2018-2019 Mid-Term Credibility Plan Review

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#	Ten Simple Rules	REVIEWER #1		REVIEWER #2	
		Considered in the Credibility Plan?	**Comments**	**Considered in the Credibility Plan?**	**Comments**
1	Define context clearly	sufficient	Might want to add "well mixed" Perhaps something further about biological context and future clinical context.	sufficient	Context is clearly defined in the accompanying narrative.
2	Use appropriate data	insufficient	I think of this rule as being the experimental data sources that the model is based on -- eg what are alternatives or potential additions to the NIST database?	sufficient	Data acquired from traceable third party sources. Some discussion as to the adequacy (or limitations) would approve credibility standing
3	Evaluate within context	insufficient	Abiotic processes? -- meaning chemical engineering reaction chambers? Saying that it's not a suitable method for abiotic makes it sound as if the model is being proposed as suitable for all biotic processes? In vivo? In vitro? Cell culture? Mammals? Yeast? -- what are the target applications?	insufficient	Excellent discussion of UQ and sensitivity analysis and their impact on model credibility. No discussion on code/simulation verification and subcomponent validation (or applicability thereof).
4	List limitations explicitly	insufficient	Assumptions != limitations, although limitations can be in part concluded from consideration of assumptions.	sufficient	Limitations are explicit listed, and location communicated.
5	Use version control	sufficient	Excellent.	sufficient	Use of the automated GitHub versioning process is made, other than that a strategy for the contributors is not detailed.
6	Document adequately	insufficient	"Sufficiently documented" -- ... is better described as "well documented"?	insufficient	Documentation is noted, but is process does not appear to be clearly defined in context of model development effort.
7	Disseminate broadly	sufficient	Kudos -- any plans or suggestions on how to the increase number of contributors? -- get other people in the field on board?	sufficient	Investigators have passively disseminated simulation model along several avenues. Credibility would be strengthened with description of how feedback is acquired, evaluated and utilized from this dissemination activity.
8	Get independent reviews	insufficient	Who? How far along? Any problems found?	insufficient	Third party review mentioned. Source of the review is not described.
9	Test competing implementations	insufficient	Anyone else in this field have a comparable simulator that could be used?	sufficient	A plan to assess code performance if implemented in alternative languages is presented. Stronger credibility may be achieved by comparison to competing algorithms.

10	Conform to standards	sufficient	Good	sufficient	Standards are identified and specified.

General Comments

Reviewer 1:

An excellent credibility plan for an ambitious project which will scale across 8 orders of magnitude -- ms to days! Additional bridging is between in vitro preparation (data sources) and in vivo. I have minor comments.

"Low variability in the predictions based on the uncertainties in the parameters provides credibility to the model outcomes." This seems tautological. When model dynamics does not depend strongly on a parameter then this is not a particularly interesting parameter -- eg artillery shell trajectory depends only weakly on time of day perhaps due to a number of factors: change of atmospheric temperature, change in equipment temperature, others. Generally this weak dependence means that one would simply omit circadian rhythm from this military model. One could reverse this and say that "High variability in the predictions" makes the model interesting and then suggests testing to see if the dependence (a prediction) is borne out in experiment.

Perhaps one could say more about the eventual, possible future clinical use of the model. What are the implications for manipulating circadian rhythm for jet lag etc by manipulating metabolites. Eg: altering blood glucose to produce shifts in phase or frequency?

"fitness landscape on which organisms compete" Here we are talking about genetic algorithms rather than genetics. In that we are doing organismal modeling I would suggest avoiding this phraseology so as to reduce confusion.

Reviewer 2:

Thank you for providing an updated credibility plan for evaluation. This credibility plan is strong in its application of UQ and sensitivity analysis and the investigators should be commended for such in depth and detailed communication in this area. . However, there are areas of improvement that could be made to further increase the user assessment of model credibility. In evaluating the model, it is recommended that verification activities and component validation tests also be discussed. As a simulation model it is recognized that global validation may present some challenges, thus insure proper model process development helps improve user assessment. It is also recommended that more detail be presented regarding documentation activities and in the implementation of third party reviews as both these contribute communicating the depth and breadth of model development for the user community.