Detecting differential interactions during Cell Cycle Exit in Drosophia Wing Development using Comparative Generalized Logical Modeling

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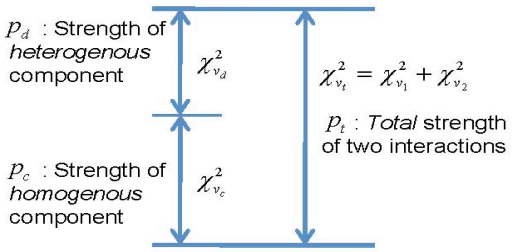
Abstract —A comparative interaction detection paradigm is proposed to study the important gene expression program in the control of cell proliferation during development. Instead of reconstructing the entire gene regulatory network involved, statistical significant differential interactions, represented by the generalized logic, are detected directly from time course data. Simulation studies suggested substantially increased statistical power of the proposed method over the intuitive reconstruct-then-compare approach. The method was applied on a comparative microarray experiment during fruit fly wing development as cells exit the cell cycle and stop proliferating, and under a condition which delays this exit, over-expression of the transcription factor, E2F. One significant differential interaction, involving the Hippo pathway, between two gene clusters was identified.

Keywords —**Chi-square test,Comparative modeling, Cell cycle exit,**

I. Introduction

An interaction is an association from one or more parent genes to a child gene. Because weak interactions may stand out when contrasted in a comparative experiment, we have developed a comparative modeling paradigm to detect novel gene interactions, represented by generalized logic, for such experiments. Our strategy, based on heterogeneity and homogeneity chi-square tests, extends meta-analysis to data under different conditions. Our new comparative modeling approach is therefore likely to uncover novel gene interactions, missed by other approaches. Our innovation is to extend the heterogeneity and homogeneity chi-square tests by associating the expression of each child gene with potential parent gene expression levels at the same or previous time points. This association takes a non-parametric form that can be highly nonlinear. Our approach generalizes the correlation-based comparisons [1], which can be considered a single-parent, linear, zero-delay, and static interaction. We use a generalized logic to represent an interaction. Our approach directly assesses the contrastive strength of a pair of potential interactions, instead of reconstructing-then-comparing the interaction under each condition. An interaction will be selected if it consistently shows either similar or differential patterns. A remarkable property of this strategy is its determination of parents without having to estimate accurately the actual generalized logic.

II. Hypothesis Test Design



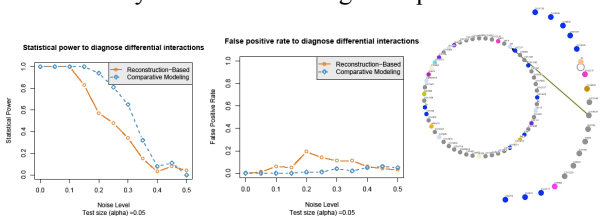
The total chi-square $-\chi_{vt}^2 = \chi_{v1}^2 + \chi_{v2}^2$

The homogenous component $-\chi_{vc}^2$

The heterogenous component $-\chi_{vd}^2 = \chi_{v1}^2 + \chi_{v2}^2 - \chi_{vc}^2$

III. RESULTS

We demonstrate through simulation study that our comparative approach can detect differential interactions more accurately without increasing false positive rates.



Through running on the Drosophia Wing cell cycle exit dataset, we have successfully detected a known direct interaction between the clusters, via CG14534 binding to Salvador in a yeast two-hybrid protein binding assay.

References

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