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Polymerisation mechanisms as the missing link in rational design of imprinted polymer networks

Carmelo Herdes

Molecularly imprinted polymers (MIPs) are synthetic polymer networks formed around template molecules to create selective molecular recognition sites. While decades of research have advanced our understanding of pre-polymerisation complexation and the properties of finished MIP materials, the polymerisation step itself remains a conceptual black box in imprinting design. This Perspective argues that polymerisation—the dynamic process by which monomers are covalently linked and cross-linked around a template—is the decisive yet under-explored stage governing the fidelity, selectivity, and function of imprinted polymer networks. We adopt a design-first, mechanism-centric viewpoint to examine how polymerisation encodes molecular recognition and catalytic function in MIPs, molecularly imprinted catalysts (MICs), and enantiopure molecularly imprinted catalysts (EMICs). We explain why conventional fixed-topology molecular simulations, such as classical molecular dynamics, are intrinsically unable to capture imprinting fidelity, and we highlight how reactive molecular dynamics approaches open new avenues for resolving cavity formation, network growth, and the emergence of functional sites. Polymerisation is reframed as a dynamic encoding process in which the trajectory of network formation—the sequence of radical initiation, propagation, and cross-linking events—critically determines the architecture and performance of binding sites. We propose mechanistic descriptors of polymer growth, including growth-front propagation patterns, cross-linking motifs, and kinetic trapping phenomena, as new design variables for imprinting that move beyond static pre-assembly metrics. Insights from MIPs are generalised to MICs and EMICs, in which polymerisation locks in transition-state-stabilising functional-group arrangements, and implications for other porous polymer and molecular-recognition materials are briefly discussed. By elucidating polymerisation mechanisms, this Perspective establishes a broadly applicable, predictive, mechanism-driven framework for the rational design of imprinted polymer networks and calls for polymerisation to be treated not as an uncontrollable curing step but as a tunable, information-rich process central to the next generation of molecularly imprinted materials.

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This Perspective reframes molecularly imprinted polymer (MIP) design by identifying polymerisation mechanisms as a central, yet underexploited, design variable in imprinted polymer networks. Rather than treating polymerisation as a passive curing step, the article conceptualises polymer network formation as a dynamic encoding process through which molecular recognition and catalytic function are written into the material. The system considered spans molecularly imprinted polymers, molecularly imprinted catalysts (MICs), and enantiopure molecularly imprinted catalysts (EMICs), highlighting how radical initiation, propagation, and cross-linking pathways govern cavity fidelity and functional-group organisation. By critically examining the limitations of fixed-topology simulations and outlining the emerging role of reactive molecular dynamics, the Perspective establishes a mechanism-centric framework that connects polymerisation pathways to performance outcomes. The insights articulated here are broadly applicable to the rational design of selective receptors, polymer-based catalysts, and porous functional materials, and aim to guide future simulation–experiment workflows toward predictive, systems-level molecular engineering.

Introduction

Molecularly imprinted polymers (MIPs) are cross-linked polymer networks synthesised in the presence of a template molecule, which is later removed to leave behind binding cavities complementary to the template.[1] In essence, a MIP functions as a synthetic receptor or antibody mimic, selectively rebinding the target molecule with high affinity

Department of Chemical Engineering, The Foundry: Centre for Digital, Manufacturing & Design, Centre for Bioengineering & Biomedical Technologies (CBio), Centre for Integrated Materials, Processes & Structures (IMPS), University of Bath, Bath, BA2 7AY, UK. E-mail: cehm21@bath.ac.uk

due to the shape, size, and functional complementarity of the imprinted cavity. Since their inception in the 1970s,[2,3] MIPs have found diverse applications in chemical sensing, separations, drug delivery, and environmental remediation.[4–7] They have also been extended into catalysis—so-called molecularly imprinted catalysts (MICs)—where the polymer matrix is designed to stabilise transition states and catalyse reactions, effectively mimicking enzyme active sites.[8] Enantioselective variants, often termed enantiopure molecularly imprinted catalysts (EMICs), aim to imprint chiral transition states or substrates such that the resulting polymer preferentially binds to, or transforms, one enantiomer over the other.[9] These advanced applications underscore the promise of imprinted polymers as tailor-made smart materials for molecular recognition and catalysis.

Despite this promise, the rational design of MIPs and related systems remains challenging. A considerable body of work has focused on the pre-polymerisation complexation stage, that is, the interactions between the template, functional monomer(s), cross-linker, and solvent prior to polymerisation.[10] It is well established that selecting monomers with complementary functional groups and optimising template–monomer binding in the pre-polymerisation mixture can improve imprinting outcomes. Computational approaches have been pivotal in this context. Early studies by Chianella *et al.* demonstrated the *in silico* selection of optimal functional monomers for a target template,[11] and Karim *et al.* reviewed strategies for identifying effective monomers to maximise template–monomer affinity.[12] Classical molecular dynamics (MD) simulations and related modelling techniques have since been widely used to screen monomer candidates, predict binding energies, and analyse hydrogen-bonding networks in pre-polymerisation solutions.[13–16] These efforts, together with post-polymerisation characterisation studies that model analyte rebinding in static polymer matrices,[14,17] have refined MIP formulations and improved understanding of factors such as monomer–template stoichiometry, solvent effects, and binding-site heterogeneity.[10,18]

However, one fundamental question remains unresolved: how does the polymerisation process itself—the chemical chaining and cross-linking of monomers around the template—give rise to specific binding and catalytic cavities? In other words, beyond knowing that monomer A binds the template more strongly than monomer B in solution, do we understand how those monomers are incorporated into a growing polymer network to form a well-defined cavity? The honest answer is not yet. Polymerisation encompasses radical initiation, chain propagation, interchain cross-linking, and solvent-mediated aggregation or phase-separation phenomena. This complex and dynamic sequence ultimately encodes the template's molecular fingerprint into the polymer network's architecture. During polymerisation, the polymer effectively "remembers" the template: the spatial arrangement of functional groups and the geometry of the cavity are fixed irreversibly once the network is fully cross-linked. Critically, in MICs and EMICs, polymerisation not only fixes binding-site geometry but also locks in the relative positioning of catalytic or stereochemical functional groups that later stabilise transition states or enforce chiral selectivity. Polymerisation is therefore the decisive stage for function, effectively encoding molecular-recognition information into the material. If this writing process is poorly controlled, the resulting memory—the binding site—will be imprecise or incorrect.

