When Data Meets Disease Head-On

New Trends in Treating and Managing Epilepsy

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For information, contact Maria Gabrani mga@zurich.ibm.com.

Contents

Introduction

With the new proliferation of digital patient data and mobile devices, the field of healthcare is seeing incredible opportunities for disease management, including the prediction of seizures, decision support for treatment directions, and behavioral coaching for patients.

IBM experts in healthcare informatics, machine learning, video processing, and other related fields are at the forefront of research into new approaches for the treatment of epilepsy. These address the data capture (e.g., through the mobile devices), data collection (e.g., IoT Hub) of previously unavailable data, data analysis, and the interpretation for disease management.

On March 9, 2018, the IBM Research – Zurich facility in Rüschlikon, Switzerland, hosted an ICU-Cockpit Workshop organized by the University Hospital Zurich and IBM Research – Zurich. More than 40 external participants attended the workshop, including clinicians, scientists, and industrial partners from pharmaceutical and technology providers.

This document provides an overview of the discussions and the insights generated during the four workshops that ran in parallel during the second part of the day. The information includes new research into approaches for epilepsy treatment, some of the issues involved, the key results, and possible future directions for the community of healthcare evangelists who are trying to improve the quality of life for epilepsy patients.

Challenges in Epilepsy Management and Treatment

Despite many new advances in drug therapy and disease understanding, we are still limited in our treatment of epilepsy and are still far from our goal of making it completely manageable for patients.

Roughly 1% of the world's population, 65 million people, suffer from epilepsy. For one third of these patients, no medical treatment options exist. These patients need to find ways to live with their condition and manage their daily lives around it. For the remaining two thirds of the patient population, medical treatment options are available but have vastly differing and constantly changing results and quality of treatment. These shortcomings in diagnosis and treatment options are caused by the fact that epilepsy – as most neurological diseases – is a highly individualized condition, i.e. it does not look the same in all patients and even for an individual patient disease expression changes over time. As a result until recently, the lack of data and measurements made the correct matching of patients and drugs into an unnecessary, long process of trial and error. Even measuring drug sensitivity was like targeting a moving goal post. Manual diaries are the basic data source, but these have been proven to be only 50% accurate. Moreover, patient diaries are specifically inaccurate for focal seizures, even though most new drugs are being developed for focal epilepsy.

With the advent of mobile devices, miniaturization, and IoT data collection platforms, new efforts are being directed towards building patient management systems. Data that is more accurate and more extensive can be used to gain an understanding of the disease and the circumstances of cycles that indicate the onset of seizures, and to provide support for decision-making.

Mobile Plus Deep Learning to Detect and Predict Seizures

According to Dr. Isabell Kiral-Kornek and Dr. Stefan Harrer at IBM Research Australia, epilepsy management can be advanced by using deep learning techniques for mobile seizure detection and prediction.

The use of mobile sensors to collect information on epilepsy offers a clear jump in what we can do and how we can help patients. For example, in Africa 4% of the population has epilepsy which is a substantially higher rate than the 0.7-1% of epilepsy prevalence we see in the Western nations. For this reason, using mobile technology for telemedicine and remote sensors represents an excellent use case for Africa. Another big advantage for mobile sensors would be their use in home monitoring as a solution for sudden epileptic events, which can often lead to death.

Deep learning has been successfully used to address a large variety of problems in the biomedical field, ranging from image classification in cancer diagnosis to the automatic interpretation of electronic health records. Scientists at IBM Research Australia are building deep neural network models to help develop personalized seizure forecasting and seizure detection, based on data collected via mobile sensors.

Their paper[1], published in Lancet's open-access journal EBioMedicine, describes the use of long-term intracranial EEG recordings to predict upcoming seizures for 10 patients. With a mean sensitivity of 69%, they surpass an equivalent random predictor for all patients by an average of 42%. The presented system is fully automatic, patient-specific, tunable, and able to run on IBM's ultra low-power neuromorphic *TrueNorth* chip.

As a continuation to this work, they are now building models to help classify scalp-EEG signals in a clinical context. Their most recent work[2] has shown the feasibility of using specialized neural networks to classify EEG data into normal/abnormal EEG and grouping different types of seizures. Once the data is classified, it can be input to AI networks in the form of automated digital seizure diaries, which can then be analyzed to predict the onset of a seizure. This solution can help in running clinical trials, to determine the efficacy and suitability of epilepsy drug treatments. Another more recent paper[3] discusses seizure type prediction.

