Comorbidity Models

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Overview

- Psychiatric Disorders: binary phenotypes
  - Lots of comorbidity
  - Substance abuse similar
- ACE model is but one of many
- Two twins, two binary variables
  - 16 outcome combinations
- Fit models by maximum likelihood
  - (alternatives exist)

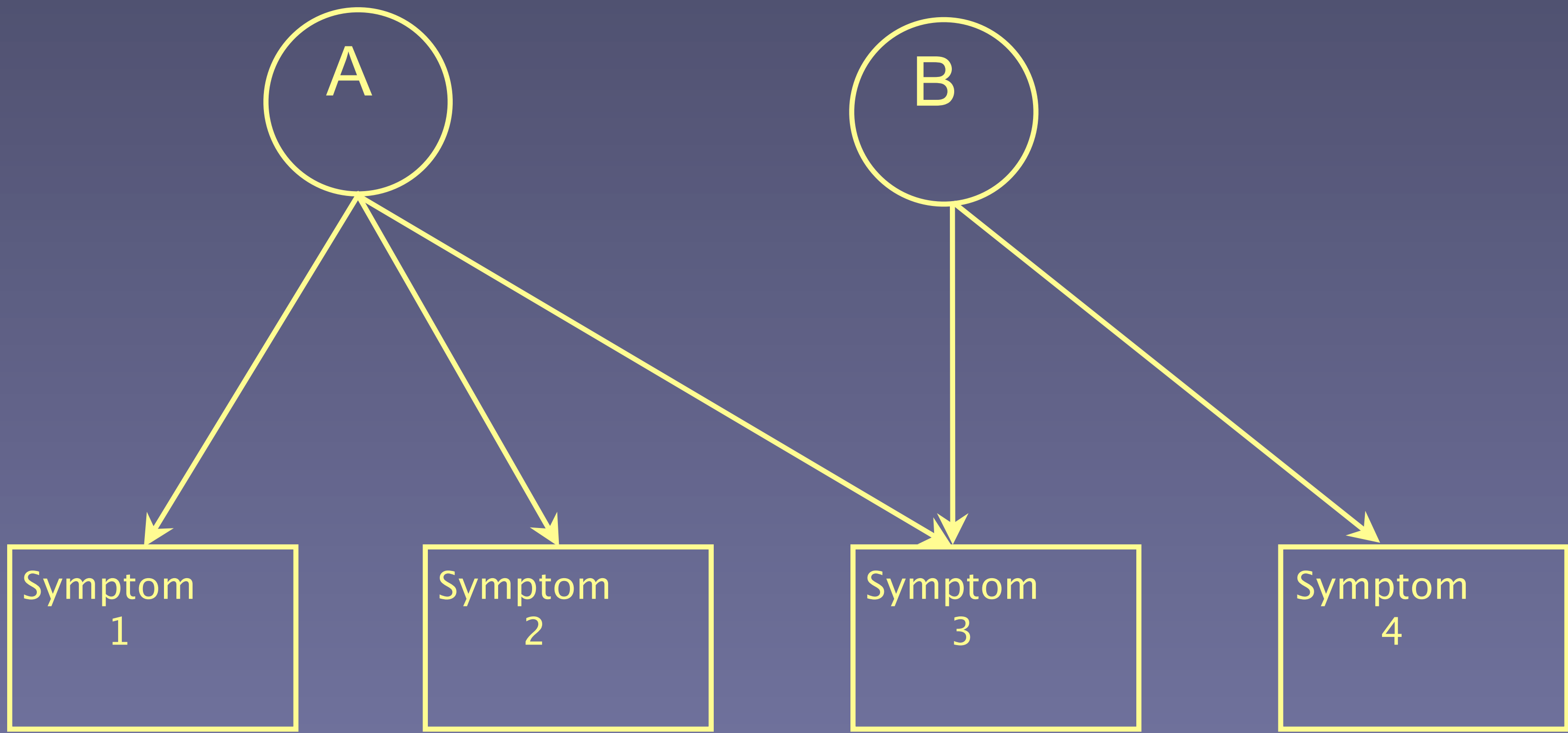
Assessment of Psychiatric Disorders

- Psychiatrists can agree on symptoms better than on diagnoses (Kendell et al 1971)
- Diagnostic and Statistical Manual of Mental Disorders (DSM-III 1980; DSM-IIIR 1987; DSM-IV 1994; DSM-IV 2012). Widespread use
- Little empirical basis for classification
- “If you believe…”

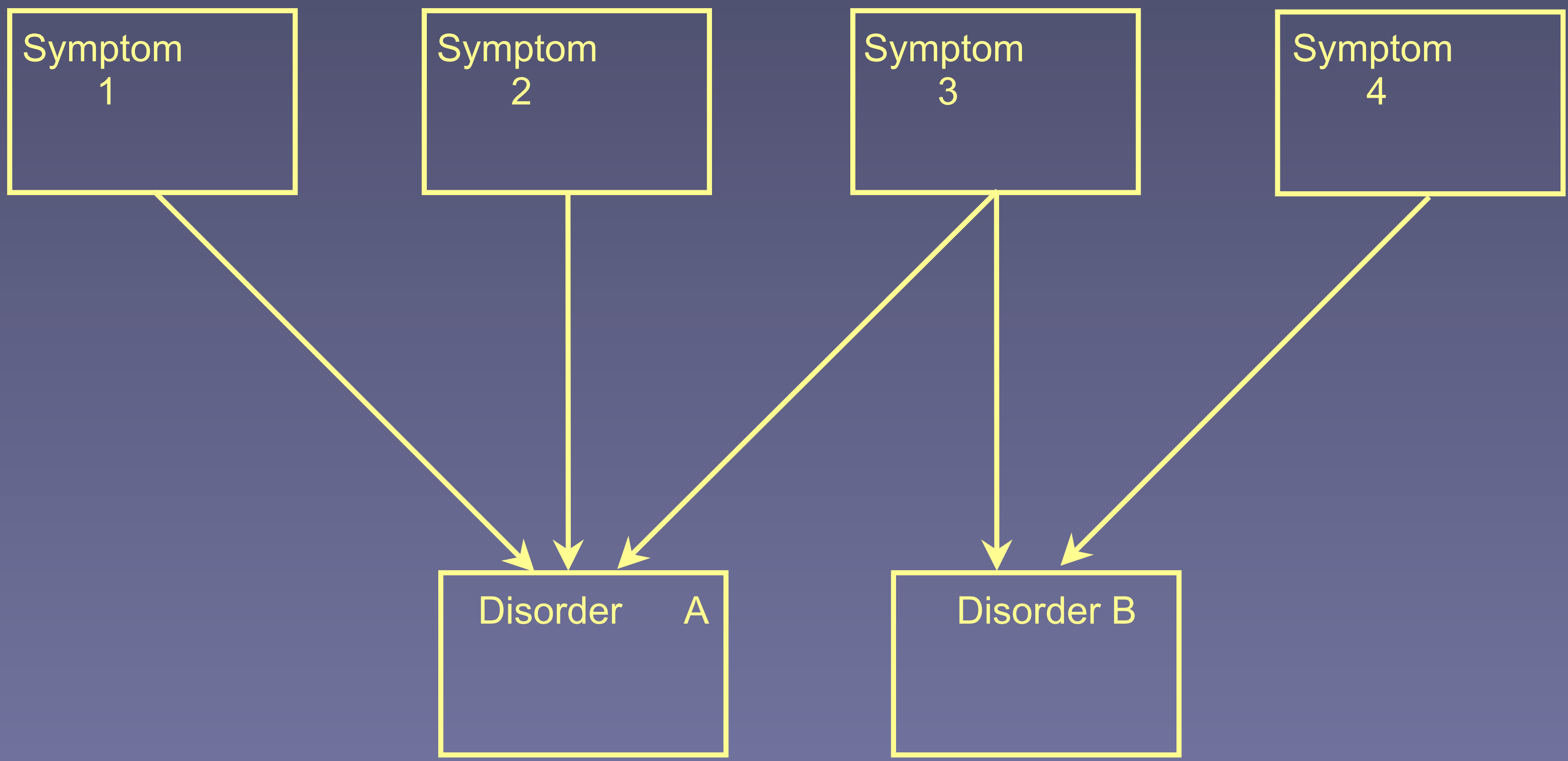
Comorbidity is High

- High for Psychiatric Disorders
  - Anxiety
  - Depression
  - Phobias
  - Panic
  - Alcohol Abuse
- 70% of those with history of 1 have history of at least one other (Kessler 1993; N=18,000)
- Similar rates in 10,000+ Virginia twins

Pure forms of two disorders A & B generate some of the same symptoms

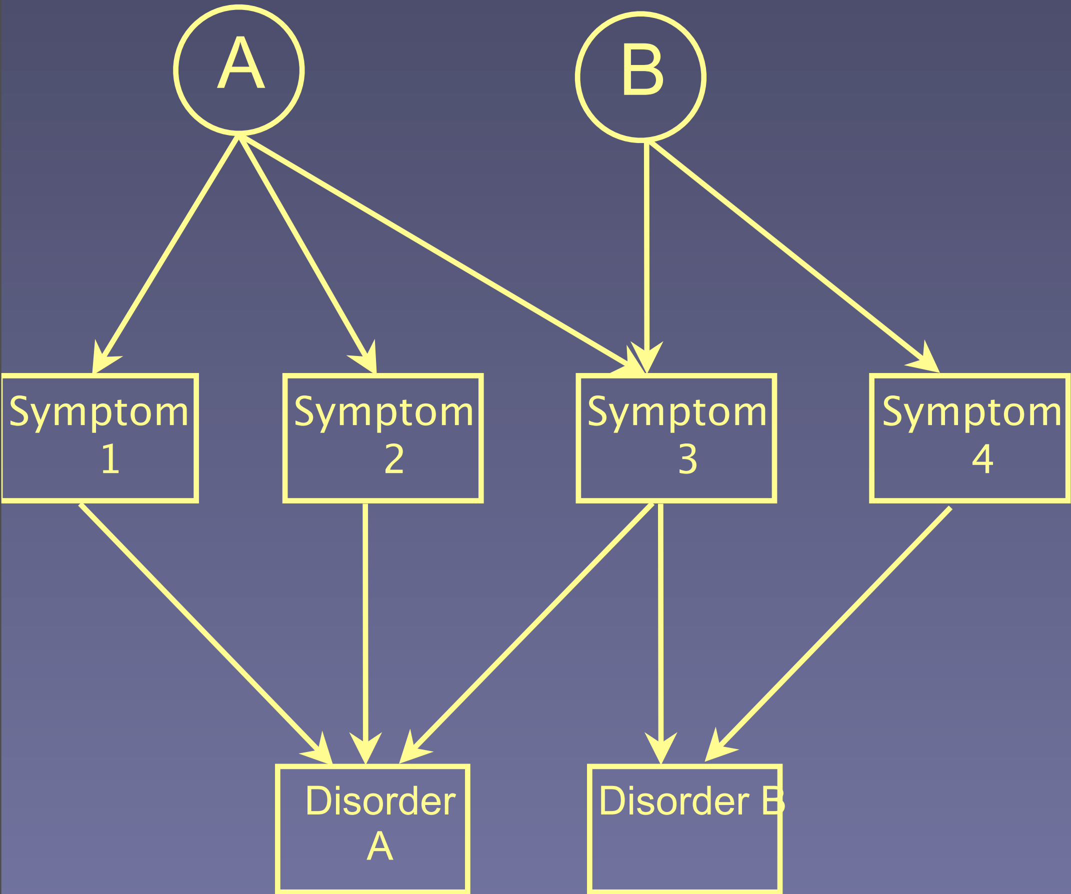


Assessments of disorders A & B share some symptoms



Cramer, Waldrop, Van der Maas, Borsboom (In Press)
Comorbidity: A network perspective. Brain Behavior Sciences

