Multiscale Modelling of Molecular Processes for Biomedical and Nanotechnology Applications with MBN Explorer

Andrey V. Solov'yov

Abstract This chapter introduces MesoBioNano Explorer (MBN EXPLORER) (Solov'yov et al. J Comput Chem 33:2412–2439, (2012), [1]), a software package for the advanced multiscale simulations of complex molecular structure and dynamics and highlights some of its biomedical and nanotechnology applications. MBN EXPLORER has many unique features, a wide range of applications in Physics, Chemistry, Biology, Material Science, and in related Industries. It is suitable for classical molecular dynamics, Monte Carlo and relativistic dynamics simulations of a large range of molecular systems of different kind, such as nano- and biological systems, nanostructured materials, composite/hybrid materials, gases, liquids, solids and various interfaces, with the sizes ranging from atomic to mesoscopic. MBN EXPLORER can be exploited together with MBN Studio (Solov'yov et al. MBN Studio, (2015), [2]), a specially developed graphical user interface.

1 Introduction

The Meso-Bio-Nano (MBN) Science is the interdisciplinary field of research studying structure-formation and dynamics of animate and inanimate matter on the nano- and the mesoscales. It bundles up several traditional topics in theoretical physics under a common theme. The range of open challenging scientific problems in this field is rather broad. They may include: structure and dynamics of clusters, nanoparticles and biomolecules; clustering, self-organization, growth and structure-formation processes, their multiscale nature and scaling laws; assemblies of clusters/nanoparticles and bio-macromolecules, hybrid bio-nano systems, nanostructured materials; surface phenomena; nanoscale phase transitions; thermal, optical and

A.V. Solov'yov (✉)
MBN Research Center at Frankfurter Innovationszentrum Biotechnologie,
Altenhöferallee 3, 60438 Frankfurt am Main, Germany
e-mail: solovyov@mbnresearch.com

A.V. Solov'yov
A.F. Ioffe Physical-Technical Institute,
Polytekhnicheskaya Ul. 26, 194021 Saint Petersburg, Russia

A.V. Solov'yov (ed.), *Nanoscale Insights into Ion-Beam Cancer Therapy*,
DOI 10.1007/978-3-319-43030-0_9

magnetic properties; collective phenomena; electron/spin transport and molecular electronics; nuclear magnetic resonance; collision, fusion, fission and fragmentation processes; channeling effects; radiation effects; radiobiological effects and many more. There are many important applications closely linked to the field. One of such important applications is the Ion-Beam Cancer Therapy (IBCT). Understanding the processes behind IBCT on the molecular, nano- and meso- scales is an open area of intensive current research, which is widely discussed in this book. The list of topical areas in the field grows rather rapidly facilitating also the development of the relevant theoretical and computational methods.

In many areas the future of many industrial products is associated with the creation of an integrated environment for numerical design and modeling. This encompasses a wide range of end-products and applications in nanoelectronics, nanomaterials and their adoption within transportation, avionics, polymer technologies, medicine, etc. In most of these areas simulations need to operate over a wide range of scales, ranging from the molecular and the nanoscale to the micro and sometimes even to macro-dimensions. Such multiscale modeling usually integrates different physical and chemical phenomena and is currently one of the hot topics of theoretical and computational research. Multiscale modeling may save crucial time and money in product development processes, and hence play a key role in industrial competitiveness. The development of multiscale modeling tools is necessarily parallel with the development and widening of modern methods of high-performance computing. The implementation and success of the versatile numerical design and modeling requires a close and wide cooperation of industrial and academic players.

Thus, the multiscale modeling is one of the most topical research fields nowadays. In order to fully exploit its potential in the field of IBCT, as well as for other biomedical and nanotechnological applications, one needs to be well familiar with the wide range of interdisciplinary topics, including

- Physics: providing the fundamental theories for the delivery of radiation and its interactions with biological targets, or for instance, explaining the fundamentals of variety of processes occurring during deposition of materials on surfaces and the formation of nanostructures;
- Chemistry: describing the chemical processes induced at specific physical conditions and providing tools for tailoring of nanoscale species to specific functions;
- Materials Science: searching for advanced materials with the unique properties or functionalization of the materials on the nanoscale;
- Life Sciences: elucidating effects on the cellular level and integrating this knowledge into clinical practices;
- Software Engineering and High Performance Computing: providing the basis for advanced computational/virtual modeling of a large variety of systems and phenomena on the scales ranging from atomic to macroscopic.

Any form of inanimate condensed matter, including biological, consists of many different components linked by numerous, different interactions. Important efforts in deepening of the molecular level understanding of different forms of condensed matter and their dynamical behaviour concern the origin, nature and evolution of various

complex molecular systems, as well as the emergence of new features, properties, processes and functions involving the systems with increasing their complexity. On the meso- and nanoscales the physics and chemistry of biological and biomolecular systems, nanosystems and materials typically deal with such behaviour. Many examples of emergence of qualitatively new features can be quoted, e.g. the development of new collective properties when going from small molecules to large clusters or the nanoparticle aggregation on surfaces or inside cells leading to the appearance of fractally shaped morphologies. The fractal morphologies, being emerged in dynamical systems on the nanoscale, remain characteristic for many systems, including biological ones, at practically all larger scales, and are present in practically all living systems.

This book contains many examples of the molecular systems and molecular processes, like DNA strand breaks, which play the important role in IBCT. Most of these processes can be modelled and simulated using modern theoretical and computational techniques. These simulations provide a basis and necessary molecular level quantitative details for the construction of the inclusive Multi-Scale Approach [3, 4], which is systematically introduced and widely discussed in several chapters of this book. The best suited software package to set up the computer simulations of various processes occurring in the irradiated molecular system on the atomic, nano- and meso-scales is MBN Explorer [1]. MBN Explorer is equipped with an advanced graphical user interface, the so called MBN Studio [2], enabling the construction of input files, simple start of simulations, as well as visualisation and analysis of the results obtained.

Below in this Chapter MBN Explorer and some of its important features are introduced and illustrated this with a number of exemplar simulations and case studies.

2 MesoBioNano Explorer and MBN Studio

MesoBioNano Explorer (MBN EXPLORER) is a software package for the advanced multiscale simulations of complex molecular structure and dynamics. It has many unique features, a wide range of applications in Physics, Chemistry, Biology, Material Science, and in related Industries, see Fig. 1. It is suitable for classical molecular dynamics (MD), irradiation driven molecular dynamics (IDMD), Monte Carlo (MC) and relativistic dynamics simulations of a large range of molecular systems of different kind, such as nano- and biological systems, nanostructured materials, composite/hybrid materials, gases, liquids, solids and various interfaces, with the sizes ranging from atomic to mesoscopic. MBN EXPLORER permits computer simulations with the sizes of molecular systems ranging from the atomic to the mesoscopic scales.

