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Evolution of optimal Hill coefficients in nonlinear public goods games

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Abstract

In evolutionary game theory, the effect of public goods like diffusible molecules has been modelled using linear, concave, sigmoid and step functions. The observation that biological systems are often sigmoid input-output functions, as described by the Hill equation, suggests that a sigmoid function is more realistic. The Michaelis-Menten model of enzyme kinetics, however, predicts a concave function, and while mechanistic explanations of sigmoid kinetics exist, we lack an adaptive explanation: what is the evolutionary advantage of a sigmoid benefit function? We analyse public goods games in which the shape of the benefit function can evolve, in order to determine the optimal and evolutionarily stable Hill coefficients. We find that, while the dynamics depends on whether output is controlled at the level of the individual or the population, intermediate or high Hill coefficients often evolve, leading to sigmoid input-output functions that for some parameters are so steep to resemble a step function (an on-off switch). Our results suggest that, even when the shape of the benefit function is unknown, biological public goods should be modelled using a sigmoid or step function rather than a linear or concave function.

Keywords: Hill Equation; Michaelis-Menten; Enzyme Kinetics; Public Goods; Game Theory; Mechanism Design; Cooperation.

Introduction

Sigmoid benefits in evolutionary public goods games

Situations in which individuals produce public goods that confer a collective benefit to a group are widespread in biology. Beside human and animal societies, the production of public goods is common in cellular interactions, where molecules that enhance fitness, like growth factors, can diffuse between cells. Public goods games in evolutionary game theory must make assumptions about the effect of such diffusible molecules, and hence of their resulting benefit: additive effects make the benefit linear (the "N-person Prisoner's Dilemma" [Hamburger 1973]); synergistic effects produce non-linear benefits, and models of non-linear games [reviewed by Archetti & Scheuring 2012] include concave, sigmoid and step functions [e.g.: Motro 1991, Hauert et al. 2006, Frank 2010, Archetti & Scheuring 2011, Archetti et al. 2011, Deng & Chu 2011, Szathmáry 2011, Cornforth et al. 2012]. Because these models have different dynamics and equilibria, it is important to understand which of these functions is the most realistic approximation of biological public goods.

Examples of sigmoid public goods are commonly found in both prokaryotes [e.g.: Chuang et al. 2010, Cornforth et al. 2012] and eukaryotes [e.g.: Karey & Sirbasku 1988; Jourdan et al 1995]. More in general, biological input-output systems often show a slow response at low input levels, followed by a steep increase in response at intermediate levels and again a decreasing sensitivity as input levels increases [Tyson et al 2003, Cornish-Bowden 2012, Zhang et al 2013, Frank 2013]. In other words, the effect of a biological molecule is often a sigmoid function of its concentration. This kinetics is often described by the Hill equation [Hill 1910; Cornish-Bowden 2012]. In many cases the switch from low to high output is so sudden (that is, the sigmoid function is so steep) that the system has

essentially a bistable response, switching between "off" and "on" like a transistor in a circuit [Sarpeshkar 2010]. Public goods in biology could then probably be modelled using a sigmoid function, or a step function as an approximation of a very steep sigmoid function. A problem remains, however: why a sigmoid shape rather than a concave shape?

Why are sigmoid functions common?

Why are biological systems often sigmoid (or step) functions? Saturation at high concentration is not surprising, since maximum output is intrinsically limited. The commonly observed low response at low input intensity followed by a steep increase at intermediate levels, however, is puzzling [Frank 2013] because the fundamental Michaelis-Menten theory of enzyme kinetics predicts a strong output sensitivity (nearly linear) at low input concentrations [Tyson et al 2003, Cornish-Bowden 2012], followed by a reduced sensitivity, that is, a saturating effect leading to a concave function. This linear sensitivity at low input predicted by the Michaelis-Menten kinetics is at odds with the weak logarithmic sensitivity at low input (that is, the sigmoid shape) commonly observed in biological systems. The question is, therefore: why do biological systems normally follows a sigmoid "Hill kinetics", rather than a concave "Michaelis-Menten kinetics"? Frank [2013] discusses the puzzle extensively.

There are various proximate explanations for the Hill equation. The most basic explanation [Cornish-Bowden 2012] is *positive cooperative binding*: since, many proteins are oligomeric, and ligands at one binding site can affect the binding affinity of the other subunits, if transforming a single molecule to an active state requires simultaneous binding by multiple input signal molecules ("positive cooperativity") the resulting kinetics is a sigmoid curve. Other explanations [Zhang et al 2013] include *titration of a repressor* (the initial reaction may inactivate the input signal molecule or reduce sensitivity to low intensity input signals), and *opposing saturated forward and back reactions* (a back reaction may return the active form produced by the initial reaction to the inactive

state, and if the back reaction saturates at low signal input intensity, then a logarithmic output will result at low input intensity).

At a different level of explanation, however, the question remains unanswered: what is the *adaptive value* of a sigmoid kinetics? We understand that positive cooperative binding, for example, leads to high Hill coefficients (steep sigmoid curves), that is, we understand that cooperative binding is a plausible *proximate* explanation; what is, however, its adaptive value? Cooperative binding in principle can be positive (if ligand binding increases the affinity of subsequent ligands) or negative (if ligand binding reduces the affinity of subsequent ligands). Only positive cooperative binding generates a sigmoid curve. Our question is, therefore: why is cooperative binding often positive rather than negative? The degree of cooperative binding (as well as the degree of titration of repressors and the speed of forward and back reactions — and, more in general, the complexity of signaling systems), are themselves under natural selection a d can easily change from one to the other [Figure 1]. Why should they evolve to generate a sigmoid shape rather than a concave shape? Does a sigmoid shape lead to higher fitness than a concave shape?

A mechanism design question

Studies of public goods in evolutionary game theory usually analyse the dynamics of games with a given benefit function and investigate how cooperation for the production of the public good is maintained. The question is interesting because of the intrinsic inefficiency in the production of public goods, due to the incentive to free-ride on the contribution of other group members. Here, however, we address a different question: what is the best shape for the benefit function? We are interested in the evolution of the game itself (more specifically, its benefit function), rather than the dynamics and equilibria of a game with a given benefit function. Ours is, therefore, a mechanism design (reverse game theory [Myerson 1998]) question: if the rules of the game itself (the input-output function) can evolve,

what game will evolve? In our case the game is defined by the shape of the benefit function.

