Quantum chemical calculation of macromolecules

１．Nオーダ（linear-scaling)分子軌道法

２．Fragment MO法

３．Hybrid quantum mechanics/molecular mechanics (QM/MM)法

４．ONIOM法

Conventional Hartree-Fock method

$$\Psi = \frac{1}{\sqrt{n!}} \begin{vmatrix} \varphi_1(1) & \varphi_2(1) & \cdots & \varphi_n(1) \\ \varphi_1(2) & \varphi_2(2) & \cdots & \varphi_n(n) \\ \vdots & \vdots & \ddots & \vdots \\ \varphi_1(n) & \varphi_2(n) & \cdots & \varphi_n(n) \end{vmatrix}$$

Slater determinant

$\downarrow$ Variation principle

SCF calculation

$$\hat{F}\varphi_i = \sum_{j=1}^{n} \varepsilon_{ji}\varphi_j$$

Hartree-Fock (HF) equation

$$\hat{F} = \hat{h} + \sum_{j=1}^{n} (2\hat{J}_j - \hat{K}_j)$$

$\downarrow$ Unitary transformation

$$\hat{F}\varphi_i = \varepsilon_i \varphi_i$$

Canonical HF

$\downarrow$ LCAO approximation

$$\varphi_i = \sum_{r=1}^{m} c_{ri}\chi_r$$

Hartree-Fock-Roothaan equation

$$\mathbf{FC} = \mathbf{SC\varepsilon}$$

Why is the conventional HF MO inapplicable to the calculation of large molecules?

従来SCF法の巨大分子への適用
ー問題点（半経験的MOの場合）ー

対角化および密度行列計算
↓
系のサイズに対するN^3依存性

解決法
linear-scaling MOの開発

例：局在化分子軌道 (Localized Molecular Orbital; LMO)を出発基底関数として用いる

従来のSCF法による演算時間
（1アミノ酸残基当たり1 second)

No. of residues	Time
2	8.0 seconds
5	2.1 minutes
10	16.7 minutes
20	2.2 hours
50	1.4 days
100	11.6 days
200	3.1 months
500	4.0 years
1,000	31.7 years
2,000	253.6 years

Liner-scaling MO

1. MOZYME

   J. P Stewart, Int. J. Quantum. Chem., **58**, 133-146 (1996).

2. Divide-and-conquer method

   W. Yang, Phys. Rev. Lett. **262**, 1438-1441 (1991).

   W. Yang and T-S Lee, J. Chem. Phys., **103**,
   5674-5678 (1995)

   V. Gogonea, L. M. Westerhoff and K. M. Merz, Jr.,
   J. Chem. Phys., **113**, 5604-5612 (2000).

3. Local SCF

Comparison between MOZYME and the conventional HF MO

	MOZYME	canonical HF MO
basis sets	LMO	atomic orbital
SCF	annihilation	diagonalization
long-range interaction	classical electrostatics	quantum mechanics
size dependence	N	N^3
algorithm	complicated	relatively simple
Applicability	except for radical, open-shell systems and excited states	all

What is a Localized Molecular Orbital？

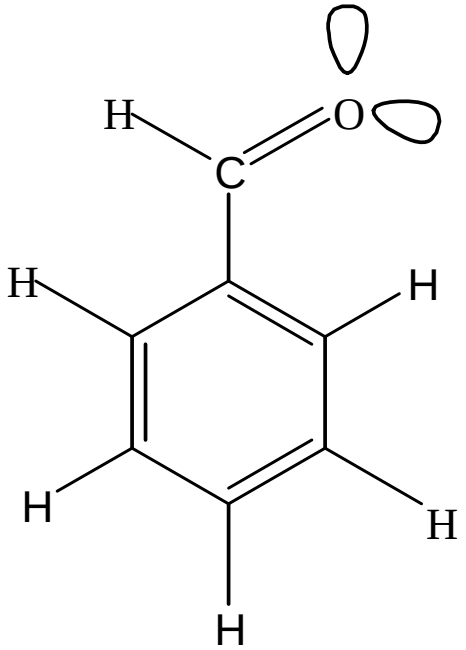
各結合に局在化した
LMO

例：benzaldehyde

σ結合：14個

π結合：４個

孤立電子対：２個



benzaldehydeのLewis構造

Why use Localized Molecular Orbitals ?

