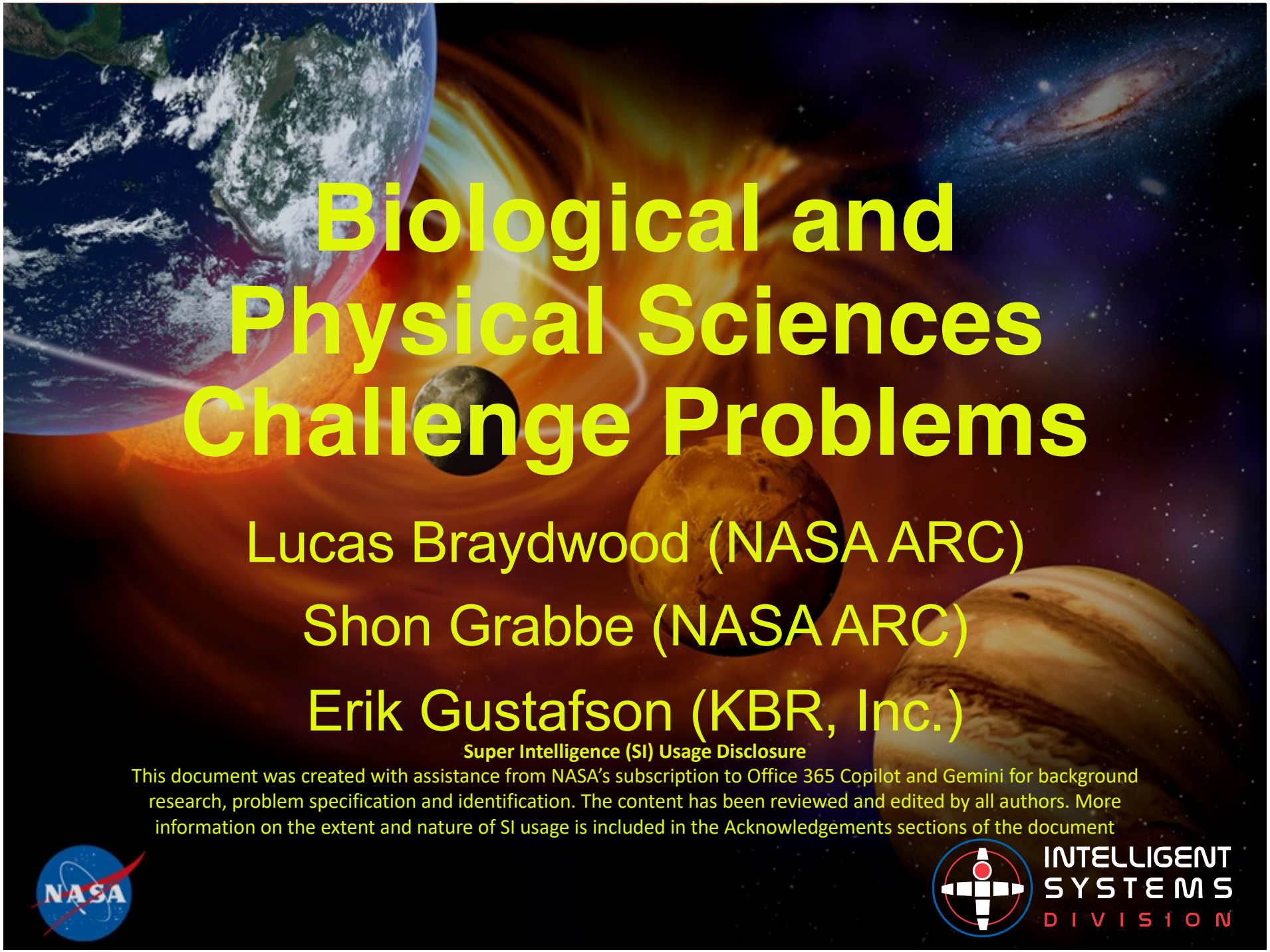


Biological and Physical Sciences Challenge Problems

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Super Intelligence (SI) Usage Disclosure

This document was created with assistance from NASA's subscription to Office 365 Copilot and Gemini for background research, problem specification and identification. The content has been reviewed and edited by all authors. More information on the extent and nature of SI usage is included in the Acknowledgements sections of the document

NASA

INTELLIGENT SYSTEMS DIVISION



1. Molecular Dynamics
    1. Drug binding and docking
    2. Wound healing
    3. Radiation Damage



Molecular Dynamics Challenge Problems

Molecular Dynamics: Bio-processes

INTELLIGENT SYSTEMS DIVISION

Application Details

- Understand the behavior of DNA damage and medicine interactions in space
- Understand effects on astronaut health and treatment paradigms
- Developments useful for other MD use cases outside of Biological & Physical Sciences (BPS)

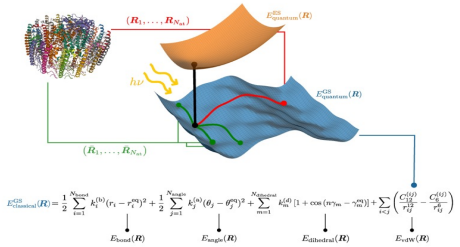


Image from A. Baiardi, M. Christandl, M. Reiher, ChemBioChem 2023, 24, e202300120 under Creative Commons Attribution-NonCommercial-NoDerivs without changes

Problem Details

- Solving the reactions and interactions of molecular systems
- Solving differential equations
- Inputs: Molecules of interest, Force Field Calculations
- Outputs: Time series of molecular positions

$$M\frac{d^2\vec{u}}{dt^2} = -\gamma\frac{d\vec{u}}{dt} - K\,\vec{u} + \vec{f}(t) + \vec{\xi}(t)$$

Current Approaches

- GPU accelerated software like GROMACS, NAMD, LAMMPS are powerful and widely used for molecular dynamics (MD) but each has limitations
- Common limitations across existing MD packages include limitations in timescale, system size, force-field, and sampling

