Maintaining, masking, and mimicking selection: the interplay of cell-intrinsic and cell-extrinsic effects upon eco-evolutionary dynamics

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ABSTRACT

Evolution is a stochastic yet inevitable process that lies at the heart of biology yet in the multi-cellular environments within patients, ecological complexities arise via heterogeneity and microenvironments. The interplay of ecology and mutation is thus fundamental to predicting the evolution of complex diseases and engineering optimal treatment solutions.
As experimental evidence of ecological interactions between disease agents continues to grow, so does the need for evolutionary theory and modeling that incorporates these interaction effects. Inspired by experimental cell biology, we transform the variables in the interaction payoff matrix to encode cell-cell interactions in our mathematical approach as growth-rate modifying, frequency-dependent interactions. In this way, we can show the extent to which the presence of these cell-extrinsic ecological interactions can modify the evolutionary trajectories that would be predicted from cell-intrinsic properties alone.
To do this we form a Fokker-Planck equation for a genetic population undergoing diffusion, drift, and interactions and generate a novel, analytic solution for the stationary distribution. We use this solution to determine when these interactions can modify evolution in such ways as to maintain, mask, or mimic mono-culture fitness differences. This work has implications for the interpretation and understanding of experimental and patient evolution and is a result that may help to explain the abundance of apparently neutral evolution in cancer systems and heterogeneous populations in general. In addition, the derivation of an analytical result for stochastic, ecologically dependent evolution paves the way for treatment approaches requiring knowledge of a stationary solution for the development of control protocols.

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Introduction

Across biology, sufficiently strong evolutionary selection pressure can alter the phenotype of an entire population over successive generations. Traditionally, this change has been considered a selection on the genotype, reflecting an intrinsic fitness under the external evolutionary pressure of the environment, whether that is drug, temperature, or other[1]. In this regard, the genetic fitness landscape has been one method of understanding this cell-intrinsic fitness, selection, and evolution.

Fitness landscapes map out the fitness or reproductive potential of an individual based on its particular genotype location in genotype space. Peaks in this landscape correspond to high fitness or reproductive potential. Fitness landscapes also allow for an understanding of neutral evolution: in this formalism, flat regions of a fitness landscape are equally fit and thus all movement is through diffusive neutral evolution (drift), resulting in increased evolutionary stochasticity[2]. Under these non-ecological assumptions, the trajectory of evolution for a mutating population is predicted based upon the mutational supply to a population and the relative fitness of each of these genotypic populations in mono-culture[3].

Whilst important, individual fitness is not the only factor of importance when considering mixed population dynamics. At this opposite extreme, ecological and game theoretical modeling approaches such as the Lotka-Volterra and replicator equations are well-established descriptions of how interactions impact the long-term dynamics and stable states of mixtures of competing populations[4–7]. It is the interplay between these two approaches (genotypic evolution and ecology) that is of particular interest in the treatment of complex, evolving, multicellular diseases. For example, whilst the heterogeneity of genotypes within a patient's disease is accepted as a driver of both pre-existing or de-novo resistance evolution, the presence of cell-cell interactions

in this mixed population may further contribute to altering the efficacy of drugs. It is often the case that personalized treatment in evolving diseases eventually encounters resistance, the reasons for which likely include stochastic, ecological, and genotypic factors at play[8,9].

In recent years, the presence of frequency-dependent selection has been directly observed and shown to be a mechanism for maintaining diversity. A wide array of experiments have demonstrated this effect in bacterial systems[10–17]. Frequency-dependent selection has also been observed in cancer cell lines and varying microenvironments; Kaznatcheev *et al.*[18] demonstrated how alectinib-resistant and parental non-small cell lung cancer cells have different fitnesses in different relative population frequencies and how the presence of fibroblasts or changing treatment results in different evolutionary games. Many papers have also used game theory to model tumor growth and composition with the presence of game interactions between cells including the interaction of competing tumor and stromal cells and the production of growth factors as a strategy[19–25]. Theoretical studies have also shown the potential of frequency-dependent selection to promote high mutation rates and to accelerate evolution[26,27].

Although an area with significant work and interest, one as yet unstudied perspective is the idea of interactions as modifiers on the intrinsic properties of cells such that they may modify evolutionary outcomes in a way that may make experimental interpretation difficult. We highlight the importance of this intersection in **Figure 1**, demonstrating how hypothetical ecological interactions could maintain, mask, or mimic the genotypic fitness differences in co-cultured populations. Whilst deterministic and stochastic approaches have been previously developed specifically to unite these areas, a general non-integral solution for stochastic eco-evolutionary dynamics and an exploration of relative cell-intrinsic and extrinsic contributors have not yet been developed.

We hypothesize that in the frequency-dependent Wright-Fisher model, game interactions can fall into three important regimes: maintenance interactions which result in the same evolutionary stable state that would occur from cell-intrinsic fitnesses alone, masking cell-intrinsic fitness interactions producing resultant neutral dynamics from intrinsic fitness differences, and mimicking cell-intrinsic fitness via interaction modifiers, producing population dynamics at odds with the ranking of cell-intrinsic fitness, (**Figure 1**)[28].

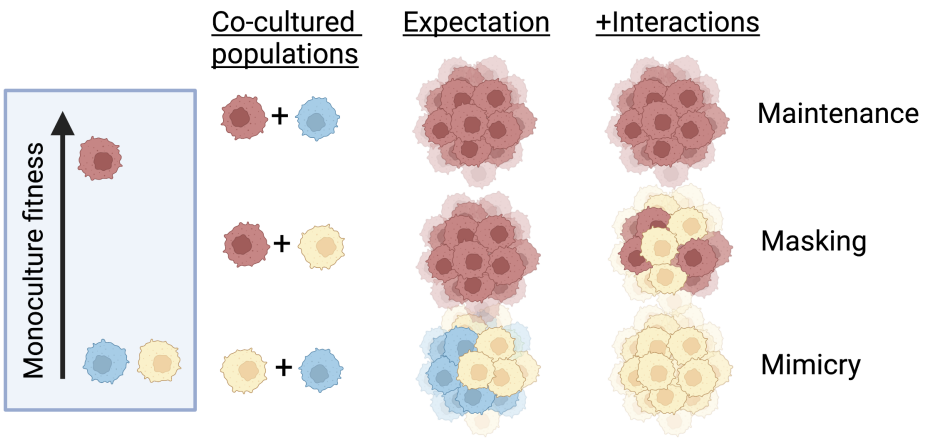

Figure 1. The concepts of maintenance, masking, and mimicry. Based upon the mono-culture fitnesses of different cell types (left), there is a baseline expectation of how the evolutionary dynamics of a mixed population would play out without interactions. We introduce the idea that those mono-culture fitness differences can be maintained, masked, or mimicked in the presence of ecological interactions.

Our work expands upon multiple works that have formalized the frequency-dependent Wright-Fisher model in multiple dimensions[29,30] and prior co-evolutionary dynamic descriptions[31–33]. An underlying assumption of many of these models, including ours, is that the strategy of a cell is set by its genotype and therefore by its parent. Under this assumption, the "payoff" of the evolutionary game is reflected in a cell's ability to replicate, i.e. producing another player of the same type. We develop an expanded game-theoretic formalism that is biologically motivated in light of growing experimental assays and evidence and decomposes cell-intrinsic and cell-extrinsic interactions. This allows the study in both deterministic and stochastic settings of variable relative interaction strengths in biological replicator populations with intrinsic growth rate differences. Using a stochastic, agent-based model, we simulate a frequency-dependent Wright-Fisher model in 1-dimension. We find stationary solutions to the Fokker-Planck equation that allow us to formally compare evolutionary stable states between deterministic and stochastic games. We derive and validate expressions for the conditions on the game interactions in the 1-dimensional case that cause the resultant evolution to maintain, mimic, or mask the dynamics of an initial genetic fitness landscape. Such a hypothesis concludes that when ecological factors and interactions change the fitness of cells, the evolution of the population can only

be modeled using game theory and population genetics in tandem. Our work emphasizes that knowledge of cell-extrinsic interaction strengths is essential in accurately predicting evolution in co-culture.

