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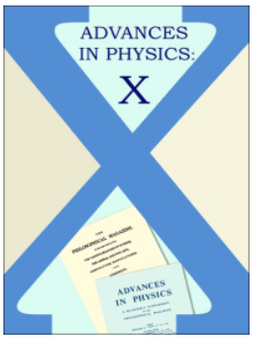

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REVIEW ARTICLE

Multiscale modeling approaches in biomolecular physics

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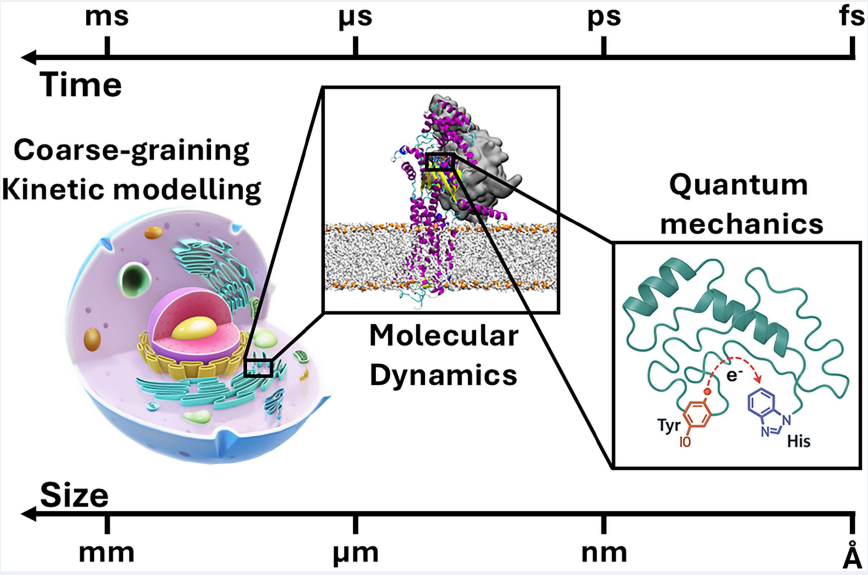
ABSTRACT

Biomolecular function arises from phenomena spanning several lengths and time scales, from electronic rearrangements and charge transfer to conformational dynamics and cellular-scale processes. To bridge these scales, multiscale modeling integrates quantum mechanical, classical atomistic, mesoscopic, and continuum descriptions into coherent frameworks. In this review, a brief overview of the state of the art methodologies used in multiscale approaches is provided, emphasizing how quantum-derived parameters inform force fields, how embedding techniques integrate active regions within complex environments, how atomistic molecular dynamics link to coarse-grained and continuum models, and how emerging machine-learning strategies accelerate or unify these techniques. Highlights of representative case studies of biomolecular electron transfers, radical-pair spin dynamics under magnetic fields, membrane phenomena, and molecular diffusion are discussed, showcasing how multiscale coupling delivers insights into real biophysical systems. Throughout, central challenges of transferability, sampling, error propagation, validation, and adaptive coupling are presented. Finally, an outline of future directions toward fully predictive, unified multiscale platforms for biomolecular physics is provided.



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1. Introduction

Biological function emerges from processes that span a remarkable range of temporal and spatial scales [1–3]. At one extreme, the fundamental events underlying enzymatic catalysis [4–6], electron transfer [7–10], or light absorption [11–13] are governed by electronic interactions on femtosecond timescales and Ångström length scales (see Figure 1). At the other extreme, these quantum events are embedded in macromolecular complexes and cellular environments, where the nanosecond to millisecond dynamics of proteins, membranes, and metabolites ultimately determine functional outcomes [14–16]. Multiscale modelling seeks to bridge these crucial regimes by combining theoretical and computational methods across quantum, atomistic, mesoscopic, and biological levels [3,17]. Its central aspect lies in enabling a mechanistic understanding of how molecular structure and dynamics translate into emergent biological phenomena.

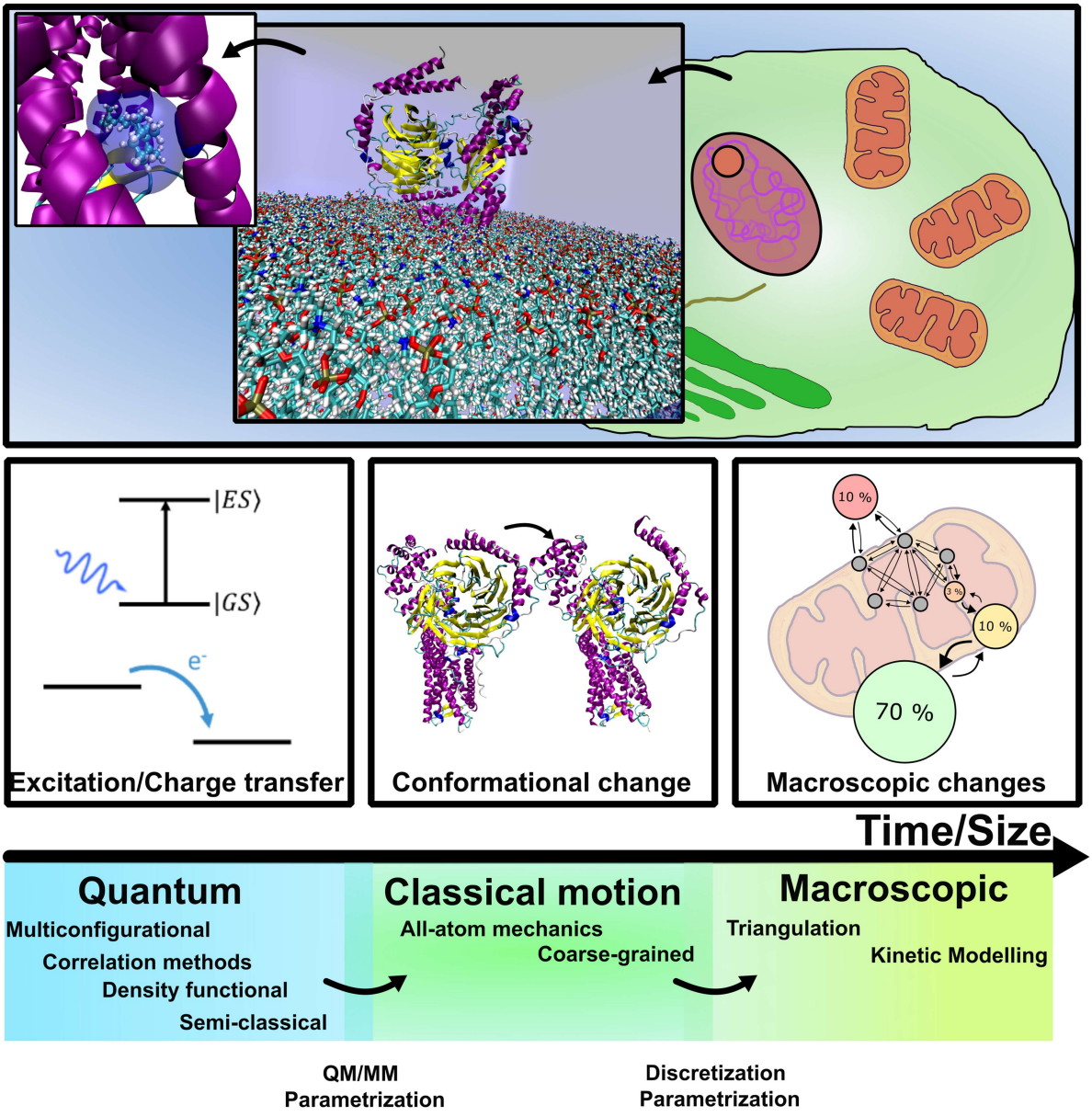

Figure 1. Multiscale modelling in biophysics requires the consideration of different temporal and spatial scales reaching from large cellular structures to subatomic dynamics. Each regime (quantum, classical motion, macroscopic) inherits various techniques with individual advantages and challenges. The leading challenge is the accurate connection between these regimes.

Over the past decades, significant progress has been made in each of the relevant methodological domains. Electronic structure simulations, such as density functional theory (DFT), wavefunction-based *ab initio* correlation approaches, and multiconfigurational techniques, provide the quantum mechanical foundation for describing bond breaking, charge transfer, and electronic excitations [18,19]. All-atom molecular dynamics (MD), supported by empirical or quantum-derived force-fields, have become the most prominent approach for simulating the conformational dynamics of proteins, nucleic acids, and membranes on microsecond scales [9,14,20–23]. Coarse-grained and continuum models further extend the accessible system sizes to the supramolecular level, such as the cellular structures [24]. In parallel, the integration of artificial intelligence has begun to reshape each of these levels, accelerating sampling, predicting quantum-level properties, and enabling adaptive coarse-graining [25]. Taken together, these advances highlight both the manifold methodologies available and the fundamental challenge of combining them consistently.

The requirement for multiscale strategies is particularly important in biomolecular physics, where functional processes often involve quantum-classical interplay. For example, charge and excitation transfer in proteins such as cryptochrome [26–28] or cytochrome [29–32] depends on electronic couplings and reorganisation energies, which are, in turn, modulated by the fluctuating environment of amino acid chains, embedded co-factors, and solvent molecules. Similarly, the magnetic field effects observed in different biological environments require an accurate description of quantum spin dynamics in a noisy protein environment [27,33–35], spanning many orders of magnitude in timescales. Lipid membrane remodelling or protein aggregation phenomena demand the representation of thousands to millions of degrees of freedom while retaining essential molecular details [22,36]. No isolated methodology alone can capture these processes in their entirety, making systematic coupling across scales the only viable route.

Bridging the scales in size and time requires careful attention to both conceptual and technical challenges. Here, the fundamental question that arises is to what extent parameters or observables derived at one scale can be reliably used at another scale. For instance, deriving force-field parameters from electronic structure calculations demands rigorous protocols to avoid inconsistencies or overfitting [37]. Another challenge is embedding different methodologies within one another. Here, treating a small quantum region within a large classical or coarse-grained environment without double-counting interactions or neglecting polarisation effects is still under active development [38]. An additional crucial aspect lies in the sampling of large phase spaces that are studied in biological systems. Rare events and long-time dynamics cannot be captured by brute force; they require enhanced sampling methods, rare event techniques, or machine learning accelerators [39]. Finally, there is the overarching challenge of validation, where multiscale models must be benchmarked against experimental observables across levels, from spectroscopic signatures to structural data and functional assays.

Despite the challenges outlined above, the multiscale paradigm has proven indispensable [3,40]. The structure of this review follows the natural hierarchy of scales. The discussion opens at the quantum-mechanical scale, surveying electronic-structure methodologies used to extract fundamental descriptors of biomolecular processes and delineating their practical limits with respect to system size and chemical complexity. The context then moves to the classical scale, emphasising atomistic molecular dynamics and enhanced-sampling strategies, and detailing how force-field models and collective variables can be parameterised and validated against quantum data. The presentation subsequently addresses the mesoscopic scale, outlining coarse-grained models and beyond that map molecular detail onto emergent collective biological behaviour. Across these scales, the incorporation of artificial-intelligence methods is treated as a unifying, cross-cutting component for model construction, acceleration, and uncertainty quantification. The multiscale paradigm is finally demonstrated through representative case studies in biomolecular physics, spanning electron transfer phenomena and weak-field spin chemistry to membrane mechanics and molecular transport under confinement.

Multiscale modelling approaches in biomolecular physics aim to answer a central question: how do the laws of quantum mechanics, operating at the scale of electrons, shape the macroscopic behaviour of living systems? By combining methods across scales and addressing the challenges of transferability, embedding, sampling, and validation, the field is steadily advancing toward predictive, mechanistic models of biological function.

2. Quantum regime

At the foundation of most multiscale approaches lies the Born–Oppenheimer approximation, which exploits the large mass difference between electrons and nuclei to separate fast electronic motion from slower nuclear dynamics. Within this picture, electronic-structure methods define the potential-energy surfaces and effective interactions on which nuclear motion can subsequently be treated at a more approximate level. The approximation breaks down, however, when electronic states become nearly degenerate and are strongly coupled by nuclear motion, as in photoinduced charge transfer, conical intersections, or other non-adiabatic processes [41]. These non-Born–Oppenheimer effects motivate excited-state and mixed quantum-classical approaches and thus form an important conceptual bridge between quantum chemistry and larger-scale dynamical modelling.

Electronic-structure methods provide a quantum-mechanical description of the electron distribution and its energetic consequences, thereby delivering the reference data that is transferred to larger-scale models. In biomolecular applications, these outputs include ground-state quantities such as equilibrium geometries, force constants, atomic charges, and potential-energy scans along torsional coordinates, which are used to parameterise classical force fields [42–45] and to define consistent quantum mechanical regions in embedding schemes [11,46–48]. In addition, electronically excited-state properties are essential for light-driven biomolecular processes. Vertical excitation energies and oscillator strengths support the interpretation of optical spectra, while transition densities and charge-transfer diagnostics can inform exciton or electron-transfer models. Time-dependent electronic-structure approaches can further provide input for reduced descriptions of non-equilibrium electron dynamics at larger scales. The following sections, therefore, organise quantum methods according to the type of electronic problem they address: ground-state electronic structure and correlation, followed by excited-state and non-equilibrium electron dynamics.

2.1. Ground-state electronic structure

2.1.1. Density functional theory—DFT

DFT is widely used in biomolecular simulations, as it provides a quantum mechanical description of the electron distribution combined with a low computational cost relative to wavefunction-based *ab initio* correlation methods [49]. The foundations of DFT are laid by the Hohenberg-Kohn theorems, which state that the ground state electron density uniquely determines all properties of an interacting electronic system and that the ground state energy can be obtained variationally from the density functional [50]. Due to its relative cost efficiency, DFT is often employed as the quantum mechanical (QM) part in QM/MM (MM - molecular mechanics) approaches to describe the chemically active region of complex biophysical systems [11,51–53]. For example, DFT is used to study the working mechanism of a reaction centre in an enzyme [54] or as a foundation to describe the ground-state density for the optical spectrum of a chromophore bound to a protein [55], where the rest of the environment is treated with classical force fields. In practice, DFT is commonly employed within the Kohn-Sham (KS) formulation, in which the fully interacting system of electrons is replaced by a fictitious system of non-interacting electrons with the same density as the original. In the KS formulation, the many-body effects are contained in the so-called exchange-correlation functional, whose general form is unknown and must be approximated [56]. These approximated functionals are usually categorised within Jacob's ladder, where each rung is supposed to represent a step towards a more accurate description [57]. Most relevant for the application to biomolecular systems are functionals from the second to fourth rungs [58,59], including generalised gradient approximation (GGA), meta-GGA, and hybrid functionals, as they provide a balance between accuracy and cost efficiency.

In addition to its low computational cost relative to *ab initio* correlation methods, DFT with approximate density functionals works well for a wide range of properties, such as geometries, vibrational frequencies, and reaction barriers [58]. One of the disadvantages of DFT is, however, that its actual performance strongly depends on the combination of functional, molecular system, and the computational task. General or more specialised benchmark studies may provide guidance for finding an appropriate

functional [59,60]. Furthermore, functionals may exhibit large systematic errors related to electron self-interaction, delocalisation, and correlation [58]. Another challenge that is particularly relevant for biological systems is the description of dispersion and van der Waals forces [58]. Methods such as Grimme's dispersion correction D4 [61] can be used to improve the description of these interactions, and their influence on the electron density is a topic of current research [62].

2.1.2. Ab initio single-reference correlation methods

The Hartree-Fock (HF) method is a wave function-based alternative to DFT for describing the electron distribution in molecular systems based on quantum mechanics. In the HF theory, each electron is described by an orbital, and the total wave function is written as a Slater determinant to ensure its fermionic antisymmetry [63]. The HF method provides the best set of orbitals concerning the energy that can be obtained for a single Slater determinant as a wave function [63]. The interaction of an electron with other electrons is described within HF as an average mean-field [63]. Therefore, HF includes the exchange interaction between the electrons (often denoted as exact exchange in the context of DFT), but it does not account for electron correlation [63].

To include the latter, *ab initio* correlation methods must be applied on top of the single determinant HF calculation, leading to single-reference correlation methods. These methods are usually divided into three main categories: (i) Configuration interaction (CI), perturbation theory (PT), and coupled cluster (CC) [63]. A prominent example is the Møller-Plesset second-order perturbation theory (MP2) which belongs to the second category and is one of the most popular *ab initio* correlation methods, as it is quite efficient and allows, for example, for the accounting of hydrogen bonding [64–67]. Furthermore, it is often used to parameterise force-fields of classical molecular dynamics (e.g. CHARMM [45,68,69]). Another popular method is CC with single and double excitations and a perturbative correction for the triples (CCSD(T)), as it can reach chemical accuracy of around 1 kcal mol^{-1} when combined with a sufficiently large basis set [70]. However, the steep scaling of conventional CCSD(T) implementations with system size limits their applicability to molecular systems of 20 to 25 atoms [71].