Impact of New/Better Solution

- Accurate to within 10% of experiment
- Precise determination of bio processes effecting astronauts in space. Better treatment protocols

Application Goals

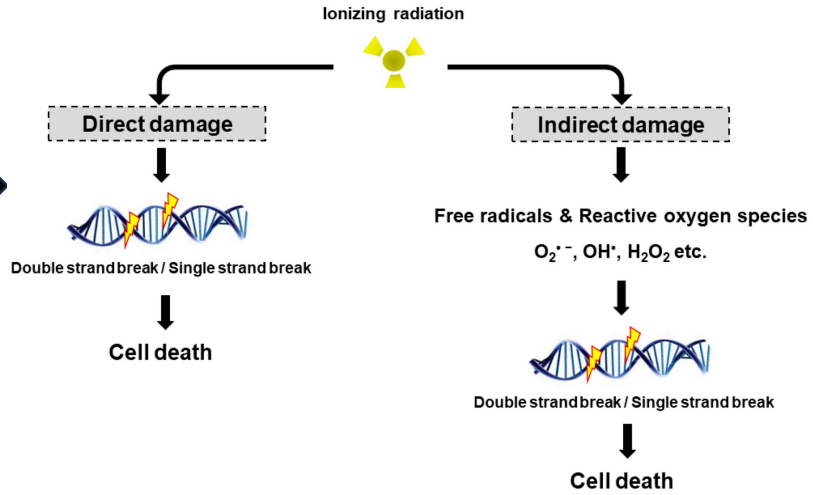
INTELLIGENT SYSTEMS DIVISION

Humans or plants in extreme environments experience biological stressors



Image credit: NASA

Environment effects biological processes



Hur, W.; Yoon, S.K. Molecular Pathogenesis of Radiation-Induced Cell Toxicity in Stem Cells. Int. J. Mol. Sci. 2017, 18, 2749. https://doi.org/10.3390/ijms18122749 is used unchanged under CC-BY-4.0

Find Computing solutions to determine best first principles solutions going forward to help produce best health outcomes for astronauts in space.

Mathematical Formulation

Equations of Motion $\frac{d\boldsymbol{r}_i}{dt} = \frac{\boldsymbol{p}_i}{m_i}, \quad \frac{d\boldsymbol{p}_i}{dt} = -\boldsymbol{\nabla}_{\mathbf{r_i}}\mathrm{U}$. Where U is a model determined potential energy surface either through techniques such as molecular mechanics or quantum methods such as density functional theory (DFT) or Hartree-Fock methods.

Potential energy surfaces are usually calculated at each time step. Approximations can be made by limiting the range of interactions this is usual called a radius of interaction limiting calculations to objects within radius r.

The general process is showcased in the figure below.

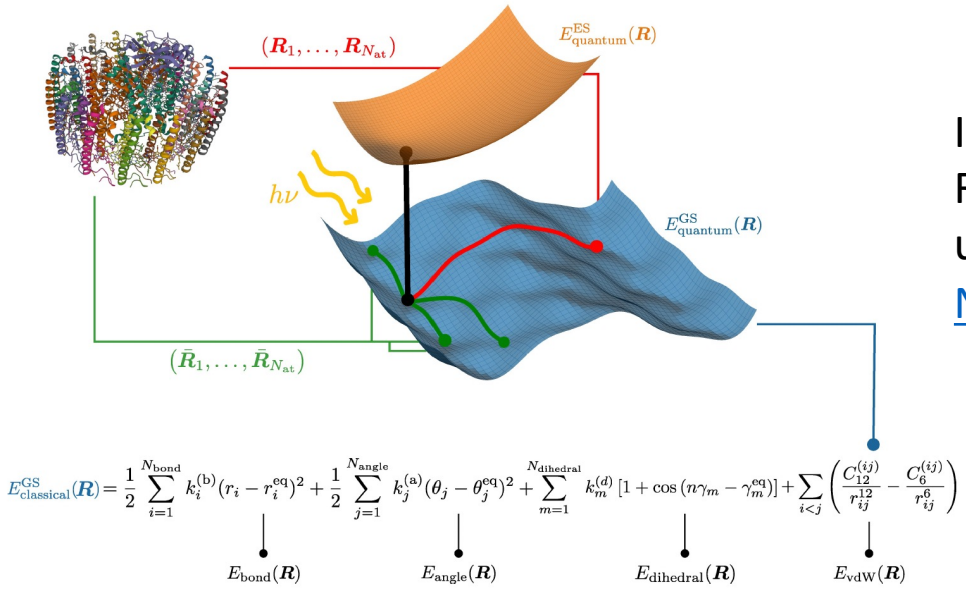


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Current Approaches

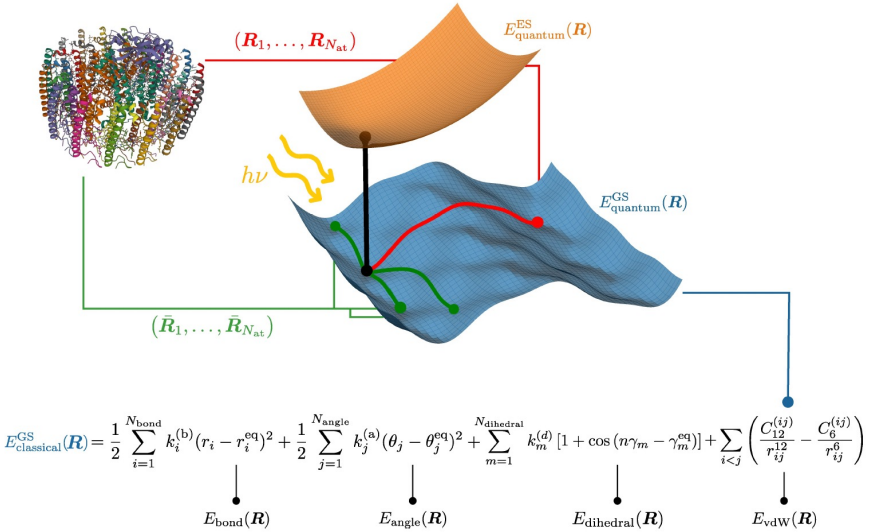


Image from A. Baiardi, M. Christandl, M. Reiher, ChemBioChem 2023, 24, e202300120 under Creative Commons Attribution-NonCommercial-NoDerivs without changes

