

Ions that seal interactions between macromolecules

Giovanni La Penna, National research council (CNR)



17 Dic. 2019

Summary

1 The project

2 Ions: atmosphere and condensation

- DNA as a polyelectrolyte
- RNA as a polyelectrolyte

3 Polyvalent ions: coordination and correlation

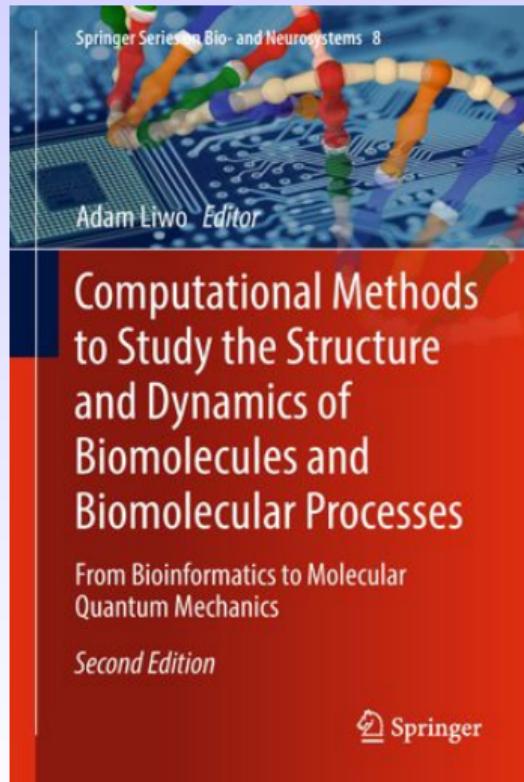
- RNA, proteins, mono-, and divalent ions

4 Multivalent cations: coordination and bridges

- Cu and prion
- Zn and non-amyloid oligomers
- Cu and non-amyloid oligomers

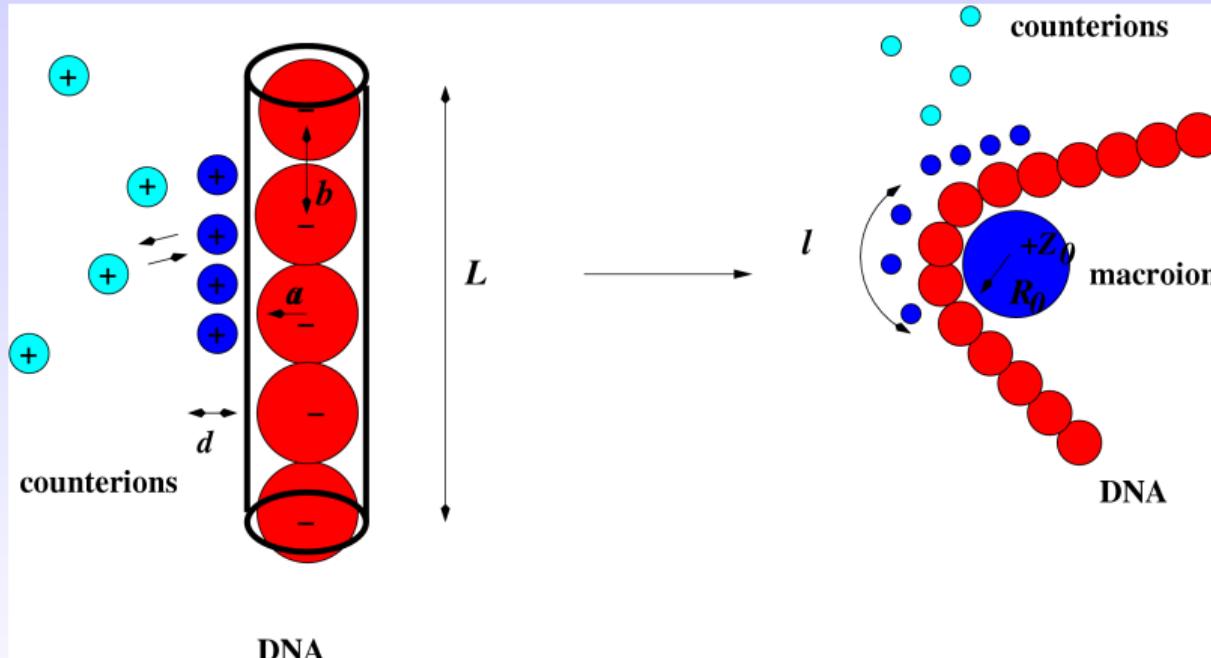
sites.google.com/view/wwwgiovannilapennait

The project



G. La Penna, O. Andreussi, 2019
When water plays an active role in electronic structure: Insights from first-principles molecular dynamics simulations of biological systems

Polyelectrolytes and ion condensation



DNA

L. Arcesi et al., *Biopolymers*, (2007)

$$\Delta F(l) = F_s(L - l) + F_c(l) + F_{c-s}(l) + F_b(l) + F_s(L) + F_c(0)$$

Polyelectrolytes and ion condensation

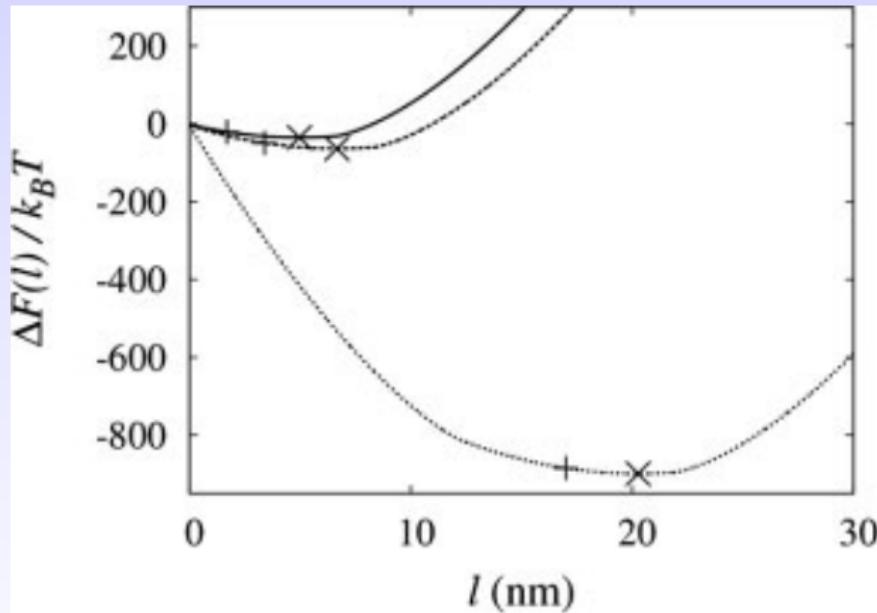


Table I Number of DNA Turns n_t^* Around Octamer in Nucleosome, CSB, and MC1 Proteins as Determined by the Present Model and as Resulting from Experiments

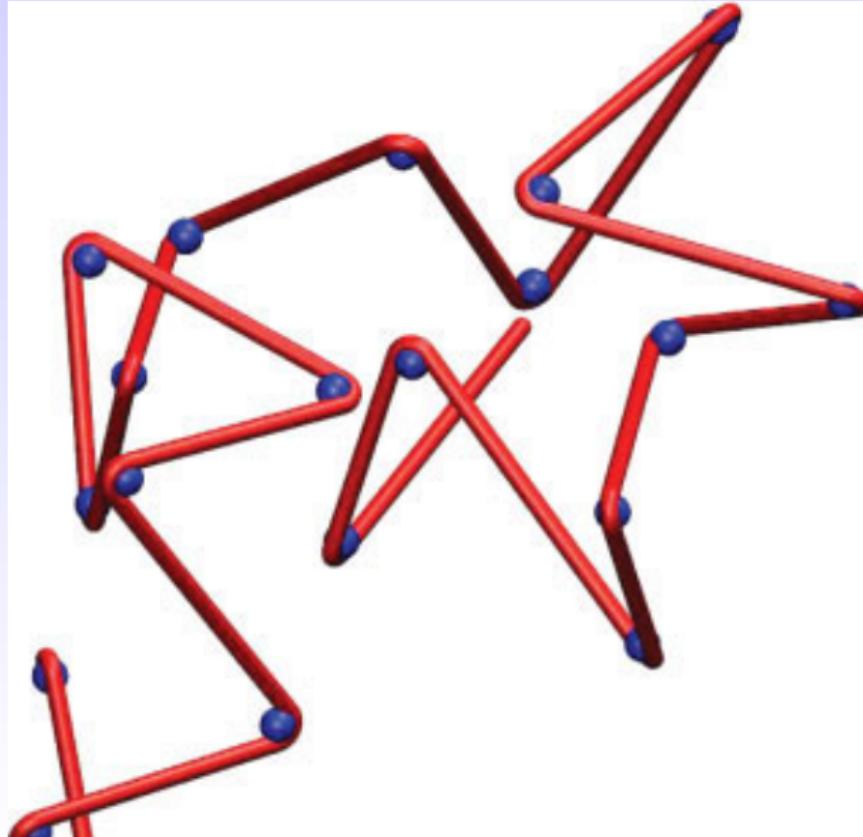
Nucleosome ($R_0 = 3.4$)		Experiment	
Z_0	100	134	$1.58^a - 1.59^{b,4}$
	1.08	1.29	
CSB ($Z_0 = 14$)			
R_0	4	6	$0.95^c,6$
	0.60	0.80	
MC1 (nm)			
R_0/Z_0	10	12	$0.32^a,7$
1.5	0.32	0.34	
1.7	0.34	0.36	

^a Electron microscopy.

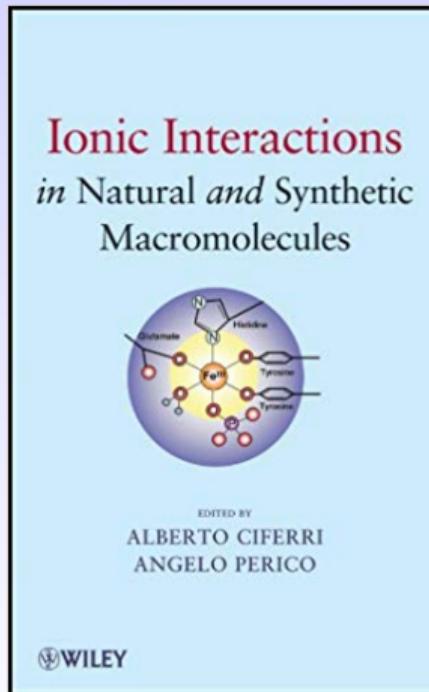
^b X-ray.

