Abstract

In the age of big data, data integration is a critical step especially in the understanding of how diverse data types work together and work separately. Among the data integration methods, the Angle-Based Joint and Individual Variation Explained (AJIVE) is particularly attractive because it not only studies joint behavior but also individual behavior. Typically scores indicate relationships between data objects. The drivers of those relationships are determined by the loadings. A fundamental question is which loadings are statistically significant. A useful approach for assessing this is the jackstraw method. In this paper, we develop jackstraw for the loadings of the AJIVE data analysis. This provides statistical inference about the drivers in both joint and individual feature spaces.

Keywords: Data integration; AJIVE; jackstraw; statistically significant.

1. Introduction

Many modern data sets such as genomic data involve multiple data types, which are measured on a common set of experimental units. For example, this is an important issue in modern cancer research studied in Section 3 where two important and complementary data types are gene expression and copy number measurements. A useful approach is to organize such different types of data into separate blocks. The Angle-Based Joint and Individual Variation Explained (AJIVE) method [1] assumes a common type of connection among these data blocks and studies the ways that they vary together as well as separately. Thus, AJIVE untangles joint and individual variation and gives unique insights into the structure of these data sets. An important open problem is statistical inference on the AJIVE loadings to determine which are significant drivers of the analysis.

Figure 1 uses a simple Gaussian simulation to illustrate how AJIVE gives modes of variation that are the basis of the inference developed in this paper. This toy example is constructed to clearly
(visibly) demonstrate the difference between the joint and individual variation and their drivers. In real data, such joint and individual variations are not always as clear as this toy example. The input data matrices of the toy sample in the left panels are the sum of the other three matrices representing joint variation, individual variation, and noise shown in other panels. Each panel is a heat map view of a data matrix whose entries are coded by colors. In all panels, the color red is coding values that are greater than 1 and blue is coding smaller than -1. White codes zero and in-between values are lighter shades of red or blue. This toy example has: Datablock 1 (shown on the top) and Datablock 2 (bottom). Both have 120 features (rows) and 160 cases (columns). The far-left panels are the simulated input data blocks of AJIVE. The first 80 rows in the top left panel (Datablock 1) have a similar pattern to the first 40 rows in the bottom left panel, representing the joint variation of the 2 data blocks. This structure came from the rank-1 joint matrices shown in the second panels on the left. These have a relatively weak signal characterized by a minimum value of -0.7 and a maximum of 0.7, as indicated by the paler red and blue colors. The last 40 rows in the top left panel (Datablock 1) have different patterns from the last 80 rows in the bottom left panel, which represents the individual structure of the data blocks. This is generated by the third panels from the left which show the rank-1 individual signal for each data block. The individual signal is relatively stronger because the minimum value of the individual matrices is -1 and the maximum is 1. The far-right panel represents the simulated independent Gaussian noise with mean 0 and variance 2.

Just like Principal Component Analysis (PCA) [2], AJIVE decomposes data into modes of variation. However, because AJIVE borrows information across blocks, it potentially gives deeper insights. The different joint/individual signal strength of the toy example in Figure 1 is carefully designed to show how AJIVE recovers signals that are poorly recovered by PCA. This example also highlights the fact that this richer information improves the statistical significance of the loadings.
Figure 1: This figure illustrates how we simulate the input of AJIVE in the toy example. The top and bottom panels show DataBlocks 1 and 2 respectively. From left to right, the panels are: input to AJIVE, simulated joint, individual, and noise matrices. Red indicates values greater than 1 and blue indicates values less than -1, in-between values are shown with less color intensity and white is zero. The simulated joint signals are weaker than the individual signal by 30% in each data block as indicated by the paler colors.

As stated in [1], two important outputs of AJIVE are the joint and individual matrices which are calculated using the common normalized scores matrix (CNS). Let $n$ be the number of cases (columns) and $M$ be the number of input data blocks of AJIVE (in the toy example $M = 2$). Let $d_m$, $m = 1, 2, ..., M$ be the number of features (rows) of each data block and $r_J$ be the rank of the joint space. Similar to PCA scores, the CNS indicates the relationships between the data vectors. The CNS is essentially the matrix of projection coefficients of each data point onto the respective
loading vectors in $\mathbb{R}^{d_m}$. Unlike the traditional PCA, the rows of CNS are also normalized so that they form $r_J$ orthonormal vectors, hence they are also direction vectors in $\mathbb{R}^n$.

