A GENERALIZED KERNEL MACHINE APPROACH TO IDENTIFY HIGHER-ORDER COMPOSITE EFFECTS IN MULTI-VIEW DATASETS

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ABSTRACT

In recent years, comprehensive study of multi-view datasets (e.g., multi-omics and imaging scans) has been a focus and forefront in biomedical research. State-of-the-art biomedical technologies are enabling us to collect multi-view biomedical datasets for the study of complex diseases. While all the views of data tend to explore complementary information of a disease, multi-view data analysis with complex interactions is challenging for a deeper and holistic understanding of biological systems. In this paper, we propose a novel generalized kernel machine approach to identify higher-order composite effects in multi-view biomedical datasets. This generalized semi-parametric (a mixed-effect linear model) approach includes the marginal and joint Hadamard product of features from different views of data. The proposed kernel machine approach considers multi-view data as predictor variables to allow more thorough and comprehensive modeling of a complex trait. The proposed method can be applied to the study of any disease model, where multi-view datasets are available. We applied our approach to both synthesized datasets and real multi-view datasets from adolescence brain development and osteoporosis study, including an imaging scan dataset and five omics datasets. Our experiments demonstrate that the proposed method can effectively identify higher order composite effects and suggest that corresponding features (genes, region of interests, and chemical taxonomies) function in a concerted effort. We show that the proposed method is more generalizable than existing ones.

1 Introduction

Modern technology allows us to overcome the challenges of assembling a multi-view dataset with a powerful combination of flexibility and low cost. Human complex diseases are typically expressed by the aberrant interplay of multiple biological sources and environmental factors. While single biomedical data view such as genome (whole genome se-
quencing), transcriptome (RNA sequencing), epigenome (e.g., DNA methylation), proteome, metabolome, lipidome, and medical images offers an essential framework for detecting biological variants contributing to complex diseases, an in-depth understanding of biological mechanisms by examining only single data may not suffice. Most biomedical data analysis methods are applicable to single or dual-views of datasets, without making full use of multi-view datasets. In addition, multi-view biomedical datasets are often complementary to each other and correspond to different feature spaces [11, 30, 23, 34, 17]. Thus, their comprehensive and systematic analysis has the potential to uncover unknown biological mechanisms of complex diseases (Figure 1). With the advent of recent technologies that make assembling of multi-view biomedical datasets (e.g., multi-omics and imaging scans) of a complex diseases possible, development of efficient analytic frameworks for such datasets is becoming an active area of scientific inquiry [29, 55, 20, 53, 41].

For an effective diagnosis of a complex disease, different types of medical imaging techniques, including computer tomography (CT), ultrasound, functional magnetic resonance imaging (fMRI), structural MRI (sMRI), positron emission tomography (PET) scans, diffusion tensor imaging (DTI), and X-Ray are used [46, 3, 9, 16, 12].

The high demand for characterizing complex diseases in biomedical science and the available technologies justify the need for more effective biomedical data integration approaches. Linear data integration approaches including supervised, unsupervised, semi-supervised learning, multi-omics factor analysis, and highlight matrix factorization methods are used to gain a deeper, more holistic understanding of the biological mechanism for complex diseases [39, 30, 6, 36, 18]. These are widely used and validated approaches but they perform poorly when data structure is non-linear and data comes from a multi-modal distribution [19]. As a consequence, non-linear integrated approaches (e.g., kernel based machine) are an important feature in comprehensive analysis of multi-view biomedical datasets [31, 8, 26]. The positive definite kernel based machine approach can overcome the non-linearity problem as well as that of dimensionality of multi-view biomedical datasets [52, 57, 11, 2, 42]. This approach can be useful in effective integration of multi-view biomedical data.

In this study, we introduce a generalized kernel machine approach to identify higher-order composite effects (GKMAHCE) in multi-view datasets. While several kernel machine approaches have been employed to identify marginal, interaction effects of datasets with continuous data, the underlying challenge remains of how to make a generalized kernel machine based model to estimate marginal, interaction, and composite effects of multi-view dataset with categorical data, which is often the case in complex diseases [55, 56, 21, 10]. This proposed approach considers multi-view data as predictor variables to allow more thorough and comprehensive modelling of complex traits.

Here, we compared the performance of our proposed method with that of existing methods using synthesized datasets and real multi-view adolescence brain development and osteoporosis datasets, with brain imaging and five-omics data. To realize adolescence brain development, sex differences in human brain are essential to understand their anatomical foundations in the brain with three view datasets: genomic, non-genomic and fMRI datasets [40]. Osteoporosis is a bone disorder, which results from a loss of bone mineral density (BMD) [43]. For more information of these data, we refer the reader to Section 4.2. Within each dataset, this study explores novel genome, epigenome, transcriptome, and chemical mechanisms, as well as robustly and efficiently identifies corresponding factors. To validate the results, we performed Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis, the gene ontology analysis of biological process category and gene-gene interaction networks analysis. We also draw causal connections, gene-gene associations, and gene-chemical associations for both of the datasets. This paper is highly novel in the following aspects:

Figure 1: An illustration of different omics data, imaging scans, and environment factors along with their global, marginal, interaction and composite on a complex trait.
To the best of our knowledge, we address a generalized kernel machine approach to identify higher-order composite effects.

For statistical testing of the marginal, the interaction, and the composite effects, we derive the test statistics.

To show that the proposed approach is highly efficient, we experiment with synthesized datasets and three-view of brain development in adolescence and five-view of osteoporosis datasets. As far as we know, this is the first five omics integration study.

Finally, we perform a comprehensive pathway and network-based analysis for the biological validation of the selected genes.

The rest of this paper is organized as follows. In Section 2, we discuss some contemporary related work. In Section 3, we explain the proposed approach, generalized kernel machine approach to identify higher-order composite effects in multi-view datasets and test statistics for statistical testing for higher order composite effects.. In Section 4, we describe the experiments conducted on both synthesized datasets and two real datasets: imaging and genetics for adolescence brain development and multi-omics datasets of osteoporosis studies. We conclude the paper with a discussion on major findings and future research in Section 5. Detailed derivation of the proposed method along with Satterthwaite approximation to the score test and the applications to real dataset can be found in the supplementary materials.

2 Related work

Kernel based multi-view data integration approaches allow the joint analysis of multiple data types to provide a global view of the biological functions and offer insights into the nature of the interactions between the different datasets. These methods offer useful ways to learn how an extensive collection of genetic variants are associated with complex phenotypes and can be used to explore the relationship between genetic markers and a disease state [10, 37, 24].

