Nested Hypotheses:
An example in Genetics

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Nested Hypotheses

- Most clinical trials today have the objective of deciding if a polymorphism is associated with a disease: That is, one is question if an allel a could be the cause of a the disease.
- Two groups, called case and control are observed to obtain the genotypic frequencies.

Genotype	AA	Aa	aa	S. Size
Case	x_{AA}	x_{Aa}	x_{aa}	n
Control	y_{AA}	y_{Aa}	y_{aa}	m

Nested Hypotheses

- The theoretical population frequencies are:

Genotype	AA	Aa	aa
Case	γ_{AA}	γ_{Aa}	γ_{aa}
Control	π_{AA}	π_{Aa}	π_{aa}

1. Test of genotypic homogeneity: $\pi = \gamma$
2. Test of allelic homogeneity:

$$Q(A)=\gamma_{AA}+.5\gamma_{Aa} = \pi_{AA}+.5\pi_{Aa}=P(A)$$

Group	Observed frequency			
	AA	AB	BB	sample
Case	55	83	50	188
Control	24	42	39	105

Group	ML estimates: genotipic homogeneity			
	AA	AB	BB	sum
Case	0,27	0,43	0,30	1
Control	0,27	0,43	0,30	1

Group	Expected frequency: genotipic homogeneity			
	AA	AB	BB	sample
Case	50,69	80,20	57,11	188
Control	28,31	44,80	31,89	105

0,37	0,10	0,88	1,35
0,66	0,17	1,58	2,41

Chi-squared 3,76

p-value 15,24%

Group	Observed frequency			
	AA	AB	BB	sample
Case	55	83	50	188
Control	24	42	39	105

Group	Allelic Frequency		
	A	B	sum
Case	193	183	376
Control	90	120	210

Group	ML allelic estimates		
	A	B	sum
Case	0,51	0,49	1
Control	0,43	0,57	1

Group	Allelic Exp. Frequency		
	A	B	Sum
Case	181,58	194,42	376
Control	101,42	108,58	210

0,72	0,67	1,39
1,29	1,20	2,49

Chi-square 3,87

p-value 4,91%

Group	Frequencia observada			
	AA	AB	BB	sample
Case	55	83	50	188
Control	24	42	39	105

	ML estimates; allelic homogeneity			
	AA	AB	BB	sum
Case	0,26	0,44	0,30	1
Control	0,28	0,40	0,31	1

Group	Expected frequency: allelic homogeneity			
	AA	AB	BB	sample
Case	49,66	82,73	55,61	188
Control	29,72	42,25	33,04	105

0.57	0.001	0.57	1.14
1.10	0.001	1.08	2.18

Chi-squar 3.32

p-value 6.85%

Group	Observed frequency			
	AA	AB	BB	sample
Case	55	83	50	188
Control	24	42	39	105

Group	Expected under HWE			
	AA	AB	BB	sample
Case	49.533	93.934	44.533	188
Control	19.286	51.429	34.286	105

HWE	Alele Freq.	
	p(A)	p(B)
case	0.5133	0.4867
control	0.4286	0.5714

Chi	p-value
2.5470	11.05%
3.5292	6.03%

$\boldsymbol{P_1}$= population frequency of AA
$\boldsymbol{P_2}$= population frequency of Aa
$\boldsymbol{P_3}$= population frequency of aa

Next generation $\boldsymbol{Q_1}$, $\boldsymbol{Q_2}$, $\boldsymbol{Q_3}$.

Type of coupling	Type of offspring		
	AA	Aa	aa
AA x AA	$(P_1)(P_1)$	0	0
AA x Aa	$(P_1)(P_2)/2$	$(P_1)(P_2)/2$	0
AA x aa	0	$(P_1)(P_3)$	0
Aa x AA	$(P_1)(P_2)/2$	$(P_1)(P_2)/2$	0
Aa x Aa	$(P_2)(P_2)/4$	$(P_2)(P_2)/2$	$(P_2)(P_2)/4$
Aa x aa	0	$(P_3)(P_2)/2$	$(P_3)(P_2)/2$
aa x AA	0	$(P_1)(P_3)$	0
aa x Aa	0	$(P_3)(P_2)/2$	$(P_3)(P_2)/2$
aa x aa	0	0	$(P_3)(P_3)$
Next Generation	Q_1	Q_2	Q_3

$$Q_1 = P_1^2 + 2\frac{P_1P_2}{2} + \frac{P_2^2}{4} = \left(P_1 + \frac{P_2}{2}\right)^2; \quad Q_3 = \left(P_3 + \frac{P_2}{2}\right)^2$$

$$Q_2 = 2\frac{P_1P_2}{2} + 2\frac{P_3P_2}{2} + 2P_1P_3 + 2\frac{P_2^2}{2} = 2\left(P_1 + \frac{P_2}{2}\right)\left(P_3 + \frac{P_2}{2}\right)$$

$$Q_1 = P_1^2 + 2\frac{P_1P_2}{2} + \frac{P_2^2}{4} = \left(P_1 + \frac{P_2}{2}\right)^2; \quad Q_3 = \left(P_3 + \frac{P_2}{2}\right)^2$$

$$Q_2 = 2\frac{P_1P_2}{2} + 2\frac{P_3P_2}{2} + 2P_1P_3 + 2\frac{P_2^2}{2} = 2\left(P_1 + \frac{P_2}{2}\right)\left(P_3 + \frac{P_2}{2}\right)$$

$$P_1 = p^2; \quad P_2 = 2p(1-p) \quad P_3 = (1-p)^2$$

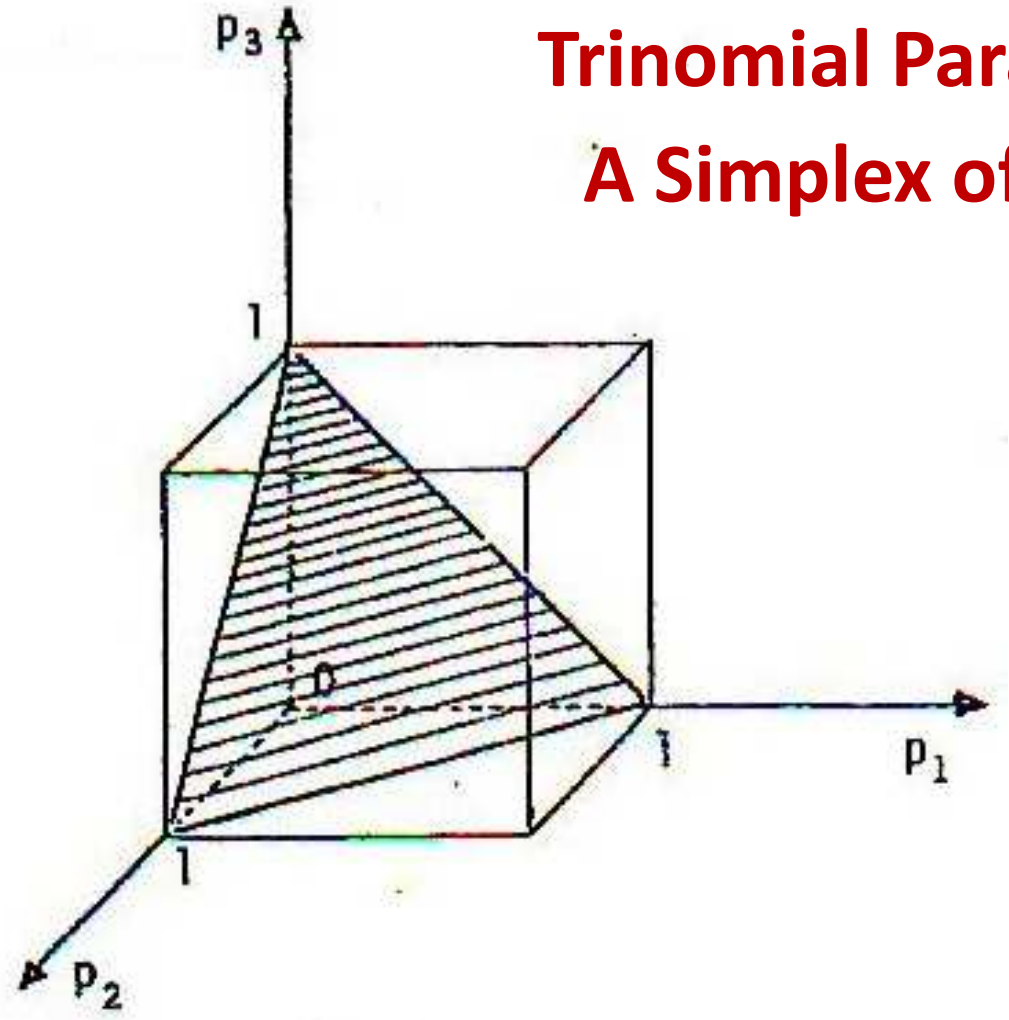
$$Q_1 = p^4 + 2p^3(1-p) + p^2(1-p)^2 = p^2; \quad Q_3 = (1-p)^2$$