The joint space, i.e. subspace of $\mathbb{R}^n$ spanned by the rows of CNS, defines the joint variation of all data blocks among the experimental subjects. The corresponding estimated joint matrices are defined as the matrix products: $D_{d_m \times n} \times (CNS^T)_{n \times r_J}CNS_{r_J \times n}$, where subscripts indicate matrix dimensions and $D_{d_m \times n}$ are the input data blocks of AJIVE. These matrices are sums of rank-one *modes of variation*, each of which gives insight into how the two data blocks vary together. After we find the joint space, the low-rank approximation of the orthogonal component in the subspace generated by the original data matrix is the individual space. This low-rank approximation can be decomposed into sums of rank-one individual modes of variation. These modes of variation reflect how the data blocks work together and separately, i.e. joint variation and individual variation. An important measure of the effectiveness of AJIVE in recovering these modes of variation is the angle between the estimated loading vector and the true underlying direction.

A useful method for statistical inference on PCA loadings is jackstraw [3], which inspires our approach to AJIVE inference. Figure 2 provides a contrast between the proposed AJIVE-jackstraw and the original PCA-jackstraw. Each panel is a heat map view of a data matrix with the same color code as Figure 1. The top panels are the AJIVE extracted rank-1 matrices with the following order from left to right: joint for Datablock 1, individual for Datablock 1, joint for Datablock 2, individual for Datablock 2. The bottom heatmaps show corresponding PCA modes of variation (rank 1 matrices as indicated in the title). The bottom panels are specifically ordered so that each mode of variation best corresponds with the panel above. The strong red and blue colors on the top show AJIVE has successfully found the 2 different signal components from the input data blocks. The pale colors on the bottom row show that the scores estimated in the PCA modes of variation are relatively weaker, showing PCA is less efficient in recovering these modes.
Figure 2: Comparison between the AJIVE-jackstraw (top row) and the original PCA-jackstraw (bottom row). Each heatmap represents the data projected in the corresponding direction indicated in the title with the same color code as Figure 1. The black and white columns on the right of each heatmap indicate the jackstraw significant features. The AJIVE-jackstraw provides more accurate results as indicated by the stronger red blue colors and more accurate black and white bars.

In Figures 2, it is clear that some features (rows) show a strong contrast between the red and blue, making them important drivers for the joint/individual spaces, while other features show less but still some contrast. This illustrates a need for a formal hypothesis test to see if a row of the estimated joint/individual matrix is significantly different from zero, this will allow us to find significant drivers. As stated in [3], the original jackstraw method has successfully found significant drivers of PCA, i.e. the important loadings. In this paper, we develop jackstraw in the richer context of AJIVE. Our method can either be applied to any separate mode of variation, either joint or individual or it can be applied to either joint or individual subspace separately or applied to the entire or joint individual subspace.

The best understanding of our hypothesis test comes from comparing the true underlying structure in Figure 1 with its corresponding estimates in Figure 2. In Figure 2, the black and white
columns on the right side of each heatmap indicate the result of the jackstraw hypothesis test, where a thin black line indicates each significant feature. Table 1 shows the accuracy of the hypothesis tests using the proportion of jackstraw significant features which agree with the corresponding true underlying features. As you can see at the bottom of Figure 2, the PCA struggles to separate the 2 underlying signal components due to the similarity of signal strength while AJIVE borrows the information from the second data block and separates the two signal levels successfully. Thus, the AJIVE-jackstraw has higher accuracy than PCA-jackstraw as indicated in the first 2 columns of Table 1. For data block 2, the last 2 columns in Figure 2, PCA gives similar signal recovery to AJIVE because the individual signal shown in the third columns of Figure 1 is stronger. However, AJIVE not only separates the signals but also provides a stronger recovery of the weak underlying signal as indicated by the stronger color contrast in the third panel in Figure 2. This also results in higher accuracy than PCA-jackstraw as indicated in the third column of Table 1. In the last column of Table 1, the PCA-jackstraw has higher accuracy than AJIVE-jackstraw because the corresponding true underlying signal component is strong and very different from the other signal component. Thus, in this example, the AJIVE-jackstraw is better when the true underlying signals are weak and similar and PCA-jackstraw can be slightly better when the true underlying signals are strong and easily separable.

