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Degeneracy allows for both apparent homogeneity and diversification in populations

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Abstract

Trait diversity – the substrate for natural selection – is necessary for adaptation through selection, particularly in populations faced with environmental changes that diminish population fitness. In habitats that remain unchanged for many generations, stabilizing selection maximizes exploitation of resources by reducing trait diversity to a narrow optimal range. One might expect that such ostensibly homogeneous populations would have a reduced potential for heritable adaptive responses when faced with fitness-reducing environmental changes. However, field studies have documented populations that, even after long periods of evolutionary stasis, can still rapidly evolve in response to changed environmental conditions. We argue that degeneracy, the ability of diverse population elements to function similarly, can satisfy both the current need to maximize fitness and the future need for diversity. Degenerate ensembles appear functionally redundant in certain environmental contexts and functionally diverse in others. We propose that genetic variation not contributing to the observed range of phenotypes in a current population, also known as cryptic genetic variation (CGV), is a specific case of degeneracy. We argue that CGV, which gradually accumulates in static populations in stable environments, reveals hidden trait differences when environments change. By allowing CGV accumulation, static populations prepare themselves for future rapid adaptations to environmental novelty. A greater appreciation of degeneracy's role in resolving the inherent tension between current stabilizing selection and future directional selection has implications in conservation biology and may be applied in social and technological systems to maximize current performance while strengthening the potential for future changes.

Keywords

Cryptic genetic variation; Degeneracy; Adaptation; Selection; Evolvability

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1. Introduction

Trait diversity is centrally important to survival and adaptation of populations at all levels of complexity, from molecules and cells (Duncan et al., 2010; Hayden et al., 2011b; Jin et al., 2008; Ogushi et al., 2010) to species and ecosystems (Booy et al., 2000; Whittaker, 1972). Various processes can contribute to the maintenance of heritable trait differences in a population, including balancing selection (e.g. frequency-dependent selection), gene flow between populations, polyploidization, assortative mating, and mutation–selection balance. Population diversity is particularly important for successful adaptation, through the selection imposed by environmental novelty (Fowler, 2008; Jump et al., 2009; Miller et al., 2009; Wiedenbeck and Cohan, 2011). Indeed, should an unexpected change in the environment occur in which a previously well-adapted population becomes less fit, a more diverse population is likelier to provide a fertile substrate for natural selection. Such an event will reshape the population, leading to improved adaptation to (or better fitness in) the new environment. Perhaps the most impressive example of such adaptation to novelty through selection from a diverse population is the adaptive immune system. An individual's adaptive immune system in a higher mammal is represented by an astronomical number of T and B lymphocyte clones, each with a unique specificity for antigen. Such a rich diversity of lymphocytes is the prerequisite for clonal selection of lymphocytes, which successfully clears novel antigens, including those that have been artificially prepared and do not occur naturally (Atamas, 2011; Edelman, 1978).

Despite the benefits of trait diversity, populations often appear relatively homogeneous with respect to most traits; i.e. the variance in quantitative traits is small compared to the change in mean value that can occur following periods of rapid adaptation (Reznick and Ghalambor, 2001). Such homogeneity is common in static populations in stable environments or in environments that change without affecting the overall fitness of the population (Brady, 2003; Ellegren, 2010; Lundberg et al., 1986; Michener and Grimaldi, 1988; Nehm and Budd, 2008; Park et al., 1997; Phipps et al., 1998; Stanley and Yang, 1987). It has been argued that stasis is the predominant mode of evolution (Hansen and Houle, 2004). While the existence of static populations is usually regarded as a trivial consequence of stabilizing selection, explaining how they can respond quickly to sudden environmental challenges is one of the most important unsolved problems in evolutionary biology (Hansen and Houle, 2004). There are, in fact, many examples of species that have been remarkably static over long time periods, but have then undergone rapid phenotypic evolution and genetic differentiation (Eldredge et al., 2005; Estes and Arnold, 2007; Nehm and Budd, 2008).

While many habitats appear stable for prolonged periods and over many generations, all habitats eventually change. Responses such as migration and habitat tracking reduce the frequency but not the inevitability of change. In habitats that remain stable for many generations, populations converge towards the most adaptive trait values, allowing for maximal exploitation of the available resources. The latter benefit may explain evolutionary stasis: mechanisms of stability against random genetic and short-term environmental perturbations – ensuring robustness, or canalization (Siegal and Bergman, 2002) – must have evolved, to “protect” the efficiency of resource exploitation by phenotypically homogenous population. However, the resulting phenotypic homogeneity should limit a population's ability to successfully adapt to novel environmental stresses, and there is an inherent opposition between stable habitat conditions, which reward population convergence to the most beneficial traits, and environmental novelty, which rewards the maintenance of heritable trait differences. Stated more abstractly, there are opposing needs to, on the one hand, maximally exploit currently stable conditions by maintaining trait homogeneity in the population and, on the other hand, to hedge the population's bets about future unexpected environmental changes by diversifying traits (Boyce et al., 2002; Childs et al., 2010).

