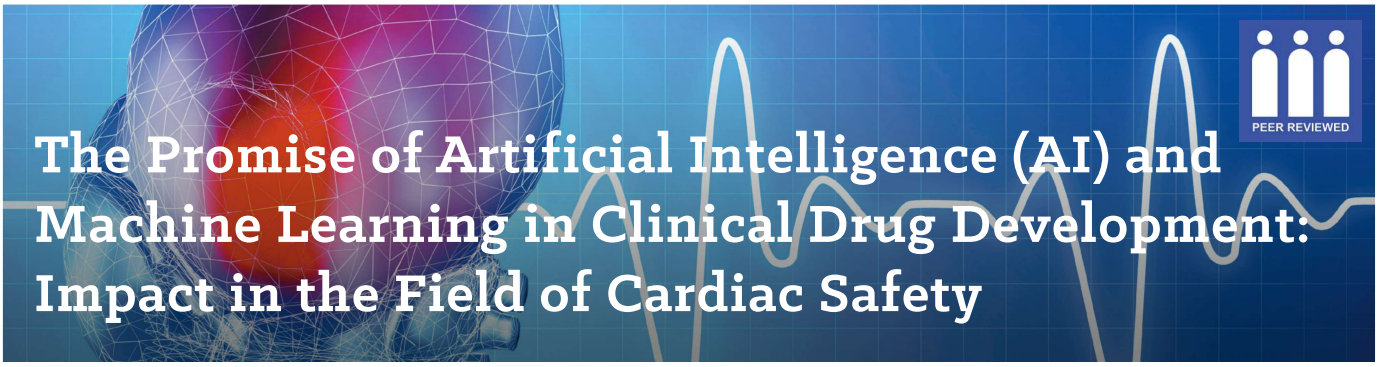

The Promise of Artificial Intelligence (AI) and Machine Learning in Clinical Drug Development: Impact in the Field of Cardiac Safety

With recent advances in technology, computer science and informatics, new techniques in medicine became available, and existing tools and measurements were drastically enhanced. Specifically, in the field of cardiac safety, we saw a change in technology and standard practice. The historical 10 seconds 12-lead ECG has served as the standard for the assessment of druginduced ECG effects, but it showed important limitations. Technological enhancements allowed the refinement of tools to the newer ECG monitoring tools, of which we are already in the third-generation[1]. Though artificial intelligence and deep learning are already established in other medical areas like radiology, they entered the field of clinical medicine only recently and carefully. This new technology will augment human intelligence to improve decision-making, resulting in optimal operational processes. But new technology is nothing if the drug development stakeholders are not ready to embrace changes it encompasses. Clinical researchers need to actively engage, adapt and reorganise their practice to benefit from modern and even future technology.

Historic Development of Automated ECG Diagnostic Algorithms

The main role of cardiac safety in the phase of drug development is to assess the drug effects on the heart. Several characteristics of an ECG trace are generally being studied, such as duration of the P wave or QRS complex, PR interval, QT interval… All these measures make it possible to describe precisely the pathologies detected using published and validated classifications such as the Minnesota Code Classification System[2] or the Lown Classification for ventricular arrhythmias assessment[3].

The estimation of these characteristics from the records requires the interpretation of one or more specialists. To reduce this manual estimation time, automated estimation solutions have been proposed in the literature for many decades, and have been used by ECG recorder manufacturers or providers of software solutions.

Most of the current algorithms on the market are based on detection and classification of QRS beats, then algorithms for measuring the different waves (in amplitude and in duration), and try to discern the complex relationships between them over time.

A few years back in 2017, the Cardiac Safety Research Consortium published results from a study including 800 digital ECGs, read and interpreted by the most widely used algorithms in place[4]. The results showed that the systematic differences among ECG interval measurements with the currently available widespread algorithms are very small. However, the reliability of the estimates made by the current algorithms is unsatisfactory and often requires corrections from the experts.

New Challenges

With the introduction of new technologies (biosensors, connected devices, implantable devices…), tools allow one to look at longer periods of monitoring and allow collecting more data that need to be processed. This will lead to analysing the ECG recordings as a whole (time changes, beat morphologies changes, extraction of abnormal pattern) rather than just assessing a single isolated beat.

Having powerful devices to acquire long-time ECG traces is crucial but it no longer seems acceptable to ask a cardiologist to review them all in a timely manner, keeping the patient's safety first in mind.

The question of the quality of a continuous ECG trace acquired by a patient in real condition also comes in first position. Indeed, if the control and the re-classification of one hundred artefacts can be carried out manually for a recording of 24 hours, the manual processing of more than 3000 artefacts is no longer possible when one deals with a recording of 30 days.

