ENERGETICS OF CALCIUM SELECTIVITY
A 3D CLASSICAL DENSITY FUNCTIONAL THEORY APPROACH

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ABSTRACT

Selectivity of a calcium channel is explored with three-dimensional density functional theory (DFT) of fluids (not electron orbitals). The model pore has millimolar Ca^{2+} affinity similar to the ryanodine receptor calcium channel. The four flexible aspartate side chains in the selectivity filter are modeled as four carboxyl groups (each as two independent, half-charged oxygen atoms) that are free to move within the selectivity filter, but cannot leave it. These oxygens coordinate the permeating ions. The energetics of selectivity are computed with three-dimensional DFT. Our approach of combining 3D DFT with state of the art computational techniques is unique in channel selectivity. Moreover, the DFT approach allows a natural decomposition of the energies involved in selectivity. The convolution-type calculations at the heart of the DFT are computed using a combination of fast transforms and analytical results. The software itself is built upon the PETSc framework from Argonne National Laboratory.

1. ALL-ATOM SIMULATION vs. DFT

Selectivity of a calcium-selective ion channel highlights the important characteristics that modeling techniques must have. Specifically, any technique must

- have three-dimensional *atomic detail:* in calcium channels, ions are distinguished by 4 glutamates or aspartates so the relevant atomic interactions must be included;
- cover experimental and *physiological timescales* (seconds): the time for ions to cross these channels is on the order of *micro*seconds, so any model must include *milli*seconds of time to have enough ion crossings to compute a statistically-significant current;
- cover experimental and *physiological concentration ranges* (sub-micromolar to molar): calcium channels operate with millimolar $[Ca^{2+}]$ on one side of the pore and micromolar $[Ca^{2+}]$ on the other, concentrations that are far too low to be modeled with MD, but concentrations that activate/control many other proteins;
- compute results in a short amount of computer time; the physics of selectivity can only be fully understood when many different conditions (e.g., ion species and concentrations) are computed, so ideally results should not take days to compute.

Density Functional Theory (DFT)

DFT is a thermodynamic theory in the grand canonical ensemble; given the particle interactions, averaging is done mathematically and equations are solved directly for averaged quantities (e.g., concentrations, energetics).

Advantages
- fast computation time (~1 hour)
- *any* concentrations are possible
- computes steady state results

Disadvantages: Atomic details and protein structures are difficult to include in DFT.

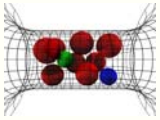
Molecular Dynamics (MD)

In MD, many ion trajectories are followed over a simulation and averaged at the end to determine quantities of interest (e.g., concentrations, energetics).

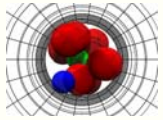
Advantages: Atomic details and protein structures are easy to include in MD.

Disadvantages
- slow computation time (days/weeks)
- large concentrations are necessary
- only covers nanoseconds of time

Here we show how we are implementing three-dimensional DFT and applying it to the 10 Å-long model calcium channel shown below.



- 4 glutamates are represented as 8 independent half-charged oxygen ions that are confined to the selectivity filter (red particles);
- the ions (blue and green particles) are charged, hard spheres (with crystal diameters).



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2. DFT of ions: Y. Rosenfeld. 1993. *J. Chem. Phys.* 98:8126-8148
   D. Gillespie, W. Nonner, and R.S. Eisenberg. 2002. *J. Phys.: Condens. Matter* 14:12129-12145.
3. PETSc: www.mcs.anl.gov/petsc

2. CHALLENGES OF 3D

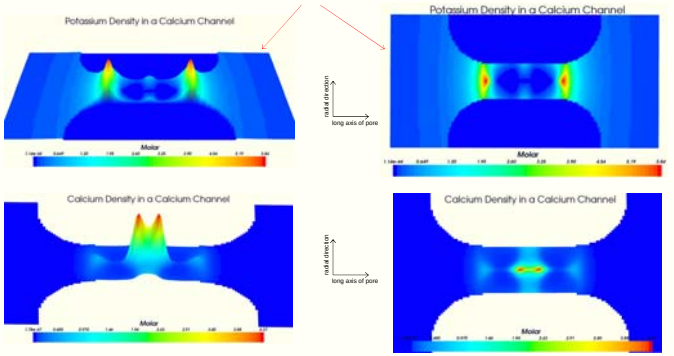
In DFT, we must resolve 0.1 Å features of proteins and ion concentration profiles in a system that is at least 100 Å long in each direction. In 1D, this leads to **thousands** of unknowns in the DFT equations that we must solve for (e.g., ion concentrations at each point of the grid). However, **in 3D, there are billions of unknowns to solve for**.

