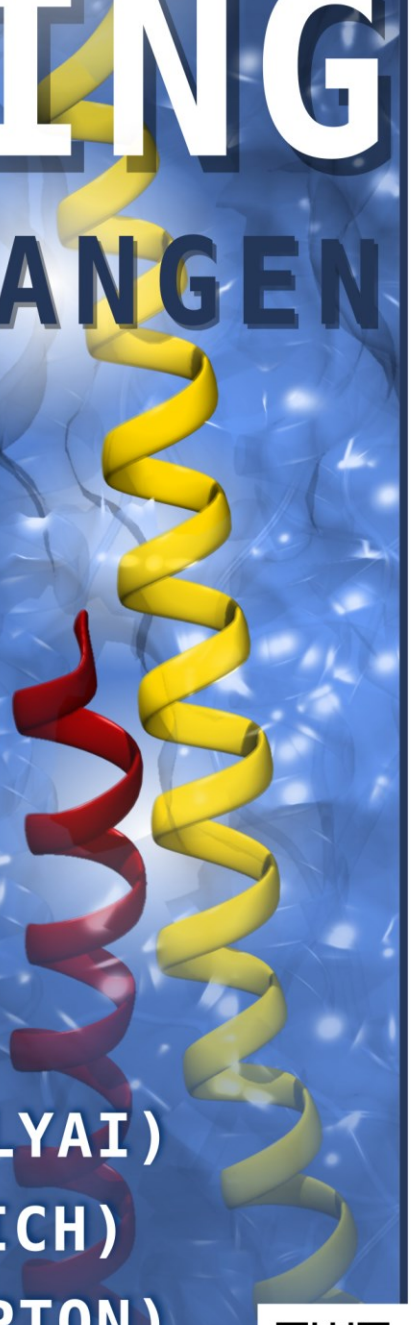
38th MM WS Erlangen

# MOLECULAR MODELLING

## WORKSHOP ERLANGEN



**MARCH 09/10 2026**

CHEMIKUM
NIKOLAUS-FIEBIGER-STR. 10
91058 ERLANGEN

**PLENARY SPEAKERS:**

VLAD COJOCARU (BABEŞ-BOLYAI)
ANTONELLA DI PIZIO (MUNICH)
JONATHAN ESSEX (SOUTHAMPTON)

molecular graphics modelling society

NHR FAU

C3 Computer Chemie Centrum

CAMP Computational Advanced Materials and Processes

FAU Friedrich-Alexander-Universität Erlangen-Nürnberg

# MOLECULAR MODELLING WORKSHOP 2026

*Welcome to the 38th Molecular Modelling Workshop (MMWS)*

It is truly a pleasure to welcome you to this year's Molecular Modelling Workshop in Erlangen, the 38th in a wonderful tradition of gatherings organized by the Molecular Graphics and Modelling Society – Deutschsprachige Sektion e.V. (MGMS-DS). This workshop has always been a special place where a wide range of topics in molecular modelling come together, from structural modelling and molecular dynamics simulations to multi-scale approaches, chemoinformatics, machine learning, and their many exciting applications across various fields.

In recognition of its broad scope, the workshop is also proudly supported as an activity of the CECAM (Centre Européen de Calcul Atomique et Moléculaire) node "Mathematics and Computation in Molecular Simulation." This node is hosted by the Atomistic Simulation Centre, a collaboration involving three national supercomputing centers: NHR@ZIB in Berlin, PC2 in Paderborn, and NHR@FAU in Erlangen. These centers provide Tier 2 high-performance computing infrastructure, training, and expert support to researchers across Germany, enabling advanced molecular modelling and simulations. A special thank you goes to NHR@FAU for their generous support of this workshop. To honor this partnership, we have a dedicated NHR@FAU session on the second day of the event.

We would also like to express our sincere gratitude to all the sponsors of this year's workshop.

Last but not least, a big thank you to everyone who helped in preparing and running this event. Your efforts are truly appreciated.

We're genuinely excited for the next two days, filled with inspiring talks, lively discussions, and the chance to connect with old friends and make new ones. We hope you enjoy the event, find it enriching, and leave with new ideas, fresh perspectives, and fond memories. Let's make this workshop a wonderful experience for everyone!

***Scientific program***

PD Dr. Anselm Horn

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## DEAR FRIENDS AND COLLEGUES,

the 38th Molecular Modelling Workshop 2026 (on March 9th / 10th) in Erlangen aims for providing especially young scientists with a platform to present their research, exchange ideas with peers, and connect with others in the field. Presentations by scientists early in their career and of work in progress are therefore highly encouraged.

Additionally, the workshop offers a valuable networking opportunity, both within academia and with industry representatives. The workshop feeds from the warm and friendly atmosphere generated by its participants.

Due to organizational issues and constraints, this year's conference is limited to two days only, which is in some way a relation to much earlier days: Originally located in Darmstadt, the MMWS comprised 1,5 days in total.

Although there is no enforced thematic focus of MMWS 2026, many contributions come from the area of atomistic simulation. However, the organizing committee welcomes submissions for poster or oral presentations, covering all fields of molecular modelling, work on methods and applications alike, in and across all disciplines.

We are excited to announce this year' plenary speakers (in order of their presentations) and are looking forward to welcoming you to an inspiring Molecular Modelling Workshop in Erlangen!

**PROF. DR. VLAD COJOCARU**
Babeş-Bolyai University, Romania

**PROF. DR. ANTONELLA DIPIZIO**
Technical University Munich, Germany

**PROF. DR. JONATHAN ESSEX**
University of Southampton, UK

## AWARDS

Traditionally, there will be two *Poster Awards* of 100 Euro each and three *Lecture Awards* for the best talks sponsored by the MGMS-DS:

***1st Winner***
Travel bursary to the *Young Modellers Forum* in the United Kingdom (travel expenses are reimbursed up to 500 Euro)

***2nd Winner***
up to 200 Euro travel expenses reimbursement

***3rd Winner***
up to 100 Euro travel expenses reimbursement

Only undergraduate and graduate research students qualify for the poster and lecture awards.

## MGMS-DS E.V. ANNUAL MEETING

The general meeting of the MGMS, German Section (MGMS-DS e.V.) will be held on tuesday (in German language). We cordially invite all conference delegates to take the opportunity and join the society to participate in the annual meeting!

## FEES

The conference fee amounts to 75 Euro (students: 35 Euro); online-only participation reduces the fee by 50%. This fee includes the annual membership fee for the MGMS-DS e.V.

## WI-FI ACCESS

During the workshop, Wi-Fi access is possible via **eduroam** (SSID). Please have your Wi-Fi configured in advance or ask your local administrator for detailed information about your eduroam access. Links to general information about eduroam can be found on the workshop website mmws2026.mgms-ds.de

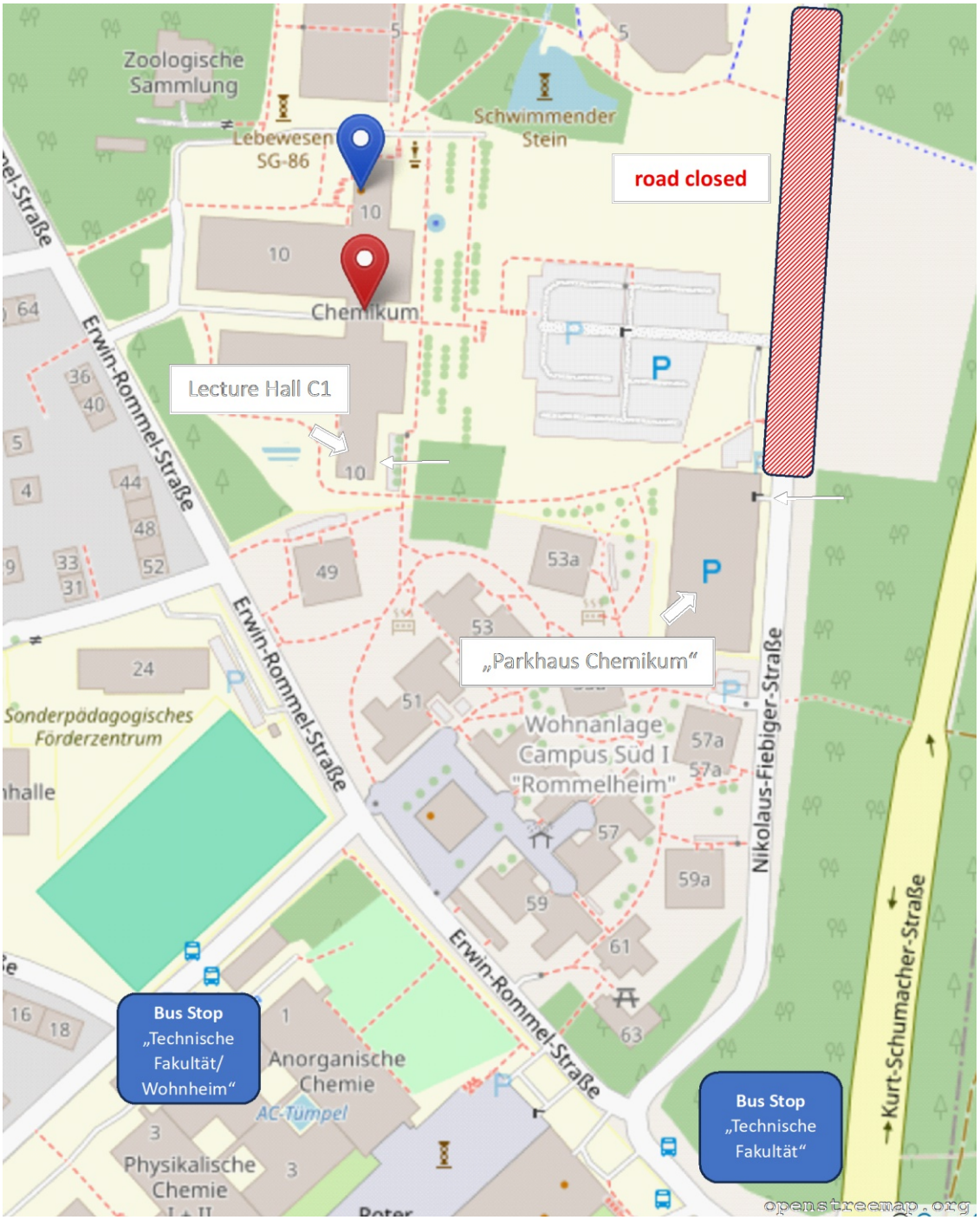
## PRE- AND POST-CONFERENCE WORKSHOP

We are delighted to follow the pre-COVID tradition of workshops held before and after the conference. Please inspect the lectures program for more details.

## LOCATION

Conference location: All talks, coffee breaks, the poster sessions and the buffet dinner on Monday, March 9th will take place at the Chemikum I, Nikolaus-Fiebiger-Straße 10, 91058 Erlangen, located on the southern campus of the university. The registration desk is next to lecture hall C1.

Public transport is available (www.vgn.de) by bus line 287 or 293 from the city center / railway station to the southern campus ("Technische Fakultät"). Note that due to construction work the bus stop "Nikolaus-Fiebiger-Straße" is not available, since the road is closed; therefore, the large parking area is also not available. However, the university parking garage nearby ("Parkhaus Chemikum") accessible from the Nikolaus-Fiebiger-Straße is open for participants travelling by car.



