Principal Component Regression of Collinear Data

**Introduction :**

Currently, the strongest risk factor for melanoma is the number of nevi (moles) a person has \cite{RN149}. The majority of nevi develop during childhood and adolescence and the number of nevi developed is influenced by a variety of environmental, behavioral, genetic, and phenotypic factors \cite{RN153, 154}. While the relationship of environmental and behavioral factors such as UV exposure and use of sun protection, respectively, have clear relationships with nevus development, the impact of impact of each factor in conjunction on nevus development needs further investigation.

In a longitudinal observational study on mole development in children from Colorado, data was collected on the child’s mole count, base skin color, eye color, hair color, ethnicity (Hispanic or non-Hispanic), number of seaside vacations since birth, and OCA2 genotype. OCA2, a gene important for melanin synthesis, has been associated with heritability in nevus count, skin color, and eye color \cite{RN152, 150}. More specifically, individuals homozygous for the g allele demonstrated a significant correlation between having higher nevi counts, blonde hair, and blue or green eyes. Whereas individuals homozygous for the a allele tended to have fewer nevi, darker hair, and brown eyes \cite{RN150, 151}. In addition to collinearity between genotype, eye color, and hair color, there is also a colinear relationship between base skin color and ethnicity. While a linear regression model excluding potential collinear variables can be conducted, there may be variation that can be explained by the factors such as eye color or hair color that is not explained by OCA2 genotype. Therefore, a method for estimating the coefficients of collinear variables is necessary in order to appropriately analyze this dataset.

**Background:**

***Methods for Regression of Collinear Data***

Principal component analysis (PCA) is powerful technique that is used in many fields to reduce high-dimensional data into fewer variables that can best explain the variance in the data. This is done by performing an orthogonal transformation on a set of variables that are likely correlated to yield a set of linearly uncorrelated variables (principal components, or PCs) \cite{RN165}. The first PC describes the greatest amount of variability in the data as possible, and each subsequent PC describes the next highest variance orthogonal to the preceding component. The output of PCA are an orthogonal basis set of vectors (each comprised of a linear combination of variables with *n* observations) which can be used to predict future data or as covariates in linear models to account for undefined structure that would confound regression analysis. For example, in a genetic case-control disease study, differences in allele frequency due to genetic ancestry can cause spurious associations if genetic ancestry is not accounted for in the model \cite{RN159}. Genetic ancestry explains much of the variance in genetic data and thus will be represented in the first several PCs in a PCA of the dataset. These PCs can then be used as a proxy for genetic ancestry and added as covariates to the model, thus correcting for ancestry as confounding factor \cite{RN158}. In addition to PCs being useful as covariates for linear regression models, variations on PCA, such as principal component regression (PCR) can be used to address multicollinearity.

PCR is a regression analysis method based on PCA that uses PCA for estimating unknown regression coefficients in a model. In PCR, the PCs of the explanatory variable are used as regressors instead of regressing the dependent variable on the explanatory variable directly as in a standard linear regression model \cite{RN164}. One of the limitations of PCA based dimensionality reduction is that if two or more variables in the dataset are highly correlated, the columns corresponding to these variables become linearly dependent and the matrix becomes rank deficient. Collinearity is handled in PCR by excluding low-variance (nearly or exactly zero eigenvalue) PCs in the regression part of the process. Depending on the purpose of the analysis, other low-variance PCs can also be excluded in the regression to reduce the effective number of parameters defining the model and mitigating potential overfitting.

However, there is a quite significant limitation to PCR in that it does not consider the response variable when deciding which principle components to drop (in the case of there being collinearity), i.e. just because a factor has a small eigenvalue does not mean it is not a strong predictor of the response variable \cite{RN163}. This means that when PCs are dropped the coefficient estimates become biased, more difficult to interpret (because they are weighted averages), and less accurate for predicting new data \cite{RN160}. It is possible for important explanatory variables to be given small eigenvalues (and vise versa with unimportant variables) and estimated coefficients in the wrong direction. In summary, PCR is an effective and easy method for identifying collinearity, though other methods should be used to estimate the coefficients, such as a partial least squares (PLS) regression or a multivariate linear regression using only the linearly independent variables.

PLS regression is similar to a PCR, except that instead of finding hyperplanes of the highest variance between the response and independent variables, it analyses the relationship between the response and independent variables as matrices \cite{RN161}. More specifically, the PLS regression finds the multidimensional direction of the independent variables that explains the greatest amount of multidimensional variation direction in the response variable matrix \cite{RN162}. Since this model incorporates the response variable in the selection of PCs that explain the most variance, it is the most appropriate for PCA-like regression of datasets that are rank deficient or have collinearity among variables and providing accurate coefficient estimates.

