Group Meeting 17 May 2017

May 17, 2018

D76N on CNT: enhancement of fibrillogenesis wrt no surface and wild type (that does not aggregate in both conditions)

Experimental condition: 37°C - 0,025M - pH 7.4

Graphite definition in OPLS-AA:

CX(CY) C chrg 0.000 eps(kcal/mol) 0.07 sig 3.55 radi 1.775(sig/2)

Idea of the project: comparison of the behavior of three different variants of b2m (the same we're studying in Proline Metadynamics),that are D76N (the most amyloidogenical), W60G (the anti-aggregation) and WT, once they are interacting with graphite

Main steps: docking –> 500ns classic MD –> parallel tempered Metadynamics

In the same experimental conditions used by Mangione, the three variant result protonated this way:

- WT **Qtot = -2** , 13HISE(0), 31HISE (0), 51HISE (0), 84 HISE (0)
- W60G **Qtot = -1** , 13HISE (0), 31HISE (0), 51HISE (0), 84HISH (+1)
- D76N **Qtot = 0** , 13HISD(0), 31HISD (0), 51HISE (0), 84HISH(+1)

PQR file (containing charges and vdW radius) are requested as input for SDA 7.2 software

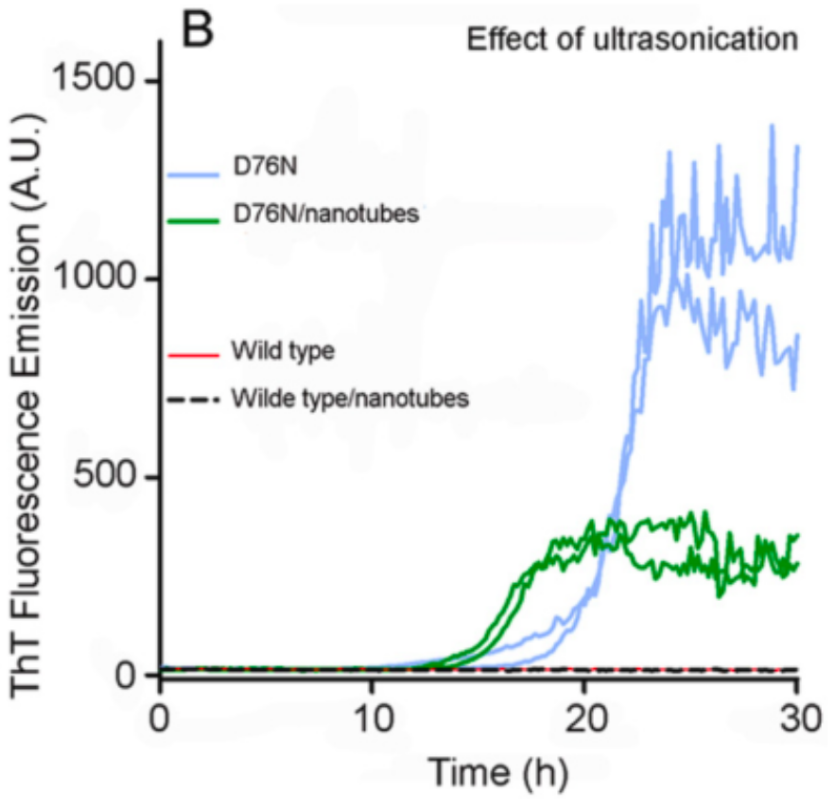

Figure 1: Time course of fibril formation by D76N under ultrasonication (light blue lines show replicate experiments) in contrast to the absence of fibrillogenesis by wild type(red line) under the same conditions. D76N fibril formation was accelerated in the presence of carbon nanotubes (greenlines), whereas wild type (dashedblack line) did not aggregate.

