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Feature Review

Towards modeling spatiotemporal processes in metal–organic frameworks

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Metal–organic frameworks (MOFs) are hybrid materials constructed from metal clusters linked by organic linkers, which can be engineered for target functional applications in, for example, catalysis, sensing, and storage. The dynamic response of MOFs on external stimuli can be tuned by spatial heterogeneities such as defects and crystal size as well as by operating conditions such as temperature, pressure, moisture, and external fields. Modeling the spatiotemporal evolution of MOFs under operating conditions and at length and time scales comparable with experimental observations is extremely challenging. Herein, we give a status on modeling spatiotemporal processes in MOFs under working conditions and reflect on how modeling can be reconciled with *in situ* spectroscopy measurements.

Highlights

Metal–organic frameworks (MOFs) can respond in an anomalous way to external stimuli, giving rise to dynamic bond rearrangement and/or large-amplitude structural transformations without breakage of the crystal.

Their dynamic response to external triggers is tunable by modifying the crystal size, defect engineering, and altering operating conditions.

To design MOFs for targeted functional applications, a fundamental understanding of the dynamic response and its entanglement with the material's spatial properties is necessary.

Experimentally, advanced *operando* and *in situ* characterization methods are needed to follow intermediate MOF structures during activated processes.

Theoretically, methods are needed that allow modeling of the spatiotemporal response of MOFs under conditions comparable with experimental setups. These should follow the dynamics governed by a wide variety of time scales and enable the modeling of length scales from the subnanometer to the micrometer scale, comparable with experimental crystal sizes.

Defining the spatiotemporal response of metal-organic frameworks

MOFs emerged in the past few decades as an intriguing and versatile class of materials showing anomalous responses to certain triggers. A few examples of such atypical behavior are: negative linear compressibility [2], where on the exertion of pressure the material expands along one or more directions instead of contracting; negative thermal expansion [3–5], where the material contracts on heating rather than expanding; and negative gas adsorption [6], where the MOF releases gas from its pores when the gas pressure of the surroundings is increased. These peculiar response properties are inherently linked to the unique building block concept of MOFs (Figure 1A). Their structure, comprising metal clusters stitched together by organic linkers, yields a broad variety of stronger (covalent, coordinative) and weaker (dispersive, stacking, and hydrogen bonds) interactions. Such bonding pattern combined with the nanoporosity of MOFs gives rise to potential extraordinary flexibility under external stimuli, where the materials can transform between various phases often accompanied by substantial volume changes while maintaining their structural integrity (Figure 1B) [7–9]. In some cases, dynamic rearrangement of bonds occurs, which in the limit may also lead to amorphization (Figure 1C). Enormous efforts have been undertaken to understand and tune these dynamic responses. However, today most of our insights are based on thermodynamic considerations, whereas the exact dynamic and kinetic responses of MOFs on external stimuli to a large extent remain to be resolved [10]. This is caused by the fact that this dynamic response is dictated by the occurrence of metastable states that are separated by energetic barriers and that are hard to assess experimentally. In this review, we show that unraveling the dynamic response from a computational point of view poses an enormous challenge as MOFs typically exhibit a broad range of intrinsic time scales, varying from molecular vibrations occurring at the picosecond time scale to more collective motions or events associated with activated processes that are much slower and occur on a time scale of seconds or hours. Moreover, recently it became clear that the dynamic response of MOFs is largely impacted by the spatial heterogeneity and crystal size of the material (Figure 1D). Downsizing MOF crystals from the micro- to the mesoscale with primary crystallite sizes between 10 nm and 1 μm substantially suppresses their responsive behavior [11–16]. However, such spatially dependent dynamic behavior is to date a largely unexplored area.

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Previous considerations allow us to coin the terminology **spatiotemporal evolution of a MOF** (see Glossary), referring to the dynamics of the material and its entanglement with the material's spatial properties. Insight into the spatiotemporal evolution of MOFs opens new perspectives to engineer their responses, giving access to new application areas such as the selective recognition of molecules or a history-dependent response to external stimuli. However, to computationally map the spatiotemporal behavior of MOFs, one needs modeling techniques that are capable of capturing phenomena on longer length and time scales than are currently accessible. In contrast to experimental characterization techniques, where one pushes the limits of spatial and temporal resolutions to systematically smaller scales, modeling adopts a bottom-up approach, starting from atomistic information and trying to bridge to experimental scales. So far, theoretically attainable length scales in the field of nanostructured materials are limited to a few tens of nanometers and common molecular dynamics (MD) runs extend well into the nanosecond range, depending on the level of theory used to calculate the forces between the atoms (Table S1 in the supplemental information online). Enhanced sampling techniques succeed in simulating rare events, but it remains a formidable challenge to grasp the dynamics of realistic materials under operating conditions [17–20]. Today, models representing complex nanostructured materials are much smaller than experimental crystal sizes and do not properly account for spatial heterogeneities at various length and time scales [21,22]. Thus, when modeling MOFs, we are still confronted with a huge spatiotemporal gap between theoretically attainable length–time scales and experimental observations. However, recently some exciting new avenues are being explored, such as the development of **machine learning potentials (MLPs)**, systematically **coarse-graining** methods and coarse-grained models (CG), and advanced MD algorithms, which open a window of opportunity to model the spatiotemporal response of MOFs.

Given these intriguing recent evolutions in the MOF field, we focus in this review on the current status and opportunities of modeling the spatiotemporal behavior of MOFs under working conditions and critically evaluate whether it is possible to model phenomena in realistic MOF structures in a spatiotemporal window similar to that attainable experimentally. The terminology of realistic MOF structures is used to contrast the real structure MOFs having intrinsic spatial heterogeneities with idealized structures. In this review, we assess to what extent the gap between experimental and theoretical **space–time windows** still exists and make the link with *in situ* spectroscopy as an ***in situ* characterization** tool to connect insights from modeling with experiment.

The importance of operating conditions for the spatiotemporal response of metal–organic frameworks

When aiming to unravel the spatiotemporal evolution of MOFs, it is important to recognize that the function and state of the material critically depend on the external conditions to which the material is exposed [23,24]. Such external conditions relate to, for example, the temperature, the pressure, and the presence of moisture and external fields. In this sense, the final aim is to model the *operando* spatiotemporal response of MOFs. The term *operando* spectroscopy was launched around 2000 in the field of catalysis, to group spectroscopic tools that enable the characterization of a working catalyst with the simultaneous evaluation of its catalytic performance [25–30]. The field has flourished since then with the development of advanced *operando* spectroscopic methods that follow the dynamic evolution of heterogeneous catalytic solids *in situ* with systematically better spatial and temporal resolution [31,32]. The true challenge from an experimental characterization point of view would be to make a molecular movie under *operando* conditions, with high temporal and spatial resolution as nicely pointed out by Weckhuysen (Figure 2) [33]. However, this target remains challenging.