Comorbidity due to symptom sharing



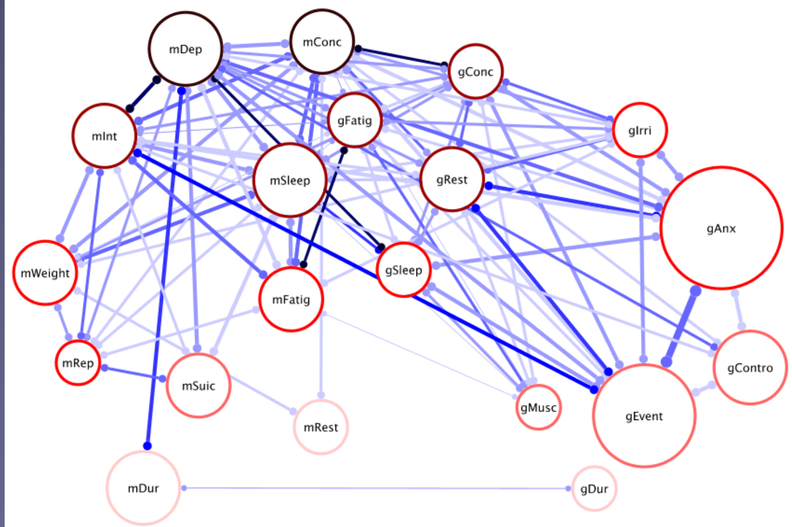


Figure 4. A comorbidity network for MDD and GAD. Larger nodes represent more frequent symptoms; darker circumference, higher centrality; thicker edges, higher frequency of co-occurrence; darker edges, stronger associations. Only edges with a log odds ratio higher than (-) 0.60 are represented. Centrally positioned nodes (*mConc*, *gConc*, *mSleep*, *gSleep*, *mFatig*, *gFatig*, *mRest* and *gRest*) represent overlapping symptoms. Non-overlapping MDD symptoms are displayed on the left of the figure, non-overlapping GAD symptoms on the right.

Not today!

Why do people get a disorder?

Single factor of large effect?

Lots of little factors of cumulative effect?

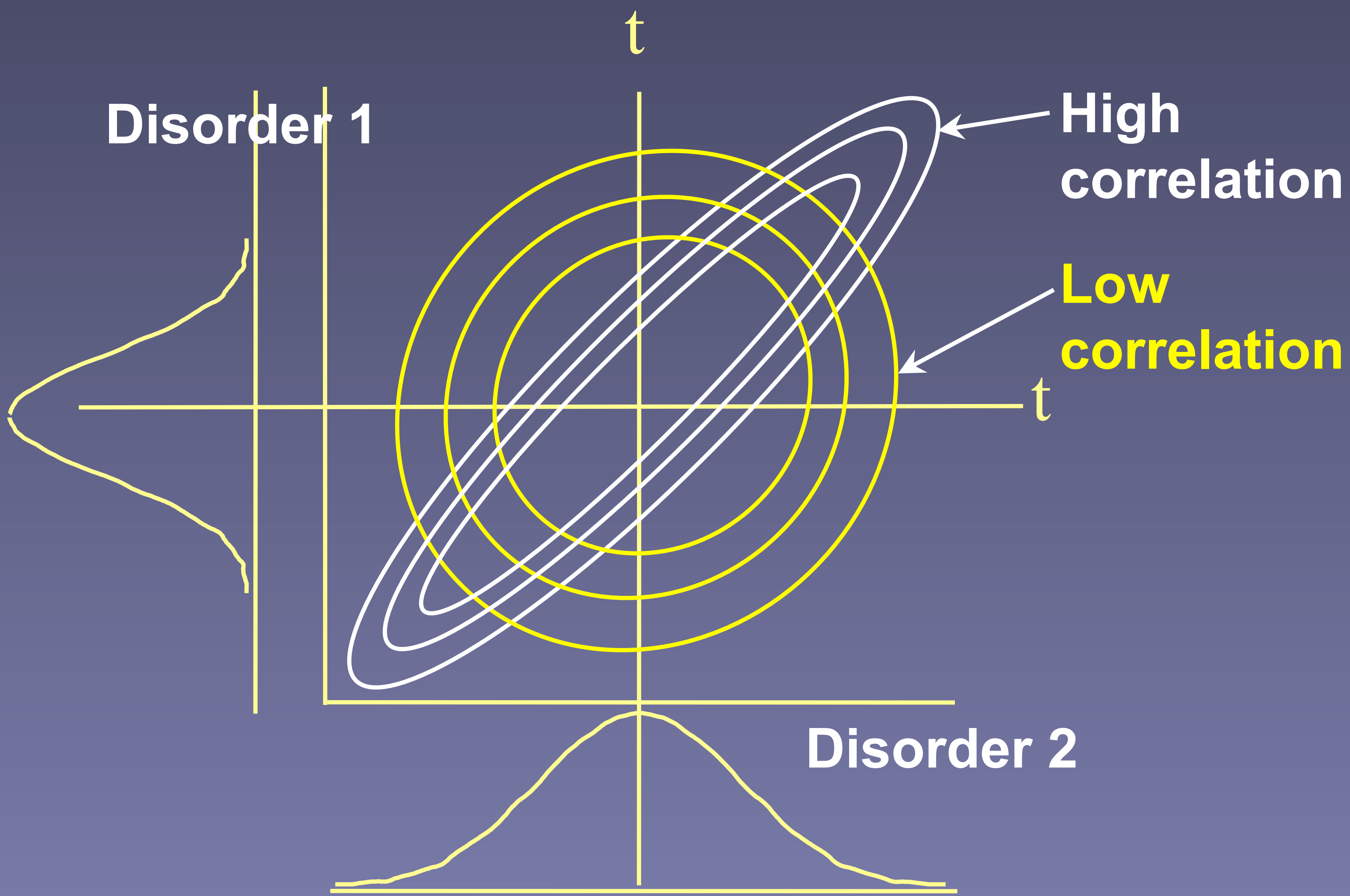
Both?

How do we find out which?

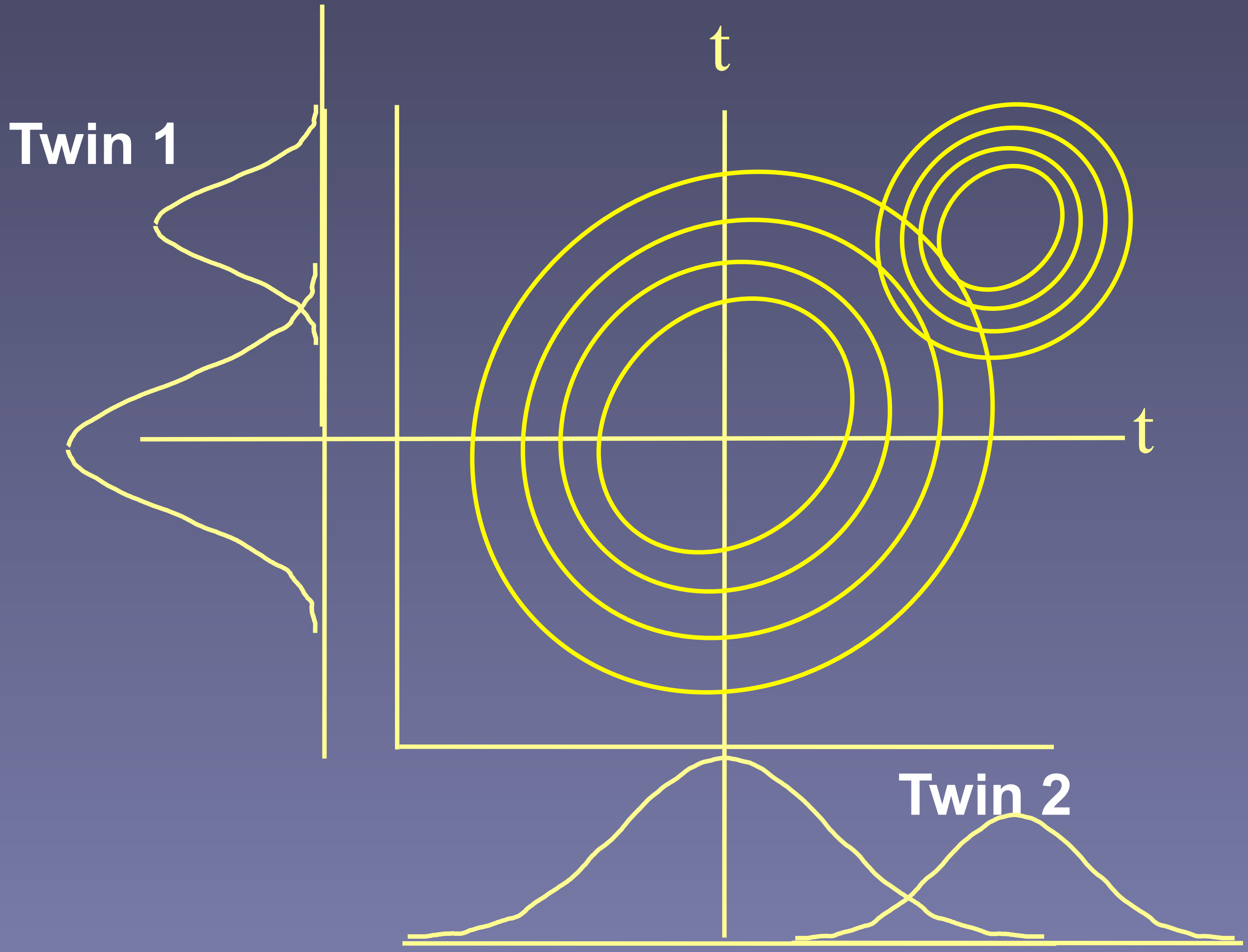
- Measure variation
- Measure covariation to understand it

Basic statistical theory

Two Dimensions: Contours



Non-normal distribution: Contours



Basic Theory

- Models for symptoms:
  - Latent class analysis
  - Factor analysis
  - Factor mixture model
  - Reprieved...

