

Part II: Learning from EHR data



**Stockholms
universitet**

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Panagiotis Papapetrou

Who are we?

DSV @ Stockholm University

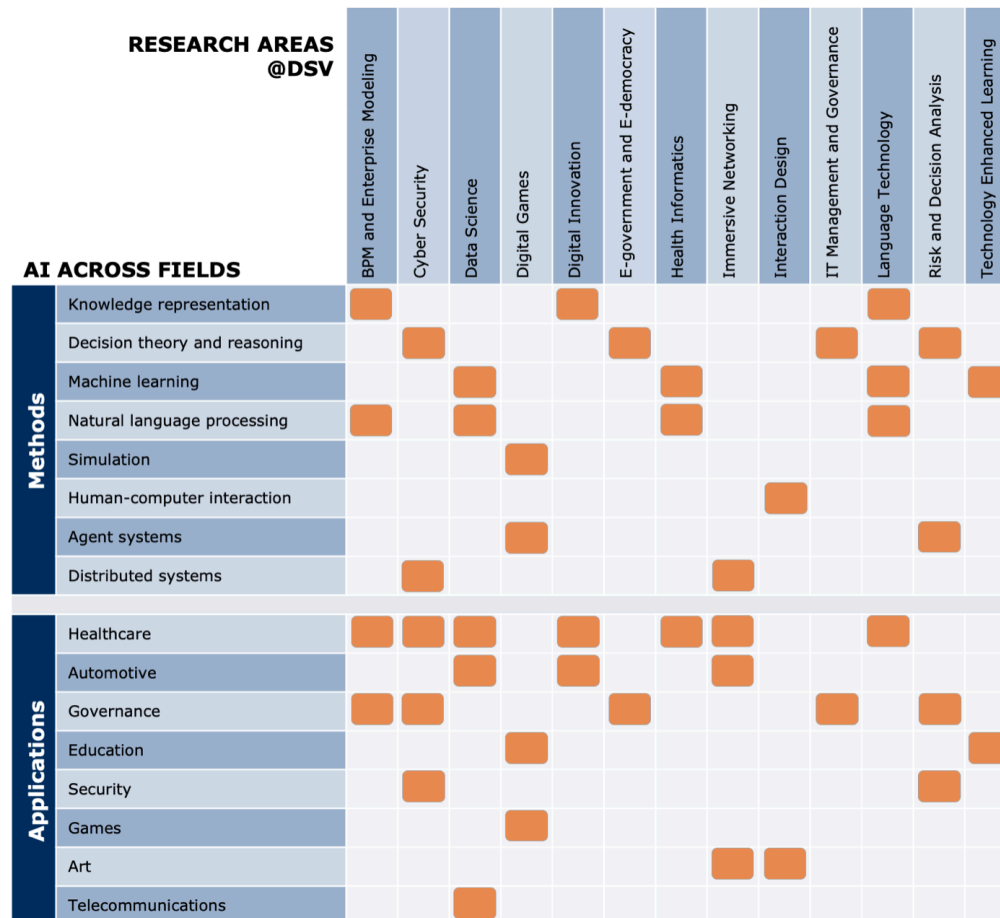
- **DSV**: Data- och Systemvetenskap (Computer and Systems Sciences)
- # of students: **approx. 5400**
- # of staff members: 176 (60 profs. / associate profs. / lecturers)



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Our AI research arena @ DSV



Research at DSV – data science group

Main research areas:

- Sequential and temporal data mining
- Interpretability and explainability of machine learning methods
- Ethics and bias in machine learning
- Machine learning for healthcare applications
- Clinical text mining and natural language processing

Current projects:

- **EXTREMUM (2020-2024):** explainable and ethical ML for healthcare
- **Covid-Sim (2020-2021):** reinforcement learning for simulation of pandemics
- **TEMPOMiner (2017-2020):** temporal data mining for detecting ADEs in healthcare

Part II - Outline

- **Temporal abstractions** for EHR data
- **Actionable models** and **counterfactual explanations** for EHR data
- **Attention-based** deep learning for healthcare event prediction
- **Interpretable ranking** and **classification** of **radiography exams**

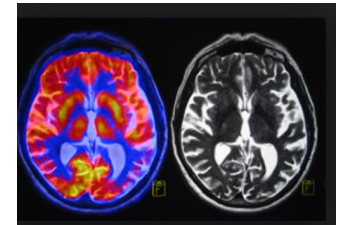
Electronic Health Records: content

Longitudinal collection of **electronic health information** about individual **patients** and **populations**

- **Diagnoses**
- **Drug prescriptions**
- **Clinical tests**
- **More complex structures**

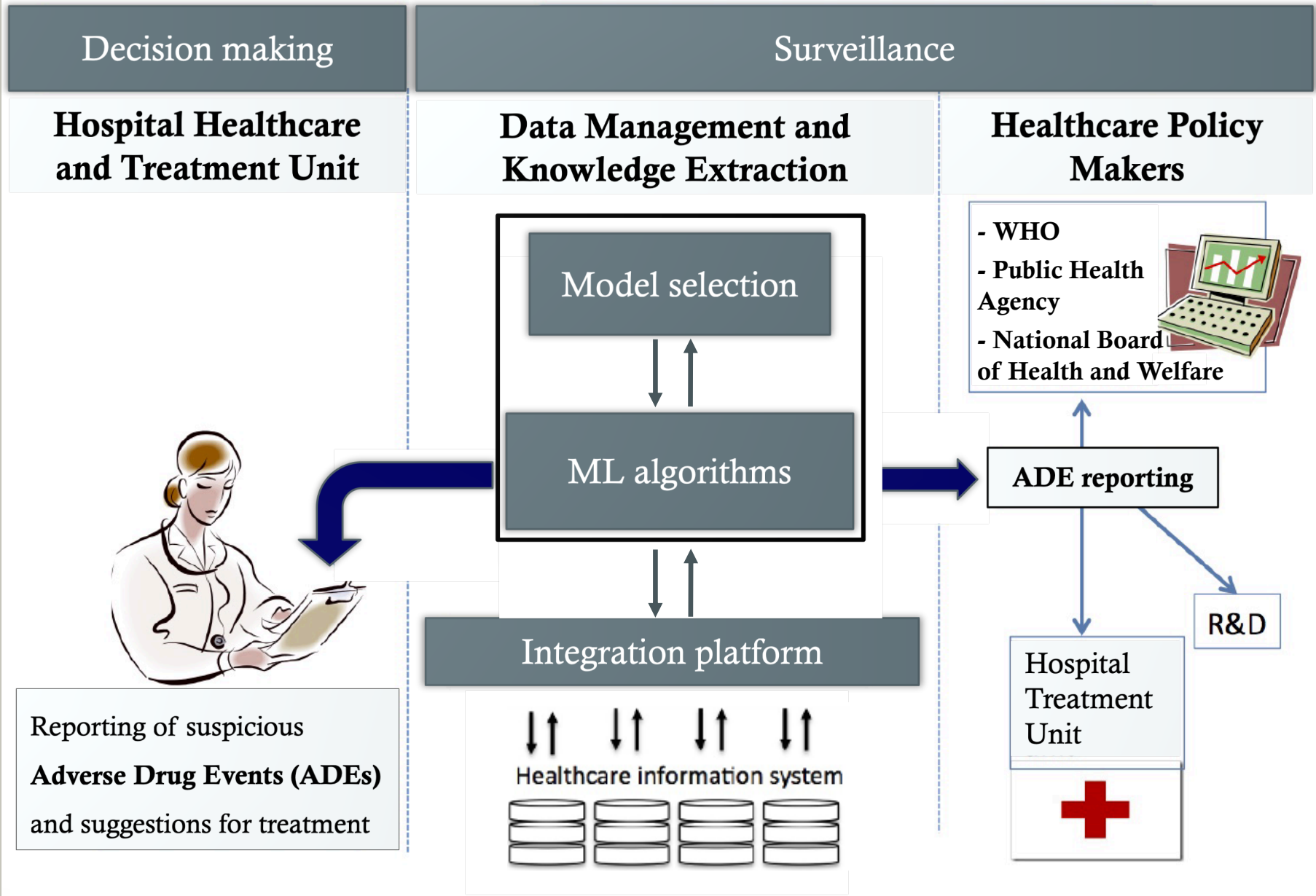
I25.110

A01AD05



- clinical notes
- medical images
- MRIs
- ECGs
- ...





ICD10* codes

- 10th revision of the **International Classification of Diseases and Related Health Problems**
- a classification system that is used to record medical activity
- the system enables classification and quantification of diseases and other health-related issues

3 -7
characters
long



* <http://www.ahima.org/icd10>

ICD10 codes: examples (total of 22 chapters)

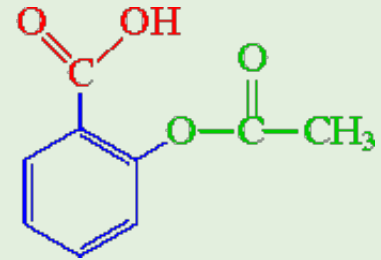
| Chapter | Code Range | Estimated # of Codes | Description |
|---------|------------|----------------------|---|
| 1 | A00-B99 | 1,056 | Certain infectious and parasitic diseases |
| 2 | C00-D49 | 1,620 | Neoplasms |
| 3 | D50-D89 | 238 | Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism |
| 4 | E00-E89 | 675 | Endocrine, nutritional and metabolic diseases |
| 5 | F01-F99 | 724 | Mental, Behavioral and Neurodevelopmental disorders |
| 6 | G00-G99 | 591 | Diseases of the nervous system |
| 7 | H00-H59 | 2,452 | Diseases of the eye and adnexa |
| 8 | H60-H95 | 642 | Diseases of the ear and mastoid process |
| 9 | I00-I99 | 1,254 | Diseases of the circulatory system |
| 10 | J00-J99 | 336 | Diseases of the respiratory system |
| 11 | K00-K95 | 706 | Diseases of the digestive system |

ICD10 codes: examples

| Code | Description |
|-----------------------|--|
| Combination Codes | |
| I25.110 | Atherosclerotic heart disease of native coronary artery with unstable angina pectoris |
| Increased Specificity | |
| S72.044G | Non-displaced fracture of base of neck of right femur, subsequent encounter for closed fracture with delayed healing |
| Laterality | |
| C50.511 | Malignant neoplasm of lower-outer quadrant of right female breast |
| C50.512 | Malignant neoplasm of lower-outer quadrant of left female breast |
| "X" Placeholder | |
| H40.11X2 | Primary open-angle glaucoma, moderate stage |

ATC* codes

- Anatomical Therapeutic Chemical codes, first published in 1976
- Used for classification of **active ingredients** of drugs
- Based on the organ/system on which they act
 - **therapeutic**
 - **pharmacological** and **chemical** properties
- Controlled by the World Health Organization Collaborating Centre (WHOCC) for drug statistics methodology



acetylsalicylic acid (aspirin)

* http://www.whooc.no/atc_ddd_index/

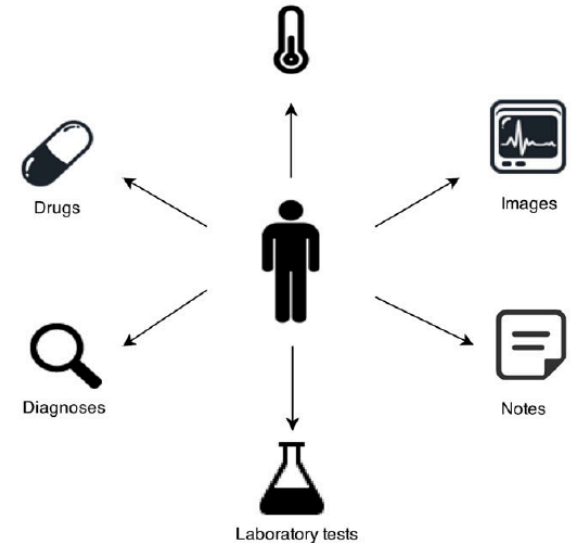
ATC codes – example: A10BA02

ATC codes classify drugs into five different levels

| Level | Content | Type | Example |
|-------|--------------------------|----------|--|
| I | anatomical main group | 1 letter | A: alimentary tract and metabolism |
| II | therapeutic subgroup | 2 digits | A10: diabetes drugs |
| III | pharmacological subgroup | 1 letter | A10B: blood glucose lowering drugs, excl. insulins |
| IV | chemical subgroup | 1 letter | A10BA: biguanides |
| V | chemical substance | 2 digits | A10BA02: metformin |

