

Yale University

MB&B
260/266 Whitney Avenue
PO Box 208114
New Haven, CT 06520-8114
Phone: 1-203-432-6105
Fax: 1-360-838-7861
mark@gersteinlab.org
<http://www.gersteinlab.org>

Editor
PLOS Computational Biology

July 26, 2016

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. In this revision, we have completely responded and incorporated all comments from reviewers, and enclosed a revised manuscript along with a separate point-by-point response. We are glad that at least four of five reviewers satisfied our revision. In particular, based on the suggestions from the fifth reviewer, we added a new equation, ~~Equation (2)~~ ^{Eq. (2)} now ~~is~~ ^{to} elaborate and clearly define the relationships between internal, purely external and interaction terms in our decomposition. We also compared and found different dynamic patterns of interaction terms between worm and fly in a new supplemental figure (Fig. S3). ~~In fact~~ ^{we} this paper ~~mainly~~ ^{is} 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.

We appreciate your work so much in long journey about reviewing this manuscript. 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 for the ~~five~~ ^{five} reviewers seem happy with this paper and just one reviewer seems a bit unhappy about our external dynamics. 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~~ ^{the} can of course subdivide and regroup external-related terms according to the ~~problems~~ ^{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

ALMOST COMPLETE

TO BE CLEAR

OK

AT HAND

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 subdivision in text*****

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

$$X_t = AX_{t-1} + BU_{t-1} = A(AX_{t-2} + BU_{t-2}) + BU_{t-1} = A^2X_{t-2} + ABU_{t-2} + BU_{t-1} = A^3X_{t-3} + A^2BU_{t-3} + ABU_{t-2} + BU_{t-1} = \dots = A^{t-1}X_1 + A^{t-2}BU_1 + A^{t-3}BU_2 + \dots + ABU_{t-2} + BU_{t-1} = \underbrace{A^{t-1}X_1}_{X_t^{\text{INT}}} + \underbrace{\sum_{k=1}^{t-2} A^k BU_{t-1-k}}_{X_t^{\text{INTER}}} + \underbrace{BU_{t-1}}_{X_t^{\text{EXT}}}$$

(2)

, where $X_t^{\text{INT}} = A^{t-1}X_1$ is defined as the expression vector of the gene components driven only internally by genes in Ω . The rest terms ^{OPTHS} $\sum_{k=1}^{t-2} A^k BU_{t-1-k} + BU_{t-1}$ capture the expression vector of the gene components in Ω affected externally by the genes in Ψ . In particular, $X_t^{\text{EXT}} = BU_{t-1}$ represents the expression vector of gene components in Ω driven purely by the genes in Ψ since it only involves B and U , and $X_t^{\text{INTER}} = \sum_{k=1}^{t-2} A^k BU_{t-1-k}$ 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 $\sum_{k=1}^{t-2} A^k BU_{t-1-k} + BU_{t-1}$ 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 $A^k BU_{t-1-k}$, $k=0,1,2,\dots,t-2$.

WE PLUS
PLUS
PLUS
PLUS
XINT

GRAM.

***** 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. 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.

TRANS

L-FZSL

In this paper, we subdivided the rest terms $\sum_{k=1}^{t-2} A^k BU_{t-1-k} + BU_{t-1}$ 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.

F FIAND