^c SFM.

Polyelectrolytes and ion condensation

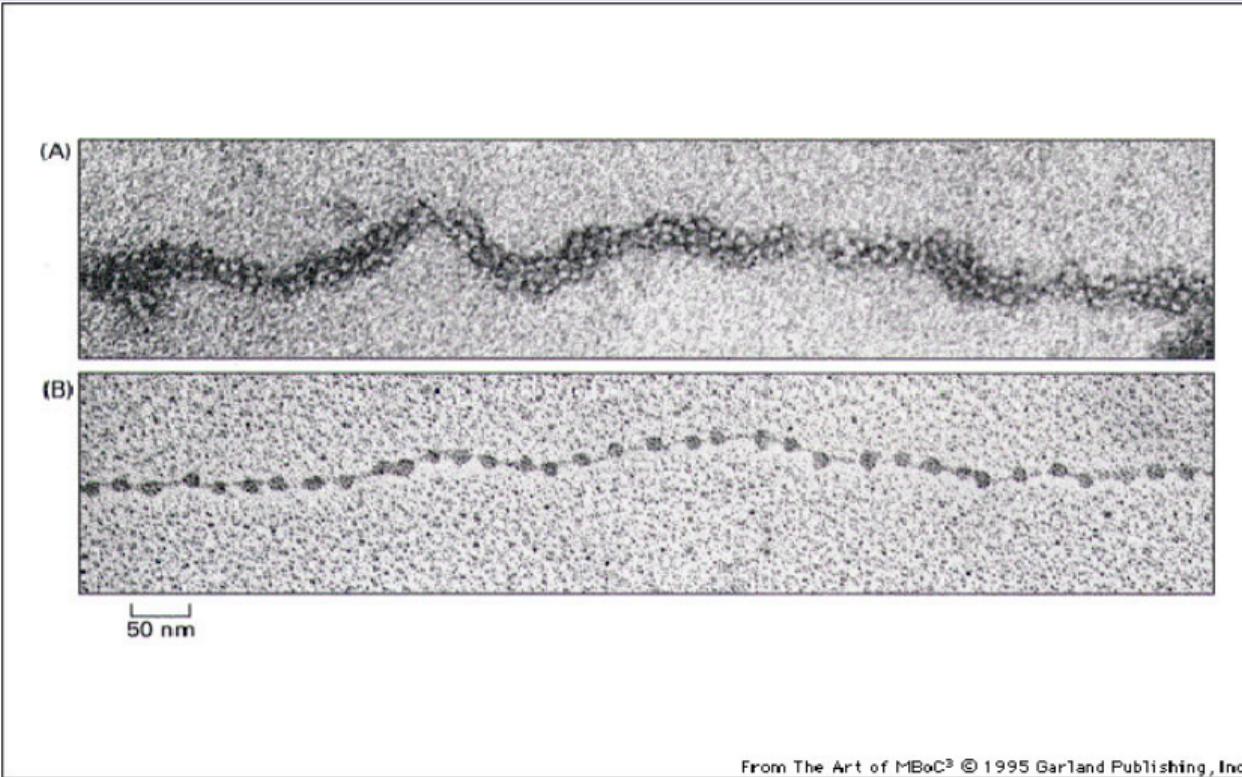


Polyelectrolytes and ion condensation



A. Ciferri, A. Perico, 2012
Ionic interactions in natural
and synthetic macromolecules

Chromatin and cell nucleus



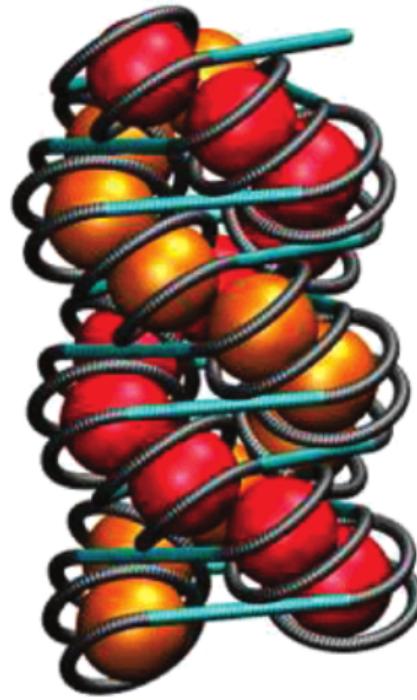
From The Art of MBoC³ © 1995 Garland Publishing, Inc.

PDB=1KX5

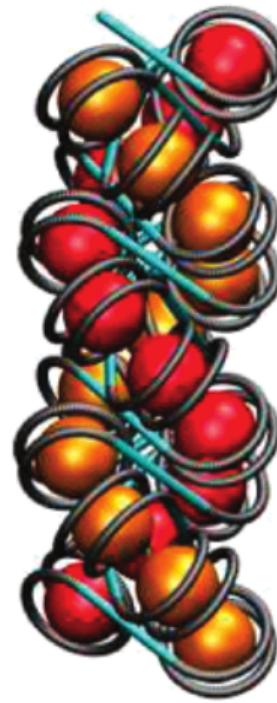


Chromatin and cell nucleus

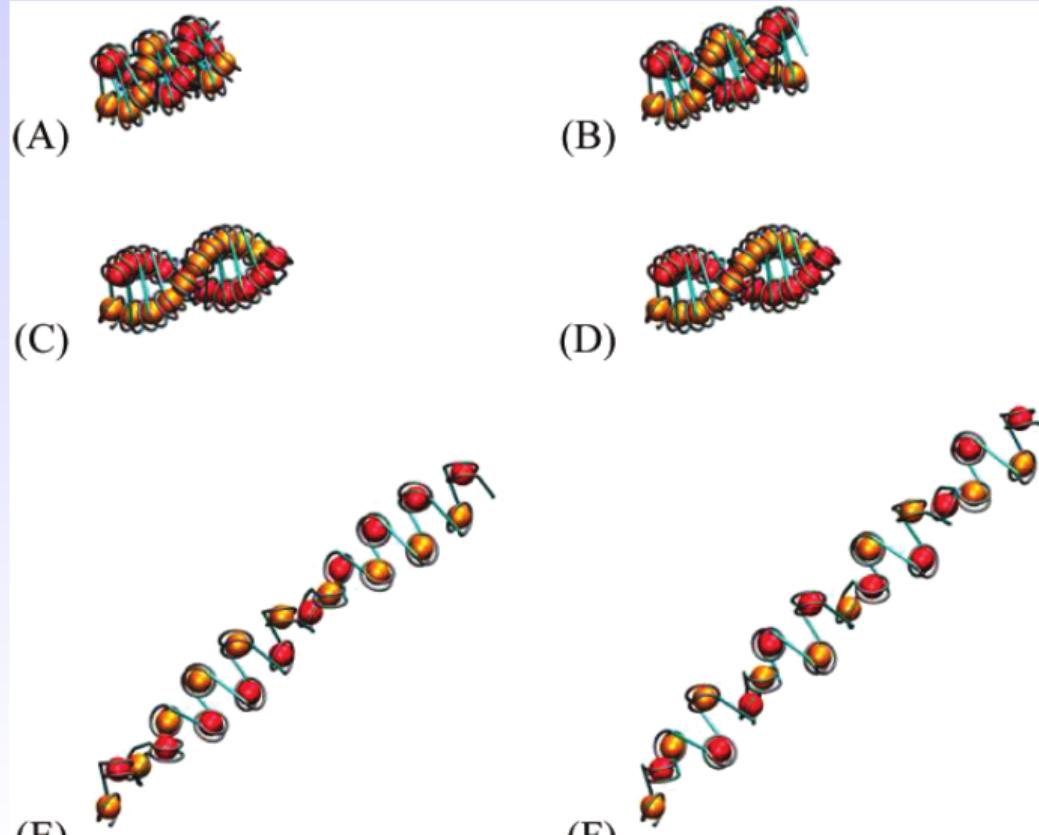
(A)

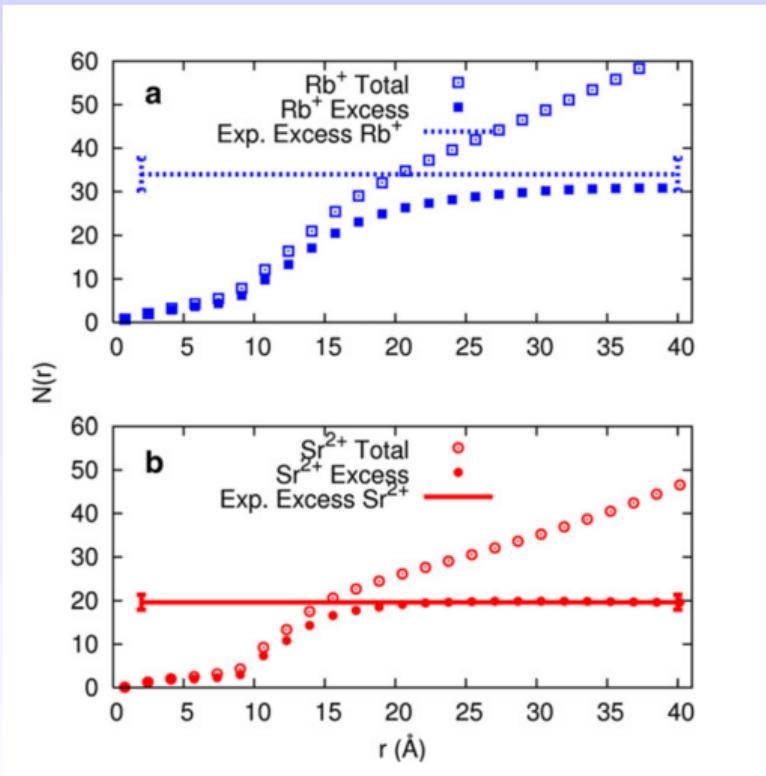


(B)

