

Atomistic Graph Analysis in Estrogen Receptor Alpha

Strömich, Léonie,¹ Ali, Simak,² Yaliraki, Sophia¹

¹Department of Chemistry, Imperial College London, UK

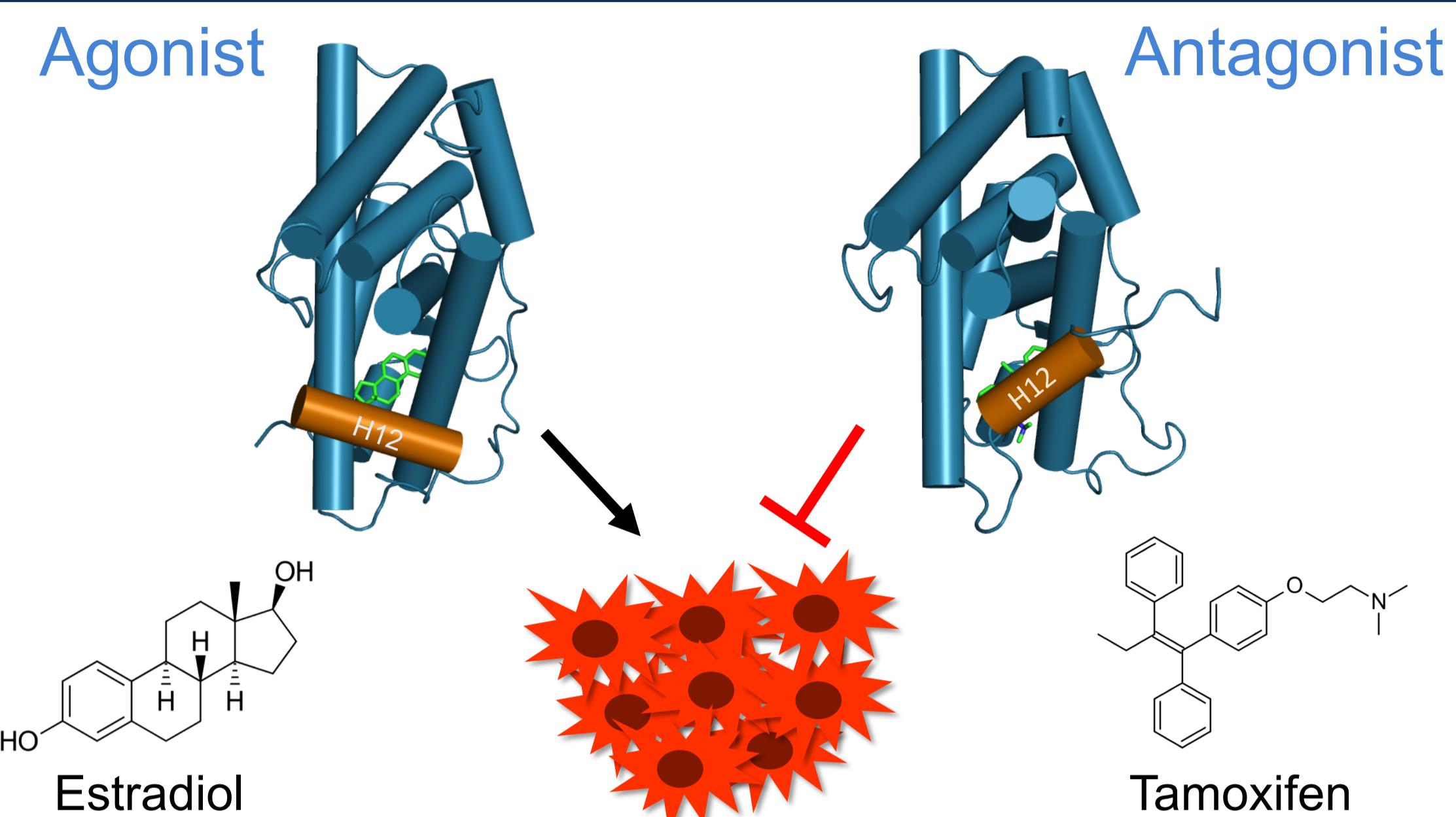
²Department of Cancer and Surgery, Imperial College London, UK

Estrogen receptor alpha is a key player in breast cancer

Estrogen receptor alpha (ER α) is the main driver in breast cancer (BC) development and progression, and drugs inhibiting ER α are the main focus of treatment in BC. Current chemotherapies based on inhibiting ER α become ineffective when recurrent tumours develop resistance against anti-estrogens.

