

We developed a linear-scaling semiempirical quantum mechanical (QM) program (DivCon). Using DivCon we can now routinely carry out calculations at the fully QM level on systems containing up to about 15 thousand atoms. We also implemented a Poisson-Boltzmann (PM) method into DivCon in order to compute solvation free energies and electrostatic properties of macromolecules in solution. This new suite of programs has allowed us to bring the power of quantum mechanics to bear on important biological problems associated with protein folding, drug design and enzyme catalysis. Hence, we have garnered insights into biological systems that have been heretofore impossible to obtain using classical simulation techniques.

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## Structure/Function Studies of Proteins Using Linear Scaling Quantum Mechanical Methodologies

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We have developed and reported on a linear-scaling semiempirical quantum mechanical (QM) program (DivCon) and we have also parallelized this program in order to leverage more performance out of this program by running it in parallel. We can now carry out calculations at the fully QM level on systems containing up to about 1-15 thousand atoms in a matter of seconds to a few hours. We have implemented a Poisson-Boltzmann (PM) method into DivCon in order to compute solvation free energies and electrostatic properties of proteins. We are in the process of evaluating the performance of this method and we are using it to garner insights into how the electronic structure of a protein is affected by the presence of an implicit solvent. We have also developed a PB approach that incorporates charge transfer at the protein/water interface. We have coded up a semiempirical parameterization program in order to derive new parameter sets (Hamiltonians) that better model protein structure and energetics at the semiempirical level. In conjunction with this project we are also developing a semiempirical water model that is compatible with existing semiempirical parameterizations (e.g., PM3 and AM1). Since the inception of this grant we have begun to pursue other ideas that were not as obvious at the time we wrote the proposal. In particular, we are examining the utility of the combined DivCon/PB approach to determine NMR chemical shifts and coupling constants for biomolecules. Using these tools we have begun development of a "Quantum Bioinformatics" database to store quantum derived quantities (e.g., charges, bond orders, etc.) of biomolecules that can then be mined by interested users via a web based interface. We also developed a novel combined QM/QM method. In this approach we use the divide and conquer strategy to integrate semiempirical quantum mechanics with high-level density functional theory (DFT) or *ab initio* quantum mechanics. This allows us to carry out highly accurate QM calculations on the key region of an enzyme using, for example, DFT (e.g., enzyme active site, etc.), while treating the rest of the system with semiempirical QM methods. This is a novel approach, that will change the way in which we study complex biological systems.

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