The role of Artificial Intelligence within *in silico* medicine

VPH Institute – Avicenna Alliance White Paper

Provisional Executive Summary June 12th 2020

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I. About the Avicenna Alliance

The Avicenna Alliance is an association of industry and academia and healthcare organisations who have a commercial or research interest in the development of *in silico* medicine.

The Alliance, established in 2016, has its origins in the Virtual Physiological Human Initiative, a European Commission endorsed research area on computer modelling and simulation. Tasked by the European Commission with developing a "Roadmap for *in silico* medicine", the Alliance now seeks to put this roadmap into policy and ensure the development of a well-functioning framework for the *in silico* medicine ecosystem.

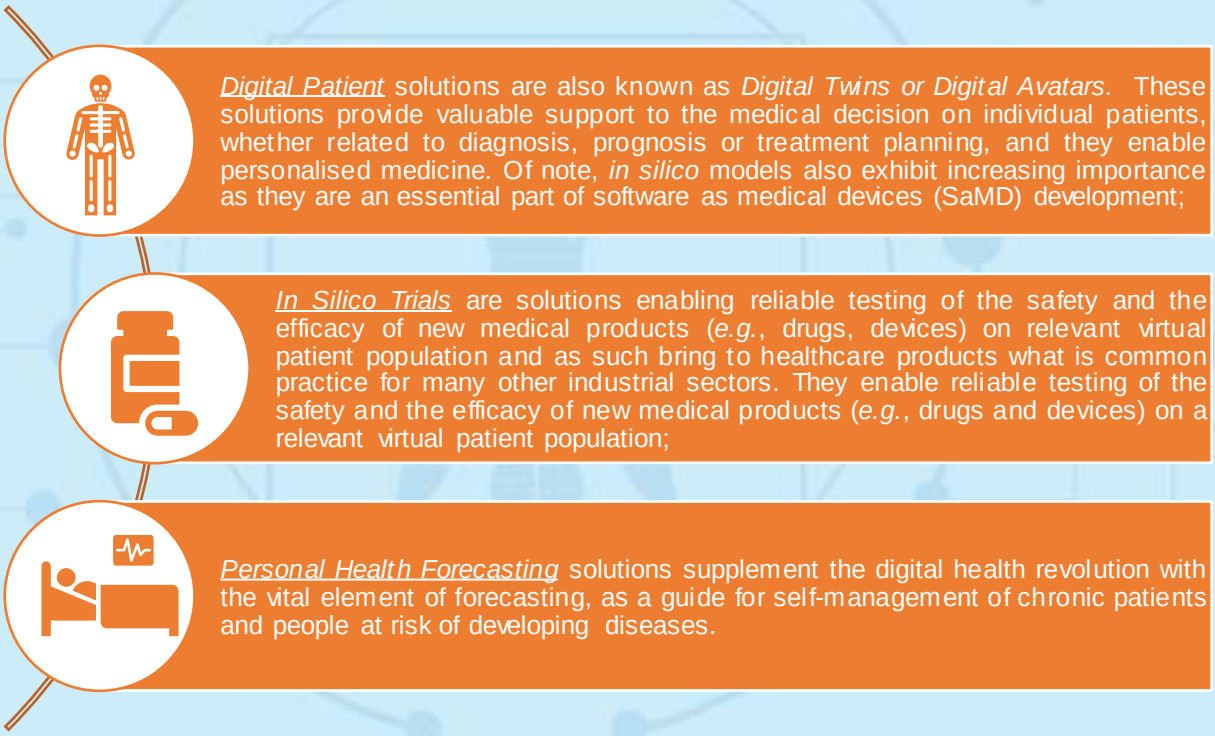
This Alliance bridges the gap between the scientific community, industry and policymakers by advocating for policy changes that take scientific and market developments into account.

II. Introduction

The Avicenna Alliance warmly welcomes the European Commission's ambitious policy package, including the White Paper on artificial intelligence (AI) aimed at making the EU fit for the digital age. Members of the Avicenna Alliance believe it is important to provide feedback to this important publication and therefore started working on an Avicenna Alliance white paper on *"the role of artificial intelligence within in silico medicine".* Given the great interest shown by the members of the Alliance and the time necessary to respond to the European Commission's public consultation on AI, it was decided to produce this provisional executive summary as an introduction to the white paper to be published later in 2020.

The past decade has produced overwhelming evidence that changes in the health status of individuals, measured by well-defined quantitative clinical endpoints, can, in many specific cases, be predicted by computer models (also known as predictive models). This has opened the door to several applications for these **computer modelling & simulation (CM&S) technologies**, which are generically referred to as ***in silico* medicine**.

