Periodic Boundary Conditions in Simulations of Proteins and Ions

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Calculations of the dynamics of proteins are of great importance to science, mathematics, and medicine. A large fraction of biological function, in health and disease, is produced by proteins, and the computation of the motions of atoms in proteins is thus a significant consumer of computer resources. The promise is that calculating protein function could have as large an impact on biology and medicine as computing properties of transistors has had on our digital technology.

Almost all protein function directly involves the electric field. A large fraction of the atoms of a protein have significant electric charge (~ 30% have more than 0.2 elementary charges). Almost all protein function depends sensitively on the presence and properties of ions (typically, sodium, potassium, calcium, and chloride ions, as well as trace concentrations of signaling molecules) in the solutions in and outside of cells. The charge of these ions creates an important component of the electric field that changes as the bulk concentrations and nature of these ions is changed, as it almost always in experiments and disease and often during normal function. Many proteins produce significant current flow, particular proteins called ion channels that are the 'valves of life' of particular importance in signaling in the nervous system and control of contraction of muscle, including cardiac muscle that allows the heart to function as a pump. Calculations and simulations must extend to nonequilibrium conditions to predict current. Ions are highly concentrated inside channels and active sites of proteins and there the small difference between the electric force and excluded volume force determines biological function, a difference that can only be computed if both forces are computed accurately.

Accurate and speedy computation of the electric field is thus as important for computing proteins as it is for computing transistors: significant precision is needed in computations of the electric field to determine even the qualitative properties of transistors.

The requirements of speed have dominated computations of proteins historically: computers have not always been as capable as they are today. Thus, approximations were introduced that restrict simulations to equilibrium and introduce significant errors in the computation of the electric field. These approximations need to be improved if the qualitative and quantitative properties of proteins and channels are to be computed as they vary with concentrations and types of ions, in health and disease, and as they carry current to perform their normal function.

The most obvious approximation that causes difficulty is that of periodicity. Early in the history of simulations, artificial periodicity was introduced into computations so simulations of ***un***charged systems were possible. Forces are relatively short range in uncharged systems, even if they are condensed phases, so boundary effects are often localized to regions near boundaries. In those cases, perturbations of boundary conditions are unlikely to have global or qualitative effects, and the perturbations produced by periodic boundary conditions can be easily checked to see if they are localized to regions near boundaries.

Simulations of proteins require treatment of the electric charges of the atoms of the proteins and the ions in water. It was natural, and perhaps necessary at first to use periodic boundary conditions to deal with the electric field, although it should be noted that related problems in semiconductors (1-4), and in the semiconductor tradition (5-8) are never treated with periodic boundary conditions because of the dominance of nonequilibrium effects. PNP devices at equilibrium (without flow of current) do not behave as transistors, for example.

Periodicity is incompatible with nonequilibrium calculations, at least as normally performed. Periodicity is also difficulty to reconcile with the fundamentally long range properties of the electric

field. Perturbations of boundary conditions in electrical systems typically have global and qualitative effects: checking that effects are localized is often impossible and always difficult in electrical systems.

Thus, the study, and probably the replacement of periodic boundary conditions is of the greatest importance in future simulations of proteins.

It is clearly necessary to evaluate the accuracy of present day approximations by making checks, e.g., checks to see that Gauss' law is actually obeyed by the charges and electric fields in the calculation on scales less than, comparable to, and larger than the periods of the periodic boundary condition (because all those scales are involved in the function of proteins). Direct comparisons should also be made with reduced problems that can be solved analytically in systems that are known experimentally to reduce to "Ohm's law" (e.g., 200 mM sodium chloride solutions at times less than say 0.1 sec), and to Fick's law (200 mM potassium chloride solutions at times longer than say 1 sec).

It is not clear whether existing periodic methods have sufficient accuracy, or can be modified to have sufficient accuracy, or whether existing semiconductor methods can be applied to ionic solutions (5-8) with sufficient accuracy and speed.

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