Theory and Results

To develop our theoretical approach, we start with a simple model of evolutionary game dynamics in the absence of noise and mutation. Game theory in general is the study of the dynamics which result from the interaction of different strategies played against each other. Specific strategies result in expected payoffs for the players and thus the average payoff depends upon the frequency of strategies in the system. Differential game theory can describe deterministic solutions for these dynamics using differential equations. In a symmetric game, the time ordering of the played strategy does not affect the payoffs for the players involved. The payoffs in a 2-strategy symmetric differential game can be presented as a payoff matrix in the following way[7,34]:

$$P = \begin{pmatrix} a & b \\ c & d \end{pmatrix} \tag{1}$$

where a is the payoff for a player with strategy 1 playing against another player of type 1, b is the payoff for a player with strategy 1 playing against a player of type 2, c is the payoff for a player with strategy 2 playing against a player of type 1, and d is the payoff for a player with strategy 2 playing against a player of type 2. These values determine the expected payoffs or "fitnesses" for each player when the frequencies of strategies in the population are known.

For our model, available "strategies" are the cell types of the populations under study. In the replicator model, a cell cannot actively choose a strategy, because the cell's strategy and identity are identically equal. Under the assumption that a cell's genome determines its strategy, we use a simplified model comprising a single locus with two alleles, the wild-type and the mutant, the latter harboring a resistance mutation at the site of interest. In genetic population models, strategy proportions change when cells undergo self-replication, with fitter strategies reproducing at a faster rate. In this type of model, the cells are called replicators: players with strategies that are determined by the strategy of their parent.

The underlying assumption of the replicator dynamics is that the fitness of a cell with strategy i is proportional to the difference between the fitness of its strategy and the average. This determines its rate of replication and this formalism and accompanying equations are referred to as replicator dynamics[6,34]. In the 2-dimensional case with payoff matrix P from **Eq. 1**, the replicator equation takes the following form:

$$\frac{\partial x}{\partial t} = x(1-x)((c-a)(1-x)-(b-d)x), \tag{2}$$

where the proportion of type 2 is x, and the proportion of type 1 is $1-x$. Without the addition of noise, the replicator equation gives us deterministic solutions for the evolutionary stable strategies present. Without mutation in the population, this equation has stationary solutions at $x=0$, $x=1$, and $x=(c-a)/((b-d)+(c-a))$. Following this, different conditions on a, b, c, and d result in various evolutionary stable solutions. These different conditions are often labeled as different types of games (Prisoner's Dilemma, Snow Drift, Stag Hunt, and Harmony). One can construct the 2-dimensional "game space", which has the axes $c-a$ and $b-d$ as shown in **Figure 2**. A game's position in one of these quadrants categorizes it into a certain universality class, with games in the same quadrant generating similar dynamics. In the top left $c>a$ and $d>b$, the mutant always outgrows the wild type. In the bottom right the converse is true. In the top right, $c>a$ but $b>d$, so the species co-exist. In the bottom left $a>c$ and $d>b$ such that there is an unstable mixed equilibrium.

Cell-intrinsic and cell-extrinsic components can be logically separated within the payoff matrix

In the payoff matrix for two distinct cell populations undergoing replicator dynamics, the diagonal terms, a and d from 1 can be understood as the intrinsic mono-culture growth rates of each population. The off-diagonal elements are the result of intrinsic growth rates and the presence of extrinsic factors from cell-cell interactions. To illustrate this clearly, we can decompose the payoff matrix as follows:

$$\begin{aligned} P &= \begin{pmatrix} g_w & g_w+\beta_{wm} \\ g_m+\beta_{mw} & g_m \end{pmatrix} \\ &\equiv g_w \begin{pmatrix} 1 & 1+\alpha_{wm} \\ 1+s_m+\alpha_{mw} & 1+s_m \end{pmatrix} \\ &\overset{g_w\to 1}{=} \begin{pmatrix} 1 & 1+\alpha_{wm} \\ 1+s_m+\alpha_{mw} & 1+s_m \end{pmatrix} \end{aligned} \tag{3}$$

Here g_w and g_m are the growth rates of the wild-type and mutant cells respectively, β_{wm} is the perturbation to the wild-type growth rate due to the mutant population, and β_{mw} the perturbation to the mutant growth rate due the wild type population.

In the third line, we have normalized all terms relative to the wild-type growth rate, defining the mutant selection coefficient $s_m = g_m/g_w - 1$ and two interaction coefficients $\alpha_{wm} = \beta_{wm}/g_w$, $\alpha_{mw} = \beta_{mw}/g_w$. When there are no cell-extrinsic interaction terms ($\alpha_{wm},\ \alpha_{mw} \to 0$), all entries within each row of the payoff matrix become equal. Additionally, when analyzing these dynamics we set the growth rate of the wild-type to 1. This normaliation is equivalent to modifying the time scale and there is no explicit time dependence in the resulting dynamics. After this variable transformation the replicator equation (Eq. 2) for the mutant can be written as follows:

$$\frac{\partial x}{\partial t} = x(1-x)((\alpha_{mw} + s_m)(1-x) - (\alpha_{wm} - s_m)x) \tag{4}$$

Therefore, when there are no cell-extrinsic interaction terms ($\alpha_{wm},\ \alpha_{mw} \to 0$), the frequency-independent evolutionary dynamics are recapitulated. We denoted the normalized game modifications to the growth rates in this system with mutant and wild-type cells as α_{wm} and α_{mw}. Thus any relative dynamics in a 2-player system can be defined by game coefficients α_{wm}, α_{mw}, and the mutant selection coefficient s_m.

As mentioned, the dynamics in a two-player game are often displayed as quadrants in a 2D plot. These quadrants correspond to different dynamical outcomes. Our variable transformation of the payoff matrix allows us to display how the quadrants are regions defined by interaction strengths relative to intrinsic selection, and we obtain their analytical forms. In this new basis the traditional game plot axes $c-a$ and $b-d$ become $a(\alpha_{mw} - s_m)$ and $a(s_m + \alpha_{wm})$ and the quadrants can be defined by conditions on α_{mw} and α_{wm} relative to the homogeneous mutant population selection coefficient s_m (**Figure 2**). For example, the Harmony quadrant (top right) is defined by $\alpha_{wm} > s_m$ and $\alpha_{mw} > -s_m$. As we move across the game-phase-space, different values of α_{wm} and α_{mw} relative to s_m allow the equilibrium behavior to be modified.

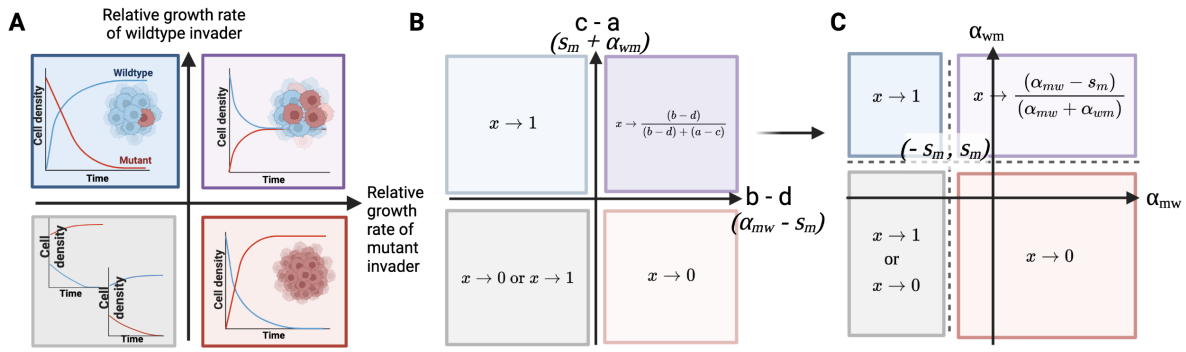

Figure 2. Resultant classes of evolutionary dynamics in the 2-player genetic game as a function of relative fitness and of interaction strength. (A) Illustration of game dynamics between two populations (wild-type and mutant cells). Evolutionary game theory between two players results in four types of dynamics. In the biological case, both the cell-intrinsic and cell-extrinsic influences on growth rate come together in co-culture to produce novel dynamics. The observed dynamics rely not only on the isolated behavior of cells but also on the precise balance between intrinsic and extrinsic factors. In the top left quadrant, the wild type dominates. In the top right quadrant, a heterogeneous mixture is promoted. In the bottom right quadrant, the resistant mutant dominates. Lastly, in the bottom left quadrant, coexistence is unstable and when the population is not at this fraction, the population is driven to the nearest stable fixed point (all wild types or all mutants). (B) The game space reflects distinct evolutionary stable states corresponding to the four quadrants in relative fitness space (b-d, c-a). (C) Using a variable transformation as in the decomposed payoff matrix, the broad classes of evolutionary games and dynamics can be plotted as a function of interaction strength α_{mw}, α_{wm}. The boundaries between the game types in this phase space occur along the lines $\alpha_{mw} = -s_m$ and $\alpha_{wm} = s_m$. The critical point occurs at the intersection of these two lines where there is no resultant fitness advantage to either cell type. The color of the quadrants and subsequent regions in this dynamics plot refers to four different classes of evolutionary games.

