Degeneracy: Demystifying and Destigmatizing a Core Concept in Systems Biology

Often relegated to the methods section of genetic research articles, the term "degeneracy" is regularly misunderstood and its theoretical significance widely understated. Degeneracy describes the ability of different structures to be conditionally interchangeable in their contribution to system functions. Frequently mislabeled redundancy, degeneracy refers to structural variation whereas redundancy refers to structural duplication. Sources of degeneracy include, but are not limited to, (1) duplicate structures that differentiate yet remain isofunctional, (2) unrelated isofunctional structures that are dispersed endogenously or exogenously, (3) variable arrangements of interacting structures that achieve the same output through multiple pathways, and (4) parcellation of a structure into subunits that can still variably perform the same initial function. The ability to perform the same function by drawing upon an array of dissimilar structures contributes advantageously to the integrity of a system. Drawing attention to the heterogeneous construction of living systems by highlighting the concept of degeneracy valuably enhances the ways scientists think about self-organization, robustness, and complexity. Labels in science, however, can sometimes be misleading. In scientific nomenclature, the word "degeneracy" has calamitous proximity to the word "degeneration" used by pathologists and the shunned theory of degeneration once promoted by eugenicists. This article disentangles the concept of degeneracy from its close etymological siblings and offers a brief overview of the historical and contemporary understandings of degeneracy in science. Distinguishing the importance of degeneracy will hopefully allow systems theorists to more strategically operationally conceptualize the distributed intersecting networks that comprise complex living systems.

Key Words: degeneracy; robustness; complexity; selection; evolvability; degeneration; systems biology

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> *Trop de spécificité nuit gravement à la survie, car elle réduit l'adaptabilité. Pour remédier à cette spécialisation, des molécules ou des cellules reconnaissent un éventail de cibles: elles sont dégénérées.*
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> Sergei Atamas, 2005 [1]

Degeneracy derives from the Latin degeneratus; the "de" prefix means "to move away from" and "generatus" means "having descended from." Although today the verb, to degenerate, often has bleak connotations, a "de"

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prefix is not always associated with negative overtones. The prefix "de" can have neutral associations, such as "delineate," "delimit," and "denominate"; negative associations, such as "deform," "defame," and "devalue"; and positive associations, such as "detoxify," "debrief," and "deodorize". Early use of the word "degeneration" was not always negative. For example, the 16th century Spanish royal cosmographer, Juan López de Velasco, believed that manners and social intercourse degenerated into disrepair among people who spent extended time in foreign climates [2,3]. Conversely, the 18th century French naturalist, Philibert Commerçon, held contrary beliefs and described the society of Tahiti as the natural state of man before it had degenerated into reason [4]. Despite the flexibility of the early usage of the word "degeneration," the association between degeneration and deleterious conditions became cemented by later scholars, most notably by German journalist, philosopher, and practicing physician, Max Simon Nordau (1849–1923), who rendered the concept of degeneration as a mental and social disease fashionable in his widely translated book, *Degeneration*, published from the 1890s to 1920s [5,6].

In the 1950s, Ukrainian-born American scientist, mathematician, and theoretical physicist, George Gamow (1904–1968), used the word "degeneracy" to refer to a theoretical concept that proved useful to understand genetic coding [7,8]. In quantum physics, degeneracy is a specialized term for different stationary states corresponding to the same energy level. Borrowing the word from quantum physics, Gamow applied the term "degeneracy" in biology to refer to different structures that could variably achieve the same outcome. The concept was highly useful in solving the coding problem of DNA [9–12], but the choice of terminology was unfortunate. By the end of the Second World War, the word "degeneracy," by its close etymological association to "degeneration," had accrued significant baggage. A politicized theory of degeneration provided biological explanations for crime and mental illness and had been swept up in eugenic theories [13–15]. Degeneration theory violently stigmatized individuals and groups. The root problem of degeneration theory was that it reduced whole individuals and groups to one or two crude, discrediting, and prejudicially attributed characteristics. Exhibiting just one of these characteristics was a metonym indicating that someone was totally "degenerate." The brutal deployment of degeneration theory by eugenicists tainted conceptualizations of diversity. In the aftermath, the word degeneration fell out of widespread scientific usage, and Gamow's conceptualization of biological degeneracy was correspondingly largely ignored or misunderstood. Researchers were understandably hesitant to adopt a term that carried such value-laden historical baggage.