Extracting features from EHRs













- **Mainly two lines of approaches:**
 - static features
 - temporal features

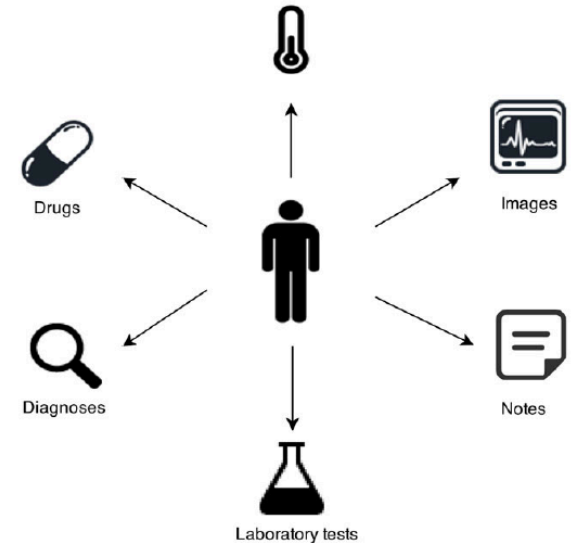


Static features

- **Mainly two lines of approaches:**

- static features
- temporal features

| | ADE |  |  |  | ... |  |  |  | ... |  |  |  | ... |
|---|-----|---|---|---|-----|---|---|---|-----|---|--|---|-----|
|  | YES | ✓ | | ✓ | ... | | ✓ | ✓ | ... | | ✓ | | ... |
|  | NO | | | ✓ | ... | | | | ... | ✓ | | ✓ | ... |
|  | NO | ✓ | ✓ | | ... | ✓ | | ✓ | ... | | ✓ | | ... |
| ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ | ⋮ |



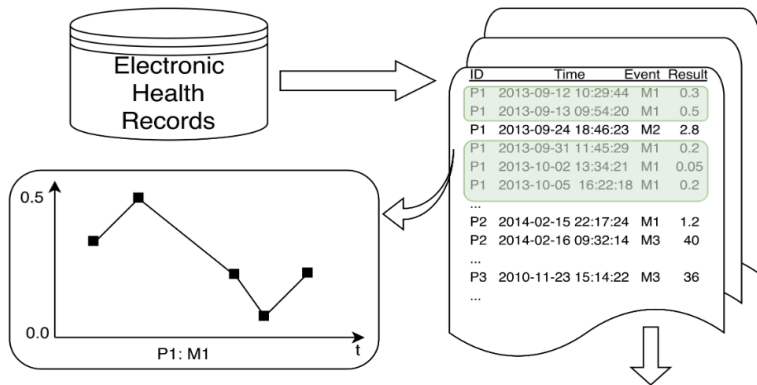
The **class labels** assigned depending on task at hand, e.g., ADE detection

- **Existing out-of-the-box classifiers are used**

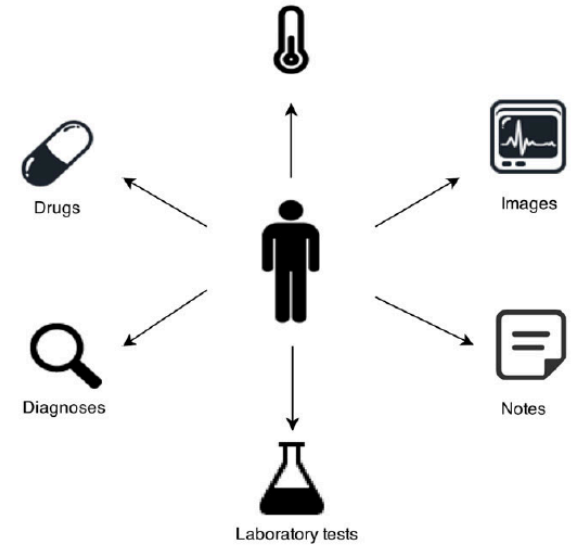
- Decision trees, random forests, SVMs, deep learning architectures [Chazard2011, Zhao2013, Karlsson2013, Shickel2018, Bampa2019]

Temporal features

- **Mainly two lines of approaches:**
 - static features
 - **temporal features**



| ID | C | M1 | M2 | M3 | ... |
|-----|-----|-----|-----|-----|-----|
| P1 | 1 | | | NA | ... |
| P2 | 0 | | | | ... |
| P3 | 1 | | NA | | ... |
| ... | ... | ... | ... | ... | ... |

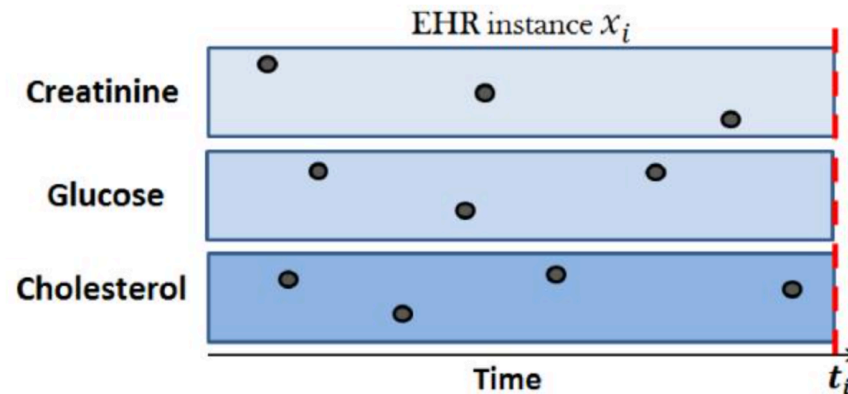


Clinical measurements:

- different units
- times of measurement
- sparsity

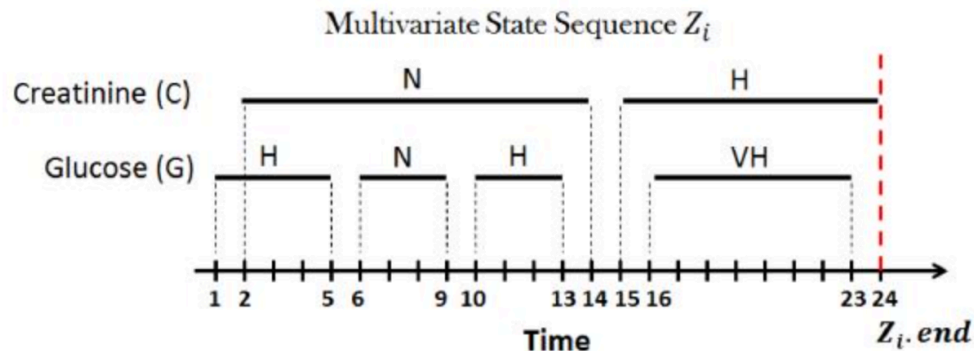
Temporal abstractions of EHRs

- Database: **EHRs of Patients**
- **Each EHR:**
 - **Multiple temporal variables** registered and evolving concurrently
 - Each variable with **multiple readings** until a **critical time point t_i** , e.g., glucose, creatinine, cholesterol
 - **Class label:** Disease/symptom detected at time t_i (**event of interest**)



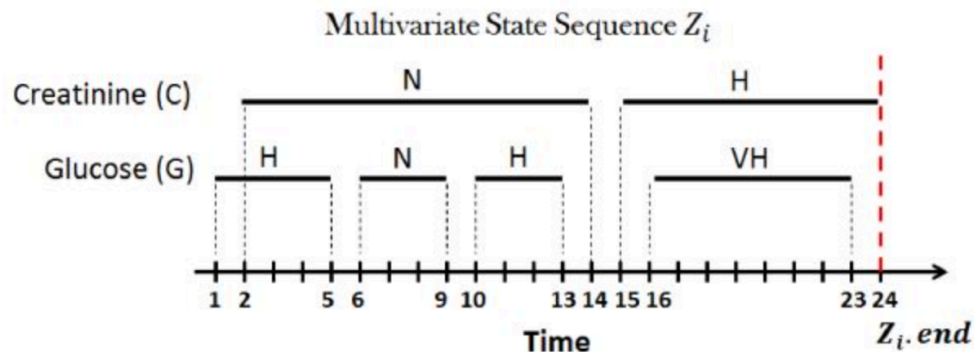
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Two types of temporal abstractions

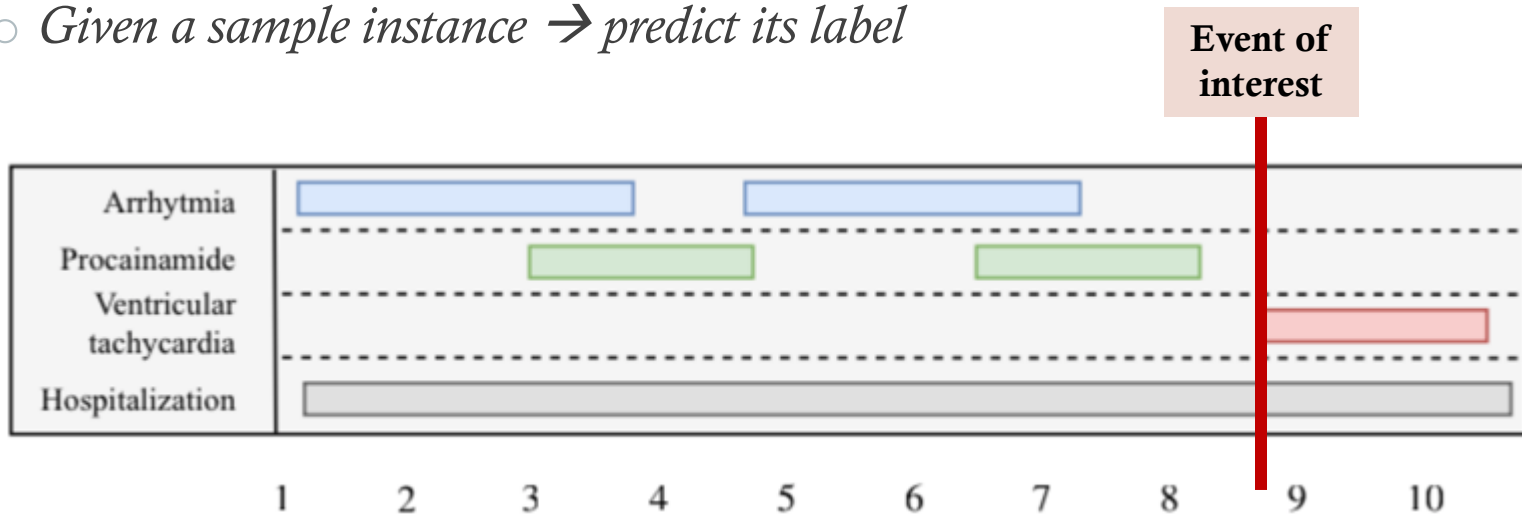
- **Trend abstraction:**
 - e.g., *decreasing*, *steady*, *increasing*
 - time series segmentation + identify slopes
- **Value abstraction**
 - e.g., *very low*, *low*, *normal*, *high*, *very high*
 - use 10^{th} , 25^{th} , 75^{th} , and 90^{th} percentiles on the lab values to define [Batal2012]



Temporal abstractions of EHRs

- **Supervised temporal prediction [Batal2012, Rebane2019]**


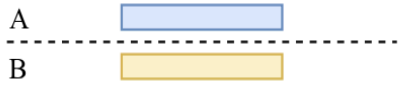
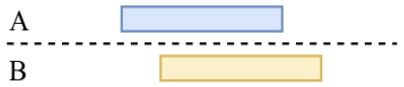
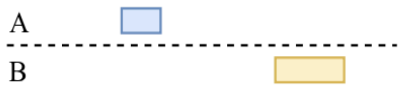



- Given a **labeled dataset** of temporal instances up to time t_i
- Find **frequently occurring** “temporal patterns” for each label
- *Given a sample instance \rightarrow predict its label*