We here present the application of novel diffusion-based approaches to identify potential new target sites in ER α and explore underlying resistance mechanisms.

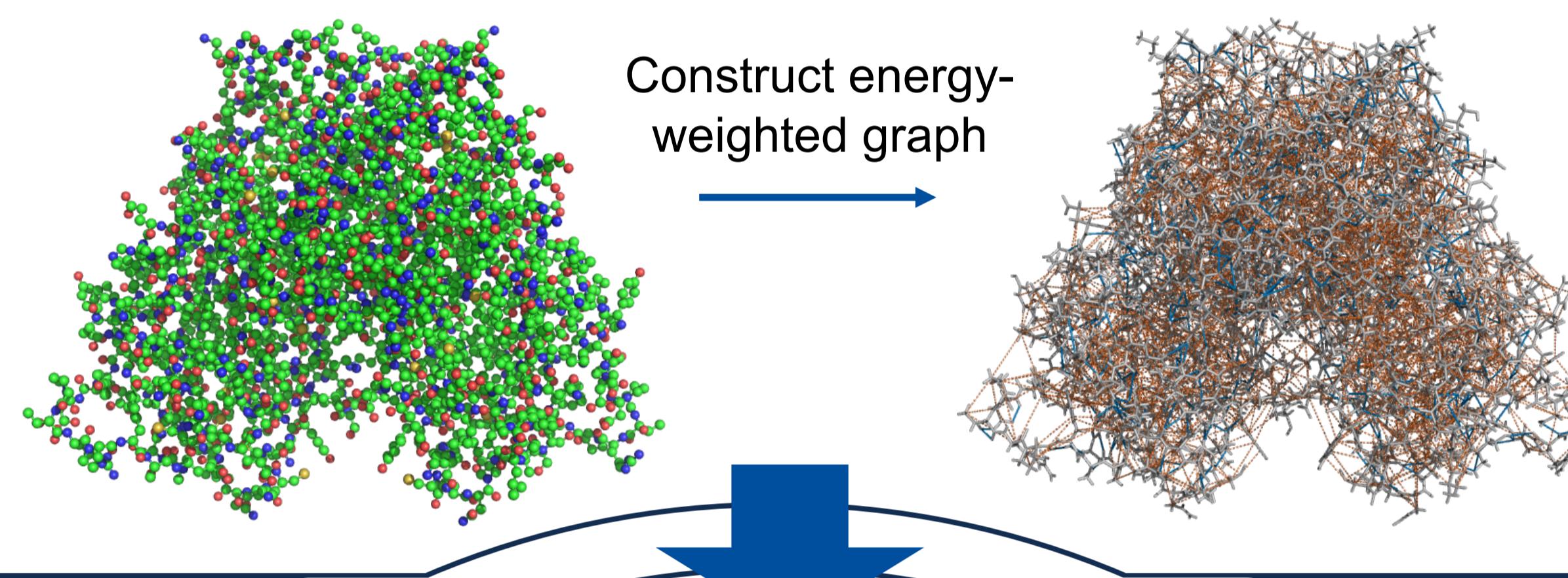
This provides an alternative approach to investigate a well-studied scenario by providing an atomistic resolution of the molecular mechanism of ER α .



Atomistic graph models reveal molecular mechanism of ER α and allow investigation of cancer mutations with high efficiency.

1. Atomistic, energy-weighted graph construction based on biological structure

Each atom in a biological structure is represented as a node in a graph. This allows us to preserve atomistic detail and distinguishes our methodology from coarse-graining approaches^{1,2}.

