Simulations of Nucleic Acids and Their Complexes†

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ABSTRACT

Recent years have seen considerable progress in simulations of nucleic acids. Improvements in force fields, simulation techniques and protocols, and increasing computer power have all contributed to making nanosecond-scale simulations of both DNA and RNA commonplace. The results are already helping to explain how nucleic acids respond to their environment and to their base sequence and to reveal the factors underlying recognition processes by probing biologically important nucleic acid−protein interactions and medically important nucleic acid−drug complexation. This Account summarizes methodological progress and applications of molecular dynamics to nucleic acids over the past few years and tries to identify remaining challenges.

Introduction

This Account attempts to summarize the methodological developments and practical applications of molecular dynamics simulations applied to nucleic acids. We have considered studies involving both DNA and RNA, on isolated molecules and on complexes with drugs or proteins. In each case, we have tried to underline recent breakthroughs and continuing difficulties. Each section is illustrated with references drawn from the past four years of publication which, without being exhaustive, should cover a sufficiently broad spectrum to demonstrate how this field of molecular simulation is progressing. For other points of view and further references, the reader is referred to some recent review articles.[1−3]

Force Fields and Methodology

Thanks to considerable progress in force fields over the past few years, stable multi-nanosecond simulations of nucleic acids are now routine. AMBER parameters Parm94 (or the slightly revised Parm98),[4] CHARMM27,[5,6] and BMS[7] force fields all yield reasonable results for the A and B conformations of DNA (Figure 1). It is also worth remarking that stable B-DNA simulations[8,9] have also been achieved with the latest GROMOS implementation.[10] A number of tests have already been performed on both the AMBER and CHARMM force fields in solution[11,12] and in crystalline environments[13] on both DNA and RNA. More stringent tests of energy barriers for conformational transitions remain to be carried out.[14] A key element in all nucleic acid simulations is electrostatics. Brutal truncation methods lead to problems, but both particle mesh Ewald[15] and atom-based force-shift approaches[16] can yield stable structures. While force field parameters are continuously being improved thanks to accurate experimental data and quantum calculations on small systems, good results on macromolecules still require some less rigorous retouching in many cases. Force field refinements such as off-atom charges and the inclusion of polarization energy should help to improve this situation.[17]

In addition to the improvement of force fields, one of the main computational challenges remains the simulation of large systems over long times. One approach to this goal is the replacement of explicit solvent with hybrid explicit/implicit[18,19] or entirely implicit models.[20,21] Poisson−Boltzmann (PB) approaches have proved to be capable of reliably predicting both solvation energies and solvent-dependent conformational changes, but their computational complexity hinders their use in MD simulations. More recent efforts have focused on Generalized Born (GB) models which are much faster and can be formulated to include both salt and cavity contributions.[20,22] Such methods can be parametrized to yield reasonable solvation energies[22,23] and pK_a shifts,[22,24] and they have already been used for MD simulations on nucleic acids,[25] although our own experience suggests that some base sequences can lead to the appearance of deformed conformations (Figure 2). Further efforts in parametrization, and perhaps in formulation, are probably necessary. Despite these caveats, both PB and GB approaches, combined with structural snapshots coming from explicit solvent MD simulations, have been used to very good effect in estimating free energies in a variety of systems.[26,27] These so-called MM/PBSA or MM/GBSA approaches open an exciting route to calculating free energy changes for processes that are not accessible to conventional free energy algorithms.

Treating very large nucleic acids or dramatically extending simulation times will require replacing conventional Cartesian coordinate atom-level dynamics with simplified representations. A first step is the introduction of collective variables,[28] which allow certain degrees of freedom to be frozen, decreasing the dimension of the conformational space to be searched and allowing longer time steps to be used. Such methods have already been developed and applied to DNA with time steps around 10 fs, with good results in terms of structure[18] and sequence-dependent curvature.[30] Other attempts have been made using a Lagrangian and quaternion formula-

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† This Account is dedicated to Peter Kollman, whose recent death is a great loss to our field. His contributions to the development of macromolecular simulations and, notably, applications to nucleic acids have been instrumental in many areas of development.