$$Q_2 = 2p^3(1-p) + 4p^2(1-p)^2 + 2p(1-p)^3 = 2p(1-p)$$

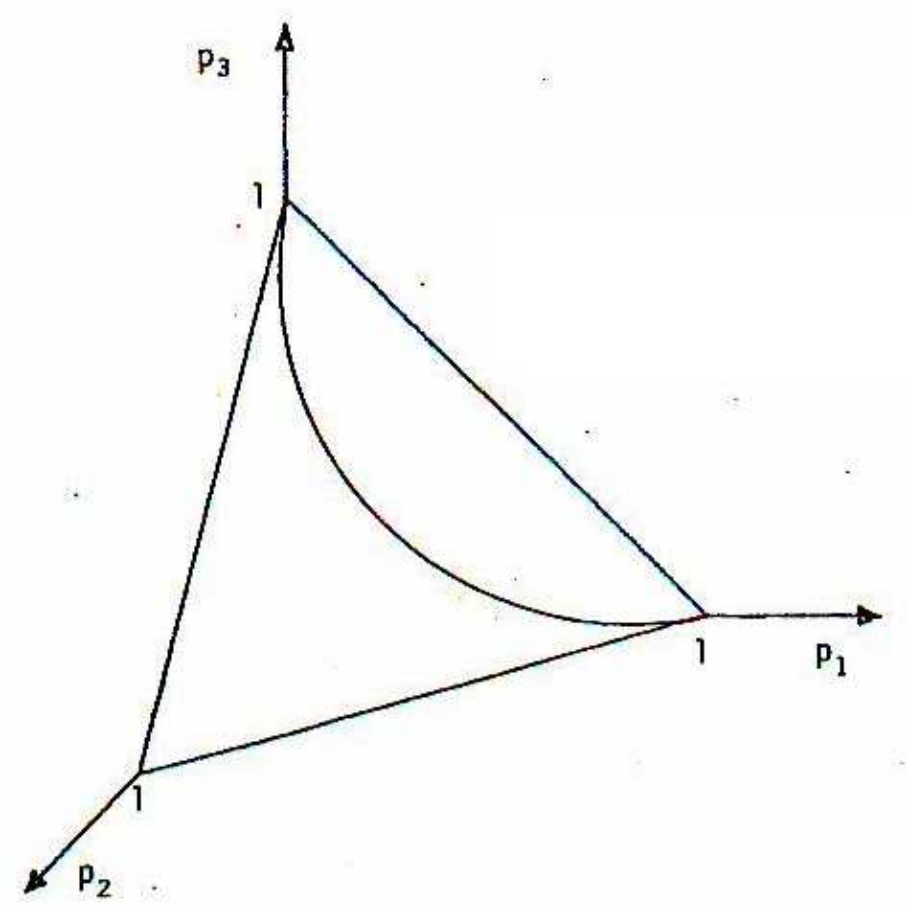
Note that $p = P_1 + \frac{1}{2}P_2 = 1 - \left(P_3 + \frac{1}{2}P_2\right)$

