計算生命科学の基礎Ⅲ　平成28年11月15日　＠神戸大学計算科学教育センター

フラグメント分子軌道法の基礎と応用

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内容:

1. フラグメント分子軌道法の基礎
2. FMO/MM融合法によるタンパク質複合体の構造最適化と FMO/PCM法による結合自由エネルギー計算
3. FMOプリ・ポスト処理支援GUIプログラムの紹介
4. まとめ

様々な大規模系の量子化学計算法が提案されている

- Divide-and-conquer(**DC**), W. Yang, PRL 66, 1438 (1991)
- Elongation method(**EL**), A.Imamura et al., JCP 95, 5419(1991)
- Incremental correlation method(**IC**), H.Stoll, PRB,46, 6700(1992)
- The fragment molecular orbital (**FMO**) method, Kitaura et.al., CPL(1999)
- Adjustable density matrix assembler (**ADMA**), T.E.Exner, P.G.Mezey, JPCA,106,11791,(2002)
- Molecular fractionation with conjugate cap approach (**MFCC**), D.W.Zhang, J.Z.H. Zhang, JCP, 119, 3599 (2003).
- Molecular tailoring (**MTA**), K.Babu, S.R.Gadre, JCC,24, 484 (2003)
- Systematic fragmentation approach(**SFA**), V.J.Deev, M.A.Collins, JCP,122,154102 (2005)
- Kernel energy method (**KEM**), Huang et al., IJQC, 103, 808(2005)
- Electrostatically embedded many-body expansion (**EE-MB**), E.E.Dahlke, D.G.Truhlar, JCTC, 3, 46 (2007).
- Generalized X-pol(**GXP**), L. L. Cembran et al., JCTC, 6, 2469(2009)

For fragment-based approaches, see M.S.Gordon et al., Chem. Rev. 112,632(2012)

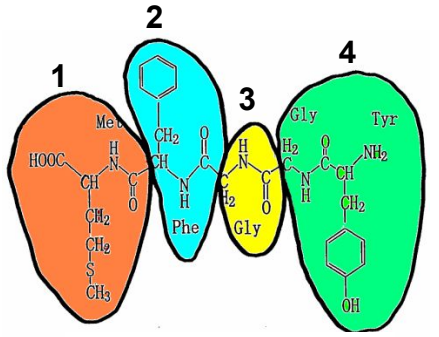
Outline of the Fragment MO (FMO) Method

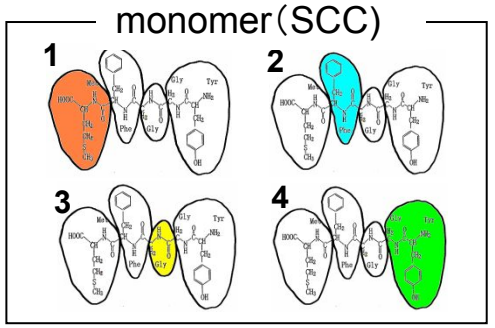
- A molecule is divided into N fragments and *ab initio* MO calculations on the fragments (monomers), fragment pairs (dimers) and optionally triples (trimers) are performed under electrostatic potential from other monomers.
- The total energy of the whole molecule (E) is calculated using the energies of the monomer (E_I), dimer (E_{IJ}) and trimer (E_{IJK});

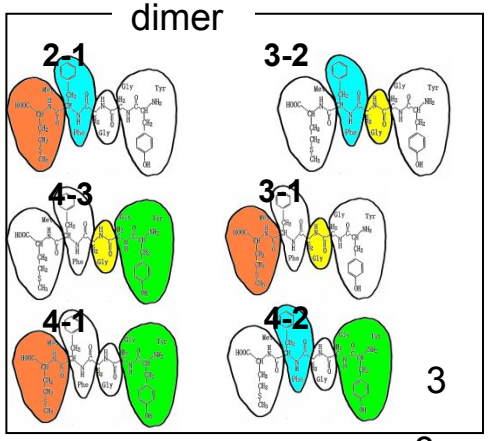
FMO2: $$E^{\mathrm{FMO2}} = \sum_I E_I + \sum_{I>J} \Delta E_{IJ}$$

FMO3: $$E^{\mathrm{FMO3}} = E^{\mathrm{FMO2}} + \sum_{I>J>K} \left(E_{IJK} - \Delta E_{IJ} - \Delta E_{JK} - \Delta E_{KI} \right)$$

$$where, \quad \Delta E_{IJ} = \left(E_{IJ} - E_I - E_J \right)$$







Computational procedure of FMO

Fock equation for fragment (monomer) and fragment pair (dimer) (x=I for monomer and x=IJ for dimer)

$$\widetilde{\mathbf{F}}^x \mathbf{C}^x = \mathbf{S}^x \mathbf{C}^x \widetilde{\boldsymbol{\varepsilon}}^x$$

$$\widetilde{\mathbf{F}}^x = \widetilde{\mathbf{H}}^x + \mathbf{G}^x ,$$

$$\widetilde{\mathbf{H}}^x_{\mu\nu} = H^x_{\mu\nu} + V^x_{\mu\nu}$$

Total energy of monomer and dimer

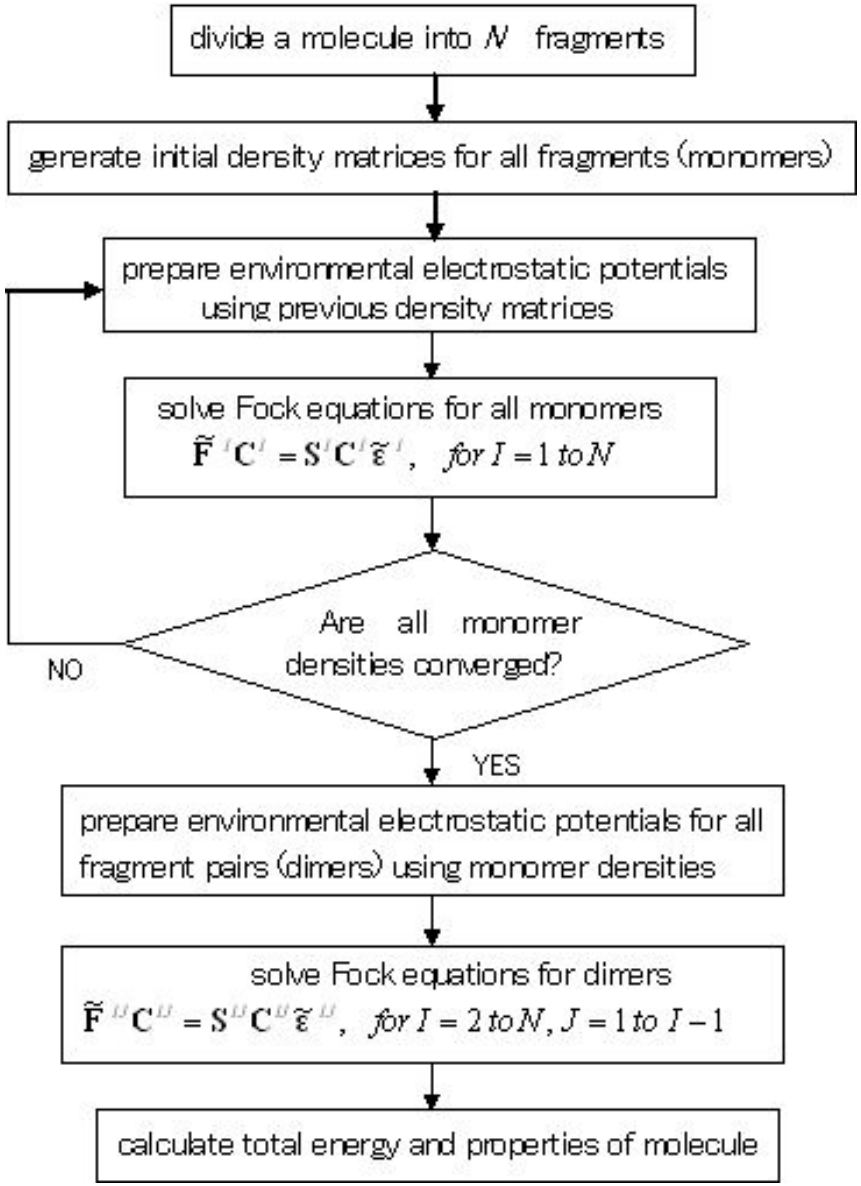
$$E_x = \frac{1}{2} Tr\left\{\mathbf{D}^x\left(\widetilde{\mathbf{H}}^x + \widetilde{\mathbf{F}}^x\right)\right\}$$

HF total energy of whole system

$$E = \sum_I E_I + \sum_{I>J}\left(E_{IJ} - E_I - E_J\right)$$

Correlation energy correction

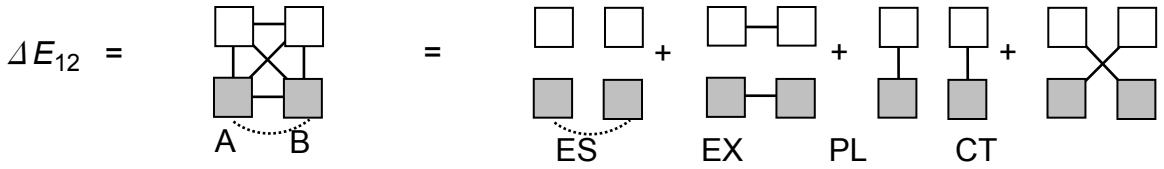
$$E^{\mathrm{corr}} = \sum_I E_I^{\mathrm{corr}} + \sum_{I>J}\left(E_{IJ}^{\mathrm{corr}} - E_I^{\mathrm{corr}} - E_J^{\mathrm{corr}}\right)$$



Basis of FMO

- **FMO is a many-body theory of molecular interactions,**

derived from the energy decomposition analysis(EDA)
(IJQC,10, 325 (1976)) of many-body molecular interactions



ES : electrostatic $E_{\mathrm{ES}} = \left\langle \Phi_1^0 \cdot \Phi_2^0 \middle| H_{12} \middle| \Phi_1^0 \cdot \Phi_2^0 \right\rangle - E_1^0 - E_2^0$

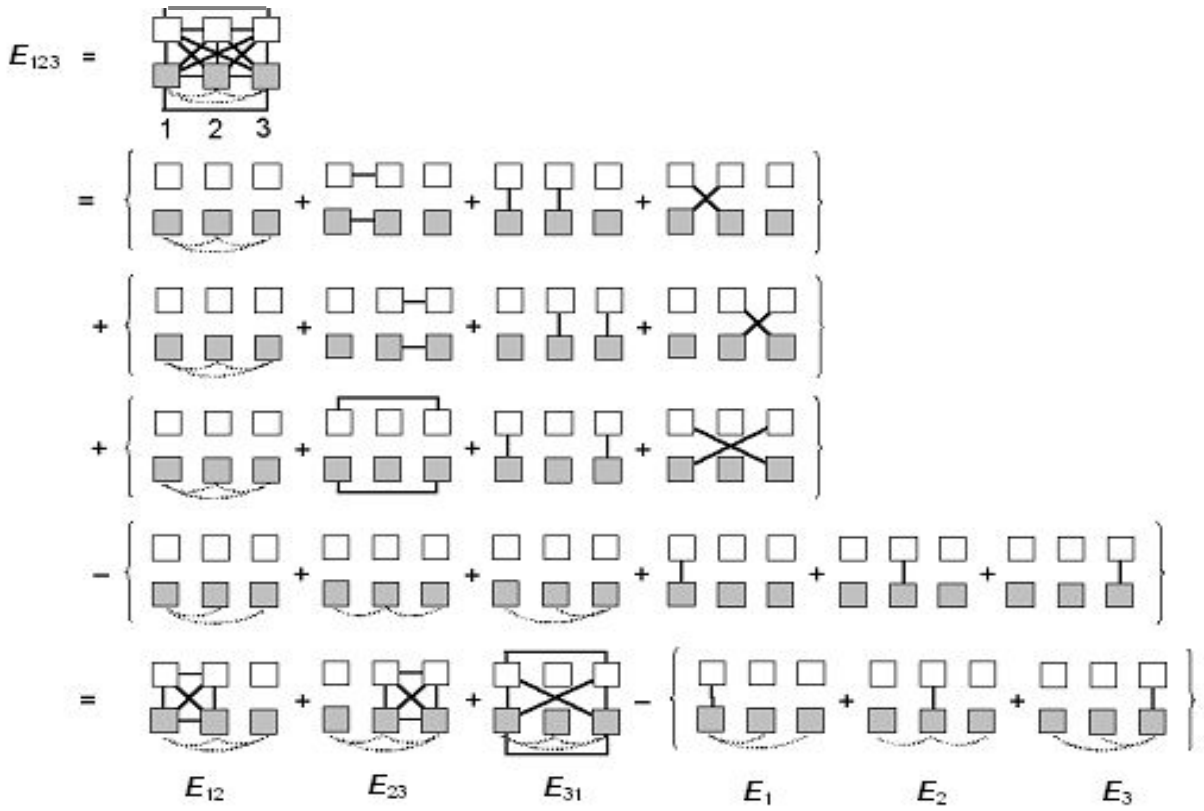
EX : exchange repulsion $E_{\mathrm{EX}} = \left\langle \mathrm{A}\left(\Phi_1^0 \cdot \Phi_2^0\right) \middle| H_{12} \middle| \mathrm{A}\left(\Phi_1^0 \cdot \Phi_2^0\right) \right\rangle - \left\langle \Phi_1^0 \cdot \Phi_2^0 \middle| H_{12} \middle| \Phi_1^0 \cdot \Phi_2^0 \right\rangle$

