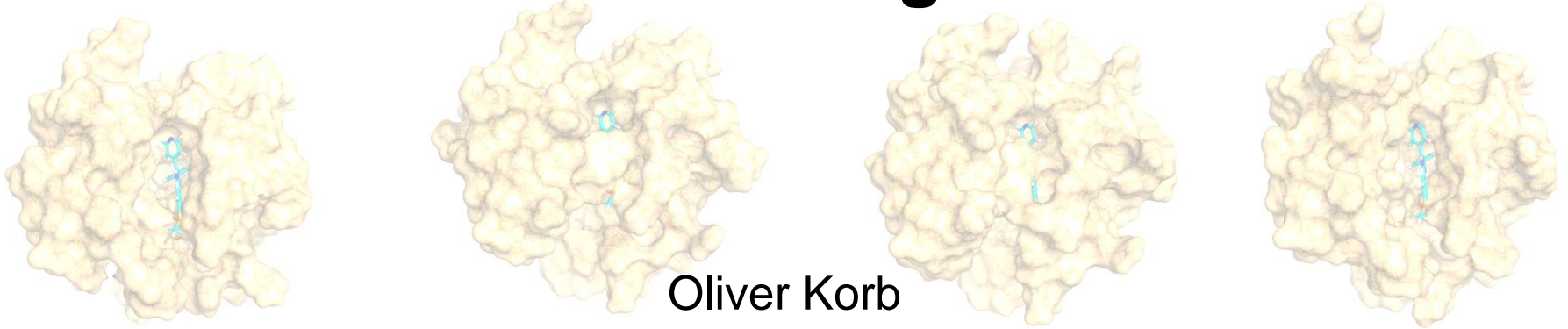


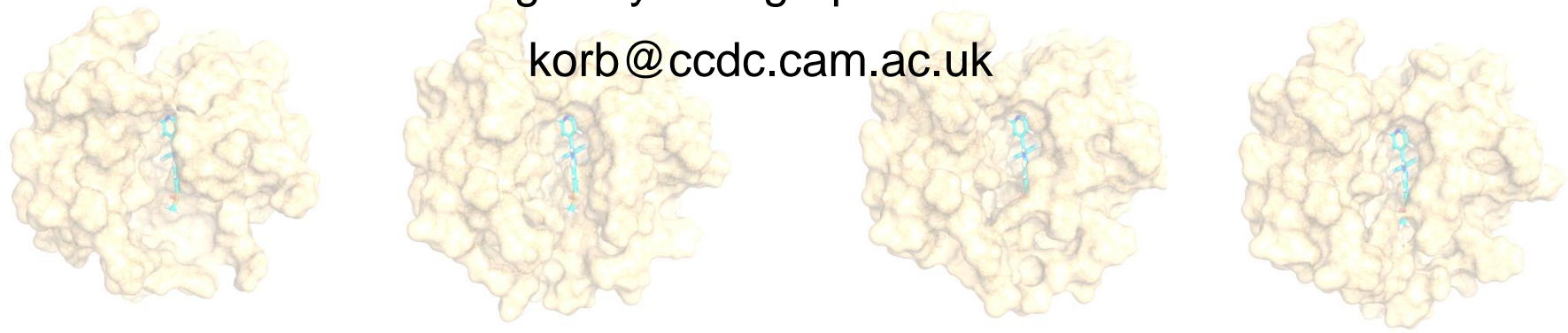
Ensemble Docking Revisited



Oliver Korb

Cambridge Crystallographic Data Centre

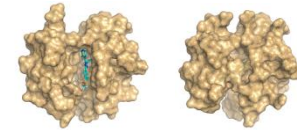
korb@ccdc.cam.ac.uk



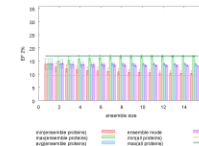


Outline

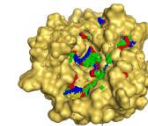
Introduction



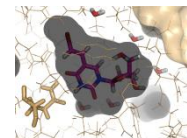
Simulated Ensemble Docking / Screening

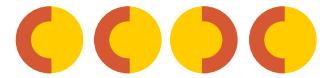


GOLD Ensemble Docking

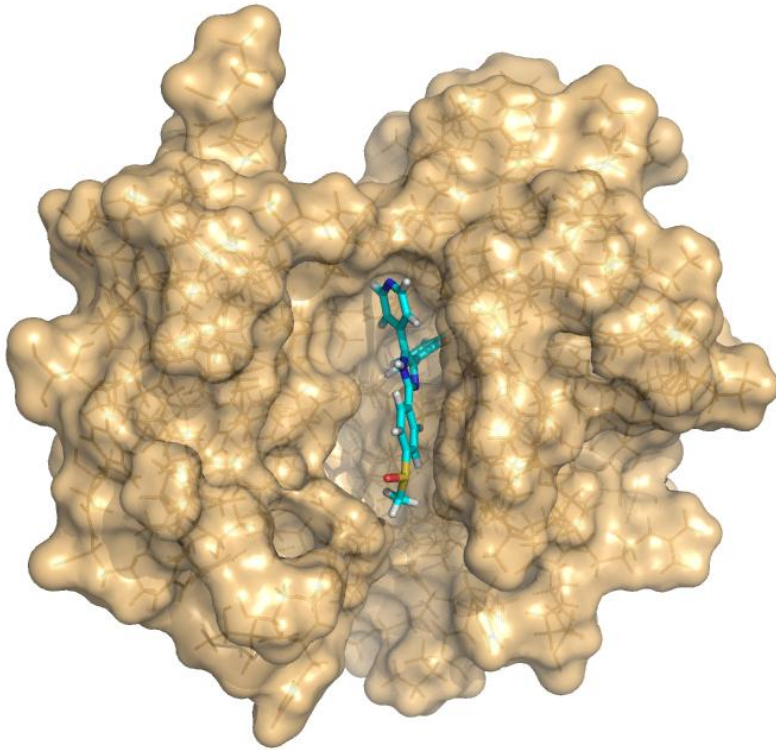


Future Work

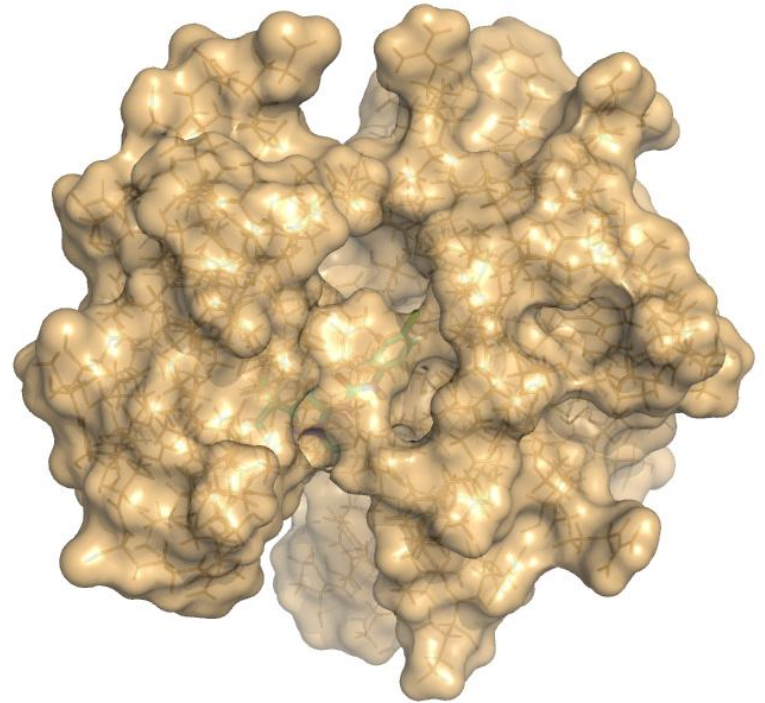




Introduction



1a9u
DFG in



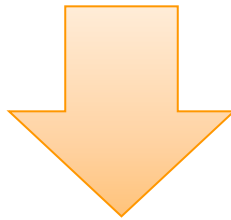
1kv1
DFG out

***induced fit* effect in p38 MAP kinase**



Introduction

- generating **meaningful** protein conformations during docking is a difficult task
- large-scale protein rearrangements can only hardly be modelled



- *ensemble*-based approaches only consider a set of discrete protein conformations

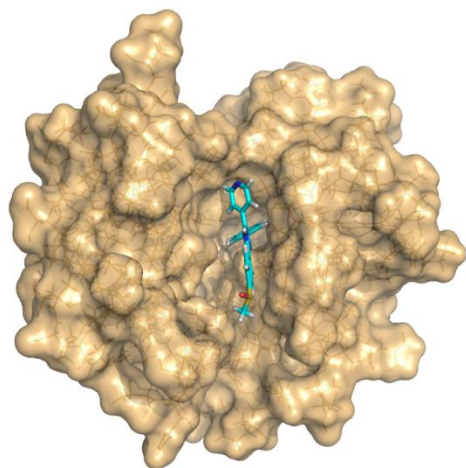


Introduction – Ensemble Docking Literature

- Claussen et al. (FlexE) *JMolBiol* 308(2), 2001, pp 377-395
- Huang et al. (DOCK) *Proteins* 66(2), 2006, pp 399-421
- Rao et al. (Glide) *JCAMD* 22(9), 2008, pp 621-627