Operando spatiotemporal characterization of MOFs is quintessential to understand and design the dynamic response of these materials. Currently, experimental endeavors are undertaken to

Glossary

Coarse-graining (CG): a technique to increase the computationally attainable spatiotemporal window by grouping atoms in effective particles (so-called CG beads) and considering these beads as the degrees of freedom during the simulation.

***In situ* characterization:** characterization of a material in its working environment, *in situ* meaning on site, in position. Within catalysis this refers to the real-time investigation of a catalyst within the reactor, typically by spectroscopy or microscopy techniques, during exposure to reactants or other external stimuli [1].

Machine learning potential (MLP): a numerical potential fitted on an underlying database of QM data using a nonlinear regression procedure, which can afterwards be used to calculate much more efficiently the PES with an accuracy matching the underlying QM data.

***Operando* characterization/ modeling:** evaluation of the function of a material under true external conditions, which may relate to temperature, pressure, presence of moisture, and external fields. *Operando* characterization in catalysis refers to one or more spectroscopy or microscopy techniques that are used to interrogate the catalytic behavior under realistic reaction conditions with real-time online analysis of reaction products [1].

Potential energy surface (PES): in the Born–Oppenheimer approximation, the fundamental energy surface that defines the interactions between different particles, which may be nuclei or atoms but also CG beads, where various atoms are grouped into larger beads. For supramolecular systems, this PES is typically highly dimensional.

Space–time window: the combination of time and length scales that are relevant for a given process or that can be accessed via experimental or theoretical characterization techniques.

Spatiotemporal evolution of a material: the dynamics of a material and its entanglement with the material's spatial properties.

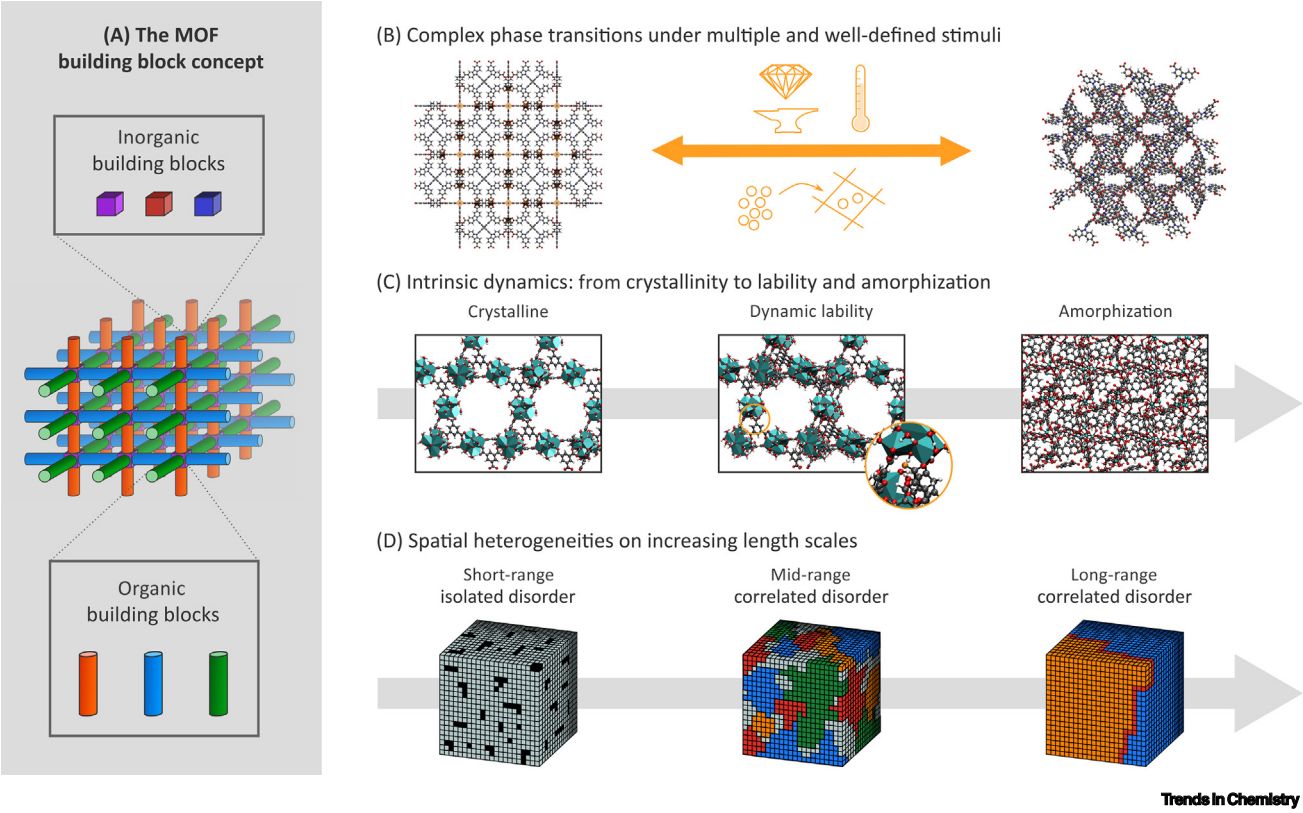

Figure 1. Schematic representation of ideal metal–organic framework (MOF) structures, the temporal response to various stimuli, and heterogeneities present in realistic MOF structures. (A) The MOF building concept. (B) Schematic illustration of the mechanism behind complex phase transitions in MOFs under the influence of multiple stimuli. (C) Illustration of the intrinsic dynamics in MOFs, moving from a perfect crystalline material towards intrinsic lability of coordination bonds towards amorphization. (D) Various types of spatial disorder in MOFs.

build dedicated *in situ* cells to unravel the spatiotemporal response of MOFs under operating conditions. Varying operating conditions may be adopted as a design tool during synthesis [13,34,35] or to tune the active working cycle of a material. As an example, we give a case study concerning the functional behavior of flexible MOFs for separation. As flexible MOFs switch between two phases at a given critical gas pressure, they are attractive for separation techniques such as pressure swing adsorption. However, to this end it is necessary to accurately predict the critical pressure under operating conditions and to investigate whether this critical pressure is retained during the MOF's lifetime. Recently, Kaskel and coworkers demonstrated that, while the critical pressure of MIL-53(Al) and ELM-11 remains constant even after 100 *n*-butane adsorption/desorption cycles, DUT-8(Ni) and SNU-9 show a characteristic increase in critical pressure under *operando* conditions [36]. This increased rigidity during the MOF's lifetime was attributed to the decrease in crystallite size after a few sorption cycles due to adsorption stress. This crystal size effect is a general phenomenon that was tentatively explained by computational tracking of the different (meta)stable phases of a MOF as a function of its crystal size, indicating that phase transitions may occur in a spatially disordered fashion and induce transient phase coexistence [22]. Under that hypothesis, downsizing of the crystallite size increases the free energy barrier to form interfacial defects and suppresses the MOF's flexibility, as illustrated in Figure 3 and in line with experimental findings [11–16,37,38].

