The gene's eye view, the Gouldian knot, Fisherian swords, and the causes of selection

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Abstract

The biological units-of-selection debate has centered on questions of which units experience selection and adaptation. Here I use a causal framework and the Price equation to develop the gene's eye perspective. Genes are causally special in being both replicators and interactors. Gene effects are tied together in a complex Gouldian knot of interactions, but Fisher deployed three swords to try to cut the knot. The first, Fisher's average excess, is non-causal, so not fully satisfactory in that respect. The Price equation highlights Fisher's other two swords, choosing to model only selection, and only the part that is transmissible across generations. The models developed here show that that many causes of organismal fitness do not cause Gouldian complications. Only two kinds of elements must be added to the focal gene for a causal explanation of its selective change: co-replicators that are associated with the focal gene and co-interactors that interact non-additively with the focal gene. Identical equations for co-replication and co-interaction describe interactions between gene copies at a single-locus or at separate loci, and also for genes situated within the same individual or in different individuals. These results resolve some of the objections to the gene-eye view.

Keywords: units of selection, gene's eye view; replicator, interactor

1. Introduction

Charles Darwin's theory of natural selection is a theory about selection on individual organisms, leading to adaptations of individual organisms. The 1960s saw the emergence of two challenges to this view, or more accurately, extensions of it. First, a long tradition of naturalists proposed adaptations that are for the good of the group or the population, but costly to the individual, with Wynne-Edwards (1962) pointing out that such adaptations would require selection at the group or population level. Second, George Williams (1966) and Richard Dawkins (1976) advocated a gene's-eye view of evolution, which dealt more naturally with selfish genetic elements and kin selection. As controversy raged, both viewpoints adapted. Group selection thinking evolved into a hierarchical multi-level selection theory which can also account for selfish genetic elements as within-individual selection. The gene's eye view took a less hierarchical approach but also covered all levels, with genes at other levels being treated as part of the focal gene's environment. Nevertheless, debate continues and it is not entirely clear to what extent to two approaches are fundamentally equivalent.

This paper focuses on the gene's eye view. It is widely used by biologists, but it has also been criticized, so it is important to clearly articulate its claims. It generally includes the following points, all of which can be found in the work of Williams (1966) and Dawkins (1976; 1982). First, natural selection can be described, and perhaps is best described, as the competition between alternative genetic replicators. Dawkins describes genetic replicators as lengths of DNA that

recombine sufficiently infrequently as to make them potentially immortal. Second, the success of a focal allele is the average fitness it experiences averaged across all the environments that it finds itself in. Third, other genes are viewed as part of this environmental context. Fourth, adaptations benefit the alleles causing them and genes act as if they were goal-directed agents. Finally, organisms are built by genes as genetic survival machines. Genetic and organismal fitness are typically equivalent but when they are not, such as with selfish genetic elements of kin-selected altruism, the genic account is argued to be better.

Critics of the gene's eye view have raised several potential issues. First, genes are not directly visible to selection; only individual phenotypes are (MAYR 1959; MAYR 1963; GOULD 1977; BRANDON 1982; BRANDON 1990; GOULD 2001). Second, these phenotypes involve incredibly complex interaction among genes and environments, and focusing on one gene ignores this complexity (SOBER AND LEWONTIN 1982). And because much of this complexity involves context dependence, a focal gene has no determinate causal effect (MAYR 1959; MAYR 1963; SOBER AND LEWONTIN 1982). Instead, its effect varies, sometimes even reversing direction, depending on other genes and the environment. Third, because of the above considerations, tracking changes in gene frequencies is simply an exercise in bookkeeping that records the effect of selection while saying nothing about causes (WIMSATT 1980; SOBER AND LEWONTIN 1982; GOULD 2001). In sum, each gene is tied up in such a Gordian knot of complex interactions that it makes no sense to focus on genes.

One or more of these critiques have been expressed by many, dating back at least to Ernst Mayr's (1959; 1963) general objections to population genetics that predated the modern controversy of genic selection. But I will choose Stephen Jay Gould as the exemplar, because of his participation in the modern debate(GOULD 1977; GOULD 1997; GOULD 2001), his wide influence, his sturdy defense of complex interactions and multi-level thinking, and because of the pleasing assonance in turning the Gordian knot into a Gouldian one. The gene's eye view appears to claim that we can dispense with the Gouldian knot, either by cutting it or untying it.

The gene's eye view draws heavily on the ideas of Ronald Fisher, who can be viewed as its Alexander the Great, trying to slice through the Gouldian knot. Of course, Fisher did this well before Gould appeared on the scene and Fisher may or may not have taken a gene's eye view. But his ideas for understanding how selection works do much to clarify the gene's eye view. Fisher deployed not just one sword but three. The first, his concept of the average excess, says that all you really need to know is the average fitness of the allele relative to the average fitness of all alleles. But to critics, this is mere bookkeeping that ignores the underlying causal complexity. To slice the knot is not to understand it. In this paper, I will pursue a causal approach that uses of Fisher's other two swords. The paper thus seeks to connect three realms of thought: the gene's eye view, Fisherian population genetics, and causal modeling. Thus, many of the ideas are not new but they arguably need better articulation.

I proceed as follows. In the next section I discuss the Price equation, which will provide the basis for the theoretical treatment. In section 3, I provide a causal

argument for the primacy of the gene in selection. Section 4 shows that a focal gene's Gouldian knot is not so complex; it involves only two classes of other genes, co-replicators and co-interactors. Section 5 carries on this task, addressing whether secondary connections make the Gouldian knot more complex. In section 6, I give a few remarks on genes and organisms. Section 8 summarizes and addresses criticisms of the gene's eye view.