# Lectures Program

## PROGRAM

**Monday, March 9th 2026**

| | |
|---|---|
| **10:00-12:00** | **Pre-Conference Workshop**<br>Schroedinger Suite |
| **12:00-14:00** | **Registration** |
| **14:00-14:10** | **Welcome remarks** |
| **14:10-15:00** | **PLENARY LECTURE I: Vlad Cojocaru**<br>Stem cell transcription factors meet chromatin under the computational nanoscope |
| **15:00-15:25** | **L01: Leo Christanell (Munich, Germany)**<br>Using Ab-Initio Simulations and Experimental $^{31}$P NMR Chemical Shifts for the Development of Improved Nucleic Acid– Metal Ion Force Fields |
| **15:25-15:50** | **L02: Sampanna Pahi (Erlangen, Germany)**<br>Mechanistic Modeling of Epoxy Reaction Barriers using Network Descriptors |
| **15:50-16:30** | **Coffee Break** |
| **16:30-16:55** | **L03: Silvana S. Zurmühl (Erlangen, Germany)**<br>Comparison of two AMBER force fields regarding structural changes in pH-responsive helical peptides |
| **16:55-17:20** | **L04: Matthias Hennemann (Cepos InSilico, Germany)**<br>Local Properties at Protein-Ligand Interfaces |
| **17:30-22:00** | **Poster Session & Buffett – Dinner** |

**Tuesday, March 10th 2026**

| | |
|---|---|
| | **NHR@FAU Session** |
| **09:00-09:50** | **PLENARY LECTURE II: Antonella DiPizio**<br>AI-Seeded Modeling and Simulations of Chemoreceptor Mechanisms |
| **09:50-10:15** | **L05: Jorge A. A. Balderas (Erlangen, Germany)**<br>Mutations in hSMUG1 and their effect in U/hmU excision: A computational study |
| **10:15-11:00** | **Conference Photo & Coffee Break** |
| **11:00-11:25** | **L06: Kristyna Pluhackova (Stuttgart, Germany)**<br>You shall (not) pass! Molecular selectivity in nanoporous carbon |
| **11:25-11:50** | **L07: Barbara K. Lech (Wroclaw, Poland)**<br>A-type helicity controls efficient nonenzymatic template copying of nucleic acids |
| **11:50-13:15** | **Lunch** |
| **13:15-14:00** | **Annual Meeting of the MGMS-DS e.V.** |
| **13:15-14:00** | **Poster Session (continued)** |
| **14:00-14:50** | **PLENARY LECTURE III: Jonathan Essex**<br>Grand Canonical Simulations for In Silico Prediction of Fragment Binding Sites, Modes, and Affinities |
| **14:50-15:15** | **L08: Thomas Trepl (Bayreuth, Germany)**<br>Time-Resolved Excitation Dynamics in a Supermolecular Light-Harvesting Complex |
| **15:15-15:35** | **Short Bio-Break** |
| **15:35-16:00** | **L09: Jonas Kaindl (Schroedinger, Germany)**<br>Let it go: exploring and learning from unbinding pathways |
| **16:55-16:20** | **L10: Dustin Vivod (Jülich, Germany)**<br>Structural and Electrostatic Asymmetry at Charged Platinum–Nafion Thin-Film Interfaces Explored by MD Simulations |
| **16:20-17:00** | **Poster & Lecture Awards, Closing** |
| **17:15-19:15** | **Post-Conference Workshop**<br>ProteinsPlus – Supporting Structure-Based Design on the Web |

# Poster Session

## POSTER SESSION

**Monday, March 9th 2026 17:30-19:00**

**P01** **Jorge A. A. Balderas (Erlangen, Germany)**
Mutations in hSMUG1 and their effect in U/hmU excision: A computational study

**P02** **Lukas Busch (Kaiserslautern, Germany)**
Identification of Structural Determinants for Amyloid Beta Sensing by Formyl Peptide Receptors

**P03** **Olena Denysenko (Erlangen, Germany)**
Exploring Antibody-Derived Beta Hairpins as Minibinders: A Molecular Dynamics Investigation

**P04** **Christiane Ehrt (Hamburg, Germany)**
Binding Site Comparison with SiteMine for the Functional Annotation of Predicted Protein Structures

**P05** **Frank R. Beierlein (Erlangen, Germany)**
DNA-Repair Mechanisms: Molecular Simulations and Computational Alchemy

**P06** **Frank R. Beierlein (Erlangen, Germany)**
Base Excision Repair by TDG: A Possible Role of Extrahelical Imino-Tautomers?

**P07** **Anselm Horn (Erlangen, Germany)**
NHR@FAU Boosts Your Atomistic Simulations

**P08** **Alina Jansen (Berlin, Germany)**
Identifying crucial amino acids in FeS cluster proteins with $pK_a$ analysis

**P09** **Christophe Jardin (Nuremberg, Germany)**
pH-dependent gating of the human voltage-gated proton channel

**P10** **Silja Jenne (Erlangen, Germany)**
Computational drug design strategy targeting herpesviral kinases

**P11** **Younes Larbi (Batna, Algeria)**
Theoretical investigation of physicochemical and biological properties of some imidazole derivatives: a DFT approach and molecular docking analysis

**P12** **Moritz Macht (Erlangen, Germany)**
On the pK of API aggregate surfaces: molecular rationalisation of oral administration drug release models

***Please kindly remove your posters on tuesday!***

## POSTER SESSION

**Monday, March 9th 2026 17:30-19:00**

**P13** **Katharina Munk (Hagenberg, Austria)**
Computational Automation of Pharmacophore Model Optimization

**P14** **Boluwatife Ogunnaiya (Wroclaw, Poland)**
Molecular Dynamics Investigation of the Role of $Mg^{2+}$ in Nonenzymatic RNA Self-Replication

**P15** **Helena K. Schatz (Erlangen, Germany)**
Comparison of two AMBER force fields for investigating the ligand binding properties of maltose-binding protein

**P16** **Debarshee Sengupta (Saarbrücken, Germany)**
How Phosphorylation Affects Peptide Interaction with Adaptor Domains

**P17** **Rinto Thomas (Marburg, Germany)**
Modeling Diffusion and Permeation Across the Stratum Corneum Lipid Barrier

**P18** **Martin Veitenhansl (Erlangen, Germany)**
Modelling Reaction-Competent Carboxypeptidase A-Peptide-Complexes

**P19** **Jennifer Wölfel (Kaiserslautern, Germany)**
Integrating Structure-Based Modelling to Characterize Formyl Peptide Recognition by FPR1 and FPR2

***All abstracts are available on the conference web site:***
***www.mmws2026.mgms-ds.de***

***Please kindly remove your posters on tuesday!***

***Please kindly remove your posters on tuesday!***

# Abstracts

# Stem cell transcription factors meet chromatin under the computational nanoscope

Vlad Cojocaru

*Computational Structural Biochemistry Group, STAR-UBB Institute, Babeş-Bolyai University, Cluj-Napoca, Romania*

I will present our efforts to understand how master regulators of stem cell pluripotency are recognizing genomic DNA in different contexts. Transcription factors such as Oct4 and Sox2 are essential proteins that bind DNA regulatory elements to establish gene regulation programs for the maintenance and induction of stem cell properties. They recognize DNA in different regions of the nuclear chromatin, the structure in which the genomic DNA is packed in the cell. Chromatin is a highly dynamic structure formed by packing of fundamental units, nucleosomes in arrays of different sizes and shapes. The nucleosome wraps 147 base pairs of DNA around a histone core formed by 4 histone proteins, each occurring twice. DNA recognition by transcription factors is highly dependent on the local chromatin structure. In nucleosome depleted regions, Oct4 and Sox2 recognize DNA mostly together via a cooperative heterodimerization mechanism. When nucleosomes are present, Oct4 and Sox2 recognize their binding sites on wrapped DNA and induce local opening of nucleosomes and chromatin. Because of this ability, they were classified tas pioneer transcription factors. We now start to understand the mechanisms by which pioneer transcription factors unravel genomic DNA wrapped in nucleosomes. I will show how we are discovering key details of these mechanisms with the computational nanoscope, visualizing Oct4- and Sox2-nucleosome complexes by molecular modeling and molecular dynamics simulations. Besides contributing to expanding our knowledge about protein-DNA recognition in chromatin, our work may also inform future strategies to optimize cell fate transitions for therapeutic purposes.

# Using Ab-Initio Simulations and Experimental $^{31}$P NMR Chemical Shifts for the Development of Improved Nucleic Acid – Metal Ion Force Fields

Leo Christanell, Karl-Jakob König, Petros Mavromatis, Julian Holzinger, Anne K. Schütz, Benjamin P. Fingerhut

*Department Chemie and Centre for NanoScience, Ludwig-Maximilians-Universität, München, Germany*

Electrostatic interactions of nucleic acids and metal ions critically affect the structure and functionality of DNA and RNA in solution. [1–3] It has therefore been a constant effort of molecular dynamics (MD) simulations of aqueous nucleic acid systems to improve the parameterization of non-bonded interactions between metal ions and the biomolecular surface, in particular for doubly charged ions, like $Mg^{2+}$. However, state of the art, non-polarizable force fields overestimate contact ion pair (CIP) formation in nucleic acids [4,5] and it is therefore an open question to derive adequate non-bonded force field parameters for the simulation of nucleic acids in solution.

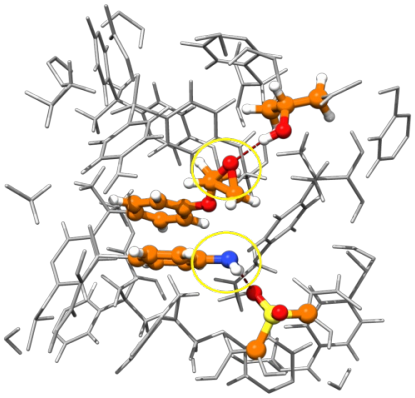
We investigate dimethyl phosphate (DMP) in presence of $Mg^{2+}$ as a model system to gain a deeper understanding of the ion-phosphate interaction motif. The analysis of experimental $^{31}$P chemical shifts for varying $Mg^{2+}$ content and ab initio (GIAO-DF-LMP2) simulated NMR chemical shifts indicate a preference for solvent separated ion pairs (SSIP) over contact ion pair (CIP) formation, [6] in agreement with previous experimental data. [7] We propose an approach that unifies preceding approaches for the parameterization of a novel force field by fitting to ab initio data from the DMP-metal-ion model system. Missing polarization effects and mismatched surface-ion interactions can be accounted for within the 12-6-4 Lennard-Jones model, which introduces an additional induced dipole term into the 12-6 Lennard-Jones interaction model. [8] An alternative approach relies on the screening of charges in condensed liquid phase, which can be effectively accounted for in a mean field way via a rescaling of charges. [9] We show that the use of non-integer ion charges and a 12-6-4 Lennard-Jones potential can be used to develop new nucleic acid-ion parameter sets. Extensive benchmark MD simulations show that the novel parametrization approach yields an improved 12-6-4 metal ion parameter set with scaled charges that has broad applicability for atomistic force field simulations of nucleic acids in solution.

