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Review

Mechanistic insights and treatment optimization in ischemic stroke: A mini-review of computational approaches

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Abstract: Stroke remains a leading cause of global mortality and disability, affecting millions of individuals annually. Computational modeling quantifies the complex pathophysiology of an ischemic stroke, paving the way for personalized therapeutic strategies. This review explores the transformative role of computational modeling and simulation in advancing ischemic stroke research and clinical translation. We systematically examine multi-scale mathematical models, including low-dimensional (0D/1D) hemodynamic representations, high-fidelity 3D computational fluid dynamics (CFD), and fluid-structure interaction (FSI) simulations, to elucidate key hemodynamic parameters such as wall shear stress (WSS), the oscillatory shear index (OSI), and the endothelial cell activation potential (ECAP), which are critical in thrombosis, plaque stability, and stroke progression. Furthermore, we highlight the application of these models in optimizing acute ischemic stroke treatments, including intravenous thrombolysis and mechanical thrombectomy, and in pioneering emerging strategies such as in silico trials and milli-spinner thrombectomy. Despite significant progress, challenges remain in standardization, real-time clinical integration, and model validation. Looking forward, we discuss the integration of multi-scale modeling, artificial intelligence, and patient-specific data toward the development of predictive digital twins and personalized therapeutic frameworks. By bridging mechanistic insights with clinical innovations, computational approaches are poised to redefine stroke care, thus enabling more precise, timely, and effective interventions.

Keywords: ischemic stroke; computational modeling and simulation; hemodynamics; blood flow; thrombectomy; thrombolysis; cerebrovascular biomechanics

1. Introduction

Stroke results from the interruption of blood flow to the brain and ranks among the leading causes of mortality and long-term disability globally, impacting millions of people every year [1]. Its pathophysiological process involves complex and multi-scale interactions, ranging from macroscale hemodynamic disturbances to microscale cellular and ionic imbalances [2]. Clinically, strokes show significant heterogeneity, with ischemic strokes [3,4], hemorrhagic strokes [5], and transient ischemic attacks [6,7] following different development paths, and individual patient factors, such as the volume of infarct lesions [8], diabetes [9] and atrial fibrillation [10,11], which significantly affect the prognosis. Among them, an ischemic stroke accounts for most cerebrovascular accidents and is characterized by the occlusion of cerebral vessels. It occurs when a blood vessel in a certain part of the brain is blocked, which causes the blood flow in that area to be cut off, and results in a functional impairment or even necrosis within a short period of time [12]. A hemorrhagic stroke occurs when blood vessels in the brain rupture or weak vessel walls cause blood to rush into the brain tissue, thus compressing the surrounding brain tissue and altering the local blood flow dynamics [13]. Due to the significant differences in pathogenesis and the pathological process between the two, this article mainly focuses on ischemic strokes.

Hemodynamic parameters such as wall shear stress (WSS) [14], time-averaged WSS (TAWSS) [15], the oscillatory shear index (OSI) [16], relative residence time (RRT) [17], and endothelial cell activation potential (ECAP) [18,19] are undoubtedly the key to understanding the mechanism of ischemic stroke. WSS, the tangential force exerted by blood flow on the vessel wall, is a fundamental hemodynamic quantity. Derived parameters such as TAWSS, OSI, and ECAP are widely used to characterize disturbed shear environments in models of vascular disease [20]. Crucially, WSS has been experimentally linked to clinical outcomes, thus establishing a direct, interpretable connection between the hemodynamic forces and the pathology [21]. Therefore, while derived indicators provide supplementary mechanistic insights, WSS is prioritized as the primary metric for clinical interpretation.

Although traditional experiments and clinical studies have laid the foundation to understand strokes, they often struggle to fully capture the high-dimensional and multi-level complexity of strokes. For instance, *in vitro* models of the neurovascular unit [22,23] cannot fully replicate the *in vivo* brain environment, and population-based clinical trials [24] may not elucidate patient-specific mechanisms. The CHA_2DS_2-VASc score [25], a common clinical tool used to assess the risk of strokes in patients with atrial fibrillation, can provide only a rough assessment and cannot reflect key pathophysiological factors such as blood stasis or endothelial dysfunction that underlie cardioembolic strokes.

Thus, computational modeling has become an important tool in cerebrovascular research [26]. These computational models span from low-dimensional (0D lumped, 1D network) to high-dimensional (3D) representations. Low-dimensional models offer computational efficiency and are well-suited for simulating global hemodynamics (such as the distribution of pressure and flow) and wave propagation effects. High-dimensional models, such as those based on computational fluid dynamics (CFD), enable the detailed analysis of complex flow patterns [27] and allow patient-specific geometries derived from medical imaging to be used for individualized assessments [28]. Furthermore, fluid-structure interaction (FSI) simulations can elucidate interactions between blood flow and vessel walls, thus providing predictive insights into disease progression and treatment outcomes [29]. Computational modeling serves as a critical bridge between mechanistic understanding and treatment optimization in ischemic strokes. These methods translate the complex pathophysiology into

quantifiable hemodynamic parameters, thus creating testable simulations of various disease states. This enables the dissection of key mechanisms, such as thrombosis and collateral compensation [30]. The insights gained from these models directly inform and refine the development of targeted therapeutic strategies.

Despite substantial progress, several challenges remain in translating these computational models into clinical practice. Key barriers include the lack of standardized and robust image-processing pipelines; current workflows from image segmentation, through parameter calibration, to model validation remain heavily reliant on manual intervention and expert knowledge. Although deep learning has advanced automated infarct segmentation, variability in imaging protocols and patient populations limit the model's generalizability across institutions and studies. Additionally, achieving real-time intraoperative model updating to guide time-sensitive clinical decisions remains a formidable challenge. Therefore, this review aims to systematically explore the prospects of computational modeling and simulations in ischemic stroke research and clinical translations, with an emphasis on the role of computational tools to optimize therapeutic strategies. To this end, we summarize recent advances in computational and machine-learning approaches, thus underscoring their transformative potential for the future of ischemic stroke care.

