METAPHYSICAL FAILINGS OF THE GENE IN THE ERA OF CRISPR-CAS9

by

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ABSTRACT

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While conversation surrounding genetic editing has been present in ethical literature throughout the 20th century, the topic exploded following the introduction of CRISPR-Cas9 technology (CRISPR). This technology represents a realization of a long-held hypothetical: bettering the human species through genetic editing, with adaptiveness serving as the measure of "betterment." In this paper, I show that we can understand this technology at three levels of analysis (LOA): (LOA-1) as a physical intervention, (LOA-2) as a consequence and test of conceptual evolutionary models and theoretical commitments, and (LOA-3) as a representation of foundational ontological models within biological theory. Analysis of orthodox accounts of CRISPR at these three levels reveals a tension between the metaphysics of biological theory and pragmatic use of this theory in genetic editing. I demonstrate that this tension arises because of the interrelation between the levels. Specifically, CRISPR cannot be used to intervene on adaptiveness under the orthodox account because of its unsuccessful ontological presuppositions.

TABLE OF CONTENTS

LIST OF FIGURES

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0 Introduction:

While conversation on genetic editing has been present in ethical literature throughout the 20th century, the topic exploded following the introduction of CRISPR-Cas9 technology (CRISPR) (Schultz-Bergin, 2018).[1] CRISPR allows for specific edits to be made to DNA. Possible edits could include deleting, inserting, or swapping out certain DNA segments depending on the desired edit.[2]

This introduction of a practical method for editing the gene turned ethical considerations into maifest problems as this technology represents the realization of a long-held hypothetical: the"betterment" of the human species. While the concept of betterment through genetic editing may be ethically controversial, this is not so in biology, where the betterment of a species is simply a measure of adaptiveness (Angeler et. al, 2019).

However, if genetic editing is to be understood in this uncomplicated sense, then we must understand CRISPR as a method of intervening on adaptiveness. The standard account would suggest that CRISPR is an intervention on adaptiveness because it modifies material DNA. Under this account, adaptiveness is just a measure of variability in material DNA. However, I argue that the standard view of adaptiveness, the gene-centered view (GCV), can't be successful as its understanding of the gene is flawed from the start.[3] This understanding fails at three levels

[1] CRISPR (Clustered Regularly Interspaced Palindromic Repeats) were first detected in *E. coli in 1987 by* Yoshizumi Ishino, serving as a natural immune response in bacteria (Barrangou, 2007). In 2012, Jennifer Doudna, Emmanuelle Charptenier, and their respective teams honed in on this innate bacterial response and manipulated it for artificial genetic editing in eukaryotic cells (Isaacson, 2021).

[2] A detailed mechanistic explanation is as follows. Required components for artificial editing with CRISPR are: i) a target segment of DNA for the desired edit ii) Cas9, or CRISPR Associated Enzyme 9 iii) a synthesized RNA strand, single guide RNA (sgRNA) sgRNA is first synthesized by researchers to guide Cas9 to the target DNA (Dounda, 2017). The Cas9-sgRNA complex binds to the target DNA and cleaves the DNA backbone, creating a double stranded break (DSB). After DNA is cleaved, the desired edit can take place (Anzalone et. al, 2020) Non-Homologous End Joining (NHEJ) mechanisms take place to repair the DSB and the process is complete.

[3] This term is not my own, I'll simply use GCV here to describe this specific understanding of the gene. There is no one standardized account of the GCV. There are several specific accounts, the earliest of which appears to be Keneth Water's interpretation, though this account is less rigid than my understanding. (Waters, 1994).

of analysis (LOA) with each successive failure explaining the previous, more narrow failure: LOA-1 as an account of how CRISPR is an intervention on adaptiveness, LOA-2 as an account of adaptiveness in general (which explains LOA-1), and LOA-3 as a deeper metaphysical commitment as to what the gene *is* within the philosophy of biology (which explains LOA-2).

The paper proceeds as follows. In Section 1, I introduce the concepts of adaptiveness and heritability. I also make the distinction between adaptiveness of a species and adaptations of an individual. In Section 2, I argue that at LOA-1, by its own presuppositions, the GCV fails to represent CRISPR as an intervention on adaptiveness. Should intervention proceed, three results could arise: detrimental intervention on naturally-occurring mutations, decreased biodiversity, and lowered ability to accommodate for environmental perturbations.These results represent lower adaptiveness of a species, contradictory to the posited goal of "betterment."

In Section 3, I argue that the flaw at LOA-1 can be explained by the flaw at LOA-2, or an incorrect account of adaptiveness. This flawed account can be attributed to an overly-constrained account of heritability, a phenomena closely intertwined with adaptiveness. The GCV assumes that only heritable information can influence adaptiveness. Such heritable information of influence must originate, and be contained within, a mutated gene. I will show that these assumptions are false using the phenomena of broad-sense epigenetics and transgenerational inheritance of maternal behavior.[4]

In Section 4, I show that the failures in LOA-1 and LOA-2 can be explained by a failure at LOA-3: the flawed metaphysics of the GCV. The GCV posits a decontextual, particular, and static gene, three features only a substance metaphysics can endorse. It must presuppose these features of the gene or editing using CRISPR would be incoherent. For this, I refer again to

