Model assumptions & extending the twin model

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Acknowledgments

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- Lindon Eaves
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First annual OpenMx HACKATHON! Friday morning (8 am) session

- I'll give you an .RData file of twin data and a specific question to test. Your job is to write an OpenMx script—from scratch—that gets the right answer!
  - The instructor has limited ability in OpenMx – it's up to you!
  - Cheating isn't bad here—it's encouraged! Use your old scripts or help from anyone in the class.
  - You have an hour to write script and to produce and interpret estimates.

Files you will need are in Faculty drive: /matt/ Assumptions_2016

- Assumptions2016_mck.pdf (PPT presentation)
- CTD.ACDE-param.indet_2016.R (OpenMx script)
- PDFs of papers describing details of what we go over here & that correspond to the approach/notation I'm using here

Structural Equation Modeling (SEM) in BG

- SEM is great because…
  - Directs focus to effect sizes, not "significance"
  - Forces consideration of causes and consequences
  - Explicit disclosure of assumptions
- Potential weakness…
  - Parameter reification: "Using the CTD we found that 50% of variation is due to A and 20% to C."
  - Should you believe that 50% of variation is truly additive genetic?

True parameters vs. Estimated parameters

A C D E: true (unknowable) values of A, C, D, E in the population (short for V_A, V_C, V_D, and V_E)

A', C', D', E': **estimated** values of A, C, D, E.

A', C', D', E', will differ from A, C, D, E due to:
1) sampling variability
2) bias

NOTE: I'm using *Y'* rather than the usual $\hat{Y}$ to denote estimates of Y simply due to technical (PPT) issues!

Quiz Question 1

1) *A'* ,*C'*, and *D'* cannot be estimated simultaneously in the classical twin design (i.e., the design that uses MZ and DZ twins only) model because: [choose all that apply]

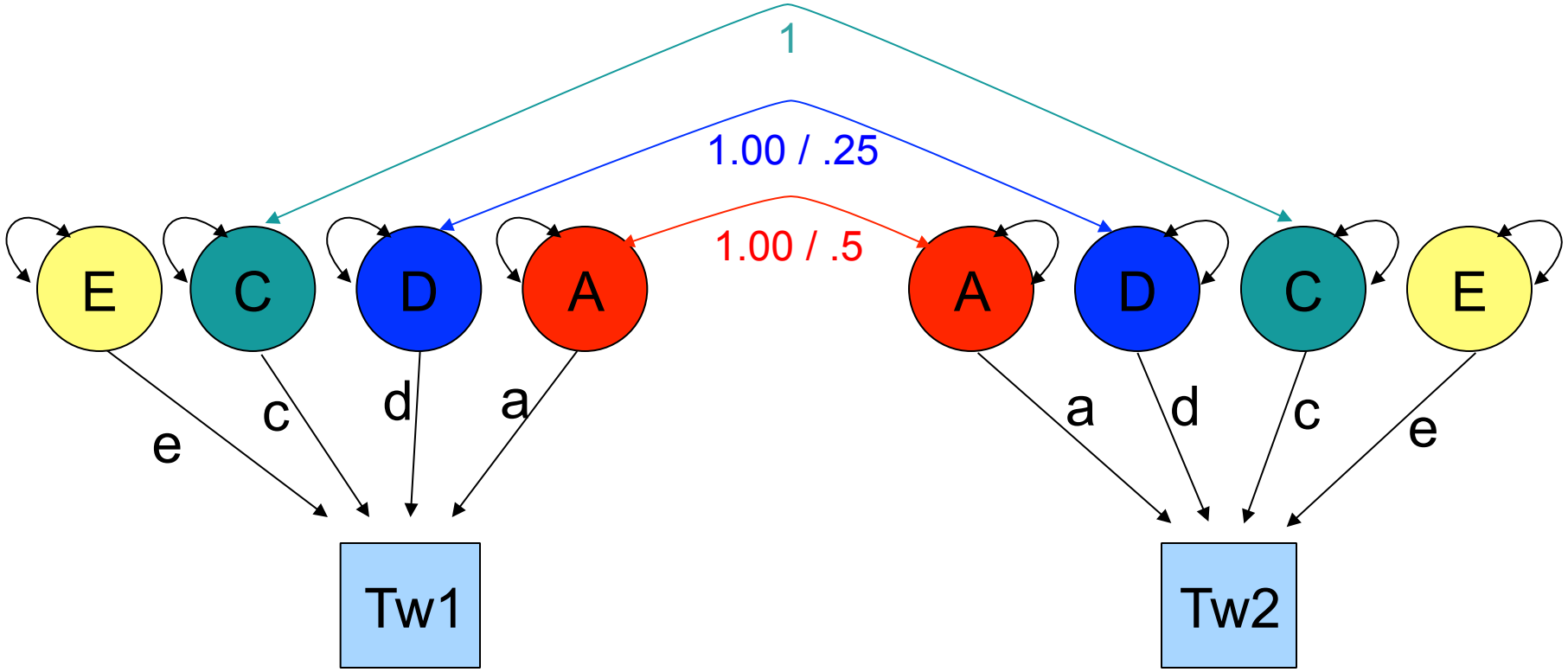
a) these estimates are too highly correlated (multicolinearity problems)

b) they **can** be estimated simultaneously; you just have to fix one of them to some specific value

c) there are more informative statistics than parameters to be estimated

d) there are fewer informative statistics than parameters to be estimated

The Classical Twin Design



Why can't we estimate *C'* & *D'* at same time using twins only?

- Solve the following two equations for *A'*, *C'*, & *D'*:

CVmz = A + D + C

CVdz = 1/2A + 1/4D + C

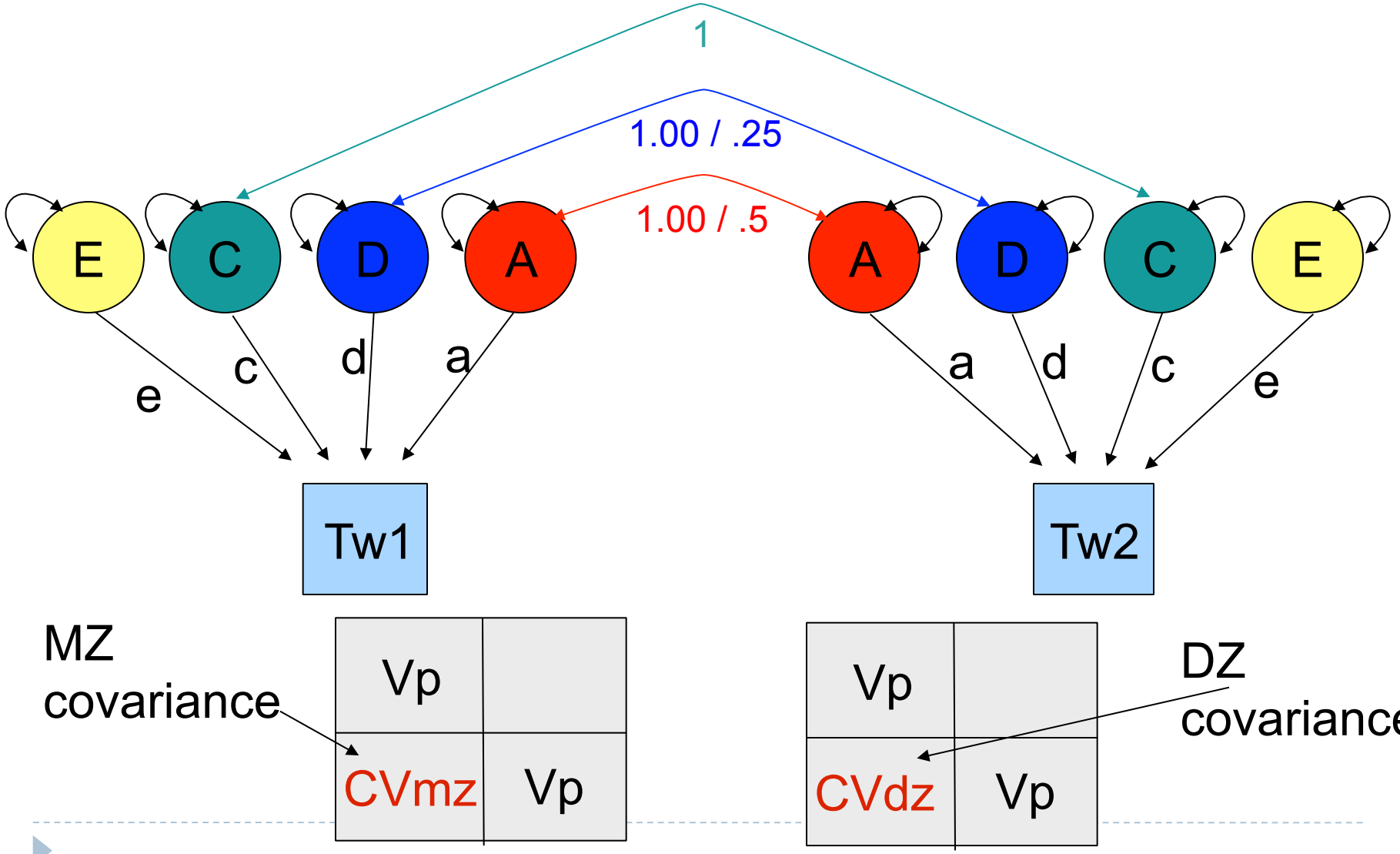
- 3 unknowns, 2 informative equations. It can't be done. The model is "unidentified".

