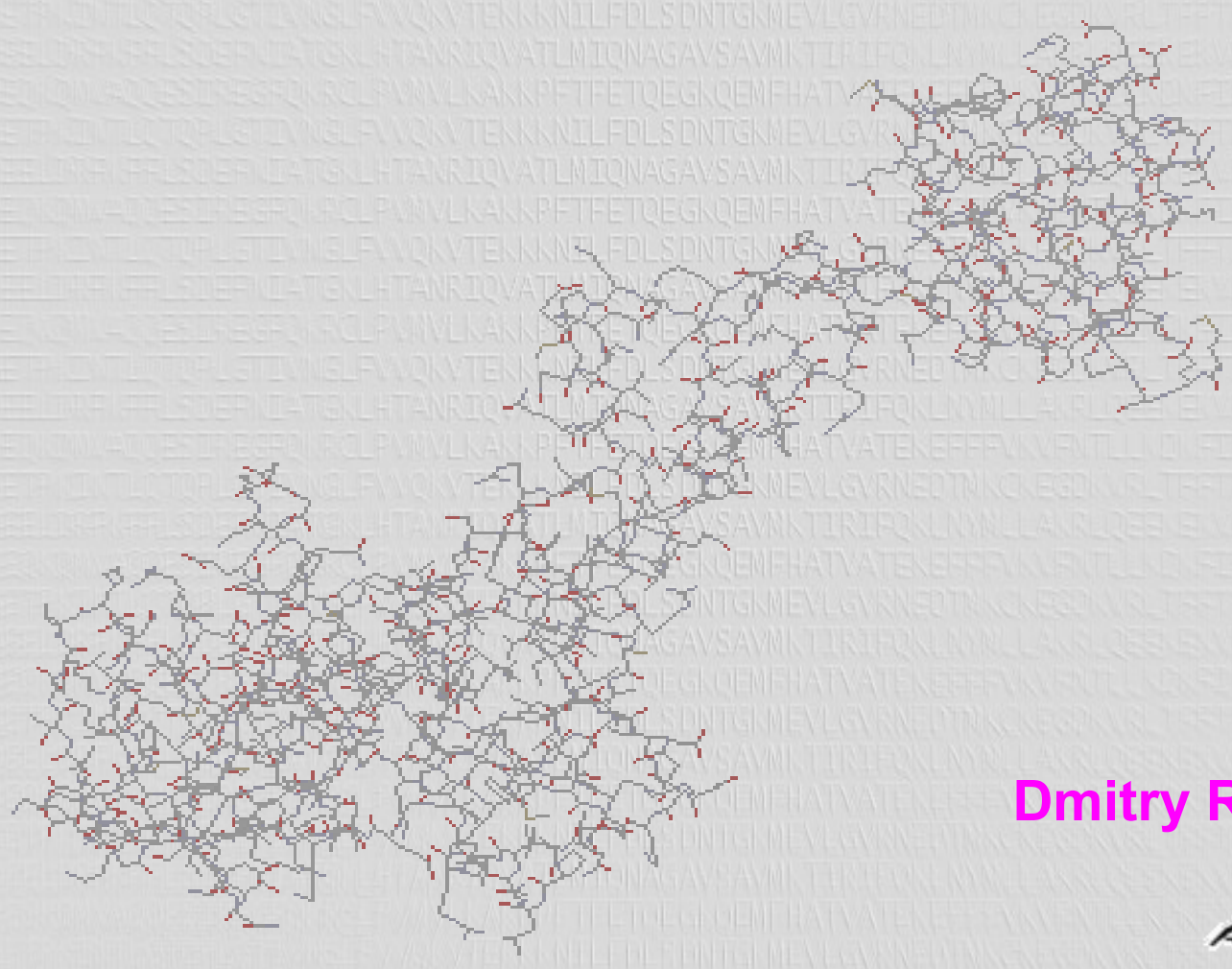
Absent In Melanoma 2 (AIM2) Homology Modeling

Structural Bioinformatics



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AIM2 belongs to a class of proteins called inflammasomes, which are multi-protein complexes that play major roles as guardians against both viral and bacterial infections. Inflammasomes also detect dangerous self-molecules associated with tissue damage.

Thomas Jefferson University (2009, January 26).
Key Protein Regulator Of Inflammation And Cell Death Discovered.

The DAPIN (Domain in Apoptosis and INterferon response) domain is an 80-100-residue domain which is found in the N-terminus of diverse vertebrate and vertebrate-specific viral proteins involved in apoptosis, cancer, inflammation, and immune response.