Table 1: Accuracy calculated as the number of jackstraw significant features which agree with true underlying significant features. AJIVE-jackstraw has generally large accuracies.

| Accuracy # | D1.(joint/PC2) | D1.(indivi/PC1) | D2.(joint/PC2) | D2. (indivi/PC1) |
|------------|----------------|----------------|----------------|-----------------|
| AJIVE-jackstraw | 0.88 | 1 | 0.95 | 0.94 |
| PCA-jackstraw | 0.68 | 0.98 | 0.93 | 0.98 |

Another useful comparison between AJIVE and PCA is based on angles between the estimated loadings vector for each mode of variation and the corresponding underlying true loading vector. Larger accuracies in Table 1 corresponds to smaller angles in Table 2. Smaller angles correspond to better visual agreement between the estimated heat maps in Figure 2 and the true underlying signal in Figure 1.
Table 2: Angles calculated using the estimated loadings vector for each mode of variation from AJIVE/PCA and the corresponding underlying true loadings vector. AJIVE-jackstraw has generally small angles showing improved performance in this example.

| Angle # | D1.joint/PC2 | D1.indivi/PC1 | D2.joint/PC2 | D2.indivi/PC1 |
|---------|--------------|---------------|--------------|---------------|
| AJIVE-jackstraw | 17° | 18° | 17° | 17° |
| PCA-jackstraw | 31° | 32° | 29° | 14° |

In the rest of this paper, the detailed jackstraw algorithm is given in Section 2. The usefulness of AJIVE-jackstraw in the context of a breast cancer genomics data set is demonstrated in Section 3.

2. Jackstraw Inference

As introduced in Section 1, CNS is the essential output reflecting the joint space of AJIVE. The parallel to CNS in the individual space is called the block-specific scores (BSS) obtained by PCA of the low-rank individual matrix. Let $r^m_I$ be the rank of the individual space of data block $m$. Let $r_J$ be the rank of the joint space. Let $V_{n \times 1}$ be one column of either $(CNS)_{n \times r_J}^T$, i.e. scores for one joint mode of variation, or $(BSS)_{n \times r_I}^T$, i.e. scores for one individual mode of variation.

For one datablock $m = 1, ..., M$, jackstraw inference is based on either joint or individual loading vectors. The corresponding loading is given by:

$$L_{d_m \times 1} = D_{d_m \times n} \times V_{n \times 1}.$$ 

This can also be viewed as the least squares solution of the following linear regression problem:

$$(D_{d_m \times n})^T = V_{n \times 1} \ast (L_{d_m \times 1})^T + (E_{d_m \times n})^T,$$

where

- Each row of $D_{d_m \times n}$ is the response $Y$ in the linear regression. It is centered before AJIVE so no intercept needs to be considered.
- $V_{n \times 1}$ represents the predictor, i.e. $X$ in linear regression.
- $L_{d_m \times 1}$ is the vector of unknown coefficients, i.e. $\beta$ in linear regression.
• $E_{d_m \times n}$ is the residual error term.

The aim of the proposed jackstraw test is to find which loadings are statistically significant. The following hypothesis test structure forms the basis of our jackstraw inference. Let $L_{d_m \times 1} = [l_1, ..., l_{d_m}]^T$. For each $j = 1, ..., d_m$, we consider a hypothesis test:

$$H_0 : l_j = 0, \quad H_1 : l_j \neq 0.$$  

For each of these tests, we define the test statistic as

$$F_j = \frac{(SSE_0 - SSE_1)/1}{SSE_1/(n-1)},$$

where $SSE_0$ and $SSE_1$ are the residual sums of squares under $H_0$ and $H_1$.

Unlike in a classical regression model, we do not expect $F_j$ to follow an F distribution. Therefore we proposed to estimate the distribution of $F_j$ under the null hypothesis using jackstraw. The proposed algorithm generates the simulated null distribution by randomly permuting $K$ rows, then computing the corresponding $K$ test statistics one from each row. This is repeated $S$ times. Thus we have $S \times K$ test statistics simulated under the null hypothesis. The $K$ and $S$ are chosen as follows:

• $K$ is the number of rows to be permuted in one step, which should be much less than $d_m$, such as 1, 10, or 100.

• $S$ is the number of times the permutation step is repeated, which should be at least 10 times $d_m$.

The key algorithmic steps are:

1. The test statistics: $F_j$s are obtained by fitting a linear regression with the rows of mean-centered AJIVE input data as the response and with rows of the selected CNS or BSS of interest as the predictors.

2. Randomly select and permute $K$ rows of the original data matrix and recalculate the AJIVE CNS and BSS. Then recalculate the test statistics as in Step 1 using the permuted data matrix and the same rows as in Step 1 of the new CNSs or BSSs to get $K$ samples from the simulated null distribution. Then Repeat $S$ times to generate $S \times K$ samples from the null distribution $F_{null}^b, b = 1, ..., S \times K$. 