- In practice, you can detect non-identification by noting that (a) model estimates depend on starting values AND (b) all final models have identical likelihoods

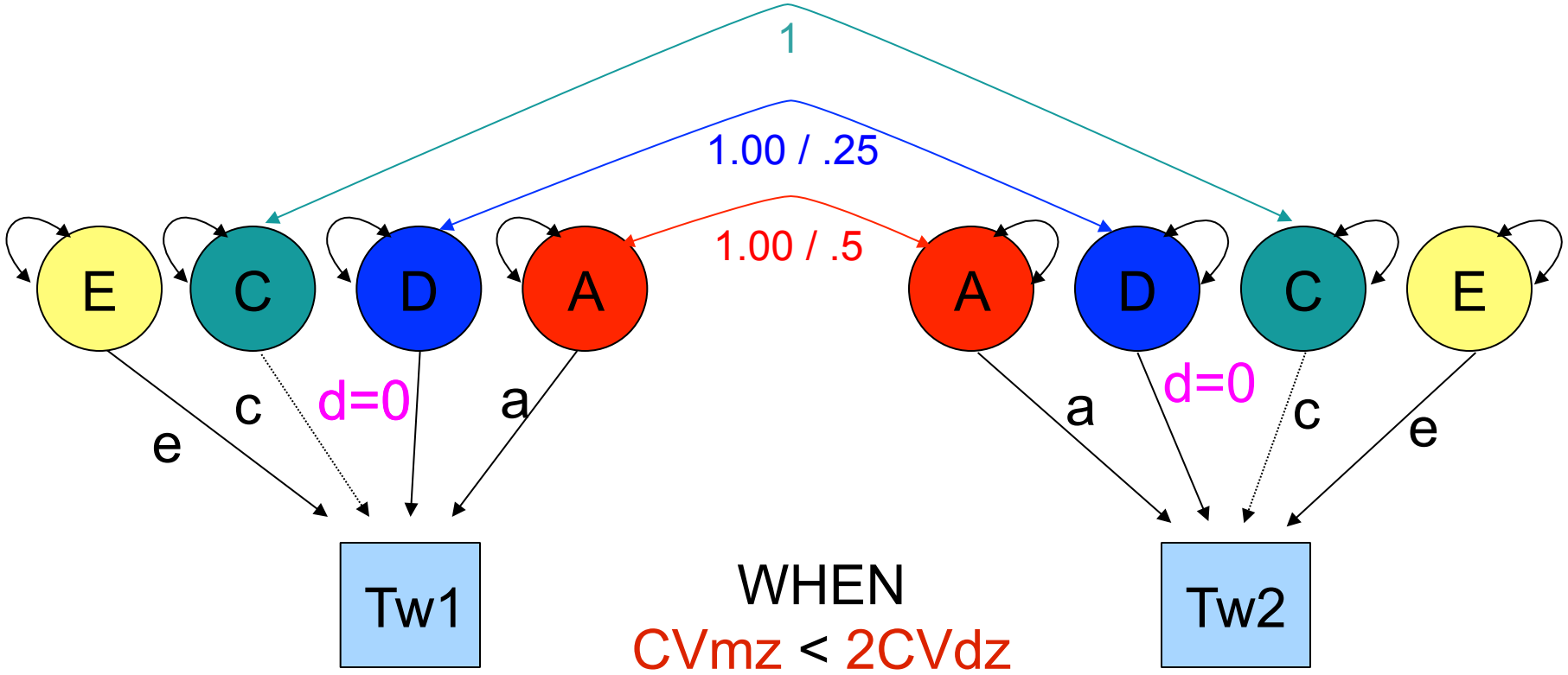
Indeterminacy: Practical 1

- Open up CTD.ACDE-param.indet.R in R
- Run this script (estimating A, D, and C using twins only) until you see "# END PRACTICAL 1." Don't close the script or R, as we'll use this same script again for other Practicals
- Write down your -2 log likelihood and your estimates of A, C, and D
- Compare these to your neighbor's results
- WHY is the -2LL the same despite different estimates (that depend on arbitrary start values)?

The CTD: Two statistics give info about within-family resemblance



ACE Model



WHEN
CVmz < 2CVdz

Vp	
CVmz	Vp

Vp	
CVdz	Vp

ACE Algebra

- Assume D = 0. Solve for *A'* & *C'*

CVmz = A + C

CVdz = ½ A + C

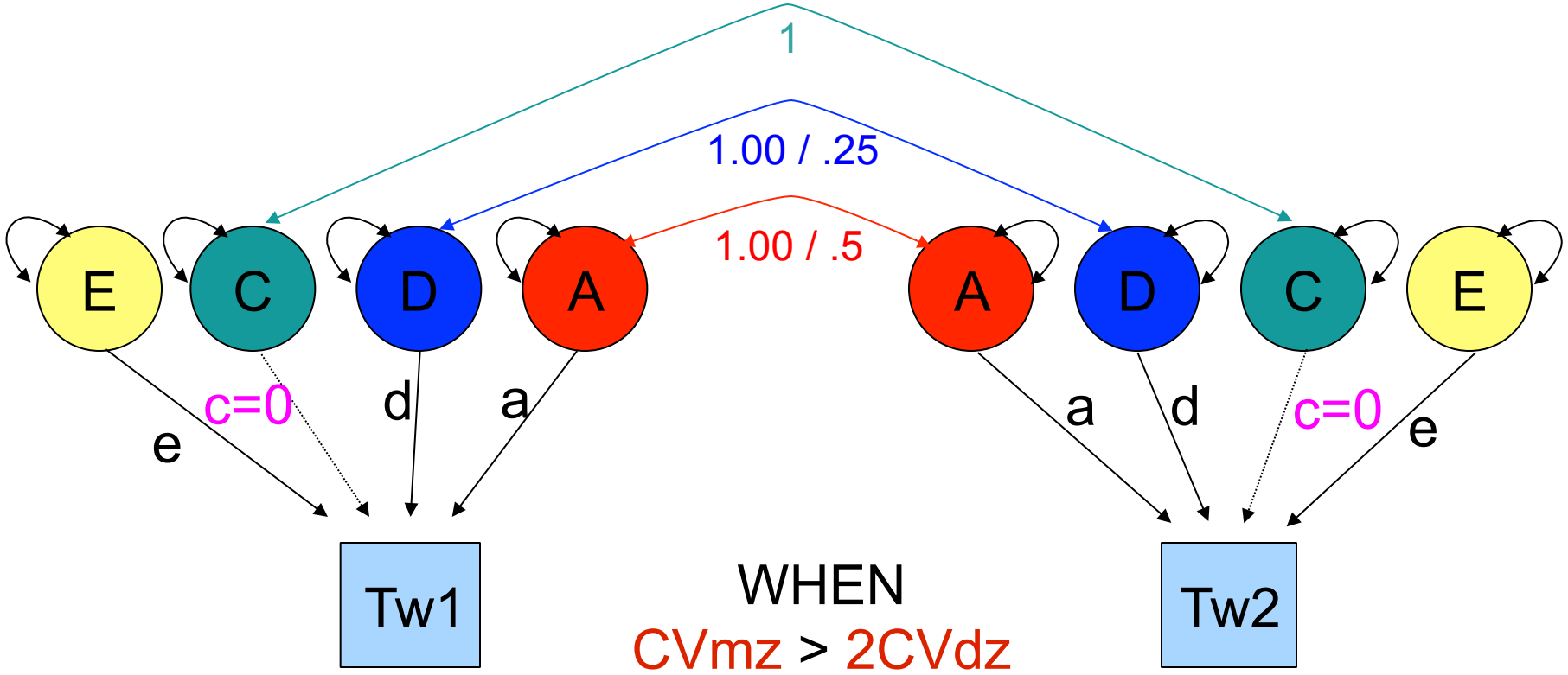
- 2 unknowns, 2 independently informative equations:

  A' = 2(CVmz-CVdz)

  C' = 2CVdz-CVmz

Note: if we tried to estimate *D'*, it would necessarily hit the 0 boundary anyway and the model wouldn't fit as well (because *D'* 'wants' to go negative), so it makes sense to solve for *C'*

The CTD: ADE Model



PRACTICAL 2: ADE Algebra & Indeterminacy

- Assume C = 0. Solve for *A'* & *D'* (here CVmz=.73 & CVdz=.35)

CVmz = A + D

CVdz = ½A + ¼D

Derive a general formula for getting these. Then solve for them in this case.

- Then reopen CTD.ACDE-param.indet.R in R & run

FROM "# START PRACTICAL 2"
TO "# END PRACTICAL 2"

- Did you get roughly the same answer for your ADE model as your formula suggested?
- Did the ACE model fit as well as the ADE model? Why?
- What happened to estimates of C & D in the DCE model?

Quiz Question 1 again – What do you think now?

1) A', D', & C' cannot be estimated simultaneously in the classical twin design (i.e., the design that uses MZ and DZ twins only) model because: [choose all that apply]

a) these estimates are too highly correlated (multicolinearity problems)

b) they **can** be estimated simultaneously; you just have to fix one of them to some specific value

c) there are more informative statistics than parameters to be estimated

d) there are fewer informative statistics than parameters to be estimated

Quiz Question 2

2) If the assumptions of the CTD model that either D or C is zero is violated (i.e., A, C, and D simultaneously affect the phenotype)... [choose all that apply]

a) the interpretation of the estimated parameters should be altered; e.g., *A'* should be considered an amalgam of A & D (in ACE model) or of A & C (in ADE model)

b) there is no point in doing the analysis at all

c) the point estimates of the estimated parameters will be biased

Bias in parameter estimates for violation of assumption that either D or C is 0

- In ACE Models (bias induced in setting *D'* = 0):

A' = A + 3/2D

C' = C – ½D

- In ADE Models (bias induced in setting *C'* = 0):

A' = A + 3C

D' = D - 2C

Quiz Question 3

3) An ADE model finds that *A'* = .30 and *D'* = .10. This implies that shared environmental factors do not influence the trait in question.

a) TRUE

b) FALSE

Quiz Question 4

4) We run an ADE model and find that *A'* = .69 and that *D'* = .05. If in truth, C = .10, what will the effect on the estimated parameters be? [choose all that apply]

a) *A'* will be biased (too low)

b) *A'* will be biased (too high)

c) *D'* will be biased (too low)

d) *D'* will be biased (too high)

e) there is no affect on the estimated parameters; however by not estimating C (aka, fixing it to zero), we underestimated C

PRACTICAL 3: Sensitivity analysis

- Sensitivity analysis: studying what the effects are on estimated parameters when assumptions are wrong
- In CTD.ACDE-param.indet.R, run:

  FROM "# START PRACTICAL 3"
  TO "# END PRACTICAL 3"

- Run one section at a time and change the value of C from 0 to other values (remember, C=c^2) in an ADE model. What happens to estimates of A and D depending on different assumed values of C?
- At end, look at -2LL 3-D plot of parameter space

Some points to consider about the biases discussed to this point

- Epistasis (across loci interactions) can increase the degree of the biases because it can reduce the CV(DZ):CV(MZ) ratio even further than the expected 1:4 under dominance.
- However, the degree of bias rests on how strong non-additive genetic influences are. This is an active area of debate in the field.
- Epistatic effects will generally come out in the estimates of D. Thus, interpret *D'* broadly, as a rough estimate of V_{NA}
- My take: V_A is almost certainly greater than V_{NA}, and evidence for much V_D per se is scant. But some traits may show high enough V_{NA} to bias estimates of V_C and V_D (V_{NA}) down and V_A up considerably from twin studies.