Whilst this variable transformation allows for evolutionary games to be framed in terms of extrinsic and intrinsic terms, the replicator dynamics above describe a deterministic system. This means that one can precisely determine the state of the system at a later time, given the state of the system at an earlier point in time. In real biological systems, genetic drift and mutation are present and both of these processes are stochastic, introducing noise into the system.

Eco-evolutionary dynamics with mutation and noise

When aiming to predict evolution in complex systems, we require approaches that capture these genetic drift and mutational effects. To model mathematically the non-deterministic evolution of a stochastic system, we can model the probability distribution for the state of the population over time. One way to describe the evolution of a probability distribution in the presence of noise is the Fokker-Planck equation. The Fokker-Planck equation[35,36] was originally derived to describe the time evolution of a particle undergoing both drag and Brownian motion. As a one-dimensional, real, stochastic variable, within a closed interval between 0 and 1, the probability distribution for the allele fraction within a population satisfies the Fokker-Planck equation. In general, the first term of this equation describes the evolution of a system under drift-like forces and the second term incorporates the random fluctuations. The form derived by Kimura in 1954[37] contains drift and diffusion terms that describe a genetic population undergoing mutation and stochastic sampling between generations. This form has been shown to accurately describe evolution under the standard Wright-Fisher model of mutation and selection.

Versions of the Fokker-Planck equation have been used successfully across physical and biological systems to describe the evolution of probability distributions in time, including in descriptions of protein folding and gene expression stability[38–41]

Kimura derived the appropriate form of the equation for genetic selection and diffusion via mutation and the form of a general equilibrium solution to this equation[37].

$$\frac{\partial \rho(x,t)}{\partial t} = -\frac{\partial}{\partial x}\Big[v(x)\rho(x,t)\Big] + \frac{\partial^2}{\partial x^2}\Big[D(x)\rho(x,t)\Big] \tag{5}$$

where $\rho(x,t)$ is the probability, at time t for a sub-population to make up fraction x of the population. For a non-interacting two-genotype system with mutation and selection, $v(x)$ and $D(x)$ are the Kimura expressions;

$$\begin{aligned} v(x) &= (1-2x)\mu + s_m g(x) \\ D(x) &= \frac{g(x)}{2N}. \end{aligned} \tag{6}$$

Where μ is the symmetric mutation rate, s_m the selection advantage of the mutant, and $g(x) = x(1-x)$.

Game-modified selection in the drift term

Game dynamics between wild-type and mutant alleles result in frequency-dependent selection with a dependence on both the intrinsic growth rates of the cells and the interactions α_{wm} and α_{mw}. To modify the Fokker-Planck to include this effect, we must derive a new frequency-dependent selection coefficient. To do this we find the frequency-dependent fitness of each allele using the payoff matrix defined in **Equation 3**. Our payoff matrix results in the following fitness vector:

$$\begin{aligned} \vec{\phi}(\vec{x}) &= P \cdot \vec{x} \\ &= \begin{pmatrix} 1 & 1+\alpha_{wm} \\ 1+s_m+\alpha_{mw} & 1+s_m \end{pmatrix} \begin{pmatrix} 1-x \\ x \end{pmatrix} \\ &= \begin{pmatrix} 1+\alpha_{wm}x \\ 1+s_m+\alpha_{mw}(1-x) \end{pmatrix} \end{aligned} \tag{7}$$

where x is the frequency of the mutants in the population, and $\vec{x}$ is the vector of frequencies of the wild-type and the mutant respectively. The first entry in $\vec{\phi}(\vec{x})$ is the fitness of the wild-type, $\phi_w(\vec{x})$, and the second entry corresponds to the fitness of the mutant, $\phi_m(\vec{x})$. We thus define the interaction selection coefficient $\sigma_m(\vec{x})$ that replaces the selection coefficient in the non-interacting case.

$$\begin{aligned} \sigma_m(x) &= \frac{\phi_m(\vec{x})}{\phi_w(\vec{x})} - 1 \\ &= \frac{1+s_m+\alpha_{mw}(1-x)}{1+\alpha_{wm}x} - 1 \\ &= \frac{s_m+\alpha_{mw}-(\alpha_{wm}+\alpha_{mw})x}{1+\alpha_{wm}x} \end{aligned} \tag{8}$$

We can also see that when there are no cell-extrinsic interaction terms ($\alpha_{wm},\ \alpha_{mw} \to 0$), this expression for the interaction selection coefficient recovers the non-interacting selection, $\sigma_m(x) \to s_m$. We use this interaction selection coefficient to modify

the drift term in the Fokker-Planck equation, replacing the selection coefficient, s_m, in $v(x)$ with the interaction selection coefficient;

$$v(x) = (1-2x)\mu + \sigma_m(x)g(x). \tag{9}$$

and the diffusion term remains constant.

Solving the Fokker-Planck equation for an interacting population with noise

With our new form of the Fokker-Planck equation, we can construct a steady-state solution for mutation and selection in the presence of growth-rate modifying interactions. A general steady-state solution to the Fokker-Planck equation has the following form[37]:

$$\rho^{eq}(x) = R\exp(-U(x)) \tag{10}$$

In Kimura's solution to the Fokker-Planck equation for evolution under mutation and selection without interactions, the potential $U(x)$ contains the selection coefficient in a linear term $s_m x$. We write a more general potential function $U(x)$ as follows:

$$U(x) = (1-2N\mu)\ln(x(1-x)) + f(x) \tag{11}$$

where our $f(x)$ is now a more generic "selection function". For our specific eco-evolutionary Fokker-Planck equation, we find that the following form of $f(x)$ in $U(x)$ for the solution $\rho^{eq}(x)$ results in a novel, non-integral stationary solution:

$$f(x, s_m, \alpha_{mw}, \alpha_{mw}) = -2N\left[\frac{(1+s_m)\alpha_{wm} + (\alpha_{wm}+\alpha_{mw})\alpha_{mw}}{\alpha_{wm}^2}\ln(1+\alpha_{wm}x) - \frac{\alpha_{wm}+\alpha_{mw}}{\alpha_{wm}}x\right]. \tag{12}$$

Therefore, for any 2-player evolutionary system defined by a symmetric with interaction coefficients α_{mw}, α_{wm}, and selection coefficient s_m, we have derived the first analytic expression for an equilibrium solution of the population frequency distribution. **Figure 3** displays the mean population fraction for a simulation with specific s_m with varying interaction coefficients and the theoretical probability density distribution given by our solution for several of these simulations.

We observe that at low mutation rates, this form of this solution is similar to the deterministic case in the absence of noise where the distributions approach delta functions at either $x = 0$ or $x = 1$, whilst the values of both α_{mw} and α_{wm} and μN alter the width of the peaks in the probability distributions. It is worth noting that the "snowdrift" game from the lower left quadrant in traditional game space ($c < a$ and $b < d$) has two peaks in its stationary Fokker-Planck solution, the height of these peaks becomes more uneven with distance away from the line $\alpha_{wm} = \alpha_{mw} - 2s_m$ and the width of the peaks in all sections increase with mutation rate, μ.

