# Molecular electrostatic potential evaluation with the fragment molecular orbital method

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## ABSTRACT
The molecular electrostatic potential (MEP) is a useful tool to analyze intermolecular electrostatic interactions and the properties of the chemical system. The most accurate way to compute MEP is to use quantum mechanics methods, but it is prohibitively computationally expensive for large chemical systems. Presently, the ability to compute MEP accurately for large systems is in high demand because of the recent advances in X-ray, cryo-electron microscopy, NMR, and mass-spectrometry techniques for elucidation of structure and conformation. The solution is to use linearly scaling QM methods, like fragment molecular orbital (FMO) method. The major problems are accurate computation of MEP, the storage of electron density and electrostatic potential in memory, and scalability of the code. To address these issues, we implemented different MEP algorithms and compared their performance. It was found that the new fragment cube method (FCM) produces accurate MEP at a fraction of cost.

## Categories and Subject Descriptors
J.2 [**Computer applications**]: Physical Sciences and Engineering – *chemistry.*

## General Terms
Algorithms.

## Keywords
Quantum mechanics, fragment molecular orbital, molecular electrostatic potential, proteins.

## 1. INTRODUCTION
The molecular electrostatic potential (MEP) is a useful tool to analyze intermolecular electrostatic interactions and the properties of the system. It is an especially important tool in X-ray, cryo-electron microscopy, NMR, and mass-spectrometry techniques for elucidation of structure and conformation. Another important area is drug design where understanding electrostatic and topographic complementarity in receptor-ligand complex is the key. This tool is used to predict ligand specificity, i.e. polarity in the active site of a receptor, for example, as a part of the docking procedure.

## 2. MEP EVALUATION WITH FMO
### 2.1 Total cube method (TCM)
The whole system is put into a cube, by leaving an extra space of GRDPAD(1) around the atoms. For each fragment I, a window in the total grid is determined, including all atoms in I and an extra space of GRDPAD(2). A subset of all grid points r in the window is denoted as $r^I$:

$$\phi^I(\mathbf{r}) = \sum_{A\in I} \frac{Z_A}{|\mathbf{r} - \mathbf{R}_A|} - \sum_{\mu\nu\in I} D^I_{\mu\nu} \int \chi_\mu(\mathbf{r}') \frac{1}{|\mathbf{r} - \mathbf{r}'|} \chi_\nu(\mathbf{r}') d\mathbf{r}'$$

Then, the total data are accumulated as by summing contributions for fragments I, whose window included $r^I$:

$$\phi(\mathbf{r}) = \sum_{\substack{I=1 \\ \mathbf{r}\in\mathbf{r}^I}}^{N} \phi^I(\mathbf{r})$$

### 2.2 Fragment cube method (FCM)
The algorithm for computing MEP is the same. The difference is of FCM from TCM in the storage of cubes. A separate cube file is created for each fragment, by constructing a cube around the fragment leaving an extra space GRDPAD(1). MEP is computed as

$$\phi(\mathbf{r}^I) = \sum_{\substack{J=1 \\ R_{IJ}\le R_{cube}}}^{N} \phi^J(\mathbf{r}^I)$$

meaning that the contribution due to fragments J is added to the potential computed for the cube around fragment I. GRDPAD(3) defines $R_{cube}$. $R_{IJ}$ is the interfragment distance in FMO.

## 3. RESULTS
The calculations have been done on PC cluster Cooley for a small tryptophan cage protein (PDB code: 1L2Y) by using FMO1 with RHF and 6-31G* basis set. On Figures 1 and 2, the preliminary results for computing MEP with TCM and FCM are shown.

The scaling curves for TCM and FCM are shown on Figures 3 and 4. As one can see, both of our developed methods TCM and FCM are scaling almost perfectly.

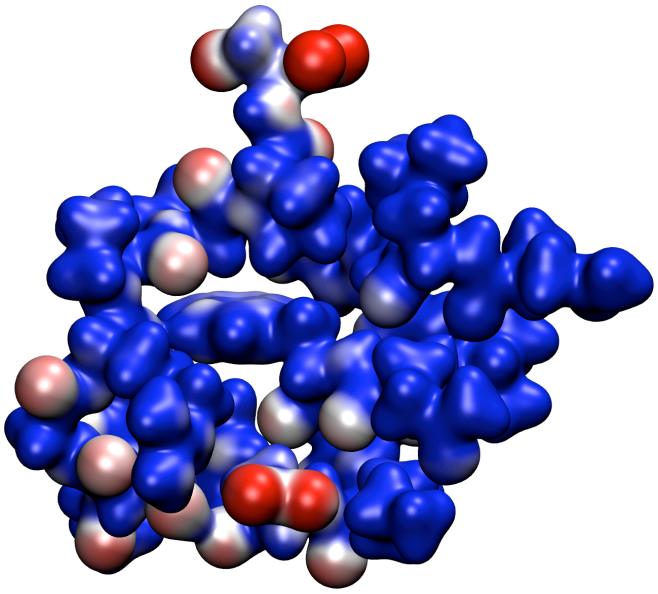

**Figure 1. MEP figure computed with TCM. MEP is computed on electron density isosurface cutoff 0.02 with GRDPAD=1,100.**

