# **Response letter for netessay resubmission**

# **(Cell Systems )**

# **Reviewer 1**

### -- Ref 1.0 Overall --

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| Reviewer  Comment | In this perspective the authors survey the field of network biology in what appears to be an attempt to disentangle the proverbial "hairball". The primary conceptually novel contribution offered by the authors is a functional division of networks into two archetypes: (1) Abstract networks - The classical graph data structure which represent an abstraction of biology, (2) Mechanistic networks - networks which add some specific aspect or property of biology to the representation - e.g. protein-protein interactions, or metabolic networks. The authors argue that the first approach offers the benefit of formalism transfer and in the latter since it is more difficult to adapt mathematical formalism directly one can/should use cross-disciplinary comparisons.  The perspective is written clearly and offers a broad survey of the field of network biology, while touching on highly relevant work from adjacent fields and providing compelling examples for many of its points. In my opinion this is the strongest aspect of this manuscript. As it stands, it offers a rather lackluster organization principle to thinking about the field. More importantly it offers little in terms of forward vision or conceptual advance over what is currently known and practiced, which in my opinion is an important component of a good perspective piece.  That said I think that if the authors were to reorganize their thinking on the topic (it is at times unclear they actually buy into the organizing principle they are peddling here), and potentially add additional discussion on where the field might be headed this could be turned into a solid perspective piece on network biology. |
| Author  Response | We appreciate the reviewer’s overall comment. We have added the discussion about the future work in the last paragraph in Conclusion (See details in the following points). In this manuscript, we actually did not divide networks into two categories. Instead, we discussed how two approaches at high level, abstract and mechanistic approaches to help gain biological insights via cross-disciplinary comparisons. |

### -- Ref 1.1 Division of biological networks--

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| Reviewer  Comment | The organization principle for this perspective dividing biological networks into abstract vs mechanistic networks seems a bit contrived and uninsightful. First, it seems that any mechanistic network can be examined as an abstract one by stripping away (i.e. ignoring) some of its mechanistic particularity. Second, it seems like even the authors find this division of little use as an organizing principle in their writing, dropping this partition midpoint in their writing. Third, it seems really unclear what's the take home to this division - I can add specific biologically motivated additions to a network model, how does this preclude abstraction? How do mechanistic aspects actually prevent the use of mathematical formalism or its interpretation/adaptation into a specific set of biological principles? |
| Author  Response | Thank the reviewer’s questions. We didn’t intend to classify all networks into two classes. As the reviewer point out, any mechanistic network can be examined as an abstract one. In fact, as shown in the text, we have used the terms “abstract approach” and “mechanistic approach”. What we intend to, is to discuss two complementary approaches for discovering meaningful biological information form hairball networks. The abstract approach facilitates the use of various mathematical machineries whereas the mechanistic approach allows one to borrow certain intuitions in several other systems. |

### -- Ref 1.2 Cross-disciplinary comparison--

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| Reviewer  Comment | Cross-disciplinary comparison should be used judiciously. In my eyes and as the authors point out in their conclusions, biology is a field already full of borrowed ideas and simplifications - I would further add abused and battered analogies to this. To prescribe this principle as some panacea for improving our understanding of the complexity of biological systems seems odd or even a downright bad idea (e.g. from the abstract "comparison of mechanistic interactions in systems for which we have much day-to-day experience can provide interpretative analogies for relatively more abstruse biological networks"). One might argue that, as it stands, this need for analogy and simplification comes far too naturally and that all too often one may have a hard time separating analogy from the underlying messy biological ground truth. I do agree with the overall sentiment presented in the first half of the abstract that there is much to gain by the transfer of mathematical concepts and formalism developed for one field into others. |
| Author  Response | Thank the reviewer. We also wanted to find the translational ideas from various borrowed ideas between biological and other systems. We thus summarized two approaches, abstract and mechanistic from many ideas, and discussed how they contributed to study biology via leveraging interdisciplinary comparisons. |

### -- Ref 1.3 Vision for the field’s future--

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| Reviewer  Comment | I suggest the authors attempt to distill their vision for the future of the field. More of the paper could be spent on identifying recent trends and highlighting future directions worthy of greater attention. Presently this is done briefly in the final concluding paragraph. |
| Author  Response | This is a good suggestion. We added additional discussions about potential future directions in network biology: 1) data integration using multilayers networks to more systematically study biological mechanisms; 2) dynamics of biological systems via comparisons with social and technological systems. |
| Excerpt From Revised Manuscript | In the last paragraph of Conclusion:  “...For example, next-generation sequencing technologies are generating a wide variety of gene regulatory data at various cellular scales, including transcription factor binding (ChIP-seq), RNA-binding proteins (CLIP-seq), histone modifications (ChIP-seq), and DNA methylations. One can thus systematically study gene regulatory mechanisms across cellular scales by integrating these datasets using multi-layer gene regulatory networks….”  “...In addition, biological, technological, and social systems are not static. They all have dynamics, and thus how to identify the dynamic patterns that distinguish these systems could be an interesting topic in the future. For example, how have the biological mechanisms evolved in biological systems compared with the changes of engineering designs in technological systems?” |