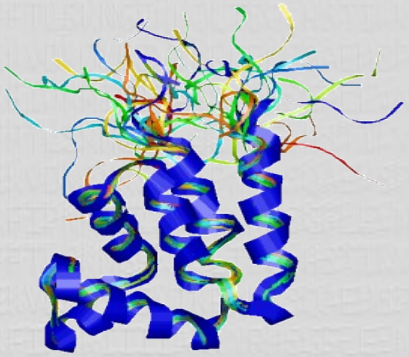
The death domain (DD) is a conserved region of about 80 residues found on death receptors, and which is required for death signalling, as well as a variety of non-apoptotic functions

HIN-200 Interferons (IFNs) are cytokines that regulate host resistance against infections by exerting antimicrobial, immunomodulatory and cell growth regulatory functions.

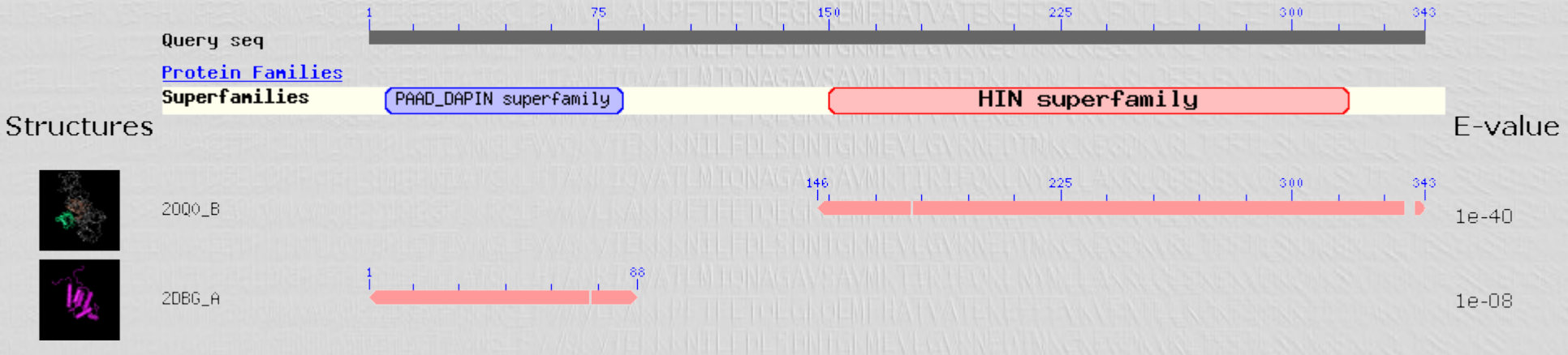
PSI-BLAST Search for homologies

Alignment	DB:ID	Source	Length	Score	Identity%	Positives%	E()
1 ☑ New	PDB:2OQ0_D	mol:protein length:206 Gamma-interferon-inducible protein Ifi-16	206	795	43	59	1e-84
2 ☑ New	PDB:2OQ0_C	mol:protein length:206 Gamma-interferon-inducible protein Ifi-16	206	795	43	59	1e-84
3 ☑ New	PDB:2OQ0_B	mol:protein length:206 Gamma-interferon-inducible protein Ifi-16	206	795	43	59	1e-84
4 ☑ New	PDB:2OQ0_A	mol:protein length:206 Gamma-interferon-inducible protein Ifi-16	206	795	43	59	1e-84
5 ☑ New	PDB:3B6Y_B	mol:protein length:200 Gamma-interferon-inducible protein Ifi-16	200	620	47	64	2e-64
6 ☑ New	PDB:3B6Y_A	mol:protein length:200 Gamma-interferon-inducible protein Ifi-16	200	620	47	64	2e-64
7 ☑ New	PDB:2DBG_A	mol:protein length:103 Myeloid cell nuclear differentiation antigen	103	336	28	49	2e-31
8 ☑ New	PDB:2YU0_A	mol:protein length:94 Interferon-activable protein 205	94	292	25	48	3e-26

PAAD-DAPIN



HIN superfamily



DAPIN DOMAIN

T-Coffee

```
O14862 -------ME---SKYKEILLLTGLDNITDEELDRFKFFLSD--EFNIATGKLHTANRIQVATLMIQNAGAVSAVMKTIRIFQKLN-YMLL
2DO9_A GSSGSSGMALARANSPQEALLWALNDLEENSFKTLKFHLRDVTQFHLARGELESLSQVDLASKLISMYGAQEAVRVVSRSLLAMN-LMEL
2DBG_A GSSGSSGMV---NEYKKILLLKGFELMDDYHFTSIKSLLAY--DLGLTTKMQEEYNRIKITDLMEKKFQGVACLDKLIELAKDMPSLKNL

cons          *     :  :  ** .:: : :  :  :*  *    :: ::    .  .::.::  : .   .  .:    .    :     *

O14862 AKRLQEEKEKVDKQYKSVTKPKPLSQAEMSPAASAAIRNDVAKQRAAPKVSPHVKPEQKQMVAQQESIREGFQKRCLPVMVLKAKKPFTF
2DO9_A VDYLNQVC---LNDYREI-------------------------------------------------------------------------
2DBG_A VNNLRKEKS--------------------------------------------------------------------------------

O14862 ETQEGKQEMFHATVATEKEFFFVKVFNTLLKDKFIPKRIIIIARYYRHSGFLEVNSASRVLDAESDQKVNVPLNIIRKAGETPKINTLQT
2DO9_A ---------------------------------------------------------------------------------------
2DBG_A ---------------------------------------------------------------------------------------


O14862 QPLGTIVNGLFVVQKVTEKKKNILFDLSDNTGKMEVLGVRNEDTMKCKEGDKVRLTFFTLSKNGEKLQLTSGVHSTIKVIKAKKKT
2DO9_A ------------------------------------------------------------------------YREHVSGPSSG
2DBG_A ---------------------------------------------------------------------------KVASGPSSG

cons                                                                              :  .. ..
```

