Correction for Ascertainment

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Ascertainment Examples

- Studies of patients and controls
- Patients and relatives
  - Twin pairs with at least one affected
    - Single ascertainment pi → 0
    - Complete ascertainment pi = 1
    - Incomplete 0 < pi <1
- Linkage studies
  - Affected sib pairs, DSP etc
  - Multiple affected families

pi = probability that someone is ascertained given that they are affected

Likelihood approach

Advantages & Disadvantages

- Usual nice properties of ML remain
- Flexible
- Simple principle
  - Consideration of possible outcomes
  - Re-normalization
- May be difficult to compute

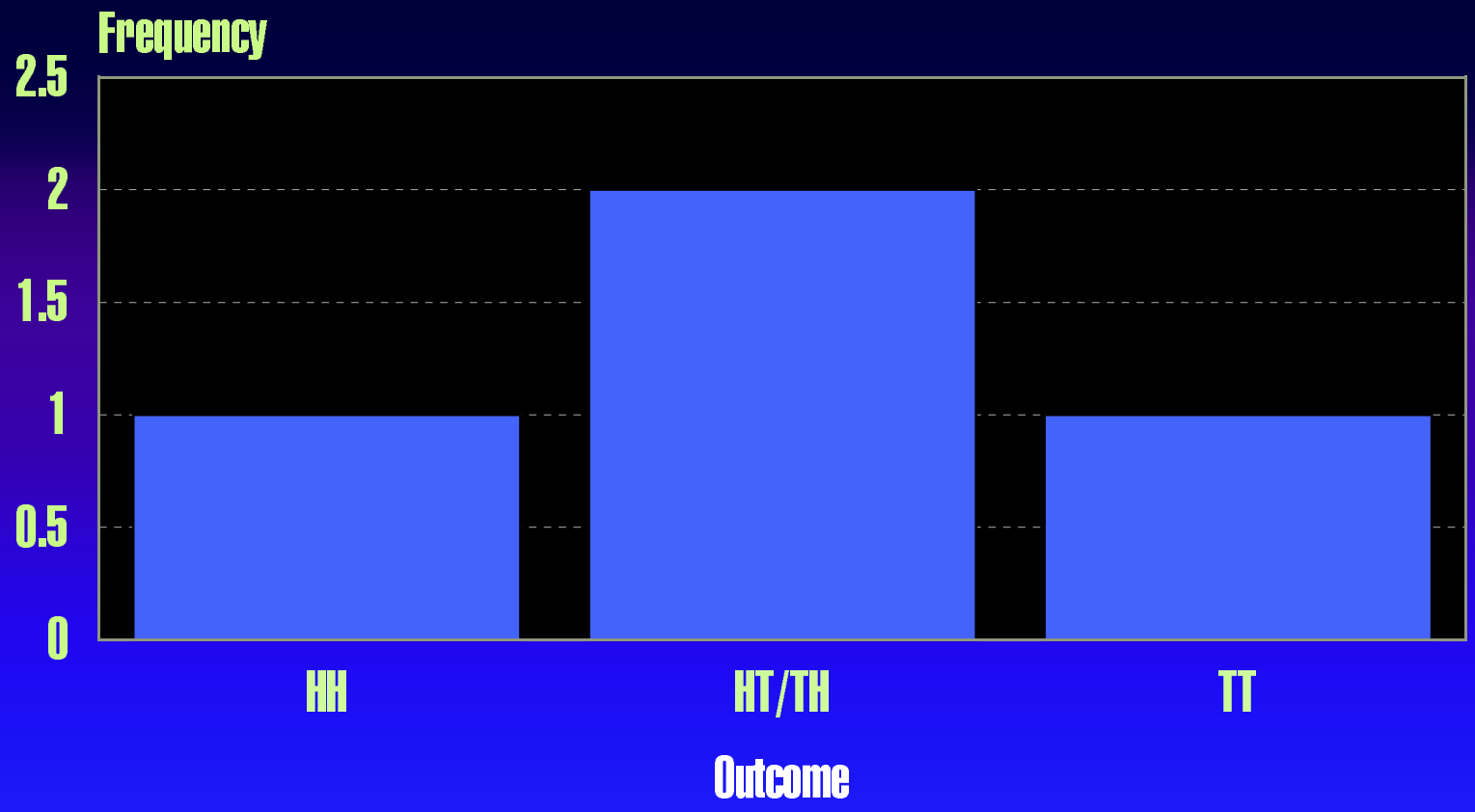
Maximum Likelihood Estimates

Have nice properties

- Asymptotically unbiased
- Minimum variance of all asymptotically unbiased estimators
- Invariant to transformations