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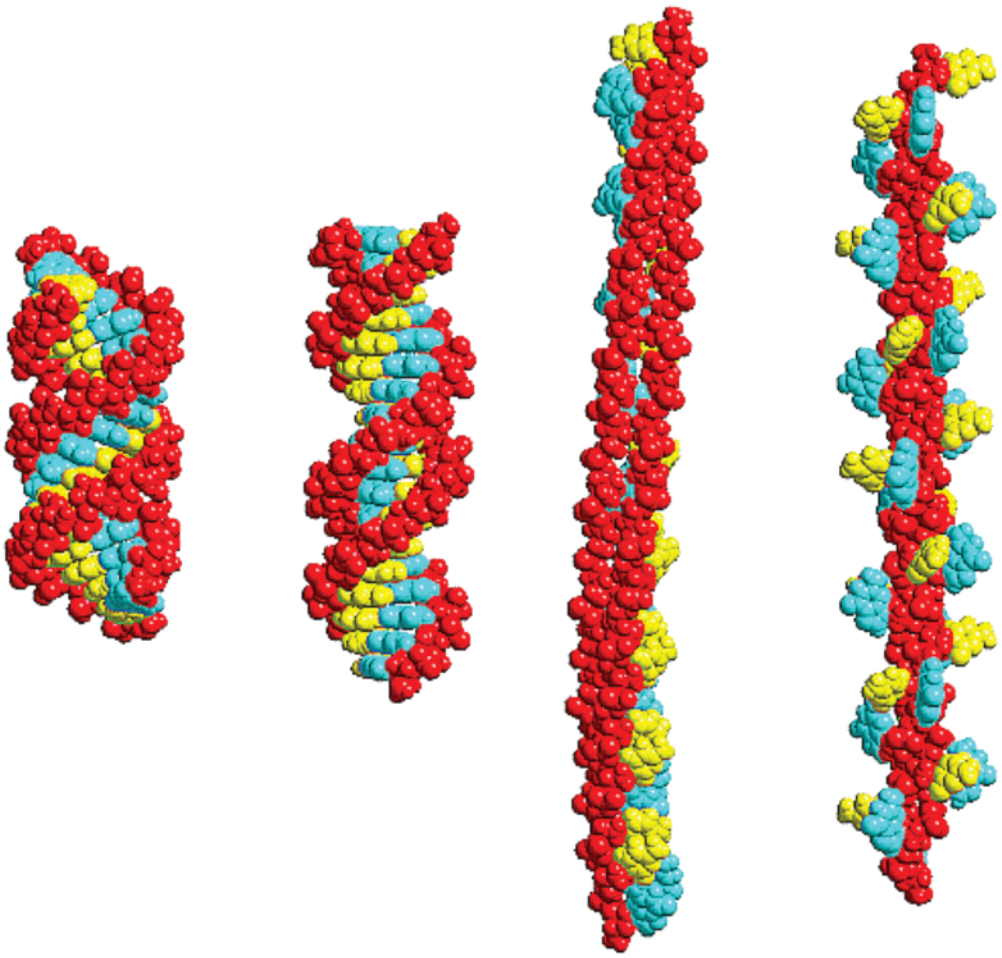

FIGURE 1. Canonical and mechanically distorted forms of helical DNA (from left to right: A-DNA, B-DNA, overstretched S-DNA,[32] overtwisted P-DNA[33]).

tion coupled with an effective force field.[31] These methods naturally pose the problem of correctly treating solvent and counterion effects. They have, however, been very useful in modeling extreme deformations, such as those induced during single-molecule experiments on DNA (Figure 1).[32,33] More extreme simplifications involving the use of elastic rod or bead models allow simulations to be extended to genome-sized fragments but also pose major questions concerning the degrees of freedom to be maintained and the parametrization of the models.[34,35]

