This submission is replacing SES15-2015-000018, which was warned for exceeding the character limit. Abstract Submitted

for the SES15 Meeting of
The American Physical Society

**Roco4 kinase crystal structures fail to capture expected dynamical behavior of LRRK2, a protein implicated in Parkinson's disease**[1] SIRUI MA, Vanderbilt Univ, HECTOR VELAZQUEZ, Oak Ridge National Laboratory — Leucine-rich repeat kinase 2 (LRRK2) is a multi-domain protein implicated in Parkinson's disease (PD). Understanding LRRK's contribution to pathogenesis requires study of the kinase domain. Unfortunately, such studies are complicated by the unavailability of LRRK2 crystal structures. Previous studies have shown that humanized Roco4 kinase may be a suitable surrogate for LRRK2 in chemical investigations. Our study assesses the dynamical behavior of humanized Roco4, compared to that of a homology model, by molecular dynamics simulations. We attempt to capture conformational changes of the activation loop from active to inactive forms, a key feature in the regulation of LRRK2 kinase activity. Our results indicate that simulations of humanized Roco4 fail to capture these conformational changes. Such a finding suggests that Roco4 may not be a suitable model for computational LRRK2 studies. We intend to conduct additional studies to further elucidate Roco4's performance as a LRRK2 mimic, though our initial results call into question its viability. A validated LRRK2 model is crucial for the development of drugs that can treat or even cure PD, and predictions of increasing disease frequency further compound the importance of LRRK2 research.

[1]Roco4 kinase crystal structures fail to capture expected dynamical behavior of LRRK2, a protein implicated in Parkinsons disease

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Date submitted: 31 Aug 2015 Electronic form version 1.4