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EVOLUTION OF THE INDIVIDUAL

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Abstract.—This article studies the transition in evolution from single cells to multicellular organisms as a case study in the origin of individuality. The issues considered are applicable to all major transitions in the units of selection that involve the emergence of cooperation and the regulation of conflict. Explicit genetic models of mutation and selection both within and between organisms are studied. Cooperation among cells increases when the fitness covariance at the level of the organism overcomes within-organism change toward defection. Selection and mutation during development generate significant levels of within-organism variation and lead to variation in organism fitness at equilibrium. This variation selects for germ-line modifiers and other mediators of within-organism conflict, increasing the heritability of fitness at the organism level. The evolution of these modifiers is the first new function at the emerging organism level and a necessary component of the evolution of individuality.

In her commentary on multilevel selection, Morrell (1996) wonders whether there is anything in biology that cannot be explained by individual selection acting on organisms that needs to be explained by selection acting on groups. Although rhetorical, this remark reflects a dominant view in evolutionary biology that most interesting questions can be addressed by viewing organisms as the sole unit of selection. But where do organisms come from? From single cells, of course. And what are multicellular organisms but groups of cells related by common descent. In this article, I discuss recent work concerning the evolutionary transition from single cells to multicellular organisms (Michod 1996, 1997). I argue that multilevel selection is needed to explain the origin of the organism—that very creation that is supposed to deny the usefulness of multilevel selection in evolutionary biology. Multilevel selection explains the origin of individuality (Buss 1987).

Individuality is an issue of central concern for all the sciences; each field must struggle with defining and then understanding its most basic units and levels. In the archaic sense, the term *individual* means indivisible; individuals cannot be divided into smaller parts; the whole is more than the sum of the parts. In philosophy, the term *individual* refers to entities that exist continuously in both space and time. Both of these uses of *individuality* apply in biology; however, in evolutionary biology the term *individual* is often used to refer to a level or unit of selection (Hull 1981). Ever since Darwin (1859), we have understood that a unit of selection must possess heritable variations in fitness, or else it can-

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not evolve adaptations at its level of organization. To understand the origin of individuality, therefore, we must understand how the properties of heritability and fitness variation emerge at a new and higher level from the organization of lower-level units that are already units of selection in their own right. For example, unicellular organisms enjoyed a long evolutionary history before they merged to form multicellular organisms. In so doing, single cells relinquished their evolutionary heritage in favor of the organism. Why and how did this occur?

Multicellular organisms are the paradigm example of the integration of evolutionary levels (genes and cells) in the creation of a new individual. To understand the origin of organisms, it is helpful to think about them as groups of cooperating cells related by common descent. Selection among cells—below the level of the organism—could destroy the harmony within the organism and threaten its individual integrity. Competition among cells might favor defecting cells that pursue their own interests at the expense of the organism. For the organism to emerge as an individual or evolutionary unit, ways must have been found of regulating the selfish tendencies of cells while at the same time promoting their cooperative interactions for the benefit of the organism. In addition, ways must have been found to ensure the heritability of the properties of these ensembles of cells so that the organism could continue to evolve as an evolutionary unit.

MODEL OF ORGANISMS

Overview

An overview of the model life cycle is given in figure 1. Multicellular organisms often develop from a zygote, and the replication of cells during development is indicated by the solid vertical arrows in figure 1. During this proliferation, mutation may lead to the loss of cell function and cooperation among cells. These mutant cells may replicate faster than cooperating cells. Because of mutation and different rates of replication of the different cell types, gene and genotype frequencies change during development of the organism (as represented by Δq_j in fig. 1). After development the adult organism contributes gametes to start the next generation (*dashed arrows* in fig. 1). In the case of sexual reproduction, these gametes fuse to form a diploid zygote. In the case of asexual reproduction, the gametes develop directly into the adults of the next generation. Gene and genotype frequencies change in the population of organisms because of differences in fitness (gamete output) between the adult organisms. The two components of frequency change—within organisms and between organisms—give rise to the total change in gene frequency Δq in the population.

There is a difference between this multilevel model of the organism and more standard group selection models. When groups are made up of organisms, the effects of cooperation are typically assumed to be uniformly positive at the group level and negative at the organism level. Selection results from the differential mortality of organisms, which are in turn caused by the interactions within

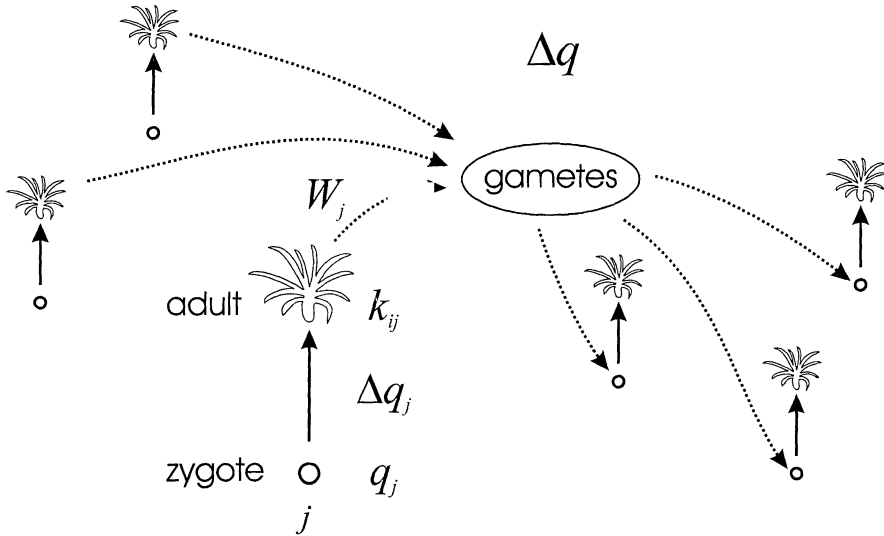


FIG. 1.—Life cycle of model organism. See the text for an explanation. (Adapted from Michod 1997.)

the group. Groups with a high proportion of cooperating individuals may end up being larger in size and thereby contribute more genes to the next generation than groups with many defecting members.

