# The Use of Collinearity Diagnostics in PK Model Building

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# The Use of Collinearity Diagnostics in PK Model Building

- Introduction - Definitions
- Types of Collinearity
- Diagnosing Collinearity
- Conclusions

# What is Collinearity?

- Collinearity:
  - Relationship where there is a <u>near</u> linear dependency between 2 independent variables

- Multicollinearity:
  - Relationship where one independent variable is <u>nearly</u> a linear combination of 2 or more other independent variables

- Ill-conditioning:
  - A small change in input (age, weight) produces a large change in output (age & weight regression coefficients)

# What is Collinearity?

Collinearity = high correlation between <u>independent</u> variables

<u>Harmful</u> Collinearity = high correlation between independent variables & wide confidence intervals

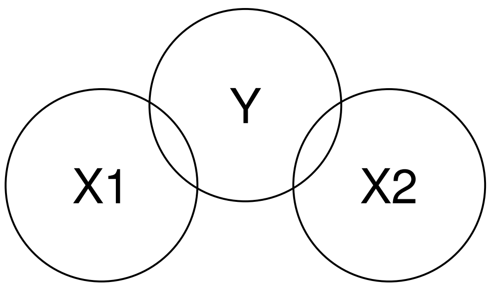
<u>Degrading</u> Collinearity = Collinearity causing minor problems

# What is Collinearity?

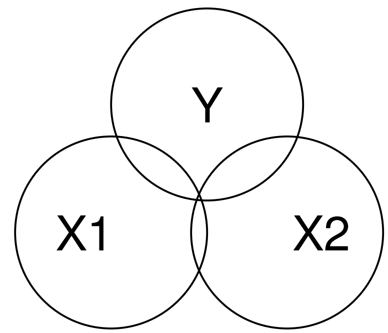
High Correlation => shared variance between independent variables, which makes it difficult to identify the individual contribution for each independent variable

E.g. If your population only has heavier old people and lighter young people, you cannot identify the independent effects of weight and age on the outcome variable

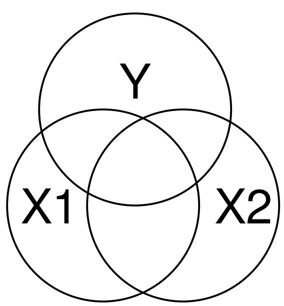
# What is Collinearity?
# Venn Diagram of Variability Sharing



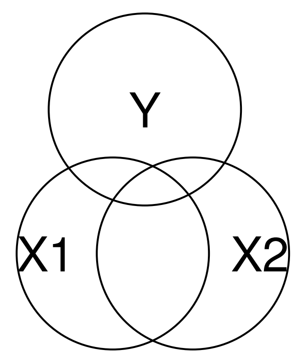

Orthogonal Predictors




Mildly Collinear Predictors




Strongly Collinear Predictors
Strong Fit




Strongly Collinear Predictors
Weak Fit

# Types of Collinearity

- Data
  - Age, weight
- Model parameters/algorithms
  - NONMEM tries to prevent model based collinearity by scaling parameters
  - “STP” = scaled transformed parameters
  - Scale so absolute value of initial estimate of a parameter is 0.1

# Diagnosing Collinearity

- Correlation matrix for indep. variables
- Determinant of correlation matrix
- VIF = Variance Inflation Factor
- Proportion of variance metrics
- Outlier review
- Sensitivity analysis

The above tools provide indicators of problems with collinearity, but are not perfect

# Diagnosing Collinearity: Correlation Matrix

- Can help identify pairwise collinearity
- Cannot identify collinearity involving three or more variables

$$\begin{matrix} 1 & .92 & .24 \\ .92 & 1 & .37 \\ .24 & .37 & 1 \end{matrix}$$

# Diagnosing Collinearity Determinant

- Det(R) ranges from 0 (Perfect Collinearity) to 1 (No Collinearity)
- The determinant of a diagonal matrix is the product of the eigenvalues. The presence of one or more <u>small</u> eigenvalues indicates collinearity

