Quantum chemical calculation of proteins

1. N-order（linear-scaling) molecular orbital method
2. FMO
3. Hybrid quantum mechanics/molecular mechanics (QM/MM) method
4. ONIOM method

分子力学 (Molecular Mechanics)

$$E_{tot} = E_{bond} + E_{angle} + E_{tors} + E_{nb}$$

$$E_{bond} = \sum_{bond} e_{bond}, \quad e_{bond} = K_b (l - l_0)^2$$ 結合伸縮エネルギー

$$E_{angle} = \sum_{angle} e_{angle}, \quad e_{angle} = K_a (\theta - \theta_0)^2$$ 変角エネルギー

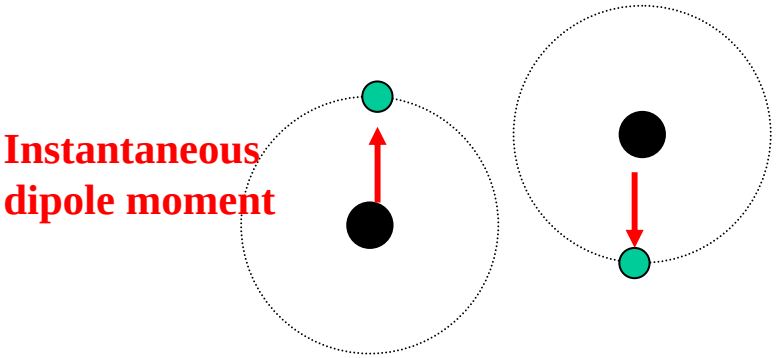
$$E_{tors} = \sum_{tors} e_{tors}, \quad e_{tors} = V_n (1 + \cos n\phi)$$ ねじれ角エネルギー

$$E_{nb} = E_{vdw} + E_{elect}$$ 非結合相互作用エネルギー

$$E_{vdw} = \sum_{i} \sum_{j \geq i+3} e_{vdw}, \quad e_{vdw} = A\left[\left(\frac{r_m}{r_{ij}}\right)^{12} - \left(\frac{r_m}{r_{ij}}\right)^{6}\right]$$ Lennard-Jones potential

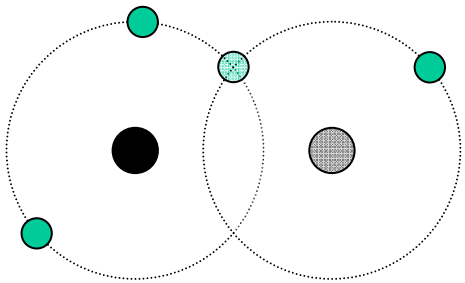
$$E_{elec} = \sum_{i} \sum_{j > i} e_{charge/charge}, \quad e_{charge/charge} = \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}}$$ 静電相互作用エネルギー

London dispersion force（ロンドン分散力）



分子（原子）間の電子相関に起因
→原子or 分子、極性or非極性に
　関わらず働く。常に引力。$1/r^6$依存性
→MP2以上の電子相関を考慮した計算
　HFやDFTはダメ

Exchange repulsion（交換斥力）



軌道のオーバラップ
→パウリの排他原理に起因する斥力
→短距離力$1/r^{12}$依存性

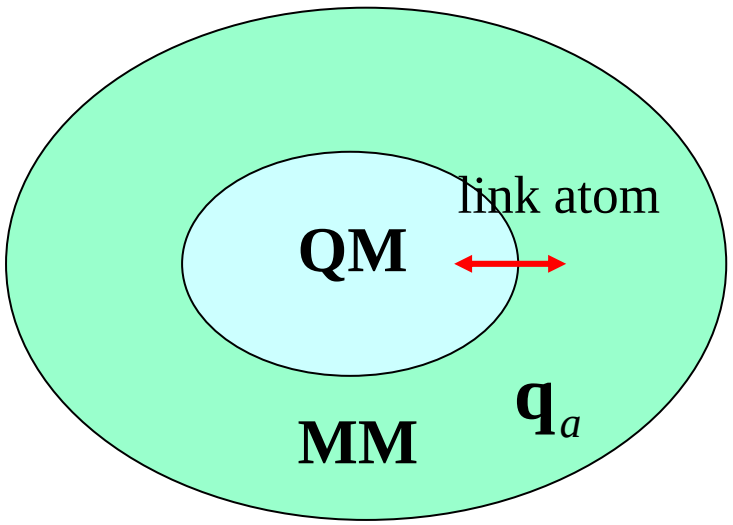
汎用プログラムと汎用ポテンシャル

プログラム名	ポテンシャル名	開発者
Amber	Amber	Kollman
Charmm	Charmm	Karplus
Gromacs	Gromos	Berendsen
	MM2, MM3	Allinger
NAMD	Charmm etc.	Shulten
	OPLS	Jorgensen
	ECEPP	Scheraga

