1-1-2019

Understanding Diabetes Through Pathway Analysis Evaluation

London Cavaletto

WAYNE STATE
College of Engineering

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Student Name
London Cavaletto

Advisor Name
Sorin Drăghici

Department Name
Computer Science

Opportunity and Significance

Metabolic disorders affect many people and identifying significantly perturbed biological processes in a metabolic disease can provide valuable insight into the disease's mechanisms.

Evaluating the proposed Metabolic Pathway Analysis Method (RAMP) will enable us to reliably use it to identify significantly perturbed metabolic pathways that could help identify disease mechanisms and potential therapy targets or disease bio-markers of a metabolic disorder.

Technical Objectives

Design an evaluation procedure for the rate of false positives of the RAMP analysis method.

Design an evaluation procedure for RAMP in the context of diabetes metabolic data.

Related Work and State of Practice

Existing methods identify a list of metabolites, which may be the effect of the disease rather than the cause.

Current methods do not take into consideration the stoichiometry of the bio-chemical reaction or the propagation of the metabolite changes from one reaction to another.

The current project proposes to evaluate a method which considers the stoichiometry and propagates the change using an impact analysis approach.

Technical Approach

1. We applied a permutation approach to evaluate the rate of false positives for the RAMP metabolic pathway analysis method.
2. We retrieved and processed publicly available metabolite data from the Human Metabolome Database (HMDB)[1] and parsed the data for biological pathways from the Small Molecule Pathway Database (SMPDB)[2]. The metabolite data and pathway information were linked through metabolite identifiers from the Chemical Entities of Biological Interest (ChEBI)[3] database.

Results

For a sample pathway with 3 reactions (7 metabolites) and a dataset generated from the standard normal distribution. The distribution of the p-values is uniform which means that the rate of false positives for a threshold of α there would be no more than α false positives in the results.

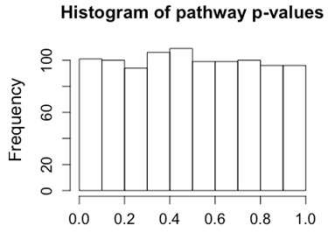

Fig. 1. 1000 p-values computed for the synthetic pathway. The null distribution was built using 2000 permutations.

We used HMDB metabolite data for patients with diabetes and control (healthy) patients. When compared to the classical enrichment approach (hypergeometric test) RAMP returned fewer and more relevant pathways (top 5 shown in Table 1).

Table 1. Comparison of top 5 pathways ranked by p-value. Significant p-values are in bold (<1%)

	RAMP			Hypergeometric test		
	Pathway	p-value	FDR	Pathway	p-value	FDR
1	Ketone Body Metabolism	**0.00199**	0.1774	Urate Degradation to Glyoxylate	0.09090	1
2	Succinyl CoA: 3-ketoacid transferase deficiency	**0.00249**	0.1774	Urate Degradation to Ureidoglycolate	0.09090	1
3	Acetate metabolism	0.02348	0.7474	biotin-carboxyl carrier protein assembly	1	1
4	Butyrate Metabolism	0.03098	0.7474	2-ketoglutarate dehydrogenase complex deficiency	1	1
5	Isobutyryl-coa dehydrogenase deficiency	0.12943	0.7474	2-Methyl-3-Hydroxybutryl CoA Dehydrogenase Deficiency	1	1

Next Steps for Development and Test

We will evaluate the method using simulated pathways and data where the perturbed pathway is known beforehand. Measures such as specificity and sensitivity will be employed to evaluate the method's performance.

We will compare the RAMP analysis method with the pathway analysis method implemented in the tool MetaboAnalyst[4] on the diabetes dataset and on other disease datasets.

Commercialization Plan & Partners

We will make RAMP and the evaluation available in a software package.

Pitch it to bioinformatics start-ups to include it in their software tools.

We will work with the resources available at WSU.

References

[1]Human Metabolome Database (HMDB), http://www.hmdb.ca/ v4.0, release July 9, 2018
[2]Small Molecule Database (SMPDB), http://smpdb.ca/ v2.0, release February 19, 2015
[3]Chemical Entities of Biological Interest (ChEBI), https://www.ebi.ac.uk/chebi/
[4]MetaboAnalyst, https://www.metaboanalyst.ca/

Thank you to the ROEU Program, College of Engineering, the Biomedical Engineering Department, Dr. Sorin Drăghici and Dr. Cristina Mitrea, for their continued support.