Games of multicellularity

Kamran Kaveh, Carl Veller, Martin A. Nowak

Program for Evolutionary Dynamics, Harvard University, Cambridge, MA 02138, USA
Department of Organismic and Evolutionary Biology, Harvard University, Cambridge, MA 02138, USA
Department of Mathematics, Harvard University, Cambridge, MA 02138, USA

HIGHLIGHTS
- Simple multicellular organisms arise by cells staying together after division.
- Staying together generates a particular population structure.
- We study deterministic evolutionary dynamics in that population structure.
- We derive conditions for natural selection to favor one strategy over another.
- Simple multicellularity promotes cooperation among cells.

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ABSTRACT
Evolutionary game dynamics are often studied in the context of different population structures. Here we propose a new population structure that is inspired by simple multicellular life forms. In our model, cells reproduce but can stay together after reproduction. They reach complexes of a certain size, \( n \), before producing single cells again. The cells within a complex derive payoff from an evolutionary game by interacting with each other. The reproductive rate of cells is proportional to their payoff. We consider all two-strategy games. We study deterministic evolutionary dynamics with mutations, and derive exact conditions for selection to favor one strategy over another. Our main result has the same symmetry as the well-known sigma condition, which has been proven for stochastic game dynamics and weak selection. For a maximum complex size of \( n = 2 \) our result holds for any intensity of selection. For \( n \geq 3 \) it holds for weak selection. As specific examples we study the prisoner's dilemma and hawk-dove games. Our model advances theoretical work on multicellularity by allowing for frequency-dependent interactions within groups.

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1. Introduction

The emergence of multicellular life forms is an important step in the evolutionary history of life on earth (Grosberg and Strathmann, 2007; Bell and Mooers, 1997; Knoll, 2011; Bonner, 1998, 2009a, 2009b; Rokas, 2008; Carroll, 2001; Rainey, 2007; Michod, 1997, 1996; Michod and Roze, 2001; Hanschen et al., 2015). Multicellularity arose numerous times in prokaryotes, including in cyanobacteria, actinomycetes, and myxobacteria (Grosberg and Strathmann, 2007; Bell and Mooers, 1997; Schirmister et al., 2011). Complex multicellular organisms evolved in six eukaryotic groups: animals, plants, fungi as well as brown, green and red algae.

A comparison between simple multicellular and their relative unicellular organisms indicates multiple evolutionary transitions. These include increase in genetic complexity, cell differentiation, cell adhesion and cell-to-cell communication (Rokas, 2008). Division of labor, efficient dispersal, improved metabolic efficiency, and limiting interaction with non-cooperative individuals have been suggested as advantageous traits offered by multicellularity (Michod and Roze, 2001; Michod, 2007; Bonner, 1998; Pfeiffer et al., 2001; Pfeiffer and Bonhoeffer, 2003; Kirk, 2005; Mora Van Cauwelaert et al., 2015) (see also Grosberg and Strathmann, 2007 and references therein.)

Multicellular organisms are usually formed by single cells whose daughter cells stay together after division (Bonner, 1998; Koschwanez et al., 2011; Maliet et al., 2015; Rossetti et al., 2011). In contrast, multicellular organisms via aggregation are formed by separate cells coming together. Staying together and coming
together lead to very different evolutionary dynamics (Tarnita et al., 2013), and pose different challenges for the problem of evolution of cooperation (Nowak, 2006b; Nowak et al., 2010a; Olejarz and Nowak, 2014). The same two modes for the evolution of complexity are also observed in the context of eusociality among insects (Wilson, 1971; Gadagkar and Bonner, 1994; Gadagkar, 2001; Hunt, 2007). A common route to eusociality is daughters staying with their mothers (Nowak et al., 2010b), but there is also the coming together of different individuals in the formation of new colonies (Wilson, 1971; Gadagkar, 2001).

Here, we carry out a theoretical study of the dynamics underlying the evolution of multicellularity. Previous studies of such dynamics, both theoretical and experimental, have often been carried out under the assumption that within-group fitnesses derive from a simple, additive cooperative dilemma. For example, cells producing ATP from an external energy resource might do so with high yield but low rate, or with low yield but high rate (Pfeiffer et al., 2001). In the context of a group of cells trying to make use of an energy resource, the former behavior characterizes cooperators, and the latter defectors, because the benefits of a high rate of resource use accrue to the individual cell, while the costs of inefficient resource use accrue more broadly within the group (Pfeiffer and Bonhoeffer, 2003). If the costs accrue equally to all group members, the strategic problem within the group can be conceptualized as an additive public goods game. Many other models of the evolution of multicellularity can be conceptualized in the same way (Penn et al., 2012). For example, the aggregation of biofilms in Pseudomonas bacteria involves the production, costly to individual providers, of the components of an extracellular matrix and other substances (Davies and Geesey, 1993; Matsukawa and Greenberg, 2004; Diggle et al., 2006).

This assumption reduces the strategic conflicts within each multicellular unit to a very simple, frequency-independent form (Michod, 1999). Because a group's reproductive success is shared equally among its constituents (no matter their type), the only within-group conflict involves the constant cost to cooperation.

This is not realistic in many scenarios. In the example of ATP production described above, if the benefits of efficient resource use accrue more locally than to the whole group (for example, to pairs of interacting cells within the group), then the strategic interactions among cells are more complicated than a linear public goods game (Fig. 1). Without taking this into account (i.e., assuming that the benefits produced by cooperators are shared evenly among group members), it would seem that defectors should always be at an advantage within the group. But once the strategic complexity of local interactions is taken into account, then cooperators can have a within-group advantage if most of their interactions within the group are with fellow cooperators (Fig. 1).

Another example where strategic interaction within the group is important is when certain cell types are preferentially found in the reproductive propagules emitted by the group. Thus, in multicellular clusters of the yeast Saccharomyces cerevisiae, experimentally selected for by gravity-based methods, some cells (cooperators) undergo apoptosis to destabilize the multicellular unit and create new propagules; having apoptosed, they cannot themselves be in these propagules (Ratcliff et al., 2012; Pentz et al., 2015).

Another example involves cells that either aggressively or passively try to sequester resources for themselves; if the presence of many aggressive types involves a destructive cost to them, then the within-group conflict resembles a hawk-dove game. Because the within-group conflicts are frequency-independent in this example, their effects in the context of the evolution of multicellularity cannot be understood under a linear public goods conceptualization.

To put it concisely, the evolution of multicellularity is often studied in a framework that does not adequately account for the interactions of cells within a group. In this paper, we place the evolution of multicellularity into an explicitly game-theoretic framework. Evolutionary game dynamics is the study of frequency dependent selection (Maynard Smith, 1982; Hofbauer and Sigmund, 1998; Nowak, 2006a). The success of a genotype (or phenotype or strategy) depends on the frequency of different genotypes in the population. Evolutionary game dynamics was initially studied in well-mixed and infinitely large populations using deterministic differential (Hofbauer and Sigmund, 1998; Maynard Smith, 1982; Weibull, 1997). More recently it has moved to finite population sizes using stochastic dynamics (Nowak, 2006a; Taylor et al., 2004; Traulsen and Hauert, 2009). Evolutionary games are also studied in structured populations (Nowak and May, 1992; Page et al., 2000; Hauert and Doebeli, 2004; Ohtsuki et al., 2006; Szabó et al., 2000; Tarnita et al., 2009a, 2009b; Hauert and Imhof, 2012; Langer et al., 2008; Antal et al., 2009b; Allen and Nowak, 2015; Cooney et al., 2016).

A game-theoretic approach to the evolution of multicellularity allows us to generalize the traditional framework by accounting for frequency-dependent competition within multicellular units.

The primary goal of our paper is to understand how the population structure of simple multicellularity affects the outcome of biological games. Previous studies have explored the evolutionary emergence of staying together (Tarnita et al., 2013) in the context of diffusible public goods (Olejarz and Nowak, 2014) and in stochastic dynamics (Ghang and Nowak, 2014). Here we study deterministic evolutionary dynamics in a population where staying together has already evolved.

In our model, single cells divide, but the two daughter cells can stay together after cell division. These cells may undergo further
division until the complex reaches a specified maximum size. Thereafter, the complex does not grow further but produces single-cellular offspring, which subsequently form new complexes. Within a complex, cells interact according to a biological game. This means that they derive payoffs which affect their reproductive rate. We consider natural selection acting on two types of cells (or strategies), determined by their genotype.

We include mutation between the two types, assumed to occur during cell division. Each offspring adopts its parent’s type with probability $1-u$ and changes to the other type with probability $u$. We shall be interested both in low rates of mutation (corresponding, for example, to nucleotide substitutions) and in very high rates of mutation (for example, genetic switches, epigenetic marking, or structural mutations deriving from a modular genetic architecture – a fuller discussion of these is provided in the Discussion section). In the absence of mutation, $u=0$, one of the two types is bound to take over the whole population (fixation). With mutation, $0<u<1$, the system goes to a mutation–selection equilibrium in which both types are present. We can say that selection favors one type if it is more abundant at equilibrium (Antal et al., 2009a; Tarnita et al., 2009b; Allen and Tarnita, 2014).