[1] Kiral-Kornek, I., Roy, S. et al. (2017). Epileptic seizure prediction using big data and deep learning: toward a mobile system. *EBioMedicine.*

[2] Roy, S., Kiral-Kornek, I., & Harrer, S. (2018). ChronoNet: A Deep Recurrent Neural Network for Abnormal EEG Identification. *arXiv preprint* arXiv:1802.00308 and Roy, S., Kiral-Kornek, I., & Harrer, S. (2018). Deep Learning enabled automatic abnormal EEG identification. Proc. IEEE EMBC 2018.

[3] Kiral-Kornek, I., Roy, S. & Harrer, S. (2018). Automatic epileptic seizure type classification using convolutional neural networks. 2018 Annual Meeting of the American Epilepsy Society (AES 2018).

Key Observations

- Seizure prediction could be useful to limit the time a stimulator has to be active and to administer medication proactively.
- The number of false alarms and long-duration alarms will be further reduced before the system can be made available to patients.
- AI, and particularly deep learning technology, enables automatic epileptic seizure detection and prediction. Automatic seizure detection allows us to build patient-specific seizure diaries that can be used to (i) optimize detection algorithms for individual patients, (ii) automatically adapt these algorithms to adjust for transient data effects and (iii) train personalized seizure prediction algorithms.
- Advances in mobile processor development allow us to run such algorithms on wearable systems.
- AI-enabled automatic, mobile epileptic seizure detection systems will substitute patient self-reporting and can thus be used to increase the efficiency and reliability of endpoint determination in clinical trials. This will substantially increase the efficiency of clinical trials.

- Epileptologists are paid for a 4-hour session to interpret 24 hours of EEG signals. Any advances that can help automate this task will be helpful in reducing costs and allow clinicians to focus on patient care.
- An epileptiform spike detection algorithm could be beneficial for automatic labeling.

Suggested Initiatives

- Multi-modal recordings of vital signs for seizure detection and prediction that consider circadian and monthly cycles.
- Objective seizure reporting that also measures duration, intensity, and pre-post episodal activities.
- A data platform that is shared across clinical trials and organizations to further research and for insights into the data gathered.

Using Real World Evidence for Clinical Decision Support

Scientists at IBM Research – Haifa, led by Dr. Yaara Goldschmidt, are investigating the use of real world evidence, combined with causal inference, to enhance support for clinical decision-making in the domain of epilepsy.

Real world evidence (RWE) refers to information on healthcare that is derived from multiple sources outside typical clinical research settings. This includes electronic health records (EHRs), claims and billing data, product and disease registries, and data gathered through personal devices and health applications. Such data gathered for millions of patients is becoming more and more available for population health studies. It offers new opportunities for building personalized treatment recommendation systems.

For example, an intensive care unit can have an average of 697 alarms per patient per day and can process in the order of 10 GB of data per day. Data of this sort can be used in epilepsy research to observe conditions that exist before seizures, correlations between the disease and non-adherence, or studies into evidence-based medicine.

The goal of computer-based clinical decision support systems (CDSS) is to use information and communication technology as the basis for helping users reach decisions[3]. In the healthcare domain, users may be physicians, nurses, healthcare policy makers, pharmacists, patients, or other individuals[2]**.**

The main hurdles holding back the acceptance of a computer system for aiding decisions are the data, and finding a way to remove the bias from this data. Data used to train CDSS is not perfect. As a result, the models may not be reliable and the user can't rely on system recommendations. Documenting how the systems were trained, on which data, and based on which parameters, is critical. Moreover, using proper statistical tools is vital to reach unbiased statistical models when it comes to treatment recommendation. For example, without considering confounding and measurement biases, there is no way to reach reliable decisions from inherently biased RWE data.

Key Observations

- Randomized clinical studies have limitations when it comes to providing all possible answers for all possible decision points. There is no way to avoid using RWE for decision-making going forward.
- Another question raised is: which stakeholders will drive the collection of personal data for research? What is the business model?

- The system must become part of the regular healthcare practice, driving effectiveness and not creating more work for the users, for example through extra documentation.
- The CDSS has to highlight what to look at, rather than make the final treatment decision. It should bring the right information to the decision point and not drown the user with information. This would be analogous to a system that forecasts the weather versus telling you to take an umbrella.
- CDSS that include data visualization are much more acceptable for humans when it comes to adherence, as opposed to statistical numbers.
- What are the possible enablers to developing CDSS and increasing their acceptance? For example, nurses may be a good target for CDSS, serving as a funnel to filter the cases for the physician.
- CDSS may be needed most and accepted in scenarios where 1) there is a lot of data in real time that a human cannot handle, or 2) it involves making decisions in life threatening situations when there is a small time window.
- For success, the system must maintain transparency. This includes publishing it and its results, and testing the system in different scenarios.
- CDSS can target different types of decisions, and not only treatment recommendations. Some decision points will be adopted easily, for example for making decisions on a facility level, or on the population level to drive new guidelines, not just for individual patients.

