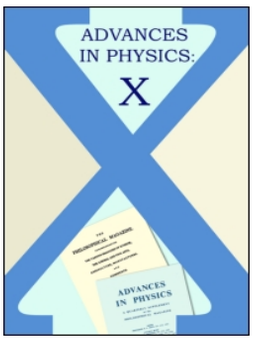
Molecular modelling of supramolecular polymers



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Molecular modelling of supramolecular polymers

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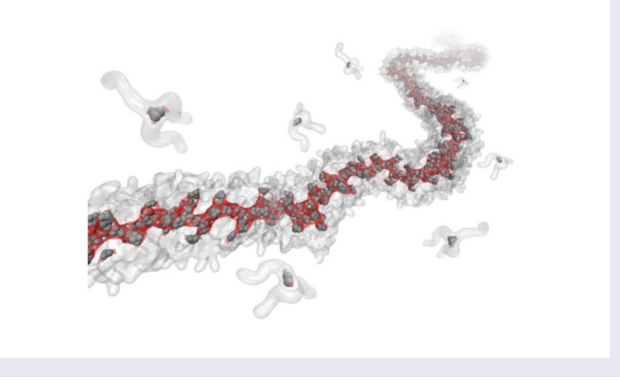
ABSTRACT

Nature uses self-assembly for building supramolecular materials possessing fascinating properties (self-healing, adaptive, reconfigurable and responsive) that are fundamental for many complex biological functions. Artificial supramolecular polymers, composed of monomers that self-assemble via non-covalent interactions, are attracting increasing interest as platforms for building innovative materials, as these possess similar bioinspired dynamic properties. However, their design still relies on an inefficient/expensive trial-and-error approach. A key question is how to design the monomers to control the properties of the supramolecular polymer. Most often, obtaining from the experiments molecular-level information on how to control these assemblies is prohibitively difficult. Molecular modelling is a fundamental support in this field, allowing investigation of the supramolecular polymer from a privileged point of view and at high-resolution. Such a 'virtual microscope' can provide information on the factors that control supramolecular polymer structure and dynamics, on the monomer–monomer interactions and their cooperativity that are precluded to the experiments, paving the way to structure–property relationships useful to advance the rational design of such materials. This review discusses the state of the art of molecular modelling and simulation of supramolecular polymers. The field is advancing quickly. But the detailed insight that can be reached and the continuous technical developments promise that this is only the beginning.



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Introduction

Supramolecular polymers are one-dimensional assemblies composed of fundamental units (monomers) that spontaneously connect via non-covalent interactions (see Figure 1(a)). The main difference respect to covalent polymers lies in the nature of the interactions between the monomers, that in the case of supramolecular polymers are much weaker and reversible, imparting a dynamic character to these structures (see Figure 1(b)) [1–3]. In these systems, the monomers in the assembly are in equilibrium with the unimers in solution, and exchange in-and-out the assembly with a characteristic rate. It is thank to such intrinsic dynamics that supramolecular polymers possess extremely interesting bio-inspired properties, such as the ability to self-heal, shape memory, stimuli-responsiveness and adaptivity, that can be used to build next-generation advanced materials [4]. Nature exploits this concept for building, for instance, microtubules or protein filaments – assemblies of protein building blocks that self-assemble in ordered way – that can self-heal or modify their structure in response to specific stimuli, and whose continuous polymerization and depolymerization is fundamental in many biological functions [5,6].

Many different motifs have been synthesized to obtain monomers that self-assemble into supramolecular polymers via hydrogen bonding, hydrophobic

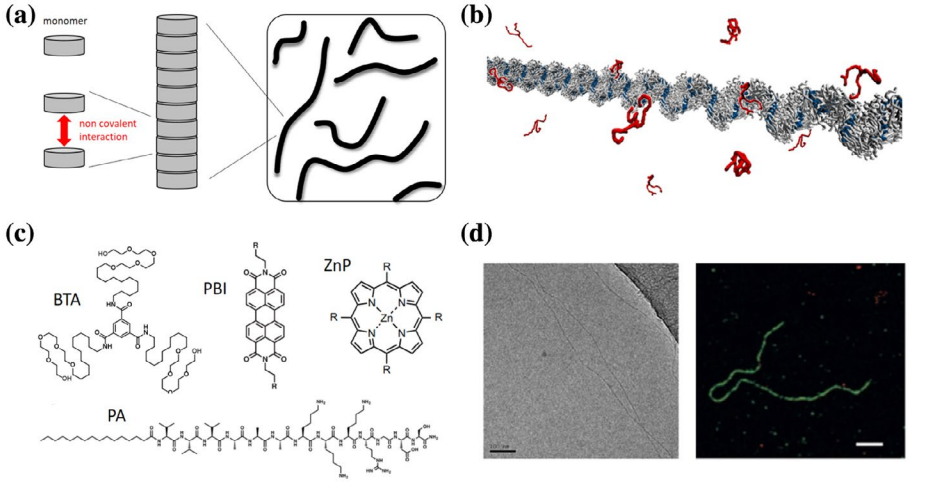

Figure 1. Supramolecular polymers. (a) Conceptual scheme of a supramolecular polymer: non-covalent interactions lead to one-dimensional fibres. (b) Cartoon representing the concept of the dynamical equilibrium between a supramolecular fibre and the monomers in its surrounding environment (solution). Adapted with permission from reference [15]. (c) Few examples of molecular motifs generating supramolecular polymers: benzene-1,3,5-tricarboxamides (BTA) [10], Zinc-Porphyrins (ZnP) [16], perylene bisimides (PBI) [17], Peptide Amphiphiles (PA) [18]. (d) Experimental images of BTA supramolecular fibres, obtained with cryo-TEM (left, scale bar 100 nm) and STORM (right, scale bar 1 μm). Adapted with permission from reference [19] (Copyright 2013 The Royal Society of Chemistry) and from reference [20] (Copyright 2014 The American Association for the Advancement of Science).

effects, van der Waals and/or electrostatic interactions, π–π stacking, metal coordination, combination thereof, etc. (see Figure 1(c)) [2,4,7–13]. While massive experimental efforts have been put in synthesizing artificial supramolecular polymers possessing bioinspired dynamic features [4,14], a key question in this field is: How to rationally design (and synthetize) the monomers to determine the structure, dynamics and overall dynamic properties the supramolecular polymer? While small modifications in the monomer structure can produce large changes in the self-assembled material properties, answering to this question is far from being easy. In fact, this requires a deep understanding of the physical factors controlling the monomer–monomer interactions and the molecular origin that controls the properties of the supramolecular polymer. However, in most cases obtaining such detailed knowledge via the experiments is almost impossible.

