ABSTRACT

MATHUR, RAVI. Discovering mQTL Signatures of Genotype-by-Diet Interactions Underlying Metabolic Syndrome in Drosophila: A Pathway Approach. (Under the direction of Dr. Alison Motsinger-Reif).

Metabolic Syndrome (MetS) is a cluster of symptoms that greatly increase the risk of type 2 diabetes and cardiovascular disease in humans. Previous studies have shown a complex etiology for these systems, including environmental, genetic and interactive risk factors. While the influence of genetics on MetS is well established, the architecture of the genetic etiology is not understood. *Drosophila melanogaster* is a well-established model organism for dissecting the architecture of complex traits due to their short generation time, genetic resources available, and the high homology of disease related genes to humans. In this study the genetic architecture of both genetic and genetic-by-diet interaction effects are analyzed for untargeted metabolomics. Metabolomics is an ‘ome’ that is growing very rapidly and many studies have discovered strong association between genetic variants and metabolic traits. In this study the genetic architecture of metabolite-quantitative trait loci (mQTL) associations are characterized using the *Drosophila* Synthetic Reference Population treated with a normal and high fat diet. Results from QTL mapping discovers mQTL which display different genetic architecture for the two tested diets.

The architecture is investigated further by applying gene set analysis (GSA) techniques, although first a simulation study is conducted to determine highly recommended GSA techniques. The simulation study compares the most popular GSA methods in a unique simulation design. The simulations are based on true data with original signal removed, thus preserving the correlation structure of real data. Furthermore, the signal added is targeted towards a gene set and the amount of signal is easily controlled by simulation parameters. The
software used for simulation is flexible, easy to use and publicly available. The simulation study identifies Gene Set Enrichment Analysis (GSEA) and sigPathway as the most powerful methods across all tested simulation parameters. These two methods are applied to the metabolomics *Drosophila melanogaster* data to identify the Beta Oxidation Long-Chain Fatty Acid pathway as enriched. Further graph based pathway analysis was conducted to identify the great influence of unidentified metabolites on the mQTL associations, thus needing the use of pathway topology based methods to infer novel metabolite architectures.
Discovering mQTL Signatures of Genotype-by-Diet Interactions Underlying Metabolic Syndrome in Drosophila: A Pathway Approach

by
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BIOGRAPHY

Ravi Mathur received Bachelors of Science and Masters of Science degrees in Bioengineering and Biomedical Engineering, respectively, from Binghamton University in the southern tier of New York state. He became inspired by big data and bioinformatics by a mentor during his Bachelor’s degree and has always had a passion for human health applications to bioinformatics and statistics. He joined the Bioinformatics program and Dr. Alison Motsinger-Reif’s Laboratory in 2012 to further develop his interests and skills. He is greatly interested in applying statistical techniques in multi-omic genetic projects. Furthermore, he is greatly interested in developing the knowledge of molecular pathways and applying techniques in understanding these networks. Outside of PhD work, Ravi has actively been involved in the University Graduate Student Association, and serving as President and Vice-President of the Genomic Sciences Graduate Student Association at NC State University.
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LIST OF ABBREVIATIONS

AMPRIL – *Arabidopsis* multiparent RIL population
ANOVA – Analysis of Variance
ARACNE – Algorithm for the Reconstruction of Accurate Cellular Networks
aveDiff – average difference t-test
BAIBA – β-aminoisobutyric acid
BMI – Body Mass Index
CAGE – Cap Analysis of Gene Expression
CAMERA – Correlation Adjusted MEan RAnk
cDNA – complementary DNA
DGRP – *Drosophila* Genetic Reference Population
DNA – Deoxyribose Nucleic Acid
DSPR – *Drosophila* Synthetic Population Resource
FANGS – Flexible Algorithm for Novel Gene set Simulation
FCS – Functional Class Scoring
FDA – US Food and Drug Administration
FDR – False Discovery Rate
FET – Fisher’s Exact Test
GC – Gas Chromatography
GEO – Gene Expression Omnibus
GGM – Gaussian Graphical Model
GO – Gene Ontology
GSA – Gene Set Analysis
GSEA – Gene Set Enrichment Analysis
GSTOF-MS – Gas Chromatography Time of Flight Mass Spectrometry
GWAS – Genome Wide Association Studies
GWRN – Genome-Wide Regulatory Network
HMDB – Human Metabolomics Database
HMM – Hidden Markov Model
IF – Impact Factor
IPA® – Ingenuity Pathway Analysis
KEGG – Kyoto Encyclopedia of Genes and Genomes
LC – Liquid Chromatography
LC-MS – Liquid Chromatography coupled with Mass Spectrometry
LOD – Logarithm of the Odds
MAGIC – Multiparent Advanced Generation Inter Cross lines
MAQC – MicroArray Quality Control
MetaCyc – Metabolic Cycles
MetS – Metabolic Syndrome
MPSS – Massively Parallel Signature Sequencing
mQTL – Metabolite-QTL
MR-GSE – Mean-Rank Gene Set Enrichment
MS – Mass Spectrometry
MSigDB – Molecular Signature Database
NAM – Nested Associated Mapping population
NEFA – Non-Esterified Fatty Acid
netGSA – Network-based Gene Set Analysis
NHGRI – National Human Genome Research Institute
NMR – Nuclear Magnetic Resonance
ORA – Over-Representation Analysis
PADOG – Pathway Analysis with Down-weighting of Overlapping Genes
PCA – Principal Components Analysis
PLAGE – Pathway Level Analysis of Gene Expression
PT – Pathway Topology
QTL – Quantitative Trait Loci
RAD – Restriction-site-Associated DNA
RIL – Recombinant Inbred Line
RNA – Ribose Nucleic Acid
RNA-Seq – RNA sequencing
SAFE – Significance Analysis of Functional Expression
SAGE – Serial Analysis of Gene Expression
SNP – Single Nucleotide Polymorphism
TGF-β – Transforming Growth Factor Beta
VIF – Variance Inflation Factor
CHAPTER 1

Pathway Analysis and Its Applications

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ABSTRACT

As the scale of genetic, genomic, metabolomics and proteomic data increases with advancing technology, new approaches leveraging domain expert knowledge, and other sources of functional annotation have been developed to aid in the analysis and interpretation of such data. Pathway and network analysis approaches that connect genetic markers or measures of gene product with phenotypes or diseases of interest have become popular in association analysis. These approaches aim to leverage big data to better understand the complex etiologies of these traits. Findings from such analyses can help reveal interesting biological traits, and/or identify potential biomarkers of disease. In the current chapter, we review broad categories of pathway analyses, and review advantages and disadvantages of each. We discuss the analytical methods available to detect phenotype-associated pathways, and review the key resources in the field of human genetics that can be used to perform such analyses.

INTRODUCTION

Recent technological developments in high-throughput genetic, genomic, and metabolomics profiling techniques have greatly expanded the potential for systems-level analysis. As such data becomes increasingly readily available for experiments, and the scale of the data increases, exciting, new opportunities are emerging for analysis of “big data”. Handling and summarizing such highly dimensional data in an efficient and interpretable way is crucial for its efficient use. While there are a number of strategies for handling big “-omics” data, the pathway and network analysis approaches are becoming standard for discovering and summarizing underlying relationships in the data. The pathway and network approaches rely on either external knowledge bases or strong correlation structure within the data to collapse the data from thousands or millions of variables to hundreds or thousands of pathways/networks for analysis. The results of such analyses are valuable for discovering the underlying mechanisms of disease or a phenotype of interest, including the events leading up to initiation, progression, and treatment of a disease.

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The National Human Genome Research Institute (NHGRI) states, “A biological pathway is a series of actions among molecules in a cell that leads to a certain product or a change in a cell” (www.genome.org). Such a pathway can describe the function of molecules in a cell (regulatory pathway), the change in chemical elements throughout the cell (metabolomics pathway), or the initiation of a disease (disease pathway). Biological pathways in a cell interact with each other to carry on the actions of the cell. A group of interacting pathways comprise a biological network. A wealth of knowledge on such interactions has been curated in pathway knowledge bases and can be leveraged by statistical analysis of specific datasets. Many pathway-based analysis approaches use these databases to predict gene function, discover new associations with a trait of interest, and better classify patients or a sample. Other approaches, typically referred to as network approaches, focus on quantifying the connections between genes, proteins, or metabolites to better understand the connections between the molecules that result in the phenotype/disease.

Biological pathways and networks can be displayed and analyzed in a graph with vertices and edges. A vertex represents each element contained in the pathway or network and an edge represents an interaction (i.e., activation, repression, methylation, series of chemical reactions) between those elements. Figure 1.1 is an example of a pathway represented as a graph. In this graph vertices 6 and 7 are hubs, and edges are labeled as “A” for an activation interaction and a “R” for a repressive interaction. The current chapter reviews the major categories of pathway and network analysis tools.

**Figure 1.1: Example of Graph Representation of a Pathway.** Each vertex corresponds to an element (e.g., gene or single nucleotide polymorphism (SNP)), and each edge corresponds to interactions between those elements. The edges are label as “A” for an activation interaction and “R” for a repressive interaction.

Most pathway analysis tools rely on a knowledge base including gene sets or pathways that have been statistically determined as influential in the dataset as opposed to random gene sets or pathways. While the fundamental statistical approaches of the methods are largely
independent of the database, in practice, many knowledge base analysis approaches have been
developed in tandem. Therefore, commonly used software relies heavily on specific databases.
Pathway analysis begins with data collection and thus the chapter commences with a short
discussion of the data collection technologies frequently used in human genetics. Many of
these resources are also available for model organisms, but we focus on tools with direct
relevance for research directly addressing human health.

While many of the approaches were originally developed for use with gene expression
(particularly microarray) data, extensions of the approaches are now frequently used with
deoxyribonucleic acid (DNA)-level variation, and with biochemical/metabolomics data.
Due to the reliance on knowledge bases, we continue with a discussion of the most commonly
used resources in human genetics. We then discuss the major classes/categories of gene set and
pathway analysis tools, and detail some of the most commonly used methods. We also consider
implementation challenges, with an emphasis on analyzing big data, which often has fewer
samples than the number of variables or features. The chapter will conclude by discussing
future research avenues and overall lessons learned from the discussed methods.

**BACKGROUND**

Pathway analysis consists of a series of statistical analysis steps, all of which influence each
other. Figure 1.2 displays the basic workflow of any pathway/network analysis. The initial step
of pathway analysis involves generating data from the “omic” elements of interest. This data
generation generally includes expression profiling (most commonly by gene expression or
ribose nucleic acid (RNA) sequencing experiments), single nucleotide polymorphism (SNP)
arrays, and metabolomics collection platforms but is rapidly expanding to include methylation
chips, copy number aberration technologies, and other technologies. Based on the elements
collected in the dataset, the appropriate database is selected. Next specific pathways included
in the database are selected. This selection may be the pathways in which the investigator is
most interested but more commonly, all pathways contained in the database are selected for
testing. Finally, differences are determined among the elements of selected pathways in
experimental groups (e.g., cases and controls) or with a quantitative trait of interest.

Details of these analyses differ in terms of the overall hypothesis tested, and the
methods used. Using categories established by Ramanan, Shen, Moore, and Saykin (2012),
major pathway and network analysis tools can be classified into three generations. These
generations serve as a guideline for considering various approaches but are not hard
classifications; many techniques use elements from more than one generation and thus
categories overlap. Due to the highly dimensional nature of sequencing and profiling
technologies, datasets may have many more variables or features than the number of samples.
In analyzing such data, additional considerations to minimize over fitting has to be performed.
The first generation include the over-representation analysis (ORA) tools, the second
generation are the Functional Class Scoring (FCS) methods, and the third generation are the
Pathway Topology (PT) approaches.
**Figure 1.2: Overall Process of Pathway Analysis.** The process starts with data generation, which is most commonly done with expression, SNP arrays, and metabolomics. From the raw output, the data is cleaned and analyzed for quality control standards. Based on the variables contained in this data and the technology utilized, a database that contains information on these variables is selected. Next the desired pathway(s) are extracted. Finally, the data is analyzed by the pathway or network analysis approach that best fits the overall hypothesis of an investigator’s experiment. The categorization of methods as ORA, FCS or PT methods, overlap in the Venn diagram.

**DATA GENERATION TECHNOLOGIES**

Any pathway or network analysis begins with collecting data within an experiment with a particular trait or disease of interest, including elements that are hypothesized to influence a particular phenotype. With high-throughput technologies, it is now possible to assay as many as millions of elements, with sample sizes rarely on the same order of magnitude. Thus the “curse of dimensionality” is a serious problem. When analyzing data with many more variables or features than the number of samples, additional considerations are necessary to conduct proper analyses.

The major technologies used in human genetics/genomics, proteomics, and metabolomics are briefly described in the following. As technologies are constantly advancing, this list may not be complete. Additionally, as each technology has very specific characteristics
that must be considered in quality control and analysis, we point to references that detail these issues for more direct guidance.

**Gene Expression**

Gene expression technologies quantify the amount of gene product produced by a particular gene. High-throughput technologies to quantify expression for the whole genome can be classified into hybridization-based techniques and sequencing-based techniques. Hybridization-based techniques include DNA microarrays (Zakharkin, 2005) and genomic tiling microarrays. Both techniques rely on the hybridization (bond of complementary DNA segments) of fluorescently labeled cDNA. Microarrays have been in common use for over a decade, and issues with batch effects and quality control as well as normalization approaches have been well studied. The MicroArray Quality Control (MAQC) project has produced excellent reviews of best practices in collection, quality control, and standard analysis of microarray data (M. Consortium et al., 2006; Shi et al., 2010). Sequencing-based techniques include serial analysis of gene expression (SAGE) (Velculescu, Zhang, Vogelstein, & Kinzler, 1995), cap analysis of gene expression (CAGE) (Kodzius et al., 2006), massively parallel signature sequencing (MPSS) (Brenner et al., 2000), and RNA sequencing (RNA-Seq) (Wang, Gerstein, & Snyder, 2009b). Sequencing-based techniques offer the benefits of reduced background noise and more accurate and reproducible quantification of expression. RNA-Seq is currently considered the most advanced and reliable technique available and is thus growing in use as the technology becomes accessible and affordable (Chu & Corey, 2012).

RNA-Seq utilizes next-generation sequencing technology to sequence RNA extracted from a population. RNA-Seq begins with the conversion of extracted RNA into a cDNA library, which is sequenced to provide the genomic sequences of thousands of small segments from the population (referred to as reads). The reads are either aligned to a known reference genome or assembled de novo (if reference genome is unknown). This step results in mapping of the whole genome. From this mapping, the number of reads that map to each gene in the genome are counted, and normalization for gene size is performed. The resultant count of each gene is a relative value for the expression of that particular gene. (Wang, Gerstein, & Snyder, 2009a). As RNA-Seq more commonly used, best practices in quality control and processing are emerging as an important area in bioinformatics research. A recent review of emerging best practices and tools available can be found in DeLuca et al. (2012).

Gene expression data (particularly microarrays) directly inspired many of the pathway and network analysis approaches discussed below, and methods with the longest track record of development (both methodologically and regarding the corresponding software implementations) are readily compatible with other data technologies.

**Single Nucleotide Polymorphism (SNP) Arrays**

A SNP refers to a specific position in the genome where two or more different nucleotides are known to appear in a specific population. Since humans are diploid, an individual’s DNA has two copies, one received from the mother and the other received from the father. These alleles can either be dominant or recessive. Therefore, SNPs are typically analyzed in terms of their genotype though allelic encoding.
SNP arrays are a high-throughput technology that analyzes thousands of SNPs in a genome. Affymetrix (www.affymetrix.com) and Illumina (www.illumina.com) are among the largest producers of SNP arrays. Both companies utilize similar technologies, which rely on the hybridization of complementary DNA segments to each other. The most recent arrays are capable of analyzing around one million SNPs on a single array, which corresponds to the number of variables in the dataset. The abundance of each allele in a SNP array is analyzed by a different probe (short, single stranded fragment of DNA) depending on the producer of the technology. For Affymetrix arrays, the probes (about 25 base pairs in length) are fluorescently labeled and targeted by their perfect complement. The fluorescence of each probe is measured by shining a laser on the array. For Illumina arrays, each probe (about 50 base pairs in length) is attached to a bead, and targeted complementary nucleotides hybridize and emit a light. For both technologies, the emitted light from the fluorescence is measured as the raw probe intensity. Affymetrix normalizes the raw probe intensities between several arrays, and Illumina technology normalized for each array. For Affymetrix arrays, the normalized probe intensities are processed by the Birdseed algorithm (Korn et al., 2008) to determine the genotypes for each SNP. For Illumina arrays, a clustering algorithm based on a transformed ratio of the probe intensities is utilized to determine the genotypes for each SNP. (LaFramboise, 2009)

SNP arrays are utilized to genotype organisms’ DNA, analyze DNA copy number variation (i.e., the number of copies of genomic segments) and loss-of-heterozygosity (i.e., the loss of one copy of a genomic area by the parent). An advantage of SNP array data is the ability to utilize linkage disequilibrium information. Linkage disequilibrium occurs when alleles at different loci are present in one individual at a rate higher than expected, which is interpreted as the correlation between SNPs. Linkage disequilibrium allows SNP chip technologies to effectively capture a large amount of variation across the genome through this correlation. Therefore, association analysis can be used to find loci with common variants associated with the disease or trait of interest without having to assay causal or directly functional variants.

The use of SNP data for pathway and network analysis is a relatively new extension of the pathway approaches designed for gene expression data. Typically, for methods that have been extended to analyze SNP data, variants are grouped within genes (using different sources of genomic annotation, including linkage disequilibrium), and measures of overall variation and association with the trait of interest are used in the pathway analysis.

**Metabolomics technologies**

Metabolomics is the study and analysis of the numerous metabolites in a sample. A metabolite occurs as a result of interactions of a genome with the environment over time. Because recent studies have shown that several metabolites are part of many regulatory processes in various organisms, they are receiving increasing attention. Most common techniques for metabolite quantification are nuclear magnetic resonance (NMR) and mass spectrometry (MS). MS technology quantifies metabolites by measuring the mass-to-charge ratio and relative intensity. Prior to MS, the chemicals are separates by liquid chromatography (LC) or gas chromatography (GC). (Putri, Yamamoto, Tsugawa, & Fukusaki, 2013).

Metabolomic assay techniques are relatively high throughput although not to the same degree as expression and SNP technologies. Metabolite data usually involves the analysis of
hundreds of metabolites as opposed to millions for expression and SNP data. This is due to the many variants (i.e., different weights, polarity, and solubility) of chemicals, which makes detection and quantification difficult. Therefore, since researchers often target specific metabolites, a certain amount of bias is present in any metabolomics analysis. The annotation level associated with metabolomics data is also rapidly evolving (Dunn, Broadhurst, Atherton, Goodacre, & Griffin, 2011).

DATA ANALYSIS PRIOR TO PATHWAY ANALYSIS

Typically, initial analysis is performed prior to pathway/network analysis to find associations of individual elements (i.e., genes or variants) with the disease or trait of interest. After appropriate quality control, traditional statistical tests are typically performed for individual elements. For example, in a gene expression experiment comparing cases and controls, a t-test comparing the distributions of individuals in the two groups for each gene in the genome is performed and a p-value and measure of effect size (i.e. fold change) recorded. In big data application, multiple testing issues are a concern, and appropriate control corrections (i.e., false discovery rate) are often used to find significant elements. For the ORA and FCS analysis approaches discussed below, the results of these association tests are used to then look for over-representation of elements from the same pathway from the significant findings. The term “pathway” is defined by which knowledge bases (or combination of knowledge bases) that are used for analysis, as discussed below.

DATABASES

For knowledge base-driven pathway analysis, several databases contain compiled information about genes and interaction elements. The diversity and number of databases is constantly growing, and we review only a small subset of the tools available here. The databases we review include Gene Ontology (GO) (Reference Genome Group of the Gene Ontology, 2009), Molecular Signature Database (MSigDB) (http://www.broadinstitute.org/gsea/msigdb/index.jsp), Kyoto Encyclopedia of Genes and Genomes (KEGG) (Kanehisa et al., 2014), and MetaCyc (Caspi et al., 2014). Table 1.1 summarizes these databases and provides URLs that can be used to access them. Each database is constructed using a mix of highly curated (often manual) annotations and predicted pathway information from computational algorithms. The most frequently used databases were initially developed using large teams of curators that pulled connections from the literature. These databases clearly indicate the source of the pathway information used, and final stages of the interpretation of pathway analysis results should consider this information. Covering details of all these databases is beyond the scope of this chapter, but we review some of the most commonly used ones here. Before implementing any combination of pathway analysis approaches, investigators should ensure they are well informed about the databases they are referencing and choose the most applicable ones for their specific domain application.
Table 1.1: A summary of common databases utilized in pathway analysis including the URL to access these databases.

<table>
<thead>
<tr>
<th>Database</th>
<th>Summary</th>
<th>Access</th>
</tr>
</thead>
<tbody>
<tr>
<td>GO</td>
<td>Provides an annotation of the function, role, and location of genes and gene products.</td>
<td><a href="http://www.geneontology.org/">http://www.geneontology.org/</a></td>
</tr>
<tr>
<td>KEGG</td>
<td>Provides information on system-wide, genomic, and chemical elements displayed as pathway maps. An overall picture of the interaction between elements is available.</td>
<td><a href="http://www.genome.jp/kegg/">http://www.genome.jp/kegg/</a></td>
</tr>
<tr>
<td>MetaCyc</td>
<td>Provides experimentally curated metabolic pathways along with enzyme kinetic information.</td>
<td><a href="http://www.metacyc.org/">http://www.metacyc.org/</a></td>
</tr>
<tr>
<td>MSigDB</td>
<td>Contains discovered gene sets including SNP level information.</td>
<td><a href="http://www.broadinstitute.org/gsea/msigdb/index.jsp">http://www.broadinstitute.org/gsea/msigdb/index.jsp</a></td>
</tr>
</tbody>
</table>

Gene Ontology (GO)

One of the oldest and most curated databases, GO uses a uniform, structured vocabulary to annotate the function, role, and location of genes and gene products in many organisms. Currently, the GO database defines over 26,000 GO terms that reference the molecular function, biological process, and/or cellular components that genes and their products are active. GO annotation is highly hierarchical, and each term is hierarchically structured within the function/process. The GO network comprises relationships in which genes may be the same (or orthologs as defined by the Reference Genome Project), a part of each other, and/or regulate each other. The PANTHER system determines homologous elements (Mi et al., 2010; Thomas et al., 2003). This method of discovering new information is both deep and broad, allowing the creation of a comprehensive database. Another advantage of the GO database is that its information is linked to other databases including SwissProt (Bairoch & Apweiler, 2000), GenBank (Benson et al., 2000), EMBL (Baker et al., 2000), DDBJ (Tateno, Miyazaki, Ota, Sugawara, & Gojobori, 2000), PIR (Barker et al., 2000), MIPS (Mewes et al., 2000), and Protein families (Pfam) (Bateman et al., 2000).
Kyoto Encyclopedia of Genes and Genomes (KEGG)

KEGG is a reference knowledge base that contains system, genomic, and chemical information applicable to various organisms. The key element of the database pertaining to pathway analysis is the pathway maps, which displays an overall picture of the interaction between elements. Such information is generally presented in a non-organism-specific way, and the KEGG Ontology information is used to specify the information for a particular organism. KEGG’s Metabolism overview maps display interaction information of chemicals, and in conjunction with KEGG Modules and KEGG Reactions, provide an overall view of metabolic networks. KEGG Medicos includes information of the interaction between drugs, extracted both from the US Food and Drug Administration (FDA) and Japanese sources. While originally an open-source effort, a fee is currently required to access the database files.