Beyond time constraints, the difficulty of sampling conformational space can also lead to difficulties, notably in searching for complex folded conformations or in attempting to dock macromolecules together. In such cases, the use of multicopy algorithms can be very helpful,[28,29] and this has recently been demonstrated with the locally enhanced sampling approach now available within AMBER.[36] Tools for controlling a dynamic trajectory are also of considerable importance, especially for studying phenomena that would normally occur too slowly. Digital filtering, which can target elements of a structure on the basis of their characteristic frequencies of their dynamics, is a recent and interesting addition to such methods.[37]

DNA Structure and Flexibility

MD simulations have been used to look at the factors underlying DNA structure and flexibility and also the sequence dependence of these properties (Figure 3). At the local level, the free energy of both base pairing[38] and base stacking[39] has been calculated using isolated bases or dinucleotide monophosphate fragments, while other studies have probed these interactions within the double helix via induced base pair opening (Figure 4).[40] The latter results show that both bases can open into either groove of the duplex and that once a base is fully opened, water can fill the gap left within the duplex. Similar behavior is seen in the case of abasic nucleotides.[41] Although normal bases open spontaneously on the millisecond time scale, unforced opening into the major groove has been seen on a subnanosecond time scale for a modified AT pair, where thymine was replaced with a more weakly binding analogue, difluorotoluene.[42]

Base sequence effects on stacking have been demonstrated with short MD runs, which confirm that ApA steps seem to have well-defined geometries, while CpA steps can show bimodal behavior.[43] Other studies have generalized the malleability of CpA to other pyrimidine−purine steps.[44,45] Similarly, in line with NMR and CD data, runs

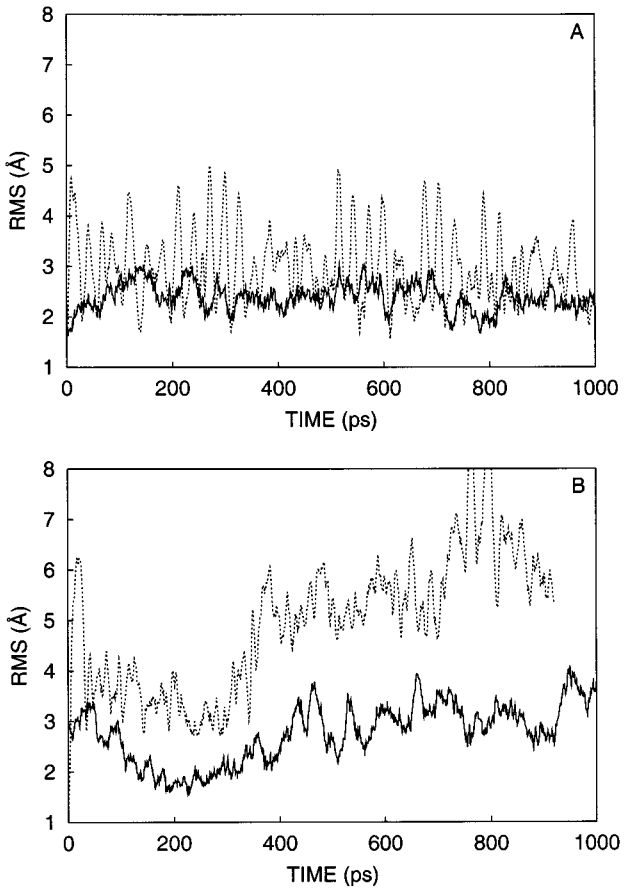

FIGURE 2. RMS deviations from a canonical B-DNA structure during dynamic simulations of 12-base-pair oligomers using explicit (solid lines) or implicit[25] (dashed lines) solvent: (a) an alternating GA sequence, (b) an alternating AT sequence (A. Lebrun, LBT Paris).

of GC base pairs have been shown to alter the stacking pattern to resemble that found in A-DNA, even if the backbone geometry remains close to that of B-DNA.[46−48]

