BIOSTAT/STAT 587 A

Statistical Methods in Infectious Diseasese

Lecture 15

February 24, 2009

What exactly is R_0 anyway?

Theory of heterogeneous mixing; critical vaccination fraction;

R_0 as the eigenvalue of the next generation matrix;

flu optimization

References

- Longini, I.M., Ackerman, E. and Elveback, L.R.: An optimization model for influenza A epidemics. *Mathematical Biosciences* **38**,141-157 (1978).
- Hill, A.N. and Longini, I.M.: The critical vaccination fraction for heterogeneous epidemic models. *Mathematical Biosciences* **181**, 85-106 (2002).
- Patel, R., Longini, I.M., Halloran, M.E.: Finding optimal vaccination strategies for pandemic influenza using genetic algorithms. *Journal of Theoretical Biology* **234**, 201-212 (2005).
- Basta, N., Halloran, M.E., Matrajt, L. and Longini, I.M.: Estimating influenza vaccine efficacy from challenge and community-based study data. *American Journal of Epidemiology* **168**, 1343-1352 (2008).

OBJECTIVES

- Formulate the critical vaccination fraction problem

- Outline two basic approaches
  - Determinantal polynomial
  - Perron-Frobenius eigenvector

- Investigate special cases

- A few words about controlling influenza

(Almost) Basic Model

$$\text{VE}_S = 1 - \theta$$

$$\text{VE}_I = 1 - \phi$$

Partition: K mutually exclusive mixing groups, *e.g.*, age groups, $k = 1, ..., K$; $\nu = 0, 1$

Hazard Rate:

$$\lambda_{k\nu}(t) = \frac{\theta^\nu}{n_k} \sum_{r=1}^{K} c_{kr} p_{kr} \left[I_{r0}(t) + \phi I_{r1}(t) \right]$$

Reproductive numbers: $R_{kr} = p_{kr} c_{kr} d_r, (k, r) = 1, ..., K$

$$\lambda_{k\nu}(t) = \frac{\theta^\nu}{n_k d_k} \sum_{r=1}^{K} R_{kr} \left[I_{r0}(t) + \phi I_{r1}(t) \right]$$

S-I-R Model With No Vital Dynamics

Partition: K mutually exclusive mixing groups, *e.g.*, age groups, $k = 1, ..., K$; $\nu = 0, 1$

$$\frac{dS_{k\nu}(t)}{dt} = -\frac{\theta^{\nu}}{n_k}\sum_{r=1}^{K} c_{kr}p_{kr}\left[I_{r0}(t) + \phi I_{r1}(t)\right],$$

$$\frac{dI_{k\nu}(t)}{dt} = \frac{\theta^{\nu}}{n_k}\sum_{r=1}^{K} c_{kr}p_{kr}\left[I_{r0}(t) + \phi I_{r1}(t)\right] - \frac{I_{k\nu}(t)}{d_{k\nu}},$$

$$\frac{dZ_{k\nu}(t)}{dt} = \frac{I_{k\nu}(t)}{d_{k\nu}},$$

$$S_{k\nu}(t) + I_{k\nu}(t) + Z_{k\nu}(t) = n_{k\nu},$$

$$n_{k1} = f_r n_k,$$

$$S_{k\nu}(0) = n_{k\nu}^{-},\ I_{k\nu}(t) = 0^{+},\ Z_{k\nu}(t) = 0$$

Next Generation Matrix With No Vaccination

Next Generation Matrix $(K \times K)$:

$$\mathbf{R} = \begin{bmatrix} R_{11} & \cdots\cdots\cdots & R_{1K} \\ \vdots & \vdots & \vdots \\ R_{K1} & \cdots\cdots\cdots & R_{KK} \end{bmatrix}$$

Basic Reproductive Number: R_0 largest eigenvalue of matrix $\mathbf{R}$

Threshold Theorem:

If $R_0 \leq 1$, *then no transmission* USUALLY

If $R_0 > 1$, *then transmission can be maintained*

Next Generation Matrix With Vaccination

Next Generation Matrix $(2K \times 2K)$:

$$\mathbf{M} = \begin{bmatrix} R_{11}(1-f_1) & R_{11}\phi f_1 & \cdots\cdots & R_{1K}(1-f_K) & R_{1K}\phi f_K \\ R_{11}\theta(1-f_1) & R_{11}\theta\phi f_1 & \cdots\cdots & R_{1K}\theta(1-f_K) & R_{1K}\theta\phi f_K \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ R_{K1}(1-f_1) & R_{K1}\phi f_1 & \cdots\cdots & R_{KK}(1-f_K) & R_{KK}\phi f_K \\ R_{K1}\theta(1-f_1) & R_{K1}\theta\phi f_1 & \cdots\cdots & R_{KK}\theta(1-f_K) & R_{KK}\theta\phi f_K \end{bmatrix}$$

$$\mathbf{f} = (f_1, f_2, ..., f_K)$$

Reproductive number: $R_{\mathbf{f}}$ largest eigenvalue of matrix $\mathbf{M}$

When $K = 1$,

LONGINI, ET AL. (1998)

$$R_{f_1} = \{1 - f_1\,[\,\mathrm{VE}_S + \mathrm{VE}_I - \mathrm{VE}_S\mathrm{VE}_I\,]\}\, R_{11}$$

Example: $R_{11} = 2$, $\mathrm{VE}_S = 0.3$, $\mathrm{VE}_I = 0.5$.

