Introducing VIKING
A Novel Online Platform for Multiscale Modeling
Korol, Vasili; Husen, Peter; Sjulstok, Emil; Nielsen, Claus; Friis, Ida; Frederiksen, Anders; Salo, Adrian B.; Solov’Yov, Ilia A.

Published in:
ACS Omega

DOI:
10.1021/acsomega.9b03802

Publication date:
2020

Document version
Final published version

Document license
CC BY

Citation for published version (APA):
Korol, V., Husen, P., Sjulstok, E., Nielsen, C., Friis, I., Frederiksen, A., Salo, A. B., & Solov’Yov, I. A. (2020). Introducing VIKING: A Novel Online Platform for Multiscale Modeling. ACS Omega, 5(2), 1254-1260. https://doi.org/10.1021/acsomega.9b03802

Terms of use
This work is brought to you by the University of Southern Denmark through the SDU Research Portal. Unless otherwise specified it has been shared according to the terms for self-archiving. If no other license is stated, these terms apply:

• You may download this work for personal use only.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying this open access version

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim. Please direct all enquiries to puresupport@bib.sdu.dk

Download date: 17. Apr. 2021
Introducing VIKING: A Novel Online Platform for Multiscale Modeling

Vasili Korol,† Peter Husen,‡ Emil Sjulstok,† Claus Nielsen,† Ida Friis,† Anders Frederiksen,† Adrian B. Salo,§ and Iliya A. Solov’yov†,‡,†,§

†Department of Physics, Chemistry and Pharmacy, University of Southern Denmark, Odense 5230, Denmark
‡Neuroscience, University of Texas Southwestern Medical Center at Dallas, Dallas 75390, Texas, United States
§Department of Physics, Carl von Ossietzky Universität Oldenburg, Oldenburg 26111, Germany

Supporting Information

ABSTRACT: Various biochemical and biophysical processes, occurring on multiple time and length scales, can nowadays be studied using specialized software packages on supercomputer clusters. The complexity of such simulations often requires application of different methods in a single study and strong computational expertise. We have developed VIKING, a convenient web platform for carrying out multiscale computations on supercomputers. VIKING allows combining methods in standardized workflows, making complex simulations accessible to a broader biochemical and biophysical society.

1. INTRODUCTION

Computational methods have in recent decades increasingly been used to model complex molecular systems and have in particular been extensively employed in the study of the biophysical and biochemical processes in living organisms.1–3 The computational modeling tools allow researchers to study molecular processes and effects that are difficult or even impossible to probe experimentally, such as quantum mechanical effects,4–6 diffusion of small molecules in various intracellular environments,7,8 protein conformational changes,9–11 and self-assembly of biomembranes.12

Molecular processes and phenomena occur at different length- and timescales (see Figure 1) and require different modeling methods. Chemical reactions, characterized by electron transfers and the formation and breaking of bonds, and processes involving quantum spin states or absorption/emission of photons all require a quantum mechanical treatment, whereas the dynamic behavior of larger biomolecules, such as proteins or DNA, are best treated with a classical molecular dynamics (MD) approach. Even larger scale phenomena, such as diffusion of macromolecules, self-aggregation of supramolecular structures, or the kinetics of a network of processes, require yet other methods, such as coarse-grained particle dynamics12,13 or Monte Carlo methods.14,15 Crucially, complex biomolecular processes, such as enzymatic reactions, often inherently consist of a system of subprocesses at a range of different scales. Correspondingly, a range of modeling techniques, therefore, needs to be applied for a comprehensive treatment.

