

Evolutionary games

Evolutionary game theory is a mathematical tool that began in the social and economic sciences with the goal to model the interactions of individuals, called players. In EGT the behavior of players is not assumed to be based on rational payoff maximization, but is thought to be shaped by trial and error – adaptation through natural selection or individual learning.

1 Generalities

We begin with a purely mathematical description. The system is described by giving a payoff matrix $G_{i,j}$. If the frequency of strategy j is x_j then the relative fitness of individuals who play strategy i is $F_i = \sum_j G_{i,j}x_j$ and the average fitness is $F = \sum_i x_i F_i$. To define the dynamics in discrete time we suppose that the $G_{i,j} \geq 0$ and let

$$x'_i = x_i F_i / F \quad (1) \quad \boxed{\text{disrep}}$$

We have a fixed point $x' = x$ with all $x_i > 0$ if and only if $F_i = F$ for all i

While the discrete time system is easy to describe, it is often easier to work in continuous time. In this case, one approach is to follow the scheme in the Moran model. Individuals are subject to replacement at rate 1, and replaced by an individual chosen with a probability proportional to its fitness. This leads to the differential equation:

$$\frac{dx_i}{dt} = -x_i(t) + \frac{x_i(t)F_i(t)}{F(t)}$$

If we turn things around and have individuals give birth at a rate equal to their fitness and replace someone chosen at random then time runs at rate $F(t)$ and we end up with the replicator equation:

$$\frac{dx_i}{dt} = x_i(t)(F_i(t) - F(t)) \quad (2) \quad \boxed{\text{repleq}}$$

Again an x with all $x_i > 0$ is a fixed point of (2) if and only if $F_i = F$ for all i .

One can also derive (2) by following Taylor and Jonker (1978) and thinking of F_i as the growth rate of type i , i.e., the number of i strategists follows $n'_i(t) = F_i n_i(t)$. The total population size $N(t) = \sum_i F_i x_i(t) N(t) = F N(t)$. Differentiating $x_i(t) = n_i(t)/N(t)$ we get

$$x'_i = \frac{n'_i}{N} - \frac{n_i}{N^2} N' = x_i(F_i - F)$$

In some situations the following variant of (2) is useful

$$\frac{d}{dt} \left(\frac{x_i(t)}{x_j(t)} \right)' = \frac{x_i(t)}{x_j(t)} [F_i(t) - F_j(t)] \quad (3) \quad \boxed{\text{xratio}}$$

To check this we note that using calculus and then (2) the left-hand side of (3) is:

$$\begin{aligned} &= \frac{x'_i(t)}{x_j(t)} + x_i(t) \left(\frac{-x'_j(t)}{x_j^2(t)} \right) \\ &= \frac{x_i(t)}{x_j(t)} (F_i(t) - F(t)) - \frac{x_i(t)}{x_j(t)} (F_i(t) - F(t)) \end{aligned}$$

which proves the desired result.

In (2) only the fitness differences are important, that is,

Lemma 1.1. *If we add the same constant to all entries in a column the solutions of (2) is not changed.*

Proof. If we let $\tilde{G}_{i,j} = G_{i,j} + c_j$ then $\tilde{F}_i = F_i + \sum_j c_j x_j$ so $\tilde{F} = F + \sum_j c_j x_j$, so $\tilde{F}_i - \tilde{F} = F_i - F$, and the replicator equation is not changed. \square

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Lemma 1.2. *Let $c_j > 0$. If we change variables $y_i = x_i c_i / \sum_j x_j c_j$, then (2) turns into a linear time change of the replicator equation for the matrix $G_{ij} c_j^{-1}$. The new game has equilibrium $\bar{y}_i = \bar{x}_i c_i / \sum_j \bar{x}_j c_j$.*

Proof. The second conclusion is clear. To prove the first, we note that calculus and (2) imply

$$\begin{aligned} y'_i &= \frac{x'_i c_i}{\sum_n x_n c_n} - \frac{x_i c_i}{(\sum_n x_n c_n)^2} \sum_m x'_m c_m \\ &= \frac{x_i c_i}{\sum_n x_n c_n} \left(\sum_k G_{ik} x_k - \sum_{j,k} x_j G_{j,k} \right) \\ &\quad - \frac{x_i c_i}{(\sum_n x_n c_n)^2} \sum_m x_m c_m \left(\sum_k G_{m,k} x_k - \sum_{j,k} x_j G_{j,k} \right) \end{aligned}$$

The second terms on the last two lines cancel. If we divide what's left by $1 / \sum_\ell x_\ell c_\ell$ (the linear time change) we have

$$= y_i \sum_k G_{i,k} c_k^{-1} y_k - y_i \sum_{m,k} y_m G_{m,k} c_k^{-1} y_k$$

which is the desired result. \square

1.1 Two player games

To get an idea of what can happen consider the two strategy case and suppose that the payoff matrix is

$$\begin{array}{cc} & \begin{array}{cc} 1 & 2 \end{array} \\ \begin{array}{c} 1 \\ 2 \end{array} & \begin{array}{cc} \alpha & \beta \\ \gamma & \delta \end{array} \end{array}$$

To classify the possible behaviors of the system, we will ignore the possibility that two matrix entries are equal. If $\alpha > \gamma$ and $\beta > \delta$ then strategy 1 dominates strategy 2, and will take over the system. Likewise if $\alpha < \gamma$ and $\beta < \delta$ then strategy 2 dominates strategy 1. In the other cases we will have an equilibrium in which

$$x\alpha + (1-x)\beta = x\gamma + (1-x)\delta$$

Solving we have

$$\bar{x} = \frac{\delta - \beta}{\alpha - \gamma + \delta - \beta} \quad (4) \quad \text{pbar}$$

which is $\in (0, 1)$ since $\delta - \beta$ and $\alpha - \gamma$ have the same sign.

2pgame

Theorem 1. *If $\alpha > \gamma$ and $\beta < \delta$ then \bar{x} is unstable. If $\alpha < \gamma$ and $\beta > \delta$ then \bar{x} is stable.*

\bar{x} is where the lines $x\alpha + (1-x)\beta$ and $x\gamma + (1-x)\delta$ intersect. Noting that the two lines have heights α and γ at $x = 1$. If $\alpha > \gamma$ then the fitness of the first type $x\alpha + (1-x)\beta > x\gamma + (1-x)\delta$ for $x > \bar{x}$, while if $\alpha < \gamma$ $x\alpha + (1-x)\beta < x\gamma + (1-x)\delta$ for $x > \bar{x}$

Proof in continuous time. The replicator equation

$$\begin{aligned} \frac{dx}{dt} &= x(F_1(t) - F(t)) = x(1-x)[F_1(t) - F_2(t)] \\ &= x(1-x)[(\beta - \delta) + (\alpha - \beta - \gamma + \delta)x] \end{aligned} \quad (5) \quad \text{rep2s}$$

In the first case the quantity in square brackets is > 0 for $x > \bar{x}$, and < 0 for $x < \bar{x}$. In the second case the quantity in square brackets is < 0 for $x > \bar{x}$, > 0 for $x < \bar{x}$. \square

Proof in discrete time. The discrete iteration is

$$x' = \frac{x[x\alpha + (1-x)\beta]}{x[x\alpha + (1-x)\beta] + (1-x)[x\gamma + (1-x)\delta]}$$

If $\alpha > \gamma$ and $x > \bar{x}$ then $x' > x$ and iteration will drive the frequency to 1. If $\alpha < \gamma$ then $x\alpha + (1-x)\beta < x\gamma + (1-x)\delta$ for $x > \bar{x}$ so $x' < x$. To show that it is not possible for $x > \bar{x}$ and $x' < \bar{x}$, we note that $(1+y)^{-1}$ is decreasing for $y > -1$, so if $x > \bar{x}$

$$\left(1 + \frac{(1-x)[x\gamma + (1-x)\delta]}{x[x\alpha + (1-x)\beta]}\right)^{-1} > \left(1 + \frac{(1-\bar{x})[\bar{x}\gamma + (1-\bar{x})\delta]}{\bar{x}[\bar{x}\alpha + (1-\bar{x})\beta]}\right)^{-1} = (\bar{x})^{-1}$$

\square

1.2 Concrete examples

Hawks and Doves. The first application of evolutionary game theory was Maynard Smith and Price's (1973) work on "the logic of animal conflict." Their aim was to explain the fact that most conflicts between animals of the same species were of the "limited war" type despite the fact that the winner gains mates, territory, or other advantages that result in having more offspring. This game was formulated in Maynard Smith's influential (1982) book as:

	H	D
H	$(V - C)/2$	V
D	0	$V/2$

In words, a Hawk will scare off a Dove and get the full reward of V , two Doves split the proceeds, but two Hawks fight and each pays a cost C for fighting. If $V > C$ then the Hawk strategy dominates the Dove strategy, while if $V < C$ then by (4) there is a mixed strategy equilibrium in which the hawk strategy is played with probability $p = V/C$.

Prisoner's Dilemma. In the classic story for this game, two prisoners are in separate interrogation rooms. If player 1 confesses (strategy D for defect) and player 2 does not (strategy C for cooperate with the other player), 1 will go free while the other will get a harsh sentence. If neither confesses they get convicted of a lesser crime. If both confess, they get a more lenient sentence since the inconvenience of a trial is avoided. For example, the payoffs might be

	C	D
C	-1	-10
D	0	-5

In general if we assume $\gamma > \alpha > \delta > \beta$ then the D strategy dominates the C strategy but we have the dilemma that the payoff from (C, C) is better than that for (D, D) . There have been many attempts to resolve this paradox by considering what happens when a population of players repeatedly play the game against each other, see Chapter 9 of [6] or Chapter 5 of Nowak (2006) book [9].

