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Selection by somatic signals: the advertisement of phenotypic state through costly intercellular signals

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SUMMARY

We develop a model of intercellular signalling, to explore the possibility that the signals exchanged between cells within a body may be subject to many of the same evolutionary pressures as signals exchanged between individuals whose genetic interests conflict. Evolutionary signalling theory maintains that signals, to be reliable indicators of need, intention or quality must be more costly than would be required merely to transmit a message. Cost guarantees that poor quality individuals are less able to display the high magnitude signals produced by the higher quality individuals. Receivers have been favoured by natural selection to attend only to the costliest signals, and thereby acquire honest information from the signaller. Hence the extravagant, costly ornamentation found among males of many species, ensures that females can accurately choose among them on the basis of their qualities. However, because somatic cells are normally perfectly genetically related, and are often denied access to the germ line, there will be minimal genetic conflicts of interest. This appears to imply that reliable intercellular signals should be produced without the need for cost to ensure their reliability. Nevertheless, we show that whenever cells vary in their phenotypic qualities in ways relevant to the fitness of the body, and given that there exists a class of cell that remains 'ignorant' of its phenotypic state, costly intercellular signalling will evolve as a form of quality control. Specifically, we show that given variation in the cell population, signal cost will aid the identification and removal of cells that over-represent their true phenotypic state, and which therefore could lower fitness. Cells that under-represent their state are simply outcompeted by other cells. The cells of a body employ signals in a variety of intercellular interactions, including the development of the nervous system, the formation of neuromuscular junctions, and during the establishment of the immune repertoire. In each of these cases, cells may employ costly signals to advertise their phenotypic quality to other cells, and we review the evidence in support of this hypothesis: in effect, the cells may possess a molecular counterpart to the peacock's tail.

1. INTRODUCTION

The application of selectionist principles to the cells of the body has recently received much attention from researchers interested in complex intercellular associations formed during development (Changeux 1985; Buss 1987; Callaway 1987; Raff 1988; Edelman 1989; Jablonka & Lamb 1995). These are often associations in which genes alone cannot be relied upon to describe each connection (Stent 1981), or in which cell fates are determined largely by local circumstances during ontogeny (Nowakowski 1987). For example, there are tens of billions of cells in the human nervous system, most of which presumably form functioning connections; a number of cells well in excess of the number of genes, and most likely in excess of genetic codes that may act as markers on target cells. Thus connections between cells will be forged through reliable epigenetic processes. In plant species, the germ line is somatically derived and only a fraction of cell lineages produce gametes. Consequently, genes in somatic cells are likely

to depend on epigenetic mechanisms for access to reproductive tissues (Klekowski 1988). During the maturation of the B cells of the immune system, cells of the pre-immune repertoire compete for access to follicular niches containing survival factors. Epigenetic signalling mechanisms operating through surface immunoglobulins appear to be able to influence differentially the success of competing cell lineages (Cyster *et al.* 1994). Each of these soma-selective processes involves reciprocal signalling interactions between cells, the precise mechanisms of which are likely to vary between different cell types. However, the same general competitive principles are likely to inhere in all of these signalling interactions, and it is these that we explore in this paper.

We are concerned with somatic cells and the conditions under which they may enter into a selective process. Darwinian selection requires phenotypic variation among individuals, differential individual fitness and the heritability of fitness (Lewontin 1970). What is constitutive of an individual has been the focus of much

attention in the evolutionary literature (Hull 1976, 1978; Brandon & Burian 1984, Buss 1987; Van Valen 1987; Williams 1994). The somatic cells of a body are derived through successive mitotic divisions and are therefore unlikely to show much genotypic variability, other than variability arising from incidental mutations or in those cases where variability is manufactured, such as in the immune system. However, genetic identity does not preclude phenotypic variation, and cells arising from identical parentage may show context dependent, and possibly cell-heritable (Jablonka & Lamb 1995) differences in their phenotypes. This variation is similar to variation in clonal organisms which may differ in their size, vigour or mortality as a result of phenotypic plasticity (Stearns 1986). Much somatic phenotypic variation shows no heritability, however this does not eliminate these cases as candidate selective systems, it merely eliminates them as candidate evolutionary systems or as evolutionary individuals. Selection is a process which statistically eliminates poorly adapted variants, whereas inheritance systems ensure the continuity of the favoured variants. Trivially stated, somatic lineages lacking phenotypic inheritance but demonstrating phenotypic variation participate in competition but not in evolution.

Another class of phenotypic variants, those possessing an inheritance system, have received a great deal of attention from biologists interested in developmental regulation and evolutionary processes occurring at the somatic level (Buss 1987; Jablonka & Lamb 1995; Otto & Orive 1995). Genetic or epigenetic inheritance systems (Maynard Smith 1990) allow the functional states of cells to be transmitted between cell generations, and potentially between organismic generations. Thus these variants qualify as Darwinian replicators or evolutionary individuals, and may enter into an evolutionary process of cumulative change. Given that most somatic cell lineages are not able to replicate indefinitely, the potential for gradual evolutionary change may be strictly limited. Only in those cases where somatic change is organismically heritable might significant evolution occur as a result of competition between cells, such as in many plant species (Karp & Bright 1985; Klekowski 1988). Nonetheless, genetic or epigenetic variation (whether heritable or not) in somatic tissue may still influence the fitness of the body, albeit not always systematically. As S. P. Otto & M. E. Orive remarked: 'Even weak selection among cell lineages within a developing individual can substantially alter the frequency of deleterious mutations observed among offspring' (Otto & Orive 1995, p. 1182).

Here we investigate models of somatic selection with or without somatic inheritance. We analyse the evolution of competition-promoting mechanisms; mechanisms put in place by selection and evolution at the organismic level to promote competition at the cellular level. These somatic selection mechanisms are viewed as a form of 'quality control selection' exercised by the body on its constituent parts, ensuring that the body is composed of the highest quality phenotypic variants. Hence somatic selection is studied with a regard to the

body's adaptive responses, or defences, against undesirable phenotypic variation.

Our models treat two cases of somatic variation: selection in short-lived cells with cell-heritable variation, and selection in long-lived cells with no heritability. We assume that phenotypic differences in short-lived cells are unlikely to adversely affect the fitness of the whole organism. Whereas genetic or epigenetic differences between these cells will potentially compromise organismic fitness as evidenced, for example, by various neoplastic growths. Non-heritable variation between long-lived cells is likely to affect body fitness, because these cells may be required to perform throughout the lifetime of the organism.