# Diagnosing Collinearity
# Variance Inflation Factor = VIF

$VIF(X_i) = 1/(1-R_i^2)$ $\qquad$ $i = 1, 2, \ldots, k-1$

k= #indep variables

$R_i^2$ = Multiple correlation coefficient of $X_i$ regressed on the other independent variables

Collinearity is present when VIF for at least one independent variable is large

Rule of Thumb:

VIF > 10 is of concern

# Diagnosing Collinearity
# Condition Number (CN)

CN = sqrt($\lambda_{max}/\lambda_{min}$)

$\lambda_{max}$= Maximum eigenvalue

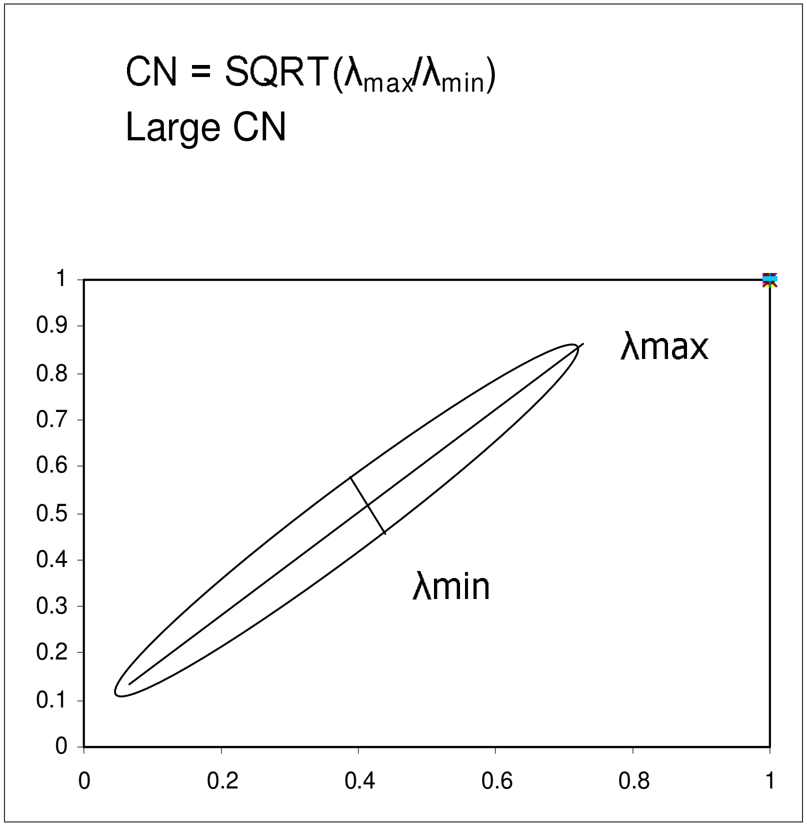