The marginal, interaction, and composite effect identifications are becoming a common challenge to multidimensional imaging and multi-omics data analysis. Preliminary works in kernel machine methods have been boldly pursued by [28], where a single modal dataset was used to test for a genetic pathway effect. [27] also proposed a kernel machine-based method for gene-gene interactions. They treated each gene as a testing unit for gene-gene interactions. A kernel machine method was then proposed for detecting multiple factor interactions where a smoothing spline-ANOVA decomposition method was adopted [27]. However, these approaches only use single or pairwise datasets. A sequence kernel association tests (SKAT) for genome wide association studies is introduced in [21]. While SKAAT is widely used in genomics studies, it is limited to only a single omics. In addition, [14] have proposed a kernel machine method for detecting the effects of interactions between multidimensional variable sets. This is an extended model of [21] to jointly model genetic and non-genetic features and their interactions. A microbiome regression based kernel association test (MiRKA T) has been proposed by [56], which directly regresses the outcome on a single omics dataset, microbiome profiles, through the semi-parametric kernel machine regression framework.

Recently, [3] has proposed a kernel machine method for detecting higher-order interactions in three views datasets which was applied to schizophrenia with a continuous trait. Although a generalized version of such methods for more than three datasets as well as both categorical and continuous traits remains elusive, such a method for multi-view biomedical data analysis is necessary to discover new information about biological systems and complex diseases.

3 Approach

Suppose we have \( n \) independent identical distributed (IID) subjects \( y_i (i = 1, 2, \ldots, n) \) with \( q - 1 \) covariates \( X_i = [X_{i1}, X_{i2}, \ldots, X_{iq}]^T \) and \( m \)-view datasets, \( M_i^{(1)}, \ldots, M_i^{(m)} \). Assuming that \( y_i \) follows a distribution in the exponential family with density

\[
f(y_i, \theta_i, \gamma) = \exp \left\{ \frac{y_i \theta_i - c_1(\theta_i)}{\gamma/w_i} + c_2(y_i, \gamma) \right\},
\]

where \( \theta_i \) and \( \gamma \) are the location and scale parameters, \( c_1(\cdot) \) and \( c_2(\cdot) \) are known functions, and \( w_i \) is know weight, respectively. The mean and variance of \( y_i \) satisfy \( E(y_i) = \frac{\partial c_1(\theta_i)}{\partial \theta_i} = c'_1(\theta_i) \) and \( \text{Var}(y_i) = \gamma w_i = c''_1(\theta_i) \). In the following generalized semiparametric model, we associate the output \( y_i \) with covariates including intercept and \( m \)-view datasets:

\[
g(y_i) = X_i^T \beta + f(M_i^{(1)}, \ldots, M_i^{(m)}), \tag{2}
\]
We can estimate the function \( f \) where
\[
\text{(1)}
\]
According to the ANOVA decomposition, the function, \( f \) can be extended as:
\[
\text{(3)}
\]
where, \( h_{M^{(i)}}(M_i^{(f)})'s \) are the main effects of the respective dataset \((\ell : 1, 2, \cdots, m)\), \( h_{M^{(i)} \times M^{(j)}}(M_i^{(f)}, M_j^{(f)})'s \) are pairwise interactions effects, \( h_{M^{(i)} \times M^{(j)} \times M^{(k)}}(M_i^{(f)}, M_j^{(f)}, M_k^{(f)})'s \) are the interactions effects of three datasets and so on. The functional space, RKHS, decomposes as:
\[
\text{(4)}
\]
equipped with an inner product, \( \langle \cdot, \cdot \rangle \) and a norm \( \| \cdot \|_H \). This generalizes kernel regression by allowing the model to be related to the response variable via a link function including kernel regression, logistics kernel regression, and Poisson kernel regression. For the binary data, the link function \( g(p) = \logit(p) = \log \frac{p}{1-p} \) provides the logistic kernel regression; for the count data, \( g(p) = \log(p) \) provides the Poisson kernel regression; for Gaussian data, \( g(p) = p \) gives classical kernel regression. The main aspect of this paper is applying this to five views: genome, epigenome, transcriptome, metabolome, and lipidome along with Low BMD and High BMD information of the subject. To do this, we associate the clinical covariates (e.g., age, weight, height) with five views including genome, epigenome, transcriptome, metabolome, and lipidome.

Let \( X_i \), denoted the \((q-1) \) covariates, where \( X_{ij}, j = 1, 2, \cdots (q-1) \) is a measure of the \( i \)-th subject.

Let \( M_i^{(1)} = [M_{i1}^{(1)}, \cdots, M_{is}^{(1)}], M_i^{(2)} = [M_{i1}^{(2)}, \cdots, M_{id}^{(2)}], M_i^{(3)} = [M_{i1}^{(3)}, \cdots, M_{id}^{(3)}], M_i^{(4)} = [M_{i1}^{(4)}, \cdots, M_{ic}^{(4)}], \) and \( M_i^{(5)} = [M_{i1}^{(5)}, \cdots, M_{id}^{(5)}] \), are a gene with \( s \) SNP markers, a gene with \( d \) methylation profiles, a gene with RNA-Seq, a chemical taxonomy class \( c \) metabolite profiles, and a chemical class with \( l \) lipid profiles of the \( i \)-th subject, respectively. Under this setting, Eq. (2), Eq. (3) and Eq. (4) becomes:
\[
\logit(p_i) = X_i^T \beta + f(M_i^{(1)}, M_i^{(2)}, M_i^{(3)}, M_i^{(4)}, M_i^{(5)}),
\]
where \( \logit(p_i) = \Pr (y_i = 1|X_i, M_i^{(1)}, M_i^{(2)}, M_i^{(3)}, M_i^{(4)}, M_i^{(5)}) \).

