

Review

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Review

Current Modeling Approaches for Drug Delivery to the Central Nervous System

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Abstract

Central nervous system (CNS) disorders constitute a significant global health challenge; however, the development of therapeutic agents is considerably impeded by the difficulty in delivering effective concentrations within the brain. This comprehensive review delineates the current landscape of computational modeling techniques employed to address the formidable challenges associated with CNS drug delivery, with a particular emphasis on the anatomical barriers and physiological transport mechanisms pertinent to major neurological diseases. We categorize modeling approaches ranging from the atomistic scale, including molecular dynamics simulations of drug-blood-brain barrier (BBB) interactions, to macroscopic continuum and Physiologically Based Pharmacokinetic (PBPK) models that elucidate systemic distribution and overall brain exposure. We critically assess these models concerning established delivery routes, such as intranasal and intrathecal administration, as well as emerging methods, including focused ultrasound-mediated BBB opening and targeted nanoparticle delivery. This review underscores the growing importance of integrating complex physiological phenomena, such as glymphatic flow and cerebrospinal fluid (CSF) dynamics, into predictive models. Finally, we explore the emerging opportunities involving multiscale digital twins of the CNS that integrate molecular interactions, vascular hemodynamics, CSF and perivascular flow, and parenchymal transport within patient-specific anatomical geometries. The role of machine learning and surrogate modeling in expediting the prediction of drug transport parameters and optimizing delivery strategies is also examined. By providing a structured overview of current computational tools, this review aims to guide researchers in the design of more robust computational platforms for CNS drug delivery.

Keywords: CNS; blood brain barrier; alzheimer's; nanoparticle; drug delivery; computational modeling; continuum; molecular dynamics; PBPK; machine learning

1. Introduction

Central nervous system (CNS) disorders represent an escalating and expensive global health issue. Neuropsychiatric and neurodegenerative conditions are among the most pressing health challenges worldwide in this century [1]. Additionally, neurological disorders like Alzheimer's disease (AD) and Parkinson's disease (PD) predominantly impact the swiftly growing elderly demographic. Patients with primary brain tumors or brain metastases have limited treatment options, primarily depending on surgical removal, systemic chemotherapy, or radiation therapy. As a result, many pharmaceutical companies have decreased their investment in CNS drug development due to high costs, lengthy regulatory processes, and historically low clinical success rates [1].

Biomaterial-based delivery systems present a promising path for rejuvenating CNS therapeutics. Recent advances in precision biomaterial synthesis allow for the creation of carriers that can be selectively functionalized, engineered to react to physiological or external stimuli, and designed

with adjustable degradation properties [2]. Despite that, delivering therapeutic agents to the CNS remains one of the greatest challenges in drug development because of the multilayered barriers protecting the brain and spinal cord, including the blood-brain barrier (BBB), nasal mucosa, and complex cerebrospinal fluid (CSF) circulation patterns. Moreover, inter-species differences and disease effects on transport barriers add to the translation challenges. Mathematical and computational models offer great potential by simulating active targeting in the human neurovascular environment, thus paving the way for optimizing drug design and in-silico clinical trials leading to accelerated drug discovery and reduced development costs [3,4].

In this Review, we explore how both normal and diseased CNS physiology affects drug delivery to the brain. We discuss the pathophysiological barriers that complicate delivery and summarize biomaterial systems that can be administered systemically, intrathecally, intranasally, or peripherally. We then examine various classes of computational models for these CNS drug delivery approaches, detailing their key assumptions, strengths, and limitations—including physiologically based pharmacokinetic (PBPK) modeling [5,6], atomistic simulations [7,8], hybrid multiscale approaches [4,9], continuum fluid–structure and solute-transport frameworks [10,11], and machine-learning–driven prediction [12,13]. The Review concludes with a perspective on emerging opportunities for multiscale digital twins, hybrid physics–ML modeling, and clinical translation challenges.

2. Blood Brain Barrier

Delivering pharmaceuticals to the CNS presents a significant challenge due to the intricate physiological barriers, particularly the BBB. The BBB functions as a highly selective, semipermeable interface between the bloodstream and the CNS, primarily composed of brain microvascular endothelial cells connected by tight junctions [14,15]. It is crucial for maintaining CNS homeostasis by regulating nutrient flow, ionic balance, and preventing the entry of potentially harmful substances. The physical barrier of the BBB is constituted by tight junction protein complexes among endothelial cells, such as occludin, claudins, and junctional adhesion molecules (JAMs), which restrict the paracellular movement of polar solutes and large molecules [15]. Endothelial cells are supported by a basement membrane, extracellular matrix (ECM), pericytes, and astrocytic endfeet, forming the neurovascular unit (NVU), a cohesive multicellular interface that governs barrier permeability and communication between the CNS and peripheral blood. The ECM presents significant transport resistance at different levels. The vascular basement membrane, which is rich in collagen, laminins, and heparan sulfate proteoglycans, constitutes a dense, highly charged barrier that impedes diffusion and obstructs the movement of macromolecules and nanoparticles in the vicinity of CNS microvessels. Beyond the vasculature, the bulk parenchymal ECM, comprising hyaluronan, chondroitin sulfate proteoglycans, and components of astrocytic scars, further restricts solute mobility by increasing tortuosity and reducing effective diffusivity, particularly under neurodegenerative or inflammatory conditions. (Figure 1).

In addition to its physical barrier properties, the BBB also possesses a metabolic barrier composed of highly expressed efflux pumps and enzymes that metabolize or expel xenobiotics. Key transporters include P-glycoprotein (P-gp/ABCB1) and breast cancer resistance protein (BCRP/ABCG2), which prevent the accumulation of many therapeutics and endogenous metabolites in the CNS [15]. This selectivity is further reinforced by the minimal pinocytotic activity of BBB endothelial cells, which limits the nonspecific uptake of circulating molecules.

Successful CNS drug delivery depends on the ability of compounds to traverse this barrier, which is determined by their molecular size, lipophilicity, charge, and structural similarity to endogenous substrates. In healthy brain tissue, the hydrophilic cleft between adjacent endothelial cells measures approximately 0.8 nm, which is significantly narrower than the 10–25 nm intercellular gaps typically observed in non-BBB microvascular endothelium [16]. Molecules with molecular weights below approximately 400–500 Da and high lipophilicity are more likely to traverse across the BBB, although this is necessary but not sufficient for brain penetration [1]. For larger or hydrophilic molecules, entry into the CNS may occur through selective transport mechanisms, including carrier-mediated

transport (e.g., glucose, amino acids) or receptor-mediated transcytosis (e.g., insulin, transferrin). Among the available receptor targets, low-density lipoprotein receptor-related protein-1 (LRP-1) is particularly attractive because it is abundantly expressed on brain capillary endothelium and frequently overexpressed in glioblastoma, enabling dual-site receptor engagement for therapeutic delivery [1,2,14]. Conversely, certain functional groups or inappropriate charge states at physiological pH can impede passive BBB transport. Additionally, the activity of efflux pumps like P-gp significantly limits brain accumulation even for molecules with favorable passive diffusion properties [15]. Due to the complexity of BBB permeability determinants, computational modeling and *in silico* prediction tools have increasingly been employed to screen and optimize CNS drug candidates in the early stages of discovery. Quantitative structure-activity relationships (QSAR), PBPK models, and machine-learning frameworks are routinely utilized to assess BBB permeability, prioritize compounds for synthesis, and guide structural modifications [1,17].

Although the BBB is known for its restrictive properties, it does allow certain peptides and proteins to pass through via adsorptive-mediated transcytosis, especially larger cationic molecules like albumin, immunoglobulins, leptin, and growth factors. Recent advancements in drug delivery have utilized receptor- or adsorptive-mediated transcytosis with ligands such as transferrin or Angiopep-2 to facilitate the transport of therapeutic agents into the brain [2]. Nonetheless, these approaches encounter obstacles, including endosomal entrapment, receptor saturation, and unintended effects on non-target areas.

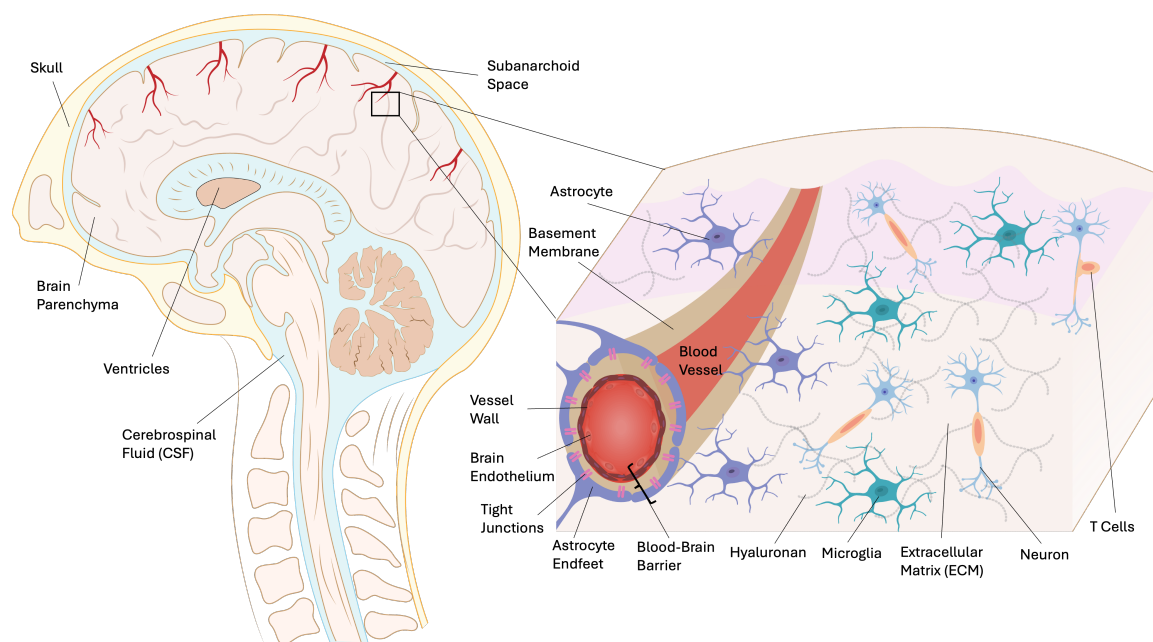


Figure 1. Central nervous system and neurovascular unit. The neurovascular unit comprises endothelial cells, pericytes, astrocytes, microglia, neurons, smooth muscle cells, and the surrounding extracellular matrix, working together to tightly regulate BBB permeability and cerebral homeostasis.

3. Pathophysiological Barriers to Effective Drug Delivery in Major CNS Diseases

The diverse pathophysiological changes associated with CNS diseases significantly alter the extracellular space, extracellular matrix, and neurovascular unit, resulting in a microenvironment that is distinctly different from that of a healthy brain. These disease-induced pathological remodeling mechanisms, which include vascular dysfunction, enzymatic remodeling, neuroinflammation, and cellular disruption, affect the structure and biophysical properties of the interstitial space, thereby impacting the penetration and distribution of drug delivery systems within the parenchyma. Such disturbances may either impede therapeutic transport by increasing tortuosity and barrier resistance or temporarily enhance permeability through the breakdown of vascular or matrix integrity. Con-

sequently, comprehending how disease physiology reconfigures these microdomains is crucial for developing delivery strategies that remain effective across various pathological contexts.

