Genetic simplex model in the classical twin design

Conor Dolan & Sanja Franic

Boulder Workshop 2016

Two general approaches to longitudinal modeling (not mutually exclusive)

Markov models:
(Vector) autoregressive models for continuous data
(Hidden) Markov transition models discrete data

Growth curve models:
Focus on linear and non-linear growth curves
Typically multilevel or random effects model

Which to use?
Use the model that fit the theory / data / hypotheses

Growth curve modeling ? If you’re interested in growth trajectories. Linear or non-linear:

Twin Research (2000) 3, 165–177

1369–0523/00 $15.00
www.nature.com/tr

Structured latent growth curves for twin data

Michael C Neale[1] and John J McArdle[2]

Autoregressive modeling ? If you’re mainly interested in stability.

Psychological Medicine (2015), **45**, 1039–1049. © Cambridge University Press 2014
doi:10.1017/S003329171400213X

ORIGINAL ARTICLE

Stability in symptoms of anxiety and depression as a function of genotype and environment: a longitudinal twin study from ages 3 to 63 years

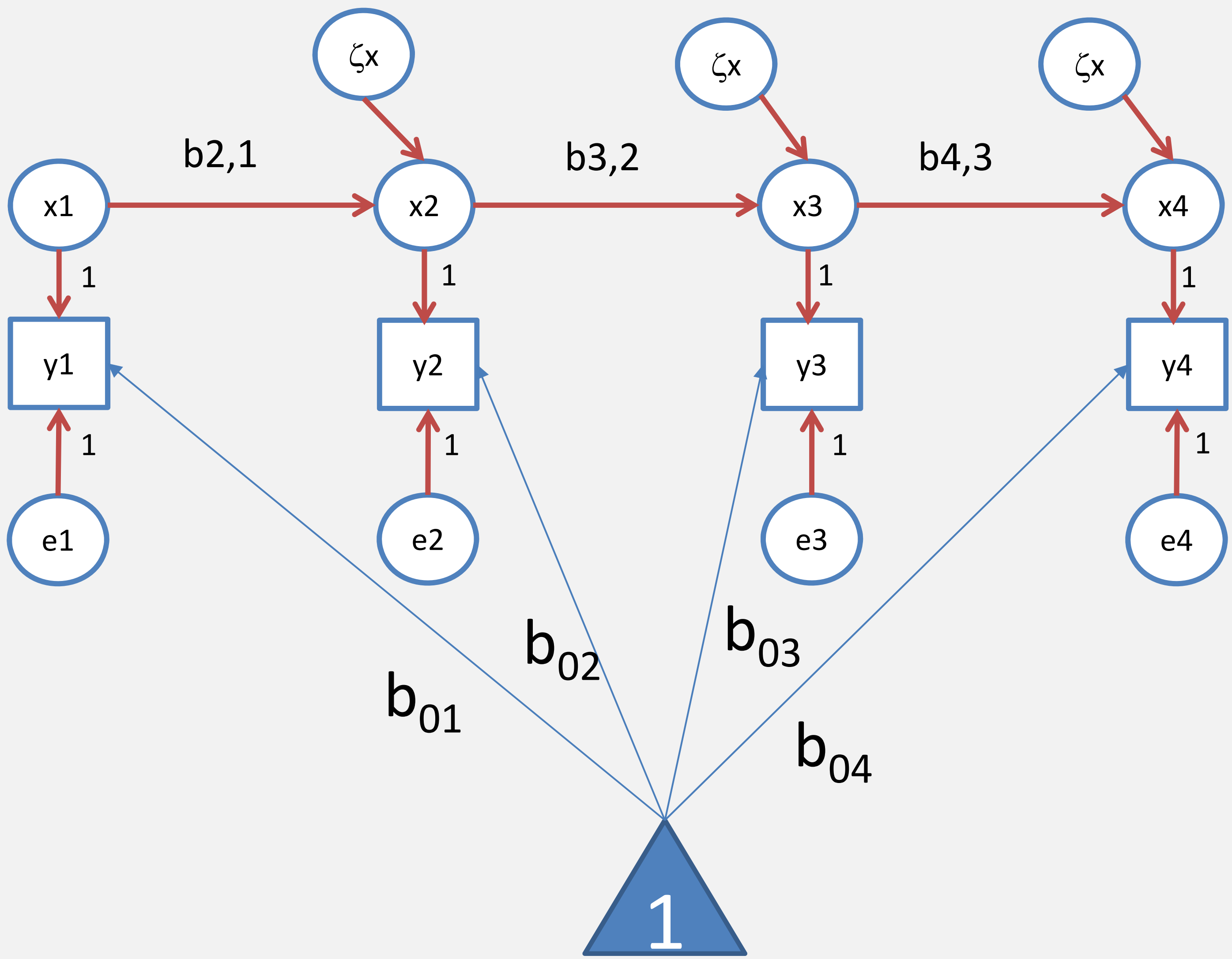
M. G. Nivard[1,2*], C. V. Dolan[1,3], K. S. Kendler[4], K.-J. Kan[1], G. Willemsen[1,5], C. E. M. van Beijsterveldt[1,5], R. J. L. Lindauer[6], J. H. D. A. van Beek[1,5], L. M. Geels[1,5], M. Bartels[1,5], C. M. Middeldorp[1,2,7]† and D. I. Boomsma[1,2,5]†

Do the Genetic or Environmental Determinants of Anxiety and Depression Change with Age? A Longitudinal Study of Australian Twins

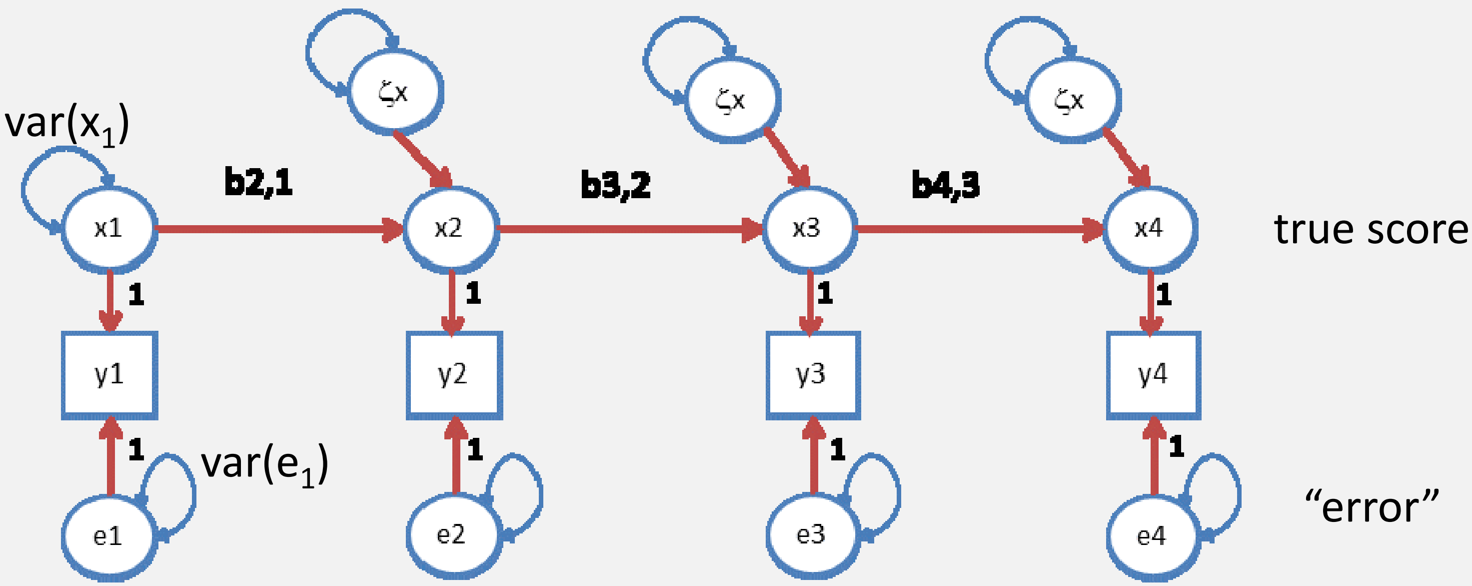
Nathan A. Gillespie[1], Katherine M. Kirk[1], David M. Evans[1], Andrew C. Heath[2], Ian B. Hickie[3], and Nicholas G. Martin[1]

Can be combined (this afternoon)

First order autoregression model. A (quasi) simplex model (var(e)>0).



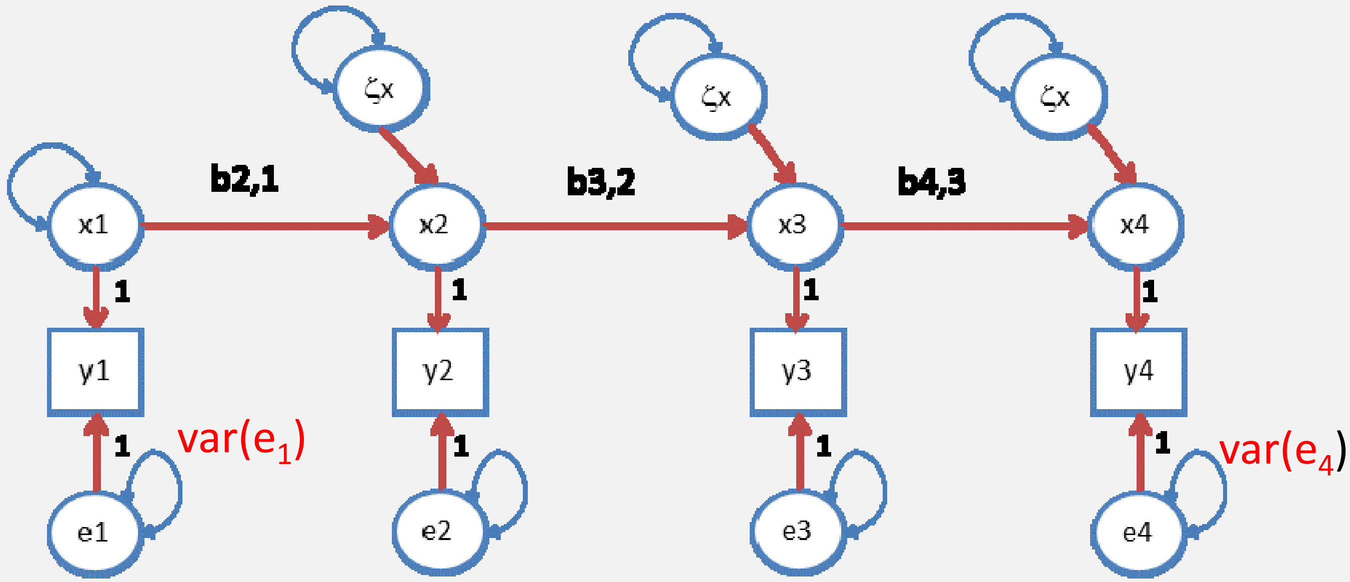
First order autoregression model. A **quasi** simplex model (var(e)>0).



$$y_{ti} = b_{0t} + x_{ti} + e_{ti}$$
$$x_{ti} = b_{t-1,t}\, x_{t-1i} + \zeta x_{ti}$$

$$var(y_t) = var(x_t) + var(e_t)$$
$$var(x_t) = b_{t-1,t}^{\,2}\, var(x_{t-1}) + var(\zeta x_t)$$
$$cov(x_t, x_{t-1}) = b_{t-1,t} var(x_{t-1})$$
$$cov(y_t, y_{t-1}) = b_{t-1,t} var(x_{t-1})$$

First order autoregression model.