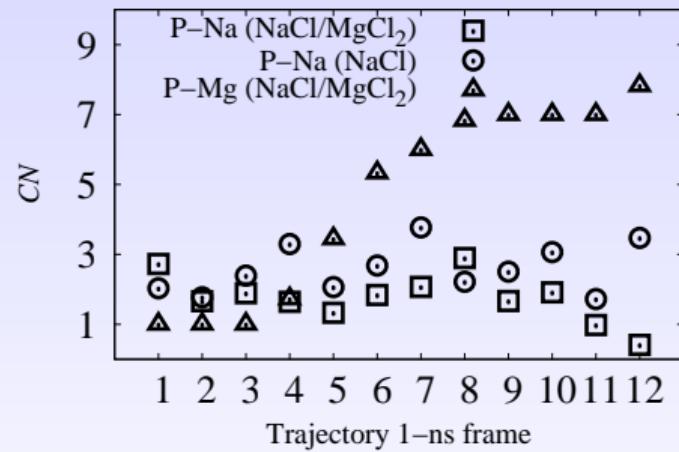


Chromatin and cell nucleus





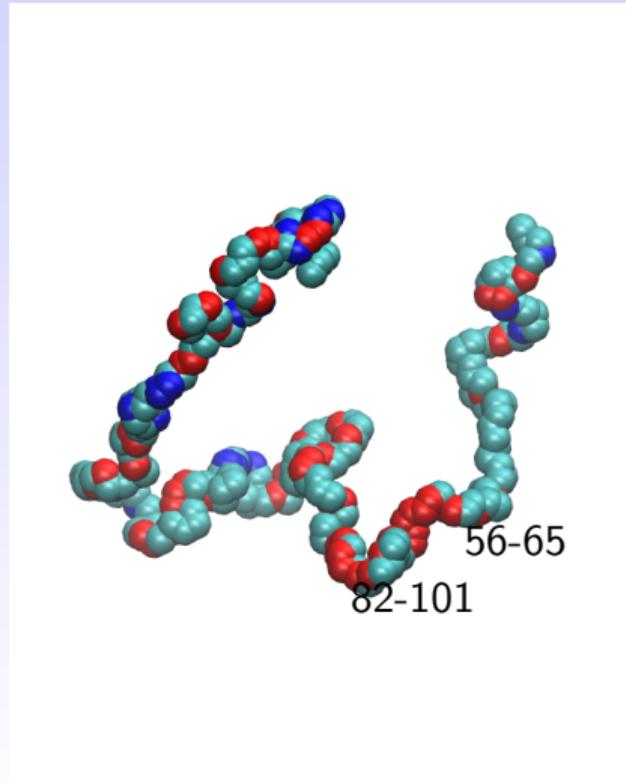
RNA of 25 bp ($Q = -48$)
S. Kirmizialtin et al., *Biophys. J.*, (2012)



RNA of 40 b ($Q = -39$)

G. La Penna et al., *Front. Chem.*, (2018)
movie...

Osteopontin (OPN)



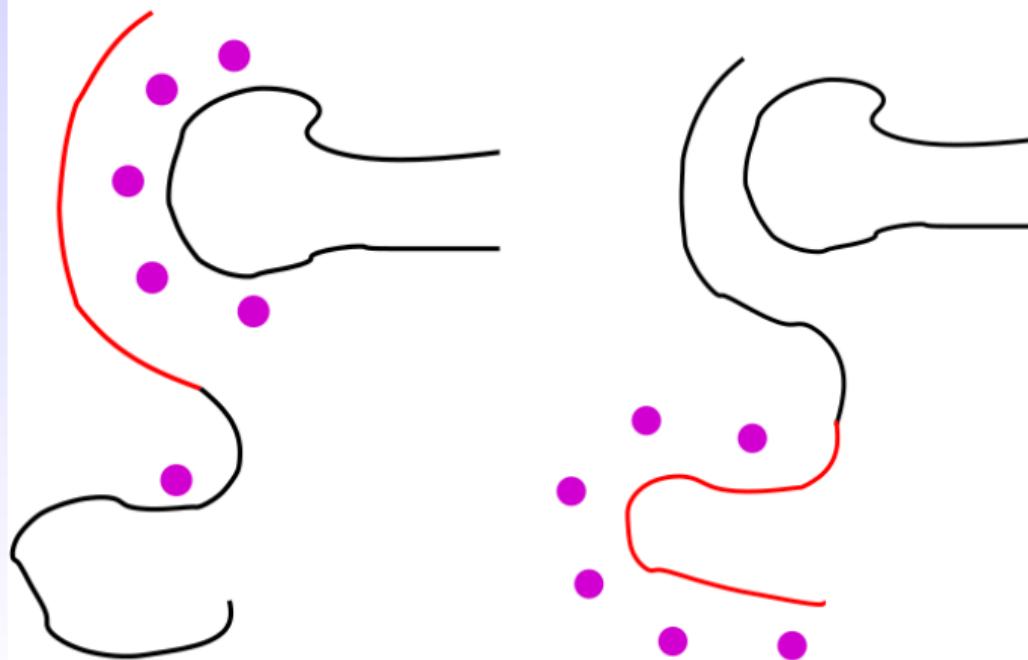
Asp/Glu
Lys/Arg

Osteopontin (OPN)

G. La Penna et al., Front. Chem. 2018

(A)

(B)



Mg: divalent cations

Shifting the Coulomb energy, empirical methods:

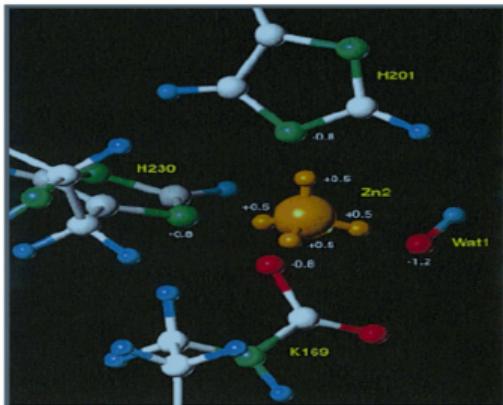


Fig. 1. A close-up view of the zinc divalent cation attached with four cationic dummy atoms used in the MD simulation of the DMP-PTE complex showing the atomic charges on the dummy atoms and zinc ligands (green = N; white = C; red = O; cyan = H; and orange = Zn).

Y-P. Pang 2001

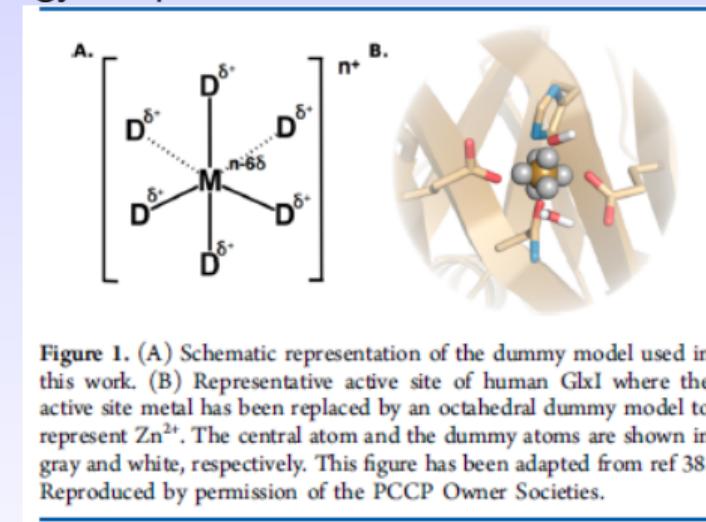
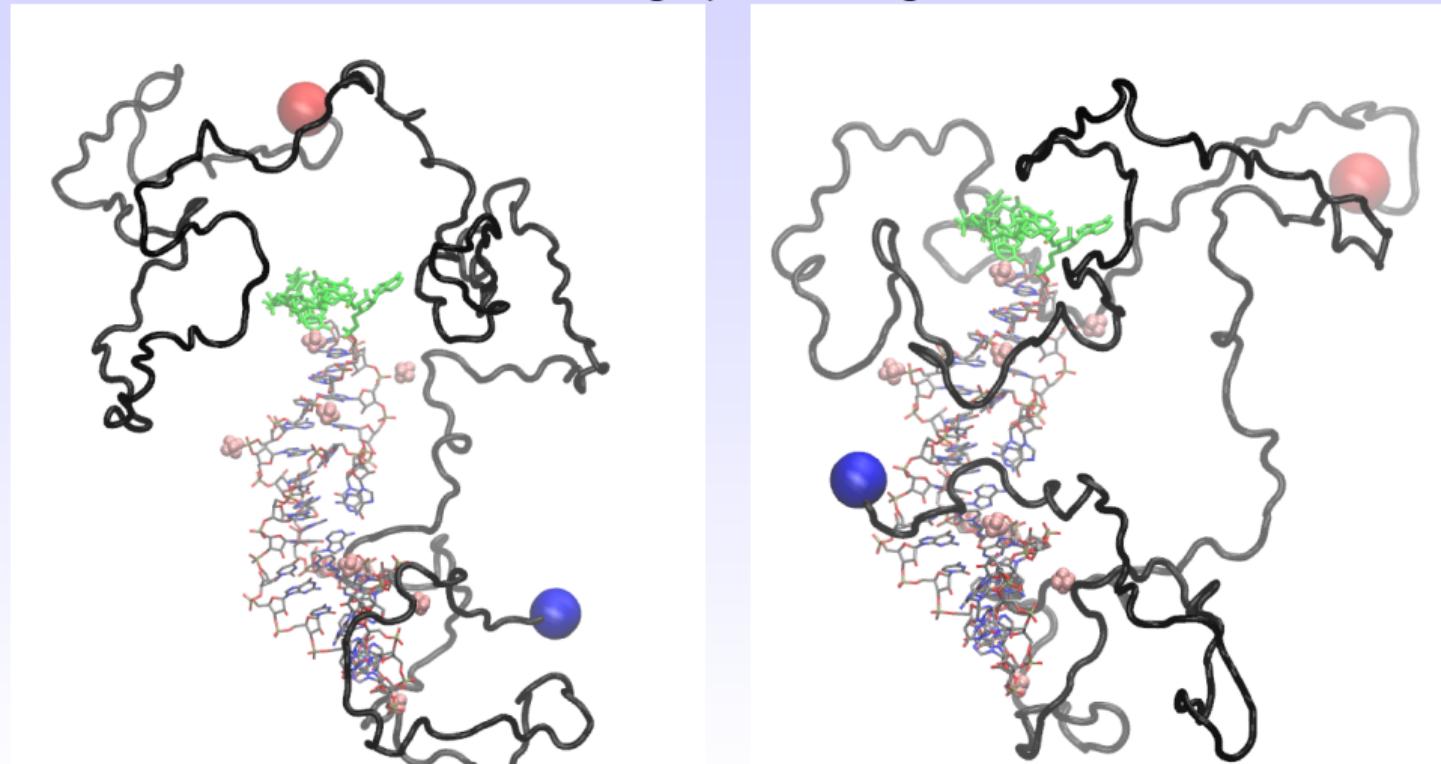


Figure 1. (A) Schematic representation of the dummy model used in this work. (B) Representative active site of human GlxI where the active site metal has been replaced by an octahedral dummy model to represent Zn^{2+} . The central atom and the dummy atoms are shown in gray and white, respectively. This figure has been adapted from ref 38. Reproduced by permission of the PCCP Owner Societies.