Our scope is to test whether Darwinian selection would lead to the sigmoid shape we usually observe in nature and, if this is the case, to understand why. A secondary question that arises is: will the production of the molecule be maximised at this equilibrium? It is possible that the *optimal* Hill coefficient from the point of view of the population is different from its evolutionarily stable value. That is, it is possible that evolutionary dynamics leads to a benefit function that is not optimal for the population.

Methods

Determining the optimal Hill coefficients

In biochemistry the fraction of macromolecule saturated by a ligand (that is, output) as a function of the ligand concentration (input) is often described by the Hill equation [Hill 1910; Cornish-Bowden 2012]:

$$o(i)=i^s/[k^s+i^s]=1/[1+(k/i)^s] \quad (1)$$

The "Hill coefficient" s controls the steepness of the input-output function [Figure 1]; k controls its inflection point (this is sometimes described as the ligand concentration occupying half of the binding sites, that is, concentration for which output is half the maximum); a Hill coefficient greater than one means that the function is sigmoid, for instance because of positive cooperative binding.

We analyse the problem of the evolution of Hill coefficients by studying systems in which individual cells with mutations for Hill coefficients arise in a population of cells, and by analysing whether these mutant cells can invade the population. Assuming that the input molecule has some autocrine and paracrine beneficial effect (that is, a beneficial effect on both producer and non-producer cells), and assuming large well-

mixed populations in which groups of size *n* are formed at random at every generation, the fitnesses of a producer cell (C) and of a non-producer cell (D) are given by, respectively

$$\pi_C(x) = \sum_{j=0}^{n-1} \binom{n-1}{j} x^j (1-x)^{n-1-j} \cdot b(j+1) - c \quad (2)$$

$$\pi_D(x) = \sum_{j=0}^{n-1} \binom{n-1}{j} x^j (1-x)^{n-1-j} \cdot b(j) \quad (3)$$

where $c>0$ is the cost paid by a producer cell for the production of the molecule; the benefit b is a function of the number (j) of other cells that produce the molecule in a group of size n (therefore a producer will be in a group with $j+1$ producers (itself plus j other), whereas a non-producer will be in a group of j producers) We assume that this benefit $b(j)$ is a normalised version of the Hill equation (1), that is

$$b(j)=o(j)/o(n) \quad (4)$$

(normalization has negligible effects for most values of s, and ensures that the maximum benefit is the same for all values of s) [Figure 1]. x is the fraction of producers in a polymorphic population or, in a monomorphic population, the probability of producing the molecule ($0 \le x \le 1$). It is also convenient to define $h=k/n$. The average fitness of the population is $x \cdot \pi_C + (1-x) \cdot \pi_D$. The evolutionary dynamics [Hofbauer & Sigmund 1998] of the system is given by the replicator equation:

$$\dot{x} = x(1-x)[\beta(x) - c] \quad (5)$$

where the fitness difference $\pi_C(x) - \pi_D(x)$ is here written in the form $\beta(x) - c$, and

$$®(x)=\sum_{j=0}^{n-1}\binom{n-1}{j}x^{j}(1-x)^{n-1-j}\cdot\Delta b_{j} \quad (6)$$

where $\otimes b_j = b(j+1)-b(j)>0$ for $j=0, \ldots, n-1$. The dynamics (5) has two trivial rest points $x=0$ and $x=1$; further possible interior rest points are given by the roots of the equations

$$®(x)-c=0 \quad (7)$$

These two interior rest points cannot be found analytically but it is known that for a sigmoid function there are at most two such points, and that the higher value corresponds to the stable point [Archetti & Scheuring 2011, 2012, Archetti 2013]. We determine the values of x and s that maximizes fitness, as well as their equilibrium values, by numerical simulations. Whether the relevant values are the equilibria or the maxima depends on what scenario we are analysing.

Different scenarios

There are three possible scenarios based on how the Hill coefficient (s) and the amount of producer cells (or the fraction of producers, x) are determined.

- *Both s and x are determined centrally.* A multicellular individual can determine the value of x and s of all its cells. The goal of our analysis in this case is simply to find the values of x and s that maximise the average fitness of the cell population (the organism itself).

- *Only s is centrally determined, while x is determined individually.* This may be the case, for example, in cancer development, where individual cells can mutate and change their production of the molecule. In this case we must first find the

equilibrium value of *x* for any given *s* and we must then find the value of *s* the maximizes fitness given the equilibrium value of *x*.

- *Both s and x are determined individually.* In a population of bacteria or unicellular eukaryotes, *s* and *x* can be determined by each individual cell independently. Therefore in this case we must find the evolutionarily stable values of both *x* and *s*. We assume that mutant cells with slightly different values of *s* and *x* (that is, phenotypically close to the resident phenotype) arise in the population and we determine whether these mutants invade the resident population. The stable values are the ones that cannot be invaded by any mutant.

In principle one could also analyse the case in which *x* is centrally determined and *s* is determined individually. Since *x* can evolve more rapidly than *s* (simply by different growth rates of producers and non-producers, rather than by the accumulation of mutations that change the Hill coefficient), this scenario is unlikely in a multicellular organism and this case can be considered a special case of the third scenario (where both *s* and *x* are determined individually, in unicellular organisms).

Results

Both s and x are determined centrally

In this case we determine the values of *x* and *s* that maximize population fitness. The results [Figure 2] can be divided in two classes:

- For high values of *h*/*c* (the bottom left part of the panels in Figure 2) the resulting benefit function is a sigmoid or almost concave function (*s* is low), especially for low values of *h*, and all cells produce the same amount of molecule (*x*=1).
- For low values of *h*/*c* the resulting benefit function is a step function, that is, an on/off switch (*s* in the highest possible), and the population is a mixture of producers and non producers

(or a monomorphic population in which all cells produce the molecule with frequency $x<1$).