近接LMO間相互作用→QM

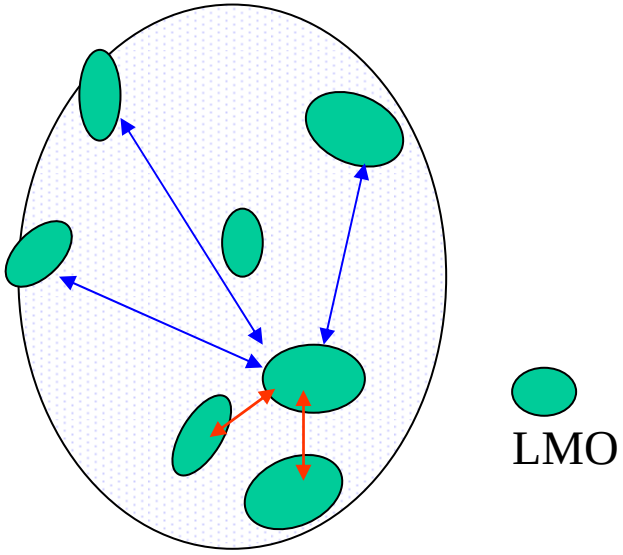
遠隔LMO間相互作用→無視

ただし、静電相互作用は古典近似

↓

計算時間・回数の減少

メモリーの節約



巨大分子の中のLMO

Distance dependence of bond order and interaction energies

(Gly)4の末端N原子と骨格原子間のbond order

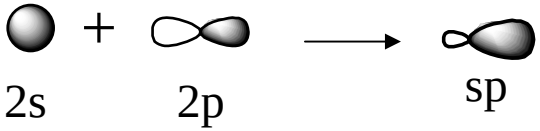
Bond to	Order	Bond to	Order
C2	1.0709	C8	0.000009
C3	0.015249	C9	0.000001
N4	0.004989	N10	0.000000
C5	0.001219	C11	0.000000
C6	0.000086	C12	0.000000
N7	0.000031		

type	Less than cutoff	Greater than cutoff	Cutoff name	Default
Two electron	All multipoles	Dipole + monopole	CUTOF2	12 Å
Two electron	Dipole + monopole	Monopole	CUTOF1	30 Å
One electron	Overlap calculated	Overlap not calcd.	CUTOFS	7 Å

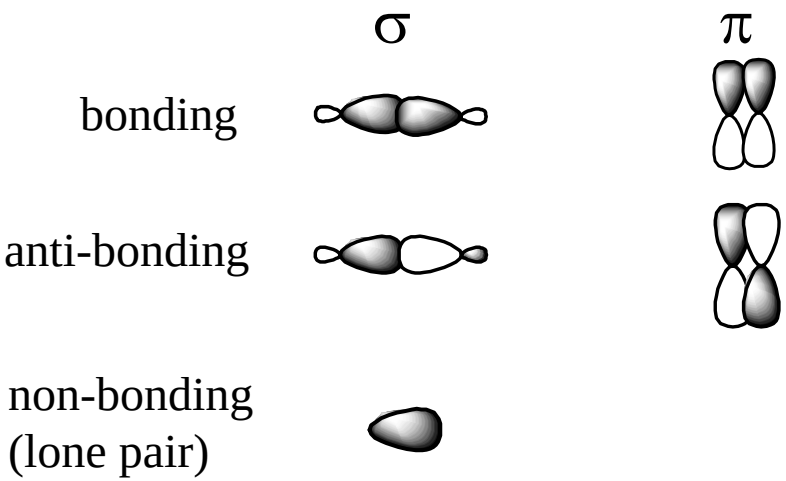
Construction of starting LMOs

Complicated algorithm

1. From atomic orbitals to hybrid orbitals



2. From hybrid orbitals to starting diatomic LMOs and lone pairs



The order of identification

i) σ diatomic orbitals

ii) lone pairs

iii) non-cyclic π bonds

iv) cyclic π bond

v) identification of ions

The orthonormal condition is satisfied between the occupied and unoccupied orbitals.

