Learning from Cohort Data
mainly for chronic disorders and their comorbidities

Myra Spiliopoulou

Dec 10, 2020
**Mission:** Serve the medical researchers, and through them physicians and patients

**Approach:** We develop

- ML methods for learning on streams of data for each patient
- ML methods for filling the gaps
- ML methods for the acquisition of labels, features and constraints
- Complete workflows and frameworks

In parallel, we work on experimental data:

- experiments and studies on human behaviour [analysis]
- experiments on crowdworking [our own designs]
Ongoing Projects:

- **ImmunLearning (2019 - 2022):** EFRE project on a diagnostic test for immunocompetence for elderly people (with U Med OVGU)
- **CHRODIS+ (2017-2020):** EU Joint Action on “Implementing good practices for chronic diseases”
- **UNITI (2020-2022):** EU project on “Unification of Treatments and Interventions for Tinnitus Patients”

Further cooperations in medical research:

- Learning on longitudinal epidemiological data (U Med Greifswald)
- Intelligent wearables for patients with diabetic foot (U Med Magdeburg)
- Phenotyping, patient evolution - clinic & m/eHealth (U Med Regensburg)
- Phenotyping and patient response to treatment (CHARITE)
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Medical Mining in the KMD Lab

Business Understanding
Termini
Medical data for learning

Learning on Static Data
Prediction with few features
Data drain

Learning on Dynamic Data
Learning on sensors
Learning on user inputs
  → Learning from the ‘long’ users
  → Prediction for (almost) all users
  → Interpreting the gaps

Closing

The KMD Team

Prof. Myra Spiliopoulou
Christian Beyer
Noor Jamaludeen
Uli Niemann
Miro Schleicher
Rafi Trad
Clara Puga
Vishnu Unnikrishnan
Anne Rother
This is Part III of Tutorial 8:

- Structure of clinical data; prediction methods; open challenges
- Structure of mobile, dynamic data; prediction methods; open challenges
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RECALL: The CRISP-DM Circle

[Chapman et al., 2000]

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Chronic Disorders / Diseases / Conditions

Example 1: Diabetes

Main symptoms of Diabetes

Central
- Polydipsia
- Polyphagia
- Lethargy
- Stupor

Eyes
- Blurred vision

Systemic
- Weight loss

Respiratory
- Kussmaul breathing (hyper-ventilation)

Breath
- Smell of acetone

Gastric
- Nausea
- Vomiting
- Abdominal pain

Urinary
- Polyuria
- Glycosuria

Example 2: Tinnitus

Attribution: Mikael Häggström, 27 Feb 2009, public domain

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Tinnitus as subject of research

Rationale

Although much progress has been made, tinnitus remains a scientific and clinical enigma of high prevalence and high economic burden.

There is no current consensus on tinnitus treatment.

A large variety of patient characteristics - including genotyping, aetiology, and phenotyping - are poorly understood, because integrated systems approaches are still missing to correlate patient’s characteristics to predict responses to combinatorial therapies.

10% of the population is affected by tinnitus
1% of the population considers tinnitus their major health issue

5H2020 project UNITI 'Unification of Treatments and Interventions for Tinnitus Patients', since Jan 1, 2020
"Items list" for tinnitus case history questionnaires

Items are ordered according to their level of significance:

Category "A" (= essential) in bold type.

**Background**
1. Age.
2. Gender.
3. Handedness.

**Tinnitus history**
5. Initial onset. Time?
6. Initial onset. Mode? Gradual or abrupt?
7. Initial onset. Associated events? Hearing change, Acoustic trauma, Otitis media, Head trauma, Whiplash, Dental Treatment, Stress, Other.
9. Site. Right ear? Left ear? Both ears? (symmetrical?) Inside head?
10. Intermittent or constant?
11. fluctuant or non-fluctuant?
12. Loudness. Scale 1-100. At worst & at best?
13. Quality. Own words / Give a list of choices.
14. Pure tone or Noise? Uncertain / polyphonic?
16. Percentage of awake time aware of tinnitus?
17. Percentage of awake time annoyed by tinnitus?
18. Previous tinnitus treatments (no, some, many)?