The situation is more complicated when the groups are the organisms themselves viewed as ensembles of cells, because the size of the group (the organism) depends on the rate at which the cells divide. I assume that cooperation takes time and energy away from replication so that cooperating cells replicate more slowly than mutant defecting cells. I also assume that adult size is indeterminate and that adult fitness is a function of both adult size and the level of cooperativity among the organism's cells. As a result of these assumptions, organisms composed of many cooperating cells end up being smaller but more functional than organisms made up of many mutant defecting cells. Because organism fitness is assumed to be a function of both size and functionality (as measured by the level of cooperation among the organism's component cells), cooperation among cells has both positive and negative effects on group (i.e., organism) fitness. Even in the absence of within-organism variation (created by within-organism mutation and selection), for cooperation to exist at all, the benefit to the organism of increased cooperation among its constituent cells must overcome the cost to the organism of a smaller adult size.

Fixed adult size for all genotypes would remove one of the temptations of defection at the cell level, since there would be no effect on group (organism) size of a defecting cell's faster rate of replication. There would still be an advantage to defection in the form of greater representation in the gametes even if adult size were fixed. Viewed in this way, fixed organism size may be seen as an ad-

aptation to help maintain the integrity of organisms by removing one of the costs of cooperation (J. Li and R. E. Michod, unpublished data).

Recurrence Equations

A single locus with two alleles, cooperate *C* and defect *D*, is assumed to control the way cells interact. The definition of terms and variables is given in the appendix. I refer to the organisms in terms of the genotype of their zygote at the cooperate defect locus. Because of within-organism change during development, the adult stage may have cells with different genotypes than those of the zygote. The *k* variables in the appendix refer to the numbers of cells of different genotypes in the adult stage. Two forces may change gene frequency between the zygote and adult stages and determine the values of the *k* variables: mutation and cellular selection. Mutation is assumed to lead to loss of cooperation and tissue function. Mutation also increases the variance among cells and enhances the scope for selection and conflict among cells within organisms. Cellular selection is represented in the appendix as differences in cell replication rate.

The fitness of the adult form, W_j , is the absolute number of gametes produced, which is assumed to depend on both the number of cells in the adult and how the cells interact. Cooperation among cells increases the fitness of the adult (parameter β), but noncooperating cells replicate faster (parameter *b*, appendix) and produce a larger but less functional adult. The simple model of cooperation considered in the appendix assumes a linear dependence of adult fitness on frequency of cooperating cells, although more complex models could easily be incorporated into the framework considered here. Organism size is assumed to be indeterminate and to depend on the time available for development and the rate at which cells divide. Indeterminate growth is most applicable to organisms such as plants or clonal invertebrates in which multicellularity likely first evolved. I find that indeterminate growth makes matters more difficult for organisms, because it allows selfish cells to reap additional fitness benefits by virtue of larger adult size, because selfish cells replicate faster than cooperative cells.

With these definitions, it is straightforward to write down the new gene frequency in the next generation as follows:

$$q' = \frac{qW_c \left(\frac{k_{CC}}{k_C} \right)}{\bar{W}} = \frac{qW_c h_{w,c}^2}{\bar{W}}$$

and

$$\bar{W} = qW_C + (1 - q)W_D. \tag{1}$$

The term in parentheses is the frequency of *C* alleles in the cells of a *C* adult and appropriately weights the total gametic output to consider only those gametes containing *C* alleles. This term equals the heritability of fitness for *C* zygotes defined as the regression of average offspring fitness on adult fitness (Michod and Roze 1997). Because of within-organism change, the heritability of

fitness is not unity as it should be for asexual haploid organisms when there is no environmental variance (as it is for D zygotes in the model).

Within-Organism Mutation Selection Model

As cells proliferate within the developing organism, mutations (rate μ per cell division) occur, leading to a loss of tissue function and cooperativity among cells. I consider only mutations from C to D (no back mutation) as this represents a worst case for the evolution of intercellular cooperation. This approach is reasonable, because it is far easier to lose a complex trait like cooperativity among cells than it is to gain it. Although the model considers a single locus, many loci are likely to affect tissue function and cooperativity among cells, and I like to think of this single locus as representing the cumulative effect of mutation at all these loci. A simple model of mutation and cellular selection is represented in figure 2 (Otto and Orive 1995). This model gives k_{CC} , k_{DC} , k_D , W_C , and W_D in terms of the parameters of mutation, selection, and the time for development. The time for development, t , is measured on the scale of time taken for a cooperating cell to divide (since I take $c = 1$), and so it gives the number of cell divisions per individual generation for cooperating cells.

Covariance Methods

The recurrence equations above are derived by directly monitoring the numbers and frequencies of cells at the different life stages. An alternative method for representing selection in hierarchically structured populations is the covariance approach developed by Price (1970, 1972, 1995). Although the covariance approach gives the same change in gene and genotype frequencies as the direct methods described earlier, it will help us better understand the results. Price's approach posits a hierarchical structure in which there are two levels—in our case, between cells within organisms, viewed as a group of cells; and between organisms within populations. Both levels of selection can be described by a single equation (Price 1972):

$$\Delta q = \frac{\text{cov}_q(W, q_1)}{\bar{W}} + E_{w_q}(\Delta q_1), \quad (2)$$

with the following vectors used as weights: $\mathbf{q} = (1 - q, q)$, $\mathbf{Wq} = (W_D[1 - q], W_Cq)$. Variables q and q_1 are the frequencies of a gene of interest in the total population and within zygotes; $\text{cov}_q(x, y)$ and $E_{w_q}(x)$ indicate the weighted covariance and expected value functions, respectively.