Biological degeneracy is conceptually distinct from degeneration theory as well as the usage of the word "degeneration" in medical science. In medical practice, degeneration is understood as a pathological condition with progressive acquisition of tissue damage resulting in a degree of functional loss. The medical term "degeneration" is used to describe macular degradation, mental decline, or cellular decomposition. In neurology, degeneration is a term used for conditions where a scientific explanation is absent. In fact, most current neurology textbooks do not include degeneration as a nosological term and the largest book on neurodegenerative diseases does not even define these illnesses [16,17]. The most accepted definition for neurodegenerative conditions itemizes a group of disorders united only by gradually progressive disintegration of the nervous system [17,18]. Developing a modeling language to understand the complex molecular physiological processes of neurodegenerative disorders has long been recognized [19]. As medical scientists and brain researchers learn more about the complex etiology of neuronal conditions associated with ageing, advances in taxonomy are supplanting the blanket use of the word "degeneration" in pathology.

Not to be confused with medical terminology, degeneracy in systems biology refers to the ability of alternate structural pathways to achieve similar functional outcomes in one context or dissimilar functional outcomes in divergent contexts. Having a variety of different structural arrangements that can selectively, but not exclusively, yield the same output under one set of conditions, and diverse outputs in different conditions, has two benefits: (1) it improves robustness to perturbation and (2) it increases the flexibility of a system to changing environments. Unlike degeneration theory and pathological degeneration, biological degeneracy does not imply negative dilapidation. Rather, biological degeneracy is an explanatory conceptual tool and neither a discriminatory label nor a descriptive classification for pathological conditions of unknown etiology.

Appearing more than once in recent *Complexity* news items [20–22], degeneracy is part of a suite of emerging concepts that are offering analytical insights into biological systems [23]. One aspect of biological degeneracy is the conditional interchangeability of different structures, illustrated, for instance, when lesions in the brain appear to have little effect within familiar contexts thus revealing useful backup structures [24]. On the flipside of degeneracy is the conditional nonspecifity of structures, demonstrated, for example, by the Bacille Calmette-Guérin (BCG) vaccine, which in addition to protection against tuberculosis also has a number of additional beneficial effects including an improved immune response to unrelated antigens

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[25,26]. Nonspecificity and degeneracy go hand in hand [8,27]. Degeneracy has been characterized in genetic codes [28–39], epigenetic programs [40], immune systems [27,41–48], respiratory networks [49], anatomical movement [50–55], cognitive neuroanatomy [56–64], neurological timing systems [65,66], cellular and molecular evolution [67,68], cancer robustness [69], language evolution [70], population dynamics [71,72], and technological innovation [73,74]. Most recently, Park and Friston [75] have reinforced the argument that degenerate structure-function mapping is crucial for understanding the nature of brain networks. During the industrial and agricultural revolution, degeneration was seen as a harmful divergence from productivity. Today, degeneracy is increasingly recognized as an important aspect of complexity, robustness, and evolvability [76–79].