In a 3D system of DFT equations,

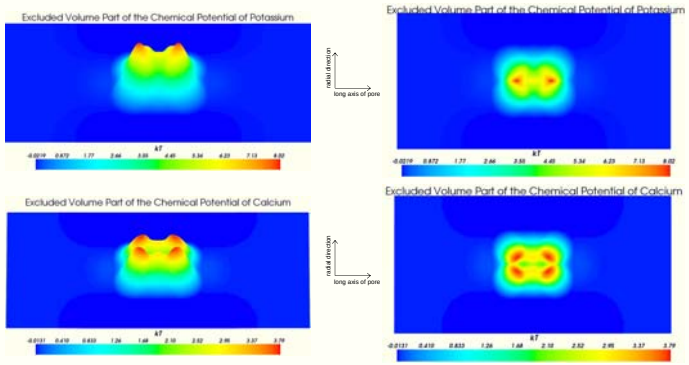
- large amounts of computer memory are needed because of the large number of unknowns;
- the equations become harder to solve because it takes significantly more iterations than in 1D;
- algorithms must be chosen carefully so that they scale linearly with system size, if possible (e.g., computation time increases by a factor 2 (and not 4+) if the number of grid points doubles;
- solution techniques become unstable even though they converge for the 1D system.

3. ADVANTAGES OF DFT

DFT computes the concentration profiles of particles that minimize the free energy of the system by computing the electrochemical potential of each particle species. These are shown below for $[K^+]$ = 150 mM and $[Ca^{2+}]$ = 0.1 mM. **Two different perspectives of the same plot are shown.**



DFT breaks the electrochemical potential into distinct components: ideal gas, excluded volume (entropic), and electrostatics. The entropic component for K^+ and Ca^{2+} are shown below.



4. OUR COMPUTATIONAL APPROACH

Solvers We have developed a specialized Picard iteration which avoids unphysical densities and optimally determines the step size for the new iterate. We have also used continuation in the bath density and external potential strength to enhance convergence to the solution.

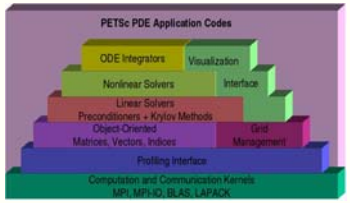
Scalability The heart of the DFT equations is a series of convolution integrals that we solve with Fast Fourier Transforms (FFT). This gives us a DFT solution algorithm that scales with the number of grid points (approximately): doubling the number of grid points, doubles the computation time; with a real-space technique, the computation time would grow by 4.

Stability We introduced a limiter into the computation of the hard-sphere functionals used to represent DFT solutions. This enabled stable computation of the equations for arbitrary 3D geometries.

5. PETSc FRAMEWORK

We have constructed the DFT simulator using the PETSc framework from Argonne National Laboratory. This greatly enhanced our productivity during development. PETSc provides:

- Cartesian grid support
- Linear and nonlinear algebraic solvers
- Automatic parallelism
- Optimized FFT through the FFTW library
- Multigrid support
- Portability to any system
- Technical support and maintenance
- Large and active user community
- Interfaces to F77, F90, C, C++, Python



Because we use the PETSc object model, we can change data formats, solvers, and FFT engines on the fly without recoding or recompiling. We will benefit from specially tuned implementations for different architectures, such the the Cray XT-4 or new GPUs, without ever changing our code.

6. CHECKING THE CODE

We have extensively tested our code to be sure that it is coded correctly and that the DFT includes the physics correctly:

- thermodynamic sum rules are satisfied, such as the equality of pressure at a hard wall and the summed density from a multispecies hard sphere liquid;
- comparison of results in 1D geometry against independent 1D-DFT results of the same system;
- in 1D problems, explicitly checking homogeneity in the other directions
- comparison of results against Monte Carlo simulations of the same system
- constant ion densities reproduce known results
- checking for electroneutrality of the system
- using two different methods to get the same answer (e.g., using both real- and Fourier-space convolution techniques)

7. CONCLUSIONS

3D-DFT has many advantages as a modeling technique:

- it computed results very quickly
- any concentrations of particles is possible
- computes infinite-time (steady state) results
- more atomic detail can be added

3D-DFT is a promising new modeling technique.