For the simple case of a maximum complex of size $n=2$, we derive exact solutions for the model and for the condition that a strategy (or type) is favored for any intensity of selection. Subsequently, we derive results for weak selection for any maximum complex size, $n \geq 3$. Our results have the same symmetry as the well known $\sigma$-condition for evolutionary graphs and evolutionary sets (Tarnita et al., 2009b). The $\sigma$-condition is an algebraic condition that describes when selection favors one strategy over another. The $\sigma$-condition holds for any population structure that treats the two strategies symmetrically for stochastic evolutionary dynamics and for weak selection. For more references on $\sigma$-conditions, see Tarnita et al. (2011), McAvoy and Hauert (2015), Nathanson et al. (2009), Nowak et al. (2010a), Allen et al. (2012). In our case $\sigma$-type condition arises for a deterministic evolutionary process. For $n=2$ it holds for any intensity of selection. For $n \geq 3$ it holds for weak selection.

We apply our finding to evolution of cooperation and to the hawk-dove game. We observe that the population structure of simple multicellularity can easily favor cooperation over defection and doves over hawks.

The paper is structured as follows. In Section 2 we introduce the basic model for a maximum complex size of $n=2$ and state the main results. In Section 3 we study evolution of cooperation and the hawk-dove game. We also discuss how the average fitness at equilibrium depends on the mutation rate in these two games. In Section 4, we discuss the model for $n \geq 3$ and derive the recurrence relations for equilibrium solutions. In Section 5, we derive generalized $\sigma$-condition for weak selection and show that the results match numerical solutions. In Appendices A and C, we discuss technical details for the $n=2$ and $n=3$ analytical solutions. In Appendix B, we address evolutionary stability for $n=2$. In Appendix D, we discuss the selection condition for an unstructured game which corresponds to $\sigma = 1$ (Antal et al., 2009a).

2. Model and results for maximum complex size $n=2$

We consider a model with two types of cells, 0 and 1. Both cell types divide and reproduce. They also have a chance of staying together to form complexes. The two-cell complexes can be either 00, 01 or 11. For the moment we limit ourselves to a model with maximum complex size, $n=2$. If a cell in a complex of size two reproduces, the daughter cell leaves and joins the pool of single cells.

During each cell division, there is a probability of mutation. An offspring of a type 0 cell mutates to a type 1 cell with probability $u$ or remains a type 0 cell with probability $1-u$. We assume symmetric mutations: the probability to mutate from 0 to 1 is the same as from 1 to 0.

The division rate of single cells is set to unity. The model is depicted in Fig. 2. Denoting the abundances of type 0 and type 1 cells by $x_0$ and $x_1$ and denoting the abundances of the complexes 00, 01 and 11 by $x_{00}$, $x_{01}$ and $x_{11}$, we can write the dynamics of these five populations as

$$
\begin{align*}
x_0 &= P_{00} x_{00} + P_{01} x_{01} + P_{11} x_{11} - x_0 - x_0 \phi \\
x_1 &= Q_{00} x_{00} + Q_{01} x_{01} + Q_{11} x_{11} - x_1 - x_1 \phi \\
x_{00} &= (1-u)x_0 - x_0 \phi \\
x_{01} &= u(x_0 + x_1) - x_0 \phi \\
x_{11} &= (1-u)x_1 - x_1 \phi
\end{align*}
$$

(1)

The coefficients $P_{00}$, $P_{01}$ and $P_{11}$ denote the rates at which these complexes generate type 0 cells, while the coefficients $Q_{00}$, $Q_{01}$ and $Q_{11}$ denote the rates at which these complexes generate type 1 cells. These coefficients depend on the payoff derived from the game, the intensity of selection and the mutation rate. They are as follows:
The parameters \(a, b, c, d\) are the elements of the 2 \(\times\) 2 payoff matrix
\[
\begin{pmatrix}
0 & 1 \\
1 & c + d
\end{pmatrix}
\tag{3}
\]
In each complex a type 0 cell obtains payoff \(a\) from another type 0 cell, and \(b\) from a type 1 cell. Similarly, a type 1 cell obtains payoff \(c\) from a type 0 cell, and \(d\) from a type 1 cell. The game interaction occurs only between cells within the same complex. The intensity of selection is denoted by \(w\) and measures how much the payoff of the game contributes to the fitness.

Note that the reproductive rate of a cell, which multiplies the frequency of that cell, is \(\rho_0\) for a type 0 cell, and \(\rho_1\) for a type 1 cell. The equilibrium abundances are obtained by setting all time derivatives in Eq. (1) equal to zero. The solutions can be expressed in terms of ratio of type 1 to type 0 singlets \(\eta^* = x_1^* / x_0^*\) and the value of average fitness at equilibrium, \(\bar{\phi}^*\):
\[
\begin{align*}
x_0^* &= \frac{\phi^*}{2 + \phi^*} \frac{1}{1 + \eta^*} \\
x_1^* &= \frac{\phi^*}{2 + \phi^*} \frac{\eta^*}{1 + \eta^*} \\
x_0 \sigma &= \frac{1 - u}{2 + \phi^*} \frac{1}{1 + \eta^*} \\
x_1^* &= \frac{u}{2 + \phi^*} \\
x_1^* &= \frac{1 - u}{2 + \phi^*} \frac{\eta^*}{1 + \eta^*}
\end{align*}
\tag{5}
\]
Eq. (5) and the values of \(\phi^*\) and \(\eta^*\) in terms of game payoffs and mutation rate are derived in Appendix A (Eqs. (A.5)–(A.7)). The total equilibrium abundances of type 0 and type 1 cells are
\[
\begin{align*}
x_{0,0}^* &= x_0^* + 2x_0 \sigma + x_0^* \\
x_{1,1}^* &= x_1^* + 2x_1 \sigma + x_1^*
\end{align*}
\tag{6}
\]
A strategy is favored by selection, if its equilibrium frequency is greater than what it is in the neutral case. Here the neutral abundance of type 0 and type 1 is \(1/2\). Thus, the condition for type 0 to be selected over type 1 is that the total number of type 0 cells is larger than total number of type 1 cells at equilibrium
\[
x_{0,0}^* > x_{1,1}^*
\tag{7}
\]
Substituting from Eq. (6), and using the fact that the average fitness is always positive, \(\phi^* > 0\), we arrive at the condition
\[
\eta^* < 1
\tag{8}
\]
Substituting for \(\eta^*\) from Eqs. (A.6) and (A.5), Eq. (8) becomes
\[
\left( u - \frac{1}{2} \right) \left( 1 - \frac{1 - u}{u} d + b - c - \frac{1 - u}{u} d \right) < 0
\tag{9}
\]
There are two zeros for the equality. We denote them \(u_1\) and \(u_2\).

We have \(u_2 = 1/2\) and
\[
u_1 = \frac{a - d}{a - d + c - b}
\tag{10}
\]
If \(u\) is outside the interval of \((u_1, u_2)\) (or \((u_2, u_1)\) if \(u_2 < u_1\)) then type 0 is favored. Inside this interval, however, type 1 is selected.

For \(u < u_1\) (assuming \(u_1 < u_2\)) the condition for type 0 to be favored simplifies to
\[
a + b > c + ad
\tag{11}
\]
Here \(\sigma = (1 - u)/u\) is only a function of \(u\) and independent of the payoff values. This condition, also known as the \(\sigma\)-condition, has been discussed in the past for other population structures for stochastic dynamics (Tarnita et al., 2009b, 2011). The value \(\sigma = 1\) leads to the risk dominance condition in unstructured evolutionary games; see Appendix D, as well as Harsanyi and Selten (1988) and Antal et al. (2009a). Notice that our result for multiclassical games holds for any selection intensity.

The same result can be intuitively argued in the weak selection limit. Inside a complex, fitness gains \(\delta_0\) and \(\delta_1\) of type 0 and type 1 cells are
\[
\begin{align*}
\delta_0 &= 2ax_0^* + bx_1^* \\
\delta_1 &= 2dx_1^* + cc_0^*
\end{align*}
\tag{12}
\]
The condition for type 0 strategy to be selected is
\[
\delta_0 > \delta_1
\tag{13}
\]
If the fineses of the two phenotypes (0 and 1) were the same we would have equal abundances for type 0 and type 1 cells in the system. At weak selection we can replace \(x_{0,0}^*, x_{1,1}^*, x_1^*\) with \(w = 0\) abundances \(x_{0,0}^* = x_{1,1}^* = (1 - u)/6, x_1^* = u/3\). Here \(\hat{k}\) denotes the \(w \to 0\) limit. Substituting these values into Eq. (13) we recover the \(\sigma\)-condition, Eq. (11). The interplay between payoffs and mutation rates can be readily seen from Eqs. (12) and (13), where values of frequencies at zero selection intensity are determined solely by \(u\) whereas the fitness gains per cell are determined by the payoffs.