2. The Price equation and causality

In this paper, I will make use of a second Fisherian sword, one that he deployed in his fundamental theorem of natural selection (FISHER 1930). Fisher's claim that fitness increased with selection met with much criticism, because evolution can lead to declines in fitness (CROW AND KIMURA 1970; KARLIN 1975; NAGYLAKI 1991). But the theorem was revitalized with the realization that Fisher's math represented only the selective or adaptive part of evolutionary change, or the *partial* change in mean fitness, relegating other changes to an unformalized term for change in the environment (PRICE 1972b; EWENS 1989; FRANK AND SLATKIN 1992; QUELLER 2017). A similar strategy seems potentially useful in the units-of-selection debate where we are primarily interested in selection and adaptation, not all the other factors that affect evolution (GARDNER AND WELCH 2011). Such a move is easily afforded by the Price equation.

The Price equation has long been used in the units-of-selection debate because it offers a powerful way to partition selection into components (HAMILTON

1971; PRICE 1972a; SEGER 1981; ARNOLD AND FRISTRUP 1982; QUELLER 1984; GRAFEN 1985; WADE 1985; HEISLER AND DAMUTH 1987). In addition, because its first term is a covariance, it intersects nicely with the causal diagrams used by path analysis (OTSUKA 2014).

The Price equation can represent average change in any quantity X_i that varies across entities indexed by i. Usually i is used to index biological individuals so it is useful to introduce it that way, but it is flexible and I will soon shift to letting i index allele copies. Each individual i has fitness W_i and offspring with average trait value X_i^0, so that the difference between parent and mean offspring is $D_i = X_i^0 - X_i$. The average trait value X_i can be written in two equivalent ways:

$$\Delta\bar{X}_i = \frac{1}{\bar{W}_i}[\mathrm{cov}(X_i, W_i) + \overline{W_i D_i}] \quad (1)$$

$$\Delta\bar{X}_i = \frac{1}{\bar{W}_1}[\mathrm{cov}(X_i^o, W_i)] + \overline{D_i} \; . \quad (2)$$

The first is the more widely used form and is due to Price (1970; 1972a), with forerunners (ROBERTSON 1966; LI 1967). The second uses the covariance between fitness and *offspring* values (FRANK 1997b; FRANK 1998; RICE 2004). They are equivalent, mathematically sound, partitions of change (FRANK 2012b). In each, the first term is primarily about selection. The second term is primarily about transmission or differences from parent to offspring due to mutation,

148 recombination, or environmental change. They differ only in which term is allocated
149 the interaction between selection and transmission.

150 For a gene's eye model, we want to track allele frequency $\Delta\bar{G}_i$, which we get if
151 we let *i* index allele copies at the locus in question and let G_i=1 for one allele and
152 G_i=0 for the other allele. W_i becomes allelic fitness, the number of descendant copies
153 or allele copy *i*. This will often be the same as individual fitness, give or take some
154 difference from random meiotic shuffling, but would not be the same for selfish
155 genetic elements. Barring mutation, the G_i of the parental allele exactly equals G_i^o,
156 the value of its offspring alleles (DNA replication is faithful and we are counting
157 descendants of the parental allele, not all descendants of the parental individual,
158 which might include other alleles). Thus, $D_i = G_i^o - G_i = 0$, so the second terms (1)
159 and (2) are zero, giving either:

160

161 $$\Delta\bar{G}_i = \frac{1}{\bar{W}_i}\mathrm{cov}(G_i, W_i) \qquad (3)$$

162 $$\text{or} \quad \Delta\bar{G}_i = \frac{1}{\bar{W}_i}\mathrm{cov}(G_1^o, W_i) \qquad (4)$$

163

164 For the genic model without mutation, these two covariances are equal and
165 can be used interchangeably. The near-perfect inheritance of alleles and the
166 consequent dropping of the second Price term makes gene's eye models particularly
167 simple. Near-perfect inheritance was also basis of Dawkins' (1976; 1982) main

168 argument for the gene being the primary unit of selection, but I will focus below on a
169 different argument using causal analysis.
170 Fisher's second sword provides another reason to ignore the second Price
171 term. The units-of-selection debate concerns selection and adaptation.
172 Transmission factors like mutation, recombination, and environmental change are
173 not adaptive. They may either increase or decrease fitness but do so haphazardly
174 and not as a result of the fit of past environments. It is the first term of the Price
175 equation that describes this part, even if the second term is needed for a complete
176 model of evolutionary change (GARDNER AND WELCH 2011). Thus, just as Fisher's
177 fundamental theorem omits non-selective change, we may choose to do likewise in
178 setting aside the second term of the Price equation. This correspondence is not
179 coincidental because the fundamental theorem is easily derived from Price's first
180 term (FRANK 1997b; RICE 2004) and it was Price (1972b) who first realized how to
181 interpret Fisher's theorem in this way.
182 The Price equation itself is a statistical statement, much like Fisher's average
183 excess equation, and neither implies anything about causality. But causality can be
184 added in at least three related ways. First, one can construct a causal model of
185 fitness W_i, and substitute it into the Price equation (QUELLER 1984; QUELLER 1985b;
186 QUELLER 1992b; FRANK 1997b; FRANK 1998). This is the method I will use most.
187 Second, one can use path analysis, invented by Sewall Wright (WRIGHT 1921).
188 Unstandardized path analysis traces causal paths (but only for additive causes) to
189 calculate covariances, and this can include the covariance term of the Price equation.
190 Path analysis is essentially a diagrammatic short-cut for the first method of

