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Towards Accurate Gene Regulatory Network Inference from Perturbations

Abstract:

Gene regulatory networks (GRNs) can be inferred using regression methods, typically from gene expression data measuring responses to gene perturbations. If the data is free from noise and other confounding factors, it is possible to obtain the correct network, but what accuracy can be expected for a given biological dataset and inference method?

To examine inference accuracy we have developed a simulation and benchmarking package GeneSPIDER (Tjärnberg et al., 2017). Using this, we show that although the best inference methods can achieve high accuracy if the data is highly informative, when using data with realistic properties their accuracy is quite low, with Matthew's correlation coefficients below 0.3 (Tjärnberg et al., 2015). We have developed new methods to improve the accuracy of GRN inference, such as optimisation of network sparsity (Tjärnberg et al., 2013), using functional association data as a prior (Studham et al., 2014), and a new bootstrapping approach.

We are applying these methods in a project employing siRNAs to perturb the GRN around the oncogene MYC. 40 genes in the MYC pathway were each perturbed in a cancer cell line, and the effect on the other genes was measured at steady state by qRTPCR. We then used our new bootstrapping approach to infer a GRN with highly confident links.

References:

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About:

Erik Sonnhammer, Ph.D., is Professor of Bioinformatics at Stockholm University and is based at Science for Life Laboratory in Stockholm. He has been active in several bioinformatics research areas and has developed dozens of bioinformatics algorithms, tools, and databases, including popular sequence analysis tools such as Dotter for dotplotting, TMHMM and Phobius for transmembrane topology prediction, and the widely used databases Pfam - protein domains, InParanoid - orthologs, and FunCoup – global protein networks. A current focus is development of methods for inferring gene regulatory networks from gene perturbation responses, and extracting data and network properties that impact network inference accuracy.