To see the connection between the two derivations, we can verify that Eq. (13) is equivalent to
\[
P_{0,0}x_{0,0}^* + P_{0,1}x_{0,1}^* + P_{1,0}x_{1,0}^* > Q_{0,0}x_{0,0}^* + Q_{0,1}x_{0,1}^* + Q_{1,0}x_{1,1}^*
\tag{14}
\]
for \(u < u_1\). This is basically the weak selection limit of the \(x_0^* > x_1^*\) condition as in Eq. (8). In the above discussion we have assumed a positive mutation rate \(u > 0\). It was implied that the \(\sigma\)-condition holds for some mutation rate \(0 < u < 1\). In fact, from Eq. (9), the condition for dominance of type 0 for \(u \to 0\) simplifies to \(a > d\). As shown in Appendix B this is the condition for type 0 to be an evolutionary stable strategy (ESS) at weak selection. If \(a < d\) then the type 1 strategy is ESS, and for \(u < u_1\) type 1 is selected.

The uniqueness of solutions for Eqs. (1)–(5) is true for \(u \neq 0\). At \(u = 0\), there are two equilibrium solutions for the model. One of the two fixed-points consists of all type 0 cells and the other is all type 1. Only one of the two strategies can be ESS. Thus for \(u = 0\) we always have an attractive (Lyapunov stable) fixed point (type 0 if \(a > d\)) and a saddle-point corresponding to the other strategy.
condition for risk dominance, \( a + b > c + d \), and the condition for evolutionary stability is the same as the Pareto efficiency, \( a > d \).

3. Examples

3.1. Cooperation

Consider the payoff matrix for a simplified game of cooperation

\[
\begin{pmatrix}
C & D \\
C & B - C - C \\
D & B & 0
\end{pmatrix}
\]

(15)

Here \( B \) and \( C \) indicate benefit and cost values respectively. Type 0 cells denote the cooperator strategy, C. Type 1 cells denote the defector strategy, D. Inside a complex, a type 0 cell pays a cost, \( C \), and provides a benefit, \( B \), to the other cell. A type 1 cell pays no cost and provides no benefit.

At zero mutation and for \( B > C \) the dynamics is driven by pure complexes, 00 and 11. Here cooperator complexes are advantaged over defector complexes. Mixed complexes, 01, are bound to become extinct. In this population structure, cooperators are evolutionarily stable. This is in contrast to evolution of cooperation in unstructured populations where defectors are stable.

For \( 0 < u < 1/2 \), the \( \sigma \)-condition can be written in terms of cost and benefit values as

\[
\frac{B}{C} > \frac{1-u}{u}
\]

The critical mutation rate is

\[
u_1 = \frac{1}{2} \left( 1 - \frac{1}{B/C} \right) < \frac{1}{2} = u_2
\]

(17)

Values of \( x_{t-0,0}^{\sigma} \) and \( x_{t-0,1}^{\sigma} \) as functions of \( u \) are plotted in Fig. 3 for parameters \( B = 5 \) and \( C = 1 \). For these parameter values we observe \( u_1 = 0.4 \) and \( u_2 = 0.5 \), in agreement with Eq. (17). In Fig. 4 frequencies of all populations (singlets and complexes) are plotted as a function of \( u \) for the same cost and benefit values and \( w = 0.1 \). We see that the condition \( x_{t-0,0}^{\sigma} > x_{t-0,1}^{\sigma} \) coincides with \( x_{t-1}^{\sigma} > x_{t-1}^{\sigma} \) in agreement with Eq. (8). Eq. (17) describes the phase boundary in the space of mutation and benefit-to-cost ratio. This is depicted in Fig. 5. The region between the curves \( (u_1, B/C) \) and \( (u_2, B/C) \) is where the defector strategy is selected. The two phase boundaries never meet as \( u_1 = u_2 = 1/2 \) does not have a positive finite solution for \( B/C \). In fact \( u = u_2 \) is the vertical asymptote of the critical benefit-to-cost ratio as a function of \( u \).

3.2. Hawk-dove

Now consider a hawk-dove game given by the payoff matrix

\[
\begin{pmatrix}
H & D \\
H & B - C \\
D & B
\end{pmatrix}
\]

(18)

Type 0 is hawk \( (H) \) and type 1 is dove \( (D) \). Inside 00 complexes each hawk gains payoff \( B/2 \) and pays the cost \( C/2 \). In a 01 complex, a hawk gains payoff \( B \) while a dove does not gain from the interaction. For 11 complexes, each dove gains \( B/2 \). From Eq. (9) and for \( u < 1/2 \), the \( \sigma \)-condition is written as

\[
\frac{B}{C} > \frac{1-u}{2u}
\]

(19)

Therefore, we have

\[
u_1 = \frac{1}{1 + 2B/C}
\]

(20)

As discussed before we expect the evolutionarily stable strategy (ESS) to dominate for small values of the mutation rate \( u < u_1 \). In the hawk-dove game, as a result of the multicellular population structure, the ESS is type 1 (dove). This can also be seen from numerical solutions of the model. The total type 0 and 1 abundances for various intensities of selection are plotted in Fig. 3 for \( B = 5 \) and \( C = 1 \). For these benefit and cost values we observe \( u_1 = 0.09 \) and \( u_2 = 0.5 \). We also plot the abundances of single cells and complexes in Fig. 4 for \( w = 0.1 \). In Fig. 5 the phase diagram of the hawk-dove game is plotted in agreement with Eq. (20). The regions between the curve \( (u_1, B/C) \) and \( (u_2, B/C) \) are where the hawk strategy is favored and vice versa. The topology of this phase diagram is different from the cooperation game as the two phase boundaries \( (u_1, B/C) \) and \( (u_2, B/C) \) meet at \( B = 2C \).
3.3. Average fitness

We now study how the average fitness at equilibrium, \( \phi^* \), depends on the mutation rate, \( u \). The average fitness at equilibrium is calculated in Appendix A, Eq. (A.4)

\[
\phi^* = -\frac{1}{2} + \frac{1}{2\sqrt{1 + 4(D_0(1 - z) + D_1z)}}
\]

Here \( z \equiv \eta^*(1 + \eta^*) = x_1^*(1 + x_1^* + x_0^*) \) is the fraction of type 1 singlets. Note that \( z \) is a function of \( u \) and of the payoff values. From Eq. (A.5), the coefficients \( D_0 \) and \( D_1 \) are

\[
D_0 = 2(1 + wa) + w(b + c - 2a)u
\]

\[
D_1 = 2(1 + wd) + w(b + c - 2d)u
\]

If \( a > d \) then type 0 is ESS and as \( u \to 0 \), we have \( z \to 0 \). In this case \( z \) is an increasing function near \( u=0 \) and therefore \( z'(u=0) > 0 \). If \( a < d \) then type 1 is ESS and as \( u \to 0 \), we have \( z \to 1 \). In this case \( z'(u=0) < 0 \). Denoting average fitness in this limit with \( \phi_0^* \), we have

\[
\phi_0^* = -\frac{1}{2} + \frac{1}{2\sqrt{9 + 8w\max(a, d)}}
\]

Similarly one can show that at \( u=1 \) the average fitness, denoted by \( \phi_1^* \), is

\[
\phi_1^* = -\frac{1}{2} + \frac{1}{2\sqrt{9 + 4w(b + c)}}
\]

For the game of cooperation, if the benefit-to-cost ratio is greater than unity, the condition \( (b + c)/2 < a = \max(a, d) \) is satisfied. Thus \( \phi_0^* \) is larger than \( \phi_1^* \). For the hawk-dove game, on the other hand, we have \( (b + c)/2 < d = \max(a, d) \) and thus \( \phi_0^* < \phi_1^* \).

We now show that for the hawk-dove game, \( \phi_0^* \) and \( \phi_1^* \) are local and global maxima of \( \phi^* \), respectively. Since \( \phi^* \) is an increasing function of \( G = D_0(2 - 1) + D_1z \), we look at derivative of this term as a function of \( u \).
Following similar steps we get the payoff values of the hawk-dove game we obtain

\[ G(u) = -w_B(1 + 2z(u = 0)) < 0 \]

\[ G(u) = -w_B(1 + 2z(u = 1)) < 0 \]  \hspace{1cm} (26)

The inequalities hold for \( B > C \). We have also used \( z(u = 0) = 0, z(u = 0) > 0 \) and \( z(u = 1) < 1/2, z(u = 1) < 0 \).

