Estimating Intergenerational Transmission

Jared V. Balbona | Matthew C. Keller

“Okay yeah, that explains a lot.”

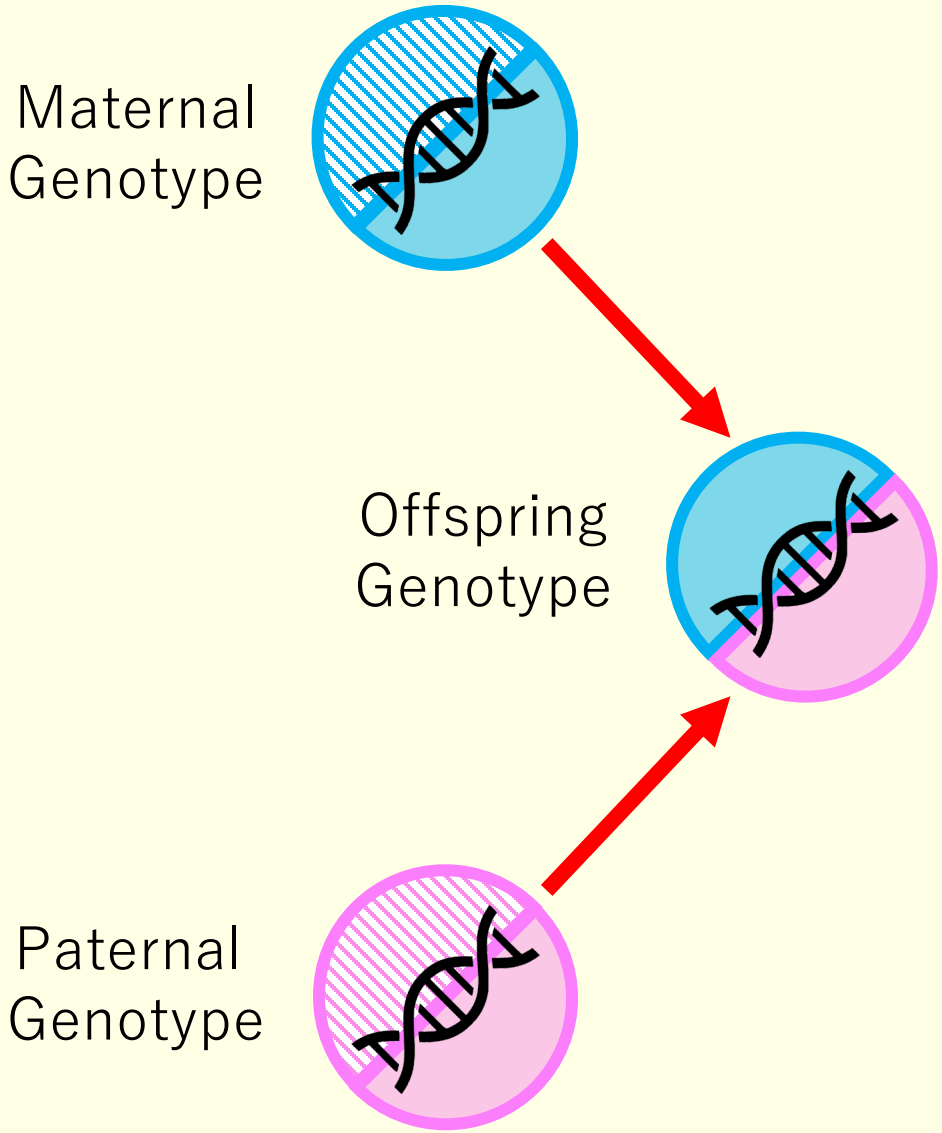
Parents and offspring tend to be quite similar.

...Why?

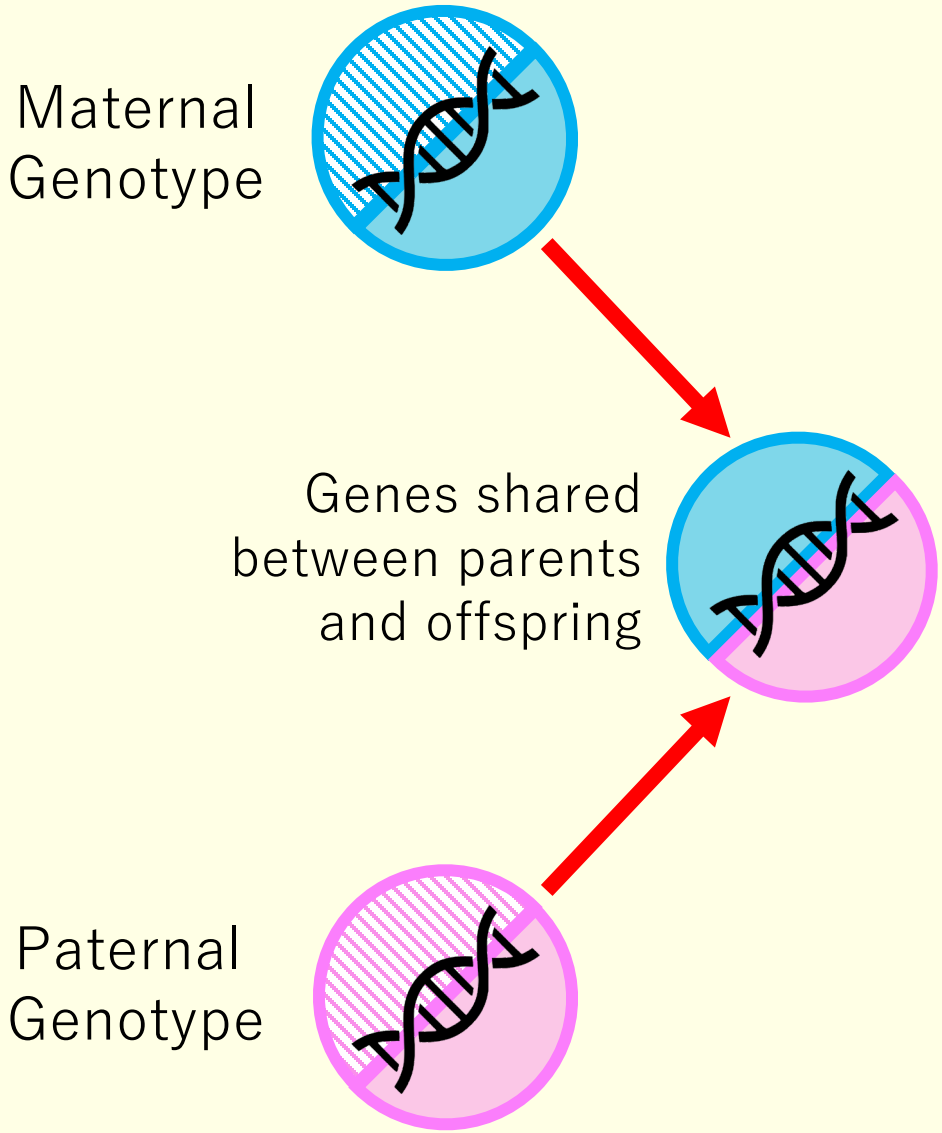
Maternal Genotype

Paternal Genotype

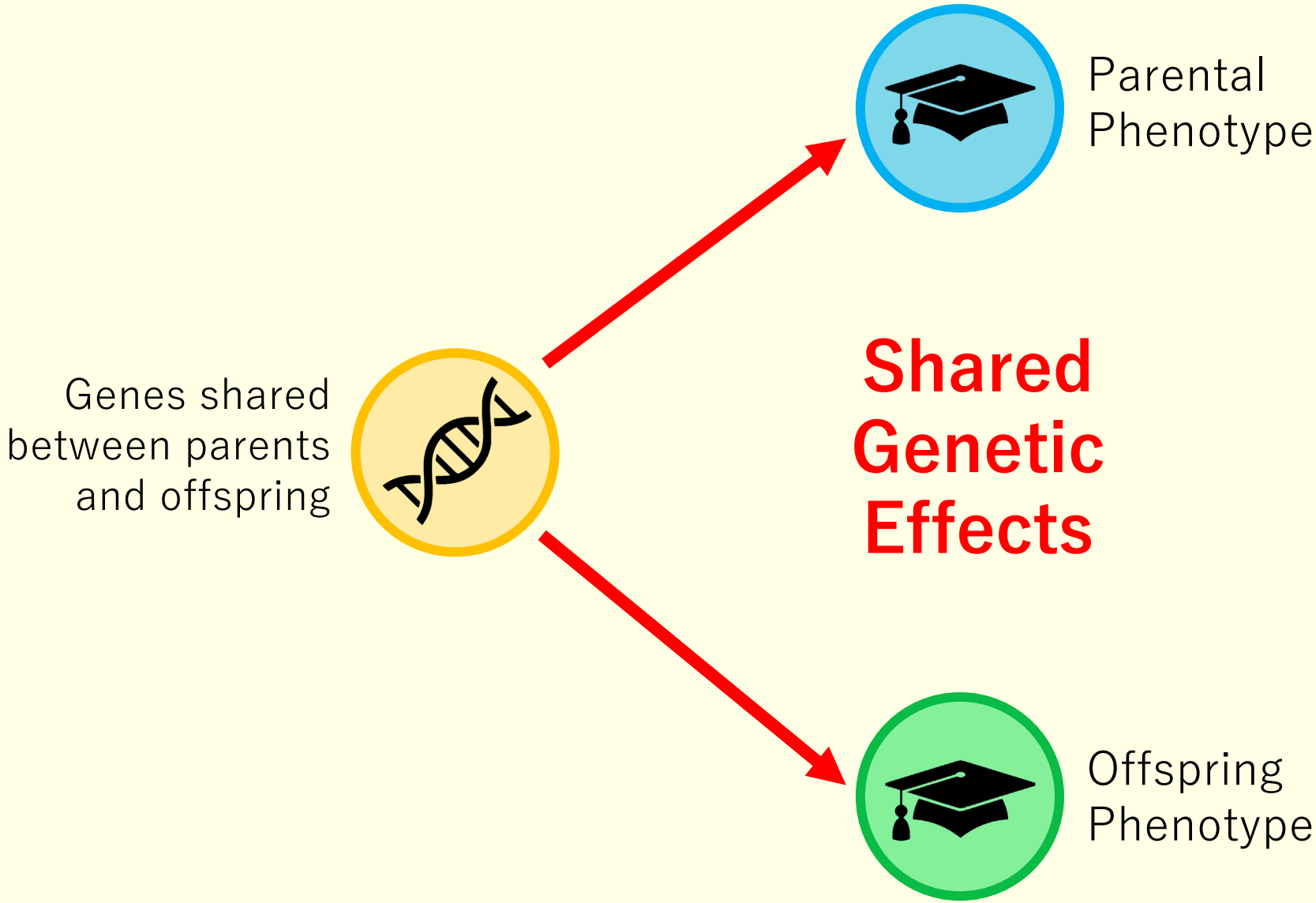
Shared Genetic Effects

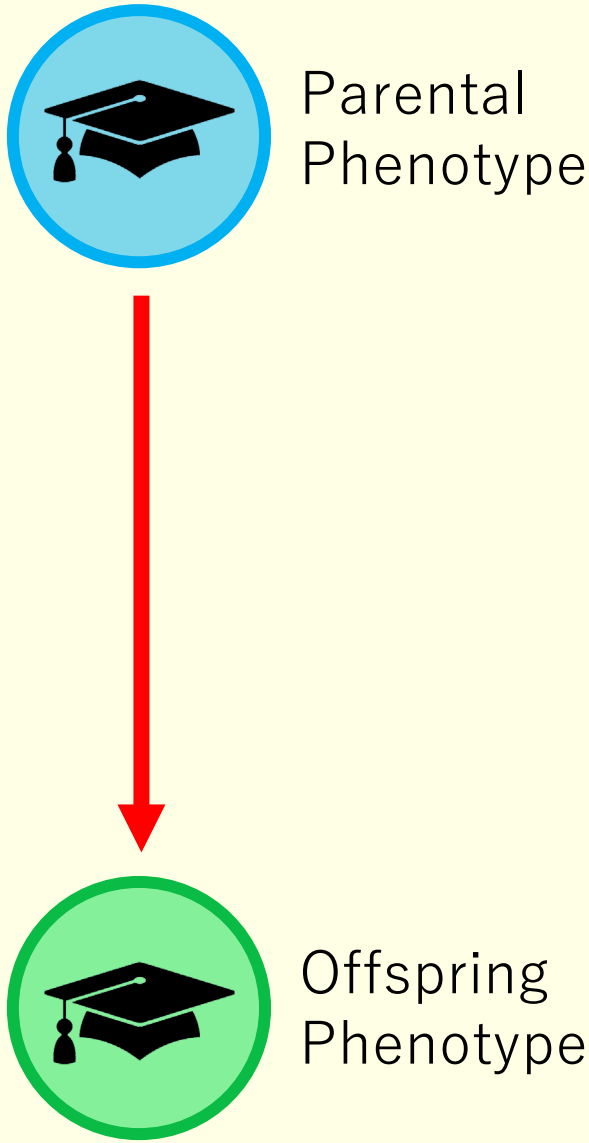


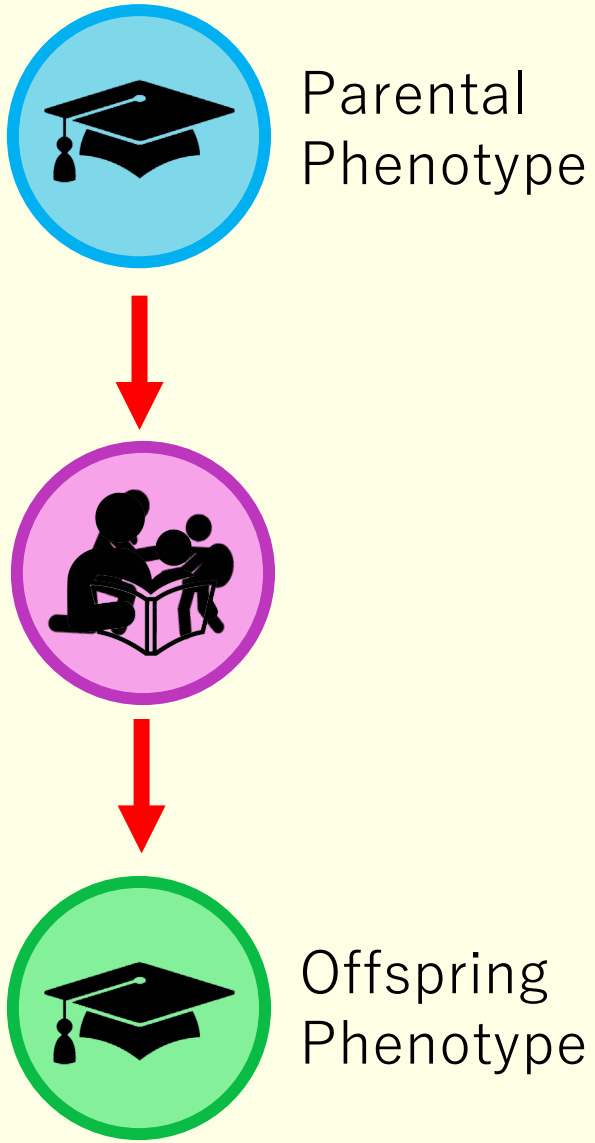
Shared Genetic Effects



Shared Genetic Effects


Parental
Phenotype
Genes shared
between parents
and offspring
Shared
Genetic
Effects
Offspring
Phenotype

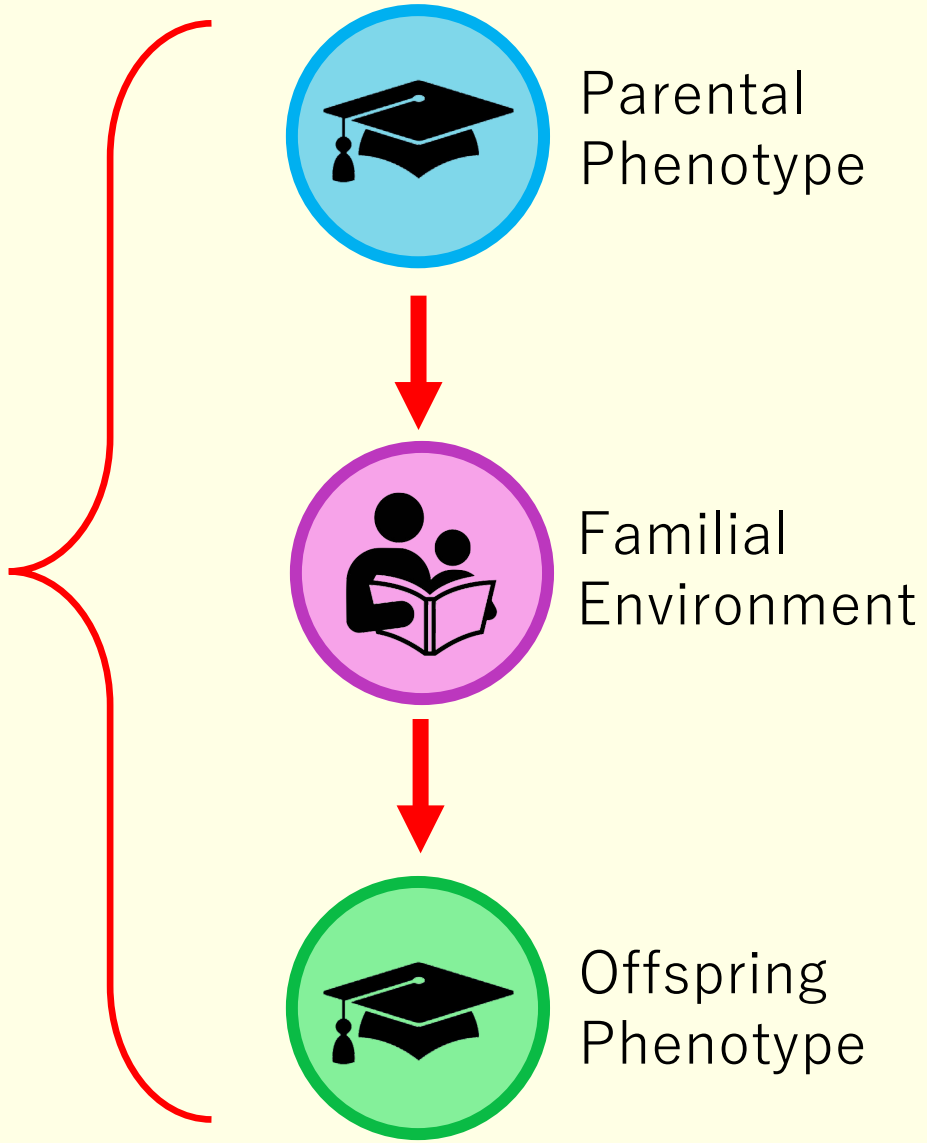

Parental
Phenotype
Offspring
Phenotype

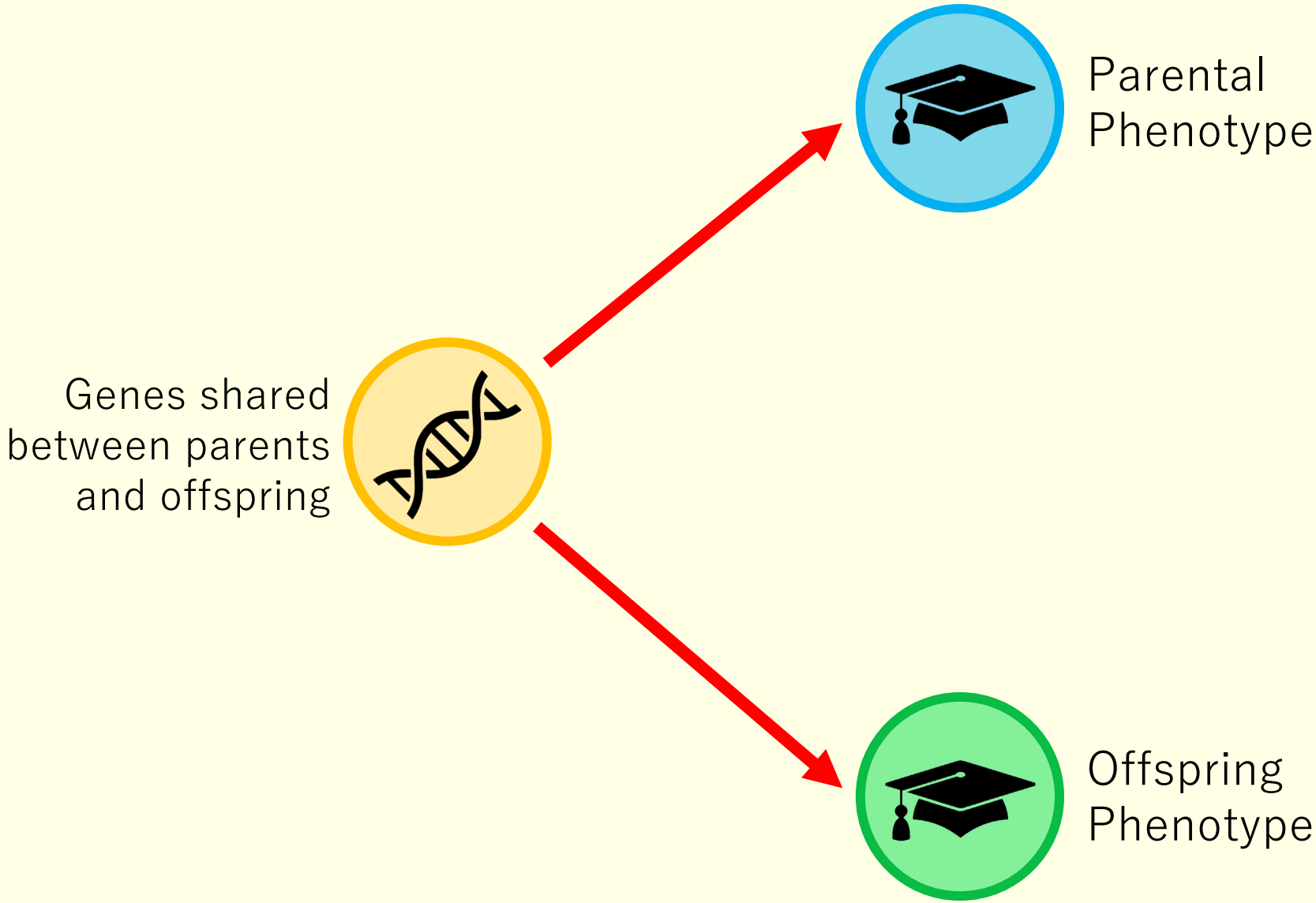

Parental
Phenotype
Offspring
Phenotype

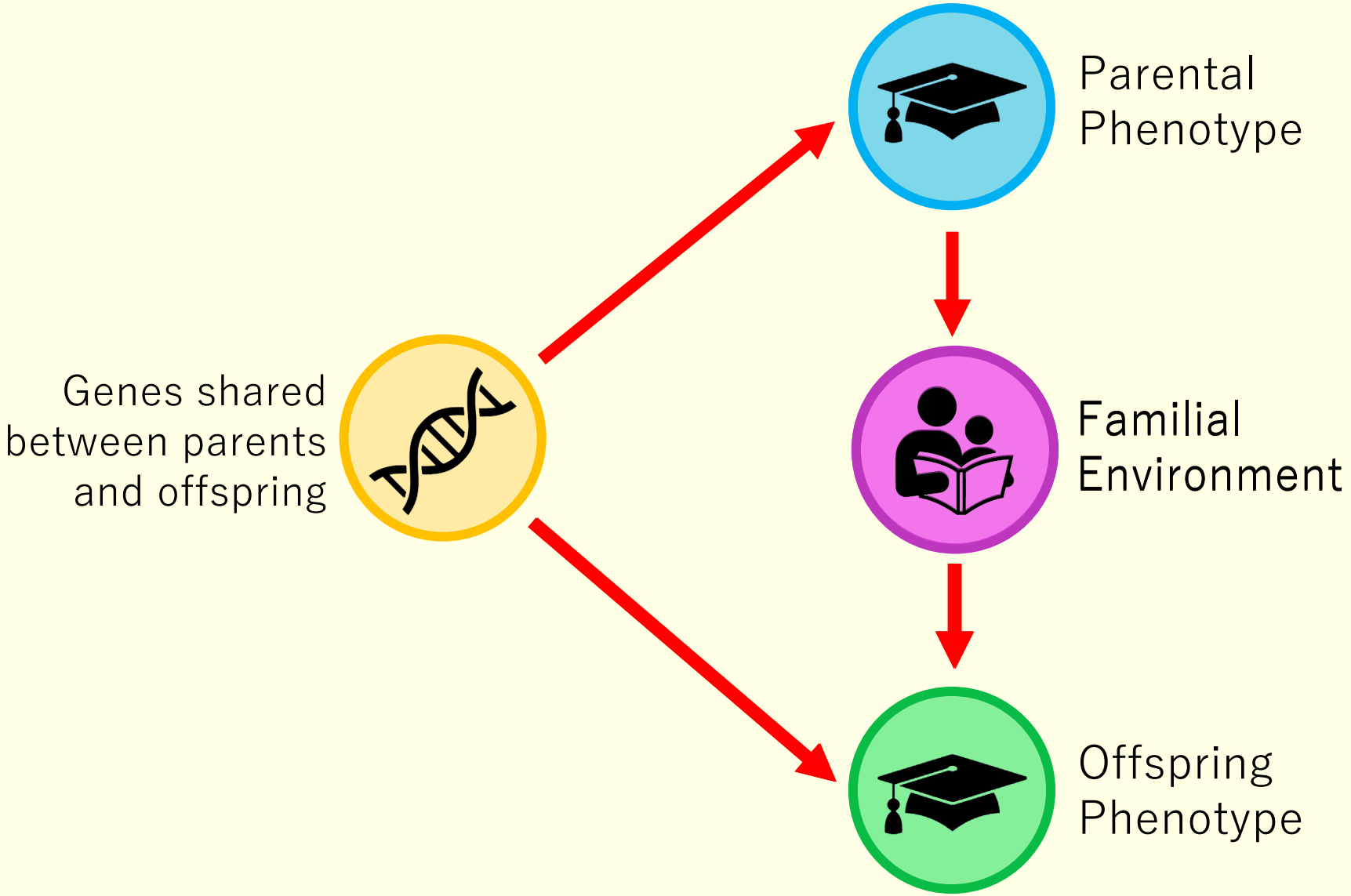
Vertical Transmission

(aka "Cultural Transmission")

The phenomenon where a parental phenotype directly influences an offspring phenotypes via the familial environment

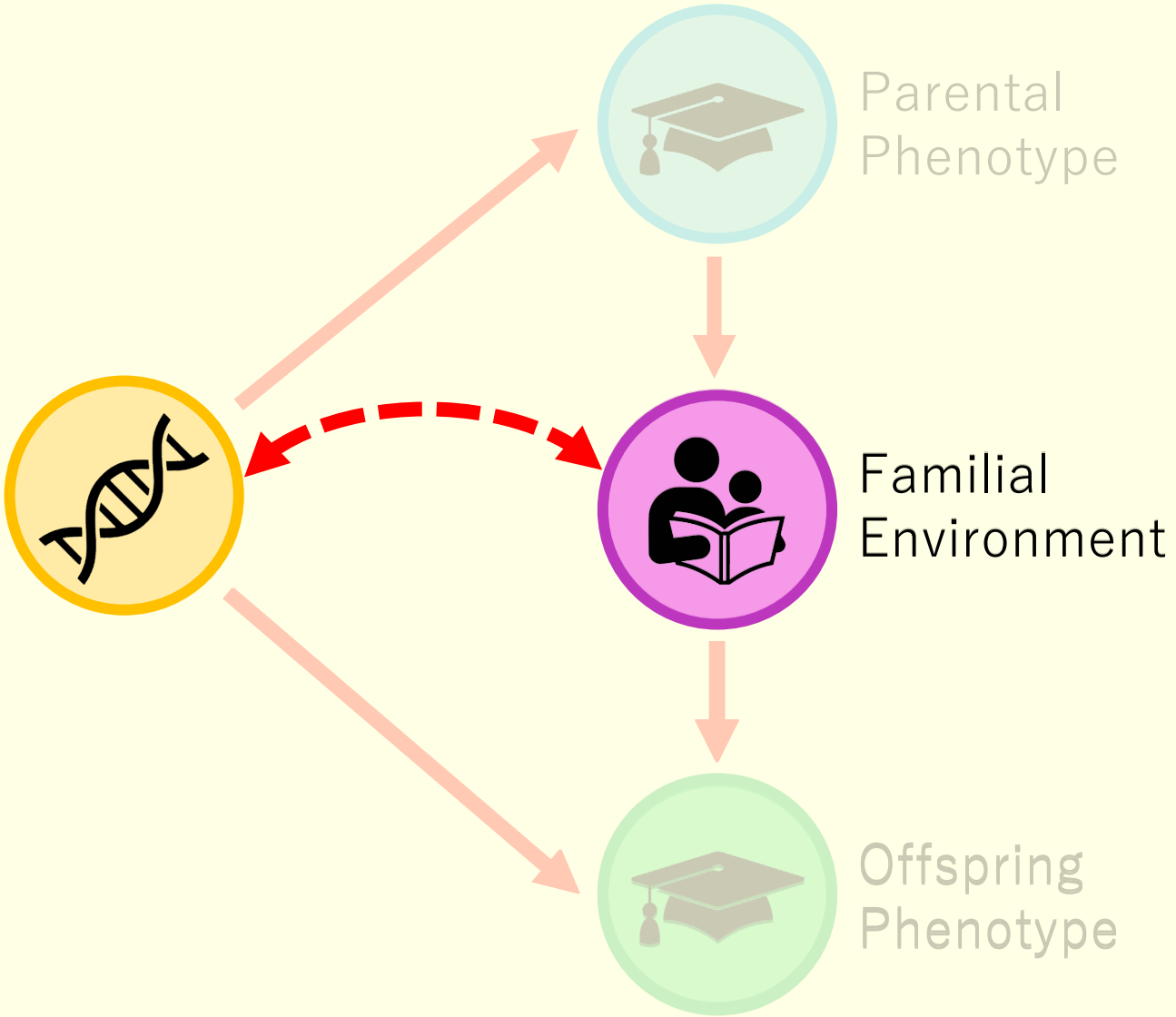


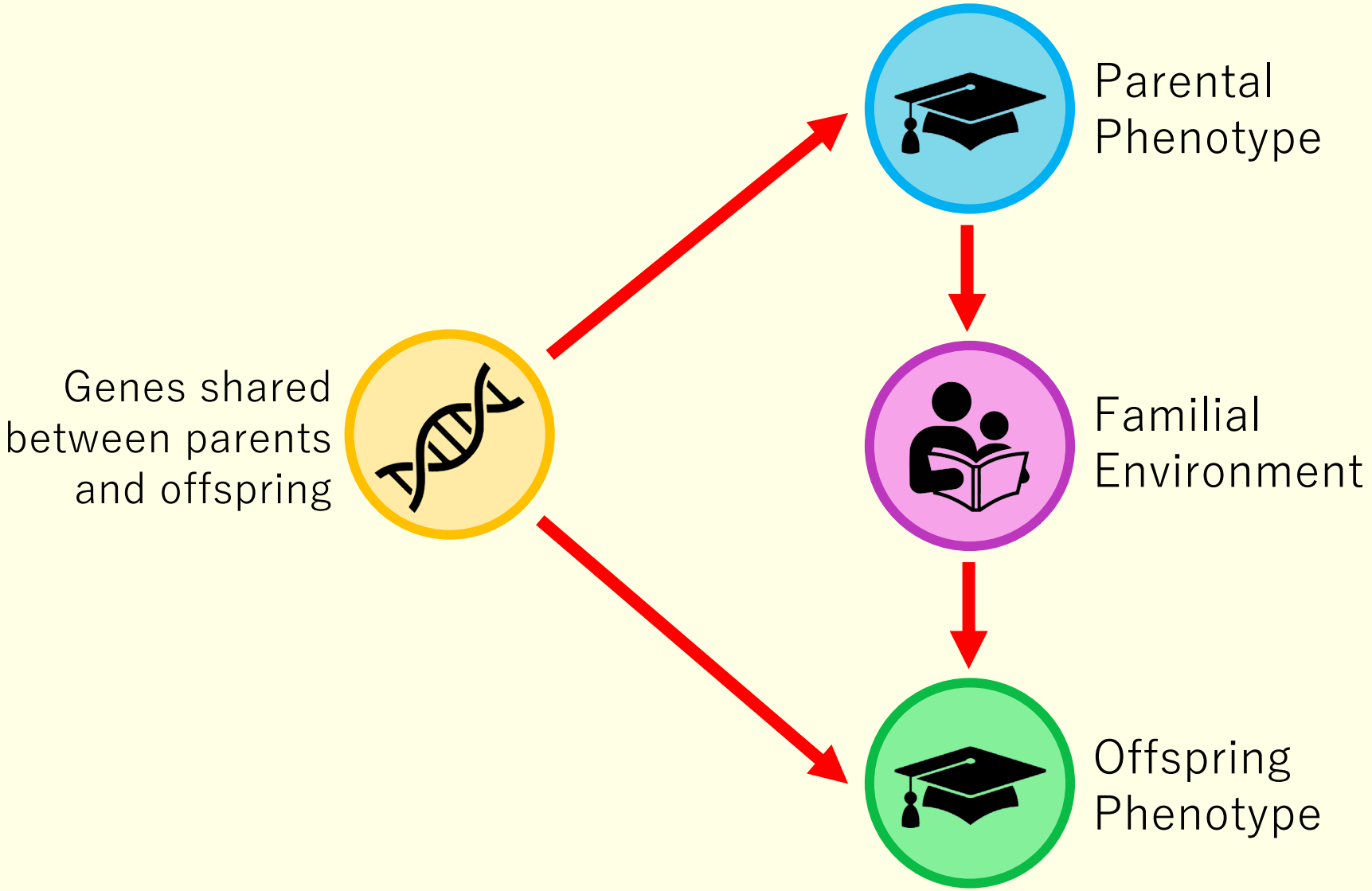

Genes shared between parents and offspring
Parental Phenotype
Offspring Phenotype


Genes shared between parents and offspring
Parental Phenotype
Familial Environment
Offspring Phenotype