3.1. Neurodegenerative Diseases

Neurodegenerative diseases are characterized by the progressive loss of neuronal structure and function, often accompanied by pathological changes within the neurovascular unit [18,19]. Evidence of endothelial degeneration and diminished BBB function has been reported in amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Alzheimer's disease (AD), underscoring the central role of neurovascular dysfunction in aging-related neurodegeneration [15]. BBB breakdown often precedes clinical symptoms and results from the compounding effect of increased reactive gliosis, neurovascular uncoupling, heightened neuroinflammation, and progressive neuronal decline [20]. These processes reflect the collapse of CNS homeostasis and pose substantial challenges for the systemic and local delivery of therapeutics. Neurovascular alterations also manifest in psychiatric conditions such as schizophrenia and chronic stress disorders. These include basement membrane thickening, astrocytic end-foot retraction, microglial activation, and chronic inflammation in the perivascular compartments (Figure 2). Emerging evidence indicates that vascular dysfunction in these disorders often precedes overt neuronal damage, supporting its causative role in pathology and cognitive dysfunction [21,22]. Chronic BBB dysregulation contributes to secondary pathologies that impede drug penetration into the CNS. Downregulation of tight junction proteins increases endothelial permeability, leading to perivascular space (PVS) enlargement and the accumulation of plasma-derived neurotoxic proteins, such as fibrinogen. Concurrently, vascular dysfunction drives ECM modifications within both the vascular basement membrane and the parenchymal interstitium. The modifications include amyloid deposition, sulfated proteoglycan accumulation, and glial scarring, which impair neurovascular integrity and transport properties. Pericytes, which are pivotal for maintaining BBB structure and function, are progressively lost in angiopathy associated with neurodegeneration, resulting in microvascular rarefaction and compromised perfusion [23–26]. These microenvironmental adaptations create barriers that challenge traditional drug delivery strategies. Formulations optimized for intact BBB penetration are hindered by altered vascular architecture, dysfunctional glymphatic clearance, and expanded perivascular spaces (PVS), necessitating innovative strategies that exploit or circumvent these pathological changes.

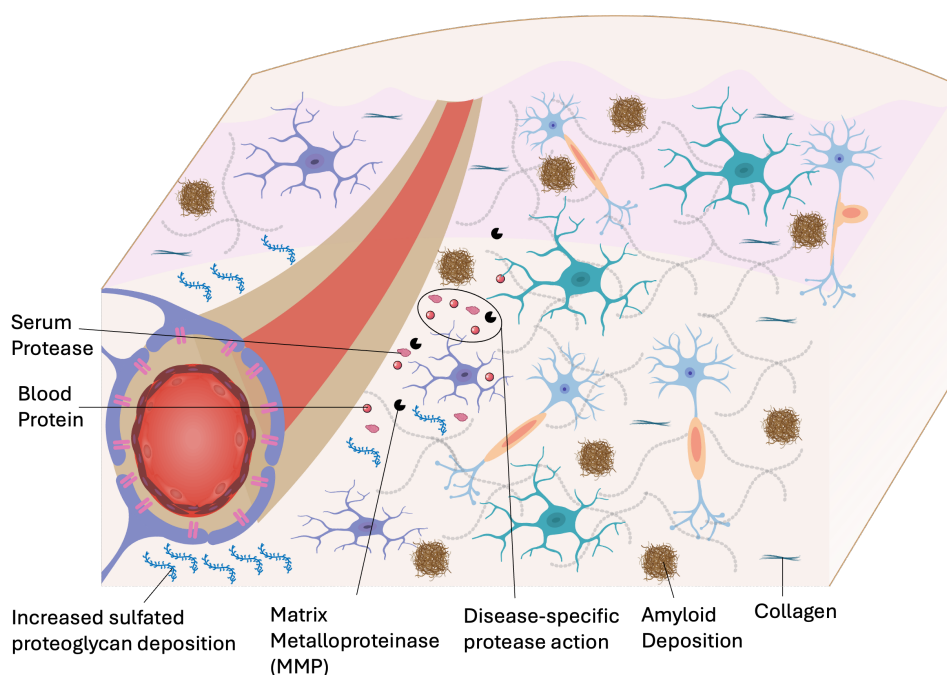


Figure 2. Neurodegeneration physiology is characterized by increased amyloid and sulfated proteoglycan deposition. Together with disease-specific protease action, these are targets for drug delivery.

3.1.1. Alzheimer's Disease

Alzheimer's disease (AD) is characterized by extracellular amyloid- β ($A\beta$) plaque formation, tau hyperphosphorylation, synaptic loss, and progressive cognitive impairment. Microvascular dysfunction is increasingly recognized not only as a consequence but also as a driver of AD pathology [27]. BBB compromise, characterized by tight junction disruption, pericyte loss, and vessel fragmentation, often arises years before the onset of clinical symptoms [28]. Vascular and metabolic dysfunction impair perivascular clearance of $A\beta$, exacerbating its deposition and accelerating neurodegeneration [29]. Impaired clearance pathways and ECM stiffening associated with amyloid accumulation adversely affect the transport and diffusion of therapeutics, particularly biologicals and nanoparticles. In response, advanced delivery platforms, such as receptor-mediated transcytosis systems, transferrin-targeted nanocarriers, and focused ultrasound-assisted BBB opening, have been developed to enhance drug penetration [14]. However, disease heterogeneity, particularly with regional variations in vascular and glymphatic integrity, underscores the need for precision delivery strategies tailored to pathological profiles of the patients.

3.1.2. Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune demyelinating condition characterized by neuroinflammation and neurodegeneration. Disruption of BBB integrity is an early and critical pathological event that allows larger solutes, as well as autoreactive T-cells and monocytes to infiltrate the CNS and propagate demyelinating damage [30]. Neuroinflammation in MS amplifies glial activation, upregulates matrix metalloproteinases (MMPs), and disrupts tight junction proteins, impairing tissue repair and exacerbating the axonal injury. Drug delivery in MS is challenged by the coexistence of inflamed, permeable BBB regions and intact barriers, requiring strategies that can selectively target pathological zones. Nanoparticle carriers functionalized to bind inflammatory endothelial markers, anti-CD49d-modified microparticles, and intrathecal administration bypassing systemic circulation are being investigated for the effective delivery of immunomodulatory molecules to the CNS [31,32]. However, beyond immunomodulation, significant challenges remain in achieving durable neuroprotection and remyelination, including limited targeting of oligodendrocyte precursor cells, an inhospitable inflammatory lesion microenvironment, and poor integration with endogenous repair pathways [33,34]. In addition, intrathecal delivery introduces distinct barriers related to compartmentalized neuroinflammation, altered CSF dynamics, and nonuniform drug distribution across focal and diffuse lesions [35]. Emerging theranostic strategies aim to address these limitations by integrating imaging-guided delivery with lesion-specific therapeutic interventions.

3.1.3. Parkinson's Disease

Parkinson's disease (PD), historically regarded as a dopaminergic disorder of the substantia nigra, is now recognized to involve considerable vascular pathologies. Early stages of PD exhibit BBB disruption, endothelial dysfunction, and altered angiogenesis, contributing to neuronal vulnerability. Reduced expression of tight junction proteins and transformation of PVS morphology foster neuroinflammation and diminish neuroprotection [36]. Aggregated alphasynuclein, a PD biomarker, accumulates in the perivascular regions, further impairing glymphatic clearance pathways [37]. Therapeutic delivery to PD-affected brain regions is hindered by BBB disruption and inflammation and microvascular stress. Focused ultrasound (FUS) combined with microbubbles has been used experimentally to transiently open the BBB, facilitating the targeted delivery of neuroprotective agents, including GDNF and anti-alpha-synuclein antibodies [38]. Meanwhile, biomaterial-based approaches — such as injectable hydrogels and cell-laden scaffolds — offer local and sustained delivery options aimed at enhancing substantia nigra resilience and neuroregeneration.

3.2. Stroke

Stroke is a complex cerebrovascular disorder encompassing both ischemic and hemorrhagic etiologies, with a lifetime risk of approximately one in four individuals worldwide [39]. Each year,

an estimated 14 million people experience stroke globally, of which approximately 70% are ischemic and approximately 30% hemorrhagic in origin [40]. The acute and chronic phases of stroke are marked by distinct pathophysiological changes that significantly affect drug delivery strategies both systemically and locally. These include dynamic alterations of BBB integrity, neuroinflammation involving multiple pathways and cell types, ECM remodeling, oxidative stress, and changes in cell–cell communication (Figure 3). Acute ischemic stroke occurs due to the occlusion of cerebral vessels responsible for regional perfusion, leading to neuronal hypoxia, excitotoxicity, and potentially irreversible damage within minutes [41]. The current first-line pharmacological therapy involves the intravenous administration of recombinant tissue plasminogen activator (tPA), which catalyzes plasmin-mediated clot dissolution [42]. While tPA has demonstrated functional benefits in several randomized controlled trials [EAST, NINDS, and ECASS III], its use is limited by a narrow therapeutic time window (<4.5 hours post-onset) and an increased risk of hemorrhagic transformation, especially at the standard systemic dose of 0.9 mg/kg [43,44].

To overcome these limitations, biomaterial-based drug delivery systems are being developed to enhance tPA specificity and modulate its mechanical release. Examples include targeted nanocarriers [45], fibrin-binding polymers [46], ultrasound-triggerable microbubbles, and matrix-anchored drug depots. These approaches aim to extend the therapeutic window while reducing systemic exposure and the associated hemorrhagic risks. Endovascular thrombectomy has revolutionized ischemic stroke management, offering significant improvements in functional outcomes for patients with large vessel occlusions. Using intra-arterial catheters, mechanical devices can retrieve obstructing thrombi up to 24 h post-stroke in selected patients with favorable imaging profiles (e.g., perfusion–diffusion mismatch) [47,48]. Moreover, these interventions enable the locoregional delivery of neuroprotective agents, anticoagulants, and anti-inflammatory molecules directly at the site of injury, bypassing systemic circulation and minimizing off-target effects. Combining thrombectomy with localized drug delivery systems, such as intra-arterial microspheres, polymeric nanocarriers, or responsive hydrogels, is being explored to modulate reperfusion injury, curb inflammatory cascades, and augment neuronal survival following recanalization.