Example: Two Coin Toss

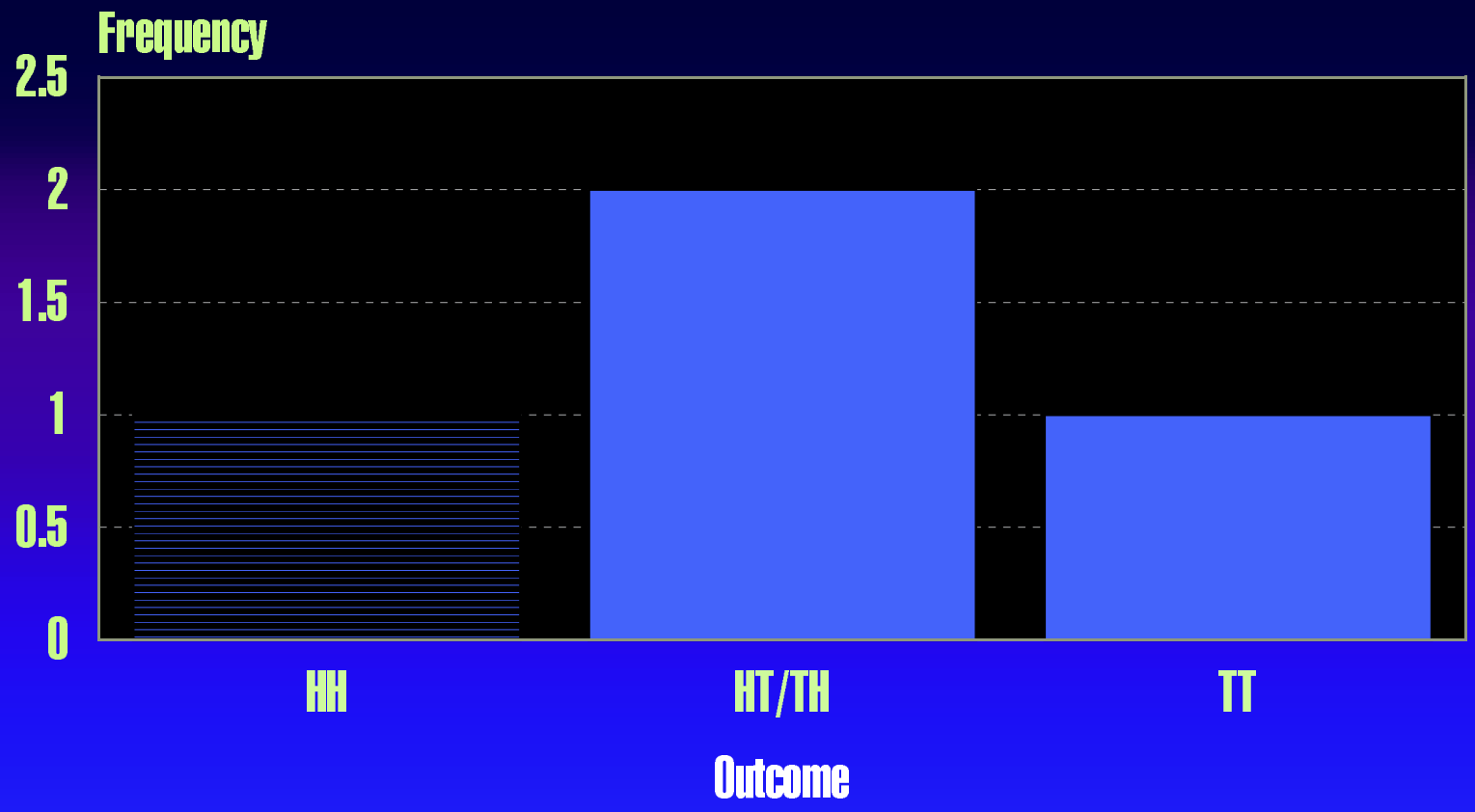
3 outcomes



Probability i = freq i / sum (freqs)

Example: Two Coin Toss

3 outcomes



Probability i = freq i / sum (freqs)

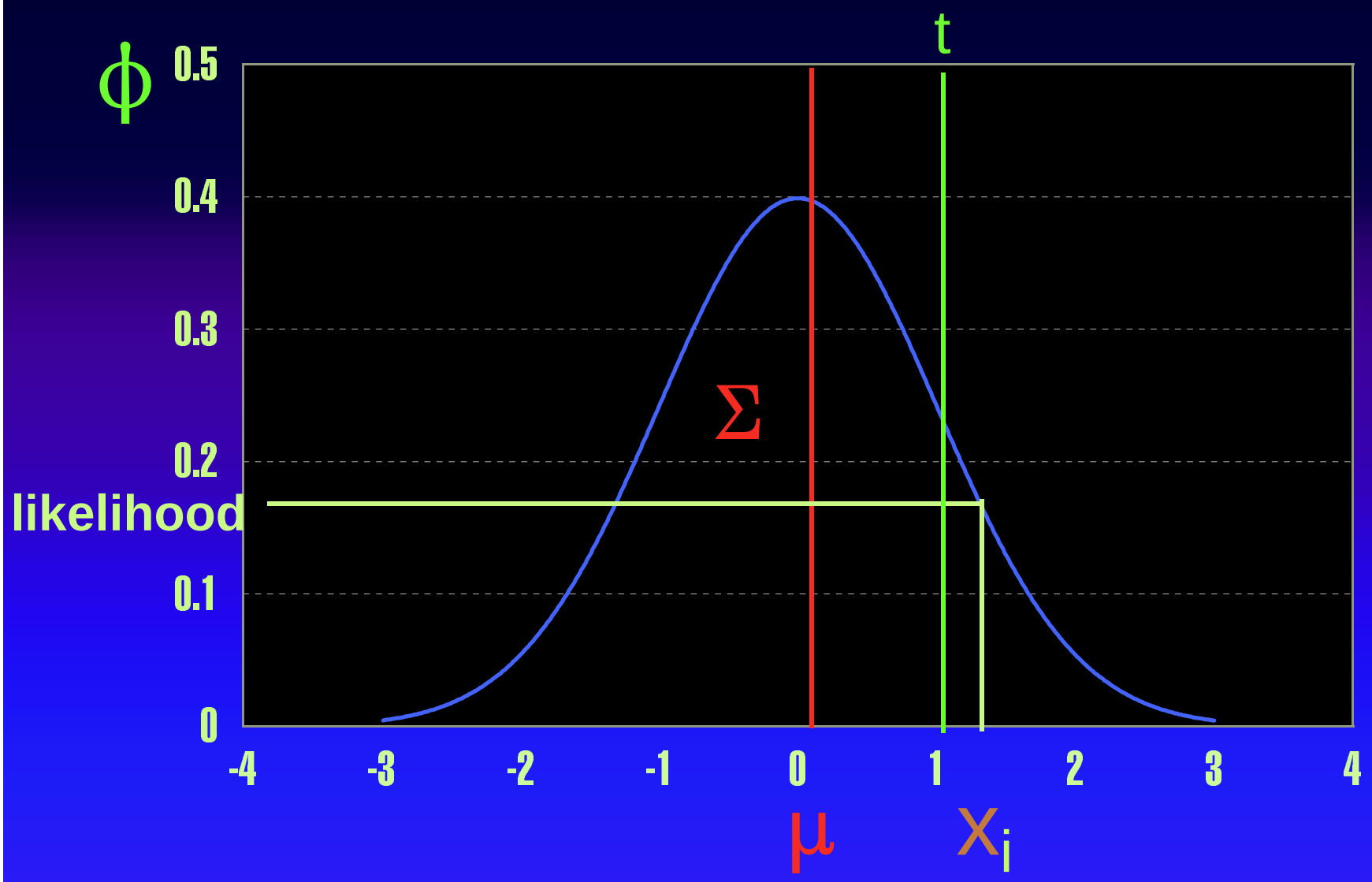
Non-random ascertainment

Example

- Probability of observing TT globally
  - 1 outcome from 4 = 1/4
- Probability of observing TT if HH is not ascertained
  - 1 outcome from 3 = 1/3
  - or 1/4 divided by 'ascertainment correction' of 3/4 = 1/3

Correcting for ascertainment

Univariate continuous case; only subjects > t ascertained



Correcting for ascertainment

Dividing by the realm of possibilities

- Without ascertainment, we compute pdf, $\phi(\mu_{ij}, \Sigma_{ij})$, at observed value x_i divided by:

$$\int_{-\infty}^{\infty} \phi(\mu_{ij}, \Sigma_{ij})\, dx = 1$$

- With ascertainment, the correction is

$$\int_{t}^{\infty} \phi(\mu_{ij}, \Sigma_{ij})\, dx = 1 - \int_{-\infty}^{t} \phi(\mu_{ij}, \Sigma_{ij})\, dx$$