Studies of backbone fluctuations have shown that phosphate movements associated with the B_{II} state ($\epsilon\zeta$ $tg^- \rightarrow g^-t$) occur for most nucleotides, although they are facilitated by YpR steps.[49,50] These transitions are linked to base unstacking and water rearrangement and are also favored by lower water activity.[51] B_{II} states can last from a few picoseconds to several nanoseconds. However, even when such backbone conformations are relatively long-lived, they only weakly influence the helical conformation of DNA.[52]

On a more global scale, a number of simulations have looked at the nature of the A → B transition. This transition, which is directly coupled to changes in sugar puckering,[53] has been shown to occur spontaneously in water, although the reverse transition does not occur in an ethanol/water mixture, presumably because of a significant energy barrier.[54] Poisson−Boltzmann or Generalized Born solvation energy calculations using MD snapshots confirm the experimental observation that GC-rich sequences are more A-philic[46] and show that the transition can be linked to a shift in the balance of inter-phosphate repulsion, desolvation, and ion−DNA interaction terms.[55]

Studies of sequence effects on global DNA structure and flexibility have mainly dealt with A-tract-induced curvature, where the consensus view is now that A-tracts are straight and that curvature is explained by a junction-type model with roll toward the major groove concentrated at the 5′-end of the A-tract.[44,56−58] In line with experiment, simulations of A-tracts show minor groove narrowing in the 5′ → 3′ direction, while TpA junctions widen the minor groove and disfavor curvature. [56,59]

Other AT sequences which have attracted the attention of several groups are the TATA box sites which are targeted, and strongly deformed, by the TATA box binding protein (TBP). In line with experiment, MD simulations have confirmed that AT sequences showing stronger and more anisotropic DNA bending toward the major groove are correlated with stronger TBP binding,[60] while PMF calculations also show a correlation with the deformation free energy necessary to reach the so-called TA conformation induced by this protein.[61,62] Beyond these cases, only limited studies of sequence effects have been made so far, although one study of simple homopolymeric and dinucleotide repeating sequences has used a harmonic analysis of MD simulations to show that only relatively small, sequence-dependent variations occur in global rodlike flexibility (twisting, bending, stretching).[63]

DNA−Ligand Complexes

Studying ligand binding with MD simulations is apparently proving to be a reliable way of understanding the static and dynamic aspects of these complex conformations in solution, avoiding difficulties which can occur in a crystalline environment, such as modified backbone conformations (e.g., B_I/B_{II} ratios) or hindered curvature.[64−66] Free energy calculations also allow reasonable calculations of binding strengths and can expose unexpected cancellations in the factors contributing to binding.[67]

Simulations remain an integral part of structure determination by NMR spectroscopy. One can note a considerable increase in the quality of such calculations, which now frequently include explicit solvent, reliable treatment of long-range electrostatics, and time-averaged constraints. Ligand−DNA complexes can still hold a number of surprises, especially as concerns dynamics, as evidenced by recent studies of a bis-intercalator which suggest that the intercalated moieties can flip over rapidly (1800 s^{-1} at 36 °C) without unstacking.[68]

Future possibilities are illustrated by an ab initio dynamics study of *cis*-platin binding to a dinucleotide monophosphate in aqueous solution. Even if such simulations currently span only a few picoseconds, there is no doubt that such approaches will give detailed insight into the chemistry of DNA interactions.[69]

DNA−Protein Complexes

Both the rapid accumulation of X-ray and NMR data and increasing computer power have contributed to an increasing number of simulations of protein−DNA complexes. Depending on whether CHARMM or AMBER is