2. Stroke pathophysiology

2.1. Pathophysiological and clinical significance of hemodynamic indices

Research on the etiological subtyping of ischemic strokes shows variations in the reported prevalence of underlying causes. Based on magnetic resonance imaging (MRI) data, Ko et al. [31] found that atherosclerotic lesions of the major arteries were the most common cause of an acute ischemic stroke (accounting for 38.3%), followed by cardiogenic embolism (22.8%), unexplained causes (22.2%), and small vessel occlusion (14.6%).

The onset and development of strokes are closely related to the hemodynamic environment. Multiple hemodynamic parameters, which reflect various flow field states within blood vessels, play a significant role in the stroke's pathophysiology. For example, highly oscillatory WSS can mediate shear-induced platelet activation, thus promoting distal embolization and ischemic stroke. Conversely, regions of low WSS often coincide with an elevated OSI, which creates a hemodynamic profile particularly prone to atherosclerosis [32−34]. Both pathways can lead to thrombus formation; plaque rupture may trigger the development of an intraluminal thrombus from an associated intimal lesion, a critical dynamic process in an acute ischemic stroke [35]. Although WSS is closely associated with the flow velocity, it cannot be approximated by velocity alone in clinical assessments due to the vascular wall elasticity [36]. TAWSS describes the average level of WSS over the entire cardiac cycle. A decrease in TAWSS often indicates a slower blood flow and an insufficient WSS, which is associated with an increased tendency for thrombosis. As a statistical measure of flow direction instability, the OSI significantly influences the plaque vulnerability and rupture risk [37].

ECAP provides an integrated metric that quantifies the combined hemodynamic risk for endothelial dysfunction and subsequent thrombus formation at a specific vascular site. Studies, such as that by Paliwal et al. [38], showed that the spatial distribution of ECAP highly overlaps with low WSS regions, which potentially reates a vicious cycle of tissue degradation and progressive hemodynamic impairment [39]. It is worth noting that the vascular wall experiences both pressure

(acting perpendicularly) and shear stress (acting tangentially), which results in two time-varying waveforms. The phase difference between these waveforms can also influence the endothelial cell biology and should be considered an independent hemodynamic indicator [40]. Furthermore, it is believed that ECAP is more sensitive than WSS or OSI alone and can better represent the true risk of thromboembolic events in atrial fibrillation [38].

RRT is an indicator used to quantify the time that blood particles stay in the regions of interest. A higher RRT indicates that blood particles stay longer near the vessel wall, thus suggesting local blood flow stagnation and an increased risk of thrombosis [41]. While RRT generally decreases with an increasing stenosis severity, it often rises at the immediate upstream and downstream shoulders of a stenosis, indicating sites of new plaque risk. When stenosis becomes critical ($\geq 90\%$), a sharp increase in the downstream RRT signals a substantially elevated risk of blockage [42]. In cardioembolic stroke research, OSI and RRT are also critical indicators [43], and RRT could potentially improve the predictive accuracy of the CHA2DS2-VASc score.

Clinically, hemodynamic parameters guide therapeutic decision-making by providing quantitative benchmarks. For example, parameters such as WSS are used to evaluate and compare the efficacy of different surgical interventions for carotid stenosis, such as endarterectomy versus stenting, by quantifying postoperative flow improvement [44]. Similarly, they enable the comparison of surgical techniques, such as patch versus primary closure after endarterectomy [45]. Furthermore, these parameters serve as critical benchmarks to validate computational models (e.g., assessing different blood viscosity models), thus informing the selection of the most accurate and efficient model for clinical simulations [46]. Notably, advanced imaging-based 3D models for WSS measurement are being developed, thereby demonstrating potential for risk stratification of strokes and guiding preventive therapies in intracranial atherosclerotic diseases [47].

In summary, an ischemic stroke should not be viewed merely as the direct consequence of vessel occlusion. Instead, it requires an integrated assessment that combines etiology, neuroimaging patterns, and pathophysiological mechanisms, including these key hemodynamic parameters to guide an individualized diagnosis, acute treatment, and secondary prevention.

2.2. Multi-dimensional mathematical models

To non-invasively estimate the hemodynamic parameters to assess the risk of an ischemic stroke, mathematical models in various dimensions have been developed, as illustrated in Figure 1. This subsection summarizes the low- and high-dimensional models that have been developed and applied to study strokes, and discusses their application scope, limitations, and the physiological phenomena they can capture.

