Emergenet Package Usage

ZeD Lab

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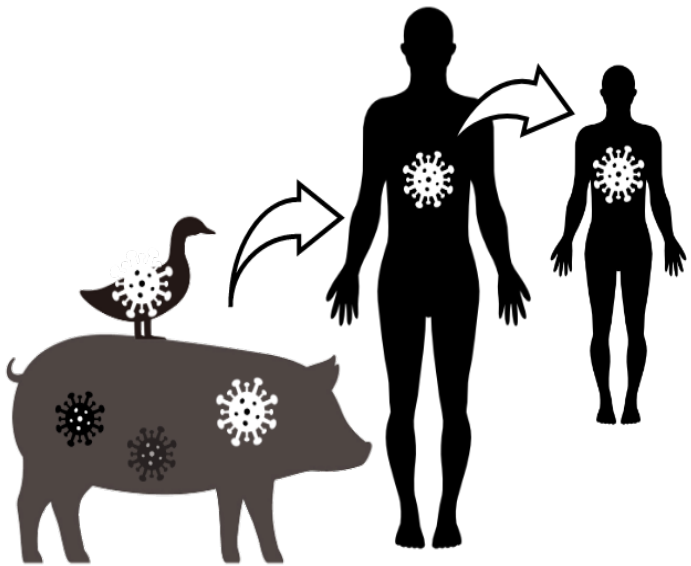
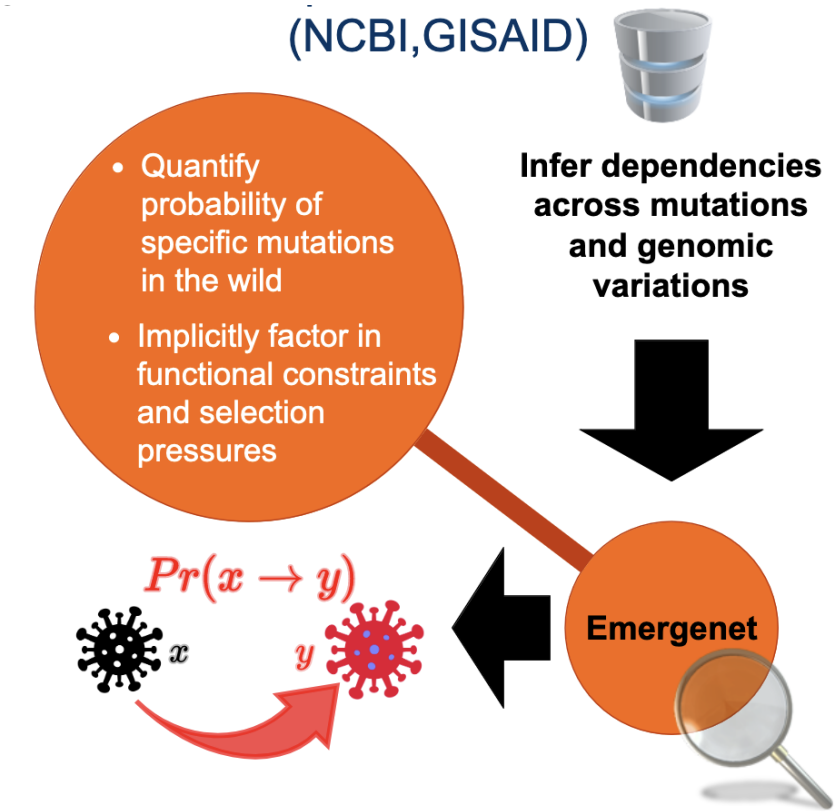


