Promoting transparency and reproducibility in enhanced molecular simulations

The PLUMED consortium unifies developers and contributors to PLUMED, an open-source library for enhanced-sampling, free-energy calculations and the analysis of molecular dynamics simulations. Here, we outline our efforts to promote transparency and reproducibility by disseminating protocols for enhanced-sampling molecular simulations.

The PLUMED consortium

Molecular dynamics (MD) simulations have become an important tool for characterizing the mechanisms underlying complex processes, interpreting experimental measurements and predicting the behavior of molecular systems. This success has been achieved through more than 60 years of innovation. During this time, a wide community of researchers has developed accurate integrators of the equations of motion; effective thermostats; accurate physicochemical models of small molecules, proteins, nucleic acids, liquids and materials; many techniques to accelerate sampling; sophisticated analysis tools; powerful, personal and dedicated computers; and efficient, user-friendly software. These advances ensure that MD provides a powerful and versatile computational microscope that can be applied in fields ranging from physics and chemistry to biology and materials science.

Innovations in this field are now emerging at an increasing pace. Areas in which there are still open challenges, and hence active development, include extension of the timescales accessible in standard simulations[1], new methods for making sense of the high-dimensional data generated by MD[2], and new integrative approaches for improving the accuracy of force fields by incorporating quantum-chemical and experimental data[3]. Furthermore, although great efforts have been made to define good practices for preparing, executing and analyzing MD simulations[4], much work is still required to ensure that the community can reap the maximal benefit from recent and ongoing developments.

The initiative that we present here stems from the realization that many of the challenges discussed above cannot be effectively overcome by individual researchers working alone. Instead, a concerted effort by the entire simulation community is required. Numerous important initiatives have thus been launched to improve the way in which data and know-how are communicated. These initiatives include SimTK (https://simtk.org), a platform for sharing software and data for the biomedical computation community; the Open Force Field Initiative (https://openforcefield.org), which has been developed in coordination with the Molecular Software Sciences Institute (https://molssi.org) to improve the physicochemical models used in MD; the Centre of Excellence for Computational Biomolecular Research (https://bioexcel.eu), whose mission is to improve biomolecular software and spread best practices; the Living Journal of Computational Molecular Science (https://www.livecomsjournal.org), which publishes and regularly updates educational reviews and best-practice papers; Materials Cloud (https://www.materialscloud.org), a platform for sharing resources in materials science; AiiDA

Box 1 | Overview of the PLUMED library

PLUMED is an open-source C++ library that can be interfaced with many state-of-the-art MD codes. Its basic functionalities are: (i) to retrieve the current atom positions from the main code; (ii) to calculate additional quantities, such as coarse-grained representations of the system (collective variables (CVs)) and external biasing potentials; and (iii) to communicate external forces back to the MD code and hence modify the dynamics. PLUMED provides all the functionalities needed to carry out MD simulations using well-established enhanced-sampling methods, such as umbrella sampling, metadynamics and steered MD. These techniques can be used in combination with a large toolbox of CVs that describe complex processes in physics, chemistry, materials science and biology. These CVs include distances between pairs of atoms, torsional angles, secondary structure content, radius of gyration, contact maps, energy of the system, various metrics to measure the distance from reference conformations, and functionalities to employ user-defined CVs based on artificial neural networks. PLUMED can also calculate these descriptors a posteriori on precalculated trajectories via a postprocessing utility called 'driver', and can perform other analyses such as dimensionality reduction and calculation of equilibrium properties of CVs not directly biased in the simulation.

PLUMED can be interfaced with the host code through the use of a single well-documented application programming interface (API) that enables the PLUMED functionalities to be imported. The API can be accessed in multiple languages (C, C++, FORTRAN and Python) and is thus compatible with the majority of the codes used in the community. The PLUMED license (L-GPL) allows it to also be interfaced with proprietary software. Several MD codes, including AMBER, LAMMPS, DL_POLY, i-PI and OpenMM, now have the interface to PLUMED natively implemented. Furthermore, the PLUMED developers currently provide and maintain a set of patches for popular MD packages, such as GROMACS and NAMD.