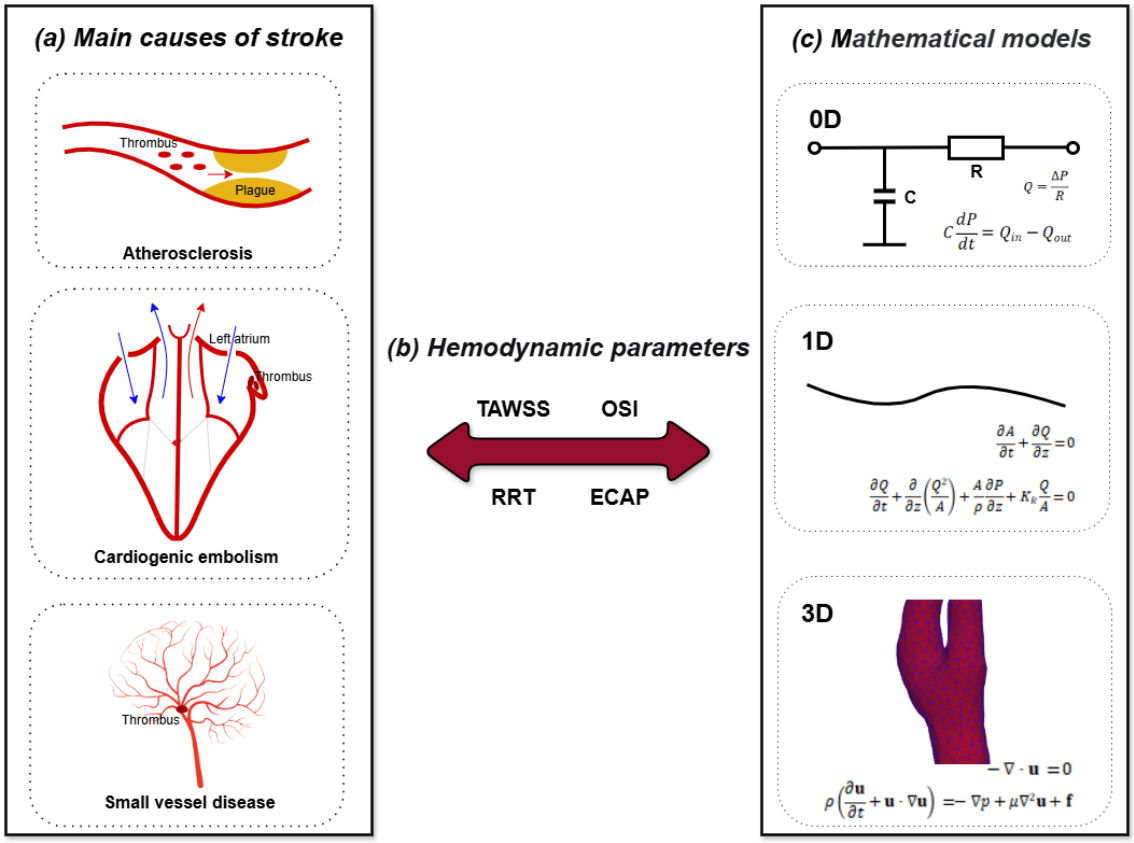

Figure 1. Schematic illustration of the causes, hemodynamic metrics, and computational modeling of ischemic stroke. (a) Commonly recognized causes of an ischemic stroke. (b) Hemodynamic parameters linking macro functions with micro mechanisms. (c) Commonly used computational models.

2.2.1. Zero-dimensional models

While few full 0D (lumped-parameter) models are directly applied to address stroke-specific problems, they are fundamental to simulate peripheral changes in pressure or flow and serve as mid-components and boundary conditions in higher dimensional models. The most common example is the Windkessel model, which uses an electrical circuit analogy to represent the arterial hemodynamics [48].

Stephen Hales proposed the earliest two-element Windkessel single-compartment model in 1733 [49]; while it reasonably depicts the cardiac afterload and diastolic aortic pressure, its accuracy is poor during systole. To address this, additional components were incorporated, which led to three-element [50], four-element [51], and more complex Windkessel models. These models describe independent physiological properties (e.g., characteristic resistance, compliance, inertance) and can be flexibly combined for various research purposes [48,52,53].

Abdi et al. found that the Windkessel model can predict the blood flow changes in the circle of Willis (CoW) under pathological conditions of a cerebral artery stenosis [54]. Zhang et al. used an resistor-capacitor-inductor (RCL) model to assess the compensatory capacity of the CoW during unilateral internal carotid artery (ICA) blockage by observing the symmetry of blood flow in both cerebral hemispheres, and confirmed that collateral circulation was formed through the anterior

cerebral artery and the ipsilateral posterior cerebral artery during an ICA blockage [55]. Otani et al. employed a 0D model to represent sparse intermediate-scale anastomotic vessels and dense occipital artery vessels, and then calculated the blood flow distribution using the pattern of many intermediate anastomoses in a middle cerebral artery (MCA) occlusion, and proved that the sparse number of intermediate anastomoses mainly provided a collateral blood supply to the upstream and downstream regions [56]. Furthermore, Loganathan et al. developed a 0D model to study the cerebral hemodynamics related to a cardiogenic ischemic stroke caused by three different recency conditions: hypertension, atrial fibrillation, and a cerebral artery occlusion [57]. This model enables researchers to quickly investigate the blood circulation of the brain under various pathological conditions. More sophisticated, closed-loop lumped-parameter models also account for the venous system's active role in hemodynamics [58,59].

0D models simulate vascular networks by representing them as analogous electrical circuits, thereby focusing on system-level hemodynamics such as pressure and flow. Their reliance on lumped parameters makes them computationally efficient and straightforward to implement, making them particularly suitable to simulate large-scale cerebral arterial networks [60]. For example, these advantages have been used to develop a computerized tomography angiography-based lumped-parameter framework for the real-time estimation of a cerebral perfusion, with the potential to serve as a preoperative planning tool in place of traditional examinations [61]. However, 0D models inherently overlook the vessel's geometry and cannot capture finer-grained local hemodynamic details, thus limiting their ability to elucidate localized pathological mechanisms such as thrombosis.

2.2.2. One-dimensional models

Due to structural simplification, the 0D model cannot reflect the propagation of pulse waves and the changes in hemodynamic parameters along the artery. Therefore, a 1D model was created either to represent the hemodynamic changes within the artery or to conduct research on pulse wave transmission. In the 1D model, the movement of blood is governed by continuity equations derived from the incompressible Navier-Strokes equations. The movement of the vascular wall, whether elastic or viscoelastic, is controlled by equilibrium equations. One of the major modeling challenges is the accurate implementation of boundary and coupling conditions within vascular networks, for which efficient strategies have recently been developed [62,63].

The 1D model has been applied to the CoW [64]. Blanco et al. analyzed a broad network that contained 2000 blood vessels and compared it with a simplified network that consisted of 86 blood vessels [65]. In their study, changes in the complexity had an impact on hemodynamics with pathological conditions. Meanwhile, the 1D model has been widely applied in the pathological conditions of vascular stenosis and has been extensively used to study the systemic behavior of cerebral hemodynamics, therefore evaluating collateral circulation [66,67]. By simulating pulse wave propagation through the 1D model, the hemodynamic effects of arterial occlusion [68] and intracranial artery stenosis [69] can be evaluated.