191 substituting linear models into covariances. Third, path analysis has been
192 generalized beyond linear models to a more general causal analysis that includes a
193 formal logic for thinking about interventions and counterfactuals (PEARL 2009;
194 PEARL *et al.* 2016).
195
196 ## 3. The causal primacy of the gene: replicator and interactor
197
198 In the long units-of-selection debate, there is one point of near-universal
199 agreement: that there are really two kinds of units. In our applications, these are
200 genes and organisms (DAWKINS 1976; HULL 1980; DAWKINS 1982). More generally
201 they have been called replicators and interactors (which Dawkins calls vehicles) to
202 emphasize that in any selective system, one needs both faithful copying and
203 interaction with the environment (that is, both heredity and selection). While this
204 distinction is valuable, the gene's eye view maintains that genes play both roles.
205 Here I will use the Price equation forms (2) and (4) because I want to make
206 inheritance explicit. The covariance between offspring value and parental fitness
207 $\mathrm{cov}(G_i^0, W_i)$ is the selective change that needs to be explained. First note that, in this
208 view, what we are seeking to explain – selection – is not a thing but rather a
209 relationship, that between fitness and inherited values. The covariance in principle
210 could be equally consistent with W_i causing G_i^0, with G_i^0 causing W_i, or with more
211 remote common causes that affect both W_i and G_i^0. But we know that the first two
212 are not true, and I suggest that it is precisely the third option, the remote common
213 cause, that we seek. A cause of selection at the most fundamental level should have

214 the property that it must be a cause of both inheritance and fitness. It must be both a
215 replicator and an interactor that performs some action that changes fitness,
216 although it need not be the entity that interacts most closely with the environment.
217 Genes meet the qualification of being both replicators and interactors, but individual
218 phenotypes do not (DAWKINS 1976; DAWKINS 1982).

219 Fig. 1 illustrates this with three possible causal models. In Fig. 1a, G_i – the
220 parental genic value – is shown as a common cause of parental fitness W_i and
221 average offspring genic value G_i^o. if we were to intervene and change the value of G_i,
222 that would have the effect of changing both W_i and G_i^0. This is the foundation of my
223 argument that the gene is the fundamental cause of selection. It is sometimes
224 objected that this is too reductive because fitness is influenced by so many other
225 causes. I will develop this point later but for now simply note that causality is about
226 differences so, strictly speaking, all the arrow means is that differences in a gene can
227 cause differences in fitness, which is hardly contestable. A gene as interactor must
228 be a difference maker for fitness (DAWKINS 1982) but does not need to explain all of
229 fitness or all of the variance in fitness.

230 The arrow from G_i to G_i^0 indicates the other causal role of the gene - as
231 replicator. It causes its descendant genes. Again, this does not mean it is the only
232 factor involved in replication; the gene usually just serves as a template and it needs
233 a very complex gene replication machinery. But, in the context of such machinery,
234 the allelic state of the gene is the replicative difference maker; offspring genes are
235 like their parent genes.

We cannot make the same causal claim at the level of the individual phenotype. First, note that there is no individual value I_i that we can play the role that genic value played in the Price equation. Individuals do *have* traits that can be tracked by the Price equation, but individuals are not themselves entities that, like genes, can be assigned a quantitative value to track. This is perhaps in itself one reason to view selection on genes as more fundamental than selection on individuals.

Nevertheless, perhaps we can rescue causality at the individual level by tracking the values of the traits or phenotypes that individual possess. Indeed, it is sometimes claimed that organismal phenotypes, not genes, are the real causes of selection (interactors) because they interact more directly with the environment (Mayr 1963; Gould 1977; Gould 2001). Fig. 1b shows a parallel diagram through which we could calculate change in phenotypic value $\text{cov}(Z_i^0.W_i,)$ where the i subscript now indexes individuals and Z_i is phenotypic value for a trait. Z_i can certainly be correlated with both individual fitness W_i (selection) and with the average phenotypic value of its descendants Z_i^0 (inheritance). But Fig. 1b does not reflect what we know about causality. An intervention changing Z_i would not generally change Z_i^0. Fig. 1b implies that it would, so it is not a proper causal model.

Fig. 1b is not useless; it is just incomplete. Tracking changes in average phenotypes from parent to offspring is precisely what quantitative genetics was designed to do (see (OTSUKA 2014) for a causal account). But it generally does so by recasting the arrow from Z_i to Z_i^0 in terms of genes or genes, which is what is needed for a causal description. Fig, 1c shows that this again puts genes as the root cause. It

is a sort of fusion of Figures 1a and 1b, but the roles of genes and phenotypes are different. The link between G and G^0 is required to get a causal explanation of inheritance. Intervening on or changing Z still would not change G_i^0.

Intervening on Z_i does, however, change fitness and this is a source of confusion. By changing fitness this intervention does affect selection in the narrow sense of effecting change within that generation. In fact, the definition of the selection coefficient is a Price-equation covariance, $\mathrm{cov}(Z_i, W_i)$ (LANDE AND ARNOLD 1983). But, not all of this change extends across generations, as Fisher formalized through his concepts of average excess, average effect, and breeding value. This is Fisher's third sword, which I will use in the rest of this paper. To understand lasting selection and adaptation, we do not need to worry about all effects on phenotypes or fitness; we only need to worry about the ones that cause selective change across generations.

4. Co-replicators and co-operators

A single gene is a fundamental causal unit of selection (Fig 1) but now I take up an important question previously deferred. If instead of a purely descriptive model that simply measures all the W_i's, we want a model that effectively summaries the W_i's in a causal manner, what do we need to include? Does the complexity of environmental, genetic and developmental factors force us back to the hopeless complexity of the whole individual, as has been widely argued?