Such knowledge is required in an enormous number of applications, e.g. in avionics and automobile industry for designing of nanostructured materials, functionalized surface coatings, stronger and lighter materials for aircrafts and cars suitable for high-performance at extreme conditions, in mechanical engineering for virtual design of superhard nanostructured materials, in medical applications for nanostruc-

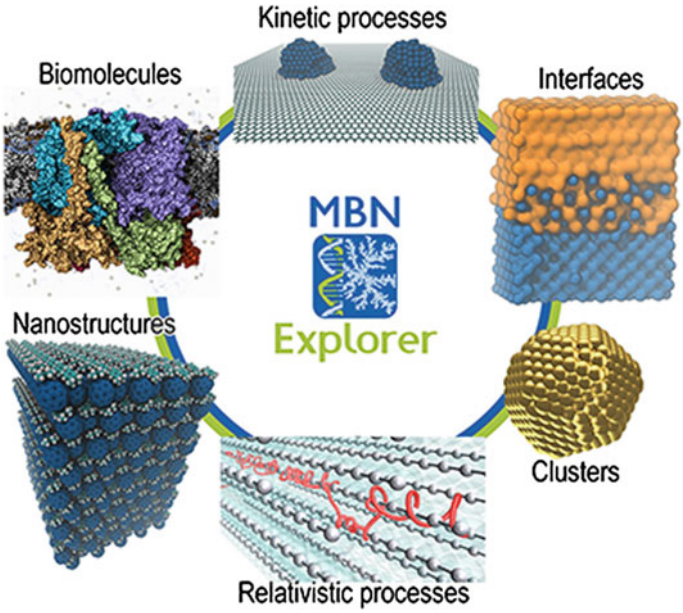

Fig. 1 Illustration of different application areas of MBN EXPLORER. Adapted from [5]

tured implants, in cement industry for the design of superplasticizers allowing the production of a concrete with higher compressive strength, in electronic and chemical industry for construction of highly efficient batteries, catalyzers, in pharm industry for drug design, etc. In many of these applications it is necessary to identify and/or design specific properties of the system determined by its molecular structure on the nanoscale and to ensure their transfer to the macroscopic scale in order to make them functional and usable. Such a transition implies a multiscale modeling supported in MBN EXPLORER through a combination of MD and MC simulations, algorithmic, coarse graining and phenomenon based approaches.

The ultimate goal of MBN EXPLORER is to expand the understanding of structure and dynamics of complex molecular systems, mechanisms of their stability, self-organization and growth, as well as the ways of their manipulation and control aiming a broad spectrum of application of this knowledge in nanotechnology, microelectronics, material science and medicine.

MBN EXPLORER version 2.0 [1] can be exploited together with MBN Studio [2], a specially developed graphical user interface. MBN Studio helps to set up and start MBN EXPLORER calculations, to monitor their progress and to examine the calculation results. It is supported by the graphical utility enabling to visualize selected inputs and outputs.

A number of built-in tools allow for the calculation and analysis of specific characteristics that are determined by the output of MD simulations. Examples include diffusion coefficients of various molecular species, heat capacities and melting tem-

peratures, radial distribution function, etc. A special modeling plug-in allows one to construct a large variety of molecular systems quickly and efficiently. By means of this plug-in one can easily construct molecular systems of different geometry built of various elements of the periodic table.

Figure 1 highlights a variety of molecular systems, which can be simulated using MBN EXPLORER. In particular, MBN EXPLORER is suited to compute the system's energy, to optimize molecular structures, as well as to explore the molecular dynamics (classical, irradiation driven, Euler, relativistic) and random walk dynamics. MBN EXPLORER supports using a large library of interatomic potentials, allowing to model a large number of very different molecular systems, which are introduced briefly below in Sect. 4.

The first release of MBN EXPLORER has been the heritage of more than a decade development. The code has been thoughtfully tested and proved to be efficient and reliable in calculations. The structure of MBN EXPLORER, its main features and capabilities are described in detail in the reference article [1] published by the Journal of Computational Chemistry. The figures, see Fig. 2, highlighting MBN EXPLORER and its 3D kinetic Monte Carlo module, were chosen for the cover page of the two JCC issues.

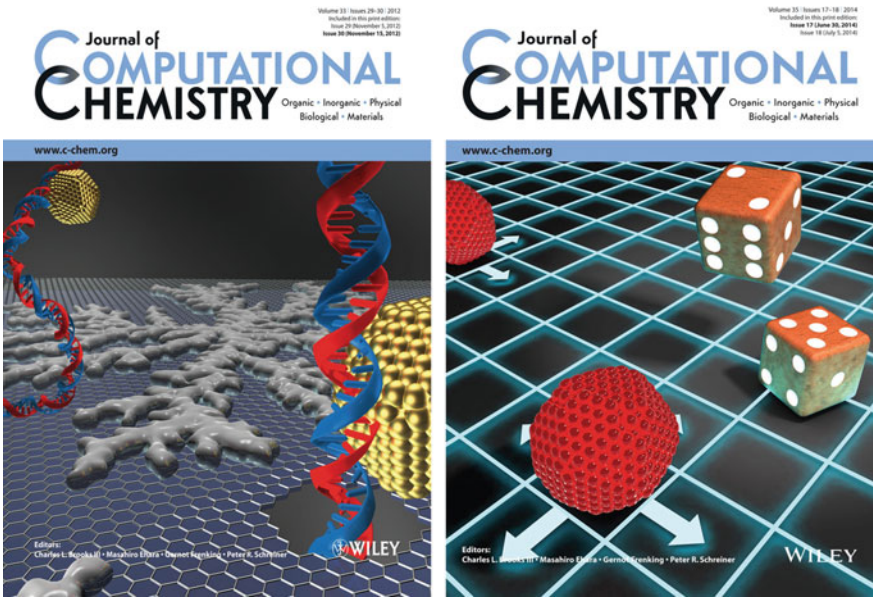

Fig. 2 Figures highlighting MBN EXPLORER for the cover page of volume 33, issue 30 (*left*) and volume 35, issue 17 (*right*) of the Journal of Computational Chemistry, in which the reference article about MBN EXPLORER [1] and its 3D kinetic Monte Carlo module [6] were published

The code is under continuous development conducted by the joined participation of world-class scientists and IT developers affiliated with MBN Research Center gGmbH, see website http://www.mbnresearch.com/.

Citing MBNEXPLORER. The authors request that all published work which utilizes MBN EXPLORER include the primary citation:

[1] *Meso Bio Nano Explorer—a universal program for multiscale computer simulations of complex molecular structure and dynamics*, I.A. Solov'yov, A.V. Yakubovich, P.V. Nikolaev, I. Volkovets, and A.V. Solov'yov, Journal of Computational Chemistry, volume **33**, pp. 2412–2439 (2012).

For specific algorithms the authors are requested to include additionally the following citations in their publications:

Relativistic Integrator:

[2] *Simulation of ultra-relativistic electrons and positrons channeling in crystals with* MBN EXPLORER, G.B. Sushko, V.G. Bezchastnov, I.A. Solov'yov, A.V. Korol, W. Greiner, and A.V. Solov'yov, Journal of Computational Physics, volume **252**, pp. 404–418 (2013).

Kinetic Monte-Carlo approach:

[3] *Efficient 3D kinetic Monte Carlo method for modeling of molecular structure and dynamics*, M. Panshenskov, I.A. Solov'yov, and A.V. Solov'yov, Journal of Computational Chemistry, volume **35**, pp. 1317–1329 (2014).

Molecular mechanics with dynamical topology- reactive CHARMM force field:

[4] *Studying chemical reactions in biological systems with MBN Explorer: implementation of molecular mechanics with dynamical topology*, G.B. Sushko, I.A. Solovyov, A.V. Verkhovtsev, S.N. Volkov, A.V. Solov'yov, European Physical Journal D, volume **70**, p. 12 (10pp) (2016).

Irradiation driven molecular dynamics:

[5] *Molecular dynamics for irradiation driven chemistry: application to the FEBID process*, G.B. Sushko, I.A. Solov'yov, A.V. Solov'yov, European Physical Journal D, volume **70**, 217 (15pp) (2016).

3 MBN EXPLORER Main Features

Universality

MBN EXPLORER is designed for studying a broad range of physical, chemical and biological systems and materials by computing their energies, optimizing molecular structures, as well as through molecular dynamics and random walk dynamics (kinetic Monte Carlo) simulations. Universality is an important feature of MBN EXPLORER, which allows modeling of a large number of molecular systems

and processes (e.g. atomic clusters, fullerenes, nanotubes, polypeptides, proteins, DNA, nanostructured materials, nanofractals, etc., composite systems like a metallic nanoparticles interacting with a biomolecule, or a DNA penetrating through a nanopore) exploiting a broad variety of interatomic potentials of different kind.

