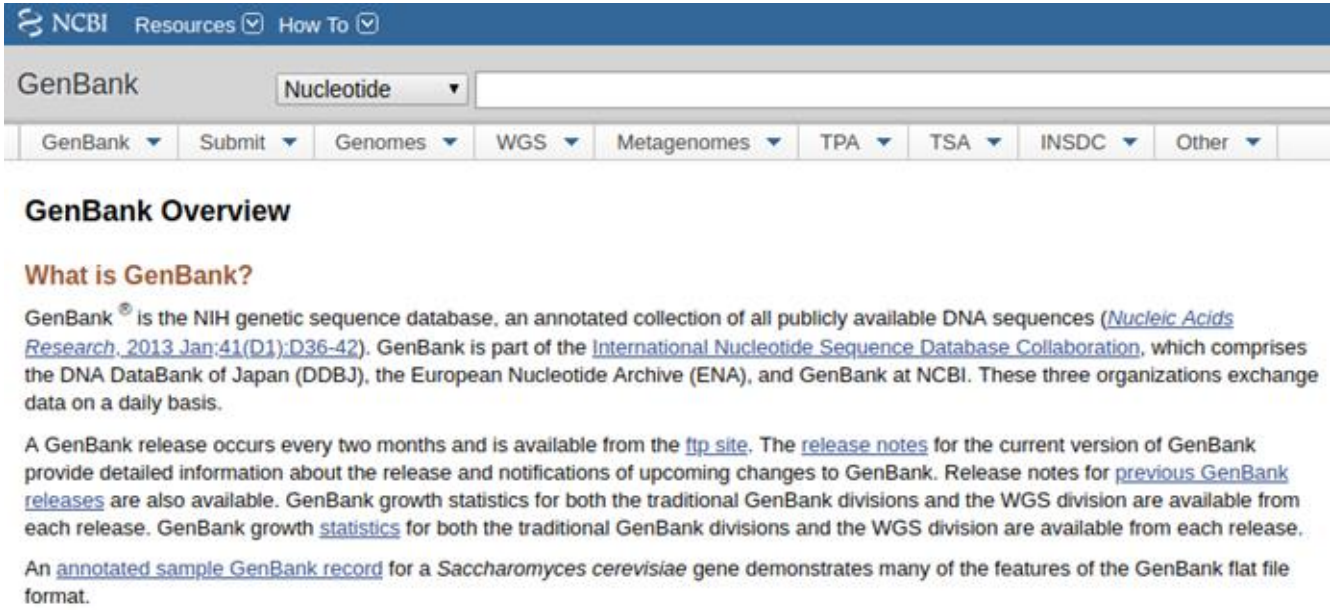
ASU College of Health Solutions
ARIZONA STATE UNIVERSITY

Phylogenetic tree and spread reconstruction

- Virus phylogeography and epidemiology research relies on nucleotide sequence repositories like **GenBank**



GenBank


NCBI
Resources
How To
GenBank
Nucleotide
GenBank
Submit
Genomes
WGS
Metagenomes
TPA
TSA
INSDC
Other
GenBank Overview
What is GenBank?
GenBank ® is the NIH genetic sequence database, an annotated collection of all publicly available DNA sequences (Nucleic Acids Research. 2013 Jan;41(D1):D36-42). GenBank is part of the International Nucleotide Sequence Database Collaboration, which comprises the DNA DataBank of Japan (DDBJ), the European Nucleotide Archive (ENA), and GenBank at NCBI. These three organizations exchange data on a daily basis.
A GenBank release occurs every two months and is available from the ftp site. The release notes for the current version of GenBank provide detailed information about the release and notifications of upcoming changes to GenBank. Release notes for previous GenBank releases are also available. GenBank growth statistics for both the traditional GenBank divisions and the WGS division are available from each release. GenBank growth statistics for both the traditional GenBank divisions and the WGS division are available from each release.
An annotated sample GenBank record for a Saccharomyces cerevisiae gene demonstrates many of the features of the GenBank flat file format.

Genbank Record and Metadata

Zika virus isolate Brazil-ZKV2015, complete genome

GenBank: KU497555.1

FASTA Graphics

Go to:

```
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DEFINITION  Zika virus isolate Brazil-ZKV2015, complete genome.
ACCESSION   KU497555
VERSION     KU497555.1
KEYWORDS    .
SOURCE      Zika virus
  ORGANISM  Zika virus
            Viruses; ssRNA viruses; ssRNA positive-strand viruses, no DNA
            stage; Flaviviridae; Flavivirus.
REFERENCE   1  (bases 1 to 10793)
  AUTHORS   Calvet,G., Aguiar,R.S., Melo,A.S., Sampaio,S.A., de Filippis,I.,
            Fabri,A., Araujo,E.S., de Sequeira,P.C., de Mendonca,M.C., de
            Oliveira,L., Tschoeke,D.A., Schrago,C.G., Thompson,F.L., Brasil,P.,
            Dos Santos,F.B., Nogueira,R.M., Tanuri,A. and de Filippis,A.M.
  TITLE     Detection and sequencing of Zika virus from amniotic fluid of
            fetuses with microcephaly in Brazil: a case study
  JOURNAL   Lancet Infect Dis 16 (6), 653-660 (2016)
   PUBMED   26897108
REFERENCE   2  (bases 1 to 10793)
  AUTHORS   Tanuri,A., Bispo,A., Thompson,F., Santana,R., Tschoeke,D., de
            Oliveira,L. and Guerra,C.
