# Developing algorithms for parallel computing: Implementation in DelPhi

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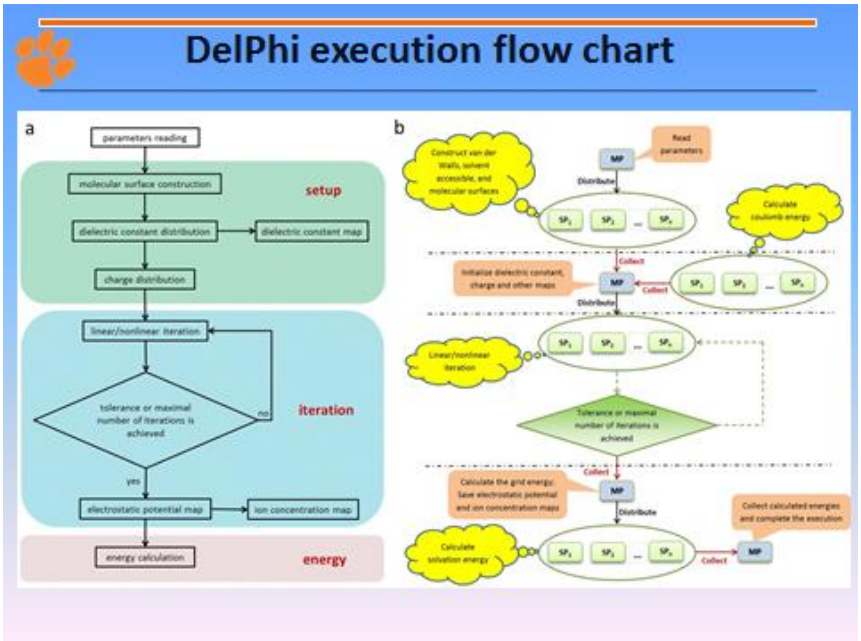
**Abstract**: Due to the enormous importance of electrostatics in molecular biology, calculating the electrostatic potential and corresponding energies has become a standard computational approach to study biomolecules and nano-objects immersed in water and salt phase or other media. However, the electrostatics of large macromolecules and macromolecular complexes, including nano-objects, may not be obtainable via explicit methods and even the standard continuum electrostatics methods may not be applicable due to high computational time and memory requirements. Here we report a new multi-level (parallelization is achieved at different levels of the algorithm) and interleaved (parallelization is implemented by interleaving the computational tasks) method, the MLIPB method, to parallelize standard methods for computing electrostatics potential and energies in the framework of the Poisson-Boltzmann equation. The MLIPB method is implemented in the popular software DelPhi and results in speedup of several folds without compromising accuracy or imposing additional assumptions. As a demonstration of efficiency and capability of this methodology, electrostatic potential distribution is calculated to illustrate the plausible pathways of electron transfer between the component complexes of the bovine mitochondrial supercomplex.

**MLIPB method**: The MLIPB method is graphically demonstrated in Figure on the left and is described in detail in the method section. Using Delphi as an example, the execution flow chart



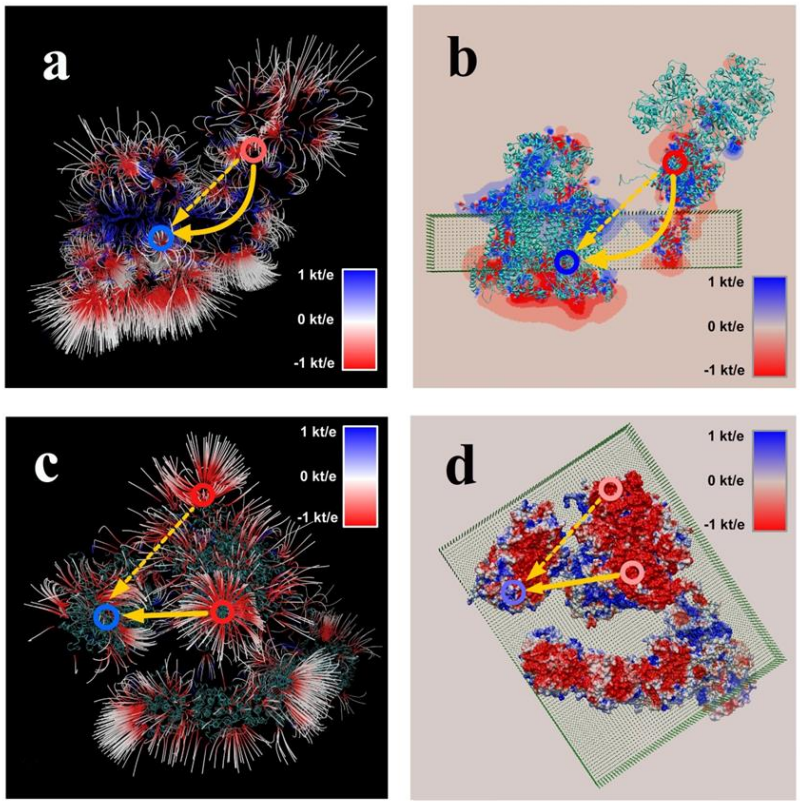

consists of 3 major tasks: surface construction, iteration and energy calculation as shown in Figure on the left. Each task is then divided into subtasks which are carried out in parallel by slave processors (green ovals in Figure on the left). Enhanced by the computational power of multiple processors, the MLIPB method reduces the