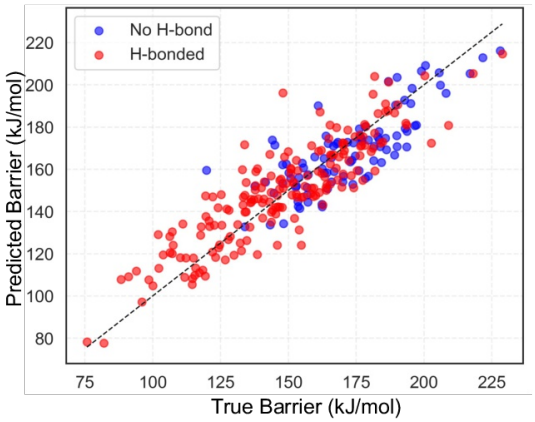
[1] A. Pyle, *J. Biol. Inorg. Chem.*, **2002**, 7, 679.
[2] J.K. Frederiksen, N.-S. Li, R. Das, D. Herschlag, and J.A. Piccirilli, *RNA*, **2012**, 18, 1123.
[3] B.P. Fingerhut, *Chem. Commun.*, **2021**, 57, 12880.
[4] M.T. Panteva, G.M. Giambaşu, and D.M. York, *J. Phys. Chem. B,* **2015**, 119, 15460.
[5] K.K. Grotz, S. Cruz-León, and N. Schwierz, *J. Chem. Theory Comput.*, **2021**, 17, 2530.
[6] L. Christanell, K.J. König, J. Holzinger, A.K. Schütz, and B.P. Fingerhut, *ArXiv,* **2026**, doi.org/10.48550/arXiv.2602.06753.
[7] J. Schauss, A. Kundu, B.P. Fingerhut, and T. Elsaesser, *J. Phys. Chem. Lett.*, **2019**, 10, 6281.
[8] P. Li, and K.M. Merz, *J. Chem. Theory Comput.*, **2014**, 10, 289.
[9] I. Leontyev, and A. Stuchebrukhov, *Phys. Chem. Chem. Phys.*, **2011**, 13, 2613.

# Mechanistic Modeling of Epoxy Reaction Barriers using Network Descriptors

Sampanna Pahi[1], Christian Wick[1], and Ana-Sunčana Smith[1,2]

*[1]PULS Group, Institute for Theoretical Physics, IZNF, FAU Erlangen-Nürnberg, 91058 Erlangen, Germany — [2]Group of Computational Life Sciences, Ruder Bošković Institute, 10000 Zagreb, Croatia*






The curing of thermosets is governed by a complex interplay between local reaction geometry and the evolving covalent network. While simplified models capture qualitative trends in activation energies, they do not resolve how the environmental constraints imposed by the forming polymer network alter reaction kinetics under realistic curing conditions.

In our earlier QM/MM study of DGEBA/DDS systems [1], we quantified how hydrogen bonding modulates activation barriers. Building on this foundation, we extend these insights toward predictive curing simulations by coupling reactive molecular dynamics with QM/MM ONIOM transition-state analyses. Reactive configurations are extracted directly from in silico curing trajectories, enabling activation barriers to be computed within their polymer environment. This analysis reveals that the evolving network strongly modulates reaction energetics: hydrogen bonding, steric confinement, and geometric distortion together determine whether a reactive event remains energetically feasible as curing progresses.

From this mechanistic understanding, we identify a minimal, yet physically meaningful descriptor set capturing reactive-site geometry and hydrogen-bond contributions. These descriptors are evaluated against a large QM/MM barrier dataset to determine which structural features correlate robustly with activation energies across diverse network environments. Using this curated dataset, we train a supervised machine-learning model on ONIOM-derived barriers, enabling it to learn the mapping between local structural environment and activation energy.

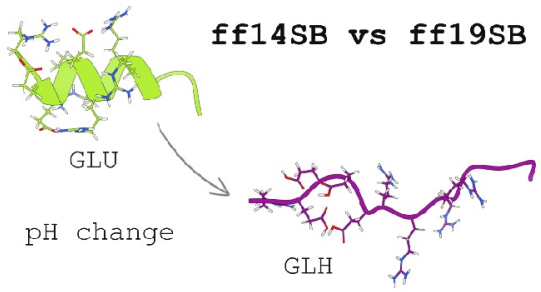
Our ML model is deployed as an energy-aware reaction gate during reactive MD curing simulations. Candidate bond-formation events are evaluated on-the-fly, and only reactions predicted to be energetically feasible are allowed to proceed. Thus, network topology evolution is constrained by activation barriers learned from quantum-mechanical reference data rather than purely geometric proximity criteria. This framework links atomistic reaction energetics with network evolution and provides a scalable route toward energetically controlled in silico curing of thermosetting polymers.

[1] M. Livraghi, S. Pahi, P. Nowakowski, D. Smith, C.R. Wick, A.-S. Smith *The Journal of Physical Chemistry B*, **2023**, *127*, 7648-7662.

# Comparison of two AMBER force fields regarding structural changes in pH-responsive helical peptides

Silvana S. Zurmühl[1], Anselm H.C. Horn[1,2], Simon Leukel[3], Jutta Eichler[3], Kathrin Castiglione[4], Heinrich Sticht[1,2]

[1]*Bioinformatics, Institute of Biochemistry, Friedrich-Alexander-Universität Erlangen-Nürnberg*
[2]*Erlangen National High Performance Computing Center (NHR@FAU), Friedrich-Alexander-Universität Erlangen-Nürnberg*
[3]*Department of Chemistry and Pharmacy, Friedrich-Alexander-Universität Erlangen-Nürnberg*
[4]*Department of Chemical and Biological Engineering, Institute of Bioprocess Engineering, Friedrich-Alexander-Universität Erlangen-Nürnberg*




We compared two AMBER biomolecular force fields (ff14SB and ff19SB) in terms of their ability to model structural changes in α-helical peptides in response to pH changes. We were particularly interested in how the two force fields model electrostatic interactions, as these are generally important for the stability of α-helices. We curated a dataset comprising nine peptides, including one non-helical control peptide and six peptides with an experimentally documented pH-dependent structural change. Two of the peptides had an unknown pH response. All systems were simulated at two protonation states, reflecting two different pH values. Both force fields modelled the same unfolding trend for the pH-responsive peptides, which is consistent with existing experimental data. Furthermore, ff14SB and ff19SB model similar side chain interactions for the helical conformation of the peptides. However, we observed differences in backbone and side chain hydrogen bond stability between the two force fields. These differences were particularly evident in peptides with a high alanine content. We propose that this is an effect of the reparameterisation of alanine in the ff19SB force field[1].

To evaluate the potential of molecular dynamics simulations in identifying pH-responsive peptides, we studied two peptides with an unknown pH response. Both force fields modelled pH-dependent unfolding of one peptide, while the other remained helical in its acidic protonation state. These findings were confirmed experimentally by performing circular dichroism spectroscopy at pH 7 and pH 2.

Our work demonstrates that ff14SB and ff19SB can be used to identify pH-responsive peptides and facilitate an understanding of the atomistic reasons behind their structural change. This may be of use when studying pH-sensitive sites in peptides and proteins, or when designing peptide-based pH-sensors. Reporting similarities and differences between the two force fields can contribute to the continuous effort to improve force field and solvent models by the MD community.

[1] C. Tian, K. Kasavajhala, K. A. A. Belfon, L. Raguette, H. Huang, A. N. Migues, J. Bickel, Y. Wang, J. Pincay, Q. Wu, C. Simmerling, "ff19SB: Amino-Acid-Specific Protein Backbone Parameters Trained against Quantum Mechanics Energy Surfaces in Solution" *J. Chem. Theory Comput.* **2020**, *16*, 528–552.

# Local Properties at Protein-Ligand Interfaces

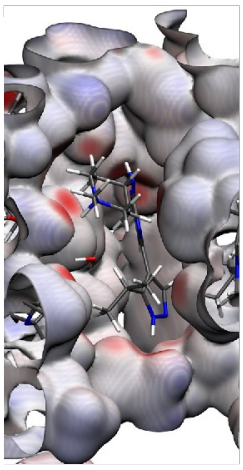
Matthias Hennemann[a] and Timothy Clark[b]

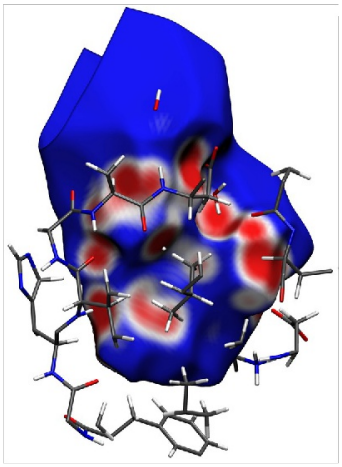
[a] *Cepos InSilico GmbH, Schützenstraße 12, 96149 Breitengüßbach, Germany.*

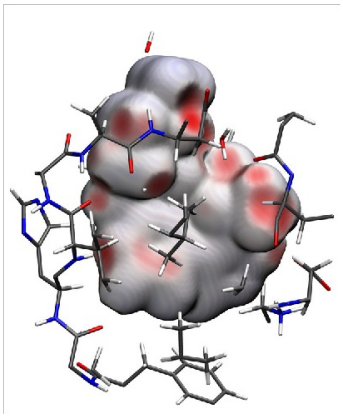
[b] *Computer-Chemistry Center, Department of Chemistry and Pharmacy, Friedrich-Alexander-University Erlangen-Nürnberg, Nägelsbachstraße 25, 91052 Erlangen, Germany.*

The ability to calculate the variational NDDO-based wavefunction [1] for a complete protein-ligand complex makes new approaches to analyzing protein-ligand interactions possible. Using EH5Cube or ParaSurf [2] to calculate local properties on molecular surfaces starting from the HDF5 wavefunction file generated by EMPIRE [3,4,5,6] we can evaluate properties such as the molecular electrostatic potentials and field, local ionization energy and electron affinity, and local hardness and electronegativity at the protein-ligand interface.

We will describe the calculations involved and present trends in ligand-protein binding, in particular the changes induced in the surface properties of the ligand by the protein (and vice versa).







[1] Self-Consistent Field Convergence for Proteins: A Comparison of Full and Localized-Molecular-Orbital Schemes C. R. Wick, M. Hennemann, J. J. P. Stewart, T. Clark, *J. Mol. Model.*, **2014**, *20*, 2159. https://doi.org/10.1007/s00894-014-2159-y

[2] https://www.ceposinsilico.de/products/parasurf.htm

[3] EMPIRE: A highly parallel semiempirical molecular orbital program: 1: Self-Consistent Field Calculations, M. Hennemann and T. Clark, J. Mol. Model. **2014**, *20*, 2331. https://doi.org/10.1007/s00894-014-2331-4

[4] EMPIRE: A highly parallel semiempirical molecular orbital program: 2: Periodic boundary conditions, J. T. Margraf, M. Hennemann, B. Meyer, T. Clark, *J. Mol. Model.*, **2015**, *21*, 144. https://doi.org/10.1007/s00894-015-2692-3

[5] EMPIRE: A highly parallel semiempirical molecular orbital program: 3: Born-Oppenheimer molecular dynamics, J. T. Margraf, M. Hennemann, T. Clark, *J. Mol. Model.*, **2020**, *26*, 43. https://doi.org/10.1007/s00894-020-4293-z

[6] https://www.ceposinsilico.de/products/empire.htm

# AI-Seeded Modeling and Simulations of Chemoreceptor Mechanisms

Antonella Di Pizio[1,2]

*[1]Professorship for Chemoinformatics and Protein Modelling, TUM School of Life Science, [2]Leibniz Institute for Food Systems Biology at the Technical University of Munich*

Taste and smell are intriguing biological systems in which an array of chemically diverse molecules is recognized by receptor repertoires. Chemosensory receptors, including odorant receptors, trace amine-associated receptors, bitter taste receptors, sweet and umami taste receptors, are the most numerous members of the G protein-coupled receptor (GPCR) superfamily. Despite its high relevance and representation, the chemosensory-GPCRome is structurally poorly characterized and the receptive range of most chemosensory receptors is unknown [1]

Advances in artificial intelligence (AI) are ushering in a new era in molecular modeling [2]. In my talk, I will highlight how AI breakthroughs are advancing our understanding of the molecular mechanisms of chemosensory perception. I will introduce AI-driven protein modeling applications to characterize the binding process of chemosensory GPCRs [3, 4], enabling the discovery of novel chemoreceptor modulators, and, overall, providing new insights into the chemistry and biology of chemosensation.