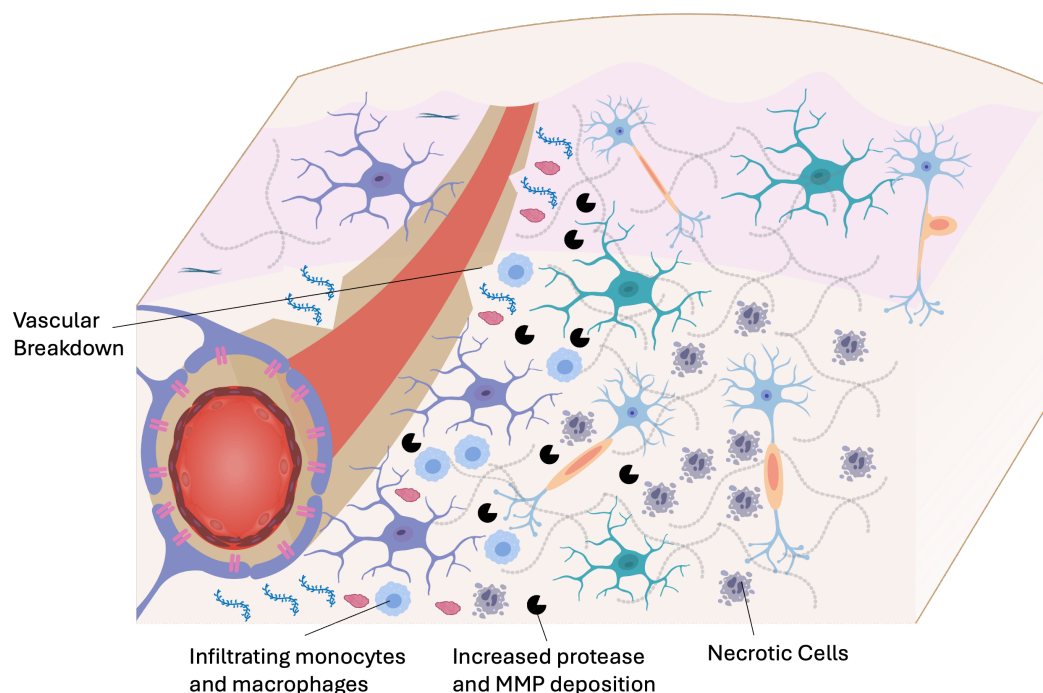


Figure 3. In stroke, vascular breakdown leads to increased tissue permeability, edema, and tissue necrosis. Major targets for drug delivery include infiltrating monocytes and macrophages as well as increased protease and MMP activity.

Following the acute period, stroke enters the subacute and chronic phases, marked by complex neuroinflammation, glial activation, angiogenesis, and ECM remodeling. These processes often culminate in a hostile microenvironment characterized by glial scar formation, hindering axonal regeneration and plasticity. Chondroitin sulfate proteoglycans (CSPGs), major components of the glial scar, act as physical and biochemical inhibitors of neural repair. The localized delivery of chondroitinase ABC, an enzyme that degrades CSPGs, has shown potential in promoting neuroplasticity and functional recovery in preclinical models [49,50]. Matrix metalloproteinases (MMPs) are another class of ECM-modifying enzymes relevant to stroke therapy. While their premature activation may exacerbate secondary injury in the acute phase, controlled MMP activity (>1 week post-stroke) can support remodeling, angiogenesis, and repair [51]. Drug delivery systems based on hydrogels [49], biodegradable microspheres [52], or nanoparticle formulations [53] have been engineered for the timed and localized release of MMPs or MMP inhibitors based on specific physiological cues. Numerous agents targeting neuroinflammation, oxidative stress, and immune modulation are being evaluated for stroke therapy. Candidates such as minocycline, natalizumab, fingolimod, and uric acid have shown promise in modulating microglial activation, leukocyte infiltration, and oxidative damage [54,55]. Additionally, the delivery of growth factors (e.g., BDNF, VEGF), stem cell-supportive cues, or gene-regulating microRNAs is being explored using depot materials or injectable scaffolds to support neural recovery and stem cell integration [56]. Innovative delivery strategies based on physiology-responsive materials, such as pH-sensitive polymers or enzyme-responsive carriers, and minimally invasive methods, such as intranasal or intra-arterial administration, have shown the capacity to bypass compromised vasculature and target specific brain regions affected by stroke [57–59].

3.3. Brain Tumors

Gliomas are the most common type of primary brain tumor, with glioblastoma multiforme (GBM) being the most aggressive and prevalent subtype. GBM is characterized by rapid infiltrative growth of tumor cells, breakdown of BBB, profound genomic instability, and elevated interstitial pressure leading to resistance against conventional treatment (Figure 4). Despite multimodal clinical care, including surgical resection, temozolomide chemotherapy, and radiotherapy, the median survival for GBM remains approximately 12–15 months [60]. Beyond primary brain malignancies, approximately 9–17% of all cancer patients develop brain metastases, frequently originating from breast, lung, and melanoma cancers [61]. Similar to GBM, metastatic brain tumors face anatomical and physiological barriers that complicate effective drug delivery.

The ECM in gliomas undergoes extensive remodeling, distinguishing it from normal brain parenchyma. Glioma cells upregulate the deposition of ECM components, such as fibronectin, tenascin-C, and hyaluronan, as well as matrix-bound growth factors not found in healthy brain tissue [62]. These components create a stiffened tumor microenvironment that not only supports tumor proliferation and migration but also hinders the penetration of drugs. Proteolytic enzymes, including matrix metalloproteinases (MMPs), urokinase plasminogen activator (uPA), and cathepsins, are overexpressed by glioma cells to degrade ECM barriers and facilitate invasion into surrounding tissues [63]. This knowledge has inspired the design of protease-responsive drug delivery systems, in which nanocarriers or hydrogels are engineered to release therapeutics in response to enzyme activity within the tumor microenvironment [64].

Gliomas profoundly reshape the immune landscape within the CNS. Tumor-derived signals recruit tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and immunosuppressive T cells, promoting an immunosuppressive niche. These cells not only facilitate tumor growth but also offer opportunities for cell-mediated drug delivery, where circulating immune cells are loaded with therapeutics or engineered *ex vivo* to penetrate the brain and target tumors [65]. Moreover, immunotherapies such as CAR-T cells, dendritic cell vaccines, and immune checkpoint blockade are being investigated for brain tumors and present further tumor-selective drug delivery options, despite the challenges posed by the immunosuppressive microenvironment [66].

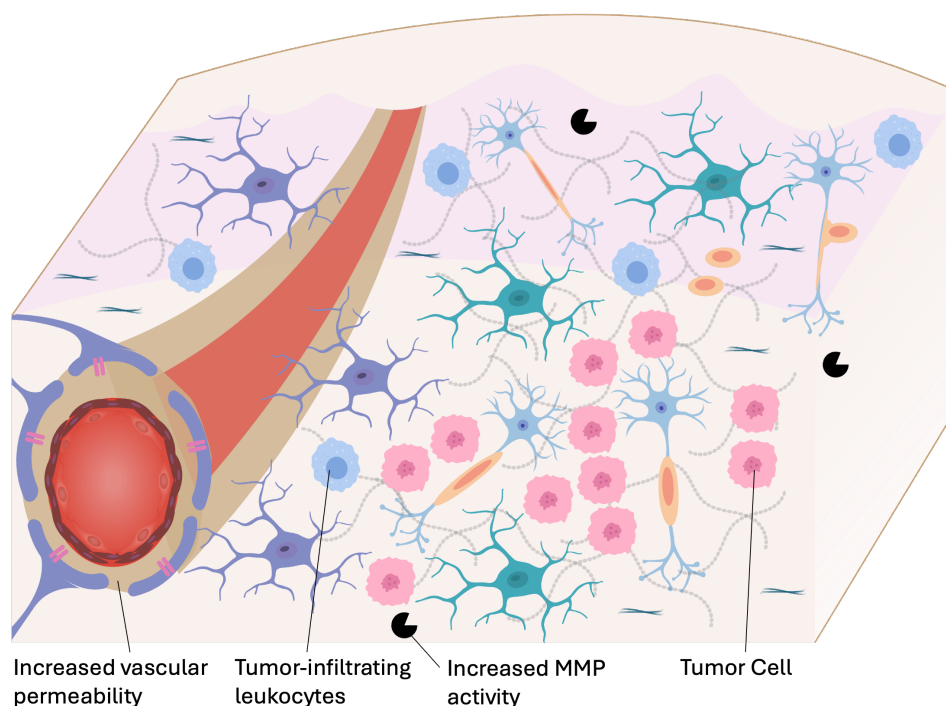


Figure 4. Brain tumors disrupt CNS physiology through breakdown of the blood–brain barrier, abnormal and leaky angiogenesis, and elevated interstitial pressure that impairs perfusion and drug delivery. Tumors induce chronic neuroinflammation, remodel the extracellular matrix via proteases, and create hypoxic, metabolically reprogrammed microenvironments.

A key challenge in treating brain tumors is the restrictive nature of the BBB, which acts as a selective interface to maintain cerebral homeostasis. However, in malignant gliomas, the BBB undergoes pathological modifications, creating what is referred to as the blood–tumor barrier (BTB) [67]. The BTB exhibits heterogeneous permeability, with regions of increased vessel leakiness interspersed with areas retaining an intact or partially intact BBB. This abnormal vasculature arises from tumor-induced angiogenesis driven by proangiogenic factors, such as vascular endothelial growth factor (VEGF) [68]. While increased permeability can facilitate drug access to certain tumor regions, it is insufficient for uniform drug distribution throughout the highly infiltrative tumor margins, where BBB function is often preserved [69]. These perfusion gradients lead to differential drug exposure, contributing to therapy resistance and tumor recurrence.

Despite BTB leakiness, systemic drug delivery remains inefficient because of heterogeneous distribution, drug efflux pumps (e.g., ABC transporters), and elevated intracranial pressure. Locoregional strategies, including convection-enhanced delivery (CED), ultrasound-mediated BBB opening, and implantable polymer wafers (e.g., Gliadel), have been developed to bypass these vascular barriers and deliver high local drug concentrations directly into or near the tumor [70,71]. Focused ultrasound (FUS) with microbubbles has emerged as a promising tool for transiently opening the BBB or BTB at precise anatomical sites, enhancing drug penetration without permanent barrier damage [72]. Biodegradable hydrogels and nanoparticles are being further refined for use in postoperative resection cavities or as systemic carriers that exploit tumor-specific cues.

4. Approaches for CNS Drug Delivery

Systemic administration to the CNS remains challenging due to the restrictive properties of the BBB. Recent advancements in nanotechnology have enhanced systemic delivery by incorporating small molecules, peptides, and nucleic acids into biocompatible lipid nanoparticles (LNPs), polymeric nanoparticles (PLGA, PEG-PCL), and liposomes, which protect the drugs from degradation and extend circulation time [55]. Hydrophobic small molecules are particularly well-suited to liposomal or lipid-based carriers due to strong bilayer interactions, whereas nucleic acids (siRNA, mRNA, plasmids)

benefit from ionizable lipids or polymeric carriers capable of endosomal escape [73]. Exosomes have emerged as promising natural carriers for proteins and RNA, offering superior biocompatibility, although they are limited by low loading efficiency and scalability [74]. While these carriers enhance drug stability and circulation, their systemic use can result in off-target distribution, rapid clearance by the mononuclear phagocyte system, and variability in BBB penetration. Local delivery strategies, including CED, ultrasound-mediated BBB opening, and Gliadel wafers, have been developed to bypass these systemic barriers [71]. Below we provide a schematic diagram (Figure 5) and a brief comparison of major approaches for CNS drug delivery (Table 1).

