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Bob Eisenberg

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The classical Brownian motion theory used so imaginatively in the article by Eli Barkai, Yuval Garini, and Ralf Metzler (PHYSICS TODAY, August 2012, page 29) ignores fluctuations in the electric field. The theory allows fluctuation in number density, or concentration, of solutes in biological systems. But those solutes are almost always charged, whether they are the "bioions" Na^+, K^+, Cl^- nearly always present in the mixtures inside and outside cells or whether they are divalents, like Ca^{2+} or Mg^{2+}; nucleic acids, like DNA and RNA; the organic acids and bases of cell metabolism; or proteins, like ion channels and enzymes.

Fluctuations in the concentration of charged species must produce fluctuations in the electric field. Although such fluctuations are not present in the classical theory of Brownian motion, fluctuations are large and unshielded on the time scales used in simulations of molecular or Brownian dynamics. And not only will the fluctuations in electric field be different in different places, they are likely to have widely variable, highly nonlinear effects.

The diffusion produced by the fluctuations is an important determinant in numerous biological functions, such as resting and action potentials, cell motility, and enzyme activity. But diffusion and thermal motion contribute very differently to various functions because cellular function involves such a broad range of structures and molecules in which electric charge moves in different ways.

The thermal motion of coupled, charged systems, which include nearly everything inside a biological cell, is likely to be anomalous when interpreted in terms of the classical Brownian motion theory of uncharged particles. Classical theory should not be used to describe the random motion or macroscopic diffusion of charged molecules. A theory is needed that includes fluctuating electric forces and that computes those forces from the fluctuating density of all the charges.

Bob Eisenberg
(beisenbe@rush.edu)
Rush University Medical Center
Chicago, Illinois

Barkai, Garini, and Metzler reply: We thank Bob Eisenberg for his comment. Indeed, the role of electrostatic effects in the complex dynamics measured in macromolecularly crowded systems is an open question. Typically, biopolymers, and many artificial crowding agents, do carry surface charges. In physiological salt conditions, counterions screen electrostatic fields over nanometer length scales and are highly mobile, yet one perhaps cannot exclude force mediation between the macromolecules in solution due to electrostatic effects. An immediate consequence should be an increased effective size of biomacromolecules due to coordinated counterion layers.

The data from numerous single-particle tracking experiments in living cells and artificially crowded environments clearly show anomalous diffusion, including observations of weak ergodicity breaking and aging. Our analysis in terms of stochastic processes remains valid, independent of the specific—and likely complex—physical description based on first principles. That validity is due to the probabilistic nature of the stochastic approach: Although it captures the detailed dynamics of a system, it is not limited to specific kinds of interactions. Future studies of the effects of temperature and charges in crowded cells should prove interesting. For example, the influence of charges on the anomalous diffusion exponent α and the anomalous diffusion constant K_α in the mean squared displacement $\langle \mathbf{r}^2(t)\rangle \simeq K_\alpha t^\alpha$ remains an open challenge for both theory and experiment.

Eli Barkai
Yuval Garini
Bar-Ilan University
Ramat Gan, Israel
Ralf Metzler
(rmetzler@uni-potsdam.de)
University of Potsdam
Potsdam, Germany
Tampere University of Technology
Tampere, Finland