Reflections on the Potential of Applying Artificial Intelligence (AI) and Machine Learning (ML) for Screening Topical Hemostatic Agents Based on Inorganic Solids for Hemorrhage Control

Guilherme de Paula Guarnieri and José Geraldo Nery*

São Paulo State University (UNESP), Physics Departament, Campus São José do Rio Preto, São Paulo, 15054-000, Brazil

Abstract: Despite significant advances in medical interventions, fatal traumatic hemorrhage remains a leading cause of death worldwide. This persistent challenge has driven extensive research and development efforts aimed at creating more effective hemostatic agents to control bleeding. While most existing hemostatic agents are organic in nature, recent studies have highlighted the promising potential of mineral and synthetic inorganic materials for hemorrhage control. These materials demonstrate remarkable properties, such as rapid water adsorption from blood via their porous structures, which leads to the local concentration of proteins and cellular elements crucial for clot formation. Additionally, their negatively charged surfaces create a favorable environment for the activation of the intrinsic coagulation cascade. Although a variety of minerals and synthetic inorganic materials are currently employed as topical hemostatic agents, a vast array of emerging classes of inorganic materials remains underexplored. Many of these materials possess untapped hemostatic potential, but their properties and mechanisms for controlling bleeding are poorly understood. Moreover, synthesizing these materials with the precise characteristics required for effective hemostasis presents significant challenges. Recent advances in artificial intelligence (AI) offer a promising avenue to address these hurdles. By leveraging the growing availability of large datasets and sophisticated algorithms, AI can identify complex relationships within multidimensional systems, such as the synthesis of advanced inorganic materials. This capability is particularly critical for materials lacking well-characterized mechanisms or those with implications for hemostasis disorders, such as severe bleeding or thrombosis. AI-driven approaches could enable the design of innovative topical hemostatic agents capable of rapidly diagnosing and efficiently intervening in life-threatening situations, revolutionizing the field of hemorrhage control.

Keywords: Hemorrhage, Uncontrolled bleeding, Inorganic biomaterials, Artificial intelligence (AI), Machine Learning (ML).

1. INTRODUCTION

1.1. Overview of the Theoretical Principles of the Coagulation Process

The primary objective of this section is to provide the reader with a theoretical foundation for the intricate coagulation process, primarily drawing upon the insights derived from prior works and the expertise accumulated by our research group, particularly in the application of zeolite materials as hemostatic agents. For a more in-depth exploration of these theoretical concepts, readers are encouraged to refer to the most recent reviews documented in the existing literature [1].

Briefly, the basis of the blood coagulation model was developed at the beginning of the 20th century, describing only the final parts of the coagulation process. However, the discovery of the specific coagulation components responsible for the generation of thrombin occurred only after the 1940s and 1950s [2]. It was only in the 1960s that two independent groups introduced a model of blood clotting. This consists of a series of steps in which the activation of each of the clotting factors leads to the activation of another, culminating in an explosion of thrombin generation. The cascade model was proposed by Macfarlane (1964) [3] and reported in the journal Nature, while shortly thereafter, the cascade model described by Davie and Ratnoff (1964) [4] was published in the journal Science [5]. The coagulation cascade involves a sequence of interconnected reactions, divided into the extrinsic pathway, in response to the contact of blood with extravascular tissues, and the intrinsic or accessory pathway, involving contact of the blood with a surface other than the normal endothelium and blood cells [6]. The extrinsic system occurs when the activation of factor VII, by tissue factor, produces the activation of factor X. Factor III, calcium, and factor VII form a complex that acts enzymatically in the presence of phospholipids to convert factor X to activated factor X (FXa) [2]. The intrinsic system is located within the blood and is initiated by the contact activation of factor XII on negatively charged surfaces, with subsequent activation of other contact components [2]. Kallikrein and high molecular weight kininogen (HMWK) can

*Address correspondence to this author at the São Paulo State University (UNESP), Physics Department, Campus São José do Rio Preto, São Paulo, 15054-000, Brazil; E-mail: geraldo.nery@unesp.br

modulate factor XII activation. Kallikrein then accelerates the conversion of factor XII to activated factor XII (FXIIa). FXIIa acts enzymatically on factor XI to activate it, while FXIa operates on factor IX, activating it. In turn, FIXa, acting with FVIIIa and platelet phospholipids FP3, activates factor X [7]. These two pathways converge into a common path, which results in the activation of factor X, converting it to activated factor X (FXa), forming a small amount of thrombin. Thrombin, in turn, acts to convert fibrinogen (factor I) into fibrin monomers, which are interconnected by activated factor XIII (FXIIIa), forming insoluble fibrin polymers. The transformation or "stabilization" of soluble fibrin into an insoluble fibrin clot is catalyzed by factor XIII, in the presence of calcium, where factor XIII, which normally circulates in the plasma in the form of an inactive proenzyme, is converted to its active form by thrombin [6,8]. The last proposed coagulation model is based on cell surfaces, with hemostasis requiring activated pro-coagulant substances that remain localized at the site of injury, for the formation of a platelet and fibrin plug. In this new model, the blood clotting process is initiated by the exposure of clotting factors located in the bloodstream [9]. The Cellular Model of Coagulation was proposed by Hoffman and Monroe [10] and suggests that coagulation does not occur as a "cascade", but in three overlapping phases: 1) initiation, which occurs in the tissue, in the presence of a cellular factor; 2) amplification, in which platelets and cofactors are activated to set the stage for large-scale thrombin generation; and 3) propagation, in which large amounts of thrombin are generated on the surfaces of platelets [11] (Figure **1**). The blood clotting process is initiated by exposure of cells that express tissue factor to the bloodstream. The tissue factor is present in the membranes of cells neighboring the vascular bed but is not normally in contact with the blood [9, 12].

