Artificial intelligence and machine learning in hemostasis and thrombosis

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ABSTRACT

Artificial intelligence (AI) is rapidly becoming more important in our daily lives, and it's beginning to be used in life sciences and in healthcare. AI and machine learning (ML) models are just starting to be applied in the field of hemostasis and thrombosis, but there are already many examples of how they can be useful in basic research/pathophysiology, laboratory diagnostics, and clinical settings. This review wants to shortly explain how AI works, what have been its uses in hemostasis and thrombosis so far and what are possible future developments. Besides the great potential advantages of a correct application of AI to the field of hemostasis and thrombosis, possible risks of inaccurate or deliberately mischievous use of it must be carefully considered. A close monitoring of AI employment in healthcare and research will have to be applied over the next years, but it is expected that the appropriate employment of this new revolutionary technology will bring great advances to the medical field, including to the hemostasis and thrombosis area. The current review, addressed to non-experts in the field, aims to go through the applications of AI in the field of hemostasis and thrombosis that have been explored so far and to examine its advantages, drawbacks and future perspectives.

Artificial intelligence and machine learning

Artificial Intelligence (AI) is becoming an inescapable tool in many aspects of contemporary life, and the place that it occupies is destined to grow exponentially in the next few years.

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Besides its current uses, going from investment advice in financial business to image analysis or self-driving vehicles, AI employment in healthcare and biomedical research is progressively growing.

Artificial intelligence (AI) has been defined as the designing of artificial systems that have an intelligence comparable to humans. This is achieved by providing knowledge to computers allowing them to learn from examples, what is conventionally defined as machine learning (ML). Deep learning is a form of ML inspired by the human brain and by cognition mechanisms and is based on neural networks (NN), which draw inspiration from how neurons compute in the human brain (https://www.youtube.com/watch?v=YKhA39T-Dxs). Deep NN learn by adjusting the strength of their connections to better convey input signals through multiple layers of artificial neurons. When data are fed into a neural network each artificial neuron that fires transmits signals to certain neurons in the next layer, which are then likely to fire when multiple signals are received. This process allows filtering out noise and retaining the most relevant features, for example in the recognition as a chicken of a chicken image broken into pixels (Figure 1) (https://www.quantamagazine.org/new-theory-cracks-open-the-black-box-of-deep-learning-20170921/).

ML employs different categories of algorithms depending on the intended uses. These include supervised learning, the most widely used, in which data fed into the system have been labeled and targets assigned by a human expert. The output is typically expressed as a class (*e.g.,* diagnosis yes or no) or as numerical data (*e.g.*, a regression coefficient).[1] This has been the most frequently adopted ML method in hemostasis and thrombosis research so far. Reinforcement learning, which has as a goal to perform a task in the fastest and most efficient way, works on the basis of a reward and penalty system. Every time the system receives a reward it reinforces that behavior. It is largely used in the development of automated robots, natural language systems or image processing and in many other potentially wide-impact applications. It has also been used in healthcare, mainly in the oncology field,[2] but apparently not for hemostasis and thrombosis research so far.

Finally, unsupervised ML does not require the involvement of a human expert and the system is aimed to identify patterns within a large amount of unselected data filtering out background noise. This category of ML has been used for the analysis of big data, including in the hemostasis field.[3]

Biomedical examples for each of the three ML algorithm categories in the hemostasis and thrombosis field are: for supervised learning, a study aimed at developing a fully automated analysis of *in vitro* platelet spreading assays captured by differential interference contrast microscopy;[4] for reinforced learning, one example close to hemostasis and thrombosis is a study aimed to pinpoint individuals susceptible to cardiovascular events among athletes, showing that this ML model provided a superior predictive value compared with traditional techniques;[5] for unsupervised ML, a study on the identification of microRNA (miRNA) intracellular signaling regulatory networks linked to cardiovascular disease in monocytes from patients with the antiphospholipid syndrome. This advanced ML approach allowed to identify specific miRNAs signatures related to cardiovascular disease in subgroups of antiphospholipid syndrome patients with distinct clinical phenotypes.[3]