Hybrid QM/MM method

QM/MM hamiltonian

$$\mathrm{H} = \mathrm{H}_0 + \sum_{i,a} \frac{q_a}{|\mathbf{r}_a - \mathbf{r}_i|} + \sum_{\alpha,a} \frac{Z_\alpha q_a}{|\mathbf{r}_a - \mathbf{r}_\alpha|} + \sum_{\alpha,\kappa} \left(\frac{A_{\alpha\kappa}}{|\mathbf{r}_\kappa - \mathbf{r}_\alpha|^{12}} - \frac{B_{\alpha\kappa}}{|\mathbf{r}_\kappa - \mathbf{r}_\alpha|^{6}} \right)$$



吸収波長の計算方法

１電子励起CI法 (singly-excited configuration interaction)

$$\Phi = C_1\Psi_{HOMO\to LUMO} + C_2\Psi_{HOMO\to LUMO+1} + C_3\Psi_{HOMO-1\to LUMO} + \cdots$$

$$\mathrm{H}\Phi = E\Phi$$

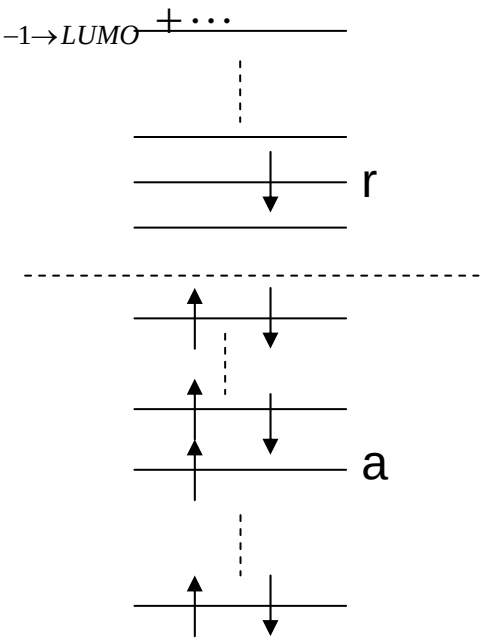
$$\sum_{i=0} C_i H\Psi_i = E\sum_{i=0} C_i\Psi_i$$

