STRUCTURE-BASED DRUG DESIGN: QUALE SOFTWARE UTILIZZARE? STUDIO COMPARATIVO TARGET-BASED TRA DIVERSI METODI FREE ED OPEN SOURCE DI DOCKING MOLECOLARE

SAPIENZA
UNIVERSITÀ DI ROMA

Facoltà di Farmacia e Medicina
Corso di Laurea in Chimica e Tecnologia Farmaceutiche
Tesi Sperimentale in Chimica Farmaceutica
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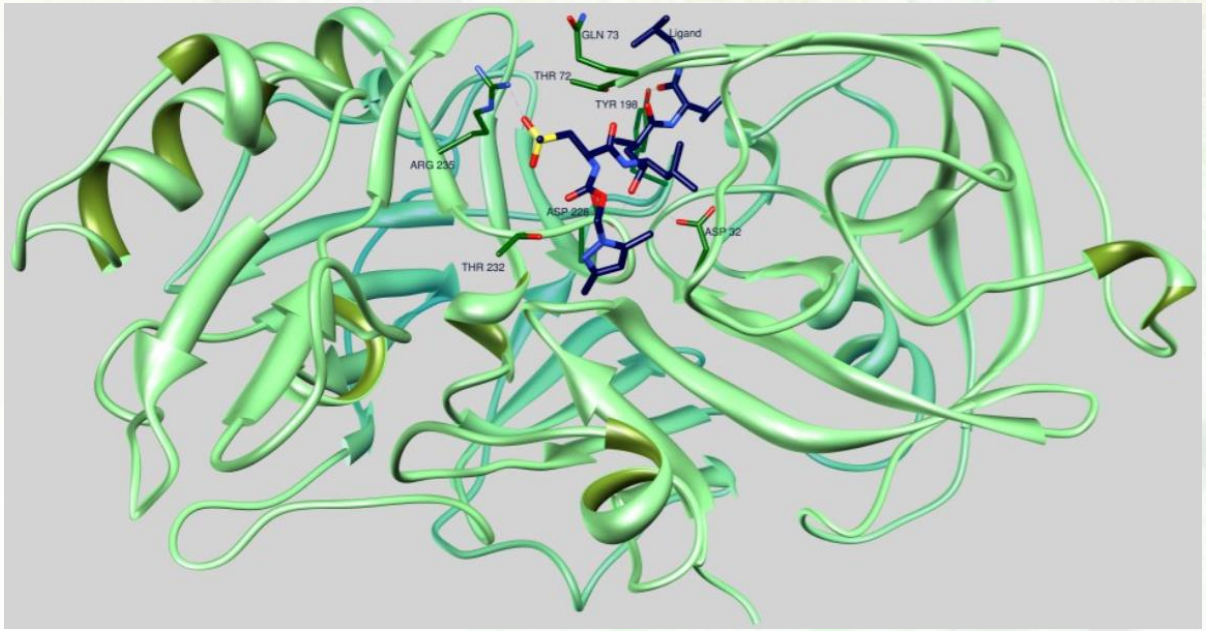
IL DOCKING MOLECOLARE