Quiz Question 5

5) What are the *typical* assumptions of a classical twin model? [choose all that apply]

a) only genetic factors cause MZ twins to be more similar to each other than DZ twins

b) either D or C is equal to zero

c) no epistasis

d) no assortative mating

e) no gene-environment interactions or correlations

What are the effects of violations of assumptions in the CTD?

a) Only genetic factors cause MZ twins to be more similar to each other than DZ twins: A and D are overestimated and C is underestimated

b) Either D or C is equal to zero: A is overestimated and D and C are underestimated

c) No epistasis: D or A is overestimated and C is underestimated

d) No assortative mating: A and D are underestimated and C is overestimated

e) No gene-environment interactions or correlations: AxC: A overestimated; AxE: E overestimated; passive Cov(A,C): C overestimated

Assortative mating (AM) consequence on V_A

- AM: phenotypic correlation between mating partners
- Many examples (e.g., height ~.2; IQ ~ .3; Social attitudes ~ .5)
- If AM leads to genetic similarity in partners (as it does if due to choice for similarity), there are genetic consequences. E.g.:
  - Height V_A increases in the population because 'tall' ('short') alleles are more concentrated in individuals than expected.
  - E.g., if you're a 'tall' allele that just got put into a new egg and are waiting around to see what other height genes you'll get paired with from that sperm swimming to you, they are more likely than chance to be other 'tall' alleles (both at the same locus and at others; & this just considers the effects on V_A in 1st gen)

$$V_{A.equil} = \frac{V_{A0}}{1 - rh^2_{equil}}$$

AM consequence on relative covariance

- AM increases genetic covariances and correlations between relatives (e.g., sibs, parents, cousins, etc).
  - While MZ genetic covariance increases, it's correlation is already 1 so it doesn't increase
- Consider again being a 'tall' allele in a zygote. This time you are watching your co-twin's zygote get formed. Regardless of whether you exist (are IBD) in your co-twin's egg, you can expect more tall alleles swimming to your co-twin's egg.
- Thus, you can also expect to share more 'tall' alleles with your sibling(s).
- The covariance between DZ twins due to additive genetics is:

$$CV_{DZ,A.equil} = .5V_{A.equil} + .5rh^2_{equil}$$

Quiz Question 6

6) In the CTD, say that CV(MZ) < 2CV(DZ), so we fit an ACE model. How would AM tend to affect parameter estimates? [choose all that apply]

a) deflates estimates of A

b) inflates estimates of A

c) deflates estimates of C

d) inflates estimates of C

Quiz Question 7

7) Let's say we add parents to the CTD. That gives us 2 additional relative covariance estimate to work with (parent-offspring and spousal) in addition to the normal CV(MZ) and CV(DZ) and allows us to _____ [choose all that apply]

a) estimate A, C, & D simultaneously

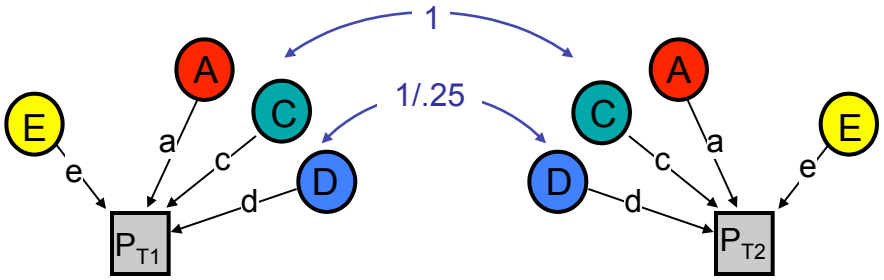
b) account for the effects of assortative mating

c) account for passive G-E covariance

d) reduce the bias in estimates of A, C, and D vis a vis the CTD

Classical Twin Design (CTD)

Assumption	biased up	biased down
Either D or C is zero	A	C & D
No assortative mating	C	D
No A-C covariance	C	D & A



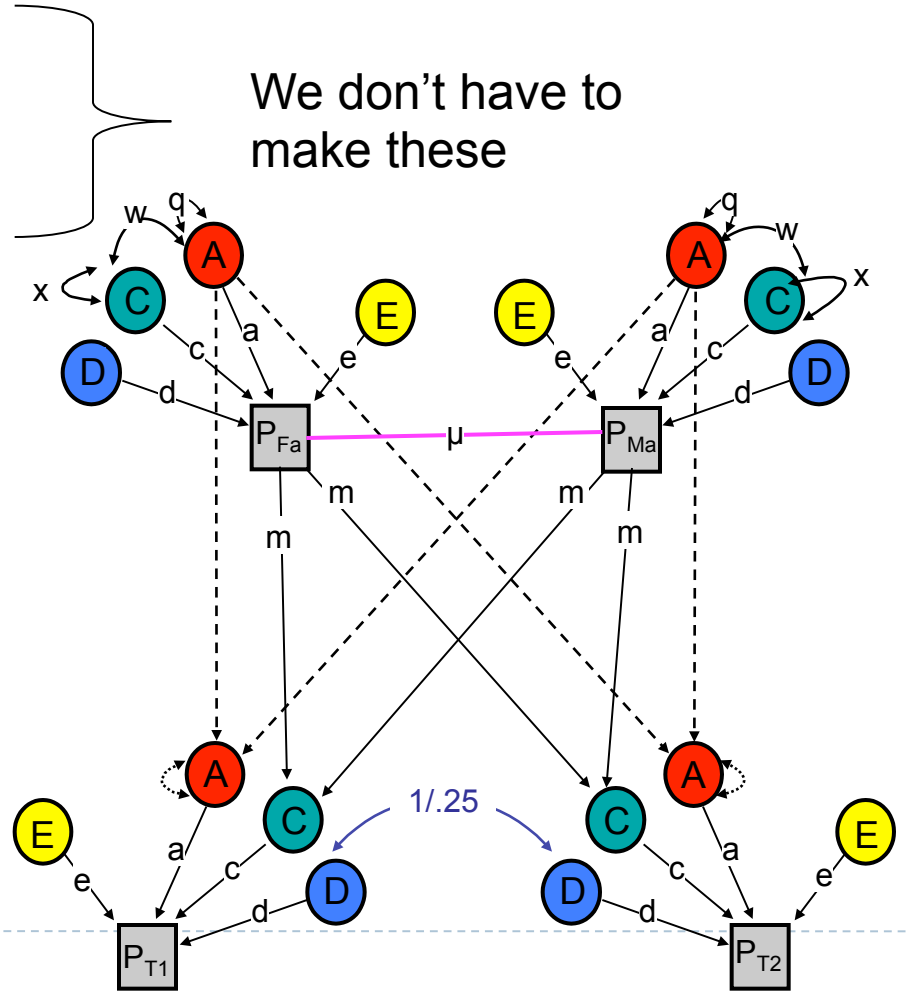
Adding parents gets us around all these assumptions

- Assumption biased up biased down

Either D or C is zero

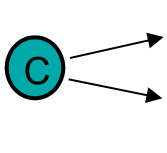
No assortative mating

No A-C covariance



We can model C as either S or F

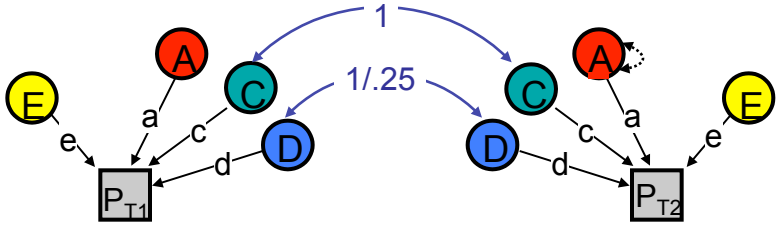
With parents, we can break “C” up into:

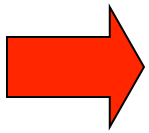


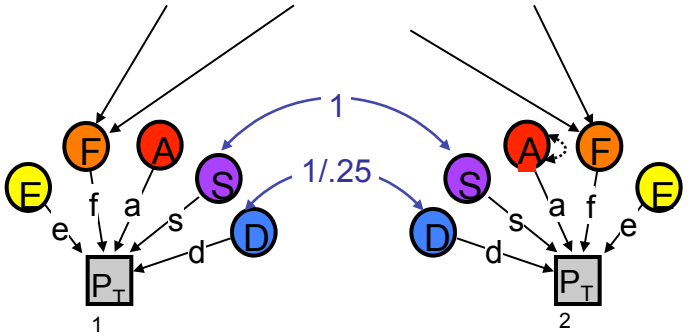
= env. factors shared only between **sibs**