Yet this decisive stage remains mechanistically unresolved, largely due to technological and methodological limitations. Experimentally, it is nearly impossible to observe polymerisation at molecular resolution in real time. Polymerisation is rapid and involves transient reactive intermediates, such as free radicals and partially formed network structures, that are difficult to characterise directly. Indirect evidence, for example, from variations in cross-linker content[6] or polymerisation temperature,[19] indicates that polymerisation conditions influence binding performance, but does not reveal how this influence arises at the molecular level. On the computational side, conventional simulation tools have historically been unable to address polymerisation. Classical MD assumes a fixed bonding topology: atoms can move and interact, but covalent bonds neither form nor break. As a result, classical MD can illuminate the structure of pre-polymerisation mixtures or equilibrate post-polymerisation models, but it cannot simulate polymer chain growth and cross-linking. Other modelling approaches have similarly avoided the polymerisation process itself. For example, algorithms that generate cross-linked polymer structures by linking monomers in pre-assembled mixtures according to distance criteria or probabilistic rules can produce realistic final networks but bypass the underlying polymerisation mechanism. One such approach is the LNKD algorithm introduced by Stevens *et al.*, which efficiently links pre-packed assemblies of monomers and cross-linkers into polymer networks.[20] While valuable for structure generation, such methods do not capture the sequence of events by which linkages form and therefore cannot reveal how network evolution influences selectivity. As noted by Nicholls *et al.* in a recent review, advanced simulations have made substantial contributions to MIP design but typically assume a pre-formed polymer matrix, leaving the imprinting mechanism itself largely unaddressed.[10] Consequently, imprinted polymer design has focused on starting conditions and final performance rather than on the dynamic process connecting the two, thereby forcing even state-of-the-art approaches to rely on empiricism and trial-and-error optimisation rather than on predictive mechanistic insight.

In this Perspective, we argue that polymerisation mechanisms constitute the missing link in the rational design of imprinted polymer networks. We show that a mechanism-centric approach, in which polymer network formation is treated as a dynamic process to be understood and tuned, provides a new foundation for the design of MIPs, MICs, and EMICs. We first examine why traditional fixed-

topology modelling approaches fall short and how emerging reactive molecular dynamics techniques can begin to open this black box. We then discuss how polymerisation can be viewed as a dynamic encoding process, in which the pathway of polymer growth determines the fidelity of imprinting. Building on this framework, we propose specific mechanistic descriptors, including growth-front patterns, cross-link connectivity motifs, and kinetic trapping events, as design variables that can be used to steer polymerisation toward high-fidelity binding sites. Finally, we extend the discussion to MICs and EMICs, highlighting how polymerisation mechanisms influence catalytic function and stereoselectivity, and outlining broader implications for related fields, including porous polymers and molecular recognition materials. Throughout, our goal is to articulate a directive viewpoint: that the field must move beyond static design by pre-assembly and embrace design by polymerisation mechanism in order to rationally engineer polymer networks at the molecular level.

Polymerisation: the decisive stage of imprinting

In the standard paradigm of molecular imprinting, considerable attention is paid to arranging the template and functional monomers in an optimal configuration prior to polymerisation. The underlying assumption is that if monomers initially surround the template in a favourable orientation, for example by maximising hydrogen bonding or electrostatic complementarity, a high-fidelity binding site will result once the polymer is formed. This assumption implicitly treats polymerisation as a gentle freezing of a pre-formed complex, as if the polymer matrix were a static mould that hardens around the template. In reality, polymerisation is a chemically and kinetically complex process, and the pathway by which the polymer forms can profoundly influence the final site geometry and chemistry. Even if an optimal template–monomer complex is present at the outset, the subsequent reactions of initiation, chain propagation, and cross-linking may or may not preserve that arrangement.

During a typical free-radical polymerisation used to synthesise MIPs, an initiator decomposes to generate radicals that add to monomers, creating growing polymer chains. These chains may or may not initiate at the template: some originate near template-bound monomers, while others begin in the bulk solution. As polymerisation proceeds, monomers, both free in solution and bound to the template, are consumed, and polymer chains begin to cross-link when a multifunctional cross-linker connects two chains. Although the template may initially stabilise certain monomers at specific positions within the pre-polymerisation complex, their incorporation into a growing chain can alter the local environment. Heat released during polymerisation, or the presence of a solvent (porogen), may induce rearrangements: a propagating chain might displace a monomer previously hydrogen-bonded to the template, or new monomers may be recruited as the network branches. As a result, the developing polymer network can either mould itself around the template in a complementary manner or distort and partially occlude the emerging binding site. The difference lies in the details of the polymerisation mechanism.

Empirical evidence supports the conclusion that polymerisation conditions critically affect imprinting quality. Polymerisation temperature and solvent choice, for example, are known to influence the binding affinity and capacity of MIPs even when the same monomer–template formulation is used.[7,16] Elevated polymerisation temperatures can accelerate kinetics but may disrupt template–monomer complexes and promote premature phase separation, leading to less well-defined cavities.[7] The porogen determines the medium in which polymer chains grow: an appropriate porogen can moderate polymerisation rates and induce phase separation at the right stage to generate a porous network with accessible sites, whereas an unsuitable one may lead to dense regions or collapsed cavities. Bird and Herdes demonstrated how different porogens alter monomer–template association in the pre-polymerisation solution of a TNT-imprinted polymer,[16] with direct consequences for sensing performance.[17] These observations indicate that the manner in which the polymer forms is at least as important as the initial configuration. In MIC systems, sensitivity to polymerisation conditions can be even more pronounced. Imprinting a transition-state analogue often requires tightly controlled polymer growth to avoid disrupting the delicate arrangement of catalytic functional groups. Indeed, Wulff's pioneering work on enzyme-mimetic catalysts emphasised that enzyme-like catalysis by MIPs relies on polymerisation locking functional groups into precise orientations relative to a transition-state analogue.[21] If the polymer network does not form in a manner that correctly fixes these groups, catalytic activity can drop dramatically.

Despite its importance, a clear molecular-level picture of imprinting polymerisation has long been lacking. Fundamental questions remain unanswered: which monomer adds first near the template; whether the template remains bound to a growing chain or diffuses in and out; when cross-links form around the template; and whether they lock in cavity geometry early or late in the process. Another unresolved issue is site heterogeneity: do most binding sites arise from similar polymerisation pathways, or do multiple routes produce a spectrum of site qualities? These questions indicate that imprinting is not solely a thermodynamic outcome of template–monomer complexation but rather a kinetic process with multiple competing pathways.