Tunable Force Fields

MBN EXPLORER includes a large variety of interatomic potentials. A distinctive feature of the program is the possibility to combine various interatomic potentials from a large library of interatomic potentials available in MBN EXPLORER. The potentials implemented in MBN EXPLORER include pairwise, many-body, and molecular mechanics potentials which are widely accepted for studying bio- and nanosystems.

The file format of molecular mechanics force field used by MBN EXPLORER is the same as that used by the programs http://www.charmm.org/ CHARMM, http://cns-online.org/v1.3/ XPLOR and http://www.ks.uiuc.edu/Research/namd/ NAMD. This compatibility allows using MBN EXPLORER for calculations of a broad range of biological molecules with minimal efforts. The results of MBN EXPLORER calculations are made compatible with standard visualization programs http://www.ks.uiuc.edu/Research/vmd/ VMD and http://www.chemcraftprog.com Chemcraft.

Unique Algorithms

Apart from many standard algorithms MBN EXPLORER contains also unique algorithmic implementations, being useful in particular application areas. For instance, it allows flexible coarse graining, i.e. grouping of particles into rigid fragments, thereby significantly reducing the number of dynamical degrees of freedom, in the system. This algorithm is especially useful for molecular dynamics simulations of large molecular systems, having well defined interacting constituent parts, which could be treated as frozen. Note that most of other molecular dynamics codes do not allow grouping of atoms in rigid bodies. Another examples include the unique algorithm for simulations of relativistic particles channeling through oriented crystals, simulation of radiation damage processes and irradiation driven molecular dynamics.

Multiscale Approach

MBN EXPLORER allows one to perform stochastic Monte Carlo dynamics of molecular systems on the time scales significantly exceeding those of the conventional atomistic molecular dynamics simulations. Such multiscale dynamics approach is ideal for the systems, in which the details of the system dynamics on the atomic scale are not so important, and can be parameterized through the kinetic rates for the dominating transformations occurring in the system. This important feature of MBN EXPLORER expands significantly its application areas and goes beyond the limits of other molecular dynamics codes usually unable to deal with the multiscale modeling.

Computational Efficiency

Despite the universality, the computational efficiency of MBN EXPLORER is comparable to and often even higher then the computational efficiency of other software packages, making MBN EXPLORER often a favorable choice.

Object-Oriented Design

The primary design objective for MBN EXPLORER is extensibility and maintainability of the code. In order to achieve this goal, MBN EXPLORER code implements an object-oriented approach with C++. The modular design of the code allows an easy integration of new algorithms and techniques for molecular dynamics simulations.

4 Applications of MBN EXPLORER

There are many different areas of application of MBN EXPLORER some of which are briefly introduced below.

Crystals, Liquids, and Gases

With MBN EXPLORER one can simulate crystals, liquids, glasses and gases, and study numerous physical and chemical phenomena involving different phase states of matter [7, 8]. For each condensed matter state there are many examples of simulations which are collected in the library of MBN EXPLORER tests and examples [9]. These examples include simulations of metallic, carbon and silicon, atomic and molecular crystals, oxides, thin films and surface coatings, liquids and their interfaces with metals and biocompatible materials, their various properties and processes with their involvement. MBN EXPLORER also provides tools for multiscale modeling of various MBN systems. These tools allow one to model kinetic behaviour of such systems far beyond the time and spatial limits of the conventional molecular dynamics simulations [6, 10] (Fig. 3).

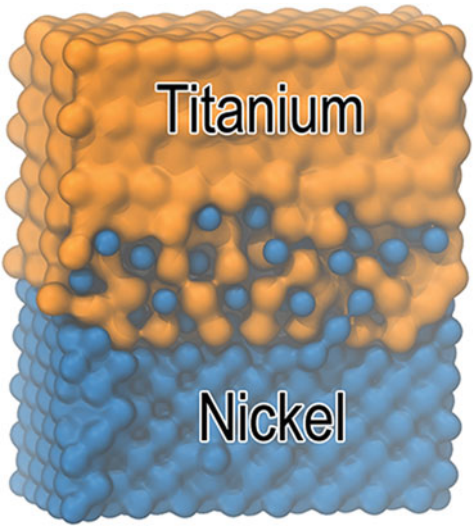

Fig. 3 Nickel-titanium interface. Adapted from [5]

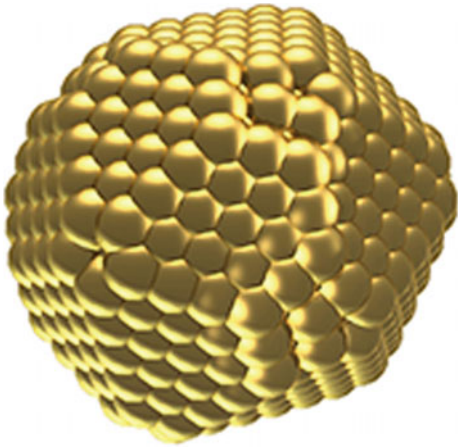

Fig. 4 Icosahedral atomic cluster. Adapted from [5]

Atomic Clusters and Nanoparticles

MBN EXPLORER is suitable for computer simulations of structure and dynamics of free, deposited and embedded atomic and molecular clusters, nanoparticles (NPs) of different types, e.g. metals, noble gases, semiconductor clusters, fullerenes, carbon nanotubes, graphene, as well as all other allotropic forms of nanocarbon materials, composite and functionalized NPs, nanoalloys etc., [11–16]. The sizes of these molecular systems could be varied from a few atoms up to a few million atoms. Possible simulations include the tasks on the structure analysis and optimization, various thermal effects, mechanical properties, nanoscale phase transitions, diffusion and a broad range of other dynamical and collision processes involving clusters and NPs [17–19] (Fig. 4).

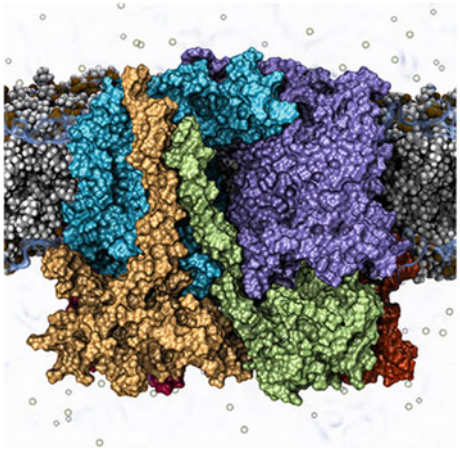

Fig. 5 Protein complex. Adapted from [5]

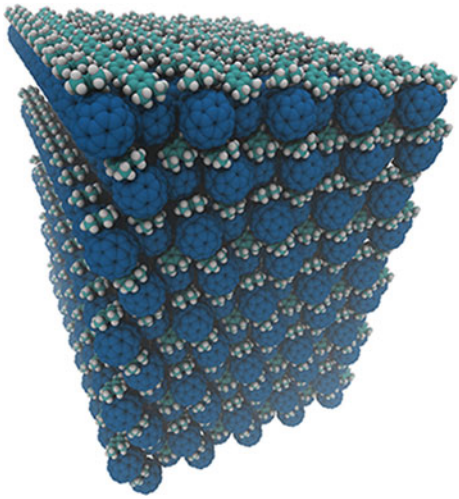

Fig. 6 C_{60}-based nanowire. Adapted from [5]

Biomolecular Systems

MBN EXPLORER allows one to simulate a large variety of biomolecules, biomolecular, hybrid bio-nano systems with various interfaces [20]. Transformations of these systems at different thermal and biologically relevant conditions, at various external stresses can be explored. Numerous possible case studies include proteins, DNA, lipid bilayers, interaction of these systems with NPs, external environments and many more. MBN EXPLORER allows one to simulate structure and dynamics of proteins, DNA, RNA and other biomolecules in ubiquitous environments [21]. Protein folding [22], antigen-antibody bounding [23], DNA unzipping [24], radiation damage phenomena [25] and many other processes involving biomolecules can be studied (Fig. 5).

