

Rosetta-based modeling of peptide-MHC I complexes

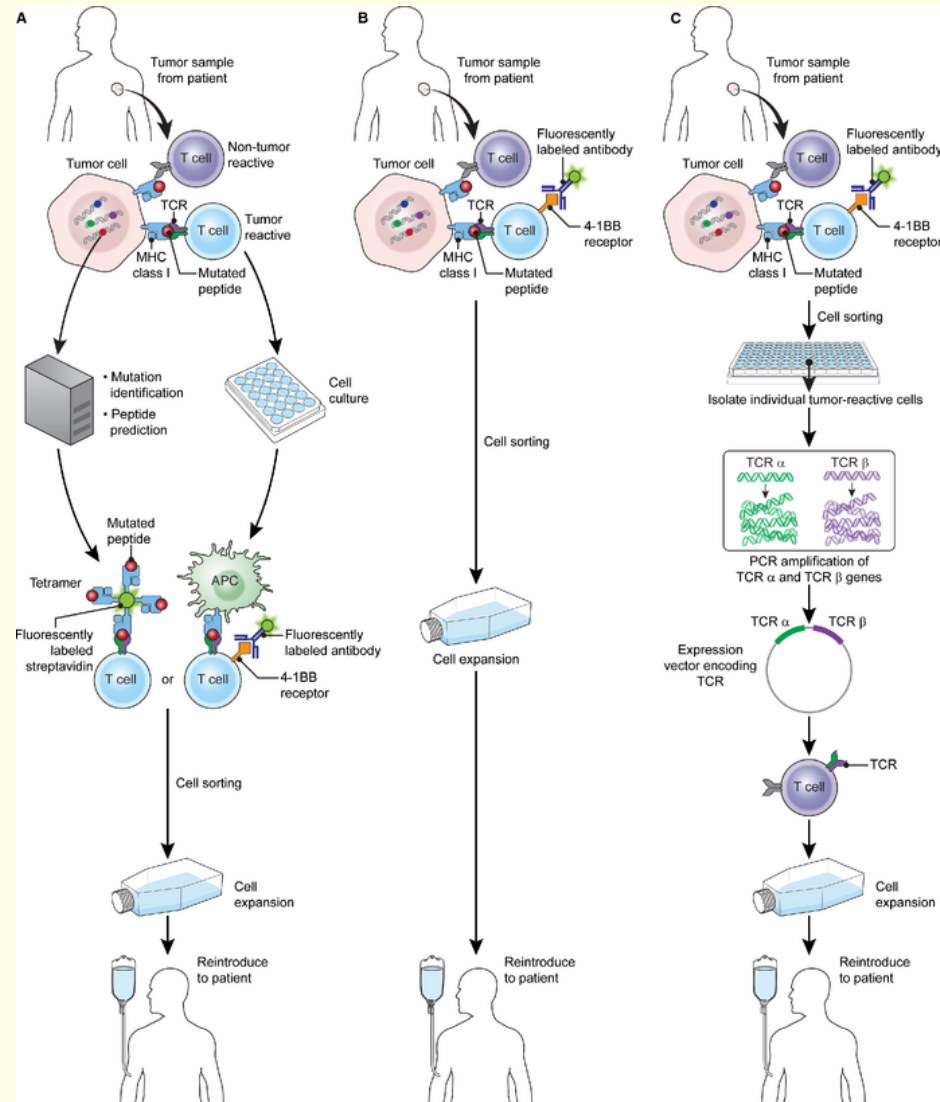
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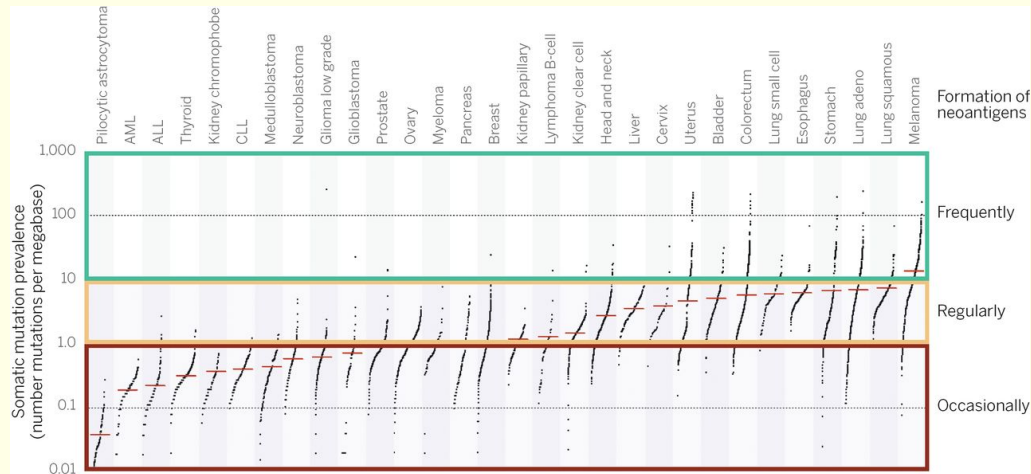
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Adoptive T-cell therapy