- Bottegoni et al. (ICM) *JMedChem* 52(2), 2009, pp 397-406
- Rueda et al. (ICM) *JChemInfModel* 50(1), 2010, pp 186-193
- Craig et al. (Glide) *JChemInfModel* 50(4), 2010, pp 511-524

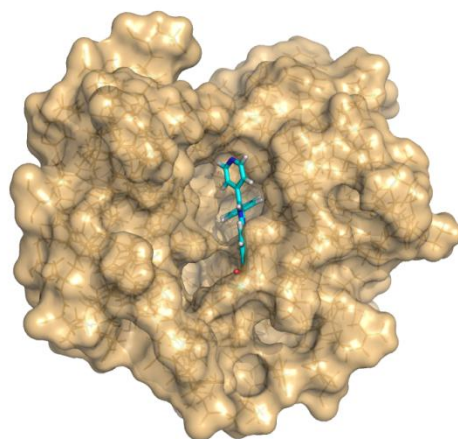


Multiple Protein Structure Docking



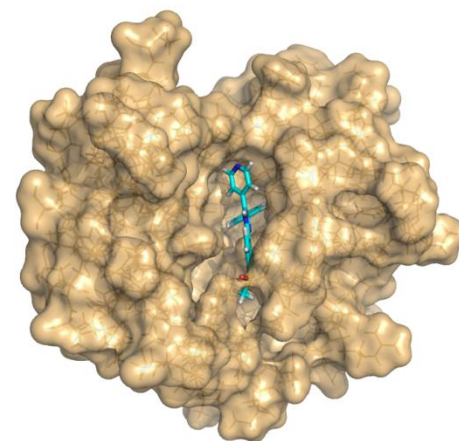
1a9u

score 74



1bl6

60



1bl7

69

- ligands get different scores in different protein structures
 - scores determine ranking performance in *virtual screening*
- ➔ **which protein structure(s) to use for *virtual screening*?**

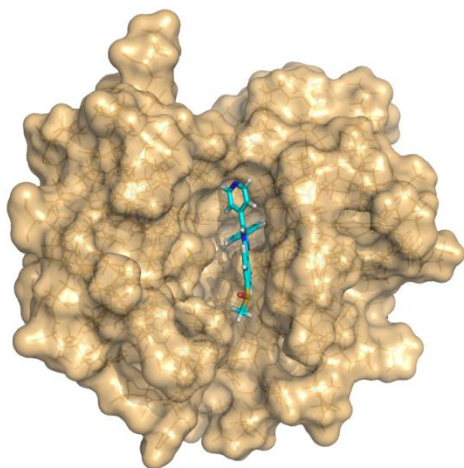


Sensitivity of Virtual Screening Results

target	# proteins	AUC			EF (all act.)			EF 10%		
		min	max	delta	min	max	delta	min	max	delta
acetylcholine esterase	21	0.41	0.70	0.29	0.0	8.8	8.8	0.4	4.6	4.2
aldose reductase	32	0.40	0.64	0.24	4.1	15.1	11.0	2.3	5.0	2.7
cyclin-dependent kinase 2	72	0.42	0.71	0.29	1.4	14.4	13.0	0.8	5.2	4.4
dihydrofolate reductase	9	0.56	0.83	0.27	2.3	9.3	7.0	1.7	4.9	3.2
factor Xa	34	0.67	0.88	0.21	4.7	16.7	12.0	3.0	7.5	4.5
heat shock protein 90	30	0.68	0.88	0.20	1.5	11.8	10.3	2.1	7.1	5.0
neuraminidase	13	0.77	0.85	0.08	2.2	11.8	9.6	2.4	5.5	3.1
p38 MAP kinase	31	0.42	0.74	0.32	0.9	10.6	9.7	0.5	3.9	3.4
phosphodiesterase 5A	5	0.67	0.74	0.07	7.9	10.7	2.9	3.7	5.1	1.4