Nanostructured Materials

Nanoscale molecular objects, such as atomic clusters, NPs, proteins, DNA fragments, etc., provide a possibility to construct new types of materials, the so-called nanostructured materials, thin films, surface coatings with the structure and properties determined by the molecular constituent building blocks. MBN EXPLORER allows one to simulate a wide spectrum of nanostructured materials and to study their properties [26]. Examples of such materials include: metals (e.g. Ni or Ti [27]), metal NPs crystals, nanocarbon (nanosilicon) based nanostructured materials (e.g. TMB-C_{60} nanowires [28–31]) and many more (Fig. 6).

Composite Materials and Material Interfaces

MBN EXPLORER has the necessary tools (appropriate force fields and algorithms) to simulate many novel composite materials consisting of components of different nature, ordered or disordered. Examples of such hybrid systems include nanoalloys,

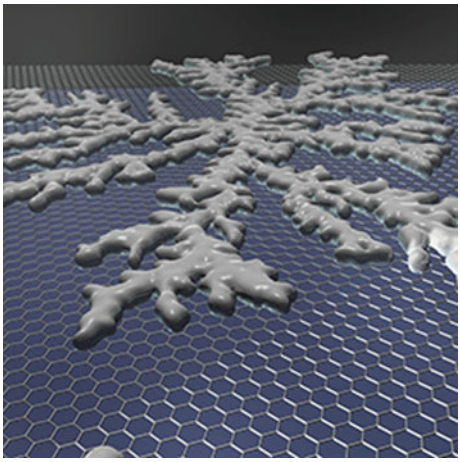

Fig. 7 Silver fractal on graphite surface. Adapted from [5]

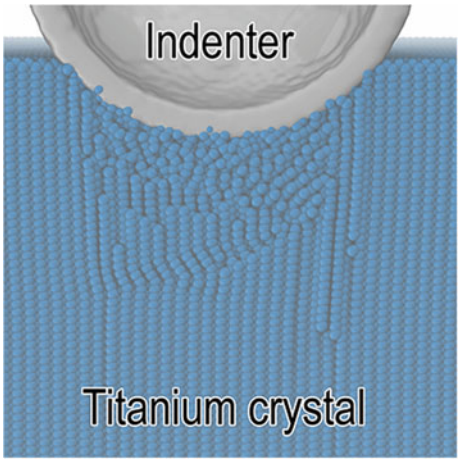

Fig. 8 Nanoindentation of Ti crystal. Adapted from [5]

nanofractals [10, 32, 33], crystalline superlattices of metal NPs linked by different organic or biological molecules, or NPs placed into the biological environments (e.g. attached to DNA, protein, or cell membrane). The latter systems appear to be of significant interest and importance in connection with the analysis of toxicity of nanomaterials and the development of advanced radiotherapies exploiting nanoprocesses and technologies [34]. With MBN EXPLORER one can simulate and investigate a variety of complex multiscale dynamical processes, for instance, diffusion and surface pattern formation (e.g. nanofractals, droplets etc.) in the course of NP, atomic or molecular deposition, morphological transitions and many more [35–38] (Fig. 7).

Thermo-Mechanical Properties of Materials

MBN EXPLORER can be utilized for simulations and investigation of the mechanical properties and thermal effects of a broad variety of the materials mentioned above. This includes analysis of elastic and plastic deformations [39] (e.g. Young's modulus, Poisson's ratio, hardness, etc.), dynamics of dislocations, nanoindentation [8], phase transitions [40], thermo-mechanical damage [41] and many more. For most of these processes and phenomena the thermal dependence of various characteristics of materials is of significant importance and interest (Fig. 8).

Collision Processes and Related Phenomena

MBN EXPLORER supports the most advanced molecular dynamics simulations for a large variety of complex molecular systems. With these methods one can study many different dynamical processes, including collisions, that occur in molecular systems (Fig. 9).

These studies include collision and fragmentation processes involving atomic clusters, NPs and biomolecules, molecular association and dissociation, nano- and microscale conformational, morphological, and phase transitions, proteins folding, DNA unzipping, NP and molecular diffusion, propagation of particles through a medium (channeling, multiple scattering, track structure analysis), collision induced thermo-mechanical medium effects, and many more. Some of these processes are discussed in detail in several chapters of this book (Fig. 10).

Novel Technologies

MBN EXPLORER is a very useful and powerful tool for the exploration of the challenging problems arising in connection with the development of new technologies [42]. There are several research areas, in which simulations performed with the use of MBN EXPLORER play an important role. One of such areas concerns the construction of novel light sources based on charged particles channeling in crystalline undulators. Another example deals with simulations of the nanoscopic molecular processes playing the key role in the ion-beam cancer therapy [3, 43, 44]. Combined with

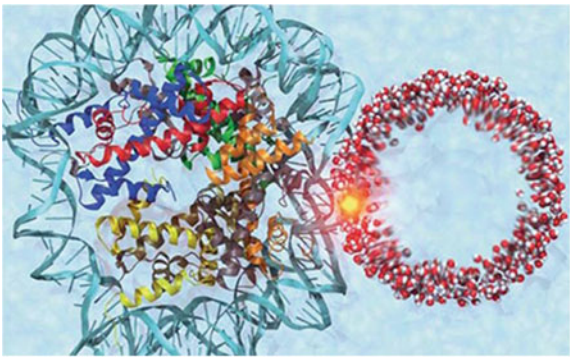

Fig. 9 Ion induced shock wave interacting with nucleosome. Adapted from [5]

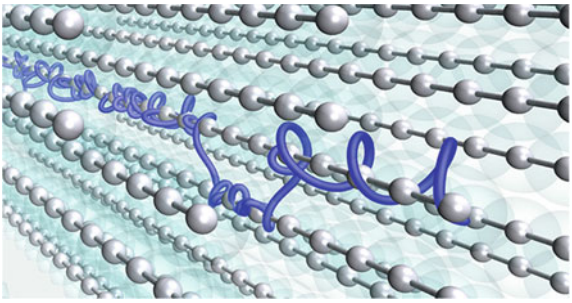

Fig. 10 Axial channeling of an ultrarelativistic electron along crystal axis. Adapted from [5]

the visualisation interface through MBN Studio or other similar visualisation tools, MBN EXPLORER in many cases can help to optimise or even substitute expensive laboratory experiments by computational modeling. Predictive power, the possibility to visualise structure and dynamics of complex molecular systems allow to percept the MBN EXPLORER based computational approach as a kind of 'computational nano- and microscope'.

It is suitable for relativistic dynamics simulations [42, 45–47]. Among other applications, MBN EXPLORER can be used to simulate thermo-mechanical damage of a biological medium, e.g. a DNA nucleosome, which is caused by the propagation of a shock wave initiated by irradiation with fast ions [48]. The results of such simulations are used then to evaluate the efficiency of radiation with different projectiles [49] within the framework of the multiscale approach to the physics of radiation damage [3] and can be applied in the field of ion-beam cancer therapy [3, 49–51].

5 Exemplar Case Studies

It is impossible in one Chapter to overview all the case studies supported by MBN EXPLORER. This deserves a whole book. Some of them are already introduced in other chapters of this book, e.g. simulation of ion induced shock waves and their damaging effects on DNA, structure and dynamics of sensitising nanoparticles, etc. Here, other important case studies relevant to the topics of this book are briefly introduced.