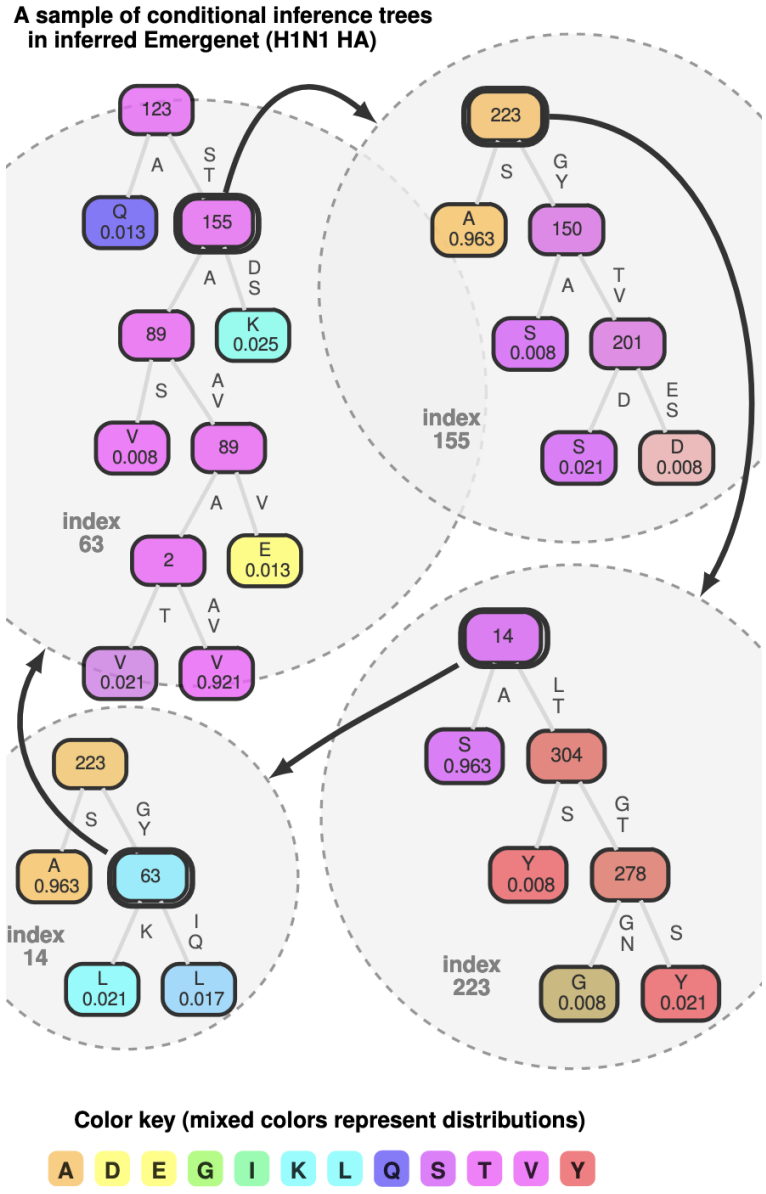
Emergenet computationally learns how new viral variants emerge using only viral sequence data

- Install Emergenet: `pip install emergenet --upgrade`
- Emergenet (recomputed for each time-period) is expected to automatically factor in the evolving host immunity and background environment
- Two applications:
  1. Forecasting dominant Influenza strains for future seasonal outbreaks
  2. Assessing risk of Influenza strains circulating in non-human hosts



Emergenet comprises an interdependent collection of local predictors

- Each aims to predict the residue at a particular index using as features the residues at other indices
- Individual predictors (one for each sequence index) are implemented as conditional inference trees in which nodal splits have a minimum pre-specified significance in differentiating the child nodes
- Each predictor yields an estimated conditional residue distribution at each index