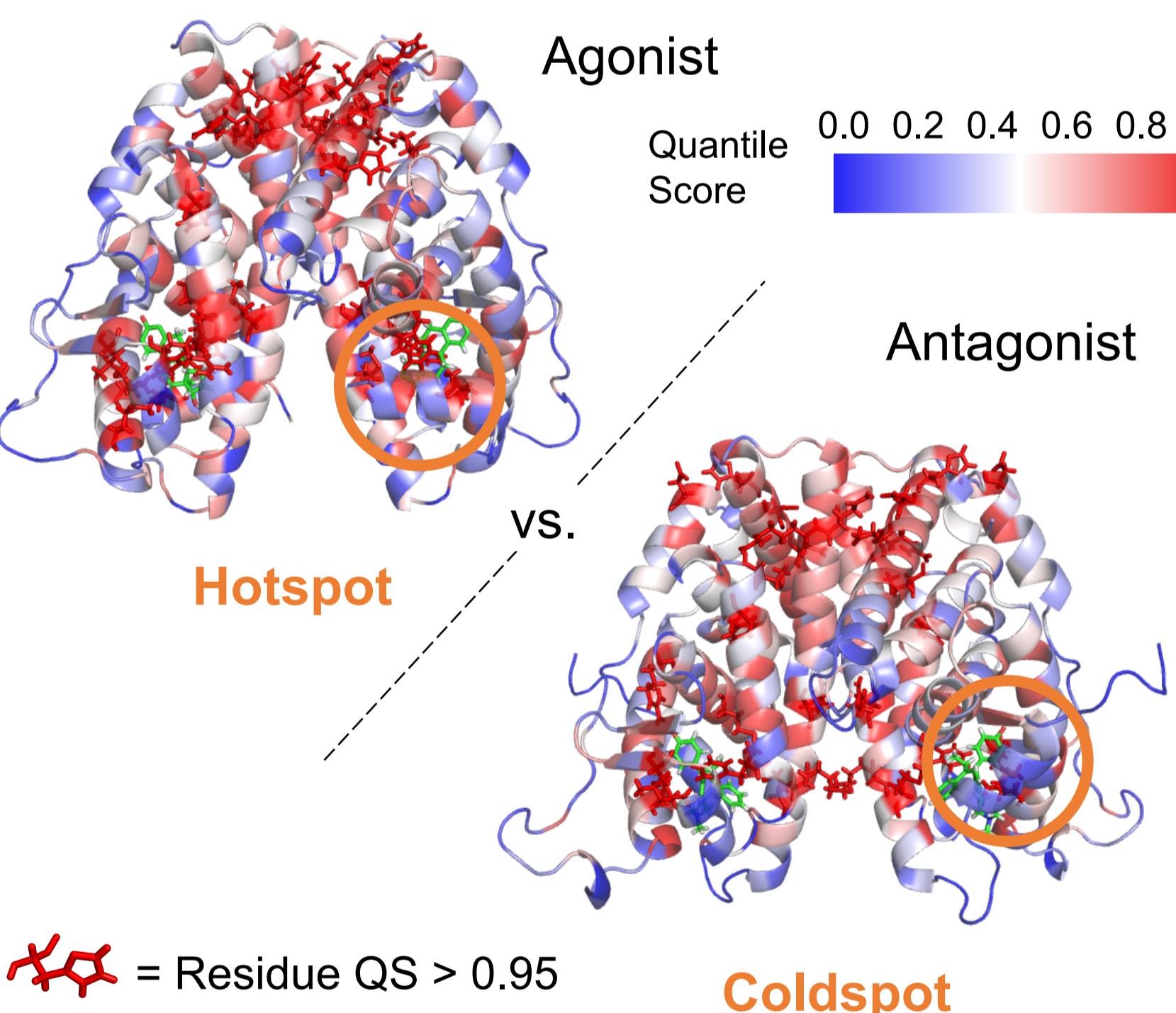


Assigning edge weight according to bond type captures physico-chemical properties of the structure.

