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Sustainable Therapeutic Strategies for Controlling Amyloid Aggregation Process

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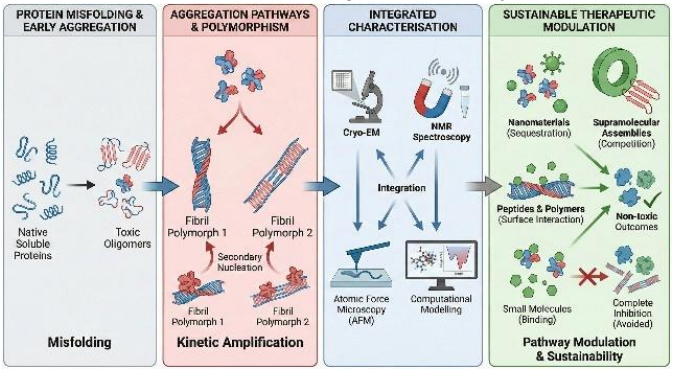
Abstract: Protein misfolding and aggregation into amyloid assemblies underlie a broad class of neurodegenerative and systemic disorders, including Alzheimer's, Parkinson's, and Huntington's diseases. Although amyloid deposition has long been recognised as a pathological hallmark, increasing evidence indicates that disease progression is driven by pathway-dependent aggregation processes involving transient oligomeric intermediates, fibril polymorphism, and surface-mediated amplification mechanisms, rendering amyloid aggregation both mechanistically complex and therapeutically challenging. Recent advances in experimental biophysics and computational modelling have substantially refined understanding of amyloidogenesis. High-resolution structural techniques, together with kinetic and spectroscopic assays, have clarified how sequence features, environmental conditions, and aggregation history shape the structural and toxic properties of amyloid assemblies. In parallel, atomistic and coarse-grained simulations, multiscale modelling, and data-driven approaches have enabled systematic interrogation of misfolding pathways, energetic landscapes, and kinetic control points that are difficult to access experimentally, while also supporting more efficient experimental design. Against this mechanistic backdrop, therapeutic development has shifted from non-specific aggregate clearance toward precise modulation of aggregation pathways. Emerging strategies emphasise sustainability-oriented principles, including selectivity, reversibility, reduced material complexity, and compatibility with green chemistry. Small molecules, nanomaterials, supramolecular assemblies, peptide-based constructs, and polymeric systems are being developed to bias aggregation trajectories, attenuate secondary nucleation, or destabilise toxic intermediates rather than enforce complete inhibition. This review highlights recent progresses in amyloid aggregation and presents a computationally guided, sustainable framework for disease-specific aggregation control.



Keywords: *Amyloid aggregation, protein misfolding, neurodegenerative diseases, computational modelling, sustainable therapeutics*

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1. Introduction

Protein misfolding and aggregation into insoluble amyloid structures constitute a fundamental pathological process underlying a diverse group of human disorders collectively known as amyloidosis.[1-2] These conditions, often grouped under the broader category of protein misfolding disorders, encompass both neurodegenerative diseases and non-

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neuropathic disorders that may be localized to specific tissues or distributed systemically. Current understanding indicates that aberrant protein aggregation contributes to several dozen distinct human diseases, underscoring its broad biomedical relevance. Representative classes of amyloid-associated disorders and their primary aggregation-prone proteins are summarized in Table 1.[3] Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) represent some of the most extensively studied amyloid-related disorders, in which the progressive accumulation of β-sheet-rich protein assemblies leads to synaptic dysfunction, neuronal loss, and irreversible cognitive or motor impairment.[4-5] In contrast, non-neuropathic amyloidoses arise when aggregation is confined to peripheral tissues, whereas systemic forms involve widespread deposition across multiple organs, reflecting differences in tissue susceptibility and biological context. Importantly, each amyloid disorder is associated with the misfolding and aggregation of a characteristic protein or peptide. Alzheimer-type neurodegeneration is defined by aggregation of amyloid-β peptides, while Parkinsonian disorders are driven by the self-assembly of α-synuclein. Huntington's disease arises from accumulation of huntingtin protein containing expanded

polyglutamine tracts that promote aggregation within neuronal inclusion bodies. Similarly, pathogenic variants of superoxide dismutase 1 are implicated in amyotrophic lateral sclerosis. Beyond the nervous system, aberrant deposition of serum amyloid A underlies AA amyloidosis in organs such as the liver, spleen, and kidneys, while type 2 diabetes is characterised by aggregation of islet amyloid polypeptide within pancreatic β-cells. Despite differences in clinical presentation, tissue involvement, and precursor proteins, these disorders exhibit a striking molecular convergence.[6-7] In each case, normally soluble proteins undergo aberrant conformational transitions that yield toxic oligomeric intermediates and highly ordered fibrillar aggregates.[8-10] Figure 1 provides an overview of these shared aggregation principles, illustrating how distinct amyloidogenic proteins converge onto common, pathway-dependent mechanisms governed by intrinsic sequence features, extrinsic environmental factors, and a rugged free-energy landscape characterised by oligomer toxicity, fibril polymorphism, and kinetic amplification processes.

Amyloid aggregation is not an isolated biochemical anomaly. Instead, it reflects a generic propensity of polypeptide chains to adopt alternative, aggregation-prone conformations when native stability is compromised.[11] This understanding has shifted the perception of amyloid diseases from protein-specific pathologies to broader disorders of protein homeostasis.[12] Central to this process is a nucleation-dependent polymerization mechanism, in which an initial energetically unfavourable nucleation event is followed by rapid fibril elongation and a cascade of secondary processes such as fragmentation and surface-catalyzed seeding.[13] These events collectively amplify aggregate formation and contribute to disease progression.[14] The molecular determinants governing amyloid formation are inherently multifactorial. Intrinsic factors such as amino acid composition, sequence patterning, and conformational flexibility play decisive roles in determining aggregation propensity.[15-16] Post-translational modifications, including phosphorylation, oxidation, and truncation, further influence structural stability and aggregation behaviour.[17-18] At the same time, extrinsic influences such as pH, ionic strength, metal ion coordination, oxidative stress, and macromolecular crowding exert profound effects on aggregation kinetics and aggregate morphology.[19-20] Together, these variables reshape the free-energy landscape of amyloidogenic proteins, altering nucleation barriers, stabilizing misfolded intermediates, and promoting intermolecular β-sheet interactions.[21-22]

A major challenge in amyloid research arises from the transient and heterogeneous nature of aggregation intermediates. Increasing experimental and clinical evidence suggests that small, soluble oligomers are often more cytotoxic than mature fibrils.[23-24] However, these species are difficult to isolate and characterise due to their short lifetimes and dynamic interconversion.[25-26] As a result, understanding the earliest stages of aggregation and developing strategies to selectively target these intermediates remain central objectives in the field. Over the past several decades, significant progress has been achieved through advances in experimental characterisation techniques. High-resolution methods such as nuclear magnetic resonance spectroscopy and cryo-electron microscopy have revealed detailed structural features of amyloid fibrils.[27-30] Atomic force microscopy and electron microscopy have enabled direct visualisation of aggregate morphology and growth processes.[31-32] Complementary fluorescence-based assays have provided kinetic insights into nucleation, elongation, and secondary aggregation events.[13, 33] Despite these advances, experimental techniques alone often struggle to fully capture the complexity of amyloid formation, particularly during the early stages when intermediates are highly dynamic and structurally diverse.

Table 1. *Representative classes of amyloid-associated disorders and their primary aggregation-prone proteins*

amyloid context	principal aggregation-prone protein or peptide
Central nervous system proteinopathies	
Alzheimer-type neurodegeneration	Amyloid-β–derived peptides
Synucleinopathies	α-Synuclein
Polyglutamine expansion disorders	Huntingtin with expanded polyQ tract
Tauopathies	Microtubule-associated protein tau
Prion-related encephalopathies	Misfolded prion protein (PrP^{Sc})
Motor neuron degeneration	Superoxide dismutase 1 variants
Systemic amyloid deposition disorders	
Immunoglobulin-associated amyloidosis	Light-chain immunoglobulin fragments
Inflammation-associated amyloidosis	Serum amyloid A–derived fragments
Transthyretin-related amyloidosis	Native or mutant transthyretin
Dialysis-associated amyloid disease	β_2-Microglobulin
Hereditary systemic amyloidoses	Mutant lysozyme, gelsolin, or cystatin C
Coagulation-related amyloidosis	Fibrinogen α-chain variants
Localised and tissue-specific amyloidoses	
Endocrine amyloid deposition	Islet amyloid polypeptide, calcitonin, prolactin
Ocular amyloid disorders	Crystallins, lactoferrin
Cutaneous amyloid conditions	Keratin-derived peptides
Vascular and age-related amyloidosis	Medin

Computational modelling has therefore become an indispensable component of amyloid research. Molecular dynamics simulations at atomistic and coarse-grained levels have provided mechanistic insight into protein misfolding pathways, oligomer formation, and fibril assembly.[34-36] Kinetic and thermodynamic models have clarified the roles of primary and secondary nucleation processes in aggregation amplification.[37] More recently, machine learning and data-driven approaches have enabled the identification of aggregation-prone regions and the rapid screening of potential aggregation modulators.[38-39] Importantly, computational techniques allow systematic exploration of large conformational and chemical spaces with minimal material input, thereby complementing experimental studies while improving overall efficiency. Beyond their mechanistic utility, computational approaches have gained renewed relevance in the context of sustainability. Traditional experimental workflows often rely on extensive trial-and-error procedures, large reagent consumption, and resource-intensive instrumentation. In contrast, predictive modelling can substantially reduce experimental redundancy by prioritising promising candidates and narrowing the design space before synthesis and testing.[40-41] This capability is particularly important as the field moves toward the development of therapeutic strategies that are not only effective but also scalable and environmentally responsible.

Therapeutic intervention aimed at controlling amyloid aggregation has long been pursued as a viable route to disease modification. Early strategies focused primarily on small molecules and peptide-based inhibitors designed to stabilise native protein conformations or disrupt β-sheet formation.[42-43] While these approaches have generated valuable mechanistic insights, many candidates have encountered limitations related to bioavailability, off-target toxicity, metabolic instability, and challenges associated with large-scale synthesis.[44] These shortcomings have prompted a re-evaluation of how anti-amyloid therapeutics are designed and developed.

In recent years, increasing attention has been directed toward sustainable therapeutic strategies that balance efficacy with long-term safety, scalability, and environmental impact. Bio-derived and naturally occurring small molecules have emerged as attractive aggregation modulators due to their structural diversity and favourable biocompatibility profiles.[45-46] Nanomaterial-based approaches, including biodegradable and surface-functionalised nanostructures, offer new opportunities to sequester toxic oligomers or redirect aggregation pathways while minimising long-term persistence and toxicity.[47] Supramolecular systems governed by reversible non-covalent interactions provide adaptable platforms for aggregation control without permanent chemical modification.[48-49] Similarly, polymeric and hybrid materials designed using principles of green chemistry are gaining recognition as multifunctional and sustainable therapeutic candidates.[50-51]

The success of these emerging strategies is closely linked to advances in computational design. Predictive modelling of binding modes, aggregation hotspots, and structure–activity relationships enable rational selection of candidate molecules and materials prior to synthesis.[52-53] This integrated approach reduces synthetic waste, accelerates optimisation cycles, and aligns therapeutic development with sustainability-oriented design principles. The convergence of computational chemistry, molecular biophysics, and materials science is therefore reshaping the therapeutic landscape of amyloid

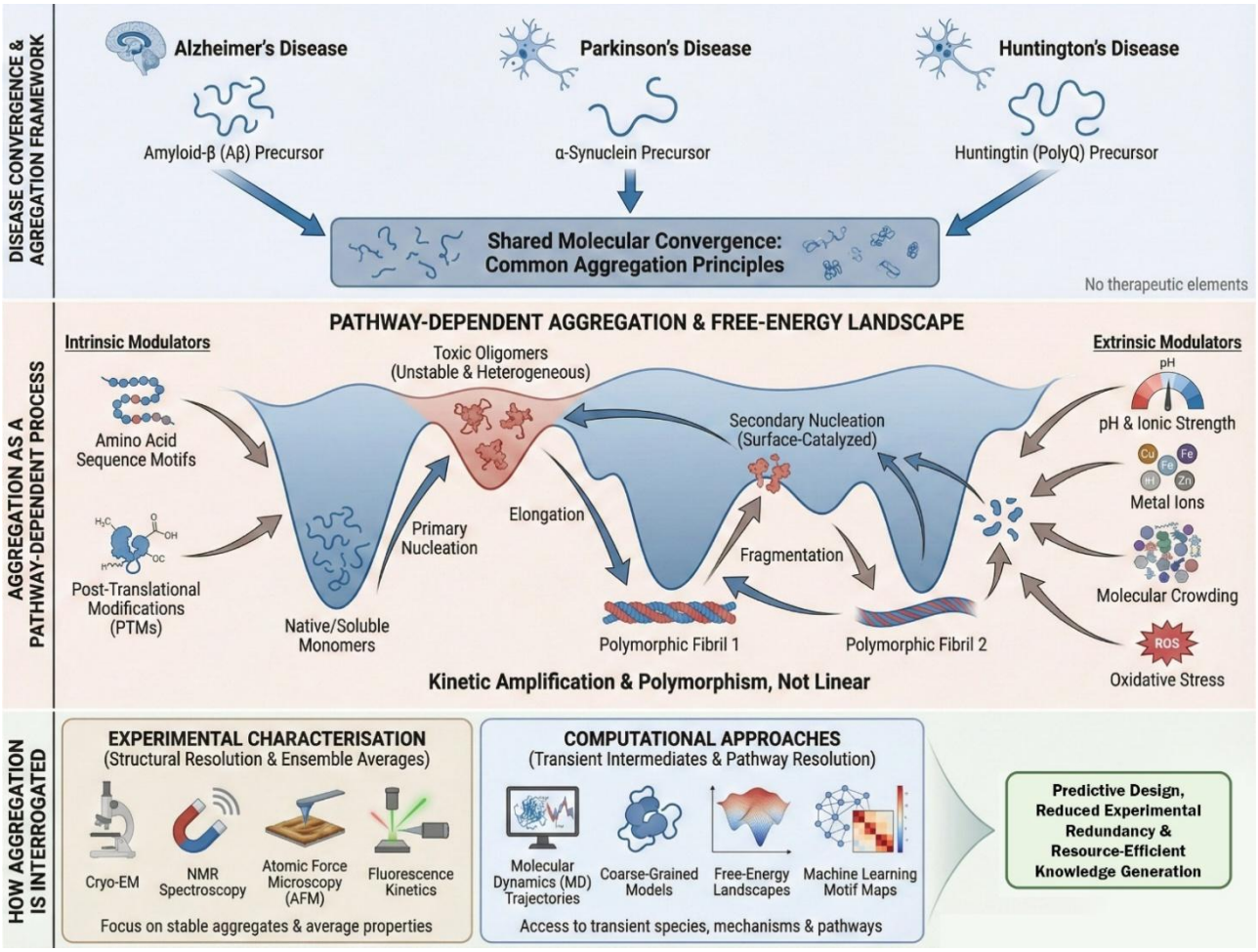

Figure 1. *Conceptual framework of amyloid aggregation and its mechanistic drivers.*

disorders. Disease-specific studies further highlight the need for tailored aggregation control strategies. Amyloid-β aggregation in Alzheimer's disease, α-synuclein assembly in Parkinson's disease, and polyglutamine-driven aggregation of huntingtin in Huntington's disease each exhibit distinct structural and kinetic features. Understanding these differences is essential for developing targeted interventions. Computational and experimental investigations have demonstrated how sequence context, post-translational modifications, and cellular environments uniquely influence aggregation behaviour in each system, reinforcing the importance of adaptable and disease-specific therapeutic frameworks.

