Seminars in Cell & Developmental Biology 88 (2019) 36–45

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Evolutionary transitions in controls reconcile adaptation with continuity of evolution

Alexander V. Badyaev

Department of Ecology & Evolutionary Biology, University of Arizona, Tucson, AZ 85721, United States

ARTICLE INFO

Article history:
Received 9 November 2017
Received in revised form 19 February 2018
Accepted 15 May 2018
Available online 19 May 2018

Keywords:
Controllability
Degeneracy
Innovation
Metabolic network
Robustness
Evolvability

ABSTRACT

Evolution proceeds by accumulating functional solutions, necessarily forming an uninterrupted lineage from past solutions of ancestors to the current design of extant forms. At the population level, this process requires an organismal architecture in which the maintenance of local adaptation does not preclude the ability to innovate in the same traits and their continuous evolution. Representing complex traits as networks enables us to visualize a fundamental principle that resolves tension between adaptation and continuous evolution: phenotypic states encompassing adaptations traverse the continuous multi-layered landscape of past physical, developmental and functional associations among traits. The key concept that captures such traversing is network controllability – the ability to move a network from one state into another while maintaining its functionality (reflecting evolvability) and to efficiently propagate information or products through the network within a phenotypic state (maintaining its robustness). Here I suggest that transitions in network controllability – specifically in the topology of controls – help to explain how robustness and evolvability are balanced during evolution. I will focus on evolutionary transitions in degeneracy of metabolic networks – a ubiquitous property of phenotypic robustness where distinct pathways achieve the same end product – to suggest that associated changes in network controls is a common rule underlying phenomena as distinct as phenotypic plasticity, organismal accommodation of novelties, genetic assimilation, and macroevolutionary diversification. Capitalizing on well understood principles by which network structure translates into function of control nodes, I show that accumulating redundancy in one type of network controls inevitably leads to the emergence of another type of controls, forming evolutionary cycles of network controllability that, ultimately, reconcile local adaptation with continuity of evolution.

Contents

E-mail address: abadyaev@email.arizona.edu

https://doi.org/10.1016/j.semcdb.2018.05.014
1084-9521/

1. General principles

1.1. Key dual requirement of evolution and transitions between robustness and evolvability

Understanding the relationship between stability and innovation remains one of the central questions in biology. In evolutionary theory, this relationship demands that the historical connectedness of elements that determine contemporary phenotypes coexist with survivability of intermediate steps in order to form uninterrupted lineages [1,2]. The interplay between homeostatic preservation of existing phenotypes (robustness) and exploration of alternative phenotypic states (evolvability) produces the general organizing principle of biological networks – a connected layered landscape of robust networks, each delineating a boundary of a phenotypic state [3–6]. Robustness within each phenotypic state is, by definition, associated with suppression of variation not conducive to the phenotype's current functioning [7–9] with accumulation of phenotypically silent variation being proportional to the complexity of adaptation [10,11]. When the threshold of robustness within a phenotypic state is exceeded as a result of environmental change, physical constraints, system failure or major mutation, the effects of newly expressed variation alter the phenotypic state and may lead to another phenotypic state [2,12–16]. To the extent that the new phenotypic state is accessible [17–21] and survivable (e.g., not associated with appreciable decline in fitness)[22,23], it is retained in evolutionary lineage. Under this perspective, the patterns of connectivity of elements that underlie a phenotypic state are formed by historical associations (physical and biological) of these elements. These patterns also necessarily delineate the pathways available for subsequent evolution.

Insights into the evolution of organismal architecture that balances robustness and evolvability are further enriched by the realization that elements of this architecture evolve at different rates and under different pressures at distinct levels of organization (e.g., molecular, cellular, organismal, ecological) [19,24,25] – not all changes at one level of organization are reflected at another. For example, not all genetic changes modify phenotype and not all phenotypic changes have a genetic basis. Further, different rates of evolution at different levels of organization imply accumulation of distinct historical contingencies and controlling propensities in their organization [26,27]: for example, genomes and phenotypes are unequally affected by the history of functioning in the same environment over the same period of time. There are also reciprocal affects of such level discordance: for example, greater robustness of complex phenotypes in smaller populations (due to inefficacy of selection in discriminating between small changes in genotypes) can lead to an increase in phenotypically neutral neighborhoods at a lower level of organization [28,29], and also to greater accumulations of unexpressed phenotype-altering solutions that become available when conditions of development change.

