Bassen D. 09/06/16

Inline reviewer responses for JuPOETs software note

#### REVIEWER 1

Reviewer #1:  
  
The paper presents an open source implementation of the Pareto optimal ensemble technique in the Julia programming language. This software tool improves a previous implementation in the  Octave language, exploiting the advantages of Julia programming.  The tool implements a multi-objective based technique to estimate  
parameter or models ensembles for robust predictions. I find this tool useful for the community, however, there are  some major issues that need to be addressed before publication.  
  
Major comments:  
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1. (BACKGROUND) The use of a multiobjective approach needs to be justified (and contextualized).  
  
1.1. Justification:  
  
Single objective optimization is broadly (and successfully) used to estimate parameters / identify biochemical models with hundreds/thousands of states and parameters, with training data from diverse sources. Taking into account that multiobjective problems are more difficult to solve than single objective problems, why to use multiobjective approaches in the first place?.  
  
From the paragraph:  
  
"Identification of biochemical models with hundreds or even thousands of states  
and parameters may not be tractable as a single objective optimization problem.  
Further, large models require significant training data perhaps taken from diverse  
sources, for example different laboratories or cell-lines. These data are often het-  
erogenous, and contain intrinsic conflicts that complicate parameter estimation.  
Parameter ensembles which optimally balance tradeoffs between submodels and  
conflicts in training data can lead to robust model performance."  
  
it is not clear what is the advantage of multiobjective approaches (instead of weighting the different data sets). Please justify your choice (multiobjective optimization), including a better explanation of what is meant by "intrinsic conflicts that complicate parameter estimation", and "optimally balance tradeoffs between submodels and conflicts in training data". The aim is to help the reader to decide when it would be convenient to use a multiobjective optimization approach instead of a single optimization one.

#### REPLY 1

We thank the reviewer for guiding us to clarify the informed use of approaches like POETs. Multiobjective optimization allows for the integration of datasets that have been collected under the same conditions and yet yield different out comes, or where multiple readouts, used under the same conditions, compete with each other within the model. In other words, a single objective optimization problem accounting for only one of these datasets would yield very different parameters. This is often the case in biological systems, where specific identification of parameters for an entire population of cell/samples is unrealistic, since each unique sample has its own parameters. Multiobjective optimization techniques allow users to generate an ensemble (population) of models in which some members may satisfy some objectives better than others. This would also be starkly different from a single objective problem where two competing datasets are used and a single set of parameters that satisfies neither objective well, instead settling for a parameter set capturing some average behavior, cannot actually recapitulate behaviors seen in members of the physical system. Please see edits in that paragraph that we hope clarify these statements to readers.

#### additional supporting reference

Bandyopadhyay, Sanghamitra, and Sriparna Saha. 2013. *Unsupervised Classification: Similarity Measures, Classical and Metaheuristic Approaches, and Applications*. *Unsupervised Classification: Similarity Measures, Classical and Metaheuristic Approaches, and Applications*. doi:10.1007/978-3-642-32451-2.

1.2 Contextualization  
Multicriteria (Pareto) optimality concepts are being increasingly used in the context of systems and synthetic biology. The introduction in my opinion is missing some initial discussion and recent examples on successful use of multi-criteria optimization methods in biology:  
  
<http://bmcsystbiol.biomedcentral.com/articles/10.1186/s12918-014-0113-3>  
<http://www.nature.com/articles/srep15147>  
<http://bmcbioinformatics.biomedcentral.com/articles/10.1186/s12859-015-0706-x>

#### REPLY 2

We thank the reviewer for providing these supporting references, especially with respect to synthetic biology. They have been incorporated into the background section.

2. (IMPLEMENTATION) The problem formulation needs to be rewritten to improve readability. It is hard to follow even for a reader familiar with multiobjective optimization:

-Please first introduce the model equations, then the objective functions and finally formulate the problem (1).  
-Please specify the type of model equations, type of decision variables (ODEs, real variables?)  
-Please define the trade-off surface  
-Please elaborate more on the modified simulated annealing approach you use (please see comment 3)  
-Please provide definitions for all the technical terms you use (Pareto optimality, computational annealing temperature,...)  
-Please describe the algorithm inputs and outputs also in the text. (you should mention already in this section that you obtain the characteristic tradeoff  
curves, given parameter bound and problem constraints)

(These are just a few points, but in general terms, the whole section should be carefully re-written)  
  
#### REPLY 3­

We thank the reviewer for the critique of this section. Please see responses below and updates implemented throughout this section.