SCORE = 60

We can see that sequence alignment is not good in this particular case that is explained by not very good e-value in our psi-blast results. In fact blast doesn't find these homologues at all.

HIN DOMAIN

T-Coffee

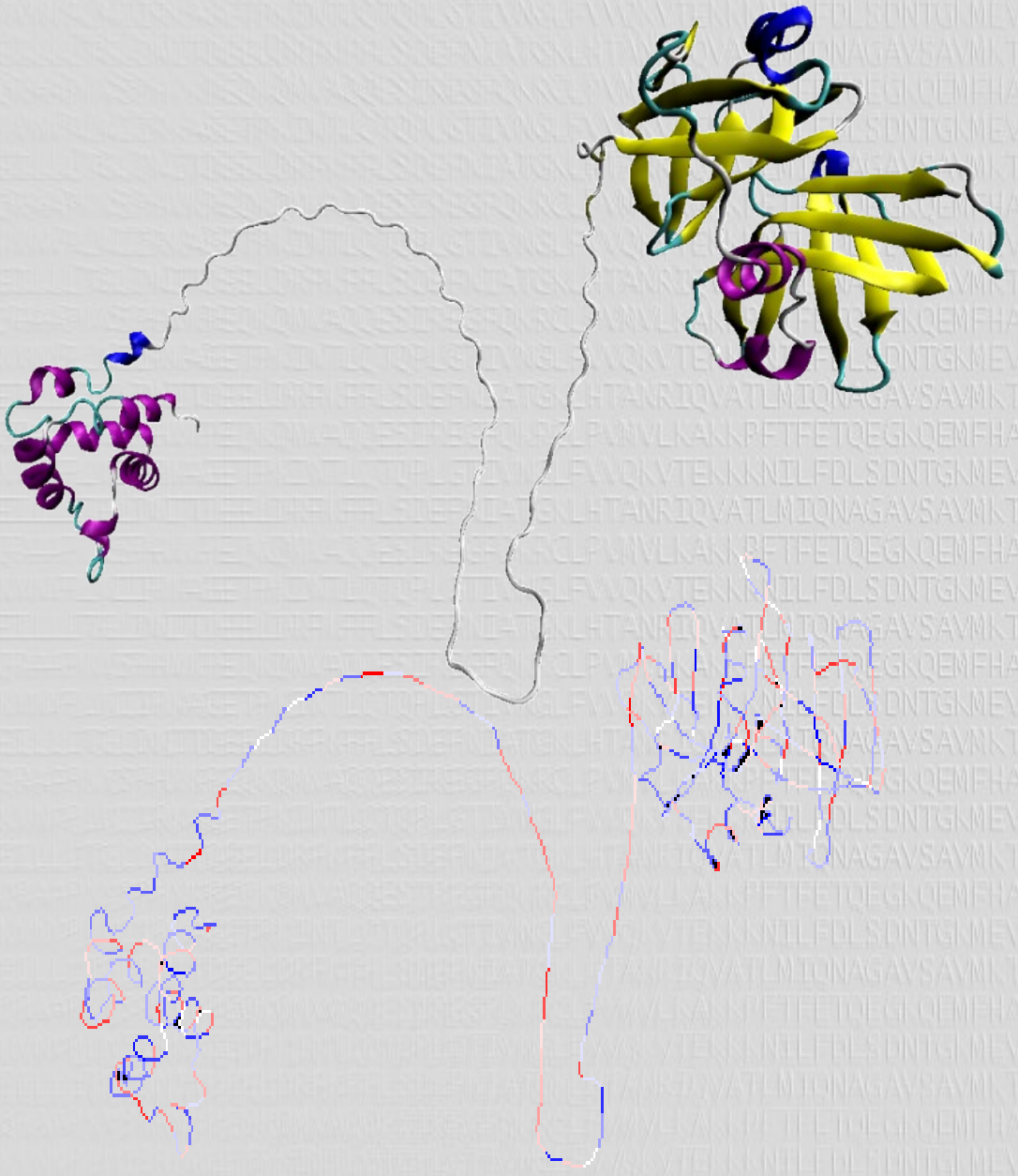
We can see this domain is well conserved