Software	Free	URL
GROMACS	Yes	Here
NAMD	Yes	Here
LAMMP	No	Here
OpenMM	Yes	Here
CPMD	No	Here

Most processes utilize classically determined force fields though:

- empirical tests, or molecular mechanics which run as fast as $\mathcal{O}(n)$
- *Ab initio* Quantum methods such as Hartree Fock or quantum chemistry can handle bond breaking etc. substantially more accurate scale as fast as $\mathcal{O}(n^3)$[1]

Simulations are **Hindered** by runtime issues; time steps need to be ~$10^{-15}s$ but biological simulations take ~$10^{-4} - 1s$ and can be come numerically unstable.

[1] This comes from the ~$O(n^3)$ cost of matrix diagonalization. Or Standard DFT implementations.

Benefits of Emerging Technology

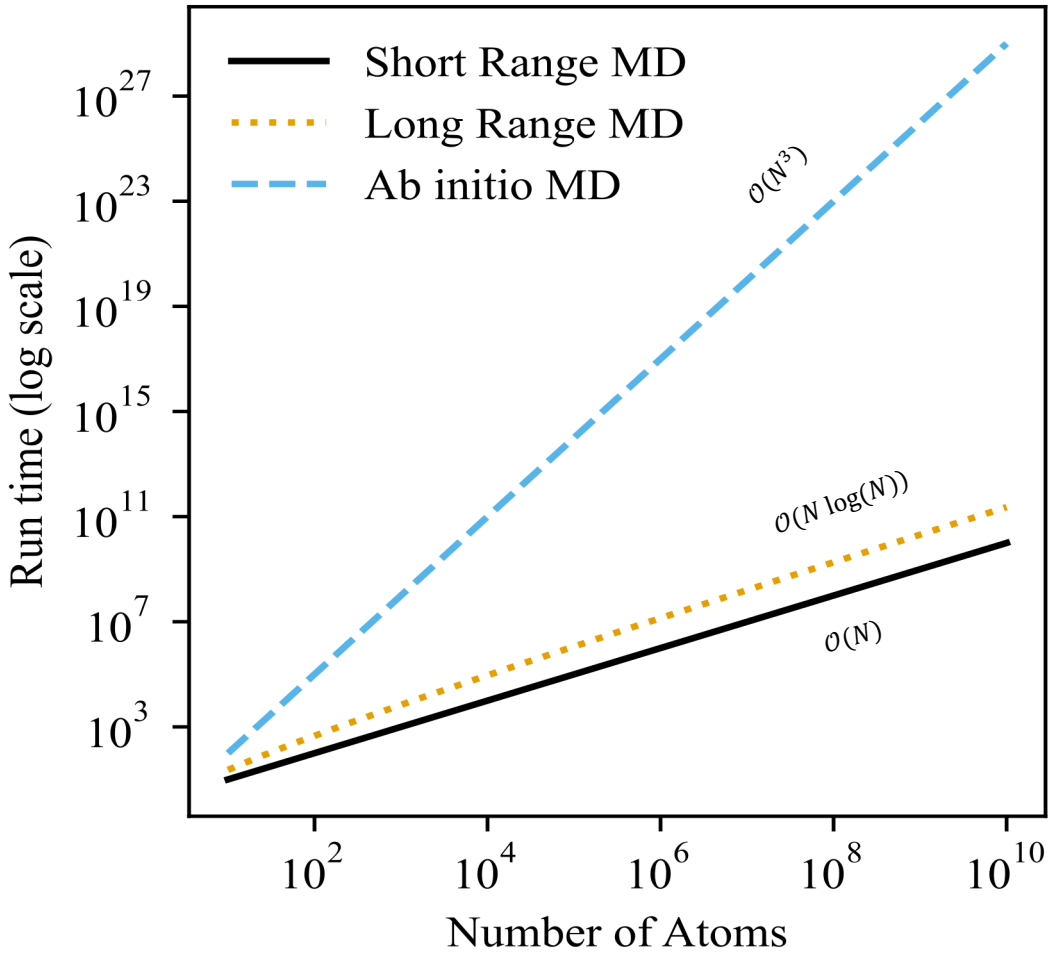
- Machine Learning / Foundation Models
  - Pros: Often very accurate and quick
  - Cons: Computationally and financially expensive to train. Require enormous data sets (>500 million structures each containing potential information)[1]
  - Cons: Can require large training datasets and have limited interpretability.
- Quantum Computing
  - Pros: Naturally represents the quantum pieces of many molecular dynamics systems.
  - Cons: Nascent technology, still actively being developed. Not many industry uses cases have shown quantum utility yet
- Experimental
  - Pros: reasonably efficient in time.
  - Cons: Noisy, can have costs associated, limited parameter exploration. Is limited by techniques available to researchers.

[1] Wood, Brandon, et al. "UMA: A family of universal models for atoms." *Advances in Neural Information Processing Systems*38 (2026): 129391-129427.

Recent Work in Biology with Machine Learning or Quantum Computing

- https://arxiv.org/pdf/2508.18147 (PasQal)
  - Molecular docking protocol with Neutral Atoms
- https://arxiv.org/abs/2508.10660
  - Protein Folding with quantum annealing
- https://arxiv.org/abs/2512.06141 & https://arxiv.org/pdf/2608.17261v1
  - Review papers
- https://arxiv.org/abs/2412.18633
  - Machine Learning for Force Fields
- https://arxiv.org/abs/2204.01821
  - Peptide structure with QAOA
- https://arxiv.org/abs/2607.28548
  - Proof of concept SQD + MD simulation
- https://arxiv.org/pdf/2608.19868
  - Molecule Docking with QAOA

Computational Difficulties in Molecular Dynamics



What Specifies a Problem Instance

Problem Specification (Fixed)

- Atom locations
- Atom weights
- Atom initial velocities
- Temperature
- Box size

Please note: this includes the "solvents" or what ever bath the principal atoms are embedded in.