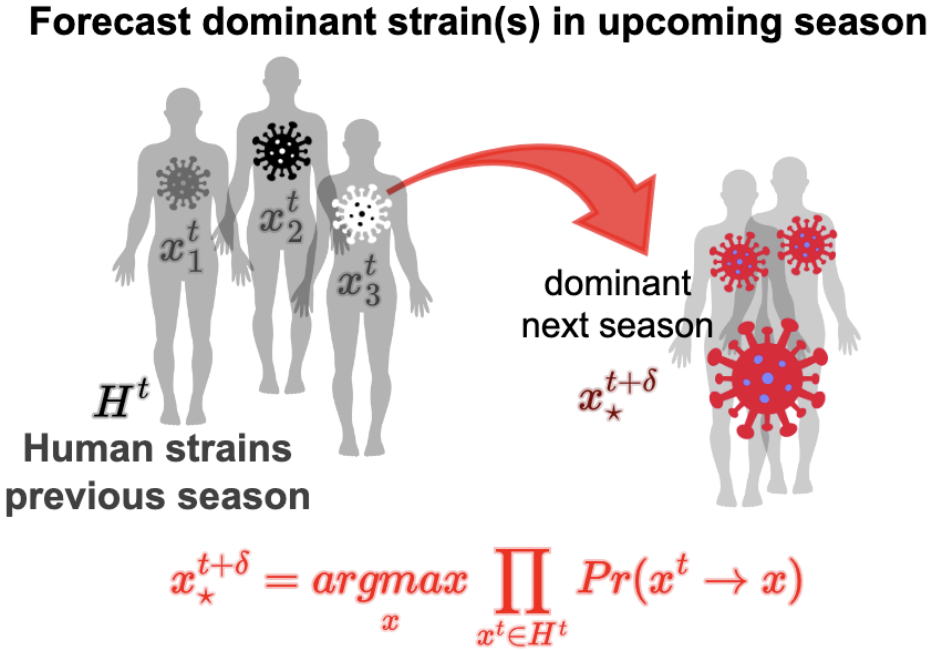


Our Emergenet-inferred **E-distance** metric adapts to the background environment and approximates the log-likelihood of spontaneous change

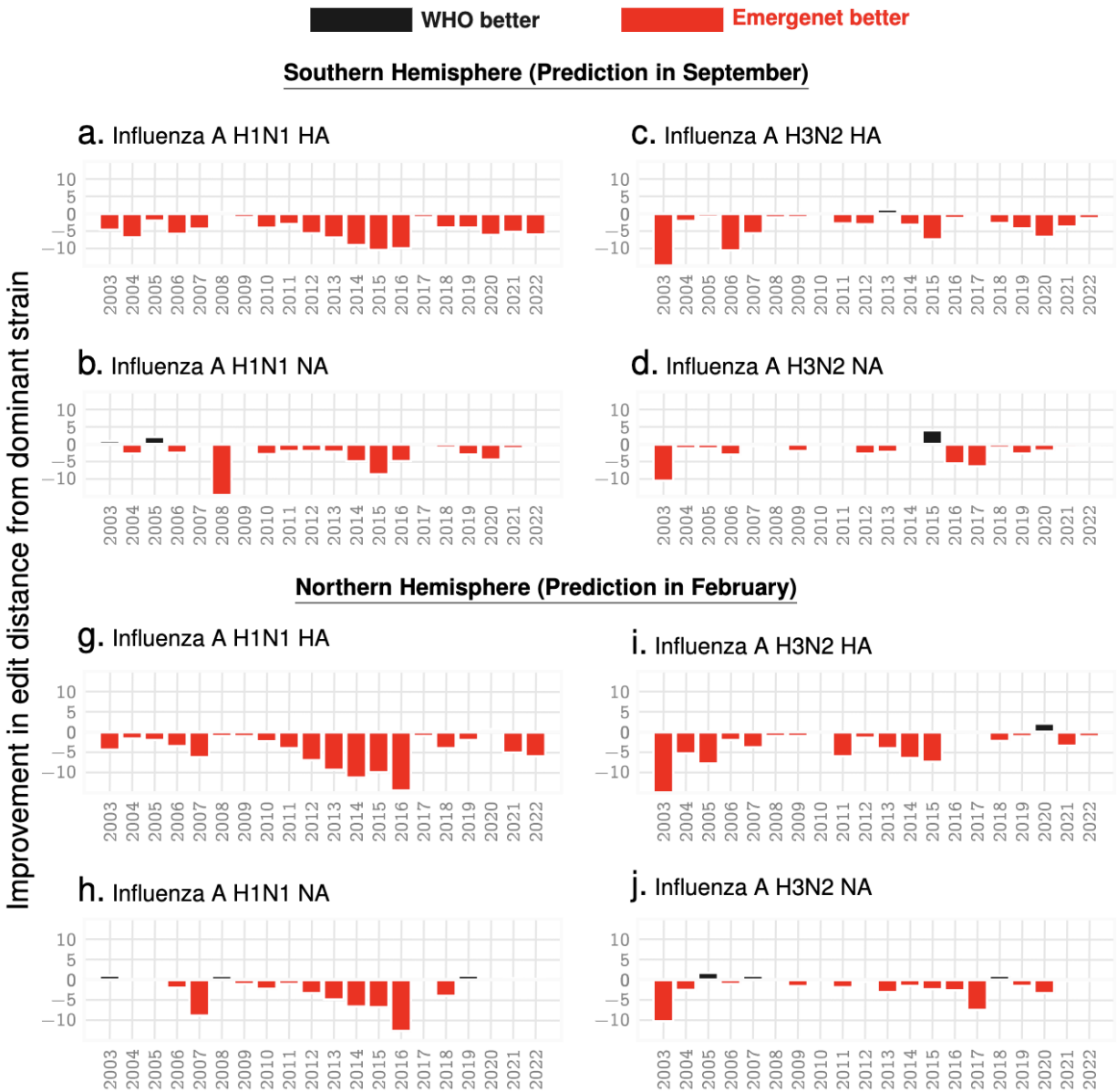
- We define the E-distance as the square-root of the Jensen-Shannon divergence of the conditional residue distributions, averaged over the sequence
- Unlike the classic edit distance, the E-distance is informed by the Emergenet-inferred dependencies, and adapts to the specific subtype, allele frequencies, and environmental variations
- The E-distance approximates the log-likelihood of spontaneous change *i.e.* $\log Pr(x \rightarrow y)$
- Model trained on current data $\rightarrow$ predict for the near future