Stochastic simulations match Fokker-Planck under varying $s_m, \alpha_{mw}, \alpha_{wm}$

To validate our theoretical results, we simulate a genetic population undergoing mutation and selection with interactions and noise, effectively a modified Wright-Fisher model. This was used to validate our equilibrium solutions of the genetic Fokker-Planck equation with interactions. For details see methods (code available at `https://github.com/rbarkerclarke/MaskMimicMaintain`).

The Wright-Fisher model predicts that with mutation and selection, the population will move to the peak of the landscape in a single peaked landscape, whereas in a flat landscape, fluctuates stochastically around equal proportions of all genotypes. Without interactions, the results of the Wright-Fisher model depend upon just the genetic fitness landscape, in particular, whether the landscape is neutral or peaked, and the degree of mutation. To explore the effect of interactions on evolutionary simulation models we added varying interaction strengths to a Wright-Fisher model of both single-peaked and flat landscapes. We simulated populations for $4,900$ random pairs of interaction coefficients (α_{mw}, α_{wm}) from a uniform distribution in the interval $[-2s_m, +2s_m]$ for each of several different selection coefficients, s_m (**Figure 4**). In the case of $s_m = 0$, we regain the four-quadrant game plot, representing the different classical games and their outcomes.

The equilibrium distribution of a system with known mono-culture fitnesses and no game interactions is well defined and understood in population genetics. As a result, the equilibrium distributions/evolutionary outcomes measured in experiments are often assumed to be the result of such pure genetic fitness differences. This assumption does not account for potential game interactions between populations. As seen in **Figure 1**, the survival of the fittest (under which the 'fittest' genotype prevails), can result in multiple populations co-occurring and becomes population and interaction dependent.

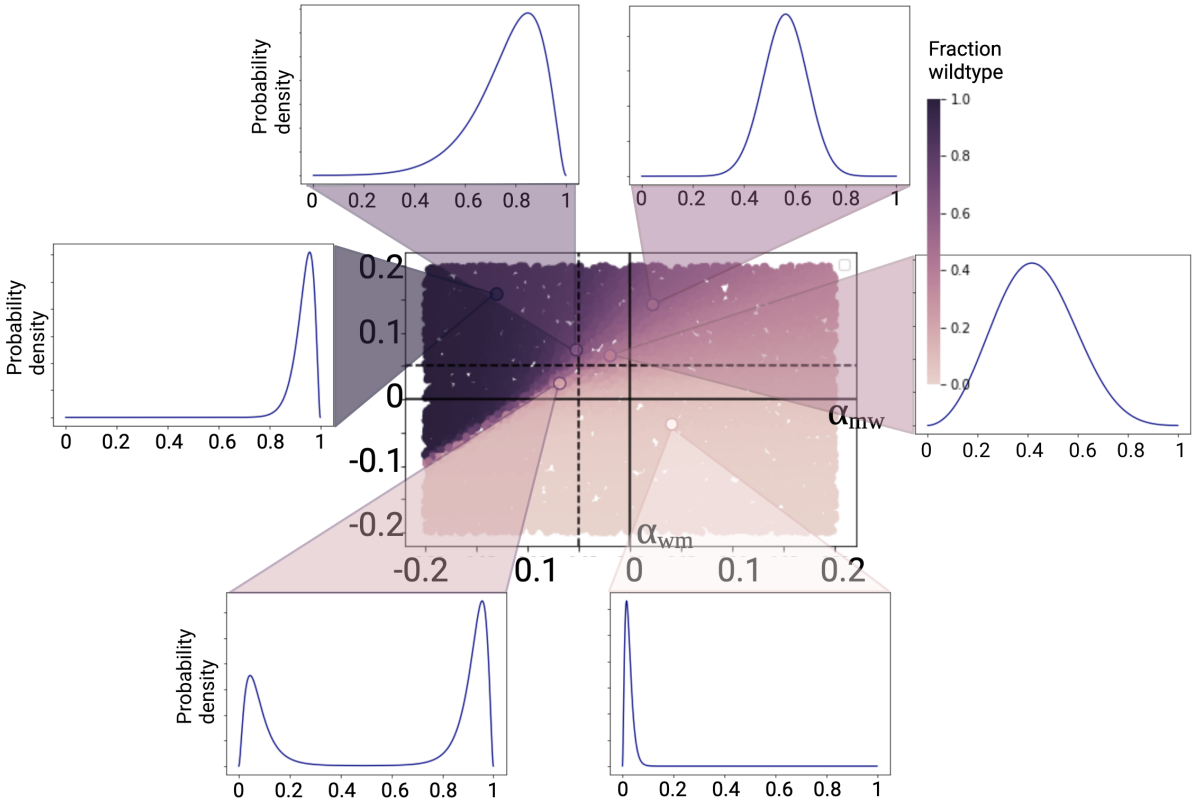

Figure 3. Fokker-Planck solution space for evolving and mutating population with noise. The central plot displays the mean value of the Fokker-Planck population probability distribution over 1,000 simulations at each data point. Mean population sizes are plotted against randomly sampled interaction strengths, with mutant selection advantage $s_m = 0.05$, $N = 1000$, $\mu = 0.005$. The average (mean) proportion of wild-type was plotted for each pair of interaction coefficients. 100% wild-type is dark purple, 0% wild-type population in cream. 10,000 random values of α_{mw}, α_{wm} in the interval $[-0.2, 0, 2]$ were sampled to populate the phase plot. Six specific examples of the analytical Fokker-Planck equilibrium solution are highlighted. The upper right quadrant shows a stable co-existence, with solutions in the bottom left quadrant representing probability distributions with two peaks, one at 100% wild-type and one at 0% wild-type.

Interactions modify the modal value of the stationary distribution

To examine the specific conditions in which interactions may alter the outcomes of biological systems and experiments, we need to understand how the distribution shifts with interaction. This is equivalent to the dependence of the modal value of the stationary solution on the interaction terms. In particular, our concepts of maintenance, masking, and mimicry rely on how this modal value changes with respect to probability density distribution without interactions.

This modal population fraction, x_{mode}, is where the peak of the probability distribution is located. The location of the mode can be determined by setting $\partial \rho^{eq}(x)/\partial x = 0$ (or equivalently $\partial U(x)/\partial x = 0$). In the no-interaction limit, $\alpha_{mw}, \alpha_{wm} \ll 1$, where $\mu \geq 0$ and intrinsic selection coefficient s_m, the peak of the stationary probability distribution is given by the following relation:

$$x_{mode}(\mu, s_m) = \frac{-2\mu + s_m + \sqrt{4\mu^2 + s_m^2}}{2s_m} \tag{13}$$

In the modification of the population by ecological interactions, our specific cases of interest reflect the position of the modal value of the population with respect to the initial position without interactions. However, whilst numerical calculation of the modal value for given interaction coefficients and intrinsic selection is possible(eg. **Fig. 3**), a general expression for the peak of the distribution with interactions is intractable.

