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PROCEEDINGS A

The origins of quantum biology

Johnjoe McFadden and Jim Al-khalili

Article citation details
Proc. R. Soc. A **474**: 20180674.
http://dx.doi.org/10.1098/rspa.2018.0674

Review timeline

Original submission:	8 December 2017
1st revised submission:	2 October 2018
2nd revised submission:	31 October 2018
Final acceptance:	31 October 2018

Note: Reports are unedited and appear as submitted by the referee. The review history appears in chronological order.

Review History

RSPA-2017-0855.R0 (Original submission)

Review form: Referee 1

Is the manuscript an original and important contribution to its field?
No

Is the paper of sufficient general interest?
Yes

Is the overall quality of the paper suitable?
No

Quality of the paper
A paper that may be acceptable after major revision.

Can the paper be shortened without overall detriment to the main message?
No

Do you think some of the material would be more appropriate as an electronic appendix?
No

For papers with colour figures – is colour essential?
Yes

If there is supplementary material, is this adequate and clear?
Not applicable

Are there details of how to obtain materials and data, including any restrictions that may apply?
Not applicable

Do you have any ethical concerns with this paper?
No

Recommendation?
Major revision is needed (please make suggestions in comments)

Comments to the Author(s)
I find the title and the purpose of the paper to be poorly posed. Is quantum mechanics essential to life? Yes in exactly the sense that QM is essential to understand chemistry. But complex systems, living and not, have emergent properties that cannot readily be predicted from the properties of their components. The exponential increase in computational requirements with size means that that QM is unlikely to help much in predicting emergent properties of living things such as cognition.
Second, what is meant by quantum mechanics here? Is it quantization, energy gaps accounting for chemical stability and reactivity or just the non-trivial aspects such as entanglement and interference? The meaning seems to shift during the article. If the former the the answer is yes, obviously. If the latter this is still a matter of current debate to which the current ms does not add. The authors may wish to consult Scholes et al. Nature 543, 647 (2017) for a more recent summary of the current state of understanding of the role of coherence in chemistry and biology.

I think the historical perspective and evolution of ideas described here could be an interesting contribution, but a very extensive rewrite is needed to clarify what is meant by "quantum" at each stage of the development of ideas.

Review form: Referee 2

Is the manuscript an original and important contribution to its field?
No

Is the paper of sufficient general interest?
Yes

Is the overall quality of the paper suitable?
Yes

Quality of the paper
A good paper worth publishing in Proceedings.

Can the paper be shortened without overall detriment to the main message?
No

Do you think some of the material would be more appropriate as an electronic appendix?
No

For papers with colour figures – is colour essential?
No

If there is supplementary material, is this adequate and clear?
Not applicable

Are there details of how to obtain materials and data, including any restrictions that may apply?
Not applicable

Do you have any ethical concerns with this paper?
No

Recommendation?
Accept as is

Comments to the Author(s)
Very nice manuscript.

Review form: Referee 3

Is the manuscript an original and important contribution to its field?
No

Is the paper of sufficient general interest?
No

Is the overall quality of the paper suitable?
No

Quality of the paper
A paper that is of insufficient interest, quality or importance.

Can the paper be shortened without overall detriment to the main message?
No

Do you think some of the material would be more appropriate as an electronic appendix?
No

For papers with colour figures – is colour essential?
Not applicable

If there is supplementary material, is this adequate and clear?
Not applicable

Are there details of how to obtain materials and data, including any restrictions that may apply?
Yes

Do you have any ethical concerns with this paper?
No

Recommendation?
Reject – article is not of sufficient interest (we will consider a transfer to another journal)

Comments to the Author(s)
I cannot recommend this for publication as a Review Article in Proceedings of The Royal Society A, as this piece - although interesting - does not seem to me to contain enough scientific detail about the ideas of the early scientists mentioned and the more modern trends in what is called quantum biology. My main problem is that this lack of detail makes it very difficult to understand what the influence of these early physicists on current thinking in QB might actually be, aside from the use of the term "quantum biology". It would seem to me that their ideas and concepts of apreiodic crystals, role of large fluctuations and the primacy of quantum mechanics in determining bonding, forces, structure, etc. was largely integrated into maninstream research - see the passage by Lounget-Higgins - leaving only the much more flimsy quantum 'elan vitale' ideas that have not really been revived or play much role in modern QB (aside from the often used by never defined statement that the systems in modern QB exploit "non-trivial" quantum effects). There is, of course, great value in pointing out the perhaps obscured origins of an important or powerful scientific idea, particularly if the originators had anticipated some of the developments that would come, but I'm afraid that I didn't see the link, here. For publication in as a review in a physics journal, I'd expect to come away with a better understanding of either the field itself or the movments/ideas that created it (who knows, one might wish to track back and try some of the many paths less travelled that appeared along the way).

Aside from this, as a article in the field of history of physics, I also felt that it is quite light on references to the academic literature on Schrodinger and - in particular - Jordan, and (minor point) some of the milestones on the timeline at the end do not have any corresponding references to the original articles. I'd also suggest that the authors have missed an important figure on their timeline - Herbert Frohlich - whose celebrated "green book" was probably much more in line with many of the "non-trivial" theoretical ideas now under discussion in photosynthesis, tunneling, etc.

Review form: Referee 4 (Erik Gauger)

Is the manuscript an original and important contribution to its field?
Yes

Is the paper of sufficient general interest?
Yes

Is the overall quality of the paper suitable?
Yes

Quality of the paper
An excellent paper making an important contribution to the field: should be published.

Can the paper be shortened without overall detriment to the main message?
No

Do you think some of the material would be more appropriate as an electronic appendix?
No

For papers with colour figures – is colour essential?
Not applicable

If there is supplementary material, is this adequate and clear?
Not applicable

Are there details of how to obtain materials and data, including any restrictions that may apply?
Not applicable

Do you have any ethical concerns with this paper?
No

Recommendation?
Accept as is

Comments to the Author(s)
The manuscript "The origins of quantum biology" by McFadden and Al-Khalili traces the roots of the topical field of quantum biology back to the early days of quantum mechanics. As the authors state, it is often assumed that quantum biology is a new discipline which has only emerged within the last couple of decades. Whilst this is arguably the case when it comes to experimental evidence of non-trivial quantum effects in biological processes, this article shows that the ideas behind quantum biology are in fact much older.