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[2] J. Jumper, et al. *Nature*, **2021**, 596(7873):583-589.
[3] P. Srivastva, A. Steuer, F. Ferri, A. Nicoli, K. Schultz, S. Bej, A. Di Pizio, O. Wolkenhauer. *J Cheminformatics*, **2024**, 16 (1): 111.
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# Mutations in hSMUG1 and their effect in U/hmU excision: A computational study

Jorge Antonio Amador Balderas[1,2], Frank Beierlein[1,2], Celine Lorentsen[3], Trond Bærheim[3], Cyrell Ann Ruales[3], Svein Bjelland[3,4], Marina Alexeeva[3], Petra Imhof[1]

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*[3]Department of Chemistry, Bioscience and Environmental Technology, University of Stavanger, 4021 Stavanger, Norway*

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Mutagenic uracil (U) arises in DNA by hydrolytic deamination of cytosine (C) while non-mutagenic U results from erroneous incorporation of deoxyuridine monophosphate opposite adenine during replication. Human single-strand-selective mono-functional uracil-DNA glycosylase 1 (hSMUG1) was first described as one of several enzymes to initiate the base excision repair (BER) pathway by excising U from DNA. hSMUG1 was also found to excise bases damaged by oxidation like 5-hydroxymethyluracil (hmU) from DNA in addition to being involved in RNA metabolism, where it has been suggested that hmU is excised from RNA.

Connected to the latter functionality, is the interaction of several hSMUG1 residues including Ser26 and Glu35 with the pseudouridine synthase Dyskerin (DKC1) protein. Our experimental work shows that the S26R/E35D double mutant shows no excision activity compared to that of U, even when both residues are far away from the active site. We also observe that replacing Pro240 with Gly (P240G) abolishes hSMUG1 activity for hmU while U activity is retained.

Unfortunately, there is no hSMUG1 crystal structure available that can help explain our results. The *Xenopus laevis* SMUG1 (xSMUG1) crystal structure has been determined without association with substrate or product. Through *in silico* modelling and molecular dynamics (MD) simulations, we managed to produce a hSMUG1-DNA complex and study the interactions between the substrate base and the active site residues.

We observed that P240 stabilizes the interaction of H239 with the substrate, which explains the reduced stabilization in the P240G mutant. We also observed that E35 is part of a hydrogen bond chain that extends to an active site residue which discriminates between hmU and thymine as substrate. When E35 is replaced with a similar amino acid as in the E35D mutant, a slight conformational change misdirects the interaction; this prevents proper hmU binding while leaving U binding unaffected.

These findings, coupled with subtle differences between hmU and U inside the active site, suggest that hmU excision is more susceptible to be affected by active site residue rearrangements, even if small.

# You shall (not) pass! Molecular selectivity in nanoporous carbon

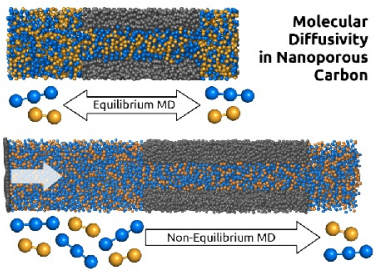
Kristyna Pluhackova

*SC SimTech, University of Stuttgart, Germany*

Nanoporous carbon materials combine high surface area, chemical stability, tunable surface chemistry, and interconnected pore networks, making them versatile platforms for applications ranging from nanoseparation and purification to catalysis and energy technologies.

In this work, we developed coarse-grained molecular models of nanoporous carbon structures to investigate solvent diffusion and nanoseparation. Systematic variation of pore diameter, geometry, surface roughness, and degree of oxidation enabled a detailed assessment of how structural and chemical material properties govern molecular transport.

Coarse-grained molecular dynamics simulations reveal that separation performance is maximized at pore diameters just above the size-exclusion limit, while surface oxidation strongly modulates the diffusivity of polar molecules. Molecular shape and pore geometry were also identified as important determinants. By employing Markov state modeling, the probability of molecules following distinct transport pathways was quantified, offering a robust framework for predicting separation efficiency in nanoporous systems under equilibrium and non-equilibrium conditions. [1]




[1] S. Kolin, M. G. Marquardt, G. Fläschner, M. Kessler, S. Naumann, K. Pluhackova, *ACS Materials. Lett.*, **2025**, 7, 11, 3714-3723

# A-type helicity controls efficient nonenzymatic template copying of nucleic acids

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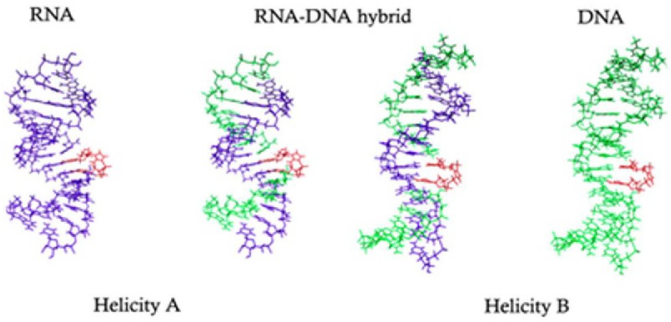
For nearly half a century, nonenzymatic RNA primer extension has been extensively studied, revealing that imidazolium-bridged dinucleotides likely play a crucial role in this process. These findings support the hypothesis that RNA was a key molecule in the origin of life [1–3]. In contrast, DNA self-replication proceeds at a much slower rate, making it largely irrelevant for prebiotic chemistry, although it remains an interesting alternative pathway for DNA synthesis. While common techniques such as solid-phase synthesis and PCR are widely used to produce DNA, they suffer from several drawbacks, including procedural complexity, high enzyme costs, and extensive solvent consumption. Notably, recent studies have demonstrated that DNA synthesis on an RNA template is significantly faster than on a purely DNA template, possibly due to the A-helical structure of RNA [5].

In this work, we performed classical molecular dynamics simulations of DNA self-replication on an RNA template with phosphoroimidazole activation. We show that the RNA template enforces A-type helicity in the hybrid DNA/RNA duplex, in contrast to the B-type helix characteristic of purely DNA-based systems. Based on detailed structural analyses, we conclude that helix type is the primary factor governing the feasibility of nonenzymatic primer extension.




[1] F. H. C. Crick, *J. Mol. Biol.*, **1968**, 38, 367–379.
[2] T. Inoue, et al., *J. Mol. Biol.*, **1982**, 162, 201–217.
[3] W. Zhang, et al., *eLife*, **2018**, 7, e36422.
[4] B. I. Andrews, et al., *J. Org. Chem.*, **2021**, 86, 49–61.
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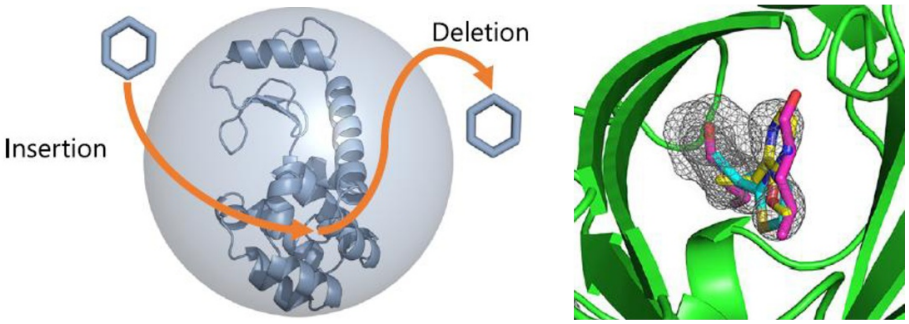
# Grand Canonical Simulations for In Silico Prediction of Fragment Binding Sites, Modes, and Affinities

Jonathan W Essex

*School of Chemistry and Chemical Engineering, University of Southampton, UK*

Fragment based drug discovery (FBDD) is widely used in the pharmaceutical industry as a route to generating lead compounds. Through knowledge of their binding sites, fragment hits may be combined into single molecules with good potency and physical properties. Computational FBDD supports experiment by providing a route to library design, virtual screening, binding site identification and binding affinity prediction.

In this talk, the development and application of grand canonical non-equilibrium Monte Carlo (GCNCMC) in this domain will be discussed. [1] By combining non-equilibrium move proposals, with grand canonical Monte Carlo acceptance tests, we are able to insert and delete small molecules into the binding sites of host-guest and protein systems, much more efficiently than conventional molecular dynamics. Through these simulations we are able to identify potential ligand binding sites by augmenting the sampling in mixed-solvent molecular dynamics. Fragment binding poses, including situations where multiple binding poses have been reported, are also readily identified. Finally, by varying the chemical potential of the simulations, absolute ligand binding free energies may be calculated, without the need for restraints or corrections to address multiple binding poses. Binding sites, poses, and affinities may all be calculated through a single series of simulations run at different chemical potentials. [2] Finally, cases where methodological improvements are needed will be discussed.

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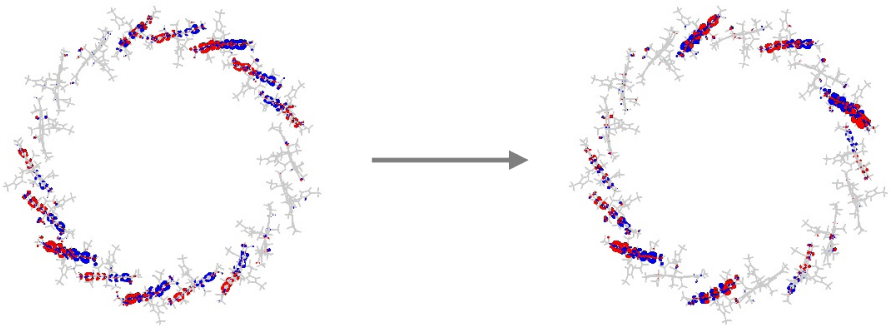
# Time-Resolved Excitation Dynamics in a Supermolecular Light-Harvesting Complex

Thomas Trepl, Ingo Schelter, and Stephan Kümmel

*Theoretical Physics IV, University of Bayreuth, 95440 Bayreuth, Germany*

Photosynthetic light-harvesting complexes are nature's fascinating solution for efficient solar energy conversion, with antenna complexes absorbing sunlight and transferring the collected energy to a reaction center with remarkable quantum efficiency. A fundamental question is how the electronic excitation is transported through the antenna complex and what role nuclear motion at ambient temperatures plays in this process. We investigate the ultrafast excitation dynamics in the B850 antenna ring in *Rhodoblastus acidophilus* following a short laser pulse and study how nuclear vibrations interplay with the electronic excitation [1].

Using time-dependent density functional theory in real time combined with Ehrenfest molecular dynamics, we simulate, on a first-principles basis, the dynamics of the 18-Bacteriochlorophyll ring system after photoexcitation. The electronic interactions of this large biomolecular assembly (almost 2000 atoms) are explicitly included in the dynamics by treating the supermolecular complex as one entire system without relying on exciton models. We compare simulations with coupled electron-nuclear dynamics with reference calculations using frozen nuclear coordinates to isolate contributions of nuclear dynamics to the excitation-energy transfer.



Initially after the laser pulse, the excitation is delocalized over almost the whole ring. Quantum interference patters appear after about 40 fs, which leads to a transient localization of the excitation energy. On the same time scale, nuclear motion noticeably influences the excitation dynamics and the B850 ring transitions into a regime in which the excitation energy is mainly localized on segments that comprise just a few Bacteriochlorophyll molecules.

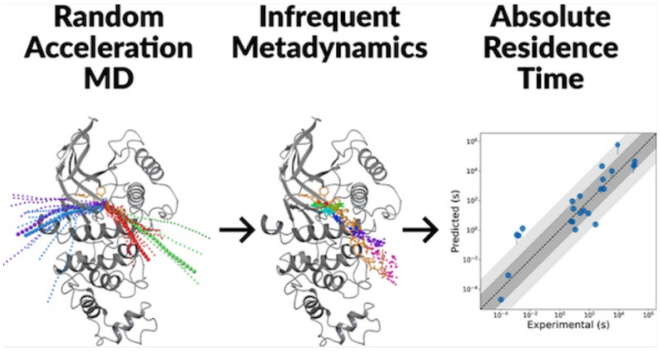
[1] T. Trepl, I. Schelter, S. Kümmel, *J. Phys. Chem. Lett.*, **2025,** *16*(42), 10891-10898.

