Artificial Intelligence for Clinical Trial Design

Stefan Harrer, PhD
Senior Technical Staff Member and Manager, Epilepsy Research
IBM Master Inventor, Member IBM Academy of Technology
Adjunct Professor, University of Technology Sydney

IBM Research

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A (very) short history of AI

Tabulating Systems Era

Programmable Systems Era

Cognitive Systems Era
Emotion
Artistic ability
Imagination
Creativity

Logic
Analytical thought
Language
Objectivity
AI = **Augmented (human) Intelligence**

- **Brain-Machine Interface**
- **Converse in spoken dialogue**
- **Comprehend text**
- **Comprehend complex images**
- Analyse sensory data (for example: vision, hearing, touch, brain activity)
- **Develop domain knowledge**
- **Derive new insights**
Data is the new natural resource

- **Social**
  - Twitter
  - Facebook
  - Instagram
  - Non traditional social platforms

- **Genomics**
  - Family history
  - Single Nucleotide Polymorphisms
  - Copy Number Variation

- **Lifestyle**
  - Wearables
    - Fitbits
    - Monitors
  - Apps
    - Phones
    - Watches
  - Socioeconomics

- **Survey**
  - Cognitive test
  - Questionnaires
  - Directed
  - Bureau of Statistics
  - Commission for Mental Health

- **Response**
  - Times to apps
  - To images

- **Clinical data**
  - Clinical GP notes
  - Exit notes from hospitals
  - Pathology laboratory

- **Imaging**
  - Eye
    - Retina
    - Movement & tracking
  - CCTV
  - Behaviour
  - Movement

- **Speech**
  - What was spoken
  - How it was said
  - Tone, volume, etc.
The pace of technological progress – a human misconception

The future comes earlier these days than it used to…

AI must be used to assist the human decision maker.
The ‘Pharma Dilemma’

Return on Investment in Pharma R&D

Source: EvaluatePharma, IRR analysis

- IRR is already below cost of capital in 2017
- 0% IRR by 2020
The Drug Development Cycle
AI for clinical trial design: from themes to functionality...

Challenges
1. EMR data harmonization (EMR interoperability problem).
2. Data privacy, integrity, and security.
3. Explainability of AI
Neurological diseases: burden on healthcare system

FIGURE: Annual costs of major neurological diseases. Costs of Alzheimer disease and other dementias, chronic low back pain, stroke, traumatic brain injury, migraine headache, epilepsy, multiple sclerosis, spinal cord injury, and Parkinson disease. Dollar figures were converted into 2014 values using the all items consumer price index for nonmedical (indirect) costs. Direct costs were converted using the medical price index.
Probability of Phase III Success

- Hematology: 75%
- Infectious disease: 73%
- Metabolic: 71%
- Urology: 71%
- Allergy: 71%
- Respiratory: 71%
- Other: 70%
- Endocrine: 65%
- Gastroenterology: 62%
- Ophthalmology: 61%
- All Indications: 58%
- Neurology: 58%
- Psychiatry: 57%
- Cardiovascular: 56%
- Oncology: 55%
- Other: 40%

2 2006–2015, BIO, Biomedtracker, and Amplion
Epilepsy: Patient Monitoring Using AI

Epileptic seizures are electro-chemical signalling disturbances in the brain.

Automatically Detecting and Classifying Seizures
- Patients are often unaware of their seizures.
- Patients keep diaries but these are vastly inaccurate.
- Drugs are tested against diaries.
- Accurate seizure counts allow better treatment evaluation.

Digital Seizure Diaries: Automatic Seizure Tracking

<table>
<thead>
<tr>
<th>Monitoring Performance</th>
<th>High</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>implant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>wearable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>external</td>
<td></td>
<td></td>
</tr>
<tr>
<td>contextual</td>
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</tbody>
</table>

Intrusiveness of Monitoring Data

We combine deep learning, mobile sensors and video data to monitor epilepsy patients for automatic real-time detection and classification of epileptic seizures. Integrating these logs with Electronic Health Records in Digital Seizure Diaries allows to design more efficient clinical trials and enables improved personalized diagnosis, treatment and disease management.