$\lambda_{min}$= Minimum eigenvalue

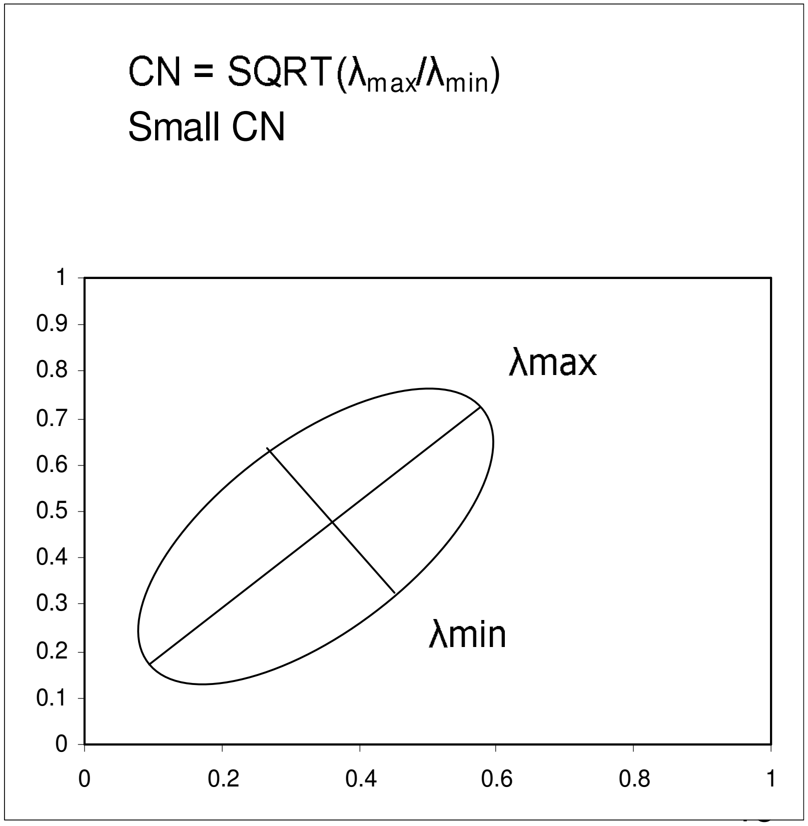
| CN | Meaning |
|---|---|
| 1 | No collinearity |
| >1 | Collinearity |
| >30 | Severe collinearity |
| $\infty$ | Perfect collinearity |

# Diagnosing Collinearity
# Condition Number (CN)

$$CN = \text{sqrt}(\lambda max/\lambda min)$$

CN = Ratio of axes lengths in likelihood surface



# Diagnosing Collinearity
# Condition Index (CI)

$CI = \text{sqrt}\ (\lambda_{max}/\lambda_i)$ $\qquad$ $i = 1, 2, \ldots, k$

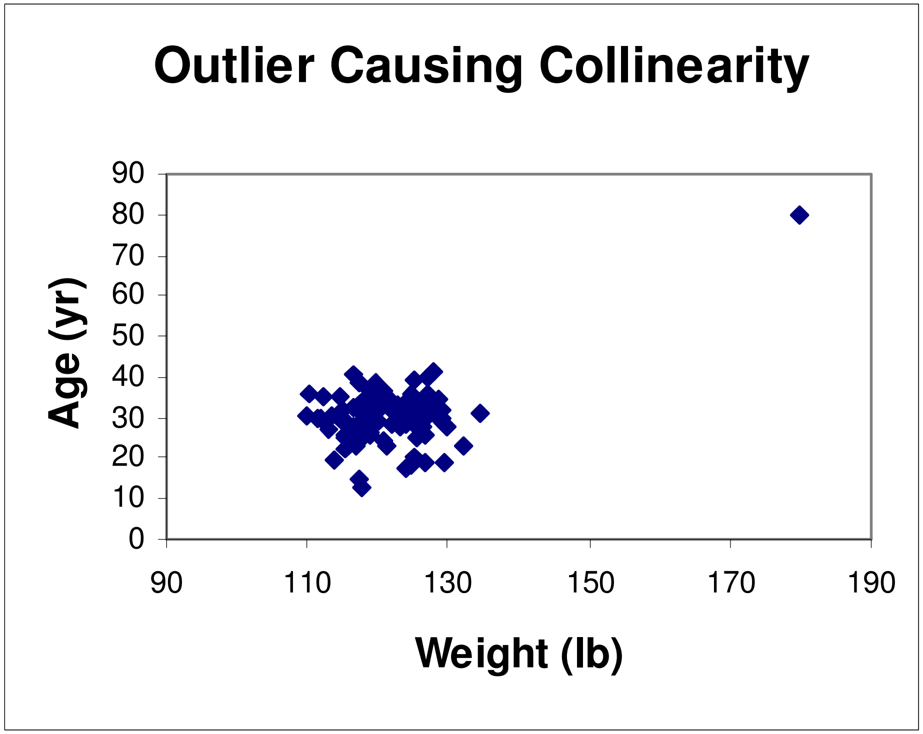
(k=# indep. Variables)

