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

LUST 2019

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Presentation Overview

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

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- In some cases, certain signiatures would seem approprite 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 $\mathbf{M}$ 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.

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Output

- Metagenes (Part I) or signiatures (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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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 $X \to Y$, if

1. $\frac{|X^+ \cap Y^+|}{|X^+|} \geq conftol$, and
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We say gene X is *eqvialent* to gene Y and write $X \approx Y$ if $X \to Y$ and $Y \to X$.

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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 it's effectiveness regulating the entire set of genes.

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

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For *noregs* $= k$ (default 5), keep $G_{X_1}, \ldots, G_{X_k}$ 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 signiature 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 $\gamma = \mathit{conftol}$. 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 $X \to Y$

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

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Expected number of relations $X \to Y$

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

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

Sensitivity - Simulations

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matrix was made to create $\mathbf{M} = \mathbf{S} + a\mathbf{N}$, using a to adjust signal-to-noise ratio. Repeated tests were run at various levels of

conftol. The conclusion was that the signals detected by Part I are

quite strong.

Sensitivity - Results

Subtitle

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

Table: *conftol* = 0.7

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$-10db$	200	0
$-12.5db$	196	0
$-15db$	50	0

Table: *conftol* = 0.6

Sensitivity - More Results

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

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Conclusions

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- Metagenes with signiatures 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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Thank you!