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Review article

Hidden in plain view: degeneracy in complex systems

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ABSTRACT

Degeneracy is a word with two meanings. The popular usage of the word denotes deviance and decay. In scientific discourse, degeneracy refers to the idea that different pathways can lead to the same output. In the biological sciences, the concept of degeneracy has been ignored for a few key reasons. Firstly, the word "degenerate" in popular culture has negative, emotionally powerful associations that do not inspire scientists to consider its technical meaning. Secondly, the tendency of searching for single causes of natural and social phenomena means that scientists can overlook the multi-stranded relationships between cause and effect. Thirdly, degeneracy and redundancy are often confused with each other. Degeneracy refers to dissimilar structures that are functionally similar while redundancy refers to identical structures. Degeneracy can give rise to novelty in ways that redundancy cannot. From genetic codes to immunology, vaccinology and brain development, degeneracy is a crucial part of how complex systems maintain their functional integrity. This review article discusses how the scientific concept of degeneracy was imported into genetics from physics and was later introduced to immunology and neuroscience. Using examples of degeneracy in immunology, neuroscience and linguistics, we demonstrate that degeneracy is a useful way of understanding how complex systems function. Reviewing the history and theoretical scope of degeneracy allows its usefulness to be better appreciated, its coherency to be further developed, and its application to be more quickly realized.

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1. Introduction

In scientific usage degeneracy refers to the idea that different structural arrangements lead to similar outputs, or, in other words, that structurally diverse system components perform the same function (Edelman and Gally, 2001). As such, degeneracy is a desirable characteristic of systems. For example, degeneracy has been implicated in making systems more robust and more evolvable (Joshi et al., 2013; Meyers et al., 2005; Tian et al., 2011; Whitacre, 2010; Whitacre and Bender, 2010). However, just like many scientific terms, degeneracy has a different meaning in everyday language, where it commonly denotes negative dilapidation. In this paper we argue that the lay meaning of degeneracy has allowed an important concept to go largely unnoticed and that, given the ubiquitous presence of degeneracy in natural and social systems, it therefore remains "hidden in plain view". We review

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fruitful applications of the notion of degeneracy to the immune system, the brain, and language, a culturally evolved system. Our aim is to bring a particular operational conceptualisation of degeneracy out of its narrow scientific usage and into a common scientific lexicon.

Degeneracy, once an 18th century theory of how species change (Lawrence, 2009), became associated with undesirable deviation, hereditary degenerative disorders, and even infectious diseases such as tuberculosis (e.g., see Johnson, 1898) in the nineteenth and early twentieth centuries (Lawrence, 2010). The negative associations proved long-lasting and today medical doctors still refer to harmful degradation as a "degenerative" condition. Negative conceptualisations of degeneration overshadow a useful concept of degeneracy that George Gamow (1904–1968) imported into biology from physics and mathematics through his involvement with the RNA tie club including Francis Crick (Mason, 2010). In quantum physics, degeneracy refers to a situation in which different measurable states correspond to the same energy level. In the 1950s, Gamow contributed to solving the coding problem of DNA by suggesting that different nucleotide sequences in DNA could code for the same amino acid (Crick, 1955). Since then, scientists have found extensive degeneracy in the genetic code (e.g., Alvager et al., 1989; Barnett and Jacobson, 1964; Frank, 2003; Goodman and Rich, 1962; Grantham, 1980; Gu et al., 2003; Jestin, 2010; Kurland, 1992; Luo, 1988; Mitchell, 1968; Reichmann et al., 1962; Sequeira-Mendes and Gómez, 2012; Weisblum et al., 1962, 1965). Recent studies of degeneracy in bacteria have shown that different synonymous codons that interact with ribosomal proteins at ranging levels of amino acid affinity allow organisms to adapt to environmental changes given different amino acid availability (Subramaniam et al., 2013).

The contemporary scientific usage of degeneracy thus refers to the variable pathways that can lead to the same outcome, or the ability of different structures to perform the same function. For example, different gestures can convey the same communicative message, different chemical pathways can be used to metabolise food, and different proteins can bind to the same molecules. Degeneracy is constructive for understanding how components come together to form a synergy (Kelso, 2009), and has been shown to be a vital property of evolutionary systems, because it plays a central role in their reliability, adaptability and robustness (Whitacre, 2010; Whitacre and Bender, 2010; Whitacre and Atamas, 2012). Having multiple different backup pathways is how living systems maintain stability over time and also how they change, adapt and evolve.