The current structure of PLUMED is modular — that is, new functionalities can be added without changes to the core of the code. New CVs and new biasing or analysis methods can thus be either distributed with the main core or loaded as separate dynamic libraries. The ease with which PLUMED can be extended is evidenced by the number of forks of the official repository (https://github.com/plumed/plumed2) that have been created on GitHub by independent groups, as well as by the growing number of additional modules contributed to PLUMED (Box 2).

Box 2 | Overview of the current PLUMED modules

All members of the consortium, as well as other researchers, can contribute an external module to PLUMED. As described in the PLUMED developer manual, contributed modules must pass quality control checks before being incorporated into the official PLUMED distribution and should have an open-source license. Currently, six modules have been contributed by groups external to the core developers of the code. All these modules are independent from the PLUMED core and need to be activated when PLUMED is configured. The largest contributed module (VES) implements the variationally enhanced sampling[26] approach and includes a number of basis functions, target distributions and optimization algorithms. The DRR module implements the extended-system adaptive biasing force method for enhanced-sampling and free-energy calculations[27]. The EDS module implements the experiment-directed simulation approach to adaptively construct linear restraints that ensure that the biased CVs sample a new target mean value[28]. The logMFD module can be used for enhanced sampling using logarithmic mean-force dynamics[29]. The piv module contains an implementation of the permutation-invariant vector[30], which is a general-purpose representation of the structure of materials that can be used to analyze and simulate the transitions between ordered and disordered forms that take place in processes such as crystal nucleation. The MAZE module[31] can be used to find multiple diverse reaction pathways for ligand unbinding. Furthermore, the PLUMED-ISDB[32] module has been contributed by a subset of PLUMED developers and enables different types of experimental data, such as measurements from nuclear magnetic resonance spectroscopy, small-angle X-ray scattering, and cryo-electron microscopy, to be integrated into MD simulations. All the CVs and enhanced-sampling approaches contributed via these modules can be seamlessly combined with all the other functionalities implemented in PLUMED. Each module is accompanied by documentation and tutorials that are integrated into the online PLUMED documentation.

(http://www.aiida.net), an infrastructure to disseminate simulation data and workflows; the E-CAM Centre of Excellence (https://www.e-cam2020.eu), which supports high-performance simulations in industry and academia; the NOMAD laboratory (https://nomad-coe.eu), which maintains a repository of input/output files for total energy calculations in materials science; the Materials Project (https://materialsproject.org), which provides open access to information on known and predicted materials; Qresp (http://qresp.org), a tool for curating and exploring reproducible scientific papers; and nanoHUB (https://nanohub.org), a platform for sharing simulation software and educational tools for nanoscience. A more exhaustive list of data repositories has been compiled by *Scientific Data*[5]. Furthermore, these initiatives have been complemented by events focused on promoting openness, transparency and reproducibility in MD simulations, such as the recent workshop 'Sharing Data from Molecular Simulations', held in Stockholm in November 2018[6].

While these initiatives have laid crucial groundwork that increases the reproducibility of MD simulations, their effectiveness is hampered by the lack of interoperability between MD codes. As a matter of fact, methods that have the potential to be useful across different fields cannot be easily incorporated across multiple MD software packages, as each one of these codes is optimized for specific applications and might be written in a different programming language. A strategy to resolve this problem was pioneered with the creation of PLUMED[7], an open-source library that provides enhanced-sampling algorithms, free-energy methods and tools for analyzing the vast amounts of data produced by MD simulations (Box 1). Similar interoperable libraries, such as the collective variables module for molecular simulation programs (Colvars)[8] and the software suite for advanced generalized ensemble simulations (SSAGES)[9], have since been developed.

Recently, PLUMED has incorporated functionalities that surpass those originally conceived by its creators. The development of an infrastructure that allows external contributions to be easily incorporated into the code (Box 2) has transformed PLUMED into a flexible open-source library[10]. Currently, PLUMED can be used with both classical and ab initio MD codes, such as ACEMD[11], Amber[12], DL_POLY[13], GROMACS[14], LAMMPS[15], NAMD[16], OpenMM[17], ABIN (https://github.com/PHOTOX/ABIN), CP2K[18], i-PI[19], PINY-MD[20] and Quantum Espresso[21]. Furthermore, PLUMED can now be used to enhance the capabilities of analysis tools such as VMD[22] and of platforms such as HTMD[23] and OpenPathSampling[24]. When new techniques are implemented in PLUMED, they can be rapidly disseminated to a large and diverse user base, thus making them accessible and easy for everyone to use. This impact across multiple communities is further accelerated by the fact that PLUMED uses a unified syntax for all the programs with which it can be used. The interoperability enabled by PLUMED ultimately allows for cross-validation between various MD softwares and cross-fertilization of ideas among computational chemistry, biophysics and materials science.

