Combinatorial Modeling and Optimization using Iterative RL Search for Inferring Sample-Specific Regulatory Network

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Understanding the cell state from the multi-omics data requires identifying the global gene regulation network described by *n-to-m* relationships between regulators and genes. In order to determine *n-to-m* relationships, we formulated an objective function that measures the deviation between observed gene expression values and estimated gene expression values derived from gene regulatory networks. In this study, we developed a two-step iterative reinforcement learning (RL) based method to predict *n-to-m* relationships by minimizing the objective function. The first step is to explore the *n-to-one* gene-oriented step that selects regulators by RL-based heuristic to add edges to the network. The second step is to explore the *one-to-m* regulator-oriented step that stochastically selects genes to remove edges from the network. In experiments on breast cancer cell line data, the proposed method constructed breast cancer subtype-specific networks from the regulator and gene expression profiles with a more accurate gene expression estimation than previous combinatorial optimization methods. Moreover, regulatory relationships involved in the networks were associated with breast cancer subtypes.