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| Dear Sir or Madam,I hope the manuscript speaks for itself. The most controversial discussion may be about the role of time scales in molecular dynamics simulations and the reality that MD simulations are chaotic. This part of the argument is NOT essential to the main thrust of the paper and I hope it is not allowed to distract you from the main point (see below). I include the discussion because it has not been sufficiently emphasized in the literature and it is important, at least in my view.I have avoided extensive documentation of the role of the difficulties in simulating the main properties of ionic mixtures like the solutions inside and outside cells, but there are many such papers in the physical chemistry literature and some are cited in my recent reviews. Similarly I have avoided extensive documentation of the role of calcium, and the importance of a handful of atoms in biological structures. In all cases, I can provide extensive documentation on a moment's notice.Lest the motivation be unclear, it is this: the enthusiasm for all atom simulations building on the magnificent structures revealed by x-ray crystallography is wonderful. But there is only so much such simulations can do. If they try to do the impossible, they will fail, and a great deal of effort will be diverted from what is needed, namely a multiscale analysis and simulation, in which the all-atom calculations play an important role. This is the approach long used in physics and engineering and will succeed (in many but not all important cases in biology) if it is used. But an all atom approach by itself without multiscale analysis cannot succeed in biology as it does not succeed in physics and engineering.Thank you for reading this far,Ever yoursBob Eisenbergmy CV and links to my publications are available at the following link if they are of interesthttps://ftp.rush.edu/users/molebio/Bob\_Eisenberg/Reprints/Webpages/Full.CV.pdf |