The success of PLUMED is due not just to the contributions of a few core developers but also to the efforts of a wider community of users and developers. To acknowledge this model, we are announcing the foundation of the PLUMED consortium, whose mission is to transform how scientists communicate MD protocols so as to increase reproducibility and maximize the impact of new research. The primary way in which the consortium achieves this goal is through the continued, community-driven development of PLUMED. Additionally, the consortium will collectively strive to promote good practices for selecting the simulation parameters to be used in enhanced-sampling MD simulations, for reporting simulation protocols and for quantifying the statistical uncertainty in calculated observables. To facilitate the adoption of these practices and to encourage the highest possible standards of scientific reproducibility, consortium members will share the input files and protocols for the simulations in their published works.

To realize the mission of the consortium, we have created the PLUMED-NEST repository (https://www.plumed-nest.org), which all members, as well as other researchers, are encouraged to use to share their PLUMED input files and all other data required to replicate the calculations presented in their papers (Box 3). This repository will not only promote scientific reproducibility but also serve as a tool that novices can use to study real-life applications of these techniques in the fields of computational chemistry, physics, materials science and biology. In this regard, the repository will help us develop resources for training new generations of scientists in the community — an objective that we will continue to work towards by organizing user meetings and both in-person and online tutorials.

The PLUMED consortium is an open community composed of developers, contributors, and all those researchers

Box 3 | PLUMED-NEST, the public repository of the PLUMED consortium

A public repository has been created to collect contributions from members of the PLUMED consortium and from other users. Dubbed PLUMED-NEST, it hosts the PLUMED input files and links to all the data required to reproduce the results of enhanced-sampling simulations or analyses that have been carried out with PLUMED. PLUMED-NEST already contains more than 50 examples of applications and method developments in the areas of computational biology, chemistry and material science. The repository can be searched by the type of contribution (method development or application in chemistry, physics, biology and materials science), author, project name and specific keywords. In the future, it will also be possible to search the PLUMED input files on the basis of the functionalities and keywords used.

All input files deposited in PLUMED-NEST are automatically tested to ensure that both the current and the development versions of PLUMED can successfully parse the input files provided. Furthermore, the keywords in input files appear as links to the documentation in the manual so that the users can easily access more information about what is being computed. It is also possible to add contextual, tutorial-like information to the input files and thus to provide additional details about what is being computed by a particular file. Finally, we envision the incorporation of commenting functionalities for the input files included in the repository so users can provide direct feedback to the authors of the original papers.

PLUMED-NEST will serve multiple functions. It will (i) promote scientific reproducibility by offering users a place to share with the community all the information that is required to repeat a simulation or analysis reported in a published paper; (ii) serve as a repository of real-life examples for educational purposes, and thus complement the tutorials that are already available on the PLUMED website; and (iii) enable the PLUMED developers to identify the functionalities that are most used, and thus guide them in improving the PLUMED core code and documentation.

whose work builds in part on PLUMED and at the same time drives its development. The consortium's member list will be updated regularly on the website (https://www.plumed.org), and the PLUMED core developers will act as coordinators. We strongly believe that this novel organization best represents the community-driven effort that is the heart and soul of open-source software development, which is a crucial part of any methodological advancement[25]. Furthermore, this decentralized organization with the support of a wide community will be essential for the long-term sustainment of PLUMED. We therefore welcome all future members who share our vision. ❐

