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Introduction

A system-level understanding of the molecular underpinnings and functioning behaviour of a cell requires an accurate representation of the underlying complex networks of gene and protein interactions. Advances in molecular biology have provided a glimpse of such complexity through diverse measurements of cellular activities, so that mathematical techniques can be used to infer and visualize such interactions.

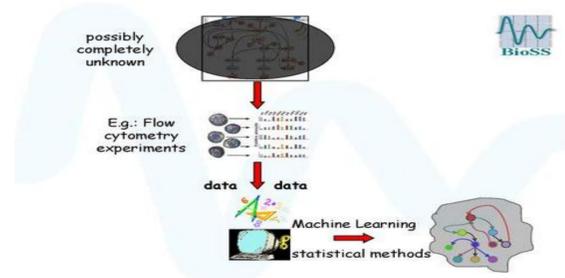


Figure 1: Diagram indicating the process of network reconstruction.

Goal of Network Biology

In systems biology, the goal of network inference or reverse engineering problems is to reconstruct the network of regulatory interactions from available measurements using mathematical framework.

In the work explained here, two inference methods are used to examine and analyze physiological cytokine network regulation during lactation.

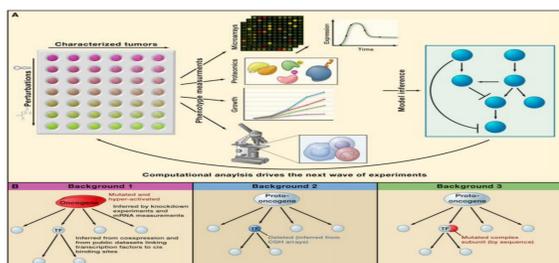


Figure 2: The overall goal of network reconstruction; a process where by network analysis can help researchers better identify the kinds of experiments to perform.

Inference Methods

Bayesian Inference Method

- A Bayesian network is a network of interacting variables (e.g. genes or proteins) is represented as a graph in which the variables are *nodes* and interactions between them are *directed edges*. Where edges between nodes are associated with a conditional probability tables containing likelihood of the states of the variables.

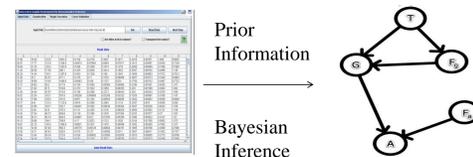


Figure 3: Diagram indicating the inference process for the Bayesian method.

Regression Based Inference Method

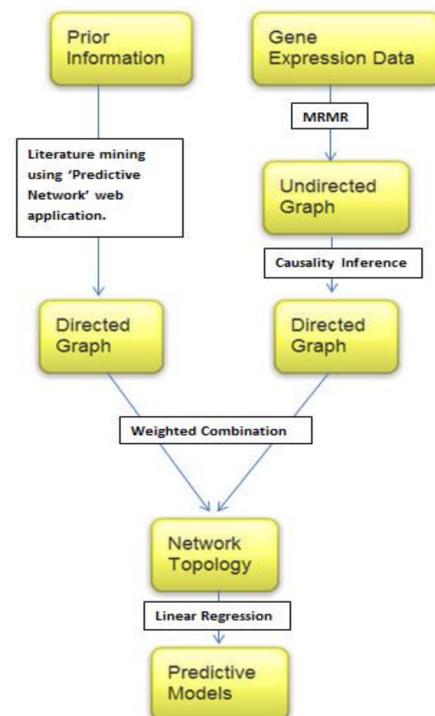


Figure 4: Schematic of the Regression based inference method used.

Results

| IL12A | CCL5 | PRL | IL13 | HSD3B1 | CYP19A1 | IFNG | CXCL1 | CCL2 | CCL3 |
|-------|-------|-----|-------|--------|---------|------|-------|------|------|
| IL1A | IL1B | IL3 | CCL11 | IL4 | IL5 | IL6 | IL9 | IL10 | CSF3 |
| TNF | IL17A | IL2 | IL12B | CSF2 | CCL4 | | | | |

Table 1: Showing the cytokines and hormones inferred.

