Statistics, Random Numbers and Stochastic Simulation

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Statistics in R

There are plenty of textbooks on this!

Here are the very basics

```
> statdata <- read.csv("stats_data.csv")
> statdata$AGEBIN <- as.factor(statdata$AGEBIN)
> head(statdata)
```

```
  ID DOSE ROUTE AGE AGEBIN WEIGHT
1  1   50     0  32      0     75
2  2   50     0  79      1     54
3  3   50     0  60      1     90
4  4   50     0  79      1     63
5  5   50     0  25      0     66
6  6   50     1  64      1     68
```

Statistics - Linear regression

The variables are both continuous

```
> result1 <- lm(WEIGHT~AGE, data=statdata)
```

Statistics - Linear regression

```
Call:
lm(formula = WEIGHT ~ AGE, data = statdata)

Residuals:
   Min     1Q Median     3Q    Max
 -9.29  -7.56  -1.47   4.32  22.79

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)   80.039      6.360   12.58  2.3e-10 ***
AGE           -0.214      0.116   -1.85    0.081 .
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 9.16 on 18 degrees of freedom
Multiple R-squared:  0.16,  Adjusted R-squared:  0.113
F-statistic: 3.42 on 1 and 18 DF,  p-value: 0.0808
```

Statistics - Analysis of Variance 1

Fact: ANOVA is a type of linear regression

The independent variable is a factor

It represented internally by “contrasts” - 0 or 1

```
> result2 <- lm(WEIGHT~AGEBIN, data=statdata)
```

Statistics - Analysis of Variance 1

```
Call:
lm(formula = WEIGHT ~ AGEBIN, data = statdata)

Residuals:
   Min     1Q Median     3Q    Max
-14.00  -6.00  -4.29   4.93  22.00

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)    70.57       3.74   18.85  2.7e-13 ***
AGEBIN1        -2.57       4.64   -0.55     0.59
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 9.9 on 18 degrees of freedom
Multiple R-squared:  0.0168,    Adjusted R-squared:  -0.0379
F-statistic: 0.307 on 1 and 18 DF,  p-value: 0.587
```

Statistics - Analysis of Variance 2

This produces the same result

```
> result3 <- aov(WEIGHT~AGEBIN, data=statdata)
```

```
             Df Sum Sq Mean Sq F value Pr(>F)
AGEBIN        1     30    30.1    0.31   0.59
Residuals    18   1766    98.1
```

Statistical output

The statistical output is stored as a list object

Lists can be nested structures of mixed data types

```
> names(result1)
```

```
 [1] "coefficients"  "residuals"     "effects"       "rank"
 [5] "fitted.values" "assign"        "qr"            "df.residual"
 [9] "xlevels"       "call"          "terms"         "model"
```

```
> result1$coefficients["AGE"]
```

```
    AGE
-0.2138
```

Repeated measures data

Use mixed-effect linear regression (lme)

This is analogous to NONMEM with fixed and random effects

```
> library(nlme)
> #lme(WEIGHT~AGEBIN, random= ~1|ID, data=repdata)
```

Stochastic simulation

The simulation of a system that has random components

Randomness comes from a random number generator

The random numbers can be modified into various distributions

- Normal
- Log-normal
- Uniform
- Bionomial

Simulation in pharmacometrics

All simulations from population models are stochastic

The stochastic components (ETA, EPS) of the model are recreated by sampling from distributions of random numbers

Examples

- Visual Predictive Check
- Simulations of model prediction intervals
- Clinical trial simulation
- Simulations of study power