= **familial** env factors passed from parents to offspring

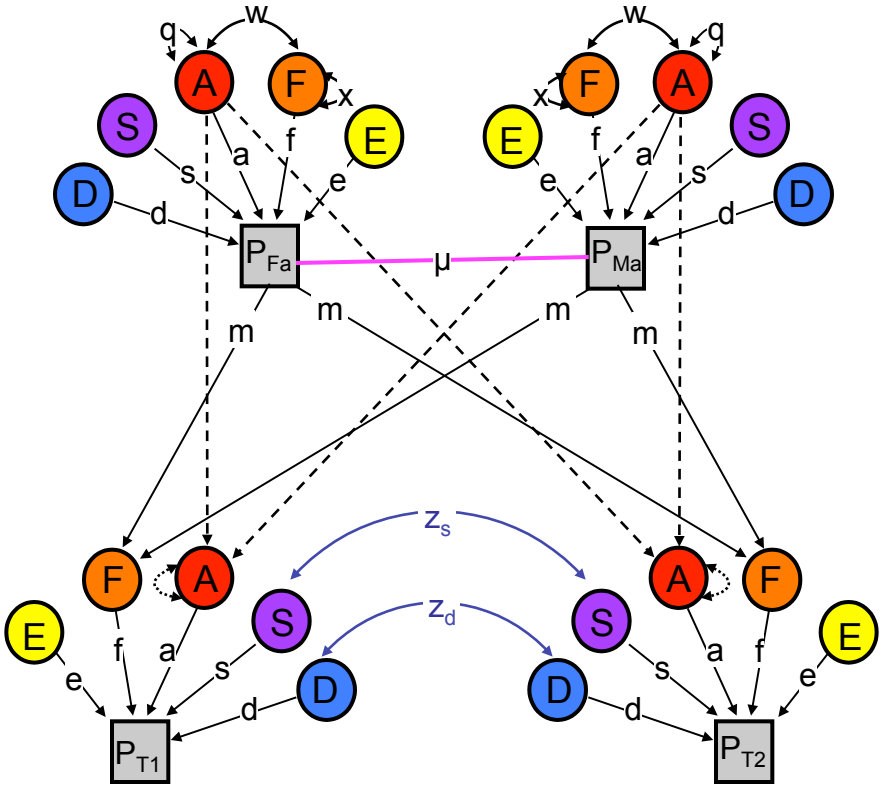
But we can only estimate one of these (or more technically, one of A, S, F, & D)







Nuclear Twin Family Design (NTFD)



Note: m estimated and f fixed to 1

PRACTICAL 4: NTFD analysis

- In CTD.ACDE-param.indet.R, run:

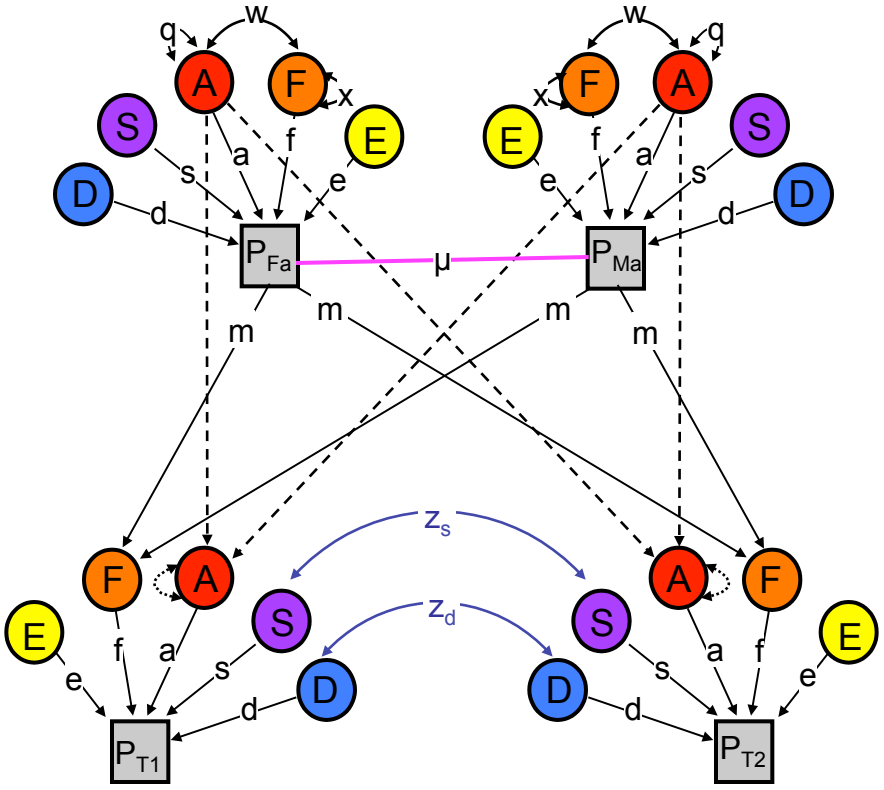
FROM "# START PRACTICAL 4"
TO "# END PRACTICAL 4"

- What are the estimated values of A, D, & S? [Note: S = sib environment, equivalent to C in the CTD]

Simulated (true) vs. CTD vs. NTFD results

TRUE values	CTD estimates	NTFD estimates
A = .30	*A'* = .68	*A'* = .32
D = .30	*D'* = .04	*D'* = .29
S = .10	*S'* = 0	*S'* = .13

Nuclear Twin Family Design (NTFD)



Note: m estimated and f fixed to 1

- Assumptions:
  - Only can estimate 3 of 4: A, D, S, and F (bias is variable)
  - Assortative mating due to primary phenotypic assortment (bias is variable)

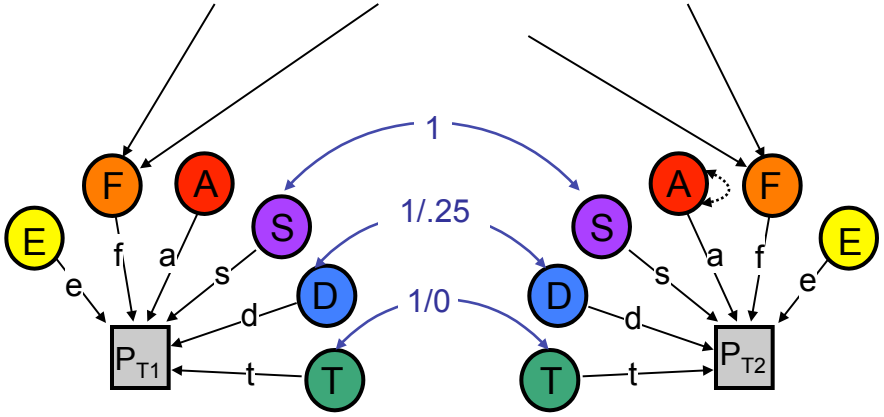
Stealth

- Include twins and their sibs, parents, spouses, and offspring…
  - Gives 17 unique covariances (MZ, DZ, Sib, P-O, Spousal, MZ avunc, DZ avunc, MZ cous, DZ cous, GP-GO, and 7 in-laws)
  - 88 covariances with sex effects

Additional obs. covs with *Stealth* allow estimation of A, S, D, F, T

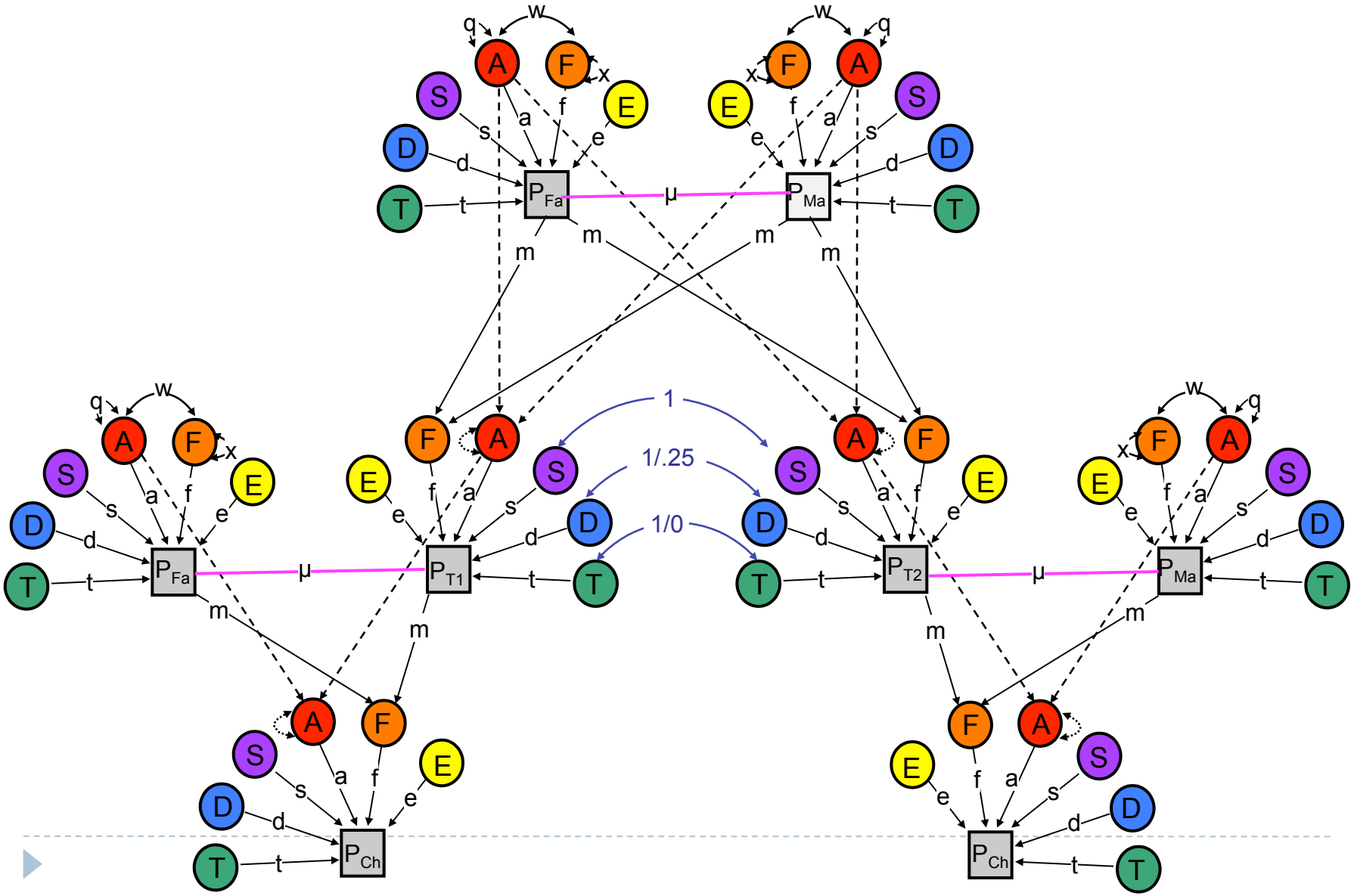
A S F D T can be estimated simultaneously

T = env. factors shared only between **twins**



(Remember: we're not just estimating more effects. More importantly, we're reducing the bias in estimated effects – although perhaps at the expense of more variance in estimates)