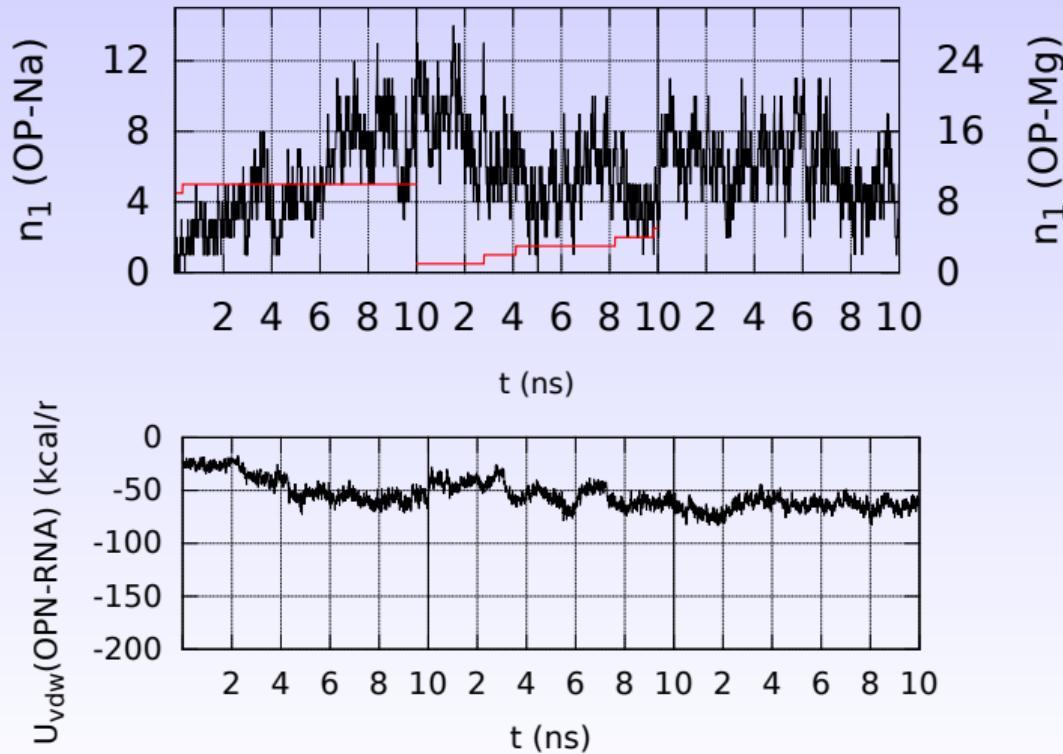
F. Duarte et al. 2014

Mg: divalent cations

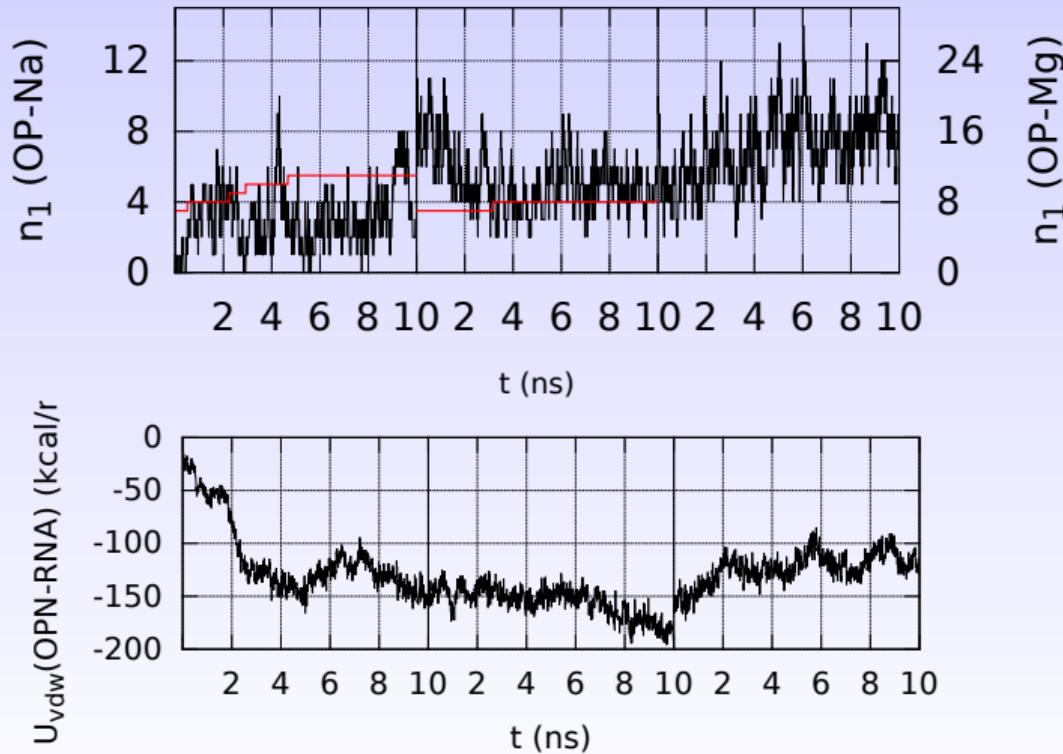
Folding-upon-binding



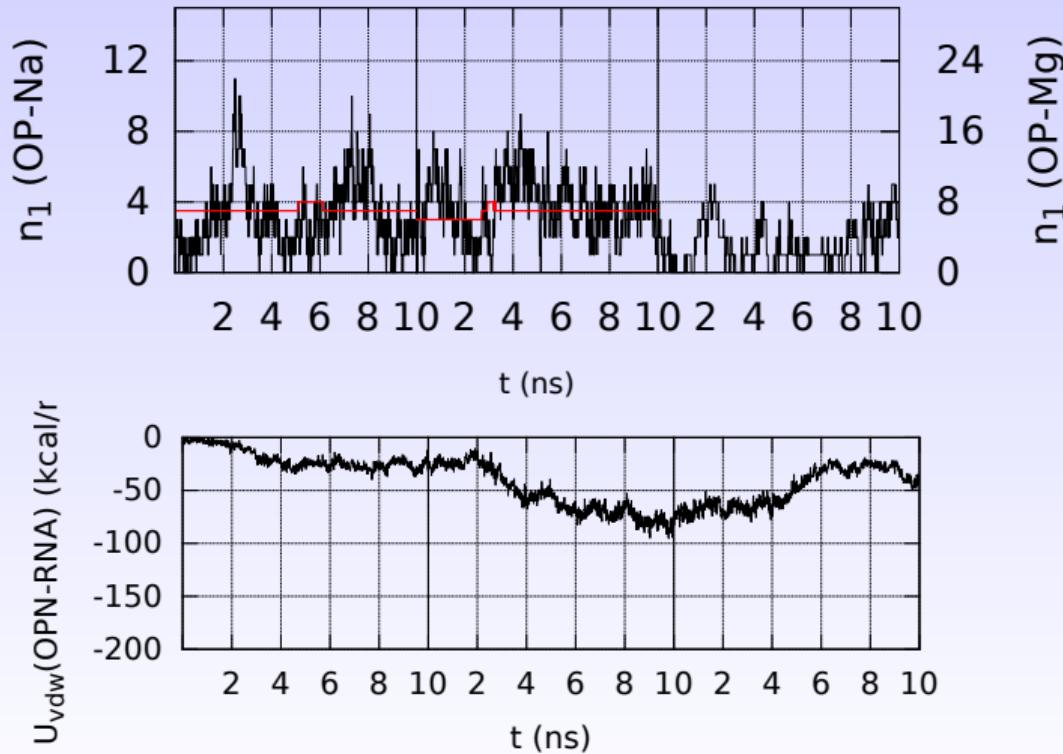
Mg: divalent cations



Mg: divalent cations

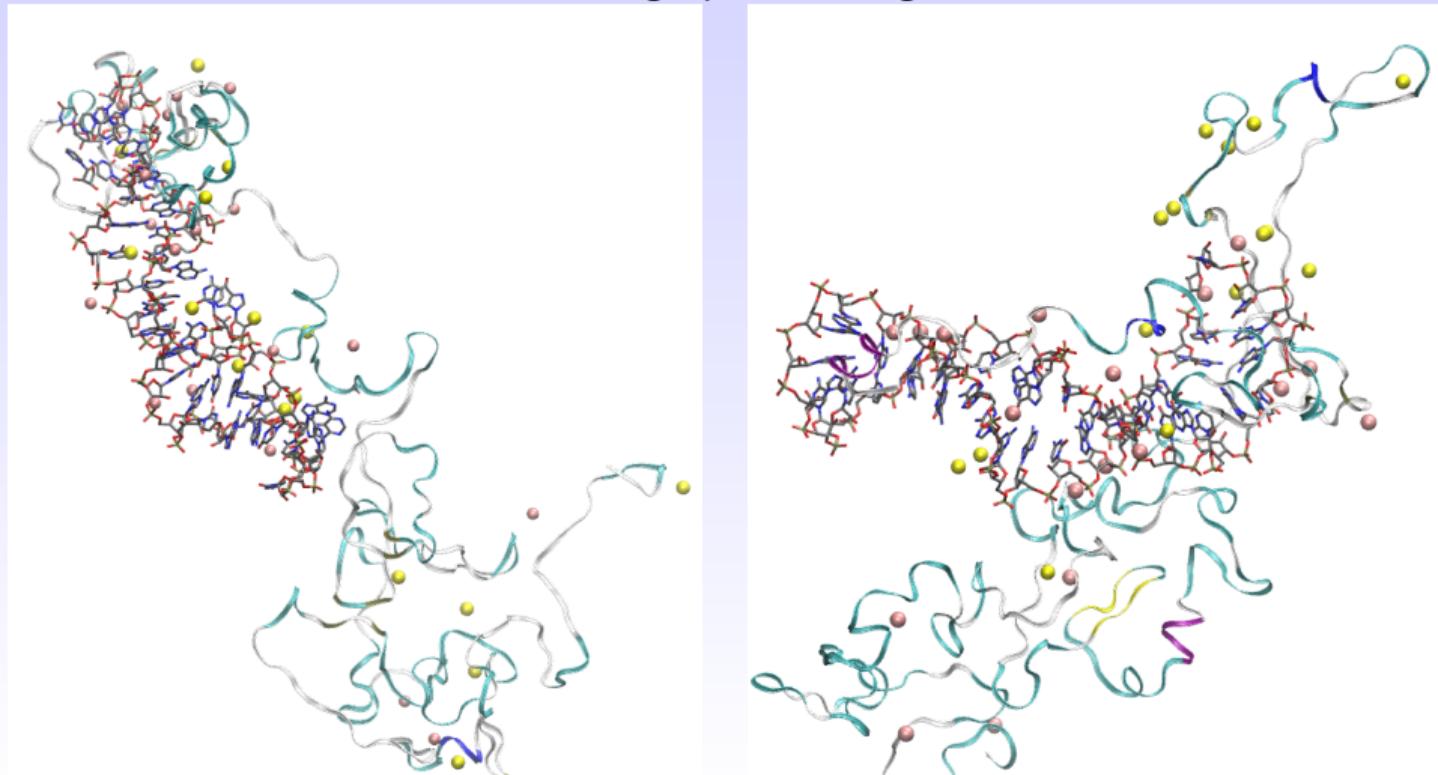


Mg: divalent cations

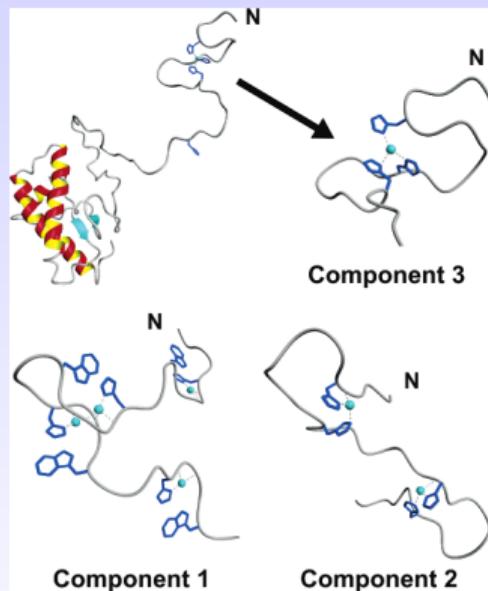


Mg: divalent cations

