Symposium

# The Brain's Best Kept Secret Is Its Degenerate Structure

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**Degeneracy is defined as multiple sets of solutions that can produce very similar system performance. Degeneracy is seen across phylogenetic scales, in all kinds of organisms. In neuroscience, degeneracy can be seen in the constellation of biophysical properties that produce a neuron's characteristic intrinsic properties and/or the constellation of mechanisms that determine circuit outputs or behavior. Here, we present examples of degeneracy at multiple levels of organization, from single-cell behavior, small circuits, large circuits, and, in cognition, drawing conclusions from work ranging from bacteria to human cognition. Degeneracy allows the individual-to-individual variability within a population that creates potential for evolution.**

*Key words:* **causation; cell biology; evolution; degeneracy; homeostasis; systems neuroscience**

**Significance Statement**

**"Degeneracy, the ability of elements that are structurally different to perform the same function, or yield the same output, is a well-known characteristic of the genetic code and immune systems. Here, we point out that degeneracy is a ubiquitous biology property and argue that it is a feature of complexity at genetic, cellular, system, and population levels. Furthermore, it is both necessary for, and an inevitable outcome of natural selection." Edelman and Gally, 2001**

It is now ~25 years since the prescient papers by Edelman and his colleagues (Tononi et al., 1998; Tononi et al., 1999; Edelman and Gally, 2001) that established the definitions of degeneracy that we use today. This definition formally distinguished between redundancy, in which two or more identical elements can influence a target molecule, neuron, circuit, etc., and degeneracy, in which two or more structurally different elements can nonetheless produce virtually identical outputs (Prinz et al., 2004; Goaillard and Marder, 2021).

Although theorists have long appreciated that multiple sets of parameters can result in similar outputs (Tononi et al., 1999; Goldman et al., 2001; Prinz et al., 2003; Prinz et al., 2004; Taylor et al., 2009; Alonso and Marder, 2019; Alonso and Marder, 2020; Alonso et al., 2023), it has taken a long time for the neuroscience community specifically, and the biological community in general, to fully appreciate the message articulated above and to understand its implications for the data we today collect and analyze.

The understanding that degeneracy is a FEATURE of all biological systems has benefitted from the advent of new anatomical, electrophysiological, molecular, and statistical tools that allow us to study the molecular compositions of single cells, either of the same cell type within a given organism or identified neurons across animals.

Appreciation of the prevalence and salience of degeneracy in biological systems has lagged partially because it is often nontrivial to identify all of the components (cells, molecules, circuits, etc.) in a biological system and/or to characterize unambiguously system output. Both of these difficulties have been partially ameliorated by the vast array of new technologies now available for studying the interactions between system components and system behavior, and therefore it is not an accident that our collective understanding of the importance of degeneracy in biological systems has increased.

The differences between biological cells and circuits and artificial intelligence highlight the remarkable features implemented in biological systems, including brains, that allow for evolution, resilience, development, and learning. While biologists have always been both fascinated by, and wary of, the differences between individual cells or organisms, most of the history of biology was dominated by the inherent belief that individual differences were biological "noise" and that the platonic ideal neuron or organism was somehow best described by means or medians. We now know that means often fail to capture the essential features of the individuals that are used to calculate the means (Golowasch et al., 2002; Marder, 2023). We now have better statistical methods to capture the relationships between properties of populations, be they cells, circuits, or organisms (Bernard, 2019).

Received July 12, 2024; revised July 26, 2024; accepted July 29, 2024.

Author contributions: L.A., C.B., N.B., E.M., and R.N. wrote the paper.

This work was supported by National Institute of Mental Health (R01 MH046742) and National Institute of Neurological Disorders and Stroke (R35 NS097343).

The authors declare no competing financial interest.

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https://doi.org/10.1523/JNEUROSCI.1339-24.2024

A number of themes recur in studies of degeneracy: (1) degeneracy occurs at all levels of organization, and (2) the homeostatic mechanisms that produce and maintain stable biological function are feasible precisely because there are degenerate mechanisms consistent with desired system performance (Liu et al., 1998; O'Leary et al., 2014; Alonso et al., 2023). These themes surface in many systems and will feature below.