$$\sum_{j=0} C_j(H_{ij} - ES_{ij}) = 0$$

$$H_{ij} = \int \Psi_i H \Psi_j d\tau$$

$$S_{ij} = \int \Psi_i \Psi_j d\tau = \delta_{ij}$$

$$\boldsymbol{HC} = \boldsymbol{EC}$$

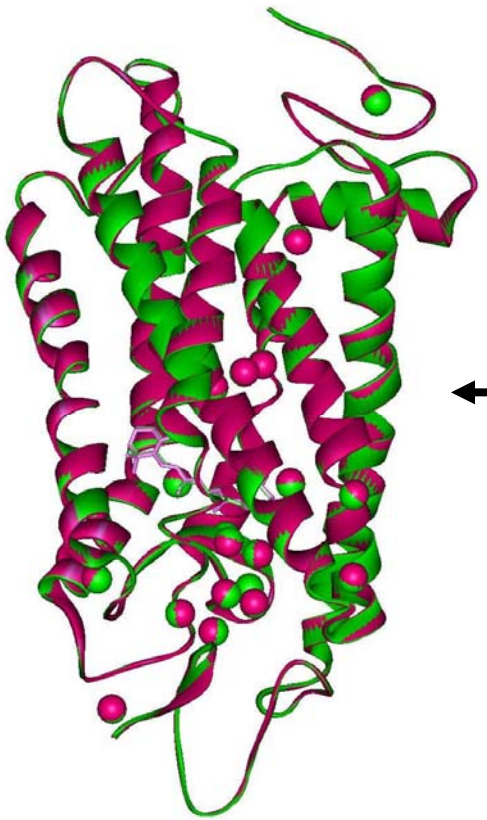


１電子励起配置

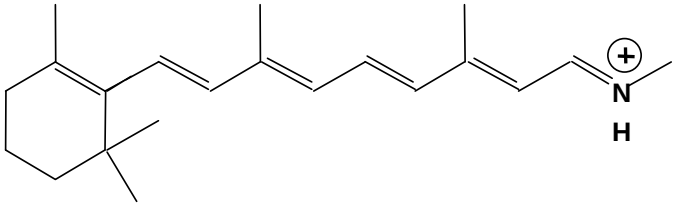
問題

ベンゼンの吸収波長を１電子励起CI法で計算するとき
CI行列の次元はいくつになるか。ただし、波動関数は
半経験的INDO/Sレベルを使用するものとする。

Retinal protein consists of apoprotein (opsin) and chromophore



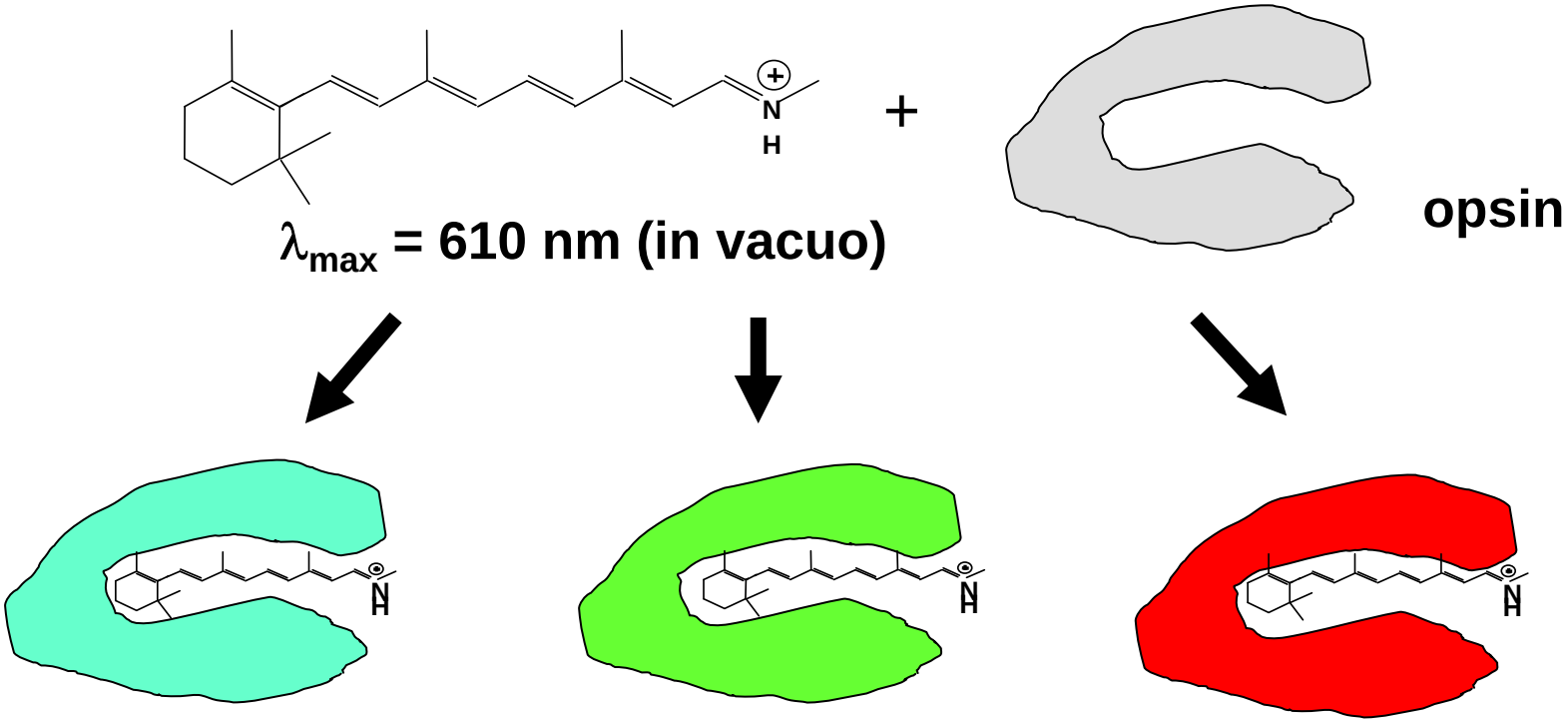
chromophore



protonated retinal Schiff base (PRSB)

Seven transmembrane α–helices

How are the absorption maxima of retinal proteins controlled by the weak interactions between the chromophore and opsin ?

