Chemical properties emerging from structural disorder in biology

Giovanni La Penna, National research council (CNR)

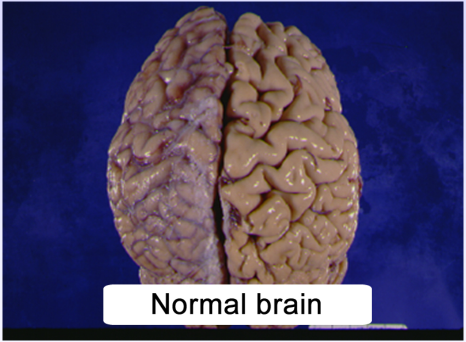
Dec 11th 2019

Overview: cell degeneration because of undesired catalysis

sites.google.com/view/wwwgiovannilapennait

Neurodegeneration: neurons die

Chapt. 10.4 CNS Aging and Alzheimer's Disease Jack C. Waymire (Univ. Texas / Houston)



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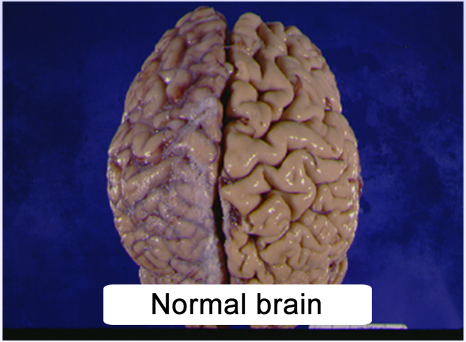
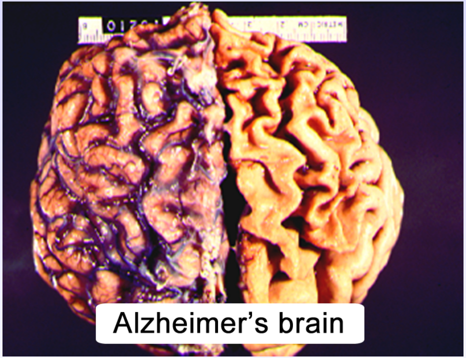
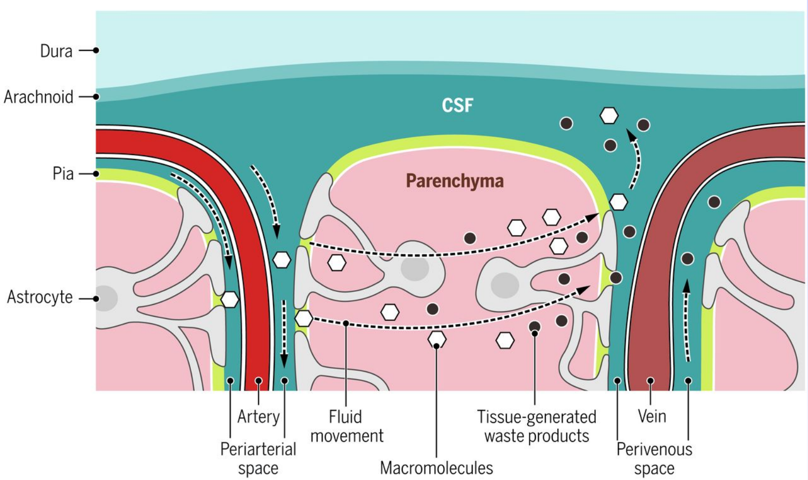




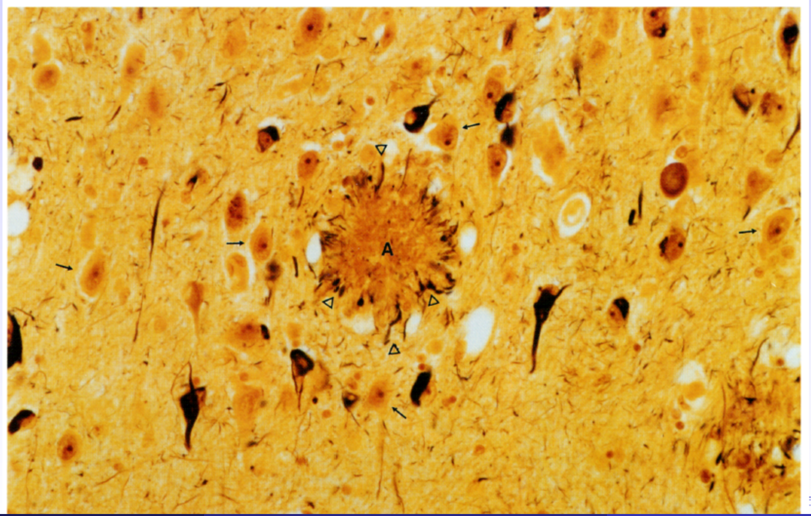
Neurodegeneration: cleaning brain with no cell replacement