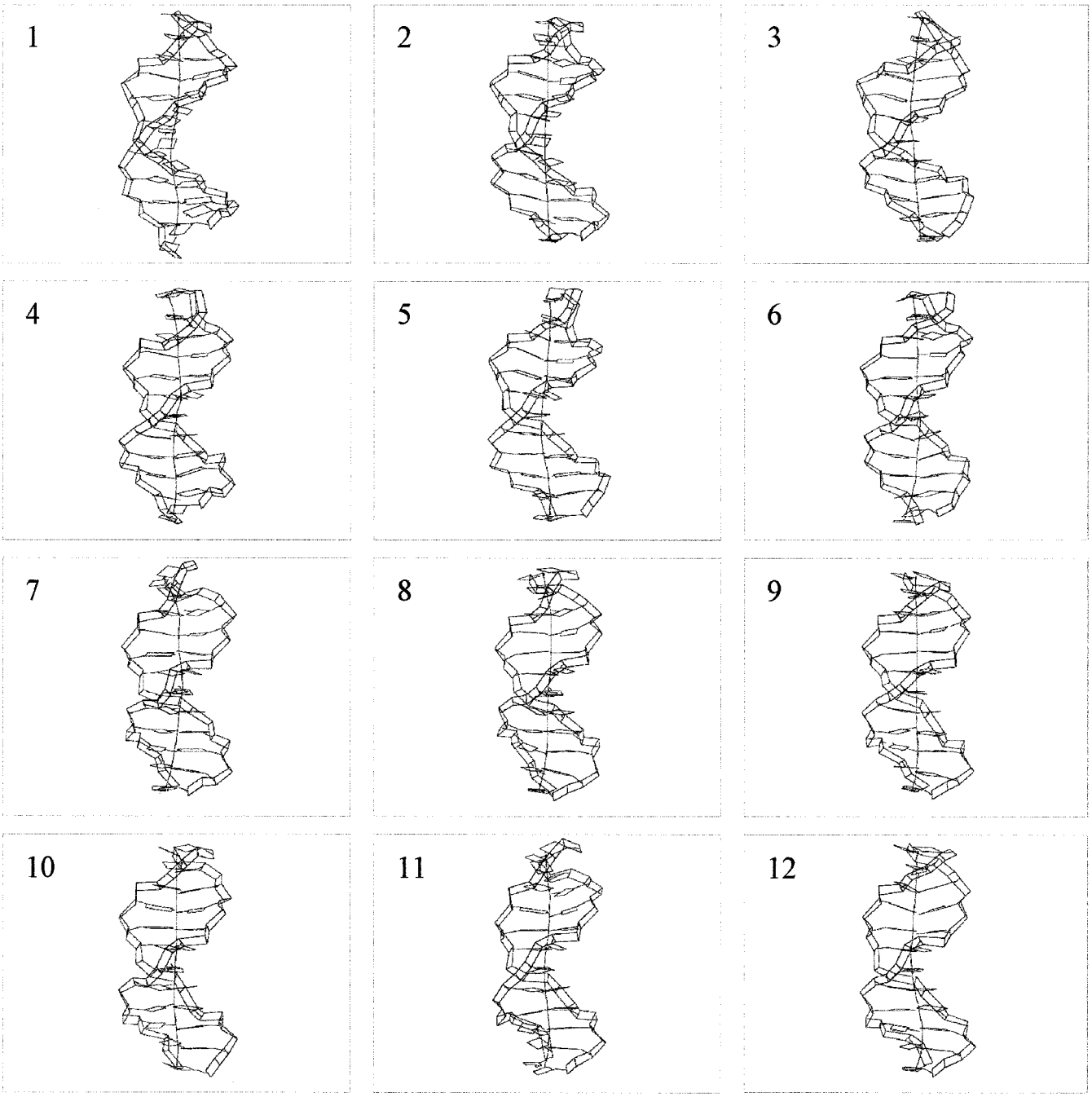

FIGURE 3. Conformational fluctuations of a B-DNA oligomer with an alternating GA sequence. The snapshots (100 ps intervals) from a simulation at 300 K using explicit solvent and counterions show axis and backbone fluctuations (E. Giudice, LBT Paris).