Generating random numbers

Many computer algorithms have been developed

Pseudo-random numbers will eventually repeat

Testing for randomness is complicated

- plot(runif(10000) ~ runif(10000))
- estimate pi

Bad algorithims repeat quickly and may be autocorrelated

- Excel had problems

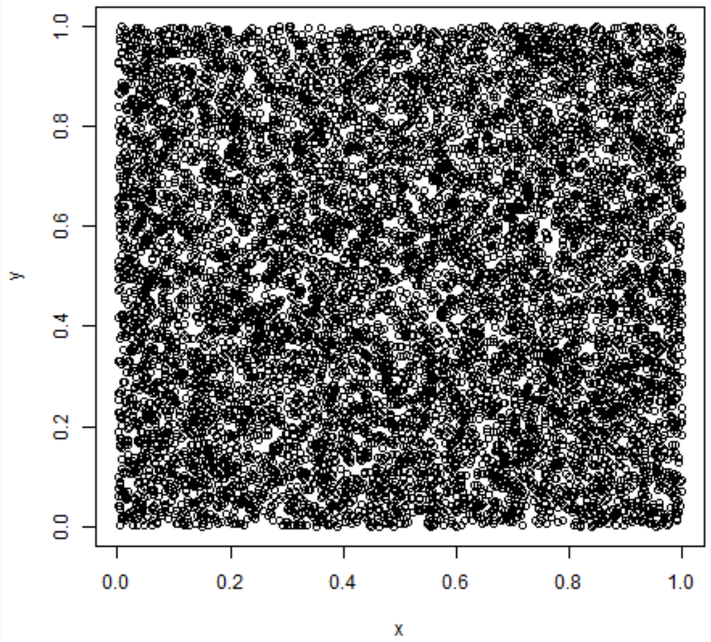
Random Number Table

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
1	8	0	9	4	2	5	2	5	8	2	4	7	1	3	4	7	7	4	3	3	3	6	2	0	1	8	9	7	2	1	3	4
2	3	5	6	3	2	1	9	8	8	2	1	1	9	0	4	5	2	6	1	8	2	7	5	1	2	6	2	7	1	0	9	5
3	1	3	3	0	6	3	3	1	3	7	5	3	9	6	9	3	8	7	3	8	6	8	1	5	1	5	3	8	8	5	4	3
4	3	5	6	5	0	0	1	6	2	2	4	3	6	4	3	2	4	7	9	6	6	0	9	5	5	2	8	3	1	6	2	0
5	7	8	5	0	5	9	2	5	5	5	8	8	7	3	1	1	2	1	9	2	4	5	4	5	3	5	3	0	5	5	8	9
6	4	4	9	0	5	4	1	7	9	7	2	7	6	1	5	3	5	9	0	1	4	8	7	8	9	9	8	0	9	8	7	7
7	6	5	4	5	9	1	0	4	9	3	1	8	8	8	1	9	7	5	3	7	2	7	8	5	9	3	7	3	2	4	4	5
8	3	6	2	6	5	9	9	5	1	2	1	5	9	7	5	3	9	2	2	3	5	6	5	8	2	9	4	4	2	8	9	9
9	4	6	6	5	4	8	2	0	7	5	5	4	0	6	1	2	9	6	8	3	4	2	5	1	9	1	3	8	1	7	0	9
10	6	4	9	8	7	5	1	9	0	4	7	4	7	8	1	8	6	8	3	2	9	6	8	3	9	8	7	2	4	0	9	0
11	6	7	2	2	9	8	6	9	9	3	6	1	7	8	7	5	4	8	8	3	1	3	1	5	9	6	7	9	8	8	3	4
12	9	7	4	8	5	9	3	2	5	1	1	5	2	7	2	1	0	0	3	3	9	3	0	3	9	7	1	3	4	0	1	2
13	5	6	4	1	1	4	1	7	1	4	1	9	7	4	3	4	8	1	6	5	7	3	6	8	1	2	1	8	5	0	3	9
14	7	4	4	4	9	2	0	0	8	8	4	0	5	8	8	2	4	3	9	8	3	9	0	4	9	1	9	9	9	3	3	6
15	8	2	7	9	3	0	1	9	4	6	7	2	3	7	4	3	3	9	7	9	4	6	8	9	9	0	2	1	6	9	9	0
16	0	1	6	1	7	6	1	7	1	0	2	4	2	3	8	7	2	8	9	1	6	6	7	7	1	5	8	5	2	4	8	2
17	7	3	8	8	9	7	5	9	7	5	5	5	6	8	2	4	9	9	7	7	2	0	0	8	5	5	9	6	9	7	4	0
18	7	8	3	0	4	7	1	4	3	6	9	5	2	9	1	9	1	8	0	4	4	0	4	4	1	0	3	4	2	5	9	7
19	9	8	8	7	4	2	1	6	6	5	2	6	4	5	3	5	8	4	3	0	5	2	7	0	9	6	0	5	0	7	6	8
20	1	2	6	1	2	5	1	6	8	5	6	9	2	3	1	0	3	9	3	9	8	7	0	3	9	8	4	1	0	3	5	3
21	3	9	4	7	4	9	3	7	7	6	3	4	2	5	4	3	6	2	3	9	7	4	5	5	2	0	5	5	7	7	9	5
22	4	5	5	0	8	1	0	3	1	2	5	0	2	3	0	4	1	1	3	8	9	7	8	8	9	1	4	4	4	5	2	6
23	1	3	4	4	9	6	9	7	2	3	8	3	6	9	7	6	6	2	5	1	4	2	0	1	2	0	3	8	6	5	5	2
24	8	9	7	6	5	8	2	3	8	4	8	7	0	4	5	0	3	1	0	6	9	1	6	6	2	7	1	7	7	6	0	1
25	7	7	1	0	9	9	4	3	6	9	7	8	8	2	7	3	9	7	1	4	9	7	0	0	1	5	6	6	2	8	8	9
26	6	9	5	9	6	0	0	8	8	4	4	2	2	2	8	2	1	5	2	4	2	5	1	7	5	8	1	8	0	0	8	1
27	7	9	4	1	2	3	1	2	2	4	3	1	6	7	0	2	9	9	8	4	3	4	6	9	3	0	8	5	4	7	6	2
28	2	2	8	4	0	8	9	6	9	1	0	7	5	5	4	2	7	3	1	9	3	7	8	2	1	0	6	8	9	5	7	4
29	9	5	9	4	7	4	1	6	9	3	6	5	6	0	4	5	1	1	8	3	5	9	1	6	9	5	9	9	1	1	4	3
30	4	6	1	3	8	5	4	9	6	3	6	9	3	2	0	8	5	1	0	9	9	6	8	0	1	1	6	8	6	1	3	3