Stealth



Stealth

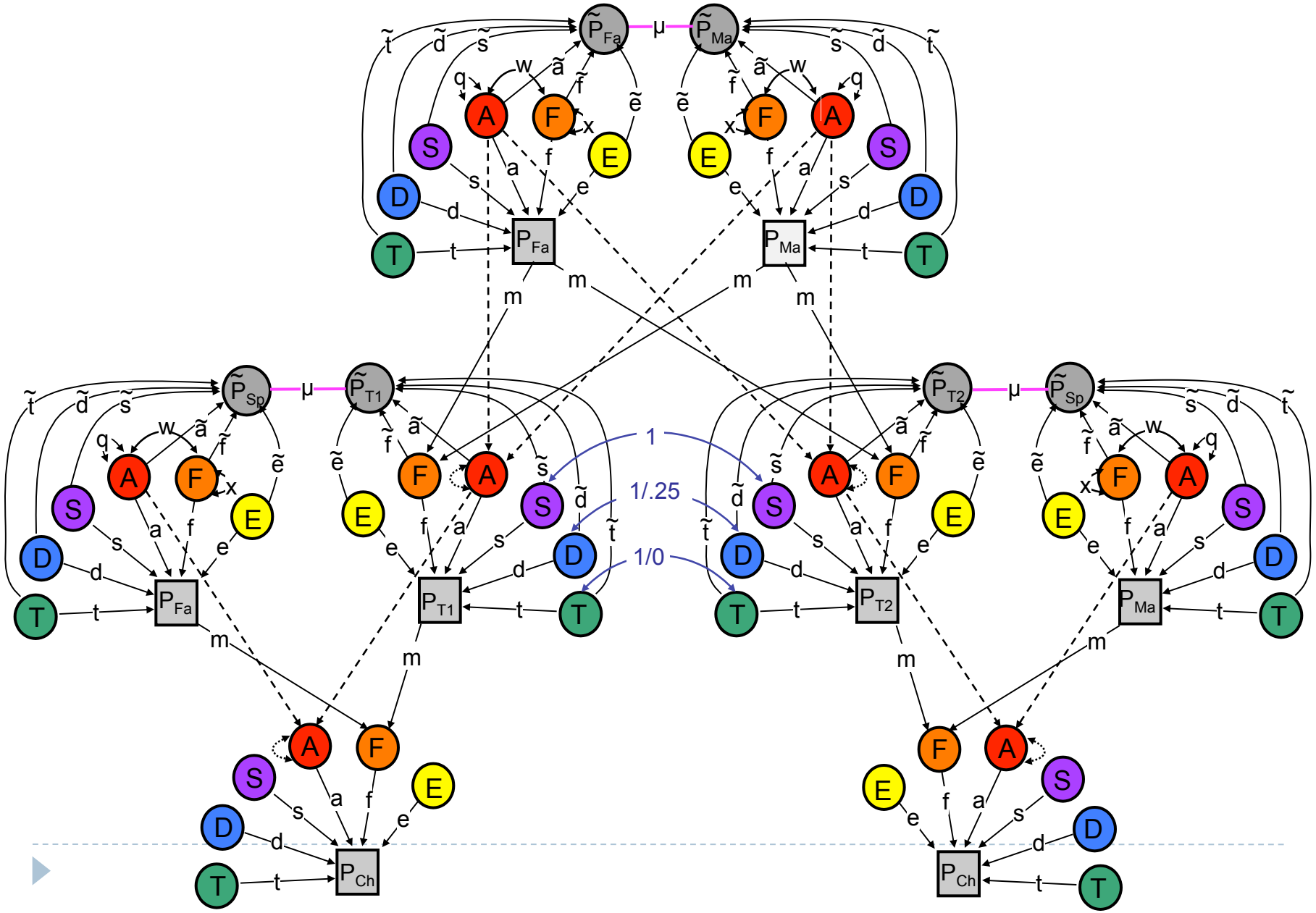
Assumption	biased up	biased down
Primary assortative mating	A, D, or F	A, D, or F
No epistasis	A, D	S
No AxAge	D, S	A

Stealth

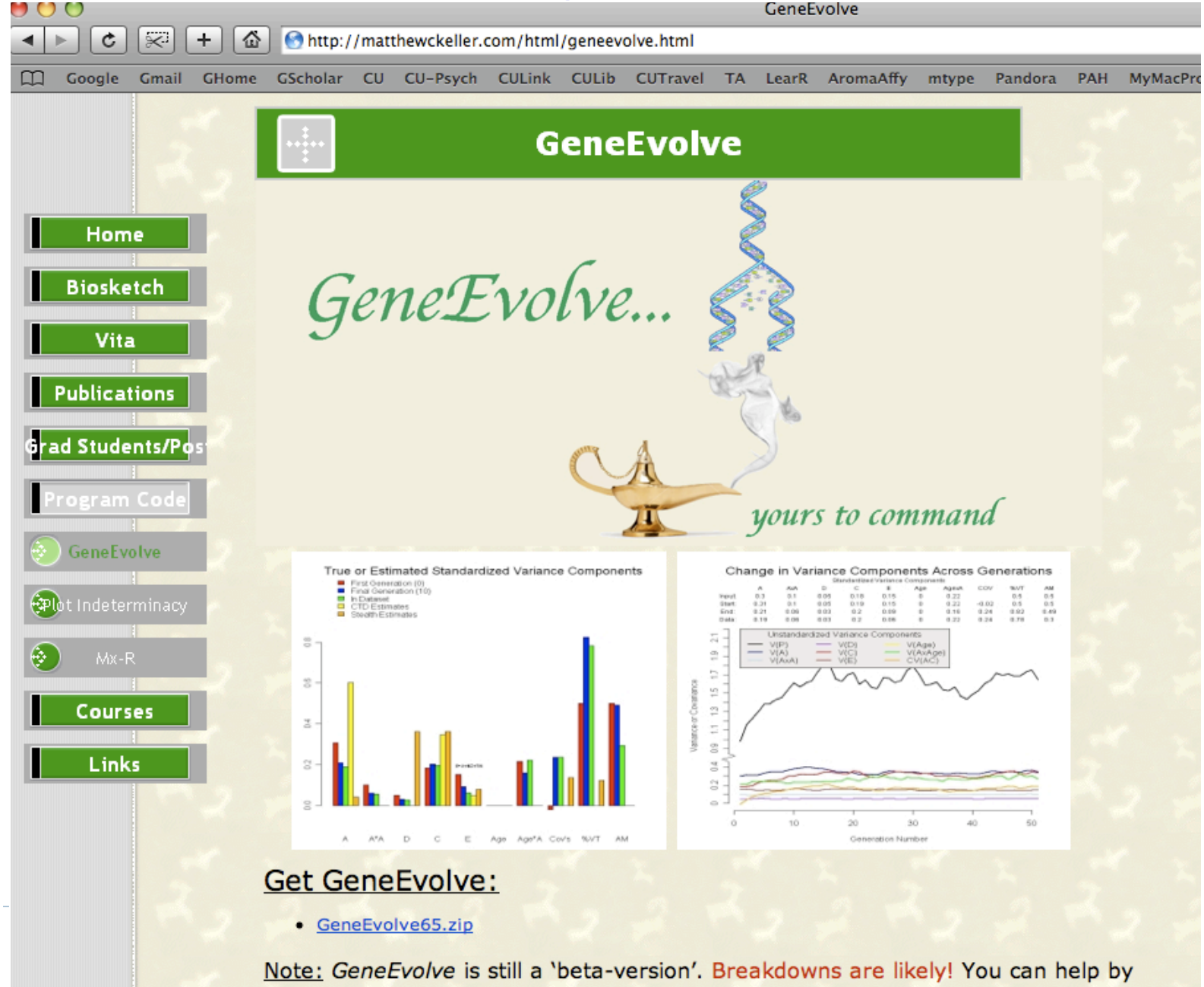
Assumption	biased up	biased down
Primary assortative mating	A, D, or F	A, D, or F
No epistasis	A, D	S
No AxAge	D, S	A

- Primary AM: mates choose each other based on phenotypic similarity
- Social homogamy: mates choose each other due to environmental similarity (e.g., religion)
- Convergence: mates become more similar to each other (e.g., becoming more conservative when dating a conservative)