When $f = 0, R_0 = 2.00$

When $f = 0.5$, then $R_{0.5} = 1.35$

When $f = 0.8$, then $R_{0.8} = 0.96$

Critical Vaccination Fraction

Critical vaccination fractions: Find $\mathbf{f}^* = (f_1^*, f_2^*, ..., f_K^*)$, such that $R_{\mathbf{f}} = 1$

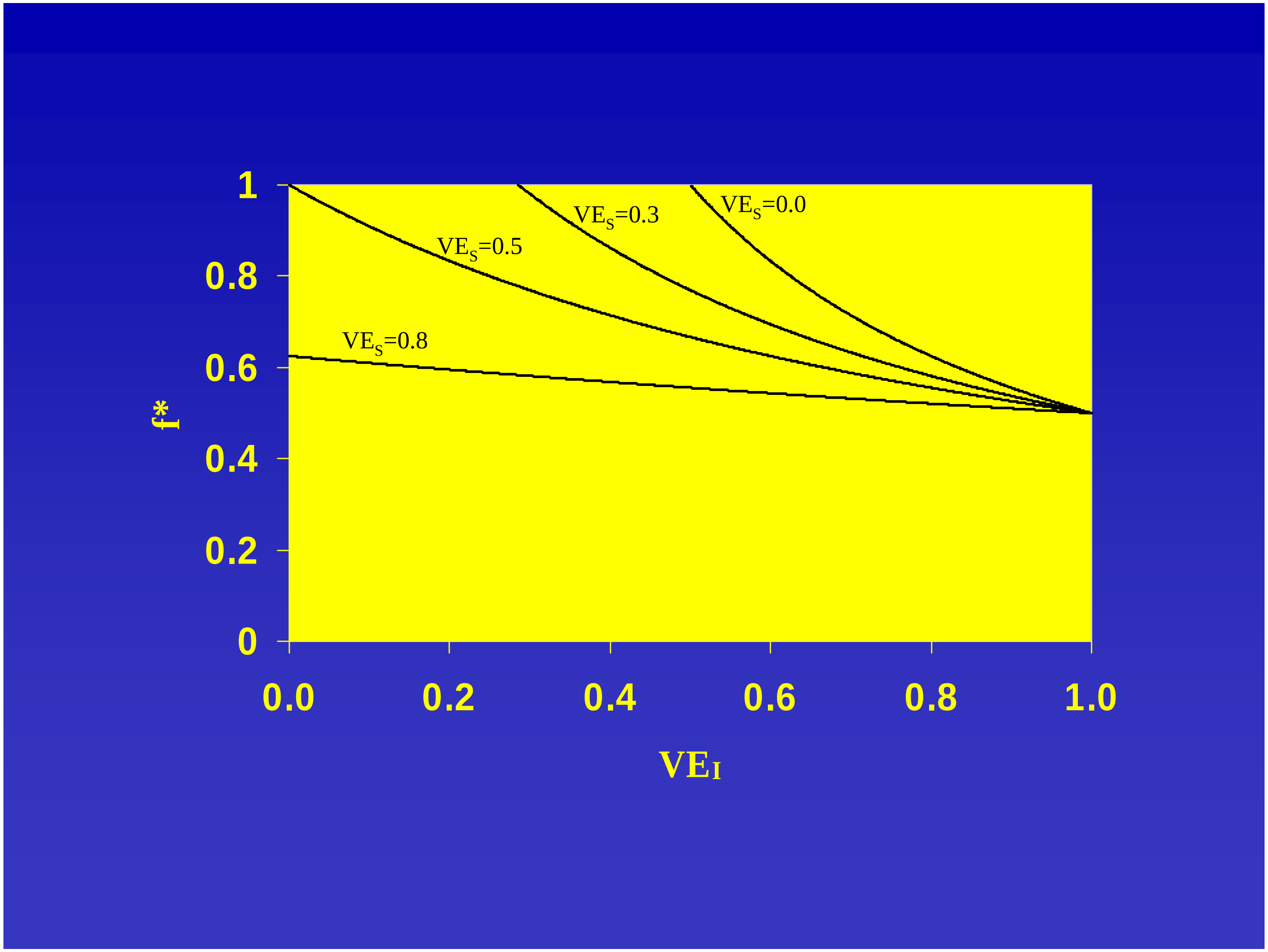
For example, when $K = 1$,

$$f_1^* = \frac{R_{11} - 1}{R_{11}\ [\mathrm{VE}_{S1} + \mathrm{VE}_{I1} - \mathrm{VE}_{S1}\mathrm{VE}_{I1}]},$$

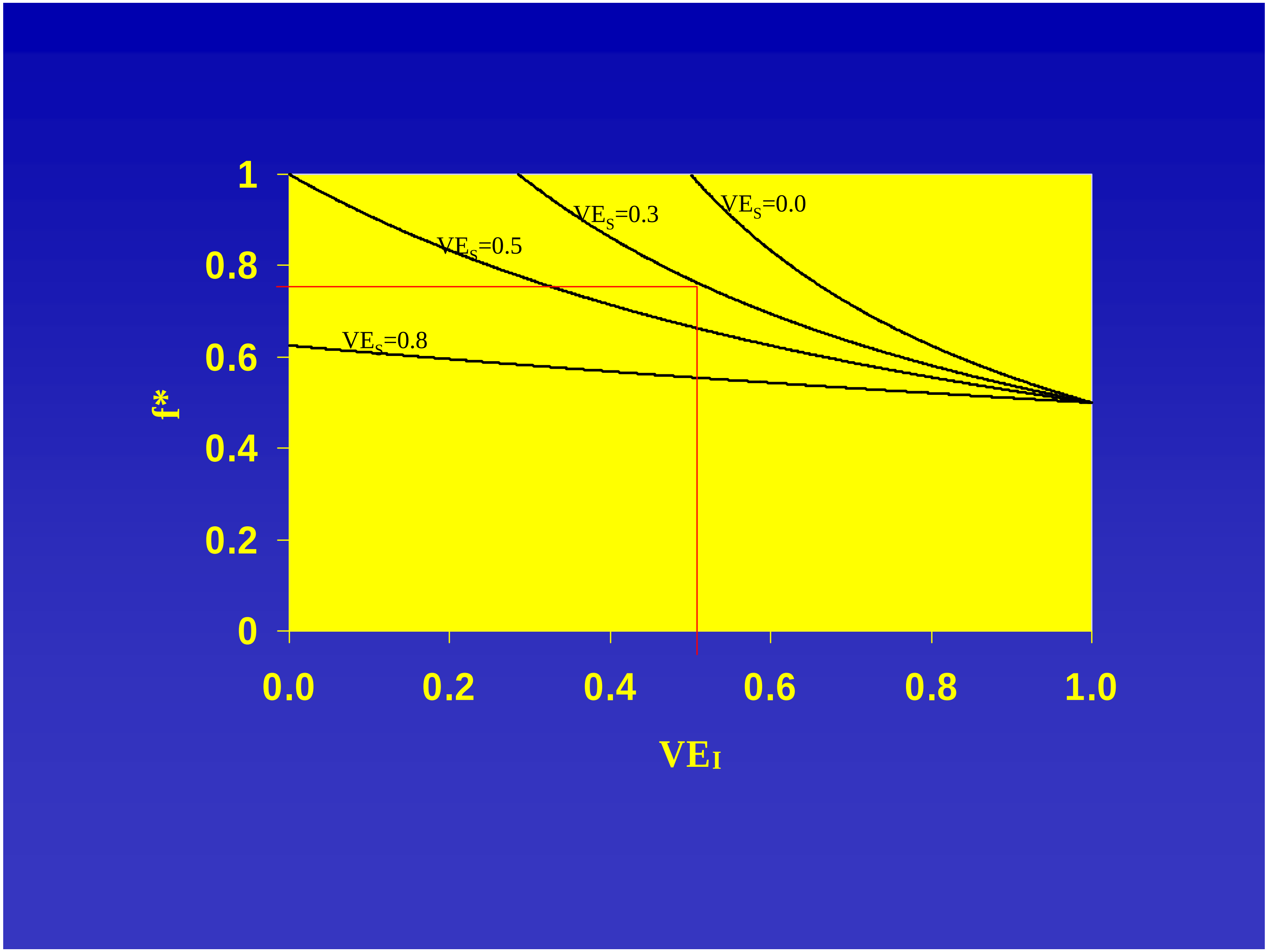
Longini, *et al.*, *Stat Med* (1998)

