STRUCTURE-BASED DRUG DESIGN (SBDD). UN' EFFICIENTE OTTIMIZZAZIONE MEDIANTE CROSS-DOCKING

SAPIENZA
UNIVERSITÀ DI ROMA

Facoltà di Farmacia e Medicina
Corso di Laurea in Chimica e Tecnologia Farmaceutiche
Tesi Sperimentale in Chimica Farmaceutica
a.a. 2011/2012

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Matricola: 1045882

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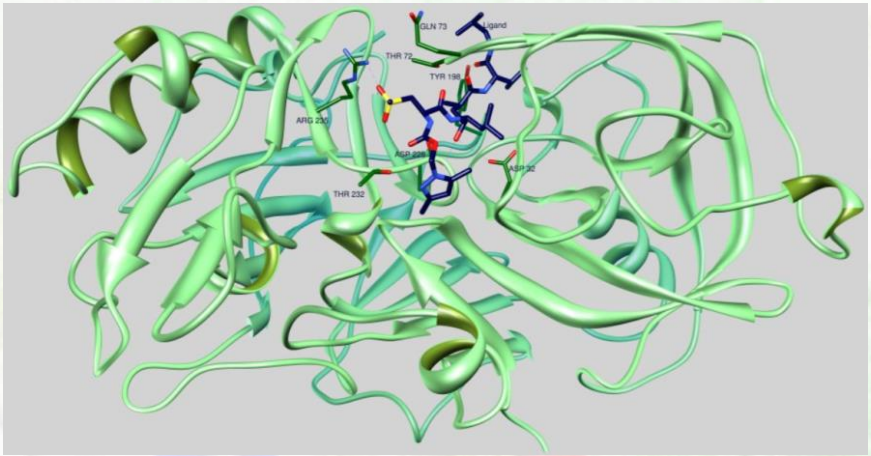
DOCKING MOLECOLARE

- **SAMPLING**
- **SCORING FUNCTION**



Identificazione di composti di interesse farmaceutico

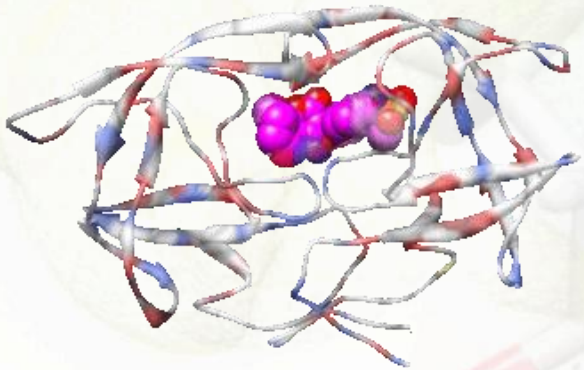
Comprensione meccanismi interazione

Ottimizzazione del *lead*

Bioremediation

Docking

Rigido



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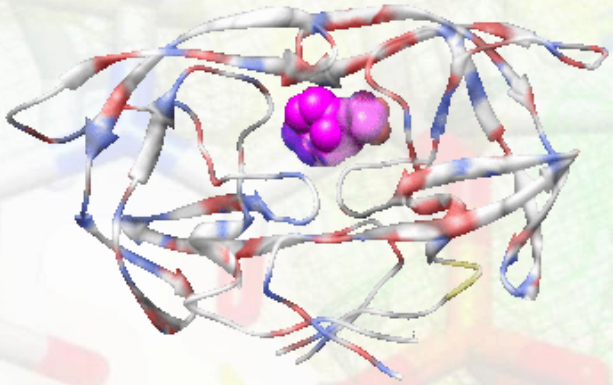
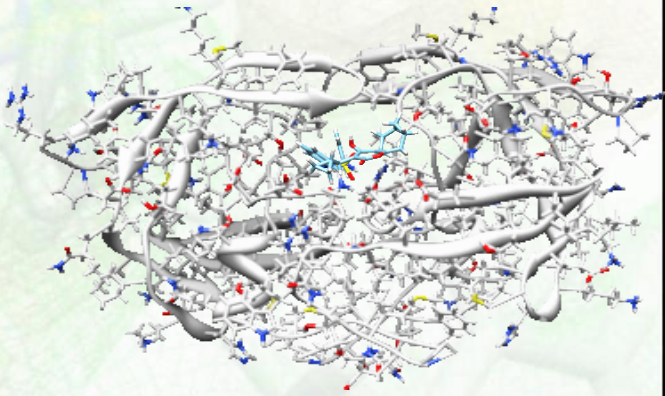
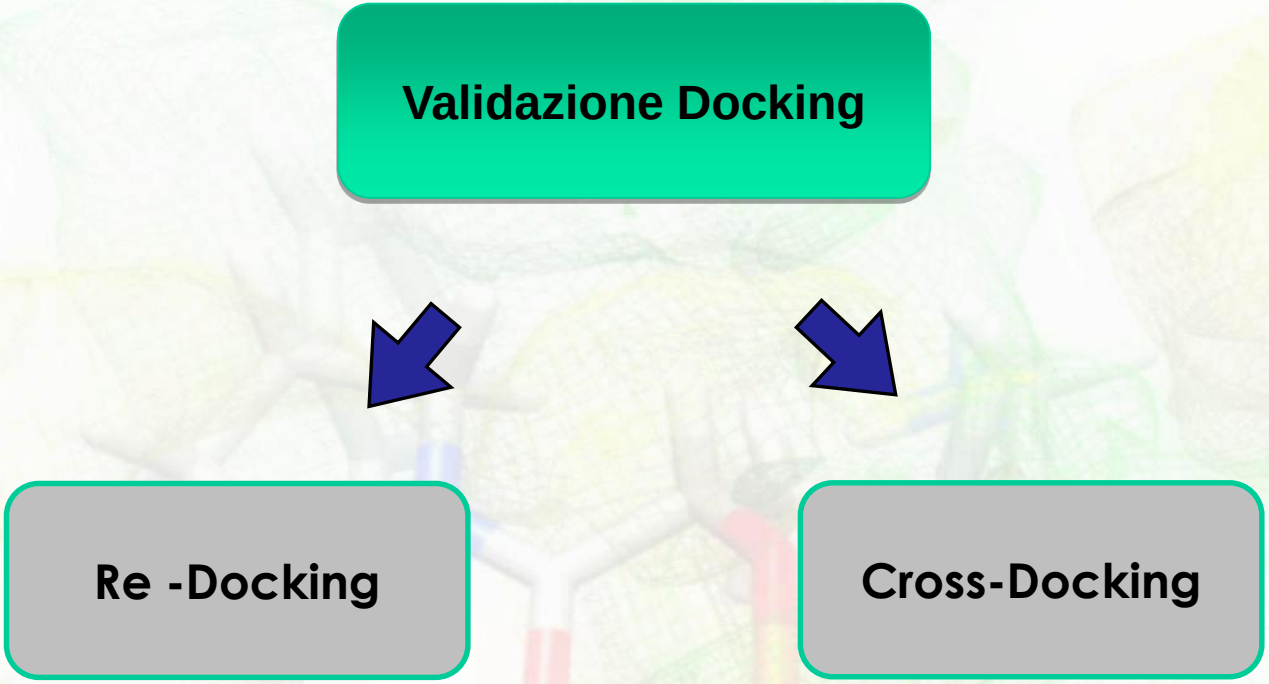