PL : polarization $E_{\mathrm{PL}} = \left\langle \Phi_1 \cdot \Phi_2 \middle| H_{12} \middle| \Phi_1 \cdot \Phi_2 \right\rangle - \left\langle \Phi_1^0 \cdot \Phi_2^0 \middle| H_{12} \middle| \Phi_1^0 \cdot \Phi_2^0 \right\rangle$

CT : charge transfer $E_{\mathrm{CT}} = \left\langle \mathrm{A}\left(\Phi_1^{\mathrm{CT}} \cdot \Phi_2^{\mathrm{CT}}\right) \middle| H_{12} \middle| \mathrm{A}\left(\Phi_1^{\mathrm{CT}} \cdot \Phi_2^{\mathrm{CT}}\right) \right\rangle - \left\langle \Phi_1^0 \cdot \Phi_2^0 \middle| H_{12} \middle| \Phi_1^0 \cdot \Phi_2^0 \right\rangle$

Total interaction energy: $\Delta E_{12}^{\mathrm{HF}} = E_{12}^{\mathrm{HF}} - E_1^0 - E_2^0 = E_{\mathrm{ES}} + E_{\mathrm{EX}} + E_{\mathrm{PL}} + E_{\mathrm{CT}} + E_{\mathrm{MIX}}$

Taking many-body interactions into energies of monomer and dimer



$$E_{123} = E_{12} + E_{23} + E_{31} - E_1 - E_2 - E_{31}$$
$$= E_1 + E_2 + E_3 + (E_{12} - E_1 - E_2) + (E_{23} - E_2 - E_3) + (E_{31} - E_3 - E_1)$$

Total energy is written as; $E = \sum_I E_I + \sum_{I>J} (E_{IJ} - E_I - E_J)$

Many-body interaction energy in FMO

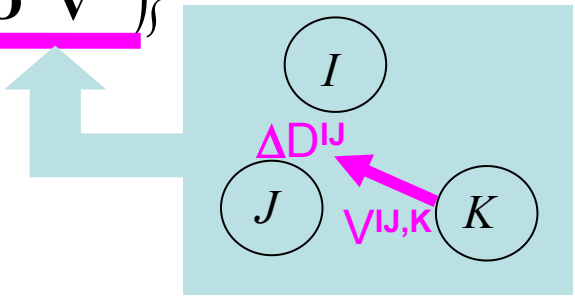
Total energy: $$E = \sum_{I}^{N} E_I + \sum_{I>J}^{N} \left(E_{IJ} - E_I - E_J \right)$$

Intenal energy: $$E'_x = E_x - Tr\left(\mathbf{D}^x \mathbf{V}^x \right)$$

Total energy in terms of internal energies

$$E = \sum_{I}^{N} E'_I + \sum_{I=1}^{N} \sum_{J>I}^{N} \left(E'_{IJ} - E'_I - E'_J \right) + \sum_{I=1}^{N} \sum_{J>I}^{N} Tr\left(\Delta \mathbf{D}^{IJ} \mathbf{V}^{IJ} \right)$$

$$= \sum_{I}^{N} E'_I + \sum_{I=1}^{N} \sum_{J>I}^{N} \left\{ \Delta E'_{IJ} + Tr\left(\Delta \mathbf{D}^{IJ} \mathbf{V}^{IJ} \right) \right\}$$



where,

$$\Delta \mathbf{D}^{IJ}_{\mu\nu} = \mathbf{D}^{IJ}_{\mu\nu} - \mathbf{D}^{I}_{\mu\nu} \qquad for\ \mu \in I, \nu \in J$$

$$\Delta \mathbf{D}^{IJ}_{\mu\nu} = \mathbf{D}^{IJ}_{\mu\nu} - \mathbf{D}^{J}_{\mu\nu} \qquad for\ \mu \in I, \nu \in J$$

$$\Delta \mathbf{D}^{IJ}_{\mu\nu} = \mathbf{D}^{IJ}_{\mu\nu} \qquad for\ \mu \in I, \nu \in J\ or\ \mu \in J, \nu \in I$$

$$\mathbf{V}^{IJ}_{\mu\nu} = \sum_{k(\neq i,j)}^{N} \left\{ \sum_{\rho,\sigma \in K} \mathbf{D}^{K}_{\rho\sigma} (\mu\nu \mid \rho\sigma) - \sum_{a \in K} \left\langle \mu \left| \frac{Z_a}{\left| \mathbf{r} - \mathbf{R}_a \right|} \right| \nu \right\rangle \right\} = \sum_{K(\neq I,J)}^{N} \mathbf{V}^{IJ,K}_{\mu\nu}, \qquad for\ \mu,\nu \in IJ$$

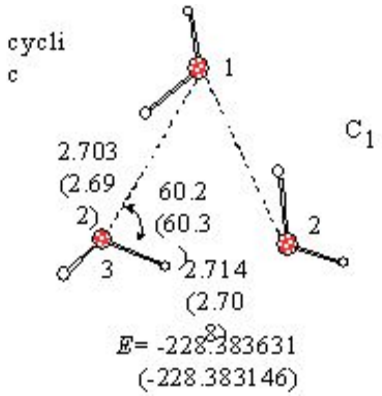
Pair Interaction Energy (PIE): $$\Delta E_{IJ} = \Delta E'_{IJ} + Tr\left(\Delta \mathbf{D}^{IJ} \mathbf{V}^{IJ} \right)$$

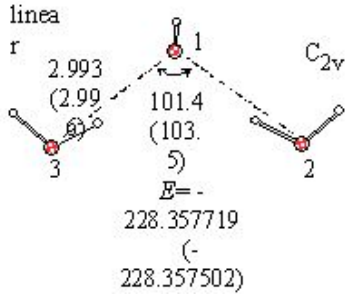
FMO-MP2 calculations of water clusters

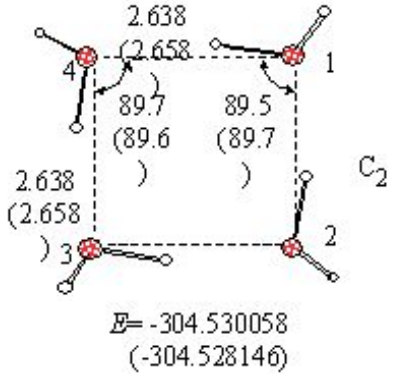
Table 1 Intermolecular interaction energies of water clusters[a]

	HF		corr.		HF+corr.	
	FMO	*ab initio*	FMO	*ab initio*	FMO	*ab initio*
$(H_2O)_3$ cyclic						
ΔE	-25.91	-25.93	-2.55	-2.32	-28.46	-28.25
$\Delta E^{(2)}$	-21.84	-21.86	-2.07	-2.05	-23.91	-23.91
$\Delta E^{(3)}$	-4.06	-4.07	-0.48	-0.27	-4.54	-4.34
$(H_2O)_3$ linear						
ΔE	-10.33	-10.18	-1.14	-1.16	-11.47	-11.34
$\Delta E^{(2)}$	-11.06	-11.03	-1.33	-1.36	-12.40	-12.39
$\Delta E^{(3)}$	0.73	0.85	0.20	0.20	0.93	1.05
$(H_2O)_4$						
ΔE	-47.45	-46.63	-3.15	-2.94	-50.60	-49.57
$\Delta E^{(2)}$	-34.52	-35.26	-1.76	-1.70	-36.28	-36.96
$\Delta E^{(3)}$	-12.13	-10.56	-1.27	-0.92	-13.40	-11.48
$\Delta E^{(4)}$	-0.80	-0.80	-0.13	-0.28	-0.93	-1.08

[a] Energies are given in kcal/mol.







Energy of isolated molecule E_I^0 , 2-body $e_{IJ}^0 = E_{IJ}^0 - E_I^0 - E_J^0$, and 3-body $e_{IJK}^0 = \left(E_{IJK}^0 - E_I^0 - E_J^0 - E_K^0\right) - e_{IJ}^0 - e_{JK}^0 - e_{KI}^0$ interaction energies in the series expansion

$$E_{12\cdots N} = \sum_I E_I^0 + \sum_{I>J} e_{IJ}^0 + \sum_{I>J>K} e_{IJK}^0 + \ldots + e_{12\cdots N}^0$$

FMO for covalent bonded system(RHF level)

Fock equation for fragment (monomer) and fragment pair (dimer)
(x=*I* for monomer and x=*IJ* for dimer)

$$\tilde{\mathbf{F}}^x \mathbf{C}^x = \mathbf{S}^x \mathbf{C}^x \tilde{\boldsymbol{\varepsilon}}^x$$

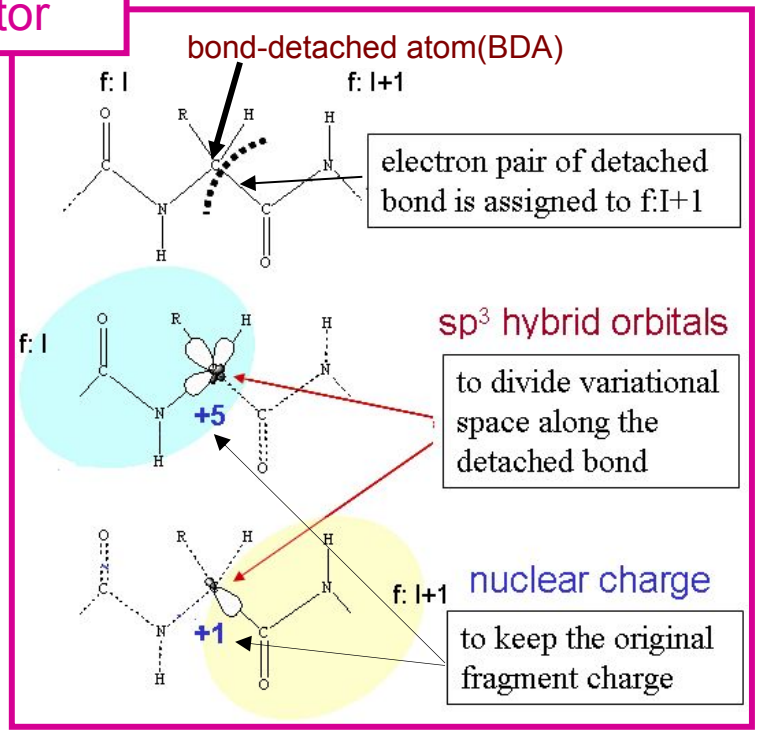
$$\tilde{\mathbf{F}}^x = \tilde{\mathbf{H}}^x + \mathbf{G}^x ,$$

$$\tilde{\mathbf{H}}^x_{\mu\nu} = H^x_{\mu\nu} + V^x_{\mu\nu} + \sum_i B\left\langle \mu \middle| \varphi_i^h \right\rangle \left\langle \varphi_i^h \middle| \nu \right\rangle ,$$

Hybrid orbital projector

Electrostatic potential

$$V^x_{\mu\nu} = \sum_{K \neq x} \left\{ \sum_{A \in K} \left\langle \mu \middle| -\frac{Z_A}{|\mathbf{r} - R_A|} \middle| \nu \right\rangle + \sum_{\rho\sigma \in K} D^K_{\lambda\sigma} (\mu\nu|\rho\sigma) \right\}$$