Selected Publications
- *MICCAI* (MLCN) 2020; “SeizureNet: Multispectral deep feature learning for seizure type classification”.

Partners
- Harvard Medical School, Boston Children’s Hospital, Royal Melbourne Hospital, The Alfred, St. Vincent’s Hospital Melbourne, Temple University

Disease burdens in the US and Europe are $15B and €20B p.a.
Personalized epileptic seizure prediction using electroencephalography (EEG) data measured by implanted electrode sensors
From Wearables to THINKables

Table 1: Possible Candidates for Incorporation into Cognitive Sensors

<table>
<thead>
<tr>
<th>Type of sensor</th>
<th>Components</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neural implants</td>
<td>Retinal stimulation electrodes</td>
<td>Bionic Eye</td>
</tr>
<tr>
<td></td>
<td>EEG and ECoG electrodes</td>
<td>Brain activity monitoring, deep brain-stimulation, controlling prostheses with thought</td>
</tr>
<tr>
<td></td>
<td>Artificial skin sensors</td>
<td>Tactile prostheses</td>
</tr>
<tr>
<td></td>
<td>Electroceuticals</td>
<td>Nerve- and brain-stimulation</td>
</tr>
<tr>
<td></td>
<td>Smart contact lenses</td>
<td>Nerve- and brain-stimulation</td>
</tr>
<tr>
<td>Tattoo sensors</td>
<td>Electrochemical tattoo batteries</td>
<td>Biomarker detection</td>
</tr>
<tr>
<td></td>
<td>Always-on EEG electrode tattoos</td>
<td>Multimodal data measurement</td>
</tr>
<tr>
<td></td>
<td>Low-cost integrated circuit patches</td>
<td></td>
</tr>
<tr>
<td>Molecular sensors</td>
<td>Nano- and Microfluidic sensors, portable DNA sequencers</td>
<td>DNA sequencing</td>
</tr>
<tr>
<td></td>
<td>Smart pills, nanodosensors, functionalized nanoparticles</td>
<td>Biomarker detection</td>
</tr>
</tbody>
</table>

*Abbreviations: ECoG, electrocorticography; EEG, electroencephalography.*
Predicting epileptic seizures

Motivation
Build algorithms that allow a patient to manage their condition, alerting them to impending seizures

Data
Long-term intracranial Electroencephalography (EEG) recordings from 15 patients provided by Melbourne St. Vincent’s Hospital and The University of Melbourne, labelled by expert neurologists

Approach
- Train deep neural network to recognise patient-specific patterns emerging before a seizure
- Design a system that allows for real-time alarms
- Allow for tuning based on patient’s needs
Data selection

Seizure Prediction Task
Train algorithm to distinguish between preictal and interictal (normal) brain signal
Interictal: at least 5 hours away from seizure

ictal (seizure)  preictal (16-1 minutes pre seizure)

el 1
measured voltage
el 16
automatically labelled  expert labelled, time-stamped
time

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Data pre-processing

16 channel iEEG signal

Spectral Information
Epileptic seizures correlate with neuronal synchronisation, which can be visualised using spectrograms.

Timing information: Seizures have been shown to follow different circadian rhythms in different patients.
Neural network architecture

Real-Time Classifications
- Network classifies each sample of 30 seconds
- Without post-processing, this would result in one prediction every 30 seconds
- Exploiting the sequential structure of the data, temporal averaging should improve classification accuracy
Epileptic seizure prediction – study results

Study strategy:
- Pseudo-prospective
- Spectrograms + time information
- Post-processing (integrate and fire)
- Network retrained once a month
- Tunable by patients (max sensitive vs. least intrusive)

Results across all patients for entire duration of study:
- Mean sensitivity of 69%
- Mean time in warning of 27%
- Mean improvement over chance 42%

Ultra-low power consumption mobile processor implementation for mobile deployment
Precursor: Predicting Epileptic Seizures - Published in EBioMedicine (2018)
Epileptic seizure detection: re-inventing the epilepsy monitoring unit
Patient Preparation
• Patients are prepared for the test.