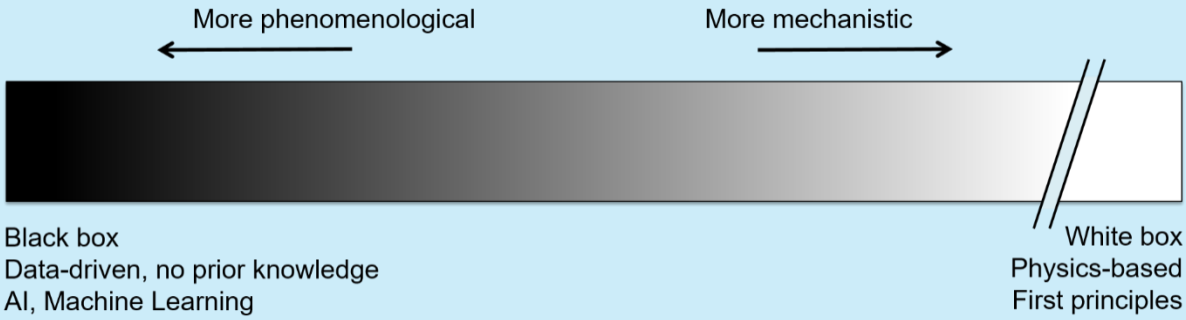
The use of CM&S leads to three main domains of healthcare solutions:



III. Mechanistic and Phenomenological Models

There are different ways to build computer models, depending on the technologies as well as the quality and strength of data and knowledge that are used. The available scientific knowledge in biophysics, biochemistry, and physiology of the human body, both in healthy and diseased states, can be translated into mathematical descriptions. **Computer models** that are **based on such cause-effect relationships** are called ***mechanistic models*** because they are built by assuming the causal "mechanism" of the phenomenon being modelled. However, this is not the only way to build computer models (Figure 1). When a sufficiently large body of empirical observations is available, it is possible to **develop a predictor without making any causal assumption.** This can be done in a number of ways: using statistics, system identification methods or more recently, artificial intelligence (AI) methods. Hereinafter these other computer models are referred by the term ***phenomenological models*** because they derive exclusively from the observation of the phenomenon to be modelled.

Figure 1. The *in silico* continuum



IV. Importance of AI methods within *in silico* medicine

AI methods are incredibly powerful, and intense research will make them even better. Although these technologies are very exciting, one should be careful of not over-promising as it could be detrimental to this emerging sector. The white paper wants to explain the **importance of AI methods within *in silico* medicine**, and to recognise the strength and limitations of mechanistic and phenomenological models in order to guide their rational and conscious adoption. Mechanistic models are neither intrinsically superior nor inherently inferior to phenomenological models. Whether a mechanistic or phenomenological approach is more viable or effective depends on the context of use, which defines the specific role and scope of the computer model used to address the health-related question of interest.[1] The context of use describes how a prediction can be used to support a decision based on the available data, the underlying assumptions and the execution of the model. The white paper highlights the enormous potential of combining mechanistic and phenomenological approaches to address very challenging scenarios as well as their impact on healthcare policies (and vice versa).

Several dimensions must be considered to determine the optimal CM&S strategy for a defined health scenario.

I A first dimension is the availability of reliable mechanistic knowledge of the phenomenon of interest. In the absence of such mechanistic knowledge, phenomenological models are the only option.

[1] ASME V&V 40 (2018). Assessing Credibility of Computational Modeling Through Verification and Validation: Application to Medical Devices, The American Society of Mechanical Engineers.

II A second dimension is the effort, defined as the computational and financial cost of conducting the simulation within the time limit imposed by the context of use. The computer models providing a real-time answer require different technologies, computing facilities and deployment strategies than computer models used in the regulatory approval process or for planning medical interventions. Besides computational cost, there is also the cost for acquisition, preparation, and management of data that will become increasingly significant, particularly for phenomenological models.

III A third dimension is linked to the requirements that each modelling strategy has in terms of quality and quantity of data required to build, run, and validate each predictive model. The availability of large high-quality data sets remains today an important challenge in healthcare.

IV A fourth and last dimension is related to the process we use to establish the credibility of a prediction obtained by such models. Both mechanistic and phenomenological models must undergo complex scrutiny before they can be used in clinical or regulatory practice. However, the extent and the nature of such scrutiny is different for these two types of models.

V. Why do we need to combine various approaches in healthcare?

The white paper describes how the greatest public health gain should be obtained by combining various approaches and gives several examples to illustrate the points made.