2.1.3. Semi-empirical quantum-mechanical methods

Semi-empirical quantum mechanical methods (SQMMs) are a class of methods derived from first-principles theories, mainly HF or DFT, by applying systematic approximations aimed at removing the associated computational bottlenecks. More specifically, in HF based SQMM, some of the integrals entering the Fock matrix are neglected, some are evaluated exactly, and for the remaining ones, parameterised expressions are used [72]. Different approximation choices result in a variety of models, such as zero-differential overlap, complete neglect of differential overlap, and neglect of differential-diatomic overlap [73]. In density-functional-based tight-binding (DFTB), the starting point is the Taylor expansion of the KS energy functional in terms of fluctuations of electron densities with respect to the densities of neutral atoms [74]. This expansion results in the DFT total energy being expressed as a sum of a tight-binding contribution, a force-field-like contribution describes the interaction of neutral atoms, and a Coulomb-like contribution accounts for the electrostatic interaction of charge fluctuations. Similarly to the HF-SQMM, different levels of approximation result in different DFTB models, all of which use a set of parametric expressions to evaluate the aforementioned contributions [75,76]. SQMMs are several orders of magnitude faster than their *ab initio* counterparts and can be used to study systems with thousands of atoms efficiently [77,78]. On the other hand, the very approximations that make these methods so efficient inevitably impose certain limitations on their accuracy. Major limitations stem from (i) the use of a minimal, atom-centred basis set, (ii) representing the charge distribution in terms of the lowest multipoles, and (iii) the fitting procedure employed for parameter determination [72]. In spite of all the shortcomings, SQMMs remain a valuable tool in computational biophysics due to their ability to provide a generally reasonable quantum description of larger systems, where pure *ab initio* methods would be too expensive. Specific examples include studying the dichroism spectra of complex systems [79], interactions of biomolecules with metallic clusters [80], and modelling proton-coupled electron transfer [81].

2.2. Multiconfigurational regimes and excited states

2.2.1. Multiconfigurational and multireference methods

Single-reference wavefunction methods such as HF, and approximate single-determinant representations in KS-DFT describe the wave function using a single Slater determinant. In contrast, multiconfigurational wave functions are built as a linear combination of several such determinants or spin-adapted configuration state functions [82]. A multiconfigurational approach is, therefore, inherently more flexible and allows for the description of systems for which a single electronic configuration is not a valid approximation, such as bond breaking and degenerate electronic states [83]. An example is the photoisomerization of the retinal chromophore, where the ground and first excited electronic states become degenerate during the photoisomerization [84]. The multiconfigurational self-consistent field (MCSCF) wave function is obtained by optimising the orbitals and expansion coefficients of the multiconfigurational ansatz, allowing for a qualitatively correct description of the electronic structure [82]. Due to the exponential cost of constructing multiconfigurational methodologies, the complete active space self-consistent field (CASSCF) method [63] has become one of the most popular approaches. Here, only a subspace of molecular orbitals is treated as a multiconfigurational picture (called active space), while the rest is simulated in a much cheaper mean-field fashion. In CASSCF, the orbitals are divided into three parts [82]: the orbitals in the inactive space are always doubly occupied, the orbitals in the external space are always unoccupied, and a full CI description is employed for the orbitals in the active space. The former two orbital parts are treated similarly to HF.

The MCSCF wave function obtained from CASSCF, however, often contains only static but not dynamic electron correlation [82]. To recover the latter, multi-reference methods are typically employed on-top of a CASSCF calculation. Similar to electron correlation methods, these methods can be primarily divided into three categories: (i) multi-reference configuration interaction (MRCI) [85], (ii) multi-reference perturbation theory (MRPT) [86], and (iii) multi-reference coupled cluster (MRCC) [83]. Complete active space second order perturbation theory (CASPT2) belongs to the class of MRPT methods and is one of the most popular multireference methods, owing to its relatively low computational cost [87]. Several variants of this method exist, such as single-state (SS-CASPT2) and multi-state (MS-CASPT2) formulations [88]. Furthermore, *n*-electron valence state perturbation theory to second order (NEVPT2) is a related method, mainly differing by the choice of the zeroth-order Hamiltonian [89].

Multiconfigurational methods allow for the most accurate description of the electronic structure, particularly in cases where the electronic state is not well represented by a single reference state. However, these methods require a careful choice of the active space, and their computational costs scale exponentially with the size of this space. One of the most accurate methods is MRCI with single and double excitations and Davidson correction for size extensivity (MRCISD + Q) [90]. However, this approach is only feasible for rather small systems, such as the pyrimidine-based nucleobases with up to 14 electrons in 10 orbitals in the active space, whereas it was already too demanding for treating the purine-based nucleobases with 18 electrons in 13 orbitals [91]. Although conventional CASSCF/CASPT2 calculations are feasible for larger active spaces of up to around 18 electrons in 18 orbitals, their exponential scaling prevents application to significantly larger systems [92]. This means that accurately describing excited states in a biological system the size of a tetrapyrrole chromophore (106 atoms) is already challenging for multiconfigurational methods [93]. In contrast to these approaches, excited states that are well described by a single-reference picture can be treated using single-reference excited-state methods such as ADC or coupled-cluster-based approaches, as discussed below.

2.2.2. Time-dependent density functional theory

Many biomolecular functions involve electronically excited states: light absorption prepares a non-equilibrium electronic distribution that can relax into charge-transfer configurations, trigger photochemical reactions, or seed downstream electron and spin dynamics. In this sense, excited-state electronic structure is not just an extension of ground-state DFT, but the entry point for a large class of multiscale workflows that ultimately connect spectroscopy and biological function.

Time-dependent DFT (TDDFT) extends DFT to the time-dependent domain [94] and is widely used as a cost-effective approach to compute excited-state properties in systems that are too large for high-level wavefunction methods. In practice, TDDFT provides a set of multiscale-relevant properties: vertical

excitation energies and oscillator strengths enable the interpretation of optical spectra; transition densities and charge-transfer diagnostics inform exciton or electron transfer models; and (within QM/MM or snapshot-based protocols) ensemble calculations connect electronic excitations to the thermal structural fluctuations that dominate spectral broadening and energetic disorder in proteins [12,55]. These features make TDDFT particularly useful for photoreceptor proteins and biochromophores, where the environment modulates excitation energies and state character across conformational substates [95].

A recurring challenge is the reliable description of states with pronounced charge-transfer character, which often requires functionals with sufficient exact exchange or range-separated forms [96]. Because the relevant errors of electron-electron interactions are frequently system- and state-specific, benchmarking against higher-level methods is essential before drawing mechanistic conclusions about biophysical properties [97,98]. Conversely, when excited-state potential energy surfaces involve strong multireference character, TDDFT may become qualitatively unreliable, motivating the complementary role of multi-configurational approaches discussed above.

Most biophysical applications employ the linear-response formulation of TDDFT [97,98], which directly yields excitation energies and oscillator strengths of electronic systems. However, real-time (RT) TDDFT, in which the electron dynamics is explicitly simulated over time, has become increasingly relevant for non-equilibrium electron dynamics and ultrafast responses in complex environments [99] such as electron transfer in proteins.

2.2.3. Single-reference excited-state wavefunction methods

For excited states that can be described within a single-reference framework, one can employ wavefunction-based excited-state methods built on a preceding HF or correlated ground-state calculation. Prominent examples include coupled-cluster-based approaches such as CC2 [100] and algebraic diagrammatic construction (ADC) methods [101], which offer a favourable compromise between accuracy and computational cost [102].

From a formal perspective, ADC methods can be derived from the polarisation propagator [101] and are closely related to Green's function many-body theory [103], although in practice, they are typically applied in a working-equation framework without explicit reference to Green's functions.

In principle, these methods allow for a systematic improvement of excited-state accuracy, but higher-order approaches are typically limited to small molecular systems [104] and are therefore of limited applicability to large biomolecules.

2.3. Linking to larger scales

2.3.1. Force-fields and parametrization

Classical MM force fields, at their core, rely on quantum mechanical reference data [105,106], and commonly used parameters are refined to reproduce experimental data [107,108]. Intramolecular parameters reproduce fast vibrations and the intrinsic flexibility of molecules [109]. For embedding schemes, however, intermolecular Coulomb-interactions are often the most relevant to induce realistic polarisations of the QM region [11]. For common classical force fields, the electronic distribution is approximated using constant atomic point-charges, which fail to incorporate conformation-dependent intramolecular polarisations and multipoles [110]. The inclusion of specific lone-pair charges aims to correct this approximation for the most relevant cases [111]. A more holistic and accurate classical description is provided by the AMOEBA force-field [112], which accounts for electrostatic multipoles and even induced intramolecular dipoles at the expense of a significantly increased computational cost.