The key fields of application of AI in medicine have been grouped into six categories, *i.e.,* image analysis systems (*e.g.,* radiology, histo-cytopathology, dermoscopy), big data analysis (the omics technologies), natural language processing (clinical reports, medical notes, scientific writing), systems for real-word data analysis (electronic health record analysis, adverse event recording), medical decision support systems (complex decision-making processes), and medical hardware-related systems (medical devices or portable sensors data analysis).[6]

A medical research investigation employing ML must typically involve some sequential steps to ensure the reliability of results. It is first necessary to check that the dataset provided to the NN is representative of its intended subsequent application. Then, the ML model to be applied should be selected, often two or more ML models may be compared for their efficiency. Subsequently, the testing of the system is made, typically using 80% of the available dataset for system training and the remaining 20% for the initial validation of the model. Finally, the model is made operational for wide testing with real-word data in the field. It is crucial that the model is then continuously validated with new datasets to avoid that slight changes in the distribution of the new data fed into the model deteriorate the performance of the system.

Pre-processing of data is often required to achieve a good performance of the study, including data selection, aimed at choosing a relevant subset of the features to be analyzed while discarding the irrelevant of redundant ones, and normalization, which involves the transformation of features in a common range.[7] A crucial prerequisite is also the definition of the optimal model architecture for the proposed task, also called hyperparameter tuning, which in simple terms means configuring the system, that should contemplate questions like how many artificial neurons should be included in each NN layer, how many layers should be considered, the number of branches that the decision tree should have, *etc*.

Artificial intelligence and machine learning in hemostasis and thrombosis

The importance that ML methods are assuming in medical research and clinical practice is documented by the number of publications. A search in Pubmed on 20 December 2023 using "machine learning" yielded over 136,190 articles, but when one adds "AND hemostasis AND thrombosis" the number of hits decreased to 45, although with an exponential growth over the last 5 years. The application of AI to the hemostasis and throm-

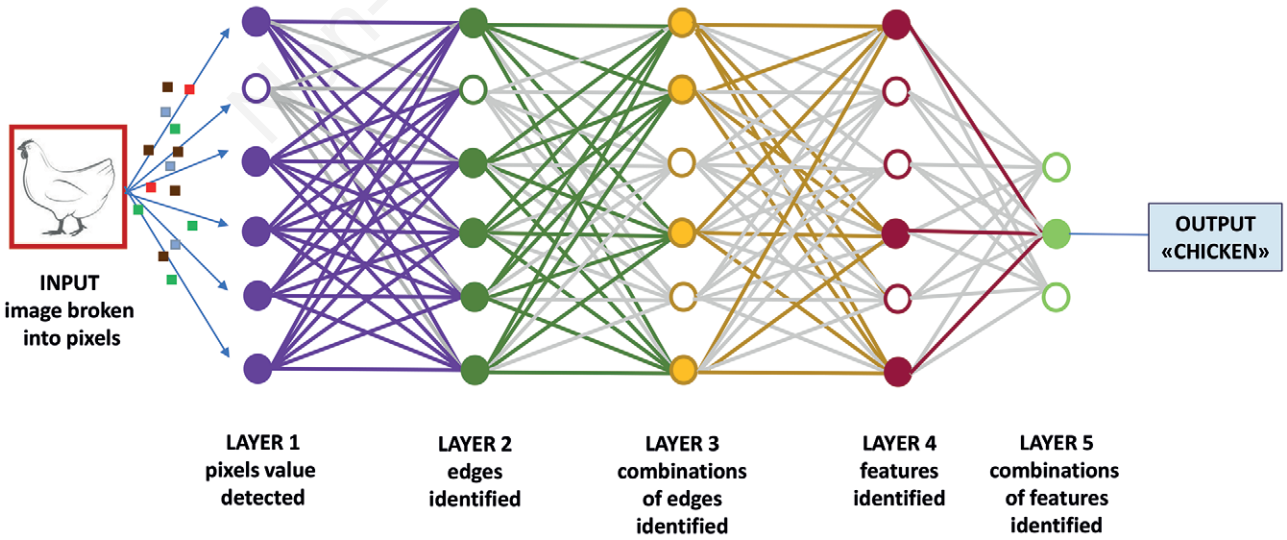

Figure 1. Schematic representation of a typical artificial neural network and its functioning. When data are fed into a neural networks (in this case a chicken image) each artificial neuron (small circles) that fires (bold small circles) transmits signals to certain neurons in the subsequent layer, which are then likely to fire if multiple signals are received. The process allows filtering out noise and retaining the most relevant features finally identifying a chicken from the broken pixels received as an input.

bosis field spans from basic research and pathophysiology, through laboratory diagnostics and the identification and validation of disease biomarkers to clinical diagnostics and prediction tools (Table 1). A few examples of the three categories will be discussed below.