[4] There are a variety of definitions of epigenetic inheritance, here I will take it to mean any inheritance that occurs outside of the gene, including extracellular inheritance.

broad-sense epigenetics and transgenerational inheritance of maternal behavior. I show that the gene cannot be understood as decontextual, particular, or static.[5] So it follows, the metaphysics of the GCV is fundamentally flawed.[6]

1: Adaptiveness and Inheritance:

Adaptiveness is the ability of a species to respond effectively to a dynamic environment. CRISPR explains adaptiveness in terms of expressed traits. For a trait to be of adaptive significance, it must be stably heritable, or able to be passed down from parent to progeny over the course of several generations (Lamm, E., & Jablonka, E., 2008) (Jablonka & Raz, 2009).[7] While this account of adaptiveness is relatively uncontested, the idea of heritability, primarily what information *can be* heritable, is controversial, a topic I will return to in §3.

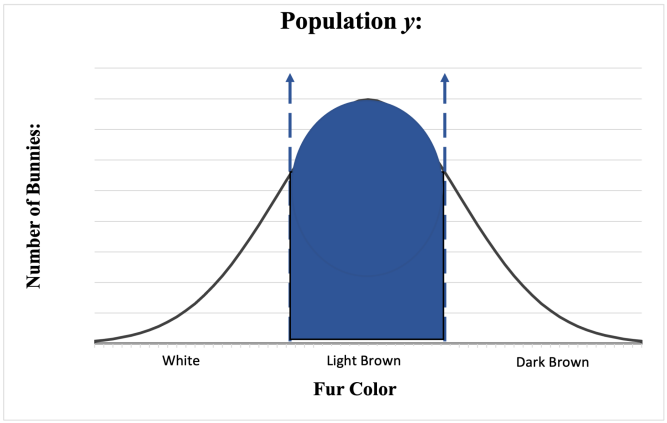
For now, I will just focus on adaptiveness. While adaptiveness occurs at the species level, adaptations occur at the individual level. Adaptations are best understood as selected traits. Adaptiveness can be understood as a measure of biodiversity of a species, or greater variation in trait expression. The greater the biodiversity of a species, the greater the adaptiveness. While what constitutes biodiversity may vary among accounts, biodiversity, itself, as a measure of adaptiveness is relatively undisputed (Frankham, 2005).

We look to adaptiveness to describe a species and to adaptations to describe individuals. Adaptations are expressions of a trait in an individual that allow it to more effectively interact with its current environment. Usually, effective interaction is measured by the number of viable offspring an individual can produce, known as reproductive fitness.[8]

[5] "Particular" taken to mean spatiotemporally localized and I adopt Penn's use of entities as referring to generic metaphysical knowables (Penn, Forthcoming) (Seibt, 1990).
[6] A substance metaphysics will hold that the fundamental entities are things. By contrast, a process metaphysics denies fundamental entities as *things* per se and instead holds that the only fundamental entities are processes or interactions.
[7] Heritable can be taken to mean stabley heritable throughout this paper.
[8] While fitness can have a variety of meanings, reproductive fitness (number of viable offspring produced) is the typical measurement (Kosova, et al. 2010). Reproductive fitness has no one quantifier; there are many factors of influence. Traits that allow for longer lifespan, and more years to reproduce, or traits that allow an individual to gather more resources and thus have more viable offspring, are just a few examples of traits that can result in greater reproductive fitness.

Such traits in individuals that increase reproductive fitness are usually selected for by evolutionary forces and, as a result, become more prevalent throughout the population. There are several different trait selection patterns that can result: stabilizing selection, disruptive selection, and directional selection. Each will be discussed in succession.

Graph I depicts stabilizing selection within a population, a geographic subset of a species. To best exemplify stabilizing selection, assume there is a population (Population *y*) of bunnies in a residential area ranging in fur color from white to dark brown. Population *y* began as a population of exclusively white bunnies. Over generations, the color spectrum broadened to include more coloring options. I will return to this broadening phenomena in §1.1.



Graph I: Graph displaying stablizing selection in a normally distributed Population y. The zone of selection, shaded in blue, represents the expression of adaptation x being actively selected for by evolutionary forces.

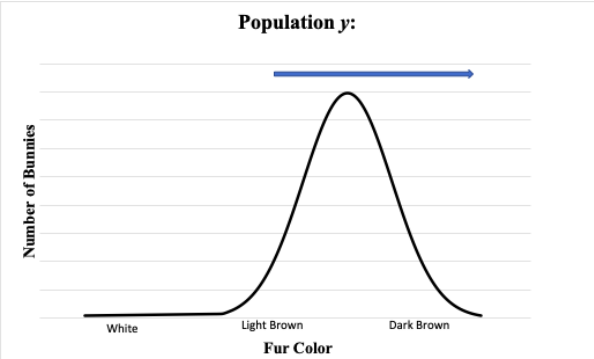
In this population, the white bunnies are easily spotted and predated upon by local coyotes and the dark brown bunnies' fur allows for greater heat absorption. Because of this,white bunnies are more susceptible to death by predation and dark brown bunnies are more susceptible to death by overheating. But light brown bunnies, falling right in the middle of the color spectrum, are less easily spotted by predators and don't have difficulty regulating heat, so they tend to survive longer and have more viable offspring. Over time, the number of light brown bunnies increases. This trait, in the middle of the spectrum of expression, is stably selected for. This selection window is displayed in Graph I.