Our approach to intercellular signalling follows the suggestion of Zahavi (1993), that one make explicit the key strategic requirements for effective associations to form between high quality cells. Zahavi contended that conventional signals, signals conveying information of adaptive importance to receivers without a cost levied on the signaller, would permit the survival of defective cells unable to gauge their own true state or quality. Hence the signals exchanged between cells of perfect relatedness, might require handicaps to ensure their reliability. The important properties of a handicap theory of signalling are that stable honest signalling requires that signals are costly, and costly in a way related to the information revealed by the signal. And that the cost of signalling is higher for low quality individuals than for high quality individuals. For example, the Thompson's gazelle upon encounter with potential predators begins to 'stot', leaping into the air with all four legs held stiff and straight, thereby signalling to the predator that they are healthy enough to outrun them despite 'handicapping' themselves in this way. The physical condition of the gazelle determines the rate at which it stots, and higher stotting rates are correlated with higher escape probabilities (FitzGibbon & Fanshawe 1988). Unhealthy individuals are unable to convince predators that they are healthy because they are unable to stot at the highest rates, cheating is therefore prevented. Following Zahavi, we envisage a comparable process in the body, in which cells display their superior qualities through extravagant signal production. To the extent that the body employs such signals, it will mean that intercellular signalling cannot be understood solely on the basis of the proximate physiological or biochemical functions of the signal. The models are derived from a class of evolutionary signalling model, used to ascertain the conditions under which signals are likely to transmit reliable information (Zahavi 1975; Maynard Smith 1985; Grafen 1990; Johnstone & Grafen 1994). Similar models have been applied to the evolution of extravagant sexual displays during mate choice (Pomiankowski 1988), and to the evolution of threat displays during aggressive interactions between competing males (Enquist 1985). Whereas these previous models have been applied to contests between whole organisms (but see Pagel 1993; Nahon *et al.* 1995), our models explore the special case of interactions between genetically related cells within the body (for interactions among relatives, see also

Godfray 1991; Maynard Smith 1991; Johnstone & Grafen 1992).

2. A MODEL OF CELL SIGNALLING HANDICAPS IN LONG-LIVED SOMATIC CELLS

We consider a population of somatic cells that vary in their phenotypes. We assume that phenotypic differences among cells equate to differences in cell quality $q \in [0,1]$, and to differences in the production of a continuous amount of signal. Differences in quality may refer to, for example, differences in the conductance of axons, in the ability to manufacture signal, in cell size, in mitochondrial content, or the level of intracellular parasitism. Cells employ this signal to form long-lived associations, on the order of the lifetime of a single body. What we shall call the 'health' of these associations (and summing across all cells, the fitness of the body), is proportional to the quality of the cell complexes. Cell quality is assumed to vary according to a Gaussian distribution, and consequently the majority of cells are of approximately equal quality. One population of cells acts as signallers, producing signals that are either positively correlated with phenotypic quality (C-type cells) or uncorrelated with quality (U-type cells). This difference in the mapping between signalling and quality is assumed to be determined by genetic or epigenetic factors, in which the U-type cells produce the deleterious effects. Effectively, a U-type cell is one in which the cell is, for whatever reason, unable to signal its true state. We assume that U-type cells arise at some fixed rate and are therefore always present in the body.

We describe the signal that a cell produces as a function of cell quality using the function $f(q) \in [0,1]$. In the C case, the magnitude of the signal provides information about quality, in which case signal magnitude is positively correlated with cell quality. In the U case, signals are produced at random magnitudes, which we denote with the mean quality S . A second population of cells acts as receivers (R). These cells seek to discriminate the quality of the signalling population by means of the magnitude of their signals. It follows that an R cell is only able accurately to infer cell quality when signalled to by a C cell. The cells of the signalling population are in competition for trophic factors produced and released by receivers, whereas the cells of the receiver population are in competition for signaller cells of high quality with which they can form long-lived cellular complexes.

Each signaller cell signals for trophic factors produced by the receiver cells. Receivers transmit trophic factor in response to the strength of the signal, and therefore the mean payoff to a signaller is a function of its quality (randomly sampled from a distribution $\pi(q)$), its level of signal $f(q)$, the cost to the cell of producing the signal $C(f(q))$ and the amount of trophic factor that it acquires (we have assumed a continuous signal, but a high and a low discrete signal could also be employed). Receiver cells each have a quota of trophic factor F . The payoff to a receiver cell decreases as its reserves of F decline, and increases with the quality of

signaller cell selected. We can write the mean payoffs to both U and C signalling cells when interacting with an R cell as a sum over all possible qualities. If we denote the payoff to a cell X when interacting with another cell Y as $E[X,Y]$, where the roles played by each are denoted by either C, U or R, then we can write the four possible payoffs as:

$$E[R,C] = \int_0^1 F - [f(q)\pi(q) + q\pi(q)] dq, \quad (1)$$

$$E[R,U] = \int_0^1 F - S + q\pi(q) dq, \quad (2)$$

$$E[C,R] = \int_0^1 [f(q)/(1+C(q))]\pi(q) dq, \quad (3)$$

$$E[U,R] = \int_0^1 \{S/[1+C(f(q=S))]\}\pi(q) dq, \quad (4)$$

The first integral describes the payoff to all receivers when signalled to by all signallers adopting the correlated strategy. The payoff is a sum of F minus the costs of producing trophic factors, which are positively correlated with q , and the benefits of selecting a cell of quality q . The second integral describes the payoff to all receivers when signalled to by all signallers adopting the uncorrelated strategy. The payoff is a sum of F minus the costs of producing trophic factors which are equal to S , and the benefits of selecting a cell of quality q . The third integral describes the payoff to all correlated signallers when signalling to all receivers. The payoff is a function of the amount of trophic factor requested (positively correlated with q) scaled by the cost of producing the signal. The fourth integral describes the payoff to all uncorrelated signallers when signalling to all receivers. The payoff is a function of the amount of trophic factor requested (a variable amount which on average is given by $S = \bar{q}$), scaled by the cost of producing the signal.