Am. J. Hum. Genet. 57:935–953, 1995

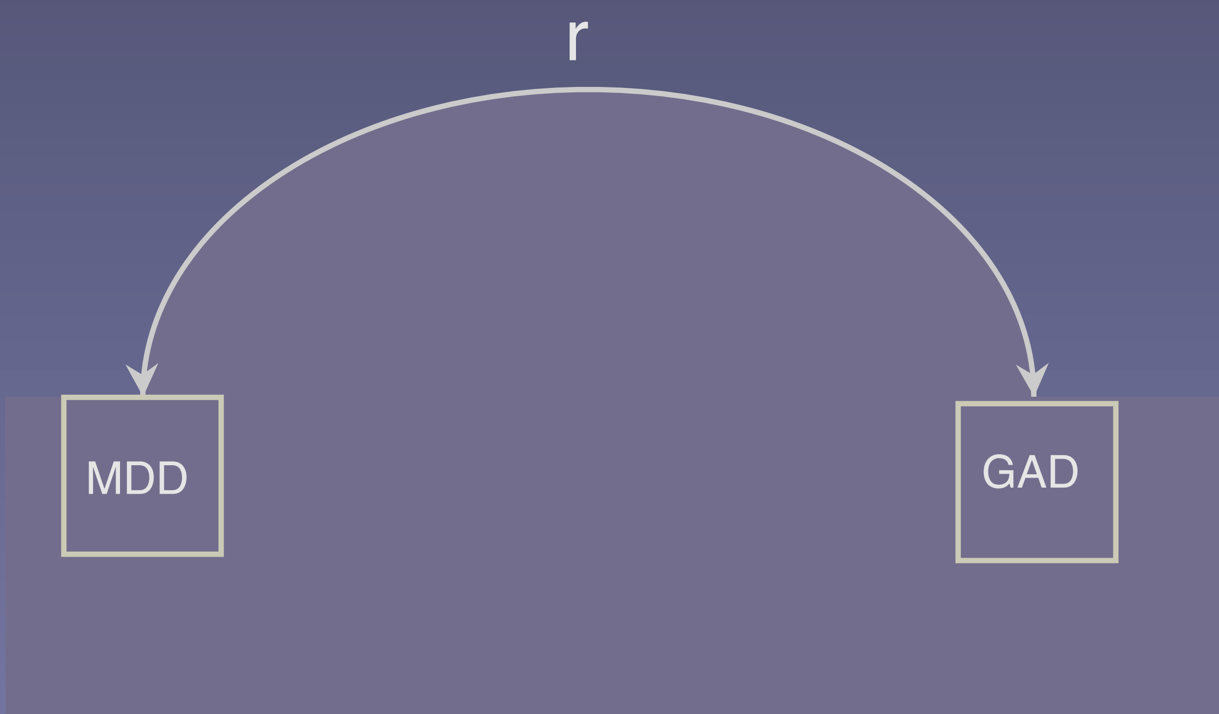
Models of Comorbidity for Multifactorial Disorders

Michael C. Neale[1] and Kenneth S. Kendler[1,2]

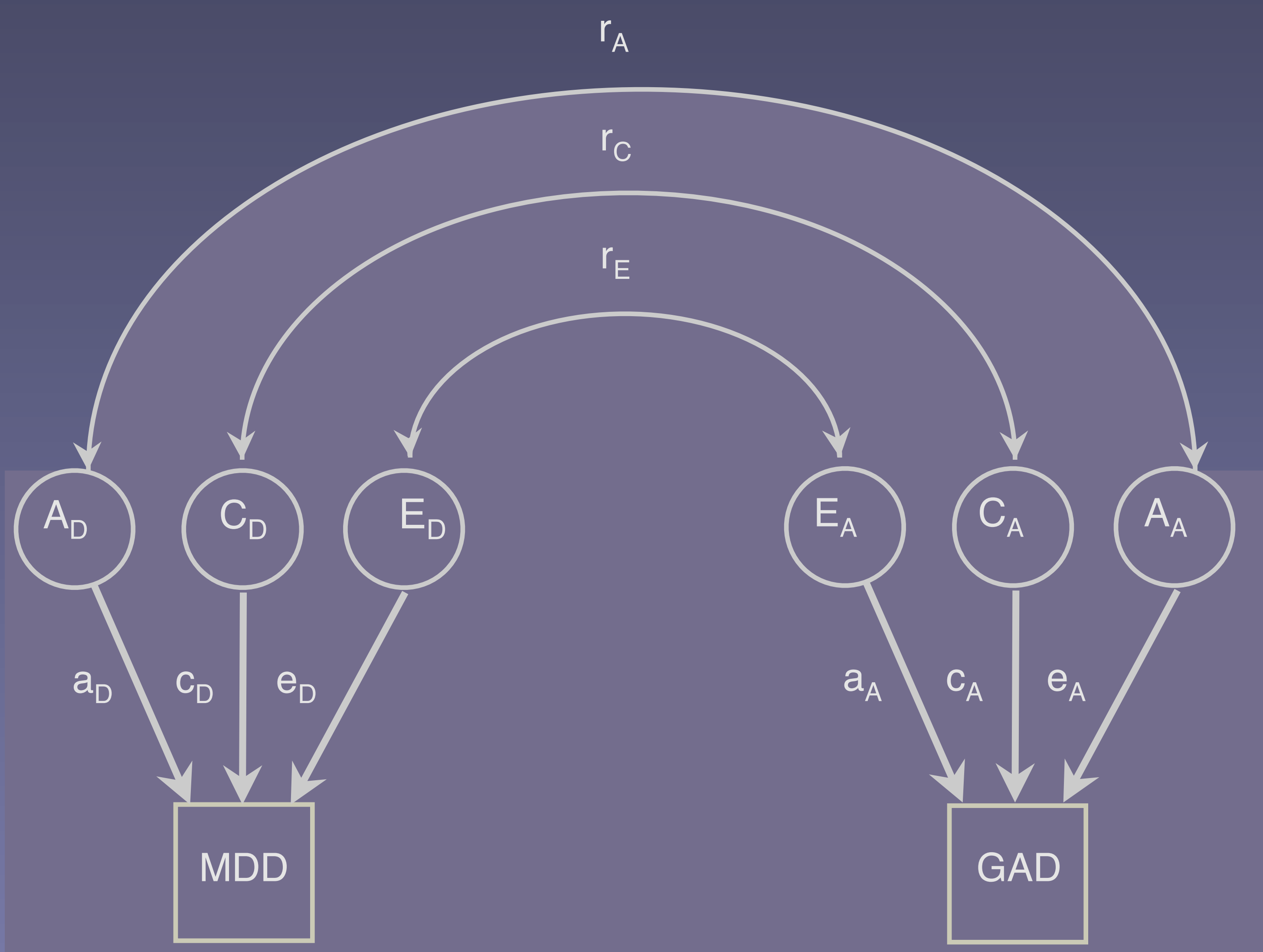
Departments of [1]Psychiatry and [2]Human Genetics, Medical College of Virginia, Richmond

Comorbidity

A correlation between (binary) traits
Neale & Kendler (1995) 13 Models
Based on Klein & Riso (1994)



