

The Use of Lattice Upstream Targeting for the Analysis of mRNA Expression for Cancers

LUST 2019

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Presentation Overview

- ① Introduction
- ② Data Setup
- ③ The Lattice Upstream Targeting Algorithm
- ④ Conclusions and Future Research

Abstract

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Results of a similar project conducted using data proprietary to the UH cancer center led to studies seeking to identify new chemical treatments.

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 - ② The second run is on the expression matrix for each metagene and supervised by survival time as the objective function using the Fisher score to rank the results. This pass identifies small predictive *signatures* for each metagene.
- In some cases, certain signatures would seem appropriate to use as guides for treatment.

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- The expression data is log transformed, quantile normalized, and row centered.
- Survival times and censoring information for each patient are contained in the clinical data and used later in the process.

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- The desired density D of non-zero entries in **M** is obtained by adjusting a threshold variable ϕ using the matrix secant method.
- For this study $D = 0.5$ for all cancers. In any particular study, one may seek to vary D to optimize the results.

Specifications

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Output

- Metagenes (Part I) or signatures (Part II) ranked by an objective function.
- For Part II only, a score placing patients into high and low risk groups.
- For Part II only, Kaplan-Meyer survival curves.

Regulation and Equivalence

Assume the density D has been fixed (0.5 in this study). We use *conftol* (in this study 0.75 for Part I and either 0.66, 0.7, or 0.74 for Part II) to adjust sensitivity.

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Definition

For a gene X , let X^+ denote the number of columns marked with 1 and x^- the number of columns marked with -1. We say X regulates Y , denoted $X \rightarrow Y$, if

- ① $\frac{|X^+ \cap Y^+|}{|X^+|} \geq conftol$, and
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In this study, default values for *overlap* were 0.5 for Part I and 0.6 for Part II. Merging was performed only once.

Objective Functions

Part I

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We use a measure of the probability of obtaining a set of vertices of size n with $|E|$ edges.

$$f(M) = \frac{|E|}{n - 1}$$

Refinement Using Upstream Regulators

Score every gene X to measure its effectiveness regulating the entire set of genes.

$$s_X = \frac{1}{N} \cdot \sum_{X \rightarrow Y} \frac{(|X^+ \cap Y^+| + |X^- \cap Y^-|)^2}{|X^+| + |X^-|}$$

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For $noregs = k$ (default 5), keep G_{X_1}, \dots, G_{X_k} with the k highest scores $p_{X,G}$ for further analysis.

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Use the logrank and Cox tests to measure the separation of these two curves. Each test produces a p -value (p_1 and p_2 , respectively). The *Fisher score* combines these measures to rank how well the signature separates the survival curves.

$$F(G_X) = -\ln(p_1) - \ln(p_2)$$

Fase Discovery Rates - Notation

Fix a density D , let $p = \frac{D}{2}$, and let $\gamma = \text{conftol}$. Consider an $m \times n$ matrix with entries from $\{-1, 0, 1\}$ assigned from uniform probability distributions with densities $p, p, 1 - 2p$.

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Probability row X has a entries 1 and b entries -1

$$g(n, a, b, p) = \binom{n}{a+b} p^{a+b} (1-2p)^{n-a-b}$$

Probability row Y has c entries 1 in a columns

$$h(a, c, p) = \binom{n}{c} p^c (1-p)^{n-c}$$

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Probability $X \rightarrow Y$

$$\sum_{1 \leq a, b \leq n} g(n, a, b, p) \left(\sum_{a \geq c \geq \gamma a} h(a, c, p) \right) \left(\sum_{b \geq d \geq \gamma b} h(b, d, p) \right)$$

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Expected number of relations $X \rightarrow Y$

$$E = m(m - 1) \cdot \text{prob}(X \rightarrow Y)$$

False Discovery Rates - In Practice

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For Part II, there are even fewer random arrows expected.

Sensitivity - Simulations

To test the sensitivity of LUST, simulations were run $5,000 \times 120$ signal matrix **S** with a step signal in the first 200 rows consisting of 30 entries of 1, 30 entries of -1 , and 60 zeros.

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Sensitivity - Results

Subtitle

SNR	Rows Found	False Positives
$-10db$	188	0
$-12.5db$	4	0
$-15db$	0	0

Table: $conf_{tol} = 0.7$

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Table: $conftol = 0.7$

SNR	Rows Found	False Positives
$-10db$	200	0
$-12.5db$	196	0
$-15db$	50	0

Table: $conftol = 0.6$

Sensitivity - More Results

Subtitle

SNR	Rows Found	False Positives
$-10db$	200	0
$-12.5db$	200	0
$-15db$	199	4

Table: $conf\text{tol} = 0.5$

Conclusions

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- Metagenes with signatures that result in the separation of Kaplan-Meier survival curves indicate biological processes of interest.
- Separating tumors by stage results in different metagenes of interest, seeming to indicate that different biological processes become more prominent as the disease progresses.

Future Investigations

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The Last Word

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Thank you!

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[github](#)

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So Helpful...