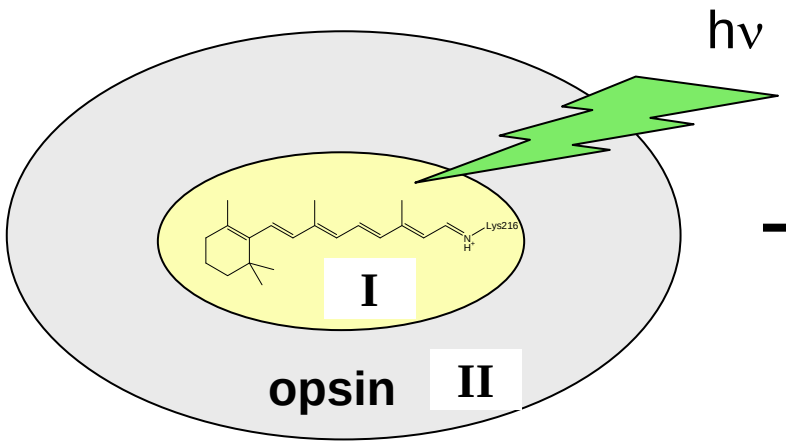


The absorption maximum of each protein is precisely tuned for the occurrence of each biological function. Thus, the elucidation of the spectral tuning mechanism is an important issue in photobiology, especially in vision of animal.

Formulation of a novel QM/MM theory for calculation of the excitation energies of photoreceptor proteins

H. Houjou et al., *J. Phys. Chem. B* , **105**, 867-879 (2001).
M. Sakurai et al., J. Am. Chem. Soc., **125**, 3108-3112 (2003)
Recent collaboration with Fujitsu Ltd. (to be published)