Altruism. Again the strategies are called cooperator and defector.

	C	D
C	$b - c$	$-c$
D	b	0

Cooperators pay a cost c in order to provide a benefit b to the other player. In this case the D strategy always dominates C . This is the paradox of altruism: why do some individuals pay a cost so that others can benefit. For example, worker bees risk their lives to defend the bee hive, and in addition, forgo their reproductive potential to raise the offspring of another individual, the queen. If $b > c$ then this is another example of Prisoner's Dilemma.

Snowdrift game. Two motorists are stuck on opposite sides of a snowdrift. If one or both shovel the snow away then they enjoy the benefit b from sleeping in their home rather than in their car. If only one shovels then he pays the full cost c , but if they both do then they

split the cost.

	C	D
C	$b - c/2$	$b - c$
D	b	0

In contrast to the previous case, there is a mixed strategy equilibrium with $\bar{x} = 1 - c/(2b - c)$.

2 Some Game Theory

The material in this section is based on Hofbauer and Sigmund (1998). Let $S_n = \{x_i \geq 0 : \sum_i x_i = 1\}$ be the n -dimensional simplex. A strategy $\hat{x} \in S_n$ is a *Nash equilibrium* if for all $x \in S_n$

$$x \cdot G\hat{x} \leq \hat{x} \cdot G\hat{x} \quad (6)$$

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In words, no other mixed strategy yields a larger payment when played against \hat{x} . Equilibria of the replicator equation with $\hat{x}_i > 0$ for all i have $(G\hat{x})_i = F_i = c$ for all i so they are Nash equilibria.

A type of behavior is said to be *evolutionarily stable* if, whenever all members of the population adopt it, no dissident behavior could invade the population under the influence of natural selection. More concretely, in one of our games $\hat{x} \in S_n$ is evolutionarily stable strategy (ESS) if for all $x \in S_n$ with $x \neq \hat{x}$ we have

$$x \cdot G(\epsilon x + (1 - \epsilon)\hat{x}) < \hat{x} \cdot G(\epsilon x + (1 - \epsilon)\hat{x})$$

for $\epsilon < \epsilon_0(x)$. The expression above can be written as

$$(1 - \epsilon)(\hat{x} \cdot G\hat{x} - x \cdot G\hat{x}) + \epsilon(\hat{x} \cdot Gx - x \cdot Gx) > 0$$

In a Nash equilibrium, the first term is 0, so for an ESS we need

$$(\hat{x} - x) \cdot Gx > 0. \quad (7)$$

Nash

To see what this condition means, we begin with

Two player games. Suppose that the game has an interior fixed point $\bar{x} = (\bar{y}, 1 - \bar{y})$ and let $x = (y, 1 - y)$. The condition in ESS is

$$(\bar{y} - y)[\alpha y + \beta(1 - y)] + (-\bar{y} + y)[\gamma y + \delta(1 - y)] > 0$$

By the definition of equilibrium

$$(\bar{y} - y)[\alpha \bar{y} + \beta(1 - \bar{y})] + (-\bar{y} + y)[\gamma \bar{y} + \delta(1 - \bar{y})] = 0$$

Subtracting the second equation from the first, we want

$$(\bar{y} - y)^2[-\alpha + \beta + \gamma - \delta] > 0$$

Recalling our two cases, we see that

- If $\alpha < \gamma$ and $\beta > \delta$ then \bar{x} is an ESS.
- If $\alpha > \gamma$ and $\beta < \delta$ then \bar{x} is not.

This motivates the following result about fixed points in the interior $S_n^+ = \{x \in S_n : x_i > 0 \text{ for all } i\}$.

Theorem 2. *If $\hat{x} \in S_n^+$ is an ESS then it is an asymptotically stable fixed point for the replicator dynamics.*

Proof. Suppose $x \in S_n^+$. Define $L(x) = \sum_i \hat{x}_i \log(x_i/\hat{x}_i)$. The first thing to check is that L is maximized at $x = \hat{x}$. Jensen's inequality applied to the random variable Y that is x_i/\hat{x}_i with probability \hat{x}_i gives

$$\sum_i \hat{x}_i \log(x_i/\hat{x}_i) = E(\log Y) \leq \log(EY) = \log\left(\sum_i \hat{x}_i(x_i/\hat{x}_i)\right) = 0$$

with strict inequality if $x_j \neq \hat{x}_j$ for some j . If $x(t)$ is a solution of the replicator equation then

$$\frac{d}{dt}L(x(t)) = \sum_i \hat{x}_i \frac{x'_i(t)}{x_i(t)} = \sum_i \hat{x}_i((Gx)_i - x \cdot Gx)$$

Since \hat{x} is an ESS, if δ is small enough then we have $(d/dt)L(x(t)) > 0$ for all starting points in $\{x : L(x) > -\delta\}$. The increase in L with time implies that trajectories do not leave this neighborhood and converge to \hat{x} . In words what we have done is to construct a local Lyapunov function. \square

2.1 Connection to Lotka-Volterra equations

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Theorem 3. *There is a differentiable invertible map from $\hat{S}_n = \{x \in S_n : x_n > 0\}$ onto $[0, \infty)^{n-1}$ mapping orbits of the replicator equation*

$$x'_i = x_i((Gx)_i - x \cdot Gx)$$

onto the orbits of the Lotka-Volterra equation

$$y'_i = y_i \left(r_i + \sum_{j=1}^{n-1} a_{i,j} y_j \right)$$

where $r_i = G_{in} - G_{nn}$ and $a_{ij} = G_{ij} - G_{n,j}$.

Proof. Let $y_n = 1$ and define the transformation from $y \in [0, \infty)^{n-1}$ to $x \in \hat{S}_n$ by

$$x_i = \frac{y_i}{\sum_{j=1}^n y_j}$$

and its inverse given by

$$y_i = \frac{x_i}{x_n}$$

Consider now the replicator equation and suppose without loss of generality that the last row $G_{ni} = 0$.

$$y'_i = \left(\frac{x_i}{x_n} \right)' = \frac{x_i}{x_n} [(Gx)_i - (Gx)_n]$$

where the last equation comes from (3). Since $(Gx)_n = 0$, we have

$$y'_i = y_i \sum_{j=1}^{n-1} G_{ij} y_j \cdot \frac{1}{\sum_{j=1}^n y_j}$$

The last term can be set = 1 by time change, so the last equation has the same orbits as the Lotka-Volterra equation. \square

With this established, we can obtain results for the replicator equation from those for Lotka-Volterra equations. In order to state our first result, we recall that x is an ω -limit of $x(t)$ if there are $t_n \rightarrow \infty$ so that $x(t_n) \rightarrow x$.

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Theorem 4. *If $J = (0, \infty)^k$ contains no rest points for the Lotka-Volterra equation then it contains no ω limit points.*

Proof. Define $\phi : J \rightarrow \mathbb{R}^k$ by $\phi_i(x) = r_i + \sum_{j=1}^k a_{ij}x_j$. If J contains no rest points then the convex set $K = \phi(J)$ does not contain 0. A well-known theorem from convex analysis implies that there is a hyperplane H through 0 which is disjoint from K . Thus there is a vector $c \neq 0$ orthogonal to H , i.e., $c \cdot x = 0$ for all $x \in H$, which has $c \cdot y > 0$ for all $y \in K$. Let $V(x) = \sum_i c_i \log x_i$. If $x(t)$ is a solution to the Lotka-Volterra equation $x' = \phi(x)$ then

$$\frac{d}{dt}V(x(t)) = \sum_i c_i \frac{x'_i}{x_i} = c \cdot \phi(x(t)) > 0$$

since $\phi(x) \in K$, so V is increasing along each orbit. If $x(t)$ has an ω -limit point $y \in J$ we get a contradiction that $V(x(t))$ must converge to a finite limit since it returns close to y , but then the positivity of $(d/dt)V(x(t))$ implies. $V(x(t)) \rightarrow \infty$ For more details see the discussion of Lyapunov's Theorem ,2.6.1 in Hofbauer and Sigmund (1998). \square

2.2 Periodic orbits

By Theorem 3 the next theorem will give us a result for replicator equations for 3×3 games.

Theorem 5. *The two-dimensional Lotka-Volterra equation*

$$\begin{aligned} x' &= x(a + bx + cy) \\ y' &= y(d + ex + fy) \end{aligned}$$

has no isolated periodic orbits.