The reason why there are two classes of results is not intuitive but can be understood by inspecting Figure 3. The average fitness for a steep function benefit declines with x if $x>h$, whereas average fitness for a concave function always increases with x. They, however, do not change (decrease and increase respectively) at the same rate with x. Therefore there are critical values of x and h for which the optimum switches from one class to the other. More in general, the rationale of this result is the following: if the benefit of a diffusible molecule is nonlinear, with diminishing returns as the concentration of the molecule increases, and if producing the molecule is costly, it is not efficient to have a population of cells in which all cells produce the molecule; the fraction of producers necessary to achieve a given benefit (or equivalently, in a monomorphic population, the production level of the molecule) and in this case, as we have seen in Figure 3, because of the very nature of sigmoid benefit functions, the optimal shape is the steepest possible function. If the cost is very low, instead, or the amount of molecule necessary (h) is high, all cells must produce the molecule and in that case the optimal shape is a sigmoid function [Figure 3].

Only s is centrally determined; x is determined individually.

In this scenario x is not centrally determined, hence we must find its equilibrium value, given that each cell has an incentive to maximize its own fitness. Once we have determined the evolutionarily stable value of x for all possible values of s, we calculate fitness at that value of x [Figure 4]. The next step is to find the value of s that leads to the maximum fitness value (given that x evolves to its equilibrium value). The result is that the value of s that maximizes average fitness is intermediate for low values of h (irrespective of c); for intermediate values of h it is the highest possible when c is high, and low or intermediate when c is low; and it is again

intermediate for high values of h (irrespective of c) [Figure 5]. In summary, there are, again, two classes of results [Figure 6]:
- For high values of h/c (the bottom left part of the panels in Figure 5) a sigmoid or almost concave benefit function (low s), and all cells produce the same amount of molecule (x=1).
- For low values of h/c a step function, that is, an on/off switch (the highest possible s), and a polymorphic population of producers and non producers (or a monomorphic population in which all cells produce the molecule with frequency x<1). For very low values of h, however, the optimal s is lower.

The reason why the Hill coefficient can evolve to be intermediate is not intuitive, but can be understood by inspecting Figure 7: because of the very shape of the benefit function, the value of s that maximizes the equilibrium value of x is often intermediate. This means that the output (benefit) at the equilibrium value of x is also maximised at intermediate values of s. While the same logic does not apply to our scenario, since we are looking at the s value that maximizes fitness (which depends also on the cost of production), rather than x or output, it provides an intuitive reason why intermediate Hill coefficients can improve fitness. Note also that at this equilibrium values of x, fitness is generally lower than the maximum possible fitness; hence the social dilemma that generally arises in collective action problems for the production of diffusible molecules by selfish replicators

Both x and s are individually determined.

Finally we analyse the scenario in which there is no central authority: both s and x are determined individually at the level of the cell. In this case not only do we have to calculate the equilibrium value of x and fitness at this value; we must also find the evolutionarily stable value of s, that is, the value of s that cannot be invaded by local mutants [Figure 8]. Figure 9 shows the equilibrium values of s. Results are similar to the previous two scenarios, although in this case a step functions evolves only for a very limited set of parameters:

- For high values of h/c (the bottom left part of the panels in Figure 9) a sigmoid or almost concave benefit function (low s), and all cells produce the same amount of molecule (x=1).
- For low values of h/c a steeper function (high s), steeper for higher values of h, and a polymorphic population of producers and non producers (or a monomorphic population in which all cells produce the molecule with frequency x<1).

Summary of the results

In summary [Figure 10], the resulting system is a steep input-output sigmoid function (essentially a bistable system that resembles an on/off switch) if the relative cost/benefit ratio of the molecule is not negligible, or even if the cost is small and h is small (unless both s and x are centrally determined); it is a less steep sigmoid function if h is high enough and the cost is negligible; it is a concave function if both s and x are centrally determined and the cost is small.

Discussion

Our results

As we have seen, the results depend, in principle, on whether individual cells act to maximise their own individual fitness (which may be the case in microbes and cancer cells) or the fitness of the organism (which is the case in multicellular organisms), as the optimal value is the one that would maximise population fitness, whereas the evolutionarily stable value is the one that natural selection actually leads to (the two are not necessarily equivalent). Although the three scenarios we have analysed could lead in principle to very different results, our results show a common pattern.

For high values of h/c the Hill coefficient s evolves to a low or intermediate value, that is, the effect of the molecule evolves to be an almost concave or slightly sigmoid function of its concentration; the fraction of producers x evolves to 1, that is, all cells produce the molecule. For low values of h/c, instead, the Hill coefficient s evolves to higher values, that is, the effect of the molecule evolves to be a steeper sigmoid curve or even a step function (an on/off switch) [Figure 10]. Not surprisingly, fitness is higher (by up to 15%) when both x and s are determined at the population level rather than at the individual level [Figure 11].

While we have not discussed the evolution of h and c, both are clearly under selection to be as small as possible: c because reducing the cost of production increases fitness, and h because the lower h is the higher the benefit is for a given amount of molecule. Arguably they are also, however, constrained by intrinsic properties of the molecule, which prevent h and c from becoming zero. Hence, we cannot predict whether evolution will tend to produce results of one class or the other, let alone the exact values of h and c. We can argue, however, that there is selection for reducing h and c.

If h is low enough, that is, if the molecules produced by one cell can induce a benefit in many other surrounding cells, our results can be summarized, roughly, by saying that a sigmoid function evolves if the cost of producing a molecule is not

negligible. As a consequence, when the production of a public good is costly, it seems generally reasonable to assume that the benefit is a sigmoid function of the amount of public good.

Further work

Clearly there are limitations in our analysis. We have assumed, for instance, that there is no cost for increasing *s*. However, while changing *s* is likely to involve some costs [Frank 2013], this would arguably only shift the equilibrium value of *s* to a lower value than the ones reported in our analysis.

A second simplification in our analysis is the assumption that there is no assortment and no relatedness among cells. This is also unlikely, and adding assortment to our model would likely lead to higher cooperation among cells. It would be interesting to study its effects on the evolution of Hill coefficients. We have assumed that the results apply to both polymorphic populations with two cell types (producers and non-producers) in which *x* defines the fraction of producer cells, and to monomorphic populations with one type producing an amount *x* of molecule per unit time (normalized between 0 and 1). The two cases may have different dynamics if relatedness is included in the model.