Identificazione di composti di interesse

Comprensione meccanismi interazione

Ottimizzazione del *lead*

Bioremediation



IL DOCKING MOLECOLARE

Rigido

Semi-flessibile

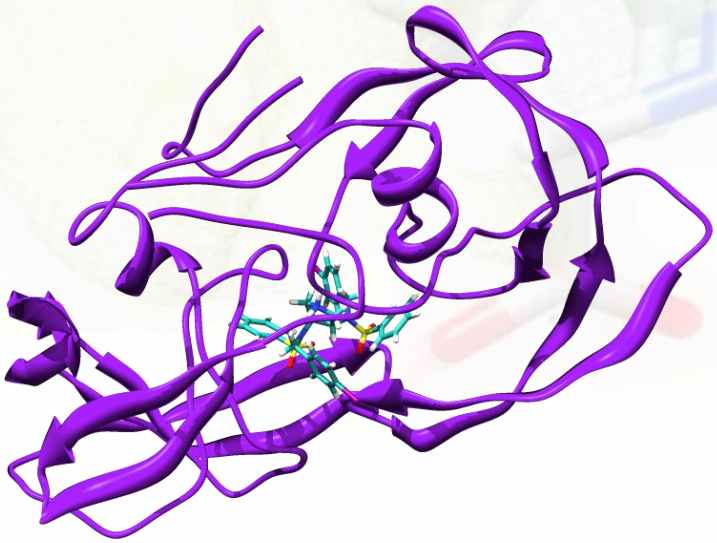
Flessibile

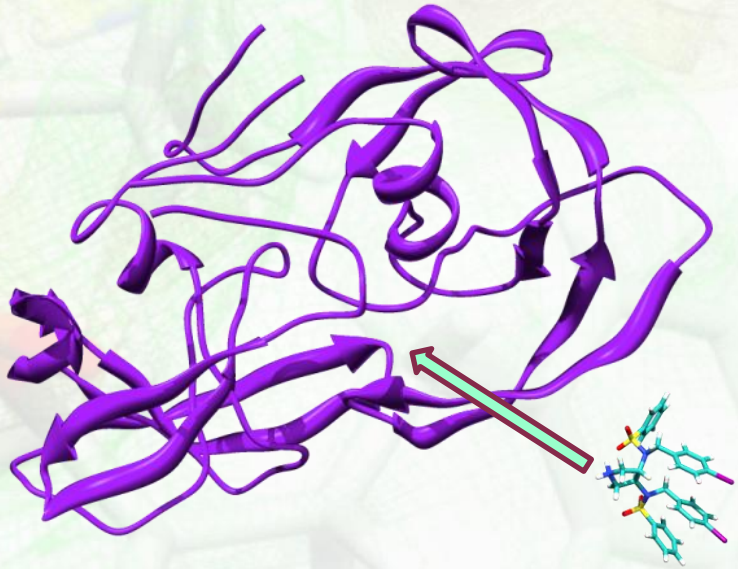
Self Re-Docking

Sampling

Scoring

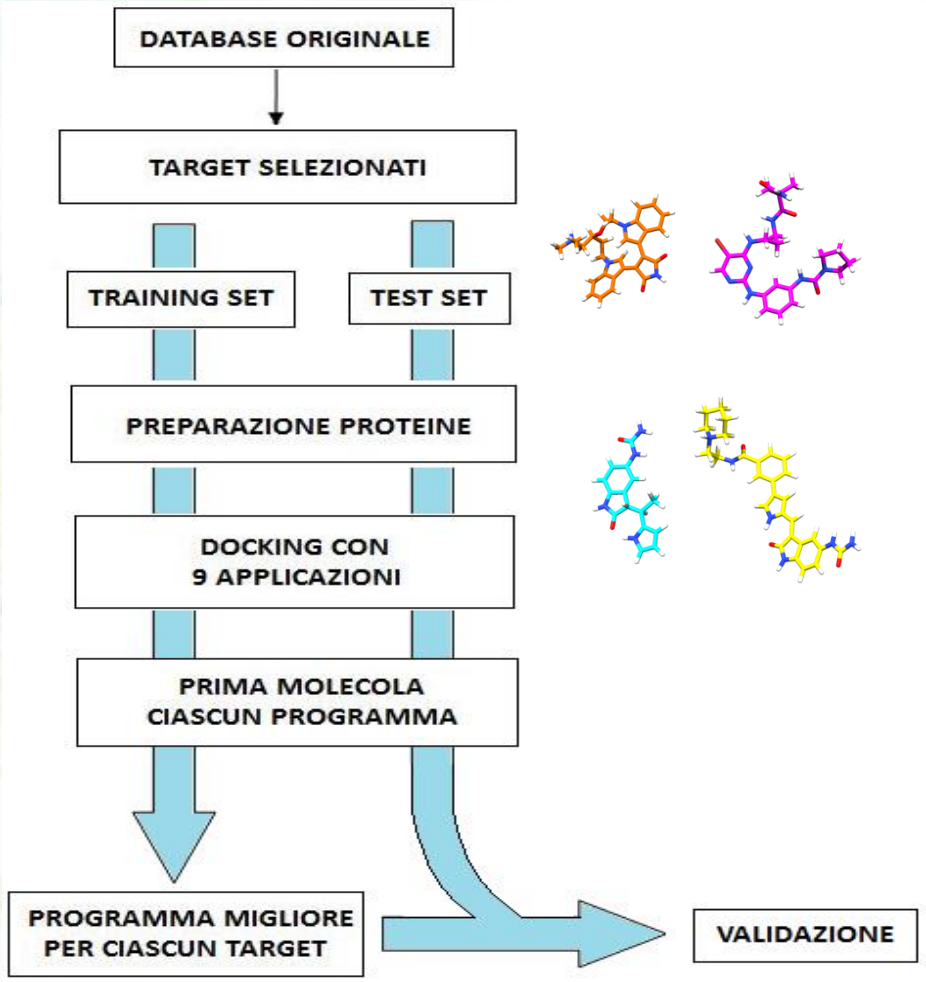
Re-Docking Modeled

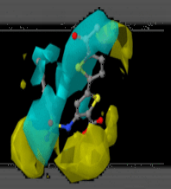




PROCEDURA GENERALE