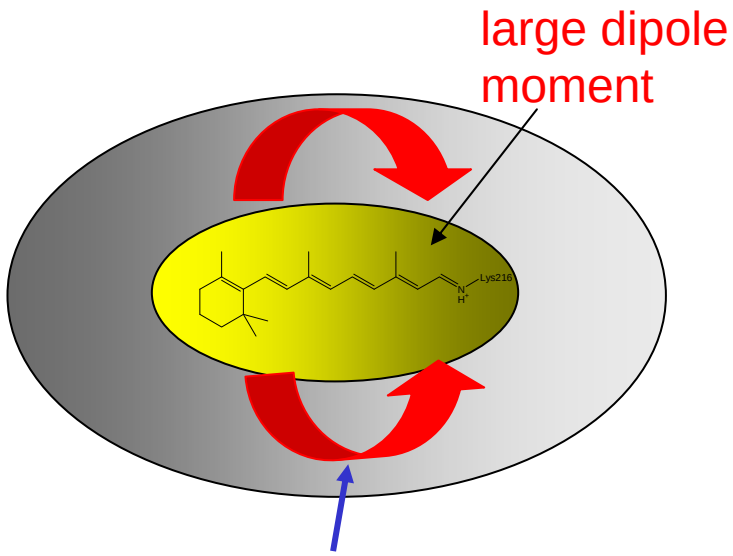
Ground state



Region I: chromophore
Region II: opsin

excitation

Franck-Condon state

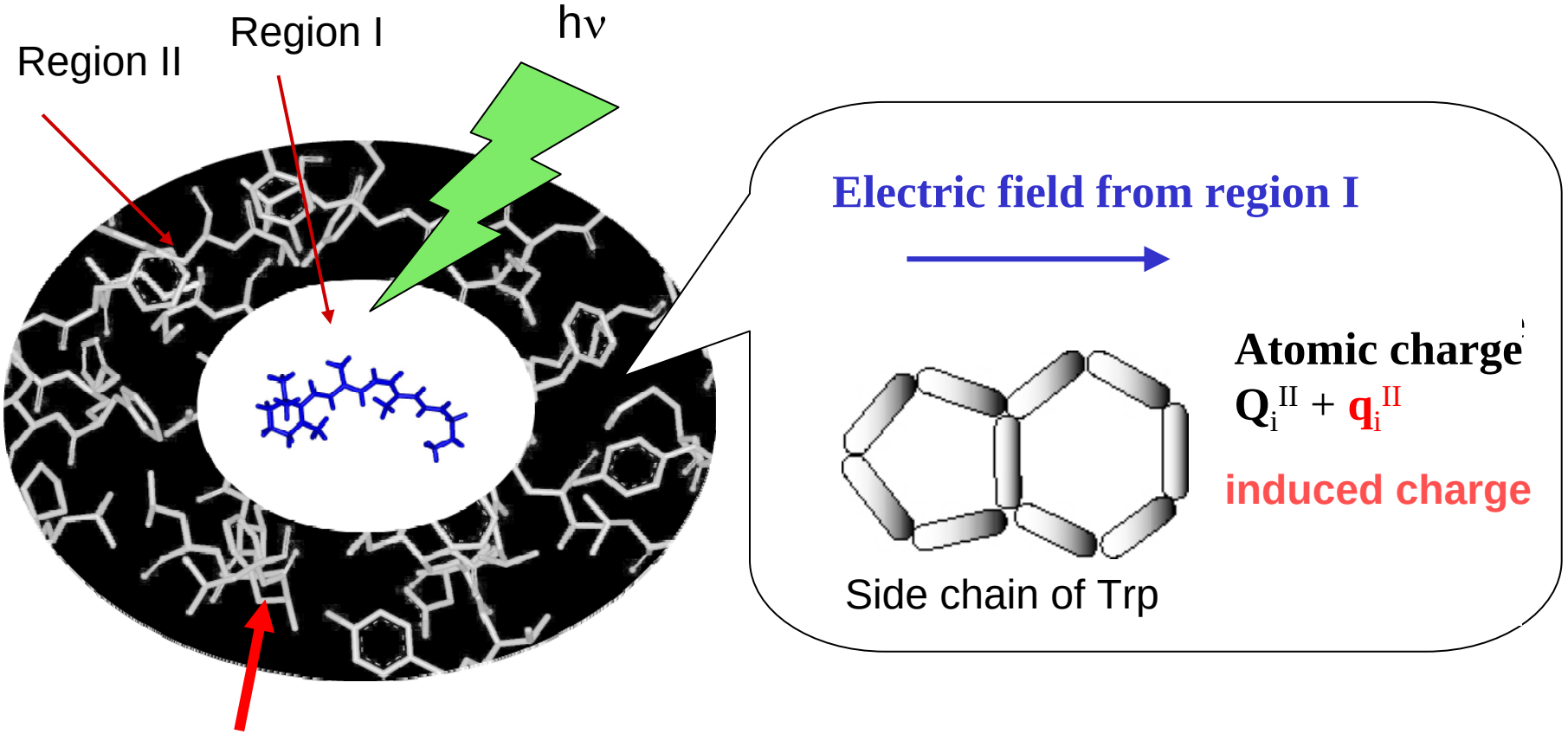


Electronic polarization of the protein environment

↓

Correlated motions of electrons between regions I and II.

How is the protein polarization effect taken into account in the calculation ?



All the covalent bonds in region II were replaced by cylindrically shaped dielectrics. The polarizability of each bond was taken from the corresponding experimental data.

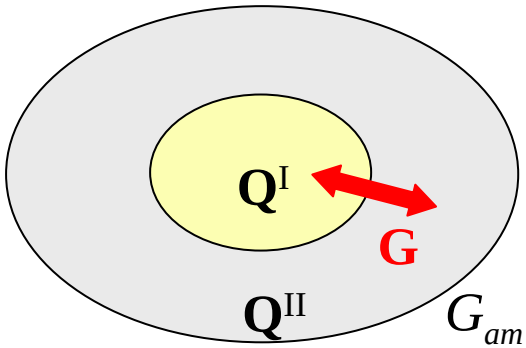
Induced charges $\mathbf{q}^{II}$ are self-consistently evaluated within region II.

Expression of the excitation energy

Ground state

$E_0 = E_0^{I} + E_0^{II} + \mathbf{Q}^{I}\mathbf{G}\mathbf{Q}^{II}$

$E_0^{II} = ½\, \mathbf{Q}^{II}\mathbf{R}\mathbf{Q}^{II}$

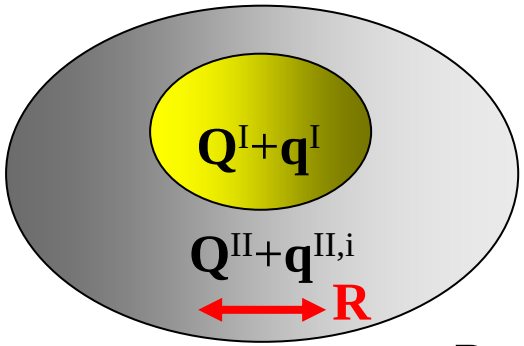


$$G_{am} = \frac{1}{|\mathbf{r}_a - \mathbf{r}_m|}$$

***i*th electronic excited state**

$E_i = E_i^{I} + E_i^{II} + (\mathbf{Q}^{I}+\mathbf{q}^{I})\mathbf{G}(\mathbf{Q}^{II} + \mathbf{q}^{II})$

$E_i^{II} = ½\, (\mathbf{Q}^{II}+\mathbf{q}^{II})\mathbf{R}(\mathbf{Q}^{II} + \mathbf{q}^{II})$



$$R_{mn} = \frac{1}{|\mathbf{r}_m - \mathbf{r}_n|}$$

Excitation energy

$\Delta E_i = E_i^{I} - E_0^{I} + (\mathbf{Q}^{I}+\mathbf{q}^{I})\mathbf{G}\mathbf{q}^{II} + \mathbf{q}^{I}\mathbf{G}\mathbf{Q}^{II}$
$+ ½\, \mathbf{q}^{II}\mathbf{R}\mathbf{q}^{II} + \mathbf{q}^{II}\mathbf{R}\mathbf{Q}^{II}$