Finally, our results were derived using a relatively low group size (*n*) for practical computational reasons; the value of *n* in groups of cells is probably higher. We know, however, that *n* affects the critical *c* value that makes the system bistable without affecting the dynamics, at least qualitatively [Archetti & Scheuring 2011, 2012]. Therefore it seems reasonable that increasing the value of *n* would only reduce the critical values of *c* we reported here.

Importance of the Hill equation

The Hill equation is widely used in biochemistry (where it describes many cases of enzyme kinetics) [e.g.: Tyson et al 2003, Cornish-Bowden 2012, Zhang et al 2013], systems biology (where the interest is focused on proximate explanations) [e.g.: Kolch et al. 2005, Kim & Ferrell 2007, Ferrell 2009, Cohen-

Saidon et al. 2009, Goentoro & Kirschner 2009, Goentoro et al 2009] and pharmacology (mainly for describing dose-response patterns) [e.g.: DeLean et al. 1978, Hoffman & Goldberg 1994, Weiss 1997, Rang 2006]. As Frank [2013] points out, while the discussion on the Hill equation is scattered through different fields, all seem to recognise it as an important issue. Cornish-Bowden's [2012] provide a useful basic introduction, and Zhang et al. [2013] review various proximate explanations. Frank [2013] discusses the different approaches, and we refer the reader to his review for further references. Frank [2013] is also the first to attempt a general explanation for the evolution of Hill coefficients, describing how aggregation, measurement and scale can explain observed input-output relations.

In evolutionary game theory, in the study of the evolution of public goods, sigmoid functions have been modelled mainly using the logistic equation to analyse the production of non-linear public goods [Archetti & Scheuring 2011, Archetti et al. 2011, Deng & Chu 2011], and it is known that concave functions [Motro 1991, Hauert et al. 2006, Frank 2010] lead to a different type of dynamics [Archetti & Scheuring 2012]. It is interesting that sigmoid input-output functions are not limited to interactions between cells and molecules [e.g.: Chuang et al. 2010, Cornforth et al. 2012, Karey & Sirbasku 1988; Jourdan et al 1995, Archetti et al. 2015], but have been described for behavioural interactions in animal societies, where the benefit of social interactions in a group are often non-linear (in some cases sigmoid) functions of the number of cooperative members [Rabenold 1984, Bednarz 1988, Packer et al. 1990, Stander 1991, Creel 1997, Yip et al. 2008]. While our argument was essentially about enzyme kinetics, and therefore we have assume that the individual players are individual cells and the population is a population of cells, our model applies beyond biochemistry, if we consider that the individuals are actual individual organisms in a population (a society).

It is perhaps worth noting that the improved efficiency we showed for the first scenario (central control of s and x), which applies to multicellular organisms, would be an additional benefit of multicellularity, besides the efficient division of

labor that is generally thought to be the main advantage of multicellularity [Maynard Smith & Szathmáry 1995].

Conclusion

In spite of the importance of the Hill equation in different fields, and in spite of the existence of many proximate explanations for sigmoid input-output functions, an adaptive explanation is still lacking. Why does natural selection often promotes the evolution of sigmoid functions in input-output systems? The puzzle [Frank 2013] arises from the fact that, as we have discussed, the fundamental enzyme kinetics described by the Michaelis-Menten equation predicts a concave function, rather than a sigmoid function. Our goal therefore was to determine whether natural selection for optimal Hill coefficients would lead to the evolution of sigmoid input-output systems. The results that emerge from our analysis seems robust to different assumptions on how the Hill coefficient is determined, and apply to unicellular and multicellular organisms: a sigmoid input-output kinetics is the most likely result of selection for mutant Hill coefficients. Our results add a further level of explanation to current proximate explanations of the Hill kinetics (cooperative binding, titration of repressors and opposing saturated forward and back reactions): the ultimate, adaptive, explanation of the Hill kinetics often observed in biological input-output systems is that a sigmoid shape of the benefit function, or even a step function, leads to higher fitness than a concave function.

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Figure 1. Sigmoid input-output functions described by the Hill equation. The benefit of a diffusible molecule is plotted as a function of x (the level of production of the molecule), for different values of the Hill coefficient s; h=0.5 (the inflection point of the Hill equation); n=20. While the Michaelis-Menten kinetics predict a Hill coefficient s close to 1, higher values are commonly observed in biological systems.

Figure 2. Equilibria when s and x are centrally determined. The values of s (the Hill coefficient) and x (the level of production of the molecule) that maximise fitness, and fitness at these values, as a function of h (the inflection point of the Hill equation) and c (the cost of producing the molecule); n=20.

Figure 3. Two classes of optimal Hill coefficients when s and x are centrally determined. The thick red curves show (left) the average fitness function (as a function of x, the level of production of the molecule) for the value of s (the Hill coefficient) that maximizes average fitness (the arrow marks the value of x at which the maximum occurs) and (right) the input-output function with that s value. In this example, when h=0.6 fitness is maximised at an intermediate value of x. When h increases to 0.7 fitness is maximised at x=1. Two classes of results occur because when the highest fitness occurs at x=1, it does for low s values; when it occurs at intermediate x it does so for the highest s. value. In both cases c=0.1, n=20.

Figure 4. The stable value of x and the corresponding average fitness when x is determined individually. Each cell shows x_{eq}, the value of the stable equilibrium of x (the level of production of the molecule), and the corresponding average fitness (w_{eq}), as a function of h (the inflection point of the Hill equation) and c (the cost of producing the molecule), for different values of s (the Hill coefficient); n=20.

Figure 5. Fitness at the equilibrium value of x when x is determined individually. The equilibrium value of fitness (w_{eq}) as a function of s (the Hill coefficient), when x (the level of production of the molecule) is determined at the level of individual cells, for different

values of h (the inflection point of the Hill equation) and c (the cost of producing the molecule — gray lines); n=20.

Figure 6. Equilibria when x is determined individually. The values of s (the Hill coefficient) that maximize the average fitness (w_{eq}) calculated when x (the level of production of the molecule) evolves to its equilibrium value (x_{eq}), x_{eq} at this value of s and w_{eq} at this value of s, as a function of h (the inflection point of the Hill equation) and c (the cost of producing the molecule); n=20.