While light brown bunnies have the greatest reproductive fitness, greater biodiversity is \still beneficial for a species even if it may be disadvantageous to an individual. Even in examples

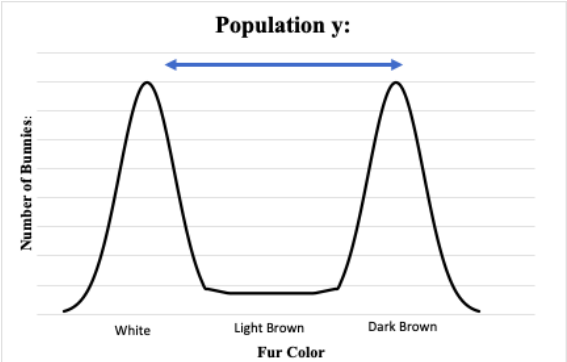
of stable selection, where one trait is heavily selected for, other traits are rarely eradicated entirely. This will be important to note later when we arrive at the dynamic changes of the trait selection window in response to the environment. For now, simply notice that the bunnies tend to be light brown, but that white and dark brown bunnies are still born and survive.

Now suppose there is a shift in the selective forces on Population *y* as a result of an environmental perturbation. E.g., there is a new housing development in town, bringing an influx of residents in. Residents are unable to see light brown bunnies when driving and often hit and kill them with their cars. However, they can easily spot white or dark brown bunnies. If there were only light brown bunnies, this population might not be able to survive this environmental flux. But, because there are still white and dark brown bunnies present, the population can accommodate this change. The selective forces on Population *y* have now shifted and represent a different perturbation the population must accommodate for survival.

Notice the distinction between adaptiveness and adaptations in this case. Greater biodiversity allows for a species with higher adaptiveness. Certain coloring options became adaptations for individuals, allowing them to more effectively interact with their current environment, increasing their lifespan and giving them more time to produce more offspring and, therefore, higher reproductive fitness. But these advantageous coloring options change dynamically with environmental conditions.



Graph II: Display of directional selection. Envirnomental forces shift from the mean and favor one extreme, in this case dark brown fur. Selection in this diection occurs, represented by blue arrow.



Graph III: Display of disturptive selection. Environmental forces shift away from the mean and towards both extremes, in this case white and dark brown fur. Selection in both directions occurs, represented by blue arrow.

Such environmental changes as above result in two different types of selection, directional and disruptive.

If deaths by predation are as high as deaths by car, while deaths by heat regulation are quite low, directional selection may result (Graph II). Alternatively, should deaths by car outweigh deaths by predation and by heat regulation, disruptive selection may take place, in which both extreme fur colors are selected for (Graph III). This would shift the selection window towards dark brown bunnies and white bunnies.

These alternative selection options exist only because of biodiversity within the population. There is a wider net of environmental change the population can cope with (Frankham, 2005). Biodiversity determines the size of this adaptiveness net. Adaptive traits in an individual can often be contrasting and context specific while the adaptiveness of a species represents a wide range of differential trait expression. This is why, though there is often a window of selection, traits outside of this window aren't always eliminated. Adaptations in every individual don't always promote adaptiveness in a species.

The two must be analyzed distinctly. In order to understand adaptiveness, one must look to a distribution of traits across a population, not just to an individual.

1.1: Adaptiveness Under the Gene Centric View:

Adaptiveness and heritability, as commonly accepted in the scientific community, are gene-centered phenomena. This means that heritable information that can influence adaptiveness is understood to be contained within the molecular genes of an individual. Under this understanding, molecular genes are synonymous with DNA nucleotides. Genes are the unit of analysis for individuals while the frequency of these genes is the unit of analysis for a species.[9] The gene determines expression of traits, which will vary within a range depending on the environmental conditions an individual is exposed to. I'll refer to this understanding of genes and trait expression as the gene-centric view (GCV). I'll also refer to the understanding of the molecular gene, as synonymous with DNA nucleotides, as the gene_{GCV}.

While §1 describes a general understanding of adaptiveness, I have not yet provided an interpretation that allows us to actually analyze adaptiveness. For such an interpretation, we need to move to the GCV-specific understanding of this phenomena. The GCV uses differential gene frequencies as the unit of analysis to measure adaptiveness. Biodiversity is understood as genetic variability under the GCV. The greater the biodiversity within a population, the greater the probability of having a genotype able to cope with environmental perturbations, as seen in the bunny example above (Oliver et. al., 2015). This variation is measured using relative genotype frequency. Both forms of measurement have hard boundaries: either an individual has a genotype of interest, or they do not.

[9] Usually the unit of analysis is said to be allele frequencies. While not entirely synonymous, gene frequencies and allele frequencies can be understood interchangeably for the purpose of this paper.

Recall that the GCV also holds that adaptations must be stably heritable. If a trait cannot be passed down from parent to progeny, it cannot be of significance to the population. The GCV holds that stably heritable information is contained entirely within material genes. Bodily cells of a parent (somatic cells) are not passed to progeny. Only certain cell types (germline cells) are heritable under the GCV. These germline cells are already contained within an individual before birth: the genes of interest are understood as existing on chromosome pairs, one from each parent, made up of DNA nucleotides. This genetic makeup will be present and pre-determined in the zygotic stages of an individual. Any interactions the organism has with its environment throughout its lifetime will be present only in somatic cells, therefore not passed to progeny.[10] Under the GCV, these interactions of an individual cannot influence adaptiveness. While the GCV will still hold that individuals can dynamically interact with their environment through other mechanisms, these interactions do not translate into genetic adaptiveness as measured by gene frequencies.