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3. Calculate an empirical p-value: \( p_j = \frac{\sum_{k=1}^{S \times K} I(F_{j} < F_{\text{null}})}{S \times K} \) for each observed test statistic \( F_j, j = 1, \ldots, d_m \).

4. Adjust p-values for multiple testing. We recommend using the Bonferroni adjustment \([4]\) for the level of the test, i.e. the regular p-value times the number of tests (in this case the number of features \( d_m \)) as the adjusted p-value. A reasonable alternative would be to consider the false discovery rate \([5]\).

2.1. Efficiency Improvements of Algorithm

As stated in \([3]\), smaller \( K \) (in Step 2) gives more precise estimation, and larger \( K \) gives faster calculation. The analyses in this paper use \( K = 1 \) and parallel computation for maximal precision per unit time.

Each of the \( S \) resamples requires one round of the AJIVE algorithm. In bioinformatic settings, no individual feature is particularly influential such as gene expression and copy number variation studied in Section 3. Thus permuting a small number \( K \) out of a large number \( d_m \) of rows will lead to minor changes in the AJIVE results. This is especially true in the case of a joint space estimated from multiple data blocks. Therefore, we recommend using the original CNS from AJIVE instead of recomputing it for each permutation step in such a situation.

We next demonstrate the effects of not recomputing AJIVE for each of the \( S \) replications of jackstraw using TCGA breast cancer data, which will be discussed in detail in Section 3. There are 2 data blocks (data matrices):

- Copy Number Variation (CNV) that includes as features (rows) Copy Number Regions (CNR),
- Gene Expression (GE) that includes as features (rows) normalized log of gene expression.

After AJIVE inference, we get 3 joint components and we proceed to apply jackstraw to find the significant genes/CNRs corresponding to each of the 3 joint components. As an investigation of the Monte Carlo variation, we run the 2 algorithms (full and approximate) 2 times using 2 different seeds, denoted as seed1 and seed2. For a convenient notation, let ‘JC’ denote ‘joint component’, ‘app’ denote ‘approximate algorithm’ and ‘full’ denote ‘full algorithm’. In Table 3, we will report the number of significant CNRs/genes. After a careful comparison, more than 95% of the significant CNRs/genes stay significant if we use different algorithms or random seeds. Surprisingly, in each row, the subset corresponding to a smaller number of significant features is always included in the
subset corresponding to the larger number. Thus, jackstraw analysis of TCGA breast cancer data is not sensitive to random seeds or algorithms.

|       | # sig features | App.seed1 | Full.seed1 | App.seed2 | Full.seed2 | Total number |
|-------|----------------|-----------|------------|-----------|------------|--------------|
| GE.JC1| 10499          | 11450     | 11450      | 11051     | 20249      |
| GE.JC2| 6735           | 7765      | 7859       | 6918      |
| GE.JC3| 5784           | 6510      | 6455       | 6288      |
| CNV.JC1| 557          | 557       | 526        | 537       | 806        |
| CNV.JC2| 292          | 197       | 276        | 276       |
| CNV.JC3| 288          | 235       | 240        | 247       |

Table 3: Numbers of significant genes/CNRs for each joint component (JC) using different random seeds and algorithms. ‘App’: approximate algorithm. ‘Full’: full algorithm. Random seeds and algorithms only have minor influence.

While the algorithms give similar results, the approximate algorithm takes 30 mins and the full algorithm takes $30 \times d_m = 30 \times 20249 = 607470$ mins for GE without parallel computation. With access to parallel computation, the full algorithm can be much faster. In practice, we recommend making a careful choice between the 2 algorithms based on whether any features are expected to be dominant.

2.2. Jackstraw Diagnostic Graph

Figure 3 shows the jackstraw results for the simulated toy example shown in Figure 1. In the left panel, the black curve is a kernel density estimate visualization of the $F_{null}^b$ distribution (on the $\log_{10}$ scale) calculated in Step 2 of the algorithm in Section 2. The red (significant) and blue (not significant) are the observed F statistics: $F_j$ calculated in Step 1. Significance is at the level of 0.05 using the Bonferroni correction. The middle panel shows the sorted jackstraw p-values, computed in Step 3, for all the genes. Out of 120 features, we find 68 significant features in the joint component. The right panel shows the results of a Kolmogorov-Smirnov test (K-S test), which tests the uniformity of the distribution of these p-values. In this panel, the colored curve is relatively far from the 45-degree line and the K-S p-value is $9.34 \times e^{-41}$, thus, indicating the first joint component has useful information and is important.
Figure 3: Jackstraw diagnostic graphs using the simulated toy example in Figure 1. Left panel: the black curve is the kernel density estimate of the null distribution and the red (significant) and blue (not significant) dots are the observed F statistics for all genes (both on log₁₀ scale). Middle panel: the sorted p-values, one for each feature. Right panel: Kolmogorov-Smirnov test of the uniformity of the p-value. This diagnostic graph shows that the first joint component is statistically significant and 68 features are the main drivers of this joint component.