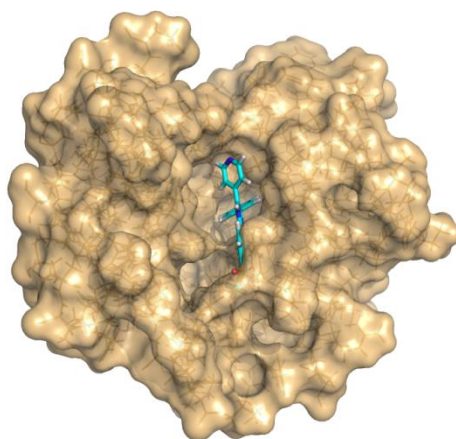


Simulated Ensemble Docking



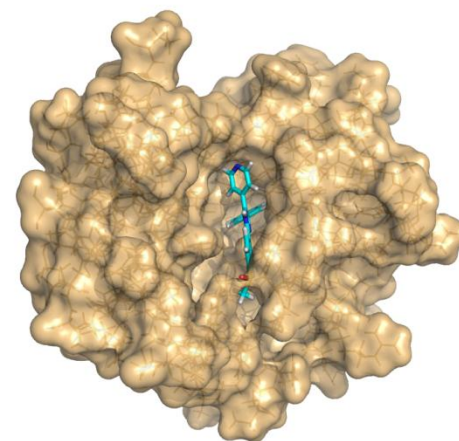
1a9u

score **74**



1bl6

score **60**



1bl7

score **69**

- for each ligand pick the best-scoring protein structure
- ➔ simulates a **perfect** ensemble docking approach



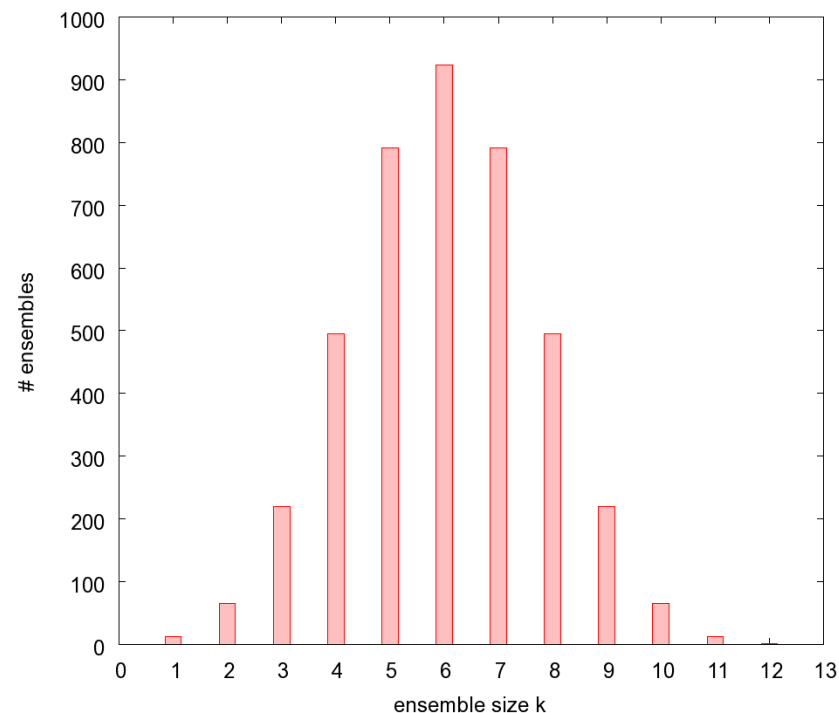
Simulated Ensemble Docking

- perform docking / screening for n protein structures

$2^n - 1$ different ensembles (size 1 or greater)

$\binom{n}{k}$ ensembles of size k

- example $n = 12$
 - 4095 different ensembles
- simulate docking into all $2^n - 1$ ensembles by post-processing n docking results





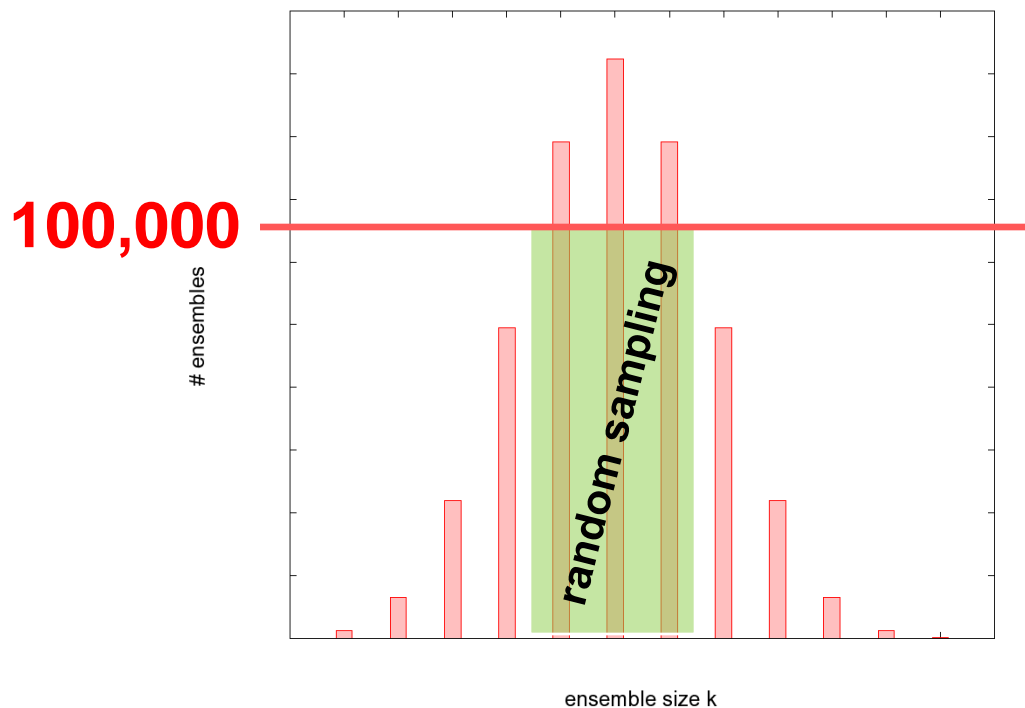
Simulated Ensemble Docking

- exhaustive enumeration of all ensembles infeasible for large n

cdk2: 72 structures

$$\binom{72}{36}$$

442 quintillion ensembles





Targets

target	PDB	# holo proteins ^a	# actives	# inactives
acetylcholine esterase	1gpk	21	105	3623
aldose reductase	1t40	32	26	902
cyclin dependent kinase 2	1ke5	72	50	1661
dihydrofolate reductase	1s3v	9	201	6496
factor Xa	1lpz	34	141	4535
heat shock protein 90	2bsm	30	24	823
neuraminidase	1l7f	13	49	1726
p38 MAP kinase	1ywr	31	240	8203
phosphodiesterase 5A	1xoz	5	51	1808

curated DUD^b set

- pose prediction results averaged over 20 independent runs
- virtual screening: single run with *autoscale* = 1.0