MetaCyc

MetaCyc is a database of experimentally curated metabolic pathways combined with enzyme kinetic information. The database includes 1,800 pathways from various organisms. The pathway classes defined in MetaCyc include:

- Activation – A chemical modification to an active compound, which increases the activity of that compound.
- Inactivation – A chemical modification to an active compound, which decreases the activity of that compound.
- Interconversion – A chemical that is converted into another form, which results in either an increase or decrease in the activity of that compound.
- Metabolic Clusters – A collection of compounds that are not directly connected but collectively describe a specific phenomenon.
- Biosynthesis – The process by which an active compound is synthesized.
- Degradation/Utilization/Assimilation – The process by which a compound is broken down into smaller, simpler compounds.

Activation, Inactivation, and Interconversion are included in a single class. Other classes include Generation of Precursor Metabolites and Energy and Detoxification. Recent advances in the database include bioenergy pathways, and the development of techniques to genetically engineer and combine pathways. Furthermore, this database has the ability to combine pathways, which are referred to as a super, conspecific, or chimeric pathways. Often the combined pathways are defined in different organisms although they describe the same or a similar phenomenon. The combination of these pathways results in an overview of the metabolic phenomenon that is being considered.

BioCyc is a pathway/genome database organized like MetaCyc. This database contains 1,700 pathways for various organisms. Three tiers of pathways are included in this database, namely those that have been extensively studied and curated for over one year, those that have been curated for less than one year, and those that are computationally created. The computationally created pathways were determined with Pathway Tools software (Caspi et al., 2014).
**Molecular Signatures Database (MSigDB)**

MSigDB is a database of discovered genes sets from several sources. It contains 10,295 gene sets, which are classified into the following collections.

- **Positional** – These correspond to specific chromosomes and are thus best used to detect chromosomal deletions.
- **Curated** – These have been collected from online databases, literature, and experts. This category contains subclasses referring to specific pathways and databases.
- **Motif** – These are genes with a cis-regulatory motif conserved across human, mouse, rat, and dog genomes.
- **Computational** – These have been discovered by computational mining of microarray data, mainly in the cancer field.
- **GO** – These were named and classified by GO.
- **Oncogenic** – These are implicated in pathways that are dis-regulated in cancer.
- **Immunologic** – These were literature curated to be influential in the immune system.

All of these databases contain vital information that assists pathway analysis software in identifying influential pathways and genes in the dataset of interest. These databases include ontology information, and users can determine whether other researchers have found information contained in their datasets or if it has been found in another organism. The pathways included in these databases can be used as gene sets for hypothesis testing performed using the pathway and network analysis approaches discussed below. Alternatively, any of the approaches discussed below could be used with custom gene sets (that an investigator builds based on prior information). However, implementing this is not as straightforward as using the tools built around these well-curated databases.

**PATHWAY AND NETWORK ANALYSIS METHODOLOGIES**

Pathway analysis is the process of discovering meaningful relationships between cellular elements, often in context of the disease or trait of interest. The definition of the cellular elements of interest depends on the data being analyzed. For expression data, genes are the cellular elements. For SNP array data, the SNP can be mapped to a particular gene or the SNP positions themselves can be used as the cellular elements. For metabolite data, the analyzed chemicals are the cellular elements. The appeal of pathway analysis is the summary information resulting from it. However, when conducting pathway analysis, the “curse of dimensionality”, which occurs when the number of variables in a dataset is much larger than the number of samples, remains an issue. With such a challenge, discovering patterns above the high noise levels generated is of great importance, and appropriate statistical methods should be used to overcome such a challenge. Furthermore, pathway analysis enables consideration of the interactions between cellular elements, which are critical to the functionality of the cell. Thus, influential interactions in the dataset can be identified.

Once the data has been collected and the proper quality control is conducted, the researcher must select pathways (defined in the knowledge bases discussed above), which should carefully reflect the overall goals of the study and the types of data and information that were used to build the resource. Relevant information can include pathways from other...
organisms, and current knowledge about the disease or mechanism under study, in addition to other aspects. This information can be tailored towards the goals of the study. Although an exhaustive search can utilize all pathways in a particular database or knowledge base, statistical and computational concerns affect feasibility. For example, Figure 1.3 displays the diabetes pathway (extracted from KEGG) of genes involved in diagnosis.

![Type 1 Diabetes Mellitus](image)

**Figure 1.3:** Diabetes pathway from KEGG. (Kanehisa et al., 2014)

The evolution of pathway analysis methods has given rise to two processes within the broad class of pathway/network analysis, generation, and association with particular disease/experimental states or phenotypes of interest. Pathway analysis methods can be classified into three generations, namely over-representation analysis (ORA), which is the first generation, functional class scoring (FCS), which is the second generation, and pathway-topology (PT), which is the third generation. ORA and FCS methods are also often referred to as gene set analysis, since they test for elements within the gene set compared to random (Khatri, Sirota, & Butte, 2012). ORA and FCS methods are used for the main task of network analysis while PT methods infer and generate networks. These tasks are often conducted sequentially when both inference and analysis of the network is desired (Khatri et al., 2012). Table 1.2 summarizes the advantages, disadvantages, and common uses of each approach. While many methodologies do not fall cleanly into these categories, the overall goals and approaches can generally be contextualized into these categories.
Table 1.2: Advantages, disadvantages, and most common utilization of ORA, FCS and PT pathway analysis methods.

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Utilization</th>
</tr>
</thead>
</table>
| ORA    | • Simple to Implement  
         • Robust Statistics | • Statistics do not consider the measurement  
         • Arbitrary threshold for determining which elements to consider.  
         • No interactions between elements considered. | Overall characterization of pathways displayed in the data. |
| FCS    | • Robust Statistics  
         • Interactions between elements are considered.  
         • Statistics consider the measurement of each element.  
         • No threshold for determining which elements to consider. | • No Interactions between pathways are considered.  
         • Measurement is only considered in the calculation of the gene-level statistic. | More in depth characterization of the pathways most represented in the dataset. |
| PT     | • Interactions between elements and pathways are considered.  
         • Pathway topology can be inferred. | • Results can be bias towards the dataset without thorough cross-validation.  
         • Little information about the interactions is known, thus validation is difficult.  
         • Topology often depends on the cell and environmental conditions. All of the scenarios are difficult to test. | Inferring the topology of the pathway, which also characterizing the statistical significance. |
ORA methods detect influential (over-represented) cellular elements from the identified pathways. The common procedure includes three steps: 1) picking/calculating a threshold measure, 2) counting the representation of input genes (within a defined pathway), and 3) conducting a statistical test. First, all elements with input measurements that do not meet a specified threshold are discarded. For example, a common threshold for expression data is over/under expressed by more or less than a specific value. For expression data, a similar threshold is the false discovery rate instead of over/under expression. If the threshold is met, the numbers of genes represented in each analyzed pathway are counted. Finally, a statistical test is conducted to assess whether the observed count is statistically significantly different from a random count. Common statistical tests include those based on hypergeometric, chi-squared, and binomial distributions. These statistical tests represent the null hypothesis in different ways, which are discussed in more detail in the section below outlining implementation considerations.

The main limitations of ORA methods are the measurement of statistical significance without consideration of the element’s intensity measurement. Therefore, each gene in the statistical test is treated equally. This statistical model may not be accurate since the measurement is often an indication of the activity of the element. Thus each element should be represented according to its measurement (and not equally). Another limitation for ORA methods is the arbitrary threshold used in the first step. Since elements not meeting this threshold are disregarded in further analyses, a more robust method of elimination should be utilized. A third limitation of ORA methods is that no interactions between elements are considered. Therefore, each element is analyzed independent of the others. Due to the assumptions involved in ORA analyses, researchers refer to these methods as gene set analysis, since a set of elements is identified and their relationships are not considered. Lastly, ORA methods typically assume that analyzed pathways are independent of each other. Since all processes in the cell are interconnected (and the pathways and gene sets defined in the knowledge bases are interconnected), this assumption is unrealistic (Khatri et al., 2012). These limitations prompted the development of the second generation of pathway analysis tools.

FCS methods directly analyze the network connections from the data analyzed. These methods utilize statistical techniques to detect both large and small changes to individual elements that significantly affect particular pathways. The dynamics of large changes in individual elements causes a direct change in the pathway. For small changes, collections of these changes are coordinated to affect the pathway. The general procedures for FCS methods include calculating gene-level and pathway-level statistics, and determining the significance of the pathway-level statistics. Gene-level statistics depend on the measurements from the dataset being analyzed. For example, expression data can be represented as differential expression. Other common gene-level statistics (independent of the data) include correlation, analysis of variance (ANOVA), q-statistic, signal-to-noise ratio, t-statistic, and z-statistic (Khatri et al., 2012; Ramanan et al., 2012). Gene-level statistics are calculated for each element in the dataset.

From these gene-level statistics, a pathway-level statistic is calculated for each analyzed pathway. For this calculation, only the elements contained in the specific pathway are included. Common statistics utilized for this include the Kolmogorov-Smirnov statistic;
the sum, mean, and median of the gene-level statistic; the Wilcoxon Rank Sum statistic; and the maxmean statistic. For these statistical tests, the null hypotheses discussed in the implementation considerations section must be considered. Pathway-level statistics offer an advantage by accounting for relationships between elements. Thus, FCS methods overcome this limitation of ORA methods. Finally, the significance of the pathway-level statistics is calculated. This can be done using a competitive or self-contained null hypothesis. For a competitive null hypothesis, the element labels of the pathways are permuted, thus allowing comparison of the discovered element set to other random sets that are not contained in the pathway under analysis. For the self-contained null hypothesis, class labels are permuted, thus allowing comparison of the discovered element set to other random sets that are contained in the dataset under analysis. A further discussion of these null hypotheses is provided in the implementation considerations section below. Significance is calculated for all pathway-level statistics. FCS methods improve on ORA methods by not implementing an arbitrary threshold, utilizing the element measurements in calculating pathway significance, and accounting for element interactions in the model. However, these techniques have limitations since the different pathways analyzed are treated independently. Further, some techniques utilize only the change in the measurement while calculating the gene-level statistic and disregard this information in further analysis. (Khatari et al., 2012)

PT methods generate the network, which is then analyzed by ORA or FCS methods. PT methods utilize the interactions represented in the pathway to calculate pathway significance. Therefore, the topology of the pathway under study is considered, improving pathway analysis. Furthermore, methods have been developed to infer the topology structure based on the dataset utilized. A limitation of PT methods is that analysis is based on the dataset used and can be difficult to generalize. However, with the advent of personalized medicine and Bayesian statistical techniques, specific models are becoming very popular. Another limitation of PT methods is that strong interactions between pathways are not typically known and thus validating the interactions discovered can be tricky. Lastly, the topology of the pathway often depends on the cell and environmental conditions, and obtaining data in all scenarios is impossible. (Khatari et al., 2012)

The most popular methods of inferring a network are relevance networks and Gaussian graphical models (GGMs). Relevance networks utilize the correlation coefficient between variables. If this correlation is above a set threshold, then a dependence exists, which is visually represented by an edge in the network. A disadvantage of this methodology is that direct dependence (as opposed to indirect dependence) cannot be distinguished. GGMs overcome this limitation by utilizing the partial correlation coefficient. The partial correlation is the correlation between two variables conditioned on the other variables in the dataset. Therefore, two variables are independent of each other if the partial correlation between them is zero. The partial correlation is estimated based on the correlation matrix, which is estimated by a standardized unbiased covariance matrix. Scafer and Strimmer (2005) presented the mathematics of this method. A disadvantages of GGMs are that the theory is best applied when the number of samples is higher than the number of variables. This is not the case in biological and genetic data, where the number of variables is far higher than the number of samples. This limitation can be overcome by reducing the dimensions of the data and only analyzing second
order partial correlations by regularized GGMs. Regularized GGMs are often the most efficient methods since regularization and moderation are introduced into the data by full Bayesian or empirical Bayes methods. More discussion on GGM can be found in Schafer and Strimmer (2005).

**Implementation Considerations**

When implementing various pathway/gene set analysis techniques, two important statistical concerns are true across all methods. First, there are two structures for the null hypothesis being tested. Second, as with any set of statistical tests (where more than a single test is performed) concerns with multiple testing and potentially inflated Type I (false positive) error rates must be addressed with some form of multiple testing correction.

Regarding the first concern, statistical analysis performed can be conducted using either self-contained or competitive hypothesis tests. These statistical tests provide one value (e.g., a score or p-value) for each pathway or gene set that summarizes the probability that the observed element differs from the given dataset by chance. The self-contained test is used when the overall null hypothesis is: “No genes in the gene set are differentially expressed.” The competitive test is used when the null hypothesis is: “The genes in the gene set are not more differentially expressed than other genes in the dataset”. The results from a competitive test are very sensitive to the number of elements included in the dataset (number of variables or features). Furthermore, if a large number of elements are changed, then the test results indicate that no gene sets are differentially expressed. The results of the competitive test often provide fewer significant gene sets than the self-contained test. While at a superficial level these hypotheses may seem similar, they are actually quite different. The self-contained test corresponds to an omics-wide test, where the competitive null hypothesis corresponds to a candidate pathway/gene-set hypothesis.

Because statistical tests are conducted multiple times for each pathway and these pathways can overlap, multiple testing statistical procedures must be implemented. The methods to correct for multiple testing include controlling the false discovery rate, Bonferroni correction, resampling, and permutation testing. Controlling the false discovery rate takes advantage of overlapping pathways. A Bonferroni correction divides the desired significance value by the total number of tests that are conducted. The resultant significance value is utilized for each test. This is a very conservative technique, but it is effective in all situations. Resampling or permutation testing involves repeating the statistical test thousands of times with the sample labels or variables permuted to obtain an empirical estimate of the test statistics that would be expected by chance. For a self-contained test, the sample phenotype labels are permuted; for a competitive test, the variables are permuted. This quantifies the probability of observing the pattern by chance. An advantage of permutation testing is the consideration of correlations between variables which can lead to more valid estimates of overall error rates when implemented correctly. A disadvantage of permutation testing is that it is extremely computationally intensive.
Solutions and Recommendations

As with the database resources, there is a large and constantly growing number of pathway and network analysis tools. In this chapter, we review some of the commonly used tools. Methods used to perform pathway/gene set analysis include GSEA (Subramanian et al., 2005), and Significance Analysis of Function and Expression (SAFE) (Barry, Nobel, & Wright, 2005). Pathway topology methods that create/infer networks include genome-wide regulatory network (GWRN) (Cowper-Sal lari, Cole, Karagas, Lupien, & Moore, 2011), weighted gene co-expression (Zhang & Horvath, 2005), Algorithm for the Reconstruction of Accurate Cellular Networks (ARACNE) (Margolin, Nemenman, et al., 2006; Margolin, Wang, et al., 2006), impact factor (Khatri, Draghici, Tarca, Hassan, & Romero, 2007), and netGSA (Shojaie & Michailidis, 2009). Table 1.3 summarizes each of these methods and provides URLs to access the software. The methods are briefly reviewed below.

Gene Set Enrichment Analysis (GSEA)

The GSEA (Subramanian et al., 2005) method falls between classification as an ORA method or a FCS method due to the flexibility of its implementation. The input to this system is a set of elements (this can be a set of elements from a pathway) that the researcher hypothesizes is influential in the trait or disease studied in the data. The set of elements in the dataset is ranked based on their association with the phenotype. For expression data, this ranking is often the differential expression of the gene. The objective of GSEA is to detect where in the ranked list the specified element set is located. From this information, an enrichment score is calculated, which measures the specified set’s maximum distance from the middle of the ranked list. From the enrichment score, a p-value is calculated by permuting the phenotype labels (self-contained null hypothesis). To correct for multiple hypothesis testing, GSEA controls for the false positives by computing the false discovery rate (FDR). The elements found to be significant are hypothesized to affect the inputted gene set based on the dataset used. GSEA is a strong method that utilizes database information and accounts for correlation structure in the dataset. However, this correlation structure is ignored when calculating significance from a dataset with small number of samples.

Subramanian et al. (2005) applied this method to several cancer expression datasets, including a dataset of lymphoblastoid cell lines (to detect the difference between males and females), the NCI-60 collection from the National Cancer Institute (to detect the difference between p53+ and p53−), a dataset for acute leukemia (to detect the different in acute lymphoid leukemia and acute myeloid leukemia), and a dataset comparing lung cancer studies. In all of these applications, biologically influential genes sets were identified, thus displaying the accuracy of the GSEA method. The leukemia application also detects chromosomal aberrations in addition to gene sets, demonstrating that GSEA is flexible in its detection capability.
Table 1.3: Pathway analysis methods, including summaries of the methods and URLs to access the software.

<table>
<thead>
<tr>
<th>Method</th>
<th>Summary</th>
<th>Access</th>
</tr>
</thead>
<tbody>
<tr>
<td>GO</td>
<td>Provides a genome annotation for different organisms including interaction information.</td>
<td><a href="http://www.geneontology.org/">http://www.geneontology.org/</a></td>
</tr>
<tr>
<td>SAFE</td>
<td>Detection of significant gene sets based on the calculation of local (gene-level) and global (gene set level) statistics</td>
<td>Bioconductor Package</td>
</tr>
<tr>
<td>IF</td>
<td>Detects changes in the pathway based on the data and calculates an impact factor.</td>
<td><a href="http://vortex.cs.wayne.edu/projects.htm">http://vortex.cs.wayne.edu/projects.htm</a></td>
</tr>
<tr>
<td>GWRN</td>
<td>Developed for SNP arrays by utilizing LD information to infer pathway topology.</td>
<td>R Package and GUI</td>
</tr>
<tr>
<td>netGSA</td>
<td>Utilizes a latent variable model to infer network structure. Analysis of the network is conducted by a mixed linear model.</td>
<td><a href="http://dept.stat.lsa.umich.edu/~shojaie/research.html">http://dept.stat.lsa.umich.edu/~shojaie/research.html</a></td>
</tr>
</tbody>
</table>
Significance Analysis of Function and Expression (SAFE)

SAFE (Barry et al., 2005) is a framework originally developed for expression data but has been extended for use in SNP arrays and metabolomics. SAFE is an example of a FCS method that is used primarily to analyze given pathways. The method begins with the calculation of a gene- (or element-) specific statistic (also referred to as the local statistic), which is most often the t-statistic. For applications in expression data, this statistic measures the association between the expression measurement and the dataset response variable. Using local statistics for each element in the dataset, a global statistic that identifies deviations in the local statistics is calculated. SAFE implements the Wilcoxon rank-sum (a non-parametric statistical model used to compare means of two populations) and the Kolmogorov-Smirnov statistic (a non-parametric statistical model used to determine if two continuous populations are equal), thus testing the presence of discovered relationships over noise. To determine the significance of the global statistic, the response variable is permuted (self-contained null hypothesis test), and a p-value is calculated. SAFE is an excellent software package that utilizes well-known robust statistical methods to obtain accurate measures of significant pathways. SAFE is available online at no cost through the R Bioconductor package. SAFE is limited to the analysis of networks and is not dynamic regarding changing topology of the network.

Berry et al. (2005) displayed the versatility of the SAFE technique on a human lung carcinoma expression dataset. The technique was used to detect influential pathways between normal and cancerous samples, compare multiple cancer subtypes, and conduct survival analysis. To adapt the technique for these analyses, the local statistic was specific to the type of inference, and the Wilcoxon rank-sum statistic was used as the global statistic. The significance of the global statistic was measured by permuting the response variable 10,000 times (self-contained null hypothesis test) and correcting for multiple testing by the FDR and the family-wise error rate. To compare between normal and cancerous samples, the absolute value of the Welch t-statistic was utilized as the local statistic. To compare the cancer subtypes (i.e., adenocarcinomas, pulmonary carcinoids, small-cell lung carcinomas, and squamous cell lung carcinoma) the ANOVA F-statistic was used as the local statistic. To conduct survival analysis a Cox proportional hazard model was utilized as the local statistic. In all studies, influential pathway functionality was identified by the GO and Pfam (protein family) databases. This study shows that pathway analysis using SAFE is adaptable to the response variable of interest and study-specific research questions.

Genome-Wide Regulatory Networks (GWRN)

The GWRN technique is used to define and analyze networks. The technique was developed for use with SNP data but can be extended to other datasets. In a GWRN, a node signifies the genomic element represented by the SNP. Many other techniques can be used to map a SNP to its closest gene although with the Encyclopedia of DNA Elements (ENCODE) (E. P. Consortium et al., 2012) information that is currently available, interaction information for individual positions of SNP may be known already. An edge in a GWRN is defined as an interaction between the elements, as described above. For SNP data, several positions of linkage disequilibrium have been identified by the HapMap consortium (Altshuler et al., 2010).
Therefore, the weights on an edge can be represented by the linkage disequilibrium of the pair of elements. Furthermore, ENCODE has identified several long-range physical and cistromic interactions that can define an edge. This technique relies heavily on the information contained in the database used, meaning that the network will be scarce when information about the dataset is unknown (Cowper-Sal lari et al., 2011).

**Weighted Gene Co-Expression**

Weighted gene co-expression (Zhang & Horvath, 2005) is a method that creates and infers a network based on inputted data. Its implementation is targeted towards expression analysis although it can be extended for use with other data. Weighted gene co-expression utilizes gene co-expression networks to represent the pathway. A gene co-expression network is based on interactions of genes in the network. As mentioned earlier, each node in the network represents a gene, and an edge between genes represents a relationship between them. Gene co-expression networks rely heavily on the adjacency matrix of the network (i.e., a matrix that describes which nodes in the network are connected). To find the adjacency matrix of the network, a similarity measure (often correlation) is defined between the input elements. The weight of each network connection is defined as the transformation of the similarities based on the adjacency function (often the sigmoid or power function). Optimizing the parameters in the adjacency function optimizes the adjacency matrix. Utilizing the power adjacency function implements soft thresholding since the degree of connection is expressed in the adjacency function and is not just binary (i.e., a connection is present or absent). Therefore, the correlation of expression values between pairs of genes is defined.

Once the network is defined, the genes are analyzed in terms of modules and extracted from hierarchical clustering of the genes. Hierarchical clustering is a technique that separates inputted elements into subgroups that have similar measurements. The separation is conducted in a tree-like (dendrogram graph), hierarchical manner. For this application, a distTOM distance measure is utilized, which is a measure of dissimilarity calculated by the topological overlap between pair of nodes to determine the relative interconnectedness of the nodes. From hierarchical clustering, clusters (or modules) are identified by cutting the dendrogram at a specific height. The information in the modules is compared to network characteristics and external information to infer its biological meaning. To infer the most influential relationships, the created network is analyzed by graph characteristics, statistics and ORA methods.

Zhang and Horvath (2005) applied this technique to a brain cancer microarray dataset. This dataset was first reduced to 8,000 genes (dimensionality reduction procedure) with the highest variance (between cancer and cancer-free patients). After optimizing both the power and step adjacency functions, six biologically significant modules were identified. The biological significance represents specific gene ontologies and modules that are highly conserved. Furthermore, intramodular gene connectivity (distribution of the edges within a module) of the network was found to be correlated to cancer prognosis. This intramodular connectivity was modeled to be scale-free, where certain genes in the networks are hubs (high adjacency to other genes). This distinction was more apparent with the use of soft thresholding (power adjacency function) as opposed to hard thresholding (step adjacency function). Therefore, weighted gene co-expression pathway analysis provides influential modules that
display characteristics of real networks in a scale-free distribution. Furthermore, inferring the influence of modules provides insight into disease characteristics.

**Algorithm for the Reconstruction of Accurate Cellular Networks (ARACNE)**

ARACNE (Margolin, Nemenman, et al., 2006; Margolin, Wang, et al., 2006) is an analysis tool and associated software package that creates and infers a network based on inputted data. The ARACNE technique begins with completely connecting gene triplets (in a graph where all pairs of nodes are adjacent). Pairwise mutual information, which is a measure of the dependence of a pair of elements, is calculated for each triplet. Next, all triplets with mutual information above a specified threshold are selected. The specific threshold is arbitrary and can often be difficult to justify. The selected triplets are further analyzed by the data processing inequality (DPI) method, where the minimum of pairwise mutual information is selected if two genes interact through another gene. Therefore, the edge is retained only if no other path between the two genes exists. In this process, an edge is always removed from the triplet. This design is relatively conservative and decreases false positives for identified relationship. When decreasing false positives, there is a risk that the number of false negatives identified may increase, which means that influential relationships may be disregarded. The main advantage of this technique is that it can build up a reliable network based on inputted data. Furthermore, triplet analysis can be extended to higher-order sets, thus improving the overall performance of the identified network.