3. TCGA Breast Cancer Data

The Cancer Genome Atlas (TCGA) [7] is a multicenter effort to generate multiple different data types for a large cohort of patients to comprehensively characterize cancer. TCGA contains many cancer types and several different data platforms. We are particularly interested in the breast cancer [8] cohort, where prior work has identified molecular subtypes of breast cancer, based on gene expression [9], [10]. Therefore, this data set is an excellent case to study the application of jackstraw on the integration of multiple data platforms. The focus here is on finding relationships between joint and individual information from GE and CNV to investigate subtype-specific relationships. The 1038 patients are classified into 4 subtypes (185 Basal cases, 81 Her2, 556 LumA, and 216 LumB). GE (20249 features), CNV(806 features), and subtype (4 subtypes) are the 3 data blocks studied here. Inclusion of the third block that indicates the subtypes could be viewed as a supervised version of AJIVE. This enables the careful focusing of the analysis on the subtypes. Each matrix has a column corresponding to each of the 1038 patients. Each column of the indicator matrix has four entries, which indicate the four subtypes using a one in the appropriate row and zeroes for the
other entries. A small example of such a subtype matrix is:

\[
\begin{bmatrix}
0 & 0 & 1 & 0 & 1 & 0 & 0 \\
1 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1
\end{bmatrix},
\]

We use the \( \log_2 \) count GE values. To construct the CNV data, we use the \( \log_2 \) ratio per gene values from GISTIC downloaded from TCGA FireBrowse website. The gene-level values were collapsed to cytobands (labeled chromosome regions) using the median value per gene in each cytoband. Each CNR is labeled as the chromosome number that distinguishes the genome location together with the letter p or q which distinguishes the chromosome arm and then by a cytoband using the following decimal number after that. For example, 10p11.1 is the cytoband on chromosome 10 arm p number 11.1. All data blocks are feature-centered as the input of AJIVE. Hence, the sign of all features is relative to the average.

Overall, \( d_1 = d_{GE} = 20249, d_2 = d_{CNV} = 806, d_3 = d_{sub} = 4 \) and \( n = 1038 \). A low-rank approximation is used in the first step of AJIVE for the first two input matrices. We use 77 for CNV, 70 for GE, and 3 for the subtype indicator matrix. This results in a rank 3 joint space i.e. 3 joint components overall, 74 and 67 individual components for CNV and GE respectively. In the following sections, we investigate the loadings of AJIVE joint and individual spaces using jackstraw.

3.1. Joint Space

Figure 4 shows a scatter plot matrix view of the supervised CNS, which shows a strong visual separation that is a consequence of strong subtype information and the supervision using the third data block. The CNS is a 3 by 1038 matrix because of 3 joint components and 1038 cases/patients. The plots on the diagonal are one-dimensional views of the scores, rows of the CNS matrix. The subtypes are illustrated with subplot kernel density estimates (KDE). Points are shown using jitter plots (i.e. random heights) to visually separate the data points in the one-dimensional plots. The overall KDEs are shown in black and the subtype KDEs are shown in subtype colors. The area under the curve of each colored KDE is proportional to its abundance so that the sum of the area under the colored curves equals 1, the area under the black curve. The off-diagonal plots are scatter plots, i.e. two-dimensional projections of the data onto the planes generated by the corresponding CNS vectors. The first joint component (joint comp 1) strongly separates Basal (red) from the
other subtypes. Joint components 2 and 3 also seem to be strongly related to subtypes even though the separation is less than component 1. The second joint component (joint comp 2) separates the three other subtypes in the order of LumA (blue), LumB (cyan), and Her2 (magenta). The third joint component (joint comp 3) separates Her2 (magenta), LumA (blue), and LumB (cyan).

Figure 4: Supervised AJIVE CNS scatter plot. The diagonal panels are jitter plots and kernel density estimates of the univariate distribution of the entries of the corresponding CNS vector. The off-diagonal panels are related scatter plots giving a pairwise comparison of the entries of the score vectors. The subtypes are indicated as follows: Basal: red; Her2: magenta; LumA: blue; LumB: cyan. This figure shows that the joint variation reflects strong cancer subtype separation.