**Materials & Methods:**

***Materials***

This study was conducted using a subset of data from a longitudinal observational study of children from Colorado followed from 6 to 10 years of age. This subset includes yearly measurements of mole count, OCA2 status, eye color, base skin color, hair color, ethnicity (Hispanic or not Hispanic),and reported number of seaside vacations since birth for 472 children. Nevi ≥5mm were counted annually during a skin examination by health care providers trained annually from the study’s lead dermatologist. OCA2 status was measured by PCR amplification and genotyping of rs12913832 from DNA extracted from saliva. Eye color, base skin color, hair color, and ethnicity were recorded during the baseline visit at age 6. Number of seaside vacations since birth was assessed via an annual survey of the children’s parents where ‘waterside location’ was explicitly defined. For the purposes of this analysis, only the mole count and number of seaside vacations reported from the baseline visit at 6 years of age was used.

***PCA***

The first step to principal component analysis is to calculate the covariance matrix of the data. Analysis of variances can be used to answer questions about whether the variable(s) in X have a relationship with Y. To begin, the mean of all the *m* variables from an *m x n* matrix, A, is calculated and stored in a single vector in , u:

μ⃗ =(1/(n−1)) (x⃗ 1+x⃗ 2+…+x⃗ n)

Then, the data can be re-centered/normalized by subtracting the mean vector from the matrix of observations:

B=[x⃗\_1−μ⃗ |…|x⃗\_n−μ⃗ ]

From the re-centered matrix, B, the covariance matrix, C, can be computed:

C =(1/(n−1))(BB^T)

C will be an m x m symmetric matrix (based on the properties of matrix multiplication) that contains the variance for each variable along the diagonal entries and the covariances between variables in the other entries of the matrix . Once the covariance matrix has been calculated, spectral theory can be applied to the matrix to calculate eigenvalues and produce orthogonal vectors.

Spectral theory states that for a symmetric matrix, S, there exists real eigenvalues and nonzero orthogonal vectors such that:

Av⃗ i=λiv⃗ i ,for i=1,2,…,n

These orthogonal vectors/eigenvectors are the principal components of the dataset.

***PCR***

Principal component regression can generally be explained by three steps: Frist, perform PCA (detailed above), then use ordinary least squares regression to regress the dataset with principal components as covariates to create a vector of estimated regression coefficients (if a PC contains extremely small eigenvalues with a high variance inflation factor, the PC can be omitted to address multicollinearity), and lastly, transform the estimated coefficients to the scale of the original covariates by multiplying the vector by the PCA loadings. This vector of coefficients represents the weights that reflect the covariance between predictor variables.

***PLS***

PLS is and PCR are similar in that both produce factor scores from linear combinations of the original variables. The difference between them is in how the scores are factored.

The general model for partial least squares regression decomposes the matrices of responses, Y, and the predictors, X, into projections U and T, respectively, which have maximal covariance between them. U and T are then transformed by the orthonogonal loading matrices Q and P, respectively. Error terms, F and E, are also added to both the response and predictor models. The resulting vector of coefficients from this method represents the weights that reflect the covariance structure between the predictor and response variables.

X = TP^T + E

Y = UQ^T + F

***Performing PCA, PCR, and PLS***

Data manipulation and linear regression analysis was conducted using R v3.6.1. to assess the contribution of different factors in mole count of 6 year-old children from Colorado. PCA was conducted using the princomp function from the package *stats* v3.6.1 (cor = T) /cite{stats}. PCR and PLS was performed with the pcr and plsr functions from the pls package v.2.7-2 /cite{pls}. Default settings were used for both analysis, with the addition of scale = T for PCR.

**Results**

***PCA***

From the PCA biplot of PCs 1 and 2 in Figure #, it is clear that genotype corresponds to three different clusters where the red (0 in the figure legend), green (1), and blue (2) correlate to the genotypes gg, ga, and gg, respectively. Additionally, we can see that eyecolor, genotype, and haircolor all have similar direction and magnitude, though genotype shows the greatest magnitude of the three. Similarly, Hispanic and base skin color also show similar direction and magnitude of effect, where Hispanic has the larger magnitude in PC1 and base skin color has the larger magnitude in PC2. These groupings are unsurprising given their known biological relationship and provide further evidence supporting their collinear association. Gender and number of seaside vacations both show independent direction and magnitude of effect in these PCs.

Despite the presence of multicollinearity, the scree plot describing the percent variance explained as a function of number of PCs shows that all PCs have non-zero contributions in explaining the variance (Fig. #). This validates further investigation of the contribution of each factor in explaining mole count in principal component and partial least squares regression.

***PCR***

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title = {The principal problem with principal components regression},

journal = {Cogent Mathematics & Statistics},

number = {just-accepted},

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ISSN = {2574-2558},

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type = {Journal Article}

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title = {Risk factors of incident melanocytic nevi: a longitudinal study in a cohort of 1,232 young German children},

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number = {1},

pages = {121-126},

ISSN = {0020-7136},

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title = {Novel pleiotropic risk loci for melanoma and nevus density implicate multiple biological pathways},

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ISSN = {1534-844X},

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url = {<https://doi.org/10.1207/s15328031us0304_4>},

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title = {Genetic determinants of hair and eye colours in the Scottish and Danish populations},

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