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





SCELTE OPERATIVE

Metodo unificato

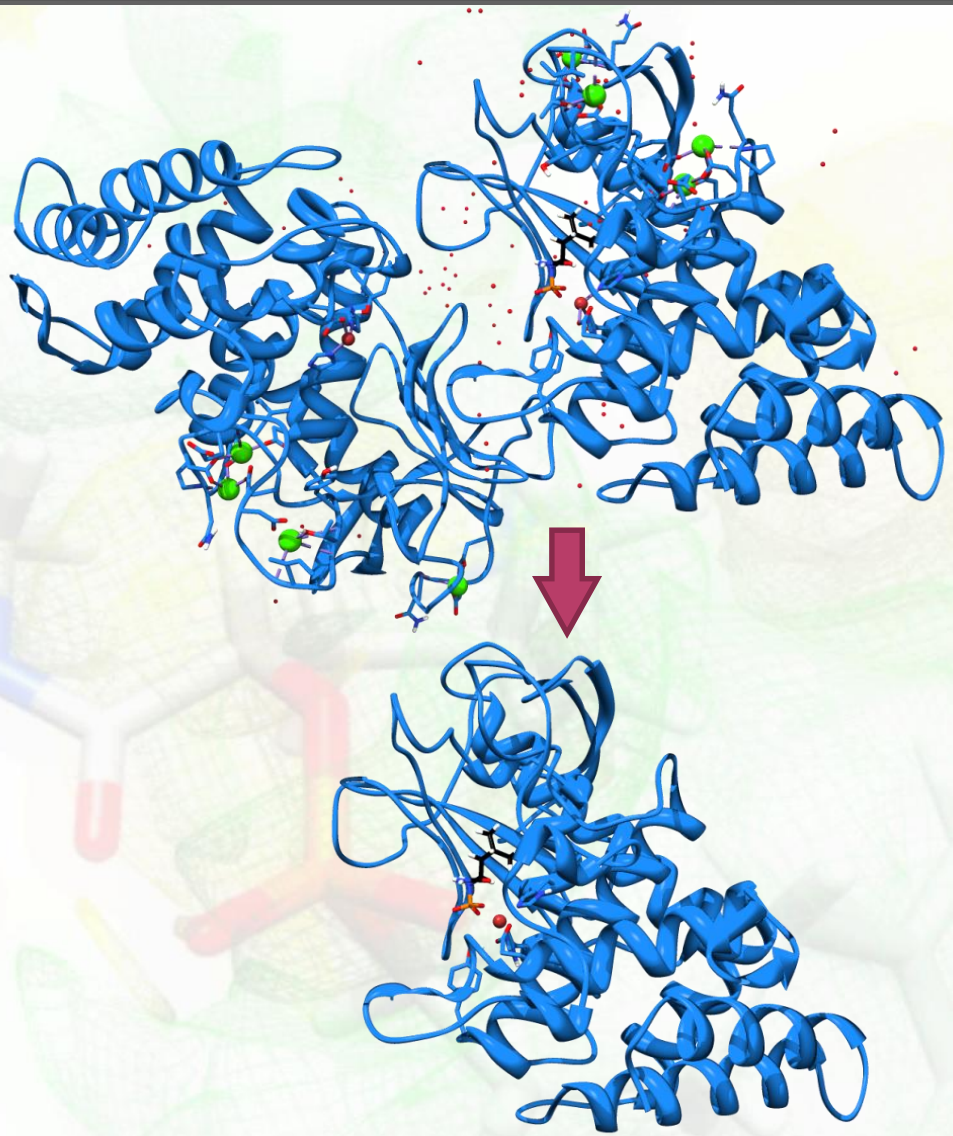
Automatizzazione

Scelta programmi

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

METODO UNIFICATO

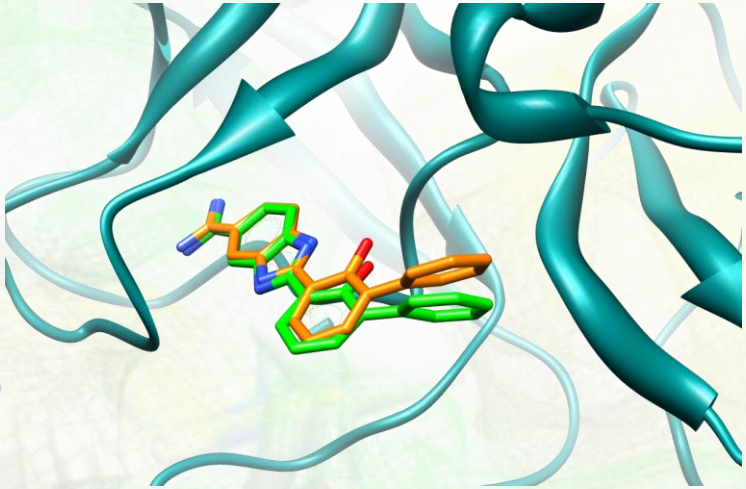
- Eliminazione solvente
- Eliminazione metalli strutturali
- Eliminazione catene
- Ricostruzione amminoacidi tagliati
- Protonazione
- Cariche amminoacidi