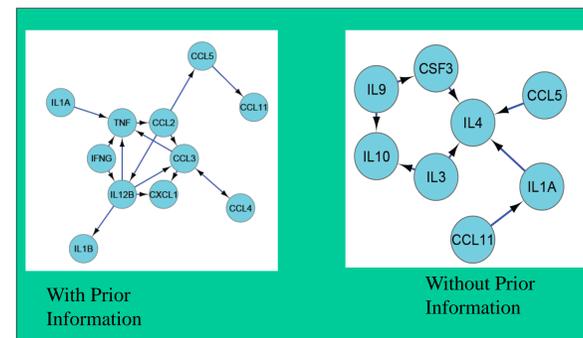


Figure 5: Network results obtained from the regression inference method. Without prior information, 8 interactions and 8 variables are recovered, while 15 interactions and 11 variables recovered.

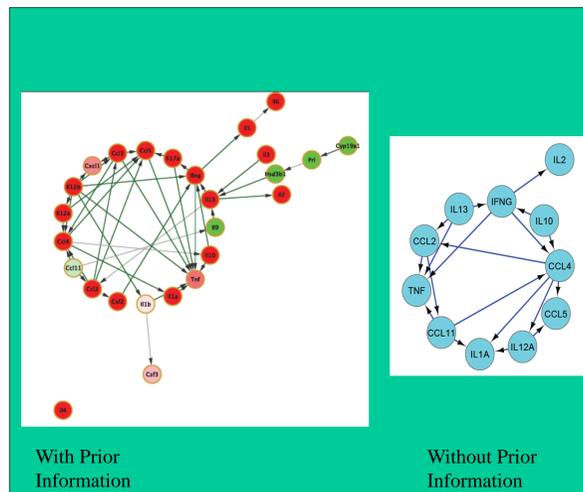


Figure 6: Network results obtained from the Bayesian inference method.

What should be noted from the above networks is the overall retention of the hub structure for the two inference methods for cases with and without prior.

Studying Disease Propagation Using Network Inference Methods

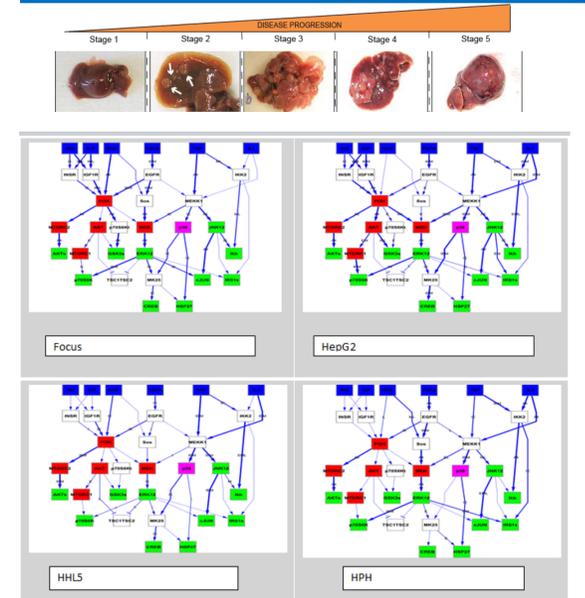


Figure 7: Time evolving signalling networks (work in progress).

Conclusion

Molecular networks are not static; rather, they exhibit dynamic adaptations in response to both internal states and external signals. Even though present techniques reconstruct interactions and relationships between variables, an approach that would also incorporate dynamics in such interactions would be more suitable for such analysis.

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References

S.L. Field, T. Dasgupta, H. Bulsara, R.S. Savage, J. Adebayo, M Cummings, J. Gunawardena, N.M. Orsi., A Bayesian network view of serum cytokines, prolactin and steroid hormones during murine lactation. 2011, *submitted*.