## Degenerate manifolds and sloppy control in bacterial homeostasis

The growth and division of bacterial cells have fascinated scientists since they were first observed under a microscope. These single-cell organisms grow, divide, and distribute their content among daughter cells over extended time spanning hundreds of cycles. During this time, all measurable phenotypes—cell size, generation time, protein content, and more—fluctuate, but homeostasis is maintained and distributions are stable (Salman et al., 2012). Modern single-cell technologies allow for longitudinal measurement of various phenotypes over hundreds of division cycles, enabling us to quantify the dynamics and the statistical properties of this process (Brenner et al., 2015; Fig. 1*a*,*b*). This has advanced our understanding of mechanisms that support growth/division homeostasis (Jun and Taheri-Araghi, 2015; Ho et al., 2018).

In addition to temporal fluctuations that can be viewed as "noise," bacterial cells also exhibit persistent individuality (Susman et al., 2018). Performing long-time averaging that suppresses the noise, one can identify average phenotypes that remain distinct among individuals. This is true also for isogenic bacteria and when external conditions are well controlled. Stated otherwise, averages over time are not equal to averages over the population.

This phenomenon has been viewed as a nuisance and sometimes interpreted as irreproducibility of experimental systems. However, recent work suggests that such persistent variability reveals an important and underappreciated aspect of the system: a structured hierarchy of degeneracy that provides a distinct mechanism to support homeostasis.

To reveal this aspect, statistical methods were developed to evaluate the relative importance of persistent individuality in single-cell data (Stawsky et al., 2022). It was found that different dynamic variables exhibit different behaviors: some tend to drift—"sloppy" variables (Gutenkunst et al., 2007), with each individual maintaining a distinct average over long times. For example, in each cell cycle that extends a duration τ, bacteria grow exponentially with a rate α (Fig. 1*b*); both of these, α and τ, are sloppy variables (Fig. 1*c*). Others are more constrained, and their averages are tightly held uniform across all bacteria. Interestingly, combinations of sloppy variables can covary with one another and form compound variables that are more constrained. From Figure 1*b* we can identify three variables in the process of growth and division that combine to form the most highly constrained combination: the cell size ratio over an entire cycle including both growth and division, $fe^{\alpha\tau}$. To maintain homeostasis of growth and division over extended time, this needs to be very close to 1; however, individual bacteria achieve this by many different degenerate compensating combinations of the constituent variables.

Examining the structure of the single-cell data in parameter space reveals the geometry of this degeneracy (Fig. 1*d*). A nonlinear manifold is formed on which the compound parameter governing functionality is fixed; this is the manifold $fe^{\alpha\tau} = 1$ in the space $(f, \alpha, \tau)$. Remaining on this manifold ensures stability over extended time; individual bacteria are widely scattered on it, reflecting the underlying degeneracy in the separate parameters.

What is the significance of such a manifold? An analogy from neuroscience can provide a possible answer. The activity of a population of neurons is often seen to lie on a low-dimensional sub-space. Experiments on learning have shown that some tasks are rapidly and easily learned, which corresponds to modifying