Similarly, opposing needs for phenotypic stasis and diversification arise within a number of socially and economically relevant non-biological systems that are subjected to variation and selection in a dynamic environment.

In population-based dynamic optimization research (Branke, 2002), evolutionary algorithms are employed where solution parameters to an optimization problem represent a genotype and the corresponding solution performance on an optimization problem's objective function (the function to be maximized or minimized) represents fitness. Using a population of these solutions, the more fit solutions are preferentially mated and mutated to generate new offspring solutions that are selectively bred in the next generation. With a static objective function, populations consistently converge over many generations to eventually display low variance in population fitness and low genetic diversity (Whitacre et al., 2010). However, the more that the population converges, the slower it adapts to changes in the objective function, thereby limiting algorithm performance (increasing time needed for completion of a given task) on dynamic optimization problems. The opposing drives to exploit current problem conditions and to maintain diversity in preparation for future problem changes has been addressed in this field using numerous tools that subvert fitness-biased selection or otherwise encourage trait diversity to be maintained. However, by enforcing diversity, the speed and extent to which the simulated population can adapt to the current problem definition is limited, thus revealing a fundamental tradeoff between short-term and long-term algorithm performance.

Understanding how the opposing needs for phenotypic stasis and diversification are resolved in natural populations could provide insights for reconciling similar opposing needs in operations research (Whitacre et al., 2010), strategic planning (Whitacre et al., 2011), systems engineering (Whitacre et al., 2011), and peer review (Lehky, 2011). Moreover, and as we elaborate later in the article, these issues are widely relevant to ecological conservation efforts and the eradication of evolvable pathogens.

2. Degeneracy Resolves the Apparent Contradiction Between the Need for Homogeneity and the Need for Diversity

2.1. Degeneracy

We propose that the conflict between the need for homogeneity and the need for diversity is resolved through a phenomenon known as degeneracy. Gerald Edelman, whose pioneering ideas have inspired this entire field of research (Edelman, 1978), has defined degeneracy as “the ability of elements that are structurally different to perform the same function or yield the same output” (Edelman and Gally, 2001). In other words, degeneracy is at play when the same function is performed by structurally diverse units of an ensemble (Fig. 1). Degeneracy is only possible if individual units are multi-functional. In biology, degeneracy is ubiquitous. On the molecular level, numerous enzymes, cell surface receptors, or antibodies have been shown to bind not only their principal substrates, ligands, or antigens, but also other molecules that may or may not be similar to these binding partners. As a result, degeneracy is manifested as enzymatic substrate ambiguity, multiple ligand-receptor cross-reactivity, and protein moonlighting (instances of a single protein with multiple functions), in proteins of every functional class (e.g. enzymatic, structural, or regulatory) (Atamas, 2005) and in protein complex assemblies (Kurakin, 2009). Degeneracy is also seen in ontogenesis (see p. 14 in Newman, 1994), the nervous system (Edelman and Gally, 2001), metabolic pathways (Csete and Doyle, 2004), and in cell signaling (Ozaki and Leonard, 2002). On the level of heredity, degeneracy is manifested not only in the well-known degenerate nature of the genetic code but also as degenerate genotype–phenotype mapping, when diverse genotypes are manifested as similar phenotypes and identical genotypes are manifested as diverse

phenotypes. This functional versatility is the defining feature in the multiple uses of organs, such as the use of fins for swimming and crawling. On the level of ecosystems, phenotypically diverse individuals in predator species will consume the same prey and, conversely, nearly or completely identical individuals (twins) will consume different kinds of prey. It is easy to extrapolate this view to social systems, as individual humans or organizations in a society act degenerately, being capable of performing similar functions despite their obvious diversity (Lehky, 2011).

Thus, degeneracy may be defined in relation to, and as an intermediate between, diversity and redundancy (Fig. 1). In degeneracy, diversity is present, but each of the diverse elements is not perfectly unique and is partially similar to other elements of a group. Redundancy is also present, but unlike completely redundant groups, the elements are not exact copies of each other but partially differ. Degeneracy may also be defined as functional micro-diversity of individual elements in a group or population, so that structurally unique elements of repertoires function similarly to other elements. In biological populations, genotypes are diverse, but phenotypes, through their flexibility, are degenerate (Atamas, 2005). A simpler definition of degeneracy equates it to “limited functional sloppiness” of the elements of structurally diverse populations (Atamas, 2003). It is important to distinguish this notion of degeneracy from the process of degeneration defined as deterioration of structure with accompanying decline or loss of function (Mason, 2010).

