Inference of Causal Networks from Time-course Transcription Data in Response to a 2 Gy Challenge Dose of Ionizing Radiation with or without a 10 cGy Priming Dose

Kai Zhang, Ju Han, Torsten Groesser, Priscilla Cooper, and Bahram Parvin

Lawrence Berkeley National Laboratory

Goal: To elucidate temporal-dependent gene templates, causal networks, and underlying biological processes that can be inferred in response to a 10 cGy priming dose with or without a later higher challenged dose.

Background and significance: Mechanistic inference of regulatory network can provide new insights into radiation systems biology. The main challenge continues to be high dimensionality of data, complex network architecture and limited knowledge of biological processes.

Approach: Our approach is to develop a novel computational method that bounds the complexities of the system, and enables a tractable solution for hypothesizing a causal network from time-course transcriptome data that is coupled with a carefully designed experiment. Our computational protocol consists of two stages. The first stage decomposes the high dimensionality of transcriptome data into a small set of templates or vocabularies, where each template represents a unique time-course profile. The second stage hypothesizes a causal network from decomposed templates, where gene-gene interactions and feedback mechanisms can be predicted. Both stages utilize the concept of “sparse” association for improved computational robustness. The time-course transcriptome data are collected at 1, 2, 4, and 8 hours following a challenge dose of 200 cGy of X-rays. The human fibroblast cell line Wi38 (p53+/+), with a finite life span, was cultured in monolayers under low oxygen (3%) cell culture conditions to examine transcriptome dynamics with and without the priming dose of 10cGy.

Results and Conclusion: The system has been applied to time-course transcript data to examine differential radiation responses to 200 cGy alone, or as a result of 200 cGy and a priming dose of 10 cGy. These differences are computed in terms of both the template libraries and inferred networks. Our preliminary results reveal a number of differentially expressed templates and two causal networks corresponding to the challenge and the subsequent adaptive responses. With respect to the early time point, both causal networks reflect an initial cascade of events that are driven by stress and inflammatory responses; however, different templates (e.g., subset of genes) are driving the networks, and there is a delayed inflammatory response as a result of the priming dose. With respect to the later time point, the causal network for the challenge dose reflects a stronger and more persistent inflammatory response than the network inferred with the priming dose followed by the challenge dose.

This research is supported in part by the DOE Low Dose SFA Program under DOE Contract No. DE-AC02-05CH11231.