Let G_1 be our focal locus, which can be as small as a single nucleotide polymorphism. Note that I am now using the subscript to denote locus number and for brevity, *I am now leaving the i index implicit, but it should always be read as being there, and to index gene copies*. For a statistical description of selection on G_1, equation (3) or (4) suffices. But they do not give a sufficient causal description unless our focal gene G_1 is actually the sole cause of its selection. We want to know what other genes, G_2, G_3, G_4 etc., need to be included in the causal model of its selection.

I will expand from Fig. 1a, blackboxing the phenotypic mediators. I focus on a simple case that I believe captures the essential elements of the causes for more complex cases as well. Fig. 2, generalized from Queller (1984 ; 1985a), shows the fitness payoffs to the two alleles of our focal G_1 gene – locus ***A*** with alleles **A** and **a** – when partnered with an allele from another gene, called G_2.

G_2 can be any other allele (GARDNER *et al.* 2007; LEHMANN AND ROUSSET 2014). It could be the other allele at the same locus in a diploid individual or alternatively it could be another locus in the same individual – call it locus ***B*** with alleles **B** and **b.** It could also be a locus in a different individual, again either another copy at the same locus ***A*** or a different locus ***B***. A given G_1 locus may of course have interactions with multiple G_2's (perhaps labeled G_3, G_4 …) of different types, but the simple model is meant to elucidate the basic properties.

This social payoff matrix is commonly filled with one variable of each entry, for example the R, S, T and P variables often used in the prisoner's dilemma and related games. I use instead an equivalent 4-variable system that better reflects

causes (QUELLER 1984; QUELLER 1985b). All payoffs include w, a baseline fitness unrelated to the effects of G_1 and G_2. When the focal gene G_1 takes on value 1, it changed its fitness by s_1, regardless of the partner gene. Similarly, when the partner gene G_2 takes on value 1, it changes G_1's fitness by s_2, regardless of G_1's value. Finally, there can be a joint effect on fitness, s_{12}, that occurs only when both partners take on value 1 ($G_1 G_2 = 1$). s_{12} thus represents an interaction effect or a deviation from additivity of the other two effects when combined. Each selection coefficient s can be positive or negative.

Using these causal variables, the focal gene's fitness can be written as:

$$W_1 = G_1 s_1 + G_2 s_2 + G_3 s_3 + G_1 G_2 s_{12} + e \qquad (5)$$

where e is an error term that includes all other effects. I continue to leave the i index implicit throughout but it should be read as present and indexing instances or tokens of G_1. Thus, G_2 should be read as G_{2i}, the value of G_2 partnered with the i^{th} copy of the focal gene G_1. This equation for W_1 can be substituted into the first term of the Price equation (3) to capture all of the selective effects (but not any environmental change effects in the Price second term), yielding:

$$\Delta\bar{G}_1 = \frac{1}{\bar{W}}[\mathrm{cov}(G_1, G_1)s_1 + \mathrm{cov}(G_1, G_2)s_2 + \mathrm{cov}(G_1, G_1 G_2)s_{12} + \mathrm{cov}(G_1, e)] \qquad (6)$$

If the error term is uncorrelated with G_1, then the last covariance is zero, and this term is lopped off by Fisher's third sword. There can be many genes affecting fitness that do not affect selection on our focal gene. Then, multiplying and dividing by $\mathrm{var}(G_1)$ turns the covariances into regressions:

$$\Delta\bar{G}_1 = \frac{\mathrm{var}(G_1)}{\bar{W}_1}[s_1 + \beta_{G_1,G_2}s_2 + \beta_{G_1,G_1G_2}s_{12}] \quad (7)$$

The focal gene's fate depends on the genetic variance and mean fitness but these affect only the rate. The direction is determined by the three terms within the brackets and my focus will be on these.

When G_2 is the same locus as G_1 residing in another individual, equation (7) clearly gives us a neighbor-modulated, non-additive version of Hamilton's rule. For the case of altruism, s_1 is $-c$, where c is the cost to the focal altruism allele, s_2 is the benefit b from a partner multiplied by regression genetic relatedness, and the added synergism term makes explicit any non-additive causal interaction between self and partner (QUELLER 1985b; QUELLER 1992b; QUELLER 2011).

More generally, the equation can describe all four game types that can be represented by Fig. 2. In each, we have three kinds of effects that need to be considered: a direct effect of the focal gene s_1, an indirect effect of the partner gene s_2, and a joint effect of both genes s_{12}. Our interest here is when we need to include G_2 in our analysis of the focal gene and what we can exclude. The second and third terms of (7) give us the two fundamental reasons for inclusion.

The second term shows that effects of G_2 matter for the evolution of the focal gene G_1 when the two genes covary. For this reason, I call such genes co-replicators of the focal gene. I already noted the social case where the association is genetic relatedness and Table 1 lists what this association is for the other cases. For a G_2 within the same individual as G_1, the association is either non-random mating or

linkage disequilibrium. For a G_2 at a different locus and in a different individual (and even species) from G_1 (FRANK 1997a; FOSTER AND WENSELEERS 2006; WYATT *et al.* 2013), there is no accepted name. I call it "role association" to reflect a covariance between loci involved in distinct roles like male and female, or species 1 and species 2. The common function of association in these four different contexts has been previously noted and formalized (BARTON AND TURELLI 1991; KIRKPATRICK *et al.* 2002; GARDNER *et al.* 2007) Although I call all four types of associated G_2's co-replicators, in each case the association can be caused either by staying together (real co-replication) or coming together (various forms of partner choice) (Table 1).