  TITLE     Direct Submission
  JOURNAL   Submitted (06-JAN-2016) UFRJ, UFRJ, Avenida Carlos Chagas Filho,
            373, Rio de Janeiro, Rio de Janeiro 21040-900, Brazil
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                     /country="Brazil"
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                     /protein_id="AMD16557.1"
                     /translation="MKNPKKKSGGFRIVNMLKRGVARVS
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Genbank Record and Metadata

/organism="Zika virus"

/host="Homo sapiens"

/collection_date="30-Nov-2015"

/country="Brazil"

```
TITLE     Detection and sequencing of Zika virus from amniotic fluid of
          fetuses with microcephaly in Brazil: a case study
JOURNAL   Lancet Infect Dis 16 (6), 653-660 (2016)
 PUBMED   26897108
```

PubMed Article

Detection and s
a case study.

Calvet G[1], Aguiar RS[2], M
Schrago CG[2], Thompson

⊕ Author information

Abstract

BACKGROUND: The incidence of microcephaly in Brazil in 2015
associated with genetic factors and several causative agents. Ep
associated with the introduction of Zika virus. We aimed to detec
pregnant women in Brazil whose fetuses were diagnosed with m

METHODS: In this case study, amniotic fluid samples from two p
diagnosed with microcephaly were obtained, on the recommend
amniocentesis at 28 weeks' gestation. The women had presente
manifestations that could have been symptoms of Zika virus infe
were centrifuged, DNA and RNA were extracted from the purifie
reverse transcription PCR and viral metagenomic next-generatio
recombination events were done by comparing the Brazilian Zik
that occur in similar regions in Brazil.

state of Paraíba in Brazil

Insufficient location information

Problem: Locations in GenBank metadata are not sufficient for Phylogeography research

- Especially for countries like USA, Canada, Russia, China, Brazil

Solution: Enrich location information in GenBank by extracting locations from the associated PubMed article using Natural Language Processing (NLP)

Natural Language Processing

1. Named Entity Recognition
   - identifying words of interest in text (usually nouns)
   - e.g. names, genes, proteins, locations, organizations, time, etc.

1. Concept Resolution
   - perform disambiguation by assigning a unique gazetteer ID
   - e.g. Paris can refer to Paris, Texas, USA or Paris, France

1. Determine Location of Infected Host (LOIH)
   - assign probabilities to all identified locations using heuristics

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PubMed Article : NER

Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study.

Calvet G[1], Aguiar RS[2], Melo ASO[3], Sampaio SA[4], de Filippis I[5], Fabri A[4], Araujo ESM[4], de Sequeira PC[4], de Mendonça MCL[4], de Oliveira L[2], Tschoeke DA[6], Schrago CG[2], Thompson FL[7], Brasil P[1], Dos Santos FB[4], Nogueira RMR[4], Tanuri A[2], de Filippis AMB[8].

⊕ Author information

Abstract

BACKGROUND: The incidence of microcephaly in Brazil in 2015 was 20 times higher than in previous years. Congenital microcephaly is associated with several causative agents. Epidemiological data suggest that microcephaly cases in Brazil might be associated with the Zika virus. We aimed to detect and sequence the Zika virus genome in amniotic fluid samples of two pregnant women who were diagnosed with microcephaly.

METHODS: We collected amniotic fluid samples from two pregnant women from the state of Paraíba in Brazil whose fetuses had been diagnosed with microcephaly, on the recommendation of the Brazilian health authorities, by ultrasound-guided transabdominal amniocentesis. The women had presented at 18 weeks' and 10 weeks' gestation, respectively, with clinical manifestations and symptoms of Zika virus infection, including fever, myalgia, and rash. After the amniotic fluid samples were centrifuged, DNA was extracted from the purified virus particles before the viral genome was identified by quantitative reverse transcription PCR and viral metagenomic next-generation sequencing. Phylogenetic reconstruction and investigation of recombination events were done by comparing the Brazilian Zika virus genome with sequences from other Zika strains and from flaviviruses that occur in similar regions in Brazil.

Locations:
Brazil
Paraiba

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Locations:	GeonamesID:
Brazil	3469034
Paraiba	3393098

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METHODS
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reverse transcription PCR and viral metagenomic next-generation sequencing. Phylogenetic reconstruction and investigation of recombination events were done by comparing the Brazilian Zika virus genome with sequences from other Zika strains and from flaviviruses that occur in similar regions in Brazil.