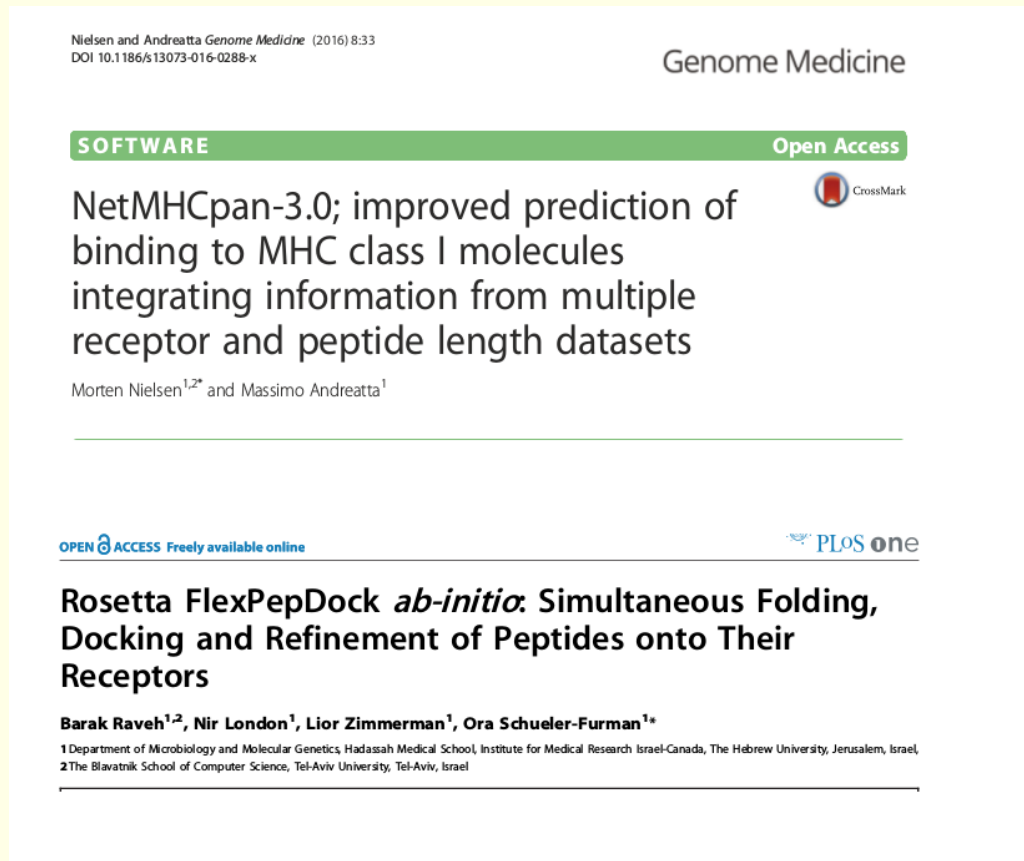
Neoantigens in cancer immunotherapy



Precision immuno pipeline (in brief), Arjun Rao

- Matched tumor/normal sequencing : exome, RNASeq
- Haplotyping (phlat)
- Variant calling : mutations/indels (mutect,radia,somaticseq,..)
- Map to AA changes and epitopes
- MHC-binding predictions (netMHCpan, Rosetta?)