2.3.2. Embedding techniques

While electronic structure calculations are crucial for an accurate description of local properties such as electronic excitation or electron transfer processes, their ultimate flaw lies in the restricted number of atoms that can be considered due to the rapid growth of computational demand. In a biological environment, thousands of atoms influence the local electron density via Coulomb interactions, polarisation, and exchange coupling.

Embedding techniques offer a practical compromise: they retain a quantum-mechanical description of the chemically active region within a biological and complex system while treating the surrounding environment at a reduced level of theory [54]. The most widely used framework is the QM/MM approximation, in which the active site of a complex system is described by electronic structure theory, and the remainder is treated by classical force fields [45,51,53,54,113,114]. Depending on the partitioning, one may choose electrostatic embedding (where the QM region is influenced only by frozen MM point charges) or polarisable embedding (where the MM environment is polarisable). More sophisticated approaches employ polarisable force fields or explicit polarisable embeddings [115], which are particularly relevant for spectroscopic and electron transfer processes in proteins [116].

Beyond classical QM/MM, density-based embedding schemes such as frozen-density embedding (FDE) [117] and projection-based embedding [118] have gained attention. These methods embed the active subsystem into an electron density or effective potential derived from the surrounding environment, thus allowing polarisation and exchange effects to be incorporated more systematically. Such schemes have been successfully applied to transition-metal cofactors, photoreceptor proteins, and charge-transfer complexes, where strong electronic coupling between subsystems must be treated beyond point-charge models [119,120].

Finally, adaptive embedding strategies extend these concepts to dynamical simulations, where the chemically relevant region may evolve over time [8,11,121]. Together, these embedding techniques form the essential methodological bridge that connects the quantum accuracy required to describe electronic processes with the biological realism provided by large-scale simulations.

3. Classical regime

Classical simulation approaches form the workhorse layer of biomolecular modelling, offering an explicit, dynamical description of large systems at atomistic (and near-atomistic) resolution while remaining computationally tractable.

This section introduces the central ingredients of the classical regime: all-atom molecular dynamics to generate realistic trajectories and ensembles of protein motion, enhanced sampling strategies that target rare events and long-time transitions, and key methodological limitations arising from fixed bonding topologies and approximate force-field energetics. The discussion then broadens to coarse-grained molecular dynamics, which systematically reduces resolution to access larger length and time scales while retaining the interactions most relevant to structure, thermodynamics, and kinetics.

3.1. All-atom molecular dynamics

Atomistic molecular dynamics is a computational method that utilises the laws of classical mechanics to simulate the time evolution of a molecular system, with force fields providing a description of interatomic interactions. A classical description of the system dynamics allows for the efficient simulation of atomistic biomolecular systems at the lower μs timescales for 10^5 atoms [122]. As a result, MD simulations have become the central tool for investigating the complex dynamics of biomolecular systems, providing deep insights into their physiological functions [123]. By integrating Newton's equations of motion, MD tracks the positions and velocities of atoms over time, providing a detailed view of molecular motions and interactions. This makes it possible to study, among others, conformational changes, binding processes, or allosteric networks [14,124–127], and other dynamic phenomena that are difficult to capture or analyse experimentally.

Coupling the simulation principle with computational advances, software packages like GROMACS [128], AMBER [129], NAMD [130], MBN Explorer [131] and OpenMM [132] can perform simulation calculations efficiently, allowing for the probing of ever longer timescales. Enhanced sampling techniques and kinetic modelling substantially extend the time scales of the processes that are accessible with MD simulations, thus bridging QM-derived energetics with the long timescale behaviour of realistic biomolecular systems.

Atomistic MD simulations are positioned perfectly in the middle of the multiscale framework (see Figure 1). In particular, atomistic resolution and robust parameterisation of the force fields based on QM calculations allow for the efficient integration of environmental dynamics into the QM/MM framework (see Section 2.3). Furthermore, MD trajectories can be used to extract general biophysical quantities such as electrostatic potential [28,133–136] or diffusion coefficients [137–139], which are essential for various continuum models of biomolecular systems [140–142]. Finally, high-resolution information on biomolecular dynamics can be used to guide coarse-grained models that preserve the thermodynamics and kinetics of biomolecules [143–146].

3.2. Sampling techniques

Although recent advances in software and hardware make MD simulations suitable for studying the dynamics of e.g. viral spike proteins [147], parasite-host interactions [148] or ion channels [149] at μs time-scales [150], many biologically relevant processes occur at substantially longer times (>ms). Driven by rare events, these processes often rely on conformational transitions between metastable states that are separated by large free-energy barriers. To overcome the limitations of standard MD simulations and to comprehensively sample biomolecular conformational space, a number of enhanced sampling techniques have been developed over the last 50 years [151]. When a process of interest can be effectively described by one or two collective variables (CV), the sampling can be enhanced by applying a biasing potential along the CVs. The bias can be a fixed harmonic potential, as in Umbrella Sampling simulations [152], or applied in an adaptive manner, as in metadynamics simulations [39,153,154]. In turn, the free-energy landscape of even rarely visited regions of the conformational space can be comprehensively quantified by unbiasing the resulting probability density with methods such as the weighted histogram analysis method (WHAM) [155] or the multistate Bennett acceptance ratio estimator (MBAR) [156]. Alternatively, the sampling can be enhanced by extending the simulated ensemble either by allowing exchange between multiple thermodynamic states (replica exchange simulations [157–159]) or by introducing an additional variable that governs the dynamics of the biasing potential, as in the accelerated weight histogram (AWH) method [160]. Finally, the adaptive seeding techniques avoid the introduction of an explicit bias into the underlying dynamics of the system, relying instead on a large number of relatively short simulation trajectories that are seeded in a way that promotes the exploration of conformational space. In particular, the weighted ensemble (WE) method [161] can be used to sample multiple interstate transition pathways, providing a rigorous estimation of both rate constants and equilibrium distributions [162]. Importantly, the WE method is not limited to all-atom MD simulations and can be efficiently applied to various kinds of stochastic simulations to study biological systems at mesoscopic and cellular scales [162].

3.3. Limitations: energies, non-equilibrium systems, chemical reactions

Although classical MD simulations provide detailed insights into the dynamics of biomolecular systems, the method has a number of methodological and practical limitations. First, the dynamics of a simulated system are governed by classical equations of motion, with atoms described as point particles. Therefore, the electronic degrees of freedom are ignored, and effects such as charge redistribution, as well as the formation and breakage of covalent bonds, are disregarded. As a result, both partial atomic charges and intramolecular connectivity remain fixed in a typical MD simulation, although the latter limitation can be partially alleviated by reactive force fields [163] and constant pH simulations [164]. Second, MD simulations strongly rely on the force fields that define the potential energy of the inter-atomic interactions by specifying their functional form as well as particular parameterisation. Although the force-field parameters are derived from experimental and QM data, the resulting potential energy is only an approximation of the true potential energy. Finally, there are practical limits on both the simulation time and system size that can be effectively handled by atomistic MD simulations. Although, in principle, classical MD simulations can already achieve the millisecond regime for a million-atom system using special-purpose machines such as Anton3 [165], typical biomolecular simulations rarely exceed a few microseconds. Whereas relatively fast biological processes like ion conduction can be properly sampled at such time scales [133,166,167],

slow processes and systems at the cellular scale are still beyond the reach of conventional atomistic MD simulations. However, atomistic MD simulations can be integrated into multiscale approaches to construct larger-scale systems that can be simulated for longer times using coarse-grained and continuum models [168].

3.4. Coarse-Grained molecular dynamics

All-atom simulations resolve classical mechanics at the highest possible resolution; however, one is swiftly limited by the available computational resources; many questions, such as the assembly of large complexes, membrane remodelling, or phase separation, demand larger systems and longer microsecond timescales than are typically practical with all-atom simulations alone. Coarse-grained (CG) models address this shortcoming by grouping atoms into beads, reducing the degrees of freedom and the cost of nonbonded calculations while retaining the interactions most relevant to the problem of interest.

A practical dynamical benefit follows from Newton's second law ($a = F/m$): because CG beads carry greater mass, the fastest motions slow down. Coupled with smoother CG potentials that suppress high-frequency bond and angle vibrations, this shifts the highest frequencies downward and permits a larger integration time step without compromising numerical stability. In effect, one can access longer trajectories and larger systems in a computationally feasible manner while keeping most of the features needed for interpretation. The potential energy surface, which is smoothed out by the coarsening approach, also facilitates conformational transitions, which further enhance the exploration of configurations at the expense of obtaining systematically increased diffusion rates and transition rate constants [169].