The Price equation (eq. [2]) gives the same change in gene frequency as the direct method given in equation (1); however, the covariance approach is more illuminating and well suited to studying conflict and cooperation among cells within organisms. Mutation and conflict among cells results in within-organism change as represented by the within-group component of equation (2), $E_{w_q}(\Delta q_1)$. The fitness and heritability of the emerging higher-level unit may be represented

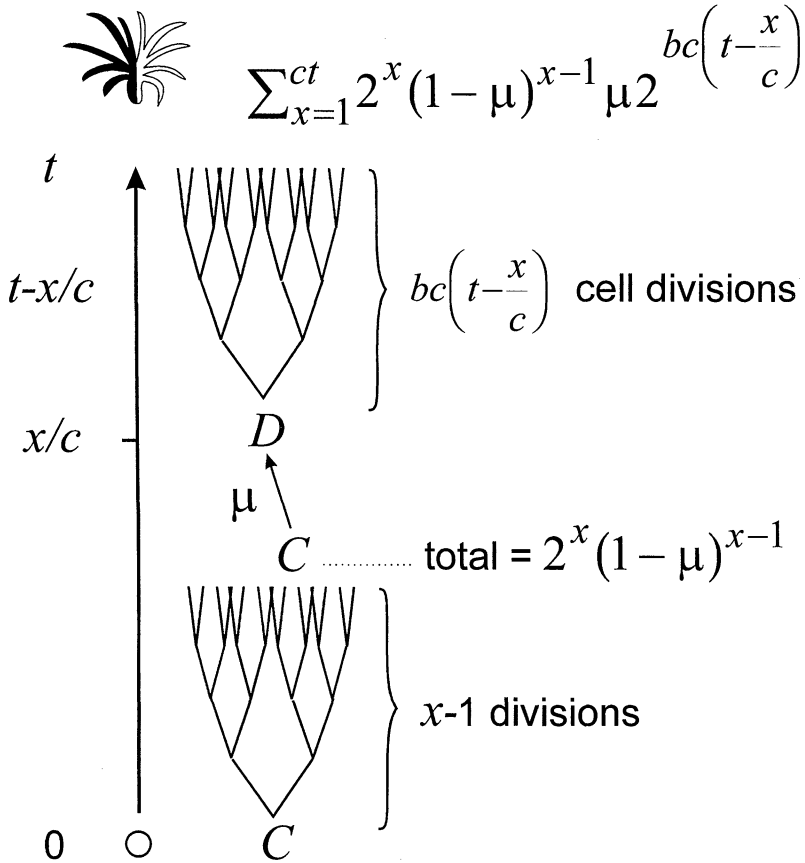


FIG. 2.—Within-organism mutation selection model. A C cell divides for $x - 1$ divisions and then mutates to D during cell division x . The figure explains the formula given in the appendix. The total number of D cells in the adult organism is represented by the color black in the adult form. Consider C cells that are in the x th cell division and have not yet mutated in any of previous $x - 1$ divisions. The total number of these cells is $2^x(1 - \mu)^{x-1}$. Some of these cells will mutate for the first time, and the resulting mutants will undergo $b(ct - x)$ more cell divisions. (The time taken to get x cell divisions is x/c . The time left is $t - x/c$. The number of cell divisions the mutant will undergo is then $cb[t - x/c] = b[ct - x]$).

by the first component of equation (2), $cov_q(W, q_1)$, or by its definition as the regression of offspring fitness on parent fitness (appendix).

EVOLUTION OF COOPERATION

The Risk of Development

For organisms to emerge as a new evolutionary unit, greater levels of cellular harmony and cooperation must be attained. Along with the many advantages of larger organism size (such as greater opportunity for different kinds of cell inter-

action and cooperation) come the risks inherent in within-organism change in which noncooperating cells have an advantage. One component of the total change in the population occurs within organisms during development (recall the second term on the right-hand side of the Price equation, eq. [2]). The buildup of variation during development has been studied previously (Michod 1997) and can be a powerful force leading to within-organism change favoring defection. Within-organism variation during development increases as a function of development time, t , mutation rate, μ , and within-organism selection, b . In addition, the parameters interact, especially selection and mutation. Although an essential ingredient, the mutation rate alone is not the critical force. Rather, both mutation and selection (as determined by the development time and replication rate at the cell level) determine the amount of within-organism change. More time for development means not only a larger adult but also greater variation in the adult form. As the variation within organisms increases, the frequency of the C allele within organisms must decrease because it is at a disadvantage at the cellular level. Recall that cooperation is assumed to take time away from cell division.

Increase of Cooperation

A basic issue concerns the conditions under which a new mutation will increase if it favors more cooperation among cells within the organism. This question is answered by studying the conditions under which the fixation equilibrium of complete defection is unstable. In the case of haploidy, the eigenvalue is given in equation (3):

$$\lambda_H = \frac{W_C k_{CC}}{W_D k_C} = \frac{W_C}{W_D} h_{w,c}^2. \quad (3)$$

This eigenvalue is a product of two components. The first component is a fitness ratio that is identical to the standard condition for increase based on between-organism or "individual" selection when there is no within-organism variation and change. The second component is a diluting effect resulting from within-organism change and equals the fraction of the cells in the adult organism that contains the C allele. The second component tends to unity as the mutation rate and within-individual variation tend to 0. It is possible to show that the second component equals the heritability of fitness in C zygotes, $h_{w,c}^2$, defined as the regression of offspring fitness on adult fitness (Michod and Roze 1997).