J. Kipnis *Science*, (2016)

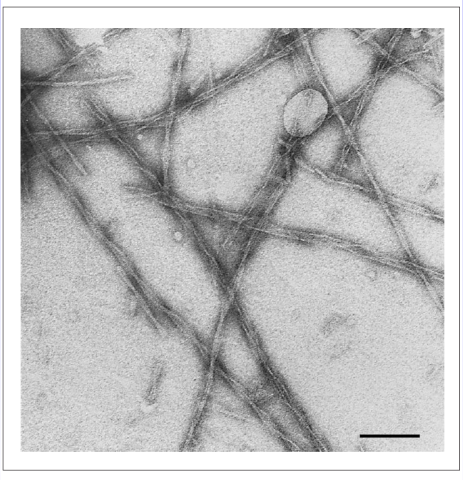
Neurodegeneration: hallmarks of neuron death

Selkoe D.J., *Neuron*, (1991)

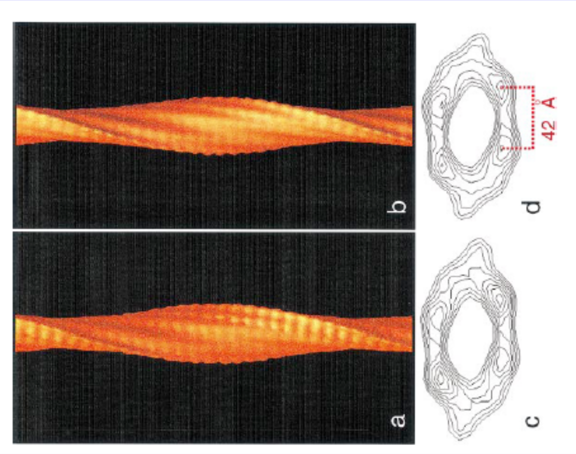


Neurodegeneration: Aβ aggregates

J.I. Gujiarro et al., *PNAS*, (1998)



J.L. Jiménez et al., *EMBO J.*, (1999)



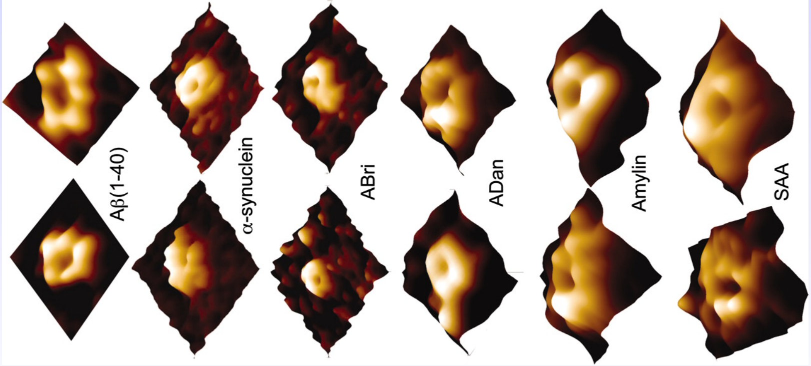
Neurodegeneration: the amyloid-β peptide (Aβ)

Negative charge
Positive charge
Histidine=avid of Cu
Target of oxidation ("weak" electrons)

D_1 A E F R_5 H_6 D S G Y_{10} E V H_{13} H_{14} Q
K_{16} L V F F A E
D_{23} V G S N K_{28} G A I I G L M_{35} V G G V V_{40} I A

Neurodegeneration: pores in membrane

Quist A. et al., *PNAS*, (2005)



Cu & reactive oxygen species (ROS)

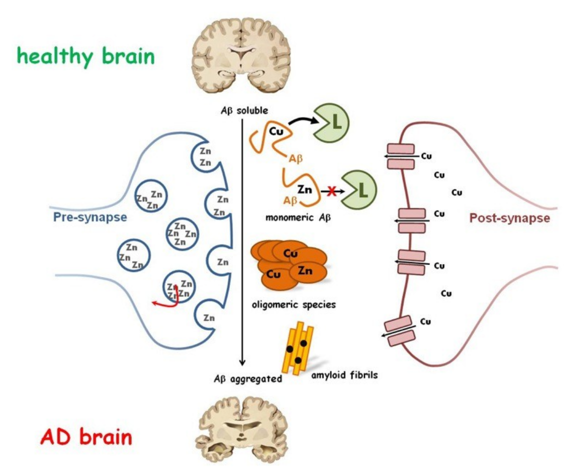
In amyloid deposits (hallmarks of Alzheimer's disease):

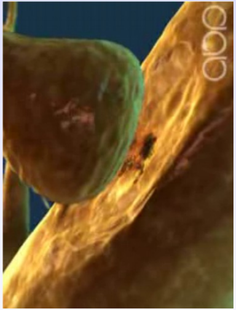
- Zn 1mM
- Cu 0.4 mM
- 80% of Zn in the body is protein-bound
- 20% is in pre-synaptic vescicles (ready for synaptic activity)
- 8% of Cu (9 mg) is in the brain (2% of body weight)