**Modifying influences**
19. Natural masking? Music, everyday sounds, other sounds?
20. Aggravated by loud noise?
21. Altered by head and neck movement or touching of head or upper limbs (specification of the respective movements)?
23. Effect of nocturnal sleep on daytime tinnitus?
24. Effect of stress?
25. Effect of medications? Which?

**Related conditions**
26. Hearing impairment?
27. Hearing aids (No, left ear, right ear, both ears; effect on tinnitus)?
28. Noise annoyance or intolerance?
29. Noise induced pain?
30. Headaches?
31. Vertigo/dizziness?
32. Temporomandibular disorder?
33. Neck pain?
34. Other pain syndromes?
35. Under treatment for psychiatric problems?

As an example of how the above items can be expressed for patients to complete see the TINNITUS SAMPLE CASE HISTORY QUESTIONNAIRE (TSCHQ)

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Example: The Tinnitus Case History Questionnaire

6 cf. [Langguth et al., 2007]

Medical data refer to answers to questionnaires before, during, and after treatment, which are recorded. Medical assessments are used to derive scores.
Medical Data for Learning

Learn what?

→ the effects of a treatment
→ the side-effects of a treatment
→ the symptoms
→ the comorbidities

... and identify predictive features

on different subpopulations
Medical Data for Learning

Learn what?

→ the effects of a treatment
→ the side-effects of a treatment
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... and identify predictive features

on different subpopulations

Learn for whom?

• the physician
• the medical researcher
Medical Data for Learning

Learn what?
- the effects of a treatment
- the side-effects of a treatment
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- the comorbidities

... and identify predictive features

on different subpopulations

Learn for whom?
- the physician
- the medical researcher

Learn on what?
- on an export of patient records
- on a cohort
- on multiple cohorts
The term “cohort”

Quoting [Glenn, 2005], page 2: “The term cohort originally referred to a group of warriors or soldiers, and the term is now sometimes used in a very general sense to refer to a number of individuals who have some characteristic in common.”
The term “cohort”

Quoting [Glenn, 2005], page 2: “The term cohort originally referred to a group of warriors or soldiers, and the term is now sometimes used in a very general sense to refer to a number of individuals who have some characteristic in common.”

The term “cohort” in “cohort analysis”

Quoting [Glenn, 2005], page 2: “Here and in other literature on cohort analysis, however, the term is used in a more restricted sense to refer to those individuals (human or otherwise) who experienced a particular event during a specified period of time. . . .
Learning on the cohorts of an RCT

Randomised Clinical Trial

- Development of a robust RCT protocol for single and combinational therapies
- Harmonization of interventions among clinical centers
- Recruitment of tinnitus patients for the RCT
- Conduction of the RCT
- Validation of the Decision Support System (DSS)

5 clinical centers
- Klinikum der Universitaet Regensburg (REG)
- Katholieke Universiteit Leuven (KUL)
- Charité – Universitaetsmedizin Berlin (CHA)
- Ethniko Kai Kapodistriako Panepistimo Athinon (UOA)
- Servicio Andaluz de Salud (GRA)

This project has received funding from European Union’s Horizon 2020 Research and Innovation Programme under Grant Agreement No 848261.
Narrowing down the subject area: Small datasets, large feature spaces, and two goals: assist the medical researcher, while reducing the data demand.
Learning: static data first

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Learning: static data first

→ To what extend can we predict \textbf{an outcome} after treatment (T1), when using only features recorded before treatment (T0)?
→ How to build a minimal set of cumulatively predictive features?
→ To what extend can we predict whether tinnitus distress will be compensated or not after treatment (T1), when using only features recorded before treatment (T0) ?
→ How to build a minimal set of cumulatively predictive features?
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Prediction and Minimization of the Feature Space

[Figure 1 from Niemann et al., 2020b]
Model learning on T0 to predict T1 for target $TQ_{\text{score}} \in \{0, 1\}$

11 algorithms: LASSO, RIDGE, Generalized Partial Least Squares (GPLS), SVM, a feedforward NN with one hidden layer, weighted kNN, NB, CART, C5.0, RF, **Gradient Boosted Trees (GBT)**

hyperparam selection: grid search

$k=10$ folds: 10-fold stratified cross validation

AUC: as performance measure

Feature filtering and scoring

Model reliance [Fisher et al., 2018]: of feature $f$ as “classification error on the original training set [vs] classification error on a modified version of the training set where the values of $f$ are randomly permuted.”