Typically, libraries of self-assembling monomers are created and the resulting supramolecular polymers are evaluated and compared in an inefficient and repetitive trial-and-error process [21]. This is particularly true in aqueous solutions. While supramolecular polymers that are soluble in water are extremely appealing for building materials that can dynamically interact with bio-environments (biomaterials, foodstuff, cosmetics, etc.) [8,22], experimentally it is difficult to understand the factors governing the assembly. This is essentially due to the small size and dynamic nature of the supramolecular polymers and to the limited contrast that these offer in solution (see Figure 1(d)).

The experimental study of the dynamics of supramolecular polymers (exchange of monomers within and in-and-out the fibre) is particularly awkward. To look at such soft self-assembled structures in solution at high-resolution it is typically necessary to freeze the system (e.g. cryo-TEM), but this compromises the dynamics of the system. On the other hand, typical crossover experimental approaches to study the dynamics of supramolecular assemblies provide average data on monomer exchange [23,24], but limited/no resolution insight onto the exchange can be obtained to understand the process at molecular-level [2,20]. Indeed, obtaining molecular-level details of these self-assembled materials is necessary to understand the factors that control their structure and dynamics, and ultimately for learning how to rationally design them.

Multiscale molecular models and computer simulations offer a fundamental support in this field. While *in silico* approaches have already been proven a reliable for the study of biological materials and their self-assembly in solution [25–27], their use in the field of synthetic supramolecular polymers is more recent. The versatility and high-resolution of molecular models may allow a high-resolution inspection of supramolecular polymers from a privileged point of view [15,28], providing details on the factors that control their dynamic behaviour that cannot be obtained by the experiments [29,30]. The following sections of this review will focus on different aspects of supramolecular polymers – from structure to dynamics – that have been recently tackled with molecular modelling. Computer simulations allow studying the key interactions that control the assembly, the

self-assembly process (polymerization), the structure of a supramolecular polymer, its intrinsic dynamics and dynamic bioinspired properties. Working as a high-resolution 'virtual microscope', molecular models are becoming more and more important tools in this field, as these hold the potential to move from a trial-and-error to a rational design approach of novel dynamic materials with controllable bioinspired properties.

Supramolecular structure at high resolution

The prime goal of molecular modelling in this field is to gain a high-resolution insight into the structure of the supramolecular polymer. Obtaining a reasonable equilibrated structure of a supramolecular polymer is a first non-trivial task. In the case of supramolecular fibres, it is possible to distinguish between two different typical modelling approaches to tackle this point: a top-down approach, where an initial reasonable configuration for the assembly is built and relaxed in experimental conditions, and a bottom-up approach, where the monomers initially dispersed in the systems undergo spontaneous self-assembly into a supramolecular polymer. Both approaches hold advantages and limitations, as it is discussed below with some relevant example cases.

Top-down simulations

Early approaches in the modelling of supramolecular polymers were based on top-down simulation approaches. A certain number of monomers are pre-stacked into a reasonable (columnar) starting configuration that is then relaxed (e.g. by means of molecular dynamics simulations, etc.) in order to obtain insight on the optimal geometry assumed by the stack, strength and cooperativity of key interactions between the monomers, etc. (see Figure 2(a)). Typically, such an approach is chosen when a reasonable initial geometry for the assembly is available (experiments, high-level simulations, etc.). In general, this approach is chosen when the complexity of the monomers is so high that there is no alternative, and a bottom-up approach is unfeasible (see next section).

Quantum mechanical calculation approaches and *ab initio* molecular dynamics (Car-Parrinello) simulations have been used on simple supramolecular stacks. To cite a few examples, the group of Spiess investigated the solid-state organization of benzene-1,3,5- tricarboxamide (BTA) stacks using Car-Parrinello Molecular Dynamics (CPMD) and NMR [31]. CPMD simulations allowed for in-depth characterization of the helical arrangement of C=O or N-centred BTA assemblies [31]. Detailed DFT calculations from the groups of de Greef, Balasubramanian and Hanabusa provided an insight into the self-assembly cooperativity: in the gas phase, the latter was found to be mainly controlled by inter-BTA H-bonding and its cooperativity [32,33], inducing (i) short range polarization and (ii) long-range amplification of the dipole–dipole interactions [34]. Lubtow et al. used semiempirical

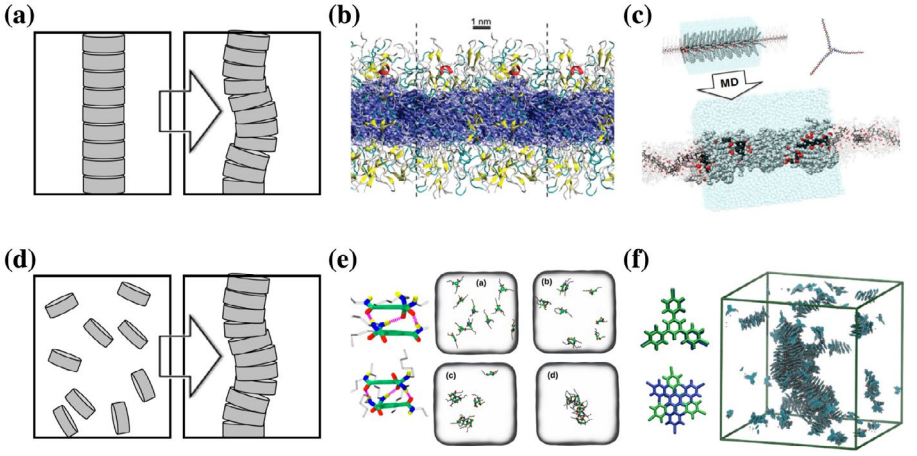

Figure 2. Approaches to molecular modelling of supramolecular polymers. (a) Scheme: top-down approach. On the same line, top-down approach used to study a cylindrical fibre composed of Peptide Amphipiles (b, [18]) and a BTA-based supramolecular polymer in water (c, [15]). Adapted with permission from reference [18] (Copyright 2011 American Chemical Society) and [15]. (d) Scheme: bottom-up approach. On the same line, bottom-up approach used to study the directional self-assembly of simple BTA-based monomers in nonane (e, [45]) and of 1,3,5-tris(4-bromophenyl)-benzene monomers in methanol and ethanol(f, [51]). Adapted with permission from references [45] (Copyright 2014 American Chemical Society) and [51] (Copyright 2017 American Chemical Society).

PM6 calculations to study columnar stacks of 9,10-Bis(phenylethynyl) anthracene dyes (BPEAs) in vacuum [35]. While such accurate quantum chemical calculations guarantee great precision, they are prohibitively expensive for larger and more realistic molecular systems due to the excessive number of atoms in the monomers (treatable systems typically do not exceed short oligomers) [33,36].