In this review, we present a comprehensive analysis of sustainable therapeutic strategies for controlling amyloid protein aggregation. We begin by outlining the molecular and physicochemical principles governing amyloidogenesis and discussing the clinical spectrum of amyloid-associated disorders. We then examine experimental and computational methodologies used to probe aggregation pathways, with emphasis on efficiency and resource-conscious approaches. Disease-specific aggregation models of amyloid-β, α-synuclein, and huntingtin are subsequently discussed to illustrate how mechanistic insight informs therapeutic development. Finally, emerging classes of sustainable aggregation inhibitors are reviewed, highlighting the central role of computationally guided design in advancing next-generation anti-amyloid therapeutics. By integrating perspectives from structural biology, computational chemistry, materials science, and sustainability-focused design, this article aims to provide a holistic view of current efforts to control amyloid aggregation. Such interdisciplinary approaches are essential for translating fundamental mechanistic understanding into clinically viable and environmentally responsible therapeutic solutions. Ultimately, sustainable strategies are poised to play a defining role in shaping the future of amyloid-targeted intervention.

2. Molecular Basis of Amyloid Aggregation

Amyloid protein aggregation represents a central molecular event underlying a wide range of neurodegenerative and systemic disorders.[11, 54] It arises from the aberrant misfolding of specific proteins that subsequently self-assemble into insoluble fibrillar structures. These fibrils are defined by a highly ordered cross-β-sheet architecture, in which β-strands align perpendicular to the fibril axis, imparting remarkable structural stability.[55] Accumulation of such aggregates, whether intracellular or extracellular, disrupts cellular homeostasis and initiates a cascade of pathological events including membrane damage, oxidative stress, inflammatory responses, and progressive tissue dysfunction.[56-57] Despite substantial diversity in amino acid sequence, native structure, and biological function among amyloidogenic proteins, the aggregation process exhibits striking mechanistic similarities. Most amyloid systems follow a nucleation-dependent polymerization pathway, in which a slow and energetically unfavourable nucleation step precedes rapid fibril elongation and amplification through secondary processes. This apparent universality suggests that amyloid formation is governed by generic physicochemical principles rather than protein-specific idiosyncrasies alone.[58] Such convergence has positioned amyloid aggregation as a fundamental problem in protein science, with implications that extend beyond individual disease contexts.

Intensive investigation over the past two decades has significantly refined the conceptual framework of amyloid aggregation. Early descriptions based largely on histopathological observations and bulk biochemical measurements have evolved into sophisticated molecular models informed by advanced biophysical characterisation and computational analysis. It is now well recognised that aggregation is not a linear transition from monomer to fibril. Instead, it proceeds through a complex network of metastable intermediates, including soluble oligomers and protofibrillar assemblies, each exhibiting distinct structural, kinetic, and toxicological profiles.[59-60] These intermediates are increasingly regarded as critical determinants of disease progression and therapeutic outcome. The aggregation behaviour of proteins in biological environments is further modulated by a confluence of intrinsic and extrinsic factors. Sequence composition, conformational flexibility, and post-translational modifications define the intrinsic aggregation propensity of a protein, while environmental parameters such as pH, ionic strength, temperature, metal ion availability, and molecular crowding exert strong extrinsic control.[61] Cellular components including molecular chaperones, membranes, and proteostasis networks also play decisive roles, either suppressing aggregation or, under pathological conditions, inadvertently promoting it.[62] Notably, many amyloid assemblies evade cellular clearance mechanisms and display prion-like features, enabling templated propagation of misfolded conformations across cells and tissues.[63]

A detailed understanding of amyloid aggregation at the molecular level is therefore essential for the rational development of therapeutic strategies. This need is particularly acute in the context of sustainable intervention design, where controlling aggregation pathways through minimal, efficient, and environmentally responsible means is a growing priority. Insight into how specific structural motifs, intermolecular interactions (Figure 2), and environmental conditions drive aggregation provides a foundation for identifying intervention points that can be targeted using bio-compatible molecules, reversible supramolecular systems, or computationally optimised inhibitors.

A comprehensive understanding of the amyloid aggregation process requires consideration of multiple interconnected dimensions. This includes the molecular origins of protein misfolding and the structural principles that define amyloid fibril architecture, as well as the physicochemical forces that regulate aggregation pathways and kinetics. Equally important is an appreciation of how these molecular events manifest across different disease contexts, giving rise to both systemic and localised amyloid disorders with distinct pathological features. Together, these aspects provide a cohesive framework for interpreting amyloidogenesis and form the conceptual foundation for the rational development of strategies aimed at controlling aggregation in a precise, effective, and sustainable manner.

2.1. Protein Misfolding Pathways and Fibrillar Architectures

Recent advances in amyloid research have substantially refined current understanding of protein misfolding and fibril architecture, shifting the field away from simplified linear models toward a structurally heterogeneous and context-dependent view of aggregation. High-resolution structural techniques, combined with multiscale computational approaches, have revealed that amyloid fibrils represent families of related polymorphs rather than a single invariant end state.[64-65] These insights, largely emerging over the past five years, have important implications for both disease mechanisms and therapeutic intervention. Cryogenic electron microscopy has been central to this conceptual transition. Structural studies from several groups have demonstrated that amyloidogenic proteins such as amyloid-β, tau, and α-synuclein can adopt multiple fibrillar conformations with distinct protofilament arrangements and surface chemistries.[29] Although cryo-EM has provided static structural snapshots, recent work has emphasized how fibril architecture is shaped by aggregation conditions and kinetic history. For example, insulin amyloid fibrils have served as an important model

system for understanding protofilament organization. Puławski, Koliński, and co-workers reported a multiscale modelling framework that integrates coarse-grained docking with atomistic molecular dynamics to reconstruct insulin protofilament structures that closely resemble experimentally resolved cryo-EM fibrils.[66-68] Their work illustrates how parallel, in-register β-sheet assemblies can emerge from sequence-driven self-assembly while accommodating structural variability at the protofilament level. Beyond mature fibrils, increasing attention has been directed toward misfolded oligomeric species that precede or coexist with fibrillar assemblies.

Over the last few years, comparative studies of toxic and non-toxic oligomers have provided mechanistic insight into how subtle structural differences translate into profound biological consequences. Work led by Limbocker et. al has been particularly influential in this area.[69] Using stabilized oligomer populations derived from the same protein sequence, these studies demonstrated that toxicity correlates strongly with solvent-exposed hydrophobic regions, membrane affinity, and conformational flexibility rather than oligomer size alone.[70-71]

Importantly, structurally similar oligomers can exhibit markedly different toxic profiles, highlighting that misfolding outcomes are not uniquely determined by aggregation extent but by specific structural features. These findings have reshaped prevailing views of amyloidogenesis by underscoring the central role of metastable intermediates. Rather than being

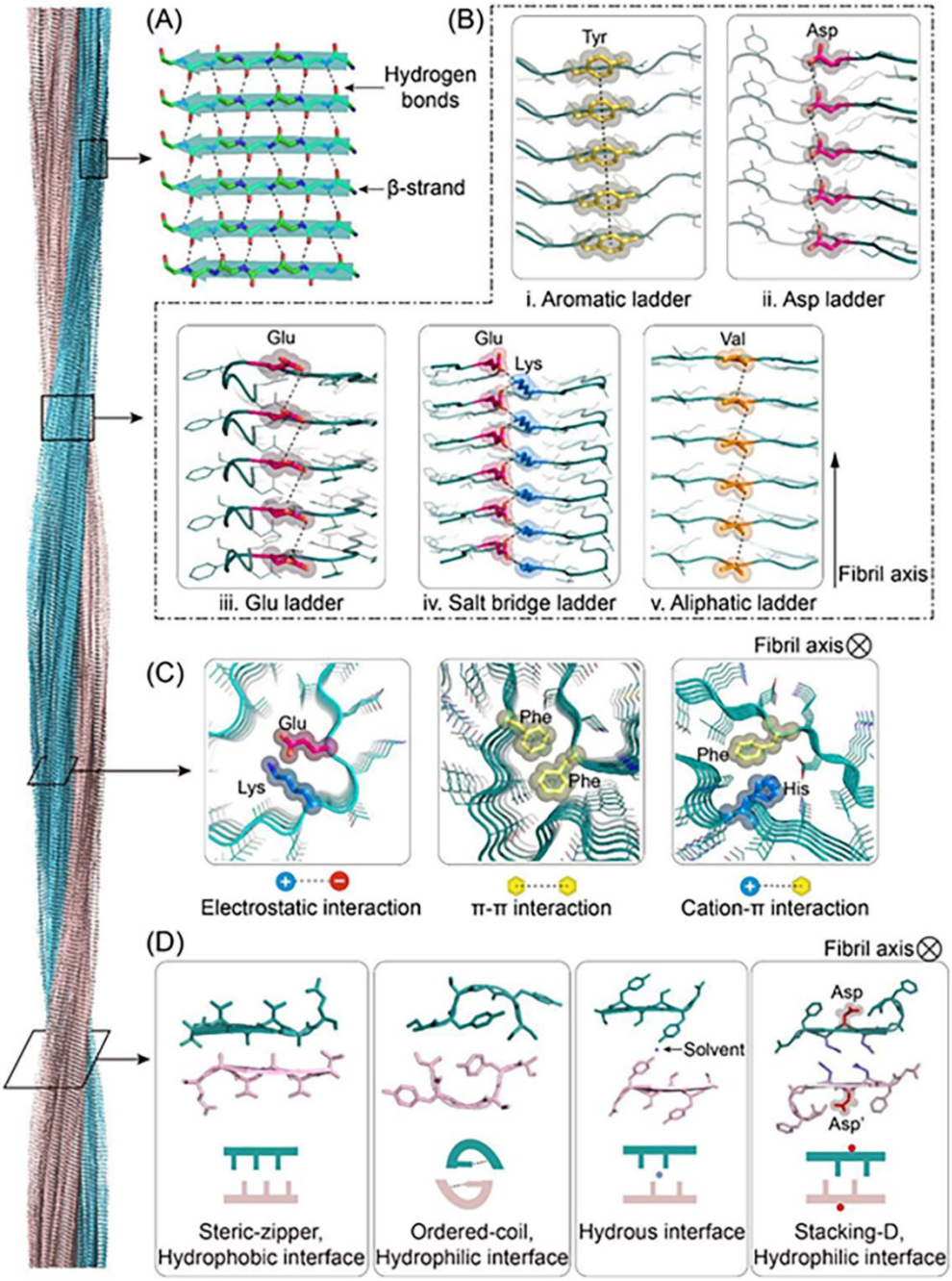

Figure 2. *Building blocks and intramolecular and intermolecular interactions in amyloid fibrils. (A) Five-stranded parallel β-sheet architecture shown in cartoon representation, with backbone atoms displayed in stick format. Inter-strand hydrogen bonds within β-sheet layers along the fibril axis are indicated by arrows. (B) Views along the fibril axis of cryo-electron microscopy (cryo-EM) amyloid fibril structures illustrating five distinct side-chain packing motifs. (C) Top views perpendicular to the fibril axis highlighting three representative side-chain interaction patterns; residues participating in side-chain ladders are shown as spheres. (D) Top views perpendicular to the fibril axis depicting four distinct modes of inter-protofilament interaction. Reproduced with permission from ref. 67 Copyright 2023 Wiley.*

simple on-pathway precursors to fibrils, oligomers are now understood as structurally diverse species that occupy distinct regions of the protein energy landscape. Their ability to interconvert, persist, or dissociate from fibril surfaces adds a further layer of complexity to aggregation models. Such behaviour complicates therapeutic strategies that target fibrils alone and reinforces the need for structural resolution across multiple aggregation states.

Computational modelling has emerged as a critical tool for bridging experimental gaps, particularly for transient and heterogeneous species that evade direct structural characterization. Recent studies have increasingly adopted multiscale strategies that combine coarse-grained sampling with atomistic refinement. The work by Puławski et. al exemplifies this trend, demonstrating how coarse-grained docking can efficiently generate fibrillar oligomer ensembles that are subsequently refined into realistic protofilament models using molecular dynamics.[67] This approach addresses longstanding challenges associated with time-scale limitations and force-field accuracy in all-atom simulations of aggregation processes. At the molecular level, simulations have also provided insight into how amyloid fibril surfaces influence secondary aggregation phenomena. Recent molecular dynamics studies by Zou and Ågren revealed that fibril surfaces can act as structural templates, inducing ordered aggregation of small molecules through cooperative hydrogen bonding and π–π stacking interactions.[72] Their work on tau fibrils demonstrated that ligands exhibit high conformational disorder in solution but adopt highly ordered, crystal-like assemblies when bound to fibril surfaces. These findings highlight the active role of fibrillar architecture in directing molecular organization and suggest that fibrils themselves can participate in templated aggregation processes beyond protein self-assembly.

