# Reply to "Comment on 'Characterization of the tunneling conductance across DNA bases' "

Radomir Zikic,[1,*] Predrag S. Krstić,[1,†] X.-G. Zhang,[2,3] Miguel Fuentes-Cabrera,[2,3] Jack Wells,[2,3] and Xiongce Zhao[3]
[1]*Physics Division, Oak Ridge National Laboratory, P. O. Box 2008, Oak Ridge, Tennessee 37831, USA*
[2]*Computer Science and Mathematics Division, Oak Ridge National Laboratory, P. O. Box 2008, Oak Ridge, Tennessee 37831, USA*
[3]*Center for Nanophase Materials Sciences, Oak Ridge National Laboratory, P. O. Box 2008, Oak Ridge, Tennessee 37831, USA*
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Lagerqvist *et al.*'s Comment regarding the calculation of the transverse conductance of a single-strand DNA heteropolymer translocated through a nanogap between two metal electrodes fully confirms the main conclusions of our study [Phys. Rev. E **74**, 011919 (2006)]. In the absence of resonant tunneling, the sensitivity to geometrical factors and the uncertainty in the density functional theory model, which is used in our study and is the basis for the parametrization of the model used by Lagerqvist *et al.*, raises doubt about the utility of static-bias measurements for DNA sequencing. A possible scheme discussed by Lagerqvist *et al.*, the stabilization of geometry by an applied strong transverse voltage (1 V), is outside the applicability range of the near-equilibrium theory they (and we) used. More advanced theories and precise gap measurements are needed to resolve these issues.

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The main disagreement between our work [1] and that of Zwolak and Di Ventra [2] is their belief that it is possible to distinguish DNA bases via differences in dc conductance even within the linear response regime, in contrast to our conclusion that, in the absence of resonant tunneling (under low voltages in this type of geometry), geometrical factors will dominate the electron transport rather than the molecule's electronic structure. Our calculations demonstrate that this dominance occurs through the exponential tails of the electrode states near the Fermi energy, which at low voltages can be largely independent of both the orbitals localized within the molecule with energies far away from the Fermi energy and of their couplings to the electrodes. As a result, it will be difficult to achieve single-base resolution due to the geometrical uncertainty (e.g., the size of the molecule and the relative orientation between the molecule and the electrodes). The myriad array of possibilities to vary the electrode and nucleotide configurations [3], as enumerated by Lagerqvist *et al.* in their Comment [4], which can lead to vastly different orders of the nucleotide conductances, only serves to highlight our point. The bias voltage dependence may be the only variable in this discussion that could be connected to electronic structure. However, as we emphasized in our paper [1], our model is a linear-response theory, similar to the one used by Lagerqvist *et al.* in [2,3]; therefore the bias voltage dependence obtained from this model should be viewed with some skepticism.

The idea by Lagerqvist *et al.*, communicated in their recent Letter [3] and repeated in their Comment [4], that it would be possible to sequence DNA nucleotides via transverse electronic transport by measuring distributions of currents for each base is ambitious. Central to their proposed protocol is the concept that a reference current distribution can be measured for each of the four nucleotides within any practical sequencing device, and that this reference would be unique for that specific device. To our knowledge, the uniqueness of such current distributions has not been proven or demonstrated within a real or model single-strand DNA heteropolymer. In general, under a range of experimental conditions, we doubt that such measured distributions would be unique, e.g., due to the presence of nucleotide-nucleotide interactions. To us, achieving unique and reproducible measurements for DNA nucleotides within DNA heteropolymers should be a high priority for those wishing to pursue transverse electrical transport for sequencing DNA.

As for the accuracy of the respective models and interpretation of their works [2,3], we stressed in our paper [1], regarding the quantitative disagreement between our results, that "it is not possible to conclude with certainty, as the main information on the electronic structure of the electrode-molecule system, i.e., the alignment of the Fermi level with the electronic structure, is not communicated in Refs. [2,3]." No quantitative information is given in Refs. [2,3] about the alignment of the Fermi level with the electronic structure of the molecule. On the other hand, we have included in our paper all information needed to reproduce our calculations. Lagerqvist *et al.* are welcome to check our calculations.

There does not exist a viable density functional theory (DFT) functional that well for both metallic electrodes and organic molecules. Our study [1] contrasted two different functionals in order to illustrate the deficiency of the DFT in this regard. We do not see any basis for the claim that a tight-binding (TB) model parametrized from a DFT calculation is numerically more reliable than direct DFT calculations. Lagerqvist *et al.* [4] raised the issue of van der Waals forces, for which the TB model is at least equally unsuitable. In our study, we did not relax the atomic positions; therefore the van der Waals force was not a factor in our model. On the other hand, the DFT certainly handles tunneling much better than the TB model.

Sai *et al.* [5] proposed that there is a correction term in the DFT exchange-correlation (XC) functional to the static local density approximation (LDA) that can be derived from the time-dependent DFT (TDDFT) and does not vanish in the

*Present address: Institute of Physics, Pregrevica 118, 11080 Belgrade, Serbia.
†Corresponding author.

 

dc limit. In their words, "the dynamical theory includes an additional XC field beyond ALDA—a field that does not vanish in the dc limit." (ALDA is the adiabatic LDA, which is the LDA of the TDDFT.) This extra XC functional also contributes to a dynamic voltage, even in the linear-response regime. This correction is not to the static DFT, which presumably could have the "exact" XC functional, but to the static DFT LDA, which makes the local approximation to the exact XC functional. Nonlocal corrections to the LDA are not new [6], and do not contradict our statement that the linear-response theory based on DFT becomes exact in the zero-bias limit.

In conclusion, the Comment by Lagerqvist *et al.* [4] provides yet another piece of supporting evidence that transverse dc conductance of DNA nucleotides depends critically on their geometric configuration, which will more than likely thwart any attempts to distinguish individual nucleotides through measurements of such conductance. No definitive conclusion can be made about the sequencing techniques with static transverse bias.

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