### 3.1 Model estimation

We can estimate the function \( f \in H \) by minimizing the penalized loss function of Eq. (5) as:
\[
\mathcal{L}(y, \beta, f) = \frac{1}{n} \sum_{i=1}^{n} L (y_i, X_i^T \beta + f) + \frac{\lambda}{2} J(f)
\]

| Error family | Link | Inverse of link | Use |
|--------------|------|----------------|-----|
| Gaussian     | Identity, \( g(y) = y \) | \( y = q^{-1}(y) \) | Normally distributed set of data, \([-\infty, \infty)\) |
| Poisson      | Log, \( g(y) = \log(y) \) | Exponential, \( \exp(y) \) | Equidispersed count set of data |
| Binomial     | Logit, \( g(y) = \log\left(\frac{y}{1-y}\right) \) | \( \frac{1 + \exp(y)}{1 + \exp(y)} \) | Binary set of data, \( 0/1 \) |
| Gamma        | Inverse gamma | \( \frac{1}{y} \) | Positive continuous set of data, \((0, \infty)\) |
where $L$ is a loss function, $F = f(M_1, M_2, M_3, M_4, M_5)$ $J(\cdot) = \|\cdot\|^2_H$ is a roughness penalty with tuning parameter $\lambda$. By considering the negative log-likelihood of the binomial distribution,

$$L = \ln(1 + e^{-y_i(X_i^T \beta + F)}),$$

the problem becomes a kernel logistic regression problem:

$$\mathcal{L}(y, \beta, f) = \frac{1}{n} \sum_{i=1}^{n} \ln \left(1 + e^{-y_i(X_i^T \beta + F)}\right) + \frac{\lambda}{2} J(f) \tag{7}$$

It is known that the complete function space of Eq. (5), $\mathcal{H}$, has the orthogonal decomposition. Hence the function $J(\cdot)$ can be decomposed accordingly (see the supplementary material for details).

It is convenient and mathematically friendly to minimize numerically. Let $p_i$ be the probability of the $i^{th}$ observation and $p = [p_1, p_2, p_3, \ldots, p_n]^T$

Following many in the literature, we have a liner mixed effects model for $p$ such that

$$\logit(p) = X\beta + h_{M(1)} + h_{M(2)} + h_{M(3)}$$

$$+ h_{M(1) \times M(2)} + h_{M(1) \times M(3)} + h_{M(1) \times M(4)}$$

$$+ h_{M(2) \times M(3)} + h_{M(2) \times M(4)} + h_{M(3) \times M(4)} + \cdots$$

$$+ h_{M(1) \times M(2) \times M(3) \times M(4) \times M(5)}, \tag{8}$$

where $\beta$ is a coefficient vector of fixed effects, $h_{M(1)}$, $h_{M(2)}$, $h_{M(3)}$, $h_{M(1) \times M(2)}$, $h_{M(1) \times M(3)}$, $h_{M(2) \times M(3)}$, and $h_{M(1) \times M(2) \times M(3) \times M(4) \times M(5)}$ are independent random effects with normal distributions. The relationship of Eq. (6) and Eq. (8) confirm that all of the effects obtained by optimizing the loss function in Eq. (6), are the equal to the best linear unbiased predictors (BLUPs) of the linear mixed effects model in Eq. (8). This relationship makes a accessibility for testing the variance component instead of testing the nonparametric function in null hypothesis, which we can estimate using the restricted maximum likelihood (ReML) approach (see the supplementary material for details).

### 3.2 Statistical testing

In this section, we address the test statistic of the overall effect, marginal effects, different interaction effects, and different composite effects.

#### 3.2.1 Overall hypothesis testing

According to our model, the testing overall effect is

$$H_0 : h_{M(1)} = \cdots = h_{M(1) \times M(2)} = \cdots = 0$$

$$= h_{M(1) \times M(2) \times M(3) \times M(4) \times M(5)} = 0$$

is equivalent to test the variance components in Eq. (8).

$$H_0 : \tau^{(1)} = \tau^{(2)} = \tau^{(3)} = \tau^{(1 \times 2)} = \tau^{(1 \times 3)} = \tau^{2 \times 3} = \cdots = \tau^{(1 \times 2 \times 3 \times 4 \times 5)} = 0.$$ 

It is known that kernel matrices are not block-diagonal and the parameter in variance component analysis are placed on the edge of the parameter space when the null hypothesis is true. While the asymptotic distribution of a likelihood ratio test (LRT) statistic is neither a chi-square distribution nor a mixture chi-square distribution under the null hypothesis, we can use a score test statistic on the restricted likelihood [3, 28]. We derive score test statistic for a generalized kernel machine approach in multi-view datasets, Eq. (5). Assuming that $\Theta(\theta) = \sigma^2 I + \sum_{i=1}^{5} \tau^{(i)} K(i) + \sum_{i=1}^{5} \sum_{j=1}^{5} \tau^{(i \times j)} K(i \times j) + \cdots + \tau^{1 \times 2 \times 3 \times 4 \times 5} K(1 \times 2 \times 3 \times 4 \times 5)$, where $\theta = (\sigma^2, \tau^{(1)}, \tau^{(2)}, \tau^{(3)}, \tau^{1 \times 2}, \tau^{2 \times 3}, \cdots, \tau^{1 \times 2 \times 3 \times 4 \times 5})$. We can write the restricted log-likelihood function of Eq. (8) as follows

$$\ell_R(\theta) = -\frac{1}{2} ln(\|\Theta(\theta)\|) - \frac{1}{2} ln(|1^T \Theta^{-1}(\theta) 1^T|)$$

$$- \frac{1}{2} (y - X \beta)^T \Theta^{-1}(\theta) 1^T (y - X \beta) \tag{9}$$
Using the partial derivative of Eq. (9) with respect to each variance component. We derive the estimate of the variance components and the score test statistic which is defined as

\[ S(\hat{\sigma}_0^2) = \frac{1}{2\sigma_0^2}(y - X\hat{\beta})^T K(y - X\hat{\beta}) \]

(10)

where \( K = K^{(1)} + \cdots + K^{(1\times2)} + \cdots + K^{(1\times3\times4\times5)} \) and \( \hat{\beta} \) is the maximum likelihood estimator (MLE) of the logistic regression coefficient under the null model \( y = X\beta + \epsilon_0 \). \( \sigma_0^2 \) is the variance of \( \epsilon_0 \). \( S(\sigma_0^2) \) is quadratic function of the variable \( y \), which follows a weighted mixture of the chi-square distribution under the null hypothesis. By the Satterthwaite method, we can approximate the distribution of \( S(\sigma_0^2) \) to a scaled chi-square distribution, \( (S(\sigma_0^2) \sim \gamma \chi_0^2) \). To estimate the the scale parameter \( \gamma \) and the degrees of freedom \( \nu \) we can use the method of moments on the mean \( (\gamma \nu) \) and variance \( (2\gamma^2 \nu) \) of the test statistic and we obtain \( \hat{\gamma} = \frac{\text{Var}[S(\hat{\sigma}_0^2)]}{2E[S(\hat{\sigma}_0^2)]} \) and \( \hat{\nu} = \frac{2E[S(\hat{\sigma}_0^2)^2]}{\text{Var}[S(\hat{\sigma}_0^2)]} \). Finally, to get the \( p- \) value of an experimental score statistic \( S(\hat{\sigma}_0^2) \) we use the scaled chi-square distribution \( \hat{\gamma} \chi_\nu^2 \).