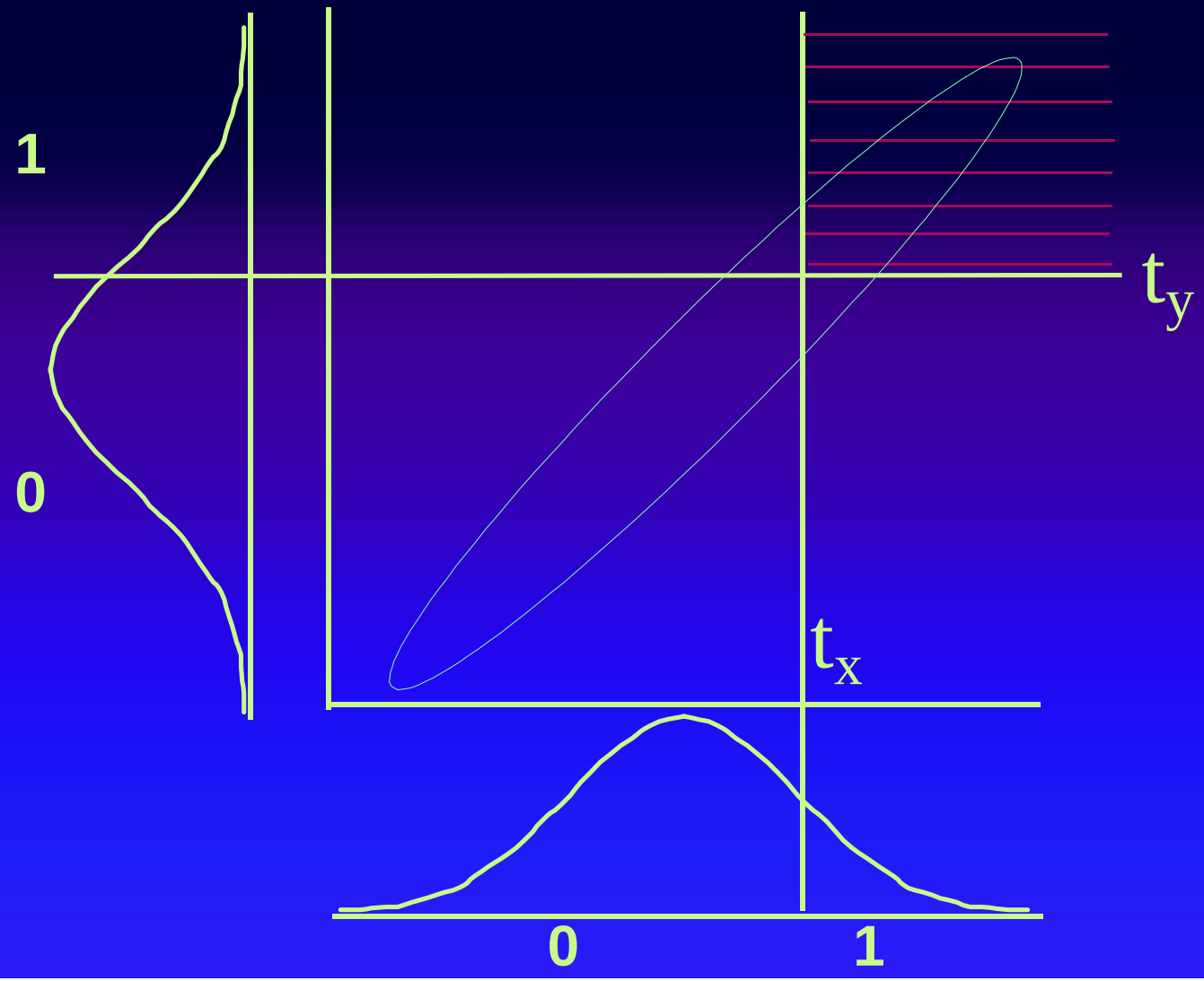
Does likelihood increase or decrease after correction?

Correction depends on model

- 1 Correction independent of model parameters: "sample weights"
- 2 Correction depends on model parameters: weights vary during optimization
- In twin data almost always case 2
  - continuous data
  - binary/ordinal data