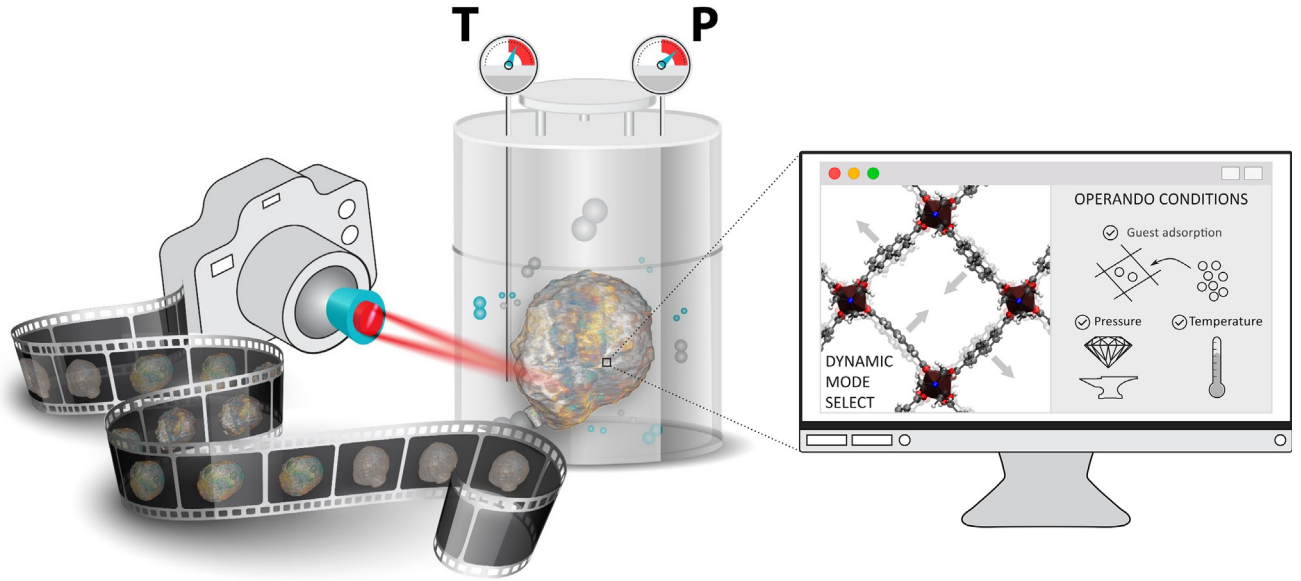

Figure 2. Reconciling experiments and simulations. Analogy between recording *in situ* a molecular movie of solids down to the level of a single particle with nanometer resolution under *operando* conditions with spectroscopic and imaging techniques on the one hand and modeling the spatiotemporal behavior under working conditions on the other hand. Adapted, with permission, from [107].

Defining comparable space–time windows from experiment and theory

A fundamental understanding of *operando* spatiotemporal behavior in MOFs requires that theory and experiment can find space–time windows that ideally show a large overlap. Spatiotemporal gradients and complexities within realistic materials can occur at various levels. In the field of catalysis, seminal work has been performed in spatiotemporal spectroscopy, which can be used as an inspiration to further progress in the MOF field [30,39,40]. Catalytic solids used in

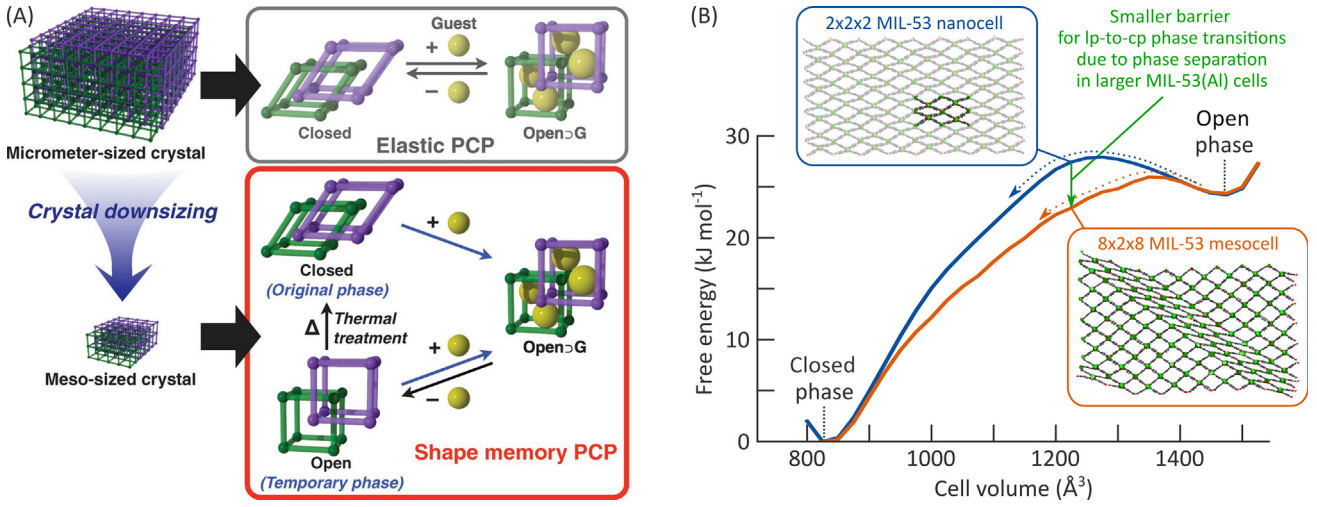

Figure 3. Size effects in stimulus-responsive metal–organic frameworks (MOFs) as probed by experiment and simulations. (A) When micrometer-sized $[Cu_2(bdc)_2(bpy)]_n$ (bdc = benzene-1,4-dicarboxylate, bpy = 4,4′-bipyridine) crystals are experimentally downsized to meso-sized crystals (~50 × 50 × 20 nm^3), the material loses its ability to undergo guest-induced transitions from its open to its closed phase. For meso-sized crystals, the original closed phase can be reobtained only by thermal treatment. (B) When increasing the simulation cell size of MIL-53(Al) from the typical nanocell to a mesocell (~13.0 × 10.7 × 1.4 nm^3), phase separation nucleates spontaneously and facilitates the transition from its open to its closed phase as shown in [22]. (A) Reproduced, with permission, from [12].

