SEMI-SUPERVISED MULTI-INSTANCE INTERPRETABLE MODELS FOR FLU SHOT ADVERSE EVENT DETECTION

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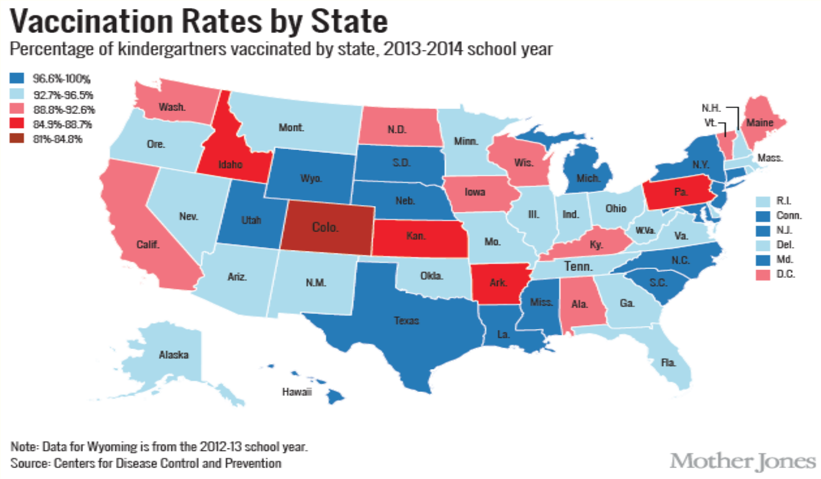
Introduction: Background.



- Vaccinations are now available worldwide.
  - flu vaccination coverage during the 2013-14 flu season was 46.2 percent of the whole U.S. population.
- Vaccines can cause adverse reactions and even lead to death.
  - A woman died of multiorgan failure and respiratory distress in Spain on October 24, 2004, which is caused by a yellow fever vaccination.
- It is imperative to develop a system which can identify adverse events promptly and accurately.

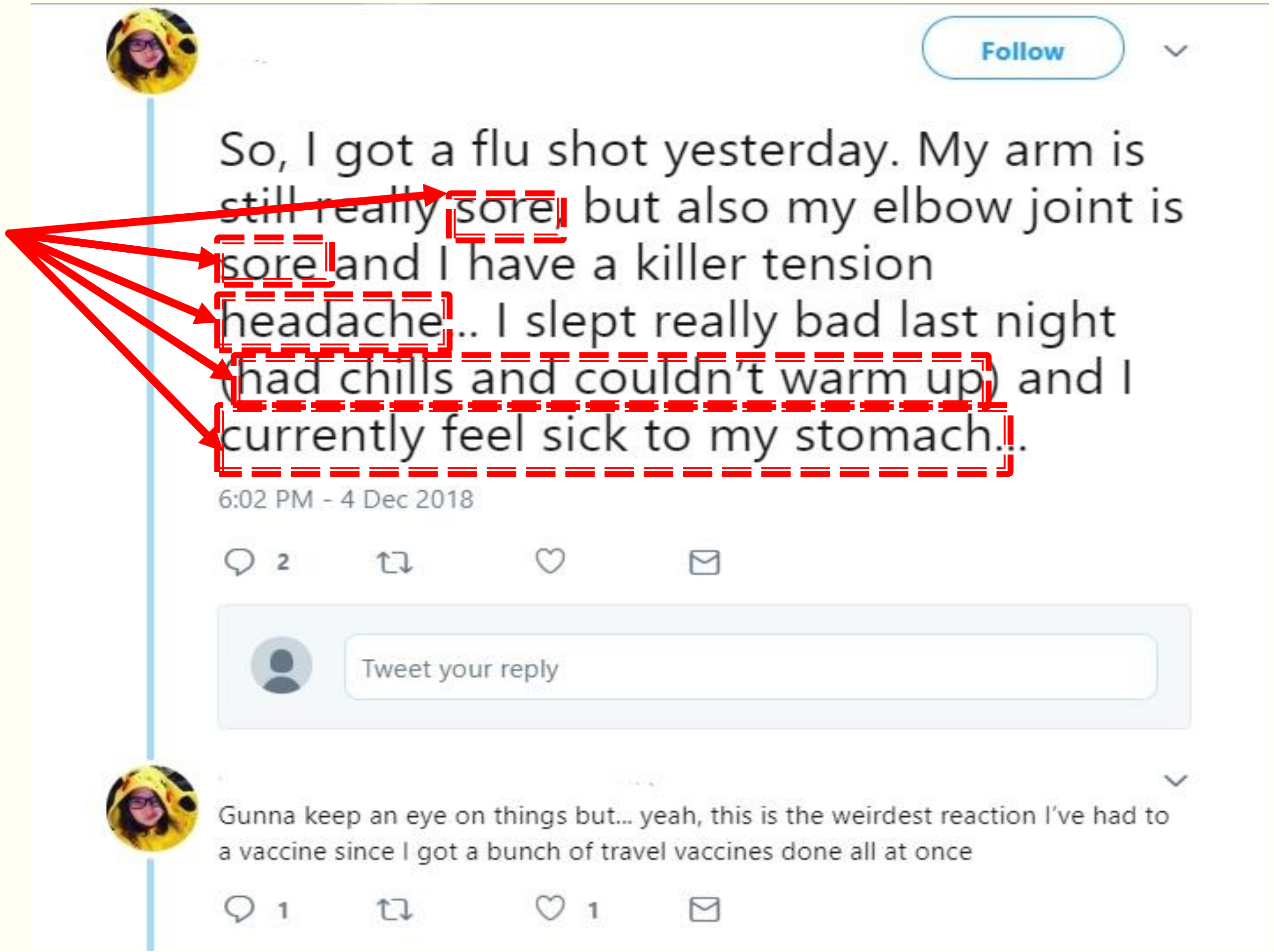
Introduction: Formal reporting systems VS Social media.