In sum, the deterministic landscape must be continuous at least at some level of organization (e.g., gene networks, protein networks, or morphogenic transformations) to enable uninterrupted traversing during evolution that assures both the maintenance of current phenotypes and search for novelties. The efficacy of traversing is a function of both the size and juxtaposition of phenotype-neutral and phenotype-altering neighborhoods, the distribution of connectivity across the neighborhoods, and of selection and drift forces that determine the distance a population can travel on this landscape in ecologically relevant time [30–33]. Such traversing includes not only movement on the landscape, but also connecting and combining previously unlinked elements of this landscape, commonly at different levels of organization [26,34]. The key metric that reflects the tempo and mode of such traversing is network controllability.

1.2. Network structure determines its control profiles

Network controllability refers to the ease and ways in which one network state can be moved to another (Fig. 1a) [35,36]. The nodes that are influential in this process, either because of their topological position, connectivity, or the effect on flux are control (or driver) nodes [37,38]. The control nodes are influential not only in the change of network configurations, but also in their functioning. For example, networks that are completely controlled by a few nodes are typical of communication and manufacturing networks, where efficient and streamlined propagation of information or products is accomplished by network subordination to a small number of control nodes. Networks with numerous distributed controls harbor significant potential for innovation and are more resilient to change in inputs, but are less suited for precise functions.

Because controllability is mechanistically determined by how many neighbors each node can directly control, a high degree asymmetry – the difference in number of incoming and outgoing links per node – contributes the most to the node's control propensity [35,37,39–41]. Which explains why hubs – the nodes that are essential for network maintenance and function and thus have low degree asymmetry – rarely control directed networks [37,42]. Instead, in biological systems, the hubs are most conserved, often encompassing a module of essential biological functions that is maintained across vast evolutionary distances and organizations [43–48].

Control nodes can be classified into three categories based on their connectivity and topology [49]: control nodes that have no incoming edges and only outgoing edges are *source* controls, control nodes that have both incoming and outgoing edges are *internal* controls, and control nodes that have no outgoing edges are *sink* controls (Fig. 1a). A convenient metric to summarize distribution of control nodes is to calculate the control profile of a network – the ratio of the three control types for each network configuration (Fig. 1a). Empirical derivation of control profiles for biological networks shows that while all three types of controls are common and change in control profiles (i.e., topological transference of control nodes) occurs in the evolution of biological networks [49], at any given state, the network is dominated by just one type of control [40,50,51]. This is an important property, enabling us to use changes in control profiles of biological networks to gain insights into the mechanism behind network change – i.e., whether the network had evolved by adding nodes at the periphery (adding sink controls), by accumulating internal connectivity and complexity (adding internal controls), or by accepting more inputs (adding source controls).

This framework is particularly illuminating in biological systems where the topological features outlined above clearly correspond to functions (Fig. 1a). For example, in ecosystems, the source controls, external to networks, but controlling it, could be predation or food input. Enzymes in a metabolic network that control flux to several alternative metabolites can be internal controls. Diverse color patterns produced by integrating internal pigments into the integument is an example of sink controls. Such correspondence between biological function and network structure enables us to infer the evolution of function from evolution of form (control profiles) and here I suggest that evolutionary transference of control profiles provides a key conceptual insight into the coexistence of robustness and evolvability in biological systems.

1.3. Evolutionary transitions in control profiles

Robustness – a preservation of a particular system or characteristics despite uncertainly of its components or environments – is required for functioning of a biological system. As such, robustness is a context-dependent filtering of variation; a boundary that