The fitness of a whole body is assumed to be given by the sum of the fitness derived from C and U cells separately, this can be written as:

$$\begin{aligned} & \text{(the probability of a C cell being produced)} \\ x & \text{(the probability of a C cell of quality } q \text{ being selected)} \\ x & \text{(the payoff to the resulting complex of C signaller and R receiver cell)} \\ + & \text{(the probability of a U cell being produced)} \\ x & \text{(the probability of a U cell of quality } q \text{ being selected)} \\ x & \text{(the payoff to the resulting complex of U signaller and R receiver cell)} \\ - & \text{(the total cost of producing signals by both C and U cells).} \end{aligned}$$

We denote with p the probability that a cell is of type C and with $(1-p)$ the probability that a cell is a type U. Then let

$$\mu = \frac{pE[C,R]}{pE[C,R] + (1-p)E[U,R]},$$

which is the relative fitness of a C-type cell, corresponding to the overall probability that C-type cells

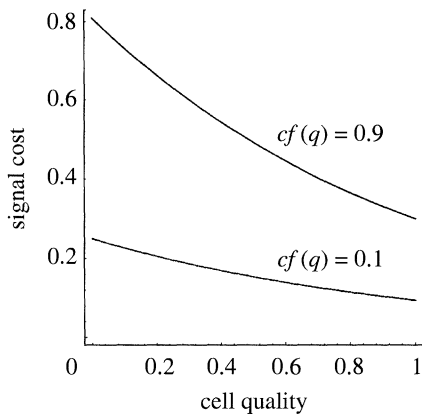


Figure 1. Total signal cost as a function of increasing cell quality. The two curves represent two different magnitudes of cell signal. We have employed the signalling function $cf(x)^2e^{-q}$, where x is either 0.9 or 0.1, and $c = 1$. The curves show how total cost decreases with an increase in true quality, whereas total cost is higher for a given true quality when signalling at a higher magnitude.

are selected by R-type cells in preference to U-type cells. Let

$$v = \frac{(1-p)E[U, R]}{pE[C, R] + (1-p)E[U, R]}$$

which is the relative fitness of U-type cells and corresponds to the overall probability that U cells are selected in preference to C-cells. The fitness of the body can then given by,

$$W = \mu E[R, C] + \nu E[R, U] - k \int_0^1 [(1-p)C_s(f(q)) + pC(f(q))]dq \quad (5)$$

The term multiplied by k represents the cost to the body of cells adopting costly signals. We assume that the constant $k \ll 1$, to capture the property that whereas the cost of producing signals is high for individual cells, the cost to the whole body is relatively low. This is because the contribution to fitness of high quality cells extends throughout the lifetime of the body, but the cost of producing these signals accounts for only a small part of the body's total expenditures. Thus the fitness of the body is principally a function of the cell quality composition of its constituent tissues. This expression for body fitness, is one of many functions that might be used to relate cell payoffs to whole body fitness.

We assume that the cost of a given signal $C(f(q)) = cf(q)^2e^{-q}$ is an increasing function of the strength of the signal and that the cost of a given signal is higher for low quality individuals than for high quality individuals (figure 1). This assumption may hold in those cases where cells differ in their supply of signal or ability to generate signal, for example, the differential ability of motor neurons to manufacture acetylcholine. For a given signalling function with these characteristics, we define c as a scalar multiplier that can

either increase or decrease costs; if $c = 0$, signals are not costly.

3. CONDITIONS FOR COSTLY SIGNALS TO INCREASE FITNESS

Our interest is whether costly signals exchanged among somatic cells can, despite reducing a cell's fitness, lead to an overall improvement in the fitness of the body. Therefore we seek conditions for which $dW/dc > 0$.

First consider the case in which p , the proportion of C-type cells is 1.0. Under these circumstances, $u = 1$, and $v = 0$, and thus body fitness, W eq (5), can be written as:

$$W = E[R, C] - k \left[\int_0^1 C(f(q)) dq \right],$$

and hence

$$\partial W / \partial c = \partial \left\{ E[R, C] - k \left[\int_0^1 C(f(q)) dq \right] \right\} / \partial c. \quad (6)$$

From (1) it can be seen that $E[R, C]$ is independent of c , and given the definition for $C(f(q))$, the second term of (6) is always positive for $c > 0$. This means that $\partial W / \partial c < 0$ when $p = 1$ and thus costly signals will always reduce fitness if all cells reliably signal their true phenotypic condition. This result accords with previous theoretical results that among perfectly related signallers costly signals are not required.

However, consider the case in which $0 < p < 1$, that is some U-type cells exist. Given the definitions for u and v , we can write $1 = u + v$, and therefore:

$$\partial W / \partial c = \partial (\mu E[R, C] + (1-\mu) E[R, U] - K) / \partial c, \quad (7)$$

where

$$K = k \left[\int_0^1 (1-p) C(f(\bar{q})) + p C(f(q)) dq \right],$$

and we are interested in the conditions for which $\partial W / \partial c > 0$. Equation (7) can be written as:

$$\partial W / \partial c = (\partial \mu / \partial c) (E[R, C] - E[R, U]) - (\partial K / \partial c) \quad (8)$$

and thus $\partial W / \partial c > 0$ requires that

$$(\partial \mu / \partial c) (E[R, C] - E[R, U]) > \partial K / \partial c.$$

As before $\partial K / \partial c$ is by definition > 0 , and thus we need to understand when the terms on the left side of this inequality are positive.