K. Barnham, A.Bush Chem. Soc. Rev. 2014

Cu & ROS: synaptic Cu creates catalysts

C. Cheignon et al., Redox Biol. 2018





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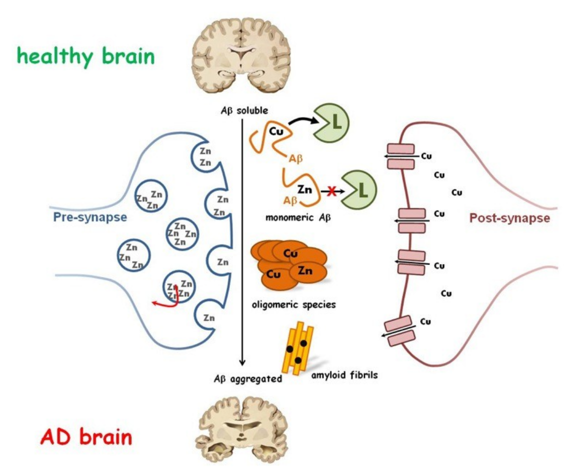
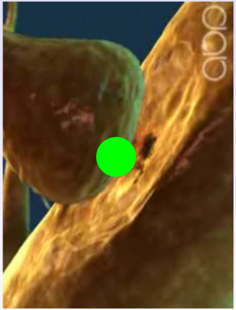
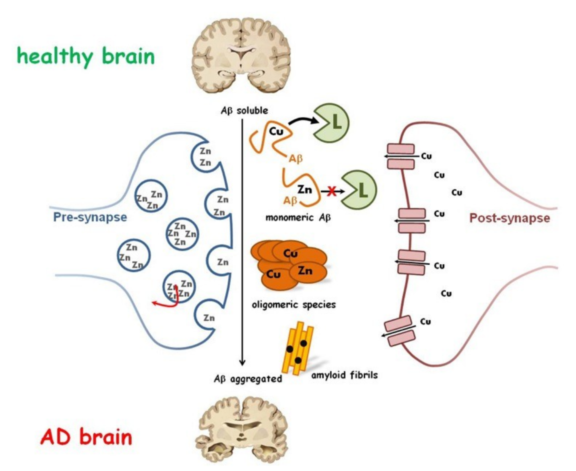
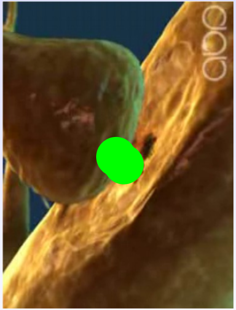




C. Cheignon et al., Redox Biol. 2018





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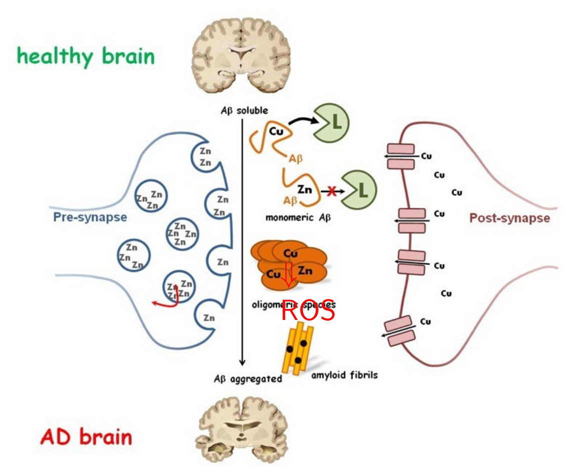
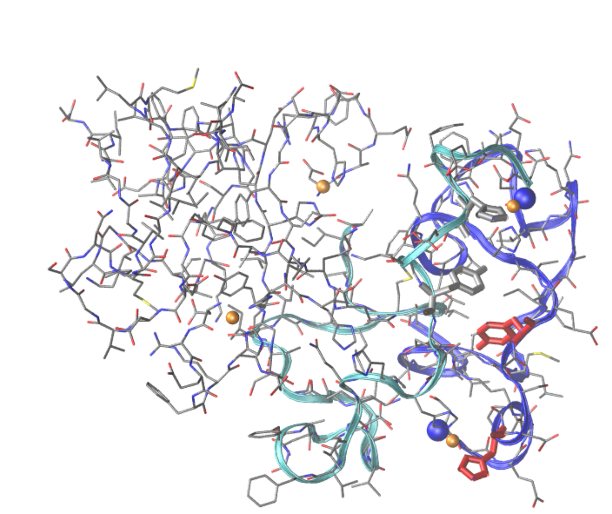
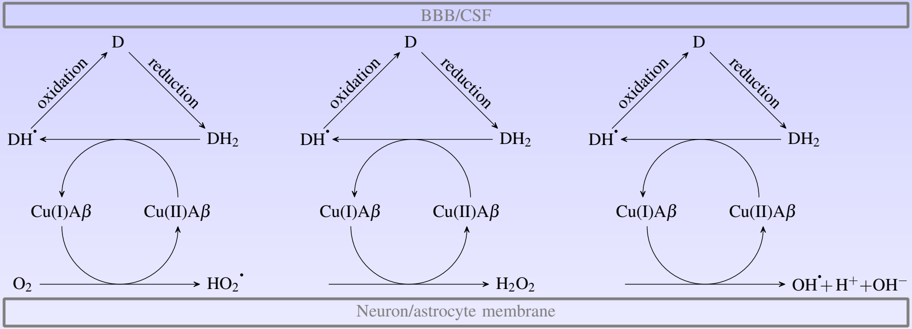


