Machine-Learning Approaches to Signal Detection in Infectious-Disease Epidemiology

Workshop on Infectious Disease Surveillance
University of Bern, 25 November 2019

Auss Abbood, Rüdiger Busche, **Stéphane Ghozzi**, Alexander Ullrich

Signale / Robert Koch Institute, Germany
ghozzis@rki.de

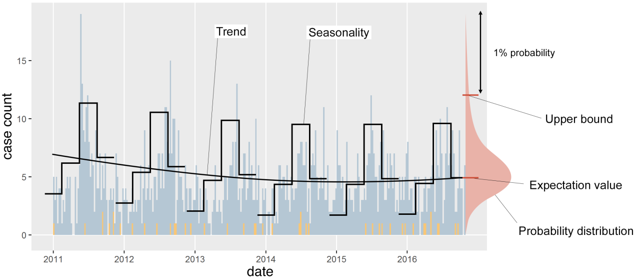
Outline

1. ML for Indicator-Based Surveillance

1.1. Automated outbreak detection as binary classification

"Are there too many cases, here and now, compared with expectations?"

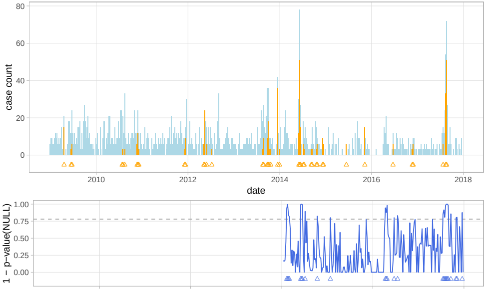
One standard approach: Univariate time series + Regression + Confidence Interval



For example:
farringtonFlexible (from R-package *surveillance*), used here for benchmarking

Noufaily et al (2013) Statistics in Medicine 32(7) 1206 http://doi.org/10.1002/sim.5595

Salmon et al (2016) Journal of Statistical Software 70(10) http://doi.org/10.18637/jss.v070.i10



label △ = week with outbreak

signal △ =
1 - P-value("no outbreak") > cut-off

Idea 1: learn what's an outbreak from the labels

Idea 2: evaluate how good the signals are:

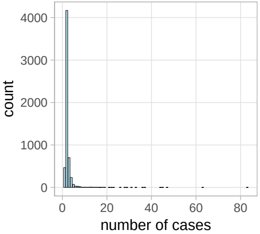
- signal & week with outbreak = true positive **TP**
- signal & week without outbreak = false positive **FP**
- no signal & week without outbreak = true negative **TN**
- no signal & week with outbreak = false negative **FN**

1.2. Outbreak labels: statistical description

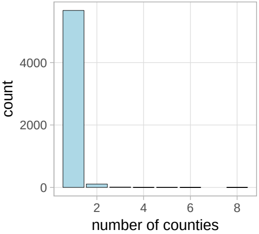
In Germany:
Outbreaks are reported, individual infection **cases are labelled with an outbreak ID**

Reported outbreaks for food-borne diseases are particularly reliable:
campylobacteriosis and salmonellosis

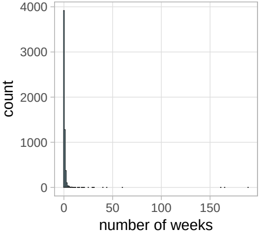
Size of outbreaks:



Extent of outbreaks:



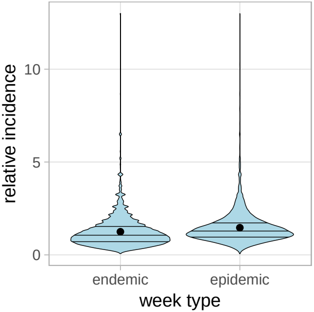
Duration of outbreaks:



Outbreaks are typically **small**, **local**, **short lived** $\Longrightarrow$ point detection might be OK

https://www.rki.de/DE/Content/Infekt/Jahrbuch/Jahrbuch_2017.pdf?__blob=publicationFile

Weekly incidences relative to 13-weeks window (only weeks with cases)



on average: outbreaks are additional cases... but *many* outbreaks are subcritical

simple univariate methods might not work well... let's use the outbreak information!

3. Supervised learning: two simple approaches

1. farringtonOutbreak

   farringtonFlexible but outbreak cases removed from training

   cut-off on 1 - P-value("no outbreak")

2. hmmOutbreak

   - hidden state $s_t \in \{0, 1\}$ ($= 1$ if outbreak in week t, else $= 0$)

   - transition probabilities $a_{ij} = \sum_t \delta_{i\, s_{t-1}} \delta_{j\, s_t} / \sum_t \delta_{i\, s_{t-1}}$