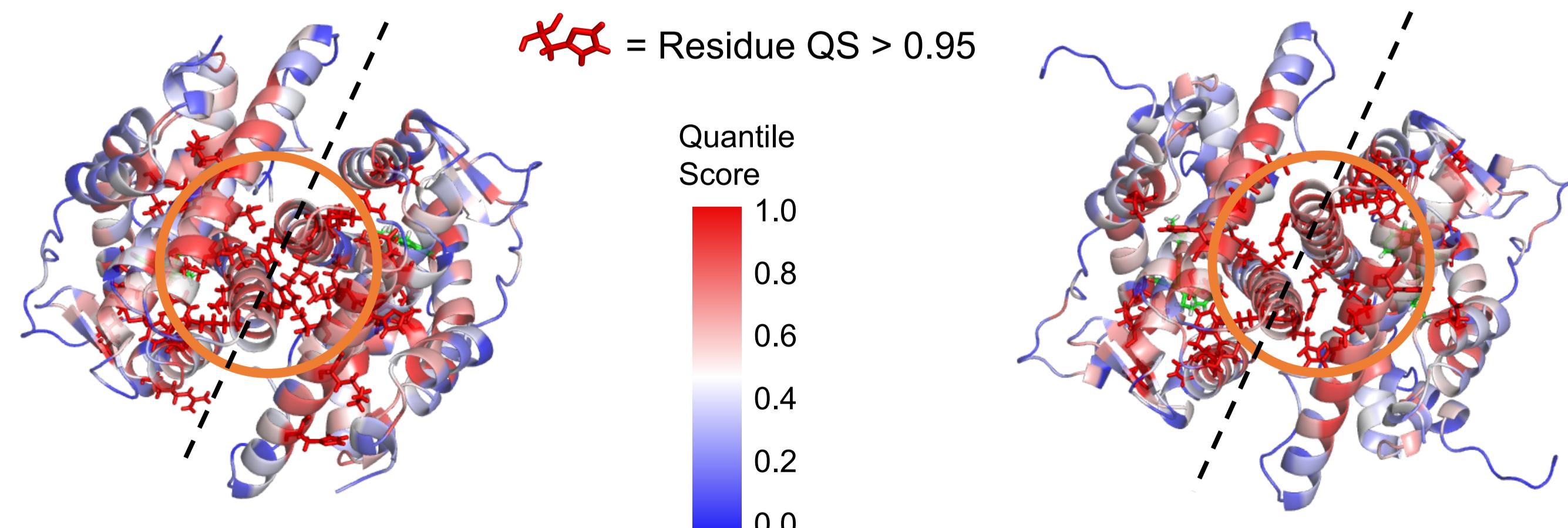
The following bond types are encoded:

1. Covalent bonds
2. Hydrogen bonds
3. Hydrophobic interactions
4. Electrostatic interactions

3. Bond-to-bond propensities reveal communication within ER α



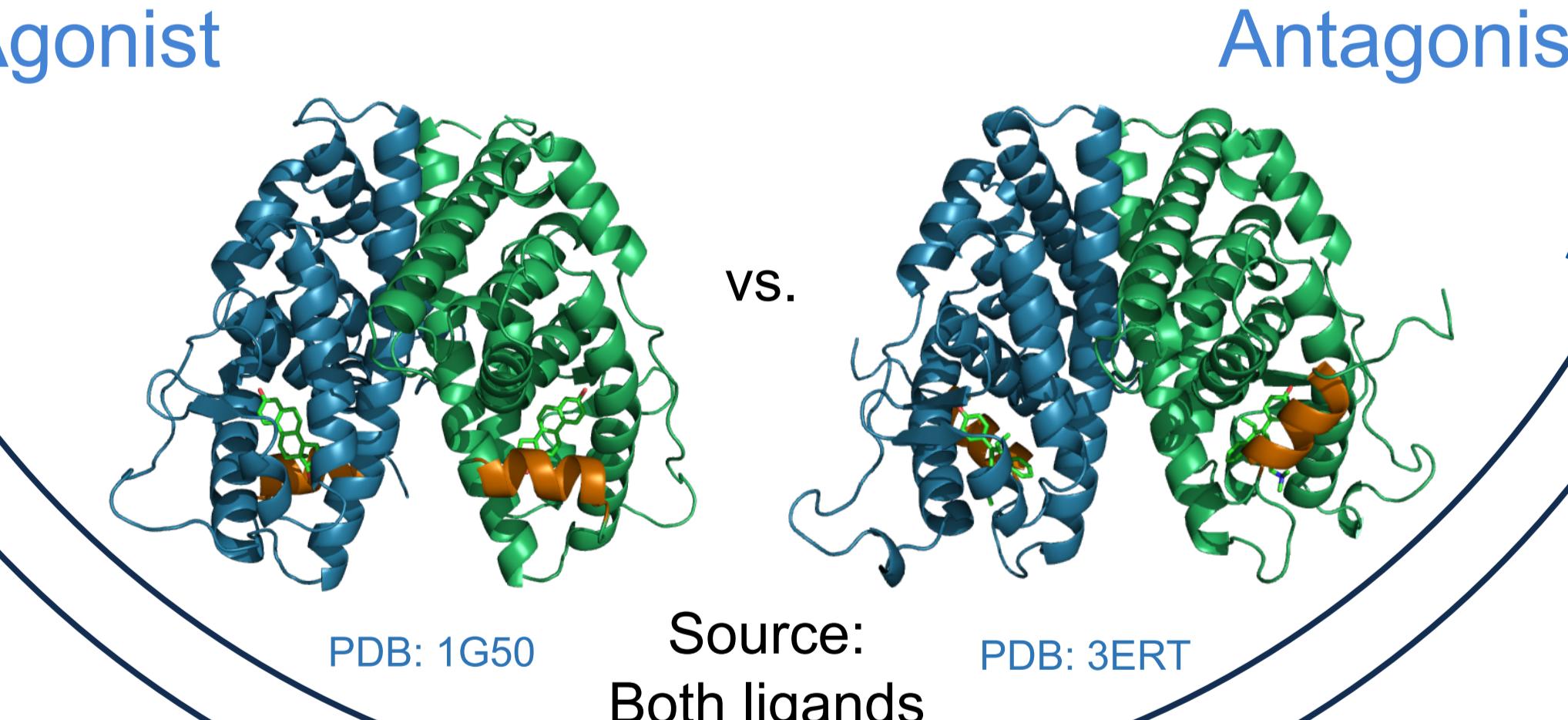
We confirm the molecular mechanism of ER α by calculating the connectivity for each residue respective to the active site. We find a high connectivity between estradiol and helix 12 which is not present in the inhibited protein. Bond-to-bond propensities also provide evidence for the necessity of dimer formation that is observed *in vivo*⁴.