Genetic Nurture

A type of Passive Gene-Environment Covariance

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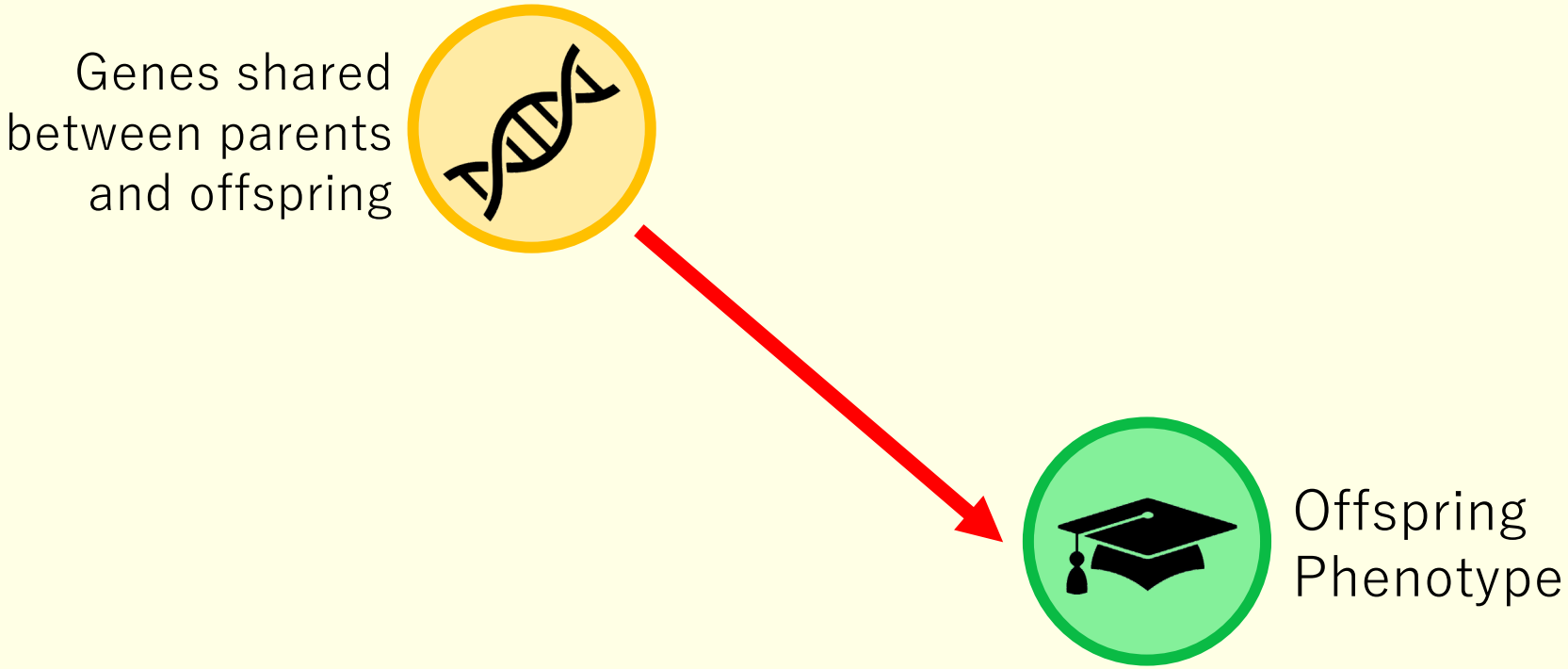
Genes shared
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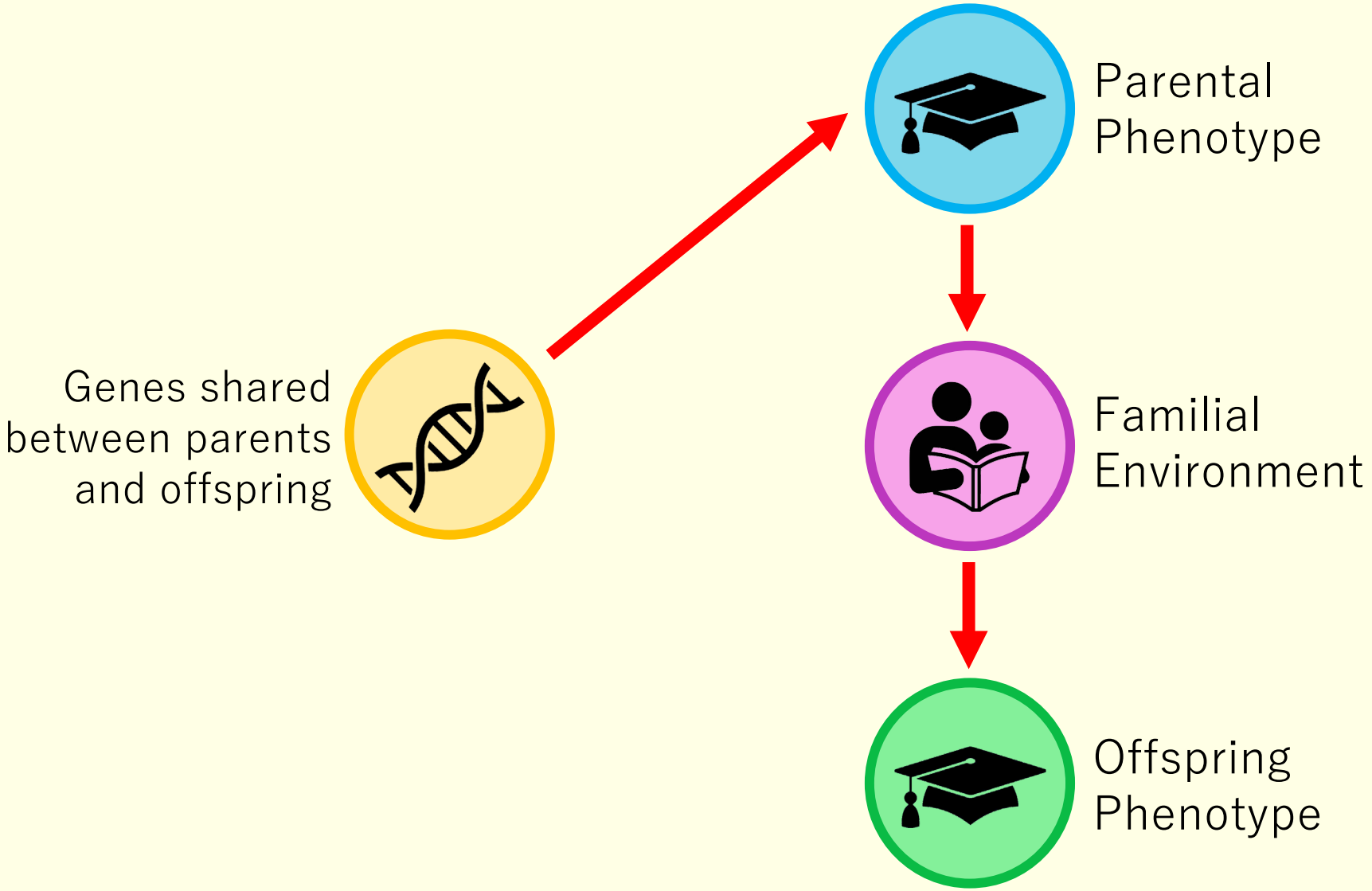
Offspring
Phenotype


Genes shared
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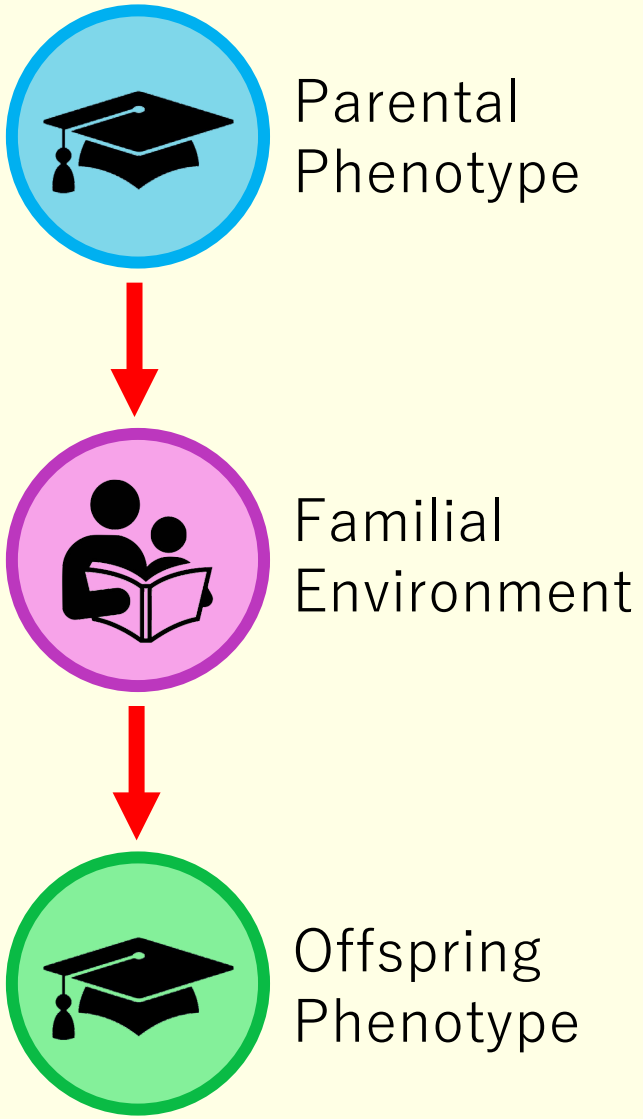
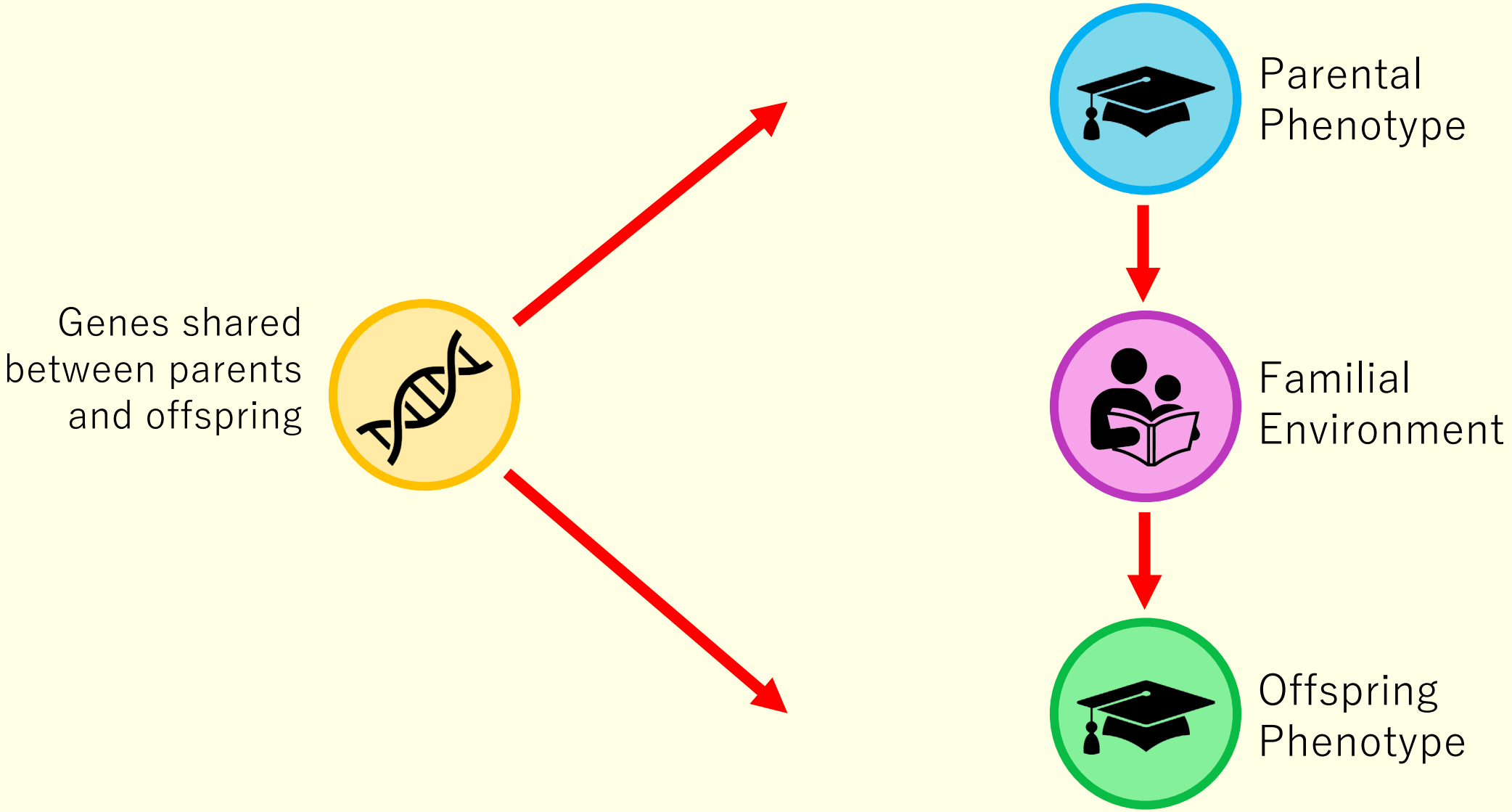
Parental
Phenotype
Familial
Environment
Offspring
Phenotype

If unaccounted for, genetic nurture and vertical transmission:

- Will upwardly bias estimates of SNP effects from GWAS
- Will downwardly bias estimates of additive genetic effects (A) in twin ACE models
- Will upwardly bias estimates of additive genetic effects (A) in twin AE and ADE models
- We'll be missing out on stuff that's just like, generally cool to know about




Genes shared between parents and offspring
Parental Phenotype
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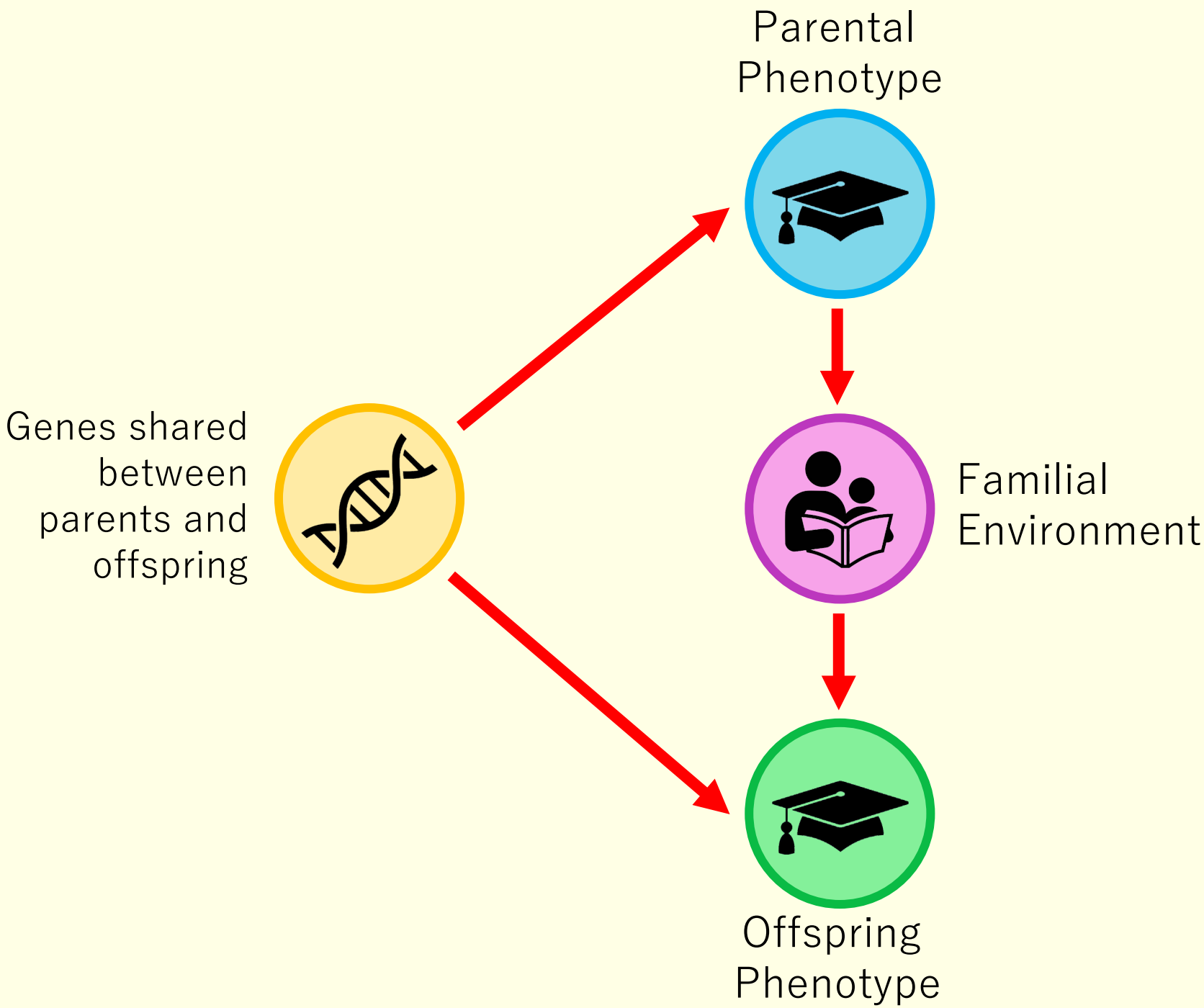
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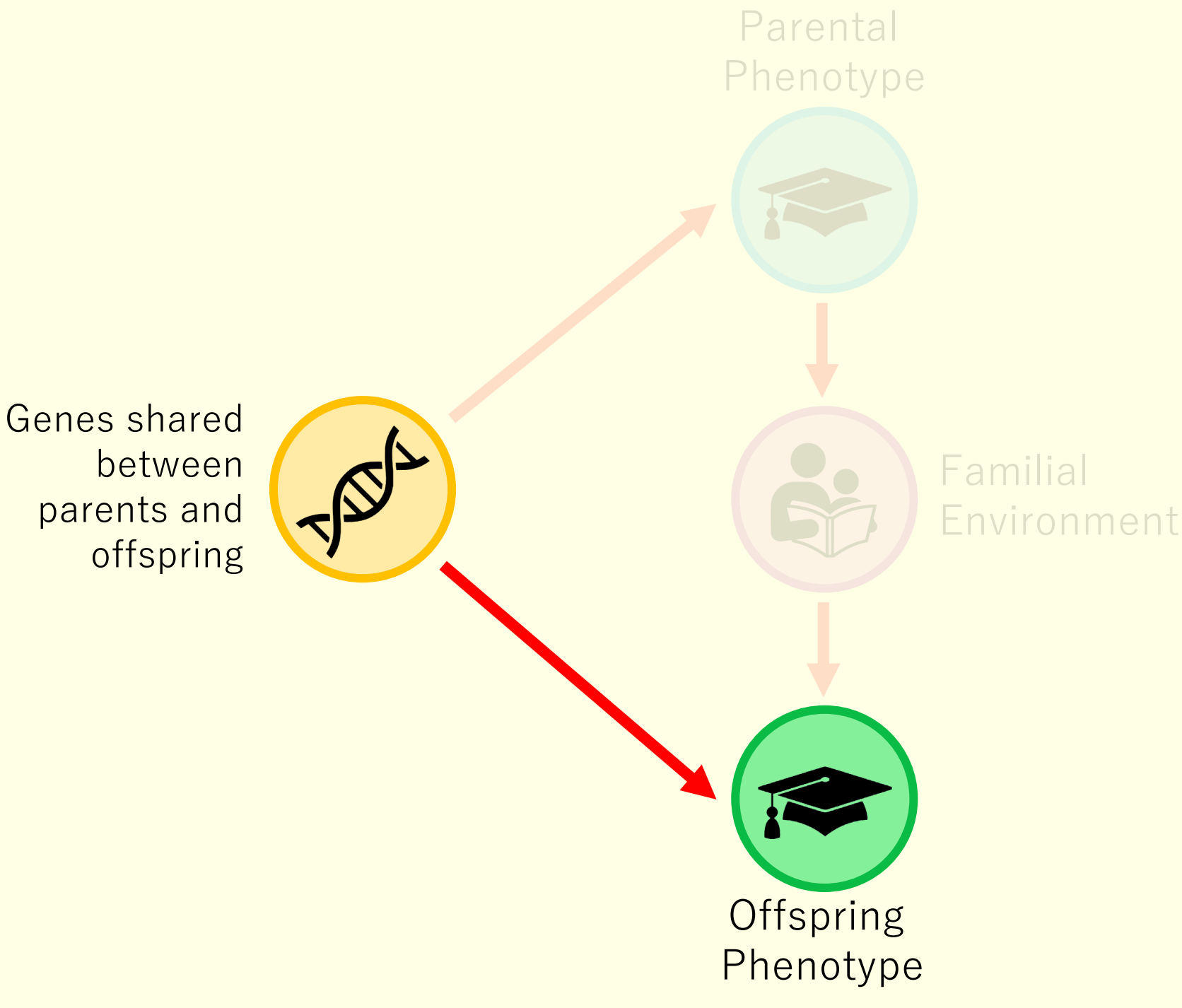
Parental Phenotype
Genes shared between parents and offspring
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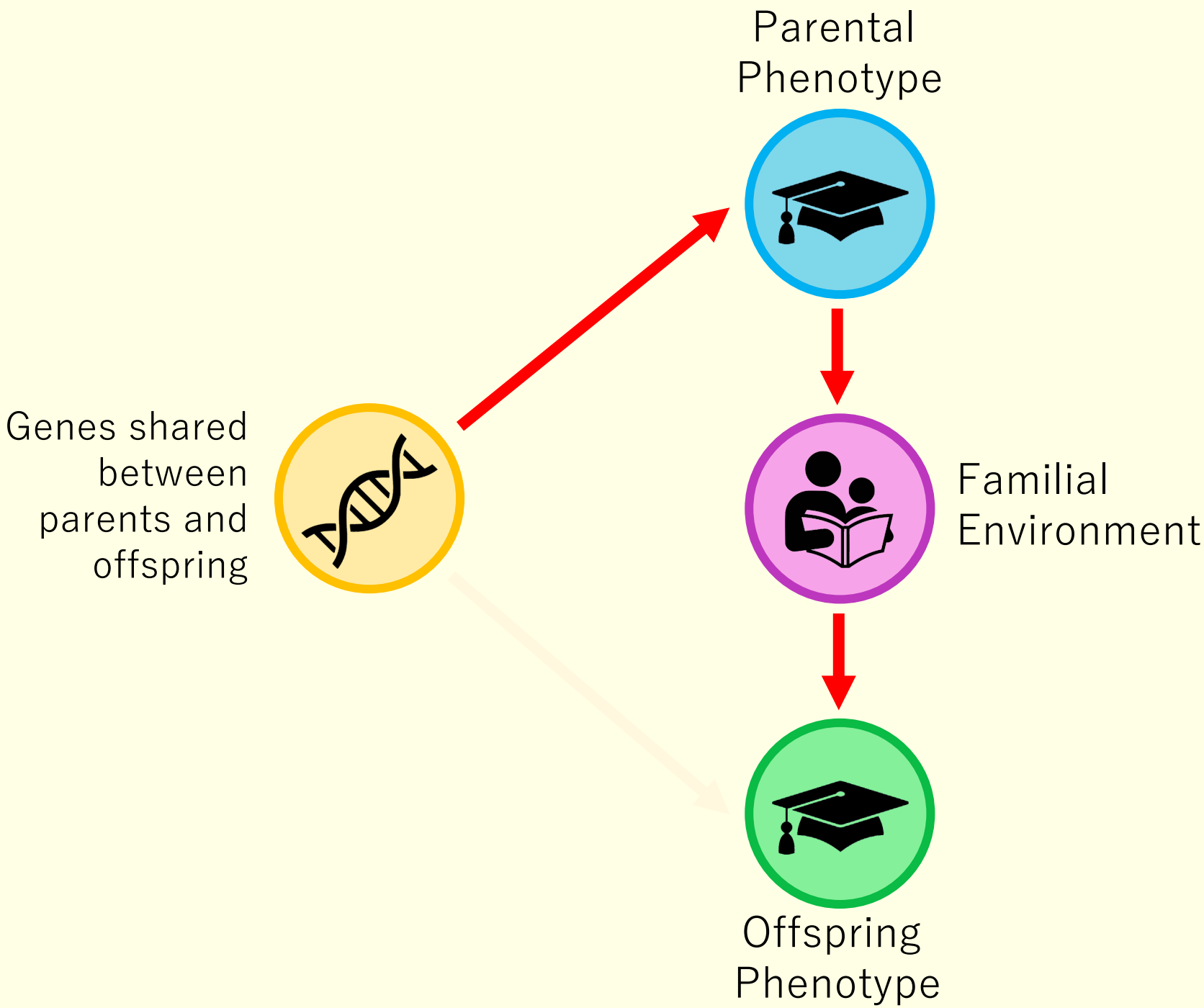
Offspring Phenotype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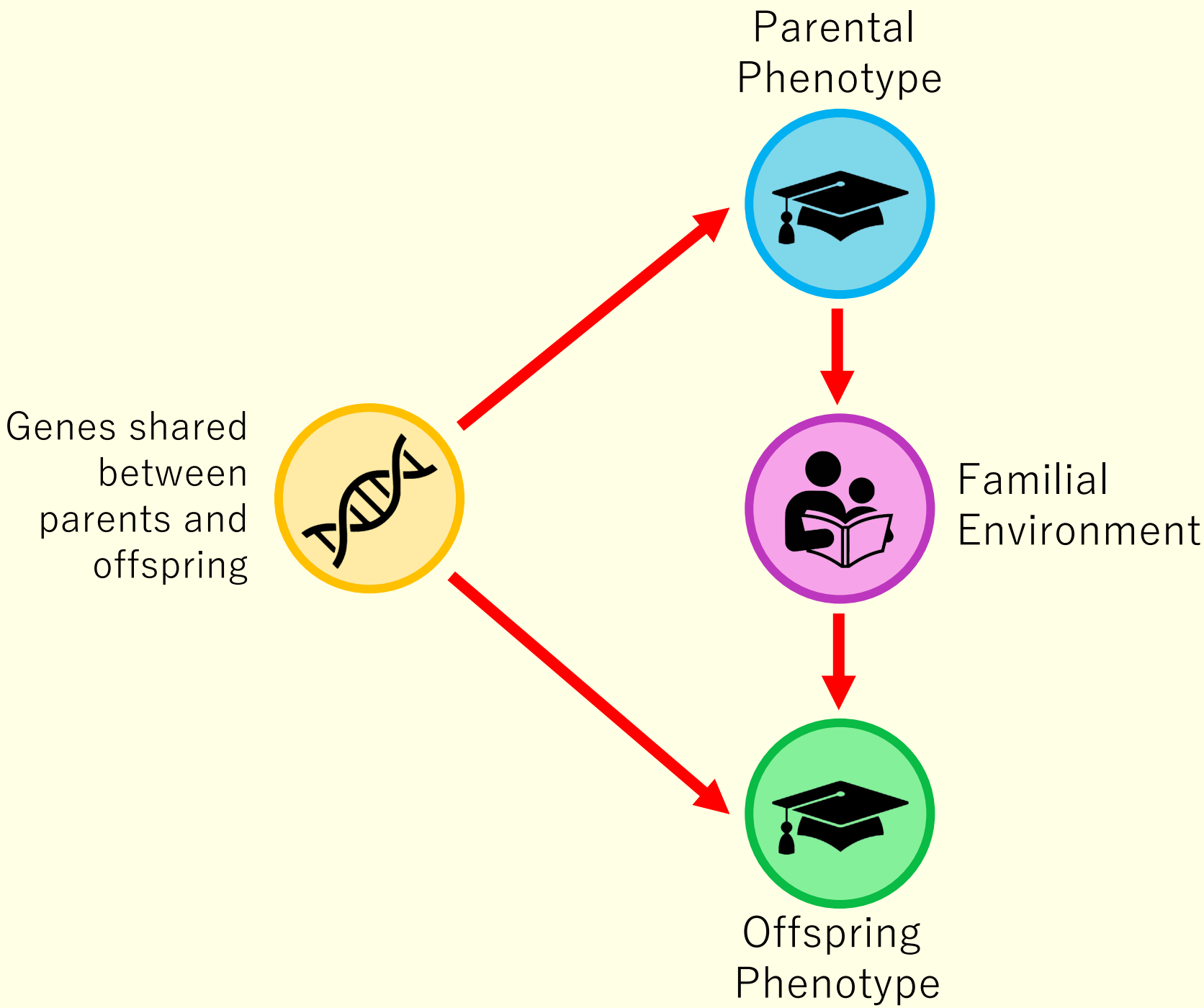
Parental
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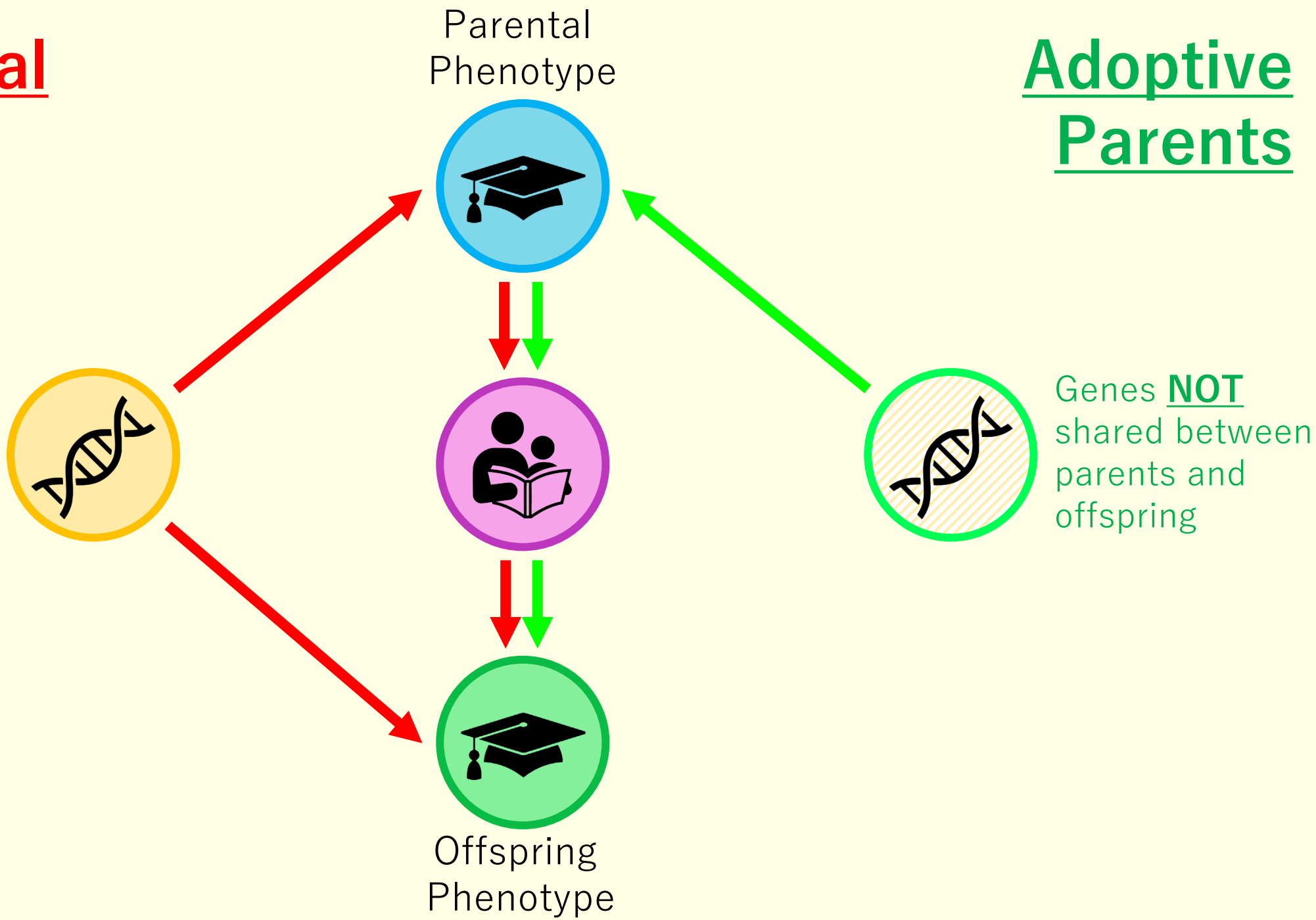
Phenotype

Biological Parents

Adoptive Parents



”All models are wrong, some are useful.”

