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Virtual Screening

Practical 27 - Molecular modelling practical

Aim

To plan and assess a reproducible virtual-screening workflow.

Principle

Docking samples poses and ranks them with an approximate scoring function. Receptor conformation, protonation, waters, cofactors and ligand states influence the result. Docking score is not a measured affinity.

Materials and Requirements

- Benign reference structures with verified stereochemistry and protonation basis
- Institution-approved software with version, parameters and model documentation
- Independent reference or validation dataset
- Approved method or teaching-data pack and a dated record sheet

Procedure

1. Define the preparation or dataset, study question and method version. Record identities, units and the criteria to be used before examining the outcome.
2. Define the endpoint and retain unmodified input structures and identifiers. Standardise salts, tautomers and stereochemistry using a documented rule.
3. Check target identity, structure quality, missing regions, relevant cofactors and the intended binding-site evidence.
4. Prepare receptor and ligands with documented state and charge choices and define a justified search region.
5. Validate by an appropriate reference-ligand redocking or other control, inspect clashes and key interactions, and compare multiple plausible poses and repeats.
6. Save input/output files, failures, parameter choices and independent validation results so the analysis can be reproduced.
7. Retain the original observations and calculations. State deviations, missing information and the limits of the conclusion; do not replace measured values with expected results.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Molecule / model	Input / settings	Output / diagnostic	Interpretation / limitation
Reference	Document	Record	Evaluate
Test molecules	Document	Record	Evaluate
Independent check	Document	Record	Evaluate

Calculations

- Pose RMSD = sqrt[sum squared distances between corresponding atoms / number of compared atoms], after the justified alignment and atom mapping

Worked Example

Illustrative four corresponding heavy atoms each differ by 1.0 angstrom, giving RMSD = 1.0 angstrom.

A low RMSD supports one aspect of pose recovery; it does not prove ranking accuracy, affinity or correct chemistry.

Screening and triage

• Curate a documented benign compound library; remove duplicates and define permitted forms and filters before screening.

• Benchmark recovery of held-out actives against appropriate decoys, retaining all screened failures and filtering counts.

• Cluster ranked candidates, inspect chemistry and artifacts, then propose orthogonal experimental confirmation. Ranking alone does not establish an active compound.

• Illustrative top 100 contains 10 actives among a 1,000-compound library with 20 actives. Enrichment factor at 100 = (10/100)/(20/1000) = 5.

Result and Interpretation

• Present the preparation record, validation, pose evidence and limitations of ranking.

• Predictions are not measured biological activity, clinical safety or regulatory approval.

Precautions

• Avoid training/test leakage and unsupported extrapolation.

• State software and model version and applicable domain.

• Do not select the best-looking model using the final test set.

Viva Questions and Answers

Does a lower score prove a stronger binder?

Scoring is approximate and needs experimental validation.

Why check protonation?

It changes interactions and charge assignment.

Why inspect atom mapping for RMSD?

Symmetry and atom correspondence can change the numerical result.

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