Degeneracy is a fundamental feature of biological systems, which is centrally important for their reliability and adaptability (Atamas, 1996, 2003, 2005, 2011; Atamas and Bell, 2009; Atamas et al., 1998; Edelman, 1978; Edelman and Gally, 2001; Mason, 2010). Degenerate repertoires are reliable because loss of an individual element will have only a small impact on the whole repertoire, due to the overlapping functionality of multiple elements. Of particular importance for this discussion, degeneracy is also central to selection-based adaptability, because degeneracy allows for modification of a system’s behavior depending on environmental context: degenerate, as opposed to diverse or redundant, ensembles appear functionally redundant in certain environmental contexts but functionally diverse in others (Atamas, 1996; Whitacre, 2010). If degeneracy exists between two functionally versatile units, this means that there will be contexts in which the two units will display behaviors that appear to be functionally the same and other contexts where the two will appear to be functionally distinct (Atamas and Bell, 2009). Degenerate units will manifest diverse, yet functionally overlapping, behavior that is versatile and can occasionally be co-opted within novel environments to display new functional relevance. As we highlight with selected examples below, this functional versatility fundamentally underpins degeneracy and exaptation (an “unintended” functionality arising from selection of a trait for a different use) in complex biological systems. Such a context-dependent similarity in functions/traits among diverse units of an ensemble, and, reciprocally, context-dependent dissimilarity of redundant units is, according to Edelman, “both necessary for, and an inevitable outcome of, natural selection” (Edelman, 1978).

We suggest that degeneracy-driven, context-dependent behavior of ensembles allows for bet-hedging between, on the one hand, the current need to maximize fitness through stabilizing selection in habitats that remain stable for prolonged periods of time and, on the other hand, the need for diversity that will form the substrate for adaptive directional selection should the environment change. Specifically, we argue that cryptic genetic variation is a degenerate mechanism utilized by biological species for such bet hedging.

2.2. Cryptic Genetic Variation

We argue that cryptic genetic variation (CGV) (Clark, 2000; Gill et al., 1993; Omland et al., 2000; Rutherford, 2000) is a specific case of degeneracy (Fig. 2, compare with Fig. 1D) by

which biological species appear to resolve the apparent discord between the need for homogeneity and the need for diversity. In a stable environment, CGV is hidden, with organism phenotypes remaining unchanged despite genetic mutation. Such mutational robustness (stability of the phenotype to genetic mutations) was originally predicted to impede evolution (Frank, 2007; Wagner, 2008) because it lowers the number of distinct heritable phenotypes that are mutationally accessible from a single genotype and reduces selective differences within a genetically diverse population (Wagner, 2008). There is still confusion about the role of CGV in evolution due to long-standing difficulties in understanding relationships between robustness and the adaptive modification of traits. Only in the last decade have arguments been put forth to explain how mutational robustness supports evolution (Ciliberti et al., 2007; Masel and Trotter, 2010; Wagner, 2008; Whitacre, 2011; Whitacre and Bender, 2010). Such support is believed to occur in two ways: (i) in a stable environment, mutational robustness establishes fitness-neutral regions in fitness landscapes from which large numbers of distinct heritable phenotypes can be sampled (via genetic mutations that lead to genotypes that are not members of the neutral set) (Wagner, 2008; Whitacre and Bender, 2010) and (ii) mutational robustness allows cryptic genetic differences to accumulate in a population with the encoded trait differences revealed in an environment-dependent manner (Whitacre, 2011).

Under stabilizing selection, individuals become more phenotypically similar, yet can accumulate (through selectively neutral mutations) genetic differences that have the potential to be revealed as trait diversity should the environment change and directional selection emerge. CGV thus preserves p under stable conditions and satisfies the need for diversity by providing the heritable trait diversity that is necessary for adaptation to new, stressful environments. Although CGV revealed by environmental change has long been implicated as a pathway for adaptation (Hayden et al., 2011a; McGuigan et al., 2011; Waddington, 1942, 1957), its role in resolving tensions between stabilizing and directional selection is not widely recognized. Importantly, by enabling the accumulation of CGV, stable environments may actually support a population's ability to rapidly adapt in new environments. Given the punctuated dynamics of ecosystem regime shifts (Holling, 1986) and the corresponding changes that often occur to habitat range and ecological opportunities, adaptation capabilities afforded by CGV may provide an essential ingredient for the persistence of life in continuously stable and then rapidly changing environments.