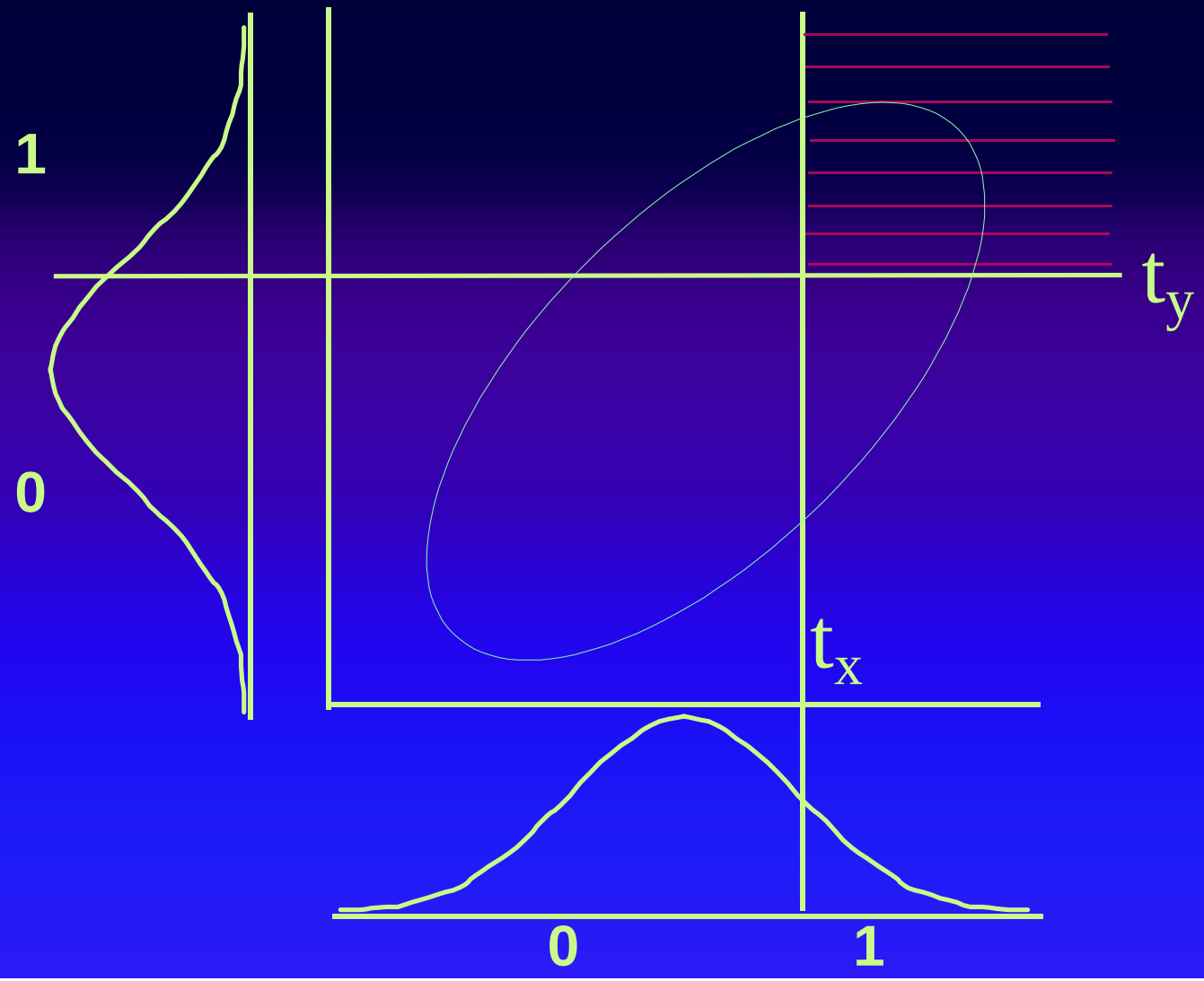
High correlation

$$\int_{tx}^{\infty} \int_{ty}^{\infty} \phi(x,y)\, dy\, dx$$



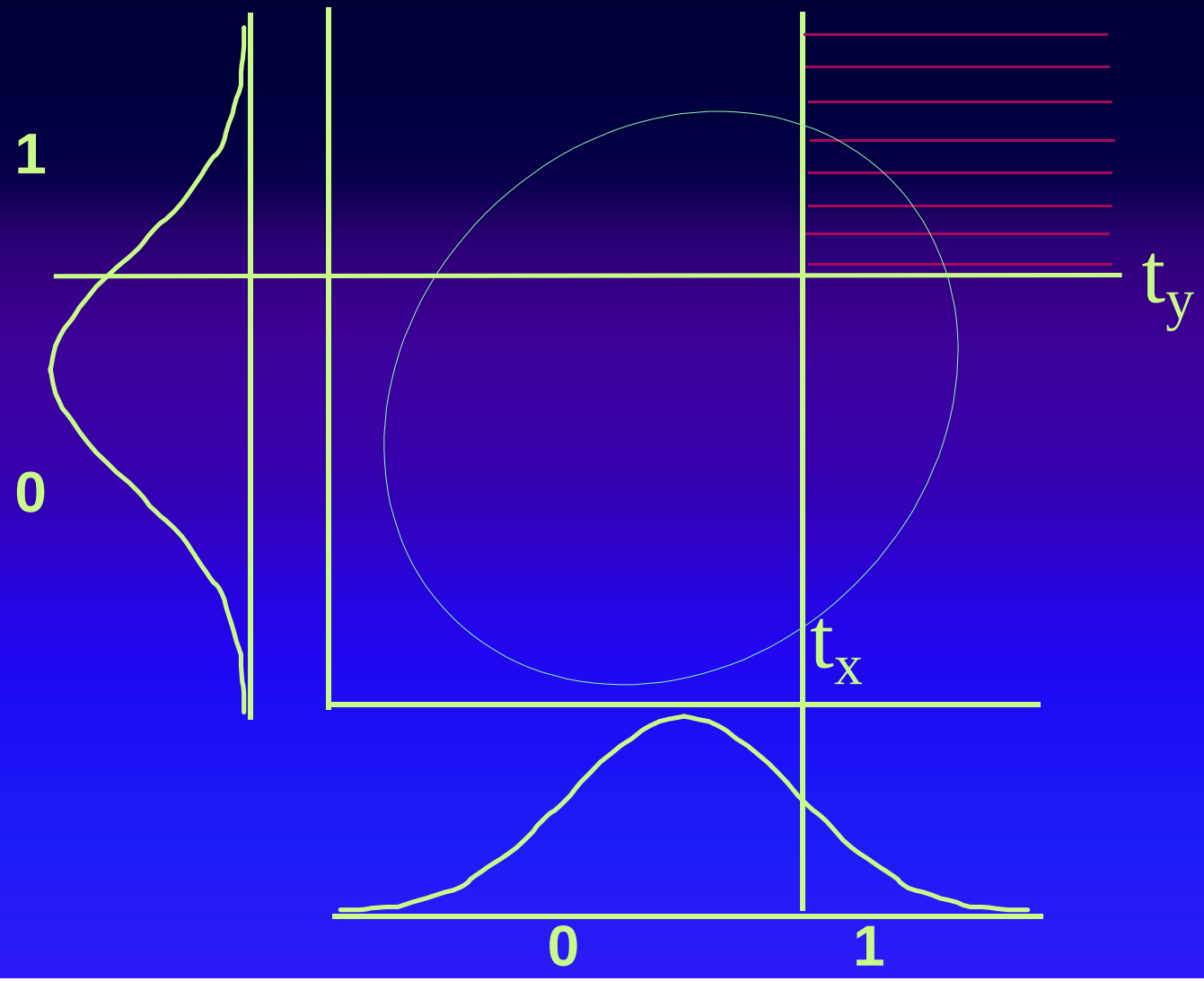
Medium correlation

$$\int_{tx}^{\infty} \int_{ty}^{\infty} \phi(x,y)\, dy\, dx$$



Low correlation

$$\int_{tx}^{\infty} \int_{ty}^{\infty} \phi(x,y)\, dy\, dx$$



Two approaches for twin data

- Contingency table approach
  - Automatic
  - Limited to two variable case
- Raw data approach
  - Manual
  - Multivariate
  - Moderator / Covariates