Locations:	GeonamesID:	LOIH Probability:
Brazil	3469034	0.00
Paraiba	3393098	1.00

Natural Language Processing

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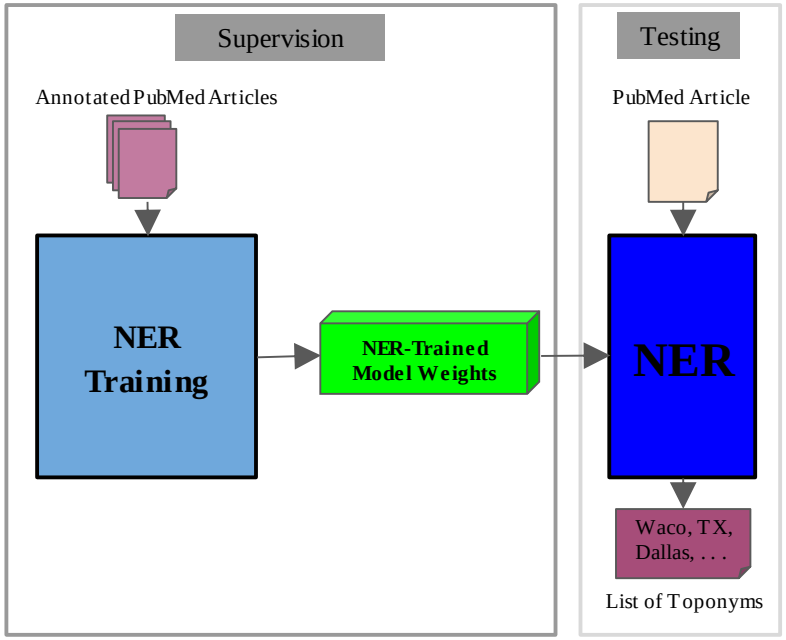
Ambiguity in Natural Language

*in **May, Russia** in 2010.*	✔
*found in **May** 2013.*	X
*pigs, **turkey** and quail*	X
*University of **Las Vegas**.*	X

Why deep neural nets?

- Rule based systems
- Machine Learning and Deep learning
  - Better performance with more annotated data

- Most times, you can only annotate a few articles.
  - So, distant supervision?



Dataset

- A set of 60 full-text articles (~300,000 words) from Pubmed containing 1881 location annotations
  - 48 for training and 12 for testing

- Distant supervision
  - Use GenBank articles where locations are known
  - Generate positive and negative examples based on rules
  - They are noisy! But, that's okay.
  - We use them to generate ~8 million training instances(words)

Collecting Distant Supervision Samples

Tacaribe virus isolate Florida segment L, complete sequence

GenBank: KF923401.1

FASTA Graphics

Go to:

```
LOCUS       KF923401               7103 bp    RNA     linear   VRL 30-JAN-2015
DEFINITION  Tacaribe virus isolate Florida segment L, complete sequence.
ACCESSION   KF923401
VERSION     KF923401.1
KEYWORDS    .
SOURCE      Tacaribe mammarenavirus
  ORGANISM  Tacaribe mammarenavirus
            Viruses; ssRNA viruses; ssRNA negative-strand viruses;
            Arenaviridae; Mammarenavirus.
REFERENCE   1  (bases 1 to 7103)
  AUTHORS   Sayler,K.A., Barbet,A.F., Chamberlain,C., Clapp,W.L., Alleman,R.,
            Loeb,J.C. and Lednicky,J.A.