The term $\partial \mu / \partial c$ describes the change in relative fitness of C-type cells with changes in cost. From the definition for u , it can be shown that $\partial \mu / \partial c > 0$ when $C(f(q)) < C_s(f(q))$, that is, when the cost to a C-cell of producing its signal, given q , is less than the cost to a U-type cell of producing its signal S , given q . Because both types of cell employ the same cost function, this inequality will be true when the U-type cell produces

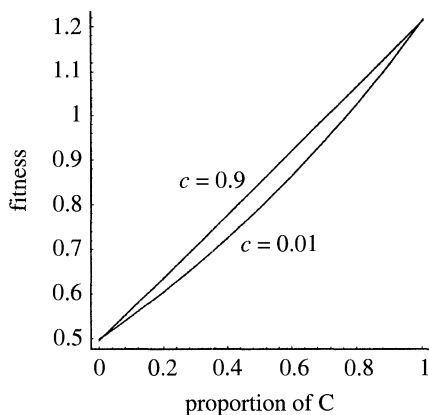


Figure 2. Body fitness as a function of the proportion of C-type cells. For each curve absolute signal cost is made to vary by modifying the parameter c in the cost function $C(f(q)) = cf(q)^2e^{-q}$. We assume that cell qualities are drawn from the scaled normal distribution $\pi(q)$, in which

$$\int_0^1 \pi(q) dq = 1, \quad \int_0^1 f(q) \pi(q) dq = 0.5 \quad \text{and} \quad k = 0.001.$$

For all values between $0 < p < 1$, signals requiring an extra investment in cost ($c = 0.9$), produce a higher body fitness than those paying very low costs ($c = 0.01$).

a stronger signal than a C-type cell, for a given quality, q ; in short when a U-type cell over-represents its true phenotypic state. C-type cells benefit from increasing costs in these circumstances because costs are disproportionately higher for higher signals, given q . The conditions for which $E[R, C] - E[R, U] > 0$ can be found directly from (1) and (2). These are:

$$\int_0^1 f(q) \pi(q) dq < S. \quad (9)$$

This condition states that R, C complexes will have higher fitness than R, U complexes when U-type cells, on average signal higher than their true phenotypic quality.

Costly signals can therefore increase the overall body fitness even among cells with no genetic conflicts of interest, if there are cells that, for whatever reason, signal at levels higher than specified by their phenotypic state. Under these conditions, costly signals can be employed to penalize these cells relative to cells adopting the appropriate signal. Costly signals thereby act as a means of identifying and removing cells of lower phenotypic quality than their signals would suggest. Costly signals are not required if cells under-represent their true worth, because in these cases the cells will be out competed by cells that signal appropriately. In short, costly signals can be gainfully employed to identify ‘liars’ but otherwise are not required.

We can illustrate these results by numerically integrating (5) assuming constant values for the parameters S , k , and y . In figure 2 we have plotted the fitness of the body as a function of the total proportion of C cells. We have assumed that signals are either costly to produce ($c = 1$) or involve very low costs

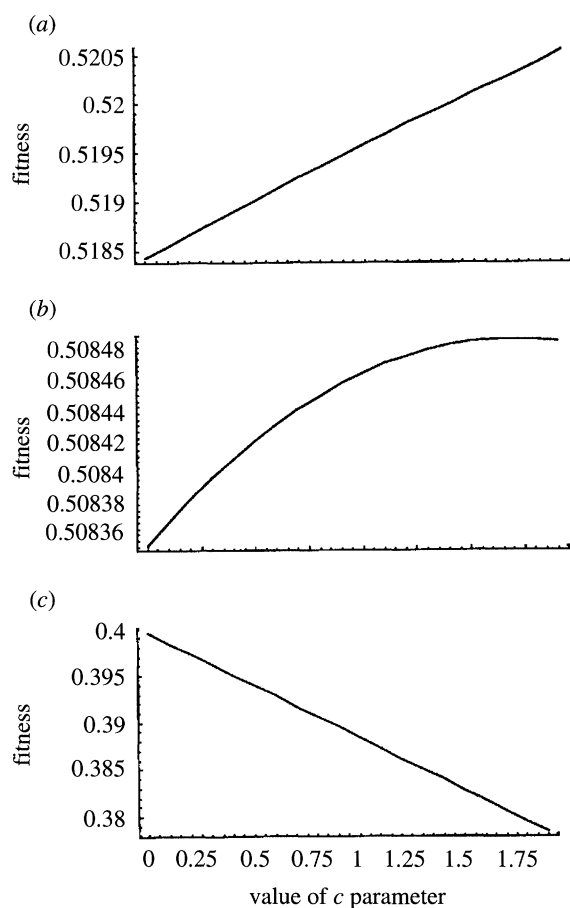


Figure 3. Sensitivity analysis of body fitness against total body cost of handicapped signalling. The parameter k determines the cost burden assumed by the body, whereas the parameter c influences the absolute cost of signalling. As the magnitude of k increases, the benefits of handicapped signalling decrease. The signalling function and distribution are as in figure 2. (a) $k = 0.01$; (b) $k = 0.05$; (c) $k = 0.1$.

($c \approx 0$). Bodies adopting the handicapped signals ($c = 1$) have a higher fitness than bodies without signalling costs for all values of p when $0 < p < 1$. This is our main result: by adopting handicapped signals, body fitness is greater than it would be if cells had not produced the extravagant signals. The magnitude of the differences in fitness between handicapped and unhandicapped bodies varies with the value of the three parameters S , k , and y . In figure 3 we have plotted body fitness against the value of the c parameter for different values of k ; as k becomes larger, overall fitness drops. At high values of k , body fitness declines with cost as predicted by equation (7), because the benefits of improved assessment are outweighed by the increase in the total costs to the body of handicapped signalling by cells.

These results can be interpreted as stating that the relative fitness of C cells increase as the cost of signalling increases, and that body fitness increases as the proportion of U cells declines. In other words, cost allows the receiver cells to gauge more accurately the quality of signallers by penalizing cells of low quality. This is most likely to occur when the signalling

function takes an accelerating form, and when U-type cells produce signals at a high magnitude. The total body fitness reflects the improved composition of its constituent cells, despite the cost stemming from the increased investment in signalling (from K). We have assumed that k takes a low value, because a body's investment in selection signals is likely to comprise only a small fraction of its total energetic investments. The costs are assumed almost entirely by the competing cells.