Disadvantages of formal reporting systems	Advantages of social media
Only a few people submit reports due to complex procedures involved.	Social media messages reflect the public’s mood and trend.
A serious time delay to release reports due to administrative processing. E.g., The FDA’s reporting system releases data every three months.	Social media messages can be posted instantly by portable mobile devices.

- Social media, as platforms to disseminate information, have begun to be used in several healthcare applications.

Introduction: An example of flu shot adverse events.

Symptom descriptions



Introduction: Challenges of flu shot adverse event detection.

- 1.The sparsity of indicative messages:

➢ Only 7.22% of messages from positive users were indicative of adverse reactions.

➢ About 33.33% users are positive users who are affected by adverse events.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"I'm about to go get my flu shot! \ud83d\ude16\ud83d\udc89", "geocoded": {"city": "San An
"Just got my flu shot, &amp; it hurt so bad. Thanks skinny arms with no muscle or fat :("
"RT @TwoInLoveEC: I talk about my relationship a lot. That's just how it is. Like it, or
"I'm so ready to get through tomorrow so it can be the weekend already!", "geocoded": {"c
"RT @GFstatus: I can find a flaw in every other I guy I look at besides my boyfriend #hes
"Thank you grandpa for making me tacos this morning! Now I can function.", "geocoded": {"
"Me &amp; Anthony laughed so hard this morning. We do the funniest things. \ud83d\ude02\u
"RT @anthonyandrew18: @_AlexisMariah only because I threw the tortilla at the window!\ud8
"@anthonyandrew18 hahaha &amp; the egg stuck on the window \ud83d\ude02\ud83d\ude02\ud83d
"&amp; the stressing begins on my math final next week. \ud83d\ude23", "geocoded": {"city
"One of these will be my two year anniversary gift from my boyfriend! #Tiffany&amp;Co &lt
"Yayyyy! Pretty much the last day of classes were today! Just next week of finals &amp; i
"Going with babe to pick up some barbecue plates!\ud83d\udc4c", "geocoded": {"city": "San
"Going to Edible Arrangements to get something for my mommy's birthday tomorrow. \ud83d\u
"Spoiled myself to some VS &lt;3 http://t.co/Ga96KaCP", "geocoded": {"city": "San Antonio
"I'm already all depressed knowing I won't get to see Anthony tomorrow. \ud83d\ude29", "g
"If your boyfriend tweets more than you, that's a problem..", "geocoded": {"city": "San A
"I can't fucking stand hypocrites.", "geocoded": {"city": "San Antonio", "country": "Unit
"I also want a matching bracelet with the necklace my boyfriend is gonna get me.. #Tiffan
"I forget I even have my nose pierced anymore.", "geocoded": {"city": "San Antonio", "cou
"RT @Gf_Moments: My boyfriend is not whipped, he respects me. #YoureJustJealous", "geocod
"RT @DGreen_14: Spurs v Rockets 830pm eastern...tune in", "geocoded": {"city": "San Anton
"My upgrade is in March or April. Maybe I'll get the iPhone 5.", "geocoded": {"city": "Sa
"The pretty lights in my room! All ready for Christmas! \ud83d\udc99\ud83c\udf84 http://t
```


Only one tweet which indicates adverse reactions.

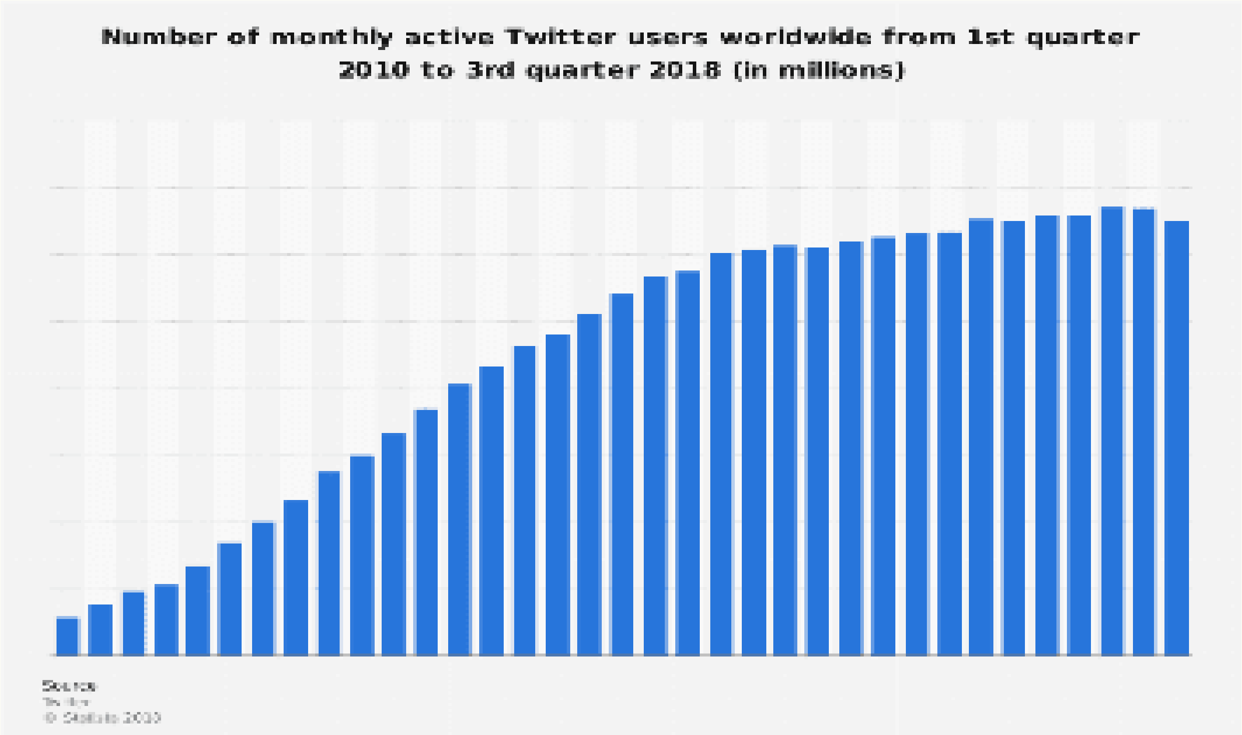
Introduction: Challenges of flu shot adverse event detection.