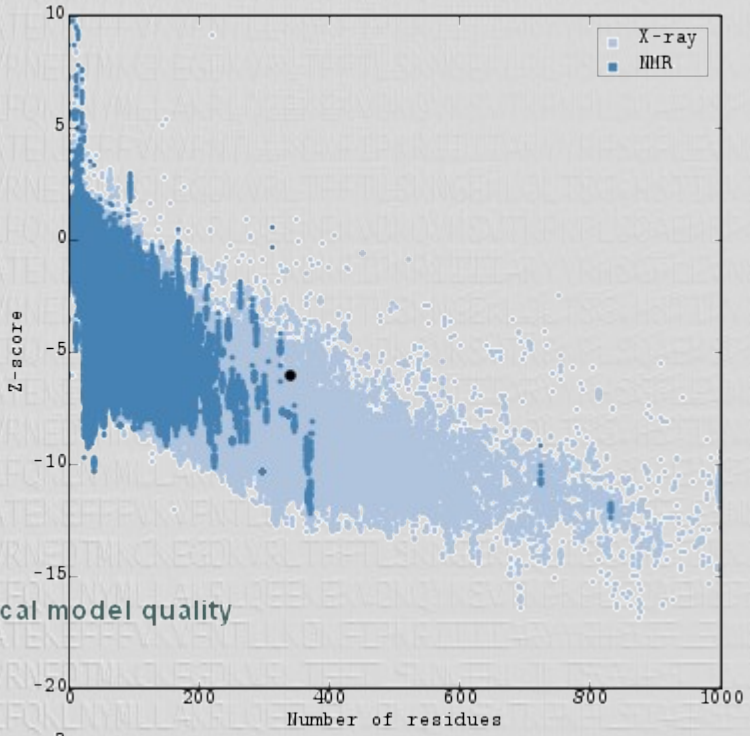
So after a quick look in the studied protein we can see that it consists in two domains. There is no homologue that cover all the protein. Moreover intent to align the sequence with all selected homologues failed (clastalw / t-coffee).

The decision to model domains separately using structural alignment is taken.

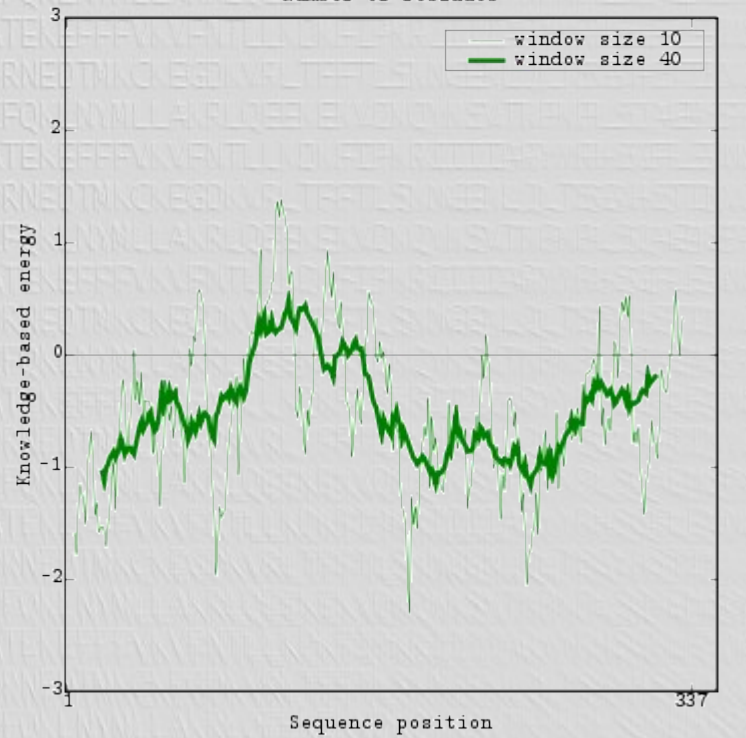
Both HIN and DAPIN domains have been separately aligned using SAP
Then HMM profiles have been built to align AIM2 (O14862) target sequence

