

Model-based approach for analysis of transcriptome perturbation reveals Ewing oncogene interaction network

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Perturbation experiments lead to lasting response of transcriptome, where many genes behave as switches and pulses.

Usual correlation based techniques suffer from the fact that many genes are formally correlated while in reality they have very different response characteristics. Therefore, we present a method that characterizes the shape of the response in more detail. We apply it to oncogene induction experiment in Ewing tumor cell-lines.

Method: from non-linear model based fit of time series to network reconstruction

To characterize numerically dynamical change of expression of every genes, we introduce two simple non-linear models of gene response, a “switch” and a “pulse”:

$$\begin{aligned} f(x) &= \alpha + \beta * \tanh(ax + b) \text{ for “switch”} \\ g(x) &= A + B * \exp \left[-((x - t)^2 \sigma^2)^\alpha \right] \text{ for “pulse”} \end{aligned}$$

From a transcriptome time series, we make a non-linear fit on every probset of these two functions (with matlab toolbox). For every fits, we compute a score: it is simply the ratio between the signal amplitude and the distance from the curve to the data points. Each probset is characterized by a score, a response time, response speed and length of pulse. It is an enhanced version of “binary signal extracting” in [1].

If the external stress on the biological system behave like a “switch” or a “pulse”, we can consider that genes that have a good fitting score are correlated with the stress. The selection of genes by their fitting scores (and other parameters) is a tool for finding the activated cellular pathways. It allows reconstructing a whole network containing the genes most probably involved in cellular response.

Once a network is constructed, dynamical simulations (based on chemical kinetics, boolean models etc.) can be applied to understand the time evolution of gene expression and produce theoretical predictions.

Results: annotated network of EWS/FLI1 effect in Ewing tumor cell lines

We apply this procedure to the Ewing tumor cells transcriptome time series produced by the experimental group of O. Delattre (Institut Curie, Paris). In the cell lines considered, chimeric gene EWS/FLI1 (responsible for tumor phenotype) can be blocked and reactivated artificially. Transcriptome response during 17 days (at 10 time points) was measured using Affymetrix microarrays.

The selection of main correlated genes with EWS/FLI1 combined with literature (21 review papers about pathways involved in cancer phenotype and 5 papers about EWS/FLI1 effect) produces the proteins influence network of the figure. It shows the main pathways induced by EWS/FLI1; the correlated genes are in green, the anticorrelated genes in red. Together with already established pathways (IGF1, TGFB etc. [2]), some other pathways appear to be involved, like p53 or Ras. Although the network is quite complicated, we can notice that the structure is mainly a flow from EWS/FLI1 to cell cycle and apoptosis, with a lot of inter-connections between pathways without too many global feedback loops.

Conclusion

The network of the figure is a first step for understanding the effect of EWS/FLI1 oncogene on tumor phenotype. Despite its complexity, it can give hints for further experimental investigations. The next step would be the application of dynamical model on the network, comparing theoretical time evolution with experimental transcriptome time series and other available data on Ewing tumor cells. An other direction of research will be the improvement of data processing in order to have a bigger and more complete network.

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Bibliography

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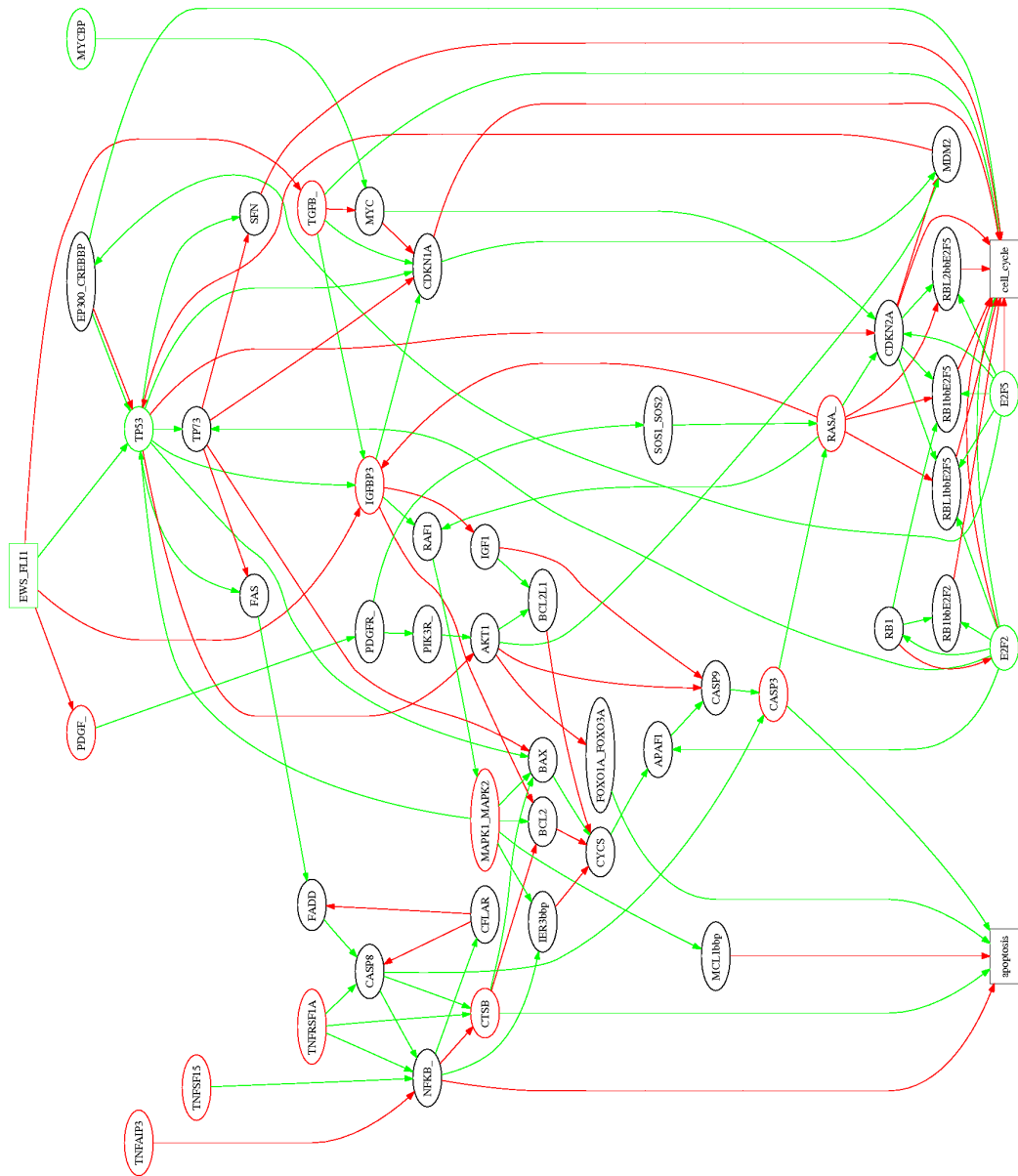


Figure 1: Network of main pathways of EWS/FLI1 in Ewing tumor cell lines. Name of genes a HUGO names. “geneA_geneB” means “GeneA or GeneB”. “bb” means “bind with”, “bbp” means phosphorylated. Node in green are correlated with EWS/FLI1 according to transcriptome time series, node in red are anticorrelated. Green arrows represent activation, red arrows represent inhibition.