Conditional mutual inclusive information enables accurate quantification of associations in gene regulatory networks

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Résumé en anglais	Mutual information (MI), a quantity describing the nonlinear dependence between two random variables, has been widely used to construct gene regulatory networks (GRNs). Despite its good performance, MI cannot separate the direct regulations from indirect ones among genes. Although the conditional mutual information (CMI) is able to identify the direct regulations, it generally underestimates the regulation strength, i.e. it may result in false negatives when inferring gene regulations. In this work, to overcome the problems, we propose a novel concept, namely conditional mutual inclusive information (CMI2), to describe the regulations between genes. Furthermore, with CMI2, we develop a new approach, namely CMI2NI (CMI2-based network inference), for reverse-engineering GRNs. In CMI2NI, CMI2 is used to quantify the mutual information between two genes given a third one through calculating the Kullback–Leibler divergence between the postulated distributions of including and excluding the edge between the two genes. The benchmark results on the GRNs from DREAM challenge as well as the SOS DNA repair network in Escherichia coli demonstrate the superior performance of CMI2NI. Specifically, even for gene expression data with small sample size, CMI2NI can not only infer the correct topology of the regulation networks but also accurately quantify the regulation strength between genes. As a case study, CMI2NI was also used to reconstruct cancer-specific GRNs using gene expression data from The Cancer Genome Atlas (TCGA). CMI2NI is freely accessible at http://www.comp-sysbio.org/cmi2ni [6].
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