Modern CG force fields are either built to balance the trade-off between resolution and speed, or they focus on a particular research question. We provide selected examples of some CG force fields [170] including MARTINI 3 [171–173] which provides a broad set of bead types and calibrated interaction parameters for proteins, lipids, and small molecules. SIRAH [174] offers protein- and nucleic-acid-focused mappings that support backmapping when local atomistic detail is required. For intrinsically disordered proteins and condensates, residue-level models such as CALVADOS [175] preserve sequence-specific interactions while making the exploration of conformational ensembles and phase behaviour tractable. These examples highlight the versatility of the CG approach, with different force fields being more suited for different systems. For instance, AWSEM [176] is suited to study protein folding, SDK [177] is used for soft matter systems, the Cooke-Deserno model [178] is applicable for large scale membrane models, and UNICORN [179,180] is designed for more heterogeneous systems, among others.

CG force fields are often derived to reproduce the structural and thermodynamic behaviour observed in atomistic simulations. All-atom MD provides the reference data-such as radial distribution functions or force correlations-from which effective CG potentials are obtained through inverse techniques like iterative Boltzmann inversion, force matching, or relative entropy minimisation [172,181]. These inverse technique methods use Monte Carlo or gradient-based optimisation to refine CG interactions until key observables match their atomistic counterparts. Alternatively, several CG force fields are parameterised directly from experimental data. For instance, partitioning free energies or interfacial tensions are commonly parameterised through experiments, yielding empirically grounded, transferable models [182].

4. Towards larger scale methods

Moving beyond the regime where atomistic or coarse-grained trajectories can directly resolve the phenomena of interest, biomolecular physics increasingly relies on mesoscale descriptions that capture collective behaviour, geometry, and long-time kinetics.

The section introduces complementary routes to that scale. Triangulated surface models, which represent membranes and other soft interfaces with molecularly informed elastic properties, as well as kinetic modelling frameworks that compress complex dynamics into transitions between a small number of states, are selected models presented here. Both approaches are naturally embedded in multiscale workflows, where parameters and state definitions are informed by lower-resolution simulations and experiments, enabling quantitative predictions for large systems and slow, often non-equilibrium processes.

4.1. Mesoscale simulations

Although CG MD can provide a description of full cells [183], accessible timescales, typically on the order of microseconds, remain insufficient to capture large-scale structural remodelling. Furthermore, advances in experimental techniques such as cryo-electron microscopy and tomography have enabled the observation of biological systems at unprecedented spatial scales, revealing fine structural details beyond the resolution of all-atom and coarse-grained models [184–187]. At this scale, the intrinsic heterogeneity of biomolecules becomes increasingly important, rendering traditional macroscopic mean-field approaches inadequate. This emerging mesoscale regime, therefore, calls for new modelling frameworks in which selected biomolecules are represented explicitly, while others, such as lipids, are treated implicitly [188]. In recent years, significant progress has been made in mesoscale modelling. Notable examples include simulations of the full cell cycle of genomically minimal cells [189], as well as the development of open-source tools for dynamically triangulated surfaces, such as FreeDTS, TriMem, and MeshMP, which model membranes at this scale [190–192]. Additional frameworks include Cytosim, which captures cytoskeletal dynamics, and recent methods by Chiang et al. for modelling chromosome organisation [193]. These advances have enabled a range of new biological insights, including nuclear pore modulation in the double membrane of the cell nucleus driven by membrane tension [194], membrane-mediated interactions in protein systems [195], and the non-equilibrium dynamics of membranes coupled to the cytoskeleton in red blood cells [196].

Mesoscale modelling systematically averages out molecular degrees of freedom that have negligible impact on large-scale structure, thereby enabling the study of collective behaviour while retaining a meaningful level of molecular fidelity. This approach allows simulations to access biologically relevant spatiotemporal scales that are typically inaccessible to AA and CG MD alone, while still being parameterised and validated against these higher-resolution methods [197]. However, reduced mesoscale resolution inevitably leads to a loss of detailed molecular information. This limitation can be addressed through targeted, computationally feasible CG MD simulations, in which structural configurations obtained from mesoscale models are transformed into CG representations using backmapping techniques [173]. Together, this hierarchical strategy establishes a robust multiscale simulation framework for cellular systems, enabling the exploration of large length and time scales while preserving an appropriate level of molecular realism [198].

4.2. Kinetic modelling

Kinetic modelling aims to describe a biochemical system as a set of just a few interconverting states while abstracting from the fine details of the system dynamics. The approach focuses on the interplay between clearly defined biochemical states of the system, providing insights into the system behaviour at the macroscopic level. The probability of the interconversion between the states is defined by rate constants that, together with the state definitions, constitute the kinetic model. Traditionally, kinetic models have been primarily built based on experimental data to reproduce the time courses of particular observables [199]. However, recent progress in biomolecular simulations has made it possible to directly link the kinetic modelling of a biomolecular system with its underlying physics-based dynamics. In particular, kinetic modelling can be efficiently combined with low-level quantum simulations to study macroscopic phenomena such as radical-based magnetoreception [33,34,200–202]. In such an approach, the core process is described by spin-dynamics simulations, whereas additional rate constants are incorporated to account for longer time-scale transitions between different states. In turn, connection of the long-scale kinetics to the underlying dynamics of the biomolecule can be established by utilising classical MD simulations to construct Markov state models (MSM) [203,204]. In this case, MSM describes kinetics in terms of the transitions between metastable states in a low-dimensional space. Such a space can be based on the CVs with the slowest dynamics, which can be defined by time independent component analysis (tICA) [205]. Importantly, MSM can capture system kinetics at time scales that go far beyond the length of the individual simulation trajectories while retaining detailed structural information at atomistic resolution [206–208]. The resulting model provides straightforward interpretation in terms of the transitions between the structurally-defined metastable states. Construction of an MSM involves multiple steps, such

as the choice of the right features and the number of states, which often require system-specific knowledge [209]. However, many of those steps can now be automated by utilising a deep learning framework based on the variational approach for Markov state processes [210,211]. Furthermore, to promote connection with experiments, the model can be additionally augmented with experimental data [212]. Thus, kinetic modelling now provides a means to bridge physics-based approaches at the level of atoms and individual spins with long time-scale biological phenomena in the framework of multiscale simulations.

5. Integration of artificial intelligence into multiscale modelling

The most fundamental tool that machine learning (ML) offers for multiscale modelling is machine learned interatomic potentials (MLIPs) [213]. MLIPs provide an approach to condensing information on chemical interactions into a neural network. Most MLIPs predict forces and energies, with errors as low as 0.2 kcal/mol for near-minimum conformer energies and torsion profiles of chemical bonding when compared to the gold standard CCSD(T) methodology [214]. DFT data routinely serve as the ground truth during training to allow for high chemical diversity, which ideally also includes various charge and spin states, as, for example, in the meta-GGA DFT basis set OMol25 [215]. MLIPs aimed at generalisation across the chemical space approximate this DFT data through graph-neural network architectures [216] using vector-equivariant input features that are constructed using Clebsch-Gordan coefficients [217]. In situations where error-control and active learning for a specific molecular system are more important than generalisability across different molecules, gaussian process regression is an appropriate alternative to graph-based architectures [218,219].

The complexity reduction of MLIPs allows to approach 1/100 of the performance of classical mechanics on a single GPU [220,221], while the CPU-bound calculations of a meta-GGA functional are 10^5-10^7 times slower than a MLIP. For biophysical simulations, SO3LR stands out in particular due to its incorporation of long-range interactions [220], but other implementations, such as MACE [221] or AIMNET [222], should not be disregarded. To achieve the goal of generating reasonable atomistic configurations, more routes beyond MLIPs are possible. Machine learned classical force fields [223,224] can avoid the rigidity of tabulated classical force fields, and neural network representations can provide a concise link to coarse-grained representations [225–227]. To avoid the resource demands and sample correlations of molecular dynamics entirely, generative models [228] can learn to predict varying protein conformations directly [229–231].

The versatility of ML allows it to enhance chemical descriptiveness beyond the generation of molecular conformers and energies. MLIPs trained on the necessary input features can learn to predict any molecular property of interest, including, for example, atomic polarizabilities for the computation of infra-red spectra [221], environment-sensitive proton-transfer processes [232], or intricate excited state dynamics [233]. To integrate MLIPs into into multiscale schemes, suitable MLIPs must incorporate appropriate descriptions of long-range intermolecular interactions, including electrostatics, which are highly important in complex molecular systems. These interactions are accounted for in machine-learned electrostatic embedding, which incorporates molecular polarizability into the training data to predict the response of the QM (or ML) region based on the point charge environment [234,235]. If, however, intermolecular interactions are already satisfactorily handled by an MM description, ML/MM mechanical embedding schemes can be used to correct intramolecular energy contributions. An exemplary application is the evaluation of the strain energy contribution of ligands within a binding pocket [236,237].