In the initiation phase, the TF/FVIIa complex (tissue factor/activated factor VII) activates FX directly and indirectly through FIX, transforming small amounts of prothrombin into thrombin, which is still insufficient for a sustained thrombin formation process. The interaction between TF and FVIIa is a fundamental step for the initiation of coagulation [10, 13]. In the amplification phase, thrombin, together with blood calcium and

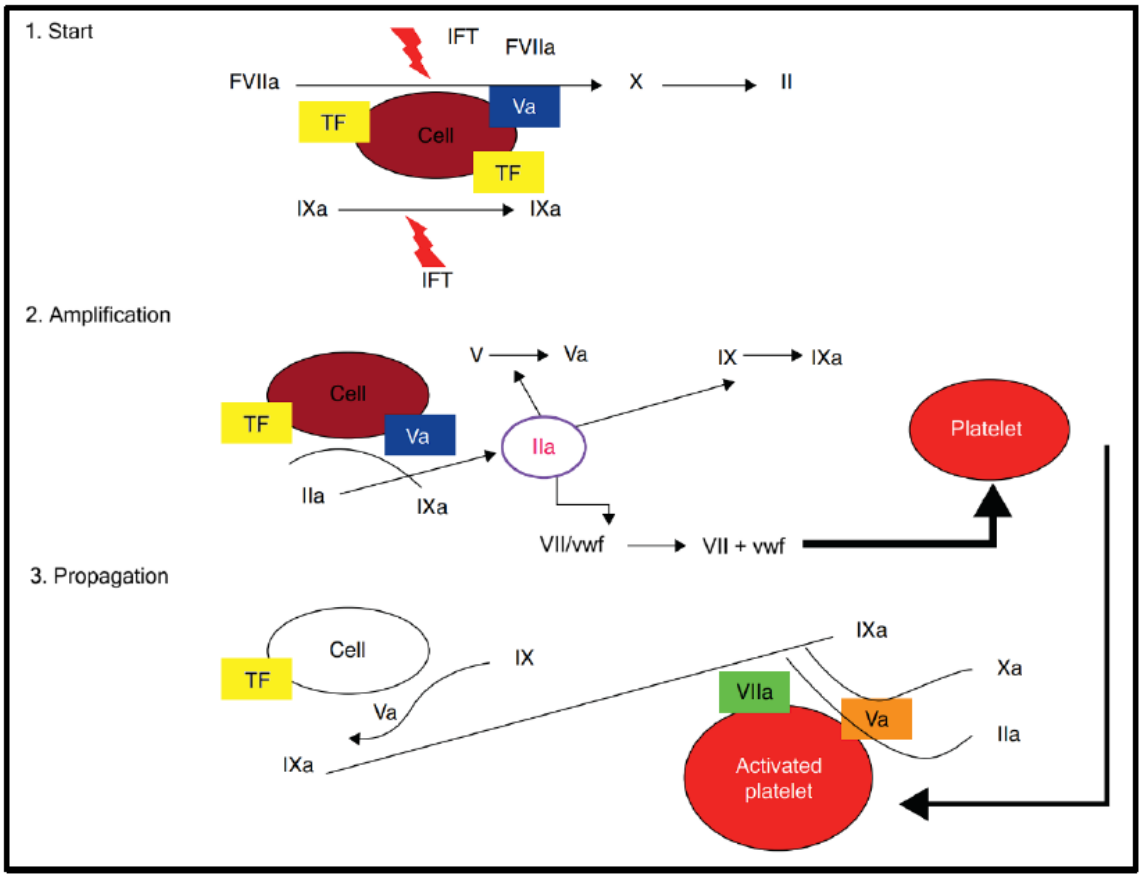

Figure 1: Coagulation cascade. Adapted from Galvez *et al.* [2, 10, 13].

platelet-derived phospholipid, actively participate in the positive feedback process for the activation of factors XI, IX, VIII, and V, and especially in accelerating platelet activation. Simultaneously, the aforementioned factors are attracted by chemotactic mechanisms to the platelet surface, where a very important process of activation and multiplication rapidly occurs [10]. A small amount of thrombin produced by the TF-FVIIa complex is essential for amplification but is insufficient for clot formation. Thrombin is a very active platelet recruitment agent, with positive feedback enabling it to also activate factors V, VIII, and XII. Amplification is also characterized by the negative feedback system involving natural anticoagulants: TFPI (TF inhibitor complex), antithrombin, and protein C, which play an important role in regulating procoagulation [13].

The propagation phase is characterized by the recruitment of many platelets to the site of injury, with the production of tenase and prothrombinase complexes on the surfaces of activated platelets [2,9]. FIXa activated during the initiation phase binds to FVIIIa on the platelet surface, forming the tenase complex. Since FXa is unable to effectively move from FT-expressing cells to the activated platelet, more FXa must be produced directly on the platelet surface by the FIXa/FVIIIa complex [9, 10]. Finally, FXa rapidly associates with platelet-bound FVa during the amplification phase, resulting in formation of the prothrombinase complex, which converts large amounts of prothrombin into thrombin. This is responsible for the cleavage of fibrinogen into fibrin monomers, which polymerize to consolidate the platelet plug [9]. The final process, always occurring on the surface of the platelet, results in the explosive generation of large amounts of thrombin and fibrin [10]. Thrombin simultaneously activates FXIII and tissue factor pathway inhibitor (TFPI), which positively adds stabilizing effects and resistance to plasmin [13]. Platelet activation alters membrane permeability, allowing the entry of calcium and the release of chemotactic substances that attract clotting factors. Factor V and phospholipids are released at the same time, providing the necessary complement for coagulation [13].