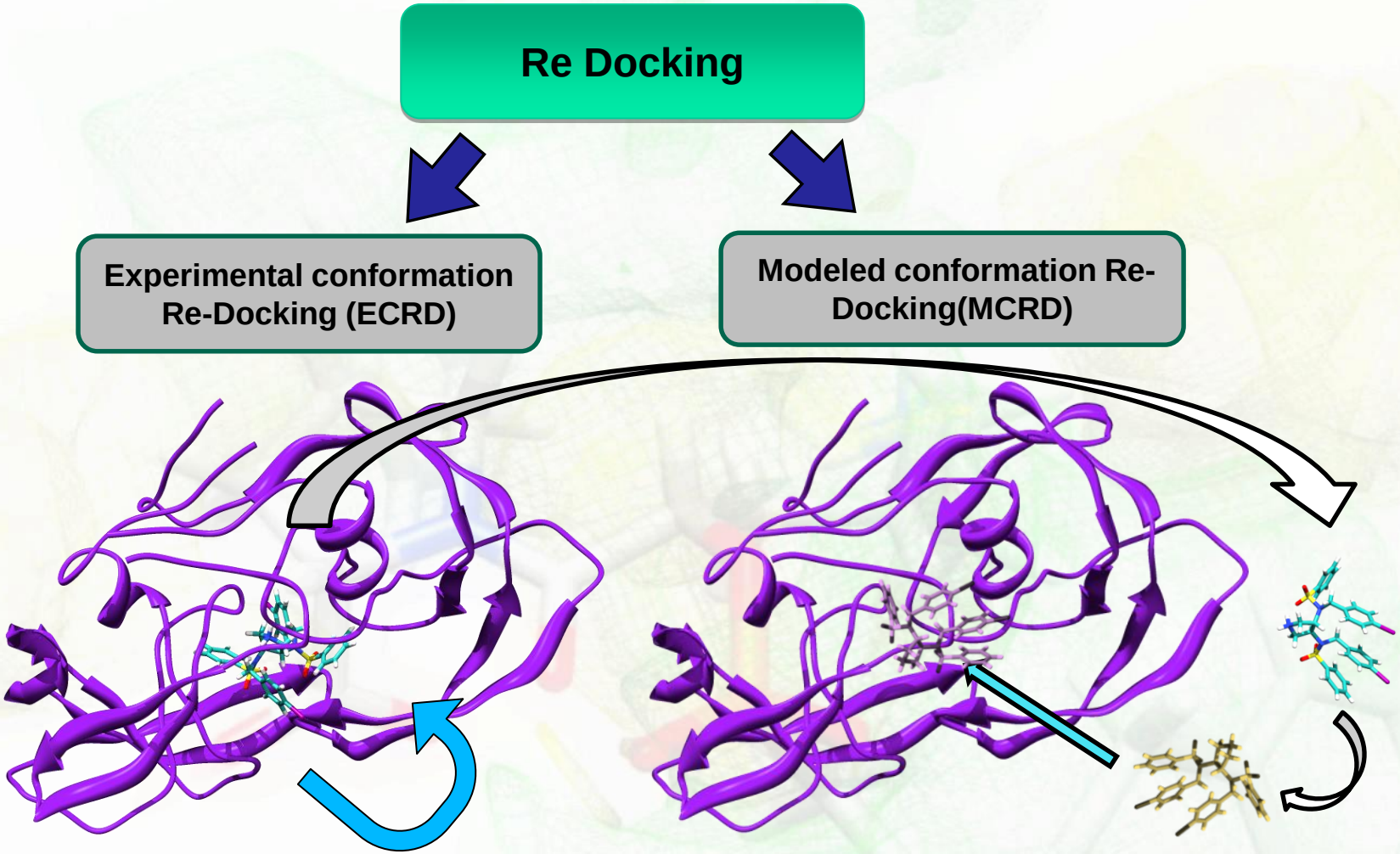
Flessibile

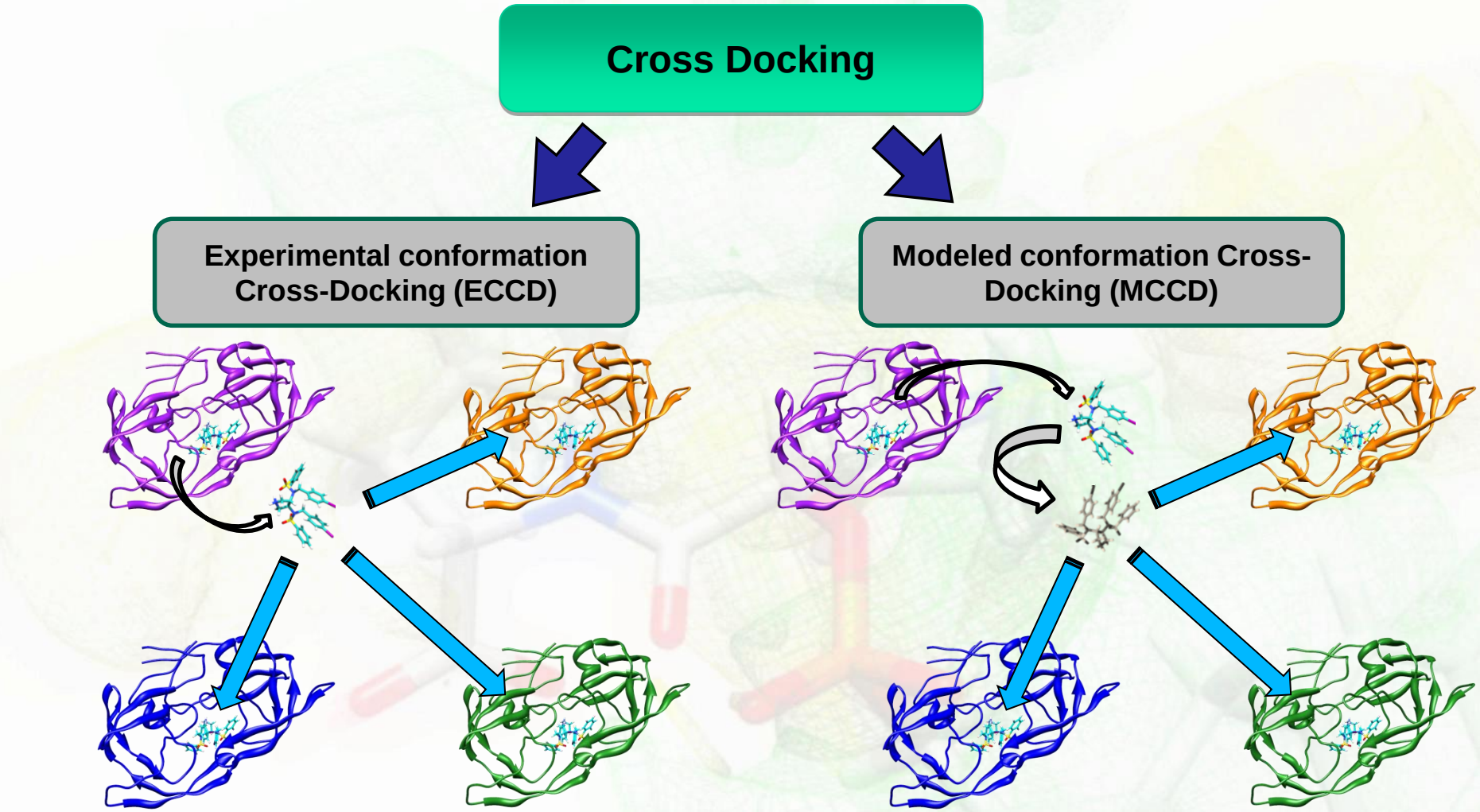


VALIDAZIONE DOCKING



RE-DOCKING (RD)




Cross Docking
Experimental conformation Cross-Docking (ECCD)
Modeled conformation Cross-Docking (MCCD)

- Surflex
- Dock
- Paradocks
  - pmf04
  - p-score
- Autodock
- Plants
  - plp
  - chemplp
  - plp95
- AutodockVina

DATABASE ORIGINALE

SELEZIONE TARGET

TRAINING SET | TEST SET

PREPARAZIONI PROTEINE

DOCKING CON 9 APPLICAZIONI