  TITLE     Isolation of Tacaribe Virus, a Caribbean Arenavirus, from
            Host-Seeking Amblyomma americanum Ticks in Florida
  JOURNAL   PLoS ONE 9 (12), E115769 (2014)
   PUBMED   25536075
  REMARK    Publication Status: Online-Only
REFERENCE   2  (bases 1 to 7103)
  AUTHORS   Sayler,K.A., Lednicky,J.A., Alleman,A.R. and Barbet,A.F.
  TITLE     Direct Submission
  JOURNAL   Submitted (02-DEC-2013) Physiological Sciences, University of
            Florida, 2015 SW 16th Avenue Building 1017, Room V2-240,
            Gainesville, FL 32608, USA
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/country="USA: San Felasco State Park, Alachua, Florida"

PUBMED 25536075

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/country="USA: San Felasco State Park, Alachua, Florida"
/collection_date="27-Mar-2012"
/collected_by="K. Sayler"
```

Process records which have fine-grained locations

Collecting Positive Samples

Isolation of Tacaribe Virus, a Caribbean Arenavirus, from Host-Seeking Amblyomma americanum Ticks in Florida. We report the re-isolation of the virus from a pool of 100 host-seeking Amblyomma americanum (lone star ticks) collected in a Florida state park in 2012.

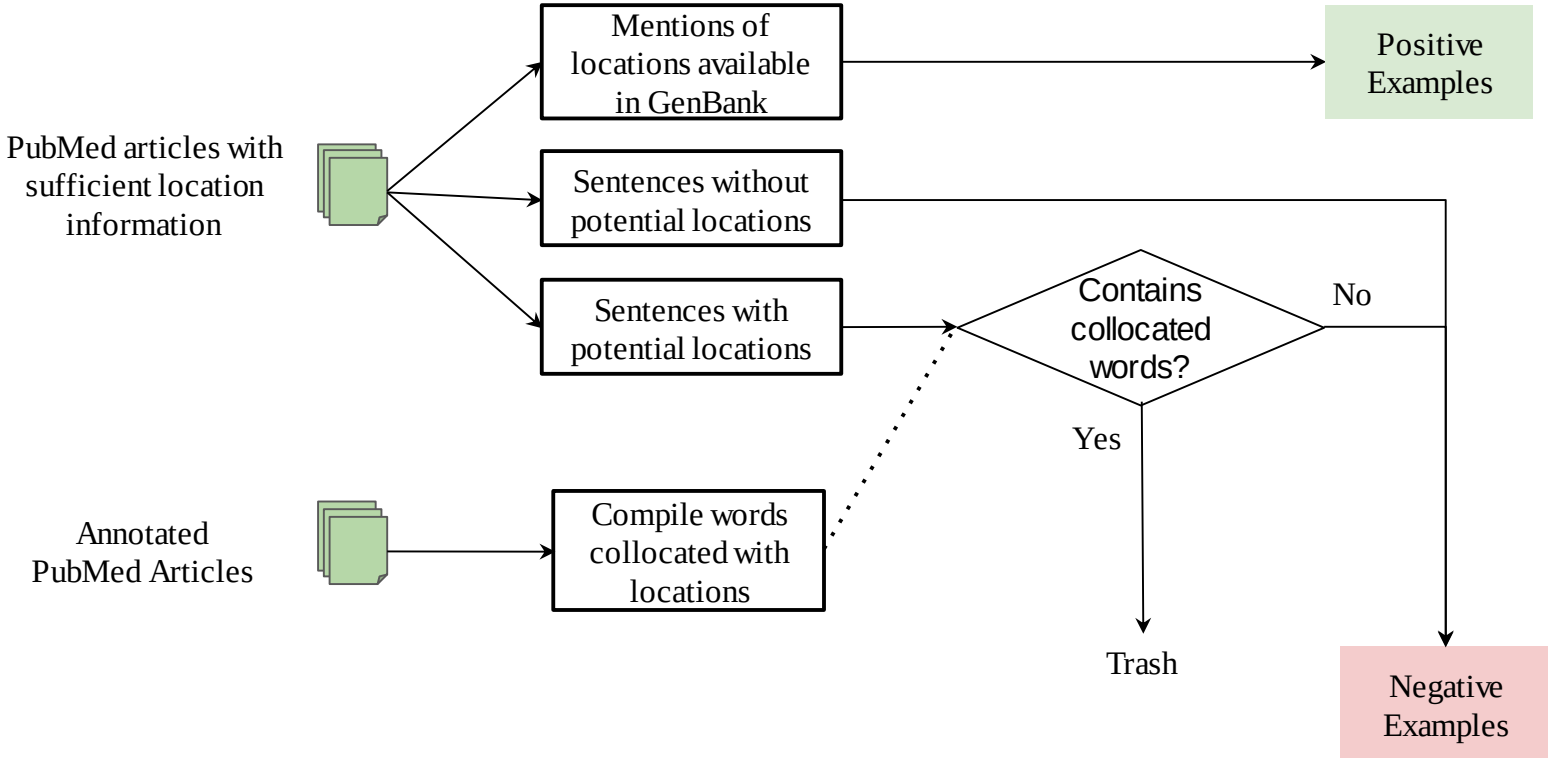
At least ten of these viruses are associated with human disease in many parts of the world including western Africa, Argentina, Bolivia, Venezuela and Brazil [2].

All tick trapping was performed in accordance with the Florida Department of Environmental Protection Research and Collection Permit #05231210.

Only host-seeking tick species common in Florida were collected because these species are most likely to attach to a person and take a blood meal.