A test of randomness

x and y are 10,000 independent random uniform numbers

```
x <- runif(10000)
y <- runif(10000)
plot(y ~ x)
```



Why simulate in R rather than NONMEM?

In NONMEM, doses and covariates are coded in the database

If you want to change these in a simulation, you make a new database

If it's complex simulation, this is usually done with R

And R might be used to plot the simulated data anyway

So cut out the middle man and use R for everything!

It may (sometimes!) be faster and easier

Generating random numbers in R

R has a family of functions for random numbers
see ?Distributions

function	distribution	examples
rnorm	normal	additive residual error, PD baseline
rlnorm	log-normal	clearance, distribution volume
runif	uniform	age
rbinom	binomial	sex, genotype

Related functions in R

For each class of distribution

function	distribution	comment
dnorm(x, mean=0, sd=1)	gives the density of x	used in maximum likelihood estimation
pnorm(x, mean=0, sd=1)	gives the distribution function	turns x into a probability
qnorm(p, mean=0, sd=1)	gives the quantile function	turns probability into a quantile
rnorm(n, mean=0, sd=1)	generate n random numbers	from a distribution with mean=0 and sd=1

Using the rnorm function

```
> randomn <- rnorm(n=10, mean=2, sd=0.5)
> randomn
```

```
 [1] 3.230 2.229 2.579 1.762 1.974 1.952 1.454 2.980 2.092 2.219
```

```
> mean(randomn)
```

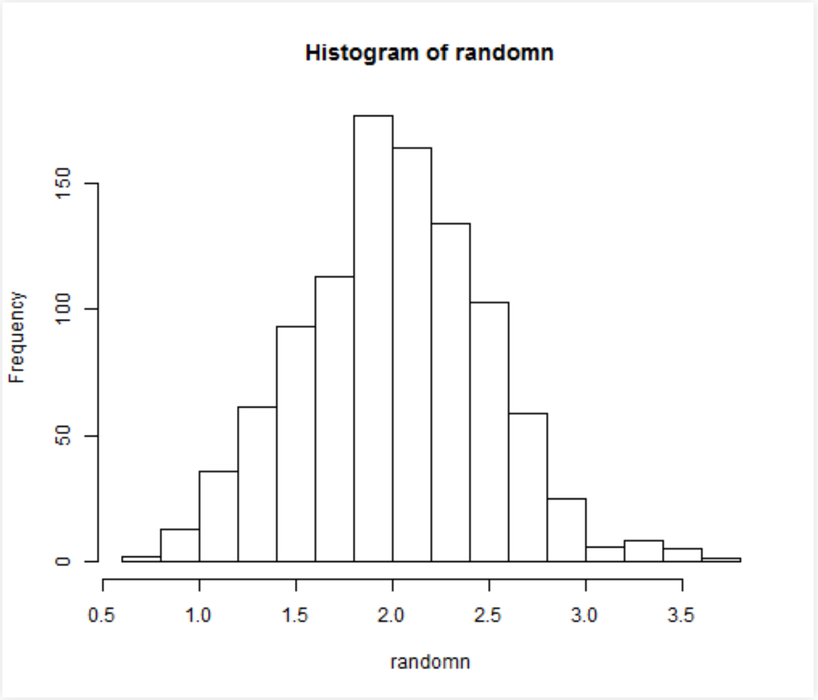
```
[1] 2.247
```

```
> sd(randomn)
```

```
[1] 0.5441
```