A system that exhibits degeneracy contains structurally different components that can perform a similar function with respect to context. Functionally similar but structurally different components are often mislabeled as redundant, a term that actually refers to identical structures. Identical copies of the same gene are redundant, whereas structurally dissimilar genes that code for the same function are degenerate. A system's ability to perform the same tasks by different mechanisms prevents intolerable fluctuations and the propagation of cascading failures [80]. In a dynamic self-organizing system, there has to be a compromise between the overstabilization of networks and the noise within and between various networks. As Sergei Atamas suggests in the epigraph [1], too much specificity goes seriously against survival because it reduces adaptability. To remedy this specialization, some molecules and cells exhibit degeneracy and recognize a range of targets. Degeneracy of antigen receptors, for example, enables any single epitope to activate many different lymphocyte clones, and simultaneously any single lymphocyte clone is able to recognize many different epitopes [44]. When more than one element can respond to environmental conditions, degeneracy of interaction with the environment leads to competition "not only between exactly similar but also between similar yet diverse elements of the repertoire" [81]. Degeneracy means that selection is not a forced event between functional and nonfunctional structures, but between different structures that perform the same function to varying degrees.

Fears of degeneration from the late 18th to the early 20th century were related to the idea that offloading the biological fitness of individuals onto extrasomatic social and technological structures would lead somatic characteristics to degenerate. The 1937 Degenerate Art Exhibition in Munich, with works by artists such as Elfriede Lohse-Wächtler, Paul Klee, and Wassily Kandinsky, was a conspicuously vindictive expression of this fear. The fear, as we now recognize, was politicized and flawed. Environmental features can buffer endogenous biological functions but, contrary to the ideas of degeneration theorists, the consequences are not necessarily detrimental. For example, a few vertebrate lineages have outsourced ascorbic acid (vitamin C) synthesis to dietary sources such as fruit thus allowing the gene responsible for endogenous ascorbic acid synthesis to accumulate mutations without deleterious outcomes [70]. In the midst of anthropogenic climate change, we might ask if a future reliance on consuming exogenous sources of cholecalciferol and ergocalciferol (vitamin D) will lead endogenous synthesis to structurally and functionally diverge. Although the dominant biomedical model might classify this biological change as "disease," contemporary systems theorists understand that such processes are part of the growing complexity of organisms and their niche. For example, shared metabolic pathways between insects and bacteria nicely illustrate the principle of degeneracy via increased structural complexity of a biological system [82,83]. The distribution of function throughout an array of internal and external components that each fractionally influences the ongoing dynamics of a system is one source of degeneracy. Other sources of degeneracy, to highlight but a few, may include duplicate endogenous structures that differentiate yet remain isofunctional, the parcellation of an endogenous structure into subunits that can still variably perform the same initial function, or the convergence of exogenous and endogenous structures onto similar functions. Integrating degeneracy into studies of structural duplication [84–88], parcellation [89,90], and functional convergence [90,91] is an important part of completing the evolutionary picture. Biologists have conscientiously distanced themselves from degeneration theory because of its politically vicious prejudices [14,15], but this divorce should not be to the exclusion of investigating how degeneracy can arise as organisms interact with their environment.

Captured by the fallacy that a single "ideal" form existed for many biological phenomena, humans have purposefully trained their bodies to achieve idealized movement capabilities. The Reich Ministry for Enlightenment and Propaganda aimed to sculpt the perfect Nazi body as exemplified by *Gemeinschaftstanz* movement choirs. Today, notions of the optimal body remain and are constructed by cultural ideals of elite performance that are reinforced by the positive drivers of consumerism, materialism, and commercialism. Studying elite skill acquisition in rugby, Downey [92] contends that cultural skills are not uniformly shared. Instead, developmentally acquired, cultural skills require idiosyncratic physiological adaptation. The distinction of expert performers is not their convergence on specific movement strategies, but their ability to transit functionally between movement coordination solutions in an array of situated tasks. Novices, in contrast,

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tend to rely on a limited repertoire of functional coordination solutions with partial efficacy to accomplish unfamiliar tasks [93]. Counter to traditional approaches in studying performance output, paying attention to movement organization reveals that movement system variability is not necessarily detrimental noise or variance error. Training athletes for functional movement variability under variable conditions has proven to increase the consistency and stability of performance outcomes [94]. The successful interaction of an elite performer with the specific constraints of the task and environment relies on the degeneracy of their perceptual and action systems [95]. In their efforts to achieve a performance ideal, athletes exploit functional variability to adapt their actions to an optimal movement goal.