Application 1: forecasting dominant strains for future seasonal outbreaks

- A dominant strain for an upcoming season may be identified as one which maximizes the joint probability of simultaneously arising from each (or most) of the currently circulating strains
- We can use the E-distance metric informed by an Emergenet constructed with hemagglutinin (HA) sequences from the previous season to predict the dominant strain for the next season



Emergenet recommendations are closer to the dominant strain than WHO yearly vaccine recommendations



Demonstration of **emergenet.domseq** usage

- Download the example data
- This tutorial analyzes H1N1 from 2021-2022, northern hemisphere
- Data downloaded from GISAID and NCBI, and parsed, merged, and cleaned with BioPython (see notebook)
- Compute current season (2021-2022) dominant strains and predict future dominant strain (2022-23) using HA sequences

```
import pandas as pd
from emergenet.domseq import DomSeq, save_model, load_model

DATA_DIR = 'example_data/domseq/'

# initialize the DomSeq, truncating HA to 565
# all sequences must be same length to train and use an Emergenet
domseq = DomSeq(seq_trunc_length=565, random_state=42)
```

Demonstration of **emergenet.domseq** usage

- *north_h1n1_21_22.csv* contains HA sequences from 02/15/2021 - 02/14/2022
- The sequences must be stored in a *sequence* column
- If you have a FASTA file, use *domseq.load_data* to load and format automatically

```
# load current season sequences
df = pd.read_csv(DATA_DIR+'north_h1n1_21_22.csv')
print('Number of sequences:', len(df))
# Number of sequences: 735

# if you have a fasta file, you can parse it using load_data
df = domseq.load_data(self, 'file.fasta', outfile='sequences.csv')
```