Cu, Aβ & ROS: one result from DECI 13th

G. La Penna & M.S. Li *PCCP* 2019



Cu & ROS: the reaction mechanism



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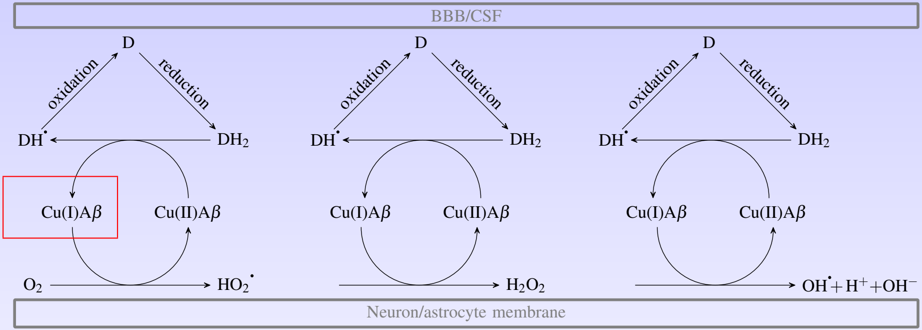

S. Furlan et al., JBIC, 2010

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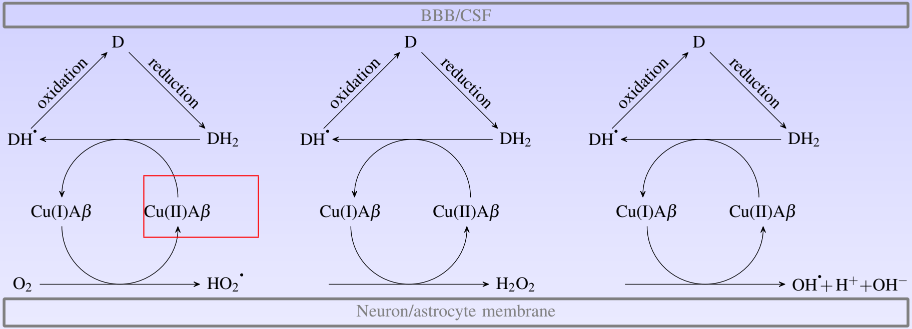

S. Furlan et al., JPCB, 2012

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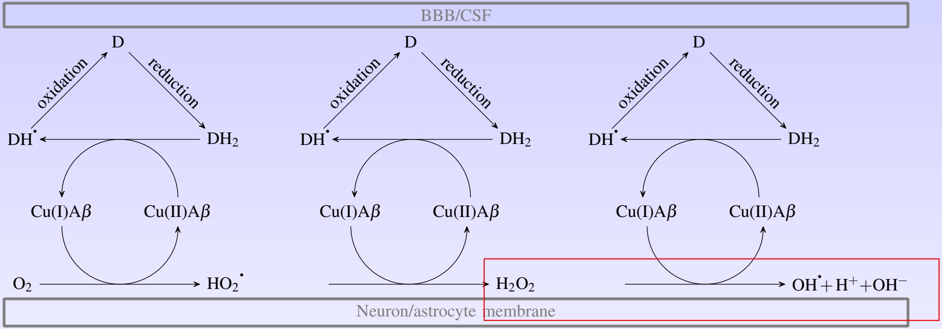

G. La Penna et al., JPCB, 2013

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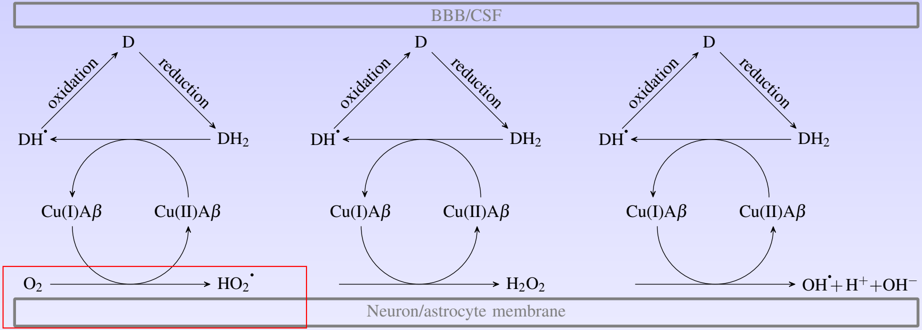
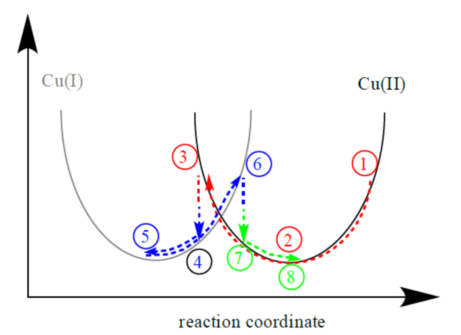
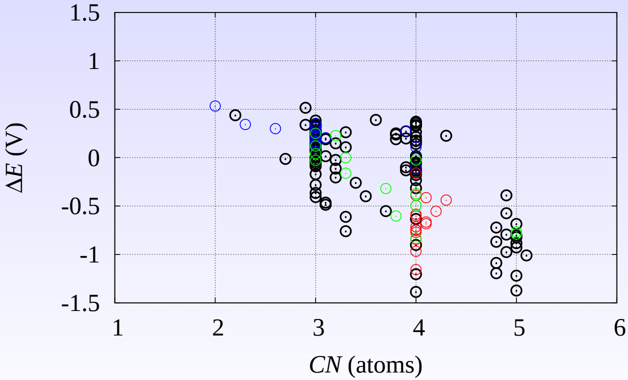