Partitioning Comorbidity

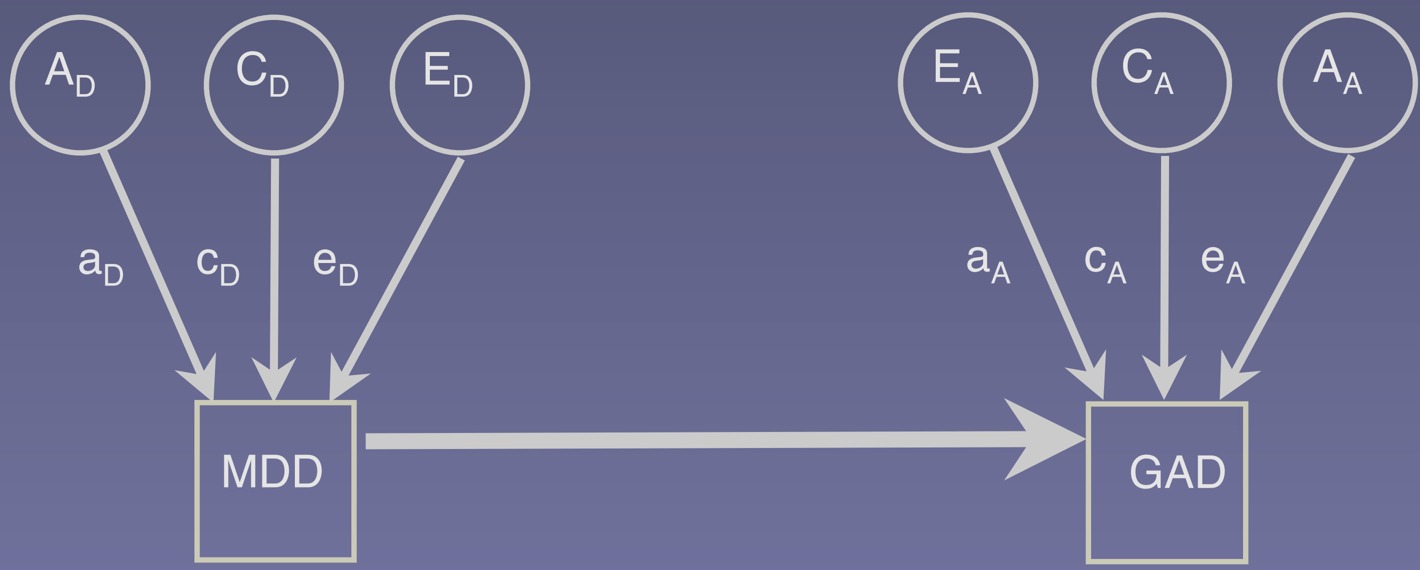


Modeling Comorbidity

Reciprocal Causation

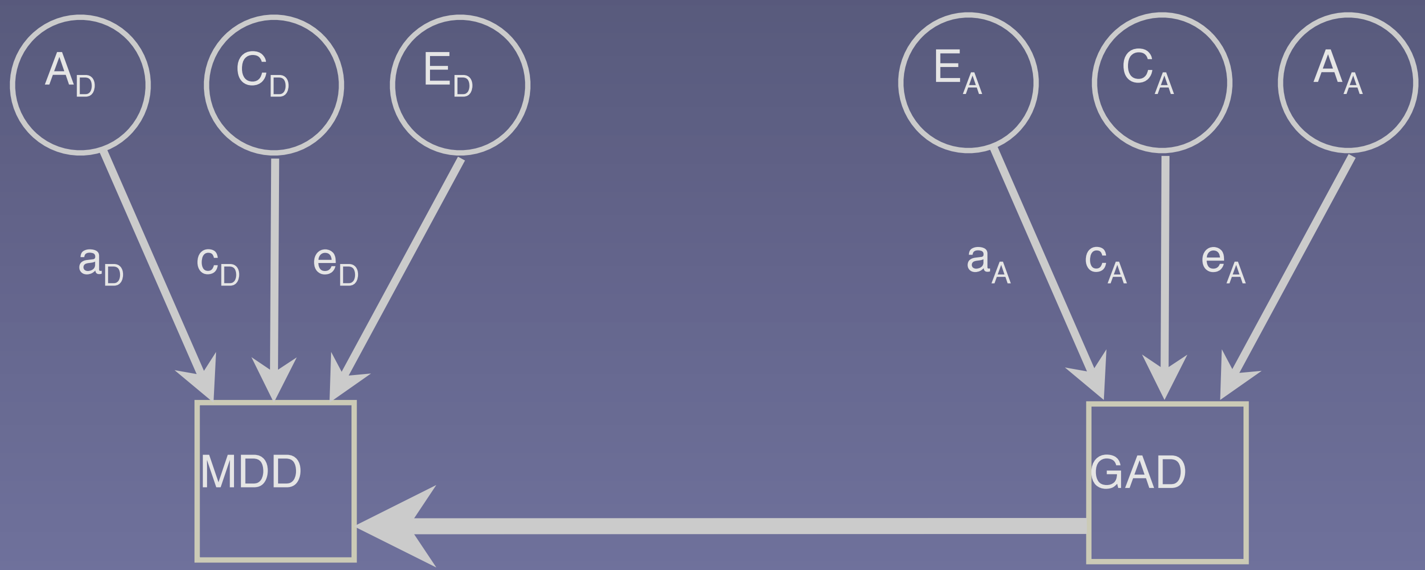
Modeling Comorbidity

Major Depression Causes Generalized Anxiety Disorder

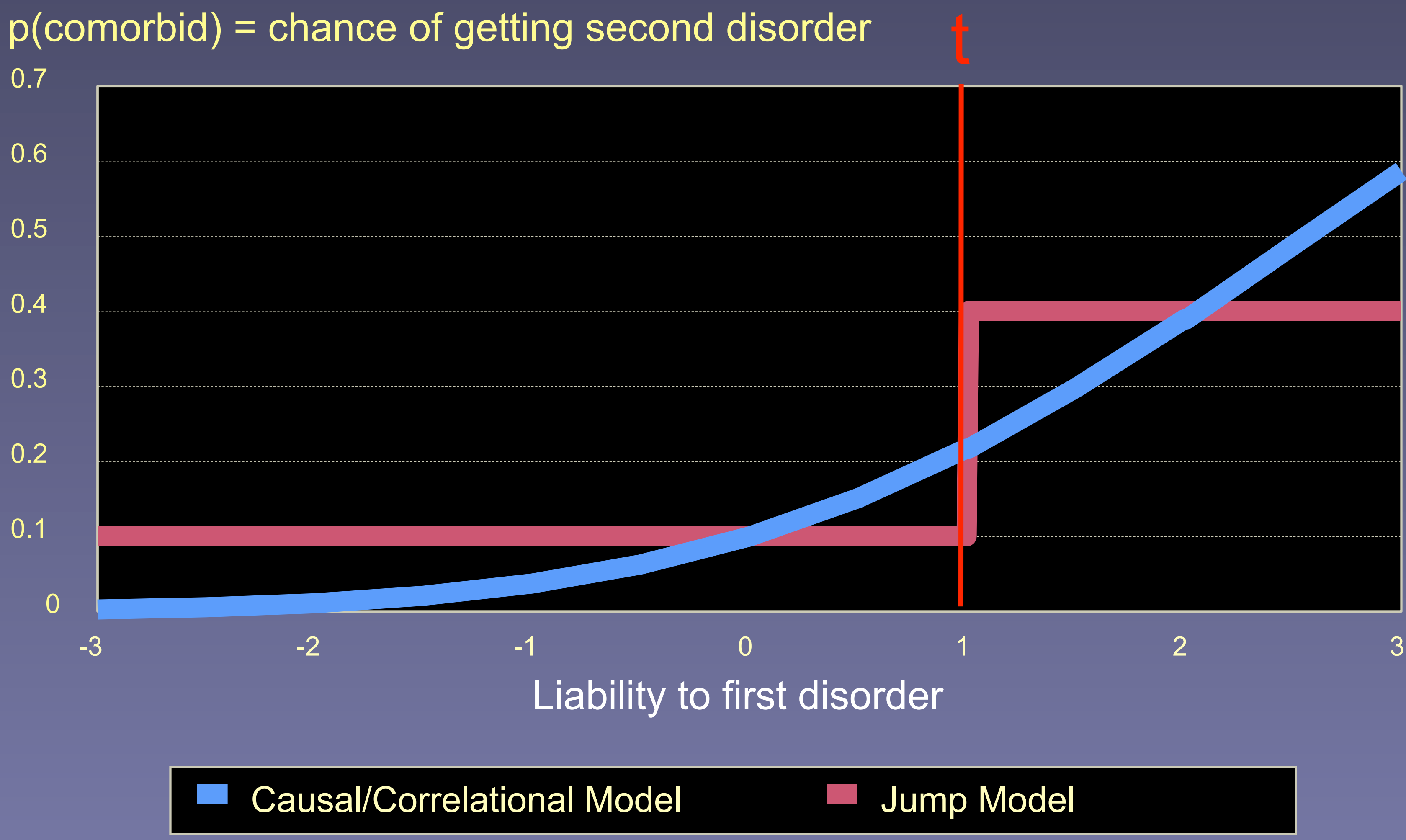


Modeling Comorbidity

Generalized Anxiety Disorder causes Major Depression

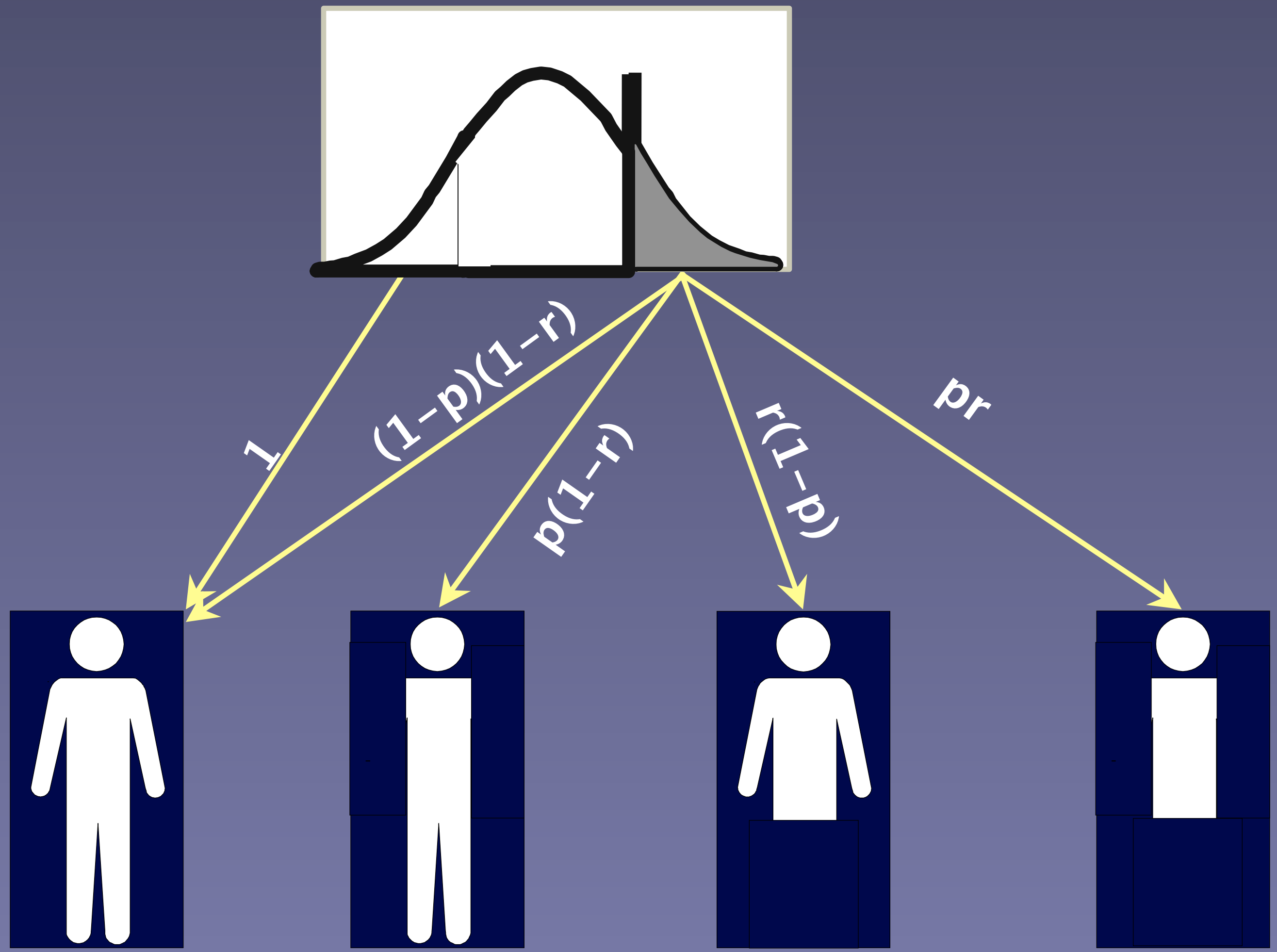


Alternative models of increasing risk to a second disorder



Threshold Model r=.5

Alternate forms: One underlying continuum



Alternate forms: More detail

$$L = \int_{-\infty}^{t_1} \phi(R)dR \quad (1)$$

$$M = \int_{t_1}^{t_2} \phi(R)dR \quad (2)$$

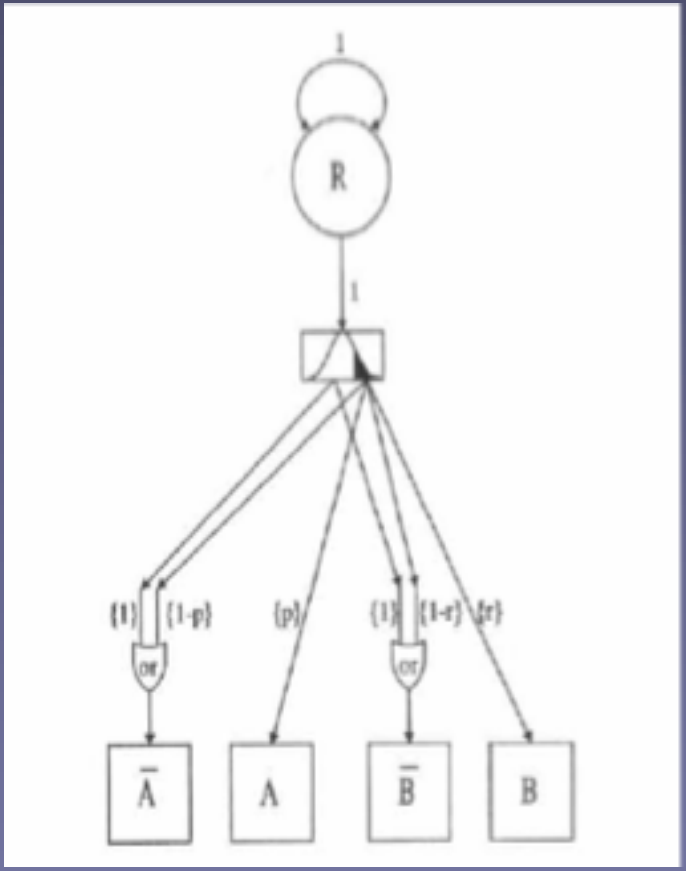
$$U = \int_{t_2}^{\infty} \phi(R)dR \,. \quad (3)$$

$$P(\bar{A}, \bar{B}) = L + (1-p)(1-r)U \quad (4)$$

$$P(\bar{A}, B) = p(1-r)U \quad (5)$$

$$P(A, \bar{B}) = (1-p)rU \quad (6)$$

$$P(A, B) = prU \,, \quad (7)$$



Alternate forms: Detail of pairs

$$P(\bar{A}1, \bar{B}1, \bar{A}2, \bar{B}2) = LL + 2(1-p)(1-r)UL + (1-p)^2(1-r)^2UU \quad (30)$$

$$P(\bar{A}1, \bar{B}1, \bar{A}2, B2) = r(1-p)LU + (1-p)^2r(1-r)^2UU \quad (31)$$

$$P(\bar{A}1, \bar{B}1, A2, \bar{B}2) = p(1-r)LU + p(1-p)(1-r)^2UU \quad (32)$$

$$P(\bar{A}1, \bar{B}1, A2, B2) = prLU + p(1-p)r(1-r)UU \quad (33)$$

$$P(\bar{A}1, B1, \bar{A}2, B2) = (1-p)^2r^2UU \quad (34)$$

$$P(\bar{A}1, B1, A2, \bar{B}2) = p(1-p)r(1-r)UU \quad (35)$$

$$P(\bar{A}1, B1, A2, B2) = p(1-p)r^2UU \quad (36)$$

$$P(A1, \bar{B}1, A2, \bar{B}2) = p^2(1-r)^2UU \quad (37)$$

$$LL_A = \int_{-\infty}^{t1_A}\int_{-\infty}^{t1_A} \phi(R_{A1}, R_{A2})dR_{A2}dR_{A1} \quad (24)$$

$$LM_A = \int_{-\infty}^{t1_A}\int_{t1_A}^{t2_A} \phi(R_{A1}, R_{A2})dR_{A2}dR_{A1} \quad (25)$$

$$LU_A = \int_{-\infty}^{t1_A}\int_{t2_A}^{\infty} \phi(R_{A1}, R_{A2})dR_{A2}dR_{A1} \quad (26)$$

$$MM_A = \int_{t1_A}^{t2_A}\int_{t1_A}^{t2_A} \phi(R_{A1}, R_{A2})dR_{A2}dR_{A1} \quad (27)$$

$$MU_A = \int_{t1_A}^{t2_A}\int_{t1_A}^{\infty} \phi(R_{A1}, R_{A2})dR_{A2}dR_{A1} \quad (28)$$

$$UU_A = \int_{t2_A}^{\infty}\int_{t2_A}^{\infty} \phi(R_{A1}, R_{A2})dR_{A2}dR_{A1}\,, \quad (29)$$

$$P(A1, \bar{B}1, A2, B2) = p^2r(1-r)UU \quad (38)$$

$$P(A1, B1, A2, B2) = p^2r^2UU\,. \quad (39)$$

OpenMx Script algebra for Alternate Forms

```
# Program: Alternate Forms

require(OpenMx)
nv<-1
# Fit Alternate Forms Model with Cell Frequencies Input, ACE.one overall Threshold
# -----------------------------------------------------------------------
AltFormsModel <- mxModel("AlternateForms",
    mxModel("ACE",
    # Matrices a, c, and e to store a, c, and e path coefficients
        mxMatrix( type="Full", nrow=nv, ncol=nv, free=TRUE, values=.6, label="a11",
name="a" ),
        mxMatrix( type="Full", nrow=nv, ncol=nv, free=TRUE, values=.6, label="c11",
name="c" ),
        mxMatrix( type="Full", nrow=nv, ncol=nv, free=TRUE, values=sqrt(.28), label="e11",
name="e" ),
    # Matrices A, C, and E compute variance components
        mxAlgebra( expression=a %*% t(a), name="A" ),