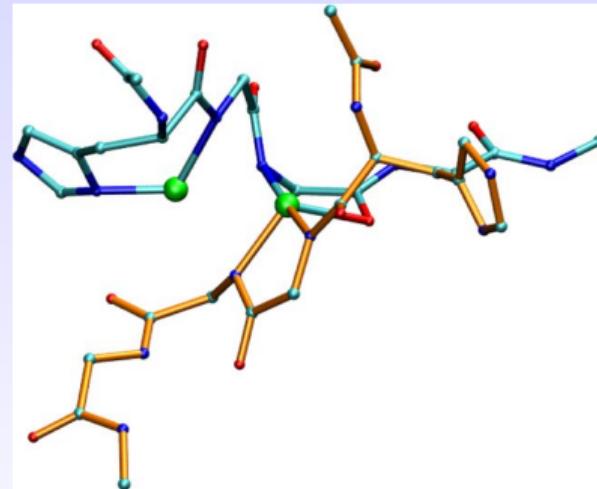
Folding-upon-binding



Cu and prion

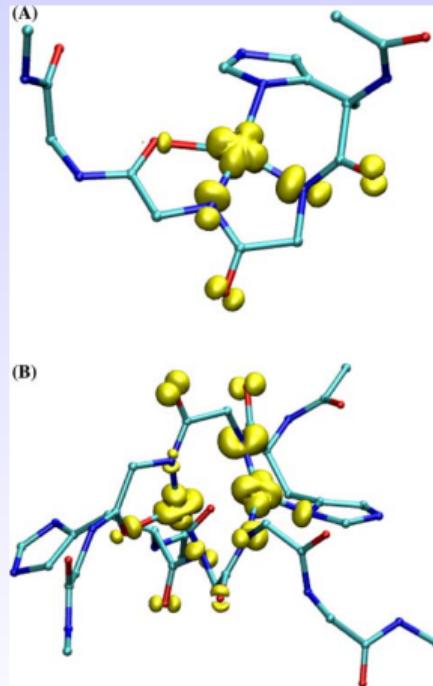


Chattopadhyay et al. JACS 2005

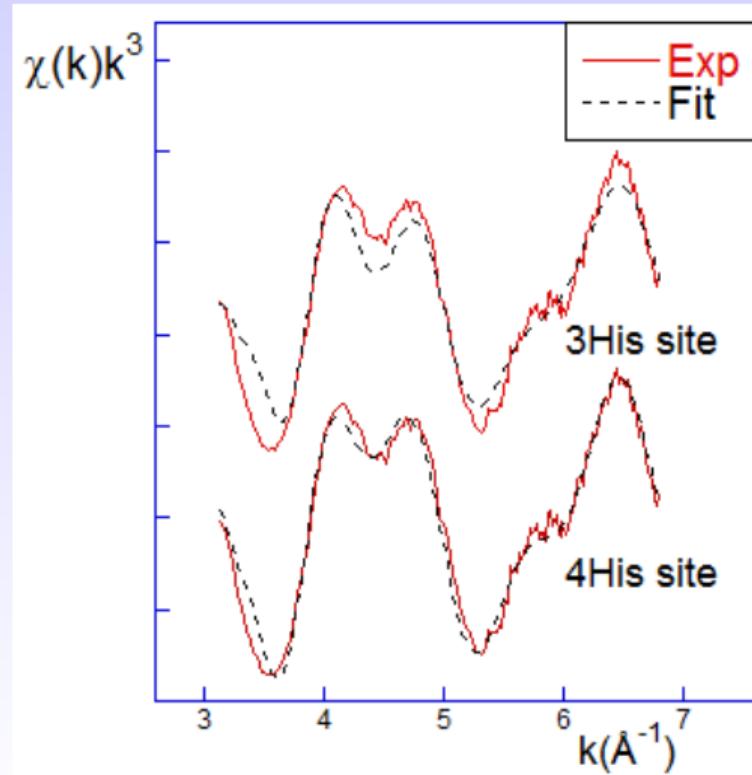


Furlan et al. JBIC 2007

Cu and prion

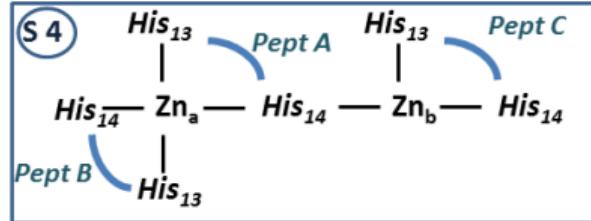
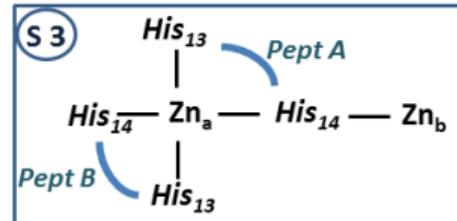
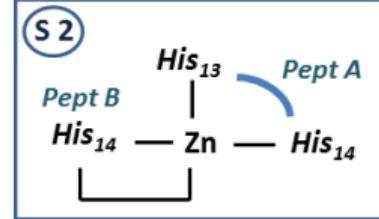
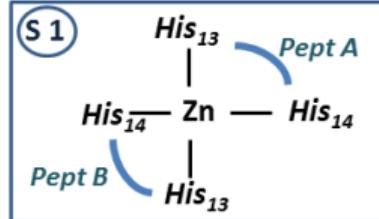