Proof. Suppose that there is a periodic orbit γ . Since γ consists of ω -limits, it follows from by Theorem 4 there must be a rest point of the differential equation. Ignoring the degenerate case in which there is a line of fixed points, we see that

$$\begin{pmatrix} b & c \\ e & f \end{pmatrix} \text{ is invertible and hence } \Delta = bf - ce \neq 0 \quad (8) \quad \boxed{\text{solve}}$$

Let $P(x, y) = x(a + bx + c)$, $Q(x, y) = y(d + ex + fy)$, and $B(x, y) = x^{\alpha-1}y^{\beta-1}$. The divergence of the vector field (BP, BQ) is

$$\begin{aligned} \frac{\partial}{\partial x}(BP) + \frac{\partial}{\partial y}(BQ) &= \alpha x^{\alpha-1}y^{\beta-1}(a + bx + cy) + x^{\alpha}y^{\beta-1}b \\ &\quad + \beta x^{\alpha-1}y^{\beta-1}(d + ex + fy) + x^{\alpha-1}y^{\beta}f \\ &= B\{\alpha(a + bx + cy) + bx + \beta(d + ex + fy) + fy\} \end{aligned}$$

Choose α and β so that $\alpha b + \beta e = -b$ and $\alpha c + \beta f = -f$. This is possible because of (8) and leads to

$$\frac{\partial}{\partial x}(BP) + \frac{\partial}{\partial y}(BQ) = \delta B \quad \text{where } \delta = a\alpha + d\beta.$$

If $\delta \neq 0$ then integrating the divergence of (BP, BQ) over the interior of a periodic orbit γ would give a contradiction so we must have

$$\frac{\partial}{\partial x}(BP) = -\frac{\partial}{\partial y}(BQ).$$

From this it follows that there is a function V so that

$$\frac{\partial}{\partial x}V = BQ \quad \text{and} \quad \frac{\partial}{\partial y}V = -BP$$

The time derivative

$$\frac{d}{dt}V(x(t), y(t)) = \frac{\partial V}{\partial x}x' + \frac{\partial V}{\partial y}y' = PQ(B - B) = 0$$

Thus the function V is an invariant of the motion and its level curves are periodic orbits. \square

To see that one can have a one parameter family of periodic orbits.

Example 1. ?? Generalized Rock-Paper-Scissors. Consider the game matrix

$$G = \begin{pmatrix} 0 & -a_2 & b_3 \\ b_1 & 0 & -a_3 \\ -a_1 & b_2 & 0 \end{pmatrix}$$

If we have $a_i = b_i = 1$ for all i then this is Rock-Paper-Scissors. Rock (1) crushes Scissors (3). Scissors (3) cuts Paper (2). Paper (2) covers Rock (1). If the frequencies are given by p then the fitnesses are

$$F_1 = -a_2p_2 + b_3p_3 \quad F_2 = b_1p_1 - a_3p_3 \quad F_3 = -a_1p_1 + b_2p_2$$

From this we see that the equilibrium has

$$\begin{aligned} -b_1p_1 - a_2p_2 + (a_3 + b_3)p_3 &= 0 & F_1 - F_2 &= 0 \\ (b_1 + a_1)p_1 - b_2p_2 - a_3p_3 &= 0 & F_2 - F_3 &= 0 \\ -a_1p_1 + (a_2 + b_2)p_2 - b_3p_3 &= 0 & F_3 - F_1 &= 0 \end{aligned}$$

Using $p_3 = 1 - p_1 - p_2$ in the last two equations leads to

$$\begin{aligned} (b_1 + a_1 + a_3)p_1 + (a_3 - b_2)p_2 &= a_3 \\ (b_3 - a_1)p_1 + (a_2 + b_2 + b_3)p_2 &= b_3 \end{aligned}$$

Solving produces a bit of a mess, but when the smoke clears the answer is not too bad:

$$\begin{aligned} p_1 &= (a_2a_3 + b_2b_3 + a_3b_2)/D \\ p_2 &= (a_1a_3 + b_1b_3 + a_1b_3)/D \\ p_3 &= (a_1a_2 + b_1b_2 + a_2b_1)/D \end{aligned} \tag{9} \quad \boxed{\text{ieRPS}}$$

where D is the sum of the nine terms in the numerator.

Consider now the game matrix

$$\tilde{G} = \begin{pmatrix} 0 & b_2 & -a_3 \\ -a_1 & 0 & b_3 \\ b_1 & -a_2 & 0 \end{pmatrix}$$

in which the roles of a and b are interchanged and the matrix is multiplied by -1 . Let

$$\begin{aligned} m_1 &= (a_2a_3 + b_2b_3 + b_3a_2)/\tilde{D} \\ m_2 &= (a_1a_3 + b_1b_3 + b_1a_3)/\tilde{D} \\ m_3 &= (a_1a_2 + b_1b_2 + b_2a_1)/\tilde{D} \end{aligned}$$

where \tilde{D} is the sum of the nine terms in the numerator. In this case it is easy to check that

$$m_1b_1 - m_2a_2 = m_2b_2 - m_3a_3 = m_3b_3 - m_1a_1 = \frac{b_1b_2b_3 - a_1a_2a_3}{\tilde{D}} \equiv \tilde{F} \quad (10) \quad \boxed{\text{magic}}$$

At this point we apply the projective transformation in Lemma 1.2 with $c_i = m_i^{-1}$ to G in order to get a new game matrix

$$H = \begin{pmatrix} 0 & -m_2a_2 & m_3b_3 \\ m_1b_1 & 0 & -m_3a_3 \\ -m_1a_1 & m_2b_2 & 0 \end{pmatrix}$$

The new stationary distribution is $q_i = p_i m_i^{-1} / \sum_j p_j m_j^{-1}$. Let $V(x) = x_1^{q_1} x_2^{q_2} x_3^{q_3}$. Differentiating $\partial V / \partial x_i$ lowers the power of x_i by 1, but the replicator equation undoes this, so the result is neat:

$$\frac{d}{dt} V(x) = \sum_i q_i V(x) [(Hx)_i - x \cdot Hx] = V \cdot [(q \cdot Hx) - (x \cdot Hx)]$$

Since $(Hq)_i$ is constant in i , and q and x are probability vectors $(q - x) \cdot Hq = 0$. Thus if we let $\xi = x - q$ then the above

$$\begin{aligned} &= -V \cdot [\xi \cdot H\xi] = \xi_1 \xi_2 [m_1b_1 - m_2a_2] + \xi_1 \xi_3 [m_3b_3 - m_1a_1] + \xi_2 \xi_3 [m_2b_2 - m_3a_3] \\ &= -F \cdot [\xi_1 \xi_2 + \xi_1 \xi_3 + \xi_2 \xi_3] \end{aligned}$$

by (10). Since $\xi = x - q$, $\xi_1 + \xi_2 + \xi_3 = 0$ and we have

$$\xi_1 \xi_2 + \xi_1 \xi_3 + \xi_2 \xi_3 = \frac{1}{2} [(\xi_1 + \xi_2 + \xi_3)^2 - (\xi_1^2 + \xi_2^2 + \xi_3^2)] \leq 0$$

We can now read off the desired answers for the behavior of the replicator equation associated with H , which in turn gives us results for G .

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Theorem 6. *Let $\Gamma = b_1b_2b_3 - a_1a_2a_3$ be the numerator of \tilde{F} and let $V(x) = x_1^{q_1} x_2^{q_2} x_3^{q_3}$ be the function defined above.*

If $\Gamma = 0$ then V is a constant, so there is a one parameter family of periodic orbits.

If $\Gamma < 0$ then V is decreasing, so trajectories spiral out toward the boundary where V is 0.

If $\Gamma > 0$ then V is increasing, so q is an attracting fixed point for H and p is one for G .

2.3 Linearizing around fixed points

A general technique for understanding the behavior of ODE's is to look at the behavior near fixed points, i.e., are they locally attracting or unstable. The replicator equation is

$$\frac{dx_i}{dt} = x_i ((Gx)_i - x \cdot Gx)$$

Let p be the equilibrium and let δ_i have $\sum_i \delta_i = 0$. Taking $x = p + \delta$

$$\frac{d\delta_i}{dt} = (p_i + \delta_i)[(G(p + \delta))_i - (p + \delta) \cdot G(p + \delta)]$$

Expanding out the right-hand side we have

$$= (p_i + \delta_i)[(Gp)_i - p \cdot Gp] + (p_i + \delta_i)[- \delta \cdot Gp] + p_i[(G\delta)_i - p \cdot G\delta] + O(\delta^2)$$

The first two terms are 0 because the relative fitness of type i in equilibrium $(Gp)_i$ is constant. From this we see that the linearization around the fixed point is

$$\frac{d\delta_i}{dt} = p_i[(G\delta)_i - p \cdot G\delta].$$

In the two strategy case, $\delta_2 = -\delta_1$ so if we let $p_1 = p$ and $p_2 = 1 - p$ then we have

$$\begin{aligned} \frac{d\delta_1}{dt} &= p[G_{1,1}\delta_1 - G_{1,2}\delta_1 - p(G_{1,1}\delta_1 - G_{1,2}\delta_1) - (1-p)(G_{2,1}\delta_1 - G_{2,2}\delta_1)] \\ &= \delta_1 p(1-p)[G_{1,1} - G_{1,2} - G_{2,1} + G_{2,2}] \end{aligned}$$

The quantity in square brackets is $\alpha - \beta - \delta + \gamma$. If this is < 0 the fixed point is stable, which agrees with Theorem 1.