SHAP value [Lundberg and Lee, 2017] of feature $f$ for instance $x$ “as change in the expected value of the prediction if for $f$ the feature vector of $x$ is observed instead of [a] random [one]”
Prediction and Minimization of the Feature Space \[\text{[Niemann et al., 2020b]}\]

8 Figure 6 from [Niemann et al., 2020b]: (A) features sorted on importance, and achieved AUC of a feature and its predecessors; (B) graph of correlations (for absolute values of 0.5 and higher)
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√ Workflows for learning on static data and showing the solutions

√ First attempts to sort out features from a huge feature space
The feature space and the *data drain* problem

**Data collection:** 4,103 tinnitus patients, older than 18 treated at the Tinnitus Center of Charité Universitätsmedizin Berlin between Jan. 2011 and Oct. 2015, having tinnitus for at least 3 months

**Four studies:**

- Prediction and feature space minimization [Niemann et al., 2020b]: 1,416 patients
  - Phenotypes at T0 and T1
    - [Niemann et al., 2020d]: 1,228 patients
  - Predicting depression severity after treatment
    - [Niemann et al., 2020c]: 1,490 patients
  - Identifying gender-specific differences among chronic tinnitus patients
    - [Niemann et al., 2020a]: 1,228 patients (m:609, f:619)

**What makes the difference?**
The feature space and the *data drain* problem

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**What makes the difference?** The medical objective
Target variable usually refers to outcome of Condition (Disease, comorbidity, other) affects Scores effect quantified as. Learn to Classify Learn to Predict. Training data now in the future may contain NULL values may contain also affect the computation of Missing Not At Random.
Learning on small static data

Open issues:

→ how to reduce the feature space

... and thus reduce the data demand [working on that ...]

→ how to exploit time and deal with gaps [comes next]
Medical data are described by Patient before, during, and after Treatment. They are recorded as answers to questionnaires and medical assessments. Scores are used to derive further data. Contributions to postings, sensory signals, and diary entries can be EMA. Temporal data can be monitored.
Learning patterns of movement for patient wellbeing

Example: Wandering

"Wandering is among the most frequent, problematic, and dangerous behaviors for elders with dementia. Frequent wanderers likely suffer falls and fractures, which affect the safety and quality of their lives." [Lin et al., 2012]

▶ "Travel behavior of nursing home residents perceived as wanderers and non-wanderers" [Martino-Saltzman et al., 1991]
▶ "Detecting wandering behavior based on GPS traces for elders with dementia" [Lin et al., 2012]
▶ "Location prediction using GPS trackers: Can machine learning help locate the missing people with dementia?" [Wojtusiak and Nia, 2019]

... on mitigating the side-effects of smartphone battery-saving

"Inferring Mobility Measures from GPS Traces with Missing Data" [Barnett and Onnela, 2020]

Thanks to Priyanka Mohan for the literature collection and to Dr. Nadine Diersch – Aging & Cognition Research Group, German Center for Neurodegenerative Diseases (DZNE), Magdeburg – working on real-world navigation behavior.
The arrowline of the mHealth potential

[Kumar et al., 2013]

Measurement → Diagnostic → Treatment/prevention → Global

where Measurement encompasses:

→ on-person or embedded sensor sampling in real time
  · Global Positioning System
  · Ecological Momentary Assessment

Conversion of the
“raw sensor data into meaningful information related to behaviors, thoughts, emotions ... and clinical states and disorders.” [Mohr et al., 2017]
The “sensemaking” approach of [Mohr et al., 2017]:

★ Clinical state

↑ “Behavioral marker: behaviors, thoughts, feelings, traits, or states . . .”

