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Dynamics in supramolecular nanomaterials

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Self-assembly of amphiphilic small molecules in water leads to nanostructures with customizable structure–property relationships arising from their tunable chemistries. Characterization of these assemblies is generally limited to their static structures – e.g. their geometries and dimensions – but the implementation of tools that provide a deeper understanding of molecular motions has recently emerged. Here, we summarize recent reports showcasing dynamics characterization tools and their application to small molecule assemblies, and we go on to highlight supramolecular systems whose properties are substantially affected by their conformational, exchange, and water dynamics. This review illustrates the importance of considering dynamics in rational amphiphile design.

1. Introduction

Spontaneous self-assembly of amphiphiles occurs when orthogonal interactions with solvent dominate different regions of the same molecule. A typical example of self-assembly in Nature, Fig. 1, illustrates a phospholipid cell membrane in an aqueous environment with embedded transmembrane and surface proteins. In contrast to this static snapshot captured in an image, active molecular components in the cell membrane (e.g., phospholipids, proteins, water, and cholesterol) are in constant motion.¹ These intrinsic dynamics mediate all intermolecular interactions, chemical reactions, and physiological responses of the membrane. The importance of dynamics is well elucidated by examining the many components of phospholipid membranes in nature. Eukaryotic membranes exhibit relatively fast dynamics that enable their rapid division, enzyme catalysis, and allosteric regulation,^{2–4} while the dynamics of archaeal membranes are slower, accounting for their temperature resistance, mechanical stability, and salt tolerance.^{5–7} From these relationships, it follows that dynamics also play an important role in synthetic supramolecular nanostructures, defined here as nanostructures constructed from amphiphilic small molecules and bound together by noncovalent intermolecular interaction. Similar to natural systems, precise tuning of dynamics within synthetic structures is an important target for achieving control over their properties.

Synthetic self-assembling molecules are modeled after the molecular architecture of their biological counterparts.

The field of molecular self-assembly has grown dramatically over the past 30 years, as evidenced by the development of theory to predict nanostructure morphologies from the packing parameters of constituent molecules⁸ and the synthesis of a vast array of new, functional supramolecular nanomaterials.^{9–11} In addition to the fundamental amphiphilic structure inspired by nature, more and more synthetic self-assembling molecules incorporate strong intermolecular cohesion (e.g., hydrogen bonding,¹² π – π stacking,¹³ charge-transfer interactions¹⁴) and stimuli-responsive moieties (e.g., photo-,¹⁵ pH-¹⁶ and enzyme-responsive¹⁷ functionalities). A significant benefit of this bottom-up design strategy is the formation of structures at molecular (<10 nm) length scales with remarkably precise spatial arrangement. Formation of nanoscale supramolecular architectures naturally yield high accessible surface areas, and the surface properties of the structure can be easily tuned by modifying the chemistry of the constituent amphiphiles.

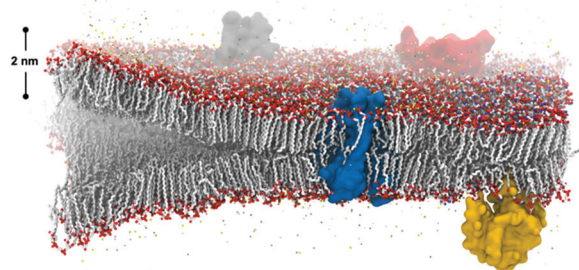


Fig. 1 The co-assembly of biological components in cell membranes gives rise to bilayers with complex functionality and adaptive, controlled dynamics that dictate their function. Image credit: Thomas Lemmin, Laboratory for Molecular Modeling, École Polytechnique Fédérale de Lausanne.

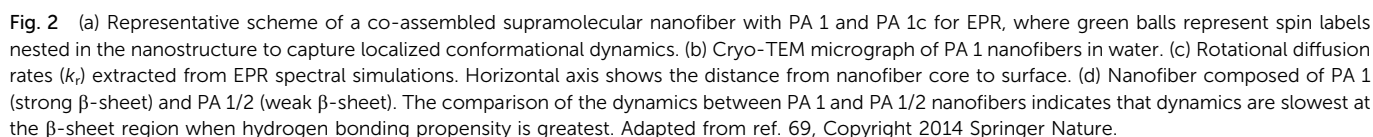
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In this review, we first introduce studies that adopt dynamics characterization tools from biochemistry. Based on these studies, we categorize the three types of dynamics as follows: (1) conformational dynamics, *i.e.* the “jiggling” of molecules; (2) molecular exchange and migration; and (3) hydration water dynamics. Then, we will highlight reports that demonstrate the significance of dynamics in supramolecular design. Computational approaches are critical in driving fundamental understanding of molecular self-assembly in water, especially through all-atom molecular dynamics (MD) simulations that implement increasingly sophisticated force fields.^{46–49} However the literature describing computational studies will be largely excluded from this review. Similarly, self-assembly of covalent polymers and organic solvent-based liquid crystals fall outside the scope of this review.