The third term of (7) shows that genes causing a joint or synergistic effect s_{12} also matter for the focal gene. Synergistic effects are non-additive or statistical interaction effects. To capture this meaning it would be nice to call them interactors, but that term has a prior usage as the unit that interacts with the environment (not necessarily non-additive interaction)(HULL 1980). I therefore call these loci co-interactors. Like the indirect effect, the synergistic effect is also multiplied by a covariance (6). or a regression coefficient (7), which has been called a synergism coefficient (QUELLER 1984). But where the association coefficients of the second term can easily be zero, the synergism coefficients will usually be positive because of the presence of G_1 on both sides of the covariance (G_1G_2 can equal 1 only when both G_1 and G_2 do). For fully penetrant alleles β_{G_1,G_1G_2} can be written as $\bar{G}_2 + (1-\bar{G}_1)\beta_{G_2G_1}$, which reduces to the population frequency G_2=1 partners when there is no association between the genes, $\beta_{G_2G_1}$ = 0. It is therefore the presence of

372 the joint effect s_{12}, rather than the association, that is determinative for a non-zero
373 synergism term. The synergism term needs to be included in the causal model only
374 if s_{12} is non-zero.

375 The synergism or co-interactor term also applies across all four kinds of G_2
376 (Table 1). When G_2 is in the same individual as G_1, this interaction is called
377 dominance or epistasis. For between-individual games, there are not really
378 accepted names, but the parallels suggest the appropriateness of "social dominance"
379 for same-locus effects and "social epistasis" for between-locus effects (either within
380 or between species) (Table 1) though "social dominance" in this context should not
381 be read as behavioral dominance.

382 It is worth pointing out how this formalizes the gene's eye view of treating
383 other genes as if they were parts of its environment. In Fig. 2, replace the partner
384 gene G_2 with an environmental factor E that can take on values 1 and 0 and has the
385 same fitness effects specified in the table. This would lead to an exact parallel to (7):

386 $$\Delta\bar{G}_1 = \frac{\mathrm{var}(G_1)}{\bar{W}_1}[s_1 + \beta_{G_1,E}s_2 + \beta_{G_1,G_1E}s_{12}] \quad (8)$$

387 where E simply replaces G_2. Thus, we need to expand our focal-gene model to other
388 environments when there is an environmental effect s_1 coupled with gene-
389 environment correlation or when there is gene-environment interaction s_{12} (see
390 also Table 1). Genes and environments are treated identically.

391

392 ## 5. Secondary connections

393

Our modeling approach does not support a strict single-gene causal approach that excludes all else. It shows that must also consider co-replicators and co-interactors. I considered one factor at a time, but we would need to add co-replicators and co-actors to the model for fitness, not until all of fitness is explained, but until the model includes everything that is important for G_1. If you estimate the fitness model and the residuals are correlated with G_1, there remains something that should be added (QUELLER 1992b; QUELLER 2011).

But just as important, the Gouldian knot doesn't seem too complicated. We can ignore all the genes that are not co-replicators or co-interactors. But I have treated one interaction at a time and the real world will of course be more complex, where a gene may have multiple co-replicators and co-interactors, at any of the five levels of Table 1. There are also multiple kinds of co-interaction, including three-way (or higher) interactions within a level, and various interactions between levels (for example additive-by-epistasis interaction). But there are fundamentally two ways of having behaviors causally interact, either by associating them together (co-replication) or by having a different consequences with different kinds of partners (co-interaction) and I believe that the simple game in Fig. 2 suffices to illuminate the nature of these causes.

But before concluding that things are relatively simple, another question must be answered. Suppose our focal gene G_1 has a gene G_2 that is either a co-replicator or co-interactor - let's call such a G_2 a primary co-replicator or primary co-interactor. Suppose further that G_2 connects to another gene G_3 as a co-replicator or co-interactor. Does that mean G_3 must also be pulled into the causal description

417 of focal G_1 as a secondary co-replicator or co-interactor, even when G_3 is not by itself
418 a primary co-replicator or co-interactor with G_0? If so, it seems that the causal
419 network might ultimately extend through almost all variable genes, giving us a very
420 tangled Gouldian knot.

421 One way to investigate this question is to model the three-gene case, with
422 two indirect effects (s_2 and s_3), three pairwise interaction effects (s_{12}, s_{13} and s_{23}),
423 and one three-way interaction (s_{123}):

424

425 $$W_1 = G_1 s_1 + G_2 s_2 + G_3 s_3 + G_1 G_2 s_{12} + G_1 G_3 s_{13} + G_2 G_3 s_{23} + G_1 G_2 G_3 s_{123} \quad (9)$$
426

427 Substitution into the first term of the Price equation (3) yields:

428

429 $$\Delta \bar{G}_1 = \frac{1}{\bar{W}_1}[\mathrm{var}(G_1)s_1 + \mathrm{cov}(G_1, G_2)s_2 + \mathrm{cov}(G_1, G_3)s_3 + \mathrm{cov}(G_1, G_1 G_2)s_{12} + \mathrm{cov}(G_1, G_1 G_3)s_{13} +$$

430 $$\mathrm{cov}(G_1, G_2 G_3)s_{23} + \mathrm{cov}(G_1, G_1 G_2 G_3)s_{123}] \quad (10)$$
431

432 The first thing to note is that co-replications alone do not generate secondary
433 connections. In the first three terms, which are the non-interaction terms, a
434 covariance between G_2 and G_3 does not appear. That is, if such a covariance occurs, it
435 does not affect selection on the focal gene G_1. This conclusion is familiar from path
436 analysis (no path is allowed that goes forward through one arrow and backward
437 through another).

