Reviewer's report

Title: Modeling of chemical inhibition from amyloid protein aggregation kinetics.

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Reviewer: Carlos W Bertoncini

Reviewer's report:

The paper by Vazquez addresses a relevant and current topic in modern anti-amyloid drug discovery, which is the efficient characterization of the inhibitory action of an anti-amyloid compound. By clever combination of Logistic and Weibull equations Vazquez develops an analytical model for the accurate description of the effect of various anti-amyloid compounds on several amyloidogenic proteins and peptides. The surface-type representation is quite useful for the evaluation of the concentration dependence of the inhibitory effect of these compounds on the kinetics of amyloid fibrillization. The paper builds correctly on previous work published on the subject, and the use of previously published data is well acknowledged.

The manuscript is well written and describes precisely the mathematical methods, some of which unfortunately escape the ability of this reviewer. Hence no consideration has been made on the derivation of the equations, which current programs such as Mathematica may check automatically.

Overall the impression of this reviewer is that the paper is a useful tool that would allow a considerable increment in the knowledge of the mechanisms by which different anti-amyloid compounds work. This may aid the future development of anti-amyloid drugs. This reviewer has, however a few concerns that if addressed properly may help to strengthen the applicability of the method.

Minor Essential Revisions:

a) Data analyzed in the manuscript arises from two methods generally used to probe amyloid formation in vitro, the increment in light scattering of the protein solution due to insolubilization, and the increase in ThT fluorescence due to amyloid binding. These two methods report on quite distinct phenomena; while the first is sensitive to the early steps in protein aggregation and does not differentiates between amorphous and amyloid aggregation, the second is insensitive to only amyloid species. In addition, light scattering usually saturates quite early in the reaction coordinate, while ThT fluorescence takes several hours and even days to saturate. It could be good to discuss these features a little more, and perhaps find some datasets that compare these two methods head to head.

b) A serious drawback in aggregation kinetics is the intrinsic variability of the experimental data that demands the usage of several replicates. In drug discovery platforms these assays are run in plate readers, with at least triplicates
or quintuplicates of the samples. It could be good to know how the analytical method can be implemented efficiently in the case of global fittings.

c) This reviewer is concerned with the implementation of the method. How does the author propose to distribute this body of work and make it accessible to the scientific community? Could a MS EXCEL plugin/spreadsheet or a web-based server be useful? Would any of the data be distributed?

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interest