In 2013, ticks were collected using the same methods as 2012 from two additional Florida state parks: Manatee Springs State Park in Chiefland, Florida (29° 29′47.401″ N, 82°58′4.429″ W) and O'Leno State Park in High Springs, Florida (29°55′11.863″ N and 82° 35′15.427″ W), to determine if the virus could be detected in other locations in North Central Florida (Fig.1).

A total of 500 host-seeking ticks were collected from three state parks located in North Central Florida, including the original field site where ticks were trapped for virus isolation attempts (Fig. 1).

Collecting Negative Samples



Filter them based on some guidelines

Positive Examples

Ticks in Florida <PAD> <PAD>

in a Florida state park

~~with the Florida Department of~~

common in Florida were collected

two additional Florida state parks

Chiefland, Florida (29

Springs , Florida (29

North Central Florida (Fig

North Central Florida, including

~~University of Florida Interdisciplinary Center~~

in Central Florida , USA

Negative Examples

<PAD> <PAD> Gene UL111A encodes

<PAD> Gene UL111A encodes viral

Gene UL111A encodes viral interleukin

UL111A encodes viral interleukin -

encodes viral interleukin - 10

viral interleukin - 10 (

interleukin - 10 (Lockridge

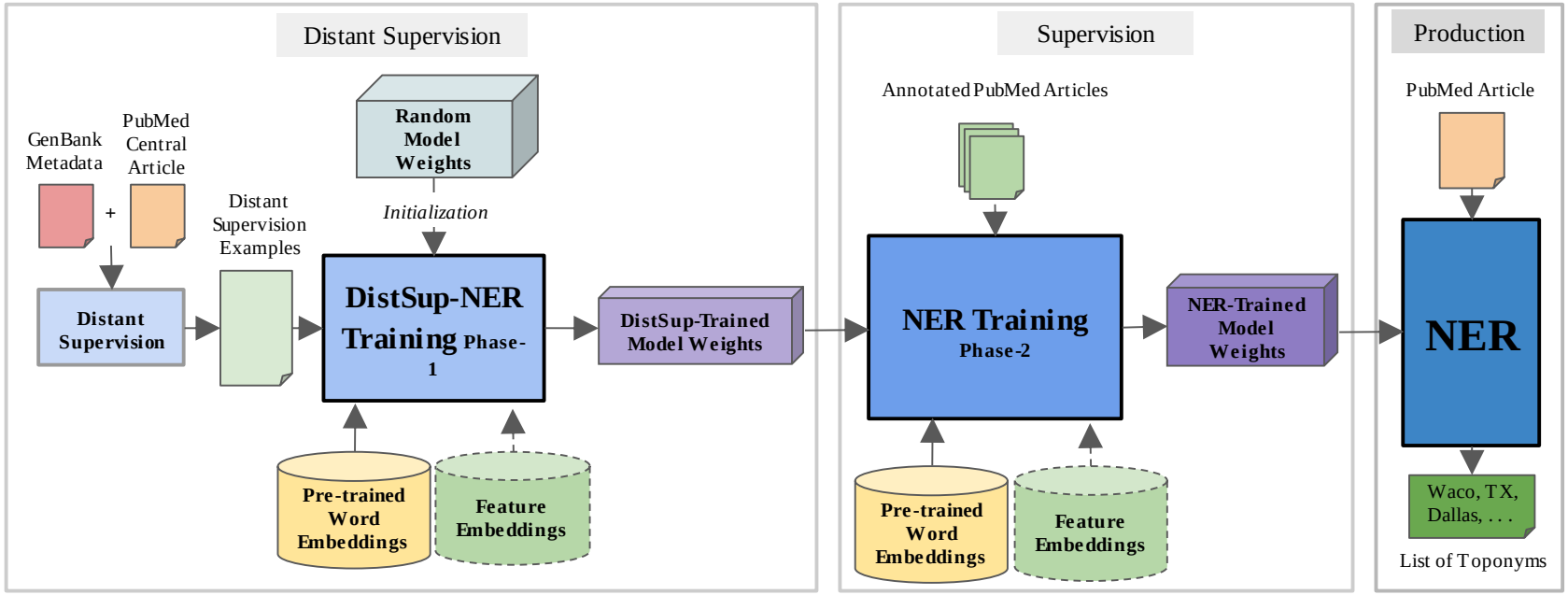
- 10 (Lockridge et

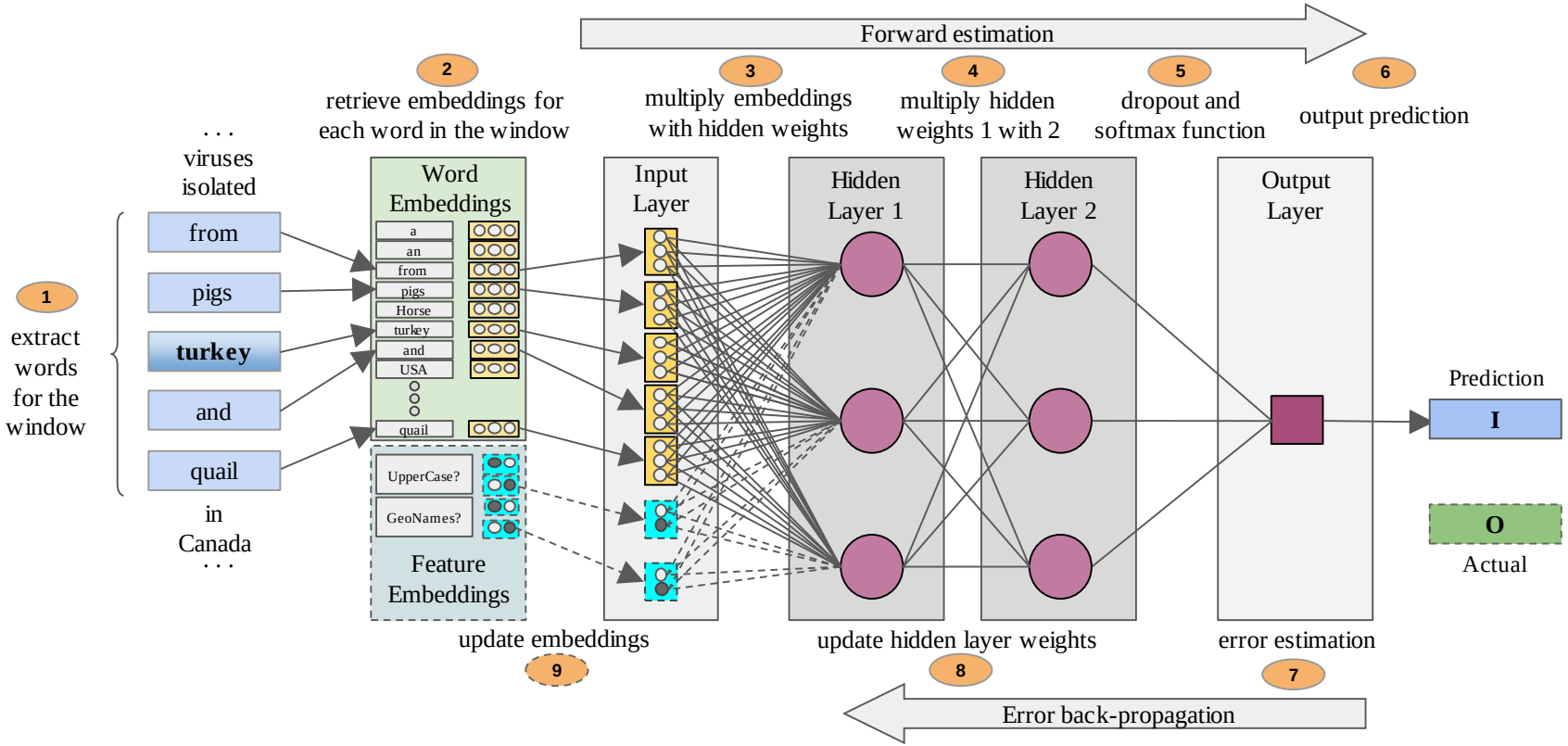
10 (Lockridge et al

(Lockridge et al .

Lockridge et al . ,

Layered training





Collobert, Ronan, et al. "Natural language processing (almost) from scratch." *Journal of Machine Learning Research* 12.Aug (2011): 2493-2537.