— George E.P. Box

— Mike Hunter

— Sarah Medland

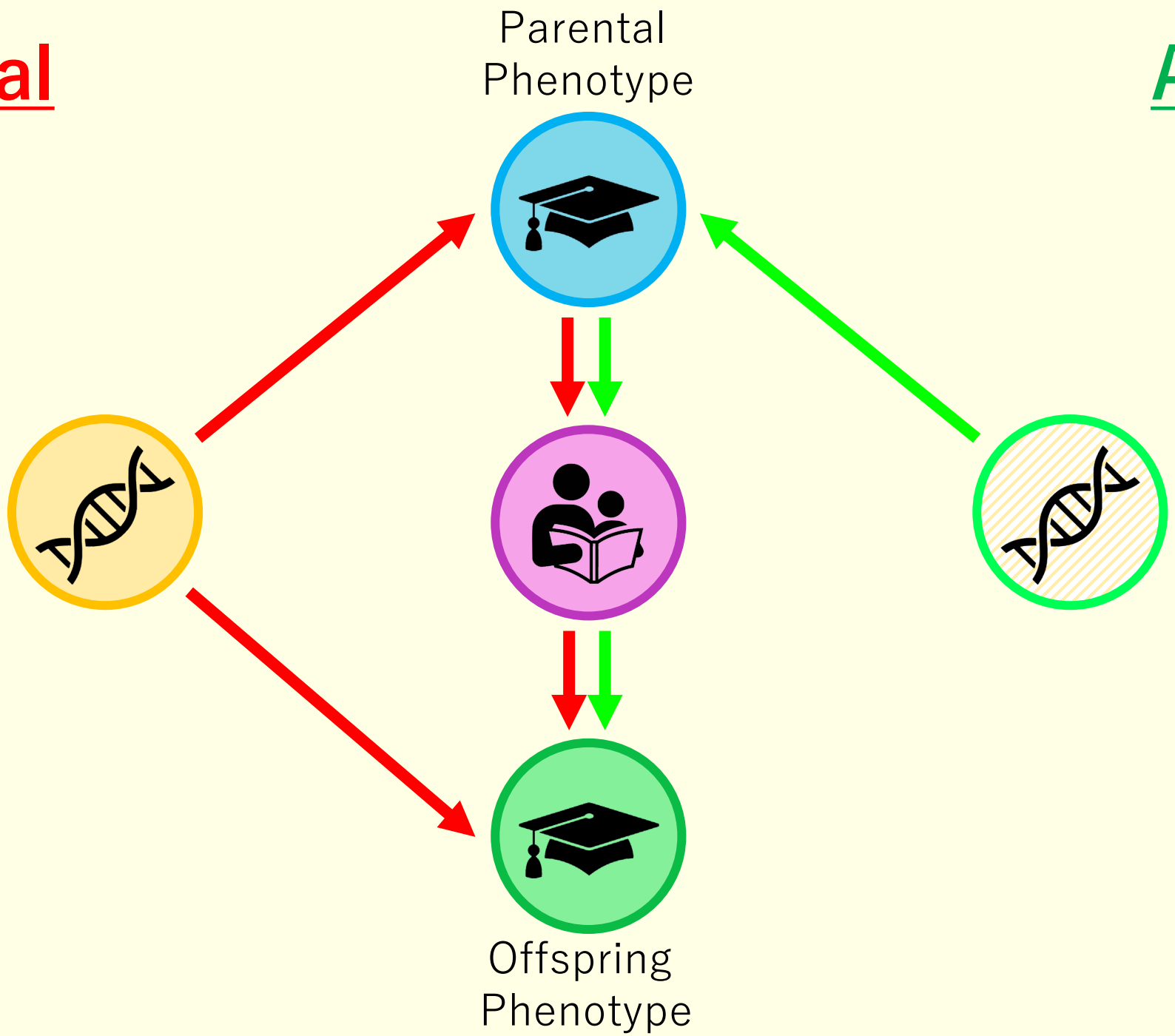
— Ben Neale

— Matt Keller

— Jared Balbona

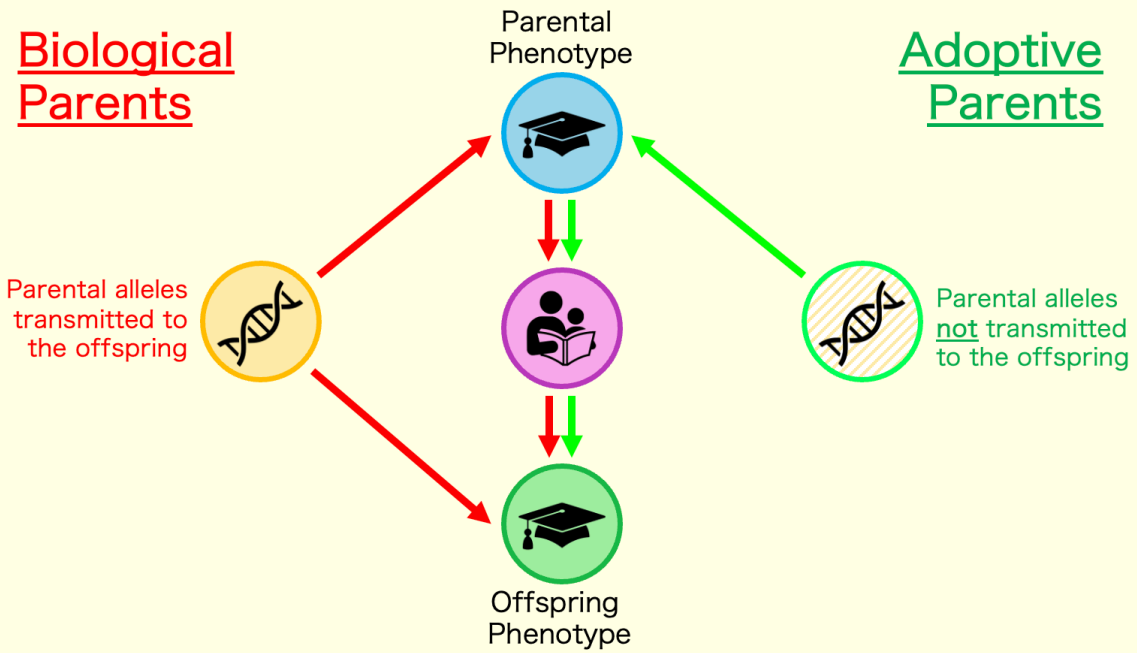
Biological Parents

Adoptive Parents



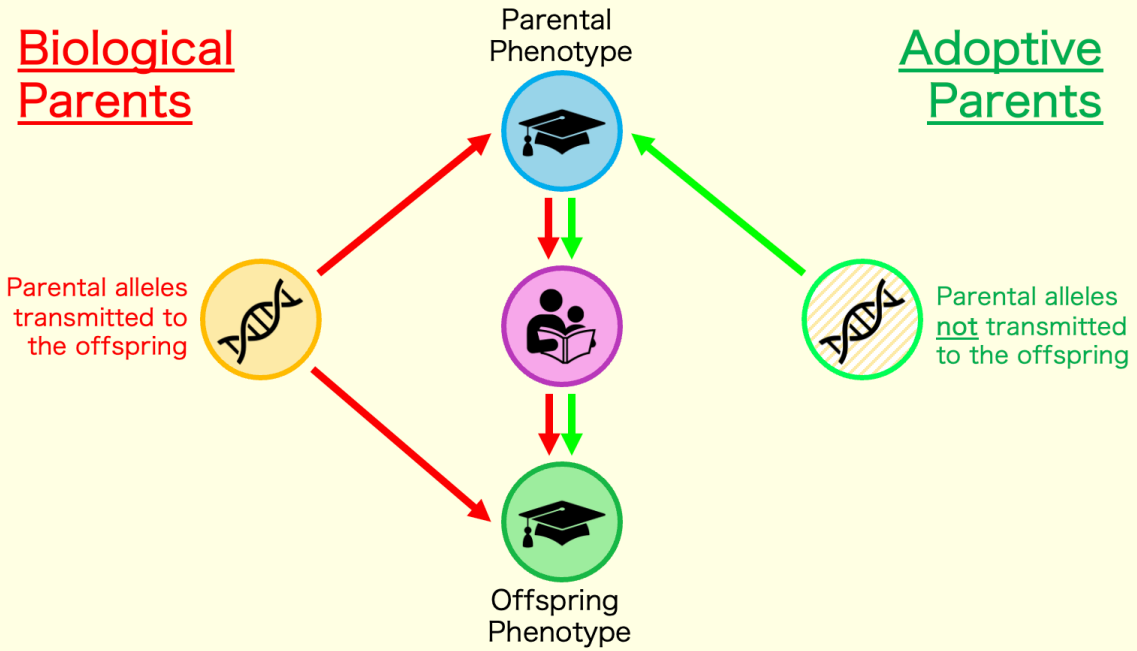
Assumptions

- Child's genotype is uncorrelated with adoptive parents'
  - No selective placement
  - No within-family adoption
- Equivalence of environments provided by biological and adoptive parents
- Random mating between the parents
- Generalizable to all individuals



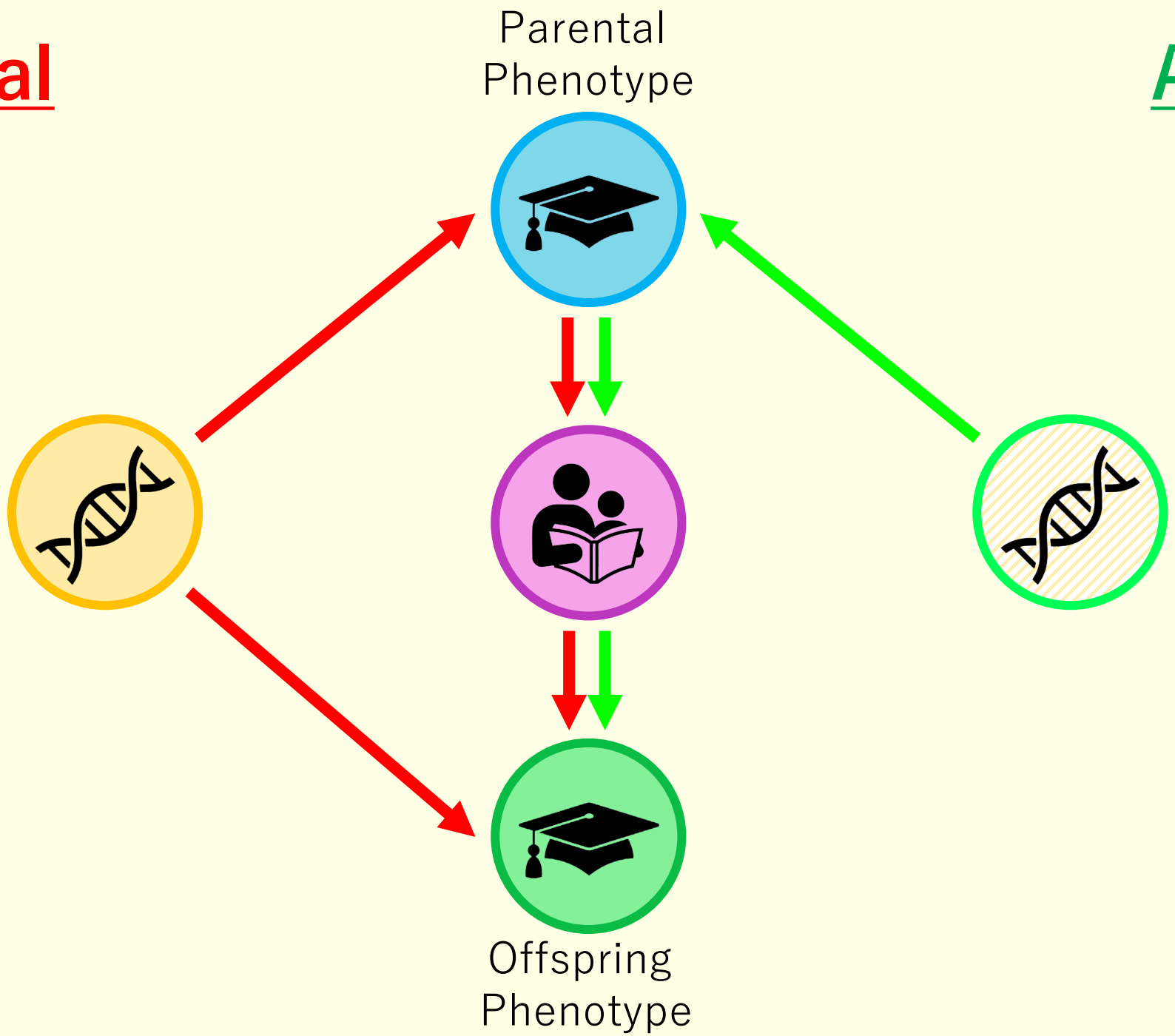
Limitations

- **Difficult sample to collect–**
  Often small and proprietary



Biological Parents

Adoptive Parents



International Journal of Epidemiology, 2018, 1229–1241
doi: 10.1093/ije/dyy015
Advance Access Publication Date: 13 February 2018
Original article

Methods

Using structural equation modelling to jointly estimate maternal and fetal effects on birthweight in the UK Biobank

Nicole M Warrington,[1] Rachel M Freathy,[2,3] Michael C Neale[4] and David M Evans[1,3,5]*

International Journal of Epidemiology, 2019, 861–875
doi: 10.1093/ije/dyz019
Advance Access Publication Date: 27 February 2019
Original article

Mendelian Randomization

Elucidating the role of maternal environmental exposures on offspring health and disease using two-sample Mendelian randomization

David M Evans ,[1,2,3]* Gunn-Helen Moen,[4,5] Liang-Dar Hwang,[1] Debbie A Lawlor[2,3,6] and Nicole M Warrington[1]

PLOS MEDICINE

RESEARCH ARTICLE

Assessing the Causal Relationship of Maternal Height on Birth Size and Gestational Age at Birth: A Mendelian Randomization Analysis

Ge Zhang[1,2]*, Jonas Bacelis[3], Candice Lengyel[2], Kari Teramo[4], Mikko Hallman[5], Øyvind Helgeland[6], Stefan Johansson[6,7], Ronny Myhre[8], Verena Sengpiel[3], Pål Rasmus Njølstad[6,9], Bo Jacobsson[8,10], Louis Muglia[2]*

RESEARCH

HUMAN GENOMICS

The nature of nurture: Effects of parental genotypes

Augustine Kong,[1,2,3]* Gudmar Thorleifsson,[1] Michael L. Frigge,[1] Bjarni J. Vilhjalmsson,[4,5] Alexander I. Young,[1,2,6] Thorgeir E. Thorgeirsson,[1] Stefania Benonisdottir,[1] Asmundur Oddsson,[1] Bjarni V. Halldorsson,[1] Gisli Masson,[1] Daniel F. Gudbjartsson,[1,3] Agnar Helgason,[1,7] Gyda Bjornsdottir,[1] Unnur Thorsteinsdottir,[1,8] Kari Stefansson[1,8]*

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Maternal Genotype

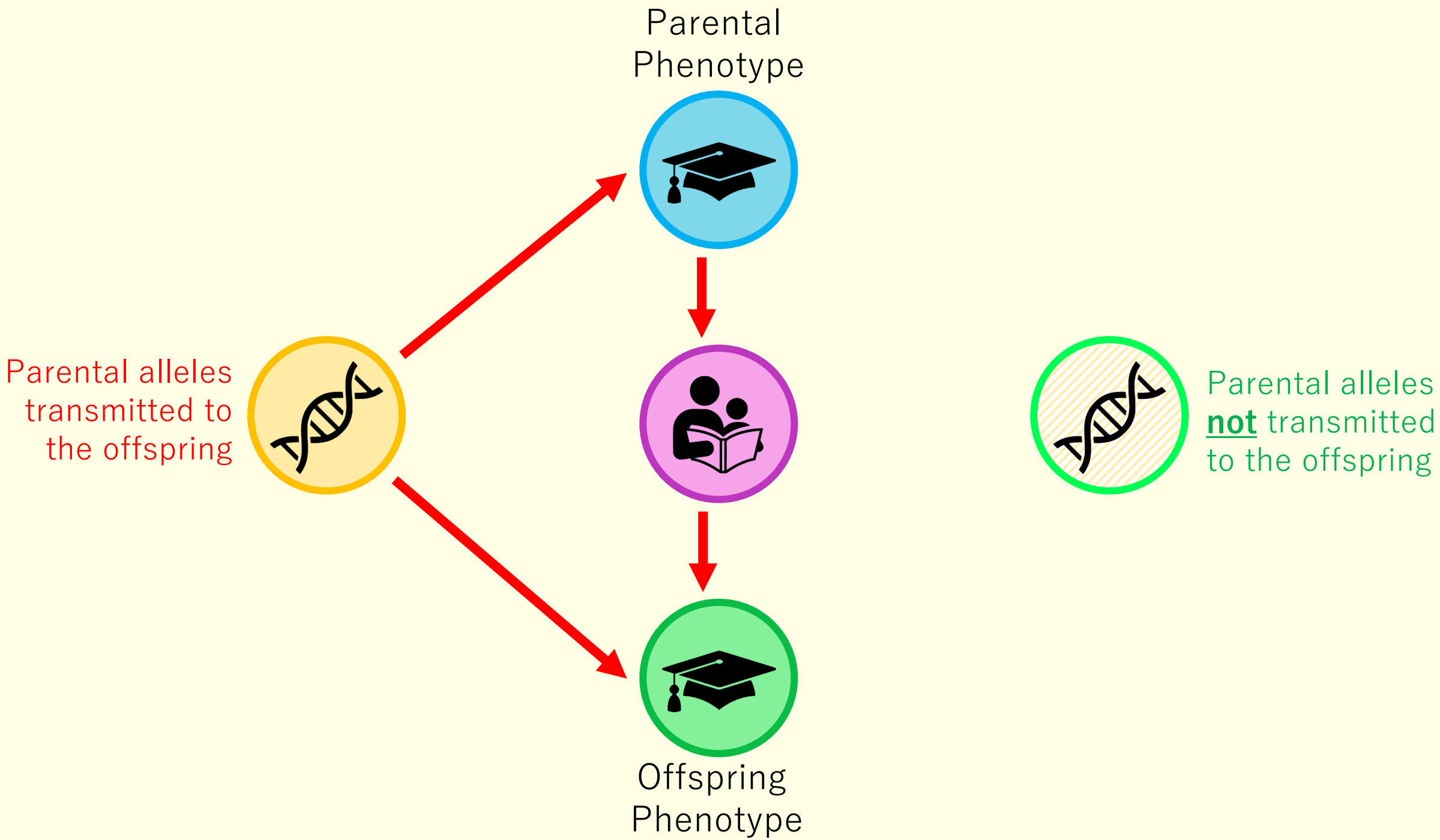
Parental alleles transmitted to the offspring

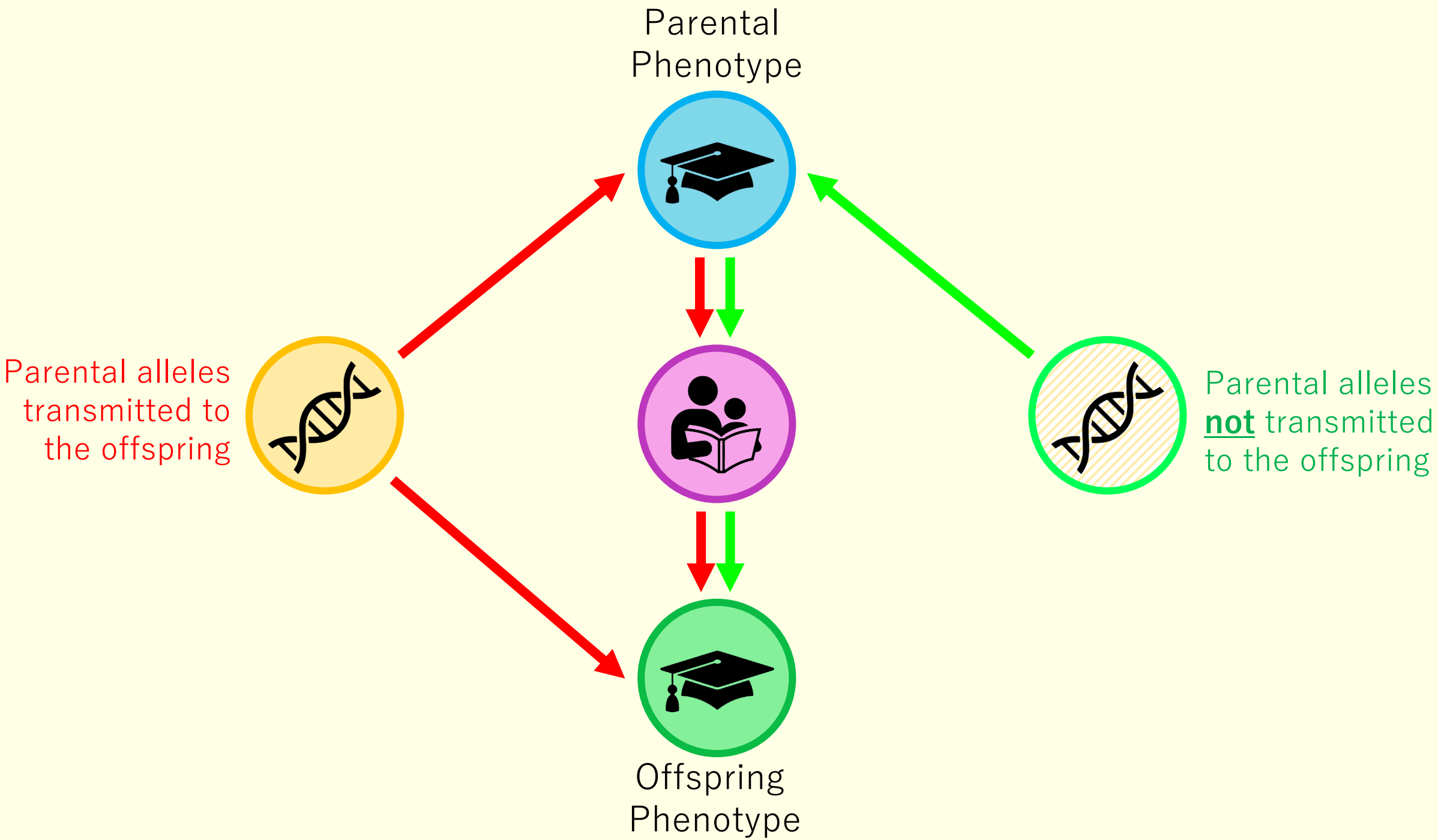
Parental alleles **not** transmitted to the offspring

Paternal Genotype

Parental alleles transmitted to the offspring

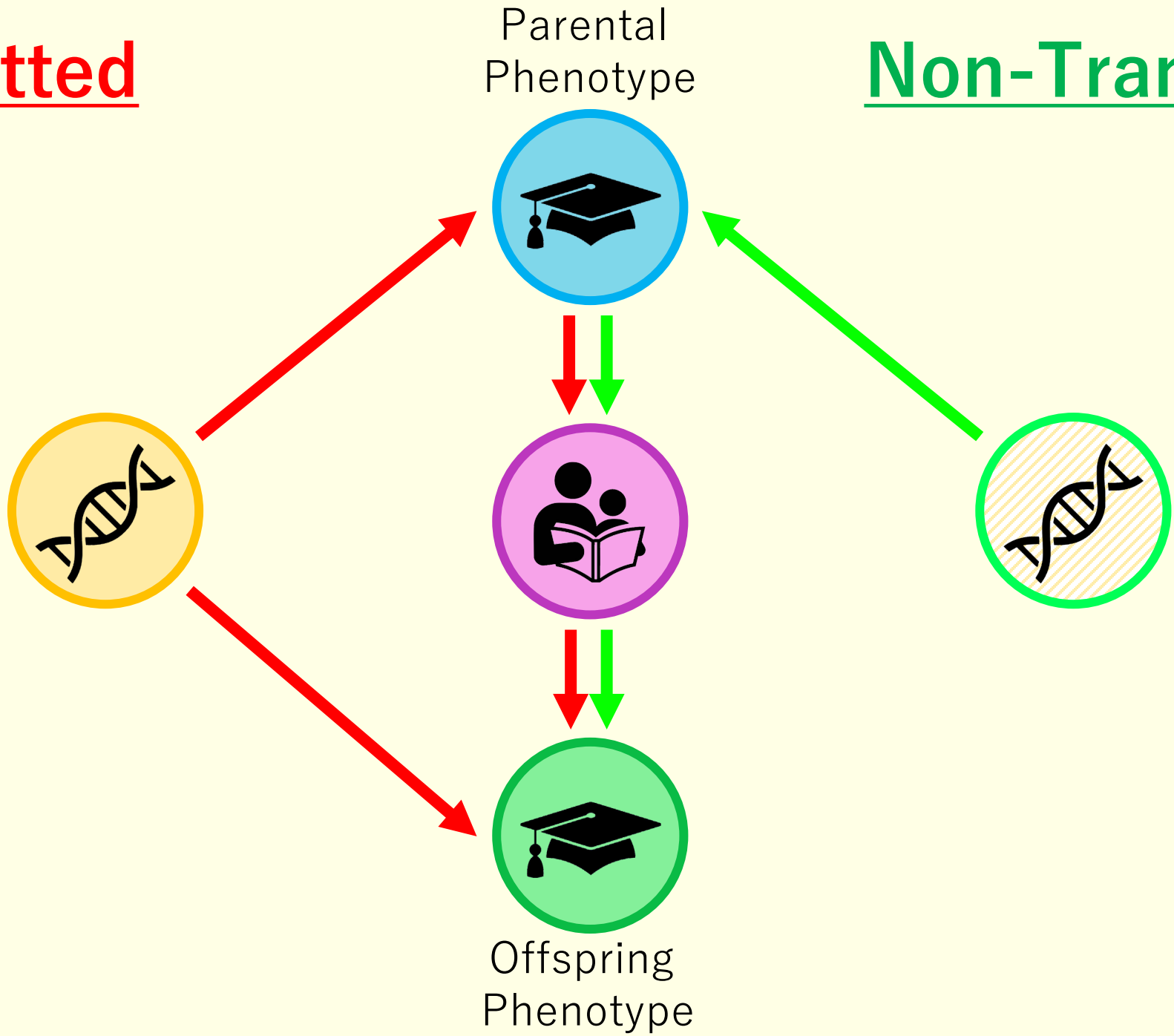
Parental alleles **not** transmitted to the offspring


Parental
Phenotype
Parental alleles
transmitted to
the offspring
Parental alleles
not transmitted
to the offspring
Offspring
Phenotype


Parental
Phenotype
Parental alleles
transmitted to
the offspring
Parental alleles
not transmitted
to the offspring
Offspring
Phenotype

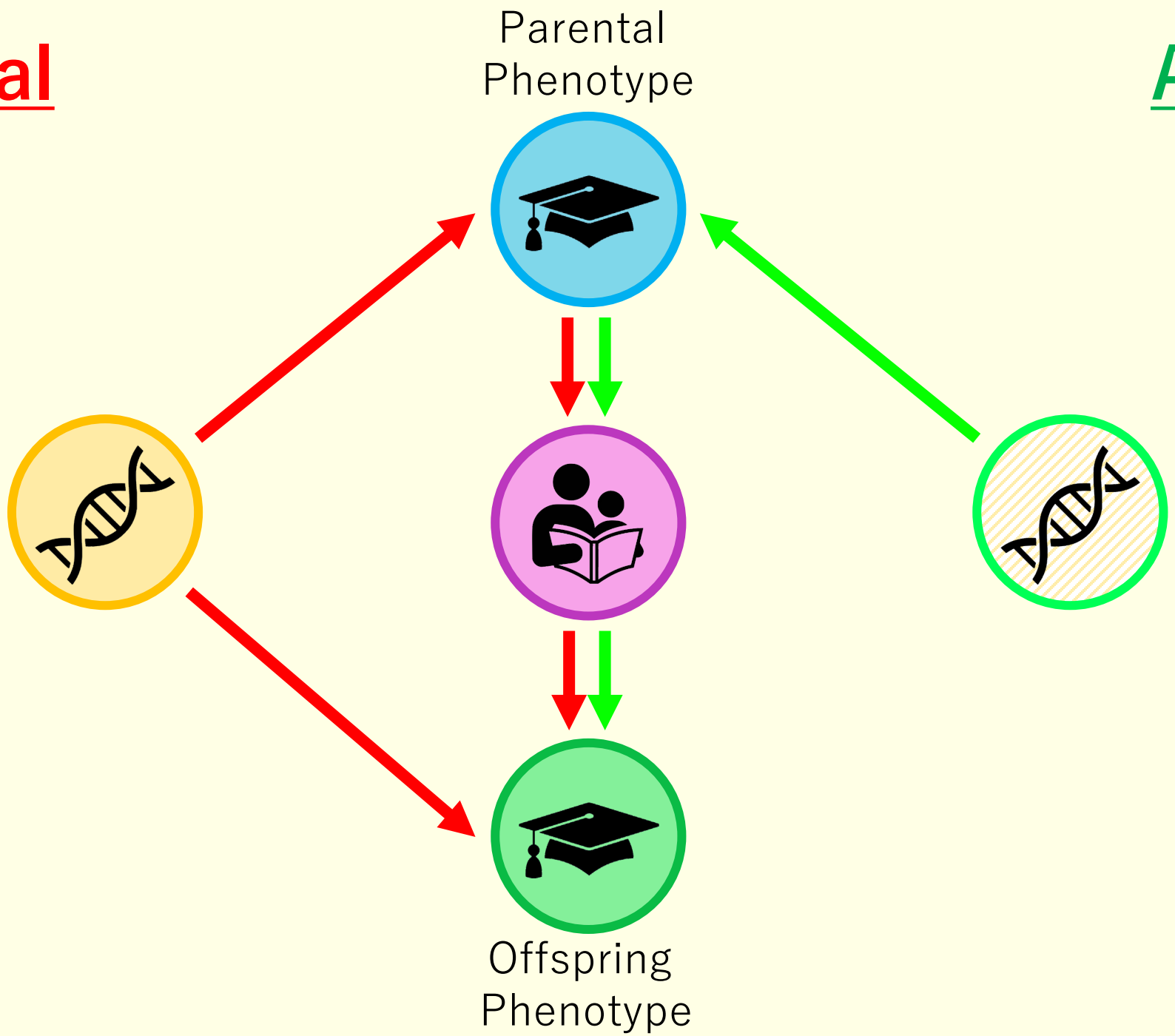
Transmitted Alleles

Non-Transmitted Alleles



Biological Parents

Adoptive Parents



Kong et al. Model

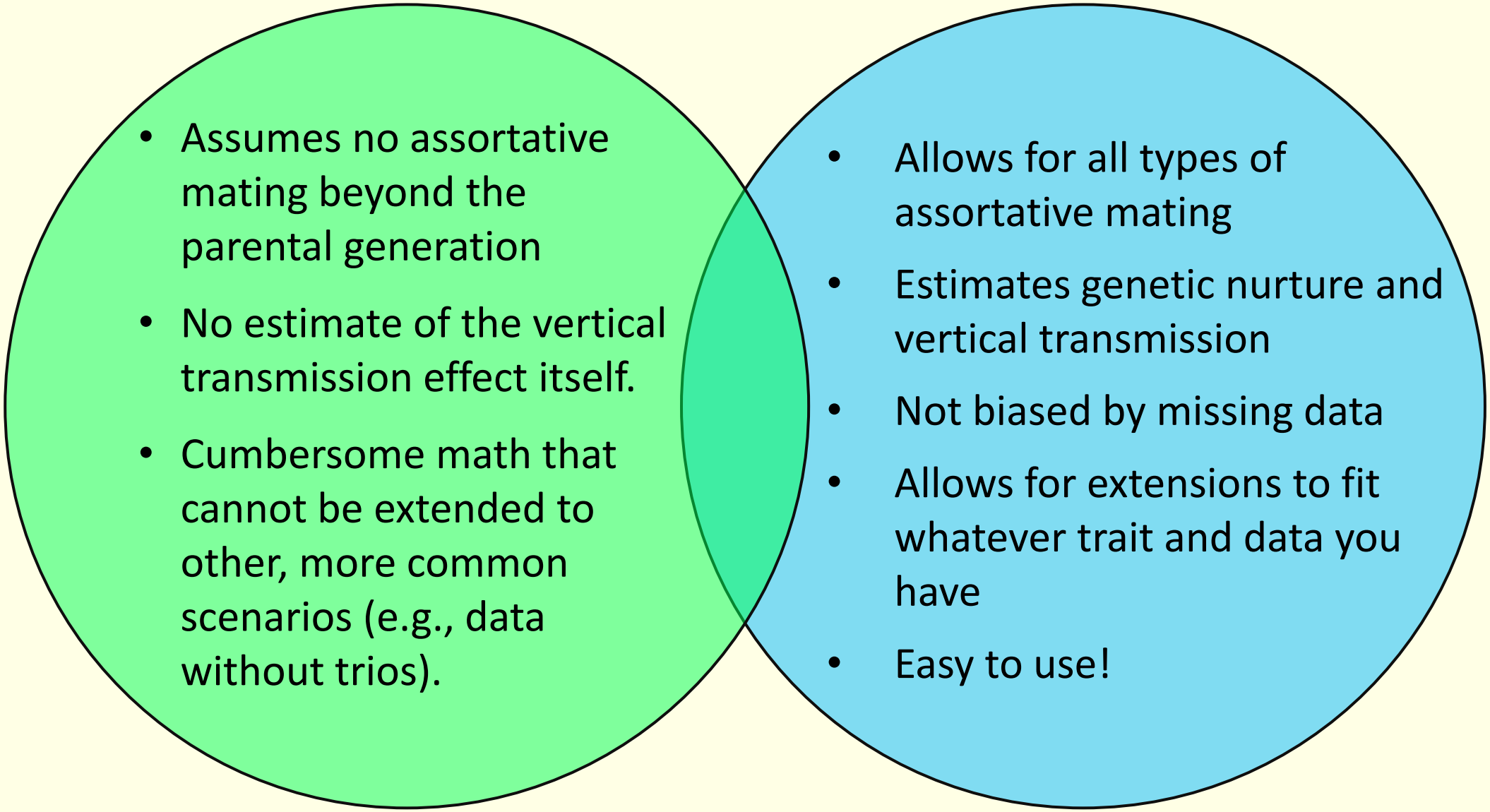
- Assumes no assortative mating beyond the parental generation
- No estimate of the vertical transmission effect itself.
- Cumbersome math that cannot be extended to other, more common scenarios (e.g., data without trios).

ORIGINAL RESEARCH

Estimation of Parental Effects Using Polygenic Scores

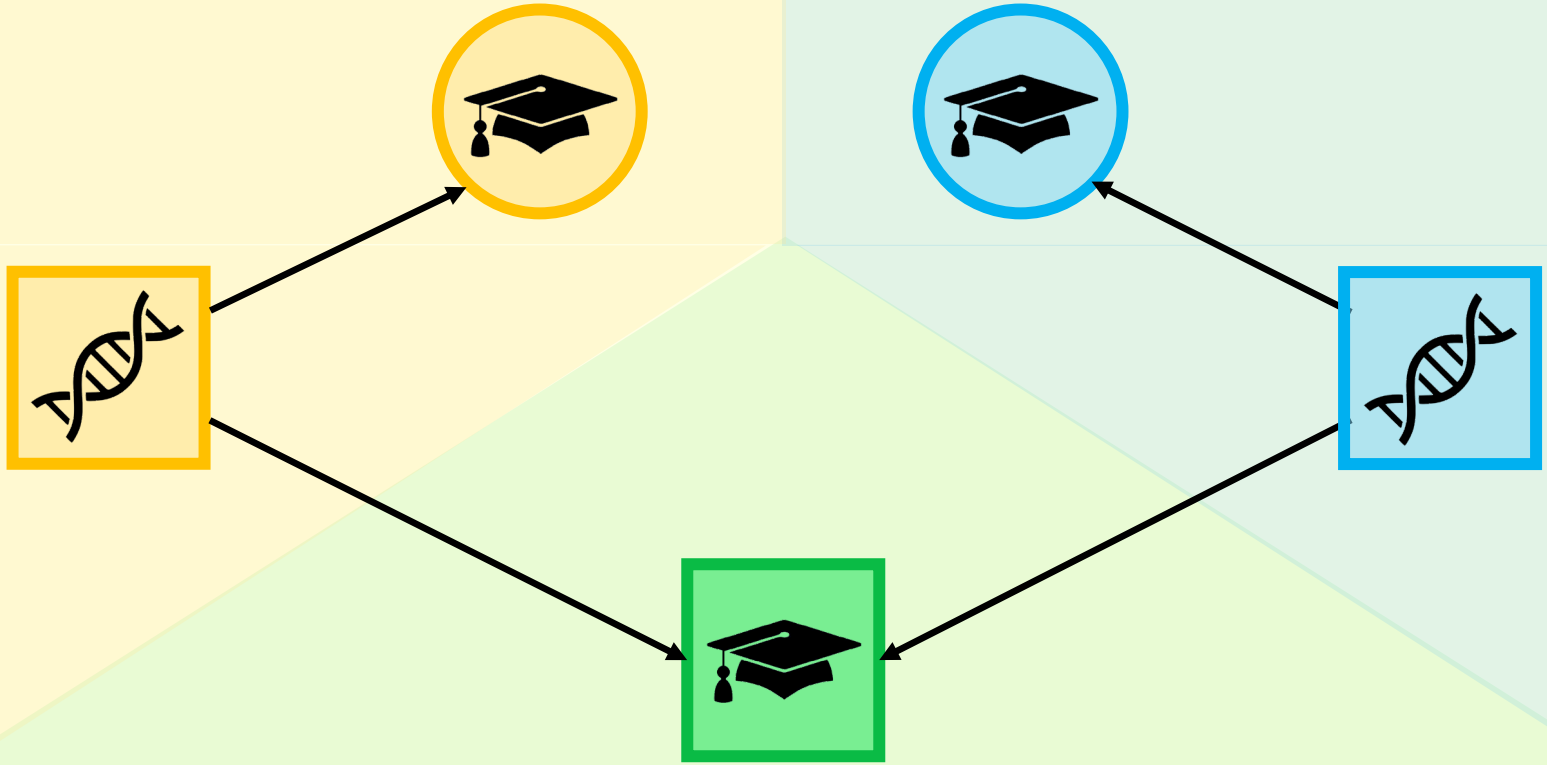
Jared V. Balbona[1,2] · Yongkang Kim[1] · Matthew C. Keller[1,2]

Received: 7 August 2020 / Accepted: 20 November 2020 / Published online: 2 January 2021

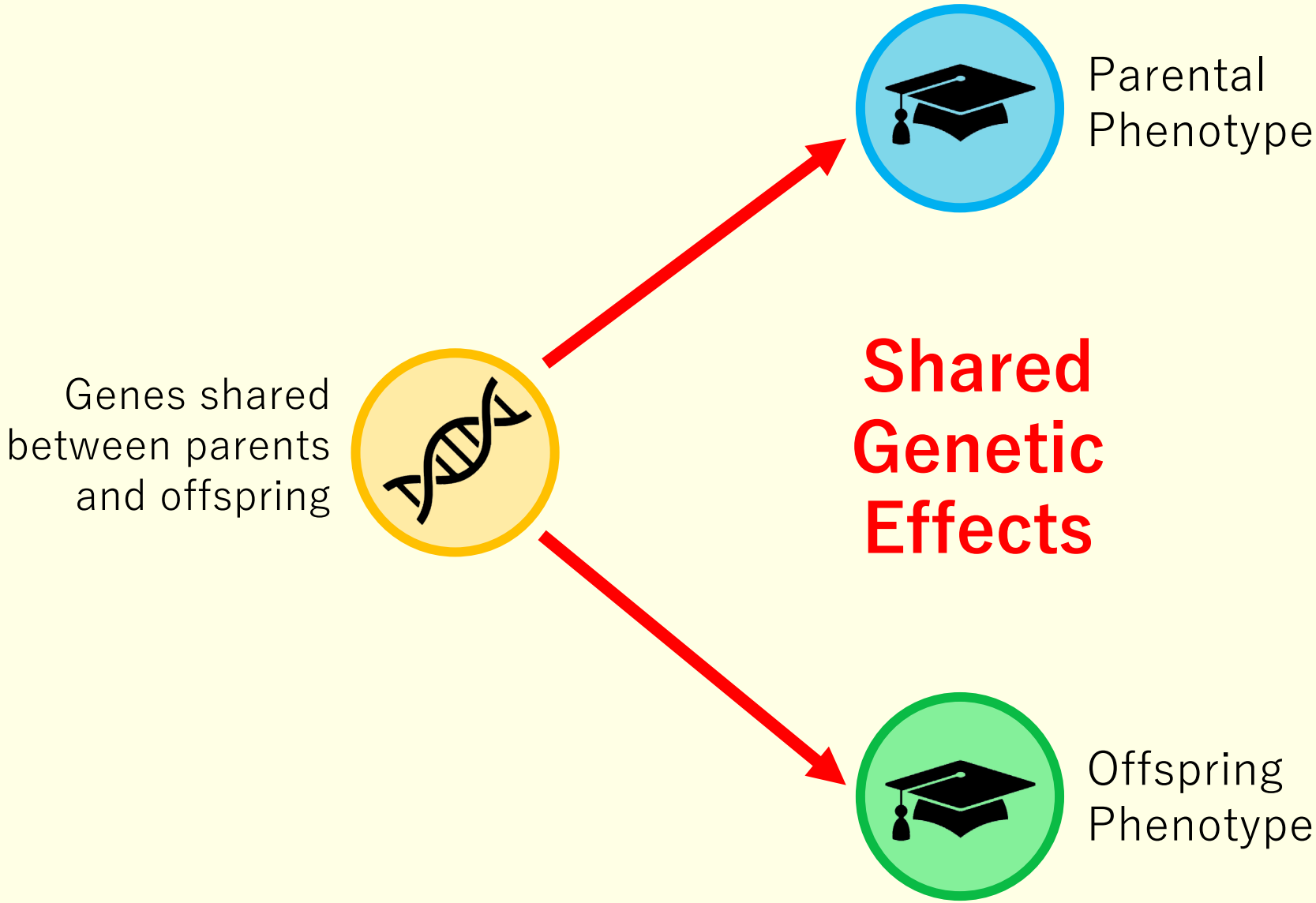

Kong et al. Model
SEM-PGS Model
• Assumes no assortative mating beyond the parental generation
• No estimate of the vertical transmission effect itself.
• Cumbersome math that cannot be extended to other, more common scenarios (e.g., data without trios).
• Allows for all types of assortative mating
• Estimates genetic nurture and vertical transmission
• Not biased by missing data
• Allows for extensions to fit whatever trait and data you have
• Easy to use!