Most one-dimensional models have simplifications, and after Womersley proposed them, the existence of shear stress in the vascular wall was ignored, and a simplified arterial system was recently used [70−73]. Here, Formaggia et al. constructed a complete systemic circulation model, but excluded cerebral blood vessels and ignored the elastic factor [74]. In contrast, Reymond and others used the cerebrovascular and left ventricular walls of the viscoelastic model to build a complete model of the

systemic circulation [75].

The 1D modeling approach is typically based on the continuity and momentum equations, and offers a relatively good predictive capability at the system level. Its primary strength lies in achieving an effective balance between the physiological detail and the computational efficiency. This enables rapid, patient-specific simulations of the dynamic blood flow [76], thus making the model particularly suitable to study pulse wave propagation, analyze pressure-flow relationships across large arterial networks, and assess the global hemodynamic impact of stenoses [48]. However, the limitations of 1D models remain significant. By assuming that the flow is uniform in the axial direction and neglecting radial variations, they cannot accurately resolve the local hemodynamic details, such as complex flow patterns or WSS distributions. Moreover, their predictive accuracy is highly sensitive to the input parameters, including the vascular radius, length, and elastic modulus, which are often difficult to precisely measure under pathological conditions, thus posing a major barrier to the reliable translation of 1D models into clinical practice.

2.2.3. Three-dimensional models

The 0D and 1D models can simulate the overall blood flow in the vasculature, but they cannot simulate the local flow field. Therefore, the 3D model was proposed to describe the local flow field. These 3D models are fundamentally based on the Navier-Stokes equations that comprise the mass and momentum conservation equations. Furthermore, they are usually implemented on an unstructured collocated mesh, where the incompressible Navier-Stokes equations are solved at each grid point [77].

Several assumptions must be made in the 3D CFD modeling process, among which the boundary conditions are crucial [78,79], due to the usual absence of in vivo data and restrictions in data capture regarding the spatial and temporal resolution. Inlet flow is usually prescribed from patient data, such as a Doppler ultrasound or a phase-contrast MRI. For example, Leyhe *et al.* used neurovascular ultrasound-derived flow velocities at the extracranial internal carotid and vertebral arteries, combined with the measured systemic blood pressure, as inlet conditions [80]. The outlets' conditions are equally complex and are also limited by medical images. Moreover, validation is rarely carried out. Outlets are commonly modeled with 0D or impedance models to represent distal vascular resistance and compliance. Recent work by Luisi *et al.* recommends against fixed-pressure outlet boundaries due to large errors; instead, multi-element Windkessel (RCR) or phase-modulated boundary conditions (BCs) produce more physiologically realistic pulsatile flows [81].

Blood rheology is typically modeled as non-Newtonian shear-thinning; common choices include the Casson or Carreau–Yasuda models. Some studies find that Newtonian approximations have a negligible effect on the pressure drop metrics, but non-Newtonian models better capture WSS variations in low-shear regions [82]. In the study by Liu et al., this result was confirmed; while the Newtonian model offered a higher computational efficiency, it tended to overestimate parameters such as OSI, WSS, and RRT. By contrast, non-Newtonian models provided predictions more consistent with the physiological reality [46].

Vessel walls are often assumed rigid for simplicity [83,84], but FSI simulations include wall compliance. Alvarez *et al.* compared FSI with a rigid-wall model and showed that the wall elasticity can introduce measurable differences in distal pressure and wall shear stress [85]. Numerically, time-stepping must resolve the cardiac cycle to capture pulsatile flow, and the convergence criteria ensure accurate solutions. Additionally, the FSI model can be used to simulate the microscopic degradation

of the arterial wall [86].

3D models can resolve the local hemodynamic parameters such as WSS and pressure gradients with high spatial detail, thus providing valuable insights into the mechanisms that underline ischemic strokes. Hattori et al. used CFD to discover that a high WSS may induce plaque instability and occlusions at the MCA branch orifice [87]. Meanwhile, a locally high WSS and larger areas of high WSS were more prone to lumen regression after one year, thus indicating that a high WSS may promote plaque stability or contraction [88]. Additionally, after stenosis exceeded 50%, the peak WSS and pressure drop significantly increased and were linearly correlated, thus indicating that a severe stenosis can cause high shear and a large pressure difference [89]. From this, we can conclude that high wall shear stress and constriction interact with each other, thereby increasing the risk of endothelial injury and plaque rupture. Even without significant stenosis, it can cause a stroke. Compagne et al. found that Carotid webs led to significant flow separation and recirculation in the cervical sinuses, thus resulting in a locally high WSS and high OSI [90], where blood flow retention and shear fluctuations in this area can induce endometrial injuries and thrombosis. Through the construction of a 3D closed-loop geometric multi-scale cerebral artery model, Sun et al. found that the proportion of the surface area that possessed a high OSI and low TAWSS was mostly greater than 60%, which led to a CoW stenosis [91]. In the study on strokes caused by atrial fibrillation, Falanga et al. utilized the 3D model to discover that the atrial mural blood flow in patients with atrial fibrillation has a higher ECAP, which can be used to identify the thrombus formation area [92]. These hemodynamic indices could augment CHA2DS2-VASc, thus enabling more personalized stroke risk stratification than clinical factors alone.