Application of artificial intelligence to basic and pathophysiological research in hemostasis

Current techniques for the study of platelet aggregation, including quite sensitive ones such as flow cytometry, cannot distinguish aggregates formed by different agonists. In a study, ML was used to enhance the resolution power of the analysis of platelet aggregates formed upon stimulation of whole blood with four different agonists. Aggregates formed upon stimulation by adenosine diphosphate, collagen, U46619, or thrombin receptor-activating peptide-6 were analyzed either by flow cytometry or by an optofluidic time-stretch microscope for image acquisition. Acquired images were used to train two different convolutional NN models that classified images based on their morphological features, a method that the authors called Intelligent Platelet Aggregate Classifier (IPAC).[8] Results showed that while aggregates formed by the four different agonists were indistinguishable by flow cytometry, the IPAC readily classified them into four different types. Besides providing a tool for the deeper analysis of platelet aggregate formation, the IPAC might provide a tool to study platelet aggregates circulating in blood, allowing to obtain potential information on the type of agonists that generated them *in vivo* or on the site of aggregate formation in the circulatory system.[8]

Other promising studies include the identification of distinct subpopulations of platelets generated by the exposure to different agonists using an unsupervised ML system,[9] or the study of platelet adhesion under flow conditions by the analysis of high frame rate videos using a semi-unsupervised learning system (Table 1).[10]

Application of artificial intelligence to laboratory diagnostics and biomarker identification in hemostasis

Preanalytical quality control is essential to ensure reliable results in diagnostic hemostasis testing but so far there are no automatic methods to identify samples in which small blood clots have formed. One study explored the use of ML in identifying clotted samples received by highly automated, high-throughput hemostasis laboratories. By employing an *ad hoc* trained NN assessing five laboratory variables (prothrombin time, activated partial thromboplastin time, thrombin clotting time, fibrinogen, and D-dimer) in 189 clotted and 2889 not clotted samples, the authors showed that the model identified with high precision the clotted ones.[11]

Another very promising study dealt with the complex problem of disseminated intravascular coagulation (DIC) diagnosis. Currently, the diagnosis of DIC is cumbersome and involves the interpretation of a combination of laboratory and clinical parameters through the use of some probability scores. In this study, the authors employed a supervised NN model analyzing 32 clinical and laboratory parameters in an initial development model on 656 patients with suspected DIC (428 without and 228 with confirmed DIC) and subsequently in an external validation model on 217 patients (137 without and 80 with DIC) and compared its diagnostic performance with that of three largely used probability scores (International Society on Thrombosis and Haemostasis, Japanese Ministry of Health and Welfare, and Japanese Association of Acute Medicine). Not only the ML model outperformed all three scores, but it also revealed that some variables usually disregarded for DIC diagnosis, like the blood eosinophil count or the platelet or red cell distribution width, have some importance in DIC diagnostics.[12]

Another controversial diagnostic issue is that of heparin-in-

Table 1. Applications of artificial intelligence to thrombosis and hemostasis.

Basic research/pathophysiology	- Platelet activation morphodynamics - Differentiation of platelet aggregates induced by different agonists - Platelet calcium calculator - Agonist- and primer-specific formation of platelet subpopulations - Shear-mediated platelet adhesion kinematics - Multiscale prediction of platelet-specific platelet function under flow
Laboratory diagnostic/biomarkers	- Identification of clotted specimens in the coagulation laboratory - Deciphered coagulation profile to diagnose antiphospholipid syndrome - Diagnosis of disseminated intravascular coagulation - Minimization of misdiagnosis of HIT - Platelet RNA-sequencing for cancer diagnostics (liquid biopsies) - D-dimer as biomarker for prognosis in TTP - Analysis of blood parameters for immune thrombotic dysregulation in COVID-19 - Role of genetic polymorphisms in VTE
Clinical diagnostics/predictions	- Characterization of antiphospholipid syndrome atherothrombotic risk by transcriptomic analysis - Prediction and diagnosis of VTE - Prediction of VTE in acutely ill medical patients - Prediction of precision warfarin dosing - Using AI to reduce non-adherence to anticoagulation therapy - Prediction of splanchnic vein thrombosis in acute pancreatitis - Processing of radiology reports for VTE detection - Prediction of recurrent VTE