^a Verdonk et al. *JCIM*, 48, 2214-2225 (2008)

^b Huang et al. *JMedChem*, 49, 6789-6801 (2006)

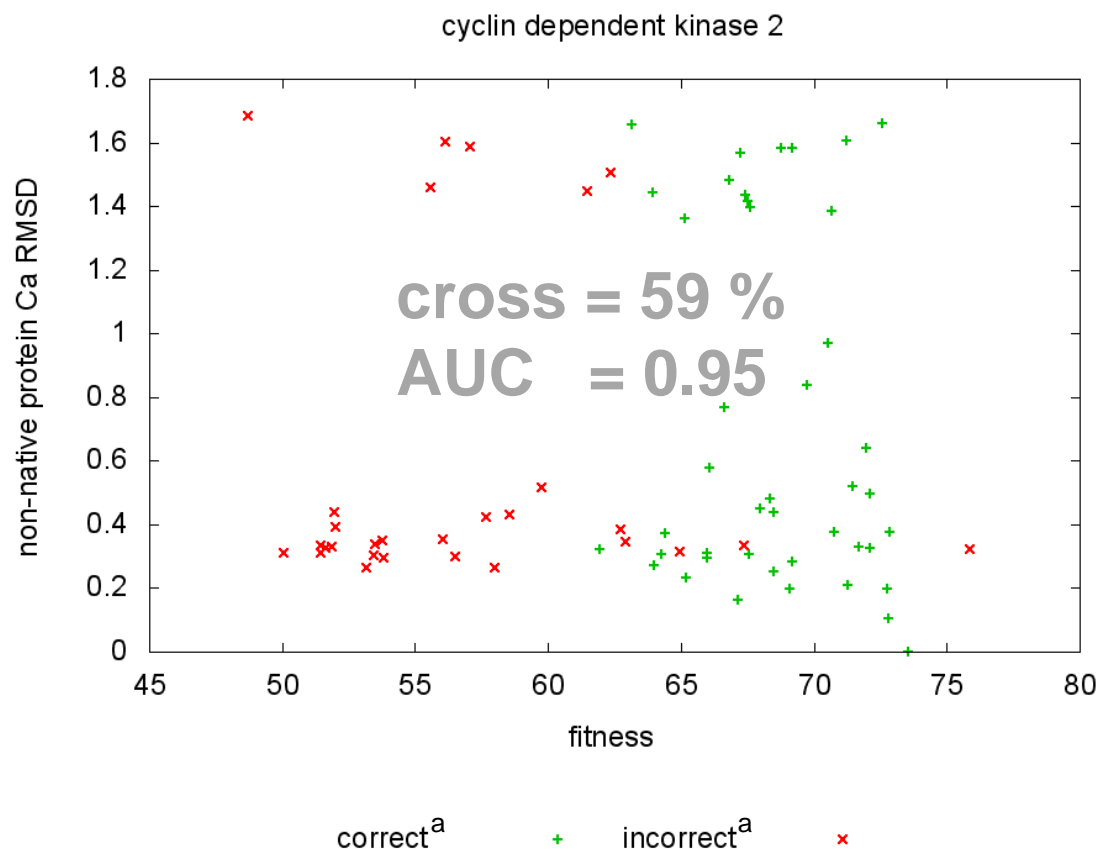


Assessing Ensemble Docking Performance

- a good ensemble scoring function should
 - exhibit a good cross-docking performance
 - discriminate well between correctly and incorrectly docked solutions
- *cross-docking performance*: number of correctly predicted poses in non-native protein structures
- *discrimination performance*: calculate AUC for discrimination between correctly and incorrectly docked solutions (ranked by fitness)



Assessing Ensemble Docking Performance

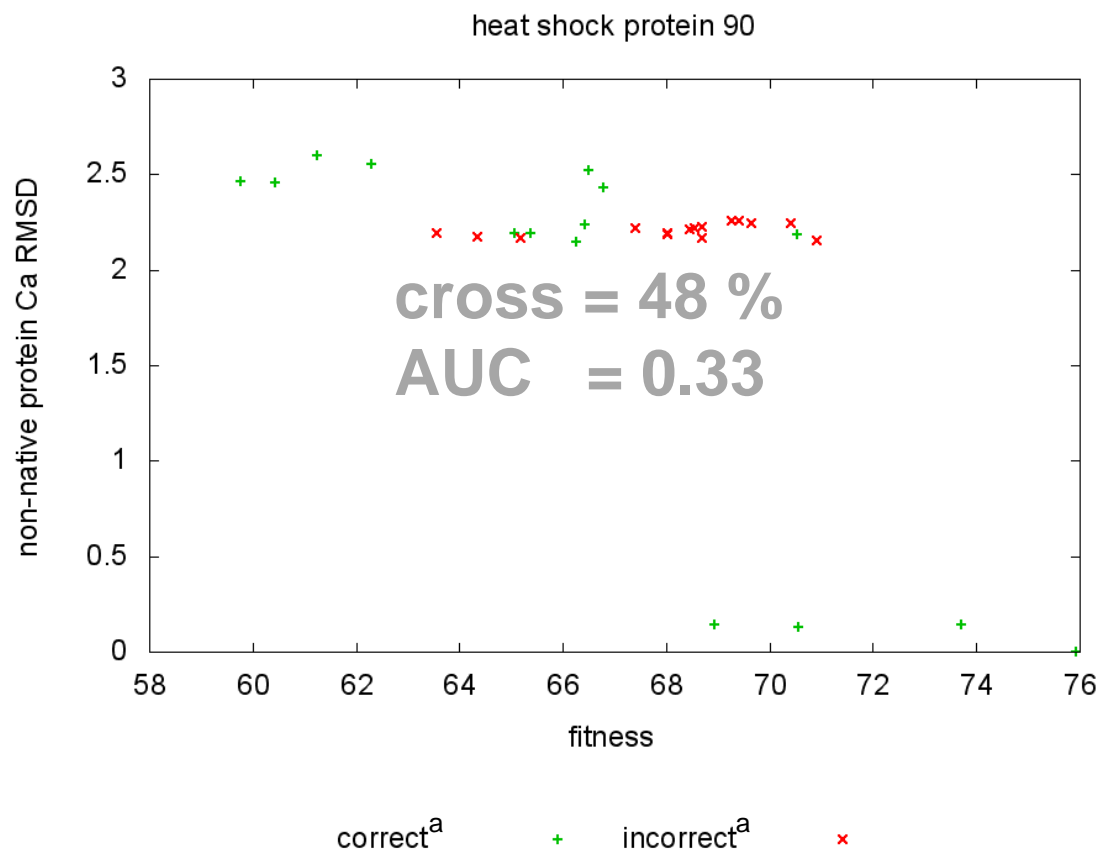


each data point represents the docking result for one protein structure (72 for CDK2)