5.1 Reactive CHARMM Force Fields

Nowadays, it has become feasible to study structure and dynamics of molecular systems that constitute of millions of atoms [52, 53] and evolve on time scales up to hundreds of nanoseconds [54] by employing the classical molecular dynamics approach, often also called molecular mechanics (MM). In this approach, a molecular system is treated classically, so that constituent atoms interact with each other through

a parametric phenomenological potential that is governed by the type of individual atoms and by the network of chemical bonds between them. This network defines a so-called molecular topology, that is a set of rules that impose constraints in the system and permit maintaining its natural shape, mechanical, and thermodynamical properties. The MM method has been widely used throughout the last decades [53, 55–57] and implemented in the well-established computational packages, such as CHARMM [58], AMBER [59], GROMACS [60], NAMD [61] and MBN EXPLORER (www.mbnexplorer.com, www.mbnresearch.com) [1].

Despite numerous successes, the conventional MM method is primarily capable of studying processes where chemical reactions do not take place. This leads to significant limitations of the method and makes it practically unsuitable for studying highly non-equilibrium processes in biomolecular systems, e.g. thermo-mechanical biodamage. This particular example involves rupture and formation of covalent bonds that cannot be simulated by the conventional MM method due to a fixed topology of the system.

Simulation of the rupture and formation of covalent bonds can be performed by using Quantum Mechanical/Molecular Mechanical (QM/MM) methods or *ab initio* MD simulations [62–64]. Both methods are computationally rather demanding and, thus, the *ab initio* approach is used typically for studying fragmentation of small biomolecules, such as DNA nucleobases or nucleotides [65, 66]. The size of such systems is far from the typical sizes of systems of biological relevance, consisting of hundred thousands of atoms, and more. This problem is addressed to some extent in QM/MM methods where a core part of a large biomolecular system is described quantum mechanically while all the surroundings are described classically using, for example, the conventional MM method [67, 68]. Thus, the rupture or formation of covalent bonds can be simulated only in a small part of the system, which is treated quantum mechanically.

In recent work [69] an extended version of the conventional MM method was implemented in MBN EXPLORER. It is based on the newly introduced reactive CHARMM force field, being an important extension of the standard CHARMM force field. It was demonstrated that this extension describes correctly the dynamically changing molecular topology of a system within the classical MD framework. The presented modification takes into account additional parameters of the system, such as dissociation energy of bonds, bonds multiplicity and the valence of atoms. The functional form of the interatomic interactions is also adjusted to account for the finite dissociation energy of the chemical bonds.

To illustrate these modifications here let us now consider the two examples that go beyond the standard MM methodology. The first example illustrates the rupture of a single C–N bond in an alanine dipeptide molecule, being one of the simplest building blocks of larger biomolecular systems like polypeptides or proteins. The second example shows the reverse process of the new bond formation.

Fragmentation of Alanine Dipeptide

To illustrate the bond breakage, following [69], let us consider the dynamics of alanine dipeptide consisting of 20 atoms, solvated in a simulation box with 95 water molecules. The alanine dipeptide molecule was considered with neutral terminals.

In order to clearly illustrate the difference between the standard CHARMM force field, utilizing the harmonic interatomic potential, and the dissociative CHARMM potential implemented in MBN EXPLORER, two simulations were carried out [69]. In these simulations, the rupture of the central C–N bond in the dipeptide, leading to the formation of two isolated alanine molecules, was monitored.

To facilitate the process, let us set the initial velocity of the C and N atoms high, which corresponds to an energy fluctuation sufficient for the bond rupture. In the simulation performed with the standard force field, the peptide bond is modeled through the harmonic potential, therefore, the bond cannot break. The behavior of the C–N bond in the harmonic approximation is illustrated in the left part of Fig. 11, and the corresponding atoms are marked with red circles. In this case, the distance between the atoms oscillates around the equilibrium value as the atoms always return to their equilibrium positions.

In the second simulation, the Morse potential was used for the description of the peptide bond. In this case the C and N atoms do not oscillate around an equilibrium

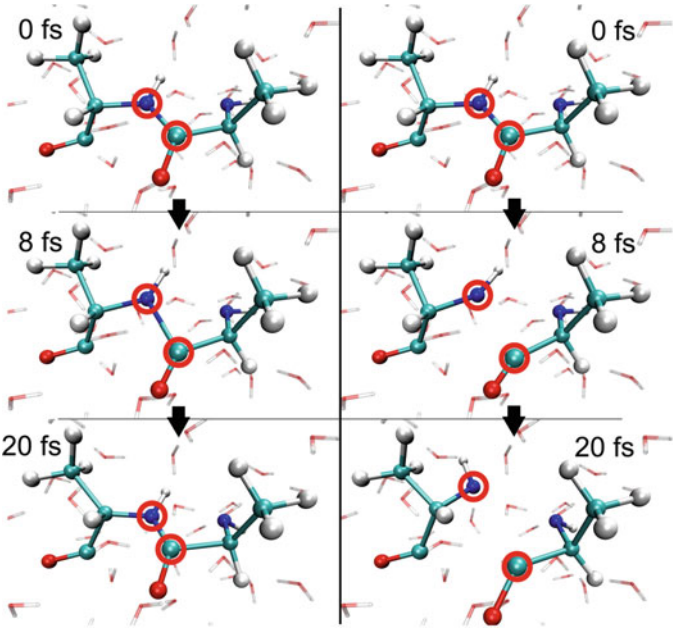

Fig. 11 Snapshots illustrating dynamics of alanine dipeptide and the C–N bond rupture simulated with the harmonic (*left*) and Morse (*right*) potentials at 0 fs (*top*), 8 fs (*middle*) and 20 fs (*bottom*). Adopted from [69]

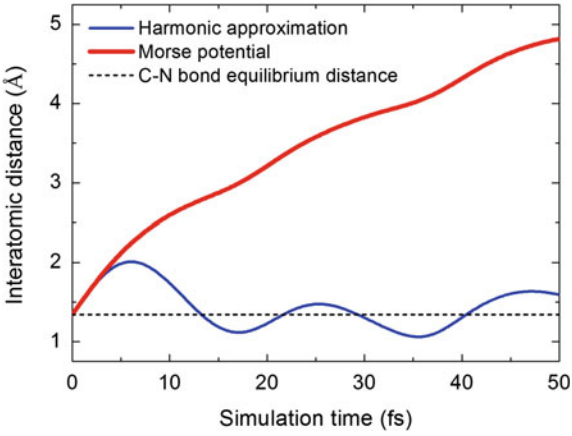

Fig. 12 Dependence of the C–N interatomic distance in alanine dipeptide as a function of the simulation time. Adopted from [69]

position, and the structure of the system after 20 fs of simulation changes significantly from the one considered above (see the right part of Fig. 11). It is evident from the snapshots that the distance between the atoms increases already after 8 fs.

When the distance between the atoms exceeds a given cutoff radius (which is equal to 2.5 Å in this example), the bond is considered as broken. Once this has happened, the carbon and the nitrogen atoms remain interacting only via the electrostatic potential and the van der Waals interactions, so that the two alanine molecules can diffuse apart. The charge redistribution does not happen in this case because both new fragments of the dipeptide were initially neutral.

Figure 12 shows the interatomic distance between the carbon and the nitrogen atoms as a function of the simulation time. The equilibrium distance between the atoms is $r_0^{\mathrm{C-N}} = 1.354\,\text{Å}$ (dashed line). The figure demonstrates that in the case of the simulation with the Morse potential, the interatomic distance monotonically increases indicating that the bond is broken and that two isolated alanine molecules drift apart.