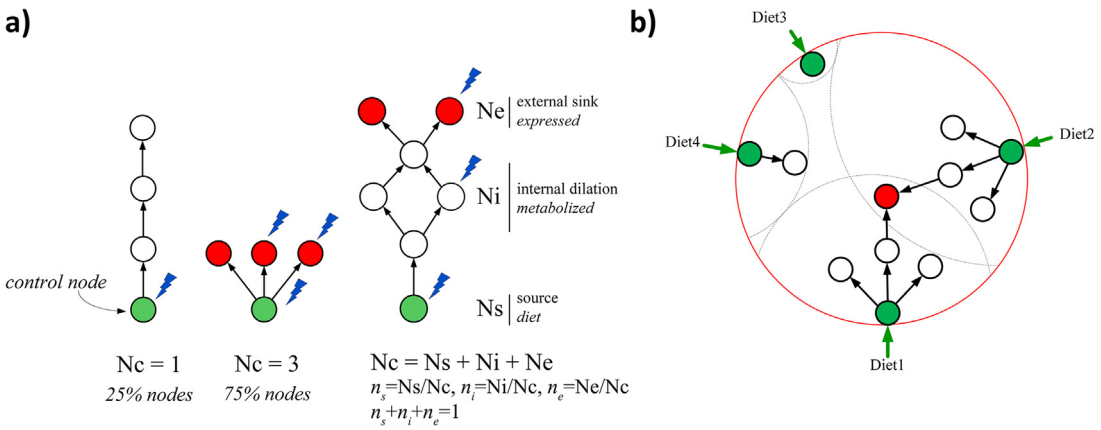

Fig. 1. Network degeneracy and controllability. **(a)** Nodes that are influential in controlling a network are control nodes (shown by lightning symbol). The linear network on the left is completely controlled by a single node (number of control nodes, Nc = 1) – at the source – irrespective the length of the pathway. The directed star at the center, with the same number of nodes, requires Nc = 3 nodes to control it. Control nodes can be classified based on their topology into source, internal, and sink controls (see text). In avian carotenoid networks, these designations correspond to biological functions of dietary, metabolized and plumage compounds (see text). **(b)** Network degeneracy illustrated by the avian space of the global carotenoid network. The connected biochemical network used by birds can be represented by a closed circle surrounded on periphery by dietary carotenoids – entry points for initiation of carotenoid metabolism by species of different ecologies. For example, Diet1 can represent dietary carotenoids acquired from seeds, Diet2 – from insects, Diet3 – from fruits, and Diet4 – from fish. Once dietary carotenoids (filled green circles) are consumed, birds can metabolically convert them to various degree (shown as nodes, linked by reactions). Avian networks are degenerate, such that any significant metabolic elaboration invades the biochemical proximity (dashed lines) of other dietary input, the nodes shared between pathways starting from different dietary entries (and thus interchangeably producible by either of the pathways) are degenerate and biochemically redundant (shown as a red node).

delineates what can be expressed at different times, life stages, and levels of organization without compromising phenotype functioning [7,52,53]. Over evolutionary time, accumulation of robustness of a system leads to its complexity. Whether or not variance suppressed by robustness (i.e., by current functioning) promotes or impedes evolvability depends on how quickly and efficiently this unmasked variance enables transitions to an alternative adaptive phenotypic state. This, in turn, is a function of both – the structure of newly expressed variation and distribution of novel phenotypic states within a scope of this variance [54,55]. Because evolutionary shifts (spatial or temporal) in network controls encompass both of these properties, they provide useful insights into transitions between robustness and evolvability.

In these shifts, former control nodes that enabled a transition from a previous to the current phenotypic state become essential elements for system functioning, but are no longer controlling, such that upon reaching the boundary of a new phenotype state, some control nodes become essential for the maintenance of adaptation. For example, the metabolic boundary of organisms can include a set of compounds that cannot be internally synthesized but must be obtained from the environment [56] – termed "the seed set" by Borenstein et al. [57]. The elements of the seed set are essentially the source controls of the phenotype's metabolic network. Phenotype robustness to fluctuations in external environment is enhanced by internalization of the seed set and corresponding transference of controls from source to internal nodes (Fig. 1b). Borenstein et al. [57] showed that transition from the source to internal control evolved twice faster than transitions from internal controls to a new source control that enabled encompassing of new external seed metabolites into an organismal network. Internalization of seed metabolites in this system maintains phenotype robustness in the current environment, whereas acquisition of new external seed metabolites enables its evolvability.