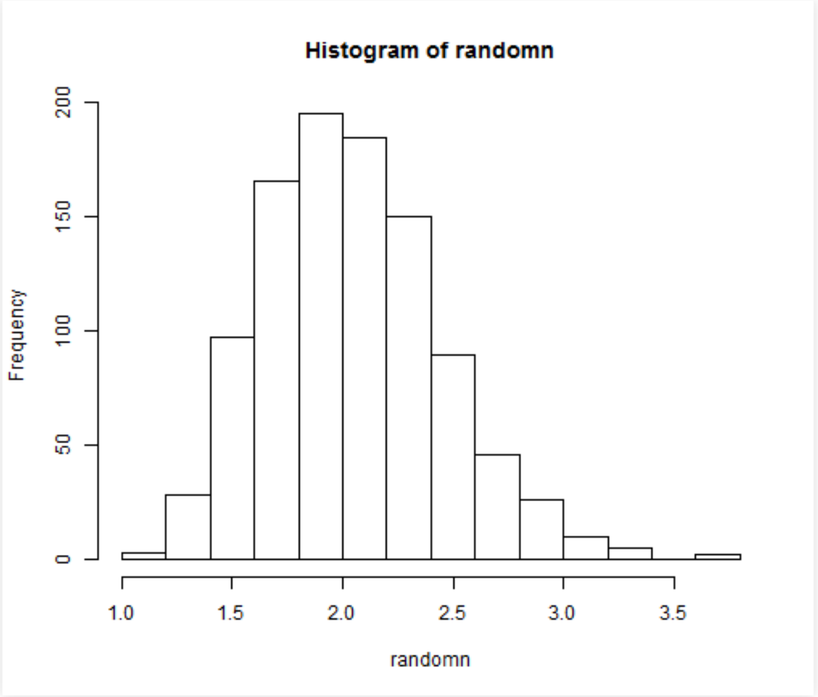
Using the rnorm function

```
> randomn <- rnorm(n=1000, mean=2, sd=0.5)
> hist(randomn)
```



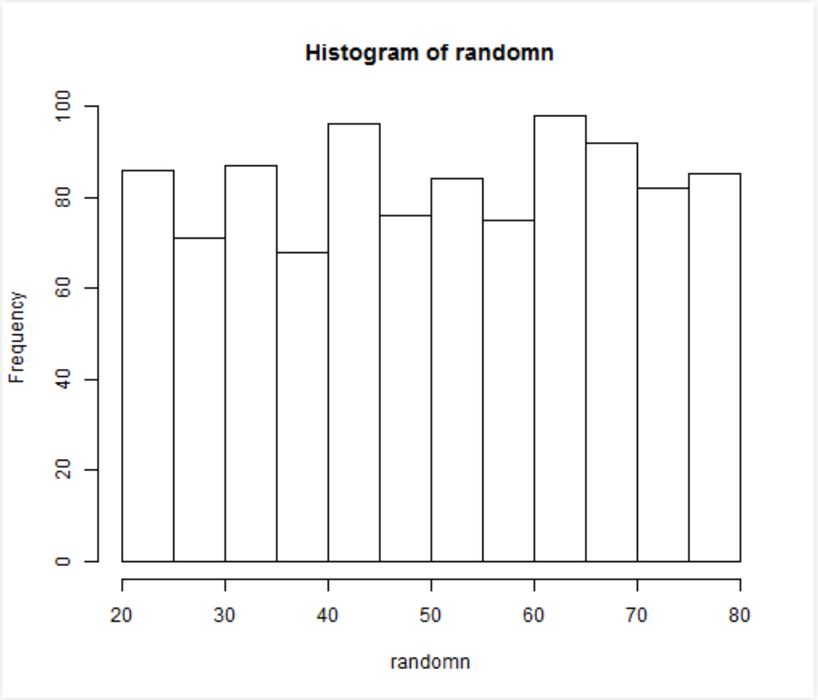
Using the rlnorm function

```
> randomn <- rlnorm(n=1000, mean=log(2), sd=0.2)
> #Note sd is now a ratio
> hist(randomn)
```