Back to bunnies. Genetic variability is essential for species survival yet the above implies that the genes already present within the population are the only ones that can exist. No more variation can be attained. But, greater biodiversity can actually be achieved in multiple ways. To the GCV, the most important way is the acquisition of random, heritable, DNA mutations in germline cells that are then selected for. Refer again to Graph I, remember Population *y* began with exclusively white bunnies. The GCV would explain the broadening in color expression as the occurrence of a random mutation in some gene(s) that resulted in dark brown fur. Dark brown fur, less susceptible to predation, was selected for.

[10] Unless the environment causes a mutation in zygotic cells.

Because of overheating, however, both white and dark brown bunnies were maintained in the population. Over time, more mutations occurred and resulted in a wider color spectrum, or more variation. While this variation was eventually selected for, it was rooted in a random mutation in some gene(s). Under the GCV, evolution is simply an accumulation of random, heritable mutations that are selected because they so-happen to serve as adaptations in an individual in its current environment. In other words, these adaptations are selected because these heritable mutations, present in an individual at birth, bear the appropriate static relationship to the species' current envirnoment. This discounts any role of development or any information an individual may have acquired over its own life-cycle that better acclimates it to its environment.

2: The Gene Centric View and CRISPR Failures:

The presumed goal of CRISPR is increased adaptiveness of the species, or aiming to edit $genes_{GCV}$ to make a "better" species. Because CRISPR operates by editing molecular genes, and this material editing is the intervention mechanism in question, CRISPR must presuppose the GCV; CRISPR requires *something* to edit and the GCV posits that thing: the $gene_{GCV}$

I argue that the GCV fails, by its own account, to represent CRISPR as an intervention on adaptiveness. CRISPR aims to edit the $genes_{GCV}$ of individuals. The goal is to better the species by editing for adaptations that make the individual more suited to current environmental conditions. Here, there is an assumption that editing for adaptations in an individual's $genes_{GCV}$ will, in turn, lead to a species with greater adaptiveness. It is this conflation of adaptations and adaptiveness where CRISPR under the GCV fails.

Under this presupposition, CRISPR usage could result in three failures of this presumed goal: detrimental intervention in naturally-occurring mutations, decreased biodiversity, and the lowered ability to accommodate for environmental perturbations. These three failures result in lower adaptiveness of a species, contradictory to the goal of CRISPR.

2.1 Detrimental Intervention in Naturally-Occurring Mutations

As discussed in §1.1, mutations are the main source of increasing biodiversity for the GCV. While mutations may be disadvantageous to an individual, they are essential to the adaptiveness of a species under the GCV. If a species no longer has the ability for individuals to accumulate heritable mutations, the gene pool will become stagnant and the species will be more susceptible to environmental perturbations.[11]

Mutations are often categorized as beneficial, neutral, or deleterious. When considering environmental interactions, however, these distinctions aren't always so clear. Some heavily mutated areas of the genome are not well understood, yet seem to serve both beneficially and deleteriously. An example of this is the major histocompatibility complex (MHC). Important in immune responses, the MHC carries many mutations that allow for infection detection but are also associated with diseases such as cancer or schizophrenia. These mutations seem to "piggy-back" on one another: altering one may alter another. Such alterations are often unpredictable (Kozubek, 2017). Jim Krozubek says the following on the subject, in reference to $genes_{GCV}$ correlated with neurodiversity:

> Furthermore, genetic variants that predispose us to risk or supposed weaknesses are precisely the same ones that turn out to have small fitness advantages (they make us better at numbers, more sensitive, alter concentration…). This is one reason I am a "neurodiversity advocate." Evolution works at the margins, and it does so through trade-offs: Often, you don't get an advantage without risking a disadvantage. This is not trivial. (Krozubek, 2017)

[11] Assuming a sexually reproducing species with no gene flow between populations.

As Krozubek states, a mutated $gene_{GCV}$ is not always exclusively deleterious or beneficial There is often context-dependent overlap, which the GCV does not consider when utilizing CRISPR.[12]

The GCV holds that biodiversity is a statistical measure that occurs as a random distribution of traits. Novel traits are brought into expression by initially random, heritable mutations. When editing takes place in the $gene_{GCV}$, an intervention on adaptiveness can occur, but one that can only result in a stagnation or decrease in biodiversity. Importantly, I am not attempting to argue that intervention on individuals cannot result in *any* change in adaptiveness. Instead, I argue that assuming that editing for adaptations in individuals as yielding a definite and predictable change in adaptiveness is incorrect. *Conflating* adaptations and adaptiveness is the issue, *acknowledging a relation* between the two is not.

Stagnation occurs when we eliminate novel random mutations, or the primary mechanism of adaptiveness on the GCV's account. I will return to this shortly. Alternatively, reduction occurs through the selection of certain existing traits and choosing to eliminate them from the gene pool through artificial mechanisms such as selective breeding (or genetic editing). We will see this in §2.2.