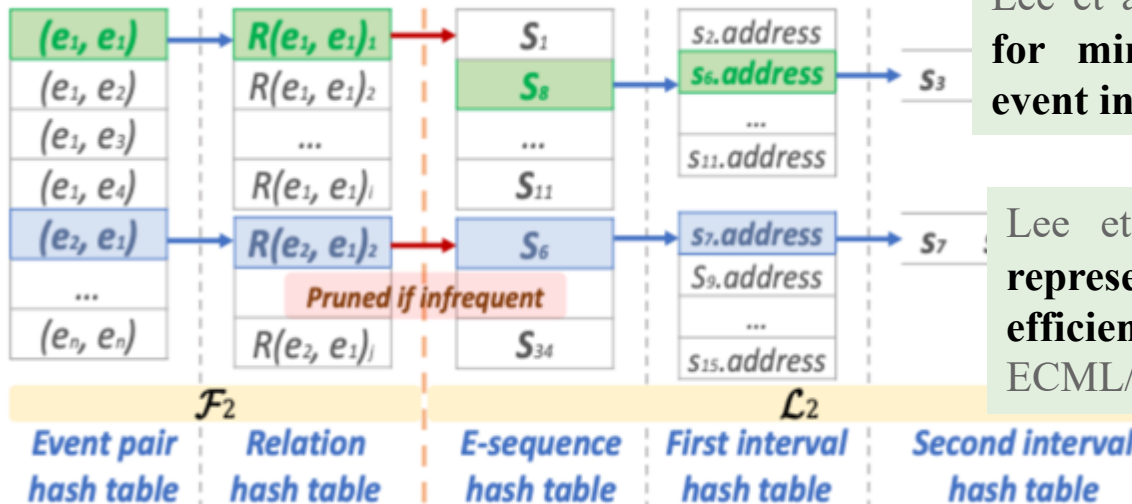
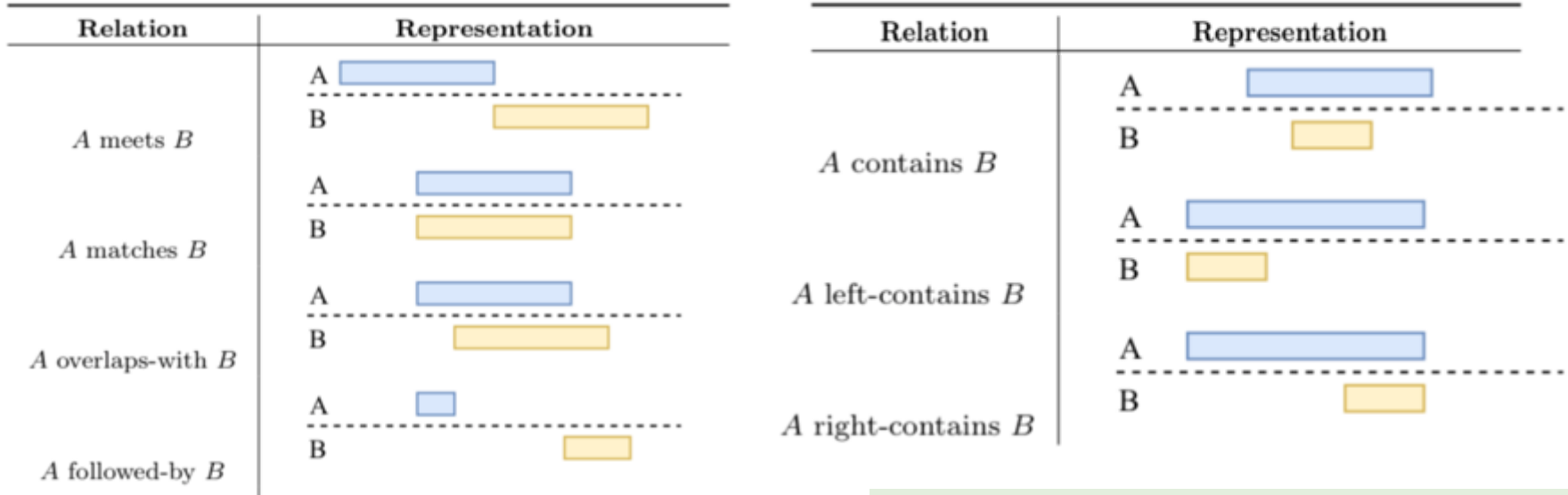
Temporal abstraction patterns

- **What is a temporal pattern?**
 - a sequence of “*temporal relations*” between state intervals A and B
- **What kind of “temporal relations”?**

Based on **Allen’s temporal logic**

| Relation | Representation |
|------------------------|---|
| A meets B |  |
| A matches B |  |
| A overlaps-with B |  |
| A followed-by B |  |
| A contains B |  |
| A left-contains B |  |
| A right-contains B |  |

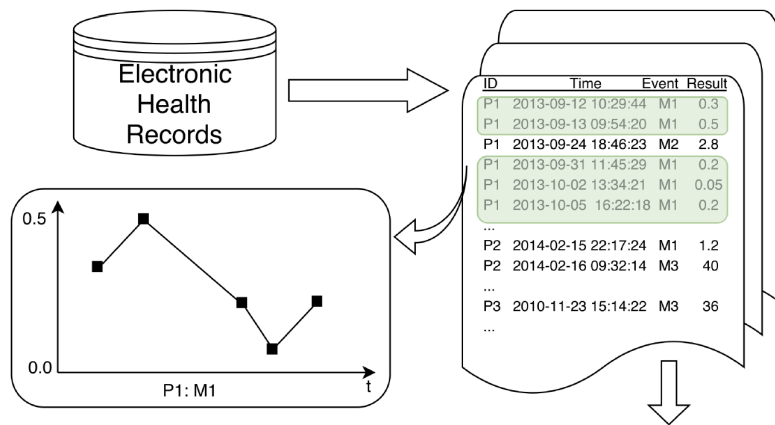
Mining temporal abstraction patterns



Lee et al., **Z-Miner: an efficient method for mining frequent arrangements of event intervals**, KDD 2020

Lee et al., **Z-Embedding: A spectral representation of event intervals for efficient clustering and classification**, ECML/PKDD 2020

Temporal abstractions of sparse EHRs



| ID | C | M1 | M2 | M3 | ... |
|-----|-----|-----|-----|-----|-----|
| P1 | 1 | | | NA | ... |
| P2 | 0 | | | | ... |
| P3 | 1 | | NA | | ... |
| ... | ... | ... | ... | ... | ... |


Hielscher et al. *Mining Longitudinal Epidemiological*

Zhao et al. *Learning from Heterogeneous Temporal*

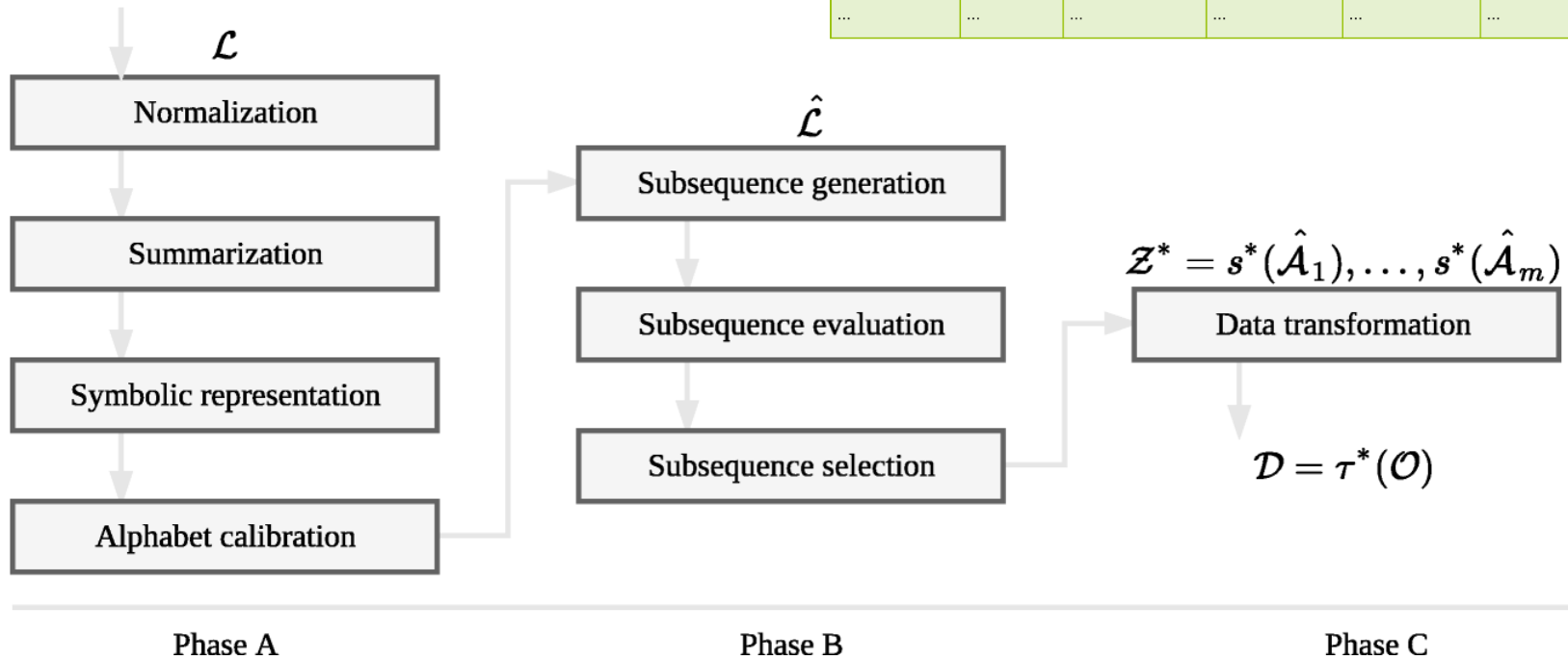
Bagattini et al. *A classification framework for exploiting sparse multi-variate temporal features with application to adverse drug event detection in medical records*, BMC Medical Informatics and Decision Making, 2019

Rebane et al. *SMILE: a feature-based temporal abstraction framework for event-interval sequence classification*, Data Mining and Knowledge Discovery, accepted [pre-print online]

Framework overview

| ID | C | M1 | M2 | M3 | ... |
|-----|-----|---|---|---|-----|
| P1 | 1 |  |  | NA | ... |
| P2 | 0 |  |  |  | ... |
| P3 | 1 |  | NA |  | ... |
| ... | ... | ... | ... | ... | ... |

Multi-variate feature representation

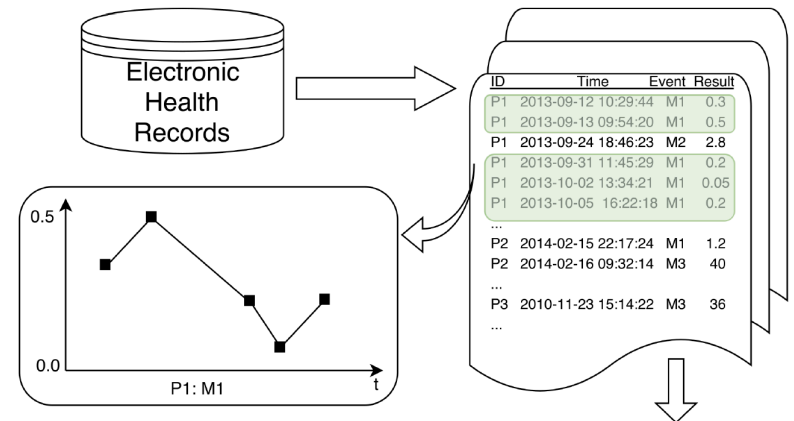


Phase A: normalization

- Z-normalization**

- Each multi-variate feature S is z-normalized:

$$S := \frac{\sum_{i=1}^{|S|} \{s_i - \mu(S)\}}{\sigma(S)}$$



| ID | C | M1 | M2 | M3 | ... |
|-----|-----|-----|-----|-----|-----|
| P1 | 1 | | | NA | ... |
| P2 | 0 | | | | ... |
| P3 | 1 | | NA | | ... |
| ... | ... | ... | ... | ... | ... |

Phase A: summarization

- Z-normalization**

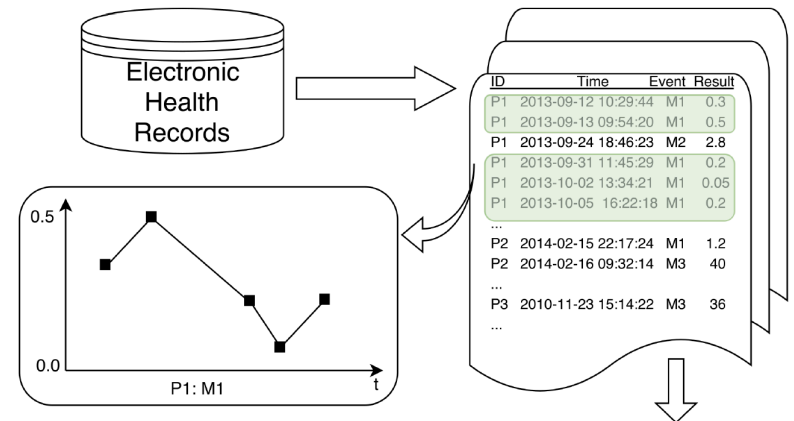
- Each multi-variate feature S is z-normalized:

$$S := \frac{\sum_{i=1}^{|S|} \{s_i - \mu(S)\}}{\sigma(S)}$$

- Summarization**

- Piecewise Aggregate Approximation (PAA)
- Dimensionality reduction from d to w

$$\bar{S} = \{\bar{s}_1, \dots, \bar{s}_w\}$$



| ID | C | M1 | M2 | M3 | ... |
|-----|-----|-----|-----|-----|-----|
| P1 | 1 | | | NA | ... |
| P2 | 0 | | | | ... |
| P3 | 1 | | NA | | ... |
| ... | ... | ... | ... | ... | ... |

$$\bar{s}_i = \frac{w}{d} \sum_{j=\frac{d}{w}(i-1)+1}^{\frac{d}{w}i} s_j$$

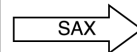
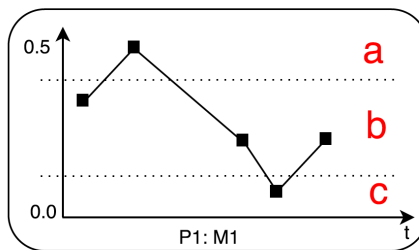
Phase A: symbolic representation

- **SAX mapping**

- each record is mapped to a string using SAX
- **length:** number of measurements
- **alphabet:** 2 – 5, or set using domain knowledge

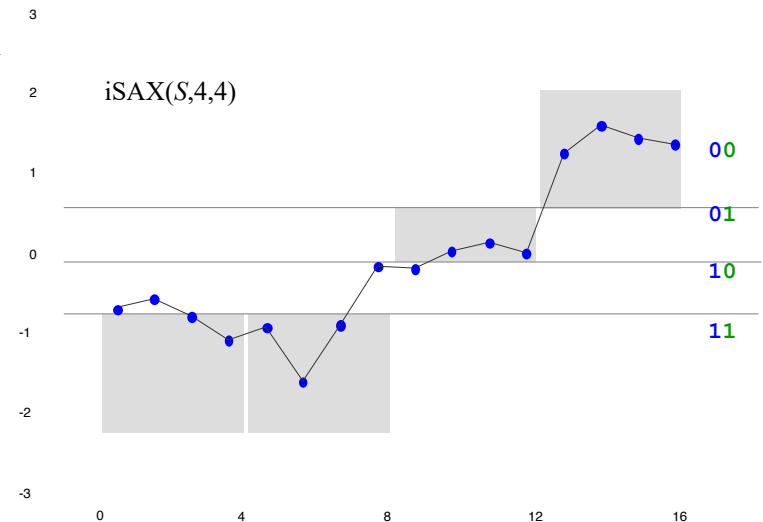
Discretize into a **vector of symbols**

- breakpoints map to small alphabet α of symbols



Sequence for P1 on M1:

"babcb"



Phase B: mapping to real features

multi-variate
feature

bacccc
cbbc
abbbba
bbbc
baaacbb
bcccab

reference feature

bbaab



distance function

real-valued
feature

3.45
1.23
5.56
...