Therefore, in order to find the general conditions on interaction coefficients α_{mw} and α_{wm} that create specific relative modal probability values, we examined the selection coefficient (**Eq. 8**) instead. The interaction selection coefficient is the difference between wild-type and mutant fitnesses that arises from the combination of intrinsic and extrinsic effects. Given we know the x

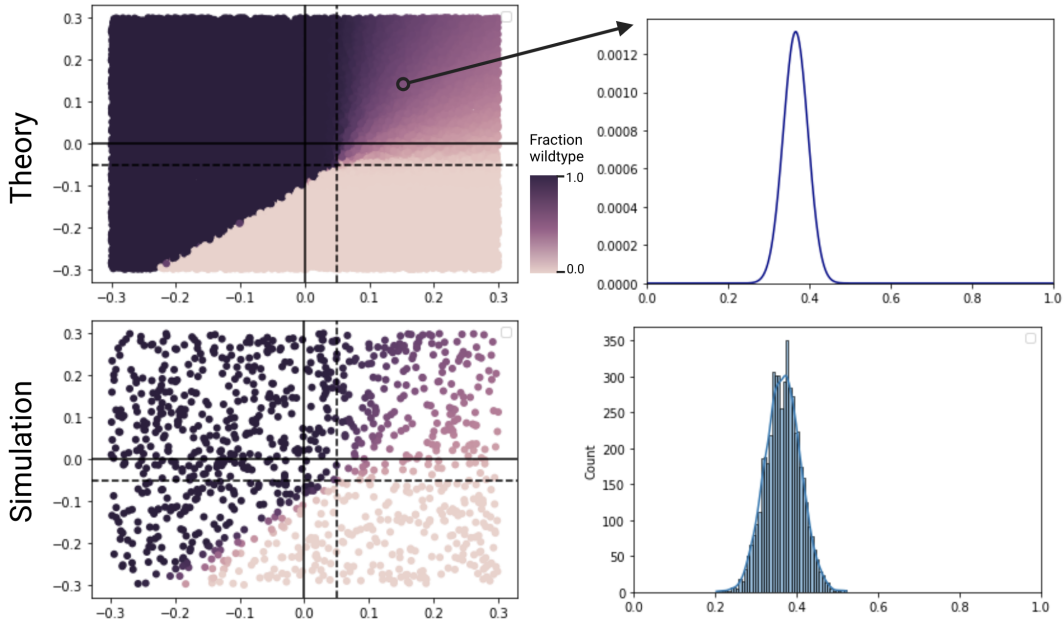

Figure 4. Fokker-Planck (FP) distribution compared to stochastic simulation results. The mean of the FP solution for $100,000$ different interaction strengths is shown (100% wild-type is dark purple and cream is 100% mutant allele fraction). Simulations are carried out and the results are averaged for a subset of $1,000$ game coordinate pairs. We also look at the shape of the population density distribution in a specific Fokker-Planck solution compared to simulations. A histogram of $4,900$ simulations, at $1,000$ generations for specific game coordinates, is shown. We contrast also the analytical probability distribution in a specific game case, $\alpha_{wm} = 0.16,\ \alpha_{mw} = 0.14$, with a sampled distribution of the population fraction at $t = 1000$ generations from 1000 simulations under these conditions.

dependence of this resultant selection coefficient, (See **Eq. 8**), we can obtain a value for the interaction selection coefficient at the initial modal value without interactions, the position within the distribution at which the maximal probability was found. By considering interactions as gradually turned on, we can derive a mutation, intrinsic selection, and interaction-dependent selection coefficient at the modal value of the no interaction probability distribution $\rho^{eq}(x)$. The interaction-dependent selection coefficient, σ_m, experienced at the value of the original modal frequency $x_{mode}(\mu, s_m)$ is:

$$\sigma_m(x_{mode}) = \frac{2s_m^2 + s_m(\alpha_{mw} - \alpha_{wm}) + (2\mu - \sqrt{4\mu^2 + s_m^2})(\alpha_{mw} + \alpha_{wm})}{2s_m + (s_m - 2\mu + \sqrt{4\mu^2 + s_m^2})\alpha_{wm}}, \tag{14}$$

and we confirm that in the case of no interactions, this again reduces to s_m. This effective selection in the presence of interactions underpins the drift of the population and thus the modal position.

Maintenance, Masking, and Mimicry

Biologically, whilst intrinsic selection advantages can be present, cells within heterogeneous populations must survive selection under eco-evolutionary dynamics. Under the presence of both ecological and mutational forces, survival of or out-competition by a sub-population will require the maintenance of existing intrinsic selection advantages, the masking of selection differences, or the mimicry of intrinsic selection in its absence. Furthermore, these concepts are of interest when we attempt to interpret the results of co-evolutionary dynamics in the outcomes of experiments.

We hypothesized that the concepts of maintenance, masking, and mimicry (as illustrated in **Fig. 1**) are the result of specific relationships between the interaction-dependent selection and intrinsic selection coefficient which are in turn determined by the relationship between the interaction coefficients. For a given interaction selection coefficient $\sigma_m(x_{mode})$, the relationship between interaction coefficients α_{mw} and α_{wm} can be found by rearranging **Eq. 14**. We use σ to represent $\sigma_m(x_{mode})$ for brevity. The relation is as follows:

$$\alpha_{wm} = \frac{2s_m(s_m - \sigma) + (s_m + 2\mu - \sqrt{4\mu^2 + s_m^2})\alpha_{mw}}{(1+\sigma)(s_m - 2\mu + \sqrt{4\mu^2 + s_m^2})} \tag{15}$$

	α_{wm} $(\mu \to 0, \sigma > 0)$	α_{wm} $(\mu > 0, \sigma > 0)$	α_{mw} $(\mu \to 0, \sigma < 0)$	α_{mw} $(\mu > 0, \sigma < 0)$
Maintenance	0	$\frac{\mu\alpha_{mw}}{\sigma(1+\sigma)}$	0	$-\frac{\mu\alpha_{wm}(1+\sigma)}{\sigma}$
Masking	$\alpha_{mw}+2s_m$	$\alpha_{mw}+2s_m$	$\alpha_{wm}-2s_m$	$\alpha_{wm}-2s_m$
Mimicry	$-\frac{\sigma}{1+\sigma}$	$-\frac{\sigma}{1+\sigma}+\frac{\mu(\alpha_{mw}-\sigma)}{\sigma(1+\sigma)}$	σ	$\sigma-\frac{\mu(\sigma+(1+\sigma)\alpha_{wm})}{\sigma}$

Table 1. Conditions for Maintenance, Masking, and Mimicry. In the no mutation regime, $\mu \to 0$, the classical game results for the payoff matrix and that correspond to the axes of the transformed game space are returned.

Using this formula we can use the limiting behaviors for each scenario to obtain simplified expressions for maintenance, masking, and mimicry which are shown in **Table 1**. For each of the cases, we also show the solution for coefficients in the case where $\mu \to 0$, these conditions recapitulate the deterministic boundary results.

In the evolutionary context, our first question was to find the conditions under which the relative interaction strengths α_{mw}, α_{wm}, and mono-culture selection coefficient s_m maintain the same selective advantage. In this context the interaction terms are non-zero but leave the evolutionary outcome unchanged, producing the same modal equilibrium value as if there were no interactions, setting $\sigma_m(x_{mode}) = s_m$. We call this behavior *maintenance* as interactions maintain the growth rates of the mono-culture populations. The simplest (trivial) case of maintenance is also in the presence of no interactions which is what the general solution reduces to in the $mu \to 0$ case.

Fitness differences between a wild-type and a mutant in mono-culture may be counteracted by interactions when they are grown in co-culture. We call this scenario whereby intrinsic fitness differences are neutralized by interactions *masking*. This is equivalent to the effective selection coefficient $\sigma_m(x_{mode}) = 0$ when $s_m \neq 0$.

The reverse case is possible, where wild types and mutants may have a neutral fitness relationship in mono-culture, but when grown in co-culture, there is a selective fitness difference. In this case the interaction coefficients allow for an advantage in the presence of no intrinsic selection differences. We call this scenario *mimicry*. At x_{mode}, we may express this as $\sigma_m(x_{mode}) = \sigma$, a constant, when $s_m = 0$.

Maintenance, masking, and mimicry are validated in simulations

To validate the theoretical restrictions (on α_{wm} and α_{mw}) that would result in the modification, masking, or maintenance discussed above we simulated the dynamics of an evolving population with and without the interaction terms (**Figure 5**). The plots at the top of this figure display the relationships from **Table 1** for each example case. We show boxplots of simulation results, where initial simulations with no interactions ("None") are compared to simulations with added interaction terms for three different intrinsic selection coefficients and two mutation rates. Each simulation model consists of a population of $1,000$ individuals undergoing mutation and selection and the boxplot represents 50 individual simulations.

In the *maintenance* case, the theoretical modal values for simulations with no interactions and different intrinsic selection coefficients are marked with dotted lines. The no-interaction cases to the left lie on these lines as expected. Along the x axis the strength of interactions (magnitude of α_{mw}) is increased and the corresponding value of α_{wm} is calculated for each set of simulations from the formulae in **Table 1**. As predicted theoretically, the mean populations in the *maintenance* case remain centered on the same theoretical value as in the none interacting case.