Contingency Table Case

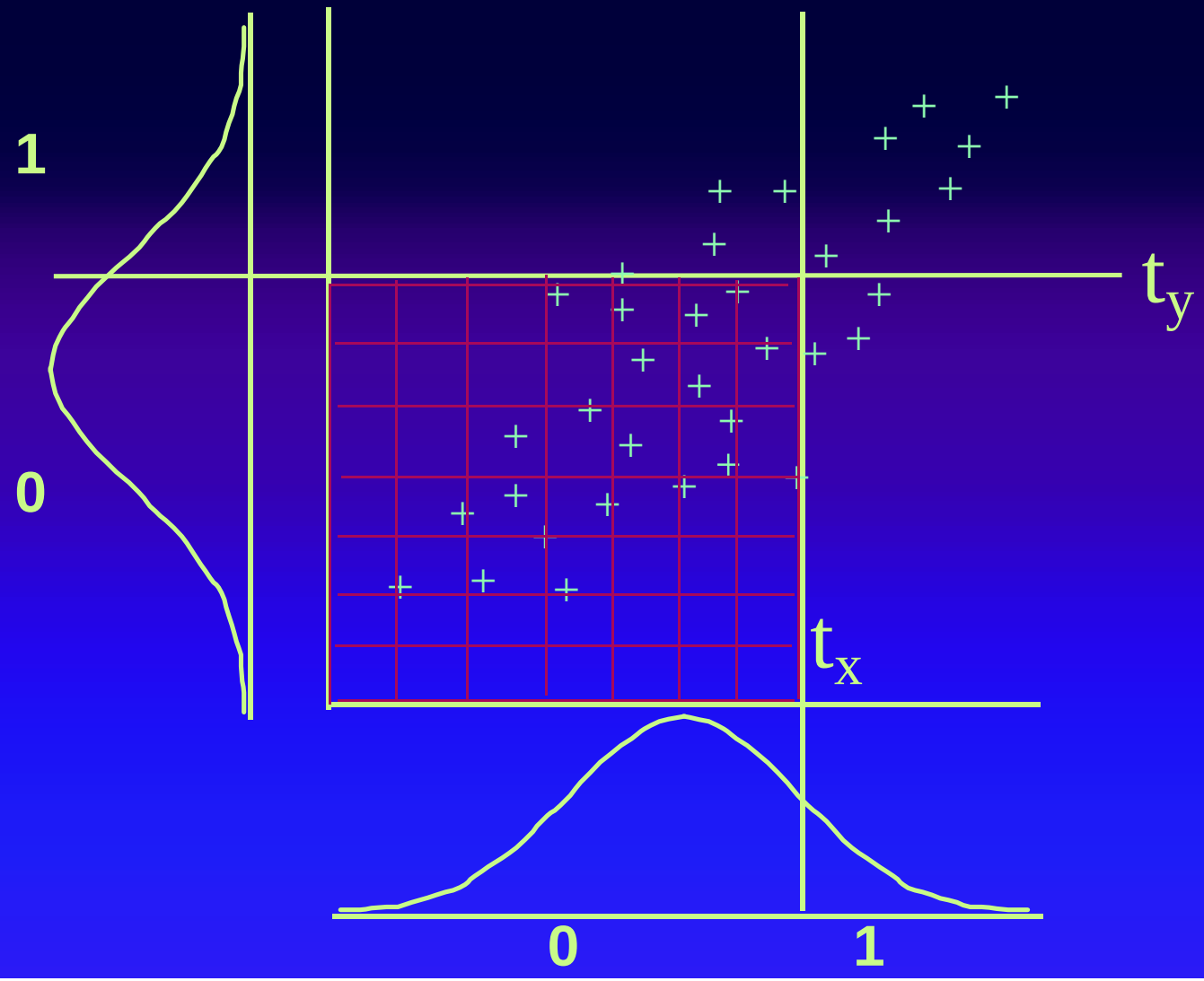
Binary data

- Feed program contingency table as usual
- Use -1 for frequency for non-ascertained cells
- Correction for ascertainment handled automatically

At least one twin affected

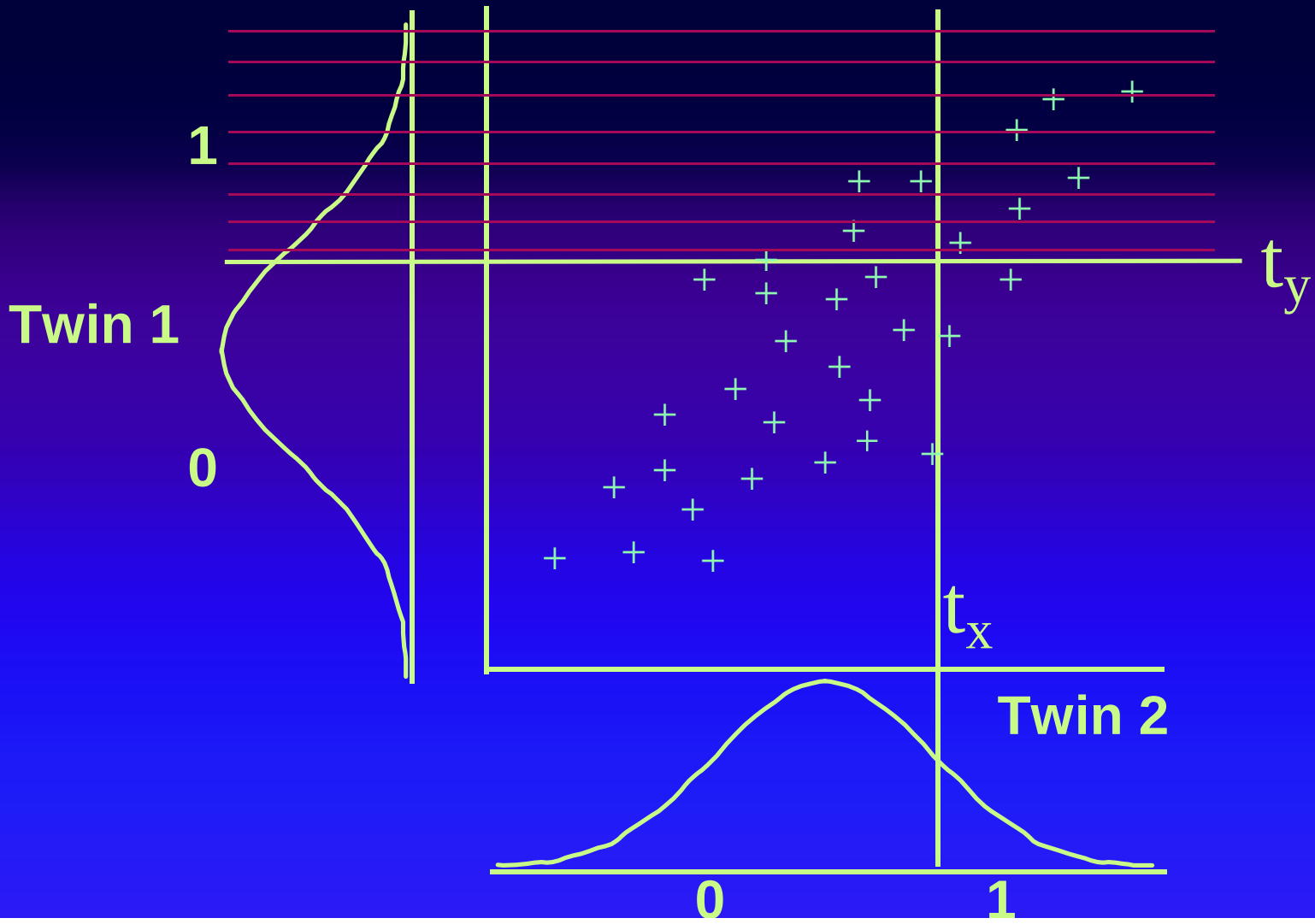
Ascertainment Correction

$$1-\int_{-\infty}^{tx}\int_{-\infty}^{ty}\phi(x,y)\,dy\,dx$$



Ascertain iff twin 1 > t

$$\int_{ty}^{\infty} \phi(y)\, dy = \int_{ty}^{\infty} \int_{-\infty}^{\infty} \phi(x,y)\, dx\, dy$$