→ **Molecular orbital calculation program**

Modification of the Fock matrix and CI matrix

$$F_{\mu\nu} = F^0_{\mu\nu} - (\mathbf{GQ}^{II})_l \quad (\varphi_\mu \in \text{atom } l)$$

SCF energy

$$E'_0 = E_0^I + \mathbf{Q}^I G \mathbf{Q}^{II}$$

CI energy (*i*th diagonal term)

$$\Delta E'_i = E_i^I - E_0^I + \mathbf{q}^{I,i} G \mathbf{Q}^{II}$$

CI energy correction

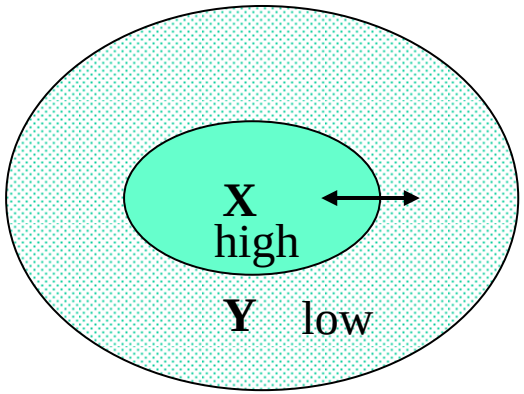
$$\Delta E_i = \Delta E'_i + (\mathbf{Q}^I + \mathbf{q}^{I,i})\mathbf{G}\mathbf{q}^{II,i} + \tfrac{1}{2}\,\mathbf{q}^{II,i}\mathbf{R}\mathbf{q}^{II,i} + \mathbf{q}^{II,i}\mathbf{R}\mathbf{Q}^{II}$$