# Let it go: exploring and learning from unbinding pathways

Jonas Kaindl

*Schrödinger GmbH, Mannheim, Germany*

The estimation of drug-target residence time has been widely adopted in drug discovery and lead optimization campaigns as a metric to control and modulate in vivo drug efficacy. Over the years, several computational approaches have been developed to simulate unbinding kinetics and calculate dissociation rates. In addition to accurately predicting residence time, understanding the molecular basis of the unbinding event is crucial to support and drive the design of drugs with optimized kinetic profiles. Here, we present the application of the unbinding kinetics workflow developed by Schrödinger to accurately predict the residence time and to study the unbinding mechanism of a set of drug-target systems [1]. We applied the presented approach to different target classes and modalities, looking at the details of the dissociation process and understanding the determinants of such an event. Overall, the results demonstrate the applicability of the workflow in assisting drug design with minimal human intervention and a computational cost compatible with drug design cycle timeline.




[1] Z. Smith, et al., *J. Chem. Inf. Model*, **2025**, *65 (24)*, 13360-13373.

# Structural and Electrostatic Asymmetry at Charged Platinum–Nafion Thin-Film Interfaces Explored by MD Simulations

Dustin Vivod, Tobias Binninger, Michael Eikerling

*Theory and Computation of Energy Materials (IET-3), Institute of Energy Technologies, Forschungszentrum Jülich GmbH, 52425 Jülich, Germany, Mail: d.vivod@fz-juelich.de*

Polymer electrolyte membrane fuel cells (PEMFCs) play a vital role in establishing a sustainable hydrogen economy, making research into their performance and durability an important endeavor. For the performance of PEMFCs, the cathode-catalyst layer (CCL) plays an important role. This layer consists of a mixture of a proton-conducting ionomer phase and platinum catalyst supported on carbon substrate. At the platinum surface, the oxygen reduction reaction (ORR) takes place forming water as the product. The ionomer phase controls the supply of protons to the catalyst surface, as required for the electrochemical reaction. These protons are transported through a thin water film at the ionomer-platinum interface [1,2]. The thin-film configuration of ionomer, water and catalyst impacts the transport of oxygen and protons and, thus, CCL performance [3]. Currently, Nafion is the most used ionomer in PEMFCs. However, their perfluorinated alkane backbone constitutes an environmental concern. Current efforts in the development of ionic polymers focus on identifying non-fluorinated replacements of Nafion with similar or even better performance and stability.

Using molecular dynamics simulations, we investigate the interface region between a platinum slab and a Nafion thin film, with a water layer in between, as depicted in Figure 1. By performing simulations with a charged platinum surface, we have calculated the electrostatic potential across the interface region, which we have used to define the effective electrode potential and to determine the differential capacitance of the charged interface (cf. Figure 2). The observed asymmetric behaviour in the differential capacitance is opposite to the expectation, and was rationalized by tracking the changes of the hydronium ions adsorbed to the surface w.r.t. the different surface charges. The favourable water content was estimated by evaluating the energy differences between systems with varying amounts of water. These complementary analyses yield vital insights into the microscopic interface region formed by catalyst, water and ionomer, which is inaccessible for experiment.

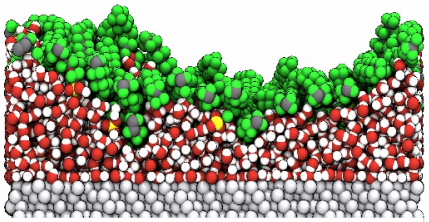


*Figure 1: Exemplary snapshot of one of the investigated systems of a water layer confined by a platinum slab on the one side, and a Nafion thin film on the other. Color code: H: white; C: black; O: red; F: green; S: yellow.*

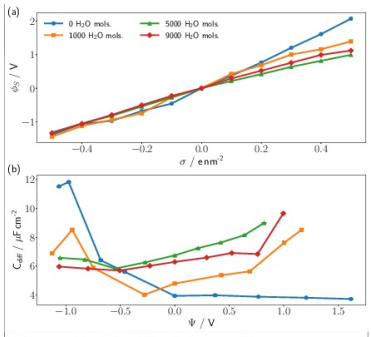



*Figure 2: (a) Electric surface potentials $\phi_s$ per surface charge for each water content. Offset so that the uncharged systems have $\phi_s$=0. (b) Differential capacitance $C_{diff}$ per electric surface potential for each water content.*

[1] F. Chabot, *et al.*, ACS Appl. Energy Mater. **2023**, *6*, 1185−1196.
[2] F. Chabot, *et al.*, J.Electrochem.Soc. **2024**, *171*, 124506.
[3] W. Olbrich, *et al.*, J. Electrochem. Soc., **2022**, *169*, 054521.

# Mutations in hSMUG1 and their effect in U/hmU excision: A computational study

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*[2] Erlangen National High Performance Computing Center (NHR@FAU), Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Martensstraße 1, 91058 Erlangen, Germany*

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Unfortunately, there is no hSMUG1 crystal structure available that can help explain our results. The *Xenopus laevis* SMUG1 (xSMUG1) crystal structure has been determined without association with substrate or product. Through *in silico* modelling and molecular dynamics (MD) simulations, we managed to produce a hSMUG1-DNA complex and study the interactions between the substrate base and the active site residues.

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These findings, coupled with subtle differences between hmU and U inside the active site, suggest that hmU excision is more susceptible to be affected by active site residue rearrangements, even if small.

# Identification of Structural Determinants for Amyloid Beta Sensing by Formyl Peptide Receptors

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*University of Applied SciencesKaiserslautern, D-66482 Zweibrücken, Germany*

Formyl peptide receptors (FPRs) are a small family of pattern recognition receptors that play a central role in the innate immune defense against invading pathogens such as bacteria and viruses. Beyond host defense, FPRs are increasingly implicated in neuroinflammatory disorders, including Alzheimer's disease, prion diseases, and multiple sclerosis. Notably, FPRs recognize a remarkably diverse spectrum of peptide ligands—including bacterial signal peptides, protein degradation products, inflammatory mediators, and neuropeptides such as amyloid beta (Aβ) and prion protein fragments—despite the absence of clear structural or sequential homology among these ligands. We recently identified human FPRs as novel detectors of non-canonical Aβ peptides and demonstrated that structurally related peptides can elicit differential cellular responses via FPR1 in a human glial model. In this study, we thus performed a detailed biochemical and functional characterization of FPR–Aβ interactions to further elucidate the molecular mechanisms governing FPR–ligand interactions and receptor activation

To this end, we employed physiological and modified Aβ variants to investigate their binding to and activation of human FPRs. Biochemical characterization included Thioflavin T aggregation assays, silver staining of PAGE gels, and bioinformatic analyses to assess the biochemical and biophysical properties of distinct Aβ variants. To map these properties to receptor activation, we next measured functional FPR responses in live-cell calcium imaging experiments using transfected HEK293T cells expressing individual FPRs. Based on these findings, we conducted initial structural modeling of receptor–peptide complexes and performed pilot docking experiments.

Our results identify distinct regions within the N- and C-termini of Aβ peptides that contribute to binding to FPR1 and FPR2, as well as FPR-subtype specific domains involved in receptor activation. Furthermore, we demonstrate that biochemical properties and structural conformation critically determine Aβ binding to FPRs and strongly influence downstream cellular responses. Taken together, these findings provide a mechanistic framework for differential FPR activation by Aβ peptides and offer new insight into the contribution of FPR signaling to the neuroinflammatory landscape of Alzheimer's disease and related neurodegenerative disorders.

# Exploring Antibody-Derived Beta Hairpins as Minibinders: A Molecular Dynamics Investigation

Olena Denysenko[1], Anselm H.C. Horn [1,2], Heinrich Sticht [1,2]

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*2.Erlangen National High Performance Computing Center (NHR@FAU), Friedrich-Alexander-Universität Erlangen-Nürnberg*

Beta-hairpins are compact structural motifs consisting of two antiparallel beta-strands connected by a short turn. They are frequently found in antibodies where they mediate antigen recognition. Their small size and structural simplicity make them attractive scaffolds for the development of minibinders targeting protein-protein interactions that are difficult to address with conventional small molecules [1, 2]. In this study, we investigated whether antibody-derived β-hairpin sequences retain antigen binding when isolated from their native protein framework.