Recent structural and computational investigations increasingly point toward amyloid aggregation as a process shaped by interdependent contributions from primary sequence, local environment, and aggregation kinetics. Rather than converging on a single structural endpoint, amyloid-forming proteins populate ensembles of fibrillar and prefibrillar states whose properties are determined by their formation pathways and molecular context. This perspective is supported by observations of fibril polymorphism and oligomer heterogeneity across multiple systems, which indicate that aggregation outcomes cannot be fully rationalised without accounting for kinetic history and surface-mediated interactions.[2, 13, 33] Such structural diversity has important consequences for therapeutic intervention, as it implies that effective modulation of aggregation requires precise targeting of specific conformational states or interfaces rather than generic suppression of fibril formation. In this regard, high-resolution structural models reported in recent years have enabled more refined identification of aggregation-prone motifs, toxic surfaces, and templating regions that govern intermolecular recognition. The growing integration of computational prediction with experimentally constrained modelling has further enhanced this capability, allowing aggregation mechanisms to be interrogated with reduced experimental overhead while maintaining mechanistic fidelity. This shift toward structure-informed and computationally guided analysis provides a foundation for developing targeted strategies that are both mechanistically robust and compatible with sustainability-oriented research paradigms.

2.2. Physicochemical Determinants Governing Aggregation

Recent studies increasingly frame amyloid aggregation as an energy-driven process shaped by a delicate balance between intrinsic sequence-encoded features and extrinsic environmental influences.[6] Rather than acting independently, these factors collectively remodel the protein free-energy landscape, thereby regulating the formation, maturation, and diversification of amyloid assemblies. Advances over the past few years have refined this view by providing quantitative and structural evidence for how aggregation pathways are selected and amplified under physiological and pathological conditions. At the molecular level, intrinsic sequence determinants remain central to aggregation propensity. Aggregation-prone regions enriched in hydrophobic and β-sheet-favouring residues have been identified as key stabilizing elements within amyloid fibrils.[15-16] Recent energetic profiling studies by the Schymkowitz and Rousseau groups have provided residue-level thermodynamic insight into this phenomenon by analysing cryo-EM-derived fibril structures of amyloid-β, tau, α-synuclein, and islet amyloid polypeptide.[73] Their 2025 work demonstrated that fibril maturation is anchored by a limited number of sequence-encoded aggregation-prone motifs that act as energetic stabilisation cores, while surrounding regions introduce varying degrees of structural frustration that enable polymorphic divergence. This framework offers a quantitative basis for understanding why distinct fibril polymorphs can arise from the same primary sequence under different conditions.

Post-translational modifications further modulate these intrinsic driving forces by altering local charge distribution, conformational flexibility, and intermolecular interaction patterns. Recent experimental and computational studies indicate that phosphorylation, truncation, and oxidative modifications can selectively stabilise or destabilise specific aggregation intermediates, thereby biasing aggregation pathways rather than simply accelerating or inhibiting fibril formation.[17-18] Such effects are increasingly interpreted through the lens of altered nucleation barriers and changes in secondary nucleation efficiency, rather than through binary aggregation outcomes. Extrinsic physicochemical conditions exert equally profound control over amyloid assembly. Solution pH and ionic strength remain among the most influential parameters, as they directly affect electrostatic interactions and protein solubility. Time-resolved cryo-EM studies on tau fibril formation have shown that subtle changes in buffer composition can reproducibly direct aggregation toward disease-relevant polymorphs.[29-30, 35] For example, the presence of divalent cations or specific salts has been shown to stabilise distinct protofilament interfaces, leading to fibril structures closely resembling those isolated from patient tissue. These findings reinforce the notion that environmental context is not merely permissive but actively instructive in amyloid assembly.

Metal ions represent a particularly important class of extrinsic modulators. Recent work has expanded earlier observations by demonstrating that metal ions can participate directly in fibril maturation rather than acting solely as aggregation accelerants.[74-75] Energetic analyses of cryo-EM fibril structures revealed that metal ions and polyanionic cofactors are frequently associated with regions of structural remodelling, where they compensate for local energetic strain and stabilise otherwise unfavourable conformations. This supports a model in which metal coordination contributes to polymorphic selection by reshaping the energetic landscape during fibril growth. Interfaces and surfaces have also emerged as critical drivers of aggregation in both experimental and biological contexts. Lipid membranes, cellular organelles, and nanoscale surfaces can locally concentrate proteins, promote partial unfolding, and lower nucleation barriers. Recent molecular simulations and spectroscopic studies suggest that membrane-associated aggregation often favours oligomeric species with enhanced membrane affinity and toxicity.[76-77] Such surface-mediated pathways are increasingly implicated in cellular dysfunction, particularly in neurodegenerative diseases where membrane integrity is compromised at early stages. Molecular crowding further complicates aggregation behaviour under physiological conditions. High macromolecular concentrations within cells restrict available

volume and alter diffusion dynamics, thereby favouring compact and aggregated states. Recent biophysical studies indicate that crowding does not uniformly accelerate aggregation but can selectively enhance secondary nucleation and fibril fragmentation processes, leading to rapid amplification of toxic species even when primary nucleation remains slow.[13, 78] Kinetic factors have gained renewed attention as dominant determinants of amyloid toxicity and propagation. Work from the Knowles and Dobson groups has emphasised that secondary nucleation processes, in which existing fibrils catalyse the formation of new aggregates on their surfaces, are often the principal source of cytotoxic oligomers.[14] This insight has shifted focus away from total fibril burden toward kinetic control points within the aggregation cascade. Recent modelling and experimental validation indicate that modest perturbations to secondary nucleation rates can produce disproportionately large effects on aggregate load and toxicity.[79]

Recent evidence therefore supports a view of amyloid aggregation in which thermodynamic stability and kinetic accessibility are inseparably linked. Aggregation pathways appear to be continuously reshaped by competition between stabilizing sequence-encoded interactions, environmentally imposed constraints, and amplification processes such as fragmentation and surface-catalyzed nucleation. Within this framework, fibril formation cannot be interpreted solely in terms of end-state stability, as relatively subtle perturbations to kinetic parameters may redirect aggregation toward structurally and biologically distinct species. Such sensitivity to pathway modulation has important implications for therapeutic intervention, since effective control of aggregation may be achieved by targeting specific kinetic bottlenecks or interfacial processes rather than suppressing fibril growth globally.[80] Approaches that exploit this selectivity, particularly when guided by quantitative modelling and constrained experimentation, offer a route to intervention strategies that are both mechanistically precise and compatible with sustainability-driven design principles.

2.3. Pathophysiological Manifestations of Amyloid Deposition

Amyloid deposition gives rise to a broad spectrum of pathophysiological manifestations that reflect both the molecular properties of the aggregating protein and the biological context in which deposition occurs. Rather than being determined solely by fibril load, tissue dysfunction emerges from a combination of aggregate structure, spatial distribution, and interaction with local cellular and extracellular components. Recent clinical and mechanistic studies increasingly support the view that amyloid-related pathology is shaped by dynamic interactions between misfolded protein assemblies and tissue-specific vulnerabilities. In systemic amyloidoses, circulating precursor proteins enable widespread deposition across multiple organs, leading to progressive and often overlapping clinical phenotypes. Transthyretin amyloidosis provides a well-characterised example of this process. Recent analyses synthesised by Tschöpe, Elsanhoury, and Kristen indicate that both hereditary and wild-type transthyretin variants can produce heterogeneous patterns of cardiac, neurological, renal, and ocular involvement, even among patients carrying the same genetic mutation.[81] This phenotypic diversity has been attributed not only to differences in tetramer stability but also to tissue-specific factors such as extracellular matrix composition, mechanical stress, and local proteolytic activity, all of which influence fibril formation and persistence.

Cardiac involvement illustrates how amyloid deposition translates into organ-specific dysfunction. In transthyretin amyloid cardiomyopathy, extracellular fibril accumulation within the myocardial interstitium increases ventricular stiffness, disrupts diastolic filling, and progressively impairs systolic performance. However, recent imaging and biomarker studies suggest that functional decline often precedes extensive fibril accumulation, implicating soluble oligomers and early fibrillar assemblies in myocardial toxicity.[82-83] This observation aligns with emerging evidence that amyloid-related cardiotoxicity reflects alterations in cellular signalling, calcium handling, and microvascular function rather than passive mechanical infiltration alone. Neurological manifestations similarly reflect complex interactions between amyloid assemblies and cellular architecture. In amyloid polyneuropathies, fibril deposition within peripheral nerves compromises axonal transport and Schwann cell function, leading to length-dependent sensory and motor deficits. Clinical data from recent cohort studies indicate that autonomic dysfunction often develops early and may progress independently of overt fibril burden, suggesting that prefibrillar species and local inflammatory responses play a significant role in neuronal injury. These findings challenge earlier models that linked neurological decline directly to cumulative fibril deposition. In disorders traditionally classified as localised amyloidoses, such as Alzheimer's and Parkinson's diseases, amyloid pathology remains spatially constrained but exhibits pronounced regional heterogeneity. Recent biomarker-driven studies in preclinical and prodromal populations have demonstrated that amyloid deposition follows reproducible spatial patterns that correlate with synaptic vulnerability and network connectivity. Work from the ALFA cohort has shown that early amyloid accumulation in specific cortical regions is associated with subtle alterations in cerebrospinal fluid biomarker ratios and structural brain metrics, even in cognitively unimpaired.[84] These observations suggest that amyloid pathology interacts with region-specific metabolic and connectivity profiles to shape disease progression.

Inflammatory responses have emerged as a unifying modifier of amyloid-associated pathology across both systemic and localised diseases. Recent studies have revealed that extracellular protein assemblies released during innate immune activation can actively participate in amyloid propagation. Notably, work by Pelegrin et. al demonstrated that oligomeric ASC specks released from activated inflammasomes can act as scaffolds for amyloid deposition, thereby linking chronic inflammation to accelerated tissue pathologies.[85] This mechanism provides a molecular explanation for the frequent coexistence of amyloid deposition with inflammatory and degenerative processes. The heterogeneity of pathophysiological manifestations is further compounded by fibril polymorphism. Cryo-electron microscopy studies have revealed that amyloid fibrils extracted from different tissues, or from different patients, often adopt distinct conformations with variable surface properties.[30, 35] Such structural variation is increasingly recognised as a determinant of tissue tropism, cellular toxicity, and responsiveness to therapeutic intervention. Differences in fibril architecture may influence interactions with membranes, extracellular matrix components, and immune receptors, thereby modulating disease course at the tissue level.

Current evidence indicates that the clinical manifestations of amyloid diseases arise from a convergence of structural, kinetic, and biological factors rather than from amyloid deposition per se. Tissue damage reflects the interplay between aggregate species, local microenvironment, and host response mechanisms. Framing amyloid pathology in this manner provides a mechanistic bridge between aggregation processes and disease phenotypes, and it supports the development of intervention strategies that target context-specific drivers of dysfunction rather than focusing exclusively on fibril removal.

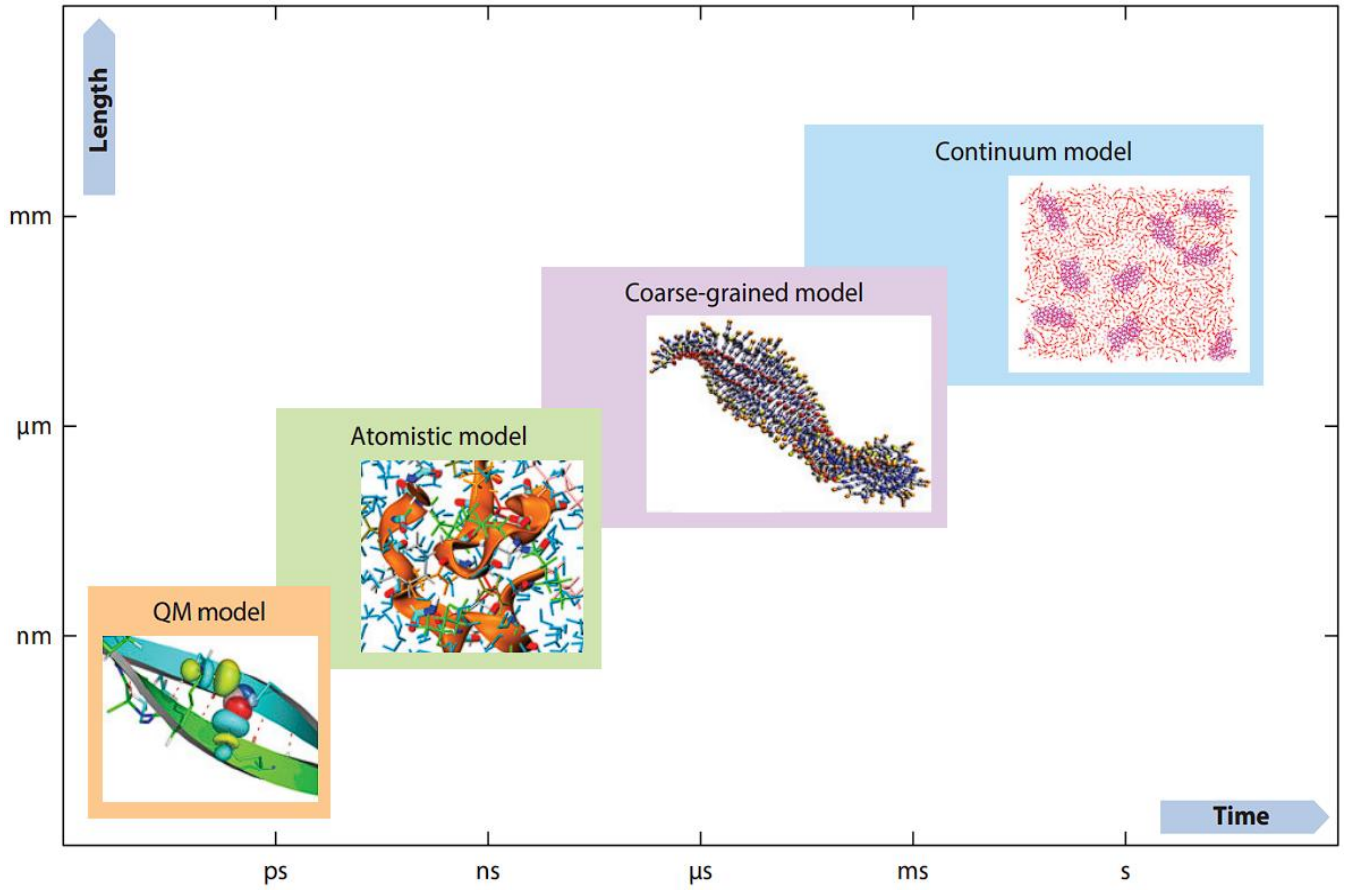

Figure 3. *The approximate timescales involved in different classes of molecular simulations: quantum mechanical (QM), atomistic, coarse-grained, and continuum models. Reproduced with permission from ref. 93 Copyright 2015 Annual Review of Physical Chemistry.*

3. Probing Amyloid Aggregation: Sustainable Characterization Approaches

A detailed interrogation of amyloid aggregation requires methodological frameworks capable of resolving both structural organisation and dynamic evolution across multiple length and time scales. Over the past several years, progress in this area has been driven by the combined application of computational modelling and experimental biophysical characterisation, which together have reshaped how aggregation pathways are examined and interpreted. Rather than relying on single-technique descriptions, contemporary studies increasingly adopt integrated strategies that allow aggregation to be followed from early misfolding events through oligomer formation and eventual fibril maturation.[86-87] As illustrated in Figure 3, quantum mechanical, atomistic, coarse-grained, and continuum models collectively span time scales ranging from picoseconds to seconds and length scales from nanometres to micrometres, enabling complementary interrogation of local electronic interactions, conformational dynamics, mesoscale assembly, and collective behaviour. Molecular dynamics simulations, coarse-grained representations, and data-driven prediction tools have therefore been used to identify aggregation-prone regions, interrogate nucleation mechanisms, and quantify free-energy barriers associated with distinct stages of assembly. Importantly, recent computational studies emphasise pathway sensitivity rather than static end states, highlighting how subtle changes in sequence, post-translational modification, or environmental conditions can redirect aggregation trajectories.[88-89] Such approaches are increasingly valued not only for their mechanistic insight but also for their efficiency, as they enable targeted hypothesis testing while reducing experimental redundancy and resource consumption.