Identification issue: $var(e_1)$ and $var(e_t)$ are not identified. Solution set to zero, or equate $var(e_1) = var(e_2)$, $var(e_3) = var(e_4)$

$var(y_t) = var(x_t) + var(e_t)$

$var(x_t) = b_{t-1,t}^2 \, var(x_{t-1}) + var(\zeta x_t)$

$cov(x_t, x_{t-1}) = b_{t-1,t} var(x_{t-1})$

$cov(y_t, y_{t-1}) = b_{t-1,t} var(x_{t-1})$

Standardized stats part I:

"Reliability" at each t, $rel(y_t)$:

$rel(y_t) = var(x_t) / \{var(x_t) + var(e_t)\}$

Interpretation: % of variance in y_t due to latent x_t

$\mathrm{var}(y_t) = \mathrm{var}(x_t) + \mathrm{var}(e_t)$

$\mathrm{var}(x_t) = b_{t-1,t}^2\,\mathrm{var}(x_{t-1}) + \mathrm{var}(\zeta x_t)$

$\mathrm{cov}(x_t,x_{t-1}) = b_{t-1,t}\mathrm{var}(x_{t-1})$

$\mathrm{cov}(y_t,y_{t-1}) = b_{t-1,t}\mathrm{var}(x_{t-1})$

Standardized stats part II:

Stability at level of X, $\mathrm{stab}(X_t,X_{t-1})$:

$b_{t-1,t}^2\,\mathrm{var}(x_t)\ /\ \{b_{t-1,t}^2\,\mathrm{var}(x_{t-1}) + \mathrm{var}(\zeta x_t)\}$

Interpretation: % of the variance in x_t due to x_{t-1}

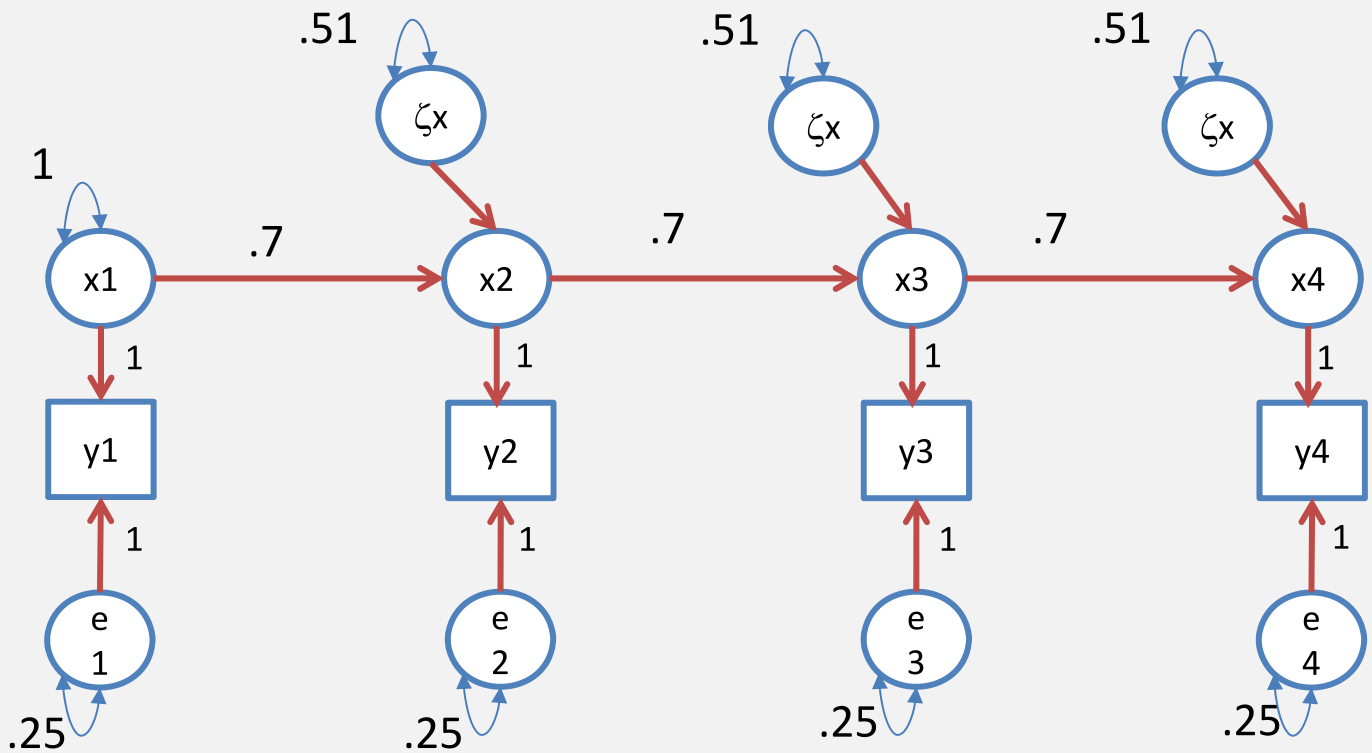
$\text{var}(y_t) = \text{var}(x_t) + \text{var}(e_t)$
$\text{var}(x_t) = b_{t-1,t}{}^2\,\text{var}(x_{t-1}) + \text{var}(\zeta x_t)$
$\text{cov}(x_t,x_{t-1}) = b_{t-1,t}\text{var}(x_{t-1})$
$\text{cov}(y_t,y_{t-1}) = b_{t-1,t}\text{var}(x_{t-1})$

Standardized stats part III:

Correlation t,t-1, cor(t,t-1):

$b_{t-1,t}\,\text{var}(x_{t-1})\ \ /\ \{\text{sd}(y_{t-1}) * \text{sd}(y_t)\}$
$\text{sd}(y_t) = \surd(\text{var}(x_t) + \text{var}(e_t))$
$\text{var}(x_t) = b_{t-1,t}\,\text{var}(x_{t-1}) + \text{var}(\zeta x_t)$

Interpretation: strength of linear relationship

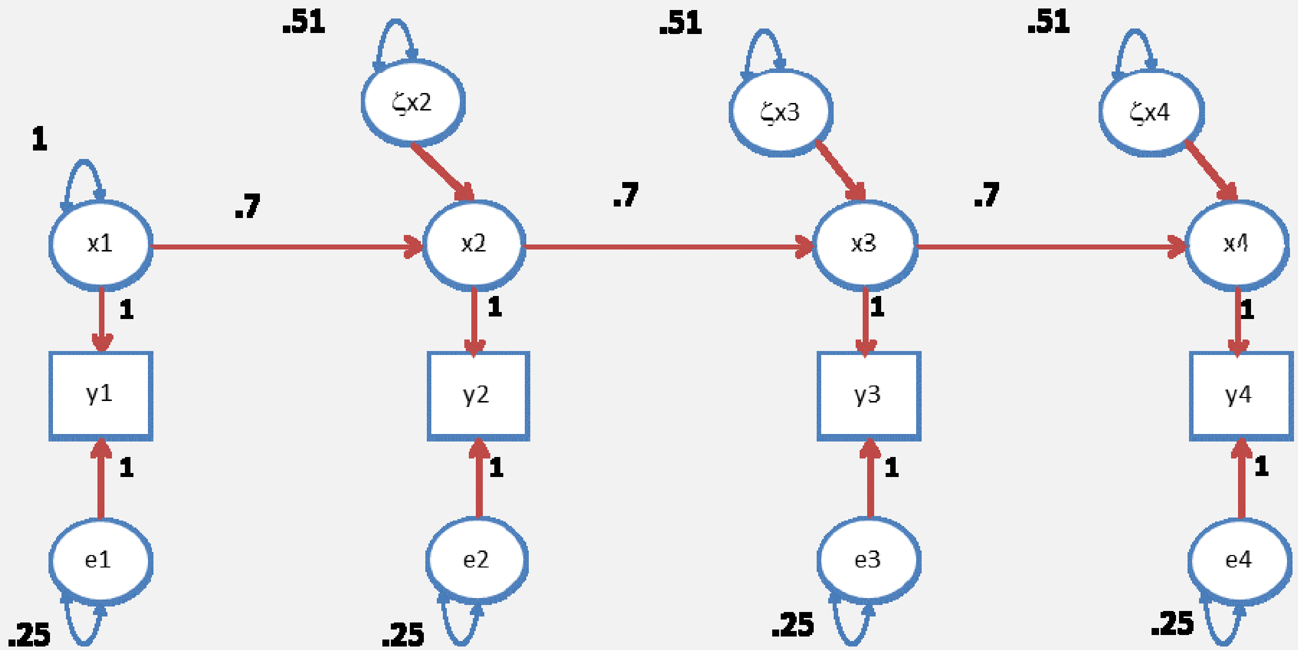


Covariance matrix

1.250	0.70	0.49	0.343
0.700	1.25	0.70	0.490
0.490	0.70	1.25	0.700
0.343	0.49	0.70	1.250