Paternal

Maternal



Offspring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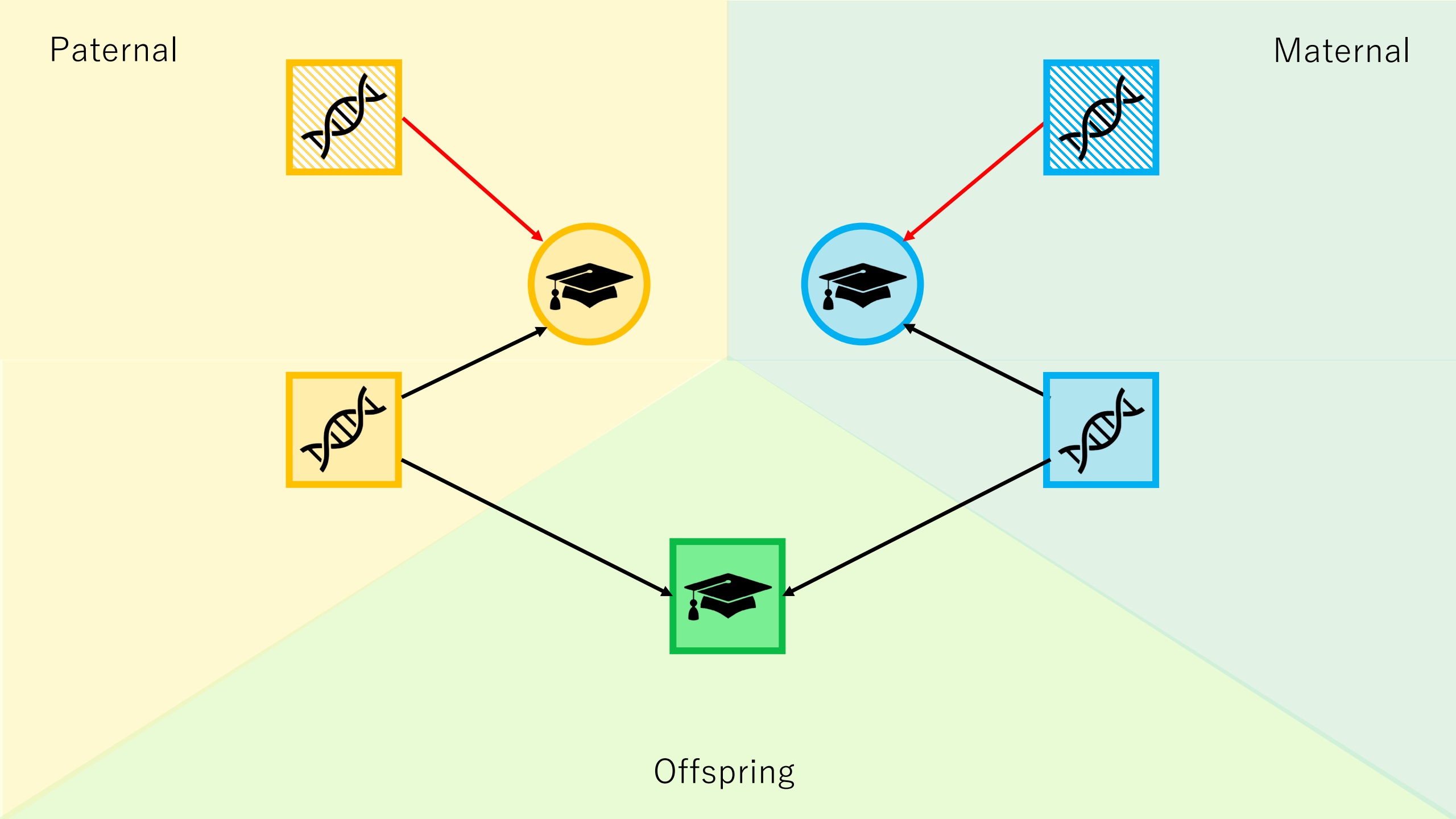
Paternal
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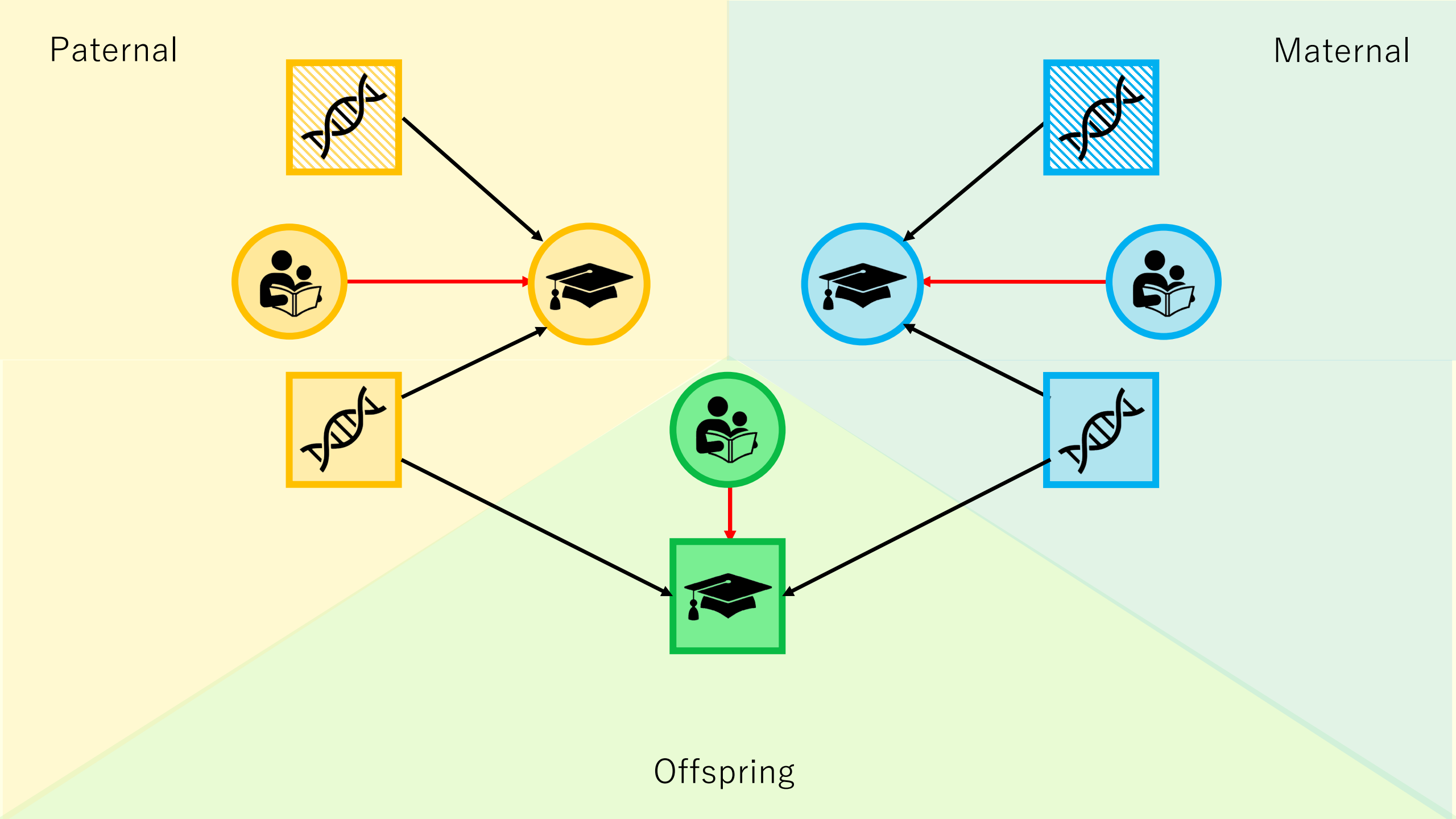
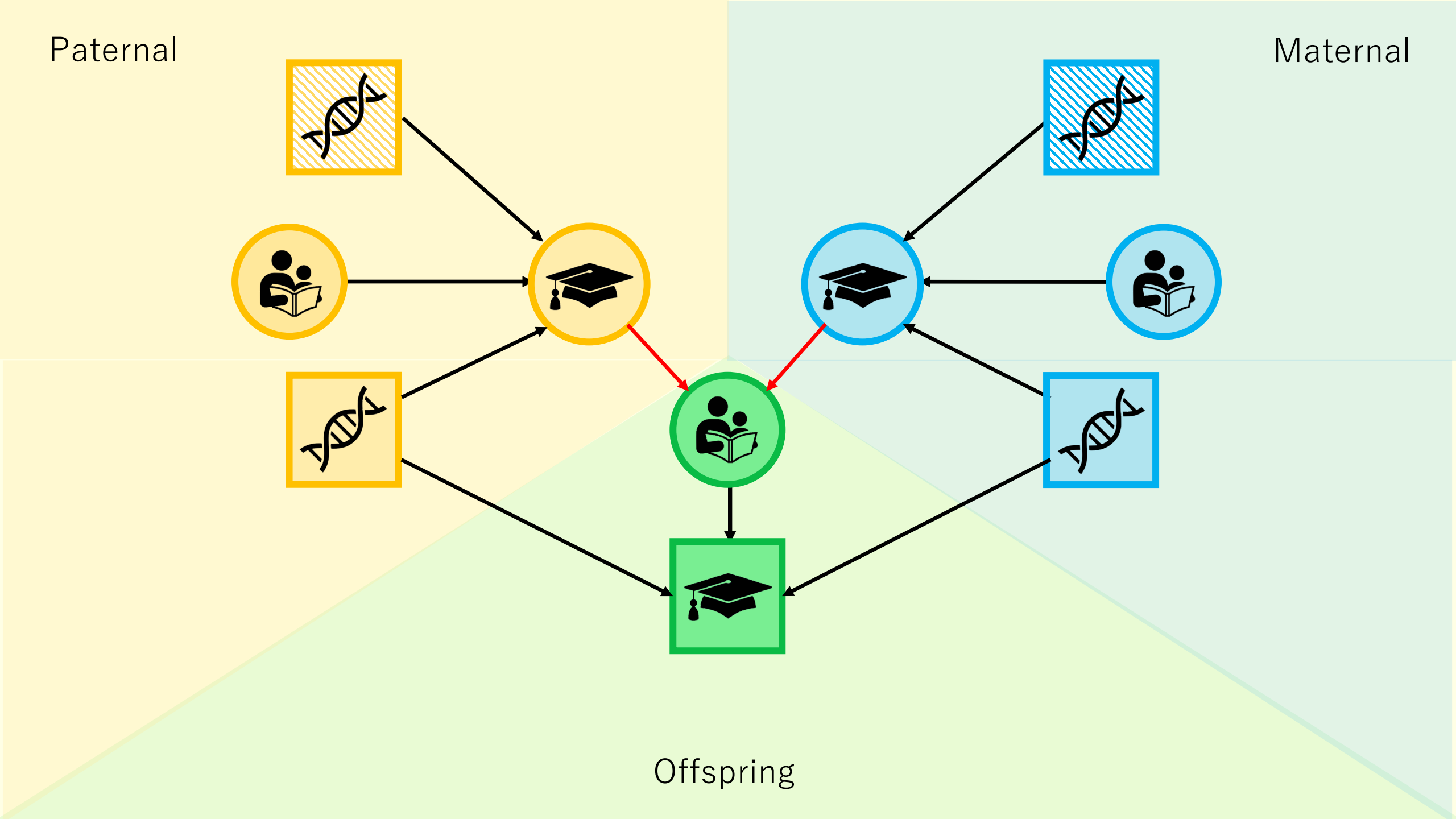
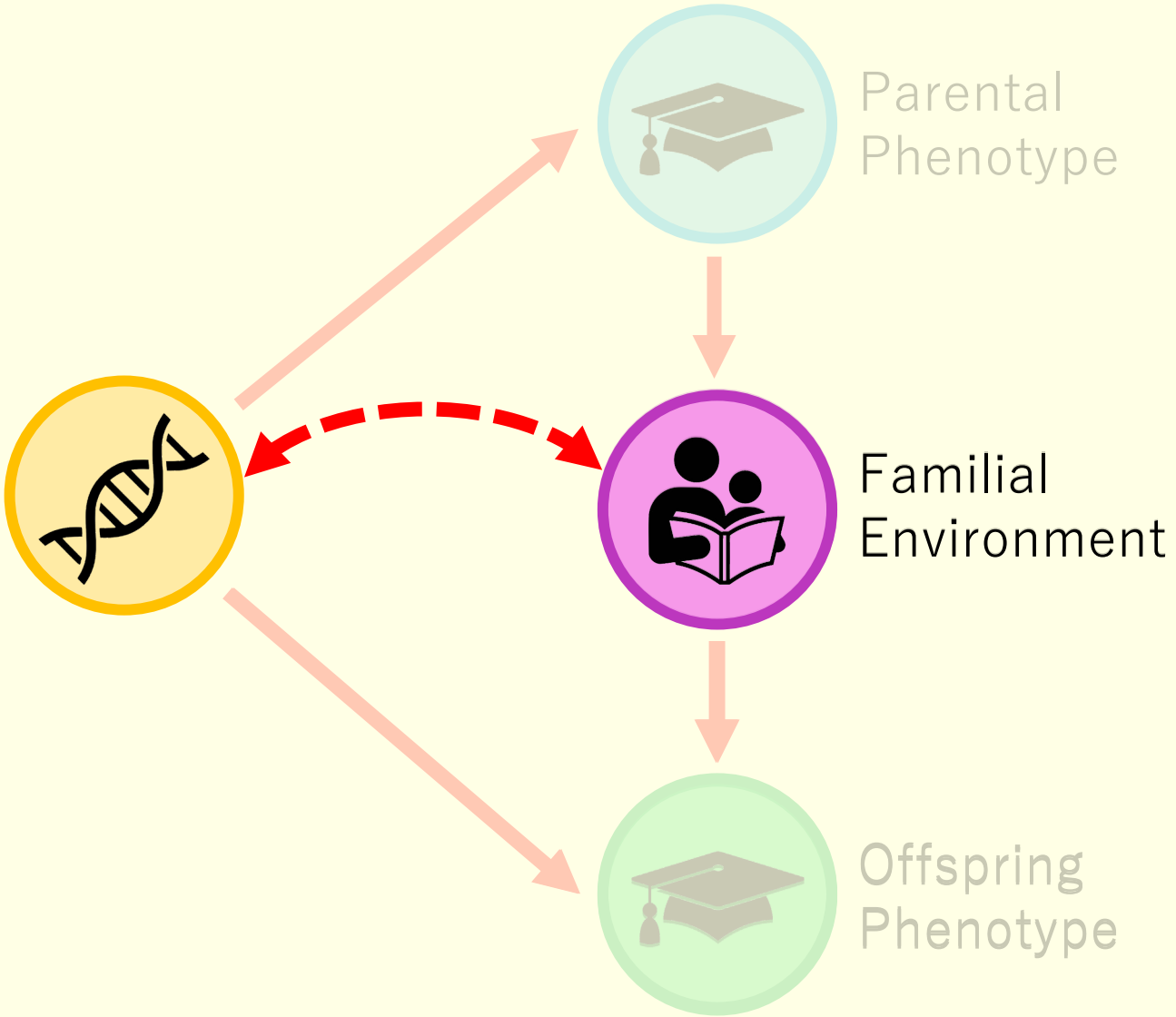
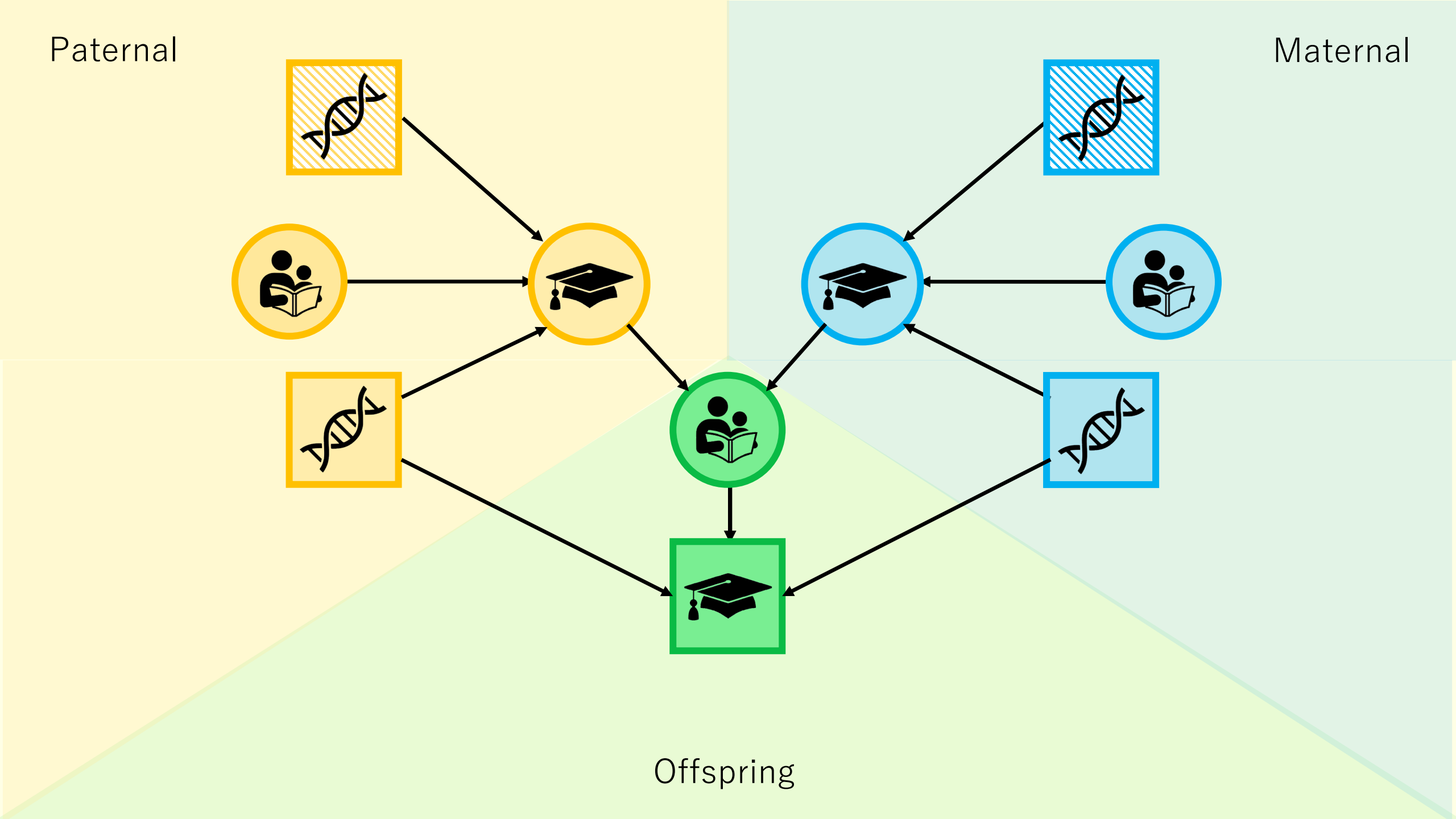

Paternal
Maternal
Offspring

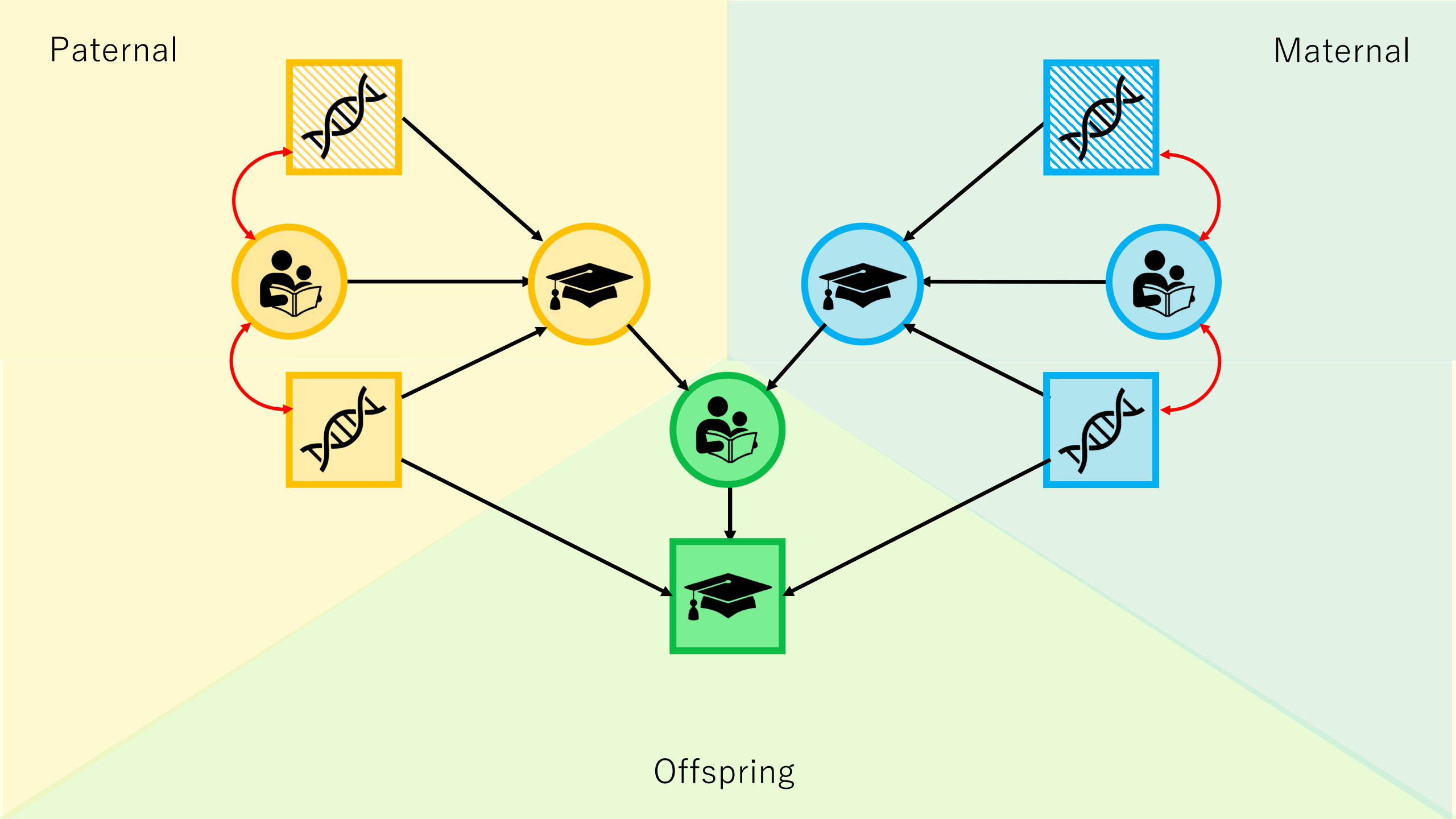

Paternal
Maternal
Offspring

Genetic Nurture

A type of Passive Gene-Environment Covariance




Paternal
Maternal
Offspring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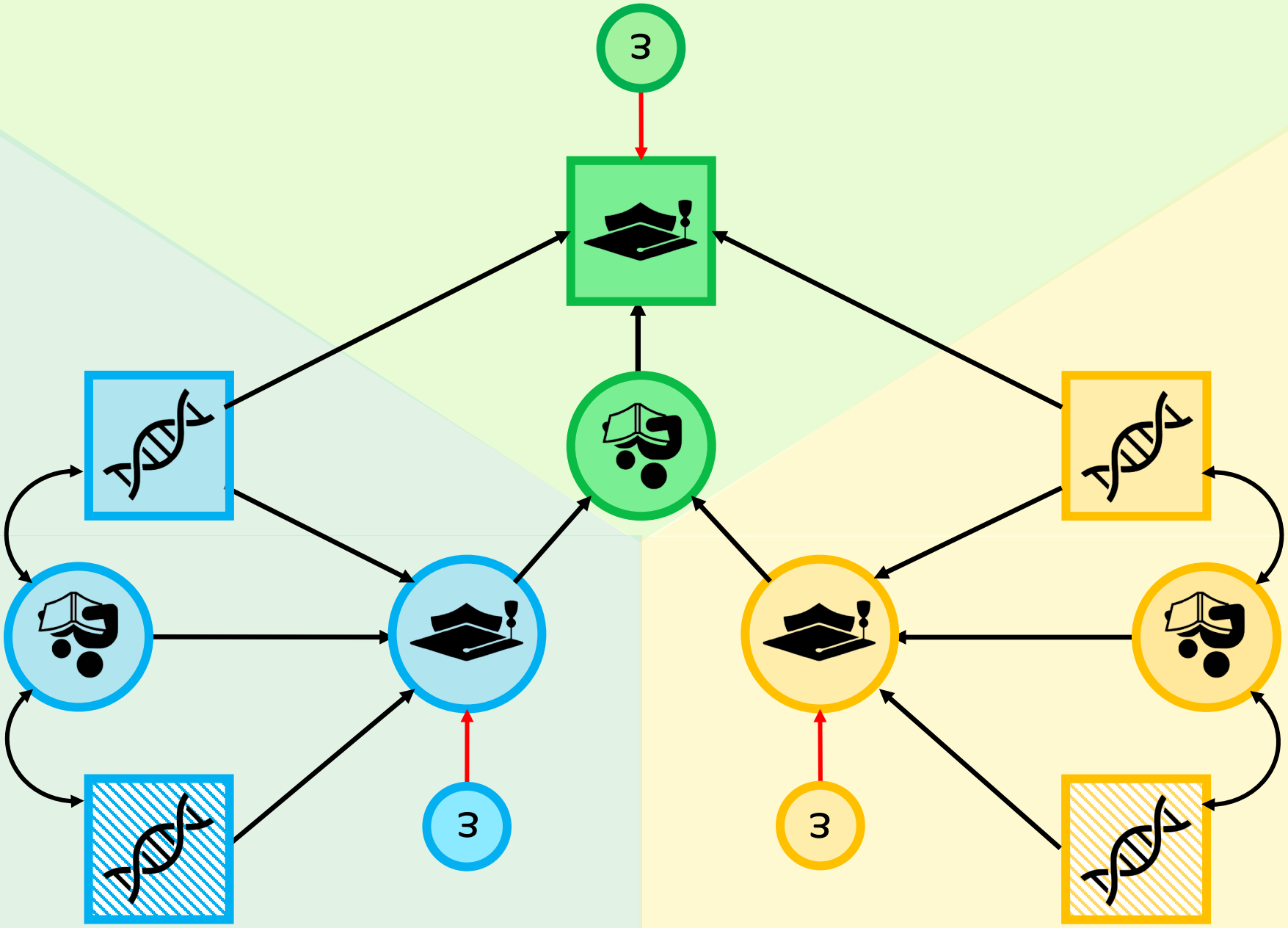
3
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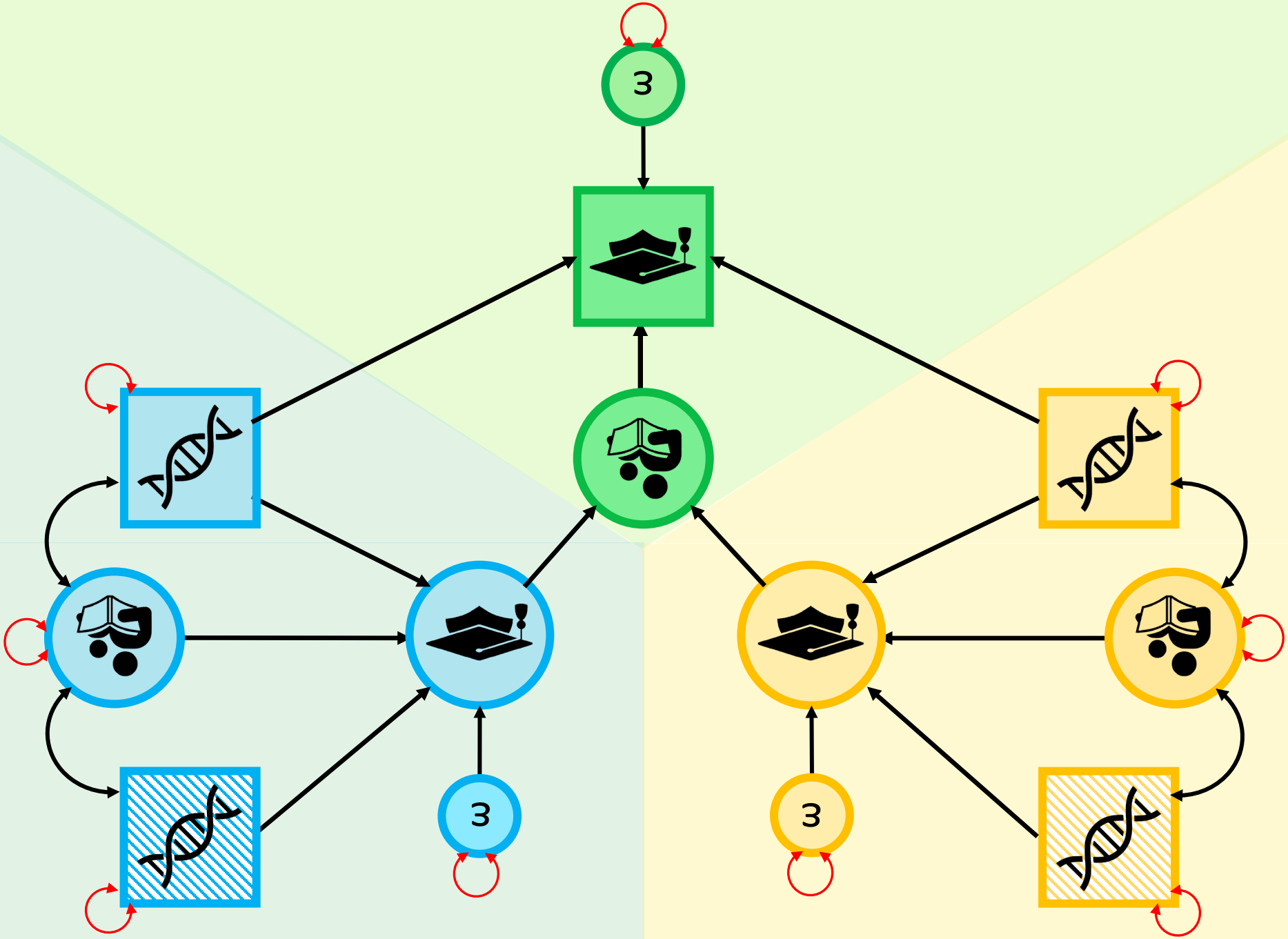
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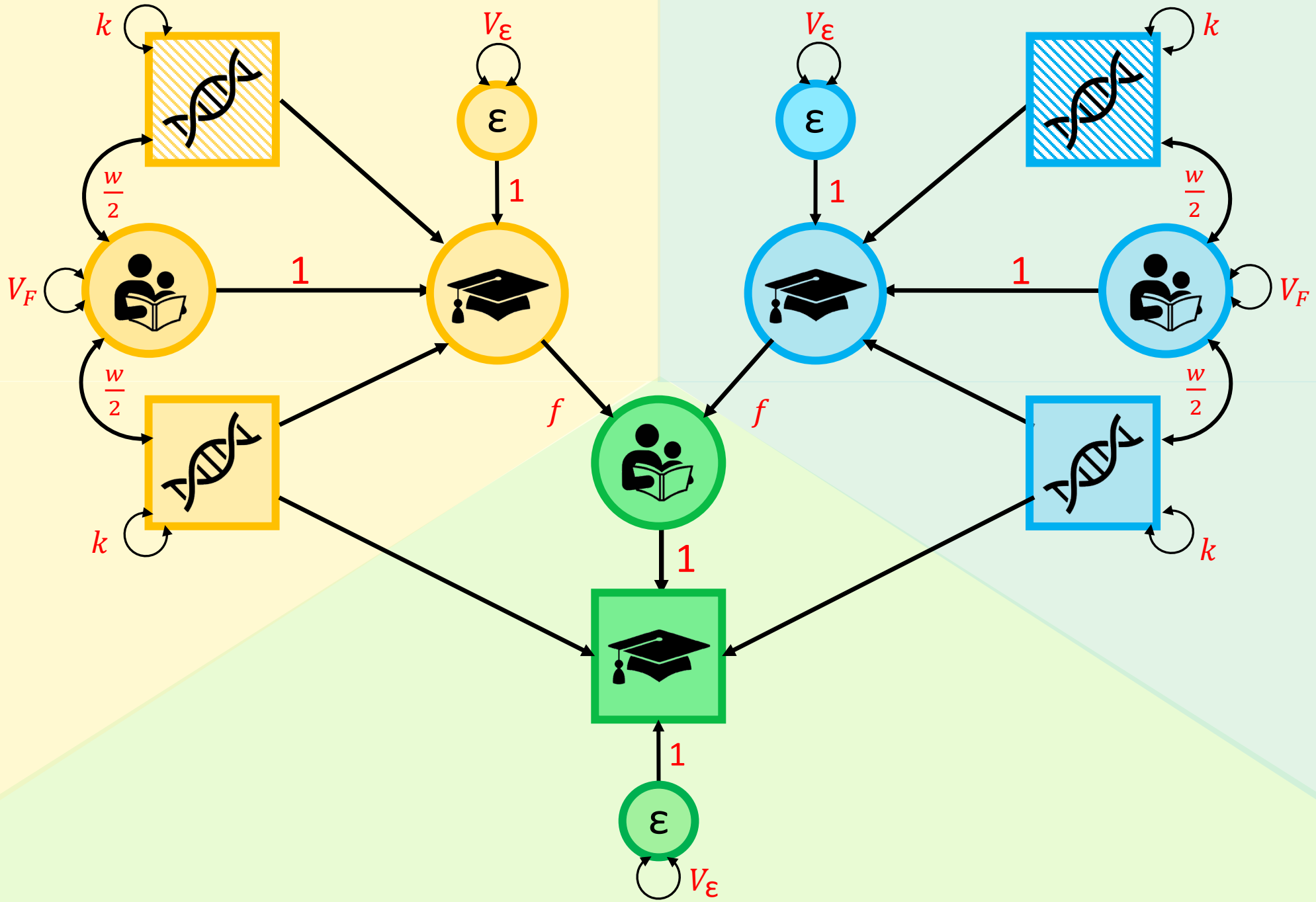
k
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V_ε
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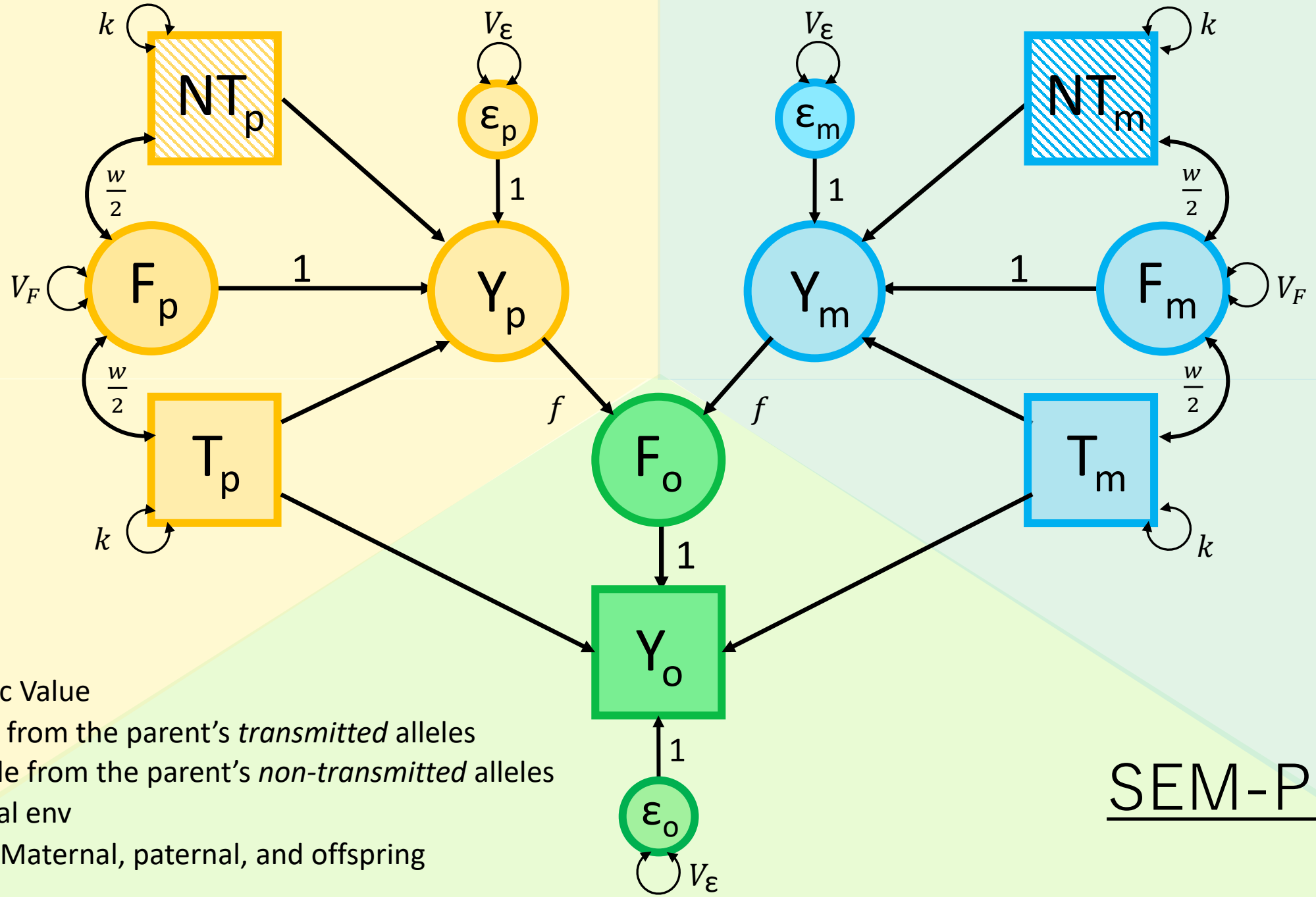
k
k
1
1
ε
V_ε