Phase B: subsequence enumeration

- *s-shapelet* generation:

- random subsequences s of length $t \in [1, l_{max}]$

l_{max} : max length of
a feature sequence

- *s-shapelet* evaluation:

- each s is converted to a **real value** based on its distance to each **multi-variate feature** sequence

$$Dist(s, \hat{S}) := \min_{s' \subseteq \hat{S}, |s'|=|s|} \{D(s, s')\}$$

Phase B: subsequence selection

- For each mutli-variate feature:
 - select the s-shapelet s^* with the max utility:

$$s^* := \arg \max_{s \in \hat{\mathcal{L}}} \text{Gain} (s, \delta_{osp}(s), \hat{\mathcal{L}})$$

$$s_{\alpha}^* := \arg \max_{s \in S_{\alpha}} \text{Gain} (s, \delta_{osp}(s), \hat{\mathcal{L}})$$

- select the alphabet size with the max utility

$$\alpha^* := \arg \max_{\alpha \in I} \text{Gain} (s_{\alpha}^*, \delta_{osp}(s_{\alpha}^*), \hat{\mathcal{L}})$$

- Final set of s-shapelets:

$$\mathcal{Z}^* = \left\{ s^* (\hat{\mathcal{A}}_1), \dots, s^* (\hat{\mathcal{A}}_m) \right\}$$

Phase C: transformation

- A function τ^* is learned:
 - transform any data object of the original multi-variate space to a set of real-valued features

$$\tau^* : \mathcal{A} \rightarrow \mathbb{R}^m$$

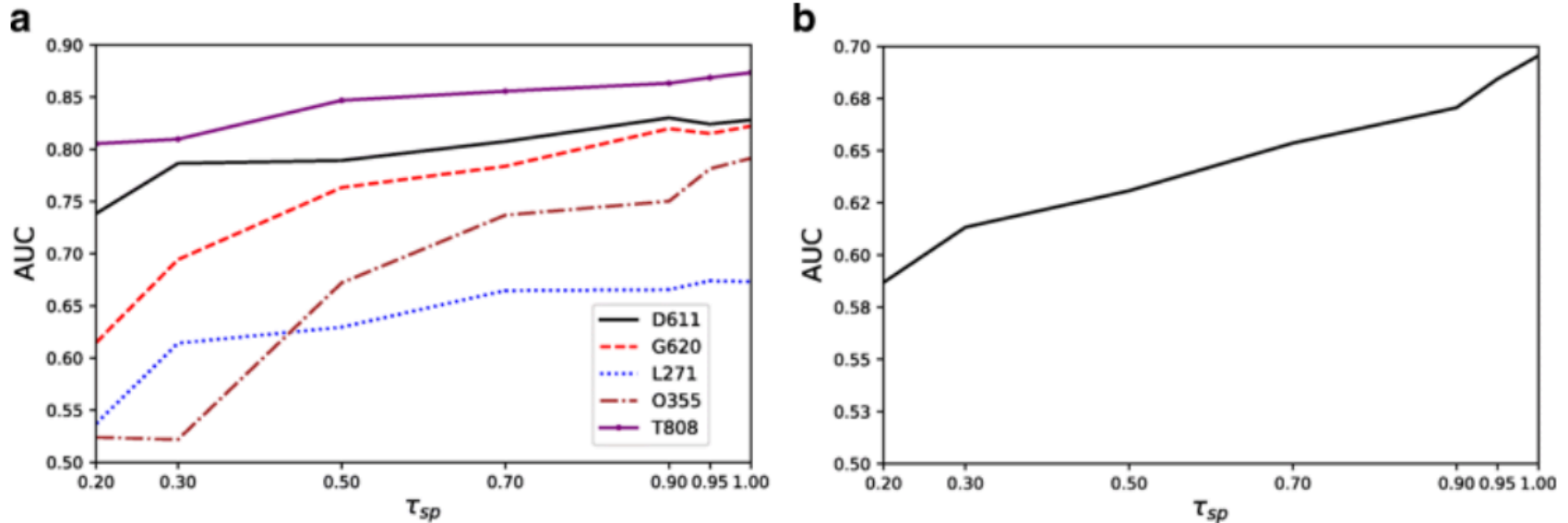
- Each data example is transformed using τ^* :

$$\tilde{O} = \tau^*(O)$$

| Dataset | Class label description | Pos. | Neg. | Feat. |
|---------|--|------|------|-------|
| D611 | Drug-induced aplastic anaemia | 593 | 105 | 285 |
| D642 | Drug-induced secondary sideroblastic anaemia | 217 | 9673 | 513 |
| D695 | Secondary thrombocytopenia | 1246 | 2148 | 450 |
| E273 | Drug-induced adrenocortical insufficiency | 70 | 259 | 229 |
| G620 | Drug-induced polyneuropathy | 96 | 783 | 258 |
| I952 | Drug-induced hypotension | 115 | 1287 | 324 |
| L270 | Drug-induced generalized skin eruption | 182 | 468 | 314 |
| L271 | Drug-induced localized skin eruption | 151 | 498 | 311 |
| M804 | Drug-induced osteoporosis with pathological fracture | 52 | 1170 | 282 |
| M814 | Drug-induced osteoporosis | 57 | 5097 | 434 |
| O355 | Maternal care for (suspected) damage to fetus by drugs | 146 | 260 | 148 |
| R502 | Drug-induced fever | 80 | 6434 | 498 |
| T782 | Adverse effects: anaphylactic shock | 131 | 856 | 293 |
| T783 | Adverse effects: angioneurotic oedema | 283 | 720 | 293 |
| T784 | Adverse effects: allergy | 574 | 415 | 294 |
| T801 | Vascular complications following infusion, transfusion and therapeutic injection | 66 | 609 | 229 |
| T808 | Other complications following infusion, transfusion and therapeutic injection | 538 | 138 | 229 |
| T886 | Drug-induced anaphylactic shock | 89 | 1506 | 363 |
| T887 | Unspecified adverse effect of drug or medicament | 1047 | 550 | 363 |

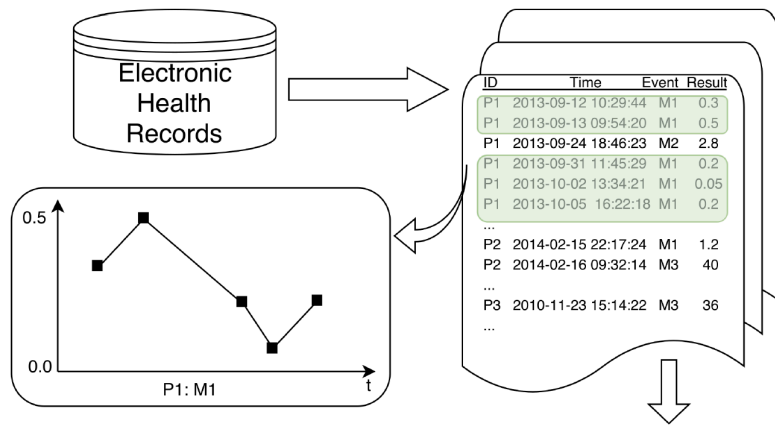
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| I | <ul style="list-style-type: none"> Adverse Drug Events (ADEs) are injuries that occur from the use of a drug, such as overdoses or dose reductions, or drug interactions They account for 3.7% of hospital admissions around the world ADEs have been estimated to come at a cost of \$3.5 billion/year in the U.S alone, despite ADEs being preventable | | | |
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lr: AUC vs feature sparsity



- As the % of **feature sparsity** increases, **AUC** also increases!
- Shorter s-shapelets (i.e., 2-8) are preferable to longer ones (> 20)

Temporal abstractions of sparse EHRs



| ID | C | M1 | M2 | M3 | ... |
|-----|-----|-----|-----|-----|-----|
| P1 | 1 | | | NA | ... |
| P2 | 0 | | | | ... |
| P3 | 1 | | NA | | ... |
| ... | ... | ... | ... | ... | ... |

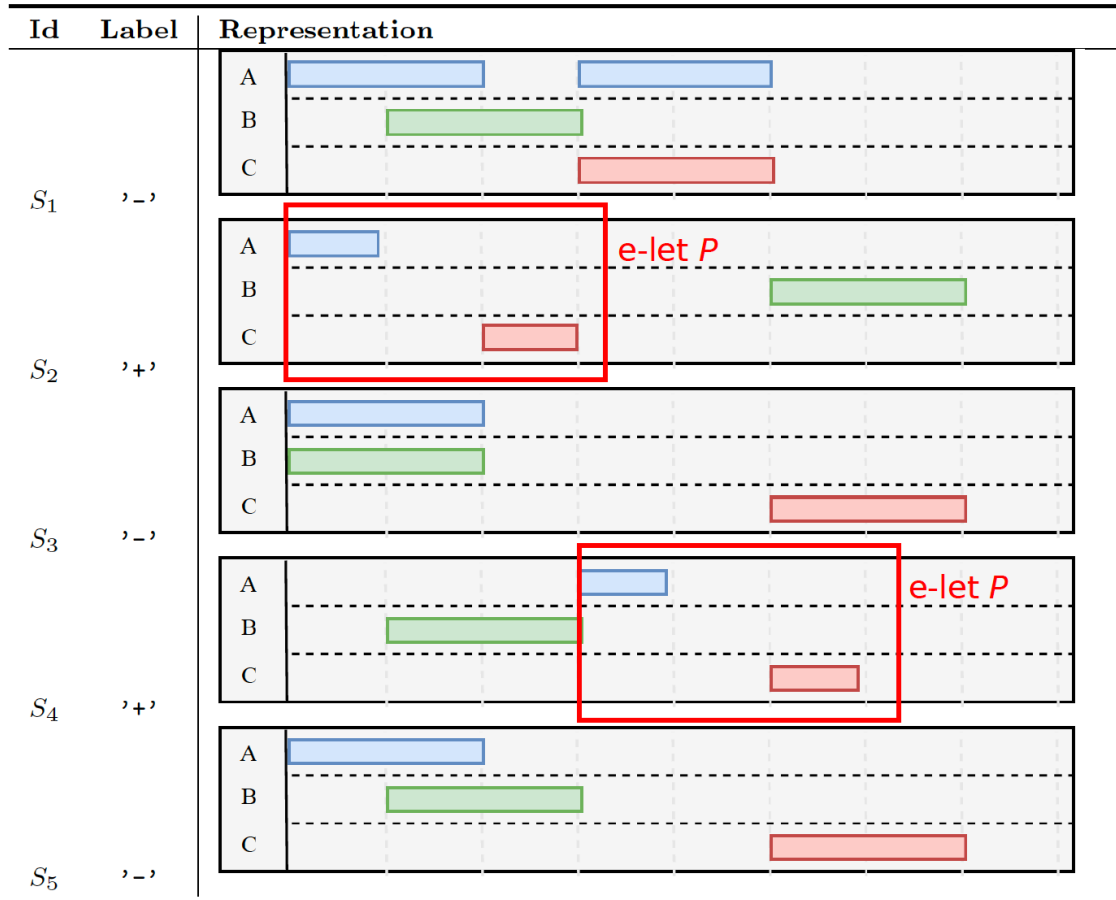
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The notion of e-lets



Class-distinctive Temporal abstraction subsequences

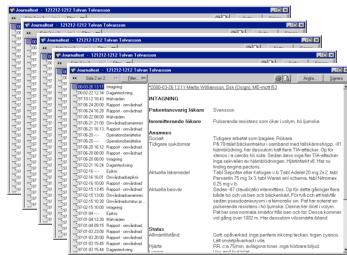
SMILE: a formulation that uses e-lets as classification features!