Correlation matrix

1.0000	0.560	0.392	0.2744
0.5600	1.000	0.560	0.3920
0.3920	0.560	1.000	0.5600
0.2744	0.392	0.560	1.0000



reliability: $rel(x_t) = var(x_t) / \{var(x_t) + var(e_t)\}$

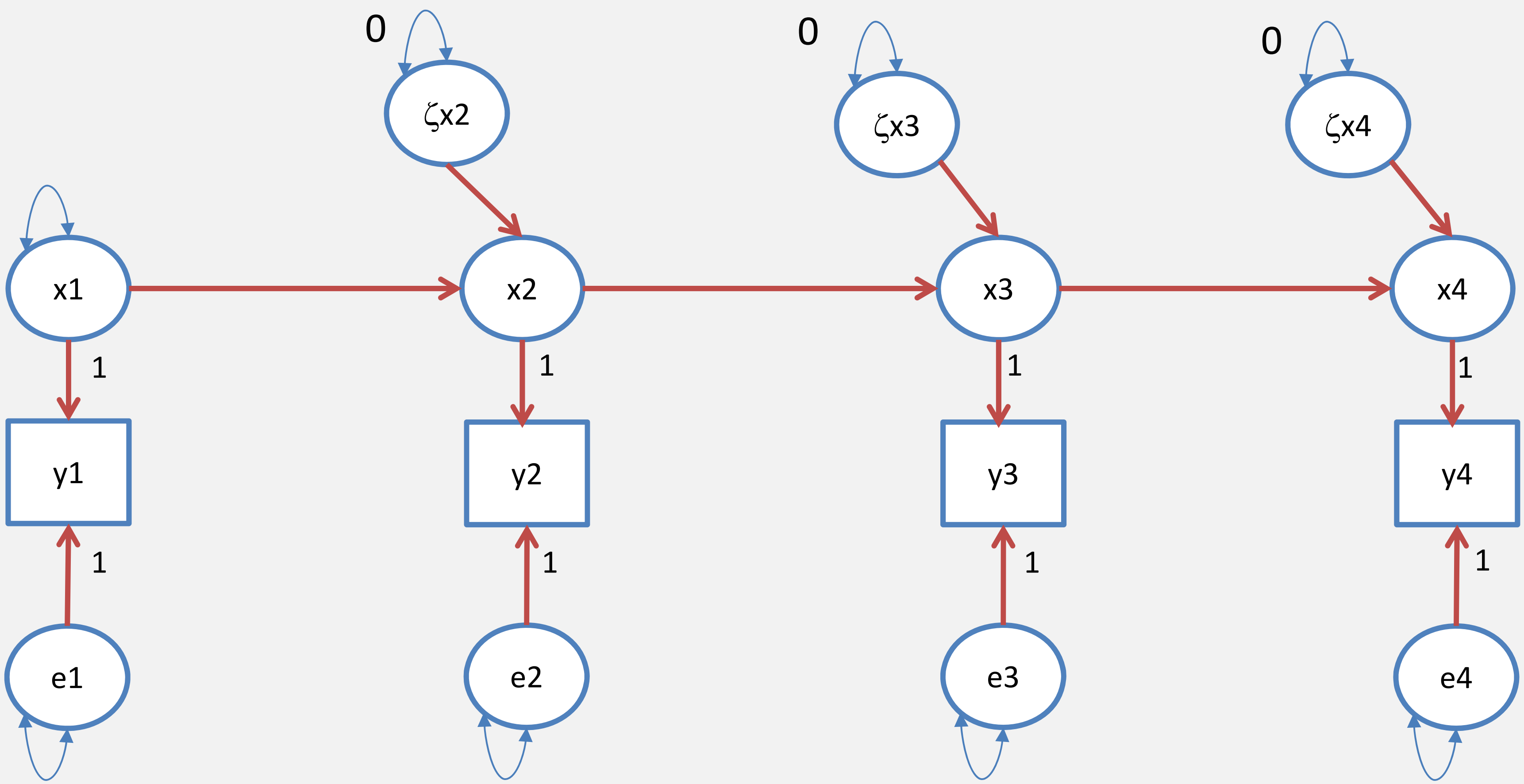
$= 1/ (1+.25) = 1/1.25 = .8$

R^2: $b_{t-1,t}{}^2 \, var(x_{t-1}) \; / \{b_{t-1,t}{}^2 \, var(x_{t-1}) + var(\zeta x_t)\}$

$= \{.7^2 * 1\} / (.7^2 * 1 + .51) = .49/1 = .49$

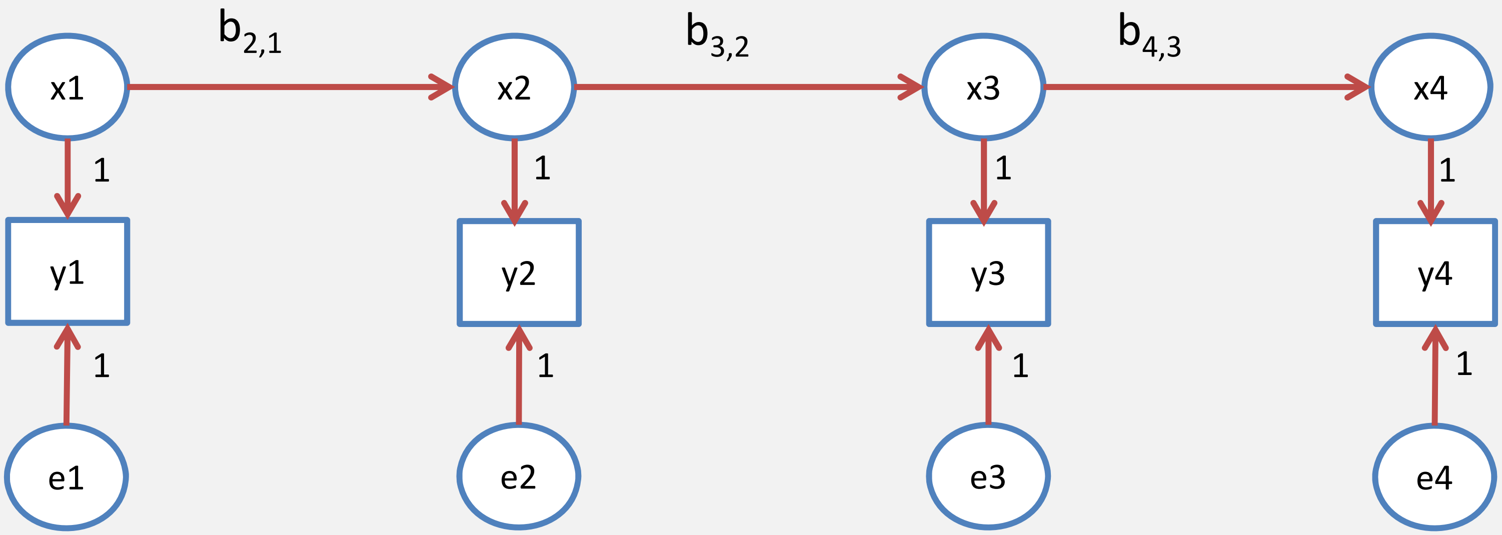
cor(t,t+1) : $b_{t-1,t} \, var(x_{t-1}) \; / \{sd(y_{t-1}) * sd(y_t)\}$

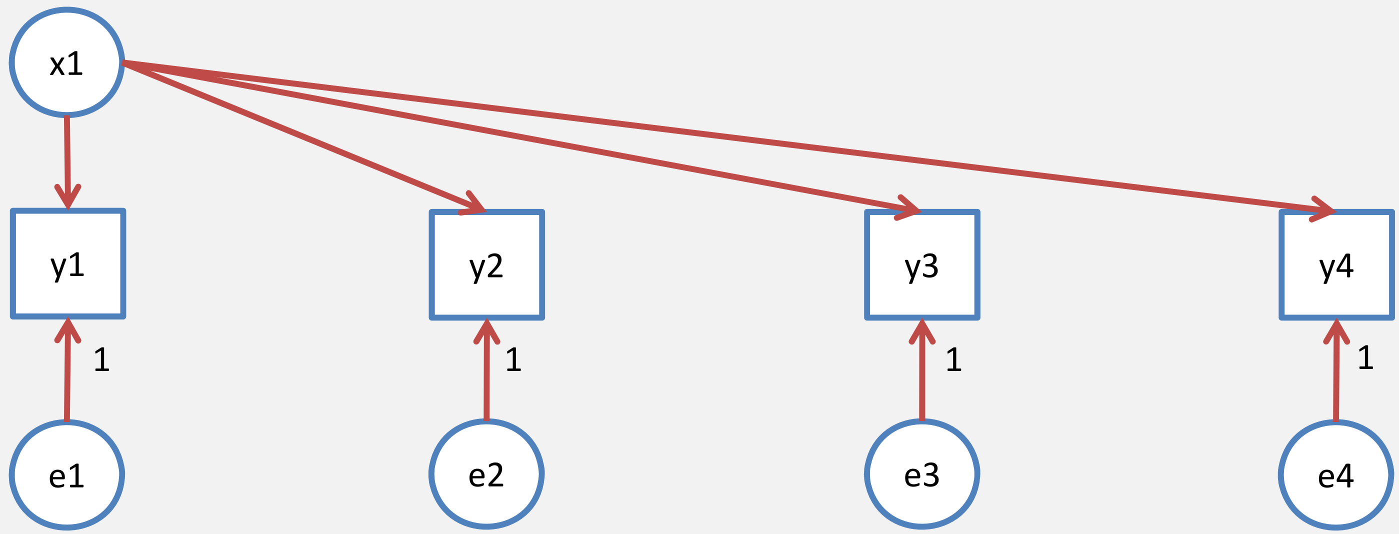
$=\{.7 * 1\} / \{\surd 1.25 * \surd 1.25\} = .56$



What happens if var(ζxt) = 0?

Special case: factor model $var(\zeta x_t)$ (t=2,3,4) = 0





Multivariate decomposition of phenotypic covariance matrix (TxT, say T=4):

$$\Sigma_{ph} = \Sigma_A + \Sigma_C + \Sigma_E$$

$$\begin{matrix} \Sigma_{ph1} & \Sigma_{ph12} \\ \Sigma_{ph12} & \Sigma_{ph2} \end{matrix} =$$

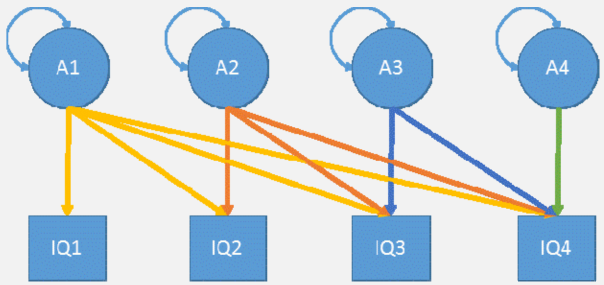
$$\begin{matrix} \Sigma_A + \Sigma_C + \Sigma_E & r\otimes\Sigma_A + \Sigma_C + \Sigma_E \\ r\otimes\Sigma_A + \Sigma_C + \Sigma_E & \Sigma_A + \Sigma_C + \Sigma_E \end{matrix}$$

(r=1 or .5)

$$\Sigma_{ph} = \Sigma_A + \Sigma_C + \Sigma_E$$

Estimate Σ_A using a Cholesky-decomp

$$\Sigma_A = \Delta_A \Delta_A^t$$



$$\Delta_A = \begin{matrix} \delta_{11} & 0 & 0 & 0 \\ \delta_{21} & \delta_{22} & 0 & 0 \\ \delta_{31} & \delta_{32} & \delta_{33} & 0 \\ \delta_{41} & \delta_{42} & \delta_{43} & \delta_{44} \end{matrix}$$