Experimental biophysical methods continue to play a decisive role by providing empirical constraints and structural validation. Spectroscopic techniques such as circular dichroism and fluorescence assays remain widely used to monitor secondary structure evolution and aggregation kinetics in real time. At the same time, high-resolution tools including cryogenic electron microscopy and solid-state nuclear magnetic resonance spectroscopy have delivered detailed structural models of amyloid fibrils, revealing their cross-β architecture and extensive polymorphism.[28, 35] Atomic force microscopy and scattering-based methods further complement these techniques by enabling direct visualisation of aggregate morphology and growth behaviour under controlled conditions. Together, these approaches have clarified how aggregation intermediates and mature fibrils differ in structure, stability, and biological interaction. Increasingly, the strength of amyloid characterisation lies in the convergence of computational prediction with experimental observation. Models generated in silico are now routinely refined and validated using spectroscopic, kinetic, and structural data, leading to more accurate representations of aggregation pathways. This reciprocal refinement has allowed researchers to move beyond descriptive characterisation toward mechanistically informed interrogation of aggregation processes.[25, 90] In the context of sustainability, such integrative methodologies support a shift toward precision-driven experimentation, where focused measurements are guided by predictive frameworks rather than extensive empirical screening. Modern characterisation strategies do more than document amyloid formation. They provide a platform for interrogating how aggregation responds to molecular perturbation, environmental change, and therapeutic intervention. This methodological perspective underpins subsequent discussions of computational and experimental tools, positioning them not as isolated techniques but as components of a coherent strategy for probing and ultimately controlling amyloid aggregation in a rational and resource-conscious manner.

3.1. Computational Modelling Approaches to Understand Amyloid Aggregation

Computational modelling has become integral to contemporary investigations of amyloid aggregation, particularly in contexts where experimental access to early or transient species remains limited. Over the past several years, advances in simulation methodologies and computational power have enabled increasingly detailed interrogation of misfolding pathways, oligomer formation, and fibril growth, allowing aggregation to be analysed as a dynamic, pathway-dependent process rather than a static structural transition.[91-92] These approaches have been especially valuable in resolving how sequence features, environmental perturbations, and intermolecular interactions reshape aggregation landscapes at molecular resolution. Atomistic molecular dynamics simulations continue to form the backbone of computational studies of amyloidogenic proteins. Recent work from groups such as Strodel, Urbanc, and Vendruscolo has focused on capturing early misfolding events and oligomerisation pathways for amyloid-β, α-synuclein, tau, and model peptides under physiologically relevant conditions.[25, 36, 70, 89] Rather than attempting to simulate complete fibril formation directly, many studies now prioritise the identification of metastable intermediates and nucleation-competent conformations. Enhanced sampling techniques, including replica exchange molecular dynamics, metadynamics, and bias-exchange schemes, have been instrumental in overcoming kinetic trapping on rugged free-energy landscapes, enabling rare but functionally important transitions to be accessed within feasible simulation times.[93-94]

Despite these advances, the intrinsic time- and length-scale limitations of all-atom simulations have necessitated the development of reduced-resolution approaches. Coarse-grained models have therefore assumed a prominent role in recent aggregation studies, particularly for exploring collective phenomena such as nucleation rates, fibril elongation, and fragmentation. Coarse-grained frameworks developed by Koliński, Knowles, and co-workers have been used to simulate protofilament assembly and fibril growth kinetics over mesoscopic scales, revealing how cooperative interactions and surface-catalyzed processes dominate aggregation behaviour once critical nuclei are formed.[67] These models have proven particularly effective for linking molecular-level interactions with experimentally observed kinetic laws. A notable trend in recent years has been the increasing integration of data-driven methods with physics-based simulations. Machine learning approaches have been employed to identify aggregation-prone sequence motifs, classify conformational ensembles, and predict aggregation propensity across protein families.[95-96] Tools derived from neural networks and graph-based representations have been trained on structural and kinetic datasets generated from both simulations and experiments, enabling rapid screening of sequence variants and environmental perturbations. Importantly, such models are increasingly used in conjunction with molecular simulations rather than as standalone predictors, allowing mechanistic hypotheses to be refined rather than replaced by statistical inference. Multiscale modelling strategies have further expanded the scope of computational amyloid research by incorporating extrinsic factors that influence aggregation in biological environments. Hybrid approaches that couple atomistic or coarse-grained protein representations with continuum descriptions of solvent, membranes, or crowded media have provided insight into how confinement, surface interactions, and macromolecular crowding modulate aggregation pathways.[97] Recent simulations of membrane-associated aggregation have shown that lipid composition and surface curvature can bias proteins toward oligomeric states with enhanced membrane affinity, offering a mechanistic basis for the early cytotoxicity observed in several neurodegenerative disorders.

Across these diverse modelling approaches, a common shift is evident in how computational results are interpreted. Rather than seeking single dominant structures or pathways, recent studies emphasise ensembles, competing routes, and sensitivity to perturbation. This perspective aligns closely with experimental observations of polymorphism and kinetic heterogeneity and has reinforced the view that aggregation outcomes are dictated by pathway selection rather than thermodynamic endpoints alone. Within this framework, computational modelling functions less as a predictive oracle and more as a hypothesis-generating and hypothesis-constraining tool, guiding targeted experiments and narrowing the space of plausible mechanistic scenarios. As simulation methodologies continue to mature, their role in amyloid research is increasingly defined by integration rather than isolation. Computational models are now routinely refined using experimental constraints and, in turn, inform experimental design by identifying critical variables and control points within aggregation cascades.[98] This reciprocal relationship supports more focused and resource-efficient investigation strategies, which is particularly relevant in the context of sustainability-oriented research and therapeutic development.

3.2. Experimental Biophysical Methods to Study Protein Aggregation

Experimental biophysical techniques remain indispensable for resolving the structural and kinetic features of amyloid aggregation and for anchoring computational predictions in empirical observation. Over the past several years, methodological advances have enabled aggregation processes to be interrogated across multiple stages, from early conformational rearrangements to mature fibril architectures, while increasingly emphasising quantitative interpretation and experimental efficiency. Rather than serving solely as descriptive tools, contemporary biophysical methods are now routinely applied to test mechanistic hypotheses and constrain aggregation models.[99] Spectroscopic techniques continue to provide sensitive readouts of conformational change during aggregation. Circular dichroism (CD) spectroscopy is widely used to monitor protein secondary and tertiary structure,

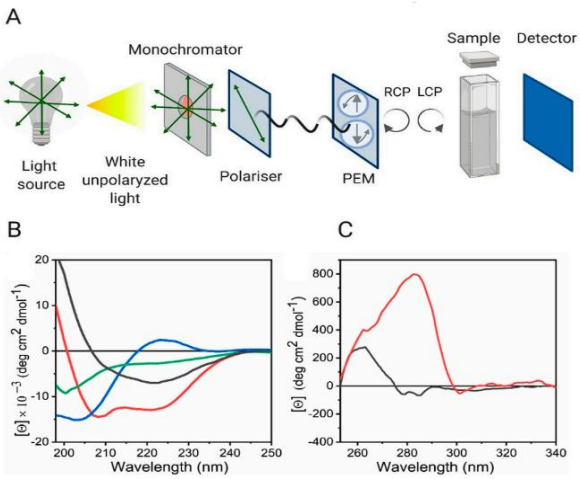

Figure 4. *Circular dichroism spectroscopy as a tool for probing protein secondary and tertiary structure. (A) Schematic illustration of a typical circular dichroism instrument configuration. (B) Representative far-UV CD spectra corresponding to characteristic protein and peptide secondary structures, including random coil, α-helix, β-sheet, and polyproline II conformations. (C) Near-UV CD spectra illustrating tertiary structural contributions from aromatic residues, shown for proteins containing both tryptophan and tyrosine and for proteins containing tyrosine alone. Reproduced with permission from ref. 101 Copyright 2020 MDPI.*

particularly the progressive enrichment of β-sheet content that accompanies amyloid fibril formation. As illustrated in Figure 4, far-UV CD spectra report on backbone conformational changes associated with random coil, α-helical, and β-sheet structures, while near-UV CD signals arise from the chiral environments of aromatic side chains and provide information on tertiary structural organisation. Recent methodological work has emphasised the importance of careful experimental design and data interpretation, as highlighted by Kardos and co-workers, who demonstrated that wavelength selection, concentration effects, and baseline corrections critically influence the reliability of CD measurements for aggregated protein systems.[100] Fourier-transform infrared spectroscopy offers complementary information by resolving amide I band components associated with distinct β-sheet arrangements, enabling discrimination between parallel and antiparallel motifs that may not be readily distinguished by CD alone.[71, 101-102]

Fluorescence-based assays remain central to kinetic analysis of amyloid formation. Thioflavin T (ThT) fluorescence is extensively employed to monitor fibril growth in real time and to extract kinetic parameters associated with nucleation and elongation.[103] However, recent studies have underscored the need for cautious interpretation, as ThT binding affinity and fluorescence response can vary significantly between fibril polymorphs and aggregation conditions. As a result, fluorescence assays are increasingly combined with orthogonal measurements to avoid overreliance on single-probe readouts and to improve mechanistic resolution. Microscopy techniques provide direct access to aggregate morphology and spatial organisation. Atomic force microscopy (AFM) has been widely used to visualise fibril growth, branching, and surface heterogeneity under near-physiological conditions.[32] Its ability to resolve height profiles and mechanical properties has proven particularly useful for distinguishing between oligomeric species, protofibrils, and mature fibrils. Transmission electron microscopy complements AFM by offering higher lateral resolution and broader field-of-view imaging, allowing aggregate populations to be assessed across different stages of assembly. Recent applications increasingly integrate microscopy with kinetic sampling, enabling structural snapshots to be correlated with specific phases of aggregation. High-resolution structural characterisation has been transformed by cryogenic electron microscopy (cryo-EM) and solid-state nuclear magnetic resonance spectroscopy (ssNMR). Cryo-EM has enabled near-atomic reconstruction of amyloid fibrils derived from diverse proteins, revealing extensive polymorphism in protofilament organisation and inter-sheet packing.[35] These structures have provided critical insight into how sequence and environment influence fibril architecture. ssNMR has further enriched this picture by resolving site-specific conformational heterogeneity and residue-level dynamics within fibrils.[28] The combination of cryo-EM and ssNMR has been particularly powerful in establishing structure–function relationships and in validating computationally derived models. Scattering techniques offer additional perspectives on aggregation in solution. Dynamic light scattering is frequently employed to detect early changes in particle size distribution and to identify the onset of aggregation under varying conditions. Small-angle X-ray scattering (SAXS) provides low-resolution structural information on aggregate shape and assembly state, enabling comparison between solution-phase species and surface-adsorbed or dried aggregates observed by microscopy.[104] Recent studies increasingly exploit SAXS as a bridge between kinetic assays and high-resolution structural methods, particularly for monitoring intermediate states.

Across these approaches, a notable shift has occurred toward integrative experimental design. Rather than applying techniques in isolation, recent studies emphasise cross-validation, quantitative consistency, and minimal redundancy. Experimental datasets are increasingly generated with explicit reference to computational predictions, allowing targeted measurements to test specific mechanistic scenarios. This convergence has improved both interpretability and efficiency, supporting a more sustainable approach to amyloid characterisation in which experimental effort is focused on resolving critical uncertainties rather than exhaustively cataloguing aggregate properties.

