'Rise of the machines': The next frontier in individualised medicine

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Artificial intelligence (AI) and *in silico* models, in conjunction with the rapid adoption of mobile health (mHealth) technologies such as smart wearables, have the potential to revolutionise the monitoring, screening, and treatment of cardiovascular disease patients. Broadly speaking, AI and machine learning (ML) are predominantly statistical methods – learning from patient data to predict outcomes, with often little to no mechanistic understanding of the underlying processes. On the other hand, the nascent but rapidly developing field of *in silico* models are mechanistic models – they use the underlying physics/chemistry to model the phenomenon of interest be that stroke and its treatment[1], heart failure[2], or cardiotoxicity[3]. A typical example of an *in silico* model we use daily is the weather forecast – where the equations of weather formation are used in conjunction with previously collected data to make predictions on how the weather will develop. A synergistic use of both these statistical and mechanistic models will have the greatest value in aiding patient evaluation and treatment.

Both AI/ML and *in silico* models, however, require data on the patient group of interest. mHealth provides an opportunity to collect continuous data that can be used to individualise patient treatment and improve outcomes. This has only been accelerated by the COVID-19 pandemic that has seen swathes of the population move to remote monitoring and tele-health solutions.

Innovations in smart wearables and mHealth have provided avenues in screening and monitoring of the cardiovascular health at a population wide level, as well as providing subject-specific data. This has generated a vast amount of data primed for analysis to aid in earlier diagnosis, initiating individualised treatment, monitoring and predicting disease progression. In conjunction with patient health records, these data can be applied in many aspects of cardiology using both AI/ML[4] and *in silico* models[5] (**Fig. 1**).

How do ML/AI and *in silico* models interact with mHealth?

The main application of AI and ML encompasses screening (e.g. using smart wearables to screen for atrial fibrillation[6]; aiding diagnosis (e.g. identifying ST-segment elevation in patients with chest pain through a smartphone application)[7]; enhancing the analysis of imaging modalities such as CT coronary angiograms[8] and prognostication[9]. Aside from the ability to translate large quantities of data into clinically meaningful output, AI-driven algorithms can aid clinical decision on test selection and strategy, providing clinicians with highly accurate tools in order to risk stratify patients more consistently, allowing better allocation of resources and perhaps, provide reassurances to the 'worried well' and reduce health-related anxiety.

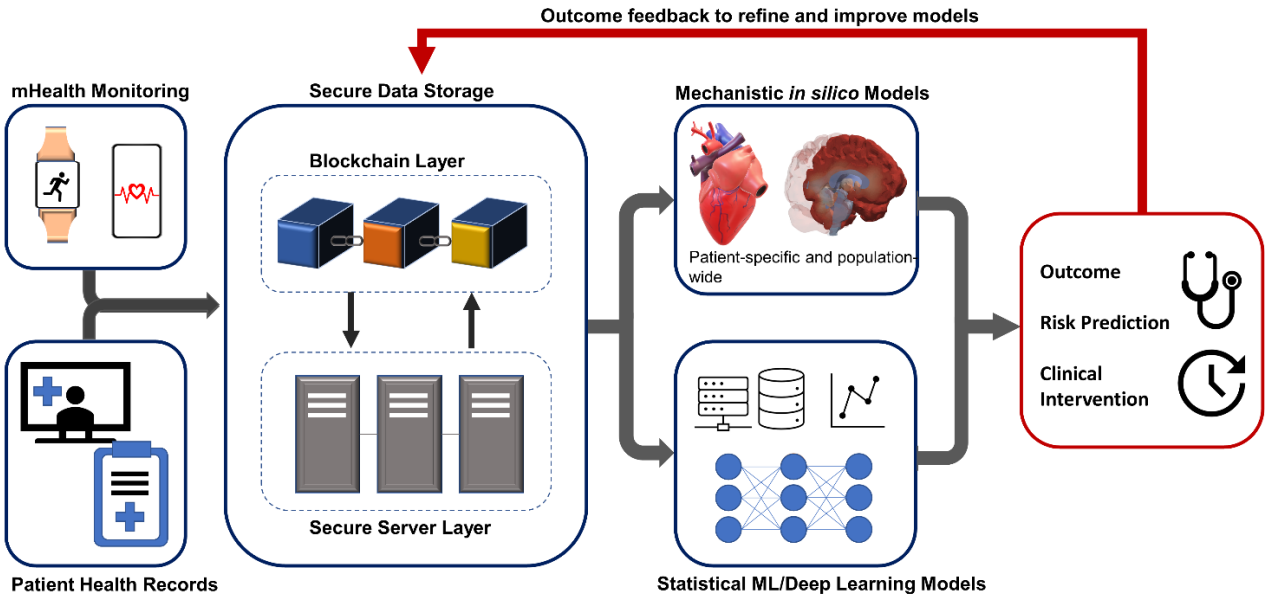

Figure 1 *Schematic of how the 'rise of the machines' can aid clinical workflow and improve patient outcome prediction and treatment. Individual patient data is collected using both mHealth monitoring and linked to patient healthcare records. These are securely stored on servers that interact with the blockchain – effectively giving control of patient data to the patient. These data can then be used to develop patient-specific in silico models, population-wide in silico clinical trials, and can be used for training ML/deep learning models for risk prediction and stratification. Outcomes of these models are fed back, in combination with the patient data, to improve and refine the in silico and ML models.*

Currently, *in silico* models have had little uptake in clinical settings, with the major exceptions being HeartFlow which predicts fractional flow reserve in coronary arteries using in-silico models, and CardioInsight where body surface potentials are used to infer the electrical activity of the heart surface. The difficulty often encountered with *in silico* models is validation – whilst the model may work on a carefully controlled virtual patient cohort, in practice these in-silico models are often unable to deal with the heterogeneity encountered in the patient population. However, with the advent of greater remote monitoring and data collection, these models will be able to recalibrate for individual patients essentially developing into a 'digital twin' for that individual[5].

Outside of direct clinical applications, a major advantage of *in silico* models comes in their ability to generate virtual populations which can be used in *in silico* clinical trials (ISCTs). These ISCTs can be used to help refine inclusion and exclusion criteria in real-world clinical trials, can be used to run trials on underrepresented populations e.g. paediatrics, as well as act as virtual control arms. AI / ML have also shown promise in research, being able to speed up the integration of large volumes of data and identifying latent relationships between factors and conditions which could have impact on novel therapies for the future.

Conclusion

One aspect that has thus far been neglected is the patient data. With the continual remote monitoring of patient health enabled by mHealth technologies a dilemma arises with patient

privacy and data ownership. One potential solution to this is by placing the patient in charge of their data allowing them to share it between different organisations and apps. This can be achieved through a further 'machine' on the rise – blockchain technology[10]. While still in its infancy, this third technology has the potential to complete the link between patient monitoring and the use of this data in clinical and research settings and by giving the patient control of how their data can be used.

Although the 'rise of the machines' seems inevitable and can potentially result in better healthcare provision, clinicians will also need to be aware of the pitfalls involved with the dependence on such systems, especially without rigorous testing and validation. The quality of their output is dependent on the quality of the data input and our understanding of disease mechanisms, and may perpetuate bias which may exacerbate inequalities in healthcare. Just like humans, AI systems and *in silico* models are not infallible – this is imperative for everyone, from developers to users, to recognise before they can be fully integrated into various aspects of medicine.

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