I enjoyed reading this well-written and well-structured manuscript. As far as I can tell it is both scientifically and historically accurate (although my opinion on the latter would be biased by having attended lectures by Prof Al-Khalili's on this very topic more than once).

A minor comment on the authors' statement "...quantum entanglement has been implicated in avian navigation [7]." Reference [7] did indeed provide strong experimental evidence for the radical pair mechanism, but I believe neither quantum coherence nor entanglement were mentioned in this paper (although it would be fair to say this is to some extent implicit in the RP model itself). To the best of my knowledge, Phys. Rev. Lett. 104, 220502 and Phys. Rev. Lett. 106, 040503 were the first papers to explicitly explore the "quantumness" of the avian compass. Other than that, I have only stumbled across some very minor typographical issues (see list below).

In summary, I believe this manuscript makes an interesting and valuable contribution, offering an important perspective on the history of quantum biology for an audience much larger than that of active researchers in this field. I am more than happy to recommend publication in Proceeding of the Royal Society A.

Best regards,
Erik Gauger, Heriot-Watt University.

Typos:
- page 4 line 37: accent missing in René Descartes

- page 4 line 38: is "essential machines" correct or should this be "essentially"?
- page 4 line 39: capitalise both words in "Industrial Revolution"?
- page 5 line 51: capitalise "Grundprobleme", "Biologie", and "Psychologie"
- page 10 line 42: grammar seems odd -- is "with" required?
- page 14 line 29: full stop missing
- page 15 lines 56,57: "Über die Natur der der Genmutation und der Genstruktur"
- page 16 line 9: umlaut missing in "Löwdin"?

Review form: Referee 5

Is the manuscript an original and important contribution to its field?
No

Is the paper of sufficient general interest?
Yes

Is the overall quality of the paper suitable?
No

Quality of the paper
A paper that may be acceptable after major revision.

Can the paper be shortened without overall detriment to the main message?
No

Do you think some of the material would be more appropriate as an electronic appendix?
No

For papers with colour figures – is colour essential?
No

If there is supplementary material, is this adequate and clear?
Not applicable

Are there details of how to obtain materials and data, including any restrictions that may apply?
Not applicable

Do you have any ethical concerns with this paper?
No

Recommendation?
Major revision is needed (please make suggestions in comments)

Comments to the Author(s)
The authors present a historical perspective on the origins of quantum biology, that is, the idea that non-trivial quantum mechanical effects (i.e. beyond chemical bonding) may play a fundamental role in biological processes. As they rightly point out, though this field has burgeoned over the past few years, there is also a longer history of scientists attempting to link both the features and philosophy of quantum mechanics with biological phenomena. It is this point, and a description of some of those attempts that form the basis of this article, with the

argument put forward that these earlier insights remain relevant for the field of quantum biology today.

The article is written in an informal style, though I found it readable and the historical aspects interesting. My main concern, however, is that it overstates the current evidence for the importance of quantum effects in biological phenomena and presents very little in the way of critical analysis of some of the earlier ideas of the quantum pioneers. For example, in the first line of the abstract, it is already suggested that biological phenomena have been demonstrated to make use of many non-trivial features of quantum mechanics (note that the same sentiment is repeated also in the first line of the introduction, and in other parts of the article, e.g. on page 12.). As far as I am aware, however, this is not the case. For example, though quantum coherence can be generated in photosynthetic systems under laboratory conditions, there is no proof yet that such features play a useful role (or indeed are even present) within the natural setting. I believe similar arguments hold true for the other examples cited (e.g. avian navigation and enzyme catalysis) and indeed the role of quantum mechanics in olfaction in particular continues to cause controversy. Note that I am not hostile to the idea of quantum biology, but I do believe it is important to be accurate with regard to its current status.

Furthermore, the earlier ideas of Jordan, Bohr, and Schroedinger, for example, are not really critiqued in any meaningful manner. How are these ideas still influential and relevant in quantum biology today? What is their legacy and status within the relevant communities?

Some minor comments:

- It is mentioned in section 2 that Bohr gave a lecture in 1929 that touched on whether quantum mechanics may play a role in biology. However, the subsequent quote gives us no indication of his thinking - is there any more insight that can be given here?

- Later in this section there is a brief discussion and related quote on Bohr and complementarity. I wasn't clear what point was being made here - could the authors expand on this?

- In section 3, there is a quote from an article by J. Haldane which states "...life takes advantage of the uncertainty principle to make certain events more probable than they would otherwise have been...". What does this mean? Is uncertainty principle used here as a proxy for quantum mechanics, or is it really the principle itself to which Haldane is referring.

- I found the description of quantum coherent systems as vibrating in phase a little misleading on page 11. Also, the relationship between quantum tunneling and jumps is not entirely clear. Usually, a jump is associated with an incoherent process or measurement, rather than a coherent one.

Decision letter (RSPA-2017-0855.R0)

15-Mar-2018

Dear Professor Al-khalili:

I am writing to inform you that your manuscript RSPA-2017-0855 entitled "The origins of quantum biology" has been rejected in its present form for publication in Proceedings A.

The Editor has made this decision based on the advice of referees, and taking into account their own opinion of your paper. With this in mind we would like to invite a resubmission, provided the comments of the referees and any comments from the Editor are taken into account. This is not a provisional acceptance.

The resubmission will be treated as a new manuscript. Please note that resubmissions must be submitted within six months of the date of this email. In exceptional circumstances, extensions may be possible if agreed with the Editorial Office.

Please find below the comments made by the referees, not including confidential reports to the Editor, which I hope you will find useful. If you do choose to resubmit your manuscript, please include details of how you have responded to the comments, and the adjustments you have made.