EPR has been used for measuring conformational dynamics on a self-assembled nanofibers composed of peptide amphiphiles (PAs). Ortony *et al.* positioned radical electron (nitroxyl) moieties into the molecular structure by SDSL, then quantified dynamics by EPR lineshape analysis.⁶⁹ The PA in this study is composed of three domains: a hydrophobic alkyl tail, a peptide sequence with a high propensity for β -sheet formation, and a charged peptide head group. The driving force for PA self-assembly is the hydrophobic effect, and the formation of β -sheets down the nanofiber long-axis promotes self-assembly into high-aspect-ratio nanofibers (Fig. 2b). While PA 1 with six peptide residues (VVAEEE) was known to form cohesive β -sheet nanofibers, mixtures of PA 1 and PA 2, with an *N*-methylated valine ($V_{N(me)}$ VAAEE), yielded PA 1/2 nanofibers with weakened β -sheets due to the disruption of hydrogen bonding. EPR spectroscopy for conformational dynamics analysis was performed on both PA 1 and PA 1/2 nanofibers, each co-assembled with spin-labeled PAs, in this study. By placing the spin label at different depths in the nanofiber (Fig. 2a), EPR revealed site-specific dynamics. EPR not only provided qualitative understanding of conformational motion based on the breadth of spectra, but the spectra were



Lou *et al.* recently demonstrated the application of HDX-MS for characterizing the nanoscale organization and exchange dynamics of self-assembled supramolecular fibrils in water. By using HDX-MS, these studies were conducted without the use of molecular probes that could perturb the structure.⁸² Benzene-1,3,5-tricarboxamide (C_{12} BTA) molecules, with three hydroxyl hydrogens at tetra(ethylene glycol) peripheries and three amide hydrogens at the core, were studied in this research (Fig. 3a). C_{12} BTA self-assembles in water *via* a combination of hydrophobic interactions and directional hydrogen bond formation into long, supramolecular nanofibers. Only two major isotopes corresponding to C_{12} BTA3D and C_{12} BTA6D were observed during HDX. C_{12} BTA3D corresponds to the substitution of three outer hydroxyl groups on C_{12} BTA, and C_{12} BTA6D corresponds to the substitution of three outer hydroxyl and three inner amide groups on C_{12} BTA, resulting from the slower exchange of amide than hydroxyl hydrogens. Time-resolved

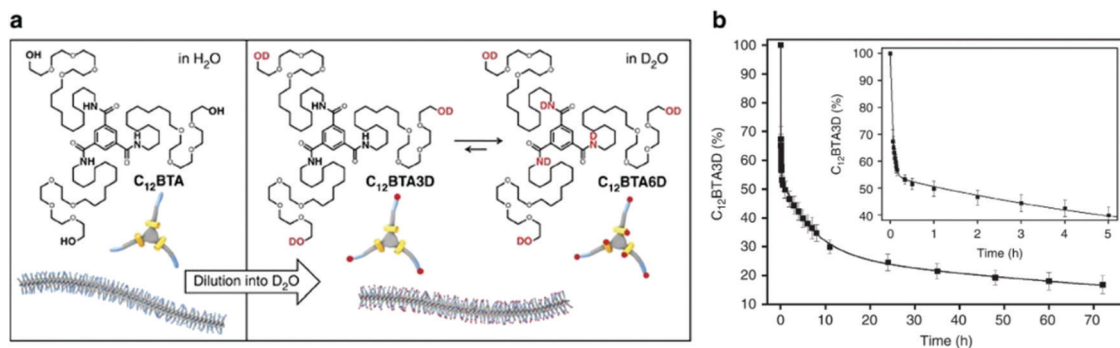


Fig. 3 (a) Chemical structures of C₁₂BTA and its deuterated analogues C₁₂BTA3D and C₁₂BTA6D, schematic representation of the supramolecular polymers formed in water and an illustration of the H/D exchange process. (b) Kinetic profile illustrates hydrogen to deuterium exchange rate of C₁₂BTA3D to C₁₂BTA6D, fit to a triexponential decay. The inset shows an enlargement of the data points and fit for the first 5 h. Adapted from ref. 82, Copyright 2017 Springer Nature.

HDX revealed that the hydrogens of the hydroxyl groups are instantaneously replaced by deuterium during exchange, whereas the transition from C₁₂BTA3D to C₁₂BTA6D presents a kinetic profile as shown in Fig. 3b. This profile was fit to a tri-exponential model with three dissimilar rate constants $k_{\text{initial}} = 1.8 \times 10^1 \text{ h}^{-1}$, $k_{\text{fast}} = 1.4 \times 10^{-1} \text{ h}^{-1}$, and $k_{\text{slow}} = 0.7 \times 10^{-2} \text{ h}^{-1}$, suggesting that the system exhibits exchange dynamics with different orders of magnitude. Further, the exchange dynamics between BTAs with undecyl and dodecyl alkyl spacers were distinguishable by HDX-MS, but not by FRET⁸³ – all BTA molecules in the system can be probed by HDX-MS, whereas only a subset of dye-labelled molecules are detectable by FRET. HDX-MS has been used to characterize other amphiphile systems,^{84,85} further demonstrating its value as a technique for probing exchange dynamics in water.