Atomistic-scale molecular dynamics (MD) simulations, allowing to simulate larger systems for longer times [18,37–39], have been recently used to explore self-assembled materials of C3 symmetric BTA-based compound [40] and bis-urea [41]. The group of Beljonne used the Dreiding [42] force field and atomistic MD simulations to obtain equilibrated structures for stacks of chiral oligophenylenevinylene (MOPV) [43], oligo(p -phenylenevinylene) ureidotriazine (AOPV3) [44] and C3 symmetric N,N′,N″-Tris[3(3′-carbamoylamino)-2,2′-bipyridyl]-benzene-1,3,5-tricarbonamide monomers [40], to name a few, whose CD spectra were then compared to the experiments. The group of Balasubramanian used all-atom molecular dynamics (MD) simulations to study BTA stacks with short alkyl side chains in an apolar solvent (nonane, see Figure 2(e)) [45]. All-atom molecular dynamics (AA-MD) simulations of different size BTA stacks showed presence of cooperativity in the BTA assembly. Monomer dimerization was found weaker in the apolar solvent than in the gas phase. Moreover, the energy necessary to remove one molecule from a BTA decamer was found larger than that in the case of a tetramer or a dimer, an evidence of cooperativity [45]. The group of Haino demonstrated with DFT calculations that dipole–dipole interactions can drive

the cooperative assembly of planar π-conjugated molecules into supramolecular stacks [46,47].

Other types of supramolecular polymers in organic solvents have been studied in similar way obtaining useful information on chirality self-sorting, on the cooperativity of dipole moment and monomer–monomer interactions in the different architectures [48–50]. While all these examples pertain to relatively simple and rigid monomers in the gas phase or in organic solvents, complexity typically increases in water due to the larger size of the water-soluble monomers and the strong hydrophobic effects involved. Molecular models are particularly useful to study supramolecular polymers in water, where it becomes increasingly difficult to obtain clear insight into these structures by the experiments.

In 2011 the group of Schatz studied the relaxation of an atomistic model of a preformed supramolecular fibre composed by 144 peptide amphipiles by means of MD simulations [18]. The radius of the equilibrated supramolecular fibre and the evidences of hydrogen bonding within the structure were found in good agreement with the experiments. Also, the AA-MD simulations identified the formation of Beta-sheets along the fibre as a driving force leading to cylindrical assemblies in water (see Figure 2(b)).

Similar evidences have been recently reported for self-replicating peptide fibres, where AA-MD simulations by the group of Marrink were compared with the experiments, providing a high-resolution picture of these complex supramolecular structures in water and an estimation of the monomer association free-energy [52].

Top-down atomistic models have been also used to study supramolecular BTA polymers in water [15]. Starting from an initial extended configuration for an infinite BTA fibre, AA-MD simulations showed strong fibre folding caused by hydrophobic effects (see Figure 2(c)). While such fibres have always been typically represented by perfectly extended/ordered cartoons, such AA-MD simulations demonstrated that these possess an intrinsic level of order/disorder in their structure emerging as a consequence of fibre folding. The models were found in optimal consistency with the available experimental evidence (fibre radius, SAXS, persistence, overall helicity, etc.). Furthermore, comparison between slightly different fibres demonstrated that small changes in the structure of the monomers can produce considerable differences into the structure and dynamics of the supramolecular polymers [15]. Comparison of pre-formed ordered BTA oligomers and disordered BTA aggregates of the growing size allowed to study the cooperativity of the different types of forces during the growth of the assembly in water [28]. In this way, it was possible to identify the electrostatic interactions as the key factor leading to the formation of ordered fibres in solution instead of disordered aggregates. In particular, inter-BTA hydrogen bonding was highlighted as a key player in the order amplification during fibre growth [28]. Interestingly in this case, despite the relative weakness of a single hydrogen bond, multiple hydrogen bonds in suitable positions can be important, like for instance in the case of the cellulose

structure, were microfibrils with high tensile strength can be formed thanks to a hydrogen bonds network [53]. Such a structural/energetic comparison allowed to propose a BTA polymerization mechanism in water where small disordered aggregates are first formed in solution, while these are subsequently converted into ordered oligomers over a certain critical size [28].

However, such top-down approaches possess intrinsic limitations. First, it is clear that the higher is the complexity/flexibility of the monomer structure, the less straightforward is the equilibration of the pre-stacked system. Very complex systems can remain trapped in long-living meta-stable states, while it can be really difficult to understand if real equilibration has been achieved. In principle, a proper (long enough) sampling of the equilibrated system would be needed, which is problematic at atomistic level for complex supramolecular systems. Proven useful in the case of complex polymeric macromolecules [54,55], enhanced sampling approaches can be useful to enhance the confidence in the minimum energy configuration that is obtained [30,56].

It is also worth to underline that, unlike biological structures as proteins, whose structure is univocally determined, the structure of a supramolecular polymer can be very dynamic and has a statistical nature (the fibres in solution can be different one from the other, etc.). What is typically obtained is a collection of average experimental information (UV, CD, SAXS, etc.) that can be related to structural features of the models, like for example the average degree of order in the assembly, helicity, hydrogen bonding, etc. Relating such average experimental data extracted from a real solution containing a statistical distribution of fibres to a detailed model representative of a small section of the assembly is not always straightforward. A safe approach is to compare between structural variants, and to check if the models can correctly capture the differences seen in the experiments [15,28,30].

While *top-down* atomistic models should be handled carefully, especially for complex structures that may suffer more of limited sampling issues, these nonetheless allow studying complex supramolecular structures at high-resolution, where studying their self-assembly in full by means of atomistic simulations would be prohibitive. Such approaches are particularly useful where high precision is needed and simplified coarse-grained models would be inadequate – e.g. study of the interaction with water molecules, ion binding, etc. For example, recent *top-down* simulations of peptide amphiphile fibres in water allowed studying the level of hydration and water dynamics in the fibbers [57]. AA-MD simulations have been also used to study ion condensation along supramolecular fibres of peptide amphiphiles [58], or their clusterization onto the surface of dendrimers controlling their assembly into dendrimer fibres, their disassembly [11], or functionalization *in situ* [59]. Similar modelling approaches have been used for other types of assemblies, such as supramolecular vesicles made of amphiphilic homopolymers formed via ad hoc electrostatic interactions with divalent ions [60].

Bottom-up simulations

In bottom-up simulations the monomers, modelled with an appropriate force field and initially randomly dispersed in a simulation box, undergo spontaneous self-assembly during a molecular simulation (see Figure 2(d)). In the case of supramolecular polymers the monomers are seen to spontaneously aggregate in time in the solvent box and to grow directionally in time. As the top-down one, this is a general simulation approach that can be applied to atomistic or coarse-grained models. However, the typical complexity of the real monomers makes the use of atomistic models at this level limited to the simplest supramolecular polymers. To simulate in exhaustive way the self-assembly of more complex polymers in an 'active' solvent (like water) it is typically necessary to accept some degrees of approximation in the description of the monomers using a coarse-graining approach. Another opportunity is to use enhanced sampling approaches that can facilitate the exploration of ordered aggregates in the system.