industrial applications show a high degree of complexity. with heterogeneities in time and space at the level of both the catalyst particle and beyond. The latter may refer to how the catalyst particles are dispersed in binders or other supports or to gradients in the reactor itself. Similarly, in MOFs one can discriminate between spatiotemporal gradients within and beyond the level of the MOF particle (Figure 4). Experimentally, spatiotemporal gradients beyond the level of the MOF particle arise when assembling MOF particles into macroscopic bodies such as mixed-matrix membranes (MMMs) or sol–gel-derived monoliths with diameters of up to a few centimeters. In addition, spatial gradients emerge within MOF particles, with a length scale that varies from the subnanometer scale to several tens of micrometers. According to their spatial extent, one distinguishes between short-range, mid-range, and long-range heterogeneities (Figure 1D and Figure 4), which may be characterized with dedicated spectroscopic methods (Box 1). Typical examples of short-range, subnanometer-scale heterogeneities are point defects, which are found as undercoordinated metal sites in, for example, MIL-53(Al,V) [41], or as isolated linker and node vacancies in, for instance, UiO-66 and HKUST-1 [42–45]. When these short-range heterogeneities coalesce, mid-range heterogeneities may arise of up to a few tens of nanometers in size. Examples are found as correlated nanoregions, such as in UiO-66 [46], or as mesopores, as in HKUST-1 [47,48]. Furthermore, MOFs may also exhibit long-range spatial heterogeneities, in which extended subdomains of the crystal simultaneously undergo phase transitions [49–53]. Obviously, the external surface of MOFs also needs to be considered. Some of these extended defects show some dimensionality; dislocations have a 1D nature, whereas external surfaces or the recently suggested layer-by-layer phase coexistence in MIL-53 would correspond to 2D defects. The interested reader is referred to a recent perspective on the nature of defects in MOFs and their characterization [54]. Finally, these spatial gradients are inherently dynamic under *operando* conditions, defining the relevant spatiotemporal gradients of the material. When modeling the *operando* spatiotemporal responses of MOFs that mimic experimental

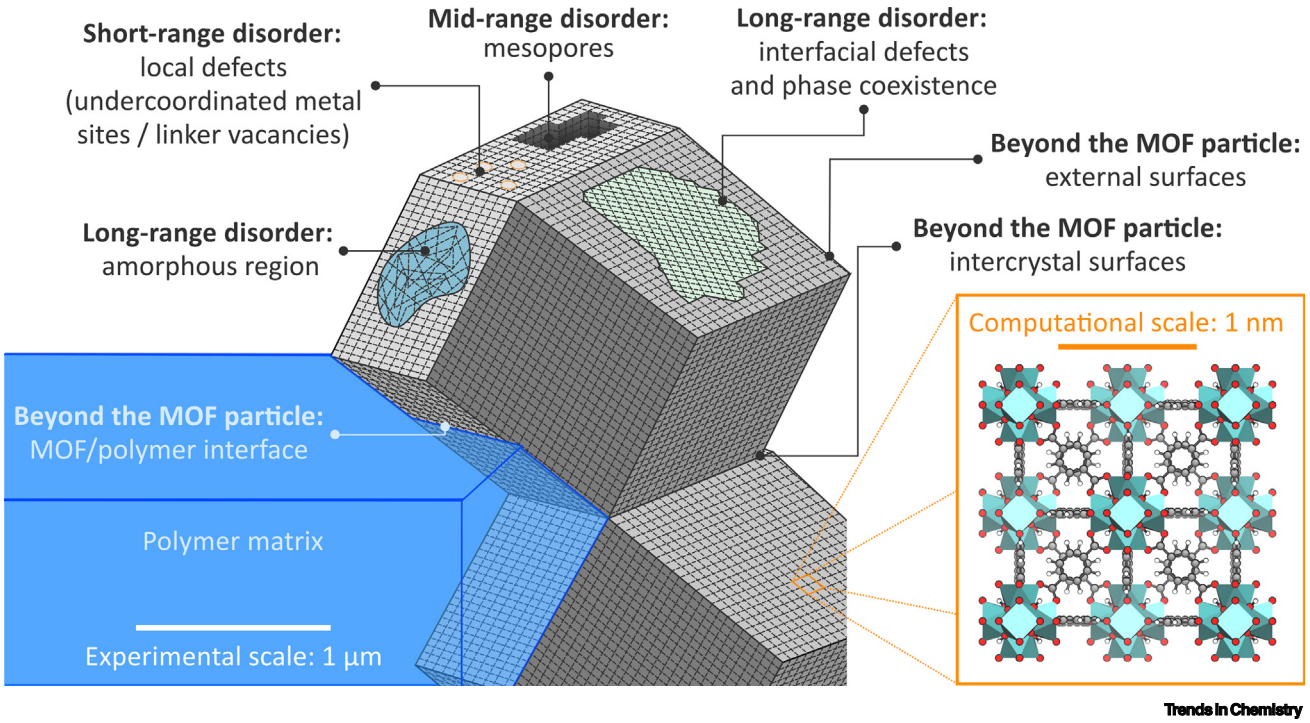

Figure 4. Various types of spatial heterogeneities at different length scales in a metal–organic framework (MOF) particle and at the interface with a polymer matrix. The different experimental and theoretical length scales relevant to interrogate these spatial heterogeneities are indicated.

Box 1. Chemical imaging tools and experimental spatiotemporal windows

Chemical imaging tools encompass spectroscopic, diffraction, and microscopy methods, each with its own space–time window. They provide a plethora of characterization tools to investigate *in situ* either local or spatially more extended effects [106,108]. Our understanding of the spatiotemporal evolution of solids has greatly evolved thanks to *in situ* ultrafast spectroscopy, such as femtosecond spectroscopy, which follows the structural changes during a reaction, and attosecond spectroscopy, which visualizes the electron motion in atoms, molecules, and solids [31,109]. However, simultaneously obtaining high temporal and spatial resolutions, necessary to make a molecular movie under *operando* conditions, remains highly challenging [40]. Herein, a non-exhaustive overview of the most important *in situ* methods to study MOFs is given.

Nuclear magnetic resonance (NMR) probes the local chemical environment, making it suitable to investigate materials lacking long-range order. To characterize dynamic phenomena in MOFs, such as switching transitions and linker flipping, one often resorts to ^{129}Xe and ^{2}H NMR [110]. A less frequently used but sometimes valuable technique is electron paramagnetic resonance (EPR), which has been successfully applied to monitor phase transitions in MOFs [111].

Vibrational spectroscopies like Raman and infrared (IR) are used to unravel the nature and evolution of adsorbed species, as they reveal structural changes in MOFs and help in understanding catalytic processes [112]. Moreover, recent advances allowed monitoring of MOF formation via *in situ* IR and Raman and probing MOF dynamics at the picosecond scale via ultrafast 2D IR [113,114]. Structural MOF dynamics can also be interpreted by analyzing vibrational spectra in the terahertz region [115]. In this regard, spectroscopic modeling is an invaluable tool to provide a nanoscopic understanding of the low-vibrational spectrum [116,117].