Necessary and sufficient condition for SCF

$$\hat{F}\,\varphi_i = \sum_{j=1}^{n} \varepsilon_{ji}\varphi_j \qquad \begin{pmatrix} F_{11} & F_{12} & \cdots & F_{1n} \\ F_{21} & F_{22} & \cdots & F_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ F_{n1} & F_{n2} & \cdots & F_{nn} \end{pmatrix}$$

Fを作用させた結果はもとの軌道関数の一次結合

↓

Hartree-Fock多様体の外に出ない

↓

$$\langle i | \hat{F} | m \rangle = 0 \qquad (m = n+1, n+2, \cdots)$$

LCAO diagonalization

LMO ?

Annihilation ?

$$\mathbf{FC} = \mathbf{SC\varepsilon} \qquad \begin{pmatrix} F_{11} & & & & 0 \\ & \ddots & & & \\ & & F_{nn} & & \\ & & & \ddots & \\ 0 & & & & F_{mm} \end{pmatrix}$$

unitary transformation

$$\begin{pmatrix} F_{11} & \cdots & F_{1n} & & & \\ \vdots & \ddots & \vdots & & 0 & \\ F_{n1} & \cdots & F_{nn} & & & \\ & & & F_{n+1,n+1} & \cdots & F_{n+1,m} \\ 0 & & & \vdots & \ddots & \vdots \\ & & & F_{m,n+1} & \cdots & F_{mm} \end{pmatrix}$$

Canonical orbitals

Annihilation of occupied-virtual interactions

SCF condition $\sum_{i=1}^{occ}\sum_{j=1}^{vir}\left|\left\langle \varphi_i \middle| \hat{F} \middle| \varphi_j \right\rangle\right| = 0$

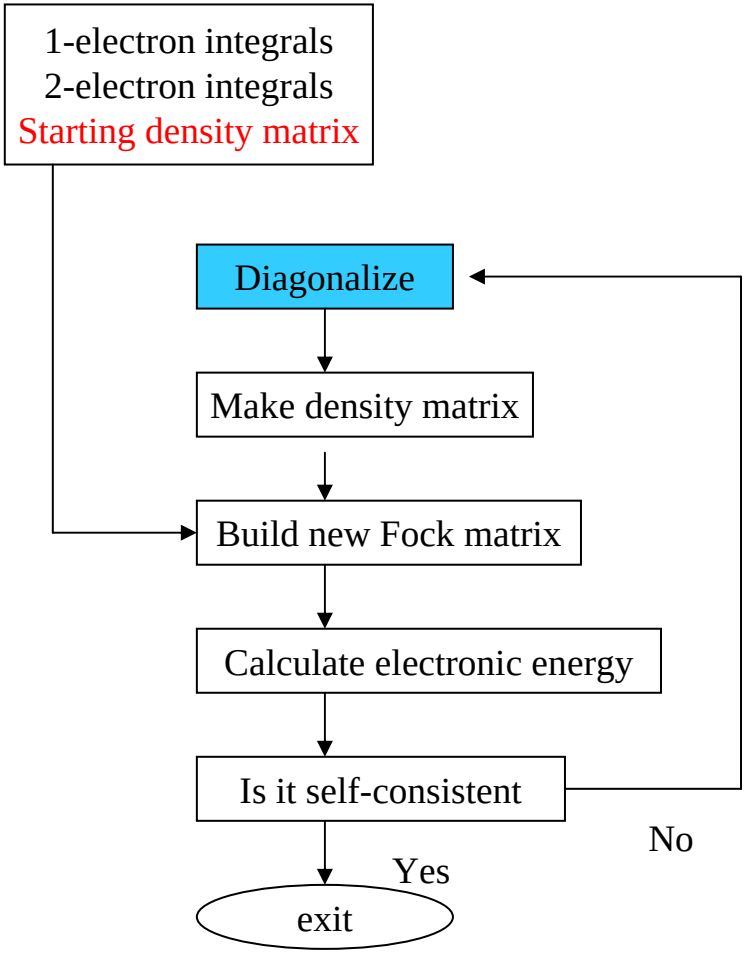
Annihilation operation for the initial Occupied and virtual LMOs