SDA 7.2 Simulation of Diffusional Association software

Main steps

1. generate pqr files for each solute (with protonation states for the experimental conditions to be modeled)
2. Compute Poisson-Boltzmann electrostatic potential grids
3. Compute the effective charges (Effective Charges for Macromolecules)
4. Compute the other grids: electrostatic desolvation, hydrophobic desolvation and soft-core repulsive grids
5. Docking production simulations with default probes **probep** = 1.7 **probew** = 1.4 (sum =3.1 Å represents an approximation to the length of a hydrogen bond)

Result of docking clusters

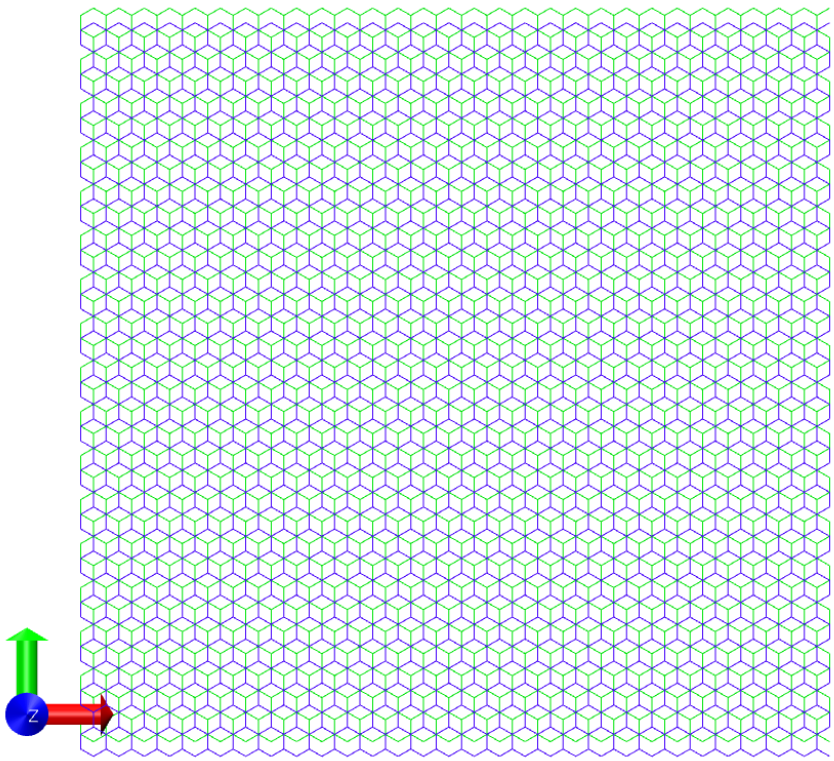

Figure 2: 3 layers of graphene with a single cell of 1.42A side. Total of 6120 atoms. The area is 70.9 A * 71.22 A. The coordinate z is 0.0 A, 3.35 A and 6.70 A

Wild Type

N	step	cl_ size	energy	cl_size with SDA	
1	177620	453	-6.479e+01	1.258137e+06	(intersection between LYS74 and 3layer)
2	53766	749	-7.907e+01	2.379139e+06	
3	149515	5	-7.891e+01	2.476000e+04	
4	43704	168	-6.940e+01	4.494750e+05	
5	133836	134	-6.959e+01	4.293740e+05	
6	90677	15	-6.541e+01	1.554900e+04	
7	98819	18	-6.112e+01	1.312500e+04	
8	25355	449	-5.951e+01	9.609290e+05	

## RunNb	StepNb	TotEn	El	ED	HD	rLJ	Occur	AvEnergy	StdAvEnergy
54	177620	-1.1079E+02	0.0000E+00	2.9168E+01	-1.1734E+01	-1.2823E+02	453	-6.479e+01	1.258137e+06
25	53766	-8.4132E+01	0.0000E+00	9.3869E+00	-7.9987E+00	-8.5520E+01	749	-7.907e+01	2.379139e+06
28	149515	-7.9696E+01	0.0000E+00	1.8096E+01	-1.0105E+01	-8.7687E+01	5	-7.891e+01	2 .476000e+04
20	43704	-7.2527E+01	0.0000E+00	7.7342E+00	-6.4271E+00	-7.3834E+01	168	-6.940e+01	4.494750e+05
83	133836	-7.1902E+01	0.0000E+00	9.8352E+00	-6.9440E+00	-7.4793E+01	134	-6.959e+01	4.293740e+05
34	90677	-6.5922E+01	0.0000E+00	9.0404E+00	-6.0320E+00	-6.8931E+01	15	-6.541e+01	1.554900e+04
77	98819	-6.3945E+01	0.0000E+00	2.1447E+01	-7.9523E+00	-7.7440E+01	18	-6.112e+01	1.312500e+04
38	25355	-6.0649E+01	0.0000E+00	8.7353E+00	-6.3685E+00	-6.3016E+01	449	-5.951e+01	9.609290e+05

