INFORMATION THEORETIC APPROACH FOR DATA-DRIVEN PROTEIN-CYTOKINE NETWORK RECONSTRUCTION IN RAW 264.7 MACROPHAGES

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MOTIVATION/BACKGROUND

- The Release of immunoregulatory cytokines during inflammatory response is mediated by a complex signaling network. However, the current knowledge does not provide a complete picture of these signaling components.
- Knowing these signaling components can help understand common regulatory modules for various cytokine responses and differentiate between the causes of their release.
- Finding a novel regulatory component will help to maximize the efficiency of a drug by affecting one or few cytokines while minimizing the effects on the homeostasis of other cytokines.

METHODS

- Estimation of mutual information for each protein-cytokine interaction using Kernel Density Estimator (KDE) [1]:

$$I(\{x_i\},\{y_i\}) = \frac{1}{N}\sum Log\frac{f(x_i,y_i)}{f(x_i)f(y_i)}$$

$$f(x,y) = \frac{1}{2\pi N h^2}\sum exp\left(-\frac{(x-x_i)^2+(y-y_i)^2}{2h^2}\right)$$

$$f(x) = \frac{1}{\sqrt{2\pi}Nh^2}\sum exp\left(-\frac{(x-x_i)^2}{2h^2}\right)$$

For given two vectors $\{x_i\}$, $\{y_i\}$, sample size N and kernel width h.

- Selection of the threshold [2]:

$p(I>I_0 \mid \bar{I}=0) \sim e^{-cNI_0} \rightarrow \text{Log } p = a + bI_0$

Where the bar denotes the true mutual information

Using these results, for any given dataset with sample size N and a desired p-value, the corresponding threshold can be obtained.

RESULTS

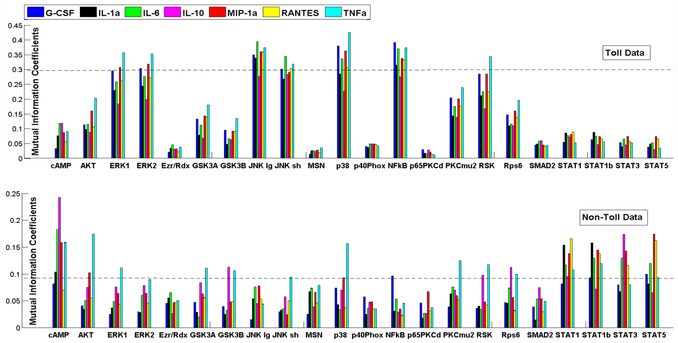

Figure 1: Mutual information coefficients of 22x7 phosphoprotein-cytokine interactions driven from toll data (the upper bar) and non-toll data (the lower bar).

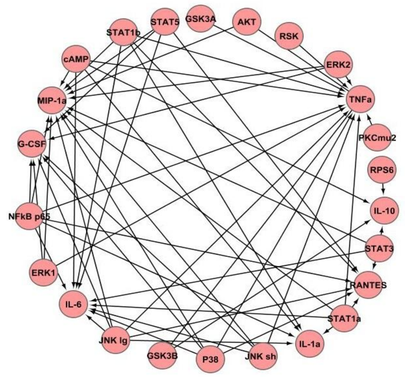

Figure 2: The data-driven phosphoprotein-cytokine network reconstructed from information theoretic approach

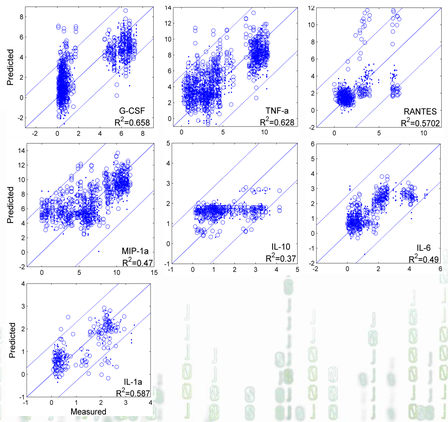

Figure 3: Prediction of training data ('.') and test data ('O') on cytokine releases.

FINDINGS

- The information theoretic model captures potentially new regulatory effect of RSK (Ribosomal S6 Kinase) on TNF-alpha (Tumor Necrosis Factor alpha).
- This model also suggests the regulatory effect of RPS6 (Ribosomal Protein S6) on IL-10 (Interleukin-10).
- Our results show good agreement with information available in literature and capture the most of known signaling components involved in cytokine releases such as the regulatory effect of P38 on G-CSF (Granulocyte/macrophage Colony Stimulating Factor) that has been recently suggested by a Principal Component Regression and model minimization approach [3].

CONCLUSION

This study demonstrated the applicability of information theoretic approach to the reconstruction of biological networks by providing a predictive model of cytokine releases in RAW 264.7 macrophages. The results of this study are important for having a clear understanding of macrophage activation during the inflammation process.

LITERATURE CITED

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