        mxAlgebra( expression=c %*% t(c), name="C" ),
        mxAlgebra( expression=e %*% t(e), name="E" ),
    # Algebra to compute total variances and standard deviations (diagonal only)
        mxAlgebra( expression=A+C+E, name="V" ),
        mxMatrix( type="Iden", nrow=nv, ncol=nv, name="I"),
        mxAlgebra( expression=solve(sqrt(I*V)), name="sd"),
    # Constraint on variance of A+C+E latent variables
        mxConstraint( alg1="V", "=", alg2="I", name="Var1"),
```

OpenMx Script algebra for Alternate Forms

```
    # Algebra for expected variance/covariance matrix in MZ
        mxAlgebra( expression= rbind  ( cbind(A+C+E , A+C),
                                        cbind(A+C   , A+C+E)), name="expCovMZ" ),
    # Algebra for expected variance/covariance matrix in DZ, note use of 0.5,
        mxAlgebra( expression= rbind  ( cbind(A+C+E     , 0.5%x%A+C),
                                        cbind(0.5%x%A+C , A+C+E)),  name="expCovDZ"),
    # Matrices for probabilities P Q R S of being affected given below/above threshold
        mxMatrix( type="Full", nrow=1, ncol=1, free=TRUE, values=.8, label="p", name="P" ),
        mxMatrix( type="Full", nrow=1, ncol=1, free=TRUE, values=.6, label="r", name="R" ),
        mxMatrix( type="Iden", nrow=1, ncol=1, free=F, name="I" ),
        mxAlgebra( expression= I-P, name="Q" ),
        mxAlgebra( expression= I-R, name="S" ),
    # Threshold parameter & matrices for (fixed at zero) means
        mxMatrix( type="Full", nrow=1, ncol=1, free=TRUE, values=1, label="tmz", name="T" ),
        mxMatrix( type="Zero", nrow=1, ncol=nv, name="M" ),
        mxAlgebra( expression= cbind(M,M), name="expMean" ),
    # Integrals for computing the pairwise probabilities of being above/below threshold - MZ
        mxAlgebra(expression=omxMnor(expCovMZ, expMean, cbind(-Inf,-Inf), cbind(T,T)),
name="bothBelow"),
        mxAlgebra(expression=omxMnor(expCovMZ, expMean, cbind(-Inf,T), cbind(T,Inf)),
name="oneBelow"),
        mxAlgebra(expression=omxMnor(expCovMZ, expMean, cbind(T,T), cbind(Inf,Inf)),
name="bothAbove"),
```

OpenMx Script algebra for Alternate Forms

```
    # Integrals for computing the pairwise probabilities of being above/below threshold - DZ
        mxAlgebra(expression=omxMnor(expCovDZ, expMean, cbind(-Inf,-Inf), cbind(T,T)),
name="bothBelowDZ"),
        mxAlgebra(expression=omxMnor(expCovDZ, expMean, cbind(-Inf,T), cbind(T,Inf)),
name="oneBelowDZ"),
        mxAlgebra(expression=omxMnor(expCovDZ, expMean, cbind(T,T), cbind(Inf,Inf)),
name="bothAboveDZ"),

    # Finally, predicted proportions in each of 10 cells for MZ
        mxAlgebra(rbind(
        bothBelow + 2*oneBelow*Q*S + bothAbove*Q*Q*S*S,
        2*(oneBelow*R*Q + bothAbove*Q*Q*R*S),
        2*(oneBelow*P*S + bothAbove*P*Q*S*S),
        2*(oneBelow*P*R + bothAbove*P*R*Q*S),
        bothAbove*Q*Q*R*R,
        2*bothAbove*P*Q*R*S,
        2*bothAbove*P*Q*R*R,
        bothAbove*P*S*P*S,
        2*bothAbove*P*S*P*R,
        bothAbove*P*R*P*R
        ),name="MZExpectedFrequencies"),
```