HIT, heparin-induced thrombocytopenia; TTP, thrombotic thrombocytopenic purpura; VTE, venous thromboembolism; AI, artificial intelligence.

duced thrombocytopenia (HIT) which also involves the combined interpretation of clinical and laboratory parameters and their implementation in various proposed algorithms.[13] In a prospective multicenter cohort study including 1393 consecutive patients with suspected HIT, a supervised ML model applied to a training data subset (75% of patients) and to a validation dataset (25% of patients) was substantially more accurate in HIT diagnosis than the currently recommended algorithms.[14] Many other examples of the potential of AI for laboratory diagnostics in hemostasis and thrombosis have been explored, including the study of the amazing genetic complexity of platelets and its exploitation for cancer diagnostics.[15,16]

Application of artificial intelligence to clinical diagnostics and risk prediction in hemostasis

A relevant clinical goal in patient management is that of predicting outcomes in subjects anticoagulated with anti-vitamin K agents based on the results of the prothrombin time expressed as international normalized ratio (INR). INR data obtained over the first 30 days after prescription from 4708 patients enrolled in the GARFIELD registry were used to train a supervised ML NN (3185 patients) and to test its prediction accuracy for clinical outcome at one year in a validation cohort (1523 patients). The model outperformed the conventionally used time in therapeutic range (TTR) parameter,[17] in the prediction of major bleeding, stroke/systemic embolism and death.[18] Several other applications of AI in the field of oral anticoagulation have been explored, such as its use in reducing the risk of non-adherence to anticoagulation therapy,[19] in deciding precise warfarin dosing or in predicting the incidence of adverse outcomes after premature discontinuation of anticoagulation in patients with pulmonary embolism (Table 1).[20,21]

Another widely explored area with very encouraging results is that of the prediction of venous thromboembolism (VTE) risk or its recurrence in different patient populations (Table 1). One interesting example is the identification of subjects at high risk for VTE among acutely ill medical patients. Currently, the prediction is based on clinical scores, such as the Padua or the IMPROVE scores, which however have a low predictive value. The application of two different supervised ensemble learning algorithms, analyzing 68 or 16 variables respectively, to patients enrolled in the APEX trial showed that both AI systems significantly outperformed the IMPROVE score in predicting VTE.[22]

The prediction and diagnosis of VTE by AI has actually been explored in several studies and a meta-analysis of 12 reports (7 studying only a training dataset and 5 both a training and a validation dataset), including 51,383 patients, showed that AI may help in the diagnosis and prediction of VTE independent of venous thrombosis type, AI model employed, type of outcome (diagnosis or prediction) and of whether the analyzed period was perioperative or not.[23]

Limitations and warnings on the use of artificial intelligence in health research and care

An impressive recent example of the potentials and risks of widely accessible generative AI is the story appeared in the news of a young child's long-lasting undiagnosed illness whose mother, after 17 unsuccessful consultations with medical doctors of various specialties, interrogated ChatGPT providing to the system all symptoms and medical reports of the child. ChatGPT suggested the diagnosis of tethered spinal cord syndrome, a rare congenital disorder due to malformations of the spinal cord, but invited to consult a medical specialist. The child was then referred to a pediatric neurosurgeon who confirmed the diagnosis (https://ts2.space/en/ai-helps-diagnose-rare-condition-in-child/#gsc.tab=0). While this case highlights the terrific potential of AI for diagnostic aid with complex clinical cases, it also alarms for its possible inappropriate widespread and unsupervised use by ordinary people with consequent erroneous self-medication, *etc*. A recent study involving 457 clinicians across 13 US States explored their diagnostic performance when asked to respond to a respiratory distress-related clinical vignette, either unassisted or with support from an AI system for chest X-ray interpretation. The study showed that diagnostic performance was only slightly increased by AI assistance but also, worryingly, that when the AI system was biased, diagnostic performance was drastically worsened.[24] Therefore, even for healthcare professionals, AI support for complex clinical case diagnostics and decision-making must be adopted carefully, strictly monitoring the system performance.[25]