Contingency Tables

- Use -1 for cells not ascertained
- Can be used for ordinal case
- Need to start thinking about thresholds
  - Supply estimated population values
  - Estimate them jointly with model

Mx Syntax

Classical Twin Study: Contingency Table

ftp://views.vcu.edu/pub/mx/examples/ncbook2/categor.mx

```
G1: Model parameters
 Data Calc NGroups=4
 Begin Matrices;
  X Lower 1 1 Free
  Y Lower 1 1 Free
  Z Lower 1 1 Free
  W Lower 1 1
 End Matrices;
 ! parameters are fixed by default, unless declared free
 Begin Algebra;
  A= X*X';
  C= Y*Y';
  E= Z*Z';
  D= W*W';
 End Algebra:
End
```

Mx Syntax

Group 2

```
G2: young female MZ twin pairs
 Data Ninput=2
 CTable 2 2
  329 83
  95 83
 Begin Matrices= Group 1
  T full 2 1 Free
 End Matrices;
 Covariances A+C+D+E | A+C+D _
             A+C+D   | A+C+D+E ;
 Thresholds T ;
 Options RSidual
End
```

Mx Syntax

Group 3

```
G3: young female DZ twin pairs
 Data Ninput=2
 CTable 2 2
  201 94
  82 63

 Begin Matrices= Group 1
  H Full 1 1
  Q Full 1 1
  T Full 2 1 Free
 End Matrices;
 Matrix H .5
 Matrix Q .25
 Start .6 All

 Covariances A+C+D+E   | H@A+C+Q@D _
            H@A+C+Q@D | A+C+D+E /
 Thresholds T ;
 Options RSidual NDecimals=4
End
```

Mx Syntax

Group 4

```
Group 4: constrain variance to 1
 Constraint NI=1
 Begin Matrices = Group 1 ;
  I unit 1 1
 End Matrices;

 Constraint I = A+C+E+D ;
 Option Multiple
End
 Specify 2 t 8 9
 Specify 3 t 8 9
End
```

Raw data approach

- Correction not always necessary
  - ML MCAR/MAR
  - Prediction of missingness
- Correct through weight formula

Types of missingness

Little & Rubin Terminology

- MCAR: Missing completely at random
- MAR: Missing at random
- NMAR: Not missing at random

Simulation Example

- Selrand: MCAR
  - missingness function of independent random variable
- Selonx: MAR
  - missingness predicted by other measured variable in analysis + MCAR
- Selony: NMAR
  - missingness mechanism related to "residual" variance in dependent variable

Method

- Simulate bivariate normal data X,Y
  - Sigma = 1 .5
  - .5 1
  - Mu = 0, 0
- Make some variables missing
  - Generate independent random normal variable, Z, if Z>0 then Y missing
  - If X>0 then Y missing
  - If Y>0 then Y missing
- Estimate elements of Sigma & Mu
- Constrain elements to population values 1,.5, 0 etc
- Compare fit
- Ideally, repeat multiple times and see if expected 'null' distribution emerges

SAS simulation script

```
OPTIONS nocenter;
FILENAME sibs 'selonx.rec';

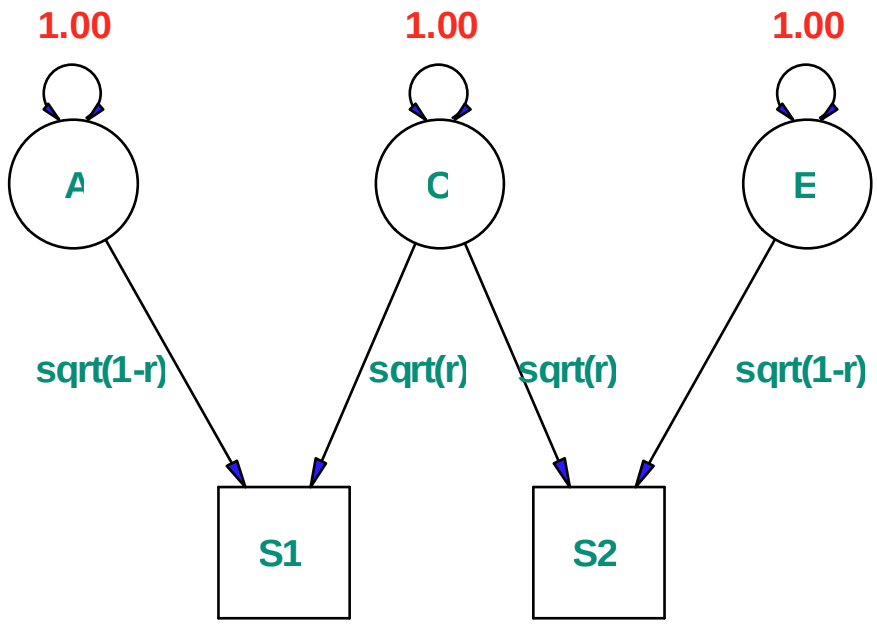
DATA NEALE1;
FILE sibs;
array v{2};
x=.5;
n=0;

sample: IF N gt 500 THEN GO TO DONE;
 n=n+1;
 famfac=rannor(0);
 v(1)=SQRT(X)*famfac + SQRT(1-X)*RANNOR(0);
 if rannor(0) gt 0 then do;
  v(2) = SQRT(X)*famfac + SQRT(1-X)*RANNOR(0);
  size=2;
  end;
 else do;
  v(2)=.;
  size=1;
 end;
  PUT v(1) v(2);
 OUTPUT;
x1=v{1}; y=v{2};

GO TO sample;

DONE: COMMENT sample complete;
```

SAS simulation 'model'



Mx Script

Rather basic, like Monday morning

```
Estimate pop cov matrix of X&Y, with Y observed iff X>0
 Data ng=1 ni=2
 Rectangular file=selonx.rec
 Begin Matrices;
  a sy 2 2 free ! covariance of x,y
  m fu 1 2 free ! mean of x,y
 End Matrices;
 Means M /
 Covariance A /
  matrix a 1 .3 1
  bound .1 2 a 1 1 a 2 2
  option rs mu
 Option issat
end

 fix all
  matrix 1 a
 1 .5 1
matrix 1 m
0 0
end
```

Mx Scripts & Data

F:\mcn\2004\sel

- Check output:
  - Summary statistics (obs means)
  - Estimated means & covariance matrices
  - Difference in fit between estimated values and population values
- Interpretation?