METODO UNIFICATO

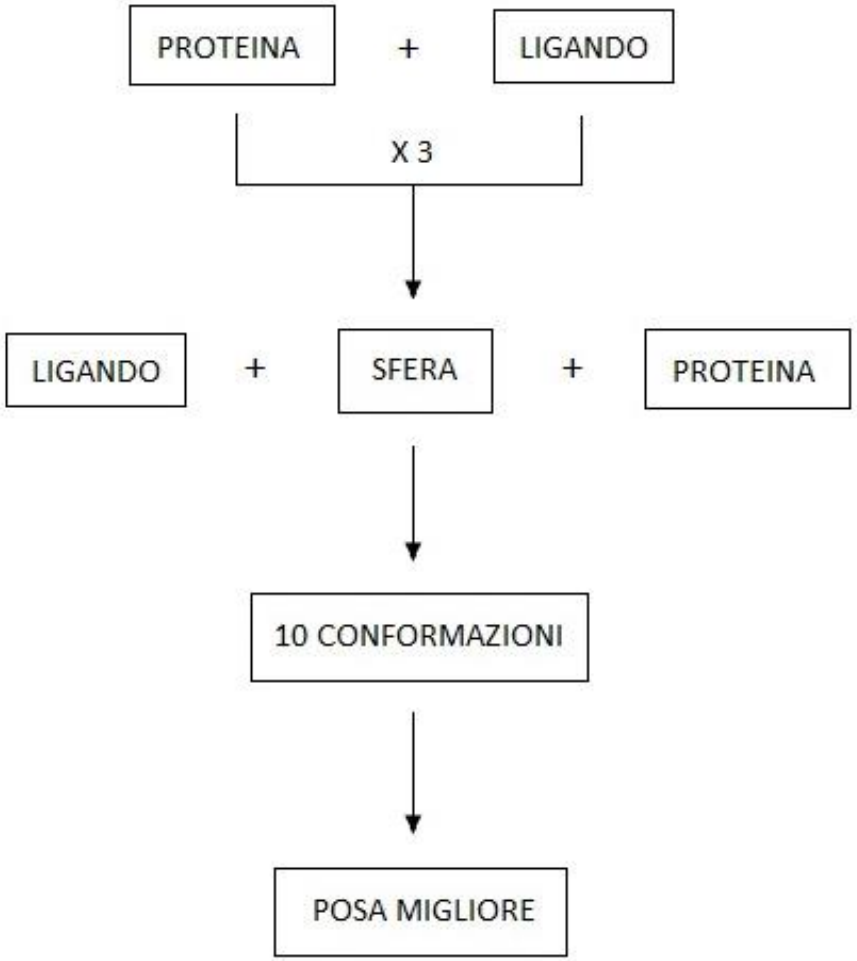
- Obiettivo
- Rapido
- Automatizzabile

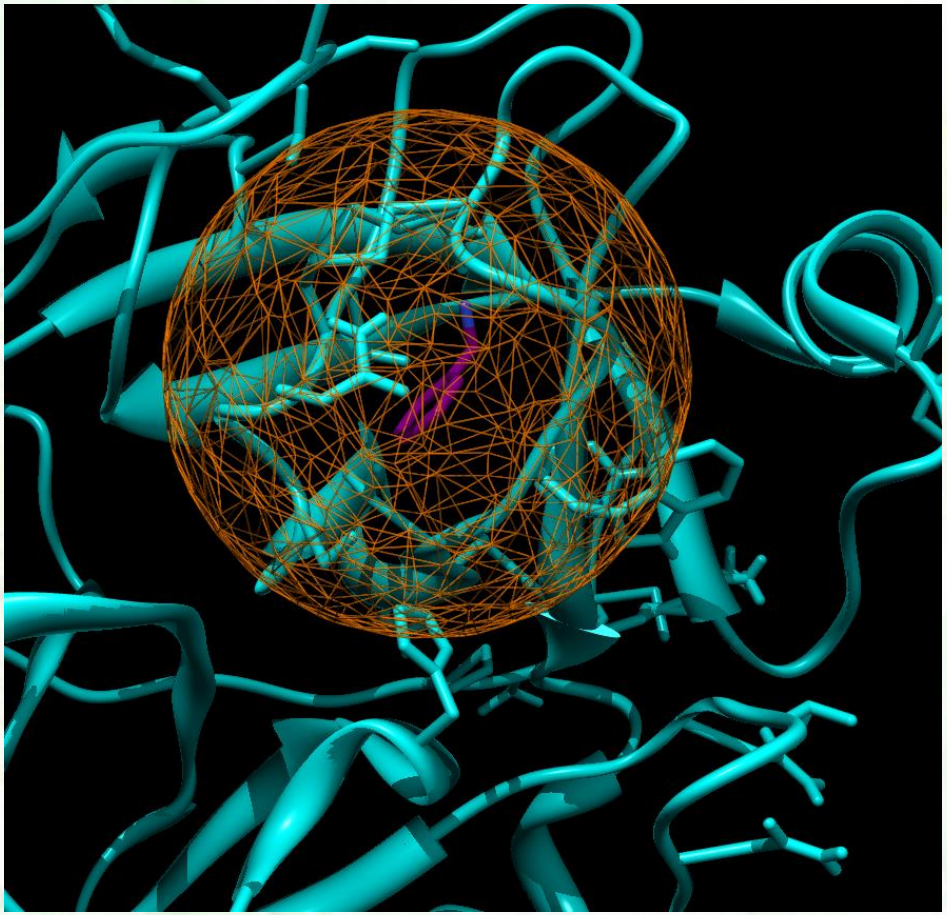
$$\mathrm{RMSD} = \sqrt{\frac{\sum_{i=1}^{n}(x_{1,i} - x_{2,i})^2}{n}}$$



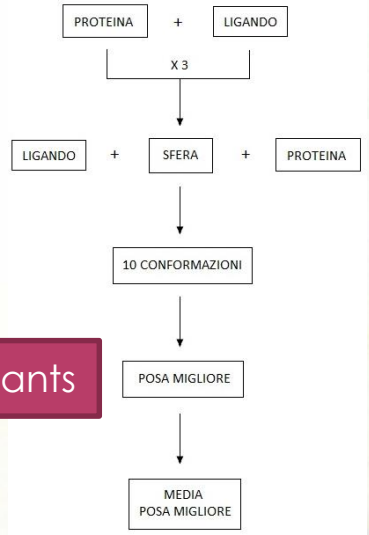
- Non considera l'energia di legame
- Risultati dipendenti dal PM