Margolin et al. (2006) applied this method to an expression dataset containing 340 B lymphocytes from normal, tumor-related, and experimentally manipulated individuals. The ARACNE software was used to generate a B-cell-specific regulatory network, which was validated by analyzing the presence of c-MYC and its neighbors. C-MYC is a proto-oncogene that has been shown to be a hub gene in B-cell regulatory networks. The ARACNE system performed well since a statistically significant number of genes adjacent to c-MYC were biologically verified. Furthermore, second-layer connections to c-MYC were not significant over noise. Therefore, ARACNE is accurate in finding direct interactions but may not locate all secondary interactions of the overall network.

**Impact Factor (IF)**

IF (Khatri et al., 2007) is a systems biology technique that detects changes that elements cause on a pathway. This change is quantified by the perturbation factor, which is dependent on both the change in measurement and the effects of elements adjacent to the element under analysis. Often, the changes detected are those that propagate throughout the analyzed pathway. From the perturbation factor, a linear additive model can be utilized to calculate the impact factor for each pathway. The linear additive model is a sum of randomly obtained pathway statistics and the effect of the dataset’s impact. The impact factor is a relative measure of the influence of the pathway. IF is a simple method to implement and is available at no cost. IF is an in-depth and robust method for finding the elements most represented in a pathway (ORA-type analysis). Concerns related to this technique include its limitation to the pathway extracted from the database, which cannot be dynamically altered by the analysis process.
Secondly, the linear additive model used to calculate the impact factor is very complex and may not be solvable for all cases.

Khatri et al. (2007) tested IF performance on a cervical microarray dataset. The dataset was preprocessed by applying a t-test (corrected p-value using FDR) to select the most significant genes (p-value ≤ 0.05). This resulted in 960 genes, which were analyzed by the IF technique. The technique was compared to ORA methods by hyper geometric distribution and GSEA. The results of the ORA methods and IF were consistent (identifying the cytokine-cytokine receptor interaction, complement and coagulation cascades, and leukocyte transendothelial migration pathways) but GSEA found no significant pathways. This is because the authors inputted the whole 19,886 genes into the GSEA system but only 960 significant genes for the ORA and IF analysis. Furthermore, IF detected more pathways (vascular endothelial growth factor signaling, toll-like receptor signaling and ECM-receptor interaction pathways) than ORA, all of which can be verified by biological information.

Network Based Gene Set Analysis (netGSA)

netGSA (Shojaie & Michailidis, 2009) includes methods to both infer a gene network and conduct an over-representation analysis. The inference of a network is based on a latent variable model that is dynamic since the weights of the model are tuned to best fit the inputted dataset. A latent variable model is similar to a linear model but latent variables represent the baseline element measure. The effect of the latent variable model is expressed in the influence matrix, where the expression of each element is modeled in terms of the latent variables. With this latent variable model, the element measures are represented and directly tune the weights of the model. Once an optimized network is established, netGSA employs a mixed linear model to identify most influential pathways and the elements within these pathways. This mixed linear model includes random effects, latent variables, and error terms. The parameters of the model are estimated by restricted maximum likelihood. The main limitation of the netGSA technique is that elements not included in a pathway cannot be inferred to be added to the pathway. Since netGSA only analyzes the elements contained in the pathway based on the knowledge base, new information cannot be inferred and added into the pathway.

Shojaie and Michailidis (2009) displayed the performance of netGSA using the benchmark data of Ideker et al. (2001), who analyzes expression and protein data in yeast. To apply netGSA, the galactose utilization pathway identified by Ideker et al. (2001) was used as input to define the influence matrix. The results from netGSA were compared to results from GSEA and the galactose utilization pathway was found to be significant from both techniques, although netGSA constructed four additional significant pathways. This application shows the ability of netGSA to discover pathways that are overlooked by other techniques.

Expansion to Other Omics Data

All the methods discussed here were developed for gene expression data, and, with some exceptions, most applications have been limited to this type of data. Weighted gene co-expression analysis is an exception, where ready extension to SNPs (with an additive encoding for the number of minor alleles) allows its easy application to SNP data. SAFE is also being used for SNP data analysis.
There are growing applications and extensions of the approaches discussed here to other omics data. Applications of such approaches for data include copy number variation and methylation data, among others. As these new applications become increasingly common, it will be important to understand the consequences of using these new technologies with existing approaches. At the level of annotation databases, new technologies will have different and often more gaps in annotation, which need to be understood and considered in the choice of database(s) used for gene set generation in pathway analysis approaches. Additionally, differences in details of the various data (e.g., distributional assumptions, missing data structures) that may superficially seem unimportant should be carefully considered before using methods that were originally understood in the microarray experiment setting. For example, while both RNA-Seq and microarrays measure gene expression, differences in technology produce data with varying underlying statistical distributions.

An Example Application

As these approaches mature, a number of applications of pathway and network analysis could be directly relevant to healthcare. As an example Zhu et al. (2013) conducted pathway analysis utilizing metabolomics data to study major depressive disorder (MDD). The researchers conducted a clinical trial to study the response of selective serotonin (5-HT) reuptake inhibitors in patients with MDD. Of great interest in this study was the effect of the drug on the methoxyindole and kynurenine subgraphs of the tryptophan pathway. Metabolomic profiling was conducted by liquid chromatography electrochemical array for serum samples extracted from MDD patients with and without dosages of sertraline. Pathway analysis was conducted by ORA, where a paired t-test was used to detect metabolite changes between the weeks’ patients were monitored. Correlation between the metabolites was calculated by the Pearson correlation coefficient. All p-values were corrected using the FDR. This study addressed questions about the pathways in the disease state itself and evaluated changes in these pathways in response to therapy. The metabolite signatures discovered were different for each week of monitoring along with a placebo. Many of the same signatures were found when comparing sertraline and placebo, indicating that that pathway structure may be shared for all individuals with MDD. While the results are preliminary, if they can be replicated across other studies, it is clear that such pathway approaches could affect healthcare. Pathway signatures shared across disease classes could aid in the diagnosis of disease. If signatures of response are found, this could aid in understanding or predicting response to treatment. The result of this study also show that the structure of the pathways themselves varies by treatment conditions, which is an important limitation of current database/annotation structures.

FUTURE RESEARCH DIRECTIONS

Pathway analysis methods development has made several key advancements with further annotation of genomes and more in-depth analysis of networks. While these advances have been rapid, the next steps present a few key challenges. First, given the difficulty and complexity of biological pathways, there has been little use of simulated data to fairly compare methods. Very few studies rely on simulation tools, which are an important component for
developing rigorous statistical methods. Few simulation tools have been developed that create artificial data based on artificial networks. Such simulated data can be used to objectively compare performance between methods and properly evaluate the tradeoffs between power and false positive rates. Such information can provide situations where one method is more appropriate than another for a range of realistic scenarios, thus improving the overall analysis and inferences made from pathway analysis methods. Di Camillo et al. (2009) developed one such data simulator that created networks and simulated expression data from the created network. In this implementation, the networks contained properties of pathways discovered in biological systems, such as a scale-free degree distribution, high clustering coefficient, and a small average distance between nodes. The expression data was specified by representing the change in expression of gene regulators and the type of relationship (enhancer or repressor) between the genes. By solving the system of differential equations, gene expression values are found that represent the relationships present in the pathway. An advantage of this simulation is the creation of network and expression measurements that represent properties observed in nature. Further, the ability to compare methods is retained since the researcher knows which relationships should arise from the pathway analysis. Only a few network simulators create completely artificial data, which is best for comparing methods. Many simulators produce benchmark datasets, which are often a perturbation of common pathways and have been heavily studied. However, for these networks and datasets, the results can be compared only to results from earlier studies. If new information is discovered, no strategy is available to verify this information since continued evaluation of a few datasets will inevitably result in false findings and produce bias in methods development towards approaches that over-fit these benchmark datasets. Furthermore, when working with real data, relationships become more complicated and the probability for new information discovery is high. Simulators should be developed and utilized for not only expression data but also SNP array and metabolomics data.

Second, there is a divide between methods that discover the topology of networks and those that analyze networks. There are limits in how the gene set methods that test for differences in pathways and the methods that detect topology can be used. Another limitation in the advancements of pathway analysis methods is the ability to add new elements and genes into existing knowledge bases. Experimentally testing all interactions of a new element is unrealistic and computational methods can be used to find influential interactions. This can be achieved by completely connecting the discovered element to a specific pathway and utilizing pathway topology techniques to find the weight or influence of each connection. A more computationally efficient method may be to search the possible connections and connect only those that are necessary based on the influence of the edge. Possible methods to conduct this type of search include evolutionary algorithms (O'Neill & Ryan, 2001) and Bayesian techniques (Christensen, 2011). A final limitation of pathway analysis techniques is the availability and use of time series data. Using this type of data would greatly enhance pathways by analyzing change in a pathway over both location and time.

Third, it is clear that current understanding of genomic annotation only scratches the surface of the complex relationships in biology (E. P. Consortium et al., 2012). Fundamentally, analysis tools that rely on knowledge bases (incorporating crucially important expert knowledge) are only be as good as the knowledge base that use. Efforts like ENCODE have
revealed that many of the simplifying assumptions that have been made (particularly about “junk” DNA) are untrue. We are also learning more and more about changes in the pathway and network structures in various tissues across time and in response to drug/chemical exposure that are not currently included in knowledge bases. As the level of detail in knowledge bases increases, methods development will need to keep pace and incorporate this added complexity.

**CONCLUSION**

This chapter surveyed the three generations of pathway analysis methods, highlighted their strengths and weaknesses, and provided a brief overview of a few of the knowledge bases available for use with these methods. Pathway analysis has become an important tool in genetics and genomics to help detect and interpret complex associations related to diseases or other outcomes of interest. Pathway analysis has been applied to gene expression, SNP array, and metabolomics data. The methods can be implemented in a relatively flexible way to test a range of questions about pathways information. Development of better annotation in knowledge bases, and innovative methods have allowed for interesting approaches to associating global changes in biological pathways and networks in a range of omics data.
REFERENCES


**ADDITIONAL READING**


**KEY TERMS AND DEFINITIONS**

**Pathway Analysis** – The process of detecting the underlying interactions between the variables in data.

**Network** – A set of vertices, edges, and relations that define the relationships between the vertices.

**Gene Expression** – The relative amount of protein being produced by a gene.

**Single Nucleotide Polymorphism (SNP)** – This occurs when a specific locus or position in the genome has multiple alleles represented in the population.
Metabolite – A change that results from a chemical modification within the cell.
Database – An assembly of data and information.
CHAPTER 2

Current Work on Metabolic Syndrome, Genetic Reference Populations in the Genetic-by-Environment Framework

Diabetes and Metabolic Syndrome

Metabolic syndrome (MetS) is a cluster of metabolically related symptoms that include high blood pressure, abnormal cholesterol levels, and excess body weight ("What Is Metabolic Syndrome?"). These symptoms have been found to significantly increase the risk for heart disease, diabetes, and stroke. ("What Is Metabolic Syndrome?"; Alberti et al., 2006) A staggering 1.4 million Americans are diagnosed with diabetes every year ("Statistics About Diabetes") and 70% of American adults are classified as overweight or obese ("Obesity Information"). Heart disease is the leading cause of death in the United States, and obesity has been shown as a leading risk factor (Fryar et al., 2012). MetS is a complex trait that is influenced by many factors, including genetics, environment, and lifestyle factors such as diet and exercise.

There is a substantial genetic component of MetS symptoms (Rahilly & Farooqi, 2006). In the current study, to better understand the genetic etiology of these symptoms, we examined several layers of molecular biology. Our examination followed the system outlined in Figure 2.1 (M.D. Ritchie et al., 2015). The layers examined include the genetic code found in deoxyribose nucleic acid (DNA), which can be modified by chemicals known as epigenome markers (epigenome). DNA is translated to RNA (transcriptome), which is translated into
proteins (proteome), which then operates on metabolites (metabolome). Figure 2.1 lists level-specific methods of collecting data (M.D. Ritchie et al., 2015). Each method varies in terms of the level of throughput, which correlates with the number of molecular elements that are analyzed simultaneously. The throughput is often higher at the genomic (millions of variants), epigenomic (thousands of methylation regions), transcriptomic (thousands of genes), and proteomics (thousands of proteins) levels compared to the metabolomic level (hundreds of metabolites). However, metabolomics is growing and over time the technology will advance to include more and more metabolites.

In addition to evaluating each of these omes at the individual level, we integrate data across the omes, and examine how the environment interacts at each levels. To build a foundation for the present work, we provide background on genetic association studies, gene-environment interaction studies, metabolomics technology, genetic mapping techniques, and the integration of metabolites and genetic mapping.
**Figure 2.1: Layers of Molecular Analysis.** The primary layers of molecular analysis within an organism includes the genome (study of a complete set of DNA); epigenome (molecular changes to the genome); transcriptome (study of complete set of expressed genes in the form of RNA); proteome (study of the complete set of proteins); and metabolomics (study of the “complete” set of metabolites). “Arrows indicate the flow of genetic information from the genome level to the metabolome level and, ultimately, to the phenome level. The red crosses indicate inactivation of transcription or translation. CSF, cerebrospinal fluid; Me, methylation; TFBS, transcription factor-binding site.” (M. D. Ritchie et al., 2015) This figure was extracted from Figure 1 of M.D. Ritchie et al. (2015).

**Molecular Studies on Metabolic Syndrome and Type 2 Diabetes**

Molecular studies on MetS have been conducted to analyze the environmental influences (e.g., diet and exercise), the genetic influence, and the interaction between the genome and the environment. Various studies on the etiology of diabetes and metabolic
syndrome-like traits have found that environmental factors are influential. Basciano et al. (2005) attributed the high incidence of obesity in the U.S. population to high consumption of fructose in the form of high fructose corn syrup found in many commercial products. Schultz et al. (2006) further studied diet habits within the U.S. comparing a group of Pima Native Americans living in Arizona to a group living in northern Mexico. The authors found that the group living in the U.S. had greater occurrences of type 2 diabetes. The genetic differences between the populations were negligible although their caloric intake and activity levels differed. Barker et al. (2010) compared a population from the Appalachian region of the U.S. to a population outside this region. The authors discovered differences in type 2 diabetes rates but no genetic differences. These studies found that environment (in these studies, diet) was a key contributor to type 2 diabetes rates.

The genetic influence of metabolic and diabetes traits has been documented in many studies. O'Rahilly and Farooqi (2006) reviewed various studies of phenotypes characterizing obesity, including body mass index (BMI) and leptin concentration. They made the case that food intake and decreased physical activity increased the incidence of obesity in twin studies although these environmental effects were not considered in isolation from genetic determinants. Furthermore, the authors found that BMI as a quantitative trait has very high heritability of between 64% and 84%, as measured in twin studies. Corella et al. (2009) studied the genetic-by-diet interaction in multiple populations using BMI as a quantitative trait. This work showed the utility of gene-by-diet interaction studies and their importance in understanding the molecular mechanism of different metabolism-related traits. To further understand the mechanisms and discover biomarkers for MetS, a systems-wide view can be
employed. From this perspective, not only the relationship between genetics and the clinical endpoint but also the intermediate steps between these are critical. One such intermediate step is metabolites (small molecules or chemicals), which can be influenced by genetic information, and are involved in regulation processes. Metabolites can also result from particular phenotypes. Understanding the interactions between metabolites and genetic information is valuable for personalized therapies, pharmacogenomics, and nutrigenomics (Corella et al., 2009).

**Molecular Analysis: QTL Mapping and Metabolomics**

**Genetic Mapping via Quantitative Trait Loci (QTL)**

Genetic mapping of quantitative traits has been successfully conducted for years to provide information on genetic variants to target for disease therapies. Several studies have shown high heritability estimates for metabolic syndrome-like traits (Corella et al., 2009; O’Rahilly & Farooqi, 2006). Quantitative trait loci (QTL) are known genomic positions that have been shown to influence quantitative traits (Mackay, 2001). QTL mapping is used to determine which QTLs are linked with the phenotype of interest in an attempt to describe the genetic variations of the phenotype. QTL mapping is conducted with thousands of molecular markers across the genome. The procedure includes a statistical test at each marker to determine if the phenotype is different from the various genotypes at the marker. The elements needed for this procedure are a population of inbred lines and the set of markers to be analyzed (targeted or across the whole genome) (Mackay, 2001). Inbred lines include individuals in which the genotype is highly similar except for variability at marker positions. Obtaining such
a population in humans is not feasible due to ethics concerns but this can be achieved in model organisms.

Many resources have developed strains of model organisms that utilize the concept of linkage when inferring associations with specific phenotypes. These resources include the collaborative cross for mice (Aylor et al., 2011; Churchill et al., 2004; Philip et al., 2011), the Arabidopsis multiparent recombinant inbred line (RIL) population (AMPRIL) (Huang et al., 2011) and multiparent advanced generation inter cross lines (MAGIC) (Kover et al., 2009) in Arabidopsis, the nested associated mapping population (NAM) in maize (Buckler et al., 2009; Li et al., 2011; McMullen et al., 2009; Yu et al., 2008), the Drosophila genetic reference population (DGRP) (Mackay et al., 2012) and the Drosophila synthetic population resource (DSPR) (King, Merkes, et al., 2012; King, Macdonald, & Long, 2012) for Drosophila melanogaster. These are linkage-based resources that maintain tens of thousands of lines for species. Collaborative Cross, AMPRIL, MAGIC, NAM, and DSPR are derived from a finite number of founder strains while DGRP is derived from a single outbred population. The resources derived from a finite number of founder strains have an advantage because all alleles are of high frequency; however, this does limit the analysis of rare variants, whose collective affects are increasingly discovered (King, Macdonald, et al., 2012). DGRP has an advantage of low allele frequencies, which allows detection of influential rare variants (Mackay et al., 2012).

The DSPR utilized in this work includes two separate synthetic populations of Drosophila. Each population originated from eight founder lines, with one line shared between the populations. The complete resource includes over 1,600 RILs after 50 generations of
intercross between the founders for each population, as shown in Figure 2.2 (King, Merkes, et al., 2012; King, Macdonald, et al., 2012).

**Figure 2.2: Intercrossing scheme for the DSPR, population A.** The population is derived from eight founder strains, including one that is shared between population A and B of the resource. The founders were mixed for 50 generations and then inbred, resulting RILs. This figure has been extracted from Figure 1 of King, Merkes, et al. (2012).

In this population, markers are included at 10 kilobase (kb) intervals throughout the whole genome. At each marker, the genotyping of the RIL was conducted by sequencing restriction-site-associated DNA (RAD) markers (Baird et al., 2008; King, Macdonald, et al., 2012). The markers were utilized in a hidden markov model (HMM) (Broman et al., 2003) to determine the probability that the marker genotype originated from each of the eight founder lines. Advantages of DSPR include high power to detect variants independent of the natural frequency of the variant and high mapping resolution due to the synthetic nature of this resource and the high number of intercrossed generations (King, Macdonald, et al., 2012). King, Macdonald *et al.* (2012) demonstrated the use of this resource along with many different genetic properties. They conducted power calculations for the resource for different allele frequency scenarios, including frequencies of 5% and 10% and found that the power to detect
these allele frequencies is very high (92% and 84%, respectively). However, this power drops for lower allele frequencies, which is attributed to the intercross nature of the resource.

**Metabolomics Technology**

Metabolomics is the study and analysis of the concentration of endogenous chemicals in a biological sample. Metabolites are highly diverse since they can be introduced into an organism from toxins in the environment or interactions with the genome, or can be a product of chemical reactions catalyzed by proteins. Metabolites have been shown to be influenced by many genetic variants in a variety of organisms for diseases that include cancer (et al., 2009), metabolic traits such as type 2 diabetes, and cardiovascular disease (Illig et al., 2010; Yousri et al., 2014). They have also been examined in many studies in pharmacogenomics (Altmaier et al., 2014; Suhre et al., 2011). Shin et al. (2014) discovered metabolite and genomic associations involving 145 loci and 400 metabolites in humans. The authors went on to functionally confirm many of the associations with in vivo experiments. Hill et al. (2015) discovered novel genetic and metabolite associations in a wheat population; Wen et al. (2014) discovered novel associations for the maize metabolome; and Williams et al. (2015) analyzed the *Drosophila melanogaster* metabolome.

Metabolomics can be analyzed as an intermediate trait between genetics and the clinical end point. Metabolomics, as the quantitative trait for genome wide association studies (GWAS) has shown high heritability of between 30% and 40% (Suhre & Gieger, 2012). Therefore, the integration of these technologies is a natural extension of known knowledge. Measuring the concentration of metabolites is most commonly conducted via nuclear magnetic resonance
(NMR) or mass spectrometry (MS) technology (Putri et al., 2013). NMR technology quantifies each small molecule by a shift in the resonance spectrum of the chemical's protons after exposure to a magnetic field. NMR offers an advantage because it not only quantifies each metabolite but also provides the chemical structure of the metabolite, which can be utilized in identifying or analyzing a metabolite (Alonso et al., 2015). MS technology identifies small molecules based on their mass-to-charge ratio and relative intensity. MS can detect a range of chemical masses due to its vast sensitivity towards various chemicals (Dunn et al., 2011). Each chemical is first ionized, and its mass-to-charge ratio is estimated by time of flight (TOF) analysis (W. B. Dunn et al., 2011). Prior to MS, chemicals in samples were separated most often by liquid chromatography (LC) or gas chromatography (GC) column. In these processes, the retention time, or amount of time each chemical passes through the column is estimated. Retention time and mass-to-charge ratio form the two axes of spectral data (Alonso et al., 2015). This spectral data is processed to identify peaks and determine the chemicals using algorithms such as BinBase (Skogerson et al., 2011) and others as outlined by Fiehn et al. (2008). Metabolomics studies can be conducted by targeting specific metabolites in a hypothesis-driven approach or untargeted by simultaneously detecting a large number of metabolites (Alonso et al., 2015).

Metabolomics is a recent technology to compare certain molecular levels (shown in Figure 2.1) to other molecular levels. Therefore, the throughput is much less for untargeted methods compared to mature genomics and transcriptomics. Currently, untargeted metabolomic techniques as described above can detect several hundred metabolites, which is much lower compared to genomics (millions of variants) and transcriptomics (thousands of
genes). One technological challenge of metabolomics techniques is due to the large variation in chemical properties. Metabolites vary in weight, polarity, and solubility, making simultaneous detection of variations across all these variables very difficult (Alonso et al., 2015).

**Drosophila melanogaster as a Model Organism**

In human populations, it is difficult to accurately determine the contributions of overall genotype and environmental effects on human variation. Furthermore, in mating studies of related individuals, it is difficult to collect a sample size with sufficient size to have the power to detect variants accurately in addition to being unethical. Therefore, model organisms such as mouse, *Arabidopsis*, zebrafish, and *Drosophila* have become very common in studies with the goal of understanding molecular mechanisms and then testing these mechanisms in humans. In the present study, all experiments were conducted with *Drosophila melanogaster* (the common fruit fly), which has been used as a model organism for over a century (Adams et al., 2000; Giot et al., 2003).