Eight distinct β-hairpin systems were selected from different antibodies that all interact with the same antigen (RBD domain of the Coronavirus spike-protein). In addition, two mutant sequences for one of the systems (7ls9) were investigated. All peptides were cyclized via a terminal disulfide bond.

```
7wd1    -----CATPATYYSGRYYYQSPAGGCDY
7rby    -----CAVPSTYYSGTYYYTSHPGGCDY
7q9m    ------CARHVVALTHLYPDYWC-----
7ps4    -----CRSRVGATGGYYDYYC-------
7orb    --------CVVVVAARNHYYNC------
7neh    ----CYYSARDFYEGSFDIWGQC-----
7kn5    -----CLTVGTYYSGNYHYTSSDDCDY
7ls9    ---CRVHRWAYCINGVCFGAYC------
7ls9-s  ---CRVHRWAYSINGVSFGAYC------
7ls9-a  ---CRVHRWAYAINGVAFGAYC------
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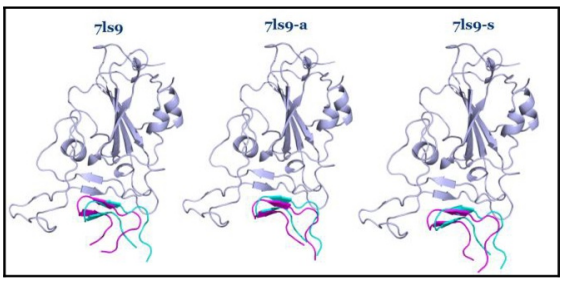


Molecular dynamics (MD) simulations were performed for both free peptides and peptide-antigen complexes with Amber [3]. Structural stability was assessed through backbone RMSD, β-turn conformational stability, and the fraction of native contacts as an indicator of binding interface preservation [4].

Our results reveal that the conformational stability varies considerably across systems: some peptides maintain β-hairpin conformations independently, while others show larger fluctuations both in free and bound states. With respect to their general properties, seven out of ten systems remained bound to the antigen indicating that MD simulations are a suitable tool to assess the conformational stability of complexes. These results suggest that antibody-derived β-hairpins can be viable scaffolds for minibinder development, with some systems retaining their functional β-hairpin structure independently of the full antibody framework.

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3. Case, D. A. et al. Amber 2023 (University of California, San Francisco, 2023).
4. Best, R. B., Hummer, G. & Eaton, W. A. Native contacts determine protein folding mechanisms in atomistic simulations. Proc. Natl. Acad. Sci. USA 110, 17874–17879 (2013).

# Binding Site Comparison with SiteMine for the Functional Annotation of Predicted Protein Structures

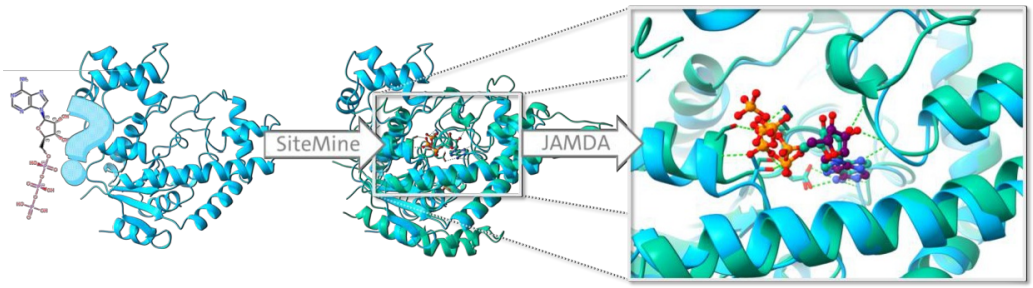
Christiane Ehrt, Joel Graef, Martin Poppinga, Matthias Rarey

*University of Hamburg, ZBH – Center for Bioinformatics*

Advances in the field of protein structure prediction enable unprecedented access to models of structurally uncharacterized proteins. Methods such as AlphaFold2[1] generate models using protein sequence information and knowledge of publicly available experimentally solved protein structures. However, these models lack the corresponding functional annotations that enable researchers to analyze these structures and utilize them in computational workflows such as virtual screening or molecular probe design. Although more recent co-folding approaches enable users to predict, for example, protein structures in complex with a known ligand, they are heavily biased toward available knowledge and the training dataset, and often lack the necessary performance.[2]

Considering these challenges, we propose SiteMine[3] as a viable alternative. It is an efficient and sequence-independent binding site comparison method, relying on the GeoMine[4] database technology that captures binding sites and their characteristics for all available PDB structures. Based on binding site similarity and the corresponding local alignment, users cannot only learn where known or unknown ligands might bind but also understand where the binding site prediction is derived from. The latter is especially beneficial to assess the quality and reliability of predictions.

In contrast to the AlphaFill[5] methodology, the method does not rely on sequence similarity, focuses on local rather than global similarities, and is not restricted to subsets of small molecules in the Protein Data Bank.




Based on a dataset of predicted protein models with known ligands, we will illustrate the applicability of SiteMine for annotating ligand binding sites and present a pipeline that enables users to predict the binding mode of the ligands in the corresponding binding site using the pose optimization functionalities of JAMDA.[6]

[1] J. Jumper, R. Evans, A. Pritzel, T. Green, M. Figurnov, O. Ronneberger *et al.*, *Nature*, **2021**, *596(7873)*, 583-589. DOI: https://doi.org/10.1038/s41586-021-03819-2
[2] E. Nittinger, Ö. Yoluk, A. Tibo, G. Olanders, C. Tyrchan, *Artif. Intell. Life Sci.*, **2025**, *8*, 100136. DOI: https://doi.org/10.1016/j.ailsci.2025.100136
[3] T. Reim, C. Ehrt, J. Graef, S. Günther, A. Meents, M. Rarey, *Arch. Pharm.*, **2024**, *357(5)*, e2300661. DOI: https://doi.org/10.1002/ardp.202300661
[4] J. Graef, C. Ehrt, K. Diedrich, M. Poppinga, N. Ritter, M. Rarey, *J. Med. Chem.*, **2022**, *65(2)*, 1384-1395. DOI: https://doi.org/10.1021/acs.jmedchem.1c01046
[5] M. L. Hekkelman, I. de Vries, R.P. Joosten, A. Perrakis, *Nat. Methods*, **2023**, *20*, 205–213. DOI: https://doi.org/10.1038/s41592-022-01685-y
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# DNA-Repair Mechanisms: Molecular Simulations and Computational Alchemy

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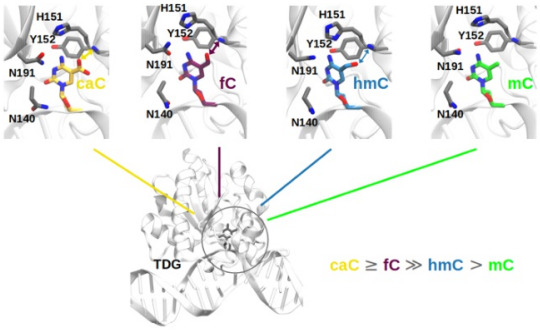


The DNA repair protein thymine DNA glycosylase (TDG) removes mispaired or damaged bases, such as oxidized 5-methylcytosines, from DNA by cleavage of the glycosidic bond between the sugar and the target base flipped into the enzyme's active site. The enzyme is active against formyl-cytosine and carboxyl-cytosine, whereas the lower oxidized hydroxymethyl-cytosine and methyl-cytosine itself are not processed by the enzyme. To investigate the substrate specifity of TDG, we used extensive molecular dynamics simulations and thermodynamic integration of TDG complexed to DNA carrying one of four different (oxidized) methyl-cytosine bases methyl-cytosine (mC), hydroxymethyl-cytosine (hmC), formyl-cytosine (fC), or carboxyl-cytosine (caC), in extra- and intrahelical conformation, and in their amino- and imino-tautomeric forms. Our results indicate that discrimination of the oxidized methyl-cytosines does not take place in the initial complex formation before the base has been flipped out into the active site, and that imino-tautomers do not play a role in substrate recognition at this stage. For the extrahelical complexes, we observe a more favorable binding affinity of the higher oxidized forms, fC and caC, compared to the nonsubstrate bases hmC and mC. Despite rather comparable, reaction-competent conformations of the flipped bases in the active site of the enzyme, more and stronger interactions with active site residues account for the preferred binding of the higher oxidized bases. Overall, our computational results indicate that the enzyme discriminates the different oxidation forms of methyl-cytosine at the formation of the extrahelical complexes, and possibly also at a later chemical step.

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# Base Excision Repair by TDG: A Possible Role of Extrahelical Imino-Tautomers?

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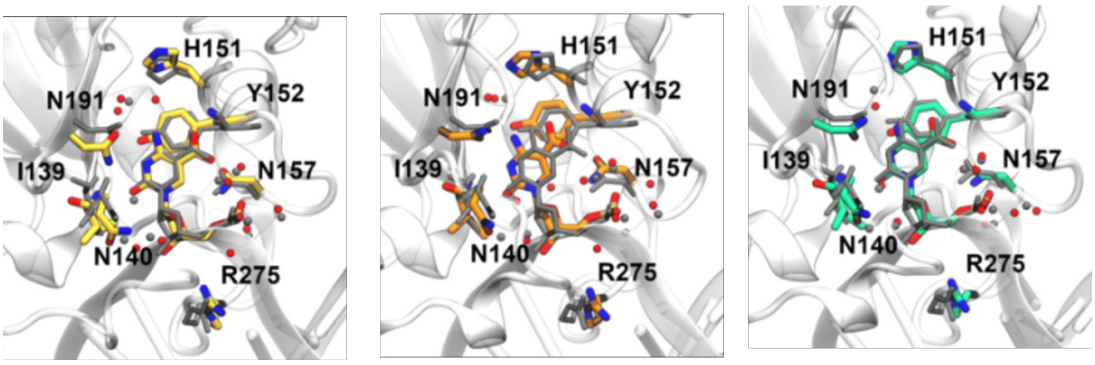


Thymine DNA glycosylase (TDG) is an important enzyme involved in DNA repair, which removes mispaired or modified DNA bases and thus ensures genetic integrity. We previously investigated possible reasons for its substrate specificity, both in the intrahelical (flipped-in) and in the extrahelical (flipped-out) state of the damaged bases 5-carboxylcytosine, 5-formylcytosine, 5-hydroxymethylcytosine and 5-methylcytosine. We showed that imino tautomers probably do not contribute to recognition in the intrahelical state, and that recognition most likely takes place once the bases are flipped out into the TDG binding pocket (extrahelical complexes). Here, only amino tautomers of the bases of interest were investigated.

We have now extended the range of possible forms of the substrates to achieve a deeper understanding of the situation in the protein substrate complex prior to the chemical reaction. For this reason, we investigated the role of imino-tautomeric forms of the damaged DNA bases flipped out into the enzyme active site as well as the effect of different protonation states of the substrate bases and an important histidine residue in the binding pocket.

The results obtained agree well with our previous work and the experimental data, and also indicate that imino tautomers might play a role in extrahelical recognition and as a starting point in the actual chemical reaction. We plan to investigate this in more detail.

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[2] S. Volkenandt, F. Beierlein, P. Imhof, *Molecules* **2021**, *26,* 5728. (DOI: 10.3390/molecules26195728)

# NHR@FAU Boosts Your Atomistic Simulations

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The Erlangen National High-Performance Computing Center (NHR@FAU) at FAU Erlangen-Nürnberg [1] was established in 2021 as a national center for HPC at German universities. Together with eight other institutions, it forms the NHR-Alliance [2]. NHR@FAU operates large-scale HPC systems and provides HPC services, related user support, and HPC training to members of German universities.

A strong focus of NHR@FAU lies on atomistic simulations and it also provides tailored hardware solutions in this area. As a key component of the NHR program, it offers exceptional competence and conducts extensive research in the field of atomistic simulations of molecular structures, with broad applications in chemistry, life sciences, materials science, and physics. With bundled atomistic structure simulation expertise, NHR@FAU helps users to select and use atomistic simulation methods in an HPC environment and actively accompanies and coordinates the development of high-performance simulation codes. An interdisciplinary approach promises not only synergy effects, e.g., through the exchange and joint development of simulation and evaluation tools, but in particular a cross-fertilization of materials and life sciences, which often use the same or similar simulation techniques.

The HPC research activities at NHR@FAU focus on performance engineering and modelling, performance tools, and research software engineering. NHR@FAU investigates and further develops hardware-efficient building blocks, programming concepts, and numerical algorithms for scalable, efficient, and robust iterative sparse matrix applications and stencil-based solvers on large-scale HPC systems.

A further core project is the education and lifelong training of scientists and engineers. The close cooperation among theory, simulation, and experiment, which has a long tradition in Erlangen, ensures that the training is not aimed specifically at modelers, but also made available to experimental colleagues. This is of particular importance in the light of increasing digitalization in science. NHR@FAU makes an essential contribution to the key technologies of scientific computing and scientific software development through the sustained concentration of methodological competence in both the application and development of computer codes and their hardware-related optimization.


NHR@FAU main compute clusters:

← Fritz (CPU)

Alex (GPU) →


**References**

[1] https://hpc.fau.de
[2] https://www.nhr-verein.de/en

# Identifying crucial amino acids in FeS cluster proteins with $pK_a$ analysis

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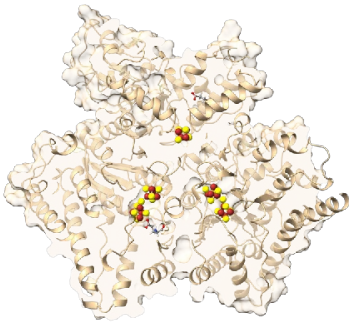