HDX-MS also enables the tracking of exchange of different types of monomers in multicomponent systems.^{86,87} This capability is achieved by employing mass spectrometry to distinguish between molecular masses. Notably, sample preparation of HDX-MS for self-assembled supramolecular systems is relatively simple and straightforward; HDX-MS in its historical use for protein science relies on protein decomposition to peptide monomers, which are then separated.⁸⁸ Peptide monomer products obtained by protein decomposition have a propensity to form higher-order structure which may complicate data interpretation. In contrast to peptides, small molecule assemblies investigated well above their critical aggregation concentrations have fewer monomers in solution and the free monomers undergo hydrogen–deuterium exchange on the orders of seconds. A recent study shows that HDX-MS kinetic profiles are insensitive to starting concentration (when 20–200 times higher than the critical assembly concentration) and diluted time for D₂O exchange.⁸⁹ Despite this feature of small molecule assemblies, quantification of the exchange dynamics in some supramolecular systems can be challenging when there are multiple labile hydrogens at different sites of the molecule, and several exchange mechanisms present.⁸⁹ Although HDX-MS does not inherently provide structural data, the technique provides detailed dynamics information at the molecular level for supramolecular systems without the constraint of introducing molecular labels.

Stochastic optical reconstruction microscopy (STORM). Most dynamics characterization techniques provide time

resolution, but lack spatial information. In contrast, stochastic optical reconstruction microscopy (STORM) can provide molecular exchange dynamics with spatial resolution. STORM, a super-resolution optical microscopy technique, can achieve ~20 nm resolution by activating random small subsets of fluorophores at a given time and then superimposing each snapshot to obtain an image of the distribution of fluorophores.⁹⁰ Albertazzi *et al.* first demonstrated this tool on BTA supramolecular fibers.⁹¹ This work successfully tracked the distribution of BTA monomers during exchange by auto-correcting and quantitatively analyzing the localization density profile, or the distribution of fluorophore localizations along the fiber. The results suggest the absence of any local ordering and hence homogeneous exchange along the BTA supramolecular fibers. In contrast to the BTA supramolecular fibers, da Silva *et al.* observed heterogeneous exchange and spatial variations in dynamics across the length of PA nanofibers by examining the localization density profiles obtained from STORM.⁹² In this study, two types of PA nanofibers tagged with distinct fluorescent dyes (Cy3-PA and Cy5-PA) were imaged and then combined in solution to probe the mechanism of exchange. After 48 hours, Cy5-PA (red) was found dispersed throughout the entire length of the Cy3-PA (green) nanofiber as shown in the localization maps (Fig. 4a). Tracking the exchange process of Cy3-labelled fiber over a shorter time span revealed that PA nanofibers follow an expulsion–reinclusion mechanism of exchange dynamics. Fig. 4b shows the autocorrelation plots and model fitting from the localization density profiles along the nanofiber backbones of Fig. 4a. At 1 min, the autocorrelation plots of Cy5-PA fiber can be modeled by a homogeneous distribution, suggesting a random exchange of monomers. As the exchange proceeds, the autocorrelation curves of the Cy5-PA fiber suggest the emergence of heterogeneous exchange behavior and the structural variations along the fiber or between fibers. The increased standard deviation of linear density of Cy5 (Fig. 4c), defined as the number of Cy5 dye localizations per nanometer arc length of initially only Cy3 labelled nanofiber, also indicates the presence of intrinsic structural diversity. The authors concluded that this heterogeneity of PA nanofibers is likely due to the highly cohesive β -sheets within the structure, whereas the supramolecular systems with