In a recent study by Wagner and colleagues using a ribozyme (RNA enzyme) as their experimental model, it was confirmed that ribozyme populations containing cryptic variation adapt more rapidly to new substrates than ribozyme populations not containing cryptic mutations (Hayden et al., 2011a). Another recent study of the three-spine stickleback by McGuigan et al., indicated that CGV enables populations experiencing evolutionary stasis to be poised for rapid adaptation in new environments (McGuigan et al.). In that study, a species was studied that had previously undergone rapid speciation when local populations were introduced to a new habitat. These adaptations were associated with readily observable trait changes that could be directly linked to survival and reproductive success within the new habitat. In their experiments, offspring from the original species were bred under the original and new-habitat conditions. When raised in the original habitat, offspring developed similar traits, while in the new habitat, trait variations were observed that corresponded with those that are beneficial to the new species. Because both populations were bred in artificially controlled homogeneous environments, the observed trait variations could readily be attributed to an environment-exposed release of CGV. In other words, a species in evolutionary stasis with few observable trait differences was shown to undergo rapid evolution using cryptic genetic variation.

2.3. Cryptic Genetic Variation is a Case of Adaptive Degeneracy

Physiological, immunological, cognitive, behavioral, and even morphological phenotypic characters demonstrate performance versatility over numerous environmental backgrounds. Furthermore, specific traits can appear to be very similar across a population in its native environment, and yet selectively relevant differences in these traits can be revealed when the population is exposed to novel stresses. The heritable component of such cryptic trait differences is aptly referred to as cryptic genetic variation. Gibson defines CGV as “standing genetic variation that does not contribute to the normal range of phenotypes observed in a population, but that is available to modify a phenotype that arises after environmental change...” (Gibson and Dworkin, 2004), with “standing genetic variation” defined as the existence of more than one allele for a trait. Thus, by the definitions of CGV and degeneracy, CGV represents a heritable form of phenotypic degeneracy in populations and, as proposed here, exemplifies a more general phenomenon for resolving the opposing drives to maintain homogeneity and to diversify in natural, social, and technological systems.

CGV describes a relationship between genotypic and environment-dependent phenotypic variation, or environment-dependent genotype–phenotype mapping. In populations with CGV, the interactions between individual genotypes and the environment (GxE interactions) are such that organisms can appear phenotypically similar in some environments but phenotypically distinct in others. CGV, GxE, and epistatic interactions provide statistical descriptions of the relationship between genotype, phenotype, and environment. Degeneracy is, by definition, an innate versatility in the physical elements that make up a phenotype and whose selective value can be revealed in the right environment through its changing interactions within a complex biological network. In this way, degeneracy and CGV provide, respectively, bottom-up and top-down descriptions of the same biological phenomena. In agreement with this view, a CGV-driven adaptation may be revealed by looking for beneficial alleles in a new environment that are present as standing variation in the ancestral population (Barrett and Schluter, 2008; Gibson, 2008) or by performing time-intensive experiments where environmental manipulations reveal previously hidden adaptive phenotypes (McGuigan et al.).

2.4. Development of Cryptic Genetic Variation in Natural Systems

The exact evolutionary origins of CGV are unknown, but the following scenario can be readily envisioned. Under this scenario, CGV is initially “inherited” by living systems from physical and chemical properties of underlying macromolecular and supramolecular structures. Then, CGV is captured and preserved by living systems, and itself becomes a target of adaptive evolution. As such, the CGV should be viewed as degeneracy at the following levels of complexity.

Initially, CGV, which by itself represents a subset of degeneracy in general, originates at a lower, less complex, level of degeneracy. The molecular structures underlying living systems are degenerate in the relationships between their structure and function. For example, proteins, such as enzymes, antibodies, or receptors, no matter how specific for their substrates, antigens, or ligands, respectively, function as degenerate binders, and will also bind other molecules, although less specifically (Atamas, 1996, 2003, 2005; Atamas et al., 1998; Calis et al., 2012; D’Ari and Casadesus, 1998; Edelman and Gally, 2001; Hafler, 2002; Khan and Salunke, 2012; Krieger and Stern, 2001; Kupiec, 2010; Lancet et al., 1993; Lazcano et al., 1995; Li et al., 2012; Negishi et al., 1996). At the protein level, ligand binding sites are functionally degenerate for several reasons. The geometry of the binding site can be simple enough (e.g. a flat surface or a simple groove) to accommodate ligands of various shapes, especially if complemented by unsophisticated distribution of hydrophobicity, charge, and capacity for hydrogen bonding. A more complex geometry of

the binding site combined with intricately distributed hydrophobicity, charge, and hydrogen bonding will ensure higher specificity of binding, yet some degeneracy will remain due to the natural conformational flexibility. The folding of the majority of proteins is such that the binding site is flexible and can easily transition between several conformational states. Thus, a given protein will form a population of temporal microstates separated by low-energy transitional barriers, each with somewhat different specificity for ligands. In this population of conformers, individual binders may further diversify following binding of ligands and undergoing ligand-induced conformational changes (induced fit). If a protein has several binding sites, binding of a ligand in one site would affect the binding in a different site within the same protein through similar stochastic choices between different microstates within a range of possible energetically similar conformations. Additional binding degeneracy comes from diverse post-synthetic modifications, such as variable glycosylation, chaperone-assisted folding, or complex-formation with other macromolecules. For a given protein molecule, binding degeneracy is defined by a unique combination of contributions from all these mechanisms.