EEG Recording
• EEG ranging from 22 minutes to several days is recorded.

EEG Interpretation
• Certified physicians interpret EEG.

EEG Report Generation
• A report of findings (e.g. abnormality) is prepared.

Normal or abnormal EEG?
Is there an epileptic seizure?
Can we timestamp it?
Which type of seizure is it?
## Seizure type

<table>
<thead>
<tr>
<th>Label, Type, [Superclass]</th>
<th>Available train and test data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
</tr>
<tr>
<td>FN Focal</td>
<td>55</td>
</tr>
<tr>
<td>GN Generalized</td>
<td>32</td>
</tr>
<tr>
<td>CP Complex Partial Focal</td>
<td>22</td>
</tr>
<tr>
<td>SP Simple Partial Focal</td>
<td>2</td>
</tr>
<tr>
<td>TC Tonic-Motor</td>
<td>5</td>
</tr>
<tr>
<td>TN Tonic Motor</td>
<td>2</td>
</tr>
<tr>
<td>AB Absence Non-Motor</td>
<td>7</td>
</tr>
</tbody>
</table>

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**Mission**

Our goal is to enable deep learning research in neuroscience by releasing the largest publicly available unencumbered database of EEG recordings. This ongoing project currently includes over 30,000 EEGs spanning the years from 2002 to present. Data collected can be used for both research and commercialization purposes.

**Get Access**

To request access to these resources, please fill out [this form](#). You will receive an automatically-generated username and password via email. Please be patient since it takes a few minutes to receive the email.

Since these databases are quite large, it is best to transfer them via hard disk. If you are interested in this option, please follow the instructions [here](#).
Identifying epileptic seizure types

Motivation:
- Patients may have more than one type of seizure
- The type of seizure may inform therapy/medication
- Tracking types and each type’s rate may further inform medication adjustments
- Type information may help in diagnosis and to make clinical trials more nuanced

Implementation:
- Convolutional neural networks for binary classifiers
- Focus on preserving spatial electrode information

Seizure classes investigated:
- Focal/General, Motor/Non-motor, Tonic/Tonic-clonic, Complex-partial/Simple-partial

![ILAE 2017 Classification of Seizure Types Expanded Version](image)
What type of epileptic seizure is it?

IBM’s AI classifies seizures with 98.4% accuracy using EEG data
Towards a fully automated digital seizure diary
Current work: multimodal data classification

Data modalities include:
- intracranial EEG, scalp EEG, ECG, body temperature, blood pressure, movement patterns, sleep data, heart rate, video, audio, electronic health records, electrodermal activity, photoplethysmogram
Trends in Pharmacological Sciences
Special Issue: Rise of Machines in Medicine
Review
Artificial Intelligence for Clinical Trial Design
Stefan Harrer, Pratik Shah, Bhavna Antony, and Jianying Hu

Artificial Intelligence
A new promising way for tackling the ‘Pharma Dilemma’: artificial intelligence for clinical trials
Stefan Harrer, Bhavna Antony, Akram Bayat and Jianying Hu
IBM Research, Australia, MIT Media Lab, USA and IBM T.J. Watson Research Center, USA

Artificial intelligence (AI) is certainly not a panacea for solving the ‘Pharma Dilemma’ in which the cost of producing new drugs continues to spiral. However, AI can be used to fundamentally change the way we perform essential steps in clinical trial design and execution, from cohort selection to patient monitoring. Merging AI and clinical expertise across engineering and medical disciplines to explore the impact of these changes on trial performance and success rates is one of the most promising leads we have for restoring efficiency and sustainability to the drug development cycle.
...and read this book:

The world is our lab
sharrer@au.ibm.com

https://www.linkedin.com/in/stefanharrer/