Please note that we have a strict upper limit of 28 pages for each paper. Please endeavour to incorporate any revisions while keeping the paper within journal limits. Please note that page charges are made on all papers longer than 20 pages. If you cannot pay these charges you must reduce your paper to 20 pages before submitting your revision. Your paper has been ESTIMATED to be 11 pages. We cannot proceed with typesetting your paper without your agreement to meet page charges in full should the paper exceed 20 pages when typeset. If you have any questions, please do get in touch.

To upload a resubmitted manuscript, log into http://mc.manuscriptcentral.com/prsa and enter your Author Centre, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Resubmission." Please be sure to indicate that it is a resubmission, and ensure you enter this ID - RSPA-2017-0855 - as the previous submission number.

Yours sincerely

Raminder Shergill
proceedingsa@royalsociety.org

Reviewer(s)' Comments to Author:

Referee: 1

Comments to the Author(s)
I find the title and the purpose of the paper to be poorly posed. Is quantum mechanics essential to life? Yes in exactly the sense that QM is essential to understand chemistry. But complex systems, living and not, have emergent properties that cannot readily be predicted from the properties of their components. The exponential increase in computational requirements with size means that that QM is unlikely to help much in predicting emergent properties of living things such as cognition.
Second, what is meant by quantum mechanics here? Is it quantization, energy gaps accounting for chemical stability and reactivity or just the non-trivial aspects such as entanglement and interference? The meaning seems to shift during the article. If the former the the answer is yes, obviously. If the latter this is still a matter of current debate to which the current ms does not add. The authors may wish to consult Scholes et al. Nature 543, 647 (2017) for a more recent summary of the current state of understanding of the role of coherence in chemistry and biology.

I think the historical perspective and evolution of ideas described here could be an interesting contribution, but a very extensive rewrite is needed to clarify what is meant by "quantum" at each stage of the development of ideas.

Referee: 2

Comments to the Author(s)
Very nice manuscript.

Referee: 3

Comments to the Author(s)
I cannot recommend this for publication as a Review Article in Proceedings of The Royal Society A, as this piece - although interesting - does not seem to me to contain enough scientific detail about the ideas of the early scientists mentioned and the more modern trends in what is called quantum biology. My main problem is that this lack of detail makes it very difficult to understand what the influence of these early physicists on current thinking in QB might actually be, aside from the use of the term "quantum biology". It would seem to me that their ideas and concepts of apreiodic crystals, role of large fluctuations and the primacy of quantum mechanics in determining bonding, forces, structure, etc. was largely integrated into maninstream research - see the passage by Lounget-Higgins - leaving only the much more flimsy quantum 'elan vitale' ideas that have not really been revived or play much role in modern QB (aside from the often used by never defined statement that the systems in modern QB exploit "non-trivial" quantum effects). There is, of course, great value in pointing out the perhaps obscured origins of an important or powerful scientific idea, particularly if the originators had anticipated some of the developments that would come, but I'm afraid that I didn't see the link, here. For publication in as a review in a physics journal, I'd expect to come away with a better understanding of either the field itself or the movments/ideas that created it (who knows, one might wish to track back and try some of the many paths less travelled that appeared along the way).

Aside from this, as a article in the field of history of physics, I also felt that it is quite light on references to the academic literature on Schrodinger and - in particular - Jordan, and (minor point) some of the milestones on the timeline at the end do not have any corresponding references to the original articles. I'd also suggest that the authors have missed an important figure on their timeline - Herbert Frohlich - whose celebrated "green book" was probably much more in line with many of the "non-trivial" theoretical ideas now under discussion in photosynthesis, tunneling, etc.

Referee: 4

Comments to the Author(s)
The manuscript "The origins of quantum biology" by McFadden and Al-Khalili traces the roots of the topical field of quantum biology back to the early days of quantum mechanics. As the authors state, it is often assumed that quantum biology is a new discipline which has only emerged within the last couple of decades. Whilst this is arguably the case when it comes to experimental evidence of non-trivial quantum effects in biological processes, this article shows that the ideas behind quantum biology are in fact much older.

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A minor comment on the authors' statement "...quantum entanglement has been implicated in avian navigation [7]." Reference [7] did indeed provide strong experimental evidence for the radical pair mechanism, but I believe neither quantum coherence nor entanglement were mentioned in this paper (although it would be fair to say this is to some extent implicit in the RP model itself). To the best of my knowledge, Phys. Rev. Lett. 104, 220502 and Phys. Rev. Lett. 106, 040503 were the first papers to explicitly explore the "quantumness" of the avian compass. Other than that, I have only stumbled across some very minor typographical issues (see list below).

In summary, I believe this manuscript makes an interesting and valuable contribution, offering an important perspective on the history of quantum biology for an audience much larger than that of active researchers in this field. I am more than happy to recommend publication in Proceeding of the Royal Society A.

Best regards,
Erik Gauger, Heriot-Watt University.

Typos:
- page 4 line 37: accent missing in René Descartes
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- page 5 line 51: capitalise "Grundprobleme", "Biologie", and "Psychologie"
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- page 14 line 29: full stop missing
- page 15 lines 56,57: "Über die Natur der der Genmutation und der Genstruktur"
- page 16 line 9: umlaut missing in "Löwdin"?

Referee: 5

Comments to the Author(s)
The authors present a historical perspective on the origins of quantum biology, that is, the idea that non-trivial quantum mechanical effects (i.e. beyond chemical bonding) may play a fundamental role in biological processes. As they rightly point out, though this field has burgeoned over the past few years, there is also a longer history of scientists attempting to link both the features and philosophy of quantum mechanics with biological phenomena. It is this point, and a description of some of those attempts that form the basis of this article, with the argument put forward that these earlier insights remain relevant for the field of quantum biology today.