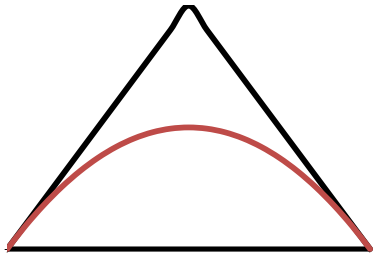
is the allelic frequency

Trinomial Parameter Space: A Simplex of Dim 2 in $\mathfrak{R}^3$

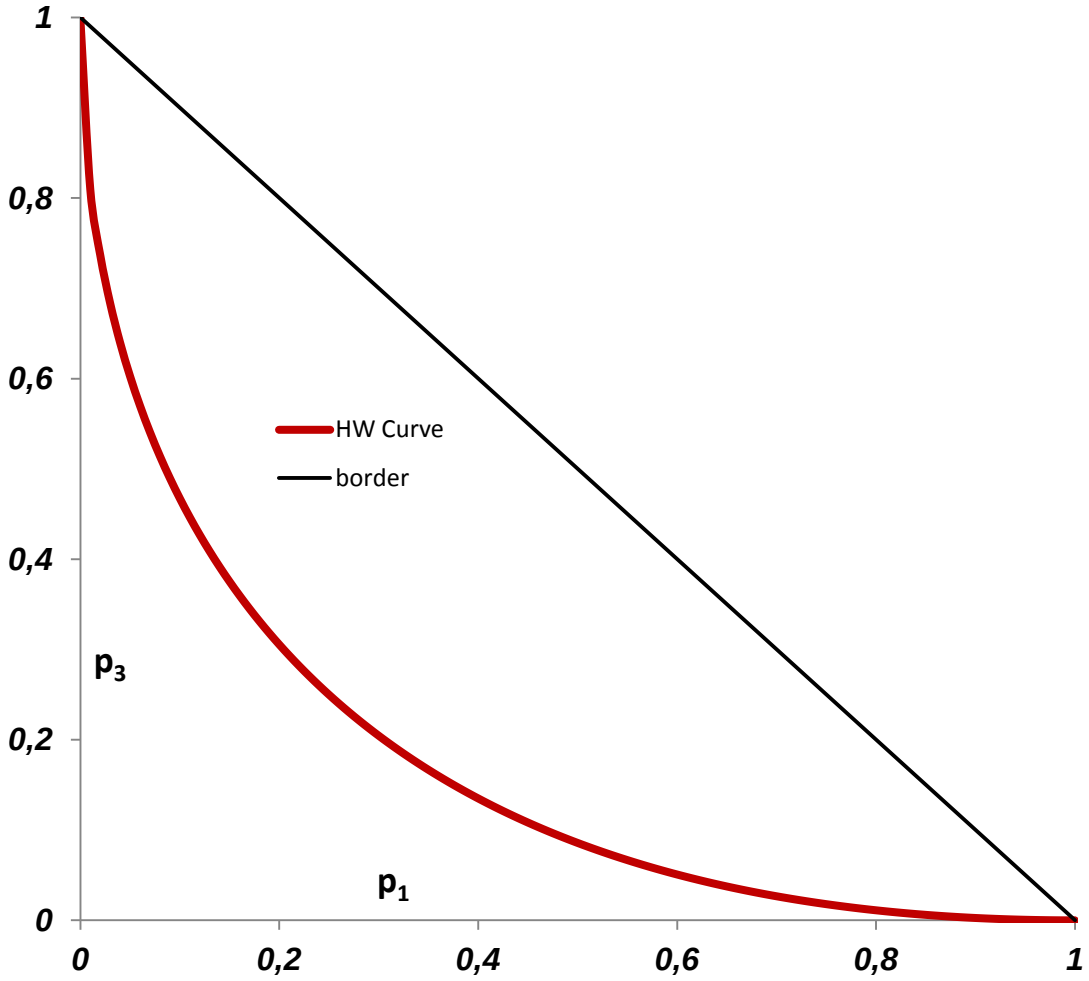


HW Equilibrium hypothesis subspace of Dim 1 in $\mathfrak{R}^3$

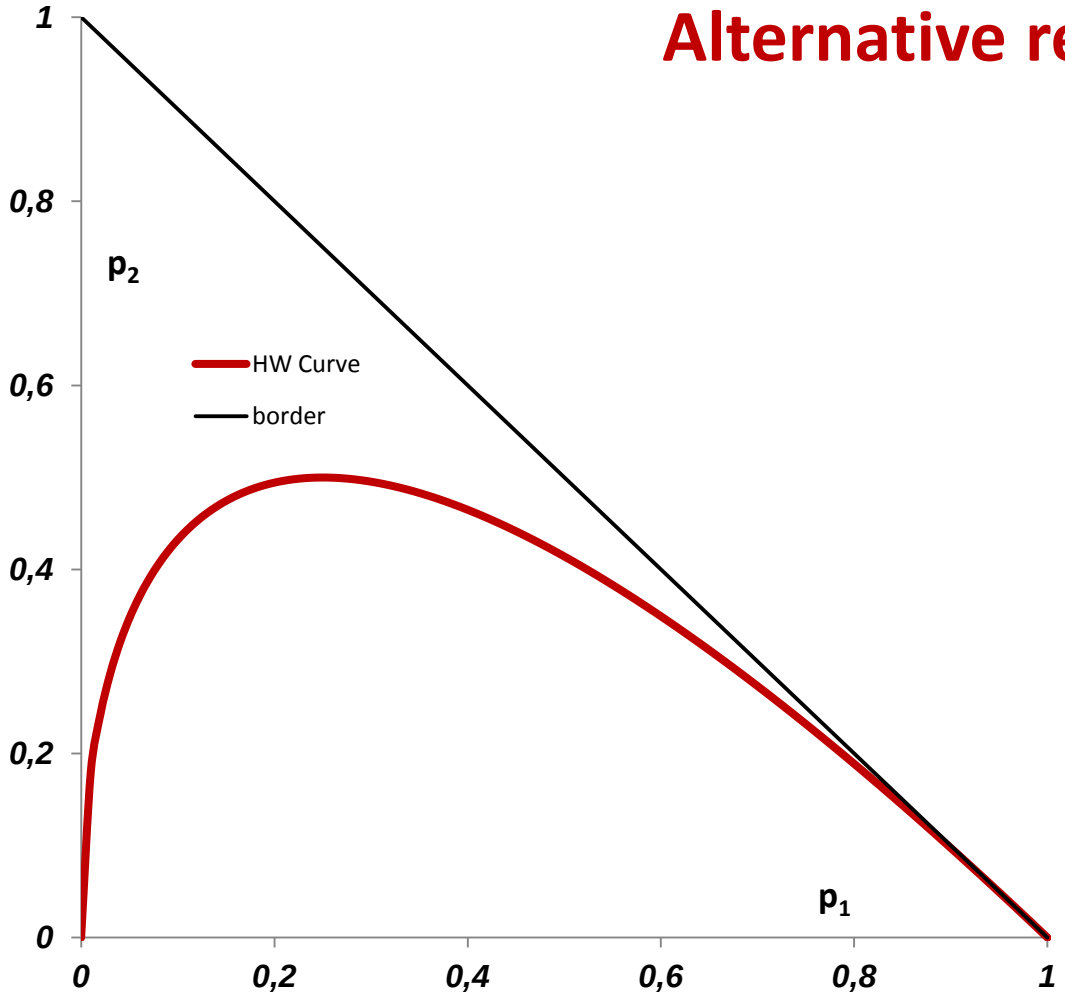




HW Equilibrium hypothesis subspace of Dim 1 in $\mathfrak{R}^2$



HW Equilibrium hypothesis subspace of Dim 1 in $\mathfrak{R}^2$: Alternative representation



aleles	A	B
A	P(AA)	P(AB)
B	P(BA)	P(BB)

aleles	A	B
A	p1	.5p2
B	.5p2	p3

Association index for binary data:
Disequilibrium Coefficient

Brentani H; Nakano EY; Martins CB; Izbicki R; Pereira CAB (2011), Disequilibrium coefficient: Bayesian perspective, *Statistical Applications in Genetics and Molecular Biology* 10(1): Article 22

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Hardy-Weimberg Law

- **Hardy-Weinberg law shows that in a Mendelian population, under certain restrictions, allele frequencies will be constant through generations; alternatively, been in HWE means that the relation of the proportions of the genotypes in a specific locus exhibit a special association between the alleles transmitted from parents.**

MATERIAL & METHODS

- In order to see if a population is in HWE one takes a sample of size $n=n_1+n_2+n_3$ and observe n_1, n_2, n_3, the absolute frequencies of the genotypes ***AA, Aa, aa***, respectively. Let π_1, π_2 , π_3 be the population frequencies of these genotypes, with $\pi_1+\pi_2+\pi_3=1$ and $\pi_i \geq 0$, **i=1,2,3**. If we consider genotypes from different individuals to be statistically independent, likelihood function can be expressed as

Likelihood

$$\mathbf{L}(\pi_1, \pi_2, \pi_3 \mid \mathbf{n_1}, \mathbf{n_2}, \mathbf{n_3}) \propto \pi_1^{\mathbf{n_1}} \pi_2^{\mathbf{n_2}} \pi_3^{\mathbf{n_3}}$$

with $\propto$ denoting proportionality. Note that the parametric space is

$$\Theta = \left\{ (\mathbf{p_1}, \mathbf{p_2}, \mathbf{p_3}) : \mathbf{p_1} \geq \mathbf{0} \wedge \mathbf{p_2} \geq \mathbf{0} \wedge \mathbf{p_3} \geq \mathbf{0} \wedge \mathbf{p_1} + \mathbf{p_2} + \mathbf{p_3} = \mathbf{1} \right\}$$

- HWE holds if, and only if, there exists $0 < \pi < 1$ such that $\pi_1 = \pi^2$, $\pi_2 = 2\pi(1-\pi)$, $\pi_3 = (1-\pi)^2$

- **The HWE null hypothesis is:**

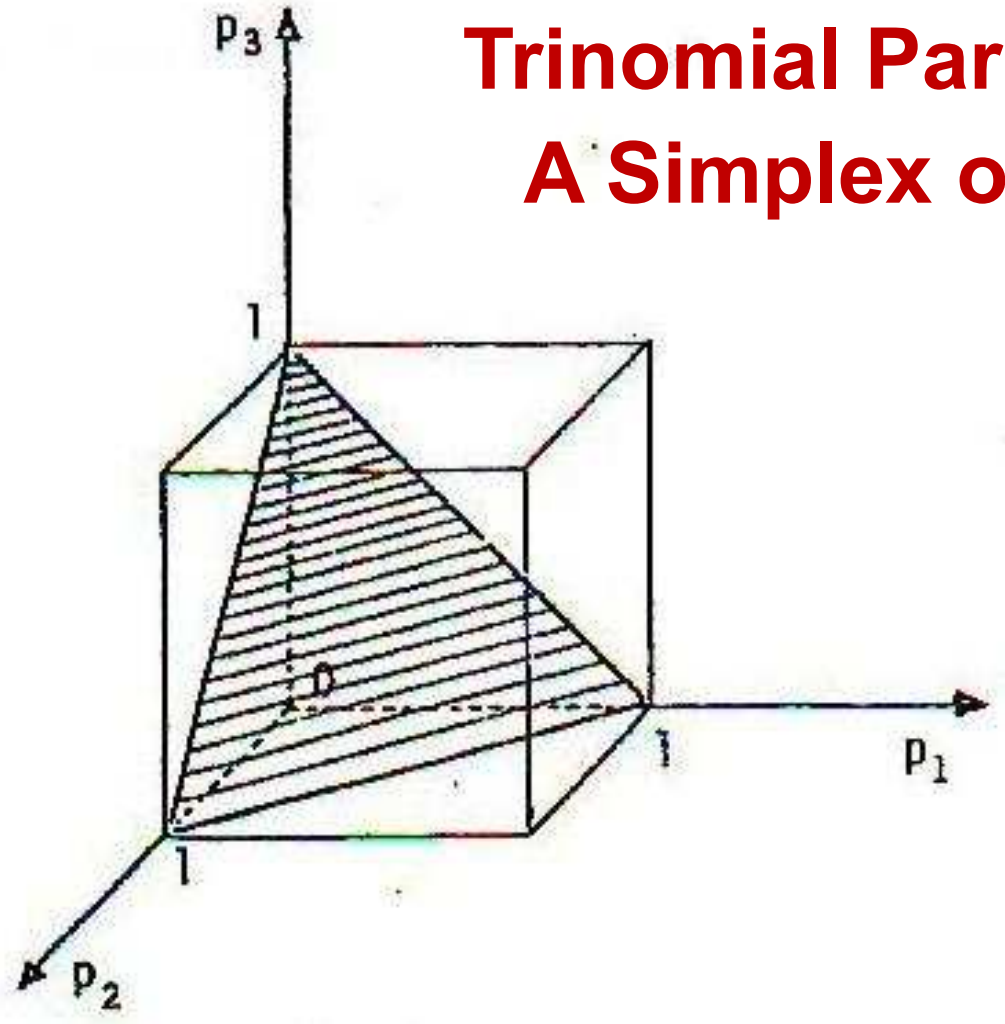
$$\mathrm{H}: \theta \in \Theta_{\mathrm{H}} \quad \textbf{with} \quad \theta = (\pi_1; \pi_2; \pi_3) \quad \&$$