Electronic properties are usually studied by UV-Vis spectroscopy and photoluminescence. Capturing the fast excited-state dynamics requires equipment with femtosecond resolution [118]. When high spatial resolution is also demanded, these methods can be coupled with microscopy, such as in fluorescence lifetime imaging microscopy [119].

The aforementioned techniques can be combined to increase their sensitivity and bridge larger spatiotemporal windows, certainly so when diffraction techniques are also incorporated. A common example is NMR spectroscopy combined with X-ray diffraction to also reveal long-range order [41,44]. Furthermore, enhanced spatiotemporal insight can be obtained through direct visualization via microscopy. In that regard, transmission electron microscopy (TEM) is highly promising within the MOF field, reaching atomic-level resolution. Time-resolved TEM studies on MOFs are still lacking, but a resolution of a few hundred femtoseconds should be possible [109].

phenomena is of interest, target space–time windows vary from the subnanometer regime to several tens of micrometers and from the nanosecond to second scale, which capture both various defect types and finite size effects due to the external surface area.

At this point, it is interesting to contrast experimentally relevant spatiotemporal scales (Box 1) with theoretically accessible space–time windows. Theoretically accessible length and time scales are inherently linked to the method used to describe the **potential energy surface (PES)**. A theoretical simulation starts bottom up from the atomic scale, where interactions are described at the quantum mechanical (QM) level (Figure 5). The PES can then be sampled with Monte Carlo or MD techniques, after which physical properties of interest can be derived under the right operating conditions. Ultimately, the obtained properties can be compared with experimental data. When the dynamic behavior of MOFs is of interest, sampling needs to be done with MD techniques that allow one to extract the time behavior of the system. With current QM methods – more specifically, density functional theory (DFT) methods, which are the QM methods of choice thanks to their attractive trade-off between accuracy and speed – attainable length and time scales are limited to a few nanometers and hundreds of picoseconds, which is often too small to describe correlated phenomena in MOFs. To increase the spatiotemporal window and allow the simulation of complex materials under operating conditions, one traditionally uses all-atom (AA) classical force fields (FFs), where the interactions between the atoms are approximated by simple analytical functions, neglecting the quantum description of the electrons [55–57]. FFs can be defined either in a bottom-up approach from *ab initio* input or in a top-down approach by tuning the interatomic potentials to reproduce macroscopic data. Using FFs, also referred to as molecular mechanics (MM) methods, accessible length–time scales increase to tens of nanometers and hundreds of nanoseconds (Figure 5). However, the main drawback of classical FFs is their lack of accuracy

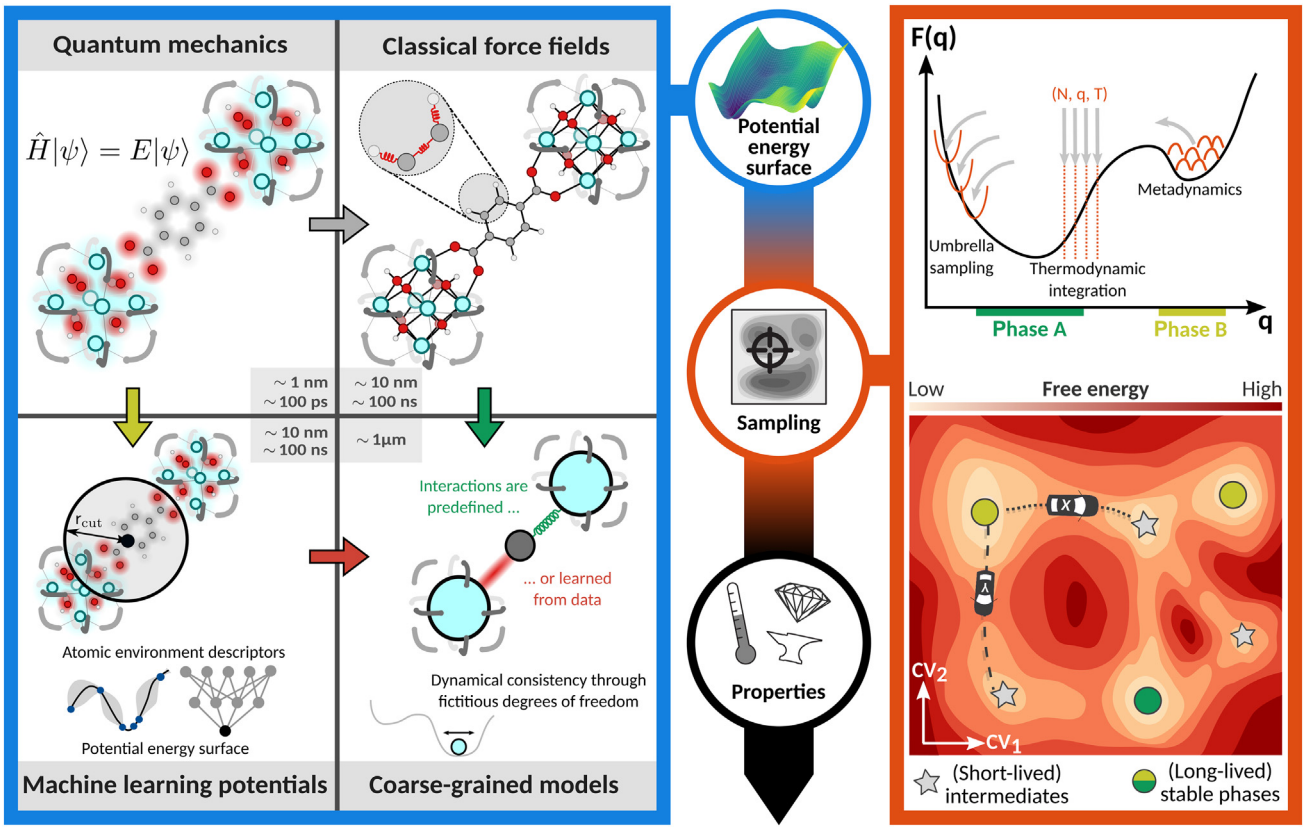

Figure 5. Mapping the potential energy surface (PES). The sequence of a modeling exercise where the basic quantity is the multidimensional PES, which needs to be sampled in the interesting regions after which the target properties under operating conditions can be derived. The PES can be calculated with various theoretical techniques, varying from quantum mechanics and classical force-field-based methods to machine learning potentials and coarse-grained models. Various enhanced sampling techniques can be used to explore interesting regions on the PES and generate a free-energy profile in terms of important collective variables that dictate an activated process.

compared with QM methods and the lack of transferability; for example, FFs derived under certain thermodynamic conditions are not necessarily applicable in other operating windows, they cannot simulate bond formation/breakage, and they are often less accurate when describing host–guest interactions. Clearly, theoretically accessible spatiotemporal windows in the MOF field are still orders of magnitude smaller than experimental observations.