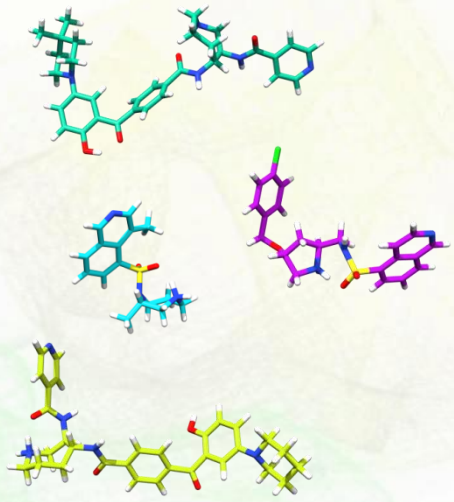
CONFORMAZIONI

CLUSTERIZZAZIONE

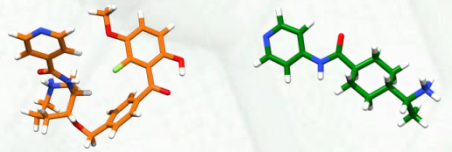
VALUTAZIONE

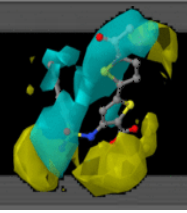
VALIDAZIONE

Training Set



Test Set





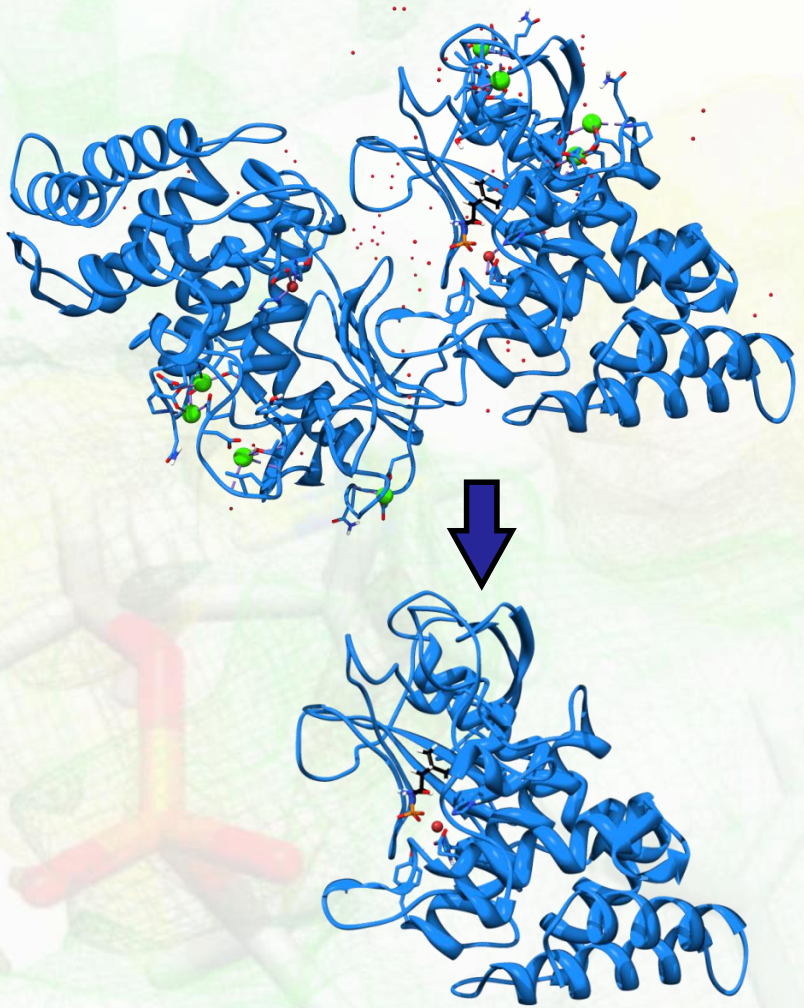
PROCEDURA

Metodo unificato | **Automatizzazione** | **Scelta Programma**

- Parametri base
- Spazio di ricerca 5Å
- Stesse molecole di partenza
- Metodica unificata per la valutazione dei risultati ottenuti