6. Case studies in biomolecular physics

The landscape of multiscale problems in biophysics is vast: proteins span an extraordinary range of sizes, architectures, and dynamical regimes, and their function often emerges from a subtle interplay between electronic structure, local chemical reactivity, conformational motion, and the surrounding solvent environment. This diversity translates into a corresponding diversity of functional mechanisms ranging from fast, localised excitations to slow, collective rearrangements, so that no single length or time scale is sufficient to capture the full physical picture.

In this section, a set of representative challenges is discussed, emphasising their intrinsically multiscale character, highlighting where coarse-grained descriptions succeed, where atomistic detail becomes indispensable, and how couplings between scales can generate qualitatively new behaviour.

6.1. Excitation properties in biomolecular systems

Electronically excited states in pigment–protein complexes are shaped by the interplay between intrinsic chromophore properties and the multiscale dynamics of their environment. Light-harvesting systems provide a paradigmatic example of how excitation propagates across spatial and temporal scales and ultimately supports biological function. Upon photon absorption, chlorophylls or bacteriochlorophylls form localised excitations that, when resonance couplings are sufficiently strong, give rise to delocalised excitonic states spanning multiple pigments. Theoretical descriptions of such exciton manifolds go back to the Förster's dipole–dipole theory [238], exciton–phonon coupling models [239], and more general approaches that include system–bath interactions [240]. For comprehensive discussions of structure-based exciton Hamiltonians, pigment–protein coupling, and excitation-energy transfer mechanisms in photosynthetic light harvesting, Ref [241]. provides a useful entry point. In the present section, photosystem II (PSII) is used as the primary example, while related insights from the Fenna–Matthews–Olson (FMO) complex, the bacterial light-harvesting complex 2 (LH2), and the plant light-harvesting complex II (LHCII) are mentioned to highlight the generality of the underlying principles.

Structure-based modelling of the PSII core complex shows how low-energy trap states in CP43 and CP47 regulate excitation transfer to the reaction centre and can render the overall excited-state decay limited by transfer into these traps [242]. A central multiscale ingredient in PSII is that, on ultrafast time scales, excitonic energies and couplings are continuously modulated by thermal fluctuations of the protein matrix. Atomistic molecular-dynamics-based approaches have been used to map site-energy fluctuations onto spectral densities, thereby providing an explicit description of how environmental motions couple to excitonic degrees of freedom [243]. In PSII, these fluctuations reshape the exciton landscape, generate static and dynamic disorder, and influence the transfer pathways that funnel excitation toward the reaction centre.

Related multiscale concepts have also been applied to other pigment–protein complexes. In the bacterial light-harvesting complex 2 (LH2), atomistic MD- and QM/MM-based exciton models have shown how coupling to charge-transfer (CT) states and environment-dependent local-exciton–charge-transfer (LE–CT) state interactions modulate static disorder and absorption-band shapes [244]. In the Fenna–Matthews–Olson (FMO) complex and in plant light-harvesting complex II (LHCII), fluctuations of local electrostatic fields have likewise been shown to reshape excitonic energy landscapes and mediate ultrafast relaxation pathways [243]. These observations support the broader picture that excitation transport in pigment–protein complexes is governed by the interplay between electronic couplings and environmental dynamics, as also captured by reduced open-system descriptions [240].

On longer time scales, slower conformational rearrangements of the protein scaffold regulate functional outcomes. In LHCII, for example, switching between light-harvesting and photoprotective states involves changes in pigment geometries and local dielectric environments, which alter excitonic couplings and open energy-dissipation pathways [245,246]. Recent multiscale QM/MM–MD studies linking excited-state properties, spectral densities, and conformational ensembles have further illustrated how environmental fluctuations can support both efficient light harvesting and regulated photoprotection [114,247].

Together, these examples show that electronically excited states in biomolecular chromophore assemblies do not evolve independently but are continuously modulated by a hierarchy of environmental motions. Multiscale modelling, combining quantum chemistry, atomistic molecular dynamics, and larger-scale conformational sampling, provides a framework for understanding how biological systems maintain efficient, robust, and adaptable photophysical functionality.

While excitonic energy transport in antenna and antenna-associated pigment–protein complexes illustrates how electronic excitations are shaped by multiscale environmental dynamics, similar multiscale principles also govern electron-transfer processes in reaction centres and other redox-active biomolecular assemblies.

6.2. Electron transfer processes in biomolecular systems

Electron transfer in biomolecular systems spans a wide range of time scales due to the interplay between fast electronic dynamics and slower nuclear motions of the environment [10]. On the purely electronic level, electron transfer can occur on the order of tens of femtoseconds, reflecting both the donor-acceptor electronic coupling and the intrinsic energy difference between the initial and final states [248]. In realistic biomolecular settings, however, the transferring electron is coupled to local vibrational modes, which modulate both the electronic energies and their coupling [249]. Moreover, conformational fluctuations of the protein matrix introduce structural changes on longer time scales, which may act as gating mechanisms that enable or suppress electron transfer events [250,251]. Thus, electron transfer processes cannot be understood solely from a purely electronic perspective but require consideration of nuclear dynamics at different scales and environmental fluctuations. Multiscale modelling provides the bridge between these scales.

Multiscale simulations that combine long-timescale atomistic MD with QM/MM embedding [51] and excited-state quantum chemistry can describe in detail the working principle and excitation pathway of the PSII reaction centre [252]. By computing electrochromic shifts for pigment assemblies within the electrostatic field of the protein matrix, it was shown that electrostatic asymmetries lead to an ordering of the molecular site energies, placing Chl_{D1} lowest on the active D1 branch, thereby identifying it as the primary electron donor, while $Pheo_{D1}$ is the exclusive initial acceptor [253]. Excited-state calculations excluded low-lying CT states within the P_{D1}–P_{D2} 'special pair' (cf. Figure 2). Instead, the low-energy spectrum is dominated by two CT states, namely $Chl_{D1}^{\delta+}\ Pheo_{D1}^{\delta-}$ and $P_{D1}^{\delta+}\ Pheo_{D1}^{\delta-}$. Their energies are further

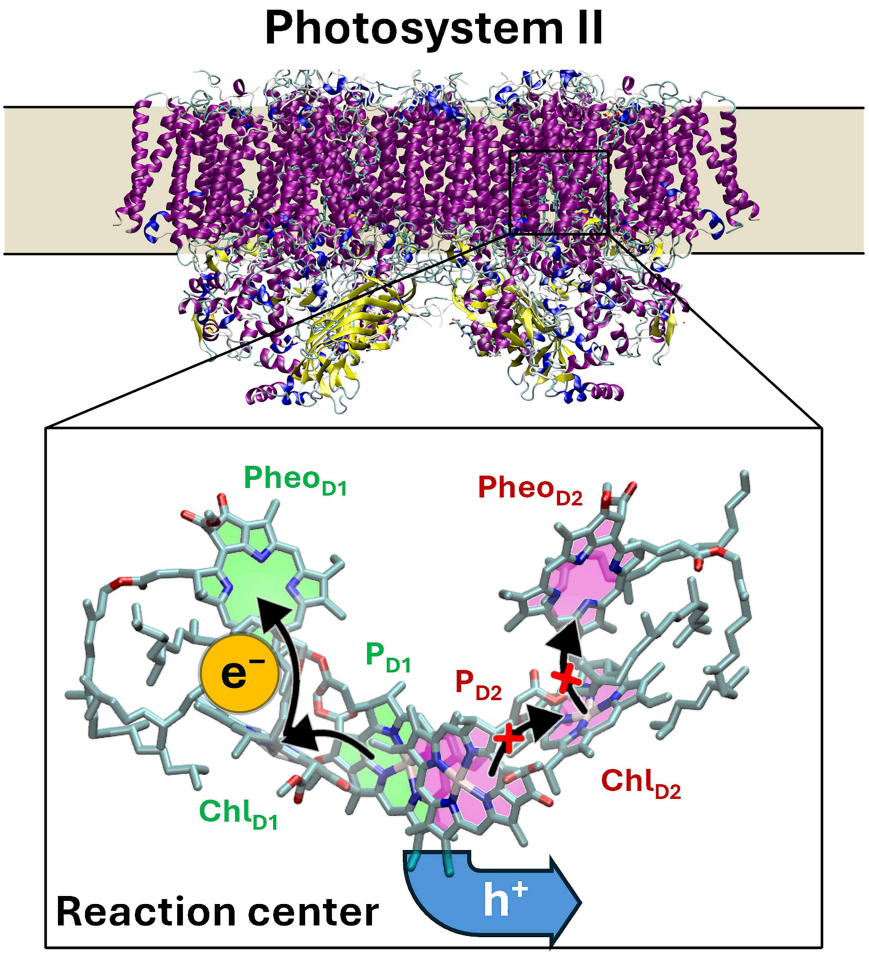

Figure 2. Top: visualisation of photosystem II (PSII) in the thylakoid membrane of oxygenic photosynthetic organisms. Bottom: zoom-in on key components in the PSII reaction centre and their involvement in the primary charge-separation process.