Total energy of monomer/dimer

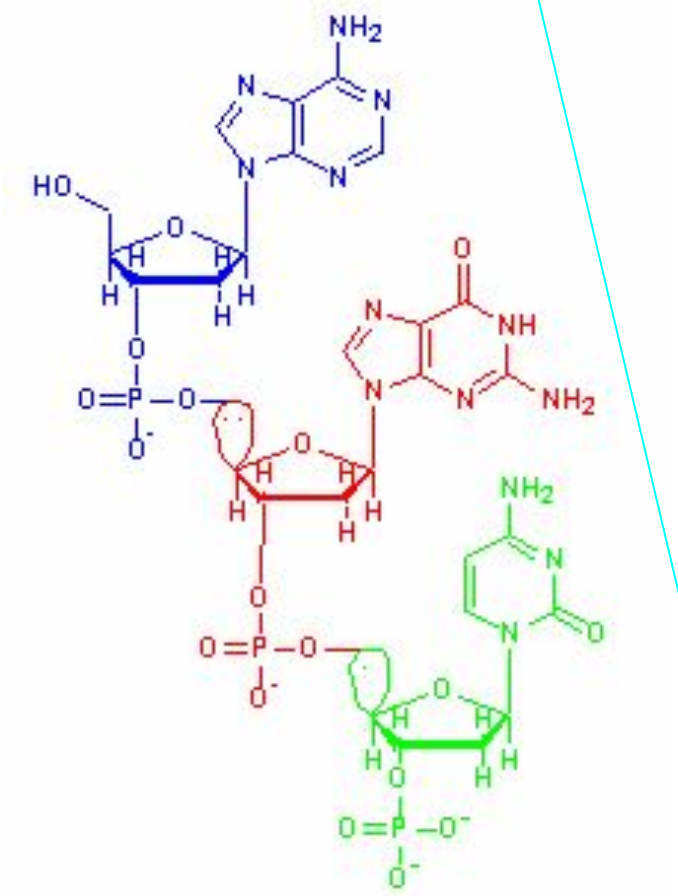
$$E_x = \frac{1}{2} Tr\left\{ \mathbf{D}^x \left(\tilde{\mathbf{H}}^x + \tilde{\mathbf{F}}^x \right) \right\} \quad (x = I, IJ)$$

Total energy of whole system

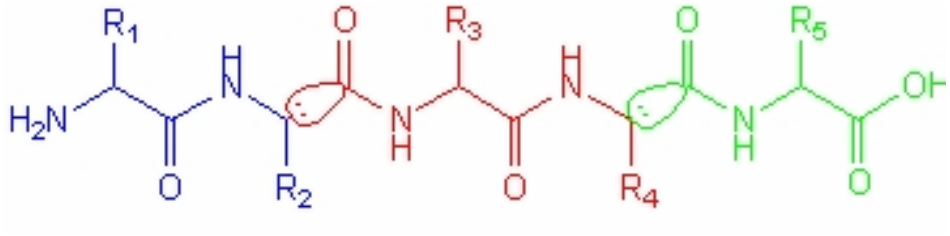
$$E = \sum_I E_I + \sum_{I>J} \left(E_{IJ} - E_I - E_J \right)$$

Examples of fragmentation in FMO

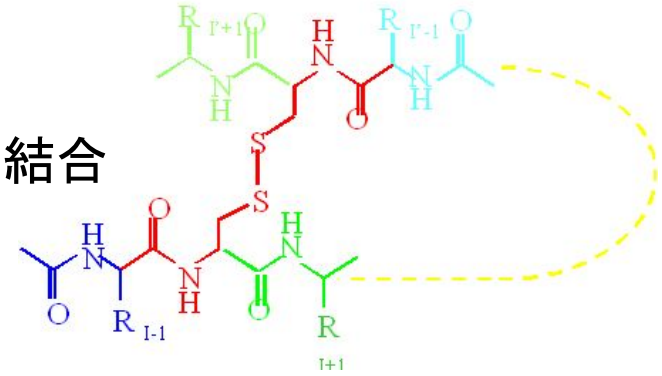
DNA/RNA



Polypeptide



S-S結合



sp^3炭素の位置で切断。他の分子の場合も、1重結合で切断すると、エラーが少ない。また、フラグメントのサイズは小さすぎると誤差が大きくなるので、最低20から30原子を含む程度にとると安心。

Intra- and inter-fragment pair interaction enegy (PIE) is obtained with FMO

$$E=\sum_{I}^{N}E_I+\sum_{I=1}^{N}\sum_{J>I}^{N}\left(E_{IJ}-E_I-E_J\right)=\sum_{I}^{N}E'_I+\sum_{I=1}^{N}\sum_{J>I}^{N}\left(E'_{IJ}-E'_I-E'_J\right)+\sum_{I=1}^{N}\sum_{J>I}^{N}Tr\left(\Delta\mathbf{D}^{IJ}\mathbf{V}^{IJ}\right)$$

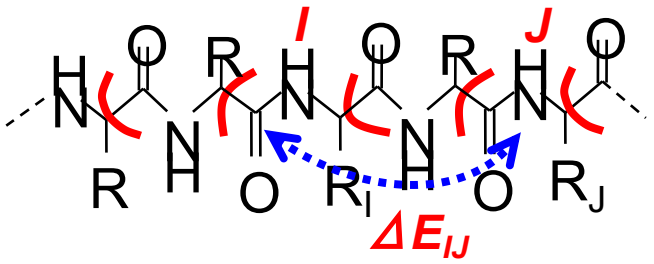
$$=\sum_{I}^{N}E'_I+\sum_{I=1}^{N}\sum_{J>I}^{N}\left\{\Delta E'_{IJ}+Tr\left(\Delta\mathbf{D}^{IJ}\mathbf{V}^{IJ}\right)\right\}$$

$$=\sum_{I}^{N}E'_I+\sum_{I=1}^{N}\sum_{J>I}^{N}\Delta E_{IJ}$$

PIE（this term can be further decomposed into EL, EX, CT interaction energies by PIEDA

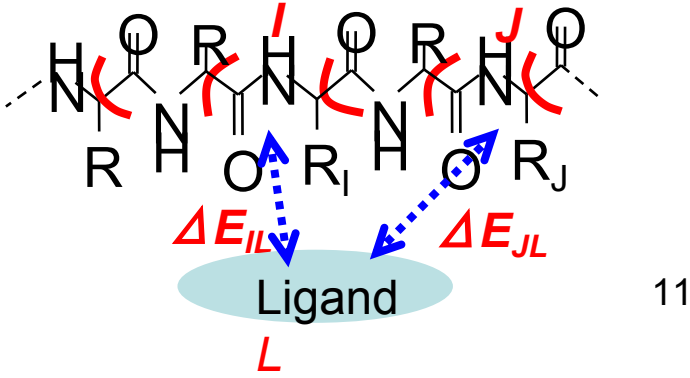
◆ Intramolecular interaction:

ΔE_{IJ} indicates interaction energy between residues except covalent bonded ones.



◆ Intermolecular interaction:

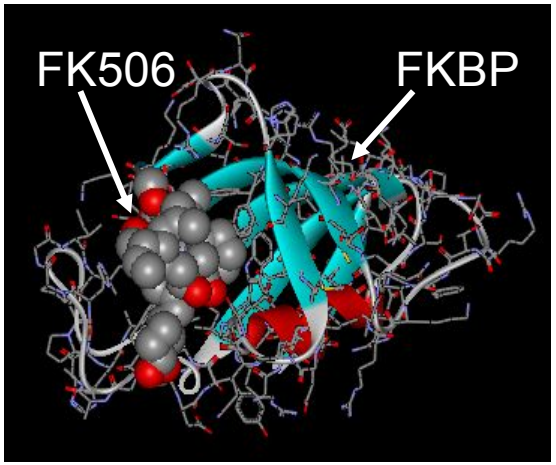
ΔE_{IL} indicates interaction energy between a residure and ligand.



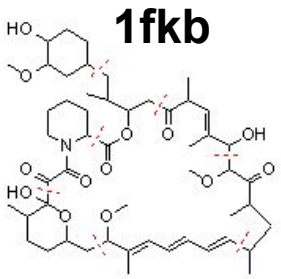
Example of PIE analysis: Intermolecular Interaction betweenFKBP and its Ligands

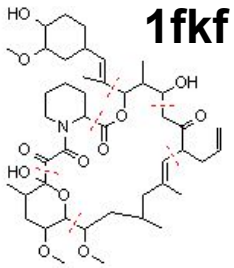
Nakanishi et al., *Proteins: Struct., Funct., Bioinf.* 68, 145 (2007)

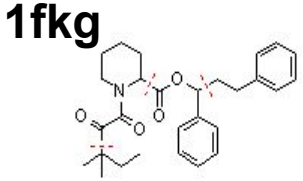
- FK506 is an immunosuppressant.
- We calculated the following four FKBP-ligand complexes by FMO.
- The complexes have 107 amino acid residues (about 1,800 atoms).
- The ligand geometries were optimized at FMO2-RHF/3-21G level using truncated 20 residues model complexes (about 500 atoms).
- The binding energies were calculated at the FMO2-MP2/6-31G* level.

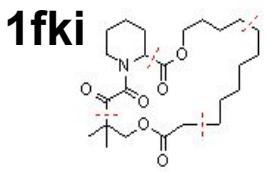


FKBP-FK506 complex (PDB:1fkf)

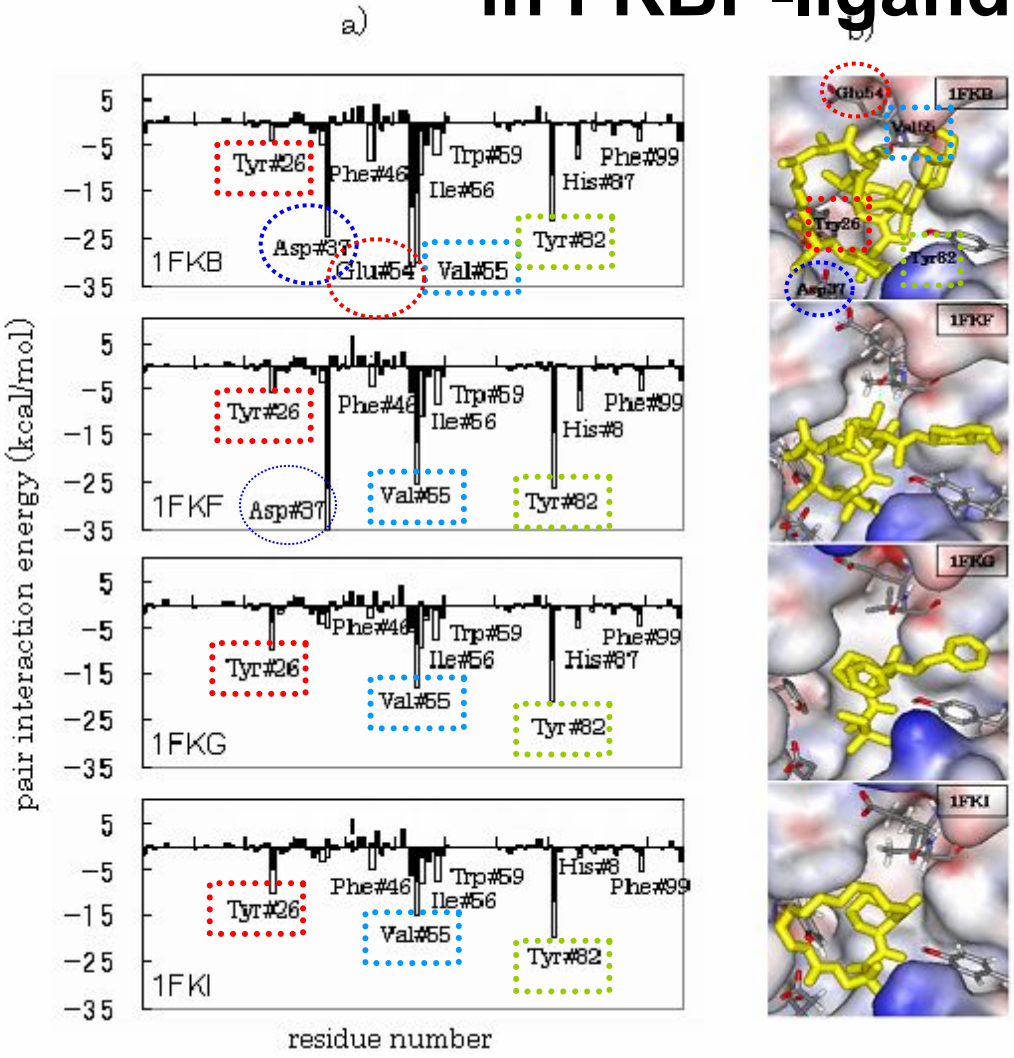








PIE between ligand and each residue in FKBP-ligand complexes



a) Empty bar:HF, filled bar: correlation energy contribution. b)Ligand binding modes. The proteins is shown by surface model.