### 4. Model for larger complexes, \( n \geq 3 \)

We now generalize the model to arbitrary maximum complex size, \( n \). Complexes of sizes 2 to \( n \) can now coexist. Each complex can be a mixture of type 0 and type 1 cells. Cells divide and offspring stay together with their parents. Thus, a complex of size \( k \) produces a complex of size \( k + 1 \). Each offspring adopts its parent’s type with probability \( 1 - u \) and changes to the other type with probability \( u \). The offspring of cells inside a complex of maximum size leave the complex and the pool of single cells. Cells inside a complex gain payoff through a biological game with pairwise interactions.

The abundance of a complex of size \( k \) with \( i \) many cells of type 0 and \( k - i \) many cells of type 1 is denoted by \( x_{ik} \). For example, \( x_{00} \) in previous notation is now \( x_{ik} \). Similarly, \( x_{01} \) becomes \( x_{i1} \), while \( x_{11} \) becomes \( x_{02} \) and so on.

The evolutionary dynamics can be written as a system of differential equations

\[ x_{i0} = \sum_{i=0}^{n} P_{i1} x_{i-1} - x_{i0} - x_{i0} \phi \]

\[ x_{01} = \sum_{i=0}^{n} Q_{i0} x_{i-1} - x_{01} - x_{01} \phi \]

\[ \vdots \]

\[ x_{ik} = P_{i-k} x_{i-k-1} + Q_{i-k} x_{i-k} - (P_{i-k} + Q_{i-k})x_{i-k} \]

\[ x_{i-k} \phi \]

\[ (1 \leq k \leq n, 0 \leq i \leq k) \]  \hspace{1cm} (27)

Again the average fitness \( \phi \) is given by the condition that total relative abundances of type 0 and type 1 cells add up to one, that is

\[ \sum_{k=1}^{n} \left( \sum_{i=0}^{k} x_{ik} \right) = 1 \]  \hspace{1cm} (28)

Thus,

\[ \phi = \sum_{k=1}^{n} \left( \sum_{i=0}^{k} \left( P_{ik} + Q_{ik} \right) x_{ik} \right) \]  \hspace{1cm} (29)

The coefficients \( P_{ij} \) and \( Q_{ij} \) are the production rates for creating a type 0 or type 1 cell inside a complex of size \( k = i + j \). They are expressed in terms of the game payoffs, the mutation rate, \( u \), and the intensity of selection, \( w \)

\[ P_{ij} = i(1 + w(a(i - 1) + b(i + j - 1)d)(1 - u) + j(1 + w(ic + (j - 1)d))u) \]

\[ Q_{ij} = i(1 + w(a(i - 1) + b(i + j - 1)d))u + j(1 + w(ic + (j - 1)d)(1 - u)) \]  \hspace{1cm} (30)

Here \( i \) is the number of type 0 cells and \( j = k - i \) is the number of type 1 cells inside the complex (Fig. 7).

The fixed points of the above system of equations are obtained by putting the right-hand side of Eq. (27) equal to zero. The
At \( w = 0 \) the dynamics is neutral. In this limit we have \( \phi^* = 1 \). Eq. \( (31) \) becomes a system of linear recurrence equations

\[
\begin{align*}
\hat{\xi}_{1,0}^* &= \frac{1}{2} \sum_{l=0}^{n} \hat{\beta}_{l,n-1} \hat{\xi}_{l,n-1}^* \\
\hat{\xi}_{0,1}^* &= \frac{1}{2} \sum_{l=0}^{n} \hat{Q}_{l,n-1} \hat{\xi}_{l,n-1}^* \\
\hat{\xi}_{i,k-i}^* &= \frac{1}{k+1} \Big( \hat{P}_{i,k-i} \hat{\xi}_{i,k-i}^* + \hat{Q}_{i,k-i} \hat{\xi}_{i,k-i}^* \Big) \quad (1 \leq k < n, 0 \leq i \leq k) \\
\hat{\xi}_{i,n-i}^* &= \left( \hat{P}_{i,n-i} \hat{\xi}_{i,n-i}^* + \hat{Q}_{i,n-i} \hat{\xi}_{i,n-i}^* \right) \quad (0 \leq i \leq n)
\end{align*}
\]  

(32)

Here \( \hat{\xi} \) denotes the \( w=0 \) limit. Similarly, \( \hat{P}_{ij} = (1 - u)i + uj \) and \( \hat{Q}_{ij} = ui + (1 - u)j \) are zero selection limits of \( P_{ij} \) and \( Q_{ij} \). The solutions \( \hat{\xi}_{ij} \) have the following properties: (i) \( \xi_{ij}^* = \xi_{ji}^* \). (ii) The frequencies of type 0 and type 1 cells are the same: \( \sum_{i,k} \xi_{i,k,i}^* = \sum_{i,k} \xi_{i,k,-i}^* = 1/2 \). (iii) The total abundance of cells in complexes of the same size, \( k \), is independent of the mutation rate.
The $\sigma$-condition for $n \geq 2$

In this section we derive the $\sigma$-condition for the generalized model introduced in previous section at the weak selection limit. For $n = 2$, we showed that $\sigma_2(u) = (1 - u)/u$. It turns out that for $n > 2$ the parameter $\sigma_n$ in Eq. (11), is now given by a ratio of two polynomials of degree $n - 1$ in $u$. In fact the general form for $\sigma_n(u)$ is $(c_n - h_n(u))/h_n(u)$. Here $h_n(u)$ is a polynomial in $u$, and $c_n$ is a numerical constant. The symmetry of the $\sigma$-condition is preserved as we increase the maximum complex size. We will later compare numerical solutions for strategy selection in the general model and analytical prediction of $\sigma$-condition. We observe that our predicted $\sigma$-condition holds well above the weak selection limit as well.

We rewrite Eq. (31) in the following form

$$\begin{aligned}
\chi_{0,0}^* &= \frac{1}{\phi^*} \left( \sum_{i=0}^{n} P_{i,n-i} x_{i,n-i}^* - x_{1,0}^* \right) \\
\chi_{0,1}^* &= \frac{1}{\phi^*} \left( \sum_{i=0}^{n} Q_{i,n-i} x_{i,n-i}^* - x_{0,1}^* \right) \\
\vdots \\
\chi_{k,k-i}^* &= \frac{1}{\phi^*} \left( \left( P_{i,k-i} x_{i,k-i}^* - Q_{i,k-i} x_{i,k-i}^* \right) \right) \\
\vdots \\
\chi_{n-i}^* &= \frac{1}{\phi^*} \left( \left( P_{i,n-i} x_{i,n-i}^* - Q_{i,n-i} x_{i,n-i}^* \right) \right) \\
(1 \leq k < n, 0 \leq i \leq k)
\end{aligned}$$

Total number of type 0 and type 1 cells are written in terms of solutions of Eq. (33) as

$$\begin{aligned}
\chi_{tot,0}^* &= \sum_{k=1}^{n} \sum_{i=0}^{k} x_{i,k-i}^* \\
\chi_{tot,1}^* &= \sum_{k=1}^{n} \sum_{i=0}^{k} (k - i) x_{i,k-i}^*
\end{aligned}$$

The condition for type 0 selection, Eq. (7), is $\chi_{tot,0}^*>\chi_{tot,1}^*$. To have a first order estimate of abundances in powers of selection intensity we substitute $x_{i,j}$ in left-hand side of Eq. (33) with $w=0$ limit solutions, $\hat{x}_{i,j}$. This way $x_{i,k-i}$ from left-hand side of Eq. (33) is expressed to zeroth and first order in $w$. Substituting solutions into Eqs. (34) and (7) gives rise to a closed form generalized $\sigma$-condition. After some straightforward algebra we get

$$\begin{aligned}
\sum_{k=1}^{n} \sum_{i=0}^{k} P_{i,k-i} \hat{x}_{i,k-i}^* > \sum_{k=1}^{n} \sum_{i=0}^{k} Q_{i,k-i} \hat{x}_{i,k-i}^* \\
(35)
\end{aligned}$$

This is a generalization of Eq. (14). We can write this in terms of fitness gains of either of type 0 and 1 strategies as we did for $n=2$ case. Denoting fitness gains for type 0 and type 1 in weak selection by $\delta_{0,n}$ and $\delta_{1,n}$, respectively, we can write:

$$\begin{aligned}
\delta_{0,n} &= \sum_{k=2}^{n} \sum_{i=1}^{k} (i - 1)a + (k - i)b \hat{x}_{i,k-i}^* \\
\delta_{1,n} &= \sum_{k=2}^{n} \sum_{i=1}^{k} (i - 1)c + (k - i)b \hat{x}_{i,k-i}^*
\end{aligned}$$

Then Eq. (35) can be rewritten as

$$\begin{aligned}
\left( u - \frac{1}{2} \right) \left( \delta_{0,n} - \delta_{1,n} \right) < 0
\end{aligned}$$

(37)
The zeros of the term $\delta_{0,n} - \delta_{1,n}$ determine $u_1$ whereas $u_2$ is zero of $u = 1/2$.