In the three strategy case, we have $\delta_3 = -\delta_1 - \delta_2$ so

$$\begin{aligned} \frac{d\delta_i}{dt} &= p_i \left\{ [(G_{i1} - G_{i3})\delta_1 + (G_{i2} - G_{i3})\delta_2] \right. \\ &\quad \left. - \sum_j p_j [(G_{j1} - G_{j3})\delta_1 + (G_{j2} - G_{j3})\delta_2] \right\} \end{aligned}$$

and the linearization is

$$\frac{d\delta_i}{dt} = \sum_j A_{i,j} \delta_j$$

where the matrix A is given by

$$\begin{aligned} A_{1,1} &= p_1(1-p_1)(G_{1,1} - G_{1,3}) - p_1 p_2 (G_{2,1} - G_{2,3}) - p_1 p_3 (G_{3,1} - G_{3,3}) \\ A_{1,2} &= p_1(1-p_1)(G_{1,2} - G_{1,3}) - p_1 p_2 (G_{2,2} - G_{2,3}) - p_1 p_3 (G_{3,1} - G_{3,3}) \\ A_{2,1} &= -p_2 p_1 (G_{1,1} - G_{1,3}) + p_2(1-p_2)(G_{2,1} - G_{2,3}) - p_2 p_3 (G_{3,1} - G_{3,3}) \\ A_{2,2} &= -p_2 p_1 (G_{1,2} - G_{1,3}) + p_2(1-p_2)(G_{2,2} - G_{2,3}) - p_2 p_3 (G_{3,1} - G_{3,3}) \end{aligned}$$

The stability of the fixed point is dictated by the signs of the real parts of the two eigenvalues of A . To avoid having to compute the two eigenvalues we note that

$$\text{trace}(A) = \lambda_1 + \lambda_2 \quad \det(A) = \lambda_1 \lambda_2$$

so we have

λ_1	λ_2	trace	det	
+	+	+	+	unstable
+	-	?	-	saddle
-	-	-	+	stable
$a + bi$	$a - bi$	$2a$	+	stable or unstable

3 Early work on cancer games

Tomlinson and Bodmer (1997) were among the first to formulate the competition between tumor and healthy cells as an evolutionary game. To motivate their study, they observed: “Classical models of tumorigenesis assume that the mutations which cause tumors to grow act in a cell autonomous fashion. This is not necessarily the case. Sometimes tumor cells may adopt genetic strategies that boost their own replication and which also influence other cells in the tumour, whether directly or as side effects.”

Here we look at an example from Tomlinson (1997). It is assumed that a cell can produce a substance to harm other tumor cells and gain a benefit from doing so. There are three types of cells.

1. **Producers** of a cytotoxic substance
2. Cells **resistant** to the cytotoxic substance
3. **Baseline** cells that are not producers or resistant.

In this interaction

- Baseline fitness is z .
- Cost of producing cytotoxin is $e > 0$.
- Disadvantage of being affected by the cytotoxin is $0 < f < z$.
- Advantage of subjecting another cell to cytotoxin is $g > e$.
- Cost of resistance is $h > 0$.

The payoff matrix $G_{i,j}$ which gives the payoff to strategy i when played against strategy j is

	P	R	B
$1 = P$	$z - e - f + g$	$z - e$	$z - e + g$
$2 = R$	$z - h$	$z - h$	$z - h$
$3 = B$	$z - f$	z	z

Following Tomlinson, we will first find the conditions for an interior fixed point (p_1, p_2, p_3) . As noted earlier, for this we need the relative fitnesses of three types to be equal: $F_1 = F_2 = F_3$. In order for $F_2 = F_3$ we must have

$$-p_1 f = -h \quad \text{or} \quad p_1 = h/f.$$

In order to have $F_1 = F_3$ we must have

$$-p_1 f = -e + p_1(g - f) + p_3 g \quad \text{or} \quad p_3 = \frac{e - p_1 g}{g} = \frac{e}{g} - \frac{h}{f}.$$

The remaining probability

$$p_2 = 1 - (p_1 + p_3) = 1 - \frac{e}{g}.$$

In order for all three components to be > 0 (and hence a probability distribution) we need

$$h < f \quad e < g \quad \frac{e}{g} > \frac{h}{f}$$

Rewriting we can reduce the number of conditions to two:

$$1 > \frac{e}{g} > \frac{h}{f} \quad (11) \quad \boxed{\text{Tom_ie}}$$

To investigate the stability of this fixed point, and the asymptotic behavior of the replicator equation, in this three strategy game, we will use a technique we learned from mathematical ecologists. We begin by investigating the three two-strategy sub-games, and then if there is an equilibrium, we see if the third strategy can invade: i.e., will increase when rare.

R vs. B.

	R	B
R	$z - h$	$z - h$
B	z	z

$h > 0$ so B dominates R .

P vs. B.

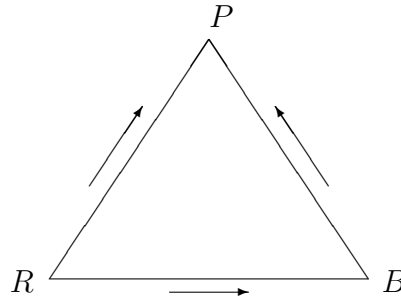
	P	B
P	$z - f - e + g$	$z - e + g$
B	$z - f$	z

In our initial discussion we have supposed $g > e$, i.e., the benefit of producing the cytotoxin outweighs the cost, so P dominates B .

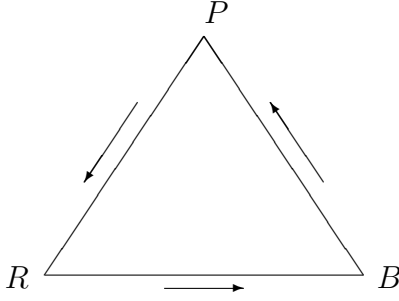
P vs. R.

	P	R
P	$z - e - f + g$	$z - e$
R	$z - h$	$z - h$

Case 1A. If $h > e$ and $h > (e + f - g)$, that is, $h - e > f - g$, then P dominates R . Since P also dominates B , the producers take over system.



Case 2A. If $h < e$ and $h < (e + f - g)$, that is, $g - f < e - h$ then R dominates P and we have a cyclic relationship between the competitors.



To reduce to generalized rock-paper scissors we want to subtract a constant from each column to make the diagonal 0.

$$\begin{pmatrix} 0 & h-e & g-e \\ e-g+f-h & 0 & -h \\ e-g & h & 0 \end{pmatrix} = \begin{pmatrix} 0 & -a_2 & b_3 \\ b_1 & 0 & -a_3 \\ -a_1 & b_2 & 0 \end{pmatrix}$$

In this situation $e < h$, $g > e$, so (1,2), (2,3), and (3,1) entries are negative, while (1,3) and (3,2) are positive. $e + f - g - h > 0$ so (2,1) is positive and we have the sign patten for Example ???. Theorem 6 implies that the stability of the interior fixed point is dictated by the sign of

$$\Gamma = b_1 b_2 b_3 - a_1 a_2 a_3 = (e + f - g - h)h(g - e) - (g - e)(e - h)h = (g - e)h(f - g)$$

Since $g > e$ and $h > 0$, the interior fixed point is attracting if $f > g$.

As a check we now compute the interior equilibrium using the formula in (9)

$$\begin{aligned} a_2 a_3 + b_2 b_3 + a_3 b_2 &= (e - h)h + h(g - e) + h^2 = hg \\ a_1 a_3 + b_1 b_3 + a_3 b_2 &= (g - e)h + (e - g + f - h)(g - e) + (g - e)^2 = f(g - e) \\ a_1 a_2 + b_1 b_2 + a_2 b_1 &= (g - e)(e - h) + [h + (e - h)](e - g + f - h) \\ &= (e - g)h + e(f - h) = ef - gh \end{aligned}$$

Adding up the three quantities we have:

$$D = hg + fg - ef + ef - gh$$

so the three components of the equilibrium are h/f , $1 - e/g$, and $e/g - h/f$ as computed before.

If neither of the two strategies P and R dominates the other, we will have a mixed strategy equilibrium. For $F_1 = F_2 = z - h$ we need $-e + p(-f + g) = h$

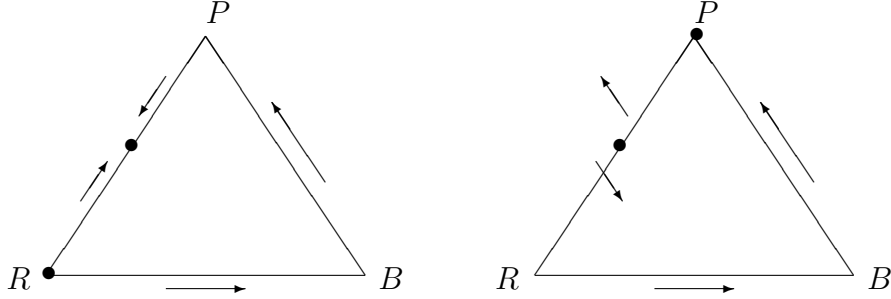
$$p = \frac{e - h}{g - f} \quad 1 - p = \frac{g - f - e + h}{g - f}$$

$0 < p < 1$ when we have:

Case 1B. $h > e$ and $h - e < f - g$ (Stable)

Case 2B. $h < e$ and $g - f > e - h$ (Unstable).

In the first case $z - e > z - h$ and $z - h > z - e - f + g$ so the $R - P$ fixed point is stable by Theorem 1. In the second case $z - e < z - h$ and $z - h < z - e - f + g$ so the fixed point on the $R.P$ edge is unstable.



Invadability. In order for B to invade the $P - R$ equilibrium we need $F_3 = z - pf > z - h = F_2 = F_1$. For this we need $pf < h$ or

$$\frac{h}{f} > p = \frac{h - e}{f - g} \quad (12) \quad \boxed{\text{Tom_stab}}$$

In case 1B, $f > g$ so cross-multiplying and simplifying the condition becomes

$$1 - \frac{g}{f} > 1 - \frac{e}{h} \Rightarrow \frac{g}{f} < \frac{e}{h} \Rightarrow \frac{h}{f} < \frac{e}{g}$$

which is the second condition for a stationary distribution given in (11). We will denote the conditions for equilibrium by EQ , and for invadability by I .

When $I = EQ$ holds, we expect that the interior equilibrium will be stable.