Using the runif function

```
> randomn <- runif(n=1000, min=20, max=80)
> hist(randomn, breaks=10)
```



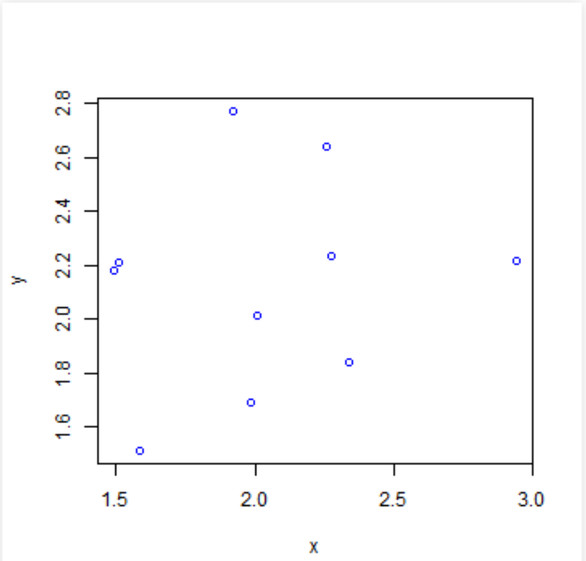
Using the rbinom function

```
> randomn <- rbinom(n=1000, size=1, prob=0.25)
> table(randomn)
```

```
randomn
  0   1
761 239
```

A simulation to understand randomness

```
> x <- rlnorm(n=10, mean=log(2), sd=0.2)
> y <- rlnorm(n=10, mean=log(2), sd=0.2)
> plot(y ~ x, col="blue")
```



We are programmed to see patterns!

Our job as scientists is to distinguish information from randomness

$p < 0.05$ means we are happy to fooled by randomness 1 time out of 20!

For low powered studies, focus on effect size and uncertainty

p-values are for *confirming* not *learning*

Setting a seed for reproducible random numbers!

```
> #No seed set
> rnorm(n=3, mean=2, sd=0.5)
```

```
[1] 2.162 1.952 1.797
```

```
> #No seed set
> rnorm(n=3, mean=2, sd=0.5)
```

```
[1] 2.218 2.603 1.539
```

Setting a seed for reproducible random numbers!

```
> set.seed(123)
> rnorm(n=3, mean=2, sd=0.5)
```

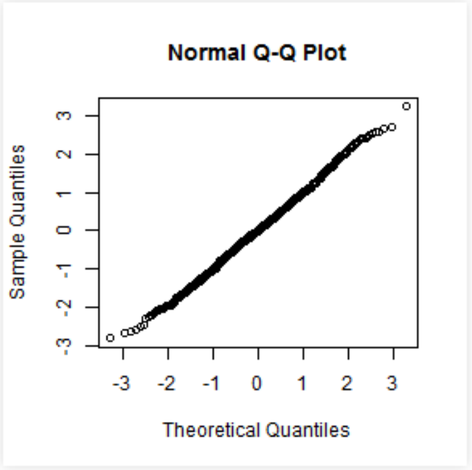
```
[1] 1.720 1.885 2.779
```

```
> set.seed(123)
> rnorm(n=3, mean=2, sd=0.5)
```

```
[1] 1.720 1.885 2.779
```

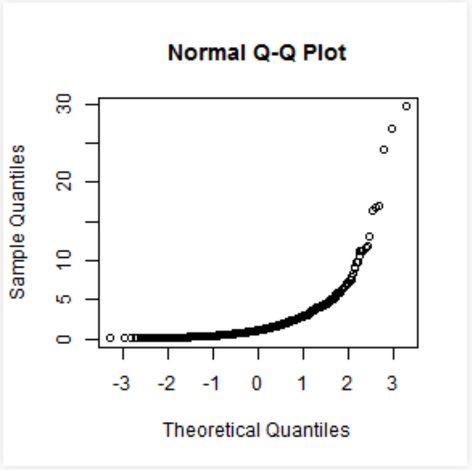
Testing normality - quantile-quantile plots

```
> x <- rnorm(1000)
> qqnorm(x)
```



