Abstract Submitted
for the MAR15 Meeting of
The American Physical Society

Optical observation of correlated motions in dihydrofolate reductase MENGYANG XU, KATHERINE NIESSEN, State Univ of NY - Buffalo, JAMES PACE, VIVIAN CODY, Hauptman-Woodward Medical Research Institute, ANDREA MARKELZ, State Univ of NY - Buffalo — Enzyme function relies on its structural flexibility to make conformational changes for substrate binding and product release. An example of a metabolic enzyme where such structural changes are vital is dihydrofolate reductase (DHFR). DHFR is essential in both prokaryotes and eukaryotes for the nucleotide biosynthesis by catalyzing the reduction of dihydrofolate to tetrahydrofolate. NMR dynamical measurements found large amplitude fast dynamics that could indicate rigid-body, twisting-hinge motion for ecDHFR that may mediate flux [1]. The role of such long-range correlated motions in function was suggested by the observed sharp decrease in enzyme activity for the single point mutation G121V, which is remote from active sites[2]. This decrease in activity may be caused by the mutation interfering with the long-range intramolecular vibrations necessary for rapid access to functional configurations. We use our new technique of crystal anisotropy terahertz microscopy (CATM)[3], to observe correlated motions in ecDHFR crystals with the bonding of NADPH and methotrexate. We compare the measured intramolecular vibrational spectrum with calculations using normal mode analysis. 1. Cameron C.E. and Benkovic S.J., *Biochemistry*, 1997. 36(50): p. 15792-15800. 2. Bhabha G., et al., *Nat Struct Mol Biol*, 2013. 20(11): p. 1243-9. 3. Acbas, G., Niessen K.A., Snell E. H., and Markelz A.G., *Nat Commun*, 2014. 5, 3076.

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Date submitted: 14 Nov 2014 Electronic form version 1.4