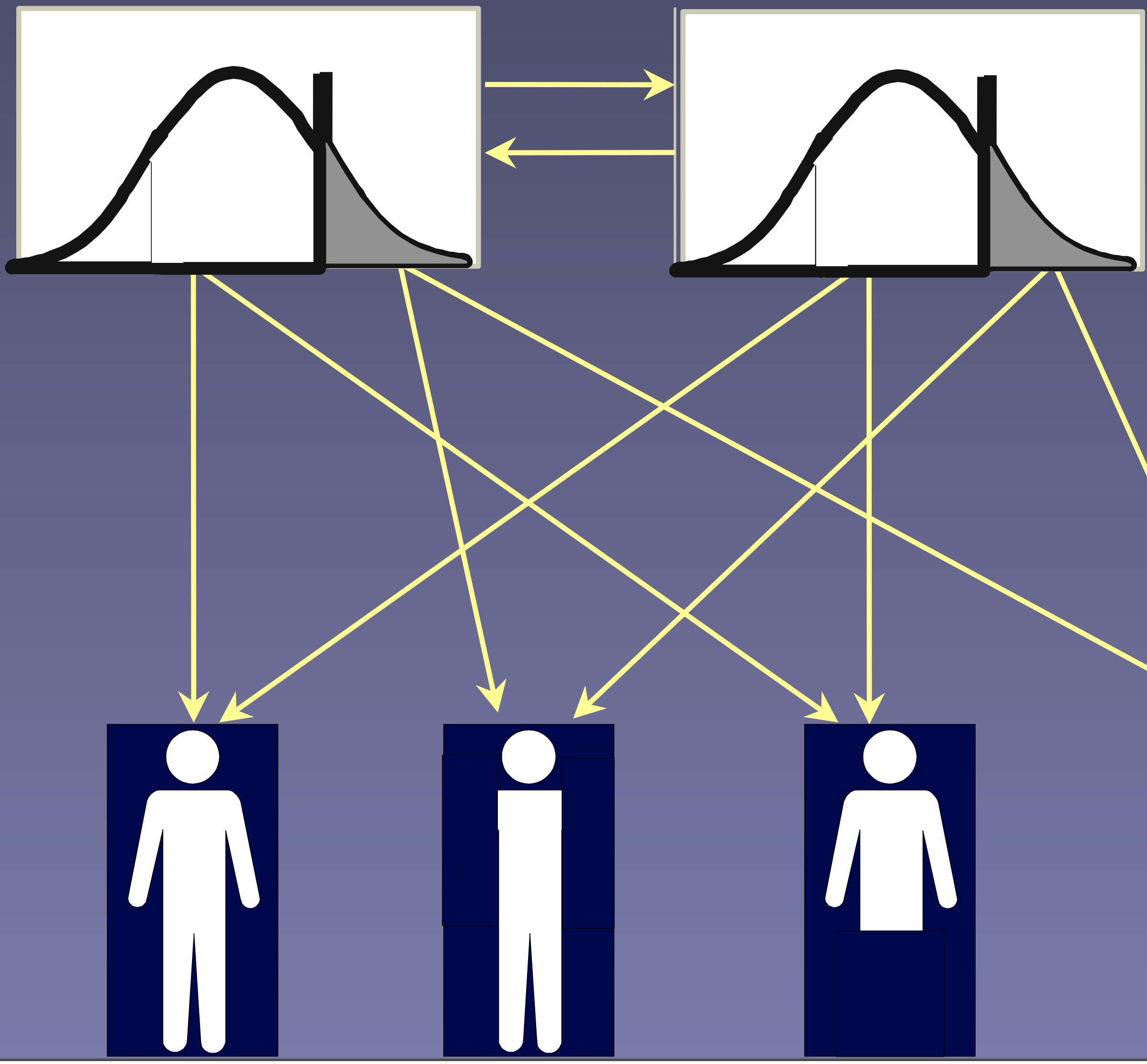
OpenMx Script algebra for Alternate Forms

```
# Finally, predicted proportions in each of 10 cells for DZ
    mxAlgebra(rbind(
    bothBelowDZ + 2*oneBelowDZ*Q*S + bothAboveDZ*Q*Q*S*S,
    2*(oneBelowDZ*R*Q + bothAboveDZ*Q*Q*R*S),
    2*(oneBelowDZ*P*S + bothAboveDZ*P*Q*S*S),
    2*(oneBelowDZ*P*R + bothAboveDZ*P*R*Q*S),
    bothAboveDZ*Q*Q*R*R,
    2*bothAboveDZ*P*Q*R*S,
    2*bothAboveDZ*P*Q*R*R,
    bothAboveDZ*P*S*P*S,
    2*bothAboveDZ*P*S*P*R,
    bothAboveDZ*P*R*P*R),name="DZExpectedFrequencies")),

mxModel("MZ",
    mxMatrix(type="Full", nrow=10, ncol=1, free=FALSE,
      values=c(141,35,32,25,15,7,33,18,39,47), name="MZObservedFrequencies"),
    mxAlgebra( -2 * sum(MZObservedFrequencies * log
              (ACE.MZExpectedFrequencies)),name="MZalgobj"),
mxAlgebraObjective("MZalgobj")),
```

OpenMx Script algebra for Alternate Forms

```
    mxModel("DZ",
        mxMatrix(type="Full", nrow=10, ncol=1, free=F, values=c(58,18,27,44,7,6,33,15,38,81),
            name="DZObservedFrequencies"),
        mxAlgebra(
                  -2 * sum(DZObservedFrequencies *
                             log (ACE.DZExpectedFrequencies)),name="DZalgobj"),
mxAlgebraObjective("DZalgobj"),
    mxAlgebra( MZ.objective + DZ.objective, name="-2sumll" ),
    mxAlgebraObjective("-2sumll")))

    AltFormsRun<-mxRun(AltFormsModel)
    summary(AltFormsRun)
```