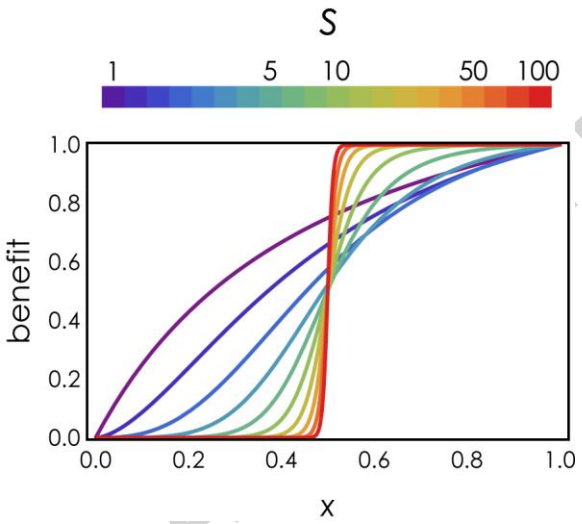
Figure 7. An intermediate Hill coefficient may lead to the highest possible output. When only s (the Hill coefficient) is centrally determined, the equilibrium value of x (the level of production of the molecule) occurs where the gradient of selection (left panel — the benefit difference between producers and non-producers) equals the cost of production c, changing from positive to negative (shown by a circle; arrows show the direction of the dynamics). As a consequence, the value of s that maximises the equilibrium value of x can be intermediate. In this case (c=0.05, n=20), the value of s that leads to the maximum equilibrium value of x is 7.4 (the corresponding functions are shown as thick black curves), which leads to a sigmoid input-output shape (right panel).

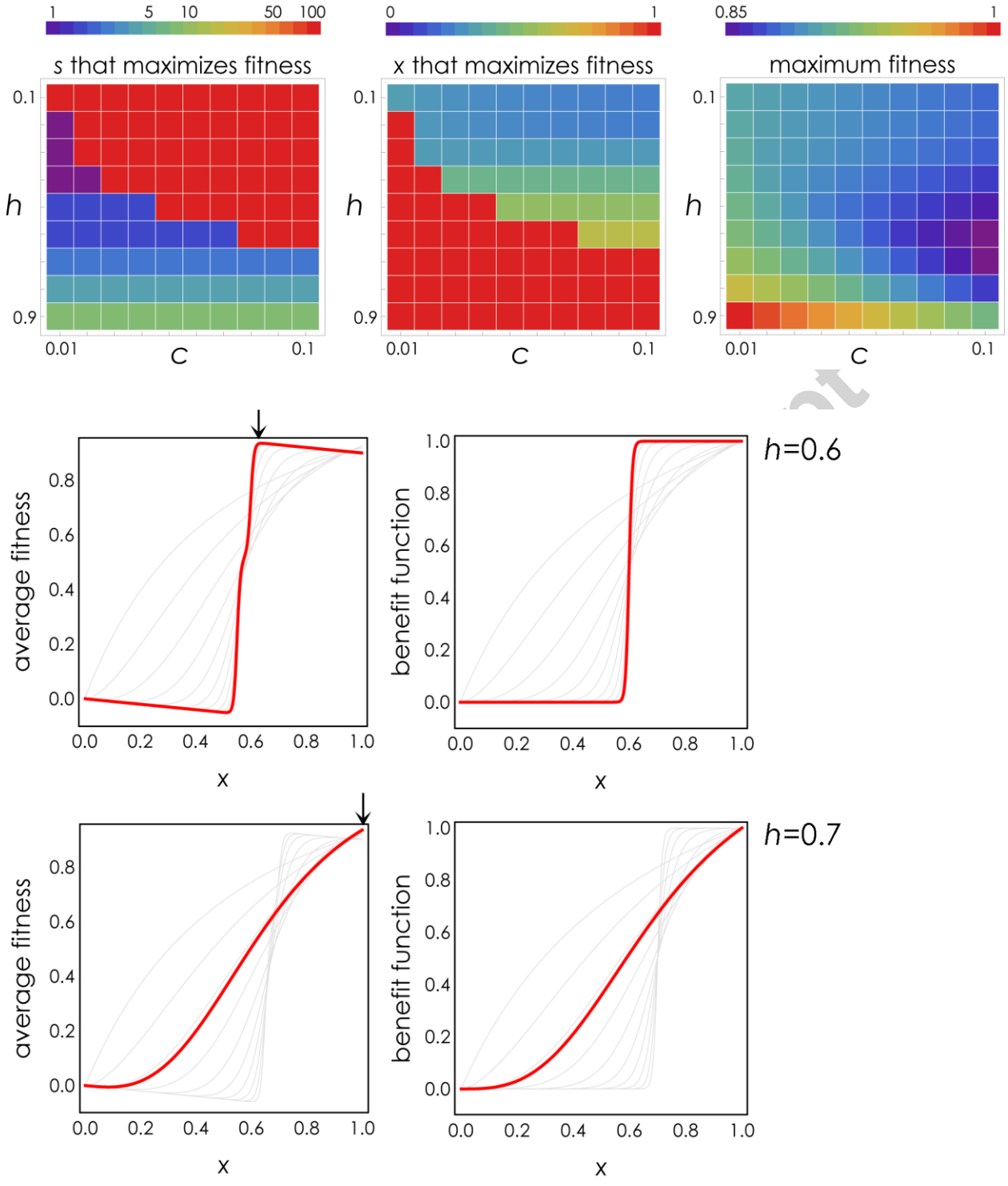
Figure 8. Evolutionary dynamics of the Hill coefficient. The stable value s of the Hill coefficient s_{eq} is found where the equilibrium fitness (calculated at the equilibrium value of x, x_{eq}) of the mutant (with a higher value of s) w^*_{eq} changes from being higher to being lower than the equilibrium fitness (at x_{eq}) of the resident phenotype (w_{eq}). Here c=0.02; h=0.5; s^*=s*1.2; n=20. Arrows show the direction of the dynamics.