Increase of the C allele when rare requires instability of the D fixation equilibrium and occurs when the eigenvalue given in equation (3) is >1 . The conditions $\lambda_H > 1$ are given in figure 3 as a function of the benefit of cooperation to the organism (β), the mutation rate (μ), and time of development (t for a fixed value of selection at the cell level, $b = 1.05$).

Cooperation increases for parameter values above the surface in figure 3A. The surfaces in figure 3B–D are two-dimensional slices through the three-dimensional surface in A. In B, critical values of β and t are plotted for fixed values of $\mu = 0.001$ and $\mu = 0.0001$. Parameter values above the surfaces in B

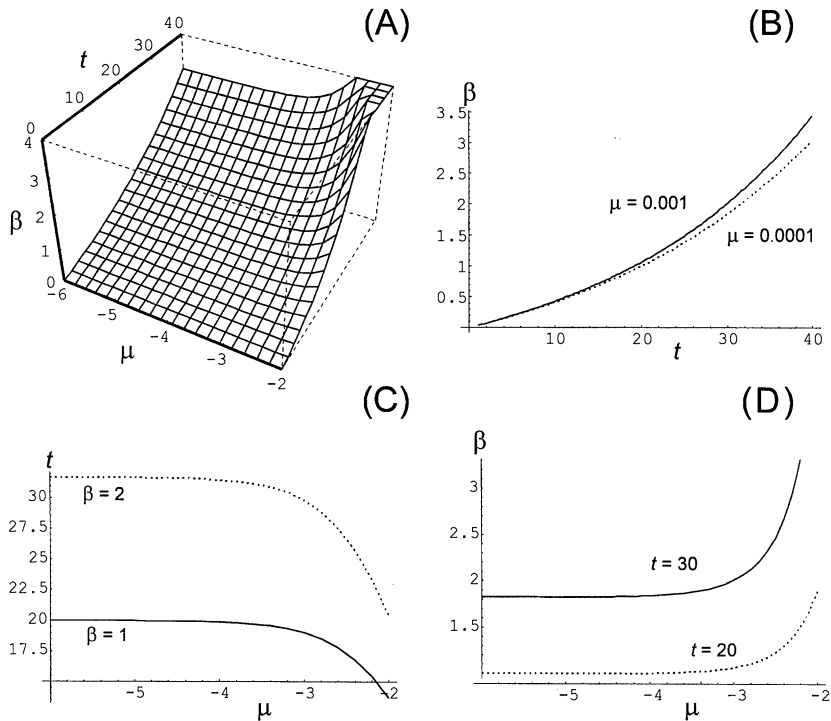


FIG. 3.—Increase of cooperation from rarity. Shown are the conditions for $\lambda_H > 1$ (eq. [3]) as a function of the time for development, t , the mutation rate, μ , and the benefit of cooperation, β , assuming the replication advantage for defection, $b = 1.05$ and $c = 1$. As explained in the text in regard to equation (4), the region for increase of cooperation is identical to the region for existence of a stable internal equilibrium in the frequency of the cooperation allele. In the three-dimensional panel (A), parameter values above the surface allow the increase of cooperation. Panels B–D are two-dimensional slices through the three-dimensional surface in panel A. Parameter values above the surfaces in B and D and those below the surface in C allow an increase of cooperation. In B, the mutation rate is fixed at values $\mu = 10^{-3}$ and 10^{-4} . In C, the benefit of cooperation is fixed at values $\beta = 1$ and $\beta = 2$. In D, the development time is fixed at values $t = 20$ and $t = 30$. See the text for more discussion.

allow cooperation to increase. There is little difference in the curves for the two mutation rates that differ by an order of magnitude. However, the increase of cooperation is quite sensitive to changes in β and t . A similar conclusion is reached in the other panels. In C, critical values of t and μ are plotted for fixed $\beta = 1$ and $\beta = 2$. Parameter values below the curves in C allow cooperation to increase. Over a wide range of mutation rates, the curves are relatively flat, which indicates again little effect of the mutation rate until it reaches values of approximately $\mu = 0.001$. Doubling the benefits of cooperation from one to two organisms may increase their adult body size by approximately 50% (from $t = 20$ to $t = 30$) over a wide range of mutation rates. Body size scales with time for development. With $t = 30$ time units for development, approximately 10^9

cells will be in the adult form (assuming no cell death). Similar conclusions may be reached from figure 3D. The replication advantage, b , and the time for development, t , have similar effects (results not shown for reasons of space). An advantage in cell replication, increased b , is compounded during development.

The results of figure 3 may be understood in terms of the differing opportunities for within- and between-organism selection. Indeed, the critical surfaces graphed in figure 3 are identical to those derived by an alternate approach of requiring the between-organism component of equation (2) to be greater than the within-organism component: $\text{cov}(W, q_1)/\bar{W} > E(\Delta q_1)$ (for small q). Consequently, greater cooperation and harmony among cells may increase, when the heritable covariance of fitness at the organism level overpowers the within-organism change toward defection.

