

*What is Creativity? Emergent Phenomena  
in Complex Adaptive Systems*

*Creativity in Science:  
Theoretical Predictions in Chemical  
and Biological Physics*

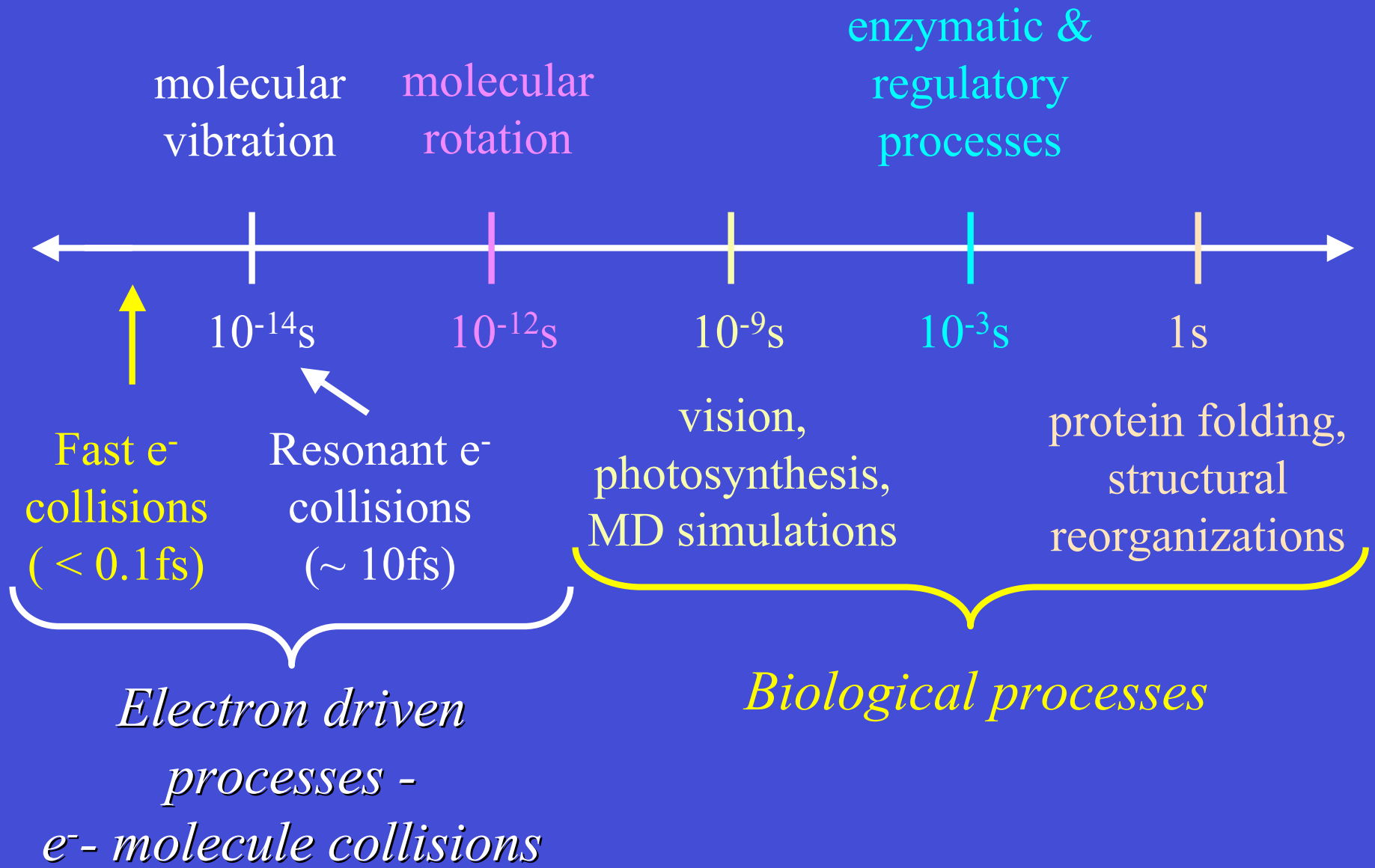
Cynthia Trevisan (cstrevisan@ucdavis.edu)

Research conducted at the  
University of California, Davis and at the  
Lawrence Berkeley National Laboratory

*Yukawa Institute for  
Theoretical Physics  
Kyoto, October 20 - 22, 2008*



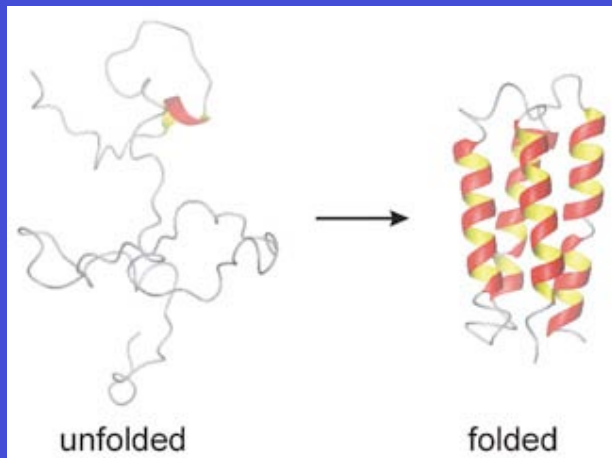
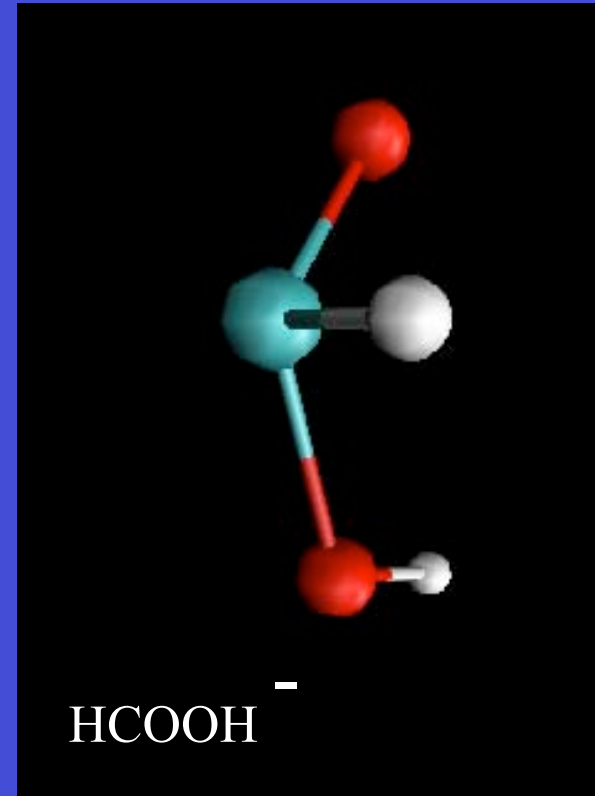
# Basic time scales



# What can theory help us predict?

## Electron Driven Processes:

Molecules can form temporary negative ion (anion) states by capturing a low-energy incident electron. This transient anion state (resonance) can *enhance by several orders of magnitude the probability of certain reactions*. It can also lead to *distortions of polyatomic molecules* necessary for a reaction to occur.



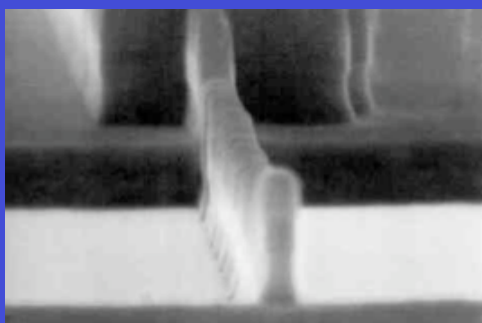
## Structure of Biological Molecules:

The mechanisms by which proteins bind metal ions may lead to *disruption of structures that are associated with disease*.

# Electronic collisions drive a multitude of common physical devices and chemical changes



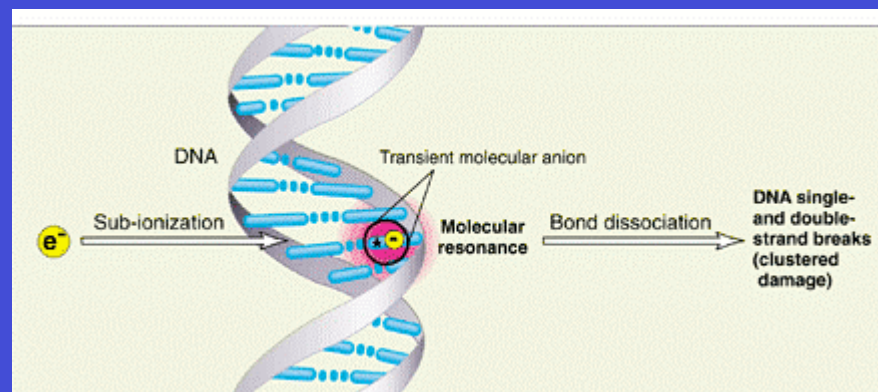
High Intensity Plasma Arc Lamp (OSRAM-Sylvania)



Plasma-etching Gate, 0.12 microns wide (Bell Labs - Lucent Technologies)

Electronic collisions are uniquely effective in transferring energy to the electronic degrees of freedom of atoms and molecules, making modern fluorescent lighting energy efficient and making plasma etching of semiconductor materials possible.

Low energy electrons with energies below the ionization energies of DNA molecules can initiate strand-breaks by attaching to components of DNA molecules and driving bond dissociation.



Most energy deposited in cells by ionizing radiation is channeled into secondary electrons between 1eV and 20eV. (Research group of L. Sanche, first findings in *Science* **287**, 1658, 2000).

# Electron-molecule interactions

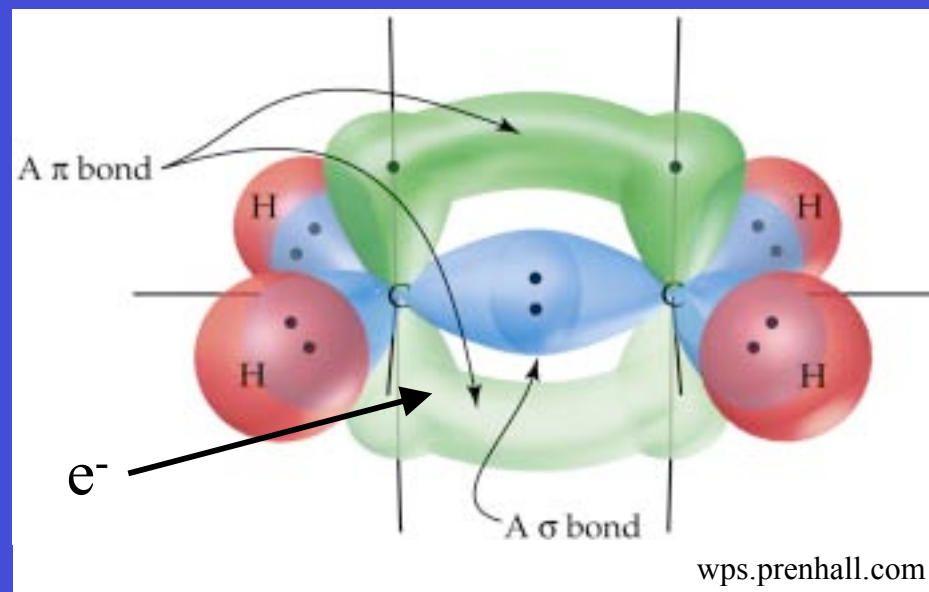
Electron-driven processes hinge on the mechanisms by which electronic energy is transferred into nuclear motion to produce reactive species by excitation and/or fragmentation.

**Resonant collisions** – Formation of a temporary negative ion

→ Incident electron either “is captured into an empty MO” (*shape resonance*) or “excites an electronic state and attaches to it” (*Feshbach resonance*).

→ Electron collision times are commensurate with molecular vibrational period (~10s of femtoseconds).

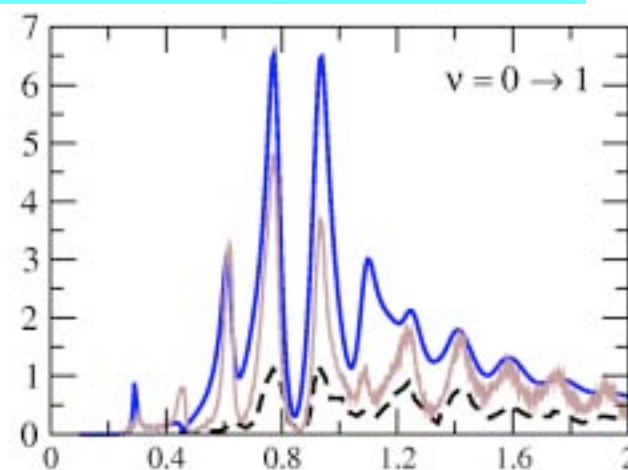
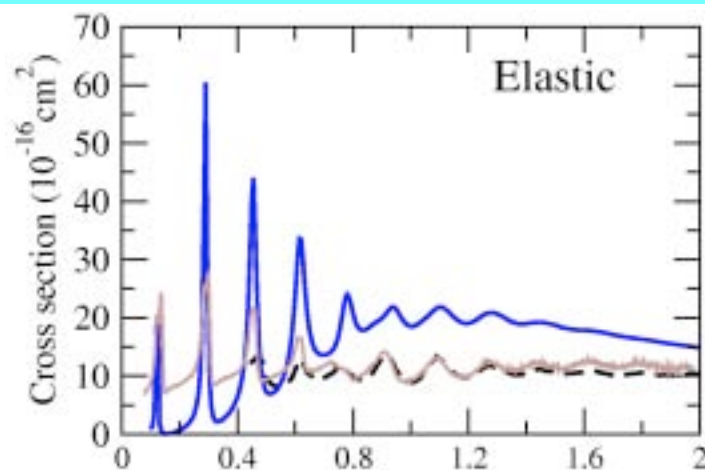
→ Multidimensional nuclear dynamics in polyatomics lead to new effects.



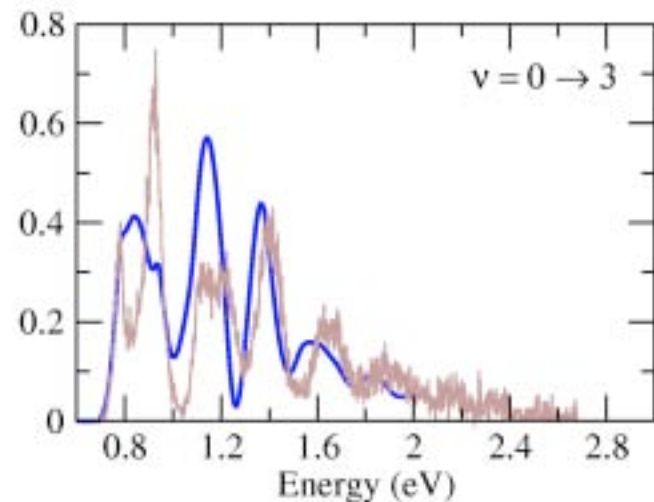
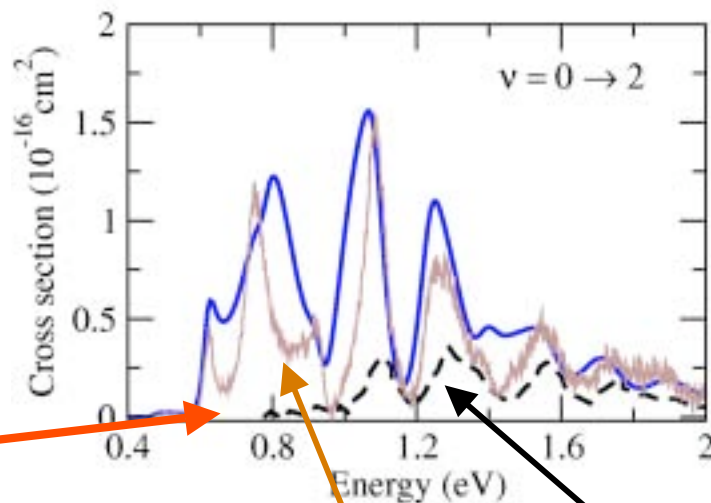
# Vibrational Excitation and Elastic Scattering – NO

(of relevance in neurotransmission and atmospheric chemistry)

- Overlapping “Boomerang” structure from three resonances

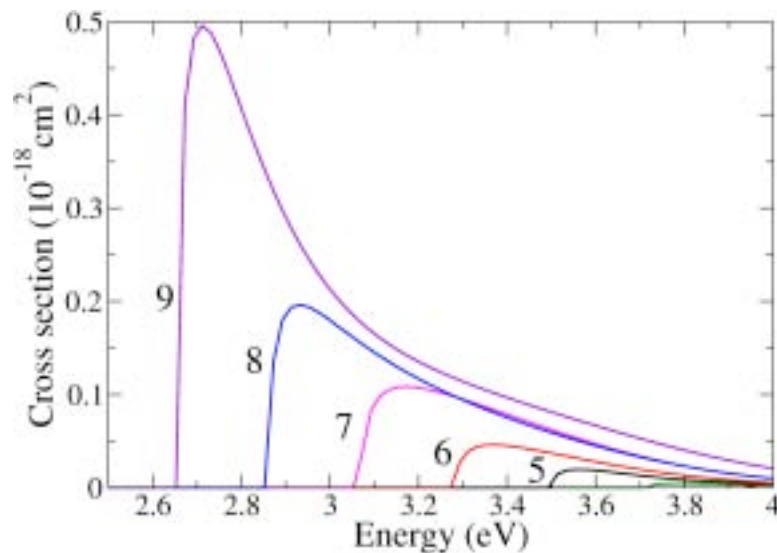
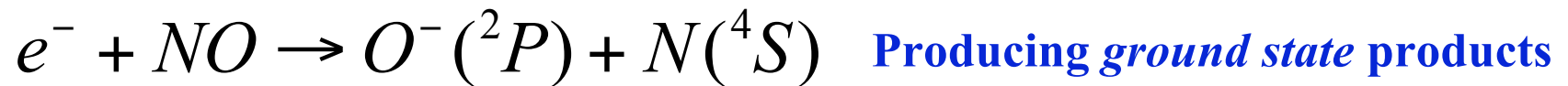


- Disagreement between experiments: The low energy peaks are suppressed in Jelisavcic *et al.*



Experiments: Allan (2005), Jelisavcic *et al.* (2003)

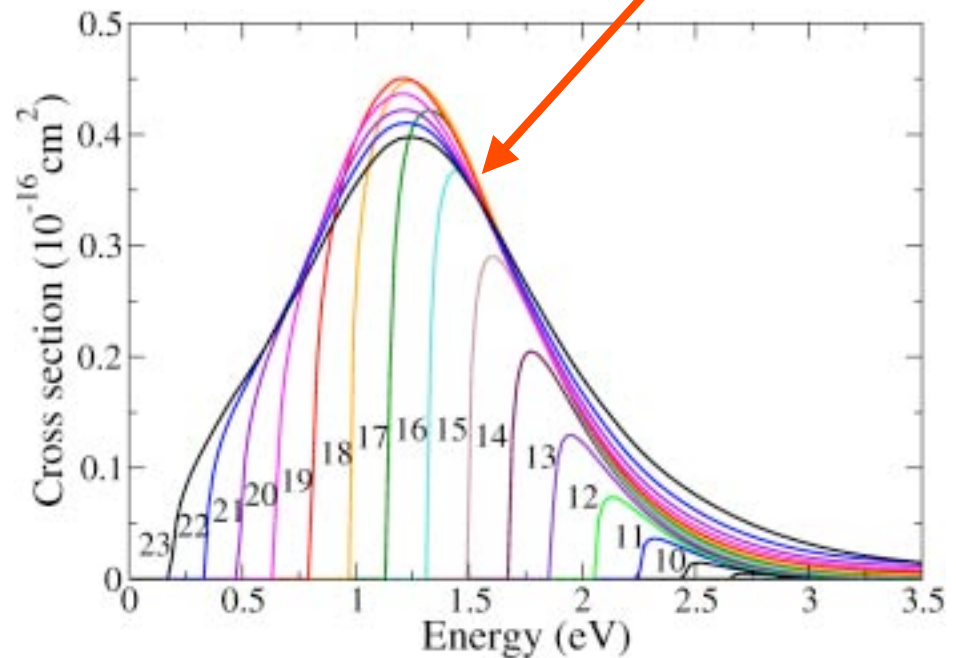
# Dissociative electron attachment to NO



From vibrational excited states  $\nu = 5$  through 9

$\sim 1000$  fold enhancement at  $\nu = 15$

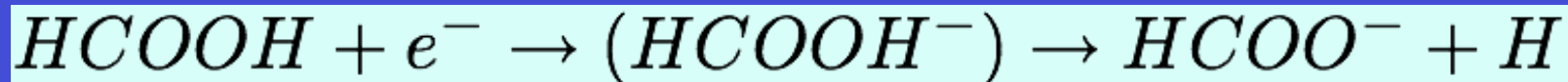
From vibrational excited states  $\nu = 10$  through 23



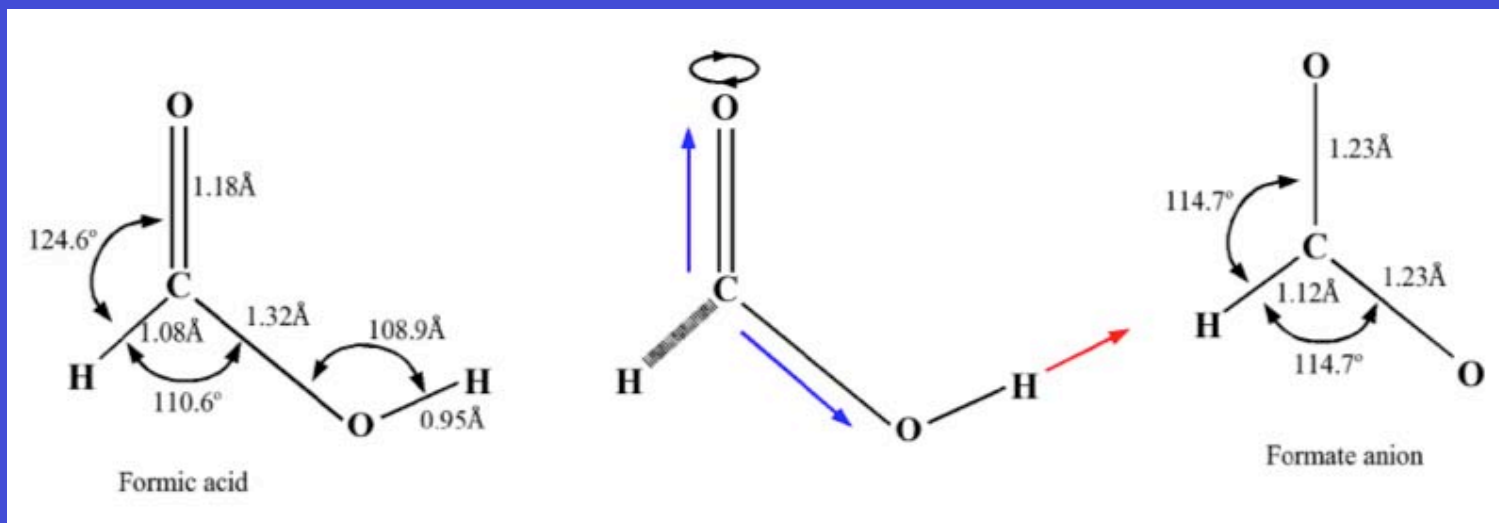
These findings stimulated a new experiment currently being performed at LBNL!

# Intrinsic polyatomic effects: formic acid

Measured DA reaction with lowest incident  $e^-$  energy ( $\sim 1.3$  eV) with fine structure oscillations on the high energy tail of the peak.

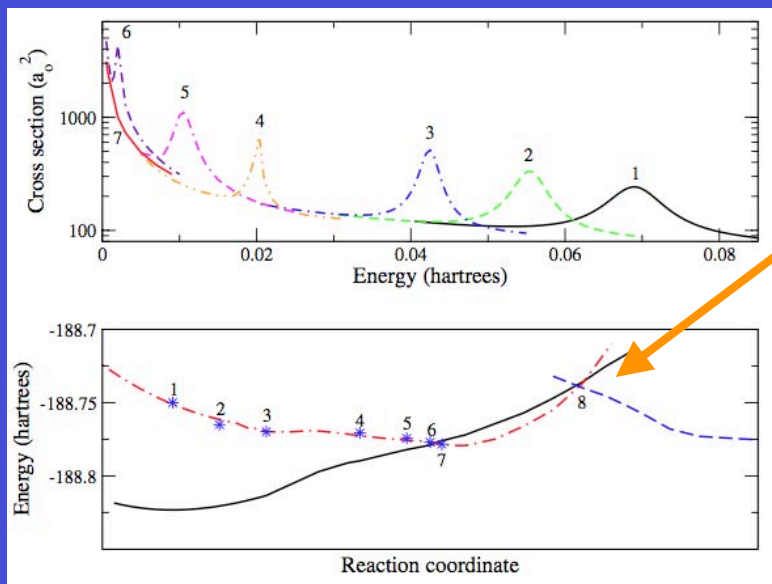


The path to stable formate ion fragments requires a symmetry breaking, non-planar deformation of  $\text{HCOOH}^-$  after capture of an electron into a  $\pi^*$  resonance orbital.



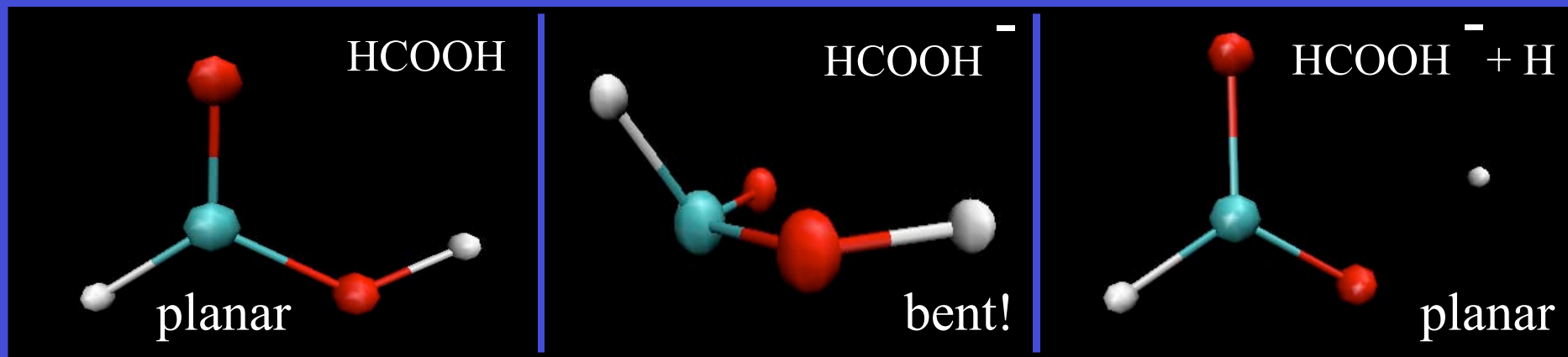


# Fixed-nuclei cross sections and potential energy curves along reaction path leading to $\text{HCOO}^- + \text{H}$



DA involves a barrier that indicates the presence of a conical intersection:  
*Intrinsically polyatomic dissociation dynamics*

Reaction *cannot* take place without the distortion of the molecule -  $e^-$  system out of its initial planar geometry => need to go beyond simple, 1D models for DA.



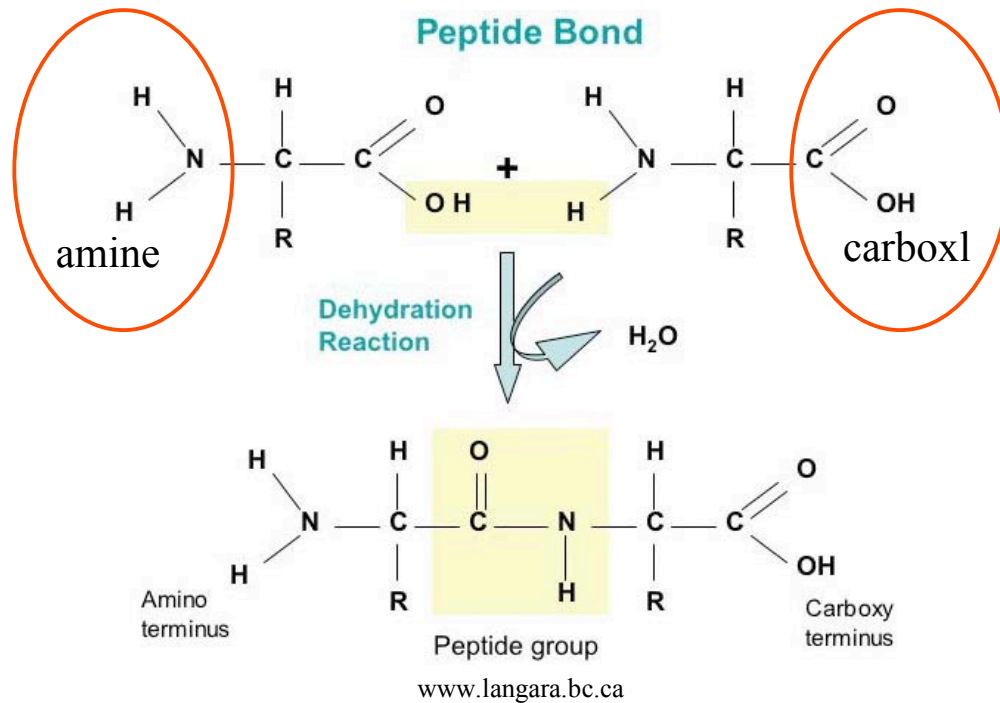
# Research at the Dept. of Physics - UC Davis -

Currently modeling proteins that are associated with neurodegenerative diseases such as:

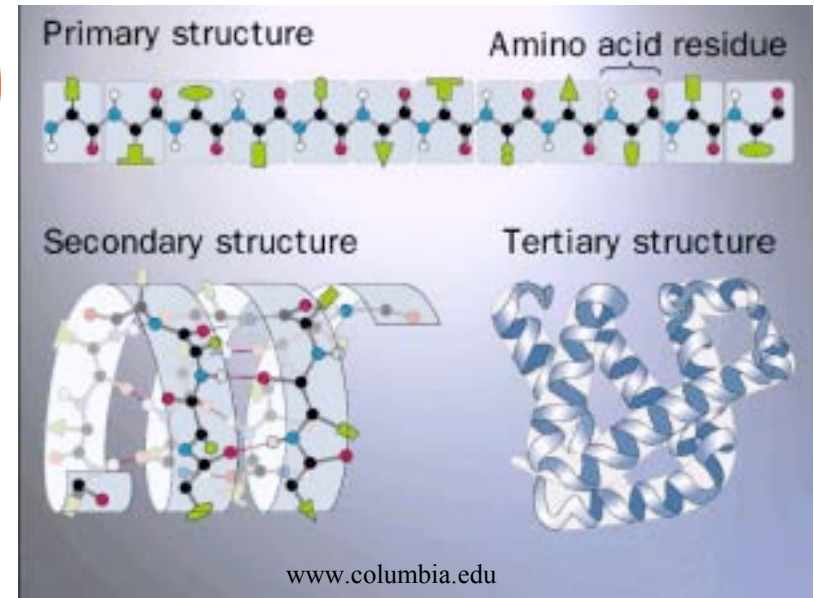
- Alzheimer's Disease (AD) - Amyloid- $\beta$  protein -
- Creutzfeldt - Jacob Disease (CJD) - Prion protein -
- Parkinson's Disease (PD) -  $\alpha$ -synuclein -

Extracellular deposits - plaques - that contain transition metals (Cu, Fe, Zn) is a common characteristics of AD & PD. Cu depletion in regions of CJD infection.

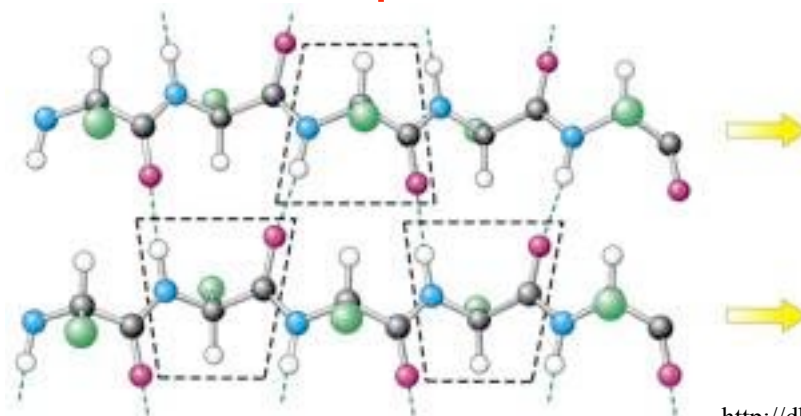
# Amino acids: building blocks of proteins



## $\alpha$ -helix

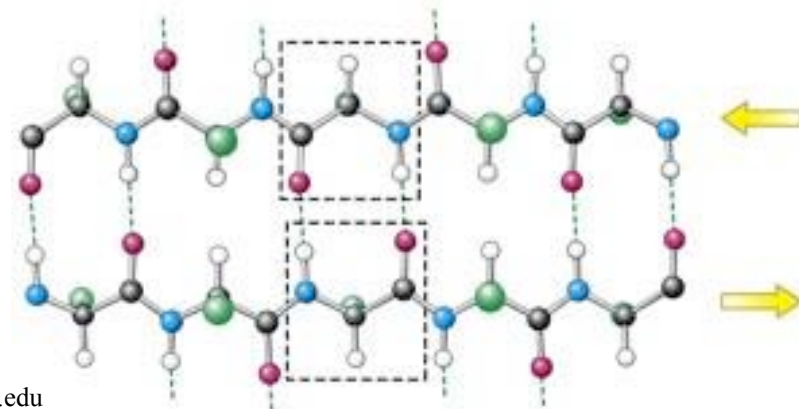


## Parallel $\beta$ -sheet

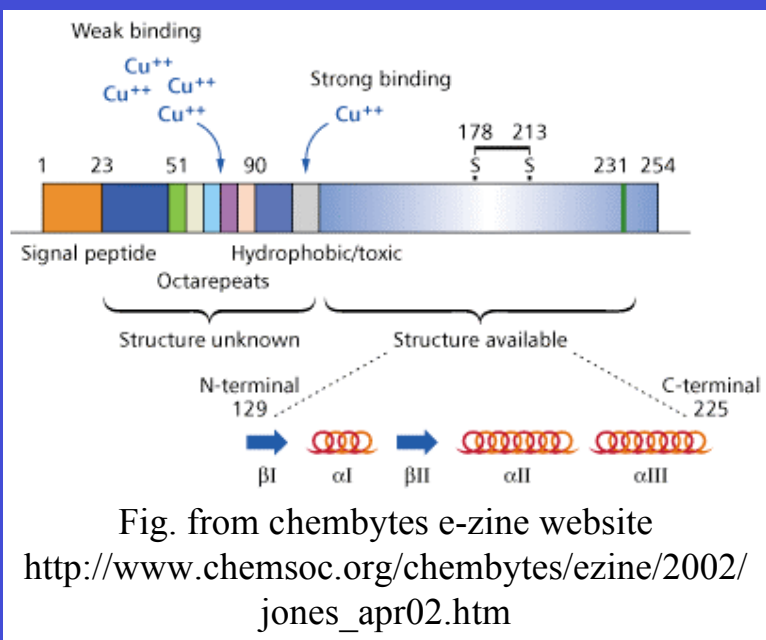
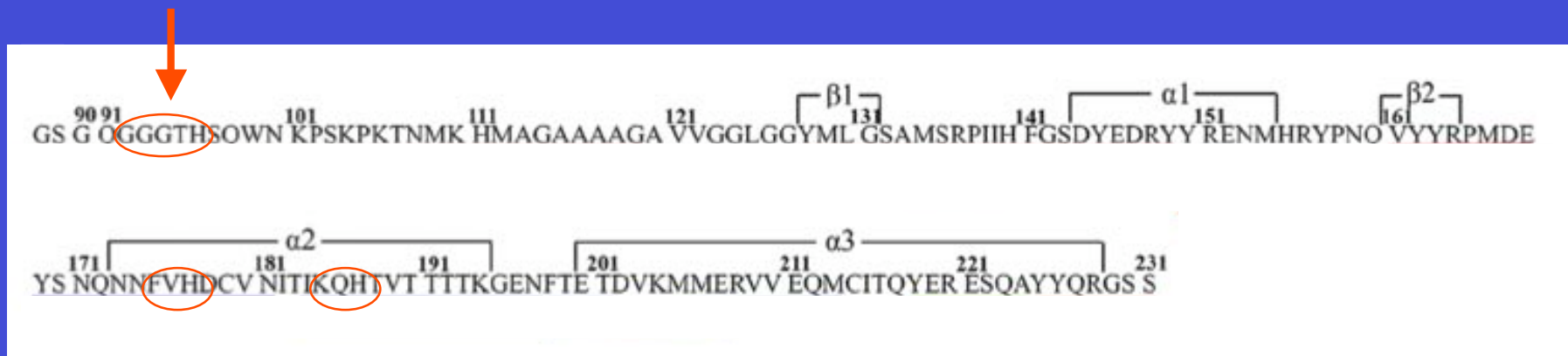


<http://dbs.umt.edu>

## Anti-parallel $\beta$ -sheet



# PrP<sup>C</sup> 88-231 primary structure



## Why?

- Breakdown of metal homeostasis as key factor in many neurodegenerative diseases.
- Debate about whether binding of metals plays a neuroprotective or neurodegenerative role in disease.

# Cu<sup>2+</sup> binding could inhibit conformational change associated with diseased form of PrP (PrP<sup>Sc</sup>)

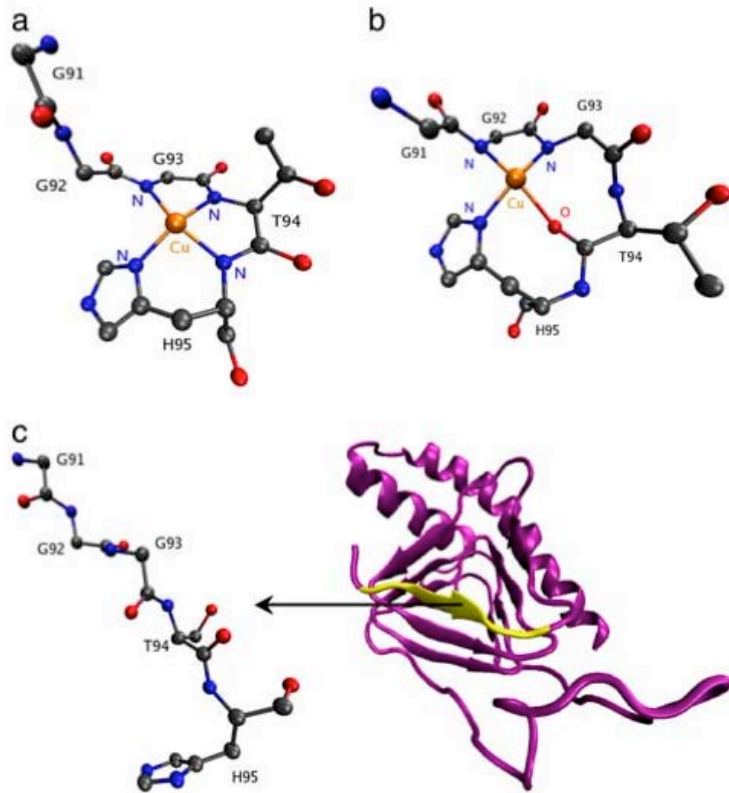
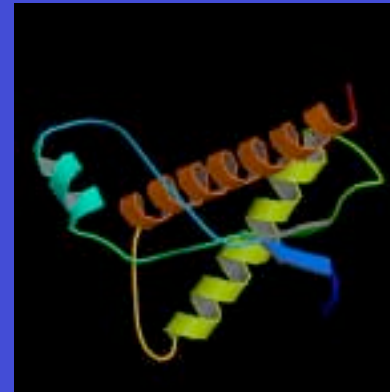


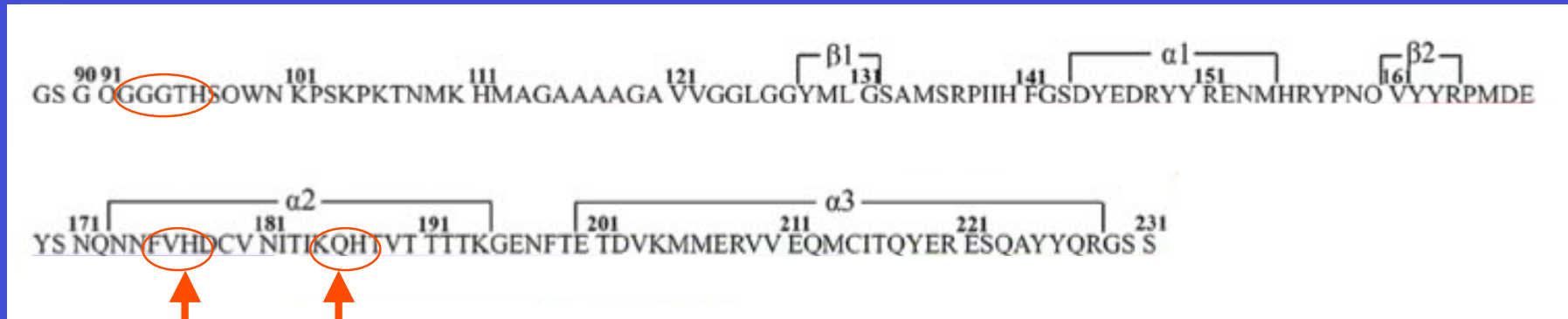
FIGURE 1 Potential copper binding motifs in the converting region of the normal (PrP<sup>C</sup>) mouse prion protein, which are consistent with ESR data (1) are shown in panels *a* and *b*. The corresponding copper-free stretch of the left-handed  $\beta$ -helix model of the infectious (PrP<sup>Sc</sup>) protein from Govaerts et al. (4) is shown in panel *c*.



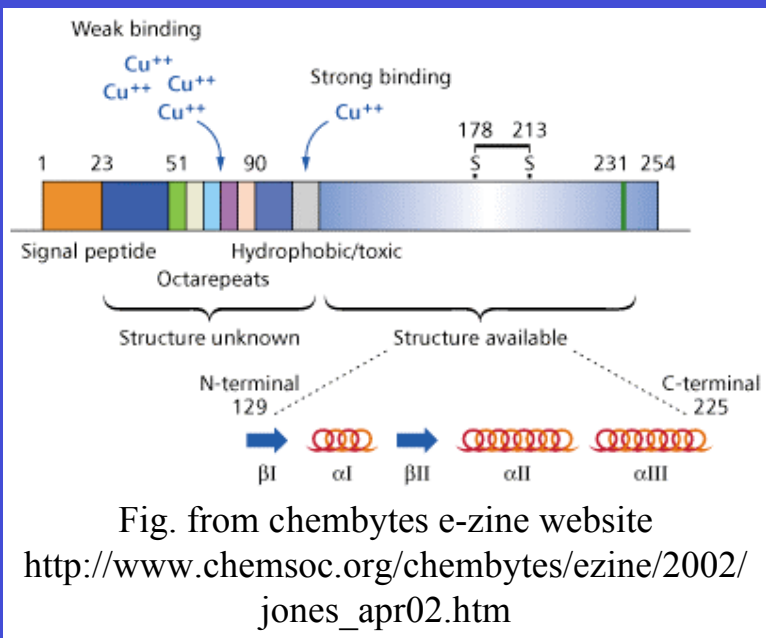
Difference between PrP<sup>C</sup> and PrP<sup>Sc</sup> is conformational

Calculations by D. Cox, J. Pan and R. Singh predict structural change when Cu<sup>2+</sup> binds to core region (sequence 92-96 GGGTH) of PrP<sup>C</sup>. Bending is *not* compatible with the straight  $\beta$ -strand backbone structure associated with PrP<sup>Sc</sup>.

# PrP<sup>C</sup> 88-231 primary structure



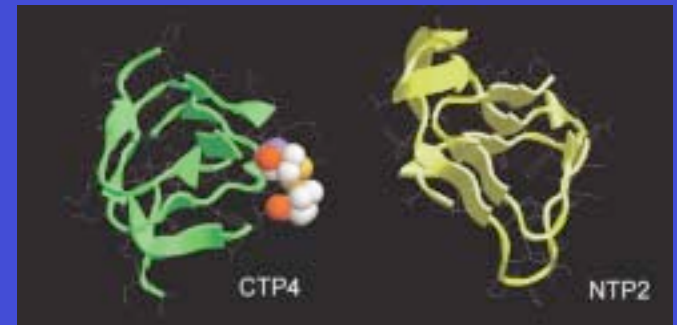
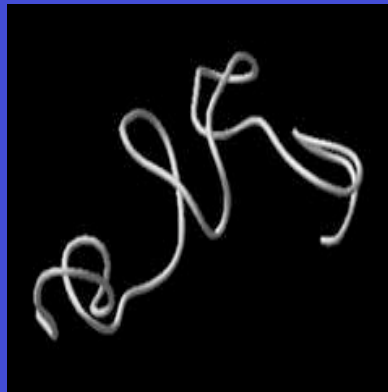
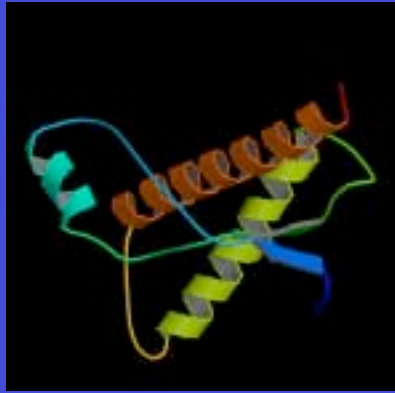
Explored Cu<sup>2+</sup> binding by histidine and neighbor amino acids in C-terminal region of prion fibrils (no experimental evidence of binding).



Why?

- Breakdown of metal homeostasis as key factor in many neurodegenerative diseases.
- Debate about whether binding of metals plays a neuroprotective or neurodegenerative role in disease.

$\text{Cu}^{2+}$  *will NOT* bind to  $\alpha$ -helical structure of PrP.



C-terminal & N-terminal left handed  $\beta$ -Helix (LH $\beta$ H) models for prion fibril (K. Kunes *et al*).

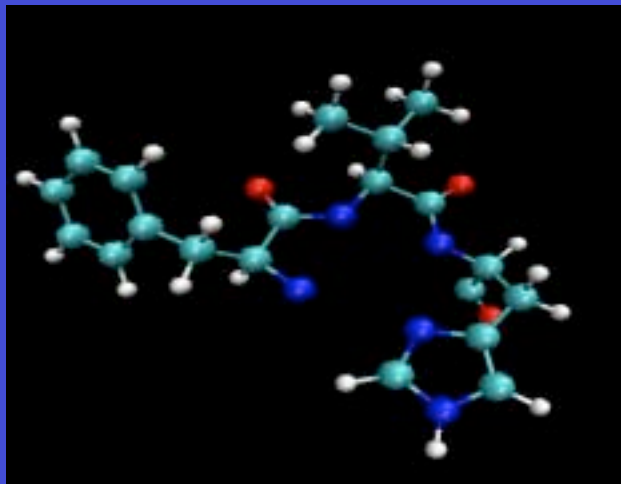


Conversion of PrP to amyloid fibrils involves disruption of  $\alpha$ -helices *enabling  $\text{Cu}^{2+}$  binding at this stage* or refolding to  $\beta$ -structure.

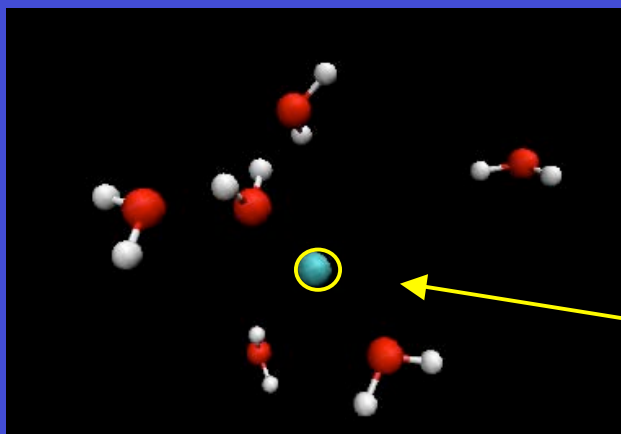
# Goal: estimate energetics of Cu-PrP binding

$$(E_{\text{binding}} = E_{\text{complex}} - E_{\text{fragment}})$$

Peptide (FVH) fragment

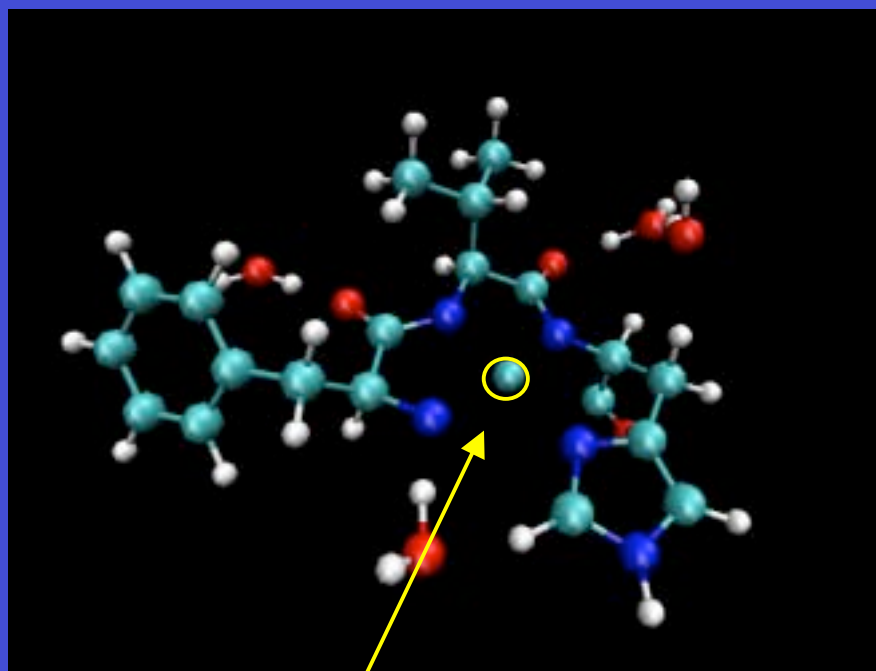


+



Cu<sup>2+</sup> - H<sub>2</sub>O fragment

Complex



Cu<sup>2+</sup>



# Which calculations will predict binding?

Studied PrP<sup>C</sup> sequence 92-96 GGGTH, known experimentally to be a strong Cu<sup>2+</sup> binding site:

- Molecular Dynamics (MD) calculations alone (using implicit solvent) DO NOT predict Cu<sup>2+</sup> binding .
- Quantum Mechanical (QM) calculations (in vacuum) predict unphysically large binding energies.

Same outcome for the sequence 175-177 FVH.

Embedded QM calculations in MD simulations using the Generalized Born (GB) approximation as implicit solvent.

## Energies from QM calculations:

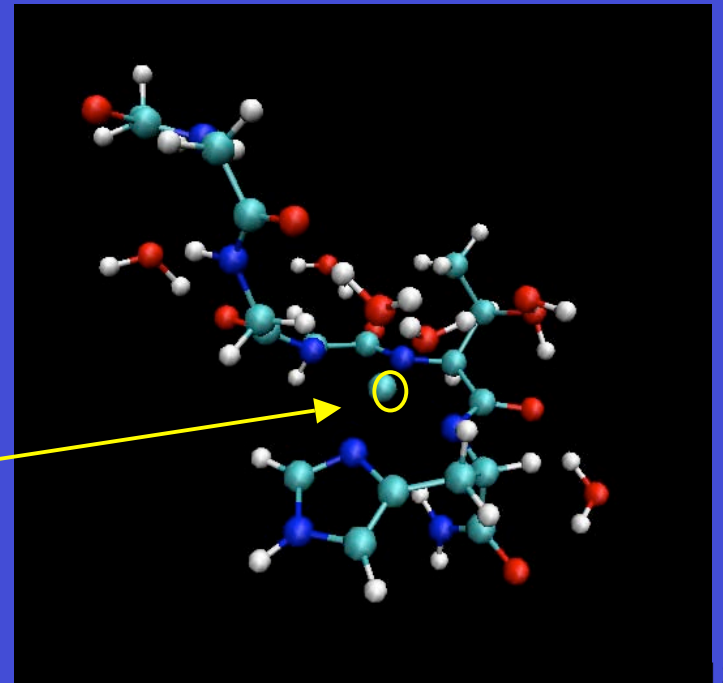
- Electrostatic energy (Coulomb interactions) between each atom of the system, which include exchange and correlation interactions between electrons.
- Total kinetic energy.

## Energies from MD simulations:

- Van der Waals interactions.
- Solvation energy.

$\text{Cu}^{2+}$

$\text{Cu}^{2+}$ - GGGTH -  $\text{H}_2\text{O}$  complex



## Results obtained by embedding QM calculations in MD simulations

*PrP sequence 92-96 GGGTH:*

Binding energies of about 2.4 eV.

*PrP sequence 175-177 FVH:*

Binding energies of about 3.0 eV.

Prion protein sequence 175-177 FVH predicted to bind  $\text{Cu}^{2+}$  at least as strongly as the 92-96 GGGTH region.

## More results

Explored the binding affinity of other transition metal ions to HGGGW of the octarepeat region of PrP:

Cu<sup>2+</sup>: 1.8 eV

Ni<sup>2+</sup>: 1.6 eV

Zn<sup>2+</sup>: 1.3 eV

Mn<sup>2+</sup>: Non-binding.

Follows trend observed experimentally, however...

### Some unresolved issues:

- Lack of good force-field parameters for most transition metals.
- Na<sup>+</sup>, Cl<sup>-</sup> ions included in MD simulation may generate environment that differs from physiological salt concentrations in the brain.

# Work & People

- Electron-driven chemistry in collaboration with the Lawrence Berkeley National Laboratory and the Applied Science Dept. at UC Davis.
  - Prof. A. Orel, Dr. T. Rescigno, Prof. C. W. McCurdy, Dr. K. Houfek, Dr. Z. Zhang.
- Theoretical modeling of aggregation processes in neurodegenerative diseases (e. g. CJD, Alzheimer's, Parkinson's) at the Dept. of Physics, UC Davis.
  - Prof. D. Cox, Dr. A. Huebsch.

# Some Acronyms

- MESA: Molecular Electronic Structure Applications
- SIESTA: Spanish Initiative for Electronic Simulations with Thousands of Atoms
- AMBER: Assisted Model Building with Energy Refinement

# Supplementary Slides

Electron Driven Chemistry  
and  
Biophysics

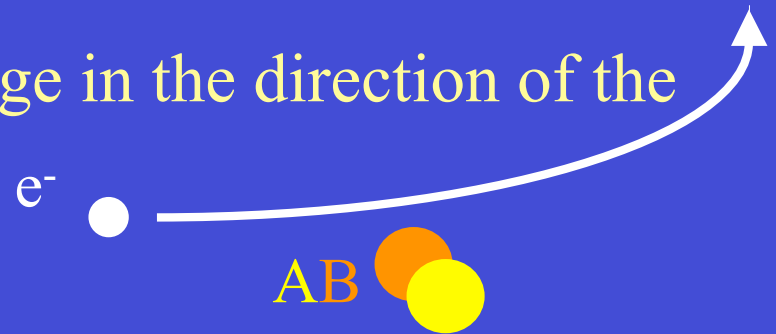
## References

- Low-energy electron scattering by formic acid, **C. S. Trevisan**, A. E. Orel and T. N. Rescigno, *Phys. Rev. A*, **74**, 042716, (2006).
- Dynamics of low-energy electron attachment to formic acid, T. N. Rescigno, **C. S. Trevisan** and A. E. Orel, *Phys. Rev. Lett.*, **96**, 213201 (2006).
- A nonlocal, ab initio model of dissociative electron attachment and vibrational excitation of NO, **C. S. Trevisan**, K. Houfek, Z Zhang, A. E. Orel C. W. McCurdy and T. N. Rescigno, *Phys. Rev. A*, **71**, 052714 (2005).
- D. L. Cox, J Pan and R. R. P. Singh, *Biophys. Lett.* **91** L11 - L13 (2006).
- C. S. Burns et. al., *Biochemistry* **42**, 6794 - 6803 (2003).
- C. Govaerts, C. H. Wille, S. B. Prusiner and F. E. Cohen, *Proc. Natl. Acad. Sci. USA* **101**:8342 - 8347 (2004)

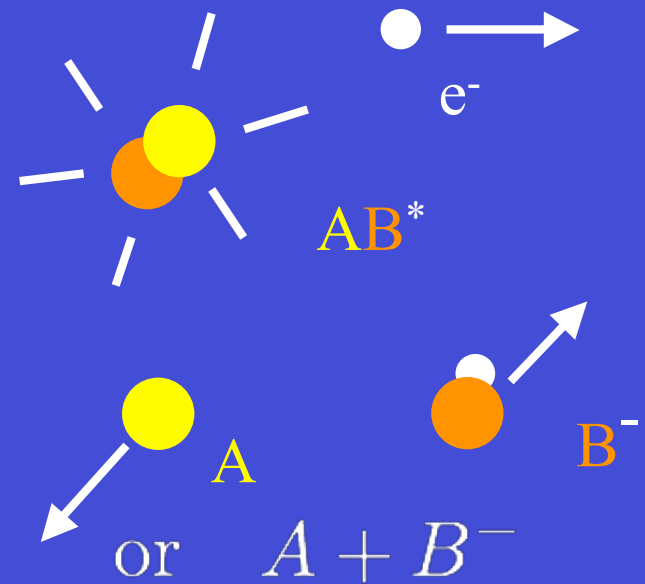


# Some electron- molecule collision processes

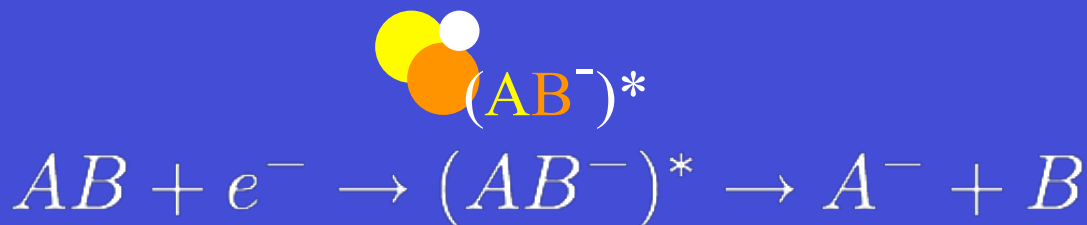
Elastic scattering (can lead to change in the direction of the scattering  $e^-$  - momentum transfer)



Vibrational, rotational, or electronic excitation

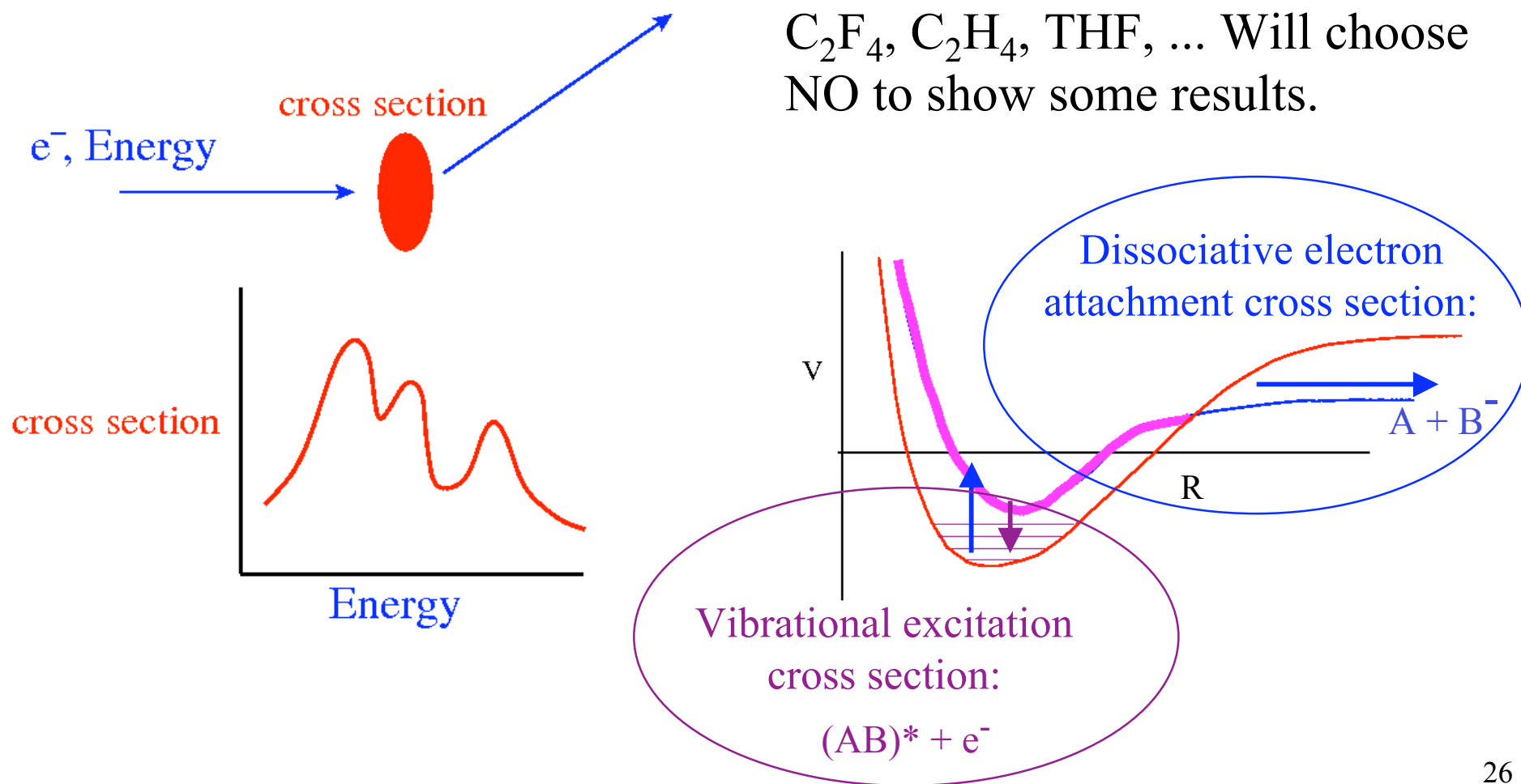


Dissociative electron attachment



The probability of a particular process is proportional to its *cross section*, which can be thought of as an *effective area* of the molecule to the incoming electron.

Studied  $e^-$  scattering by NO, CF,  $C_2F_4$ ,  $C_2H_4$ , THF, ... Will choose NO to show some results.



# Sequence 175-177 FVH in human PrP<sup>C</sup>

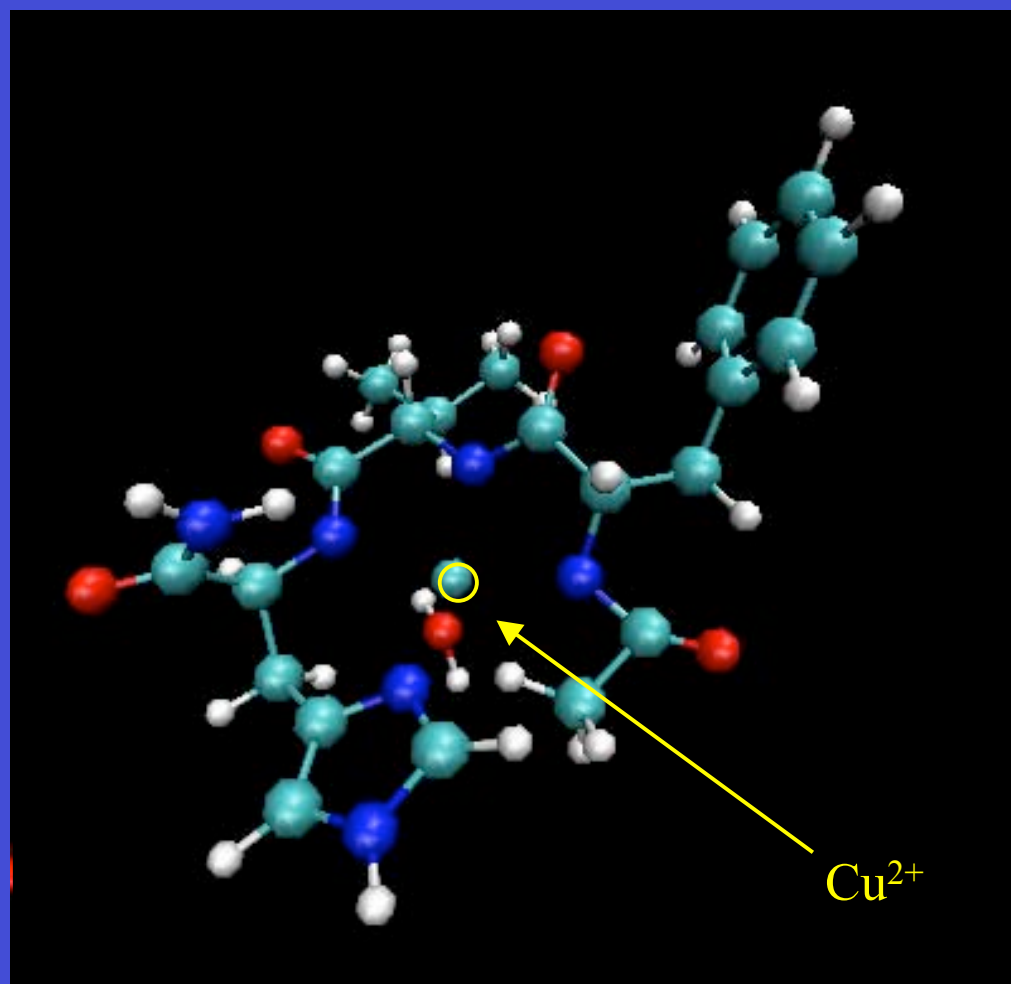
90 91 101 111 121 131 141 151 161  
GS G OGGGTHSOWN KPSKPKTNMK HMAGAAAAGA VVGGLGGYML GSAMSRPIIH FGSDYEDRYR RENMHRYPNO VYYRPMDE

171 181 191 201 211 221 231  
YS NONNFVHDCV NITIKQHI VT TTKGENFTE TDVKMMERVV EQMCITQYER ESQAYYQRGS S

$\beta 1$   $\alpha 1$   $\beta 2$   
 $\alpha 2$   $\alpha 3$



Candidate structure for sequence 175-177 FVH:  
 $\text{Cu}^{2+}$  coordination by N atoms of HFV backbone, H  
side chain and O atoms of  $\text{H}_2\text{O}$ .



Candidate structures  
created using  
visualization software  
(e.g. VMD, PyMol,  
Swiss-PDB).

Local structure  
(geometry) minimized  
using quantum  
mechanical -Density  
Functional Theory  
calculations (SIESTA).

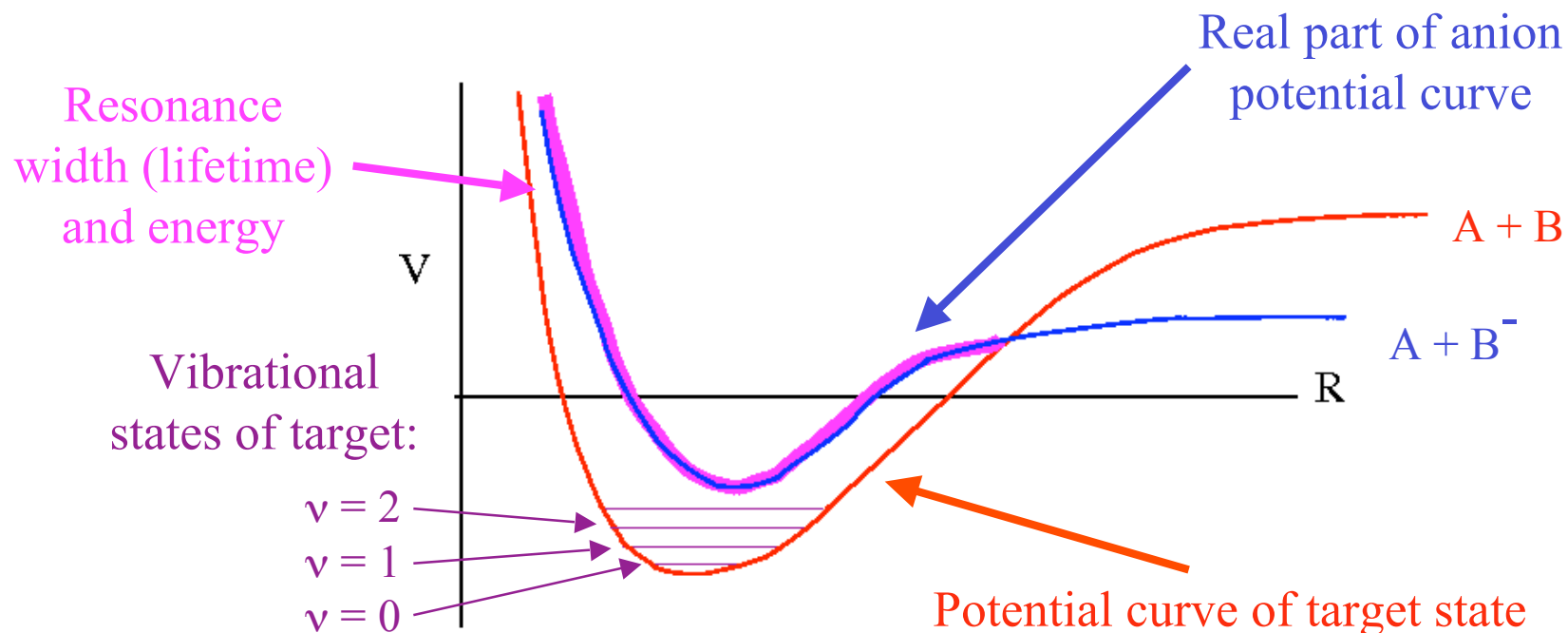
# Breaking up electron-molecule collision problems into two parts:

I. For each molecular geometry (internuclear distance,  $R$ ):

- Electronic structure calculations (MCSCF, CAS, MRCI, MRCISD, etc).

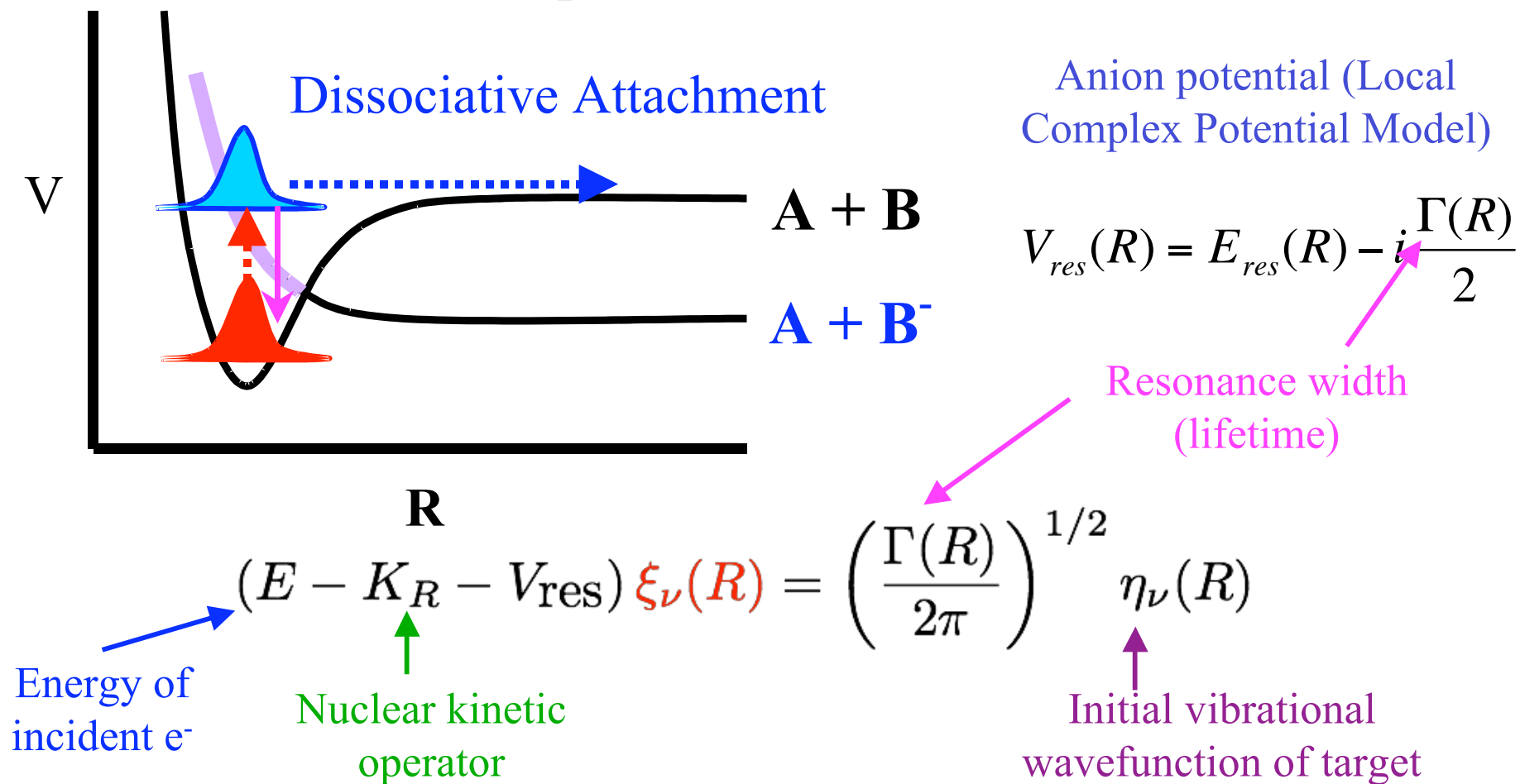
*Complete quantum calculations with quantum electron dynamics.*

- Electron scattering calculations (Complex Kohn Variational Method).



## II. Nuclear dynamics calculations

(Time-independent formulation):



Cross section (probabilities) from the asymptotic behavior of  $\xi(R)$ ,  
 (nuclear wavefunction associated with electronic resonance state)

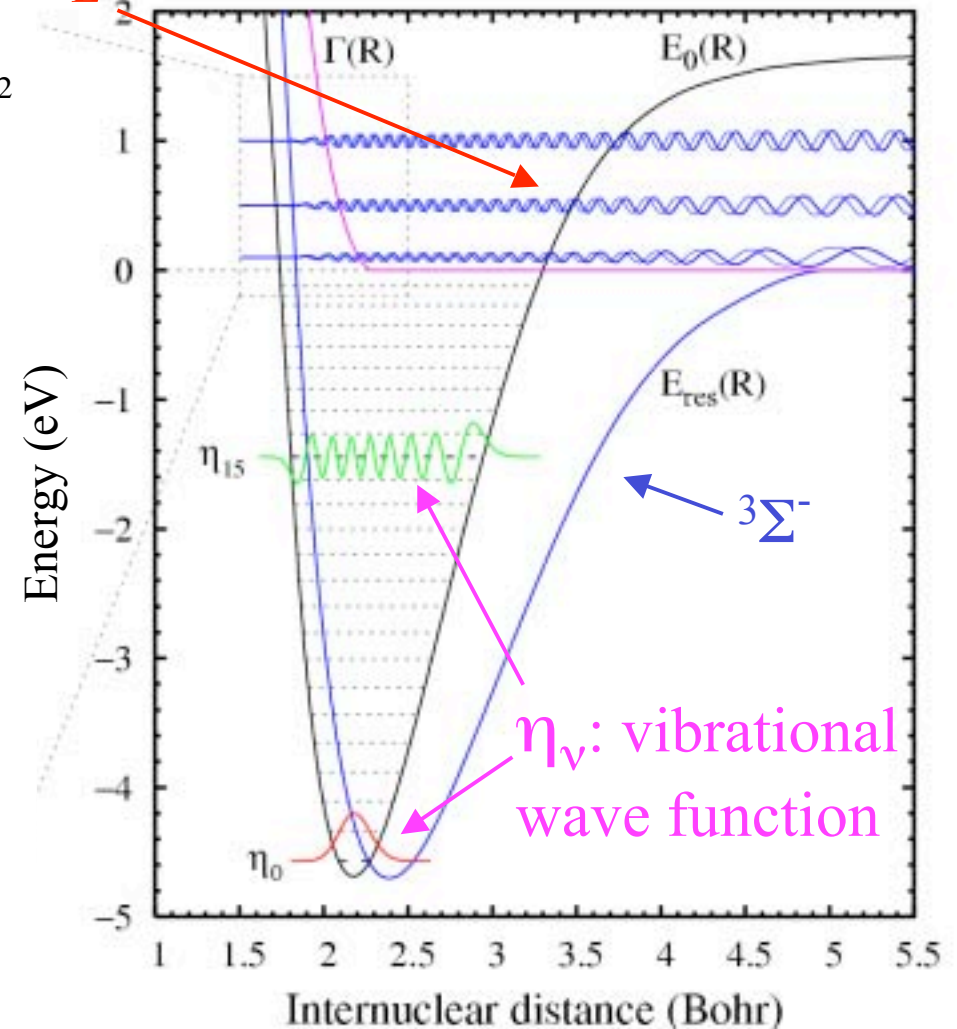
# Dissociative Attachment to NO – The Mechanism for Vibrational Enhancement

$$\sigma = g \frac{4\pi^2}{E_e} \frac{\mu}{K} \left| \left\langle \psi_E \left| \gamma^{1/2} \left( \frac{\Gamma(R)}{2\pi} \right)^{1/2} \eta_\nu(R) \right\rangle \right|^2$$

Dissociative Attachment  $\sigma$ 's

$\propto \eta_\nu \times \psi_E \Rightarrow$   
 larger overlap with  
 increasing vibrational  
 quantum number,  $\nu$

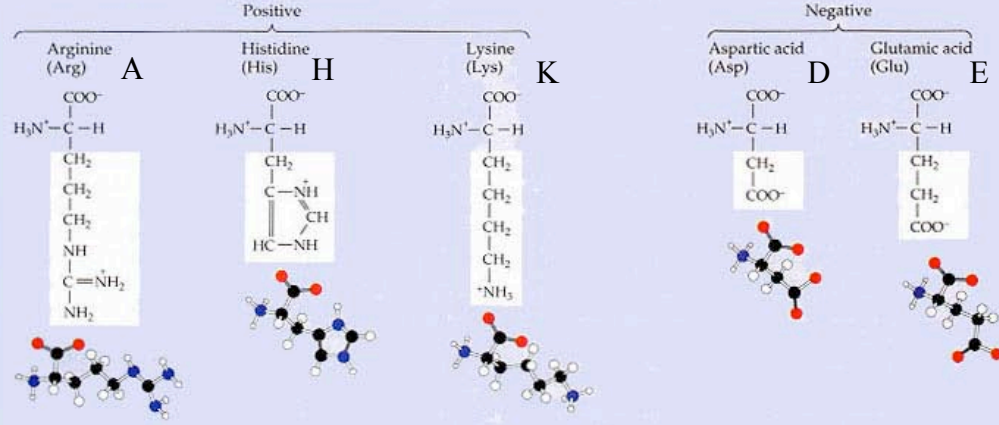
$\psi_E$  : scattering function



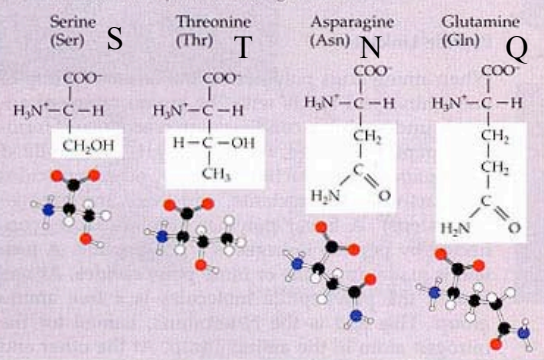
# Amino Acids Cheat Sheet

TABLE 3.1  
Twenty amino acids found in proteins

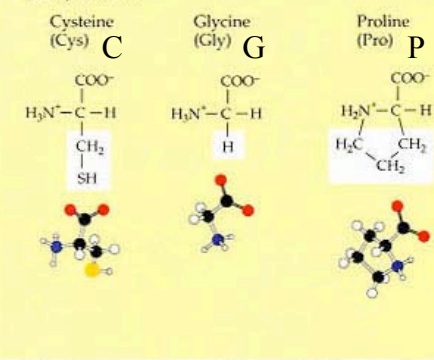
A. Amino acids with electrically charged side chains



B. Amino acids with polar but uncharged side chains



C. Special cases



D. Amino acids with hydrophobic side chains

