A217 · Hyaline: Structure and Leakage-Aware Prediction of Kinase Conformational Selectivity

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Protein kinases are premier drug targets whose druggability is governed less by sequence than by conformation: the same catalytic domain adopts distinct activation loop states, canonically DFG-in and DFG-out, that expose different pockets and admit either Type I or Type II inhibitors. Because these states share one sequence, sequence-based models are blind to what governs selectivity, and we show they also leak. A pocket sequence classifier scores 0.95 AUROC under a random split but collapses to 0.62 under grouped leave-one-kinase-out, revealing that it memorizes kinase identity rather than conformation. We present Hyaline, a structure-based framework that computes two interpretable geometric descriptors from the real KLIFS pocket: the DFG to αC distance and a hinge activation loop angle. Under grouped leave-one-kinase-out these training free descriptors classify DFG state at 0.834 AUROC, generalizing to unseen kinases without leakage, and a known drug analysis recovers five of six canonical Type I and Type II assignments. Hyaline exposes this as an analyze command that annotates any experimental or predicted structure, including AlphaFold models, returning the DFG and αC state, the geometric fingerprint, and a Type I, Type II, or allosteric accessible call with provenance. We also release an offline atlas of 318 human kinases with accessible states, known inhibitors, and a Type II opportunity score. A synthetic ablation confirms the mechanism, that structure rather than sequence carries the signal and that inhibitor size interacts with DFG displacement. Hyaline offers an interpretable, leakage aware route to conformation selective inhibitor design.

Hyaline: Structure and Leakage-Aware Prediction of Kinase Conformational Selectivity

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