If not, $I^c = EQ^c$, then the one on the $R - P$ boundary will attract.

In case 2B, $g - f > e - h > 0$, so we multiply the numerator and denominator of p by -1 and then cross-multiply to get

$$\frac{g}{f} - 1 > \frac{e}{h} - 1 \Rightarrow \frac{g}{f} > \frac{e}{h} \Rightarrow \frac{h}{f} > \frac{e}{g}$$

which is the OPPOSITE of EQ .

When $I = EQ^c$ holds, then we expect that all trajectories to tend to P in the limit.

When $I^c = EQ$ holds, the $P - R$ equilibrium is a saddle point and P is attracting, so the interior equilibrium will be unstable.

1A.	$h > e$	$h - e > f - g$		convergence to all P
1B1.	$h < e$	$h - e < f - g$	$h/f < e/g$	interior equilibrium stable
1B2.	$h < e$	$h - e < f - g$	$h/f > e/g$	$P - R$ fixed point attracting
2A.	$h < e$	$g - f < e - h$		cyclic competition
2B1.	$h < e$	$g - f > e - h$	$h/g > e/g$	convergence to all P
2B1.	$h < e$	$g - f > e - h$	$h/g > e/g$	convergence to all P

Concrete Examples. Tomlinson considered a number of examples in his Table 1. We will only look at those with $g > e$. following Tomlinson's notations, and write the frequencies of strategies

1. PRODUCERS, p
2. RESISTANT, q
3. BASELINE, r

In the new notation our equilibrium is

$$p = \frac{h}{f} \quad q = 1 - \frac{e}{g} \quad r = \frac{e}{g} - \frac{h}{f}$$

Example 2. $h = 0.25$, $e = 0.1$, $f = 0.4$, $g = 0.2$. Here $h > e$, $h - e = 0.15 < 0.2 = f - g$, $h/f = 0.25/0.4 = 0.625 > 0.5 = 0.1/0.2 = e/g$ so we are in case 1B2, and the boundary fixed point is attracting. The boundary equilibrium has $p = (h - e)/(g - f) = 0.15/0.2 = 0.75$, and $q = 0.25$ in agreement with fourth line in Table 1.

Example 3. $h = 0.25$, $e = 0.1$, $f = 0.4$, $g = 0.15$. Here $h > e$, $h - e = 0.2 < 0.25 = f - g$. $h/f = 0.25/0.4 = 0.625 < 0.666 = 0.1/0.15 = e/g$, so we are in case 1B1 and the interior fixed point is stable. The interior equilibrium has $p = h/f = 0.625$, $q = 1 - e/g = 1/3$, $r = 1 - p - q = 0.04166$ in agreement with the ninth line in Table 1.

Example 4. $h = 0.3$, $e = 0.4$, $f = 0.8$, and vary g .

g	p	q	r
0.75	0	1	0
0.70	0	1	0
0.65	0	1	0
0.62	0	1	0
0.6	0.325	0.350	0.325
0.5	0.375	0.200	0.425

$e < h$ and $h - e = 0.1 > 0 > g - f$ so we are in case 2A. The interior equilibrium has $p = h/f = 0.375$ so the value for $g = 0.6$ is a typo. $q = 1 - e/g = 0.333$ for $g = 0.6$, $q = 1 - e/g = 0.2$ for $g = 0.5$. $r = e/g - h/f = 0.666 - 0.375 = 0.261$ for $g = 0.6$, $r = 1 - 0.375 - 0.2 = 0.425$ for $g = 0.5$.

Example 5. $h = 0.1$, $e = 0.15$, $g = 0.2$, and vary f . $e < h$ and $h - e = 0.1 > 0 > g - f$ so again we are in case 2A.

f	p	q	r
0.25	0.400	0.250	0.350
0.24	0.417	0.250	0.333
0.23	0.435	0.250	0.315
0.22	0.457	0.250	0.293
0.212	1	0	0

Here $q = 1 - e/g = 0.25$ in the first four rows, and $p = h/f$.

4 Glycolytic phenotype

It has been known for some time that cancer cells commonly switch to anerobic glycolysis for energy production. To investigate this using evolutionary game theory, Basanta et al [4] considered a thee strategy game in which cells are initially characterized as having autonomous growth (*AG*), but could switch to glycolysis for energy production (*GLY*), or become increasing motile and invasive (*INV*). The payoff matrix for this game (which is the transpose of the one in their Table 1) is:

$$\begin{array}{rcccl}
 & & 1 & 2 & 3 \\
 1 = AG & & \frac{1}{2} & 1 & \frac{1}{2} - n \\
 2 = INV & & 1 - c & 1 - \frac{c}{2} & 1 - c \\
 3 = GLY & & \frac{1}{2} + n - k & 1 - k & \frac{1}{2} - k
 \end{array}$$

Here c is the cost of motility

k is the cost to switch to glycolysis

n is the detriment for nonglycolytic cell in glycolytic environment, which is equal to the bonus for a glycolytic cell.

To investigate the properties of this game, we begin by studying the two strategy games it contains.

1. AG vs INV. If $c \geq 1/2$ the AG strategy dominates INV, so we will assume $0 < c < 1/2$. For equilibrium the fraction p of AG's must satisfy:

$$F_1 = p \cdot \frac{1}{2} + (1 - p) \cdot 1 = p \cdot (1 - c) + (1 - p) \cdot \left(1 - \frac{c}{2}\right) = F_2$$

which holds if

$$1 - \frac{p}{2} = 1 - \frac{c}{2} - \frac{cp}{2}$$

i.e., $p_{AG}^1 = c/(1 - c)$ which means $p_{INV}^1 = 1 - p_{AG}^1 = (1 - 2c)/(1 - c)$. Since $1/2 < 1 - c$, Theorem 1 implies that the equilibrium is stable.

2. INV vs GLY. We are assuming $c < 1/2$ and $k > 0$ so $1 - c > 1/2 - k$. If $k > c/2$ then INV dominates GLY. If $k < c/2$ then there is a fixed point where

$$p \left(1 - \frac{c}{2}\right) + (1 - p)(1 - c) = p(1 - k) + (1 - p) \left(\frac{1}{2} - k\right)$$

Rewriting this becomes

$$1 - c + \frac{cp}{2} = \frac{1}{2} - k + \frac{p}{2} \quad \text{or} \quad 2 - 2c + cp = 1 - 2k + p$$

so we have

$$p_{INV}^2 = \frac{1 + 2k - 2c}{(1 - c)} \quad p_{GLY}^2 = \frac{c - 2k}{1 - c}$$

When $k > 0$ and $c < 1/2$, $p_{INV}^2 > (1 - 2c)/(1 - c) > 0$. For $p_{INV}^2 < 1$ we need $c > 2k$. To check that the equilibrium is stable using Theorem 1 note that $c/2 > k$ implies $1 - c/2 < 1 - k$.

3. AG vs GLY. If $k < n$ GLY dominates AG. If $n < k$ AG dominates GLY.

Invadability. To determine the behavior of the three strategy game we will see if the third strategy can invade the other two in equilibrium. In the $1, 2 = AG, GLY$ equilibrium

$$\begin{aligned} F_2 &= F_1 = 1 - \frac{c}{2(1-c)} \\ F_3 &= 1 - k + \frac{c}{1-c} \left(-\frac{1}{2} + n \right) \\ &= 1 - \frac{c}{2(1-c)} - k + \frac{cn}{(1-c)} \end{aligned}$$

For $3 = INV$ to be able to invade the $1, 2$ equilibrium we need

$$k < \frac{cn}{1-c} \quad (13) \quad \boxed{3i12}$$

To see when $1 = AG$ can invade $2, 3 = INV, GLY$ in equilibrium, we note that

$$F_1 - F_3 = k - n(p_{GLY}^2) = \frac{k(1-c) - n(c-2k)}{1-c} > 0$$

when the numerator is positive, that is,

$$k > \frac{cn}{1-c+2n} \quad (14) \quad \boxed{1i23}$$

Interior equilibria. We return to using numbers for the three types.

$$\begin{aligned} F_1 &= p_1 \cdot \frac{1}{2} + p_2 + (1 - p_1 - p_2) \left(\frac{1}{2} - n \right) \\ F_2 &= 1 - c + p_2 \cdot \frac{c}{2} \\ F_3 &= p_1 \left(\frac{1}{2} + n - k \right) + p_2(1 - k) + (1 - p_1 - p_2) \left(\frac{1}{2} - k \right) \end{aligned}$$

Simplifying we have

$$\begin{aligned} F_1 &= \left(\frac{1}{2} - n \right) + p_1 n + p_2 \cdot \left(\frac{1}{2} + n \right) \\ F_2 &= 1 - c + p_2 \cdot \frac{c}{2} \\ F_3 &= \left(\frac{1}{2} - k \right) + p_1 n + \frac{1}{2} p_2 \end{aligned}$$