2. RESULTS AND DISCUSSION

In this paper, we introduce VIKING, the Scandinavian online kit for multiscale modeling, which is tailored to model a broad range of molecular processes occurring at different scales. Many powerful software toolkits for computational modeling of molecular systems exist, like NAMD,14 Gromacs,15 AMBER,16 MBN Explorer,17,18 and AutoDock Vina19 for classical atomistic study, and Gaussian,20 GAMESS,21 Dalton,22 ORCA,23 Molcas,24 and Molspin, which enable modeling quantum chemical processes. These programs are generally highly specialized for a particular modeling technique and scale of modeling, whereas VIKING integrates a number of these tools in a single easy-to-use multiscale platform that provides tools for setting up simulations, data analysis, and visualization. VIKING not only alleviates the need for specialized know-how, which is traditionally required for each individual modeling technique, but also provides a standardized workflow, making the elaborate work of integrating multiple methods in a single study significantly more tractable and reproducible. Available completely in a regular web browser at https://viking-suite.com, VIKING is designed to be a powerful tool for both experts in computational modeling and researchers, who do not usually make use of computational modeling. This lowers the entry threshold for running multiscale simulations, which will eventually cause computational methods to be more widely used in new research areas.

Received: November 8, 2019
Accepted: November 29, 2019
Published: December 17, 2019
Processes occurring at different time and length scales can be modeled using different methods. (a) Ions penetrating a molecule in ion beam therapy, which may be crucial for biological function, can be modeled through computational quantum chemistry. (b) Absorption spectra of ligand molecules, which may be crucial for biological function, can be modeled through computational quantum chemistry. (c) Diffusion of small molecules in various biomolecular environments, (d) ensembles of possible conformations of mobile parts of proteins, and (e) larger scale conformational changes and adhesion to surfaces of proteins can all be studied through MD simulations. (f) Diffusion of macromolecules, such as proteins, within a cell can be modeled using Monte Carlo-based methods.

Concept and workflow of VIKING. Computational tasks are configured in the web interface by supplying the input data (structures, potentials, input field values, etc.), from the local computer or an online database. The simulation is then performed on a supercomputer (Stampede2, Marconi and Abacus 2.0 are currently supported), and the results are aggregated and represented visually in the web browser. Supercomputer photograph courtesy of iStockphoto LP. Copyright 2012.
Furthermore, VIKING offers a gateway to an increasing number of supercomputers and allows researchers to make use of these high-performance computing (HPC) resources at the click of a button. As the multiscale simulations often rely on large datasets, spanning up to millions of atoms, and the most appropriate methods for specific modeling have a high computational complexity, the link to supercomputers is critical to enable successful molecular multiscale studies. Users can link their existing supercomputer accounts with the VIKING interface, allowing the platform to operate with the computational resource on behalf of the user. VIKING automatically takes care of data transfer to and from an HPC resource and manages jobs in the queueing system, thus encapsulating the intricacies of working with individual supercomputers and allowing the researcher to focus on the higher level protocol of a computational study. The computational tasks of a single study can even be spread across separate supercomputers, whereas the researcher interacts seamlessly with the molecular structures and simulation data in the same interface—including extending simulations, transferring structures between different methods, and analyzing results.

The computational tasks that can be solved through VIKING include MD simulations, various quantum chemistry (QC) calculations, virtual screening, spin chemistry, and genome studies. These tasks are configured step by step in the browser, providing a similar interface and workflow across a diverse set of computational methods. The step-by-step process is tailored for each class of computations in order to provide just the necessary configuration options. Different calculation types can be combined by using the output of one task as the input of another: for example, the extracted parts of a structure resulting from an MD simulation can be used to start quantum chemical calculations, and equilibrated protein structures can be used for virtual screening simulations. Such seamless interlinking of simulations in VIKING facilitates comprehensive studies of multiscale processes by creating networks of tasks using different computational methods. The general workflow of VIKING is shown in Figure 2.

In order to measure the efficiency of VIKING in comparison with alternative approaches to setting up computational tasks, a benchmarking experiment has been carried out, involving 19 users with different levels of experience with computer simulations and molecular modeling.

The participants of the experiment carried out several simulations (see verbose description in the Supporting Information) in VIKING, using Abacus 2.0, the Danish national supercomputer located at the University of Southern Denmark. Each participant measured the time spent on configuring the simulation in VIKING from scratch, as well as the time spent on analyzing the results; the time spent on actually running the simulation was not measured. The recorded timings were collected and processed anonymously. Additionally, each respondent reported the self-estimated levels of experience with various IT-related and scientific disciplines. The recorded times were then compared with the corresponding times obtained by experts, who attempted to perform the same computations in a traditional manner without using VIKING.