computational time of the parallelized DelPhi program several folds without compromising the accuracy or imposing additional assumptions. It should be clarified that the MLIPB method is not merely parallelization via the standard spatial domain decomposition; instead, the proposed algorithm delivers the solutions by applying specific techniques to each of the three major tasks and reflects the physical nature of the quantities being modeled. Thus, the construction of the molecular surface, being a geometrical problem, is parallelized via the methods of geometrical clustering and duplicated calculations at extended boundaries; the iterations of calculating the electrostatic potential, being long-range, are parallelized via a combination of numerical techniques and specific software design but without invoking any assumptions, and finally, the calculations of the corresponding electrostatic energies, being independent of the geometry, are parallelized via multi-threading. The resulting solutions obtained with the parallelized code, in terms of the electrostatic potential and energies, track the solutions obtained with the serial algorithm to double precision. Although such accuracy may not be biologically relevant for many current applications, keeping the parallelized and serial code consistent is important for future code developments.

**Applications**: Electron transfer pathway determination. Recent work revealed the 3D structure of bovine mitochondrial supercomplex and indicated that the arrangement of the components within the complex supports the solid state model of organization. The same investigation suggested the binding sites for various cofactors (ubiquinones and hemes) and a small protein electron carrier: cytochrome c. However, the specific pathways guiding the electron from one site to another are still under debate. Here we use the electrostatic potential and field maps calculated with MLIPB to reveal the role of electrostatics in the electron transport processes, and to suggest plausible pathways among the electron donor and acceptor sites.

The potential map was calculated with parallelized DelPhi and visualized using VMD viewer. Figure on the left shows the electrostatic field lines and the potential distribution in the case of the membrane being oriented perpendicular to the view. As pointed out in the original paper, the electron is supposed to be transferred via ubiquinol from 49-kDa and the PSST subunit near the first FeS-cluster above the membrane in complex I (indicated with red circle in the Figure) to the cytochrome b subunit in complex III (indicated with blue circle in the Figure). It can be seen in the Figure that electrostatic potential at donor and acceptor sites is quite similar and does not provide a driving force for the ubiquinone translocation.

The donor and acceptor sites are far apart and the ubiquinone is supposed to travel a long distance to deliver the electron. Two pathways were proposed: a pathway throughout the protein-membrane moiety of approximate length of 130Å (solid yellow arrow in the Figure) and a pathway involving run throughout the water phase of approximate length of 116Å (dashed yellow arrow in the Figure). The ubiquinone is very polar due to the partial charges of carbonyl oxygens which result in a strong electrostatic dipole. The preferable pathway for such polar particle would be to follow the electrostatic field lines. The Figure indicates that the two alternative pathways have completely different electrostatic properties. The pathway running throughout the protein-membrane moiety (solid yellow arrow in the Figure) practically does not require the ubiquinone to cross the electrostatic field lines. In contrast, the plausible pathway running through the water phase (dashed yellow arrow in the Figure) would require crossing dense electrostatic field lines, which would result in traveling in perpendicular direction to the electrostatic force. Because of that, we speculate that the pathway of ubiquinone translocation is much more likely to be via the protein-membrane moiety (yellow arrow in the Figure).




On the opposite side of the membrane, the binding of a small electron carrier protein, the cytochrome c, occurs. The original work 32 suggested two alternative binding sites of cytochrome c: the c1 subunit of complex III (shown in red circles in Figure) and sequential translocation to a binding site near two Cu atoms in subunit II of complex IV (shown in blue circle in Figure). The length of the path between the donor and the acceptor sites for first alternative binding site (shown with solid yellow arrow in the Figure) is about 110Å, while it is about 100Å (dashed yellow line in the Figure) if the cytochrome binds to the other site (other red circle in the Figure). Having in mind that cytochrome c is positively charged both binding sites (red circles in the Figure) provide favorable electrostatic interactions since both are

located at surface patches calculated to have negative potential. However, there is a clear difference in the electrostatic field lines with respect to cytochrome c translocation from c1 subunit to subunit II of the complex. The pathway involving the site on the underside of the c1 subunit (shown with solid yellow arrow in Figure) does not require the charged cytochrome to cross the electrostatic field lines, but to follow them. Charged particles, if driven by electrostatics, move in direction to the field lines. In contrast, the second plausible pathway (dashed yellow arrow in Figure) would require passing through dense electrostatic field lines, which is very unlikely. Based on this observation, we support the original hypothesis that the primary binding site of cytochrome c is indeed the site at the beginning of the solid yellow arrow in Figure. It should be reiterated that these results cannot be obtained by modeling individual subunits within the supercomplex, but require the entire structure to be used in the Poisson-Boltzmann calculations; a task for which the MLIPB method is particularly suitable.