The PLUMED consortium

Massimiliano Bonomi[1,2]*, Giovanni Bussi[3]*, Carlo Camilloni[4]*, Gareth A. Tribello[5]*, Pavel Banáš[6], Alessandro Barducci[7,8,9,10], Mattia Bernetti[3], Peter G. Bolhuis[11], Sandro Bottaro[12], Davide Branduardi[13], Riccardo Capelli[14], Paolo Carloni[14], Michele Ceriotti[15,16], Andrea Cesari[3], Haochuan Chen[17], Wei Chen[18], Francesco Colizzi[19], Sandip De[20,77], Marco De La Pierre[21], Davide Donadio[22], Viktor Drobot[23], Bernd Ensing[11], Andrew L. Ferguson[24], Marta Filizola[25], James S. Fraser[26,27], Haohao Fu[17], Piero Gasparotto[28,29], Francesco Luigi Gervasio[30,31], Federico Giberti[15,16], Alejandro Gil-Ley[32], Toni Giorgino[33], Gabriella T. Heller[34], Glen M. Hocky[35], Marcella Iannuzzi[36], Michele Invernizzi[37,38], Kim E. Jelfs[39], Alexander Jussupow[40,41], Evgeny Kirilin[42], Alessandro Laio[3,43], Vittorio Limongelli[44,45], Kresten Lindorff-Larsen[46], Thomas Löhr[34], Fabrizio Marinelli[32], Layla Martin-Samos[47], Matteo Masetti[48], Ralf Meyer[49], Angelos Michaelides[28,29], Carla Molteni[50], Tetsuya Morishita[51], Marco Nava[52], Cristina Paissoni[4], Elena Papaleo[53,54], Michele Parrinello[12,38,55], Jim Pfaendtner[56], Pablo Piaggi[38,55], GiovanniMaria Piccini[38,55], Adriana Pietropaolo[57], Fabio Pietrucci[58,59,60], Silvio Pipolo[61,62], Davide Provasi[25], David Quigley[63], Paolo Raiteri[64,65], Stefano Raniolo[44], Jakub Rydzewski[66], Matteo Salvalaglio[29,67], Gabriele Cesare Sosso[68], Vojtěch Spiwok[69], Jiří Šponer[70], David W. H. Swenson[71], Pratyush Tiwary[72,73], Omar Valsson[74], Michele Vendruscolo[34], Gregory A. Voth[75] and Andrew White[76]

[1]Department of Structural Biology and Chemistry, Institut Pasteur, Paris, France. [2]UMR 3528, CNRS, Paris, France. [3]International School for Advanced Studies (SISSA), Trieste, Italy. [4]Dipartimento di Bioscienze, Università degli Studi di Milano, Milano, Italy. [5]Atomistic Simulation Centre, Queen's University Belfast, Belfast, UK. [6]Faculty of Science, Palacký University, Olomouc, Czech Republic. [7]Centre de Biochimie Structurale de Montpellier, Montpellier, France. [8]UMR 5048, CNRS, Montpellier, France. [9]U 1054, INSERM, Montpellier, France. [10]Université de Montpellier, Montpellier, France. [11]Van 't Hoff Institute for Molecular Sciences, University of Amsterdam, Amsterdam, the Netherlands. [12]Italian Institute of Technology, Genova, Italy. [13]Schrödinger Inc., Cambridge, UK. [14]Computational Biomedicine (IAS-5/INM-9), Forschungszentrum Jülich, Jülich, Germany. [15]Institute of Materials, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland. [16]National Centre for Computational Design and Discovery of Novel Materials (MARVEL), Lausanne, Switzerland. [17]Research Center for Analytical Sciences, College of Chemistry, Nankai University, Tianjin, China. [18]Department of Physics, University of Illinois, Urbana-Champaign, Urbana, IL, USA. [19]Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology (BIST), Barcelona, Spain. [20]Institute of Materials, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland. [21]Pawsey Supercomputing Centre, Kensington, Western Australia, Australia. [22]Department of Chemistry, University of California, Davis, Davis, CA, USA. [23]Department of Chemistry, Lomonosov Moscow State University, Moscow, Russia. [24]Pritzker School of Molecular Engineering, University of Chicago, Chicago, IL, USA. [25]Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [26]Department of Bioengineering and Therapeutic Science, University of California, San Francisco, San Francisco, CA, USA. [27]California Institute for Quantitative Biology, University of California, San Francisco, San Francisco, CA, USA. [28]Department of Physics and Astronomy, University College London, London, UK. [29]Thomas Young Centre, London, UK. [30]Department of Chemistry, University College London, London, UK. [31]Institute of Structural and Molecular Biology, University College London, London, UK. [32]National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA. [33]Biophysics Institute (IBF-CNR), National Research Council, Milan, Italy. [34]Department of Chemistry, University of Cambridge, Cambridge, UK. [35]Department of Chemistry, New York University, New York, NY, USA. [36]Department of Chemistry, University of Zurich, Zurich, Switzerland. [37]Department of Physics, ETH Zurich, Lugano, Switzerland. [38]Faculty of Informatics, Università della Svizzera italiana, Lugano, Switzerland. [39]Department of Chemistry, Imperial College London, London, UK. [40]Department of Chemistry, Technical University of Munich, Garching, Germany. [41]Institute of Advanced Study, Technical University of Munich, Garching, Germany. [42]Belozersky Institute of Physico-Chemical Biology, Lomonosov Moscow State University, Moscow, Russia. [43]International Centre for Theoretical Physics (ICTP), Trieste, Italy. [44]Faculty of Biomedical Sciences, Institute of Computational Science, Università della Svizzera italiana, Lugano,