The list of assignments included several computational tasks, such as: equilibrium MD of two different systems, free-energy perturbation calculations, geometry optimization, electronic properties calculation, virtual screening, infrared (IR) spectroscopy, Raman spectroscopy (RS), circular dichroism spectroscopy (CDS) modeling, as well as nuclear magnetic resonance (NMR) shielding tensor determination and spin dynamics modeling of radical pairs.

In order to obtain the characteristic timings for the simulations without VIKING, we asked seven experts in computational biophysics to perform the same tasks using conventional methods, which required configuring various software packages (NAMD, VMD, and Gaussian09) and processing the output data manually. The experiment data (participant expertise estimation and measured times) are presented in Tables S1–S3 in the Supporting Information. The results of the experiment are presented in Figure 3. It illustrates that by using VIKING, novice users, even those without any prior experience with biophysical simulations, are able to work almost as efficiently as professionals. Moreover, VIKING also reduces the time needed for the experts to configure the simulations and analyze the results compared to conventional methods involving manual usage of specialized software.

These results show that VIKING is a promising tool for the computational biophysics and biochemistry communities, lowering the barrier to entry of computational methods significantly. By making the use of computational methods more widespread, VIKING will lead to crucial opportunities for interdisciplinary studies, combining experimental and computational efforts to investigate the hypotheses in biophysics and biochemistry. At the same time, VIKING makes complex computational studies using multiple methods both more tractable and more reproducible thanks to the simplified and standardized workflow, which is independent of the use of specific supercomputers.

3. METHODS

VIKING supports a number of different task types based on different computational methods. Every task is configured using a step-by-step interface, and the task types can be combined by using the results of one simulation as the input for another one. At each step, VIKING runs appropriate software packages, extracts the results, and presents them to...
the user. In this section, a description of each computational task type in VIKING is provided.

3.1. Equilibrium MD: General Concepts. MD simulations provide a powerful tool to study biomolecular systems, with an atomistic resolution. They can be used to investigate the mechanical and thermal properties of proteins, transport events, and enzyme reaction mechanisms to name a few examples.

At its core, the MD task implementation in VIKING functions as a user-friendly interface to the NAMD software package. Setting up an MD simulation only requires the user to provide a molecular structure, e.g. a protein, and to set thermodynamic parameters, such as the temperature and pressure, while running the simulation, file handling and data analysis is done internally.

As the output, VIKING produces plots of energy and temperature as a function of simulation time and a dynamic trajectory of the structure. A completed MD simulation can also be further analyzed to study the stability of a structure or the time evolution of separation distances for the chosen selection of atoms, all directly from the overview of the results of the MD simulation task. Furthermore, the data rendered during the MD simulation could also be employed for the energy perturbation calculation or drug docking tasks. The typical workflow for running an MD simulation in VIKING is illustrated in Figure S2 in the Supporting Information.

3.2. Drug Discovery. An important application that goes beyond the standard MD workflow is related to modern drug discovery. Computational drug discovery has become an important part of pharmaceutical research as it allows for screening of hundreds of thousands of ligands in an efficient and cheap way, such that only the top candidate compounds are tested in the lab. Drug discovery involves computational docking of candidate ligands from a library of small molecules to a receptor protein, in order to find leads in medical drug design.

VIKING allows automatic docking of ligands to receptor structures, relying on the AutoDock Vina software package. The user may select a receptor and either upload the ligands or retrieve them from the PubChem online database (see Figure S3 in the Supporting Information for the illustration of the workflow in VIKING).

As a result of the drug discovery screening task, VIKING presents the list of best candidate ligands, arranged by a calculated docking score and the interaction energy between the receptor and the ligand. The user can observe each combined receptor–ligand structure using the VIKING structure viewer in the browser and use them for further modeling tasks, such as an MD simulation to refine the docked structure and provide better sampling of the interaction energy.