Demonstration of **emergenet.domseq** usage

- *domseq.compute_domseq* does not rely on the Emergenet at all; it returns the cluster-wise dominant sequences of the input sequences, against which we evaluate our predictions from the previous season
- *domseq.compute_domseq* automatically clusters sequences and returns the centroid strain and cluster size for each cluster

```
# compute dominant sequences for 2021-2022
dom_seqs = domseq.compute_domseq(seq_df=df)

# save dominant sequences
dom_seqs.to_csv(DATA_DIR + 'dom_seqs_21_22.csv', index=False)
print(dom_seqs[['name','sequence','cluster_size']])
```

	name	sequence	cluster_size
15	A/Togo/0172/2021	MKAILVVLLYTFTTANADTLCIGYHANNSTDTVDTVLEKNVTVTHS...	531
197	A/Bangladesh/9004/2021	MKAILVVMLYTFTTANADTLCIGYHANNSTDTVDTVLEKNVTVTHS...	193
165	A/Wisconsin/04/2021	MKAVLVVLLYTVTNANADTLCIGYHANNSTDTVDTVLEKNVTVTHS...	2
89	A/Mecklenburg-Vorpommern/1/2021	MEAKLFVLFCVFTALKADTICVGYHANNSTDTVDTIMEKNVTVTHS...	1
60	A/Gansu-Xifeng/1194/2021	MKARLFILFCAFTALKADTICVGYHANNSTDTVDTILEKNVTVTHS...	1
82	A/Wisconsin/03/2021	MKAVLVVLLYTFTTANADTLCIGYHANNSTDTVDTVLEKNVTVTHS...	1
516	A/Denmark/36/2021	MKAILVALLYTFATANADTLCIGYHANNSTDTVDTILEKNVTVTHS...	1
372	A/SouthAfrica/PET20744/2021	MKAILVVLLYTFTTANADTLCIGYHANNSTDTVDTVLEKNVTVTHS...	1
24	A/Gansu-Xifeng/1143/2021	MKARLFILFCAFTALKADTICVGYHANNSTDTVDTILEKNVTVTHS...	1
9	A/Parana/10835/2021	MKAILVVLLYTFATTNADTLCIGYHANNSTDTVDTVLEKNVTVTHS...	1
281	A/SouthAfrica/PPET20447/2021	MKAILVVLLYTFTTANADTLCIGYHANNSTDTVDTVLEKNVTVTHS...	1
90	A/Mecklenburg-Vorpommern/1-A/2021	MEAKLFVLFCVFTALKADTICVGYHANNSTDTVDTIMEKNVTVTHS...	1

Demonstration of **emergenet.domseq** usage

- Next, we predict dominant strains for 2022-2023
- First train the Emergenet using sequences from 2021-2022
- We use 3000 to demonstrate the *sample_size* parameter, but it does nothing here as *df* contains 735 sequences

```
# train enet
enet = domseq.train(seq_df=df, sample_size=3000, n_jobs=1)
# save enet
save_model(enet=enet, outfile=DATA_DIR+'enet.joblib')
```

Demonstration of **emergenet.domseq** usage

- *north_h1n1_21_22_pred.csv* contains human HA sequences from 09/15/2001 - 02/14/2022 (all candidate sequences from the past)
- Get predictions from the three largest clusters
- Since our candidate sequence dataframe is large (18,057 sequences), this will take a while

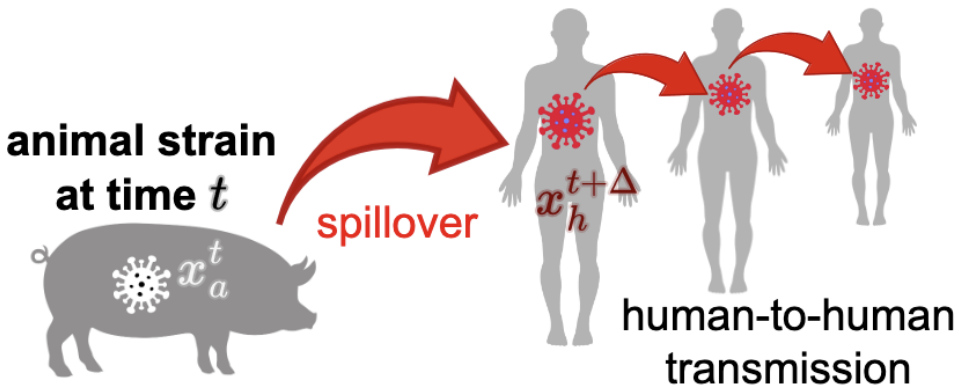
```
# load candidate sequences for recommendation
candidate_df = pd.read_csv(DATA_DIR+'north_h1n1_21_22_pred.csv')
print('Number of sequences:', len(candidate_df))
# Number of sequences : 18057

# compute prediction sequences (predictions from 3 largest clusters)
pred_df = domseq.predict_domseq(seq_df=df, pred_seq_df=candidate_df,
      enet=enet_model, n_clusters=3, sample_size=3000)

# save predictions
pred_df = pred_df.sort_values(by=['cluster_size'], ascending=False)
pred_df.to_csv(DATA_DIR+'predictions_for_22_23.csv', index=False)
print(pred_df[['name','sequence','cluster_size']])
```