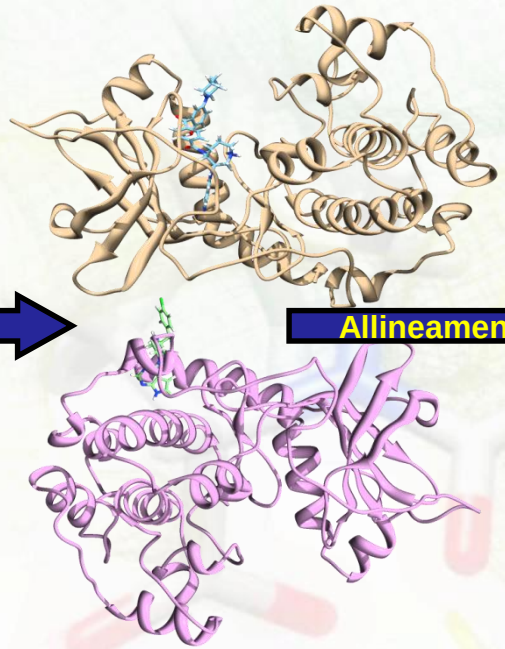
PULIZIA DELLE PROTEINE

- Eliminazione solvente
- Eliminazione metalli strutturali
- Eliminazione catene inutili
- Ricostruzione amminoacidi tagliati
- Protonazione
- Cariche amminoacidi
- Allineamento Complessi
- Divisione in Cluster



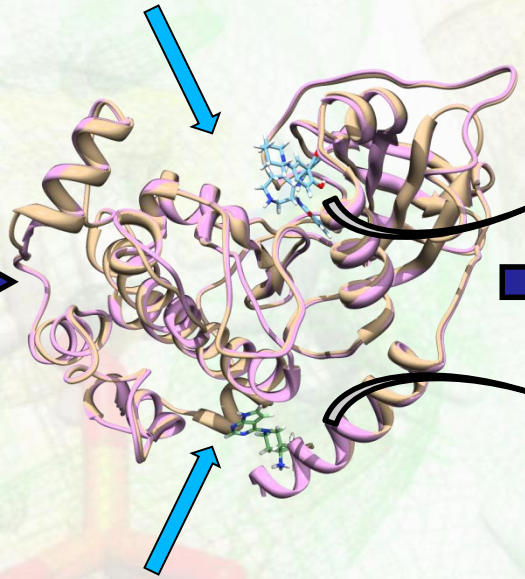
cAMP-dependent protein Kinase catalytic subunit alpha