Level of Cooperation among Cells within Organisms

Fixation of cooperation cannot occur because of recurrent mutation, $\mu > 0$, which leads to loss of cell and tissue function. The best we can hope for is that cooperation among cells increases when rare and reaches high levels in the population and within the organism. The internal equilibria of the system are of interest for this reason. For haploidy, a single possible internal equilibrium is given in equation (4) (it requires $W_C > W_D$ to be meaningful):

$$\hat{q}_H = \frac{W_C h_{w,c}^2 - W_D}{(W_C - W_D)}. \quad (4)$$

Again, we see the diluting effect of heritability in weighting the fitness of C organisms. The eigenvalue describing the stability of this equilibrium \hat{q}_H is the inverse of the eigenvalue at $q_H = 0$ or $1/\lambda_H$, where λ_H is given by equation (3). When cooperation increases from rarity, it reaches a stable internal equilibrium. Consequently, the regions for increase of cooperation given in figure 3 are also regions for the existence and stability of biologically meaningful equilibria.

The level of cooperation and synergism attained among cells in organisms is studied in figure 4 (using eq. [4]) as a function of the development time (A), the mutation rate (B), the benefit to organisms of cooperation (C) and the advantage to cells of defecting (D). Many combinations of parameter values have been studied; however, figure 4 is typical, especially with respect to the qualitative threshold nature of the curves. One interesting aspect of the curves is that cooperation typically remains high up to a limiting value for the parameter considered, even though within-organism variation and change are increasing continuously as the parameters t , μ , and b increase (see Michod 1997). We will consider this matter further later.

In figure 4A we see that a rather abrupt limit in size exists for haploid organisms (at $\sim 10^9$ cells for $t = 30$). Cooperation remains high up to this threshold and then drops off precipitously in an almost steplike manner. The weaker the mutation rate, the more precipitous the drop (compare the two curves in fig. 4A); however, the mutation rate does not seem to drastically affect the limit value in

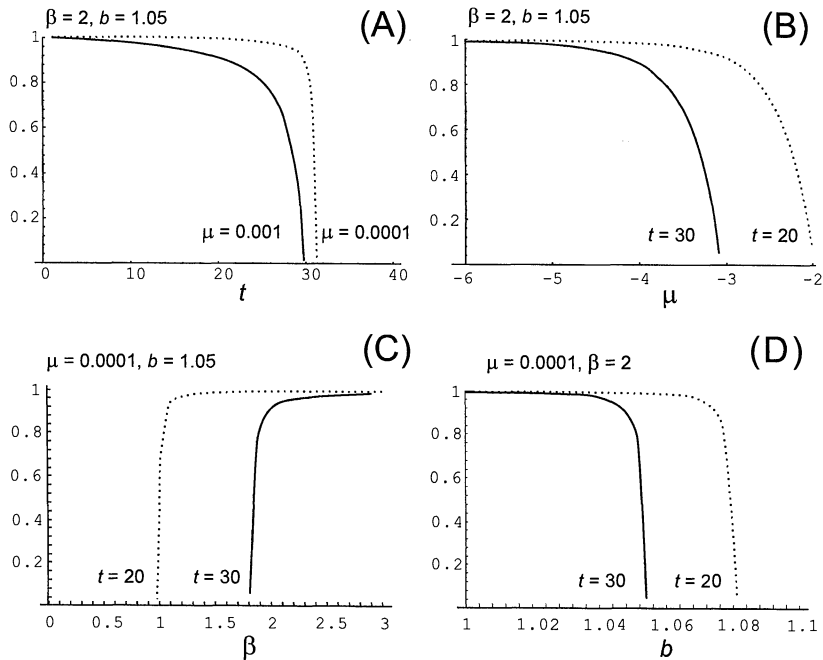


FIG. 4.—Level of cooperation. The vertical axis in all panels is the equilibrium frequency of cooperation as a function of development time, t (A), mutation rate, μ (B), benefit of cooperation, β (C), and benefit of defection, b (D). Fixed parameter values are given above each panel. The dotted line in all panels corresponds to a lower level of within-organism change ($\mu = 0.0001$ in A, and $t = 20$ in B–D). Only locally stable equilibria are shown.

development time, which may be viewed as a limit value in adult size. Such a threshold always exists, but the exact value of the threshold depends on the other parameters, especially β . There are similar threshold values for the selection parameters at the two levels (fig. 4C, D). The steplike nature of the level of cooperation suggests that when multicellular haploid organisms can exist, they attain a high level of cooperation and synergism among their component cells. Poorly organized and barely functional haploid creatures are not predicted by these results. More intense selection at the cell level (higher levels of b) does not qualitatively affect the lessons drawn from figure 4A–C. The general shape of the curves are the same but are offset to the left in all panels except in C, where the curves move to the right. In other words, for larger b , the thresholds mentioned with regard to figure 4 occur for lower values of t (smaller organisms) and μ and greater values of β .

Fitness of Organisms

To further clarify the forces and factors shaping the evolution of cooperation among cells within organisms, we now consider organism fitness and its covariance with zygote genotype as the parameters describing within-organism variation change.