Modeller v9.5 built model



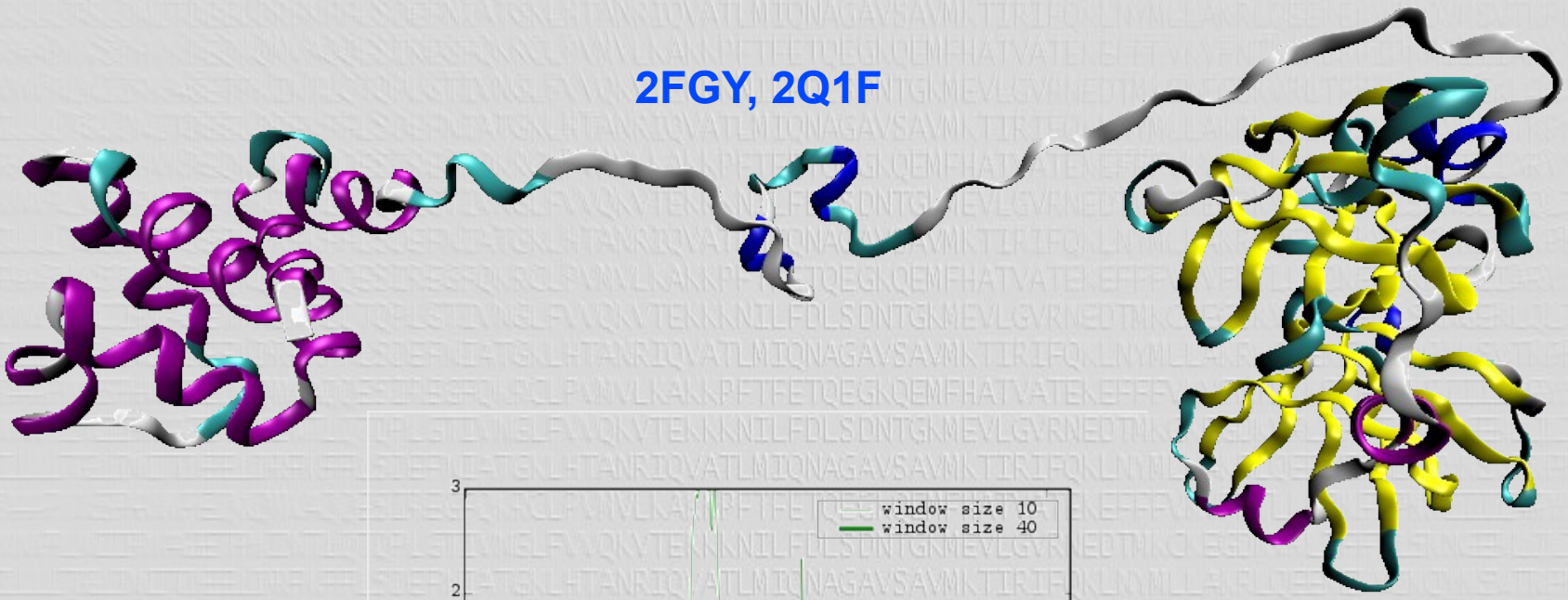


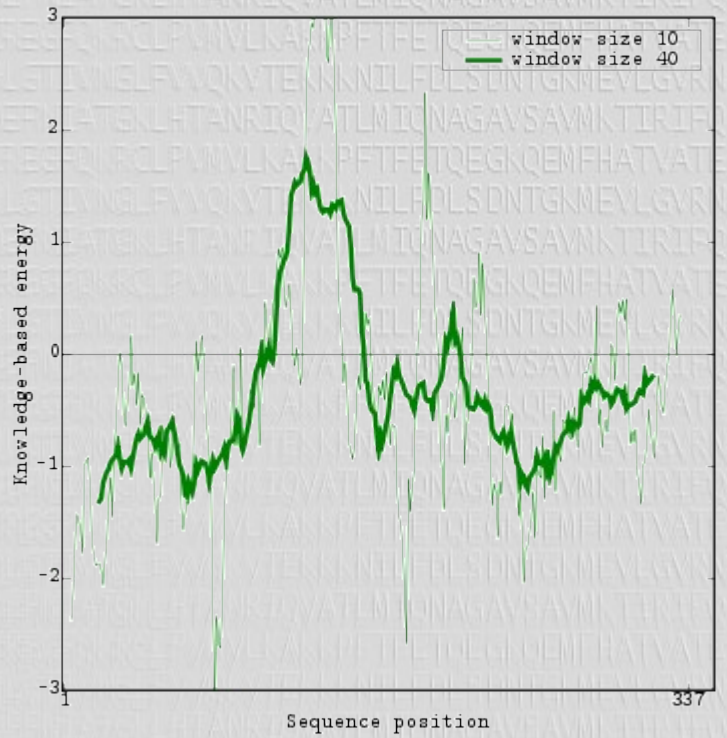
Local model quality



Try to remodel missed part using VERY remote proteins ... failed...