^a correct if top-ranked solution rmsd < 2 Å, incorrect otherwise



Assessing Ensemble Docking Performance



each data point represents the docking result for one protein structure (30 for HSP90)

^a correct if top-ranked solution rmsd < 2 Å, incorrect otherwise



Ensemble Docking – Pose Prediction

	AUC ^a	# correct	# proteins	% correct	rank ^b	improvement ^c
CHEMPLP						
acetylcholine esterase	0.55	10	20	50	1	●
aldose reductase	0.83	15	31	48	1	●
cyclin dependent kinase 2	0.95	42	71	59	2	●
dihydrofolate reductase	1.00	7	8	88	1	●
factor Xa	0.61	16	33	48	1	●
heat shock protein 90	0.33	14	29	48	1	●
neuraminidase	1.00	12	12	100	1	●
p38 MAP kinase	0.65	3	30	10	5	●
phosphodiesterase 5	1.00	2	4	50	1	●
avg.	0.77			56		
GOLDScore						
acetylcholine esterase	0.22	2	20	10	15	●
aldose reductase	0.89	11	31	35	2	●
cyclin dependent kinase 2	0.75	36	71	51	1	●
dihydrofolate reductase	0.58	6	8	75	1	●
factor Xa	0.66	26	33	79	1	●
heat shock protein 90	0.77	26	29	90	1	●
neuraminidase	1.00	12	12	100	1	●
p38 MAP kinase	0.51	3	30	10	2	●
phosphodiesterase 5	1.00	1	4	25	1	●
avg.	0.71			53		

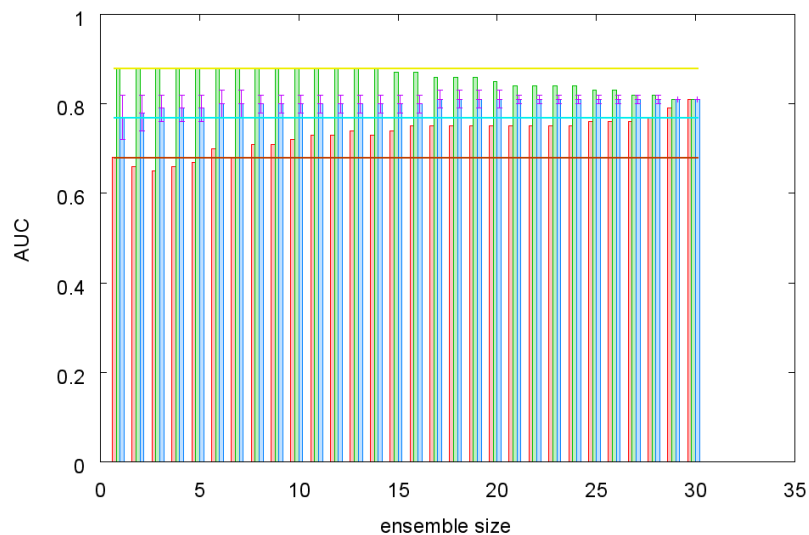
^a discrimination between correctly and incorrectly predicted solutions

^b rank of first correctly docked solution

^c ● if ensemble docking performs better than the average single protein structure, ● otherwise

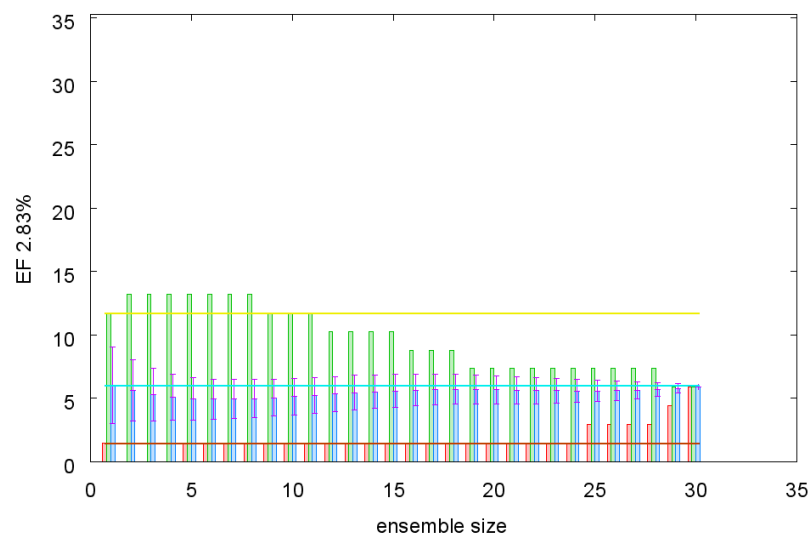


Virtual Screening – Heat Shock Protein 90



worst ensemble best ensemble ensemble avg. ensemble avg.

medium improvement

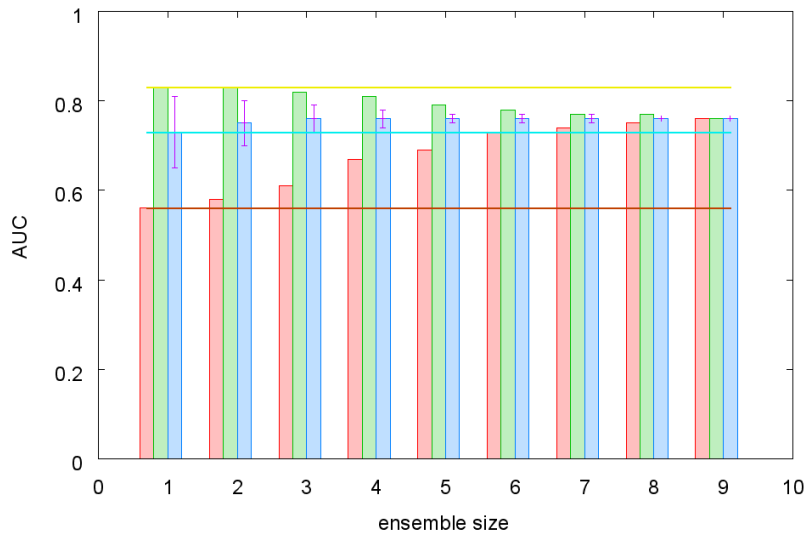


worst ensemble best ensemble ensemble avg. ensemble avg.