4. A MODEL OF SOMATIC HANDICAPS IN SHORT-LIVED CELLS: HERITABLE PHENOTYPES AND SIGNALLING STRATEGIES

As in the previous model, cells are assumed to vary in their qualities and in the production of signal. In contrast to the previous model, cells are now capable of replication and we assume that signalling strategies, or cell types, are heritable. In addition, cells are able to act as both signaller and receiver. We consider a case in which cells employ signals to maintain the quality of short-lived associations, for example in a tissue matrix. Heritability ensures that the more successful cell types do not simply account for a greater proportion of the tissue's composition, but that they will out compete the lower payoff signalling strategy through a higher replication rate. Thus bodies will eventually be made up principally from the cell type obtaining the highest payoff. The signalling functions remain as they were, whereas the receiving functions are modified to incorporate the cost to a cell complex of producing a costly signal. Cost is now assessed against each cell complex because the replication rate of a cell complex should reflect its instantaneous payoff. If we denote the payoff of a cell of type XY with signalling function X and receiving function Y , when interacting with an identical cell as $E[XY,XY]$, then we can write the payoff functions as:

$$E[CR, CR] = F - \int_0^1 \pi(q) [f(q)/(1+C(q)) - f(q) + q/(1+C(q))] dq, \quad (9)$$

$$E[CR, UR] = F - \int_0^1 \pi(q) [f(q)/(1+C(q)) - S + q/(1+C(q=S))] dq, \quad (10)$$

$$E[UR, CR] = F - \int_0^1 \pi(q) [S/(1+C(q=S)) - f(q) + q/(1+C(q))] dq, \quad (11)$$

$$E[UR, UR] = F - \int_0^1 \pi(q) [S/(1+C(q=S)) - S + q/(1+C(q=S))] dq, \quad (12)$$

These integrals are simply the sum of the payoffs to the signallers and the receivers as described in the earlier model, only now the cost of signal production

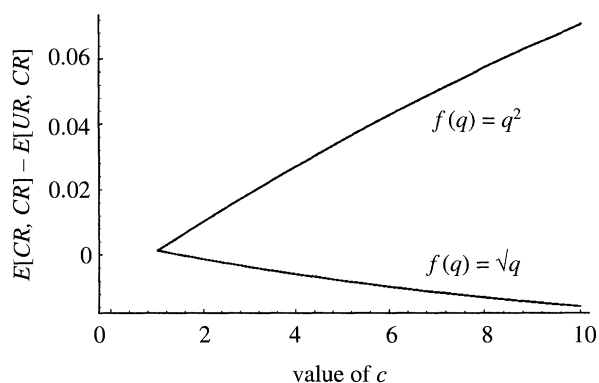


Figure 4. The relative payoff advantage of CR,CR complexes over UR,CR complexes, assuming different shapes of the signalling function for C-type cells, as a function of the absolute cost of signalling. The adaptive value of handicapped signals depends on the mapping from true cell quality through to the level of displayed signal.

has been factored directly into the receiver payoff, and therefore no k term is required. We seek to find the conditions under which CR is an evolutionarily stable strategy within the body. Assuming that the probability of producing a CR cell is p , and the probability of producing a UR cell is $(1-p)$, then we can write the evolutionarily stable strategy (ESS) conditions for CR (Maynard Smith 1982) as

$$W[CR] > W[UR], \quad (13)$$

where

$$W[CR] = pE[CR, CR] + (1-p)E[CR, UR], \quad (14)$$

and

$$W[UR] = pE[UR, CR] + (1-p)E[UR, UR], \quad (15)$$

because we assume that $p \ll 1$, this requires that

$$E[CR, CR] > E[UR, CR]. \quad (16)$$

Or

$$E[CR, CR] = E[UR, CR] \text{ and } E[CR, UR] > E[UR, UR]. \quad (17)$$

The conditions which satisfy these inequalities are derived as follows.

$$E[CR, CR] > E[UR, CR] \Rightarrow \int_0^1 \pi(q) \left[\frac{f(q)}{1+C(f(q))} - \frac{S}{1+C_s(f(q))} \right] dq > 0 \Rightarrow \int_0^1 f(q) \pi(q) dq < S \text{ is a sufficient condition for } E[CR, CR] > E[UR, CR].$$

is a sufficient condition for $E[CR, CR] > E[UR, CR]$.

Hence if the U-type cells signal, on average, at levels in excess of their qualities, then the first inequality in (18) will be true and costly signals can increase the

overall fitness of the body. If, however, the U-type cells signal at low levels, cost is not required because they will simply be out competed by the C-type cells.

These results assume that the fitness of the body is equivalent to the payoff to the most successful cell type. Unlike the previous model, the cost of producing signals is not treated in a separate expression. This is because costs are continually paid throughout the lifetime of the body and hence cost has been factored into the receiver component of fitness. As with the previous model, the magnitude of a cell type's advantage will depend on the value of the parameters c and y . In figure 4 we plot the difference between $E[CR, CR]$ and $E[UR, CR]$ for different values of the parameter c . The result is qualitatively similar to those found earlier: all else being equal, given an appropriate signalling function, signal cost can increase body fitness above the fitness of bodies not handicapped in their production of signals.

5. DISCUSSION

Our model describes the interactions among the normally perfectly related cells of the body. We view the selection and retention of the highest quality cells capable of producing accurate signals in the body as a means for the body to increase its fitness. We view quality as some state of a cell which contributes to its proper function, this might be conductance differences in motor neurons, random differences in the level of energy reserves, differences in spatial position leading to differential resource sequestration, differences in mitochondria populations, or different levels of intracellular parasitism. Our model shows that, even when there are no genetic conflicts of interest among somatic cells, costly signals are required to ensure that cells do not inadvertently misrepresent their qualities. This hypothesis was first suggested by Zahavi (1993) as a means by which the cells of a body could identify and eliminate mistakes in signals. The model confirms Zahavi's intuition that cells that over-represent their true states, are penalized relative to those cells that signal their true states. In this way, signal-cost acts as a quality control device to aid the body in the identification of unreliable cells. Bodies that do not make use of costly signals do not have to pay the costs of signalling but suffer the effects of being composed of lower quality cells.

Our modelling approach assumes explicitly that the majority of cells in the body 'know' and can signal their true state, but that some proportion of cells will always misrepresent themselves. We assume that the latter fraction arise spontaneously as a result of mutation or developmental noise. However, our qualitative conclusions do not depend upon this cohort of cells. We could have assumed that very few of the cells in the body 'knows' its true state, and asked what must be true of the signals they employ to ensure that signal receivers can correctly apprehend the quality of a signaller. The answer turns out to be the same: only if the cells employ costly signals will it be possible to relate signal strength in a reliable way to cell quality. In this circumstance cells would simply emit their

maximum signal and the cost of the signal would determine what that level was for each given cell quality. This form of handicapped signal has been referred to as a 'revealing' handicap (Maynard Smith 1985). Without it any cell that mis-signalled its true state, for whatever reason, would prosper within the body alongside cells that signalled their states reliably, and overall body fitness could suffer.