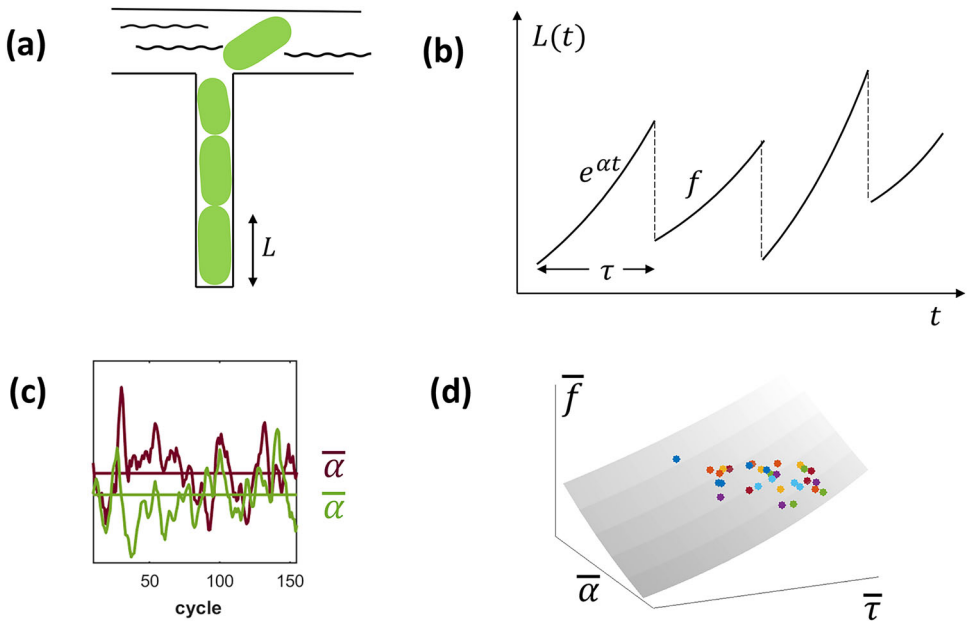


**Figure 1.** Dynamic degeneracy in bacterial growth and division homeostasis. ***a*** Rod-shaped *E. coli* bacteria are grown in a microfluidic device enabling longitudinal measurement of their length with time, L(t). ***b***, L(t) increases exponentially with a rate α until they divide by a fraction *f* after time τ. The fold change over the entire cycle is $fe^{\alpha\tau}$. ***c***, Growth rate α is a sloppy variable; cells exhibit persistent individuality in the average of this variable. (So is τ.) ***d***, The manifold $fe^{\alpha\tau} = 1$ defines the functionality of the system. Parameters of individual bacteria are scattered in this manifold.

the neurons' activity inside the manifold. In contrast, tasks that require out-of-manifold changes are more difficult to learn (Sadtler et al., 2014). Similarly, for bacteria, the existence of a manifold of degenerate compensating variables supporting the crucial function of growth homeostasis may provide flexibility to learn new behaviors and adapt to new conditions. Thus, the degeneracy in the sloppy degrees of freedom provides a mechanism that supports homeostasis and robustness while preserving the system's functionality.

## A cascade of degeneracy in encoding neural systems

The two fundamental requirements of any encoding system are (1) to continually and efficiently adapt to an ever-changing environment so that the responses of the system match the stimulus distribution that is being encoded and (2) to maintain stability in the process of such adaptation, to avoid scenarios that disrupt homeostasis or preclude sustainable future adaptations (Abraham and Robins, 2005; Turrigiano, 2011; Kirkpatrick et al., 2017; Rathour and Narayanan, 2019; Mishra and Narayanan, 2021b; Seenivasan and Narayanan, 2022). How is degeneracy helpful in achieving these apparently contradictory goals (Rathour and Narayanan, 2019)? Systematic efforts to assess the manifestation of the cascade of degeneracy across scales have been lacking, especially in mammalian encoding systems (Westlin et al., 2023).

Assessing the role of degeneracy in the brain is tricky for multiple reasons. First, such assessment must span different biological scales (Fig. 2*A*,*B*). Second, systems at each scale execute distinct, specialized functions. For instance, at the molecular scale, ion channels perform different functions than enzymes. At the cellular scale, excitatory and inhibitory neurons are endowed with distinct physiology. Third, these specialized functions are accomplished through specific combinations of disparate subsystems. Fourth, the definitions of what constitutes individual subsystems and what collective function(s) the complex system is executing are scale- and system-dependent. For instance, at the level of networks, individual neurons might be subsystems that interact to yield complex network behavior. At the same time, neurons are complex systems that emerge from interacting subsystems at the molecular level (Fig. 2*C*). Moreover, biological scales of analysis do not operate in isolation (Noble, 2012; Braganza and Beck, 2018; Mishra and Narayanan, 2021b; Noble, 2022; Noble and Ellis, 2022; Mittal and Narayanan, 2024), as changes in one scale induce changes or drive adaptation at another scale.