no improvement

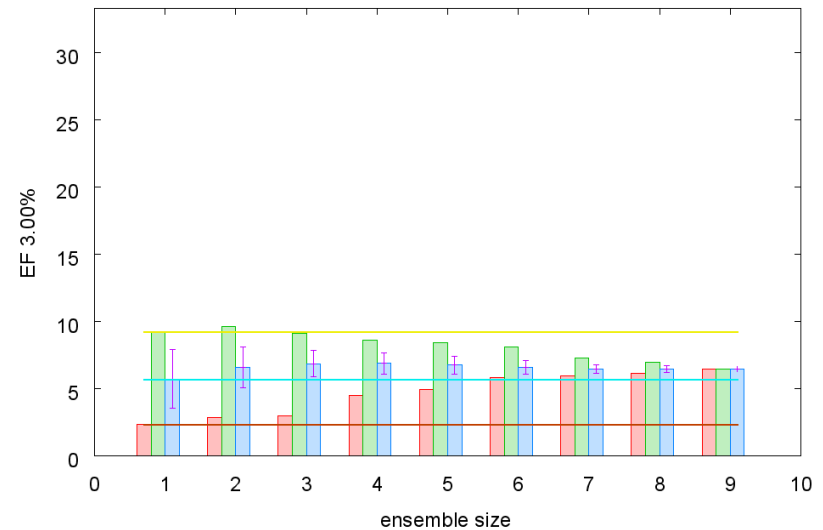


Virtual Screening – Dihydrofolate Reductase



worst ensemble best ensemble ensemble avg.

medium improvement



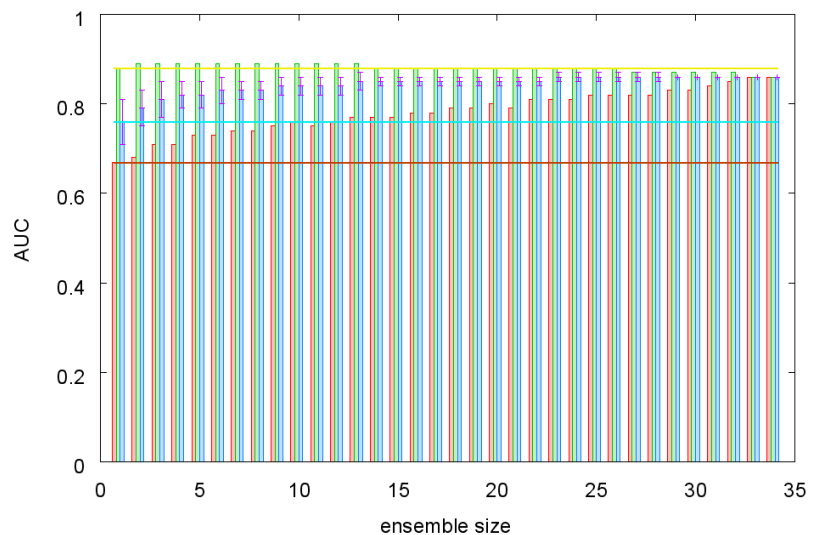
worst ensemble best ensemble ensemble avg.

medium improvement



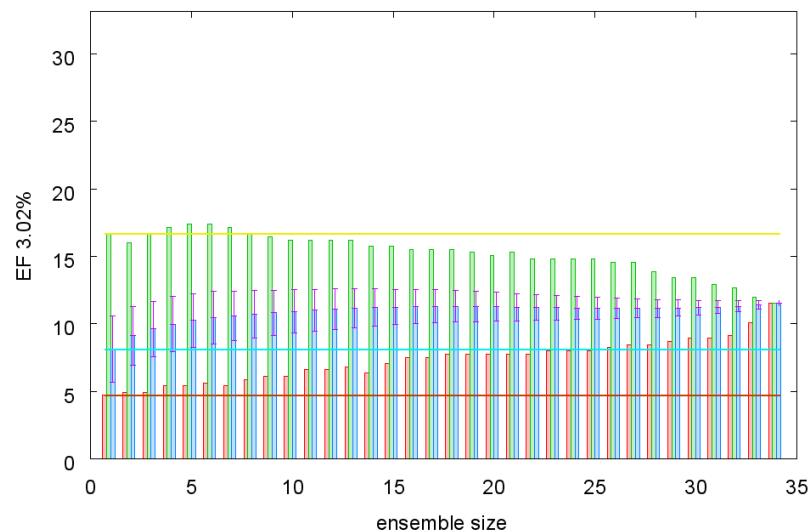


Virtual Screening – Factor Xa



worst ensemble best ensemble ensemble avg.

major improvement



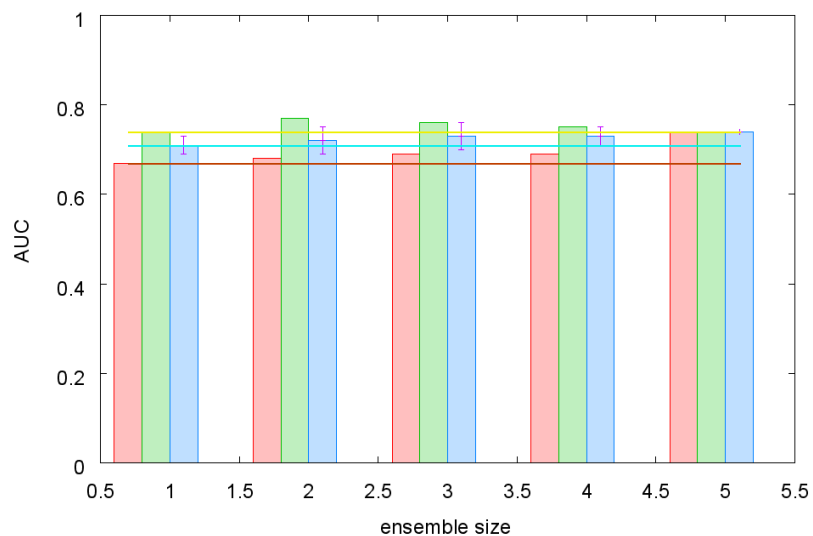
worst ensemble best ensemble ensemble avg.

major improvement



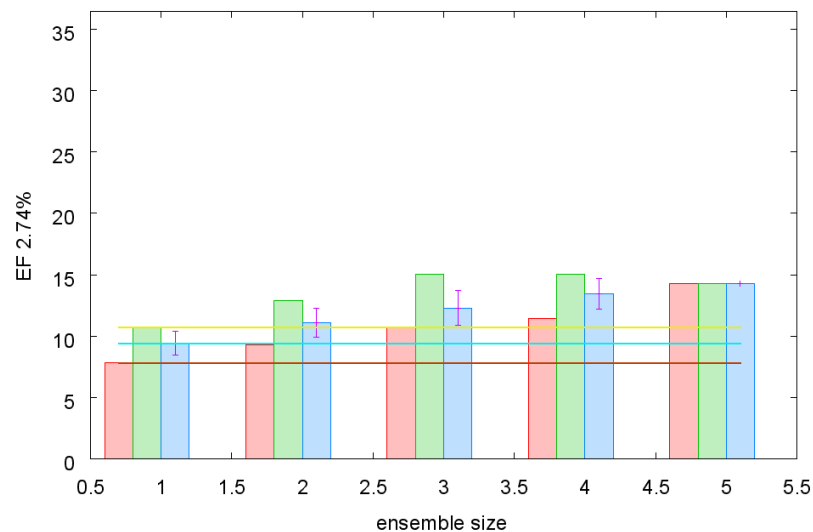


Virtual Screening – Phosphodiesterase 5A



worst ensemble best ensemble ensemble avg.