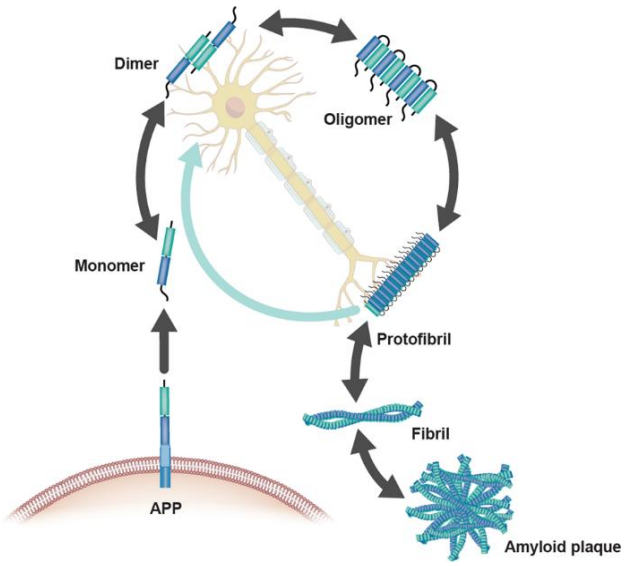

Figure 5. *Overview of in vivo strategies for staging amyloid-β pathology across the clinical progression of Alzheimer's disease, integrating molecular imaging modalities with advanced computational and algorithm-driven analytical frameworks. Reproduced with permission from: ref. 105 Copyright 2021 Springer Nature.*

4. Disease-Specific Insights into Amyloid Control

Computational approaches have become increasingly influential in clarifying how general principles of amyloid aggregation manifest in specific disease contexts. While the physicochemical drivers of misfolding and assembly share common features across amyloid systems, disease-associated proteins exhibit distinct sequence compositions, cellular environments, and pathological trajectories that shape their aggregation behaviour. Recent computational studies have therefore shifted toward protein- and disease-specific modelling, aiming to resolve how universal aggregation mechanisms are modulated by molecular context and biological constraints. In neurodegenerative disorders, such disease-focused computational analyses have provided insight into why structurally related aggregation processes give rise to divergent pathological outcomes. Simulations of amyloidogenic proteins now routinely interrogate not only fibril formation but also the dynamic equilibrium between monomers, oligomers, and higher-order assemblies under conditions relevant to disease progression. This has been particularly important for understanding how differences in aggregation kinetics, structural polymorphism, and intermolecular interactions translate into variable toxicity and propagation patterns across disorders.

In Alzheimer's disease, computational modelling of amyloid-β peptides has been central to dissecting the molecular origins of aggregation heterogeneity at the molecular level. Recent simulations have examined how peptide length, sequence composition, and environmental factors influence nucleation pathways and oligomer stability, revealing that amyloid-β aggregation proceeds through multiple competing assembly routes rather than a single

dominant pathway. At the systems and clinical scale, these molecular insights complement in vivo imaging approaches that track the spatial and temporal progression of amyloid pathology. As illustrated in Figure 5, molecular imaging combined with advanced algorithmic analysis enables staging of amyloid-β deposition across the clinical continuum of Alzheimer's disease, providing a macroscopic correlate to the heterogeneous aggregation processes identified through computational and biophysical studies.[105] Such findings have contributed to a more nuanced understanding of toxicity, in which pathogenicity is linked to specific conformational states rather than total fibril burden.

Comparable insights have emerged from computational investigations of α-synuclein aggregation in Parkinson's disease. Owing to its intrinsically disordered nature, α-synuclein presents particular challenges for structural characterisation, making computational approaches especially valuable. Recent simulations have examined how transient secondary structure formation, long-range intramolecular contacts, and intermolecular β-sheet alignment cooperate to drive oligomerisation and fibril growth.[59, 106] These studies also demonstrate how familial mutations and post-translational modifications bias aggregation pathways by altering conformational ensembles and interaction networks, thereby predisposing proteins toward pathogenic assembly. Computational studies of polyglutamine-expanded huntingtin fragments have further illustrated how sequence repetition and chain length influence aggregation dynamics. Simulations performed over the past several years have revealed that polyglutamine tracts exhibit length-dependent transitions from disordered coils to β-sheet-rich assemblies, with intermediate states that promote cooperative aggregation. These models have provided mechanistic insight into how expansion beyond a critical threshold alters nucleation barriers and stabilises aggregation-prone conformations, offering a molecular explanation for the sharp onset of pathology in Huntington's disease.

Across these disease contexts, integration of computational modelling with experimental observation has become increasingly sophisticated. Multiscale approaches that combine atomistic resolution with mesoscale dynamics allow aggregation processes to be examined under conditions that better approximate the crowded and heterogeneous cellular environment. Machine learning methods applied to simulation-derived datasets have further enabled rapid identification of aggregation-prone motifs and sensitivity to perturbation, supporting comparative analysis across disease-relevant proteins. Disease-specific computational studies underscore that amyloid aggregation cannot be fully understood without accounting for protein identity, cellular milieu, and pathological context. Rather than treating aggregation as a uniform process, recent work emphasises how subtle molecular differences are amplified into distinct disease phenotypes. This perspective provides a rational basis for developing targeted strategies aimed at controlling amyloid formation in a context-dependent manner, with computational modelling serving as a critical tool for identifying and prioritising disease-relevant intervention points.

4.1. Amyloid-β Aggregation in Alzheimer's Disease

Aggregation of amyloid-β peptides remains one of the most intensively studied molecular processes in Alzheimer's disease, owing to its central role in plaque formation and downstream neurotoxicity.[107-108] Computational modelling has been particularly influential in refining current understanding of how amyloid-β transitions from a largely disordered monomeric

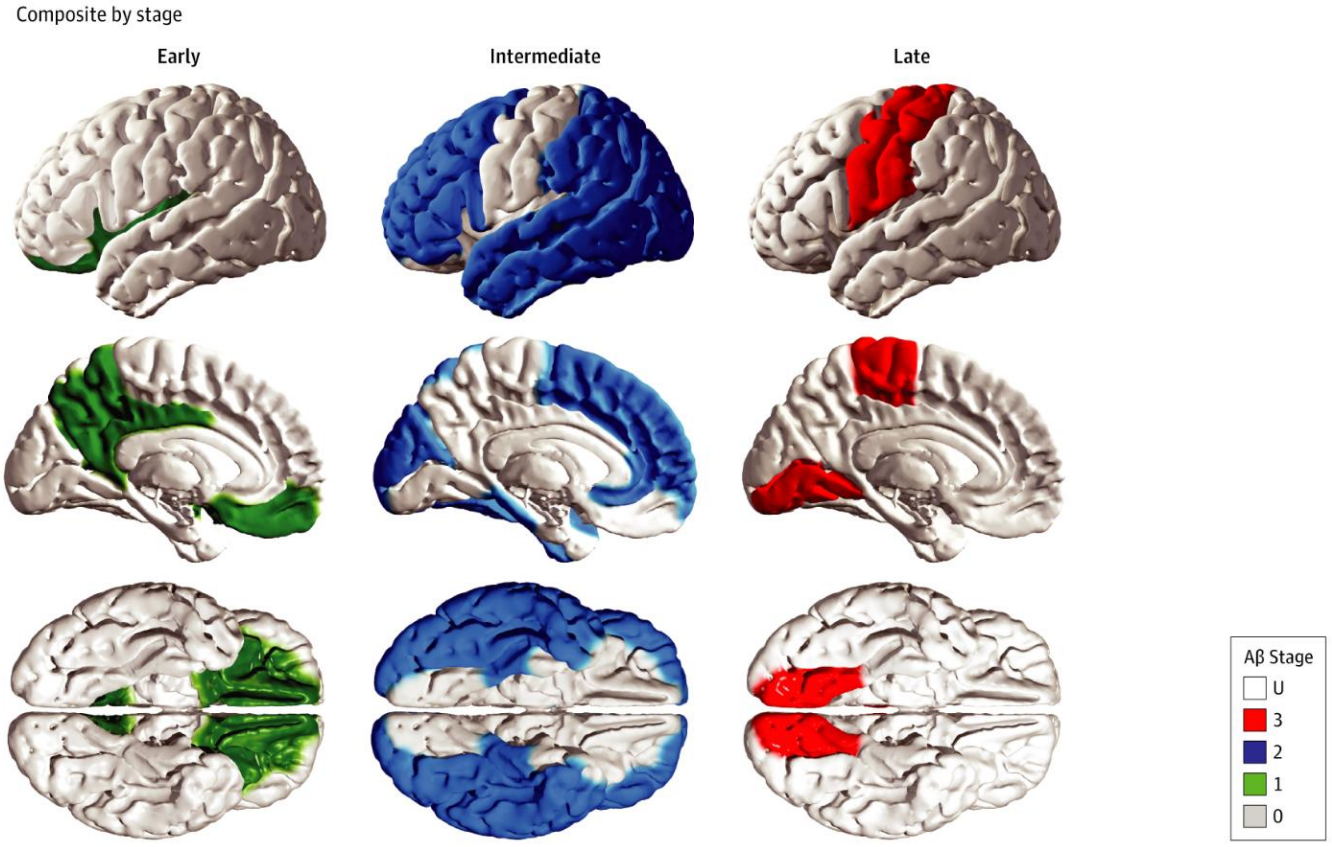

Figure 6. *In vivo staging of amyloid-β deposition along the Alzheimer's disease clinical continuum using molecular imaging and algorithm-based analysis. Composite neocortical distributions of [^{18}F]-florbetapir PET signals are shown for early (stage 1), intermediate (stage 2), and late (stage 3) amyloid-β accumulation, enabling both regional and global assessment of amyloid plaque burden across disease progression. Adapted with permission from: ref. 111 Copyright 2019 American Medical Association.*

ensemble into oligomeric and fibrillar assemblies. Rather than depicting aggregation as a single linear pathway, recent simulations increasingly describe a network of competing conformational routes that are sensitive to peptide length, sequence composition, and local environment.[93, 109] Atomistic molecular dynamics simulations have provided detailed insight into early misfolding events that precede stable aggregate formation. Studies from groups such as Shea, Strodel, Urbanc, and Vendruscolo have examined how transient β-hairpin formation and inter-residue hydrophobic contacts promote intermolecular association of Aβ peptides.[110-112] Enhanced sampling approaches, including replica exchange molecular dynamics and metadynamics, have been critical for accessing these rare but aggregation-relevant conformational states.[113-114] Recent work has demonstrated that short sequence motifs within the central hydrophobic core and C-terminal region play a disproportionate role in stabilizing nucleation-competent conformations, with familial mutations altering local flexibility and intermolecular contact patterns in ways that bias aggregation pathways.[115]

While atomistic simulations excel at resolving early-stage conformational transitions, coarse-grained models have enabled exploration of aggregation kinetics over extended length and time scales. Over the past several years, coarse-grained frameworks developed by Knowles, Koliński, and co-workers have been used to investigate secondary nucleation, fibril elongation, and fragmentation processes that dominate amyloid-β aggregation under physiological conditions.[58, 67, 116] These studies demonstrate that surface-catalyzed nucleation on existing fibrils is a major source of new oligomeric species, supporting experimental evidence that pathogenicity is more closely linked to kinetic amplification processes than to total fibril mass.[14] At the clinical scale, these molecular and kinetic insights are complemented by in vivo imaging approaches that track the spatial progression of amyloid pathology. As shown in Figure 6, positron emission tomography using [^{18}F]-florbetapir enables staging of amyloid-β deposition across early, intermediate, and late phases of Alzheimer's disease, providing a macroscopic readout of aggregate accumulation that reflects the cumulative outcome of underlying aggregation dynamics. Integration of such imaging data with computational and biophysical models supports a multiscale framework in which molecular mechanisms of aggregation are linked to region-specific patterns of plaque burden observed during disease progression.[36, 117] This perspective challenges earlier assumptions that a single dominant oligomer species drives toxicity and instead supports a model in which structural heterogeneity and interconversion are intrinsic features of the aggregation process. Computational predictions of oligomer stability and interfacial exposure have also been used to rationalise differences in membrane affinity and synaptic toxicity reported in experimental studies.[69]

Computational approaches have also been applied to interrogate how environmental factors relevant to Alzheimer's disease modulate amyloid-β aggregation. Simulations incorporating metal ions, lipid membranes, and molecular crowding have demonstrated that these extrinsic elements can selectively stabilise specific aggregation pathways.[61, 118] In particular, membrane-associated simulations suggest that lipid composition and surface curvature influence oligomer structure and persistence, providing a mechanistic basis for early membrane disruption observed in neuronal systems.[119]

4.2. α-Synuclein Assembly in Parkinsonian Disorders

Misfolding and aggregation of α-synuclein constitute a central molecular event in Parkinsonian disorders, where intracellular inclusions enriched in fibrillar α-synuclein are closely associated with neuronal dysfunction and loss.[65, 120] Unlike many amyloidogenic proteins, α-synuclein is intrinsically disordered in its monomeric state, a feature that confers pronounced conformational plasticity and complicates structural characterisation.[121] Computational modelling has therefore assumed a particularly prominent role in elucidating how this disordered ensemble evolves toward aggregation-competent states under pathological conditions. Atomistic molecular dynamics simulations have been extensively employed to explore the conformational landscape of monomeric and oligomeric α-synuclein. Recent studies from groups including Strodel and Vendruscolo have demonstrated that transient secondary structure formation, particularly within the non-amyloid-β component region, promotes intermolecular association by stabilizing β-sheet-prone conformations.[122-123] Enhanced sampling techniques such as replica exchange molecular dynamics and metadynamics have been essential for capturing these low-population conformers, which are rarely observed in unbiased simulations but appear to play a decisive role in early oligomerisation. These findings support a model in which aggregation is initiated not by global folding transitions but by localised structural ordering within an otherwise disordered chain.

Coarse-grained simulations have complemented atomistic studies by enabling exploration of aggregation kinetics over extended length and time scales. Recent multiscale investigations have examined how monomer concentration, sequence composition, and environmental variables influence nucleation and fibril growth. Such models indicate that α-synuclein aggregation is highly sensitive to solution conditions, with modest changes in pH, ionic strength, or crowding leading to pronounced shifts in aggregation pathways. Familial Parkinson's disease mutations, including A30P, E46K, and A53T, have been shown in simulations to alter intramolecular contact patterns and intermolecular alignment, thereby biasing the system toward distinct oligomeric and fibrillar assemblies.[123-124] A defining feature of α-synuclein pathology is the apparent ability of aggregates to propagate in a prion-like manner. Computational studies have contributed to mechanistic understanding of this phenomenon by examining how preformed fibrils and oligomers template the conversion of soluble monomers into aggregation-competent conformations.[63] Simulations of fibril surface interactions suggest that templated β-sheet formation is facilitated by complementary electrostatic and hydrophobic interactions along exposed fibril interfaces. This surface-mediated process provides a molecular explanation for experimental observations of seeded aggregation and intercellular spread.