Testing normality - quantile-quantile plots

```
> y <- rlnorm(1000)
> qqnorm(y)
```



Log-normal distributions in biology

Normal distributions arise from additive process
c(mean+1, mean+3, mean+0, mean-2, mean+2)

Log-normal distributions arise from multiplicative processes
c(mean*2, mean/3, mean*1, mean/2, mean*4)

Log-normal distributions are common in biological systems

No zero values, right skewed, occasional high values

Described by the geometric mean, the standard deviation is a ratio

If x is normal, log(x) is log-normal
If x is log-normal, exp(x) is normal

Truncated & Censored distributions

A metric may have normal distribution

But our ability to measure the metric might be censored:

- LLOQ of an assay
- Ethical limits for thermal pain tests

The distribution we measure is censored or truncated

This may need to replicated in a model

Non-normal distributions

Skewed

- Left (median > mean)
- Right (median < mean)

Kurtotic

- Unimodal (median = mean)
- Platykurtic, thin-tailed, peaky
- Leptokurtic, fat-tailed, flat

Multi-modal

- More than 1 peak

Transformed distributions

NONMEM simulations assume an underlying normal distribution for ETA

A transformation may replicate a skewed parameter distribution

Transformations try to “normalize” a distribution

- Log-normal
- Box-Cox
- Manly

See Petersson et al., *Pharm Res* 2009 26:2174-85

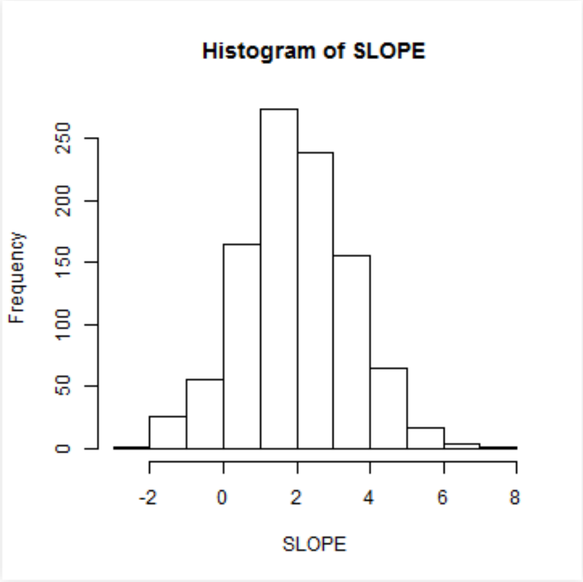
Additive Between Subject Variability

Effect = Baseline + Slope*Conc

```
> nsubs <- 1000
> SLOPEpop <- 2
> ETA <- rnorm(nsubs, mean=0, sd=1.5)
> SLOPE <- SLOPEpop + ETA
```

ETA is normally distributed
SLOPE is normally distributed
SLOPE can take negative values

```
> hist(SLOPE)
```


Histogram of SLOPE
Frequency
0
50
100
150
200
250
-2
0
2
4
6
8
SLOPE

Exponential Between Subject Variability

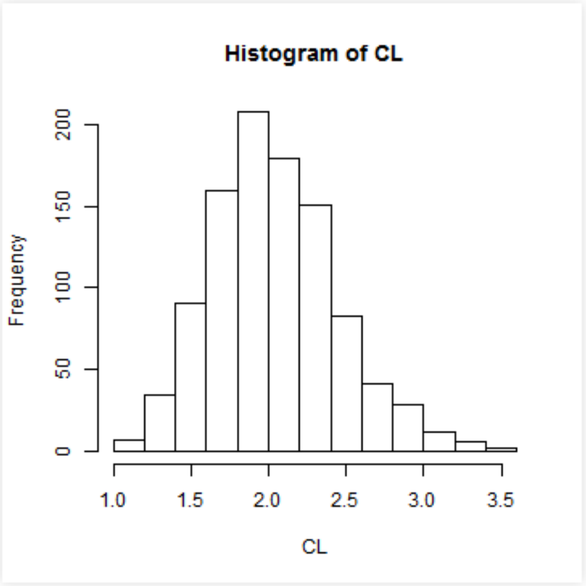
CL = CLpop*exp(ETA)

```
> nsubs <- 1000
> CLpop <- 2
> ETA <- rnorm(nsubs, mean=0, sd=0.2)
> CL <- CLpop*exp(ETA)
```

