Comment on "Characterization of the tunneling conductance across DNA bases"

Johan Lagerqvist,[1] Michael Zwolak,[2] and Massimiliano Di Ventra[1,*]
[1]*Department of Physics, University of California, San Diego, La Jolla, California 92093-0319, USA*
[2]*Physics Department, California Institute of Technology, Pasadena, California 91125, USA*
(Received 19 December 2006; published 9 July 2007)

In a recent paper, Zikic *et al.* [Phys. Rev. E **74**, 011919 (2006)] present first-principles calculations of the DNA nucleotides' electrical conductance. They report qualitative and quantitative differences with previous work, in particular with that of Zwolak and Di Ventra [Nano Lett. **5**, 421 (2005)] and Lagerqvist *et al.* [Nano Lett. **6**, 779 (2006)]. In this comment we address the alleged discrepancies, showing that they come from a misrepresentation of our research. Further, we discuss in more detail the issue of geometric fluctuations previously investigated by us, and raised again in the work of Zikic *et al.* In addition, we point out erroneous comments made by Zikic *et al.* regarding the use of density functional theory calculations in transport.

DOI: 10.1103/PhysRevE.76.013901 PACS number(s): 87.15.−v, 82.39.Jn, 87.64.Aa

Recently, Zikic *et al.* [1] report the conductance of passivated DNA nucleotides located in between nanoscale gold electrodes using density-functional theory (DFT) within the known exchange-correlation (XC) functionals. In several places throughout their paper, they compare their findings with previously published results by us [2,3], and conclude that there are both qualitative and quantitative differences with their work. We point out that Zikic *et al.* misrepresent the existing literature by leaving out important details, and, further, make comparisons that are at odds with their own approach and conclusions. Also, some comments in their work raise general questions about the adequacy of static approaches to transport and the differences between such approaches. We address these issues below.

Zikic *et al.* correctly state that the electronic signature of nucleotides is strongly dependent on what they call "geometrical factors." Their work is an explicit demonstration of a well-known concept: the tunneling current depends exponentially on the width of the tunneling barrier, which is here formed by the reduced coupling between the electrodes and the nucleotide. For the case of DNA between electrodes, this means that changes in nucleotide orientation modify their coupling to the electrodes, and therefore can drastically change the electrical conductance. In addition, if one fixes the sugar-phosphate backbone position, the different sizes and geometries of the bases will cause them to be more or less close to the electrodes, and therefore cause a difference in their relative conductance. Zikic *et al.* seem to indicate that these conclusions are qualitatively and quantitatively different from ours. Instead, we understood this fact and we stated explicitly in Ref. [2] that "[how well the highest occupied (HOMO) and lowest unoccupied molecular orbital (LUMO)] states couple to both electrodes determines the overall magnitude of the relative currents [between the bases]." In addition, well prior to their work, recognizing the importance of geometrical factors, we explored this issue in much more detail by investigating realistic structural fluctuations in Ref. [3].

Due to the importance of geometry in the conductance (and relative conductance) of the different nucleotides, one cannot quantitatively compare the results of Ref. [1] with those of Refs. [2,3]. In addition, Zikic *et al.* state that their DFT calculations give what they call mutually consistent results with different exchange-correlation functionals. By *mutually consistent* they mean that the ordering of the current magnitudes is the same regardless of the XC functional used. Consistency may hold true for the current averaged over all their configurations and at small bias, but it is obvious from their own work that it does not hold true otherwise. For instance, by examining either the conductance or the current in their Figs. 8, 9, 10, 11, or 12, one can extract essentially any desired ordering in the nucleotides' conductance.

Thus, we point out that it is incorrect for them to claim that our results in Ref. [2] are not consistent with our results in Ref. [3] based on the change in conductance ordering. This claim leaves out crucial facts that are clearly written in our papers: from one paper to the other we did change (i) the bias, (ii) the electrode spacing, and (iii) the nucleotide configurations. Any one of these changes can modify the values of the conductance, and even the relative conductance.

Zikic *et al.* also fail to mention that in our second work, Ref. [3], we are sampling over more than 1000 nucleotide configurations. Thus, one expects that by sampling over a nonrandom subset of configurations—as they do in their work by only varying one angle—one can obtain different orderings of the conductance. In fact, the alleged discrepancies instead highlight and reinforce one of the main conclusions of our work (see Ref. [3]): in order to successfully sequence DNA via transverse electronic transport, each device has to be first calibrated by reading a known strand, such that the current distributions for all four nucleotides can be obtained. These distributions are unique to *each and every* device, and are determined by the microscopic geometry of the pore and electrodes.

We now want to turn to two important questions: (1) why is it that geometric factors are important in the conductance of nucleotides? and (2) how can "distinguishability survive averaging over possible conformations of single stranded DNA"?