Improved performance

Implementation	P	R	F1
Knowledge-based *(Weissenbacher et. al. 2015)*	0.58	0.88	0.70
CRF-All *(Weissenbacher et. al. 2017)*	0.85	0.76	0.80
Stanford-NER	0.89	0.85	0.872
Train $_{D_{train}}$ and Test $_{D_{test}}$	0.96	0.86	0.910
Train $_{D_{dist}+D_{train}}$ and Test $_{D_{test}}$	**0.97**	**0.89**	**0.927**

92.7% on tokenwise evaluation

91.5% on strict evaluation

Limitations and Future Work

- Potential for improving performance
  - Deal with table data
  - Second layer of supervision for trying advanced recurrent models like Bi-LSTM-CRFs
- What is the improvement to resolution/normalization?
- Any improvements to the phylogeographic models?
- Distant supervision *and* Supervision - a systematic analysis of how much data for both is sufficient
- Validate with other entities like hosts, virus, genes etc.

One last thing . . . since we are at ISMB

Tell your peers:

Even though the field says *country*

please add in addition to *country* information:

- state
- county (if available)
- city (if available)

Softwares and Applications

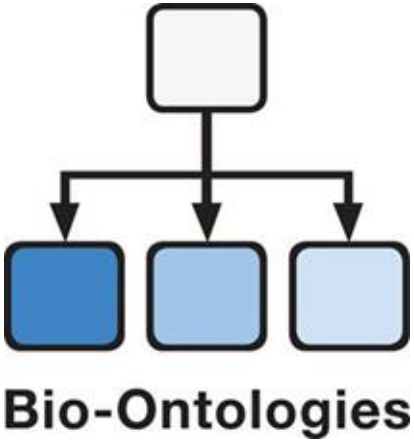
NER (source code) : https://github.com/amagge/ner-topo-ff

GeoBoost v1 : https://tinyurl.com/geoboost (Tahsin *et. al. 2017*)

ZoDo (under development): https://zodo.asu.edu/zodo

ZooPhy (under development): https://zodo.asu.edu/zoophy

Acknowledgments



For the travel grant to present at ISMB

Funding and Acknowledgments

Principal Investigators:

Dr. Matthew Scotch

Dr. Graciela Gonzalez

Collaborators:

Dr. Davy Weissenbacher

Dr. Abeed Sarker

Annotators:

Karen O'Connor

Megan Rorison

Briana Trevino

NIH National Institute of Allergy and Infectious Diseases

ASU Biodesign Institute Arizona State University

ASU Department of Biomedical Informatics Arizona State University

Penn Department of Biostatistics Epidemiology & Informatics

NVIDIA

Thank you!

Questions?

ASU College of Health Solutions
ARIZONA STATE UNIVERSITY

Social Media Mining for Pharmacovigilance: challenges and opportunities

Case-control studies from Twitter???

Health Language Processing Lab – Penn IBI

Graciela Gonzalez-Hernandez, PhD

email: gragon@pennmedicine.upenn.edu

@gracielagon

Funded by NLM/NIH Grant R01LM011176

Perelman School of Medicine
University of Pennsylvania

SM data for pharmacovigilance studies

- **There are about 38,220 tweets / minute about the user's current medical conditions**[1,2,3]
- **Patient reporting brings different perspective**, more detail, info on severity and impact of ADRs in daily life. (34 studies - PMID 27558545).
- **Abundant adverse event reports in SM, with a** higher frequency of adverse events, particularly for 'mild' adverse events. (51 studies = PMID 26271492).

[1]http://www.pewinternet.org/fact-sheets/health-fact-sheet/
[2]http://www.statista.com/statistics/282087/number-of-monthly-active-twitter-users/
[3]http://www.internetlive**stats**.com/twitter-**statistics**/

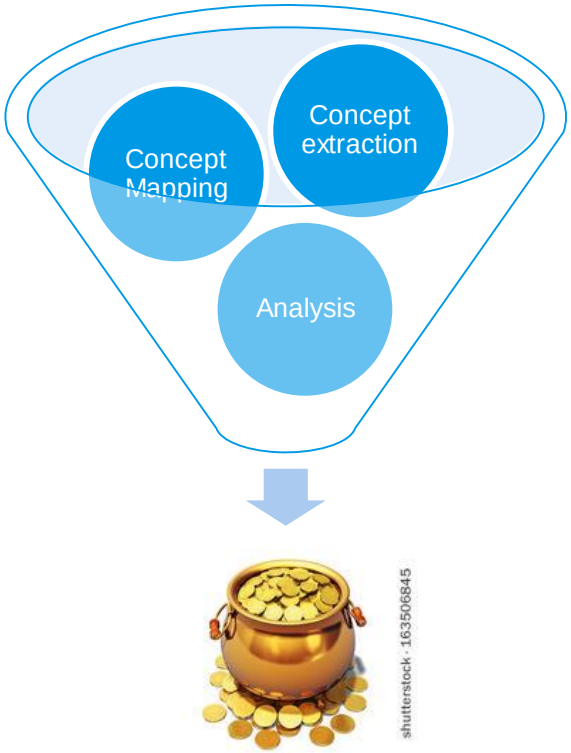
Work during first funding cycle

- Our prior work addressed the challenges of automatically collecting and processing SM reports on medication side effects.