ETA is normally distributed
CL is log-normally distributed
CL can't take negative values
SD of CL is 0.2
VAR of CL is $0.2^2 = 0.04$

Exponential Between Subject Variability

```
> hist(CL)
```



Additive Residual Error

Y = F + EPS

F is model predicted concentration (fake with uniform random numbers!)

```
> nobs <- 1000
> F <- runif(nobs, min=0, max=10)
> EPS <- rnorm(nobs, mean=0, sd=1.5)
> Y <- F + EPS
```

Y (DV) is F with RUV

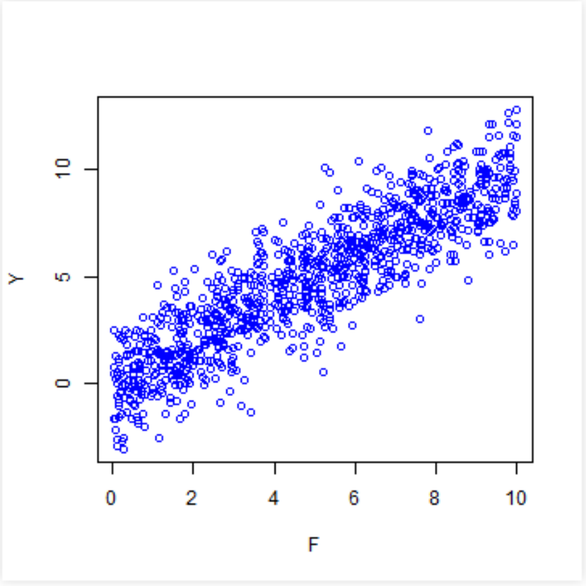
F is never negative

Y has negative values

shape = “tram tracks”

Additive Residual Error

```
> plot(Y ~ F, col="blue")
```



Proportional Residual Error

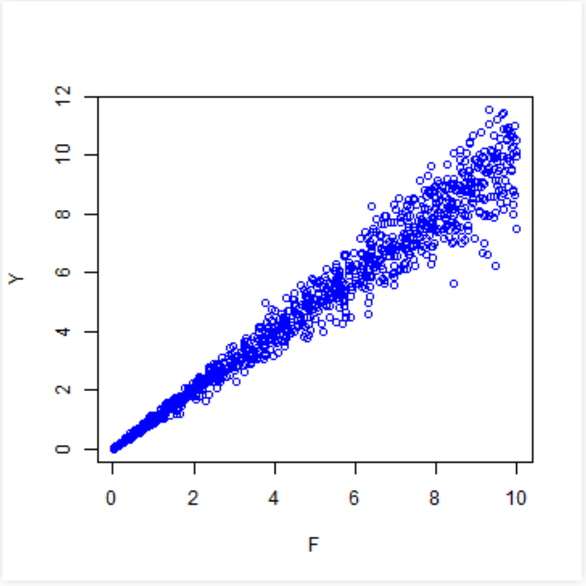
Y = F*(1 + EPS) or Y = F + F*EPS

```
> nobs <- 1000
> F <- runif(nobs, min=0, max=10)
> EPS <- rnorm(nobs, mean=0, sd=0.1)
> Y <- F*(1 + EPS)
```

Y (DV) is F with RUV
F is never negative
Y is never negative
(unless sd is large!)
shape = “cone”

Proportional Residual Error

```
> plot(Y ~ F, col="blue")
```



Additive and Proportional Residual Error

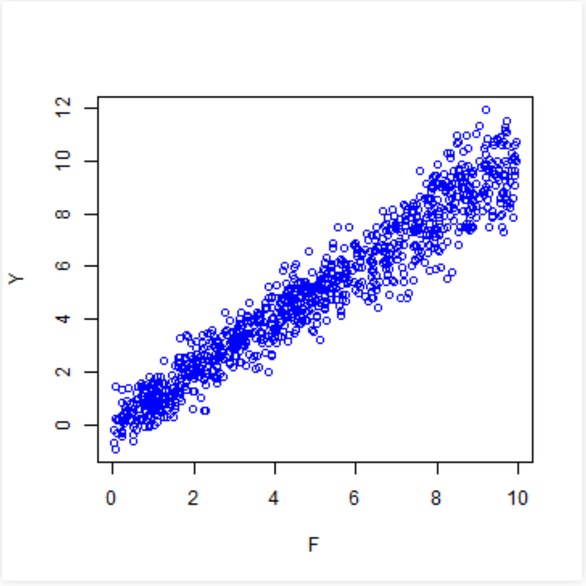
Y = F*(1 + EPS1) + EPS2

```
> nobs <- 1000
> F <- runif(nobs, min=0, max=10)
> EPS1 <- rnorm(nobs, mean=0, sd=0.1)
> EPS2 <- rnorm(nobs, mean=0, sd=0.5)
> Y <- F*(1 + EPS1) + EPS2
```