The group of Balasubramanian explored the formation of stacks of 1,3,5-benzenetricarboxamide (BTA) monomers in organic solvent (nonane) by atomistic simulations (see Figure 2(e)) [45]. Two variants of the DREIDING atomistic force field were compared. Thanks to a biased approach, during the simulations the BTA monomers were seen to form ordered stacks in the apolar solvent starting from a monodisperse solution. In this particular case, this effect was facilitated by the reduced length of the BTA side chains and by the presence of the apolar solvent: the BTA monomers stay extended during the simulation favouring the ordered stacking. In organic solvent, the interaction between the monomers is highly directional and mainly controlled by the threefold hydrogen bonding between the amides of the BTAs, and the simulations reported evidence of a cooperative self-assembly mechanism in nonane [45].

Chami and Wilson reported MD simulations of rigid anionic azo dyes self-assembling of into stacked aggregates in explicit water molecules [61]. Using the General Amber Force Field [62], AA-MD simulations allowed to study the mechanism and energetics of self-assembly, indicating that the latter was mainly isodesmic. The same set-up was also recently used to study the self-assembly of monomers with a triple AAA-DDD hydrogen bonding motif into macrocycles and intermediate aggregates in dichloromethane [63]. In these cases, the system was simple enough to observe self-assembly at atomistic resolution during normal MD simulations. However, this strongly depends on the complexity of the free-energy landscape for the self-assembly phenomenon. In most cases the system remains stuck into local minimum energy configurations from which it cannot escape during the timescale accessible during a classical AA-MD run. Enhanced sampling simulations can be useful to tackle this limitation.

Biased simulation approaches have been used to study crystallization and self-assembly of rigid monomers. The group of Parrinello combined classical AA-MD simulations and well-tempered metadynamics to study the crystallization of urea in explicit solvent (water) and in the presence of additives [64]. In

this case, the use of an advanced sampling technique (metadynamics) allowed to explore various assembled states [65], obtaining a comprehensive view of the self-assembling system [66]. Similar advanced simulation approaches have also been recently adopted to study the nucleation and growth of 1,3,5-tris(4-bromophenyl)-benzene columnar assemblies (see Figure 2(f)) [51], or the aggregation of small amyloid peptides into fibrils [67–69]. However, to date such advanced methods based on a throughout exploration of the self-assembly pathways have been efficiently used only for molecular systems with reduced complexity: low number of relatively simple and rigid monomers, etc. When the structure of the monomers becomes more complex and/or monomers start becoming non-rigid (e.g. typical water-soluble monomers), the self-assembly process can become too slow to be observed within the timescale accessible during unbiased AA-MD simulations and too complex to be effectively described with a low number of critical collective variables (e.g. in metadynamics simulations). In such a case, it is typically more effective to accept some approximations in the description of the monomers, and to build coarse-grained models for the self-assembling units.

Coarse graining of supramolecular polymers

A way to play around the problems mentioned above is to coarse grain the system. The detail in the description of the atomistic models can be simplified into coarse-grained (CG) representations of the systems that can be very effective. In fact, not only the CG model system becomes less computationally demanding to simulate (reduced number of particles and larger time steps can be used), but the dynamics of the system itself is also accelerated thanks to the fact that the potential energy surface becomes smoother in the CG description. Altogether, these effects can effectively speed up the simulations by order of magnitudes compared to the corresponding AA models [70], and make the bottom-up approach very efficient also in the case of complex supramolecular systems.

A major challenge is to ensure that the simplified CG model behaves consistent to the more detailed AA models in the key features that control the behaviour of the system. Namely, despite the structural simplifications, the CG model must be able to capture the correct physical behaviour of the system.

The group of Balasubramanian developed an *ad hoc* CG model for BTA monomers with short alkyl chains, and studied the spontaneous self-assembly of small ordered oligomers in organic solvent (nonane) [72]. The coarse-grained model included an intrinsic dipole embedded on one of the CG beads to impart a macrodipole moment to the oligomers and to model hydrogen bonding during aggregation. The CG-MD simulations showed that the BTA monomers self-assemble in nonane via a cooperative mechanism with a nucleus size of three.

The MARTINI force field is a very popular coarse-grained force field in the field of biomolecular simulations [73,74], and recently started to be used also for the modelling of synthetic polymeric assemblies and their interaction with lipid

bilayers [75,76]. In 2012 the group of Schatz used the MARTINI force field to model the self-assembly of peptide amphiphiles (PAs) into cylindrical fibres in water (see Figure 3(d) and (e)) [71]. The PA monomers were seen to aggregate very rapidly into spherical micelles that subsequently spontaneously merged into a single infinite cylindrical fibre spanning through the PBC box. In agreement with the previous atomistic study [18], water molecules were not seen to penetrate into the hydrophobic core of the fibre while most of the fibre surface was covered by the peptide sequence [71].

CG models have been also built for BTA supramolecular polymers [29,30]. A fine CG approach was chosen (1 CG bead every 3 heavy atoms, see Figure 3(a)), and the MARTINI force field was used as a base for the model, to guarantee facile transferability and to benefit of the large variety of molecular structures, solvents, etc. already available. Starting from water-soluble BTA monomers, the CG models were then opportunely refined on the AA models for the same