3.2.2 Testing marginal effects

By using the respective kernel matrix, we can test the marginal effect for each view data. We known that the testing marginal effect

\[ H_0 : h_{M(\ell)} = 0, \ell = 1, 2, 3, 4, 5. \]

is equivalent to test the variance components in Eq.(8).

\[ H_0 : \tau^{(\ell)} = 0. \]

The test statistic is

\[ S(\tau^{(\ell)}) = (y - X\hat{\beta})^T K^{(\ell)}(y - X\hat{\beta}) \]

\( \ell = 1, 2, 3, 4, 5 \)

This is same as the sequence kernel association test (SKAT) [51].

3.2.3 Testing interaction effect

By considering no marginal effects, i.e., \( \tau^{(\ell)} = 0, \ell = 1, \cdots, 5 \), we can also test the interaction effects. We know that the testing interaction effect

\[ H_0 : h_{M(\ell \times \ell)} = 0, \ell < \xi = 1, 2, 3, 4, 5 \]

is equivalent to test the variance components in Eq.(8).

\[ H_0 : \tau^{(\ell \times \ell)} = 0. \]

The test statistic is

\[ S(\tau^{(\ell \times \ell)}) = (y - X\hat{\beta})^T K^{(\ell \times \ell)}(y - X\hat{\beta}) \]

\( \ell < \xi = 1, 2, 3, 4, 5 \)

Also by considering no marginal effects, i.e., \( \tau^{(\ell)} = 0, \ell = 1, \cdots, 5 \), and all second order interactions are zero \( \tau^{(\ell \times \ell)} = 0 \), we can also test the 3rd order interaction effects.

\[ H_0 : \tau^{(\ell \times \ell \times \ell)} = 0. \]

The 3rd order test statistic is

\[ S(\tau^{(\ell \times \ell \times \ell)}) = (y - X\hat{\beta})^T K^{(\ell \times \ell \times \ell)}(y - X\hat{\beta}) \]

\( \ell < \xi < \zeta = 1, 2, 3, 4, 5 \)

and so on.
3.2.4 Testing composite effects

If lower order effects are statistically significant, we want to test higher order effects is called composite hypothesis testing. To test the 3rd order interaction effect, we mansion that testing the null hypothesis $H_0$:

$$h_{M^{(1)} \times M^{(2)} \times M^{(3)} \times M^{(4)} \times M^{(5)}}(\cdot) = 0$$

is equivalent to testing the variance component: $H_0 : \tau^1 \times 2 \times 3 \times 4 \times 5 = 0$. Let

$$\Sigma = \sigma^2 I + \tau^{(1)} K^{(1)} + \cdots + \tau^{1 \times 2} K^{(1 \times 2)} + \cdots + \tau^{2 \times 3 \times 4 \times 5} K^{(2 \times 3 \times 4 \times 5)}$$

and all $\tau$, and $\sigma^2$ are model parameters under the null model. We formulate a test statistic

$$S_t(\tilde{\theta}) = \frac{1}{2\sigma^2} y^T B_t K^{(1 \times 2 \times 3 \times 4 \times 5)} B_t y,$$

where $\tilde{\theta} = (\sigma^2, \tau^{(1)}, \tau^{(2)}, \tau^{(3)}, \tau^{(1 \times 2)}, \tau^{(2 \times 3)})$, and $B_t = \Sigma^{-1} - \Sigma^{-1} X (X^T \Sigma^{-1} X)^{-1} X^T \Sigma^{-1}$ is the projection matrix under the null hypothesis.

Similar to the overall effect test, we can use the Satterthwaite method to approximated the distribution of higher order interaction test statistic $S_t(\tilde{\theta})$ by a scaled chi-square distribution with scaled $\gamma_t$ and degree of freedom $\nu_t$ i.e.,

$$S(\tilde{\theta}) \sim \gamma_t \chi^2_{\nu_t}.$$  

The scaled parameter and degree of freedom are estimated by MOM, $\hat{\gamma}_t = \frac{\text{Var}[S_t(\tilde{\theta})]}{2\text{E}[S_t(\tilde{\theta})]}$ and $\hat{\nu}_t = \frac{2\text{E}[S_t(\tilde{\theta})]}{\text{Var}[S_t(\tilde{\theta})]}$ receptively. In practices, the unknown model parameters are estimated by their respective ReML estimates under the null hypothesis. Lastly, the $p-$ value of an observed higher order interaction effect test score statistic $S_t(\hat{\theta})$ is obtained using the scaled chi-square distribution $\gamma_t \chi^2_{\hat{\nu}_t}$, and so on.

3.2.5 Kernel machine based model selection

The result of kernel-based machine learning approaches is highly influenced by the kernel and its parameters. The model selection with a suitable kernel is essential in machine learning. As a result, machine learning approaches suffer from weak selection of a suitable model. Suppose $k : \mathcal{X} \times \mathcal{X} \rightarrow \mathbb{R}$ is a positive definite kernel. A linear positive definite kernel, $k(X_i, X_j) = X_i^T X_j$, where $X, X \in \mathcal{X}$, on $\mathbb{R}$ can define the similarity measure in the Euclidean space. This linear kernel suffers from more complexity in the function space for high-dimensional datasets. Instead of linear kernel, we can use a polynomial kernel to make it possible to use higher order correlations among data points. A polynomial kernel, $k(X_i, X_j) = (X_i^T X_j + c)^d$, ($c \geq 0, d \in \mathbb{N}$) has two free parameters: $c$ is a tradeoff between higher order and lower order in the polynomial and $d$ is the degree of the polynomial. The dependency measure depends on the finite bounded degree. Another limitation of linear and polynomial kernel is boundedness, i.e., both kernels are unbounded.

From a finite dimensional space the Gaussian kernel can map the input space (data space) into an infinite dimensional space [42] and is defined as:

$$k(X_i, X_j) = e^{-\frac{1}{2\sigma^2} ||X_i - X_j||^2}, \sigma > 0.$$

It has a free parameter to select but consist of numerous theoretical properties including boundedness, consistence, universality, robustness, and so on [45]. To fix the free parameter, we can use the median of the pairwise distance [13, 44].