Working with *Drosophila melanogaster* offers many advantages, including extensive genetic tools, short generation time, ability to control mating designs, and high homology to humans. Many genetic tools have been established for *Drosophila*, including a synthetic reference population (King, Merkes, *et al.*, 2012; King, Macdonald, *et al.*, 2012) and a natural reference population (Mackay *et al.*, 2012). Short generation time and ability to conduct genetic screens mean the organism is relatively easy to study in the lab.
Researchers have determined that 75% of known human disease-related genes are conserved in *Drosophila melanogaster* (Reiter et al., 2001; Trinh et al., 2013). For metabolic syndrome and obesity studies, *Drosophila melanogaster* is an excellent fit due to the high degree of homology with human metabolic processes (Trinh et al., 2013). Many organs that are known to be involved in metabolic processes in humans have functionally analogous counterparts in *Drosophila*. For example, liver, pancreas, and adipose tissue in humans is analogous to the fat body and midgut in the functionality of digestion, lipid storage and mobilization, glycogen storage, and carbohydrate homeostasis. Furthermore, type 2 diabetes symptoms can be produced by utilizing high sugar and high fat diets in *Drosophila melanogaster* (Trinh et al., 2013). Studying the interactions between genetic variants, metabolomics, and the overarching influence of diet is highly tractable in *Drosophila melanogaster*.

**Integrating Metabolomics and Genetic Data**

Due to the complex nature of metabolic and MetS-like traits, providing a systems-wide view on how each molecular component interacts with the other is valuable. One method to achieve this is metabolite-QTL (mQTL) mapping, which incorporates metabolomics and genetic variant information. The resources and tools available for metabolomics and genetic variant analysis are vast, and studies on the metabolome of genetic populations has grown in popularity.

Heinrichson et al. (2014), collected metabolomics information and analyzed the effect of high fat diet on the metabolome and transcriptome in *Drosophila*. The authors found that
high fat diets have a deleterious effect, including increases in triglyceride and glucose levels and decreases in stress tolerance and lifespan in humans, analogous to Drosophila. Furthermore, this study also displayed large fold changes in metabolites involved in carbohydrate and amino acid metabolism, including the metabolites pyruvate, urea, and uric acid. The researchers conducted further transcriptomic analysis to discover a gene, which, when knocked out, increased fatty acid levels. Thus, they discovered that this gene is required for normal levels of triglyceride.

Williams et al. (2015) extended the work by Reed et al. (2014) and discovered genomic variants that influence transcriptomic and metabolomics profiles. These studies utilized the same dataset of 187 metabolites along with expression and metabolomics profiles for Drosophila treated with four diet regiments. The effects of genetics, the environment and their interaction were determined by a linear model, with each metabolite as the response. Many strong genetic and gene-by-environment interaction effects for both transcripts and metabolites were discovered. Functional confirmation by clustering and GO annotation resulted in many significant metabolic processes. Furthermore, there was little overlap between the identified loci in different diets.

The integration of metabolomics and genetic variants, including QTL mapping, is becoming very popular (Fall et al., 2016; Illig et al., 2010; Shin et al., 2014). mQTL studies on genetic-by-environment interactions have been conducted in other species, including humans in GWAS and maize and wheat, although no such study has yet been reported for Drosophila melanogaster. Hill et al. (2015) conducted a thorough study of the effect of the metabolome along with agronomic factors and genetics in a wheat population. They collected a large dataset
of metabolites by Liquid Chromatography coupled with Mass Spectrometry (LC-MS) (558 metabolites, 197 of which were identified) and analyzed genome-wide QTLs on metabolic and agronomic phenotypes. A custom linear mixed-model pipeline was used, with each metabolite as an independent response variable. The model for genome-wide analysis included random effects for genotypes, fixed effects for the parental lines, and five known causal loci as cofactors. The promising results revealed that a total of 238 metabolites across 159 QTLs were significantly associated. Furthermore, the authors calculated very high heritability for each metabolite, with median heritability of 54%. They compared the significant QTLs for each metabolite and found eight QTLs that affected both metabolic and agronomic phenotypes.

Wen et al. (2014) conducted a comprehensive study on the maize metabolome by integrating genetic, metabolite, and expression data. The authors collected an impressively large dataset of 983 metabolites (184 of which are known) by LC-MS in 702 maize genotypes. The complete population comprised lines from three inbred populations of maize. They conducted GWAS by using Zhou et al.’s (2010) implementation of a compressed mixed linear model, with each metabolite as an independent response variable. GWAS identified 1,459 significant mQTL associations. The variance explained for each metabolite was calculated to be a decent heritability at a median of 7.8% (total for all identified loci). Along with GWAS the authors conducted a linkage analysis of two RIL populations. The linkage analysis was carried out by Composite Interval Mapping software available through Windows QTL cartographer (Zeng, 1994) which uses a linear model-based method. This analysis identified further mQTL associations and explained between 3% and 80% of the variance for each metabolite. The authors identified 1,197 candidate genes, which were determined from the
genomic positions that overlapped between the GWAS and linkage analyses (14% of those identified). Five of these candidate genes were functionally verified by re-sequencing, eQTL, linkage, mutant and/or transgenic approaches. Two of these candidate genes confirmed the association identified by GWAS and linkage analyses.

Carreno-Quintero et al. (2012) utilized MetaNetwork software (Fu et al., 2007) to conduct a thorough mQTL analysis in a potato population. MetaNetwork software conducts QTL mapping using likelihood-based methods and reconstructs metabolite networks using the correlation between metabolite peak intensities. This resulted in significant mQTL associations that were validated based on a literature search.

Krumsieck et al. (2012) conducted a unique metabolomics study by combining an analysis of both known and unknown metabolites in a human population using blood samples from the KORA cohort. The metabolites and SNPs were first analyzed as a GWAS and then GGM was conducted to display further associations between the metabolites.

**Conclusions**

Identifying molecular biomarkers and environmental factors for MetS, obesity, and heart disease is vital for advancing personalized therapies. Due to the complex nature of the trait, a complex interaction of genetic, environmental, and lifestyle factors influence MetS. Therefore, integrating information from different molecular levels is informative to determine systems-wide architecture. Conducting such experiments in *Drosophila melanogaster* provides the advantages of short generation time and availability of genetic resources, along with metabolic homology with humans. DSPR has been used successfully in genetic screening
studies and to identify many influential genetic loci. The integration of metabolomics, genetic variants, and environmental factors such as diet provides insights into the complex interactions involved in MetS-like traits.

Such integration to identify metabolite-QTL (mQTL) interactions interventions has been conducted in humans, wheat, and maize populations but not in Drosophila melanogaster. Further, the interaction of dietary influences on genetic variants has not been mapped. This presents an opportunity to conduct such studies in Drosophila and extend the results to analyze networks of genetic variants or metabolites. The work presented in the subsequent chapters studies the influence of normal and high fat diets on mQTL associations in a DSPR population, utilizing a pathway based approach.
References


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CHAPTER 3

Gene Set Analysis Methods: A Systematic Comparison

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Abstract

Motivation: Gene set analysis is a valuable tool to summarize high-dimensional gene expression data in terms of biologically relevant sets. This is an active area of research and numerous gene set analysis methods have been developed. Despite this popularity, systematic comparative studies have been limited in scope. In this study, we present a semi-synthetic simulation study based on a real dataset to test and compare commonly used methods.

Results: A software pipeline, Flexible Algorithm for Novel Gene set Simulation (FANGS), was used to develop simulated data based on a prostate cancer dataset with differential expression of the KRAS and TGF-β pathways. The FANGS software is compatible with other datasets and targets other pathways. Comparison results tested using the MSigDB knowledge base are presented for Gene Set Enrichment Analysis (GSEA), Significance Analysis of Function and Expression (SAFE), sigPathway, and Correlation Adjusted MEan RAnk (CAMERA) methods. The false positive rates and power of each method were estimated and compared. Recommendations are made for the utility of the methods’ default settings and each method’s sensitivity to various effect sizes.

Availability: https://github.com/rmathur87/FANGS

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Supplementary Information: Supplementary data are available online.

Introduction

Gene expression data, especially at the whole genome level, is a powerful tool in modern genomics. Microarray and, more recently, RNA-Sequencing data have been leveraged to investigate a wide variety of problems in biology (Du et al., 2016; Ferrari et al., 2016; Lim et al., 2005; Mortazavi et al., 2008). Gene expression data has been collected for a wide variety of study designs and is most commonly used to compare gene expression patterns across

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groups/classes (i.e., cases vs. control or exposed vs. unexposed). Such group comparisons are performed with the goal of answering various questions in biology, which can be broadly categorized as class comparison (e.g., is differential expression associated with case/control status?), class prediction (e.g., can gene expression data be used to predict disease?), or class identification (e.g., can gene expression data be used to diagnose a disease or disease subtype?). While the exact details of analysis depend on the particulars of the data and the questions to be answered, common workflows have emerged.

Data analysis workflows for gene expression analysis have evolved significantly over the last 15 years, with numerous quality control and association tools and multiple testing control approaches developed specifically for such data. The first step of a gene expression study typically involves the evaluation of expression at the single gene level, which produces a list of associated genes ranked by the magnitude of the statistical association. In addition to this crucial step, investigators often conduct genome-wide expression analysis to gain a more global view of expression changes. This allows placement of these gene-level results into a broader biological context, which is highly desirable. Gene set analysis (GSA), also referred to as pathway analysis, is a commonly utilized approach to address these goals. In GSA, genes are aggregated into gene sets based on shared biological or functional properties defined by a reference knowledge base. Knowledge bases are database collections of molecular information and may include molecular interactions, regulation, molecular product(s), and even phenotype associations. The resultant gene sets are analyzed as a whole to determine which of these properties are relevant to the phenotype of interest. Such an analysis typically strives to generate hypotheses on the mechanistic processes for the phenotype of interest, which should
be further validated in replication studies or functionally examined in laboratory experiments. A number of GSA methods have been developed for gene expression data and have led to novel biological hypotheses about important clinical conditions. These methods suggest new avenues for therapeutic intervention based on the unexpected involvement of biological functions and pathways in a variety of disease processes (Dubash et al., 2016; Enge et al., 2009; Ferrari et al., 2016; Kučerová et al., 2016; Lamb et al., 2006; Liesenfeld et al., 2015; Mougeot, Li, Price, Wright, & Brooks, 2011; Mullighan et al., 2007; Planas-Paz et al., 2016; Sdelci et al., 2016).

While gene set methods have been under development and used in applications for well over a decade, there have been very few formal evaluations and comparisons of commonly used tools and algorithms. The few comparative papers published so far offer mainly theoretical evaluations of GSA methods; statistical evaluations are rare and limited in scale (Goeman & Bühlmann, 2007; Khatri et al., 2012; Maciejewski, 2014; Ramanan et al., 2012). Additionally, the majority of comparative studies have used benchmark data for comparison, as opposed to simulated data. For example, Tarca et al. (2013) compared 16 methods (including methods from the over representation analysis and functional class scoring) using 42 datasets retrieved from the Gene Expression Omnibus (GEO) for different disease phenotypes. The authors utilized the Kyoto Encyclopedia of Genes and Genomes (KEGG) (Kanehisa et al., 2014) and Metacore® Disease Biomarker Networks (https://portal.genego.com) knowledge bases. The authors found that the GSEA (Subramanian et al., 2005) and sigPathway (Tian et al., 2005) methods have inflated false positive rates and that Pathway Level Analysis of Gene Expression (PLAGE) (Tomfohr et al., 2005), GLOBALTEST (Goeman et al., 2004), Pathway
Analysis with Down-weighting of Overlapping Genes (PADO) (Tarca et al., 2012) and Mean-Rank Gene Set Enrichment (MR-GSE) (Michaud et al., 2008) were the best overall methods. The datasets analyzed in this study are real datasets without signal alteration and thus an accurate estimation of power cannot be calculated.

Simulation experiments are a crucial component of the evaluation and comparison of methods as bias, variance, and power properties can only truly be assessed in simulations with known solutions. The few simulation experiments that have been performed were limited in scope because they utilized gene sets defined by grouping genes based on the dataset as in those conducted by Maciejewski et al. (2014), Wu and Smyth (2012), and Fridley et al. (2010), instead of real world knowledge bases with realistic gene sets. Furthermore, these studies had a purely synthetic data correlation structure as opposed to correlations resulting from biological mechanisms. Without sufficient understanding of the statistical properties of GSA, there is a risk of drawing erroneous conclusions (either false positives or false negatives), which may subsequently lead to unnecessary investments in functional follow-up studies.

In this study, we evaluate and compare the statistical properties of the most commonly used GSA methods and corresponding software packages, including GSEA (Subramanian et al., 2005), SAFE (Barry et al., 2005), sigPathway (Tian et al., 2005), and CAMERA (Wu & Smyth, 2012). We take an end user focused approach to comparison, beginning with default and author recommended parameter settings for each method. We generated a wide range of simulated datasets using real data from Gene Expression Omnibus (GEO) (Barrett et al., 2013) dataset GSE62872 (Penney et al., 2015), which includes 424 samples, with 264 prostate cancer and 160 normal tissue samples, and Affymetrix gene expression data to provide realistic
genome-wide expression profiles for the simulations. We then simulated a range of effect sizes for a gene set chosen from a commonly used knowledge base, varying several parameters in the experiment.

Our results clearly demonstrate the overall and relative performance of the methods evaluated. For several methods, the results highlight concerns with the default parameter settings; therefore, alternative implementations were performed, and the results were compared. These results are the first benchmark of GSA approaches using data simulated with real gene expression data and signals signal relevant to known gene sets. The results can provide important guidance to end users of GSA approaches.

Methods

Key elements of GSA include the knowledge base (i.e., the known gene sets against which testing will be done), the type of hypothesis being tested, the statistical method, and control of false positive error rates. A detailed review of the broad classes of methods and a discussion about their statistical properties be found in Khatri et al. (2012). GSA methods can be classified into three loosely defined generations: over-representation analysis (ORA), functional class scoring (FCS), and pathway topology (PT) methods. ORA methods typically test whether elements in the datasets are over-represented in a given pathway from a knowledge base. FCS methods typically strive to detect changes to elements in the dataset that cause alterations in the given pathway from the knowledge base. PT methods incorporate known or estimated structures of the biological network to account for correlations among genes.
A number of knowledge base resources have been established by government, academic, and private entities. These include gene ontology (GO) (Ashburner et al., 2000), KEGG (Kanehisa et al., 2014), MetaCyc (Caspi et al., 2014), Metacore® Disease Biomarker Networks (https://portal.genego.com), Ingenuity Pathway Analysis (IPA®) (QIAGEN Redwood City, www.qiagen.com/ingenuity) and Molecular Signatures Database (MSigDB) (Subramanian et al., 2005). MSigDB version 5.0 was used in the presented study because it includes information from the other databases (a total of 10,295 gene sets) and is widely used. Using biologically defined sets, the simulation results parallel the procedures performed by typical end users. MSigDB contains eight categories of gene sets: positional (c1, 326 sets), literature curated (c2, 4726 sets), motif (c3, 836 sets), computation (c4, 858 sets), GO (c5, 1454 sets), oncogenic (c6, 189 sets), immunologic (c7, 4,872 sets), and hallmark (h, 50 sets). A more detailed description of the MSigDB database can be found in Subramanian et al. (2005).

Each GSA method evaluated here relies on gene sets from MSigDB to determine whether the gene sets are significantly associated with the disease or trait of interest. Each method involves a slightly different approach to statistical testing and corresponds to different null hypotheses. Self-contained and competitive null hypotheses are common across GSA methods (Goeman & Bühlmann, 2007a). A self-contained null hypothesis states that genes in the gene set are not more differently expressed than what is expected to randomly occur. A competitive null hypothesis states that the genes in a given gene set are not more differently expressed than the other genes in the dataset. The competitive null hypothesis addresses questions about comparing the pathways to each other while the self-contained hypothesis addresses more general questions about the activities of genes within each pathway. Typically,
competitive tests are more conservative compared to self-contained tests due to the burden of multiple comparisons. Both tests are sensitive to the number of gene sets tested and the number of genes in the dataset (Khatri et al., 2012). Therefore, controlling false positive error rates is a challenging task in either context and is further complicated due to significant overlap of genes contained in different gene sets. To control the false positive error rate, Bonferroni (O. J. Dunn, 1959, 1961), false discovery rate (FDR) (Benjamini & Hochberg, 1995) and resampling (Good, 2006) or permutation testing (Fisher, 1935; Good, 2005) can be used. As mentioned above, we chose the most commonly used GSA methods for our comparison and utilized the corresponding software packages that are freely available.

**Gene Set Enrichment Analysis (GSEA)**

GSEA ranks all the genes in a dataset based on differential expression. To test a gene sets’ significance, an enrichment score, which is defined as the maximum distance from the middle of the ranked list, is used. The enrichment score indicates whether the genes contained in a gene set are clustered towards the beginning or the end of the ranked list. Both self-contained and competitive hypothesis testing can be conducted with GSEA by altering how randomization is completed. For a self-contained hypothesis, the phenotype labels are permuted; for a competitive hypothesis, the genes are permuted. A total of 1,000 permutations are performed to estimate the empirical p-values for the gene sets. Details of GSEA can be found in Subramanian et al. (2005).
Significance Analysis in Function and Expression (SAFE)

SAFE is a method that involves calculating both local and global statistics. This two-stage procedure allows analysis of a set of genes instead of a single gene association. The local statistic describes the significance of association with the response for each gene in the dataset. The local statistics implemented by the SAFE Bioconductor package (Barry et al., 2015) include Student’s t-test, Welch’s t-test, paired t-test, F-statistic from ANOVA, and t-statistic from a linear model. For the results reported here, Student’s t-test is used as the local statistic since it is the default setting in the software. The global statistic describes the significance of a competitive hypothesis test for each gene set or pathway. The implemented global statistics include Wilcoxon rank-sum, Fisher’s exact test, Pearson’s chi-squared statistic and a t-statistic for average difference; all statistics are reported in the results for comparison. Permutation of the class labels was conducted to control for false positive error rate. Details of the SAFE method can be found in Barry et al. (2005 and 2008), and details about the package can be found in Barry et al. (2015).

sigPathway

sigPathway offers both a competitive hypothesis test and a variation of a self-contained test although only the competitive hypothesis was used in the present work. First, a gene-level statistic for the association of each gene with the phenotype of interest is calculated. Second, a statistic is calculated for each gene set by calculating the weighted sum of the gene-level statistics, normalizing this gene set statistic to account for the size and correlation structure of the gene set, ranking the normalized gene set statistics, and determining the significance of the
gene set statistics by resampling. The default settings use a t-statistic for the gene-level statistic and the Wilcoxon rank-sum for the gene set level statistics. Details of the sigPathway methodology can be found in Tian et al. (2005), and details about the package can be found in Lai et al. (2015).

**Correlation Adjusted MEan RAnk (CAMERA)**

As with SAFE, CAMERA is a two-stage procedure with gene-level and gene set-level statistics. The gene-level statistic is based on linear regression and determines whether the coefficient of the gene is zero. This is similar to a t-test but provides more flexibility. The gene-level statistic includes the least squares estimate of the fold change, t-statistic, moderated t-statistic (using an empirical Bayes posterior estimate of the variance), and normalized moderated t-statistic. CAMERA adjusts the gene set test statistic for inter-gene correlations. The inter-gene correlation is estimated by the variance inflation factor (VIF) and incorporated into the parametric or rank-based hypothesis test. The VIF is calculated using the correlation structure of the dataset, which can be efficiently estimated by QR decomposition of the design matrix (of the linear model corresponding to the gene set) and the independent residuals from this linear model. A number of gene set tests, including the Wilcoxon rank-sum test are implemented in the software and include extensions of a t-test between two gene set groups, each containing the gene-wise statistics of the genes they include and their inter-gene correlation. More details about the methodology of CAMERA can be found in Wu and Smyth (2012), with implementation details in M.E. Ritchie et al. (2015).
Flexible Algorithm for Novel Gene set Simulation (FANGS)

FANGS is a semi-synthetic simulation tool that simulates data based on a user-defined dataset to maintain realistic patterns of variation and correlation. We chose a prostate cancer dataset from the Gene Expression Omnibus (GEO) database (Barrett et al., 2013) (GSE62872). The dataset contains a total of 424 samples (264 prostate cancer and 160 non-matched normal tissue samples) (Penney et al., 2015). Gene expression data was collected on the Affymetrix GeneChip Human Gene 1.0 ST Microarray (33,297 probes). All probes that mapped to multiple gene products (as defined by Affymetrix annotation) were removed from the dataset. This resulted in 30,202 probes in the final dataset, of which 19,276 mapped to known genes. The simulation process is summarized in Figure 3.1.

The dataset preprocessing included background correction by the RMA algorithm (Gautier et al., 2004), quantile normalization, and centering of each probe’s expression at zero to remove the existing signal. RMA corrects for bias introduced by technical confounders (e.g., batch effects) across samples. While there are a number of approaches for normalization, quantile normalization is commonly used because it is robust and the resulting signal is independent of expression technology. Centering removes any original signal in the dataset while preserving the inherent correlation structure among genes. Supplemental Figure 3.1 shows a heat map of the correlation structure (calculated by the Pearson coefficient) of the dataset after preprocessing and normalization.
Figure 3.1: **FANGS flow chart.** A specific dataset is selected as baseline and the raw data is preprocessed as described in the methods section. This includes RMA, quantile normalization, and centering of the data so that each gene has a mean zero to remove the existing signal. Next, a gene set is selected for simulation, and association signals with a range of effect sizes (\(\tau\) parameter) are introduced. A user-defined proportion of the genes in the gene set are selected for associated with disease status (\(\pi\) parameter). One-hundred bootstrapped data sets are generated for each set of simulation parameters. The simulated data is tested for each method and power to detect the differentially expressed gene set.

Next, the simulated signal was added to genes in a specific gene set, as defined by the MSigDB database. There are three important parameters in this simulation experiment: 1) gene set selection, 2) proportion of genes within the set that are differentially expressed, and 3) differential expression effect size. We selected two gene sets previously found to be associated with prostate and other cancers (Hanahan & Weinberg, 2011): 1) the KRAS down regulated pathway (‘KRAS.PROSTATE_UP.V1_DN’ in MSigDB) and 2) the TGF-\(\beta\) (Transforming Growth Factor Beta) signaling pathway (‘TGF_BETA_SIGNALING’). The KRAS pathway contains a total of 144 genes, 127 of which are included in the prostate cancer dataset. The TGF-\(\beta\) signaling pathway contains a total of 54 genes, all of which are included in the prostate cancer dataset.
By selecting gene sets of different sizes, the impact of the number of genes in a gene set can be evaluated. The proportion of genes differentially expressed (\(\pi\)) in the simulations defines the proportion of the genes randomly selected in the gene set that are differentially expressed (as it is not expected that all the genes in a gene set are differentially expressed). This proportion ranged from 0.05 to 1.0 in this experiment. A signal range was then introduced into the data by shifting the gene expression in the case group according to a range of values (\(\tau\)). The magnitude (or effect size) (\(\tau\)) of the differential expression given by \(\tau \times sd(expr)\) defines the magnitude of alteration of the expression of each probe.

To assess the power of each GSA method, 100 bootstrapped samples from the differentially expressed datasets were created, retaining the case-control balance from the original study (264 cases/160 controls). The power in all simulations was calculated as the proportion of bootstrapped datasets where the differentially expressed gene set displays a significant (p-value \(\leq 0.05\)) gene set level statistic.

Three negative control simulations were conducted to assess the false positive rate for each of the tested GSA methods. First, we simulated the negative control by permuting the class labels without changing the expression level (\(\tau\)) and breaking the association between the expression profile and the response. Second, we sampled the expression for each probe from an independent identically distributed (iid) standard normal distribution and randomly assigned sample labels, breaking the association between the expression profile and the response as well as the correlation structure between the genes. Third, we normalized and centered the data with \(\tau=0\), thus adding no signal. The power of the negative controls was calculated as the proportion of pathways in the negative control simulations with a p-value below 0.05.
Implementation

The software to create simulated datasets was implemented in the R statistical programming language (https://www.r-project.org/) version 3.2.2. FANGS version 1.0 is open-sourced software that is available online at https://github.com/rmathur87/FANGS. The algorithm is flexible and can incorporate user-defined data with other knowledge base configurations. The parameters of the simulation can be easily altered to test different values, for example, sample size or sampling schemes.

Table 3.1: List of default parameters.