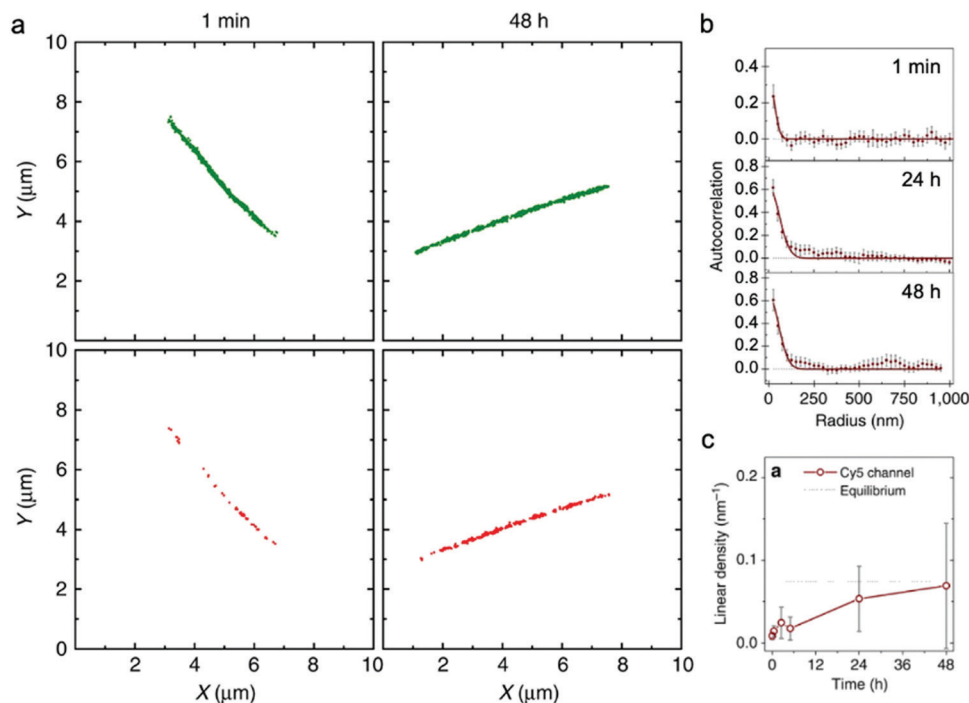


Fig. 4 (a) Localization maps of PA nanofibers with photo-switchable sulfonated cyanine dyes Cy3 (green) and Cy5 (red) reconstructed from STORM. (b) Averaged autocorrelation plots for Cy5-labelled PAs are fit to random exchange models. (c) Time course-averaged linear density of red dye (Cy5) on nanofibers that were initially only labelled with green dyes (Cy3). Adapted from ref. 92, Copyright 2016 Springer Nature.

weak internal cohesion can exchange molecules to produce completely homogeneous structure.

Similar to EPR, and in contrast to HDX-MS, STORM requires labeling the supramolecular nanostructure with molecular probes, which in some cases could disturb self-assembly or surface chemistry.⁹³ Additionally, higher spatial resolution characterization (*e.g.*, cryo-TEM, X-ray scattering) is frequently carried out to complement the spatial resolution (25 nm–1 μm) and time resolution (~10 minutes) of STORM. In summary, STORM is a powerful technique that allows one to obtain both timescale and spatial information of exchange dynamics, while providing analysis of exchange mechanisms, in supramolecular nanostructures. STORM is also generally applicable to most supramolecular nanomaterials systems and can be used to observe irreversible nucleation and growth mechanisms through the process of self-assembly.⁹⁴

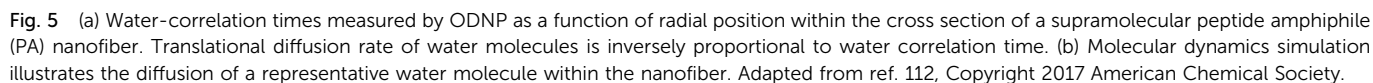
2.3 Water dynamics in supramolecular systems

The dynamics of water around biological structures is critical to their function and substantially impacts their structural stability and physiological function.⁹⁵ For example, water at the surface of a protein is likely to mediate binding-efficacy.⁹⁶ Motions of water in aqueous systems are categorized into three types with distinct dynamics: bulk water, hydration water (located at interface of water and solute), and bound or structural water. The latter two types of water are also expected to play important roles in the structure and properties of supramolecular systems. A few experimental tools allow access to water dynamics information such as dielectric

spectroscopy,^{97,98} NMR,⁹⁹ neutron scattering techniques,¹⁰⁰ and infrared spectroscopy.¹⁰¹ Although these are valuable tools for investigating water dynamics, challenges in spatial resolution and site-specificity pose limitations to their applicability to supramolecular structures. In this subsection, we introduce an emerging EPR-based technique, Overhauser dynamic nuclear polarization relaxometry (ODNP), which can be used to quantify the translational diffusion rate of water molecules over a broad range of water correlation times (200–900 ps) within less than a nanometer of a spin label.¹⁰² ODNP has previously been used to investigate water dynamics in polymers, hydrogels, biological macromolecules, and membranes.^{103–108} Although the technical details of ODNP exceed the scope of this review, we refer interested readers to a number of articles and book chapters, which provide details of theory, data analysis, and experimental protocols.^{109–111}

Ortony *et al.* mapped water dynamics through the cross-section of a supramolecular PA nanofiber using ODNP.¹¹² For ODNP, nitroxyl spin labels were covalently attached by SDSL at different positions along the peptide amphiphile. Local water dynamics in the supramolecular nanostructure were measured at each spin label site. Water correlation times measured by ODNP (Fig. 5a) reveal that water in the nanofiber's aliphatic core is fast moving, with short correlation times, whereas the water at the surface of nanofibers moves slowly with long correlation times. These results were corroborated by MD simulations (Fig. 5b). The water dynamics profile indicates that water becomes “stuck” in the highly hydrophilic and charged head group domain. The suppressed surface water dynamics





Matsumoto *et al.* demonstrated that exchange dynamics dictate nanostructure architecture by studying BTA (benzene-1,3,5-