Y: Phenotypic Value

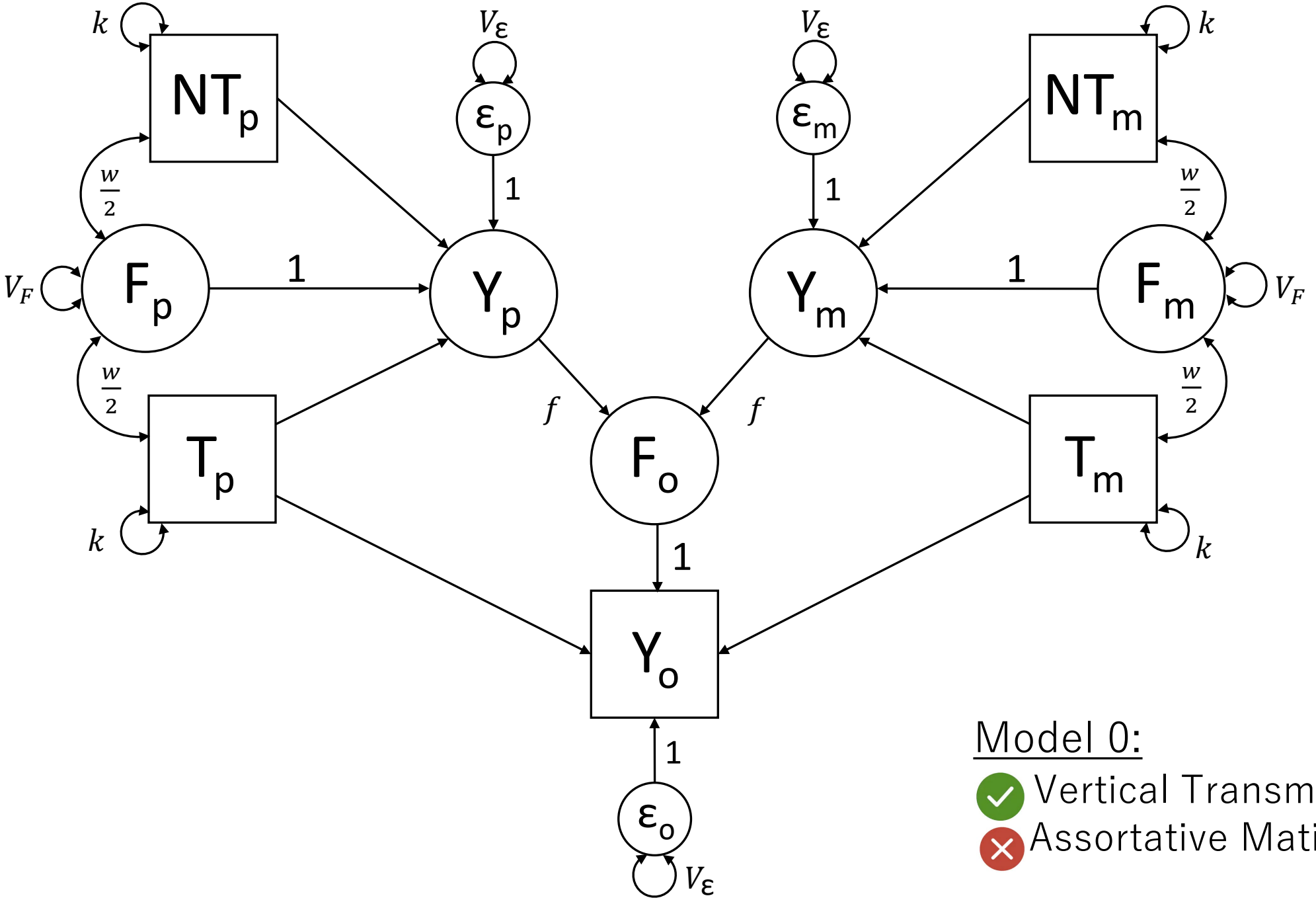
T: PGS made from the parent's *transmitted* alleles

NT: PGS made from the parent's *non-transmitted* alleles

F: The familial env

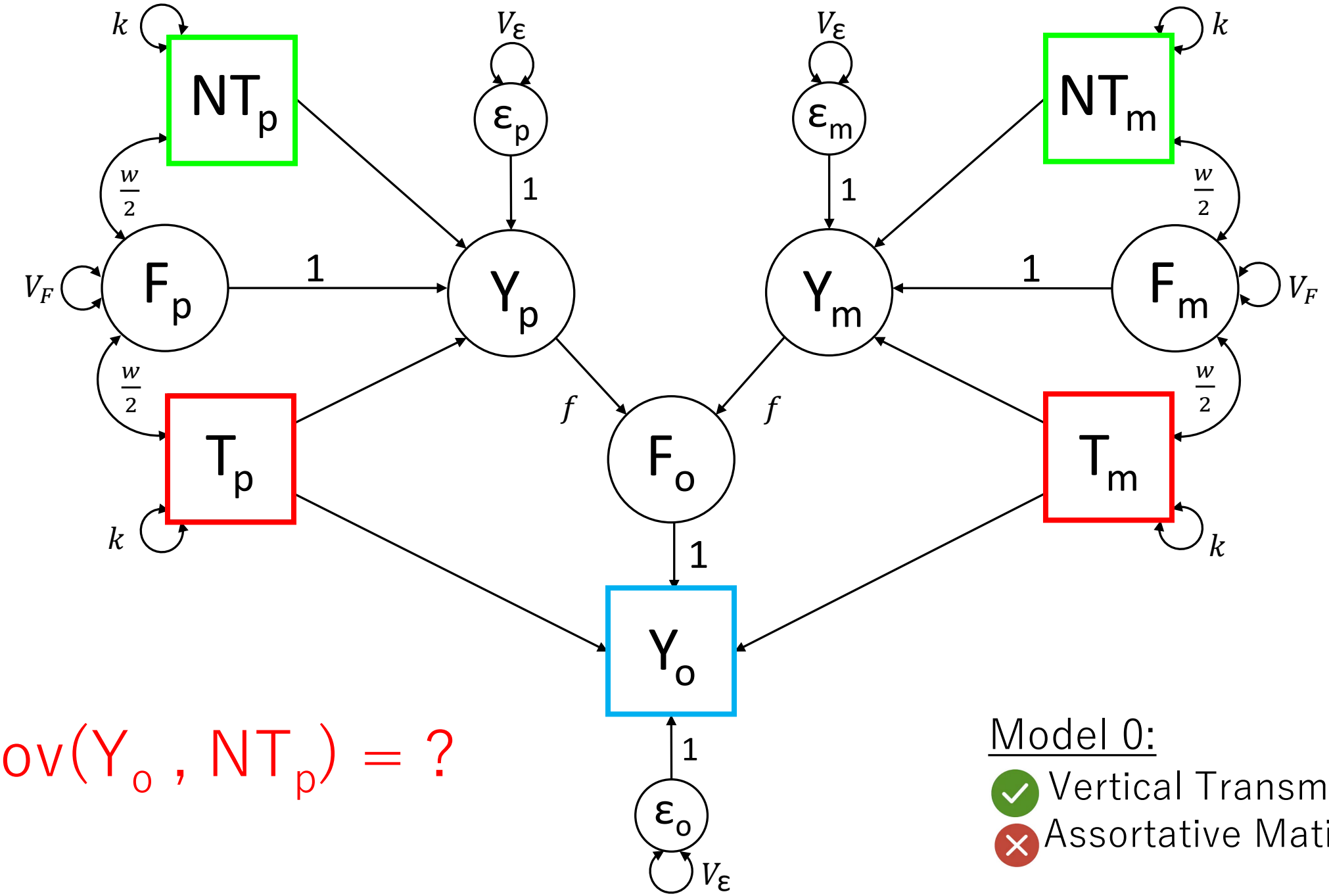
m, p, and o: Maternal, paternal, and offspring

SEM-PGS



Model 0:

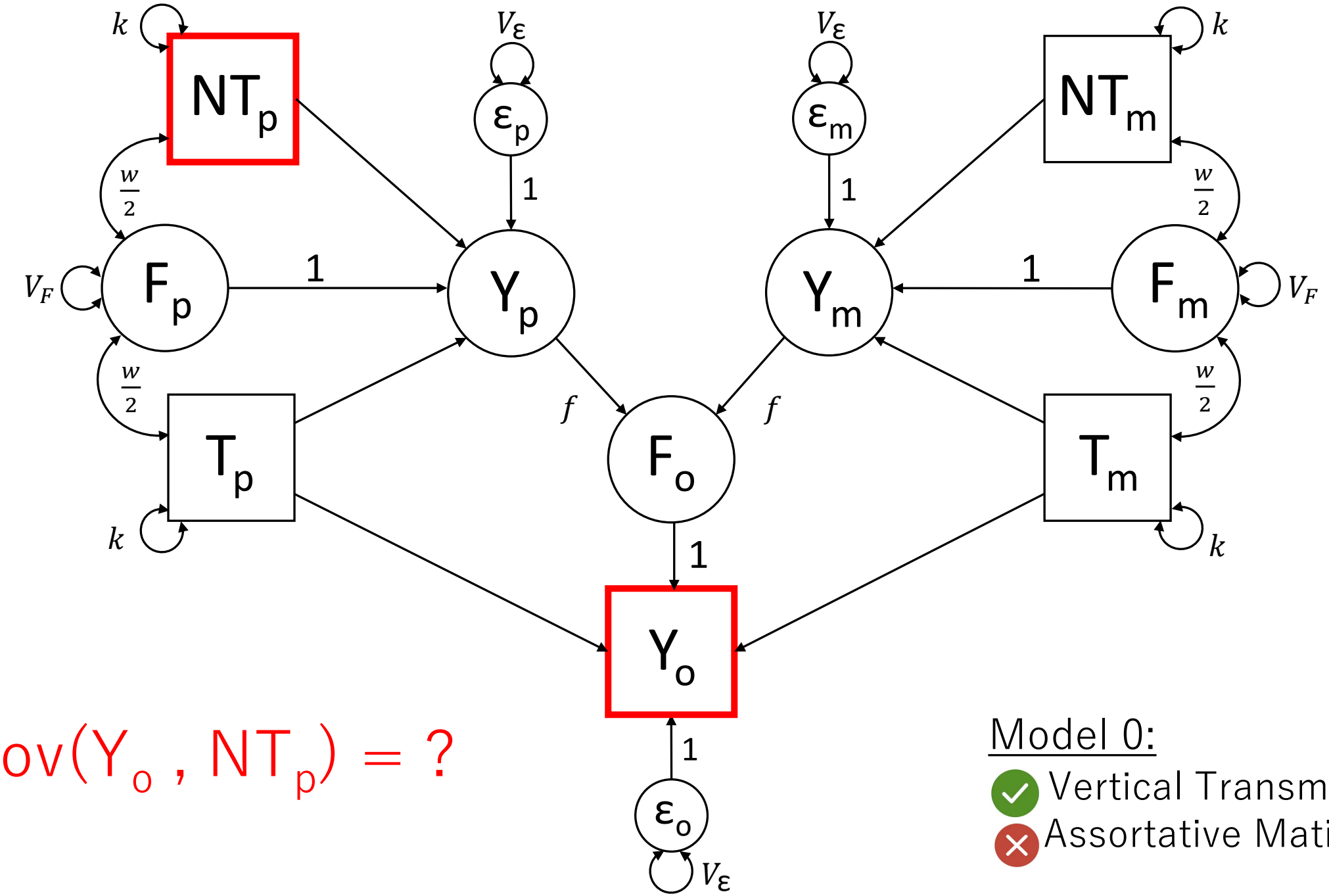
- Vertical Transmission
- Assortative Mating



$\mathrm{cov}(Y_o, NT_p) = ?$

Model 0:

- ✓ Vertical Transmission
- ✗ Assortative Mating



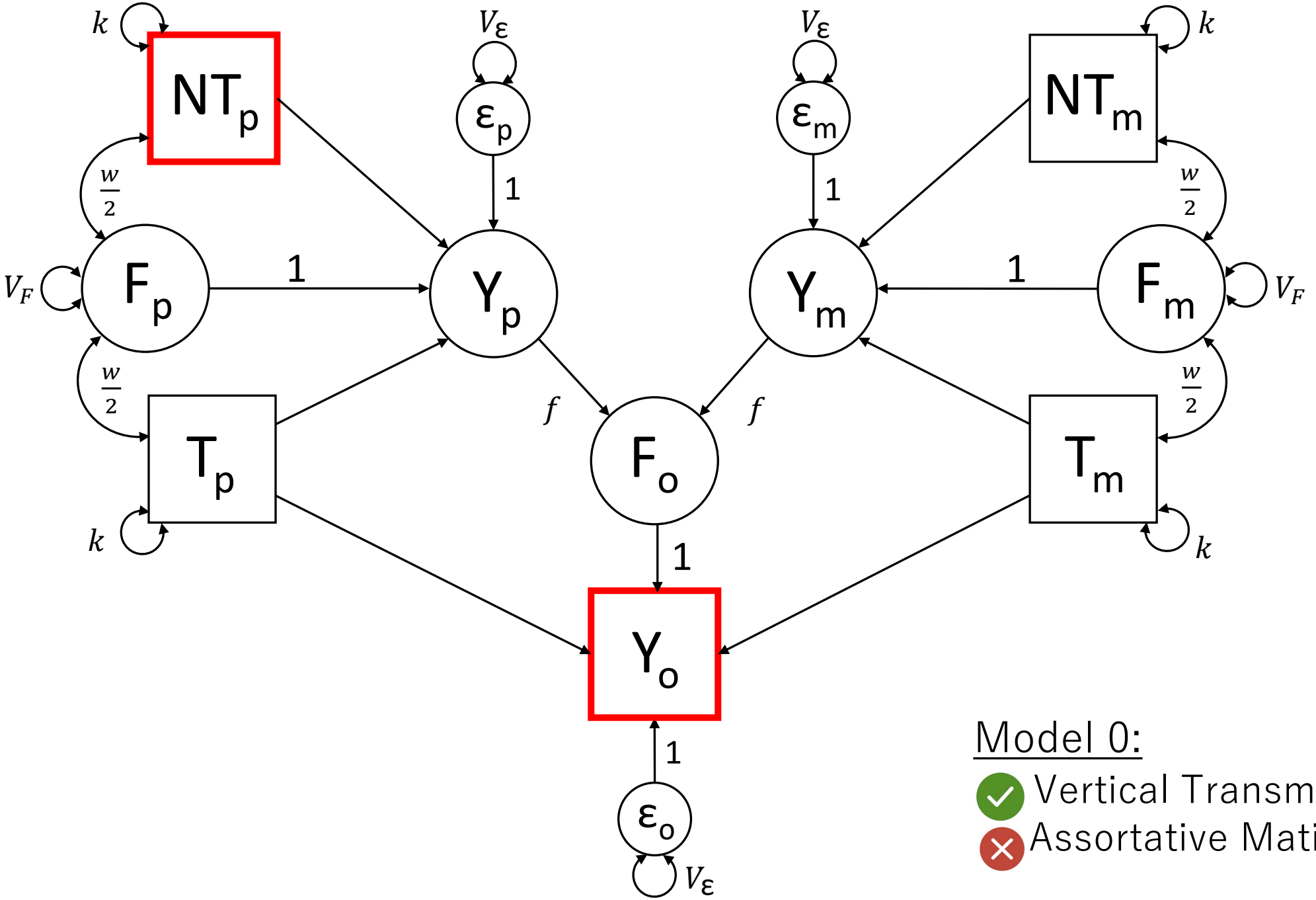
$\mathrm{cov}(Y_o, NT_p) = ?$

Model 0:

- ✓ Vertical Transmission
- ✗ Assortative Mating

Path Tracing Rules (described in Balbona et al., 2021)

1. A chain begins by travelling backwards against the direction of a single or double-headed arrow (from the arrow's head to its tail). However, once a double-headed arrow has been traversed, the direction reverses such that the chain now travels forwards, in the direction of the arrows.
2. A chain must include exactly one double-headed arrow (a variance or a covariance term), which is equivalent to stating that a chain must change directions exactly once. This is necessary because double-headed arrows provide the proper scaling for the coefficients in each chain.
3. All chains must be counted exactly once and each must be unique. However, the order of the links in the chains matters. For example, despite being algebraically equivalent, the chain $Y_p \rightarrow NT_p \rightarrow T_p \rightarrow Y_p$ is distinct from the chain $Y_p \rightarrow T_p \rightarrow NT_p \rightarrow Y_p$ in Figure1. Both are unique and both must be counted in determining the variance of Y_p .
4. Co-paths may only be traversed once in a given chain, and a chain must be legitimate before traversing the co-path. However, once the co-path is crossed, the first two rules above reset. A chain must therefore contain exactly one double-headed arrow before traversing the co-path, and one double-headed arrow after traversing the co-path. Thus, co-paths connect two legitimate chains to create a single, longer chain.



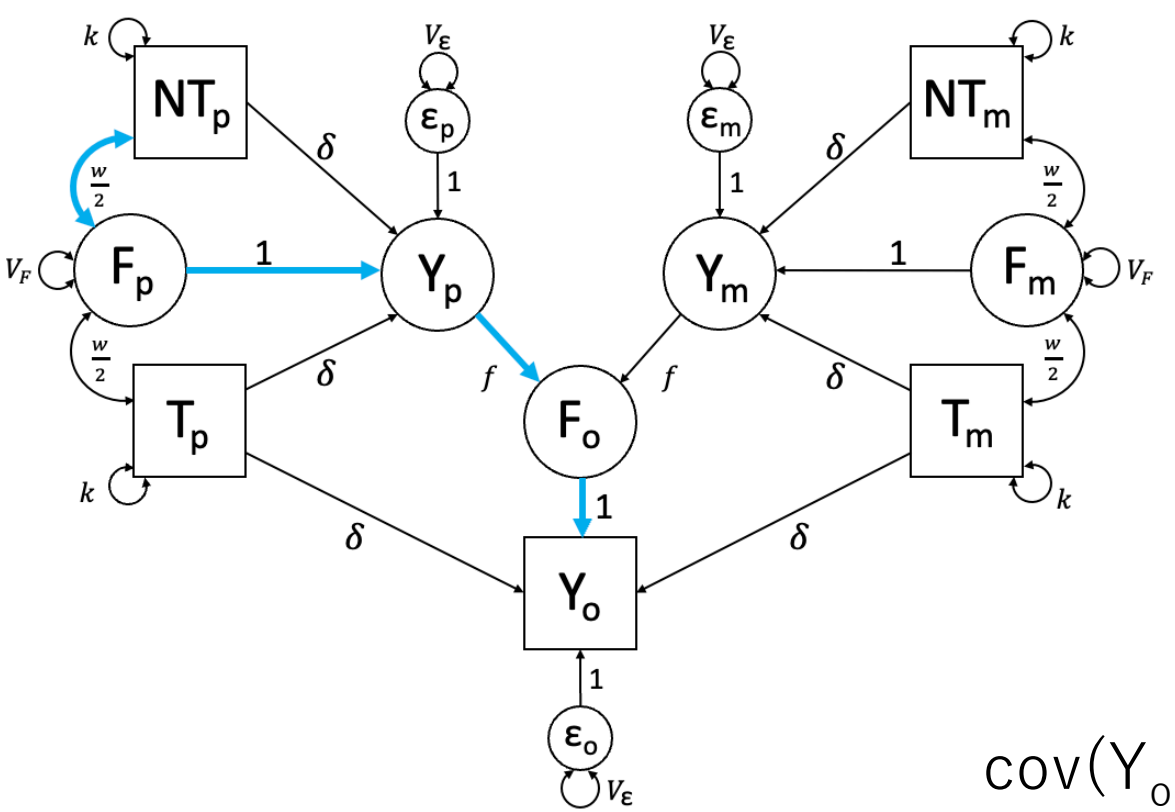
Model 0:

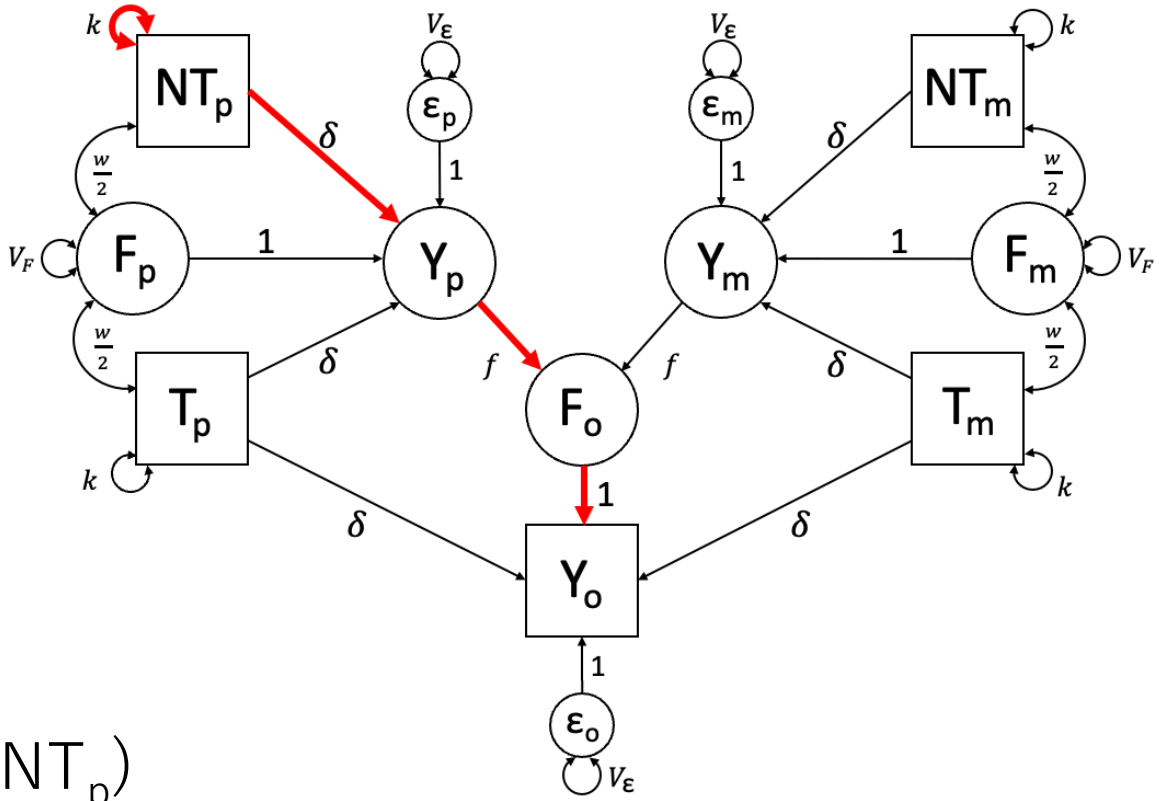
- Vertical Transmission
- Assortative Mating

Model 0:

✓ ✗ rtical Transmission

✓ ✗ Assortative Mating

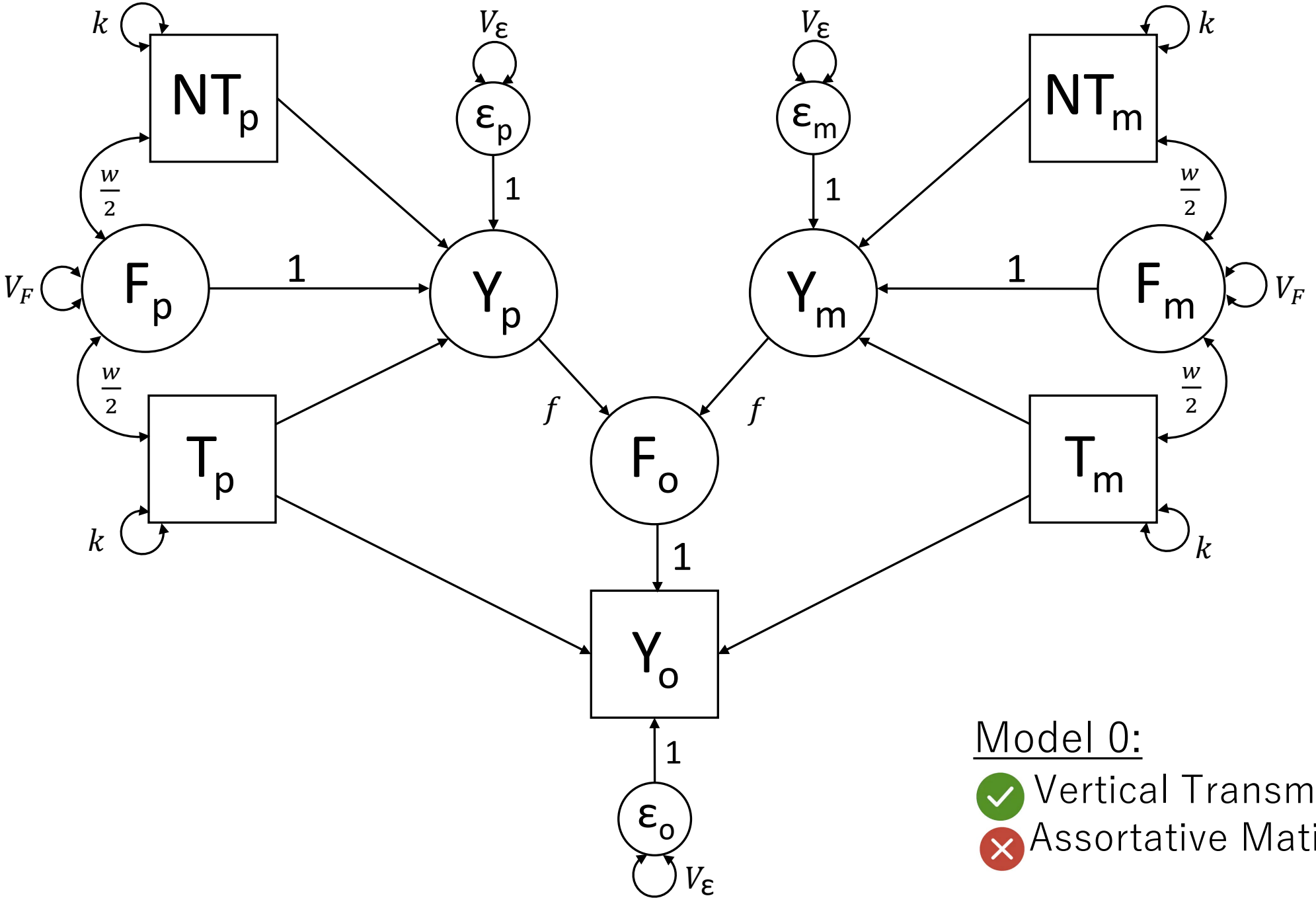




$$\mathrm{cov}(Y_o, NT_p)$$

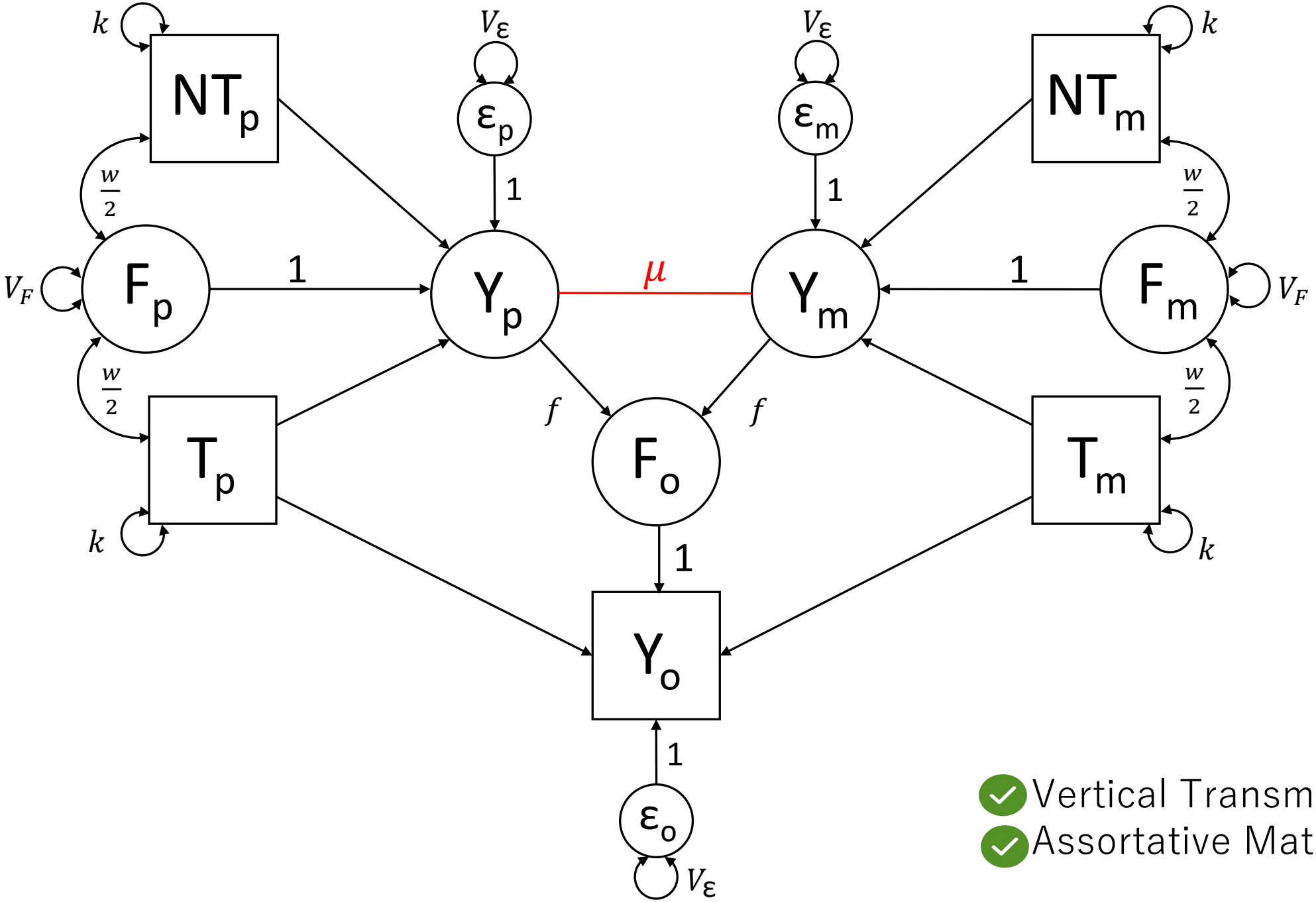
$$= \left(1 * f * 1 * \frac{w}{2}\right) + (1 * f * \delta * k)$$