AUTOMATIZZAZIONE DOCKING: PLANTS

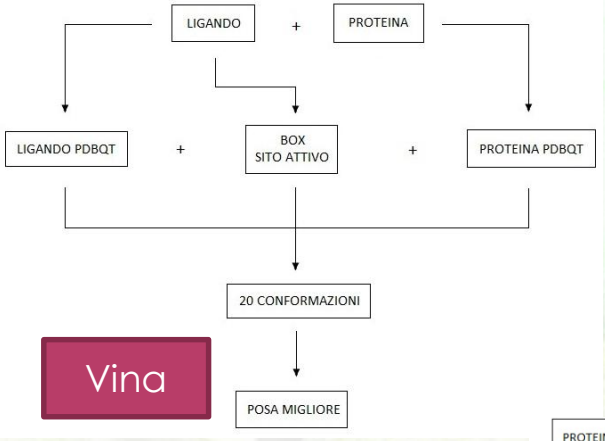




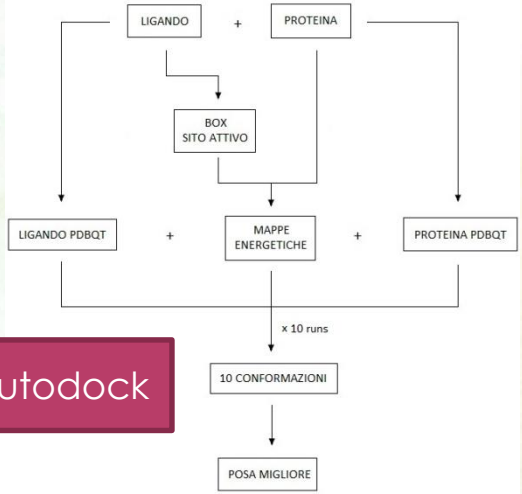
AUTOMATIZZAZIONE DOCKING



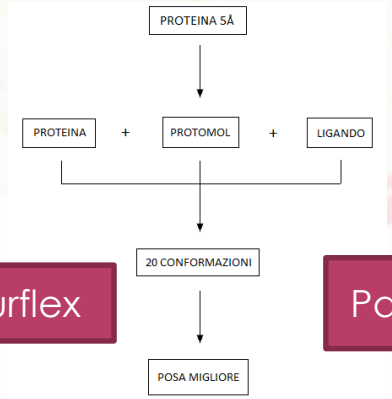
Plants



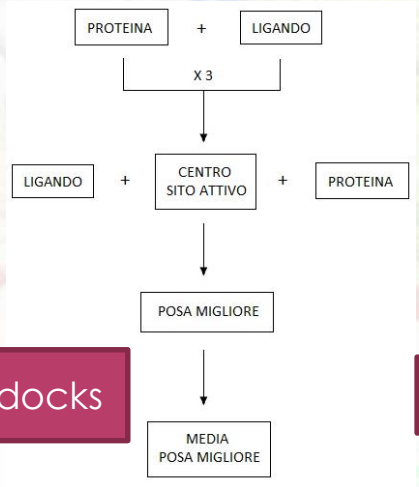
Vina



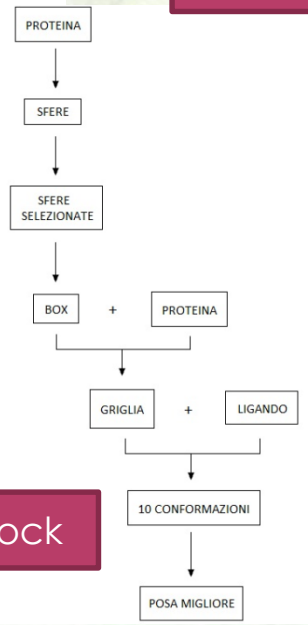
Autodock



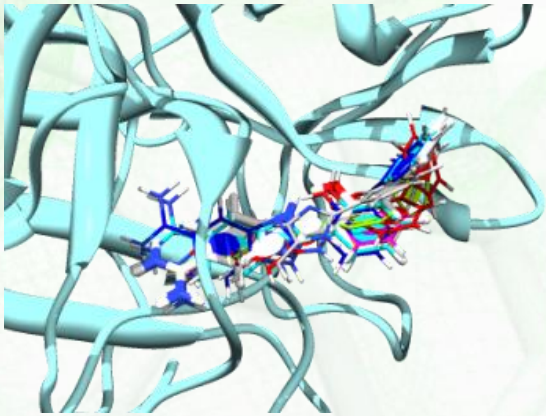
Surflex



Paradocks

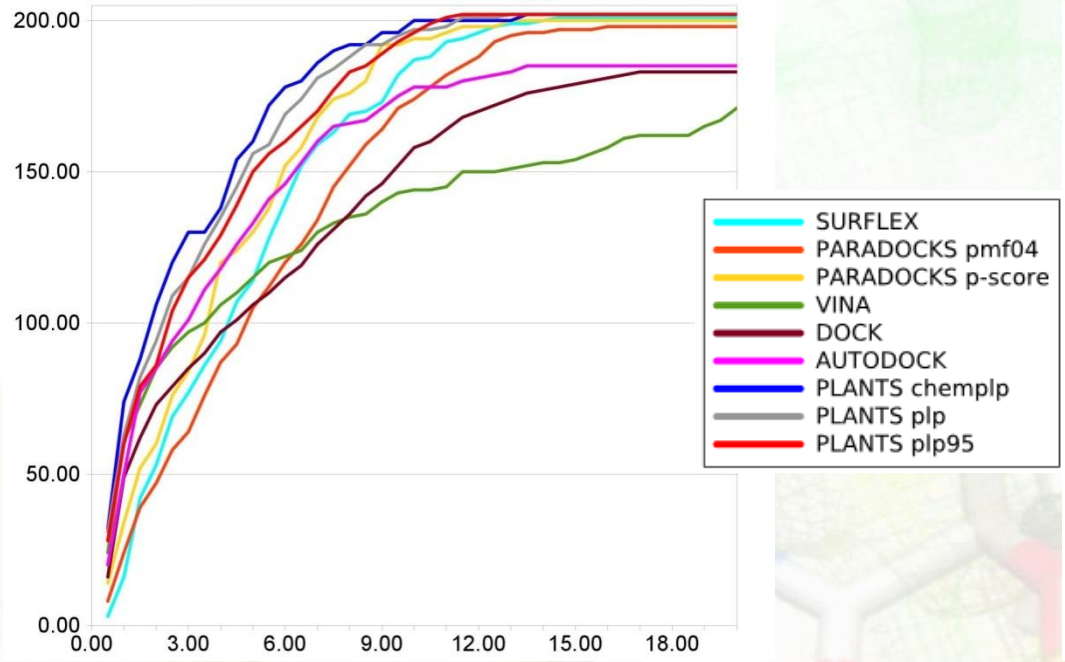


Dock

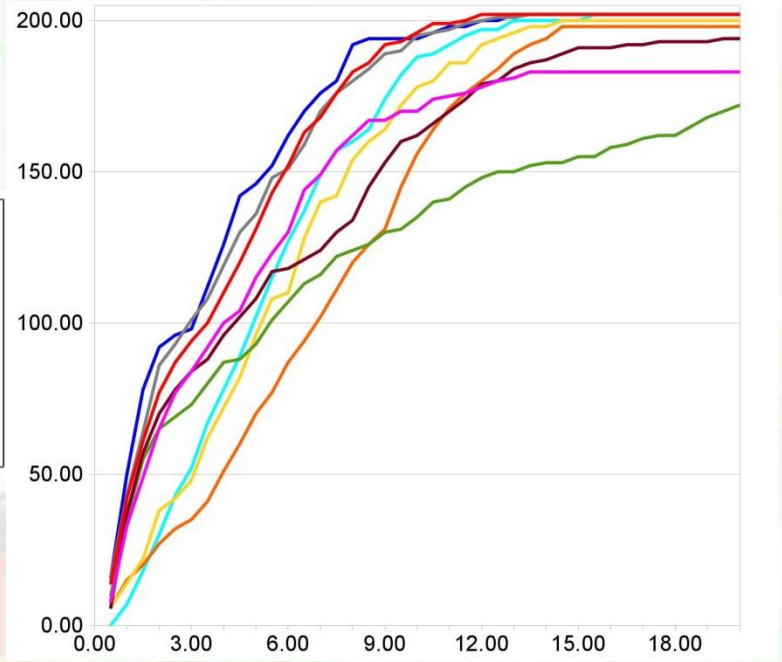