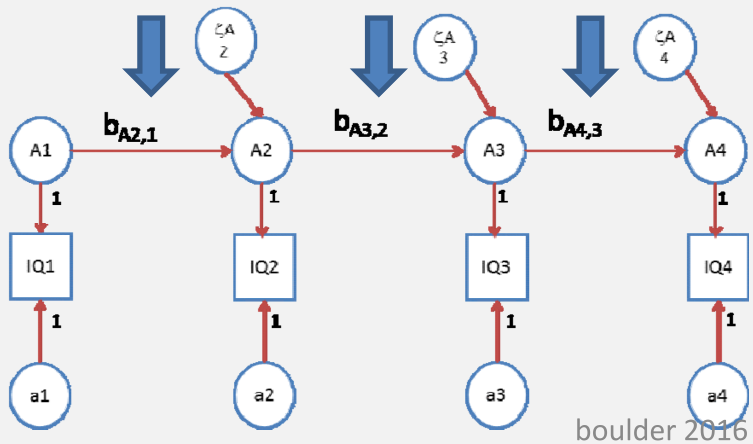
$$\Sigma_{ph} = \Sigma_A + \Sigma_C + \Sigma_E$$

Model Σ_A using a simplex model

$$\Sigma_A = (I-B)_A^{-1}\, \Psi_A\, (I-B)_A^{-1t} + \Theta_A$$

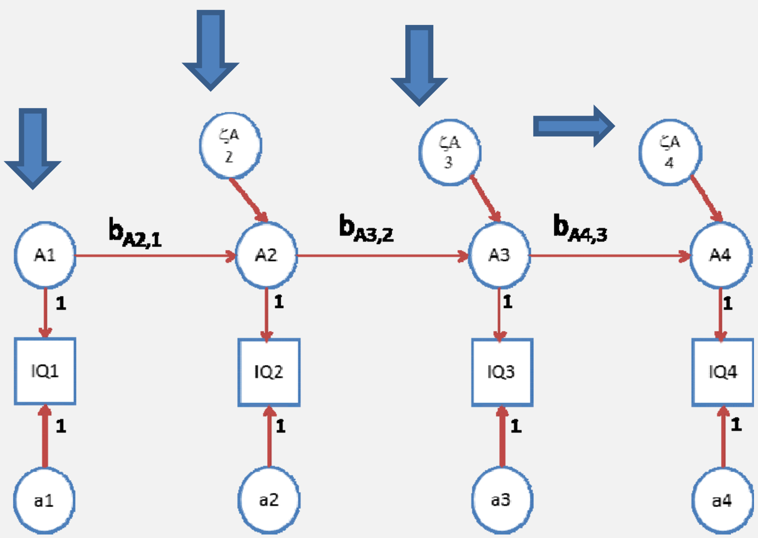
$$\Sigma_A = (I - B_A)^{-1}\, \Psi_A\, (I - B_A)^{-1\,t} + \Theta_A$$

$$B_A = \begin{matrix} 0 & 0 & 0 & 0 \\ b_{A21} & 0 & 0 & 0 \\ 0 & b_{A32} & 0 & 0 \\ 0 & 0 & b_{A43} & 0 \end{matrix}$$



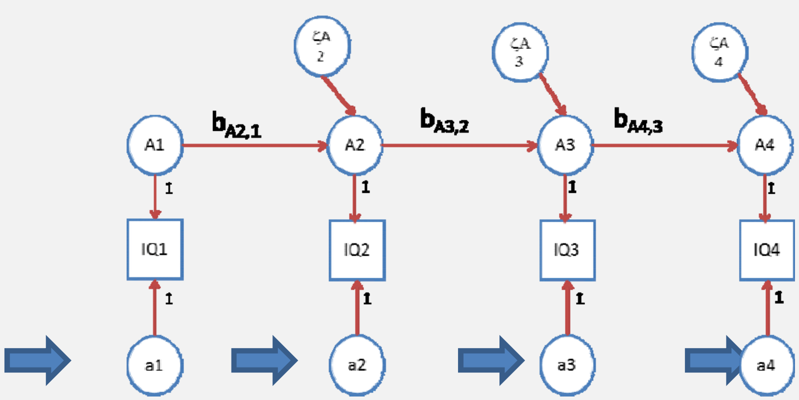
$$\Sigma_A = (I - B_A)^{-1} \Psi_A (I - B_A)^{-1\,t} + \Theta_A$$

$$\Psi_A = \begin{matrix} var(A_1) & 0 & 0 & 0 \\ 0 & var(\zeta_{A2}) & 0 & 0 \\ 0 & 0 & var(\zeta_{A3}) & 0 \\ 0 & 0 & 0 & var(\zeta_{A4}) \end{matrix}$$

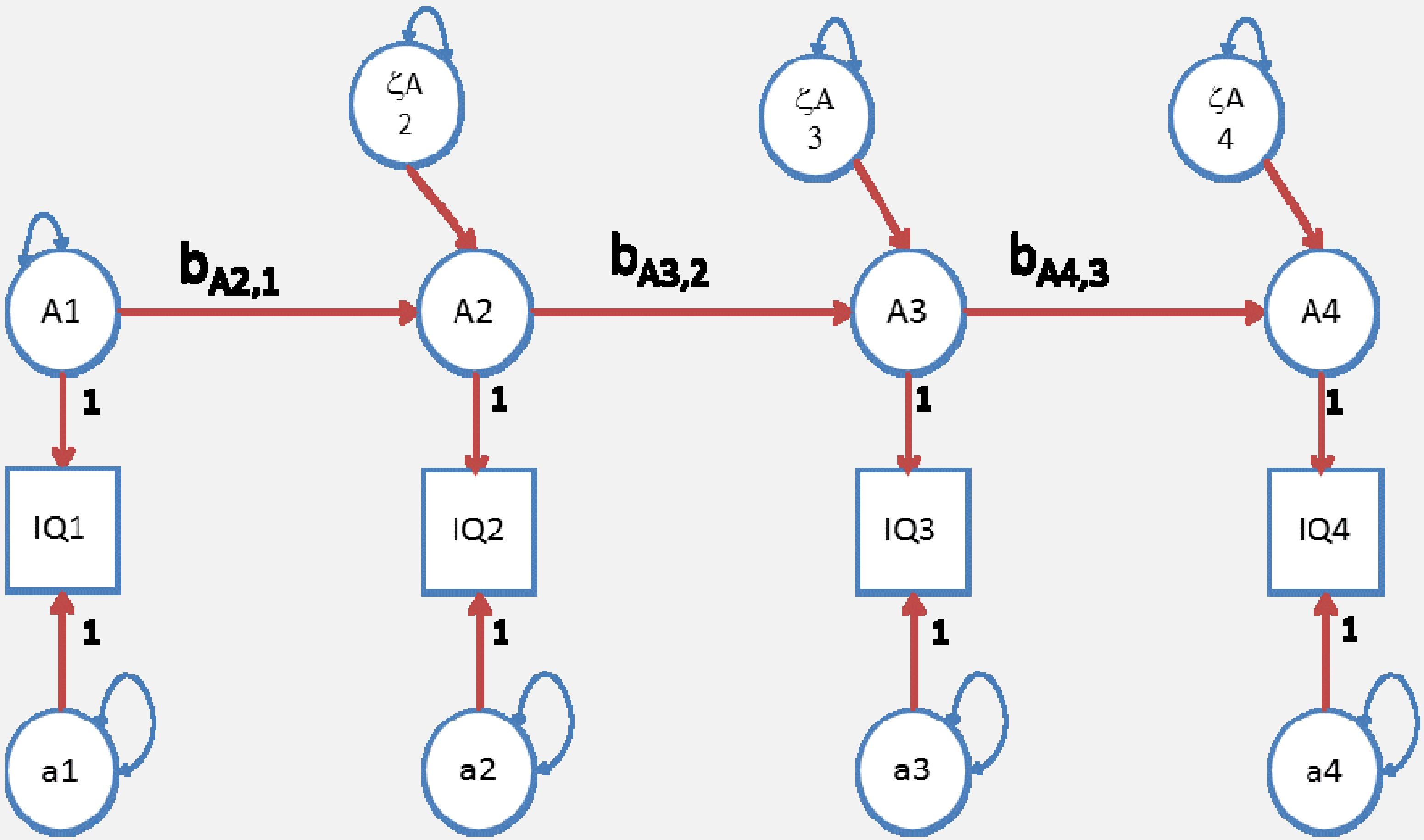


$$\Sigma_A = (I - B_A)^{-1} \Psi_A (I - B_A)^{-1\tau} + \Theta_A$$

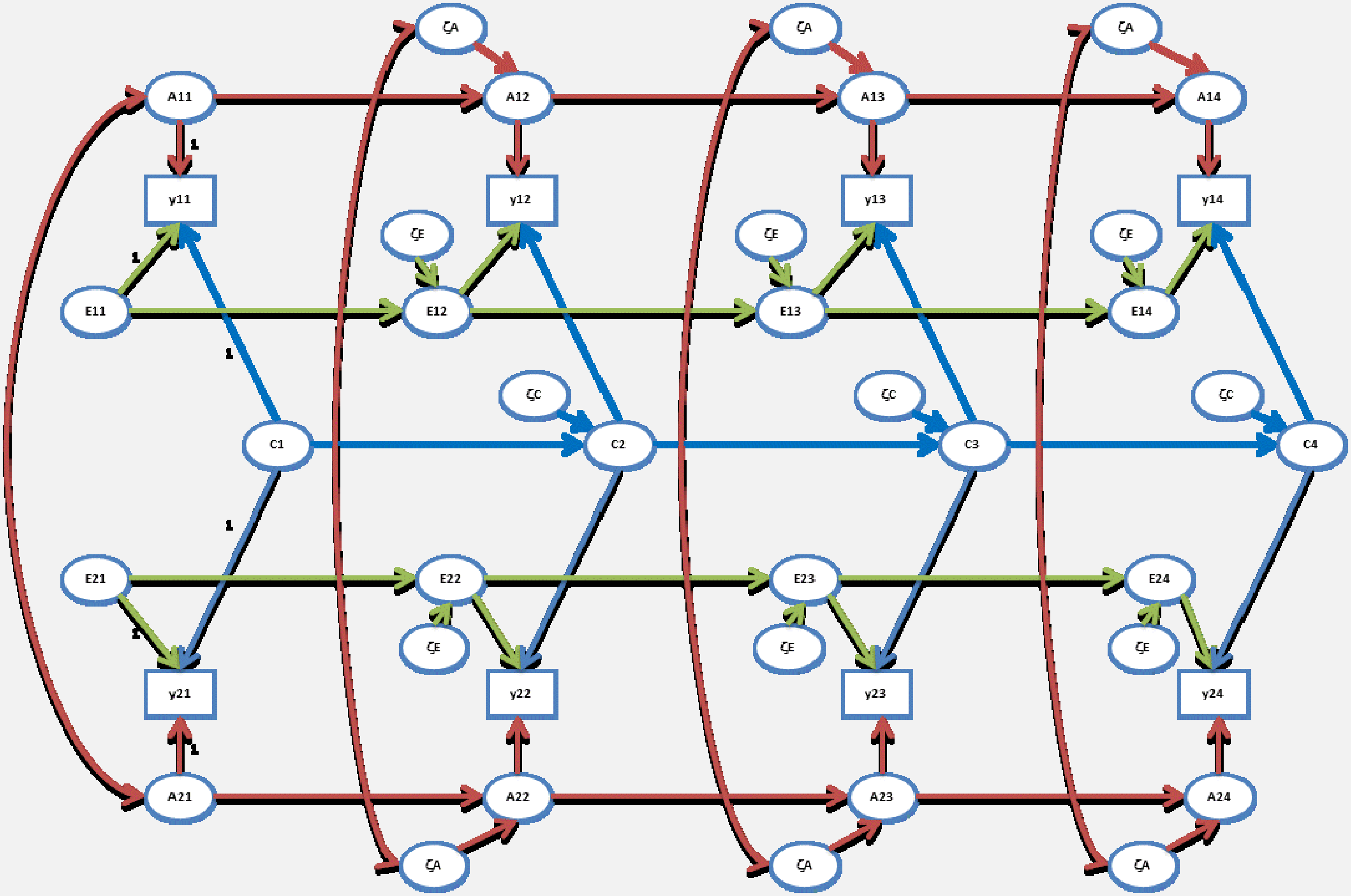
$$\Theta_A = \begin{matrix} var(a_1) & 0 & 0 & 0 \\ 0 & var(a_2) & 0 & 0 \\ 0 & 0 & var(a_3) & 0 \\ 0 & 0 & 0 & var(a_4) \end{matrix}$$