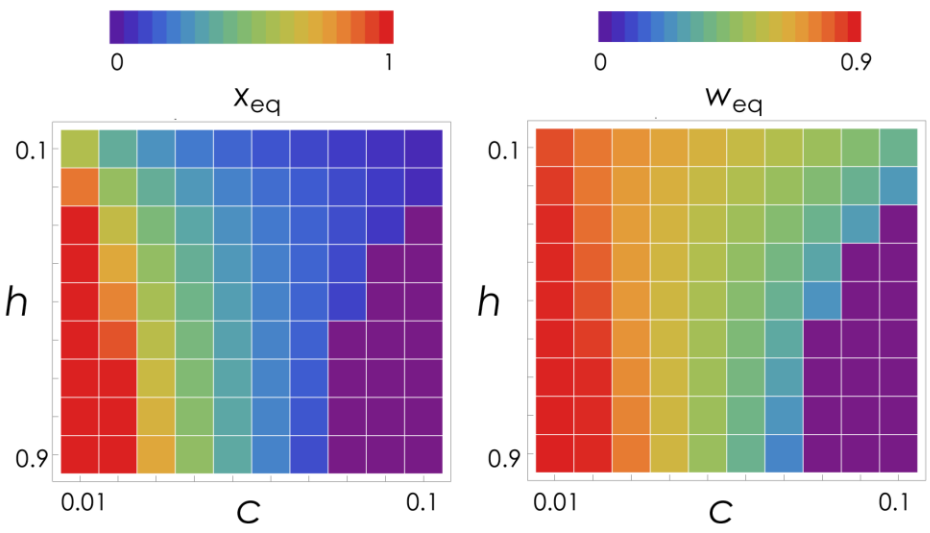
Figure 9. Evolutionary equilibria of input-output dynamics when s and x are individually determined. The equilibrium value of s as a function of h (the inflection point of the Hill equation) and c (the cost of producing the molecule), given that both s (the Hill coefficient) and x (the level of production of the molecule) evolve to their equilibrium value; n=20.

Figure 10. Shape of the input-output function evolving under the three scenarios. The input-output (benefit) function resulting from the stable Hill coefficient (s) under the three scenarios for h=0.2 and h=0.5, and for c=0.01 (dotted curve) and c=0.1 (solid curve); for reference, gray curves show the function for values of s ranging from 1 (concave function) to 100 (approaching a step function); n=20

Figure 11. When control depends on individual cells, inefficiency increases. The difference in fitness (at the equilibrium value of s) between the case in which control of x and s is centralised at the level of the population (W_1, from Figure 2) and the case in which both x and s are decided at the level of the individual (W_2, from Figure 9). The left panel is a detail of the right panel for low values of c; n=20.




1
5
10
50
100
s that maximizes fitness
0
1
x that maximizes fitness
0.85
1
maximum fitness
h
c
0.1
0.9
0.01
0.1
average fitness
benefit function
x
0.0
0.2
0.4
0.6
0.8
1.0
h=0.6
h=0.7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x_{eq}
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h
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C
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h
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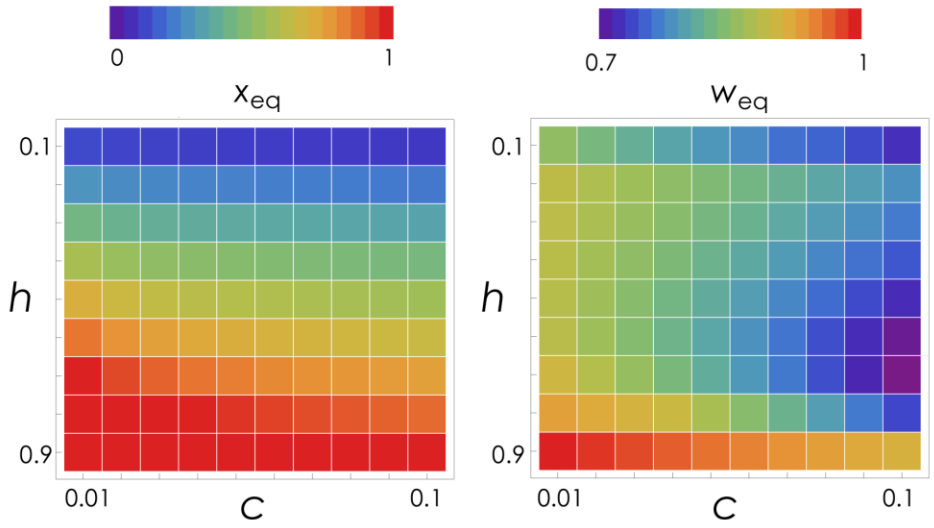
C
0.1

s=1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x_{eq}
0.1
h
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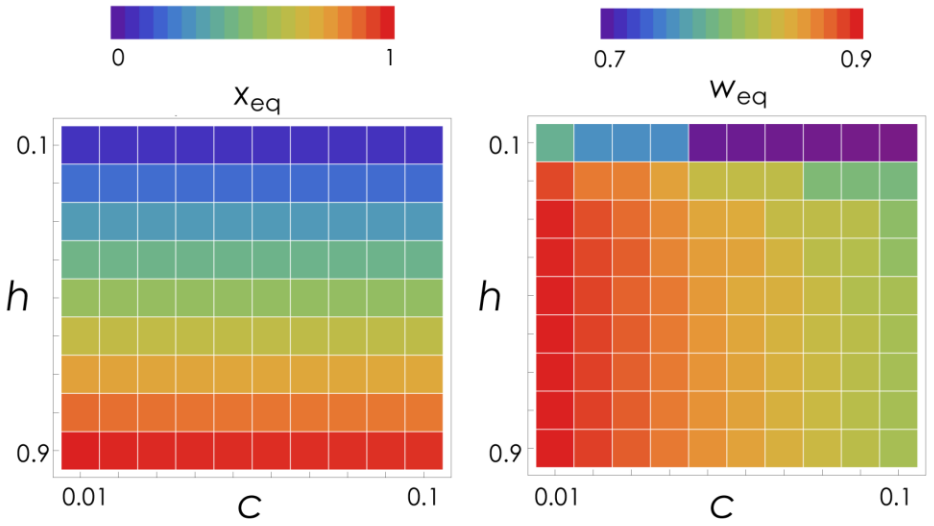
C
0.1