The article is written in an informal style, though I found it readable and the historical aspects interesting. My main concern, however, is that it overstates the current evidence for the importance of quantum effects in biological phenomena and presents very little in the way of critical analysis of some of the earlier ideas of the quantum pioneers. For example, in the first line of the abstract, it is already suggested that biological phenomena have been demonstrated to make use of many non-trivial features of quantum mechanics (note that the same sentiment is repeated also in the first line of the introduction, and in other parts of the article, e.g. on page 12.). As far as I am aware, however, this is not the case. For example, though quantum coherence can be generated in photosynthetic systems under laboratory conditions, there is no proof yet that such features play a useful role (or indeed are even present) within the natural setting. I believe similar arguments hold true for the other examples cited (e.g. avian navigation and enzyme catalysis) and indeed the role of quantum mechanics in olfaction in particular continues to cause controversy. Note that I am not hostile to the idea of quantum biology, but I do believe it is important to be accurate with regard to its current status.

Furthermore, the earlier ideas of Jordan, Bohr, and Schroedinger, for example, are not really critiqued in any meaningful manner. How are these ideas still influential and relevant in quantum biology today? What is their legacy and status within the relevant communities?

Some minor comments:

- It is mentioned in section 2 that Bohr gave a lecture in 1929 that touched on whether quantum mechanics may play a role in biology. However, the subsequent quote gives us no indication of his thinking - is there any more insight that can be given here?

- Later in this section there is a brief discussion and related quote on Bohr and complementarity. I wasn't clear what point was being made here - could the authors expand on this?

- In section 3, there is a quote from an article by J. Haldane which states "...life takes advantage of the uncertainty principle to make certain events more probable than they would otherwise have been...". What does this mean? Is uncertainty principle used here as a proxy for quantum mechanics, or is it really the principle itself to which Haldane is referring.

- I found the description of quantum coherent systems as vibrating in phase a little misleading on page 11. Also, the relationship between quantum tunneling and jumps is not entirely clear. Usually, a jump is associated with an incoherent process or measurement, rather than a coherent one.

Board member comments (if available):

Board Member: 1
Comments to Author(s):
I would agree with the assessment of Referees 1 and 3: the paper is not written as a piece of scientific work, but rather as a historical/societal overview of the origins of quantum biology. I would expect a review in the Proceedings to be giving a state-of-the-art of a subject of current interest and clearly, quantum biology is an active field of research nowadays. The focus of the paper is not in line with this requirement. If the paper was unearthing a scientific aspect from the past which has been consequently forgotten, then the historical approach would be justified, but that is not the case either. This is why I am recommending reject. The referees provide some pointers to ways of correcting the course of the paper, and a resubmission can be suggested. In their comments to the Editor, one of the referees pointed out that "Some of the historical material is interesting some just silly. Did Bohr "tower" over Schrodinger, Heisenberg and Dirac? (p3 L11). Dwelling on Jordan's Nazi sympathies seems irrelevant unless this is a work of social science." I also agree with those points.

Author's Response to Decision Letter for (RSPA-2017-0855.R0)

See Appendix A.

RSPA-2018-0674.R0

Review form: Referee 3

Is the manuscript an original and important contribution to its field?
Yes

Is the paper of sufficient general interest?
Yes

Is the overall quality of the paper suitable?
Yes

Quality of the paper
A good paper worth publishing in Proceedings.

Can the paper be shortened without overall detriment to the main message?
No

Do you think some of the material would be more appropriate as an electronic appendix?
No

For papers with colour figures – is colour essential?
Not applicable

If there is supplementary material, is this adequate and clear?
Not applicable

Are there details of how to obtain materials and data, including any restrictions that may apply?
Not applicable

Do you have any ethical concerns with this paper?
No

Recommendation?
Accept as is

Comments to the Author(s)
The present MS is very engaging, sheds a new perspective on a timely 'hot topic' and will be of broad appeal to the wide readership of Proceedings A. I recommend publication., as is.

Review form: Referee 5 (Ahsan Nazir)

Is the manuscript an original and important contribution to its field?
Yes

Is the paper of sufficient general interest?
Yes

Is the overall quality of the paper suitable?
Yes

Quality of the paper
A good paper worth publishing in Proceedings.

Can the paper be shortened without overall detriment to the main message?
No

Do you think some of the material would be more appropriate as an electronic appendix?
No

For papers with colour figures – is colour essential?
Yes

If there is supplementary material, is this adequate and clear?
Not applicable

Are there details of how to obtain materials and data, including any restrictions that may apply?
Not applicable

Do you have any ethical concerns with this paper?
No

Recommendation?
Accept as is

Comments to the Author(s)
The manuscript has significantly improved as a result of the revisions made and I am now happy to recommend publication.

Ahsan Nazir, University of Manchester

Review form: Referee 6 (Gregory Scholes)

Is the manuscript an original and important contribution to its field?
Yes

Is the paper of sufficient general interest?
Yes

Is the overall quality of the paper suitable?
Yes

Quality of the paper
An excellent paper making an important contribution to the field: should be published.

Can the paper be shortened without overall detriment to the main message?
No

Do you think some of the material would be more appropriate as an electronic appendix?
No

For papers with colour figures – is colour essential?
No

If there is supplementary material, is this adequate and clear?
Not applicable

Are there details of how to obtain materials and data, including any restrictions that may apply?
Not applicable

Do you have any ethical concerns with this paper?
No

Recommendation?
Accept as is

Comments to the Author(s)
This is a beautifully written essay that examines the history of quantum biology. The value f the paper is the interesting perspective provided for the current status of the quantum biology field in light of the past work.

Decision letter (RSPA-2018-0674.R0)

26-Oct-2018

Dear Professor Al-khalili,

On behalf of the Reviews Editor, I am pleased to inform you that your Manuscript RSPA-2018-0674 entitled "The origins of quantum biology" has been accepted for publication in Proceedings A. Please find the referees' comments below. We now require your files for typesetting.

To resubmit your manuscript (with your source files), log into https://mc.manuscriptcentral.com/prsa and enter your Author Centre, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission process.

In addition to addressing all of the reviewers' and editor's comments, your revised manuscript MUST contain the following sections before the reference list (for any heading that does not apply to your work, please include a comment to this effect):

- Data accessibility
- Competing interests
- Authors' contributions
- Acknowledgements

- Funding statement
- Ethics statement

See https://royalsociety.org/journals/authors/author-guidelines/ for further details.