Figure 5 indicates the relationship between subtypes for each joint mode of variation illustrated in Figure 4 by showing the subtype CNS loadings. These loadings indicate the impact of each subtype on the mode of variation. This gives another interpretation of the 3 joint components:

1. contrast of Basal vs the rest; contains little Her2 information;
2. contrast of (Her2 & LumB) vs LumA; contains little Basal information;
3. contrast of LumB vs (Her2 & LumA); contains little Basal information.
Based on this AJIVE outcome, we implement the jackstraw method to identify the statistically significant genes and CNRs for each joint mode of variation. This enables us to focus on a smaller (and hence more biologically interpretable) set of significant variables and to remove the unimportant variables to the variation of interests. Table 4 shows the number of jackstraw significant genes and CNRs for each joint component (using the approximate algorithm). For joint component 1, the strong differences between Basal-like subtype and non-Basal in Figures 4 and 5 appear in Table 4 as a large number of significant genes. However, the differences between numbers of significant features within the non-Basal subtypes are smaller in Figures 4 and 5 which is consistent with fewer jackstraw significant genes in joint components 2 and 3.

| Joint Significant # | comp 1 | comp 2 | comp 3 | total number of features |
|---------------------|--------|--------|--------|-------------------------|
| GE                  | 11288  | 7058   | 6274   | 20249                   |
| CNV                 | 526    | 247    | 302    | 806                     |

Table 4: Numbers of significant genes and CNRs for each joint component. These smaller subsets are used in later analyses. The joint components 2 and 3 have a smaller number of significant features in both GE and CNV, which is consistent with the observations in Figures 4 and 5. These smaller subsets are used to give sharper statistical inference in Figure 9.
Our AJIVE version of jackstraw allows us to focus on a set of statistically significant features, giving insight into how GE and CNV work together. There are many mechanisms of gene regulation including copy number mutation and gene methylation. In cancer, one important mechanism is copy number variation that can influence expression by increasing or decreasing the numbers of copies per gene. Hence significant copy number variation is expected to lead to significant gene variation. We want to see if genes that are significant in joint space are joint because the copy number is directly regulating expression, however, it’s important to note that there can be many genes located in one CNR. We are interested in the *cis effects* when the copy number variation directly regulates the gene expression. As shown in the second row of Table 5, almost all significant CNRs contain some significant genes. This is consistent with GE being influenced by its local copy number. There are a few CNRs that are not associated with significant genes, of the 22 non-overlapping CNRs in comp 1, 11 of them are near *centromeres*. The centromeres link a pair of sister chromatids (a dyad), which are important in cell division. These are typically gene-poor chromosome regions, such as 10p11.1, 12p11.1. Because the copy number is often consistent across neighboring cytobands, it’s not surprising that some centromere regions are joint CNV significant but did not have a corresponding gene expression joint significant region. This is also observed in components 2 and 3 with 7 out of 15 non-overlapping significant CNRs near centromeres in component 2 and 4 of 20 respectively in component 3.

| Overlapped Joint Significant % | comp 1 | comp 2 | comp 3 |
|-------------------------------|--------|--------|--------|
| Significant CNRs containing significant genes (%) | 95.27  | 94.57  | 91.67  |
| Significant genes located in significant CNRs (%) | 69.17  | 39.68  | 36.27  |

Table 5: Percentage of overlapped significant genes and CNRs for each joint component. Most CNRs contain significant genes, but only some significant genes are located in significant CNRs.

The significant CNRs are likely to have a local effect on the corresponding significant genes. However, as shown in the third row of Table 5, not all significant genes in joint space have a dependency on significant CNRs. There are other mechanisms for GE regulation that are still important and show up in the joint space without having a direct dependency on the CNRs. These may be related to a *trans effect* (non-local regulation) or by strongly correlated genes in the same pathway.

Figure 6 gives insight about gene/CNR loadings and jackstraw significance. Each panel contains
colored curves which show the sorted loadings for each gene/CNR. The x-axis represents the full set of the sorted features. The y-axis shows the corresponding loadings. Recall loading vectors have length one, so the sum of the squared entries must be one. In each panel, the curves show joint components 1 (black), 2 (green), and 3 (yellow). Each variable is also plotted using jitter plots (i.e. random heights) for joint components 1, 2, 3. The GE loadings are very similar across the three curves in the left panel, yet the CNV loadings are substantially different in the right panel. In particular, CNV has very few CNRs with very negative loadings as discussed around Figure 7. Relatively speaking, the signal and gene expression is spread over more genes, so there are fewer loadings that are much different from zero. Jackstraw significant genes or CNRs are identified with a red dot and non-significant features with a blue dot. There are 20249 genes and only 806 CNRs, thus the jitter plots on the left are much denser than those on the right. In both panels, joint component 1 has more significant features than joint components 2 and 3. This is consistent with the fact that joint component 1 has the most shared variation and is driven mostly by Basal subtype information, which is known to be associated with large genomic changes [11]. Generally, features with large loadings tend to be more significant.