<table>
<thead>
<tr>
<th>Method</th>
<th>Default Parameters</th>
</tr>
</thead>
</table>
| GSEA          | Data File: Inputted txt file  
Response File: Inputted txt file  
Knowledge base: mSigDB gmx file  
Num. Permutations: 1,000  
Permutation Type: Gene or Phenotype  
Scoring Scheme: Weighted  
Ranking Metric: Signal To Noise |
| SAFE          | Data Matrix (X.mat): Inputted rda file  
Response Vector (y.vec): Inputted rda file  
Gene Category Assignments (C.mat): Created from gmt file  
Method: Permutation  
Min Category Size: 2  
Max Category Size: Inf  
by.gene: FALSE  
Local Statistic: Student T-Test (“t.Student”)  
Global Statistic: Wilcoxon Rank Sum (“Wilcoxon”)  
Args.global: list(one.sided=F)  
Num. of Permutations (‘Pi.mat’): 1,000  
Multiple Testing Correction (‘error’): FDR.BH |
| sigPathway    | Data File: Inputted rda file  
Knowledge base: mSigDB gmx file  
Min gene set size: 1  
Max gene set size: 10,000  
allPathways: TRUE  
Number of Pathways: length (mSigDB gmx file) |
| CAMERA        | Data File: Inputted rda file  
Response Inputted rda file  
Knowledge base: mSigDB gmx file |
In all simulations presented here, 100 bootstrapped replicates were generated using each combination of $\tau$, and $\pi$ for the two selected gene sets. The $\tau$ values tested were 0.25, 0.5, 1, 2, and 10. The $\pi$ values tested were 0.05, 0.1, 0.25, 0.5, and 1. The GSA methods were tested using the implementations provided by the original authors with the recommended default parameters (Table 3.1) and alternate parameters as appropriate (Table 3.2). SAFE (Barry et al., 2015), sigPathway (Lai et al., 2015) and CAMERA (M. E. Ritchie et al., 2015) were accessed using Bioconductor. GSEA (Java) was downloaded from (http://software.broadinstitute.org/gsea/). SAFE was utilized with alternative parameters as suggested in Barry et al. (2008). All computation times were estimated on Dell’s PowerEdge R620 rack servers which includes two Intel Xeon processors for a total of 16 cores and 128 GB of RAM.

Table 3.2: List of alternative parameters.

<table>
<thead>
<tr>
<th>Method</th>
<th>Alternative Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSEA</td>
<td>Calculating the FDR q-values based on the reported p-values as opposed to the q-values reported, which are based on the median.</td>
</tr>
<tr>
<td>SAFE</td>
<td>Method: Bootstrap (&quot;Bootstrap.q&quot;)</td>
</tr>
<tr>
<td></td>
<td>Global Statistic: aveDiff, FET, Pearson</td>
</tr>
<tr>
<td></td>
<td>Num. of Permutations (Pi.Mat): 10,000</td>
</tr>
<tr>
<td>sigPathway</td>
<td>Not applicable</td>
</tr>
<tr>
<td>CAMERA</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

Results

To fairly evaluate power, the overall Type I error rate for each method must be determined. Figure 3.2 displays the results for the three negative control simulations across the
methods (all implemented SAFE global statistics with default settings; alternative settings are shown in Supplemental Figure 3.2). The median power (and 95% confidence) across the 100 replicates from all gene sets within MSigDB is displayed. All methods except the FET global statistic in SAFE have mean values and tight confidence intervals around 0.05 (raw values shown in Supplemental Table 3.1), with demonstrates that false positive rates are generally well controlled. This is in contrast with Tarca et al. (2013) who found that sigPathway and GSEA had inflated false positive rates.

Figure 3.2: Power of negative controls. Statistical power as detected by negative control data for all tested GSA methods. The mean power (for 100 bootstrap datasets) of the three negative controls is plotted along with a 95% confidence interval for the mean for each method.

Power results for the range of simulations using the default parameter settings are shown in Figure 3.3, with raw values provided in Supplemental Tables 3.2 and 3.3. Results for the KRAS pathway simulations are shown in panel (a), and results for the TGF-β signaling
pathway are shown in panel (b). Overall, trends were as expected. Power was higher for the KRAS pathway than the TGF-β pathway, which is expected given a larger size for the KRAS pathway. Further, as the proportion of differentially expressed genes in the gene set increased, the power of the methods increased. Generally, as the effect size increased, power increased (although an exception is discussed below).

The relative performance of the methods was also evident, with a few notable trends. The Wilcoxon global statistic for SAFE revealed no signal at any signal strength, supporting previous results that SAFE is a conservative approach (Khatri et al., 2012). CAMERA had sufficient power to detect higher effect sizes ($\tau=1,2,10$) but struggled at lower effect sizes. sigPathway displayed strong power to detect a wide range of signal strengths. Generally, this is also true for GSEA although there is a counterintuitive result for very strong signals ($\pi=1; \tau=2,10$).

Simulation with SAFE’s default settings produced extremely low power, prompting the exploration of other parameter settings, including increasing the number of permutations (increased p-value resolution) and conducting other global statistical tests to assess sensitivity and determine if bootstrap sampling improves power for large signals (Barry et al., 2008). The results with alternative and default parameters using SAFE for the KRAS down regulated and TGF-β signaling pathways are shown in Figure 3.4. For large effect sizes, bootstrap sampling had higher power compared to permutation testing (even with a larger number of permutations), which supports previous work with bootstrap sampling (Barry et al., 2008). The power decreased significantly for lower signals ($\pi=0.5$ and thus the signal must be relatively strong for detection by SAFE.
Further examination of the GSEA results highlights an unusual property of the false discovery rate (FDR) q-value calculated by this method. GSEA reports have FDR values based...
on the median of the p-value distribution, as opposed to the standard approach of using the extreme values (Benjamini & Hochberg, 1995). To evaluate whether the counterintuitive results were due to this FDR calculation, we repeated the GSEA analysis with a more traditional FDR implementation by Benjamini and Hochberg (1995). We calculated FDR q-values based on the reported permutation-tested empirical p-values via the stats package (“p.adjust” function) in the R programming language. Differences in the power results between the two implementations of FDR are shown in Figure 3.5. These results reveal that unusual behavior is corrected with the more commonly used FDR implementation.

One issue with GSA is the overlap of gene sets in a pathway, as genes in a gene set are included in additional gene sets. To examine how these methods, perform on the gene sets that were not targeted in the simulation, the gene sets that overlap with the targeted gene set are shown in Figure 3.6 for the most powerful methods, including sigPathway, GSEA, and CAMERA for high (π=1) and low (π=0.1) effect sizes. The fact that these methods are sensitive towards this overlap is not surprising since some of the genes contained in these gene sets are differentially expressed. Competitive GSEA detected the most signal while sigPathway and self-contained GSEA detected a signal only for very high effect sizes. CAMERA had the lowest relative power.

Another consideration for end users is software availability and run times. Table 3.3 lists the computational times for the software packages.
Figure 3.4: Power for SAFE alternative settings. Statistical power for results with alternative settings and default settings for SAFE. The alternative settings tested include 10,000 permutations ('-10k' labels) and bootstrap sampling ('-boot' labels). The default setting is with 1,000 permutations ('-1k' labels). All power values are shown as a significance value of 0.05. (a) The KRAS.PROSTATE_UP.V1_DN pathway was differentially expressed. (b) The TGF-β SIGNALING pathway was differentially expressed.
Figure 3.5: Power for GSEA alternative settings. Statistical power for results with alternative settings and default settings for GSEA. The alternative setting consists of calculating the FDR q-values based on the extremes as opposed to the median reported in GSEA. All power values are shown as a significance value of 0.05. (a) The KRAS.PROSTATE_UP.V1_DN pathway was differentially expressed. (b) The TGF-β SIGNALING pathway was differentially expressed.
Discussion

GSA has become an important tool in gene expression analysis. GSA approaches that are tied to knowledge bases such as MSigDB are among the most popular and successful, and many related methods have been developed (Khatri et al., 2012; Ramanan et al., 2012). While there are many differences among the methods and benchmark datasets have been used to demonstrate the relative performance of methods, few simulation experiments have been conducted to compare popular methods. Simulation experiments provide important guidance in choosing methods and their parameter settings.

The current study takes a practical approach to comparing methods and used the implementations and recommended parameter setting for several of the most commonly used GSA methods along with real data for semi-synthetic simulations. This strategy has advantages compared to benchmark datasets since false positive rates and power can be accurately estimated. The results show the relative performance of the methods.
Figure 3.6: Power of overlapping pathways. Statistical power for results with recommended methods (CAMERA, GSEA with user-defined FDR q-values, and sigPathway) for pathways with genes overlapping the targeted pathway, denoted by the overlap proportion. Proportions of differential expression parameter (π) values of 0.1 and 1 are shown here and other values are displayed in Supplemental Figures 3.3 and 3.4. All power values are shown at a significance value of 0.05. (a) The KRAS.PROSTATE_UP.V1_DN pathway was differentially expressed. (b) The TGF-β SIGNALING pathway was differentially expressed.
Table 3.3. Average run time for each GSA method.

<table>
<thead>
<tr>
<th>Method</th>
<th>Average Run Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAFE</td>
<td>Default global statistics</td>
</tr>
<tr>
<td></td>
<td>• aveDiff: 18 mins</td>
</tr>
<tr>
<td></td>
<td>• Pearson: 16 mins</td>
</tr>
<tr>
<td></td>
<td>• FET: 17 mins</td>
</tr>
<tr>
<td></td>
<td>• Wilcoxon: 17 mins</td>
</tr>
<tr>
<td></td>
<td>10,000 permutations: 149 mins</td>
</tr>
<tr>
<td></td>
<td>10,000 bootstraps: 134 mins</td>
</tr>
<tr>
<td>sigPathway</td>
<td>4:08 mins</td>
</tr>
<tr>
<td>GSEA</td>
<td>Competitive: 39:58 mins</td>
</tr>
<tr>
<td></td>
<td>Self-contained: 34:28 mins</td>
</tr>
<tr>
<td>CAMERA</td>
<td>00:15 mins</td>
</tr>
</tbody>
</table>

The default parameters for SAFE found in the software package were ineffective for discovering any signal although bootstrap sampling improved performance for larger effect sizes. The default parameters of GSEA (both self-contained and competitive) had surprisingly low power for very large effect sizes but relatively high power for lower effect size models. This result is likely due to the FDR calculation based on the median instead of the extreme values of the gene set p-values in the distributed software. Implementing GSEA with the traditional Benjamini-Hochberg FDR resulted in more expected power results and overall higher power. CAMERA’s performance was excellent for higher effect sizes but relatively poor for low or intermediate effect sizes. sigPathway had the highest power of all the methods across the full range of effect sizes. The competitive GSEA and sigPathway methods detected a signal in other gene sets that overlap with the simulated signal, but the sensitivity was much less for the other methods. The methods had varied power to detect the TGF-β signaling pathway and the KRAS pathway due to different pathway sizes. Importantly, all the methods
except the SAFE Fisher’s Exact Test (FET) implementation controlled Type I errors in our experiments.

Based on these results, a few practical recommendations can be made for end users. The most powerful method was sigPathway, but GSEA with user-calculated q-values displayed similar performance and detected signals across gene sets. Therefore, GSEA displayed better performance for identifying the specific signal along with the gene sets correlated and related to the simulated signal, which may be desirable for those seeking hypothesis generation from the methods. However, this can also complicate the interpretation of “enriched” pathways identified with GSEA, as it is unclear whether the enrichment is due to signal in the pathway, or secondary enrichment due to correlation or overlap. On the other hand, sigPathway was more powerful in detecting smaller effect sizes in the dataset. Furthermore, sigPathway had a relatively shorter computational runtime of about five minutes compared to about 45 minutes for GSEA, about 15 minutes for 1,000 permutations and over two hours for 10,000 permutations or bootstrap sampling for SAFE. CAMERA was the most efficient algorithm, with runtime of 16 seconds for one dataset. Based on the comparison of the two FDR implementations within the GSEA method and using the classical FDR controlling approaches, we recommend that users implement their own FDR control instead of the q-values calculated within the software package.

While we attempted to simulate a reasonable range of simulation parameters, several factors were not included in the current study. Future studies should focus on the effect of sample size on the power results. Additionally, other real datasets should be used as the basis of the simulations to evaluate the impact of a range of correlation structures, sample size, and
other factors on the results. Errors and complications in data sets, such as missing data, limits of detection, or class misspecification should also be considered. Additionally, the impact of preprocessing choices (e.g., normalization) should be evaluated. Importantly, future studies should extend the methods compared and the types of data simulated. While GSA has most often been utilized with microarray data, RNA-Seq data has data structures and variance properties that have prompted the development of additional GSA methods. Further, RNA-Seq data should be simulated in a similar framework and proteomics and metabolomics data should be considered in future simulation experiments.

Additionally, while we implemented some of the most commonly used methods, development of methods is an active research area. Additional methods should be considered for comparison as permitted. A number of popular commercial software packages are available, including Ingenuity Pathway Analysis (IPA®) (QIAGEN Redwood City, www.qiagen.com/ingenuity) but licensing agreements prevent benchmarking studies.

Finally, we used only a single knowledgebase for methods comparison MSigDB. We used the literature-curated (c2), motif (c3), computation (c4), GO terms (c5), oncogenic (c6), immunologic (c7), and hallmark (h) categories within MSigDB. Numerous knowledge bases are available, and many are geared specifically towards new technologies (i.e., metabolomics) or specific genetic systems (i.e., plants). Comparing the performance of the various approaches with a range of knowledge bases and with limited categories within the knowledge bases is an important next step.
Acknowledgements

We would like to thank Drs. Fred Wright and William Barry for their assistance with reasoning and diagnosing issues with the results from SAFE. We would also like to thank Drs. Daniel Rotroff and John Jack for valuable edits and insights.

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Conflict of Interest: none declared.
References


CHAPTER 4

Influence of Genetics on the Metabolome under Different Environment Conditions for Metabolic Syndrome in 
*Drosophila melanogaster*

Introduction

As discussed in Chapter 2, metabolic syndrome (MetS) is a cluster of conditions that significantly influences the risk of type 2 diabetes and cardiovascular disease. MetS is influenced by many factors, including genetics, epigenomics, transcriptomics, proteomics, and metabolomics. These factors are influenced, in turn, by environmental factors, including diet and lifestyle factors such as exercise. This chapter studies the genetic and metabolomic levels in more depth and aims to discover genetic positions that influence the quantitative untargeted metabolomics phenotype under the influence of an environmental factor (i.e., a high fat diet). All experiments were conducted in the model organism *Drosophila melanogaster*, which presents an excellent system for studying metabolic traits due to the high homology of metabolic processes and pathways to humans.

Methods

Drosophila Stocks and Experimental Design

A total of 380 RILs from Population A of the Drosophila Synthetic Resource Population (DSPR) were utilized (King, Merkes, et al., 2012). All flies were maintained at 25 °C at 50% humidity on a 12-hour light-dark cycle and fed a standard cornmeal-molasses diet.
(Reed et al., 2010) for at least two generations before the experiment. The experiment consisted of raising the fly larvae in a controlled environment with normal (standard cornmeal-molasses) and high fat (normal diet with the addition of 3% coconut oil by weight) diets. The high fat diet increased the saturated fat by 0.26 g per 10 g vial of food (Reed et al., 2010; U. S. Department of Agriculture, 2008). To further interrogate the population, a round-robin crossing scheme was utilized, shown in Figure 4.1. The scheme included 20-30 lines per round, where 30 females and 15 males were placed in laying chambers with an apple agar plate supplemented with reconstituted active dry yeast. First instar larvae were placed on normal and high fat diets at a density of 50 larvae per 10 g vial of food. Third instar larvae were collected 72 hours later and starved on a water agar plate for 3-4 hours. A 30 mg sample from the third-instar larvae was extracted to quantify the metabolic signatures.

![Figure 4.1: Round-robin crossing scheme.](image)

**Metabolomics Profiling**

A total of 760 samples were utilized, including 380 genotypes (the RILs described above) for each diet. This resulted in sampling for each genetic polymorphism at least 47 times
for each diet. Untargeted primary metabolites were determined by gas chromatography time of flight mass spectrometry (GSTOF-MS) in the Fiehn Laboratory at the West Coast Metabolomics Center. The sample preparation and specifics of the GSTOF-MS experiments are described in Fiehn et al. (2008). A total of 422 metabolites were quantified, with confirmed chemical identification for (complete information about the annotation of each of the metabolites is shown in Appendix B, Supplemental Table 4.3). The processing and quantification was conducted by the Fiehn Laboratory using the BinBase algorithm and database (Skogerson et al., 2011). The metabolites were vector normalized (conducted by the Fiehn lab) by Equation 4.1.

\[
M_{ij,n1} = \frac{M_{ij,raw}}{mTIC_j \times mTIC_{ave}}
\] (4.1)

where \(M_{ij,raw}\) is the metabolite intensity for sample \(j\) and metabolite \(i\); \(mTIC_j\) is the sum of all peak heights of all identified metabolites for sample \(j\); and \(mTIC_{ave}\) is the average of all \(mTIC_j\) values. This normalization resulted in consistent intensity values across metabolites. The samples were run in randomized blocks with a pooled standard run every 11th sample for normalization reference. This blocking scheme was conducted to allow complete and intermittent cleaning of the mass spectrometry machine. To account for these random blocks, intensities were further normalized over the mean intensity for each metabolite in the measured pooled samples using Equation 4.2.

\[
M_{ij,n2} = \frac{M_{ij,n1}}{M_{j,pool}}
\] (4.2)

where \(M_{ij,n1}\) is the resultant intensity from Equation 4.1 for sample \(j\) and metabolite \(i\) and \(M_{j,pool}\) is the mean intensity for metabolite \(j\) for the pooled samples. Throughout the metabolomics
dataset, a missing value represents an intensity that was below the detectable range. Therefore, missing values were interpolated by the minimum non-zero value for the specific metabolite. To assure that the normalization minimized the influence of the block effects, the linear Analysis of Variance (ANOVA) model shown in Equation 4.3 was run using the R statistical programming language, and p-values for each element of the model were extracted. The blocking scheme was coded in the data by three factors, namely run block (RB), order (Or), and subset (S). Run block is the set of samples run between complete washes of the mass spectrometry machine. Order corresponds to the sequence samples were run. Subset is the set of samples run between intermittent cleaning of the mass spectrometry machine. Furthermore, the subset and order variables were nested within the run block, and the order variable was nested in the subset variable.

\[
\log(M_{ij,n2}) \sim RB + (S|RB) + (Or|RB) + (Or|S) \tag{4.3}
\]

\(M_{ij,n2}\) is the resultant intensity from Equation 4.2. The model results show that 378 of 422 metabolites (about 90%) displayed significant effects for one or more of the block effects and thus the normalization was not sufficiently effective in reducing the effect of the blocking factors. To minimize the influence of the block effects on the metabolite intensities the residuals of Equation 4.3 were extracted and utilized in all subsequent analyses. By design, these residuals are independently and identically distributed (iid) as a normal distribution, which is desirable for the QTL mapping pipeline. Therefore, the residuals were utilized as the quantitative response variable in the mapping pipeline.
QTL Mapping Statistical Analysis

The statistical modeling was conducted in the R programming language (R Development Core Team version 3.2.2 2014). The haplotype probabilities are available via the DSPRqtl and DSPRqtlDataR packages, which can be accessed at http://FlyRILs.org/. These packages report the probability that the RIL shares its haplotype with each of the eight founder strains at 10 kB intervals throughout the genome. The probabilities show that nearly the entire genome is homozygous. King and Macdonald et al. (2012) found very high confidence levels in the founder probabilities.

To test for linkages, the model includes random effect terms for the month the cross was processed, the round-robin group in which the RIL was contained, the vial in which the RIL was contained, and the cross from which the sample is a result. These random effects were included as average effects over the two diets along with diet interaction terms. Furthermore, founder probabilities for all 64 founders by maternal and paternal combinations were included. The null model (without any genetic effects) is shown in Equation 4.4.

\[
Y_{mijkl} = \mu + D_k + b_m + \alpha_i + \alpha_j + c_{ij} + M D_{mk} + b D_{nk} + \alpha D_{ik} + \alpha D_{jk} + c D_{ijk} + V_{ijkl} + \epsilon
\]

where the round robin blocks, \( b_m \), are indexed by \( m \), and \( M_m \) is the month corresponding to block \( m \). Maternal and paternal RILs, \( i \) and \( j \), are indexed by \( i \) and \( j \). The diet group and all diet effects are indexed by \( k \), and \( l \) corresponding to the vial for the cross by diet. Lastly, \( \mu \) is the overall mean. \( Zb \) refers to the random effects in all subsequent model formulations.

The model was first fit under the null model with no founder terms to estimate variance components for each random group. The founder haplotype frequencies for each RIL, \( p_{ijkl} \),
were utilized to compute the fixed effect coefficients $x_{ij}$ for additive, dominant and full models as shown in Equation 4.5.

$$\begin{align*}
\text{Additive:} & \quad x_{a_{ij}} = p_{a_i} + p_{a_j}, a = 1, \ldots, 8 \\
\text{Dominance:} & \quad x_{d_{ij}} = p_{d_i} * p_{d_j} + p_{d_i} * p_{d_j}, d = 1, \ldots, 32 \\
\text{Full:} & \quad x_{F_{ij}} = p_{F_i} * p_{F_j}, f = 1, \ldots, 64
\end{align*}$$

(4.5)

The maternal and paternal RILs are indexed by $i$ and $j$, respectively.

Diet interaction terms were determined by multiplying the diet term by thesehaplotype frequencies. We found that many of these frequencies were poorly represented at many locations, which resulted in a non-full rank design matrix. Inference of the model with a non-full rank design matrix resulted in computational instability and inflated $p$-values. Thus, for each model fit, we included all possible terms and reduced the model using principal components analysis (PCA) (Mardia et al., 1979; Venables et al., 2002) on the full design matrix. PCA is a method used to reduce the design matrix into orthogonal components (Mardia et al., 1979; Venables et al., 2002). We removed any principal components that explained less than 0.001 of the variance. Combining the terms and writing the random terms in the model as $Zb$ (as shown above), we fit the six non-null models corresponding to additive, dominant, and full main and diet interaction effects at each location, as shown in Equation 4.6.
$M_0 : Y = \mu + D_k + Zb + e$

$M_1 : Y = \mu + [x_{aij}]^T \beta_a + D_k + Zb + e$

$M_2 : Y = \mu + [x_{aij}, x_{dij}]^T \{ \beta_a, \beta_d \} + D_k + Zb + e$

$M_3 : Y = \mu + [x_{aij}, x_{dij}, x_{Fij}]^T \{ \beta_a, \beta_d, \beta_F \} + D_k + Zb + e$

$M_4 : Y = \mu + [x_{aij}, x_{dij}, x_{Fij}]^T \{ \beta_a, \beta_d, \beta_F \} + D_k + [x_{Daij}]^T \{ \beta D_a \} + Zb + e$

$M_5 : Y = \mu + [x_{aij}, x_{dij}, x_{Fij}]^T \{ \beta_a, \beta_d, \beta_F \} + D_k + [x_{Daij}, x_{Ddij}]^T \{ \beta D_a, \beta D_d \} + Zb + e$

$M_6 : Y = \mu + [x_{aij}, x_{dij}, x_{Fij}]^T \{ \beta_a, \beta_d, \beta_F \} + D_k + [x_{Daij}, x_{Ddij}, x_{DFij}]^T \{ \beta D_a, \beta D_d, \beta D_F \} + Zb + e$

where $Zb$ corresponds to the random effect terms and $e$ is the error term. Statistical inference was conducted by calculating the $\chi^2$-statistic as shown in Equation 4.7 based on the difference in model log-likelihoods ($l$) and determining p-values based on the $\chi^2$-distribution with the appropriate degrees of freedom (which vary based on the genomic position).

