Translational Informatics To Link Gene Activity To Ontologies With and Without Context

Kshitij Marwah[1], Natalya F. Noy[2], Marco F. Ramoni[1*] and Gil Alterovitz[1]

[1] Children's Hospital Informatics Program at Harvard-MIT Division of Health Sciences and Technology [2] Stanford Center for Biomedical Informatics Research, Stanford University [*] Deceased

Abstract

• Traditional gene enrichment methods for assigning functional attributes to a group of genes identified in an experiment are limited to using Gene Ontology[2] data.

• To uncover broad patterns and determine if gene subset shows over-representation of specific characteristics, current methods need to be extrapolated to other ontologies[1].

• We present here a computational framework for enrichment analyses using experimental datasets from Gene Expression Omnibus[3] by propagation over context and non-context functional maps to Gene Ontology.

• Our preliminary results show that there is a definite need for such translational research to allow biological scientists to better interpret the results of their experiments.

Introduction

• Biological researchers have generally used Gene Ontology[2] to complement microarray analysis.

• Once low level analysis is complete and a group of differentially expressed genes have been identified, enriching these groups for ontology attributes allows researchers to find over-representation of a biological characteristic.

• We enhance such analysis to express enrichments on other ontologies by using pre-computed functional mappings to Gene Ontology.

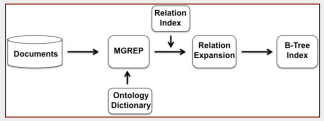
Methods

• We consider experimental abstracts and raw data from Gene Expression Omnibus.

• We use our in-house pipeline (Figure at Bottom) to compute context and non-context based links using correlation metrics (Figure at Right) present in the abstracts[4].

• After determining significant over- or under-expressed genes from raw data, we propagate enrichments using mappings to Gene Ontology.

• To circumvent the complexity of enrichment space, we use a depth first, branch and bound heuristic to prune insignificant attributes.



(Right) Figure 2. 2 x 2 contingency table to test relationship between ontology terms.

(Bottom) Figure 1. Pipeline used for caching sufficient statistics for model scoring.

Results

• We consider 200 ontologies[5], containing about 3 million terms, and about 15,000 experimental abstracts from Gene Expression Omnibus.

• We then apply our in-house algorithm to integrate Gene Ontology (24,987 concepts) with all other ontologies (Figure 3) within the context of Human Disease (12,033 concepts).

• Further, using these maps we compute enrichments for various gene-lists available in the experimental datasets (Figure 4).

• Our preliminary results empirically indicated that our context-based mappings allowed us to leverage more information, and accordingly yielded more accurate descriptions of enrichments.

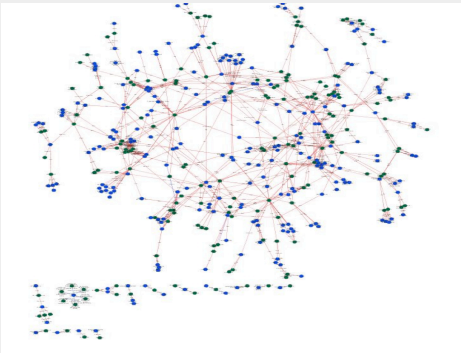


Figure 3. Mapping network showing links between Gene Ontology (blue circles) and Minimal Anatomical terminology (green circles) under Human Disease.

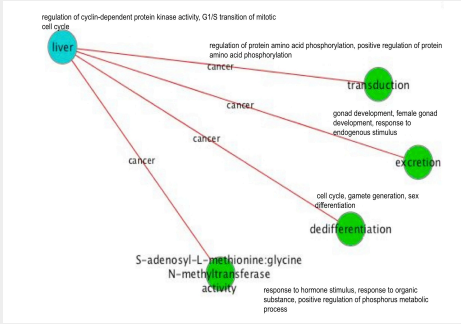


Figure 4. Snapshot showing translation of Gene Ontology to Anatomy under Human Disease used for computing enrichments.

Conclusions

• We present here a principled framework for domain-wide identification of biological, pharmaceutical or disease based characteristics.

• Our work provides a new approach using translationalized functional spaces for the identification of significantly enriched attributes.

• Such an integrative approach can not help researchers use and apply quantitatively the available biological knowledge to their experiments and analyses.

• We plan to validate and scale the promise of such translational approaches on much larger datasets and experiments.

• For more information please see: http://bcl.med.harvard.edu

References

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