

Editorial Note: This manuscript has been previously reviewed at another journal that is not operating a transparent peer review scheme. This document only contains reviewer comments and rebuttal letters for versions considered at *Nature Communications*.

REVIEWERS' COMMENTS

Reviewer #2 (Remarks to the Author):

This is a revised version of a paper that I have previously reviewed for NCB. The authors have done a great job of revising the manuscript, and I believe that the simpler InfleCS clustering is cleaner than the MSM analysis presented originally. [Incidentally, I still find the question of exchange rates very interesting to understand, but realize that an in depth analysis of this would be well beyond this current work]. I am still not 100% convinced that the two states (or something very similar) seen in the crystal are sampled in solution, but I nonetheless agree that this is a very solid step forward, and that the data presented certainly points to an interesting and dynamic system. Congrats to the authors for a very interesting piece of work.