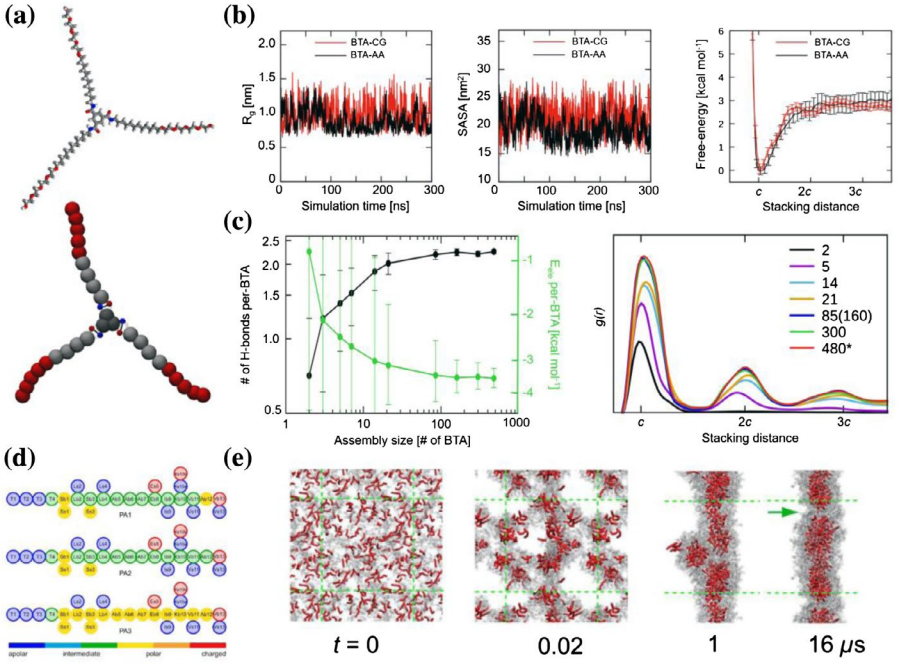

Figure 3. Coarse-grained modelling of supramolecular systems. (a) Structure of a BTA water soluble monomer, in its atomistic and coarse-grained representations. The coarse-grained model includes an explicit dipole mimicking the hydrogen bonding capability of the amide units [29]. (b) Validation of the BTA coarse-grained model, in terms of behaviour of a single monomer in water (R_g and SASA) and interaction of the cores (dimerization free energy) [29]. (c) Cooperativity of the interactions (average number of H-bonds and H-bonding energy) and amplification of order in aggregates of different sizes, up to supramolecular fibres [29]. Data adapted from reference [29]. (d) Coarse-grained representation of three different peptide amphiphiles (Pas), in the framework of the MARTINI force field [71]. (e) Spontaneous formation of a single infinite (spanning through the PBC) supramolecular fibre made of PAs by means of 16 μs CG-MD simulations [71]. Adapted with permission from reference [71] (Copyright 2012 American Chemical Society).

monomers to ensure that these were able to reproduce all the key characteristics of the supramolecular assembly – (i) the behaviour of the monomer in solution, (ii) the strength of monomer–monomer interaction, (iii) the cooperativity of the self-assembly and of the key interactions, and (iv) order amplification in the fibres during their growth (see Figure 3(b) and (c)) [29]. (i) The BTA monomers fold in water due to hydrophobic effects: comparison of the radius of gyration (R_g) and solvent accessible surface area (SASA) with the AA ones ensured that the folding was correctly treated in the CG model (Figure 3(b)). (ii) The strength of the interactions was tuned by choosing the appropriate MARTINI beads that best reproduced the atomistic free-energy profile of dimerization obtained via metadynamics simulations. This CG model also included the option of an explicit treatment of hydrogen bonding between the BTAs in similar way than in most common atomistic force fields. Explicit $\pm q$ dipoles were inserted in the amide CG beads of the BTA explicitly mimicking the hydrogen bonding as an electrostatic interaction (see Figure 3(a)). (iii) Finally, the cooperativity of the key interactions (hydrophobic effects, hydrogen bonding) was verified by creation and equilibration of oligomers of different sizes, as previously done for a full atomistic model [28]. The radial distribution function *g(r)* between the BTA cores was used as an indicator of the average level of order inside the oligomers, demonstrating similar amplification of order in the growing oligomers to what seen at atomistic level [28].

After the complete validation of the models described above, top-down and bottom-up CG-MD simulations provided consistent equilibrated supramolecular structures for these BTA fibres, demonstrating the reliability of the equilibrium configuration for the fibres obtained with these CG models (not possible with AA models) [29]. Such CG models allowed to observe *live* and to study the mechanism of supramolecular polymerization in water. Moreover, keeping high the resolution in the CG model (fine CG) allowed to compare between slightly different fibres, ensuring that the CG model could capture the effect of small changes in the monomer structure or in the external conditions consistent with the experiments. Detailed analysis of the structure of these CG fibre models revealed that a certain number of stacking defects are intrinsically present along the fibre [30]. Such defects were subsequently found to be important for the supramolecular dynamics of the fibre, as it will be discussed later on in this review. Furthermore, the possibility to go from monomers to supramolecular polymers live during CG-MD simulations opened the possibility of studying the supramolecular polymerization mechanism, as it is described in the next session.

Supramolecular polymerization

The study of supramolecular polymerization mechanism by the experiments is a difficult task. Typically, the self-assembly process is very fast, which makes it prohibitive to be followed by the experiments. Temperature variations are often used in the experiments to observe the evolution of the system from a disassembled

state to supramolecular polymers at room temperature [77], while the results on polymer structuring as a function of temperature are then fitted to mathematical models [78]. However, these approaches provide indirect average data and do not allow obtaining molecular-level information on the mechanism of supramolecular polymerization. In this context, molecular simulations are very helpful, allowing a facile and direct observation of the supramolecular polymerization mechanism (given the possibility of simulating the whole process) at a resolution that cannot be achieved by the experiments (in typical CG models based on the MARTINI force field, the resolution is ~5 Å). With such great details one can observe not only the polymerization occurring, but also what does happen to the different types of interactions during the growth, revealing the key factor controlling the process. The main difficulty is to go from the monomers to supramolecular polymers with accurate atomistic models, or to ensure that the polymerization process is correctly modelled when an approximate CG model is used.

The group of Balasubramanian studied the polymerization process of BTA-based supramolecular polymers in nonane at AA and CG level [45,72]. The group of Bolhuis recently used transition path sampling to monitor the stability and growth mechanism of cyclic peptide nanotubes in water at atomistic level [79]. Explicit-water CG models (see above) for BTA monomers also allowed to follow supramolecular polymerization in time, monitoring the growth of the aggregates and the amplification of order (core–core coordination, see Figure 4) inside them during the cooperative polymerization process [29].

Despite the advantages given by such CG models, as far as these are based on an explicit treatment of the solvent, they are always intrinsically limited in the number of monomers that can be effectively simulated and in the monomer concentration in the system. Typically, explicit solvent molecular simulations are even orders of magnitude more concentrated than the experiments, but for the dynamic supramolecular polymerization process this can be a non-negligible factor (kinetic effects may depend on the concentration). Lowering the concentration in an explicit solvent model would result in decreasing the number of the monomers in the system down to the statistical irrelevance, or into increasing the simulation box and the number of solvent molecules to the level that simulation becomes unfeasible. Implicit-solvent CG models may tackle this limitation. Recently it has been reported an implicit solvent model for water soluble BTA polymers that allowed the study of the polymerization mechanism at different concentrations, down to the experimentally diluted ones [80]. This study demonstrated that the mechanism of supramolecular polymerization is dependent on monomer concentration, while in experimentally dilute conditions (nM) any kinetic effect related to monomer concentration disappears from the system and polymerization proceeds following to the 'thermodynamic path' [80].