   - emission function $c_t \sim \psi$ NegBin with

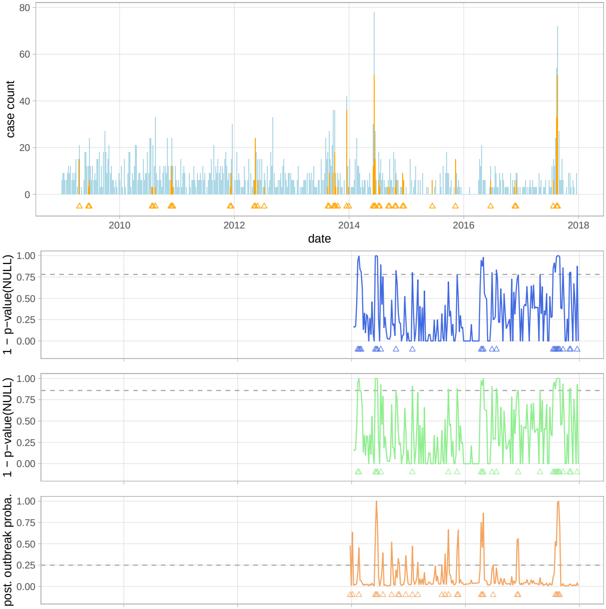
     $$\log \mu_t = \beta_0 + \sum_{i=1}^{3} \beta_i\, t^i + \beta_4 \cos\left(\frac{2\pi}{52} t\right) + \beta_5 \sin\left(\frac{2\pi}{52} t\right) + \beta_6\, s_t,$$

     and constant over-dispersion

   - posterior outbreak probability (one-week ahead: one-step forward algorithm)

     $$p_t = a_{s_{t-1} 1} \cdot \psi(c_t; s_t = 1, t) / \sum_{i=0,1} a_{s_{t-1} i} \cdot \psi(c_t; s_t = i, t)$$

   - **cut-off** on p_t



farringtonFlexible, farringtonOutbreak, hmmOutbreak

1.4. Evaluating and comparing algorithms

- Data:

  weekly reported infection cases and outbreaks for notifiable diseases in Germany

  1 time series for each county

  with frequency of weeks with outbreaks between 2% and 98%

  time range 2009-2017 = 8 years

- Training and test sets = 5 years + 1 week

  training = 5 years

  test on next week (prospective 1 week ahead: data available until last week)

- Scores = functions of TP, FP, TN, FN

  sensitivity, specificity, precision, F1...

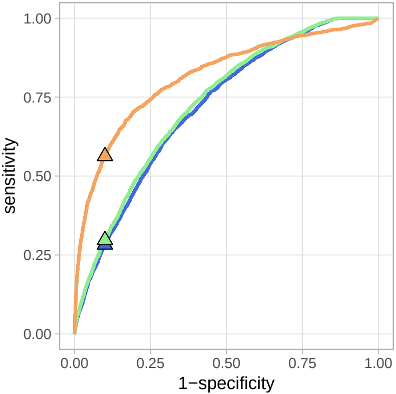
Enki et al (2016) PLOS ONE 11(8) e0160759 http://doi.org/10.1371/journal.pone.0160759

Bédubourg, Le Strat (2017) PLOS ONE 12(7) e0181227 http://doi.org/10.1371/journal.pone.0181227

Hoffmann, Dreesman (2010) PAE-project report, Niedersächsische Landesgesundheitsamt (NLGA) / ESCAIDE poster

Evaluation 1: with varying cut-off

ROC curve (sensitivity vs. 1-specificity): sensitivity $= TP/(TP+FN)$, specificity $= TN/(TN+FP)$



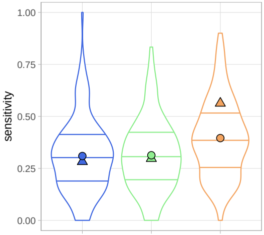
farringtonFlexible, farringtonOutbreak, hmmOutbreak

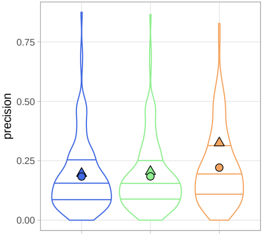
Evaluation 2:
cut-offs set so that specificity $= 0.9$ on each time series (and overall as well)

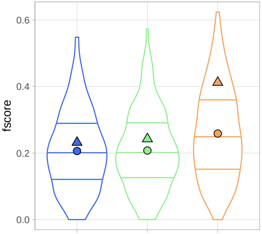
sensitivity

precision
$= TP/(TP + FP)$

F1 score
$= 2\,TP/(2\,TP + FP + FN)$







farringtonFlexible, farringtonOutbreak, hmmOutbreak

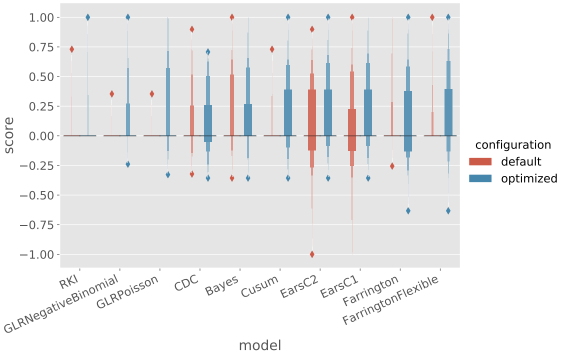
distributions with 25th, 50th and 75th percentiles; ● = mean, ▲ = overall

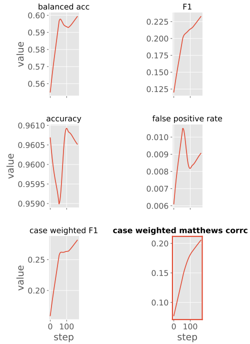
1.5. Hyperparameter optimisation

Find parameters that maximise score function

Here:

- Weighted Matthews Correlation Coefficient (weight = weekly count)
- time-dependency of dataset taken into account

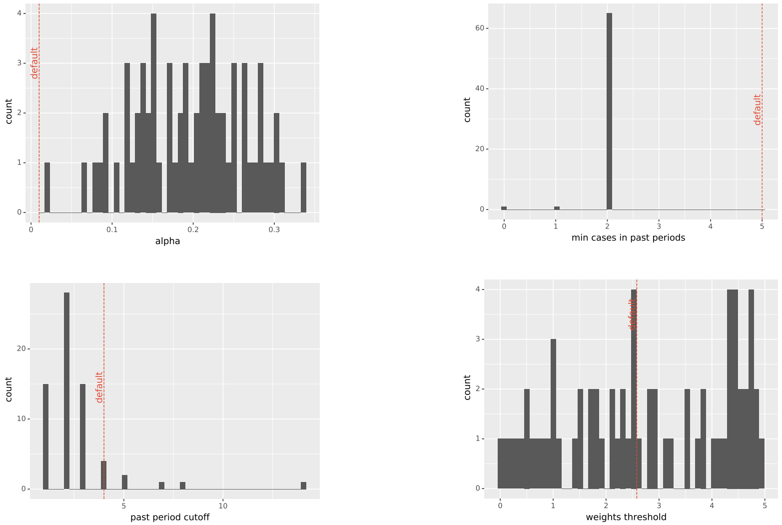




MCC = (TP · TN − FP · FN)/((TP + FP)(TP + FN)(TN + FP)(TN + FN))$^{1/2}$

Busche (2019) Master Thesis https://www.rki.de/EN/Content/infections/epidemiology/signals/projects/Optimisation_Outbreak_Detection_MasterThesis_Busche_2019.pdf?__blob=publicationFile

Example: 4 optimised hyperparameters for farringtonFlexible:



1.6. IBS: Conclusion and outlook

- supervised learning is a **promising** venue for outbreak detection!

  - labelled data are available

  - simple HMM more transparent (explicit probability) and performs better

- towards a framework for developing and **benchmarking**:

  - devise, optimise, combine and compare ML algorithms

  - review of international available datasets

  - **Focus Group AI for Health** of ITU/WHO, Topic Group Outbreaks:
We are recruiting partners!

2. ML for Event-Based Surveillance

2.1. A labeled dataset

worked with 2 Public-Health Intelligence groups:

- INIG at RKI
- **DVA at WHO, part of the EIOS community (in piloting)**

learn from the experts in the DVA team of WHO

a binary classification: 1 article is "signal" or "not signal"

signals = URLs in signals list + Ebola alerts compiled by DVA team $\Longrightarrow$ **labels**

articles = EIOS, 2 boards followed by DVA, in English $\Longrightarrow$ **data**

time ranges:
signals: 1 Nov 2017 - 29 Sep 2019
EIOS: 1 Nov 2017 - 31 Aug 2019

https://www.rki.de/EN/Content/Institute/DepartmentsUnits/ZIG/INIG/INIG_node.html

inig@rki.de

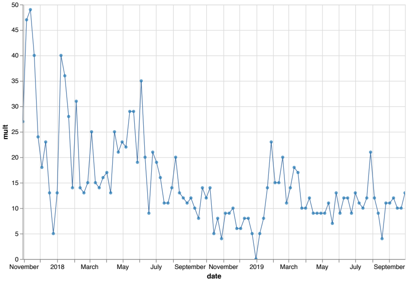
https://www.who.int/csr/alertresponse/epidemicintelligence/en/

eios@who.int

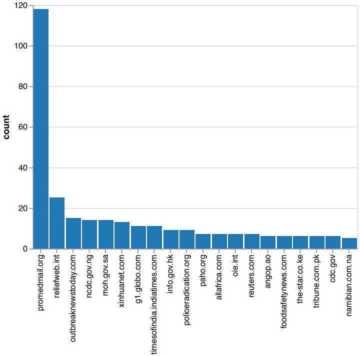
Signals

- w/o Ebola alerts: 3,499 signals, of which 861 have 1 or more "media" URLs

weekly count



web sites (top 20 of 520)



- 1,315 Ebola alerts, of which 22 have 1 or more "media" URLs

EIOS articles

Sequentially:

- remove duplicate URLs, keeping the oldest ones
- keep only texts with at least 30 Latin letters
- keep only articles in one of the two boards followed (if not signal)
- keep only texts in English (using `langdetect()`)

$\Longrightarrow$ 492,036 - 9,617 + 1 = **482,420 articles**

that's an average of 722 articles/day

Matching signals / EIOS

Of 932 unique signal URLs, 274 could be matched to EIOS, of which 20 were removed

$\Longrightarrow$ **254 articles labeled "signal"**

Looking at signals with 7 days delay: 896 signals
- of those: 245 have **web site** not in the EIOS dataset, most not English
- of the 375 w/ web site in EIOS but not matched, **manual inspection** of 100 (in the top 10 domains): no error in matching, rather language is not English or were presumably not categorised in the boards

