

Selected comments from reviewers of “Why Decussate? Topological Constraints on 3D Wiring”.

- The manuscript is not clearly written.
- The paper is very well written.
- The argument that these results can contribute to our understanding of regeneration is doubtful.
- The paper makes excellent points regarding reorganization and rehabilitation.
- The manuscript presents ‘fraudulent’ work involving an attempt to ‘trick’ the reader.
- This is the kind of manuscript I look forward to reading.
- The authors mention non-existent impairments in function. Surely this is a joke.
- The authors’ analysis is simplified but very insightful.
- The work is scientifically unsound and is too insignificant to warrant publication in any journal.
- I congratulate the authors on a thought provoking article.
- The work is not mathematically rigorous at all.
- This is an article of importance in its field.
- The simulation is dubious.
- This is an interesting well written manuscript that provides novel insight into how geometrical constraints influence the necessity and utility of organizing the CNS as a decussated network.
- The manuscript contains no mathematical substance.
- This is a weak paper on many counts. The analysis and model is abstract and generic, far removed from biology.
- I cannot accept the central premise.
- The initial premise presented by the authors is rather straightforward yet intriguing.
- The authors make a serious error in biology by stating that many brain areas contain 3D representations.
- No one has ever suggested that there exists a 3D homunculus in any brain area above the level of the spinal cord.
- Most spatial representations in the brain are 2D, not 3D.
- Three dimensionality is a red herring as the body surface is 2D.
- The results are very striking obtained in a rather elegant manner.
- Obviously reflected images do not introduce any discontinuities.
- The authors suggest that translating the two halves of the brain will minimize the number of crossings. This is false of course.
- There is not enough comparative anatomy.
- The numbers of crossings calculated are incorrect.
- The authors are to be congratulated on attacking the problem of decussation using a novel, mathematically-based approach.
- Cajal’s argument that image continuity requires decussation is not clearly mentioned.
- The citations appear almost random, including works that seem completely irrelevant and neglecting relevant sources (e.g. Vehicles, by Braitenberg).
- Contralateral escape reflexes are likely the antecedent of all decussations.
- The data analysis, collection and interpretation are inadequate.
- The underlying mathematics are not included in sufficient detail.
- The implications and support are not sufficiently clear.
- The manuscript does not do an effective job of presenting the argument.
- This manuscript certainly shows us that much thought has been put into understanding decussation since we were taught that simplistic way of thinking about neuronal wiring.
- The paper is not acceptable for review in Biophysical Journal as it does not deal with experimentally-based models or biophysical mechanisms.
- The Editors feel that your paper is not suitable for publication in the Journal of Theoretical Biology and is unlikely to be favorably reviewed by the referees.
- The arguments are presented in a very accessible style, the article is clearly structured and well written, and the main points are illustrated with instructive and well-designed figures.
- It is false in all pathways that the spatial relationships in spatial maps are preserved.
- The relevance of the motor control example is unclear.