2. INORGANIC SOLIDS AS HEMOSTATIC AGENTS

The intrinsic hemostatic mechanism of the human body has a limited capacity and may need assistance from hemostatic materials or devices for rapid hemostasis, particularly in emergency situations, when hemorrhage is severe [14]. In general, hemostatic materials may be divided into external (local) hemostatic materials (including inorganic substances, hemostatic peptides/proteins, hemostatic polysaccharides, and synthetic polymers) and internal (intravenous) hemostatic agents (such as those involving fibrin, coagulation factor, and platelets) [15] (Figure **2**). Hemostatic agents based on inorganic materials, including zeolites and clays, have been shown to effectively accelerate blood coagulation. Compared to organic biomaterials, inorganic biomaterials with specific advantages or characteristics may be more effective in hemostasis and wound healing. Inorganic biomaterials generally exhibit much higher surface energy than the organic ones, making them hydrophilic or even super-hydrophilic, with good biocompatibility, high bioactivity, high absorption of blood, promotion of blood coagulation, and release of bioactive ions. These features have attracted considerable interest, especially because these inorganic biomaterials can rapidly absorb water and achieve ultra-rapid hemostasis. Furthermore, inorganic biomaterials possess various functionalities, such as bioactive ion release, photothermal properties, magnetothermal properties, photodynamic properties, and conductivity, which make them excellent candidates for future development [16].

Many inorganic biomaterials have been developed during the last two decades, including zeolites. A zeolite is a crystalline aluminosilicate with a porous structure that is highly favorable for the absorption of water. This characteristic can assist in increasing the local concentrations of platelets and clotting factors. The negative surface charge can activate positively charged factor XII, triggering an endogenous clotting cascade reaction. These special properties resulted in the first commercial zeolite hemostatic products being introduced as first aid equipment for the U.S. military in 2002, under the tradename of QuikClot®. In the last two decades, other inorganic materials such as mesoporous silica materials, graphene oxides (GO), graphene/montmorillonite composite sponges (GMCS), and graphene-immobilized montmorillonite (MMT) have been prepared and their hemostatic properties systematically studied [14, 17]. Nevertheless, it is important to note that these hemostatic agents based on inorganic biomaterials have advantages and disadvantages, as widely discussed in the literature. It has been pointed out that there are challenges in the preparation of active inorganic-based biomaterials with

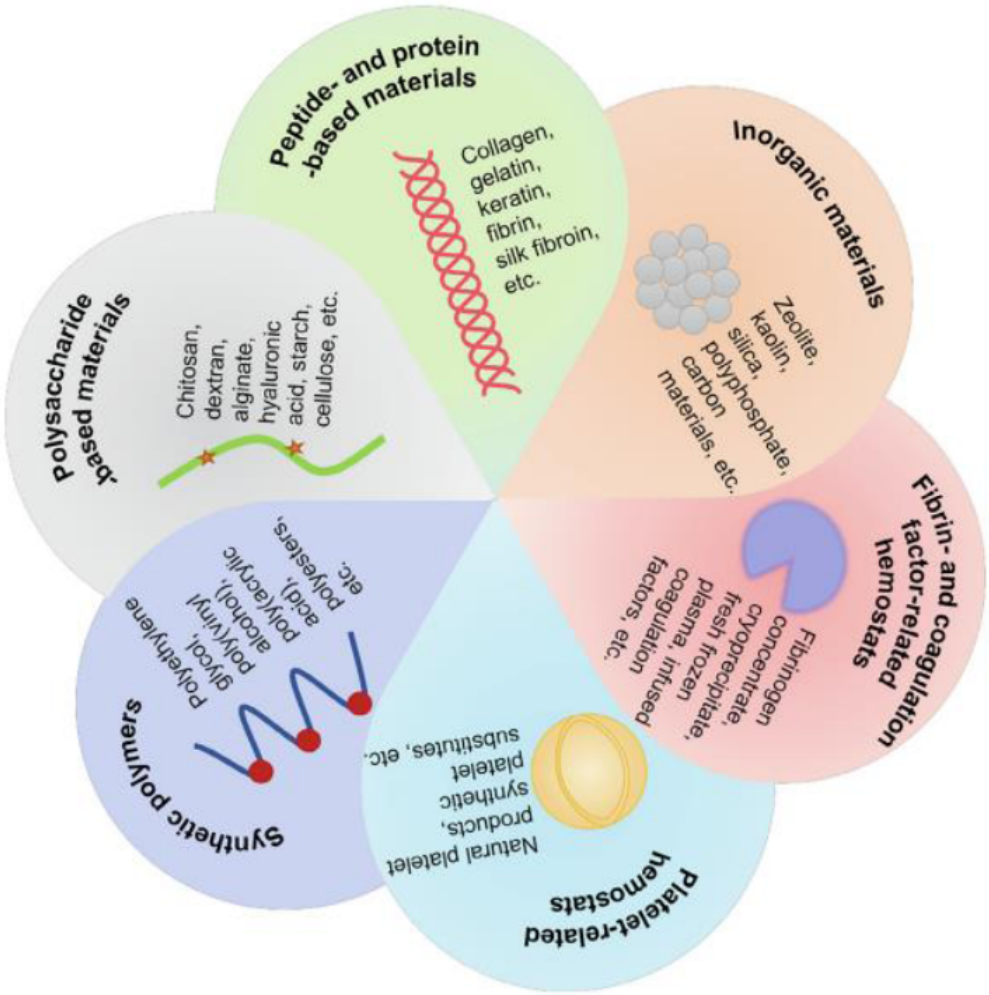

Figure 2: Emerging hemostatic materials. From Li *et al.* [15].

enhanced hemostatic properties, taking into consideration both functional and application aspects [18]. One possible way forward is to use artificial intelligence (AI) in the development of these materials.