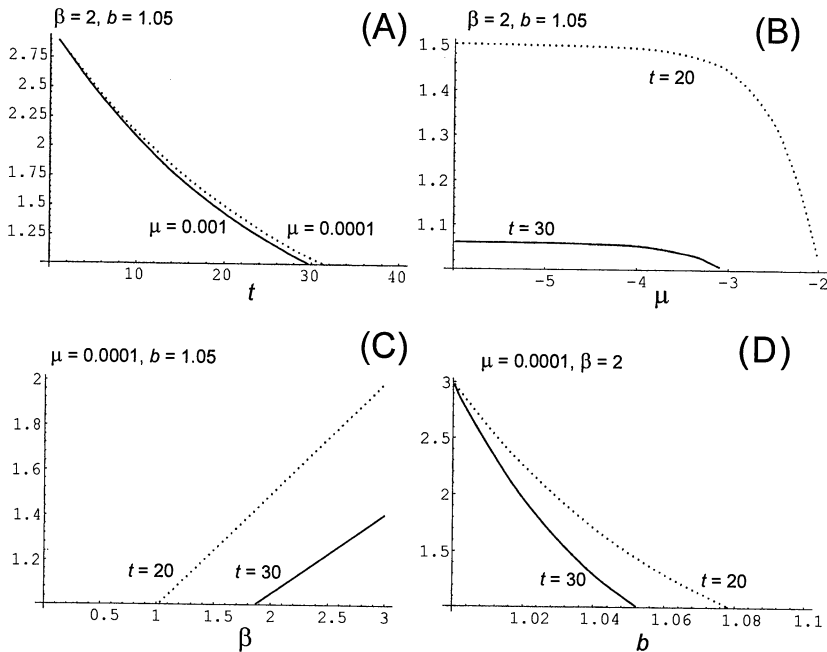


FIG. 5.—Average organism fitness at equilibrium. Panels and parameter values correspond to those given in figure 4. Statistics are based on relative organism fitness obtained by dividing absolute fitness by the absolute fitness of the defecting genotype, D , so that $W_D = 1$ at all points in all panels. Note that organism fitness does not depend on the gene and genotype frequencies in the population of organisms (it does depend on the frequencies of cell types within the organism, however). The legend is the same as that for figure 4.

Average organism fitness is graphed in figure 5 for the equilibrium populations studied in figure 4. Population fitness declines with the parameters describing within-organism variation and selection: development time, t (A), mutation rate, μ (B), and the advantage of defection to cells, b (D). Average fitness increases with the benefit of cellular cooperation, β (C). Apart from these predictable relations, the average fitness of organisms is not that informative. Average fitness departs only slightly in the regions of differences observed in figure 4 and does not explain important aspects of the curves, especially the steplike nature of figure 4A, C, and D. For example, as already mentioned, cooperation remains high up to the limiting development time of about $t = 30$ (fig. 4A) even though the average fitness of the population declines steadily over this region (fig. 5A). Similar differences may be observed in panels C and D of figures 4 and 5. The average population fitness declines continuously as within-organism change builds up; however, the level of cooperation within organisms is somehow buffered from this change. We now consider the underlying reasons for this buffering effect.

The different components of the Price equation—the variances, covariances, and regressions involving organism fitness, within-organism selection, and indi-

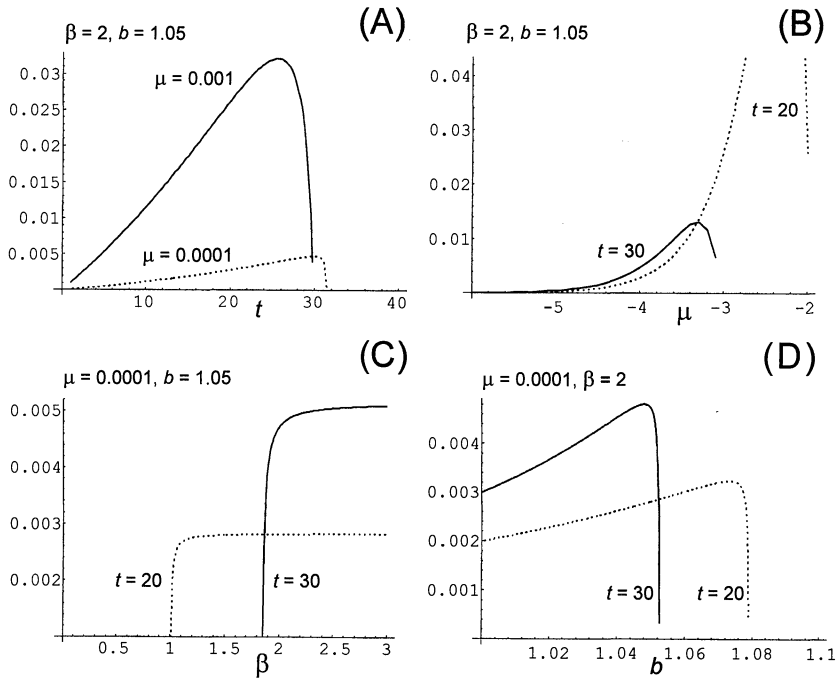


FIG. 6.—Fitness covariance at equilibrium. The vertical axis in all panels is the first part of the right-hand side of the Price equation: $\text{cov}_q(W, q_i)/\bar{W}$ (eq. [2]). At equilibrium this must equal in magnitude the weighted average of within-organism change, $E_{wq}(\Delta q_i)$ (eq. [2]). This is because the populations are at equilibrium, and so equation (2) must equal 0. Therefore, the two parts on the right-hand side of equation (2) must equal one another in magnitude (the first part is positive, and the second part is negative). Statistics are based on relative organism fitness as discussed in the legend for figure 5. Panels and parameter values correspond to those given in figure 4, and the rest of the legend is the same as that in figure 4.

vidual gene frequency—all have something different to tell about the underlying causes of evolutionary change. In figure 6, we consider the first part of the Price equation (eq. [2]), $\text{cov}_q(W, q_i)/\bar{W}$, the weighted covariance of fitness with individual frequency, for the equilibrium populations studied in figure 4. The panels and parameter values in figure 6 correspond with those in figure 4.

Populations at equilibrium must exactly balance the two levels of selection—within and between organisms—because within-organism change is never zero because of mutation. Higher values of fitness covariance imply correspondingly high levels of within-organism change, or else the population would not be in equilibrium. For this reason, the weighted covariances graphed in figure 6 must equal the negative of the average within-organism change—that is, the second part of the right-hand side of equation (2). Consequently, the curves in figure 6 may be interpreted in two ways: either as the weighted covariance of organism fitness with individual frequency or as the amount of within-organism change (which is negative because within-organism selection disfavors the *C* allele).