For a multi-omics study, to captures the pairwise similarity across a number of SNPs in each gene we can use a identity-by-state (IBS) kernel (nonparametric function of the genotypes) [25]:

$$k(M_i, M_j) = 1 - \frac{1}{2s} \sum_{b=1}^{s} |M_{ib} - M_{jb}|,$$

where $s$ is the number of SNP markers of the corresponding gene. It is assumption free on the type of genetic interactions. Hence, it can capture any genetic effects on the phenotype. In this paper, we used the IBS for the genetic dataset and for all other datasets, respectively.

4 Experiments

We conducted experiments on both the Monte Carlo simulation and two real multi-view datasets: an imaging and genome datasets from the adolescence brain development and five omics datasets from osteoporosis studies, respectively. The goal is to select a feature based on significant composite effects among the datasets. We considered the Gaussian kernel (the median of the pairwise distance as the bandwidth) For all datasets but the genetic dataset. For
We compare our simulation and real data results with three other methods: principal component SKAT, partial principal component regression (pPCAR), and full principal component regression (fPCAR) as logistic regression setting. The SKAT approach is a flexible and computational method in GWAS [51, 21]. To identify an interaction effect of two genes, a principal component analysis based approach has been proposed by [27]. [3] has been considered each method as a simple regression setting. Here, we switched each method as a logistic regression setting.

4.1 Simulation studies

To evaluate the performance of the proposed method, we do simulation studies. To that end, we use the following model to generate synthesized qualitative phenotype:

\[ y_i = \text{logit} |X_i^T \beta + \sum_{\ell=1}^{5} \alpha_1 h_M(\ell) (M_i^{(\ell)}) + \sum_{\ell<\xi} \alpha_2 h_M(\ell,\xi) (M_i^{(\ell)}, M_i^{(\xi)}) + \sum_{\ell<\xi<\zeta} \alpha_3 h_M(\ell,\xi,\zeta) (M_i^{(\ell)}, M_i^{(\xi)}, M_i^{(\zeta)}) + \sum_{\ell<\xi<\zeta<\tau} \alpha h_M(\ell,\xi,\zeta,\tau) | \]

where \( X_i \) is a vector of covariates (height and weight) with an intercept of \( i \)-th subject \((i = 1, 2, \ldots, n)\) and \( \beta \) is a coefficient vector, the random error, \( \epsilon_i \), follows the Gaussian distribution with zero mean and unit variance and \( \sigma \) is the standard deviation of the error and is fixed to \( 10^{-2} \). Here \( M_i \)'s represent five different datasets. Each function \( h_M(\ell) \)'s is defined as in different non-linear form.

In this setting, we simulated data under different values of parameters \((\alpha_1, \alpha_2, \alpha_3, \alpha_4, \alpha_5)\) to evaluate the performance of the test. For example, \( \alpha_1 = \alpha_2 = \alpha_3 = 0 = \alpha_4 = \alpha_5 = 0 \) means all effects have vanished and we can examine the false positive rate for the score test under the overall effect. Similarly, we take into account the main effects (2nd order interaction effects) but no higher order interaction effects to evaluate the power of the score test. To get consist results, we performed 1000 simulations for each setting.

The simulation results of different methods can be found in Table 2. In this table, we report the power of that higher-order composite score test in different parameter settings. Overall, we made two observations. First, we noticed that the false positive rate of the test for higher-order composite effects score test was controlled by fixing the nominal \( p \)-value threshold to 0.05. All four methods have the same observations for the false positive rate. Second, when considering the power analysis \((\alpha_5 \geq 0)\), we observed that the proposed method performs better than other methods and its power exceeds 0.80 (Table 2). On the other hand we observed that the state-of-the-art methods (pPCAR, fPCAR and SKAT) can significantly overstate the false positive rates and result in significant loss of statistical power.

We also plot several visualization of the ROC with all interrelated parameters \((\alpha_2 = \alpha_3 = \alpha_4 = \alpha_5)\) values are random but the linear parameter is fixed to \( \alpha_1 = 1 \). We allocate each number with probability 0.5. A random number is uniformly distributed either in a range or at 0. In Figure 2 we look into the results from the receiver operating characteristic (ROC) with three sample sizes, \( n \in \{100, 500, 1000\} \). The sensitivity is plotted against (1-specificity) for each \( p \)-value in the range of 0 – 1 with a step size 0.0001. The power gain of the proposed method relative to the alternative ones is evident in all situations.

4.2 Real data analysis

We apply the proposed method to two real multi-view datasets including an fMRI imaging dataset and five omics datasets from the adolescence brain development and osteoporosis studies, respectively.

4.2.1 Application to adolescence brain development

The Philadelphia Neurodevelopmental Cohort (PNC) is a research initiative that focuses on characterizing brain and behavior interaction with genetics. Sex differences in human brain are essential to understand their anatomical foundations in the brain [40, 49]. Our goal here is to select features using the test composite effect on the sex differences in cognition in youth. To that end we consider three view datasets: genomic, non-genomic and fMRI imaging datasets. Table 3 presents the configuration of the three datasets along with phenotype. The gene consists of genetic features (SNPs); the non-genomic data consists of 116 clinical measurements; and the ROI consists of imaging features (voxels). We consider each gene, all non-genomic data and each ROI as a unique testing unit. To apply the proposed
Table 2: The power of higher-order composite score test of the proposed method (GJNAGCE), and state-of-the-art methods using dimension reduction regression (e.g., pPCAR, fPCAR) and sequence kernel association test (SKAT)

| Parameters | GKMAHCE | Simulation - 1 State-of-the-art methods |
|------------|---------|----------------------------------------|
| \((a_1, a_2, a_3, a_4, a_5)\) | pPCAR | fPCAR | SKAT |
| (0.1, 0, 0, 0, 0) | 0.059 | 0.048 | 0.0500 | 0.043 |
| (0, 0, 0, 0, 0.1) | 0.841 | 0.044 | 0.053 | 0.042 |
| (0, 0, 0, 0.5) | 0.849 | 0.043 | 0.052 | 0.043 |
| (0, 0, 0.1) | 0.828 | 0.047 | 0.052 | 0.045 |
| (1, 1, 1, 0.1) | 0.840 | 0.044 | 0.048 | 0.042 |
| (1, 1, 1, 0.5) | 0.836 | 0.049 | 0.048 | 0.043 |
| (1, 1, 1, 1) | 0.834 | 0.050 | 0.050 | 0.044 |

Figure 2: The Receiver Operating Characteristics of the kernel methods and relevant ones for higher-order composite effects detection with three sample sizes, \(n \in \{100, 500, 1000\}\) for all interrelated parameters \((a_2 = a_3 = a_4 = a_5)\) values are random but the linear parameter is fixed to \(a_1 = 1\).

method, first we selected 231 most significant genes out of 13,150 genes using the SKAT approach and 241 ROIs out of 264 (since 23 ROIs contain missing values). In total, we get 55,671 (231 \times 1 \times 241) triplets to test. The overall test gives us 3000 significant triplets \((p < 0.05)\) out of 55,671. In Figure 3 we visualize the plot of \(-\log(10(p))\) for 3000 triplets. The vertical solid, doted and double doted lines correspond to the p-values of 0.05, 0.01, and 0.001, respectively. At p-values of 0.05 and 0.001 we detected 33 and 14 significant genes, as well as 19 and 12 significant ROIs, respectively.