RISULTATI SUI SINGOLI PROGRAMMI

Self Re-Docking



Re-Docking Modeled



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

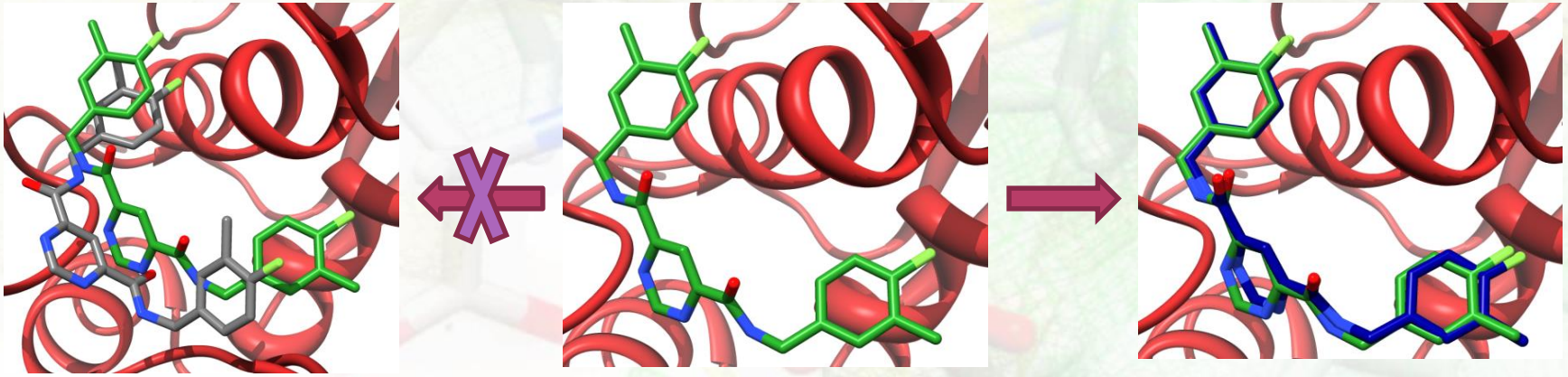
	SURFLEX	PARADOCKS pmf04	PARADOCKS p-score	VINA	DOCK	AUTODOCK	PLANTS chemplp	PLANTS plp	PLANTS plp95
RMSD	4,78	5,06	3,99	6,20	4,07	3,02	2,88	3,15	3,38
Tempo	37,86	1140,55	1112,76	3455,88	214,61	2005,36	153,01	123,34	99,61
DA	18	19,5	28	31,5	27	38,5	51	45,5	42,5