Memory + balancing: **random sample: 10%** of EIOS that are not signals

$\Longrightarrow$ **48,217 articles labeled "not signal"**

2.2. Data processing

Vectorisations

= ways of translating texts into numbers

1. **Bag-of-words,** with tf-idf:
   1 text ~ frequencies of its words, with overall frequencies in corpus discounted

2. **Word embeddings,** with Word2vec (Google News corpus, 3m words):
   1 word ~ vector in "semantic space" 300-dimensional representation
   1 text ~ mean of the embeddings of its words

Example of **word embeddings:**

Coordinates of “Ebola”:

```
> [0.065, -0.0048, 0.030, 0.11, -0.065, 0.0081, -0.11, -0.059, 0.045,
-0.043 ... ]
```

Words most similar to “Ebola”:

```
> [('Ebola_virus', 0.78), ('Marburg_virus', 0.75), ('Ebola_outbreak',
0.70), ('haemorrhagic_fever', 0.69), ('Ebola_fever', 0.69), ('ebola',
0.68), ('Marburg_hemorrhagic_fever', 0.67), ('Ebola_hemorrhagic_fever',
0.67), ('Marburg_fever', 0.67), ('Ebola_haemorrhagic_fever', 0.67)]
```

Text preprocessing

sentence and then word **tokenisation**

keep only **Latin letters** (accents included), **digits**, and **dots**

remove **stop words**

token processing:

- **tfidf:** remove dots, numbers, accents; lower case; lemmatisation; stemming
- **w2v:** replace digits with "#"

keep tokens with **2 or more characters**

train **bi- and trigrams**

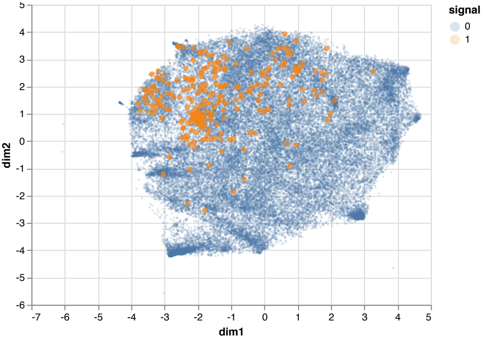
```
> trigram_simple_pp[bigram_simple_pp[['human','immunodeficiency','virus']]]
> ['human_immunodeficiency_virus']

> trigram_simple_pp[bigram_simple_pp[['human','immunodeficiency','apple']]]
> ['human_immunodeficiency', 'apple']
```

2.3. Data exploration

Sentiment and topics

quick and dirty... Nothing much

2d visualisations of embeddings (t-SNE)



2.4. Different approaches

Training and test datasets

1 partition training / test sets (80% / 20%)

add **reduced tfidf** (~PCA, 300 components) to the 2 vectorisations

upsampling of training data:
- none
- duplicate
- ADASYN (linear interpolation)

standardisation:
- none
- standardise (tfidf: not centred because sparse)

all transformations trained on training set, then applied to training and test sets

Classification algorithms

- complement naive Bayes
- logistic regression
- multilayer perceptron
- random forest
- support vector machine (non-linear)

overall
$(5\text{ algorithms}) \times (3\text{ vectorisations}) \times (3\text{ upsamplings}) \times (2\text{ standardisations}) - 1 \times 2 \times 3 \times 2$
approaches

$\Longrightarrow$ **78 approaches** to test

CNB needs positive features: no w2v and no reduced tfidf

2.5. Classification performance

Output of the algorithms: for each article, **probability of being "signal"**

Threshold t:
- if $p(\text{signal}) \geqslant t$, then prediction = "signal",
- else prediction = "not signal"

For each t:
confusion matrix = (# true negatives, # false positives, # false negatives, # true positives)

Scores (computed from the confusion matrix):
accuracy / recall (sensitivity) / specificity / precision / F1 / Matthews correlation coefficient / balanced accuracy / geometric mean / index balanced accuracy of the geometric mean

Scores (threshold independent):
- AUC / Relative probability gap

ba = average of recall obtained on each class
geom_mean = root of the product of sensitivity and specificity
rel_p_gap = $2(\mu(p_{\text{signal}}) - \mu(p_{\text{not signal}}))/(\sigma(p_{\text{signal}}) - \sigma(p_{\text{not signal}}))$

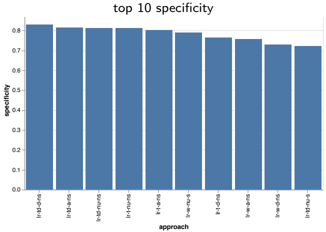
Best scores with t / recall $\approx$ 0.9

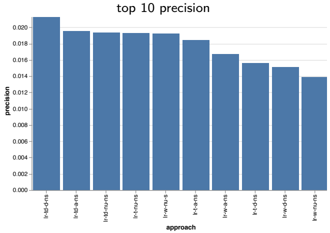
Logistic regression / reduced tfidf / duplicate / no standardisation

is best along all scores...

accuracy	0.83
precision	0.021
specificity	0.83
f1	0.042
mcc	0.13
ba	0.88
geom_mean	0.87
iba_gm	0.76