These are non-genomic roots of binding degeneracy of proteins. Genetic variations in the amino acid sequence will affect all these factors (Betts and Russell, 2003). However, a point mutation substituting an amino acid with a different yet physico-chemically similar amino acid will often remain cryptic, due to the intrinsic degenerate structure–function relationship in proteins. For example, a substitution of a hydrophobic amino acid with a different one, e.g. valine with tryptophane, may not substantially affect binding of “traditional” ligands by a protein. However, it may expand the protein’s ability to bind new, currently not present, ligands. The functional outcomes of this genetic variation will remain cryptic until such new ligands become available. Similarly, changes in protein glycosylation and disulfide bonding stemming from a serine to cysteine (or a reverse) substitution may go unnoticed – cryptic – in a current environment, but become manifest should the environment change in a way that brings the importance of glycosylation or disulfide bonding of the protein to light. These considerations are easily expanded beyond ligand binding or protein stability. Physical durability, flexibility, elasticity, or susceptibility to proteolytic degradation of proteins and protein structures may be similarly affected and remain cryptic until it is revealed by environmental changes, sometimes as subtle as changes in diet (Ledon-Rettig et al., 2010) or temperature (Berger et al., 2011). Similar considerations may be applied not only to proteins but also to other biopolymers and molecular superstructures, as well as whole organs and/or behavioral patterns. In the latter cases, previously cryptic genetic variations are exposed to natural selection not only under direct effects of the environmental stress, but also due to developmental plasticity induced by phenotypic effects of organ “use and disuse” (Palmer, 2011). These considerations suggest, and mathematical modeling confirms, that CGV is likely to be an effective source of useful adaptations at a time of environmental change, relative to an equivalent source of random variation (mutation, recombination) that has not spent time in a hidden state (Masel, 2006; Palmer, 2011). Furthermore, CGV may affect multiple traits, suggesting that reconfiguring existing polymorphisms into novel combinations, rather than selection for new mutations, may lead to rapid evolution of novelty (Lauter and Doebley, 2002).

Thus, CGV originates from the degenerate physical and chemical nature of the components of living systems, as well as from genetic mechanisms. At the next step, CGV by itself becomes the substrate of evolution. One could speculate that if environmental stressors reveal CGV to the benefit of populations faced with environmental novelty, it is conceivable that a sensor of stress would arise, through natural selection, such that it enhances this adaptive mechanism by detecting stress and facilitating phenotypic manifestations of currently cryptic variations. Epigenetic mechanisms – those driven by environmental signals and promoting long-term phenotypic changes without affecting target nucleotide sequences

– centrally contribute to genotype-to-phenotype mapping (Mazzio and Soliman, 2012; Poleshko et al., 2010) and thus may affect CGV. Naturally occurring methylation and demethylation of genes can produce novel phenotypes or hide existing phenotypes (Kalisz and Purugganan, 2004), and so can potentially modification of histones, chromatin remodeling, and activity of non-coding RNAs. It has been suggested that the heat-shock protein Hsp90 centrally serves this function (Mittelman and Wilson, 2010; Queitsch et al., 2002; Rutherford and Lindquist, 1998). Normally, Hsp90, an ubiquitous molecular chaperone, assists in folding of diverse proteins, particularly signal transducers. When its function is impaired, numerous previously silent mutations manifest themselves phenotypically (Chen and Wagner, 2012; Queitsch et al., 2002; Rutherford and Lindquist, 1998; Sangster et al., 2004, 2008; Yeyati et al., 2007). Furthermore, Hsp90 may canalize, or buffer, variability in traits not only by controlling protein folding, but also by suppressing the mutagenic activity of transposons (Gangaraju et al., 2011; Specchia et al., 2010). Thus, Hsp90 serves as an evolutionary “capacitor” that silences phenotypic manifestation of CGV, thus creating conditions for accumulation of cryptic mutations. Under stress, this silencing is broken, and the previously accumulated CGV becomes manifest, offering a rich substrate for natural selection. Thus, Hsp90 has evolved as a promoter of evolvability through making genetic variations cryptic or manifest, depending on the environmental conditions. In an independent example of CVG evolution, CGV has become “captured” in the genomic structures and associated mechanisms responsible for generating the vast spectrum of degenerate immune specificities of lymphocytes as discussed below.