<table>
<thead>
<tr>
<th>Genetic Models</th>
<th>Additive: $-2^*(l_{M1} - l_{M0})$</th>
<th>$DF_{M1} - DF_{N0}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dominant: $-2^*(l_{M2} - l_{M1})$</td>
<td>$DF_{M2} - DF_{M1}$</td>
</tr>
<tr>
<td></td>
<td>Full: $-2^*(l_{M3} - l_{M2})$</td>
<td>$DF_{M3} - DF_{M2}$</td>
</tr>
<tr>
<td></td>
<td>Main: $-2^*(l_{M4} - l_{M3})$</td>
<td>$DF_{M4} - DF_{M3}$</td>
</tr>
</tbody>
</table>

| Genetic-by-Diet Models             | Additive-by-Diet: $-2^*(l_{M4} - l_{M3})$ | $DF_{M4} - DF_{M3}$ |
|------------------------------------| Dominant-by-Diet: $-2^*(l_{M5} - l_{M4})$ | $DF_{M5} - DF_{M4}$ |
|                                    | Full-by-Diet: $-2^*(l_{M6} - l_{M5})$    | $DF_{M6} - DF_{M5}$ |
|                                    | Diet: $-2^*(l_{M6} - l_{M5})$             | $DF_{M6} - DF_{M5}$ |

Four model contrasts were analyzed for genetic effects, including additive (M1 vs. Null), dominant (M2 vs. M1), full (M3 vs. M2) and main (M3 vs. Null). Four additional model contrasts were analyzed for genetic-by-diet effects, including additive-by-diet (M4 vs. M3), dominant-by-diet (M5 vs. M4), full-by-diet (M6 vs. M5), and diet (M6 vs. M3).

The response variable of interest here is the residuals from the metabolite linear model shown in Equation 4.3. The mapping for each metabolite was conducted independently. A
significant mQTL peak was determined at a Bonferroni multiple testing correction with a significance level of $\alpha=0.05$. This resulted in a significance threshold of a $-\log_{10}$ p-value of 5.37. To define the genomic area of influence around the peak, a 95% confidence interval was determined by converting F statistics (shown in Equation 4.7) to Logarithm of the Odds (LOD) values and computing a LOD drop confidence interval. The “findCI” function from the DSPRqtl R package was utilized to compute this confidence interval (Manichaikul, Dupuis, Sen, & Broman, 2006). Since nearby locations have the same number of principal components, the interval was not affected by changing degrees of freedom.

**Results**

**Significant mQTL Interactions:**

The results from QTL mapping are often presented by Manhattan plots, which display the strength of association between genetic components and the phenotype or trait. In this analysis, the quantitative trait was each metabolite, and the genetic component was the haplotype frequency of each genomic position (as described in the methods section). Manhattan plots for each of the metabolites and each model contrast were created (data not shown). An example of one such Manhattan plot for the mapping result of the diet model for glycolic acid is shown in Figure 4.2. The top of each significant peak (explained in the methods section and displayed by the horizontal red line) is indicated by a red dot, which can be analyzed further by comparing peaks at each genomic position across all metabolites.
Figure 4.2: Manhattan plot for QTL mapping results for glycolic acid for the diet model. The QTL position separated by each chromosome (chromosomes 2 and 3 are separated by their two arms, ‘R’ and ‘L’) is presented along the x-axis and the -log10(p-value), representing the strength of association is presented along the y-axis. The threshold for significance is shown by the red horizontal line, which represents the Bonferroni multiple testing threshold with α=0.05. The top of each significant peak is marked by a red dot.

To summarize the mapping results, Manhattan plots from each metabolite were overlaid to enable discovery of genomic positions that influence multiple metabolites and identify metabolites that are influenced by multiple genomic positions. Figures 4.3 and 4.4 show the Manhattan plots for all genetic effect models (i.e., additive, dominant, full and main effects) and genetic-by-diet effect models (i.e., additive-by-diet, dominant-by-diet, full-by-
diet, and diet effects), respectively. Only the tops of the significant peaks (-log_{10}(p-value) above 5.0) are shown since 5.37 is the Bonferroni threshold for association significance (horizontal black line). From the Manhattan plots, it can be seen that several QTL positions or genomic regions influence multiple metabolites. The circled region in the main model (Figure 4.3d) includes the phosphate and hydroxycarbamate metabolites at the genomic region of 2R: 10.94-11.98 Mb. The circled region in the diet model (Figure 4.4d) includes the phosphate and alanine metabolites at the 2R: 11.25-11.3 Mb region.

A significant mQTL association was determined by extracting the QTL position corresponding to the top of each peak for all metabolites. Overall, the mapping results from genetic effect models across all metabolites resulted in 753 significant mQTL peaks. These peaks involved 122 different metabolites and 636 different QTLs. For the additive, dominant, full, and main models, 30, 179, 251, and 225 significant peaks involving 17, 59, 87, and 69 different metabolites and 30, 174, 242, and 214 different QTLs were identified, respectively. For the genetic-by-diet effect models across all metabolites, 2,280 significant mQTL peaks involving 273 different metabolites and 1,657 different QTLs were identified. For the additive-by-diet, dominant-by-diet, full-by-diet, and diet models, 64, 480, 807, and 929 significant peaks involving 43, 127, 204, and 206 different metabolites and 63, 443, 721, 822 different QTLs were identified, respectively.
Figure 4.3: Manhattan plots overlaid for each metabolite as the quantitative trait (displayed by each color) for each genetic model. (a) additive, (b) dominant, (c) full, and (d) main models. The Manhattan plots are shown for the top genomic peaks above a negative log_{10} p-value of 5.0 since 5.37 is the Bonferroni threshold (black horizontal line). The circled peak (d) at the genomic region 2R: 10.94-11.98 Mb includes associations with the phosphate and hydroxycarbamate metabolites for the main model.
Figure 4.4: Manhattan plots overlaid for each metabolite as the quantitative trait (displayed by each color), for each genetic-by-diet interaction model. (a) additive-by-diet (b) dominant-by-diet (c) full-by-diet and (d) diet. Manhattan plots are shown for the top genomic peaks above a negative log_{10} p-value of 5.0 since 5.37 is the Bonferroni threshold (black horizontal line). The circled peak (d) at the genomic region 2R: 11.25-11.3 Mb includes associations with the phosphate and alanine metabolites for the diet model.

To identify metabolites influenced by multiple genomic regions and genomic regions influencing multiple metabolites, the peak information is alternatively presented as heat maps in Figures 4.5 through 4.8. In Figures 4.5 and 4.6, which present the genetic and genetic-by-
diet effects, respectively, the mQTL interactions are colored based on significance of the interaction. This representation indicates the high significance level of the peaks. In Figures 4.7 and 4.8, which present the genetic and genetic-by-diet effects, respectively, the mQTL interactions are colored based on which metabolite is involved in the interaction. The loci that influence multiple metabolites can be seen in this presentation, as indicated in Figures 4.3 and 4.4. Furthermore, while several metabolites are influenced by many different loci throughout the genome (an example is indicated by the circled area in Figure 4.3d, which corresponds to the phosphate metabolite and its associations in the main model), others are influenced by only one loci (an example is indicated by the circle in Figure 4.3d, which corresponds to an unidentified metabolite coded as 118602 and its association in the main model). Tables 4.1 and 4.2 list the identified metabolites (all metabolites are shown in Appendix B, Supplemental Table 4.1) with more than two significant mQTL interactions for the genetic and genetic-by-diet effects, respectively. Analyzing the peak information showed that for the genetic effects mQTLs, 0.71%, 7.11%, 9.24%, and 8.29% of all metabolites in the dataset (a total of 422) had more than one significant peak for the additive, dominant, full, and main models, respectively. For the genetic-by-diet effects mQTLs, 2.84%, 18.25%, 27.73%, and 31.99% of all metabolites in the dataset (a total of 422) had more than one significant peak for the additive-by-diet, dominant-by-diet, full-by-diet, and diet models, respectively. To further investigate the overlap of genomic regions influencing different metabolites with metabolites that are influenced by multiple regions, these peaks were compared in the next step.
Table 4.1: List of the top-25 identified metabolites with the most peaks. The number of peaks for each model and the total number of peaks for all genetic models are listed. Data on all metabolites can be found in Appendix B, Supplemental Table 4.1.

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Total</th>
<th>Additive</th>
<th>Dominant</th>
<th>Full</th>
<th>Main</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate</td>
<td>71</td>
<td>0</td>
<td>18</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>Citrulline</td>
<td>32</td>
<td>0</td>
<td>7</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Pantothenic Acid</td>
<td>26</td>
<td>0</td>
<td>10</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Glycolic Acid</td>
<td>22</td>
<td>1</td>
<td>6</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Myo Inositol</td>
<td>16</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Hydroxycarbamate</td>
<td>15</td>
<td>0</td>
<td>3</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Lactic Acid</td>
<td>13</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>N-Epsilon Trimethyllysine</td>
<td>9</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Glycerol</td>
<td>9</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Pyruvic Acid</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Inosine</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Cyanoalanine</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>2</td>
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Table 4.2: List of identified metabolites influenced by multiple QTLs for all genetic-by-diet models. Data on all metabolites can be found in Appendix B, Supplemental Table 4.1.

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<tr>
<th>Metabolite</th>
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<th>Dominant-by-Diet</th>
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Table 4.2 Continued
Table 4.2 Continued

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Figure 4.5: Heat map of significant mQTLs for all genetic effect models (colored by significance). Genomic positions across the genome are shown across the x-axis, and the analyzed metabolites are shown across the y-axis (in the arbitrary order in which they are found in the dataset). A point is included if a significant mQTL exists for the (a) additive, (b) dominant, (c) full, and (d) main effect models. The different colors of the points display the strength of significance (where 5-8 satisfies Bonferroni correction for each metabolite mapping; 8-10 satisfies Bonferroni correction for all metabolite mapping; and 10+ is very strong evidence of association) of the peak. The circled area at metabolite index 42 is the phosphate metabolite, which is influenced by 45 QTLs. The circled area at metabolite index 170 is an unidentified metabolite (ID: 118602) influenced by one QTL.
Overlap in Identified mQTL Peaks: Genomic Regions Influencing Multiple Metabolites and Metabolites Influenced by Multiple Genomic Regions

As discussed in the methods section, the genetic region of influence for a mQTL peak is determined with a 95% confidence interval. These intervals were calculated for each significant mQTL peak. Based on these confidence intervals, mQTL intervals that overlap for multiple metabolites (for the same model) are grouped together with the region defined by the union of confidence intervals. For these regions, a set of QTLs influence multiple metabolites. The set of QTLs is defined by any overlap of the 95% confidence interval although many of these regions are relatively large and thus the collective influence of multiple genes or a strong influence of one QTL is biologically possible. However, this distinction is difficult to detect from these results, and further characterization of the mQTLs is needed. Tables 4.3 and 4.4 show mQTL regions where at least four (or five for the genetic-by-diet effects) metabolites are influenced by the genomic region for the genetic and genetic-by-diet effects, respectively. All of the peaks, including isolated mQTL regions and those with less than four metabolites, are shown in Appendix B, Supplemental Table 4.2.
Figure 4.6: **Heat map of significant mQTLs for all genetic-by-diet effect models (colored by significance).** Genomic positions across the genome are shown across the x-axis, and the analyzed metabolites are shown across the y-axis (in the arbitrary order in which they are found in the dataset). A point is included if a significant mQTL exists for the (a) additive-by-diet, (b) dominant-by-diet, (c) full-by-diet, and (d) diet effect models. The different colors of the points display the strength of significance (where 5-8 satisfies Bonferroni correction for each metabolite mapping; 8-10 satisfies Bonferroni correction for all metabolite mapping; and 10+ is very strong evidence of association) of the peak.
Figure 4.7: Heat map of significant mQTLs for all genetic effect models (colored by metabolite). Genomic positions across the genome are shown across the x-axis, and the analyzed metabolites are shown across the y-axis (in the arbitrary order in which they are found in the dataset). A point is included if a significant mQTL exists for the (a) additive, (b) dominant, (c) full, and (d) main effect models. The colors of the points represent the different metabolites (cycling through five colors) utilized as the quantitative response variable in the mapping analysis. The circled area at metabolite index 42 is the phosphate metabolite, which is influenced by 45 QTLs; the circled area at metabolite index 170 is an unidentified metabolite (ID: 118602) influenced by one QTL.
Figure 4.8: Heat map of significant mQTLs for all genetic-by-diet effects (colored by metabolite). Genomic positions across the genome are shown across the x-axis, and the analyzed metabolites are shown across the y-axis (in the arbitrary order in which they are found in the dataset). A point is included if a significant mQTL exists for the (a) additive-by-diet, (b) dominant-by-diet, (c) full-by-diet, and (d) diet effect models. The colors of the points represent the different metabolites (cycling through five colors) used as the quantitative response variable in the mapping analysis.

Table 4.3: Genetic effect mQTL peaks where a genomic region influences at least four metabolites.

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<tr>
<th>Model Type</th>
<th>Metabolites</th>
<th>Chr</th>
<th>Lower Bound (Mb)</th>
<th>Upper Bound (Mb)</th>
<th>Length (Mb)</th>
<th>Ave P-Value</th>
<th>Num Metabolites</th>
<th>Num QTLs</th>
</tr>
</thead>
<tbody>
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<td>Dominant</td>
<td>Glycerol; Glycolic Acid; X_1380; X_116942</td>
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<td>10.12</td>
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<td>Lactic Acid; X_2813; X_21683; X_1380</td>
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<td>17.51</td>
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<tr>
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### Table 4.4: Genetic-by-diet effect mQTL peaks where a genomic region influences at least five metabolites.

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<th>Lower Bound (Mb)</th>
<th>Upper Bound (Mb)</th>
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<th>Ave P-Value</th>
<th>Num Metabolites</th>
<th>Num QTLs</th>
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<td>Hydroxycarbamate; 3-Methoxytryptamine; X_46292; X_18345; X_5576</td>
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| Diet | UDP-N-Acetylgluconamine; Kynurenine; Hydroxycarbamate; Alpha Aminoacidic Acid; X_118602; X_88583; X_2439; X_1872 | X | 21.2 | 21.65 | 0.45 | 6.22 | 8 | 8 |
| Diet | Tocopherol-Gamma; Pantothenic Acid; Inosine; Hypoxanthatine; Guanidinoacetic; Glycolic Acid; X_115903; X_105164; X_18305; X_1380 | 2L | 10.08 | 10.22 | 0.14 | 6.88 | 10 | 7 |
| Diet | Tocopherol-Gamma; 3-Aminoacobtyric Acid; X_21763; X_18345; X_3618; X_2813; X_479 | 3R | 24.7 | 24.77 | 0.07 | 6.24 | 7 | 4 |
| Diet | Threitol; X_116942; X_3200; X_1380; X_479 | 3L | 11.47 | 11.57 | 0.1 | 6.58 | 5 | 5 |
| Diet | Pyruvic Acid; Inosine; Hydroxycarbamate; Dodecanolic Acid Isopropanol; X_111255; X_479 | 3R | 20.02 | 20.1 | 0.08 | 5.95 | 6 | 5 |
| Diet | Pyrrole-2-Carboxylic Acid; Glycyl-Proline; Citrulline; X_104131; X_3143; X_2900 | 2L | 0.07 | 0.35 | 0.28 | 5.97 | 6 | 5 |
| Diet | Phosphate; 3-6-Anhydro-D-Galactose; X_118602; X_117193; X_110008; X_16591; X_5576; X_3143; X_1872; X_462 | 2R | 7.44 | 7.49 | 0.05 | 5.92 | 10 | 4 |
| Diet | Pelargonic Acid; Hydroxycarbamate; Capric Acid; X_117313; X_104788; X_1878; X_307 | 2R | 11.25 | 11.3 | 0.05 | 7.96 | 7 | 4 |
| Diet | Palmitoleic Acid; Alanine; X_1724; X_1709; X_307 | X | 1.45 | 1.76 | 0.31 | 8.62 | 5 | 5 |
| Diet | Oxoproline; Kynurenine; Glycolic Acid; Capric Acid; Butyrolactam; Arachidonic Acid; X_66517; X_65017; X_21683; X_657 | 2L | 8.18 | 8.27 | 0.09 | 6.06 | 10 | 6 |
| Diet | Nicotinic Acid; Cytidine-5-Monophosphate; Alpha Aminoacidic Acid; X_113510; X_88583; X_1771; X_307 | 3R | 19.05 | 19.15 | 0.1 | 6.27 | 7 | 5 |
| Diet | Malic Acid; Kynurenine; Inosine; Alpha Aminoacidic Acid; X_62 | 3L | 7.35 | 7.45 | 0.1 | 6.40 | 5 | 4 |
| Diet | Lysine; Citrulline; Benzonic Acid; X_21763; X_67178; X_42424; X_490 | X | 10.33 | 10.5 | 0.17 | 6.51 | 7 | 5 |
| Diet | Inosine; X_117193; X_46128; X_4746; X_479 | 3L | 10.28 | 10.58 | 0.3 | 6.66 | 5 | 3 |
| Diet | Hypoxanthine; X_118602; X_117555; X_99881; X_453 | X | 14.97 | 15.07 | 0.1 | 7.50 | 5 | 3 |
| Diet | Hydroxycarbamate; X_117313; X_108052; X_46292; X_1996; X_1681; X_307 | 2R | 11.8 | 11.93 | 0.13 | 7.75 | 7 | 7 |
| Diet | Glycerol; Arachidonic Acid; X_117193; X_62284; X_490 | 2L | 9.97 | 10.07 | 0.1 | 6.20 | 5 | 4 |
| Diet | Glycerol; Citrulline; Adenosine; X_117348; X_88583; X_62409 | 3L | 9.5 | 9.6 | 0.1 | 9.46 | 6 | 6 |
| Diet | Citrulline; Adenosine; X_47170; X_46292; X_4937 | 2R | 10.87 | 11.1 | 0.23 | 8.28 | 5 | 5 |

Differences between mQTL Interactions between Genetic and Genetic-by-Diet Effects

A unique characteristic of both the metabolites listed in Tables 4.1 and 4.2 and the mQTL regions in Tables 4.3 and 4.4 is that the mQTL signatures for the main effect contrasts
differ from those of the diet effect contrasts. To analyze this further and provide insights into potential mechanisms, the mQTLs discovered in the genetic and genetic-by-diet effect models were compared. Figure 4.9 displays a stacked bar plot for each metabolite with significant genetic and genetic-by-diet effect peaks (total of 107 metabolites). The peaks are compared so that all genetic effect peaks (regardless of whether they are from the additive, dominant, full, or main model) is compared to all genetic-by-diet effect peaks (regardless of whether they are from the additive-by-diet, dominant-by-diet, full-by-diet, or diet model). The proportion of peaks shared between the main effect and diet models is relatively low, as displayed by the low proportion of green bars. Only 17 of the metabolites (15.89%) overlap with 11 of these identified chemicals. The higher proportion of genetic-by-diet effects was expected due to the higher number of genetic-by-diet effect mQTL peaks compared to genetic effect peaks. Table 4.5 shows the raw values from Figure 4.9 for all identified metabolites. This result suggests that the genetic architecture of the metabolites differs between the high fat diet and the normal diet. One potential explanation of this difference in architecture is rewiring of the architecture of the mQTL associations. These results display three main architectures, namely a simple genetic architecture where one gene influences one metabolite, a hub gene architecture where one gene influences multiple metabolites (as shown in Figures 4.5 and 4.7 and Tables 4.3 and 4.4), and a hub metabolite architecture where multiple genes influence one metabolite (as shown in Figures 4.4 and 4.5). The rewiring is such that the simple genetic architecture is displayed in one diet but is not present in the other diet. Furthermore, the hub metabolite architecture is such that that a particular set of genes influence one metabolite in one diet while a completely different set of genes influence this same metabolite in another diet. Lastly, the
hub gene architecture is such that one gene influences multiple metabolites in one diet while the same gene influences a different set of metabolites in another diet.

Figure 4.9: Proportion of metabolites that overlap between the genetic and genetic-by-diet interaction models. A total of 107 metabolites exhibited significant peaks for both genetic and genetic-by-diet models.
Table 4.5: Proportion of identified metabolites that overlap between the genetic and genetic-by-diet interaction models.

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<th>Proportions</th>
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Discussion

The mQTLs associations identified in this study involve many metabolites of biological and clinical interest, including arachidic acid, glycolic acid, tocopherol-gamma, palmitic acid, 3-aminosobutyric acid, myo-inositol, and glycerol. The biological implications of these metabolites are discussed further in the following sections.

Arachidic Acid

The mapping result for arachidic acid displays 19 significant peaks across all genetic-by-diet models (Table 4.2) and six peaks across all genetic models (Table 4.1). Furthermore, arachidic acid has been shown to be influenced by three different regions, along with 14 other metabolites (across all mQTLs involving arachidic acid). Arachidic acid is a long-chain fatty acid involved in the biosynthesis of unsaturated fatty acid pathway. Lahsteiner et al. (2010) studied many lipid and carbohydrate metabolism compounds, including arachidic acid, and found that they influence sperm viability. The authors found that the tested lipids, including arachidic acid, act as an energy resource and fuel for the tricarboxylic acid cycle. Furthermore, arachidic acid’s involvement in lipid and carbohydrate metabolism provides support for the finding that its peaks are 75% unique to genetic-by-diet models since saturated fat is increased in the high fat diet.

Glycolic Acid

Glycolic acid was identified in 22 and 38 peaks for the genetic and genetic-by-diet models, respectively (Tables 4.1 and 4.2). Furthermore, one genetic mQTL and three genetic-
by-diet mQTLs involve multiple metabolites influenced by a specific genomic region. The three genetic-by-diet mQTLs involve 23 different metabolites, including arachidic acid, tocopherol-gamma, and myo-inositol, all of which have been implicated in metabolic traits (Lahsteiner et al., 2010; Q. Jiang, Christen, Shigenaga, & Ames, 2001; Yin et al., 2016) Glycolic acid is the smallest α-hydroxy acid and is commonly found as glycolate in its ester form (PubChem, https://pubchem.ncbi.nlm.nih.gov/). It has been found to be involved in eight KEGG pathways involved with different metabolic processes, including glyoxylate and dicarboxylate metabolism, chlorocyclohexane and chlorobenzene degradation, and carbon metabolism (Kanehisa et al., 2014).

**Tocopherol-gamma**

The presented results show that tocopherol-gamma has 13 genetic-by-diet effect peaks and three genetic effect peaks. Furthermore, it is involved in two genetic-by-diet mQTLs which involve 16 different metabolites, including glycolic acid. Tocopherol-gamma (commonly called γ-tocopherol) is a natural tocopherol and includes a family of vitamin E compounds that have been shown to have less antioxidant activity compared with the more studied α-tocopherol. γ-tocopherol is found in vegetable oils and nuts and has been shown as the major form of vitamin E in the U.S. (Q. Jiang et al., 2001). The results show that 81% of the mQTL peaks for γ-tocopherol are unique to the genetic-by-diet effect, which can be attributed to the high fat diet with added coconut oil.
Palmitic Acid

The presented results show that palmitic acid is involved in the most complex mQTL peak since the region influences 15 different metabolites. Palmitic acid is a common saturated long-chain fatty acid that has been found naturally in oils such as palm and olive oils and many body lipids. Furthermore, palmitic acid is involved in fatty acid synthesis, or lipogenesis, as the first fatty acid produced in this process (PubChem, https://pubchem.ncbi.nlm.nih.gov/). It is involved in eight pathways in KEGG including those involving biosynthesis, elongation, and degradation of fatty acids and biosynthesis of unsaturated fatty acids (Kanehisa et al., 2014). Pavićević et al. (2014) discovered that fatty acids such as palmitic acid bind to human serum albumin (HSA). This binding was found to alter HSA’s accessibility and reactivity, which may lead to other metabolic diseases.