Suggested Initiatives

- Collaborative efforts can be made to ensure more accurate data and more accurate collection of data.
- Digital health technologies can be used to enhance the types of data gathered for each patient, such as monitoring activities or adherence alongside other aspects. This will allow a holistic view of the patient, and training statistical models that do not miss information.

[1] Real-world evidence—what is it and what can it tell us. Sherman, R.E. et al. *N Engl J Med*, 375(23), pp.2293-2297, 2016

[2] Clinical Decision Support: The Road Ahead. Edited by Robert A. Greenes, *Elsevier*, 28 Apr 2011

[3] Changing the approach to treatment choice in epilepsy using big data. Devinsky et al. *Epilepsy and Behavior*, 2016

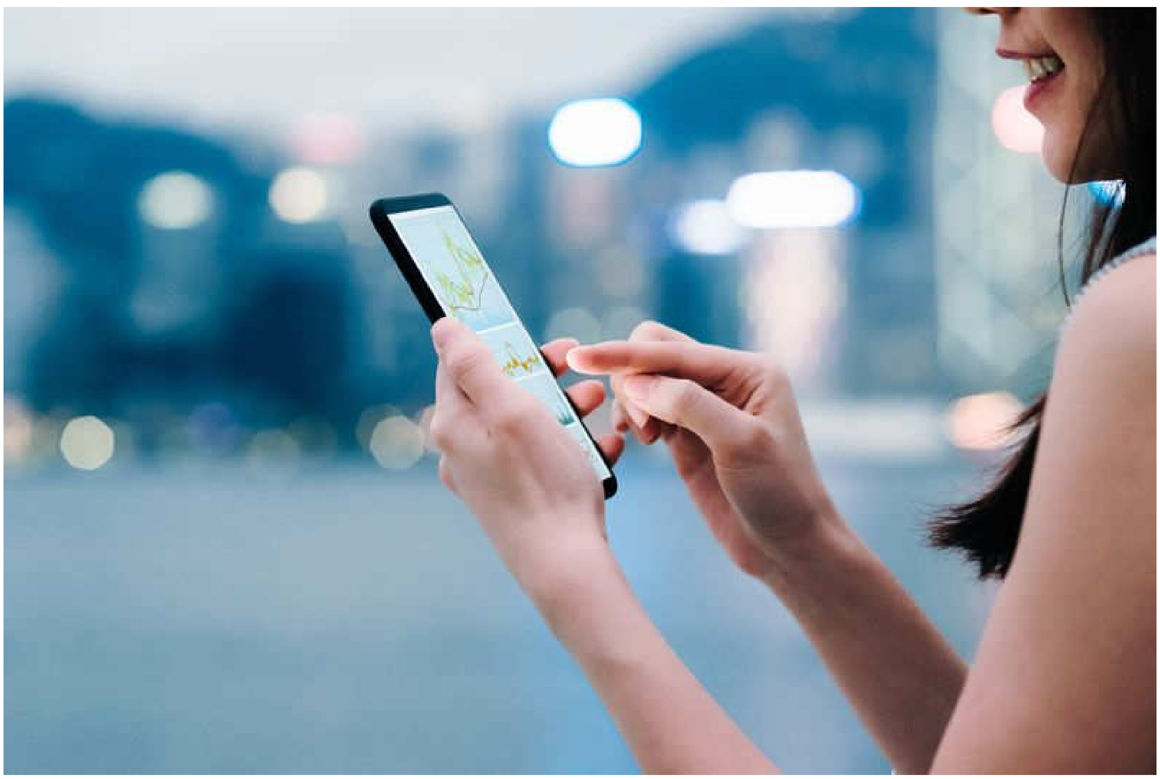
Using Sensors to Track Symptoms and Coach Patients

Sensors are introducing new mobile-health opportunities for predictive care, as well as personalized coaching of seizure patients in their daily life. Thomas Brunschwiler, Ph.D., from IBM Research – Zurich, are delving into the benefits human-centric sensing can bring to epilepsy treatment.

Key Observations

Requirements for Home Monitoring

Healthcare can benefit from a platform that connects all relevant mobile devices and allows the sharing of data (with the approval of patients) between various medical studies. Currently, data is stored in closed silos and the communication of the devices are often proprietary. Furthermore, clinical studies are performed with mono-morbid patient groups representing only a small population, as co-morbidities are the norm.