2.5. A Broader View of Degeneracy, Cryptic Genetic Variation, and Evolution

Degeneracy facilitates adaptation at many levels of biological organization (Atamas, 2003, 2005; Edelman and Gally, 2001; Mason, 2010; Whitacre, 2010). In some cases, degeneracy facilitates adaptation through the provision of functional redundancy, whereas in other cases, it provides functional diversity and enables adaptive phenotypic change, as seen with CGV in natural populations (Beverly et al., 2011; Mellen, 2010; Nelson et al., 2011; Ozaki and Leonard, 2002). The adaptive immune response of T cells provides a practical example of degeneracy-driven adaptation that is useful for integrating, yet also distinguishing between, degeneracy and CGV (Tierl et al., 2007, 2010). Naïve T cells typically display similar (inactive) phenotypes under “normal” conditions (devoid of antigens), but can also reveal large phenotypic differences when presented with novel (antigen) environments that, in turn, drive rapid clonal expansion. Because these environment-revealed trait differences are heritable through genetic differences in the alpha/beta chain segments of the T cell receptor (TCR), this cell population is thereby poised to rapidly evolve using cryptic genetic variation (Atamas, 2011).

It might seem then that CGV adequately explains this adaptive response and there is no need to confuse the discussion by mentioning degeneracy. However, proper functioning of the adaptive immune system is vitally dependent on binding ambiguity (loose specificity of binding) between TCR and MHC-antigen complexes found on the surfaces of professional Antigen Presenting Cells (APCs). This binding promiscuity – degeneracy incarnate – provides each TCR with sufficient affinity to drive T cell activation in response to numerous distinct antigens. Without this promiscuity, impossibly large TCR repertoires (and T cell populations) would be needed in order to effectively cover the antigenic space (Cohn, 2005; Mason, 1998). In other words, TCR degeneracy allows a finite population to adapt to a much wider range of antigenic contexts. On the other hand, partial overlap in TCR affinity also allows the T cell population to invoke similar responses under conditions devoid of antigens. In particular, similarities facilitate non-trivial cell–cell adhesion events between T cells and APCs that enable scanning for cell surface antigens with inactivation under normal conditions. Thus, degeneracy – conditional similarities and differences – in the versatile

TCR repertoire enable rapid adaptation within a changing antigenic environment. More generally, degeneracy can facilitate rapid adaptation because some of the elements in the population are already pre-adapted to some degree and can be further elaborated over several generations to enhance functionality and fitness. If the elements in a population exhibited extreme functional specificity that relied on precise environmental conditions, adaptation would be highly unlikely and could only occur by chance. These basic relationships between versatility and exaptation (Gould and Vrba, 1982) are not limited to the adaptive immune response, but are fundamental attributes of adaptive responses throughout many biological systems (Edelman and Gally, 2001).

Degeneracy may also be relevant to the adaptation of non-biological systems, such as social and technological systems (Bender and Whitacre, 2011; Clark et al., 2011; Frei and Whitacre, 2011; Lehky, 2011; Randles et al., 2010), because degeneracy will arise amongst any set of versatile components that modify their function in response to a variety of contexts. Unlike high-specificity components whose functionality is limited to a very specific context, degenerate components are likely to exhibit a change in function upon environmental stress. Many of these changes in function are likely to be maladaptive; however, those that are not, will be numerically expanded and will reshape the assortment, leading to improved fitness and formation of a new degenerate substrate for the subsequent selection of possible additional beneficial adaptations. These dynamics have been best described at the level of protein evolution where proteins can maintain one functionally relevant conformation while occasionally sampling other conformational structures that are sometimes co-opted for useful new functions in new environments (Aharoni et al., 2005; Tokuriki and Tawfik, 2009). Degeneracy, or functional versatility, has been well characterized at the molecular level, but related considerations equally apply to environment-revealed differences in traits involving adaptive foraging, nest-building, and predator avoidance.

A population with high trait diversity but no degeneracy would not harbor characters that flexibly respond to environmental change, because any beneficial trait discovered would have to constitute a highly specific genotype–environment pairing by chance. In theoretical biology, these points of difference between degenerate and non-degenerate systems can be related to rugged and smooth fitness landscapes. In rugged landscapes, adaptations occur by chance alone, while in smooth landscapes, genotypic and fitness changes are correlated so that the benefit of a genotype suggests a non-negligible likelihood of additional beneficial mutations nearby. Theoretical considerations have suggested that only fit-ness landscapes with neutrality created by degeneracy will provide access to the phenotypic diversity needed to enhance a population's evolutionary potential (Whitacre and Bender, 2009, 2010; Whitacre et al., 2010). From these theoretical perspectives, degeneracy thus appears to contribute to a mechanistic foundation for realizing the Darwinian concepts of heritable variation and selection (Edelman and Gally, 2001; Solé et al., 2002; Whitacre, 2010).