Although 3D CFD/FSI models excel at resolving the local hemodynamics with high spatial detail and thus offer a significant advantage over 0D and 1D models, the translation of 3D models into direct clinical decision-making also remains limited. A primary challenge lies in their high sensitivity to BCs. Clinically, it remains difficult to obtain truly patient-specific inputs (e.g., exact flow rates and pressure waveforms) and in vivo validation data. Moreover, common simplifying assumptions such as treating blood as a Newtonian fluid and vessel walls as rigid can underestimate critical hemodynamic metrics such as WSS and pulsatile vessel responses, further constraining the models' physiological realism. To address these uncertainties, approaches such as data assimilation (e.g., integrating imaging data with models, as demonstrated by Gaidzik et al. [93]) have been explored to improve the robustness. While promising, such methods remain largely confined to research settings due to their complexity and data requirements. Finally, the substantial computational cost and time associated with 3D simulations present a practical constraint, thus limiting their feasibility for rapid clinical decision-making or large-scale patient-specific analysis.

It is worth noting that in recent years, multi-scale coupling models have attracted increasing attention. These models strategically integrate 0D/1D (systemic circulation) and 3D (local region) components, thereby effectively combining the computational efficiency and global hemodynamic representation of low-dimensional models with the local detail of high-fidelity 3D simulations. This integrated approach has been demonstrated to improve the physiological consistency and accuracy of simulations, partly by providing more physiologically grounded boundary conditions for the 3D domain, thereby mitigating the inherent trade-off between accuracy and efficiency seen in single-scale models [94]. However, even these advanced multi-scale frameworks remain primarily applicable to research scenarios at present, and have not yet fully overcome the above-mentioned barriers to widespread clinical applications [95].

3. Stroke treatment

3.1. Clinical perspectives of stroke treatment

For stroke patients, time is of the essence. Medical staff and researchers have always been striving to find better drugs or more effective treatment plans to extend the time window for patients and increase the success rate of treatment. Currently, the main methods for treating strokes are intravenous thrombolysis (IVT) and a mechanical thrombectomy (MT). Clinically, for patients with an acute ischemic stroke within 4.5 hours of onset, IVT is recommended [96]. For patients with an embolism caused by a large vessel occlusion and meeting specific imaging criteria, such as the presence of ischemic penumbra, a MT is recommended within 6−24 hours of onset [1].

The commonly used drugs for thrombolysis treatments are alteplase, but studies have shown that Tenecteplase, which requires a single injection, is more convenient than alteplase and can shorten the preparation time for treatment [97]. For patients with a large vessel occlusion within 4.5 hours, Tenecteplase is also more recommended for thrombolysis treatment [96,98].

An MT is the standard therapy for acute ischemic strokes caused by large vessel occlusions. It is mainly divided into a stent-retriever thrombectomy (SRT) and an aspiration thrombectomy (AT). Goyal et al. proved through experiments that although an SRT is an invasive surgery, its safety is not significantly different from a simple drug treatment, and the probability of achieving a good prognosis is about 2.5 times that of only using a drug treatment. This established SRT as a new standard for the treatment of a large vessel occlusive stroke [99]. As a relatively new AT has also been proven to be an effective first-line treatment option, its operation is simple and its effectiveness and safety are not inferior to an SRT [100,101].

Compared with using a single technique for treatment, the combination of multiple techniques may lead to a better efficacy. Mocco et al. pointed out in experimental data that for patients with an acute ischemic stroke caused by a large vessel occlusion, they should first receive an IVT treatment and then undergo AT [102]. Although the statistical significance is insufficient due to a relatively small sample size, the results show that a combined treatment has a positive trend in improving the functional prognosis of patients and reducing the mortality. Additionally, it is worth noting that Lapergue et al. innovatively proposed to simultaneously use an SRT device and an intermediate catheter aspiration [103]. Although their results did not show that combined treatments significantly benefit over a simple SRT, it may become a breakthrough in technology after it becomes more mature.

3.2. Treatment methods

The effective acute management of an ischemic stroke hinges on rapid intervention to restore blood flow, with a narrow therapeutic window for optimal outcomes [104−106]. The current cornerstone treatments to achieve reperfusion are IVT and MT [107], which are illustrated by Figure 2. Despite their established efficacy, limitations persist, thus driving continuous research into refining these techniques and exploring novel approaches.

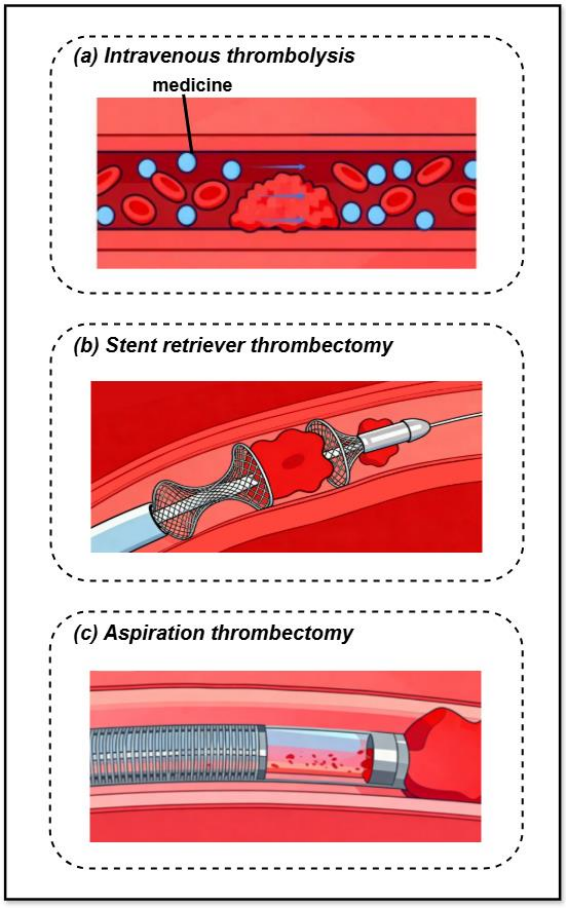

Figure 2. Schematic diagram of (a) the intravenous thrombolysis, (b) the stent-retriever thrombectomy, and (c) the aspiration thrombectomy. Images are generated using the DOUBAO AI image generation tool.