This specifies the what that's being simulated.

Problem Specification (Open Choice)

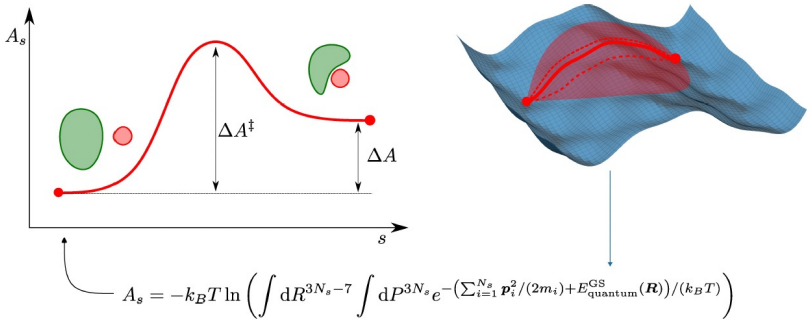
- Force Field Calculation Method
  - Ab initio / interaction range
- Update schema (PDE solver)
- These govern solution methods
  - Better classical, or novel quantum

This specifies how the problem gets simulated through molecular dynamics. This is where speed ups occur

Classes of Problems

INTELLIGENT SYSTEMS DIVISION

Medicine interactions



Molecular dynamics pipeline from Fig 2 in A. Baiardi, M. Christandl, M. Reiher, *ChemBioChem* 2023, 24, e202300120. used under Creative Commons Attribution-NonCommercial-NoDerivs

Wound Healing

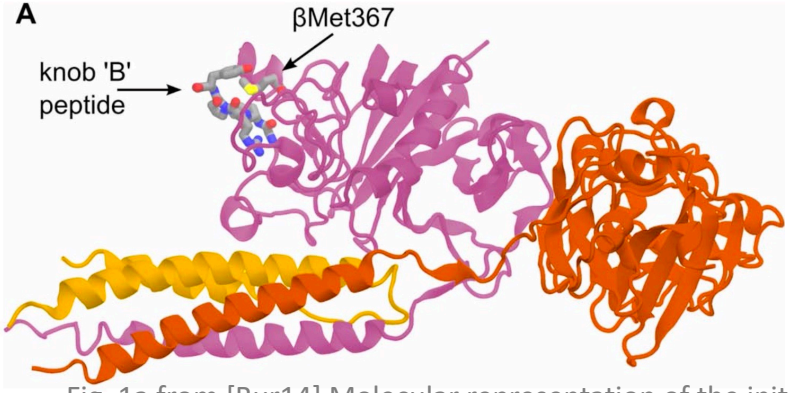
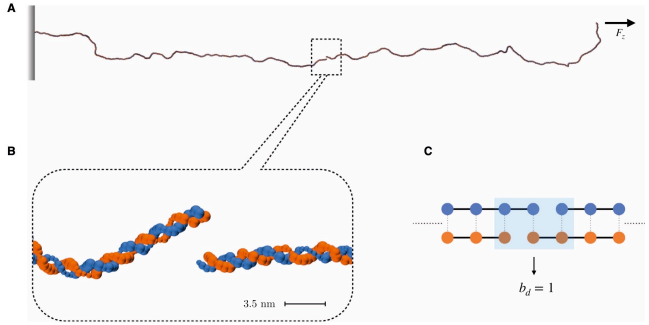


Fig. 1a from [Bur14] Molecular representation of the initial structure of the D region corresponding to PDB 2Z4E for \beta Met367. Used under https://creativecommons.org/licenses/by/4.0/ without change.

Environmental damage



Double-strand break image from Fig 1 of [Mic23]. Figure used without change under https://creativecommons.org/licenses/by/4.0/

[Mic23] M. Micheloni, et al., Kinetics of radiation-induced DNA double strand breaks through coarse-grained simulations, Biophysical Journal 122, 3314-3322, Aug 22, 2023

