Supporting Material:

Electrostatic channeling in *P.falciparum* DHFR-TS: Brownian dynamics and Smoluchowski modeling

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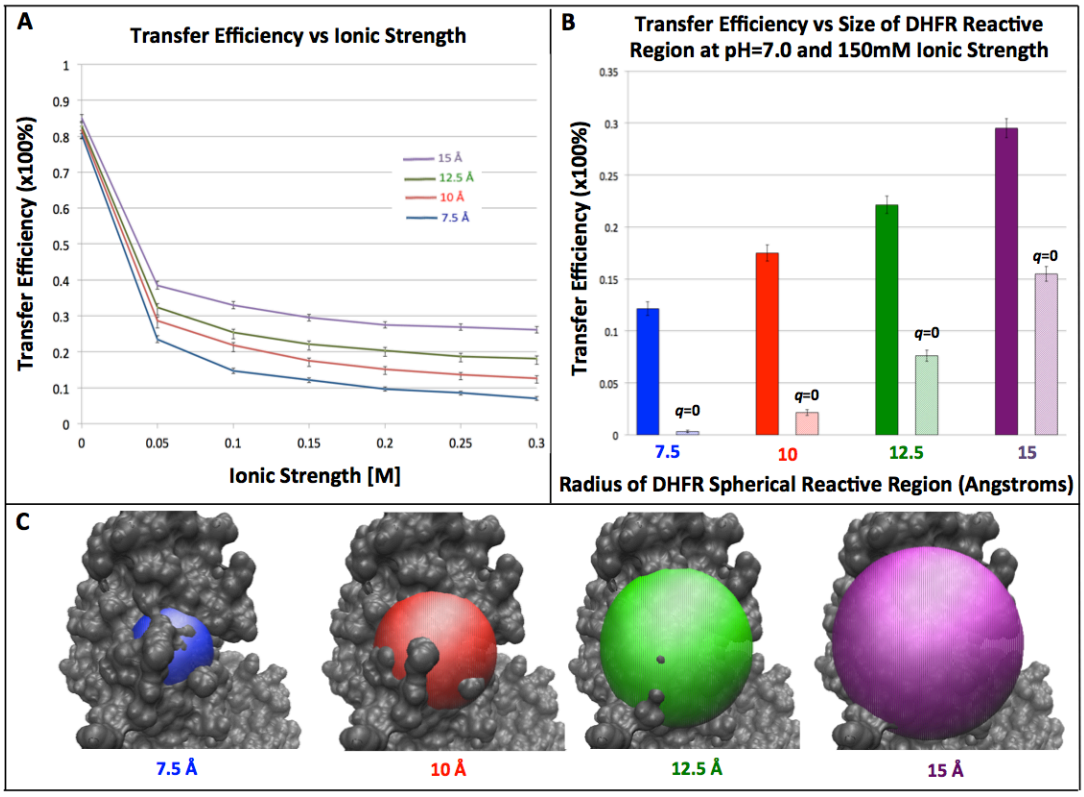
A: Brownian Dynamics of DHFR Reactive-site Size

Because experimental evidence indicates that *L. major* DHFR-TS has a dihydrofolate transfer efficiency of approximately 80% (1), Brownian dynamics simulations were performed on a variety of *L. major* systems each with a unique active-site definition (as defined by a sphere centered at an atom in the approximate "middle" of the solvent-accessible active-site). The "12.5 angstrom" active-site size resembles the definition used in *L. major* DHFR-TS BrownDye simulations, which were shown to reproduce experimentally predicted channelling efficiency of this system. As shown in Fig. S1 below, increasing the size of the DHFR reactive-region increases the predicted channelling efficiency. We selected the 12.5 Angstrom-sized reactive zone for *P. falciparum* for reasonable comparison with *L. major*.

Figure S1: Brownian Dynamics of DHFR Reactive-Site Size for *Plasmodium falciparum* DHFR-TS



B: List of Basic Residues Assigned Zero Charge in "Charge-Removed" System

Note: Residue ID's below are from PDB 1J3I and all atoms in these amino acids were assigned a charge of zero for both monomers of the bifunctional *P. falciparum* DHFR-TS. These residues were first postulated by (2) as possibly being involved in forming two electropositive "paths" connecting the TS and DHFR-TS active sites and are listed below:

path 1: 19, 28, 49, 114, 115, 117, 122, 373, 377, 402

path 2: 19, 49, 56, 114, 115, 117, 122, 345, 416, 417, 457, 464, 471, 530, 575, 581

Supporting Citations

1. Elcock, A. H., M. J. Potter, D. A. Matthews, D. R. Knighton, and J. A. McCammon. 1996. Electrostatic channeling in the bifunctional enzyme dihydrofolate reductase-thymidylate synthase. Journal of molecular biology 262:370-374.
2. Yuvaniyama, J., P. Chitnumsub, S. Kamchonwongpaisan, J. Vanichtanankul, W. Sirawaraporn, P. Taylor, M. D. Walkinshaw, and Y. Yuthavong. 2003. Insights into antifolate resistance from malarial DHFR-TS structures. Nat Struct Biol 10:357-365.