3. ARTIFICIAL INTELLIGENCE (AI) AND MACHINE LEARNING (ML) IN MATERIALS SCIENCE

Artificial intelligence is a branch of computer science capable of analyzing complex medical data. Its potential to exploit meaningful relationships within a data set can be used in diagnosis, treatment, and outcome prediction in many clinical scenarios. In the pharmaceutical industry, it has facilitated processes of drug discovery and development, as well as drug repurposing, improvement of pharmaceutical productivity, and clinical trials [19-22]. Recent advances in artificial intelligence (AI) coupled with increased accessibility to large data sets have allowed the development of new algorithms and statistical methods capable of extracting relationships between variables in multidimensional systems [23]. In particular, the use of machine learning (ML), a subfield of AI that relies on complex mathematical models that can effectively “learn” from past data to find complex patterns embedded within large data sets, in materials science has revolutionized our ability to map intricate behavior to process variables, especially in the absence of well-understood mechanisms. ML has already revolutionized many areas in materials science by enhancing our ability to map intricate behavior to process variables, especially in the absence of well-understood mechanisms as is the case with the synthesis of molecular sieves [24-27]. Zeolites as hemostatic topic agents have been used since the beginning of the 21st century. However, the application of zeolitic materials in hemostasis was initially limited due to the strong exothermic reaction triggered on the tissue surface by the adsorption of water molecules from the blood, leading to localized burns. To address these issues, QuikClot® was replaced by Combat Gauze (CG) in 2008, a hemostatic dressing made of

rayon/polyester gauze embedded with kaolinite powder, a layered hydrated aluminosilicate. Combat Gauze offered rapid action, high efficacy, and thermal safety, becoming the hemostatic dressing of choice for the Committee on Tactical Combat Casualty Care (CoTCCC). It remains a critical component of prehospital first aid as recommended by the American Technical Committee on Emergency. Despite its advantages, concerns about kaolin detachment and potential wound contamination persist, as these could increase the risk of distal vascular thrombosis.

In 2019, advancements in hemostatic technology led to the development of a mesoporous zeolite-cotton hybrid hemostat, which resolved the exothermic reaction issues associated with granular zeolite materials and eliminated risks of kaolin powder detachment. Building on this innovation, a zeolite-based hemostatic gauze was FDA- and CFDA-approved in 2021. This product has been evaluated for its effectiveness and safety in a swine model simulating gunshot-induced junctional femoral artery hemorrhage. Despite the discovery of over ten active components capable of promoting coagulation in laboratory research, current leading commercial hemostatic products are predominantly based on single active components, each functioning through specific procoagulant mechanisms [28-31]. This limitation underscores the need for further innovation in multi-functional hemostatic technologies and how the research and development in AI and ML applied to zeolite science [24-27] can advance the development of more effective zeolites applied to hemostasis. Besides zeolites a plethora of new materials discovered by employing AI and ML have been found as reported in the work of Cubuk *et al.* [32], who using a state-of-the-art neural network tool called GNoME (Graph Networks for Materials Exploration), reported the discovery of 2.2 million crystalline structures, with around 380,000 of them apparently sufficiently stable for the development of next-generation technologies, ranging from improved electric car batteries to superconductors for ultra-efficient computers as stated for the authors of this remarkable study [32].

Hybrid nanostructures combining biomolecules and inorganic nanomaterials represent a rapidly growing area of research, with vast potential in bioimaging, biosensing, and nanomedicine. Achieving innovative applications from these materials requires an in-depth understanding of the dynamic interactions at the nano–bio interface. Building on recent advancements, the work published by Pihlajamäki *et al.* (2024) on the GraphBNC framework method introduces a computational approach to predict atomic-scale interactions between water-soluble gold nanoclusters (AuNCs) and critical blood proteins, including albumin, apolipoproteins, immunoglobulins, and fibrinogen [33]. The methodology integrates graph-based modeling and neural networks to estimate interaction strengths at a coarse-grained scale. These predictions are refined through Monte Carlo structural optimizations and subsequently validated with atomic-scale molecular dynamics (MD) simulations. By training on extensive MD datasets, the framework demonstrates high reliability and precision in predicting AuNC–protein interactions. Furthermore, this approach is adaptable to other biomolecule–nanomaterial systems, provided sufficient data is available, and effective coarse-graining of the nanostructure's bioactive regions is achieved. Combining computational predictions with atomistic validation, this methodology lays the groundwork for the rational design of hybrid nanostructures tailored for biomedical applications. The main potential drawbacks of both organic and inorganic hemostatic agents include possible blood-borne disease, neurotoxicity, and reduction of pH that can cause inflammation and hemolysis. Their high swelling ability and foreign body reactions may make them less effective for patients with thrombocytopenia or coagulopathies. Furthermore, they may cause neural pain or numbness, cytotoxicity, and exothermic reactions [1, 14, 34-37]. The possibility of using the remarkable findings of Cubuk *et al.* [32] and Pihlajamäki *et al.* [33] as a basis for preparation of more effective topical hemostatic agents with inorganic structures is highly attractive from the perspectives of both materials science and medicine. Artificial intelligence has already contributed to many advances in the pharmaceutical industry, demonstrating its potential to address the challenges associated with the development of treatments tailored for patients in life-threatening hemorrhagic situations.