Mobile-health applications for seizure patients

An accurate reporting of seizures outside of the hospital is still missing; thus, research should be performed on automatic reporting of seizures. Such a solution would support the accelerated drug selection and their dosage, as well as a more precise patient segmentation. Furthermore, the efficacy of novel drugs could be proven with improved accuracy. Ideally, the solution would be discreet and not allow a person to be identified as a seizure patient. In the best case, the vital sign recording could be performed with devices used by healthy persons, as well.

Seizure predictions are much more challenging and need to be tackled on different levels. Too many false positives are not acceptable, as they cause high mental stress in patients. Short-term predictions given a few minutes before a seizure could allow the patient to stop dangerous activities and get into a safe position. One could also try to derive risk levels (e.g., from red to green) indicating the probability of experiencing a seizure. Recommendations to avoid certain activities or specific behaviors (e.g., prevent stressful activities) could be provided, based on the actual risk level.

It is believed that multi-model vital signal recordings and the consideration of circadian and monthly cycles are needed for the detection and prediction of epileptic seizures with high sensitivity and specificity.

Seizure patient coaching opportunities

The potential of mobile-health applications to improve the quality-of-life of seizure patients is estimated to be high. Advances in miniaturization have enabled the integration of sensing, computation, and communication in wearable formfactors for human-centric sensing and computing. The available cloud infrastructure allows us to collect the acquired data continuously at scale. It also supports advanced pattern recognition for individuals and across cohorts, to provide actionable real-time insights. The availability of these technologies supports mobile-health solutions that objectively track patient symptoms and can provide personal coaching outside of the traditional healthcare setting. The opportunities are predictive and preventive health measures, as well as improved quality-of-life for patients[1].

At IBM Research – Zurich, scientists are exploring the usability of connected devices, the accuracy of objective symptom tracking compared to self-reported outcomes, and life-style coaching by virtual agents. For example, one project offers quality-of-life management of COPD patients, considering a physician-patient communication channel, including connected devices, symptom apps, and virtual coaching. The solution can be applied as a COPD therapy program, as well as to support clinical trials for new medications[2]. Another example that integrates sensor data for healthcare is IBM's IoT work on Project BlueSky, a system to improve how clinical trials are conducted for Parkinson's disease drugs in development.

Dr. Adriano Nogueira is collaborating with the Swiss Integrative Center for Human Health on seizure prediction based on the analysis of temperature in the sleep-wake cycle. In an initial study with hospitalized patients, an accuracy of 80.6% was achieved in predicting seizures one day ahead. This result was achieved based on skin temperature readings through a commercially available wearable watch.

Suggested Initiatives

- Initiating an infrastructure for multi-modal disease tracking and data sharing across research projects involves the issue of data sharing and public governance. Governmental or patient organizations would have the highest trust to run such an infrastructure. Business models need to be identified and tested, such as data brokerage and free drugs for data, with patients in full control of their own data sets. Here, the field of neurological disease could be a main driver, due to the complexity of the diseases with the need to deal with multi-modal data fusion.
- The immediate benefits of wearing mobile health devices must be clear to patients if they are to cooperate. Accordingly, we discussed the potential to provide personalized coaching for the patient through mobile apps. The apps could be used to improve the awareness for the disease or to connect to peers with the same seizure symptoms. Family members and friends could be included as well, to support them in critical situations. Furthermore, behavioral support could be provided, depending on the current risk situation of the patient.

[1] R. Straessle et al., "Cognitive Companion Enabling High-Quality Monitoring at Home," *IEEE Healthcom*, Dalian, China, 2017.

[2] T. Brunschwiler et al., "CAir : Mobile-Health Intervention for COPD Patients," *IEEE Healthcom*, Dalian, China, 2017.

Streaming Analytics from Devices in the ICU Environment

Multimodal streams hold the promise of saving lives in the ICU, but also present a host of challenges related to analyzing this data. Dr. Emanuela Keller, M.D., University Hospital Zurich is tackling these hurdles with various creative approaches.

Key Observations

ICU IT infrastructure lessons learned

Over the last few years ICUs have implemented hospital information systems (HIS) to collect medical data. HIS offer several advantages: less administrative work and more time for patient care, better data quality and patient safety, as well as opportunity for automatic data analysis.