$$\Theta_{\mathrm{H}} =$$

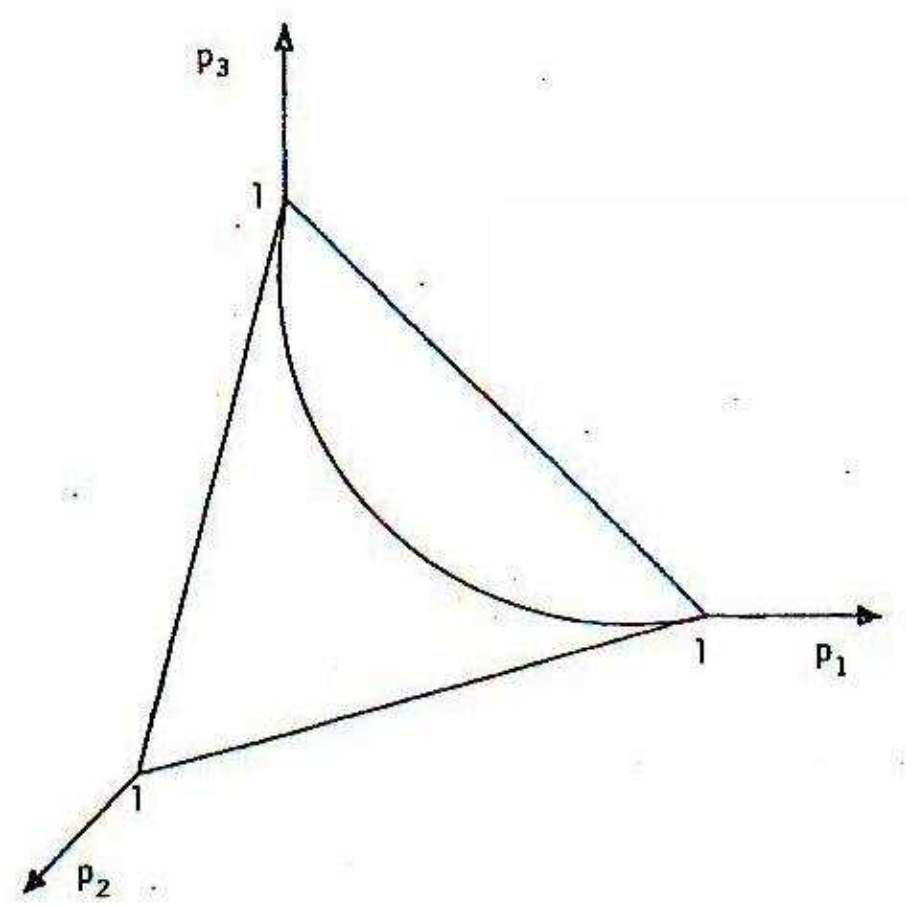
$$\left\{ (p_1, p_2, p_3) : \exists\, p \in [0;1] \therefore \left(p_1 = p^2\right) \wedge \left(p_3 = (1-p)^2\right) \right\} \subset \Theta.$$

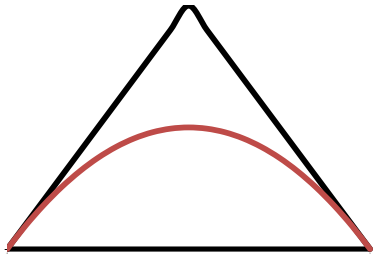
$$\Theta = \left\{ (p_1, p_2, p_3) : \forall i;\, p_i \geq 0 \wedge p_1 + p_2 + p_3 = 1 \right\}$$