- 2. Cost of labeling health states.

Number of active Twitter users(million) in 2018	Number of tweets per month user has in 2018	Number of tweets per month(million) in 2018
335	50	15000

➢ In order to label accurately, all tweets from a user should be checked thoroughly.

➢ Labeling cost increases with the surge of Twitter users.



Problem Formulation: Mathematical formulation.

- Flu shot adverse event detection task aims to detect the health states of Twitter users based on their Twitter messages.

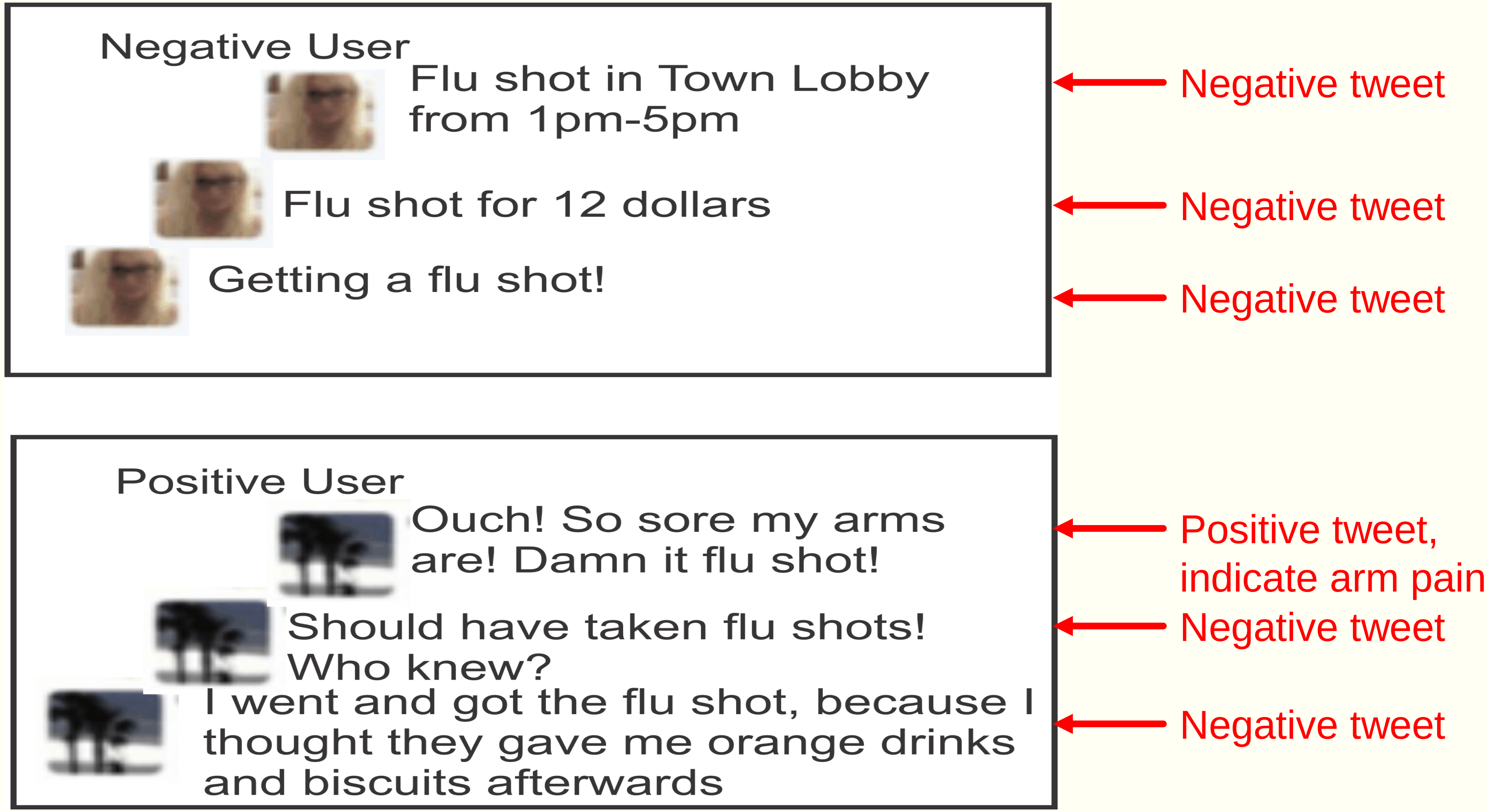
- Problem input: $X_{u,i}$ (the i-th tweet from user u).
