# LAWS:
# Local Alignment for Water Sites

## A method to analyze crystallographic water in simulations

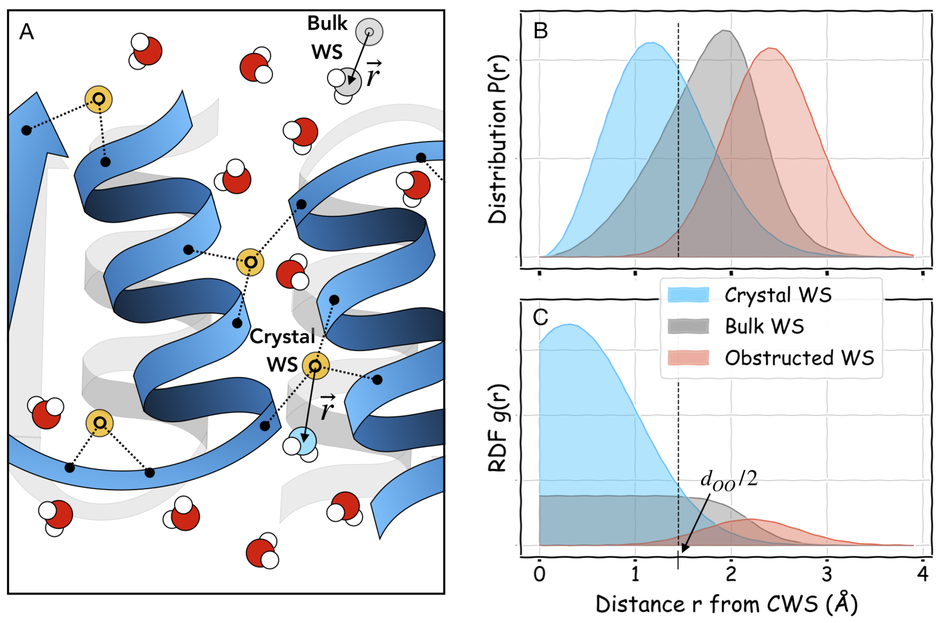
Check out our code

## METHOD

- **Track CWS** (yellow) in simulation based on distances to protein atoms by minimizing **LAWS error** (A):

$$\mathrm{LAWS}(x,y,z) = \sum_{i=1}^{n} w_i^2 (\sqrt{(x-x_i)^2 + (y-y_i)^2 + (z-z_i)^2} - \hat{d}_i)^2.$$

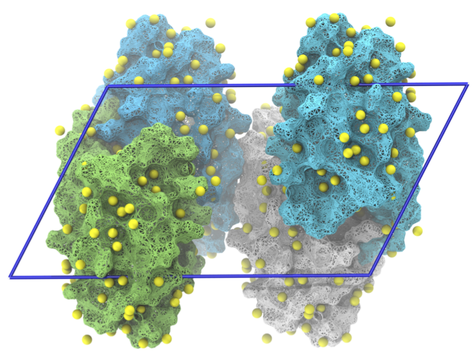
- Randomly sample **Bulk WS** (grey) at least 6 Å from protein (A).
- Compute ***P(r)*** - distribution of distance ***r*** to nearest neighbour water (B).
- Compute ***g(r)*** - radial density profile by ***r²*** normalization (C).
- Classify a CWS into (i) **crystal**, (ii) **bulk-like**, and (iii) **obstructed**.




## APPLICATION

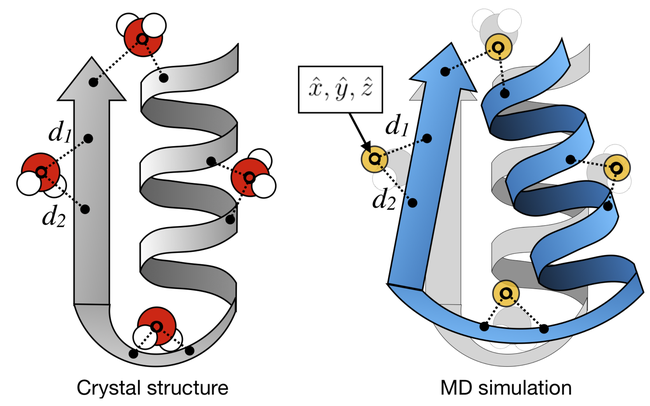
1 μs simulation of protein crystal (single unit cell)