| Dataset | Accuracy | | | | Area under ROC | | | |
|-------------|--------------|--------------|--------------|--------------|----------------|--------------|-------|--------------|
| | RF | LR | DT | SVM | RF | LR | DT | SVM |
| AUSLAN2 | 0.485 | 0.335 | 0.465 | 0.305 | 0.686 | 0.668 | 0.674 | 0.696 |
| BLOCKS | 1.000 | 0.995 | 0.995 | 0.986 | 1.000 | 0.994 | 0.975 | 1.000 |
| CONTEXT | 0.988 | 0.979 | 0.963 | 0.996 | 1.000 | 0.999 | 0.969 | 0.997 |
| HEPATITIS | 0.831 | 0.735 | 0.769 | 0.823 | 0.890 | 0.789 | 0.788 | 0.813 |
| PIONEER | 0.988 | 0.981 | 0.950 | 0.969 | 1.000 | 1.000 | 0.894 | 0.969 |
| SKATING | 0.977 | 0.970 | 0.972 | 0.847 | 0.999 | 0.999 | 0.973 | 0.966 |
| D611 | 0.945 | 0.874 | 0.921 | 0.929 | 0.878 | 0.744 | 0.628 | 0.523 |
| D642 | 0.988 | 0.976 | 0.981 | 0.976 | 0.991 | 0.943 | 0.897 | 0.793 |
| D695 | 0.745 | 0.726 | 0.688 | 0.729 | 0.813 | 0.793 | 0.659 | 0.726 |
| E273 | 0.586 | 0.619 | 0.581 | 0.607 | 0.690 | 0.628 | 0.580 | 0.517 |
| G620 | 0.854 | 0.750 | 0.854 | 0.816 | 0.902 | 0.661 | 0.767 | 0.500 |
| I952 | 0.876 | 0.751 | 0.826 | 0.876 | 0.670 | 0.543 | 0.568 | 0.500 |
| L270 | 0.672 | 0.611 | 0.605 | 0.561 | 0.734 | 0.637 | 0.611 | 0.509 |
| L271 | 0.746 | 0.647 | 0.709 | 0.692 | 0.800 | 0.611 | 0.624 | 0.521 |
| O355 | 0.875 | 0.713 | 0.839 | 0.826 | 0.944 | 0.773 | 0.826 | 0.853 |
| R502 | 0.977 | 0.964 | 0.975 | 0.977 | 0.816 | 0.591 | 0.507 | 0.500 |
| T801 | 0.917 | 0.892 | 0.896 | 0.913 | 0.819 | 0.623 | 0.716 | 0.501 |
| T782 | 0.750 | 0.763 | 0.727 | 0.723 | 0.508 | 0.628 | 0.575 | 0.500 |
| T783 | 0.857 | 0.686 | 0.732 | 0.796 | 0.750 | 0.568 | 0.642 | 0.558 |
| T886 | 0.771 | 0.788 | 0.838 | 0.786 | 0.834 | 0.759 | 0.696 | 0.502 |
| Avg. | 0.841 | 0.788 | 0.814 | 0.807 | 0.836 | 0.748 | 0.728 | 0.672 |

Interpretable and actionable models

- Trade-offs between **interpretability** + accuracy
- Ability to **understand the** outcomes **without compromising** interpretability

I can tell you **what changes need to be done** to the patient record, so that I can **change my prediction** 😊



| ID | DATE | PARAMETER | VALUE |
|-----------|------------|----------------|-----------------------|
| 112121212 | 2012-01-01 | Age | 75 |
| 112121212 | 2012-01-01 | Weight | 80 |
| 112121212 | 2012-01-01 | Heart Rate | 72 |
| 112121212 | 2012-01-01 | Blood Pressure | 120/80 |
| 112121212 | 2012-01-01 | Cholesterol | 200 |
| 112121212 | 2012-01-01 | Sugar | 100 |
| 112121212 | 2012-01-01 | Smoking | Yes |
| 112121212 | 2012-01-01 | Diabetes | No |
| 112121212 | 2012-01-01 | Hypertension | Yes |
| 112121212 | 2012-01-01 | Heart Failure | No |
| 112121212 | 2012-01-01 | Stroke | No |
| 112121212 | 2012-01-01 | Angina | No |
| 112121212 | 2012-01-01 | Medication | Aspirin, Beta-blocker |

black box classifier

The patient will die from HF in **2 days!**

Now what? Please tell me **why?**



ADE prediction (Yes/No)

- Main task:**

predict the **presence** or **absence** of an ADE in a patient's **next visit** given EHR data entries from **all previous visits!**



Adverse drug event ICD-10 codes

| | |
|------|--|
| D611 | Drug-induced aplastic anaemia |
| D642 | Drug-induced secondary sideroblastic anaemia |
| D695 | Secondary thrombocytopenia |
| E273 | Drug-induced adrenocortical insufficiency |
| G620 | Drug-induced polyneuropathy |
| I952 | Drug-induced hypotension |
| L270 | Drug-induced generalized skin eruption |
| L271 | Drug-induced localized skin eruption |
| M804 | Drug-induced osteoporosis with pathological fracture |
| M814 | Drug-induced osteoporosis |
| O355 | Maternal care for (suspected) damage to fetus by drugs |
| R502 | Drug-induced fever |
| T782 | Adverse effects: anaphylactic shock |
| T783 | Adverse effects: angioneurotic edema |
| T784 | Adverse effects: allergy |
| T801 | Vascular complications following infusion, transfusion and therapeutic injection |
| T886 | Drug-induced anaphylactic shock |

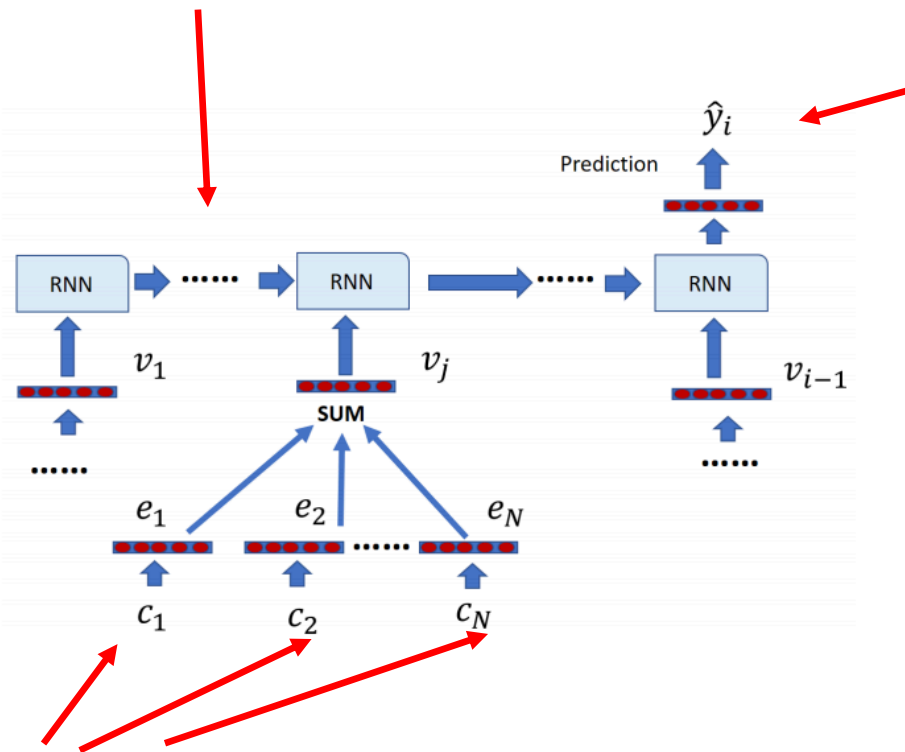
Main goals

- Empirically evaluate **which** code-level interpretable deep learning architecture provides the **best performance** for ADE prediction
- Examine **which** data sources (**diagnoses, medications, lab tests**) best aid in ADE **predictive performance** and **medical interpretability**
- Determine the extent in which code-level **attention mechanisms** contribute to **interpretability for ADE predictions**

Methods (Vanilla RNN)

Pass info from **one visit to the next** within network

Predict ADE yes/no
in the future



Input: **medical codes c** for each **medical visit v** to train the network across patients

Limitations of Vanilla RNN

- Standard seq2seq models are normally composed of an **encoder-decoder architecture**
- **Encoder:** processes the input sequence and summarizes the information into a **context vector** of **fixed length**
- This representation is expected to be a **good summary** of the entire input sequence
- **Decoder:** initialized with the context vector and uses it to generate the transformed output

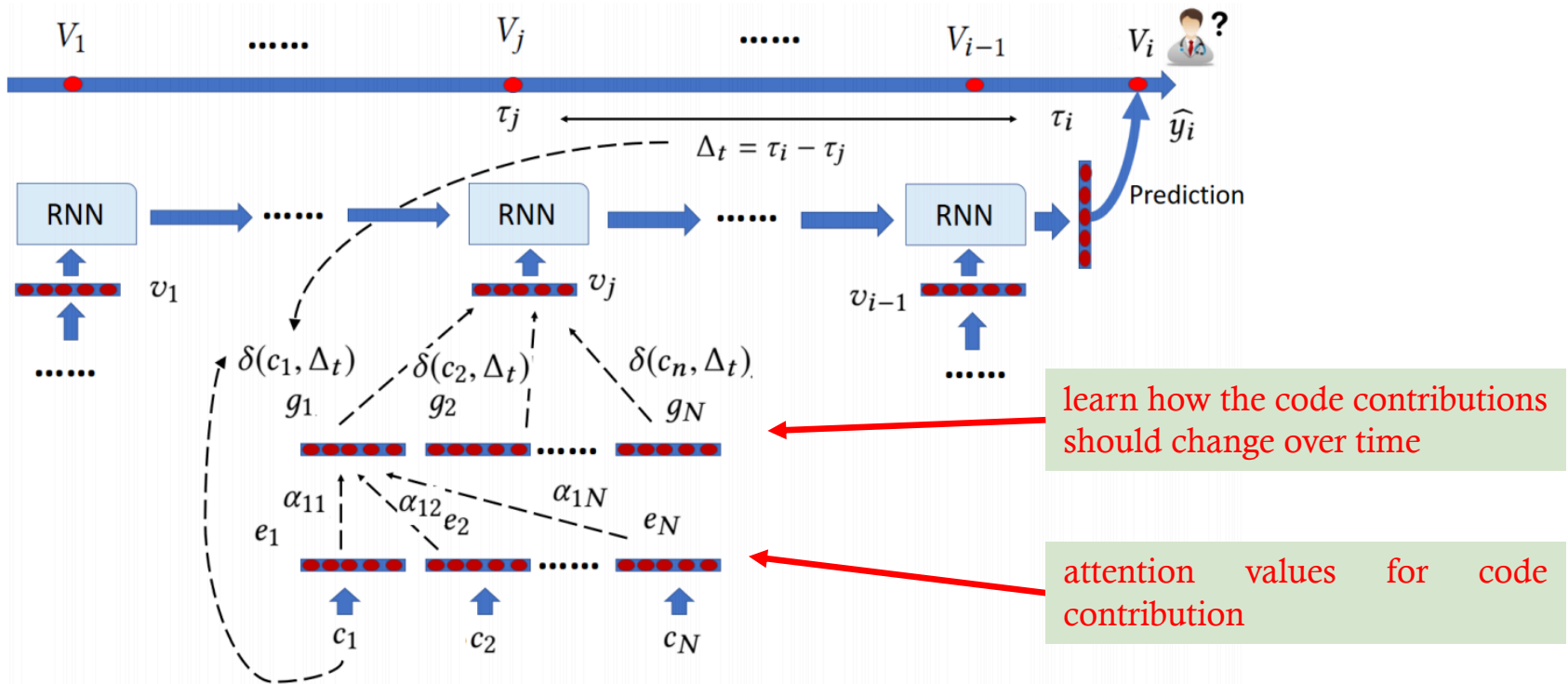
Limitations of Vanilla RNN

- Structural limitation:
 - **fixed-length** context vector
- Why?
 - **inability** of remembering longer sequences
 - **earlier parts** of the sequence are **forgotten** once the entire sequence is processed
- The **attention mechanism** concept was born to resolve this problem
- **Attention mechanism:** keep the intermediate encoder states and **utilize all of them** in order to construct the context vectors required by the decoder to generate the output sequence

Medical ”attention”