In general, scientists have overlooked the concept of degeneracy not only because of the term's dominant negative meaning but also, we would suggest, because degeneracy is predicated upon a view of causality as being manifold and distributed. Such a view underpins the idea of multiple arrangements yielding the same output. This view of causality clashes with a traditional scientific analytical approach that favors isolating single causes for a given outcome. Geneticists looking for a single gene for a given function or neuroscientists looking for the brain area responsible for a specific behavior are examples of biases that hide degeneracy from scientific models. Furthermore, technological and methodological limitations have until recently restricted researchers to investigate one structure and one function at a time.

Besides being difficult to study, degeneracy is often confused with "redundancy," another term that is used differently in everyday speech and science. In everyday speech, we often use the word "redundant" to refer to something that is unnecessary. To be made "redundant" at the workplace, for example, is to lose your job. In science, redundancy refers to multiple copies of identical structures that perform the same function (Fig. 1). In information theory, redundancy refers to the transmission of more information than is strictly necessary to decode a message (Shannon, 1948). In both cases, redundancy is generally something positive. For example, redundant encoding of messages is argued to increase the success of transmission in noisy conditions (Hailman, 2008). The fact that both redundancy and degeneracy are generally considered positive system characteristics in science makes them very confusable. In line with this, degeneracy is often confused with redundancy, or a type of redundancy sometimes referred to as partial or functional redundancy. For example, two different genes that code for the same function are often labelled redundant even though they may be at different sites, may have different expression patterns, or may be additionally involved in other biological functions. We believe such a case is more aptly described as degenerate. The case of structurally dissimilar components realizing a similar function ("degeneracy") needs to be kept distinct from the case of structurally similar components realizing the same function ("redundancy"). Systems that exhibit degeneracy are not fixed to singular outcomes. In this sense, degenerate systems are pluripotent. While a redundant system has a set function, degenerate systems are functionally plastic. Articulating the distinction between degeneracy and redundancy is important if we are to work out the basic organising principles of complex systems. Inexact lexicons, reductionist biases, historical trends, and technological limitations are all impeding an unrestricted engagement with degeneracy.

Contemporary research findings are progressively giving cause to challenge reductionist approaches. Researchers have been gradually uncovering heterogeneous pathophysiology in clinical conditions such as Alzheimer's disease (Lock, 2013), Huntington's disease (Domínguez D. et al., 2013), Parkinson's disease (Lewis et al., 2005), schizophrenia (Dumit, 2004), asthma (Boulet et al., 2015; Reddel, 2012), chronic obstructive pulmonary disorder (Hardaker et al., 2013; Timmins et al., 2012), and sleep apnea (Dempsey et al., 2014; Eckert et al., 2013), among others. The interindividual variability of these conditions has implications for therapeutic approaches (Wang et al., 2011; Wang et al., 2013;

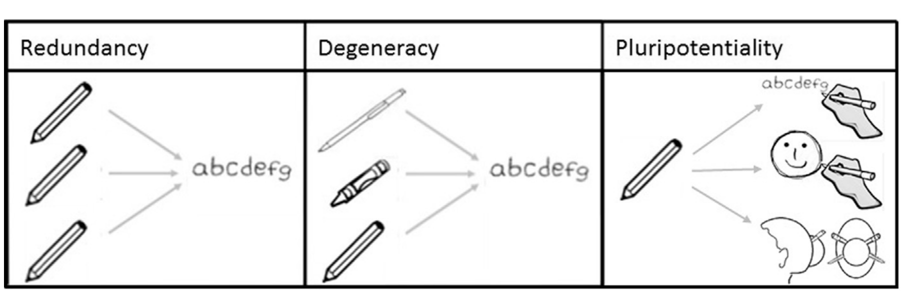

Fig. 1. Redundancy refers to identical structures, such as pencils, recruited for a similar task, such as writing. Degeneracy refers to nonidentical structures, such as pens, crayons, and pencils, recruited for a similar task, such as writing. Pluripotentiality refers to a structure, such as a pencil, being recruited for a selection of nonidentical tasks, such as writing, drawing, and as chopstick fashion accessories to hold hair in a bun.