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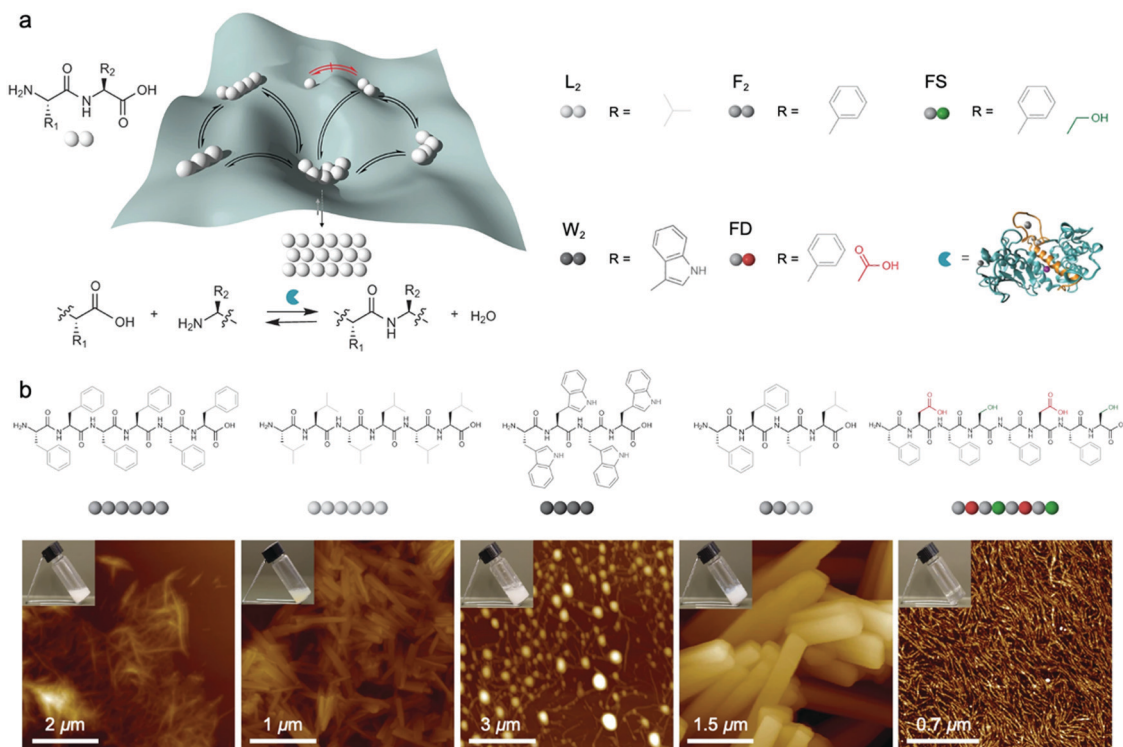


Fig. 6 (a) Potential energy of peptide oligomers (strings of beads) formation and chemical inputs (selected dipeptides from original report and thermolysin). (b) Chemical structure and AFM images of the peptide assemblies that were amplified in the searchable dynamic peptide libraries. Adapted from ref. 120, Copyright 2016 Springer Nature.

tricarboxamide) amphiphiles.¹²² In the case shown in Fig. 7, the length of the carboxylic acid-terminated aliphatic arm of amphiphilic BTA molecules was varied. BTA 2 assembles into a diverse assortment of membranes and ribbons due to the formation of bilayers, whereas BTA 3 forms hollow tubes in addition to the morphologies observed in BTA 2. HDX-MS of BTA 3 nanostructures shows slower monomer exchange with an increase in amphiphilicity. In contrast to BTA 2A, BTA 3 shows temperature-dependent monomer exchange rates (Fig. 7b). Also upon increasing temperature, the tubular assemblies of BTA 3 are elongated into well-ordered hollow nanotubes, as shown in Fig. 7c. Based on this knowledge, the authors concluded that polymorphism of BTA 3 originates from the trade-off between slow exchange dynamics and the higher energetic cost of exposing the membrane edges to solvent. Therefore, optimizing exchange dynamics is as critical as molecular structure or solvent condition in molecular engineering of self-assembled architectures. Several recent studies also revealed dynamics-controlled polymorphism in different self-assembly systems by altering temperature,¹²³ pH,¹²⁴ and ultrasonication conditions.¹²⁵

Defect-induced dynamics

Baker *et al.* reported the first observation of structure–property relationships with regard to equilibrium dynamics in water-soluble supramolecular polymers.⁹³ In this study (1) achiral and (2) chiral BTA molecules were designed. The chiral BTA contains stereogenic methyl groups, whereas the achiral BTA

does not (Fig. 8a inset). Upon self-assembly, nearly identical dimensions of BTA nanofibers of (1) and (2) were observed by cryo-TEM, X-ray scattering (SAXS), and STORM. FRET studies reveal that the addition of the stereogenic methyl groups greatly reduces monomer exchange between the fibers, as shown in Fig. 8a. This significant difference in equilibrium dynamics between achiral (1) and chiral (2) was further investigated by MD simulations. Despite average self-assembly energies (ΔE) which are calculated to be similar for (1) and (2), and which suggest that (2) fibers are not particularly more stable than (1) fibers, the internal ordering and uniformity of ΔE along the fibers gives rise to detectable differences. While the ΔE of (1) fibers show a random distribution around an average value, (2) fibers show sequences of stable BTAs for 5–7 monomers interrupted by unstable points (Fig. 8b). Following up on this observation, atomistic, coarse-grained modelling combined with advanced simulation approaches revealed the molecular exchange mechanism in this supramolecular system.¹²⁶ It is understood from this study that the monomer exchange from the fiber surface is a stepwise process, where monomers diffuse first from the center to structural defects/discontinuities (A to B), and then diffuse into the water (B to C), as shown in Fig. 8c. The theoretical kinetics analysis shows that, although the mechanism of exchange in and out these fibers is globally similar, each exchange step is slowed down by ~ 1 to 2 orders of magnitude in chiral nanofibers (2) compared to achiral nanofibers (1), consistent with the experimental observation. Since exchanging monomers directly from the nanofiber core to the