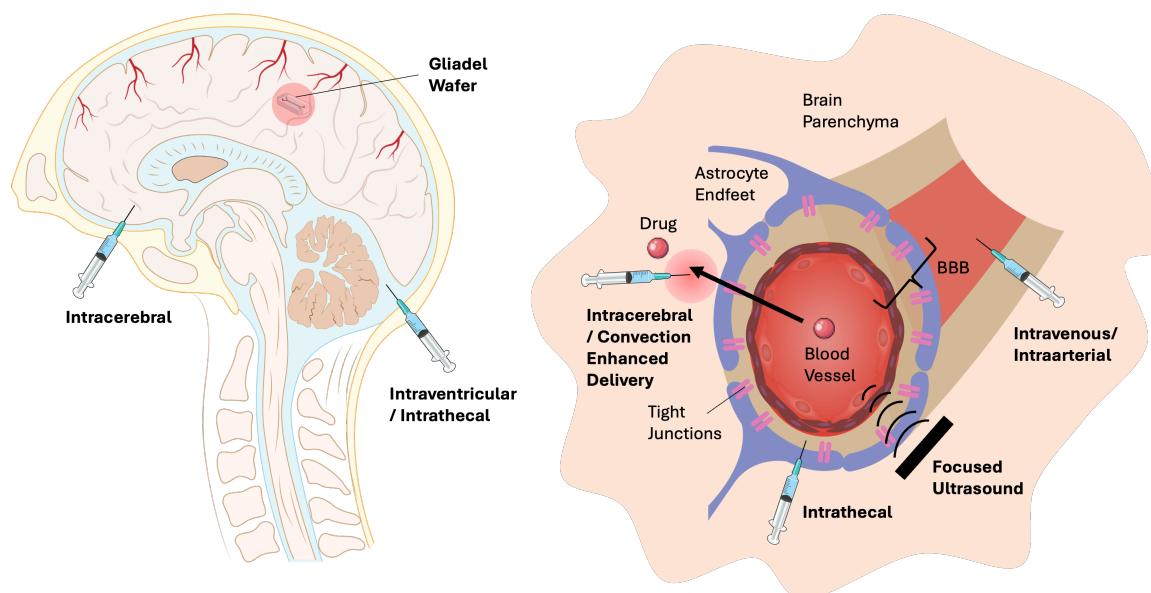


Figure 5. Schematic diagram showing major drug delivery approaches to the CNS.

4.1. Intravenous Drug Delivery

Intravenous (IV) administration remains the predominant method for CNS drug delivery; however, its efficacy is inherently constrained by the restrictive nature of the BBB. While small lipophilic compounds may traverse passively, most biologics and nucleic-acid therapies rely on receptor-mediated transcytosis pathways, such as those targeting the transferrin (TfR) receptor [75]. Advanced carriers, including PEGylated immunoliposomes, lipid nanoparticles (LNPs), and polymeric nanoparticles, enhance circulation time, stability, and ligand-specific uptake; nonetheless, their overall brain penetration remains limited [76,77]. Engineered exosomes have emerged as promising natural carriers for proteins and RNA, offering superior biocompatibility, although they are limited by low loading efficiency and scalability [78]. To augment IV delivery, pharmacological BBB modulation has been investigated using hyperosmotic agents (e.g., mannitol), bradykinin analogs, and histamine derivatives to transiently widen tight junctions and increase paracellular permeability. This controlled opening facilitates the passage of large molecules, including antibodies, enzymes, and nanoparticle-encapsulated therapeutics, and can be synergistic with nanoformulations whose size and surface properties are optimized to exploit these transient windows of permeability [79,80]. However, both IV delivery and pharmacological BBB disruption encounter limitations, including systemic toxicity, heterogeneous permeability, and risks of cerebral edema or neuroinflammation, underscoring the necessity for more targeted, reversible, and disease-aware strategies for CNS drug delivery.

4.2. Intra-Arterial Drug Delivery

Intra-arterial (IA) administration delivers therapeutics directly into brain-supplying arteries, achieving higher local concentrations while limiting systemic exposure [81]. This approach is suitable for chemotherapeutics, neuroprotective small molecules, nanoparticles, and stem cells in stroke and brain tumors. Polymeric nanoparticles (e.g., PLGA, PEG-NPs) and liposomes perform well due to

controlled release and vascular interactions [82]. Pharmaceutical BBB disruption is again used to transiently open tight junctions, enabling enhanced IA delivery of antibodies and nanoparticle-based drugs. IA delivery of resveratrol-loaded nanoparticles enhances neuroprotection after ischemia–reperfusion injury [83]. Limitations include the risk of embolism (notably with cells), BBB permeability constraints, and hemodynamic variability.

4.3. Focused Ultrasound

Focused ultrasound (FUS) is an enabling BBB-modulation strategy used in conjunction with systemic (typically IV) drug administration. Along with microbubbles, it produces spatially targeted, reversible BBB opening, facilitating delivery of antibodies, chemotherapeutics, nucleic acids, and stem cells [84]. Liposomal doxorubicin, polymeric nanoparticles, and LNP-siRNA formulations show significantly enhanced uptake with FUS [85]. Microbubble–nanoparticle hybrids offer integrated imaging and delivery functionalities [86]. Challenges include variability in BBB opening, microhemorrhage risk at high intensities, and the need for MRI guidance for targeted delivery. However, commercial products are available for image (MRI) - guided FUS BBB disruption [87,88].

4.4. Transnasal (Intranasal) Delivery

Intranasal delivery exploits the olfactory and trigeminal neural pathways to circumvent the BBB, enabling direct access to the CNS and allowing administration of proteins, peptides, gene therapies, and stem cells without systemic exposure [89]. Peptides such as vasoactive intestinal peptide (VIP), brain-derived neurotrophic factor (BDNF), and nucleic acids (siRNA, mRNA) have been successfully delivered via this route due to short transport distances and avoidance of hepatic metabolism [90,91]. Suitable carriers include mucoadhesive polymeric nanoparticles (chitosan, PEG-PCL), lipid nanoparticles, nanoemulsions, and engineered exosomes [92]. Exosomes provide excellent biological compatibility and neuronal tropism, although manufacturing challenges persist [93]. The limitations of intranasal delivery include small dosing volumes, mucociliary clearance, and potential epithelial toxicity at high nanoparticle concentrations.

4.5. Intrathecal and Intraventricular Delivery

The intrathecal (IT) and intraventricular (IVT) routes bypass the BBB by administering therapeutics directly into cerebrospinal fluid (CSF), ideal for macromolecules such as enzymes, nucleic acids, peptides, and chemotherapeutics [31]. Hydrogels, liposomes, and polymeric nanoparticles serve as effective carriers, enabling sustained release and reduced dosing frequency [94]. Exosomes show promise for gene and protein delivery with minimal immunogenicity, though CSF flow limits distribution [95]. Risks include infection, catheter malfunction, and uneven drug distribution.

4.6. Intracerebral Injection

Intracerebral injection facilitates the highly localized delivery of adeno-associated virus (AAV) vectors, CRISPR systems, neurotrophic factors, and oncolytic viruses, with viral vectors remaining the predominant modality due to their high transduction efficiency, despite concerns regarding immunogenicity [96,97]. Hydrogels, dendrimers, and other biomaterial carriers further support the local deposition of proteins, enzymes, engineered cells, and nucleic acid therapies, although this method is inherently invasive and offers limited tissue coverage beyond the injection site. CED builds on the same principle of direct parenchymal access but utilizes pressure-driven bulk flow to achieve a significantly broader distribution of chemotherapeutics, proteins, nucleic acids, and viral or cellular therapeutics [98]. Although traditionally performed through intracerebral cannulation, similar pressure-assisted infusion principles have also been applied in intratumoral, intraventricular, and intrathecal contexts; nevertheless, the most robust experimental and clinical evidence for CED remains anchored in parenchymal delivery. Nanoformulations, such as liposomes and polymeric nanoparticles, are particularly well-suited for CED due to their size control and structural stability, whereas hydrogels and exosomes enable sustained release and efficient movement through extracellular matrix

microchannels [99]. Despite these advantages, both intracerebral injection and CED encounter procedural challenges, including catheter backflow, mechanical tissue disruption, and heterogeneous tissue resistance, necessitating careful optimization of infusion parameters and delivery geometry.

4.7. Polymeric Wafer Implants for Local Drug Delivery

Gliadel wafers represent one of the earliest clinically implemented and FDA-approved strategies for localized chemotherapeutic delivery to brain tumors, specifically engineered to overcome the significant transport limitations imposed by the BBB [100]. These biodegradable polyanhydride implants, containing the alkylating agent carmustine (BCNU), are strategically placed directly into the surgical resection cavity during glioma surgery. As the polymer matrix undergoes hydrolytic degradation, it releases high concentrations of BCNU into the surrounding parenchyma, facilitating penetration into infiltrative tumor margins while minimizing systemic exposure and toxicity. This localized approach entirely bypasses vascular barriers and provides sustained drug release over a period of days to weeks, thereby offering therapeutic access to regions that are poorly perfused or inaccessible through intravascular routes [71,101]. In contrast, systemically administered chemotherapeutics encounter substantial challenges in reaching brain tumors. The intact BBB at infiltrative margins restricts passive drug entry, while the abnormal, heterogeneous vasculature within tumor cores results in inconsistent perfusion, elevated interstitial fluid pressure, and rapid drug efflux. Diffusion through a dense extracellular matrix, metabolic degradation, and poor transcytosis further limit effective intratumoral concentrations. Collectively, these features create a highly restrictive microenvironment for drug transport, underscoring the necessity for localized delivery platforms such as Gliadel wafers or convection-enhanced delivery in contemporary neuro-oncology. Gliadel wafers are limited by their shallow drug penetration (only 1–3 mm), which prevents BCNU from reaching infiltrative tumor cells that extend beyond the resection margin. They can only be implanted during surgery, carry risks of local toxicity and edema, and provide fixed, non-adjustable dosing. As a result, their clinical benefit is modest and insufficient for highly invasive gliomas like GBM.

Table 1. Comparison of major CNS drug-delivery approaches, including carriers, disease applications, strengths, limitations, and references.