	name	sequence	cluster_size
0	A/Netherlands/00475/2020	MKAILVVLLYTFTTANADTLCIGYHANNSTDTVDTVLEKNVTVTHS...	527
1	A/Bangladesh/9004/2021	MKAILVVMLYTFTTANADTLCIGYHANNSTDTVDTVLEKNVTVTHS...	193
2	A/North_Dakota/12226/2021	MKAILVVLLYTFTTANADTLCIGYHANNSTDTVDTVLEKNVTVTHS...	3

Application 2: assessing risk of Influenza strains circulation in animals

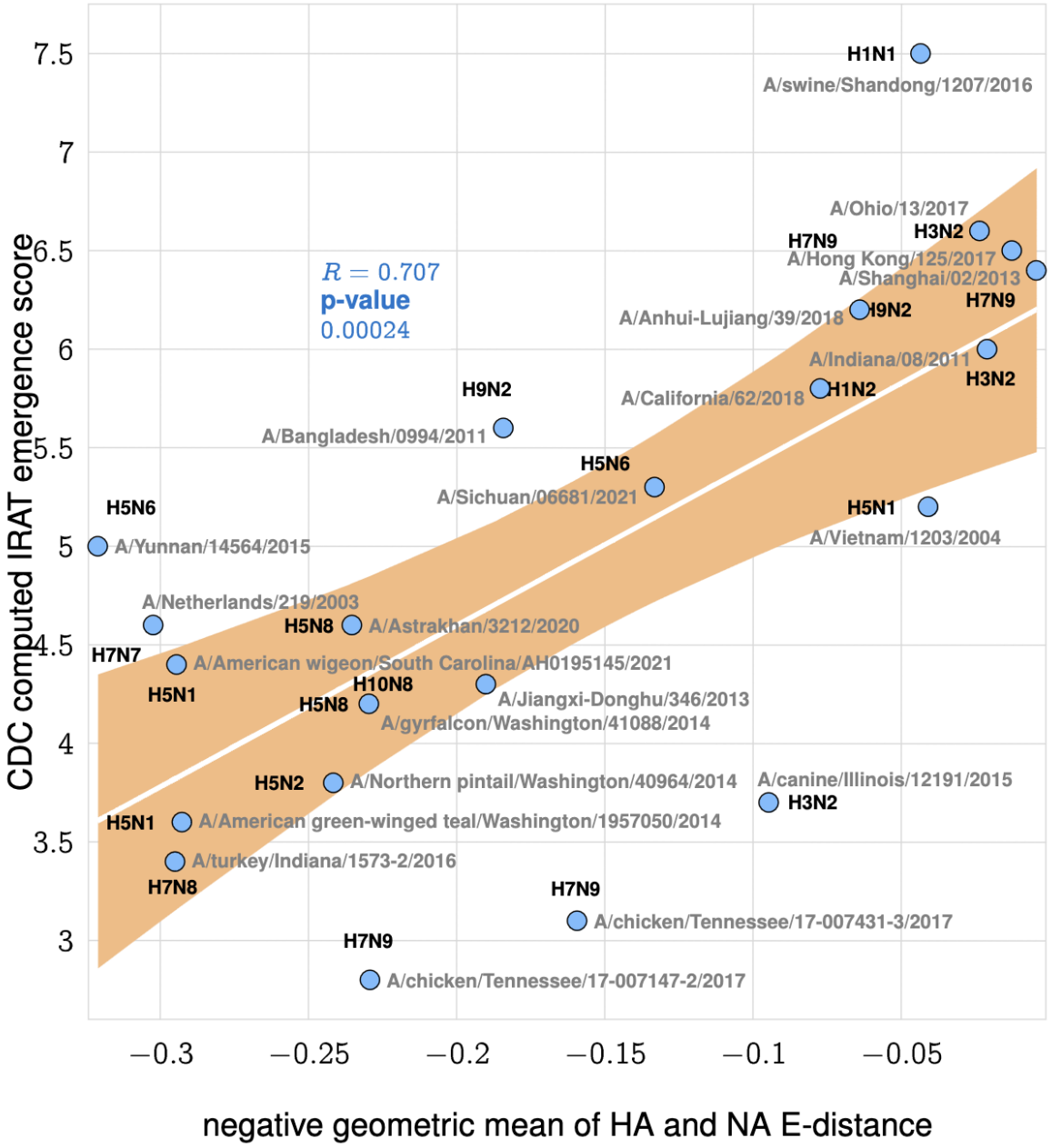
- The Center for Disease Control's (CDC) current method is the Influenza Risk Assessment Tool (IRAT)
- Scalability issue: IRAT depends on multiple experimental assays, possibly taking weeks to compile for a single strain
- We estimate the pandemic potential of novel animal strains, via a time-varying **E-risk** score, computed using the E-distance informed by the Emergenet trained on recent human hemagglutinin (HA) and neuraminidase (NA) strains