Example continued, $f_1^* = 0.769$

f^* *vs* VE_S and VE_I when $R_0 = 2$



f^* *vs* VE_S and VE_I when $R_0 = 2$



The Perron-Frobenius Theorem
(Rao and Rao, 1998; Hunter, 1983)

Let A be a nonnegative indecomposable matrix and let $\rho(A)$ denote its spectral radius.

Then:

1. $\rho(A) > 0$ and $\rho(A)$ is an eigenvalue of A.
2. With $\rho(A)$ can be associated strictly positive left and right eigenvectors. This is the only eigenvalue for which this happens.
3. If λ is any other eigenvalue of A, then $|\lambda| \leq \rho(A)$.
4. $\rho(A)$ has algebraic multiplicity 1. That is, $\rho(A)$ is a simple eigenvalue.
5. If $0 \leq B \leq A$ and β is an eigenvalue of B, then $|\beta| \leq \rho(A)$. If $|\beta| = \rho(A)$, then $B = A$, so that $\rho(A)$ increases when any element of A increases.

Determinantal Polynomial

Both $\mathbf{R}$ and $\mathbf{M}$ have the same rank

Let $\psi = 1 - \theta\phi$

Define $d_k = 1 - \psi f_k$ and $(m \times 1)$ vector $\mathbf{d} = \mathbf{1} - \psi\mathrm{f}$,

diagonal matrices $\mathbf{F} = diag(f_1, \ldots, f_m)$, and $\mathbf{D} = \mathbf{I} - \psi\mathbf{F}$

Then R_f is the largest eigenvalue of the $(m \times m)$ matrix $\mathbf{RD}$

So $\det(\mathbf{RD} - \mathbf{I}) = \mathbf{0}$ forces the existence of a eigenvalue of 1 (not necessarily the largest)

BASIS VECTOR OF $\underline{R}$ ↓ $e_i \otimes \begin{pmatrix} 1 \\ 0 \end{pmatrix}$

HYPERSURFACE — ONE OR MORE CONNECTED COMPONENTS

ONE CORR. TO $R_{\underline{f}} = 1$

Perron-Frobenius Eigenvector

If $\mathbf{R}_f = 1$, there exists a positive $(m \times 1)$ vector $\mathbf{v}$ such that $\mathbf{DRv}' = \mathbf{v}'$.

Then

$$\left\{ f_k = \psi^{-1} \left[1 - \frac{v_k}{(\mathbf{Rv})_k} \right] : \|\mathbf{v}\| = 1, v_k > 0 \forall k \right\}$$