Second PDZ domain of human LNX2 protein



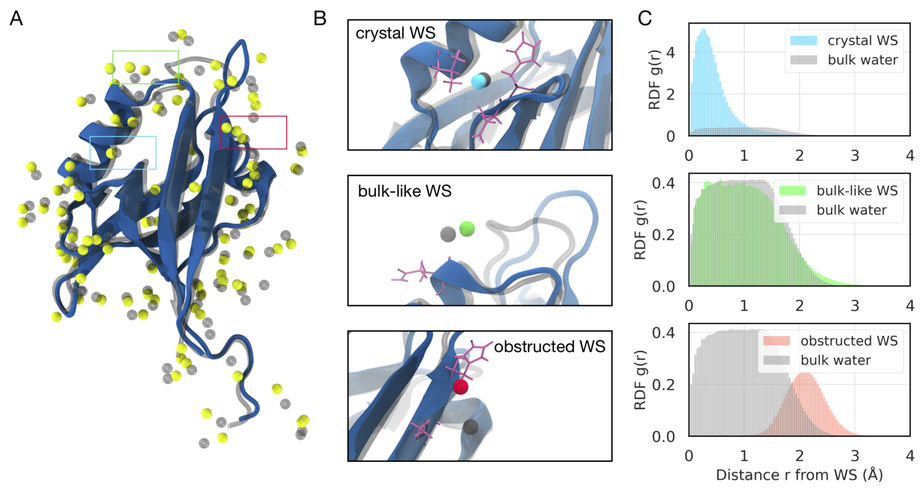
## MOTIVATION

- Accurate **modeling of protein-water** interactions is important for understanding **protein function**.
- X-ray diffraction provides **crystallographic water sites** (**CWS**) – strong benchmark for modeling accuracy, but methods for **comparison with MD** are required.
- Existing methods rely on **global alignment** of the protein on crystal structure (**introduce errors**), we propose a new method (**LAWS**).
- LAWS considers **contacts formed by CWS and protein atoms** in crystal structure and uses these interaction distances **to track the CWS** in simulation.

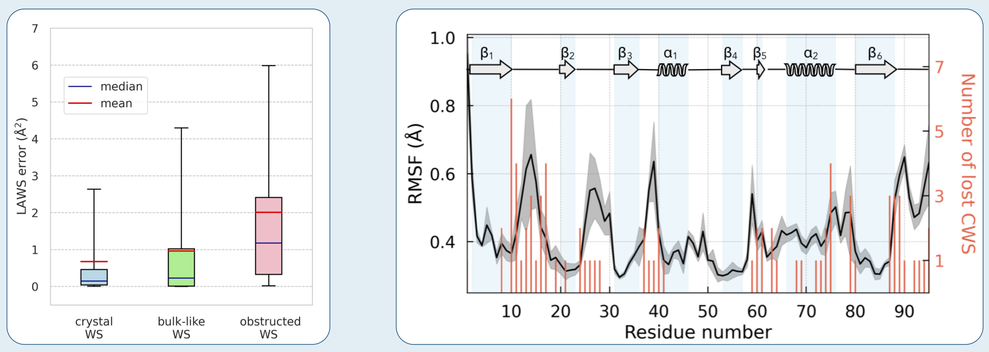



Crystal structure MD simulation

## RESULTS




LAWS classifies WS into **crystal** (blue), **bulk-like** (green), and **obstructed** (red). **(A)** Simulated structure (blue) is overlapped with crystal structure (grey). **(B)** Representative WS from each group. **(C)** Corresponding radial density profile g(r) for each WS.

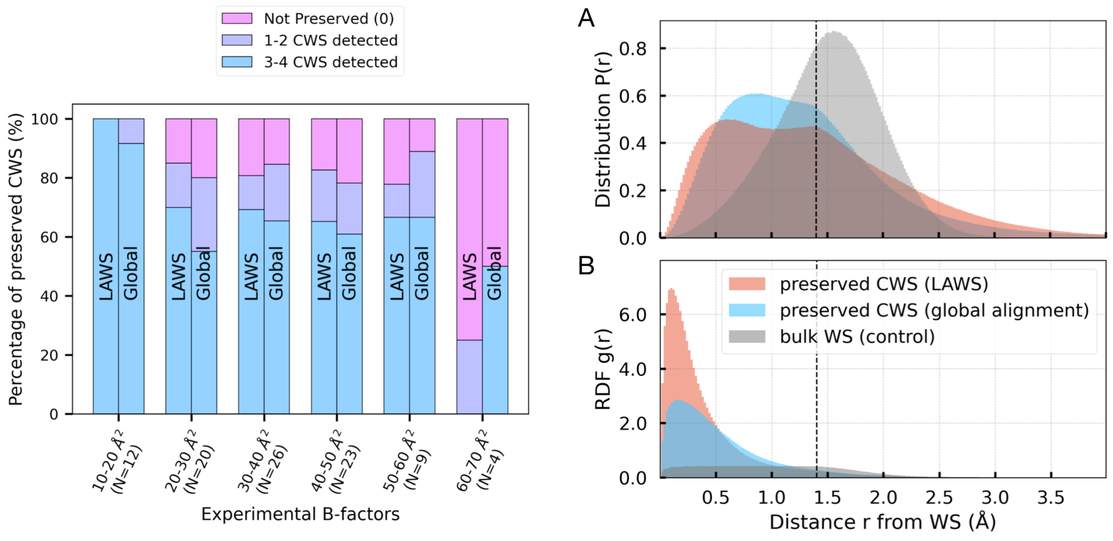



1. **Lost CWS have a perturbed protein environment** – large LAWS error.
2. **Lost CWS are located near flexbile regions of protein** – with high RMSF.

## ADVANTAGES OVER EXISTING METHODS

- Higher overall recall of CWS in simulations (table)
- Perfect recall of high confidence (low B-factor) CWS (bar chart)
- Higher water density for detected CWS (distribution)

| Methods | Preserved CWS | Bulk-like WS | Obstructed WS |
|---|---|---|---|
| LAWS | 76% | 11% | 14% |
| Global alignment | 68% | 9% | 23% |





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