438 Interactions are somewhat more complex. Only the last two terms of (10)
439 are relevant to our question about secondary connections. The first, second, and

fourth terms involve only G_1 and G_2 and are simply the terms from our original model. The third and fifth terms apply only when G_3 is either a primary co-replicator or primary co-interactor with the focal gene G_0, and hence not brought in by secondary connections via G_2. The final term represents three-way interactions. For these, do we say that G_1 and G_3 were already interacting without G_2, or that G_2 brings in G_3? Either way, G_3 is part of G_1's causal network.

This leaves the penultimate term of (10) most relevant to secondary connections. It can be re-written as:

$$\bar{G}_2 \operatorname{cov}(G_1, G_3) + \bar{G}_3 \operatorname{cov}(G_1, G_2) + E[(G_1 - \bar{G}_1)(G_2 - \bar{G}_2)(G_3 - \bar{G}_3)] \qquad (11)$$

(BOHRNSTEDT AND GOLDBERGER 1969). The covariance in the first term presupposes that G_3 is already a primary co-replicator ($\operatorname{cov}(G_1,G_3)\neq 0$) and thus not added by interaction. The second term is more interesting. If G_2 is a primary co-replicator with G_1 ($\operatorname{cov}(G_1,G_2)\neq 0$) it makes the term non-zero and brings an interacting G_3 into G_1's causal orbit. This makes sense; co-replicators are tied together, so an interaction for one becomes an interaction for the other. But what about if G_1 covaries with neither G_2 nor G_3? Then the third term becomes relevant. Such third moments disappear if the variables are multivariate normal, which may often be the case, though it is not true in this simple model where variables are binary. However, we can still say that if the three variables are independent and do not covary, the last term will be zero.

462 In sum, secondary connections do not generally form for either co-replicators
463 or co-operators alone, but a locus can forge a secondary connection when it co-
464 replicates with one locus and co-interacts with another.
465
466 ## 6. Organisms
467
468 Where is the individual organism in all this? Genic selection accounts are
469 usually, but not always, equivalent to individual selection accounts. Fig. 3, which
470 adds organismal fitness as a mediating variable to Fig. 1a, illustrates the causal logic.
471 Genic value G_i usually affects genic fitness W_i via organismal fitness $W_{org(i)}$. It is
472 usually sufficient to know organismal fitness because which allele a sexual organism
473 passes on is meiotically random. However, there are genetic elements that have
474 unconventional pathways to fitness that do not align perfectly with organismal
475 fitness, including meiotic drivers, cytoplasmic elements like mitochondria,
476 transposons, and sex chromosomes (Fig. 3, dashed line). In these cases, of course,
477 using organismal fitness alone will be incorrect. When the dashed line is absent, the
478 genic and organismal accounts are equivalent. At a first pass, organisms can be
479 thought of as collections of genes whose genic fitnesses are mostly mediated
480 through a shared organismal fitness, which is consistent with the view that the
481 organism can be defined as a biological unit that has very high internal cooperation
482 and very low conflict (QUELLER AND STRASSMANN 2009; STRASSMANN AND QUELLER
483 2010). The reader should not take the small amount of space devoted to organisms
484 as a sign of lack of importance. Organisms are clearly important and one of the

virtues of the gene's eye view is that it offers a path for understanding how organisms evolved in the first place.

7. Discussion

I concur with Dawkins (DAWKINS 1976) that the gene can be viewed as the ultimate basis of selection, but with some differences. Dawkins argued that the gene, as a small chunk of tightly linked chromosome, is the only entity that has sufficient persistence through evolutionary time to serve this role, an argument that has been criticized, but also generalized to collectives that persist long enough to be seen by selection (FRANK 2012a). The results in this paper are similarly a generalization in that they allow for association due to causes other than tight linkage. Associated genes can be of any type, including genes in other individuals, and associations can arise from multiple causes (Table 1). For a given degree of association, the logic is the same for linked genes versus genes associated for other reasons. In this view, the causal unit is dispersed rather than being a physical chunk of chromosome. This makes the unit of selection less concrete and more abstract, but perhaps more logically consistent. Regardless of type of co-replicators or co-interactors, we get identical equations for gene frequency change.

My main argument for the primacy of the gene is one which Dawkins also makes when he speaks of genes as replicators and as difference makers. Only the gene serves as the root cause of both fitness and inheritance. This could change with other evolutionary systems, such as cultural memes or certain forms of epigenetic

inheritance. But I would argue both that genes are the basis for most of biological evolution and that even for non-genic evolution, the goal would be to identify the root cause of both fitness and inheritance. Our lack of understanding of those causes is an important reason why meme theory has yet to attain the rigor and support of genetic selection theory.

(a) Dormant units, units of fitness, and units of selection

With respect to the Gouldian knot, the present analysis arrives at a position intermediate between an extreme single-gene perspective and Gould's insistence on the importance of the whole individual, but perhaps closer to the former. A causal model of G_1's evolutionary change must include effects from other genes, provided they are correlated (co-replicators), and also if there are joint or interaction effects (co-interactors). But the causal net does not extend endlessly outward via secondary connections. It extends outwards only in that co-replicators partake of each other's interactions.

Any large metabolic diagram or protein interaction network makes it appear that everything is irreducibly linked to everything else. But we should not assume that this entire knot of interaction is fashioned with strands relevant to the selection of interest. I suggest that we have been confused by conflating true causes (G_1 itself, its co-replicators, and its co-interactors) with all causes of fitness and with potential causes of fitness.