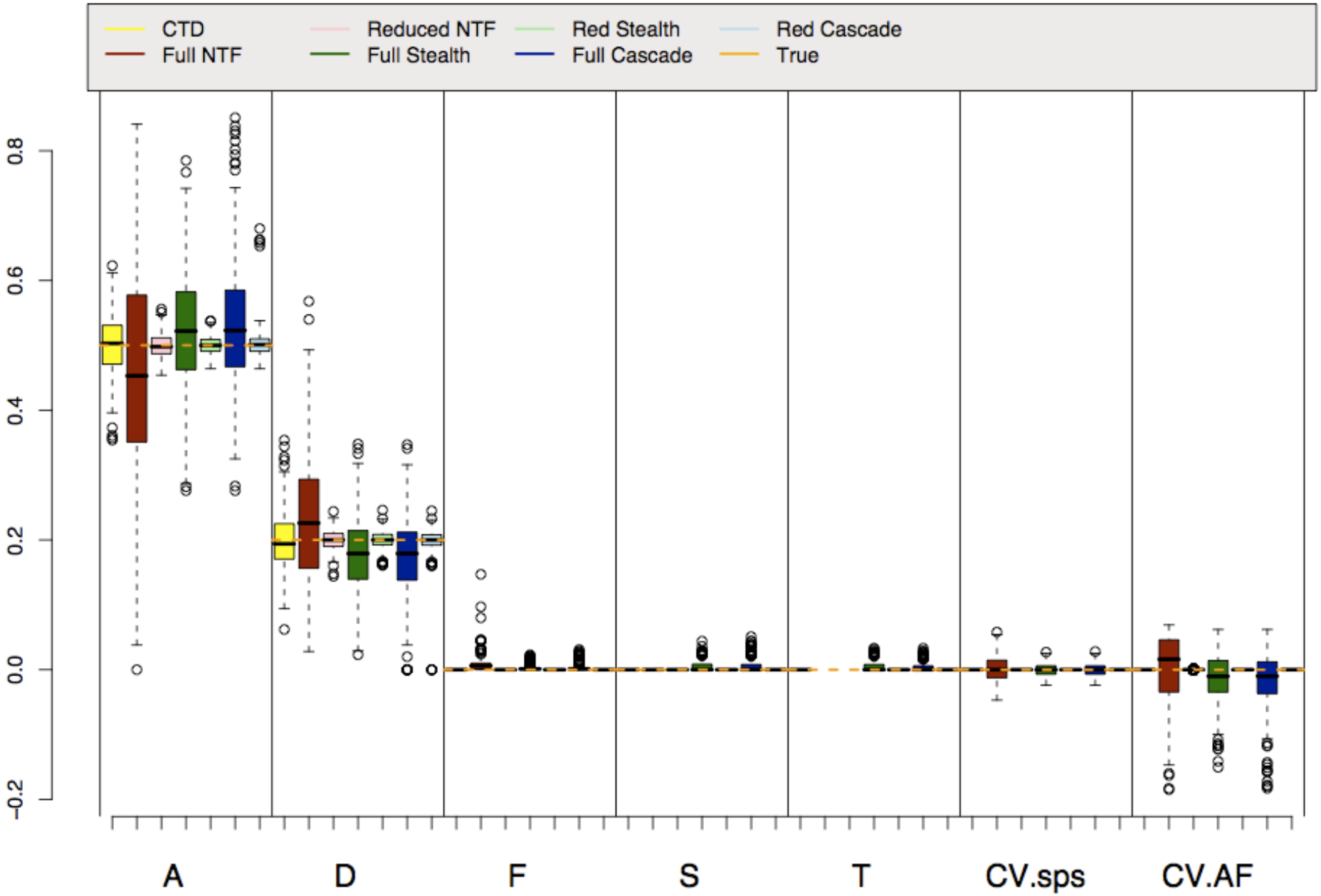
Cascade



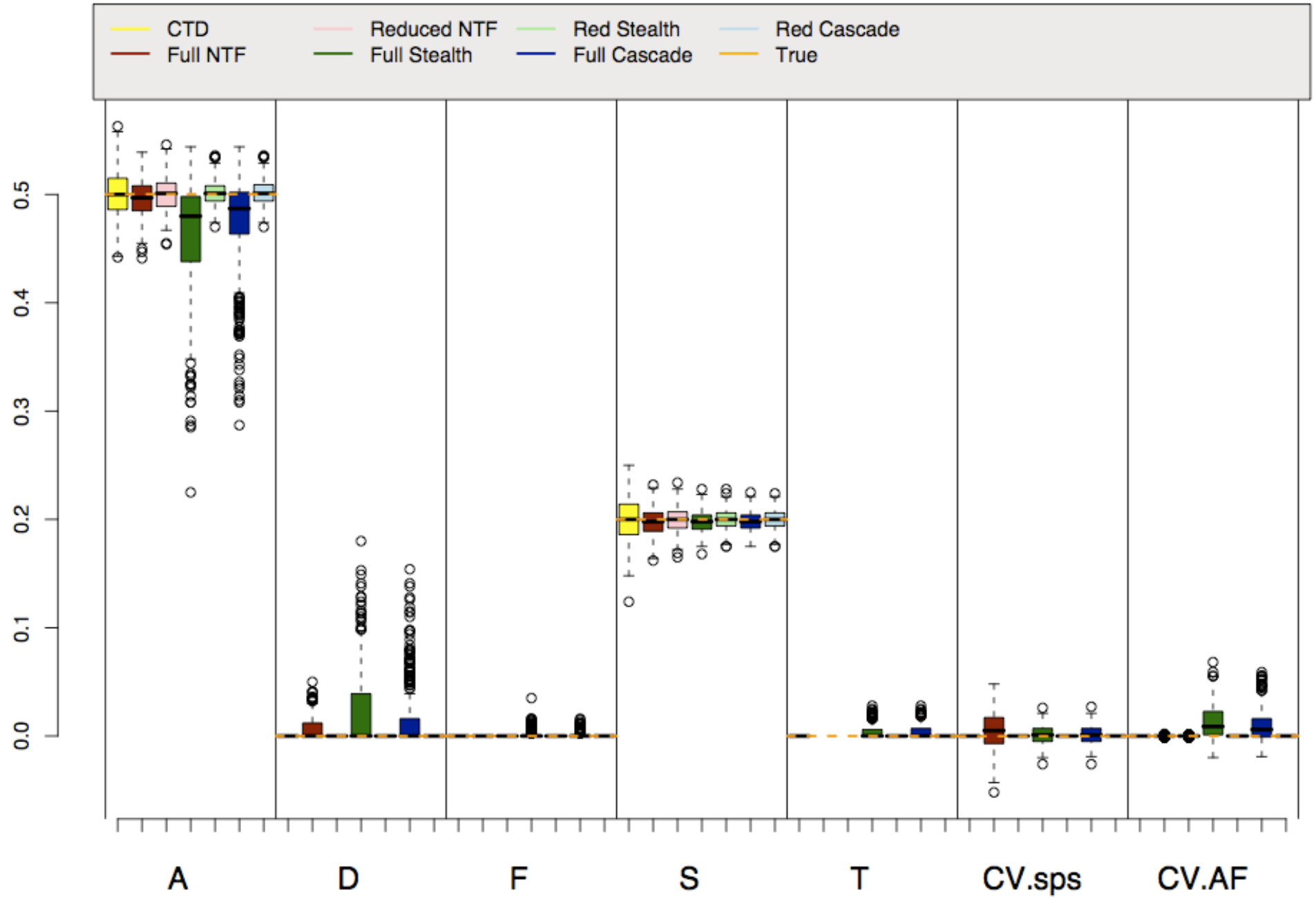
Simulation program: GeneEvolve



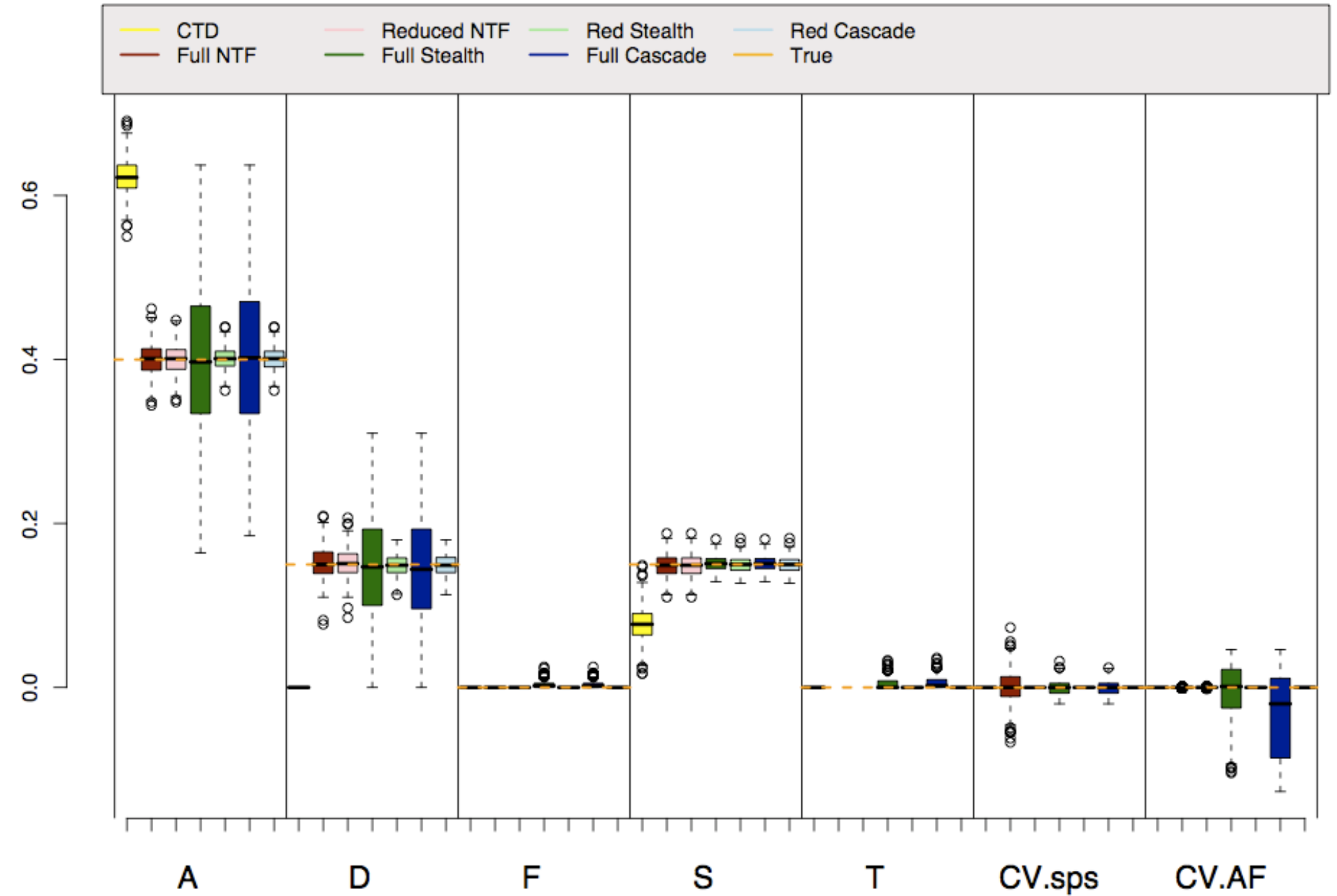
Reality: A=.5, D=.2