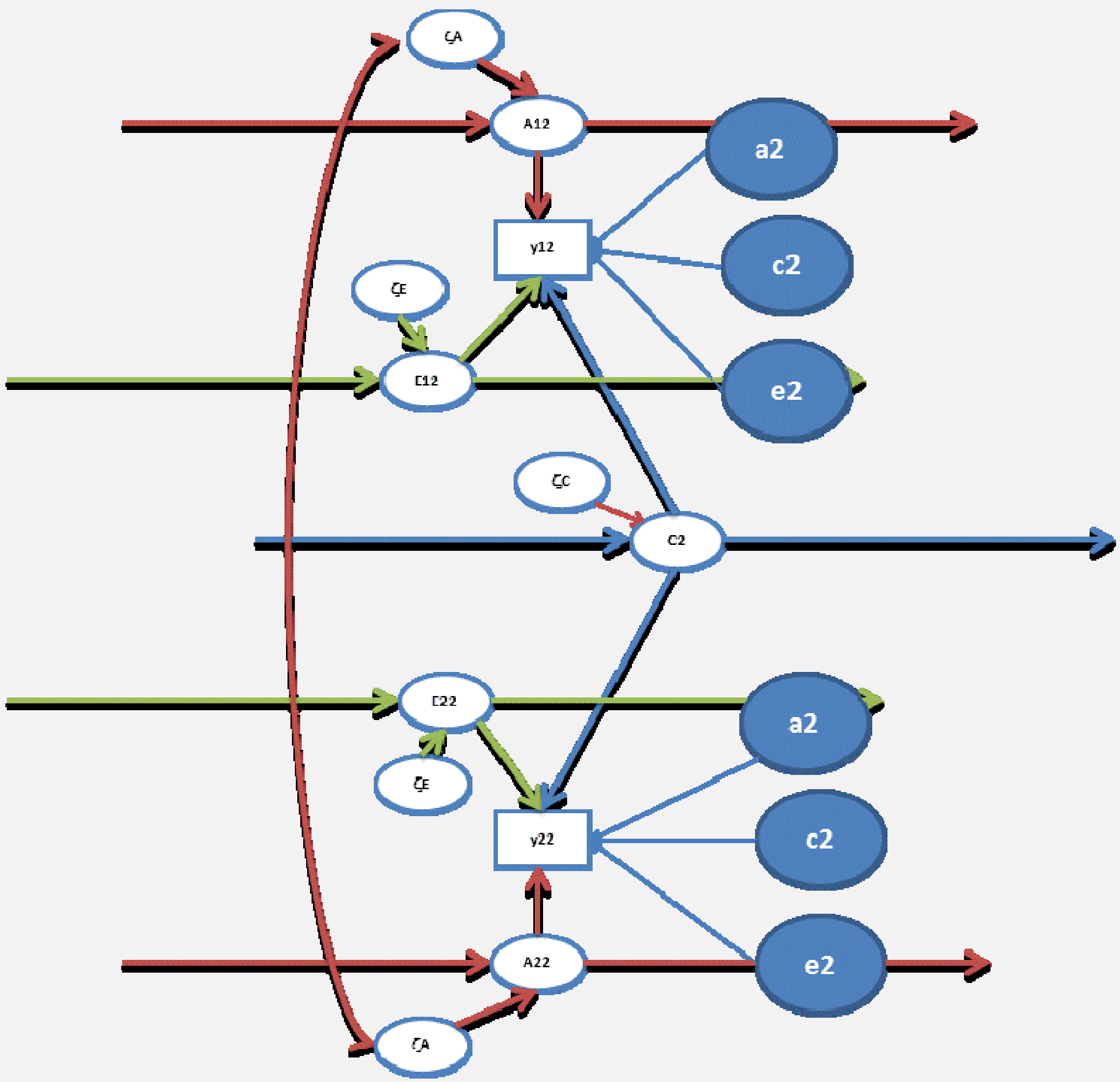
required:
var(a1) = var(a2)
var(a3) = var(a4)



The genetic A simplex



ζA
ζA
ζA
A11
A12
A13
A14
1
y11
y12
y13
y14
ζE
ζE
ζE
1
E11
E12
E13
E14
1
ζC
ζC
ζC
C1
C2
C3
C4
1
E21
E22
E23
E24
1
ζE
ζE
ζE
y21
y22
y23
y24
1
A21
A22
A23
A24
ζA
ζA
ζA



Occasion
specific
effects

required:
var(a1) = var(a2)
var(a3) = var(a4)

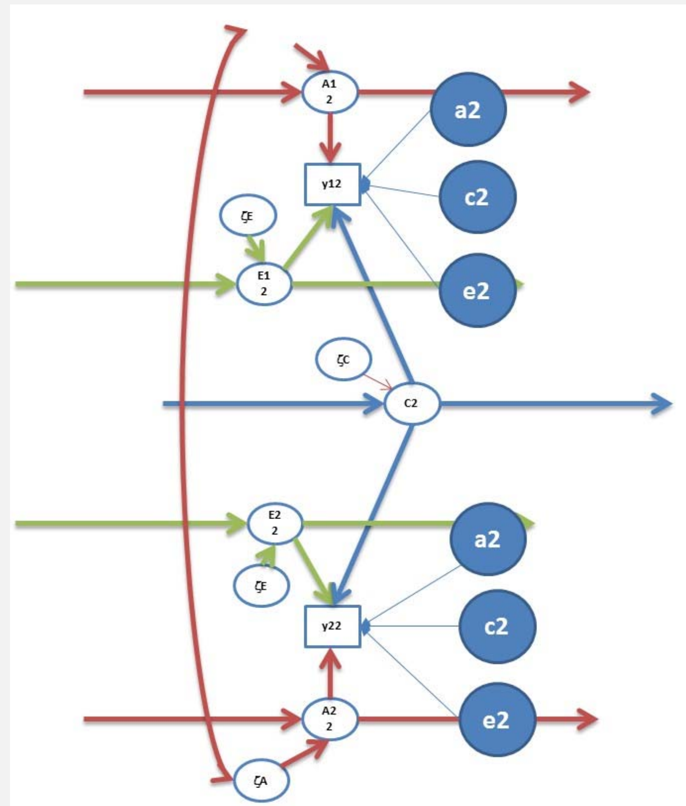
var(e1) = var(e2)
var(e3) = var(e4)

var(c1) = var(c2)
var(c3) = var(c4)

Question: h^2, c^2, and e^2 at each time point?

$var(y_t)$ =
$\{var(A_t) + var(a_t)\} + \{var(C_t) + var(c_t)\} + \{var(E_t) + var(e_t)\}$

$h^2 = \{var(A_t) + var(a_t)\} / var(y_t)$
$c^2 = \{var(C_t) + var(c_t)\} / var(y_t)$
$e^2 = \{var(E_t) + var(e_t)\} / var(y_t)$

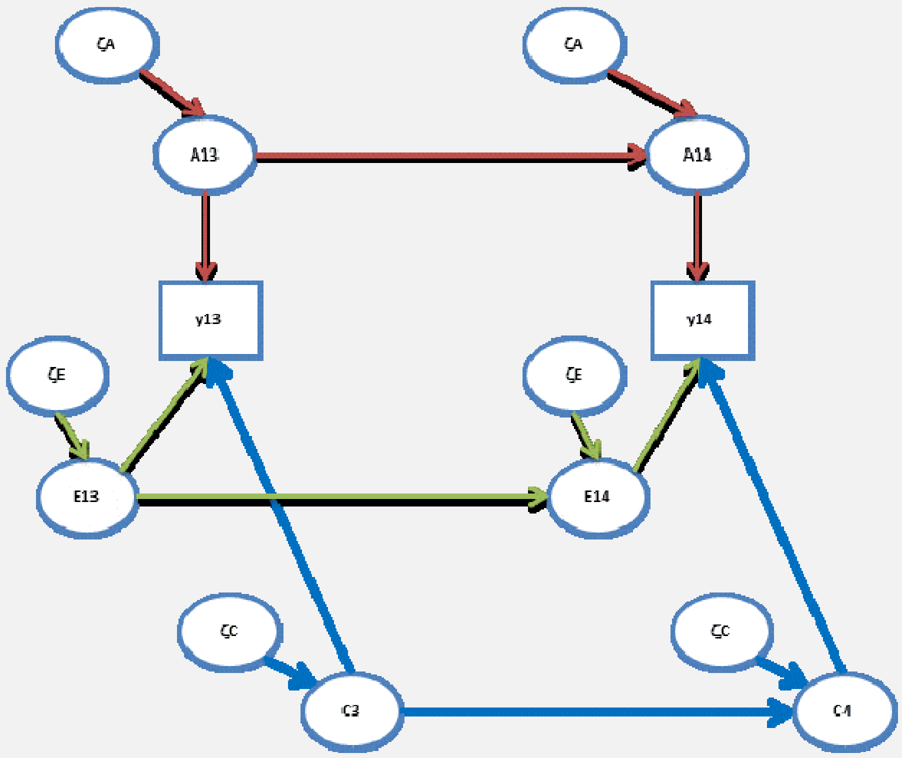


contributions to stability (A,C,E) t-1 to t

$b_{At-1,t}^2 \, var(A_{t-1}) \;/\; \{b_{At-1,t}^2 \, var(A_{t-1}) + var(\zeta A_t)\}$