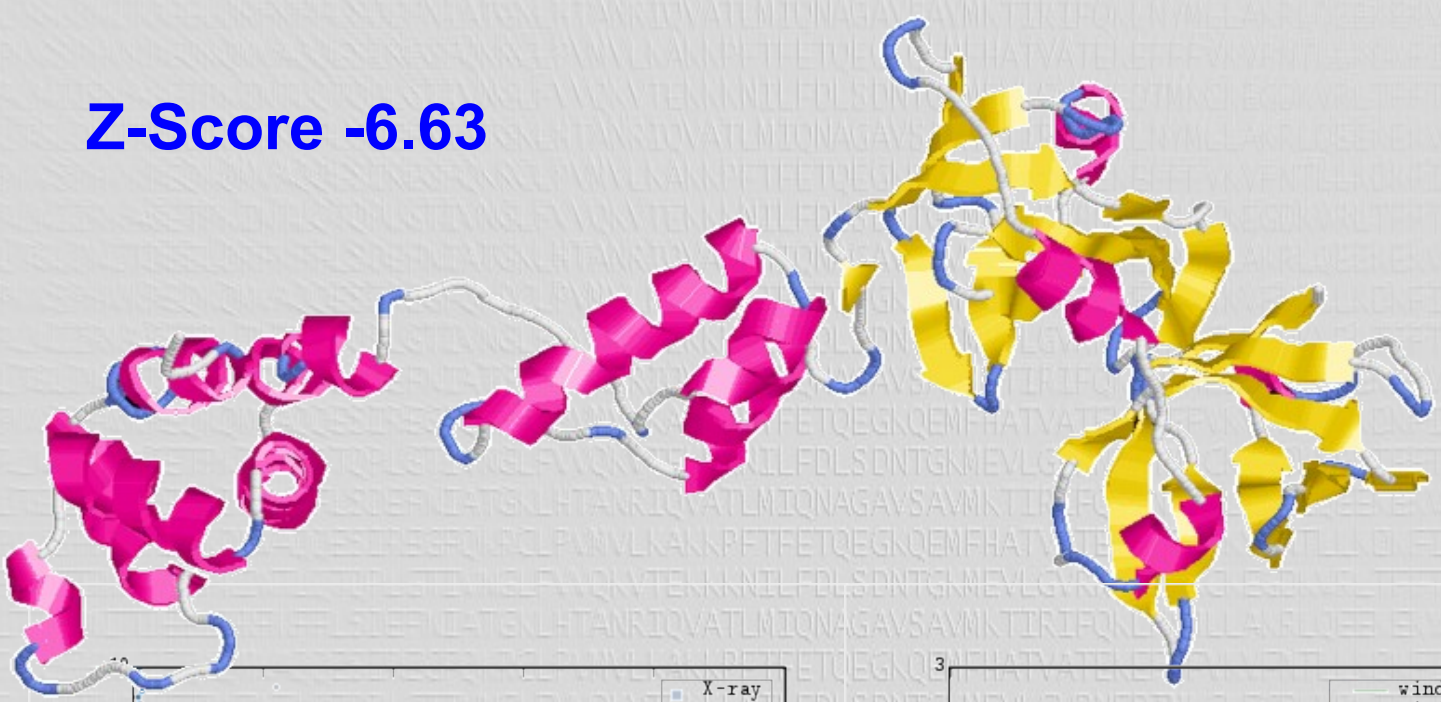
2FGY, 2Q1F

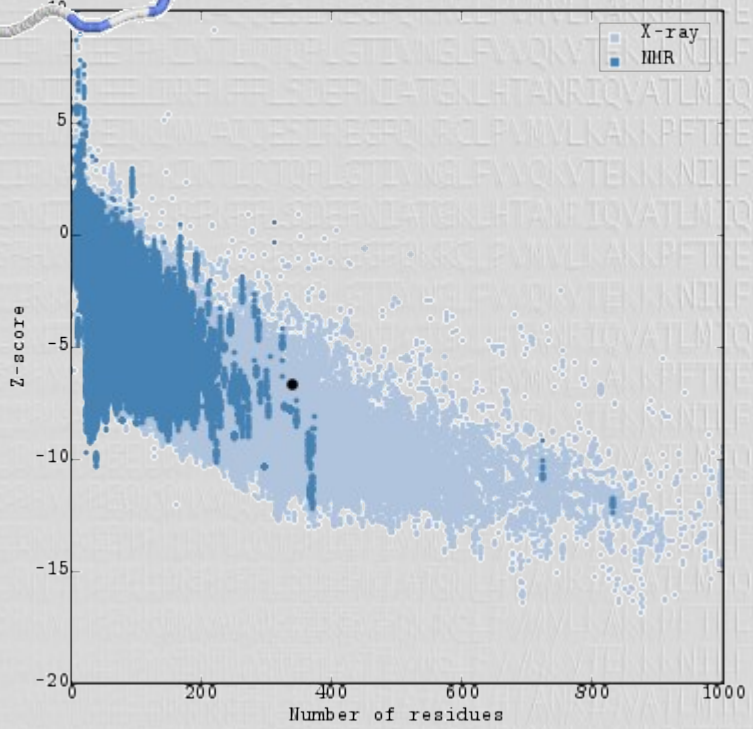


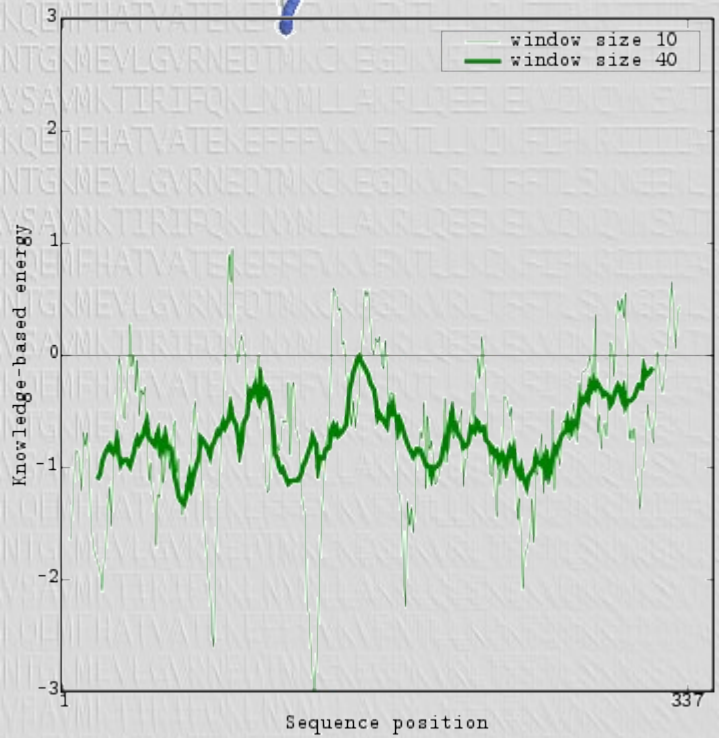


Try to remodel missed part using SAM_T08

