**Structural Bioinformatics Approaches for Studying Bisphenol A Binding and Its Functional Impact on Human Nuclear Receptors**

**Background:** Human exposure to endocrine-disrupting chemicals (EDCs), such as Bisphenol A (BPA), is an increasing concern for public health. BPA is a synthetic compound widely used in the production of polycarbonate plastics and epoxy resins, and it is ubiquitously present in the environment. Its use has been linked to adverse health effects, including hormone-sensitive cancers, infertility, and metabolic disorders (Riu et al., 2011; Karmaus et al., 2021). BPA exerts its effects by mimicking endogenous hormones and binding to hormonal nuclear receptors, particularly estrogen receptors (ERα, ERβ), the androgen receptor (AR), the aryl hydrocarbon receptor (AhR), among others, potentially altering gene expression and cellular behavior (Fenichel et al., 2013). Despite growing experimental evidence of BPA's pro-proliferative effects, the structural basis of its interaction with target proteins remains poorly understood. Modern structural bioinformatics techniques offer powerful tools to investigate ligand–receptor interactions at the atomic level and to predict the functional consequences of such interactions. These approaches allow the simulation of binding events, exploration of dynamic conformational changes, and assessment of BPA's impact on the structural integrity and functional regulation of nuclear receptors.

**AIM of the Project and PhD Plan:** The main objective of the project is to investigate, through structural bioinformatics techniques, the molecular mechanisms underlying BPA binding to human nuclear receptors and its effects on receptor dynamics and function. The project will employ molecular docking, molecular dynamics (MD) simulations, and free energy calculations to study BPA interactions with key endocrine receptors.

**AIM 1: Structural modeling and docking of BPA to nuclear receptors (Months 1–9)**. I will begin by selecting a panel of human nuclear receptors known to interact with EDCs (e.g., ERα, ERβ, AR, PXR, AhR). High-resolution crystallographic structures available in the Protein Data Bank (PDB) will be used as templates. In the absence of resolved structures, homology modeling will be applied. Using molecular docking software such as AutoDock Vina, I will predict BPA binding poses and compare them with those of natural ligands to assess potential competition, characterizing the receptor–ligand interaction profiles (Zhang et al., 2018).

**AIM 2: Molecular dynamics simulations and conformational analysis (Months 6–18)**. To understand the dynamic behavior of BPA-bound receptors, I will perform all-atom molecular dynamics simulations (e.g., with GROMACS). Both apo forms (ligand-free) and holo forms (BPA-bound) will be simulated to evaluate ligand-induced conformational changes. Key parameters such as RMSD, RMSF, hydrogen bonds, and principal component analysis (PCA) will be monitored.

**AIM 3: Free energy calculations and mutagenesis prediction (Months 12–24)**. I will estimate binding free energies using MM/PBSA or FEP methods to quantify BPA's affinity for each receptor. Based on key interaction sites, I will perform in silico mutagenesis to predict the effect of amino acid substitutions on BPA binding. These predictions could guide future experimental validations or risk assessment models.

**AIM 4: Integration with transcriptomic and structural data (Months 18–30)**. The structural results will be integrated with public transcriptomic datasets (e.g., GEO or TCGA) to identify gene expression patterns associated with BPA exposure and receptor activation. Structure–function correlations will be mapped, linking binding modes and molecular dynamics to downstream effects on gene regulation.

**AIM 5: Thesis writing and dissemination of results (Months 30–36)**. The final phase will be dedicated to writing the doctoral thesis, publishing the results in peer-reviewed journals, and presenting the findings at conferences in bioinformatics, structural biology, and environmental health.

**Expected Results:** I expect to achieve a detailed structural and energetic characterization of the interactions between BPA and major nuclear receptors. I aim to identify specific binding features and induced conformational changes that may explain BPA's endocrine-disrupting potential. These findings could support the development of safer analogs or antagonists and contribute to computational tools for the risk assessment of EDCs.

| | Activity |
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| 1-9 months | Selection of receptors, structure preparation, Docking analysis (AIM 1) |
| 6-18 months | Setup and execution of simulations, analysis of simulation data (AIM 2) |
| 12-24 months | Free energy and mutagenesis studies (AIM 3) |
| 18-30 months | Start of transcriptomic integration and completion of structure–function integration (AIM 4) |
| 30-36 months | Thesis writing, publications, dissemination (AIM 5) |

**REFERENCES:**


- Zhang, J., Li, T., Wang, T., Yuan, C., Zhong, S., Guan, T., Li, Z., Wang, Y., Yu, H., Luo, Q., Wang, Y., & Zhang, T. (2018). Estrogenicity of halogenated bisphenol A: in vitro and in silico investigations. *Archives of toxicology*, *92*(3), 1215–1223.
- Riu, A., Grimaldi, M., le Maire, A., Bey, G., Phillips, K., Boulahtouf, A., Perdu, E., Zalko, D., Bourguet, W., & Balaguer, P. (2011). Peroxisome proliferator-activated receptor γ is a target for halogenated analogs of bisphenol A. *Environmental health perspectives*, *119*(9), 1227–1232.
- Fenichel, P., Chevalier, N., & Brucker-Davis, F. (2013). Bisphenol A: an endocrine and metabolic disruptor. *Annales d'endocrinologie*, *74*(3), 211–220.