In the *masking* case, the theoretical modal values for simulations with no interactions and different intrinsic selection coefficients are marked with dotted lines. The no-interaction cases to the left lie on these lines as expected from the selective differences. Along the x axis the strength of interactions (magnitude of α_{mw}) is increased and the corresponding value of α_{wm} is calculated for each set of simulations from the formulae in **Table 1**. As predicted theoretically, the mean populations in the *masking* case are all centered on the equal 50:50 split, the theoretical value for the masked (neutral) case.

In the *mimicry* case, the theoretical modal values for all simulations with no interactions are at 50% as marked with the purple dotted line. The no-interaction cases are all neutral in the mimicry scenario. Along the x axis the strength of interactions (magnitude of α_{mw}) is increased and the corresponding value of α_{wm} is calculated for each set of simulations from the formulae in **Table 1**. As predicted theoretically, the mean populations in the *mimicry* case all lie on the theoretical means for the three selection coefficients. The theoretical values for the mimicry case.

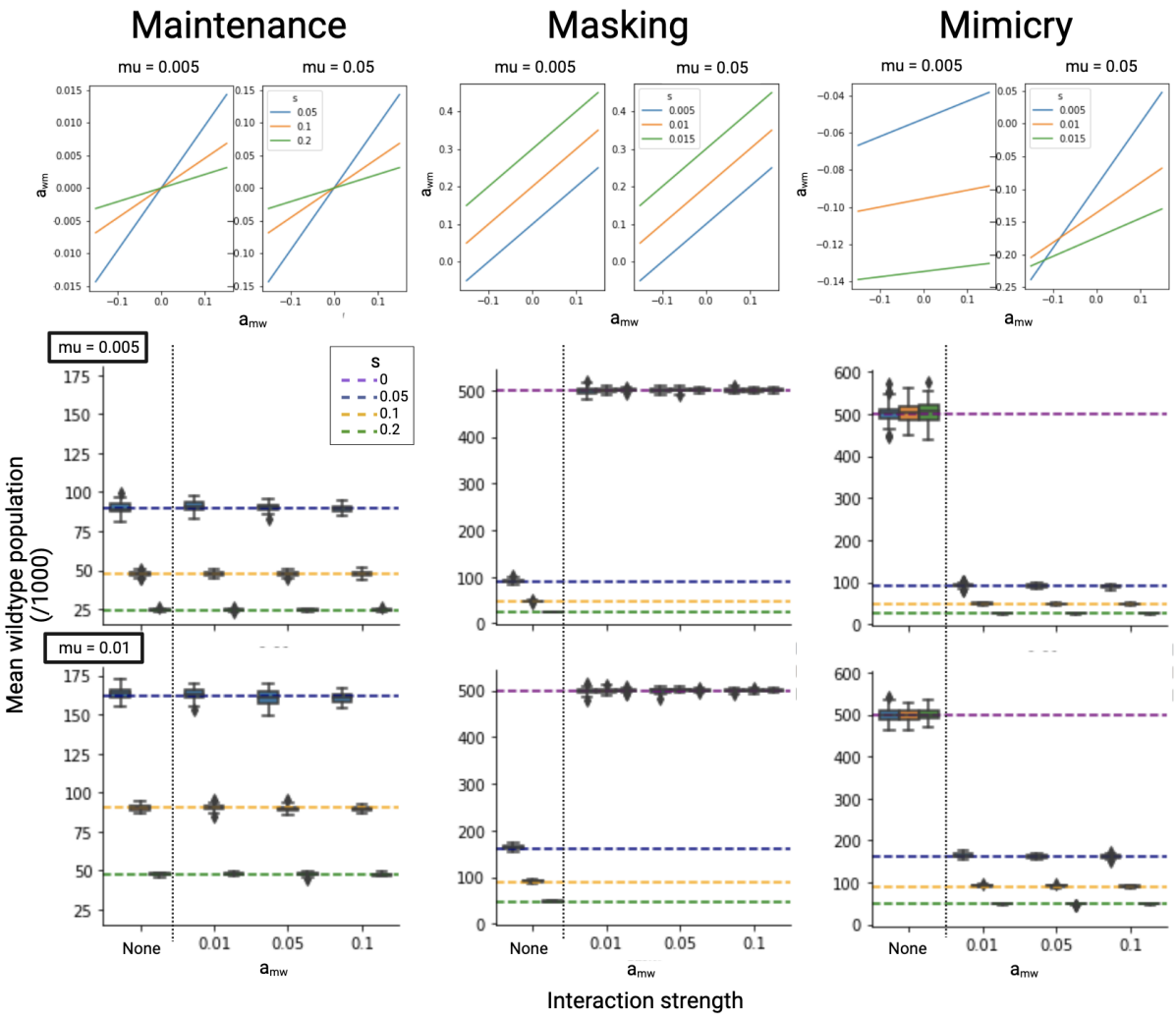

Figure 5. Maintenance, Masking, and Mimicry conditions and simulations are shown. Top The linear relationships as defined in **Table 1** are plotted for two mutation rates and varying intrinsic selection. **Bottom** Simulations were carried out for each of the specific scenarios for genetic populations with two alleles ($N = 1000$), with no interactions (None), and with interactions. Dashed lines represent the theoretical modal value of the wildtype fraction at different intrinsic selection values. For all scenarios, we compare non-ecological simulations with interaction coefficients $\rightarrow 0$ (None), with simulations with increasing strength of ecological interactions. Added ecological interactions have the ratios defined in **Table 1**. For maintenance, the simulations maintain the same mean wild-type fraction as in the case with no interactions. For the masking scenario, the initial modal fraction of the wild type at each selection coefficient is not 50%. When interactions are introduced, the modal population changes to 50%, the equivalent of no selection. In the mimicry case, the initial population is 50% as the mutant population has no intrinsic selection coefficient. With the mimicry interactions, we recapitulate the specific selection coefficients in each case. All simulations show agreement with our theoretical conditions across different strengths of α_{mw} and different values of s and μ. Mean population values are averaged over 3000 generations after an initial 1000 generations. Each box plot represents 50 independent simulations. Initial conditions for the simulations were a 50:50 wild-type (0) and resistant population.

Discussion

The approach of the cell biologist often requires the isolation of microscopic populations to understand their properties. Ecologists, however, focus primarily on the interactions of populations on a macroscopic scale. Whilst both agree that interactions between populations can have implications, they work under assumptions often at extreme ends of the spectrum. We focus on the eco-evolutionary regime in which both of these play a role.

These ideas find importance in the future of human diseases, where $in-vitro$ work has also solidified the existence of cell-cell interactions and their importance. Novel "game assays" have also begun to quantify these interactions between cells in culture. Understanding how to bridge the gap between the co-evolution in complex disease and the theory is critical to future treatment approaches. We use ecology and game theoretical concepts to model and explore the possible impacts of these interactions as they become increasingly important in the disease and cell-biology perspectives[42].

Our work builds on existing experimental and mathematical descriptions of eco-evolutionary dynamics[8,31–33]. To bridge the gap between theory and biology, we acknowledge that in laboratory experiments where cell lines are typically isolated, mono-culture fitnesses of cells are typically the most well-studied property. By reframing the game matrix such that the interactions and mono-culture fitnesses are separated, we come to a form that can both be interpreted within Fokker-Planck formalism but also better understood from the perspective of evolutionary population dynamics in cell lines.

We highlight the critical nature of game interactions from an experimental perspective, demonstrating exactly how the presence of game interactions in addition to the underlying genotypic fitness difference has the potential to modify the evolutionary outcome of an evolving population to any desired outcome. We derive a general expression for the equilibrium distribution of a population obeying the Fokker-Planck equation with selection and arbitrary interactions. We reveal, using mathematics and simulations, the potential impacts of game interactions and their ability to completely alter evolutionary dynamics. We find the critical boundaries at which these game dynamics either maintain a population at the originally fitter genotype (maintenance), move a population from the fixation of the fitter genotype in mono-culture to the fixation of the other (mimicry), or even promote the heterogeneity of a population by leveling the playing field (masking).