There are several lines of evidence for degeneracy from distinct neuronal subtypes in the hippocampal formation, a brain region that is central to several forms of learning and memory. Each neuronal subtype manifests signature physiological characteristics, with some showing intrinsic oscillations (Alonso and Llinas, 1989) and others showing bursting behavior (Masukawa et al., 1982). The ability of disparate molecular components to elicit similar cellular physiology has been demonstrated in neurons in hippocampal and associated regions (Rathour and Narayanan, 2012; Rathour and Narayanan, 2014; Srikanth and Narayanan, 2015; Beining et al., 2017; Migliore et al., 2018; Mittal and Narayanan, 2018; Mishra and Narayanan, 2019; Jain and Narayanan, 2020; Mishra and Narayanan, 2021a; Mittal and Narayanan, 2022; Roy and Narayanan, 2023; Schneider et al., 2023). There is evidence for network-scale degeneracy in hippocampal networks implementing decorrelation (Mishra and Narayanan, 2019, 2021c).

Neurons in the hippocampal formation encode external space through the firing rate as well as through timing of spikes (Andersen et al., 2006). The same amount of spatial information could be transmitted through either a rate code or a phase code while maintaining characteristic physiological properties of respective neuronal subtypes (Basak and Narayanan, 2018; Basak and Narayanan, 2020; Seenivasan and Narayanan, 2020; Roy and Narayanan, 2021).

Synapses differ in the extent and time-courses of the plasticity that they display. At shorter time scales, some synapses show paired-pulse depression, whereas others show paired-pulse facilitation (Zucker and Regehr, 2002). At longer time scales, frequency- and timing-dependent plasticity profiles are synapse dependent (Abbott and Nelson, 2000; Andersen et al., 2006; Jorntell and Hansel, 2006). Disparate cellular components can result in similar short- (Mukunda and Narayanan, 2017) or long-term (Anirudhan and Narayanan, 2015; Shridhar et al., 2022) plasticity profiles in hippocampal synapses. Likewise, long-term plasticity mechanisms can emerge despite differences in ion channel composition, structural, and synaptic properties (Anirudhan and Narayanan, 2015; Shridhar et al., 2022).

Plasticity in disparate components can yield efficient adaptation to a changing environment while also maintaining stability (Fig. 2*D*–*E*). Examples of plasticity degeneracy include the ability of disparate combinations of ion channel plasticity to yield similar circadian transitions (Nagaraj and Narayanan, 2023) and disparate combinations of ion channels and neuromodulators to yield temperature compensations in rhythmogenic circuits (Städele et al., 2015; O'Leary and Marder, 2016; Haddad and Marder, 2018; Alonso and Marder, 2020; Powell et al., 2021; Ratliff et al., 2021; Stadele and Stein, 2022).

## Degeneracy allows the existence of hidden or "cryptic" changes in neurons and circuits

Degeneracy is seen in many rhythmogenic circuits (Prinz et al., 2004; Goaillard and Marder, 2021), in feeding circuits of *Aplysia* (Cropper et al., 2016; Wang et al., 2019), and in thermosensory circuits (Beverly et al., 2011).

The central pattern generating networks of the crustacean stomatogastric nervous system consist of neurons that are individually identifiable and large enough for voltage-clamp analyses of membrane currents, followed by single-cell molecular analysis of mRNA levels (Schulz et al., 2006; Schulz et al., 2007; Northcutt et al., 2016; Schulz and Lane, 2017; Northcutt and Schulz, 2019; Northcutt et al., 2019). These studies have revealed that ion channel expression can vary 2–6-fold in the same neuron across animals, although their electrophysiological properties are very similar. Interestingly when these preparations are perturbed by high extracellular potassium (He et al., 2020; Rue et al., 2022) or by long-term exposure to unusually warm ocean temperatures (Marder and Rue, 2021; Alonso et al., 2023), the networks' resilience to further environmental challenges is altered, although there is no indication of these changes under control conditions.

The existence of these cryptic states depends on the degeneracy of the system and likely occurs as the neurons and circuits respond to perturbations but do not return to the same place in parameter space on the manifold that defines successful solutions to that activity pattern after the perturbations (Fig. 3).

