**Reviewer 2:**

**Major comments:**

Line 73-75: More details about the t-score should be added here, i.e. the assumptions and observed data for the t-test.

**################## Prepared by Jianying and Ty ########################################**

The main motivation using a “t-score” was to achieve the cross-species projection from a model animal (mice or rats) experiment to another species or human when a perturbation was not directly applicable (Wu, S.P. et al. 2015). With a model animal (mice or rats) experiment, normally the animals are randomly assigned into two groups, where one group will receive “placebo” and/or no treatment and another group will receive the perturbation treatment. Experimental measurement will be properly collected from both groups (i.e. gene expression profile from a Microarray experiment). Significantly changed genes/probes (signatures) will be obtained from this analysis according to some thresholds followed by a statistical analysis with directionality (up/down regulation). Such a list of genes/probes are deemed collectively as the “gene expression signature” of biological responses to a particular perturbation. And these genes are referred as “signature genes”. This finding and information will be projected into another animal system (i.e. human) of interest bearing the assumption that the experimental animal of interest would respond similarly if the perturbation were applied.

In a separate experiment of interest that is done with species of interest (i.e. human), the homologous genes of those previously identified genes/probes from the experimental species will be selected, and the experimental measurement from this study (GEO accession: GSE58144, (Koot et al. 2016)) will be used. The directionality information will be used to group these genes into two separate groups. A normal t-statistics will be calculated from these two groups of measurement to represent the responses in a new species and new experiment set up of interest. Since this calculation was originated from a standard t-test statistics and the term “T-score” was coined firstly by Wu, S.P. et al (Wu, S.P. et al. 2015) and have been widely used in other research projects. Samples of interest (i.e. human) with T-score larger than 0, which share a similar signature gene expression profile from the original model animal, were classified as having gene signature activities and vice versa.