New comments from Reviewer1:

The paper somewhat improved, but it is still difficult to read by someone not directly involved in this project. My recommendation is to focus on Abstract and Introduction to clearly describe the key ideas. Then the rest of the paper can be more easily understood. Specifically, when I read abstract, the meaning or purpose of the following terms is unclear to me:

- line 30: a model system (a biological system?), a human tissue (omit this term completely?), a T-score calculation (too generic, T-score of what?)

Revised accordingly.

- line 31: complex human system (complex human biology?),

Revised accordingly.

- line 33: specimen (in expression assay?)

Revised accordingly.

 - line 36: T-score (of what?)

Revised accordingly.

- line 39: If the SEM is limited to 3 nodes, it would be useful to make a comment here whether it is too limiting, or what other applications can be considered, and whether 2 input and 1 output variable are always assumed

Yes, a 3-node SEM model is the most popular choice. There are many other kinds of SEM models with more nodes that fit different hypotheses. In our practice, we focus on the 3-node SEM model to test our hypotheses and help to explore potential relationship among other “factors”, which are represented as the variables/nodes in the SEM model.

- line 43: not sure if removing 'in silico' would actually improve the clarity of this sentence

We chose the word “*in silico*” because it helps us with hypothesis generation exploration. Not only does it save resources, but it also helps us to narrow down the candidates and ultimately saves us plenty of time to conduct the experiment.

To illustrate further, I am looking at the supplementary file.

-  page 1: 'in the SEMIPs project' more clear would be 'in the proposed SEMIPs method' and 'we tested the relationship among 3 variables assuming a three-node SEM model' and it would be better to clarify what variables are assumed; next sentence says 'each of these factors' but it is unclear what factors are meant, since no factor was mentioned previously; and again, T-score is mentioned, but it is unclear what quanitity the T-score is calculated for

Revised accordingly.

Furthermore, in Figure 1, where is the SEM considered? It may be useful to emphasize it.

Revision was made to the figure 1 by enclosing the SEM model with a green rectangle and the legend was revised accordingly by “through a 3-node SEM model indicated by the green rectangle.”

In Figure 3, what are the white circles overlaping labels?

Revision was made to the figure 3 legend “The while circles represent targeted subset of genes to be eliminated in both bootstrap simulations.”

Figure 4 makes it clear what 3-variable SEM looks like, perhaps the general version of this model should be shown and explained earlier in the manuscript.

Revision was made to the figure 4 legend “Model fit statistics for the joint regulation of the SOX17 gene expression levels by GATA2 and PGR activities in the GEO accession: GSE58144 dataset illustrated in the 3-node SEM. Two exogenous variables are “Gene Signature of GATA2 Direct Downstream Targets” and “PGR Gene Signature” respectively, and one endogenous variable is “SOX17 Expression Levels”.”