## Neural degeneracy from a causal and computational perspective

In biology, the notion of degeneracy explicitly connects structure with function. Crucially, this connection is not one-to-one but

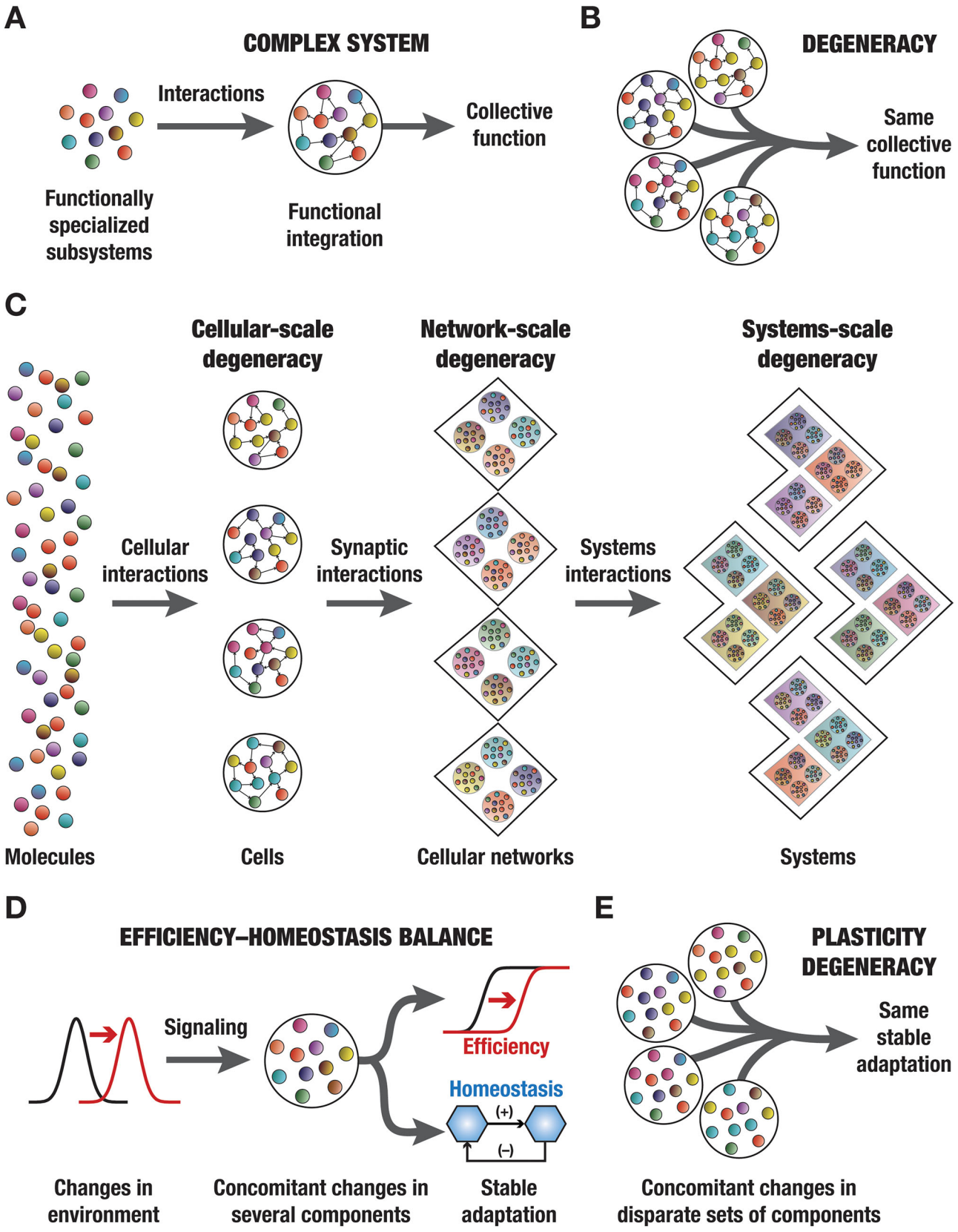


**Figure 2.** Cascade of degeneracy in biological complex systems. ***A***, A complex system is characterized by several functionally specialized subsystems that interact to yield collective function. The motif-based interactions among the subsystems result in functional integration toward achieving precise goals, despite the specializations associated with the individual subsystems. ***B***, Complex systems express degeneracy, whereby disparate combinations of functionally specialized subsystems yield the same collective function of the complex system. An important characteristic of complex systems is that the combinations of functionally specialized subsystems that can yield a specific collective function are neither completely random nor are uniquely determined. Specific combinations of functionally specialized subsystems and interactions among them yield similar function, thus placing complex systems in the regime of intermediate randomness. ***C***, Biological systems are complex systems at each scale of analysis and therefore manifest a cascade of degeneracy. Cellular-scale degeneracy: disparate combinations of molecules (e.g., ion

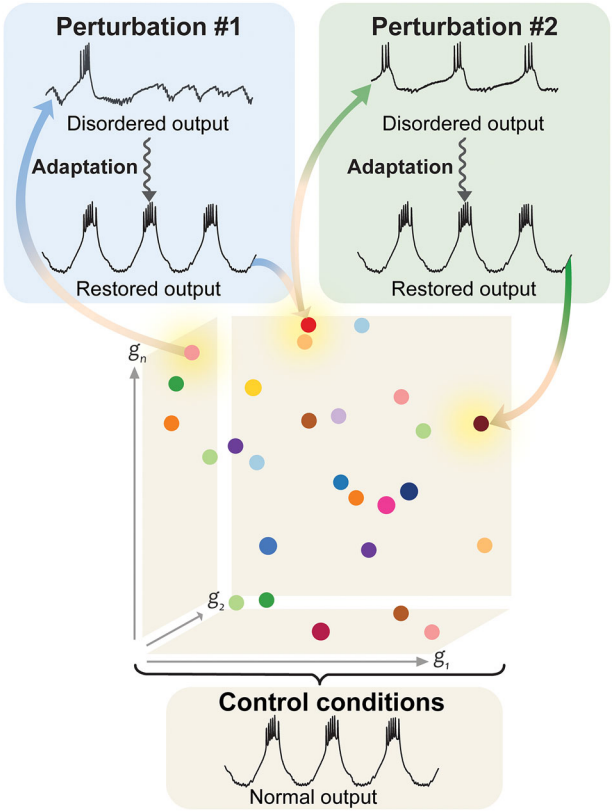


**Figure 3.** Movement through parameter space as a consequence of perturbations. All dots represent neurons with different sets of conductances that produce similar responses. Perturbation #1 disrupts activity, and then the preparation adapts to recover close to normal activity, but when it is returned to control conditions, it has moved in conductance space. A second perturbation has a less dramatic effect because of these cryptic changes. Figure drawn by Dr. Sonal Kedia.