ML estimation under different missingness mechanisms

Missingness	mean x	mean y	var x	cov xy	var y	LR Chisq
MCAR (rand) MLE <sample>						
MAR (on x) MLE <sample>						
NMAR (on y) MLE <sample>						

ML estimation under different missingness mechanisms

Missingness	mean x	mean y	var x	cov xy	var y	LR Chisq
MCAR (rand) MLE	-0.0116	-0.1	1.0505	0.4998	0.8769	6.492
sample	-0.0116	-0.0919	1.0505		0.8839	
MAR (on x) MLE	0.0048	0.0998	1.0084	0.4481	1.1025	5.768
sample	0.0014	0.4437	1.0084		0.9762	
NMAR (on y) MLE	-0.0204	0.6805	0.9996	0.1356	0.2894	227.262
sample	0.0448	0.7373	0.9996		0.2851	

Screen + Examination

Only a subset, selected on basis of screen, are examined

- Bivariate analysis of screen & exam
  - No ascertainment correction required
  - Example: all pairs where at least one screens positive are examined
  - Works for continuous & ordinal
- Undersampling: some proportion of pairs concordant negative for screen are also examined
  - Ascertainment correction required
  - Different correction for screen -- vs +-/-+/++

Normal Theory Likelihood Function

For raw data in Mx

$$\ln L_i = f_i \quad \ln \left[\sum_{j=1}^{m} w_j \; g(x_i, \mu_{ij}, \Sigma_{ij}) \right]$$

x_i - vector of observed scores on n subjects

μ_{ij} - vector of predicted means

Σ_{ij} - matrix of predicted covariances - functions of parameters

Likelihood Function Itself

The guts of it

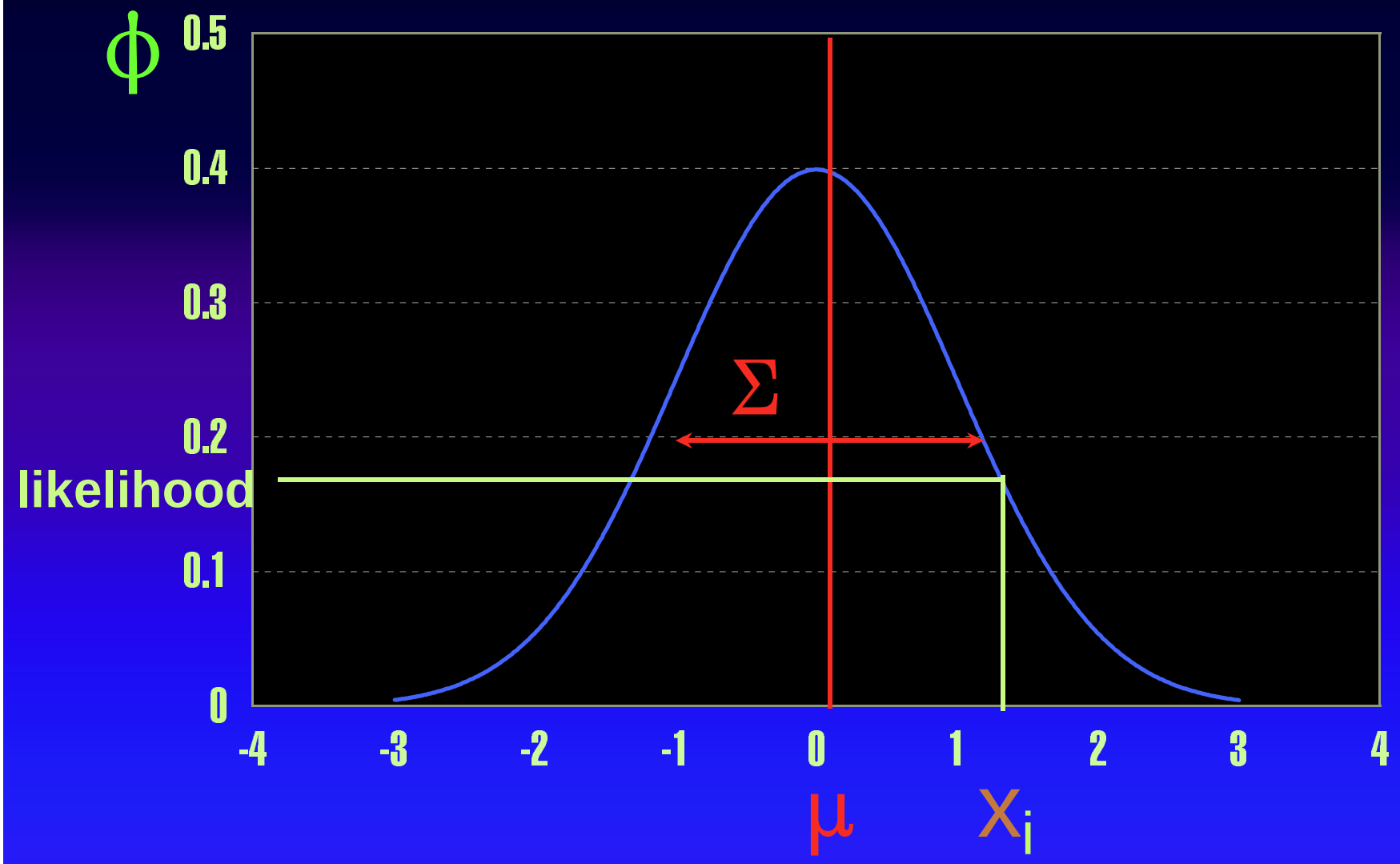
$$\ln L_i = f_i \ln \left[\sum_{j=1}^{m} w_{ij} \; g(x_i, \mu_{ij}, \Sigma_{ij}) \right]$$

$g(x_i, \mu_{ij}, \Sigma_{ij})$ - likelihood function

- Example: Normal pdf

Normal distribution $\phi(\mu_{ij}, \Sigma_{ij})$

Likelihood is height of the curve



Weighted mixture of models

Finite mixture distribution

$$\ln L_i = f_i \ln \left[\sum_{j=1}^{m} w_{ij} \; g(x_i, \mu_{ij}, \Sigma_{ij}) \right]$$