Binding of Two Alanine Amino Acids

The second example illustrates the process of binding two alanine molecules together into a single dipeptide through the formation of a new covalent bond in the molecular system [69]. In this case, six isolated alanine amino acids surrounded by 54 water molecules were placed in a small simulation box of $24 \times 24 \times 24\,\text{Å}^3$ with periodic boundary conditions, and the dynamics of the system was simulated for 80 ps at a fixed temperature of 1000 K controlled by the Langevin thermostat with the damping time constant of 1 fs. Each alanine molecule was modeled with unsaturated N– and C–termini, i.e. having two unpaired chemical bonds.

In the course of the simulation, all distances between the different termini of alanines are monitored. When the distance between a pair of terminal atoms became smaller than the predefined cutoff radius (equal to 3 Å in this example), a new covalent bond is considered to be formed. Figure 13a illustrates a spacial conformation of two

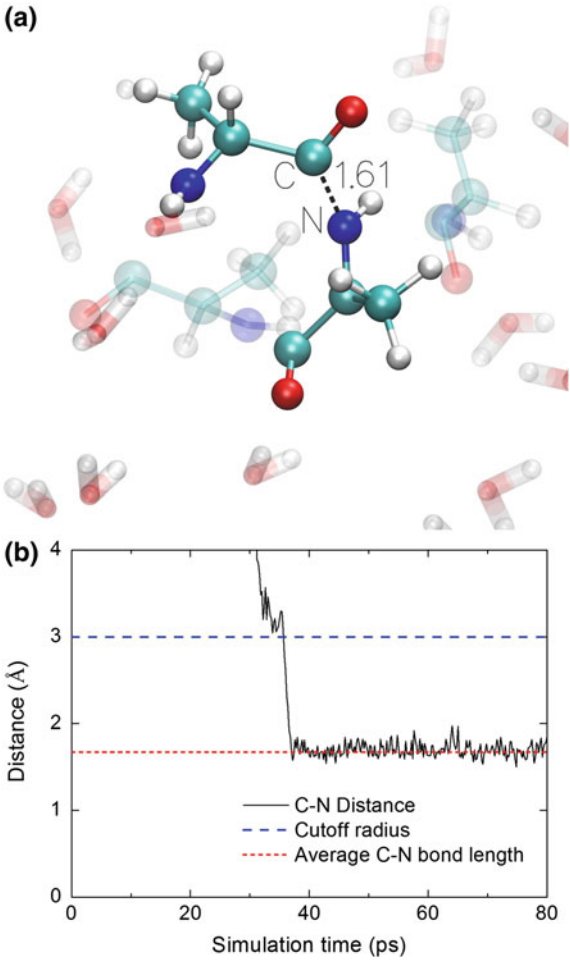

Fig. 13 **a** Two alanine molecules approaching each other to form a new C–N bond. **b** Dependence of the distance between C and N atoms for the two alanine molecules. Adopted from [69]

amino acids in the simulation leading to the formation of a new bond. Figure 13b gives the dependence of the distance between C and N atoms for the two molecules shown in the upper part. At some point, this distance becomes smaller than the cutoff radius (blue dashed line), and the two molecules become connected. Note that after 40 ps the distance between the C and N atoms oscillates around a constant value corresponding to the C–N bond equilibrium length. Since six alanines are considered in this simulation, more of them could self-assemble in a polypeptide chain but this would require longer simulation. In this system, each initial alanine molecule has a total charge equal to zero. Therefore, after the formation of a new molecule the charge redistribution step was not necessary.

Having proven the force field to work on a simple molecules one can generalize the framework towards macromolecules. This allows for studying the systems of

biologically relevant sizes, on the time scales which are not accessible by means of *ab initio* methods. In [69] the example illustrating the process of water splitting and the issue of chemical equilibrium were analysed using the reactive CHARMM force field. It was demonstrated that the results of the simulation are in a reasonable quantitative agreement with those of the analytical calculations.

5.2 Irradiation Driven Molecular Dynamics

There are many examples in which chemical transformations of complex molecular systems are driven by irradiation. Often such modifications carry important outcomes to the functional properties of the irradiated molecular systems. Enough to mention the radiobiological phenomena, in which living cells can be inactivated by irradiation due to the induced DNA complex strand breaks [3], the formation and composition of cosmic ices and dusts in the interstellar medium and planetary atmospheres is largely a result of the interplay of the molecular surface adsorption and surface irradiation [70], the formation of biologically relevant molecules under extreme conditions involving irradiation [71],[1] and many more. Irradiation driven chemistry is nowadays utilized in modern nanotechnology, such as focused electron beam deposition (FEBID) [72, 73] and extreme ultraviolet lithography (EUVL) [74, 75]. These technologies belong to the next generation of nanofabrication techniques allowing the controlled creation of nanostructures with nanometer resolution which is attractive in both, basic and applied research. The fabrication of smaller and smaller structures has been the goal of the electronics industry for more than three decades and still remains one of this industry's biggest challenges. Furthermore, irradiation chemistry is a key element in nuclear waste decomposition technologies [76] and medical radiotherapies [77, 78].

Irradiation driven chemistry (IDC) is based on the quantum transformations that are induced in molecular systems by their irradiation by external fields of different modality (X-rays, lasers, electrons/positrons, ions, etc.) and the dynamics of molecular system which can be also influenced by external factors like temperature, pressure, external fields, etc. Highly perturbed dynamical molecular systems can only be described from first principles within the time dependent density functional theory (TDTDFT), or any of its equivalents, if the size of the molecular system is sufficiently small, typically hundreds of atoms [79–82]. This strong limitation makes TDDFT of limited use for the description of the IDC of complex molecular systems.

Classical molecular dynamics (MD) could be considered as an alternative for the theoretical description of IDC. However, in spite of the manyfold advantages, classical MD is often inapplicable for simulations of chemical reactions and IDC processes, because it does neither account for coupling of the molecular system to radiation, nor does it describe quantum transformations in the molecular system

[1] See COST Action "The Chemical Cosmos: Understanding Chemistry in Astronomical Environments" www.cost.eu/COST_Actions/cmst/CM0805.

induced by the irradiation. In the recent work [83] these deficiencies of MD were overcome and a new methodology for simulation of irradiation driven chemical transformations of complex molecular systems was suggested. There it was suggested to model irradiation induced quantum transformations in a molecular system as random, fast and local processes involving small molecular fragments (typically on sub-nanometer scale) of the entire system. The modeled transformations include molecular bond breakages, saturation of dangling bonds, chemical reactions in the system, and changes in the molecular topology of the system. These transformations are introduced according to the specific rates that are coupled to the irradiation field and the probabilities of the corresponding quantum processes are established through *ab initio* quantum approaches, such as many-body theory, DFT, collision theory, or taken from experiments. The fundamental basis for such an approach relies on the Born-Oppenheimer theory justifying uncoupling of the fast electronic motion in molecular systems from the slow motion of the ionic subsystem and the fact that the characteristic time scale for the fast quantum transformations in the system is typically within the femtosecond range, i.e., about the duration of one time step in MD simulations. Furthermore, the spatial dimension of the region where an irradiation induced quantum transformation takes place is much smaller than the size of the molecular systems under consideration. Therefore, if the outcomes of the quantum transformations are properly accounted for on the basis of quantum mechanics or simply taken from experiment and correctly embedded as random and local modifications of the classical force fields, it becomes feasible to model structure and dynamics of large molecular systems under irradiation through the irradiation driven molecular dynamics (IDMD), as demonstrated in [83]. This methodology is designed for the molecular level description of the irradiation driven chemistry of complex molecular systems arising in various circumstances introduced above.