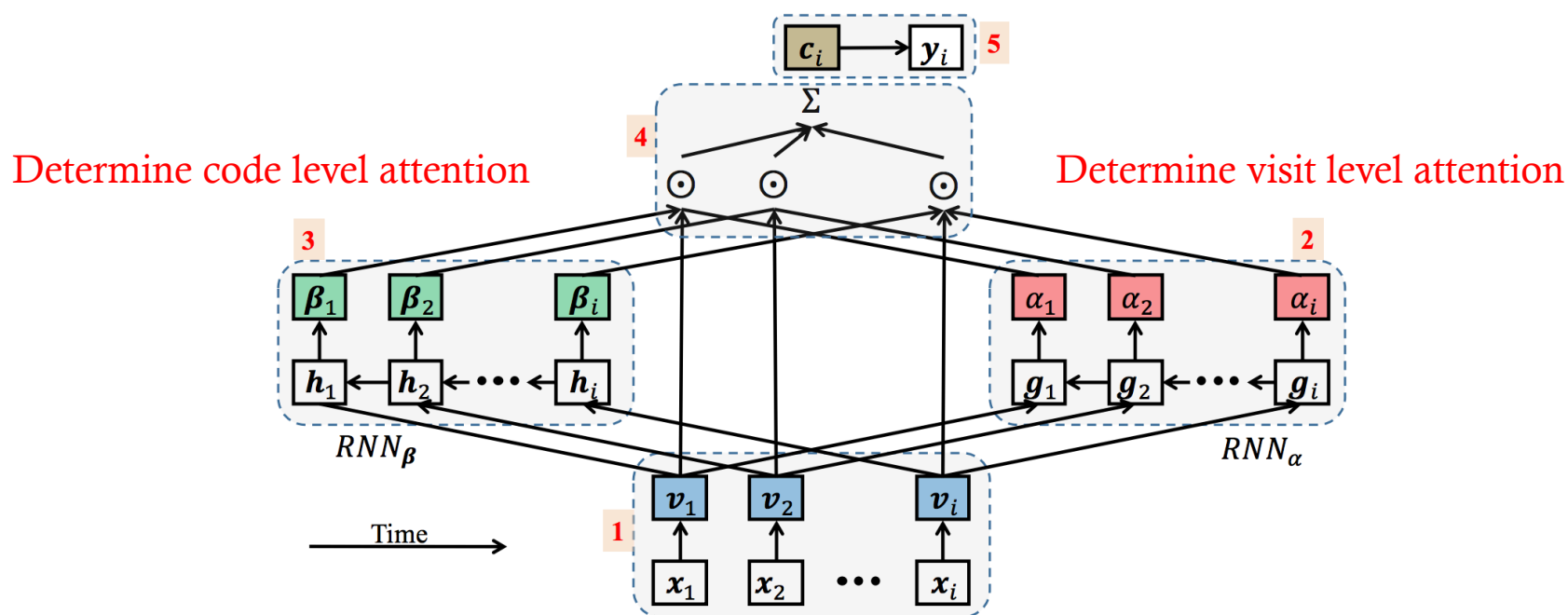
- We may want the decoder to **focus more** on, e.g., visits 1 and 3, while **paying less attention** to the remaining visits of the patient
- Solution:
 - Train a **feed forward neural network**
 - **learn** to identify **relevant encoder states**
 - generate a **high score** for the visits for which attention is to be paid while **low score** for the visits which are to be ignored

Methods (Timeline, Bai 2018)



$$\phi(c_x) = \sum_{j=1}^N \delta(c_j, \Delta t) \alpha_{j,x}$$

Methods (RETAIN, Choi 2016)



$$\omega(y_i, x_{j,k}) = \alpha_j W(\beta_j \odot W_{emb}[:, k])x_{j,k}$$

Experimental Setup

- **RETAIN** and **Timeline**:
 - proven to be **competitive** state-of-the-art architectures which permit thorough **interpretability** down to the code-level
 - **trained for ADE prediction** using an original data source consisting of information for 1,4 million patients obtained from HealthBank at Stockholm University

Experimental Setup

- Non-ADE ICD-10 and ATC codes were reduced to higher level hierarchical categories by selecting only the first three characters
- Such categories correspond to main categories of ICD-10 codes and to therapeutic subgroups in the case of ATC codes
- # of ICD-10 categories: 1692
- # of ATC subgroups: 109
- Visits defined on a monthly basis
- Patients also needed at least three such visits to be included
- Two data sets: including or excluding medication data

Results: AUC / F1

| Dataset | Area under ROC | | Micro F1-Score | |
|--------------------|----------------|----------|----------------|----------|
| | RETAIN | Timeline | RETAIN | Timeline |
| Without medication | 0.765 | 0.668 | 0.789 | 0.699 |
| With medication | 0.759 | 0.693 | 0.775 | 0.754 |

RETAIN was determined to be the **best performing architecture** under the conditions of using diagnoses data

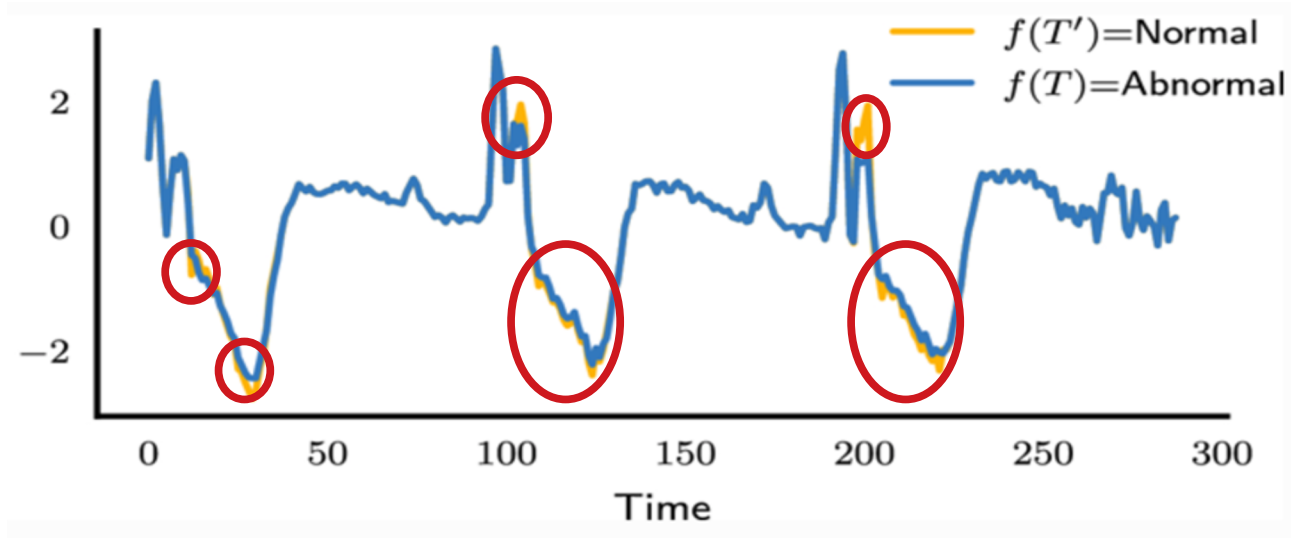
Interpretability of RETAIN

| Code | Description | Score |
|-------------------|----------------------------------|-------|
| Visit 1 | | |
| L50 | Urticaria | 0.214 |
| Visit 2 | | |
| R42 | Dizziness and giddiness | 0.034 |
| A02 [†] | Drugs for acid related disorders | 0.049 |
| Visit 3 | | |
| L50 | Urticaria | 0.239 |
| R06 [†] | Antihistamines for systemic use | 0.344 |
| H02 [†] | Corticosteroids for systemic use | 0.321 |
| Visit 4 | | |
| L50 | Urticaria | 0.225 |
| R06 [†] | Antihistamines for systemic use | 0.322 |
| C01 [†] | Cardiac therapy | 0.205 |
| H02 [†] | Corticosteroids for systemic use | 0.230 |
| Prediction | | |
| T784 | Adverse effects: allergy | 0.891 |

Rebane et al. **Exploiting Complex Medical Data with Interpretable Deep Learning for Adverse Drug Event Prediction.** Journal of AI in Medicine

Very high risk from given history

Time series counterfactuals



Problem: What is the min # of changes to the **abnormal** time series to convert it to **normal** ?

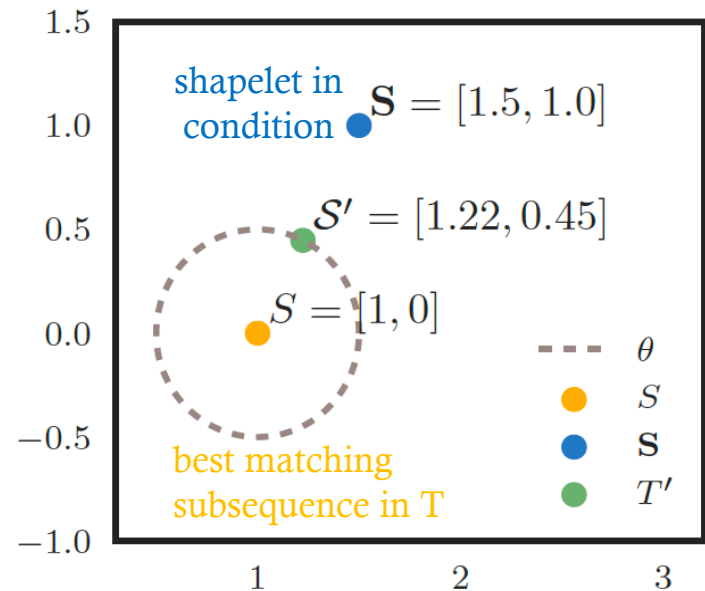
Karlsson et al. **Locally and globally explainable time series tweaking.** In Knowledge and Information Systems 2020

Solution outline

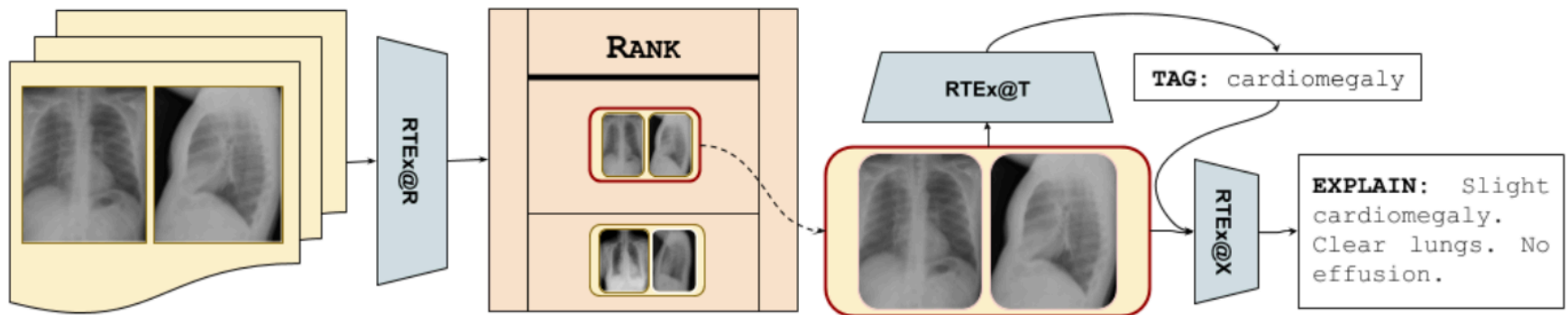
- Consider S as an **m-dimensional point**
- Define an **m-sphere** with S as its center and radius θ

- The **transformed time series counterpart of \mathbf{S}** is given by the following equation:

$$\tau_{\mathcal{S}}(\mathbf{S}, p_{ik}^j, \epsilon) = \mathcal{S}_k^j + \frac{\mathcal{S}_k^j - \mathbf{S}}{\|\mathcal{S}_k^j - \mathbf{S}\|_2} (\theta_k^j + (\epsilon \delta_{ik}^j))$$

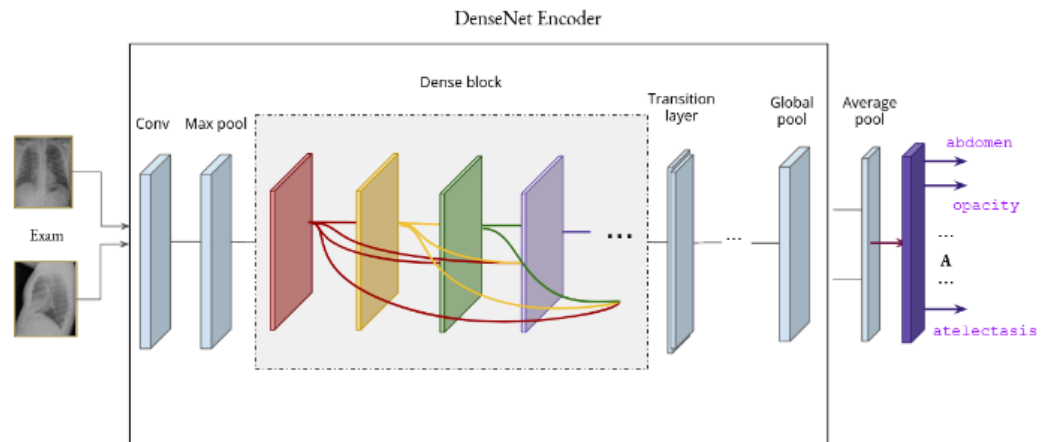


Automated ranking/tagging/captioning of radiography exams

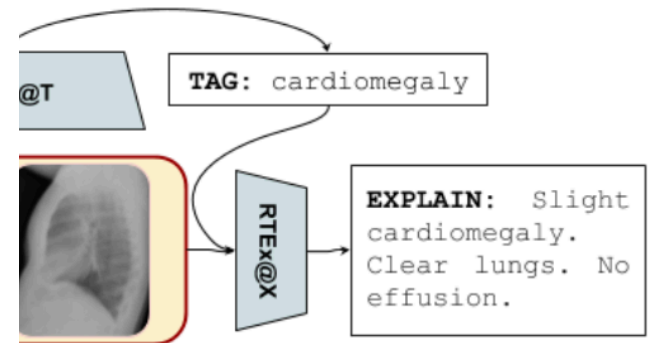


Diagnostic text: The cardiac contours are normal. XXXX basilar atelectasis. The lungs are clear. Thoracic spondylosis. Lower cervical XXXX arthritis.