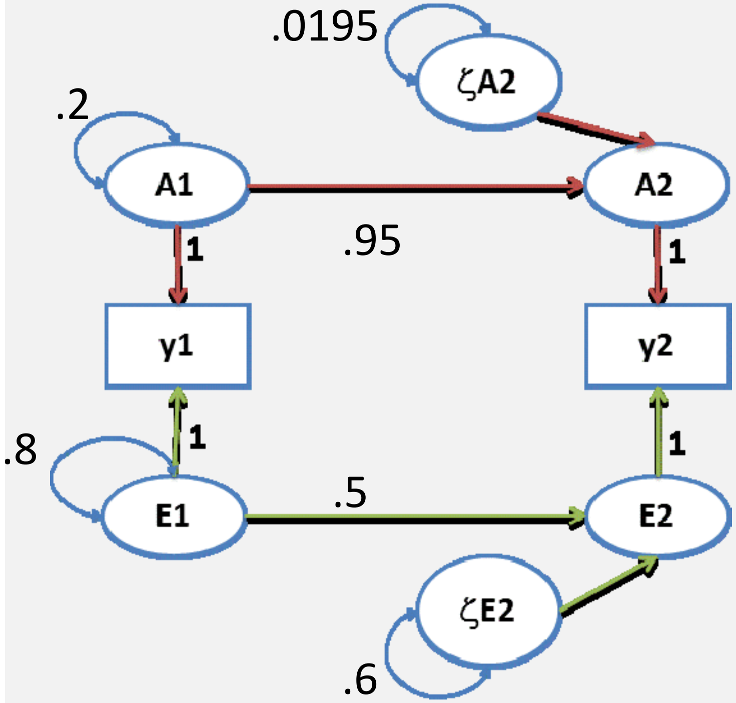
$b_{Ct-1,t}^2 \, var(C_{t-1}) \;/\; \{b_{Ct-1,t}^2 \, var(C_{t-1}) + var(\zeta C_t)\}$

$b_{Et-1,t}^2 \, var(E_{t-1}) \;/\; \{b_{Et-1,t}^2 \, var(E_{t-1}) + var(\zeta E_t)\}$



contributions of A to Phenotypic stability t-1 to t

$$\frac{b_{At-1,t}^{2}\,var(A_{t-1})}{\{b_{At-1,t}^{2}\,var(A_{t-1}) + var(\zeta A_{t})\} + \{b_{Ct-1,t}^{2}\,var(C_{t-1}) + var(\zeta C_{t})\} + \{b_{Et-1,t}^{2}\,var(E_{t-1}) + var(\zeta E_{t})\}}$$



$$\Sigma_A = \begin{matrix} .2 & .184 \\ .184 & .2 \end{matrix}$$

$$\Sigma_A = \begin{matrix} .8 & .4 \\ .4 & .8 \end{matrix}$$

$$\Sigma_y = \Sigma_A + \Sigma_A = \begin{matrix} 1 & .584 \\ .584 & 1 \end{matrix}$$

h^2 at t=1? answer: .2 (e^2=.8)

h^2 at t=2? answer: .2 (r^2=.8)

correlation between A1 and A2? .184 / (√.2*√.2) = .92

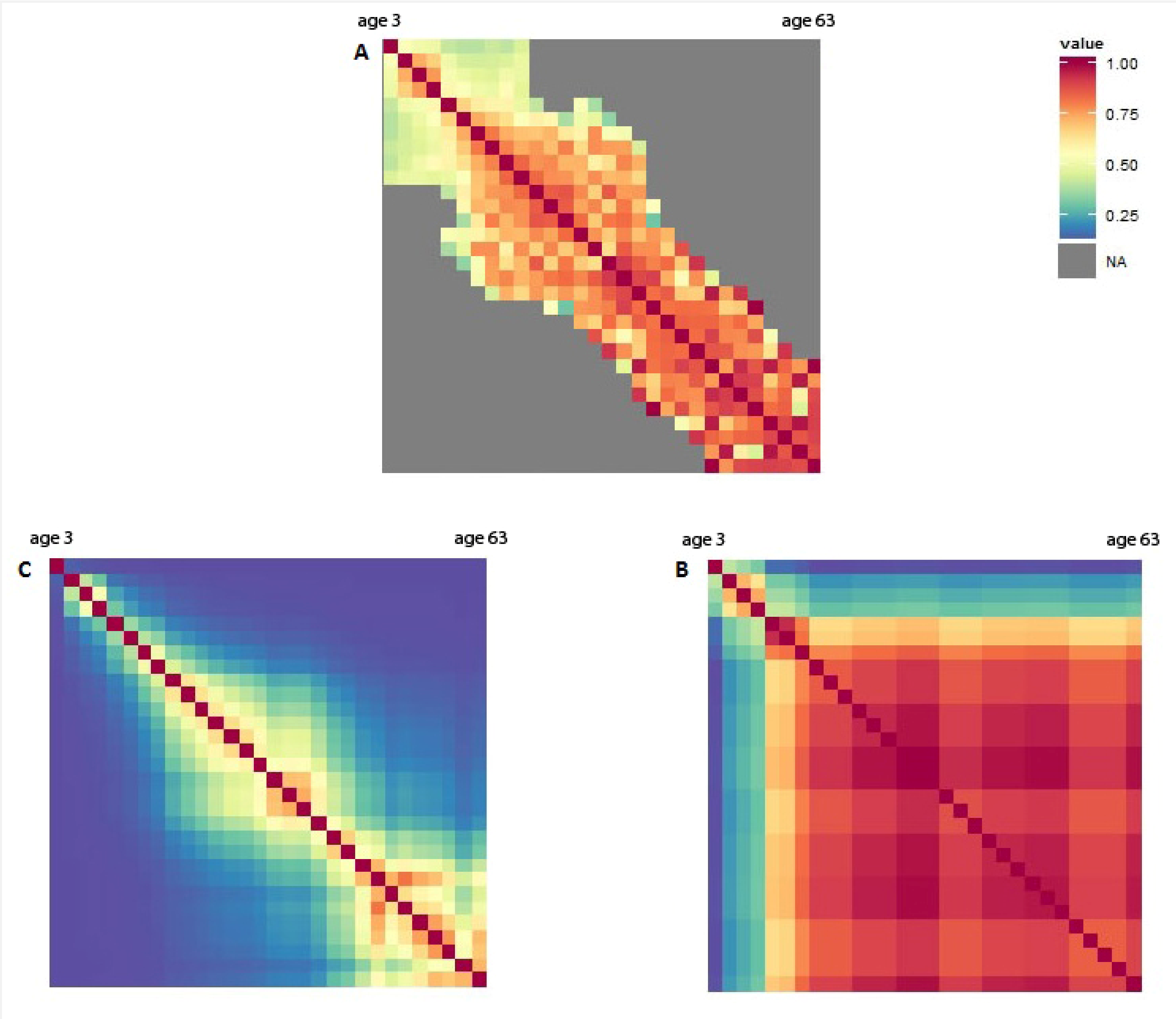
correlation between E1 and E2? . 4 / (√.8*√.8) = .50

covariance between Y1 and Y2? .584

contribution of A to covariance Y1 and Y2? .184/.584 = .315

contribution of E to covariance Y1 and Y2? .4/.584 = .685

Nivard et al, 2014



Anx/dep stability due to A and E from 3y to 63 years

Sanja's Practical: the genetic simplex model applied to FSIQ at 4 occasions.

But first ....

Variations on the theme

Jouke-Jan Hottenga, Dorret I. Boomsma, Nina Kupper, Danielle Posthuma, Harold Snieder, Gonneke Willemsen, and Eco J. C. de Geus

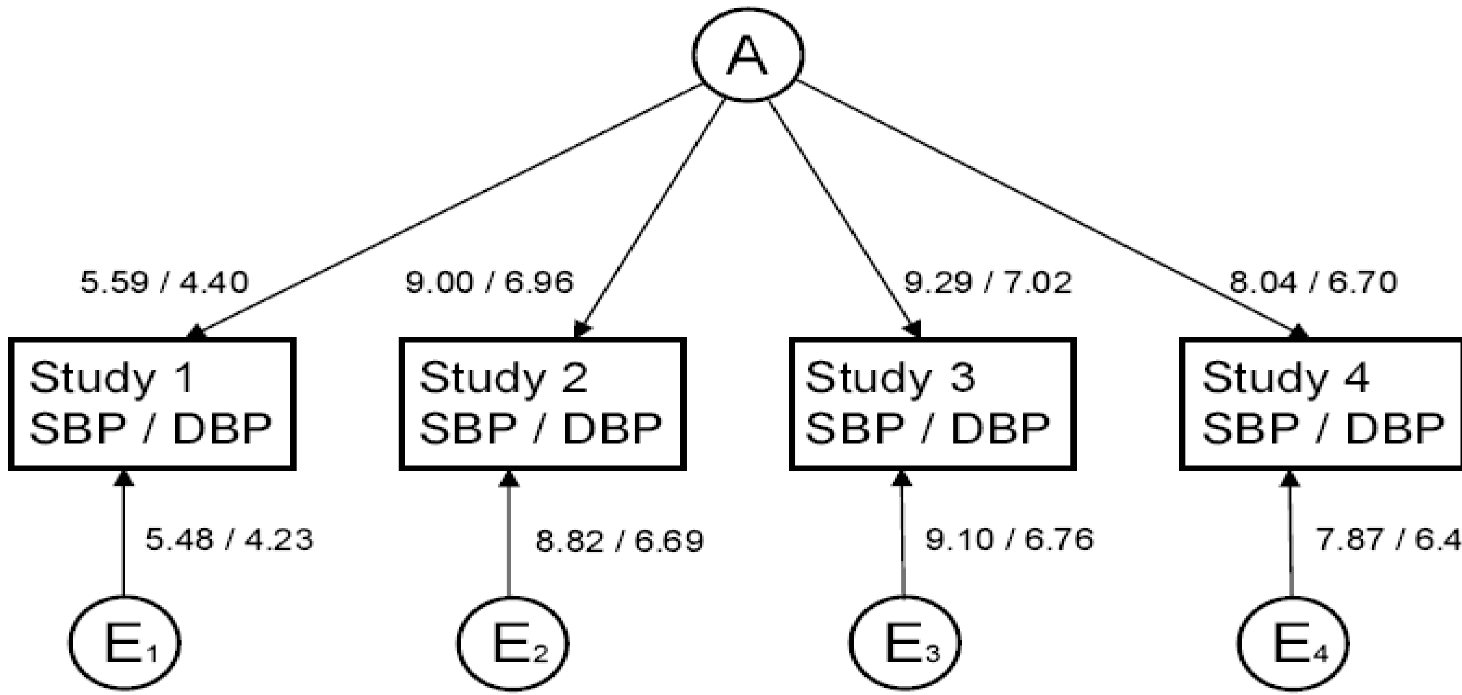


Figure 1

Pathway model showing latent genetic and environmental influences on the measured systolic and diastolic blood pressure corrected for sex and age at measurement.