→ INDO/S method

ONIOM

$$E(X-Y) = E_{low}(X-Y) - E_{low}(X) + E_{high}(X)$$

$$E_{low}(X-Y) - E_{low}(X)$$
$$= E_{low}(Y) + E_{\text{interlayer}}(X,Y)$$



S. Dapprich, I. Komáromi, K. S. Byun, K. Morokuma and M. J. Frisch, J. Mol. Struct (Theochem), **461-462**, 1-21 (1999).

ONIOM energy and gradient

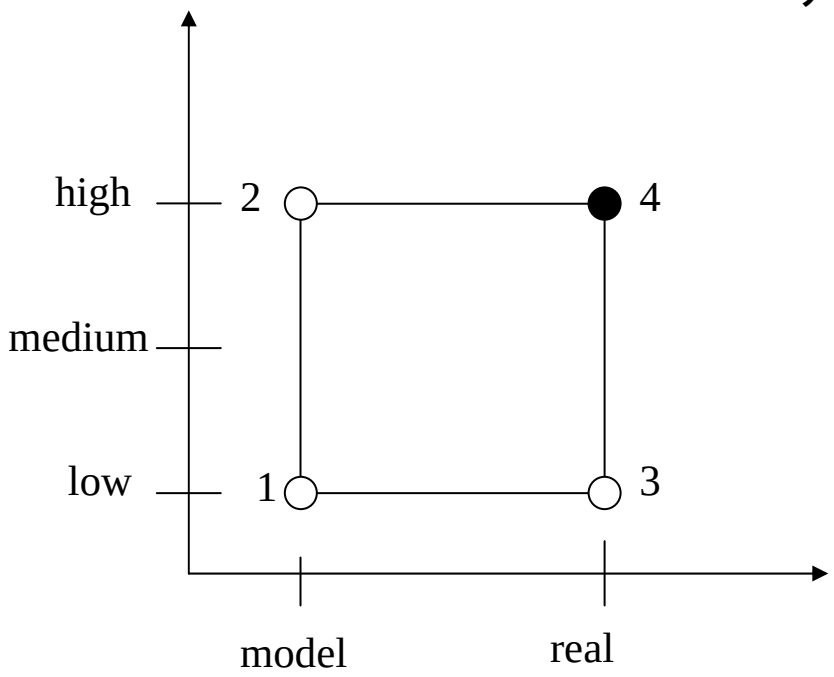
$$E_{ONIOM} = E_3 - E_1 + E_2$$

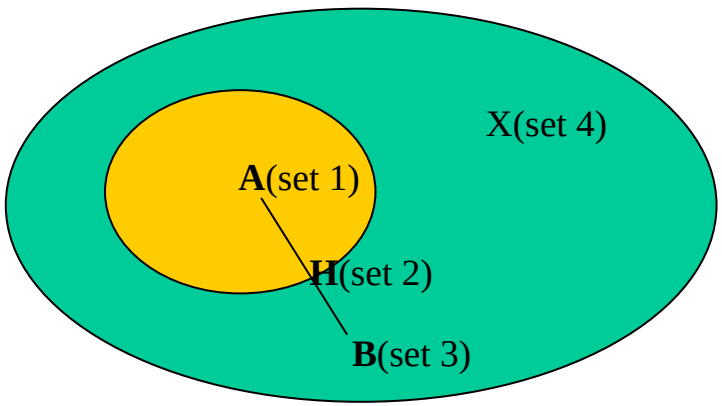
$$E_{ONIOM} = E_{ONIOM}(\mathbf{R_1}, \mathbf{R_3}, \mathbf{R_4})$$

$$\mathbf{R_2} = f(\mathbf{R_1}, \mathbf{R_3})$$

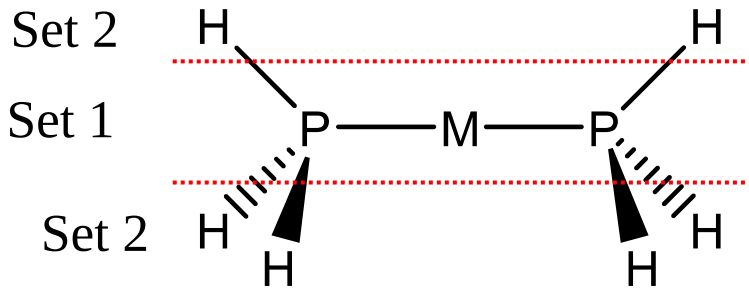
$$\nabla E_{ONIOM} = \nabla E_3 - \nabla E_1 * \mathbf{J}(\mathbf{R_2}; \mathbf{R_1}, \mathbf{R_3}) + \nabla E_2 * \mathbf{J}(\mathbf{R_2}; \mathbf{R_1}, \mathbf{R_3})$$

Jはすべてのリンク原子（set 2)にかかる力をset 1及びset 3原子に射影するためのヤコビアン

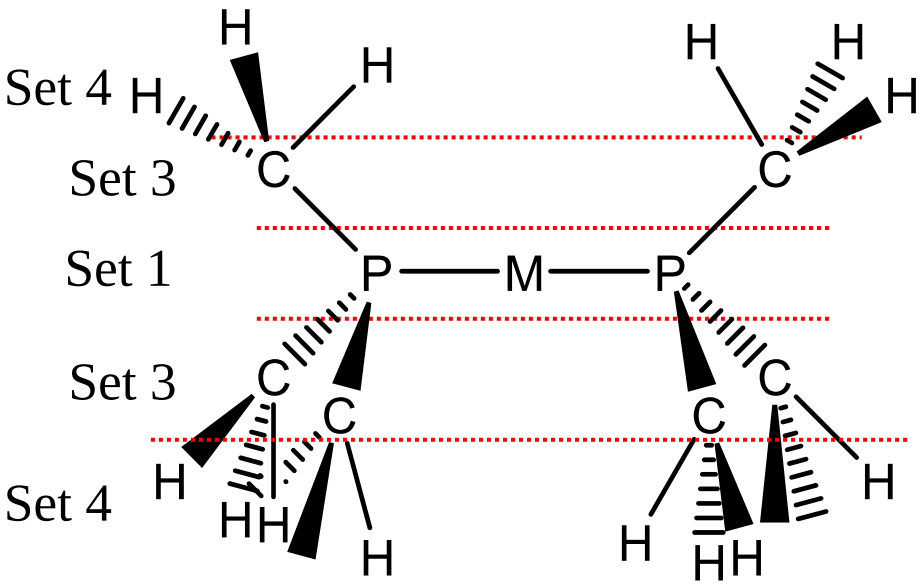




Model system



Real system



$$\mathbf{R_2} = f(\mathbf{R_1}, \mathbf{R_3})$$

$$\downarrow$$

$$\mathbf{r}_2 = \mathbf{r}_1 + g(\mathbf{r}_3 - \mathbf{r}_1)$$

$$\frac{\partial E}{\partial \vec{r}_1} = \sum_{r_2} \frac{\partial E}{\partial \vec{r}_2} \cdot \frac{\partial \vec{r}_2}{\partial \vec{r}_1}$$

$$\frac{\partial E}{\partial \vec{r}_3} = \sum_{r_2} \frac{\partial E}{\partial \vec{r}_2} \cdot \frac{\partial \vec{r}_2}{\partial \vec{r}_3}$$

$$\frac{\partial r_{2,a}}{\partial r_{3,b}} = g\delta_{a,b}$$

$$\frac{\partial r_{2,a}}{\partial r_{1,b}} = (1-g)\delta_{a,b}$$

Application of an integrated MOZYME + DFT method to pKa calculations for proteins