- Problem output: Y_u (the health state of user u).
- Then we want to learn the mapping

A bag of tweets from user u

$$f:\{\boxed{X_{u,1}, X_{u,2}, \cdots, X_{u,n_u}}\} \rightarrow Y_u$$

- $Y_u = 1$ denotes that user u is positive(i.e., affected by adverse events), while
- $Y_u = 0$ denotes that user u is negative(i.e., unaffected by adverse events).

Problem Formulation: An illustration.



Our method: Semi-supervised Multi-instance learning model.

- Select representative tweets automatically.

Positive Users	Negative users
At least one tweet indicates abnormal description	None of tweets should imply any abnormal description

- This idea can be summarized as “**the max rule**”.

$$p_{u,i} = sigmoid\left(X_{u,i}; \beta; \beta_0\right)$$

$$p_u = \max_{i=1,\cdots,n_u} p_{u,i}$$

$$H_u(\beta, \beta_0) = -Y_u \log p_u - (1 - Y_u) \log(1 - p_u)$$

➢ The max rule biases for positive users and hence

reduces the imbalance from a majority of negative users.

p_u: the probability of labeling user u as positive.
$p_{u,i}$: the probability of labeling user u as positive from the i-th tweet.
$X_{u,i}$: The i-th tweet from user u.
β: The coefficient vector of the classifier.
β_0: The intercept of the classifier.
n_u: The number of tweets from user u.
$sigmoid(\cdot)$: The sigmoid function.
$H_u(\cdot)$: The log-loss function.

Our method: Semi-supervised Multi-instance learning model.

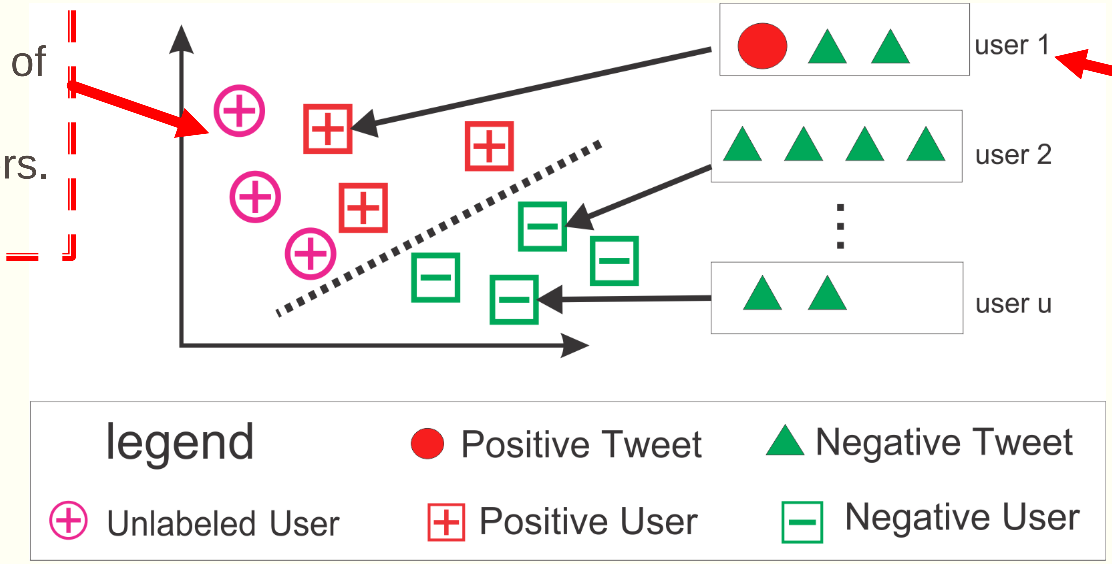
- Utilize unlabeled users.

p_u	>0.5(Positive)	<0.5(Negative)
$L(\cdot\,;\cdot)$	$-\log(p_u)$	$-\log(1-p_u)$

$$L_u(\beta;\beta_0) = -\min(\log(p_u)\,,\log(1-p_u))$$
$$= \max(-\log(p_u)\,,-\log(1-p_u))$$

p_u: the probability of labeling user u as positive.
β: The coefficient vector of the classifier.
β_0: The intercept of the classifier.
$L_u(\cdot\,;\cdot)$: The semi-supervised loss function.

Introduce unlabeled user to
1. Improve the generalization ability of the classifier.
2. Reduce the noise by labeled users.



The max rule: a positive tweet is indicative of a positive user.

Our method: Semi-supervised Multi-instance learning model.

- Overall model.

$$(\beta^*, \beta_0^*) = argmin_{\beta,\beta_0} \underbrace{\boxed{\sum_{u \in U_1} H_u(\beta;\beta_0)}}_{\text{Supervised Log-loss from labeled users}} + \underbrace{\boxed{\nu \sum_{u \in U_2} L_u(\beta;\beta_0)}}_{\text{Semi-supervised Log-loss from unlabeled users}} + \underbrace{\boxed{\lambda \|\beta\|_1}}_{\text{Regularization term}}$$

β: The coefficient vector of the classifier.
β_0: The intercept of the classifier.
ν, λ: two tuning parameters.
U_1: labeled user set.
U_2: unlabeled user set.

Optimization: nSSM and sSSM.