Causal or correlated models

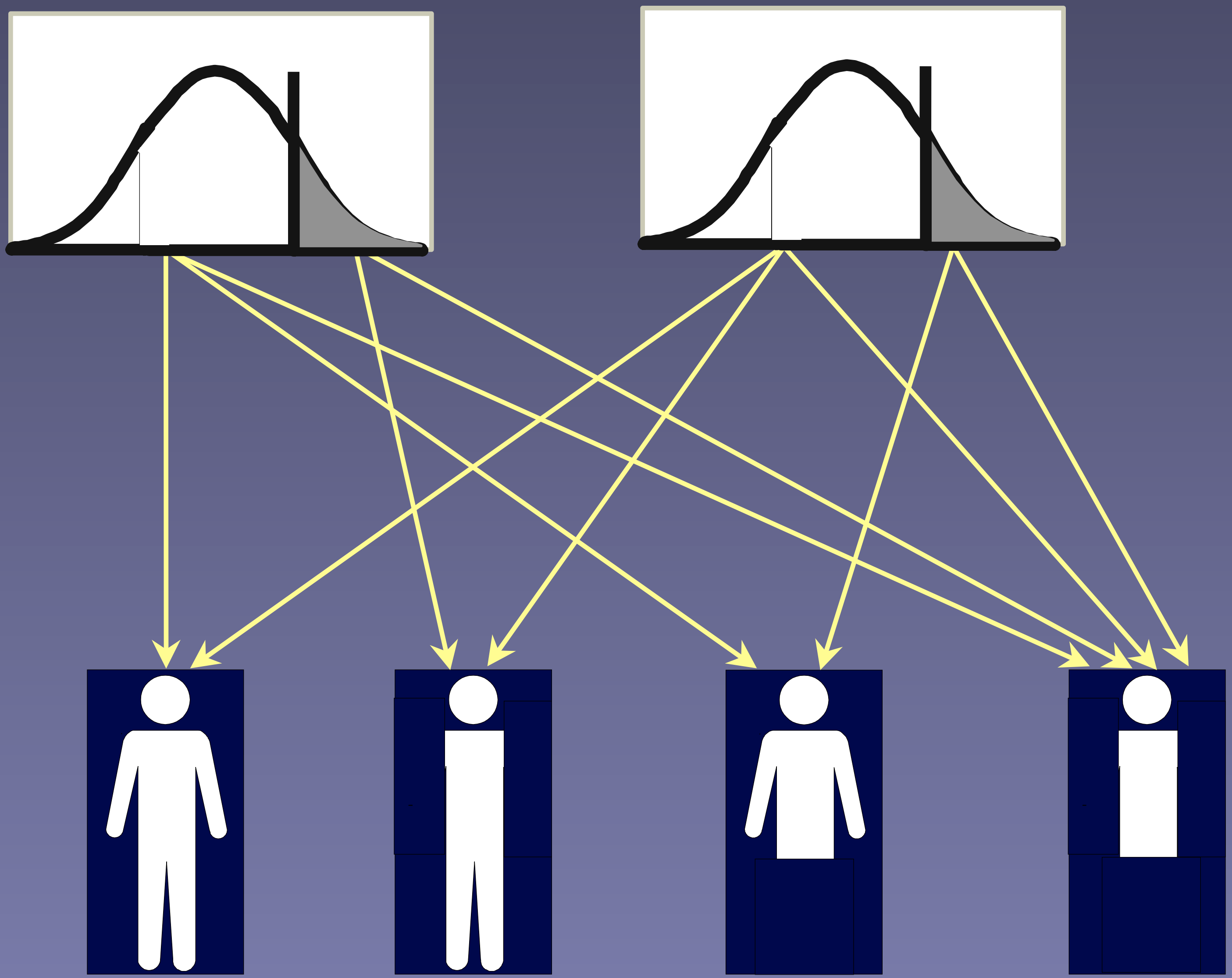


Correlated Liabilities

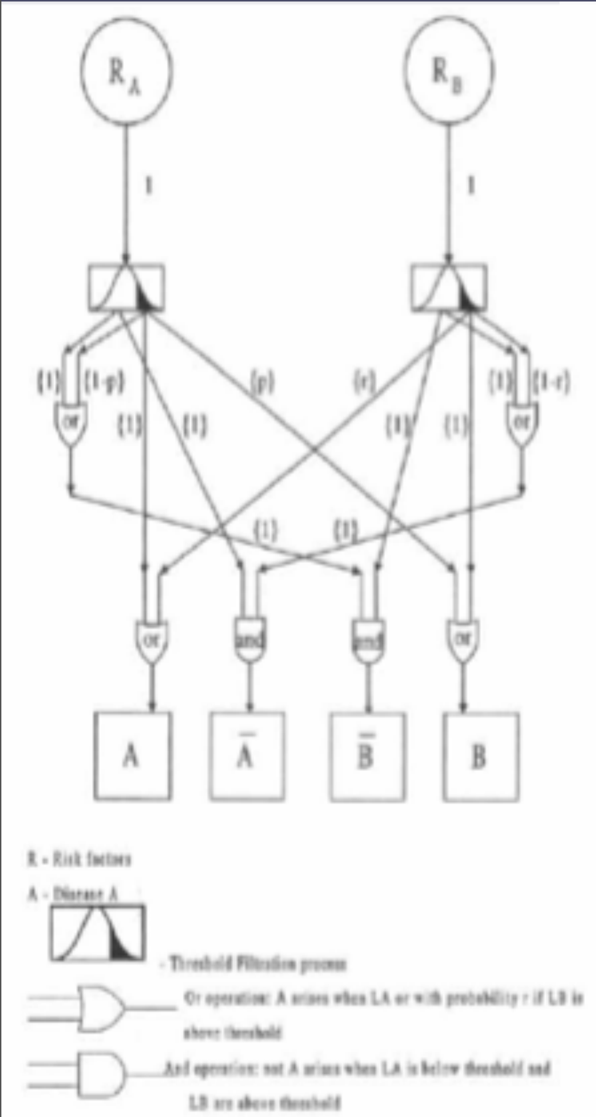
$$
\begin{aligned}
& P(\mathrm{A1}, \mathrm{B1}, \mathrm{A2}, \mathrm{B2}) \\
&= UUUU_{\mathrm{A1,B1,A2,B2}} \\
&= \int_{t_{\mathrm{A}}}^{\infty} \int_{t_{\mathrm{B}}}^{\infty} \int_{t_{\mathrm{A}}}^{\infty} \int_{t_{\mathrm{B}}}^{\infty} \phi(R_{\mathrm{A1}}, R_{\mathrm{B1}}, R_{\mathrm{A2}}, R_{\mathrm{B2}}) \\
&\quad dR_{\mathrm{B2}} dR_{\mathrm{A2}} dR_{\mathrm{B1}} dR_{\mathrm{A1}}
\end{aligned} \tag{70}
$$

Inherent in OpenMx Ordinal Data Analysis
We can do it by hand as well

Jump Model: Actually having one disorder raises chance of getting second



Random Multiformity: Detail



$$P(\bar{A}, \bar{B}) = L_A \cdot L_B \qquad (8)$$

$$P(\bar{A}, B) = (1 - r)L_A \cdot U_B \qquad (9)$$

$$P(A, \bar{B}) = U_A \cdot (1 - p)L_B \qquad (10)$$

$$P(A, B) = U_A \cdot (U_B + pL_B) + rL_A \cdot U_B\,, \qquad (11)$$

$$P(\bar{A}1, \bar{B}1, \bar{A}2, \bar{B}2) = LL_A \cdot LL_B \qquad (40)$$

$$P(\bar{A}1, \bar{B}1, \bar{A}2, B2) = LL_A \cdot (1 - r)LU_B \qquad (41)$$

$$P(\bar{A}1, \bar{B}1, A2, \bar{B}2) = (1 - p)LU_A \cdot LL_B \qquad (42)$$

$$P(\bar{A}1, \bar{B}1, A2, B2) = LU_A \cdot (pLL_B + LU_B) + LL_A \cdot rLU_B \qquad (43)$$

$$P(\bar{A}1, B1, \bar{A}2, B2) = LL_A \cdot (1 - r)^2 UU_B \qquad (44)$$

$$P(\bar{A}1, B1, A2, \bar{B}2) = (1 - p)LU_A \cdot (1 - r)LU_B \qquad (45)$$

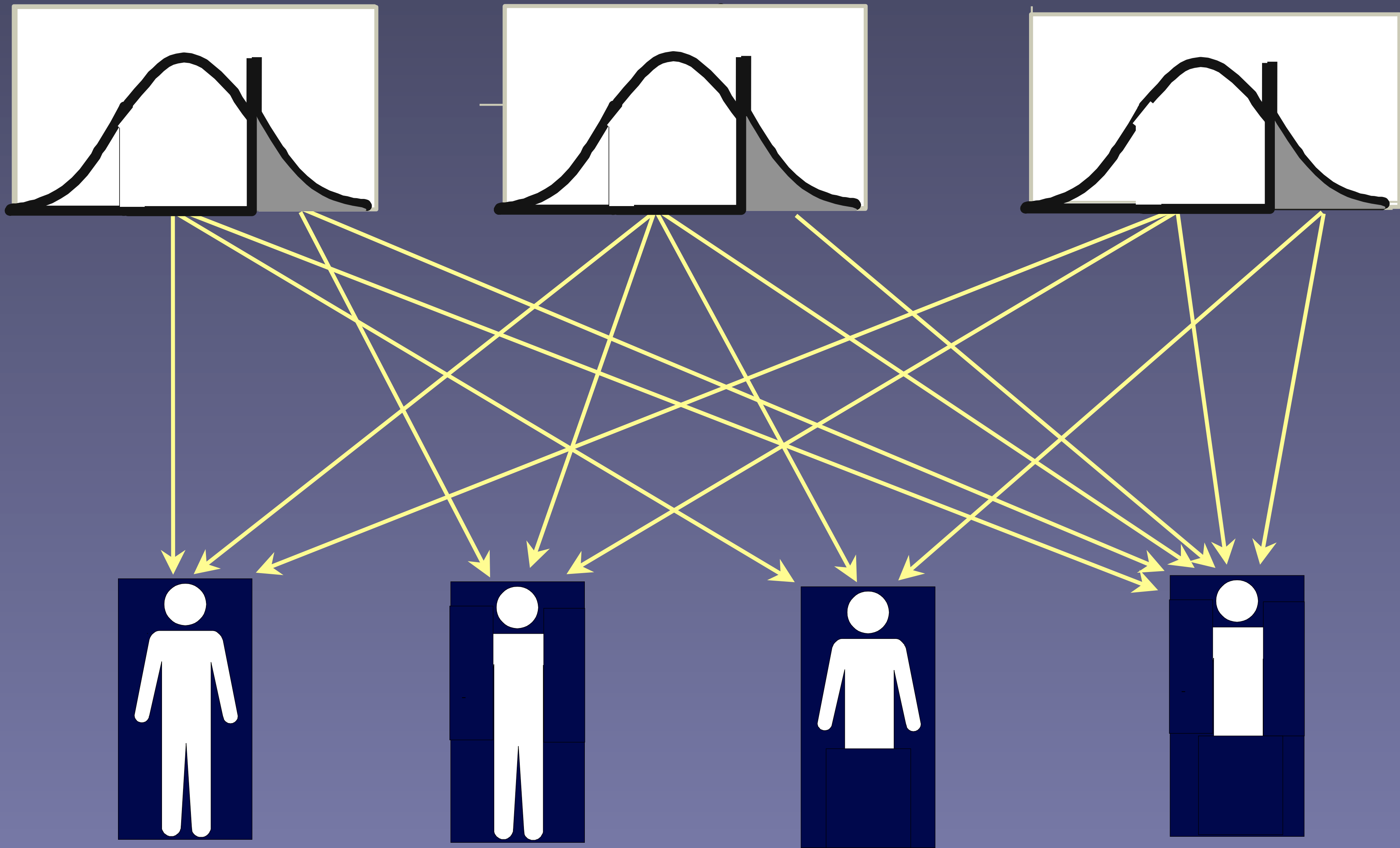
$$P(\bar{A}1, B1, A2, B2) = (1 - r)LU_A \cdot (pLU_B + UU_B) + LL_A \cdot rLL_B \qquad (46)$$

$$P(A1, \bar{B}1, A2, \bar{B}2) = (1 - p)^2 UU_A \cdot LL_B \qquad (47)$$

$$P(A1, \bar{B}1, A2, B2) = UU_A \cdot (p(1 - p)LL_B + (1 - p)LU_B) + (1 - p)LU_A \cdot rLU_B \qquad (48)$$

$$P(A1, B1, A2, B2) = p^2 UU_A \cdot LL_B + 2pUU_A \cdot LU_B + UU_A \cdot UU_B + LU_A \cdot 2rUU_B + 2pLU_A \cdot rLU_B + LL_A \cdot r^2 UU_B\,. \qquad (49)$$

Three separate disorders



Friday, March 5, 2010

Three Independent Disorders

$$P(\bar{A}1, \bar{B}1, \bar{A}2, \bar{B}2) = LL_A \cdot LL_{AB} \cdot LL_B \quad (60)$$

$$P(\bar{A}1, \bar{B}1, \bar{A}2, B2) = LL_A \cdot LL_{AB} \cdot LU_B \quad (61)$$

$$P(\bar{A}1, \bar{B}1, A2, \bar{B}2) = LU_A \cdot LL_{AB} \cdot LL_B \quad (62)$$

$$P(\bar{A}1, \bar{B}1, A2, B2) = L_A \cdot LL_{AB} \cdot LL_B + LU_A \cdot LL_{AB} \cdot LU_B \quad (63)$$

$$P(\bar{A}1, B1, \bar{A}2, B2) = LL_A \cdot LL_{AB} \cdot UU_B \quad (64)$$

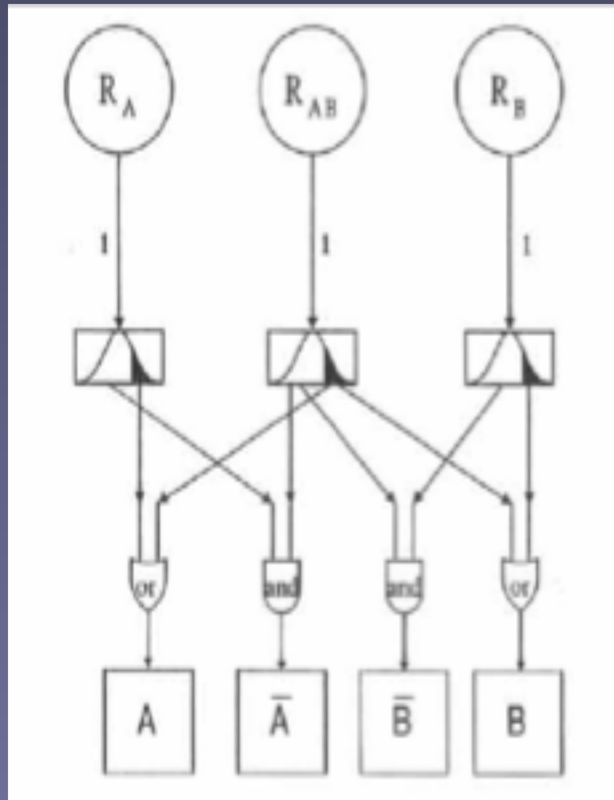
$$P(\bar{A}1, B1, A2, \bar{B}2) = LU_A \cdot LL_{AB} \cdot LU_B \quad (65)$$

$$P(\bar{A}1, B1, A2, B2) = L_A \cdot LU_{AB} \cdot U_B + LU_A \cdot LL_{AB} \cdot UU_B \quad (66)$$