To solve we note that

$$F_1 - F_3 = k - n + np_2 = 0 \quad \text{when } p_2 = 1 - k/n$$

We have $F_1 = F_2$ when

$$\begin{aligned} np_1 &= 1 - c - \left(\frac{1}{2} - n\right) + p_2 \left(\frac{c}{2} - \frac{1}{2} - n\right) \\ &= \frac{1}{2} - c + n + \left(1 - \frac{k}{n}\right) \left(\frac{c}{2} - \frac{1}{2} - n\right) \\ &= -\frac{c}{2} - \frac{k}{n} \left(\frac{c}{2} - \frac{1}{2} - n\right) \end{aligned}$$

and it follows that

$$p_1 = \frac{-cn - ck + k + 2nk}{2n^2} = \frac{2nk - cn + (1 - c)k}{2n^2}$$

which agrees with the formula for p' on page 983 of [4]. Writing

$$p_2 = 1 - \frac{2k}{2n^2}$$

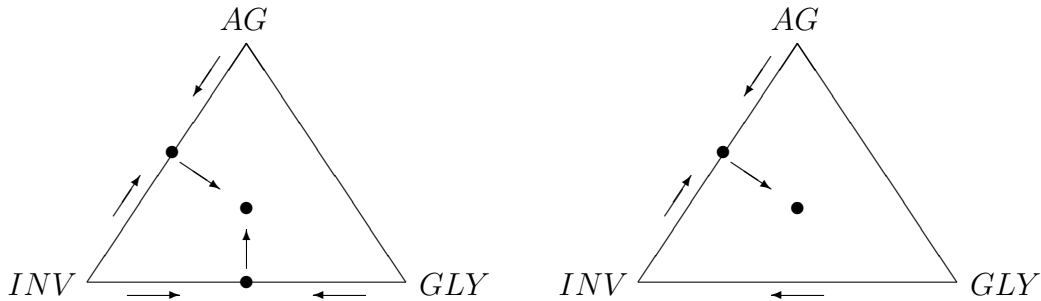
we see that the third component is

$$p_3 = \frac{cn - (1 - c)k}{n^2}$$

To check positivity of the coordinates we note that

- $p_1 > 0$ when $k > cn/(1 - c + 2n)$ the condition for 1 to invade 2,3
- $p_3 > 0$ when $k < cn/(1 - c)$ the condition for 3 to invade 1,2
- $p_2 > 0$ when $k < n$, which for $c < 1/2$ is weaker than $k < cn/(1 - c)$

There are two different pictures that lead to an interior equilibrium. We always suppose $C < 1/2$. The AG, GLY edge is blank because it does not matter which one dominates the other.



The figure on the left shows the case $k < c/2$, in which there is an INV, GLY equilibrium. The two invadability conditions shows that there is an interior equilibrium, and suggests that when it exists it is stable.

The picture on the right shows the case $k > c/2$, in which $INV > GLY$. In this case, we only have to check to see if 3 can invade 1,2 which is $k < cn/(1 - c)$. As for the other condition $cn/(1 - c + 2n) < c/2$, it follows from $k > c/2$.

Extension to four player game in [3].

5 Multiple Myeloma

Normal bone remodeling is a consequence of a dynamic balance between osteoclast (*OC*) mediated bone resorption and bone formation due to osteoblast (*OB*) activity, which is partly dependent on the receptor activator of nuclear factor- κ B (*RANK*), *RANKL* ligand (*RANKL*), and osteoprotegerin (*OPG*). Multiple myeloma (*MM*) cells disrupt this balance in two ways. For references to the biological background see Dingli et al. [5].

(i) *MM* and stromal cells produce a variety of cytokines including interleukin 1β (*IL-1 β*), *RANKL* and MIP- 1α , collectively called ‘osteoclast activating factors’ (*OAF*) that stimulate the growth of the *OC* population.

(ii) Secretion of *DKK1* by myeloma cells directly inhibits *Wnt3a* regulated differentiation of osteoblasts, reduces *OPG* expression and alters the *OPG* – *RANKL* axis against *OB* activity.

These considerations lead to the following game matrix $G_{i,j}$

	<i>OC</i>	<i>OB</i>	<i>MM</i>
<i>OC</i>	0	a	b
<i>OB</i>	e	0	$-d$
<i>MM</i>	c	0	0

To reduce the number of parameters Dingli et al. use a projective transformation $H_{i,j} = G_{i,j}/\phi_j$ with $\phi_j > 0$ to rewrite the matrix as

	<i>OC</i>	<i>OB</i>	<i>MM</i>
<i>OC</i>	0	1	β
<i>OB</i>	1	0	$-\delta$
<i>MM</i>	β	0	0

If x is an equilibrium for H then $y_i = x_i\phi_i / \sum_j x_j\phi_j$ is one for G . Since $G_{i,j} = H_{i,j}\phi_j$, conversely if y is an equilibrium for G then $x_i = y_i/\phi_i / \sum_j y_j/\phi_j$ is one for H .

Again to study the properties of the game we begin with the two strategy games it contains.

1. OC vs. OB. $(1/2, 1/2)$ is a mixed strategy equilibrium. Since $1 > 0$, Theorem 1 implies that it is stable.

2. OC vs. MM. $(1/2, 1/2)$ is a mixed strategy equilibrium. Since $\beta > 0$, Theorem 1 implies that it is stable.

3. OB vs. MM. $MM > OB$.

Invadability. To determine the behavior of the three strategy game, we will see when the third strategy can invade the other two in equilibrium.

In the *OC, OB* equilibrium, $F_{OC} = F_{OB} = 1/2$ while $F_{MM} = \beta/2$ thus *MM* can invade (i.e., the frequency will increase when small) if $\beta > 1$.

In the *OC, MM* equilibrium $F_{OC} = F_{MM} = \beta/2$ while $F_{OB} = (1 - \delta)/2$. Thus *OB* can invade if $\beta + \delta < 1$.

Since $\delta > 0$, these two conditions cannot be satisfied at the same time. Thus we have three cases

- $\beta > 1$, $(1/2, 1/2, 0)$ is unstable, while $(1/2, 0, 1/2)$ is stable
- $\beta < 1$, $\beta + \delta > 1$: $(1/2, 1/2, 0)$ and $(1/2, 0, 1/2)$ are stable. There is an interior fixed point that is a saddle point
- $\beta + \delta < 1$, $(1/2, 0, 1/2)$ is unstable, while $(1/2, 1/2, 0)$ is stable

To find the unstable interior equilibrium, we introduce numbers for the types: $1 = OC$, $2 = OB$, $3 = MM$. We want

$$p_2 + \beta p_3 = p_1 - \delta p_3 = \beta p_1$$

From this we see that $p_3 = p_1(1 - \beta)/\delta$, and

$$p_2 = \beta(p_1 - p_3) = p_1\beta(\delta + \beta - 1)/\delta$$

To make $\sum_i p_i = 1$ we set $p_1/\delta = 1/D$ where $D = \delta + \beta(\delta + \beta - 1) + 1 - \beta$, and the fixed point is

$$\left(\frac{\delta}{D}, \frac{\beta(\delta + \beta - 1)}{D}, \frac{1 - \beta}{D} \right)$$

From the analysis of the system we see that if $\beta > 1$ the only stable equilibrium is the co-existence of MM and OC cells. This behavior is observed clinically, patients with higher MIP-1 α levels have more bone resorption and lytic bone lesions, and shorter survival time due to a higher tumor burden. Consequently therapies which reduce β should decrease disease progression and prolong survival.

6 Tumor-Stroma Interactions

Tumors are made up of a mixed population of different types of cells that include normal structures as well as ones associated with malignancy, and there are multiple interactions between the malignant cells and the local microenvironment. These intercellular interactions effect tumor progression. In prostate cancer it has been observed that one can have three different outcomes:

- (i) the tumor remains well differentiated and relatively benign. In this case the local stromal cells (also called connective tissue) may serve to restrain the growth of the cancer.
- (ii) Early in its genesis the tumor acquires a highly malignant phenotype, growing rapidly and displacing the stromal population (often called small cell prostate cancer).
- (iii) The tumor co-opts the local stroma to aid in its growth.

To understand the origin of these behaviors Basanta et al [2] formulated a game with three types of players S = stromal cells, I = cells that have become independent of the micro-environment, and D = cells that remain dependent on the microenvironment. The payoff matrix is:

	S	D	I
S	0	α	0
D	$1 + \alpha - \beta$	$1 - 2\beta$	$1 - \beta + \rho$
I	$1 - \gamma$	$1 - \gamma$	$1 - \gamma$

Here γ is the cost of being environmentally independent

β cost of extracting resources from the micro-environment

α is the benefit derived from cooperation between S and D

ρ benefit to D from paracrine growth factors produced by I

In what follows we assume $\beta < 1$, $\gamma < 1$.

1. S vs. D. We have assumed $\beta < 1$ so $1 + \alpha - \beta > 0$. If $\alpha \leq 1 - 2\beta$, strategy D dominates S , which we write as $D > S$. If $\alpha + 2\beta > 1$ there is an equilibrium with

$$\alpha(1 - p_S^1) = 1 - 2\beta + (\alpha + \beta)p_S^1 \quad \text{or} \quad p_S^1 = \frac{\alpha + 2\beta - 1}{2\alpha + \beta} \quad p_D^1 = \frac{\alpha - \beta + 1}{2\alpha + \beta}$$

Since $1 - \beta + \alpha > 0$ it follows from Theorem 1 that the fixed point is attracting.

2. D vs. I. Noting that $1 - 2\beta < 1 - \beta + \rho$ we see that if $\gamma < \beta - \rho$, $I > D$, while if $\gamma > 2\beta$, $D > I$. If $\beta - \rho < \gamma < 2\beta$ then in equilibrium we have

$$1 - \gamma = 1 - \beta - \beta p_D^2 + \rho(1 - p_D^2) \quad \text{or} \quad p_D^2 = \frac{\gamma - \beta + \rho}{\beta + \rho} \quad p_I^2 = \frac{2\beta - \gamma}{\beta + \rho}$$

When the fixed point exists $1 - 2\beta < 1 - \gamma$ so by Theorem 1 the fixed point is stable.