Riunificazione lock/key nel complesso



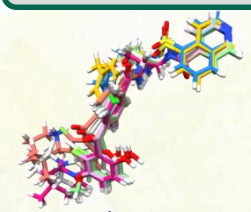
Proteine Pulite

Allineamento

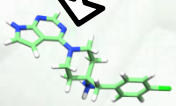


Binding site 1

Binding site 2

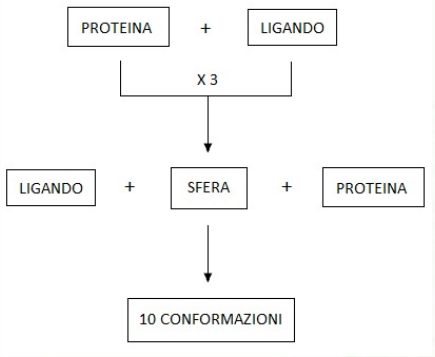


Cluster 1

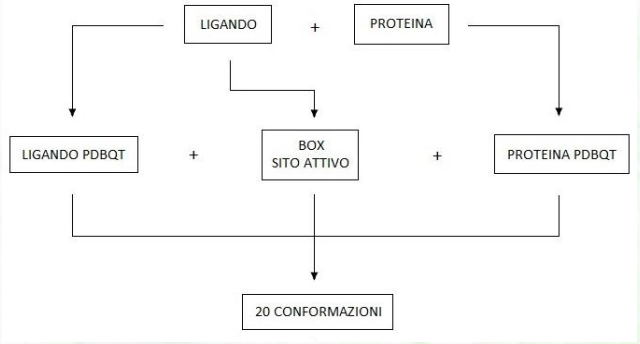


Cluster 2

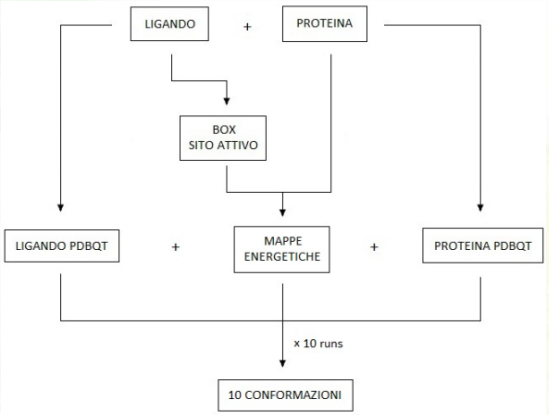
Divisione complessi in lock e key



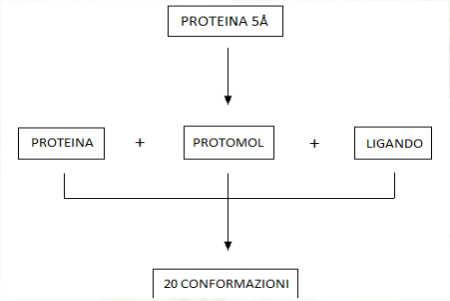
Plants



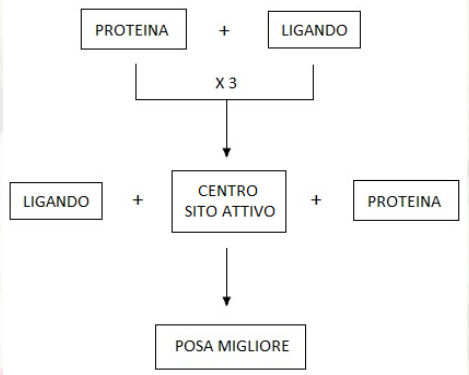
Vina



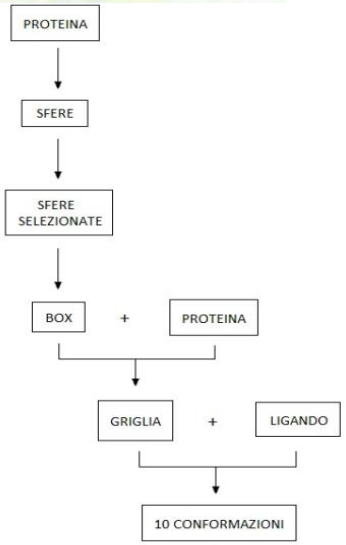
Autodock



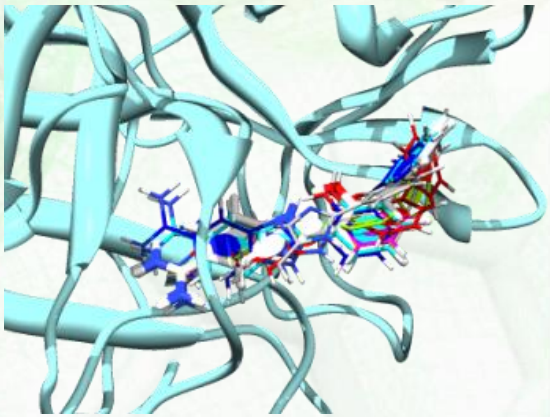
Surflex



Paradocks



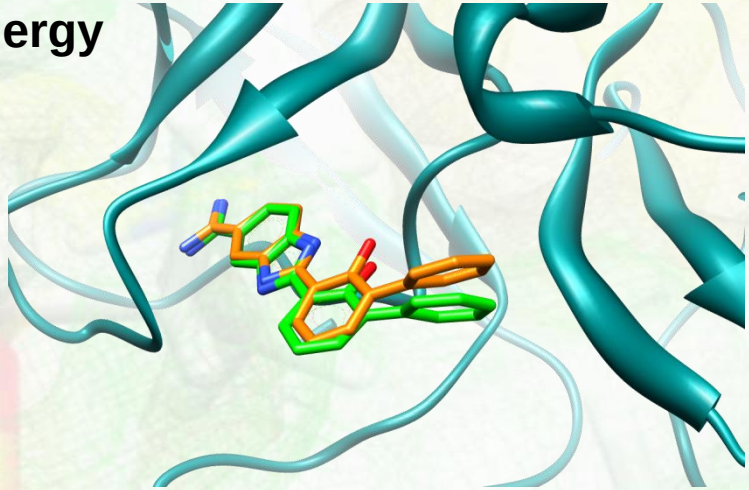
Dock



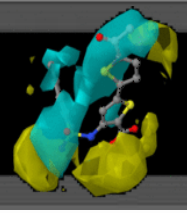
Predizione Binding mode → **Clusterizzazione**

- **BD (Best Docked)** → **Binding Energy**
- **BC (Best Cluster)** → **RMSD**

$$\mathrm{RMSD} = \sqrt{\frac{\sum_{i=1}^{n}(x_{1,i} - x_{2,i})^2}{n}}$$



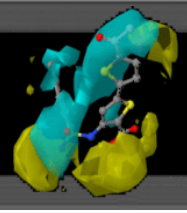
originale docking



EXPERIMENTAL vs MODELED

$$DA\ (Docking\ Accuracy) = f_{RMSD\leq 2} + 0.5\ (f_{RMSD\leq 3} - f_{RMSD\leq 2})$$

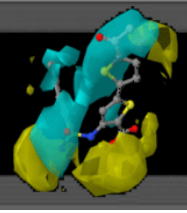
	ECRD	MCRD	ECRD vs MCRD
Software	DA%		ΔDA%
Surflex	32.75	18.20	-14.56
Paradocks pmf04	27.22	15.19	-12.03
Paradocks p-score	35.28	22.78	-12.50
Vina	46.84	35.08	-11.76
Dock	41.93	36.08	-5.85
Autodock	49.05	41.11	-7.94
Plants chemplp	57.91	47.31	-10.60
Plants plp	53.64	45.25	-8.39
Plants plp95	52.06	42.88	-9.18
Media	44.08	33.76	-10.31



EXPERIMENTAL vs MODELED

$$DA\ (Docking\ Accuracy) = f_{RMSD\leq 2} + 0.5\ (f_{RMSD\leq 3} - f_{RMSD\leq 2})$$

	ECCD		MCCD		ECCD vs MCCD
	BD	BC	BD	BC	BD
Software	DA%		DA%		ΔDA%
Surflex	52.85	49.84	48.10	45.41	-4.75
Paradocks pmf04	46.84	47.63	41.46	41.77	-5.38
Paradocks p-score	60.92	60.60	49.84	52.37	-11.08
Vina	69.78	57.59	65.19	53.64	-4.59
Dock	53.64	53.48	52.37	52.37	-1.27
Autodock	70.09	65.03	65.98	62.97	-4.11
Plants chemplp	72.47	70.73	68.35	64.40	-4.12
Plants plp	70.41	66.14	65.51	61.71	-4.91
Plants plp95	69.15	70.25	66.61	66.61	-2.53
Media	62.90	60.14	58.16	55.69	-4.75



RE-DOCKING vs CROSS-DOCKING

$$DA\ (Docking\ Accuracy) = f_{RMSD\leq 2} + 0.5\ (f_{RMSD\leq 3} - f_{RMSD\leq 2})$$

