**DETAILED RESPONSE TO REVIEWERS’ COMMENTS**

We are enclosing a revised version of our manuscript, “Learning to Predict Chemical Reactions” submitted to JCIM. The revised version takes into account all the comments made by the anonymous reviewers whom we thank for helping us to improve the manuscript. A detailed reply to the reviewers’ comments (*in italics*) with the corresponding list of main changes to the manuscript can be found below.

**REVIEWER 1**

*Recommendation: Publish after minor revisions noted.*

*Comments:  
The manuscript “Learning to Predict Chemical Reactions” by Kayala, Azencott, Chen, and Baldi describes a machine-learning model for the prediction of products of organic reactions.  This represents an extension and an improvement of the rule-based expert approach described in publications such as “No Electron Left Behind: A Rule-Based Expert System To Predict Chemical Reactions and Reaction Mechanisms” by Chen and Baldi (J. Chem. Inf. Model., 2009, 49(9), 2034-2043).  This approach provides a middle ground in terms of detail and sophistication that will likely find utility in “validating synthesis design, creating virtual libraries, or elucidating plausible mechanistic pathways,” as the authors note.  
  
The work described herein is an improvement upon the solely rule-based systems in that it attempts to circumvent the limitations of those knowledge-based approaches to the prediction of reaction products.  Significantly, this work enhances the generality of the tool and overcomes a problematic feature of the Reaction Explorer system, which is arduous to update with new transformations.  The key features of the new work include the use of: a simplified and idealized molecular orbital approach; a dataset to mine; and a statistical ranking approach to decision making.  The problem-solving method described by the authors offers a significant advantage in that it is not restricted to problems similar to those already catalogued by the system.  
  
The authors thoroughly describe how the idealized molecular orbitals are conceptualized, and they explain the implementation and validation of the machine learning system.  The system for defining molecular orbital interactions was clearly articulated, notably through Figure 4, and the application of this system to a reaction was nicely illustrated in Figure 5.  In Figure 5, I wonder if it would be possible to have the first mechanistic arrow on the enolate better illustrate the deposition of electrons between oxygen 1 and carbon 2.  Currently, the arrow almost appears to indicate an attack on the carbon-carbon pi bond.*

This is an excellent point. We are well aware of this problem which is produced by the third-party (ChemAxon) depiction software that we use. We have notified ChemAxon of this problem several times and hope that it will be corrected in the near future. For the time being, we have manually fixed the placement of all the arrows in the Figure of the paper. Thus Figure 5 has been fixed. Obviously manual fixes are not possible for the Web server version which at this point in time must rely on ChemAxon’s depiction tool.

*Similary, in Figure 9, I wonder if the precision of the arrows can be tightened a bit.  Specifically, the arrow from the enolate pi bond appears to attack a carbon-carbon single bond, rather than the carbonyl carbon.  Although it is less of a problem, it would also be helpful if the collapse of the tetrahedral intermediate clearly showed the oxygen atom’s lone pair collapsing in between the oxygen and the adjacent carbon to form the carbonyl pi bond.*

Figure 9 has been fixed, similarly.

*The ability of the system to rank viable mechanistic outcomes will be exceedingly useful for synthetic chemists who may consider subtle steric and electronic effects within a particular system that might sway the reaction outcome to one considered less probable in a structurally related system.  
  
On page 29, line 10, I believe that the “7” has been inadvertently omitted from “bromo-hept-1-en-2-olate.”  One would also probably want to be consistent in regard to the use of a hyphen between the “bromo” and “hept” or “oct”  in lines 10-12.  Typically, hyphens are not used to separate letters, but only to separate letters from numbers.  Note that this latter comment would also apply to lines 52-53 in the Figure caption on the same page.*

We thoroughly agree with the reviewer and have fixed these issues to follow standard usage.