Table 3: The configuration of the three data views of adolescence brain development

| Feature | Genomic SNP | Non-genomic Clinical measurement | Imaging Voxel |
|---------|-------------|----------------------------------|---------------|
| Subject | 95639       | 116                              | 921429        |
| Gene    | 13150       | ROI                              | 264           |
| common  | 863         | 8719                             | 897           |
| Covariate | Age     | Gender                           |               |
| Phenotype | 421 male and 377 female |                     |               |
Table 4 presents the ReML estimates of all parameters, $\sigma^2$, $\tau^{(1)}$, $\tau^{(2)}$, $\tau^{(3)}$, $\tau^{(1 \times 2)}$, $\tau^{(1 \times 3)}$, $\tau^{(2 \times 3)}$, and $\tau^{(1 \times 2 \times 3)}$ and the $p$-values for both the proposed and SKAT methods for each of the 10 triplets. By the proposed method, these 10 triplets were identified to have significant interactions at a level of $p \leq 1.0 \times 10^{-7}$. At this $p$-value, we observe 5 unique genes (RPA3OS, ESR1, WWOX, RG57, PALLD) and 6 ROIs (CFL.L: Left cerebrum frontal lobe; CSL.R: Right cerebrum sub lobar; CCL.R: Right cerebrum limbic lobe; CSS.R: Right cerebrum cub-lobar; CFL.R: Right cerebrum frontal lobe), that may have significant effects of sex on adolescence brain development [5][3].

To test whether genes interact with each other, we constructed a gene-gene interaction network analysis using STRING which imports gene/protein association knowledge from databases on both physical interactions and curated biological pathways [4]. In STRING (e.g. STRING 11.0), the simple interaction unit is the functional relationship between two genes. This relationship can play a role to a common biological purpose. Figure 4 illustrates the gene-gene network based on the protein interactions with the selected 14 genes (including 7 individual selected genes). In this figure, the color saturation of the edges represents the confidence score of a functional association. Further network analysis shows that the number of nodes, number of edges, expected number of edges, average node degree, clustering coefficient, $p$-values are 119, 1478, 710, 24, 0.654 for $p \leq 1.0 \times 10^{-10}$, respectively. This analysis confirmed that the selected genes had significantly more interactions than expected and indicates that these genes may function in a concerted manner.

For investigating classification accuracy of the proposed method, the genome, non-genome, fMRI imaging datasets and only selected features via the proposed method are used to classify the sex-related brain differences followed by the three classifiers: the K-nearest neighbors algorithm (KNN) and the support vector machine (SVM) (the linear kernel and the Gaussian kernel). For the proposed approach, we considered triplets that have significant effects on the gender: 14 genes and 12 ROIs only (from Table 4). The classifier is used to distinguish the adolescence brain development between the female and the male. Table 5 presents the train classification error with different datasets and the selected features only. These results demonstrated that the proposed method is a better tool for feature selection.
Figure 4: Network analysis of 7 individual (for example) selected genes ((a), (b), (c), (d), (e), (f), and (g)) and all 14 selected genes with the proposed methods: the network has significantly more interactions than expected. The color saturation of the edges represents the confidence score of a functional association. The colored nodes, white nodes, empty nodes, and filled nodes are noted for query proteins and the first shell of interactors, second shell of interactors, proteins of unknown 3D structure, and some 3D structure is known or predicted, respectively.

Table 5: The training classification error of discriminating low BMD subjects from high BMD with the K-nearest neighbors (K-NN) algorithm and the support vector machine (linear kernel and Gaussian kernel)

| Dataset             | K-NN algorithm | Linear kernel | Gaussian kernel |
|---------------------|----------------|---------------|-----------------|
| Genome              | 23.06          | 0.02          | 0.03            |
| Imaging             | 21.06          | 0.05          | 0.10            |
| Non-genome          | 23.18          | 0.02          | 0.03            |
| Only selected features | 21.05         | 0.02          | 0.07            |
Table 6: The configuration of the five data views of the osteoporosis study (CT: chemical taxonomy)

| Feature  | SNP  | Methylation | RNA-sequencing | Metabolome profiling | Lipidome profiling |
|----------|------|-------------|----------------|----------------------|-------------------|
| Genome   | 3997535 | 46690       | 56             | 27                   | 7                |
| Epigenome| 25442 | 4676        | 22682          |                      |                  |
| Transcriptome| 129 | 128        | 128            |                      |                  |
| Subject  | 108  |             |                |                      |                  |
| Covariate| Age, Height and Weight |
| Phenotype| Bone mineral density (BMD) |

Figure 5: The Venn diagram of the number of selected genes for CCOut, LCCAOut, KCCAOut and LIMM methods with (a) the genome data; (b) the epigenome data and (c) the transcriptome data.

4.2.2 Application to osteoporosis study

Osteoporosis is a bone disorder which is largely attributable to the increased bone resorption and/or decreased bone formation by osteoclasts and osteoblasts, respectively. We apply the proposed method to a multi-omics datasets from an osteoporosis study [54, 32, 4]. This dataset included genome, epigenome, transcriptome, metabolome, and the lipidome data from 57 Caucasian females with high BMD and 51 with low BMD. Table 6 presents the configuration of the five datasets along with phenotype. The original genomic data consists of 3,997,535 SNPs which annotated to 25,442 genes. The epigenome data consists of 46,690 methylations which annotated to 4,676 genes. This methylation analysis focus on gene level/sliding windows. The transcriptome data has 22,682 genes expression profiles. The metabolome data contains of 28 chemical taxonomies including 291 metabolic profiles. The lipidome data covers 7 chemical taxonomies including 56 lipid profiles.