Polymerisation should therefore be viewed as a designable dynamic process. Rather than treating it as a black box in which a pre-arranged set of components simply hardens into place, polymerisation conditions and mechanisms should be regarded as integral design parameters. Relevant factors include the initiation rate, which controls how rapidly radicals are generated; the relative reactivity of functional

monomers and cross-linkers, which determines whether chains forming around the template are enriched in functional units or diluted by cross-linker; solvent polarity and viscosity, which influence diffusion of radicals and monomers; and temporal aspects such as continuous *versus* pulsed initiation. Each of these factors can bias the polymerisation pathway. For example, slower initiation may allow more time for template–monomer complexes to recruit monomers before the local network freezes, yielding more homogeneous, high-fidelity sites. In contrast, very rapid polymerisation may trap templates in suboptimal configurations or embed them within dense polymer regions, leaving only shallow or surface-accessible imprinting.

These considerations become even more important in multi-component imprinting formulations containing more than one functional monomer.[10,12,40–42] In such systems, imprinting fidelity depends not only on whether each monomer can interact favourably with the template in the pre-polymerisation mixture, but also on whether those monomers are incorporated competitively or cooperatively during network growth. Two functional monomers may both exhibit favourable template association in isolation, yet during polymerisation one may dominate local incorporation because it reacts more rapidly, diffuses more effectively, or is preferentially encountered by a growing radical front. Conversely, cooperative incorporation of chemically complementary monomers near the same template region may generate binding sites of greater affinity or selectivity than any single-monomer formulation can achieve. Reactive molecular dynamics is particularly attractive in this context because it offers a route to resolve not only which monomers are present near the template, but when and in what sequence they become fixed into the developing network.

Relative monomer reactivity is therefore a central mechanistic variable rather than a secondary kinetic detail.[22,28,43–45] In formulations containing functional monomers, cross-linkers, or multiple functional monomers with distinct radical-addition kinetics, differences in reactivity ratio can bias the spatial distribution of reactive species around the template and alter the conversion stage at which specific functionalities become immobilised. A highly reactive cross-linker, for example, may promote early local rigidification that preserves a favourable arrangement, but it may also freeze a suboptimal structure before cooperative functional-group organisation is achieved. Likewise, a slower-reacting functional monomer may contribute strongly to pre-assembly yet become underrepresented in the final cavity if it is incorporated only after the local environment has already become sterically restricted. Mechanistically informed design must therefore consider not only template affinity, but the coupled sequence of association, reaction, and local network densification that determines how composition is translated into site architecture.

This discussion underscores a central thesis: the fidelity and functionality of imprinted sites are governed not only by thermodynamics, which determines which complexes form, but by kinetics, which determines which polymerisation pathway is followed. Polymerisation is the decisive stage at which selectivity is encoded into the material. By bringing polymerisation mechanisms into focus, we set the stage for mechanistic insights that can inform improved design, as discussed next through the lens of modern simulation tools.

Limitations of fixed-topology simulations

The limitations of traditional modelling approaches have compounded the difficulty of understanding imprinting mechanisms. Classical molecular dynamics (MD), one of the most widely used computational tools in this field, inherently assumes a fixed bonding topology throughout a simulation. While MD accurately captures the motion of atoms and molecules under a given force field, it cannot describe the formation or breaking of covalent bonds, as such events would alter the system topology. For many applications, this limitation is acceptable, but for simulating polymerisation, it is prohibitive.

In the context of MIPs, classical MD has nevertheless proven valuable for two specific purposes: simulating pre-polymerisation mixtures of templates and monomers, and simulating interactions within fully formed polymers. Many rational design studies have used MD or Monte Carlo simulations of a template combined with various functional monomers, often in the presence of a porogen solvent, to identify favourable monomer identities and stoichiometries. The success of this approach is well documented. For example, Chianella *et al.* computationally predicted a functional monomer that led to an effective MIP for the toxin microcystin-LR,[11] and other studies have employed binding free energy calculations or radial distribution functions to screen monomers for targets ranging from pharmaceuticals to peptides.[10] Classical MD has also been used to analyse binding in completed MIPs. Experimentally synthesised or computationally generated polymer structures can be probed by simulating rebinding of the template or its analogues to assess cavity fit and solvent displacement. For instance, Herdes and Sarkisov developed atomistic models of imprinted polymer matrices and simulated the adsorption of volatile organic compounds, demonstrating how imprinted and non-imprinted polymers differ in adsorption capacity.[14] Such studies confirm the enhanced affinity of imprinted cavities and visualise interactions such as hydrogen bonding and π–π stacking within the binding site.

In all these cases, however, the polymer network is either absent or already fully formed. What is missing is the formation of the network itself. Classical MD-based design paradigms therefore examine snapshots before polymerisation, consisting of monomers and template in solution, or after polymerisation, consisting of a finished polymer, but never the transition between these states. This is analogous to attempting to understand how a jigsaw puzzle

is solved by examining only the unassembled pieces and the completed image, without observing the assembly process.

To address the inability to model bond formation, several workarounds have been developed. One common approach is to link monomers stochastically within a simulation snapshot. Given an equilibrated mixture of monomers and template obtained from MD, an algorithm can identify pairs of monomers to be connected by cross-links, typically using distance criteria combined with probabilistic rules, join them, relax the structure, and repeat the procedure iteratively. Stevens *et al.* applied the LNKD algorithm to model molecularly imprinted polymer nanoparticles, generating cross-linked networks by iteratively connecting monomers to mimic random bond formation.[20] While such methods produce plausible final structures and are computationally efficient, they do not reproduce the reaction kinetics or sequence of events involved in polymerisation. A monomer may be linked simply because it was spatially close in a snapshot, even though in reality it might polymerise much later or only after a chain has already formed. In addition, these approaches can impose unrealistic uniformity or introduce biases that obscure the inherent heterogeneity of polymer growth pathways.

Alternative strategies include statistical-mechanical and coarse-grained models that capture certain aspects of imprinting without explicitly simulating bond formation. For example, Curk *et al.* introduced a lattice model to study MIP design within a statistical-mechanical framework, capturing binding-site heterogeneity and suggesting optimal designs under specific conditions.[13] However, the polymer was treated implicitly rather than through explicit chemical reactions. Similarly, kinetic models have been developed to estimate how polymerisation rates or monomer reactivity ratios influence imprinting efficiency.[22] These approaches provide useful macroscopic insight but remain at the level of rate equations and phenomenological reasoning, without access to molecular-scale mechanisms.