3.3. MD: Free-Energy Perturbation Method. One of the most accurate ways to calculate the free energy of binding between two molecules, for example, receptor and ligand, is using the MD free energy perturbation (MDFEP) method. VIKING supports free-energy calculations of receptor–ligand complexes using the alchemical approach in a series of simulations based on NAMD, the interactions between the ligand and its surroundings are gradually decoupled, essentially annihilating the ligand, either in the binding site of the receptor or in the solvent, and the resulting free-energy changes are sampled and used to reconstruct the total binding free energy. Unlike pure force field interaction energy calculations, the free-energy perturbation method crucially captures the entropic contributions to the free energy of binding. This information can be crucial, when investigating the factors that may affect the binding of drugs or other ligands, for example, studying drug resistance, or as a part of predicting the free energies and rates of enzymatic reactions.

Running an MDFEP task in VIKING requires the user to supply a simulation state consisting of a set of atom positions and velocities for a molecular structure and specifying the part of the structure to be considered as the ligand. The simulation state can be uploaded as a set of files or chosen directly from a previous MD task. Restraints can then be applied to avoid the ligand diffusing away from the binding site, when interactions with the protein are turned off. This is important, as the MDFEP framework requires the decoupling transformation to be reversible. VIKING ensures this by performing both an annihilation, “forward” transformation, turning off the interactions between the ligand and its surroundings, and a subsequent “backward”, or creation, transformation, turning the interactions back on. A separate set of simulations is automatically set up to measure the free-energy error because of the artificial constraints, and VIKING ensures proper bookkeeping to assemble this information at the end of the FEP task to provide the binding free energy to the user. The MDFEP workflow in VIKING is illustrated in Figure S4 in the Supporting Information.

3.4. Atomic and Molecular Properties. It has been well established that polarization interactions play a key role in biochemical systems, whereas the conventional MD simulations typically rely only on Lennard-Jones and Coulomb potentials, which do not take polarization into account. In order to consider polarizabilities and different quantum phenomena in molecular structures of increased complexity, QC simulations are needed to fully account for these aspects. The main difficulty of the QC calculations is the poor scalability, making it unbearable, even on modern supercomputers, to accurately treat systems with more than ~1000 atoms quantum-mechanically. Despite this limitation, a great deal of successful QC algorithms and programs have been developed, and in particular, VIKING employs the popular Gaussian09 software package for the QC calculations described here.

VIKING offers several QC task types for calculating atomic and molecular properties, specifically geometry optimization, electronic properties calculation, and NMR properties calculation. A wide variety of calculation methods provided by Gaussian09, such as the Hartree Fock, Møller–Plesset perturbation theory (MP2), or density functional theory with a variety of different functionals, can be selected, jointly with all the standard basis sets typically used for the wave function expansion, including variants with polarization or diffuse functions. It is also possible to add constraints to certain atom coordinates, bond lengths, or angles or to divide the molecular structure into fragments to provide a better starting guess for the chosen QC method.

After a successful calculation, VIKING analyzes the output files from Gaussian09 and collects the relevant data for the chosen QC task. These data are visually presented to the user on the results page, and, in case of a geometry optimization task, the resulting optimized structure is available for use in other computational tasks in VIKING. The general workflow for the QC tasks is illustrated in Figure S5 in the Supporting Information.
3.5. Molecular Spectroscopy. VIKING provides a tool for studying the properties of smaller molecules and is specifically equipped with capabilities to perform a variety of molecular spectroscopy calculations. Every spectroscopy task is designed to reveal specific properties of the molecules, and VIKING supports IR spectroscopy, RS, NMR spectroscopy, and circular dichroism spectroscopy.

As for the task types in the previous section for determining atomic and molecular properties, the spectroscopy tasks in VIKING also rely on the Gaussian09 software package\textsuperscript{25} to carry out the computations, and the same set of QC methods and basis sets are available. To set up a spectroscopy calculation task, the user is required to supply the molecular structure, select the charge and spin states of the molecule, and select the calculation method to use.