S vs. I. $S < I$ since we have assumed $\gamma < 1$.

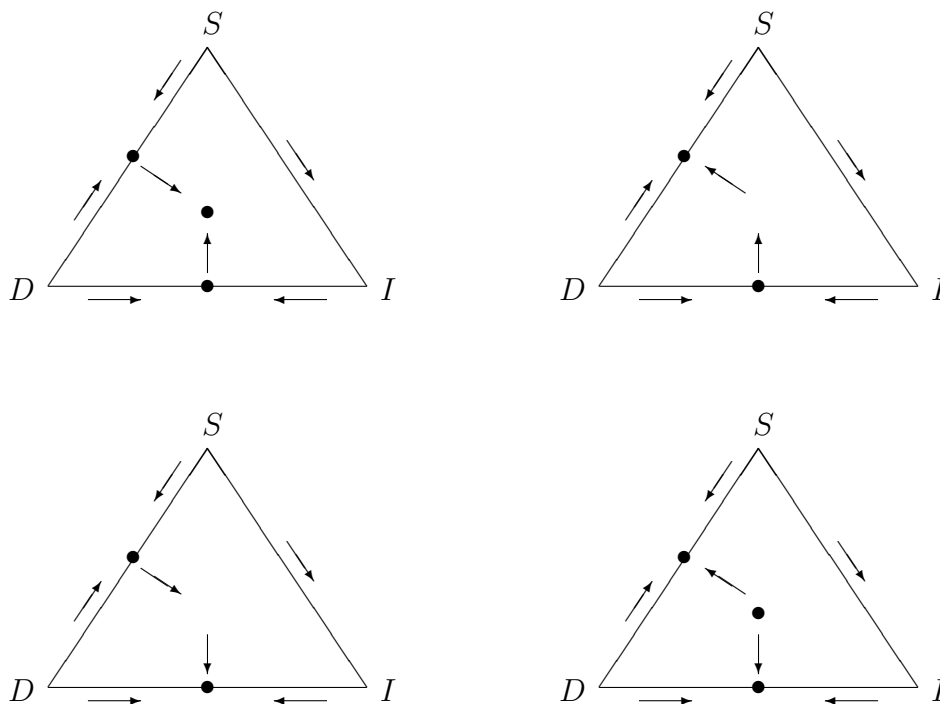
Invadability. To understand the behavior of the three strategy game, we need to examine the stability of the boundary fixed points. I can invade the S, D equilibrium if

$$1 - \gamma > \alpha p_D^1 = \alpha \frac{\alpha - \beta + 1}{2\alpha + \beta} \quad (15) \quad \boxed{\text{InvSD}}$$

S can invade D, I if

$$1 - \gamma < \alpha p_D^2 = \alpha \frac{\gamma - \beta + \rho}{\beta + \rho} \quad (16) \quad \boxed{\text{SinvdI}}$$

The next picture explains our interest in invadability: if the two boundary fixed points can be invaded then the interior fixed point will be attracting. If only one is invadable then the other will be the attracting fixed point. If both can be invaded then the interior equilibrium is unstable.



Interior fixed point. For all three species to coexist we need

$$\alpha p_D = 1 - \gamma = 1 - \beta + \alpha p_S - \beta p_D + \rho(1 - p_S - p_D)$$

From this we see $p_D = (1 - \gamma)/\alpha$. $(\alpha - \rho)p_S = \beta - \gamma - \rho + (\beta + \rho)p_D$ and hence

$$p_S = \frac{\beta - \gamma - \rho}{\alpha - \rho} + \frac{\beta + \rho}{\alpha - \rho} \frac{1 - \gamma}{\alpha}$$

The three frequencies have to add up to 1, so

$$\begin{aligned} p_I &= 1 - \frac{\beta - \gamma - \rho}{\alpha - \rho} - \left(1 + \frac{\beta + \rho}{\alpha - \rho}\right) \frac{1 - \gamma}{\alpha} \\ &= \frac{\alpha - \beta + \gamma}{\alpha - \rho} - \frac{\alpha + \beta}{\alpha - \rho} \cdot \frac{1 - \gamma}{\alpha} \end{aligned}$$

$p_D > 0$. If we suppose that $\rho > \alpha$ then the condition for $p_S > 0$ is

$$\frac{1 - \gamma}{\alpha} < \frac{\gamma - \beta + \rho}{\beta + \rho}$$

which is (16). The condition for $p_I > 0$ is

$$\frac{1 - \gamma}{\alpha} > \frac{\alpha - \beta + \gamma}{\alpha + \beta}$$

This does not look much like (15) but cross-multiplying gives

$$(\alpha + \beta)(1 - \gamma) > \alpha(\alpha - \beta + \gamma)$$

and adding $\alpha(1 - \gamma)$ to each side

$$(2\alpha + \beta)(1 - \gamma) > \alpha(\alpha - \beta + 1)$$

which is equivalent to (15)

Combining our calculations we see that there is an attracting interior fixed point if $\alpha > \rho$

$$\alpha + 2\beta > 1 \quad \beta - \rho < \gamma < 2\beta \tag{17} \quad \boxed{\text{line1}}$$

$$\frac{\alpha - \beta + 1}{2\alpha + \beta} < \frac{1 - \gamma}{\alpha} < \frac{\gamma - \beta + \rho}{\beta + \rho} \tag{18} \quad \boxed{\text{line2}}$$

Note that the quantity in the center of the second line is p_D . When $\alpha < \rho$ the conditions for $p_S > 0$ and $p_I > 0$ are the opposite of the invadability conditions, so the interior fixed point will be unstable.

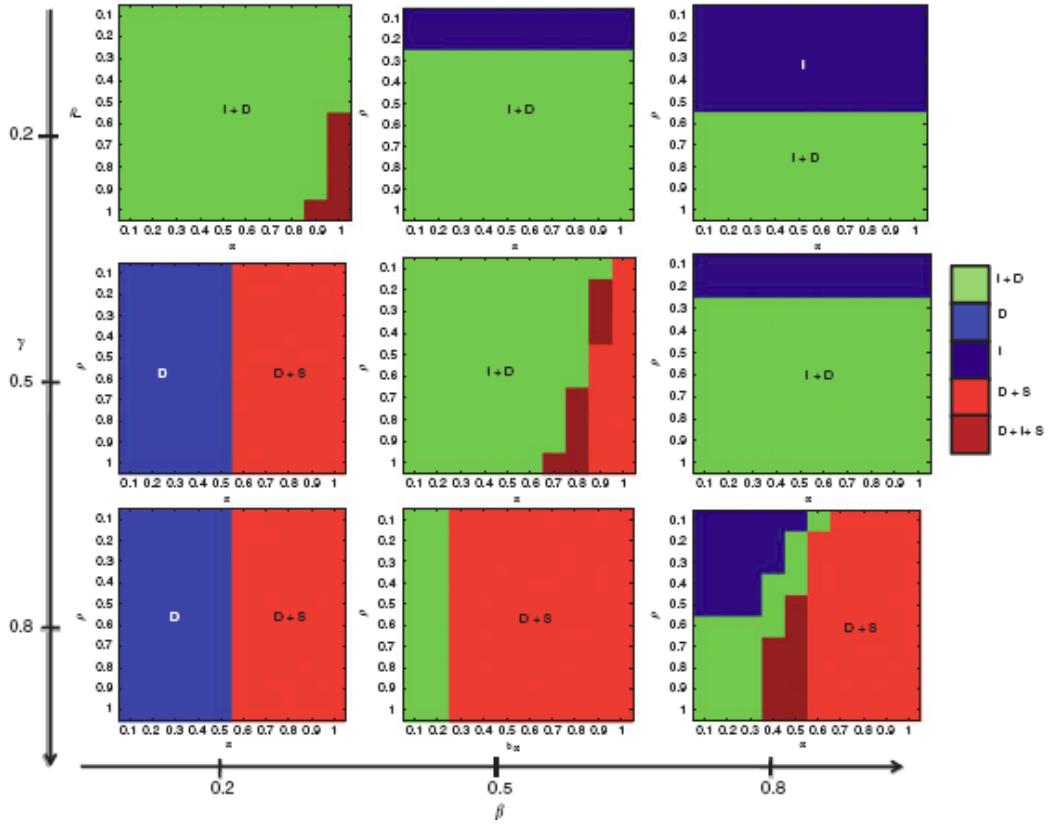


Figure 1: Phase diagram from Basanta et al (2012)

fig:phased.

To compare with Figure 1 we now consider some concrete examples.

I. The diagonal $\beta = \gamma$. The two strategies have the same cost, which facilitates coexistence if the rewards are high enough.

Case I.1. $\beta = 0.8, \gamma = 0.8$. In this case (17) becomes

$$\alpha + 1.6 > 1 \quad 0.8 - \rho < 0.8 < 1.6$$

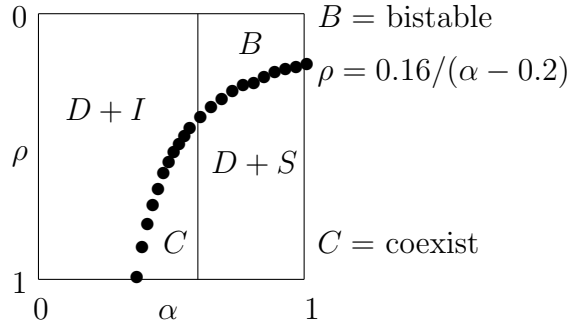
so these conditions always hold. (18) is

$$\frac{\alpha + 0.2}{2\alpha + 0.8} < \frac{0.2}{\alpha} < \frac{\rho}{0.8 + \rho}$$

The left inequality is $\alpha(\alpha + 0.2) < 0.4\alpha + 0.16$ or $\alpha^2 - 0.2\alpha - 0.16 < 0$. Solving the quadratic equation this is $\alpha < \alpha_0$ where $\alpha_0 = (0.2 + \sqrt{0.04 + 0.64})/2 = 0.512$. The right-hand inequality is

$$0.16 + 0.2\rho < \alpha\rho \quad \text{or} \quad \rho > \frac{0.16}{\alpha - 0.2}$$

When $\alpha = 0.36, \rho = 1$, when $\alpha = \alpha_0$ this is $\rho > 0.16/0.312 = 0.513$, so the computed region agrees with the one found by simulation.