Knowledge-based vs. knowledge-based:

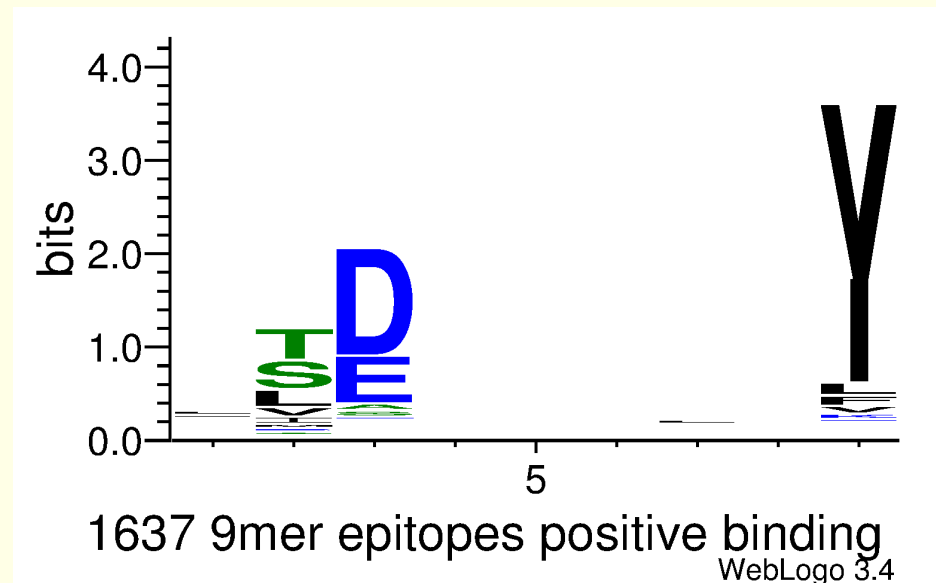


- NetMHCpan : neural-network classifier trained on 186,684 peptide-MHC affinity measurements from IEDB
- FlexPepDock : MCMC search over fragment database built from current* PDB database; detailed/realistic all-atom energy function

Test case : allele HLA-A*01:01

P1	CTELKLNDY	4NQX	flu (H7N9)
P2	CTELKSNDY	4NQV	flu (H7N9)
P3	EVDPIGHLY	5BRZ	MAGE-A3
P4	ESDPIVAQY	5BS0	Titin
P5	EADPTGHSY	3BO8	MAGE-A1
P6	EADPTGHSY	1W72	MAGE-A1

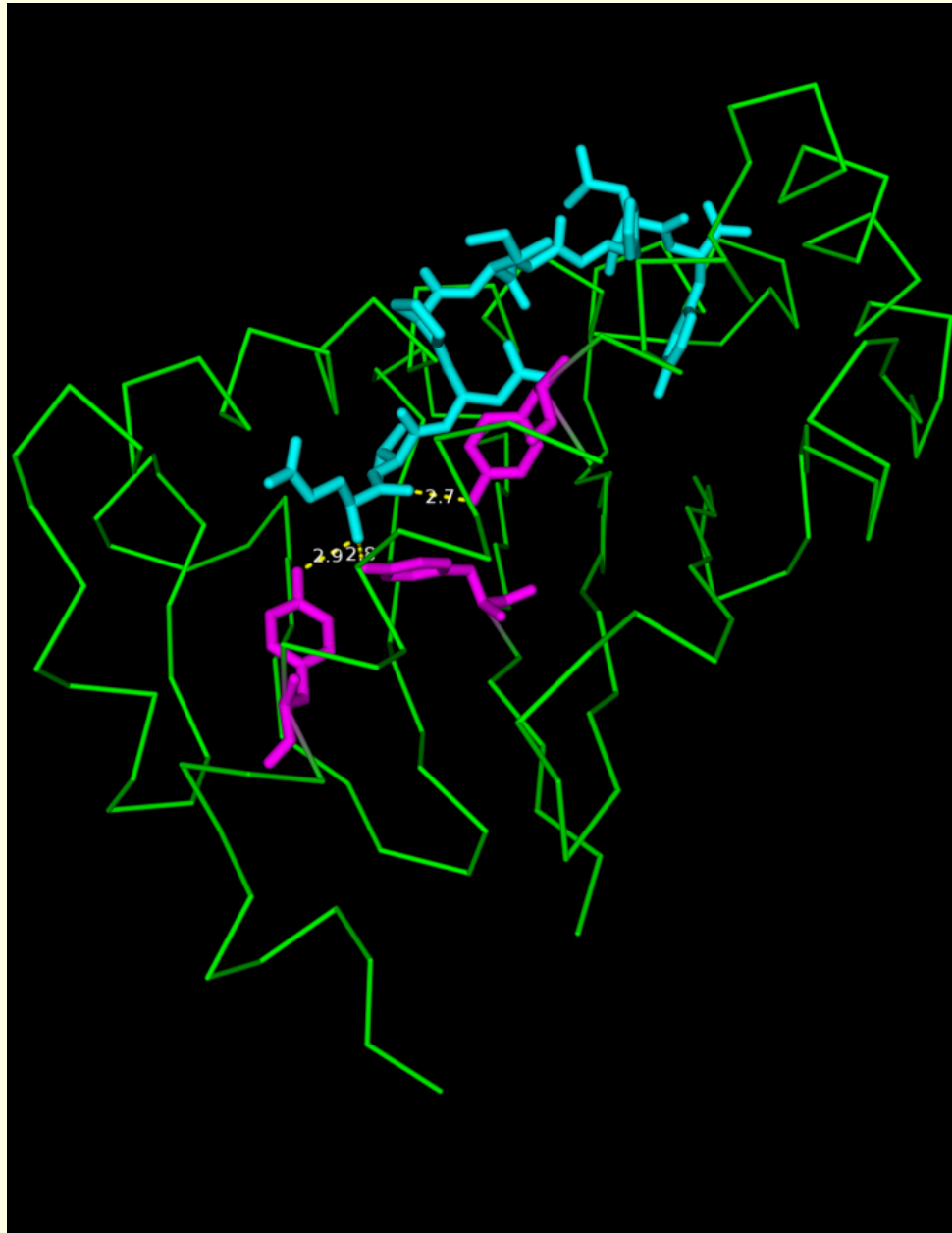
IEDB binding data:



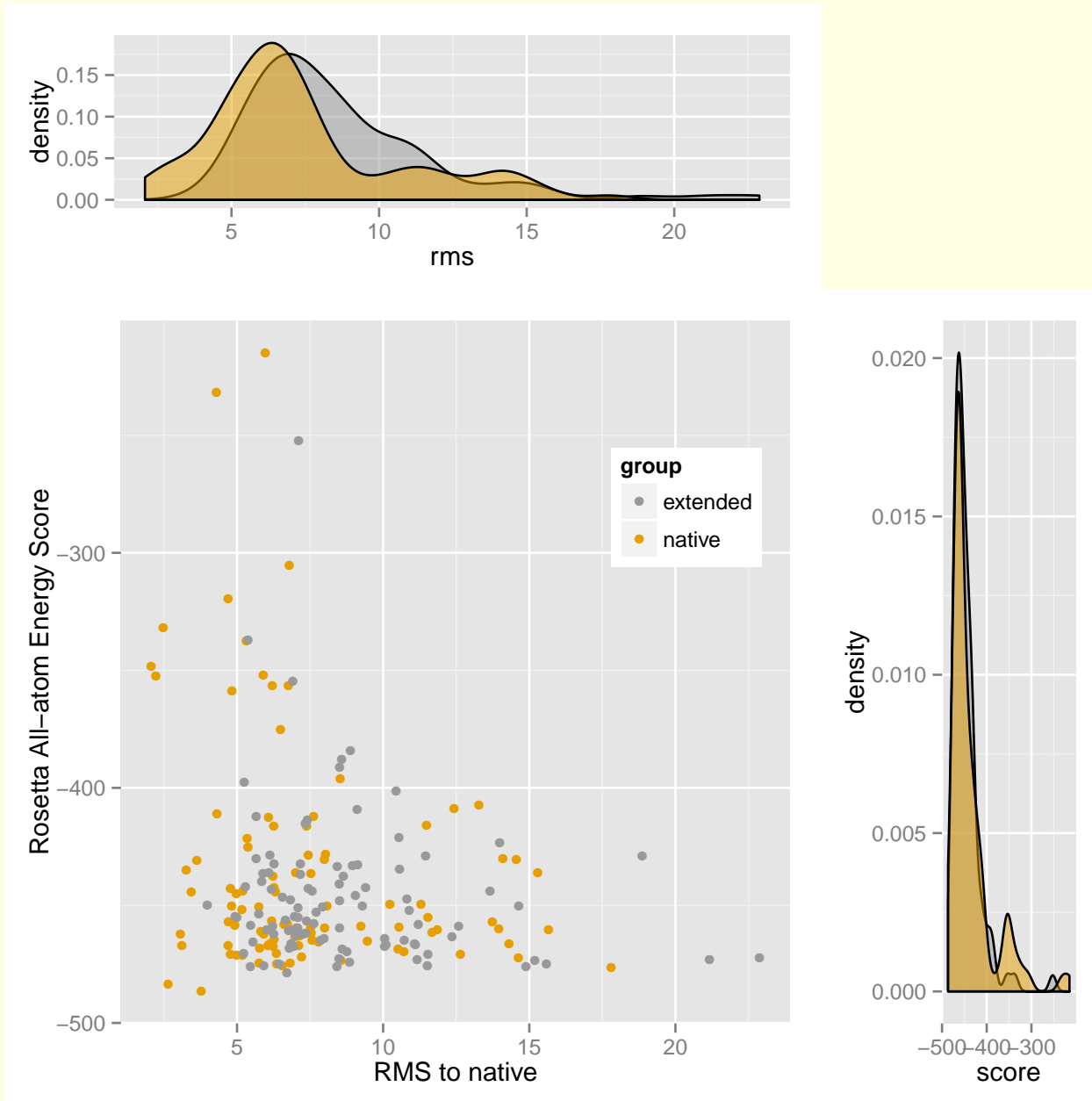
Overview : peptide-MHC-I binding in 5BRZ