In summary, fixed-topology simulations and static modelling techniques have been indispensable for identifying suitable monomers and analysing binding in finished materials, but they are intrinsically incapable of describing bond formation and network evolution. As a result, key mechanistic questions remain unresolved. For example, does stronger monomer–template binding necessarily correlate with improved imprinting, or could a monomer with slightly weaker binding produce a superior cavity because it polymerises more favourably? This limitation has been explicitly recognised for more than a decade. Cowen *et al.* noted in 2016 that computational design of synthetic receptors, including MIPs, typically neglects the polymerisation step in favour of static interactions.[18] A decade later, the gap persists: Nicholls *et al.* concluded that although molecular dynamics simulations are now central to MIP development, no study yet directly describes how radical polymerisation encodes specificity at the molecular level.[10] In effect, the field has been designing with one hand tied behind its back, unable to simulate or rationalise the most critical step.

To enable truly rational design, simulation approaches must allow the bonding topology to evolve, enabling bonds to form and break during polymerisation. This requirement motivates the use of reactive molecular dynamics, which is discussed next.

Reactive MD: opening the black box of network formation

Advances in computational chemistry have enabled the relaxation of the fixed-topology constraint through reactive molecular dynamics (rMD), in which the force field is formulated to allow chemical reactions, including bond formation and bond breaking, to occur during the simulation.[23] One of the most established frameworks for rMD is the ReaxFF reactive force field, developed by van Duin and co-workers.[24] ReaxFF abandons the fixed bonding rules of classical force fields in favour of a bond-order formalism that continuously updates bonding as a function of atomic distance and chemical environment. In practice, if two atoms approach closely and bond formation is energetically favourable according to calibrated parameters, a bond can form; conversely, bonds can break when they become unfavourable. Over the past two decades, ReaxFF has been parametrised for a wide range of chemical systems, enabling simulations of combustion reactions, surface chemistry, battery electrolytes, and, importantly, polymer chemistry.[25]

Applying ReaxFF or related reactive MD methods to radical polymerisation in MIPs represents an obvious yet largely underexploited opportunity. With a suitably parametrised force field for the relevant monomers and cross-linkers, such as methacrylic acid (MAA) and ethylene glycol dimethacrylate (EGDMA), it becomes possible to simulate key stages of imprinting polymerisation *in silico*. A typical simulation would begin from a pre-polymerisation mixture containing the template, functional monomer, cross-linker, initiator (or an initiator-derived radical), and solvent molecules within a simulation box. Polymerisation can then be triggered, for example, by introducing a radical or applying a thermal perturbation to mimic initiator decomposition. The system subsequently evolves under the reactive force field: monomer radicals propagate, cross-linkers form bridges between chains, and the polymer network grows dynamically in the presence of the template, which continues to influence local reactions.

Such simulations offer access to mechanistic information that is experimentally inaccessible. One can track the temporal sequence of monomer interactions with the template, for example, determining whether a given monomer initially binds to the template but is displaced before polymerisation, or whether it polymerises early and remains fixed in place. Chain-propagation patterns can be observed directly, revealing whether a single polymer chain wraps around the template or whether multiple shorter chains anchor at distinct locations before

becoming cross-linked. The formation and stabilisation of cavities can also be monitored: a contiguous cavity may emerge early, with polymer walls forming around an embedded template, or may only become well-defined at later stages, after polymer relaxation. Importantly, rMD can also capture unfavourable events, such as cross-links forming at the mouth of a cavity that block access, or kinetic trapping of the template when polymer chains encircle it too tightly to allow diffusion. Processes that were previously inferred only indirectly or relegated to speculation thus become observable and analysable.

These new capabilities come with significant computational challenges. Reactive MD simulations of polymerisation are demanding, as the timescales associated with network formation, typically nanoseconds to microseconds for modest system sizes, exceed those commonly accessible to fully atomistic MD, and numerous reactive events must be sampled. In addition, ReaxFF is an approximate method whose reliability depends critically on the quality of its parametrisation for the chemistry of interest. Meaningful application, therefore, requires careful calibration. A practical workflow often combines multiple levels of theory: classical MD to equilibrate the pre-polymerisation mixture and to sample template–monomer complexation; reactive MD to simulate polymerisation; and quantum-chemical calculations, such as density functional theory, to validate key reaction steps. For example, quantum calculations can be used to verify that radical-addition barriers, termination reactions, or dominant cross-linking motifs predicted by the force field are chemically plausible and that spurious reaction pathways are not artificially favoured. This combination of classical MD, rMD, and quantum refinement is essential for establishing confidence in mechanistic conclusions.

Despite these challenges, reactive MD has already demonstrated considerable promise in related polymer systems. Vashisth *et al.* employed accelerated ReaxFF simulations to model thermoset polymer cross-linking, achieving degrees of polymerisation comparable to experiment and gaining insight into cross-link distributions.[26] In another example, reactive MD was used to simulate the formation of hyper-crosslinked polystyrene networks, revealing how reaction conditions influence cross-link density and network topology.[27] Although these studies did not directly address molecular imprinting, they provide strong evidence that ReaxFF can capture complex radical polymerisation networks and generate physically meaningful structural information.

The distinctive aspect of applying reactive MD to MIPs is the presence of a specific templating agent and the need to resolve polymer structure locally around that template. This enables a powerful comparative strategy: simulations can be performed both with and without the template, corresponding to imprinted and non-imprinted polymers. Differences in network formation and local structure that arise solely from the presence of the template then constitute the mechanistic basis of imprinting. Early steps in this direction were taken by Dourado *et al.*, who compared atomistic models of imprinted and non-imprinted polymers and analysed differences in binding behaviour.[15] Reactive MD extends this comparison to the formation process itself, rather than restricting analysis to final structures.

At present, reactive MD remains the only practical approach for simulating imprinting polymerisation at full atomistic resolution. *Ab initio* molecular dynamics is computationally prohibitive for the system sizes and timescales required to capture network formation, while coarse-grained reactive models would sacrifice chemical detail critical for selectivity, such as specific hydrogen-bonding patterns and functional-group orientation within binding sites. ReaxFF therefore occupies a unique position as an enabling tool. As comprehensively reviewed by Senftle *et al.*, its versatility and demonstrated success across diverse chemistries make it well suited to a new frontier: the mechanistic, simulation-driven design of imprinted polymers.[23]

A practical question is what system sizes and timescales are realistically accessible for such simulations in the context of imprinting. At present, atomistic reactive MD is most informative when targeted at local, template-centred polymerisation environments rather than the full macroscopic synthesis volume. In practice, this means simulating a chemically representative domain large enough to include the template, its first few shells of monomers, cross-linkers, and solvent, together with sufficient surrounding reactive material to permit meaningful growth-front development and local cross-link formation. Depending on composition and model resolution, such simulations will typically span roughly 10^4 to 10^6 atoms, with the most chemically detailed studies generally concentrated toward the lower end of this range. The most accessible timescales are typically in the nanosecond regime, with longer trajectories only possible under favourable conditions or with accelerated strategies.[23,26,27,46]

These scales are nevertheless sufficient to interrogate many of the mechanistic questions most relevant to imprinting. The goal is not to reproduce the entire bulk polymerisation process atom-by-atom, but to resolve representative early and intermediate polymerisation trajectories around the template: where initiation occurs, whether propagation remains template-directed, when local cross-links appear, and whether functional cavities begin to emerge or become kinetically compromised. In this sense, reactive MD should be viewed as a local mechanistic probe of cavity formation, whose outputs can later be connected to larger-scale models or experiments, rather than as a brute-force simulation of the full synthesis flask.