broadened by conformational dynamics, providing a mechanistic route for far-red charge separation (beyond chlorophyll's 'red limit'). Combining these QM/MM results with Landau–Zener-type non-adiabatic transitions yields the electron kinetics. This exhibits two operative pathways with distinct timescales: a fast, short-range $Chl_{D1} \rightarrow Pheo_{D1}$ route (~100 fs to a few ps) and a slow, long-range P_{D1} $P_{D2} \rightarrow Pheo_{D1}$ route (~100 ps to ns), both funneling to $(P_{D1}P_{D2})^{+}Pheo_{D1}^{-}$ [254]. Together, this multiscale protocol, including explicit electrostatics, excited-state methods, and dynamics-aware kinetics, provides a picture of PSII's primary charge separation that is aligned with experiments.

6.3. Magnetic field effects in biomolecular systems

Magnetic field effects in biology provide a striking example of how quantum spin dynamics may transfer into physiological function. A prominent candidate mechanism is the radical pair mechanism, which has been proposed as the physical basis for effects observed in biological systems, such as lipid peroxidation in membranes [255] or magnetoreception in migratory birds, with cryptochrome proteins acting as primary sensors for the geomagnetic field [27,40,256]. In the cryptochrome scenario, photoexcitation initiates a cascade of electron transfer steps that generates a spin-correlated radical pair (two spatially separated unpaired electrons). As sketched in Figure 3, coherent singlet-triplet interconversion during the radical-pair lifetime is driven by internal spin interactions and can be perturbed by weak external magnetic fields. Because singlet and triplet radical-pair states typically follow different chemical pathways, the spin dynamics are encoded in spin-selective reaction yields and can thereby modulate downstream signalling.

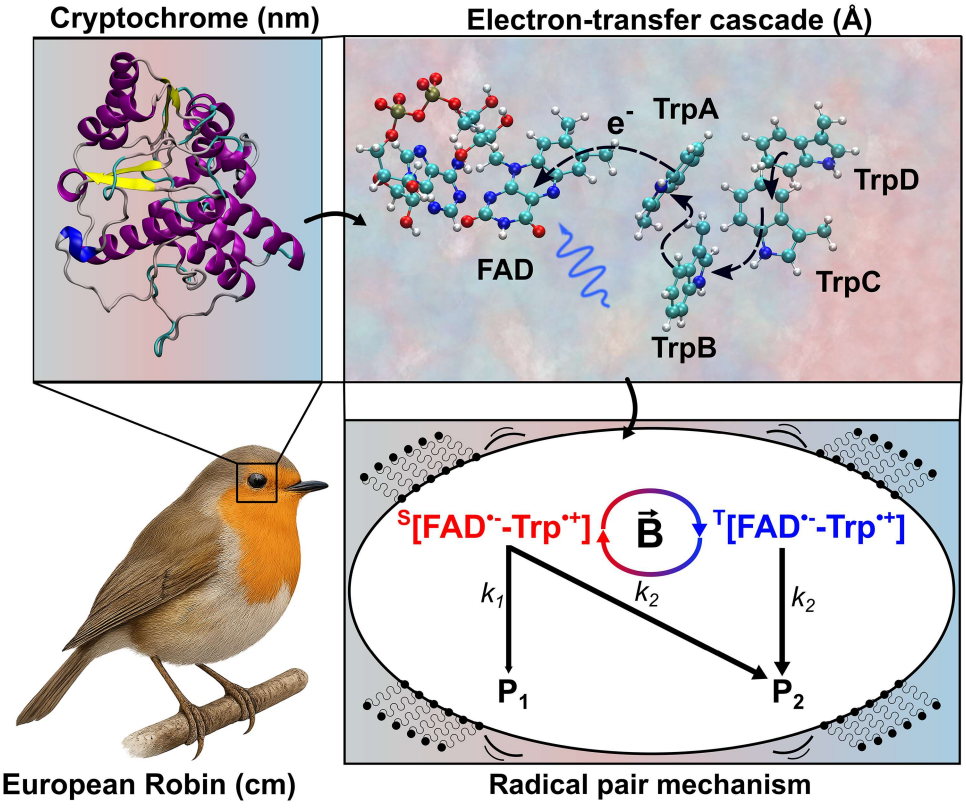

Figure 3. Schematic illustration of the radical pair mechanism proposed for avian magnetoreception. Cryptochrome 4a in the retina is proposed to be involved in magnetic sensing in migratory birds such as the European robin. Upon blue-light excitation, the flavin adenine dinucleotide (FAD) cofactor initiates an electron transfer cascade along a chain of tryptophan residues, forming a spin-correlated radical pair. Hyperfine interactions as well as electron–electron exchange and dipolar couplings drive coherent singlet–triplet evolution, which can be perturbed by an external magnetic field $\vec{B}$. Spin-selective reaction channels then translate spin dynamics into product yields. A central multiscale challenge is that protein and solvent motions modulate the spin interactions and induce decoherence, which constrains magnetic sensitivity on geomagnetic field scales of $\sim 50\mu$T.

A key difficulty in modelling such processes is their inherently multiscale character. On the electronic scale, hyperfine couplings and electron-electron spin interactions (exchange and dipolar couplings) govern the coherent evolution of the spin-correlated radical pair [40,257,258]. On the atomistic scale, the conformational dynamics of the protein modulates these interactions by changing relative distances, orientations, and the local electrostatic environment of the radicals [21,35,259]. At longer time and length scales, the functional lifetime of the spin-correlated radical pair, which can extend into the microsecond regime [258], necessitates a coupled description of quantum spin dynamics, dissipative environmental motion, and chemical reaction kinetics. Bridging these scales is essential for connecting quantum-level spin interactions to measurable biological responses.

Recent work has demonstrated the feasibility of this connection. Xu et al. [27] provided experimental evidence for magnetic field effects on cryptochrome-mediated radical pairs, underscoring the biological relevance of long-lived spin coherence. Complementary theoretical studies [33,40,260] have developed multiscale spin-dynamics frameworks that couple quantum spin evolution to protein fluctuations and environmental noise using all-atom molecular dynamics and density functional theory. These approaches enable the construction of time-dependent spin Hamiltonians from structural ensembles and allow one to quantify how interaction fluctuations shape singlet-triplet interconversion and reaction yields.

At the same time, the quantitative understanding of decoherence in *wet and noisy* biomolecular environments remains a central bottleneck. Stochastic fluctuations of hyperfine and electron-electron couplings can rapidly dampen spin coherence and thereby suppress, reshape, or wash out weak-field effects [40,258,259]. Importantly, however, fluctuations are not universally detrimental. If environmental motion modulates inter-radical interactions in a structured way, it can also open additional singlet-triplet mixing pathways and thereby amplify magnetic field effects. Indeed, Smith et al. showed that the driven modulation of the inter-radical distance can enhance geomagnetic-field sensitivity in strongly coupled radical pairs by inducing additional non-adiabatic singlet-triplet transitions [261]. Disentangling when environmental dynamics primarily induces decoherence and when it can instead enhance sensitivity is, therefore, a key open challenge for predictive multiscale models of biomolecular magnetosensitivity.

6.4. Coarse-grained membrane phenomena

Cholera remains a serious global health burden, causing substantial mortality and economic disruption in regions without reliable access to clean water [262]. The disease is driven by cholera toxin, an AB5 toxin secreted by Vibrio cholerae, whose B-subunit pentamer (CTxB) mediates the initial attachment of the holotoxin to host-cell membranes. CTxB binds with high affinity to the ganglioside GM1, a glycosphingolipid in the outer leaflet of the plasma membrane, and this interaction is known to reorganise the local membrane structure [263]. All-atom MD simulations of CTxB bound to GM1-containing bilayers capture the key structural features of the toxin-lipid interface. The trajectories show stable engagement of GM1 at the five identical binding sites of the pentamer on the membrane surface. By reconstructing the bilayer shape from atomic coordinates, the simulations demonstrate that a single CTxB generates a localised curvature of the membrane beneath the protein [264].