3-Aminosobutyric Acid

The metabolite 3-aminosobutyric acid was found to have the highest percentage of diet-only mQTLs (Table 4.5). This metabolite was involved in four genetic-by-diet effect mQTL regions involving 24 metabolites. 3-aminoisobutyric acid or β-aminoisobutyric acid (BAIBA), is a product of the catabolism, or breakdown, of the DNA nucleotide thymine (PubChem, https://pubchem.ncbi.nlm.nih.gov/). Begriche et al. (2010) discovered that BAIBA improves fatty acid oxidation and reduces body weight in mice. The mechanism of this effect was found via the production of leptin by white adipose tissue. Such metabolic links may explain the difference in architecture between the genetic-by-diet and genetic effect mechanisms although such a hypothesis must be functionally validated.
Myo-Inositol

The metabolite myo-inositol was identified in a variety of mQTL associations, including 16 genetic effect peaks. It is also among the metabolites with the most genetic-by-diet effect peaks, with 72 peaks (Table 4.2). Myo-inositol was found to be involved with two of the mQTL peaks involving multiple metabolites for one genomic region. The two overlapping mQTLs involve a total of 11 different metabolites, one of which is glycolic acid, which has been shown to have a link to metabolic traits. Myo-inositol is the natural form of inositol, a sugar found in many different components of cells (PubChem, https://pubchem.ncbi.nlm.nih.gov/). Yin et al. (2016) recently conducted a metabolomics study that found myo-inositol increased significantly in treatment with benzyl butyl phthalate, which induces developmental and reproductive toxicity within a cell and dysregulates adipogenesis. Jiang et al. (2015) conducted metal toxicity experiments in fish and found that myo-inositol protected fish muscles from lactic acid dehydrogenases, which is involved in oxidative damage of the muscles triggered by exposure to copper.

Glycerol

In the presented results, glycerol has a total of nine peaks across the genetic effect models and 33 peaks across the genetic-by-diet effect models. Furthermore, we discovered two and four mQTL associations for the genetic and genetic-by-diet effect models, respectively. These mQTL associations involved six metabolites for the genetic effect models and 22 for the genetic-by-diet effect models. Glycerol is a key intermediate in carbohydrate and lipid metabolism. Kahn et al. (2006) reviewed many different mechanisms linking obesity to insulin
resistance and type 2 diabetes. In their study, the role of glycerol included its release by adipose tissue along with non-esterified fatty acids (NEFA), hormones, and pro-inflammatory cytokines, specifically for obese individuals. Chu et al. (2013) discovered glycerol’s role in restoring fatty acid transport of the kAE1 mutant, which has been known to alter trafficking and cause distal renal tubular acidosis (an inherited disease characterized by metabolic acidosis).

**N-epsilon trimethyllysine**

The metabolite N-epsilon trimethyllysine had the highest percentage of genetic effect only mQTLs, with a total of nine genetic effect peaks and one genetic-by-diet effect peak. The enzyme trimethyllysine is coded by the TMLHE gene, which has an ortholog in *Drosophila melanogaster* named CG4335 (http://flybase.org/). Unfortunately, the ortholog gene was not included in any of the mQTL peaks. The enzyme has been found to be involved in catalysis in the first step of the carnitine biosynthesis pathway. Carnitine plays a crucial role in transporting long chain fatty acids into the mitochondria (Leung et al., 2010). Due to the direct role of trimethyllysine, possibly as a gene product, the high degree of genetic effect only components in the mapping results supports this potential role.

**Conclusions and Future Work**

This study on metabolite and quantitative trait loci (QTL) association is one of the first to examine mQTL interactions under multiple diet scenarios. The discovered QTLs had
different architecture for high fat and normal diets, which may suggest different modes of action for the two diets. Follow up should be done for the discovered mQTLs, with the highest priority on those replicated across different models and influenced by multiple genomic regions. Furthermore, there is ongoing analysis of the mapping results from population B from the DSPR (King, Merkes, et al., 2012; King, Macdonald, & Long, 2012) lines and ongoing studies on the DGRP (Mackay et al., 2012) lines. These studies will provide insight into how the founders in population B of DSPR influence mapping results and the natural Drosophila population in the DGRP.

The current results independently treated each metabolite as the quantitative trait although this assumption of independence is biologically limited. The tested metabolites may be involved in common processes and pathways and high correlation between these metabolites would be unsurprising. Furthermore, some of the metabolites are chemical products of each other which further increases the correlation between their intensities. The next chapter presents a gene set and pathway approach for further study of the metabolites and how they are influenced by genetic and environmental factors.
References


CHAPTER 5
Applying Pathway and Gene Set Analysis on Drosophila Metabolomics Data

Introduction

The mQTL mapping described in Chapter 4 revealed a number of strong associations with both genetic and genetic-by-diet interactive effects. While these results indicate several findings, further evaluation of the data from pathway analysis approaches was desired.

As discussed throughout this dissertation, pathway and network analysis methods use information on the etiology of pathways and networks to detect coordinated signals. The mQTL associations reveal various potentially interesting underlying genetic architectures, which are summarized in Figure 5.1. Possible architectures include simple cis associations (one gene influences one metabolite), hub gene architectures (one gene influences many different metabolites), and hub metabolite architectures (many genes influence one metabolite). Furthermore, comparing the mQTL associations for main effects and gene-environment (diet) effects revealed that the architecture of the associations was relatively distinct between the two. This hints at an architectural change influenced by diet. This chapter uses gene set and pathway analysis methods to characterize further the architecture and complex interactions underlying trait etiology.

The methods comparison results presented in Chapter 3 motivated the choice of specific pathway methods and parameter settings. This analysis revealed pathways from knowledge bases that are associated with the phenotypes of interest. Additionally, because
many of the metabolites collected in this study were unknown thus not included in the annotation of the knowledge bases, we explored the data with network-based approaches (as discussed in Chapters 1 and 3) to generate hypotheses about novel connections among metabolites.

**Figure 5.1:** Three architectures detected from the mQTL association results. The simple genetic architecture consists of a single gene or genomic region influencing a metabolite. The hub metabolite consists of multiple genes or genomic regions influencing a single metabolite. The hub gene consists of a single gene influencing multiple metabolites.
Methods

Gene Set Analysis Methods

The recommended methods, sigPathway (Tian et al., 2005) and Gene Set Enrichment Analysis (GSEA) (both self-contained and competitive hypotheses) (Subramanian et al., 2005), from the Flexible Algorithm for Novel Gene set Simulation (FANGS) simulation study were used to further evaluate *Drosophila melanogaster* metabolomics data. While the data simulated in the methods comparison were based on gene expression data, metabolomics data are continuous data with similar statistical properties. These methods have been successfully used in metabolomics data in a range of real data applications, including variations of GSEA utilized by Persicke et al. (2012) and Kankainen et al. (2011), work by Carroll et al. (2015), and the integrated application discussed by Welzenbach et al. (2016).

Based on the high power and nominal false positive rate of the approaches, sigPathway and GSEA were chosen (as shown in Chapter 3). The sigPathway method was run using default settings as previously discussed, and the GSEA software was run using default settings and p-values were used to calculate the FDR based on the Benjamini-Hochberg method (Benjamini & Hochberg, 1995). Self-contained and competitive versions of GSEA were implemented. Both methods were run on the same hardware as the FANGS simulation study (Chapter 3). A FDR < 0.10 was considered statistically significant.

Metabolomics Data

The metabolomics data analyzed was described in Chapter 4. Briefly, *Drosophila melanogaster* samples were treated with two diets: normal (standard cornmeal) and high fat
(3% coconut oil added). The data includes 760 samples for 422 quantified metabolites. Metabolite measurements were taken via gas chromatography time of flight mass spectrometry (GSTOF-MS). The metabolite intensities were vector normalized, resulting in consistent intensities across samples. Furthermore, the data was normalized to account for batch effects introduced due to the cleaning schedule of the mass spectrometry machine. Finally, the residual of a linear model including the batch effects for each metabolite was used as the metabolite intensity. The details of sample preparation and normalization are discussed in Chapter 4. Only the identified metabolites (a total of 169) were used for the enrichment analysis since these can be potentially mapped to known pathways based on information in the knowledgebase. Annotation of the metabolites was determined by the technique described in Chapter 4 and conducted by the Fiehn Laboratory with the BinBase algorithm and database (Skogerson et al., 2011). Complete annotation information is shown in Appendix C, Supplemental Table 4.3.

**Knowledge Base: Human Metabolomics Database (HMDB)**

Both GSA methods rely on a knowledge base that defines gene sets based on biologically known functions and dependencies. The knowledgebase used for analysis depends on a number of factors, including the type of data collected. For example, in the methods comparison simulation study, the MSigDB database was used because of its popularity, inclusion of many public knowledge bases, and focus on gene expression data. Because the present study considers metabolites, MSigDB was not the best choice. The Human Metabolomics Database (HMDB) (Wishart et al., 2007, 2009, 2013) version 3.6 was selected for this work due to the high degree of homology of metabolic traits between *Drosophila* and
humans (Reiter et al., 2001; Trinh et al., 2013) and the high annotation coverage of the metabolites tested. The HMDB database has provided human metabolome annotation and information since its introduction in 2007 at no charge. The resource has grown to include 41,514 metabolites involved in 442 metabolic pathways. Recently, both detected metabolites with measured concentration intensities and expected metabolites contained in known pathways but un-detected in the human body have been included in the database (Wishart et al., 2013). Of the 422 metabolites contained in the dataset, 169 have chemical identifications. The KEGG ID (148 of 169 metabolites) of each chemical was utilized to determine that 130 of these metabolites are included in HMDB, representing 42 different pathways. This high coverage along with the utility of applying the discovered mechanisms to humans mean the HMDB database is an ideal fit.

Network Approach of mQTLs

The mQTL associations identified in Chapter 3 are characteristic of a genomic region influencing multiple metabolites (listed in Tables 4.3 and 4.4 and in Appendix B, Supplemental Table 5.2). To create a network representation of these metabolites, a fully connected undirected graph was created for metabolites influenced by the same genomic region (implemented in the Python programming language version 2.9 with network visuals created in Cytoscape - http://www.cytoscape.org/). In this network, each node represents a metabolite (identified or unidentified) involved in a significant mQTL association, and an edge is created between metabolites influenced by the same genomic region (or no edge for simple genetic architecture). To determine the type of metabolites connected in this network, this information
was outputted by a Python script for further examination. Statistical analysis was conducted to test whether the identified or unidentified metabolites involved in significant associations were different than those expected by chance by conducting a t-test of proportions. Furthermore, to test whether the involvement of identified and unidentified metabolites was different, a t-test was conducted in the R statistical programming language.

Results

Gene Set Analysis (GSA)

The complete results for all 42 pathways (and the number of metabolites from the dataset included in each pathway) are shown in Table 5.1, which also displays the false discovery rate (FDR) values and gene set rank for each method. The beta oxidation of very long chain fatty acids pathway was statistically significant across all methods and was the top-ranked pathway for all three methods. This pathway includes a total of 10 metabolites in the HMDB database, three of which are included in the analyzed dataset. These three metabolites are capric acid, lauric acid and lignoceric acid.

While these results are promising, the limited number of significant findings may be due to several reasons. One possible explanation is the low number of metabolites that map to HMDB pathways, which are shown in the size column in Table 5.1. With few metabolites mapping to pathways, overall pathway coverage is limited, with only 169 of the 422 annotated metabolites.
Table 5.1: Complete GSA results. The gene sets are sorted based on the rank for the sigPathway method results.

<table>
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<th>Size</th>
<th>Beta Oxidation of Very Long Chain Fatty Acids</th>
<th>Gluconeogenesis</th>
<th>Fructose and Mannose Degradation</th>
<th>Nicotinate and Nicotinamide Metabolism</th>
<th>Mitochondrial Beta-Oxidation of Long Chain Saturated Fatty Acids</th>
<th>Propanoate Metabolism</th>
<th>Galactose Metabolism</th>
<th>Starch and Sucrose Metabolism</th>
<th>Purine Metabolism</th>
<th>Sphingolipid Metabolism</th>
<th>Biotin Metabolism</th>
<th>Glutamate Metabolism</th>
<th>Lysine Degradation</th>
<th>Ammonia Recycling</th>
<th>Glycine and Serine Metabolism</th>
<th>Betaine Metabolism</th>
<th>Valine, Leucine and Isoleucine Degradation</th>
<th>Citric Acid Cycle</th>
<th>Carnitine Synthesis</th>
<th>Aspartate Metabolism</th>
<th>Amino Sugar Metabolism</th>
<th>Ketone Body Metabolism</th>
<th>Phosphatidylinositol Phosphate Metabolism</th>
<th>Methionine Metabolism</th>
<th>Arachidonic Acid Metabolism</th>
<th>Fatty Acid Biosynthesis</th>
<th>Bile Acid Biosynthesis</th>
<th>Nucleotide Sugars Metabolism</th>
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<th>Tryptophan Metabolism</th>
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Network Structure of mQTLs

To further evaluate the genetic architecture of the mQTL signals detected, a graph theory-based visualization approach was used. A network representation was created to further analyze the metabolites involved in mQTLs. Figure 5.2 shows the network structure for the genetic effect (a) and genetic-by-diet effect (b) mQTLs. The number of edges corresponding to full or full-by-diet and main or diet models are higher due to the higher number of mQTLs discovered from these models, as shown by the large proportion of blue (full and full-by-diet) and red (main and diet) edges. Furthermore, these networks include many unidentified metabolites because they represent the vast majority of metabolites in the dataset. Superimposing these two networks on each other and coloring the edges in a different way (with genetic models in blue and genetic-by-diet models in red) resulted in the graph shown in
Figure 5.3. In this network, it is apparent that many of the edges correspond to genetic-by-diet effect mQTLs, which is expected due to the high number of discovered associations. In addition, the influence of unidentified metabolites (purple nodes) is apparent, due to their higher degree compared to identified metabolites (light blue nodes). Node degrees of the top 25 metabolites are shown in Table 5.2, 10 of which are unidentified metabolites).

To further investigate the influence of unidentified metabolites on the discovered mQTL associations, these networks were examined to determine the type of metabolites influenced by the same genomic location.

**Figure 5.2: Genetic (a) and genetic-by-diet (b) effect mQTL networks.** Each node represents a different metabolite involved in an mQTL association. The identified metabolites are light blue and the unidentified metabolites are purple. An edge is present between metabolites influenced by the same genomic region for the same model. The additive and additive-by-diet associations are indicated by a black edge; the dominant and dominant-by-diet associations are indicated by a green edge; the full and full-by-diet associations are indicated by a blue edge; and the main and diet associations are indicated by a red edge.
Figure 5.3: Comparison mQTL network. Each node represents a different metabolite involved in an mQTL association. The identified metabolites are light blue and the unidentified metabolites are purple. An edge is present between metabolites when they are influenced by the same genomic region for the same model. The genetic effect models (regardless of whether they are additive, dominant, full or main) are indicated by blue edges and the genetic-by-diet effect models (regardless of whether they are additive-by-diet, dominant-by-diet, full-by-diet, or diet) are indicated by red edges.
Table 5.2: Degree distribution of the top-25 metabolites involved in the mQTL networks. All metabolites are shown in Appendix C, Supplemental Table 5.1.

<table>
<thead>
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<th>Metabolite</th>
<th>Degree</th>
<th>Metabolite</th>
<th>Degree</th>
</tr>
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<td>Hydroxycarbamate</td>
<td>98</td>
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<td>116942</td>
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<td>Hypoxanthine</td>
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Influence of Unidentified Metabolites on the Discovered mQTL Associations

Further analyzing the hub gene and simple genetic architectures is useful for discovering which types of metabolites are influenced by the same genomic region and which act only in a simple genetic architecture. Figure 5.4 shows the proportion of mQTL associations involved in hub gene architectures (labeled as ‘Others’ and shown in red) and those in simple genetic architectures (labeled as ‘Itself’ and shown in blue). The unidentified metabolites are located towards the left of the graph, and the identified metabolites are located towards the right. The average values of these proportions are shown in Table 5.3. It is interesting that the proportion of simple genetic architecture mQTLs for the genetic effect is much higher than for the genetic-by-diet effect (p-value < 0.05). Furthermore, the t-test of proportions revealed that the proportions shown for itself (unidentified and identified) are...
significant for the genetic-by-diet mQTLs while only the identified metabolites are significant for the genetic mQTLs. Splitting the hub gene architecture mQTLs into those with identified (red) and unidentified (light red) metabolites again displays different patterns between the main and diet effect models. This shows that a majority of the hub gene architecture mQTLs involve unidentified metabolites (significant p-value for identified metabolites for the genetic effect models and significant unidentified t-test p-value for unidentified metabolites for the genetic-by-diet effect models). Because a high number of the mQTLs involve unidentified metabolites, functionally verifying mQTLs is a challenge due to the unknown factor of the source of the unidentified metabolite. The source could be via high correlation with identified metabolites, contaminants in the sample, an error in the mass spectrometry machine, or because it truly is a different chemical from the others identified.

Table 5.3: Average proportion of mQTL associations for the genetic effect and genetic-by-diet effect models corresponding to identified and unidentified metabolites. Significance values of the t-test of proportions are *α=0.1, and **α=0.05. Significance values of the t-test are •α=0.1, and ••α=0.05.

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<th>Other – ID</th>
<th>Other – Not ID</th>
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<td>0.7808**</td>
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<td>0.4537**</td>
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<td>0.7808**</td>
<td>0.3271</td>
<td>0.4537**</td>
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</table>
Figure 5.4: Analysis of mQTL network architecture. The proportion of mQTLs that are simple architectures (labeled as ‘Itself’ and shown in blue) compared to gene hub architectures (labeled as ‘Others’ and shown in red) is shown for each metabolite involved in mQTL associations for the (a) genetic and (b) genetic-by-diet effects. The gene hub architecture is further split in the bottom panels, where the proportion of architectures with identified metabolites is shown in dark red, and the proportion of architectures with unidentified metabolites is shown in light red.

Conclusions and Future Work

This work aims to discover the mode of action for the different architectures of discovered mQTL associations (from Chapter 4). Gene set analysis (GSA) is one statistical method used to answer this question and is described in Chapter 1. FANGS is method of comparison and is described in Chapter 3. GSA with recommended methods, namely GSEA
(Subramanian et al., 2005) (both self-contained and competitive null hypotheses) and sigPathway (Tian et al., 2005), was conducted with the metabolite intensity residuals (after normalization as previously discussed). GSA revealed that the beta oxidation very long-chain fatty acids pathway was the only pathway tested (out of a total of 42) that displayed close to significant FDR corrected results. This pathway includes three metabolites included in the metabolomics dataset, namely capric acid, lauric acid and lignoceric acid. Lignoceric acid is one of the metabolites with both genetic and genetic-by-diet associations with QTLs although none of the genomic regions overlap, as shown by Figure 4.9 in Chapter 4. Capric acid is involved in many significant mQTL associations, as shown in Table 4.2 (Chapter 4). The results show that this metabolite was influenced by seven different QTLs for the genetic-by-diet models. Furthermore, it was included in three mQTLs where multiple metabolites were influenced by multiple genomic regions (as shown in Table 4.4 in Chapter 4). The beta oxidation cycle is often highly involved in the degradation of fatty acids in many mammals, plants, and humans (Salway, J.G., 2004; Vance, D.E., and Vance, J.E., 2002). In humans, this process occurs in the peroxisome and the mitochondria. Studies have shown that very-long-chain fatty acids are initially oxidated in the peroxisome after being further oxidated in the mitochondria (Salway, J.G., 2004; Vance, D.E., and Vance, J.E., 2002). This is surprising since the difference in diet in the experiments conducted in the present study was due to 3% added coconut oil, which is a short-chain fatty acid. This suggests contrary information on the beta oxidation long-chain fatty acid process or a different mechanism in *Drosophila melanogaster*. A potential different mechanism that is specific to *Drosophila* would not be represented in the
HMDB pathways. The results should be further verified in both humans and *Drosophila melanogaster*.

Analyzing the mQTL associations further revealed the high frequency of the unidentified metabolites for these associations. Furthermore, the difference in architecture between the genetic and genetic-by-diet effect models was displayed by the different proportions of mQTLs involved in gene hub architectures and those with a simple genetic architecture.

Although these results reveal novel mQTL associations that can be tested further, the influence of unidentified metabolites makes functional confirmation difficult. For further testing of these mQTL interactions and to infer a more exact metabolite network, third-generation (or pathway topology) pathway analysis techniques should be utilized. These methods strive to infer a network structure based on the given data. Gene set analysis techniques are then utilized to detect which elements of the network are the most influential. These methods enable the discovery of novel metabolomics architectures that have yet to be annotated in knowledge bases. Therefore, the GSA methods’ reliance on knowledge bases and mature information about annotations is necessary and can be overcome by pathway topology analysis methods.
References


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CHAPTER 6

Future Directions for the *Drosophila* mQTL Mapping Project and Extensions of the FANGS Simulator

The results presented in this dissertation provide insights into both the development and application of methods for pathway analysis of genetic and metabolomics data. These exciting results provide motivation and support for several directions for future work. In this final chapter, we discuss a number of the most immediate future directions. We will discuss future directions from the perspectives of both methods development and applied aspects of the work.

**Gene Set Simulator**

The FANGS software was developed to simulate data for gene set analysis methods. The software allows users to vary parameters in a simulation study, including the dataset on which simulations are based, the gene set targeted for differential expression, the proportion of the gene set differentially expressed \( (\pi) \), and the effect size of the differential expression \( (\tau) \). The analysis presented results in Chapter 4 tested a limited range of simulation parameters. This work varied the gene set that was targeted (the KRAS and TGF-\( \beta \) signaling pathways) and used many different \( \pi \) and \( \tau \) combinations. Additional simulation experiments should be performed to assess the impact of other parameters. In addition, other datasets should be tested with the software to determine the influence of different correlation structures on the power of
GSA methods. These datasets should include a wide array of diseases along with normal tissue. Furthermore, these datasets should have a range of sample sizes. Different sample sizes can also be achieved by under-sampling the datasets used in the simulation study presented in Chapter 4. In this way, the influence of sample sizes on the power of GSA methods can be analyzed. Furthermore, pilot data can be utilized for power calculations by oversampling.

Another important aspect of the study that should be further investigated is the choice of data preprocessing methods. The analysis presented in Chapter 4 used RMA normalization, quantile normalization, and centering. The influence of preprocessing can be further investigated by testing other normalization techniques, including log transformation, and Lowess normalization.

Lastly, it is likely that the choice of knowledge base used GSA methods impacts results. Further experiments should evaluate the impact of varying both the overall knowledge base, and the categories or types of gene sets within the knowledge base. The Molecular Signatures Database (MSigDB) (Subramanian et al., 2005) was used for the analyses in Chapter 4. As described earlier, MSigDB includes eight different gene set categories, positional (C1), literature curated (C2), motifs (C3), computational (C4), gene ontology terms (C5), oncogenic (C6), immunologic (C7), and hallmarks of cancer (H). Like all statistical testing, the power of pathway analysis methods depends on issues with multiple testing so the size of the knowledge base should be varied to better understand the impact. The gene set categories should be tested individually and together in a systematic method. Furthermore, other knowledge bases such as the Human Metabolome Database (HMDB) (Wishart et al., 2013) and Kyoto Encyclopedia of Genes and Genomes (KEGG) (Kanehisa et al., 2014) should be included to fully understand
the importance and influence of the knowledge base in the interpretation and reliability of GSA method results.

The FANGS simulator software is flexible and modular software coded in the R programming language. It is easy to use, including modifying the parameters, but a formal R package should be implemented so software is easily accessible by the public. With such a package, anyone can download the simulation software. Several other genetic simulation software tools have been successfully utilized and are publically available. The Genetic Simulation Resources (https://popmodels.cancercontrol.cancer.gov/gsr/search/) maintained by the National Cancer Institute provides a list of simulation software programs and links to download free versions. In addition, Bioconductor in the R statistical programming language contains several genetic simulation software programs, including ChIPsim (for the simulation of ChIP-seq experiments), compcodeR (for the simulation of RNA-Seq data), OncoSimulR (a forward genetic simulation for cancer progression with epistasis included), RSVSim (for structural variations), and SpacePAC (identification of mutations in 3D protein structures).