ECRD	vs	BD-ECCD

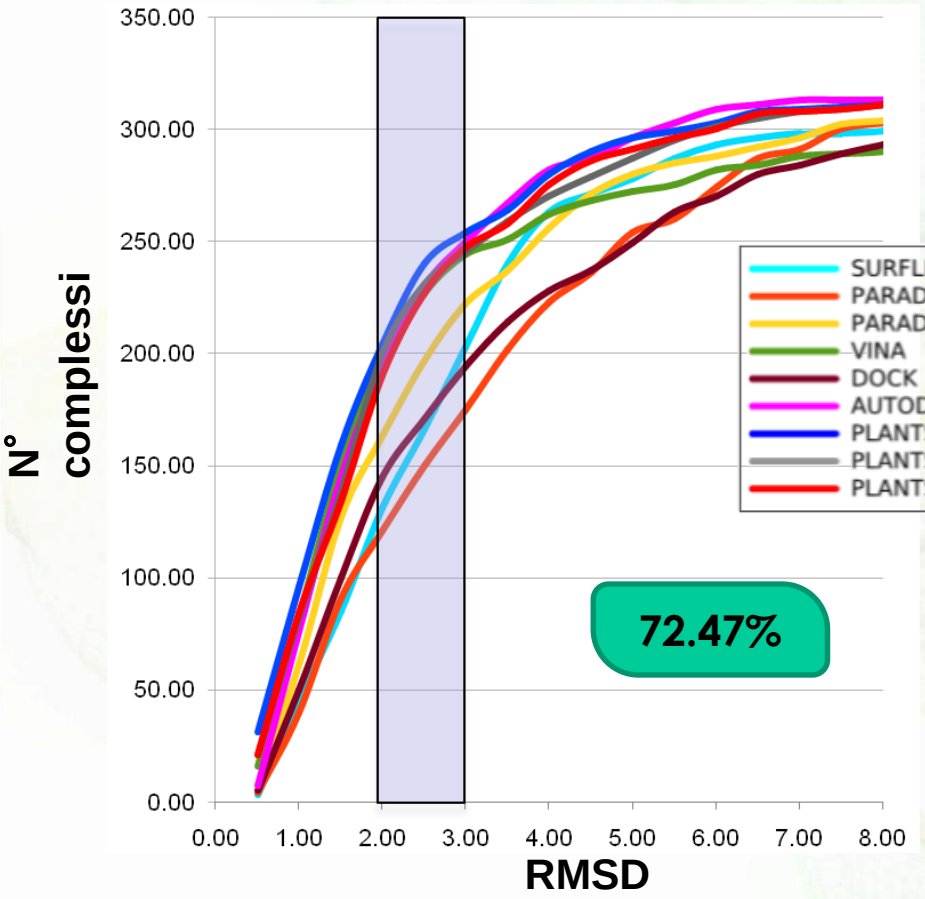
Software	ΔDA%
Surflex	+20.09
Paradocks pmf04	+19.62
Paradocks p-score	+25.63
Vina	+22.94
Dock	+11.71
Autodock	+21.04
Plants chemplp	+14.56
Plants plp	+16.77
Plants plp95	+17.09
Media	+18.83

MCRD	vs	BD-MCCD

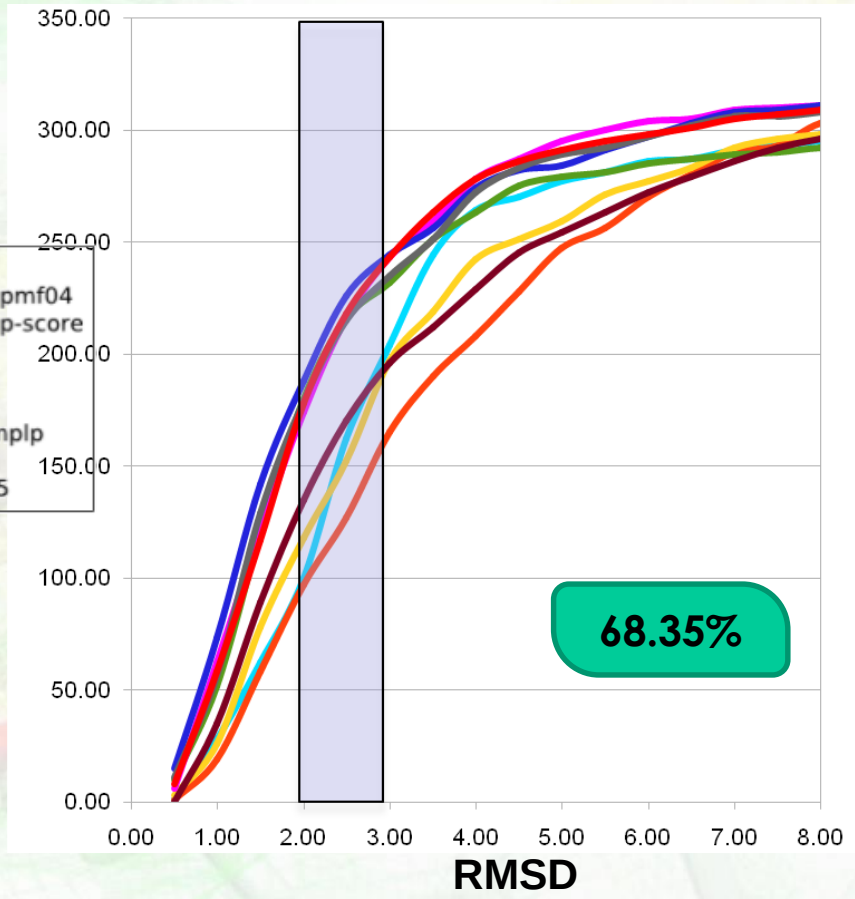
Software	ΔDA%
Surflex	+29.91
Paradocks pmf04	+26.27
Paradocks p-score	+27.06
Vina	+30.11
Dock	+16.30
Autodock	+24.87
Plants chemplp	+21.04
Plants plp	+20.25
Plants plp95	+23.73
Media	+24.36