- The nonsmooth model(sSSM):

$$
\begin{aligned}
(\beta^*, \beta_0^*) = \arg\min_{\beta,\beta_0} \sum_{u\in U_1} & (\log(1+\exp(\max_{i=1,\cdots,n_u}(X_{u,i}\beta+\beta_0))) \\
& - Y_u \max_{i=1,\cdots,n_u}(X_{u,i}\beta+\beta_0) + \lambda\|\beta\|_1 \\
& + \nu \sum_{u\in U_2} (\log(1+\exp(\max_{i=1,\cdots,n_u}(X_{u,i}\beta+\beta_0))) \\
& - \min(\max_{i=1,\cdots,n_u}(X_{u,i}\beta+\beta_0, 0))) \qquad (5)
\end{aligned}
$$

- The smooth model(sSSM) model is obtained by approximating nonsmooth terms max(·) and min(·) by the smooth max function:

- $\max(x_{i=1,\cdots,n}) \simeq \frac{\log\sum_{i=1}^{n} e^{Ax_i}}{A}, A > 0$
- $min(x_{i=1,\cdots,n}) \simeq \frac{\log\sum_{i=1}^{n} e^{Bx_i}}{B}, B < 0$

$$
\begin{aligned}
(\beta^*, \beta_0^*) = \arg\min_{\beta,\beta_0} \sum_{u\in U_1} & (-Y_u \log p_u - (1-Y_u)\log(1-p_u)) \\
& + \nu \sum_{u\in U_2} \log(e^{-B\log(p_u)} + e^{-B\log(1-p_u)})/B + \lambda\|\beta\|_1 \\
& s.t.\ p_u = 1/(1+(\sum_{i=1}^{n_u} e^{A(\beta X_{u,i}+\beta_0)})^{-1/A}) \qquad (6)
\end{aligned}
$$

- Two models are solved by Alternating Direction Method of Multipliers(ADMM).

Experiments: Data Setup.

- Synthetic Dataset

- 10000 bags and 55,195 instances.
- Each bag had at most 10 instances. Each instance is generated either by $N(\mu_1, I)$ or $N(\mu_2, I)$.
- $N(\cdot,\cdot)$ is a multivariate normal distribution of a 100-dimensional vector.
- μ_1 is a zero vector, μ_2 is a vector whose elements are all 0.3, I is an identity matrix.
- One bag was considered as positive if at least one of the instances was generated by $N(\mu_2, I)$.
- One bag was considered as negative if all of the instances was generated by $N(\mu_1, I)$.
- 1974 bags were positive while 8026 bags were negative.

Experiments: Data Setup.

- Twitter data: Two-stage data collection.

➢ The first stage:

➢ Number of retrieved Tweets: 11,993,211,616.

➢ Time interval: between Jan 1,2011 and Apr 15,2015.

➢ Country: United States.

➢ The second stage:

➢ Queried these users again within 60 days since they received vaccination.

User class	Number of users	Number of corresponding Tweets
Positive users	566	41438
Negative users	1006	
Unlabeled users	1567	48847

Experiments: Parameter Settings

- Two tuning parameters ν and λ were both set to 1 based on the 5-fold cross validation on the training set.
- A and B in the sSSM model were set to 10 and -10, respectively.
- We also investigate the effect of ρ (a key parameter in the ADMM algorithm) on the classification performance. Three different types of ρ were chosen:
- ρ(1). The constant $\rho = 1$.
- ρ(2). if $r^k > 4s^k$, then $\rho^{k+1} = 2\rho^k$. If $4r^k < s^k$, then $\rho^{k+1} = \rho^k/2$ with $\rho^0 = 1$. Here r and s are primal and dual residuals in ADMM.
- ρ(3). $\rho^{k+1} = \rho^k + 2/MAX\_ITER$ with $\rho^0 = 1$, where MAX_ITER is the optimal iteration. The MAX_ITER in the nSSM and sSSM model were set to 2000 and 20, respectively.

Experiments: Metrics and comparison methods

- Metrics:

	Negative	Postive
negative	TN	FP
positive	FN	TP

- Accuracy(ACC)=(TN+TP)/(TN+FP+FN+TP)
- Precision(PR)=TP/(FP+TP)
- Recall(RE)=TP/(FN+TP)
- F-score(FS)=2RE*PR/(PR+RE)
- Area Under ROC curve(AUC): compute the Area under Receiver Operating Characteristic (ROC) curve.
- Area Under PR curve(AUPR): compute the Area under Precision Recall(PR) curve.

- Comparison methods:

- Multi-instance learning: Constructive Clustering based Ensemble (CCE), Multi-instance learning with graph (miGraph) Multi-instance Learning based on the Vector of Locally Aggregated Descriptors representation (miVLAD), Multi-instance Learning based on Fisher Vector representation (miFV).
- Semi-supervised learning: WEakly LabeLed Support Vector Machines (WELLSVM).