For the special case of the SIR epidemic

$$-\ln(\mathbf{1} - \mathbf{v}) = \mathbf{Rv}$$

and

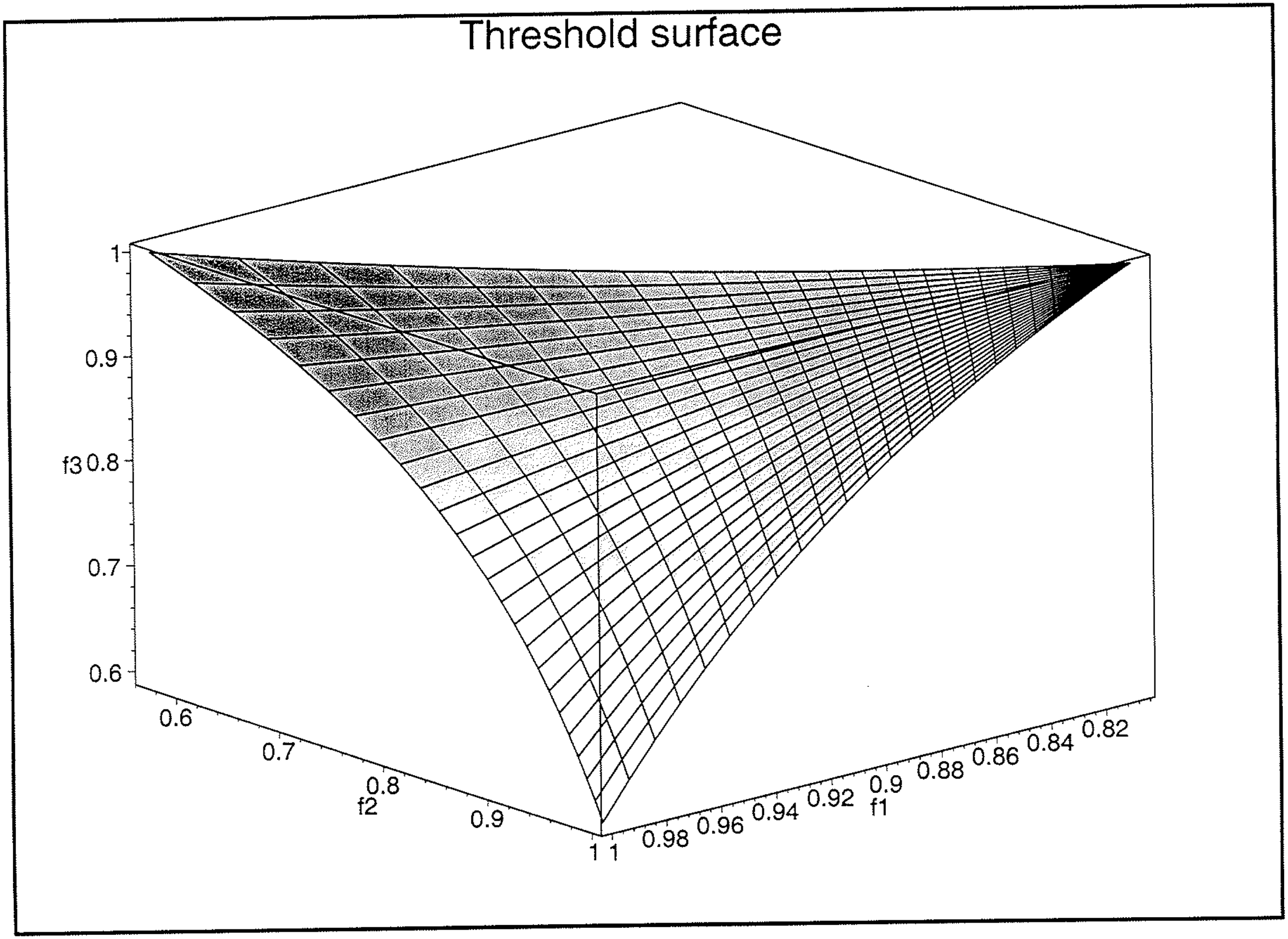
$$f_k = \psi^{-1} \left[1 - \frac{v_k}{-\ln(1 - v_k)} \right]$$

Britton (2001)

Example: $m = 3$

$$\mathbf{R} = \begin{bmatrix} 5.2 & 2.7 & 4.3 \\ 6.5 & 2.3 & 5.8 \\ 5.3 & 2.7 & 2.5 \end{bmatrix}$$

$R_0 = 12.3$; the other eigenvalues are -0.6 and -1.6



Threshold surface
1
0.9
f3 0.8
0.7
0.6
0.6
0.7
0.8
f2
0.9
1 1
0.98
0.96
0.94
0.92
0.9
f1
0.88
0.86
0.84
0.82

Example: $m = 3$

$$\mathbf{R} = \begin{bmatrix} 1.8 & 3.7 & 1.6 \\ 2.5 & 3.0 & 3.7 \\ 3.2 & 0.7 & 3.7 \end{bmatrix}$$