The role of cellular membranes has also been a major focus of recent computational work. α-Synuclein exhibits strong affinity for lipid bilayers, and simulations incorporating membrane models have shown that membrane binding stabilises partially helical conformations that can either suppress or promote aggregation depending on lipid composition and curvature. Under certain conditions, membrane-associated oligomers exhibit enhanced stability and membrane-disruptive potential, offering a mechanistic link between aggregation and early synaptic dysfunction observed in Parkinsonian disorders.[59-60, 69] Within this evolving computational framework, α-synuclein aggregation is increasingly viewed as a context-dependent process shaped by competing interactions rather than a single deterministic pathway. Computational analyses have therefore shifted toward identifying aggregation-sensitive regions, interfacial contacts, and environmental triggers that govern pathway selection. Such insights are being used to prioritise intervention points that target early misfolding events or surface-mediated amplification processes, rather than focusing exclusively on mature fibrils.[125] This approach aligns with broader efforts to develop mechanism-guided strategies for modulating aggregation in Parkinsonian disorders.

4.3. Polyglutamine Expansion and Huntington's Disease

Huntington's disease arises from the expansion of polyglutamine tracts within the huntingtin protein, leading to aberrant self-assembly and progressive neurodegeneration. Unlike amyloid-β or α-synuclein, polyglutamine-driven aggregation is dominated by repetitive sequence motifs whose length-dependent behaviour strongly influences disease onset and severity. Computational modelling has therefore played a central role in clarifying how polyglutamine expansion alters conformational preferences, aggregation kinetics, and structural organisation at multiple scales.[126-127] Atomistic molecular dynamics simulations have been widely applied to examine the conformational landscapes of polyglutamine segments of varying lengths. Recent studies indicate that expansion beyond a critical threshold promotes stabilisation of β-sheet-rich conformations that are otherwise transient or weakly populated in shorter polyglutamine tracts.[128-130] These simulations further show that polyglutamine chains exhibit a pronounced tendency toward intermolecular hydrogen bonding and side-chain interdigitation, features that facilitate nucleation and early oligomer formation. The influence of flanking sequences has also been examined, with computational results suggesting that adjacent non-polyglutamine regions can modulate aggregation by altering chain flexibility, solvent exposure, and intermolecular alignment.[131-132]

While atomistic simulations provide detailed insight into early conformational transitions, coarse-grained approaches have been essential for probing aggregation dynamics over extended time and length scales. Recent coarse-grained studies have explored how polyglutamine length governs cooperative assembly, revealing that nucleation rates and fibril growth exhibit strong non-linear dependence on repeat number. These models suggest that aggregation in Huntington's disease is not simply accelerated by expansion but qualitatively altered, with longer polyglutamine tracts accessing aggregation pathways that are kinetically inaccessible to shorter sequences. Such findings offer a mechanistic explanation for the sharp disease threshold observed clinically.[133] Data-driven computational strategies have further expanded understanding of polyglutamine aggregation. Machine learning-assisted analyses applied to simulation-derived ensembles have been used to identify structural transitions and interaction patterns associated with increased aggregation propensity and cellular toxicity. Rather than relying on sequence composition alone, these approaches emphasise conformational features such as β-sheet persistence, intermolecular contact lifetimes, and solvent exposure as predictors of pathogenic behaviour. This shift reflects a broader trend toward integrating structural dynamics into aggregation models.[134-135]

Computational investigations have also addressed how cellular factors influence polyglutamine aggregation. Simulations incorporating molecular crowding, confinement, and interaction with cellular components suggest that aggregation pathways are strongly modulated by the intracellular environment. Under crowded conditions, compact and aggregation-prone conformations are preferentially stabilised, potentially accelerating nucleation and promoting the formation of toxic oligomeric species. These observations are consistent with experimental reports of enhanced aggregation in cellular and in vivo systems relative to dilute in vitro conditions.[136-137] From a mechanistic standpoint, computational studies increasingly portray polyglutamine aggregation as a process dominated by repeat-length–dependent loss of conformational plasticity rather than by competition among multiple aggregation routes. Once the polyglutamine tract exceeds a critical length, simulations indicate that intramolecular disorder is progressively replaced by persistent intermolecular β-sheet networks that favour irreversible assembly. In this regime, aggregation kinetics become less sensitive to environmental modulation and more strongly governed by chain length and cooperative hydrogen-bonding patterns. This behaviour distinguishes polyglutamine disorders from other amyloid diseases in which aggregation pathways remain highly tuneable. Computational analyses of huntingtin therefore highlight a fundamental constraint on aggregation control, namely that effective modulation must occur upstream of repeat-driven conformational locking. This insight has direct implications for therapeutic strategy development, as it emphasises the importance of targeting early chain-level conformational bias rather than later-stage fibrillar structures.[138]

5. Sustainable Therapeutic Strategies to Regulate Amyloid Aggregation

Protein misfolding and amyloid aggregation represent attractive yet challenging targets for therapeutic intervention, as these processes lie upstream of irreversible cellular and tissue damage in a wide range of disorders. Early therapeutic efforts largely focused on alleviating downstream symptoms or clearing accumulated deposits, often with limited long-term success. In recent years, attention has increasingly shifted toward strategies that directly modulate aggregation pathways at the molecular level, with the aim of altering misfolding trajectories, suppressing toxic intermediate formation, or destabilising pathogenic assemblies before extensive deposition occurs.[139-140] This shift has coincided with a broader reassessment of how anti-amyloid therapeutics are conceived and evaluated. Rather than prioritising maximal aggregate clearance, contemporary approaches increasingly emphasise selectivity, reversibility, and compatibility with biological and environmental constraints. In this context, sustainability extends beyond material sourcing or synthetic efficiency and encompasses the ability of therapeutic agents to exert controlled modulation of aggregation with minimal off-target effects, reduced systemic burden, and scalable design principles.[141-142] Such considerations have become particularly relevant as mechanistic insight has revealed that indiscriminate suppression of aggregation can disrupt physiological protein homeostasis and lead to unintended consequences.

At the molecular level, most anti-amyloid strategies aim to disrupt the specific non-covalent interactions that stabilise misfolded conformations and drive cooperative self-assembly. Advances in structural biology and computational modelling have enabled precise identification of aggregation-sensitive regions, fibril surfaces, and kinetic control points that govern pathway selection.[55] As schematically illustrated in Figure 7, therapeutic agents such as carbon nanotubes and small molecules can interfere with amyloid formation at multiple stages by suppressing β-sheet organisation, destabilising oligomeric intermediates, or promoting the remodelling and disassembly of preformed fibrils. These effects are mediated through a combination of aromatic stacking, hydrogen bonding, electrostatic, and hydrophobic interactions that compete with protein–protein contacts essential for fibril growth. Importantly, such interventions are increasingly designed to bias aggregation pathways away from toxic species rather than enforcing complete inhibition, consistent with emerging views of pathway-dependent amyloid toxicity. The range of modulators explored, spanning small molecules, nanostructured materials, supramolecular assemblies, peptides, and polymeric systems, reflects both the mechanistic complexity of amyloid aggregation and the need for adaptable, interaction-specific therapeutic strategies.[143-146] Rather than treating these approaches as interchangeable, recent studies increasingly examine how chemical composition, size, flexibility, and interaction modality influence aggregation control, biocompatibility, and long-term stability. This comparative perspective has helped clarify which design

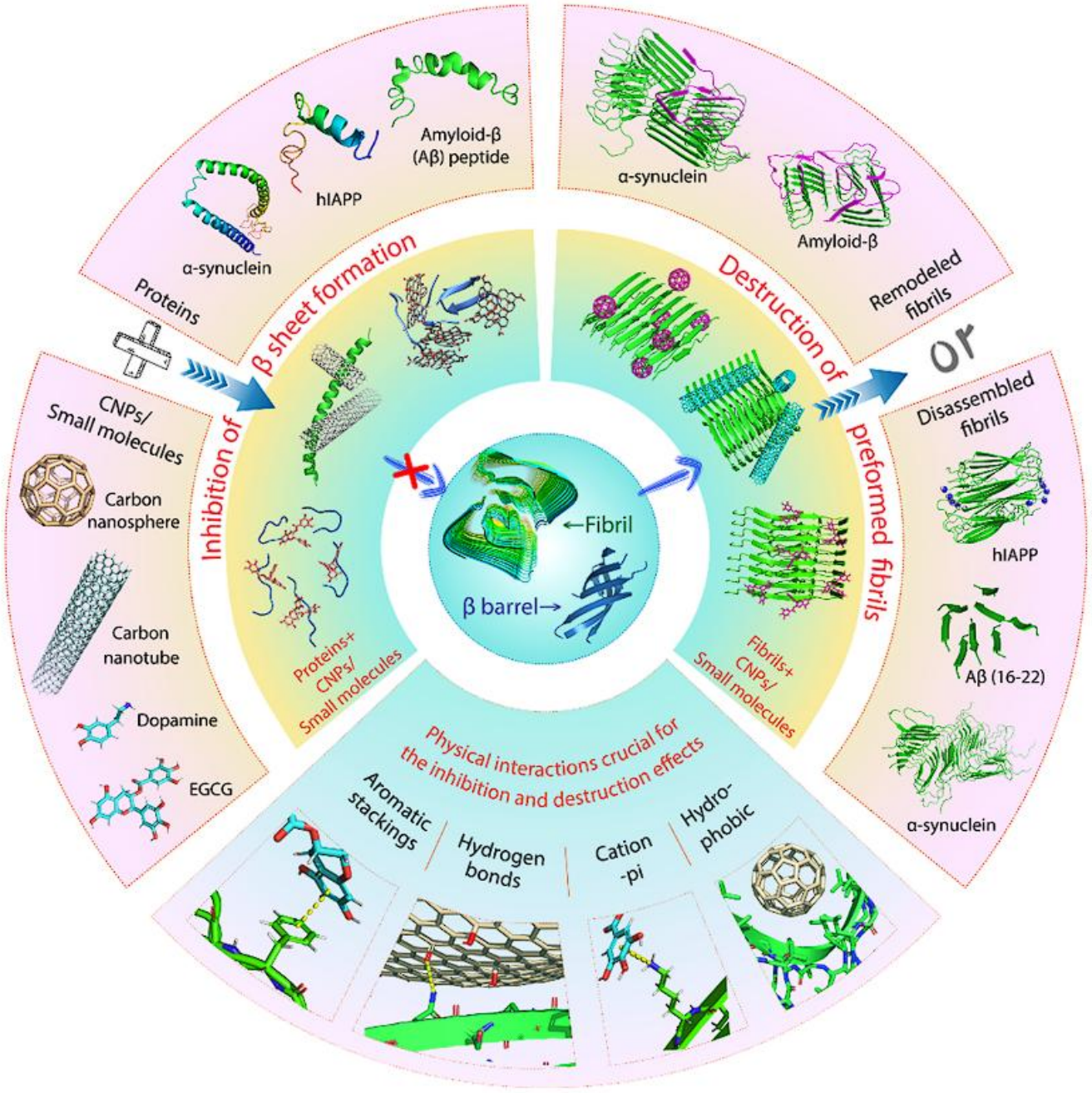

Figure 7. *Schematic overview illustrating the mechanisms by which carbon nanotubes (CNTs) and small-molecule inhibitors regulate amyloid protein aggregation. Amyloidogenic proteins and peptides can self-associate to form β-sheet-rich oligomeric intermediates, including β-barrel-like assemblies, which subsequently evolve into protofibrils and mature fibrils. CNTs and small molecules interfere with these aggregation pathways by inhibiting β-sheet organisation and by destabilising or disrupting preformed protofibrillar and fibrillar structures through non-covalent interactions. These interactions ultimately reduce the formation and persistence of pathogenic amyloid assemblies. Owing to space constraints, representative CNT systems and selected small-molecule inhibitors are illustrated. Reproduced with permission from ref. 145 Copyright 2021 American Chemical Society.*

principles are most effective under specific pathological conditions.

Within this evolving landscape, sustainable therapeutic development is closely linked to rational design and predictive validation. Computational screening, structure-guided optimisation, and targeted experimental evaluation are now routinely combined to reduce empirical trial-and-error and to focus resources on the most promising candidates.[52] This integrated strategy not only accelerates therapeutic discovery but also aligns aggregation control with broader goals of efficiency, safety, and translational feasibility.

5.1. Small Molecule Modulators with Green Design Principles

Small molecules continue to occupy a central position in efforts to regulate amyloid aggregation, owing to their structural tunability, well-established pharmacological profiles, and potential for scalable production. In recent years, however, their development has increasingly been guided by considerations that extend beyond potency alone. Contemporary studies place growing emphasis on molecular simplicity, biocompatibility, and environmentally responsible synthesis, reflecting a broader shift toward green design principles in anti-amyloid drug discovery.[142] Mechanistically,

small molecule modulators exert their effects by interacting with aggregation-sensitive regions of amyloidogenic proteins, thereby altering misfolding trajectories and assembly kinetics. Rather than acting as non-specific aggregation suppressors, many recently reported compounds preferentially stabilise native or partially folded conformations, disrupt early oligomerisation events, or interfere with surface-mediated secondary nucleation.[10, 147] Computational studies have played a key role in identifying these interaction modes by mapping binding hotspots, predicting conformational bias, and evaluating structure–activity relationships prior to synthesis. This predictive capability has reduced experimental redundancy and enabled more focused exploration of chemical space.[148-150] Natural and bio-derived small molecules have attracted particular attention within this framework. Polyphenols, flavonoids, alkaloids, and other secondary metabolites offer chemically diverse scaffolds that are often accessible through low-impact extraction or green synthetic routes. Recent experimental and computational investigations suggest that many of these compounds interact with amyloidogenic proteins through a combination of hydrogen bonding, aromatic stacking, and hydrophobic contacts, allowing them to modulate aggregation without permanently stabilizing off-pathway complexes.[151-152] Their relatively low toxicity and metabolic compatibility further enhance their appeal as sustainable aggregation modulators.

Alongside naturally inspired compounds, rationally designed small molecules with reduced structural complexity have also gained prominence. Minimalist scaffolds that retain key interaction motifs while avoiding excessive functionalisation are increasingly favoured, as they offer improved solubility, reduced off-target interactions, and simplified synthesis. Computational screening and fragment-based design approaches have been particularly effective in this context, enabling systematic optimisation of binding efficiency while adhering to green chemistry principles such as atom economy and reduced solvent usage.[153-154] Importantly, recent studies increasingly evaluate small molecule modulators in terms of how they influence aggregation pathways rather than whether they completely inhibit fibril formation. Compounds that selectively attenuate secondary nucleation or destabilise toxic oligomeric species have been shown to exert disproportionate effects on aggregate load and cytotoxicity, even at relatively low concentrations.[14] This pathway-focused perspective aligns well with sustainability goals, as it favours precise modulation over high-dose intervention and minimises the risk of disrupting normal protein homeostasis.