$$\begin{cases} \varphi_i^1 = \alpha\varphi_i^0 + \beta\varphi_j^0 \\ \varphi_j^1 = -\beta\varphi_i^0 + \alpha\varphi_j^0 \end{cases}$$

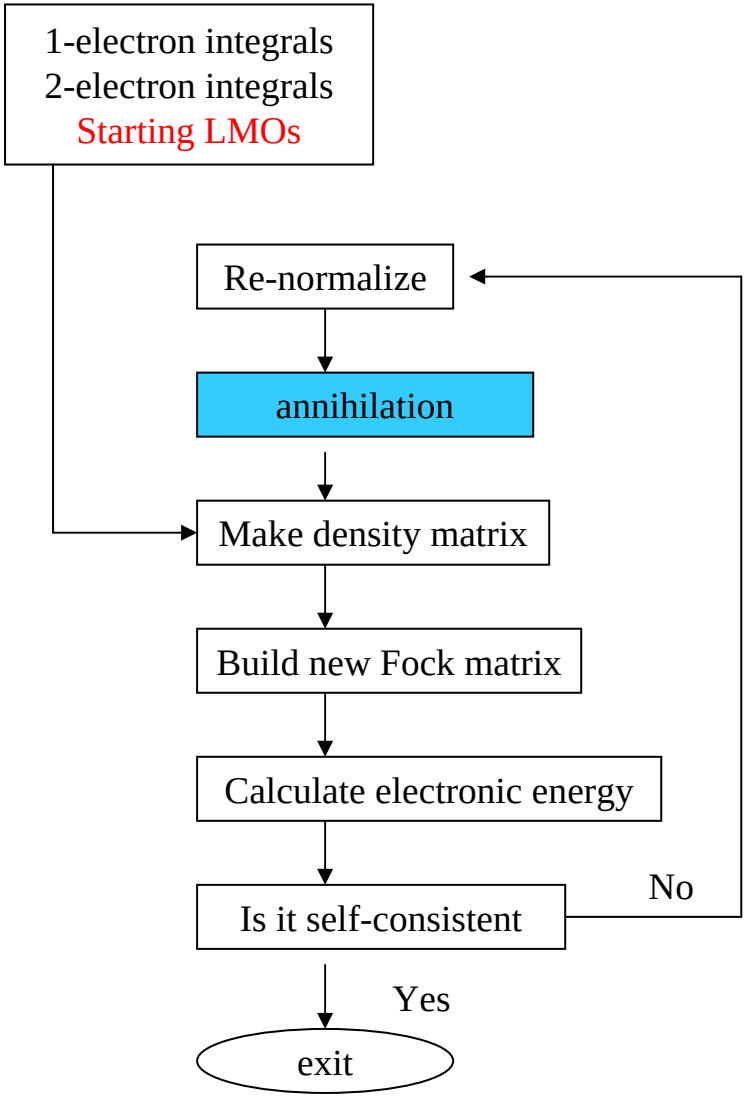
$$\alpha = \sqrt{\frac{1}{2}(1+D)/\sqrt{4F_{ij}^2 + D^2}} \qquad \beta = \phi\sqrt{1-\alpha^2}$$

$$D = F_{ij} - F_{ji} \qquad \phi = 1(F_{ij} < 0) \qquad \phi = -1(F_{ij} \geq 0)$$