Note: A represents the additive genetic factors common to the four measurements. E_1–E_4 shows the unique environmental influences at each time point/study. Path coefficients are shown. The proportions of measured variance for the latent variables are SBP: A = 51%, E = 49%; and DBP: A = 52%, E = 48%.

Hottenga, etal. Twin Research and Human Genetics, 2005

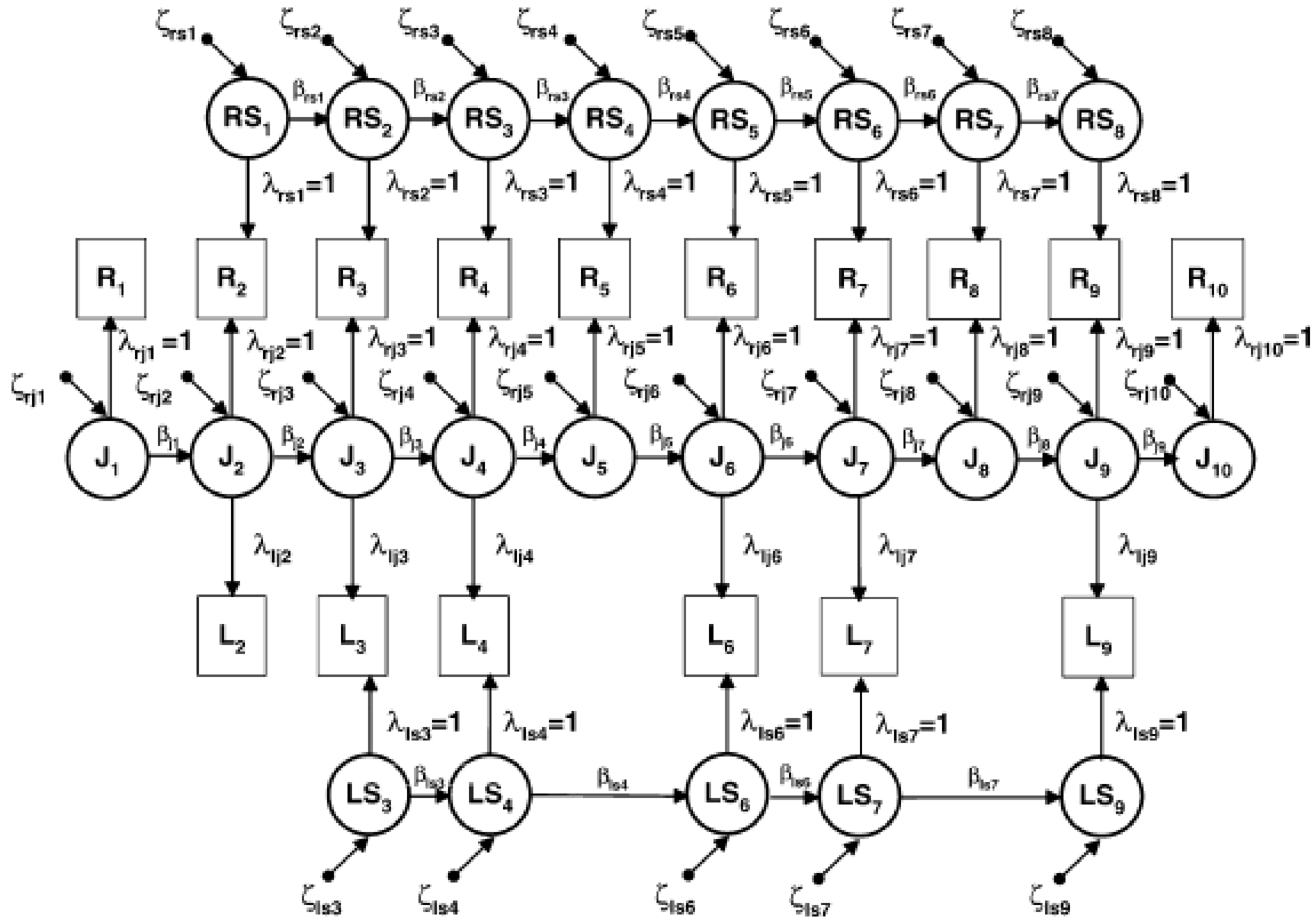


Fig. 3. Specification of the bivariate simplex model for the time course of the observed measurements □. There are 10 time points for breath and 6 time points for the blood alcohol concentrations. The joint latent genetic (*A*) (or QTL (*Q*)) process as estimated from the covariance between blood and breath alcohol readings is indicated by ○ as with labels $J_{1\text{-}10}$. The symbols, $RS_{2\text{-}8}$ or $LS_{2,3,4,6,7 \text{ and } 9}$, relate to those simplex processes that are respectively specific to breath or blood measures at the indicated times. Innovations of variance ($\xi_{rj1-rj10}$) are shown for the common genetic (or QTL) covariance, the covariance specific to blood and that specific breath, are shown as ↘. They are depicted in the identified model in relation to the latent variables. Transmission paths (β) for the specific process for blood, breath and those for the process common to both breath and blood are related to the timing of readings by the respective suffixes, (βls, βrs, and βj) . The transmission paths for blood readings take into account missing time points. Latent or λ variables are specified for the common pathway to enable the relative contributions of blood and breath readings in the time series to be compared. The model shown in this diagram is fitted for both *A* and *Q*. In addition a Cholesky decomposition of *E* is fitted.

Birley et al. Behav Genet 2005

“Niche-picking”

During development children seek out and create and are furnished surrounding (E) that fit their phenotype.

A smart child growing up will pick the niche that fits her/her phenotypic intelligence.

A anxious child growing up may pick out the niche that least aggrevates his / her phenotypic anxiety.

Phenotype of twin 1 at time t -> environment of twin 1 at time t+1

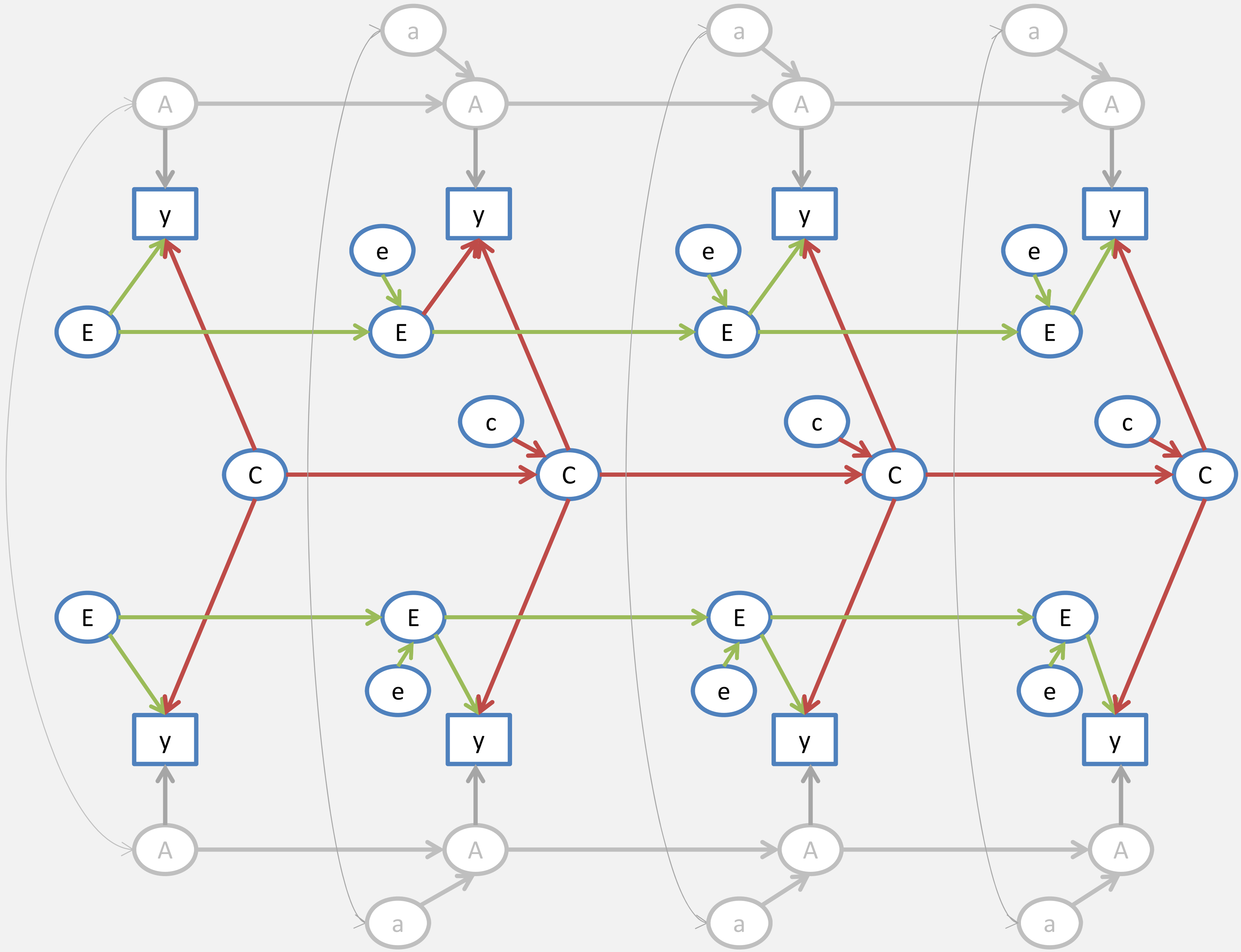
Mutual influences

During development children's behavior may contribute to the environment of their siblings.