At the next step in the resolution, coarse-grained simulations provide the scale needed to translate atomistic binding geometry into membrane-level mechanical consequences. Using Martini 3 [172], CTxB is simulated on membrane patches large enough for the curvature to develop and persist over microsecond trajectories without being quenched by the periodicity of the simulation box, see Figure 4. The pentamer associates readily with GM3-containing bilayers and remains membrane-bound throughout the simulations, and two-dimensional density maps show a robust enrichment of GM lipids directly beneath the protein. Curvature analysis of the reconstructed membrane surface reveals that a single membrane-associated CTxB induces a distinct, localised curvature, closely matching the magnitude inferred from atomistic calculations but now resolved across a substantially larger spatial footprint [24]. Additionally, the CG approach allows for the simulation of multiple proteins on the membrane surface, as has been shown for Annexin [265].

A natural next step is to apply the same mesoscale strategy used for Shiga toxin to CTxB [197]. In the Shiga toxin containing system, curvature values extracted from molecular simulations were implemented directly in a dynamically triangulated surface model, yielding large (approx. 100 nm) tubular invagination.

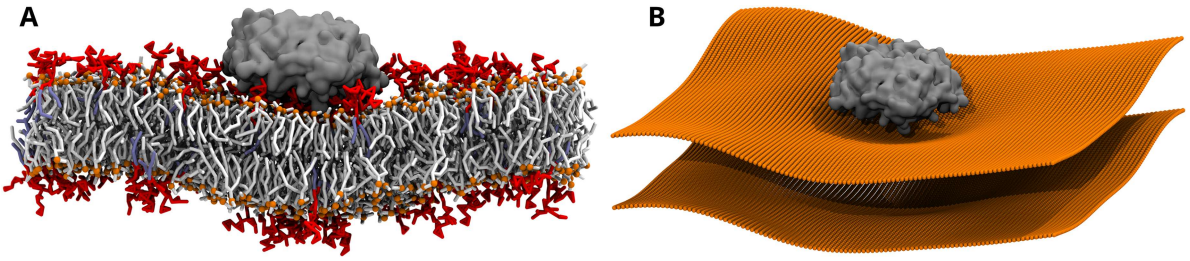

Figure 4. Cholera toxin subunit B on a POPC-GM1 containing membrane. (A) A cross section of the membrane, visually confirming induced curvature. (B) A Fourier-surface fit based on the head group of the POPC lipids highlight the magnitude of the curvature of the membrane.

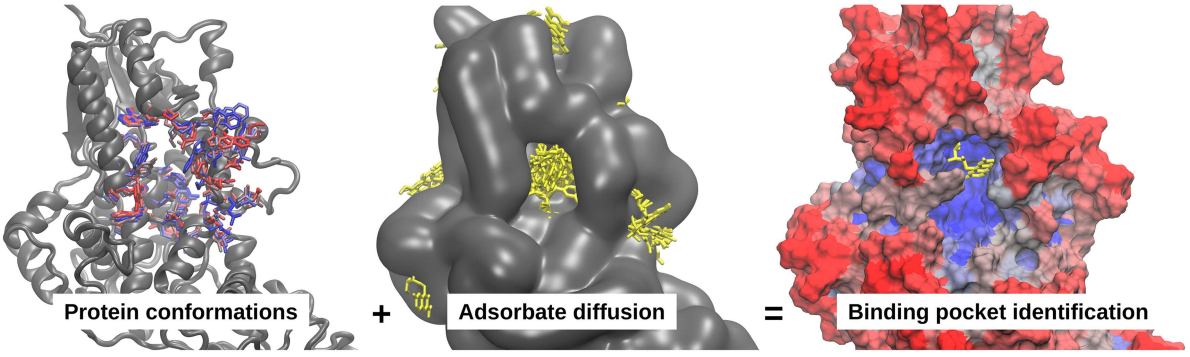

Figure 5. Proteins are flexible structures that can be found in various conformations (coloured sidechains to the left). Small adsorbates explore this dynamic interaction surface (middle). Combining information from the protein and adsorbate dynamics reveals the most favourable binding sites (right).

Running an analogous mesoscale simulation with CTxB, while using the induced curvature values obtained from coarse-grained trajectories, would complete the multiscale progression [266].

Generating a detailed understanding of how Shiga and cholera toxins enter cells can directly inform the development of future drug delivery strategies, as their subunits can be repurposed to carry and deliver therapeutic molecules.

6.5. Diffusion of adsorbates within proteins

Molecular adsorbates in or on proteins are often central to their function [30,267,268]. However, their binding configurations are frequently only temporary intermediates. The light-sensitive molecule retinal, which is central to human vision, needs to unbind from its activated receptor in order to be recycled into its ground state form [267]; the terminal parts of the respiratory complexes temporarily bind ubiquinol and O2 to produce an electrostatic gradient across the membrane [30]; the binding kinetics of pharmaceutical ligands are relevant for predicting their efficacy as competitive inhibitors [268].

A typical way to reduce the complexity of the aforementioned process is to decouple the dynamics of adsorbate diffusion from the internal protein dynamics. In molecular docking approaches, for example [269], the adsorbate freely explores the landscape of the approximately static protein, which reduces the parameter space to that of the usually significantly smaller adsorbate, as well as some selected flexible parts [270]. Figure 5 illustrates how the decoupling of dynamics can be executed in practice when studying the binding of the chromophore 8HDF to cryptochrome 3 from *Arabidopsis thaliana*. Using MD simulations, the protein conformations were sampled to generate an ensemble that was subjected to docking calculations. This allowed for the reproduction of the known molecular binding pocket. If one were to delve deeper, the coupling of protein and ligand conformations can be accounted for in the context of end-point

approximations such as alchemical free energy perturbations [271,272] or even more accurately via enhanced sampling strategies designed for unbinding calculations [273–275].

We note here that the current state of ML co-folding models that generate protein-adsorbate complexes [276–278] has been shown to learn patterns of binding modes rather than the underlying physical interactions [279,280]. The application of co-folding is therefore currently limited to within-sample predictions, and results should always be sanity-checked and validated, e.g. through docking approaches.

7. Outlook and future perspectives

Over the past decades, multiscale modelling in biomolecular physics has evolved from a collection of largely independent techniques into an increasingly coherent toolbox [12,281]. Quantum electronic-structure methods, atomistic and coarse-grained molecular dynamics, kinetic and continuum models, and data-driven approaches can now be combined to address concrete biological questions. At the same time, most current workflows remain problem-specific and require substantial manual expertise at each interface between scales. A central future challenge is, therefore, not the development of ever more specialised individual methods, but the systematic integration of existing ones into robust, interoperable, and predictive multiscale frameworks.

One key direction is the automation and standardisation of information transfer across scales. This includes reliable pipelines for deriving force-field and coarse-grained parameters from quantum calculations, back-mapping between coarse-grained and atomistic resolutions, and embedding schemes that couple localised quantum descriptions to realistic, fluctuating environments. Here, machine-learning models will play a central role as flexible, controllable surrogates that can approximate expensive quantum or mesoscale calculations while retaining a clear link to underlying physical observables. Examples include ML-accelerated QM/MM schemes, machine-learned interatomic potentials that can be embedded into classical or coarse-grained environments, and data-driven kinetic models that connect atomistic simulations to long-time biological function.

A second crucial development will be the explicit treatment of uncertainty and error propagation throughout multiscale workflows. As modelling chains become longer, quantifying how approximations at one level affect observables at another will be essential for predictive power. This demands rigorous benchmarking against experimental data but also the adoption of ensemble-based strategies, sensitivity analyses, and Bayesian or probabilistic formulations that associate confidence estimates with model outputs. Joint experimental-computational protocols, in which spectroscopic, structural, and single-molecule data are directly integrated into model construction and refinement, are likely to become standard.

Finally, advances in high-performance computing, software engineering, and open science will shape how multiscale models are used in practice. Exascale hardware, GPU-centric algorithms, and modular open-source codes will enable routine simulations that couple quantum dynamics, large biomolecular assemblies, and mesoscale descriptions within a single workflow. At the same time, community benchmarks, shared datasets, and interoperable formats will lower the barrier to applying such methods to new systems. In the long term, these developments point toward digital, physics-based 'twins' of biomolecular systems in which electronic processes, conformational dynamics, and cellular-scale behaviour are described within a unified multiscale framework. Such models will not only deepen the mechanistic understanding of biomolecular function but also guide the rational design of biomimetic materials, sensors, and therapeutic strategies.

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Author contributions

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