3.2.1. Intravenous thrombolysis

IVT is a crucial treatment method for ischemic strokes, which utilizes thrombolytic drugs to activate the fibrinolytic system in the human body, thereby promoting thrombus dissolution and achieving rapid reperfusion [108]. Its greatest limitation lies in the extremely narrow therapeutic time window, with the best therapeutic effect occurring within 3 to 4.5 hours after symptom onset, which significantly restricts its application scope [109]. This section summarizes thrombolytic drug development and reviews how computational modeling provides a scientific basis to advance IVT efficacy and safety.

Through successive generations, from streptokinase and urokinase to alteplase and tenecteplase, thrombolytic drugs have progressively improved in the efficacy and safety. Streptokinase achieves its thrombolytic effect by indirectly activating and forming a complex with fibrinogen [110,111]. Urokinase can directly convert fibrinogen into fibrin by cleaving peptide bonds [112]. Due to the insufficient specificity of both for fibrin, they may lead to the systemic activation of fibrinogen and increase the risk of bleeding, thus prompting the development of alteplase, a drug with high specificity for fibrin, whose activity is limited to the thrombus site [113,114]. However, the half-life of alteplase is only about 5 minutes, and it is rapidly cleared by the liver. Therefore, tenerplase with a longer half-

life has been developed. More importantly, in clinical trials, tenerplase has outperformed alteplase in achieving early recanalization and can also reduce the risk of a cerebral hemorrhage.

Computational modeling has emerged as a crucial tool to enable the optimization of thrombolytic therapy, particularly in the dosing regimen design and targeted drug delivery strategies. Dosing is a critical, modifiable factor in IVT outcomes. Therefore, Piebalgs et al. developed a 3D pharmacokinetic model to simulate the dissolution efficacy of different doses of recombinant tissue-type plasminogen activator (tPA) on the fibrin radius thrombi, and the results showed that an increase in tPA dose indeed accelerates thrombus dissolution [115]. Through a pharmacokinetic-pharmacodynamic model, Yang et al. found that a combined alteplase with a variant pro-urokinase (m-proUK) thrombolysis strategy achieved recanalization in comparable time while preserving the plasma concentration of fibrinogen, followed by higher levels and remaining stable at around 7.5 μM after a slow depletion over 50 min, which is potentially a decreased hemorrhage risk, which suggests that an optimized dosing could leverage dual-therapy advantages [116]. In the clinical trials completed by Sun et al., it was found that the current 0.25 mg/kg dose of tenecteplase (OR 1.3, 95% CI: 0.79–2.5) had the highest probability of achieving a good functional outcome at 90 days. For safety outcomes, 0.25 mg/kg tenecteplase had incidences of a symptomatic intracranial hemorrhage (OR 0.88, 95% CI: 0.35–1.8), death within 90 days (OR 0.91, 95% CI: 0.54–1.4), and serious adverse events (OR 1.0, 95% CI: 0.47–2.3). Hence, 0.25 mg/kg tenecteplase is the best choice in terms of the benefit-risk ratio [117]. Furthermore, hemodynamic models reveal that the thrombus location and size critically influence drug delivery and thrombolysis efficacy. In small distal cerebral arteries, a reduced flow decreases the delivery efficiency, and the time required for thrombolysis scales nearly quadratically with the clot volume, not linearly [118]. These insights underscore the need for patient-specific, anatomy-aware dosing models.

To maximize clot dissolution while minimizing systemic exposure, Gu et al. used a 1D model to identify the optimal infusion rate and found that the thrombolysis rate increases with the infusion rate, subject to the limit that rates which induce significant systemic fibrinogen depletion must be avoided, as they would not lead to a faster vascular recanalization but instead increase the risk of bleeding [119]. This model defined the constraint that the optimal dosing regimen should maintain a sufficiently high tPA level throughout the treatment process to maximize the dissolution rate while limiting the degradation of fibrinogen in the systemic plasma, and directly motivated their subsequent work. Gu et al. developed a multi-physics field model to explore a targeted thrombolytic therapy through activated platelet-targeted tPA-loaded nanovesicles (tPA-NV), a method that leverages the long-term circulation and the targeted accumulation of nanodrugs at the thrombus site [120]. It computationally demonstrated that at only 10% of the standard dose, tPA-NV achieved an efficacy equivalent to free tPA, thus providing an in-silico proof-of-concept for a dramatic, model-optimized dose reduction strategy.

Despite advances, key limitations in the current modeling approaches persist. First, studies often use idealized vascular models that fail to adequately capture the true anatomy and complex local hemodynamics, thus limiting the clinical translatability [121]. Second, models often assume homogeneous fibrin clots, thus neglecting cellular components such as red blood cells and platelets as well as a heterogeneous structure, thus inaccurately representing the thrombolysis process [122]. Addressing these gaps through patient-specific, multi-component clot models integrated with high-fidelity hemodynamics is essential for the next generation of truly personalized, model-optimized thrombolytic therapy.

3.2.2. Mechanical thrombectomy

MT has revolutionized ischemic stroke care by enabling direct clot removal. Its superiority over IVT hinges on not only achieving rapid, complete recanalization (particularly the first-pass effect) [123,124], but also achieves an extended therapeutic time window [125]. The efficacy of MT is fundamentally governed by the thrombus permeability and collateral circulation that determines the survival of the ischemic penumbra and the effective treatment window. Equally critical are microemboli, which influence the technical difficulty of removal and the risk of procedure-related complications such as distal embolization [126]. Furthermore, after treatment with MT, many patients do not get reperfusion [127].