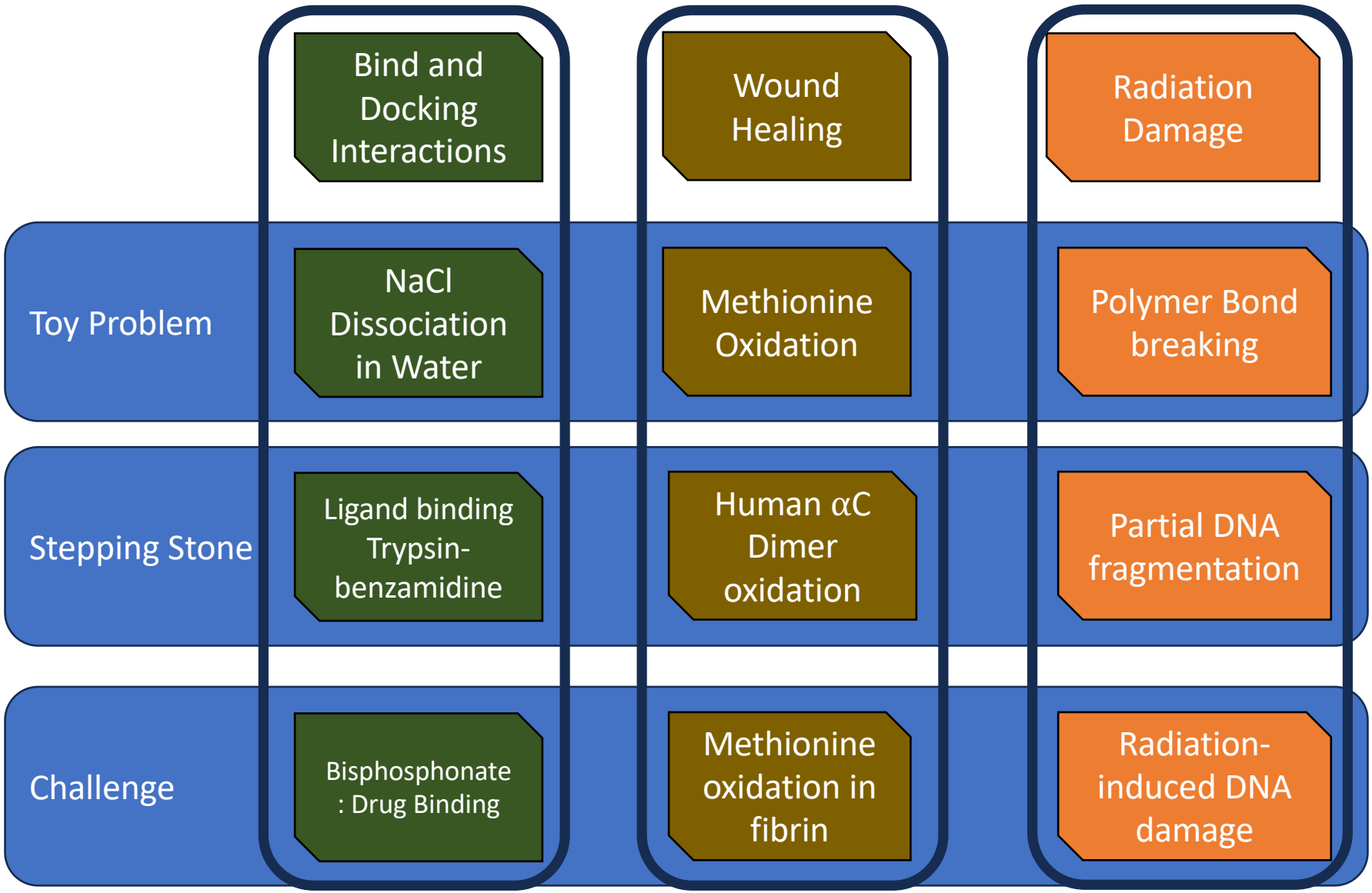
[Bur14] P.R. Burney, et al., Structural Effects of Methionine Oxidation on Isolated Subdomains of Human Fibrin D and \alpha C Regions, PLoS ONE 9 (1) e86981 (2014). doi:10.1371/journal.pone.0086981

Context for Better Solutions

Does not involve speeding up the update steps as this is a relatively straightforward PDE.

Does involve faster and more accurate solutions to the force field calculations.

Problem Scaling





Binding and Docking Interactions

Dissociation, Ligand Protein, Drug Docking

What does this Enable?

Better understanding of interactions for medicine in space.

Challenge problem of Bisphosphonates interactions in astronauts

Background references:
-https://pmc.ncbi.nlm.nih.gov/articles/PMC11352369/
-https://accp1.onlinelibrary.wiley.com/doi/10.1002/jcph.70240

Toy Problem Instance

INTELLIGENT SYSTEMS DIVISION

Dissociation of NaCl

Inputs:

- Box size 12.5Å
- 64 Water molecules
- Water molecules near center replace with Na+ Cl- ion pair separated by 2.7Å
- Simulate for 6 ps
- Following https://pubs.aip.org/aip/jcp/article/132/11/114510/939701/Dissociation-of-NaCl-in-water-from-ab-initio
- Calculation method for Force fields (Open Choice)

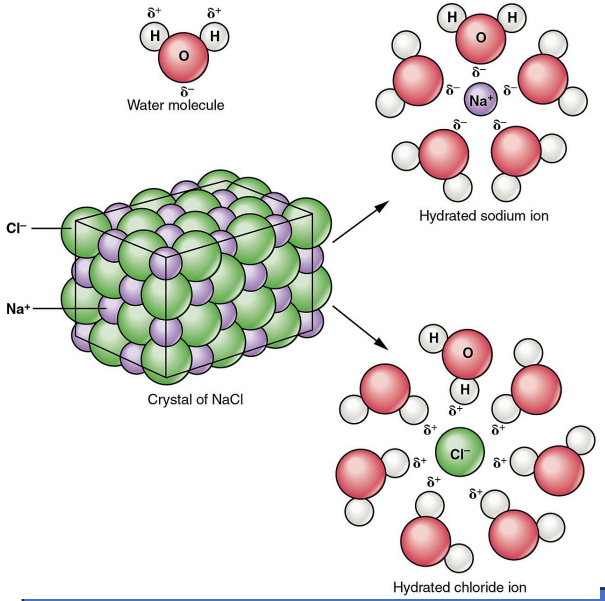


Image to the left was created by OpenStax College is used unchanged under the Creative Commons Attribution 3.0 Unported license

Outputs

Time series data for molecules in MD simulation which can be used to calculate secondary observables. Rate of dissociation (0.5 – 5 ps). stoichiometry (ligands/protein), residence time, binding/unbinding kinetics, and conformational changes

Goals

Accuracy equivalent to DFT methods.