Degeneracy plays a role in both healthy and unhealthy organism function. For example, multiple pathological pathways can lead to the clinical symptoms of asthma [96,97], different pathophysiological states are correlated with the motor symptoms of dystonia [98], and heterogeneous pathologies are also implicated in conditions such as attention-deficit/hyperactivity disorder [99], neuropathic pain [100], and Autism [101] among others. In healthy individuals, degeneracy is also present. Rhythm generation and chemosensory modulation in the respiratory system both recruit multiple distinct networks whose outputs are similar [49], elite athletes exhibit a large amount of variability in movement kinematics across repetitions of the same task [51,95], and different populations of neurons in the brain can produce similar behavioral outputs in response to identical external stimuli [56,102]. In addition to degeneracy within single organisms, degeneracy can even be found across individuals. For example, indigenous highlanders at similar altitudes in the Tibetan Plateau in Asia and the Andean Altiplano in South America have adapted to oxygen-thin air by different physiological and molecular pathways: a respiratory route for the Tibetans and a hematological route for the Andeans [103–106]. Compared to people at sea level, Tibetans take more breaths per minute and they are able to increase blood flow to increase oxygen intake because their lungs synthesize large amounts of the vasodilator nitric oxide. Andeans, conversely, have higher hemoglobin concentrations and carry more oxygen in each red blood cell. Visibly, degeneracy operates within and across multiple levels of complexity. Yet, seduced by the reductionist hypothetico-deductive methods of experimental science, researchers commonly essentialize the etiology of biological functions and dysfunctions, with mental disorders being a prime example [107]. Essentializing etiology to a single cause is in clear discord with the genotypic and phenotypic heterogeneity of biological processes. More than simply a philosophical concern, between-patient heterogeneity is an important consideration in making decisions about medical funding that has proven consistent with an efficient use of limited resources [108].

The customary scientific practice of pooling data, grouping effects, and examining measures of central tendency across large samples can lead to misrepresentations that neglect or ignore variation [109]. Making group level inferences in brain data, for example, is problematic due to gross variability in cortical thickness, folding, and functional localization between separate individuals or subject populations [110]. Furthermore, degeneracy in the brain makes it prone to diverse architectural configurations, both within and across cultures [92]. In fMRI studies, group-averaged data reveal brain regions sufficient but not necessary for a given cognitive function [57,111,112] given that each region is part of a network that exhibits degeneracy, with several regions capable of subserving the same function [57,112]. Determining the necessary brain regions for particular functions is possible using single cases of unique neurological conditions such as brain lesion studies [112]. Functional neuroimaging is useful in single case studies where a discrepancy exists between external stimuli and brain activity such as out-of-body experience [113], epilepsy, blindsight, and synesthesia [112]. In healthy subjects, brain imaging studies are benefitting from the incorporation of qualitative data and ethnographic approaches in what has been termed cultural neuroscience by some [114–120] and neuroanthropology by others [121–127]. Given that cultural experience shapes human expression and also the neural pathways by which individuals become aware and assess their feelings [128], a principal aim of this combined approach is to construct a model to study and understand the cultural brain of healthy individuals [121].

With some methodological and interpretative issues remaining to be resolved, integrative analyses centering on the individual are proving fruitful in mental health [129–132] with a multipronged approach being promoted where counsellors, social workers, and social policy makers among others can all view their engagement as interlinked, with no particular agent offering a complete solution on their own [133]. Similarly, personalized approaches are being used in patient monitoring and risk assessment of lung health [134–136] with a focus on multidisciplinary interventions tailored to individuals following a person-centered management plan [137–139]. Personalized medical approaches are being adopted widely in medicine [140–147] and are believed to reduce future global disease burden and improve population health and longevity [148]. The individualized approach is being promoted in sleep health [149,150], arthritis treatment [151], cancer therapy [152–158], diabetes management [159,160], veterinary medicine [161], and sports training

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[162], to name but a few examples. Researchers, clinicians, and educators, benefitting from the ongoing commercialization of the body [163], are putting the individual at the nucleus of critical inquiry. With the individual at the center, reductionism is defied by situating the person as a relational being whose intersubjectivity, life history, and cultural experience are variously factored in all their splendor and complexity.

