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Editor

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Re: DREISS: Using state-space models to infer the dynamics of gene expression driven by external and internal regulatory networks

Dear Editor,

We hereby submit our revised manuscript entitled “DREISS: Using state-space models to infer the dynamics of gene expression driven by external and internal regulatory networks” by Wang et al.

We want to acknowledge the efforts of the editorial team and five reviewers in the reviewing process.. We also compared and found different dynamic patterns of interaction terms between worm and fly in a new supplemental figure (Fig. S3). In fact, this paper mainly focuses on the internal part, and the major results on the internal patterns have been never changed from the beginning when we submitted the original manuscript on June 2015.

1. Overview – long rong

This paper has went a long road…. We submitted this a year ago! We originally received a good set of reviews and then because of our procedural issues, it was sent to more viewers. We might point out that at least four the fire reviewers seem happy with this paper and just one reviewer seems a bit unhappy about our external dynamics.

1b) we’ve done every req. in this last round

in particular,

1. Paper is focusing on the Internal dynamics –

We want tro emphasize this is not what is not what is being criticiszed all of rthe crit is about the extenerl

All the results are on internal – the external is just for the reviewers

1. The crit of reviewer 2 on the ext was right in the first round – we made a typo – but is totally irrelevant now – it is just about arbitrary re-arranging of terms. We explicitly show this basedo nthe good suggestion of reviewer #5

We agree that we made and fixed a small mathematical typo pointed by the second reviewer in the previous revision, but this error was totally irrelevant to the central point of this paper, which is about the internal dynamics. In this round of review, the second reviewer questioned about the definition of “external” dynamics. We thus added this Eq. (2) to provide a full decomposition about the dynamics. As described underneath Eq. (2), we should emphasize that the subdivision of the rest non-internal terms is arbitrary. In this paper, we subdivided it into a purely external term and an interaction term. One can of course subdivide and regroup external-related terms according to their problems. Therefore, unlike the internal part, there is not a unique and correct answer to define the “external” term. Once again, our paper focuses on the internal dynamics and the Eq. (2)’s elaboration does not change our major results and conclusions about the purely internal dynamic patterns of worm and fly embryonic developments.

We hope that the reviewers can see the valuable contribution about this manuscript. Thank you for giving us the opportunity for revising our manuscript. We are looking forward to hearing from you.

 Yours faithfully,

 Mark Gerstein

 Albert L. Williams Professor

 of Biomedical Informatics

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*new text about subdividion in text\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

Equation (1), the state can be expanded as follows:

 (2)

, where is defined as the expression vector of the gene components driven only internally by genes in Ω. The rest terms captures the expression expression vector of the gene components in Ω affected externally by the genes in Ψ. In particular, represents the expression vector of gene components in Ω driven purely by the genes in Ψ since it only involves *B* and *U*, and captures the expression vector of gene components in Ω driven by the interactions between internal and external groups for involving *A*, *B* and *U*. In fact, we should emphasize that the subdivision of the rest terms is arbitrary; i.e., though we subdivided it into a purely external term and an interaction term here, one can subdivide it to multiple different terms, each of which sums up a group of , *k*=0,1,2,…,*t*-2.

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\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* new response to 2nd reviewer\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

We appreciate the reviewer’s comments. We provided a new equation, Equation (2) by a full decomposition to elaborate and clearly define internal, external and interaction components and their relationships with parameters of Equation (1): an internal component, X\_INT that is driven purely by internal group, an external component in that it only involves A, X\_EXT that is driven purely by external group and an interaction component in that it involves B and U, X\_INTER that is driven by the interactions between internal and external genes for involving all A, B and U.

We thnk the reviewer for pointing out the typo in the lats rougnd

Now the reviewer is criticisinzg the definition of the ext terms

Here we wish to point out this is somewhat arb .

Our paper focusses on the internal

In particular, here we subdiviede

The reviewer said our definition about the external dynamics was utterly wrong. However, we should argue that there is not unique answer about the definition of external dynamics.

In this paper, we subdivided the rest terms except purely internal one, into a purely external term and an interaction term: X\_EXT is purely determined by the external genes; i.e., input (or control) term should capture the external signals that are not related to the internal system. This definition of course can be very arbitrary and also extended to any term involving external parts, B and U. One can of course subdivide and regroup external-related terms according to their problems. Therefore, unlike the purely internal component, there is not a unique and correct answer to define the “external” dynamics. In this paper, we defined an interaction term X\_INTER in Equation (2) to capture the component driven by the interactions between internal and external genes. Finally, we have to emphasize again that in this paper, we focus on the internal part (i.e., iPDPs) and compare them across different biological systems. Thus, this new equation can help elaborate our decomposition and does not change our conclusions and results at all.

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