As populations reach the limits at which selection can no longer maintain cooperation (discussed in reference to fig. 4), within-organism change increases until it overwhelms selection at the organism level (fig. 6A, B, D). As already pointed out, the level of cooperation in figure 4 is relatively insensitive to this buildup of within-organism change (until the limiting values are reached). The effect of increased within-organism change on the frequency of cooperation is compensated for by increased covariance of fitness at the organism level so that cooperation and harmony within the organism are preserved (fig. 4).

With regard to panel C of figure 6, there is little effect of changes in β on the amount of within-organism change. This is because changes in the selection parameter at the organism level, β , cannot affect within-organism change, so the curves in panel C are relatively flat until the threshold is reached. Although β does not affect the change within an organism, it does affect the fitness of C adults and, consequently, the average taken in equation (2). As the threshold is reached, small changes in β drastically change the weighted covariance and weighted average level of within-organism change.

Strengths and Weaknesses of the Model

The transition in evolution from single cells to multicellular organisms involves selection at several different levels, including the cell and the group of cells that make up the organism. The evolution of conflict and cooperation among cells within organisms has been represented in terms of several basic parameters and variables at a single locus. This simplification permits mathematical analysis of the consequences of development, but the limitations of the approach discussed elsewhere (Michod 1997) should be kept in mind. Selection within the organism depends on the rate of cell division; cell death, known in practice to be common, is ignored. Including cell death should only increase the levels of within-organism change, as more cell divisions would be required to achieve a given adult size. Within-organism variation after development is represented by the expected number of cells of different types in the adult form—the k_i and k_{ij} variables defined in the appendix. Many aspects of the analysis, especially the various equilibria and their stability (eqq. [1]–[4]), could be obtained without explicitly specifying values for these variables. For the numerical studies reported in the graphs, specific models of fitness (linear) and within-organism variation had to be assumed (appendix). There may be other, more realistic mutation selection models for the k_{ij} variables, and the model was set up as a framework with this possibility in mind. Although only haploid asexuality is considered here, both diploidy and sexuality have been considered previously, and it was found that reproductive mode can have profound effects on the evolution of cooperation (Michod 1996, 1997).

I assume organism fitness is a linear function of the frequency of cooperating cells in the adult. In modern organisms with many specialized cell and tissue types, the dependence on cell interactions is highly nonlinear, with fitness dropping to zero if there are too few cells of a necessary tissue type or too many cells of a malignant tumor. However unrealistic, the assumption of linearity has several virtues. Besides being simple and susceptible to analytical treatment, lin-

erarity likely underrepresents the importance of cell-cell interaction to the organism and for this reason represents a kind of worst case for the evolution of cooperation. As already pointed out, the basic structure of the model holds (eqq. [1]–[4]), no matter what assumptions are made concerning the details of fitness and within-organism change.

The complexity of interaction among different cell types is represented by a single variable: cooperativity. This assumption is really no different than representing the interactions in a wasp colony, with diverse castes and functions, by studying a single cooperative strategy. This approach has led to a deep understanding of the evolution of social behavior of organisms within social groups, and I believe a similar approach will prove useful in studying the social behavior of cells within organisms.

Although based on a probabilistic model of cell proliferation (fig. 2), the model is deterministic because it makes use of the expected values of the different cell types, the k variables, in the determination of fitness. The consequences of relaxing this assumption are difficult to predict a priori, and this is a matter worthy of careful study. Stochastic changes would likely increase the variance in distribution of cell types both within and between organisms.

Emergence of Individuality

For the organism to emerge as a new unit of selection, within-organism change must be controlled so as to increase heritability of fitness at the organism level. How might evolution modify the parameters of within-organism change so as to increase the fitness of the organism? According to Buss (1987), the individual integrity of complex animal organisms is made possible by the germ line—the sequestered cell lineage set aside early in development for the production of gametes. When a group of cells is sequestered early in development, the opportunity for variation and selection is limited. As a consequence, evolution depends on the fitness of organisms and the covariance of adult fitness with zygote genotype, not the fitnesses of the cells that comprise the organism. The heritability of organism traits encoded in the zygote is thereby protected. The trait of interest here concerns the level of specialization and differentiation among cells within organisms, which is represented here by the level of cooperativity among the cells.

Maynard Smith and Szathmary (1995) argue that close kinship among cells should be sufficient to regulate the selfish tendencies of cells in an organism. By often reproducing through a single cell stage—the zygote—organisms ensure close genetic relatedness among their component cells. Another hypothesis argues that organisms evolve means of directly “policing” the selfish tendencies of their component cells, thereby reducing the benefits of defection even if this costs the organism (Frank 1995).

Missing from these discussions is a quantitative framework for evaluating and comparing the different hypotheses. The model developed in the first part of this article has been extended to study these ideas (Michod 1996; Michod and Roze 1997). By considering evolution at a second modifier locus, I have investigated

these and other hypotheses by which the organism may mediate conflict within. The second locus is assumed to modify the parameters of within-organism change at the first locus (see the appendix for the basic setup of the model). For example, a germ-line modifier is assumed to sequester a group of cells with shorter development time, t_M , and possibly a lower mutation rate, μ_M , than those of the soma. Once within-organism variation reaches a critical level, germ-line modifiers increase and sweep through the population even though they effect a cost in terms of fitness by taking cells away from the soma. My results also indicate that adaptations to police cells' selfish tendencies can be expected to evolve once organisms reach a critical size.