When uploading your revised files, please make sure that you include the following as we cannot proceed without these:

1) A text file of the manuscript (doc, txt, rtf or tex), including the references, tables (including captions) and figure captions. Please remove any tracked changes from the text before submission. PDF files are not an accepted format for the "Main Document".

2) A separate electronic file of each figure (tif, eps or print-quality pdf preferred). The format should be produced directly from original creation package, or original software format.

3) Electronic Supplementary Material (ESM): all supplementary materials accompanying an accepted article will be treated as in their final form. Note that the Royal Society will not edit or typeset supplementary material and it will be hosted as provided. Please ensure that the supplementary material includes the paper details where possible (authors, article title, journal name). Supplementary files will be published alongside the paper on the journal website and posted on the online figshare repository (https://figshare.com). The heading and legend provided for each supplementary file during the submission process will be used to create the figshare page, so please ensure these are accurate and informative so that your files can be found in searches. Files on figshare will be made available approximately one week before the accompanying article so that the supplementary material can be attributed a unique DOI. Alternatively you may upload a zip folder containing all source files for your manuscript as described above with a PDF as your "Main Document". This should be the full paper as it appears when compiled from the individual files supplied in the zip folder.

Article Funder

Please ensure you fill in the Article Funder question on page 2 to ensure the correct data is collected for FundRef (http://www.crossref.org/fundref/).

Media summary

Please ensure you include a short non-technical summary (up to 100 words) of the key findings/importance of your paper. This will be used for to promote your work and marketing purposes (e.g. press releases). The summary should be prepared using the following guidelines:

*Write simple English: this is intended for the general public. Please explain any essential technical terms in a short and simple manner.
*Describe (a) the study (b) its key findings and (c) its implications.
*State why this work is newsworthy, be concise and do not overstate (true 'breakthroughs' are a rarity).
*Ensure that you include valid contact details for the lead author (institutional address, email address, telephone number).

Cover images

We welcome submissions of images for possible use on the cover of Proceedings A. Images should be square in dimension and please ensure that you obtain all relevant copyright

permissions before submitting the image to us. If you would like to submit an image for consideration please send your image to proceedingsa@royalsociety.org

Once again, thank you for submitting your manuscript to Proceedings A and I look forward to receiving your revision. If you have any questions at all, please do not hesitate to get in touch.

Best wishes

Alice Power
Publishing Editor
Proceedings A
proceedingsa@royalsociety.org

on behalf of
Professor Michel Destrade
Reviews Editor
Proceedings A

Reviewer(s)' Comments to Author:

Referee: 3

Comments to the Author(s)
The present MS is very engaging, sheds a new perspective on a timely 'hot topic' and will be of broad appeal to the wide readership of Proceedings A. I recommend publication., as is.

Referee: 5

Comments to the Author(s)
The manuscript has significantly improved as a result of the revisions made and I am now happy to recommend publication.

Ahsan Nazir, University of Manchester

Referee: 6

Comments to the Author(s)
This is a beautifully written essay that examines the history of quantum biology. The value f the paper is the interesting perspective provided for the current status of the quantum biology field in light of the past work.

Comments from Reviews Editor:

As the two original reviewers who were quite critical of the first version of this manuscript are now happy with the re-submission, I'm happy too to recommend "accept as is". This is confirmed by a third review.

I noticed that "Wiltschko" was misspelled in the timeline.

Author's Response to Decision Letter for (RSPA-2018-0674.R0)

See Appendix B.

Decision letter (RSPA-2018-0674.R1)

31-Oct-2018

Dear Professor Al-khalili

On behalf of the Editor, I am pleased to inform you that your manuscript entitled "The origins of quantum biology" has been accepted in its final form for publication in Proceedings A.

Our Production Office will be in contact with you in due course. You can expect to receive a proof of your article soon. Please contact the office to let us know if you are likely to be away from e-mail in the near future. If you do not notify us and comments are not received within 5 days of sending the proof, we may publish the paper as it stands.

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Thank you for your submission. On behalf of the Editors of the journal, we look forward to your continued contributions to the Journal.

Best wishes

Raminder Shergill,
Proceedings A Editorial Office
proceedingsa@royalsociety.org

on behalf of
Reviews Editor
Michel Destrade
Proceedings A

Appendix A

Response to referees

We firstly must apologise for the delay in resubmission of this manuscript. We have taken on board all the comments of the referees and have addressed each of them as carefully as we can, as outlined below. In most cases, we have tightened wording, added references and further clarifications and expansions. However, as might be expected, we disagree strongly with certain comments and therefore state our position, hopefully, more clearly (both in the notes below and in the manuscript itself). The referees' comments are **in bold** and our responses are below them.

We note that referees 2 and 4 recommend publication, albeit with some minor corrections and valid points made by referee 4. Referee 5 is also favourable but makes a number of comments and suggestions which we have taken on board. Referees 1 and 3 are more critical. While it is disappointing that the board member sides with them rather than the other three referees, we have tried our best to address their often very valid points. There is, inevitably with such thoughtful and thorough reviewing, a number of common points and criticisms (such as the need for a much more nuanced and thorough critique of the legacy and influence of the early quantum pioneers such as Bohr and Schrödinger.

Response to Referee 1:

"I find the title and the purpose of the paper to be poorly posed. Is quantum mechanics essential to life? Yes, in exactly the sense that QM is essential to understand chemistry.

This reviewer principle criticism seems to be that quantum biology (QB) does not really exist as a discipline distinct from either quantum mechanics or biology. This could perhaps have been argued with some truth a decade ago but with hundreds of scientific articles citing the discipline, the existence of the field cannot be doubted. It is not really the purpose of this paper to defend the validity of QB but to highlight its largely unappreciated history. Our title makes this purpose clear.