Stepping Stone Instance

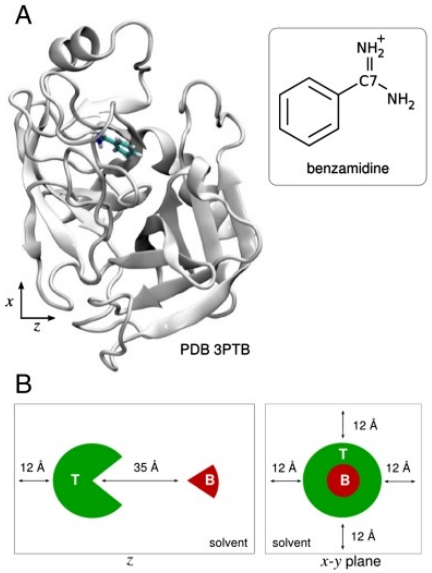
INTELLIGENT SYSTEMS DIVISION

Ligand Binding in Trypsin-benzamidine

Inputs

- Box: 71x64x82 Å^3
- The ligand was placed in the bulk at z = 35 $\mathring{A}$ from the binding pocket
- 10604 Water molecules as solvent
- Force Field Calculations methods (Open Choice)
- 70ps runtime.

https://pmc.ncbi.nlm.nih.gov/articles/PMC3121846/#F1



Graphic from fig. 1 of Buch et al. https://pmc.ncbi.nlm.nih.gov/articles/PMC3121846/#F1

Outputs

Time series data for molecules in MD simulation which can be used to calculate secondary observables. Binding orientation, strength, stochiometry (ligands / proteins)

Goals

Accuracy equivalent to or better than existing methods in reference

Challenge Problem

INTELLIGENT SYSTEMS DIVISION

Drug Binding and Molecular Interactions

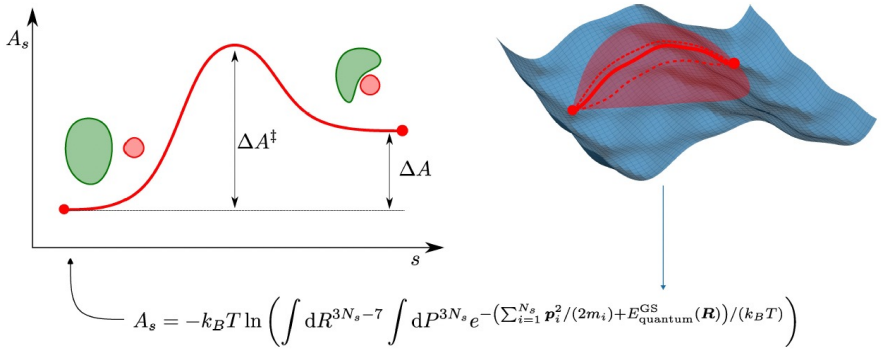
Bisphosphonate binding with calcium in bones.

Inputs:

- System Volume: 100x100x100 Å^3
- Water density 1g/cm^3
- Bisphosphonate compound chosen
- Hydroxapatite slab
- Simulated in zero-low gravity environment.

Outputs:

- Energy for docking
- Configurations that work



Molecular dynamics pipeline from Fig 2 in A. Baiardi, M. Christandl, M. Reiher, *ChemBioChem* 2023, 24, e202300120. used under Creative Commons Attribution-NonCommercial-NoDerivs

Goals

Chemical accuracy full docking for Bisphosphonate with calcium in bones

Determine efficacy in space environment versus known earth studies.

Useful References on Bisphosphonate

Silverman, S., Christiansen, C. Individualizing osteoporosis therapy. *Osteoporos Int* 23, 797–809 (2012). https://doi.org/10.1007/s00198-011-1775-y

Journal of Bone and Mineral Research, Volume 25, Issue 10, 1 October 2010, Pages 2251–2255, https://doi.org/10.1002/jbmr.103

Reid et al. “Intravenous Zoledronic Acid in Postmenopausal Women with Low Bone Mineral Density” New England Journal of Medicine https://doi.org/10.1056/nejmoa011807

Shinichiro Kuroshima, Virginia-Arlene A. Go, Junro Yamashita, Increased Numbers of Nonattached Osteoclasts After Long-Term Zoledronic Acid Therapy in Mice, *Endocrinology*, Volume 153, Issue 1, 1 January 2012, Pages 17–28, https://doi.org/10.1210/en.2011-1439



Wound Healing

Methionine Oxidation effects, Human alphaC dimer, and Oxidation of Fibrin Proteins

What does this Enable?

Better understanding of injuries and healing in zero-g environments

Challenge problem of coagulation and wound healing of astronauts

Toy Problem Instance

INTELLIGENT SYSTEMS DIVISION

Oxidation of Methionine-containing peptide

Inputs:

- 70 angstrom cubic box
- 1 fs time step
- Met(O) (methionine sulfoxide)
- Runtime 200 ns
- Temperature: 300K
- Imbedded in water a 1g/cm^3
- Pressure: 1 atm

Goals:

This type of problem while not directly related to wound healing

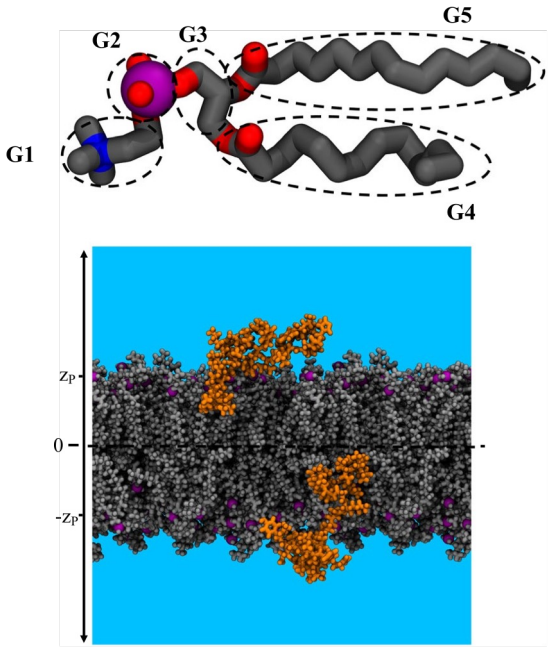


Image from Fig2 in Ref [Lock19] under http://creativecommons.org/licenses/by/4.0/

Outputs:

- Compare conformational preferences (e.g., via RMSD, secondary structure) between reduced and oxidized forms.
- Validate against peptide MD benchmarks.