D76N

N	step	cl_ size	energy	cl_size with SDA	
1	127281	102	-1.020e+02	3.007160e+05	
2	154753	423	-8.224e+01	1.449473e+06	
3	73631	19	-6.918e+01	2.392290e+05	
4	135175	12	-6.752e+01	1.076330e+05	(intersection LYS75)
5	126232	21	-6.692e+01	4.603300e+04	
6	122622	10	-5.686e+01	5.485700e+04	(intersection LYS75)
7	141978	83	-5.424e+01	3.113820e+05	

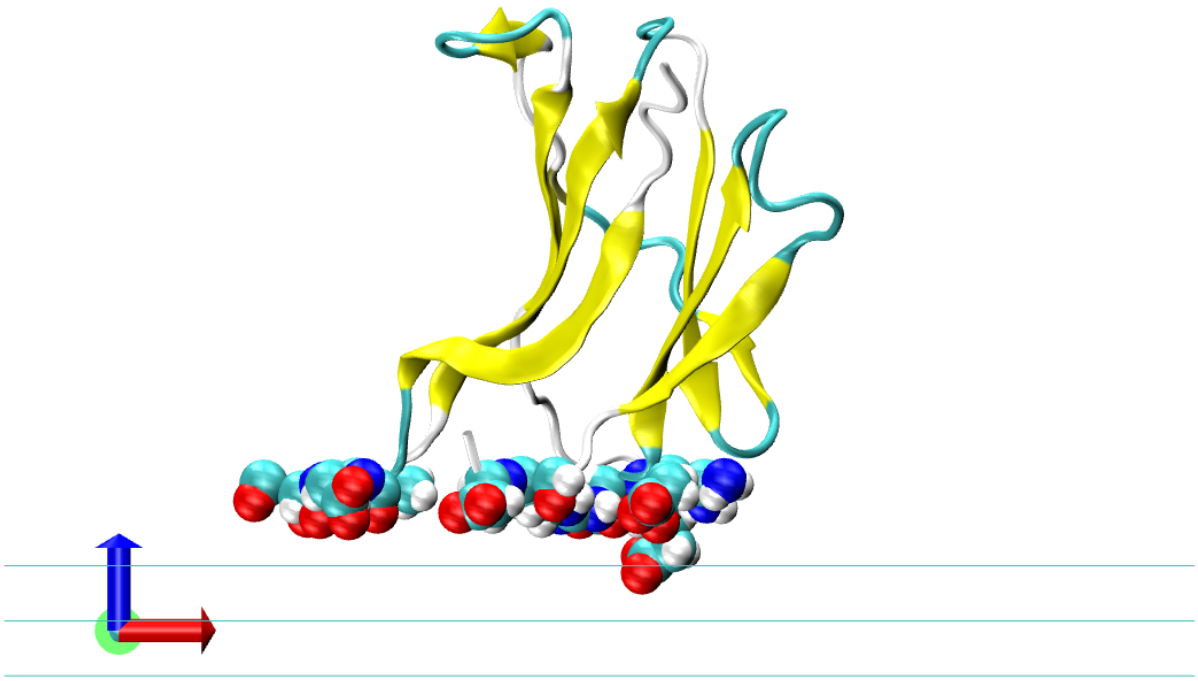

Figure 3: WILD TYPE Cluster 0001. Contact residues ALA15, GLU16, ASN17, LYS94, ASP98, ARG97, ASP76, GLU74, ASN42

8	86707	58	-5.417e+01	1.710950e+05
9	75640	1254	-5.432e+01	2.426124e+06
10	67850	2	-5.412e+01	9.380000e+02