In the following section, we examine how mechanistic information from reactive MD can be distilled into actionable design principles. By treating polymerisation as a trajectory through reaction space, we show how understanding this trajectory enables imprinting outcomes to be quantified, compared, and ultimately predicted.

Polymerisation trajectories as dynamic encoding of function

One of the most compelling insights to emerge from a mechanism-centric view is that not all polymerisation trajectories are equivalent. We hypothesise that high-fidelity binding cavities arise predominantly from a limited subset of polymerisation pathways, namely those in which polymer growth around the template proceeds favourably. If this is the case, an important implication follows: formulating a pre-polymerisation mixture with the "right" components is necessary but not sufficient. Polymerisation must also be steered along favourable pathways, or at least biased toward them, to achieve a high-quality imprint. In this sense, polymerisation can be viewed as a mapping from initial conditions to final structure, in which multiple reaction sequences can yield markedly different binding-site architectures, even when starting from the same ingredients.

What might favourable and unfavourable polymerisation trajectories look like? Based on physical intuition and emerging mechanistic studies, several representative scenarios can be outlined.

Trajectory A: template-centred growth

In a favourable scenario, polymerisation initiates near the template, for example, when an initiator-derived radical attacks a monomer bound to the template. A growing polymer chain is then anchored to the template surface from the outset. As propagation continues, this chain effectively coats the template, looping around it and forming a scaffold that mirrors its shape. Cross-linkers subsequently connect this template-bound chain with nearby chains, knitting a cage around the template. Upon template removal, a well-defined cavity remains because the polymer network was formed around the template during polymerisation.

Trajectory B: bulk-initiated growth

In a less favourable pathway, polymerisation predominantly initiates in the bulk solution, away from the template. Polymer chains grow independently and may only encounter the template after they have partially polymerised or become locally rigid. Although the template may still be embedded in the forming network, particularly if it has some affinity for the polymer, the process is more stochastic. The template may occupy a void that is not specifically shaped for it, or become trapped at the interface between growing polymer clusters, leading to cavities that are incomplete or only partially complementary.

Trajectory C: premature cross-linking trap

Another unfavourable trajectory arises when cross-linking events occur too early around the template, freezing a suboptimal arrangement. For example, polymer chains on opposite sides of the template may become cross-linked before they have grown sufficiently to contour the template surface. This can prevent further monomer access, producing cavities with inaccessible regions or multiple disconnected voids rather than a single contiguous site. In extreme cases, the template may become covalently trapped within the polymer matrix, yielding a material with no accessible binding sites and complicating template removal. Such kinetic trapping is a recognised risk when polymerisation conditions are poorly controlled, for instance, at excessively high initiator concentrations that promote local gelation around templates.[28]

Trajectory D: porogen-mediated phase separation

Many MIPs are synthesised in porogenic solvents that induce phase separation during polymerisation, generating porosity. The timing and nature of this phase separation constitute an additional dimension of the polymerisation trajectory. In favourable cases, the template and its surrounding monomers are incorporated into polymer-rich microdomains, thereby directing network growth around the template. In an unfavourable scenario, early or overly vigorous phase separation can expel the template into solvent-rich regions, resulting in porous polymers whose cavities are poorly shaped or unrelated to the template.

These representative trajectories are summarised schematically in Fig. 1–4, which illustrate how differences in initiation location, propagation history, cross-link timing, and phase-separation behaviour can produce markedly different cavity architectures even when the starting formulation is nominally unchanged. From these scenarios, a set of mechanistic descriptors can be defined. These descriptors are intended to be illustrative rather than exhaustive and serve as quantifiable signatures of polymerisation trajectories that can be used to analyse and predict imprint quality.

Initiation proximity

Does polymerisation initiate on a template-bound monomer or in the bulk? A useful descriptor is the fraction of radical-initiation events occurring within the template's first solvation shell. Higher values indicate template-centred growth and are expected to correlate with improved imprinting fidelity.

Propagation bias

Once initiated, does radical propagation preferentially occur along monomers in contact with the template, or does it rapidly diverge into bulk solution? This can be quantified as the ratio of polymer segments formed in contact with the template to those formed away from it during early polymerisation. A strong bias toward template-contact propagation suggests continuous template-directed growth.

Cross-linking motifs

The spatial pattern of cross-link formation relative to the template is critical. Descriptors may include the number of

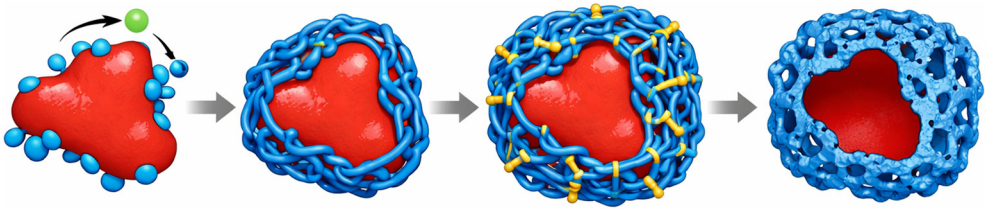

Fig. 1 Trajectory A – template-centred growth. Polymerisation initiates near the template, for example, through radical attack on a template-bound monomer, so the growing chain is anchored to the template surface from the outset. Continued propagation allows the chain to contour the template, while subsequent cross-linking stabilises the surrounding network. After template removal, this pathway yields a well-defined, accessible cavity because the polymer matrix forms directly around the template.