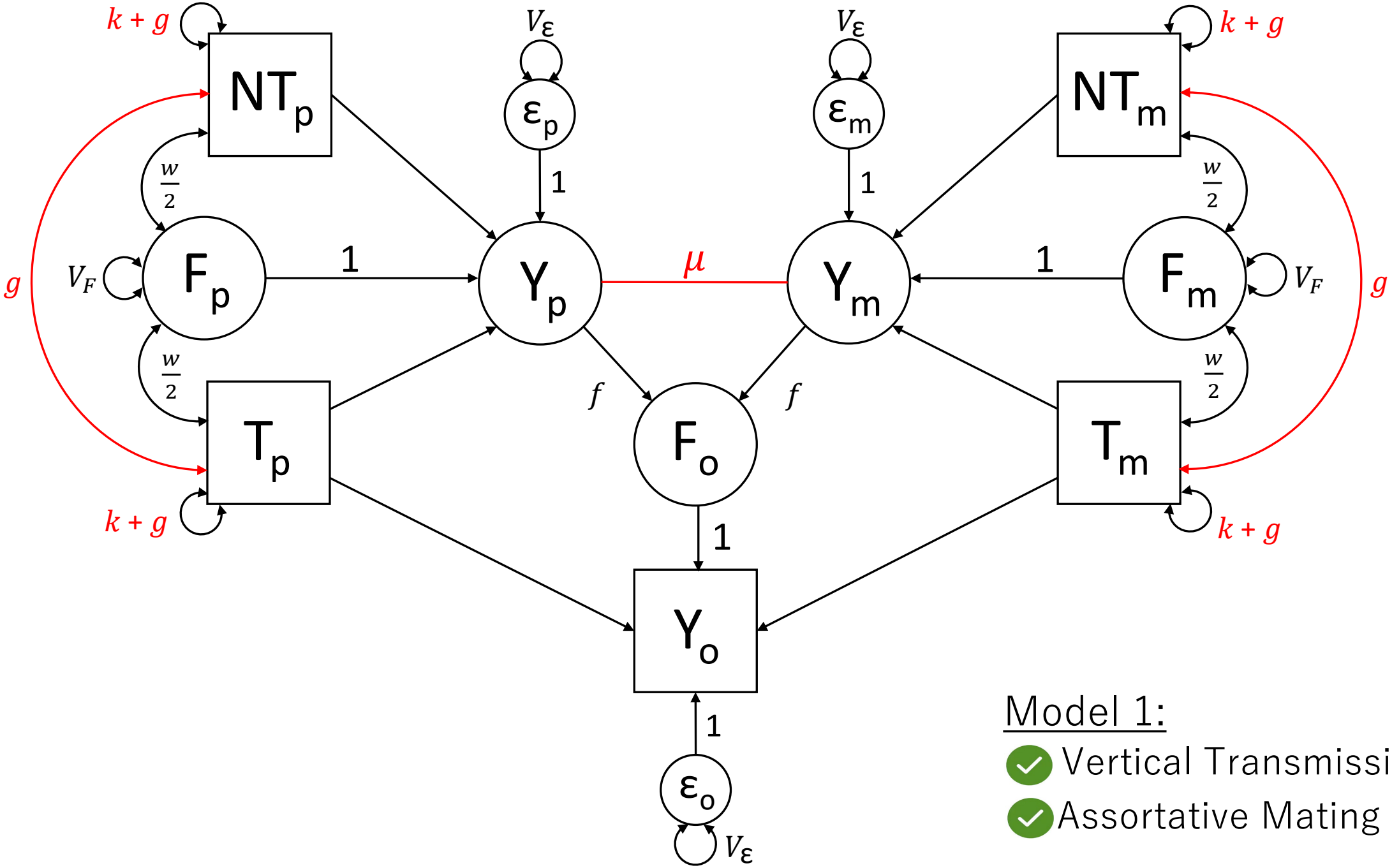
$$= \frac{1}{2} f w + f \delta \mathrm{k}$$



Model 0:

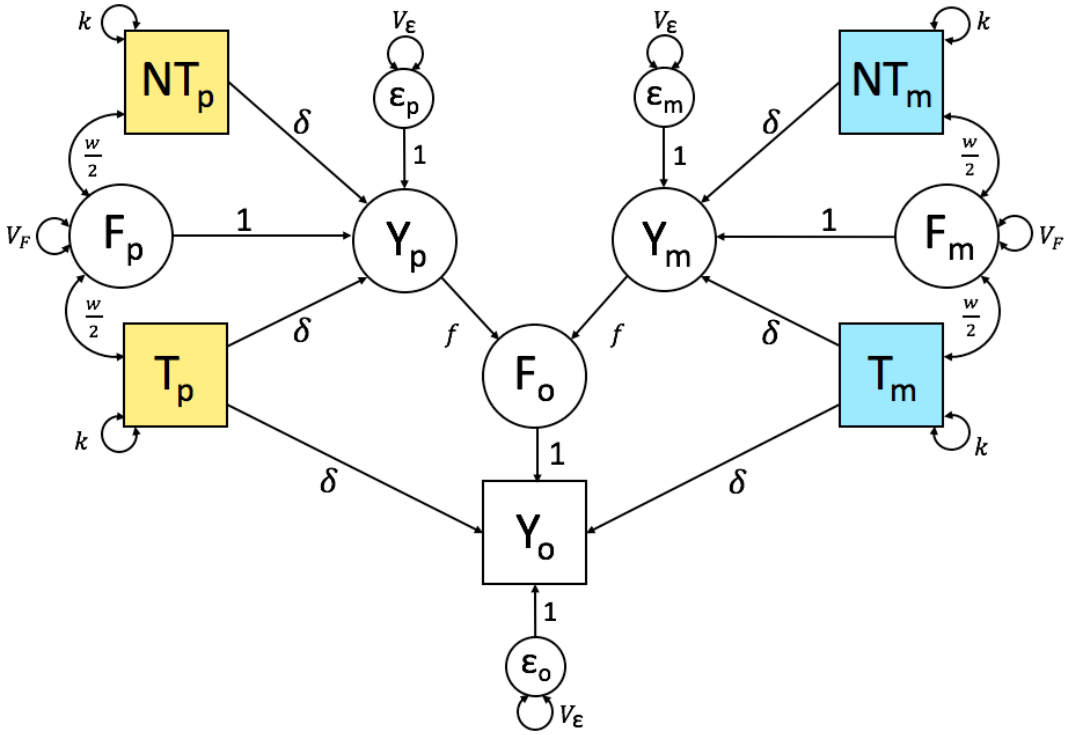
- Vertical Transmission
- Assortative Mating


k
NT_p
V_ε
ε_p
V_ε
ε_m
k
NT_m
$\frac{w}{2}$
1
1
$\frac{w}{2}$
V_F
F_p
1
Y_p
μ
Y_m
1
F_m
V_F
$\frac{w}{2}$
f
f
$\frac{w}{2}$
T_p
F_o
T_m
k
1
k
Y_o
1
ε_o
V_ε
Vertical Transmission
Assortative Mating

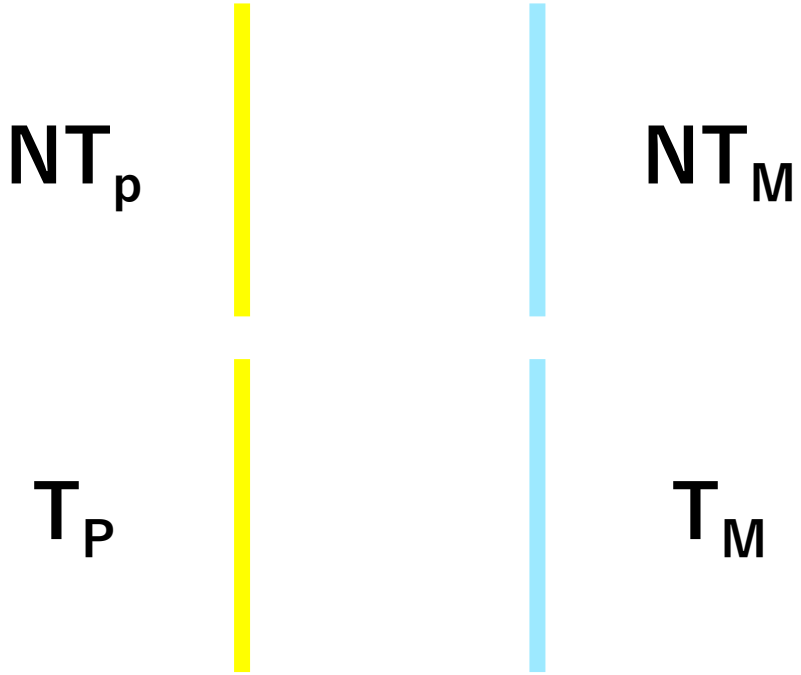


Model 1:

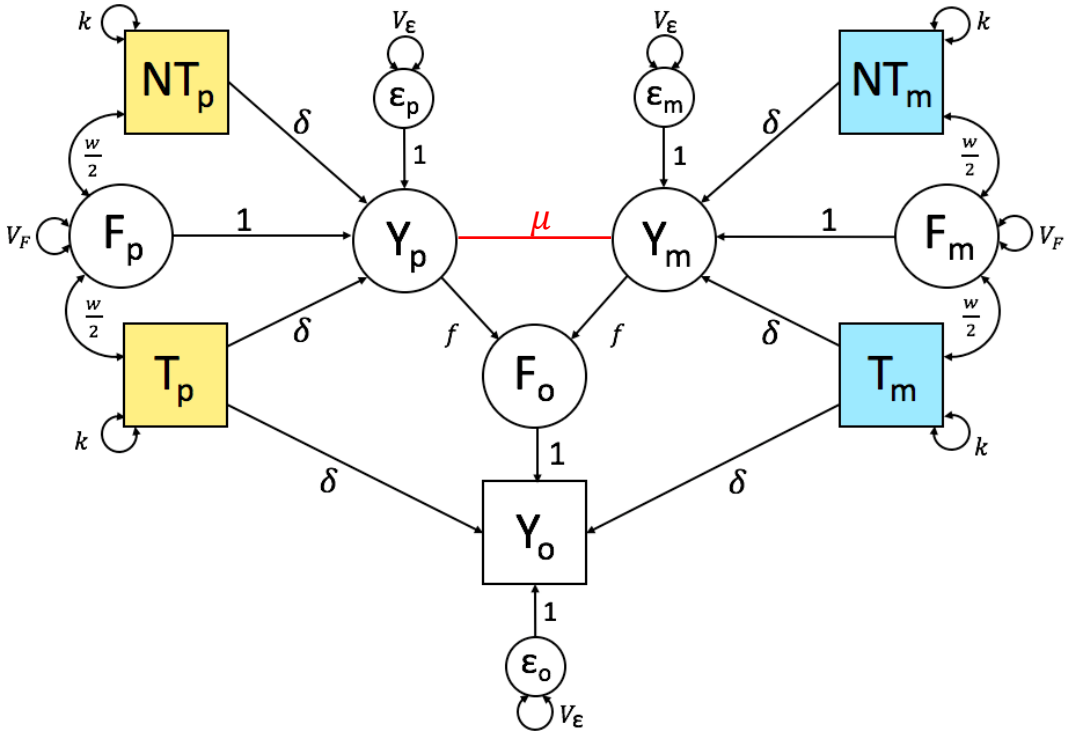
- Vertical Transmission
- Assortative Mating



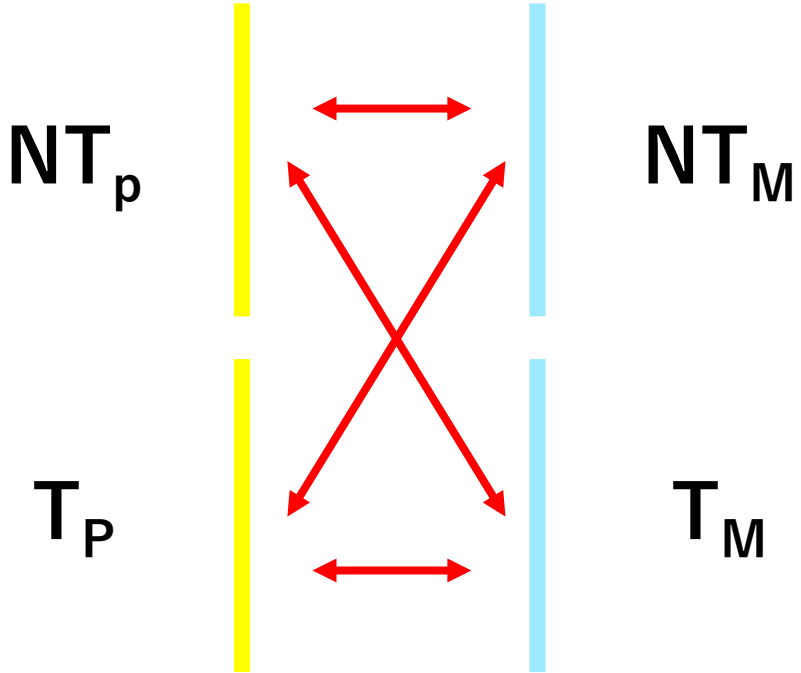
Offspring's Genome



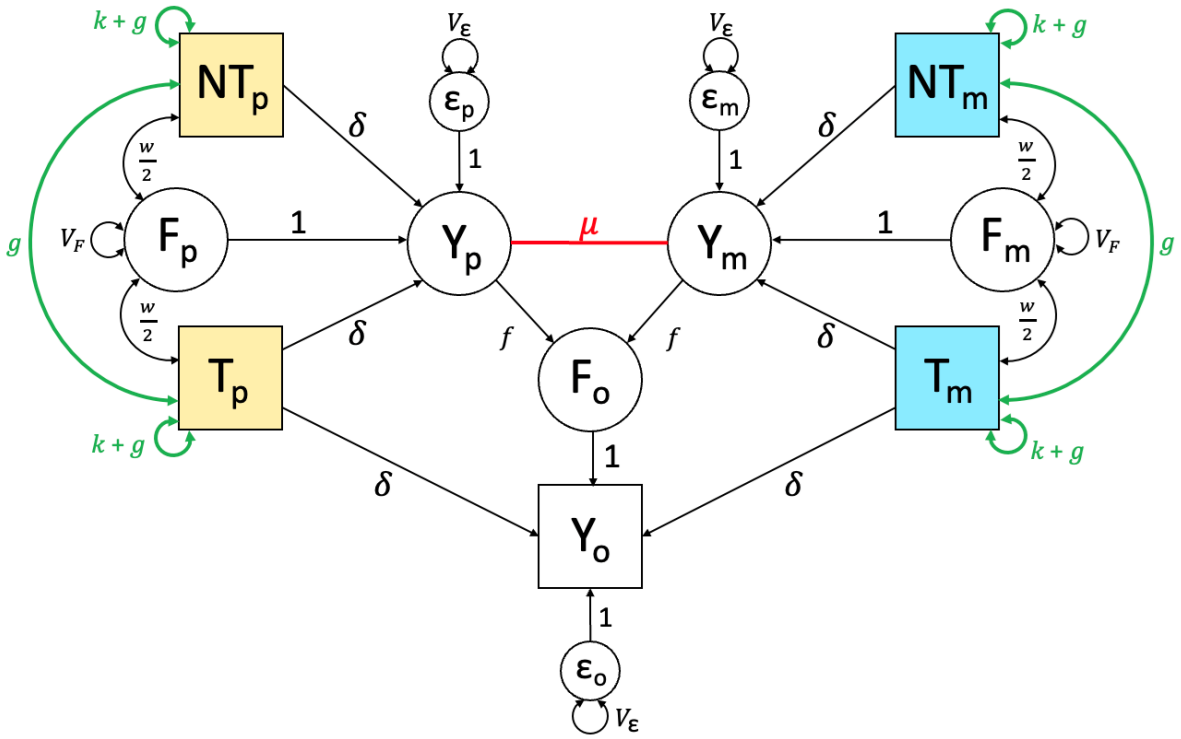
No Assortment



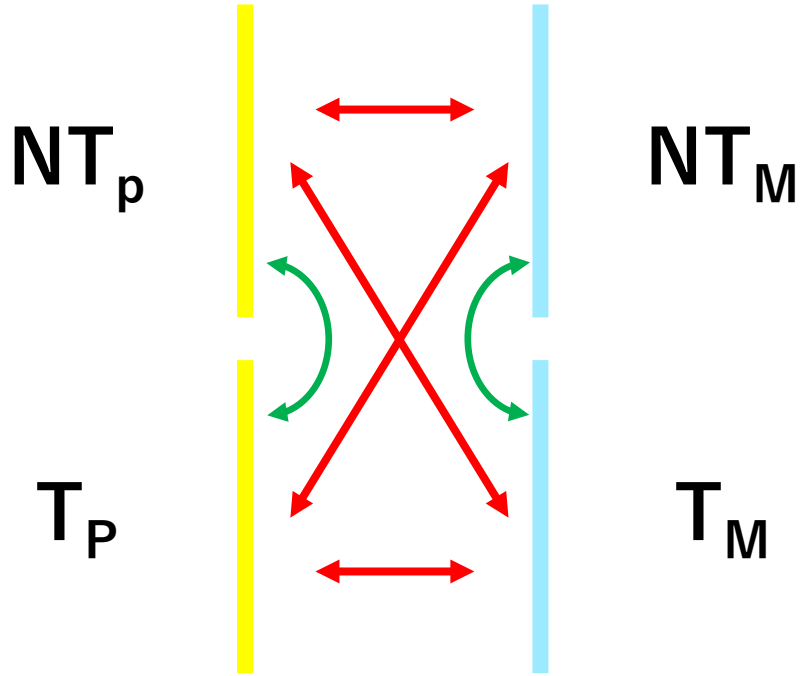
Offspring's Genome



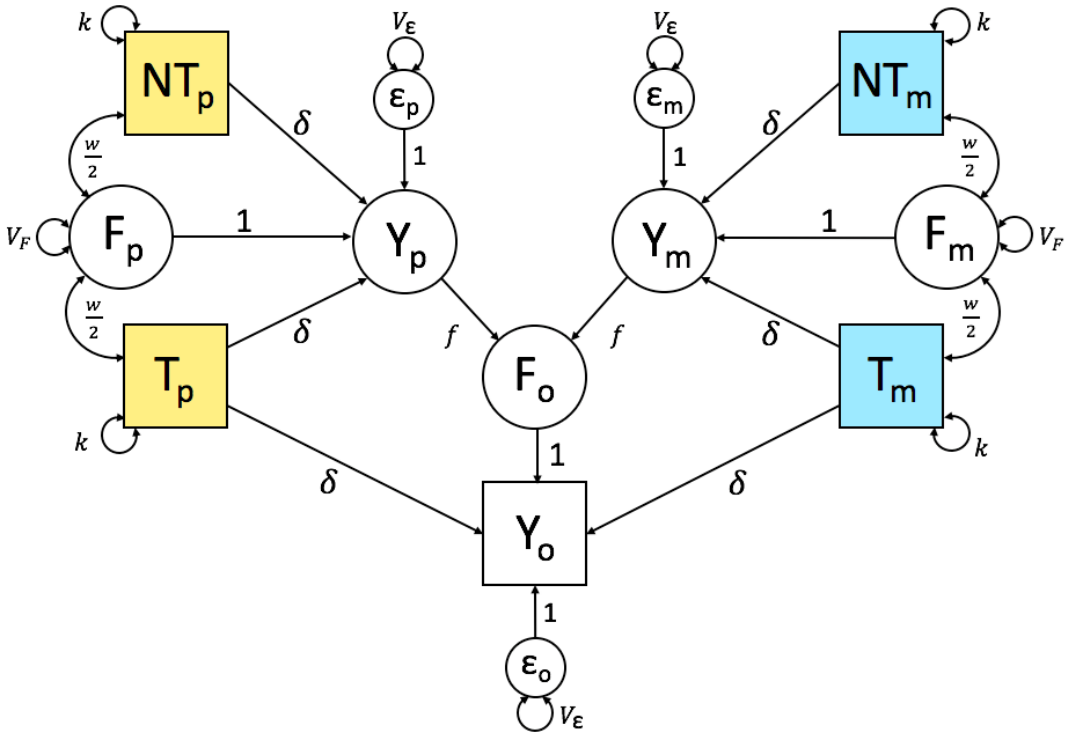
1 Generation of Assortment



Offspring's Genome

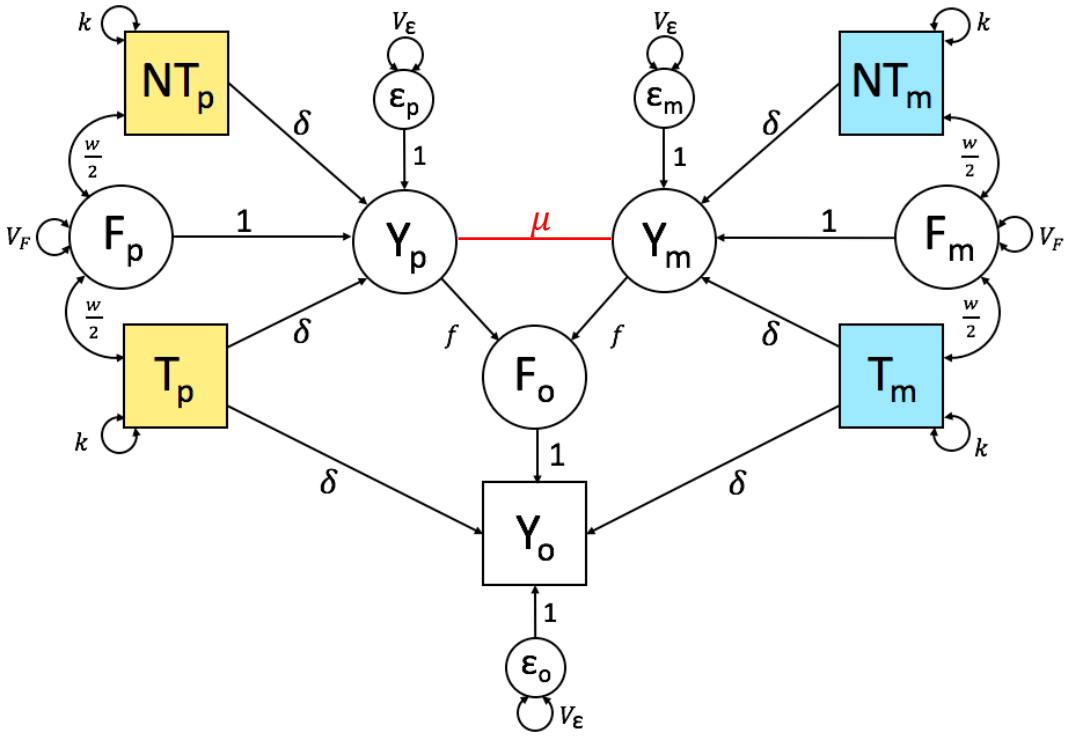


>1 Generation of Assortment



	T_p	NT_p	T_m	NT_m
T_p	k	0	0	0
NT_p		k	0	0
T_m			k	0
NT_m				k

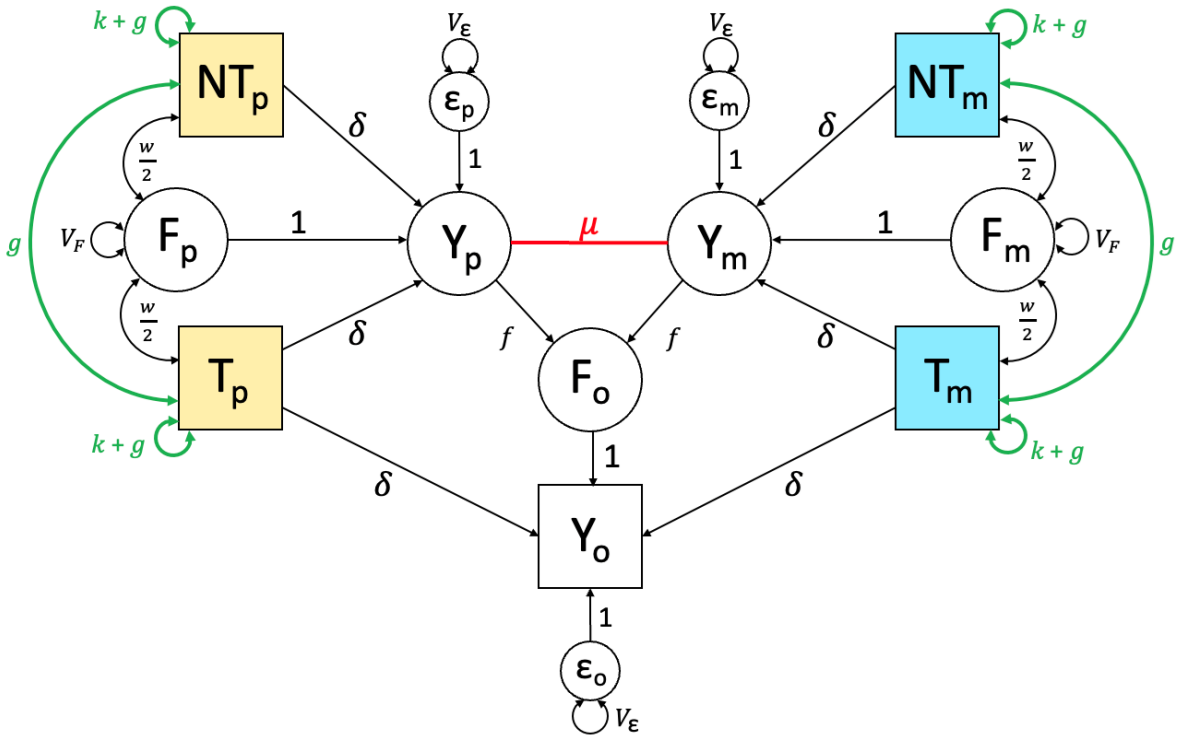
No Assortment



g : Increase in PGS (co)variances due to AM

	T_p	NT_p	T_m	NT_m
T_p	k	0	g	g
NT_p		k	g	g
T_m			k	0
NT_m				k

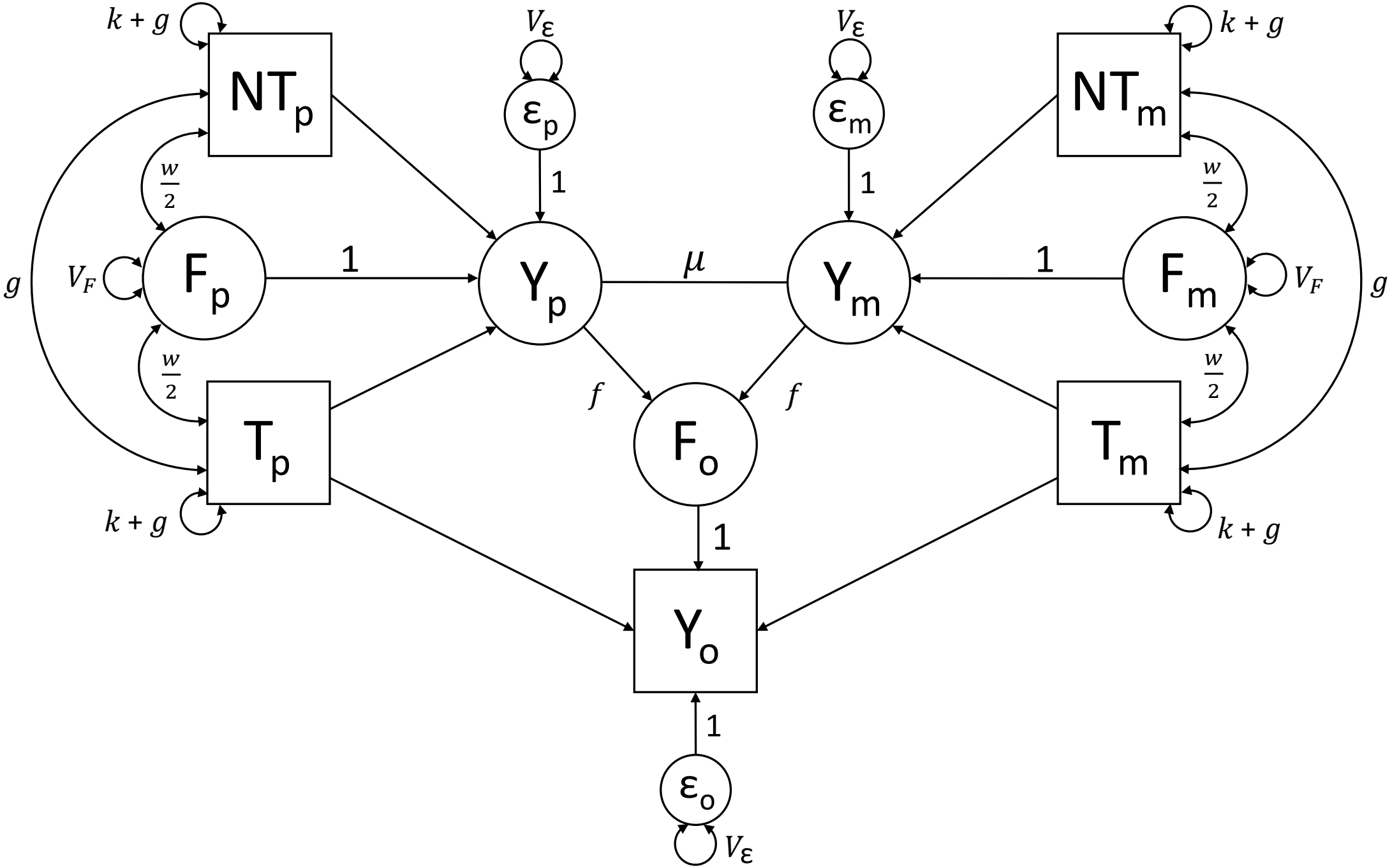
1 Generation of Assortment

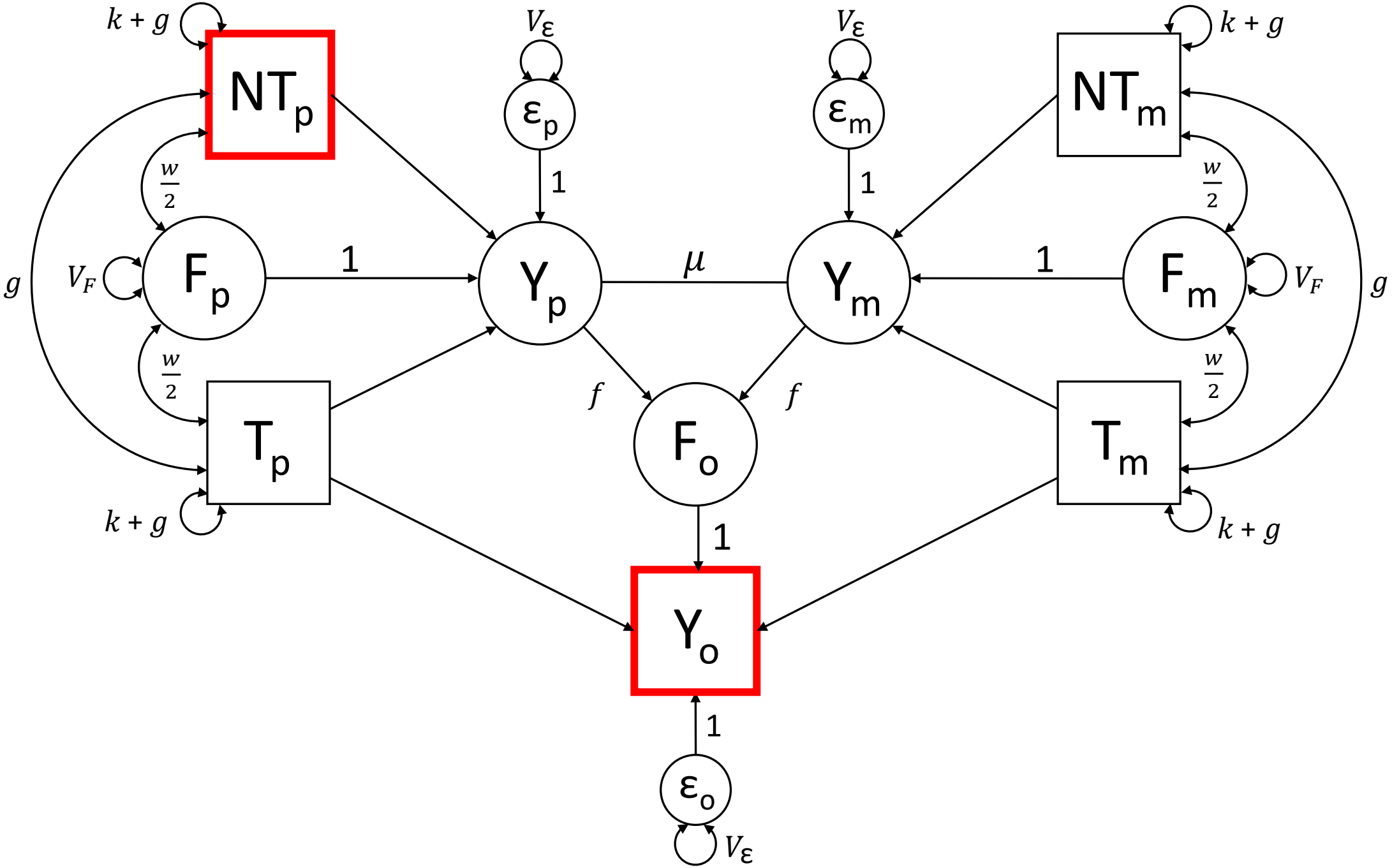


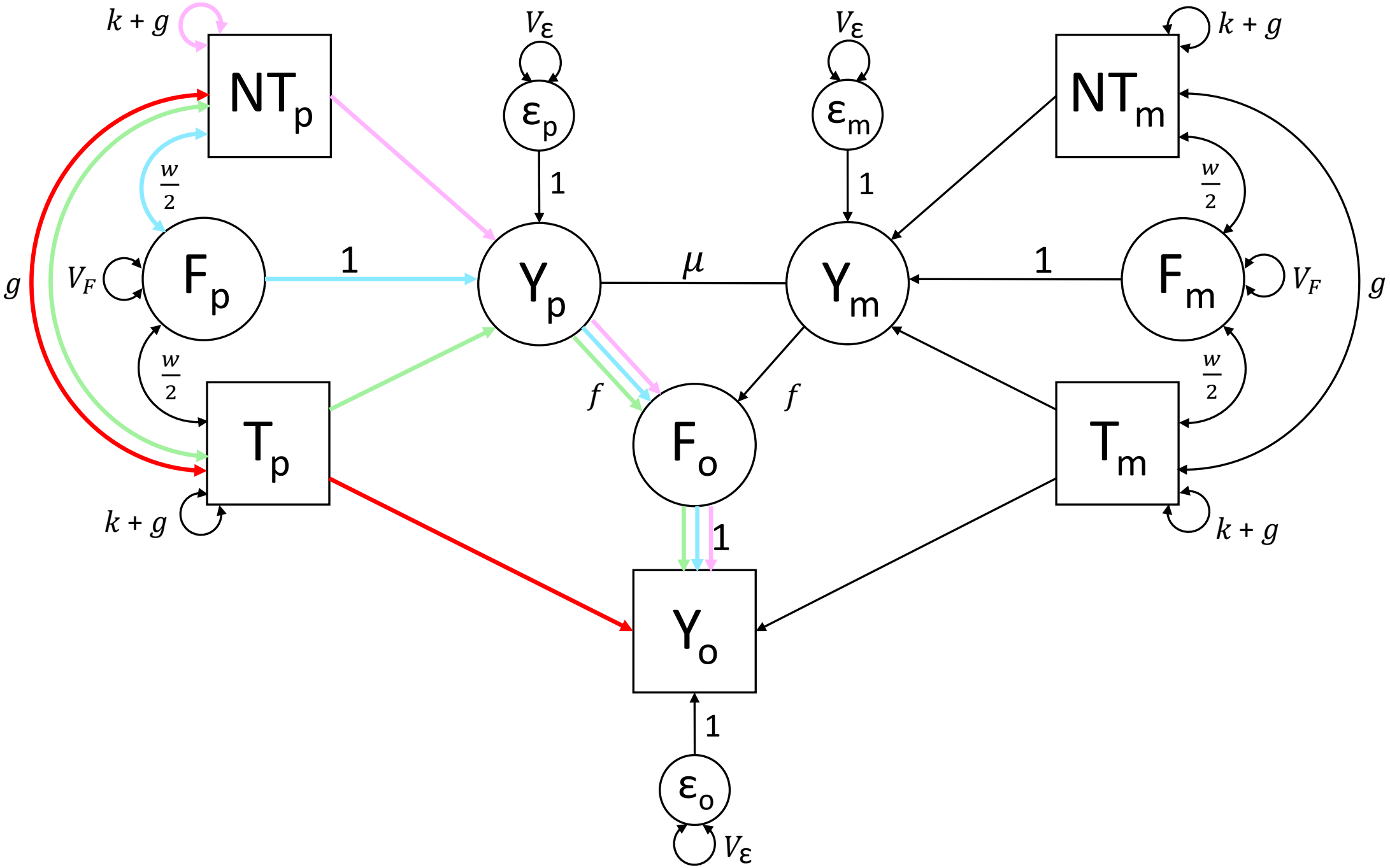
g : Increase in PGS (co)variances due to AM