We find that the ability for interactions in co-culture to maintain the same relative mono-culture fitness advantage depends on the mutation rate between the two alleles. Additionally, the interaction strengths required to mask selection and promote neutral evolution and co-existence are independent of mutation rate. Finally, we find that equally fit populations in mono-culture can interact in ways in co-culture to perfectly mimic the composition resulting from the co-evolution of genotypically distinct populations. This result means that the measured outcome of any mixed population, such as tumor cells, must be interpreted with caution.

Our work is limited to a two-genotype, non-spatial system at carrying capacity. We do not cover the mechanistic aspects of these interactions or include environmental parameters or interaction effects that vary with time.

Even in our simplified case, the (observed) fitness of the cells in question can be significantly altered by moderate cell-cell interactions. We posit that growth dynamics in mixed populations may readily bear little resemblance to mono-culture growth rates and that initial seeding (eg. experimental or metastatic) ratios may have strong impacts on resultant dynamics. Without specific techniques designed to robustly assay frequency-dependent game interactions[8,17], the magnitude and impact of cell-extrinsic interactions cannot be quantified. These effects have widespread potential ramifications, for example when assaying chemotherapeutic drugs in isolated cell lines, when developing cancer cell lines *ex vivo*, and when interpreting evidence for neutral evolution in tumors[43–47].

Whilst the first part of our work focused on the equilibrium distribution after a long period, we also observed that systems with games present often have altered forms of evolutionary dynamics over time. This has been noted in previous work[27], where Kaznatcheev demonstrated that evolution is, in some cases, accelerated by game interactions. We observed that the magnitude of stochastic fluctuations in population size appeared distinct between game and non-game cases. To explore this property further, we suggest future work has the potential to derive explicit signatures of game dynamics encapsulated in the shape of the equilibrium solutions. Identifying these factors may be critical in interpreting the existence and strength of cell-cell interactions in experimental populations. Decomposition of the payoff matrix provides a biologically meaningful formulation of the payoff matrix and the ability to independently modify the cell-intrinsic and cell-extrinsic contributions to the growth rate. In addition to supplying a new modeling paradigm and analytical solution in the case of added noise, this formalism provides an ideal starting point for the integration of existing pharmacokinetic understanding into game theoretical models. This model framework also more readily permits the integrated modeling of evolutionary treatment, and control in the presence of experimentally motivated drug and micro-environmental-dependent cell-cell interactions[8,48].

Methods

Simulations

We used our Python-based ABM/CA model to observe the evolutionary trajectories before and after the addition of games, in particular asking whether our simulation results are consistent with game interactions designed to maintain, mimic, or mask the expected evolutionary outcome based on mono-culture fitnesses alone.

The simulation involved a constant population of size N comprised of two species, denoted wild-type ('0') and mutant ('1'), undergoing mutation (rate μ) and selection at each generation. The sampling frequency of each population was based on the frequency-dependent fitness of each population calculated at each generation. The constant population size N, mutation rate μ, and mutant advantage s_m were all predetermined. When random payoff matrices were required, they were generated using a uniform distribution of coefficients. In each simulation, populations were allowed to evolve from the initial fraction x_i for 1000 generations, at which point the population fraction from each simulation was extracted.

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Code and data availability

All of the Mathematica and Python scripts in this project can be found on GitHub at https://github.com/rbarkerclarke/GamesModifyEvolution. All processed data needed for the reproduction of the results of the paper are available in the same repository. All raw data files were published on GEA (accession number GSE98787).

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Supplemental

0.1 Derivations

We describe a system of interacting wild-type cells and mutant cells in the framework of the Wright-Fisher model. Each genotype follows stochastic replicator dynamics (a form of geometric Brownian motion) with fixed carrying capacity. In section 0.1.1, we write our model in a reduced form such that we use the minimum number of parameters to describe our system. In what follows, we describe the states of the model, how fitnesses and selection coefficients are calculated, and how interactions modify these fitnesses and selection coefficients.

In section **??** we derive the Fokker-Planck equation for a Wright-Fisher model of a haploid population, including the effects of mutation, and interaction-dependent selection.

0.1.1 Interaction Selection Coefficient

The state of our system is given by a vector of frequencies:

$$\begin{aligned}\vec{x} &= \begin{pmatrix} x_w \\ x_m \end{pmatrix} \\ &= \begin{pmatrix} 1 - x_m \\ x_m \end{pmatrix} \\ &= \begin{pmatrix} 1 - x \\ x \end{pmatrix}\end{aligned} \tag{16}$$

The second component is justified by the requirement that the components of the state vector must sum to 1. The fitnesses or replication rates of the wild-type and mutant without interactions are given by f_w and f_m respectively. Additionally, we have made the notational simplification $x_m \to x$. We define a selection coefficient (s_m) which reflects the relative fitnesses between the mutant and the wild-type without interactions:

$$s_m = \frac{f_m}{f_w} - 1 \tag{17}$$

In our model, we allow for interactions, whose strengths are modulated by the parameters α_{wm} and α_{mw}. The addition of interactions modifies the selection coefficient by modifying the fitness of each genotype. These fitnesses may be calculated if one knows the form of a payoff matrix as well as the state vector. In the language of game theory, the genotypes are "strategies", and the payoff matrix defines a "game". Here we assume the genotypes are playing a symmetric game. In this case, the distinction between a genotype being "player 1" or "player 2" does not matter. The payoff matrix may be written (in a reduced form) as follows:

$$\begin{aligned}P &= \begin{pmatrix} P_{ww} & P_{wm} \\ P_{mw} & P_{mm} \end{pmatrix} \\ &= P_{ww} \begin{pmatrix} 1 & P_{wm}/P_{ww} \\ P_{mw}/P_{ww} & P_{mm}/P_{ww} \end{pmatrix} \\ &= P_{ww} \begin{pmatrix} 1 & 1 + \alpha_{wm} \\ 1 + s_m + \alpha_{mw} & 1 + s_m \end{pmatrix} \\ &\overset{P_{ww} \to 1}{=} \begin{pmatrix} 1 & 1 + \alpha_{wm} \\ 1 + s_m + \alpha_{mw} & 1 + s_m \end{pmatrix}\end{aligned} \tag{18}$$

Here P_{ww} is a scaling factor, which we set to 1. In equation 3, we use the more biologically relevant notation, where $P_{ww} = g_w$, $P_{wm} = g_w + \beta_{wm}$, $P_{mw} = g_m + \beta_{mw}$, and $P_{mm} = g_m$. In the presence of interactions our fitnesses are now $\phi_w(\vec{x})$ and $\phi_m(\vec{x})$, and the selection coefficient (s_m) is now:

$$\sigma_m(\vec{x}) = \frac{\phi_m(\vec{x})}{\phi_w(\vec{x})} - 1 \tag{19}$$

The interaction fitnesses are given by the multiplication of the frequency vector with the payoff matrix to give the expected payoff:

$$\begin{aligned}\vec{\phi}(\vec{x}) &= P\vec{x} \\ &= \begin{pmatrix} 1 & 1+\alpha_{wm} \\ 1+s_m+\alpha_{mw} & 1+s_m \end{pmatrix} \begin{pmatrix} 1-x \\ x \end{pmatrix} \\ &= \begin{pmatrix} 1+\alpha_{wm}x \\ 1+s_m+\alpha_{mw}(1-x) \end{pmatrix}\end{aligned} \tag{20}$$

Plugging the interaction fitnesses, we now have the interaction selection coefficient:

$$\begin{aligned}\sigma_m(x) &= \frac{\phi_m(\vec{x})}{\phi_w(\vec{x})} - 1 \\ &= \frac{1+s_m+\alpha_{mw}(1-x)}{1+\alpha_{wm}x} - 1 \\ &= \frac{s_m+\alpha_{mw}-(\alpha_{wm}+\alpha_{mw})x}{1+\alpha_{wm}x}\end{aligned} \tag{21}$$

Plugging in $\alpha_{wm} = \alpha_{mw} = 0$ returns the selection coefficient without games, *i.e.* $\sigma_m(\vec{x}) = s_m$. Additionally, $\sigma_w(\vec{x}) = s_w = 0$ in both the interacting and non-interacting cases.