many-to-one, with multiple structures achieving the same or similar functions. For example, intersubject variability is evident across scales, from ion channels (Goaillard and Marder, 2021) to the structural and functional connectivity of larger brain regions (Gordon and Nelson, 2021).

Within individuals, degeneracy can occur not only between different anatomical brain structures that perform overlapping functions but also among anatomically similar units, like neurons or minicolumns, because their connections with each other partially overlap (Fig. 4). In networks of causally interacting units, degeneracy and redundancy can be quantified using tools from information theory and causal analysis (Tononi et al., 1999; Pearl, 2000; Hoel et al., 2013; Albantakis et al., 2019).

Translated into the language of cause and effect, degeneracy means there are multiple distinct ways to cause the same effect. In contrast, redundancy means there are multiple equivalent causes for the same effect, as illustrated in Figure 4*A*. In this figure, neuron $N_5$ receives four suprathreshold inputs from neurons $N_{1-4}$. Each input alone is enough to make neuron N5 fire, making them redundant causes. In Figure 4*B*, neuron $N_5$ receives subthreshold inputs with different strengths from neurons $N_{1-4}$. Only specific combinations, like $N_1 + N_3$ or $N_1 + N_4$, are now sufficient to make neuron $N_5$ fire, making these combinations degenerate. This example highlights how different inputs can produce the same effect, illustrating the many-to-one nature of degeneracy.