In all multicellular organisms, signals provide the means by which individual cells can integrate their processes, and thereby ensure the viability of the whole organism. Intercellular signals will, we suggest, be exaggerated or 'ornamented' in ways similar to signals exchanged between individuals with conflicting genetic interests. Thus, at least part of the nature of intercellular signals cannot be understood solely in terms of the proximate biochemical or physiological mechanisms required of the signalling task.

Our models have relied on maximizing the fitness of the entire body. Because bodies are a composite of individual cells, our arguments may be thought to depend on group selection. However, given that the cells of a body are normally perfectly related, individual cells maximize their fitness by maximizing the genetic contribution of the body's germline to the next generation. Our model shows that this contribution can be highest when individual cells are handicapped in the production of signal.

We have not investigated how or whether cell receiving strategies might be affected by the presence of cell signals that cannot always be trusted. For example, rather than always act upon signals as if they are reliable, as in our models, might not a strategy of discounting high-level signals be valuable because it is the high-level signals that can potentially lead the receiver to select a cell that is in fact of low quality. There may indeed be some optimal receiver discounting function given the presence of cells that may misrepresent their quality. However, to discount all cells that signal at a high level will necessarily miss the many that are not misrepresenting themselves, and therefore a discounting strategy, if it exists, will be a matter of degree and not kind (Krakauer & Pagel 1995). This does not then alter our main conclusion, that signal-cost can be useful in removing cells that over-represent their qualities, because this effect acts upon the fitness of the signalling cell *per se* and not via the receiver's strategy.

6. A MOLECULAR BIOLOGICAL PERSPECTIVE ON HANDICAPS

Intercellular signals vary in their properties and these often reflect the ecology and function of different cell types. Molecular biologists traditionally classify intercellular signals according to the distances over which they operate, and their intended target cells (Alberts *et al.* 1983): 'endocrine' when a systemic effect is observed and in which hormones act on cells distant from their site of release; 'paracrine' when effects are restricted to neighbouring cells only; and 'autocrine' when cells respond to their own signals. We have

undertaken to investigate those signals mediating the selection of a small number of cells, chosen from a larger population of cognate cells competing for survival factors. These are most likely to be paracrine signals in tissues, because these signals fulfil our model requirement, that receivers control which cells receive the trophic factors. In each case, signal scarcity ensures that only a fraction of the initial population of the dependent cells (signallers) survive, and we suggest that signal-cost can ensure that this fraction represents the highest quality cells.

Somatic selection: selection within the body at any level above the DNA (Van Valen 1988), requires an over-production of cells and phenotypic variation in cell populations. These conditions will promote competition, the resolution of which is often achieved through signalling interactions (Raff 1992). Signals will need to provide information about the states of cells to an appropriate selective agency, where these states determine the survival chances of the cell. We are interested in those cases in which cell states are of adaptive significance to the whole organism. We have grouped these important states under the banner of 'cell quality', such that bodies with a large proportion of high quality cells are deemed more fit than bodies with a lower proportion of high quality cells. We have assumed that there is phenotypic variation among cells, while acknowledging that bodies are made up from cells with approximately identical genomes. Variation must therefore be induced by properties of the cell's environment, through some mischance during development or increased rates of mutation and recombination.

How much evidence is there for somatic variation within single bodies, and is this variation likely to be of consequence? The differential success of individual cells in selection events during development, may provide indirect evidence for phenotypic variation; for example, the differential survival in the peripheral nervous system of neurons with acetyl choline receptors (Balice-Gordon & Lichtman 1994). If we do not accept that somatic variation occurs in cells of the same fate, then we must suppose that selection of the surviving cells occurs randomly. If this were so, we should need to know why overproduction of cells takes place, assuming that the body could minimize its energetic expenditures by reducing the amount of wasted cells produced. In other words, evolution is assumed to increase the efficiency of development by reducing the amount of protein synthesized (Wolpert 1990). To determine the organismically selective advantages of overproduction, we must therefore establish the extent to which a relaxation in competition at the cellular level, might increase the probability of random cell survival. And concomitantly, correlate random survival with a reduction in body fitness. We now briefly review the evidence for phenotypic variation within identical cell types of a single body, discussing data permitting, the effects of random rather than competitive cell selection. We must first establish that variation exists, before we can discuss how signals in particular might act as a somatic selective force. The immune system which offers such a clear example of

variation has been omitted, because cellular selection and signalling are poorly understood in this system.

7. SOMATIC VARIATION

(a) *Variation in nervous system*

Most studied of the long-lived somatic cell lineages are the cells of the nervous system. Many neurons are overproduced during early development, and enter into competition for target cells which provide neurons with survival factors (Raff *et al.* 1993). This competitive process is usually viewed as a mechanism to ensure that the correct connections are formed, and to balance the number of innervating neurons to the target cell numbers (Oppenheim 1991). The most detailed investigations of neuronal competition are those involving the neuromuscular junction. In newborn mice, muscle fibres are innervated by several motor neurons, only one of which will form a lasting connection. The ability of a single cell to out compete its rivals on a single synapse appears to depend on its production of acetylcholine (ACh) (Balice-Gordon & Lichtman 1994). Focal blockade of the ACh receptor (AChR) causes the directly overlying synaptic terminal to regress. Blockade of all AChRs on a synapse, allows all of the confluent terminals to persist.

Variation in the production of ACh is therefore the key to variation in cell survival and consequently to the formation of functioning neuromuscular junctions. Variation occurs between identical cell types producing identical neurotransmitters, hence these selection events can not be explained in terms of ensuring connections between cognate cell types. Also, given that there are invariably more neurons than targets, competition is not required for matching cell numbers as connections could form according to a first come first served rule.

In the mammalian peripheral nervous system, axons are enveloped by Schwann cells, that divide to provide neurons with an essential myelin sheath. Neurons and glial cells engage in complex reciprocal signalling exchanges, during which the Schwann cells proliferate, and preferentially myelinate large-caliber axons (Snipes 1994). Not all axons are myelinated; variation in axon caliber determines the relative success of neurons in this acquisitive process. Similarly, not all Schwann cells are equally effective at myelinating axons, and defective myelination can lead to several life threatening neuropathies, such as motor neuron disease.