... but it's a tight race...





confusion matrix = (TN 7999, FP 1657, FN 3, TP 36)

2.6. EBS: Conclusion and outlook

1 approach stands out at high recall (sensitivity):
TN 7999, FP 1657, FN 3, TP 36
i.e. to find (more than) 36 of the 39 signals, just read ~1,700 articles out of ~9,700

Already works well and could be helpful:
no automatisation, but **ranking**

Low precision and F1. . . are maybe OK:
there might be hidden or discarded signals

Many signals lost, mostly because not in English

Immediate tasks

Use **all available articles,** not just a sample

Proper **cross-validation,** hyperparameter **optimisation**

Manual inspection of predicted positives

Apply similar analysis to **events**
- cf. named entity recognition for INIG at RKI

Perspective

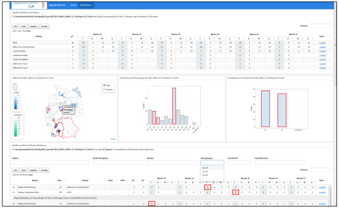
Beyond English:
- automatic translation (is being used by experts!)
- language-specific analyses

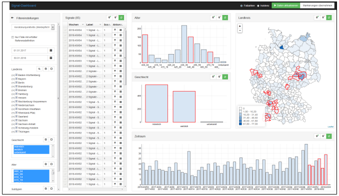
Context:
- as supplementary features for classification

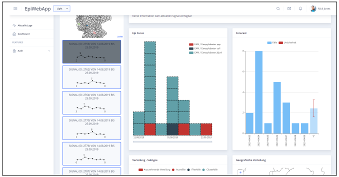
Fancier approaches:
- Stacking (combination of approaches)
- Transfer learning of word embeddings, document embeddings, transformer models...
- Deep learning

Web application:
- prototypical implementation in an interactive dashboard
- evaluation of usefulness (with new, unfiltered data)
- cf. EventEpi for INIG at RKI

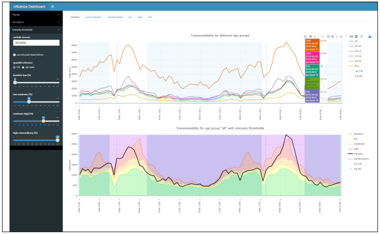
3. Bonus: Interactive Reports and Websites



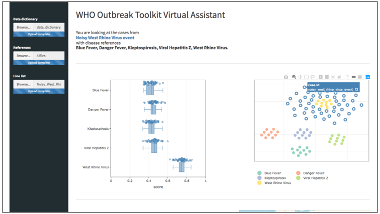




with Fabian Eckelmann and Knut Perseke (Signale/RKI)


Influenza Dashboard
Transmissibility for different age groups
Transmissibility for age group "all" with intensity thresholds


Enter model formula: count ~
Choose model family
model analysis
Actual vs Predicted
Model Prediction


Data dictionary
References
Line list
WHO Outbreak Toolkit Virtual Assistant
You are looking at the cases from
Noisy West Rhine Virus event
with disease references
Blue Fever, Danger Fever, Kleptospirosis, Viral Hepatitis Z, West Rhine Virus.
Blue Fever
Danger Fever
Kleptospirosis
Viral Hepatitis Z
West Rhine Virus
score

4. Conclusion

Machine (supervised) learning can support signal detection in different surveillance settings

No assumption on *what* is a signal

Annotated data, i.e. **output of expert evaluation**, are extremely valuable

They should be **systematically** saved in a **structured** fashion in **databases**

Thank you!

Acknowledgements:

- RKI: Doris Altmann, Hermann Claus, Bettina Rosner (outbreak data)
- RKI: Benedikt Zacher (HMM)
- RKI: Sandra Beermann, Sarah Esquevin, Raskit Lachmann (public-health intelligence)
- WHO: Philip Abdelmalik, Émilie Péron, Johannes Schnitzler (EIOS)
- WHO: Sooyoung Kim, Annika Wendland (EBS signals, risk assessment)

IBS: **Focus Group AI for Health** of ITU/WHO, Topic Group Outbreaks:
https://www.itu.int/en/ITU-T/focusgroups/ai4h/Pages/outbreaks.aspx

EBS: work done for INIG at RKI:
Abbood et al (2019) medRxiv, https://doi.org/10.1101/19006395

SIGNALE

signale@rki.de

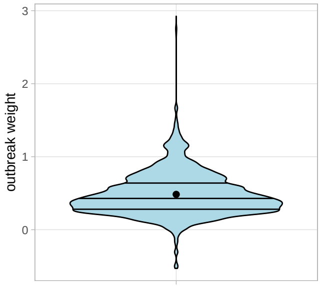
rki.de/signale-project

Supplementary Information

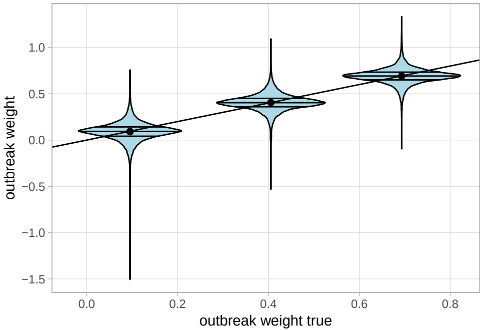
Dynamical properties can be inferred from hmmOutbreak, for example:

Outbreak weight β_6 (weeks with outbreaks have e^{β_6} more cases):

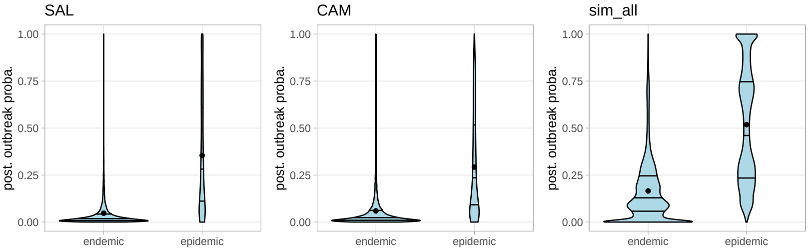
Campylobacteriosis



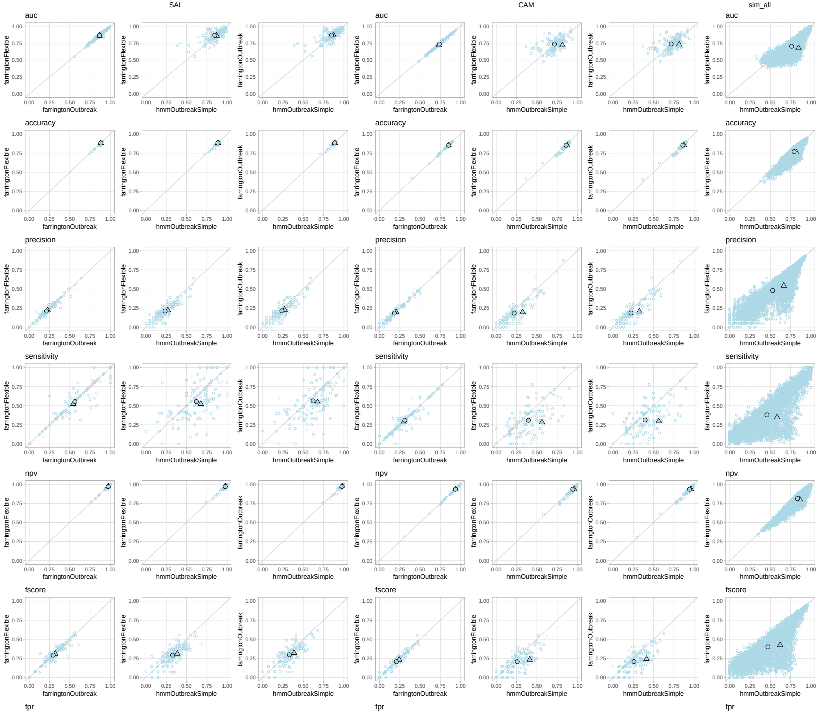
Simulations



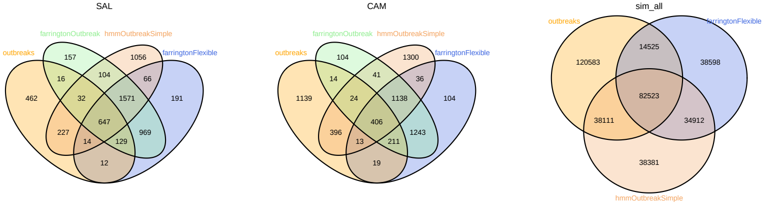
For campylobacteriosis:
- weeks with outbreaks indeed have significantly more cases
- on average $e^{0.5} \approx 1.6$ more cases in outbreak weeks, all other things equal



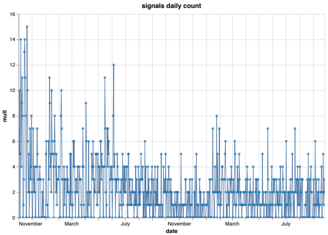
SAL
CAM
sim_all
post. outbreak proba.
1.00
0.75
0.50
0.25
0.00
endemic
epidemic

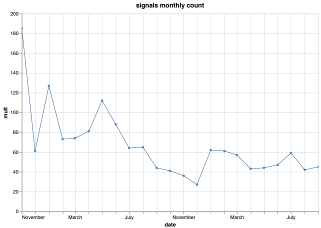


SAL
CAM
sim_all
auc
accuracy
precision
sensitivity
npv
fscore
fpr
farringtonFlexible
farringtonOutbreak
hmmOutbreakSimple
0.00
0.25
0.50
0.75
1.00

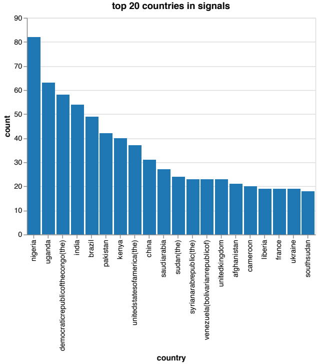

SAL
farringtonOutbreak
hmmOutbreakSimple
outbreaks
farringtonFlexible
157
1056
16
104
66
462
32
1571
191
647
227
969
14
129
12
CAM
farringtonOutbreak
hmmOutbreakSimple
outbreaks
farringtonFlexible
104
1300
14
41
36
1139
24
1138
104
406
396
1243
13
211
19
sim_all
outbreaks
farringtonFlexible
14525
120583
38598
82523
38111
34912
38381
hmmOutbreakSimple