0.1.2 Fokker-Planck Equation for a Modified Wright Fisher Model

The standard Wright-Fisher Model describes the change in the frequency of alleles in a population. Parents are chosen randomly in a uniform way with replacements. These parents have offspring, which form the next generation of parents. In a parental population of N organisms and G possible alleles, we define the frequency of each allele (A_i) as x_t^i. The full set of frequencies is a state vector given by $\vec{x}_t = (x_t^1, \ldots, x_t^G)$. The addition of selection and mutation modifies the probability that a certain allele is chosen[37]. Instead of choosing parents based on the frequency vector $\vec{x}_t$, we choose parents based on the frequency vector $\vec{\psi}(\vec{x}_t)$. For the population described in section 0.1.1, we assume a constant mutation rate (μ). To obtain the Fokker-Planck equation, we must consider infinitesimally small time increments ($\delta t \ll 1$) and how, at these time scales, $\vec{\psi}(\vec{x}_t)$ drifts. The specific equations for $\psi^i(\vec{x}_t)$ are similar to the standard modification to $\vec{x}_t$, except we include an interaction-selection coefficient σ_m instead of s_m. In the case where $G = 2$, we have:

$$\begin{aligned}\psi^i(\vec{x}_t) &\approx x_t^i + ((1-2x_t^i)\mu + x_t^i(\sigma_i(\vec{x}_t) - \sigma_m(\vec{x}_t)x_t))\delta t \\ &= x_t^i + v_i(x\vec{T}ot)\end{aligned} \tag{22}$$

where $v_i(\vec{x}_t)$ is a drift coefficient to be used in the Fokker-Planck equation. Here, we are interested in the time dependence over multiple generations. Instead of simply writing $\vec{x}$, we now have $\vec{x}_t$.

Since $x_t^m = x_t$, we may directly consider a 1-dimensional system. In this case, we consider:

$$\begin{aligned}\psi^m(\vec{x}_t) &\approx x_t + ((1-2x_t)\mu + x_t(\sigma_m(\vec{x}_t) - \sigma_m(\vec{x}_t)x_t))\delta t \\ &= x_t + ((1-2x_t)\mu + \sigma_m(\vec{x}_t)x_t(1-x_t))\delta t \\ &= x_t + v_m(\vec{x}_t)\delta t\end{aligned} \tag{23}$$

where $v_m(x_t)$ is a drift coefficient to be used in the 1-dimensional Fokker-Planck equation. The drift coefficient can alternatively be written as:

$$\begin{aligned}v_m(x_t) &= (1-2x_t)\mu + \sigma_m(\vec{x}_t)x_t(1-x_t) \\ &= (1-2x_t)\mu + \sigma_m(\vec{x}_t)g(x_t)\end{aligned} \tag{24}$$

Here, $g(x_t) = x_t(1-x_t)$. We define the diffusion coefficient as:

$$D(x_t) = \frac{g(x_t)}{2N} \tag{25}$$

Taking the continuum limit in space and time, we have the following drift and diffusion coefficients:

$$
\begin{aligned}
v(x) &= (1-2x)\mu + \sigma_m(x)g(x) \\
D(x) &= \frac{g(x)}{2N}
\end{aligned}
\tag{26}
$$

And the 1-dimensional Fokker-Planck equation is given by:

$$
\frac{\partial \rho(x,t)}{\partial t} = -\frac{\partial}{\partial x}\Big[v(x)\rho(x,t)\Big] + \frac{\partial^2}{\partial x^2}\Big[D(x)\rho(x,t)\Big]
\tag{27}
$$

We are interested in the equilibrium solution $\rho^{eq}(x)$, which is the value of $\rho(x,t)$ at which the time derivative is zero. We now make an Ansatz that $v(x) = -D(x)\frac{\partial \Phi(x)}{\partial x}$ for some function $\Phi(x)$. In this case $\rho^{eq}(x) = R\exp(-U(x))$, which is the form of a Boltzmann distribution. Here $U(x) = \Phi(x) + \ln(D(x))$ and R is a normalization constant. We solve for $\Phi(x)$ in the following way:

$$
\begin{aligned}
v(x) &= -D(x)\frac{\partial \Phi(x)}{\partial x} \\
\frac{\partial \Phi(x)}{\partial x} &= -\frac{v(x)}{D(x)} \\
\int \frac{\partial \Phi(x)}{\partial x}dx &= -\int \frac{v(x)}{D(x)}dx \\
\Phi(x) &= -\int \frac{v(x)}{D(x)}dx
\end{aligned}
\tag{28}
$$

Here, we do not need to worry about the constant of integration since it can be absorbed into the normalization constant R. Plugging in the expressions for $v(x)$ and $D(x)$, we have:

$$
\begin{aligned}
\Phi(x) &= -\int \frac{v(x)}{D(x)}dx \\
&= -\int \frac{(1-2x)\mu + \sigma_m(x)g(x)}{g(x)/(2N)}dx \\
&= -2N\mu\int \frac{1-2x}{g(x)}dx - 2N\int \sigma_m(x)dx \\
&= -2N\mu\int \frac{1-2x}{x(1-x)}dx - 2N\int \frac{s_m + \alpha_{mw} - (\alpha_{wm}+\alpha_{mw})x}{1+\alpha_{wm}x}dx \\
&= -2N\left[\mu\ln(x(1-x)) + \frac{(1+s_m)\alpha_{wm} + (\alpha_{wm}+\alpha_{mw})\alpha_{mw}}{\alpha_{wm}^2}\ln(1+\alpha_{wm}x) - \frac{\alpha_{wm}+\alpha_{mw}}{\alpha_{wm}}x\right]
\end{aligned}
\tag{29}
$$

For the potential ($U(x)$) we have:

$$
\begin{aligned}
U(x) &= \Phi(x) + \ln(D(x)) \\
&= -2N\left[\mu\ln(x(1-x)) + \frac{(1+s_m)\alpha_{wm} + (\alpha_{wm}+\alpha_{mw})\alpha_{mw}}{\alpha_{wm}^2}\ln(1+\alpha_{wm}x) - \frac{\alpha_{wm}+\alpha_{mw}}{\alpha_{wm}}x\right] \\
&+ \ln(x(1-x)/2N) \\
&= -2N\left[\left(\mu - \frac{1}{2N}\right)\ln(x(1-x))\right. \\
&\left. + \frac{(1+s_m)\alpha_{wm} + (\alpha_{wm}+\alpha_{mw})\alpha_{mw}}{\alpha_{wm}^2}\ln(1+\alpha_{wm}x) - \frac{\alpha_{wm}+\alpha_{mw}}{\alpha_{wm}}x\right] - \ln(2N)
\end{aligned}
$$

We can move the factor of $-\ln(2N)$ into the normalization constant R to obtain:

$$\begin{aligned} U(x) = -2N\Bigg[&\left(\mu - \frac{1}{2N}\right)\ln(x(1-x)) \\ &+ \frac{(1+s_m)\alpha_{wm} + (\alpha_{wm}+\alpha_{mw})\alpha_{mw}}{\alpha_{wm}^2}\ln(1+\alpha_{wm}x) - \frac{\alpha_{wm}+\alpha_{mw}}{\alpha_{wm}}x\Bigg] \\ &= (1-2N\mu)\ln(x(1-x)) + f(x) \end{aligned}$$

Where we have defined the "selection function" $f(x)$:

$$f(x) = -2N\left[\frac{(1+s_m)\alpha_{wm} + (\alpha_{wm}+\alpha_{mw})\alpha_{mw}}{\alpha_{wm}^2}\ln(1+\alpha_{wm}x) - \frac{\alpha_{wm}+\alpha_{mw}}{\alpha_{wm}}x\right] \tag{30}$$

For the equilibrium distribution, we have:

$$\rho^{eq}(x) = R\exp(-U(x)) \tag{31}$$

and the normalization constant (R) can be found in the following way:

$$R = \left(\int_0^1 \exp(-U(x))dx\right)^{-1} \tag{32}$$

In this case, R is difficult to solve analytically for arbitrary coefficients s_m, μ, α_{wm}, and α_{mw}, but it can be computed numerically.