3. The Implications of Degeneracy in Evolution, Technology and Society

The opposing needs for preserving homogeneity and diversity exist because natural selection in stable environments appears to continually remove the very heritable trait diversity that is later needed when changes in selection take place. Phenotypic degeneracy in general, and CGV in particular, might resolve this paradox because diverse cryptic changes can accumulate in a population without noticeable phenotypic effects, yet can ultimately provide the trait differences necessary for adapting to future environmental novelty. With degeneracy appearing to be ubiquitous at all levels of biological organization (Edelman and Gally, 2001) and heritable through CGV, a growing number of researchers are viewing degeneracy as a major contributor to evolution (Edelman and Gally, 2001; Solé et al., 2002).

Here we briefly explore how the degeneracy concept could provide new insights into evolutionary processes that arise in a variety of biological and non-biological domains.

One important example is seen in evolutionary ecology where the relevance of CGV is not widely appreciated. In conservation biology, intraspecific genetic diversity is a well-known factor in extinction risk. However, only genetic variants that reveal trait differences under the environmental stresses encountered can mitigate extinction risks. It should be possible to quantify GxE interactions for environmental stresses that endangered species are expected to encounter with greater frequency and magnitude in the future, e.g. by selecting stresses based on well-established predictive models of regional climate change. CGV that is revealed under such conditions should provide a more adaptively significant measurement of biodiversity than existing measures of intraspecific genetic variation and thus a more valuable metric for determining which individuals and lineages are important to species conservation efforts. With limited conservation budgets, preserving this much smaller CGV footprint should provide a more realistic and realizable conservation goal. Similar approaches can be extended to transform existing measures of species richness into more contextual measures of species-response diversity (Elmqvist et al., 2003) that are anticipated to be most relevant to future ecological resilience.

A better understanding of degeneracy allows not only for preserving populations but can also be used in their eradication. In highly evolvable infections and diseases, such as aggressive cancers, the accumulation of CGV is likely to play an important role in the rapid evolution of therapeutic resistance. As cancer cells divide, they accumulate additional somatic mutations, which, while silent by themselves, may facilitate resistance to a current therapy and/or change in therapy in the patient (Frank and Nowak, 2004; Stratton, 2011). Oncologists have yet to consider strategies for reducing tumor evolvability by eliminating CGV. The arguments reviewed here suggest that environmental stability (continued use of the same therapy) facilitates CGV accumulation in tumors and plays an important role in the evolution of therapeutic resistance. Therapeutic strategies that rapidly change the administered therapy over time should help to eliminate CGV and thereby provide a novel strategy for reducing the evolutionary potential of cancers that contain high levels of genetic diversity (Tian et al., 2011).

We have demonstrated how degeneracy could be directly exploited for eradication of unwanted sub-populations in an artificial molecular system, such as the modified polymerase chain reaction (PCR). In previous work we have shown that PCR primers bind to the target templates degenerately, leading to amplification of less-specific products (Atamas et al., 1998). We designed and tested degenerate non-amplifying competitor primers that model CGV by binding to numerous targets, which are similar to, yet distinct from, the intended amplification target. Subsequent experiments tested the amplification of targets by functional primers in the presence of these degenerate competitors. The degenerate non-amplifying competitors were more competitive for the binding sites that were less homologous, but still retained some degree of homology to the functional primers, thus increasing the specificity of amplification. Such functionality was possible because in a set of degenerate competitors, most sequences will have structural homology with the templates that are less specific for the functional primer used but that resemble the specific template. As a result, degenerate competitors annealed better to the templates that were less specific for the functional primer and thus prevented the amplification of less-specific products (Atamas et al., 1998). These results showed, in agreement with the arguments outlined in this review, that non-amplifying competitor primers with broader degeneracy in annealing to diverse templates block amplification of the unwanted targets more efficiently than functional primers with narrow specificities would amplify them (Atamas et al., 1998).

This approach can be expanded beyond PCR, to hybridization-based array technologies or to DNA-based computing (Shu et al., 2011).