- It resulted in over 16 publications, numerous annotated datasets, and novel automatic language processing (NLP) methods for side effect mention extraction and normalization to a standardized vocabulary (the UMLS/MedDRA).

Overview

- **Develop novel NLP methods to leverage SM data for specific pharmacovigilance efforts that are hindered by known drawbacks of SRSs.**
- **We focus on methods to facilitate the use of SM data for exploring**
  - (a) factors affecting medication adherence and persistence among the general population (Aim 1), and
  - (b) possible associations between medications taken during pregnancy and pregnancy outcomes (Aim 2).
- **These are areas of significant impact for which SM data could meaningfully complement current PV efforts**

Social Media Mining pipeline



The Aims

- ***Develop and evaluate NLP methods to identify non-adherence and non-persistence and related information from Twitter data.***
- ***Develop and evaluate NLP methods to identify medication use during pregnancy and pregnancy outcomes from Twitter data.***
- ***Develop and evaluate methods for automatic selection of control groups to address the challenge faced when information from SM is to be used for epidemiological studies.***

Aim 1

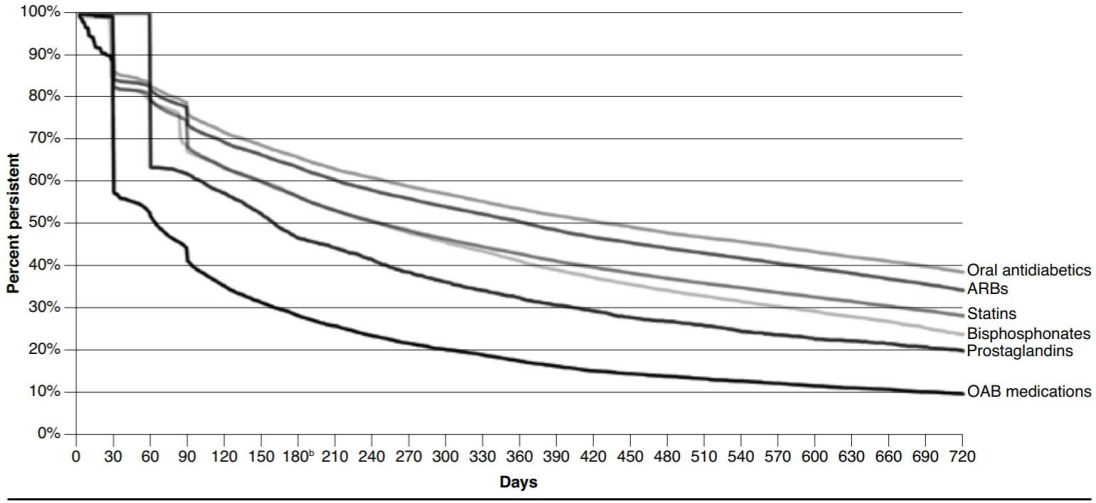
- ***Develop and evaluate NLP methods to identify non-adherence and non-persistence and related information from Twitter data. The methods will***
  - dynamically collect a cohort of SM users that stopped taking or switched medications, did not fill a prescription, or altered their treatment,
  - extract information from the user's *timeline* (publicly available postings over time) and *conversation threads* (postings by the user and others in reply to a posting of interest) relevant to
    - (a) an expressed reason for these actions,
    - (b) dosage/duration of treatment,
    - (c) concomitant treatments, and
    - (d) diagnosed health conditions.

Adherence/persistence studies from SM

- **Social media may be particularly useful for identifying sources of intolerability that lead to non-adherence/non-persistence**
- **These are often not reported by physicians or patients through standard means because are considered "mild", "not serious" or are unexpected**
- **Significant problem, given that, on average:**
  - 30% of treated patients have a beneficial response
  - 30% do not respond
  - 10% have only side effects
  - 35%-70% are non-adherent / non-persistent, often due to side-effects or perceived/real non-response

6-month persistence rate

FIGURE 2 Time to Discontinuation[a] of 6 Chronic Therapy Classes, Allowing for 60-Day Treatment Gap



- prostaglandin analogs 47%
- statins 56%
- bisphosphonates 56%
- oral antidiabetics 66%
- angiotensin II receptor blocker 63%
- overactive bladder medications 28%

“I stopped taking” & “made me”

Aim 2

- ***Develop and evaluate NLP methods to identify medication use during pregnancy and pregnancy outcomes from Twitter data.***
  - Development and evaluation of NLP methods to dynamically collect a cohort of SM users who report a pregnancy, and
  - Methods to extract information from the user's timeline to
    - (a) distinguish when mention of a medication indicates possible intake of it,
    - (b) infer the estimated pregnancy timeframe (beginning and end of pregnancy), and
    - (c) extract or infer pregnancy outcomes from those postings (including at least live birth, fetal death, hemorrhage, miscarriage, low-birth weight, pre-term birth, and reported congenital malformations)

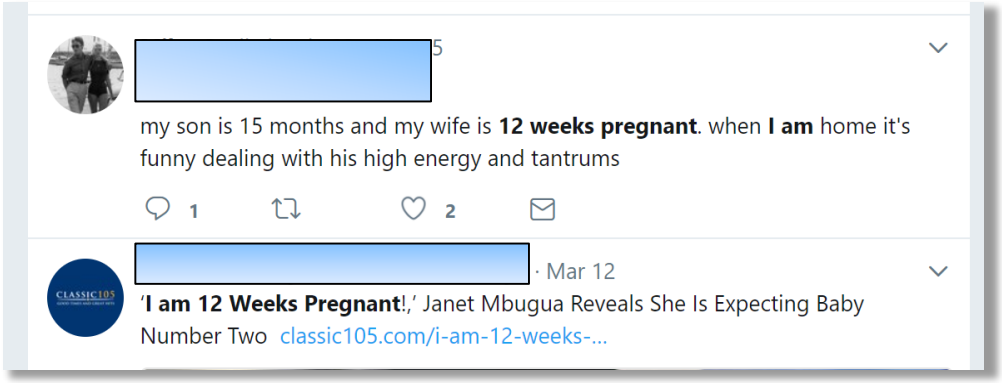
Case-control study with SM data?