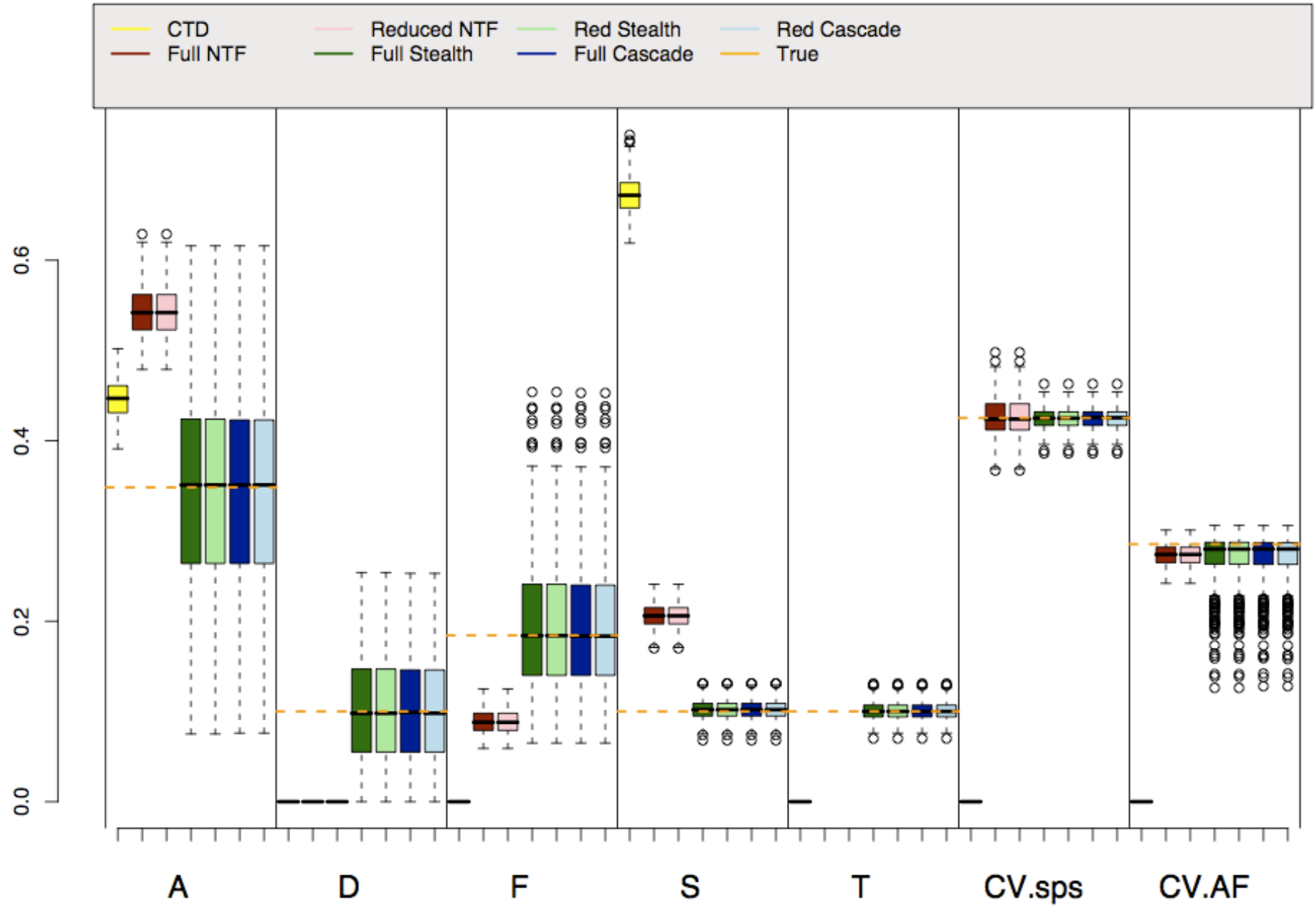
Reality: A=.5. S=.2



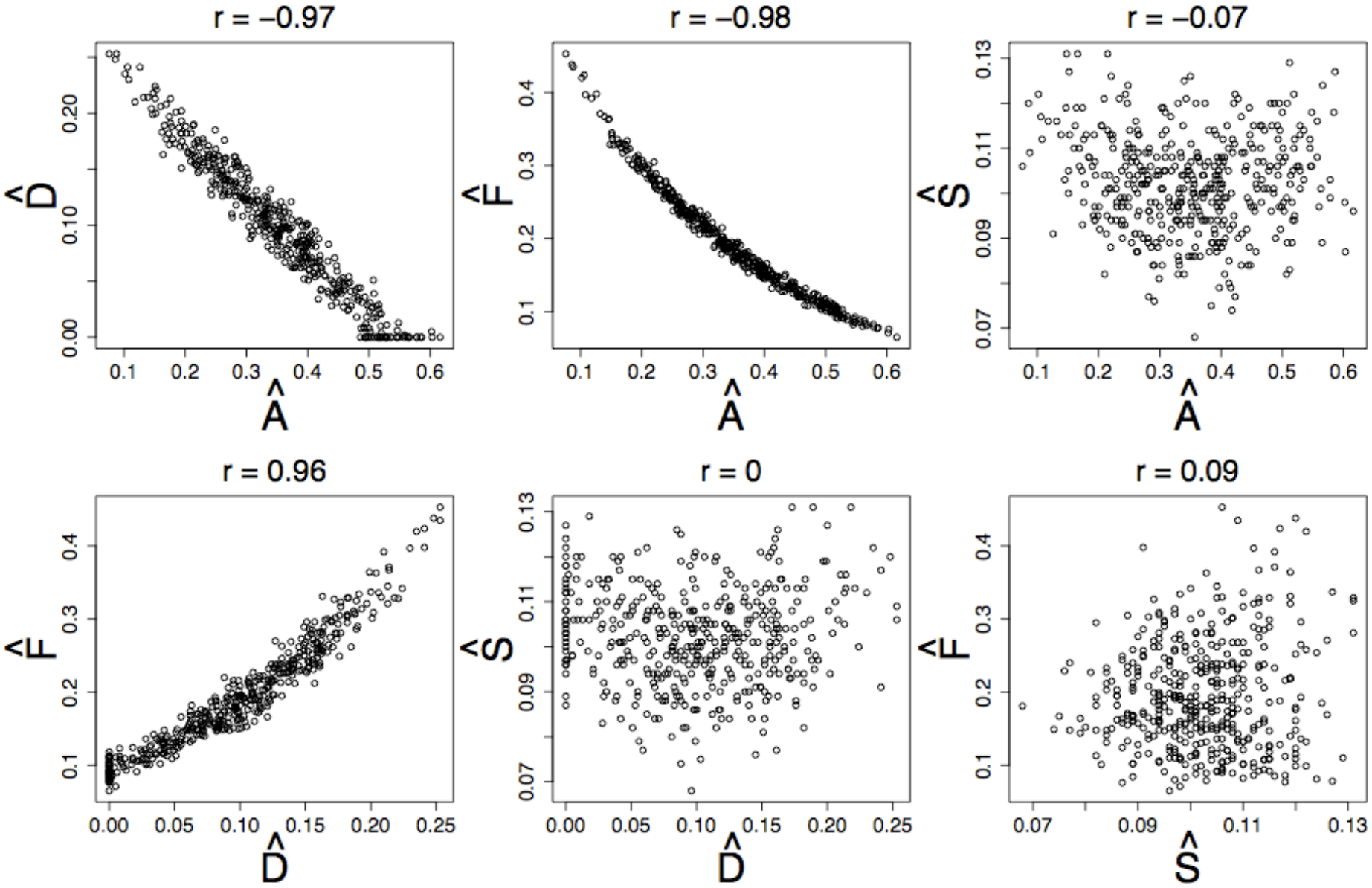
Reality: A=.4, D=.15, S=.15



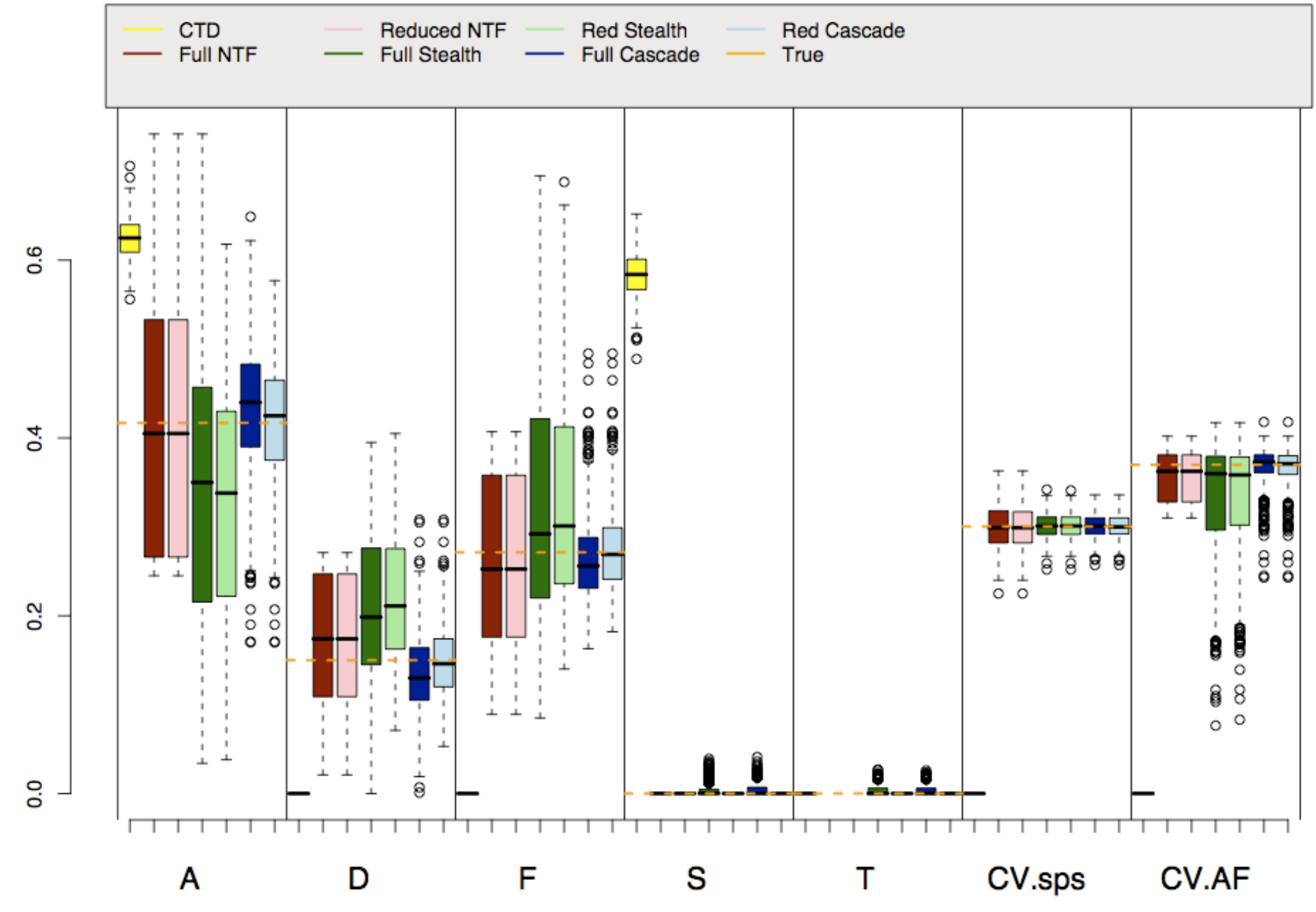
Reality: A=.35, D=.15, F=.2, S=.15, T=.15, AM=.3