5.2. Nanomaterial-Based Interventions

Nanomaterial-based strategies introduce a fundamentally different mode of interaction with amyloidogenic proteins by exploiting nanoscale interfaces rather than discrete molecular recognition alone. In contrast to small molecule modulators, nanomaterials exert their influence primarily through surface-driven effects, where size, curvature, and surface chemistry collectively determine how misfolded proteins adsorb, reorganise, or dissociate. Recent studies increasingly frame nanomaterials not as passive aggregation inhibitors but as active modulators of the aggregation energy landscape.[155-156] A defining feature of nanomaterials is their high surface area coupled with tuneable physicochemical properties. Experimental and computational investigations have shown that nanoscale surfaces can selectively bind misfolded monomers or oligomeric species through multivalent interactions, effectively lowering their local concentration in solution and altering nucleation kinetics. Depending on surface chemistry, such interactions can either suppress aggregation by stabilizing non-productive conformations or redirect assembly toward less toxic pathways. This duality has been highlighted in recent work on graphene derivatives, metal oxide nanoparticles, and polymer-coated nanostructures, where subtle changes in surface functionalisation produce markedly different aggregation outcomes.[157-160] Nanoparticles and nanocomposites have been particularly informative in dissecting surface-mediated aggregation mechanisms. Molecular simulations and spectroscopic studies suggest that adsorption onto nanoparticle surfaces can induce partial unfolding or conformational rearrangement of amyloidogenic proteins, thereby disrupting the alignment required for β-sheet propagation. At the same time, excessively strong binding has been shown to promote surface-catalyzed aggregation under certain conditions, underscoring the importance of balanced interaction strength. This sensitivity has prompted increased emphasis on rational surface design guided by computational modelling rather than empirical optimisation alone. Nanotubes and fibrillar nanostructures introduce additional geometric considerations. Their elongated morphology and anisotropic surfaces can template protein alignment along specific axes, influencing fibril growth directionality and polymorphism. Recent simulations indicate that curvature and surface roughness play decisive roles in determining whether such materials inhibit fibril elongation or inadvertently stabilise protofibrillar assemblies.[161] These findings reinforce the view that nanomaterials function as kinetic modifiers whose effects depend strongly on structural compatibility with aggregation intermediates.

From a sustainability perspective, nanomaterial-based interventions have undergone significant conceptual refinement in recent years. Earlier approaches often relied on inorganic or non-degradable materials with limited translational relevance. More recent efforts increasingly focus on biodegradable, bio-derived, or hybrid nanostructures designed to minimise long-term persistence and toxicity.[159, 162] Functionalisation with peptides, polysaccharides, or small organic ligands has been used to enhance selectivity while reducing non-specific protein adsorption. Computational screening of surface chemistries has further enabled prioritisation of designs that achieve aggregation modulation at low material loadings, aligning therapeutic efficacy with resource efficiency. Functionalisation also enables targeting strategies that are difficult to realise with small molecules alone. Ligand-decorated nanomaterials can be engineered to preferentially interact with specific protein conformers, cellular compartments, or microenvironments associated with disease pathology. Recent studies combining multiscale simulations with cellular assays suggest that such targeting can bias nanomaterial–protein interactions toward early aggregation species, thereby modulating pathway selection rather than merely scavenging mature fibrils.[163]

5.3. Supramolecular and Self-Assembled Systems

Supramolecular and self-assembled systems introduce a mode of amyloid regulation that is fundamentally distinct from both small molecule inhibition and nanoscale surface interactions. Rather than relying on permanent binding or physical sequestration, these systems operate through dynamic and reversible non-covalent interactions that compete directly with protein–protein contacts driving aggregation. This reversibility allows supramolecular assemblies to respond adaptively to changes in aggregation state and molecular environment, closely paralleling principles of biological recognition and regulation.[164-165] Recent studies have demonstrated that supramolecular hosts constructed from macrocycles, foldamers, and hydrogen-bonded networks can selectively engage aggregation-prone motifs within amyloidogenic proteins. By forming transient host–guest complexes, these systems interfere with the alignment and stabilisation of β-sheet-rich assemblies without irreversibly trapping protein molecules.[166] Such behaviour has been shown to bias aggregation pathways away from cooperative fibril growth and toward less ordered or non-propagating states. The

dynamic nature of these interactions is particularly advantageous in systems where aggregation intermediates continuously interconvert, as it allows sustained modulation without stoichiometric excess.

Self-assembled supramolecular architectures have also been explored as competitive scaffolds that mimic structural features of amyloid fibrils. Peptide-based assemblies, aromatic stacks, and hydrogen-bonded frameworks can present complementary interaction surfaces that engage misfolded proteins through multivalent but reversible contacts.[167-168] Experimental and computational investigations suggest that these assemblies can disrupt early oligomerisation by diverting aggregation-prone segments into alternative association modes that are incompatible with fibril elongation. Unlike rigid nanomaterials, supramolecular systems often exhibit adaptive reorganisation upon protein binding, further influencing aggregation kinetics. Computational modelling has played a central role in guiding the design of supramolecular aggregation modulators. Molecular simulations and docking studies have been used to identify favourable host geometries, binding orientations, and interaction strengths that enable effective competition with protein–protein contacts.[169-170] Recent work increasingly integrates free-energy calculations with experimental validation to ensure that supramolecular binding remains sufficiently strong to perturb aggregation while retaining reversibility. This balance is critical, as overly stable complexes may introduce off-pathway aggregation or unintended sequestration effects.

From a sustainability perspective, supramolecular systems offer several advantages that align with green therapeutic design. Many assemblies rely on self-organisation driven by simple building blocks rather than extensive covalent synthesis, reducing synthetic complexity and waste.[171-172] Their activity is often achieved at low concentrations due to cooperative binding effects, further limiting material usage. In addition, the reversible nature of supramolecular interactions reduces the likelihood of long-term accumulation and persistent off-target effects, which are important considerations for translational viability.

5.4. Peptide and Peptidomimetic Inhibitors

Peptide- and peptidomimetic-based inhibitors exploit a level of sequence specificity that is difficult to achieve with small molecules or supramolecular assemblies. By directly mimicking aggregation-prone segments of amyloidogenic proteins, these inhibitors are designed to engage misfolded species through homologous recognition, thereby competing with native protein–protein interactions that drive self-assembly.[173-175] This strategy capitalises on the intrinsic selectivity of peptide–peptide interactions, allowing aggregation to be modulated at the level of sequence-encoded recognition rather than through generic binding mechanisms. Recent studies have demonstrated that short peptides derived from amyloidogenic core regions can effectively disrupt aggregation by forming hetero-oligomeric complexes with monomers or early oligomers. These complexes often adopt conformations that are incompatible with further β-sheet propagation, thereby arresting fibril growth at an early stage.[176-177] Importantly, the efficacy of such inhibitors depends not only on sequence complementarity but also on conformational flexibility, as overly rigid peptides may themselves nucleate aggregation. This balance between mimicry and misrecognition has become a central design consideration in contemporary peptide-based approaches.

Advances in peptide engineering have significantly expanded the applicability of these inhibitors. Chemical modifications such as cyclisation, backbone N-methylation, and incorporation of non-natural amino acids have been used to enhance proteolytic stability, reduce self-aggregation, and improve membrane permeability.[178-179] Peptidomimetics that retain key side-chain functionalities while replacing labile peptide bonds offer additional control over pharmacokinetic properties. Recent work increasingly favours minimalist designs that preserve essential recognition motifs while limiting peptide length and synthetic complexity, aligning functional performance with sustainability considerations.[180-182] Computational modelling has played a critical role in guiding the development of peptide and peptidomimetic inhibitors. Docking studies and molecular dynamics simulations are routinely used to evaluate how candidate sequences interact with aggregation-prone regions of target proteins and to assess whether binding promotes or suppresses β-sheet alignment. Free-energy calculations further allow discrimination between productive inhibitory binding and unintended stabilisation of aggregation intermediates.[183] Such predictive frameworks have reduced empirical screening requirements and enabled more focused optimisation of peptide sequences.

Beyond direct inhibition of monomer association, peptide-based strategies have also been explored for targeting fibril surfaces and secondary nucleation processes. Simulations suggest that peptides designed to recognise specific fibril interfaces can interfere with surface-catalyzed oligomer formation, a major source of cytotoxic species in several amyloid disorders.[184-185] This surface-directed approach differs fundamentally from fibril disassembly strategies, as it seeks to modulate ongoing aggregation dynamics rather than remove existing deposits. From a sustainability perspective, peptide and peptidomimetic inhibitors occupy an intermediate position between small molecules and larger self-assembled systems. While peptide synthesis can be resource-intensive, recent advances in solid-phase synthesis, sequence optimisation, and computational pre-screening have substantially reduced material usage and experimental redundancy.[186] The high specificity of peptide-based inhibitors also enables activity at lower concentrations, mitigating concerns related to dosage and off-target interactions.

5.5. Polymeric and Hybrid Materials

Polymeric and hybrid materials regulate amyloid aggregation through mechanisms that are fundamentally distinct from molecular recognition-driven inhibitors. Rather than relying on discrete binding events, polymer-based systems exert control through collective, multivalent interactions distributed along extended and often dynamically reorganising architectures. This property enables simultaneous engagement with multiple regions of misfolded or partially unfolded proteins, allowing polymers to influence aggregation behaviour at mesoscopic length scales where steric confinement, local concentration effects, and environmental buffering become dominant.[3, 62, 187-189] Within this broad class, polymeric gels and polymer-rich networks represent a particularly versatile subset, encompassing chemically crosslinked hydrogels, physically associated supramolecular gels, and peptide–polymer hybrid assemblies. These materials span a wide range of compositions, from fully synthetic systems to biohybrid constructs incorporating peptides, proteins, or degradable backbones. Studies on peptide–polyester and peptide–polymer hybrids have demonstrated how grafting density, chain flexibility, and secondary structure propensity can be used to tune aggregation, crystallisation, and assembly behaviour of the polymer matrix itself, thereby indirectly modulating protein self-association.[50, 190-194] Such systems illustrate that gels are not a monolithic material class but instead encompass diverse architectures and formation pathways, including ring-opening polymerization–derived biohybrids, physically assembled networks, and hierarchical micro- and nanostructured domains.[193-195]

From a mechanistic perspective, polymeric gels influence amyloid aggregation primarily by reshaping the physical context of assembly.[195] Polymer networks with balanced hydrophobic and hydrophilic domains can preferentially associate with exposed hydrophobic patches on misfolded proteins, reducing the probability of productive protein–protein encounters without enforcing rigid or irreversible binding.[191] In contrast to small-molecule inhibitors, these interactions are inherently adaptive and dynamic, allowing sequestration of oligomeric species while preserving conformational reversibility. This mode of action distinguishes polymeric gels from supramolecular hosts and highlights their capacity to bias aggregation pathways rather than suppress fibril formation outright. Hybrid polymeric systems further expand this design space by integrating functional elements such as nanoparticles, peptides, or small molecules within polymer matrices. These composites combine the environment-modulating capability of polymer networks with the chemical or structural specificity of embedded components, enabling cooperative regulation of aggregation. Experimental and computational studies indicate that such hybrid materials can simultaneously buffer local protein concentration, interfere with nucleation events, and modulate fibril surface activity. These combined effects are particularly relevant for attenuating secondary nucleation processes, which are highly sensitive to surface availability and local physicochemical conditions. Stimuli-responsive polymeric gels introduce an additional layer of control by coupling aggregation modulation to environmental triggers such as pH, redox state, or enzymatic activity. Rather than constitutively interacting with amyloid species, these systems undergo conformational or phase transitions under pathological conditions, enabling conditional and spatially confined engagement. This behaviour offers a route to minimise off-target effects while maintaining effective aggregation control in diseased tissues.[196-199]

Computational modelling has played a central role in rationalising and optimising polymer- and gel-based aggregation regulators. Simulations of polymer–protein interactions have elucidated how chain length, flexibility, charge distribution, and functional group density influence binding behaviour and aggregation outcomes. Coarse-grained approaches, in particular, have been effective in capturing how polymer networks reshape aggregation kinetics by modifying