$R_0 = 7.87$; the other eigenvalues are $0.26 \pm 1.24i$

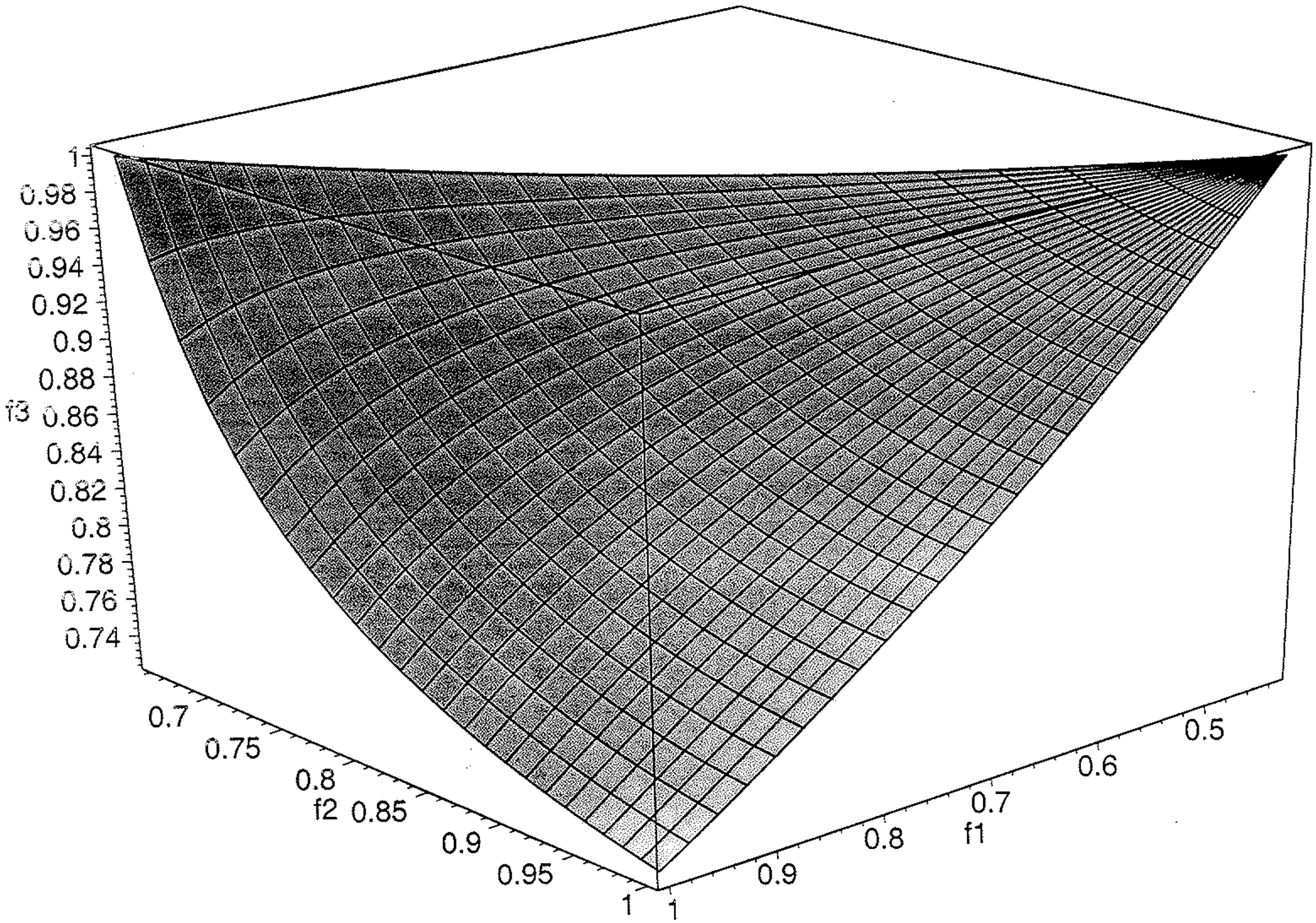
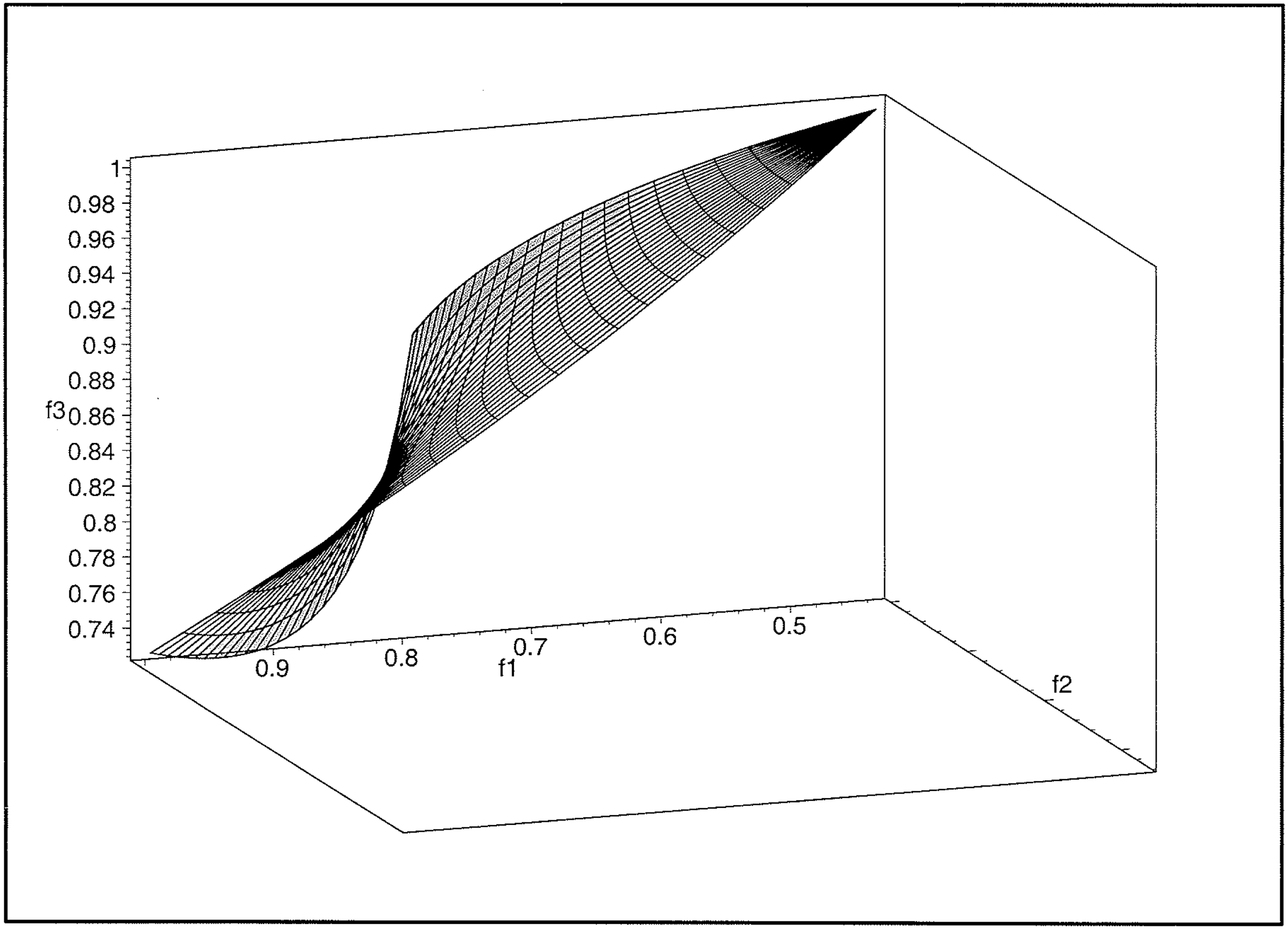


Figure 8.2: Threshold surface for matrix (8.2)


1
0.98
0.96
0.94
0.92
0.9
0.88
f3
0.86
0.84
0.82
0.8
0.78
0.76
0.74
0.9
0.8
0.7
f1
0.6
0.5
f2

Example: Influenza

$K = 5$ age groups: 1- preschool, 2 - school, 3 - young adults, 4 - middle-aged adults,

5 - old adults

Longini, *et al.*, *Math Biosc* (1978)

$$\mathbf{R} = \begin{bmatrix} 0.6 & 0.1 & 0.1 & 0.1 & 0.1 \\ 0.2 & 1.7 & 0.3 & 0.2 & 0.2 \\ 0.4 & 0.3 & 0.5 & 0.4 & 0.3 \\ 0.2 & 0.1 & 0.3 & 0.2 & 0.1 \\ 0.1 & 0.1 & 0.1 & 0.1 & 0.1 \end{bmatrix}$$

$$R_0 = 1.9$$

$$\mathbf{v} = (0.32, 0.83, 0.58, 0.33, 0.20)'$$

Some Special Cases (Continued)