- The manuscript includes a number of seemingly arbitrary statements.
- The abstract approach used obscures the biological relevance of the models.
- The reasoning is murky.
- The cartoons shown do not represent the body surface in any meaningful way.
- The paper neglects mapping strategy using crossings and rotations.
- The evolutionary simulation is underdeveloped and insufficiently specified.
- I do not see how the arrangement of processing units along a sheet of cortex has any relevance to the processing performed.
- While this mathematical framework may not explain all biological aspects of specific decussations, it provides a fresh and inspiring perspective that should serve as a good starting point for further objective wiring studies.
- The orientation of the cortical sheet cannot have anything to do with the brain's interpretation.
- Maps are generated using developmental morphogens, and so wiring errors don't arise.
- Map topology is not shown to be important to function.
- Introducing folds in surfaces will not lead to any changes whatsoever.
- The chirality effect discussed is strictly a property of viewpoint.
- Axons can approach a cortical sheet from either side.
- It is unclear why only some connections are decussated.
- The underlying assumptions are flawed.
- The discussion is truly well done and very refreshing to read as it contains very thought-provoking ideas.
- The paper is posed and solved incorrectly.
- Drawing a plane through points as shown is not always possible.
- The definitions in the paper are not robust because minor displacements may disentangle interlocked loops.
- The argument against alternative solutions is not convincing.
- There is no problem with mappings lacking crossings.
- The figure showing mirror images of 2 loops is incorrect.
- The assumption that topology of spatial organization is preserved is true in some cases but is not a rule.
- There seems to be a confusion between the physical space that the nervous system monitors continuously and the intrapersonal space that is occupied by the sensorimotor nervous system and body parts.
- The text and figures are confusing.
- The discussion is loose and repetitive.
- Accompanying explanations are insufficient.
- The authors have not provided an explanation for why decussation occurs and their view is not in accord with modern information.
- The authors make no effort to demonstrate that number of crossings should be minimized.
- The authors have not demonstrated that other topological mappings do not have fewer crossings.
- The paper does not account for when decussation should occur and when it should not.
- The theory does not provide an explanation for decussations, and does not contain the biological relevant processes for establishing the coordinate system and for reading it out.
- The manuscript does nothing to explain the phenomenon of crossing. The standard idea is that crossed pathways originated in escape responses from dangerous stimulae.
- I am unable to make any sense of the definition of crossing that the authors use.
- There is no change in topology of connections in the figure shown.
- It is obvious that regenerated wiring must recapitulate the old wiring and decussation has no impact on this per se.
- The situations examined are biologically unrealistic.
- I do not know of any example of the surfaces of a cube mapping onto the surfaces of an identical cube.
- Axons are observed to cross over other axons and so we do not know how important it is to minimize the number of crossings they make. Empirical data is essential here.
- The simulations do not add much.
- The paper is not well presented.
- Nomenclature is a bit unhelpful.
- The discussion about the ordering of fibers is fairly opaque.

- The paper contains a number of fatal errors.
- The authors merely draw lines in their figures to produce the illusion of crossings.
- The work is far removed from experiment and it is not at all clear that the work leads to an experimentally testable hypothesis. This work will not have an impact on either computational or experimental biology.
- I do not see how the simulation indicates a plausible mechanism for evolution of a decussated system since an ipsilateral system does NOT evolve toward a decussated structure.
- The authors fail to take into account that there are as many pathways that do not decussate as ones that do.
- I do not find an explanation as to why some fibers within a tract may or may not decussate.
- The initial conditions are not justified and are misspecified, introducing a critical flaw in the logic of this submission.
- The description of 2D vs 3D processing of information is a serious mischaracterization.
- The statement that the results are purely mathematical is unfortunately right, and this halfhearted description points to the problem of setting initial conditions properly.
- The retina and skin are appropriately modeled as simple 2D sheets, not 3D ones. Representations in most of the CNS are 2D and 1D. Thus the text and elegant analysis applies to 3D representations that do not actually exist in biological systems.
- The assertion that decussation minimizes targeting errors is problematic; especially, the presence of numerous initial errors in development is not discussed.
- Crossings are not defined in a mathematically rigorous way.
- There is nothing wrong with the reflection of somatotopy.
- Several sentences are meaningless and make me suspect the authors of homunculus fallacy.
- The article demonstrates that the apparently poor engineering solution may make very good design sense after all.
- Incorrect quotation of Ramon y Cajal's explanation of crossing of the optic chiasm.
- Manuscript presents a poor and confused elaboration of the principle proposed.
- Since 2D to 2D connections are possible, there is no singularity in 3D.
- The definition of crossings is ambiguous and the description used is inaccurate.
- Projections from the eyes and olfactory bulb contain plenty of crossings, which is not addressed.
- Chemical guidance eliminates the need to limit crossings.
- The manuscript lacks a clear description of the model under study.
- It is not clear which kind of simulations were performed.
- The text is mainly intuitive and it is difficult to evaluate what is supported by simulations.
- The numerical results are unclear and insufficient.
- Decussation and crossing have not been sufficiently discriminated, and that their conflation impacts the conclusions of the study.
- The article does not convincingly address the issue of decussations, as opposed to crossings within fiber bundles.
- There are several problems concerning the putative link between structure and function, as well as the postulated role of genetics in the development of decussated anatomy.
- There is a lack of detail that is provided regarding some of the computational models.
- The authors have not convincingly demonstrated that issues governing crossings within bundles have anything to do with decussations.

And finally:

- This reviewer reserves the right to add more points of critique should the manuscript be resubmitted.