A. Mirats et al., PCCP, 2015; K. Reybier et al., Angew. Chem. 2016

Cu & ROS: the ligand modulates the reduction potential

G. La Penna et al., *JPCB*, 2013; *Mol. Sim*, 2014/ *JCP*, 2014; Springer 2019
CN=Cu coordination number





Cu & dioxygen activation: can be a smooth process

G. La Penna & Mai Suan Li, *Chemistry Eur. J.* 2018

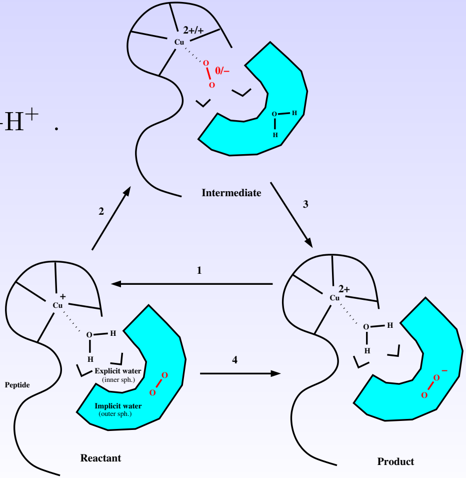
$$\mathrm{L{-}Cu^{2+}{-}(H_2O) + Asc^-} \longrightarrow \mathrm{L{-}Cu^{+}{-}(H_2O) + Asc^{\cdot} + H^+} \,. \quad (1)$$

$$\mathrm{L{-}Cu^{+}{-}(H_2O) + O_2} \longrightarrow \mathrm{L{-}Cu^{+}{-}(O_2) + H_2O} \quad (2)$$

$$\mathrm{L{-}Cu^{+}{-}(O_2)} \longleftrightarrow \mathrm{L{-}Cu^{2+}{-}(O_2{}^-)} \quad (2a)$$

$$\mathrm{L{-}Cu^{2+}{-}(O_2{}^-) + H_2O} \longrightarrow \mathrm{L{-}Cu^{2+}{-}(H_2O) + O_2{}^-} \quad (3)$$

$$\mathrm{Asc^- + O_2} \longrightarrow \mathrm{Asc^{\cdot} + H^+ + O_2{}^-} \quad (4)$$



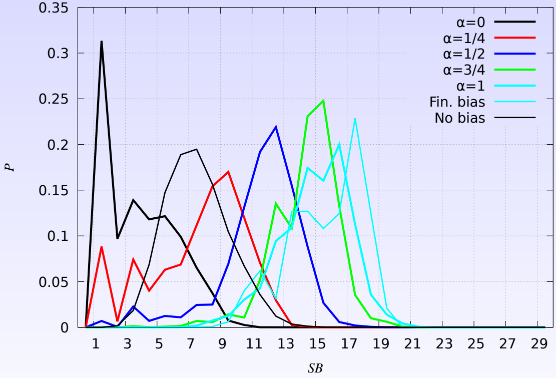
Methods: generalized statistical ensembles

How to combine N independent simulations in one unique statistical ensemble
1) choose a collective variable, CV (CV=energy, as in MC and MD, is not useful for macromolecules);
2) obtain a uniform density in CV: $n(CV) = const$
$\rightarrow$ let one trajectory to explore a domain different from the other trajectories
$\rightarrow$ "le traiettorie non devono pestarsi i piedi l'una con l'altra"
But trajectories must communicate $\rightarrow$ detailed balance
$\rightarrow$ unique statistical ensemble
$\rightarrow$ metadynamics and metastatistics
3) if the probability generating the uniform $n(CV)$ is known:
$\rightarrow$ reweighting
$\rightarrow$ from metastatistics to thermodynamic ensemble.

Methods: generalized statistical ensembles

To perform 1-2, altruistic metadynamics:

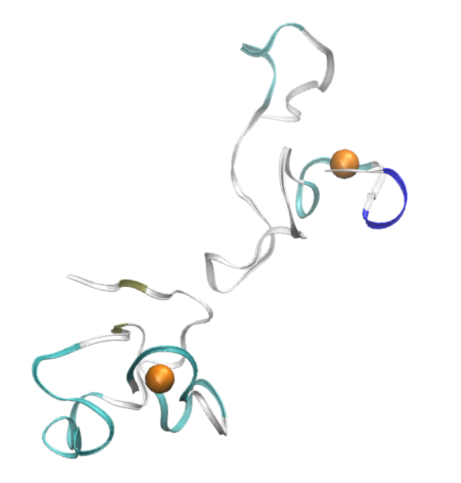
$$F = -V_{bias} = -[(2-\alpha)\sum_{t'\le t} hg_{j,t'} + \frac{\alpha}{N-1}\sum_{i=1,i\neq j}^{N}\sum_{t'\le t} hg_{i,t'}]$$