Thus, the optimization of MT is fundamentally about maximizing the recanalization success while minimizing the procedural risks such as distal embolization or vascular injury. Additionally, it is vital to investigate the effect of perfusion on ischemic strokes, thereby assisting to predict final infarcted brain tissue and choose the suitable treatment. Computational modeling serves as a critical tool for this optimization in terms of understanding physiological constraints, optimizing the device design and virtual surgery, optimizing the procedural parameters, and enabling in silico trials for patient-specific strategy selection. The MT efficacy is not solely device-dependent but is governed by patient-specific physiology. Modeling enables the quantification and integration of these factors into treatment planning. For example, 1D hemodynamic models demonstrate that collateral flow is the dominant factor for good outcomes, defining the viable penumbra, and thus the effective, patient-specific treatment window for MT optimization [128]. FSI models simulate a deformable emboli motion, thus providing initial forecasts of embolization severity [129]. Porous medium models attribute failed reperfusion post-MT to microemboli burden, thereby identifying it as a key risk factor to mitigate [130]. Multiscale (1D-3D) models that integrate a patient-specific CoW anatomy can estimate perfusion territories, which assists in predicting the final infarct volume and informs the suitability of MT [131]. Additionally, sensitivity analyses validate that 1D models can estimate reasonable blood pressures and perfusion; however, 3D models are needed for an accurate volumetric flow rate optimization [132].

The two primary technical approaches to MT are SRT and AT. SRT involves deploying a self-expanding stent to engage and entrap the thrombus, which is then withdrawn under continuous aspiration. Receiving SRT within 6-24 hours post-stroke leads to better outcomes compared to the standard treatment method [133]. AT removes clots by directly applying negative pressure to the thrombus face via a large-bore catheter. Although many studies have shown that AT is non-inferior to SRT [134−139], the surgical strategies to use AT have been continuously optimized. AT is limited by poor deliverability and geometric dependence. For example, tortuous vascular anatomy may prevent large-bore aspiration catheters from reaching the occlusion [140]. In addition, the obvious angulation at the thrombus and vascular interface reduces the contact between the catheter and the thrombus, which decreases the inhalation efficiency and increases the failure rate of the first pass [141].

For SRT, modeling primarily optimizes the device design, selection, and retrieval mechanics to improve engagement and reduce fragmentation. A finite element analysis (FEA) enables virtual surgical simulations, thus allowing clinicians to evaluate and compare the performance of different stent retriever devices in the same patient-specific vascular and clot conditions, and thereby supports the selection of the most appropriate SRT strategy for individual patients [142]. Additionally, FEA demonstrated that an increased friction between the stent retriever and clot elevates the mechanical stress within the thrombus, thus highlighting the importance of optimizing the device manipulation

and retrieval mechanics to prevent fragmentation [143]. Integrated with smoothed particle hydrodynamics (SPH), FEA-SPH models can test novel stent designs and simulate challenging scenarios (e.g., tortuous anatomy) that are difficult to replicate in vivo or in vitro [144]. Additionally, verified models can simulate microemboli dynamics to optimize retrieval paths and prevent distal embolization [145,146].

For AT, modeling focuses on optimizing procedural parameters such as pressure, flow rate, and catheter placement to maximize the suction efficacy while preserving perfusion. CFD models evaluated how the aspiration pressure magnitude alters the cerebral flow, thus supporting pressure-selection strategies that balance the suction efficacy and perfusion preservation [147]. A multiscale computational framework quantified the effects of catheter tip location and aspiration flow rate, thereby showing that the mean middle cerebral artery flow is minimally affected by the aspiration position but is more sensitive to the applied aspiration rate [148]. Beyond steady aspiration settings, a time-dependent model of recanalization through cyclic aspiration has been developed, thus enabling the in silico optimization of aspiration waveforms [149]. Furthermore, FEA studies that investigated failure mechanisms in long clots suggested that optimizing the aspiration mode from continuous to a cyclic pressure loading can improve the outcomes [150]. Additionally, the technologies used in AT are constantly being optimized, one of the important AT techniques is the A Direct Aspiration first Pass Technique (ADAPT). Its initial clinical success rate is 75% and it is a fast, safe, simple, and effective method [151,152]. In a large retrospective study, the rate of final successful reperfusion achieved in ADAPT was 83%, with the site of arterial occlusion and procedural delay being the predictors for reperfusion [153]. The ASCEND (Aspiration with Steam-shaped Catheter, Excluding additioNal Devices) technology improves upon the ADAPT technology by using a simple step of steam-shaping the aspiration catheter, thus saving time and cost without affecting the performance and safety [154]. When the initial AT fails, the 3D stent retriever can be combined as an emergency strategy [155].

Beyond single-device optimization, modeling also enables the systematic evaluation of strategies across virtual populations. In silico trials (IST) address the need for efficient, patient-centric MT optimization by reducing the reliance on large-scale clinical trials. Using an event-based modeling approach to generate cohorts of virtual patients and abstract disease progression and treatment, IST is expected to reduce the number of patients required for clinical trials [156]. Projects such as INSIST (IN-Silico trials for treatment of acute Ischemic STroke) build large-scale virtual patient cohorts for preliminary evaluation, and frameworks such as Discrete Event Simulation Framework for In Silico Trials (*Des-ist*) using directed acyclic graphs to integrate trial components, thus enhancing the efficiency [157,158]. Although generating virtual patients can enhance the efficiency of clinical trials, verification cannot bypass real-world data. Due to this limitation, the current IST is still in the exploratory stage. Moreover, digital twins also face severe ethical challenges. To promote IST, regulatory authorities need to take responsibility to enhance its credibility [159].

Additionally, modeling guides the development of next-generation technologies. For instance, simulations underpin the design of milli-spinner thrombectomy devices, which optimize clot disruption via micro-rotational forces to reduce the volume and embolization risk [160]. A prototype uses synergistic compression-shear forces to reduce the thrombus volume by 95%, with in vitro/animal experiments confirming rapid ablation and high-fidelity vascular recanalization, thus mitigating a distal embolization risk [160]. Advancing this concept, a magnetically driven milli-spinner robot is capable of navigating complex vasculature at high speeds and integrating complementary functions such as aspiration and drug delivery, thus showcasing the potential as a comprehensive future platform [161].