1. Please first introduce the model equations, then the objective functions and finally formulate the problem (1).
   1. We have presented the implementation of the general routine within the POETs.jl package. The design of the specific examples have been previously published.
2. Please specify the type of model equations, type of decision variables (ODEs, real variables?)
   1. Our POETs implementation can handle ODEs, real, as well as categorical variables, as illustrated in the definition of equation 1 (page 3).
3. Please define the trade-off surface
   1. Generally, the tradeoff surface is a region in the space of the objective functions on which error is optimally balanced between objectives (clarified in text).
4. Please elaborate more on the modified simulated annealing approach you use (please see comment 3)
   1. It should be clarified that the simulated annealing use in JuPOETs does not modify degree of parameter perturbation at each iteration, but rather, the acceptance probability for keeping a solution in the current population. This allows the system to search with an increasing dependence on Pareto rank (see equation 3, definition of acceptance probability).
5. Please provide definitions for all the technical terms you use (Pareto optimality, computational annealing temperature,...
   1. We hope that the computational annealing temperature is further clarified by our response to concern 4 in this list and have explicitly defined Pareto optimality.
6. Please describe the algorithm inputs and outputs also in the text. (you should mention already in this section that you obtain the characteristic tradeoff  
   curves, given parameter bound and problem constraints)
   1. Table 1 contains input objectives for the algebraic formulations, with the biochemical model fully formulated in references 28/29\*. \*old reference numbering ####
   2. (####JEFF: We discussed **adding** to the text for the biochemical model)

3. (CONCLUSIONS)  
  
The following paragraph is misleading: "Many evolutionary approaches e.g., the non-dominated sorting genetic algorithm (NSGA) family of algorithms, have been adapted to solve multiobjective optimization problems [30, 31]. It is unclear if JuPOETs will perform as well as these other approaches; one potential advantage that JuPOETs may have is the local refinement step which temporarily reduces the problem to a single objective formulation. Previously, this hybrid approach led to better convergence on a proof-of-concept signal transduction model."  
  
"It is unclear if JuPOETs will perform as well as these other approaches" this needs to be solved before publishing the method (otherwise, why not implementing NSGA instead?). I think that the problem is again related to a poor justification/contextualization of the tool.  Hybrid optimization combines global and local optimization methods.  The authors claim in the introduction and implementation sections that they use simulated annealing (which is global) without mentioning (at least explicitly or in a clear way) the combination with local search. Does JuPOETs implement a hybrid method? if yes, it should be specified in the implementation section. This would provide already an advantage over other methods (NSGA):

Hybrid methods are shown to perform very efficiently in previous works (in the context of biochemical systems)  
  
<http://bmcsystbiol.biomedcentral.com/articles/10.1186/s12918-014-0113-3>  
  
and examples (in the context of biochemical systems) are found in which hybrid solvers outperform pure evolutionary methods (NSGA-II), see:  
  
<http://pubs.acs.org/doi/pdf/10.1021/ie0605433>  
  
  
"one potential advantage that JuPOETs may have is the local refinement step which temporarily reduces the problem to a single objective formulation", the authors need to explain this with more detail already in the implementation section.

#### REPLY 4

We compared JuPOETs to our available implementation in octave that was used in our previous references e.g. refs 17-20. Since open source implementations of other non-linear/ensemble methods are not implemented in Julia, we felt we could make a significant contribution in the confines of a software note. We thank the reviewer for pointing out the vagueness to which this is discussed in the text and have edited the text to reflect this, including references. **We have also modified the implementation section to reflect the optional use of a hybrid mode with local refinement step.**

Minor comments:  
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The paper needs careful proofreading (including some uncomplete references, for example names are missing in ref 4).

#### REPLY 5

We thank the reviewer for noting these errors, a variety of which have been corrected throughout the text.

#### REF4 is entered correctly, middle names format as initials.

#### REVIEWER 2

Reviewer #2: The paper describes a software update of the one in references 24/25. From the technical point of view, it is fair but for my comments below. Yet, I do not think the new software version adds enough technical  improvements to deserve a full paper. I would see it as a short note.

It is not clear in what particular sense  the authors use the concept of ensemble modelling. From the examples shown, it seems that they refer to the possibility of considering fitness to different experimental data sets as different goals, thus producing a set of parameter sets along the Pareto front. Hence, different parameter sets are more or less optimal for different goals (exp. data sets), and an average  set can be chosen to perform reasonable for all goals. While this idea is good, it is not a new one. The same can be used e.g. when there is lack of identifiability (see e.g. Villaverde etal. (2015) A consensus approach for estimating the predictive accuracy of dynamic models in biology. Computer Methods and Programs in Biomedicine 8:113 ) or when a reduced nonlinear model is to be fitted to different input signals that would require additional structure for the corresponding outputs to be fitted in a single model, etc. In any case, the sense in which the authors are  
using the concept of ensemble modelling seems too forced, as strict ensemble modelling requires either (post)processing of the ensembles of models (e.g. Simidjievski etal (2016) Modeling Dynamic Systems with Efficient Ensembles of Process-Based Models. PLoS ONE 11(4) ) or of the ones of parameters sets to give more than an adhoc solution lo lack of identifiability.