Zn and non-amyloid oligomers

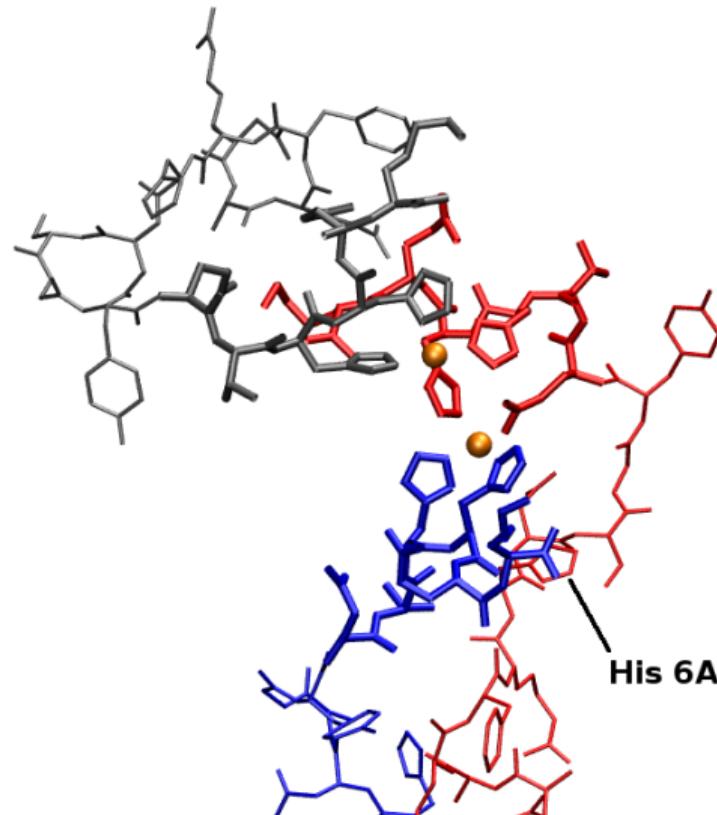


V. Minicozzi et al., JBC, 2008

Zn and non-amyloid oligomers

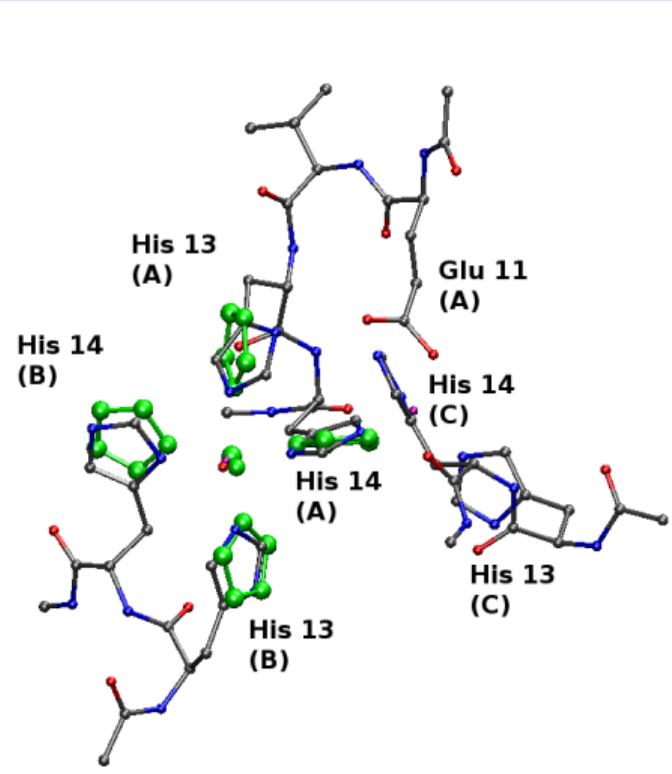


Zn and non-amyloid oligomers

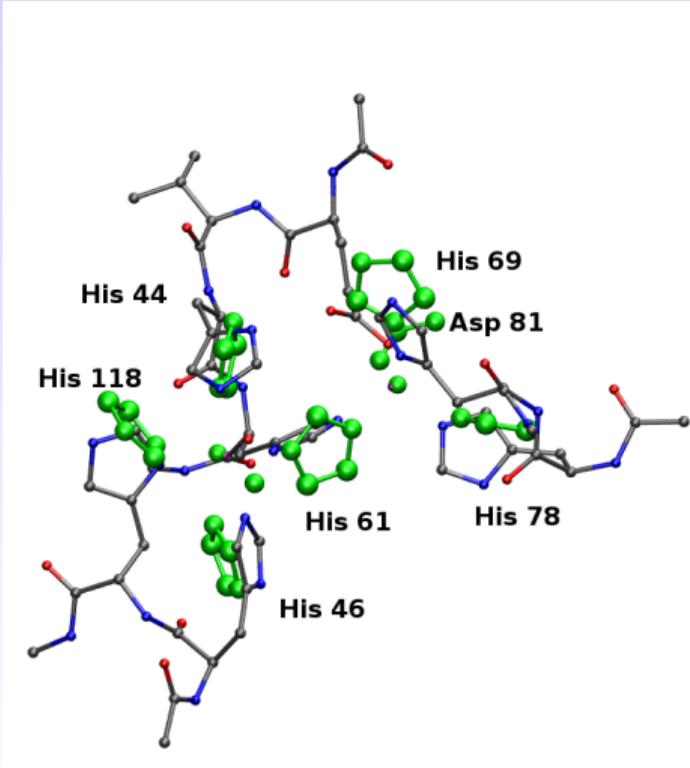


P. Giannozzi et al., Metallomics, 2012

Zn and non-amyloid oligomers

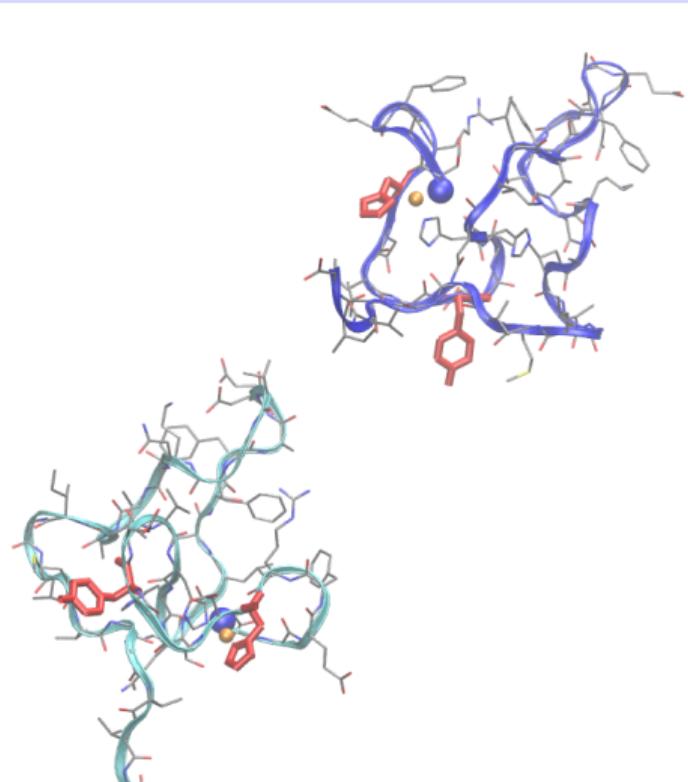


Zn and non-amyloid oligomers

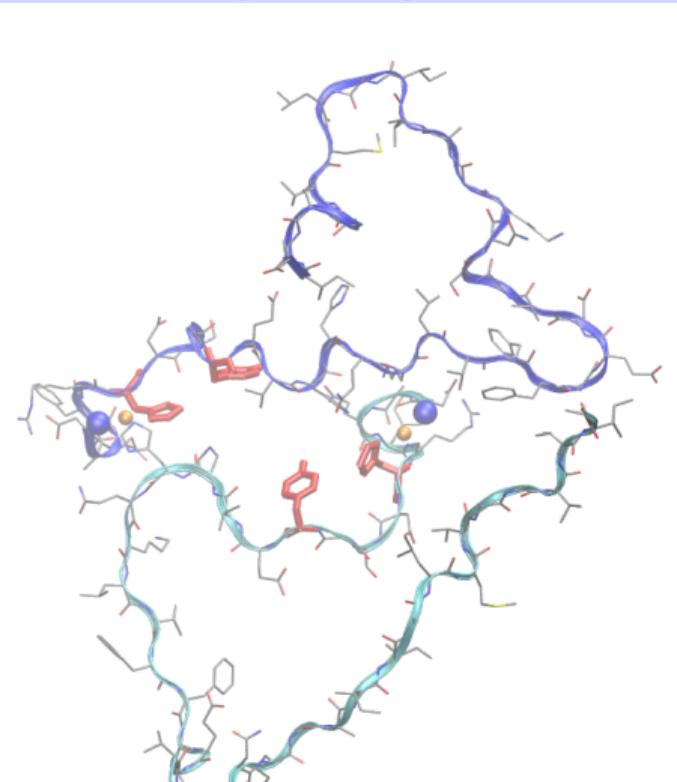


Cu and non-amyloid oligomers

$2 \times \text{Cu-A}\beta_{42}$

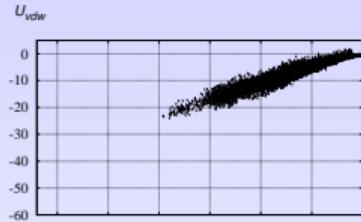


$[\text{Cu-A}\beta_{42}]_2$

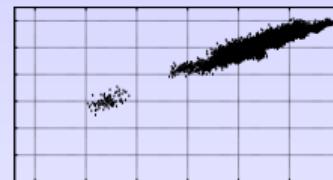


Cu and non-amyloid oligomers

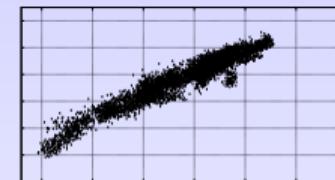
$2 \times A\beta_{42}$



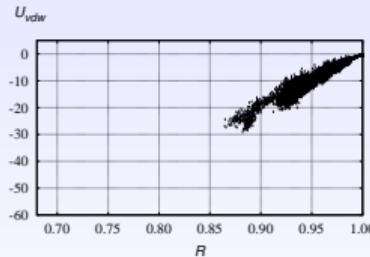