In the field of biomolecular modeling, much larger spatiotemporal windows are being accessed with the help of massive parallelization and innovative methods (Box 2) [58,59]. Also here, one is confronted with a broad range of intrinsic time scales, ranging from picosecond-scale atomic vibrations to millisecond-scale folding events. Advances in both methods and software/hardware were pivotal to accurately determine the various conformations that biomolecules can adopt. For instance, the well-known Folding@Home project pioneered by Shirts and Pande succeeded in generating 6 ms of data for the lysine methyltransferase protein SETD8, a structure containing more than 35 000 atoms, through massively parallel MD simulations [60]. Besides this huge gain in accessible time scale, in recent years several studies have reported nanosecond simulations for biomolecular structures larger than 100 nm and containing several hundreds of millions of atoms [58,61,62]. Parts of these concepts and ideas can be adapted and transferred to the field of nanostructured materials. However, as nanomaterials have a completely different building pattern with their own specificities, simply adapting methods is not sufficient and substantial

Box 2. Hardware and software advances to access larger space–time windows

The enormous time and length scales that are currently accessible in state-of-the-art biomolecular simulations can be largely attributed to massive hardware parallelism and the rapid and widespread emergence of powerful graphics processing units (GPUs) over the past decade. Historically, most molecular mechanics (MM) engines (e.g., NAMD [58], GROMACS [59], LAMMPS [120]) were designed for hardware architectures in which all computations are performed by central processing units (CPUs). The advent of massively parallel GPU accelerators – with a peak performance in computing power that is two to three orders of magnitude larger than similarly priced CPUs – has induced significant changes in how these MM engines operate to optimize their performance on these GPU-accelerated computing platforms. As a result, most modern MM engines now rely on GPUs for the (partial) evaluation of the interatomic potentials, because this is traditionally the most expensive part of an MD simulation. In addition, more recent developments have now made it possible to execute the entire simulation pipeline on the GPU (as recently implemented in OpenMM [121], NAMD, and GROMACS), leading to further increases in the computational efficiency. A recent benchmark has demonstrated the enormous potential of this heterogeneous computing approach by simulating a massive >200 million atoms at a rate exceeding 30 ns/day [58]. For MM in particular, it is important to note that there exists a wide range of algorithmic improvements that are more or less independent from the underlying hardware infrastructure, but which do improve the performance significantly. Notable examples are the multiple time-stepping algorithms (e.g., r-RESPA) to increase the maximum time step, the fast multipole method (FMM) to evaluate electrostatics with O(n) complexity, and mixed-precision computing schemes [122].

Besides MM, GPUs have played a crucial role in the development of deep neural networks and in particular neural-network-based MLPs with millions of parameters as accurate representations of the QM PES. In more recent years, researchers and software developers have also started to focus on improving the performance of DFT calculations on heterogeneous platforms, although the benefits of GPU offloading are so far much less pronounced due to the nature of the current DFT algorithms. For example, due to the newest developments in the Vienna *Ab Initio* Simulation Package (VASP), GPU acceleration is now already expected to yield up to a tenfold increase in performance; algorithmic improvements over the next decade can increase the acceleration even more [123].

methodological advances will be necessary. Despite this limitation, we can be greatly inspired by the field of biophysics to further progress in the MOF field [63–65].

For MOFs, such an impressive boost in accessible time–length windows has not yet been reached, although important milestones have been achieved recently (Table S1 in the supplemental information online). Kollias and colleagues, for example, succeeded in modeling the early nucleation stages of the MIL-101(Cr) material through enhanced MD simulations extending up to 7 ms for a system of a few nanometers in size and containing 12 000 atoms [66]. Similarly, to obtain insight on the experimentally observed suppression of a MOF's flexibility by decreasing the crystallite size of these materials, nanosecond advanced MD simulations for MOFs with a critical length scale larger than 10 nm and containing several tens to hundreds of thousands of atoms were performed [21,22]. When studying heterogeneities beyond the MOF particle, even larger systems are required. For instance, to investigate the effect of beyond-particle heterogeneities on polymer/MOF mixed membranes, Ozcan and colleagues reported microsecond-scale enhanced MD simulations for a PIM-1/ZIF-8 system with a critical length larger than 50 nm [67]. This additional increase in accessible time–length windows was achieved by removing the fastest time scales in the material and reducing the number of interaction beads via CG, a technique that is further outlined in the following text.

Besides these notable examples, which aim to increase the accessible theoretical spatiotemporal window, previous considerations show that there is still a huge spatiotemporal gap between theoretically attainable scales and experimental observations.

Climbing the computational spatiotemporal ladder: towards mesoscopic metal–organic framework simulations

To extend the spatiotemporal simulation window, new modeling approaches in the MOF field need to be explored. Herein, we highlight some promising avenues with great potential; namely, MLPs, CG, and enhanced sampling. MLPs and CG methods enable to describe the PES in more efficient ways, whereas enhanced sampling methods enable efficient sampling of the PES and explore its most interesting regions (Figure 5).

Machine learning potentials

While a FF description of the PES increases the spatiotemporal simulation window compared with a QM description, the conversion from a QM PES to a FF PES is typically accompanied by a substantial loss of accuracy and, for nonreactive FFs, does not allow the description of phenomena that are accompanied by bond rearrangements. To overcome these limitations, MLPs can be derived, where a numerical potential is derived from an underlying database of QM data using some (nonlinear) regression procedure [68–71]. MLPs can be used to calculate much more efficiently the PES with an accuracy matching the underlying QM data. The field of MLPs is in full expansion from the methodological side; however, to date there is only one paper where a MLP was generated for a MOF – namely, for MOF-5 [72]. The field of MLPs was initiated by Behler and Parrinello [73] with their seminal paper that proposed a neural-network methodology with atom-centered symmetry function (ACSF) descriptors to represent the chemical environment of the atoms. Since then, the field has rapidly evolved and different classes of MLPs have now emerged each with their own mathematical framework, such as neural-network-based MLPs [72,74,75], Gaussian approximation potentials (GAPs) [76], kernel ridge regression [77], and gradient-domain machine learning (GDML) [78]. The construction of MLPs comprises various steps (Figure 5). First, one needs to define descriptors, which obey the correct symmetries and invariances of the output variables. These can then be fed into various regression methods to fit a numerical potential producing the energies, forces, and stresses. In end-to-end methods, like the SchNet deep neural network, the descriptors are learned from the data itself [74].

In principle, the application and extension of MLPs to the MOF field could induce a paradigm shift by accessing larger spatiotemporal windows with an accuracy comparable with the underlying QM data, but major benchmarking will be necessary and methodological hurdles need to be overcome to transfer the MLP concept to the MOF field. One major challenge is finding systematic ways to generate an extensive and representative QM dataset that enables the description of MOFs close to but also far from equilibrium. The latter is necessary to describe phase transformations and other phenomena with large deformations. Compared with small molecules and more traditional solids, MOFs are inherently large periodic systems with often a few hundred atoms in their unit cell, so that generating the QM dataset is computationally the heaviest step when deriving MLPs for MOFs. To partially circumvent this problem, Behler built their MOF-5 MLP by training not on periodic QM data, but rather on smaller representative clusters, similar to our original QuickFF approach to derive traditional FFs [79]. Even so, they still required more than 25 000 DFT calculations. However, the extrapolation of this cluster-based approach is less straightforward for MOFs with 1D inorganic chains or 2D inorganic layers, which cannot be divided into clusters without cutting through these inorganic moieties. Another major point of attention is how to describe host-guest interactions and more generally long-range interactions. Treatment of long range interactions is a major challenge within the field of MLPs [80]. Clearly, to extend the field of applicability of MLPs towards all types of MOFs, including 1D and 2D MOFs but also flexible MOFs, it will be crucial to obtain deep knowledge of the intricate properties of the targeted MOFs and to work closely with the method development community on MLPs. Once a successful MLP has been derived, it has the potential to be used on much larger systems than the one on which it was trained and to sample phase space more efficiently. Such approach was recently applied by Jinnouchi and colleagues to describe the phase transition of hybrid perovskites using MLPs [81].

Coarse-graining

Another strategy to increase the accessible space–time windows by several orders of magnitude are CG methods, which describe a system's spatiotemporal evolution no longer in terms of individual atoms or on an AA basis, but in terms of groups of atoms, so-called CG beads, onto which the atoms are mapped (Figure 5) [63,82]. CG methods can be divided into inversion approaches,

such as (iterative) Boltzmann inversion and inverse Monte Carlo, which aim to reproduce the radial distribution functions between beads, and bottom-up approaches that fit the interactions between the CG beads based on higher-resolution FF data. Inherently in CG models, one loses atomic resolution. This may be an added value in interpreting the behavior of complex nanostructured materials; for example, to determine which motions determine large structural transformations or properties like the bulk modulus. While routinely used for biomolecular systems, the application of CG FFs to nanoporous materials remains in its infancy [83,84]. In 2014, Sarkisov and colleagues followed a CG-like approach to predict the potential flexibility of MOFs by approximating their structures as rigid units connected through flexible hinges [85]. Later, Dürholt and colleagues proposed various CG FFs for HKUST-1, obtained at different resolutions, by following a bottom-up strategy akin to their AA FF protocol MOF-FF [83]. Depending on the CG resolution, semiquantitative predictions of the structural and mechanical properties were achieved. However, macroscopic effects depending on local deformation modes, such as negative thermal expansion, could not be described properly. On an even coarser level, the micromechanical model was recently proposed in which the CG beads of interest are defined by a MOF's unit cell, further reducing the amount of interaction beads [86].

CG methods are attractive to study long-range effects and slow dynamics in MOFs. A typical example are MOF/polymer MMMs, to study the affinity of the two components, which was successfully done to describe the interface of HKUST-1 with poly(vinyl alcohol) [84]. The CG model for HKUST-1 has also been used to describe the stability of mesopores with radii of up to a few nanometers, which were also observed experimentally [87]. Further upscaling of such methodologies could eventually lead to isolated MOF nanoparticles embedded in a polymer matrix and thus account for heterogeneities beyond the MOF particle (Figure 4). While the previous examples show the potential of CG methods, the approach followed thus far is not straightforwardly extendable to more complex MOFs or MOFs with multiple (meta)stable phases.

To routinely apply CG approaches for MOFs, various hurdles need to be overcome. First, consistent mapping between the atomistic and the CG representation is necessary that finds a balance between the accuracy and the sparseness of the CG representation. To systematically propose mappings rather than defining mappings solely based on chemical intuition, dimensionality reduction methods similar to those used to identify collective variables (CVs) for enhanced sampling methods (*vide infra*) can be adopted to find the slowest degrees of freedom, which are also most interesting to access in a CG system. Second, by removing the highest frequencies in the system, CG particles generally experience less friction and are therefore artificially accelerated. To counteract this, dynamically consistent CG models need to be derived; for instance, by introducing fictitious particles that interact with the CG beads [88]. Finally, in many cases detailed atomistic information is necessary at the end; for instance, to calculate surface areas. As this requires a reconstruction of the atomic structure, hybrid AA/CG models are promising to describe parts of the system at the coarser level and others at the finer level, comparable with hybrid QM/MM methods. As with QM/MM methods, hybrid AA/CG methods require theoretically founded models to correctly describe how particles at the AA/CG interface behave.

Enhanced sampling methods

For systems with a clear disparity in time scales, such as biomolecules and MOFs, enhanced sampling methods are necessary to efficiently sample slower degrees of freedom, which are termed the order parameters or CVs. These CVs partition the phase space and are used either to steer the system out of already visited regions via nonequilibrium techniques, such as metadynamics, or to sample the phase space along constrained values of the CV, using equilibrium techniques such as umbrella sampling (US), free energy perturbation, and thermodynamic

integration (Figure 5) [89]. A large variety of enhanced sampling methods exist, for which the reader is directed to more specialized reviews [17–20]. A major challenge when applying enhanced sampling methods to complex systems, such as MOFs, is to define a proper set of CVs that are able to distinguish between the metastable states and remain sufficiently small for computational efficiency.

The application of enhanced sampling methods in the MOF field has recently been adopted to describe both chemical and physical transformations in MOFs [90]. Metadynamics methods and US simulations were successfully used to follow on the fly the dynamic rearrangement of bonds in the zirconium-based UiO-66 [91,92]. The material can withstand structural deformations during activation processes such as linker exchange, dehydration, and defect formation, where the zirconium coordination number changes in a dynamic way, creating open metal sites for catalysis [93]. ***Operando* modeling** techniques based on enhanced sampling showed how protic solvents may facilitate such changes in the metal coordination.

The usage of enhanced sampling techniques has also greatly contributed to understanding of the phase transformations in soft porous crystals, a terminology that was first coined by Kitagawa and colleagues for materials showing bistable or multistable behavior with long-range structural order [7]. Prominent examples of such SPCs are flexible MOFs. From experiment, one cannot construct the underlying Helmholtz free energy surface associated with the transition, as the material undergoes various irreversible structural transitions between (meta)stable equilibrium states [90]. By efficiently sampling along the unit cell volume with dedicated methods in which the cell shape could also vary, we were able to construct pressure versus volume profiles for a large variety of MOFs for which the volume is a good CV [94]. Promising materials were discovered for mechanical energy storage applications and nanoscale switching devices in close synergy with experimentalists [95,96].