First, there are many genes that are causes of fitness, but not co-replicators or co-interactors with G_1, are irrelevant. They affect fitness equally for the two alleles at the focal gene, so they will not affect its evolution. The focus on organismal replicators has tended to obscure this distinction. Of course, these genes are causes of selection for themselves (and for other genes with which they co-replicate or co-interact) but not for our focal gene.

There are also countless dormant causal factors that potentially affect fitness but did not do so during the time of the selection of our focal gene. Because they had no variation, these did not partake in the causal process of differences generating differences. These can be viewed as potential causes that were not actual causes (WATERS 2007). They may still be important in other biological contexts and absolutely vital to the organism; a knockout of a dormant gene might well be lethal. But that does not suffice to make this gene a cause of selection on our focal gene. The concept of dormancy helps address the problem of scaffolding raised by Godfrey Smith (2009). He argued that genes are not very good Darwinian individuals because they cannot replicate themselves without the scaffolding of a lot of cellular machinery outside of the gene itself. But this causal machinery would normally be dormant with respect to our gene's evolution. It is necessary for replication, but the relative success of alleles at our focal gene does not generally depend on differences in the cellular machinery.

The Gouldian knot is indeed very complex. The Fisherian sword of average excess can slice right through it, but only as long as we are not interested in how the strands of the knot actually cause selection. But even when we are interested in

causes of selection, Fisher's other two swords still cut through much of the complexity. We do not need to include non-selective effects when we are considering units of selection. And we do not need to explain all of fitness but only those parts that are relevant to between-generation change.

(b) Relation to population and quantitative genetics

The importance of interactions and correlations will hardly come as a surprise to quantitative geneticists or to population geneticists. Within quantitative genetics these are the impetus for models involving more than the additive genetic variance - dominance variance, epistatic variance, and various more complex various kinds of interactions. Such quantitative genetics models have been extended into the social realm (MOORE *et al.* 1997; WOLF *et al.* 1999) though not, so far as I am aware, into between-species interactions. Quantitative genetics employs some of the same assumptions and tactics used here.

Within the population-genetic tradition, an approach that has many parallels to the treatment given here is the multilocus model of Barton and colleagues (BARTON AND TURELLI 1991; KIRKPATRICK *et al.* 2002; GARDNER *et al.* 2007). They provide a general formalism that, in principle, can take into account all possible genic correlations and interactions. Their models can provide guidance as to what needs to be included in a minimal or sufficient model, though this was not made explicit. My goal has been to make this explicit in a simple way by starting from the focal gene and asking what kinds of other genes needed to be included.

576

577 **(c) Critiques of the gene's eye view**

578

579 The gene's eye view is widely used by practicing evolutionary biologists, at
580 least as a mental model, but it has elicited a range of objections. The causal models
581 suggested here address many of these criticisms. I am not claiming, or even seeking,
582 a decisive win in what some see as a battle to the death between gene's eye,
583 individual, and multi-level approaches. We have obviously derived great value the
584 individual approach, beginning with Darwin. The multi-level approach can also be a
585 useful way to partition selection. But I believe there is also great value in the
586 bottom-up gene's eye view. My goal is simply to clarify the gene's eye approach and
587 remove some objections that I believe to be wrong or overstated. The controversy is
588 too large to be settled in this paper, but I will briefly address three major related
589 criticisms: that genes are mere bookkeeping, the invisibility of genes to selection,
590 and the context-dependence of genes.

591 First, the causal approach immediately addresses what Gould (2001) called
592 the "central logical error" of gene selectionism. According to this objection, the
593 gene's eye view may be fine for "bookkeeping" because it is always possible to
594 express change in terms of genes and the average fitnesses they experience, but that
595 is not a causal model (WIMSATT 1980; SOBER AND LEWONTIN 1982; GOULD 2001). This is
596 a fair criticism against some versions; Fisher's average excess and the Price
597 equation are themselves simply statistical descriptions of change, not causal models.
598 The formalization here confirms that this a good causal account only in a world that

599 is additive (GOULD 2001; OKASHA 2006) and also non-correlative. But it also shows
600 how to take non-additivity and correlation into account, removing the bookkeeping
601 objection.

602 Actually, the bookkeeping objection never seemed very compelling in the
603 first place for several reasons. First, just about everyone agrees that a gene-
604 centered approach is necessary to understand selfish genetic elements like
605 transposons or meiotic drivers. But how Gould's "central logical flaw" of
606 bookkeeping is avoided in this case has never been explained. Second, the objection
607 can also be applied to the individual-level models offered as alternatives. Take the
608 frequently discussed case of heterozygote advantage, a case of strong non-additivity
609 at the single-locus level. When this is modeled at the individual level by positing
610 three fitnesses, W_{AA}, W_{Aa} and W_{aa}, we still have average fitnesses experienced, in this
611 case by three genotypes, that give an adequate prediction but not an adequate
612 causal explanation if there are any additional non-additivities or correlated effects.
613 Compared to a simplest genic average excess model (but not the one developed
614 here), the individual-level model does account for one additional causal factor:
615 dominance. But it is still averaging over effects for each of the three genotypes and
616 so it still just keeping the books on other causal effects. Of course, when these
617 additional causal effects are known or posited, they can be incorporated into either
618 the individual model, but also, as shown above, in a genic one.