Let us consider $n=3$ as an example. In this case Eq. (35) is written as

$$\begin{aligned}
P_{3,0} \hat{x}_{3,0}^* + P_{3,1} \hat{x}_{2,1}^* + P_{3,2} \hat{x}_{2,0}^* + P_{3,3} \hat{x}_{0,3}^* + P_{3,4} \hat{x}_{0,2}^* + P_{3,5} \hat{x}_{0,1}^* \\
+ P_{3,6} \hat{x}_{0,0}^* + P_{3,7} \hat{x}_{0,0}^* &> Q_{3,0} \hat{x}_{3,0}^* + Q_{3,1} \hat{x}_{2,1}^* + Q_{3,2} \hat{x}_{2,0}^* + Q_{3,3} \hat{x}_{0,3}^* + Q_{3,4} \hat{x}_{0,2}^* + Q_{3,5} \hat{x}_{0,1}^* \\
+ Q_{3,6} \hat{x}_{0,0}^* + Q_{3,7} \hat{x}_{0,0}^* + Q_{3,8} \hat{x}_{0,0}^*
\end{aligned}$$

(38)

The terms corresponding to singlets $\hat{x}_{1,0}, \hat{x}_{0,1}$ can be dropped from both sides of the inequality since they do not confer any fitness gain or loss. Similarly Eq. (37) is

$$\begin{aligned}
\left( u - \frac{1}{2} \right) \left( \delta_{0,3} - \delta_{1,3} \right) < 0
\end{aligned}$$

(39)
The fitness gains $\delta_{0,3}$ and $\delta_{1,3}$ are

$$\begin{aligned}
\delta_{0,3} &= 2a \hat{x}_{3,0}^* + b \hat{x}_{2,1}^* + 6a \hat{x}_{2,0}^* + 2\left( a + b \right) \hat{x}_{1,2}^* + 2b \hat{x}_{1,1}^* \\
\delta_{1,3} &= 2d \hat{x}_{2,2}^* + c \hat{x}_{1,3}^* + 6a \hat{x}_{1,2}^* + 2\left( d + c \right) \hat{x}_{1,2}^* + 2c \hat{x}_{1,1}^*
\end{aligned}$$

(40)

The $n=3$ solutions for Eq. (32) are

$$\begin{aligned}
\hat{x}_{1,0} = \hat{x}_{0,1} &= \frac{3}{22} \\
\hat{x}_{2,0} = \hat{x}_{3,0} &= \frac{1 - u}{22} \\
\hat{x}_{1,1} &= \frac{u}{11} \\
\hat{x}_{2,1} = \hat{x}_{3,1} &= \frac{(1 - u)^2}{11} \\
\hat{x}_{2,2} = \hat{x}_{3,2} &= \frac{u(2 - u)}{11}
\end{aligned}$$

(41)

Substituting the above results back into Eq. (40) we can write the $\sigma$-condition, Eq. (39), as

$$\begin{aligned}
\left( u - \frac{1}{2} \right) \left( (a - d) - 4u^2 + 9u + 7 \right) < 0
\end{aligned}$$

(42)

Now $u_1$ is the solution of $(a - d) - 4u^2 + 9u + 7 = 0$.

We have numerically solved the model for $n=3$ and $\beta = 5$ and $C = 1$ for the cooperation game and the hawk-dove game. Predicted values for $u_1$ and $u_2$ are in excellent agreement for various selection intensities (Fig. 8). The phase diagrams for these games are depicted in Fig. 9 for $w=0.1$ and 0.3. The phase boundaries match very well with the results from Eq. (42).

The same method can be used for larger maximum complex sizes at weak selection. Substituting for $\hat{x}_{i,k-i}$ from solutions of Eq. (32) into Eq. (36) we can write

$$\begin{aligned}
\delta_{0,n} &= (c_n - h_n(u))a + h_n(u)b \\
\delta_{1,n} &= h_n(u)c + (c_n - h_n(u))d
\end{aligned}$$

(43)

From Eq. (36), the polynomial $h_n(u)$ and the constant $c_n$ are expressed in terms of $\hat{x}_{i,k-i}$ solutions

$$\begin{aligned}
h_n(u) &= \sum_{k=1}^{n} \sum_{i=0}^{k} i(k - 1) \hat{x}_{i,k-i}^* \\
c_n &= \sum_{k=1}^{n} \sum_{i=0}^{k} i(k - 1) \hat{x}_{i,k-i}^*
\end{aligned}$$

(44)
Using properties of Eq. (32) solutions, we can show that \( c_0 \) is in fact a constant. For \( n = 2 \), we have \( q_0(u) = 1 \) and \( h_2(u) = u \). For \( n = 3 \), from Eq. (42) we have \( q_0(u) = 7 \) and \( h_3(u) = -4u^2 + 9u \) (up to a constant common factor). Repeating the same steps for higher complex sizes we have computed \( c_n \) for \( n = 2, \ldots, 7 \). To avoid long formulas, below we write \( c_n \) for only \( n = 2, \ldots, 7 \)

\[
\begin{align*}
\sigma_2 &= \frac{1 - u}{u} \\
\sigma_3 &= \frac{4u^2 - 9u + 7}{-4u^2 + 9u} \\
\sigma_4 &= \frac{-8u^3 + 28u^2 - 35u + 23}{8u^3 - 28u^2 + 35u} \\
\sigma_5 &= \frac{32u^4 - 160u^3 + 308u^2 - 281u + 163}{-32u^4 + 160u^3 - 308u^2 + 281u} \\
\sigma_6 &= \frac{-64u^5 + 432u^4 - 1176u^3 + 1640u^2 - 1215u + 639}{64u^5 - 432u^4 + 1176u^3 - 1640u^2 + 1215u} \\
\sigma_7 &= \frac{256u^6 - 2240u^5 + 8160u^4 - 5968u^3 + 17980u^2 - 11439u + 5553}{-256u^6 + 2240u^5 - 8160u^4 + 15968u^3 - 17980u^2 + 11439u + 5553}
\end{align*}
\]

The results are plotted for \( n = 2, \ldots, 20 \) in Fig. 10. As can be seen from above results, \( h_3(u) \) always has a zero at \( u = 0 \). Also \( c_0 \) is always a positive constant. The value of the critical mutation, \( u_1 \), is obtained from the equality

\[
\sigma_n(u_1) = c - \frac{b}{a - d} \tag{46}
\]

which can be solved for \( u_1 \) using Eq. (45). These estimated values of \( u_1 \) are compared with numerical solutions of the model for various \( n \), for the game of cooperation (Table 1) and the hawk-dove game (Table 2). Numerical values of \( u_1 \) are calculated for two selection intensities, \( w = 0.01 \) and \( w = 0.1 \) up to \( n = 7 \) while theoretical estimate of \( u_1 \), Eq. (46), is presented up to \( n = 20 \).

We can now ask, for the general model, if the condition for evolutionary stability of a strategy is the same as in the case \( n = 2 \), which is \( \alpha > d \). Proving a strategy is ESS by calculating the eigenvalues of the Jacobian is a cumbersome procedure for arbitrary \( n \). Instead we assume that limit of \( u \rightarrow 0 \) of \( \sigma \)-condition leads to type 0 being ESS. We proved this in Appendix B for \( n = 2 \) in weak selection. For \( u \rightarrow 0 \) and \( 2 \leq n \leq 7 \), \( \sigma_n \)’s from Eq. (45) having the limiting forms

\[
\begin{align*}
\sigma_2(u \rightarrow 0) &= \frac{1 - u}{u} \\
\sigma_3(u \rightarrow 0) &= \left(\frac{7}{9}\right) - \frac{u}{u} \\
\sigma_4(u \rightarrow 0) &= \left(\frac{23}{35}\right) - \frac{u}{u} \\
\sigma_5(u \rightarrow 0) &= \left(\frac{163}{281}\right) - \frac{u}{u} \\
\sigma_6(u \rightarrow 0) &= \left(\frac{639/1215}{u}\right) - \frac{u}{u} \\
\sigma_7(u \rightarrow 0) &= \left(\frac{5553/11439}{u}\right) - \frac{u}{u}
\end{align*}
\]

The leading term coefficients, 7/9, 23/35, ... are all positive and thus in the limit \( u \rightarrow 0 \) lead to \( \alpha > d \).