The $pK_a$ values of amino acids and, as a result, their protonation states are subject to conformational changes in the protein, e.g. upon ligand binding. In the double cubane cluster protein (DCCP) and its reductase (DCCP:R), ATP-binding introduces conformational changes that are proposed to tune the redox potential of its FeS clusters [1],[2]. Changes in protonation states of critical amino acids link the conformational changes to the redox potential. A thorough conformational and $pK_a$ analysis, prior to relatively expensive dynamic calculations, allows for first insights into its mechanisms upon ATP-binding and -hydrolysis.
The $pK_a$ values are obtained with the Karlsberg$^{2+}$ package [3],[4]. Karlsberg$^{2+}$ solves the Poisson-Boltzmann equation for pH-adapted conformations to calculate the $pK_a$ values of titratable amino acids. These estimated $pK_a$ values are compared for different structures before and after ATP-binding to identify crucial amino acids.
Preliminary findings with this workflow indicate protonation of Glu157$_{DCCP:R}$ in proximity of the [4Fe4S] cluster upon ATP-binding. In direct proximity to the unusual [8Fe9S] double cubane, deprotonation of Glu140$_{DCCP}$ causes the formation of a salt bridge to Lys146$_{DCCP}$, potentially playing a role in the substrate reduction at this cluster.
With these findings, future quantum chemical calculations can be better targeted to the identified amino acids, enabling the quantification of their impact on the redox potential of FeS clusters and the corresponding catalytic mechanism.

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# pH-dependent gating of the human voltage-gated proton channel

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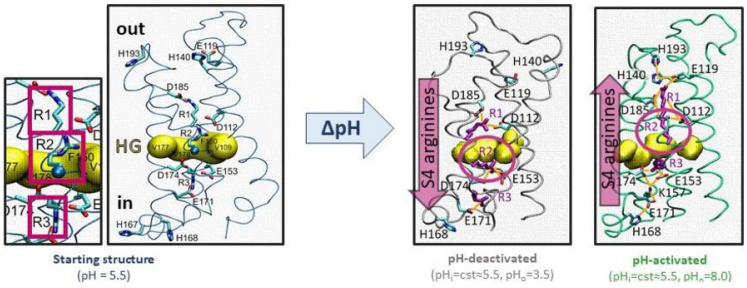
Gating of the voltage-gated proton channel $H_V1$ is strongly controlled by pH which evidently involves the sidechains of titratable amino acids. Despite experimental investigations to identify the amino acids involved in pH sensing only few progress has been made, including one histidine that is involved in sensing intracellular pH. We have used constant pH molecular dynamics simulations in symmetrical and asymmetrical pH conditions across the membrane to investigate the pH- and ΔpH-dependent gating of the human $H_V1$ channel. Our simulations captured initial conformational changes between a deactivated and an activated state of the channel induced solely by changes of the pH. The pH-dependent gating is accompanied by an outward displacement of the three S4 voltage sensing arginines (R1-R3 in figure below) that moves the second arginine past the hydrophobic gasket (HG) which separates the inner and outer pores of the channel. $H_V1$ activation, when outer pH increases, involves amino acids at the extracellular entrance of the channel that extend the network of interactions from the external solution down to the HG. Whereas, amino acids at the cytoplasmic entrance of the channel are involved in activation, when inner pH decreases, and in a network of interactions that extend from the cytoplasm up to the HG.

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# Computational drug design strategy targeting herpesviral kinases

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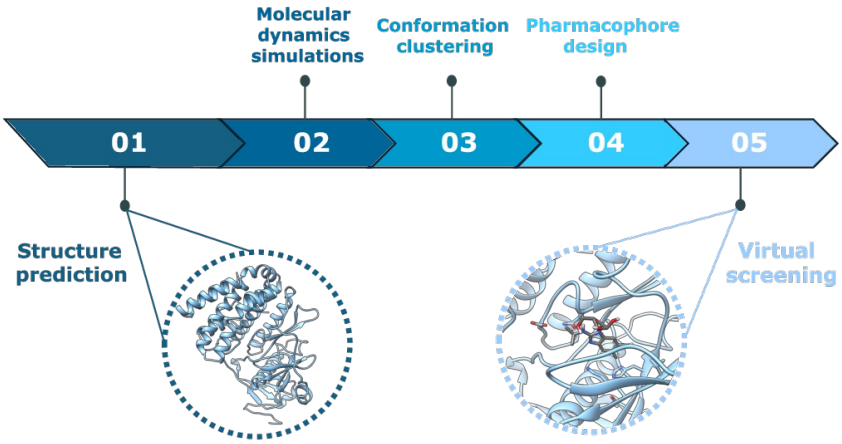
Herpesviruses are a large family of DNA viruses that establish lifelong persistence in humans. A key feature of these viruses is their ability to remain latent after primary infection and reactivate under certain conditions, such as immunosuppression. [1] Among them, human cytomegalovirus (HCMV) and the Epstein–Barr virus (EBV) are of particular clinical importance. HCMV can cause severe disease in immunocompromised individuals and newborns, while EBV is best known as the cause of infectious mononucleosis and is associated with several malignancies. Despite their clinical relevance, treatment options during active infection remain limited, especially for HCMV due to drug toxicity and the emergence of antiviral resistance. [2,3]

HCMV and EBV encode viral kinases, pUL97 and BGLF4, respectively, which are critical for viral replication, nuclear egress, and the modulation of specific host processes, including cell cycle progression and DNA damage signaling. [1] While these kinases share functional similarities with human cyclin-dependent kinases (CDKs), they diverge significantly in sequence and domain architecture, especially within their N-terminal regions and key kinase motifs. Although pUL97 has been established as a therapeutic target, and BGLF4 is increasingly recognized as a promising candidate, detailed structural and pharmacological characterization, particularly of BGLF4, remains limited.




To address this gap, we employ a structure-guided strategy to characterize and target the ATP-binding sites of pUL97 and BGLF4. High-confidence structural models of both kinase domains, generated by AI-based protein structure prediction tools, serve as the basis. The most representative protein structures of clustered all-atom molecular dynamics simulations were compared with experimentally resolved human CDK structures to identify key residues and structural differences within the ATP-binding pockets. Based on this analysis, we aim to develop pharmacophore models to identify novel small-molecule inhibitors targeting the viral kinases, thereby enabling the identification of antiviral inhibitors and advancing the treatment options for HCMV and EBV.

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# Theoretical investigation of physicochemical and biological properties of some imidazole derivatives : a DFT approach and molecular docking analysis

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We present in this work the density functional theory (DFT) calculations of the geometric parameters, electronic structure, reactivity analysis, and spectroscopic properties on Schiff's bases substituted with: –CH3, –CH2CH3, –OCH3, and –Cl groups in the para position, 2–(4–R–phenyl)–4,5–diphenyl–1H–imidazoles (Imd), Imd1–Imd4 in ethanol solvent. Torsion and dihedral angles scanning elucidate the intramolecular interaction regarding the steric and electronic effects of the substituent on the energetic stability of title compounds. A quantum chemical calculation provides the relationship between corrosion inhibition and molecular reactivity descriptors. Molecular electrostatic potential (MEP) is stimulated for identifying the better reactive sites for electrophilic and nucleophilic attacks. The computation of HOMA and FLU indexes indicates the reduction of aromaticity when going from Imd1 to Imd4 compounds, because of the presence of the chlorobenzene ring, as shown by the HOMA and FLU values of the last compound (HOMA = 0.963 and FLU = 1.013). Imd3 has significant luminescence, given by the value of Stokes shifts (55.33). The calculated linear polarizability and static first-order hyperpolarizability showed that the material exhibited good nonlinear optical behavior and could be used for NLO devices. Drug-likeness and ADME prediction have revealed that all structures presented a good absorption and oral bioavailability. Molecular docking has been used to study the anticancer activity of the investigated molecules against vascular endotherial growth factor receptors (VEGFR–1 and VEGFR–2). All compounds demonstrated high affinity to the active sites of the two protein targets with a binding energy of [8.3–8.8 kcal mol-1] For VEGFR–1 and [10.3–10.9 kcal mol-1] for VEGFR–2. The selected molecules hold strong potential as drug candidate for the development of new anticancer agents.

Key words: Hyperpolarizability, Spectroscopic properties, Corrosion inhibition, NLO, Anticancer activity.

# On the pK of API aggregate surfaces: molecular rationalisation of oral administration drug release models

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The kinetics of drug release from molecular crystals is commonly described by the Nernst-Brunner model developed in 1904 – and since then, numerous empirical evidence supporting its suitability as a mathematical approximation has been gathered [1]. However, providing mechanistic rationales turned out to be much more complex [2,3]. Elaborating on the molecular mechanisms of acid-induced carbamazepine (CBZ) dissolution, a molecular simulation case study of "Nernst-Brunner type" drug release into an aqueous solution featuring an interfacial "diffusion" layer is presented [4].

Here, we demonstrate the application of the 'instantaneous pK' approach to the molecular dynamics simulation of a carbamazepine form III crystallite exposed to an acidic solvent environment [5,6]. Mimicking pH = 2, we find drastic protonation of the drug crystallite model, followed by the dissolution of both single CBZH+ solutes and fragments from the crystal edges. The latter results in the release of [CBZHn]n+ aggregates (with n = 2–8) into solution, thus creating a dynamic interplay among different solute species. Similar to the concept of two-step crystal nucleation, we propose a two-step crystal dissolution mechanism that encompasses solute aggregates within a "dense-solutes domain". Within an interfacial region between the crystal and the bulk solvent, these aggregates are suggested as "puffer species" that account for a constant concentration of fully solvated solute species.

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# Computational Automation of Pharmacophore Model Optimization

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Pharmacophore modeling and virtual screening play a central role in modern drug discovery by enabling the identification of promising therapeutic candidates. The quality of the underlying pharmacophore models is therefore critical for achieving accurate and meaningful screening results. In practice, researchers often iteratively adjust and refine pharmacophore models to improve their predictive performance. However, the manual refinement of pharmacophore models to identify a higher number of active candidates while minimizing inactive ones remains time-intensive and inefficient. Manually optimizing multiple models for a single drug target can take several weeks, slowing down the overall drug-development process.
Therefore, we introduce a computational, fully automated approach to streamline the manual optimization process by developing algorithmic solutions that replicate expert-driven optimization strategies. Implemented in Python as an autonomous command-line workflow, the system interfaces directly with LigandScout [1], eliminating the need for manual intervention and ensuring consistent, reproducible refinement of pharmacophore models. Starting from the standard model, over feature tolerance adaptations to increase the number of actives hits, to precise placement of exclusion volumes to decrease the number of inactive hits, the automated workflow covers all optimization steps. The resulting pipeline reduces researcher workload while maintaining high model quality, effectively accelerating the optimization stage of drug discovery.
Initial results show that the optimization of a single model has a runtime of around four hours, when using an active library with approx. 780 compounds and an inactive library with approx. 260 compounds. Additional tests, using 2000 inactives and 50 actives, led to a runtime of around 8-10 hours for the optimization of one model. This means that optimizing multiple models for a single drug target would take only a few days, compared to several weeks when the optimization is performed manually. Additionally, preliminary analyses of automatically optimized models indicate similar or even better quality than the manually optimized models.