619 Another criticism of the gene's eye view is that genes are invisible or not
620 directly visible to selection, that selection sees only organismal phenotypes (Mayr
621 1963; Gould 1977; Gould 2001). Sometimes this is framed in terms of the logical

causal concept of screening off (Brandon 1982; Brandon 1990) but Hitchcock (1997) has criticized this view. Screening off can show causal irrelevance for causal relations of the form *B*<-A->*C* but the selection question has the form *G*->Z->W, where phenotype Z is simply a variable that mediates the causal effect of *G* on *W*. To deny that *G* is a cause in this sequence would seem to deny the role of causal chains and causal mediation in general.

I would add two points. First, if only phenotypes are visible to selection, this would also be true for selfish genetic elements but, gain, virtually everyone accepts them as genic causes of evolution. Second, there is no single phenotype at the individual level. A genetic difference sets in motion a whole cascade of phenotypic differences: different RNAs are made; different protein is made from RNA; the protein acts differently as an enzyme in a pathway; the pathway makes different amounts of product, the product differentially affects the state of the cell; the cell sends different amount of a signals to other cells; the cells develop into different sized organs, the organs function differently, and the organisms survive differentially. The visibility-to-selection argument, would seem to render all but the very last step in the chain just as causally irrelevant as the gene itself. That can hardly be what Mayr and Gould, champions of developmental interaction and complexity, had in mind.

A third objection to the gene's eye view also dates back to Mayr, specifically to his (MAYR 1959; MAYR 1963) "genetic theory of relativity". He argued, quite rightly, that the effects of genes are nearly always context dependent so their selection will depend on other genes. This has led some to argue that there is no

causal upshot of a possessing a gene - it depends on circumstance (SOBER AND LEWONTIN 1982). In a limited sense this is true - there is no *single* casual upshot. But selection can still operate on the appropriately averaged causal upshots and this is embodied in the synergism terms of various equations in this paper. Just as the invisibility objection seems to deny causal mediation, the genetic relativity argument appears to reject the role of another linchpin of causal analysis: causal moderation or causal interaction. The whole thrust of the modern enterprise of causal analysis, summarized by Pearl (2009) is about extending the causal viewpoint of path analysis to non-additive interactions.

Heterozygote superiority is often used as an example of how the gene's eye view is supposedly thwarted by genetic relativity (SOBER AND LEWONTIN 1982). Under extreme heterozygote superiority, where homozygotes have zero fitness, an equilibrium gene frequency of one half will be attained because only heterozygotes survive. Sober and Lewontin (1982) argue that the genic view will get that but will miss the fact that the population fluctuates between genotypic frequencies of 0, 1, 0 just after selection to 1/4, 1/2, 1/4 just after heterozygotes separate. But this is comparing apples and oranges. It compares a genotypic model that includes transmission effects and a genic one that does not. Genic models can certainly incorporate transmission effects like segregation when desired (GARDNER *et al.* 2007). But it can also be useful to deploy Fisher's second sword and focus on the selective, adaptive parts of the evolutionary process, as seems reasonable when considering units of selection.

In sum, the inclusion of a limited number of co-replicators and co-interactors allows for a causal gene's eye view that addresses many of the historical criticisms. The gene's eye view will presumably not replace the organismal viewpoint, both because organisms are more observable than genes, and because most genic selection is mediated through organismal fitness. But the gene's eye view does provide a theoretically broader account that includes organismal selection but also selection within-organisms and selection before real organisms existed.

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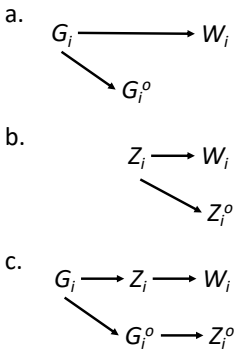
838 **Figure legends**

839

840 Figure 1. Possible causal models.



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844 Figure 2. Fitness payoffs to different alleles of gene G_1 when paired with different

845 alleles of G_2. G_2 can be another copy of the same locus ***A*** or a copy of an allele at a

846 second locus ***B***, and it can be in the same individual as G_1 or in a different individual.

when paired with partner allele

A Same locus **a**

B Other locus **b**

Fitness payoff to allele:		G_2=1	G_2=0
	A G_1=1	$w+s_1+s_2+s_{12}$	$w+s_1$
	a G_1=0	$w+s_2$	w

847

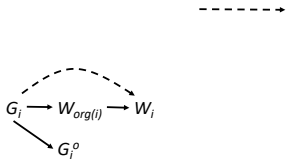
848

849

850 Fig. 3. Gene copy *i* usually exerts its effects on genic fitness via the mediating cause

851 of organismal fitness of $W_{org(i)}$. But in the case of selfish genetic elements, there is

852 also a direct path from genic value to fitness (dashed line).



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855 **Tables**

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Type of G_2 partner in relation to G_1	$\mathrm{Cov}(G_1, G_2)$ or β_{G_1,G_2}: co-replicator's association with G_1, from either: 1. staying together or 2. coming together	s_{12}: co-interactor's non-additive interaction with G_1
Same locus in same individual	Inbreeding coefficient: 1. mating with kin 2. assortative mating	Dominance
Another locus in same individual	Linkage disequilibrium: 1. linkage 2. preference for mate traits	Epistasis
Same locus in another individual	Relatedness coefficient 1. local kinship 2. partner choice	Social dominance
Another locus in another individual	Role association: 1. co-transmission 2. partner choice	Social epistasis
Environmental factor	Gene-environment correlation 1. limited dispersal 2. habitat choice	Gene-environment interaction

857 Table 1. Co-replicator associations and co-interactor interactions for different kinds

858 of gene interactions. Associations can arise in two ways: 1) staying together and 2)

859 coming together.

860