Artificial gene editing is an entirely human phenomenon. Humans will only selectively reduce the number of random mutations in an individual and, over time, the population. Gene editing is performed with the intention of eliciting some known effect, not to introduce novel mutations into the gene-pool. So, implementation of artificial editing techniques will destroy

[12] CRISPR has the ability to edit mutations in the gene. While what mutations one ought, or ought not, edit for is a topic heavily discussed in ethics, I don't wish to make an ethical argument here, but a metaphysical one. To mount this argument, we needn't assume what one would or wouldn't edit for, simply that an edit in the gene can take place.

random distribution of traits in favor of non-random distribution, a trait distribution artificially selected for humans by humans.

This correction of a mutation may seem like a positive feature of CRISPR, as mutations can be deleterious. However, this is not always the case. For one, the mutation may serve some unknown beneficial feature for the individual. Or, perhaps the interactions that mutation will have is unknown and altering one mutation will have unpredicted effects, as in the example of theMHC above.[13] If CRISPR becomes widely implemented, and mutation correction occurs at a statistically significant level, a closely monitored and corrected genome will not allow new mutations to occur. Without mutations, the gene pool becomes stagnant and unable to react and respond to its environment.

Let's return to our population of bunnies. Assume an idealized world where most bunnies have access to prenatal CRISPR for germline cell editing. In this assumed time-frame, only white bunnies exist. Two bunny parents are anticipating the arrival of their bunny baby. During the typical CRISPR screening, Dr. Bunny notices a mutation in the $gene_{GCV}$ of the embryo. This mutation would go on to code for dark fur, but this was unknown at the time. The mutation was novel and it was unknown if it could have been deleterious. The parents utilize CRISPR to correct the mutation and it is not introduced into the gene pool.[14] The gene pool remains stagnant. Then, there occurs a mild winter during which coyotes were able to hunt for a longer period of the year, increasing predation. While a bunny population with a wider range of fur color could accommodate for this shift, this population is unable to and eventually dwindles. A

[13] Sickle cell anemia is an example of a concurrently beneficial and deleterious mutation. This condition can cause frequent episodes of pain and a lower life expectancy. However, it also provides a significant benefit: protection against malaria (Luzzatto, 2012).

[14] This is a hypothetically selected trait. Color expression can often be complex and interactive between $gene_{gcv,}$ not controlled by a single base pairing.

small population size is a risk to species survival as it has less adaptive capacity. Here, CRISPR fails to promote adaptiveness, contradicting its stated goal.

The above represents a stagnation in biodiversity, a risk to species survival, but not a reduction in it. This reduction is the second failure of intervention: decreased biodiversity.

2.2 Decreased Biodiversity

As discussed in §1.1, the GCV posits that biodiversity is not only beneficial for a species, but essential to survival. Referencing Graph I, it is often advantageous for a species to have a wide spectrum of trait expression. This allows for a wider net of environmental perturbations a population can compensate for. Biodiversity allows for natural selection to utilize its "creative" power (Griffiths and Stotz, 2013).

§2.1 focused on stagnation of biodiversity via overcorrection of novel mutations that could be added to the gene pool. But CRISPR usage could cause not only *stagnation* of biodiversity but *reduction* of it as well. Recall that adaptations are usually quantified as traits that bring about greater reproductive fitness in an individual. Since CRISPR aims to edit for adaptations in the effort to better the species, it will aim to edit out traits that could result in lowered reproductive fitness, such as a disease that shortens lifespan, leaving an organism with less time to reproduce.

With traits that lower reproductive fitness being targeted to edit out, the resulting gene pool will be more homogenous, with decreased biodiversity. It bears repeating that this is not just the stagnation as seen in §2.1, but a reduction of biodiversity by elimination of a trait. With most traits that result in disease, this seems beneficial. But, remember that biodiversity is essential for evolution to occur and for species survival, even when detrimental to the individual.

As the gene pool becomes more homogenous, biodiversity decreases, and susceptibility to harmful environmental perturbations increases.

To see this reduction in biodiversity, we will leave our hypothetical bunnies and instead consider the Irish Potato Famine. During the mid-19th century, potatoes were a staple crop in Ireland. Only a single variety of potato was grown, the Irish Lumper, because of their size, nutritional content, and ability to thrive in the relevant environment. In 1843, the organism *Phytophthora infestans* began to spread quickly via wind spores to potato crops in New York City, causing decay of the plant. Shortly thereafter, most likely from a shipment of potato seeds across the Atlantic Ocean, *P. infestans* reached Europe and had the same effect. Despite affecting potato crops in all countries, Ireland suffered the most, losing half and three quarters of the crop in 1845 and 1846, respectively. The reason Ireland was so affected was because of its reliance on Irish Lumber: "The lack of genetic variability in the Irish potato population created a susceptible host population for the organism." (Powderly, 2019). In other countries, there were multiple potato strains. This left room for strains that had more resistance to *P. infestans*. As we can see, the ability of a population to compensate and adapt to environmental conditions is related to diversity present in the population.

When this strand of potato was selected for, biodiversity decreased and the gene pool of potatoes became quite homogenous, The population couldn't cope with an environmental perturbation, in this case, infestation. There was no over-correction of mutations that *could have* brought about novel traits into the population, as seen in §2.1, but instead an elimination of existing traits in the form of potato strains.