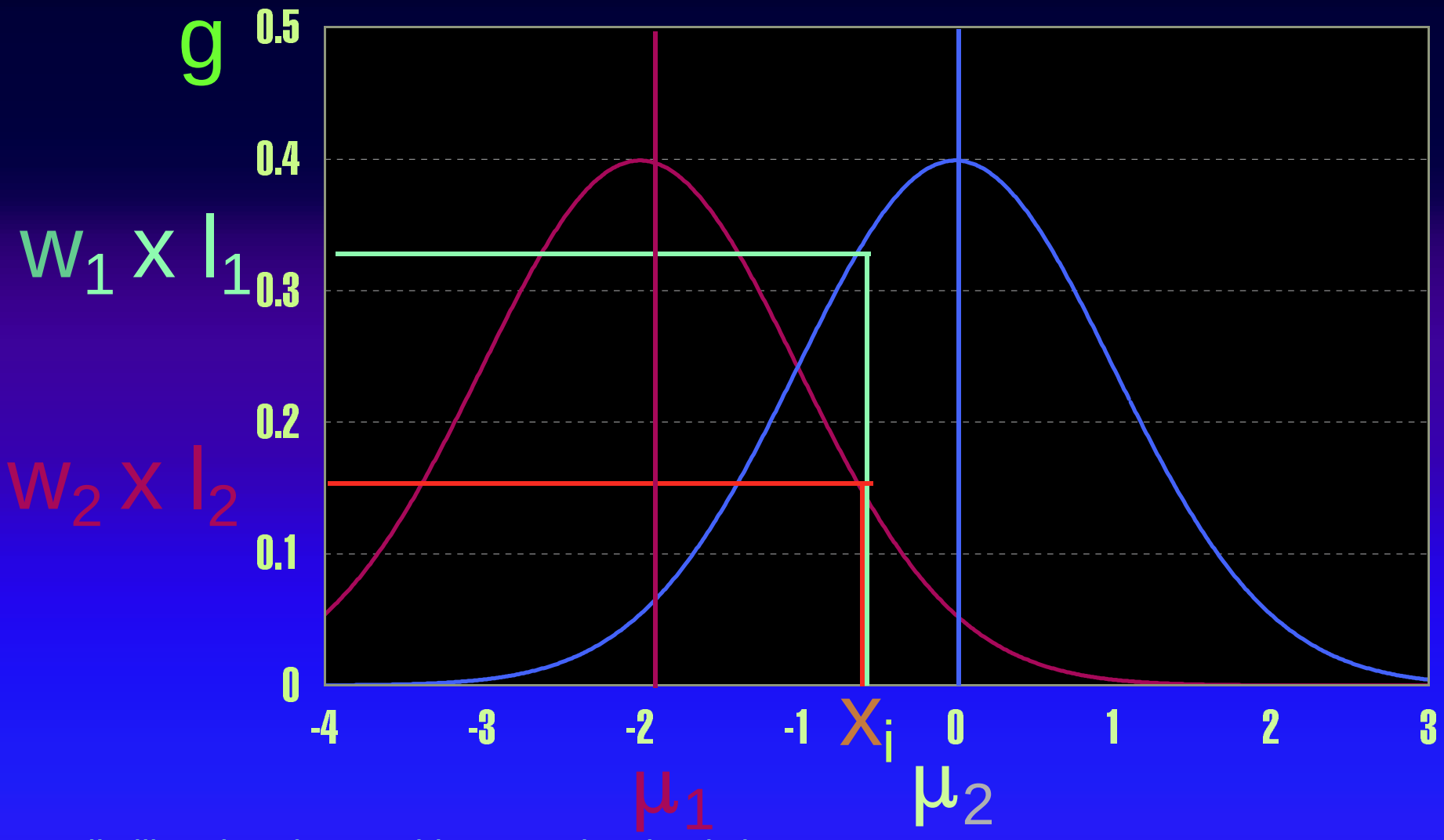
$j = 1....m$ models

w_{ij} Weight for subject i model j

e.g., Segregation analysis

Mixture of Normal Distributions

Two normals, propotions w1 & w2, different means



But Likelihood Ratio not Chi-Squared - what is it?

General Likelihood Function

Finally the frequencies

$$\ln L_i = f_i \ \ln \left[\sum_{j=1}^{m} w_j \, g(x_i, \mu_{ij}, \Sigma_{ij}) \right]$$

f_i - frequency of case i

- Sample frequencies binary data
- Sometimes 'sample weights'
- Might also vary over model j

General Likelihood Function

Things that may differ over subjects

$$\ln L_i = f_i \ln \left[\sum_{j=1}^{m} w_{ij}\, g(x_i, \mu_{ij}, \Sigma_{ij}) \right]$$

i = 1....n subjects (families)

- Model for Means can differ
- Model for Covariances can differ
- Weights can differ
- Frequencies can differ

How do we make things vary?

Definition variables

- Read in rectangular or ordinal data
- Definition command like backwards select
  - Deletes variables to be analyzed
  - Makes them available for individual-based analyses
  - Variable can be placed in any modifiable matrix element

Raw Ordinal Data Syntax

- Read in ordinal file
- May use frequency command to save space
- Weight uses \mnor function
- \mnor(R_M_U_L_K)
  - R - covariance matrix (p x p)
  - M - mean vector (1xp)
  - U - upper threshold (1xp)
  - L - lower threshold (1xp)
  - K - indicator for type of integration in each dimension (1xp)
    - 0: L=-∞
    - 1: U=+∞
    - **2:** $\int_L^u$
    - **3:** L=-∞ **U**=∞

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  Z Lower 1 1 Free
  W Lower 1 1
 End Matrices;
 ! parameters are fixed by default, unless declared free
 Begin Algebra;
  A= X*X';
  C= Y*Y';
  E= Z*Z';
  D= W*W';
 End Algebra:
End
```

Mx Syntax

```
G2: MZ twin pairs
 Data Ninput=3
 Ordinal File=mz.frq
 Labels T1 T2 Freq
 Definition Freq ;
 Begin Matrices= Group 1
  T full 2 1 Free
  F full 1 1 ! Frequency
 End Matrices;
 Specify F Freq
 Covariances A+C+D+E | A+C+D _
             A+C+D   | A+C+D+E ;
 Thresholds T ;
 Frequency F;
 Options RSidual
End
```

Mx Syntax

```
G3: DZ twin pairs
 Data Ninput=3
 Labels T1 T2 Freq
 Ordinal File=dz.frq
 Definition Freq ;

 Begin Matrices= Group 1
  H Full 1 1
  Q Full 1 1
  T Full 2 1 Free
  F full 1 1 ! Frequency
 End Matrices;
 Specify F Freq
 Matrix H .5
 Matrix Q .25
 Start .6 All

 Covariances A+C+D+E   | H@A+C+Q@D _
             H@A+C+Q@D | A+C+D+E /
 Thresholds T ;
```

Mx Syntax

```
Group 4: constrain variance to 1
 Constraint NI=1
 Begin Matrices = Group 1 ;
  I unit 1 1
 End Matrices;

 Constraint I = A+C+E+D ;
 Option Multiple
End
 Specify 2 t 8 9
 Specify 3 t 8 9
End
```

Ascertainment additional commands

```
Begin Algebra;
 M=(A+C+E|A+C_A+C|A+C+E);
 N=(A+C+E|h@A+C_h@A+C|A+C+E);
 J=I-\mnor(M_Z_T_T_Z); ! Z = [0  0]
 K=I-\mnor(N_Z_T_T_Z); ! DZ case
End Algebra;

Weight J~;  ! for MZ group
Weight K~;  ! DZ group
```

Why inverse of J and K?

Correcting for ascertainment

Linkage studies

- Multivariate selection: multiple integrals
  - double integral for ASP
  - four double integrals for EDAC
- Use (or extend) weight formula
- Precompute in a calculation group
  - unless they vary by subject

Conclusion

- Be careful when designing studies with non-random ascertainment
- Usually possible to correct
- In principle, heritability should not change
- In practice, it might