Abnormality tags: Atelectases, Cervical Arthritis, Atelectasis, Spondylarthritis, Thoracic Spondylosis.

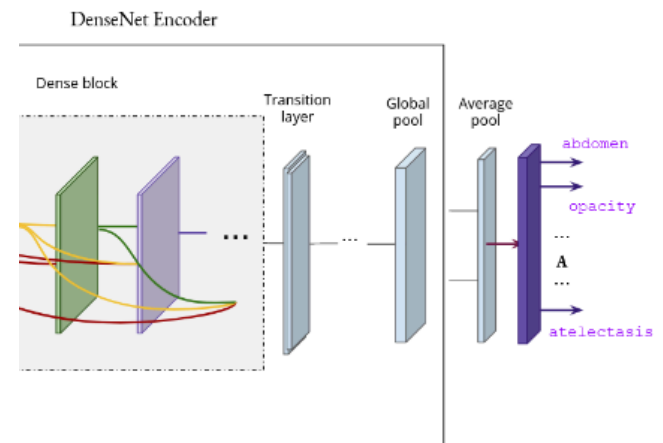


Automated ranking/tagging/captioning of radiography exams

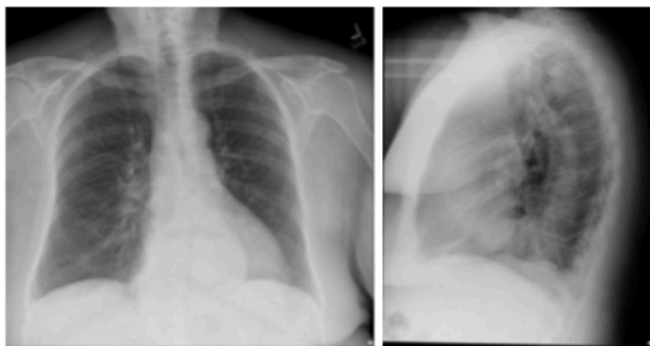
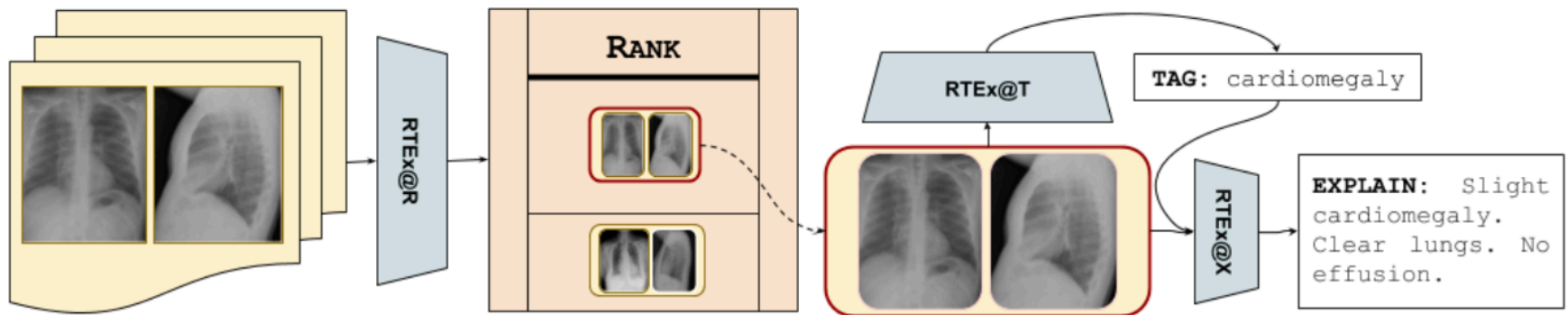


Diagnostic text: The cardiac contours are normal. XXXX basilar atelectasis. The lungs are clear. Thoracic spondylosis. Lower cervical XXXX arthritis.

Abnormality tags: Atelectases, Cervical Arthritis, Atelectasis, Spondylarthritis, Thoracic Spondylosis.

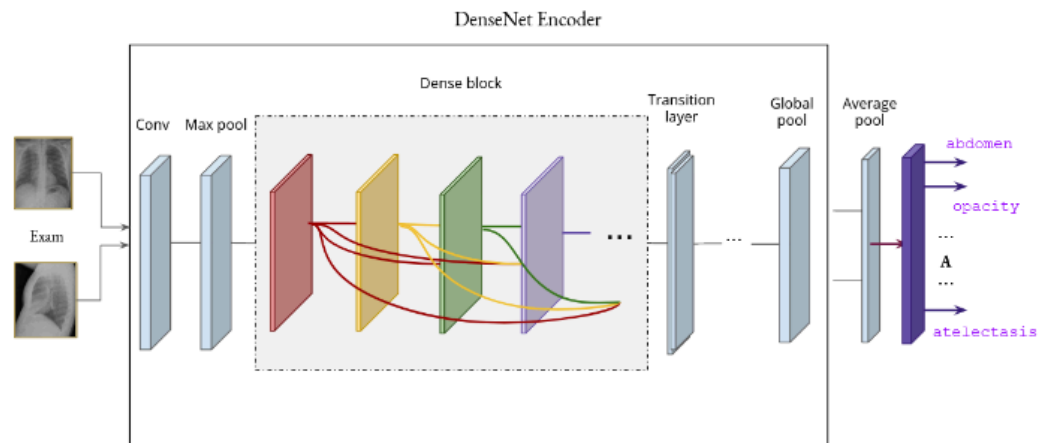


Automated ranking/tagging/captioning of radiography exams

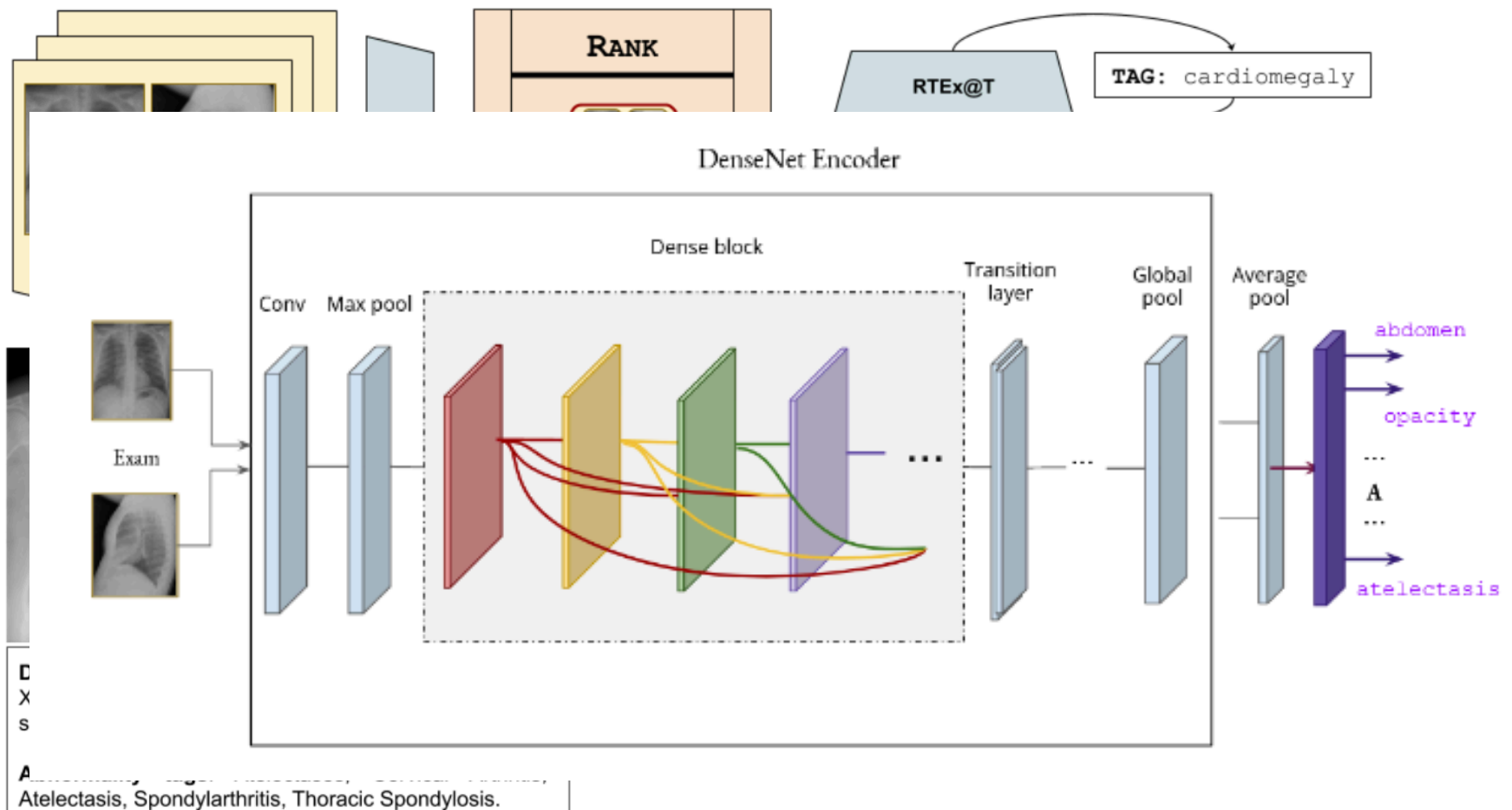


Diagnostic text: The cardiac contours are normal. XXXX basilar atelectasis. The lungs are clear. Thoracic spondylosis. Lower cervical XXXX arthritis.

Abnormality tags: Atelectases, Cervical Arthritis, Atelectasis, Spondylarthritis, Thoracic Spondylosis.



Automated ranking/tagging/captioning of radiography exams



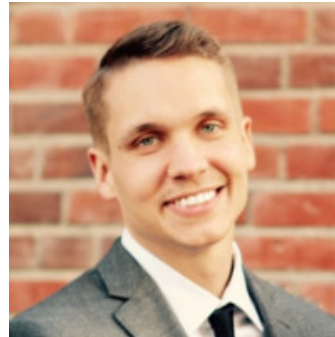
Closing remarks

- Security and privacy issues
- Hard to convince public authorities to make more data available to researchers
- Hard to convince doctors to adopt new “black box” models
- Cloud solutions are in many cases unacceptable
- Need to federated learning solutions
- Many players/systems are used by practitioners
- Need for a unified cross-border database of medical records

Thanks to...



Isak Karlsson



Jon Rebane



Maria Bampa



Aristides Gionis



Hans E. Persson



Henrik Boström



Hercules Dalianis

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<https://datascience.dsv.su.se>

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Extra slides

Solution

- Let x be a true-negative instance
- **Goal:** minimum number of feature tweaks (changes) so that x becomes true-positive, x'

Observe:

- If the prediction of the RF is -1, then **at least half of its trees** predict -1
- If the prediction of a tree is -1, then **the example is passed through a negative path**, i.e., a path that predicts the class to be -1
- **Solution:** **revert these paths** and consequently the trees!

Note: if a single transformation results in changing another tree's decision, then ignore it!

- Focus on the trees that **predict -1**
- For each tree: **explore the positive paths**, i.e., those that **predict +1**
- **Apply the transformations imposed by the positive path**

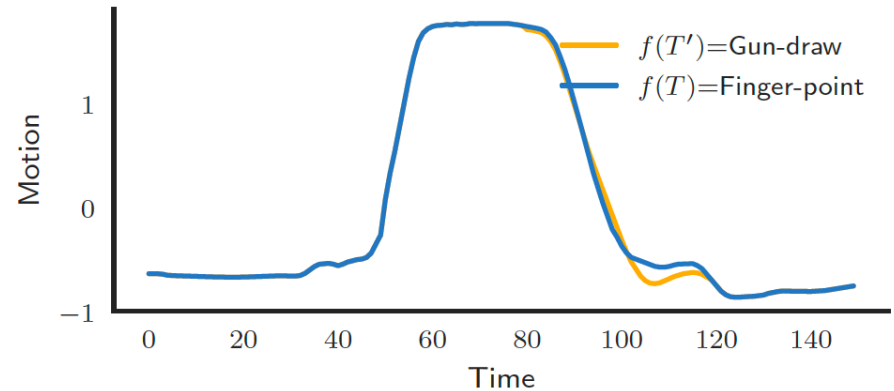
$$\mathbf{x}_{j(\epsilon)}^+[i] = \begin{cases} \theta_i - \epsilon & \text{if the } i\text{-th condition is } (x_i \leq \theta_i) \\ \theta_i + \epsilon & \text{if the } i\text{-th condition is } (x_i > \theta_i) \end{cases}$$

- Choose the transformation with the **minimum cost**

$$\mathbf{x}' = \arg \min_{\mathbf{x}_{j(\epsilon)}^+ \in \Gamma \mid \hat{f}(\mathbf{x}_{j(\epsilon)}^+) = +1} \left\{ \delta(\mathbf{x}, \mathbf{x}_{j(\epsilon)}^+) \right\}$$

Time series tweaking

What is the **minimum number of changes** to apply to a time series T so that a **given opaque classifier** changes its prediction?