When K=2

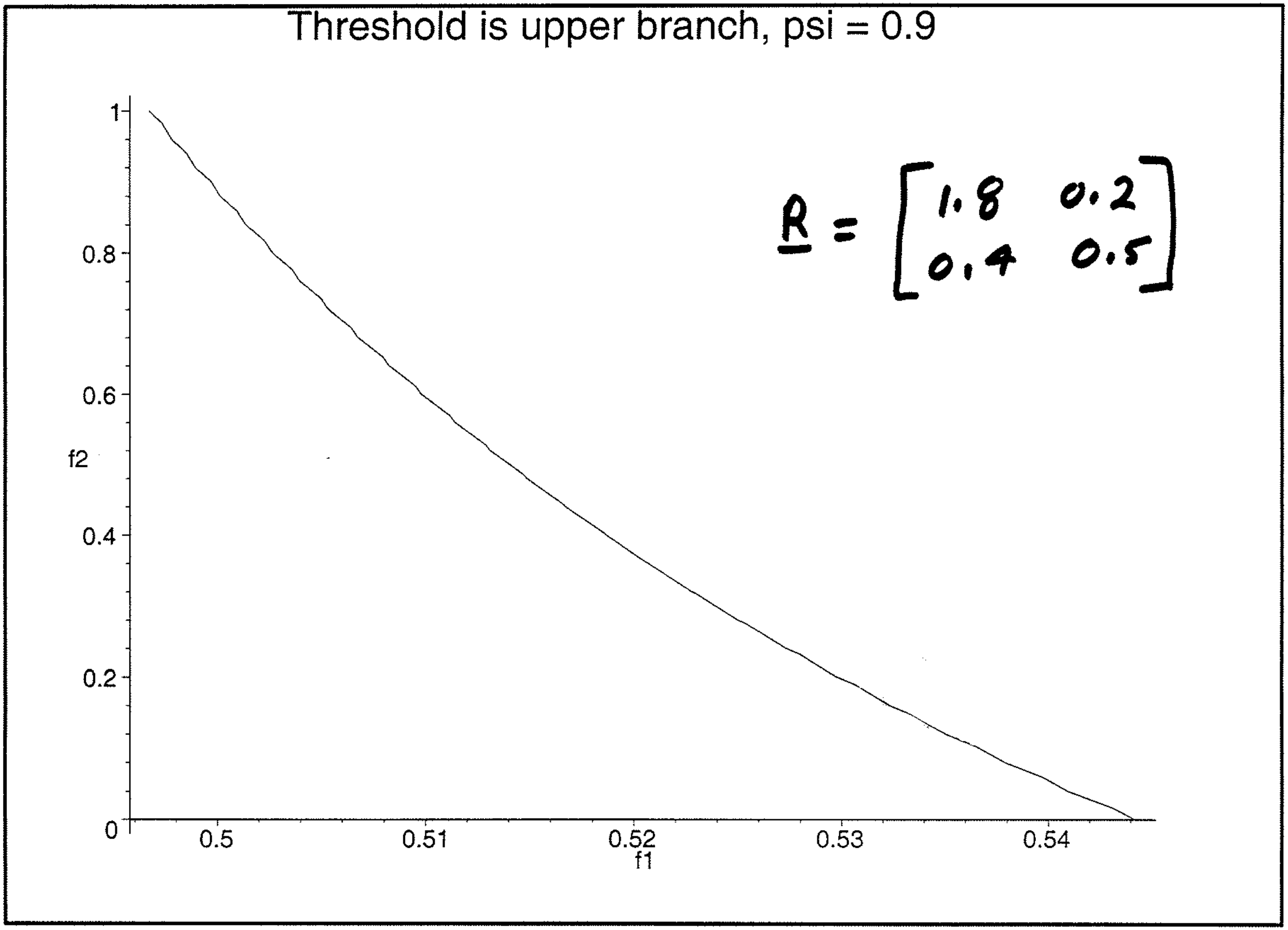
Influenza example: $K = 2$, 1 - children, 2 - adults

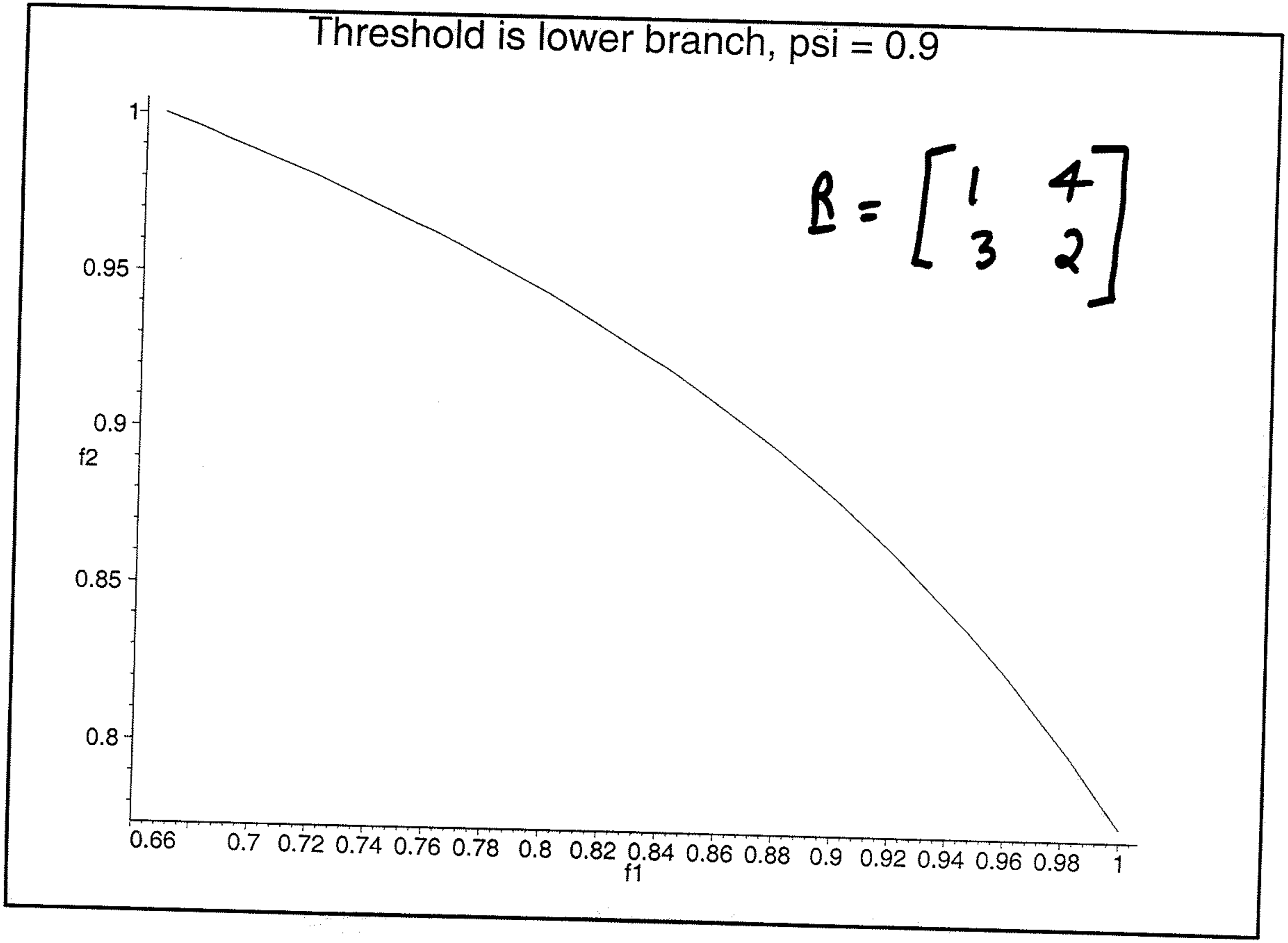
$$\mathbf{R} = \begin{bmatrix} 1.8 & 0.2 \\ 0.4 & 0.5 \end{bmatrix}$$