With more than one output neuron, degeneracy may also arise as a complement of "plurifunctionality" (having multiple effects; Friston and Price, 2003; Goaillard and Marder, 2021). This occurs when individual input neurons affect partially overlapping sets of output neurons (Fig. 4*C*), making the input–output mapping many-to-many. Notably, just as subsets of inputs may have joint effects, subsets of output neurons may form irreducible "high-order" mechanisms with joint causes (Albantakis et al., 2019). In Figure 4*C*, for example, the two output neurons $N_5$ and $N_6$ may perform not just two but three distinct computations due to their partially overlapping units. This is because together, $N_5$ and $N_6$ may specify irreducible information about their joint inputs, which is not captured by either N5 or N6 alone. Degeneracy thus enables rich causal structures composed of many irreducible high-order mechanisms and the relations between their causes and effects (Albantakis et al., 2019; Grasso et al., 2021).

Recurrent systems naturally implement many-to-many mappings between their units, leading to inherent plurifunctionality and many irreducible high-order mechanisms (Fig. 4*D*). Biological networks, including the brain, are prime examples of selective, recurrent connectivity, explaining why plurifunctionality is a fundamental feature of these systems. Higher-order mechanisms are also prevalent in complex computational systems (Albantakis and Tononi, 2015) and are conceptually related to the notion of distributed computation. However, achieving a rich causal structure composed of many mechanisms at all orders—from elementary units to the entire system—requires the right balance between functional integration and segregation (Tononi et al., 1999; Albantakis et al., 2023). Causal composition thus connects degeneracy with complexity, as first highlighted in (Tononi et al., 1999), who also recognized the critical role of considering all system subsets in defining a quantitative measure of degeneracy in biological networks.

Although degeneracy allows for causal redundancy and thus robustness, it also facilitates computational efficiency by enabling causal composition, allowing systems to pack more functions onto the same number of units, which is of adaptive advantage (Albantakis et al., 2014). Especially across individuals, degeneracy also facilitates selection, leading to increased evolvability (Friston and Price, 2003; Whitacre and Bender, 2010). Finally,

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channels, cytosolic buffers, transmembrane pumps, cytoskeletal proteins) could yield characteristic cellular function (e.g., action potential firing properties, oscillations) through interactions between molecular components and cellular variables. Network-scale degeneracy: several disparate combinations of cells (e.g., excitatory neurons, inhibitory neurons, neuromodulatory neurons, glial cells) interact to yield characteristic network functions (e.g., network rhythm generation, continuous attractor dynamics, latent dynamics in a reduced dimensional space) through synaptic interactions. Systems-scale degeneracy: disparate cellular networks (in same or different regions) could interact to yield characteristic systems-scale outcomes (e.g., interactions with the external world, breathing) through systems-level interactions. ***D***, Encoding systems must continually adapt to a changing environment (shown as a rightward shift in the distribution of the encoded variable). Changes in several components drive efficient adaptation (shown as a rightward shift in the sigmoidal response of the system) to environment changes coupled to homeostatic balance of specific system characteristics (shown as a negative feedback loop). Plasticity is governed by mechanisms that sense environmental changes and associated signaling cascades. Systems maintain the balance between efficiency and homeostasis to achieve stable adaptation. ***E***, Plasticity degeneracy: encoding systems achieve similar stable adaptation through disparate plasticity routes. Each plasticity route involves changes in several components and is distinct from the other routes in terms of the components that change or the nature of changes in each component.

