Machine Learning in Medicine

Early Recognition of Sepsis

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Machine Learning and Personalized Medicine

Goals

- Machine learning tries to detect statistical dependencies in large datasets.
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Machine Learning and Personalized Medicine

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- Machine learning tries to detect statistical dependencies in large datasets.
- Personalized medicine tries to exploit wealth of health data for improved diagnosis, prognosis and therapy decisions, tailored to the properties of each patient.
Machine Learning in Medicine

Key topics

- Automation of diagnoses and treatment

Original Investigation
December 12, 2017


Babak Ehteshami Bejnordi, MS1; Mitko Veta, PhD2; Paul Johannes van Diest, MD, PhD3; et al

Machine Learning in Medicine

Key topics

- Automation of diagnoses and treatment

The Artificial Intelligence Clinician learns optimal treatment strategies for sepsis in intensive care

Matthieu Komorowski, Leo A. Celli, Omar Badawi, Anthony C. Gordon, & A. Aldo Faisal

Machine Learning in Medicine

Key topics

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- Biomarker discovery
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- Biomedical data management
Machine Learning in Medicine

Key topics

- Automation of diagnoses and treatment
- Biomarker discovery
  - Early prediction of sepsis
- Biomedical data management

World Sepsis Day Infographics
A Global Health Crisis

- 27,000,000 - 30,000,000 people per year develop sepsis
- 7,000,000 - 9,000,000 die - 1 death every 3.5 seconds
- Survivors may face lifelong consequences
The Need for Biomarkers for Sepsis
Predicting Sepsis

What is sepsis and why is early recognition relevant?

- Sepsis-3 definition: Sepsis is a life-threatening organ dysfunction, caused by a dysregulated host response to infection (Singer et al., 2016).
Predicting Sepsis

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  - Currently, when sepsis is detected, organ damage has already progressed.
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**Detecting and treating sepsis earlier could be of highest clinical impact.**
Predicting Sepsis

Input: Patients’ ICU data
- Temperature
- Heart rate
- Blood pressure
- Respiratory rate
- O₂ saturation

Output: Predicting sepsis
- Onset
- Septic shock
- Mortality

Figure: Monitoring of vital parameters
Two perspectives

1. Association mapping in time series  (Bock et al., ISMB 2018)
2. Classification of time series  (Moor et al., MLHC 2019, Bock et al., ICDM 2019, Togninalli et al., NeurIPS 2019)
1. Association Mapping in Clinical Time Series
Reoccurring Temporal Subsequences as Biomarkers
Association Mapping in Time Series

Shapelets (Ye and Keogh, 2009)

- A (short) time series subsequence $S$ with associated similarity threshold $\theta$
- Any time series with a subsequence $S'$ where $d(S', S) < \theta$ contains this feature.
Association Mapping in Time Series

Shapelets (Ye and Keogh, 2009)

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Goal: Finding shapelets that are enriched in one class of time series
Multiple Testing Problem

Enormous number of hypotheses

- Assume: Any subsequence can be a shapelet.
- Total number of candidate shapelets is
  - linear in the number of time series, \( n \),
  - quadratic in the length of the time series, \( m^2 \),
  - linear in the number of possible similarity thresholds, \( n + 1 \).
- Total number of tests: \( O(n^2 m^2) \)
- For 100 time series of length 100: \( 10^8 \) candidate shapelets!
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Need for algorithms that can cope with this problem: S3M (Bock et al., 2018)
Biomarker Discovery in ICU data with S3M
Data Selection

**MIMIC-III Data Set** (Johnson et al., 2016)

**Exclusion criteria**
- Patient < 15 y/o
- Missing chart values
- Patients logged with CareVue

**Vital signs (First 75 hours)**
- Heart rate
- Respiratory rate
- Systolic blood pressure

Cases 355
Controls 355
Data Selection

Case definition
Sepsis-3 definition by Seymour et al. (2016)

Control definition
- Neither suspicion of infection (SI) nor organ failure score (SOFA score) increase
- Only SI or only SOFA score increase
Results: Most Significant Shapelets

- Heart rate: Long term HRV might indicate sepsis
- Respiratory rate: Sudden drop into abnormal regime (Kellett et al., 2017) with sharp increase
- Systolic blood pressure: Characteristic spike

(a) Heart rate 
\(p = 7.91 \times 10^{-18}\)

(b) Respiratory rate 
\(p = 5.42 \times 10^{-20}\)

(c) Systolic blood pressure 
\(p = 8.27 \times 10^{-13}\)
2. Predicting Sepsis through Time Series Classification
Time Series Classification
# State of the Art - Early Prediction of Sepsis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Dataset</th>
<th>Label</th>
<th>Method</th>
<th>3h AU-ROC /-PR</th>
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Sepsis Prediction as a Classification Task

Challenges

- **Comparability:**
  - Heterogeneous label definitions (some insufficient for early detection)
  - Heterogeneous label extraction (even for the same definition and same dataset)

- **Reproducibility:**
  - Code for label extraction rarely provided

- **Circularity:**
  - Same measurements used to define and to predict sepsis

- **Evaluation:**
  - Time horizon analysis: choice of controls
  - Awareness of class imbalance
Results

Early onset prediction on MIMIC-III (Moor et al., MLHC 2019)
Personalized Swiss Sepsis Study

- Consortium of 22 research labs and 5 university hospitals in Switzerland
- Goal: Predict sepsis and sepsis-related mortality
- Approach: Integrate clinical data and molecular data for joint biomarker discovery

- Duration: 3 years (2018-2021)
- Total funding: 5.3 Million CHF
Machine Learning Frontiers in Precision Medicine
Automation, biomarker discovery, and biomedical data management will remain key research topics.
Outlook

- Automation, biomarker discovery, and biomedical data management will remain key research topics.
- Data growth in three dimensions will pose extreme new challenges for machine learning in medicine
  - Population-scale datasets of individuals
  - Life-long recordings of health state
  - Highest-resolution information of the health state
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- Highest-resolution information of the health state

How to mine (handle and use) this data?
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- Population-scale datasets of individuals
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How to mine (handle and use) this data?

Many branches of the life sciences face very similar or analogous problems.
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Plenty of opportunities for machine learning in precision medicine!
Thank you

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References II

T. F. Mackay, J. H. Moore, Genome Medicine 6, 42 (2014).