Y (DV) is F with RUV
F is never negative
Y can be negative
(at low concentrations)
shape = “tramtracks+cone”

Additive and Proportional Residual Error

```
> plot(Y ~ F, col="blue")
```



How many simulations?

Enough!

Simulations are repeated until the effect of randomness on summary statistics (e.g. mean and CI) are minimal

Some rules of thumb:

- 200 times for a mean
- 1,000 times for a confidence interval
- 10,000 times for study power

Capacity may be limited by computer memory for big problems(64 bit helps)

Covariance

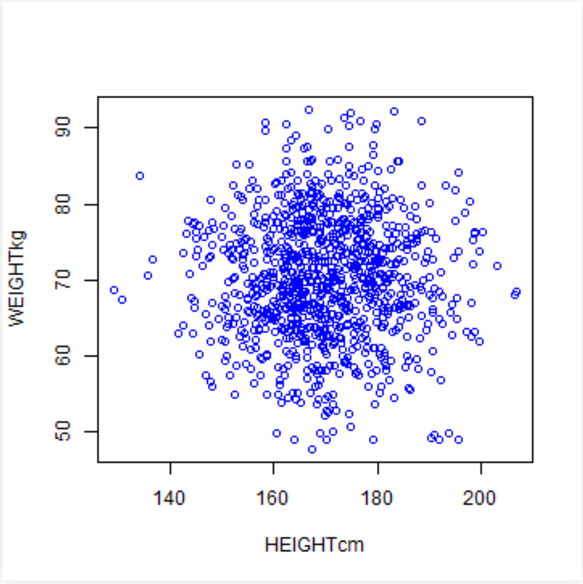
Covariance is a measure of how much two random variables change together

Not accounting for covariance may mean simulating implausible combinations of random numbers

```
> HEIGHTcm <- rnorm(1000, mean=170, sd=12)
> WEIGHTkg <- rnorm(1000, mean=70, sd=8)
```

Without Covariance

```
> plot(WEIGHTkg ~ HEIGHTcm, col="blue")
```



Covariance

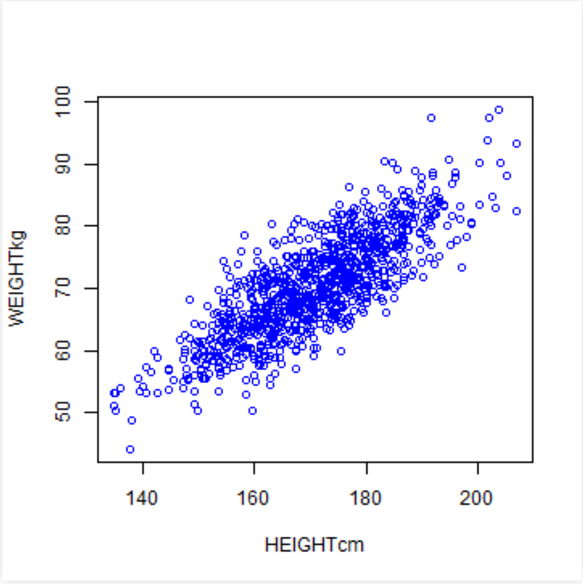
Covariance in NONMEM comes from $OMEGA BLOCK

Simulating correlated random numbers is complex

```
> library(MASS)
> OMEGA <- matrix(c(150,80,40,65),2,2)
> result <- mvrnorm(n=1000, mu=c(170,70), OMEGA)
> HEIGHTcm <- result[,1]
> WEIGHTkg <- result[,2]
```

With Covariance

```
> plot(WEIGHTkg ~ HEIGHTcm, col="blue")
```



Summary

Generating random numbers shows the influence of randomness on data

- Use simulation to educate yourself about how randomness affects your data

Random numbers are at the heart of every population model

- Use simulation to educate yourself about how randomness affects your model

Study design and study power are moving toward simulation based methods