### -- Ref 1.4 Exploration of other network models--

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| Reviewer  Comment | One suggestion for an alternative organizing principle for this perspective could follow the familiar advice of George E.P. Box "All models are wrong, some are useful.". The authors could explore how different ways of thinking about networks in biology is wrong (i.e. does not appropriately capture the biological complexity) and how and in what ways these models are still useful. I think much of the currently presented text could naturally be recast from this perspective. |
| Author  Response | We appreciate the advice of George E.P. Box very much. However, we want to focus on the importance of cross-disciplinary analysis, and therefore we have spent much of the text on the good side of the comparison. We have a short section that discuss certain downside of various models (see the sections Criticisms on the abstract approach to networks and the conclusion). |

### -- Ref 1.5 grammar and style --

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| Reviewer  Comment | The paper would benefit from a some careful editing for proper grammar and style. E.g.: - "For perfectionist, in particular, networks have often prove frustrating because their abstract patterns don't always yield easily to precise molecular description." |
| Author  Response | Thank the reviewer for pointing out. We have fixed the typos and grammars through the entire document. |
| Excerpt from revised manuscript | “...For perfectionists, in particular, networks have often proved frustrating because their abstract patterns do not always yield easily to precise molecular description…” |

### -- Ref 1.6 “scale-free” of mechanistic networks --

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| Reviewer  Comment | Unclear what scale-free properties of networks tell us about "mechanistic networks". |
| Author  Response | Again, we are referring to the approach that explores the mechanistic nature of networks. While the scale-free property is a statistical property, we have explained several physical mechanisms leading to the scale-free property. |

### -- Ref 1.7 graph theory and graph data structure --

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| Reviewer  Comment | Graph theory and graphs as data structures predate computational social science and "Big Data". E.g. the first methods for solving sets of linear equations were based on flow networks. |
| Author  Response | Thank the reviewer. We added an example about flow networks in the section of “A spectrum of cellular descriptions”. |
| Excerpt from revised manuscript | “...For example, the flow network was used to model and analyze traffic in road systems…” |

# **Reviewer 2**

### -- Ref 2.1 Overall comment --

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| Reviewer  Comment | This perspective paper is a "call-to-arms" for computational biology research to investigate and incorporate the network science work being in other disciplines. This is an important point and the message needs to be spread throughout the field. The authors create compelling arguments for studying the work outside of biology by thoroughly surveying topical questions within computational biology and for each example showing relations outside of the field. This has the wonderful effect of being a complete survey while introducing a need within the field. The paper is easy to read and a great addition to the field. It has relevance to everyone from lead investigators and to beginning students in the field. |
| Author  Response | Thank the reviewer. We appreciate it that the reviewer thinks this paper is of interests to a broad audience in the field. |

### -- Ref 2.2 future directions --

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| Reviewer  Comment | It would be nice within the conclusion to give some direction on how to attack and address these problems with current techniques from other fields. The majority of examples give compelling evidence but little detail on directions. (Of course I don't expect the group to give away their research agenda, but a small amount in this direction would be nice.) The figures help convey the story, in particular, figure 4 is excellent. |
| Author  Response | Thank the reviewer’s point. In the last paragraph, we added two concrete examples about future directions: 1) the exploration of gene regulatory mechanisms using multi-layers network; 2) the comparison of the evolutionary dynamics of biological versus social & technological systems. |
| Excerpt from revised manuscript | In the last paragraph of Conclusion:  “...For example, next-generation sequencing technologies are generating a wide variety of gene regulatory data at various cellular scales, including transcription factor binding (ChIP-seq), RNA-binding proteins (CLIP-seq), histone modifications (ChIP-seq), and DNA methylations. One can thus systematically study gene regulatory mechanisms across cellular scales by integrating these datasets using multi-layer gene regulatory networks….”  “...In addition, biological, technological, and social systems are not static. They all have dynamics, and thus how to identify the dynamic patterns that distinguish these systems could be an interesting topic in the future. For example, how have the biological mechanisms evolved in biological systems compared with the changes of engineering designs in technological systems?” |

### -- Ref 2.3 typos--

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| Reviewer  Comment | On second page, first sentence after Abstract approach:… has two periods. In the same section, third paragraph, Second the last sentence has an extra space.  In the mechanistic approach section, third paragraph I believe the italics extends beyond the author's intent. In same paragraph there is a problem with a special character on the citation for Vazquez. The same typo appears in the bibliography.  In the conclusion, the second paragraph has another sentence with an extra period.  There are some capitalization issues in the bibliography, both with initials and with journal names. |
| Author  Response | Thank the reviewer for pointing out typos. We have fixed the typos, grammar, and references through the entire document. |