Experiments: Classification performance on synthetic dataset

Multi-instance learning

Semi-supervised learning

Methods	ACC	PR	RE	FS	AUC	AUPR
CCE	0.8408	0.8166	0.2494	0.3818	0.9067	0.6991
miGraph	0.8026	0	0	0	0.5	0
miFV	0.8380	0.6998	0.3179	0.4241	0.7875	0.5666
miVLAD	0.8364	0.6634	0.3458	0.4527	0.7796	0.5563
WELLSVM	0.7823	0.4804	0.2978	0.3125	0.7694	0.4284
nSSM(ρ(1))	0.9124	0.8383	0.6893	0.7563	0.9442	0.8488
nSSM(ρ(2))	0.9105	0.8631	0.6510	0.7411	0.9433	0.8471
nSSM(ρ(3))	0.9125	0.8397	0.6883	0.7562	0.9441	0.8486
sSSM(ρ(1))	0.9121	0.8610	0.6622	0.7481	0.9449	0.8504
sSSM(ρ(2))	0.9125	0.8545	0.6718	0.7515	0.9446	0.8496
sSSM(ρ(3))	0.9127	0.8551	0.6723	0.7521	0.9446	0.8496

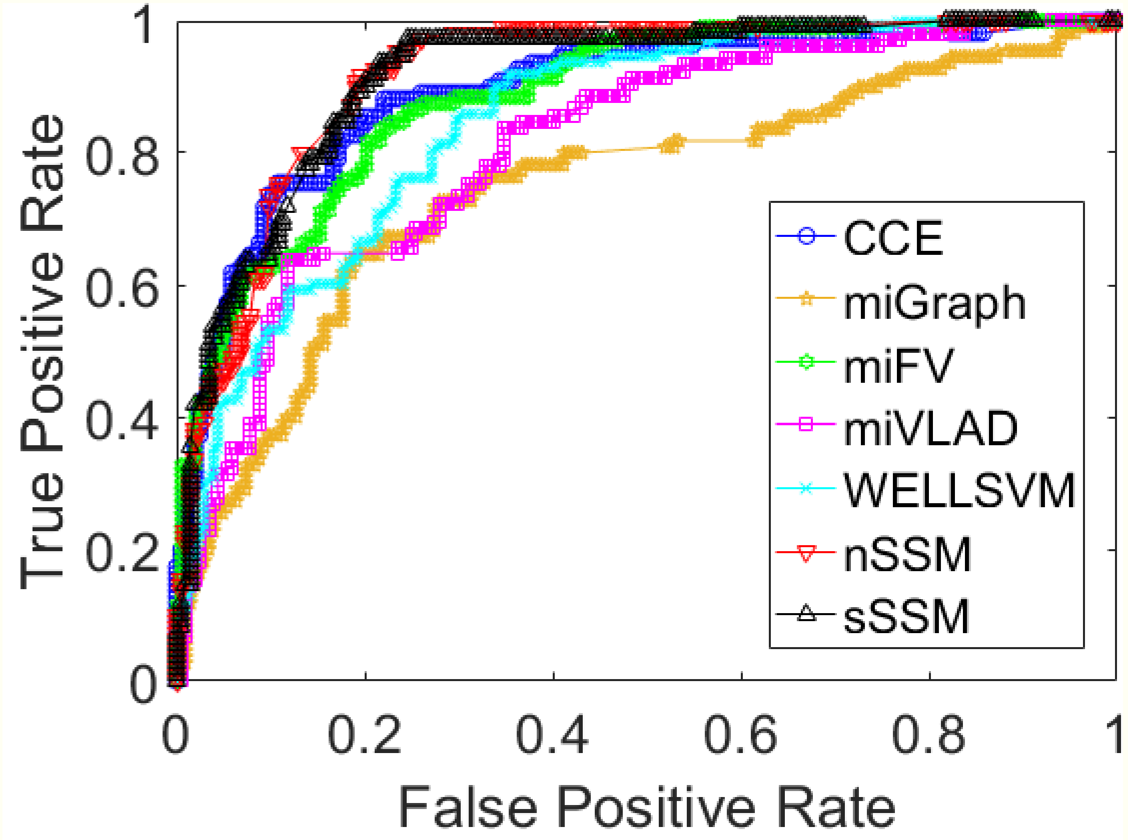
- nSSM and sSSM performed the best in general.
- The semi-supervised learning method outperformed multi-instance learning methods.

Experiments: Classification performance on Twitter dataset

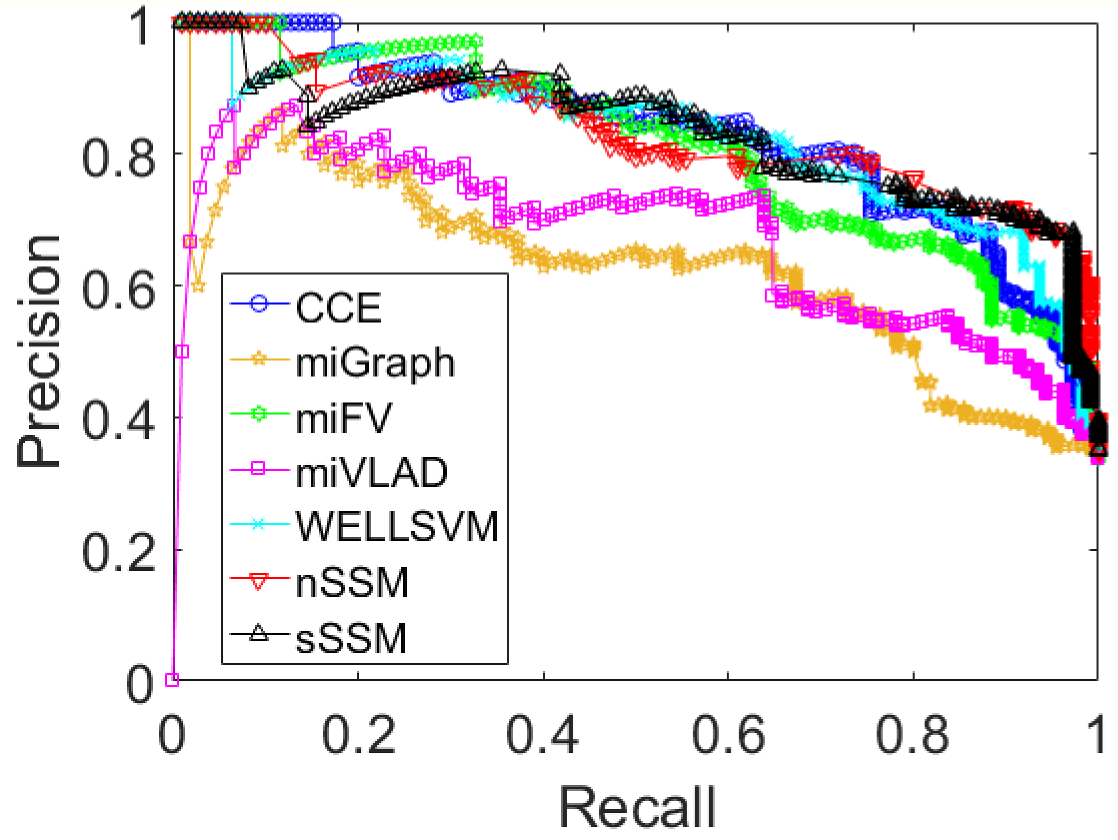
	Methods	ACC	PR	RE	FS	AUC	AUPR
Multi-instance learning	CCE	0.7405	0.7616	0.4124	0.5308	0.8118	0.7136
	miGraph	0.7188	0.6779	0.4229	0.5194	0.7415	0.6246
	miFV	0.7761	0.7324	0.6010	0.6595	0.8405	0.7564
	miVLAD	0.7538	0.6721	0.6217	0.6453	0.7841	0.6806
