Mathematics and Molecular Biology

Life is different because it is inherited. All life comes from a blueprint (genes) that can only make proteins. Proteins are studied by more than one hundred thousand scientists and physicians every day because they are so important in health and disease. The function of proteins is on the macroscopic scale, but atomic details control that function, as is shown in a multitude of experiments. The structure of proteins is so important that governments have spent billions of dollars studying them. Structures are known in exquisite detail determined by crystallographic measurement in some 10^5 cases. But the forces that govern the movement and function of proteins are not visible in the structure. Mathematics is needed to compute both function and forces so comparison with experiment can be made. The mathematics must be multiscale because atomic details control macroscopic function. The device approach of engineering and physiology provides the dimensional reduction needed to solve the multiscale problem. Mathematical analysis of hundreds of experiments has been successful in showing how some properties of an important class of proteins—ion channels— work. I will present the Fermi Poisson approach started by Jinn Liang Liu and being developed much further by Dexuan Xie. The Fermi distribution is used to describe the saturation of space produced by crowded spherical ions. A fully consistent mathematical description produces macroscopic features of the atomic detailed structures that fit data in a wide range of conditions surprisingly well with a handful of parameters never changed.

Finite size ions can fill space with aâ€”not described by Poisson Boltzmann or PNP theories. Saturating concentrations are difficult to compute using inter-ionic forces, particularly in three dimensions. A Fermi-like distribution derived by J.-L. Liu (2013: J Comp Phys; 2015: Phys Rev E) describes saturation by spheres by the entropy of any mixture of any diameter spheres dissolved by spherical polarizable water molecules. Voids are used (and needed) to fill space. Correlations are described using Santangeloâ€™s mathematically consistent decomposition of Coulomb forces (Phys Rev E 2006) into near and far components, in the spirit of the Chandler-Weeks treatment of nonelectrolytes, using a fourth order partial differential equation that we call Fermi-Poisson theory, after reduction to a pair of second order partial differential equations with careful choice of boundary conditions. Important outputs of the theory are the close packing of spheres and saturation of concentration at high fields and the variation of dielectric coefficient with concentration and location. (1) Geometric singularities of molecular surfaces, (2) strong electric fields and resulting exponential nonlinearities, and the (3) enormous concentrations (> 10 M) often found where ions are importantâ€”in and near channels, nucleic acids, enzyme active sites, interfaces, catalysts, and electrodesâ€”pose severe challenges for converged, calibrated numerics. Wide ranging bath concentrations of Ca2+ (101 to 10-8 M) make matters worse. Challenges are met by methods used in computational electronics and numerical results are checked against exact solutions and Monte Carlo

simulations. Gramicidin and L-type calcium channels are computed in three dimensions and the spatial variation of water and ion density, electric potential and polarization are outputs of the calculation, along with IV curves, occupancy, and the AMFE. Fermi-Poisson allows successful calculation (with one parameter) of the activity of bulk and Na+Clâˆ’ solutions that have (more or less) parabolic dependence on salt concentration. Interstitial voids and screeningâ€”along with the steric effect and polarization of water moleculesâ€”play an important role in the first and second hydration â€˜shellsâ€™ surrounding these ions.