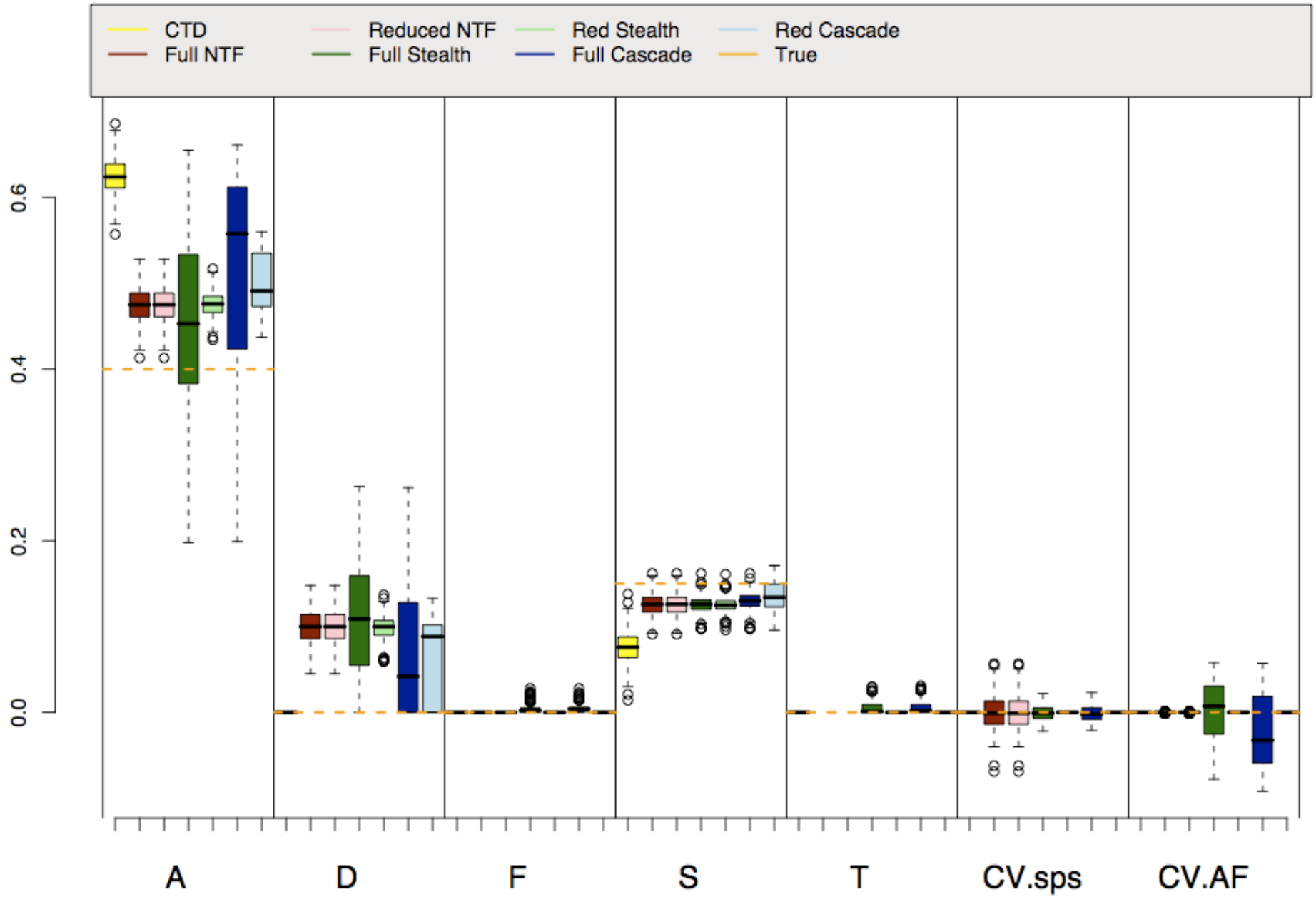
A,D, & F estimates are highly correlated in Stealth & Cascade



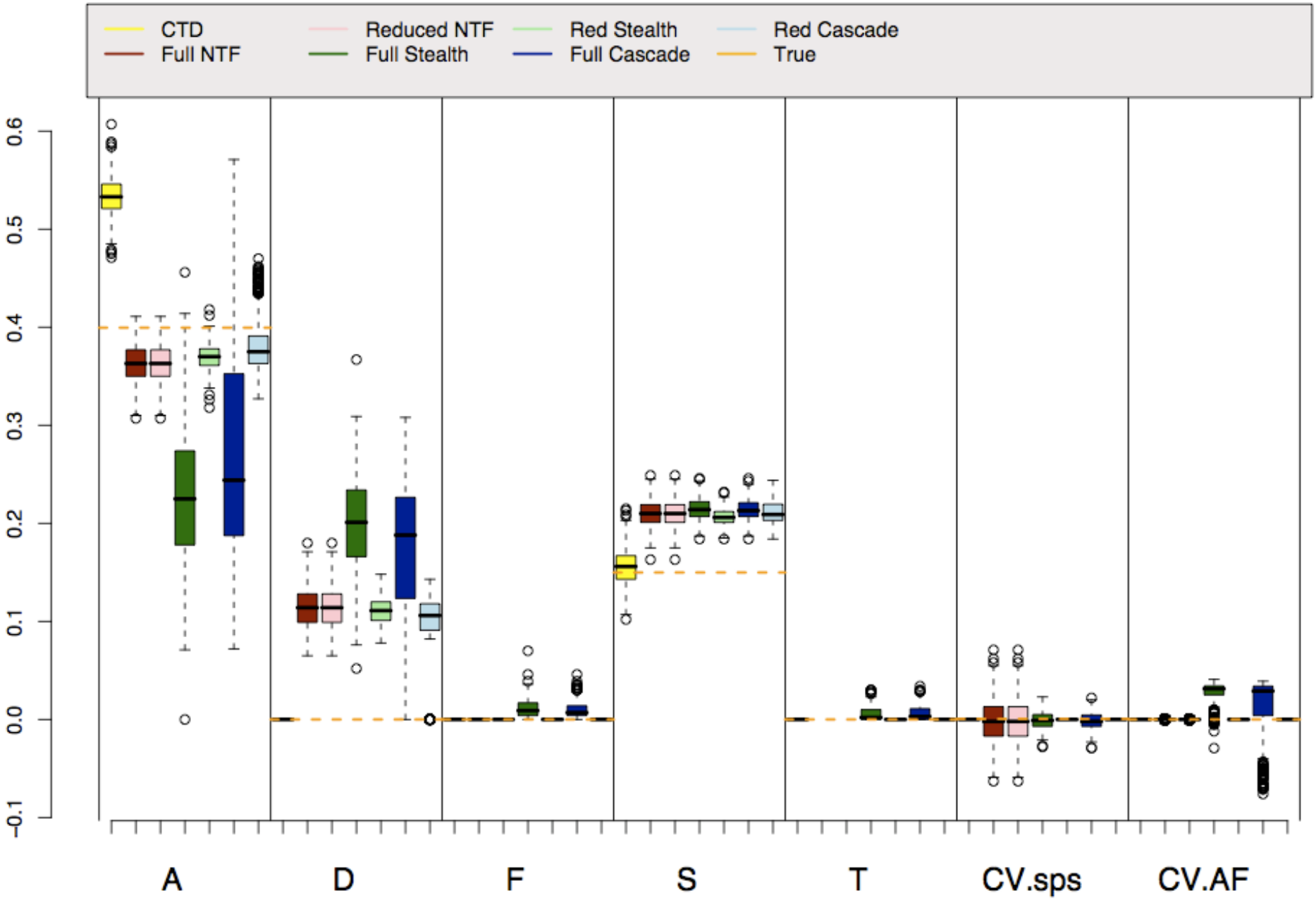
Reality: A=.45, D=.15, F=.25, AM=.3 (Soc Hom)



Reality: A=.4, A*A=.15, S=.15



Reality: A=.4, A*Age=.15, S=.15



Conclusions

- All models require assumptions. Generally, more assumptions = more biased estimates
- Simulations provide independent assessments of the NTFD, *Stealth*, and *Cascade* models
  - These complicated models work as designed, but they have drawbacks
- In all models, but especially the CTD, be cautious of reifying parameter estimates!
  - A is amalgam of mostly A but also D & C. A (in ACE models) or A+D (in ADE models) is a decent estimate of broad sense h^2.
  - D & C are likely to be underestimates

Discussion questions

- Are extended twin family methods worth the trouble? Or should we simply adjust our interpretations of estimates from simpler models?
- Should we report full or reduced parameter estimates?
- Should we fit variances of latent variables rather than pathways, and hence allow variance component estimates to go negative?

Stealth application

Twin Research (1999) 2, 99–107


http://www.stockton-press.co.uk/tr

Frequency of church attendance in Australia and the United States: models of family resemblance

KM Kirk[1], HH Maes[2], MC Neale[2], AC Heath[3], NG Martin[1] and LJ Eaves[2]

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[2]*Virginia Institute for Psychiatric and Behavior Genetics, Richmond*
[3]*Department of Psychiatry, Washington University School of Medicine, USA*

Data on frequency of church attendance have been obtained from separate cohorts of twins and their families from the USA and Australia (29 063 and 20 714 individuals from 5670 and 5615 families, respectively). The United States sample displayed considerably higher frequency of attendance at church services. Sources of family resemblance for this trait also differed between the Australian and US data, but both indicated significant additive genetic and shared environment effects on church attendance, with minor contributions from twin environment, assortative mating and parent–offspring environmental transmission. Principal differences between the populations were in greater maternal environmental effects in the US sample, as opposed to paternal effects in the Australian sample, and smaller shared environment effects observed for both women and men in the US cohort.

Keywords: religion, church attendance, extended kinship model, twins, cultural inheritance, assortative mating, twin environment

Further reading on this lecture

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