This represents a huge amount of data and is an excellent venue for algorithm automation. It is therefore necessary to develop new data detection and access methods that allow experts to provide the most reliable analysis possible.

The other challenge is to leverage even more the output of these readings and to provide drug development stakeholders with new biomarkers that can help going beyond the standard QT interval measurement that is currently used.

Continuous and automatic reading represents a real opportunity to better understand the evolution of the morphology changes in discriminating specific types of heartbeats that are the root cause of some cardiac events. CiPA initiatives increasing preliminary screening of arrhythmias ahead of clinical study raises the need for new biomarkers that would carry more intensive assessments of cardiac safety monitoring. One of the perfect examples is the automatic assessment of JTpeak interval[5].

Current State and Limitations of AI-based Cardiac Monitoring

With the advent of modern computational and more specifically machine learning techniques, the diagnostic power of ECG has expanded exponentially. The stakeholders of cardiac safety assessment and AI researchers started working together on new tools for classification, clustering and analysis of ECG data, with the goal of classifying with more accuracy continuous ECG recording.

Currently, there are many machine learning (ML) solutions which can be used for analysing and classifying ECG data. Several categories of solutions stand out and have been described in depth in literature[6]:

- Artificial or convolutional neural networks (CNNs),
- Bayesian networks,
- Decision trees,
- Fuzzy logic,
- Genetic and hybrid algorithms.
- Linear and quadratic discriminants (LD),
- Rough set theory and Hidden Markov Mode,
- Random forests,
- Support vector machines (SVM).

The standard approach in developing an automated machine learning classification technique is to extract characteristic features from the waveform using signal processing techniques such as Fourier Transforms (FTs) or Wavelets. Some strategies focus on the temporal intervals (QRS interval, QT duration, heart rate…) while others focus on morphological features extraction (slopes, peaks, amplitudes) to describe the shape of the ECG waves (template).

A scientific paper has reported that most of the machine learning methods mentioned present similar good performances in terms of precision (approx. 95–99%) and have been previously successfully applied to the ECG arrhythmias detection tasks[7].

However, many problems come with the complexity to find the most appropriate features:

- Most of the time, the ECG recording needs to be pre-processed in order to remove the noise that comes with many external factors such as the contraction of the muscles, respiratory movements, poor electrode contact and presence of other external devices.
- These machine learning applications require considerable amounts of data correctly validated by experts to allow artificial intelligence to learn properly. Indeed, they are not able to detect a specific pattern they have never encountered during the learning curve.

One of the suggested solutions is to use a new branch of technology named deep learning[8] (often referred to as a sub-domain of machine learning) which represents an advance in precision medicine and substantial potential for clinical research. As with all general machine learning techniques designed to drive statistical algorithms (classification, regression, etc.), deep learning approaches are used to produce predictive models in part of non-structured data. Deep learning wants to mimic the visual cortex using a succession of many intermediate layers of artificial "neurons". By learning feature detectors that are optimised for classification, deep learning can substantially outperform systems that rely on features supplied by experts in the domain or that are designed by hand.

From the clinical perspective, two important benefits can be highlighted. Firstly, deep learning models may allow the analysis of the ECG without any pre-processing of the signal, which avoids the need for prior information on the biomarkers and may help discover new knowledge. Secondly, the outcomes of deep learning, contrary to a standard approach, are clinically interpretable, providing the opportunity to discover new biomarkers and enhance their importance.

Conclusions

When/how should AI-based cardiac monitoring be used in drug development?

A primary objective is to identify how one can provide a reasonable level of confidence in the performance of algorithms in a way that maximises the advantages of AI while minimising risks to product quality and patient safety.

Involvement of regulatory agencies and industry are critical in this effort, as both need to trust the science behind the technology. Recently, some medical device to use AI in order to detect atrial fibrillation has been approved by the FDA. This is a major step and demonstrates the path to follow in the (near) future for cardiac safety as well.

The alliance of technologies and science will for sure reshape the drug development process, and the use of continuous reading algorithms presents many benefits: improvement of cardiac biomarkers determination, reduction of variability… and will allow a reduction of the number of patients to be enrolled and, as a result, reduction of the cost of the research.

Does it mean that artificial intelligence in the broader sense will have to replace our cardiologists? "Today, the mass extinction of physicians remains unlikely." However, as outlined by Hinton[9], the emergence of a radically different approach to AI, i.e. deep learning, has the potential to effect major changes in clinical medicine healthcare delivery and certainly in the field of cardiac safety when developing new drugs.

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