Approach	Suitable Drug Carriers	Disease Targets	Strengths	Limitations	Key References
Intravenous (IV) Delivery	<ul style="list-style-type: none"> • PEGylated immunoliposomes • Lipid nanoparticles • Polymeric nanoparticles • Engineered exosomes 	<ul style="list-style-type: none"> • AD, PD, MS • Glioma, metastases • Gene and RNA therapies 	<ul style="list-style-type: none"> • Clinically mature and scalable • Supports ligand-targeted RMT • Compatible with biologics/RNA drugs • Synergistic with pharmaceutical BBB modulation 	<ul style="list-style-type: none"> • Limited BBB penetration • Systemic toxicity • Heterogeneous BBB permeability • Edema and inflammation risk 	[76,77,80]
Intra-arterial (IA) Delivery	<ul style="list-style-type: none"> • PLGA and PEG-NPs • Liposomes • Nanoemulsions • Stem cells 	<ul style="list-style-type: none"> • Stroke • Brain tumors • Ischemia–reperfusion injury 	<ul style="list-style-type: none"> • High local concentration • Reduced systemic exposure • Effective for nano/formulated drugs 	<ul style="list-style-type: none"> • Embolism risk (cells) • BBB limits penetration • Hemodynamic variability 	[81,83]
Focused Ultrasound (FUS)	<ul style="list-style-type: none"> • Liposomal doxorubicin • Polymeric nanoparticles • LNP–siRNA • Microbubble–NP hybrids 	<ul style="list-style-type: none"> • AD, PD • Glioma • Brain metastases • Protein/antibody delivery 	<ul style="list-style-type: none"> • Local, reversible BBB opening • MRI-guided spatial precision • Enhances uptake of large molecules • Supports theranostic strategies 	<ul style="list-style-type: none"> • Variable BBB permeability • Microhemorrhage risk • Requires imaging support 	[84–86]
Intranasal Delivery	<ul style="list-style-type: none"> • Mucoadhesive polymeric NPs • Lipid nanoparticles • Nanoemulsions • Engineered exosomes 	<ul style="list-style-type: none"> • AD, PD • Epilepsy, stroke • Brain tumors (adjunct) • Peptide and RNA therapies 	<ul style="list-style-type: none"> • Bypasses BBB entirely • Non-invasive, rapid CNS access • Avoids hepatic metabolism • Suitable for proteins and RNA 	<ul style="list-style-type: none"> • Small dosing volume • Mucociliary clearance • Epithelial toxicity at high dose • Anatomical variability 	[90–92]
Intrathecal / Intraventricular Delivery	<ul style="list-style-type: none"> • Hydrogels • Liposomes • Polymeric nanoparticles • Exosomes 	<ul style="list-style-type: none"> • Lysosomal storage disorders • Tumors • Chronic pain • Gene/protein delivery 	<ul style="list-style-type: none"> • Bypasses BBB • Ideal for large biologics • Enables sustained release • Avoids systemic toxicity 	<ul style="list-style-type: none"> • Infection/catheter risks • CSF flow–limited distribution • Variable parenchymal penetration 	[31,94]
Intracerebral Injection	<ul style="list-style-type: none"> • AAV/viral vectors • Hydrogels • Dendrimers • Liposomes & polymeric NPs • Exosomes 	<ul style="list-style-type: none"> • GBM, DIPG • PD gene therapy • Epilepsy • Focal degeneration 	<ul style="list-style-type: none"> • Precise anatomical targeting • High local concentrations • CED achieves wide distribution • Compatible with cellular/genetic therapies 	<ul style="list-style-type: none"> • Highly invasive • Tissue injury/backflow risk • Heterogeneous tissue resistance • Limited spread without CED 	[97–99]
Polymeric Wafer Implants (Gliadel)	<ul style="list-style-type: none"> • Carmustine (BCNU) • Polyanhydride matrices • Drug-loaded biodegradable wafers • Local chemotherapeutic depots 	<ul style="list-style-type: none"> • GBM, high-grade glioma • Post-resection residual disease • Local tumor recurrence 	<ul style="list-style-type: none"> • Completely bypasses BBB • Sustained local release (days–weeks) • High BCNU concentration at tumor margins • Minimizes systemic toxicity 	<ul style="list-style-type: none"> • Shallow penetration (1–3 mm) • Only for surgical cases • Local edema, seizures, wound issues • Fixed, non-adjustable dosing 	[71,100,101]

5. Modeling Approaches

The diversity of delivery routes, including systemic intravenous administration across the BBB, intrathecal delivery into CSF spaces, intranasal nose-to-brain pathways, and FUS-mediated BBB opening, necessitates computational frameworks capable of capturing processes across the molecular, cellular, tissue, and organ scales. Computational modeling efforts have historically developed along distinct methodological lines, including pharmacokinetic/pharmacodynamic (PK/PD) models, molecular dynamics (MD) simulations, hybrid and multiscale frameworks, and continuum biophysical models based on computational fluid dynamics (CFD). Recently, machine learning (ML) and data-driven approaches have become prominent, complementing mechanistic models and enabling predictions from high-dimensional datasets. This review organizes CNS drug delivery modeling into five major paradigms and examines their core assumptions, mathematical structures, applications to each delivery route, and persistent challenges (Table 2). The goal is to provide a unified picture of the multi-scale modeling landscape and outline integrative paths forward for next-generation CNS drug-delivery design.

5.1. Physiologically Based Pharmacokinetic (PBPK) Models

PBPK and related pharmacokinetic/pharmacodynamic (PK/PD) models conceptualize organisms as networks of interconnected compartments, which correspond to the plasma, peripheral organs, subregions of the brain, and, in certain instances, explicit CSF spaces. Within each compartment, drug concentrations are assumed to be spatially homogeneous, with intercompartmental transfer driven by blood flow, membrane permeability, or empirically estimated rate constants. In the context of CNS drug delivery, PBPK models typically differentiate between blood, brain tissue, and CSF, aiming to mechanistically separate BBB permeation from tissue binding, metabolism, and clearance.

One of the earliest mechanistic PBPK frameworks for CNS delivery was developed by Ball et al., who modeled BBB exchange in rats by decomposing brain uptake into permeability-driven transport and reversible binding within brain tissue [102]. This framework was subsequently extended and generalized to preclinical CNS drug development by the authors [103]. Subsequent work by Yamamoto et al. formalized CNS PBPK structures capable of predicting concentration-time profiles across multiple brain and CSF compartments [5]. More recent works have highlighted PBPK as a model-informed drug development (MIDD) tool for CNS therapeutics, summarizing its strengths and limitations in capturing BBB transport, CSF turnover, and species-specific differences [104,105].

Mathematically, PBPK models consist of coupled ordinary differential equations that enforce mass balance in each compartment. For a two-compartment blood–brain model, the governing equations can be written as

$$\frac{dC_{\text{blood}}}{dt} = \frac{Q_{\text{brain}}}{V_{\text{blood}}}(C_{\text{art}} - C_{\text{blood}}) - \frac{P_{\text{BBB}}A_{\text{BBB}}}{V_{\text{blood}}}(C_{\text{blood}} - C_{\text{brain}}) - k_{\text{elim,sys}}C_{\text{blood}}, \quad (1)$$

$$\frac{dC_{\text{brain}}}{dt} = \frac{P_{\text{BBB}}A_{\text{BBB}}}{V_{\text{brain}}}(C_{\text{blood}} - C_{\text{brain}}) - k_{\text{elim,brain}}C_{\text{brain}}, \quad (2)$$

where C , Q , and V are the drug concentration, flow rate, and volume in each compartment, respectively. C_{art} is the arterial input concentration of drug. P_{BBB} is the permeability of the BBB accounting for the passive, A_{BBB} is the BBB surface area, and $k_{\text{elim,*}}$ denotes systemic and brain elimination rate constants.

In many CNS applications, Equations (1)–(2) are augmented with a permeation flux J that models an additional exchange pathway. For the case of a saturable receptor-mediated transcytosis (RMT), the flux takes the form

$$J_{\text{RMT}} = \frac{V_{\text{max}}C_{\text{blood}}}{K_m + C_{\text{blood}}}, \quad (3)$$

where V_{max} and K_m are the maximum transport capacity of the RMT pathway and the Michaelis–Menten constant, respectively. Equation (3) is first converted into volumetric concentration rate through multiplication by (A_{BBB}/V) , and then the resulting term is incorporated as

a loss in the blood compartment (Equation (1)) and a corresponding gain in the brain compartment (Equation (2)). Sato et al. recently leveraged such a formulation in a translational PBPK model of transferrin receptor (TfR)-mediated brain delivery, demonstrating a bell-shaped dependence between ligand affinity (K_d) and brain exposure arising from the competition between binding and recycling kinetics [6].

In the context of systemic delivery across the BBB, PBPK models are typically integrated into comprehensive whole-body frameworks. These frameworks incorporate perfusion-limited or permeability-limited transport terms for various tissues. Brain compartments may be further divided into vascular, interstitial, and intracellular spaces, or into anatomically distinct regions such as the cortex, CSF, and tumor tissue, each characterized by unique permeabilities, blood flows, or binding capacities [106,106]. These models have been applied to both small molecules and biologics, with particular emphasis on interspecies differences in transporter systems and receptor expression levels.

Intrathecal and intra-CSF delivery are incorporated into PBPK structures by introducing dedicated CSF compartments (e.g., lumbar, cisternal, and ventricular spaces) and specifying the exchange rate constants that describe CSF turnover and CSF-to-brain transfer. In these models, complex CSF hydrodynamics, including pulsatility and mixing, are typically simplified into effective clearance or transfer coefficients. Monine et al. described such CNS-expanded PBPK frameworks and highlighted their utility in predicting CSF drug exposure and brain penetration following intrathecal administration [107]. Other translational studies have integrated CSF pharmacokinetic (PK) profiles with intracerebral microdialysis or imaging to infer effective tissue permeabilities [108].

For intranasal nose-to-brain delivery, PK models generally introduce a nasal dosing compartment with two parallel uptake routes: (i) systemic absorption followed by BBB transport and (ii) direct transport via olfactory and trigeminal pathways. Drath et al. summarized preclinical evidence supporting these parallel pathways and described PK analyses that attempt to deconvolve direct brain uptake from indirect systemic contributions [109]. Rygg and colleagues have proposed combining such PK structures with computational fluid dynamics (CFD)-derived regional deposition estimates to evaluate bioequivalence for nose-to-brain drug products [110].

Focused ultrasound (FUS)-mediated BBB opening is naturally incorporated into PBPK models by allowing the BBB permeability P_{BBB} to become a time-dependent function $P_{\text{BBB}}(t)$ that increases transiently following sonication. Burgess et al. reviewed the underlying mechanism through which microbubble-assisted FUS disrupts the BBB, providing an experimental basis for such PBPK extensions [111]. Subsequent preclinical and clinical studies have quantified the magnitude and duration of BBB opening with neuronavigation-guided FUS, enabling the incorporation of temporally resolved permeability profiles into PBPK models [112].

Overall, PBPK models are adept at capturing systemic disposition, inter-organ exchange, and intersubject variability at a relatively low computational cost. They are highly valuable for dose selection, sensitivity analyses, and species scaling. However, their assumptions of well-mixed compartments and the lack of explicit anatomical geometry limit their ability to capture spatially heterogeneous processes that are critical in intrathecal, intranasal, and FUS-modulated delivery. Parameter uncertainty remains a key challenge, particularly in BBB permeability, CSF-to-brain exchange rates, and nanoparticle-specific transport kinetics.

5.2. Continuum Models

Continuum models represent one of the most advanced classes of computational methodologies for CNS drug delivery, particularly for pathways where fluid dynamics and anatomical geometry significantly influence solute distribution. Within these frameworks, blood or CSF is modeled as an incompressible continuum, the brain parenchyma as a porous medium, and therapeutics as solutes transported through advection, diffusion, and reaction processes. The governing equations comprise the incompressible Navier–Stokes equations for CSF or blood flow, coupled with advection–diffusion–reaction equations for solute transport, and in porous tissues, Darcy or Darcy–Brinkman constitutive relations.

For an incompressible fluid, the Navier–Stokes equations take the form

$$\rho \left(\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} \right) = -\nabla p + \mu \nabla^2 \mathbf{u}, \quad (4)$$

$$\nabla \cdot \mathbf{u} = 0, \quad (5)$$

where \mathbf{u} is the velocity field, p is the pressure, ρ is the density, and μ is the dynamic viscosity. Solute transport in the same domain is governed by

$$\frac{\partial C}{\partial t} + \mathbf{u} \cdot \nabla C = \nabla \cdot (D_{\text{eff}} \nabla C) - k_{\text{clear}} C - f(C) + S, \quad (6)$$

where C represents the solute concentration, D_{eff} refers to the effective diffusivity that accounts for extracellular tortuosity, k_{clear} signifies an effective clearance rate arising from cellular uptake, efflux across barriers, and elimination through CSF outflow. The term $f(C)$ captures nonlinear binding processes, including reversible binding to ECM, receptor–ligand interactions, or enzyme-mediated degradation. S is a source term representing injection of drug, controlled release from an implant, or drug uptake from systemic blood circulation. For the brain tissue, a porous medium formulation was employed:

$$\mathbf{u} = -\frac{K}{\mu} \nabla p, \quad (7)$$

where K indicates the hydraulic permeability of the extracellular matrix.