- The sum of pair interaction energies correlates well with the experimental binding affinity, 1fkb>1fkf>1fkb>1fki.
- Val55, Tyr82 and Try26 are common important residues for the all ligand bindings.
- The stronger binders have additional interactions with Asp37 (1fkb and 1fkf) and Glu54(fkb).
- The correlation contribution is very large: 70-80% of binding energy.

Availabel free FMO Programs

1) FMO in **GAMESS**, coded by D.G.Fedorov et al.

http://www.msg.ameslab.gov/GAMESS/GAMESS.html

2) **ABINIT-MP**, coded by T.Nakano et al.

http://www.fsis.iis.u-tokyo.ac.jp/en/result/software/

3) **PAICS,** coded by T.Ishikawa

http://www.paics.net/get_paics.html

GUI programs for FMO pre- and post-processing

- Facio for GAMESS: http://www1.bbiq.jp/zzzfelis/Facio_Jp.html
- FU for GAMESS: https://sourceforge.net/projects/fusuite/
- BioStation for ABINIT-MP:

  http://www.advancesoft.jp/product/advance_biostation/
- PAICS View: http://www.paics.net/get_paics.html

いろんな電子状態理論のFMO法

FMO2-RHF : original FMO (2-body expansion), Kitaura et al., *CPL*,313,701(1999)

FMO3-RHF : 3-body expansion FMO, Fedorov et al., *JCP*,120, 6832 (2004)

FMO2,3-UHF: 開殻系の非制限Hartree-Fock法, Nakata et al., JCP,137,044110 (2012)

FMO2,3-ROHF: 開殻系の制限Hartree-Fock法, S.R.Pruitt et al., JCTC,6,1(2010)

FMO2,3-DFT: FMO-based density functional theory, Fedorov et al., *CPL*,389, 29 (2004).

FMO2,3-MP2 : FMO-based 2nd order Møller-Plesset perturbation theory, Fedorov et al., *JCP*, 121, 2483 (2004), Mochizuki et al.,*CPL*,396, 473(2004)

FMO2-MCSCF: FMO-based MCSCF, Fedorov et al.,*JCP*,122,54108(2005).

FMO2,3-CC: FMO-based coupled cluster theory, Fedorov et al., *JCP*, 123, 134103 (2005)

FMO1-CIS and CIS(D) : FMO-based configuration interaction singles, Mochizuki et al., *CPL*, 406, 283 (2005).

MFMO : FMO-based multilayer method, Fedorov et al., *JPCA*,109,2638 (2005).

FMO1,2-TDDFT : FMO-based time dependent DFT, Chiba et al., *JCP*, 127, 104108 (2007).

FMO/PCM : FMO combined with polarizable continuum model (PCM), Fedorov et al., *JCC,* 27, 976 (2006).

FMO/EFP: FMO combined with effective fragment potential method, Nagata et al., *JCP,* 131, 024101 (2009).

Capabilities of FMO in GAMESS

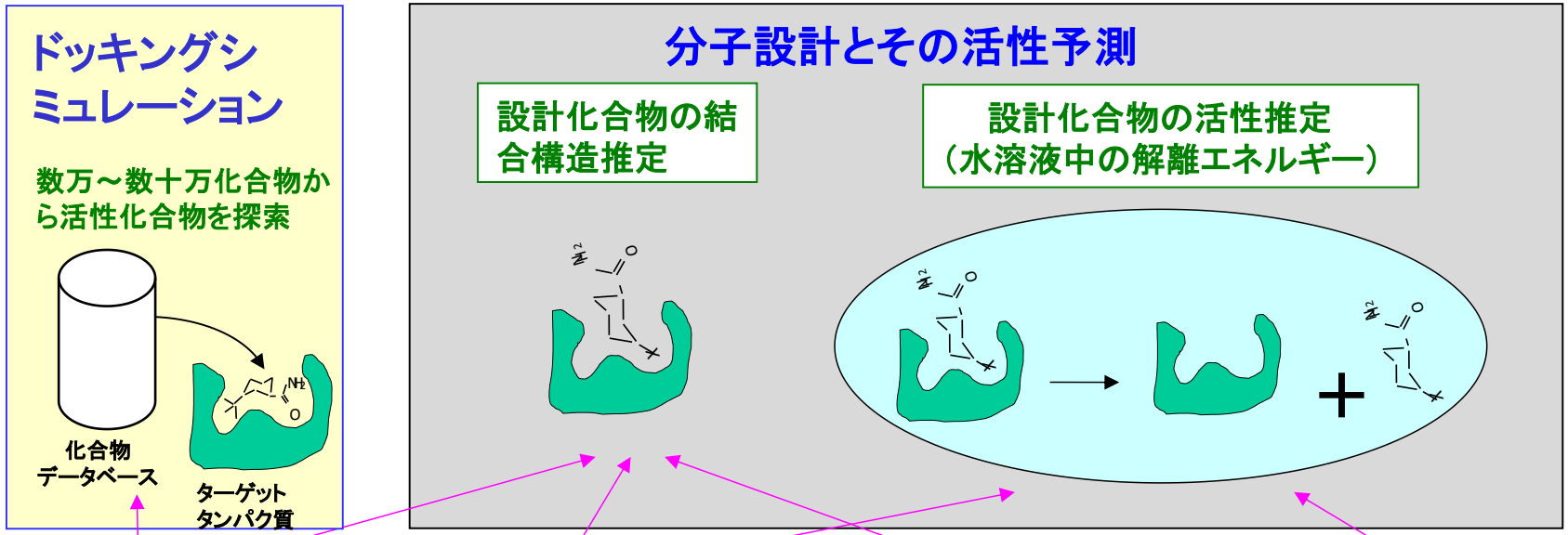
http://www.msg.chem.iastate.edu/gamess/capabilities.html

SCFTYP=	RHF	ROHF	UHF	GVB	MCSCF
	---	----	---	---	-----
SCF energy	CDFpEP	CDFpEP	CDFpEP	CD-pEP	CDFpEP
SCF analytic gradient	CDFpEP	CDFpEP	CDFpEP	CD-pEP	CDFpEP
SCF analytic Hessian	CDFp--	CDFp--	CDFp--	CD-p--	-D-p-
VB energy	C-----	C-----			
MP2 energy	CDFpEP	CDFpEP	CD-pEP	------	CD-pEP
MP2 gradient	CDFpEP	-D-pEP	CD-pEP	------	------
CI energy	CDFp--	CD-p--	------	CD-p--	CD-p--
CI gradient	CD----	------	------	------	------
CC energy	CDFpE-	CDF-E-	------	------	------
EOMCC excitations	CD--E-	CD--E-	------	------	------
DFT energy	CDFpEP	CD-pEP	CDFpEP	n/a	n/a
DFT gradient	CDFpEP	CD-pEP	CDFpEP	n/a	n/a
DFT Hessian	CD-p--	CD-p--	CD-p--	n/a	n/a
DFTB energy	yes/F	------	yes	n/a	n/a
DFTB gradient	yes/F	------	yes	n/a	n/a
DFTB Hessian	yes	------	yes	n/a	n/a

Recently, Nishimoto et. al. have developed FMO-DFTB(J PCL 6 (2015) 5034) and implemented its codes into GAMESS.

Here:
C= conventional storage of AO integrals on disk
D= direct evaluation of AO integrals whenever needed
F= Fragment Molecular Orbital methodology is enabled, "F" pertains to the gas phase; for FMO with PCM or EFP see manual.
p= parallel execution
E= Effective Fragment Potential discrete solvation
P= Polarizable Continuum Model continuum solvation

Useful FMO methods in drug design



Fast geometry optimization calculations

- Frozen domain FMO (FMO/FD)

  Fedorov et al.,JPCL, **2** (2011).

Computations and analysis of molecular interaction energy

- PIE/PIEDA analysis
- QM:QM hybrid method for accurate calculations (ONIOM+FMO)

  Asada et al., J. Phys. Chem. Lett.,3 (2012)

Geometry opts

- Analytic gradients

  Nagata et al. (2012)
- MQ/MM hybrid (FMO/MM)

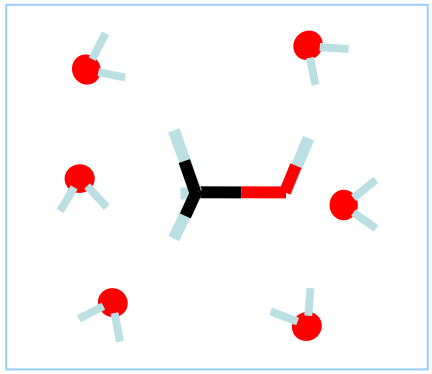
  Fedorov et al.,Acc Chem. Res(2014)
- Geometry opts in solution(FMO/PCM gradients) Nagata et al., (2012)

Solvation energy

- PCM model (FMO/PCM)
- EFP,PCM model (FMO/EFP/PCM)
- Binding energy analysis(FMO/PCM/PIEDA) Fedorov et al., JPCA, 116 (2012).

溶媒モデル

溶媒分子をあらわに考慮する

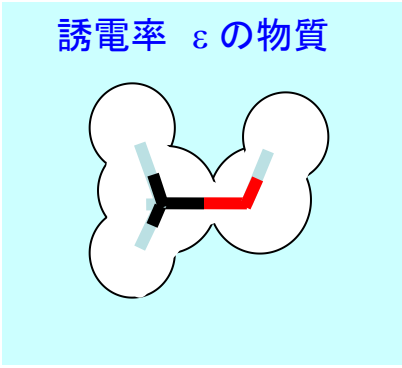


・系全体のMDシミュレーションを行い、溶質と溶媒分子の相互作用エネルギーの平均値を求める。

・熱力学積分法(TI)などで自由エネルギー計算も可能。

・長時間のシミュレーションを行う必要がある。

溶媒を誘電体で近似する



・誘電体に空孔をあけて(キャビテーションエネルギー)、溶質分子をいれ、溶質と溶媒の相互作用エネルギー(静電、分散エネルギーなど)を計算する。

・静電エネルギーは誘電体理論で、その他は経験式で評価する。

・PBSA 、GBSAやPCMモデルがある

Polarizable Continuum モデル（PCM）

J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.*, 105 (2005) 2999.

・溶質の電子分布を分子軌道法で求めて、キャビティ表面に誘起されるとself-consistentに解く。分子軌道法計算で最もよく用いられる溶媒モデル。

・溶媒和自由エネルギー

$$G_{\mathrm{sol}} = \Delta G_{\mathrm{in}} + G_{\mathrm{sol}}^{\mathrm{ele}} + G_{\mathrm{sol}}^{\mathrm{rep}} + G_{\mathrm{sol}}^{\mathrm{disp}} + G_{\mathrm{sol}}^{\mathrm{cav}}$$

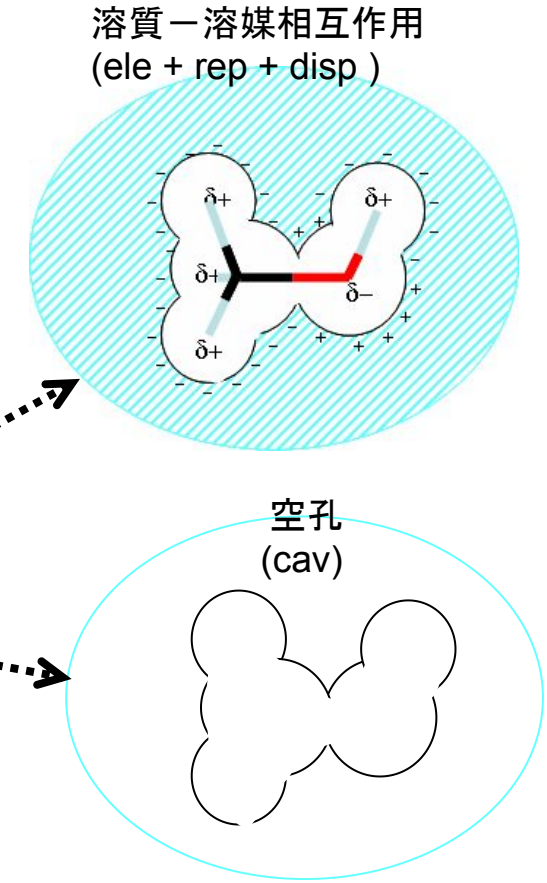
ΔG_{in} ：溶質分子の内部エネルギー変化（気相との差）

$G_{\mathrm{sol}}^{\mathrm{ele}}$ ： 溶質分子と溶媒の静電相互作用エネルギー項

$G_{\mathrm{sol}}^{\mathrm{rep}}$ ： 溶質分子と溶媒の交換反発エネルギー項

$G_{\mathrm{sol}}^{\mathrm{disp}}$ ：溶質分子と溶媒の分散エネルギー項

$G_{\mathrm{sol}}^{\mathrm{cav}}$ ： キャビテーションエネルギー項



PCMの静電エネルギー項；$G_{\mathrm{sol}}^{\mathrm{ele}}$

溶質の電子分布とその空孔表面に誘起される電荷をself-consistentに解き、溶質分子と溶媒との静電エネルギーを求める。

空孔表面の誘起電荷；**q**

$$\mathbf{q} = -\frac{\varepsilon - 1}{4\pi\varepsilon}\mathbf{C}^{-1}\mathbf{V}$$