4. ARTIFICIAL INTELLIGENCE (AI) AND MACHINE LEARNING (ML) IN HEMOSTASIS AND THROMBOSIS

The integration of artificial intelligence (AI) and machine learning (ML) has profoundly impacted various fields of medicine, including hemostasis and thrombosis. These technologies excel at processing extensive datasets, uncovering intricate patterns, and delivering insights that traditional approaches often cannot achieve. By utilizing these advanced computational tools, researchers and clinicians are better equipped to understand the mechanisms of

hemostasis and thrombosis, refine diagnostic approaches, and improve risk prediction for thrombotic and hemorrhagic disorders [38].

AI has played a pivotal role in advancing our understanding of the molecular mechanisms governing hemostasis and thrombosis. By analyzing multi-omics datasets—such as genomics, transcriptomics, proteomics, and metabolomics—AI algorithms have identified critical pathways and molecular interactions that regulate coagulation and platelet function. For example, deep learning models have been applied to predict the effects of genetic variants on clotting factor activity, shedding light on the genetic basis of bleeding and thrombotic disorders [39-42]. Additionally, AI-driven simulations of the coagulation cascade provide insights into the dynamic interactions between procoagulant and anticoagulant factors under both physiological and pathological conditions, facilitating the development of targeted therapies [43-45].

In diagnostics, AI has proven transformative, particularly in biomarker discovery and the interpretation of laboratory tests. By analyzing high-dimensional data from coagulation assays, flow cytometry, and mass spectrometry, AI tools have uncovered novel biomarkers with high specificity and sensitivity for thrombotic and hemorrhagic risks [46]. Machine learning algorithms have optimized laboratory protocols, improving the reproducibility and accuracy of assays measuring clotting times, platelet activity, and fibrinolysis. Furthermore, AI facilitates the integration of diverse diagnostic data, including imaging, laboratory tests, and electronic health records, to create a holistic assessment of a patient's hemostatic status [47-50].

In clinical practice, AI offers powerful tools for diagnosing hemostatic disorders and predicting outcomes. Machine learning-based risk prediction models are widely used to assess the likelihood of venous thromboembolism (VTE), disseminated intravascular coagulation (DIC), or bleeding events. These models incorporate patient-specific data such as genetic predispositions, laboratory results, clinical history, and comorbidities to generate personalized risk scores [38, 51]. Additionally, AI-powered clinical decision support systems (CDSS) provide real-time recommendations to clinicians, aiding in timely diagnoses and optimizing therapeutic strategies. For instance, AI has been employed to predict bleeding risks in patients receiving direct oral anticoagulants (DOACs), enhancing patient safety and outcomes [52-56].

The profound implications of hemostasis disorders, including life-threatening bleeding or clotting, highlight the critical need for rapid diagnosis and intervention. Artificial intelligence (AI) and machine learning (ML) models are emerging as transformative tools in this domain, offering the potential to enhance diagnostic accuracy, optimize intervention timing, and improve overall patient outcomes. In parallel, AI/ML has revolutionized materials science, where it has enabled the discovery of novel materials by unraveling complex relationships between synthesis parameters and material properties. The development of next-generation hemostatic agents presents a challenge that could greatly benefit from these tools. Existing hemostatic materials, both organic and inorganic, face limitations such as cytotoxicity, inflammation, and potential inefficacy in patients with coagulopathies. The integration of AI/ML into this research can accelerate the rational design of hybrid materials with tailored properties. By harnessing tools like GNoME and GraphBNC, it may be possible to design inorganic nanostructures with enhanced biocompatibility, stability, and effectiveness in controlling hemorrhagic events. These computational strategies could help mitigate the drawbacks of current hemostatic agents, paving the way for safer and more efficient solutions.

5. CONCLUSIONS AND PERSPECTIVES

The development of next-generation topical hemostatic agents remains a significant challenge, requiring materials that are non-toxic (or minimally toxic), free from adverse exothermic reactions, cost-effective, highly stable, and, most importantly, effective for patients with complex conditions such as thrombocytopenia or coagulopathies. Existing hemostatic agents—both organic and inorganic—face critical limitations, including cytotoxicity, inflammation, and inefficacy under certain pathological conditions. Addressing these limitations necessitates innovative approaches to material synthesis and design. Recent advancements in machine learning (ML) and artificial intelligence (AI), particularly tools like GNoME (Graph Networks for Materials Exploration) and GraphBNC, provide a transformative opportunity in this field. These computational frameworks have already demonstrated their ability to revolutionize materials discovery by predicting stable and functional nanostructures with remarkable accuracy. By leveraging AI-driven approaches, it becomes possible to design hybrid hemostatic materials with tailored properties, such as enhanced biocompatibility, stability, and precision in controlling hemorrhagic events. AI/ML integration not

only accelerates the rational design and optimization of new hemostatic agents but also bridges the gap between materials science and clinical application. Furthermore, the application of AI in pharmaceutical development has already showcased its potential to overcome challenges in drug synthesis and personalized medicine. Extending this paradigm to the synthesis and characterization of novel hemostatic materials opens the door to innovative, patient-centric solutions for life-threatening bleeding scenarios. By harnessing the power of AI/ML, researchers can unlock a new generation of hemostatic agents that are safer, more efficient, and accessible to both developed and underdeveloped regions, ultimately advancing global healthcare and improving patient outcomes.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ACKNOWLEDGMENTS

J.G. Nery acknowledges the State of São Paulo Research Foundation (FAPESP, grants awards #2022/16214-9 and #2019/01858-5) and the National Council for Scientific and Technological Development (CNPq) for grant awards #406761/2013-2 and #317030/2021-3. G.P. Guarnieri thanks the Coordination for the Improvement of Higher Education Personnel (CAPES) for a fellowship (#88887.661419/2022-00).