Another illustrative case that shows the lights and shadows of AI use in the medical field is an experiment carried out by Valentin Fuster, editor-in-chief of the Journal of the American College of Cardiology (JACC), who asked a generative AI tool (ChatGPT) to re-write a published JACC manuscript in author-specific styles. In <60 min the system produced the paper rewritten in 8 different styles, including Valentin Fuster's, Bob Dylan's, and William Shakespeare's, with incredible plausibility and a perfect style.[26] However, in the interpretation of results the AI model lacked accuracy and included generic statements. The conclusions of the authors were that while AI may provide great benefits for scholarship writing, its use warrants caution from the authors for generating conclusions and discussions.[26]

Besides these possible faults, there may be real cases of deliberate misuse of AI for health. In an experiment carried out by a group of Australian investigators, the authors instructed some publicly accessible generative large-language models to create blogs aimed at spreading vaccine disinformation. In 65 min 102 very convincing anti-vax blogs were generated, showing that when the guardrails of AI instruments are not strict, the risks of health disinformation may be very high. The authors suggested that the key principles of pharmacovigilance, including transparency, surveillance, and regulation, could be an inspiring example for managing the risks of AI misuse in health care.[27]

Final remarks

Despite its great potential and its already wide penetration in several domains of human activities, AI is still at its early stages of application for clinical and research studies in healthcare, particularly in hemostasis and thrombosis. Indeed, there are several reasons that slow down AI adoption in this field, including the fact that healthcare data are more heterogeneous and variable than data in other sectors, lack of patient confidence, regulatory and ethical issues, methodologic concerns, and the primary role that quality and safety have in healthcare respect to other domains.[28]

One critical aspect limiting the wide application of ML models in healthcare is their interpretability, since most of them are based on highly complex calculations and the elaboration of a large number of parameters (in the order of millions) making the decisions taken by the model often impossible to understand, especially because no justification for the decisions taken is provided, the so-called black-box models.[29] Lack of interpretability in predictive ML models should raise caution, especially when the decisions taken may impact patients' health and lives.[30] Indeed, AI models most often lack the broader clinical context that is relevant for patient care[25] thus a new clinical knowledge-enhanced ML pipeline is being developed to improve model performance and physicians' confidence with their application.[31] The training on data using both "explainable" and "black box" ML models to enhance confidence in the system and the involvement of a multidisciplinary team of clinicians, data scientists, software engineers, and statisticians in ML model design may be ways to overcome the current limitations of the application of AI/ML to healthcare.[1,30]

The possible mistakes or misuse of AI in medicine prompt strict regulations, from both scientific societies and government authorities, ensuring continuous monitoring with built-in mechanisms allowing speedy regulatory updates permitting to guide the continuously evolving capabilities of AI for medicine and science.[26,30] Indeed, an executive order on AI implications for healthcare organization was issued by President Biden on October 30th 2023, calling on agencies to establish standards for safe and trustworthy AI use, the European Union has drafted AI use rules which will be adopted in the coming months and the World Health Organization has released a detailed document on regulatory considerations on AI for health (https://www.who.int/news/item/28-06-2021-who-issues-first-global-report-on-ai-in-health-and-six-guiding-principles-for-its-design-and-use). A watchful control over the evolving implications of AI employment in healthcare and research, with the setting of boundaries to avoid misuse, balanced by the awareness of the great advantages and progress that AI may bring, seems to be the best way to govern the application of this new revolutionary technology to the medical field without stifling its innovative and beneficial potential.[32,33]

Conclusions

After several years of research, AI has undergone an incredible acceleration in the last few years becoming a technology that may transform our society and broadly reshape medicine.[33] Not realizing this may delay the chance that AI provides to expand the access to more accurate, efficient and cost-effective healthcare. In medical research too, AI may speed up the discovery and translation of new knowledge from research into clinical improvement. The hemostasis and thrombosis community must seize the opportunity that AI offers to fasten the advancements in the field, but a very close and continuous scrutiny, watching over the adoption of appropriate methodological and ethical rules, will have to be exerted in order to avoid misuse or bias in the results obtained.

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