However, the reviewer does make a valid point that there is some difficulty in defining the meaning of 'quantum biology'. In the original and revised manuscript we go to great lengths to define the term, as biology that involves non-trivial quantum phenomena, such as long-lived quantum coherence and superposition, quantum tunnelling and even quantum entanglement. We of course accept that biology is chemistry and chemistry is physics, but, despite this fact, chemistry is nevertheless a discipline distinct from physics. Similarly, QB is a distinct discipline from either QM or biology. So when the referee states that of course QM is essential for life in the same way that it is essential to understand chemistry, they are missing the point of what we are saying. Of course we must use the quantum rules to understand molecular and atomic bonding, electron orbitals and discrete energy levels etc. in biology just as we do in chemistry. This is all entirely correct... *but it has nothing to do with quantum biology*. We make this clear in the very first sentence of the Introduction, stating that there is now strong evidence that certain mechanisms within living cells 'make use of many of the non-trivial features of quantum mechanics. That so many researchers have been surprised or even astonished that, for example, long-lived coherence plays a role in phenomena such as photosynthesis, demonstrates how 'non-trivial' this statement is. One of the biggest challenges in QB is too understand the nature of environmental noise within living systems that allows such quantum effects to persist.

But complex systems, living and not, have emergent properties that cannot readily be predicted from the properties of their components. The exponential increase in computational requirements with size means that that QM is unlikely to help much in predicting emergent properties of living things such as cognition."

Nowhere in the paper do we make such a claim that QM will help us in "predicting emergent properties of living things such as cognition". The computation requirements are irrelevant to the validity of observations that, for example, quantum coherence plays a role in photosynthesis or quantum tunnelling plays a role in enzyme action at the macroscopic level of enhanced function, see, for example Scholes, Gregory D., et al. "Using coherence to enhance function in chemical and biophysical systems." Nature 543.7647 (2017): 647.

Second, what is meant by quantum mechanics here? Is it quantization, energy gaps accounting for chemical stability and reactivity or just the non-trivial aspects such as entanglement and interference?

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We acknowledge that we may not be entirely consistent and clear about this vital distinction. We have addressed this at various places in the ms. Of course, "quantization, energy gaps accounting for chemical stability and reactivity" are nothing to do with what we mean by quantum biology (as we explained above). So, yes, we do mean the referee's latter definition (that quantum biology deals with the 'non-trivial' aspects of QM). We have expanded our discussion about this point, taking into account, and referencing several recent articles on this matter (eg Scholes, as well as the work of Plenio and others). While it is true that the jury is still out on many of these effects, there is no doubt that non-trivial quantum mechanics plays an important role in many important biological phenomena. We make this clearer in the ms, outlining that the field of QB is still emerging, but while speculative, it is nevertheless interesting enough to explore further.

I think the historical perspective and evolution of ideas described here could be an interesting contribution, but a very extensive rewrite is needed to clarify what is meant by "quantum" at each stage of the development of ideas.

This is an important point, which we have addressed in the revised manuscript.

Referee: 2

Very nice manuscript.

Referee: 3

..As this piece - although interesting - does not seem to me to contain enough scientific detail about the ideas of the early scientists mentioned and the more modern trends in what is called quantum biology. My main problem is that this lack of detail makes it very difficult to understand what the influence of these early physicists on current thinking in QB might actually be, aside from the use of the term "quantum biology".

This is a valid point and we have attempted to address this more carefully. It is of course vitally important to understand the distinction between what the early quantum pioneers meant by quantum effects in biology in comparison with the current interest in the subject.

It would seem to me that their ideas and concepts of aperiodic crystals, role of large fluctuations and the primacy of quantum mechanics in determining bonding, forces, structure, etc. was largely integrated into mainstream research - see the passage by Lounget-Higgins –

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It's fair to say that the early pioneers certainly did *not* anticipate the developments of the past couple of decades, such as importance of quantum tunnelling in electron and proton transport within cells, or its potential and still speculative role in olfaction and point mutations between DNA base sites, let alone their prediction of the role of environmental noise in prolonging rather than destroying quantum coherence. Similarly, Max Planck did not

predict the direction that quantum mechanics would take just as, when formulating special relativity, Albert Einstein did not predict its application for nuclear energy. We point out in our manuscript that both Erwin Schrödinger and Pascual Jordan had the insight to recognize that the key feature of living cells that makes quantum mechanics important in biology was the exponential amplification achieved by biochemical dynamics which amplify molecular signals to the macroscopic level. This remains a crucial element of modern quantum biology. We have also added a new paragraph highlighting that Erwin Schrödinger's book *What is Life?* provides a powerful link between the past and the present and provides the continuity in thinking and a justification for this historical narrative.

For publication in as a review in a physics journal, I'd expect to come away with a better understanding of either the field itself or the movements/ideas that created it (who knows, one might wish to track back and try some of the many paths less travelled that appeared along the way).

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Aside from this, as an article in the field of history of physics, I also felt that it is quite light on references to the academic literature on Schrodinger and - in particular - Jordan, and (minor point) some of the milestones on the timeline at the end do not have any corresponding references to the original articles.

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I'd also suggest that the authors have missed an important figure on their timeline - Herbert Frohlich - whose celebrated "green book" was probably much more in line with many of the "non-trivial" theoretical ideas now under discussion in photosynthesis, tunneling, etc.

There is now a new section on the work of Herbert Frohlich and the Fröhlich hypothesis, as well as some revived current interest in testing it with high intensity terahertz radiation.

Referee: 4

The manuscript "The origins of quantum biology" by McFadden and Al-Khalili traces the roots of the topical field of quantum biology back to the early days of quantum mechanics. As the authors state, it is often assumed that quantum biology is a new discipline which has only emerged within the last couple of decades. Whilst this is arguably the case when it comes to experimental evidence of non-trivial quantum effects in biological processes, this article shows that the ideas behind quantum biology are in fact much older.

I enjoyed reading this well-written and well-structured manuscript. As far as I can tell it is both scientifically and historically accurate.