Despite advances, current models have limitations, including limited patient-specific datasets and population variability [142], insufficient large-scale experimental or clinical validation [162], simplified representations of clot material behavior without damage or fragmentation mechanisms [144], and the omission of key physiological factors such as blood flow dynamics, aspiration effects, and realistic vascular heterogeneity [144−146].

4. Discussion and future perspectives

Computational modeling and simulations have profoundly expanded our understanding of stroke pathophysiology and treatments, evolving from explanatory tools to predictive platforms with tangible clinical potential. As highlighted in this review, the integration of multi-scale models, from 0D lumped-parameter systems to 3D patient-specific CFD and FSI simulations, has been instrumental in elucidating the hemodynamic mechanisms, optimizing thrombolytic strategies, and advancing mechanical thrombectomy techniques, as summarized in Table 1. Nevertheless, the translation of these in silico advances into routine clinical practice remains a work in progress, facing several pivotal challenges and opportunities.

Table 1. A summary of computational models and their applications in ischemic stroke.

Model Dimensionality	Modeled Phenomena	Key Metrics	Clinical Relevance
0D	Systemic/cerebral pressure-flow relationships, collateral circulation function.	Pressure, flow, impedance, compliance.	Assessing collateral compensatory capacity; Serving as BCs for higher-order models.
1D	Pulse wave propagation in arterial networks, impact of stenoses. Balance between drug infusion rate and systemic fibrinolytic activation.	Pressure & flow waveforms along vessels, pulse wave velocity.	Studying global hemodynamic impact of large artery stenosis; Optimizing IVT infusion rates to balance efficacy and bleeding risk.
3D CFD	Local complex flow fields. Effect of aspiration pressure / flow on cerebral perfusion during thrombectomy.	WSS, TAWSS, OSI, RRT, ECAP, pressure gradients.	Identifying vulnerable plaque locations; Evaluating post-operative flow improvement; Optimizing AT parameters.
3D FSI	Interactions among thrombectomy devices, thrombus, and vessel.	WSS, TAWSS, OSI, RRT, ECAP, pressure gradients, wall stress & strain.	Simulating disease progression more realistically; Optimizing stent-retriever design and simulating clot engagement to predict fragmentation risk.
Multiscale Coupling	Embedding local high-fidelity simulation within a global physiological context.	Integrating local and global metrics.	Enabling physiologically consistent simulations for personalized treatment planning.

A primary future objective is the development of clinically integrated predictive models capable of guiding real-time decision-making. Current tools often operate in an investigational vacuum. The next generation must prioritize robust, automated image-processing pipelines to reduce inter-operator variability and improve the reproducibility. Deep learning approaches for segmentation and parameterization must be generalized across diverse imaging protocols and patient populations. Furthermore, for models to impact acute stroke care, they must achieve near real-time performance through advances in reduced-order modeling, efficient algorithms, and hardware acceleration, thus enabling intraoperative simulation updates. Beyond anatomical personalization, future frameworks should also integrate multiparametric data, including genomics, proteomics, and real-time physiological monitoring, to capture true pathophysiological individuality.

Given that a stroke is inherently a multiscale disorder, future work must more seamlessly integrate biological and mechanical dynamics. This entails incorporating models of endothelial dysfunction, platelet activation, and blood-brain barrier dynamics into hemodynamic simulations, as well as linking flow parameters to clinical outcomes such as infarct growth and penumbral salvage. Such an integration requires coupling fluid dynamics with models of oxygen transport, cellular metabolism, and ischemic cascades.

IST represents a paradigm shift, thereby offering a cost-effective and ethical means to test hypotheses, optimize interventions, and stratify patients. Moving forward, effort should focus on creating validated patient-specific "digital twins" that mirror the cerebrovascular physiology and pathology, thus enabling personalized treatment planning and outcome predictions [163]. To gain a broader clinical and regulatory acceptance, these approaches will require standardized validation frameworks, benchmark datasets, and demonstrated predictive accuracies across diverse populations.

Moreover, computational models will be critical in evaluating emerging technologies. They can simulate the biomechanics of novel devices such as milli-spinners or magnetically guided micro-robots, thus optimizing the design for efficacy and safety prior to clinical trials. Multiphysics modeling of nanomedicine-based thrombolysis can inform the design of targeted drug carriers, thereby optimizing dosing and release kinetics. Additionally, simulations are ideal to explore the synergistic effects of combined therapies and to identify optimal treatment sequences and timing. Despite this promise, key challenges persist. High-fidelity models remain constrained by the resolution and accuracy of the clinical input data concerning the flow, pressure, and vessel properties, thus necessitating advancements in non-invasive imaging and sensing. Rigorous validations against in-vivo data are still scarce, thus underscoring the need for comprehensive uncertainty quantification. Finally, realizing the full potential of computational stroke medicine will demand sustained interdisciplinary collaborations among clinicians, engineers, data scientists, and industry partners to ensure the models are clinically relevant, usable, and actionable.

In summary, computational modeling and simulations have changed the landscape of stroke research, thus providing unprecedented insight into its complex mechanisms and therapeutic opportunities. The continued integration of multiscale modeling, artificial intelligence, and real-time clinical data holds the promise of transforming stroke care from a reactive discipline to a proactive, personalized practice. By addressing the current limitations and fostering interdisciplinary innovations, computational tools are poised to become indispensable in the global effort to reduce the burden of strokes, thus guiding the way toward more precise, effective, and timely interventions for every patient.

Use of generative-AI tools declaration

Images in Figure 2 are generated using the DOUBAO AI image generation tool.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

Writing – original draft: Y. B., M. L., S. X.; Writing – review & editing: Y. B., M. L., N. K., X. M., H. W.; Conceptualization: H. W.

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