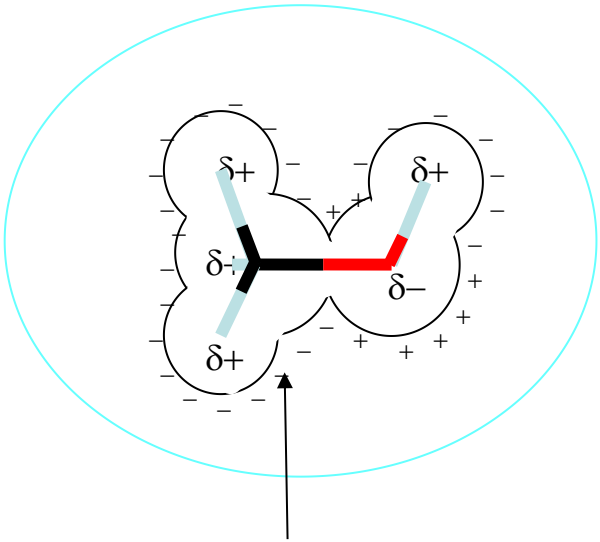
ε:溶媒の誘電率
V:表面テセラの静電ポテンシャル
C:構造行列

誘起電荷の影響下で溶質分子の電子状態を解く

$$F_{\mu\nu} = F_{\mu\nu}^{0} + W_{\mu\nu}$$

$$W_{\mu\nu} = -\sum_{i=1}^{N_{TS}} q_i w_{\mu\nu}^{i}$$

$$w_{\mu\nu}^{i} = \langle \mu | \frac{1}{|\mathbf{r} - \mathbf{R}_i|} | \nu \rangle$$



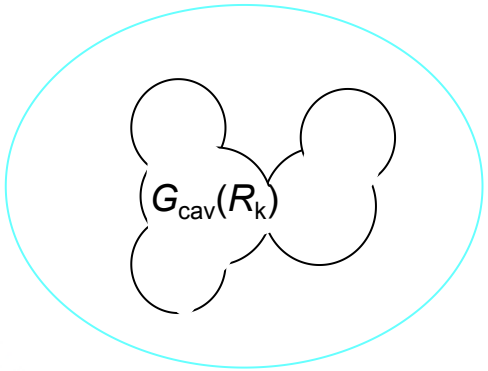
キャビティ表面のテセラ上に誘起された電荷、**q**

PCMの静電以外の項；G_{cav}，G_{rep}，G_{disp}

キャビテーションエネルギー：G_{cav}

$$G_{\mathrm{cav}} = \sum_{k=1}^{N} \frac{A_k}{4\pi R^2{}_k} G_{\mathrm{cav}}(R_k) \quad (\mathrm{Pierotti-Claverie\ の式})$$

$$G_{\mathrm{cav}} = RT\left\{ -\ln(1-y) + \frac{3y}{1-y}\left(\frac{R_{\mathrm{M}}}{R_{\mathrm{S}}}\right) + \left[\frac{3y}{1-y} + \frac{9}{2}\left(\frac{y}{1-y}\right)^2\right]\left(\frac{R_{\mathrm{M}}}{R_{\mathrm{S}}}\right)^2 \right\}, \quad \mathrm{y} = \frac{\pi}{6}(2R_{\mathrm{S}})^3\rho$$



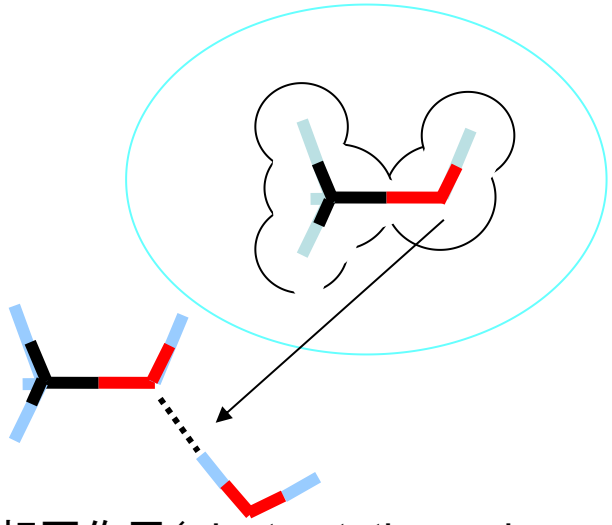
交換反発エネルギー：G_{rep}

$$G_{\mathrm{rep}} = \rho_{\mathrm{s}} \sum_{k\in\Gamma} \sum_{s\in S} N_{\mathrm{s}} \sum_{m\in M} a_k \vec{A}_{\mathrm{ms}}(\vec{r}_{\mathrm{m}k})\cdot\vec{n}_k$$

$$\vec{A}_{\mathrm{ms}}(\vec{r}_{\mathrm{ms}}) = -\frac{1}{9}\frac{d^{(12)}_{\mathrm{ms}}}{r^{12}_{\mathrm{ms}}}\vec{r}_{\mathrm{ms}}$$

分散エネルギー：G_{disp}

$$\vec{A}_{\mathrm{dis,ms}} = -\frac{d^{(6)}_{\mathrm{ms}}}{3r^{6}_{\mathrm{ms}}}\vec{r}_{\mathrm{ms}}$$



分子間相互作用（electrostatic, exchange-repulsion, dispersion, charge-transfer）

FMO/PCM法

♦ FMO is combined with polarizable continuum model (PCM)

♦ Solute electrostatic field V on cavity surface is calculated from many-body series expansion;

$$V_i = \sum_{I=1}^{N} V_i^I + \sum_{I>J}^{N} \left(V_i^{IJ} - V_i^I - V_i^J \right) + \cdots$$

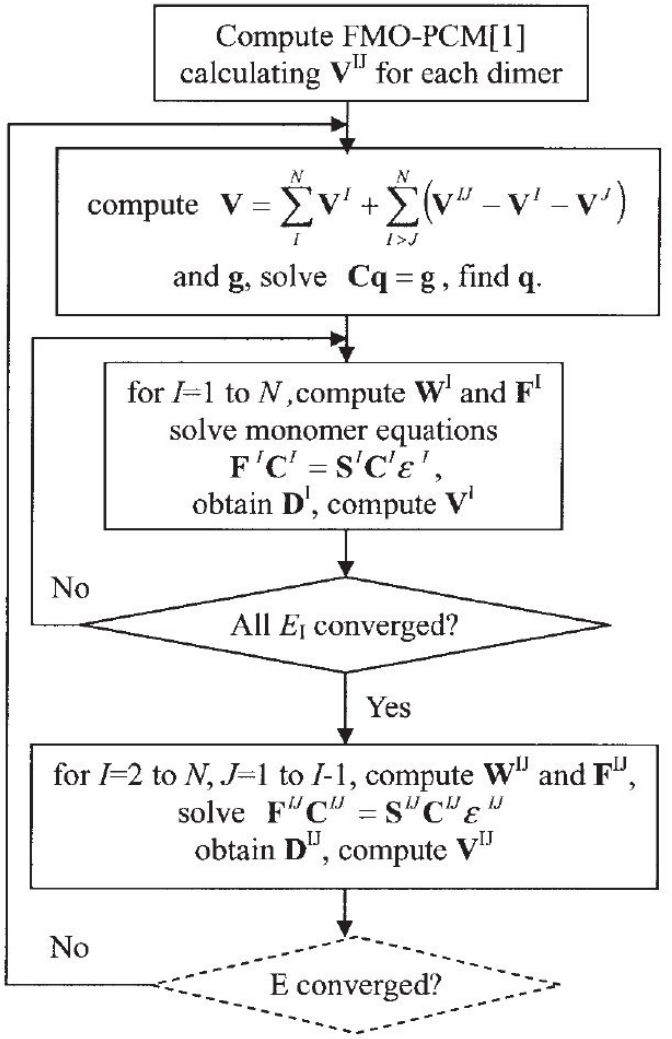
$$V_i^x = -Tr\left(\mathbf{D}^x \cdot \mathbf{w}^i \right) + \sum_{\alpha \in X} \frac{Z_\alpha}{\left| \mathbf{R}_\alpha - \mathbf{R}_i \right|}$$

$$w_{\mu\nu}^i = \left\langle \mu \left| \frac{1}{\left| \mathbf{r} - \mathbf{R}_i \right|} \right| \nu \right\rangle, \quad \mu\nu \in x$$

♦Several approximation levels are possible depending on V and electron density (D^x) expansion:

(1) FMO/PCM[1] uses one-body expansion V and one-body density
(2) FMO[2] uses two-body V and two-body density
(3) FMO[1(2)] uses two-body V and two-body density (no self-consistent)

FMO/PCM[1(2)] is recommended



flowchart of FMO/PCM[2]

FMO/MM: FMO-based IMOMM

D.G.Fedorov, et al., J. Phys. Chem. A 2007, 111, 2722.

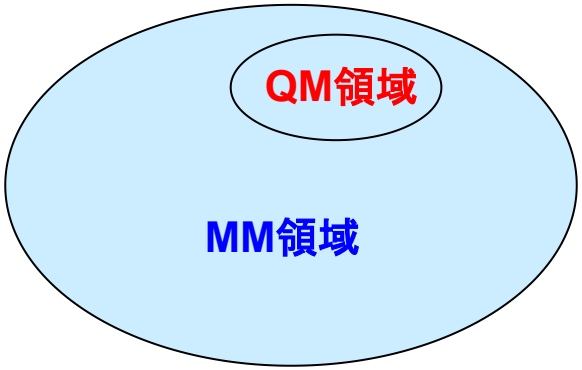
IMOMM: Maseras, F.; Morokuma, K. JCC 1995,16,1170.
SIMOMM: Shoemaker J. R.; Burggraf, L. W.; Gordon, M. S. JPCA 1999,103, 3245.

The total energy E and its gradient are divided into FMO and MM contributions,

$$E = E_{\mathrm{FMO}}(\mathbf{R}_1) + E_{\mathrm{MM}}(\mathbf{R}_1, \mathbf{R}_2)$$

$$\frac{\partial E}{\partial \mathbf{R}_1} = \frac{\partial E_{\mathrm{FMO}}}{\partial \mathbf{R}_1} + \frac{\partial E_{\mathrm{MM}}}{\partial \mathbf{R}_1}$$

$$\frac{\partial E}{\partial \mathbf{R}_2} = \frac{\partial E_{\mathrm{MM}}}{\partial \mathbf{R}_2}$$



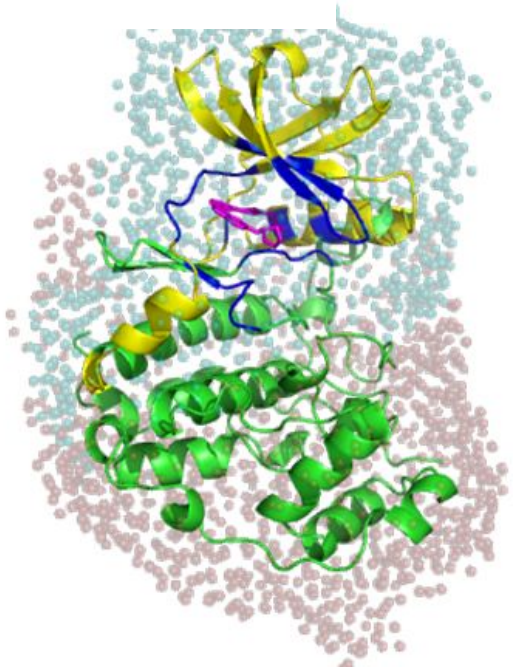
where **R1** and **R2** are a set of atomic coordinates in the FMO region and atomic coordinates in the MM region, respectively. Note that the interaction energy between FMO and MM atoms are included in and the link atoms in FMO region do not feel MM forces.