Commercially available HIS, however, do not fulfil the specific requirements of ICUs, where the monitoring is multimodal and generates a huge amount of data. They focus mainly on the administrative needs of hospitals and reiterate the format of paper charts. Data logging and storage is performed only intermittently and no analytical power is included in the systems. To understand the complex pathophysiology, incorporating all interconnections and coupling between the organ systems, data from all monitoring and measurement devices have to be collected in a high time-resolution[1]. Computer-supported data analysis is required, mostly on the collection and archiving of a huge amount of data. However, several obstacles have been identified to develop streaming analytics in the ICU environment. Time synchronization of data coming from different devices is not guaranteed. This is also attributed, for example, to the fact that the connected devices have different timestamps. Moreover, practice has shown that research IT infrastructure has to be customized and adapted to every hospital IT infrastructure[2,3]. This dependency on hospital IT creates a regulatory dependency. Another critical aspect remains the protection of critical patient data.

Video-based patient monitoring

Patient care is a critical and a life-saving task, especially in ICUs monitoring patients on a 24-hour basis to detect signs of state deterioration or imminent complications. Manual monitoring by specially trained and highly experienced ICU personnel complements the vital signs monitoring devices, such as EEG, to address issues such as false alarms, misdetections, and overall patient state assessment. Full-time bedside care is difficult and not cost-effective. Severe burnout syndrome is present in about 50% of critical care physicians and in one third of critical care nurses.

ICU personnel rely on the alarm systems of devices monitoring vital signs, which tends to weigh on sensitivity rather than specificity, and thus generate numerous false alarms. ICU personnel are trained to filter those alarms in their subconscious, but inevitably may miss critical alarms due to conflicting priorities or mis-filtering. Video monitoring can complement the existing monitoring systems by covering the idle times between manual inspections and thus detect signs of patient state deterioration that are missed either by the vital signs monitoring devices or the ICU personnel. The IBM Research – Zurich team developed and demonstrated a patient monitoring solution based on sparse coding and dictionary learning that learns stable state patterns for individual patients and detects epileptic seizures in the form of anomaly detection[4]. The team also extracted and demonstrated initial results in video-based heart-rate extraction. IBM Research Australia is developing a fully automated seizure detection system aimed to assist ICU personnel in monitoring and responding to patient states in real-time with minimum false alarm rate. Initially focused on analyzing EEG and video data, the system will use a multitude of fully integrated wearable and bedside sensors.

Video monitoring of patients generates petabytes of data per day, adding a significant load to the already stressed Big Data problem of the ICU Cockpit framework. However, these data are rich, carrying critical information that can be combined with the vital signals and patient information to enhance the system’s capability to detect critical states in an early, robust and personalized way. This has the potential to significantly improve patient care and personnel effectiveness. Specifically, it has been observed that there is an increase in heart-rate before seizures (heart-rate variability). This is something we can examine more closely as we analyze signals from the video, as they reflect motion and appearance along with vital signs, such as heart-rate.

Suggested Initiatives

- Solving the synchronization of the various multimodal vital sign signals detected by the various devices in an ICU is a major focus. An approach to be further pursued is to take artificial signal (as f.e. implemented in ECG stream for electro-cardioversion) as a "pacemaker".
- To resolve data protection for the patient, the recommended approach is to implement the server/IT infrastructure within the hospital environment.

[1] Schwab P, Keller E, Muroi C, Mack D.J., Strässle C, Karlen W (2018) Not to cry wolf: distantly supervised multitask learning in critical care Proc 35th Int Conf Mach Learn (ICML), 80:4518-27

[2] Wadehn F, Mack DJ, Keller E, Heldt T (2018) A multiscale intracranial pressure signal simulator. Computing in Cardiology, submitted

[3] Muroi C, Meier S, De Luca V, Mack DJ, Strässle C, Schwab P, Karlen W, Keller E (2018) Motion detection-based automated alarm classification in a real life intensive care setting. Neurocritical Care, submitted

[4] M. Pediaditis et al., “Personalized Analysis of Valence and Arousal from Videos”, 13th International Conference on Automatic Face and Gesture Recognition, 2018 (submitted)

Contact Us for More Information

Emanuela Keller, University Hospital Zurich, Emanuala.Keller@usz.ch

Yaara Goldschmidt, IBM Research Haifa, yaarag@il.ibm.com

Stefan Harrer, IBM Research Australia, sharrer@au.ibm.com

Isabell Kiral-Kornek, IBM Research Australia, isabeki@aus1.ibm.com

Thomas Brunschwiler, IBM Research Zurich, tbr@zurich.ibm.com

Maria Gabrani, IBM Research Zurich, mga@zuroch.ibm.com