K. Ohno, N. Kamiya, N. Asakawa, Y. Inoue, M. Sakurai *

Chemical Physics Letters 341 (2001) 387–392

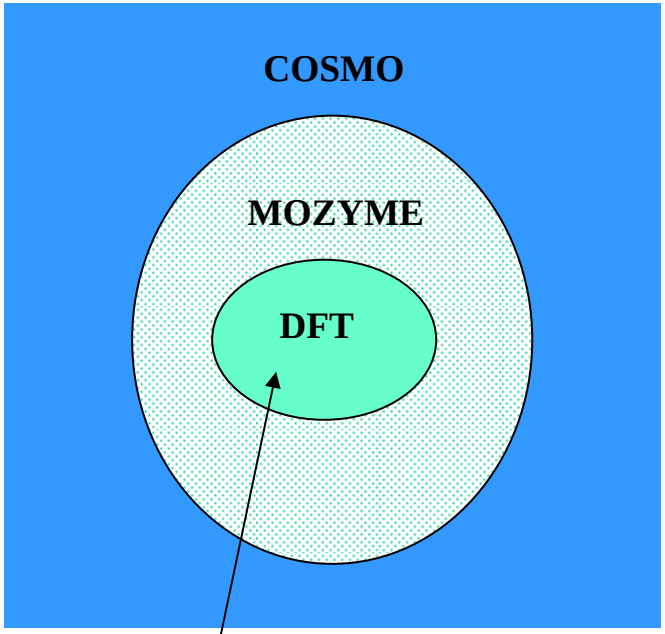
Theory

$$E^{\mathrm{ONIOM}} = E^{\mathrm{MOZYME}}_{\mathrm{whole}} + E^{\mathrm{DFT}}_{\mathrm{first}} - E^{\mathrm{MOZYME}}_{\mathrm{first}}$$

$$-RT \ln \mathrm{Ka} = \Delta G_{\mathrm{aq}}$$
$$= G_{\mathrm{aq}}(\mathrm{H}^+) + G_{\mathrm{aq}}(\mathrm{A}^-) - G_{\mathrm{aq}}(\mathrm{HA})$$

$$\mathrm{pKa} = (G_{\mathrm{aq}}(\mathrm{H}^+) + G_{\mathrm{aq}}(\mathrm{A}^-) - G_{\mathrm{aq}}(\mathrm{HA}))/2.303RT$$

$$\Delta\mathrm{pKa} = \Delta G_{\mathrm{aq}}/2.303RT \simeq \Delta E/2.303RT.$$



$AH^+ + B^- \Leftrightarrow A + BH$

$G_{aq}(H^+)$ is taken from the experimental data (259.50 Kcal/mol).

レポート課題　提出先：msakurai@bio.titech.ac.jp、締切：7/15

X. He, L. Fusti-Molnar, G. Cui and M. Merz Jr, Importance of dispersion and electron correlation in ab initio protein folding, J. Phys. Chem. B, **113**, 5290-5300 (2009)
を読んで以下の問に答えよ。

問1．この研究の背景と目的を簡単に述べよ。

問2．これまで巨大分子の量子化学計算法として様々なものが開発されているが、この研究ではFMO法を採用している。その主な理由を述べよ。

問3．PDB等から取得した蛋白質構造（原子座標）の実験データには、しばしば不都合な構造歪や立体障害が含まれているため、分子軌道計算を実行する前に構造最適化計算が必要である。この研究では、この点に関しどのように対処しているか。

問4．分子間相互作用エネルギーを評価する際は、基底関数重なりの誤差（basis set superposition error:BSSE）を補正する必要がある。BSSEの意味とこの研究で用いている補正法（counterpoise correction法）について簡単に説明せよ。

問5．分散エネルギー（dispersion energy)と電子相関の関係及びこの研究で用いているそれらの評価法について簡単に説明せよ。ただし、CCSD(T) CBS計算については言及する必要は無い。

問6．Fig. 3のデータに関する著者の解釈を簡単にまとめよ。

問7．Protein Decoy Detectionの節(p.5295-5299)の内容を簡潔にまとめよ。

問8．この研究の結論を簡潔に述べよ。