↑ “[Low level] feature: a measureable property of a phenomenon, which is proximal to, and constructed from, sensor data”

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↑ Raw sensor data

Example [Mohr et al., 2017] (Sections 2.3, 3.1)

- Behavioral marker: Sleep disruption
- Low-level features: Bedtime/waketime, phone usage, movement intensity, ambient noise
- Clinical targets: depression, bipolar disorder, schizophrenia
The arrowline of the mHealth potential

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"Ambulatory assessment" [Fahrenberg et al., 2007]

Quoting from https://psycnet.apa.org/record/2007-18155-002:

*Ambulatory assessment refers to the use of computer-assisted methodology for self-reports, behavior records, or physiological measurements, while the participant undergoes normal daily activities.*
CHRODIS+ “Implementing good practices for chronic diseases” \(^{10}\)

Joint Action (09/17 - 11/20) funded by the EU and participating organisations

**GOAL:** Contribute to reducing the burden of chronic diseases by promoting the implementation of policies and practices that have been demonstrated to be successful. The development and sharing of these tested policies and projects across EU countries is the core idea behind this action.

**WP7:** Fostering the quality of care for people with chronic diseases:
through the implementation of a set of quality criteria and recommendations defined in the previous JA CHRODIS.

**Task 3 on mHealth tools:** three pilot studies on self-empowerment of patients with help of mobile technology:

- Cantabrian Health Service – CSC in Spain
- National Center of Public Health and Analyses – NCPHA in Bulgaria
- University Hospital Regensburg – UHREG in Germany

\(^{10}\)http://chrodis.eu/about-us/
EMA for different CHRODIS+ T7.3 pilot studies

T7.3: NPCHA pilot on diabetes → [Unnikrishnan et al., 2020a]

T7.3: UHREG pilot TinnitusTips on tinnitus [Unnikrishnan et al., 2020b]

Questionnaire – many times a day

<table>
<thead>
<tr>
<th>ID</th>
<th>Item description and valuerange</th>
</tr>
</thead>
<tbody>
<tr>
<td>s01</td>
<td>Did you perceive the tinnitus right now? Y/N</td>
</tr>
<tr>
<td>s02</td>
<td>How loud is your tinnitus right now? 0…100</td>
</tr>
<tr>
<td>s03</td>
<td>How distressed are you by your tinnitus right now? 0…100</td>
</tr>
<tr>
<td>s04</td>
<td>How well do you hear right now? 0…100</td>
</tr>
<tr>
<td>s05</td>
<td>How much are you limited by your hearing right now? 0…100</td>
</tr>
<tr>
<td>s06</td>
<td>How stressed do you feel right now? 0…100</td>
</tr>
<tr>
<td>s07</td>
<td>How exhausted do you feel right now? 0…100</td>
</tr>
<tr>
<td>s08</td>
<td>Are you wearing a hearing aid right now? Y/N</td>
</tr>
</tbody>
</table>

Groups of participants: Y, A, B

Groups Y and A received non-personalized tips from the beginning; group B received the tips only from the middle of the study onwards.
1. Learning from the ‘long’ users
Analyzing EMA on TrackYourTinnitus

[Probst et al., 2017]

- Total assessments: 25,863 Retained: 17,209, after excluding assessments with missing values in any of the target variables and days with less than three assessments.
- 350 participants (253m/94f) with average age 45.4 (over 333, SD=12.1) and median since tinnitus onset 5.4Y (from 0 to 61.8Y)
- Median days per participant 11 (from 1 to 415) with median number of assessments per day 4 (from 3 to 18)
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Selection of findings

- “tinnitus was significantly louder in the late evening compared to the afternoon and early evening.”
- “stress-level increased from morning to afternoon, decreased from afternoon to evening, and did not differ compared to the night”
- “the effects of time-of-day on tinnitus loudness and tinnitus distress were still significant (i.e., after controlling for the effects of stress).”
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What about users with missing EMA values and less EMA per day?
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TrackYourTinnitus data distribution
[Schleicher et al., 2020]
2. Prediction for (almost) all users
Data and model augmentation for distress prediction

[Unnikrishnan et al., 2019]

Modeling the prediction problem

Given is a set of participants, for the EMA of whom we have the distress values - but only for the first $m$ EMA. For each patient $x$ and EMA $o_{x,j}$ with $j > m$, predict the distress value of $o_{x,j}$.
Data and model augmentation for distress prediction
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Data cleaning