These selection events early in ontogeny are what Edelman (1987) has called developmental variation and selection; in which selection is viewed as a local mechanism for ensuring robust global connectivity. We suggest that quality control may also be an important factor promoting competition, and is an explanation consistent with overproduction. Quality control selection is not to be confused with the theory of 'Neural Darwinism' which deals with 'experiential selection' (Edelman 1993). Experiential selection has been invoked to account for the development and plasticity of cognition (Changeux 1985; Edelman 1989), arising from differential success of neuronal groups. However,

these two processes of 'neural Darwinism' and quality-control-selection may over an evolutionary timescale be related; in which the need for quality control, provided the initial impetus for the evolution of selective mechanisms. These mechanisms could then have been appropriated by cognitive processes, to provide high levels of perceptual plasticity. Thus quality control mechanisms might have preadapted the nervous system for experiential selection.

(b) Variation in the reproductive system

Both the angiosperms and gymnosperms abscise a large proportion of their flowers and young fruits, consequently the seeds matured by individual plants represent only a sample of early zygote phenotypes (Stephenson 1981). Variation in the number of pollen grains deposited on the stigma can lead to variance in the number of seeds produced by a single individual, and it has been shown that fruits with fewer seeds are more likely to abort (Quinlan & Preston 1961). Seed number is often important to plants, and hence the selection of abortive fruits will require directed choice mechanisms.

During oogenesis and folliculogenesis in mammals, the somatic tissues of the ovarian follicle develop into a support network for the developing oocyte. The differentiating follicles and oocytes show considerable heterogeneity in structure, composition and in the distribution of organelles, where these differences have important developmental significance (Schuetz 1985). The follicular cells enveloping the oocytes are involved in preventing oocyte death and atresia. Nevertheless, most of the oocytes degenerate before birth, after seven months of gestation, in a wave of atresia while the eggs remain arrested in pachytene (Tsafriri & Braw 1984; McLaren 1988). The fact that the eggs remain diploid at this stage, does not rule out genetic and environmentally induced differences between cells. Mutation, crossing over, and mitotic gene conversion might create diversity in a uniform diploid lineage (Hastings 1989). Competition and selection may then eliminate unfavourable variants before selection acts on the adult organism. A purely random survival of eggs could lead to the conservation of deleterious recombinants, and might imply that the somatic reduction of oocytes during gestation is a non-adaptive process.

In *Drosophila* larvae, the cells of the salivary gland, and the neural ganglion cells possess markedly different chromosome types (Rees & Naylor 1959). Similarly, in the cells of the ovary, a proportion of cell nuclei remain diploid, whereas others are polyploid (Hertweig 1935). Chromosomes may therefore vary whereas other properties of tissues remain largely invariant. In the anthers of rye grasses, variation among chromosome populations may reflect the early distribution of nutrients and other trophic factors. These factors influence the replication potential of lineages by affecting the timing of meiotic divisions: chromosomes with higher rates of chiasmata formation reach metaphase earlier (Rees & Naylor 1959). Selection is therefore likely to act on cells, to preserve more efficient karyotypes.

(c) Variation in healthy tissues

The hepatocyte cells of the liver are involved in the production of many of the plasma proteins not manufactured by the immune system. Comparisons between small populations of these cells, show that there are high levels of heterogeneity, in which each population of cells is functionally specialized for the production of a given plasma protein (Michaelson 1989). Furthermore, as in the immune system, the activation of albumin genes appears to be stochastic, and the state of gene expression remains heritable within a cell lineage (Michaelson 1991). The functional output of the liver, reflects the proportions of each of the cell states which can vary throughout the lifetime of an individual (Nahon 1987). The majority cell-state must reflect the needs of the body, and hence selection must be directed by the titres of circulating antigens, and not by random replication and cell death. The complicating factor in such variation, is that no single quality or state is ever adaptive throughout the whole course of ontogeny. Hence those qualities which are favoured in cell selection events, will be determined by transient features of the tissue environment.

Genomic imprinting, in which the expression of genes derived paternally or maternally are not equivalent, can in some cases lead to variation in cell lineages. In mammals, one of a pair of X chromosomes remains inactive as a result of imprinting in the early embryo, for example, the inactivation of the paternal X in the extraembryonic membranes of female mice (Takagi & Sasaki 1975). Evidence suggests that methylation is important in the maintenance of dosage compensation in X-linked genes (Monk & Grant 1990), where cells may differ in their expression of protein products. Imprinting can therefore create somatic variation, potentially leading to competition.

(d) Variation in diseased tissues

The cells of most tissues show a minor propensity to develop neoplastic cell lineages; whereas some tissues can show an inherited tendency to transform, such as in retinoblastoma. Neoplastic cells show some degree of escape from normal growth controls (controls mediated by signals), and this provides these cells with a selective growth advantage over the cell strain from which it was derived. Instability in cell state, can lead to the sequential selection of variant subpopulations within a neoplastic lineage (Nowell 1976). Cancerous cells are therefore one of the most heterogeneous groups of somatic cells, in which genetic and epigenetic mechanisms conspire to create unregulated tissues. Among the properties of neoplastic cells are: decreased growth factor requirements, the loss of capacity for growth arrest, the loss of dependence on anchorage for growth, the loss of contact inhibition, and a modified morphology. These properties are related largely to alterations on the surfaces of these cells, including an increased mobility of surface proteins, and an increased release of growth factors and protease enzymes (Lodish *et al.* 1995). Of those oncogenes that have been analysed, their proto-oncogenes have been involved in

the production of growth factors, growth factor receptors, signal transducers, transcription factors, and cell cycle proteins. Hence neoplastic cells are cells which often vary in essential signalling pathways.

In addition to spontaneous mutation, nonpermissive cells can be transformed into neoplastic cells by several DNA viruses, for example the papoviruses, that are able to integrate their viral oncogenes into the host genome (Baltimore 1970). RNA tumour viruses, on the other hand, are able to reverse transcribe oncogenes into the host genome directly (Bishop & Varmus 1984). In both cases, heterogeneity in cell lineages will be created by the unique pattern of viral infectivity in the tissue.