Furthermore, a major drawback of the current simulation software is it limitation to gene expression data. Further developments should extend the software for other datasets, including other omic technologies such as metabolomics and new transcriptomics technologies stemming from RNA sequencing technology. With RNA sequencing technology, the statistical methods for GSA must be slightly altered since measurements will be counts as opposed to a continuous measure displayed in microarray technology. This statistical property must be taken into account when calculating the gene-level statistic utilized in GSA methods.
While the methods tested in the present results include some of the most well-known GSA methods, many more exist. One heavily utilized is Ingenuity Pathway Analysis (IPA®). IPA is a commercial product released by Qiagen Bioinformatics and has produced favorable results. This method includes an extensive knowledge base that the company has manually curated. The statistical analysis conducted by this method is a two-tier system similar to the methods presented in the FANGS simulation study. Therefore, the knowledge base curated by IPA is the key difference, suggesting that many public knowledge bases such as MSigDB may need to be manually refined and curated to be more informative. Further experiments and simulations with both knowledge bases should be conducted.

An entirely different class of methods exists for pathway topology analysis. As discussed in Chapter 1, these methods are aimed at discovering the correlation network between molecular elements within a dataset. This has the advantage of inferring completely novel associations that do not exist in any knowledge bases. A simulator to create data to test these methods should be developed and matured. This simulator would differ from FANGS since it asks questions about inference as opposed to enrichment in the second-generation methods targeted for the FANGS simulations. The simulator could create a network architecture, for example, the formulation presented by Di Camillo et al. (2009). Based on this network architecture data could be created that reflects interactions in the network. Di Camillo et al. (2009) established this theoretically, although software to implement this has not been created.
Metabolite-QTL (mQTL) Mapping

The mQTL associations that were discovered (described in Chapters 3 and 5) have different architectures under normal and high fat diets. Furthermore, the influence of unidentified metabolites was shown to be relatively significant for the high fat diet. Therefore, to further understand the architecture of mQTL associations, pathway topology methods should be applied to infer unique interactions between molecules. Additionally, the utility of more data for any system is well known. Therefore, discovery of additional genomic (SNP array) or transcriptomic (gene expression) associations at each level along with a system-wide view would be beneficial. This data would allow GSA using metabolite data to be conducted at these levels as well. There have been a number of recent methodological developments related to integrating information across omics levels. That work, reviewed in M.D. Ritchie et al. (2015) can be incorporated in future analyses.

Additionally, there are a number of opportunities to functionally validate the discovered mQTL associations. An immediate opportunity is repeating the experimental design on other Drosophila populations. This includes population B of the DSPR (King, Macdonald, et al., 2012), which includes a different set of founders. This experiment would enable the comparison of mQTL mapping results from two different populations with similar origins. Furthermore, the DGRP (Mackay et al., 2012) should be used to compare the synthetic population of DSPR to the natural DGRP. The similarities and differences between these populations will shine light on the variability of the species and indicate how the mode of action may be altered due to this variability. Additionally, wet lab experiments to functionally
validate the discovered associations should be conducted. This can include knocking out
candidate genes coupled with target metabolomics.
References


APPENDICES
Supplemental Figure 3.1: Correlation Structure of Prostate Cancer Dataset. Each row and column refers to genes in the dataset, and the value plotted in the heat map is the Pearson correlation coefficient between the expressions of those genes. The density of correlation values is shown in the top left corner.
**Supplemental Figure 3.2: Power of SAFE GSA Method on Negative Controls.** Statistical power as detected by negative control data for the alternative parameters for the SAFE GSA method. The mean power (for 100 bootstrap datasets) of the three negative controls is plotted along with a 95% confidence interval for the mean of each method.
**Supplemental Table 3.1: Statistical false positive rates for the three controls, negative, double negative and no signal (tau 0).** All values are shown at a significance value of 0.05.

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<th>Control Type</th>
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### Supplemental Table 3.2: Statistical power values for simulation results (for both pathways and all pairs of \( \pi \) and \( \tau \) tested)
for all methods along with GSEA alternative settings. All power values are shown at a significance value of 0.05.

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Supplemental Figure 3.3: Power of Overlapping Pathways for all effect sizes for the KRAS Pathway. Statistical power for results with recommended methods for overlapping pathways for experiments with differential expression of the KRAS pathway. The recommended methods include CAMERA, GSEA with user-defined FDR q-value, and sigPathway. The x-axis denotes the proportion of the pathway that overlaps with the KRAS pathway. Each point in the graph represents an overlapping pathway. All power values are shown as a significance value of 0.05.
Supplemental Figure 3.4: Power of Overlapping Pathways for all Effect Sizes for TGF-β Pathway. Statistical power for results with recommended methods for overlapping pathways for experiments with differential expression of the TGF-β pathway. The recommended methods include CAMERA, GSEA with user-defined FDR q-value and sigPathway. The x-axis denotes the proportion of the pathway that overlaps with the TGF-β pathway. Each point in the graph represents an overlapping pathways. All power values are shown as a significance value of 0.05.
Supplemental Table 4.1: List of all metabolites with at least one peak in the genetic or genetic-by-diet interaction (GxD) interaction models. The metabolites are sorted by the total number of peaks for all models.

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Supplemental Table 4.2 Continued

| Dominant | 401    | 1380  | 8592 | 3L  | 20.21 | 20.4 | 0.19 | 5.881 | 1 | 1 |
| Dominant | 223    | 111670 | 8634 | 3L  | 20.74 | 20.79 | 0.05 | 7.458 | 1 | 1 |
| Dominant  | 42     | phosphate | 8844 | 3L  | 22.82 | 22.89 | 0.07 | 8.691 | 1 | 1 |
| Dominant  | 45     | pantothenic acid | 9221 | 3R  | 1.97  | 2.39  | 0.42 | 6.299 | 1 | 1 |
| Dominant  | 215; 384 | 116942; 1996 | 9307; 9310 | 3R  | 2.94  | 3.34  | 0.4  | 7.031 | 2 | 2 |
| Dominant  | 343    | 13146  | 9347 | 3R  | 6.07  | 6.1   | 0.03 | 6.335 | 1 | 1 |
| Dominant  | 295    | 62284  | 9879 | 3R  | 8.79  | 9     | 0.21 | 5.665 | 1 | 1 |
| Dominant  | 293    | 62409  | 9920 | 3R  | 9.33  | 9.37  | 0.04 | 5.753 | 1 | 1 |
| Dominant  | 27; 245 | shikimic acid; 105164 | 9949; 9950 | 3R  | 9.64  | 9.67  | 0.03 | 7.156 | 2 | 2 |
| Dominant  | 401; 106; 215; 102 | 1380; glycerol; 116942; glycolic acid | 10006; 10008; 10009; 10013 | 3R  | 10.12 | 10.32 | 0.2  | 7.005 | 4 | 4 |
| Dominant  | 42; 376 | phosphate; 2900 | 10139; 10142 | 3R  | 11.4  | 11.6  | 0.2  | 11.732 | 2 | 2 |
| Dominant  | 131    | citrulline | 10210 | 3R  | 12.1  | 12.35 | 0.25 | 12.034 | 1 | 1 |
| Dominant  | 215    | 116942  | 10357 | 3R  | 13.69 | 13.79 | 0.1  | 7.048 | 1 | 1 |
| Dominant  | 55     | N epsilon trimethyllysine | 10383 | 3R  | 13.95 | 14    | 0.05 | 5.624 | 1 | 1 |
| Dominant  | 15     | tocopherol gamma | 10437 | 3R  | 14.51 | 14.54 | 0.03 | 5.593 | 1 | 1 |
| Dominant  | 351    | 6066   | 10483 | 3R  | 14.98 | 15.02 | 0.04 | 5.958 | 1 | 1 |
| Dominant  | 190    | 117313 | 10526 | 3R  | 15.33 | 15.44 | 0.11 | 5.611 | 1 | 1 |
| Dominant  | 418; 215 | 99; 116942 | 10559; 10560 | 3R  | 15.5  | 15.85 | 0.35 | 5.642 | 2 | 2 |
## Supplemental Table 4.2 Continued

| Dominant | 130 | cyanoalanine | 10673 | 3R | 16.87 | 16.9 | 0.03 | 6.982 | 1 | 1 |
| Dominant | 45 | pantothenic acid | 10699 | 3R | 17.07 | 17.19 | 0.12 | 8.649 | 1 | 1 |
| Dominant | 215 | 116942 | 10790 | 3R | 18 | 18.11 | 0.11 | 6.502 | 1 | 1 |
| Dominant | 245 | 105164 | 10803 | 3R | 18.17 | 18.2 | 0.03 | 5.379 | 1 | 1 |
| Dominant | 102; 256 | glycolic acid; 104131 | 10811; 10811 | 3R | 18.24 | 18.29 | 0.05 | 6.662 | 2 | 1 |
| Dominant | 132; 161 | citric acid; 3 phosphoglycerate | 10824; 10824 | 3R | 18.39 | 18.43 | 0.04 | 5.834 | 2 | 1 |
| Dominant | 357 | 5263 | 10869 | 3R | 18.77 | 18.86 | 0.09 | 5.930 | 1 | 1 |
| Dominant | 411 | 307 | 10933 | 3R | 19.44 | 19.51 | 0.07 | 5.458 | 1 | 1 |
| Dominant | 215 | 116942 | 10956 | 3R | 19.69 | 19.73 | 0.04 | 9.453 | 1 | 1 |
| Dominant | 42; 131 | phosphate; citrulline | 10968; 10969 | 3R | 19.83 | 19.86 | 0.03 | 5.780 | 2 | 2 |
| Dominant | 215 | 116942 | 11028 | 3R | 20.43 | 20.45 | 0.02 | 8.022 | 1 | 1 |
| Dominant | 131 | citrulline | 11087 | 3R | 21.02 | 21.05 | 0.03 | 13.126 | 1 | 1 |
| Dominant | 183 | 117757 | 11119 | 3R | 21.34 | 21.36 | 0.02 | 5.469 | 1 | 1 |
| Dominant | 93 | hydroxycarbamate | NIST | 11198 | 3R | 22.12 | 22.16 | 0.04 | 5.661 | 1 | 1 |
| Dominant | 42 | phosphate | 11214 | 3R | 22.29 | 22.31 | 0.02 | 6.324 | 1 | 1 |
| Dominant | 215 | 116942 | 11305 | 3R | 23.19 | 23.22 | 0.03 | 6.023 | 1 | 1 |
| Dominant | 59 | myo inositol | 11387 | 3R | 24 | 24.04 | 0.04 | 5.680 | 1 | 1 |
| Dominant | 170 | 118602 | 11426 | 3R | 24.38 | 24.45 | 0.07 | 6.603 | 1 | 1 |
| Dominant | 42 | phosphate | 11468 | 3R | 24.8 | 24.86 | 0.06 | 19.734 | 1 | 1 |
| Dominant | 351 | 6066 | 11512 | 3R | 25.25 | 25.31 | 0.06 | 7.420 | 1 | 1 |
| Dominant | 321; 231 | 21683; 110189 | 11571; 11578 | 3R | 25.77 | 25.95 | 0.18 | 6.268 | 2 | 2 |
| Dominant | 45 | pantothenic acid | 11703 | 3R | 27.1 | 27.2 | 0.1 | 9.126 | 1 | 1 |
| Dominant | 55 | N epsilon trimethyllysine | 11738 | 3R | 27.53 | 27.6 | 0.07 | 8.155 | 1 | 1 |
| Full | 75 | linoleic acid | 103 | X | 1.11 | 1.23 | 0.12 | 5.875 | 1 | 1 |
| Supplemental Table 4.2 Continued |
|---------------------------------
| **Full** | 15; 394 | tocopherol gamma ; 1725 | 138; 139 | X | 1.51 | 1.55 | 0.04 | 5.976 | 2 | 2 |
| Full | 144 | arachidic acid | 200 | X | 2.13 | 2.17 | 0.04 | 6.361 | 1 | 1 |
| Full | 311 | 26736 | 261 | X | 2.73 | 2.77 | 0.04 | 6.861 | 1 | 1 |
| Full | 42 | phosphate | 266 | X | 2.8 | 2.82 | 0.02 | 13.653 | 1 | 1 |
| Full | 131 | citrulline | 422 | X | 4.36 | 4.39 | 0.03 | 10.747 | 1 | 1 |
| Full | 374 | 3143 | 455 | X | 4.68 | 4.74 | 0.06 | 6.446 | 1 | 1 |
| Full | 373 | 3200 | 473 | X | 4.86 | 4.89 | 0.03 | 5.707 | 1 | 1 |
| Full | 91 | hypoxanthine | 483 | X | 4.97 | 5.01 | 0.04 | 6.587 | 1 | 1 |
| Full | 42 | phosphate | 502 | X | 5.16 | 5.19 | 0.03 | 15.370 | 1 | 1 |
| Full | 131 | citrulline | 507 | X | 5.21 | 5.23 | 0.02 | 7.464 | 1 | 1 |
| Full | 210 | 117192 | 524 | X | 5.35 | 5.45 | 0.1 | 6.240 | 1 | 1 |
| Full | 215 | 116942 | 571 | X | 5.85 | 5.87 | 0.02 | 6.270 | 1 | 1 |
| Full | 84 | isomaltose | 635 | X | 6.49 | 6.52 | 0.03 | 5.577 | 1 | 1 |
| Full | 401 | 1380 | 645 | X | 6.59 | 6.61 | 0.02 | 8.258 | 1 | 1 |
| Full | 45 | pantothenic acid | 651 | X | 6.65 | 6.68 | 0.03 | 6.228 | 1 | 1 |
| Full | 37 | pseudo uridine | 669 | X | 6.82 | 6.85 | 0.03 | 5.414 | 1 | 1 |
| Full | 384; 215 | 1996; 116942 | 682; 694 | X | 6.96 | 7.11 | 0.15 | 6.169 | 2 | 2 |
| Full | 331 | 17537 | 813 | X | 8.26 | 8.3 | 0.04 | 5.771 | 1 | 1 |
| Full | 93; 377 | hydroxycarbamate NIST; 2813 | 894; 894 | X | 9.08 | 9.11 | 0.03 | 5.581 | 2 | 1 |
| Full | 33 | pyruvic acid | 931 | X | 9.45 | 9.47 | 0.02 | 6.121 | 1 | 1 |
| Full | 102; 215 | glycolic acid; 116942 | 955; 961 | X | 9.68 | 9.82 | 0.14 | 7.911 | 2 | 2 |
| Full | 42; 45 | phosphate; pantothenic acid | 973; 974 | X | 9.85 | 9.95 | 0.1 | 12.604 | 2 | 2 |
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| Full | 33 | pyruvic acid | 1007 | X | 10.21 | 10.23 | 0.02 | 5.733 | 1 | 1 |
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| Additive-by-Diet | 421 | 47 | 4842 | 2R | 3.76 | 3.83 | 0.07 | 5.478 | 1 | 1 |
| Dominant-by-Diet | 1; 104 | xylulose NIST; glycerol alpha phosphate | 7135; 7138 | 3L | 5.77 | 5.83 | 0.06 | 5.702 | 2 | 2 |
| Dominant-by-Diet | 1 | xylulose NIST | 7235 | 3L | 6.77 | 6.8 | 0.03 | 5.481 | 1 | 1 |
| Dominant-by-Diet | 1; 102 | xylulose NIST; glycolic acid | 10519; 10526 | 3R | 15.23 | 15.45 | 0.22 | 6.327 | 2 | 2 |
| Dominant-by-Diet | 9; 113; 135 | urea; gluconic acid; bisphosphoglycerol NIST | 1638; 1639; 1641 | X | 16.52 | 16.58 | 0.06 | 6.121 | 3 | 3 |
| Dominant-by-Diet | 9; 278 | urea; 67178 | 1850; 1859 | X | 18.61 | 18.75 | 0.14 | 7.078 | 2 | 2 |
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| Dominant-by-Diet | 9; 89 | urea; inosine 5 monophosphate | 6273; 6269 | 2R | 18.05 | 18.11 | 0.06 | 6.610 | 2 | 2 |
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| Dominant-by-Diet | 135; 215; 356; 384 | bisphosphoglycerol NIST; 116942; 5269; 1996 | 5699; 5699; 5695; 5696 | 2R | 12.31 | 12.39 | 0.08 | 6.629 | 4 | 3 |
| Dominant-by-Diet | 135; 324 | bisphosphoglycerol NIST; 18361 | 9944; 9947 | 3R | 9.54 | 9.67 | 0.13 | 6.790 | 2 | 2 |
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| Dominant-by-Diet | 146 | alpha ketoglutarate | 1632 | X | 16.46 | 16.5 | 0.04 | 5.774 | 1 | 1 |
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| Dominant-by-Diet | 408 | 479 | 7346 | 3L | 7.89 | 7.99 | 0.1 | 7.914 | 1 | 1 |
| Dominant-by-Diet | 408 | 479 | 10139 | 3R | 11.49 | 11.59 | 0.1 | 6.228 | 1 | 1 |
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| Dominant-by-Diet | 411 | 307 | 2016 | X | 20.28 | 20.32 | 0.04 | 6.401 | 1 | 1 |
| Dominant-by-Diet | 411 | 307 | 2699 | 2L | 4.81 | 4.83 | 0.02 | 6.095 | 1 | 1 |
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| Full-by-Diet | 42 | phosphate | 9669 | 3R | 6.84 | 6.86 | 0.02 | 13.375 | 1 | 1 |
| Full-by-Diet | 42 | phosphate | 10978 | 3R | 19.91 | 19.96 | 0.05 | 11.300 | 1 | 1 |
| Full-by-Diet | 43; 45; 55 | phenylalanine; pantothenic acid; N epsilon trimethyllysine | 2303; 2301; 2302 | 2L | 0.83 | 0.87 | 0.04 | 6.507 | 3 | 3 |
| Full-by-Diet | 44 | pelargonic acid | 6106 | 2R | 16.42 | 16.44 | 0.02 | 5.489 | 1 | 1 |
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| Full-by-Diet | 45; 215; 288; 293; 346 | pantothenic acid; 116942; 66287; 62409; 9489 | 1764; 1760; 1769; 1759; 1762 | X | 17.72 | 17.91 | 0.19 | 5.693 | 5 | 5 |
| Full-by-Diet | 45 | pantothenic acid | 2488 | 2L | 2.7 | 2.73 | 0.03 | 6.291 | 1 | 1 |
| Full-by-Diet | 45; 411 | pantothenic acid; 307 | 2664; 2665 | 2L | 4.43 | 4.5 | 0.07 | 9.230 | 2 | 2 |
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| Full-by-Diet | 147; 164; 250; 364; 401 | alpha aminoadipic acid; 3 aminoisobutyric acid; 104788; 4744; 1380 | 7368; 7367; 7369; 7365; 7369 | 3L | 7.94 | 8.15 | 0.21 | 6.481 | 5 | 4 |
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| Full-by-Diet | 149; 164 | alanine; 3 aminoisobutyric acid | 6268; 6266 | 2R | 18.01 | 18.06 | 0.05 | 8.285 | 2 | 2 |
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|------------|------------------------------------|-------------------------------------------------------------------------------------------------|---------|-----|--------|--------|-------|-----|------|---|---|
| Diet       | 11; 35                             | UDP N acetylglucosamine; pyrophosphate                                                         | 3191; 3190 | 2L | 9.7    | 9.75   | 0.05 | 5.894 | 2 | 2 |
| Diet       | 12                                 | UDP glucuronic acid                                                                             | 11605 | 3R | 26.17  | 26.22  | 0.05 | 5.495 | 1 | 1 |
| Diet       | 15; 45; 90; 91; 100; 102; 216; 245; 326; 401 | tocoherol gamma ; pantothenic acid; inosine; hypoxanthine; guanidinosuccinate; glycric acid; 115903; 105164; 18305; 1380 | 3228; 3235; 3226; 3237; 3236; 3236; 3230; 3236; 3238; 3238 | 2L | 10.08  | 10.22  | 0.14 | 6.880 | 10 | 7 |
| Diet       | 15; 254                            | tocoferol gamma ; 104312                                                                          | 5127; 5140 | 2R | 6.62   | 6.85   | 0.23 | 5.559 | 2 | 2 |
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### Supplemental Table 4.2 Continued

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| Diet | 18; 215; 373; 401; 408 | threitol; 116942; 3200; 1380; 479 | 7706; 7708; 7709; 7705; 7707 | 3L | 11.47 | 11.57 | 0.1 | 6.576 | 5 | 5 |
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| Diet | 20; 79; 121 | tagatose; lactic acid; ergosterol | 11371; 11374; 11375 | 3R | 23.84 | 23.92 | 0.08 | 6.475 | 3 | 3 |
| Diet | 26 | sorbitol | 371 | X | 3.84 | 3.87 | 0.03 | 5.385 | 1 | 1 |
| Diet | 29; 41 | salicylaldehyde; phosphoenolpyruvate | 4853; 4847 | 2R | 3.83 | 3.92 | 0.09 | 7.529 | 2 | 2 |
| Diet | 29; 293 | salicylaldehyde; 62409 | 9697; 9697 | 3R | 7.12 | 7.14 | 0.02 | 7.623 | 2 | 1 |
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| Diet | nicotinic acid; cytidine 5 monophosphate NIST; alpha aminoacidic acid; 113510; 88583; 1771; 307 | 10891; 10891; 10892; 10897; 10898; 10897; 10890 | 3R | 19.05 | 19.15 | 0.1 | 6.271 | 7 | 5 |
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| Diet | nicotinamide; 116942; 111255 | 7799; 7797; 7798 | 3L | 12.39 | 12.45 | 0.06 | 7.434 | 3 | 3 |
| Diet | myo inositol | 365 | X | 3.74 | 3.81 | 0.07 | 12.858 | 1 | 1 |
| Diet | myo inositol; 17233 | 437; 438 | X | 4.51 | 4.54 | 0.03 | 6.503 | 2 | 2 |
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| 91; 180; 413  | hypoxanthine; 117820; 257 | 7145; 7145; 7144 | 3L | 5.87 | 5.9 | 0.03 | 6.642 | 3 | 2 |
| 223           | hypoxanthine; gluconic acid; 111670 | 7429; 7429; 7429 | 3L | 8.72 | 8.74 | 0.02 | 6.385 | 3 | 1 |
| 91; 329       | hypoxanthine; 18082 | 7839; 7839 | 3L | 12.81 | 12.85 | 0.04 | 5.693 | 2 | 1 |
| 91; 164       | hypoxanthine; 3 aminoisobutyric acid | 8540; 8540 | 3L | 19.83 | 19.92 | 0.09 | 6.204 | 2 | 1 |
| 91; 373       | hypoxanthine; 3200 | 9368; 9369 | 3R | 3.81 | 3.86 | 0.05 | 8.299 | 2 | 2 |
| 91; 389; 657  | hypoxanthine; 1872; 10004; 10006; 10005 | 3R | 3.81 | 3.86 | 0.05 | 8.299 | 2 | 2 |
| 404           |              |                 |                 |                 |                 |                 |                 |                 |
| 93; 325; 411  | hydroxycarbamate NIST; 18345; 307 | 309; 309; 312 | X | 3.23 | 3.38 | 0.15 | 6.083 | 3 | 2 |
| 411           |              |                 |                 |                 |                 |                 |                 |                 |
| 93; 401       | hydroxycarbamate NIST; 1380 | 748; 747 | X | 7.6 | 7.66 | 0.06 | 9.970 | 2 | 2 |
| 889           | hydroxycarbamate NIST | 9.01 | 9.06 | 0.05 | 12.558 | 1 | 1 |
| 93; 126; 199  | hydroxycarbamate NIST; cytidine 5 monophosphate NIST; 117227 | 2567; 2576; 2571 | 2L | 3.48 | 3.66 | 0.18 | 6.415 | 3 | 3 |
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Supplemental Table 4.3: Annotation of all 422 metabolites from the Drosophila melanogaster metabolomics dataset. All unknown values are shown as “NA”. The “Metabolite Index” is the order in which the metabolites are included in the dataset. Metabolites that have a number as their BinBase name are unidentified.

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