This intervention failure is closely intertwined with that of §2.1. The reduction of

biodiversity seemed positive, the Irish Lumper thrived in its environment. But in actuality, the disregard for potential changes in the environment, or the assumption of a static relationship between individual-species-environment, led to a population at risk.

2.3 Lowered Ability to Accommodate for Environmental Perturbations

Our final failure of intervention focuses on the assumption of a static environment, as seen in §2.2. Under the GCV, CRISPR is able to manipulate many traits in or out of the gene pool. In *Altered Inheritance*, Francoise Baylis suggests editing $genes_{GCV}$ to address the current concerns facing our species, such as climate change (Baylis, 2019). Baylis posits the selection, or creation, of a $gene_{GCV}$ that evokes a red meat allergy in humans. This would lower greenhouse gas emissions from farming.

Evolution by Baylis's suggestion would mean adjusting future generations to meet current conditions, assuming these conditions will persist unchanged.

But this is not an accurate understanding of evolutionary trends. General trends in evolution enhance adaptiveness of a species to a current *and future* environment (Carroll, 2001). Using CRISPR to edit to better adapt to current environmental conditions assumes our environment will remain as is and the current $genes_{GCV}$ are, and will always be, best suited to that environment.

But, environments are never static. Every CRISPR edit would be reactionary to a current environmental condition that may or may not persist into the future.The altering of traits to better meet current conditions does not allow greater adaptiveness to an environment constantly in flux. The GCV assumes that the most accurate causal control of traits comes from the editing of a molecular gene, not modifying the environment (Waters et, al., 2006).

Neglect of the environment is erroneous as even minor environmental differences can yield significant effects on traits (Waters et, al., 2006).

To strengthen this claim, suppose Baylis' suggestion is adopted. A $gene_{GCV}$ is edited such that humans with this $gene_{GCV}$ are allergic to red meat. This seems advantageous as greenhouse gas emissions from animal agriculture are a current threat to humans. Assume, over generations, CRISPR is very successful and most humans are now allergic to red meat. A new strand of disease spreads rapidly, affecting crops and farm animals alike. Most cows happen to have a naturally acquired resistance to this disease and are still viable options for human consumption. However, since most humans are allergic to red meat, the species cannot accommodate for this environmental perturbation, similar to the Irish potato famine, and the species is at risk.

This concern is closely connected with the reduction in biodiversity in §2.2.. The difference here is what *brought about* that reduction. In §2.2, an existing strand of potato was selectively bred, resulting in a reduction of natural biodiversity. In Baylis's example, our current environmental conditions are assumed static: the environmental threats that face us now will continue to face us. A trait, allergy to red meat, is manipulated and introduced into the population, resulting in an artificial reduction of biodiversity in the hopes of addressing the concern of greenhouse gas emissions.

3: What The Gene Centric View is Committed to: Flawed Heritability

Section 2 assumed the GCV's tenets to be correct. Even by its own account, the GCV fails to represent CRISPR as an intervention on adaptiveness. This failure is indicative of a larger flaw, an incorrect account of heritability. Recall §1, where this phenomena was first encountered.

There, we saw that successful intervention on adaptiveness requires a correct account of heritability.

The GCV, however, holds two demonstrably false positions on heritability.

Throughout this section, the term "information" can be taken to mean any changes an organism acquires within their life-cycle or through inheritance that results in some differential trait expression (i.e germline mutations, acquired traits, etc.). Remember that, while heritability is not sufficient for adaptive significance, it is necessary; if information cannot be passed down from parent to progeny, it is not able to have a species-wide effect. So it follows that a flawed account of heritability will lead to a flawed account of adaptiveness.

The GCV presupposes the following on heritable information: **i)** Heritable information must originate as a mutation in the $gene_{GCV}$ of a germline cell **ii)** Only heritable information that originates through **i)** can have a species wide effect. I will use broad-sense epigenetics (E_{BS}) to discredit presupposition **i)** and transgenerational inheritance of maternal behavior to discredit presupposition **ii).**[15]

3.1: Broad Sense Epigenetics (E_{BS})

The GCV holds that only somatic cells will reflect environmental perturbations.[16] Under the GCV, these cells are not heritable and changes within them are not reflected in the $gene_{GCV.}$ This means that any information an individual acquires during its life-cycle cannot be of adaptive significance.

E_{BS} is an example of heritable information in an organism that did not begin as a selected mutation. Instead, this change is reflected in differential phenotypic expression in an individual.

[15]So as to not strawman the GCV, it is important to note that most GCV proponents would not deny the existence of epigenetic inheritance. However, they may deny it being stably inherited, and having adaptive and evolutionary significance, (Griffiths and Stotz, 2018). As noted in Footnote 2, heritability is taken to mean stable heritability for the duration of this paper. It is worth noting that epigenetics have been shown to be stably inherited (Lamm, E., & Jablonka, E., 2008) (Jablonka & Raz, 2009).

[16] Certain perturbations, like exposure to radiation, can affect germline cells.

This expression is a direct response to an environmental perturbation. Genetic assimilation, a type of E_{BS}, best captures this.