Modifiers lowering the mutation rate ($\mu_M < \mu$) are also selected for in my studies. Maynard Smith and Szathmary (1995) suggest that germ-line cells may enjoy a lower mutation rate but do not offer a reason why. Bell (1985) interpreted the evolution of germ cells in the *Volvocales* as an outcome of specialization in metabolism and gamete production to maintain high intrinsic rates of increase while algae colonies became larger. I think there may be a connection between these two views. As metabolic rates increase, so do levels of DNA damage. Metabolism produces oxidative products that damage DNA and lead to mutation. It is well known that the highly reactive oxidative by-products of metabolism (e.g., the superoxide radical O_2^- and the hydroxyl radical $\cdot OH$ produced from hydrogen peroxide H_2O_2) damage DNA by chemically modifying the nucleotide bases, by inserting physical cross-links between the two strands of a double helix, or by breaking both strands of the DNA duplex altogether. The deleterious effects of DNA damage make it advantageous to protect a group of cells from the effects of metabolism, thereby lowering the mutation rate within the protected cell lineage.

This protected cell lineage—the germ line—may then specialize in passing on the organism's genes to the next generation in a relatively error-free state. Other features of life can be understood as adaptations to protect DNA from the deleterious effects of metabolism and genetic error (Michod 1995): keeping DNA in the nucleus protects the DNA from the energy-intensive interactions in the cytoplasm, nurse cells provision the egg so as to protect the DNA in the egg, and sex serves to effectively repair genetic damage while masking the deleterious effects of mutation. The germ line may serve a similar function of avoiding damage and mutation. By sequestering the next generation's genes in a specialized cell lineage, the germ line protects these genes from the damaging effects of metabolism in the soma.

The evolution of modifiers of within-organism change lead to increased levels of cooperation within the organism and increased heritability of fitness at the organism level (Michod and Roze 1997). The evolution of these conflict mediators are the first new functions at the organism level. An organism is more than a group of cells related by common descent; to exist, organisms require adaptations that regulate conflict within. The evolution of modifiers of within-organism change is a necessary prerequisite to the emergence of individuality and the continued well-being of the organism.

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APPENDIX

TERMS AND VARIABLES IN MODELS

Variables in the multilevel selection model are defined as follows: k_{ij} , the number of i cells in the adult stage of a j zygote, where $i, j = C, D$; k_j , the total number of cells in the adult stage of a j zygote after development, where $j = C, D$; W_D , the adult fitness of a D zygote: αk_D ; W_C , the adult fitness of a C zygote: $\alpha k_{CC} + k_{DC} + \beta k_{CC}$; β , the benefit to an adult organism of cooperation among cells; $q_1, \Delta q_1$, the initial frequency and change in frequency of a C gene within organisms; $q, \Delta q$, the initial frequency and change in frequency of a C gene in the total population; and h_{w}^2 , the heritability of fitness defined as $\text{cov}(W_p, W_o)/\text{var}(W_p)$, where W_p and W_o are the fitness of parents and the average fitness of offspring, respectively. In C zygotes, $h_{w,C}^2 = k_{CC}/k_C$.

Variables in the within-organism mutation and cellular selection model are defined as follows: μ , the within-organism mutation rate from C to D per cell division; t , the time for development; c , the rate of cell division for cooperating cells; b , the advantage to the cell of defection (in terms of replication rate; $b > 1$); cb , the rate of cell division for defecting cells; $k_{CC} = 2^{ct}(1 - \mu)^{ct}$; $k_{DC} = \sum_{x=1}^{ct} 2^x(1 - \mu)^{x-1} \mu 2^{b(ct-x)} = (\mu 2^{bct} - 2^{ct}[1 - \mu]^{ct} \mu)/(-1 + 2^{b-1} + \mu)$; $W_D = 2^{bct}$; and $W_C = k_{CC} + k_{DC} + \beta k_{CC}$.

Variables in the two-locus germ-line modifier model are defined as follows: i, j , the index for genotype 1, 2, 3, 4 = CM, Cm, DM, Dm ; k_{ij} , the number of i cells in the adult stage (soma) of a j zygote; k_j , the total number of cells in the adult stage (soma) of a j zygote; K_{ij} , the number of i cells in the germ line of a j zygote; K_j , the total number of cells in the germ line of a j zygote; W_j , the adult fitness of a j zygote: $W_j = k_j + \beta(k_{1j} + k_{2j})$; r , the recombination rate between C/D and M/m loci; and x_j , the frequency of a j genotype in the total population.

Other terms and variables for the two-locus germ-line modifier model are given among those for the multilevel selection model. The k and K variables are the number of cell types in the adult stage or germ line, respectively, and may be calculated from the parameters of mutation and selection according to the within-organism mutation and cellular selection model in figure 2. For the organisms having the germ-line allele (M), the $K_{i,j}$ (numbers of cell types in the germ line) are given by expressions similar to those in the within-organism mutation and cellular selection model but with μ and t being replaced by μ_M and t_M , the mutation rate from C to D in the germ line and the development time of the germ line. The development time for the germ line is assumed to be less than that in the soma ($t_M < t$). For organisms having the m allele, there is no germ line, which means that the gametes are taken from the adult stage. In this case, we have $K_{ij} = k_{ij}$, $K_j = k_j$. The system of dynamic equations is $x_{i,t+1} = (\mathbf{W}x_t)^T \mathbf{R}_i(\mathbf{W}x_t) / \overline{W}_t^2$, where \mathbf{R}_i is a matrix of recombination parameters. A simple modification of the model allows the study of self-policing modifiers or modifiers that reduce the mutation rate (Michod 1996).

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