Please also make these changes:  
  
1. TOC image: Fix the size per journal guidelines (2 in x 2 in) corrected  
  
2. References: In both the main file and the supporting information, fix the style of all references to use JPCL formatting (check all references carefully) corrected  
  
3. Abstract: Shorten the abstract to 150 words or fewer new word count 145  
  
4. Supporting information: Title in SI must match title in main file corrected  
  
We ask that you submit your revision within two weeks. Here at JPC Letters we try to expedite the processing of your manuscript. Your prompt response is greatly appreciated.

Reviewer(s)' Comments to Author:  
  
Reviewer: 1  
  
Recommendation: This paper is publishable subject to minor revisions noted.  Further review is not needed.  
  
Comments:  
This is a well-conceived study that presents a case study used to validate an approach (called SEEKR) for MD-based predictions of binding kinetics of small ligands. The dataset is restricted, but coherent. The manuscript is well written and technically sound. The proposed approach is able to predict the correct trend of the kinetics observables (kon, koff) while also being able to return thermodynamic values for ligand binding. And, all this is obtained with a considerable acceleration compared to plain MD.   
While I am not an expert in milestoning, I appreciate the exploitation of advanced MD methods for enhanced sampling to design novel approaches to predict binding kinetics, which is a timely relevant problem for drug optimization (De Vivo et al, J Med Chem 2016, Perspective). I have no major concerns. The manuscript reports a nice piece of work and will contribute to the discussion on the prediction of binding kinetics. Of course, the ultimate validation will be the prospective application of SEEKR to predict kinetics of ligands, but I assume the authors are already working in this direction.  
  
One minor: In general, in general – is repeated, on page 10—removed second instance  
  
  
Additional Questions:  
Urgency: Top 10%  
  
Significance: Top 10%  
  
Novelty: High  
  
Scholarly Presentation: High  
  
Is the paper likely to interest a substantial number of physical chemists, not just specialists working in the authors' area of research?: Yes  
  
  
Reviewer: 2  
  
Recommendation: This paper is publishable subject to minor revisions noted.  Further review is not needed.  
  
Comments:  
The manuscript titled “Quantitative Ranking of Ligand Binding Kinetics with a Multiscale Milestoning Simulation Approach” describes the application of SEEKR method in ranking a series of 7 small cyclodextrin ligands by their kinetic and thermodynamic binding parameters. Although, the SEEKR method, which combines Brownian dynamics and Molecular dynamics simulations using Milestoning theory, has been described previously, the current work demonstrates its effectiveness in ranking koff and DeltaG of  the small molecules with reduced computational cost compared to brute force MD.  The kon values of the system show modest variation and neither their absolute or their relative values can be predicted with SEEKR. The system studied (beta-cyclodextrin) is a standard model system which is well defined and has the advantage that it allows the authors to investigate the influence of e.g. considering two binding routes individually or together in the calculations. On the other hand, while the results look encouraging, the extent to which they will translate to more complex systems such as protein drug targets is unclear.    
The authors have systematically compared the results for two different force fields used: GAFF and Q4MD, and this comparison could be useful for future studies with cyclodextrins.  The authors have also described the best practices that should be followed when using the SEEKR approach for other systems. The work is comprehensive and well-written, and the length of the manuscript adheres to the requirements of the journal’s guidelines. With the growing interest in evaluating kinetic parameters in drug-design studies, this manuscript should be of interest for the drug-discovery community.  
There are a few minor corrections that need to be addressed:  
  
Figure1a) The labels for the milestone distances are too small to read. Increased distance font size, while still preventing overlap/clutter  
  
Supporting info, page 3: The authors mention that from equilibrium simulation of 160 ns, configurations were selected every 2ns (or is it 0.2 ns?): so, this results in 80 configurations (not 800) per milestone? 0.2ns is correct   
  
Supporting info, page 4: 8000 reversals or 800 reversals? 8000 is correct—800 configurations times 10 trajectories per configuration  
  
The spelling of “bootstrapping” should be corrected throughout the manuscript corrected all instances  
  
  
Additional Questions:  
Urgency: High  
  
Significance: High  
  
Novelty: Moderate  
  
Scholarly Presentation: Top 10%  
  
Is the paper likely to interest a substantial number of physical chemists, not just specialists working in the authors' area of research?: Yes