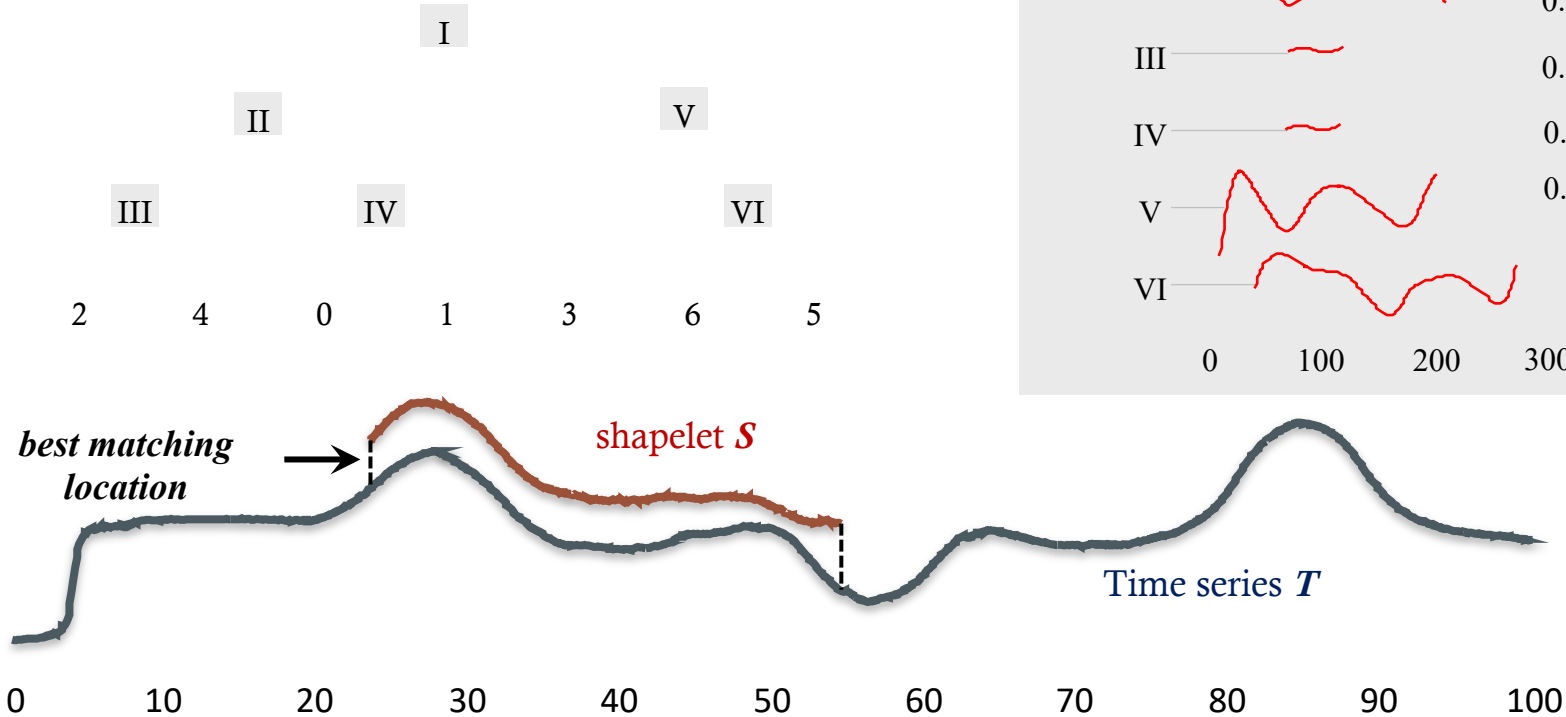
$$\mathcal{T} \rightarrow \mathcal{T}^1 \rightarrow \mathcal{T}^2 \rightarrow \dots \rightarrow \mathcal{T}'$$

- **Reversible tweaking:** each subsequent transformation can override a previous one
- **Irreversible tweaking:** each subsequent transformation cannot override a previous one

Random Shapelet Forests

Shapelets: class-distinctive time series subsequences capturing local trends in time series

Shapelet Tree*



* Figures taken from Eamonn Keogh

Time series tweaking: solution

- Focus on the trees that **predict -1**
- For each tree, explore the positive paths, i.e., those that **predict +1**
- Try to **force those trees to predict +1** by "tweaking" **shapelet features** of T

Given a non-leaf node (S_k^j, θ_k^j)

- **Increase distance:**

- If S_k^j exists in T , that is $d_s(S_k^j, \mathcal{T}) \leq \theta_k^j$
- and the current node condition demands otherwise
- ✓ Increase the distance of **all matching instances** of S_k^j , so that they all fall **above the distance threshold** θ_k^j

Time series tweaking: solution

- Focus on the trees that **predict -1**
- For each tree, explore the positive paths, i.e., those that **predict +1**
- Try to **force those trees to predict +1** by "tweaking" features of T

Given a non-leaf node (S_k^j, θ_k^j)

- **Decrease distance:**

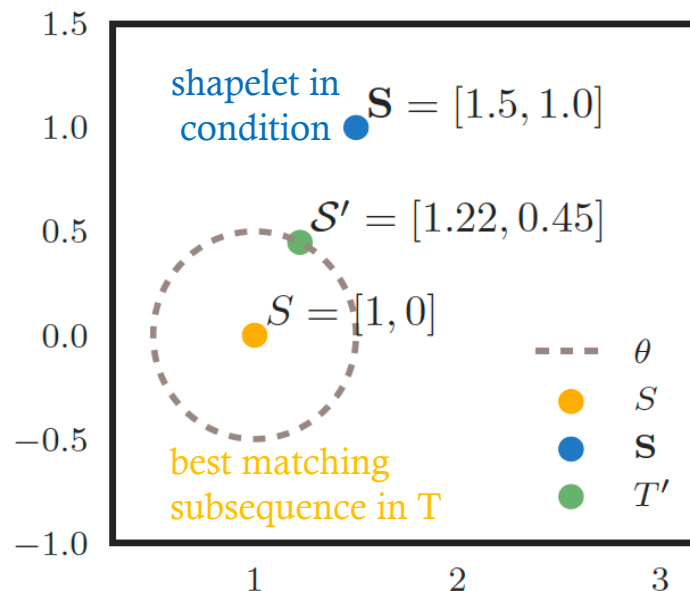
- If S_k^j does not exist in T , that is $d_s(S_k^j, T) > \theta_k^j$
- and the current node condition demands otherwise
- ✓ Decrease the distance of **the best matching instance** of S_k^j , so that it falls **below the distance threshold** θ_k^j

How to transform the time series?

- Consider S as an **m-dimensional point**
- Define an **m-sphere** with S as its center and radius θ

- The **transformed time series counterpart of S** is given by the following equation:

$$\tau_S(\mathbf{S}, p_{ik}^j, \epsilon) = \mathcal{S}_k^j + \frac{\mathcal{S}_k^j - \mathbf{S}}{\|\mathcal{S}_k^j - \mathbf{S}\|_2} (\theta_k^j + (\epsilon \delta_{ik}^j))$$



Experimental setup

- **UCR time series repository:**
 - all binary classification datasets (26 datasets)
- **Competitor:**
 - 1-NN under the Euclidean distance

$$\tau_{NN}(\mathcal{T}, y') = \arg \min_{\{\mathcal{T}' | (\hat{y}, \mathcal{T}') \in \mathcal{D}, \hat{y} = y'\}} d_E(\mathcal{T}, \mathcal{T}')$$

Evaluation – metrics

Average cost of successful transformation, i.e.,
how costly is the transformation?

$$c_{\mu}(\tau, y') = \frac{1}{n} \sum_{i=1}^n c(\mathcal{T}_i, \tau(\mathcal{T}_i, y'))$$

Compactness of transformation, i.e.,
how much of the time series is changed?

$$\text{compact}(\mathcal{T}, \mathcal{T}') = \frac{1}{|\mathcal{T}|} \sum_{i=1}^{|\mathcal{T}|} \text{diff}(T_i, T'_i),$$

where

$$\text{diff}(T_i, T'_i) = \begin{cases} 1, & \text{if } |T_i - T'_i| \leq e \\ 0, & \text{otherwise.} \end{cases}$$

Evaluation – result

| Dataset | Cost | | | Compactness | | | Accuracy | |
|---|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| | τ_{RT} | τ_{IRT} | τ_{NN} | τ_{RT} | τ_{IRT} | τ_{NN} | RSF | NN (1) |
| Reversible tweaking results in the least costly transformations | 7.3810 | 7.3810 | 26.6223 | 0.5737 | 0.5737 | 1.0000 | 0.8750 | 0.7500 |
| | 4.5071 | 4.5098 | 15.6695 | 0.5048 | 0.5169 | 1.0000 | 1.0000 | 0.6250 |
| | 1.1447 | 1.1846 | 1.9178 | 0.3824 | 0.1809 | 1.0000 | 1.0000 | 1.0000 |
| | 2.2197 | 2.5132 | 22.4809 | 0.4123 | 0.4044 | 1.0000 | 0.7000 | 0.4900 |
| | 0.9314 | 1.1150 | 1.1704 | 0.5917 | 0.4466 | 0.9999 | 0.7886 | 0.7143 |
| | 2.2725 | 3.1455 | 30.0943 | 0.7449 | 0.7577 | 1.0000 | 0.7826 | 0.6630 |
| | 1.8730 | 1.9080 | 4.1428 | 0.7976 | 0.7686 | 1.0000 | 0.8750 | 0.9500 |
| ECGFiveDays | 1.9722 | 2.0158 | 4.2143 | 0.5215 | 0.4913 | 1.0000 | 1.0000 | 0.9944 |
| GunPoint | 1.9787 | 1.9942 | 3.6975 | 0.4712 | 0.4460 | 0.9998 | 1.0000 | 0.9250 |
| Irreversible tweaking results in the most compact transformations | 2.1744 | 2.2187 | 7.8253 | 0.6791 | 0.6621 | 0.9999 | 0.8605 | 0.7907 |
| | 1.2492 | 1.2488 | 3.5817 | 0.4563 | 0.4060 | 0.9999 | 0.5000 | 0.3846 |
| | 1.1791 | 1.2645 | 1.3088 | 0.7262 | 0.6397 | 0.9998 | 0.9726 | 0.9589 |
| | 3.2741 | 3.9266 | 18.9703 | 0.7470 | 0.7071 | 1.0000 | 0.6667 | 0.6667 |
| | 0.6685 | 0.9877 | 0.6791 | 0.6182 | 0.4493 | 0.9999 | 0.8258 | 0.7753 |
| | 2.4413 | 2.5313 | 6.0249 | 0.5602 | 0.4834 | 1.0000 | 0.9685 | 0.9213 |
| | 0.6979 | 0.9568 | 0.7574 | 0.6186 | 0.5116 | 0.9998 | 0.8421 | 0.7782 |
| ProximalPhalanxOutlineCorrect | 0.5895 | 1.0056 | 0.5326 | 0.6552 | 0.4121 | 0.9997 | 0.8315 | 0.8090 |
| SonyAIBORobotSurface1 | 1.7384 | 1.7260 | 4.7213 | 0.4429 | 0.4394 | 1.0000 | 0.9919 | 1.0000 |
| SonyAIBORobotSurface2 | 1.8601 | 1.8566 | 5.6126 | 0.4133 | 0.3584 | 1.0000 | 0.9796 | 0.9949 |
| The baseline is too naive | 1.2082 | 1.3628 | 1.2802 | 0.6644 | 0.5464 | 0.9999 | 0.9695 | 0.9797 |
| | 3.1200 | 3.1436 | 14.7768 | 0.3871 | 0.3718 | 1.0000 | 0.9259 | 0.7407 |
| | 5.4407 | 5.8238 | 17.8733 | 0.6173 | 0.5705 | 1.0000 | 0.9697 | 0.7879 |
| | 0.9112 | 1.0671 | 1.3517 | 0.4966 | 0.4028 | 0.9999 | 1.0000 | 0.9957 |
| TwoLeadECG | 3.0135 | 3.1419 | 8.6207 | 0.7152 | 0.6676 | 0.9999 | 0.9958 | 0.9979 |
| Wafer | 0.5052 | 0.9301 | 0.1708 | 0.7529 | 0.3452 | 0.9996 | 1.0000 | 1.0000 |
| Wine | 5.7723 | 7.2023 | 28.7383 | 0.4416 | 0.4219 | 1.0000 | 0.8269 | 0.7308 |
| WormsTwoClass | 5.7723 | 7.2023 | 28.7383 | 0.4416 | 0.4219 | 1.0000 | 0.8269 | 0.7308 |
| Avg. | 2.3132 | 2.5329 | 8.9552 | 0.5733 | 0.4942 | 0.9999 | 0.8924 | 0.8240 |