## RunNb	StepNb	TotEn	El	ED	HD	rLJ	Occur	AvEnergy	StdAvEnergy
35	127281	-1.0525E+02	0.0000E+00	2.2775E+01	-1.0474E+01	-1.1755E+02	102	-1.020e+02	3.007160e+05
11	154753	-9.3274E+01	0.0000E+00	3.7407E+01	-1.0670E+01	-1.2001E+02	423	-8.224e+01	1.449473e+06
28	73631	-7.4568E+01	0.0000E+00	1.0836E+01	-7.8346E+00	-7.7569E+01	19	-6.918e+01	2.392290e+05
22	135175	-6.8901E+01	0.0000E+00	2.0450E+01	-1.0216E+01	-			

7.9134E+01 12 -6.752e+01 1.076330e+05

40 126232 -6.8453E+01 0.0000E+00 1.6291E+01 -7.0773E+00 -7.7666E+01 21 -6.692e+01 4.603300e+04

53 122622 -5.7779E+01 0.0000E+00 1.7379E+01 -6.7710E+00 -6.8388E+01 10 -5.686e+01 5.485700e+04

38 141978 -5.6298E+01 0.0000E+00 8.1943E+00 -5.8315E+00 -5.8661E+01 83 -5.424e+01 3.113820e+05

60 86707 -5.5749E+01 0.0000E+00 9.1106E+00 -5.8845E+00 -5.8975E+01 58 -5.417e+01 1.710950e+05

51 75640 -5.5712E+01 0.0000E+00 9.9028E+00 -5.8799E+00 -5.9735E+01 1254 -5.432e+01 2.426124e+06

83 67850 -5.4284E+01 0.0000E+00 1.6570E+01 -5.8952E+00 -6.4959E+01 2 -5.412e+01 9.380000e+02

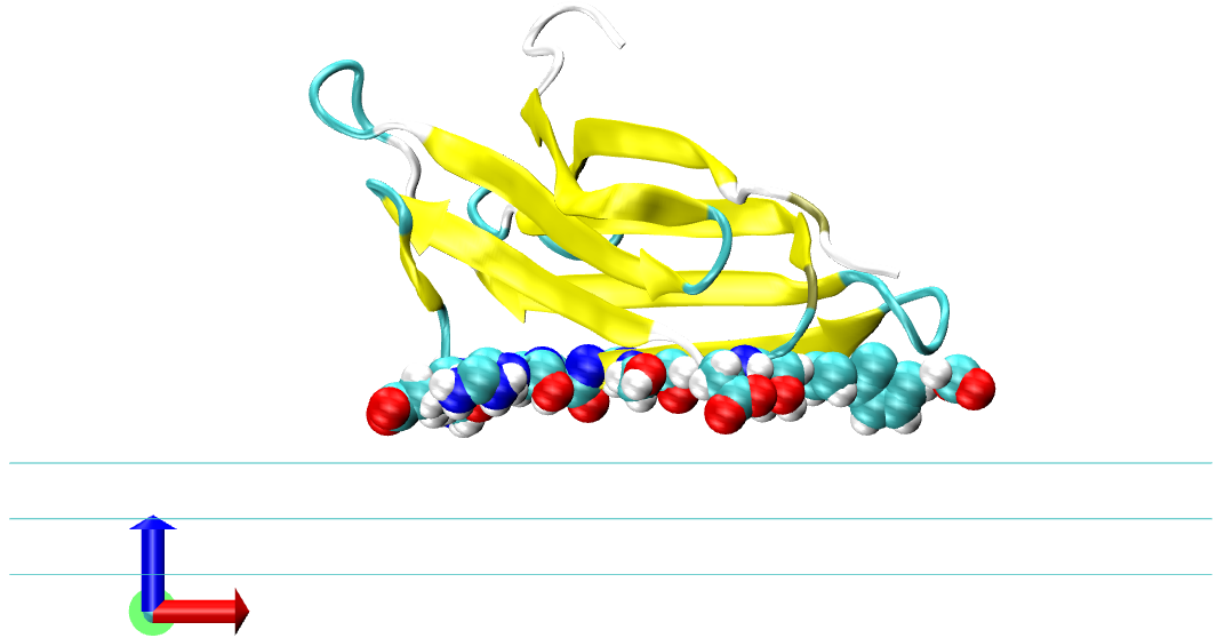

Figure 4: D76N Cluster 0001. Contact residues ASP59, PHE56, LEU54, ASP53, SER52, GLU50, VAL49, LYS48, GLU47, ARG45, ASP34, ILE35