*I’m not qualified to comment on the computational methods themselves.  However, as a synthetic organic chemist and an educator, I can say that this appears to be an important step forward which will help to correct a noticeable dearth of useful computational tools for research and teaching.  The high level of accuracy allows for the prediction of multi-step reaction products.  The generalization of the system makes it useful for exploring reactions outside of the system’s “training,” and the ranking of possible outcomes makes the system more appealing to individuals who can use their chemical intuition to further refine the results.  I expect that advances of this sort will be welcomed by investigators who wish to validate synthetic approaches and by students who seek additional opportunities for practice.  
  
I’m pleased to recommend this manuscript for publication.  
  
Additional Questions:  
Please rate the quality of the science reported in this paper (10 - High Quality/ 1 - Low Quality): 9  
  
Please rate the overall importance of this paper to the field of chemical information or modeling (10 - High Importance / 1 - Low Importance): 10*

**REVIEWER 2** *Recommendation: Publish after minor revisions noted.  
  
Comments:  
  
This paper reports an analysis of chemical reactions which deserves publication. It builds on "Reaction Explorer" the author's earlier work. The new program uses machine learning to analyse a database of over 4000 reactions.  
  
The discussion shows some impressive examples of the output of the program. However, it is not clear how similar they are to examples in the database used to train the program. Figure 9 shows a useful analysis of a multistep reaction. Is it the same as an example in the database? How similar is it to examples in the database? If it is identical to something in the database, this is a trivial example. The paper needs to provide enough information for the reader to have the answers to these questions.*

The output shown for Figure 9 (multi-step reaction) comes from a careful validation experiment in which all of the reactants (and thus all reactions over these reactants) are held out as a separate testing set. However, the text in the original submission did not clearly articulate this. The section's text and corresponding figure caption have been updated to properly convey this important information to the reader.

*The same applies to Figure 10 – is this an impressive example of inductive learning, or is it repeating an example from the database?*

Likewise, all the examples shown in the Discussion come from cross-validation experiments. The text has been updated accordingly to further clarify this important point. Thus Figure 10 is a true example of inductive learning.

*Figure 13 is hard to interpret. Did the database contain data on cation rearrangements, or does the figure illustrate intermediates in longer reaction sequences, which may not have been characterized directly? If the latter, than either product might be obtained depending on the details of the reaction conditions.  
The authors should address these issues.*

The figure represents intermediate products in longer (multi-step) reaction sequences. We show the two reactions as examples of subtle chemistry where our “incorrect” rankings are actually intelligible and meaningful. Furthermore, by returning both of these plausible reactions highly in the ranking, may allow one to explore both pathways and incorporate knowledge about possible subsequent carbocation rearrangements. The figure caption and corresponding text have been expanded to discuss and clarify this point in greater detail. *Is the program and the database available? The algorithm is not given precisely enough for anyone else to duplicate the work, so the results have to be taken on trust, unless the authors have an arrangement to make the program accessible.*

To address this issue, we have created a public web interface to the machine learning based mechanistic reaction prediction system. The interface can be accessed via our chemoinformatics portal (<http://cdb.ics.uci.edu>) under the Toolkits section or directly at <http://reactions.igb.uci.edu/rxnpred/>. The interface allows the entry of reactants and reaction conditions, displaying the predicted reactive sites and ranked reactions. The web accessible system uses models trained with all available data. A section describing the system’s availability has been added to the Discussion.

Furthermore, we will make the reactive site and reaction ranking feature and label machine learning data available through the UCI Machine Learning Repository (<http://archive.ics.uci.edu/ml/>) and our chemoinformatics portal (<http://cdb.ics.uci.edu>) under the Supplementary Materials section upon acceptance of the manuscript. Text to reflect the data’s availability has been added to the Data section.

*Additional Questions:  
Please rate the quality of the science reported in this paper (10 - High Quality/ 1 - Low Quality): 8  
  
Please rate the overall importance of this paper to the field of chemical information or modeling (10 - High Importance / 1 - Low Importance): 8*