SCELTA PROGRAMMA PER TARGET

RMSD medio

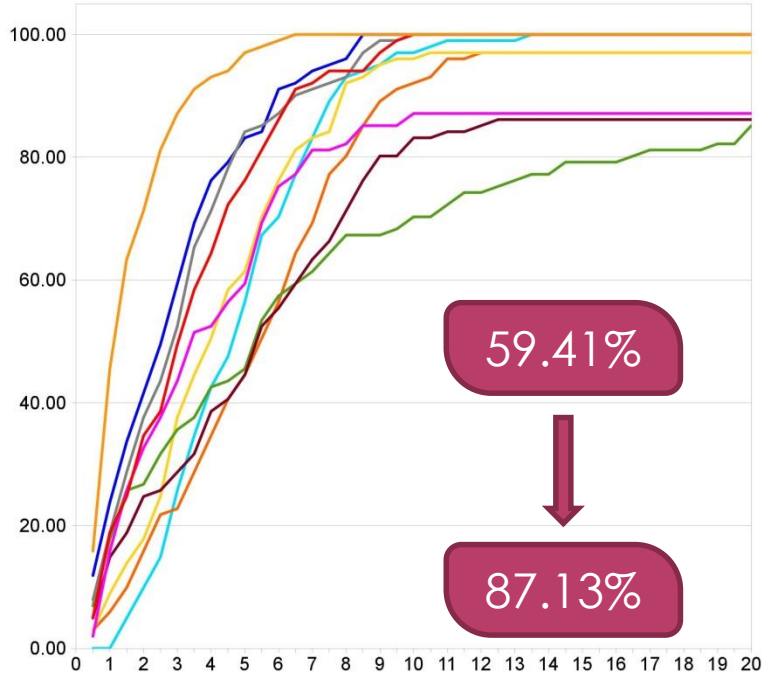
Deviazione Standard RMSD

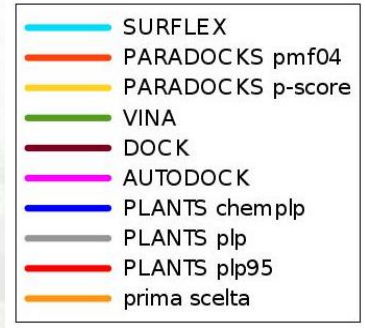
Tempo medio



PRIMA SCELTA

Self Re-Docking

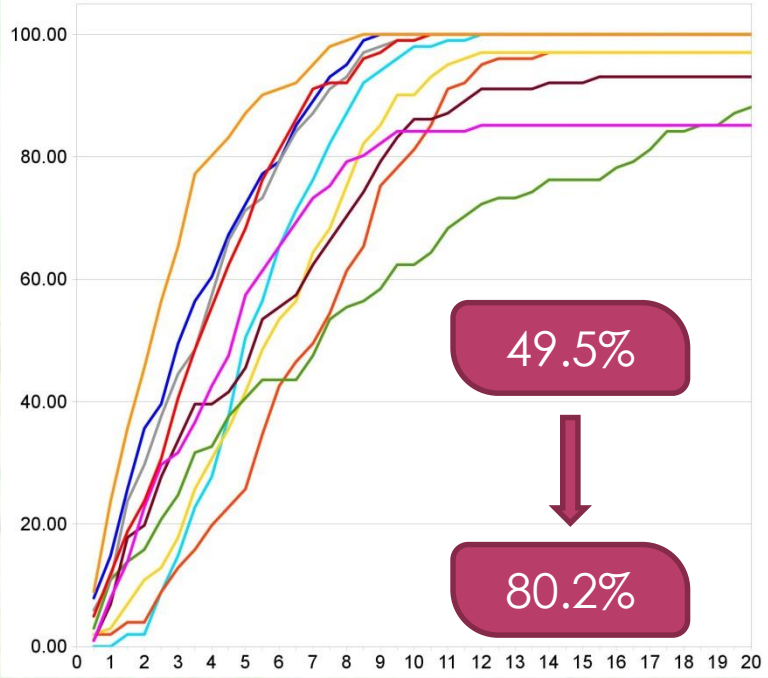




+ 57%

51 → 80

Re-Docking Modeled



+ 30%

43 → 56

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

VALIDAZIONE (1)