s=10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1
x_{eq}
0.1
h
0.9
0.01
C
0.1
0.7
0.9
w_{eq}
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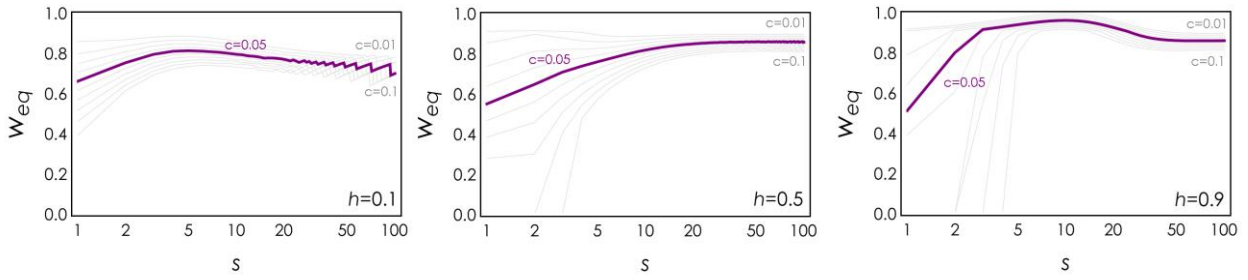
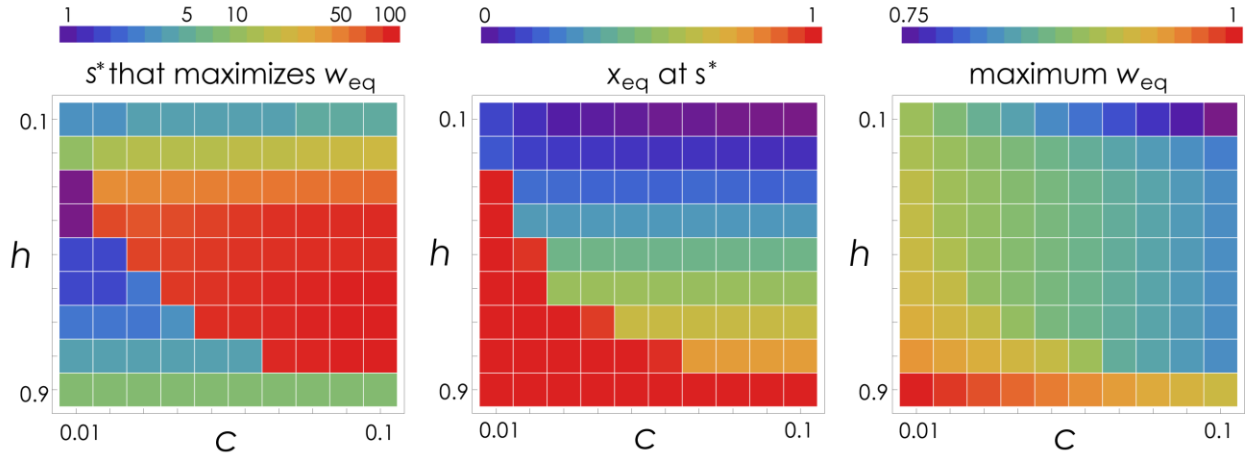
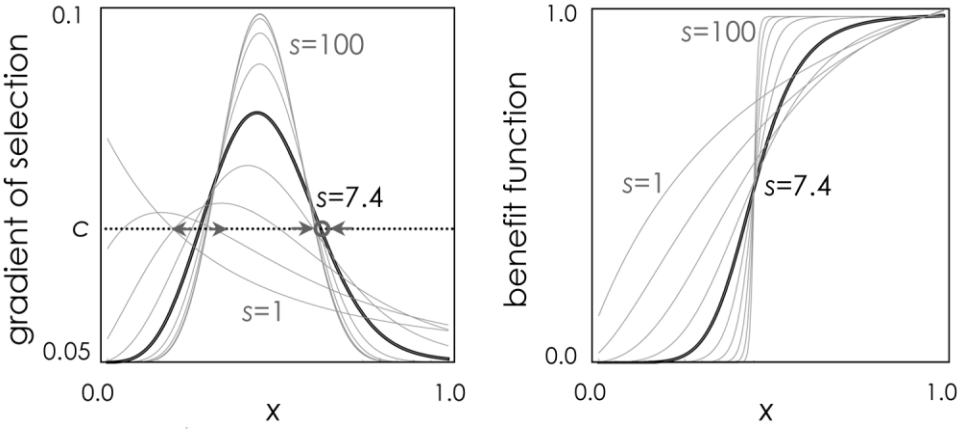
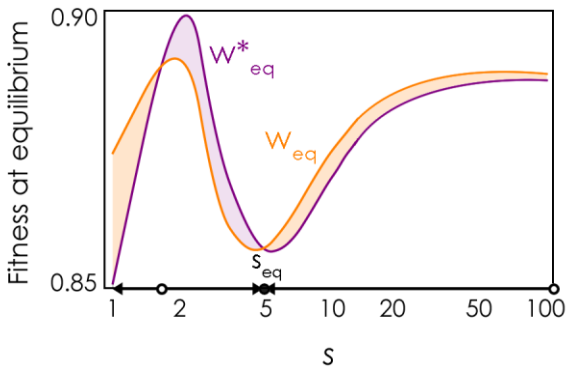
h
0.9
0.01
C
0.1