Geometry optimization of protein by FMO/MM

D.G.Fedorov, et al., Acc. Chem. Res, Acc. , 2014, 47, 2846.
浅田直也、博士論文(京都大学)2012

Computational Details:

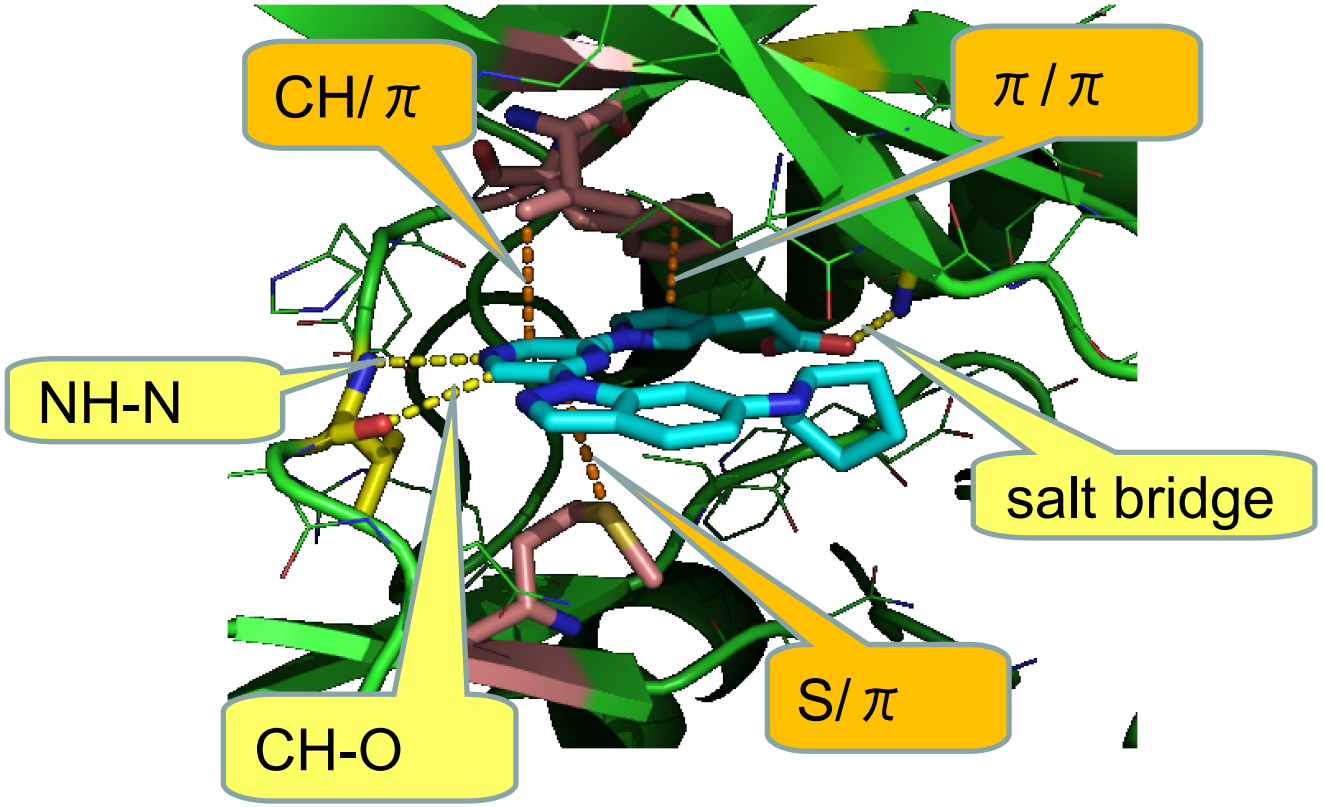
1. System: alpha subunit of protein kinase 2 (CK2) and its ligand ((1-{6-[6-(cyclopentylamino)-1H-indazol-1-YL]pyrazin-2-YL}-1H-pyrrol-3-YL)acetic acid)
2. FMO2 at the RHF-D/6-31G level (D:empiric dispersion) and AMBER f99 (protein) and gaff (ligand) force fields and TIP3P (water) were employed for MM.
3. The FMO region was defined to include the ligand and the amino acid residues and water molecules separated by the unitless FMO distance70 of 2.0 from the ligand.
4. We optimized all FMO atoms (667) and 1980 of MM atoms.
5. A single point calculation took about 36 min on the Heian cluster (112 CPU cores of Xeon 3.0 GHz) and 470 FMO steps were required for convergence.



FMO atoms are colored in purple (ligand) and blue (the binding pocket of the protein). MM atoms are shown as yellow (optimized) and green (frozen) for the protein, and cyan (optimized) and pink (frozen) for water.

Intermolecular interaction between the protein and ligand

The protein recognizes its ligand with various kind of non-bonding interactions at multiple interaction sites. These interactions should be described in a well balanced mannar.



Dispersion interaction is indispensable to obtain reasonable binding structure

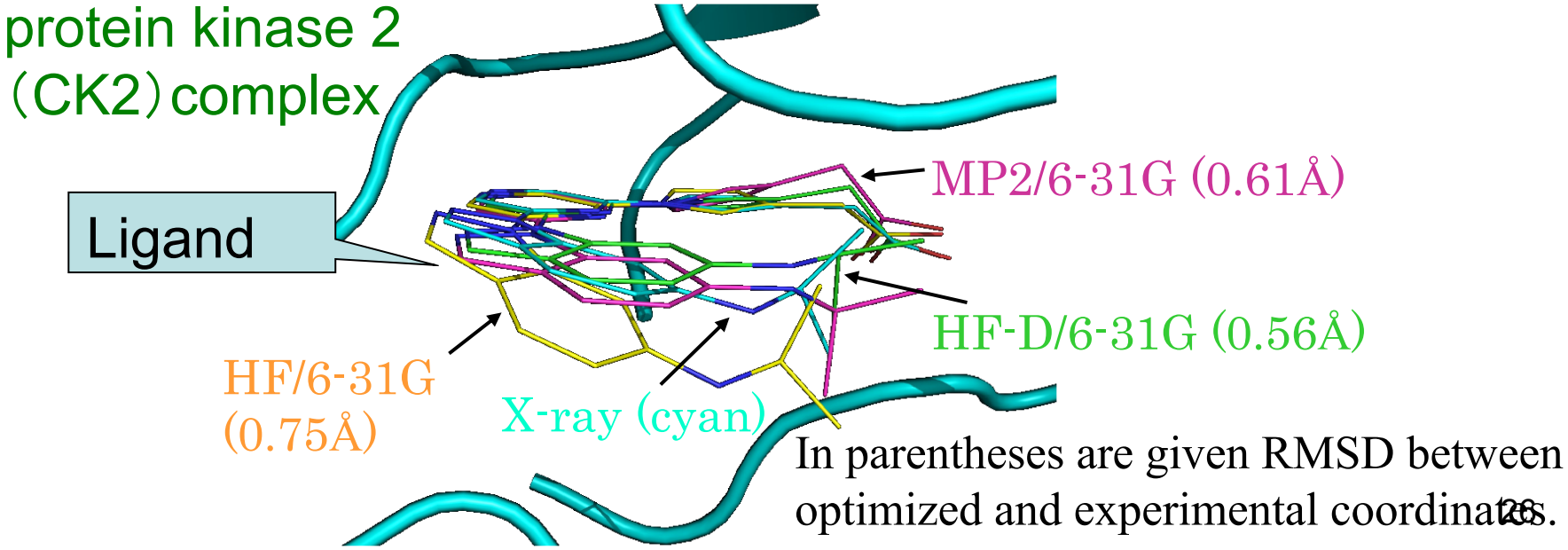
♦FMO-HF/6-31G failed to reproduce the binding structure (RMSD:0.75Å)

♦ FMO-MP2 reproduced experimental structure with RMSD of 0.61Å

♦ Convenient HF-D also reproduced the binding structure (RMSD:0.56Å)

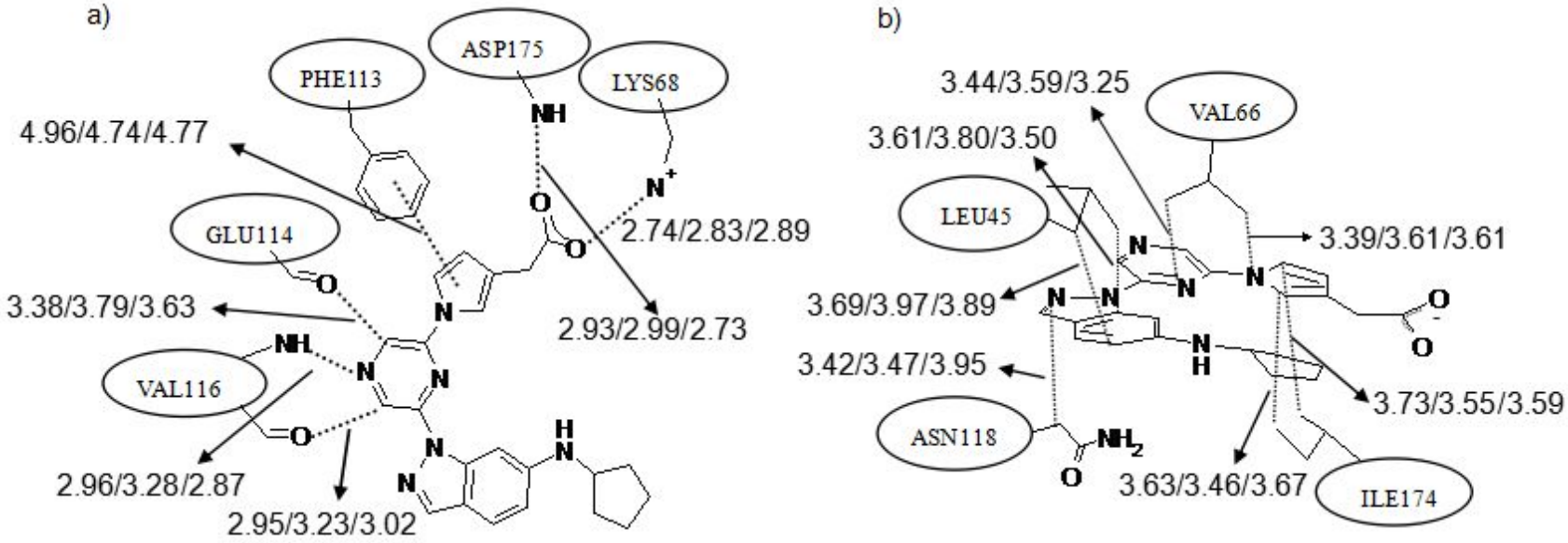
HF-D: RHF augmented with empirical dispersion force (S. Grimme, JCC, 25, 1463(2004)).

$$E_{\mathrm{disp}} = -s_6 \sum_{i=1}^{N_{\mathrm{at}}-1} \sum_{j=i+1}^{N_{\mathrm{at}}} \frac{C_6^{ij}}{R_{ij}^6} f_{\mathrm{dmp}}(R_{ij}), \qquad C_6^{ij} = \sqrt{C_6^i C_6^j}, \qquad f_{\mathrm{dmp}}(R_{ij}) = \frac{1}{1 + e^{-d(R_{ij}/R_{\mathrm{r}} - 1)}}$$



In parentheses are given RMSD between optimized and experimental coordinates.

Optimized Structure of Ligand Binding Site

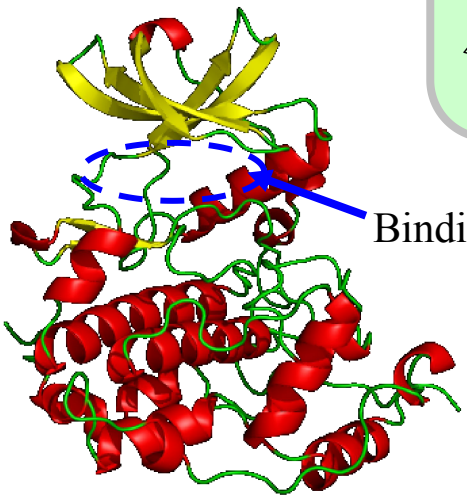


The left and right panels show the top and side views of the binding site, respectively. For each distance between heavy atoms (Å), three numbers are given, corresponding to the FMO/MM minimum, MM minimum and experimental values, respectively.