Figure 6: The colored curves are formed by the sorted loadings of genes/copy number regions. If the corresponding feature is significant, a red dot is placed in the central bands (jitter plots), otherwise, a blue dot is placed. Features with large loadings are more likely to be selected as significant. Distributions of loadings of CNR for joint components 2 and 3 are dramatically different than what is observed in component 1.

Figure 7 displays the top 40 significant CNRs with the largest absolute loading values for joint
component 2. These are drawn from the extremes of the green curve in the right panel of Figure 6 highlighting the extremely negative values. The strongest on the negative side are more associated with Her2 & LumB vs the positive side LumA. These top features are found only in chromosomes 17 and 8, which are highly associated with Her2 positive cancers. The 17q21.1 CNR is within the ERBB2 (HER2) amplicon that is an important gene in both Her2 enriched and LumB cancers. Prior work [12] has shown that 8q is most enriched in Her2 positive cancers. This clearly shows that the jackstraw analysis has picked up biologically important regions previously identified in these types of cancers. This defines a clinically important subset of breast cancers that can be treated with drugs that target Her2.

Figure 7: The bar graph of the top 40 genes in terms of the largest absolute values of joint component 2 loadings. Heights of bars indicate the loadings of corresponding CNRs (name shown on each bar). The most negative loading is from 17q21.1.

To better demonstrate the impact of jackstraw, we use heatmaps to separate and understand the difference between the significant and non-significant features. Figure 8 shows heatmap views of the CNV joint matrices for each joint component (rows). The left column shows heatmaps with all features. To give the clearest view of jackstraw significant features, the middle column has the insignificant features whited out. Notice that these views look rather similar even though in the top middle panel, 300 of the rows are white. This is an artifact of the plotting software. For a clear view of the non-significant features, the right column shows the significant features whited out. The color bar on the bottom of each panel represents the tumor subtypes (same colors as Figure 4). The color bar on the right of each panel indicates the 23 chromosome positions with each color representing a chromosome. In the top panels (joint component 1), the color contrast is very clear for the Basal subtype (colored red in the bottom bar) and the non-Basal subtypes.
This is consistent with Figures 4 and 5 that the first joint component separates Basal from the rest. However, the Her2 subtype, which is colored magenta, has nearly 0 values. This indicates that joint component 1 is related to only some or even none of the variations in Her2. The top middle panel focuses on the 526 significant features. As seen in Table 4, more than half of the genes and CNRs are significant in joint component 1, which is not surprising since Basal is considered to be genomically very different from the other cancer types. Therefore, we see a high similarity between the top left and top middle heatmaps and a very light color shade in the non-significant features on the top right panel, indicating a very small impact.

For joint components 2 (middle) and 3 (bottom) in Figure 8, the Her2 subtype (colored magenta) is also very clear. The strongest projections (strongest colors) on joint component 2 are observed in chromosomes 8 (chocolate), 17 (light mocha), and 20 (orange). As stated in [12], chr8q is mostly amplified in Her2 subtypes, which is consistent with the fact that the Her2 columns are the reddest in chr8q for the middle panel and the bluest for the bottom middle panel. Chr20 is amplified the most in LumB (cyan) and was seen to be LumB enriched in [12].
Another interesting question is: how do these jackstraw significant features (genes/copy number regions) improve our ability for subtype separation? This is assessed using the Direction-Projection-Permutation high dimensional hypothesis test (DiProPerm) \cite{13}, \cite{14} to quantify subtype separations based on different feature sets. Test results are on the scale of Z-score. Error bars are included to reflect the simulated variation of the Z-score using balanced permutations as explained in Section 3.2 in \cite{14}. Each error bar in Figure 9 shows the confidence interval of the Z-score of each test, where a large Z-score indicates more significance.