$$R_0 = 1.9, \lambda = 0.441$$

$$(\psi f_1 - 0.390)(\psi f_2 + 1.195) = 0.119$$

When $\psi = 0.9, \mathbf{f}^* = (0.5, 0.7)$


Threshold is upper branch, psi = 0.9
R = [1.8 0.2; 0.4 0.5]
f2
1
0.8
0.6
0.4
0.2
0
0.5
0.51
0.52
0.53
0.54
f1



Threshold is lower branch, psi = 0.9
R = [1 4; 3 2]
1
0.95
0.9
f2
0.85
0.8
0.66
0.7
0.72
0.74
0.76
0.78
0.8
0.82
0.84
0.86
0.88
0.9
0.92
0.94
0.96
0.98
1
f1

Some Further Special Cases

Vaccinating 2 out of $K > 2$ groups

Successive determinant expansions.

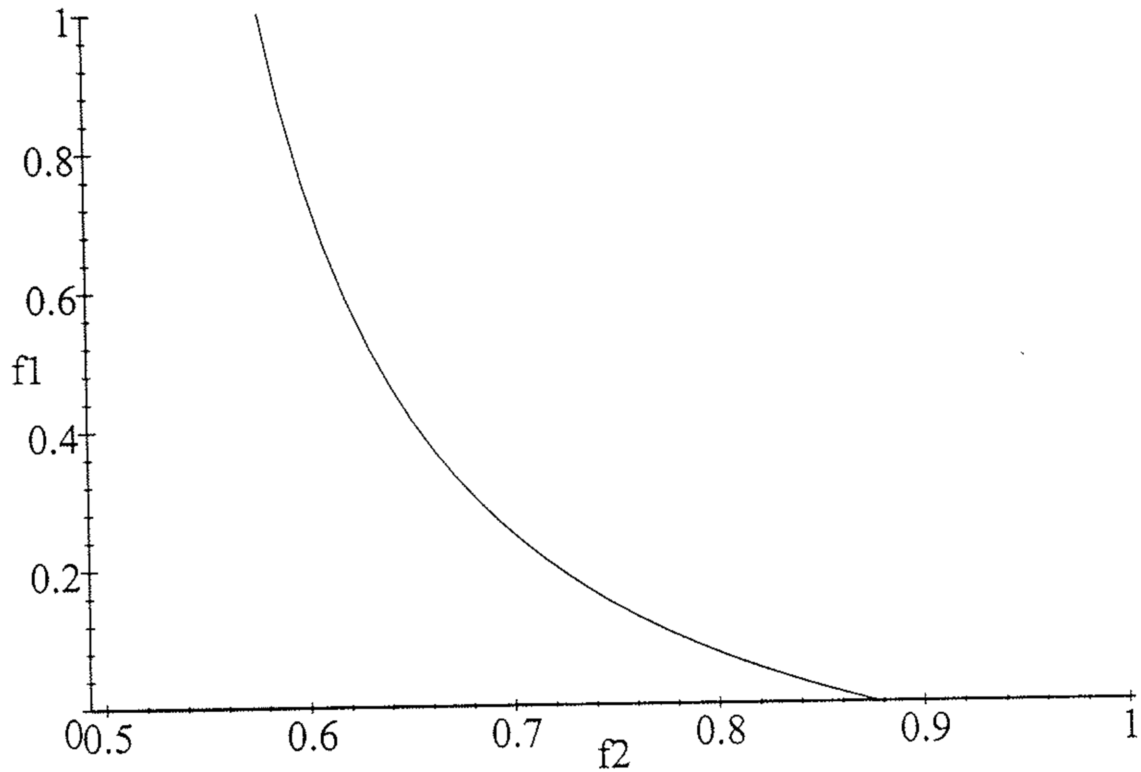
Influenza example, when $K = 5$:

$$f_1^* = -5 \left[\frac{-37 + 43\psi f_2^*}{\psi(-361 + 751\psi f_2^*)} \right]$$

Three possible strategies are $\mathbf{f}^* = (0.25, 0.70, 0, 0, 0, 0)$, $\mathbf{f}^* = (0, 0.88, 0, 0, 0, 0)$,

$\mathbf{f}^* = (1, 0.58, 0, 0, 0, 0)$

Plot of f_2^* vs f_1^* When K > 2



MAJOR DILEMMA

WHEN A LIMITED SUPPLY OF VACCINE IS AVAILABLE, ITS DISTRIBUTION INVOLVES RESOLVING THE FOLLOWING CONFLICT: SHOULD THE HIGH-SPREADING AGE GROUPS, SUCH AS CHILDREN AND YOUNG ADULTS, BE VACCINATED TO LIMIT SPREAD OF THE AGENT, OR SHOULD THE HIGH RISK AGE GROUP (*I.E.*, OLDER ADULTS ≥ 65 YRS. OLD) AND OTHER HIGH RISK PERSONS BE VACCINATED TO LIMIT EXCESS MORTALITY AND MORBIDITY?