Trinomial Parameter Space: A Simplex of Dim 2 in $\mathfrak{R}^3$

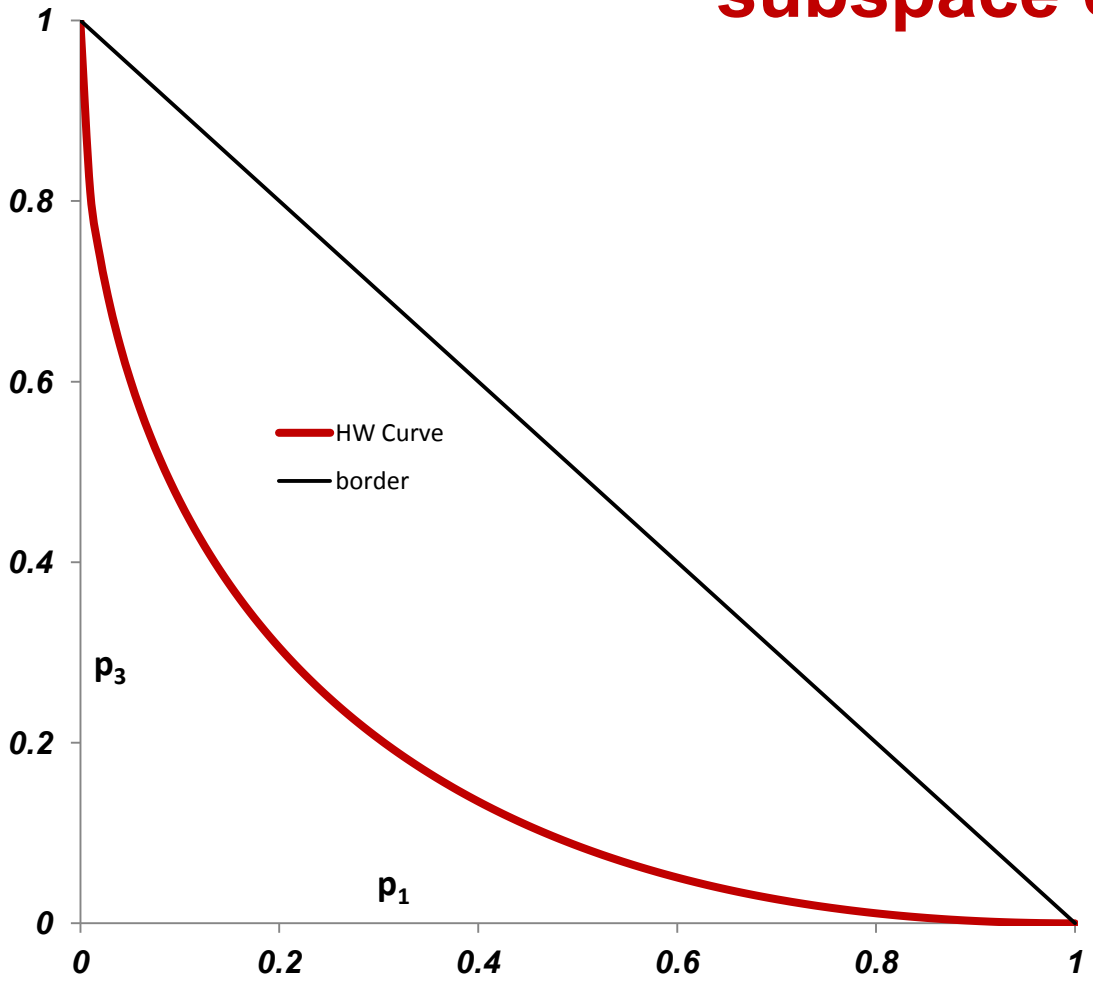


HW Equilibrium hypothesis subspace of Dim 1 in $\mathfrak{R}^3$

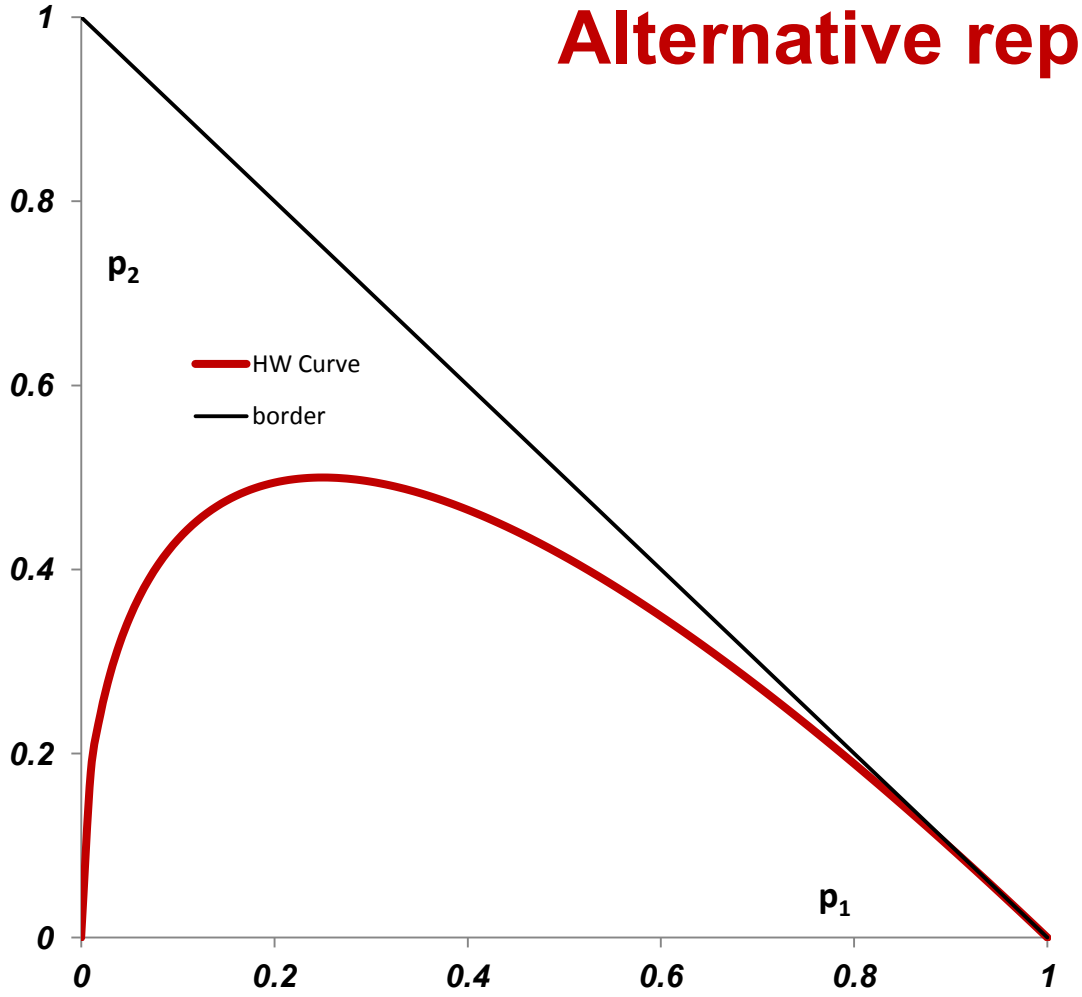




HW Equilibrium hypothesis subspace of Dim 1 in $\mathfrak{R}^2$



HW Equilibrium hypothesis subspace of Dim 1 in $\mathfrak{R}^2$: Alternative representation



Conjugate Bayesian Operation: Prior/Posterior

$$f(\theta \mid d) = \Gamma(n+a)\prod_{i=1}^{3}\frac{\pi_i^{(n_i+a_i-1)}}{\Gamma(n_i+a_i)} \qquad \text{for } \theta \in \Theta$$

Taking $A_i = n_i + a_i$ for $(a_1; a_2; a_3)$ the prior parameter:

$$\hat{\theta} = \mathbf{E}(\theta \mid \mathbf{d}) = \left(\frac{\mathbf{A_1}}{\mathbf{A}}, \frac{\mathbf{A_2}}{\mathbf{A}}, \frac{\mathbf{A_3}}{\mathbf{A}}\right) = \left(\hat{\theta}_1, \hat{\theta}_2, \hat{\theta}_3\right) \quad \&$$

$$\Sigma = \frac{1}{\mathbf{A}+1}\left(\begin{pmatrix} \hat{\theta}_1 & 0 & 0 \\ 0 & \hat{\theta}_2 & 0 \\ 0 & 0 & \hat{\theta}_3 \end{pmatrix} - \begin{pmatrix} \hat{\theta}_1 \\ \hat{\theta}_2 \\ \hat{\theta}_3 \end{pmatrix}\left(\hat{\theta}_1, \hat{\theta}_2, \hat{\theta}_3\right)\right)$$

Disequilibrium Coefficient

- **The disequilibrium coefficient, denoted by λ, is now defined and will be explained and motivated in the next section. In fact this coefficient is a modification of the one presented by Pereira and Rogatko (1984). This new is based on the correlation coefficient proposed by Yule (1912) to measure association of two binary variables.**

Definition

- **Since we have the complete specification of the parameter θ and the fact that λ is simply a function of θ, we may obtain also the specification of the distribution of λ.**
- **Definition: The Hardy-Weinberg disequilibrium coefficient is defined as follows:**

$$\lambda = \frac{\sqrt{\pi_1\pi_3} - \frac{1}{2}\pi_2}{\sqrt{\pi_1\pi_3} + \frac{1}{2}\pi_2} \quad \in [-1;1]$$

Motivation

Table 1: Frequency data, ***n***, (parameters, π) in a multinomial classification

$_{t}\backslash^{g}$	g	G
t	$n_1(\pi_1)$	$n_{12}(\pi_{12})$
T	$n_{21}(\pi_{21})$	$n_3(\pi_3)$

Dirichlet prior parameter = $(a_1;a_{12};a_{21};a_3)$, data = d = $(n_1;n_{12};n_{21};n_3)$, & Dirichlet posterior parameter = $(A_1;A_{12};A_{21};A_3)$; $A_i=a_i+n_i$

$$\text{Cross product ratio is } \psi = \frac{\pi_1\pi_3}{\pi_{12}\pi_{21}} \text{ with}$$

$$E(\psi \mid d) = \frac{A_1A_2}{(A_{12}-1)(A_{21}-1)} \;\&\; V(\psi \mid d) = \frac{A_1A_3(A_1+A_{12}-1)(A_3+A_{21}-1)}{(A_{12}-1)(A_{21}-1)(A_{12}-2)(A_{21}-2)}$$

Yule´s Association Coefficient

- Yule (1912) understood that although ψ could be considered an association coefficient, it is unbounded & unbalanced: negative association occurs if $\psi \in (0;1)$, independence if $\psi = 1$, and positive association if $\psi \in (1;\infty)$. Hence, defined

$$\lambda = \frac{\sqrt{\pi_1\pi_3} - \sqrt{\pi_{12}\pi_{21}}}{\sqrt{\pi_1\pi_3} + \sqrt{\pi_{12}\pi_{21}}} = \frac{\sqrt{\psi} - 1}{\sqrt{\psi} + 1} \in (-1;+1)$$