[Lock19] Lockhart, C., Smith, A.K. & Klimov, D.K. Methionine Oxidation Changes the Mechanism of Aβ Peptide Binding to the DMPC Bilayer. *Sci Rep* **9**, 5947 (2019). https://doi.org/10.1038/s41598-019-42304-9

Stepping Stone Problem:
Human αC-Domain Dimer Oxidation

INTELLIGENT SYSTEMS DIVISION

Fibrinogen αC-Domain Dimer Oxidation (Met476)

Inputs:

- 100A box for unoxidized dimer
- 150A box for oxidized dimer
- Periodic boundary conditions

- 1fs time step
- Human aC-domain dimer[1]
- Oxidized structure with Met^{476} using 100 relaxation steps

- Runtime 300 ns
- Temperature: 300K
- Imbedded in water a 1g/cm^3
- Pressure: 1 atm

Outputs:

- Investigate inter-domain binding and stability via replica-exchange MD.
- Compare dimerization propensities in Met vs Met(O).
- Flexibility of the dimer
- H-O bond stabilities

[1] Structure available in Galina Tsurupa, Roy R. Hantgan, Robert A. Burton, Igor Pechik, Nico Tjandra, Leonid Medved; Structure, Stability, and Interaction of the Fibrin(ogen) αC-Domains . *Biochemistry*29 December 2009; 48 (51): 12191–12201. https://doi.org/10.1021/bi901640e

Challenge Problem

INTELLIGENT SYSTEMS DIVISION

Methionine oxidation on fibrin
[see notes]

Inputs:

- Proteins parameterized using the Amber 99SB-ildn force field
- Glycosylation and associated asparagine residues parameterized with GLYCAM06 force field
- Methionine sulfoxide residues parameterized in Amber's antechamber using GAFF force field
- Long range Van der Walls forces were smoothly reduced to zero between the range of 0.8 to 1.0 nm but shifting the Lennard-Jones potential
- Coulombic interactions cut off at 1.0 nm
- 2 fs time steps

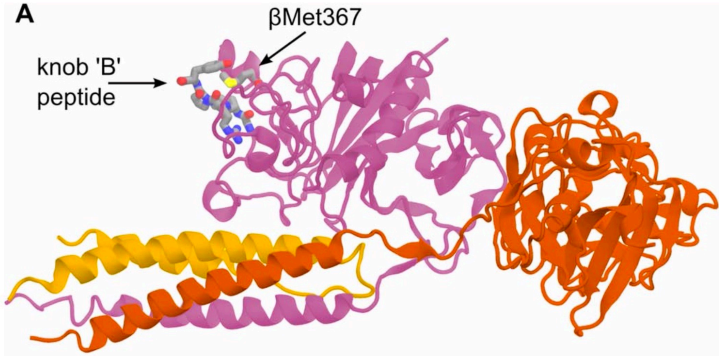


Fig. 1a from [Bur14] Molecular representation of the initial structure of the D region corresponding to PDB 2Z4E for \beta Met367 Used under https://creativecommons.org/licenses/by/4.0/ without change.

Outputs:

- Analysis of the effects of oxidation on the protein structure and characteristic fluctuations were tracked by the Cα root-mean-square deviation (RMSD) and fluctuation (RMSF) over the course of the 350 ns NPT (constant number, pressure, temp.) simulations

[Bur14] P.R. Burney, et al., Structural Effects of Methionine Oxidation on Isolated Subdomains of Human Fibrin D and \alpha C Regions, PLoS ONE 9 (1) e86981 (2014). doi:10.1371/journal.pone.0086981



Radiation Damage

Crystalline Polymer Breaking, Partial Fragment Breaking, and DNA double strand breaking from radiation

Toy Problem

INTELLIGENT SYSTEMS DIVISION

Bond Breaking in Crystalline Polymer Bonds

Inputs:

- Glycine molecule in center
- Hydroxyl 3 angstrom away from CH_2 portion of Glycine30^3 Angstrom box
- Temperature 300K
- 5 ps runtime
- 0.1 fs time step updte
- Zero-g environment

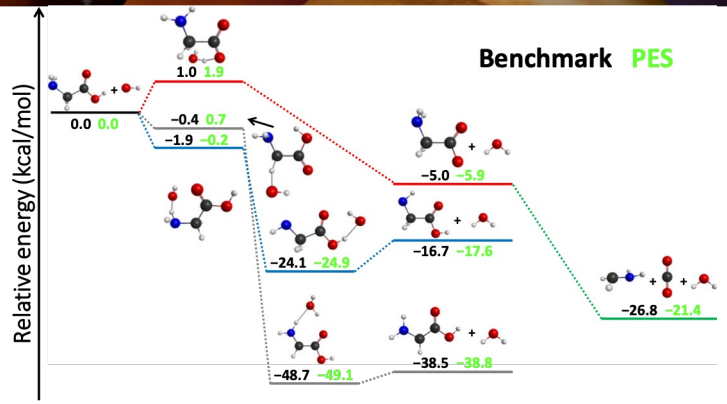


Image from [Gru26] Fig. 1 used without changes under https://creativecommons.org/licenses/by/4.0/

Outputs:

- Time for bond breaking
- Chance of bond breaking

[Linc10] Lin, RJ., Wu, CC., Jang, S. *et al.* Variation of reaction dynamics for OH hydrogen abstraction from glycine between *ab initio* levels of theory. *J Mol Model* **16**, 175–182 (2010). https://doi.org/10.1007/s00894-009-0532-z

[Gru26] Gruber, B., Czakó, G. Site- and conformer-specific reaction dynamics of glycine with the hydroxyl radical. *Commun Chem* **9**, 16 (2026). https://doi.org/10.1038/s42004-025-01823-5