P. Hošek et al., JPCB 2016

G. La Penna, M.S. Li , Chem. Eur. J. 2018

Methods: generalized statistical ensembles



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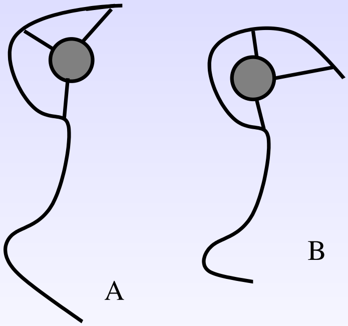

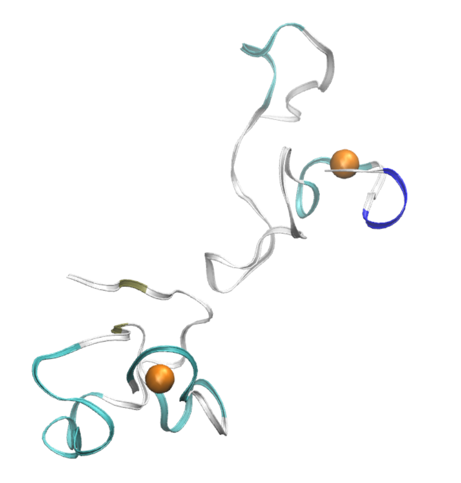

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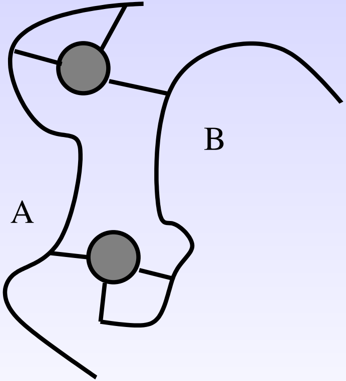
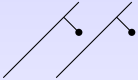
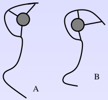


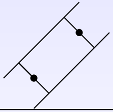
Methods: dimers & tetramers

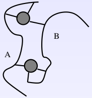
$2\times$ Cu-Aβ_{42}





[Cu-Aβ_{42}]$_2$





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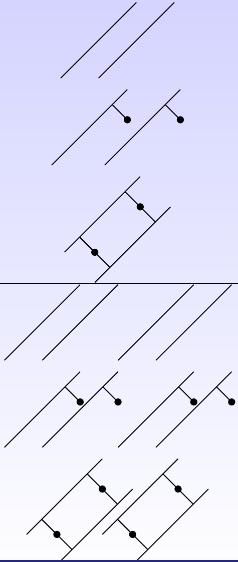
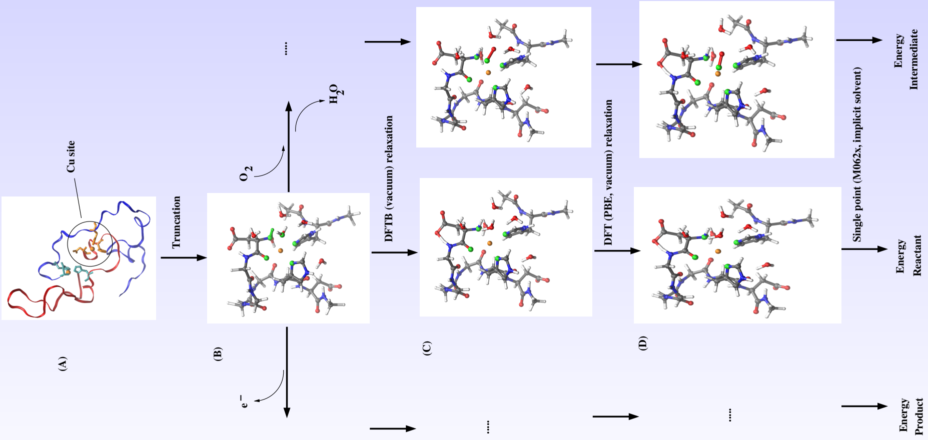
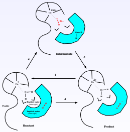


$2\times$ Aβ_{42}	128
$2\times$ Cu-Aβ_{42}	128
[Cu-Aβ_{42}]$_2$	55
$4\times$ Aβ_{42}	125
$4\times$ Cu-Aβ_{42}	126
$2\times$ [Cu-Aβ_{42}]$_2$	127

Methods: sampling quantum-mechanical properties (emerging chemistry)



Cu-Aβ & dioxygen activation



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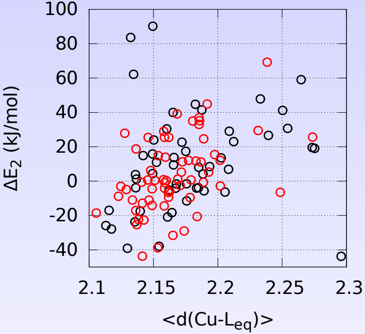

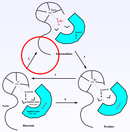

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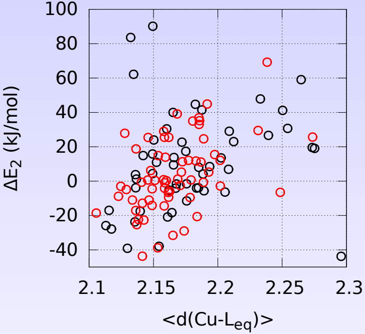