The persistence and spread of technological and cultural artifacts through time with variation is analogous to variation with heritability in that both are examples of what Darwin called “descent with modification” (Nehaniv et al., 2006). Biased (non-random) selection can be imposed on both types of processes and consequently both can undergo a form of evolution. While species appear to successfully resolve the opposing needs for short-term stability and long-term directional selection, this cannot be said of the short- and long-term objectives that arise in the planning and operation of adapting socio-technical systems or in systems engineering. While CGV is a purely biological phenomenon, the broader concept of degeneracy captures system properties that can be clearly articulated and defined for any system comprised of functionally versatile elements. Currently, there are several research programs exploring how the degeneracy concept can be translated into better designs to create more flexible and resilient systems in several disciplines (Frei and Whitacre, 2011; Randles et al., 2010; Whitacre et al., 2010, 2011). For instance, in military defense capability studies, we have shown using simulations that fleets of land vehicles with high degeneracy in capability can improve operational robustness within anticipated mission scenarios, while at the strategic level, such fleets provide exceptional design and organizational adaptability for responding to unanticipated challenges (Whitacre et al., 2011). More than just an academic exercise, this role of degeneracy in adaptation has attracted the interest and financial support of Australian Defense, with the goal of developing better approaches to strategic planning and mitigating strategic uncertainty (Bender and Whitacre, 2011). Because the degeneracy concept is itself very versatile, we are looking at how this concept can also be translated into the design of more flexible manufacturing and assembly systems (Frei and Whitacre, 2011) and for better performance in population-based dynamic optimization (Whitacre et al., 2010). Still others are using these concepts to understand some of the weaknesses of the scientific peer review process (Lehky, 2011) and the requisite conditions for embodied and simulated artificial life (Clark et al., 2011; Mendao et al., 2007).

4. Summary

Speaking anthropomorphically, diverse aggregates, whether in biology, society, or technology, are often faced with a dilemma: to limit or to expand their diversity. In stable environments, narrowing the diversity around the most beneficial traits allows for maximal resource exploitation. However, even those environments that remain stable for prolonged periods change sooner or later. If the change decreases the fitness of the population, broader diversity ensures survival, because it forms a broader substrate for the subsequent adaptation of the population through natural selection. Thus, populations appear to be torn between the need to narrow their diversity around the traits that are beneficial currently and the need to diversify, and thus to hedge their bets on the future stability of the environment. Empirical observations show that many species remain remarkably static over long time periods, but then undergo rapid phenotypic evolution and genetic differentiation, thus successfully resolving the opposing imperatives to exploit present resources and to explore novel opportunities. This review article argues that such resolution occurs through a general phenomenon known as degeneracy, which in the case of species is represented by cryptic genetic variation. The novel concept is that cryptic genetic variation and degeneracy reflect complementary top-down and bottom-up conceptualizations of the same phenomenon, which are critical for selection-driven adaptation. As the commonalities between degeneracy (a general phenomenon) and cryptic genetic variation (a particular case) become better appreciated, and their fundamental roles in evolution become more widely accepted, we anticipate that this new understanding will transform how we think about evolutionary

processes and the origins of innovation. Such an improved understanding will allow for development of more efficient ecological conservation approaches and may be applied in social and technological systems dealing with the uncertainty of the future.

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Abbreviations

CGV cryptic genetic variation

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Fig. 1.

Schematic representation of types of relationships between multiple structures and functions. In strict specificity (A), each structural type performs a unique function. Examples are some highly selective enzymes or antibodies. High specificity allows for precise separation of diverse functional responses to the environment. However, high specificity is costly, because each structural type needs to be maintained independently of other types. It also makes the system vulnerable, because a loss of a structural type completely abrogates the corresponding function (for example, in some gene defects). These characteristics in contrast to redundancy (B), which assures high level of systemic reliability: a loss of a structural type will have limited effect on functional performance. The generation of multifunctional systems (C) is least costly, with one structural type performing multiple functions, but independent regulation of functions in such systems poses challenges. As a result, a change in any function will be accompanied by changes in all other functions associated with the structural type, manifesting as indiscriminate uniformed response to varied environmental influences. The benefits of all these systemic principles are combined and their corresponding weaknesses diminished in degenerate systems (D). In the depicted case, Structure 1 is capable of performing Functions 1 and 2 equally well, Function 3 less efficiently, Function 4 with minimal efficiency, but unable to perform Function 5 at all. Of note, Functions 2–4 are “covered” by both structures. The functionality of each structural type and of the overall degenerate set is context-dependent, meaning that a particular structural type will or will not manifest a particular function depending on the systems’ environmental situation. See text for detailed discussion.

Fig. 2.

The relationship between genetic variation and phenotypic manifestation is degenerate in nature. In the depicted case, the trait value contributing to the manifest phenotype is driven mainly by the genetic variation 2, but similar yet somewhat distinct trait values may be produced by variation 3 and, to a lesser extent, by variation 1. Under current conditions, variations 1 and 2 remain cryptic, as they manifest in the phenotype that is very similar to that driven by the predominant variation 2. Changes in the environment may induce a different phenotype, now predominantly driven by one or more of previously cryptic variations.