In each panel of Figure 9, we quantify the amount of separation between subtypes and corresponding components indicated in the titles using the three feature subsets of the input GE data:

1. All 20249 features (shown as ‘All’ in the left)
2 jackstraw significant features for each joint component (shown as ‘Sig.’ in the middle)

3 Non-significant features for each joint component (shown as ‘Non.sig’ in the right)

The titles of Figure 9 come from the relationships shown in Figure 5. Comp1 corresponds to Basal vs Rest, comp2 corresponds to (Her2&LumB) vs LumA and comp3 corresponds to (Her2&LumA) vs LumB. For all 3 panels, the tests using all features have very strong Z-scores, indicating strong separations of the subtypes. When we focus on significant features only, the separations become even stronger as indicated by larger Z-scores demonstrating the value of focusing on the jackstraw significance. However, the non-significant features have relatively small Z-scores, but still, retain some signals (Z-scores greater than 2). The confidence intervals show that all of these differences are statistically significant relative to the natural permutation variation. In summary, jackstraw significance provides a stronger subtype distinction.

For further insights, we calculate the angles between each joint component loading vector and the mean difference vector from the original data. These angles are shown in the titles of Figure 9. The angle between the first joint component loading vector and the mean difference vector of Basal vs the rest using the original data (input of AJIVE) is only 4°, which is extremely small in high dimensional settings. This is yet another way of seeing that the first joint component extracts the Basal signal from the rest. The angle between the second joint component and the mean difference vector of (Her2&LumB) vs LumA is 18°. The angle between the third joint component and the mean difference vector of (Her2&LumA) vs LumB is 32°. Although 18° and 32° are not as small as 4°, they are still relatively small in high dimensional space, where random angles tend to be close to 90° as shown in [15]. Even in samples with higher angles, focusing on the jackstraw significant features improves classification and separation of subtypes in the DiProPerm test.
Figure 9: DiProPerm Test Z-score confidence intervals of GE expression. Left: the test of Basal vs rest, middle: (Her2&LumB) vs LumA, right: (Her2&LumA) vs LumB. In each panel, each error bar is a confidence interval of the Z-score of the given test based on: all features (left), significant features (middle), non-significant features (right). The AJIVE-jackstraw significant features give a higher z-score verifying the stronger signal level.

3.2. Individual space

While AJIVE is very effective at finding the joint structure between all three data blocks of GE, CNV, and subtype, it does not find structures that are joint between only two. The DiProPerm investigation of the individual GE did not find significant subtype information, i.e. z-score of 0.59. However, as shown by the more clear blue and red colors in the left-hand panel of Figure 10 and also indicated by the scores in the right-hand panel of Figure 10, the individual CNV did have a significant DiProPerm relationship of LumA vs LumB, i.e. z-score of 12, which is not joint with GE. Thus, we further investigate the individual space of CNV that is independent of GE, using a further 2-Datablock AJIVE. The inputs of this second AJIVE analysis are the CNV individual matrix and the supervision subtype matrix (introduced at the beginning of Section 3). We use 77 as the initial rank for the CNV individual matrix and 3 for the subtype indicator matrix. These initial ranks give only 1 joint component. Figure 10 shows the jackstraw and AJIVE results of this analysis. In the left panel, we only show the jackstraw significant CNRs using a similar heatmap as Figure 8. In contrast to Figure 8 instead of whiting out the significant CNRs, they are deleted, which better reveals chromosomes with many significant CNRs. The Basal and Her2 cases have little color contrast and thus we only focus on LumA and LumB cases. In this analysis, jackstraw
identified 100 significant CNRs from 13 chromosomes. This indicates that after removing the joint variation between GE and subtypes, there is still subtype-related CNR remaining, though not as large as those that are also joint with GE subtype as shown in Table 4. In particular, we notice three chromosome arms were strongly associated. In chromosome 8 (chocolate), 17 (light mocha), and 20 (orange), almost the entire chromosome remains significant. We found different directions of the two chromosomes arms: more positive direction for the p arms while the q arms were more associated with LumB and had negative loadings in chromosome 8 (chocolate) and 17 (light mocha). This is consistent with the observations of [12]. The right panel of Figure 10 shows the distribution of CNS. The LumA tends to stay on the left side while the LumB tends to stay on the right side. This is consistent with what we found in the DiProPerm results: the joint component separates LumA from LumB. In conclusion, in the joint space of the first AJIVE, especially, GE plays a strong role. However, there remain informative GE-independent CNRs that can differentiate LumA and LumB.

Figure 10: This figure is based on a two-data block AJIVE color-coded as in Figure 8. The inputs are the CNV individual block from the 3-way AJIVE above and the subtype supervision matrix. The heatmap on the left only shows the jackstraw significant CNRs. The scores distributions shown on the right only include LumA (blue) and LumB (cyan) cases. This shows that the CNV subtype information not captured jointly with GE reveals an important difference between LumA and LumB.

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