Classical molecular dynamics (MD) has been introduced for the description of quantum molecular systems with the use of the classical Newtonian equations [84]. The justification of this approach is based on the Born-Oppenheimer theorem, which separates the light electronic and heavy ionic subsystems and elucidates the quasi-classical motion of the nuclei in the system. In this approach all the information about the quantum-mechanical properties of the system is included in the parameters of the classical force fields guiding the motion of the nuclei. Within the classical MD the trajectories of atoms and molecules are determined through the numerical solution of Newton's equations, where forces between the particles and their potential energies are calculated using interatomic potentials and force fields. Such a simplification of the description of motion of a quantum system provides significant advantages for computer simulations as already discussed above. The method was originally developed within the field of theoretical physics in the late 1950s [85] but is applied today mostly in chemical physics, materials science and the modelling of biomolecules.

The classical MD approach does not describe the electron dynamics and, therefore, most of the quantum transformations that may occur during the system dynamics. These transformations are often induced in the system through exposure to external perturbations such as external fields or irradiation by charged particles (electrons, protons, ions, etc.) or photons. The resulting effects may have a global character

(electric current, spin ordering, polarisation, magnetisation, etc.) or be local (atomic or molecular excitation, ionisation, dissociation, charge transfer, etc.).

Irradiation induced local quantum perturbations of a molecular system typically occur on the sub-femtosecond time scale and involve only those atoms that are directly affected by the irradiation. This results in the creation of secondary electrons, ions, reactive species (radicals), and excited molecules, which can further interact with the molecular system and cause further chemical transformations. This complex local dynamics typically involves the nearest environment of the targeted molecular site, being a small part of the entire molecular system, and is completed within femtoseconds. During this time some of the initial perturbations of the system, such as quasi-free electrons, electron holes, ionic charges, relax and vanish, due to the high electronic mobility and the Coulomb attraction. The femtosecond time scale is, however, still significantly shorter than the characteristic timescales responsible for the motion of the entire molecular system. Indeed, in classical MD a typical integration time step is 1–2 fs, corresponding to the oscillation period of a hydrogen atom at room temperature.

The notable outcome of the process described above will be the emergence of bond breaks in the system. These events are most significant as they affect the dynamical behaviour and chemical transformations in the molecular system on the larger time scales, up to nanoseconds and beyond, being the typical time frame for the classical MD. The bond breaks arise in those parts of the molecular system which are targeted by the irradiation. They occur randomly with a probability depending on the intensity and the modality of irradiation. The probabilities of these events are related to the cross sections of the involved irradiation induced processes (elastic and inelastic scattering, electronic and vibrational excitation, dissociative electron attachment, collision dissociation, etc.) occurring in the system on the femtosecond time scale and can be elaborated from the collision theory or be taken from experiment.

Irradiation conditions of a molecular system can differ substantially and depend on the radiation modality, duration of the system exposure to irradiation and the system geometry. Irradiation can be a swift single event, like a single ion track crossing the molecular system, or it can last a certain period of time up to some nanoseconds and even longer. In the latter case the irradiation induced bond breaks and charge redistribution in the system occurs during the entire irradiation period. Irradiation can be homogeneous within a certain volume or strongly inhomogeneous. The choice of the irradiation conditions corresponds to each particular case study. In the follow up sections we consider these for the FEBID process.

The above described scenario defines the irradiation driven molecular dynamics (IDMD). The IDMD can be introduced as classical MD with the superimposed random process of molecular bond breakage related to the irradiation conditions. The bond breakage is defined as the local alteration of the system force fields, which involves (i) creation of reactive atomic species (radicals) with dangling bonds, (ii) the possibility of dangling bonds' closure and creation of new molecular bonds or molecules, (iii) accounting for molecular topology changes (in the cases when it is defined, e.g. molecular mechanics force fields). The characterisation of these modifications of the classical MD force fields can be elaborated on the basis of quantum

chemistry methods. Examples of such characterisation for the FEBID process are given below.

The IDMD methodology aims to account for the major dissociative transformations of the molecular system induced by its irradiation and possible paths of further reactive transformations. The latter are sensitive to statistical mechanical factors, like the concentration of the reactive spices, their mobility (diffusion), the temperature of the medium, etc. All these factors are automatically accounted for in a correct way through the Langevin MD describing the molecular system as a NVT statistical mechanics ensemble. The local deviations from the statistical mechanics equilibrium arising in the vicinity of the breaking bonds caused by the local deposition of energy into the system leads to minor perturbations of the large molecular system and can be incorporated into IDMD as a perturbation.

The concept of IDMD introduced recently in [83] is general. It is applicable to any kind of molecular system treated with any type of classical force field. The method is implemented in the MBN EXPLORER software package and can operate with the large library of classical potentials, many-body force fields (including the recently implemented reactive CHARMM force field [69]) and their combinations. The limited number of parameters that determine molecular force fields, and their irradiation driven perturbations, results in a countable number of modifications that could occur in a molecular system upon irradiation and makes the method efficient and accurate.

This implementation opens a broad range of possibilities for modelling of irradiation driven modifications and chemistry of complex molecular systems. In order to highlight these possibilities let us present an example of the FEBID process simulated by means of IDMD and reported in [83]. These simulations have been thoroughly examined and compared with experiment.

A snapshot of MD simulation of the initial irradiation phase in the FEBID process is shown in Fig. 14. The interaction of $W(CO)_6$ precursor molecules with the cylindrical electron beam depicted in green leads to the precursor fragmentation and the formation of W clusters on the surface, illustrated in Fig. 14 in blue.

Following [83], let us now demonstrate that the morphology, the type of emerging surface nanostructure and its composition depend strongly on the irradiation driven chemistry of precursors. For this purpose let us consider the models A and B. In both models, for the atoms with open bonds the algorithm of searching for the atomic open bond neighbours of the suitable type is implemented. In the case of model A the searching for the reactive neighbours is performed only among the atoms located beyond the the molecular structure to which a chosen atom belongs. In the model B the searching is performed over all open valence atoms in the system including the molecular structure to which a chosen atom belongs.

The nanostructures presented in Figs. 15 and 16 emerge after 150 ns of simulated irradiation (15 rounds of irradiation 10 ns each at the conditions corresponding to the e-beam current 1.2 μA). These figures show that the chained structures of W (blue dots) with the C-O fragments attached to the most of W atoms are formed within model A, while model B results in the formation of more compact and dense molecular structure with the larger W content. The relative content of tungsten in

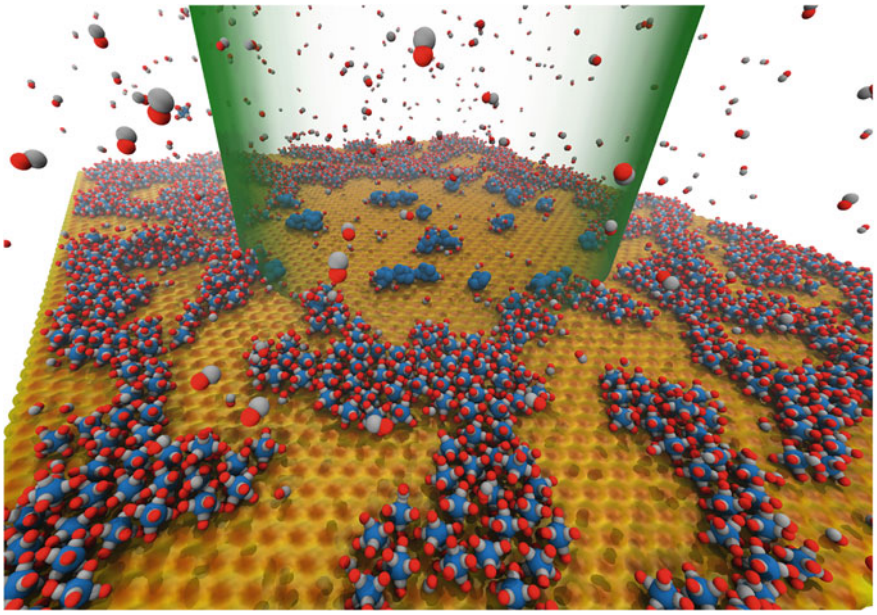

Fig. 14 Snapshot of MD simulation of adsorption of $W(CO)_6$ precursor molecules on a SiO_2 surface in the case of model A (see text) experiencing the early stage of irradiation by the electrons beam (shown as transparent green cylinder). The interaction of precursor molecules with the beam leads to fragmentation of molecules and formation of W clusters, shown in blue. Adopted from [83]