When $\alpha > \alpha_0$, (15) fails. If (16) still holds then the D, S fixed point will be attracting.

If (15) and (16) both fail then there will be an interior fixed point that is unstable, so the limiting behavior depends on the initial condition.

When $\alpha \leq 0.36$ or $\alpha > 0.36$ and $\rho < 0.16/(\alpha - 0.2)$, (16) fails. If $\alpha < \alpha_0$ then (15) holds and the D, I fixed point will be attracting.

Thus our analysis does not predict the existence of a regime in which only I 's are present. However if $\beta = \gamma = 0.8$ $p_I^2 = 0.8/(0.8 + \rho)$ is close to 1 when ρ is small.

Case I.2. $\beta = 0.5, \gamma = 0.5$. In this case (17) becomes

$$\alpha + 1 > 1 \quad 0.5 - \rho < 0.5 < 1$$

so these conditions always hold. (18) is

$$\frac{\alpha + 0.5}{2\alpha + 0.5} < \frac{0.5}{\alpha} < \frac{\rho}{0.5 + \rho}$$

The left inequality is $\alpha(\alpha + 0.5) < \alpha + 0.25$ or $\alpha^2 - 0.5\alpha - 0.25 < 0$. Solving the quadratic equation this is $\alpha < \alpha_0$ where $\alpha_0 = (0.5 + \sqrt{0.25 + 1})/2 = 0.809$. The right-hand side inequality is

$$0.25 + 0.5\rho < \alpha\rho \quad \text{or} \quad \rho > \frac{0.25}{\alpha - 0.5}$$

When $\alpha = 0.75$, $\rho = 1$, when $\alpha = \alpha_0$ this is $\rho > 0.25/0.309 = 0.809$. The phase diagram thus looks similar to the previous case. Three of the regions are the same as in Figure 1 but there are differences in the bistable region B .

II. The three examples above the diagonal $\beta > \gamma$. The cost of extracting resources is larger than the cost of independence, so the S die out and we only have I, D or I .

Case II.1. $\gamma = 0.2$, $\beta = 0.8$. If $\rho < \beta - \gamma = 0.6$ then $I > D$. Since $0.2 = \gamma < 2\beta = 1.6$, the D, I equilibrium exists if $\rho > 0.6$. The next step is to see if I can invade the S, D equilibrium, i.e., if

$$(1 - \gamma)(2\alpha + \beta) > \alpha^2 + \alpha(1 - \beta) \\ \text{or} \quad \alpha^2 + c\alpha - (1 - \gamma)\beta < 0$$

where $c = (1 - \beta) - 2(1 - \gamma)$. Since the quadratic is convex, this holds for all $\alpha \in [0, 1]$ if and only if it holds at the end points. The value at 0, $-(1 - \gamma)\beta < 0$, so we need

$$1 + (1 - \beta) - 2(1 - \gamma) - (1 - \gamma)\beta < 0 \\ \text{or} \quad 2\gamma - (2 - \gamma)\beta < 0 \tag{19} \quad \boxed{\text{CII1}}$$

For the values under consideration we have $0.4 - (1.2)(0.8) < 0$.

To rule out an interior fixed point we need to check that S cannot invade D, I , i.e.,

$$1 - \gamma > \alpha \cdot \frac{\gamma - \beta + \rho}{\beta + \rho} = \alpha \cdot \left(1 + \frac{\gamma - 2\beta}{\beta + \rho}\right)$$

The right-hand side is maximized by taking $\alpha = 1$, and is increasing in ρ if $\beta > \gamma/2$ so for the condition above to hold for all α and ρ we need

$$1 - \gamma > \frac{1 + \gamma - \beta}{1 + \beta} \quad \text{or} \quad \gamma \cdot \frac{2 + \beta}{1 + \beta} < 1 - \frac{1 - \beta}{1 + \beta}$$

which is

$$\gamma < 2\beta/(2 + \beta) \tag{20} \quad \boxed{\text{CII2}}$$

When $\beta = 0.8$ this is $\gamma < 1.6/2.8 = 0.5714$.

Case II.2. $\gamma = 0.5$, $\beta = 0.8$. If $\rho < \beta - \gamma = 0.3$ then $I > D$. Since $0.5 = \gamma < 2\beta = 1.6$, the D, I equilibrium exists if $\rho > 0.3$. To see that I can invade the S, D equilibrium, we plug the new values into (19) to get

$$1 - 1.5(0.8) < 1$$

Since $0.5 < 0.5714$, S can never invade the D, I equilibrium.

Case II.3. $\gamma = 0.2$, $\beta = 0.5$. If $\rho < \beta - \gamma = 0.3$ then $I > D$. Since $0.2 = \gamma < 2\beta = 1$, the D, I equilibrium exists if $\rho > 0.3$. To see that I can invade the S, D equilibrium, we plug the new values into (19) to get

$$0.4 - 1.6(0.5) < 1$$

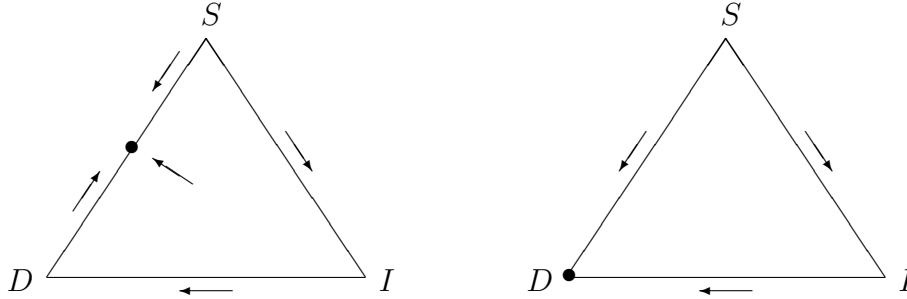
Since $0.5 < 0.5714$, S can never invade the D, I equilibrium.

III. The three examples below the diagonal $\beta < \gamma$. The cost of extracting resources is smaller than the cost of independence, so the I 's die out and we only have S, D or D .

Case III.1. $\beta = 0.2$, $\gamma = 0.8$. $\gamma > 2\beta$ so $D > I$. The D, S equilibrium exists when $\alpha > 1 - 2\beta = 0.6$. To check $I \not\rightarrow D, S$, we have to check that for $\alpha \in [0.6, 1]$

$$0.2 = 1 - \gamma < \alpha \frac{\alpha - \beta + 1}{2\alpha + \beta} = \frac{\alpha^2 + 0.8\alpha}{2\alpha + 0.2}$$

A little algebra shows that we want $\alpha^2 + 0.4\alpha - 0.04 > 0$ for $\alpha \geq 0.6$, which is true. As the graphs show the system will converge to the D, S equilibrium when it exists and to D otherwise, which agrees with Figure 1.



Case III.2 $\beta = 0.2$, $\gamma = 0.5$. $\gamma > 2\beta$ so $D > I$. The D, S equilibrium exists when $\alpha > 1 - 2\beta = 0.6$. To check $I \not\rightarrow D, S$, we have to check that for $\alpha \in [0.6, 1]$

$$0.5 = 1 - \gamma < \alpha \frac{\alpha - \beta + 1}{2\alpha + \beta} = \frac{\alpha^2 + 0.8\alpha}{2\alpha + 0.2}$$

A little algebra shows that we want $\alpha^2 - 0.2\alpha - 0.1 > 0$ for $\alpha \geq 0.6$. The quadratic has roots at $[0.2 \pm \sqrt{0.04 + .4}]/2$ both of which are < 0.6 so this is true.

Case III.3 $\beta = 0.5$, $\gamma = 0.8$. This time $\beta - \rho < \gamma < 2\beta$ so the D, I equilibrium exists. The D, S equilibrium exists when $\alpha > 1 - 2\beta = 0$. To see when $I \not\rightarrow D, S$, we have to see when

$$0.2 = 1 - \gamma < \alpha \frac{\alpha - \beta + 1}{2\alpha + \beta} = \frac{\alpha^2 + 0.5\alpha}{2\alpha + 0.5}$$

A little algebra shows that we want $\alpha^2 + 0.1\alpha - 0.1 > 0$. The quadratic has roots at $[-0.1 \pm \sqrt{0.01 + 0.4}]/2$. Turning to the other fixed point $S \rightarrow D, I$ if

$$0.2 = 1 - \gamma < \alpha \frac{\gamma - \beta + \rho}{\beta + \rho} = \alpha \frac{0.3 + \rho}{0.5 + \rho}$$

which is $0.1 + 0.2\rho < 0.3\alpha + \alpha\rho$, or

$$\alpha > \frac{0.1 + 0.2\rho}{0.3 + \rho} = 1/3 - \frac{0.1333}{0.3 + \rho}$$

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