Self Re-Docking

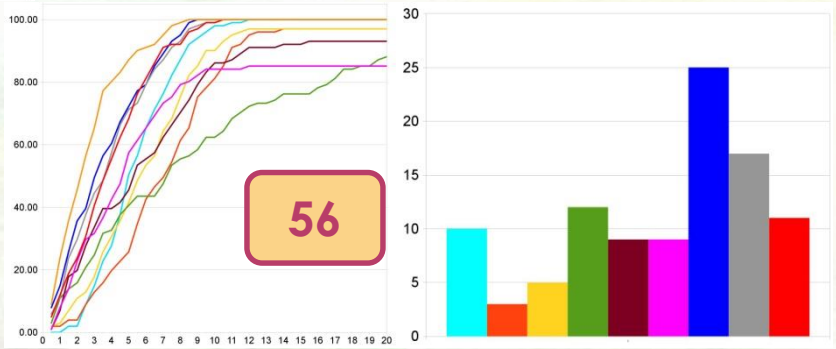
Training set

Test set

SURFLEX
PARADOCKS pmf04
PARADOCKS p-score
VINA
DOCK
AUTODOCK
PLANTS chemplp
PLANTS plp
PLANTS plp95
prima scelta

Re-Docking Modeled

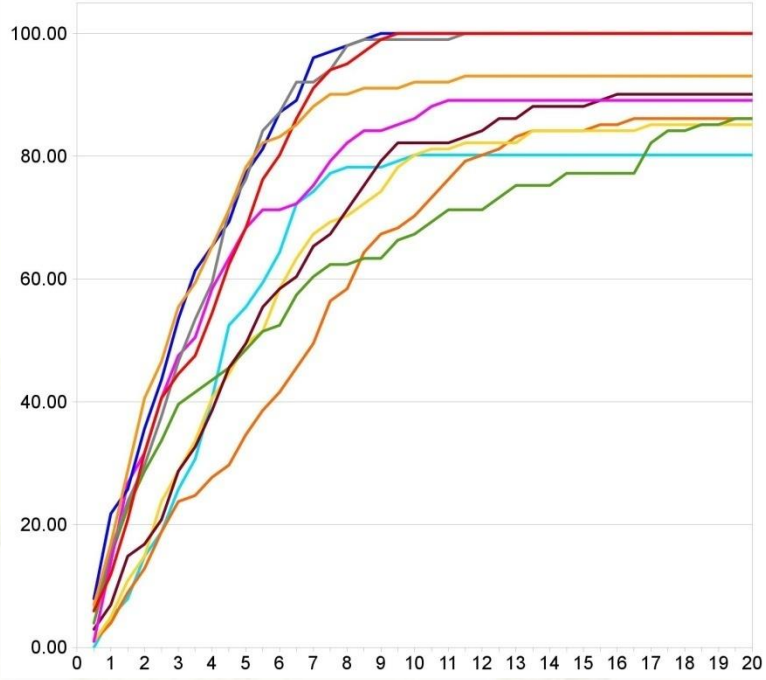
Training set

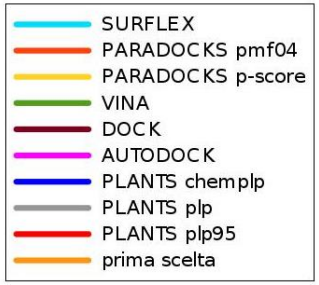


Test set

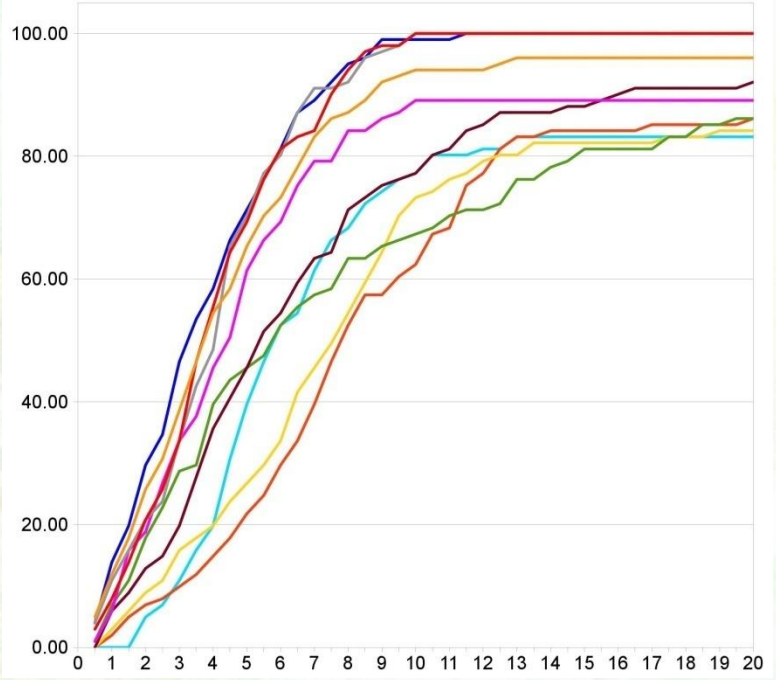
VALIDAZIONE (2)

Self Re-Docking





Re-Docking Modeled



Cross-Docking

CONCLUSIONI

- Nuovo approccio
- I dati confermano i presupposti
- Limitazioni
- Ulteriori studi in corso

GRAZIE PER L'ATTENZIONE