The resulting spectra and other calculated molecular properties are presented directly in the web interface, and normal mode vibrations calculated in the IR spectroscopy, RS, and CDS tasks can be visualized as animations in the structure viewer.

3.6. Spin Chemistry. Radicals have received renewed interest as possible biological implications of radical pairs have been suggested, in particular, the radical pair mechanism of avian magnetoreception\textsuperscript{48,49} and the possible adverse health effects of radiofrequency radiation\textsuperscript{50–52}.

The radical pair dynamics task in VIKING is designed to allow the investigation of radical pair processes in various ways, including studies of how the quantum yields are affected by static magnetic fields or radiation, or calculation of the time evolution of radical pair ensembles. VIKING can track the energy levels of the radical pairs in a new and innovative way that may help tremendously in interpreting any unexpected results. In particular, the energy levels may be obtained as a function of, for example, external magnetic field strength or time, and the spin states involved in each energy level are color-coded in the figures produced by VIKING. With the capability to include time-dependent magnetic fields, it is possible not only to study magnetic resonance experiments or the effects of radiofrequency radiation but also to simply calculate the set of resonance frequencies that may affect the dynamics of a radical pair.

Describing a radical pair requires a range of parameters that are normally obtained from quantum chemical calculations. As VIKING supports these types of quantum calculations, all the parameters needed for the radical pair can be imported directly from the other VIKING tasks through a visual interface. The workflow of the radical pair dynamics task is illustrated in Figure S6 in the Supporting Information.

The radical pair dynamics task in VIKING relies on the MolSpin software,\textsuperscript{53} which has been developed separately by the members of the VIKING development team. It is a dedicated spin dynamics software package, which is designed to be able to perform any kind of calculation on the spin systems of arbitrary complexity.

3.7. Genome Editing. Apart from providing interfaces for the existing program packages, VIKING features a specialized tool for analyzing profiles from genome editing studies, ProfileIt\textsuperscript{54} (https://cobotechnologies.com/software/indel-analysis-software/). Sponsored by Cobo Technologies, it allows INDEL (insertion/deletion of bases) profiling of sample data produced by Applied Biosystems genetic analyzer devices. ProfileIt provides an interactive interface for visualizing, selecting, and subtracting INDEL peaks, as well as displaying various statistics and export of profile data and publication-quality images. The user is only required to provide the files obtained from an analyzer device and assign a control sample and, optionally, a negative control. The peak discovery process in VIKING is tuned for an accurate detection of profile extrema exceeding a given threshold and calculation of their basic properties. The sample profiles are visualized in an interactive plot in the interface.

3.8. Molecular Editor. VIKING provides a fully functional molecular editor which is a diverse and intuitive tool for constructing and editing the molecular structures the user wishes to simulate. The collection of editing tools is integrated in VIKING, and no additional programs are needed to apply the desired manipulations.

In addition to common translation and rotation tools, VIKING provides extended possibilities to construct custom structures. This set of tools includes generating chemical bonds, placing single atoms, and merging multiple structures. This allows the user to construct small molecules from scratch and incorporate them in bigger structures or construct large protein complexes. The implemented tools can also be used to delete and replace atoms in molecules or structures with just a few clicks.

The support for different representations allows the user to choose between visualizing individual atoms in a structure or showing the secondary structures of a protein, if the latter is more convenient. This allows for utilizing the editor in a multiscale fashion: it is possible to choose to work with single atoms at a time, or choose to work with bigger chunks of a structure, like an entire β-sheet or α-helix, making it easy to select and edit many individual atoms at once.