First Example

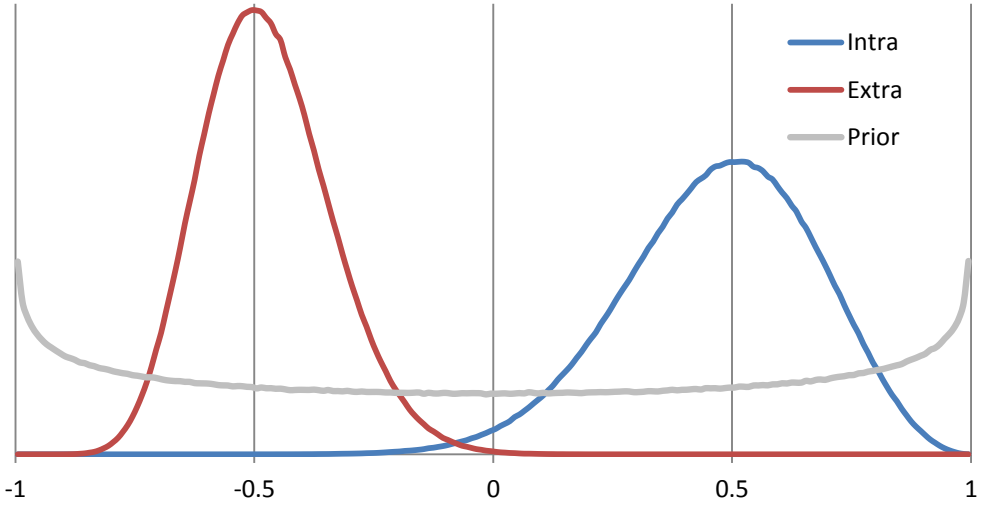
Jefrey´s prior

$$(\pi_1;\pi_{12};\pi_{21};\pi_3) \approx \mathrm{D}\left(\frac{1}{2};\frac{1}{2};\frac{1}{2};\frac{1}{2}\right)$$

TABLE 2: Outcomes of the diagnostic tests for 93 children

	Extra-hepatic			Intra-hepatic			Total
Results	E^+	E^-	Sum	E^+	E^-	Sum	
$\varepsilon+$	5	9	14	28	12	40	54
$\varepsilon-$	28	6	34	1	4	5	39
Sum	33	15	48	29	16	45	93

Figure 1: Jeffreys' prior and posterior densities for extra- & intra-hepatic groups



Statistics

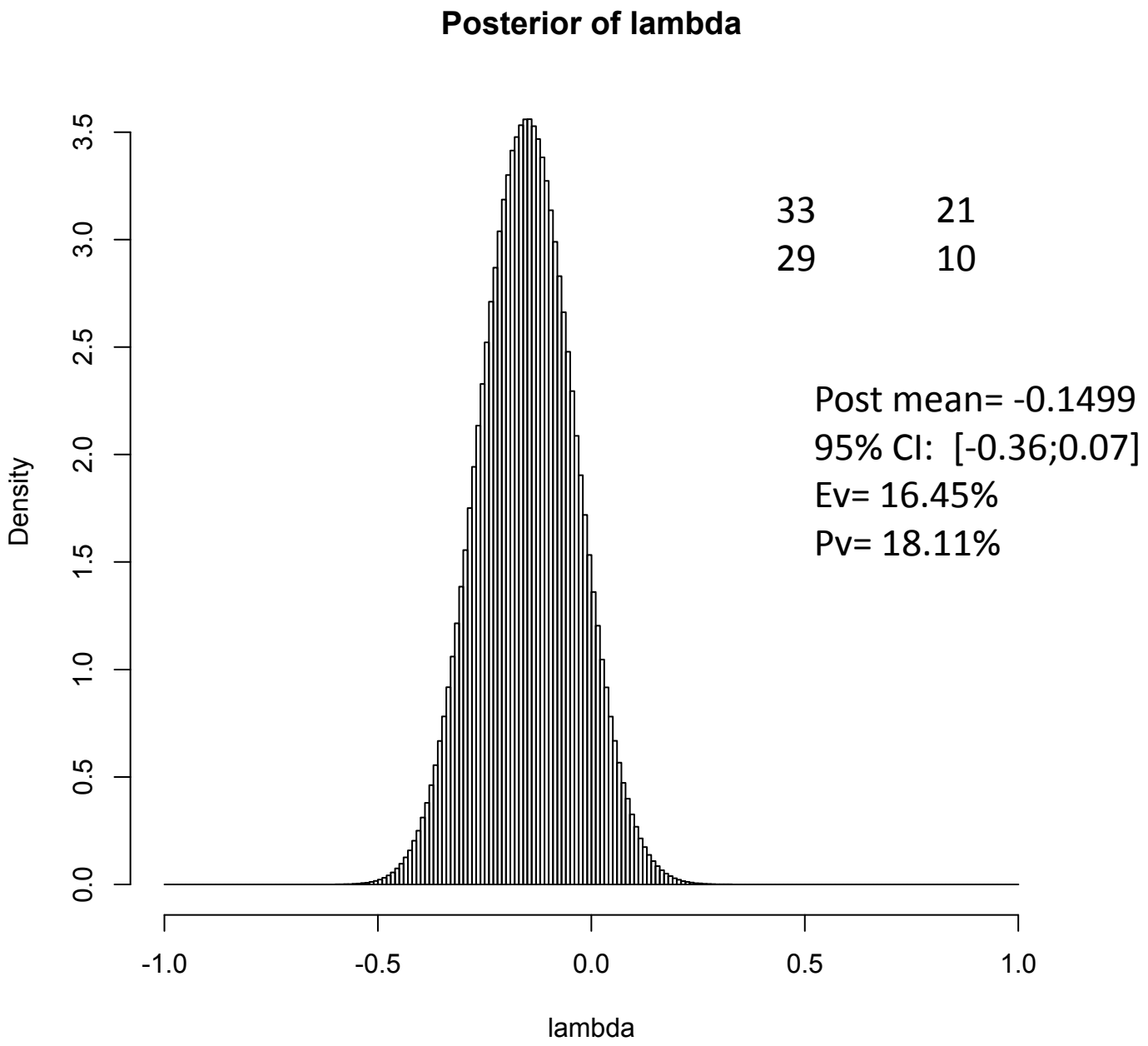
$$\text{Bayes Estimates: } E(\lambda \mid d) = \begin{cases} -0.4750 \text{ for Extra} - \text{Hepatic} \\ 0.4723 \text{ for Intra} - \text{Hepatic} \end{cases}$$

$$\text{MLEstimates: for EH is } (-.49) \text{ and for IH is } (.51).$$

$$95\% \text{ credible sets: } \begin{cases} (-.72;-.21) \text{ for Extra} - \text{Hepatic} \\ (+.08;+.85) \text{ for Intra} - \text{Hepatic} \end{cases}$$

$$\text{Significance Index: Bayes (ev)} \begin{cases} 0.13\% \text{ for Extra} - \text{Hepatic} \\ 1.96\% \text{ for Intra} - \text{Hepatic} \end{cases}$$

$$\text{Significance Index: } \chi^2 \quad (\text{pv}) \begin{cases} 0.12\% \text{ for Extra} - \text{Hepatic} \\ 1.81\% \text{ for Intra} - \text{Hepatic} \end{cases}$$


Posterior of lambda
Density
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
-1.0
-0.5
0.0
0.5
1.0
lambda
33 21
29 10
Post mean= -0.1499
95% CI: [-0.36;0.07]
Ev= 16.45%
Pv= 18.11%

Disequilibrium coefficient based in the Yule´s association coefficient

		Father´s Allel A	Father´s Allel D
Mother´s Allel	A	$n_1(\pi_1)$	$n_{12}(\pi_{12})$
	D	$n_{21}(\pi_{21})$	$n_3(\pi_3)$

Having the secondary diagonal cells be confounded in one, we replace the table by

		Father´s Allel A	Father´s Allel D
Mother´s Allel	A	$n_1(\pi_1)$	$.5n_2(.5\pi_2)$
	D	$.5n_2(.5\pi_2)$	$n_3(\pi_3)$