employed, the systems modeled generally solvate the complex within a water sphere and either use shift/switch technology for long-range interactions or use periodic boundary conditions and particle-mesh Ewald electrostatics. Recent studies belonging to the first category have dealt with complexes of EcoRI,[70,71] the minor groove binding protein SRY,[72,73] the 434cI repressor,[74] the glucocorticoid receptor,[75] and the non-sequence-specific protein HMG-D.[76] Examples of the second category include Hin-recombinase,[77] three zinc fingers belonging to TFIIIA,[78] and the Trp repressor.[79] Systems solvated with water spheres typically involve of the order of 20 000 atoms, while this number can rise to 40 000 when periodic boundary conditions are used on large systems.[79] Simulations have reached the nanosecond range only in recent years, and we can assume, as for smaller systems, that longer simulations will reveal new categories of dynamic movement. With this caveat, present simulations nevertheless result in stable protein−DNA interfaces, reproduce most, or all, of the specific interactions observed experimentally, and, often, emphasize the role played by water-mediated hydrogen bonding between the two partners.[70,74,79] In the case of the zinc fingers of TFIIIA, a particularly impressive agreement was achieved with NMR data on the placement of solvating waters at and around the protein−DNA interface.[78]

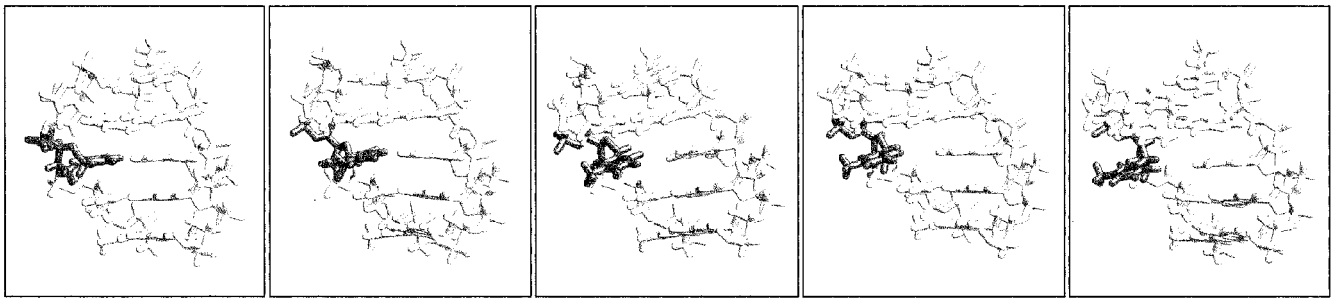

FIGURE 4. Induced base opening within B-DNA. Images show the conformational changes associated with moving thymine (bold) into the major groove of an oligomer with an alternating GA sequence.[40]

Computer simulations are also powerful tools for analyzing the components of recognition processes. This can involve looking at structural adaptation upon binding[70,72−74] or the consequences of point mutations.[71,73,75] Another interesting approach used a simulation of the largely hydrophobic TBP−DNA complex to interpret hydroxyl radical cleavage data in terms of both sugar accessibility and fluctuations of the protein side chains contacting the DNA backbone.[80] A challenge which still lies largely in the future is the development of reliable protein−DNA docking procedures. [76]

DNA Triple and Quadruple Helices

Three- and four-stranded DNA conformations continue to attract a great deal of attention because of their potential applications in artificial gene regulation and in cancer therapy. Dynamic simulations in this area have clearly helped in understanding the structure and stability of such structures.[81−84] Recent refinements include studies of the stabilization of runs of GCC^+ triplets by the replacement of some cationic cytosines with neutral amino tautomers[85,86] and also studies of ion binding to quadruplexes, which can occur along the axis of the base tetrads, in the grooves, or in the loops of intramolecular complexes.[83,87,88] Simulations are also being used actively in the design of modified nucleotides, such as 8-amino guanine, which reinforces Hoogsteen GC pairs,[89,90] or of modified backbones which replace anionic phosphates with neutral linkers, as in PNA,[91] or even with cationic groups, such as S-methylthiourea.[92] Ligands which can specifically stabilize triplexes or quadruplexes, such as the family of disubstituted amidoanthraquinones,[93,94] are also being investigated.