Phenomenological elements can be introduced in mechanistic models to complement, assess or accelerate the models and their computation by simulating parts of the modelled phenomenon for which insufficient experimental data exists. When personalising mechanistic models with patient specific data, the mechanistic model needs to be inverted to find the appropriate parameter values and their uncertainties. In many cases, simple fitting techniques will not work properly, and developers will need to resort to advanced phenomenological methods. Finally, to meet requirements on accuracy and speed of simulations, the mechanistic model can be replaced (completely or part of it), by a phenomenological (surrogate) model. The combination of mechanistic and phenomenological models allows the modelling as a whole to be computationally affordable while maximising the benefits of the mechanistic baseline.

In the other direction, **mechanistic elements can substantially augment phenomenological models**. To develop phenomenological models with strong predictive power, large amounts of data (big data) are necessary. In many medical applications, however, the amount of clinical data available is by far not enough to sufficiently train a phenomenological model. A valid mechanistic model can be used as a source of data to enhance the predictive power of phenomenological models, among others for rare events. Alternatively, the explicit inclusion of the mechanistic model as prior knowledge will help to reduce the size of the training data set required to train the phenomenological models. Several phenomenological methods have a means of explicitly accounting for a priori causal knowledge in the derivation of the predictive model. Another way in which mechanistic models can be used to enhance phenomenological models is to provide a benchmark against which the accuracy of the developed algorithms can be tested.

VI. Conclusion

The white paper concludes with a discussion on the **connection between *in silico* medicine and health policies.**

Health policies can lead to the development of powerful *in silico* technologies (in the broadest meaning). The explicit inclusion of modelling in regulatory legislation (MDR[2] and IVDR[3]) has given an impetus to the relevant stakeholders to consider modelling and simulation in their respective processes. The current AI and data strategies will have an important impact on the further development of not only phenomenological models but of *in silico* medicine as a whole. Reciprocally, *in silico* models, be they mechanistic, phenomenological or hybrid, can drive health policies. Given the European Commission's Pharmaceutical Strategy (including the orphan and paediatric regulation), *in silico* models can have a major impact on the risk assessment and overall safety of the medicinal treatments and contribute to make more affordable new drugs available by reducing their development time and cost.

The members of the Avicenna Alliance from medtech, pharmaceutical, digital and life science industries as well as from the *in silico* medicine academic community and healthcare organisations **call on the European Commission** to:

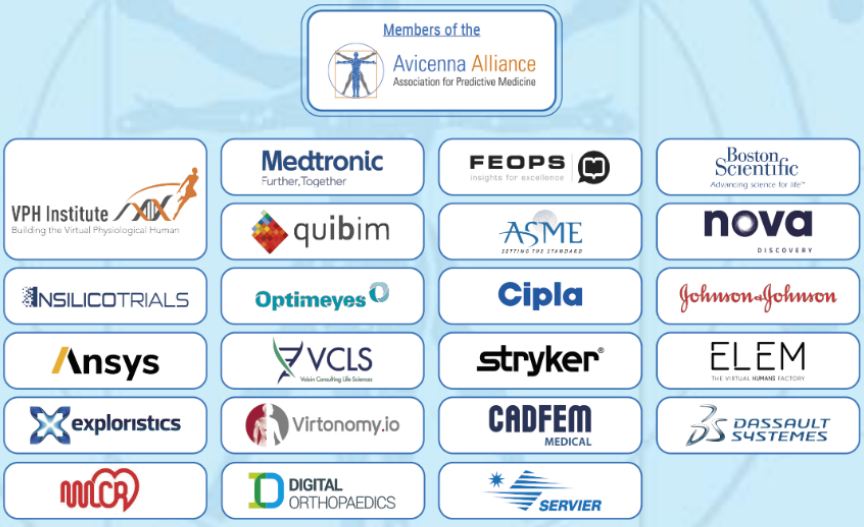
I. Recognise the added value that *in silico* technologies have in healthcare by paying particular attention to it in the new pharmaceutical strategy.

II. Take into account, when revising existing pharmaceutical legislation, the benefits generated by *in silico* technologies. It is particularly the case for the production of digital evidence for treatment development, especially for paediatric and rare diseases, which cannot be generated by the *in vitro* or *ex vivo* models, or is very challenging to generate data using *in vivo* (animal and patient) models.

III. Include the whole spectrum of *in silico* technologies in its future legislative and non-legislative proposals and funding schemes for the health sector.

IV. Consider the context of use when regulating *in silico* technologies.

This Provisional Executive Summary is endorsed by the 22 Members of the Avicenna Alliance on Friday 12 June 2020:



[2] MDR: Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

[3] IVDR: Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU