

# *Applied TDDFT - II: a Biochemist's Perspective*

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- **Biochemist's Interests**
  - Photobiology
- **Mixed Method: QM /MM:**
  - QM/MM Schemes + QM/MM Energy Formulation.
  - Boundary Schemes
  - TDDFT in Mixed Methods
- **Fragment-density analysis in Real-time TDDFT**
  - Fragment-density and AIM theory
  - Local Dipole Analysis in real-time TDDFT
  - Application to LHC-II
- **Fundamentals of Subsystem TDDFT**
  - Fundamentals of Subsystem DFT
  - Frozen Density Embedding Theory
  - Subsystem TDDFT

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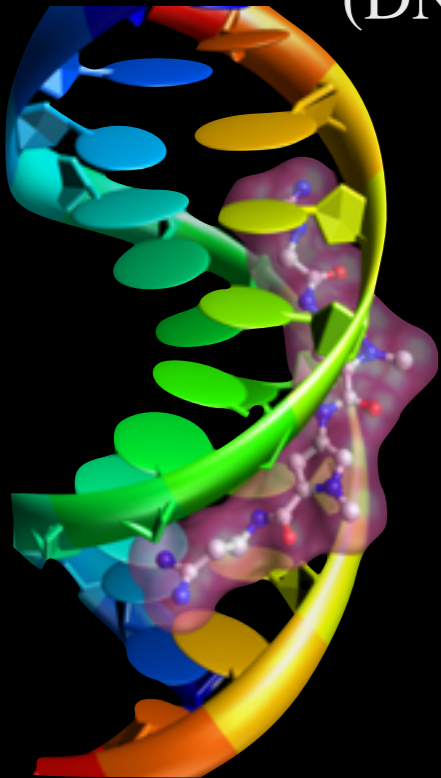
# Biochemist's Interests

From Wikipedia:

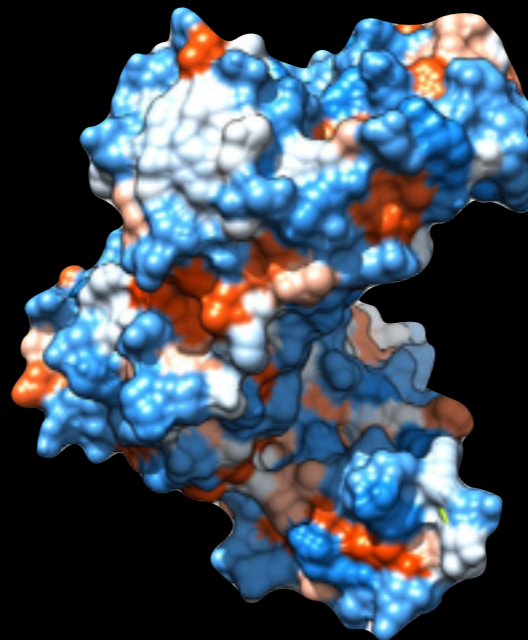
**Biochemistry**, sometimes called biological chemistry, is the study of chemical processes within and relating to living organisms.[...]

Over the last decades of the 20th century, *biochemistry* has become **so successful at explaining living processes** that now almost all areas of the life sciences from *botany* to *medicine* to *genetics* are engaged in biochemical research. Today, the **main focus** of pure biochemistry is on **understanding how biological molecules** give rise to the processes that occur within living cells.

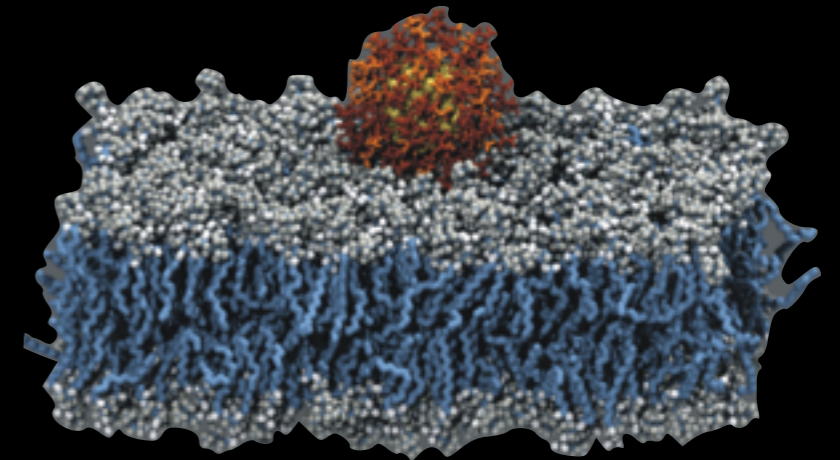
Nucleic Acid  
(DNA, RNA)



Aminoacid  
(Proteins)



Lipides  
(Membrane)

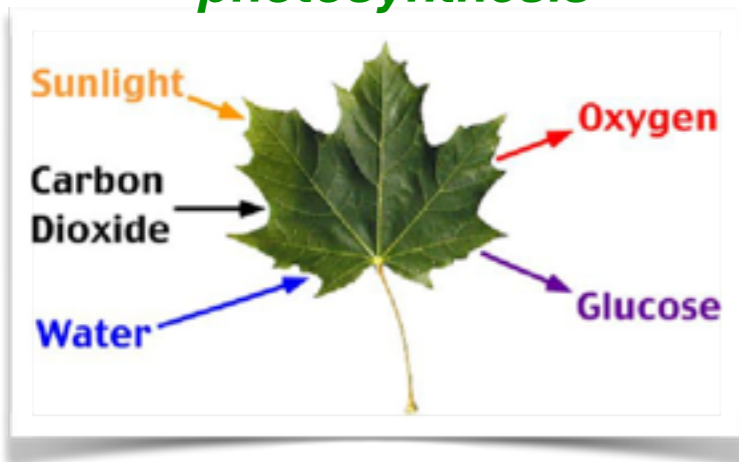


# Biochemist's Interests

From Wikipedia:

**Photobiology** is the scientific study of the interactions of light (technically, non-ionizing radiation) and *living organisms*. The field includes the study of *photosynthesis*, *visual processing*, *circadian rhythms*, *bioluminescence*, and *ultraviolet radiation effects*. The division between ionizing radiation and nonionizing radiation is typically considered to be 10 eV, the energy required to ionize an oxygen atom.

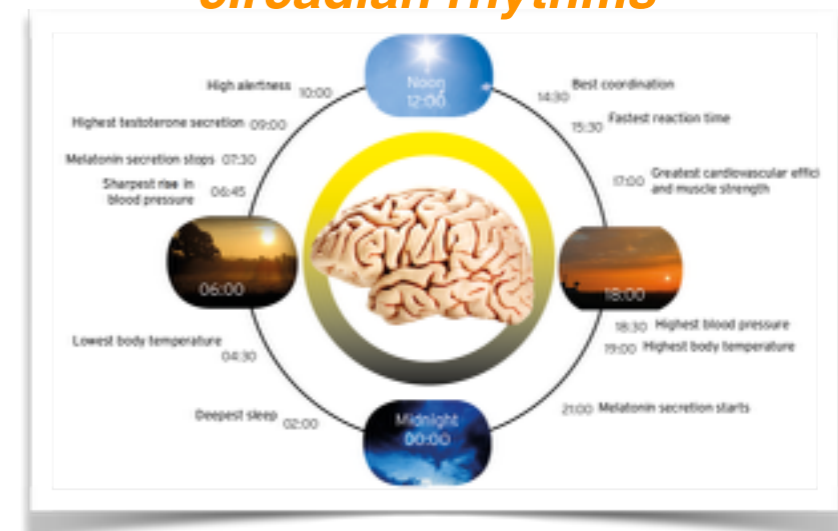
*photosynthesis*



*visual processing*



*circadian rhythms*



*ultraviolet radiation effects*



*bioluminescence*



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All these processes start or take place at the nano-scale (i.e. macromolecular size, from 10 nm to several hundred nanometers).

A theoretical/computational approach will therefore need:

- theoretical model for matter in the energy range [0 to few tens of eV]
- *description of the interaction with the environment (condensed phase)*
- description of chemical reactions (structural changes)

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... which translates into:

- electronic structure theory and ways to solve the corresponding equations
- *approximate solutions for the description of the interaction with the environment.*
- solution of the equations of motion for atoms and electrons + statistical mechanics (from the microcanonical to the canonical ensemble)

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All these processes start or take place at the nano-scale (i.e. macromolecular size, from 10 nm to several hundred nanometers).

... and in practice:

- HF, CI, MPn, CAS, ..., DFT and corresponding theories for excited states —> TDDFT
- *periodic boundary conditions (PBC) for homogeneous systems and hybrid schemes, for inhomogeneous systems: QM/MM, coarse grained, hydrodynamics, ...*
- time dependent theories for adiabatic and non adiabatic dynamics of atoms and electrons: mixed-quantum classical molecular dynamics

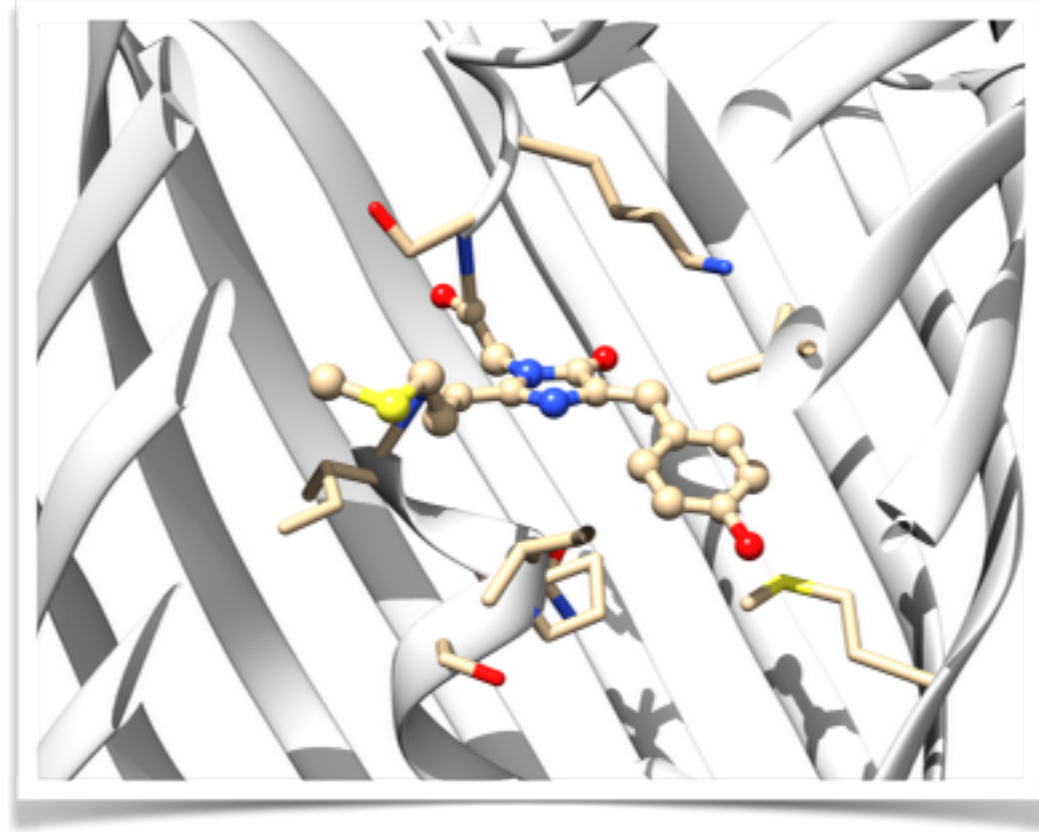
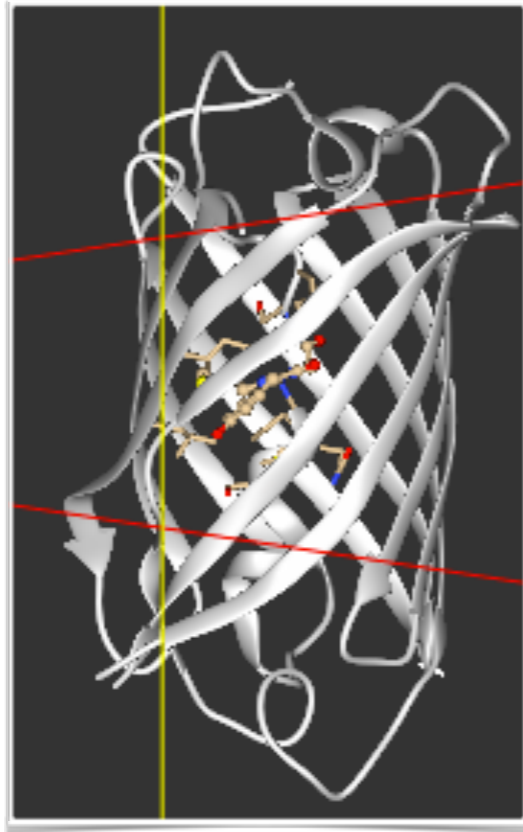


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# Mixed Methods QM/MM

## Motivation

Green Fluorescent Protein (mPlum)



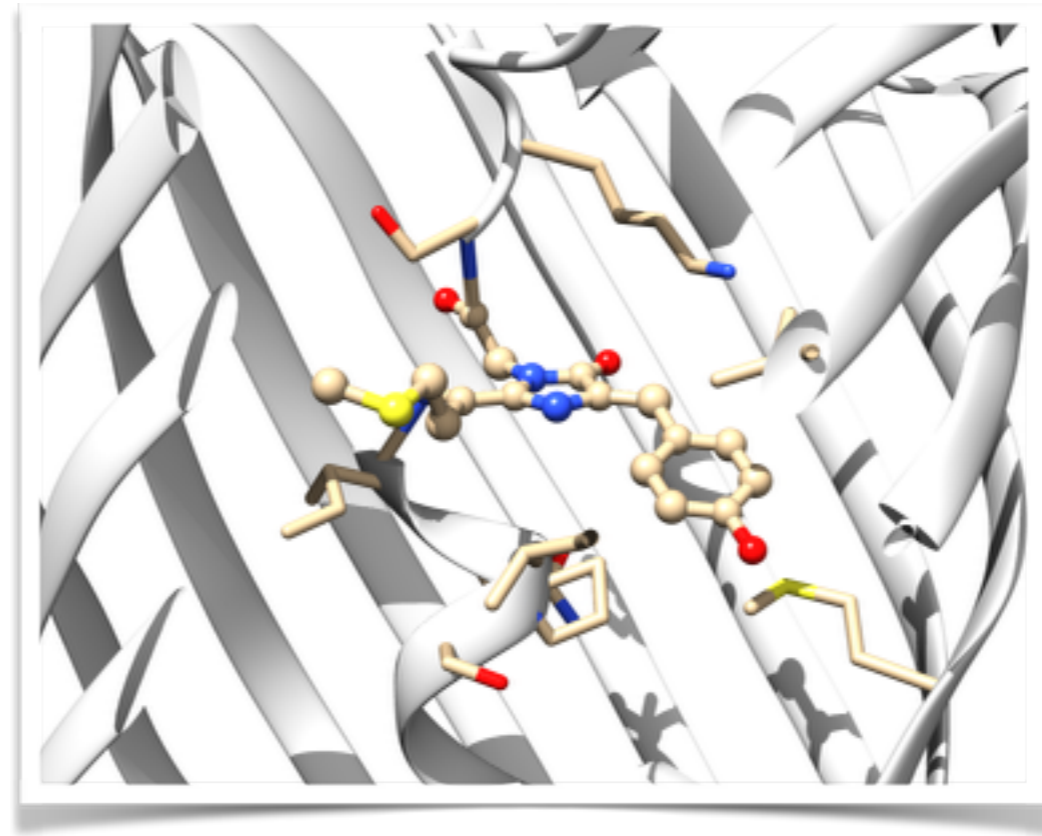
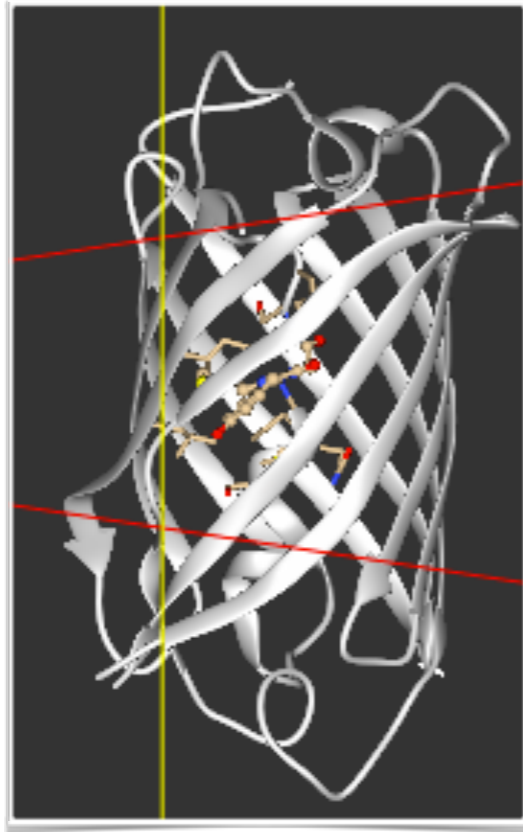
**Quantum-mechanical (QM)** methods are required for describing chemical reactions and other **electronic processes**, such as charge transfer or electronic excitation, but they are restricted to systems of up to a few hundred atoms.

However, the size and conformational complexity of **biomolecules** calls for **methods capable of treating up to several 100 000 atoms** and allowing for simulations over time scales of tens of nanoseconds.

This is achieved by highly efficient, **force-field-based molecular mechanics** (MM) methods.

## Motivation

Green Fluorescent Protein (mPlum)



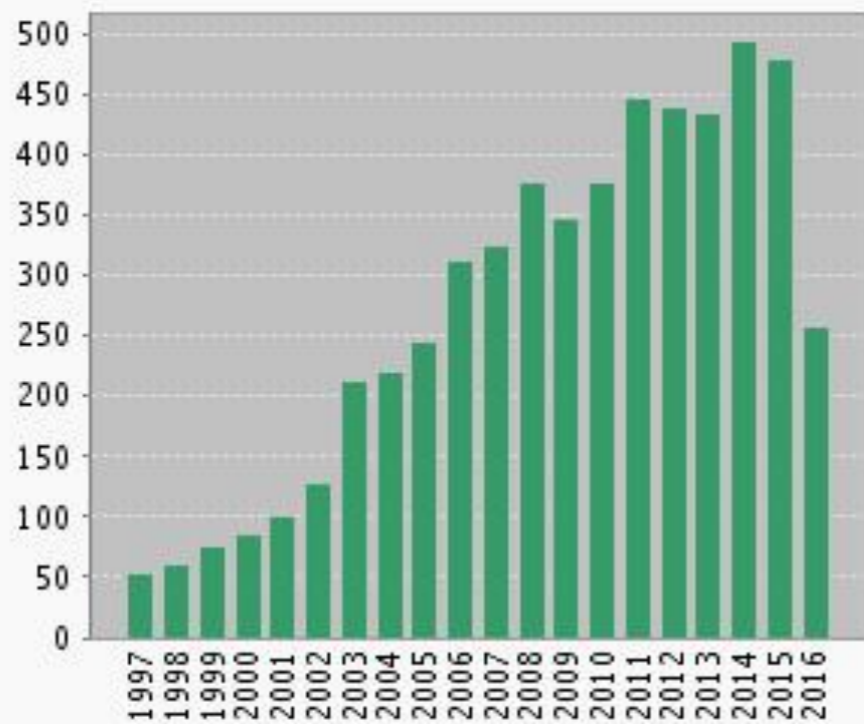
Thus to model large biomolecules the logical approach is to **combine the two techniques** and to use a **QM method for the chemically active region** (e.g., substrates and co-factors in an enzymatic reaction) and an **MM treatment for the surroundings** (e.g., protein and solvent).

The resulting schemes are commonly referred to as combined or hybrid **QM/MM methods**. They enable the modeling of reactive biomolecular systems at a reasonable computational effort while providing the necessary accuracy.

# Mixed Methods QM/MM

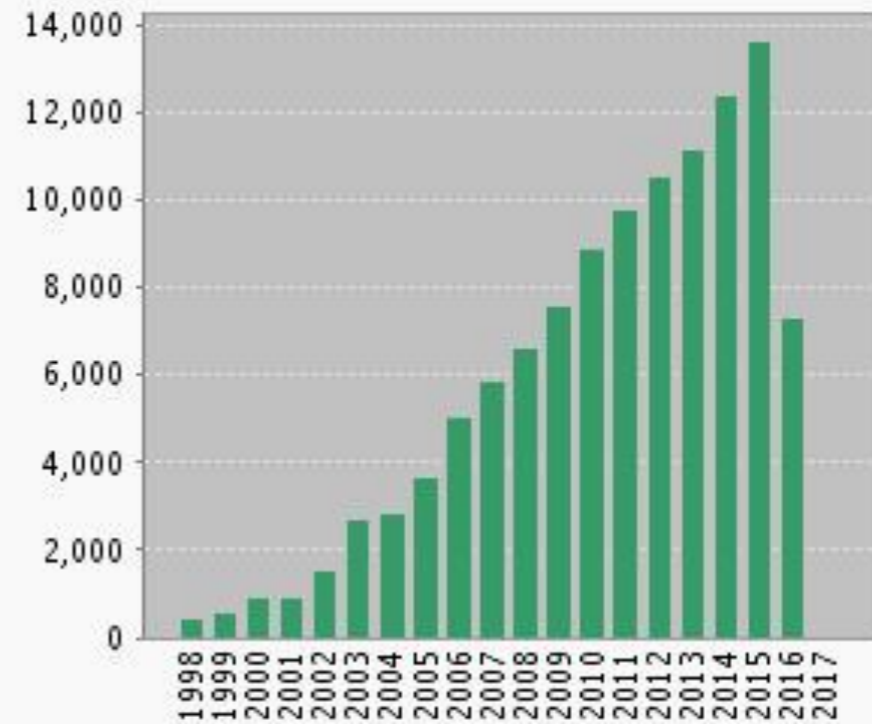
The **wide success of QM/MM methods** can be visualised in terms of the number of publication and citations in the last years.

### Published Items in Each Year



The latest 20 years are displayed.

### Citations in Each Year



The latest 20 years are displayed.

## Historical Aspects

### The Nobel Prize in Chemistry 2013



Photo: A. Mahmoud  
**Martin Karplus**  
Prize share: 1/3



Photo: A. Mahmoud  
**Michael Levitt**  
Prize share: 1/3



Photo: A. Mahmoud  
**Arieh Warshel**  
Prize share: 1/3

The Nobel Prize in Chemistry 2013 was awarded jointly to Martin Karplus, Michael Levitt and Arieh Warshel "for the development of multiscale models for complex chemical systems".

**1976 - Introduction, for the first time, a semiempirical QM/MM approach to describe an enzymatic reaction.**

#### Theoretical Studies of Enzymic Reactions: Dielectric, Electrostatic and Steric Stabilization of the Carbonium Ion in the Reaction of Lysozyme

A. WARSHEL AND M. LEVITT

*Department of Chemical Physics  
The Weizmann Institute of Science  
Rehovot, Israel*

*(Received 12 September 1975, and in revised form 10 February 1976)*

A general method for detailed study of enzymic reactions is presented. The method considers the complete enzyme-substrate complex together with the surrounding solvent and evaluates all the different quantum mechanical and classical energy factors that can affect the reaction pathway. These factors include the quantum mechanical energies associated with bond cleavage and charge redistribution of the substrate and the classical energies of steric and electrostatic interactions between the substrate and the enzyme. The electrostatic

#### Calculation of Ground and Excited State Potential Surfaces of Conjugated Molecules.<sup>1</sup> I. Formulation and Parametrization

A. Warshel and M. Karplus\*

*Contribution from the Department of Chemistry, Harvard University,  
Cambridge, Massachusetts 02138. Received January 31, 1972*

**1972 - Method of GS and ExS calculation of conjugated molecules. Different mechanical treatment of  $\sigma$  and  $\pi$  electrons.**

account of all bond length and bond angle variations. To permit rapid determination of the potential surfaces, the  $\sigma$  potential function and SCF-MO-CI energy of the  $\pi$  electrons are expressed as analytic functions of the molecular coordinates from which the first and second derivatives can be obtained. Illustrative applications to 1,3-butadiene, 1,3,5-hexatriene,  $\alpha,\omega$ -diphenyloctatetraene, and 1,3-cyclohexadiene are given.

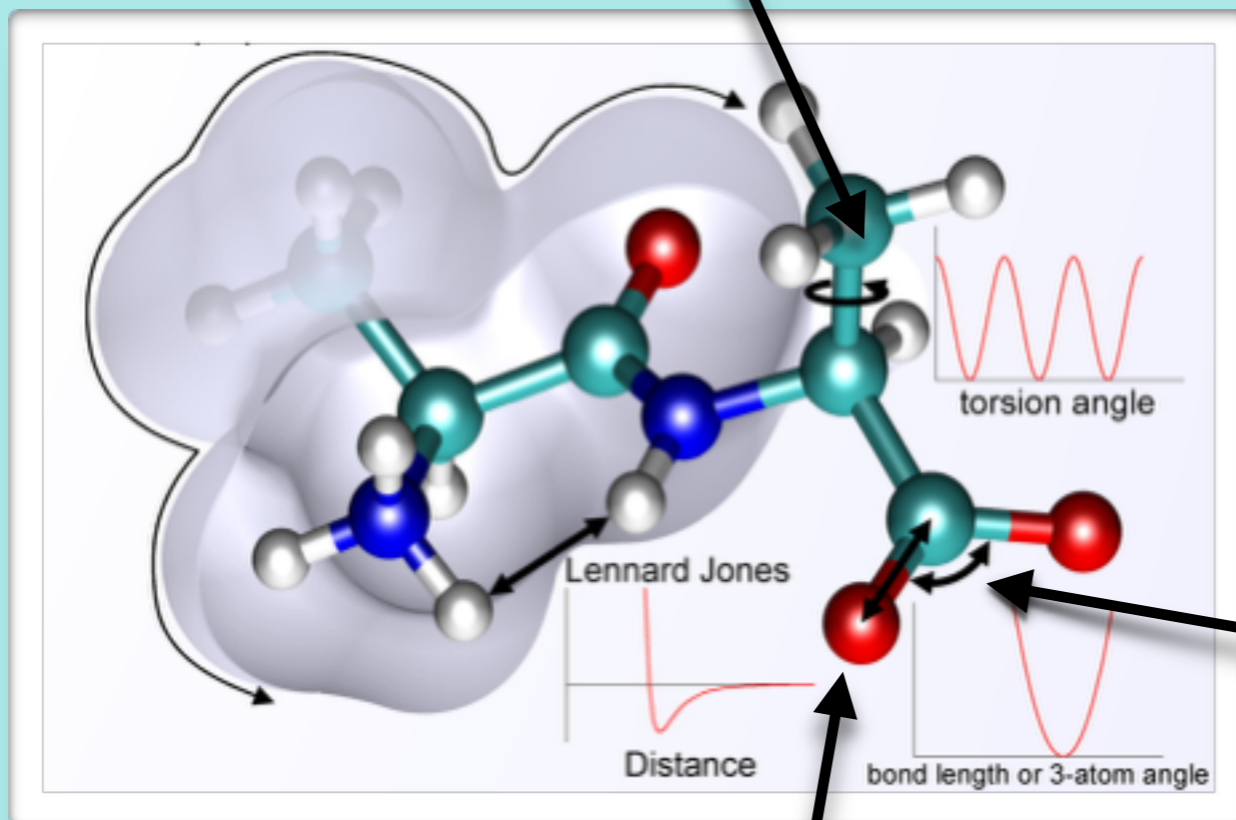
# Mixed Methods QM/MM

## General Remark

The entire **system is partitioned** into an inner region (QM-treatment), and outer part (MM-treatment).

### MM ForceField Expressions

$$E_{rotation} = k_{\phi} \cdot [1 + \cos(n\phi + \phi_0)]$$



$$E_{stretching} = k_{bond} \cdot (d - d_0)^2$$

$$E_{bending} = k_{\theta} \cdot (\theta - \theta_0)^2$$

### QM

$$\hat{H}\Psi_n = \epsilon_n \Psi_n$$

$$-i\hbar \frac{\partial}{\partial t} \Psi_n = \hat{H}\Psi_n$$

BUT, due to the (strong) QM-MM interaction, the total energy of the entire system **cannot** be written as the *sum of the energies of the subsystems*.

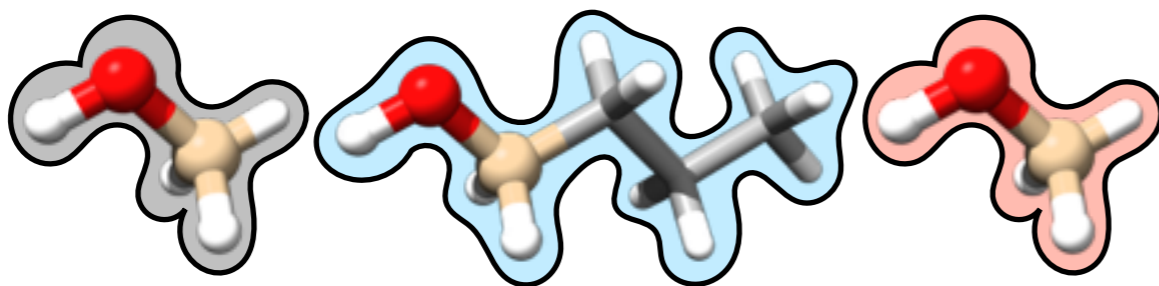
# Mixed Methods QM/MM

## Mixed Methods Schemes: How can we “cut” our system ?

Most of the current QM/MM methods use either a subtractive or an additive QM/MM scheme for the description of the energy of the full system.

### Subtractive Scheme

$$E_{QM/MM} = E_{QM}(QM) + E_{MM}(QM + MM) - E_{MM}(QM)$$

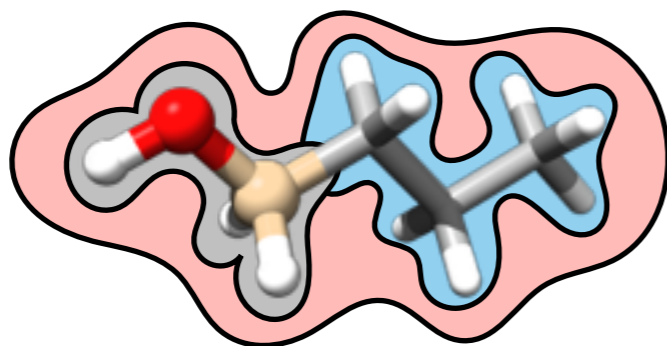


**Advantage:** Simplicity and Straightforward implementation.

**Drawback:** Require a complete set of MM parameters for the inner subsystem. The QM/MM coupling is treated at MM level.

### Additive Scheme

$$E_{QM/MM} = E_{QM}(QM) + E_{MM}(MM) + E_{QM/MM}$$



**Advantage:** very different levels of theory can be used to describe the QM, MM and QM-MM regions.

**Drawback:** the creation of an abrupt quantum/classical boundary. The electrons cease to exist when crossing from QM to MM.

**Most of the QM/MM methods use and additive scheme.**

# Mixed Methods QM/MM

## QM/MM Energy Formulation

In the additive scheme, one assume that the electron density can be partitioned into two regions:

$$\rho(\mathbf{r}) = \rho_{QM}(\mathbf{r}) + \rho_{MM}(\mathbf{r})$$

BUT, due to the (strong) QM-MM interaction, the total energy of the entire system cannot be written only as the sum of the energies of the subsystems:

$$E_{QM/MM} = E_{QM}(QM) + E_{MM}(MM) + E_{QM/MM}$$

## QM Energy Expression

In this embedding scheme, any *ab-initio* method from quantum mechanics can be applied to obtain the energy of the “inner” region.

As it concerns us, we can write the energy expression obtained from Density Functional Theory

$$E_{QM}^{DFT} = T_s[\rho] - \sum_I \int d\mathbf{r} \rho(\mathbf{r}) \frac{Z_I}{|\mathbf{R}_I - \mathbf{r}|} + \frac{1}{2} \int \int \frac{\rho(\mathbf{r})\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} d\mathbf{r} d\mathbf{r}' \\ + E_{xc}[\rho] + \frac{1}{2} \sum_I \sum_J \frac{Z_I Z_J}{|\mathbf{R}_I - \mathbf{R}_J|}$$

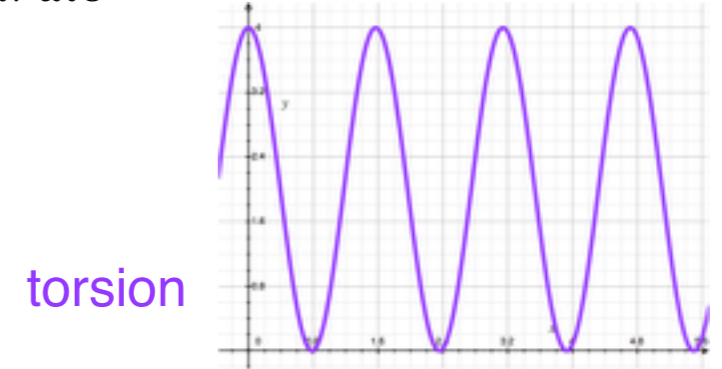
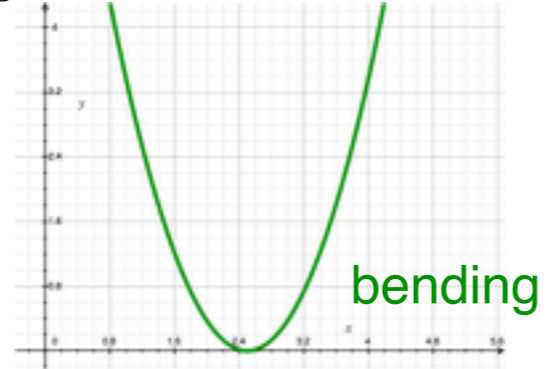


# Mixed Methods QM/MM

## MM Energy Expression

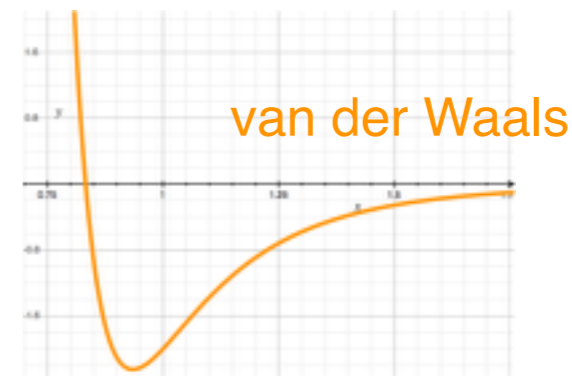
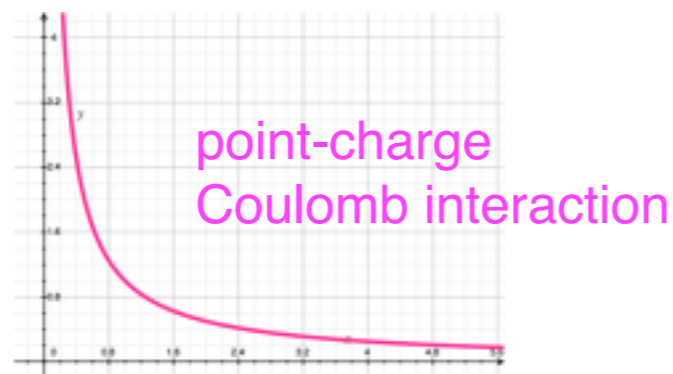
in the same manner, the potential energy function of the outer regions are described by classical mechanics (the “force-field”) containing *bonded terms*:

$$E_{MM}^{bonded} = \sum_{bonds} \frac{1}{2} k_d (d_{IJ} - d_0)^2 + \sum_{angles} \frac{1}{2} k_\theta (\theta_{IJK} - \theta_0)^2 + \sum_{dihedrals} k_\phi [1 + \cos(n\phi_{IJKL} + \delta)]$$



and non-bonded terms

$$E_{MM}^{nonbonded} = \frac{1}{2} \sum_{I \in MM} \sum_{J \in MM} \frac{q_I q_J}{R_{IJ}} + \frac{1}{2} \sum_{I \in MM} \sum_{J \in MM} 4\epsilon_{IJ} \left( \left( \frac{\sigma_{IJ}}{R_{IJ}} \right)^{12} - \frac{\sigma_{IJ}}{R_{IJ}} \right)^6$$



where the kinetic energy contribution has been considered constant, due to the “frozen” character of the MM electronic density.

# Mixed Methods QM/MM

## QM-MM Energy Expression

The exact form of the QM–MM coupling term  $E_{QM-MM}$  defines a particular QM/MM method. In accordance with the interactions considered in the force field, it includes **bonded**, **van der Waals**, and **electrostatic interactions** between QM and MM atoms

$$E_{QM-MM} = E_{QM-MM}^{bond} + E_{QM-MM}^{vdW} + E_{QM-MM}^{el}$$

The **electrostatic coupling** between the QM charge density and the charge model used in the MM region can be handled at different levels of sophistication, characterised essentially by the extent of mutual polarisation :

- Mechanical embedding
- Electrostatic embedding
- Polarised embedding

# Mixed Methods QM/MM

## Mechanical Embedding (unpolarized)

- The QM-MM interaction is treated on the same footing as in the MM part.

$$E_{QM/MM} = \frac{1}{2} \sum_{I \in QM} \sum_{J \in MM} \frac{Q_I q_J}{R_{IJ}}$$

**Advantage:** Conceptually straightforward and computationally efficient.

**Drawback:** (1) MM charge do not interact with the QM density (no direct polarised by the environment)  
(2) Derivation of appropriate  $Q_I$  charges is not trivial (it has to take into account electrons+nuclei).

## Electrostatic Embedding (QM polarized)

- Include QM-MM electrostatic interactions in the QM calculation.

$$\hat{H}_{QM-MM}^{el} = - \sum_{i \in QM}^N \sum_{J \in MM}^L \frac{q_J}{|\mathbf{r}_i - \mathbf{R}_J|} + \sum_{\alpha \in QM}^M \sum_{J \in MM}^L \frac{Q_\alpha q_J}{|\mathbf{R}_\alpha - \mathbf{R}_J|}$$

**Advantage:** The electronic structure of the QM part can adapt to changes in the charge distributions of the MM part (important when doing MD, or geometry optimisations).

**Attention:** Special care have to be done on the boundaries of the QM/MM, where the MM part can cause overpolarisation.

It remains the general issue of compatibility of the MM and QM. (parameters are not primarily designed to provide a faithful representation of the real charge distribution)

## Polarized Embedding (Fully Polarised)

- Include a flexible MM region polarised by the QM charge distribution. (direct polarised or fully self-consistent polarisation formalism)

**Attention:** The inclusion of all polarisable effects seriously increases the computational cost.

# Mixed Methods QM/MM

## Other contributions

In addition to the electrostatic contributions there are also the **van der Waals** and **bonded** contributions to the QM-MM coupling term.

Their treatment is considerably simpler as they are **handled purely at the MM level**, irrespective of the class (subtractive or additive) of QM/MM scheme.

$$E_{QM-MM}^{bonded} = \sum_{bonds} \frac{1}{2} k_d (d_{II'} - d_0)^2 + \sum_{angles} \frac{1}{2} k_\theta (\theta_{I''J''K''} - \theta_0)^2 \\ + \sum_{dihedrals} k_\phi [1 + \cos(n\phi_{I''J''K''L''} + \delta)]$$

$$E_{QM-MM}^{vdW} = \frac{1}{2} \sum_{I \in QM} \sum_{J \in MM} 4\epsilon_{IJ'} \left( \left( \frac{\sigma_{IJ'}}{R_{IJ'}} \right)^{12} - \frac{\sigma_{IJ'}}{R_{IJ'}} \right)^6$$

where I refers to an atom on the QM regions, I' runs over MM atoms, and I''' refers to a set of atoms where a least one atoms belongs to the QM region.

**Are good enough the standard MM parameters when covalent bonds crosses the QM-MM boundaries ?**

# ***Mixed Methods QM/MM***

## **Boundary Schemes**

Several approaches have been devised to treat with covalent bonds crossing the QM-MM boundaries.

Then three issues have to be dealt with: **1)** The dangling bond of the QM atom must be capped; **2)** For electrostatic or polarized embedding, overpolarization of the QM density by the MM charges has to be prevented, **3)** The bonded MM terms involving atoms from both subsystems have to be selected such that double-counting of interactions is avoided.

## **Link Atom**

An additional atom centre L (usually H-atom) is covalently bound to the Q1 and saturates its free valency.

## **Boundary Atoms**

the first MM atom is replaced by a special boundary atom that appears in both QM and MM calculation. On the QM side, it mimics the cut bond and possibly also the electronic character of the MM moiety attached to Q; in the MM calculation, it behaves as a normal MM atom.

## **Frozen Localised Orbitals**

Hybrid orbitals at the boundary and keep some of them frozen. They serve to cap the QM region, replacing the cut bond.

# Mixed Methods QM/MM

## TDDFT in Mixed methods

Mixed TDDFT/MM schemes are mostly used to compute excitation energies influenced by the electrostatic potential of the environment.

The implementation of a QM/MM scheme for the calculation of excitation energies within LR-TDDFT and a nonpolarizable MM environment is straightforward. Because all excited-state properties are calculated solely as functionals of the ground-state electron density.

All that is needed is to include the effect of the MM part into an additional contribution to the external potential

$$v_{ext}(\mathbf{r}, \mathbf{R}^{QM}, \mathbf{R}^{MM}) = \sum_{I \in QM} \frac{Z_I}{|\mathbf{R}_I - \mathbf{r}|} + \sum_{m \in MM} \frac{q_m}{|\mathbf{R}_m - \mathbf{r}|}$$

The new external potential generates a new (polarized) ground-state density (and KS orbitals), and its linear response to a frequency-dependent perturbation yields the new excitation energies  $\omega_n$  via Casida's equations

$$\begin{pmatrix} \mathbf{A} & \mathbf{B} \\ \mathbf{B}^* & \mathbf{A}^* \end{pmatrix} \begin{pmatrix} \mathbf{X} \\ \mathbf{Y} \end{pmatrix} = \Omega \begin{pmatrix} -\mathbf{I} & \mathbf{0} \\ \mathbf{0} & \mathbf{I} \end{pmatrix} \begin{pmatrix} \mathbf{X} \\ \mathbf{Y} \end{pmatrix}$$

# Mixed Methods QM/MM

## Practical Issues

### The QM part

#### *Choice of the QM Method:*

The QM/MM formalism houses for all types of QM methods.

- **Semiempirical methods:** large QM regions and large times scales (100ps-1ns), but its performance has to be carefully evaluated.
- **DFT-based methods:** ~100 atoms and comprise 10-100ps.
- **MC-CASSCF/CASPT2** and higher: limited to static QM/MM application, for a limited number of configurations.

#### *Choice of the QM Region:*

- It is always based in previous information.
- Ideally the density of the QM subsystem should match the density of the full QM system within the region of interest — **fairly large QM systems** are needed for quantitative results.

### The MM part

#### *Commonly used Force Fields in Biochemistry*

Force fields parametrise most of the **biological molecules**: proteins and nucleic acids, and less frequently carbohydrates or lipids.

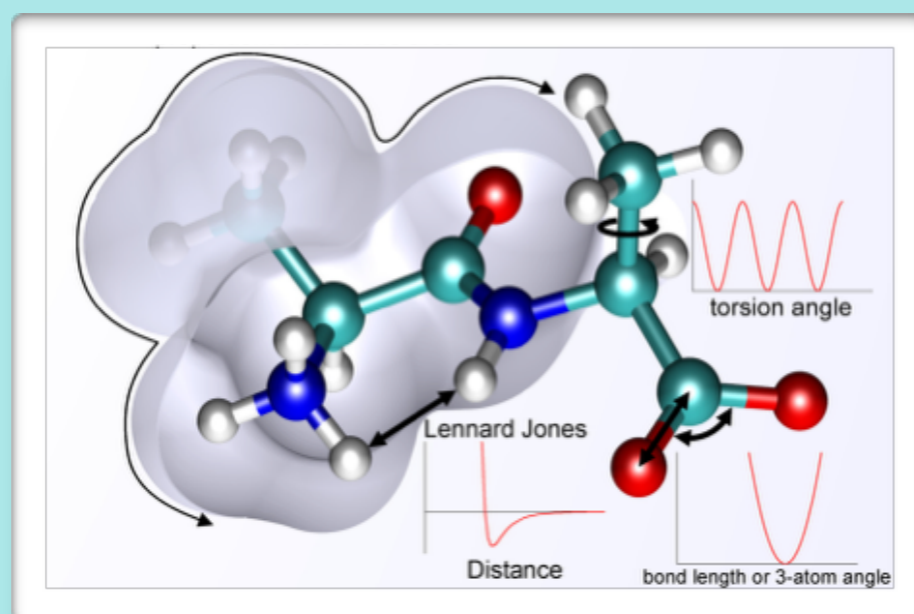
- AMBER, CHARMM, GROMOS, OPLS-AA,

Other types of molecular interactions have to be previously fitted or treated from ab-initio methods.

## Extended reviews

- Hans Martin Senn and Walter Thiel, “QM/MM Methods for Bimolecular Systems” *Angew. Chem. Int. Ed.* **2009**, 48, 1198-1229
- Elizabeth Brunk and Ursula Rothlisberger, “Mixed Quantum Mechanical/Molecular Mechanical Molecular Dynamics Simulations of Biological Systems in Ground and Electronically Excited States.” *Chem. Rev.* **2015**, 115, 6217-6263

## MM ForceField Expressions



## QM

$$\hat{H}\Psi_n = \epsilon_n \Psi_n$$
$$-i\hbar \frac{\partial}{\partial t} \Psi_n = \hat{H}\Psi_n$$

**Need of Force Field  
Parametrisation  
for each kind of atom  
combination !!**



What about complex systems with more than one active centre?

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# Fragment-density analysis in real-time TDDFT

**Objective:** to compute the contribution of the individual chromophores for any observable on complex systems.

## Hohenberg-Kohn theorem (1964)

Every observable quantity of a quantum system can be calculated from the electron density of the system ALONE !

**Principle:** split the global density on fragments belonging to each subsystem.  
Compute the expectation value on the local domain.

$$\rho(\mathbf{r}) = \rho_{tot}(\mathbf{r}) = \sum_I \rho_I(\mathbf{r});$$

### Strong Approximation:

The non-additive terms can be assumed negligible.

Reasonable, since the global density are computed taking into account also interacting terms between fragments

# Fragment-density analysis in real-time TDDFT

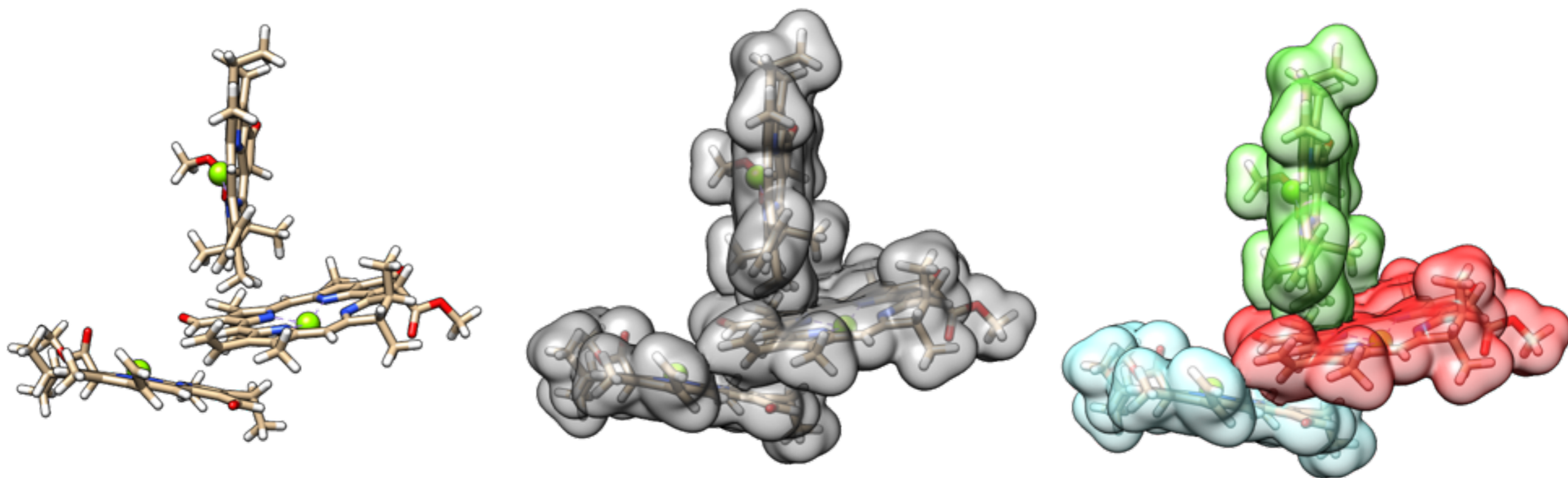
## Fragment-density and AIM theory

The local electronic densities are obtained by performing a division of the ground-state density based on the Bader charge-topological approach.

$$\rho(\mathbf{r}) = \rho_{tot}(\mathbf{r}) = \sum_I \rho_I(\mathbf{r});$$

Bader partitioning scheme: Atoms in Molecules theory.

(Richard F. W. Bader, "Atoms in Molecules: A Quantum Theory" )



# Fragment-density analysis in real-time TDDFT

## Local Dipole Analysis in real-time TDDFT

- 1 Do a ground state Kohn-Sham calculation: obtain  $\{\varphi_i\}$

$$\hat{H}_{KS}[n](\mathbf{r}, t)\varphi_i(\mathbf{r}, t) = \epsilon_i\varphi_k(\mathbf{r}, t)$$

- 2 Time propagation of the KS orbitals (in 3 orthogonal directions)
  - Apply a short perturbative field (usually an instantaneous perturbation).
  - Propagate the KS orbitals for a long time (the longer the propagation, the higher the energy resolution).

- 3 Sample the dipole moment in time series.

$$\mu_\gamma(t) = \int \mathbf{r}_\gamma \cdot \mathbf{n}(\mathbf{r}, t) d\mathbf{r}$$

- 4 Fourier transform to obtain the dynamic polarisability

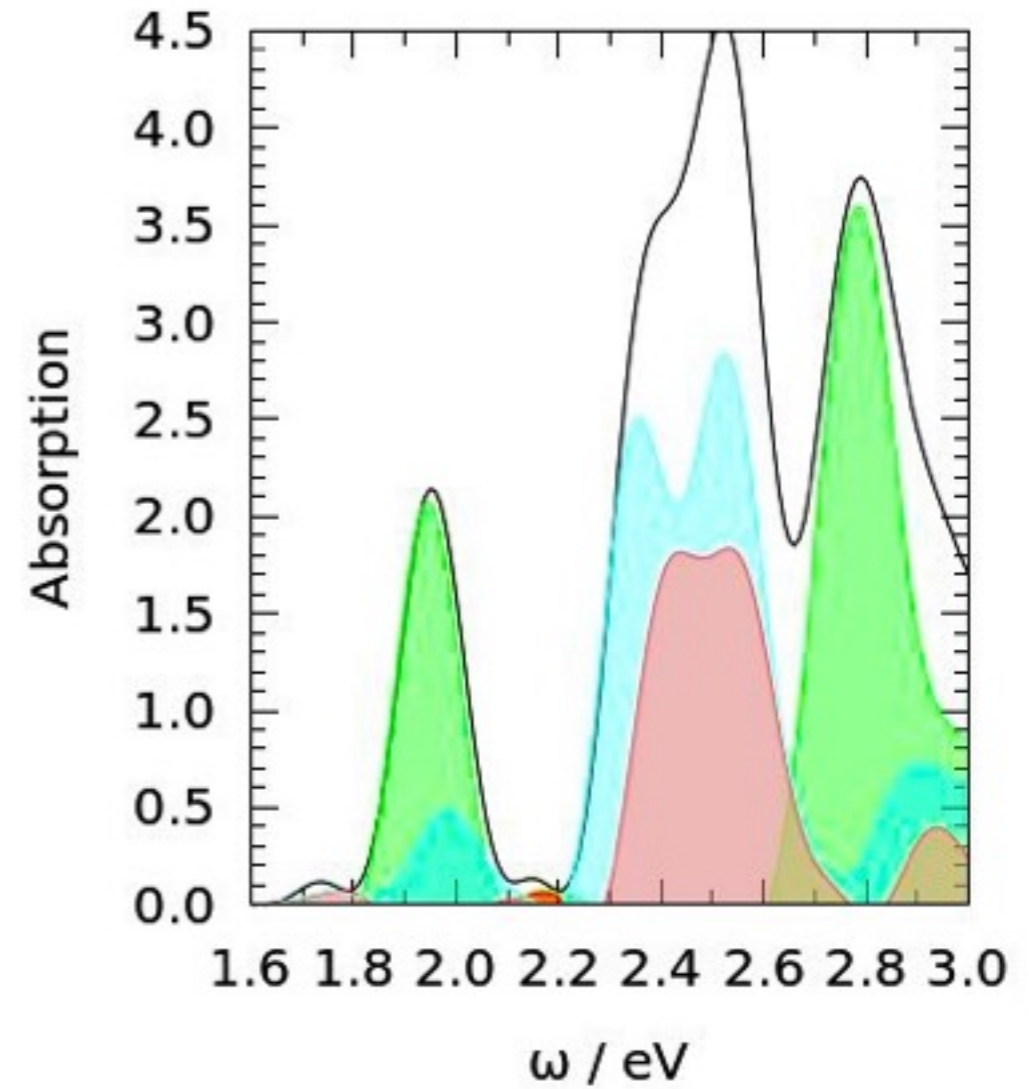
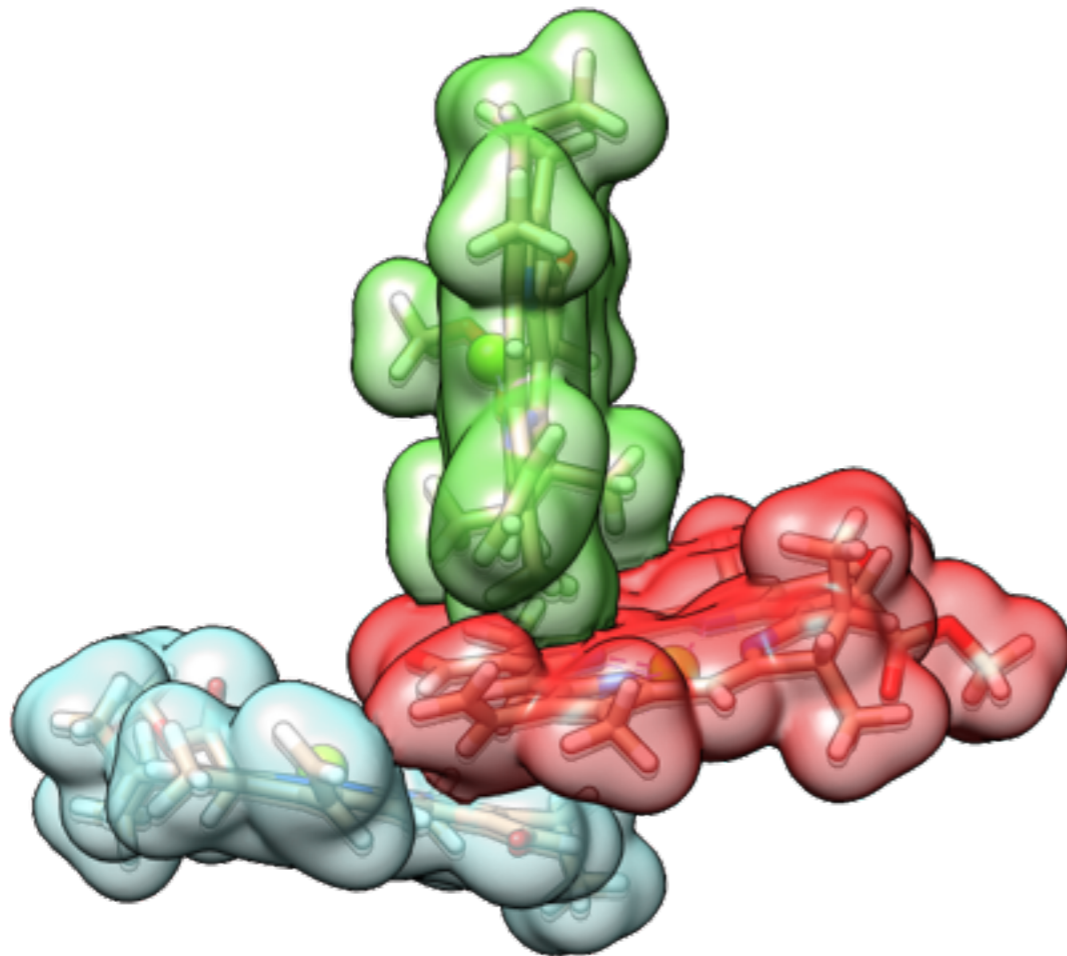
$$\alpha_{\gamma\delta}(\omega) = \frac{1}{K_\delta} \int_0^\infty dt [\mu_\gamma(t) - \mu_\gamma(0)] e^{-i\omega t}$$

- 5 Spectrum can be obtained from the photo absorption cross-section:

$$\sigma(\omega) = \frac{4\pi\omega}{3c} \Im\text{m}[\alpha(\omega)]$$

# Fragment-density analysis in real-time TDDFT

## Local Dipole Analysis in real-time TDDFT



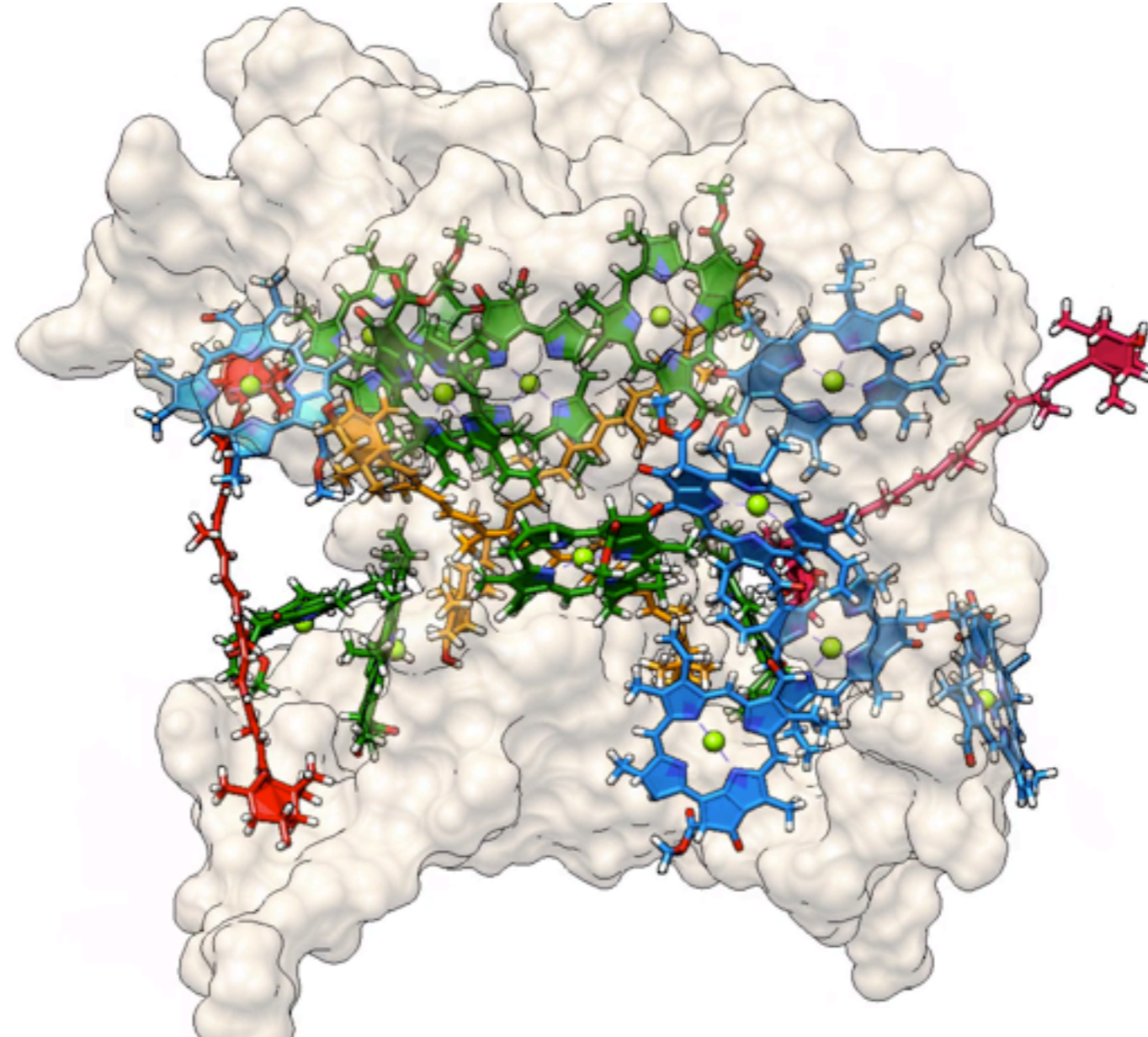
# Fragment-density analysis in real-time TDDFT

LHC-II Complex: ~17000 atoms

Chromophore Network

Stroma

Lumen



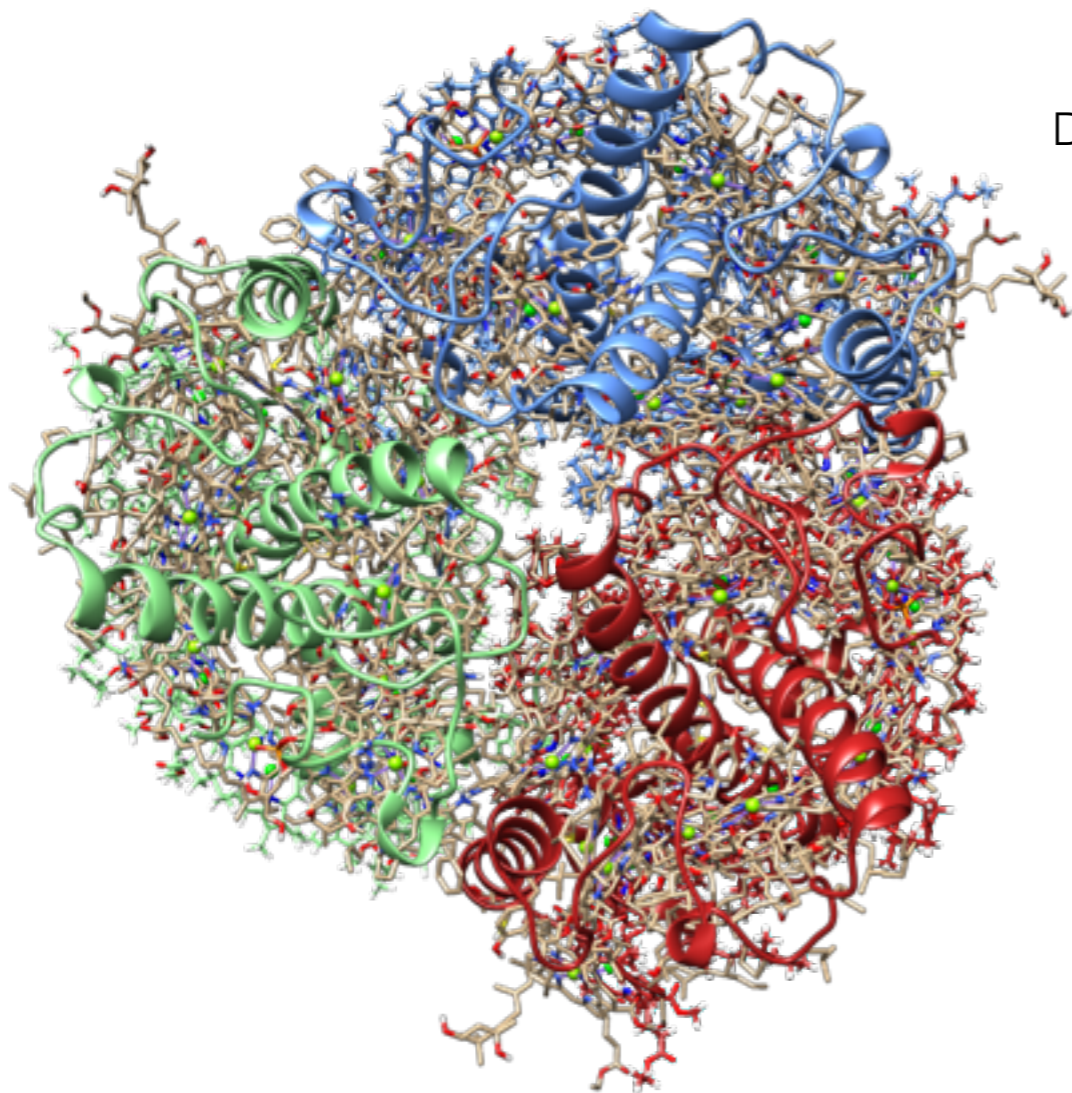
6 Chlorophyll b: 3 Stroma + 3 Lumen

8 Chlorophyll a: 5 Stroma + 3 Lumen

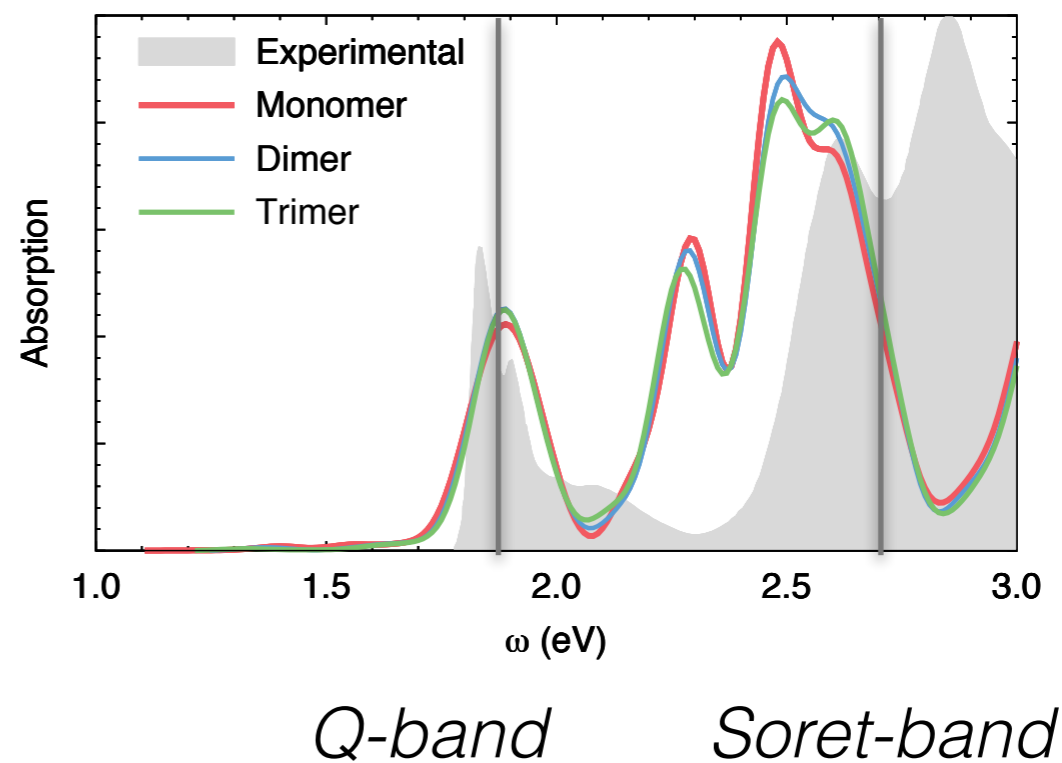
4 Carotenoids: Photoprotection Role



## Absorption Spectra Chlorophyll's Network



D.Siefermann-Hamms, *Biochim. Biophys. Acta*, 1985, **811**, 325



### **Monomer Chl's Network**

(2025 atoms, ~2600 states, 1440 CPUs,  
11s/iter, 20000 iter = 40fs)

= Good agreement on Q-band. ( $\Delta E \sim 0.05\text{eV}$ )

= Red shifted Soret-band ( $\Delta E \sim 0.35\text{ eV}$ )

### **Aggregated Chl's Network**

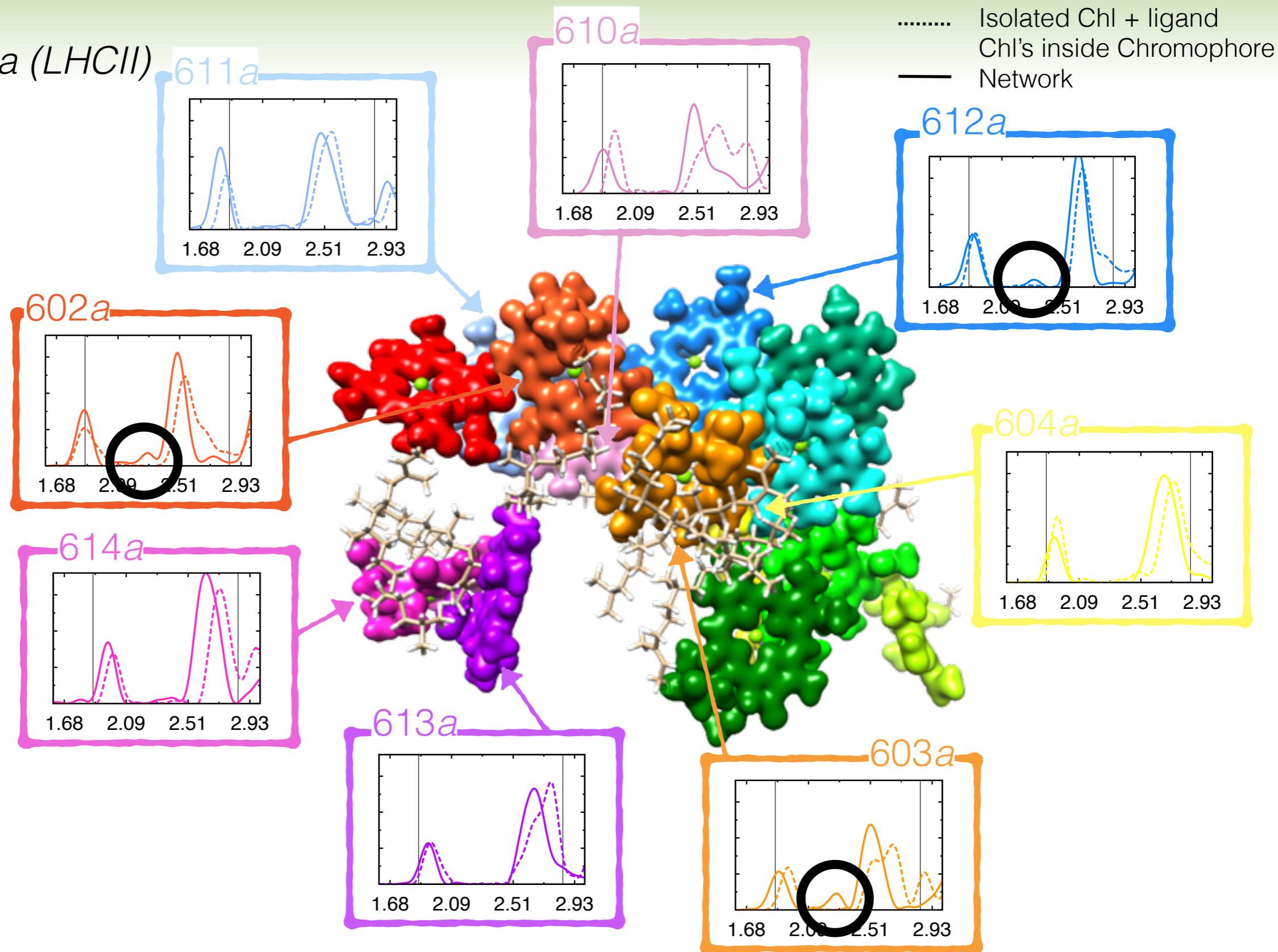
(6075 atoms, ~8000 states, 5120 CPUs,  
30s/iter, 20000 iter = 40fs)

= Only minor inter-monomer perturbations.

= Absorption process is governed by intra-monomer interactions.

# Fragment-density analysis in real-time TDDFT

Chlorophyll *a* (LHCII)



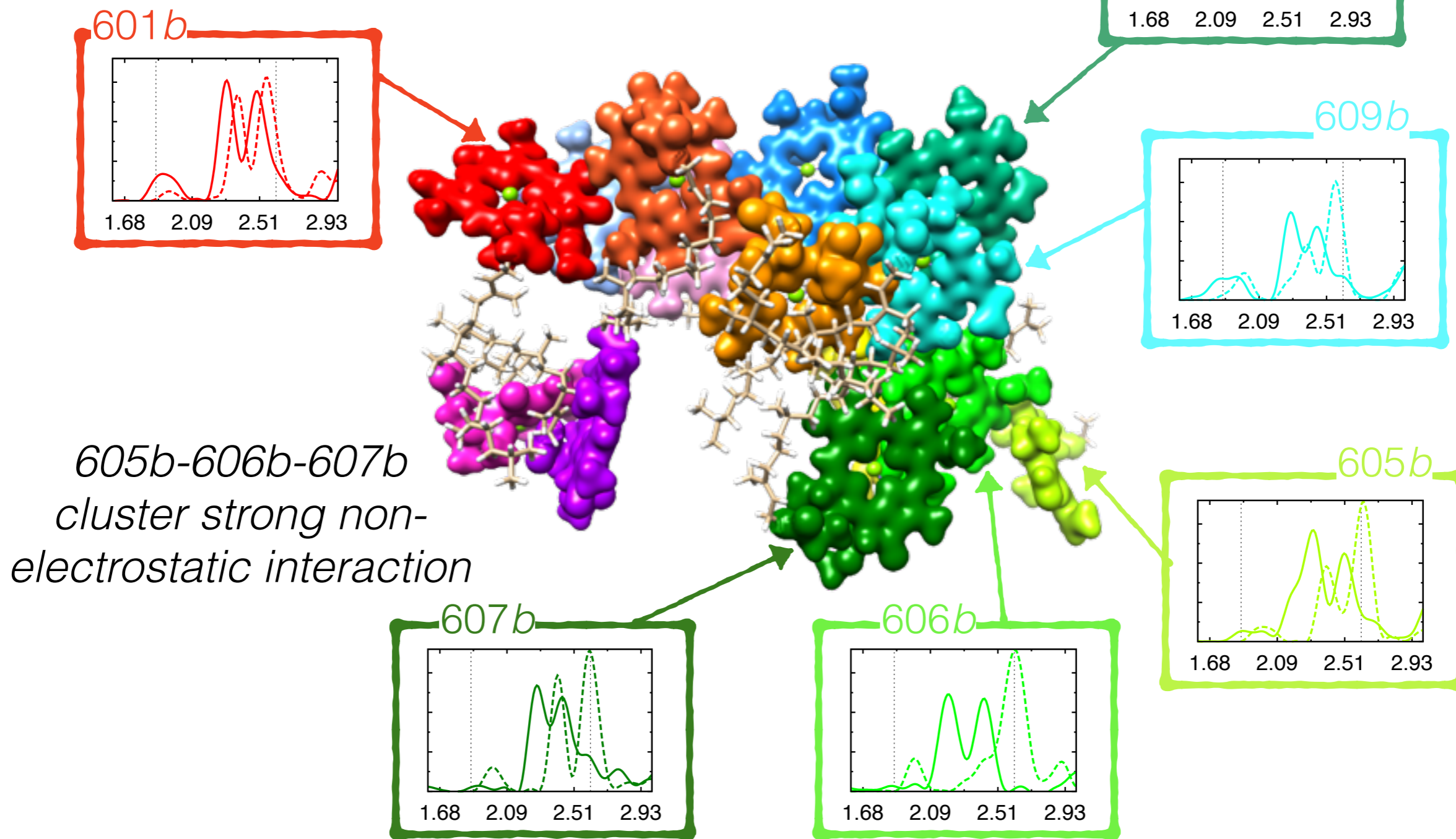
*General red-shift due to electrostatic effect*

*“Hidden peak” apparition attributed to oscillator strength transfer*

# Fragment-density analysis in real-time TDDFT

Chlorophyll *b* (LHCII)

*Low interacting Chlb: enhancement of Q-band peak*



..... Isolated Chl + ligand

— Chl's inside Chromophore Network

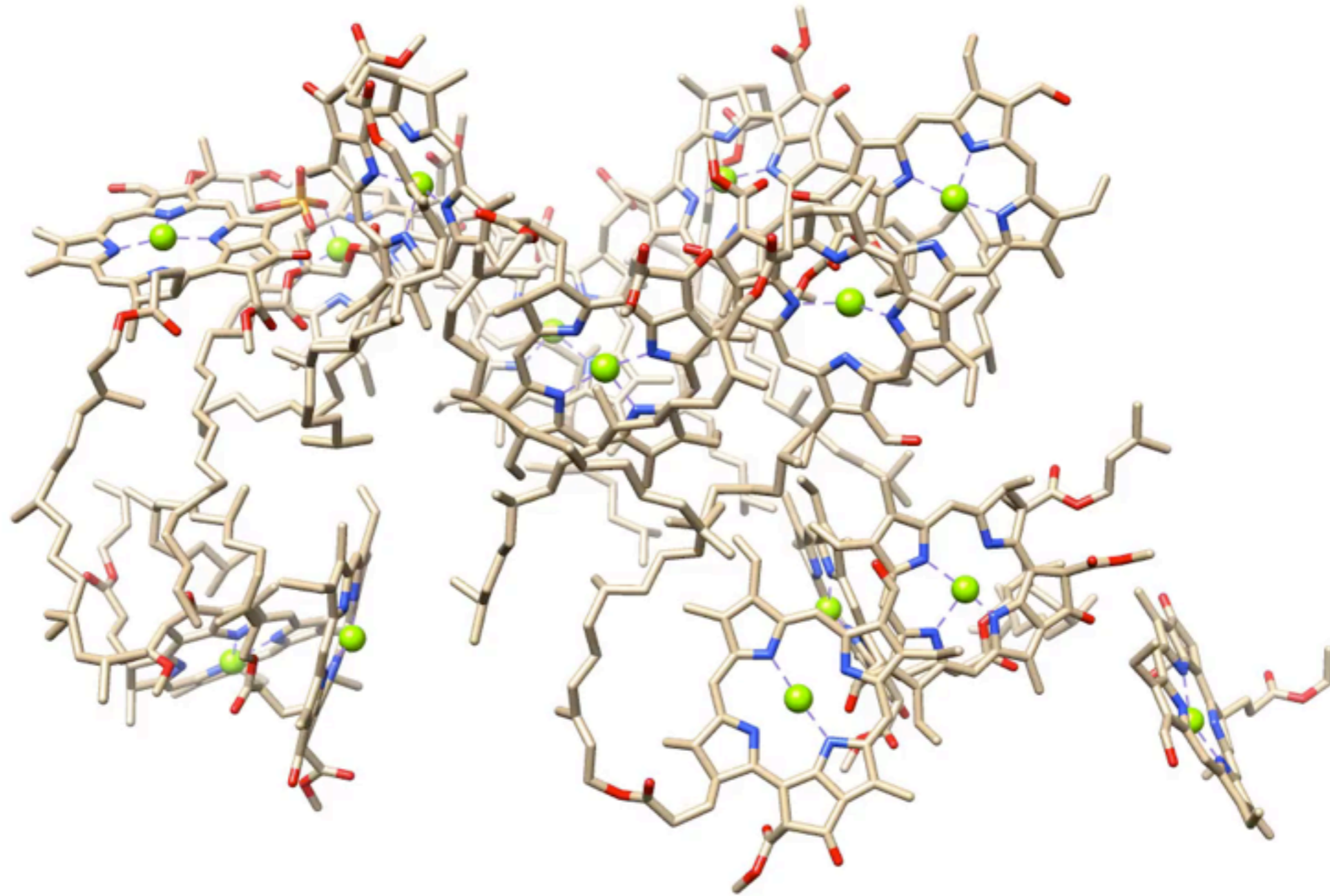
**Insights into colour-tuning of chlorophyll optical response in green plants**

JJornet-Somoza, *Phys.Chem.Chem.Phys.*, 2015, 17, 26599

# Fragment-density analysis in real-time TDDFT

## Excitonic Dynamics: rt-TDDFT

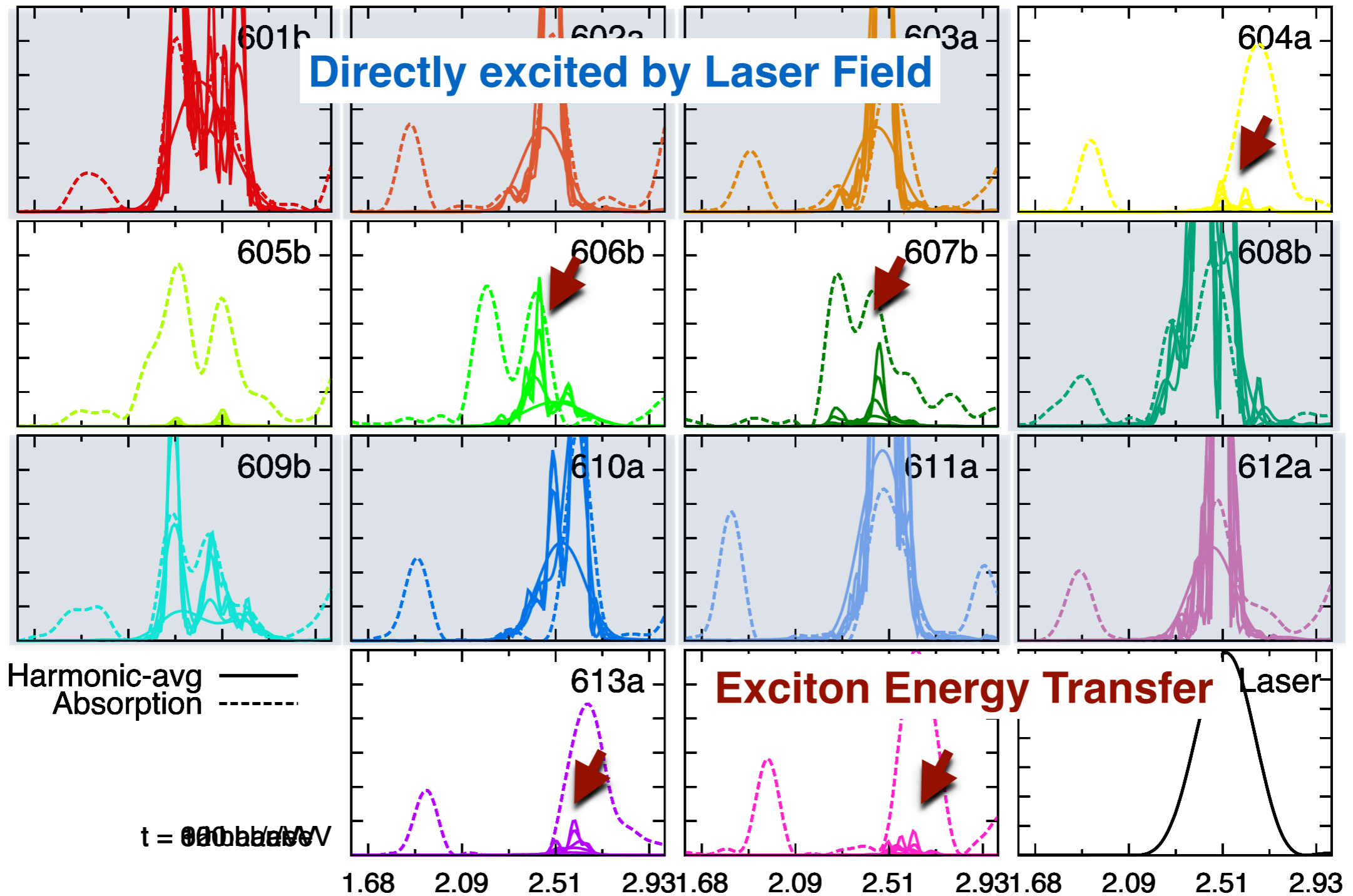
Propagation Time = 0.000 a.u. = 0.000 fs



# Fragment-density analysis in real-time TDDFT

## Excitonic Dynamics: rt-TDDFT

Fourier transform of induced dipoles for the chl's network (solid line) vs Absorption spectra (dashed lines)



- Biochemist's Interests
  - Photobiology
- Mixed Method: QM /MM:
  - QM/MM Schemes + QM/MM Energy Formulation.
  - Boundary Schemes
  - TDDFT in Mixed Methods
- **Fragment-density analysis in Real-time TDDFT**
  - Fragment-density and AIM theory
  - Local Dipole Analysis in real-time TDDFT
  - Application to LHC-II
- **Fundamentals of Subsystem TDDFT**
  - Fundamentals of Subsystem DFT
  - Frozen Density Embedding Theory
  - Subsystem TDDFT

# Fundamentals of Subsystem TDDFT

## The Kohn-Sham Formalism

The total energy in the KS DFT is usually written as

$$E[\rho] = T_s[\rho] + V_{nuc}[\rho] + J[\rho] + E_{xc}[\rho] + V_{nn}$$

The kinetic energy term for the non-interacting system are in general not known as functionals of the electronic density, and can be approximated to a functional of the non-interacting orbitals

$$E[\{\psi_i\}] = T_s[\{\psi_i\}] + V_{nuc}[\rho] + J[\rho] + E_{xc}[\rho] + V_{nn}$$
$$T_s[\{\psi_i\}] = \sum_i \langle \psi_i | -\nabla^2/2 | \psi_i \rangle$$

Minimisation of the energy with respect to the KS orbitals leads to the *single-particle Kohn-Sham equations*

$$\left( -\frac{\nabla^2}{2} + v_{eff}[\rho](\mathbf{r}) \right) \psi_i(\mathbf{r}) = \epsilon_i \psi_i(\mathbf{r})$$

# Fundamentals of Subsystem TDDFT

## Subsystem DFT

Starting point: partitioning of the electron density

$$\rho(\mathbf{r}) = \rho_{tot}(\mathbf{r}) = \sum_I \rho_I(\mathbf{r}); \quad \rho_I(\mathbf{r}) = \sum_{i_I}^{n_I} |\psi_{i_I}(\mathbf{r})|^2$$

The essential difference is that we are no longer able to use the non-interacting  $T_s[\{\psi_i\}]$

Instead, we can define the subsystem kinetic energies :

$$T_s[\{\psi_{i_I}\}] = \sum_{i_I}^{n_I} \langle \psi_{i_I} | -\nabla^2/2 | \psi_{i_I} \rangle \longrightarrow T_s[\{\psi_i\}] = \sum_I T_s[\{\psi_{i_I}\}] + T_s^{nad}[\{\psi_i\}, \{\psi_{i_I}\}]$$

**subsystem kinetic energy**

**non-additive kinetic energy term**

The non-additive kinetic energy term can be formulated in terms of the electronic densities of each subsystem

$$T_s^{nad}[\rho_I] = T_s[\rho_i] - \sum_I T_s[\rho_I] \quad T_s[\rho_I] = \min_{\{\psi_{i_I}\} \rightarrow \rho_I} \sum_i^{n_I} \langle \psi_{i_I} | -\nabla^2/2 | \psi_{i_I} \rangle$$



# Fundamentals of Subsystem TDDFT

The total energy expression for the Subsystem DFT becomes:

$$E[\{\psi_{i_I}\}] = \sum_I T_s[\{\psi_{i_I}\}] + V_{nuc}[\rho] + J[\rho] + E_{xc}[\rho] + T_s^{nad}[\{\rho_I\}] + V_{nn}$$

Minimisation of this expression with respect to the **KS-like orbitals**  $\{\psi_{i_K}\}$  of **subsystem K**, *under the constraint that the subsystem orbitals are orthonormal and the electron densities of the other subsystems are fixed*, leads to the KS equation with constrained electron density (KSCED)

contains all terms of KS potential for the isolated subsystem K.

$$\left( -\frac{\nabla^2}{2} + v_{eff}^{(K)}[\rho_K](\mathbf{r}) + v_{emb}^{(K)}[\rho_K, \rho_{tot}](\mathbf{r}) \right) \psi_{i_K}(\mathbf{r}) = \epsilon_{i_K} \psi_{i_K}(\mathbf{r})$$

depends on the nuclear potential of other subsystems and includes *non-additive terms* for the **kinetic energies** and the **exchange-correlation functionals**.

$$v_{emb}^{(K)}[\rho_K, \rho_{tot}](\mathbf{r}) = \sum_{I, I \neq K} v_{nuc}^{(I)}(\mathbf{r}) + v_{Coul}[\rho_{tot} - \rho_K] + \left( \frac{\delta T_s[\rho_{tot}]}{\delta \rho_{tot}(\mathbf{r})} - \frac{\delta T_s[\rho_K]}{\delta \rho_K(\mathbf{r})} \right) + \left( \frac{\delta E_{xc}[\rho_{tot}]}{\delta \rho_{tot}(\mathbf{r})} - \frac{\delta E_{xc}[\rho_K]}{\delta \rho_K(\mathbf{r})} \right)$$

the coupled equations have to be **solved self-consistently** with respect to the other subsystems

# Fundamentals of Subsystem TDDFT

## Frozen Density Embedding Theory

Starting from a subsystem description, one can set up embedding methods in which one particular subsystem is considered to be embedded in an effective environmental potential. FDET arises when this potential is derived from a given environmental density.

$$\rho(\mathbf{r}) = \rho_{\text{active}}(\mathbf{r}) + \rho_{\text{environment}}^{\text{frozen}}(\mathbf{r})$$

The environment density is previously defined based on a reasonable starting point (usually the density of the environment without the active system). Then one calculates the **density of the active system** by employing the embedded potential in the *KSCED equations*. (previous slide). However, this derivation introduces some  $v$ -representability problems.<sup>1</sup>

<sup>1</sup> *v*-representability problem: if the target density can be obtained from a non-interacting system, then the minimisation of  $E$  leads to the correct total density and energy. Necessary condition; target density  $\geq 0$  everywhere, and is not always fulfilled.

# Fundamentals of Subsystem TDDFT

Original reformulation (disconnected from subsystem DFT) done by Wesolowski and Warshel (*J.Phys.Chem*, **1993**, 97, 8050) define the **target/active density** as the density that **minimise the total energy of the total system**.

$$E_{\text{FDE}}[\{\psi_{i_A}\}, \rho_e^{\text{frozen}}] = T_s[\{\psi_{i_A}\}] + T_s[\rho_e^{\text{frozen}}] + T_s^{\text{nad}}[\rho_A, \rho_e^{\text{frozen}}] \\ + V_{\text{nuc}}[\rho] + J[\rho] + E_{\text{xc}}[\rho] + V_{\text{nn}}$$

The solution can be obtained analogously to the KS equation :

$$\left( -\frac{\nabla^2}{2} + v_{\text{eff}}^{\text{FDE}}[\rho_A, \rho_e^{\text{frozen}}](\mathbf{r}) \right) \psi_{i_A}(\mathbf{r}) = \epsilon_{i_A} \psi_{i_A}(\mathbf{r})$$

↙

$$v_{\text{eff}}^{\text{FDE}}[\rho_A, \rho_e^{\text{frozen}}](\mathbf{r}) = v_{\text{eff}}^{\text{KS}}[\rho_{\text{total}}] + \frac{\delta T_s^{\text{nad}}[\rho_A, \rho_e^{\text{frozen}}]}{\delta \rho_A}$$

As a consequence **FDE is no longer able to lead to the exact GS** energy and density of the whole system, but yield an upper bound for the energy.

# Fundamentals of Subsystem TDDFT

## Practical Issues

The embedding potential has important properties:

$$v_{emb}^{(K)}[\rho_K, \rho_{tot}](\mathbf{r}) = \sum_{I, I \neq K} v_{nuc}^{(I)}(\mathbf{r}) + v_{Coul}[\rho_{tot} - \rho_K] + \left( \frac{\delta T_s[\rho_{tot}]}{\delta \rho_{tot}(\mathbf{r})} - \frac{\delta T_s[\rho_K]}{\delta \rho_K(\mathbf{r})} \right) + \left( \frac{\delta E_{xc}[\rho_{tot}]}{\delta \rho_{tot}(\mathbf{r})} - \frac{\delta E_{xc}[\rho_K]}{\delta \rho_K(\mathbf{r})} \right)$$

- Is exact in the limits of the exact functionals.
- The main contribution are usually the electrostatic potentials (nuclei and coulomb)
- The exchange-correlation effects can be treated as in KS-DFT calculations.
- Includes polarisation effects.
  
- Electron-leak problem: electrons can be unphysical localised at the nuclei of the frozen environment if no additional contribution are added.
- This effect can be corrected on the approximation of the non-additive kinetic energy.

# Fundamentals of Subsystem TDDFT

## Subsystem TDDFT

The first assumption of the Subsystem TDDFT is that the response density can also be partitioned into subsystems contributions

$$\delta\rho_{tot}(\mathbf{r}) = \sum_I \delta\rho_I(\mathbf{r}) \quad \delta\rho_I(\mathbf{r}_1, \omega) = \sum_{(ia)_I} 2\delta P_{(ia)_I}(\omega) \varphi_{i_I}(\mathbf{r}_1) \varphi_{a_I}(\mathbf{r}_1)$$

It assumes that can be expanded **ONLY** in terms of intrasubsystem orbital transition.  
**No Charges Transfer between subsystems.**

And also, the external perturbational potential will include non-additive terms.

$$\delta v_{ai}^{(I)}(\omega) = \delta v_{ai}^{ext(I)}(\omega) + \delta v_{ai}^{el(I)}(\omega)$$

where

$$\delta v_I^{el}(\mathbf{r}_1) = \sum_K \int \left( \frac{\delta v_{eff}^{(I)}(\mathbf{r}_1)}{\delta\rho_K(\mathbf{r}_2)} + \frac{\delta v_{emb}^{(I)}(\mathbf{r}_1)}{\delta\rho_K(\mathbf{r}_2)} \right) \delta\rho_K(\mathbf{r}_2) d\mathbf{r}_2$$

# Fundamentals of Subsystem TDDFT

After some algebra, we can see that the matrix elements of the induced potential are given:

$$\delta v_{(bj)_I}^{el} = 2 \sum_{(ia)_J} K_{(jb)_I(ia)_J}^{eff} \delta P_{(ia)_J}$$

where instead of the kernel for the isolated subsystem, we have an *effective kernel*, which take into account the *non-additive terms*.

$$K_{(jb)_I(ia)_J}^{eff} = \int d\mathbf{r}_1 \varphi_j(\mathbf{r}_1) \varphi_b(\mathbf{r}_1) \times \int d\mathbf{r}_2 \left( \frac{1}{|\mathbf{r}_1 - \mathbf{r}_2|} + \frac{\delta^2 E_{xc}[\rho_{tot}]}{\delta \rho_{tot}^2} + \frac{\delta^2 T_s[\rho_{tot}]}{\delta \rho_{tot}^2} - \frac{\delta^2 T_s[\rho_{tot}]}{\delta \rho_{tot}^2} \Big|_{\rho_I} \delta_{IJ} \right) \varphi_a(\mathbf{r}_2) \varphi_i(\mathbf{r}_2)$$

Similar to super molecular case we arrive

$$\delta P_{(jb)_I} = \chi_{(jb)_I}^s \left[ \delta v_{(bj)_I}^{ext} + 2 \sum_{(ia)_J} K_{(jb)_I(ia)_J}^{eff} \delta P_{(ia)_J} \right]$$

Analogously to the TDDFT formalism, we can set up an eigenvalue problem to determine the excitation energies:

$$[\mathbf{\Omega}^{sub} - \omega_k^2] \mathbf{F}_k^{sub} = 0$$

# Fundamentals of Subsystem TDDFT

where the matrix can be divided into intrasubsystems (diagonal terms) and intersubsystems (off-diagonal) blocks.

$$\left[ \begin{pmatrix} \Omega_{AA} & \Omega_{AB} & \cdots & \Omega_{AZ} \\ \Omega_{BA} & \Omega_{BB} & \cdots & \Omega_{BZ} \\ \vdots & \vdots & \ddots & \vdots \\ \Omega_{ZA} & \Omega_{BZ} & \cdots & \Omega_{ZZ} \end{pmatrix} - \omega_k^2 \begin{pmatrix} 1_{AA} & 0_{AB} & \cdots & 0_{AZ} \\ 0_{BA} & 1_{BB} & \cdots & 0_{BZ} \\ \vdots & \vdots & \ddots & \vdots \\ 0_{ZA} & 0_{BZ} & \cdots & 1_{ZZ} \end{pmatrix} \right] \begin{pmatrix} \mathbf{F}_k^A \\ \mathbf{F}_k^B \\ \vdots \\ \mathbf{F}_k^Z \end{pmatrix} = \begin{pmatrix} 0_k^A \\ 0_k^B \\ \vdots \\ 0_k^Z \end{pmatrix}$$

Main differences with respect to the isolated formulation:

- The intersystem coupling blocks.
- The matrix elements carry xc and kinetic-energy contribution from all subsystems.
- The orbitals and energies are obtained from GS subsystem calculation, i.e. the non-additive kinetic contribution are also present.

Two main approximation to solve the above eigenvalue equations:

1. **FDEu (uncoupled)** - ONLY the response of the embedded systems itself has to be taken into account (off-diagonal blocks are zero).
2. **FDEc (coupled)** - starting from the FDEu eigenvectors, a unitary transformation can be done that enable a numerical evaluation of the off-diagonal blocks elements and solve the truncated eigenvalue problem.

## Detailed derivation are extended in :

- Christoph R. Jacob and Johannes Neugebauer  
“Subsystem density-functional theory”  
*WIREs Comput. Mol. Sci.* **2013**, 00: 1-34 doi: 10.1002/wcms.1175
- Johannes Neugebauer  
“Couplings between electronic transitions in a subsystem formulation of time-dependent density functional theory”  
*J. Chem. Phys.* **2007**, 126, 134116



# ***Fragment-density analysis in Real-time TDDFT***