

Response to Referee Reports

Referee Report 1

Altogether, this is a valuable contribution and I recommend publication provided the authors consider the following (in the order of appearance):

1. On page 1 and page 2 the word “decease” appears. Is this a typo for the word “disease”? The paper needs some editing for other possible typos (see below)

Our response: Agreed, and done. We have removed all offending instances found by the referees, as well as others that we found our own. We have also made minor edits for readability.

2. On page 4 last paragraph. Could you please explain a little more what do you mean by “very special case”? Is it about having only one reversible state (i.e. X_2 to X_1) or is it special due to some underlying biological assumption? Please also include a citation for the statement “There are vastly more general theorems...”.

Our response: We have included an additional explanation of why the case described is a very special case (as there is a single irreversible state). We have changed the statement from “vastly more general” to “more general” and provided the statement of Theorem 3.2 as evidence of the claim.

3. On page 4 last paragraph. The last phrase, “The interesting reader might wish to prove...”, should read “The interested reader...”. But I am not sure this phrase is appropriate. It sounds more like an entry in a textbook where the author invites the student to do an exercise. I think you can remove the phrase and simply leave the Theorem 3.2 as is.

Our response: We agree with removing the “interesting (interested) reader” phrasing, and have done so.

4. On page 6 Theorem 4.1. I understand the argument in the proof but it seems to me that this theorem is the most important contribution of this paper. If a rigorous proof is not difficult, as stated, perhaps it would be better to include it here.

Our response: The formal proof is now included, along with the informal reasoning that guides the intuition.

5. On page 7. This might be a matter of taste but I would discard “Friends, have a theorem. You’ll love it”.

Our response: We reluctantly agree and have replaced this statement with a more formal introduction to the Theorem.

6. On page 8 second paragraph. Again, a careful check for language errors is needed: “sarcastically immune to cancer” I take it should read “stochastically immune to cancer”?

Our response: We agree. We are grateful to the referee for this careful reading. The recommended changes have been made.

7. The paper lacks a conclusions section which should be written even if it ends up being brief. The authors can include an example to illustrate why none of the models

described in section (4) are a good fit for the elderly population. Maybe elaborate more on what could constitute the “correct” model, what assumptions, what mathematical challenges are likely, etc. In fact, the Introduction could also be more generous. Many readers, when surveying multiple papers, read only the introduction and the conclusions and these two sections should be clear on: what has been investigated, what is the main contribution, and what are the implications for future research.

Our response: We have expanded on the list of references that explain that none of the models are adequate in old age. Also, we have incorporated a short conclusion section reiterating the historical importance of Armitage and Doll’s paper and also our own contribution to the literature. We thank the referee for this productive suggestion.

Referee Report 2

The review of the assumptions around the Armitage and Doll (AD) model and the history of its use in the literature is interesting. While I am not up on oncology modeling past nor present, I think the structure of this article and context may provide a nice resource for those that are. The overall writing is solid. I have only a few suggestions to add some details to make the article that much more readable. Some minor corrections are listed afterward. Suggestions:

1. Might read better to have sentences for each of Nordling’s reasons for being less well-known e.g. (1) Nordling’s data analysis methodology was ... [too coarse or too confounding, etc].

Our response: We have modified that portion of the paper to include a list of reasons and a subsection for each reason to increase readability. We thank the referee for this productive suggestion.

2. Some additional written details around the proof of the theorems I think is in order. Why are you defining the function $F(T)$ (cumulative?) the way you do? So $F'(T)$ is the PDF? How is it that the sequence of steps in the proof shows the result you wish? This will be helpful to the target readers.

Our response: We agree with this in principle. We have added some verbiage in the main text. We also hope that the proofs in the Mathematical Appendix are sufficiently detailed to address this point.

3. A simple definition of power law would be useful for completeness.

Our response: A brief definition of power law has been included immediately following the first mention of the term.

4. Should state why you are not proving Theorem 3.2.

Our response: The statement of Theorem 3.2 is a demonstrative example to show that Theorem 3.1 can be generalized. However, it is Theorem 3.1 (which has a very simple and combinatorial proof) that demonstrates that irreversability is not necessary to obtain a power law. We hope that the text of this section now makes this clear.

5. Should describe what a hazard function is in 4.1.

Our response: We agree. The definition, along with an informal explanation, of a hazard function have been added to this section, along with the relevant property of the hazard function used to define the Weibull distribution.

6. Authors state that proof of Theorem 4.4 is in this paper’s appendix, which does not seem to exist.

Our response: We apologize for this oversight. The Appendix is now included at the end of the text after the references.

7. Capitalization following a colon. e.g. “...flexibility: Cancer...” (other spots as well).

Our response: We agree and thank the referee for this catch. We have made this recommended change in all of the places where the AMS style guide recommends capitalization after a colon.

8. “...power law of held even...” no “of”?

Our response: We have made the recommended change.

9. “with these [minor]...” needs left quote marks.

Our response: We have made the recommended change.

10. AD model assumption list. All Capitalized to start or not.

Our response: We have made the recommended change.

11. Use `\left` (and `\right`) in Latex in Theorem 3.1 $F(T) = \dots$ (and other spots)

Our response: We have made the recommended change.

12. Wording in proof of Theorem 3.3 could be broken up into a couple of sentences for easier reading.

Our response: We agree, and have restructured the wording of the Theorem to implement this suggestion.

13. Use `\mbox{}` (e.g. `\mbox{or}`) to avoid italicized English words in math expressions.

Our response: We have made the recommended change in Theorems 3.2 and A.1, which we believe are the only places where it is needed.

14. In 4.2: *well* should be *will*

Our response: We have made the recommended change.

15. In 4.2: *albeit* is one word

Our response: We have made the recommended change.

Other changes

- (a) We have included additional clarification about the usage of an improper survival function to both the text and the proof of Theorem 4.6.
- (b) We have expanded upon the third part of the proof of Theorem 4.6.