As mentioned earlier, VIKING is able to visualize trajectories from the MD tasks as well as the individual steps of a geometry optimization procedure. This allows the user to choose specific configurations of a simulated system, edit them, and apply them for further studies. Moreover, VIKING makes it possible to extract a specific part of a structure from a specific frame of a trajectory from MD simulations and apply the extracted structure in a quantum chemical task. Furthermore, VIKING supports visualizing structures in an immersive three-dimensional experience using virtual reality devices. The interface of the molecular viewer and editor can be seen in Figure S7 in the Supporting Information.
Ida Friis: 0000-0001-7001-4799
Anders Frederiksen: 0000-0001-6712-2975
Adrian B. Salo: 0000-0003-4978-3408
Ilia A. Solov'yov: 0000-0002-8626-145X

Notes
The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

Financial support by the Lundbeck Foundation, the Danish Councils for Independent Research, Volkswagen Stiftung (Lichtenberg professorship to IAS), and the DFG (GRK1885) is greatly acknowledged. Computational resources for the simulations were provided by the DeIC National HPC Center, University of Southern Denmark. This publication is based upon work from COST Action TUMIEE (CA17126), supported by COST (European Cooperation in Science and Technology).

**REFERENCES**

(1) O’Connor, M.; Deeks, H. M.; Dawn, E.; et al. Sampling molecular conformations and dynamics in a multiuser virtual reality framework. *Sci. Adv.* 2018, 4, No. eaat2731.

(2) Fisher, J.; Henzinger, T. A. Executable cell biology. *Nat. Biotechnol.* 2007, 25, 1239.

(3) Solov'yov, I. A.; Korol, A. V.; Solov'yov, A. V. Multiscale Modeling of Complex Molecular Structure and Dynamics with MBN Explorer; Springer International Publishing, 2017.

(4) Domratcheva, T.; Fedorov, R.; Schlichting, I. Analysis of the primary photocycle reactions occurring in the light, oxygen, and voltage blue-light receptor by multiconfigurational quantum-chemical primary photocycle reactions occurring in the light, oxygen, and voltage blue-light receptor by multiconfigurational quantum-chemical methods. *J. Chem. Theory Comput.* 2006, 2, 1565–1574.

(5) Salo, A. B.; Alberg-Fløjborg, A.; Solov’yov, I. A. Free-electron production from nucleotides upon collision with charged carbon ions. *Phys. Rev. A* 2018, 98, 012702.

(6) Melo, M. C. R.; Bernardi, R. C.; Rudack, T.; et al. NAMD goes quantum: an integrative suite for hybrid simulations. *Nat. Methods* 2018, 15, 351.

(7) Wang, Y.; Cohen, J.; Boron, W. F.; et al. Exploring gas permeability of cellular membranes and membrane channels with molecular dynamics. *J. Struct. Biol.* 2007, 157, 534–544.

(8) Voth, G. A. Computer Simulation of Proton Solvation and Transport in Aqueous and Biomolecular Systems. *Acc. Chem. Res.* 2006, 39, 143–150.

(9) Pitera, J. W.; Swope, W. Understanding folding and design: Replica-exchange simulations of “Trp-cage” miniproteins. *Proc. Natl. Acad. Sci. U.S.A.* 2003, 100, 7587–7592.

(10) Okazaki, K.-i.; Takada, S. Dynamic energy landscape view of coupled binding and protein conformational change: induced-fit versus population-shift mechanisms. *Proc. Natl. Acad. Sci. U.S.A.* 2008, 105, 11182–11187.

(11) Ishikawa, H.; Kwak, K.; Chung, J. K.; et al. Direct observation of fast protein conformational switching. *Proc. Natl. Acad. Sci. U.S.A.* 2008, 105, 8619–8624.

(12) Grafmüller, A.; Shillcock, J.; Lipowsky, R. The fusion of membranes and vesicles: pathway and energy barriers from dissipative particle dynamics. *Biophys. J.* 2009, 96, 2658–2675.

(13) Marrink, S. J.; Risselada, H. J.; Yefimov, S.; et al. The MARTINI force field: coarse grained model for biomolecular simulations. *J. Phys. Chem. B* 2007, 111, 7812–7824.

(14) Lomakin, A.; Asherie, N.; Benedek, G. B. Monte Carlo study of phase separation in aqueous protein solutions. *J. Chem. Phys.* 1996, 104, 1646–1656.