A minor comment on the authors' statement "...quantum entanglement has been implicated in avian navigation [7]." Reference [7] did indeed provide strong experimental evidence for the radical pair mechanism, but I believe neither quantum coherence nor entanglement were mentioned in this paper (although it would be fair to say this is to some extent implicit in the RP model itself). To the best of my knowledge, Phys. Rev. Lett. 104, 220502 and Phys. Rev. Lett. 106, 040503 were the first papers to explicitly explore the "quantumness" of the avian compass. Other than that, I have only stumbled across some very minor typographical issues (see list below).

A fair point. We have rewritten the text to more accurately reflect that there was no explicit mention of quantum entanglement in ref [7] – indeed that the very notion of quantum entanglement itself is an emotive issue with many quantum physicists and chemists. We have tried to tread more carefully and have added those two PRL references.

In summary, I believe this manuscript makes an interesting and valuable contribution, offering an important perspective on the history of quantum biology for an audience much larger than that of active researchers in this field. I am more than happy to recommend publication in Proceeding of the Royal Society A.

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- page 16 line 9: umlaut missing in "Löwdin"?

All addressed.

Referee: 5

The authors present a historical perspective on the origins of quantum biology, that is, the idea that non-trivial quantum mechanical effects (i.e. beyond chemical bonding) may play a fundamental role in biological processes. As they rightly point out, though this field has burgeoned over the past few years, there is also a longer history of scientists attempting to link both the features and philosophy of quantum mechanics with biological phenomena. It is this point, and a description of some of those attempts that form the basis of this article, with the argument put forward that these earlier insights remain relevant for the field of quantum biology today.

The article is written in an informal style, though I found it readable and the historical aspects interesting. My main concern, however, is that it overstates the current evidence for the importance of quantum effects in biological phenomena and presents very little in the way of critical analysis of some of the earlier ideas of the quantum pioneers. For example, in the first line of the abstract, it is already suggested that biological phenomena have been demonstrated to make use of many non-trivial features of quantum mechanics (note that the same sentiment is repeated also in the first line of the introduction, and in other parts of the article, e.g. on page 12.). As far as I am aware, however, this is not the case. For example, though quantum coherence can be generated in photosynthetic systems under laboratory conditions, there is no proof yet that such features play a useful role (or indeed are even present) within the natural setting. I believe similar arguments hold true for the other examples cited (e.g. avian navigation and enzyme catalysis) and indeed the role of quantum mechanics in olfaction in particular continues to cause controversy. Note that I am not hostile to the idea of quantum biology, but I do believe it is important to be accurate with regard to its current status.

A valid point, which we have addressed. In the revised manuscript we have made it clear that the evidence for quantum effects in biology is still being debated and is far from settled.

Furthermore, the earlier ideas of Jordan, Bohr, and Schroedinger, for example, are not really critiqued in any meaningful manner. How are these ideas still influential and relevant in quantum biology today? What is their legacy and status within the relevant communities?

We have, in the revised ms, provided a more critical analysis of the contribution of these early pioneers that remains relevant to modern QB.

Some minor comments:

- It is mentioned in section 2 that Bohr gave a lecture in 1929 that touched on whether quantum mechanics may play a role in biology. However, the subsequent quote gives us no indication of his thinking - is there any more insight that can be given here?

Words added.

- Later in this section there is a brief discussion and related quote on Bohr and complementarity. I wasn't clear what point was being made here - could the authors expand on this?

We feel that our words on this topic:

> … Like Jordan, he [Bohr] was influenced by the organicists' view that the mysterious ingredient of life was yet to be discovered; but rather than opting for quantum indeterminacy, Bohr claimed instead that the mystery ingredient was a quantum concept that he helped to conceive: complementarity. Often

> referred to as *wave-particle duality*, this was for many of its founding fathers the central tenet of quantum mechanics. Indeed, for Bohr, the notion of complementarity went deeper than merely describing the dual nature of quantum entities and he would later in life attempt to expand it into a broader philosophical notion. But, in its simplest form it can be applied, for example, to the nature of light, which can exhibit both wave-like and particle-like properties, but never both at the same time: the properties are complementary. Bohr attempted to extend this notion of complementarity into biology by arguing that there was an analogous complementarity between the functionality of life and our ability to study it…

speak for themselves. Bohr was, as we state, looking for that mystery ingredient of life. But unlike others, such as Jordan (who though it was connected with quantum indeterminacy) or Delbrück and Schrödinger (amplification), Bohr suit to link it to his developing ideas on complementarity. We did not wish to dwell to long on this as Bohr himself never crystalized these views.

- In section 3, there is a quote from an article by J. Haldane which states "...life takes advantage of the uncertainty principle to make certain events more probable than they would otherwise have been...". What does this mean? Is uncertainty principle used here as a proxy for quantum mechanics, or is it really the principle itself to which Haldane is referring.

This has been addressed. A longer quote is now included, and Haldane's position explained more clearly.

- I found the description of quantum coherent systems as vibrating in phase a little misleading on page 11. Also, the relationship between quantum tunnelling and jumps is not entirely clear. Usually, a jump is associated with an incoherent process or measurement, rather than a coherent one.

We have tightened up on the wording.

Board Member comments that one of the referees' comments to the editor states:

"Some of the historical material is interesting some just silly. Did Bohr "tower" over Schrodinger, Heisenberg and Dirac? (p3 L11). Dwelling on Jordan's Nazi sympathies seems irrelevant unless this is a work of social science." I also agree with those points.

We have removed the comment about Bohr towering over the other quantum physicists of the time. However, it is disappointing that the referee in question did not appreciate our point here. We do not mean that he was towering intellectually, or in terms of his contribution to the field per se, but rather through his well-known influence on the thinking of those younger physicists around him, as well as on later generations. The whole point of the early development of quantum biology is that the likes of Delbrück and Jordan were indeed strongly influenced by Bohr.

On the matter of Jordan's Nazi sympathies, we find it quite surprising that the referee cannot see why this is relevant. When we state that "... after Germany's defeat, Jordan's highly politicised ideas became anathema" our claim is that one of the most important reasons for this work on the application of quantum mechanics to biology to have fallen into disrepute after the war was precisely due to Jordan's political views. It is also disappointing to read that an article on the history of the development of a scientific field should somehow be devoid of social science. How else can one assess the reasons for the failure of quantum biology to develop in the 30s and 40s if not by exploring the socio-political landscape of the period?