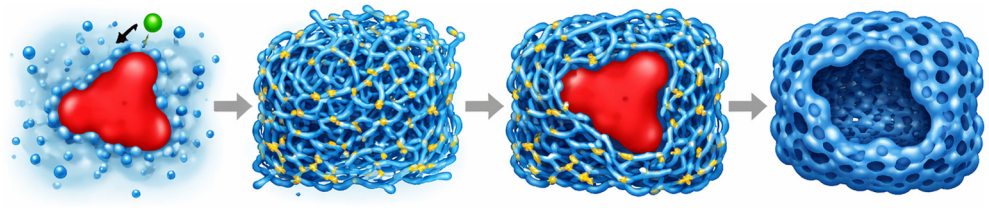

Fig. 2 Trajectory B – bulk-initiated growth. Polymerisation predominantly initiates in the bulk solution, away from the template, leading to the formation of chains that grow independently before encountering the template. As a result, the template becomes only incidentally embedded within the evolving network. This stochastic incorporation limits structural complementarity, often producing cavities that are poorly matched, incomplete, or located at interfaces between polymer domains rather than being specifically encoded.

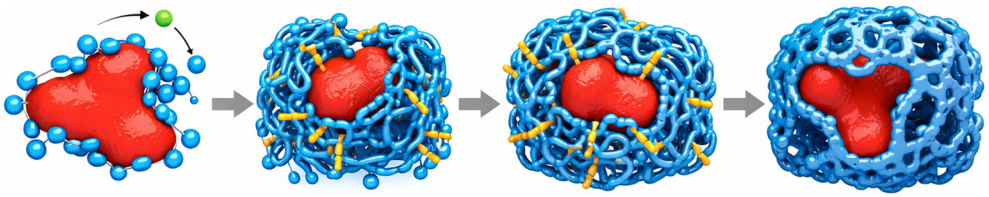

Fig. 3 Trajectory C – premature cross-linking trap. Polymerisation begins near the template, but cross-linking occurs too early, locking chains into a suboptimal configuration before they can fully contour the template surface. This premature network formation restricts monomer access and prevents further structural refinement. As a consequence, the resulting cavity may be partially blocked, distorted, or fragmented, and in extreme cases the template may become trapped within the matrix, hindering removal and eliminating accessible binding sites.

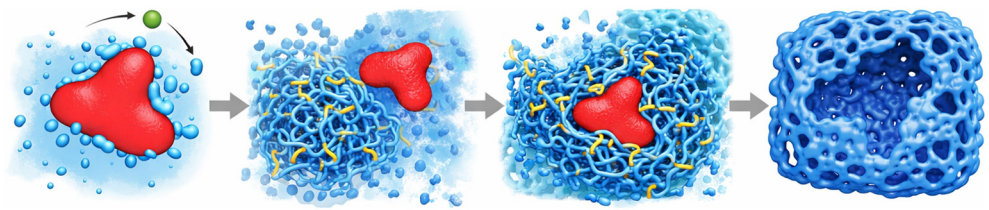

Fig. 4 Trajectory D – porogen-mediated phase separation. Polymerisation occurs in the presence of a porogenic solvent that induces phase separation into polymer-rich and solvent-rich domains. The evolving partitioning of the template between these domains governs how effectively the surrounding network can develop around it. If the template is incorporated within polymer-rich regions, cavity formation is supported; however, if it is excluded or unevenly partitioned, the resulting structure exhibits heterogeneous porosity and weak or non-specific cavity encoding.

cross-links connecting polymer segments on opposite sides of the template, which can indicate a risk of cavity capping, or the density of cross-links formed within a defined distance from the template surface. Such local cross-links can stabilise cavity geometry if formed at the appropriate stage, or degrade fidelity if formed prematurely.

Growth-front topology

This descriptor captures the morphology of the polymerisation front as it encases the template. Polymer growth may proceed as a smooth, continuous front or *via* multiple discrete clusters that later merge. Network or cluster

analysis can quantify the number of polymer nuclei forming around a template and the point at which they coalesce into a single network. Fewer, more coordinated growth fronts are likely to yield more regular cavities, whereas numerous small clusters may trap irregular voids.

Template residence time

The duration for which the template remains bound or in close proximity to growing polymer chains during polymerisation is another key descriptor. Templates that repeatedly dissociate and reassociate may undergo partial cavity formation in their absence, resulting in looser binding sites. This can be quantified as the fraction of polymerisation time (or conversion) during which the template remains within a specified distance of the polymer chains.

Encapsulation *versus* accessibility

At high conversion, the extent to which the template is buried within the polymer network can be assessed. Fully encapsulated templates with no accessible exit path correspond to non-functional sites, whereas templates residing in cavities connected to the bulk *via* pores correspond to functional binding sites. Descriptors may include cavity volume, mouth diameter, or the number of polymer atoms within a defined radius of the template.

For readers less familiar with simulation-based language, these descriptors may be understood as mechanistic observables that connect polymer growth history to site quality. Initiation proximity reports where the first reactive events occur relative to the template; propagation bias describes whether chain growth remains focused near the templating interface or escapes into bulk solution; cross-linking motifs describe how and where the evolving network becomes locally locked; and growth-front topology captures whether the cavity emerges through coordinated encasement or through irregular cluster coalescence. Together, these descriptors provide a vocabulary for discussing imprinting in dynamic rather than purely structural terms, and they offer a starting point for comparing different formulations, initiation modes, and curing protocols on a common mechanistic basis. Recent reviews on reactive force fields, computational MIP design, and related polymer-network modelling provide useful entry points for readers seeking methodological background.[10,18,23,29,47]

These descriptors are not merely post-mortem analysis tools; they can serve directly as design variables. If simulations or experiments reveal that initiation proximity strongly correlates with imprinting success, initiators could be designed to preferentially localise near the template, for example, through non-covalent association with the template or monomer complexes. If particular cross-linking motifs are detrimental, cross-linker length, flexibility, or concentration could be adjusted to delay or redirect cross-link formation. Similarly, if insufficient template residence time limits fidelity, stronger template–monomer interactions or reversible covalent strategies could be employed to retain the template during network formation. In this way, mechanistic insight can be translated into concrete synthetic strategies.

More broadly, identifying descriptors that correlate with successful imprinting enables prediction rather than trial and error. Candidate monomer–template systems can be screened *in silico* by simulating polymerisation, extracting descriptors such as propagation bias or cross-link motif frequency, and assessing the likelihood of producing high-fidelity sites. If unfavourable signatures dominate, polymerisation conditions can be modified computationally before any experimental effort is invested. This represents a shift from empirical optimisation to outcome-driven design.

To illustrate this concept, consider the design of an MIP for a small-molecule pharmaceutical. A conventional strategy might screen functional monomers solely on the basis of binding energy. A mechanistic approach would additionally simulate polymerisation for each monomer choice and analyse trajectory descriptors. Two monomers may exhibit similar binding energies in the pre-polymerisation mixture, yet reactive MD simulations might reveal that one yields coordinated growth around the template with minimal premature cross-linking, while the other promotes cluster formation that traps the template. The prediction is that the former produces a more selective MIP, a hypothesis that can then be tested experimentally. Such examples illustrate the potential of trajectory-based design.