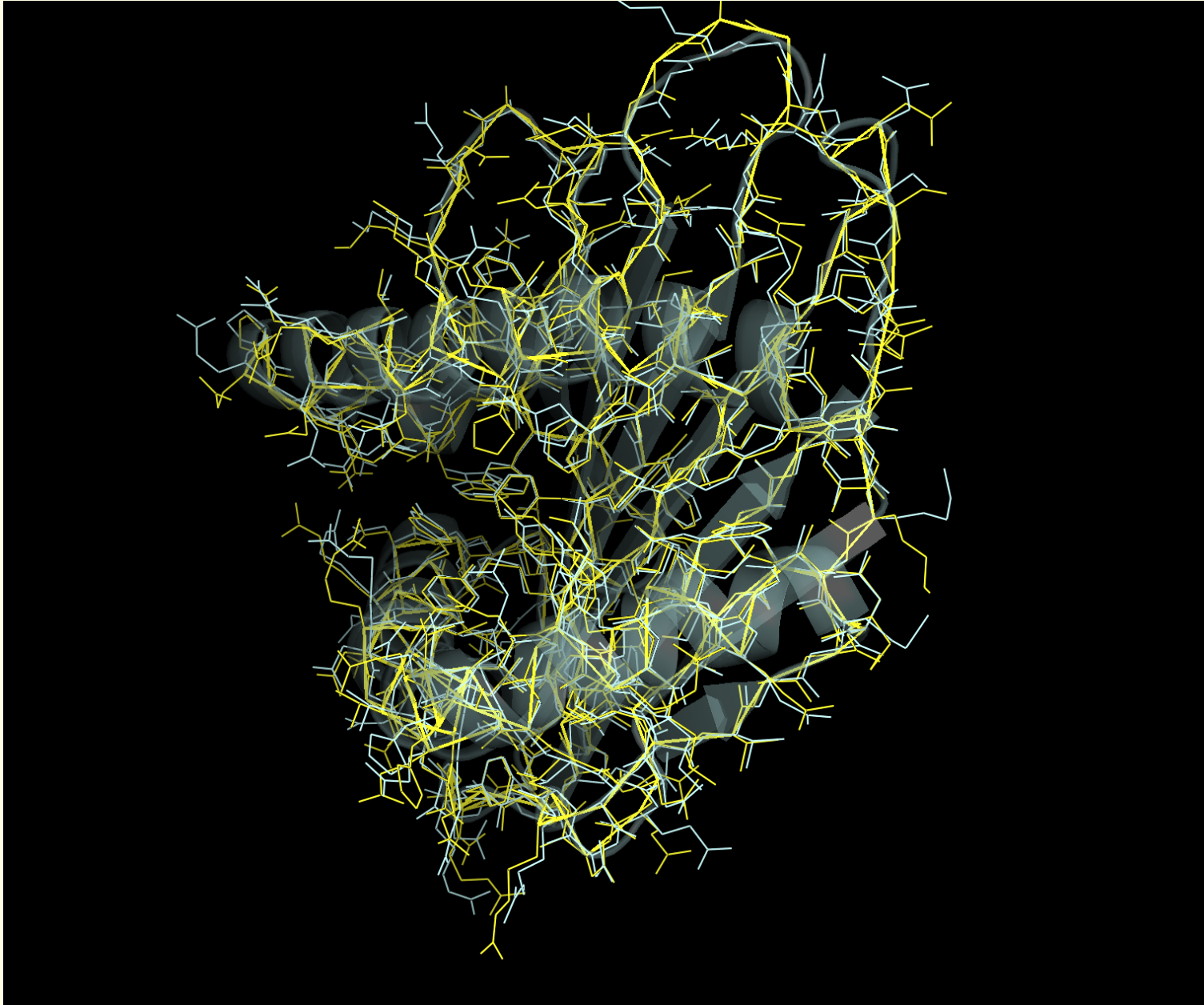
Sequence-independent peptide-MHC-I binding in 5BRZ