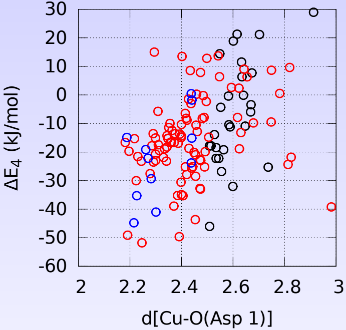

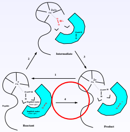

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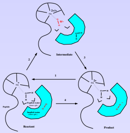

$$\Delta E_2 = -5 \text{ kJ/mol}$$
$$\Delta E_3 = -4 \text{ kJ/mol}$$
$$\Delta E_4 = -9 \text{ kJ/mol}$$

distance	reactant	intermediate	product
N(Asp 1)-Cu	2.14	2.12	2.09
O(Asp 1)-Cu	2.36	2.37	2.08
Nδ1(His 6)-Cu	2.03	2.05	2.04
Nϵ2(His 13)-Cu	2.09	2.11	2.06
O_{ax}-Cu	2.82	2.03	2.55

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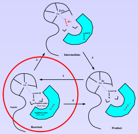

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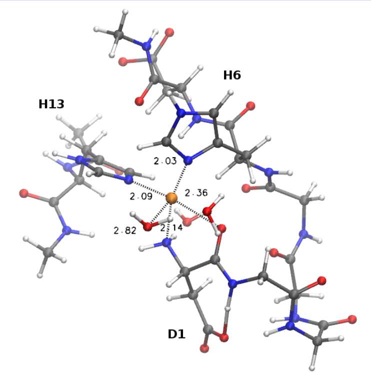

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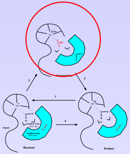

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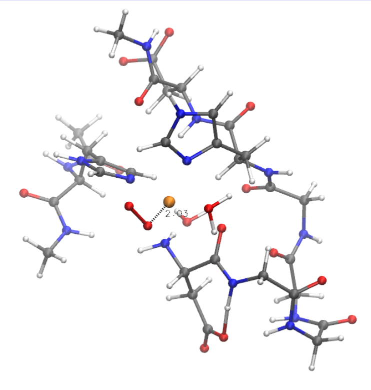

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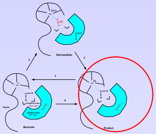
Cu-Aβ & dioxygen activation



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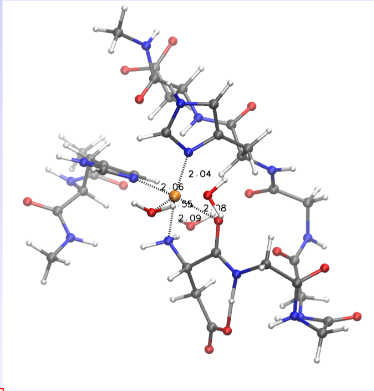

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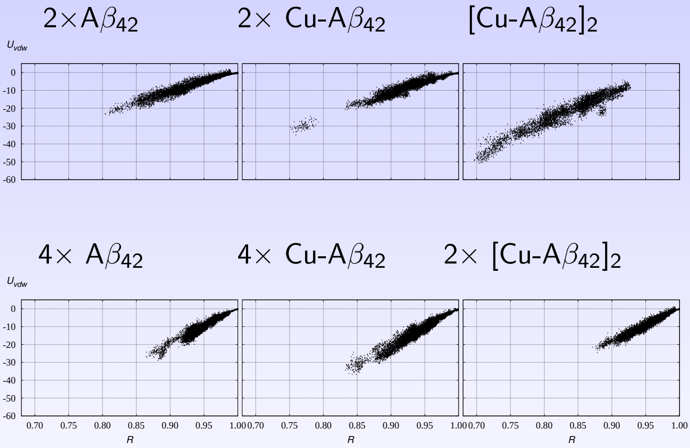
Aβ and Cu-Aβ oligomers

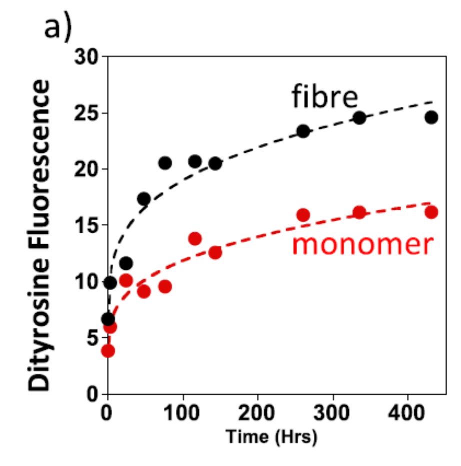


$$R = \frac{SASA(AB)}{[SASA(A)+SASA(B)]}$$

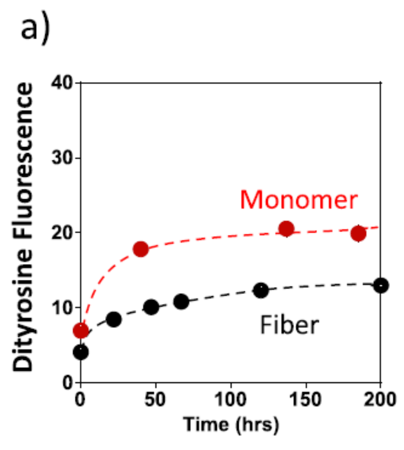
SASA=solvent accessible surface area

Cu-Aβ & oxidation: Tyr-Tyr crosslinks

Reducing env.