Estimate pandemic potential of animal strains



$$\text{risk}(x_a^t) \propto \langle \log Pr(x_a^t \to x_h^{t+\Delta}) \rangle$$

Emergenet scores are correlated with IRAT emergence scores, R = 0.707



Demonstration of **emergenet.emergenet** usage

- Download the example data
- This tutorial analyzes the risk of our target sequence, A/Ohio/13/2017, assessed by IRAT in July 2019
- Initialize the HA Enet with a FASTA file containing only the HA segment of A/Ohio/13/2017; initialization with a Python string is also possible (see notebook)

```
1  import numpy as np
2  from emergenet.emergenet import Enet, save_model, load_model,
       irat_risk
3
4  DATA_DIR = 'example_data/emergenet/'
5
6  # initialize the Enet with A/Ohio/13/2017 HA
7  enet_ha = Enet(seq=DATA_DIR+'ha_target_sequence.fasta',
       seq_trunc_length=550, random_state=42)
8
9  print(enet_ha.seq_metadata, '\n')
10 print(enet_ha.seq, '\n')
```

```
A/Ohio/13/2017|A_/_H3N2|$SEGMENT_NAME|2017-07-14|EPI1056653|

MKTIIALSHILCLVFAQKLPGNDNNMATLCLGHHAVPNGTIVKTITNDQIEVTNATELVQSFSTGEICNSPYQILDGENCTLIDALLGDPQCDGFQNNKWDLFVERSKAHSNCYP
YDVPDYASLRSLVASSGTLEFNNESFNWTGVTQDGASSSCKRRSSNSFFSRLNWLTHLNFKYPALEVTMPNNEQFDKLYIWGVHHPATDKDQISLYAQAAGRIIVSTKRNQQAVI
PNIGSRPRVRDIPSRISIYWTIVRPGDILLINSTGNLIAPRGYFKIRSGKSSIMRSDAPIGKCNSACITPNGSIPNDKPFQNVNRITYGACPRYVKQNTLKLATGMRNIPEKQTR
GIFGAIAGFIENGWEGMVDGWYGFRHQNSEGRGQAADLKSTQAAIDQINGKLNRLIGKTNEKFHQIEKEFSDVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTDSEM
NKLFEKTKKQLRENAEDMGNGCFKIYHKCDNACIGSIRNGTYDHDVYRNEALNNRFQIKGVELKSEYKDWILWISFAISCFLLCVALLGFIMWACQKGNIKCNICI
```