Substituting the above results into Eq. (46), one can see that no matter how large \( n \) is, the value of \( u_1 \) always remains positive. In other words, the phase boundary \((u_1, 3/(C))\) does not hit the \( y \)-axis for some large-\( n \). If type 0 is ESS for a given game at a small value of \( n \), it will remain ESS also for large \( n \). Interestingly the plot of sigma versus the mutation rate also represents part of the phase boundary in the hawk-dove game. From Eq. (46) and substituting payoffs values for the hawk-dove game, we have \( \sigma(u_1) = 2(5)/C \). For large-\( n \), as can be seen from Fig. 10, the phase boundary seems to be reaching an asymptote. We can confer from this observation that for large complex sizes we still expect dove to be the dominant strategy.
game-theoretic (i.e., frequency-dependent). One particularly clear example is when some cell types are more likely than others to act as reproductive propagules. In the demonstration of Ratcliff et al. (2012) that some cells in multicellular yeast clusters undergo apoptosis (ostensibly to help break the group up into several smaller multi-cellular propagules), apoptosed cells obviously cannot propagate further (Libby et al., 2014). If the likelihood of a cell’s apoptosing depends on its genotype, then a model that is not game-theoretic cannot account for this important phenomenon.

Another example of explicitly game-theoretic interactions within multicellular groups is the competition between ‘co-operator’ and ‘cheater’ strains of yeast which use different glucose metabolism (MacLean and Gudelj, 2006; Pfeiffer et al., 2001). In such setups, selection dynamics between different phenotypes with different rates of ATP yield follow a prisoner’s dilemma (MacLean and Gudelj, 2006). If staying together (and the concomitant ability to form groups) has already evolved in the population, a model that accounts for this frequency dependence is required if we are adequately to model the evolutionary dynamics of the population.

For these reasons, the construction of a more general, frequency-dependent framework is desirable. In the model developed in this paper, cells divide and stay together until they reach a complex of a certain size. Subsequent cell divisions lead to single cells that leave and start their own complexes. The reproductive

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**Table 1**
The critical mutation rate, $u_1$, for the game of cooperation. Cooperators are favored if $u < u_1$. Parameter values are $B = 5$ and $C = 1$. Numerical solutions for $w = 0.01$ and $w = 0.1$ are shown up to $n = 7$.

<table>
<thead>
<tr>
<th>Max. size, $n$</th>
<th>$u_{c,\text{analytic}}$</th>
<th>$u_{c,\text{num}; w = 0.01}$</th>
<th>$u_{c,\text{num}; w = 0.1}$</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>20</td>
<td>0.231</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**Table 2**
The critical mutation rate, $u_1$, for the hawk-dove game. Doves are favored for $u < u_1$. Parameter values are $B = 5$ and $C = 1$. Numerical solutions for $w = 0.01$ and $w = 0.1$ are shown up to $n = 7$.

<table>
<thead>
<tr>
<th>Max. size, $n$</th>
<th>$u_{c,\text{analytic}}$</th>
<th>$u_{c,\text{num}; w = 0.01}$</th>
<th>$u_{c,\text{num}; w = 0.1}$</th>
</tr>
</thead>
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</tr>
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<td>10</td>
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<td>–</td>
<td>–</td>
</tr>
<tr>
<td>15</td>
<td>0.034</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>20</td>
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</table>
rate of a cell is determined by a game based on interactions of cells within a complex, and is therefore explicitly frequency-dependent. This game can represent competition for resources, exchange of nutrients, cellular communication, or energy sharing mechanisms.

Studying the evolutionary dynamics of this setup, we determined how this population structure affects the outcome of evolutionary games in the presence of mutation. In particular, we showed that the condition for one strategy to be more abundant than the other strategy in the mutation-selection equilibrium has the same symmetry as the $\sigma$ condition of stochastic evolutionary dynamics (Tarnita et al., 2009b). We calculated the value of $\sigma$ and examined it for the game of cooperation and the hawk-dove game.

An important feature of our model is the suppression of the cheater phenotype during the evolution of multicellularity. Since the selection dynamics inside each complex is frequency-dependent (for example, a prisoner’s dilemma), a cheater phenotype that appears inside a cooperating colony has a lower chance of becoming abundant inside the group. In other words, game-theoretic interactions at all levels, individuals and groups, can lead to suppression of the cheater strategy without the need for evolution of new mechanisms of conflict mediation. This is the case when the cooperative phenotype is evolutionarily stable for small mutation rates. Our model also allows us to characterize the critical level of group diversity, the mutation rate $u_{c,1}$, above which a cheater phenotype destabilizes cooperation inside the group.

We see our study primarily as a contribution toward understanding how population structure affects evolutionary dynamics (Nowak et al., 2010a). We have quantified to what extent the population structure of simple multicellularity, perhaps as found at the various origins of multicellularity, is conducive to favoring cooperation. Cooperation is thought to be crucially involved in evolutionary transitions such as the emergence of multicellularity (Maynard Smith and Szathmáry, 1997; Nowak, 2006a; Nowak and Highfield, 2011). Conversely, the somatic evolution of cancer is seen as a breakdown of cooperation among the cells of an organism.

We have allowed throughout for the possibility of very high mutation rates. This is no mere theoretical fancy. While mutations by nucleotide substitution and gene conversion are relatively rare, there are many other sources of frequent mutation.

Mutation in our model is perfectly consistent, for example, with epigenetically-induced heritable phenotype switching, such as that observed in experimental populations of Pseudomonas bacteria (Beaumont et al., 2009), a model organism in the field of experimental multicellularity (Rainey and Rainey, 2003; Nikolaev and Plakunov, 2007; Hammerschmidt et al., 2014). Epigenetic mutations in general, so long as they are heritable, are consistent with our model, and are known in some cases to occur far more frequently than sequence mutations (van der Graaf et al., 2015).

Another source of frequent mutation involves unstable genetic architectures. In Pseudomonas, for example, modularity of the genetic architecture underlying the group-forming phenotype allows it to arise often and in multiple different ways (McDonald et al., 2009; Rainey and Kerr, 2010).

The directed gene transposition and epigenetic control underlying mating-type switching in yeast (Klar and Fogel, 1979; Klar, 1987, 2007), another model organism in experimental multicellularity (Koschwanez et al., 2011; Ratcliffe et al., 2012), are also consistent with our model. In fission yeast (Schizosaccharomyces pombe), mating-type switching is more regular than mutation is in our model (Miyata and Miyata, 1981; Egel, 1984), but its high frequency and heritability (Klar, 1987, 2007) suggest that genetic mechanisms of the sort underlying it could justify the consideration of very high mutation rates in our model.

These examples all suggest that high mutation rates might be sufficiently common in organisms undergoing the transition to multicellularity to justify the importance of high mutation rates in our model and its results. It is important to note that mutations in our model must be heritable; for example, non-heritable phenotype switching and cell differentiation in response to environmental cues are ruled out.

Extensions of our model to include cases where staying together is stochastic, which means that cells can leave a given complex with a certain probability, more complicated life cycles, as well as asymmetric mutations are subjects of future works. While our current model is deterministic, the extension to stochastic dynamics and finite total population size should be straightforward.

Our model does not study important questions such as the different implications of staying together versus coming together (Tarnita et al., 2013) or the evolution of germ line soma separation (Michod and Nedelcu, 2003; Michod and Roze, 2001) or the evolution of simple versus complex multicellularity (Knoll, 2011) for which we refer to the existing literature.

Acknowledgments

Support from the John Templeton Foundation is gratefully acknowledged.

Appendix A. Exact solutions for $n=2$

In this appendix we present derivation of equilibrium solutions for $n=2$. Putting time derivatives to zero in Eq. (1), we have

$$x_0^* = \frac{1}{\phi^* + 1} (P_{00} x_{00} + P_{01} x_{01} + P_{11} x_{11})$$

$$x_1^* = \frac{1}{\phi^* + 1} (Q_{00} x_{00} + Q_{01} x_{01} + Q_{11} x_{11})$$

$$x_{00} = \frac{x_0^*}{\phi^*} x_{00}^*$$

$$x_{01} = \frac{x_1^*}{\phi^*} x_{01}^*$$

$$x_{11} = \frac{x_1^*}{\phi^*} x_{11}^*$$

(A.1)

Substituting for complex abundances from last three equations into first two equations in (A.1) and dividing them we obtain the following relation for $\eta^* = x_1^*/x_0^*$

$$\eta^* = \frac{(P_{00}(1-u) + Q_{00}u) + (Q_{11}(1-u) + Q_{01}u)\eta^*}{(P_{00}(1-u) + P_{01}u) + (P_{11}(1-u) + P_{01}u)\eta^*}$$

(A.2)

Average fitness function at equilibrium, $\phi^*$, can be expressed in terms of $\eta^*$ as well

$$\phi^* = \eta^* + 1$$

$$= \frac{1}{1 + \eta^*} \left\{ (P_{00} + Q_{00})(1-u) + (P_{01} + Q_{01})u \right\}$$

$$+ \left\{ (P_{11} + Q_{11})(1-u) + (P_{01} + Q_{01})u \eta^* \right\}$$

(A.3)