While such CG models allow crossing the spatiotemporal scales of what can be simulated with AA models, still these allow reaching simulation times of micro-seconds. As said, one of the most interesting features of supramolecular polymers

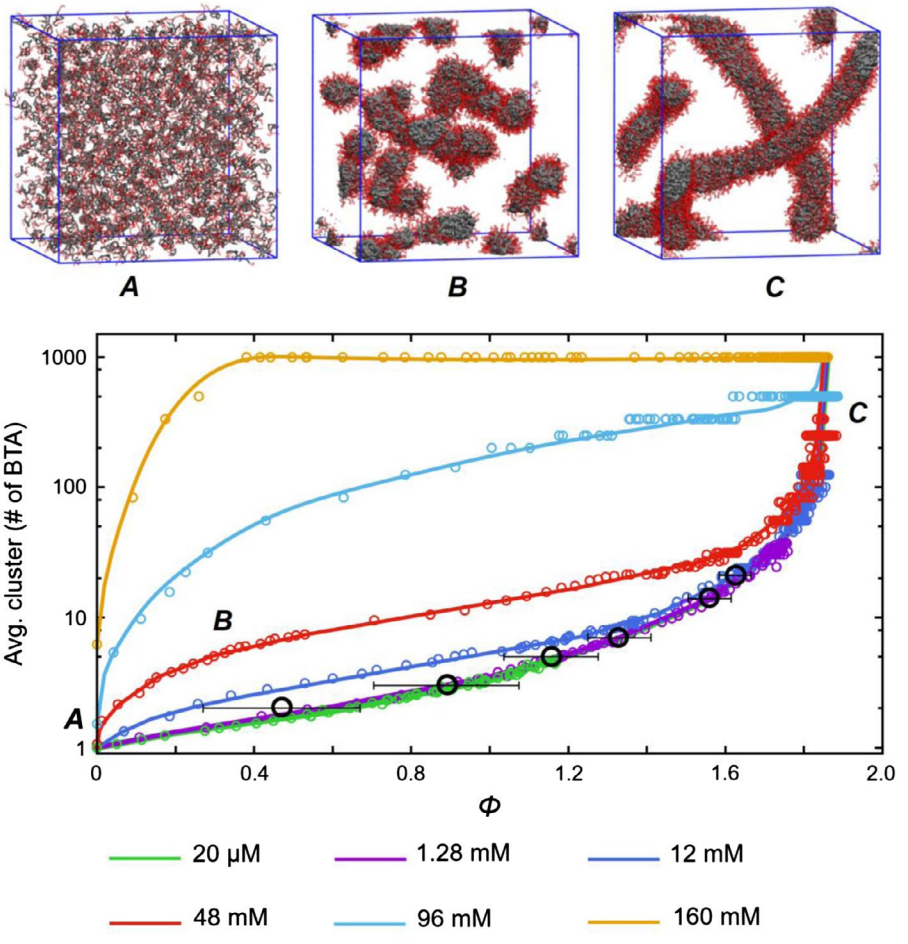

Figure 4. Polymerization paths of BTA supramolecular fibres studied obtained from implicit-solvent coarse-grained model [80]. At 48 mM, randomly dispersed monomers (A) rapidly aggregate into small disordered clusters (B), that on longer time scales evolve into supramolecular fibres (C). Thanks to the advantages given by the absence of the solvent, BTA concentrations close to the experimental ones have been reached. The polymerization paths show concentration dependent kinetic effects: formation of disordered aggregates during polymerization disappears at low concentrations. Adapted with permission from reference [80] (Copyright 2017 American Chemical Society).

is in their supramolecular dynamics – i.e. dynamic exchange of monomers – that is intrinsic in their structure and determines their dynamic bioinspired properties, such as the ability to self-heal, to dynamically change/reconfigure their structure and to respond to external stimuli in time. However, such exchange events usually occur on much longer timescales, and thus cannot be observed via classical MD simulations. Advanced simulation approaches can be extremely useful to this purpose, as described in the next section.

Supramolecular dynamics at submolecular resolution

Supramolecular polymers possessing intrinsic dynamic properties are very promising for the development of new adaptive and self-healing materials. Different from covalent polymers, supramolecular polymers continuously exchange monomers with the surrounding according to a well-defined supramolecular equilibrium [1,3]. Experimentally, attempts to characterize such a monomer exchange between fibres in solution used, for example, STochastic Optical Reconstruction Microscopy (STORM) [2,20] and Förster Resonance Energy Transfer (FRET) [15,23]. In the case of BTA supramolecular polymers in water, the kinetics of exchange between the fibres in solution was found to follow a multi-exponential behaviour, which suggested that in this system the exchange is a complex multi-step phenomenon, which is extremely sensitive to slight changes in the monomer structure. However, the limited spatial and temporal resolution that can be achieved in the kinetic experiments demands for a deeper investigation of the molecular factors governing these complex dynamic processes.

Ideally, for the rational design of controllable dynamic materials, one would need to observe the dynamic exchange events at a nearly atomistic resolution. However, within the limited timescales accessible by classical high-resolution simulations (nano-microseconds), the exchange of monomers in-and-out a supramolecular polymer is a rare event. This typically prevents direct observation of supramolecular exchange events during unbiased MD simulations.

In the last years, enhanced sampling computational techniques have been proven very effective to tackle this issue [81–86]. For example, Botzakis et al. recently used transition path sampling simulations to identify the pathway of incorporation (polymerization) in tubules of peptide macrocycles [79]. Particularly interesting, infrequent well-tempered metadynamics (WT-MetaD) [81] simulations were recently proven an efficient tool to explore rare exchange events, providing information on the pathway, rate limiting steps and their relative kinetics in once [82]. For example, the group of Parrinello used WT-MetaD simulations to study drug unbinding from protein binding pockets [87], or the condensation of Argon droplets from supersaturated vapour [88]. Recently, it was demonstrated that similar approaches combined with atomistic and coarse-grained models also allow investigating the intrinsic dynamics of supramolecular polymers [30].

WT-MetaD simulations demonstrated that monomer exchange in water-soluble BTA supramolecular polymers starts from the defects that are intrinsically present all along these fibres (exchange hot spots, see Figure 5(a)) [30]. The monomers stacked onto these surface hot spots (i) first de-stack and remain adsorbed onto the supramolecular polymer surface and from such absorbed configuration (ii) on a second time exchange with water (see Figure 5(b) and (c)).

Infrequent WT-MetaD simulations demonstrated that in these fibres step (ii) is much slower than step (i), highlighting the bioinspired nature of these supramolecular polymers, were their skin is much more dynamic than their interior. Comparison between two fibre variants where the monomers differ by one carbon