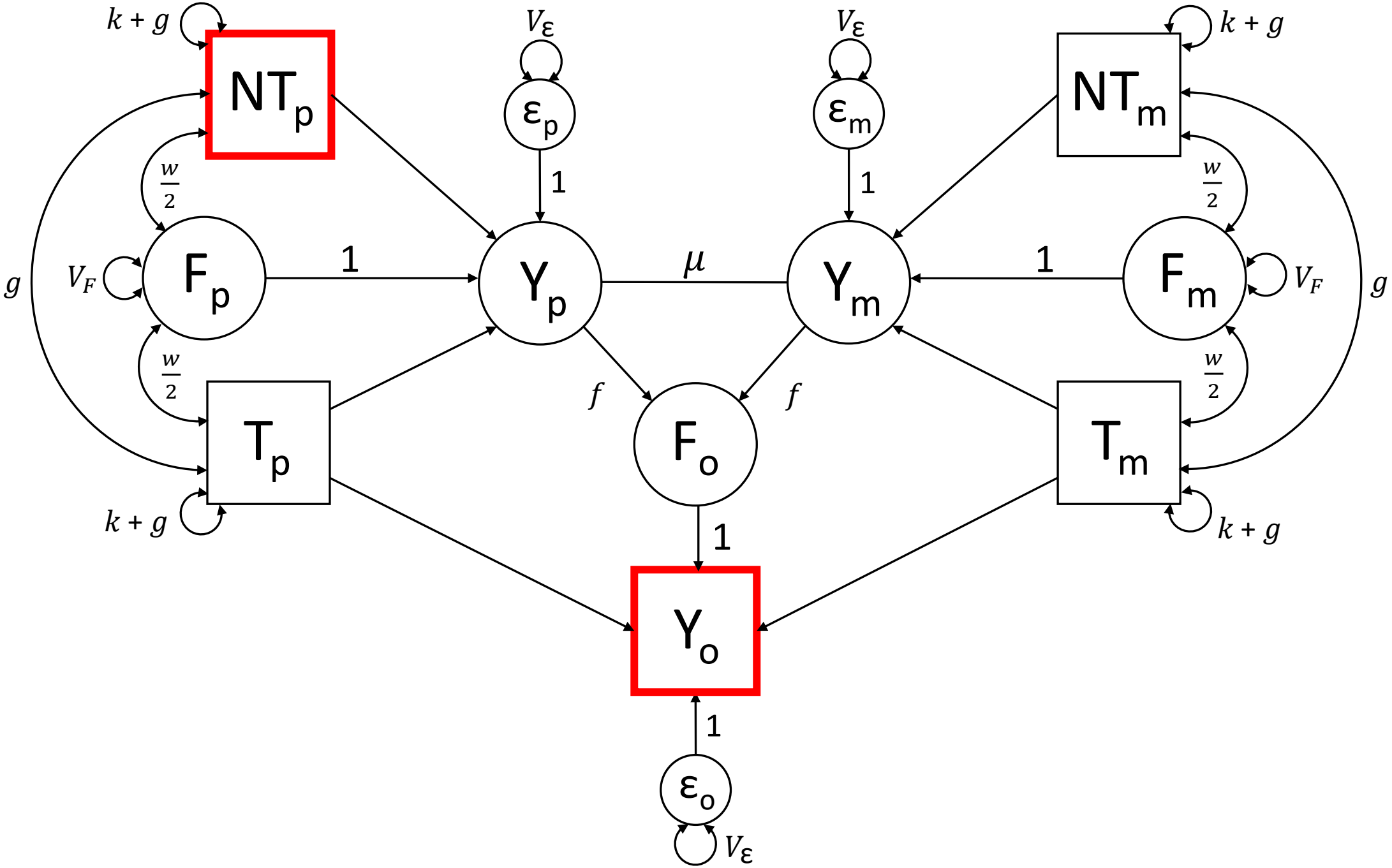
	T_p	NT_p	T_m	NT_m
T_p	$k+g$	g	g	g
NT_p		$k+g$	g	g
T_m			$k+g$	g
NT_m				$k+g$

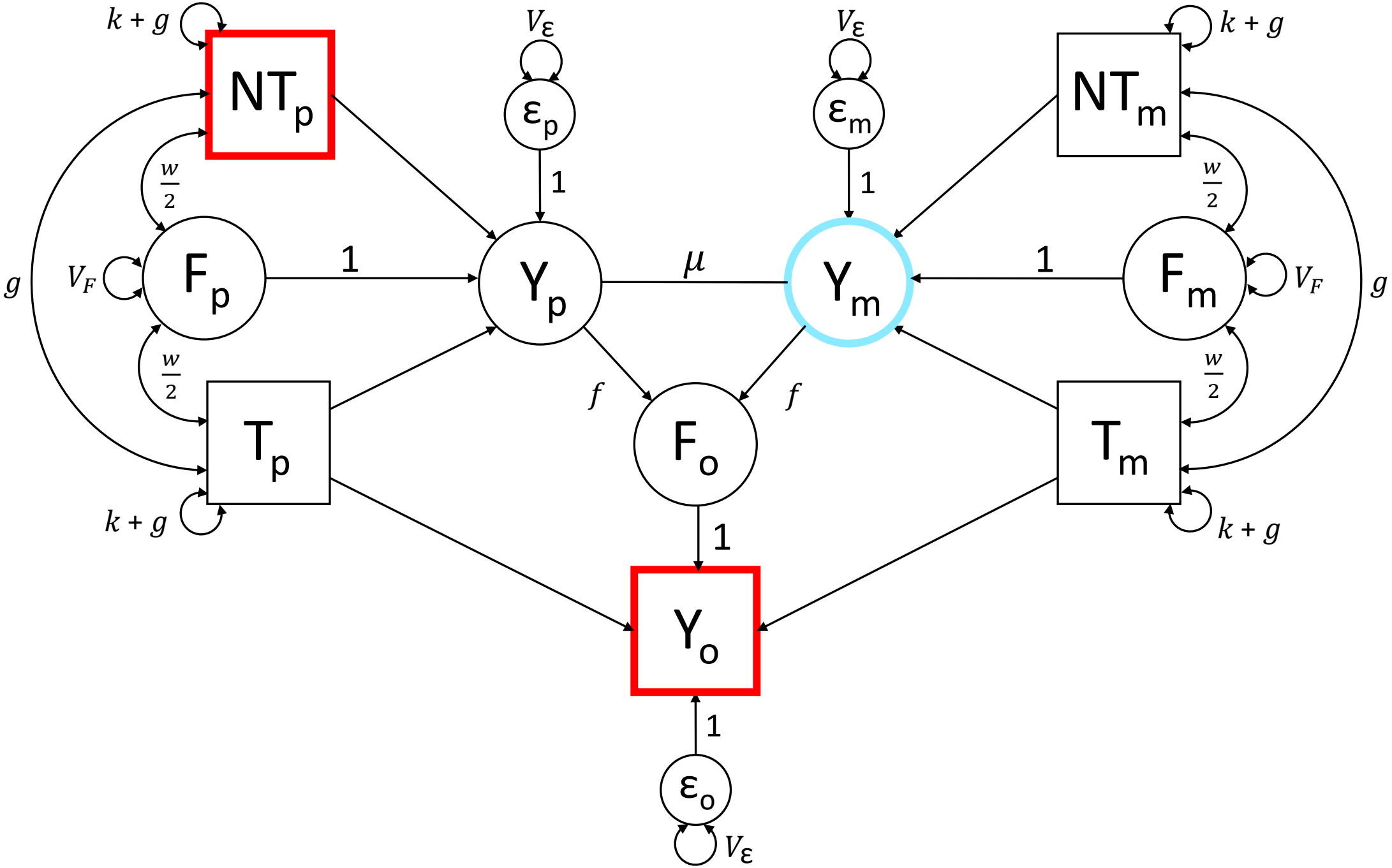
>1 Generation of Assortment


$k + g$
NT_p
V_ε
ε_p
V_ε
ε_m
$k + g$
NT_m
$\frac{w}{2}$
1
1
$\frac{w}{2}$
g
V_F
F_p
1
Y_p
μ
Y_m
1
F_m
V_F
g
$\frac{w}{2}$
$\frac{w}{2}$
f
f
T_p
F_o
T_m
$k + g$
1
$k + g$
Y_o
1
ε_o
V_ε


$k+g$
NT_p
V_ε
ε_p
1
V_ε
ε_m
1
$k+g$
NT_m
$\frac{w}{2}$
g
V_F
F_p
1
Y_p
μ
Y_m
1
F_m
V_F
g
$\frac{w}{2}$
$\frac{w}{2}$
f
f
T_p
F_o
T_m
$k+g$
1
$k+g$
Y_o
1
ε_o
V_ε

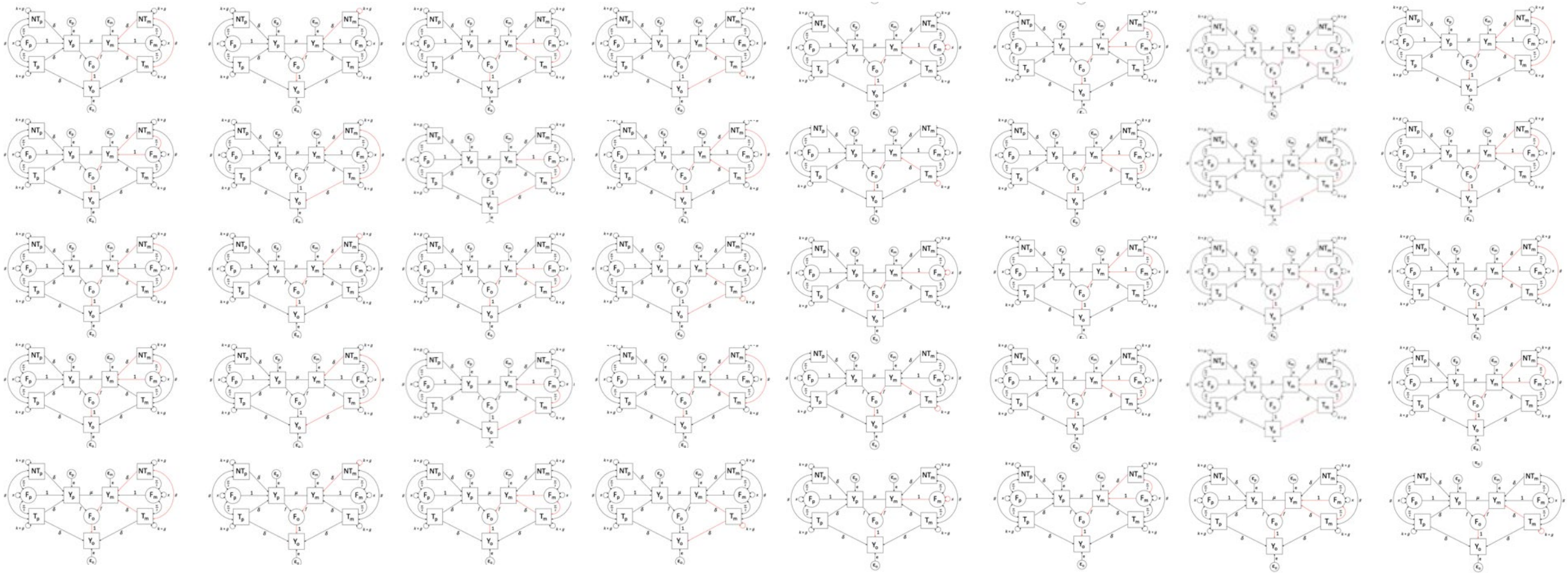

$k+g$
NT_p
V_ε
ε_p
V_ε
ε_m
$k+g$
NT_m
$\frac{w}{2}$
1
1
$\frac{w}{2}$
g
V_F
F_p
1
Y_p
μ
Y_m
1
F_m
V_F
g
$\frac{w}{2}$
$\frac{w}{2}$
f
f
T_p
F_o
T_m
$k+g$
1
$k+g$
Y_o
1
ε_o
V_ε

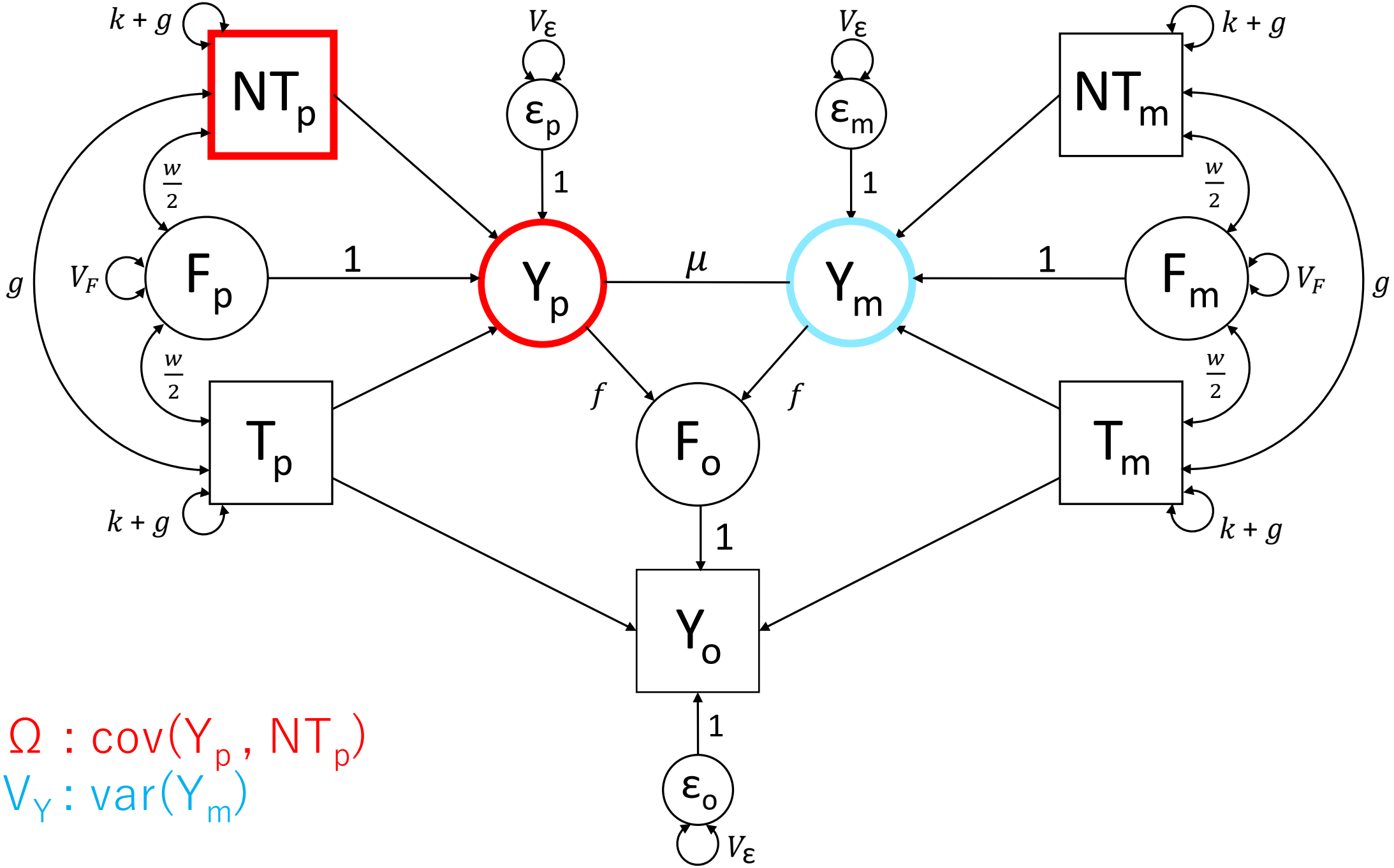

$k+g$
NT_p
V_ε
ε_p
1
V_ε
ε_m
1
$k+g$
NT_m
$\frac{w}{2}$
g
V_F
F_p
1
Y_p
μ
Y_m
1
F_m
V_F
g
$\frac{w}{2}$
$\frac{w}{2}$
f
f
T_p
F_o
T_m
$k+g$
1
$k+g$
Y_o
1
ε_o
V_ε


$k+g$
NT_p
V_ε
ε_p
V_ε
ε_m
$k+g$
NT_m
$\frac{w}{2}$
1
1
$\frac{w}{2}$
g
V_F
F_p
1
Y_p
μ
Y_m
1
F_m
V_F
g
$\frac{w}{2}$
$\frac{w}{2}$
f
f
T_p
F_o
T_m
$k+g$
1
$k+g$
Y_o
1
ε_o
V_ε

Model 1:

- ✓ Vertical Transmission
- ✓ Assortative Mating

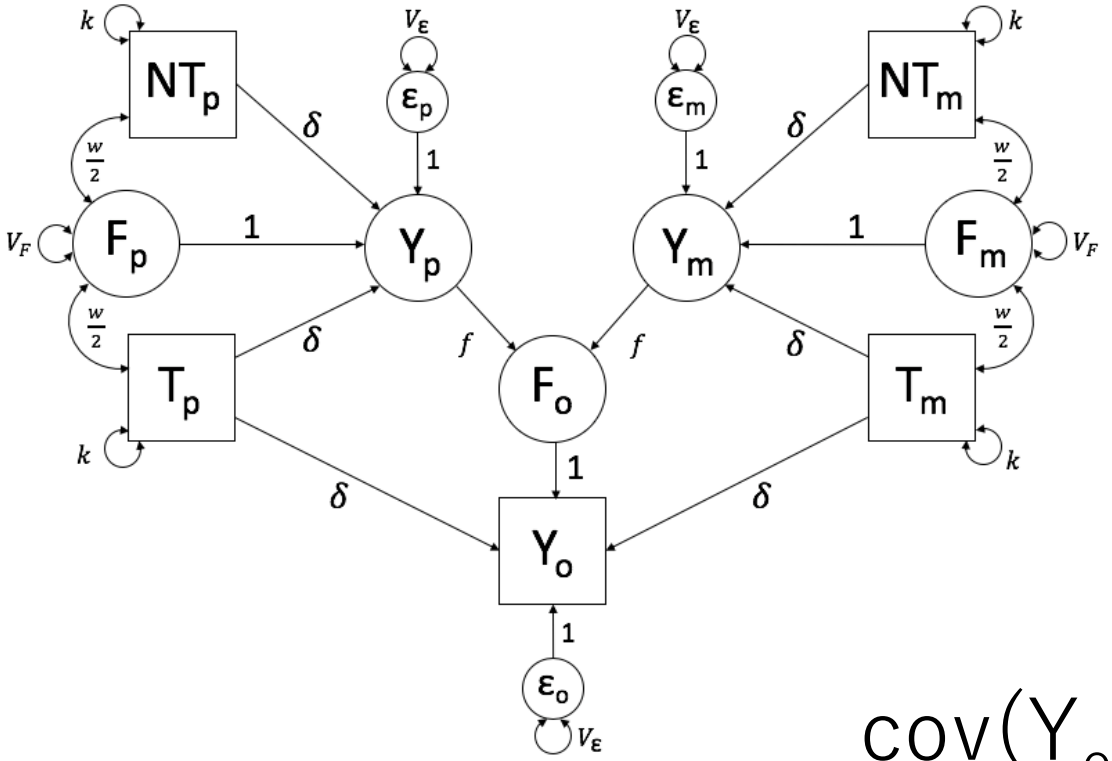




1. Ω : $\mathrm{cov}(Y_p, NT_p)$
2. V_Y : $\mathrm{var}(Y_m)$

Model 0:

- ✓ Vertical Transmission,
- ✗ Assortative Mating



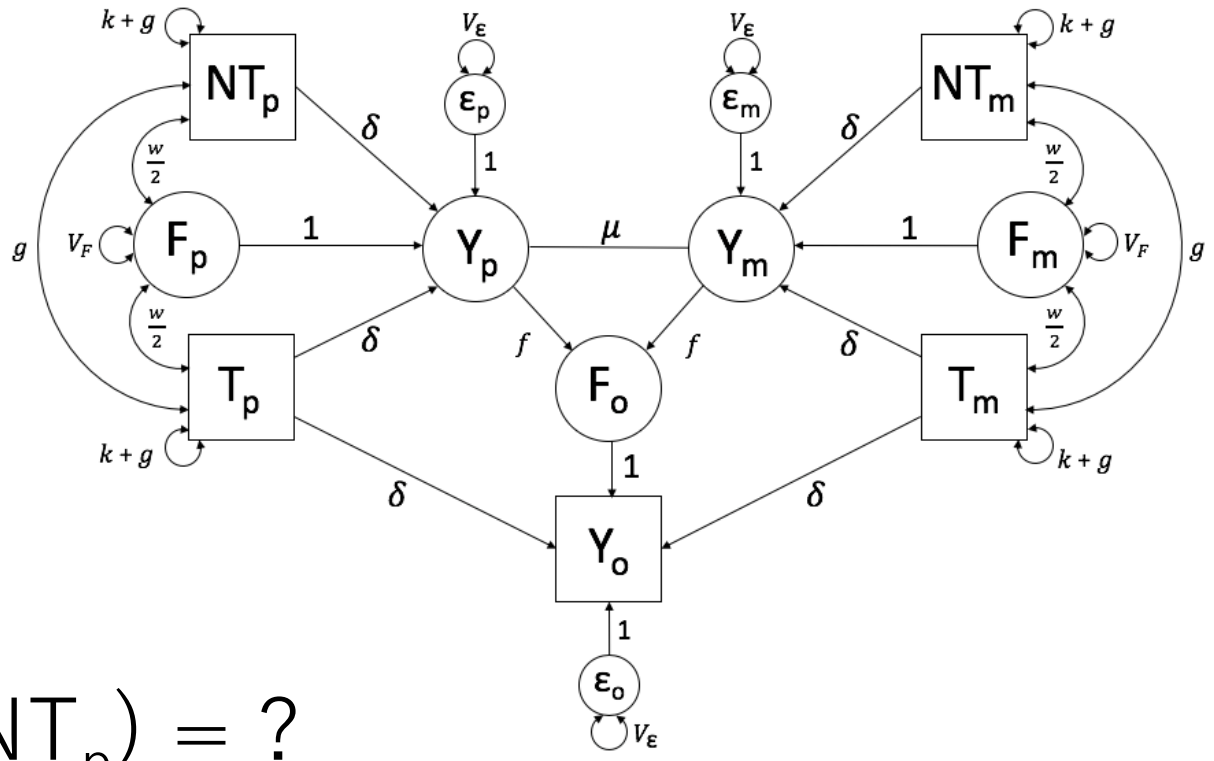
$$= f\left(\frac{w}{2} + \delta \mathrm{k}\right)$$

$$= f\Omega$$

$$\mathrm{cov}(\mathrm{Y_o}, \mathrm{NT_p}) = ?$$

Model 1:

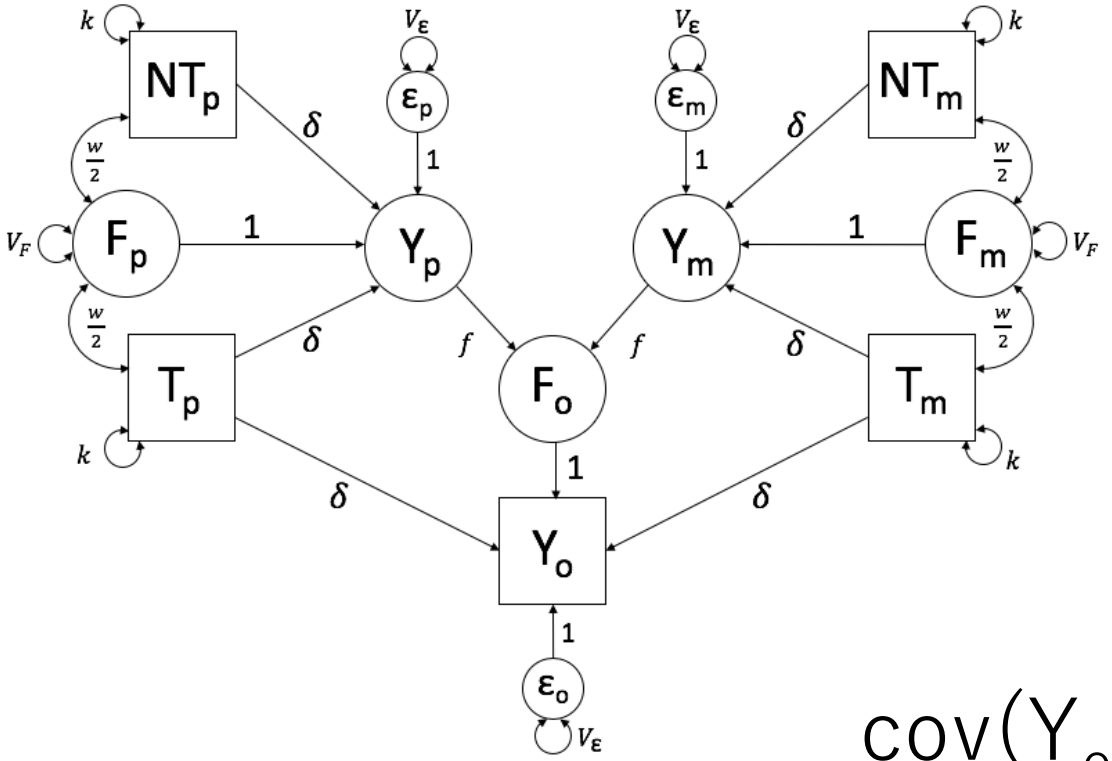
- ✓ Vertical Transmission,
- ✓ Assortative Mating



$$= f\Omega\left(1 + V_y\mu\right) + 2\delta g$$

Model 0:

- ✓ Vertical Transmission,
- ✗ Assortative Mating



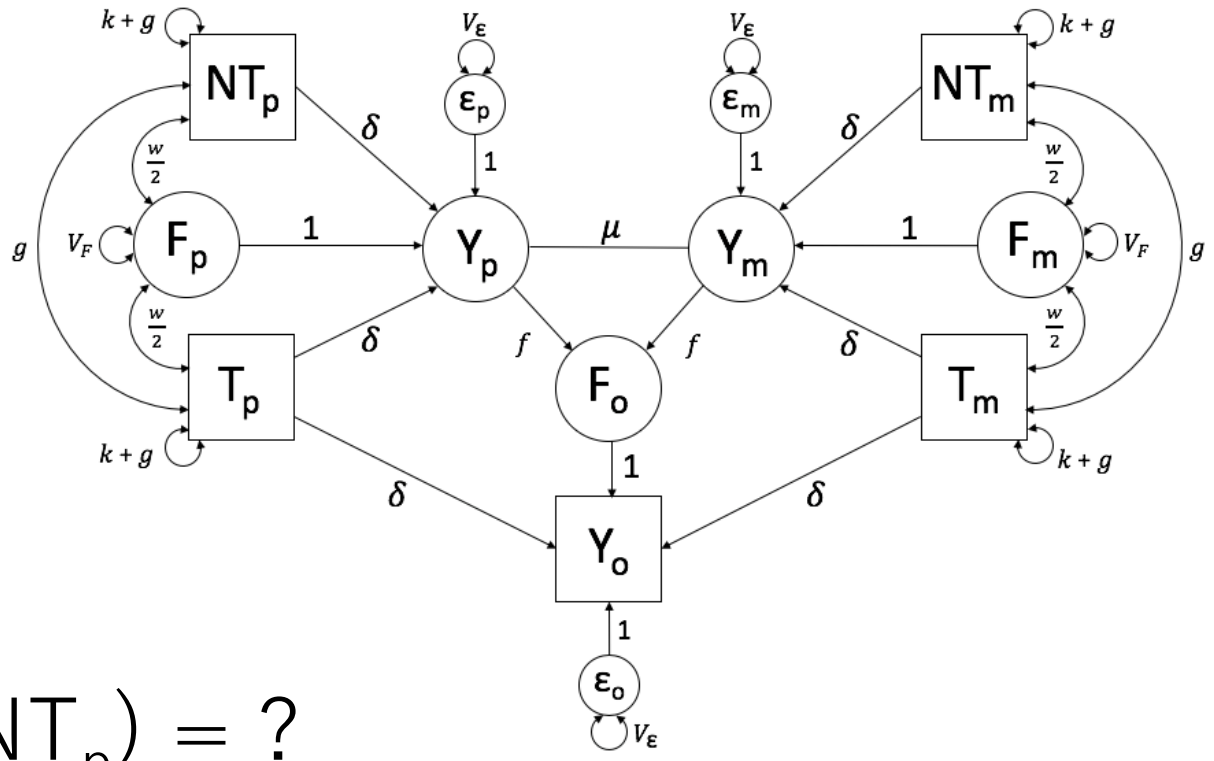
$$= f\left(\frac{w}{2} + \delta \mathrm{k}\right)$$

$$= f\Omega$$

$$\mathrm{cov}(\mathrm{Y_o}, \mathrm{NT_p}) = ?$$

Model 1:

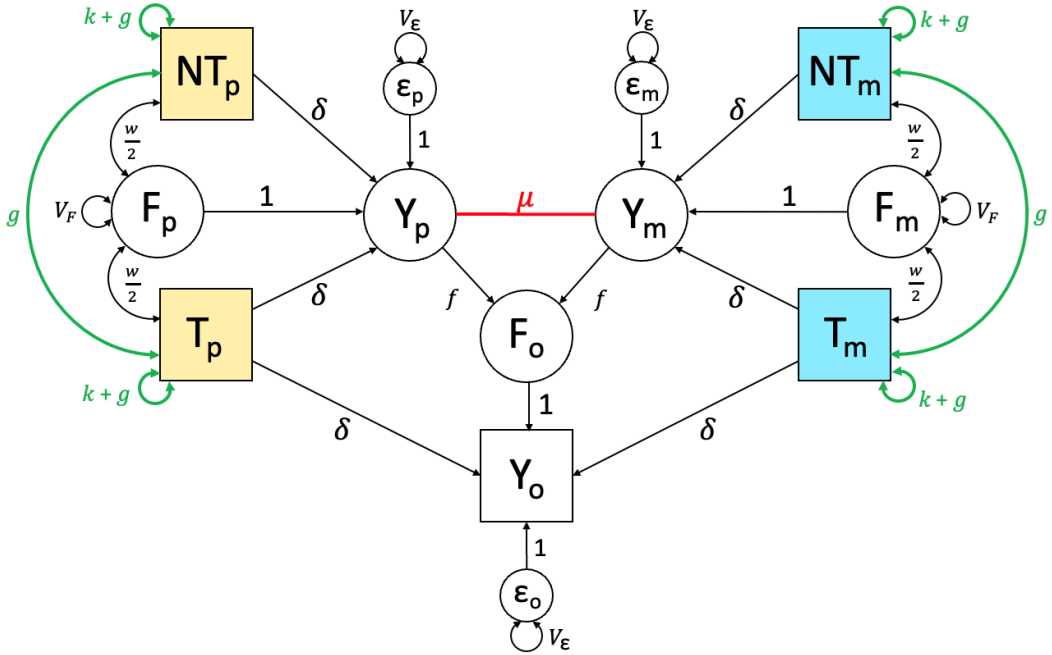
- ✓ Vertical Transmission,
- ✓ Assortative Mating