In summary, polymerisation trajectories provide a powerful new lens through which imprinting fidelity can be understood as an emergent property of network-formation pathways. By resolving and quantifying these pathways through simulation, polymerisation can be transformed from a hidden, qualitative process into a set of measurable parameters that can be deliberately monitored, compared, and optimised.

From MIPs to MICs and EMICs: mechanistic design across imprinted systems

The discussion so far has focused primarily on MIPs designed for molecular recognition, in which the objective is the selective binding of a target analyte. We now extend this framework to molecularly imprinted catalysts (MICs) and enantiopure MICs (EMICs), a subset of imprinted systems in which the goal is not merely to bind a target but to stabilise a transition state or orient functional groups to catalyse a chemical reaction. Mechanistically, MICs introduce an additional layer of complexity: in addition to forming a cavity complementary to a target or transition-state analogue, polymerisation must position catalytic functionalities correctly within that cavity to promote reactivity, analogous to the precise placement of residues in an enzyme active site.

From the perspective of polymerisation mechanisms, this requirement implies that multiple components must be

coordinated with high precision during network formation. Consider, for example, an MIC designed to catalyse ester hydrolysis by imprinting a transition-state analogue, such as a phosphonate mimicking the tetrahedral intermediate, in the presence of functional monomers bearing imidazole and carboxylic acid groups to emulate histidine- and acid-catalysed chemistry. In the pre-polymerisation mixture, the transition-state analogue may form a complex with these functional monomers through hydrogen bonding or electrostatic interactions. However, whether these monomers ultimately occupy the correct spatial positions in the final polymer depends on the polymerisation pathway. If polymerisation proceeds such that both the imidazole- and acid-bearing monomers are incorporated and cross-linked in place around the template, the resulting cavity, once the analogue is removed, will present a cooperative catalytic arrangement. If, by contrast, one functional monomer reacts too slowly or diffuses away during polymerisation, it may be replaced by a non-functional unit, yielding a cavity that binds a substrate but lacks catalytic activity. In this sense, polymerisation determines not only whether a cavity forms, but also whether it is catalytically competent.

Accordingly, the mechanistic descriptors introduced earlier can be extended to MICs and EMICs. In addition to monitoring propagation around the template, one must consider the co-propagation of different functional monomers. For instance, a relevant descriptor might quantify the fraction of polymer segments near the template that incorporate both imidazole- and acid-bearing monomers. Another descriptor concerns timing: if catalytic groups must be fixed early to define an active site, the conversion at which each functional monomer is incorporated near the template becomes critical. A mismatch in incorporation times, where one catalytic group is added only at late stages, may signal a suboptimal active-site geometry.

Chirality introduces further subtlety in EMICs. Even when a chiral transition-state analogue is used, achieving high enantioselectivity remains challenging, and many EMICs exhibit residual affinity for the undesired enantiomer. From a mechanistic standpoint, one can ask whether polymerisation amplifies small differences in how each enantiomer interacts with monomers and growing polymer chains. One enantiomer may form slightly more stable or longer-lived complexes, biasing polymer growth to conform more closely to its geometry, whereas the opposite enantiomer may fail to template polymerisation as effectively. Jalink *et al.* explored simulation approaches for EMIC design and emphasised the need for fine-grained, multi-point chiral recognition.[9] A mechanistic interpretation suggests that enantioselectivity may arise from the cumulative effect of many small biases during polymerisation. For example, a modest preference at each propagation step could, over the course of network formation, yield a cavity strongly biased toward one enantiomer. Reactive MD offers a potential route to capturing such effects, provided that steric and non-bonded interactions responsible for chirality are adequately represented.

From a design perspective, mechanistic insight into MICs and EMICs provides guidance on selecting catalytic monomers and polymerisation conditions that preserve delicate template–monomer assemblies. In some cases, slower or staged polymerisation, for example through photopolymerisation or stepwise imprinting strategies, may be advantageous, as it allows functional monomers more time to align with the template before being fixed in place. If simulations indicate that a functional monomer tends to drift away or incorporate only at late stages, polymerisable analogues of the template or grafting strategies may be employed to retain key components until polymerisation is nearly complete, an approach commonly used in surface and epitope imprinting. Mechanistically, these strategies serve to maintain template control over the polymerisation trajectory.

Although the design objectives differ between MIPs, MICs, and EMICs, the underlying process of polymer network formation is the same. In all cases, a polymer matrix is sculpted around a template; what differs is the functional requirement of the resulting cavity. Consequently, the mechanistic descriptors introduced earlier, such as initiation proximity, propagation bias, and cross-linking motifs, apply across all imprinted systems, but with increasingly stringent targets for catalytic and enantioselective applications. A binding site may tolerate modest geometric imprecision and still exhibit affinity, whereas a catalytic site often requires precise positioning to lower a reaction barrier. Mechanism-driven design is, therefore, arguably even more critical for MICs and EMICs than for binding-only MIPs.

Linking polymerisation mechanisms to catalytic performance also offers an opportunity for experimental validation. If two polymerisation protocols yield materials with similar binding affinities but markedly different catalytic turnover rates or enantioselectivities, these differences can be traced back to mechanistic descriptors extracted from simulation. For example, one protocol may generate a more rigid, well-defined active site, characterised by specific cross-linking motifs, that behaves more like a pre-organised enzyme active site. Such insights are particularly valuable in a field where the development of new polymer catalysts still relies heavily on empirical optimisation.

Finally, the implications of mechanism-driven polymer design extend beyond imprinting. In porous polymer synthesis, templating and polymerisation-induced phase separation are routinely used to generate pore architectures, and the mechanism of network formation dictates pore size and connectivity. A mechanistic understanding of polymerisation dynamics could therefore inform the design of hierarchical porous materials and polymer monoliths with tailored structures.[29] More broadly, many molecular recognition systems, including aptamer-inspired polymers, synthetic nano-pockets, and dynamic combinatorial libraries, rely on structure emerging from a synthesis or assembly

pathway.[30] The lessons learned from imprinting polymerisation regarding pathway dependence and kinetic control may be transferable to these systems.