Our methods validate the basis of ER α functionality: positioning of helix 12 and necessity of dimerization.

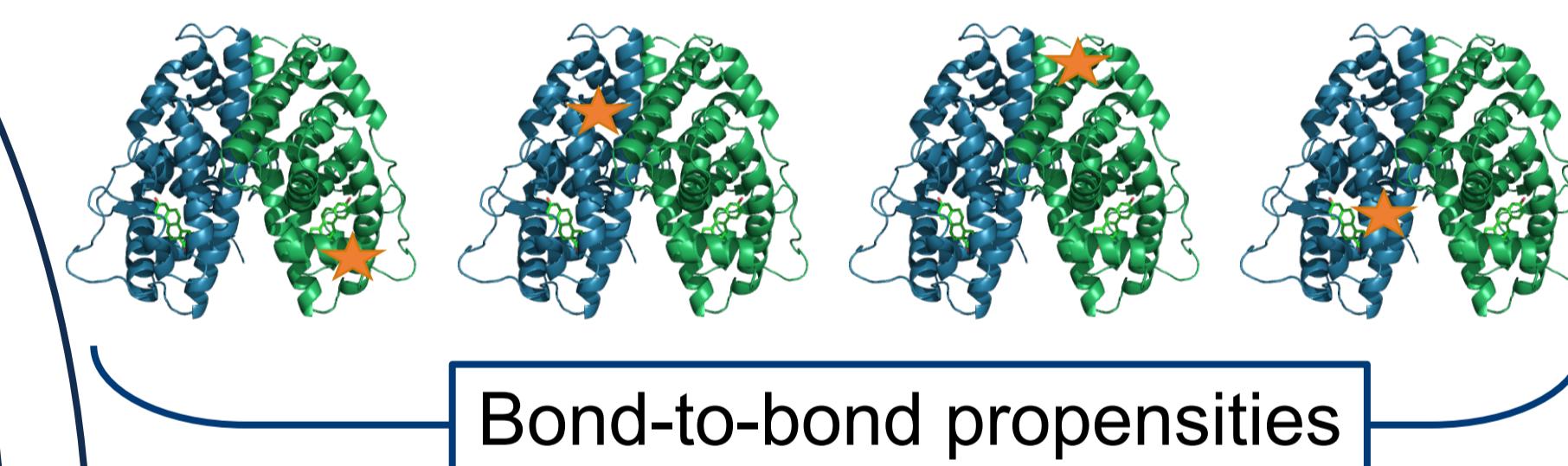
2. Bond-to-bond Propensities

Measure the impact of energy fluctuations of source bonds on any other protein bond. Allow discovery of instantaneous communication between source and target bonds. Quantile regression provides a quantitative ranking of all bonds and subsequently residues. Detection of allosteric pathways and sites in proteins and biological complexes³.