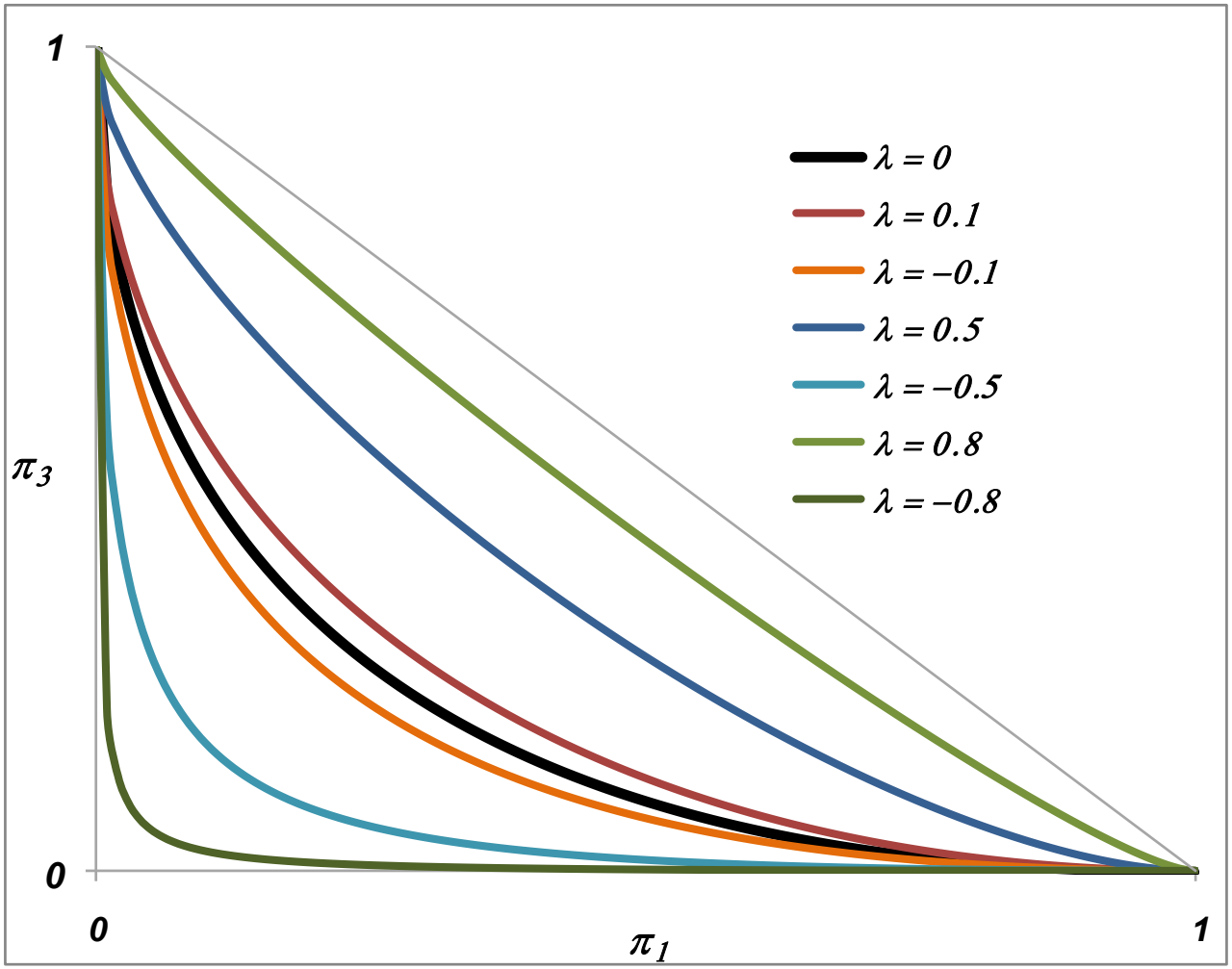
$n_2=n_{12}+n_{21}$ & $\pi_2=\pi_{12}+\pi_{21}$

$$\lambda = \frac{\sqrt{\pi_1\pi_3} - \frac{1}{2}\pi_2}{\sqrt{\pi_1\pi_3} + \frac{1}{2}\pi_2} =$$

Pereira & Rogatko (1984) introduced $\rho=\psi^{-1}$.

$$= \frac{\sqrt{\rho^{-1}} - 1}{\sqrt{\rho^{-1}} + 1} \in [-1;1] \text{ for } \rho = \frac{\pi_2^2}{4\pi_1\pi_3}$$

Disequilibrium Curves



Molecular Biology Examples

- **Using data from published studies we calculated the disequilibrium coefficient and plotted the posterior density curves. To date, the APOE-ε4 is the only recognized risk factor to Alzheimer Disease (AD). It is well established that whenever one carries a ε4 allele, his AD risk increases in an allele dose dependent manner.**
- **Previous reports have suggested that additional factors within the APOE locus, in other genes and from the environment might also modulate risk.**
- **Table 3 presents all statistical results and looking at Figure 3a one should see that controls are in HWE. As expected, the density curve includes the zero with high density (tails having large areas). On the other hand, the density curve for the disease state seems to be out of HWE since the zero has low frequency (tails having small areas).**

FIGURE 3 – Posterior Density distributions of cases and controls genotyped for SNPs in APOE gene (a, b, c) and IL6 gene (d).

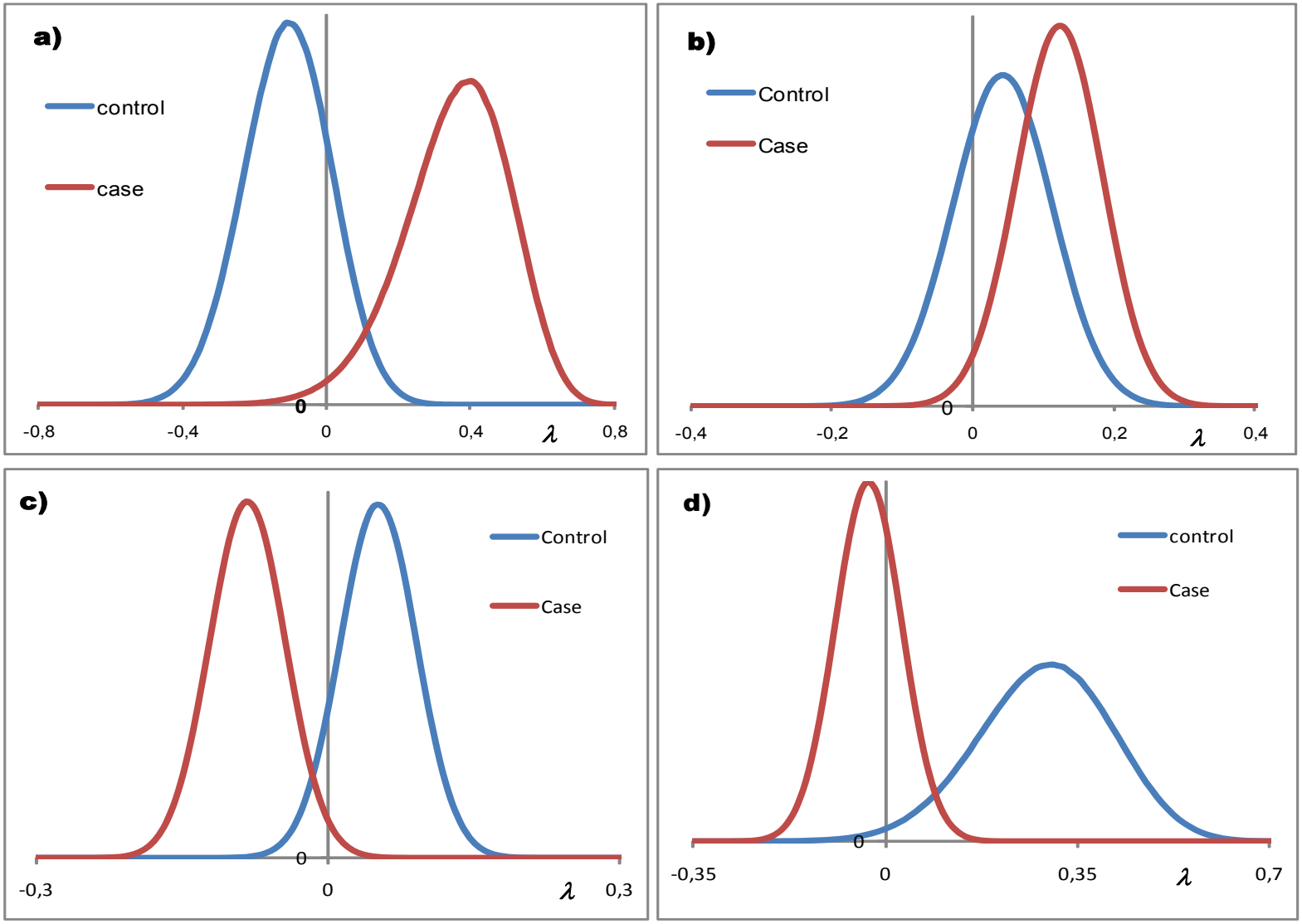


TABLE 3 – Statistical end-points for evaluating disequilibrium.