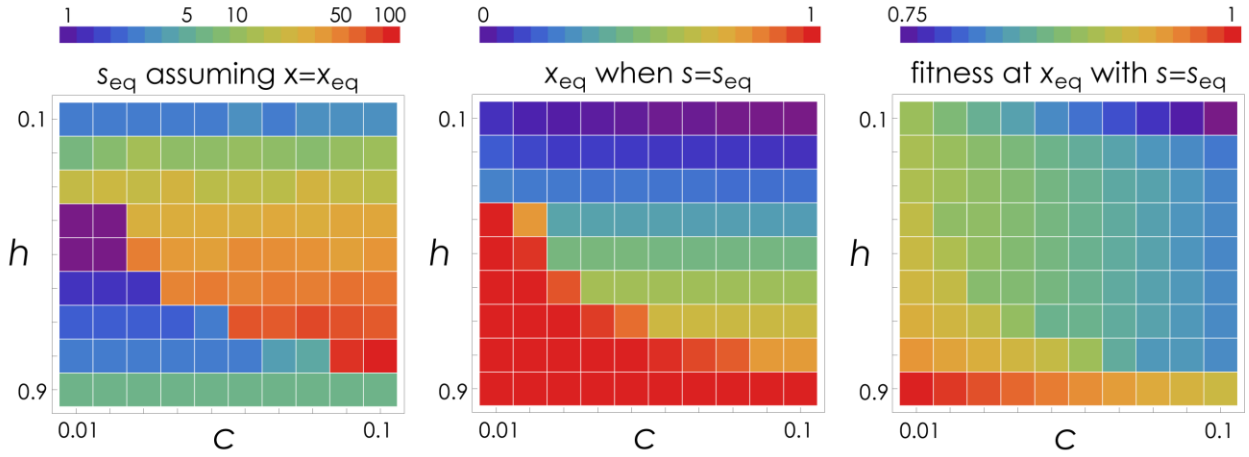
s=100

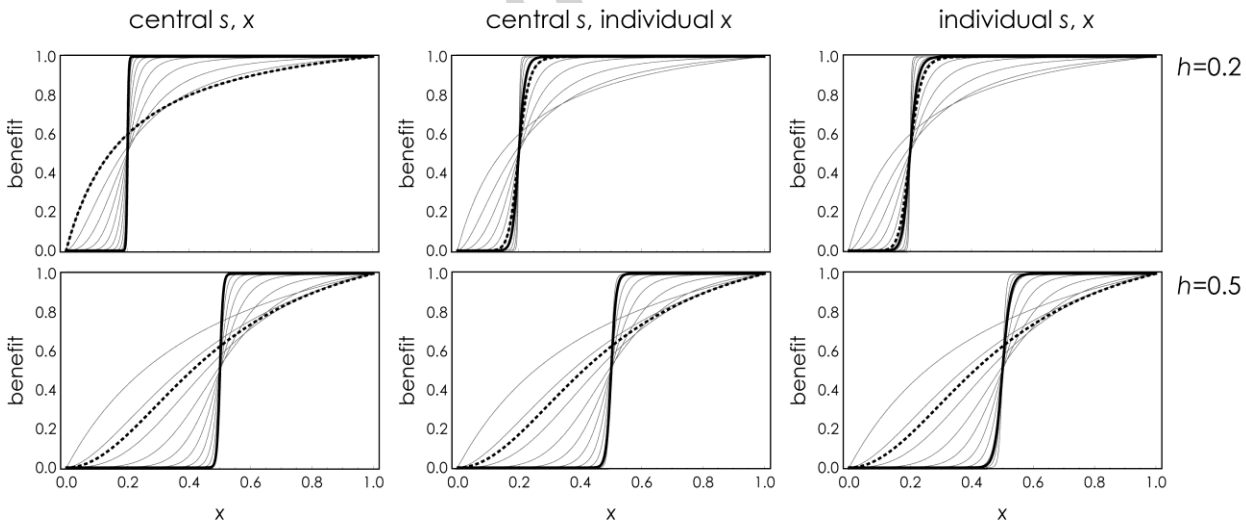

1.0
0.8
0.6
0.4
0.2
0.0
w_{eq}
c=0.05
c=0.01
c=0.1
h=0.1
1 2 5 10 20 50 100
s
h=0.5
h=0.9

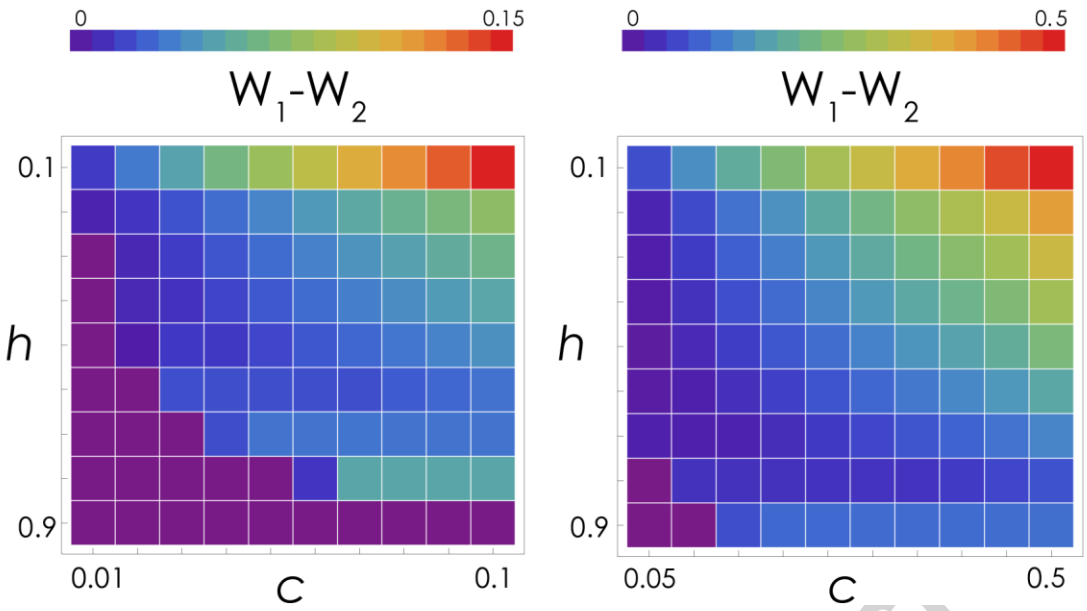

1 5 10 50 100
s* that maximizes w_{eq}
0 1
x_{eq} at s*
0.75 1
maximum w_{eq}
0.1
0.9
h
0.01
c
0.1


0.1
0.05
gradient of selection
c
s=100
s=7.4
s=1
0.0
1.0
x
benefit function


Fitness at equilibrium
0.90
0.85
W*eq
Weq
seq
1
2
5
10
20
50
100
s


1
5
10
50
100
seq assuming x=xeq
0
1
xeq when s=seq
0.75
1
fitness at xeq with s=seq
0.1
h
0.9
0.01
C
0.1


central s, x
central s, individual x
individual s, x
h=0.2
h=0.5
benefit
0.0
0.2
0.4
0.6
0.8
1.0
x



Highlights

- Public goods games often assume sigmoid effects for biological molecules
- Sigmoid effects are not readily predicted by the Michaelis-Menten kinetics
- We model selection on mutations that affect the shape of enzyme kinetics
- We show that evolutionary dynamics often leads to a sigmoid shape