Comparison of SCF calculation between the conventional canonical MO and MOZYME methods



Conventional SCF



MOZYME

Times for one SCF calculation

residues	Atoms	MOPAC (s)	MOZYME(s)	ratio
1	10	1.3	0.6	0.5
2	29	3.5	8.2	0.4
4	62	27.8	24.3	1.1
8	114	189.6	118.8	1.6
16	255	2662.8	541.7	4.9
32	481	(17871)	1244.7	(14)
64	992	(156766)	5489.0	(29)
128	1995	(1275107)	1752.2	(73)
256	3924	(9702977)	63321.2	(153)
265	4046	(10636424)	65266.0	(163)

MOZYMEの利用
タンパク質の立体構造構築原理と機能部位予測

An insight into the general relationship between the three dimensional structures of enzymes and their electronic wave functions: Implication for the prediction of functional sites of enzyme

K. Fukushima, M. Wada, M. Sakurai, Proteins, **71**, 1940-1954 (2008)

Fragment Molecular Orbital (FMO) Method

K. Kitaura et al., Chem. Phys. Lett., **313**, 701-706 (1999).

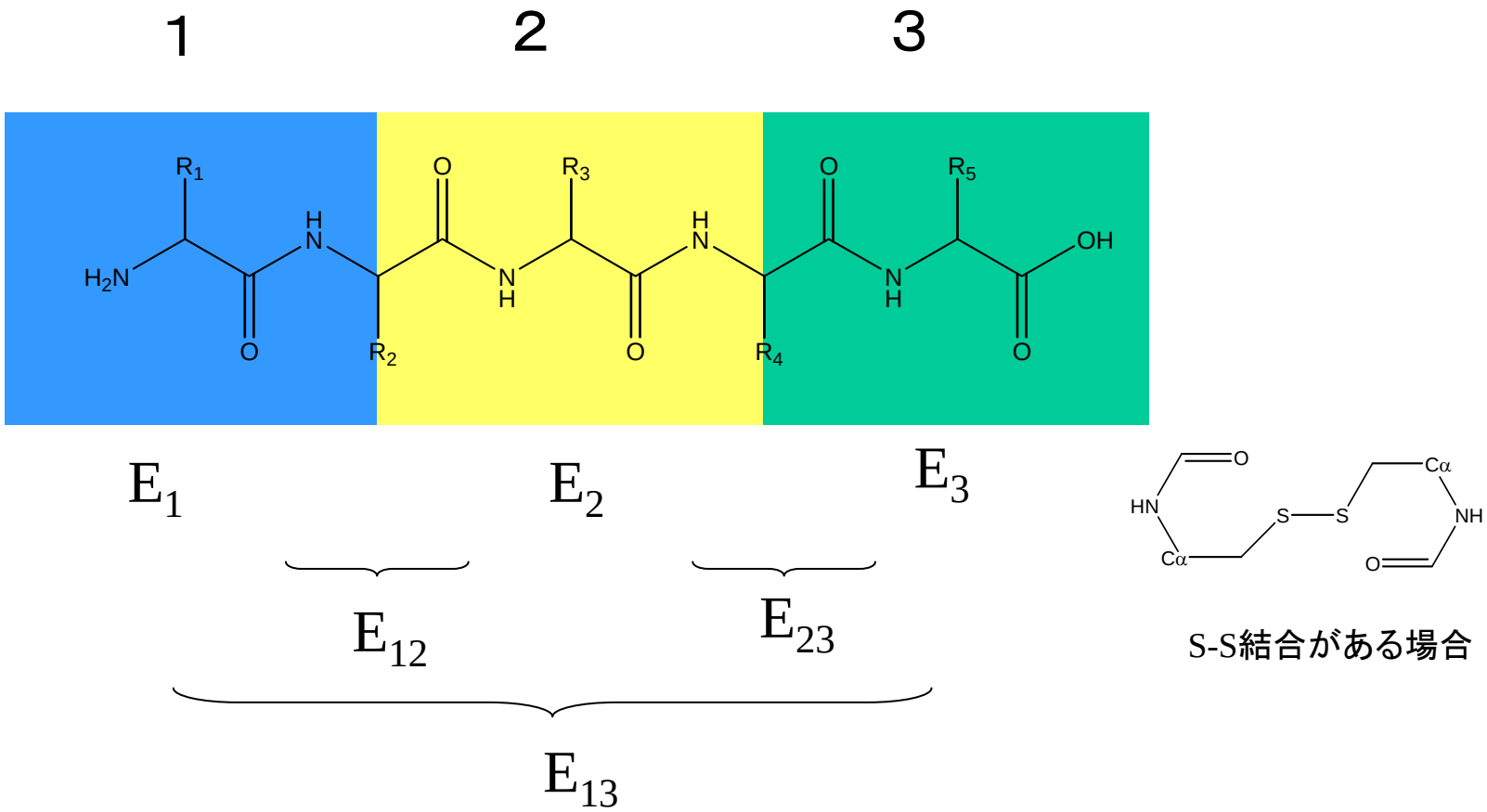
FMO法は、全系をN個のフラグメントに分割し、フラグメント（モノマー）の全エネルギーE_I、フラグメントペア（ダイマー）の全エネルギーE_{IJ}、フラグメントのトリマーの全エネルギーE_{IJK}などを用いて、次式により全系の全エネルギーを近似的に計算する方法である。