Z-Score -6.63

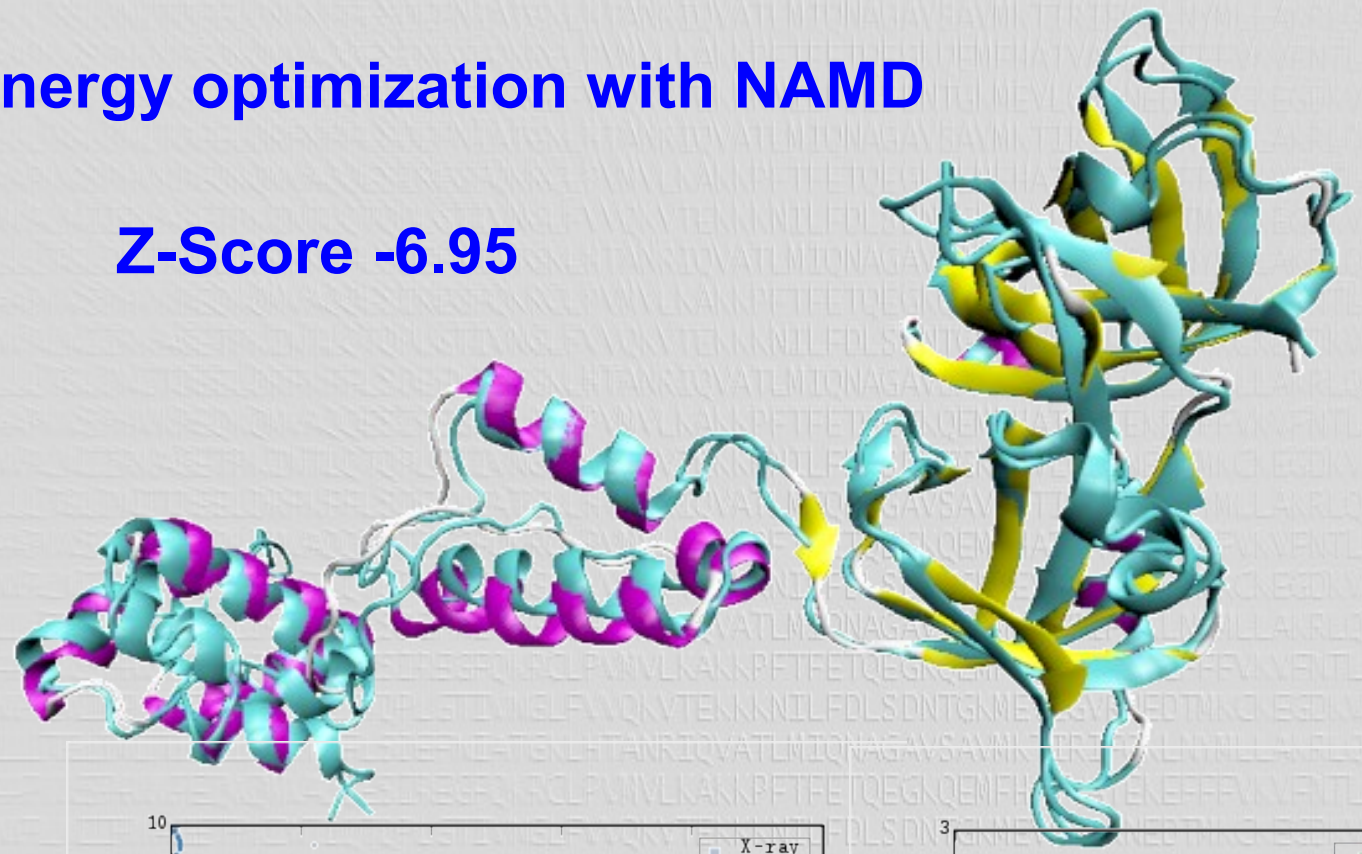


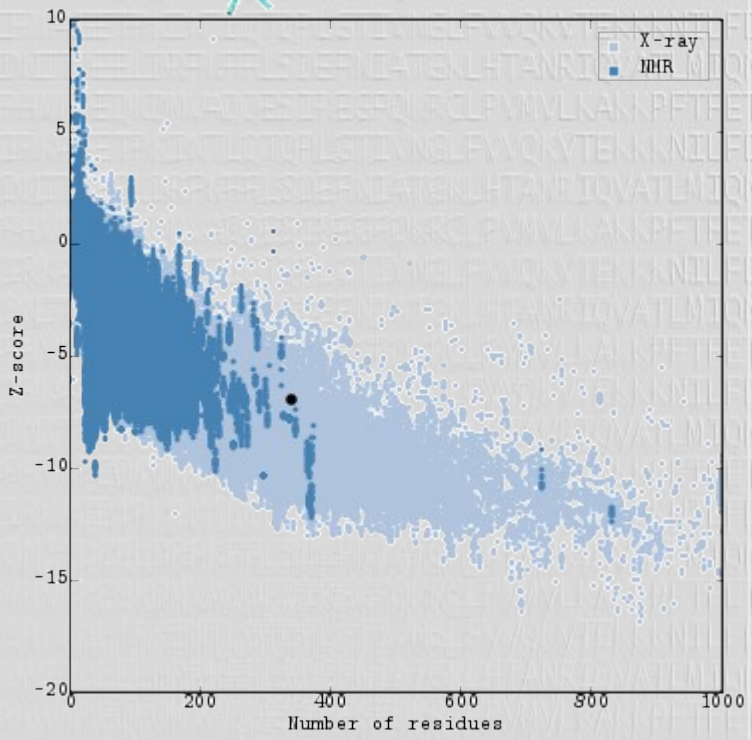


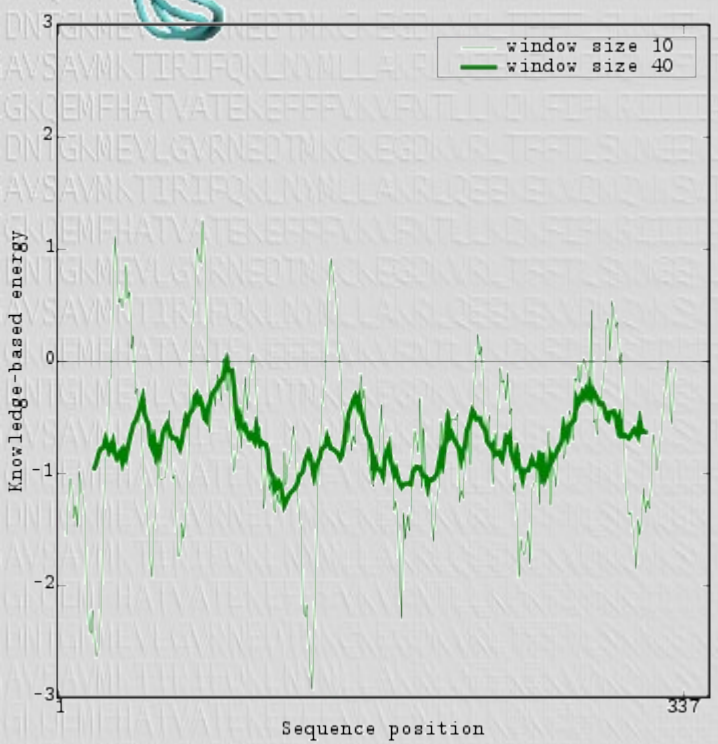


Energy optimization with NAMD

Z-Score -6.95







THANK YOU

Big thanks to my colleagues Laia Codó and Romina Royo for their advices, support when I almos gave up with this witchcraft...