The above equations, (A.2) and (A.3), can be rewritten as quadratic equations

$$A(\eta^*)^2 + B\eta^* - C = 0$$

$$\langle \phi^* \rangle^2 + \phi^* - \frac{1}{1 + \eta^*}(D_0 + D_1\eta^*) = 0$$

(A.4)

Coefficients $A, B, C, D_0$ and $D_1$ are expressed in terms of payoff coefficients and mutation rate.
\[ A \equiv (1 - u)P_{11} + uP_{01} = (-2 + w(c - b - 2d)u + (b + 2d)w + 3)u \]
\[ B \equiv (P_{00} - Q_{11})(1 - u) + (P_{01} - Q_{01})u \]
\[ = (2w(a - b + c - d)u^2 + w(4d - a) + b - c)u + 2w(a - d) \]
\[ C \equiv Q_{00}(1 - u) + Q_{01}u = (b - 2a - c)w - 2)u^2 + (2a + c)w + 3)u \]
\[ D_0 \equiv (P_{00} + Q_{01})(1 - u) + (P_{01} + Q_{00})u \]
\[ = 2(1 + wa)(1 - u) + (2 + w(b + c))u \]
\[ D_1 \equiv (P_{11} + Q_{11})(1 - u) + (P_{10} + Q_{01})u \]
\[ = 2(1 + w)(1 - u) + (2 + w(b + c))u \]

Values of \( \eta^* \) and \( \phi^* \) are thus given by

\[ \eta^* = \frac{-B + \sqrt{B^2 + 4AC}}{2A} \]
\[ -1 + \sqrt{1 + 4(D_0 + D_1\eta^*)} \]
\[ \phi^* = \frac{1}{2} \]
\[ \text{(A.6)} \]

Coefficients \( A, C, D_0 \) and \( D_1 \) in Eq. (A.5) are positive since coefficients \( P_{00}, P_{01}, P_{11} \) and \( Q_{00}, Q_{11} \) are positive for \( 0 < u < 1 \). Both \( \eta^* \) as the ratio of two abundance, and \( \phi^* \) as average fitness should be positive as well. Thus solutions for Eq. (A.6) are unique positive solutions of Eq. (A.4). Given \( \eta^* \) and \( \phi^* \), abundances of singlet and doublet complexes at equilibrium \( x_0^*, x_1^*, x_{00}^*, x_{01}^*, x_{11}^* \) are

\[ x_0^* = \frac{\phi^*}{2 + \phi^*} \frac{1}{1 + \eta^*} \]
\[ x_1^* = \frac{\phi^*}{2 + \phi^*} \frac{\eta^*}{\eta^* + 1} \]
\[ x_{00}^* = \frac{1 - u}{2 + \phi^*} \frac{1}{1 + \eta^*} \]
\[ x_{01}^* = \frac{u}{2 + \phi^*} \]
\[ x_{11}^* = \frac{1 - u}{2 + \phi^*} \frac{\eta^*}{\eta^* + 1} \]
\[ \text{(A.7)} \]

We used \( x_0^* + x_1^* = \phi^*(2 + \phi^*) \). This can be checked by substituting steady state solutions \( x_{00}^*, x_{01}^*, x_{11}^* \) from Eq. (A.1) into identity \( x_0^* + x_1^* = 2(x_{00}^* + x_{01}^* + x_{11}^*) = 1 \).

**Appendix B. Evolutionary stability for \( n=2 \)**

In this appendix we present some technical details of the results on stability of the equilibrium solutions and ESS condition for \( n=2 \). We write Eq. (1) as

\[ \frac{dx_i}{dt} = f_i(x_0, x_1, x_{00}, x_{01}) \]
\[ \text{(B.1)} \]

where \( i \in \{0, 1, 00, 11\} \). Mixed complex \( x_{01} \) is expressed in terms of other variables

\[ x_{01} = \frac{1}{2}(1 - x_0 - x_1 - 2x_{00} - 2x_{11}) \]
\[ \text{(B.2)} \]

To address stability we linearize time derivative operator, \( f_i(x_0, x_1, x_{00}, x_{11}) \) around a fixed point. For a stable fixed point, all real parts of eigenvalues of the linearized \( f_i(x_0, x_1, x_{00}, x_{11}) \), i.e. Jacobian, should be negative. At \( u=0 \) and for zero-selection, \( w=0 \), average fitness \( \phi=1 \). Jacobian has following eigenvalues and eigenvectors:

\[ x_{(0)}^* = 0, \lambda_1 = (-1, 1, -1, 1), \lambda_2 = (-1, \bar{\nu}_2 = (0, 0, 1, 1) \]

At \( x_{(0)}^* = -3, \bar{\nu}_1 = (2, -2, -1, 1), \lambda_4 = -3, \bar{\nu}_4 = (2, 2, 1, 1) \), weak selection the above eigen-directions are slightly modified due to game payoff contribution to the fitness of type 0 and type 1 strategies. Particularly, the direction corresponding to \( \lambda_1 = 0 \) can become unstable.

To check this we focus on the type 0 fixed point \( x_{(0)}^*, 0, x_{00}^*, 0 \) (denoted by (i)). We perturb it along the \( \bar{\nu}_1 \) direction.

![Fig. B1. Numerical results for eigenvalues for the game of cooperation (top) and hawk-dove game (bottom). The eigenvalues are plotted as a function of \( B/C \) for \( u = 0 \) and \( w = 0.5 \). Eigenvalues of type 0 fixed point, \( \lambda_{(i)} \), and type 1 fixed point, \( \lambda_{(j)} \), are plotted. ESS condition for type 0 is \( B/C > 1 \) for the game of cooperation. As can be seen at value \( B = C, \lambda_{(i,j)} \) changes sign. For the hawk-dove game however, dove strategy is always ESS at \( u = 0 \).](image-url)
\[ x_0 = x_0^* - \frac{\delta x}{3} \]
\[ x_1 = 0 - \frac{\delta x}{3} \]
\[ x_{00} = x_{00}^* - \frac{\delta x}{3} \]
\[ x_{01} = 0 - 0 \]
\[ x_{11} = 0 - \frac{\delta x}{3} \]

\[ (B.3) \]

This corresponds to introducing a small fraction \( \delta x \) of type 1 cells to the system: \( x_{01} \to \delta x, x_{00} \to 1 - \delta x \). Substituting into Eq. (1) (or Eq. (B.1)) and keeping terms up to lowest order in \( \delta x \) we obtain linearized equation around the fixed point \((x_0^*, x_1^* = 0, x_{00}, x_{01} = 0, x_{11}^* = 0)\). Introducing corresponding eigenvalue \( \lambda^{(i)} \approx -(2w/3)(a - d) \). For \( a > d \) and independent of off-diagonal payoff coefficients, \( b \) and \( c \), a fixed point of \((x_0^*, x_1^*, 0, x_{00}, x_{01} = 0)\) is ESS. Similar condition can be obtained by linearizing time operator around type 1 fixed point, \((0, x_1^* = 0, x_{11}^*)\). This leads to eigenvalue, \( \lambda^{(ii)} \approx (2w/3)(a - d) \) \( \approx \delta x \) denotes type 1 fixed point. Thus for the Jacobian matrix, \( J_q \), defined as
\[ J_q = \frac{\partial f_i}{\partial x_i} \bigg|_{x_i=x^*}, \quad \mathbf{x} = (x_0, x_1, x_{00}, x_{01}) \]
\[ (B.5) \]

all the eigenvalues can be calculated to the leading order of selection intensity. For type 0 fixed point we obtain
\[ \lambda^{(i)} \approx -\frac{2}{3}(a - d)w + O\left(w^2\right) \]
\[ \lambda^{(ii)} \approx -1 - \frac{2}{3}aw + O\left(w^2\right) \]
\[ \lambda^{(iii)} \approx -3 + \left(a - \frac{1}{3}d + ia - di\right)w + O\left(w^2\right) \]
\[ \lambda^{(iv)} \approx -3 + \left(a - \frac{1}{3}d - ia + di\right)w + O\left(w^2\right) \]
\[ (B.6) \]

We numerically calculated all the eigenvalues around both fixed-points at \( u = 0 \). For \( w = 0.01 \) results matched very well with Eq. (B.6). For larger intensities of selection there are deviations from Eq. (B.6). However it seems that the ESS condition, \( a > d \), still holds away from weak selection as well. Fig. B1 shows numerical results for eigenvalues around both fixed points at \( u = 0 \) for the game of cooperation and the hawk-dove game. Eigenvalues are plotted as a function of \( \beta C \) and for \( w = 0.5 \). For the game of cooperation as the benefit to cost ratio passes unity, \( \beta C = 1 \), the eigenvalue \( \lambda^{(i)} \) switches sign thus indicating the type 0 is evolutionary stable for \( \beta > C \).