W60G

N	step	cl_ size	energy	cl_size with SDA
1	155733	1024	-7.681e+01	2.250242e+06
2	107871	40	-6.835e+01	1.164370e+05
3	68979	260	-6.148e+01	1.843730e+05
4	168851	154	-6.108e+01	1.754500e+05

##	RunNb	StepNb	TotEn	El	ED	HD	rLJ	Occur	AvEnergy	StdAvEnergy
76	155733	-8.1824E+01	0.0000E+00	1.0976E+01	-6.2573E+00	-8.6543E+01	1024	-7.681e+01	2.250242e+06	
80	107871	-7.1118E+01	0.0000E+00	1.8814E+01	-7.0591E+00	-8.2873E+01	40	-6.835e+01	1.164370e+05	
40	68979	-6.3340E+01	0.0000E+00	1.0197E+01	-5.8636E+00	-6.7673E+01	260	-6.148e+01	1.843730e+05	
3	168851	-6.1993E+01	0.0000E+00	1.8080E+01	-7.0483E+00	-7.3024E+01	154	-6.108e+01	1.754500e+05	

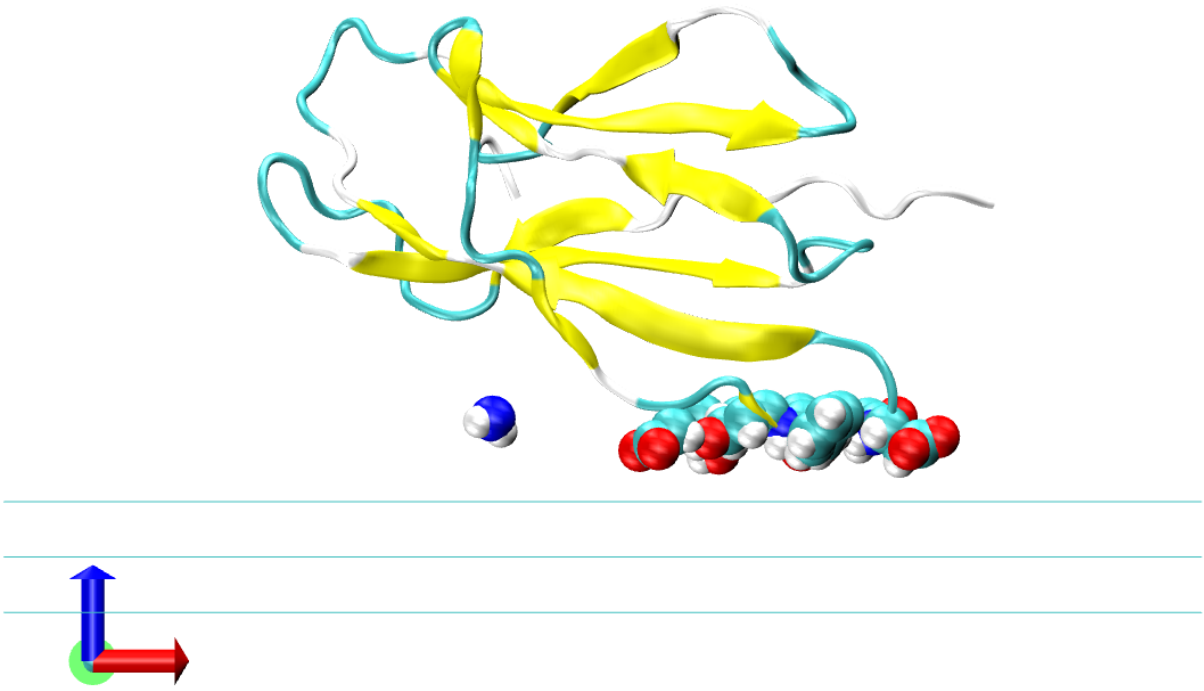

Figure 5: W60G Cluster 0001. Contact residues ASP53, SER55, PHE56, TYR63, SER57, ASP59