Oxidizing env.



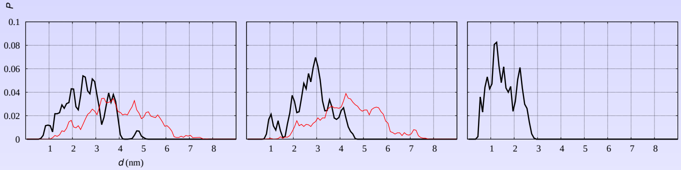
M. Gu et al., Sci. Rep., 2018

Cu-Aβ & oxidation: Tyr-Tyr crosslinks

$2\times A\beta_{42}$

$2\times$ Cu-Aβ_{42}
Monomers

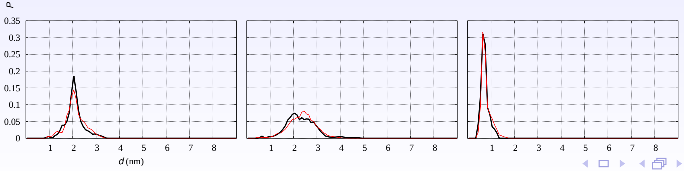
[Cu-Aβ_{42}]$_2$
Dimers



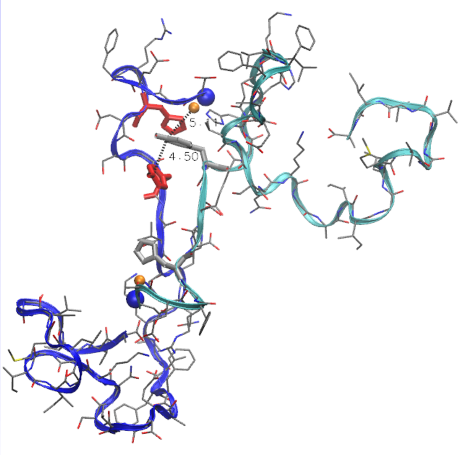
$4\times A\beta_{42}$

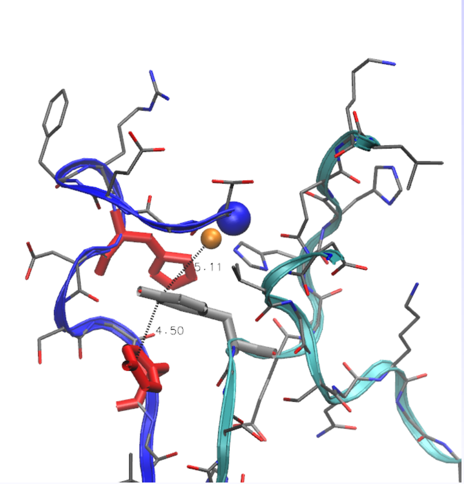
$4\times$ Cu-Aβ_{42}
Dimers

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

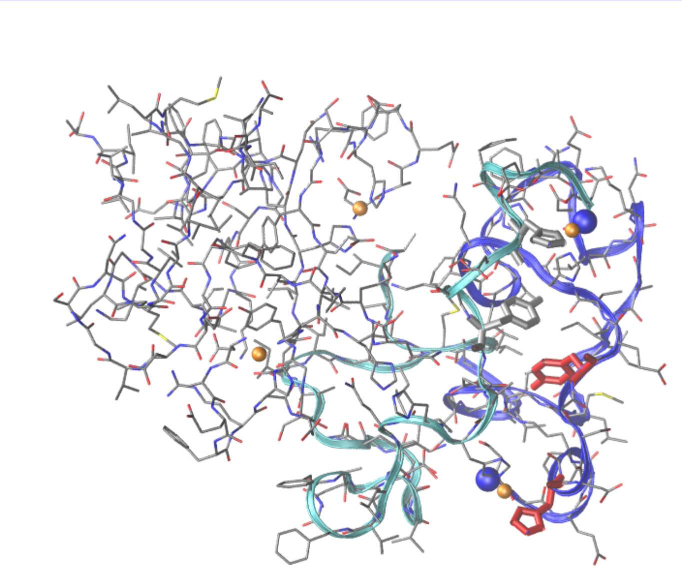


Cu-Aβ & oxidation: Tyr-Tyr crosslinks





Cu-Aβ, oxidation & aggregation: a transient enzyme (oxidase)



Conclusion: Ions as driving force

Neutralization

Conclusion: Ions as driving force

Neutralization

$\Downarrow$

Overcharging

Conclusion: Ions as driving force

Neutralization

$\Downarrow$

Overcharging

$\Downarrow$

Coordination

Conclusion: Ions as driving force

Neutralization

$\Downarrow$

Overcharging

$\Downarrow$

Coordination

$\Downarrow$

Electron transfer

People involved: statistics, QM & HPC

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