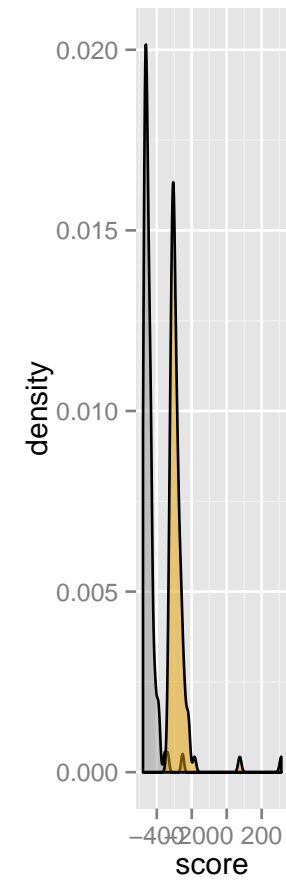
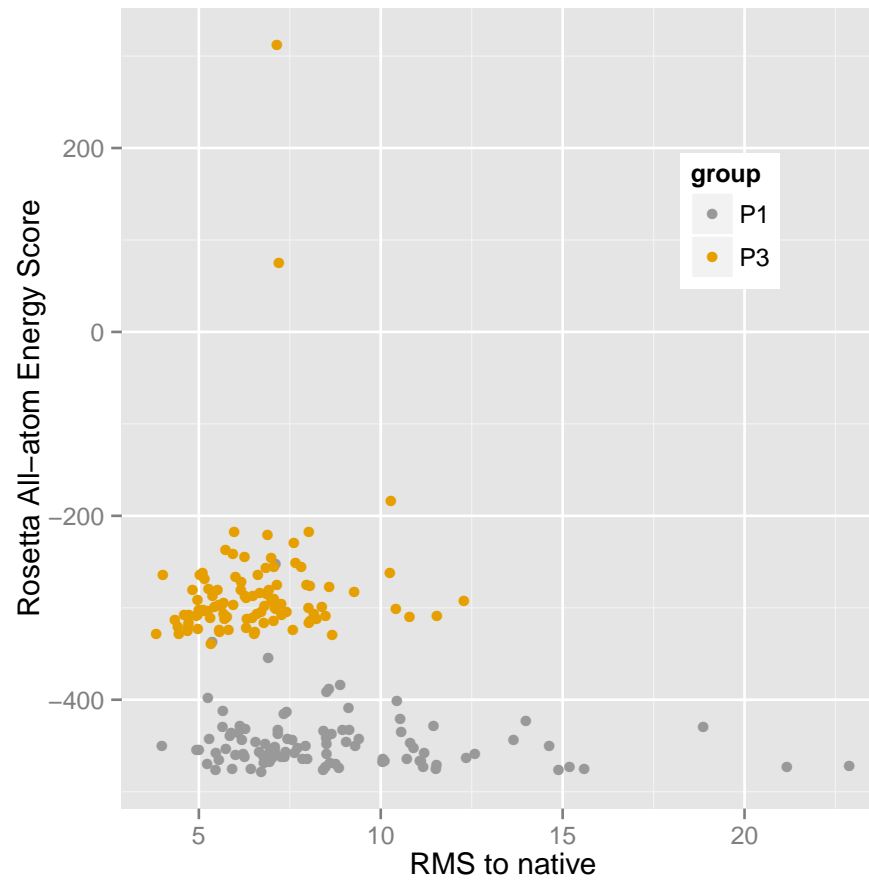
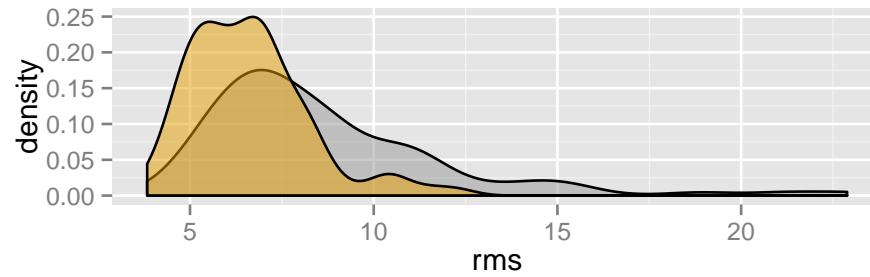
Peptide P1 : “near” native vs. extended, 100 decoys