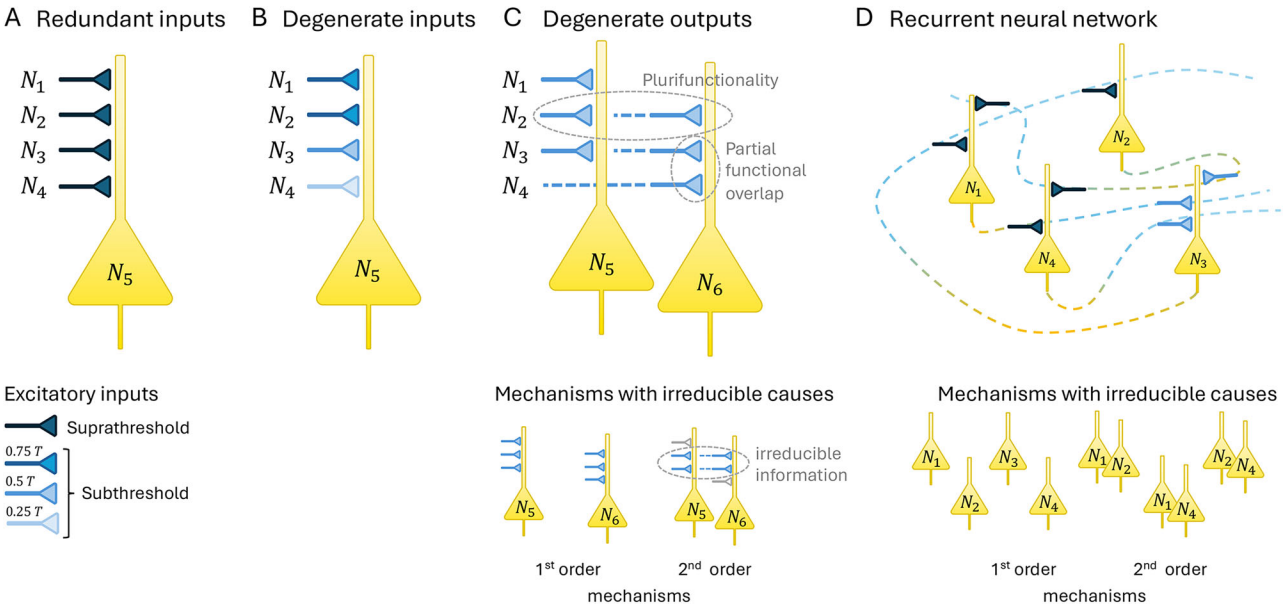


**Figure 4.** Redundant and degenerate causes exemplified by neuronal interactions. ***A***, Redundancy: a neuron (N5) receives four suprathreshold synaptic inputs from other neurons ($N_{1–4}$). If neuron $N_5$ fires an action potential, all active inputs are considered redundant causes, as each input alone is sufficient to activate $N_5$. The input neurons in this example are thus structurally equivalent. ***B***, Degeneracy: neuron $N_5$ receives multiple subthreshold synaptic inputs with varying weights. Only specific combinations of active synapses are sufficient to activate $N_5$ (e.g., $N_1 + N_3$ or $N_1 + N_4$). These combinations form degenerate causes. While they can activate the neuron in the current context, their effects may differ, e.g., if the neuron's firing threshold changes due to short-term plasticity. The heterogeneity in synaptic weights thus makes the input neurons structurally different. ***C***, Neurons $N_{1–4}$ can also become structurally different by connecting to multiple, partially overlapping target neurons ($N_{5,6}$), which highlights the link between degeneracy and plurifunctionality (multiple effects). Moreover, neurons with partially overlapping inputs, like $N_5$ and $N_6$, may form "high-order" mechanisms, providing that they specify irreducible information about their joint inputs not captured by either constituent ($N_5$ or $N_6$) alone. ***D***, In recurrent neural networks inputs and outputs implement a many-to-many mapping, resulting in inherent plurifunctionality and degeneracy, as well as rich causal structures with many irreducible high-order mechanisms.

degeneracy promotes the emergence of mesoscopic functional units organized into higher-level systems that may be more causally specific and integrated than the underlying microscopic system (Hoel et al., 2013; Marshall et al., 2018).

The structural richness associated with degenerate systems poses challenges for researchers in identifying the causal origins of systemic disorders or predicting the effects of interventions (Price and Friston, 2002). Combining advanced causal analysis techniques with increasingly accurate whole-brain models may be one way to make significant process (Deco et al., 2015).

## Concluding remarks

Evolution and adaptation to diverse environments depend on degeneracy. As experimental tools allow increased measurements of system components and their interactions at every level in biological systems, we anticipate that the future will provide new understanding of the interactions and correlations among system components that allow stable and resilient physiological processes to occur.

Authors are listed by last-name alphabetical order. All authors contributed to writing and editing of the manuscript.

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