In the future several extensions are planned, including the incorporation of heuristic strategies, aim to further improve performance and broaden applicability to large-scale virtual screening campaigns, ultimately supporting faster and more resource-efficient identification of novel drug candidates.

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# Molecular Dynamics Investigation of the Role of $Mg^{2+}$ in Nonenzymatic RNA Self-Replication

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The nonenzymatic self-replication of RNA is a key concept in origin-of-life research, yet the molecular details of how this process occurs are still not fully understood [1]. In particular, divalent metal ions such as $Mg^{2+}$ play an essential catalytic role in promoting phosphodiester bond formation [2]. In this study, we present a computational investigation of RNA primer extension with imidazole-activated nucleotides, with special attention to how $Mg^{2+}$ ions affect the structural dynamics of different dinucleotide intermediates. By combining molecular dynamics (MD) simulations with quantum mechanics/molecular mechanics (QM/MM) approaches, we examine how $Mg^{2+}$ coordinates with RNA to stabilize reactive conformations and facilitate bond formation. Our simulations are designed to clarify how $Mg^{2+}$ helps maintain conformations that favor bond formation under enzyme-free conditions. Overall, these findings offer new molecular-level insights into the role of metal ions in RNA chemistry and deepen our understanding of RNA's potential for self-replication in prebiotic environments.

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# Comparison of two AMBER force fields for investigating the ligand binding properties of maltose-binding protein

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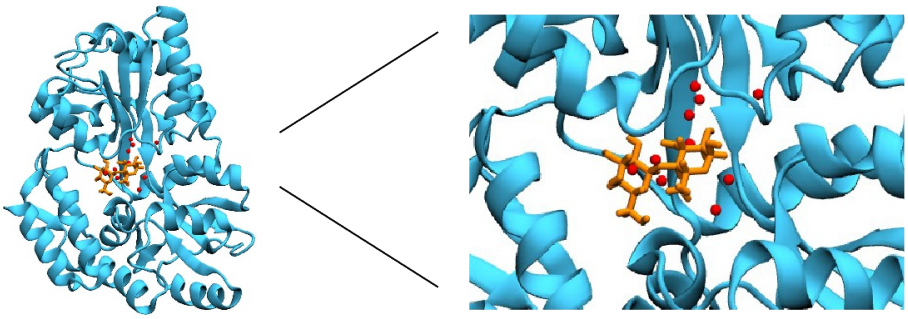
Maltose-binding protein (MBP) belongs to a superfamily of bacterial receptor proteins. It consists of two domains exhibiting a large conformational change upon ligand binding, which can be utilized to engineer biosensors that report ligand concentration. [1]



To set the necessary groundwork for designing an MBP-based biosensor, here we performed molecular dynamics (MD) simulations of MBP with maltose as its ligand starting from the known complex crystal structure [2]. This allows the analysis of MPB conformational stability and ligand binding properties within a dynamic state. A comparison of the two AMBER force fields *ff14SB* (with TIP3P water model) and *ff19SB* (with OPC water model) was done to assess whether they produce similar results.

We could show that both force fields produce highly similar protein dynamics and ligand binding properties. Large fluctuations of the water molecules in the ligand binding pocket were observed regardless of the force field and water model used, indicating that these water molecules are much more dynamic than previously expected from the static crystal structures. This finding is relevant for the future design of altered ligand binding specificity and further demonstrates the need to investigate the ligand binding properties of MBP in a dynamic setting.

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# How Phosphorylation Affects Peptide Interaction with Adaptor Domains

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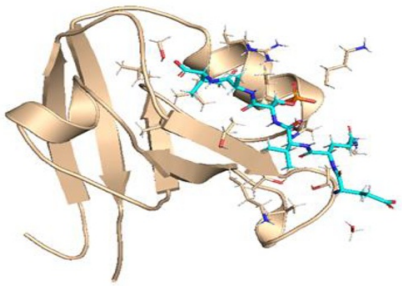

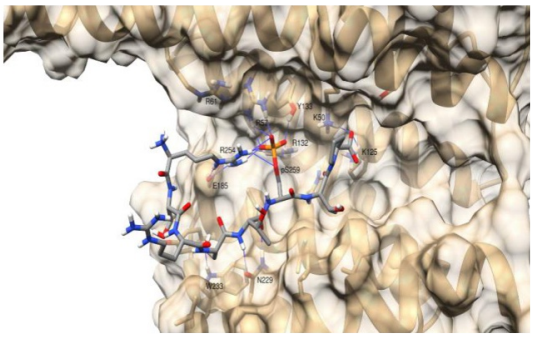

Protein-protein interactions (PPIs) are of fundamental relevance to numerous cellular processes and hence the focus of considerable experimental and computational efforts. They are often modulated by posttranslational modifications such as phosphorylation, which can either favor or disfavor the formation of a particular complex. Molecular dynamics (MD) simulations have emerged as a powerful tool to reversibly simulate the association and dissociation of protein complexes, providing insights into binding free energies and kinetic rates that often align well with experimental data. However, recent findings indicate limitations in the AMBER and CHARMM force fields when modeling phosphorylated residues. For example, Rieloff et al.[1] observed that phosphorylated statherin peptides adopted overly compact conformations in simulations using both AMBER and CHARMM36 force fields, diverging from small-angle X-ray scattering data. Similarly, our previous work on phosphorylated versus non-phosphorylated peptides binding to hPTP1E and MAGI1 PDZ domains revealed an overstabilization of phosphorylated peptides by approximately -8 kJ/mol with the CHARMM36m force field and TIP3P water [2]. To address these discrepancies, we are currently evaluating the TIP4P water model for potential improvements in binding free energy predictions and extended our studies to other PDZ domains, including Scribble, Shank and DLG. For complexes lacking crystallographic data, we generated high-confidence structural models of protein:peptide complexes using AlphaFold. These efforts aim to refine the accuracy of MD simulations in capturing the nuanced effects of phosphorylation on PPIs.

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# Modeling Diffusion and Permeation Across the Stratum Corneum Lipid Barrier

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Human skin is a complex, multilayered organ of millimeter thickness. Its barrier function resides almost completely in the topmost layer, the stratum corneum (SC).[1] We investigate the barrier against chemical permeation in the SC lipid matrix by employing atomistic, force-field-based molecular dynamics (MD) simulations.

We carried out our study on the short periodicity phase (SPP)[2] of the SC lipid bilayer. As conventional MD simulations cannot sample permeation through lipid bilayers due to high free-energy barriers, we employ a range of enhanced sampling techniques, including umbrella sampling and metadynamics. Nevertheless, extensive sampling on microsecond timescales is necessary to converge potentials of mean force in all of these techniques.[3]

We present various structural and dynamical metrics that require long-timescale sampling, such as lipid flip-flop events that lead to long-lived asymmetries. We determine position-dependent diffusivities using two complementary analyses based on the same set of simulations and evaluate their accuracy through propagator analysis. [4] The two approaches provide upper and lower bounds for the true diffusivity, which, when combined with free-energy profiles, yield permeabilities relevant for modeling macroscopic skin transport.

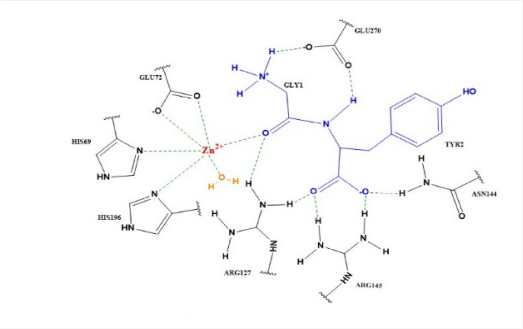
[1] Z. Nemes, P. M. Steinert, *Exp. Mol. Med.*, **1999**, *31*, 5–19.
[2] E. Wang, J. B. Klauda, *J. Phys. Chem. B*, **2018**, *122*, 11996–12008.
[3] R. Thomas, P. R. Prabhakar, D. J. Tobias, M. von Domaros, *J. Phys. Chem. B*, **2025**, *129*, 1784–1794.
[4] R. Thomas, P. R. Prabhakar, D. J. Tobias, M. von Domaros, *ES&T Air*, **2026**, DOI: 10.1021/acsestair.5c00412.

# Modelling Reaction-Competent Carboxypeptidase A-Peptide-Complexes

Martin Veitenhansl, Leon Völcker, Senta Volckenandt, Petra Imhof

*Computer Chemistry Center*

*Friedrich-Alexander-Universitaet Erlangen-Nuernberg*




Carboxypeptidase A is a zinc-dependent protease that hydrolyses peptides at the C-terminal end and is specific to residues with hydrophobic side chains. According to the proposed mechanisms in the literature, catalysis requires a water molecule to be close to the zinc center.

In our study, we designed two complexes: one with Ala-Gly-Tyr and another with Ala-Ala-Gly-Tyr. These complexes are analogous to the known Gly-Tyr complex[1]. We performed molecular dynamics simulations with AMBER using the 12-6-4-LJ[2] and EZAFF[3] (Extended Zinc AMBER Force Field) models and compared their properties.

Our modeling approaches resulted in stable simulations with the ligand bound to the active site of the complex. This approach allows us to observe the interactions between the ligand and the complex and to compare the 12-6-4 and EZAFF models. The EZAFF model aims for a natural 5-fold geometry (without bound water) or a 6-fold geometry (with bound water) at the zinc center, whereas the 12-6-4 model produces unnatural 6- to 7-fold coordinating geometries. The behavior of water, which is essential for the expected mechanism, differs significantly as well. Moreover, our modelling results give hints about the reactivity of the ligand. The smaller Ala-Gly-Tyr ligand enables mechanistically important coordination of water to the zinc center; however, this is spatially blocked by the larger Ala-Ala-Gly-Tyr ligand.

[1] Jorge Antonio Amador Balderas, Frank Beierlein, Anselm H. C. Horn, Senta Volkenandt, Leon Völcker, Nikoo Mokhtari, Jules Cesar Epee Ndongue, and Petra Imhof. Mode of metal ligation governs inhibition of carboxypeptidase a. International journal of molecular sciences, 25(24), 2024. doi: 10.3390/ijms252413725
[2] Pengfei Li and Kenneth M. Merz. Taking into account the ion-induced dipole interaction in the nonbonded model of ions. Journal of chemical theory and computation, 10(1):289#297, 2014. doi: 10.1021/ct400751u.
[3] Zhuoqin Yu, Pengfei Li, and Kenneth M. Merz. Extended zinc amber forcefield (ezaff). Journal of chemical theory and computation, 14(1):242#254, 2018. doi: 10.1021/acs.jctc.7b00773.

# Integrating Structure-Based Modelling to Characterize Formyl Peptide Recognition by FPR1 and FPR2

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Formyl peptide receptors (FPRs) are part of the G protein-coupled receptor family involved in innate immune recognition of formyl peptides released by bacteria. Activation triggers inflammatory processes such as chemotaxis, phagocytosis, ROS and calcium release. There are three FPR subtypes in humans (FPR1, FPR2 and FPR3), with FPR1 and FPR2 exhibiting a high sequence similarity of 69%. Both receptors also show structural similarities and a common agonist portfolio with some differences and preferences in their interaction with formyl peptides. Here, we combine functional characterisation using calcium imaging with structure-based modelling to investigate structural determinants of ligand binding in FPR1 and FPR2. Internal, unpublished data have shown that the addition of a lysine group to f-MLFYLA and f-MGFFIS activates not only FPR1 but also FPR2 in calcium imaging experiments. To investigate the interactions between receptor and ligand, the two peptides with and without lysine were constructed using Avogadro and geometrically optimised prior to molecular docking. Comparative docking analyses were performed to evaluate variations in binding orientation and predicted interaction networks within the ligand binding pockets of FPR1 and FPR2, thereby explaining the functional differences of the tested peptides.

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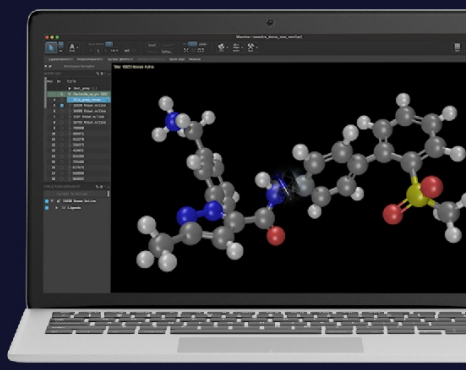

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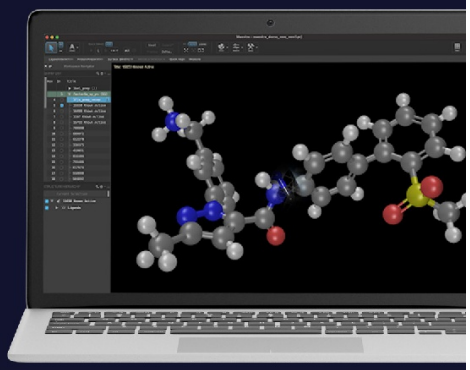

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## MATH CHALLENGE

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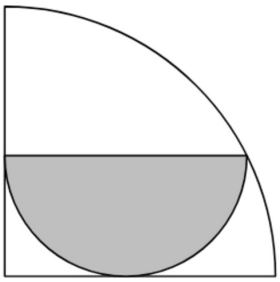
What is the area of the depicted quarter circle?
(Hint: It is an integer value.)



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