As shown in the figure, the FMO/MM and MM structures show in general somewhat similar deviations from experiment. However, the NH...N and CH...O hydrogen bonds between the pyrazine moiety of the ligand and VAL116 are not well described by the force field. In this particular complex, multiple weak interactions are reasonably described by both FMO/MM and MM methods.

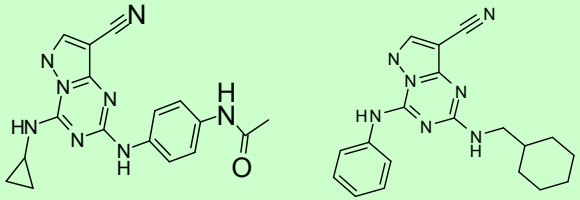
Calculation of binding free energy

- Target system is the complexes of protein kinase 2, CK2
- CK2α (α-subunit) is a potential target for nephritis therapy.
- Variety of CK2α ligands were selected for binding free energy calculations



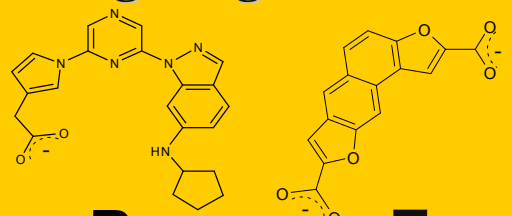
Structure of CK2α (α subunit)

polar ligand



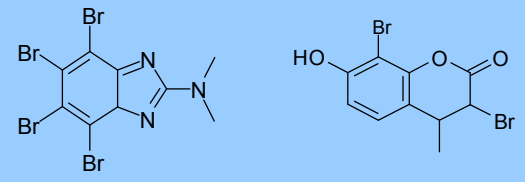
A C

charged ligand



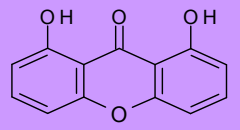
B E

bromo



D F

tetraquinone



G

Affinity: A > B > C > D > E > F >G

Binding free energy in solution was calculated with FMO/PCM (polarizable continuum solvent model)

- Binding energy of protein-ligand complex (PL) in solution

$$\Delta G_b^{sol} = G_{PL}^{sol} - G_P^{sol} - G_L^{sol}$$

$$G_X^{sol} = G_X^{internal} + G_X^{ele} + G_X^{cav} + G_X^{disp} + G_X^{rep} \quad (X = PL, P, L)$$

- 1) FMO-MP2/PCM/6-31G*
  2) conductor-like PCM in GAMESS
  3) cavity was created with the simplified united atomic radii, H:0.01Å, C:1.77Å, N:1.68Å, O:1.59Å, and S:2.10Å
  4) 60 tesserae per sphere.

Entropy term:quasi-harmonic approximation

ΔS : quasi-harmonic analysis

Levy, et. al., Macromolecules, 1984, 17, 1370-1374

covariance matrix: $\sigma_{ij} = \left\langle \left(x_i - \left\langle x_i \right\rangle \right) \left(x_j - \left\langle x_j \right\rangle \right) \right\rangle$

$\downarrow$ $\boldsymbol{\sigma}' = \mathbf{M}^{1/2} \boldsymbol{\sigma} \mathbf{M}^{1/2}$

quasi-mode frequenceis: $\omega = \left(k_B T / \lambda' \right)^{1/2}$

$\downarrow$

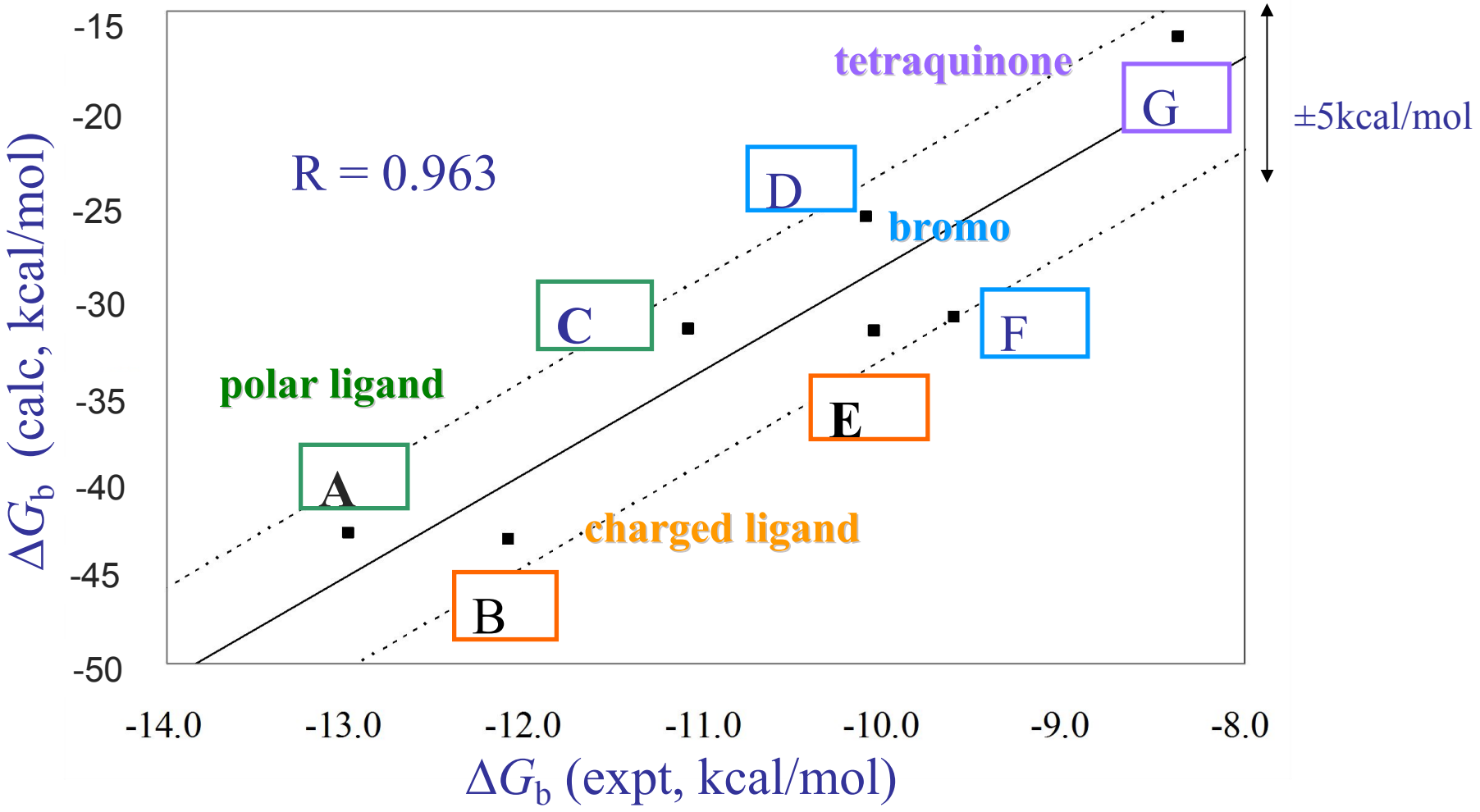
$$\Delta S = S^{QH}_{PL} - S^{QH}_{PL(P)} - S^{QH}_{PL(L)}$$

♦MD simulation for entropy term

- Initial structures and restraint conditions were the same as used for the structure refinement.
- 10 ns MD simulation : NPT ensemble (1 atm, 300K) with 1000 kcal/mol restraint to fixed domain (production run: last 5ns)
- ff99, gaff and RESP charges were used.
- AMBER9 program

30

Calculated binding free energy vs Experiment



The calculated values are well correlated with experiments including charged ligands

FMOに関する包括的情報の入手先

https://staff.aist.go.jp/d.g.fedorov/

The FMO method
- Download FMO resources (oral presentation etc)
  - Basics of FMO(フラグメント分子軌道法の基礎)
  - FMO implementation in GAMESS (GAMESS FMO使用の手引き)

過去に開催されたFMO講習会の資料

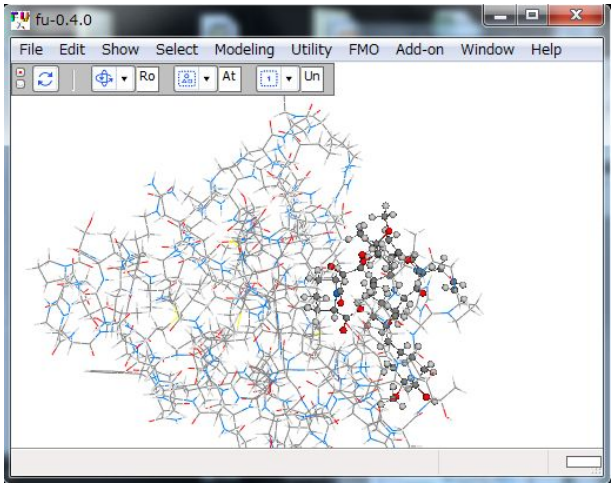
http://www.cms-initiative.jp/ja/research-support/about-kobe-support

CMSI神戸ハンズオン
- CMSI神戸ハンズオン(アプリケーション講習会)
  - 過去の講習会一覧・資料など
    - 【 第23回: FMOチュートリアル 】

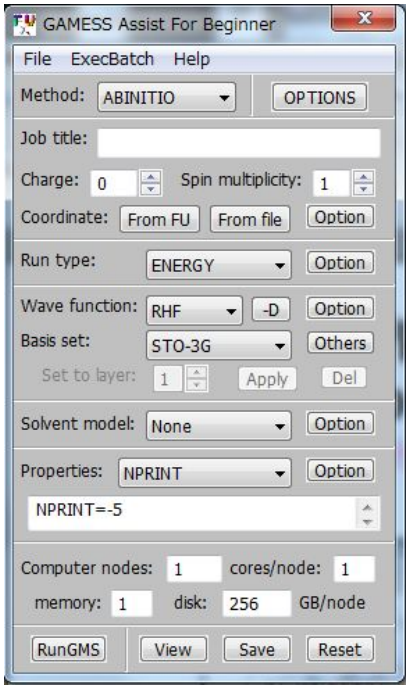
FU: Open source GUI software for GAMESS-FMO calculations

https://sourceforge.net/projects/fusuite/

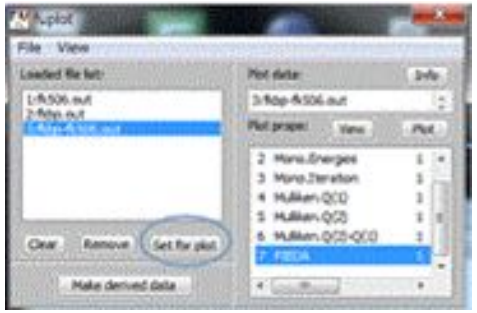
Structure modelings



GAMESS Input data generation and computations



Result visualisations



FUを用いたFMO計算の実際

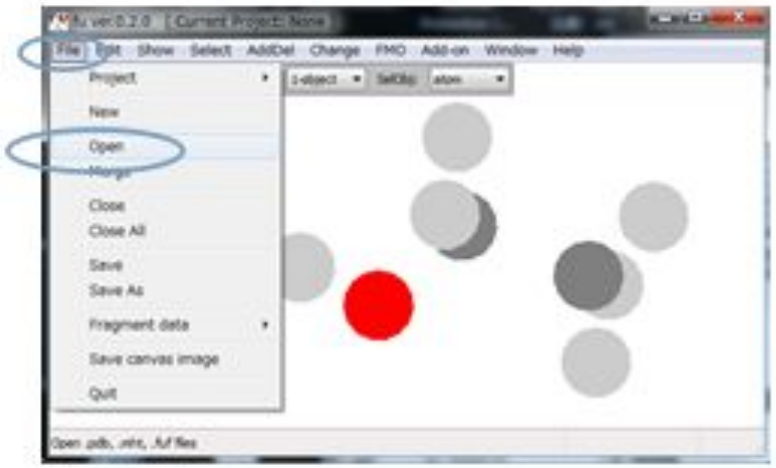
「FMOチュートリアル実習テキスト」(平成27年5月25日)より抜粋

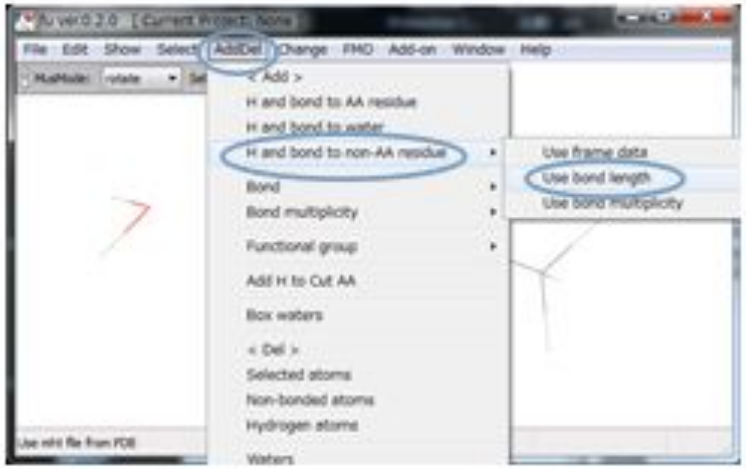
内容：

1. FMO-RHF/STO-3Gの1点計算
2. FMO-DFT/STO-3Gの１点計算
3. FMO-MP2/STO-3Gの１点計算
4. FMO-RHF/STO-3Gでの構造最適化計算
5. FMO-RHF-D/STO-3Gの構造最適化計算
6. RHF/STO-3G(ab initio MO）の1点計算
7. FMO-RHF/PCM/STO-3G計算
8. 水和モデルの作成とマルチレーヤFMO計算

