

The LUST Algorithm: A Discrete Mathematical Method for Analyzing Genetic Expression Data

LUST 2019

Tristan Holmes J.B. Nation et al

University of Hawaii at Manoa
tristanh314@gmail.com

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Presentation Overview

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

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Per J.B. Nation the UH Manoa Cancer Center separately used the results of these efforts to direct studies seeking to identify new chemical treatments.

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- The **discrete** expression data is analyzed again to find smaller sets of genes that regulate metagene expression, these smaller sets are called *signatures*.
- A model θ is produced that takes **continuous** expression data for signatures as input and outputs a real number. Values of θ can be used to place patients in high and low risk categories.

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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.

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Output

- Metagenes (Part I) or signatures (Part II) ranked by an objective function.
- For Part II only, Kaplan-Meyer survival curves and a model scoring each metagene based on survival.

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 set of columns marked with 1 and X^- the set of columns marked with -1. We say X regulates Y , denoted $X \rightarrow Y$, if

- ① $\frac{|X^+ \cap Y^+|}{|X^+|} \geq conftol$, and
- ② $\frac{|X^- \cap Y^-|}{|X^-|} \geq conftol$.

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We say gene X is equivalent to gene Y and write $X \approx Y$ if $X \rightarrow Y$ and $Y \rightarrow X$.

Forming Groups

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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. For Part I, the resulting groups are then examined by hand to identify representative *metagenes*.

Objective Functions

Part I

For a given group from the previous step G with n genes, we consider M as a directed graph with edges determined by $X \rightarrow Y$, and let E be the set of edges of this graph.

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Choose representative G 's for each clustering of groups, these representatives are the *metagenes* we analyze in Part II.

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.

Eigen-Survival Analysis

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Use the logrank and Cox tests to measure the separation of these two curves. The *Fisher score* combines the p -values to rank the signature.

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For metagenes with high Fisher scores, the eigen-survival score is a model that may be useful for classifying risk, see [melanoma]

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

Sensitivity - Simulations

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

Sensitivity - Results

SNR	Rows Found	False Positives
$-10db$	188	0
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SNR	Rows Found	False Positives
$-10db$	200	0
$-12.5db$	196	0
$-15db$	50	0

Table: $conf\text{tol} = 0.6$

Sensitivity - More Results

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

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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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- Use the algorithm to study continuous data related to other diseases, specifically where the diseased tissue can be isolated and sampled.

The Last Word

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The Last Word

"LUST is good...

...and so is the algorithm." - J.B. Nation

References



[Adiricheva, Nation, et al \(2015\)](#)

Measuring the Implications of the D-basis in Analysis of Data in Biomedical Studies

[github](#)



[Nation, Okimoto, et al \(2019\)](#)

A Comparative Analysis of mRNA Expression for 33 Different Cancers, Part 1:
The LUST Algorithm

[github](#)



[Nation \(2019\)](#)

A Genetic Signature Predicting Survival and Metastasis for Melanoma Patients

[github](#)

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Thank you!