- **Select cohort of pregnant women from SM[1]**
  - About 120 thousand, 700 million tweets
- **Within that, find cases of interest**
  - *"Women who gave birth to a child with a birth defect and whose public tweets include tweets during pregnancy"*
- **Annotate (100% of the data found)**
- **Find matching (control) subjects**
  - *"Women pregnant around the same time, for whom there is no evidence that their child was born with a birth defect"*

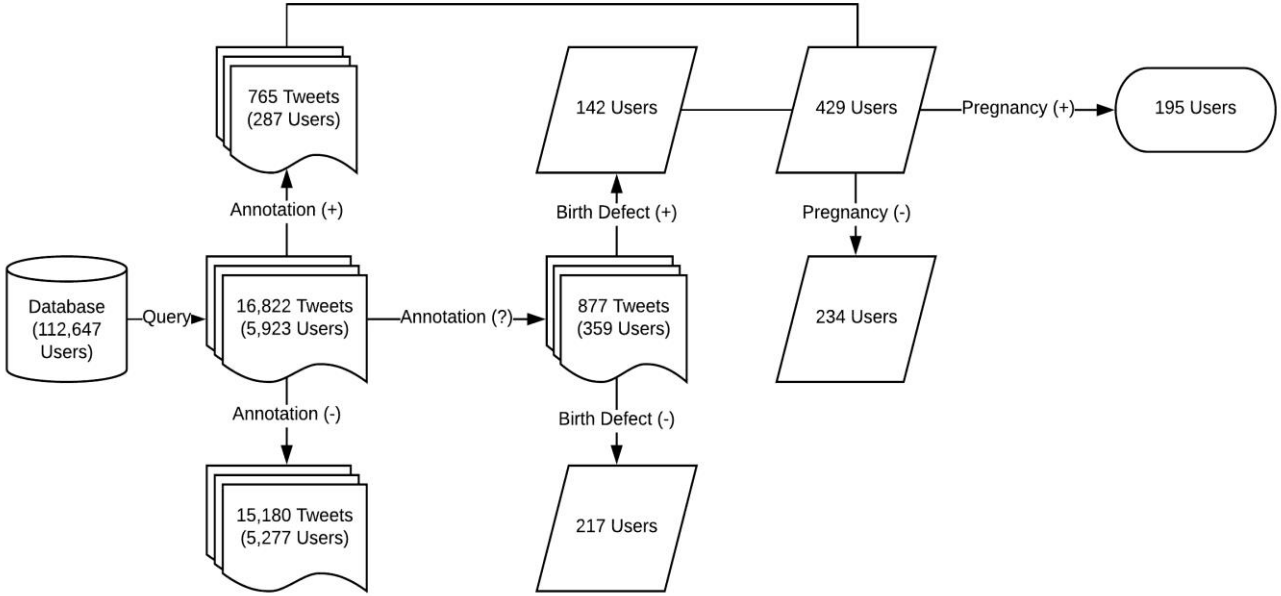
1. Sarker *et al* Discovering cohorts of pregnant women .. **J Med Internet Res**. 2018

From Twitter, “I am 12 weeks pregnant”

From Twitter, noise



Finding cases – birth defects cohort



Klein et al, 2018 (in preparation)

Birth defects data from Social Media

	Cases (n=197)	Controls (n=196)	OR or t-test [95% CI]	P-value
Age				
Median Age (IQR)	23 (20 to 28)	21 (19 to 23)	2 (1 to 3)	0.0001
Mean Age (range)	25 (17 to 42)	22 (16 to 37)	2.52 (1.38 to 3.66)	<0.0001
Women <30 years	80% (134/168)	91% (129/141)	0.37 (0.17 to 0.77)	0.004
Women <35 years	93% (156/168)	98% (138/141)	0.28 (0.05 to 1.08)	0.04
Missing data on age	14% (28/196)	28% (55/196)	0.43 (0.25 to 0.73)	0.0008
Race/Ethnicity				
Caucasian	73% (120/164)	55% (102/184)	2.19 (1.36 to 3.54)	$chi^2 = 23.69$, d.f. = 5 P < 0.001
Black	13% (22/164)	27% (51/184)	0.40 (0.22 to 0.72)	
Hispanic	9% (14/164)	12% (21/184)	0.72 (0.33 to 1.56)	
Asian	2% (4/164)	3% (5/184)	0.90 (0.17 to 4.24)	
Other (Islander, Native American/Indian, Multiracial/Mixed)	2% (4/164)	2% (5/184)	0.90 (0.17 to 4.24)	
Missing data on race	16% (32/196)	6% (12/196)	0.99 (1.44 to 6.58)	

Klein et al, 2018 (in preparation)

Thank you!

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HLP lab (datasets and software available):
https://healthlanguageprocessing.org