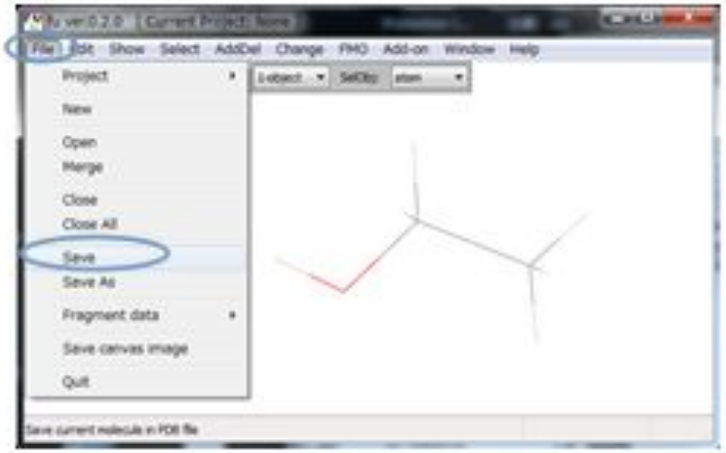
1．FMO-RHF/STO-3Gの1点計算...c2h5oh-h2o

1) fu.exeをckickして、fumodelを起動する。
2) PDBデータ形式の座標データ(ファイル名："c2h5-h2o.pdb")　を読み込んで、メニュー"AddDel/(Add)"-"Bond"-"Use bond length"で結合データを付加する(fumodelのメインウィンドウの背景色はdefaultは黒であるが、本稿では白に変更してある)。



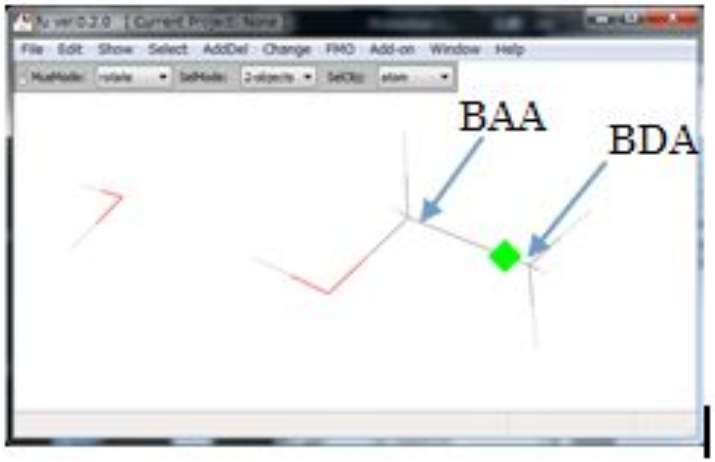


3) "File"-"Save"メニューで保存する。



4) メニュー"FMO"-"Fragmentation tool"-"BDA setting"を実行する。

5) マウスでBDAとBAAをこの順番で左クリック (L-Click)する。



6) メニュー"FMO"-"Fragmentation tool"-"BDA setting"のチェックを外す（モードを解除する)。ここで、" File" -" Fragments data" -" Save fragment data as" を実行して、fragment データを保存する（ファイル名は、" c2h5oh-h2o.frg" とする)。

7) メニュー"Add-on"-"gamess-user.py"を実行する。"GAMESS Assist For Beginner"パネルが開く。

8) "GAMESS Assist For Beginner"パネルの"Method"で" FMO" -" FMO2" 、" Wave function" で" RHF" 、"Basis set"選択窓で"STO-3G"を選ぶ。さらに、" Coordinate" の" From FU"ボタンを押す。最後に、パネル下部にある"Save"ボタンを押し、入力データを" c2h5oh-h2o-fmo-rhf.inp" の名前で保存する。

（補足）パソコンで GAMESS 計算する場合は、"Computer" (node 数、core 数、メモリ量 (GB)とディスク量 (GB)を入力する）で"node 数"は常に 1 とし、"cores 数"はパソコンのコア数に対応した適当な値を入力し、数字入力後" ENTER"キーを押す。

9) "RunGMS" ボタンを押し、GAMESS を実行する。

実行中の GAMESS の出力が" Run GAMESS"パネルに

初めて GAMESS を実行する場合、GAMESS の path とコマンドなどの入力が要求される。ここで入力したデータは、FUDATASET¥Programs¥gamess¥gamesspath.win ファイルに保存される(Mac OSX の場合のファイル拡張子は、.mac)。

計算結果は以下のとおり。

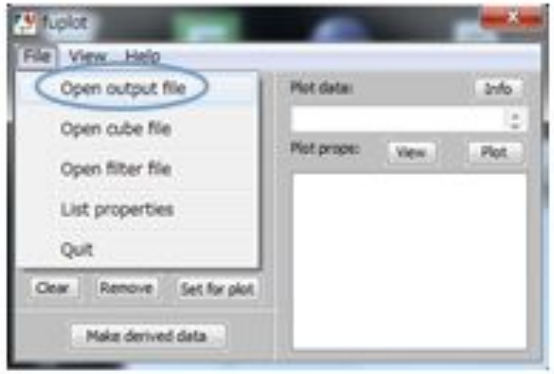
Total energy of the molecule: Euncorr(2)= -227.107862151

(この値は、後で ab inito MO 計算の結果と比較する)

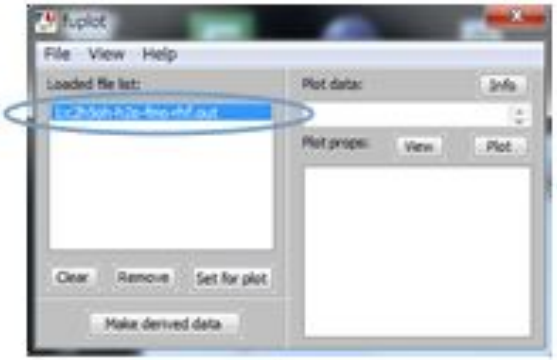
次いで、FMO 計算結果のグラフ表示を行う。

10) fumodel のメニュー “Add-on” -” fuplot.py” を実行し、fuplot 起動する。

11) fuplot のメニュー "File"-"Open output file" を実行する。ここで、c2h5oh-h2o-fmo-rhf.out を読み込む。すかさず、filter ファイルの読み込み filer が開くので、ここで” gamess-fmo.filter” ファイル (FUDATASET/Filters フォルダーにある) を読み込む。



Output file を open する際、Filter file の読み込みが要求される。ここで、gamess-fmo.filter ファイルを読み込む。

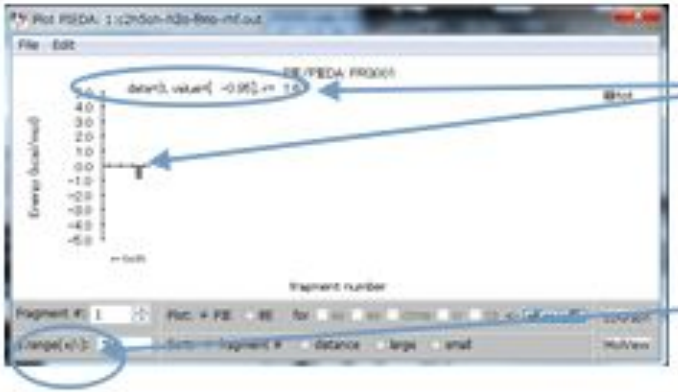


Open した output file が左窓に表示される。

12) fuplotパネルの”Set for plot”ボタンを押す。パネル右側の”Plot props”窓で”PIEDA”を選択して、”Plot”ボタンを押す。

パネル右側に、この output file の plot 可能な property（fiter file で定義されたもの）がリストされる。”PIEDA"を選んで、”Plot"ボタンを押す。

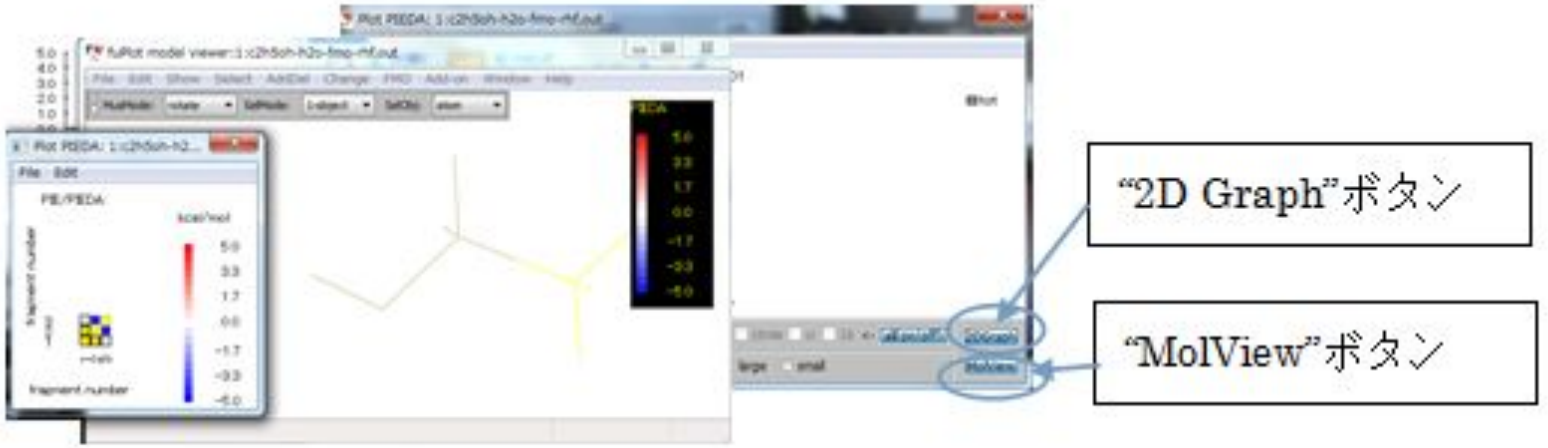
13) ”PIEDA”パネルのグラフのバーをクリックするとその値が表示される。左下方の”y.range(+/-)”に数字を入力して”Enter”キーを押すとｙ軸の最大/最小値を変更できる。これを”5.0”に変えて”Enter”キーを押す。



グラフのバーを click すると、その fragment の PIEDA(PIE)の値が表示さ

ｙ軸の最大値設定。数字を入力して”ENTER”キーを押す。

14) ”PIEDA”パネルの右下の”2DGraph”を押すと2次元グラフ、”MolView”ボタンを押すと分子模型が表示される（これは描画に時間がかかるので完全に描画されるまで待つこと）。これらは、”Plot PIEDA”パネルの”Fragment #”で選択したデータと連動して変わる。”PIEDA”(相互作用成分がある）プロットの場合、これらには”tot”の値が表示される。



まとめ

- フラグメント分子軌道法は、ほぼリニアスケーリングであり、大規模並列計算も可能である。実際、京コンピュータの20万コアを用いて、約2万原子からなるタンパク質複合体のFMO-RIMP2/6-31G*による1点計算が11分で計算できた。
- 力場との融合法（FMO/MM法）を用いると、構造最適化計算も現実的な時間で実行できる。
- PCM溶媒モデル（FMO/PCM)により、溶媒和自由エネルギーが計算できる。
- PIE（PIEDA)により、分子内、分子間のフラグメントを単位とした相互作用解析が行えるので、巨大・複雑分子系の構造とエネルギーに関する詳細な情報が得られる。タンパク質の分子認識機構の理解やドラッグデザインに有用だろう。
- FMO計算を容易にするためのGUIソフトウェアが開発され公開されている。