REFERENCES

[1] R.L. Gruen, K. Brohi, M. Schreiber, Z.J. Balogh, V. Pitt, M. Narayan, R. V Maier, Haemorrhage control in severely injured patients, The Lancet 380 (2012) 1099-1108. https://doi.org/10.1016/S0140-6736(12)61224-0

[2] S.A. Smith, The cell-based model of coagulation, Journal of Veterinary Emergency and Critical Care 19 (2009) 3-10. https://doi.org/10.1111/j.1476-4431.2009.00389.x

[3] R.G. Macfarlane, An Enzyme Cascade in the Blood Clotting Mechanism, and its Function as a Biochemical Amplifier, Nature 202 (1964) 498-499. https://doi.org/10.1038/202498a0

[4] E.W. Davie, O.D. Ratnoff, Waterfall Sequence for Intrinsic Blood Clotting, Science (1979) 145 (1964) 1310-1312. https://doi.org/10.1126/science.145.3638.1310

[5] J.P. Riddel, B.E. Aouizerat, C. Miaskowski, D.P. Lillicrap, Theories of blood coagulation, Journal of Pediatric Oncology Nursing 24 (2007) 123-131. https://doi.org/10.1177/1043454206298693

[6] M. Marília, L. Carlos, P. Dantas, F. De, S. Freitas, Estudo da Cascata de Coagulação Sangüínea e seus Valores de Referência, Acta Veterinaria Brasilica 1 (2007) 49-55.

[7] R.F. Franco, Fisiologia da coagulação, anticoagulação e fibrinólise, Medicina (Ribeirão Preto) 34 (2001) 229-237. https://doi.org/10.11606/issn.2176-7262.v34i3/4p229-237

[8] V. Johari, C. Loke, Brief overview of the coagulation cascade, Dis Mon 58 (2012) 421-423. https://doi.org/10.1016/j.disamonth.2012.04.004

[9] C.N. Ferreira, M. de O. Sousa, L.M.S. Dusse, M. das G. Carvalho, O novo modelo da cascata de coagulação baseado nas superfícies celulares e suas implicações, Rev Bras Hematol Hemoter 32 (2010) 416-421. https://doi.org/10.1590/S1516-84842010000500016

[10] M. Hoffman, D. Monroe, A Cell-based Model of Hemostasis, Thromb Haemost 85 (2001) 958-965. https://doi.org/10.1055/s-0037-1615947

[11] M. Hoffman, Remodeling the Blood Coagulation Cascade, J Thromb Thrombolysis 16 (2003) 17-20. https://doi.org/10.1023/B:THRO.0000014588.95061.28

[12] R.C. Becker, Cell-based models of coagulation: a paradigm in evolution, J Thromb Thrombolysis 20 (2005) 65-68. https://doi.org/10.1007/s11239-005-3118-3

[13] K. Galvez C., C. Cortes L., Thromboelastography: New concepts in haemostasis physiology and correlation with trauma associated coagulopathy, Colombian Journal of Anesthesiology 40 (2012) 224-230. https://doi.org/10.1097/01819236-201240030-00011

[14] Y. Guo, M. Wang, Q. Liu, G. Liu, S. Wang, J. Li, Recent advances in the medical applications of hemostatic materials, Theranostics 13 (2023) 161-196. https://doi.org/10.7150/thno.79639

[15] X.-F. Li, P. Lu, H.-R. Jia, G. Li, B. Zhu, X. Wang, F.-G. Wu, Emerging materials for hemostasis, Coord Chem Rev 475 (2023) 214823. https://doi.org/10.1016/j.ccr.2022.214823

[16] S. Pourshahrestani, E. Zeimaran, I. Djordjevic, N.A. Kadri, M.R. Towler, Inorganic hemostats: The state-of-the-art and recent advances, Materials Science and Engineering: C 58 (2016) 1255-1268. https://doi.org/10.1016/j.msec.2015.09.008

[17] J.B. Laurenti, G. Zazeri, A.P.R. Povinelli, M.F. de Godoy, D.M. Braile, T.R.F. da Rocha, É.A. D'Amico, J.G. Nery, Enhanced pro-coagulant hemostatic agents based on nanometric zeolites, Microporous and Mesoporous Materials 239 (2017) 263-271. https://doi.org/10.1016/j.micromeso.2016.10.020

[18] Y. Zheng, J. Wu, Y. Zhu, C. Wu, Inorganic-based biomaterials for rapid hemostasis and wound healing, Chem Sci 14 (2023) 29-53. https://doi.org/10.1039/D2SC04962G

[19] D. Paul, G. Sanap, S. Shenoy, D. Kalyane, K. Kalia, R.K. Tekade, Artificial intelligence in drug discovery and development, Drug Discov Today 26 (2021) 80-93. https://doi.org/10.1016/j.drudis.2020.10.010

[20] P. Hamet, J. Tremblay, Artificial intelligence in medicine, Metabolism 69 (2017) S36-S40.. https://doi.org/10.1016/j.metabol.2017.01.011

[21] J.H. Holmes, L. Sacchi, R. Bellazzi, N. Peek, Artificial Intelligence in Medicine AIME 2015, Artif Intell Med 81 (2017) 1-2. https://doi.org/10.1016/j.artmed.2017.06.011

[22] Amisha, P. Malik, M. Pathania, V. Rathaur, Overview of artificial intelligence in medicine, J Family Med Prim Care 8 (2019) 2328. https://doi.org/10.4103/jfmpc.jfmpc_440_19

[23] M.I. Jordan, T.M. Mitchell, Machine learning: Trends, perspectives, and prospects, Science (1979) 349 (2015) 255-260. https://doi.org/10.1126/science.aaa8415