RNA and RNA Complexes

Simulations involving RNA are accumulating rapidly, although the size, charge, and structural variety of these molecules continue to pose significant challenges. Several studies have addressed the dynamics of the basic motifs found in folded RNA, including mispairs such as flexible water-bridged UC pairs,[95] or coaxial stacking, where the absence of backbone continuity causes kinking and untwisting but does not enhance flexibility.[96] Studies of stem loops show that nanosecond dynamics maintain stable conformations but cannot sample extensively enough to identify conformational substates.[97] Similar problems occur with bulged bases, where energy barriers prevent sampling of stacked and expelled base conformations during single trajectories.[98] Despite some courageous attempts,[99] many problems confront the use of simulations for structural predictions on larger fragments. One positive step is the estimation of relative free energies using MM/PBSA or MM/GBSA approaches, which has already correctly predicted RNA tetraloop conformations and, in the case of PB calculations, hairpin/duplex equilibria.[100,101]

Despite sampling problems, it is impressive to see the size of the systems which are now being treated, the most striking being a stable simulation of $tRNA^{Phe}$ with more than 8000 waters—although some rearrangement in the core region raises the question, and the difficulties, of adding Mg^{2+} ions to such simulations.[102]

Most protein−RNA studies have targeted the U1A−RNA system where structural data exist for both the U1 stem loop and the UTR internal loop binding sites. Simulations show that stable complexes are maintained on the nanosecond time scale in low salt[103,104] and can be dissociated in high salt.[105] Recognition processes depend on initial electrostatic interactions but also involve the deformation and stiffening of the macromolecular partners and specific hydrogen bonding with bases. MM/PBSA studies have again been used successfully to estimate binding free energies and the consequences of site mutations.[106,107] RNA−drug complexes are also attracting much attention. An interesting example involves a general model for binding aminoglycoside antibiotics, where the ammonium groups of the drug substitute for Mg^{2+} binding sites.[108] The readers are referred to a recent review for other examples.[101]

Water and Ion Distributions

Longer and more stable simulations have sparked a deeper analysis of the role of water and ions in stabilizing both DNA and RNA conformations. First-shell water residence times can extend to the nanosecond range, and this is also true for monovalent ions.[109−112] Waters are found around the backbones and in both grooves of the helix, although long-lived hydration patterns are mainly confined to the narrower groove of both DNA and RNA and appear more sequence dependent in the case of DNA.[109,113] Ions occupy

both major and minor groove sites and are strongly coupled to DNA bending[110] via major groove interactions with CpG steps and possibly to minor groove width in AT-rich tracts, although this conclusion depends on the definition of ion binding.[110,111,114] First-shell hydration and ion binding have also been studied with respect to the B → A transition, where the electrostatics dominate, although many factors contribute to a subtle sequence-dependent free energy balance.[110,114,115]

Conclusions

Stable multi-nanosecond trajectories of both helical and folded nucleic acids showing good agreement with experimental data are now within reach. The effects of base sequence and of environmental changes are also becoming accessible. Such studies provide an atomic-scale view of thermally induced fluctuations, allow the characterization of conformational substates and the location of transition pathways, and, in optimal cases, allow a detailed structural and energetic analysis which goes beyond current experimental possibilities. Given the polyelectrolyte nature of nucleic acids, particularly interesting developments involve a better understanding of how solvent and counterions influence the behavior of these environmentally sensitive macromolecules. Outstanding challenges concern the simulation of comparatively slow and complex processes such as the formation of nucleic acid−protein complexes or the folding of RNA domains, the simulation of much larger molecular systems, and the treatment of chemical reactions. Solving these problems will require effort on many fronts, including the definition of better continuum solvent models, the formulation of mesoscopic models (which implies decisions on crucial degrees of freedom and the development of reliable effective force fields), and the creation of interfaces between classical and quantum dynamics.

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