Switzerland. [45]*Department of Pharmacy, University of Naples "Federico II,", Naples, Italy.* [46]*Department of Biology, University of Copenhagen, Copenhagen, Denmark.* [47]*CNR-IOM/Democritos National Simulation Center, Istituto Officina dei Materiali, Trieste, Italy.* [48]*Department of Pharmacy and Biotechnology, Alma Mater Studiorum–University of Bologna, Bologna, Italy.* [49]*Institute of Experimental Physics, Graz University of Technology, Graz, Austria.* [50]*Physics Department, King's College London, London, UK.* [51]*CD-FMat, National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba, Japan.* [52]*Department of Chemistry, University of Illinois, Urbana-Champaign, Urbana, IL, USA.* [53]*Danish Cancer Society Research Center, Copenhagen, Denmark.* [54]*Novo Nordisk Foundation Center for Protein Research, University of Copenhagen, Copenhagen, Denmark.* [55]*Department of Chemistry and Applied Biosciences, ETH Zurich, Lugano, Switzerland.* [56]*Department of Chemical Engineering, University of Washington, Seattle, WA, USA.* [57]*Dipartimento di Scienze della Salute, University of Catanzaro, Catanzaro, Italy.* [58]*Institut de Minéralogie, de Physique des Matériaux et de Cosmochimie, Sorbonne Université, Paris, France.* [59]*UMR 7590 CNRS, Paris, France.* [60]*Muséum National d'Histoire Naturelle, Paris, France.* [61]*Department of Chemistry, Université de Lille, Lille, France.* [62]*UMR 8181, CNRS, Lille, France.* [63]*Department of Physics, University of Warwick, Coventry, UK.* [64]*School of Life and Molecular Sciences, Curtin University, Perth, Western Australia, Australia.* [65]*Curtin Institute for Computation, Curtin University, Perth, Western Australia, Australia.* [66]*Institute of Physics, Faculty of Physics, Astronomy and Informatics, Nicolaus Copernicus University, Torun, Poland.* [67]*Department of Chemical Engineering, University College London, London, UK.* [68]*Department of Chemistry, University of Warwick, Coventry, UK.* [69]*Department of Biochemistry and Microbiology, University of Chemistry and Technology, Prague, Czech Republic.* [70]*Institute of Biophysics of the Czech Academy of Sciences, Brno, Czech Republic.* [71]*Centre Blaise Pascal, École Normal Supérieure de Lyon, Lyon, France.* [72]*Department of Chemistry and Biochemistry, University of Maryland, College Park, MD, USA.* [73]*Institute for Physical Science and Technology, University of Maryland, College Park, MD, USA.* [74]*Max Planck Institute for Polymer Research, Mainz, Germany.* [75]*Department of Chemistry, the University of Chicago, Chicago, IL, USA.* [76]*Department of Chemical Engineering, University of Rochester, Rochester, NY, USA.* [77]*Present address: BASF SE, Ludwigshafen, Germany.*
**e-mail: massimiliano.bonomi@pasteur.fr; bussi@sissa.it; carlo.camilloni@unimi.it; g.tribello@qub.ac.uk*

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Author contributions

All members of the PLUMED consortium contributed to writing of the manuscript.

Competing interests

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