Appendix B

Response to referees

We firstly must apologise for the delay in resubmission of this manuscript. We have taken on board all the comments of the referees and have addressed each of them as carefully as we can, as outlined below. In most cases, we have tightened wording, added references and further clarifications and expansions. However, as might be expected, we disagree strongly with certain comments and therefore state our position, hopefully, more clearly (both in the notes below and in the manuscript itself). The referees' comments are **in bold** and our responses are below them.

We note that referees 2 and 4 recommend publication, albeit with some minor corrections and valid points made by referee 4. Referee 5 is also favourable but makes a number of comments and suggestions which we have taken on board. Referees 1 and 3 are more critical. While it is disappointing that the board member sides with them rather than the other three referees, we have tried our best to address their often very valid points. There is, inevitably with such thoughtful and thorough reviewing, a number of common points and criticisms (such as the need for a much more nuanced and thorough critique of the legacy and influence of the early quantum pioneers such as Bohr and Schrödinger.

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However, the reviewer does make a valid point that there is some difficulty in defining the meaning of 'quantum biology'. In the original and revised manuscript we go to great lengths to define the term, as biology that involves non-trivial quantum phenomena, such as long-lived quantum coherence and superposition, quantum tunnelling and even quantum entanglement. We of course accept that biology is chemistry and chemistry is physics, but, despite this fact, chemistry is nevertheless a discipline distinct from physics. Similarly, QB is a distinct discipline from either QM or biology. So when the referee states that of course QM is essential for life in the same way that it is essential to understand chemistry, they are missing the point of what we are saying. Of course we must use the quantum rules to understand molecular and atomic bonding, electron orbitals and discrete energy levels etc. in biology just as we do in chemistry. This is all entirely correct... *but it has nothing to do with quantum biology*. We make this clear in the very first sentence of the Introduction, stating that there is now strong evidence that certain mechanisms within living cells 'make use of many of the non-trivial features of quantum mechanics. That so many researchers have been surprised or even astonished that, for example, long-lived coherence plays a role in phenomena such as photosynthesis, demonstrates how 'non-trivial' this statement is. One of the biggest challenges in QB is too understand the nature of environmental noise within living systems that allows such quantum effects to persist.

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The authors present a historical perspective on the origins of quantum biology, that is, the idea that non-trivial quantum mechanical effects (i.e. beyond chemical bonding) may play a fundamental role in biological processes. As they rightly point out, though this field has burgeoned over the past few years, there is also a longer history of scientists attempting to link both the features and philosophy of quantum mechanics with biological phenomena. It is this point, and a description of some of those attempts that form the basis of this article, with the argument put forward that these earlier insights remain relevant for the field of quantum biology today.

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Furthermore, the earlier ideas of Jordan, Bohr, and Schroedinger, for example, are not really critiqued in any meaningful manner. How are these ideas still influential and relevant in quantum biology today? What is their legacy and status within the relevant communities?

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We feel that our words on this topic:

> … Like Jordan, he [Bohr] was influenced by the organicists' view that the mysterious ingredient of life was yet to be discovered; but rather than opting for quantum indeterminacy, Bohr claimed instead that the mystery ingredient was a quantum concept that he helped to conceive: complementarity. Often

> referred to as *wave-particle duality*, this was for many of its founding fathers the central tenet of quantum mechanics. Indeed, for Bohr, the notion of complementarity went deeper than merely describing the dual nature of quantum entities and he would later in life attempt to expand it into a broader philosophical notion. But, in its simplest form it can be applied, for example, to the nature of light, which can exhibit both wave-like and particle-like properties, but never both at the same time: the properties are complementary. Bohr attempted to extend this notion of complementarity into biology by arguing that there was an analogous complementarity between the functionality of life and our ability to study it…

speak for themselves. Bohr was, as we state, looking for that mystery ingredient of life. But unlike others, such as Jordan (who though it was connected with quantum indeterminacy) or Delbrück and Schrödinger (amplification), Bohr suit to link it to his developing ideas on complementarity. We did not wish to dwell to long on this as Bohr himself never crystalized these views.

- In section 3, there is a quote from an article by J. Haldane which states "...life takes advantage of the uncertainty principle to make certain events more probable than they would otherwise have been...". What does this mean? Is uncertainty principle used here as a proxy for quantum mechanics, or is it really the principle itself to which Haldane is referring.

This has been addressed. A longer quote is now included, and Haldane's position explained more clearly.

- I found the description of quantum coherent systems as vibrating in phase a little misleading on page 11. Also, the relationship between quantum tunnelling and jumps is not entirely clear. Usually, a jump is associated with an incoherent process or measurement, rather than a coherent one.

We have tightened up on the wording.

Board Member comments that one of the referees' comments to the editor states:

"Some of the historical material is interesting some just silly. Did Bohr "tower" over Schrodinger, Heisenberg and Dirac? (p3 L11). Dwelling on Jordan's Nazi sympathies seems irrelevant unless this is a work of social science." I also agree with those points.

We have removed the comment about Bohr towering over the other quantum physicists of the time. However, it is disappointing that the referee in question did not appreciate our point here. We do not mean that he was towering intellectually, or in terms of his contribution to the field per se, but rather through his well-known influence on the thinking of those younger physicists around him, as well as on later generations. The whole point of the early development of quantum biology is that the likes of Delbrück and Jordan were indeed strongly influenced by Bohr.

On the matter of Jordan's Nazi sympathies, we find it quite surprising that the referee cannot see why this is relevant. When we state that "... after Germany's defeat, Jordan's highly politicised ideas became anathema" our claim is that one of the most important reasons for this work on the application of quantum mechanics to biology to have fallen into disrepute after the war was precisely due to Jordan's political views. It is also disappointing to read that an article on the history of the development of a scientific field should somehow be devoid of social science. How else can one assess the reasons for the failure of quantum biology to develop in the 30s and 40s if not by exploring the socio-political landscape of the period?