Continuum models and partial differential equations (PDE) were foundational to understanding brain microphysiology [113] and have become the prevailing standard for intrathecal and CSF-based drug delivery systems. Continuum modeling has also played a pivotal role in explaining the barrier roles of diffusion, convection, binding and capillary clearance. Additionally, Peclet number explains why diffusion dominates for small molecules and convection for macromolecules, NPs etc. [114,115]. Khani et al. implemented a realistic cervical subarachnoid space geometry to investigate the impact of injection parameters on intrathecal solute transport, utilizing pulsatile CSF flow simulations in conjunction with advection-diffusion transport [3]. They presented a framework through comprehensive parameter sweeps involving catheter placement, injection waveforms, and physiological conditions, thereby introducing the concept of "human in silico trials" for optimizing intrathecal delivery (Figure 6). Their results were corroborated by in vitro flow-phantom experiments, demonstrated that minor alterations in injection location or timing can significantly influence drug dispersion along the spinal canal and cisternal/ventricular CSF spaces. Kouzehgarani et al. reviewed these fluid-dynamic models alongside pharmacokinetic analyses and clinical data, positing that CSF circulation can be harnessed to deliver large biologics into deeper brain structures when infusion protocols are meticulously calibrated [116].

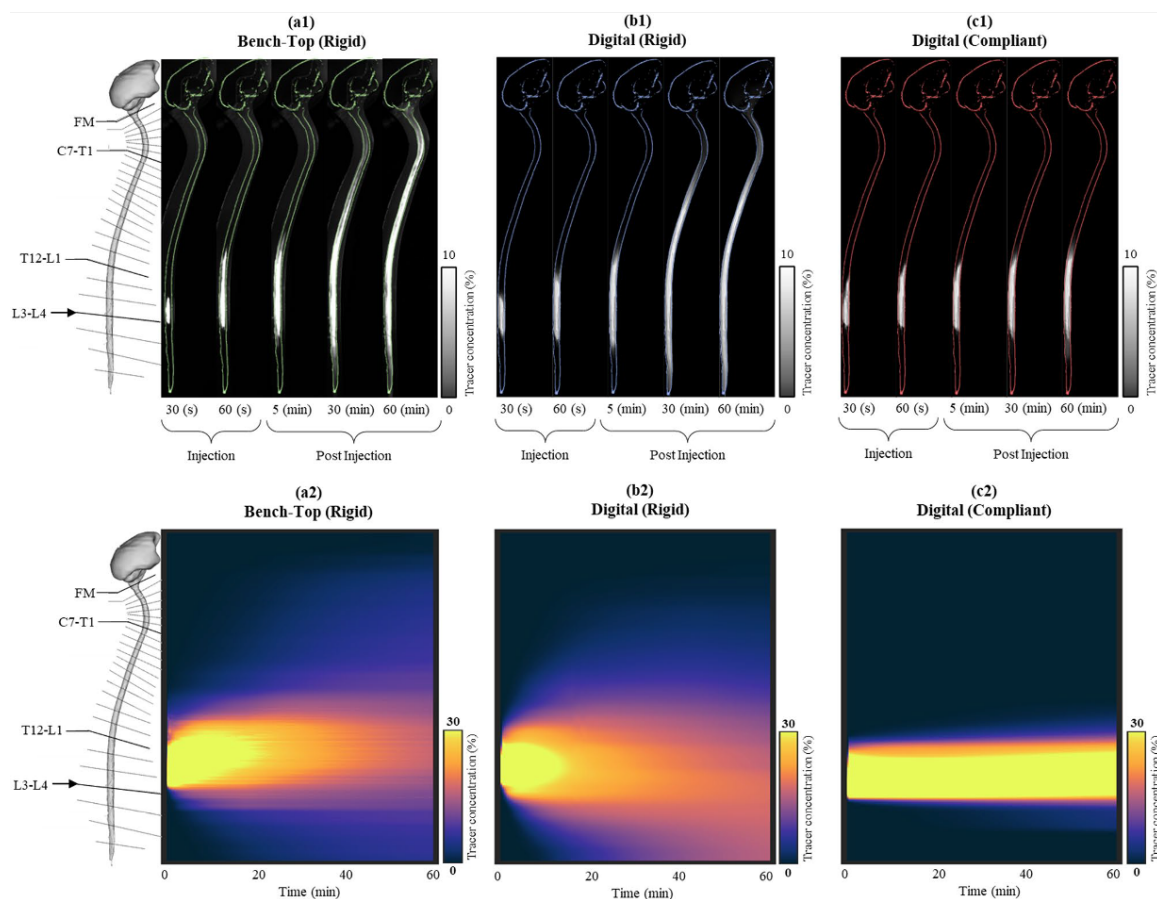


Figure 6. Computational fluid dynamics simulation of intrathecal drug delivery in an anatomically idealized model of the human central nervous system. Spatio-temporal representation of tracer concentration as a percentage of injected dose over 1-hour for the (a) rigid bench-top model, (b) rigid digital model, and (c) compliant digital model. (Image reproduced from Khani et al. [3] under Creative Commons CC BY 4.0 License).

Continuum modeling plays a pivotal role in elucidating glymphatic and perivascular transport mechanisms, with significant implications for both intrathecal and systemic drug delivery. Mestro et al. investigated periarterial solute movement driven by arterial pulsations [117], while Vinje et al. conducted simulations of solute transport within periarterial spaces and the parenchymal extracellular space, examining the interaction between diffusion and convection [10]. They integrated multimodal MRI with forward and inverse modeling to quantify subject-specific CSF tracer transport parameters in humans, highlighting the close relationship between imaging and continuum mechanics. Bohr et al. provided a comprehensive review of glymphatic models utilizing advection–diffusion–reaction equations in MRI-informed geometries [118]. Quirk et al. developed a brain-wide model incorporating explicit pial perivascular spaces, demonstrating that CSF-driven solute penetration is highly sensitive to the size and connectivity of PVS [119]. Nose-to-brain delivery has also been extensively studied using CFD and particle-tracking simulations. Models constructed in patient-specific nasal geometries have quantified device-dependent olfactory deposition, identified breathing patterns that optimize upper nasal delivery, and evaluated the impact of surgical modifications on deposition efficiency [11]. Vishnumurthy et al. synthesized these studies in a systematic review and meta-analysis, identifying robust CFD predictors of olfactory deposition and emphasizing parameters crucial for nose-to-brain targeting [120]. Boyuklieva et al. combined computational, *in vitro*, and *in vivo* measurements to assess the predictive power of CFD for nose-to-brain exposure, underscoring both its utility and current limitations [121]. In the context of FUS-mediated BBB opening, continuum models typically simulate drug transport downstream of the sonication event, with the FUS action represented as a localized, transient increase in BBB permeability. Burgess and Hynynen’s seminal review outlined how microbubble-assisted FUS enhances BBB permeability for chemotherapy and biologics [111].

Subsequent studies have incorporated spatially varying permeability maps derived from imaging or acoustic models into advection–diffusion simulations to predict regional drug accumulation following FUS [122]. Continuum and CFD-based models have also been employed to simulate drug transport from polymeric wafer implants by solving coupled diffusion–reaction–convection equations within realistic brain-tumor geometries reconstructed from MRI data [123]. These simulations incorporate Darcy’s law to account for interstitial fluid flow, enabling quantitative comparisons of various chemotherapeutic agents. The models predict how tissue heterogeneity, drug degradation kinetics, and physicochemical properties influence local concentration profiles and penetration depths. The modeling demonstrates that wafer-delivered drugs distribute unevenly across the tumor–cavity interface and underscores transport limitations that are not experimentally observable, thereby informing the optimization of local delivery strategies.

Overall, the strengths of continuum models lie in their ability to incorporate anatomical realism, spatial heterogeneity, and complex CSF or vascular-flow patterns. They are particularly effective for addressing route-specific questions, such as optimal intrathecal injection protocols or nasal device design. However, their limitations include the simplified treatment of barrier crossing and cellular uptake via effective permeability coefficients, as well as the high computational cost associated with whole-brain or whole-spine simulations. Predictions can also be sensitive to uncertain tissue parameters, such as permeability, porosity, and effective diffusivity.

5.3. Molecular Dynamics and Atomistic Simulations

Molecular dynamics (MD) and related atomistic methodologies operate at the opposite extreme to whole-body PBBK models, from nanometer and nanosecond to microsecond scales, aiming to elucidate the molecular mechanisms underlying barrier crossing, ligand binding, nanoparticle deformation, and carrier-membrane interactions. Within the context of the CNS, MD has been predominantly applied to investigate small-molecule permeation across lipid bilayers that mimic the BBB, peptide or ligand interactions with receptor targets involved in receptor-mediated transcytosis (RMT), and nanoparticle interactions with endothelial membranes [7,55].

In classical MD, atomic or coarse-grained trajectories are derived by integrating Newton’s equations of motion under a specified force field. The total potential energy is typically decomposed into bonded contributions, including bond stretching, angle bending, and dihedral rotations, as well as non-bonded interactions, comprising Lennard-Jones van der Waals potentials and Coulombic electrostatics. Coarse-grained models, such as Martini force fields, aggregate several atoms into beads with effective interaction potentials, facilitating simulations over larger spatial and temporal scales at a reduced computational cost. MD outputs encompass structural observables, diffusion coefficients, permeation-free energies, residence times, and metrics of lipid or nanoparticle deformation.

Numerous studies have employed MD simulations to explore BBB permeation at the molecular scale. Pedram et al. utilized all-atom and coarse-grained MD to simulate magnetic nanoparticle translocation across model endothelial bilayers under externally applied magnetic fields, quantifying the impact of nanoparticle size, hydrophobicity, and surface charge on the likelihood of membrane penetration [124]. Ivanczi et al. performed MD simulations of several cell-penetrating peptides (CPPs) and their drug-conjugates interacting with explicit lipid-bilayer models (Figure 7). They found that Linear CPPs show major conformational changes at membranes while cyclic CPPs stay structurally stable, demonstrating that peptide architecture strongly influences membrane penetration [8]. Ouyang et al. provided a review of MD simulations of BBB-crossing and tumor-homing peptides, illustrating how free-energy calculations, umbrella sampling, and conformational ensemble analysis can identify peptide motifs with high affinity and favorable insertion profiles for CNS drug delivery [7].