Removal of:

- participants with less than 5 EMA  \( \rightarrow \) 516 participants

Histogramm: #days per participant
Data and model augmentation in two feature spaces

[Unnikrishnan et al., 2019]

3. kNN-based predictors in $D_{EMA}$

- **Predictor 1 (model augmentation):**
  for each $y$ in the neighbourhood of $x$ (including $x$), learn a linear regression model $m_y$;
  average the parameters $m_y,\text{slope}$ and $m_y,\text{intercept}$ into a final model $m_x$.

- **Predictor 2 (data augmentation):**
  place all EMA of $x$ and of its neighbours into a pool;
  learn a linear regression model for $m_x$ over the pool.
### Data and model augmentation in two feature spaces

[Unnikrishnan et al., 2019]

#### 2. Exploiting the EMA dataset $D_{EMA}$ and the registration data $D_R$ for learning

- The kNN neighbourhood of each participant $x$ is built on $D_R$
- Time series of participants are aligned across the time axis – no gaps are filled in $D_{EMA}$

#### 3. kNN-based predictors in $D_{EMA}$

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**Note:**

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1. Combining tinnitus loudness and distress levels on $D_R$

Three clusters on loudness and two clusters on distress levels:

<table>
<thead>
<tr>
<th>Tinnitus Loudness</th>
<th>Low TD</th>
<th>High TD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#P</td>
<td>Avg TD</td>
</tr>
<tr>
<td>Low TL</td>
<td>81</td>
<td>7.4</td>
</tr>
<tr>
<td>Mod TL</td>
<td>83</td>
<td>8.1</td>
</tr>
<tr>
<td>High TL</td>
<td>35</td>
<td>9.2</td>
</tr>
</tbody>
</table>
Prediction for the six phenotypes [Unnikrishnan et al., 2019]

![Graph showing prediction for the six phenotypes](image)

- G1 (High, High)
- G2 (High, Mod)
- G3 (High, Low)
- G4 (Low, High)
- G5 (Low, Mod)
- G6 (Low, Low)
- Global
3. Interpreting the gaps
User Adherence in TrackYourTinnitus

[Schleicher et al., 2020]

Adherence as combination of

★ Interaction duration
- Days until first break

★ Interaction intensity as:
- Return after first break (Y/N)
  within the observation horizon of 30 days

Materials:
- EMA of 1252 users
  - For time series classification: 852 users, after removing 440 users that had only one EMA
  - For interpretation of interaction intensity: 816 users, after removing users with incomplete time series and/or missing values

Methods:
- For time series classification on each EMA item separately:
  - 7 Time series classification algorithms with various distance functions
  - 6 conventional classification algorithms
- For interaction intensity interpretation:
  - Classification rule induction

Results...
User Adherence in TrackYourTinnitus

[Schleicher et al., 2020]

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For interaction intensity interpretation: classification rule induction
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**Methods**

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For interaction intensity interpretation: classification rule induction

**Results**
Closing: Learning on small mHealth data

Huge potential for

- patient empowerment
- assistance towards caregivers
- better diagnostics
- deeper insights to chronic diseases
Closing: Learning on small mHealth data

Huge potential for
- patient empowerment
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- deeper insights to chronic diseases

The dilemma of time series length:
- long time series: useful for phenotyping and prediction
- short time series: little to learn on, very little to predict

Some solutions:
- entity-centric methods that prevent building a global model mainly on the data of very few users
- methods for learning and predicting despite the gaps
- methods for the identification of influence factors
Closing: Learning on small dynamic data

Open issues:

→ How to exploit ML-methods designed for large dense datasets
→ Gaps are missing data not at random – how to deal with this?
→ Exploration/Exploitation problem – how to learn with even fewer data?
THANKS TO:

- This work was partially supported by the CHRODIS+ Joint Action on “Implementing good practices for chronic diseases”.
- This work is partially supported by the European Union’s Horizon 2020 Research and Innovation Programme, Grant Agreement Number 848261.
Thank You!
Bibliography I

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