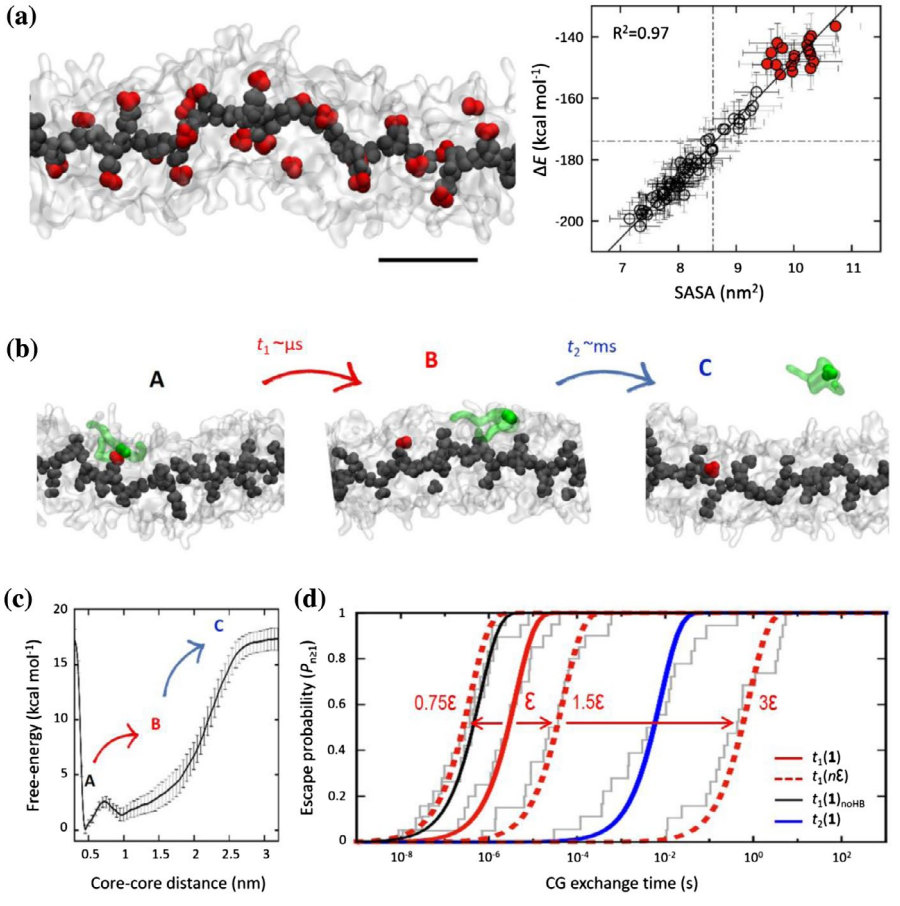

Figure 5. Intrinsic supramolecular dynamics in a BTA supramolecular polymer studied by a combination of coarse-grained models and advanced simulation techniques [30]. (a) Exchange hot spots on the surface of the BTA fibre: monomers whose core is highlighted in red (left) are identified by higher SASA and less favourable binding energy than average (right). (b) Two steps mechanism of monomer exchange with water in a BTA supramolecular polymer as identified by well-tempered metadynamics simulations. The activated green monomer (A) first detaches from the hot-spot (B) and after surfing on the surface can jump into the solution (C). (c) Free energy profile of the two steps exchange process along one reaction coordinate (distance from the nearest hot-spot). (d) Transition time distributions for monomer unbinding and exchange on the fibre surface obtained from multiple infrequent WT-MetaD simulations. Computational models have been used to study how to modify the monomer–monomer interactions to control the exchange [30]. Adapted with permission from reference [30].

more/less in the alkyl spacers showed the same exchange mechanism, but all exchange steps slowed down by ~1–2 orders of magnitude in the more hydrophobic fibre [30]. These findings were found in agreement with the experimental evidences [15,20].

These modelling efforts allowed characterizing the exchange mechanism and kinetics in supramolecular polymers at submolecular resolution, which is prohibitively difficult at experimental level. However, the real power of such models goes also beyond this. Taking advantage of the flexibility of such models, it is possible

to understand the role of all individual types of interaction on the dynamics of the supramolecular polymer, obtaining structure–dynamics relationships which open the way towards the rational design of supramolecular polymers with predetermined dynamics (see Figure 5(d)) [30].

Towards modelling stimuli responsiveness

Supramolecular polymers possess dynamic properties that remind those of other materials in nature. For example, they are capable of self-heal or dynamically reconfigure their structure when perturbed or stimulated. Owing to their supramolecular character, they are typically sensitive to changes in the external environment and intrinsically reversible (they can disassemble and reassemble). They also possess shape memory, and can be designed to respond selectively to determined stimuli or interactions [4]. The factors that control such fascinating bioinspired properties are encoded into the structure of the monomers, and are controlled by the monomer–monomer interactions. Thus, to understand how to design bioinspired supramolecular polymers with controllable dynamic properties it is mandatory to study their stimuli-responsiveness at high-resolution to understand the molecular factors that control the assembly. While we already discussed the limits and difficulty of dealing with this point at experimental level, molecular simulations can be a precious support to this end [89].

For example, atomistic MD simulations have been used to study the stimuli responsiveness of supramolecular fibres made of PPI dendrimers and cadmium acetate ions (see Figure 6(c)) [11]. The AA-MD simulations demonstrated that the directional assembly of the dendrimers in the fibre is controlled by a combination of electrostatic effects with the ions, and by the non-symmetric amphiphilic nature of the acetate ions, that create hydrophobic patches on the dendrimer surface along which fibre growth proceeds. Once high-resolution AA-MD simulations elucidated the factors that control the assembly, these suggested that ions could be used on the fibres to disassemble or functionalize them. For instance, strong ionic substitution by ions from dissociated NaCl was observed along a pre-equilibrated dendrimer oligomer, leading to disassembly consistent with the experiments [11]. On the other hand, ionic competition between SH^- (from dissociated Na_2S in solution) and acetate ions triggered the formation of sulphur clusters in correspondence of Cd^{2+} ions along the fibre during AA-MD, consistent with the *in situ* formation of CdS quantum dots along these fibres observed in the experiments [59]. Similar stimulus responsiveness to selective divalent ions has been recently investigated by means of AA-MD simulations in the case of homopolymeric monomers generating vesicles [60].

Other types of external environmental stimuli (and their effect on supramolecular materials) that can be effectively explored by MD simulations are temperature [29,90,91], pH variations [92], etc. The group of Balasubramanian used AA-MD simulations demonstrating that the application of an external electric field can