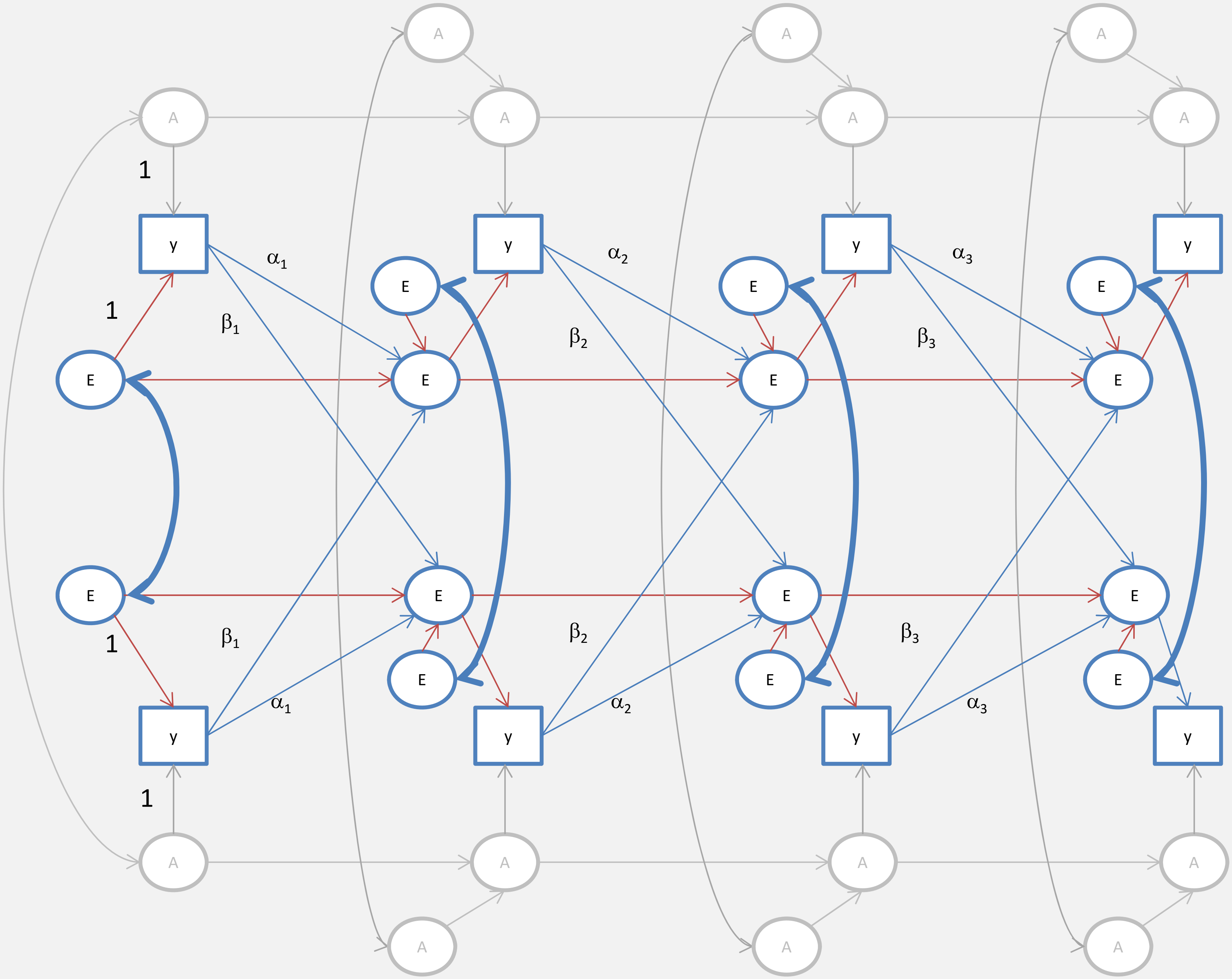
A smart child growing up will pick the niche that fits her/her phenotypic intelligence and in so doing may influence (contriibute to) the environment of his or her sibling.

A behavior of an anxious child may be a source of stress for his or her siblings.

Phenotype of twin 1 at time t -> environment of twin 2 at time t+1



A, C, E uncorrelated


A
1
y
α_1
α_2
α_3
β_1
β_2
β_3
E

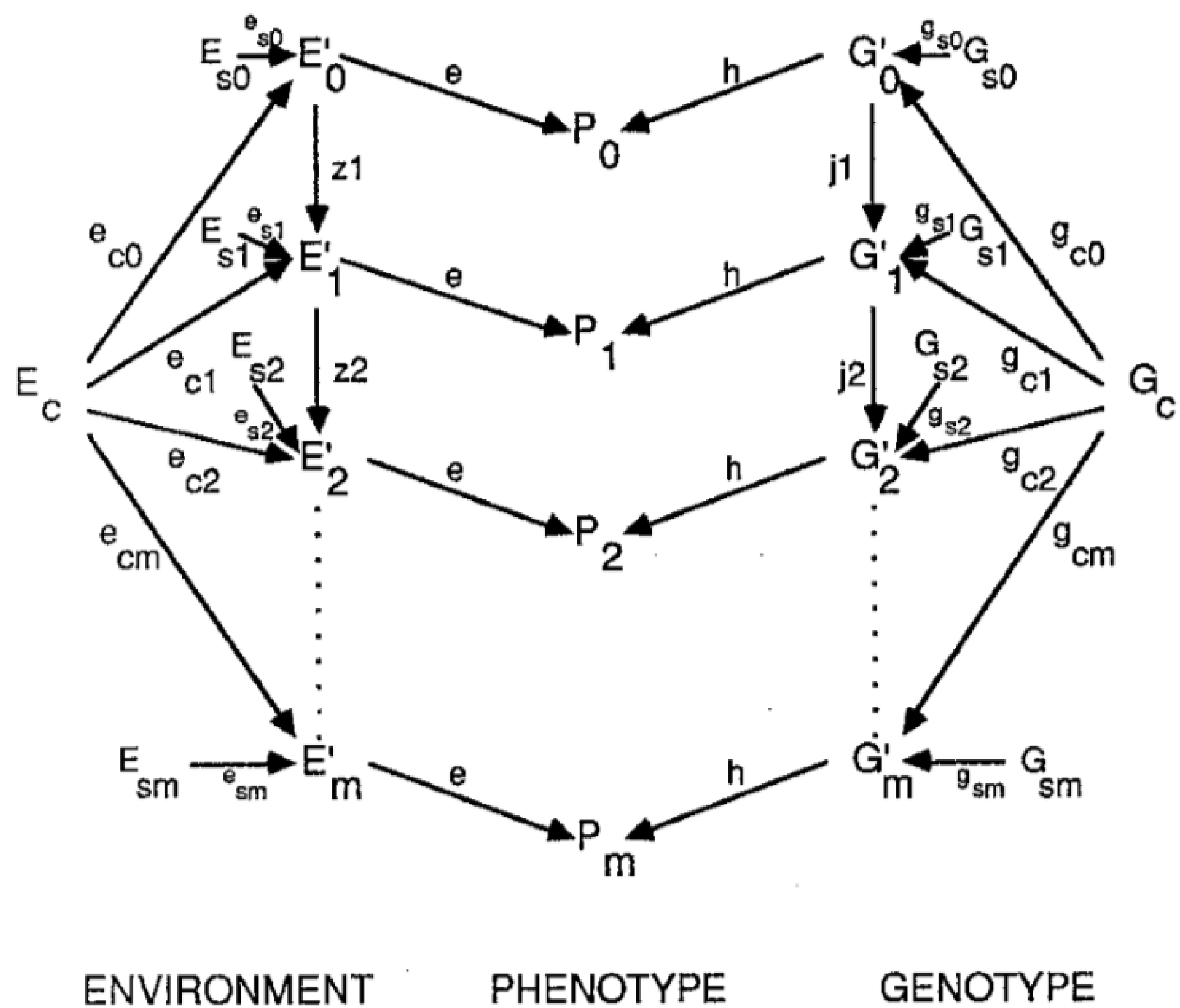


Fig. 1. The developmental path model for an individual.

Behavior Genetics, Vol. 18, No. 2, 1988

Resolving Causes of Developmental Continuity or "Tracking." I. Longitudinal Twin Studies During Growth

J. K. Hewitt,[1] L. J. Eaves,[1] M. C. Neale[1], and J. M. Meyer[1]

Br. J. math. statist. Psychol. (1977), **30**, 1–42 *Printed in Great Britain* 1

A progressive approach to non-additivity and genotype-environmental covariance in the analysis of human differences.

L. J. Eaves, Krystyna Last, N. G. Martin and J. L. Jinks

Environments selected by genotypes (Scarr & McCartny, 1983; Plomin, DeFries & Loehlin, 1977)

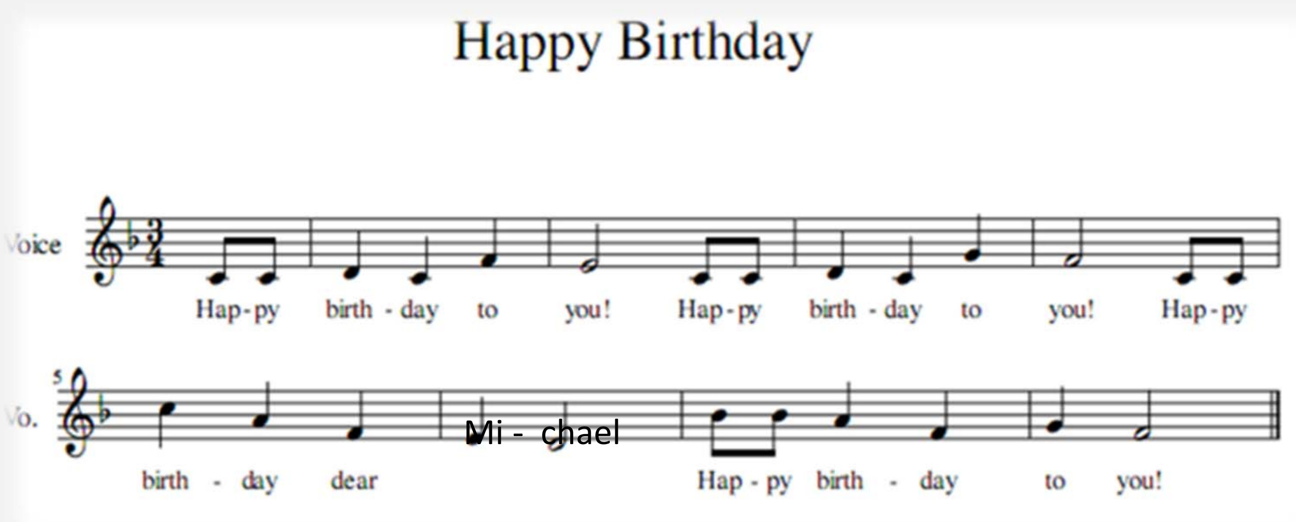
Sibling effects *(*Carey, 1986, Behav Genet 16:319–341*)*

Behav Genet (2014) 44:240–253
DOI 10.1007/s10519-014-9659-5

ORIGINAL RESEARCH

GE Covariance Through Phenotype to Environment Transmission: An Assessment in Longitudinal Twin Data and Application to Childhood Anxiety

Conor V. Dolan · Johanna M. de Kort · Toos C. E. M. van Beijsterveldt · Meike Bartels · Dorret I. Boomsma


Happy Birthday
Voice
Hap-py birth - day to you! Hap-py birth - day to you! Hap-py
Vo.
birth - day dear
Mi - chael
Hap - py birth - day to you!