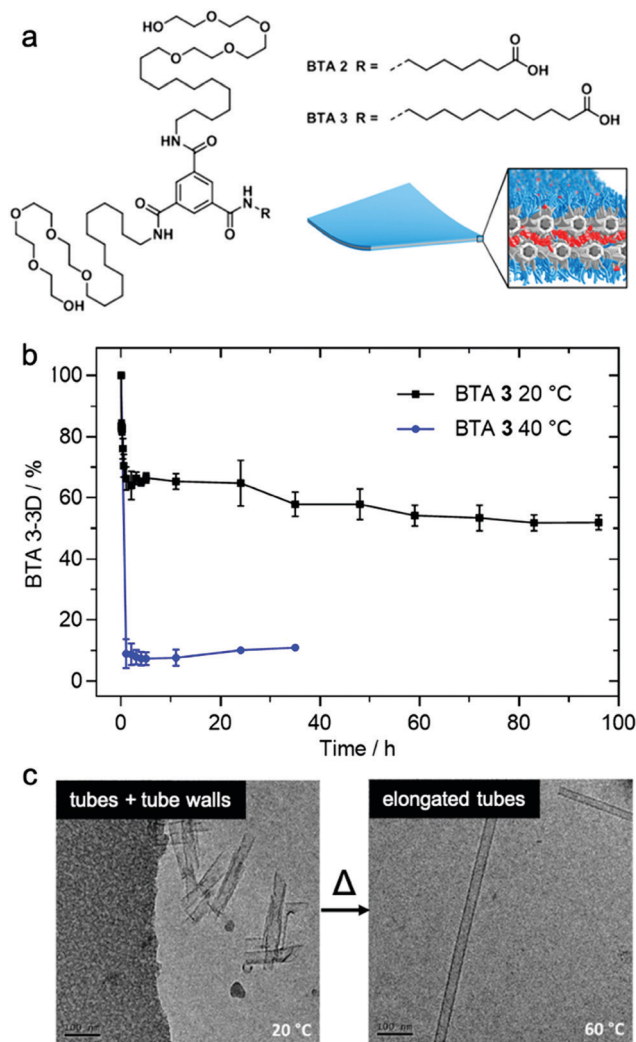


Fig. 7 (a) Chemical structure of BTA 2 and BTA 3, which are schematically illustrated to form a membrane packing morphology. (b) Exchange rates illustrated by HDX-MS reveals the conversion of BTA 3-3D into BTA 3-6D at 20 and 40 °C. (c) Cryo-TEM images of BTA 3 show a transformation from short nanotubes with ill-formed tube walls to well-formed nanotubes after heating from 20 °C to 60 °C. Adapted from ref. 111, Copyright 2018 American Chemical Society.

solvent is energetically unfavorable, controlling the structural defects along the nanofiber is key for their dynamics. The presence of defects in self-assembling nanostructures is currently a topic of interest,^{127,128} and the relationship between local dynamics near defects and the “average” dynamics that we can observe experimentally is still an open question for the field. Understanding molecular-level exchange dynamics may allow us to rationally design bioinspired materials with controllable dynamic properties.

Optimized molecular exchange drives the formation of hierarchical structure

Freeman *et al.* recently reported a hierarchical superstructure self-assembled from PA-DNA conjugates and PAs, which only occurred within a limited range of monomer exchange

dynamics.¹²⁹ Mixing the aqueous solution containing self-assembled PA nanofibers with complementary oligonucleotides (Fig. 9a) not only yielded a cross-linked gel, as expected, but also a superstructure in which large micrometer-sized bundles of fibers segregated within a network of individual fibers. MD simulations highlighted that only homogeneous hydrogels were formed when the molecular exchange of DNA monomers between PA nanofibers was prohibited, whereas bundles of nanofibers were formed when molecular exchange is allowed between PA nanofibers (Fig. 9b). Monomer exchange was also confirmed experimentally by FRET in this report. These observations indicate that exchange dynamics can impact and modify the macroscopic and hierarchical structure in supramolecular self-assembly. Furthermore, MD simulation also showed that the bundle growth rate is sensitive to the balance between the monomer–monomer association energy and the energy associated with conjugated interaction across the fiber. Following this concept, Wester *et al.* experimentally proved that the formation of bundled hierarchical filaments can be controlled by altering the intermolecular cohesion of self-assembled monomers.¹³⁰ PAs with oppositely charged surface groups and with or without β -sheet domains were synthesized as shown in Fig. 9c. Thorough structural investigation *via* TEM, SAXS and FTIR revealed that that assemblies without β -sheet domains – that is, with weak interactions and fast exchange dynamics – readily form fibrous superstructures of bundled filaments as molecules redistribute upon mixing. In contrast, assemblies with β -sheet domains – strong, cohesive interactions and slow exchange dynamics – suppress superstructure formation as shown in Fig. 9d. Additionally, the viscosity of the former mixture increased drastically after mixing and bundled filaments are formed, indicating a new method in processing of supramolecular materials to create 3D structures. This finding once again demonstrates the dynamics–property relationships in supramolecular self-assembly, and suggests that controlling dynamics can be important for future applications of molecular self-assembly.