$2 \times Cu-A\beta_{42}$



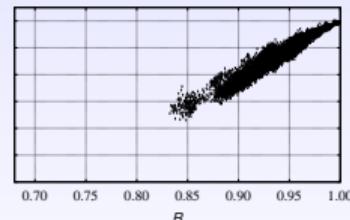
$[Cu-A\beta_{42}]_2$



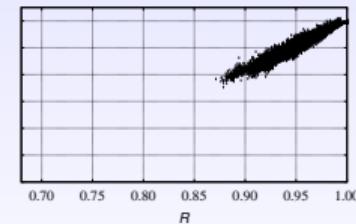
$4 \times A\beta_{42}$



$4 \times Cu-A\beta_{42}$

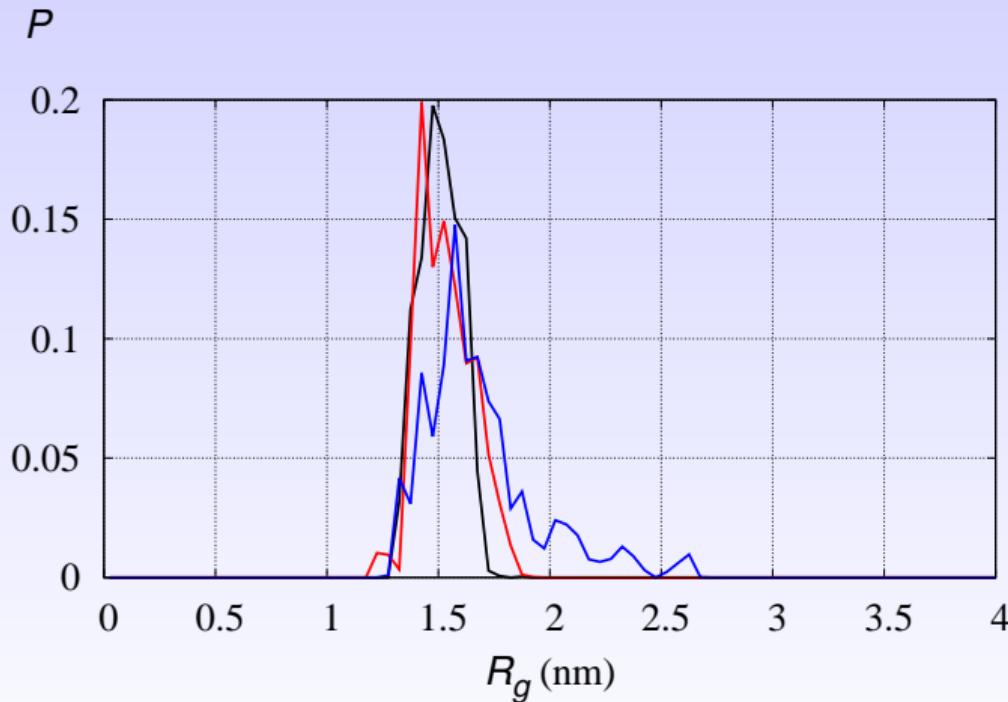


$2 \times [Cu-A\beta_{42}]_2$



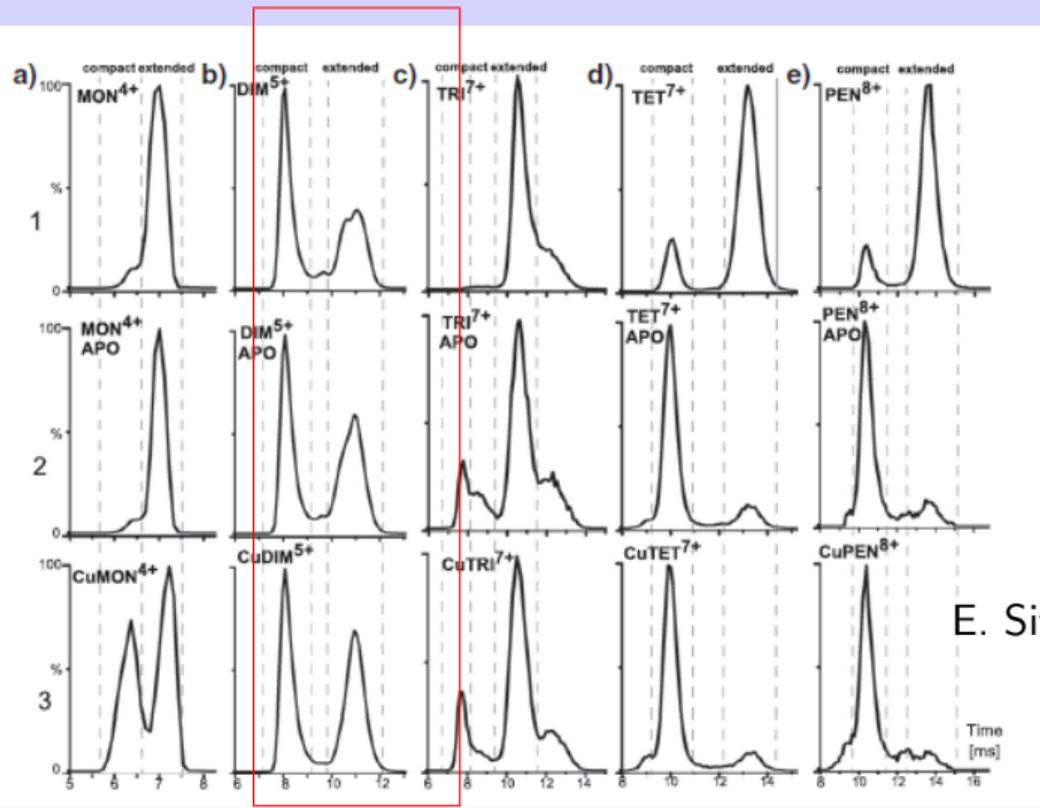
$$R = \frac{SASA(AB)}{[SASA(A)+SASA(B)]}$$

Cu and non-amyloid oligomers



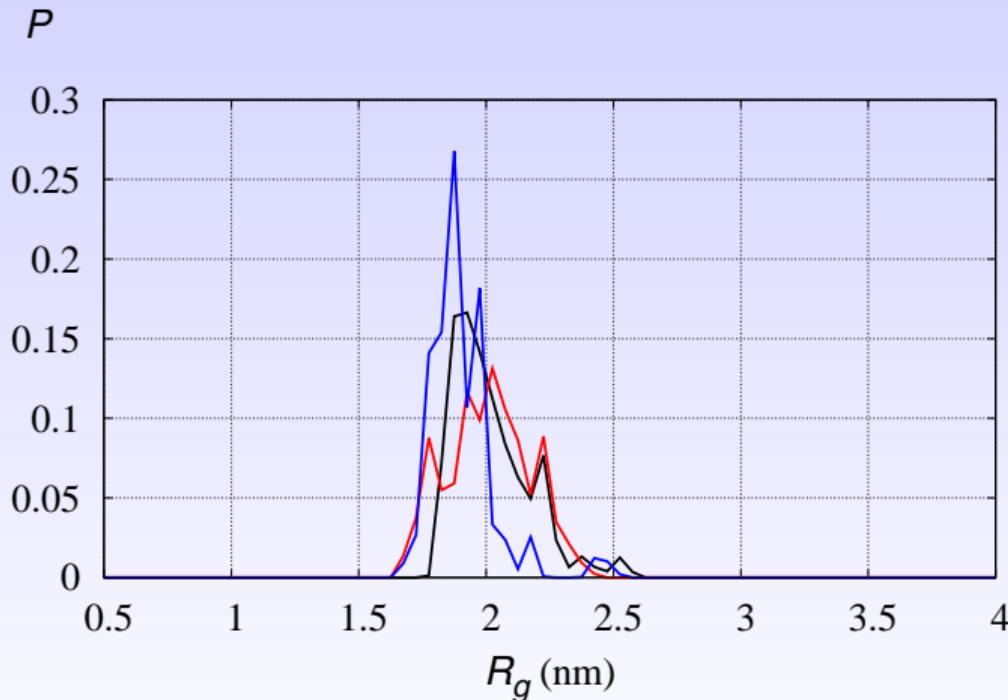
Dimers: $2 \times A\beta$ $2 \times Cu-A\beta$ $[Cu-A\beta]_2$

Cu and non-amyloid oligomers



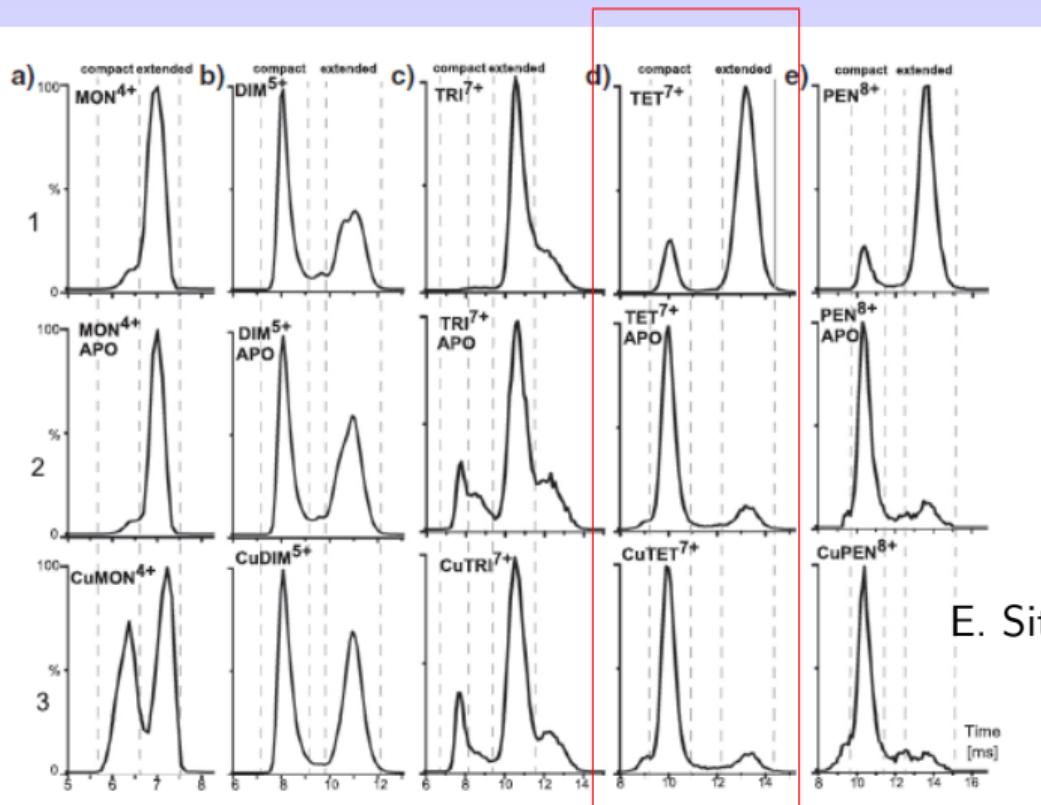
E. Sitkiewicz et al. J. Mol. Biol., 2014

Cu and non-amyloid oligomers



Tetramers: $2 \times [2 \times A\beta]$ $2 \times [2 \times Cu-A\beta]$ $2 \times [Cu-A\beta]_2$

