

WaterRank

A geometric scoring method for structural water molecules in protein-ligand complexes.

Waters play an important role in ligand binding, and significant gains in affinity and selectivity can be achieved by targeting the right waters.

WaterRank assigns crystallographic water molecules a geometric rank score, so researchers can quickly discriminate waters that play a genuine role in binding from waters that can safely be ignored.

Each water is classified according to its interactions with neighbouring protein atoms and other water molecules, based on how far it deviates from ideal tetrahedral coordination.

$$Rank = \sum_n \left\{ (2.80 \text{ \AA} / r_n) + \left[\sum_m \cos(\Theta_{Td} - \Theta_{ym}) \right] / 6 \right\}$$

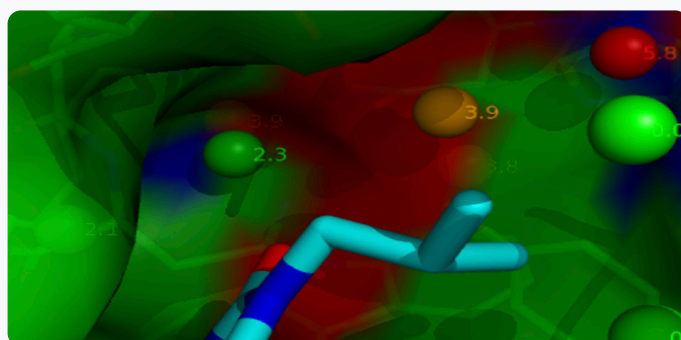
Where:

- r_n — the distance between the water oxygen and the hydrogen-bonded heavy atom n (up to 4 interacting atoms.)
- 2.80 Å — the median hydrogen-bonding distance in the Cambridge Structural Database for C=O acceptors interacting with OH and NH donors, used to scale each contact.
- Θ_{Td} — the ideal tetrahedral angle, 109.5°
- Θ_{nm} — the angle between contact atoms n and m ($m = 1$ to $n - 1$.)
- A maximum of two donors and two acceptors are considered per water, and any contact angle below 60° is excluded from the analysis. Water-water contacts are only included where the contacting oxygen's own score is above the 2.0 threshold.

Colour-coding of Rank score

Structural waters are colour coded by their score, from green (easily replaceable) through to red (tighter-binding):

Colour	Score	Meaning
Green	2.3 – 4.0	Easy to replace
Amber	2.3 – 4.0	Possible to replace with suitable polar functionalities
Red	4.0 – 6.0	Unlikely to replace



Why it matters

- Rank scores run from 0 (no hydrogen bond) to 6 (four hydrogen bonds in ideal tetrahedral coordination)
- Waters scoring below 2.0 — not involved in two or more good hydrogen bonds — are excluded from the analysis.

Rank scores give easy, at-a-glance identification of bound waters worth targeting in ligand design experiments.



Get in touch to discuss how
WaterRank could benefit your
organisation, and to arrange
a demonstration and free trial.

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