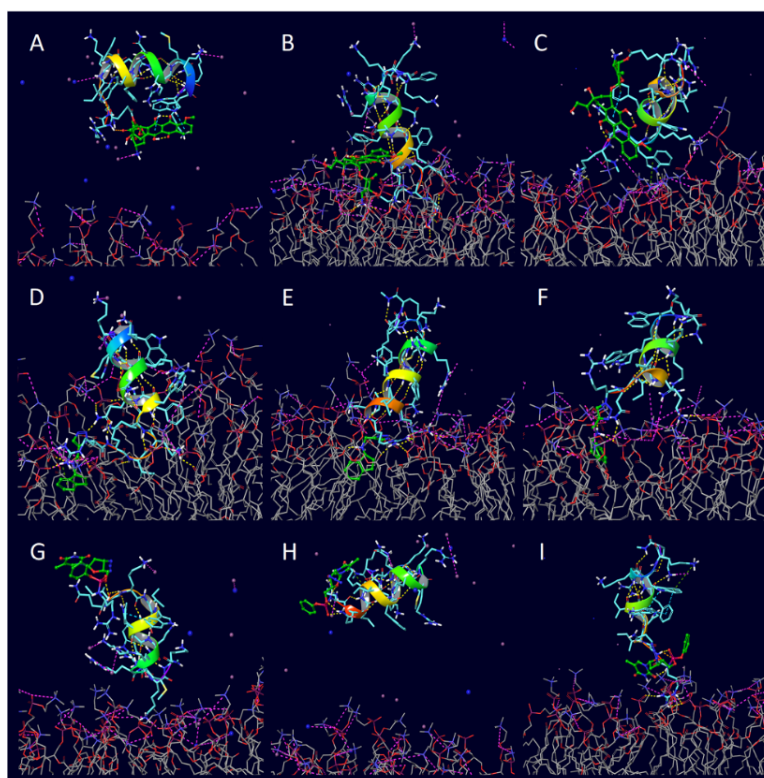


Figure 7. MD simulation of initial and final positions of different unconjugated cell-penetrating peptides (CPP) conjugates during 1000 ns membrane simulations: (A) penetratin–doxorubicin, (B) 6,14-Phe-penetratin–doxorubicin, (C) dodeca-penetratin–doxorubicin, (D) penetratin–rasagiline, (E) 6,14-Phe-penetratin–rasagiline, (F) dodeca-penetratin–rasagiline, (G) penetratin–zidovudine, (H) 6,14-Phe-penetratin–zidovudine, (I) dodeca-penetratin–zidovudine. (Image reproduced from Ivanczi et al. under Creative Commons CC BY 4.0 license [8])

More broadly, MD studies have been integrated into the larger field of nanomedicine for brain delivery. Reviews by Saraiva et al. and others emphasize how MD, in conjunction with imaging and *in vitro* data, elucidates the influence of nanoparticle size, shape, ligand density, and surface charge on membrane wrapping, endocytosis, and intracellular trafficking [55]. These studies underscore the role of atomistic simulations in guiding the rational design of brain-targeting nanocarriers.

Although less common, MD and mesoscale simulations have been employed to investigate the biophysical effects of ultrasound-induced cavitation on biological membranes. These models represent lipid bilayers and either explicit or implicit gas bubble interfaces, applying oscillatory perturbations representative of focused ultrasound exposure. The resulting membrane thinning, pore nucleation, and transient defect formation have been characterized in several computational studies, providing mechanistic insights into FUS-mediated increases in BBB permeability [125].

MD has also been applied to intranasal and mucosal delivery. For instance, Gao et al. utilized MD simulations to compare mucoadhesive versus mucus-penetrating nanoparticle designs by simulating all-atom interactions between various NPs and the main nasal mucin. They found that PEG-PLGA-based particles exhibited minimal interaction (favoring penetration), whereas chitosan-derived particles showed strong mucin binding (mucoadhesion) [126]. Similar principles apply to nanoparticle behavior in CSF-like environments, although MD studies explicitly modeling the ionic composition and protein content of CSF remain sparse.

The principal advantage of MD lies in its high mechanistic fidelity, which effectively captures molecular recognition, conformational dynamics, and nanoscale transport events that are beyond the reach of continuum-scale or pharmacokinetic/pharmacodynamic (PK/PD) models. Nevertheless, MD is limited by constraints related to time and length scales. Even with the use of coarse-grained models and enhanced sampling techniques, the simulation of complete transcytosis pathways, long-distance

diffusion across endothelial thickness, or vesicular trafficking remains impractical. Additionally, the actual geometries of the BBB and epithelial tissues are significantly more complex than the planar bilayers typically employed in MD simulations. The parameterization of force fields for novel nanoparticles continues to be a challenging task. To impact organ-level predictions, properties derived from MD, such as permeability, free energy, and diffusion coefficients, must be meticulously upscaled and integrated into hybrid or PBPK models.

5.4. Hybrid and Multiscale Models

Hybrid and multiscale models endeavor to integrate microscopic mechanisms with macroscopic transport behavior by incorporating molecular or cellular kinetics into tissue- and organ-scale transport frameworks. This methodology is particularly advantageous for CNS drug delivery, where the translocation of a therapeutic agent across the BBB or nasal mucosa is dictated by molecular-level recognition and membrane interactions. The binding kinetics and transcytosis of these therapeutic carriers (NPs and exosomes) are stochastic in nature and thus require molecular scale models. In contrast, subsequent dispersion through CSF, perivascular pathways, or brain parenchyma relies on continuum-scale flow and diffusion phenomena. In this context, multiscale models provide a comprehensive mathematical description that synthesizes the physics of molecular binding, cellular trafficking, fluid mechanics, and tissue-level heterogeneity [9,127].

Conceptually, multiscale CNS drug-delivery frameworks consist of at least two hierarchical tiers. At the microscopic level, molecular dynamics, Monte Carlo, agent-based simulations, or stochastic models can be utilized to quantify binding affinities, receptor-mediated transcytosis, vesicular trafficking, nanoparticle endocytosis, and intracellular transit. Such simulations reveal how particle size, surface charge, PEGylation, and hydrophobicity modulate biological interactions relevant to systemic circulation, mucus penetration, and transcytosis [126,128]. These molecular-level parameters, in turn, inform mesoscale or continuum transport models through effective permeabilities, binding rate constants, and release kinetics derived from bottom-up simulation. The outputs of these simulations and stochastic models, including binding and unbinding rates, internalization rate constants, receptor recycling times, and binding probabilities, are subsequently coarse-grained into effective kinetic parameters. In [4,129], the total solution of the PDEs is split into coarse (resolved) and fine (subgrid) scales. The fine scales account for microscopic adhesion kinetics governed by a stochastic particle adhesion model. These fine scales are variationally projected into coarse scales to yield a stabilized and computationally robust formulation (Figure 8). At the macroscopic scale, drug or nanoparticle concentration fields are represented by advection-diffusion-reaction equations, whose reaction terms incorporate these coarse-grained kinetic processes. A representative tissue-level transport equation takes the form

$$\frac{\partial C(\mathbf{x}, t)}{\partial t} + \mathbf{u}(\mathbf{x}, t) \cdot \nabla C = \nabla \cdot (D_{\text{eff}}(\mathbf{x}) \nabla C) - k_{\text{uptake}}(\mathbf{x}, t) C, \quad (8)$$

In this context, the uptake coefficient k_{uptake} encapsulates the influence of receptor density, cellular uptake kinetics, and microvascular surface area. The negative sign indicates drug consumption in the cellular uptake process. In perfused tissues, these equations are integrated with vascular-side flow and transport models, alongside interface conditions that delineate solute exchange across vascular or perivascular boundaries.

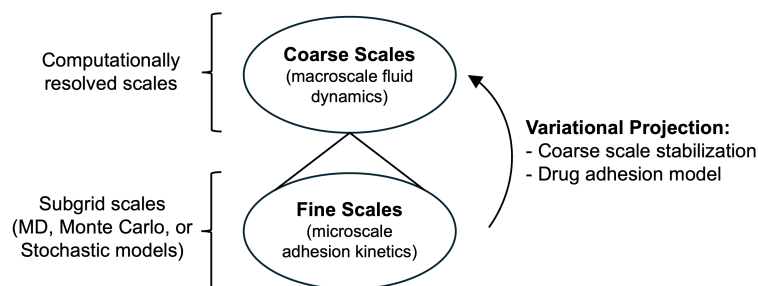


Figure 8. Schematic diagram showing coarse-graining of microscale kinetics into macroscale fluid dynamics in hybrid models [4,129].

Hybrid particle–continuum models integrate discrete dynamics at the nanoparticle or cell scale with continuum fluid flow and reaction–diffusion transport (Figure 9). For instance, Akalin et al. developed a hybrid scheme that couples continuum hemodynamics with discrete nanoparticle trajectories to predict vascular margination, wall adhesion, and transmural transport [130]. In the field of oncology, multiscale tumor models integrate evolving microvascular networks, interstitial flow, anti-angiogenic responses, and convection–diffusion–reaction drug transport to capture heterogeneous intratumoral exposure [131]. These models facilitate the simultaneous representation of vascular remodeling, transport barriers, and drug–tissue interactions, which cannot be resolved by single-scale methods.

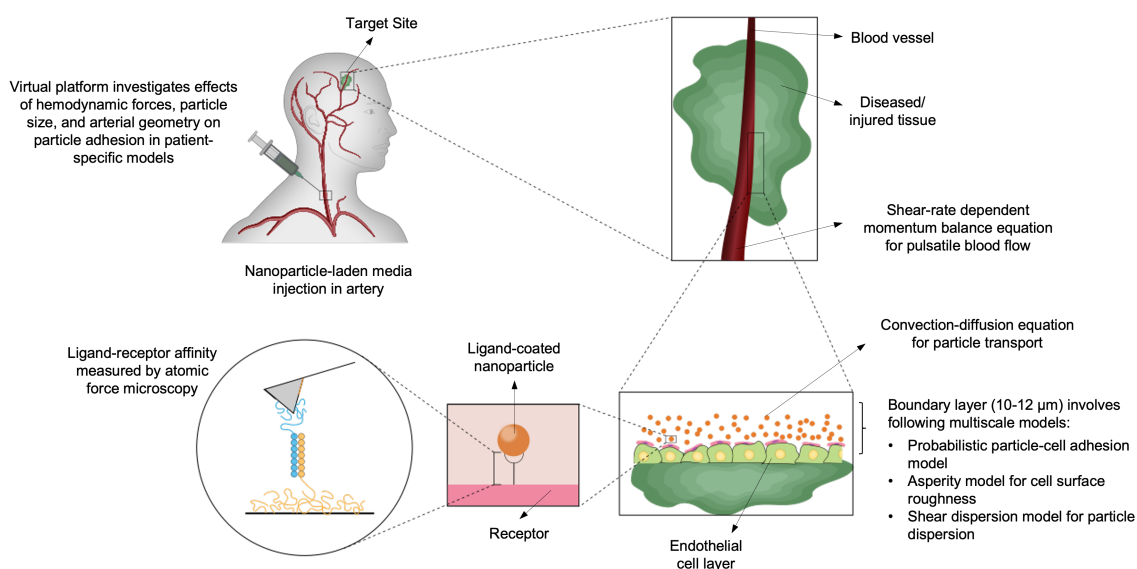


Figure 9. Schematic diagram of drug delivery using nanocarriers designed for active targeting in circulation. The experimentally validated computational model serves as a digital twin, enabling investigation of the effects of hemodynamic forces and particle geometry on particle adhesion in patient-specific arterial models. A shear-rate dependent blood flow model along with resistance boundary conditions for downstream pressure is used to simulate pulsatile blood flow in the arterial system. Adhesion kinetics are simulated through various multiscale models that incorporate experimentally measured parameters in the boundary layer at the target sites [129].

Recently, multiscale modeling has been extended to nanoparticle-mediated intravascular and brain-targeted drug delivery, where molecular-scale binding, vascular flow physics, and tissue perfusion must be concurrently represented. A 2024 physics-based *in silico* framework integrated nanoparticle design, blood flow, and tissue-level transport to evaluate systemic nanocarrier delivery [132]. Similarly, the combination of advanced imaging with computational modeling has enabled multiscale prediction of nanoparticle accumulation in the brain [133]. Emerging approaches also incorporate

machine learning as a bridge across scales, utilizing data-driven models trained on CFD, MD, or PK simulations to accelerate parameter exploration in complex delivery systems [12].