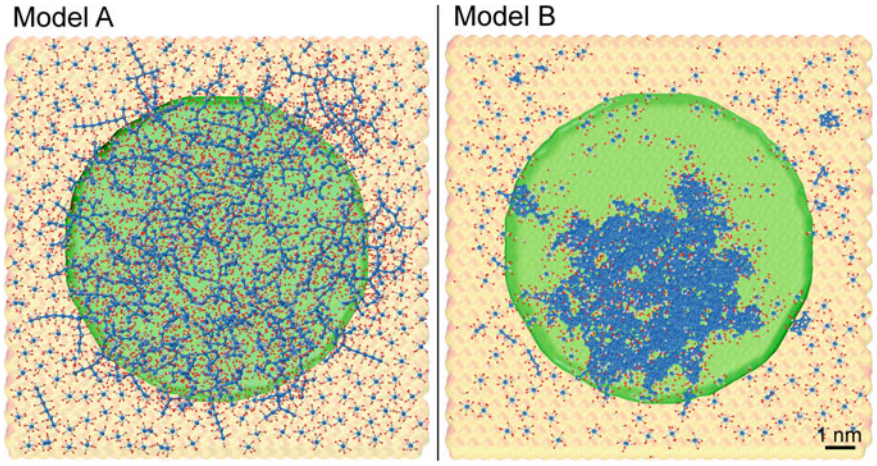

Fig. 15 Top view of morphologies of W enriched nanostructures atop the hydroxylated SiO_2 surface simulated within models A and B after 15 irradiation/adsorption cycles. Adopted from [83]

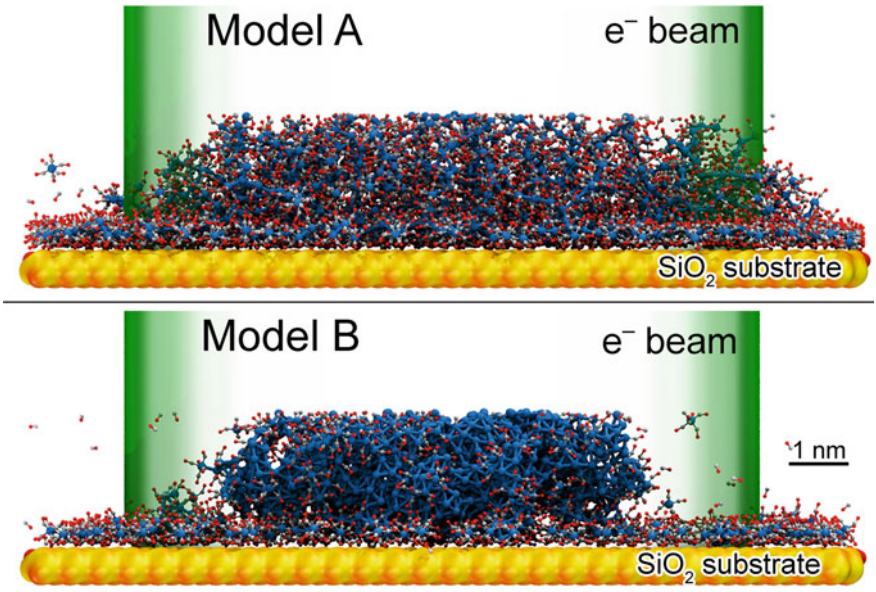

Fig. 16 Side view of morphologies of W enriched nanostructures shown in Fig. 15. Adopted from [83]

these nanostructures is ∼15 % (model A) and ∼46 % (model B). These simulations also indicate that formation of chemical bonds within the growing nanostructure is essential for the emergence of the crystalline-like molecular structure with higher content of tungsten atoms. The increase of the number of bonds between W atoms leads to the decrease of the CO content and the total number of atoms in the growing nanostructure, i.e. its growth rate.

These simulations demonstrate that the IDMD approach provides a powerful computational tool to model the growth process of W granular metal structures emerging in the FEBID process at the atomistic level of detail. The morphology of the simulated structures, their composition and growth characteristics are consistent with the available experimental data as demonstrated in [83]. Moreover, the observed dependencies like increasing of the volume growth rate per incident electron with decreasing the e-beam current, or the growth of the W content with increase of the e-beam current are reproduced correctly by within the developed models.

The performed analysis indicates also the need of further wide exploitation of the IDMD methodology in FEBID and many other processes in which the irradiation of molecular systems and irradiation driven chemistry play the key role.

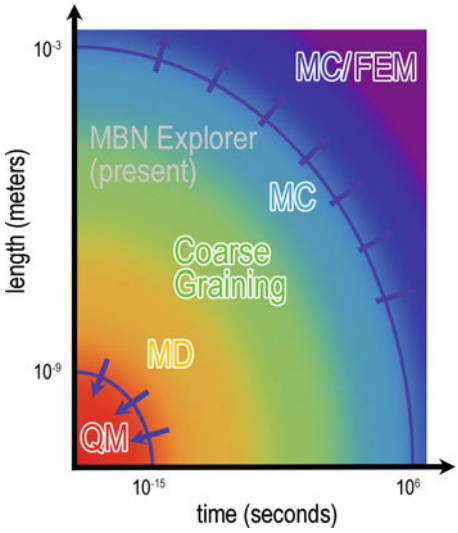

Fig. 17 Temporal and spatial system scales and the corresponding simulation methods. Adopted from MBN EXPLORER Tutorials [5]

6 Conclusions and Outlook

The further technical development of MBN EXPLORER, MBN Studio and their biomedical and nanotechnology applications will involve the creation of new modules allowing various types of multiscale modeling by linking different modeling methodologies (Quantum Mechanics (QM), Molecular Dynamics (MD), Coarse Graining, Monte Carlo (MC), Finite Element Method (FEM) and others) well-established for different temporal and spatial scales as illustrated in Fig. 17. In the figure, lines indicate the limits of the current version of MBN EXPLORER and arrows show the directions for the further development.

One of the important directions for the further development concerns the multiscale approach to the ion-beam cancer therapy allowing quantitative understanding of the medical treatments on the molecular level. The recent advances in this direction that are reported in this book will be integrated in a form of special module of MBN EXPLORER. This module could be utilised for further studies of the molecular processes behind the IBCT and the optimisation of the existing treatment planning protocols. The similar modules have already been implemented in other areas of application of MBN EXPLORER, for details see [83].

The realization of these plans should allow increasing the number of application areas, case studies and the universality of the software package much beyond of its current limits. Some of the above mentioned multiscale methodologies have already been successfully implemented in the latest release of MBN EXPLORER [5]. This process will be continued in the future. The complete realization of this programme means a long term development aiming at a large number of customers and wide exploitation of this universal and powerful software package in numerous areas of its application.

7 How to Get MBN EXPLORER and MBN Sudio?

MBN EXPLORER and MBN Studio are the software products developed by MBN Research Center gGmbH, http://www.mbnresearch.com/. Different types of licences for MBN EXPLORER and MBN Studio can be acquired from MBN Research Center via its website http://www.mbnresearch.com/, and the access to the software, the user's guide and a library of representative examples can be obtained. Inquiries about the more detailed information on the types of licences and the prices should be sent to info@mbnexplorer.com.

The further details about the current and future releases of MBN EXPLORER and MBN Studio can be found on the website: http://www.mbnexplorer.com/.

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