		Fenotype			λ estimate		95% Credible		e-value	p-value
study	sample	AA	AD	DD	Bayes	MLE	LimInf	LimSup	FBST	$\chi 2$
AD 121 (1)	case	4	18	94	0.357	0.366	0.066	0.649	0.016	0.018
	control	6	53	74	-0.112	-0.114	-0.352	0.128	0.361	0.362
AD 121 (2)	case	57	118	100	0.122	0.123	0.003	0.242	0.045	0.046
	control	58	97	48	0.042	0.042	-0.095	0.179	0.550	0.550
AD 121 (3)	case	120	361	194	-0.084	-0.084	-0.16	-0.007	0.032	0.032
	control	206	309	142	0.051	0.051	-0.026	0.128	0.198	0.197
AD 108 (4)	case	110	148	44	-0.031	-0.031	-0.149	0.088	0.611	0.611
	control	34	22	12	0.290	0.295	0.051	0.529	0.018	0.022

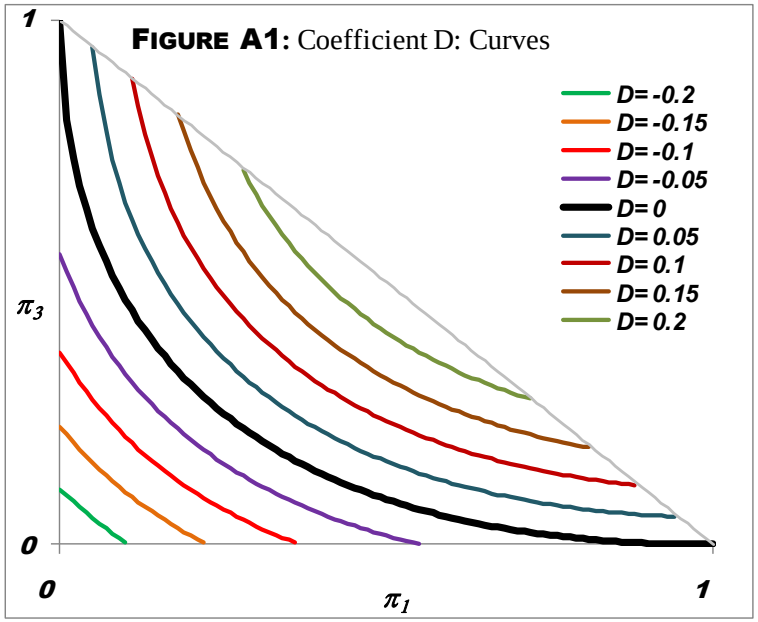


FIGURE A1: Coefficient D: Curves

FIGURE A3: Contour curves of Figure A2

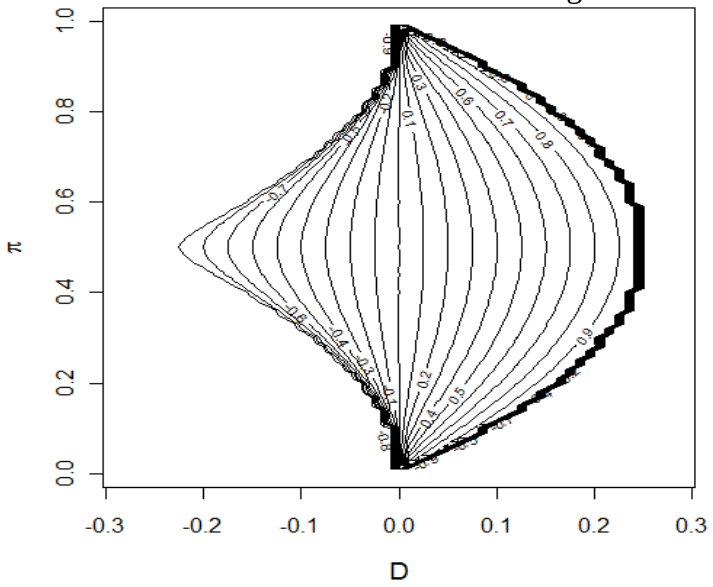
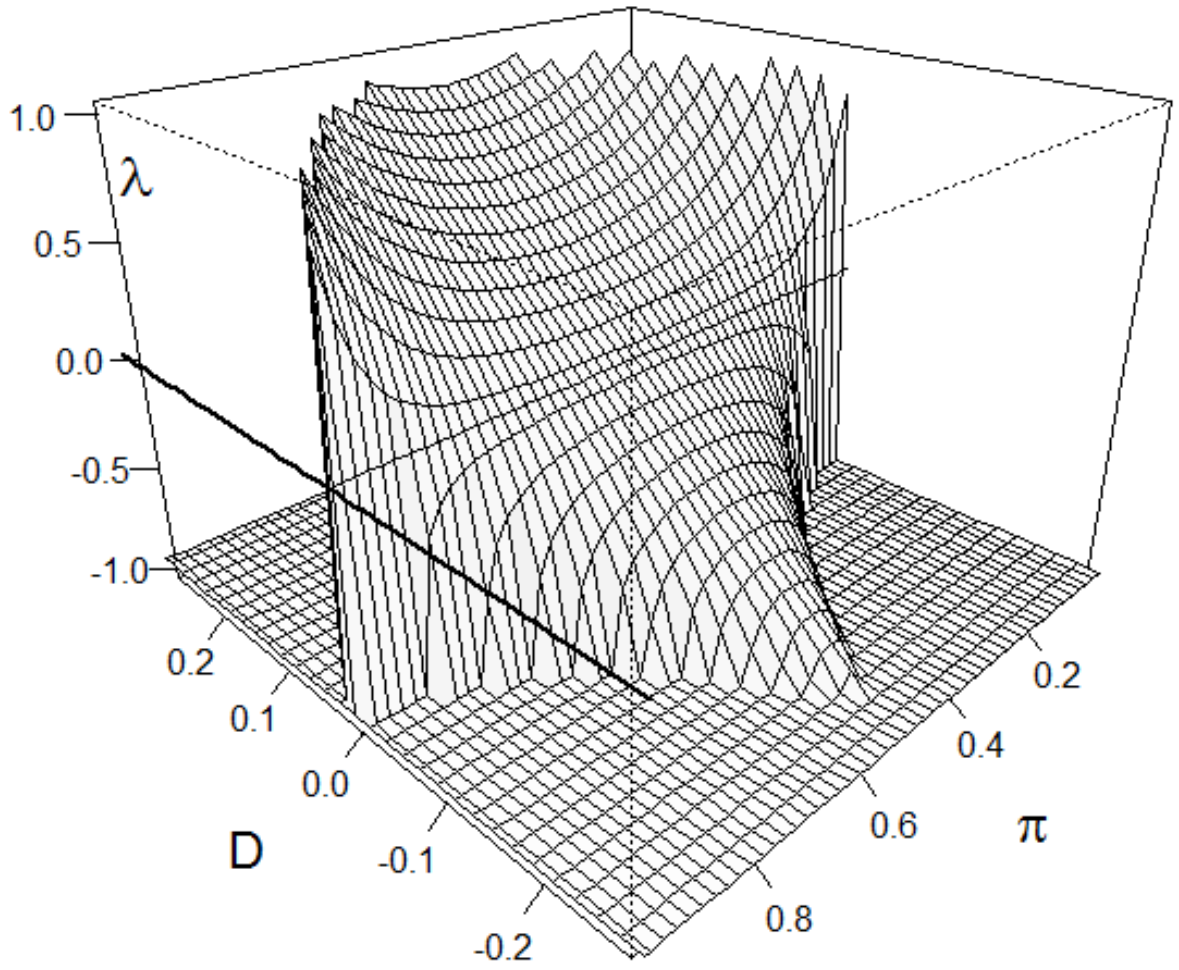


FIGURE A2: λ as a function of (π,D)



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