For \( n > 2 \) the above analysis can be tedious but in principle the same steps can be done. The same result, however, can be intuitively understood. For finite \( u \) there is a single equilibrium state that is globally attractive inside the multi-dimensional simplex of states. As \( u \to 0 \) this fixed point moves approaches to the ESS fixed point among the two fixed point for \( u = 0 \). This is indicated by the \( \sigma \)-condition. The strategy that is favored by \( \sigma \)-condition as \( u \to 0 \) is the ESS.

**Appendix C. Exact solutions for \( n = 3 \)**

Here we present a sketch of derivation of exact solutions for model with maximum three-cell complexes. The equilibrium abundances for \( n = 3 \) satisfy the coupled system of equations:
\[ x_0^* = \frac{1}{1 + \phi^*}\left(\frac{P_3,0}{x_0^*} + P_2,1x_1^* + P_1,2x_2^* + P_0,3x_3^*\right) \]
\[ x_1^* = \frac{1}{1 + \phi^*}\left(\frac{Q_3,0}{x_0^*} + Q_2,1x_1^* + Q_1,2x_2^* + Q_0,3x_3^*\right) \]
\[ x_2^* = \frac{P_2,0}{Q_2,0} + \phi^*P_1,0x_0^* \]
\[ x_3^* = \frac{P_1,1 + Q_1,1 + \phi^*}{P_0,2 + Q_0,2 + \phi^*}x_1^* \]
\[ x_{01} = \frac{1}{\phi^*Q_0,2x_0^*} \]
\[ x_{12} = \frac{1}{\phi^*P_0,2x_1^*} \]
\[ x_{02} = \frac{1}{\phi^*P_0,2x_1^*} \]
\[ x_{00} = \frac{1}{\phi^*P_0,2x_1^*} \]

\[ (C.1) \]

Coefficients \( P_{ij} \) and \( Q_{ij} \) are given by Eq. (30). We also have \( P_{i0} = Q_{i1} = 1 - u, P_{0i} = Q_{i1} = u \). Similar to \( n = 2 \) case, solutions \( x_{01} = x_{12}^{\ast} \) can be expressed in terms of ratio of singlets \( x_i^* = x_i^*/x_0^* \) and total fitness \( \phi^* \). Upon dividing the first two equations in Eq. (C.1) and substituting for abundances from rest of the equations we obtain a quadratic equation for \( \eta^* \)
\[ \eta^* = \left\{ \begin{array}{l} Q_{3,0} \left( \frac{P_{2,0}}{\phi^* + P_{2,0} + Q_{2,0}} (1 - u) \right) \\
+ Q_{2,1} \left( \frac{P_{2,1}}{\phi^* + P_{2,1} + Q_{1,1}} (1 + \eta^*) + \frac{Q_{2,0}(1 - u)}{\phi^* + P_{2,0} + Q_{2,0}} \right) \\
+ Q_{2,2} \left( \frac{P_{2,2} (1 - u)}{\phi^* + P_{2,2} + Q_{2,2}} \right) \end{array} \right. \]
\[ + Q_{0,3} \left( \frac{Q_{0,3}(1 - u)}{\phi^* + P_{2,0} + Q_{2,0}} \right) \]
\[ + Q_{3,0} \left( \frac{Q_{3,0} (1 - u)}{\phi^* + P_{2,1} + Q_{1,1}} \right) \]
\[ + Q_{2,1} \left( \frac{P_{2,1}}{\phi^* + P_{2,1} + Q_{1,1}} (1 + \eta^*) + \frac{Q_{2,0}(1 - u)}{\phi^* + P_{2,0} + Q_{2,0}} \right) \]
\[ + P_{2,2} \left( \frac{P_{2,2}(1 - u)}{\phi^* + P_{2,2} + Q_{2,2}} \right) \]
\[ + P_{0,3} \left( \frac{Q_{0,3}(1 - u)}{\phi^* + P_{2,0} + Q_{2,0}} \right) \]

\[ (C.2) \]

singlet and complex abundances, up to the common factor, \( x_{01} + x_{12}^{\ast} \), are expressed in terms of \( \eta^* \) and \( \phi^* \) from Eq. (C.1).
\[ x_{0,0}^* = \frac{1 - u}{\phi^* + P_2,0 + Q_{2,0}} \left( x_{0,0} + x_{0,1} \right) \]
\[ x_{1,1}^* = \frac{u}{\phi^* + P_{1,1} + Q_{1,1}} \left( x_{1,0} + x_{1,1} \right) \]
\[ x_{0,2}^* = \frac{1 - u}{\phi^* + P_{0,2} + Q_{0,2}} \left( x_{0,0} + x_{0,1} \right) \]
\[ x_{2,0}^* = \frac{1 - u}{\phi^* + P_{2,0} + Q_{2,0}} \left( x_{2,0} + x_{2,1} \right) \]
\[ x_{2,1}^* = \frac{u}{\phi^* + P_{2,1} + Q_{2,1}} \left( x_{2,0} + x_{2,1} \right) \]
\[ x_{2,2}^* = \frac{1 - u}{\phi^* + P_{0,2} + Q_{0,2}} \left( x_{2,0} + x_{2,1} \right) \]

Substituting these into condition \( x_{0,0}^* + x_{0,1} + 2(x_{0,0}^* + x_{1,1}^* + x_{2,0}^*) + 3(x_{0,0}^* + x_{1,0}^* + x_{1,1}^* + x_{2,0}^*) = 1 \), we obtain \( x_{0,0}^* + x_{0,1}^* \) in terms of \( \eta^* \) and \( \phi^* \):

\[ x_{0,0}^* + x_{0,1}^* = \phi^* \left( \eta^* + 1 \right) \left( 3(P_{2,0} + Q_{2,0}) + 2\phi^* \right) - u + \left( 3(P_{0,1} + Q_{1,1}) + 2\phi^* \right) \left( 1 + u \right) \]

\( \phi^* \) is obtained from substituting above solutions, Eqs. (C.3) and (C.4) into \( \phi^* = (P_{2,0} + Q_{2,0})x_{0,0}^* + (P_{0,1} + Q_{1,1})x_{0,1}^* + (P_{2,0} + Q_{2,0})x_{2,0}^* + (P_{0,3} + Q_{3,0})x_{0,3}^* + (P_{2,0} + Q_{2,0})x_{2,0}^* + (P_{1,1} + Q_{1,1})x_{1,1}^* + (P_{0,2} + Q_{2,0})x_{0,2}^* + x_{0,0}^* + x_{2,1}^* \)

Eqs. (C.2) and (C.5) combined with Eq. (C.4) can be solved to obtain closed form solutions for \( \phi^* \) and \( \eta^* \), which upon substituting into Eq. (C.3) gives all abundances in terms of payoff values and mutation. This approach in principle is generalized to n-cell complex model as well. We always get a quadratic equation in \( \eta^* \) coupled with a degree-n equation for \( \phi^* \). The condition for the strategy selection, however, can be answered in weak selection limit without exact knowledge of individual abundance of different complexes as discussed in Section 5.

Appendix D. Well-mixed games with mutation

In this appendix we briefly review unstructured game in the presence of mutations and compare the condition for neutrality with the one we obtained for game of multicellularity, Eq. (1). Derivations for finite populations are done in the literature (Tarnita et al., 2009b; Traulsen et al., 2008; Antal et al., 2009a). Consider a well-mixed population of two populations 0 and 1 with abundances \( x_0 \) and \( x_1 \). Each individual can replicate based on its payoff values determined by the game and the offspring can mutate with probability \( u \). The dynamics for two populations is written as,

\[ \dot{x}_0 = x_0(p_{0,0} + p_{1,0})(1 - u) + x_1(q_{0,0} + q_{1,0})u - x_0 - x_0\phi \]

\[ \dot{x}_1 = x_0(p_{0,1} + p_{1,1})(1 - u) + x_1(q_{0,1} + q_{1,1})(1 - u) - x_1 - x_1\phi \]

where fitness functions, \( p_{0,1}, q_{0,1}, \) are given in terms of payoff coefficients \( a, b, c, d, \) and intensity of selection \( w \)

\[ p_0 = (1 + wa) \]

\[ p_1 = (1 + wb) \]

\[ q_0 = (1 + wc) \]

\[ q_1 = (1 + wd) \]

\( \phi \) is given by

\[ \phi = x_0(p_{0,0} + p_{1,0} + x_1(q_{0,0} + q_{1,0}) - 1 \]

Enforcing the condition that total frequencies add up to unity, \( x_0 + x_1 = 1 \). Calling \( x_0 = x(t) \), we have

\[ \frac{d}{dt}x(t) = (1 - u - x(t)p_0 + p_1(1 - x(t))) \]

Putting LHS of the above equation to zero for equilibrium solutions \( x^* \) and assuming type 0 is selected, i.e., \( x^* > 1/2 \), after some straightforward algebra we get

\[ a + b > c + d \]

which is the \( \sigma \)-condition with \( \sigma = 1 \). Notice that this relationship is independent of \( u \).

References