The primary advantage of hybrid and multiscale modeling lies in its capacity to represent mechanistic insights from molecular and cellular scales while still predicting organ-scale drug distribution, regional accumulation, or glymphatic clearance patterns. However, these models also entail substantial complexity, often involving numerous parameters that are challenging to measure. Model validation across scales remains difficult, and workflow standardization is limited in this field. Despite these challenges, the increasing availability of cross-scale experimental data—from microfluidic BBB platforms, high-field MRI, single-cell transcriptomics, and *in vivo* imaging—is anticipated to render hybrid and multiscale modeling approaches integral to future CNS drug-delivery research.

5.5. Machine-Learning and Data-Driven Models

Machine learning (ML) methodologies offer a complementary approach to mechanistic modeling by leveraging empirical patterns in extensive and often high-dimensional datasets. These techniques have proven valuable across various CNS drug-delivery challenges, including predicting BBB permeability, nanoparticle brain uptake, extracting imaging-derived biomarkers, and constructing surrogate models that approximate computationally intensive CFD simulations.

Initial ML research concentrated on small-molecule BBB permeability, where models trained on extensive chemical libraries demonstrated improvements over traditional QSAR-based methods. Wang et al. demonstrated that support vector machines, random forests, and ensemble resampling strategies significantly enhance predictive accuracy by capturing nonlinear interactions among molecular descriptors and addressing the inherent class imbalance between BBB-permeable and impermeable compounds [17]. Deep learning models, such as graph neural networks, have also been applied to BBB permeability prediction, showing improved performance for complex chemotypes [13].

Recently, ML has been extended to nanoparticle-mediated brain delivery. Yousfan et al. compiled the largest nanoparticle CNS delivery dataset to date, with 403 nanocarriers characterized for brain uptake, and trained multiple ML models to identify the physicochemical determinants of CNS penetration [2]. Their feature-importance analyses revealed that surface charge, ligand density, and material composition often surpass particle size as predictors of brain accumulation, providing mechanistic hypotheses for subsequent experimental or multi-scale model validation. A comprehensive review by Alves et al. situates these ML methods within the broader modeling ecosystem, emphasizing their synergy with PBPK models, MD simulations, and multi-omics characterization of BBB transport [1].

In intranasal delivery, ML-based surrogate models trained on CFD outputs have been employed to rapidly predict nasal deposition patterns and guide device or formulation optimization [134]. In the intrathecal context, surrogate models have been developed to approximate CSF drug-dispersion outcomes across wide parameter ranges, significantly reducing the computational cost associated with thousands of CFD simulations [3].

ML plays an increasingly significant role in image-based modeling. Brain-wide glymphatic studies have integrated ML techniques to detect tracer propagation patterns, estimate subject-specific diffusion and convection parameters, and initialize continuum-scale solute transport models. Deep learning frameworks have been developed for the segmentation of PVS, ventricles, and CSF flow features, providing anatomical and geometric inputs for downstream continuum simulations [135]. Similar approaches have been explored for estimating glymphatic efficiency metrics from MRI time-series data [136].

Despite their potential, ML methods encounter challenges, including data heterogeneity, limited standardized datasets for nanoparticles and biologics, inconsistent experimental protocols, and difficulties in interpretability. Overfitting is common, and extrapolation beyond the training domains remains uncertain. Therefore, the most promising future direction is hybrid ML–mechanistic modeling, wherein ML is utilized to estimate uncertain parameters, discover latent features, or provide computational surrogates, while physics-based continuum or PBPK models ensure mechanistic interpretability and physically consistent extrapolation.

Table 2. Comparison of major computational modeling approaches for CNS drug delivery.

Modeling Approach	Major Assumptions	Strengths	Limitations	References
PBPK Models	<ul style="list-style-type: none"> Body is represented as interconnected well-mixed compartments. BBB transport modeled via permeability or RMT kinetics. CSF treated as one or more lumped compartments. Spatial gradients and geometry ignored. 	<ul style="list-style-type: none"> Efficient for whole-body PK and dose selection. Captures systemic disposition and CNS exposure. Supports cross-species scaling and sensitivity analysis. 	<ul style="list-style-type: none"> No spatial resolution or local flow patterns. Limited mechanistic insight into BBB microstructure. Key parameters (e.g., permeability, efflux) often uncertain. 	[5,6,105,110]
Continuum Models (CFD, Advection–Diffusion, Porous Media)	<ul style="list-style-type: none"> CSF and blood treated as incompressible fluids. Brain parenchyma modeled as a porous medium (Darcy/Brinkman). Transport governed by Navier–Stokes and advection–diffusion–reaction equations. 	<ul style="list-style-type: none"> Captures patient-specific flow and solute distribution. Essential for intrathecal, nasal, and glymphatic transport analysis. Resolves pulsatility, mixing, and perivascular flow patterns. 	<ul style="list-style-type: none"> High computational cost for brain-wide simulations. Barrier crossing and cellular uptake treated via effective coefficients. Results sensitive to uncertain tissue properties (porosity, permeability, D_{eff}). 	[3,10,11,116,123]
Molecular Dynamics / Atomistic Simulations	<ul style="list-style-type: none"> Atoms or coarse-grained beads obey Newtonian dynamics. Membranes modeled as idealized lipid bilayers. Temporal and spatial scales limited to ns–μs and nm–μm, respectively. 	<ul style="list-style-type: none"> High-resolution mechanistic fidelity. Captures binding, membrane insertion, and free-energy barriers. Provides nanoscale parameters for higher-scale models. 	<ul style="list-style-type: none"> Cannot simulate organ-scale or physiological timescale behavior. Simplified geometry relative to true BBB architecture. Challenging force-field parameterization for novel materials. 	[7,8,125]
Hybrid and Multiscale Models	<ul style="list-style-type: none"> Microscale binding, endocytosis, and trafficking coarse-grained into rate laws. Tissue-level transport described by advection–diffusion–reaction PDEs. Multi-tier coupling between molecular, cellular, and organ scales. 	<ul style="list-style-type: none"> Integrates nanoscale kinetics with tissue-level distribution. Mechanistic and predictive; supports route-specific optimization. Bridges BBB transport, CSF flow, and parenchymal uptake. 	<ul style="list-style-type: none"> Mathematically complex and involve large parameter sets. Computationally intensive workflows. Requires experimental data and validation at multiple scales. 	[4,128,132,133]
Machine-Learning / Data-Driven Models	<ul style="list-style-type: none"> Learn empirical patterns from chemical, imaging, or simulation data. Do not require explicit governing equations. Often used as surrogates for PK, CFD, or deposition models. 	<ul style="list-style-type: none"> High predictive accuracy for BBB permeability and brain uptake. Scalable to large datasets; rapid inference once trained. Complement mechanistic models by estimating uncertain parameters. 	<ul style="list-style-type: none"> Limited interpretability and poor extrapolation outside training domain. Strongly dependent on data quality and standardization. Difficult to enforce physical laws (e.g., mass conservation). 	[12,13,120]

6. Future Perspective

Mathematical and computational modeling has frequently demonstrated remarkable efficacy in elucidating the structure, mechanisms, and design principles across a wide range of biological systems. Nevertheless, no single model serves as a universal solution, and the central nervous system (CNS), characterized by incomplete parameter knowledge, hierarchical interactions, and emergent collective phenomena, remains one of the most challenging domains for quantitative prediction. Consequently, the future of CNS drug delivery modeling hinges not only on methodological innovation but also on the clarity of assumptions, transparent limitations, and rigorous validation. Exemplary models are founded on explicit hypotheses, make falsifiable predictions, and remain open to refinement as new physiological data become available. Although they may be less realistic than *in vivo* studies, these models serve as essential complements that facilitate counterfactual experiments, optimization of drug design, and *in silico* clinical trials, thereby accelerating therapeutic development and reducing costs. To sustain this virtuous cycle, models should clearly differentiate between results and interpretations and delineate their domains of applicability as explicitly as possible.

A significant opportunity lies in the development of next-generation multiscale digital twins of the CNS. Such frameworks will integrate molecular-scale receptor binding and transcytosis, mesoscale endothelial mechanics, intravascular hemodynamics, CSF and perivascular flow, and parenchymal diffusion–reaction processes within a unified computational framework. Patient-specific digital twins incorporating MRI, CT, or optical imaging will enable validation and individualized predictions of drug dispersion for intrathecal biologics, intra-arterial nanoparticles, focused ultrasound–enabled therapies, or intranasal formulations. Realizing this vision will necessitate advances in image registration, parameter estimation, reduced-order modeling, uncertainty quantification, and machine learning–augmented inference.

Equally important is the need to model the dynamic and heterogeneous nature of the BBB and neurovascular unit. Single-cell atlases have revealed substantial spatial variations in endothelial, astrocytic, and pericyte phenotypes, including the zonation of transporters, tight junction proteins, and signaling receptors [137]. Future models must incorporate this heterogeneity, as well as age-related or disease-induced changes in stiffness, inflammation, oxidative stress, and vascular morphology. BBB transport should be considered an actively regulated process rather than a static barrier, responding to shear stress, neurovascular coupling, and metabolic demand.

Translating rodent models to human applications remains a significant challenge. Many existing formulations were developed for lissencephalic rodent brains, which differ from the human CNS in terms of geometry, vascular resistance, CSF turnover, sleep architecture, glymphatic topology, and arteriole–venule ratios. While scaling arguments based on the Peclet number, Womersley number, or dimensionless permeability offer guidance, they cannot fully account for species-specific neuroanatomy or biomechanics. Successful translation will necessitate models that accommodate these anatomical and physiological differences while integrating human microdialysis measurements, CSF sampling, positron emission tomography (PET) tracers, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), and multimodal neuroimaging.

A promising parallel approach is the development of hybrid physics–machine learning frameworks. Machine learning can infer uncertain parameters (such as permeability, receptor density, and uptake rate constants) from imaging or omics data, learn surrogate mappings to accelerate CFD or PDE simulations, and classify CNS transport phenotypes. Physics-informed neural networks, graph neural networks for CNS geometry, and diffusion models for generating virtual cohorts will increasingly support large-scale *in silico* trials in the future. Crucially, hybrid models must incorporate physical constraints, such as mass conservation, boundary conditions, and transport limits, to avoid biologically implausible extrapolations.

Finally, future progress will depend on standardization, reproducibility, and the availability of shared data resources. Variations in geometry fidelity, boundary conditions, and parameter choices remain major obstacles to comparing models across studies. Publicly available reference geome-

tries, curated nanoparticle delivery datasets, validated BBB permeability libraries, and benchmarking problems for intrathecal and perivascular CFD simulations would significantly accelerate research in this field. Model categories, such as those summarized in Table 2, help organize prior work and highlight opportunities for impactful advances; however, their utility depends on continued experimental grounding. Ultimately, each model should be applied where it is most informative, validated experimentally whenever possible, including in vivo, and used in combination with complementary approaches when necessary. Collectively, these directions point toward a future in which CNS drug delivery modeling becomes increasingly integrative, predictive, and clinically actionable. By merging mechanistic biophysics with data-driven inference and patient-specific neuroimaging, next-generation models have the potential to guide therapy design, personalize dosing strategies, and uncover new biological principles governing drug movement in the brain.

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