(15) Nikjoo, H.; Uehara, S.; Khvostunov, I.; et al. Monte Carlo track structure for radiation biology and space applications. *Phys Med* 2001, 17, 38–44.

(16) Nielsen, C.; Nerby, M. S.; Kongsted, J.; et al. Absorption Spectra of FAD Embedded in Cryptochromes. *J. Phys. Chem. Lett.* 2018, 9, 3618–3623.

(17) Husen, P.; Solov’yov, I. A. Spontaneous Binding of Molecular Oxygen at the Qo-Site of the bc1 Complex Could Stimulate Superoxide Formation. *J. Am. Chem. Soc.* 2016, 138, 12150–12158.

(18) Husen, P.; Solov’yov, I. A. Mutations at the Qo site of the cytochrome bc1 complex strongly affect oxygen binding. *J. Phys. Chem. B* 2017, 121, 3308–3317.

(19) Frahs, S. M.; Reek, J. C.; Scott, C.; Tuft, S.; et al. Prechondrogenic ATDC5 cell differentiation on graphene foam; modulation by surface functionalization with fibroenectin. *ACS Appl. Mater. Interfaces* 2019, 11, 41906.

(20) Friis, I.; Solov’yov, I. A. Activation of the DNA-repair mechanism through NBS1 and MRE11 diffusion. *PloS Biol.* 2018, 16, 4, e1006562.

(21) Phillips, J. C.; Braun, R.; Wang, W.; et al. Scalable Molecular Dynamics with NAMD. *J. Comput. Chem.* 2005, 26, 1781–1802.

(22) Van Der Spoel, D.; Lindahl, E.; Hess, B.; et al. GROMACS: fast, flexible, and free. *J. Comput. Chem.* 2005, 26, 1701–1718.

(23) Case, D. A.; Cheatham, T. E.; Darden, T.; et al. The AMBER biomolecular simulation programs. *J. Comput. Chem.* 2005, 26, 1668–1688.

(24) Solov’yov, I. A.; Yakubovich, A. V.; Nikolaev, P. V.; et al. MesosBioNano Explorer – A Universal Program for Multiscale Computer Simulations of Complex Molecular Structure and Dynamics. *J. Comput. Chem.* 2012, 33, 2412–2439.

(25) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; et al. Gaussian 09, revision D.01; Gaussian, Inc.: Wallingford, CT, 2013.

(26) Schmidt, M. W.; Balbridge, K. K.; Boatz, J. A.; et al. General atomic and molecular electronic structure system. *J. Comput. Chem.* 1993, 14, 1347–1363.

(27) Aidas, K.; Angeli, C.; Bak, K. L.; et al. The Dalton quantum chemistry program system. *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* 2014, 4, 269–284.

(28) Neese, F. The ORCA program system. *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* 2012, 2, 73–78.

(29) Karlström, G.; Lindh, R.; Malmqvist, P.-Å.; et al. Molcas: A Program Package for Computational Chemistry. *Comput. Mater. Sci.* 2003, 28, 222–239.

(30) Trott, O.; Olson, A. J. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multitreading. *J. Comput. Chem.* 2010, 31, 455–461.

(31) Humphrey, W.; Dalke, A.; Schulten, K. VMD – Visual Molecular Dynamics. *J. Mol. Graph.* 1996, 14, 33–38.

(32) Paci, E.; Karplus, M. Forced unfolding of fibronectin type 3 modules: an analysis by biased molecular dynamics simulations. *J. Mol. Biol.* 1999, 288, 441–459.

(33) Lu, H.; Israelewitz, B.; Krammer, A.; et al. Unfolding of Titin Immunoglobulin Domains. *Biophys. J.* 2000, 79, 51–65.

(34) Lu, H.; Israelewitz, B.; Krammer, A.; et al. Unfolding of Titin Immunoglobulin Domains by Steered Molecular Dynamics Simulation. *Biophys. J.* 1998, 75, 662–671.