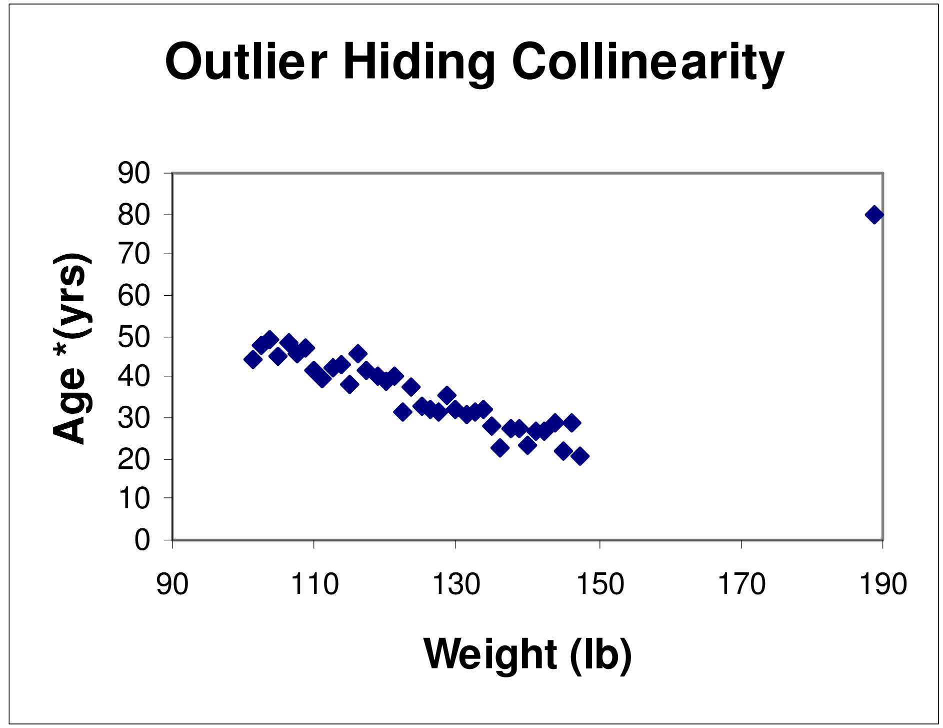
where

$\lambda_{max}$= Maximum Eigenvalue

$\lambda_i$= ith Eigenvalue

# Diagnosing Collinearity
# Outliers



# Diagnosing Collinearity Sensitivity Analysis

- Sensitivity Analysis is the best method for identifying collinearity in nonlinear models
- Perturb data with random draws and re-estimate parameters
- If parameters fall outside of a predetermined limit, then problems exit. However, problem may be due to things other than collinearity

# Diagnosing Collinearity
# Correlation Matrix

| | V1 | V2 | V3 | V4 | V5 | V6 | V7 |
|---|---|---|---|---|---|---|---|
| V1 | 1.00000 | 0.85708 | 0.47847 | 0.56881 | 0.76677 | 0.92704 | 0.97076 |
| V2 | **0.85708** | 1.00000 | 0.46069 | 0.46398 | 0.54601 | 0.84522 | 0.85447 |
| V3 | 0.47847 | 0.46069 | 1.00000 | 0.38089 | 0.37356 | 0.46340 | 0.47993 |
| V4 | 0.56881 | 0.46398 | 0.38089 | 1.00000 | 0.68275 | 0.58777 | 0.65794 |
| V5 | 0.76677 | 0.54601 | 0.37356 | 0.68275 | 1.00000 | 0.67216 | 0.75815 |
| V6 | **0.92704** | 0.84522 | 0.46340 | 0.58777 | 0.67216 | 1.00000 | 0.97847 |
| V7 | **0.97076** | **0.85447** | 0.47993 | 0.65794 | 0.75815 | **0.97847** | 1.00000 |