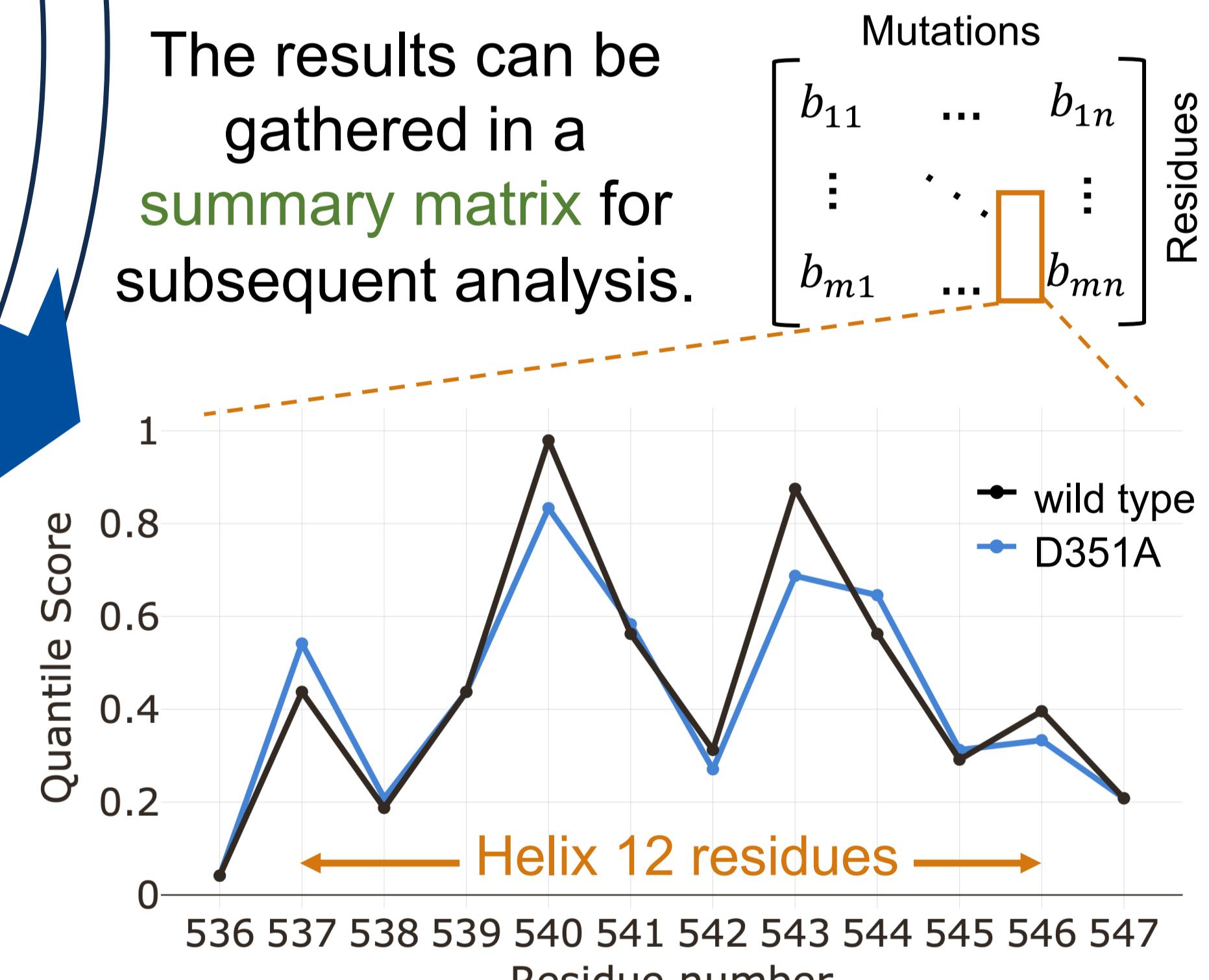


4. In-silico mutational studies identify path-disrupting mutations

We run computational alanine scans.



The results can be gathered in a summary matrix for subsequent analysis.



With this data we can gain insights into changes in communication towards helix 12: D351A is a mutation which decreases connectivity between estradiol and H12 and might hint to a new drug target.

The computational efficiency of our methodology allows mutational studies to identify impactful residues.

Try it yourself!

Our methodologies will be available online in form of a user-friendly, interactive webserver: proteinlens.io