[24] M. Moliner, Y. Román-Leshkov, A. Corma, Machine Learning Applied to Zeolite Synthesis: The Missing Link for Realizing High-Throughput Discovery, Acc Chem Res 52 (2019) 2971-2980. https://doi.org/10.1021/acs.accounts.9b00399

[25] F. Daeyaert, F. Ye, M.W. Deem, Machine-learning approach to the design of OSDAs for zeolite beta, Proceedings of the National Academy of Sciences 116 (2019) 3413-3418. https://doi.org/10.1073/pnas.1818763116

[26] S. Ma, Z.-P. Liu, Machine learning potential era of zeolite simulation, Chem Sci 13 (2022) 5055-5068. https://doi.org/10.1039/D2SC01225A

[27] X. Li, H. Han, N. Evangelou, N.J. Wichrowski, P. Lu, W. Xu, S.-J. Hwang, W. Zhao, C. Song, X. Guo, A. Bhan, I.G. Kevrekidis, M. Tsapatsis, Machine learning-assisted crystal engineering of a zeolite, Nat Commun 14 (2023) 3152. https://doi.org/10.1038/s41467-023-38738-5

[28] C. Wang, C. Shi, J. Huang, X. Wei, Y. Shi, L. Xiao, J. Fan, Synergistic Procoagulant Mechanism and Application of Kaolin-Zeolite Composite Hemostat for Effective Hemorrhage Control, ACS Appl Mater Interfaces 16 (2024) 49186-49196. https://doi.org/10.1021/acsami.4c12623

[29] Y. Li, X. Liao, X. Zhang, G. Ma, S. Zuo, L. Xiao, G.D. Stucky, Z. Wang, X. Chen, X. Shang, J. Fan, In situ generated thrombin in the protein corona of zeolites: Relevance of the functional proteins to its biological impact, Nano Res 7 (2014) 1457-1465. https://doi.org/10.1007/s12274-014-0505-0

[30] L. Yu, X. Shang, H. Chen, L. Xiao, Y. Zhu, J. Fan, A tightly-bonded and flexible mesoporous zeolite-cotton hybrid hemostat, Nat Commun 10 (2019) 1932. https://doi.org/10.1038/s41467-019-09849-9

[31] J. Wang, H. Zhang, J. Wang, F. Pan, H. Zhang, J. Luo, C. Guo, K. Li, T. Li, Efficacy of New Zeolite-Based Hemostatic Gauze in a Gunshot Model of Junctional Femoral Artery Hemorrhage in Swine, Journal of Surgical Research 263 (2021) 176-185. https://doi.org/10.1016/j.jss.2020.12.040

[32] A. Merchant, S. Batzner, S.S. Schoenholz, M. Aykol, G. Cheon, E.D. Cubuk, Scaling deep learning for materials discovery, Nature 624 (2023) 80-85. https://doi.org/10.1038/s41586-023-06735-9

[33] A. Pihlajamäki, M.F. Matus, S. Malola, H. Häkkinen, GraphBNC: Machine Learning-Aided Prediction of Interactions Between Metal Nanoclusters and Blood Proteins, Advanced Materials 36 (2024). https://doi.org/10.1002/adma.202407046

[34] D.A. Hickman, C.L. Pawlowski, U.D.S. Sekhon, J. Marks, A. Sen Gupta, Biomaterials and Advanced Technologies for Hemostatic Management of Bleeding, Advanced Materials 30 (2018). https://doi.org/10.1002/adma.201804635

[35] D.S. Kauvar, R. Lefering, C.E. Wade, Impact of Hemorrhage on Trauma Outcome: An Overview of Epidemiology, Clinical Presentations, and Therapeutic Considerations, Journal of Trauma: Injury, Infection & Critical Care 60 (2006) S3-S11. https://doi.org/10.1097/01.ta.0000199961.02677.19

[36] A. Malik, F.U. Rehman, K.U. Shah, S.S. Naz, S. Qaisar, Hemostatic strategies for uncontrolled bleeding: A comprehensive update, J Biomed Mater Res B Appl Biomater 109 (2021) 1465-1477. https://doi.org/10.1002/jbm.b.34806

[37] P. Yu, W. Zhong, Hemostatic materials in wound care, Burns Trauma 9 (2021). https://doi.org/10.1093/burnst/tkab019

[38] H.H. Rashidi, K.A. Bowers, M. Reyes Gil, Machine learning in the coagulation and hemostasis arena: an overview and evaluation of methods, review of literature, and future directions, Journal of Thrombosis and Haemostasis 21 (2023) 728-743. https://doi.org/10.1016/j.jtha.2022.12.019

[39] T. Feng, Y. Wang, W. Zhang, T. Cai, X. Tian, J. Su, Z. Zhang, S. Zheng, S. Ye, B. Dai, Z. Wang, Y. Zhu, H. Zhang, K. Chang, D. Ye, Machine Learning-based Framework Develops a Tumor Thrombus Coagulation Signature in Multicenter Cohorts for Renal Cancer, Int J Biol Sci 20 (2024) 3590-3620. https://doi.org/10.7150/ijbs.94555

[40] A. Rawal, C. Kidchob, J. Ou, Z.E. Sauna, Application of machine learning approaches for predicting hemophilia A severity, Journal of Thrombosis and Haemostasis 22 (2024) 1909-1918. https://doi.org/10.1016/j.jtha.2024.04.019

[41] C.-H. Yeh, Y.-J. Chou, T.-H. Tsai, P.W.-C. Hsu, C.-H. Li, Y.-H. Chan, S.-F. Tsai, S.-C. Ng, K.-M. Chou, Y.-C. Lin, Y.-H. Juan, T.-C. Fu, C.-C. Lai, H.-K. Sytwu, T.-F. Tsai, Artificial-Intelligence-Assisted Discovery of Genetic Factors for Precision Medicine of Antiplatelet Therapy in Diabetic Peripheral Artery Disease, Biomedicines 10 (2022) 116. https://doi.org/10.3390/biomedicines10010116