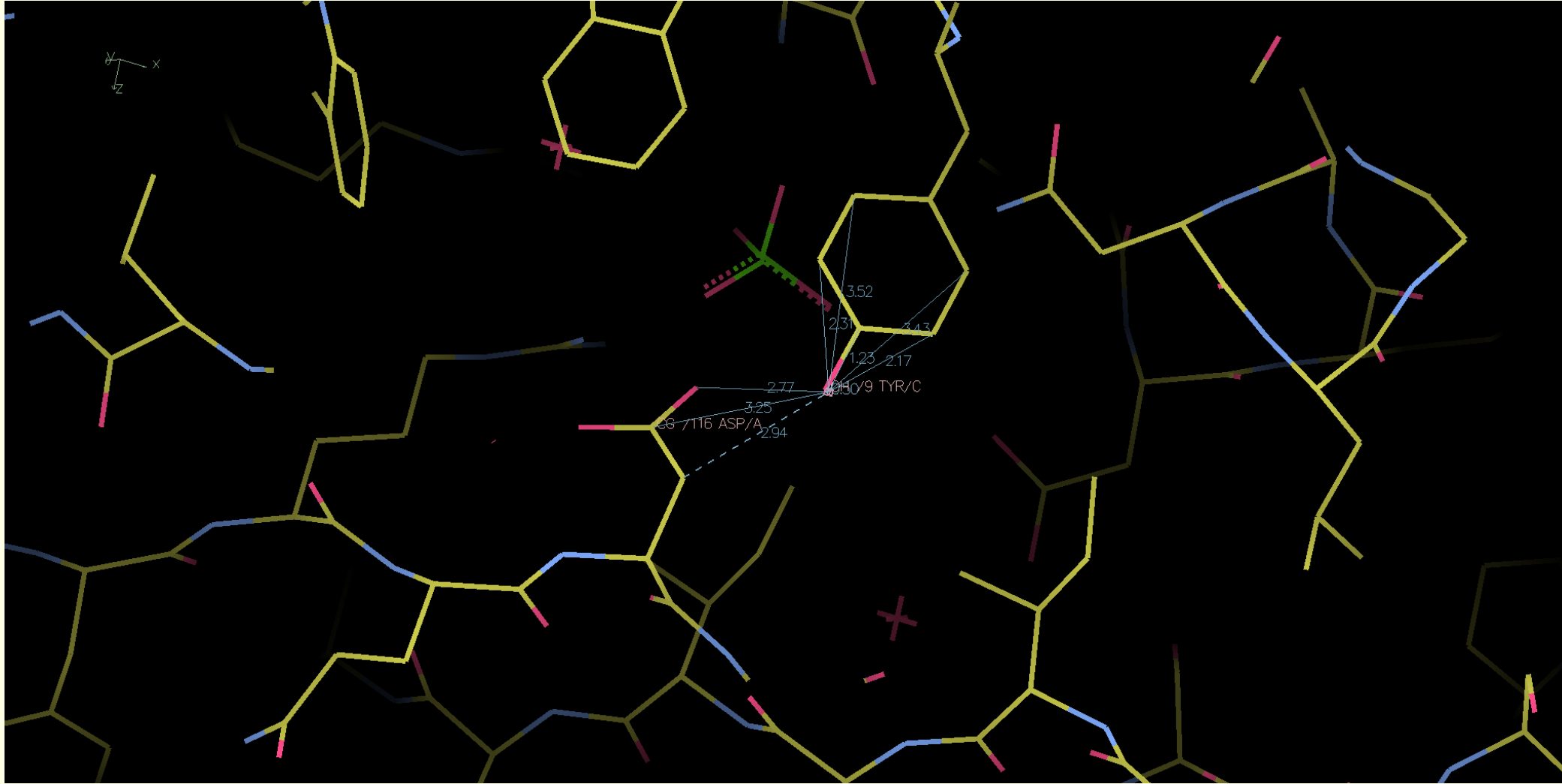
Superimposed MHC receptors : 4NQX and 5BRZ