As systems theorists are left trying to piece together the tiniest fragments that scientific reductionism has teased apart, labels for interconnecting dynamic processes are often found lacking. Degeneracy is a key term that helps researchers to operationally conceptualize the variable intersecting factors that heterogeneously construct living systems. If integrating the term "degeneracy" widely into contemporary scientific nomenclature is too uncomfortable for some, then perhaps we can introduce a hyphen to distinguish the theory of "degeneration" associated with eugenics from the concept of "degeneracy" attributable to George Gamow. "De-generacy" with a hyphen may satisfy the need for a more precise vocabulary and distance the word from its historical baggage. This linguistic maneuver might allow researchers to offer descriptions such as: the degeneracy of the jaw-bones of Permo-Triassic mammal-like reptiles released a tiny craniomandibular ossicle from its original function and allowed it throughout evolution to migrate into the middle ear, where, by virtue of its small size and accurate responsiveness to vibration, it became an important part of the hearing system [164–167]. However, to borrow the words of Scheper-Hughes and Lock [168], will scientists be "left suspended in hyphens" trying to reconnect "fragmented concepts?"

The engagement with and acceptance of a scientific theory is a socially situated process inflected by a range of historically constituted discursive practices. Unpacking complex biological processes demands the development of innovative vocabulary. Correspondingly, scientists are continually grappling with new language. The history of the scientific investigation of fermentation is an excellent case example. In the 19th century, fermentation was at first understood as a process that was not decomposable into a chemical explanation. Then, in 1897 the German organic chemist Eduard Buchner isolated the enzyme zymase in a cell-free extract of yeast and posited a direct localization of biological fermentation. This explanation soon proved limited and inadequate. By the 1930s, researchers recognized that fermentation was a many step process involving many different enzymes and coenzymes each responsible for different parts of the biochemical process. Researchers were effectively able to move beyond a direct localization in the late 1890s to a complex localization in the 1930s [169,170]. Learning by analogy, we can recognize the importance of thinking about the complex localization of structure–function relationships in other systems. One structure does not always map purely to one discrete function. Degeneracy is a key concept that attunes scientists to the notion that multiple pathways can lead to flexible endpoints.

As the basic organizing principles of biological systems are beginning to unravel, scientists are pushed to remain open to exploratory conceptual frameworks, fast-changing vocabularies, and increasingly complex localizations of biological processes. When it has come to mapping the structural variation underlying functional plasticity in complex adaptive systems, the descriptive vocabulary has been available but all too often disregarded. Incorporating degeneracy more liberally into scientific discourse is an avenue to develop new hypothetical frameworks, fresh theoretical insights, and novel innovative interventions. For example, conditions such as arthritis, asthma, coeliacs, eczema, Hashimoto's thyroiditis, lupus erythematosus, and multiple sclerosis are variously conjectured to be a consequence of an overactive immune system. However, considering the relation of such diseases to levels of degeneracy in the immune system may offer a more fruitful systems-oriented approach. Would vaccines that manipulate the specificity or non-specificity of the immune system [26] have any beneficial effect on autoimmune conditions? Indeed, recent promising trials have shown that the BCG vaccine reduced the likelihood of developing multiple sclerosis (MS) among patients who experienced a single episode of MS-related symptoms and showed signs of the first demyelinating event in brain scans [171]. Degeneracy is a distributed property of complex adaptive systems that has been hidden in plain sight [67], commonly overlooked because of a reductionist bias [1,76], and ignored because the term itself is misleading [7]. Biological degeneracy deserves further investigation [172]. For the purposes of explaining the intricacies and interconnectedness of living systems, the concept of degeneracy is too important to ignore due to etymological misunderstandings and historical misuse.

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