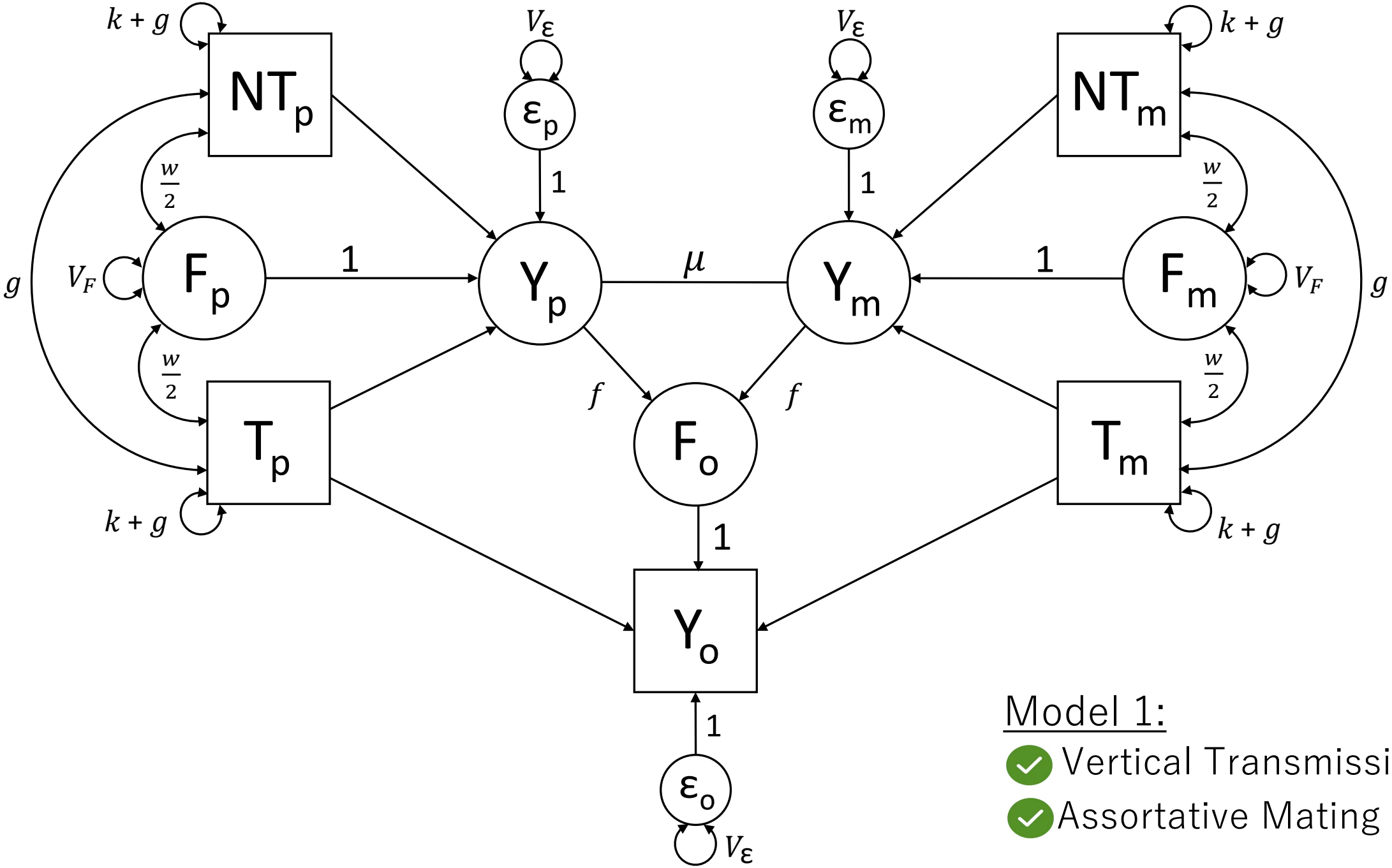
$$= f\Omega\left(1 + V_y\mu\right) + 2\delta g$$

Assumptions / Limitations

- Does not look at the *full* impact of parental influence *
- Requires sufficiently predictive PGS's
- Results can be biased if the discovery GWAS themselves are biased by stratification
- Does not account for horizontal transmission (i.e., sibling effects)

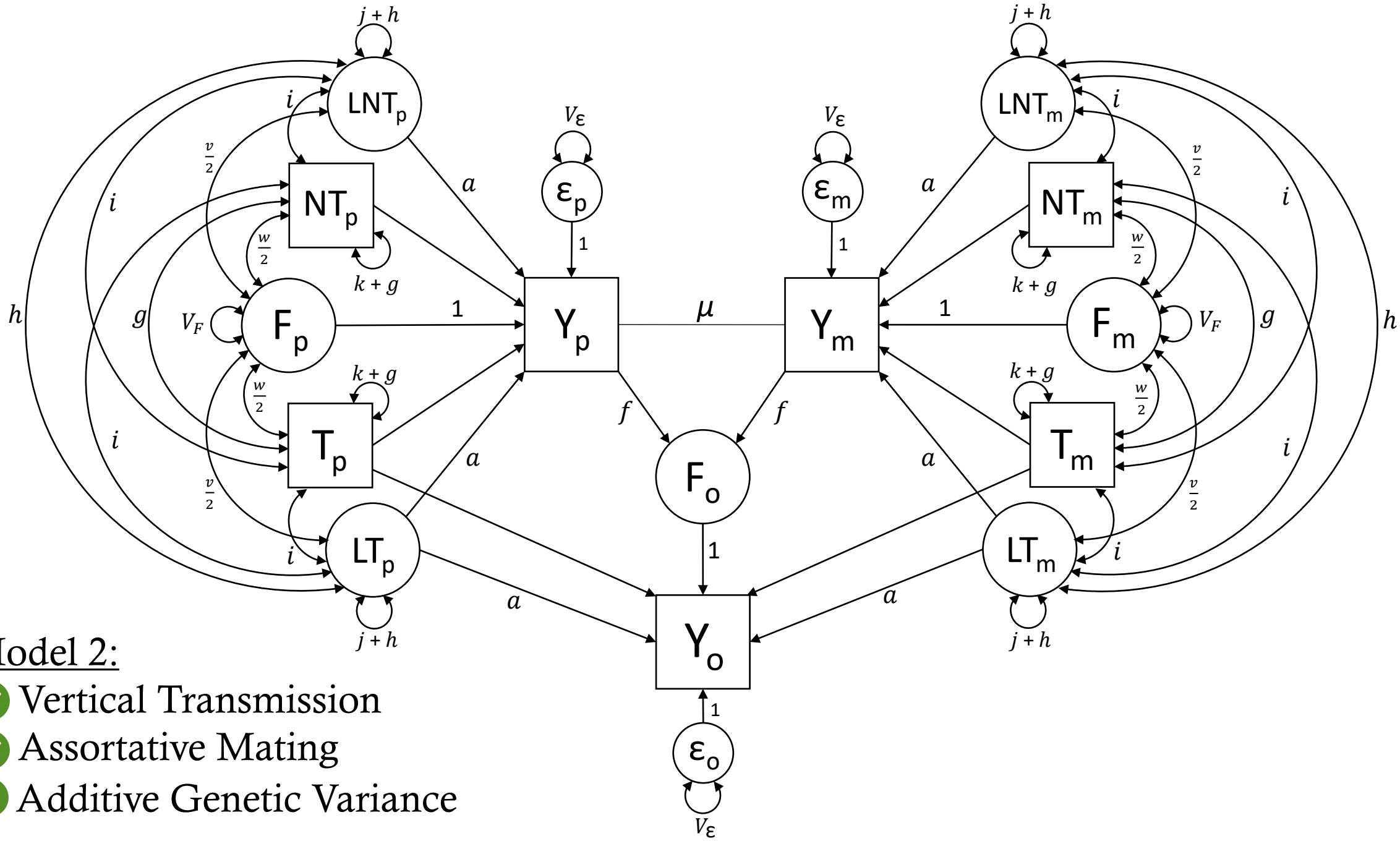


Some other extensions we’re working on



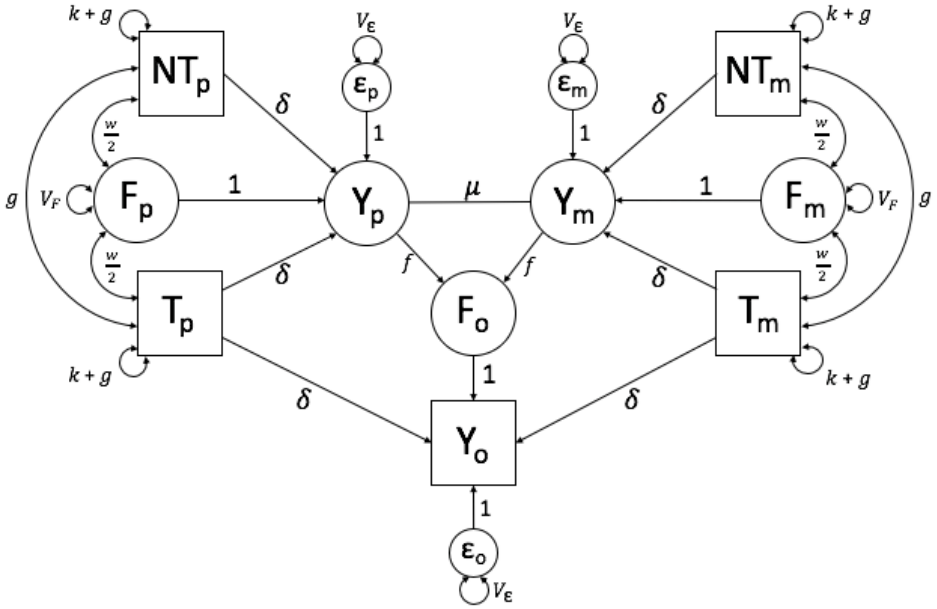
Model 1:

- Vertical Transmission
- Assortative Mating

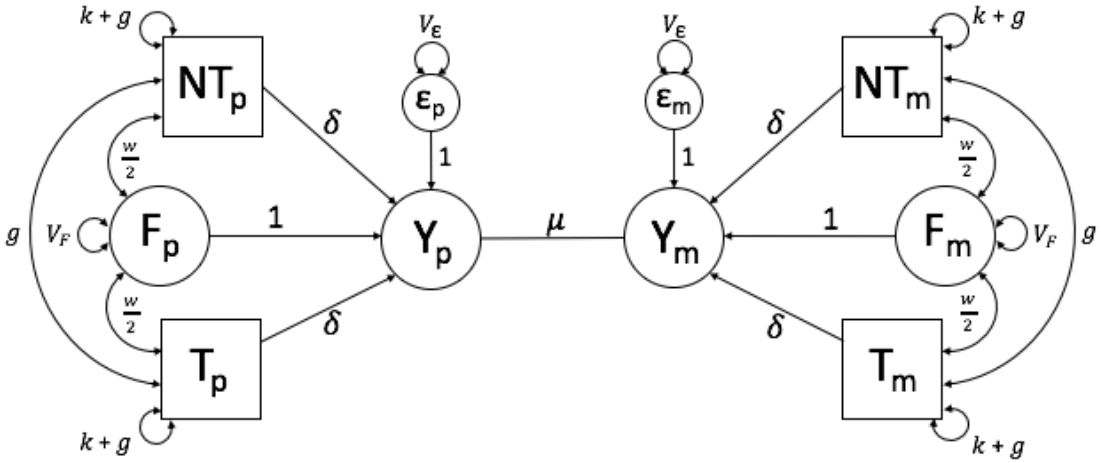


Model 2:

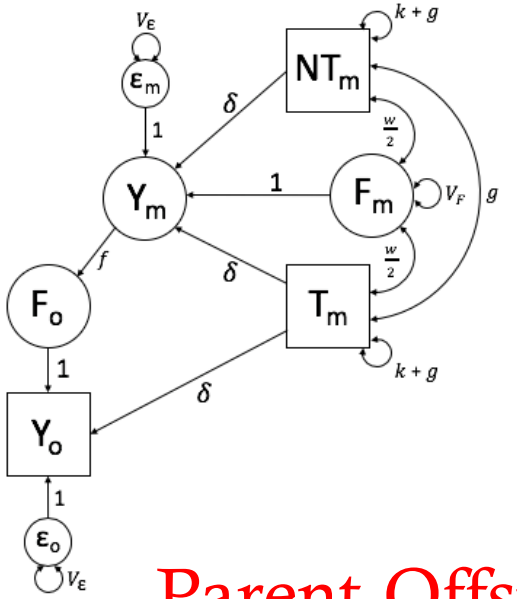
- ✓ Vertical Transmission
- ✓ Assortative Mating
- ✓ Additive Genetic Variance



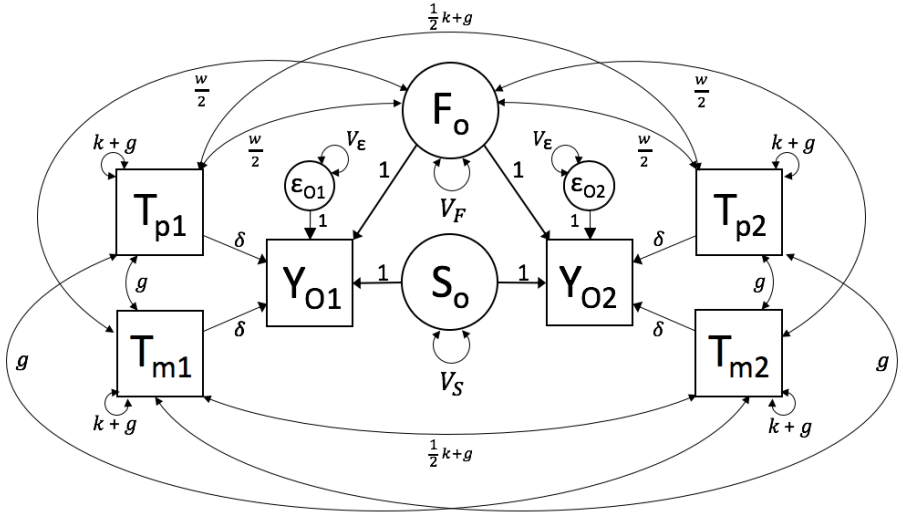
Trio



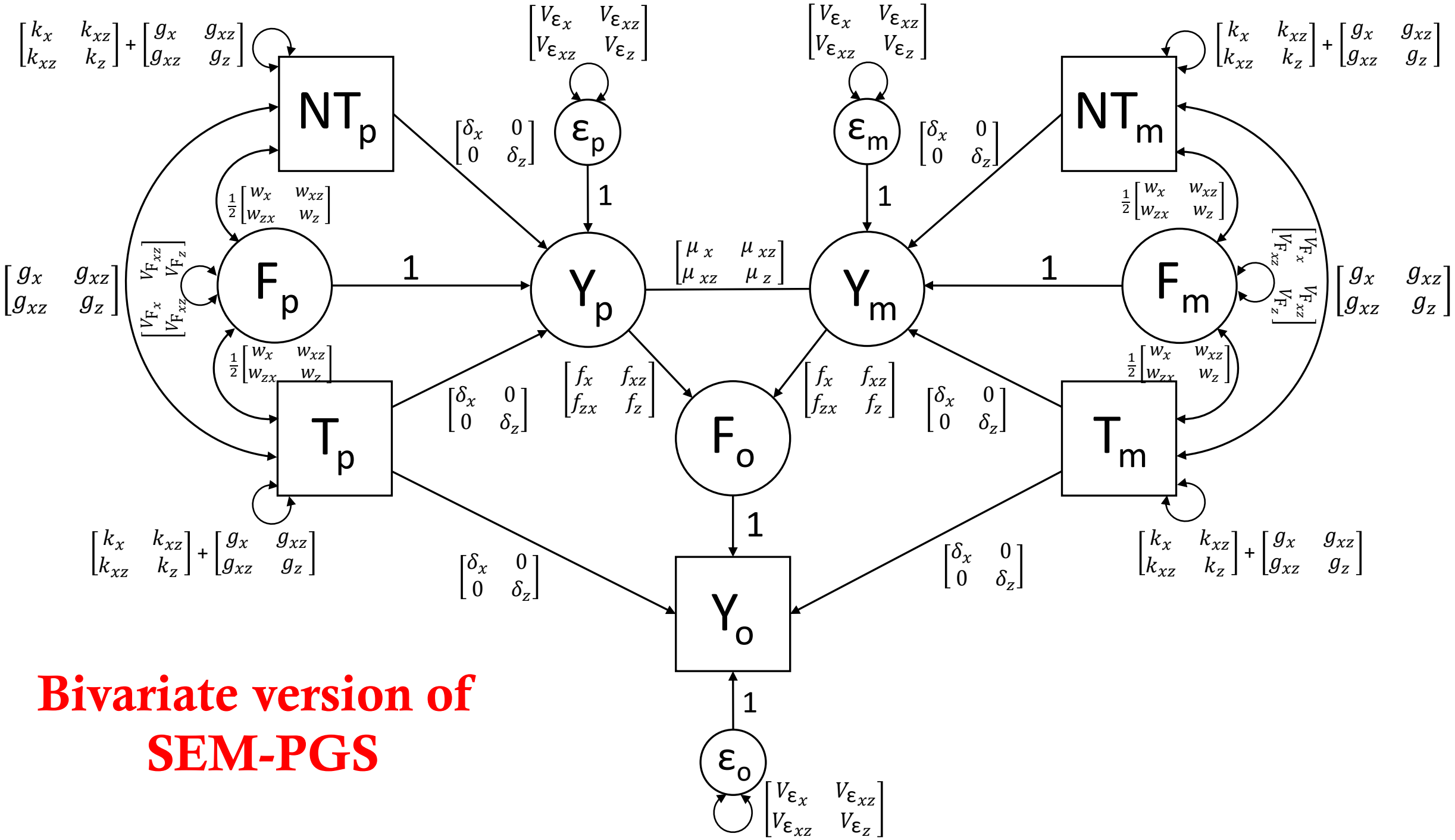
Spouse

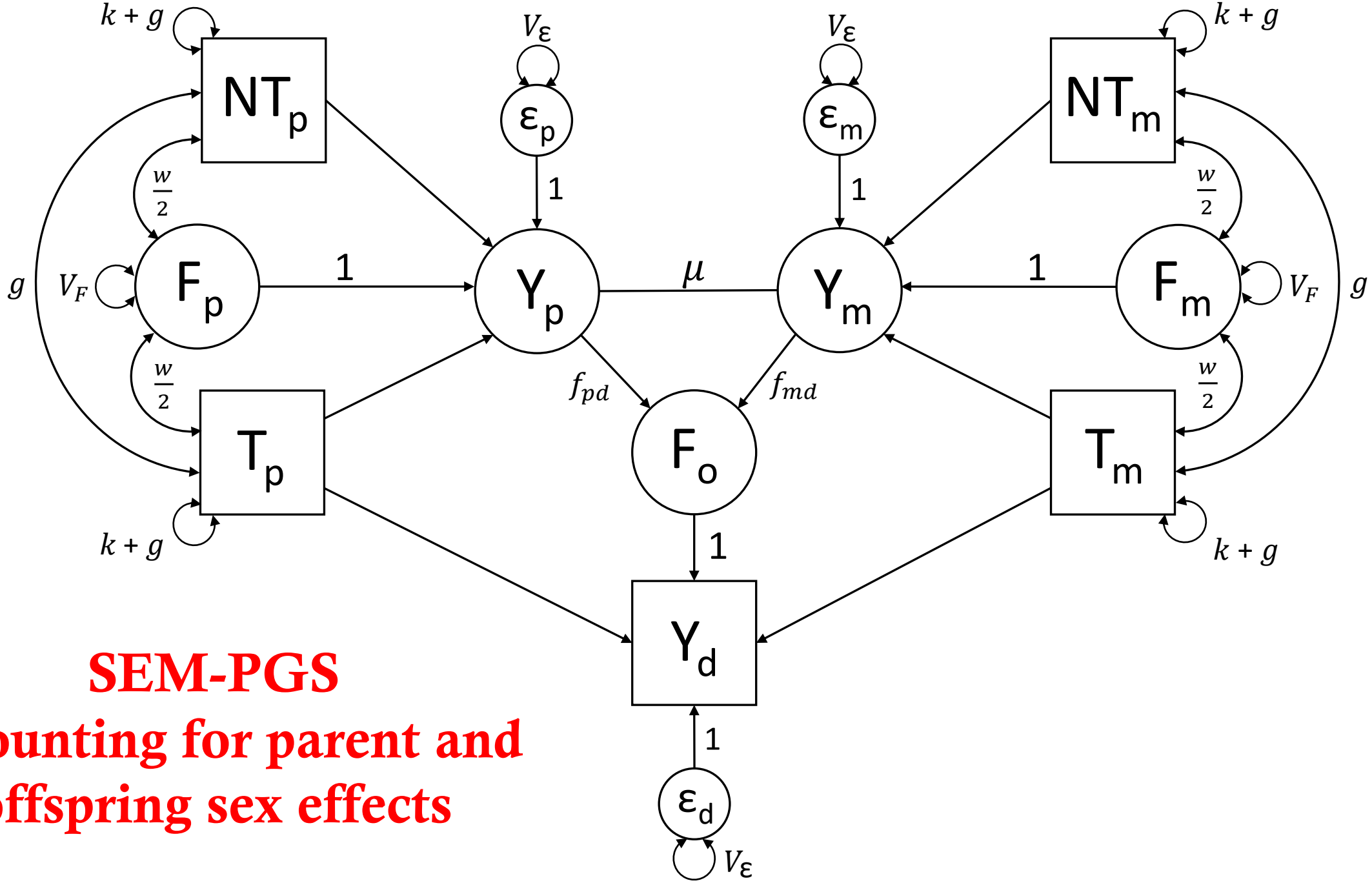


Parent-Offspring



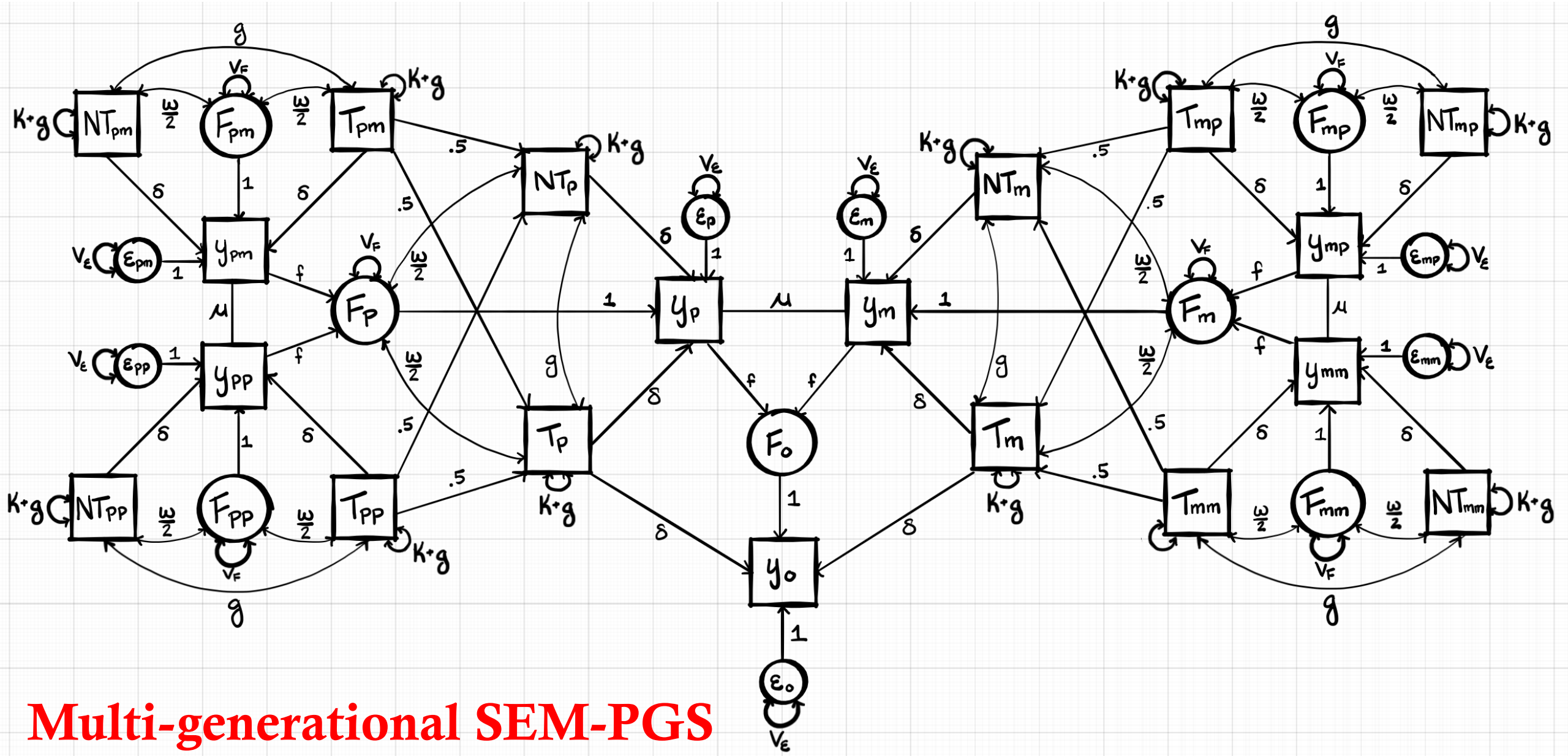
Sibling


NTp
εp
NTm
εm
Fp
Yp
Ym
Fm
Tp
Fo
Tm
Yo
εo
1
Bivariate version of
SEM-PGS



SEM-PGS

accounting for parent and offspring sex effects



Multi-generational SEM-PGS

Final Note

Overview of the Script

Step 1

$x = 2yz$

$y = x/z - y$

$z = (x + z) / 3y$

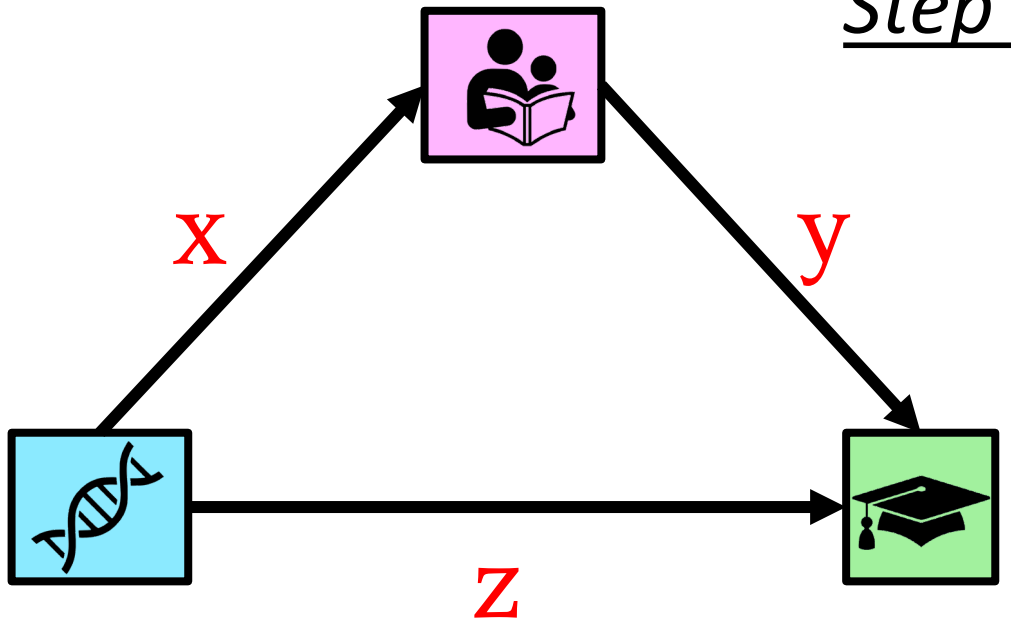
Step 1

$x = 2yz$

$y = x/z - y$

$z = (x + z) / 3y$

Step 2



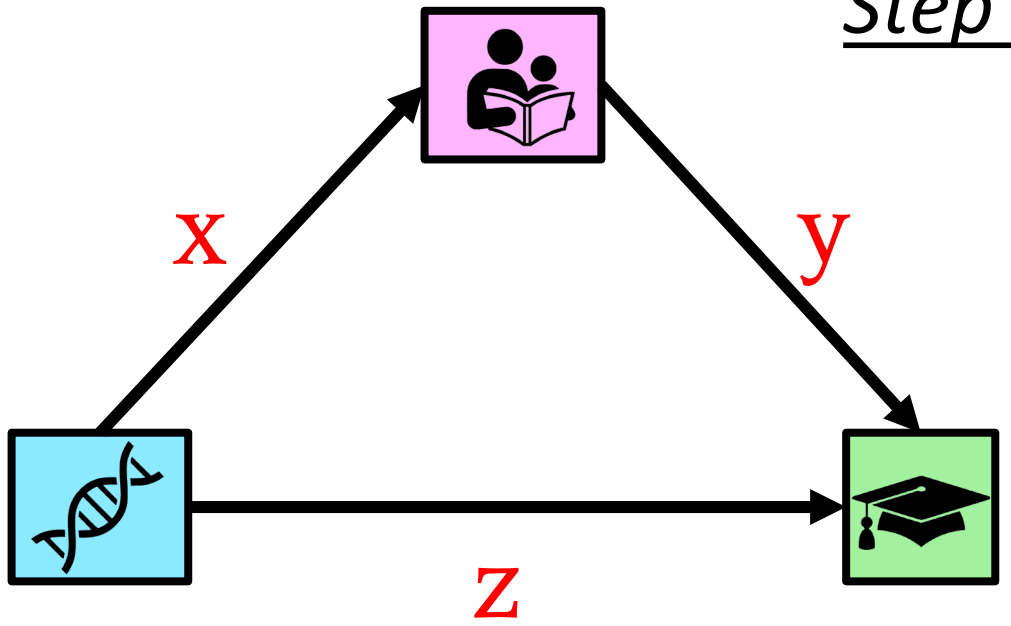
Step 1

$$x = 2yz$$

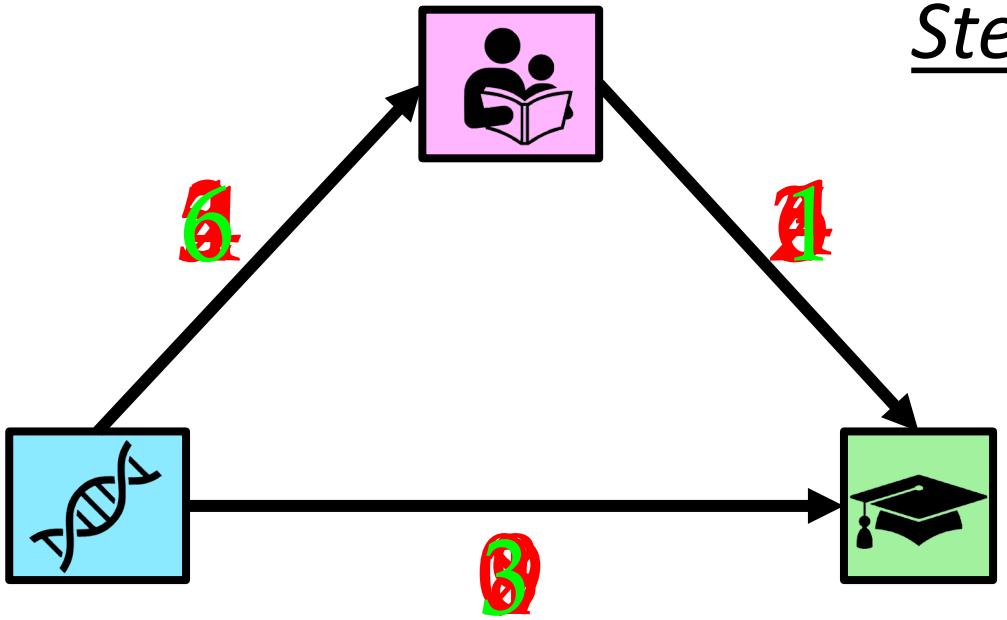
$$y = x/z - y$$

$$z = (x + z) / 3y$$

Step 2



Step 3



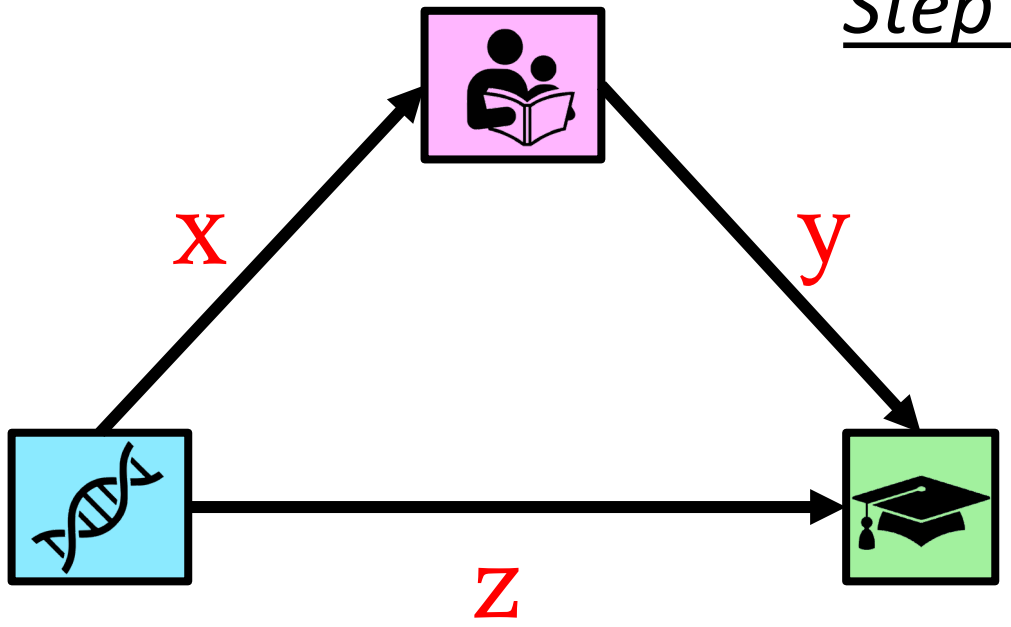
Step 1

$$x = 2yz$$

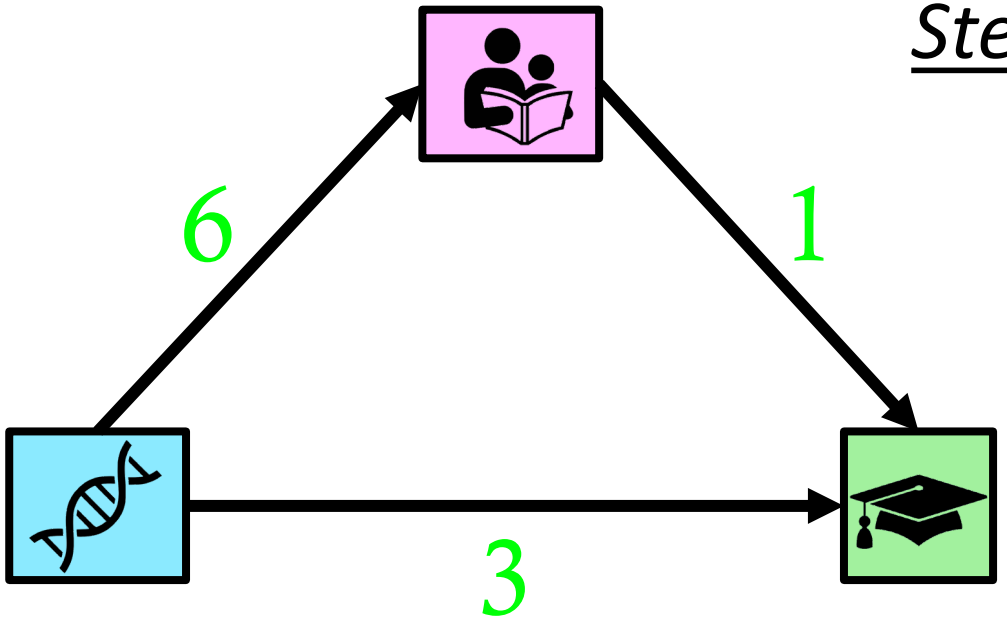
$$y = x/z - y$$

$$z = (x + z) / 3y$$

Step 2



Step 3



Step 4