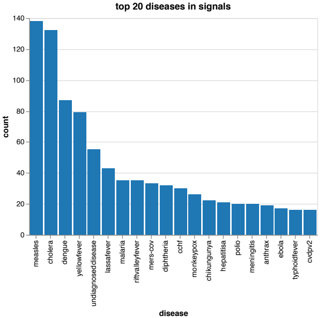
Signals (w/o Ebola alerts)

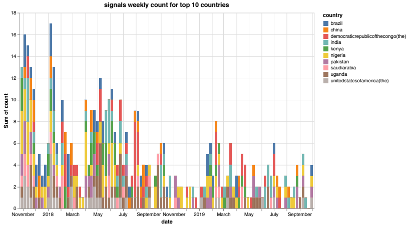


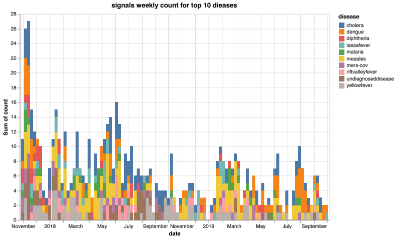


Signals (w/o Ebola alerts)



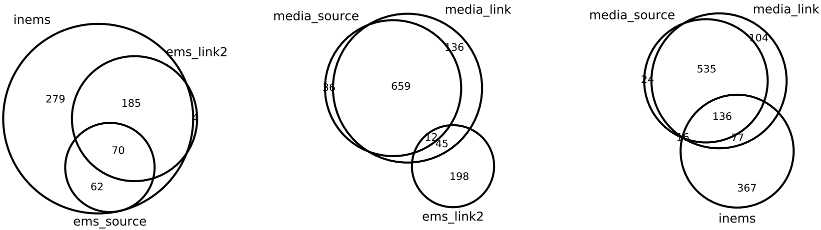






Signals (w/o Ebola alerts)

media and EMS links



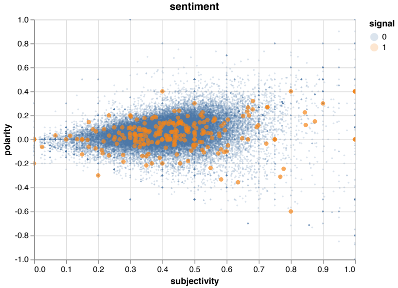
Word2vec trained on Google News, examples:

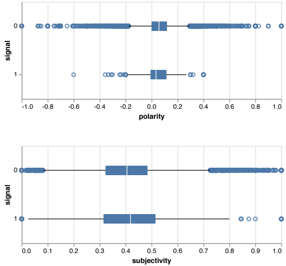
```
> w2v.vectors_norm[w2v.vocab['HIV'].index]
> [-0.027214931, 0.005086286, -0.00077202555, -0.024440594, -0.061563876, -0.0069028167, -0.04993808, 0.028800268,
-0.024704818, -0.03778384 ... ]

> w2v.most_similar('HIV')
> [('HIV_AIDS', 0.8241558074951172), ('HIV_infection', 0.8100206851959229), ('HIV_infected', 0.782840371131897),
('AIDS', 0.763182520866394), ('HIV_Aids', 0.7069978713989258), ('HIV_AIDs', 0.7062243223190308), ('Hiv',
0.6802983283996582), ('human_immunodeficiency_virus', 0.6724722981452942), ('Aids', 0.6655842065811157), ('H.I.V.',
0.6647853255271912)]

> w2v.vectors_norm[w2v.vocab['influenza'].index]
> [0.015480349, 0.00036750827, 0.023640532, 0.04224095, 0.008460191, -0.015480349, -0.08640195, -0.03648082,
0.058801327, -0.027600622 ... ]

> w2v.most_similar('influenza')
> [('flu', 0.8435951471328735), ('H#N#', 0.8313145041465759), ('H#N#_influenza', 0.8289912939071655),
('H#N#_virus', 0.8022348880767822), ('seasonal_influenza', 0.8018087148666382), ('H#N#_flu', 0.7963185906410217),
('Influenza', 0.7937184572219849), ('H#N#_influenza_virus', 0.7823264598846436), ('flu_virus', 0.7783315181732178),
('influenza_virus', 0.7776930332183838)]

> w2v.vectors_norm[w2v.vocab['H#N#'].index]
> [0.040303856, -0.08500449, 0.014717014, 0.027357768, -0.03615134, 0.020884724, -0.085981555, -0.023327382,
0.043479312, 0.0054959804 ... ]

> w2v.most_similar('H#N#')
> [('H#N#_virus', 0.9167306423187256), ('H#N#_flu', 0.8859533071517944), ('swine_flu', 0.8520038723945618),
('H#N#_influenza', 0.850509524345398), ('influenza', 0.8313145041465759), ('H#N#_swine_flu', 0.8082534074783325),
('bird_flu', 0.7901098728179932), ('H#N#_influenza_virus', 0.7855583429336548), ('avian_influenza',
0.7841204404830933), ('H#N#_strain', 0.7841016054153442)]
```

