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oxDNA: coarse-grained simulations of nucleic acids made simple

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Software

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Summary

The fields of DNA and RNA nanotechnology have progressed from pioneering, proof-of-principle experiments to fully-fledged applications in material science, biology and medicine. These applications exploit the intrinsic programmability of nucleic acids to generate nano- and even micro-scale structures with tailored properties. However, the design of the DNA/RNA sequences that self-assemble into a desired structure is not straightforward and often relies on expensive trial-and-error experimental protocols. A complementary approach is provided by computer simulations, which can model biomacromolecules at different levels of detail, ranging from atomistic to continuous, and can be leveraged to investigate the whole range of time- and length-scales relevant for applications. Here we present `oxDNA`, a software package that has been designed to efficiently run coarse-grained simulations of DNA and RNA and also features an analysis suite aimed at post-processing the analysis of oxDNA/oxRNA trajectories.

Statement of need

The simulation of nucleic acids has become an important tool from the fundamental point of view to understand how these biomacromolecules behave and, from an application standpoint, to predict their behaviour under specific conditions (Dans et al., 2016). The ideal model for each specific problem, and therefore the level of detail with which DNA and RNA are to be described, depends on the time and length scales of interest: at one end of the spectrum there is quantum chemistry modelling, which can be used to probe the microscopic properties of a small number of nucleotides (Šponer et al., 2008), while at the other end there are continuum descriptions based on polymer theories such as the worm-like chain model (Nomidis et al., 2019) that can be used to study the behaviour of long DNA strands. A middle road is provided by coarse-grained models that describe nucleic acids at the nucleotide level (Doye et al., 2013). At this level of detail the oxDNA, oxDNA2 and oxRNA models has become popular choices to investigate the dynamics, thermodynamics and self-assembly behaviour of DNA and RNA systems (Sengar et al., 2021; Šulc et al., 2014), and have been used in more than a hundred publications to date.

Functionality

Here we present an updated version of the `oxDNA` code, an efficient, multi-technique simulation package written in C++ and specifically developed to carry out simulations of coarse-grained

nucleic acid systems described with the oxDNA and oxRNA models. The package, which is named after the original oxDNA model, can perform both molecular dynamics (MD) and Monte Carlo (MC) simulations. MD simulations can be run on single CPUs or single CUDA-enabled GPUs, while MC simulations, which can only be run serially, can exploit the Virtual Move Monte Carlo algorithm (Whitelam & Geissler, 2007) to greatly speed-up equilibration and sampling, and Umbrella Sampling biasing to efficiently obtain free-energy profiles. The package also features a Forward-Flux Sampling interface to study the kinetics of rare events (Allen et al., 2009), and makes it possible to alter the behaviour of the systems by adding *external forces* that can be used, for instance, to pull on or apply torques to strands or confine nucleotides within semi-planes or spheres.

The package can also be used to compute nucleic-acid-related quantities such as the energy due to hydrogen bonding or stacking, the distance between groups of nucleotides, the list of hydrogen-bonded nucleotides or of over-stretched bonds, and much more. The analysis can be performed while the simulation is running or on trajectory files produced by finished simulations.

The version of the code we present here is hosted on GitHub and has been modernised with respect to earlier versions (see *e.g.* (Rovigatti et al., 2015)) to exploit the C++-14 and CUDA 11 standards. This new version also includes `oxpy`, a Python library which makes it possible to control the behaviour of the simulation using Python scripts, as well as examples that demonstrate how to leverage `oxpy` to write backends to run replica-exchange (Sugita & Okamoto, 1999) and well-tempered metadynamics (Barducci et al., 2008) simulations which are popular techniques in modern molecular dynamics to improve sampling efficiency.

The simulation engine is complemented by an updated version of `oxDNA_analysis_tools` (`oat`) (Poppleton et al., 2020), a Python library aimed at facilitating the analysis of oxDNA/oxRNA trajectories. `Oat` provides numerous common simulation trajectory analysis tools including alignment, mean structures, subsetting trajectories, distances between nucleotides, interduplex angles, and comparison in hydrogen bonding patterns between the trajectory and an idealised structure. `Oat` was previously published as a standalone Python package (Poppleton et al., 2020), however, since the initial publication, substantial improvements have been made including a new Cython-based random access file parser which accelerated computation of mean structures by more than 10x, and close integration with `oxpy`, which sped up and simplified calculation of nucleotide interactions by more than 100x. `Oat` was developed with the intention of facilitating other, more specific, analysis tasks. The file readers and utility functions are available for import into users' Python projects and the scripts themselves are well-commented to serve as examples for users to extend them for their own needs.

Related software

Molecular dynamics simulations of oxDNA and oxRNA can also be performed with the `LAMMPS` software package, whose efficient parallel-computing algorithms make it possible to simulate large systems on HPC clusters (Henrich et al., 2018). However, at the moment it lacks GPU support, it cannot be used to build free-energy profiles by biasing discrete reaction coordinates (*e.g.* number of correct basepairs) and there are no tools to analyse LAMMPS-generated trajectories such as `oat` (Poppleton et al., 2020) or `oxview` (Bohlin et al., 2022). In addition, the LAMMPS engine supports many more (often oxDNA-unrelated) options, which may make it harder to correctly setup oxDNA simulations compared to `oxDNA`. Therefore, the `oxDNA` simulation package presented here complements the `LAMMPS` version, which also bears the "oxdna" name, rather than competing with it.

Finally, we note that there are many software packages that either use `oxDNA` or take as input, output or manipulate configurations generated with the `oxDNA` package. The list comprises `MrDNA` (Maffeo & Aksimentiev, 2020), `Adenita` (Llano et al., 2020), `TacoxDNA` (Suma et al., 2019), `oxDNA.org` (Poppleton et al., 2021), `scadnano` (Doty et al., 2020), `MagicDNA` (Huang

et al., 2021) and ENSnano (Levy & Schabanel, 2021).

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