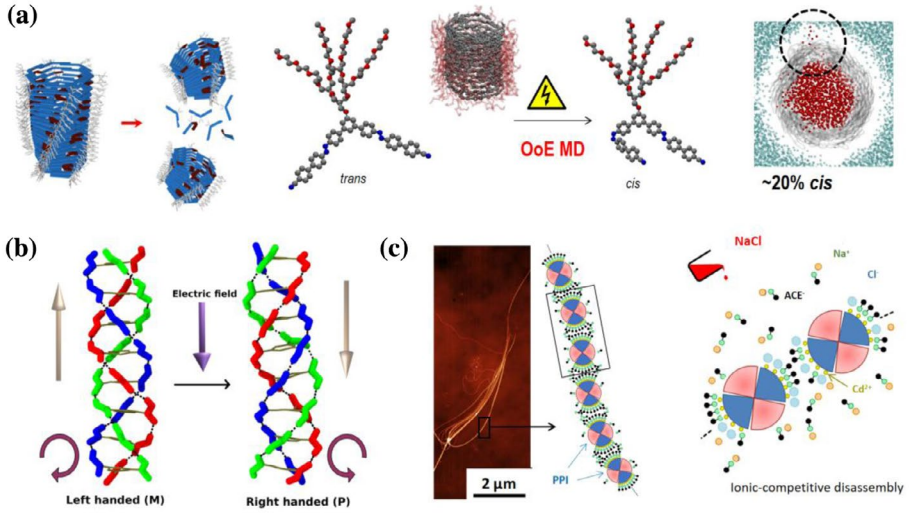

Figure 6. Stimuli responsiveness in different supramolecular systems. (a) Irradiation with UV light can lead to destabilization and breakage of supramolecular tubules made by angular monomers containing azobenzene tails, caused by their *trans* to *cis* transition. Out of equilibrium atomistic MD simulations (OoE MD) showed the formation of holes in the supramolecular structure at 20% *cis* percentage, in agreement with experimental observations [94]. (b) Electric field can reverse the helical handedness in a columnar BTA stack, by reorientation of the amide groups [93]. Adapted with permission from reference [93] (Copyright 2015 American Chemical Society). (c) Supramolecular fibres made of PPI dendrimers and cadmium acetate ions self-assemble directionally assembly by a combination of electrostatic effects and the non-symmetric amphiphilic nature of the acetate ions. AA-MD simulations elucidated the factors that control the assembly, and suggested that ions could be used on the fibres to disassemble or functionalize them. Indeed, NaCl was observed to lead to disassembly [11]. Adapted with permission from reference [11] (Copyright 2012 American Chemical Society).

trigger the reorientation of the amide groups (dipoles) in a BTA fibre, provoking a switch in the helicity of the fibre (see Figure 6(b)) [93]. Recently, they also showed that such switching is absent in the case of *N*,*N*′,*N*″,*N*‴-*tetra*-(Tetradecyl)-1,3,6,8-pyrenetetracarboxamide stacks albeit the external stimulus is the same [48].

In general, the approach is very similar in all these cases: (i) the assembly is equilibrated, (ii) the stimulus is introduced into the system and (iii) the perturbation provoked by the latter on the assembled material is explored during the simulations [89]. The introduction of the stimulus into the system (ii) brings the system temporarily out-of-equilibrium, while in the phase between (ii) and (iii) the system evolves to a new equilibrium state. While the modelling approaches described above point the attention at the difference between equilibrium states, there are slightly different cases that have recently been explored by means of atomistic simulations, where the attention has also been pointed at what happens to the assembly while this is out-of-equilibrium.

A few examples have been reported where atomistic and coarse-grained molecular simulations have been used to investigate assemblies of monomers containing azobenzene units. Upon UV irradiation, the azobenzene moieties in

the monomers undergo transition from *trans* to *cis*. When this happens into an assembly, such transition generates distortions and changes in the properties of the supramolecular structure [95–97]. This has been recently studied in the case of 4′-(biphenyl-4-ylazo)-biphenyl-4-thiol (ABPT) monoloyers on Au(111) by means of a combination of combined atomistic-QM MD simulations [98]. At atomistic level, the effect of light onto the assembly can be modelled, for example, by modifying the –C–N=N–C– dihedral angles in the azobenzenes so that these are favoured to autonomously undergo *trans* to *cis* transition during an MD simulation. Such an approach has been used to understand the effect of the transition onto the surface of Au-nanoparticles decorated with azobenzene units [99]. It was demonstrated that the *cis* to *trans* transition has an effect on water entrapment into the NP and on NP aggregation. Another recent example, more related to supramolecular polymers, pertains to a self-assembled nanotube formed by angular monomers containing azobenzene tails [94]. Upon UV irradiation, it was observed a strain buildup into the tubules leading to (i) breakage into shorter tubules and (ii) disassembly. Out-of-equilibrium AA-MD simulations allowed to observe the assembly during the *trans* to *cis* transition of the monomers, showing that the structure is seriously damaged over a certain threshold, consistent with the experimental evidence (see Figure 6(a)) [94].

Supramolecular polymers that can respond in dynamic way to specific interactions with biological targets are also extremely interesting. AA-MD simulations have been used to explore the effect of the specific binding of ligands present onto the monomers with complementary proteins [100]. The high-resolution in the models allowed to understand the key types of interactions involved in the binding-induced destabilization of the assembly, the role of multivalency, etc. Strongly coarse-grained Montecarlo simulations (1 CG bead per monomer) were used to statistically model the reconfiguration of a BTA fibre incorporating positively charged monomers due to superselective binding with oppositely charged ssDNA strands of different length [23]. While reproducing the clustering trends obtained in the experiments after proper tuning of the key parameters (interaction energy between the DNA and the monomer), such coarse models lose the submolecular details necessary to understand the factors that control stimuli responsiveness.

In order to obtain molecular-level information useful to the rational design of dynamic bioinspired supramolecular polymers, it would be necessary to study its dynamic responsiveness to the stimulus at high (submolecular) resolution. This is not easy, but the recent computational efforts described above suggest that an ad hoc combination of atomistic, coarse-grained models and advanced simulation approaches can be a way to reach such an ambitious goal.

Conclusions

Supramolecular polymers are attracting increasing interest as platforms to build advanced materials. Thanks to their supramolecular nature, these possess dynamic bioinspired properties (self-healing, adaptive, stimuli responsive, etc.) that are

reminiscent of natural materials. However, the rules to rationally design the monomers to obtain controlled dynamic supramolecular polymers are most often inaccessible by the experiments, and their synthesis is mostly limited to a repetitive trial-and-error approach.

Molecular models constitute a fundamental support in this field, providing high-resolution details of the structure and dynamics of supramolecular polymers that cannot be obtained with the experiments. Molecular simulations at different levels of resolution may help to understand how the structure of the monomers controls that of the assembly and to elucidate the characteristics of the polymerization process. Advanced simulation approaches can be used to characterize the dynamic exchange of monomers in the supramolecular polymer. More importantly, gaining access to the dynamics of the assembly at high resolution is a great advantage, providing the opportunity of building structure–dynamic relationships in feasible way. Finally, all these approaches can be used in concert to characterize, to understand and master dynamic bioinspired properties of the supramolecular polymers, such as the ability to self-heal when damaged, to dynamically reconfigure their structure or respond in controlled way to specific stimuli.

These soft self-assembled materials are not simple systems, and a throughout exploration with different simulation methods is necessary to understand their behaviour. Great knowledge of the systems is also necessary. In this context, we would like to stress the importance of continuous exchange between simulation and the experiments. While not always straightforward, this is useful to guarantee the reliability of the models. Another important point to bear in mind is what it is reasonable to expect from a certain model of simulation. Coarse-grained models are useful, but always approximated to some extent. Atomistic models, while more precise, are limited. Advanced simulation approaches can be useful, but these are not trivial to handle in correct way when the system is very complex. Nonetheless, the structural and dynamic complexity of supramolecular polymers requires the use of multiple state-of-the-art approaches. The challenge of multiscale modelling in this field is still at the beginning, but the premise for exciting results is actual.

Disclosure statement

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