Semi-supervised learning	WELLSVM	0.6985	0.8635	0.1942	0.3111	0.8373	0.7271
	nSSM(ρ(1))	0.8015	0.7813	0.6236	0.6931	0.8804	0.7870
	nSSM(ρ(2))	0.8009	0.7790	0.6234	0.6924	0.8745	0.7827
	nSSM(ρ(3))	0.7977	0.7356	0.6872	0.7098	0.8755	0.7775
	sSSM(ρ(1))	0.7901	0.7497	0.6234	0.6802	0.8699	0.7761
	sSSM(ρ(2))	0.7913	0.7572	0.6200	0.6810	0.8696	0.7755
	sSSM(ρ(3))	0.7939	0.7535	0.6344	0.6876	0.8673	0.7726

- nSSM and sSSM performed the best in general.
- The semi-supervised learning method outperformed multi-instance learning methods.

Experiments: ROC and PR curve on the Twitter dataset.



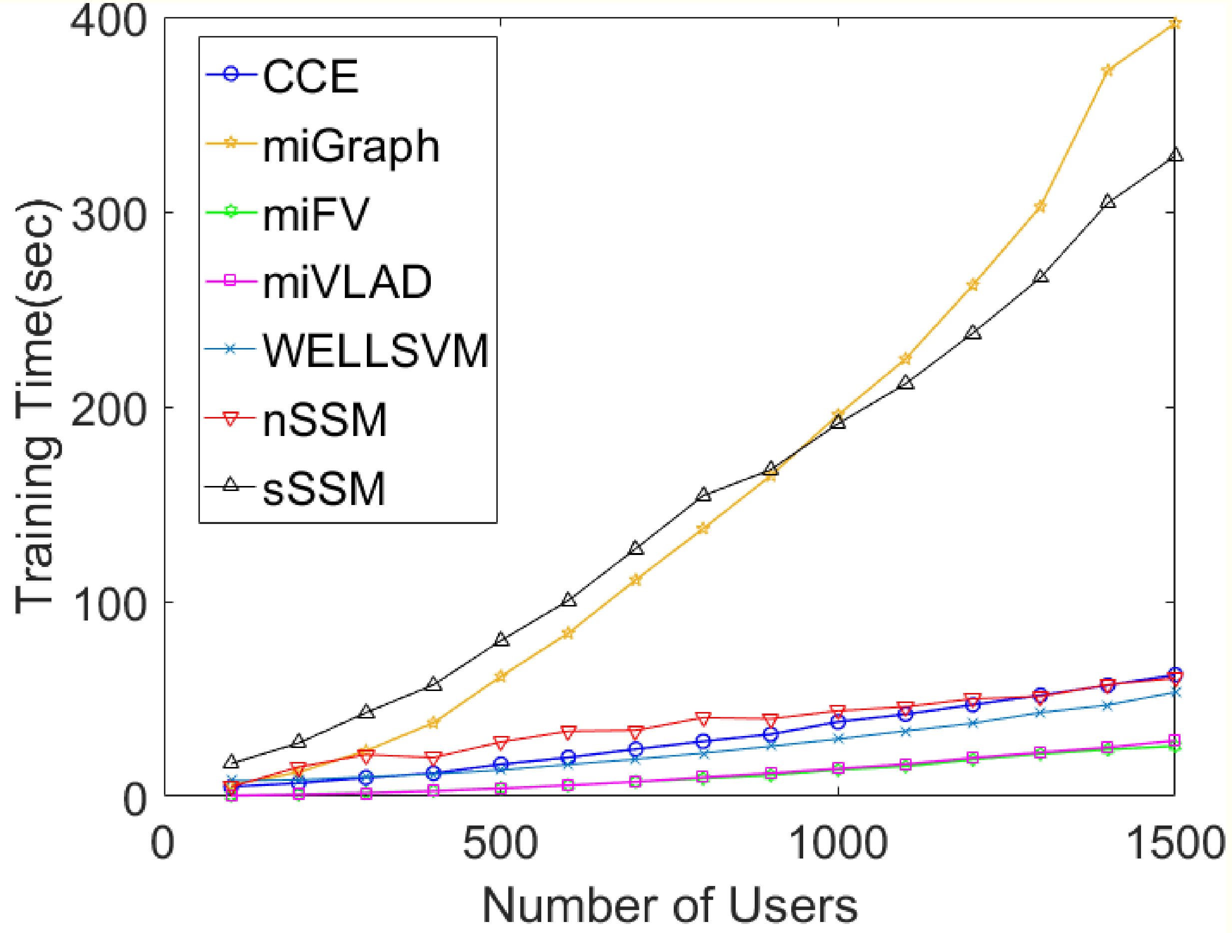
ROC curve

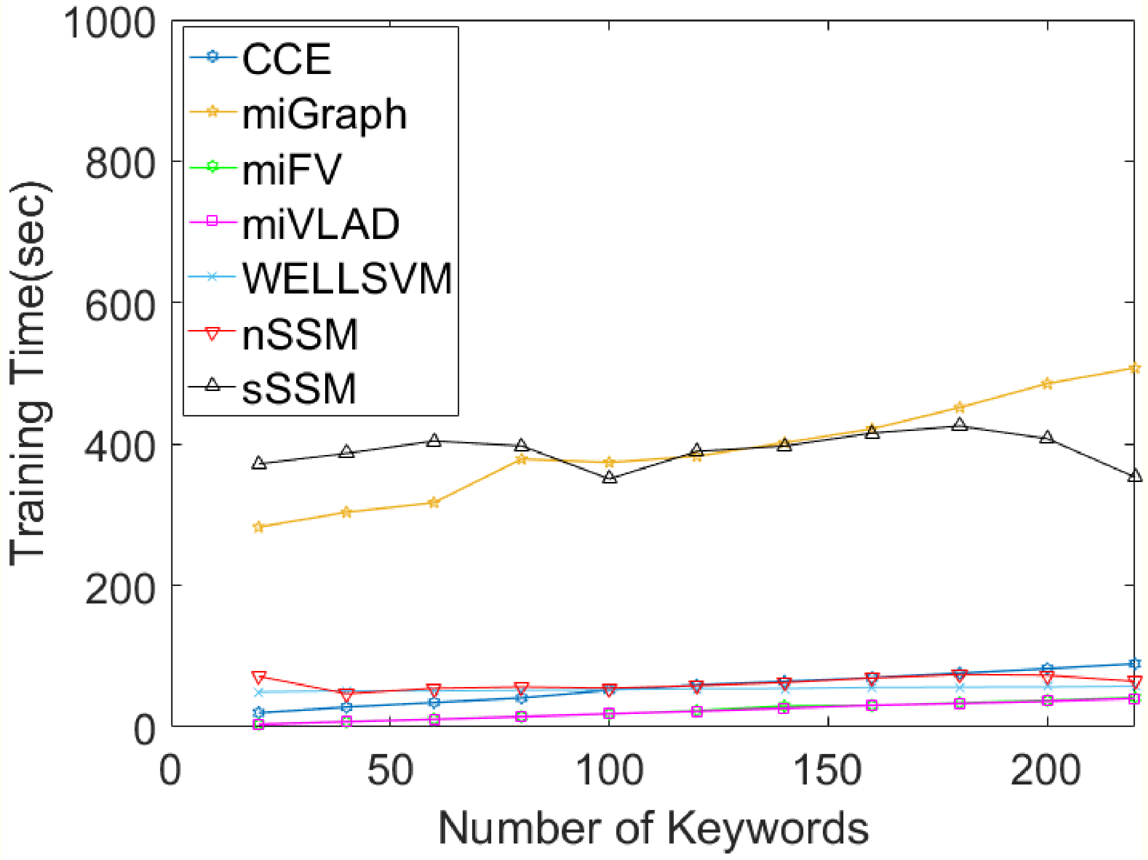


PR curve

- nSSM and sSSM performed the best in general.
- The semi-supervised learning method outperformed multi-instance learning methods.

Experiments: Scalability analysis.





- Nearly all methods increase linearly with number of features and petitions.

Experiments: Case studies.

adverse-relevant

Rank	Positive Tweets	Negative Tweets
1	headache	bad
2	sore	feeling
3	sick	cold
4	arm	cause
5	throat	face
6	swollen	flu
7	bad	shot
8	flu	heart
9	shot	sick
10	pain	cool

Experiments: Case studies.

Symptoms	Positive tweets extracted by nSSM
arm pain	Flu shot this afternoon = very sore arm this evening
	My arm still sore from that flu shot
	As soon as I walk in my apartment my arm decides to remind me I got a flu shot today
	I got my flu shot. Hate how it hurts when they give the shot they do it slow arm hurts like hell. hate doctors and shots.
	How does a simple flu shot immobilize ones left arm? Im weak as hell... sore
headache	got a flu shot yesterday and here comes a headache.
	Oohh this headache... from flu shots?
	Flu shot this morn. Now I have a headache. ARGH.
neck pain	I got a flu shot. Body aches are real. The back of my neck is killing me :(
throat pain	Flu shot update: My throat continues to feel tight and clogged, although not so much that I can't breathe.
	Flu shot dooo Walnut in my throat I cant feel my face.
fever	Receive a flu shot several days ago, now my nose is clogged, my eyes are heavy, my throat is so sore that I can't talk and I'm so tired, I can't stop coughing! small fever.

- Arm pain was the most common symptom; Headache, neck pain and throat pain happened sometimes.

Our Dataset

The link of our dataset and code

http://mason.gmu.edu/~lzhao9

Feel free to contact Junxiang Wang (jwang40@gmu.edu) if you have any questions.

Thank you. Any questions?