Stabilizing the nanostructure slows down dynamics

Although the studies described above highlight the importance of optimizing dynamics in more fluid assemblies such as those for biomaterials applications, a different approach by Christoff-Tempesta *et al.* presents small-molecule amphiphiles which form ultra-stable nanostructures in water by completely suppressing molecular exchange.¹³¹ Non-covalent intermolecular interactions in supramolecular systems are usually relatively weak, and as a result, they often lead to fast dynamics and are unstable in air, where they lack the hydrophobic driving force required to maintain their nanostructure. In this study, a Kevlar-inspired domain was introduced into the amphiphile molecular structure in order to suppress conformational and exchange dynamics (Fig. 10a). In this case, aromatic amides (aramids) were positioned between a hydrophilic head group and an aliphatic tail to yield “aramid amphiphiles” (AAs). AAs spontaneously self-assemble into nanoribbons upon addition of water, with collective hydrogen bonding propagating down the long-axis, and interplane



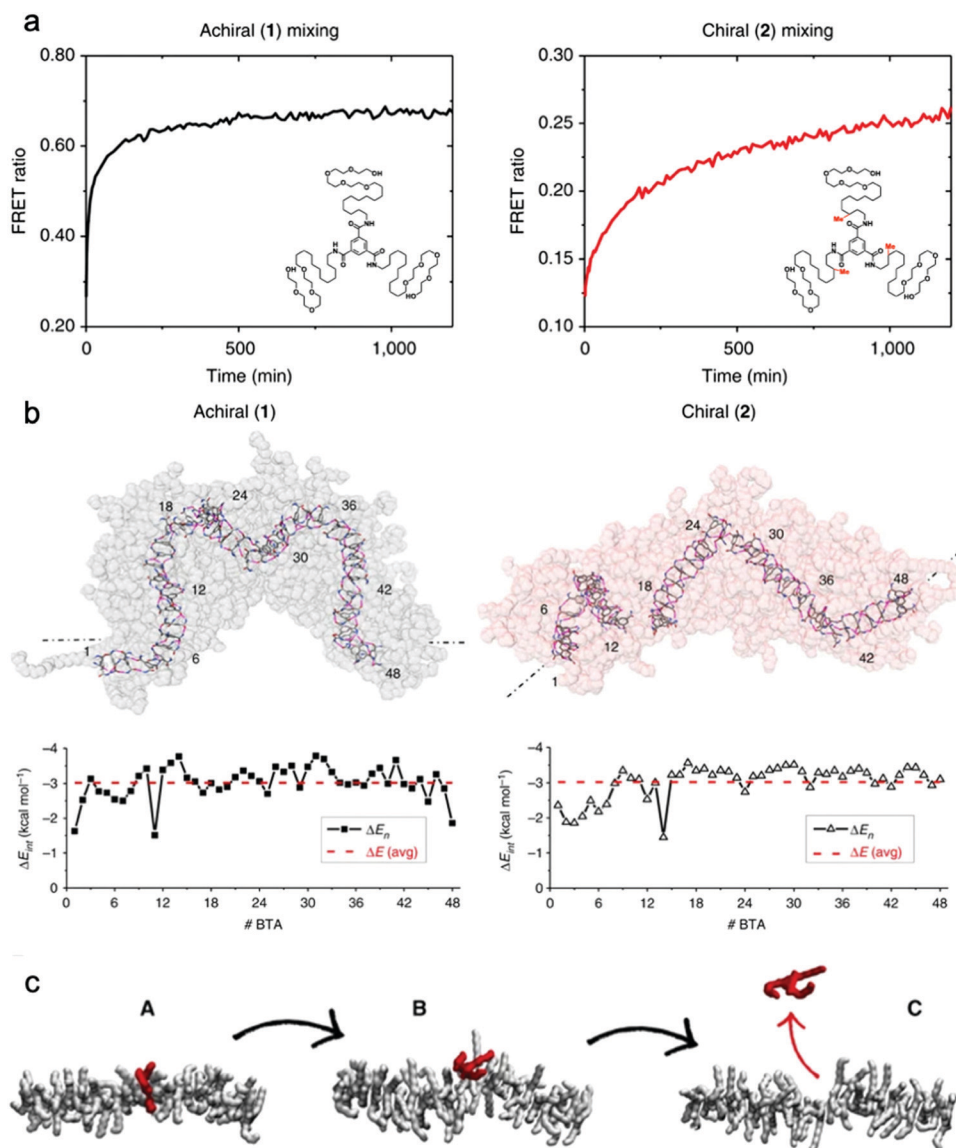


Fig. 8 (a) Kinetic profiles of achiral (1) and chiral (2) fibers measured by FRET with their chemical structures inset. (b) Last snapshots of MD simulations of achiral (1) and chiral (2) fibers with self-assembly interaction energies (ΔE) of individual BTA molecules as a function of their positions. ΔE is defined as the energy gain for one BTA to stay incorporated with the fiber rather than being molecularly dissolved in solution. Adapted from ref. 93, Copyright 2015 Springer Nature. (c) A stepwise mechanism of monomer exchange shows that a defect/breakage must be first created along the stack (A and B transition) from which the monomer can jump out from the fiber (B and C transition). Adapted from ref. 126, Copyright 2017 Springer Nature.

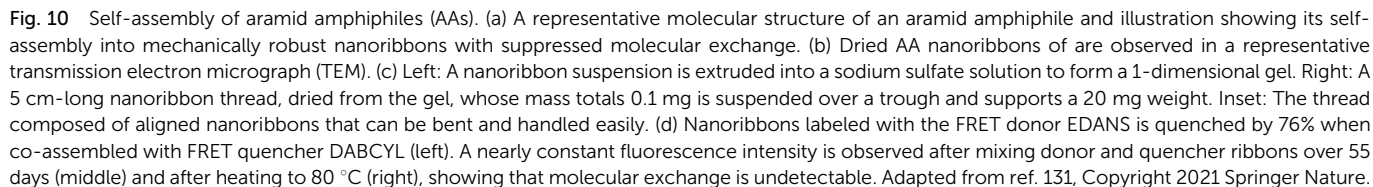
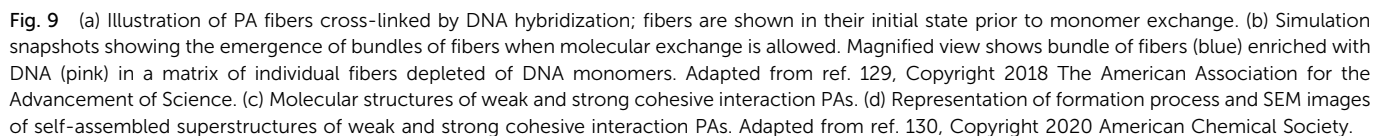
π - π stacking dominating across the nanoribbon width. Statistical topographical analysis of atomic force micrographs revealed that individual nanoribbons exhibit a Young's modulus of 1.7 GPa and tensile strength of 1.9 GPa. Similar to PAs,¹³² AA nanoribbons' high surface charge densities allow them to be shear-aligned in divalent salt solution to form a 1-dimensional gels of arbitrary length (Fig. 10c). The mechanical stability of the individual nanoribbons, combined with the strong interfacial interactions, allow AAs to maintain their structural stability upon drying, forming flexible, solid-state threads of aligned nanoribbons that support 200 times their weight (Fig. 10c). In this study, the AA motif was intentionally designed to minimize the dynamics in this system, where undetectably slow exchange was observed by FRET (Fig. 10d). This study provides a route to nanostructured,