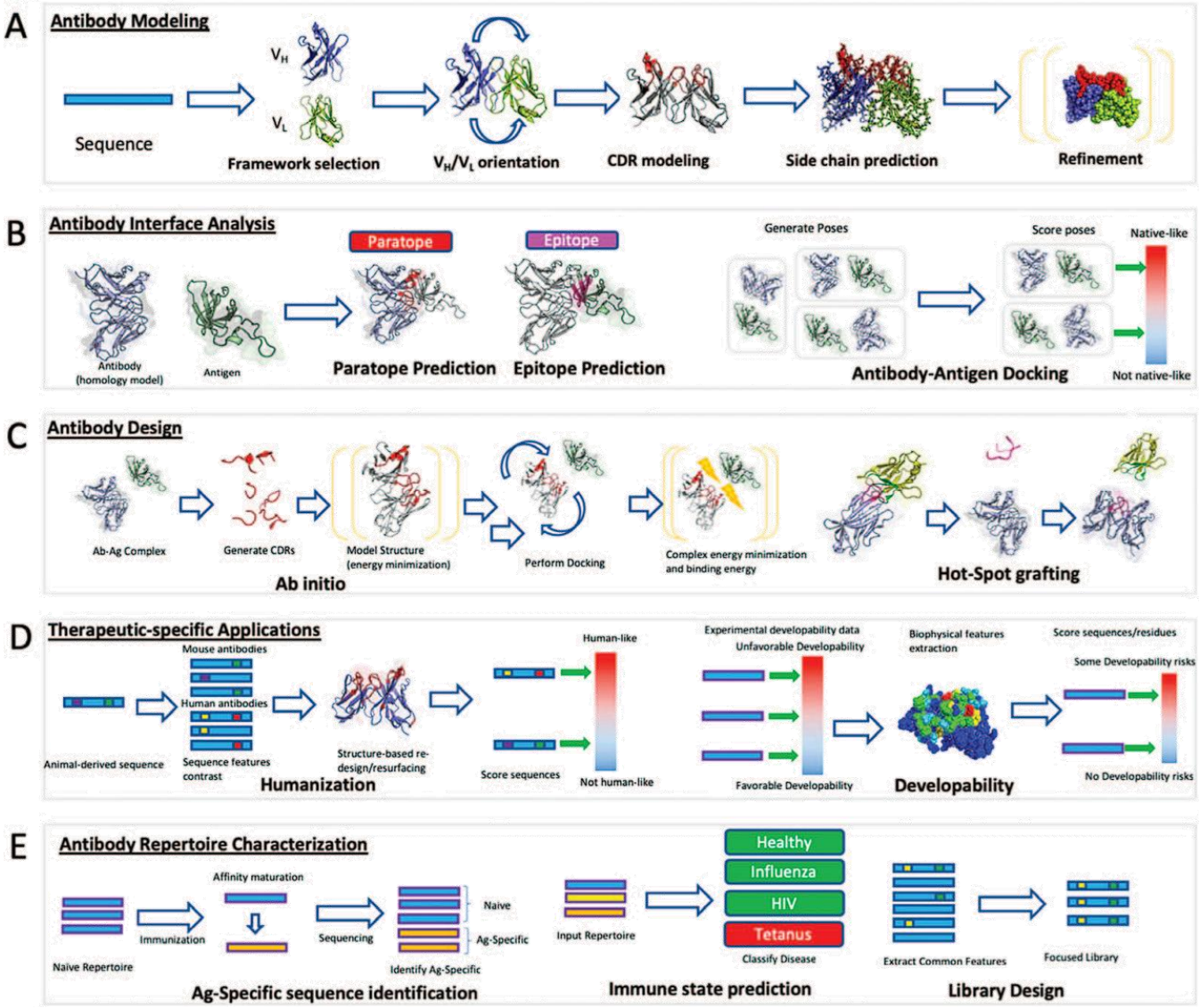

Figure 8. *Conceptual workflow of computational approaches applied to antibody research. (A) Antibody structure prediction converts amino acid sequence information into three-dimensional molecular models. (B) Interface mapping methods are used to identify antibody residues that participate in antigen recognition, defining the paratope–epitope interaction landscape. (C) Computational antibody design refines binding affinity and specificity toward a selected epitope through iterative modelling, docking, and energy optimisation procedures. (D) In parallel, candidate antibodies are evaluated for immunological safety and favourable biophysical characteristics to ensure suitability for therapeutic application. (E) Large-scale analysis of antibody repertoires provides system-level insight into the organisation and functional principles of adaptive immune responses. Reproduced with permission from ref. 200 Copyright 2019 Oxford University Press.*

diffusion, confinement, and intermolecular encounter rates.[169, 197, 200] These studies consistently show that relatively modest changes in polymer architecture or network topology can produce disproportionate effects on aggregation pathways, reinforcing the importance of design at the mesoscale.

From a sustainability perspective, polymeric and hybrid gel systems present both challenges and opportunities. While polymer synthesis can be resource-intensive, increasing emphasis on biodegradable backbones, renewable monomers, and simplified architectures has improved compatibility with green design principles. Importantly, the multivalent and cooperative nature of polymer–protein interactions often enable effective aggregation modulation at low material loadings, reducing overall resource demand. When combined with computationally guided design, polymeric gels emerge as adaptable platforms capable of balancing mechanistic efficacy, material efficiency, and translational feasibility.

6. Integrating Computational Design with Sustainable Therapeutics

The growing integration of computational modelling with the development of sustainable therapeutic strategies reflects an important methodological evolution in amyloid research. Computational approaches are increasingly incorporated at early stages of therapeutic exploration, not only to rationalise experimental observations but also to inform decisions related to molecular design, material selection, and mechanistic targeting. This integration has been facilitated by advances in structural biology, aggregation kinetics, and data-driven modelling, which together provide a more detailed and predictive description of amyloid assembly processes. Across the range of therapeutic modalities discussed in this review, computational design contributes to improved selectivity and efficiency by narrowing the space of viable intervention strategies. Molecular simulations and predictive frameworks are now commonly used to identify aggregation-prone regions, evaluate interaction modes, and assess the likelihood that a given intervention will stabilise or destabilise specific aggregation intermediates. When applied at an early stage, such analyses can reduce reliance on extensive empirical screening and support a more focused allocation of experimental effort. In this sense, sustainability is reflected not only in the nature of the therapeutic agents themselves but also in the design strategies that guide their development.

Recent computational studies further demonstrate that modulation of amyloid aggregation can be achieved through rational, pathway-specific intervention strategies rather than complete suppression of fibril formation (Figure 8).[201] In this context, computational antibody-based approaches provide a structured framework for designing aggregation-modulating therapeutics through sequential and well-defined modelling steps. As illustrated in Figure 8A, antibody modelling enables the generation of high-resolution three-dimensional antibody structures directly from sequence information, providing the structural foundation for downstream analyses. Building on this, Figure 8B depicts antibody–antigen interface prediction, where computational tools identify paratope residues on the antibody that interact with aggregation-prone epitopes on amyloidogenic proteins. These predictions allow selective targeting of structurally and kinetically relevant aggregation intermediates. Subsequently, Figure 8C highlights antibody design and optimisation, in which iterative cycles of molecular modelling, docking, and energy minimisation are employed to enhance binding affinity and specificity toward selected amyloid epitopes. This step is particularly important for biasing aggregation pathways by stabilizing non-toxic conformations or interfering with secondary nucleation processes. In parallel, Figure 8D emphasises the evaluation of immunological safety and biophysical properties, ensuring that candidate antibodies exhibit favourable stability, solubility, and low immunogenic risk, which are essential for translational applicability. At a broader level, Figure 8E illustrates how large-scale antibody repertoire analysis can be leveraged to extract general principles governing adaptive immune recognition. Such analyses inform antibody engineering strategies by identifying sequence and structural patterns associated with effective and selective binding, thereby reducing empirical trial-and-error in therapeutic development. Importantly, this computational workflow aligns closely with sustainability-oriented design principles. By prioritising in silico screening, optimisation, and safety evaluation prior to experimental validation, computational antibody approaches minimise material consumption and experimental redundancy. When integrated with experimental feedback, these strategies support the development of aggregation-modulating therapeutics that operate at lower effective concentrations and with reduced off-target effects. More broadly, Figure 8 exemplifies how computational design enables informed, efficient, and mechanistically precise intervention in amyloid aggregation pathways.

The integration of computational and sustainable perspectives also influences how therapeutic outcomes are evaluated. Rather than focusing exclusively on reductions in aggregate load, recent work increasingly considers changes in aggregation dynamics, intermediate populations, and pathway selection as indicators of therapeutic relevance. Computationally derived metrics, when interpreted alongside experimental data, provide a more mechanistic basis for assessing intervention efficacy and for comparing different therapeutic strategies. Looking ahead, further progress in this area is likely to depend on iterative workflows that more tightly couple predictive modelling with targeted experimentation. Advances in automation, data curation, and model validation may facilitate such cycles, enable refinement of therapeutic designs while maintain control over resource use. As computational methods continue to mature, their role in shaping translational and regulatory considerations may also expand, particularly in contexts where long-term safety and environmental impact are important.

The studies discussed in this review illustrate how amyloid aggregation can be approached as a process amenable to informed and measured intervention. Computational design provides a framework for linking molecular-level understanding with therapeutic strategy development, while sustainability considerations encourage restraint, specificity, and efficiency. Continued integration of these perspectives is expected to support the development of aggregation-modulating interventions that are both mechanistically grounded and compatible with broader biological and practical constraints.

7. Challenges, Opportunities, and Translational Perspectives

Despite substantial progress in understanding and regulating amyloid aggregation, several conceptual and practical challenges continue to limit translation of aggregation-modulating strategies into clinically viable therapies. Many of these challenges arise not from a lack of mechanistic insight, but from the intrinsic complexity of protein aggregation in biological systems, where heterogeneity, temporal evolution, and context dependence complicate both prediction and intervention. Addressing these issues requires careful alignment between molecular-level understanding and translational constraints. One persistent challenge lies in reconciling in vitro aggregation models with in vivo behaviour. While simplified experimental systems and computational simulations have been indispensable for dissecting aggregation mechanisms, they often fail to capture the full complexity of cellular environments, including molecular

crowding, compartmentalisation, and dynamic regulation by proteostasis networks. As a result, aggregation pathways identified under controlled conditions may not fully reflect those operating in diseased tissues. Bridging this gap remains a central concern, particularly for therapeutic strategies that rely on precise modulation of early aggregation events. A related issue concerns the identification of appropriate therapeutic targets within the aggregation cascade. Increasing evidence suggests that toxicity is frequently associated with transient oligomeric species rather than mature fibrils. However, these intermediates are structurally heterogeneous, short-lived, and difficult to characterise experimentally. Targeting such species therefore poses both conceptual and technical challenges, as interventions must be sufficiently specific to avoid stabilizing off-pathway assemblies or disrupting normal protein function. Computational models offer valuable guidance in this context, but their predictive accuracy remains dependent on the quality and scope of available experimental data.

Translational development is further complicated by considerations of delivery, bioavailability, and long-term safety. Many aggregation modulators, particularly peptides, nanomaterials, and polymer-based systems, face barriers related to tissue penetration, metabolic stability, and clearance. Strategies that appear effective at the molecular level may encounter unforeseen limitations when deployed in complex biological settings. These issues underscore the importance of incorporating translational constraints early in the design process, rather than treating them as secondary optimisation steps. At the same time, the current landscape presents significant opportunities. Advances in multiscale modelling, machine learning, and integrative characterisation provide increasingly sophisticated tools for navigating aggregation complexity. When combined with targeted experimental validation, these approaches enable more realistic assessment of how aggregation pathways respond to perturbation under biologically relevant conditions. Such capabilities support the development of intervention strategies that are adaptable rather than static, an attribute that may be particularly important for chronic and progressive disorders.

Opportunities also arise from a growing emphasis on sustainability and precision in therapeutic design. By prioritising pathway modulation over aggregate elimination, and by favouring agents that operate effectively at low concentrations, recent strategies align more closely with translational feasibility and long-term use. Computationally guided design plays a critical role in this shift, enabling rational trade-offs between efficacy, safety, and material complexity. This perspective encourages development pathways that are not only scientifically robust but also economically and environmentally responsible. From a translational standpoint, progress will likely depend on tighter integration between mechanistic studies and disease-relevant models. Longitudinal investigations that track aggregation dynamics alongside functional outcomes may provide more informative benchmarks for therapeutic evaluation than static measures of aggregate burden. In parallel, regulatory and clinical frameworks may need to adapt to accommodate interventions that modulate dynamic biological processes rather than produce binary on–off effects.

In this context, amyloid aggregation research occupies a position of both challenge and opportunity. The field has moved beyond descriptive characterisation toward mechanistically informed control, yet translation remains contingent on continued refinement of models, metrics, and design principles. Sustained progress will require coordinated efforts that balance depth of molecular insight with practical considerations of delivery, safety, and sustainability. Computational approaches, when integrated with experimental and translational perspectives, are well positioned to facilitate this balance and to support the next generation of amyloid-targeted therapeutic strategies.

8. Concluding Remarks and Future Outlook

Amyloid aggregation represents a central molecular driver of numerous neurodegenerative and systemic disorders, including Alzheimer's, Parkinson's, and Huntington's diseases. Advances in experimental biophysics and computational modelling have transformed current understanding of this process, establishing amyloid formation as a dynamic, pathway-dependent phenomenon that can be modulated rather than merely observed. High-resolution structural methods and kinetic assays have clarified how misfolded proteins populate heterogeneous oligomeric and fibrillar states, while multiscale computational approaches have enabled interrogation of free-energy landscapes, kinetic bottlenecks, and aggregation-sensitive interfaces that are difficult to resolve experimentally. Together, these developments have provided a mechanistic foundation for rational intervention.

Importantly, this mechanistic insight has enabled the emergence of material-based strategies with clear application potential. Small molecules and supramolecular systems offer chemically tunable platforms for selectively biasing early misfolding events and secondary nucleation processes. Nanostructured materials, including carbon-based and hybrid nanomaterials, provide surface-mediated routes to modulate aggregation kinetics and sequester toxic intermediates. Polymeric and hybrid materials introduce additional functionality through multivalent interactions, environmental buffering, and stimuli responsiveness, enabling conditional and context-dependent aggregation control. Collectively, these material classes expand the therapeutic design space beyond conventional inhibitors and open opportunities for combination strategies that integrate molecular specificity with mesoscale control.

From an application perspective, the ability of these materials to operate at low effective concentrations, modulate aggregation pathways rather than enforcing complete inhibition, and be engineered for biodegradability and controlled interaction profiles enhances their translational relevance. Such properties are particularly advantageous for chronic disorders, where long-term safety, dosing restraint, and compatibility with endogenous proteostasis mechanisms are critical. Computationally guided design further strengthens this application potential by enabling early-stage screening, optimisation, and prioritisation of candidates with favourable efficacy–safety–sustainability trade-offs. Looking ahead, the most promising applications are likely to arise from adaptive and disease-specific intervention frameworks. Genetic background, mutation profiles, and cellular environments strongly influence aggregation behaviour, suggesting that materials designed to target conserved kinetic control points or interfacial processes may offer broader applicability across disease contexts. Integration of computational prediction with targeted experimental validation will be essential for advancing these materials toward preclinical and translational stages. In parallel, increasing understanding of endogenous modulators of protein homeostasis, including molecular chaperones, degradation pathways, and membrane-associated processes, offers opportunities to design materials that complement or amplify natural protective mechanisms.

The convergence of materials science, computational modelling, and mechanistic biophysics is redefining how amyloid aggregation can be controlled. While significant translational challenges remain, the material platforms reviewed here provide a versatile and increasingly application-oriented toolkit for modulating amyloid formation. Continued interdisciplinary integration is expected to accelerate progress

toward therapeutically viable, scalable, and biologically compatible strategies for amyloid-associated diseases.

Author Contribution Declaration & Information

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Data Availability Declaration

This review neither generates nor analyzes new data, nor does it present any primary research findings or employ specialized software.

Declaration of Conflict of Interest

The authors have no conflict of financial interest.

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