# Diagnosing Collinearity

**Algorithm:**

**Execute Nonmem control file with INFN subroutine to create correlation matrix from variance covariance matrix**

```
$SUBR   ADVAN1 TRANS2 INFN = c:\nmv\run\runlog2ab.for
========================================
C rulog2ab .for
SUBROUTINE INFN(ICALL,THETA,DATREC,INDXS,NEWIND)
      common /rocm6/ omegaf(lvr,lvr)
      common /cm2/ neta
     do 37 i = 1,neta
     do 36 j = 1, neta
     corromg(i,j)=omegaf(i,j)/sqrt(omegaf(i,i)*omegaf(j,j))
 36     continue
 37     continue
```

# Diagnosing Collinearity

**Algorithm:**

**Execute Splus Program Collin.ssc which generates collinearity diagnostics using the variance covariance matrix as input**

**=========================================**

```
mdata = matrix (scan( "omegacorr.txt"),ncol=7,byrow=T)
#calculate the determinant
ddata <- det(mdata)
#get vif
vif=diag(solve(mdata))
#perform principal component analysis when input is a correlation
      matrix
 pdata <- princomp(covlist=mdata2,cor=T)
#calculate the condition number
condnumber <- (max (eigenvalue) / eigenvalue)
#examine proportion of variance explained = (eigenvalue/(sum of
      eigenvalues))
```

# Diagnosing Collinearity

**Table 1: Output of COLLIN.S**

```
> [1] "DETERMINANT" Det ~0 indicates Potential Collinearity
[1] 2.495433e-05

> [1] "VIF" VIF > 10 indicates Potential Collinearity
    V1        V2        V3        V4        V5        V6        V7
 43.63222 4.54154 1.360764 4.06083 3.799957 56.60333 178.7016

➢[1] "PROPORTION OF VARIANCE" CI > 30 + Prop Var > .5 => Collinearity

                 CONDITION
   Eigenvalue     INDEX     V1     V2     V3     V4     V5     V6     V7
P1 5.04673909  1.000000 0.0008 0.0065 0.0097 0.0051 0.0069 0.0006 0.0002
P2 0.72302579  2.641974 0.0000 0.0095 0.7045 0.0463 0.0496 0.0000 0.0000
P3 0.69939050  2.686245 0.0016 0.0511 0.2387 0.1325 0.0344 0.0017 0.0002
P4 0.31780946  3.984942 0.0026 0.0510 0.0264 0.2803 0.4144 0.0009 0.0000
P5 0.15870578  5.639090 0.0016 0.7776 0.0064 0.0049 0.1162 0.0290 0.0033
P6 0.05048966  9.997794 0.2717 0.1041 0.0034 0.0586 0.3648 0.1025 0.0003
P7 0.00383972 36.253975 0.7216 0.0003 0.0109 0.4724 0.0138 0.8653 0.9960
>
```

# Conclusions

- **Identifying collinearity problems in NONMEM output can be difficult**
- **Correlation matrix derived from NONMEM output does not provide sufficient information**

# Conclusions

- **The determinant, VIF, and proportion of variance matrix pinpoint the specific variables with collinearity problems that should be removed from the next run**
- **Examine collinearity diagnostics <u>and</u> regression coefficient confidence intervals to determine if collinearity is harmful**

# References


- Belsely, DA, Kuh, E., & Welsch, RE 1980. Regression diagnostics: Identifying influential data and sources of collinearity. New York
- Bonate, Peter 2006. Pharmacokinetic-Pharmacodynamic Modeling and Simulation. Springer, New York
- Mason, RL, & Gunst, RF Outlier-Induced Collinearities Technometrics, Vol. 27, No. 4 (Nov., 1985) , pp. 401-407