Genetic assimilation is described as the conversion of information acquired within an individual's lifetime into information that is heritable (Waddington, 1961). Experimentally, this was first captured by C.H Waddington using *Drosophila melanogaster*, or fruit flies.

Waddington exposed a subpopulation of fruit flies to high-temperatures after a critical developmental stage. Some individuals of this population developed a novel, abnormal phenotype; differential crossvein expression on their wings. Because this heat-exposure occurred far after the embryonic stage, this is acquired information and is not reflected in germline cells. When this subpopulation of flies was selectively bred, the abnormal phenotype was produced even without high-temperature exposure (Waddington, 1961). In other words, the phenotype was heritable and stably so; when selected for, it persisted through several generations.

The wing pattern was acquired as a direct response to a novel environmental condition: heat exposure. This abnormal wing pattern in fruit flies was not the result of a random mutation. This exposure also took place post-embryonic stage, so the GCV must say that this acquisition is not reflected in germline cells. Genetic assimilation is an example of heritable information that did not originate as a random mutation in the $gene_{GCV}$ of a germline cell. This is not possible under the GCV and as such, presupposition **i)** cannot hold.

3.2: Transgenerational Inheritance of Maternal Behavior

So much for presupposition **i)**. Recall presupposition **ii):** Only heritable information that originates through **i)** can have a species wide effect**.** The focus of §3.1 was the acquisition of a trait from an environmental stimuli. The focus of this section is the *persistence* of such an

acquired trait. The acquisition I'll focus on is transgenerational inheritance of maternal behavior.

Postpartum care of offspring, and how this may affect the development of that offspring, is well covered in scientific literature, particularly in anxiety responses in rats (Champagne, 2003). Maternal care (e.g licking patterns, access to resources for pups, social behavior) that female offspring receive can be passed down to *their* respective offspring as well (Champagne, 2008). This means the maternal behavior a rat exhibits to her daughter can be stably inherited by her granddaughter and following generations. This resembles E_{BS} in that a stimulus *brought about* some heritable trait. But here, instead of how the trait was *acquired,* the focus is how the trait *persists.* Researchers who study parental effects have found that some parental behaviors do persist as they are also stably inherited.[17]

Inherited maternal behavior is an example of a trait that resulted extraneously, acquired from behavior, that has the capacity to have a species-wide effect. While proponents of the GCV would not deny that epigenetic inheritance can take place, they would deny that this type of inheritance could have such a species-wide effect. Thus, presupposition **ii)** cannot hold.

4: Flawed Metaphysics: .

Section 2 displayed the GCV as failing to represent CRISPR as an intervention on adaptiveness (LOA-1). §3 showed that a flawed account of heritability might explain such failings, as a flawed account of adaptiveness will follow from a flawed account of heritability (LOA-2). In this section, I discuss the failure at LOA-3, the metaphysics of the GCV, which explains why the GCV cannot provide an adequate account of heritability.

[17] It is important to note that evolutionary models suggest that even traits that are not stably inherited can have a species wide effect (Griffiths and Stotz, 2018).

The GCV holds the following three tenets: **a)** the $gene_{GCV}$ is a particular entity back to which all trait expression can be traced. **b)** the $gene_{GCV}$ and its expression can be understood absent of environmental context**. c)** the $gene_{GCV}$ can bear a static relationship to its environment

I'll begin with tenet **a)**, which holds that all expressed information must be localizable to a material segment of a $gene_{GCV}$ or interactions between $genes_{GCV}$. The $gene_{GCV}$ can be understood as a particular, material unit with clear boundaries (DNA nucleotides). I need to show that the gene is not particular, all expressed information cannot be traced back to some material heritable entity. For this, I'll return to the example of transgenerational maternal behavior first covered in §3.2.

Meredith West and Andrew King found that certain development processes an organism is introduced to in its environment can be inherited, stabley so, even though these processes are *not* encoded in the genome of an individual.

These processes, termed developmental niches, include transgenerational maternal behavior. Researchers cannot "point" to any segment of a rat genome and spot where/how these processes are inherited, despite the fact that inheritance does occur. (West and King 1987).

This means that some aspects of heredity cannot be localized, and do not exist as entities.[18] In other words, developmental processes are inherited as such, as processes *not* particulars. Thus, heritability itself can not be understood as something contained within a particular unit, in this case the $gene_{GCV}$ and tenet **a)** cannot hold.

So much for tenet **a)**, we cannot understand the gene as particular. Tenet **b)** tells us that the relationship between the $gene_{GCV}$ and trait expression is unidirectional, from $gene_{GCV} \rightarrow$ trait expression. In other words, we can understand and accurately predict expression simply from

[18] Some epigenetic inheritance is localized through differential DNA methylation patterns but this is not the case for all aspects of the developmental niche (Griffiths and Stotz, 2018) (West and King, 2018).

analyzing the $gene_{GCV}$ alone. While environmental perturbations can affect *selection* of variants of trait expression, these types of expression are still all encapsulated within the $gene_{GCV}$. This is not to say that the $gene_{GCV}$ does not play an important role in transmission of heritable information in the form of DNA. Depending on the temporal frame of interest, DNA can be stable enough to be treated as a localized entity. However, *transmission* of heritable information through generations is not synonymous with *expression* of information, though it is treated as such under the GCV. The assumption here is that expression options of heritable information can always be reduced to a localized and definable $gene_{GCV}$ or relationships between several $genes_{GCV}$.