While successful, these simulations also showed how difficult the proper choice of CVs may be for MOFs having an inherent complex behavior with many degrees of freedom. Recently, Demuynck and colleagues used linear dimensionality reduction methods to investigate the phase transformations in zirconium-based MOFs with flexible linkers [97]. Although such methods are promising to unravel complex forms of flexibility, future investigations may have to go beyond linear CV definitions and resort to, for example, kernelized tICA or VAMPnets to systematically construct complex nonlinear CVs [98,99]. Their effectiveness has already been demonstrated in the construction of Markov state models (MSMs) for various biomolecular systems [100], but more extensive benchmarking and testing in the MOF field is necessary. Alternatively, it is possible to perform enhanced sampling without an explicit definition of (non)linear CVs, as, for example, in transition path sampling (TPS), where an ensemble of transition paths is created on the basis of an initial trajectory, which may lead to new reaction paths [101]. However, so far, the method has, to the best of our knowledge, not been used in the MOF field, partly due to its computational expense.

In other, related fields where one is confronted with similar time- and length-scale problems, like crystal nucleation and the growth of typical solid-state systems, TPS and other techniques have been explored [102]. Crystal nucleation is a typical example of a rare event controlled by an activation barrier where TPS proved to be useful. Crystal growth and diffusion-controlled aggregation occur on very long time scales (longer than microseconds) and necessitate other techniques, such as kinetic Monte Carlo or more advanced simulation methods [102]. Inspired by these studies, it might be interesting to explore the possibilities of the aforementioned multilength- and time-scale methods for the study of MOF nucleation and crystallization, as much remains to be learned in this area [103,104].

All sketched enhanced sampling methods can in principle be combined with either a QM or a FF description of the PES;, however, ideally such methods will be combined in the future with MLPs to extend the spatiotemporal simulation window. Enhanced sampling methods can also be combined with a CG description of the system, although care needs to be taken in how to interpret time and deduce dynamic properties (transport, residence times, diffusion) in such simulations because the Hamiltonian dynamics of the CG system often fails to reproduce the dynamic properties of the atomistic reference in the CG degrees of freedom [105].

Reconciling theoretical and experimental observations

Clearly, an essential leap forward in modeling the dynamic behavior of realistic MOF structures is necessary to access length and time scales that are comparable with experiment. To compare modeling results with experimental observations, one needs to rely on time-resolved *operando* techniques, which can give temporal information at various scales. A key challenge for experimentalists is to capture intermediate states during operation, which would help in understanding the mechanism of flexible behavior and possibly give more insight into the energetic barriers involved when traversing from one (meta)stable state to another. The specific experimental technique to be used will largely depend on the phenomenon under investigation and the typically associated time scales; for example, structural transformation of frameworks requires other techniques than dynamic rearrangements of bonds at the metal node of a MOF. Despite major developments in the field of spectroscopic and imaging techniques (Box 1), ensemble-averaged measurements cannot capture heterogeneities in time and space. Bon and colleagues contributed with an excellent review on *in situ* spectroscopic and diffraction techniques and their applications to MOFs [106]. As pointed out by these authors, the smart design of dedicated *in situ* cells relying on either diffraction or spectroscopic techniques is necessary to assess the material's behavior under the working conditions. Many advances have occurred in the development of *in situ* NMR, EPR, and optical techniques, but the key challenge is to capture temporal evolution at disparate time scales.

Concluding remarks

The ability to tune the dynamic response of MOFs on one or multiple external stimuli is one of the greatest challenges in the MOF field. Such a dynamic response can be tuned by varying the spatial heterogeneities and crystal size of the material, as was recently evidenced from experiment. Also, the operating conditions strongly affect the MOF response. These observations lead to the potential to explore and design the *operando* spatiotemporal behavior of MOFs and target a dedicated functional material response. To reach this goal, a full understanding of the dynamic spatial behavior under operating conditions will be necessary, requiring a close partnership between the modeling and experimental communities (see Outstanding questions). From an experimental point of view, dedicated *in situ operando* cells will have to be built to track intermediate metastable states during the dynamic response on external stimuli. From a modeling point of view, the material needs to be modeled in an inclusive way under realistic operating conditions, thereby accounting for various forms of spatial heterogeneities extending over length scales that are comparable with experimental crystal sizes from the nanometer to the micrometer scale, for example, accounting for finite size effects, short-, mid-, and long-range defects, and cooperative active sites. To track the dynamic response governed by disparate time scales, advanced sampling techniques are necessary. Clearly, major methodological advances will be necessary to model the spatiotemporal response of MOFs at scales comparable with experimental measurements. Inspiration can be sought in other fields like biomolecular simulations. However, multiple strategies will have to be explored, such as the development of MLPs or CG techniques in combination with enhanced sampling techniques in a finer phase space. In any case, a synergistic approach between various communities will be needed to unravel the spatiotemporal behavior of MOFs. Even when major

Outstanding questions

How can we build structural models for realistic MOF particles, including short-range disorder on the subnanometer scale such as isolated defects, mid-range spatial disorder such as correlated nanoregions or mesopores, and long-range disorder with phase coexistence or partly amorphized regions? Can we construct realistic models that capture finite size effects with potentially functionalized external surfaces?

How can we compare modeling results with observations from experimental spectroscopy and imaging techniques at different length and time scales? Can we use a complementary set of characterization tools ranging from averaging techniques like X-ray diffraction (XRD) to optical characterization tools and quantitative, direct, and local structural characterization of materials like transmission electron microscopy (TEM) to determine spatial heterogeneities at various length scales?

Can we develop MLPs for complex materials like MOFs, which afford the characterization in a time-resolved way of processes far from equilibrium, such as structural transformations, amorphization, or bond rearrangements in the MOF lattice?

Can we use CG methods where atoms are grouped in beads to determine large-amplitude structural transformations in MOFs? Can we deduce dynamic properties such as diffusion constants and transport properties (e.g., at MOF interfaces) from these simulations?

Can we use enhanced sampling methods to map the dynamic response of realistically constructed MOF models and capture the dynamic response at various time scales? Can we compare dynamically derived properties such as proton conductivity and diffusion constants with experimental observations?

Can advanced *in situ* experimental approaches be developed in the MOF field that allow simultaneous high temporal and spatial resolution, necessary to make a molecular movie under *operando* conditions?

advances are made in modeling the spatiotemporal behavior of realistic MOF crystals, it might be interesting for modelers to reconcile their observations from bottom-up nanoscopic theories with established classical theories; for example, nucleation models, thermodynamic laws, or even empirically determined laws. Such comparison may lead to a greater understanding of the physics driving the observed macroscopic behavior. In summary, a greater understanding of the spatiotemporal response of MOFs will open new, promising avenues where one can engineer the functional response of MOFs to target applications such as the selective recognition of molecules for energy-efficient separations, highly selective sensors for the detection and decomposition of volatile organic compounds, and many others.

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Declaration of interests

No interests are declared.

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