To apply the proposed method, we considered each gene of the genome, epigenome, and transcriptome data and each chemical taxonomy of the metabolome and lipidome data as a single testing unit. To make it feasible, we reduced the dimensionality of the genome, epigenome and transcriptome data using four approaches including the kernel based gene shaving approach [4]. Figure 5 presents the Venn-diagram of the t-test, canonical correlation analysis based gene shaving (CCAOut), kernel canonical correlation analysis based gene shaving (KCCAOut) and Linear Models for Microarray based gene shaving (LIMMA) methods for three datasets: (a) genome data (b) epigenome data, and (c) transcriptome data. From this figure, we observed that the number of disjointedly selected genes from CCOut, LCCAOut, KCCAOut and LIMMA methods for the genome data are 1,326, 406, 442, 19, 796; for the epigenome data are 193, 281, 287, 4645; and for the transcriptome data are 279, 2, 416, 2, 529, 22, 027, respectively. All methods selected 20, 53 and 61 common genes for the genome, epigenome and transcriptome data, respectively. In addition, we have 28 and 7 chemical taxonomies of metabolome and lipidome dataset, respectively. In total, we get 12220740
Figure 6: The plot of $-\log_{10}(p_{adj})$ with 281,993 quinlets (overall significance in the mode out of 12,2207,40).

Table 7: The number of significant genes (genome, epigenome and transcriptome datasets) and chemical taxonomy (Mmetabolome and Lipidomoe datasets) of the proposed method using adjusted p-values

| $p_{adj}$-values | Genes | Epigenome | Transcriptome | Chemical taxonomy |
|-------------------|-------|-----------|---------------|-------------------|
| $10^{-2}$         | 19    | 51        | 61            | Metabolome 27, Lipidome 7 |
| $10^{-3}$         | 19    | 46        | 56            | Metabolome 26, Lipidome 7 |
| $10^{-4}$         | 19    | 40        | 46            | Metabolome 24, Lipidome 7 |
| $10^{-5}$         | 18    | 28        | 35            | Metabolome 22, Lipidome 7 |
| $10^{-10}$        | 17    | 35        | 32            | Metabolome 21, Lipidome 7 |

(201 $\times$ 53 $\times$ 61 $\times$ 27 $\times$ 7) quinlets to test. Figure 6 shows the plot of $-\log_{10}(p)$ for 12220740 quinlets. The overall test gives us 281993 significant quinlets ($p \leq 0.05$). The vertical solid, doted and double doted lines correspond to the p-values of 0.05, 0.01, and 0.001, respectively. Table 7 presents the number of significant genes and chemical taxonomies using different adjusted p-values of the proposed method. A list of genes (genome, epigenome and transcriptome data) and list of chemical taxonomies (metabolome and lipidome data) are tabulated in Table 8.

We also extracted the gene-gene interaction networks using STRING: functional protein association networks. Figure S1, (in the Supplementary material) shows the gene-gene networks based on the protein interactions among the selected (8118 + 28 + 35) genes by the proposed method of the genome, epigenome, and transcriptome datasets. In this figure, the color saturation of the edges represents the confidence score of a functional association. In addition, network analysis demonstrates that the number of nodes, number of edges, expected number of edges, average node degree, clustering coefficient, PPI enrichment p-values are 93, 155, 121, 3.33, 0.39 and 0.00188, respectively. This network analysis confirms that the selected genes have significantly more interactions than expected. It also indicates that the selected genes may function collaboratively.

To confirm the biological roles of the most prominent identified features, we accessed the biomedical and genomic information using the national center for biotechnology information (NCBI, https://www.ncbi.nlm.nih.gov/) tools and the Human gene database (GeneCards: https://www.genecards.org/) [13]. NCBI offers a wide variety of data analysis tools for manipulating, aligning, visualizing, and evaluating biological data. On the other hand, the primary goal of the GeneCards database is the unequivocal identification of enhancer elements and uncovering their connections to genes for understanding gene regulation and the molecular pathways. Recent studies have shown that the bone marrow, kidney, testis, and thyroid diseases have widespread systemic manifestations including their effects on developing osteoporosis. [38, 22, 48, 50]. So, we hypothesized that the selected genes, with the proposed method, would provide more ubiquitous expression (reads per kilo base per million mapped reads (RPKM)) of bone marrow, kidney, testis, and thyroid tissue samples. To that end, we used NCBI’s tools. Figure 7 illustrates the expression patterns of three selected genes (ABL1, GCNT7, ZNF144) across 27 different tissues from 95 human individuals. These results show
Table 8: The selected significant genes (genome, epigenome, and transcriptome datasets) and chemical taxonomies (metabolome and lipidome datasets) using the proposed at $p \leq 10^{-05}$

| Genome | ABCB8 | ACTBP2 | AP005122 | DOCK10 | EXOSC3P2 | FG5 | GPLD1 | LINC00461 | CHGB | NIPA2P5 | NIPAL1 |
|--------|-------|--------|----------|--------|----------|-----|--------|-----------|-------|---------|---------|
| Epigenome | AICF | ALLC | APIG1 | ATP2B2 | BACH2 | CA13 | CDCC11 | DNE8 | DYM | FASTK2 | GCNT7 |
|          | HGST | INPSF | KIAA1365 | KCND1 | NGT1 | LGTN | LMB1 | LOC28371 | MAPKAPK2 | MAST4 | MDC1 |
|          | NOCL | NNL | SLC40A3 | TRAP | UBE2D2 | VPS26A | ZNF700 |       |       |         |        |
| Transcription | ABL1 | ACER3 | ADCY3 | ALOX12B | AUNP | BND | BTNL3 | CDKN1A | Cl001105 | CROCC | CSMD3 |
|          | CTSLP2 | GALT | HEDC | HLA-DRA | HM3 | HMDOXA | IGHHBP2 | SERPINB6 | SLC3A9 | TECTA | TGFB3L |
|          | NEURL4 | NIN | NPHS1 | PRF5958 | RALBP1 | RNFL1 |       |       |       |       |        |
| Metabolome | Azoles | BENZ | BSD | CAD | CBS | CXAD | DIA | FAE | FAL | HAD | HDMC |
|          | IDA | LAC | PHE | PLA | PLL | PRNS | PRVD | SPHG | STSD | TTRD |       |
| Lipidome | AA | DGLA | DHA | EA | EPA | ISTD | LA |       |       |       |        |