medium improvement



worst ensemble best ensemble ensemble avg.

major improvement





Improving Upon the Best Single Protein Structure

protein 1

L1 70

D 50

L2 40

protein 2

L2 60

D 45

L1 30

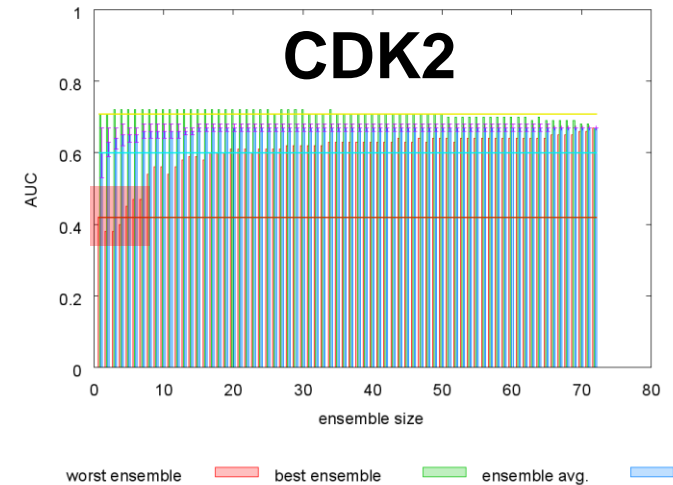
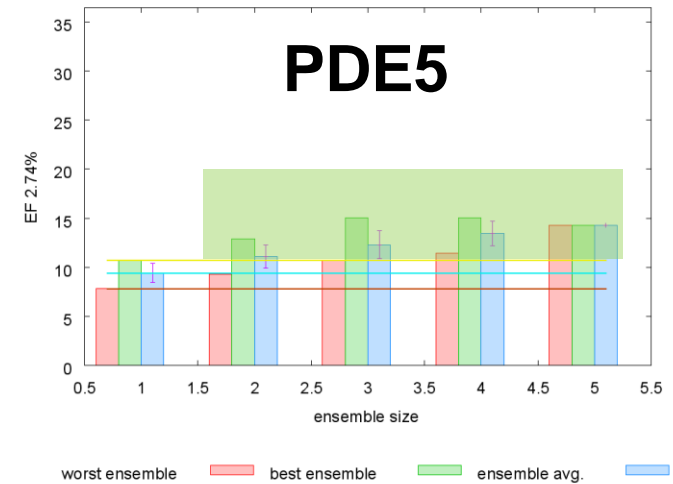
ensemble

L1 70

L2 60

D 50

... but also





Virtual Screening Results

target	AUC	EF (all act.)	EF 10%
acetylcholine esterase	medium improvement	medium improvement	no improvement
aldose reductase	no improvement	no improvement	no improvement
cyclin dependent kinase 2	major improvement	medium improvement	major improvement
dihydrofolate reductase	medium improvement	medium improvement	medium improvement
factor Xa	major improvement	major improvement	major improvement
heat shock protein 90	medium improvement	no improvement	no improvement
neuraminidase	medium improvement	medium improvement	medium improvement
p38 MAP kinase	no improvement	major improvement	medium improvement
phosphodiesterase 5A	medium improvement	major improvement	medium improvement

ensemble performance compared to average performance of single protein structures