Demonstration of **emergenet.emergenet** usage

- *ha_sequences.fasta* contains human HA sequences from 7/1/2018 - 6/30/2019 (one year prior to IRAT assessment)
- Train the HA Emergenet using these sequences; it will take a couple minutes

```
# load fasta data
df_ha = enet_ha.load_data(filepath=DATA_DIR+'ha_sequences.fasta')
print('Number of sequences:', len(df_ha))
# Number of sequences: 12389

# train enet (automatically includes target sequence with df)
enet_ha1 = enet_ha.train(seq_df=df_ha, sample_size=1000, n_jobs=1)
# save enet
save_model(enet=enet_ha1, outfile=DATA_DIR+'ha_enet.joblib')
```

Demonstration of **emergenet.emergenet** usage

- Compute the HA emergence risk score and variance under the trained HA Emergenet model
- This will take a couple seconds

```
# compute risk score
risk_score_ha, variance_ha = enet_ha.emergence_risk(seq_df=df_ha,
    enet=enet_ha1, sample_size=1000)

print('Emergenet Risk Score:', risk_score_ha)
print('Variance:', variance_ha)
# Emergenet Risk Score: 0.020315896450399634
# Variance: 1.673019568927247e-05
```

Demonstration of **emergenet.emergenet** usage

- We repeat the last three slides, but with NA

```
# initialize the Enet with A/Ohio/13/2017 NA
enet_na = Enet(seq=DATA_DIR+'na_target_sequence.fasta',
    seq_trunc_length=449, random_state=42)

# load fasta data
df_na = enet_na.load_data(filepath=DATA_DIR+'na_sequences.fasta')
print('Number of sequences:', len(df_na))
# Number of sequences: 12388

# train enet (automatically includes target sequence with df)
enet_na1 = enet_na.train(seq_df=df_na, sample_size=1000, n_jobs=1)
# save enet
save_model(enet=enet_na1, outfile=DATA_DIR+'na_enet.joblib')

# compute risk score
risk_score_na, variance_na = enet_na.emergence_risk(seq_df=df_na,
    enet=enet_na1, sample_size=1000)

print('Emergenet Risk Score:', risk_score_na)
print('Variance:', variance_na)
# Emergenet Risk Score: 0.03050091990424366
# Variance: 1.564767759048388e-05
```

Demonstration of **emergenet.emergenet** usage

- Finally, we compare our scores to IRAT
- The geometric mean of HA and NA scores is 0.024893, as seen in the IRAT vs. Emergenet figure
- *irat_risk* uses our GLM models (see S-Tab. 4-5 in the paper) to predict the IRAT emergence and impact risk scores: 6.3 and 6.4, respectively
- IRAT's scores are 6.6 and 5.8, respectively

```
geom_mean_risk_score = np.sqrt(risk_score_ha * risk_score_na)
irat_emergence_prediction, irat_impact_prediction = irat_risk(
    risk_score_ha, risk_score_na)

print('Geometric Mean of HA and NA risk scores:', round(
    geom_mean_risk_score, 6))
print('Emergenet prediction of IRAT emergence estimate:', round(
    irat_emergence_prediction, 1))
print('IRAT emergence estimate: 6.6')
print('Emergenet prediction of IRAT impact estimate:', round(
    irat_impact_prediction, 1))
print('IRAT impact estimate: 5.8')
# Geometric Mean of HA and NA risk scores: 0.024893
# Emergenet prediction of IRAT emergence estimate: 6.3
# IRAT emergence estimate: 6.6
# Emergenet prediction of IRAT impact estimate: 6.4
# IRAT impact estimate: 5.8
```

Links to additional resources

- To download the package, visit our package page on PyPI
- For the theoretical framework of Emergenet and full results of our experiments, see our paper
- For source code and examples, visit our GitHub repository