Table 9: The GeneHancer identifier, GeneHancer score, gene association score, total score, major-related diseases, and PubMed database (PMID) of 6 selected genes

| Gene ID | GeneHancer ID | GeneHancer Score | Association Score | Total Score | Source (Total No.) | Related Disease |
|---------|---------------|-----------------|------------------|------------|-------------------|-----------------|
| ABL1    | GBH09130833   | 2.3             | 541.3            | 1214.2     | [81]: 1; 11202148; 3010448; 83066020; 1249448; 25345799 | Bone marrow; Brain; Endometrium; Lymphnode |
| APIG1   | GBH18071807   | 2.1             | 529.0            | 1096.7     | [103]: 12773481; 11782361; 24000625; 12807982; 25823584 | Bone marrow; Kidney; Brain; Testis; Thyroid |
| GCNT7   | GBH20056524   | 0.4             | 500.1            | 221.23     | (2): 25902600; 25100324 | Bone marrow; thyroid |
| PANK1   | GBH20056524   | 2.2             | 506.1            | 1126.6     | [2]: 12319294; 11809413; 14520902; 20838480; 23343702 | Liver; Kidney; Bone marrow; Thyroid |
| ZNF35   | GBH03044484   | 1.0             | 500.7            | 915.0      | [17]: 2100922; 5477855; 3308682; 1372646; 20180568 | Testes; Thyroid; Urinary bladder; Endometrium; Brain; Bone marrow |
| ZNF114  | GBH01351024   | 2.4             | 518.1            | 1242.1     | [5]: 9467795; 30860597; 31054888; 31054888; 25413566 | Thyroid; Brain; Placenta |

Table 8 indicates that these genes have remarkably high RPKM value for bone marrow, kidney, testis, and thyroid tissue samples. These tissue related diseases including their effects may play a role in the development of osteoporosis. To provide insight into the gene regulatory elements (promoters and enhancers) for 6 selected genes (ABL1, APIG1, GCNT7, PANK1, ZNF35, ZNF114), we used the GeneCards database. Table 9 presents GeneHancer identifier, GeneHancer score, gene association score, total score, and literature review in the past studies. According to the disease annotation, the selected genes are highly associated with complex diseases, which are higher risk of developing osteoporosis (the results of all selected genes are in Supplementary material).

To further explore whether that the selected chemical taxonomies of metabolic and lipidomic features will have unique relationships in the low BMD and high BMD groups. We infer a causal relationship with a Hill-Climbing approach among the selected chemical taxonomies in each group of both datasets (metabolome and lipidome). The causal relationships of the metabolome and the lipidome datasets: (a) low BMD and (b) high BMD is illustrated in Figure 8 and Figure 9 respectively. In both datasets, we observed that the causal relationships are different in both the low BMD and high BMD for both datasets. For the metabolomic data TTRD has an important impact on the low BMD but has an negative impact on high BMD but DA has an important impact on the high BMD. In case of the lipidome data, we observed that the LA has an impact on the low BMD but does not have any impact in the high BMD. By this observation, we concluded that the selected chemical taxonomies may contribute on BMD status but not in general.

Finally, we investigated classification accuracy via only selected features of the proposed method. To classify the low BMD subjects from the high BMD subjects followed by the three classifiers: the KNN and the SVM (the linear kernel and the Gaussian kernel). For the proposed approach, we considered triplets that have significant (from Table 8) effects on the BMD. The classifier is used to classify the low BMD subject from the high BMD subject. Table 10 presents the train classification error with different datasets and the selected features only. These results are also demonstrating that the proposed method is a better tool for feature selection.
Figure 7: The expression patterns of three selected genes (ABL1, GCNT7, ZNF114) across 27 different tissues. RPKM, reads per kilo base per million mapped.

Table 10: The training classification error of discriminating low BMD subjects from high BMD with the K-nearest neighbors (K-NN) algorithm and the support vector machine (linear kernel and Gaussian kernel).

| Dataset       | K-NN algorithm | Linear kernel | Gaussian kernel |
|---------------|----------------|---------------|-----------------|
| Genome        | 30.28          | 28.18         | 2.07            |
| Epigenome     | 26.01          | 22.03         | 3.04            |
| Transcriptome | 21.29          | 0.00          | 0.05            |
| Metabolic     | 29.63          | 0.00          | 0.22            |
| Lipidomic     | 25.92          | 33.33         | 0.21            |
| Only selected feature | 12.96          | 0.00          | 0.08            |

5 Concluding remarks

The technology of biomedical science has accelerated the cycle of discovery. In this we propose a novel generalized kernel machine approach to identify higher-order composite effects in multi-view biomedical datasets. This semi-parametric approach considers multi-view data as prediction variables to allow comprehensive modeling of complex disease trait.

The power of the proposed method is further demonstrated by its application to both synthesized and two real multi-view datasets, i.e., adolescence brain development and osteoporosis study. In simulation studies, we have shown that the false positive rate of the test for higher-order composite effect is mitigated by fixing the nominal p-value threshold along with other state-of-the-art-methods. From the power analysis, our proposed method not only performs better than other methods. The ROC curves also showed the gain of power by the proposed method in all scenarios.
In adolescence brain development experiments, we found five unique genes and 6 ROIs along with the non-genomic factor that may have significant gender effects on adolescence brain development. In addition, by the gene-gene interaction networks, we confirmed that the selected genes have significantly more interactions than expected. This result implies that the genes and their functional interactions form the backbone of the cellular machinery.

In the osteoporosis study, the network analysis confirmed that the selected genes of genome, epigenome, and transcriptome datasets also have significantly more interactions than expected. It also indicates that the selected genes may function in a collaborative effort. We found that they function in a concerted effort and have biological relevance to osteoporosis. Furthermore, using a causal relationship, we conclude that the selected chemical taxonomies (metabolome and lipidome) may contribute to development of BMD status.
The primary focus of our paper is to comprehensively characterize complex disease (e.g., adolescent brain development, or osteoporosis). Collectively, we can use this approach to derive a statistic for testing the composite effect. These studies explore novel genomic, epigenomic, transcriptomic and chemical mechanisms to identify corresponding factors. The significant triplet, quartet, quintet of extracted features suggest that these effects might highlight biological targets for drug development. Extrapolating these findings enable an advanced understanding of normal cellular processes. Our proposed method can be applied to the study of any disease models, where multi-view data analysis is commonly used.

We acknowledge that the kernel machine is sensitive to contaminated data, even if bounded positive definite kernels are used. Further work on robust kernel methods including M-estimator based methods. They will allow us to uncover the rich, hidden connections in biological system, and may provide a more comprehensive modeling of complex traits.

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