THE QUESTION

GIVEN THAT A LIMITED QUANTITY OF VACCINE IS AVAILABLE PRIOR TO AN EPIDEMIC, WHAT PROPORTION OF EACH AGE GROUP SHOULD BE VACCINATED IN ORDER TO MINIMIZE THE EFFECTS OF THE EPIDEMIC?

Differential Equation Model

Partition: K mutually exclusive mixing groups, *e.g.*, age groups, $k = 1, ..., K;\ \nu = 0, 1$

$S_{k\nu}(t)$

$$\frac{dS_{k\nu}(t)}{dt} = -\frac{\theta_k^\nu}{n_k}\sum_{r=1}^{K} c_{kr}p_{kr}\left[I_{r0}(t) + \phi_r I_{r1}(t)\right],$$

$S_{k\nu}(t)$

$$\frac{dI_{k\nu}(t)}{dt} = \frac{\theta_k^\nu}{n_k}\sum_{r=1}^{K} c_{kr}p_{kr}\left[I_{r0}(t) + \phi_r I_{r1}(t)\right] - \frac{I_{k\nu}(t)}{d_{k\nu}},$$

$$\frac{dZ_{k\nu}(t)}{dt} = \gamma_{k\nu} I_{k\nu}(t),$$

$$S_{k\nu}(t) + I_{k\nu}(t) + Z_{k\nu}(t) = n_{k\nu},$$

$$n_{k1} = f_r n_k,$$

$$S_{k\nu}(0) = n_{k\nu}^-,\ I_{k\nu}(t) = 0^+,\ Z_{k\nu}(t) = 0$$

Optimal Distribution of Vaccine

Total Quantity of vaccine: V.

Constraints:

$$\sum_{k=1}^{K} f_k n_k \leq V$$

$$0 \leq f_k \leq \pi_k$$

Impact weights: $\mathbf{w} = (w_1, w_2, ..., w_K)$

Pathogenicity: $\boldsymbol{\psi} = (\psi_1, \psi_2, ..., \psi_K)$

Illness attack rates: $\rho_{ck\nu} = \psi_k \rho_{k\nu}$

Optimal vaccination fractions: $\mathbf{f}^o = (f_1^o, f_2^o, ..., f_K^o)$

$$\min \left\{ \sum_{k=1}^{K} \left(\sum_{\nu=1}^{2} \rho_{ck\nu} n_{k\nu} \right) w_k \right\} = g\left(\mathbf{f}^o\right) \geq 0,$$

subject to the constraints

POPULATION AGE DISTRIBUTION*

	AGE GROUP	AGE RANGE	%
1.	Preschool	0-4	7.7
2.	School	5-17	24.1
3.	Young Adult	18-44	37.5
4.	Middle-Aged Adult	45-64	20.4
5.	Old Adult	65+	10.3

*Based on 1975 Census Projections

INFECTIOUS CONTACT RATES

ASIAN

.305	.132	.205	.099	.041
.032	.923	.158	.074	.028
.042	.132	.183	.099	.041
.032	.101	.158	.067	.029
.032	.101	.158	.074	.032

HONG KONG

.056	.063	.105	.044	.025
.053	.330	.291	.140	.028
.056	.113	.259	.135	.071
.035	.106	.184	.089	.040
.029	.086	.161	.049	.075

PROPORTION AT HIGH RISK

	Age Group	Age	Proportion at High Risk
1.	Preschool	0- 4	.074
2.	School	5-17	.074
3.	Young Adult	18-44	.173
4.	Middle-Aged Adult	45-64	.228
5.	Old Adult	65+	1.000

BASELINE EPIDEMICS

AGE GROUP	ATTACK RATES	
	ASIAN	HONG KONG
1. Preschool	.352	.348
2. School	.570	.352
3. Young Adult	.246	.348
4. Middle-Aged Adult	.199	.327
5. Old Adult	.139	.305
Average	.312	.340

OPTIMIZATION PROBLEM PARAMETERS (1976)

- Killed vaccine: $VE_S = 0.7$, $VE_I = 0$
- Expected Monetary Cost:

  $\mathbf{w} = (53, 53, 75, 88, 261)$

- Expected Remaining Years of Life Lost:

  $\mathbf{w} = (0.0036, 0.0032, 0.0221, 0.2010, 0.5150)$

ASIAN INFLUENZA

(MONETARY COST)

AVAILABLE VACCINE V/N	MIN. COST $ $F(\bar{v}^*)$	OPTIMAL VACCINE DISTRIBUTION % v_1^*	v_2^*	v_3^*	v_4^*	v_5^*	AVERAGE AR σ_{AVE}
.00	22.81	0	0	0	0	0	.308
.10	15.26	0	42	0	0	0	.201
.20	6.59	0	83	0	0	0	.084
.30	2.30	77	100	0	0	0	.032
.40	1.59	100	100	22	0	0	.021
.50	1.22	100	100	49	0	0	.017
.60	.99	100	100	75	0	0	.014
.70	.83	100	100	100	0	7	.012
.80	.72	100	100	100	2	100	.012
.90	.65	100	100	100	51	100	.011
1.00	.59	100	100	100	100	100	.010

ASIAN INFLUENZA
(LOST LIFE)

AVAILABLE VACCINE V/N	MIN. YRS. LOST $X10^{-2}$ $F(\bar{v}^*)$	OPTIMAL VACCINE DISTRIBUTION % v_1^*	v_2^*	v_3^*	v_4^*	v_5^*	AVERAGE AR σ_{AVE}
.00	10.470	0	0	0	0	0	.308
.10	3.673	0	0	0	0	97	.288
.20	.239	0	40	0	0	100	.185
.30	.096	44	100	0	0	25	.034
.40	.035	74	100	0	0	100	.025
.50	.025	100	100	21	0	100	.019
.60	.019	100	100	48	0	100	.015
.70	.016	100	100	74	0	100	.013
.80	.013	100	100	49	95	100	.012
.90	.015	100	100	73	100	100	.011
1.00	.010	100	100	100	100	100	.010