$$E = \sum_{I}^{N} E_I + \sum_{I>J}^{N} (E_{IJ} - E_I - E_J) +$$
$$\sum_{I>J>K}^{N} \{ (E_{IJK} - E_I - E_J - E_K) - (E_{IJ} - E_I - E_J) - (E_{JK} - E_J - E_K)$$
$$- (E_{KI} - E_K - E_I) \} +$$

通常は、第2項までで打ち切った式を用いる。

$$E = \sum_{I}^{N} E_I + \sum_{I>J}^{N} (E_{IJ} - E_I - E_J) = \sum_{I>J}^{N} E_{IJ} - (N-2) \sum_{I}^{N} E_I$$

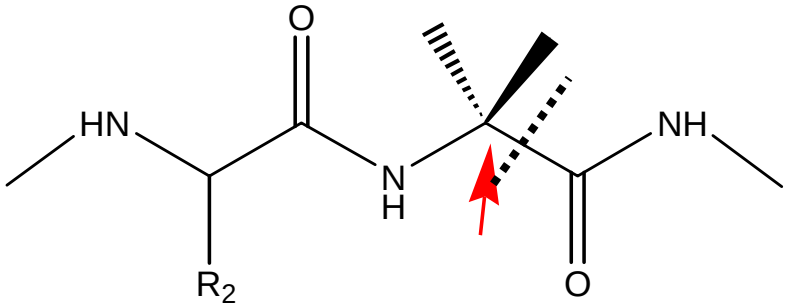
アミノ酸のモノマー単位で分割した場合



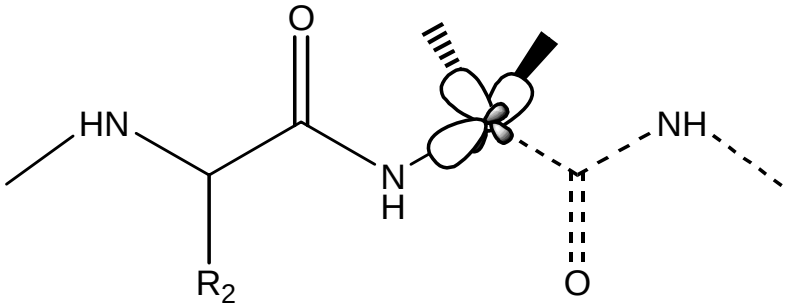
S-S結合がある場合

多体の相互作用を取り込むため、各モノマー（各ダイマー）は、それ以外の残基のつくる静電ポテンシャルの中におかれているという設定の下でエネルギーを計算する。