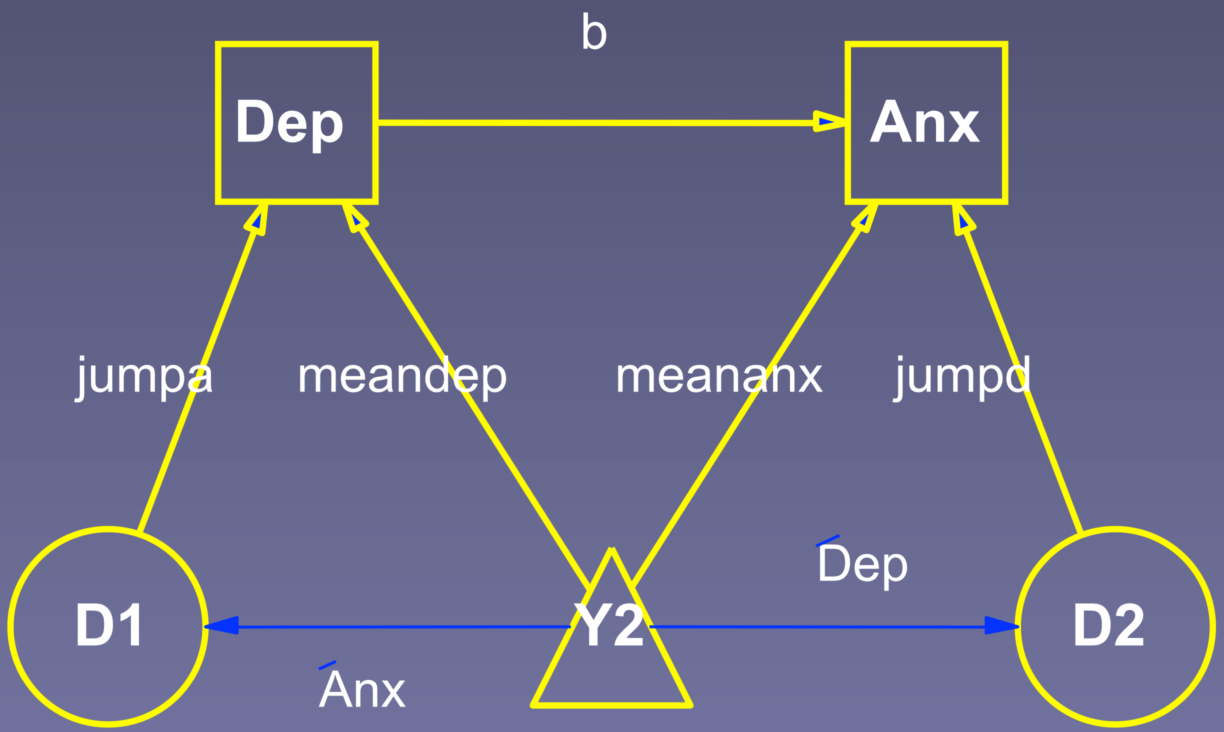
$$P(A1, \bar{B}1, A2, \bar{B}2) = UU_A \cdot LL_{AB} \cdot LL_B \quad (67)$$

$$P(A1, \bar{B}1, A2, B2) = L_A \cdot LU_{AB} \cdot L_B + UU_A \cdot LL_{AB} \cdot LU_B \quad (68)$$

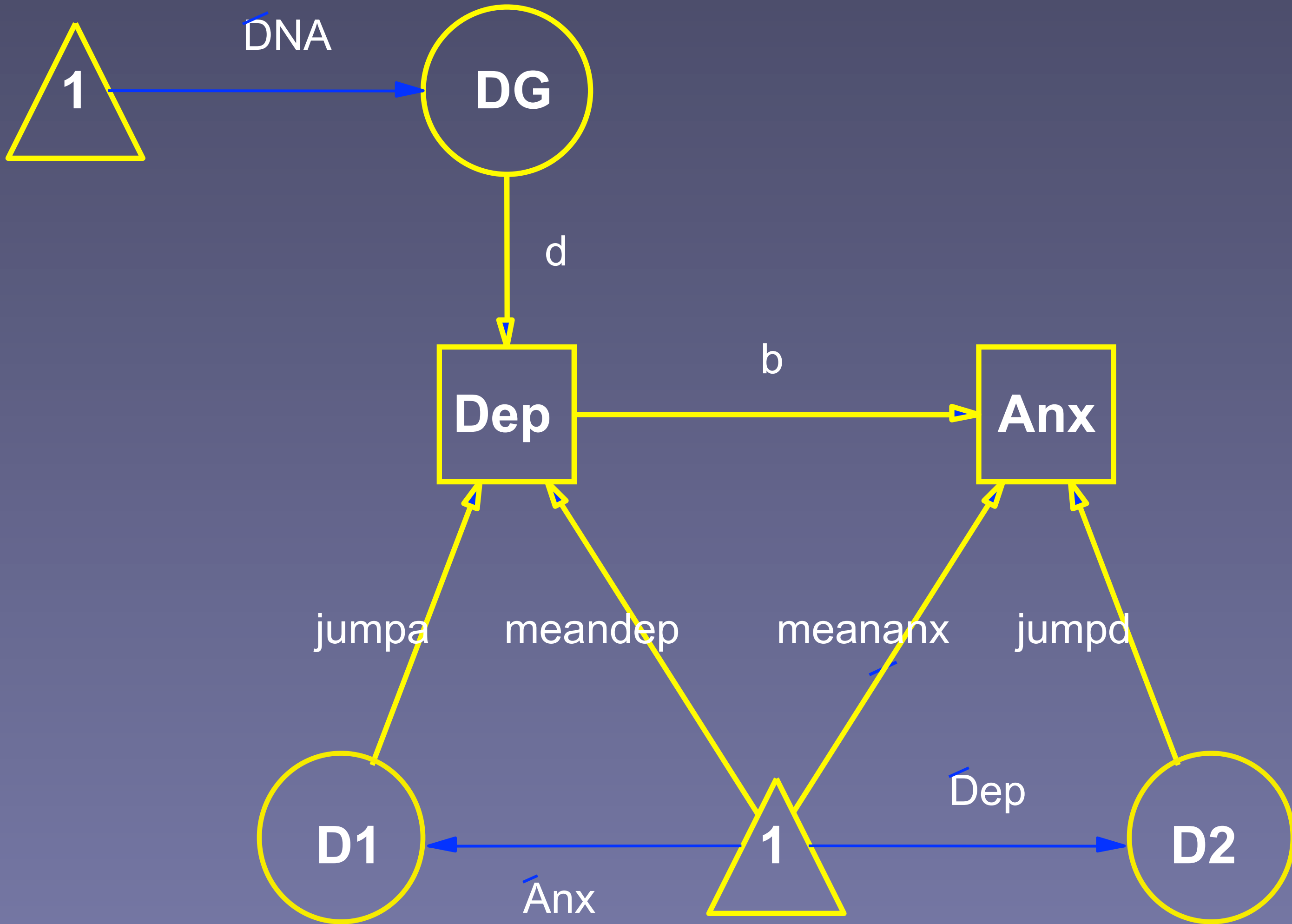
$$P(A1, B1, A2, B2) = UU_{AB} + UU_A \cdot LL_{AB} \cdot UU_B + 2U_A \cdot LU_{AB} \cdot U_B \,. \quad (69)$$



Unified Comorbidity Model?



Unified Genetic Comorbidity Model?



Sources for comorbidity scripts

- http://ibgwww.colorado.edu/cadd/software
- Soo Rhee’s website! Excellent!
- Includes covariates e.g., age (Rhee et al submitted)
- Clinical selected samples as well
- Exercise: download and fit the examples and decide on best fit model

- http://www.vcu.edu/mx/examples
- Mike Neale’s script website.
- More than a little bit dusty

OpenMx User-defined Functions

- Can specify AlgebraObjective

```
mxAlgebra( MZ.objective + DZ.objective, name="-2sumll" ),
    mxAlgebraObjective("-2sumll"))
```

- Any mxAlgebra you like!
  - Woohoo!
- See, e.g., http://openmx.psyc.virginia.edu/repoview/1/trunk/models/passing/oneLocusLikelihood.R
- One & two locus ABO blood group examples

Comorbidity with covariates

- Soo Rhee’s website again
- http://ibgwww.colorado.edu/cadd/software
- These scripts are in classic Mx
- Look out for updates

Possible Extensions

- More than two disorders
- More than one point in time
- More than pairs of twins
- Covariates & GxE

- Models for symptoms (IRT)
- Dynamical systems models
- Generalization to continuous liability

Possible Exercises

- Modify directionofCausation.R to fit:
  - Anxiety (P2) causes depression (P1)
  - Bidirectional causation (tricky, may need bounds)
  - Test hypothesis that comorbidity in ACE bivariate is purely due to rG
- Use tableFitStatistics function to compare results of ACE & other comorbidity models
- Find some other data, rinse & repeat...

Comorbidity Depression & Anxiety Disorders

DSM IIIR MD & Alcohol Abuse