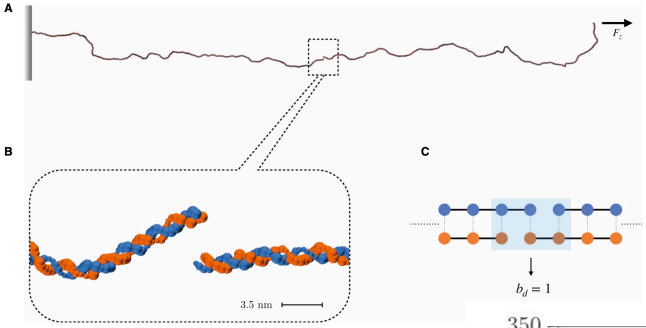
Stepping Stone Problem: Partial DNA Fragmentation

INTELLIGENT SYSTEMS DIVISION

Radiation Induced fragmented DNA Double-strand Break (DSBs)

Inputs:

- 20-bp, double-stranded DNA sequence in the B conformation
- 250^3 Angstrom box with PBC
- Add Energy deposition at bp=10 (midpoint)
- Timestep = 1fs
- Forcefields choice: capable of dynamic bond breaking (ab inititio)



Double-strand break image from Fig 1 of [Mic23]. Used under https://creativecommons.org/licenses/by/4.0/ without change.

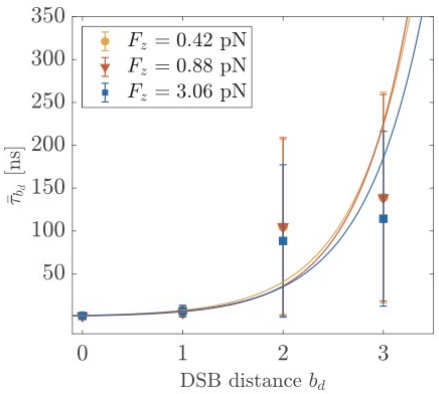


Fig. 3a from [Mic23] average rupture times as a function of the DSB distance. Used under https://creativecommons.org/licenses/by/4.0/ without change.

Outputs:

Backbone bond break events (time, position).
Base-pair disruption (melting profiles).
Helical parameters (twist, rise, bending).
Fragment separation distances post-break.
Energy redistribution curves.

[Mic23] M. Micheloni, et al., Kinetics of radiation-induced DNA double strand breaks through coarse-grained simulations, Biophysical Journal 122, 3314-3322, Aug 22, 2023

Challenge Problem Instance: DNA Fragmentation

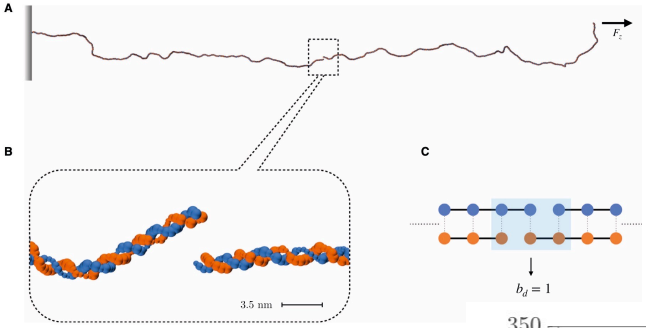
INTELLIGENT SYSTEMS DIVISION

Radiation Induced DNA Double-strand Break (DSBs)

Results in chromosomal aberrations and leads to cell apoptosis

Inputs:

- 3855-bp, double-stranded DNA sequence in the B conformation
- oxDNA2 CG force field
- Dynamics of the DNA molecules were accessed in the NVT ensemble at T=310 K and a monovalent salt concentration of 0.15 M
- Δt=5x10^-3 \tau, damping coefficient of the Lengevin thermostat = 2.5 \tau
- Target elongations of 1000, 1100, 1200 nm considered – 76%, 85%, and 92% of the control length L (~1310 nm) of the chain



Double-strand break image from Fig 1 of [Mic23]. Used under https://creativecommons.org/licenses/by/4.0/ without change.

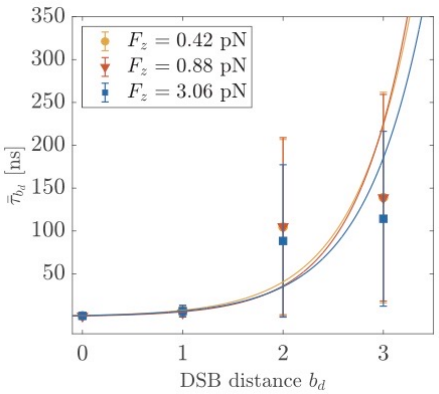


Fig. 3a from [Mic23] average rupture times as a function of the DSB distance. Used under https://creativecommons.org/licenses/by/4.0/ without change.

Outputs:

- Internal energy contribution to the DNA rupture as a function of the DSB distance, b_d, and applied force
- Average rupture times, $\overline{\tau_{bd}}$, from the different DSB motifs and DNA extensions

[Mic23] M. Micheloni, et al., Kinetics of radiation-induced DNA double strand breaks through coarse-grained simulations, Biophysical Journal 122, 3314-3322, Aug 22, 2023

Useful References

Human Health during Space Travel

C. Krittanawong, et al., Human Health during Space Travel: State-of-the-Art Review, Cells 2023, 12, 40. : State-of-the-Art R

Radiation Induced DNA Damage

M. Micheloni, et al., Kinetics of radiation-induced DNA double-strand breaks through coarse–grained simulations, Biophysical Journal 122, 3314-3322, Aug. 2023

Methionine Oxidation of Fibrin

P.R. Burney, et al., Structural Effects of Methionine Oxidation on Isolated Subdomains of Human Fibrin D and \alpha C Regions, PLoS ONE 9 (1) e86981 (2014). doi:10.1371/journal.pone.0086981

https://www.rcsb.org/structure/2RJY

Who did we talk to?

NASA Ames BPS Team members

Jonathan Galazka (NASA Ames)

Walter Alvarado (NASA Ames)

Ryan Scott (Amentum Services Inc. / NASA Ames)

Amanda Savaria-Butler (Amentum Services, Inc / NASA Ames)

James Casaletto (Blue Marble Space / NASA Ames)

Samrawit Grebe (NASA Ames)



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