To hold this view, the GCV must endorse that one can manipulate a $gene_{GCV}$ absent of environmental context and yield a predictable result; one can understand the $gene_{GCV}$ decontextually. If this is the case, we could not manipulate the $gene_{GCV}$ in virtue of manipulating the environment as that would be a case of bidirectional flow of information. Instead, naturally occurring novelty in expression can only be the result of previously encoded information within a $gene_{GCV}$. To support tenet **b)**, the GCV must hold that the explanatory power for all expressed traits is contained within the $gene_{GCV}$.

Recall §2 where I showed that such an assumption, an edit on the genotype resulting in a predictable phenotype, was not acceptable. This metaphysical tenet is exactly how the GCV must view the $gene_{GCV}$ in order to intervene on adaptiveness using CRISPR.

However, I can further discredit tenet **b).** In order to do this, we need to understand the gene as having bidirectional communication between expressed traits and $gene(s)_{GCV}$. For this, we can return to genetic assimilation, covered in §3.1.

An environmental perturbation, heat-shock, communicated with cells and allowed for a novel phenotype that was not contained originally within the $gene_{GCV}$. The information was then inherited. The GCV would have to concede a bidirectional flow of information: from trait expression (brought about by environment)→$gene_{GCV}$. One could not accurately predict trait expression when considering the $gene_{GCV}$ outside of environmental context. So it follows that trait expression cannot be understood using a decontextualized $gene_{GCV}$ and tenet **b)** cannot hold.

Closely related is the third tenet the GCV holds: **c)** the $gene_{GCV}$ can bear a static relationship to its environment. This static relationship is permissible because of the two features of the gene discussed in tenets **a**) and **b**), as particular and decontextual. Recall that the unidirectional nature of the $gene_{GCV}$ → trait expression means that we can edit a particular entity and yield a predictable result, implying a static relationship between the $gene_{GCV}$ and the environment where trait expression takes place.

The GCV would then have to say that phenomena like genetic assimilation are relational between two entities: the $gene_{GCV}$ and its environment. However, this is not the case, the connection between the gene and environment is not *relational* but *interactional.*

When considering relations, we can treat participants in these relations as particular entities. I've already shown this cannot be the case by discrediting tenet **b)**. Genetic assimilation showed us that we cannot understand the gene in its own right, we need an environmental context. Part of what the gene metaphysically *is* is responding to the dynamic interactions of its environment, and we must understand it as such. For this reason, tenet **c)** cannot hold, the $gene_{GCV}$ cannot bear a static relationship to its environment.

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Instead, the $gene_{GCV}$ should be understood as a dynamic entity taking place in dynamic interactions with its environment.

The idea that one can accurately understand some entity as decontextualized, particular, and static is a key feature of a substance metaphysics.[19] While a substance metaphysics wouldn't deny *relationships* between entities (i.e gene and environment) it would deny the interdependence of the *interactions* between two, that a part of the gene's identity *is* its dynamic interactions with its environment. We saw the importance of this nuanced distinction in tenet **c)**.

So it follows that the GCV holds a substance metaphysics. But, tenets **a)-c)** are inaccurate; the $gene_{GCV}$ is not particular, decontextualized, or static. So, the substance metaphysics underlying the GCV is not an accurate manifestation of the gene.[20] This broad fundamental flaw at LOA-3 affects the narrower flaws at LOA-2 and LOA-1: attempting to understand the gene as a particular, decontextual, and static unit of hereditary leads to an inability to accommodate observable phenomena, like E_{BS} and transgenerational inheritance of maternal behavior. This flawed understanding, particularly the fact that it does not account for the ability of epigenetic inheritance to have species wide effects, leads to a flawed understanding of adaptiveness and what information has the capacity to influence adaptiveness.It is this flaw that leads to an inaccurate representation of CRISPR as an intervention on adaptiveness.[21]

5: Conclusion:

The GCV fails at three levels of analysis. The failure at LOA-1 is a flawed intervention on adaptiveness using CRISPR, with possible detrimental effects to the species. Such effects

[19] Specifically attributable to the "traditionalist" substance ontology (Seibt, 1990).
[20] Here, I move from discussion of the $gene_{GCV}$ to understanding of the gene *outside* of the GCV's account
[21] In the companion paper to this piece, I discuss a positive account for metaphysically understanding the gene, Developmental Systems Theory, (Ford and Lerner, 1992) (Griffiths and Stotz, 2018). There, I provide support for understanding the gene as a dynamic entity and how this understanding allows us to use CRISPR as a successful tool for intervening on adaptiveness.

include stagnation and reduction of biodiversity and the inability to accommodate for environmental perturbations. The failure at LOA-2 is the GCV's constrained view on heritability, which fails to accommodate demonstrable phenomena such as E_{BS} and transgenerational maternal behavior. Failure at LOA-2 explains failure at LOA-1 because an incorrect understanding of heritability will result in an incorrect understanding of adaptiveness (as explained in §1). Failure at LOA-2 can be explained by LOA-3, the substance metaphysics which the GCV presupposes. The GCV understands the gene as a particular entity that can be understood decontextually while participating in static relationships. These are features only a substance metaphysics can endorse and such an account represents an inaccurate understanding of the gene.

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