The same mechanistic logic applies, albeit with additional challenges, when the template is not a small molecule but a larger, more heterogeneous biological target, such as a protein, a peptide domain, or a nucleic acid.[32–39] In these systems, the complexity of polymerisation control increases substantially because the template is often flexible, diffusion is slower, and the chemically relevant recognition elements may be confined to only a subset of surface-exposed epitopes. A full atomistic reactive simulation of an entire biomacromolecular imprinting experiment is therefore unlikely to be tractable or even conceptually optimal in most cases. Instead, the most realistic use of reactive MD may be to focus on local polymerisation events near accessible epitopes or interfacial regions, where the relevant questions concern whether functional monomers are incorporated in a manner that preserves epitope geometry and accessibility. This localised viewpoint is well aligned with contemporary trends such as epitope and surface imprinting, in which only a restricted portion of the biological target is intended to direct recognition-site formation.

Related considerations apply to ordered framework materials. In covalent organic frameworks and metal–organic frameworks, templating agents or modulators are often used to direct assembly and defect formation.[31] Although these materials crystallise rather than form random networks, the principle that assembly pathways influence final structure remains valid. Similarly, in molecularly imprinted nanoparticles and surface-imprinted materials, polymerisation occurs under geometric confinement.[32,33] Understanding nucleation, growth, and cross-linking mechanisms in these contexts could enable better control over particle size, site accessibility, and surface fidelity.[34]

In summary, polymerisation mechanisms lie at the heart of MIPs, MICs, and EMICs, as well as a broader class of functional polymer materials. By demystifying these mechanisms and treating polymerisation as a dynamic encoding of molecular information, we provide a framework that encourages researchers to consider time, sequence, and growth pathways alongside composition. The following section concludes with an outlook on how this approach can be implemented and its potential impact on the future of molecular imprinting and related fields.

Outlook and conclusion

The rational design of molecularly imprinted polymer networks stands on the cusp of a paradigm shift. Traditionally, attention has focused on what goes into a polymer, namely, which monomers, cross-linkers, and templates are used, and on what comes out, in terms of binding affinity and selectivity. The mechanistic story in between has largely been overlooked. This Perspective has argued that polymerisation mechanisms represent the missing chapter that, once articulated, can bridge this gap and enable genuinely predictive design. By understanding and controlling how polymer networks form, imprinting can move from a discipline guided by heuristic rules and trial-and-error optimisation to one grounded in mechanism-driven molecular systems design.

The implications of embracing this approach are far-reaching. In the short term, researchers designing new MIPs or MICs can incorporate reactive molecular dynamics into their workflows to screen not only monomer identity, but also polymerisation conditions. Such simulations can reveal whether stable cavities are likely to form and whether catalytic group arrangements emerge as intended, thereby reducing wasted experimental effort on formulations that appear promising in pre-polymerisation studies but fail during polymerisation. In the medium term, as mechanistic data accumulates across systems, a set of transferable design principles may emerge. Much as medicinal chemists rely on rules of thumb in drug design, polymer chemists could develop guidelines such as "for templates of type X, delayed gelation improves site fidelity" or "for chiral imprinting, ensure a minimum fraction of template-centred initiation events," all grounded in mechanistic insight.

At a broader level, this reframing aligns with the growing recognition that chemical synthesis and materials formation are information-rich processes that can be deliberately steered. Just as flow chemistry and automated synthesis platforms have brought increased control to molecular reactions, reactive MD and mechanistic imprinting design offer analogous control over polymer network formation at the molecular scale. We foresee a future in which the design of an imprinted polymer begins not only with the choice of monomers, but also with a polymerisation protocol tailored to the desired function. This may involve controlling the sequence of monomer addition, employing multi-step curing strategies, or externally modulating conditions such as temperature or light during polymerisation to programme network growth. In this vision, polymer chemists act as network architects who design the evolution of a structure, rather than simply mixing components and hoping for a favourable outcome.

Realising this vision will require continued advances on several fronts. Experimentally validating simulation-derived predictions is essential. If reactive MD identifies a specific polymerisation trajectory as favourable, experiments must be designed to test whether those conditions indeed yield superior binding or catalytic performance. Advances in time-resolved spectroscopy or imaging may even allow partial observation of polymerisation intermediates. On the modelling side, improving the accuracy and transferability of reactive force fields for polymerisation, potentially aided by machine-learning-assisted parametrisation, will broaden the range of chemistries that can be addressed. Hybrid multiscale approaches, in which coarse-grained models incorporate insights from atomistic rMD, will also be important for extending predictions to larger systems and

longer timescales than are currently accessible. Progress will depend on close, iterative coupling between simulation and experiment, with mechanistic descriptors proposed computationally and validated against measurable performance metrics.

A particularly important consequence of a mechanism-centric approach is its potential to address longstanding concerns about reproducibility and robustness in molecular imprinting. MIPs are sometimes criticised for batch-to-batch variability or unpredictable performance, issues that often stem from subtle, unrecognised differences in polymerisation conditions. By explicitly considering polymerisation mechanisms, such sources of variability become identifiable and controllable design variables. Choices such as initiator type, initiation mode (thermal *versus* photochemical), or polymerisation rate can then be treated as critical parameters rather than minor procedural details. This shift is essential if imprinted polymers are to be reliably translated into practical technologies such as sensors, assays, or catalytic systems.

In closing, polymer scientists have long relied on structure–property relationships as a guiding principle for materials design. This Perspective advocates the explicit inclusion of an intermediate link: structure–mechanism–property relationships. In imprinted polymer networks, the structure responsible for molecular recognition or catalysis is itself the product of the formation mechanism. By elucidating and mastering that mechanism, we gain a powerful lever to control structure and, in turn, function. What has long been treated as a missing link in imprinting design can thus be made explicit and actionable.

Molecular imprinting has often been described as an art informed by experience and intuition. Transforming it into a fully predictive science requires the mechanistic clarity outlined here. The necessary tools are now emerging: reactive molecular dynamics, complemented by quantum calculations and innovative experimental probes, provides access to the transient processes of polymerisation. It is now incumbent upon the community to exploit these tools. The reward will be a new level of control over molecularly engineered polymer systems, enabling smart polymers, catalytic materials, and recognition platforms designed with a precision that rivals, and in some cases surpasses, natural molecular assembly.

Finally, although this Perspective has emphasised computational insight, its ultimate goal is to influence experimental practice. By framing polymerisation as a central design element, we encourage researchers to report and interrogate not only what materials are synthesised, but how they form at a mechanistic level. Such a cultural shift, coupled with continued methodological development, will help establish a robust foundation for the rational design of imprinted polymer networks and related functional materials.

Author contributions

Carmelo Herdes: conceptualisation, investigation, writing – original draft, writing – review and editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

This article is a Perspective and does not report new experimental or computational data. All information discussed is based on previously published literature, which is cited in the reference list. No new data were generated or analysed as part of this work.

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