Damage in DNA can interrupt and alter its conformational flexibility—which drives crucial site-specific functions—leading to aberrant DNA diseases. It is not fully understood exactly what role these conformations play in the processes undertaken by DNA, nor how they might be affected by various damage. Here we present an overview and comparison of two novel and emergent techniques to study such conformations; single molecule Förster resonance energy transfer (smFRET) and X-ray scattering interferometry (XSI). We are focusing on the RNaseH2 complex, mutations that are responsible for Aicardi-Goutières syndrome (AGS), to establish how the search space is minimised as it finds and cleaves RNA/DNA hybrids, and whether this is driven by conformational changes. We also introduce O6-methylguanine (O6-MeG), ribonucleotide, nicks and gaps; all prevalent modifications to DNA which without repair would lead to toxic intermediates. It is hypothesised that when the damage is present the increase in flexibility of DNA signals proteins to promote repair. smFRET was used to measure the conformational changes when the different types of damage, were present in a DNA duplex. A change in FRET efficiency is seen for all the types of damage, with the nick and gap damage having a greater impact on the mean and spread of the FRET efficiency. These results provide initial support for the hypothesis that damage alters the overall structure and dynamics of DNA duplexes and that the presence of these lesions and their respective repair mechanisms binds the DNA in varying levels of flexibility.

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Interphase chromosomes of the *Aedes aegypti* mosquito are liquid crystalline and can sense mechanical cues

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Within the nucleus, the genome of eukaryotes folds into partially organized three-dimensional structures specific to the cell type and phase of life. While the physical mechanisms and the molecular machinery behind the formation of genome architecture seem to be largely shared among organisms, the resulting genome architectures are far from unique. Ongoing efforts characterizing the genomic structural ensembles of many species have found an assortment of distinct chromosomal spatial organizations. How the two processes of phase separation and lengthwise compaction generate this collection of shapes remains an open question. Here, we use data-driven physical simulations to study the three-dimensional architecture of the *Aedes aegypti* genome. Hi-C maps exhibit both a broad diagonal and compartmentalization with telomeres and centromeres clustering together. Physical modeling reveals that these observations correspond to an ensemble of 3D chromosomal structures that are folded over and partially condensed, resembling liquid crystalline properties. Clustering of the centromeres and telomeres near the nuclear lamina appears to be a necessary condition for the formation of the observed structures. Further analysis of the mechanical properties of the genome reveals that the chromosomes of *Aedes aegypti*, by virtue of their atypical structural organization, are highly sensitive to the deformation of the nuclei. This last finding provides a possible physical mechanism linking mechanical cues to gene regulation.

Platform: Protein-Small Molecule Interactions

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Predicting the mechanism of actions of capsid assembly modulators from a combination of molecular dynamics and machine learning

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Interfering with the self-assembly of viral nucleocapsids is a recent and effective approach in the development of novel antivirals. Capsid assembly modulators (CAMs) targeting hepatitis B virus (HBV) have two classes. They can target the virus by either accelerating nucleocapsid assembly or misdirecting it into non-capsid-like particles. In our previous work, molecular dynamics simulations were used to study early nucleocapsid assembly intermediates, such as tetramers and hexamers of the core protein Cp149 with and without bound CAMs. We observed distinct conformations of these intermediates, depending on whether the bound CAM accelerates or misdirects assembly. Here, we have developed and tested several machine learning models in order to distinguish between apo-tetramer structures and those bound to accelerating or misdirecting CAMs. Models based on tertiary structural properties of the capsid protein tetramers and their inter-dimer orientation, as well as models based on direct and inverse contact distances between protein residues, were investigated. The models distinguished the apo states and the two CAM-bound states with very high accuracy. Furthermore, tertiary structure models and residue distance models highlighted different tetramer regions as important for classification. Our models can be used to better understand structural transitions that govern nucleocapsid assembly as well as for selection of structures from molecular dynamics simulations for subsequent docking.

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How does a ligand exit from a buried receptor cavity? Atomistic simulations of unbinding pathways with rigorous kinetics

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Hypoxia-inducible factors (HIFs) are heterodimeric transcription factors that can promote cancer growth. The development of small-molecule drugs that can inhibit the formation of the dimer is therefore a promising route to the treatment of cancer. Here, we focus on the relevant domain of the protein, the HIF2α PAS-B domain, which contains a preformed, buried cavity that binds artificial small-molecule ligands that allosterically perturb the formation of the HIF heterodimer. We examine how a representative ligand (THS-017) dissociates and re-enters the buried cavity using atomistic simulations. To enable these simulations, we applied the weighted ensemble path sampling strategy, which can generate continuous pathways with rigorous kinetics (i.e., rate constants) in orders of magnitude less computing time compared to standard simulations. Results reveal a diverse set of pathways for both the ligand unbinding and rebinding processes with estimated rate constants and methyl order parameters that are consistent with experiment.

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The effect of PFASs on PPAR-gamma/RXR-alpha heterodimer

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Nuclear hormone receptors (NRs) are the main protein superfamily that regulates gene expressions in eukaryotic cells. Given the importance of their roles in cells, they become one of the main targets in drug discovery, including thiazolidinediones that act through an NR named peroxisome proliferator-activated receptor gamma (PPAR-gamma). 1 PPAR-gamma can perform as homodimer as well as heterodimer with retinoid X receptor alpha (RXR-alpha) in cells, and the heterodimer is known to impact the regulation of the synthesis of proteins responsible for insulin sensitivity. Per- and polyfluoroalkyl substances (PFASs) are forever chemicals that are being used in numerous industrial applications, including water-repellent coatings, fire-fighting foams, furniture, oil-repellents, and many more. PFAS compounds are very difficult to degrade due to their chemical properties. In recent years, the impact of PFASs on human health as well as on the environment has started to be investigated. Numerous studies show that these compounds disturb many biological systems in humans, including insulin and cholesterol regulation mechanisms, thyroid hormone levels, and so on. It has been shown that PPAR-gamma/RXR-alpha heterodimer is one of the potential targets for PFAS compounds, leading to problems in insulin metabolism. Here, we investigated the effects of selected PFAS compounds on PPAR-gamma/RXR-alpha heterodimer using molecular dynamics simulations and binding free energy calculations. We see that the chain length of PFAS compounds as well as the selection of functional groups impact the binding strength of PFAS compounds. Furthermore, L-carnitine compound, which is shown to have mitigating effects against PFASs, was also investigated.

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Molecular fingerprint in hyaluronan-peptide interactions: Cooperation of electrostatics and side-chain specificity in enhanced arginine effect

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