(35) Gao, J. Catalysis by enzyme conformational change as illustrated by orotidine 5-monophosphate decarboxylase. *Curr. Opin. Struct. Biol.* 2003, 13, 184–192.

(36) Wu, N.; Mo, Y.; Gao, J.; et al. Electrostatic stress in catalysis: Structure and mechanism of the enzyme orotidine monophosphate decarboxylase. *Proc. Natl. Acad. Sci. U.S.A.* 2000, 97, 2017–2022.

(37) Diit, S. B.; Chipot, C. Can absolute free energies of association be estimated from molecular mechanical simulations? *The biotin-streptavidin system revisited*. *J. Phys. Chem. A* 2001, 105, 9795–9799.

(38) Woo, H.-J.; Roux, B. Calculation of absolute protein–ligand binding free energy from computer simulations. *Proc. Natl. Acad. Sci. U.S.A.* 2005, 102, 6825–6830.

(39) Pearlman, D. A. A comparison of alternative approaches to free energy calculations. *J. Phys. Chem.* 1994, 98, 1487–1493.
Warshel, A.; Levitt, M. Theoretical studies of enzymic reactions: Dielectric, electrostatic and steric stabilization of the carbonium ion in the reaction of lysozyme. *J. Mol. Biol.* 1976, 103, 227–249.

Sjulstok, E.; Olsen, J. M. H.; Solov’yov, I. A. Quantifying electron transfer reactions in biological systems: what interactions play the major role? *Sci. Rep.* 2016, 5, 18446.

(42) Salo, A. B.; Husen, P.; Solov’yov, I. A. Charge transfer at the Qo-site of the cytochrome bc1 complex leads to superoxide production. *J. Phys. Chem. B* 2017, 121, 1771–1782.

(43) Nielsen, C.; Hui, R.; Lui, W.-Y.; et al. Towards predicting intracellular radiofrequency radiation effects. *PLoS One* 2019, 14, No. e0213286.

Pedersen, J. B.; Nielsen, C.; Solov’yov, I. A. Multiscale description of avian migration: from chemical compass to behaviour modeling. *Sci. Rep.* 2016, 6, 36709.

Sal, Y.; Molnar, L. F.; Jung, Y.; et al. Advances in methods and algorithms in a modern quantum chemistry program package. *Phys. Chem. Chem. Phys.* 2006, 8, 3172–3191.

Roothaan, C. C. J. New Developments in Molecular Orbital Theory. *Rev. Mod. Phys.* 1951, 23, 69–89.

Møller, C.; Plesset, M. S. Note on an approximation treatment for many-electron systems. *Phys. Rev.* 1934, 46, 618.

Parr, R. G.; Yang, W. *Density-Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.

Hore, P. J.; Mouritsen, H. The Radical-Pair Mechanism of Magnetoreception. *Annu. Rev. Biophys.* 2016, 45, 299–344.

Usselman, R. J.; Chavarriaga, C.; Castello, P. R.; et al. The Quantum Biology of Reactive Oxygen Species Partitioning Impacts Cellular Bioenergetics. *Sci. Rep.* 2016, 6, 38543.

Usselman, R. J.; Hill, I.; Singel, D. J.; et al. Spin biochemistry modulates reactive oxygen species (ROS) production by radio frequency magnetic fields. *PLoS One* 2014, 9, No. e93065.

Naarala, J.; Kesari, K. K.; McClure, I.; et al. Direction-Dependent Effects of Combined Static and ELF Magnetic Fields on Cell Proliferation and Superoxide Radical Production. *BioMed Res. Int.* 2017, 2017, 5675086.

Nielsen, C.; Solov’yov, I. A. MolSpin—Flexible and Extensible General Spin Dynamics Software. *J. Chem. Phys.* 2019, 151, 194105.

König, S.; Yang, Z.; Wandall, H. H.; et al. In CRISPR Gene Editing. *Methods in Molecular Biology*; Luo, Y., Ed.; Humana Press: New York, NY, 2019; Vol 1961.