Quick and dirty:

Sentiment

"polarity" = negative to positive sentiment



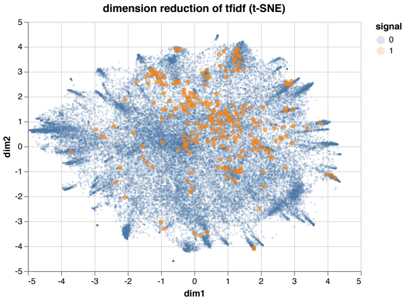


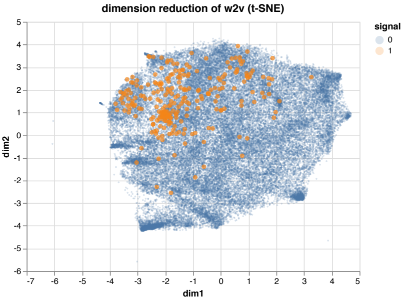
Topics

"topic modelling" ~ clustering of bag-of-words

Nothing meaningful

2d visualisations (t-SNE)

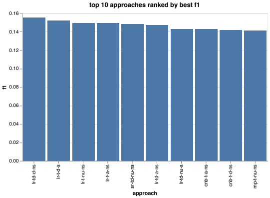


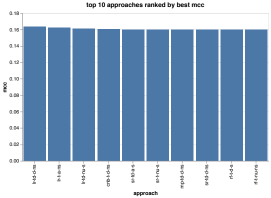


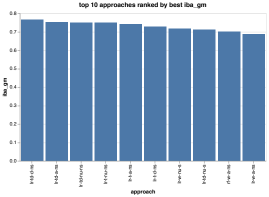
tfidf first reduced to 300 components (~PCA)

Best scores achieved with varying t

score_type	score_value	approach	confusion_matrix
f1	0.15	logistic_regression-tfidf_dr-duplicate-no_st	TN 9576 / FP 80 / FN 29 / TP 10
mcc	0.16	logistic_regression-tfidf_dr-duplicate-no_st	TN 9576 / FP 80 / FN 29 / TP 10
ba	0.88	logistic_regression-tfidf_dr-duplicate-no_st	TN 7999 / FP 1657 / FN 3 / TP 36
geom_mean	0.87	logistic_regression-tfidf_dr-duplicate-no_st	TN 7999 / FP 1657 / FN 3 / TP 36
iba_gm	0.76	logistic_regression-tfidf_dr-duplicate-no_st	TN 7999 / FP 1657 / FN 3 / TP 36
auc	0.92	logistic_regression-tfidf_dr-adasyn-no_st	None
rel_p_gap	1.75	logistic_regression-w2v-duplicate-no_st	None



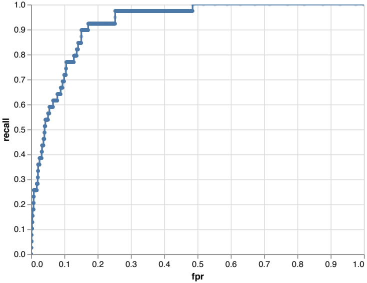


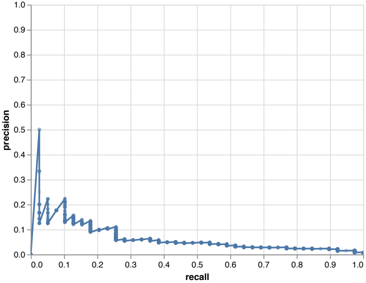


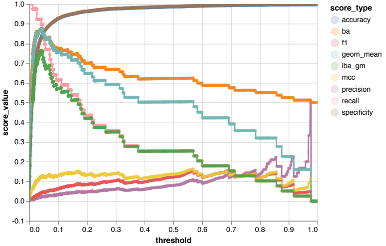
recall of 1 resp. specificity of 1 can always be achieved with $t = 0$ resp. $t = 1$

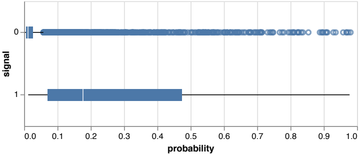
best accuracy and precision not meaningful (~no positives)

Logistic regression / reduced tfidf / duplicate / no standardisation









fpr = 1 - specificity

Apply similar analysis to **events (in EMS)** and not just signals:

- "event" defined as disease + country + time range → **collection of articles**
- match with EMS database
- predict **(risk) assessments**

  `IHR Assessment` (0/1), `Serious Public Health Impact (WHO)` (0/1), `Unusual or Unexpected (WHO)` (0/1), `International Disease Spread (WHO)` (0/1), `Interference with international travel or trade (WHO)` (0/1)

  `RRANationalRiskLevel` (0/1/2/3/4), `RRARegionalRiskLevel` (0/1/2/3/4), `RRAGlobalRiskLevel` (0/1/2/3/4)
- events and signals partially **linked**
- labeled datasets **already prepared!**