[42] T.J.S. Lopes, T. Nogueira, R. Rios, A Machine Learning Framework Predicts the Clinical Severity of Hemophilia B Caused by Point-Mutations, Frontiers in Bioinformatics 2 (2022). https://doi.org/10.3389/fbinf.2022.912112

[43] A. Bouchnita, P. Nony, J.-P. Llored, V. Volpert, Combining mathematical modeling and deep learning to make rapid and explainable predictions of the patient-specific response to anticoagulant therapy under venous flow, Math Biosci 349 (2022) 108830. https://doi.org/10.1016/j.mbs.2022.108830

[44] J. Xiao, R.L. Melvin, F.R. Salsbury, Probing light chain mutation effects on thrombin via molecular dynamics simulations and machine learning, J Biomol Struct Dyn 37 (2019) 982-999. https://doi.org/10.1080/07391102.2018.1445032

[45] S.L.N. Brouns, J.P. van Geffen, E. Campello, F. Swieringa, L. Spiezia, R. van Oerle, I. Provenzale, R. Verdoold, R.W. Farndale, K.J. Clemetson, H.M.H. Spronk, P.E.J. van der Meijden, R. Cavill, M.J.E. Kuijpers, E. Castoldi, P. Simioni, J.W.M. Heemskerk, Platelet-primed interactions of coagulation and anticoagulation pathways in flow-dependent thrombus formation, Sci Rep 10 (2020) 11910. https://doi.org/10.1038/s41598-020-68438-9

[46] I. Yoon, J.H. Han, H.-J. Jeon, Advances in Platelet-Dysfunction Diagnostic Technologies, Biomolecules 14 (2024) 714. https://doi.org/10.3390/biom14060714

[47] X. Wang, S. Luo, X. Cui, H. Qu, Y. Zhao, Q. Liao, Machine learning-based predictive model for the development of thrombolysis resistance in patients with acute ischemic stroke, BMC Neurol 24 (2024) 296. https://doi.org/10.1186/s12883-024-03781-2

[48] T. Yu, R. Shen, G. You, L. Lv, S. Kang, X. Wang, J. Xu, D. Zhu, Z. Xia, J. Zheng, K. Huang, Machine learning-based prediction of the post-thrombotic syndrome: Model development and validation study, Front Cardiovasc Med 9 (2022). https://doi.org/10.3389/fcvm.2022.990788

[49] D. Hasegawa, K. Yamakawa, K. Nishida, N. Okada, S. Murao, O. Nishida, Comparative Analysis of Three Machine-Learning Techniques and Conventional Techniques for Predicting Sepsis-Induced Coagulopathy Progression, J Clin Med 9 (2020) 2113. https://doi.org/10.3390/jcm9072113

[50] Y. Miyagi, K. Tada, I. Yasuhi, K. Tsumura, Y. Maegawa, N. Tanaka, T. Mizunoe, I. Emoto, K. Maeda, K. Kawakami, A Novel Method for Determining Fibrin/Fibrinogen Degradation Products and Fibrinogen Threshold Criteria via Artificial

Intelligence in Massive Hemorrhage during Delivery with Hematuria, J Clin Med 13 (2024) 1826. https://doi.org/10.3390/jcm13061826

[51] P. Gresele, Artificial intelligence and machine learning in hemostasis and thrombosis, Bleeding, Thrombosis and Vascular Biology 2 (2024). https://doi.org/10.4081/btvb.2023.105

[52] A.D. Meid, L. Wirbka, A. Groll, W.E. Haefeli, Can Machine Learning from Real-World Data Support Drug Treatment Decisions? A Prediction Modeling Case for Direct Oral Anticoagulants, Medical Decision Making 42 (2022) 587-598. https://doi.org/10.1177/0272989X211064604

[53] D.L. Labovitz, L. Shafner, M. Reyes Gil, D. Virmani, A. Hanina, Using Artificial Intelligence to Reduce the Risk of Nonadherence in Patients on Anticoagulation Therapy, Stroke 48 (2017) 1416-1419. https://doi.org/10.1161/STROKEAHA.116.016281

[54] M.C. Vedovati, A. Mancuso, L. Pierpaoli, U. Paliani, S. Conti, A. Ascani, G. Galeotti, F. Di Filippo, C. Caponi, G. Agnelli, C. Becattini, Prediction of major bleeding in patients receiving DOACs for venous thromboembolism: A prospective cohort study, Int J Cardiol 301 (2020) 167-172. https://doi.org/10.1016/j.ijcard.2019.11.105

[55] D.A. Mei, J.F. Imberti, N. Bonini, G.F. Romiti, B. Corica, M. Proietti, M. Vitolo, G.Y.H. Lip, G. Boriani, Performance of HAS-BLED and DOAC scores to predict major bleeding events in atrial fibrillation patients treated with direct oral anticoagulants: A report from a prospective European observational registry, Eur J Intern Med 128 (2024) 63-70. https://doi.org/10.1016/j.ejim.2024.06.022

[56] S. Zeng, W. Zhu, S. Guo, H. Hong, Predictive performance of HAS-BLED, ORBIT, ABC, and DOAC scores for major bleeding in atrial fibrillation patients on DOACs, Eur J Intern Med 128 (2024) 131-133. https://doi.org/10.1016/j.ejim.2024.06.027

Received on 07-11-2024 Accepted on 20-12-2024 Published on 30-12-2024

https://doi.org/10.31875/2410-4701.2024.11.11