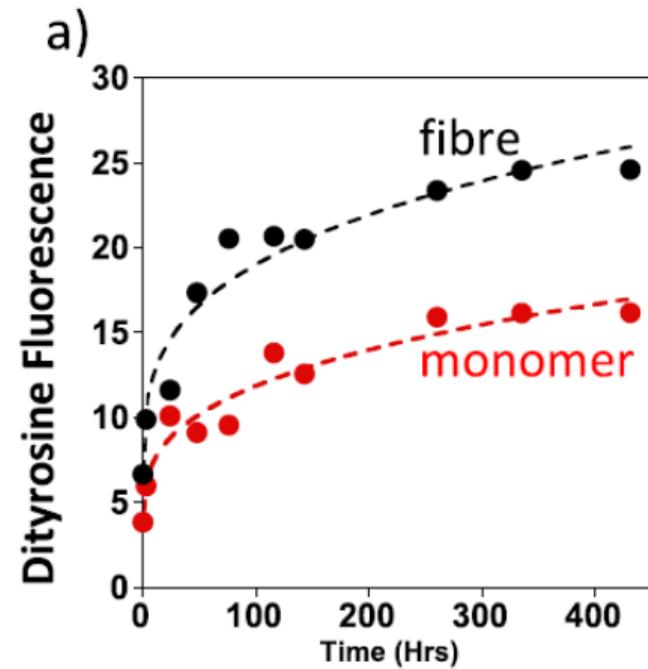
Cu and non-amyloid oligomers



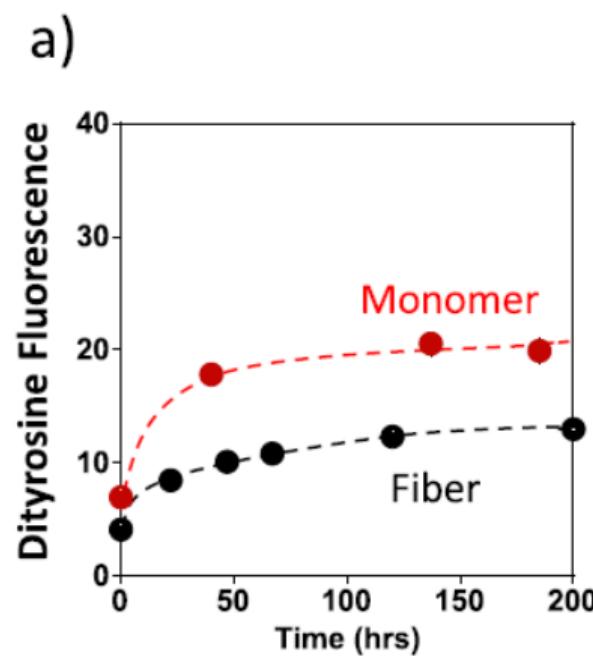
E. Sitkiewicz et al. J. Mol. Biol., 2014

Cu and non-amyloid oligomers

Reducing env.



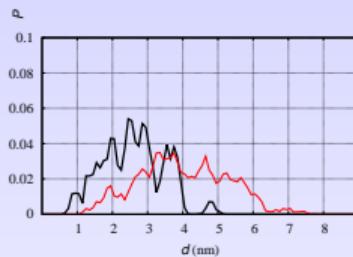
Oxidizing env.



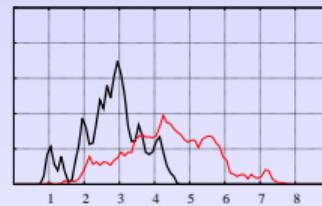
M. Gu et al., Sci. Rep., 2018

Cu and non-amyloid oligomers

$2 \times A\beta_{42}$



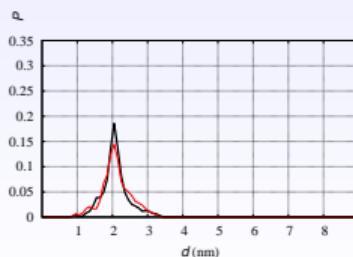
$2 \times Cu-A\beta_{42}$
Monomers



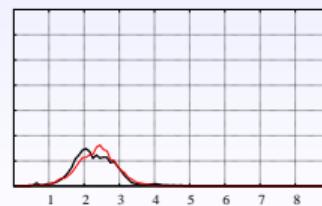
$[Cu-A\beta_{42}]_2$
Dimers



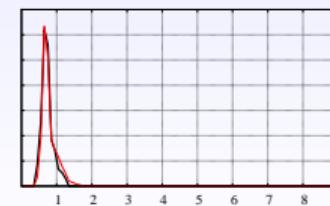
$4 \times A\beta_{42}$



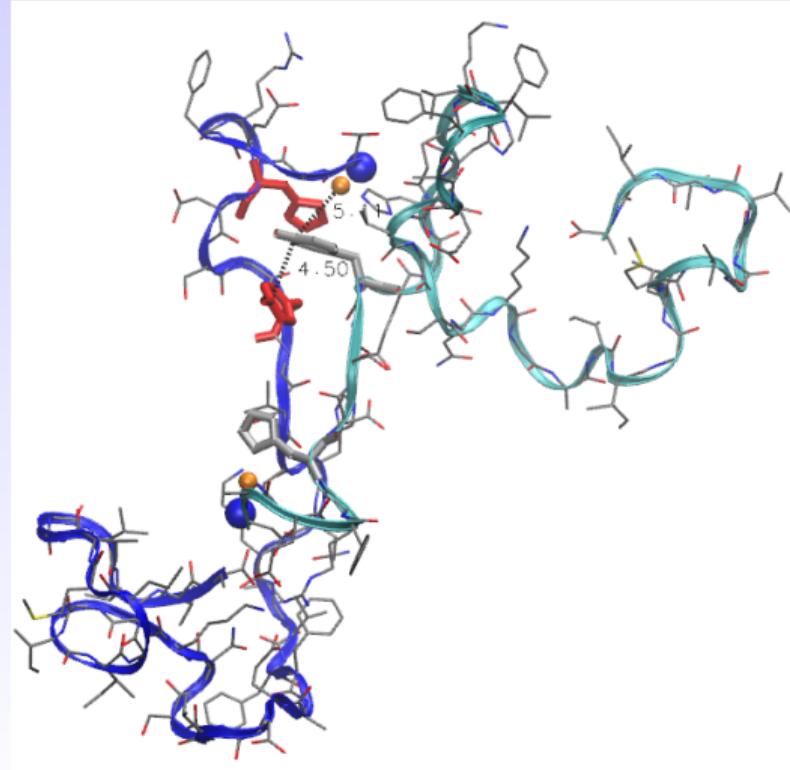
$4 \times Cu-A\beta_{42}$
Dimers



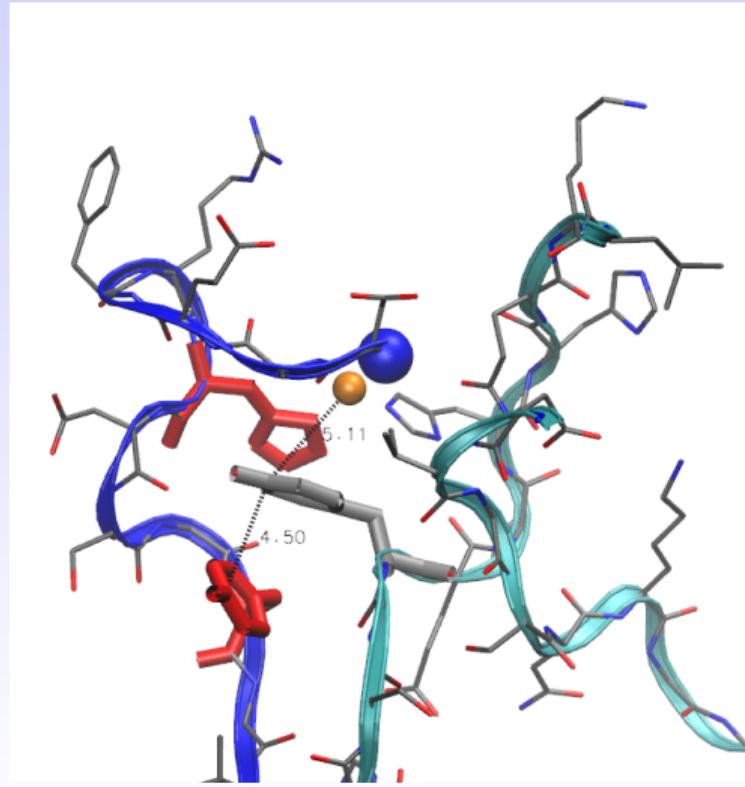
$2 \times [Cu-A\beta_{42}]_2$
Dimers of dimers
(tetramers)



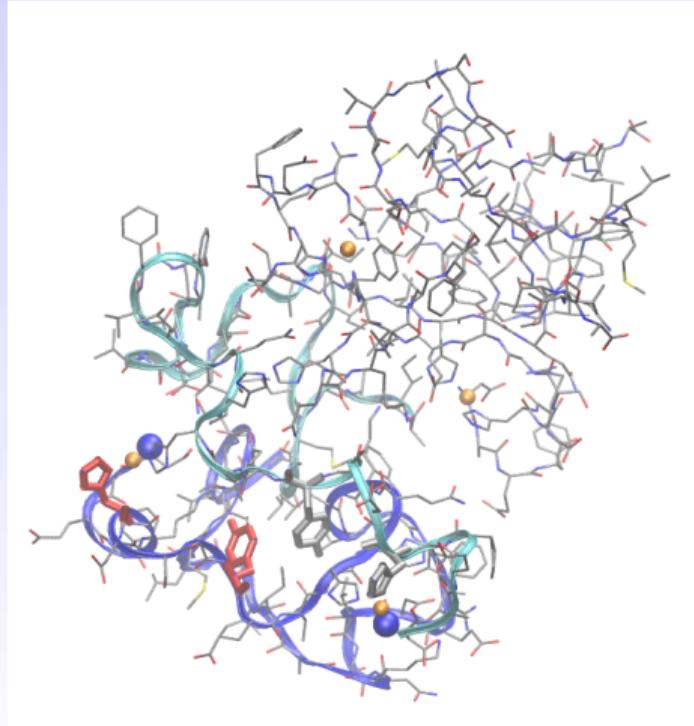
Cu and non-amyloid oligomers



Cu and non-amyloid oligomers



Cu and non-amyloid oligomers



G. La Penna, M.S. Li, PCCP, 2019

Summary: useful experimental techniques

Experimental techniques to obtain information about ions collected by weak interactions (out of coordination chemistry and structural biology):

- SAXS/ASAXS, XAS
- EPR (ESEEM, DEER)
- IM-MS
- FRET
- Fluorescence di X-X vs X