PRESTAZIONI SINGOLI PROGRAMMI

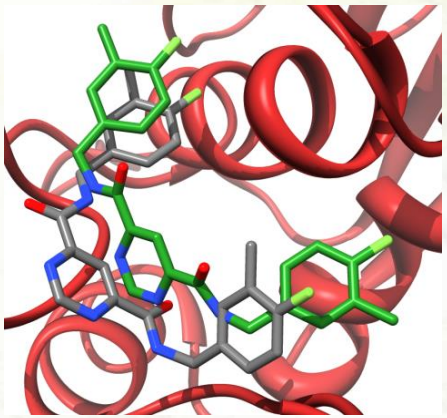
ECCD



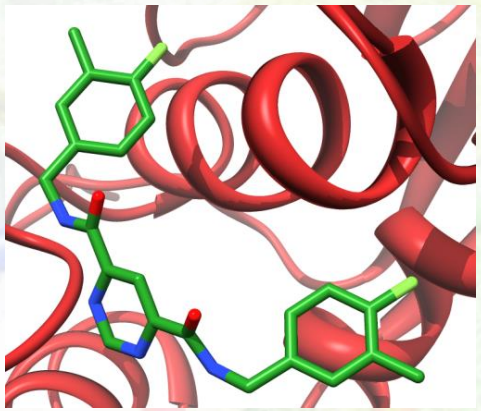
MCCD



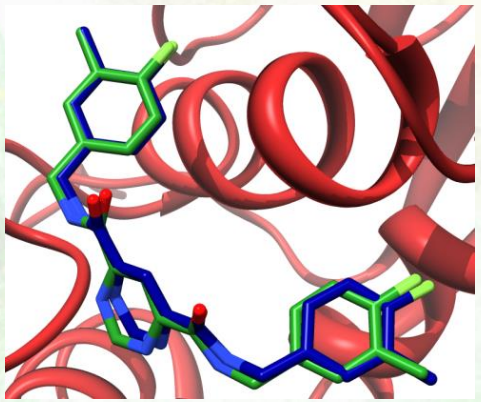
RMSD medio	Deviazione Standard RMSD



Autodock



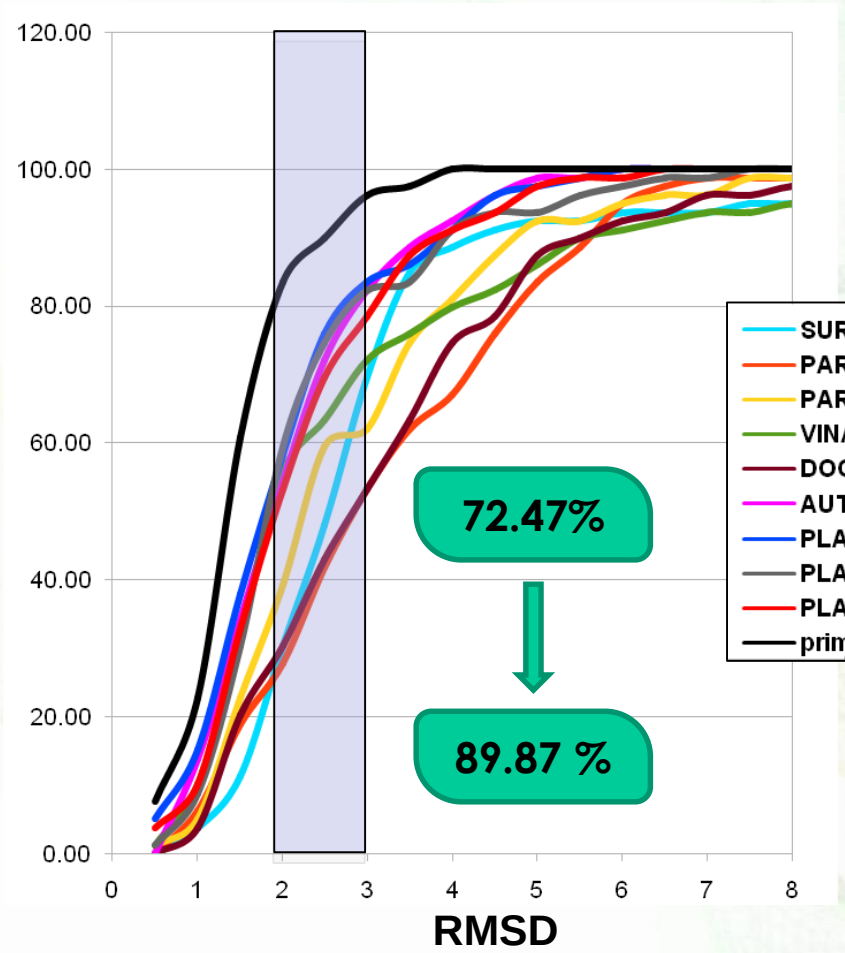
Sperimentale



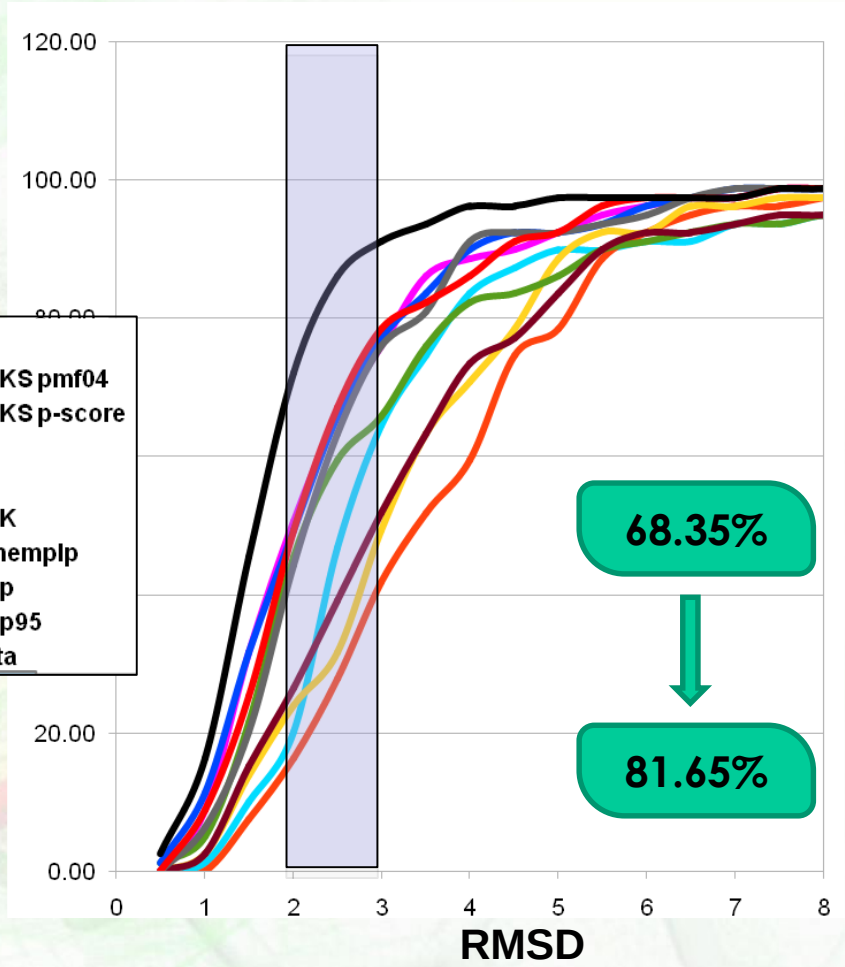
PLANTS chemplp

PRESTAZIONI PRIMA SCELTA

ECCD

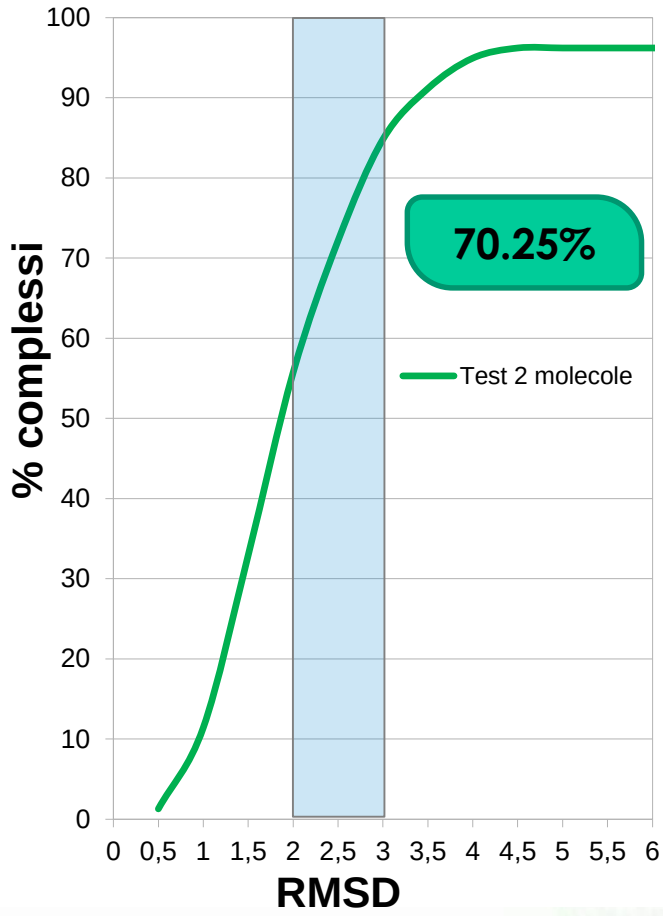


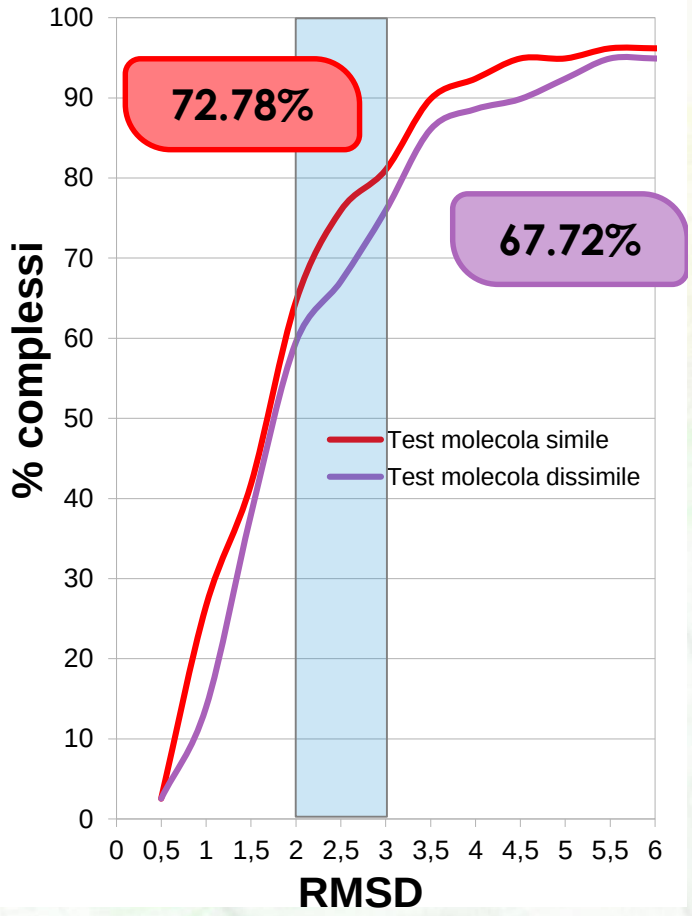
MCCD

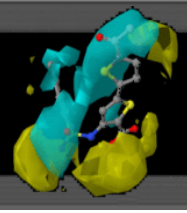


VALIDAZIONE ESTERNA

Validazione Modeled conformation Cross- Docking







CONCLUSIONI

- Nel Re-Docking i programmi sono molto influenzati dalla scelta della conformazione di input (ΔDA% ~10%). Con il Cross-Docking (ΔDA% ~4%) tale influenza e' stata ridotta di circa il 60%.
- In termini di *docking accuracy* il Cross-Docking (~70-75%) garantisce prestazioni maggiori del Re-Docking (~50-60%).
- L'implementazione del metodo "prima scelta" incrementa ulteriormente la DA% (~80-90%) ed in fase di applicazione su un test set esterno ha dimostrato di essere effettivamente predittiva.
- Limitazioni.
- Al fine di confermare i risultati ottenuti, ulteriori studi sono in corso sia su un più vasto numero di complessi per ogni target e sia su altri target non ancora inclusi.
- Il protocollo qui sviluppato sarà incluso nel server 3-D QSAR (www.3d-qsar.com) sviluppato dall'RCMD.

GRAZIE PER L'ATTENZIONE