no improvement 

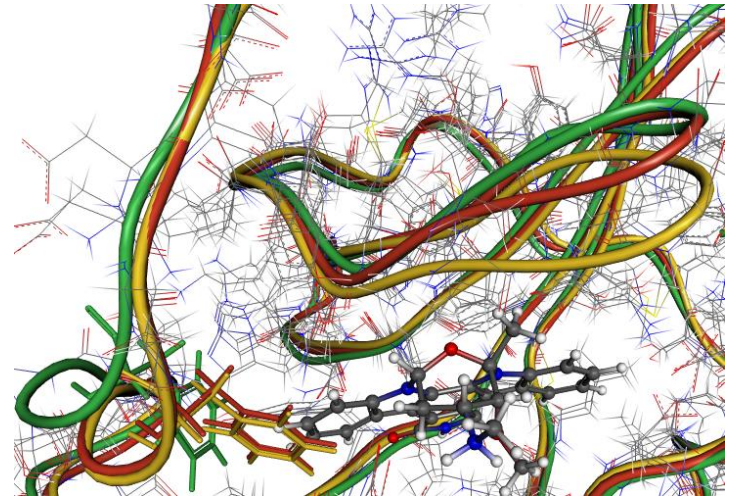
medium improvement 

major improvement 



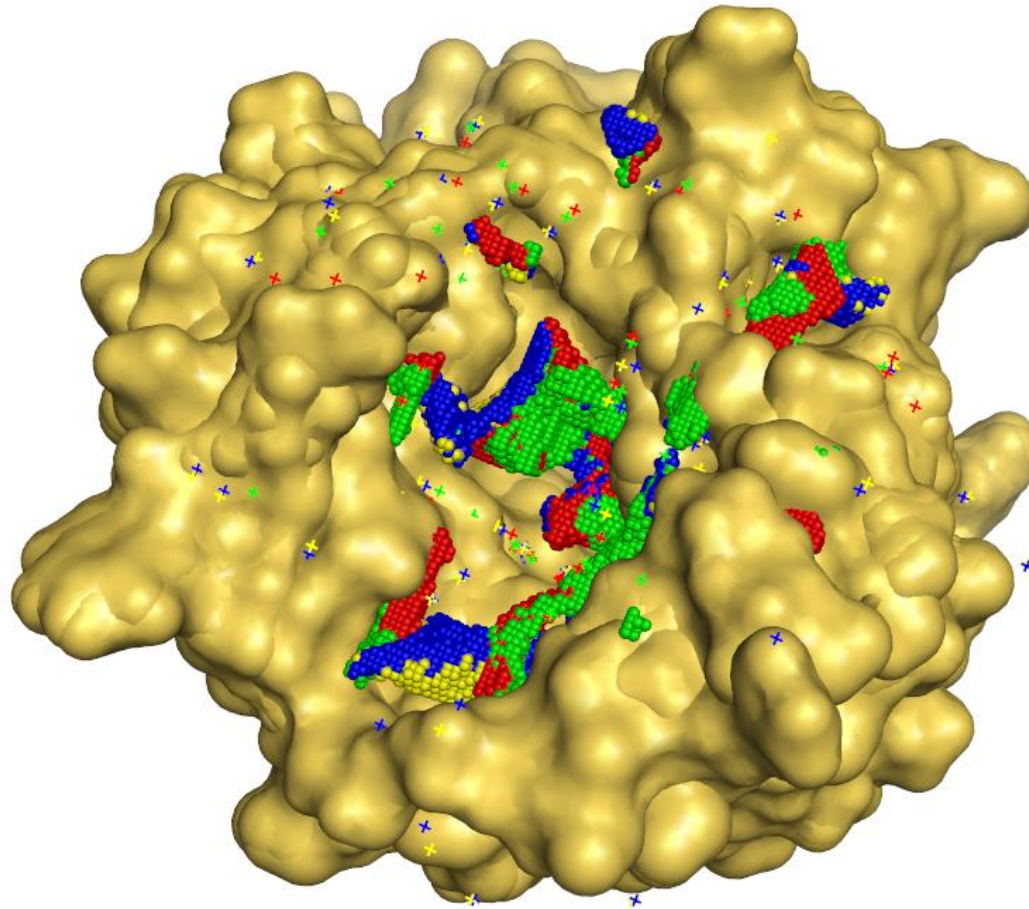
GOLD ensemble

- results so far based on sequential docking
- modified *genetic algorithm* to treat protein ensembles
- requires a superimposed set of protein structures
- searches all protein conformations **concurrently**



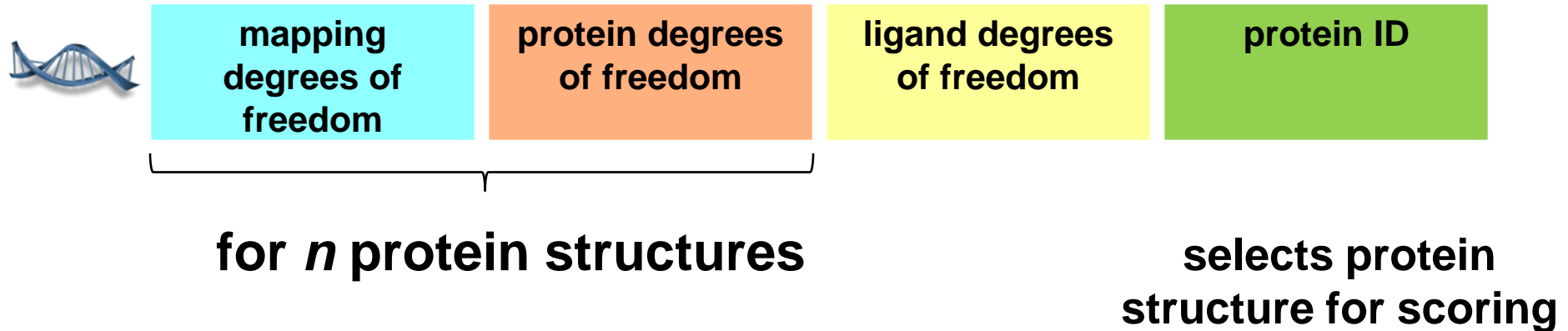


GOLD ensemble - Fitting Points





GOLD ensemble – Genetic Algorithm



- **ID mode:** change the protein during the GA-search by *mutation*
- **island mode:** search all protein structures concurrently



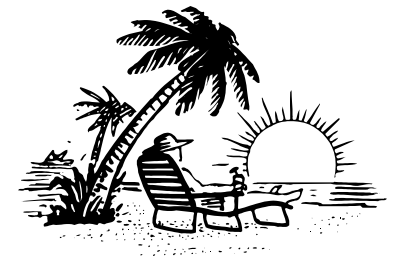
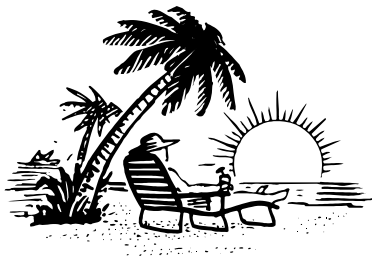
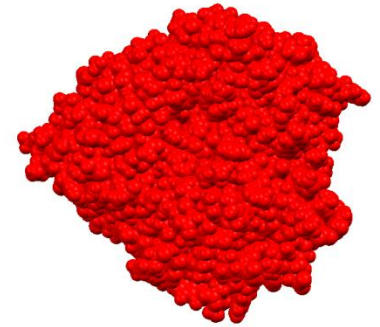
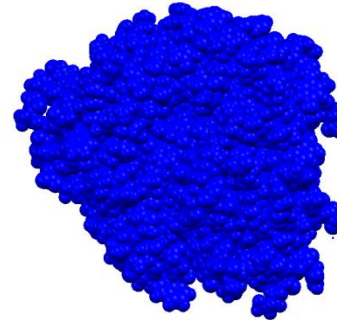
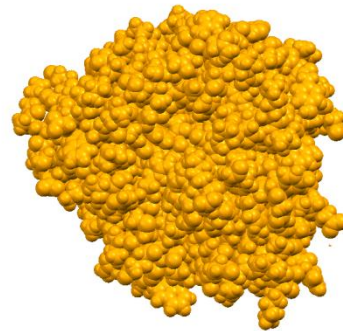
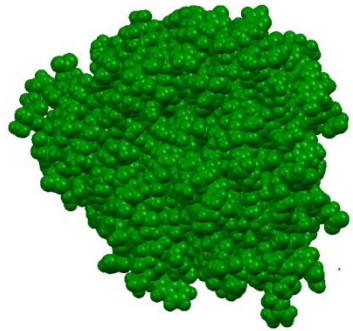
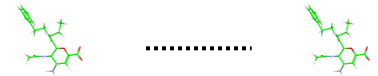
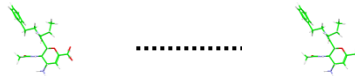
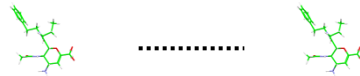
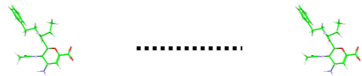
GOLD ensemble – Island Mode

 protein ID: 1

 protein ID: 2

 protein ID: 3

 protein ID: 4



island 1

island 2

island 3

island 4

up to four times faster than sequential docking depending on the number of proteins and ligand size



Conclusions

- ensemble docking can improve hit rates
 - increases worst and average case performance in many cases
 - performs sometimes as good as the best single protein structures
- trends suggest to use multiple protein structures in an ensemble protocol (minimise the risk of picking a bad one)
- GOLD has been extended to search ensembles time-efficiently



Future Work

- analysis of *chemotype* enrichment
- investigation of protein energies
- combine ensemble docking with flexible side-chains and switching of explicit water molecules