air-stable molecular materials by slowing exchange dynamics to overcome the instabilities pervasive in small molecule assemblies.

4. Conclusions and outlook

In this review, we introduced recently established experimental tools for dynamics investigation of small molecule assemblies, and we highlighted several reports that reveal the importance of these dynamics. While structure-property relationships have long been a prevailing design concept in synthetic self-assembling systems, attention to dynamic behavior and structure-dynamics-property relationships has recently come into focus. Techniques including EPR, HDX-MS, STORM and ODNP, have





nanometer resolution, and is now more accessible due to advances in synthetic techniques and EPR lineshape analysis software. HDX-MS can be used to characterize monomer exchange in supramolecular systems without disturbing the structure, and

is broadly applicable to constituent amphiphiles with discrete molecular weights and labile hydrogens, even in multicomponent systems. STORM is a powerful technique to obtain both timescale and spatial information of exchange dynamics in supramolecular structures, and can provide insight into exchange mechanisms. ODPN requires spin labeling, and is useful for investigating the dynamics of water molecules with site specificity. The use of these experimental tools in supramolecular assemblies has shown the value in studying their dynamics. Additionally, it is important to continue adopting new biophysical characterization tools such as state-of-the-art fluorescence spectroscopy,¹³³ magnetic resonance spectroscopy,¹³⁴ *in situ* X-ray techniques,¹³⁵ and others. This improved understanding of dynamics will allow us to think of self-assembled nanostructures not only in 3-dimensional space, but also propagating in time.

Author contributions

J. H. O. conceived the topic of this review. Y. C. designed the structure of this manuscript and reviewed the literature. Y. C. and J. H. O. wrote the manuscript. Y. C., T. C.-T. and S. J. K. edited the manuscript, with direction from J. H. O.

Conflicts of interest

The authors declare no competing interests.

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