In the case of cancer, somatic variation is to be guarded against, and it is in the interest of the body to deny transformed cells vital nutrients and growth factors. Although cancer can be interpreted as a case of selfish cells subverting the natural competitive and selective mechanisms of the body, the body is likely to have responded by coevolving new mechanisms of selection to reduce the threat from these cells. We shall now discuss the possible application of handicapped signals in competition and quality control selection, and the ways in which quality dependent cost might ensure the survival of the highest quality variants.

8. SIGNALS AS A SELECTIVE FORCE: A PUTATIVE ROLE FOR COSTLY HANDICAPPED SIGNALS AMONG SOMATIC CELLS

Cells in multicellular organisms form highly specific and highly stable cell to cell contacts by making use of a large number of signal and receptor molecules. Many of these come from large families of multiadhesive matrix proteins, such as the integrins (Hynes 1987), fibronectins (Hynes 1989), cadherins (Geiger & Ayolon 1992), selectins (Lasky 1992) and members of the immunoglobulin (Ig) superfamily (Cunningham *et al.* 1989). In addition, regulation may be achieved by direct cell-cell contact, involving general purpose signalling proteins. Each of these molecules may differ in their distributions, specificities and binding affinities. Here we shall discuss only a few them.

The N-CAMs are a class of calcium independent adhesion molecules found in the nervous tissue and in muscle (Edelman 1988). These molecules regulate homophilic interactions between cells expressing similar N-CAM molecules. The adhesive properties of these molecules are modified by variable length chains of negatively charged sialic acid (sugar) residues. The chain length influences the strength of the adhesion, with longer chains forming less stable interactions. Early in development, the ability to sever connections with cells is essential for healthy development, whereas in the mature organism, stable connections are required. These are therefore phenotypically variable signals, that achieve their binding affinities by means of differential glycosylation of the N-CAM molecule (Rutishauser & Jessell 1988). This raises the intriguing possibility that cells engaging in the production of the large sugar molecules can thereby demonstrate the

extent of their energy stores or sequestration abilities, features of adaptive importance to all cells. The importance of variation between cells is supported by the observation that cells expressing different levels of the same CAM are able to sort from one another, and end up performing different functions (Crossin 1994). According to the handicap view of signalling, those cells producing much signal (or more accurately, more costly signals), should function in a capacity requiring consistently high CAM production throughout ontogeny. This view is opposed to that one which asserts that high CAM production is only important in permitting selection, irrespective of final cell function.

The cell surface proteins, Notch N (receptor) and Delta D1 (ligand), found in *Drosophila* have been implicated in determining the competence of diverse cell types in responding to signals (Fehon *et al.* 1990). Both N and D1 contain a large number of extracellular EGF amino acid repeats. Loss of function mutations produce a characteristic result in the nervous system in which there is an hypertrophy of neuroblasts. For example, in the sensory system during normal development, a single cell from a group of cells forming the proneural cluster, is selected to form the sensory organ precursor cell, while the remaining cells form epidermoblasts. With a loss of function mutation in N or D1, several cells from the proneural cluster become precursor cells. Thus this receptor-ligand pair is involved in the competitive interactions between cells sharing a common fate. The reasons why any one cell should become a long-lived sensory cell, and the others short-lived dermal cells remains unclear. But we might speculate that long-lived cells are required to be of a higher quality, given that they are rarely replaced. The quality of the selected cell could be either an intrinsic property of the cell, or the result of factors preferentially delivered to that cell thus biasing the competitive process.

During the formation of the neuromuscular junction, any one postsynaptic membrane can be multiply innervated early in development, but always ends up connected to only a single cell later in ontogeny (Redfern 1970). The loss of the presynaptic terminal is correlated with a reduction in postsynaptic acetylcholine receptors (AChRs) (Rich & Lichtman 1989). Balice-Gordon & Lichtman (1994) have analysed the changes in AChR distributions by using focal and junction-wide receptor blockades. They find that the stabilization of synapses involves a reciprocal signalling interaction between the terminals and the muscle fibre membrane. The greater the production of ACh by any one terminal, the greater the inhibition of rival terminals by signals produced in the muscle fibre membrane, and the greater the trophic feedback to the best competitor. This inhibition of the alternative sites is achieved through a down regulation of the AChRs at these sites. If all of the AChRs are blocked, all of the terminals remain over the membrane. Such an interaction lends itself to an interpretation as a signalling handicap, where the cost lies in the excessive production of ACh by the terminal, and in which the information necessary for selection is transmitted directly to the synapse. The theory would predict that

signal release during selection should exceed signal release during motor control at a fully formed terminal, and that the selected cell differs from its rivals in its ability to function as a motor neuron.

9. CONCLUSIONS AND SUMMARY

1. We have demonstrated using a formal model, that the imposition of high costs on the production of signals, enables bodies to preferentially select cells of high quality. Quality refers to some phenotypic or genotypic feature of a cell able to influence its ability to function.

2. These signals are more costly than would be required merely to transmit information about cell quality in a population made up purely from C-type cells, and represent an investment by the body in signal reliability.

3. A sufficient requirement for the evolution of handicapped intercellular signals, is therefore that occasionally cells should arise, that are unable to produce the signal appropriate to their phenotypic quality, and which routinely over-represent their true quality: U-type cells.

4. A costly signalling mechanism acts as a form of quality control, in which selection acting at the level of whole organisms, has imposed additional costs at the level of the cells. These costs might ensure the continued health of important tissues and organ systems.

5. A brief review of the literature provides evidence for somatic variation, and for somatic selection based on the production of high magnitude signals, such as in activity dependent selection in nerve cells. These mechanisms are most evident in those examples involving long-lived cells, whose quality is presumably more important to the body.

6. The hypothesis makes a number of clear predictions: (i) signal cost (often simply signal magnitude) must be employed as a means of selecting a single cell from among a population of similar cells; (ii) the signal employed in the selection of the winning cell must be directly related to the future role of the cell, and not act merely as a tag or label for effective discrimination; (iii) the level of signal production during selection should exceed signal production during normal function once selection has occurred; (iv) long-lived cells are more likely to adopt handicapped signals than short-lived cells, given their protracted importance to the body; (v) preventing selection based on handicapped signalling between cells, should quantitatively reduce the fitness of the whole body; and (vi) handicaps require competition and are therefore incompatible with an instructionist mechanism for selection.

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