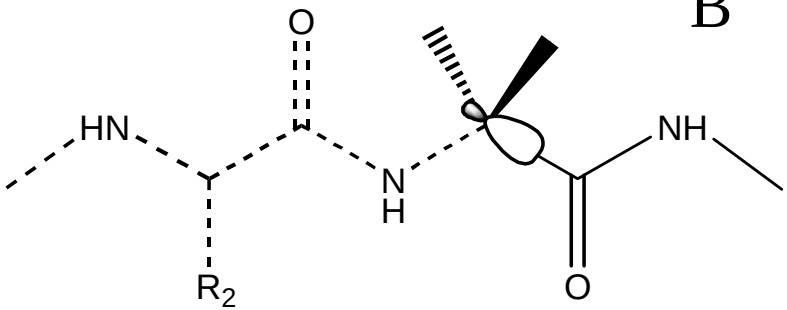
切断する結合境界の処理



A

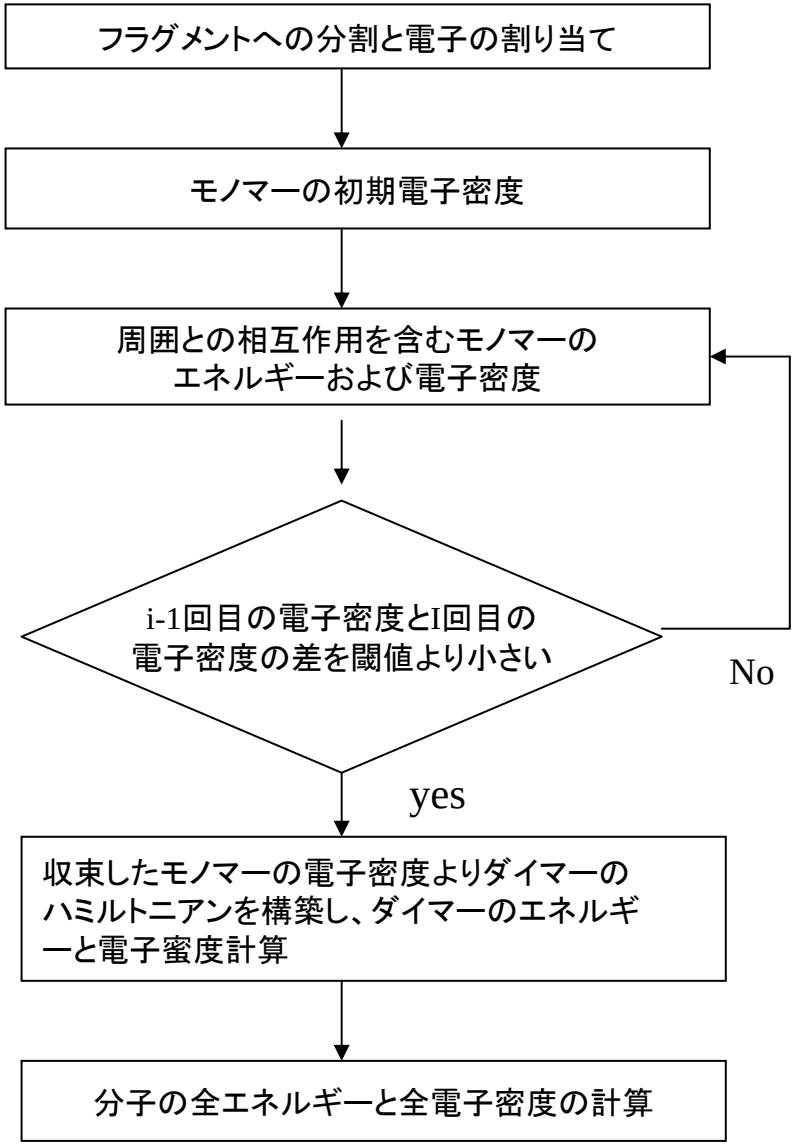


B

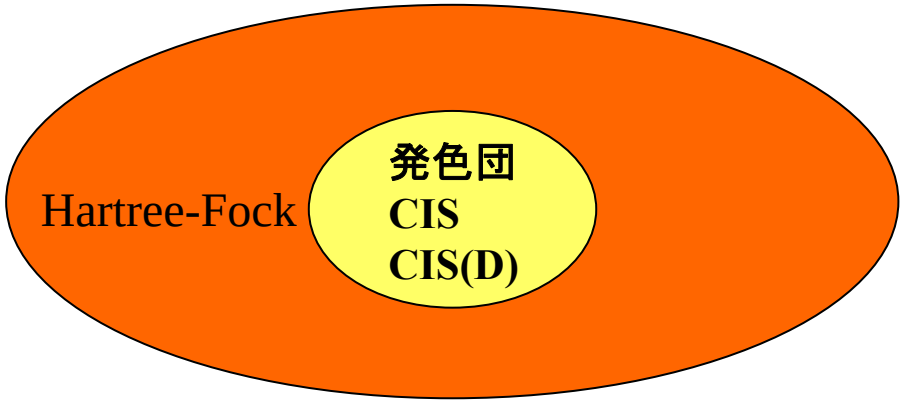


Detached atom（↑）
炭素原子のsp^3混成軌道を2組に分ける。Bには一つを割振り、核電荷を+1とする。Aには残りの混成軌道を割振り、核電荷を+5とする。

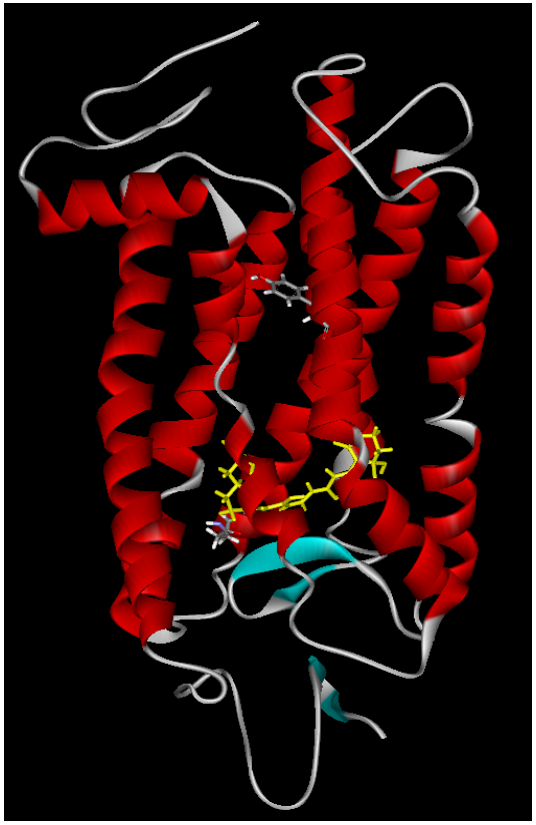
Flow chart of the fragment MO



多層FMO法による蛋白質の励起エネルギーの計算



1.全体（発色団＋周囲）をHFレベルでFMO計算する
２．得られた発色団のMOを使って、CIS計算を実行する
→周囲の効果を考慮した励起エネルギー



ロドプシン
黄色：レチナール

多層FMOの研究例

Fragment molecular orbital calculations on red fluorescent protein (DsRed)

Yuji Mochizuki, Tatsuya Nakano, Shinji Amari, Takeshi Ishikawa, Kiyoshi Tanaka, Minoru Sakurai, Shigenori Tanaka

Chemical Physics Letters, **433**, 360–367 (2007)

Fragment Molecular Orbital Calculations on Red Fluorescent Proteins (DsRed and mFruits)

Naoki Taguchi, Yuji Mochizuki, Tatsuya Nakano, Shinji Amari, Kaori Fukuzawa, Takeshi Ishikawa, Minoru Sakurai, and Shigenori Tanaka

J. Phys. Chem. B, **113**, 1153-1161(2009)