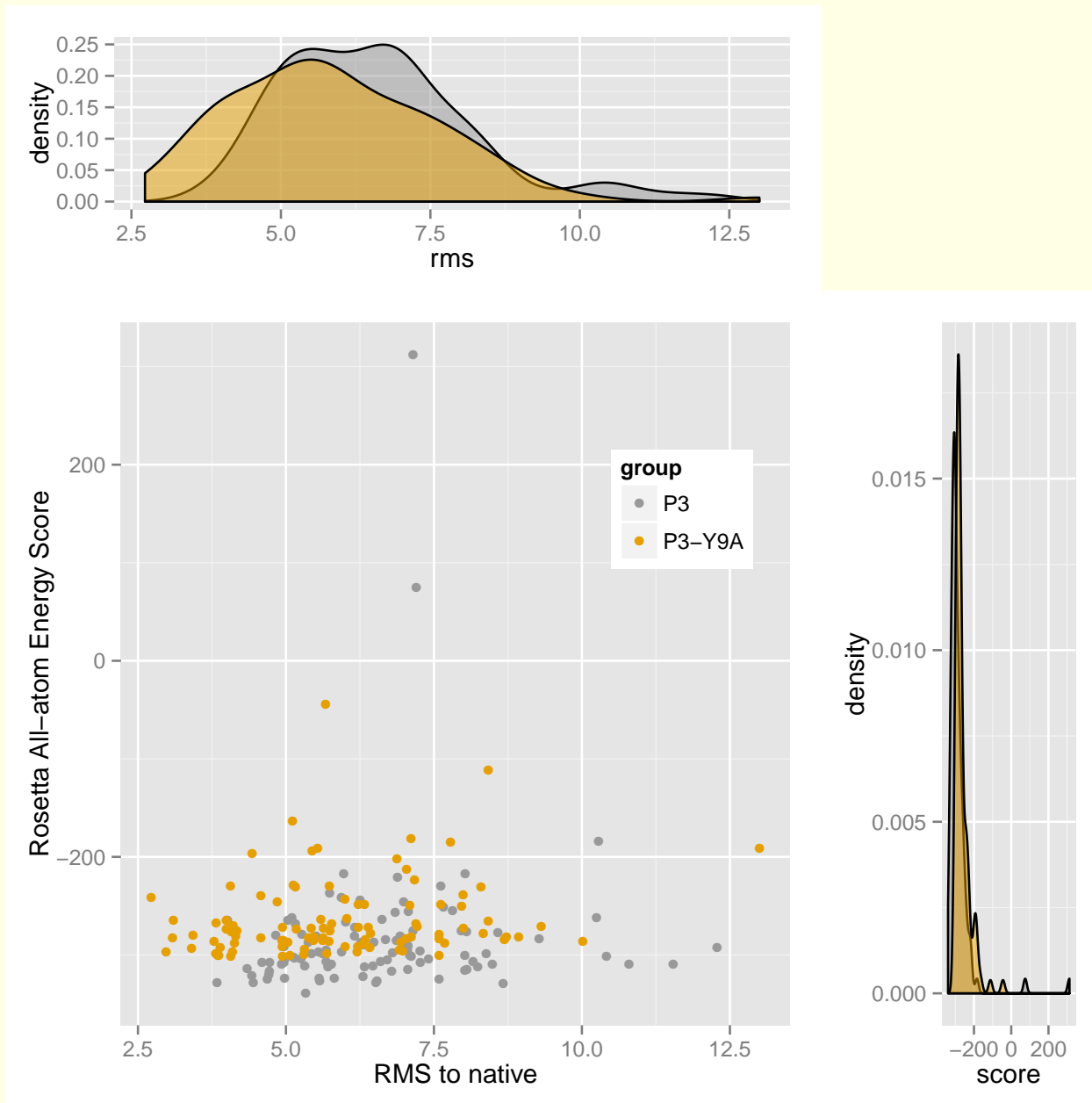
Peptides P1 and P3, extended, 100 decoys



5BRZ : Contacts to C-terminal Tyr 9



Native and Modified P3 (Y9A) , extended, 100 decoys



Next steps:

- Scale up to productions runs.
- Investigate existing FlexPepDock alternative score terms.
- Correlate IEDB training database with FlexPepDock score terms.
- Model water binding?