The answer to the first question is something not stated by either Zikic *et al.* or us. There are two factors that enable one

*diventra@physics.ucsd.edu

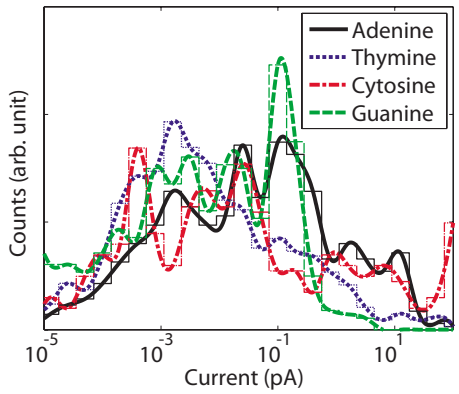

FIG. 1. (Color online) Probability distributions of currents, for unstabilized poly$(dX)_{15}$ as the strand propagates through a pore with embedded electrodes. X is adenine, thymine, cytosine, and guanine for the solid black, dotted blue, dash-dotted red, and dashed green curves, respectively. The thin lines show the actual current intervals used for the count, while the thick lines are an interpolation.

to focus mainly on the geometry of the nucleotide-electrode configuration: (1) the HOMO and LUMO energies of the different bases are close in energy compared to their distance from the gold Fermi level; (2) for all four bases, the HOMO and LUMO states are delocalized around the base, and thus one can substitute the atomic structure of the bases as an approximate representation of the spatial extension of the molecular states. Contrary to the conclusions of Zikic *et al.*, one cannot say from their results that the HOMO and LUMO states are less important than geometry, only that, when comparing molecules of similar factors (1) and (2), the geometry would be the dominant factor. Further, this leads to a very important conclusion: in the case of sensors to detect the DNA bases using electrical currents, the nucleotide configurations have to be at least partially controlled. In terms of a nanopore-based device, one way to do this is to use a transverse electric field induced by the transverse electrodes or by an external capacitor across the whole device [3]. Of course, there will be other important factors to consider besides geometric fluctuations of the nucleotides themselves, including the effects of ions.

The answer to the question of how the distinguishability survives by averaging over possible conformations of ssDNA can be found by examining, in the context of a nanopore-based device, the geometric configurations of DNA as it translocates through a pore in the absence of any control. This is the basis of our work in Ref. [3]. The geometrical fluctuations cause the different nucleotides to have large fluctuations in the value of their current, as shown in Fig. 1. With no stabilizing transverse field added, the current distributions for a given set of initial conditions of the different nucleotides (calculated as reported in Ref. [3], for an electrode bias of 0.1 V and an electrode spacing of 15 Å) span several orders of magnitude, and have significant overlap, as shown in the figure. These large fluctuations will cause the bases to be essentially indistinguishable. However, in the presence of a transverse field that is much larger than the driving field, the nucleotides can be stabilized, and thus distinguished by a relatively modest ensemble measurement [3].

We conclude by discussing the differences in using a tight-binding (TB) approach compared to DFT calculations for the problem at hand. Similarly to the DFT approach within any available XC functional, a TB approach has its own limitations. Nonetheless, in the present context it has a clear advantage. In particular, it satisfies two conditions required by any method to investigate the relative conductance of the nucleotides. First, since the coupling (i.e., geometry) is the large determining factor in the relative conductance, one needs to adequately reproduce the spatial distribution of the molecular wave functions. Second, the energies of the molecular states need to be calculated fairly accurately. For our chosen TB parameters, both of these quantities compare well with results of DFT calculations for isolated nucleotides. This, together with the reduced computational complexity of TB, allows us to look at many different geometric configurations to more realistically capture structural fluctuations that would be present in an experiment.

In addition, there is no reason to believe that DFT, within the XC functionals used by Zikic *et al.*, can represent more accurately the nucleotide-electrode coupling compared to TB in this particular geometry, where the nucleotides are not covalently bonded to either electrodes [4]. Indeed, the exchange-correlation functionals employed in Zikic *et al.*'s work do not include the long-range van der Waals interactions that are present in this weak-coupling case. The fact that the two different XC functionals employed by Zikic *et al.* show order of magnitude differences in the conductance may be a result of this problem.

Finally, Zikic *et al.* state that "As far as the self-consistency of the electron transport is considered, this leads to a procedure that is asymptotically exact in limit of zero electric bias." This is a misconception about static approaches to transport, and would not be correct even if one had the exact *static* XC functional. Two of the present authors (M.Z. and M.D.) have shown [5] that, even in the limit of zero bias, with the inclusion of self-consistency, the current obtained using static DFT does not include dynamical many-body effects, which can only be captured by using time-dependent approaches such as time-dependent DFT [6]. In Ref. [5] we have evaluated these dynamical corrections specifically for the local density approximation functional; however, the statement is true regardless of the static XC functional chosen: no static XC functional (even the exact one) can fully capture the true nonequilibrium nature of transport problems. Incidentally, these dynamical many-body effects are also absent in the TB static approach to transport that we have employed.

[1] R. Zikic, P. S. Krstić, X.-G. Zhang, M. Fuentes-Cabrera, J. Wells, and X. Zhao, Phys. Rev. E **74**, 011919 (2006).
[2] M. Zwolak and M. Di Ventra, Nano Lett. **5**, 421 (2005).
[3] J. Lagerqvist, M. Zwolak, and M. Di Ventra, Nano Lett. **6**, 779 (2006).
[4] See, e.g., H. Rydberg, M. Dion, N. Jacobson, E. Schroder, P. Hyldgaard, S. I. Simak, D. C. Langreth, and B. I. Lundqvist, Phys. Rev. Lett. **91**, 126402 (2003).
[5] N. Sai, M. Zwolak, G. Vignale, and M. Di Ventra, Phys. Rev. Lett. **94**, 186810 (2005).
[6] M. Di Ventra and T. N. Todorov, J. Phys.: Condens. Matter **16**, 8025 (2004).