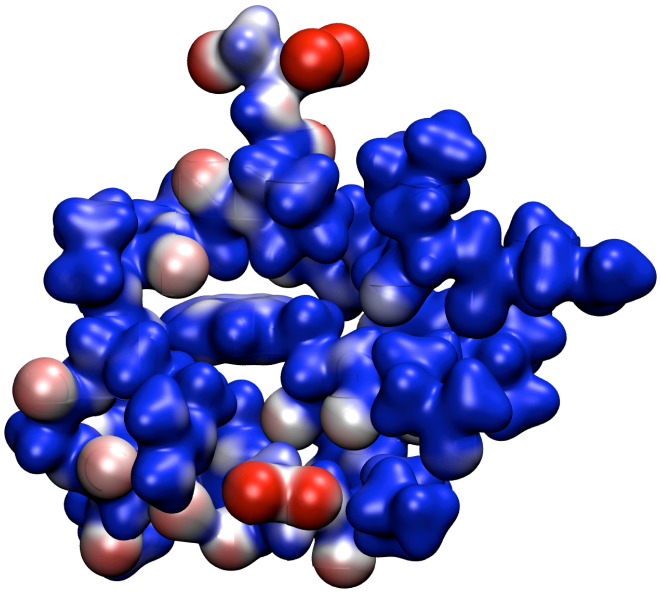

**Figure 2. MEP figure computed with FCM. MEP is computed on electron density isosurface cutoff 0.02. MEP is computed for GRDPAD=1,1,100. Compared to TCM there are a few barely noticeable stitches on the fragment cube boundaries.**

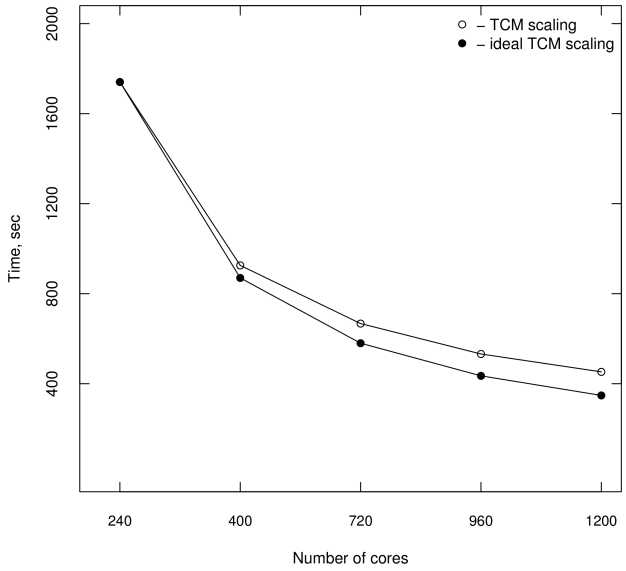


**Figure 3. TCM scaling curve.**

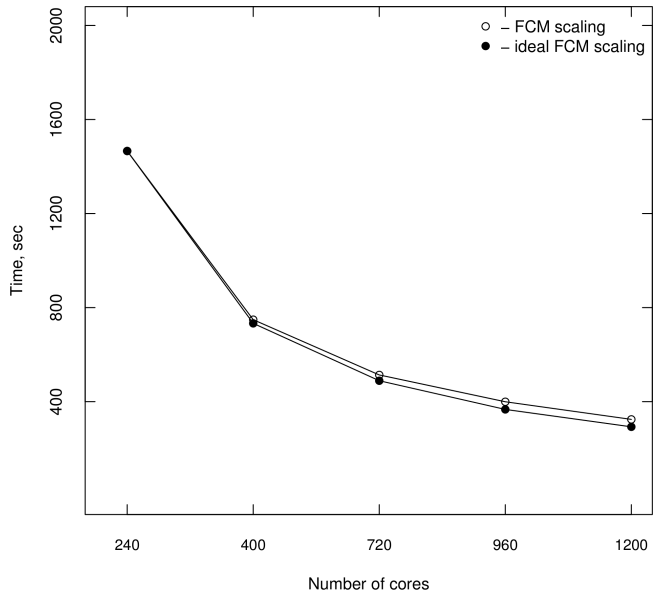


**Figure 4. FCM scaling curve.**

## 4. CONCLUSIONS

In this work, we developed and parallelized two new algorithms to compute and store MEP of large chemical systems which can be computed with FMO. We found that FCM is a more scalable solution and it also provides the shortest time to solution compared to TCM. Both TCM and FCM are significantly faster than MEP calculations with traditional QM calculations, at the same time TCM/FCM are more accurate than MEP computed with APBS.

## 5. ACKNOWLEDGMENTS

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