Mechanistically, gaining controllability for a node is a consequence of changes in the distribution and directionality of network edges. For example, gaining an additional source control link on Fig. 2b makes each of the previously controlling links functionally redundant, whereas an additional link between existing source-controlled modules can transfer control of the network from source to internal nodes (Fig. 2c). Although the source control nodes remain essential for network functioning in Fig. 2b, they are no longer controlling [58]. Several mechanisms can produce transition between redundancy (structurally similar components involved in the same function) and degeneracy (structurally different components contributing to the same function) [59–65]. Importantly, the transition between redundancy and degeneracy are associated with changes in control profile – redundancy in one type of control leads to the emergence of another, rather than to accumulation of controls, results which are supported by recent modelling [3] and empirical [51] studies. Transference of control necessarily connects distinct phenotypic states; internal controls provide bridges to new adaptations (Fig. 2d), leading to prediction that internalization of controls enables continuity of evolution.

The distribution of control nodes on a network emerges as a compromise between competing demands of robustness and evolvability [3,66–68], leading to some general principles of organization in development and metabolism. For example, hierarchical organization of control nodes is common in development and thought to reconcile robustness of a newly acquired state and its developmental modifications [69]. Novel features are primarily added downstream in hierarchies, where they have less detrimental effects on phenotypic integration during development (and conversely are less controlled by the preceding structures than more basal additions). Close interconnection and feedback loops within developmental modules (e.g., within gene regulatory network kernels) preserves these modules, forcing modifications into nodes linking these modules. Together these forces determine the topology of control nodes, ultimately forming developmental hierarchies [70,71]. Indeed, temporal traveling of control nodes might be important to developmental stability during both major evolutionary innovations [72–75] and microevolutionary change [76]. In fact, the traversing might be an inevitable consequence of the biasing effect of past natural selection on the patterns of subsequent developmental variation – where correlated external selection (source controls) leads to the evolution of internal regulatory interactions (internal controls) among elements [77]. Findings that the rate of gene evolution depends on gene topology along metabolic hierarchies [genes at downstream and terminal positions evolve faster [78]] and that topology of flux controlling nodes varies with selection regime [79] corroborate these ideas.

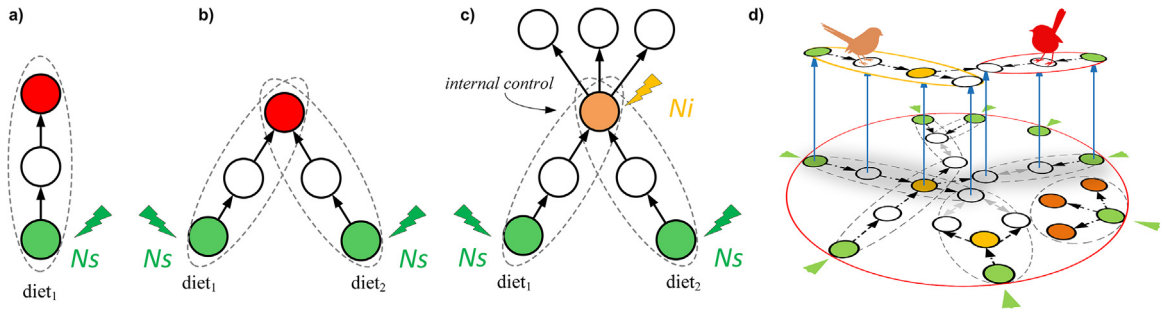

Fig. 2. Degeneracy enables shifts in network controls. **(a)** Linear path from a dietary input (green node) to the product (red node) is fully controlled by the source. **(b)** When the same product can be derived by a different source-controlled path, each of the structurally distinct pathways become functionally redundant, reducing the controllability of each source by a half. **(c)** When number of outgoing reactions in the redundant node (orange) exceeds that of the incoming reactions, the redundant node acquires internal control over the network that can exceed that of each of the source controls, illustrating how a source- dependent system can internalize control through changes in topology. **(d)** Internal controls act as bridges between different adaptations, shown here as diet-specific modules (dashed ellipsoids starting with dietary carotenoid on avian biochemical space from Fig. 1b), and thus enable continuity of evolution.

1.4. Integration among levels of organization: spatial and temporal transference of controls

Evolutionary consequences of control transfer are enhanced by hierarchical organization of biological systems, because different levels of organization provide the context and selective environments for each other. For example, internalization of control by a metabolic network (e.g., by making a product of dietary input redundant, Fig. 2c, see below), necessarily affects control profiles at a higher level of organization (such as in tissues that depend on reliable supply of that product) [26]. Similarly, hierarchical and multilevel organization enables retention of changes that are functionally beneficial at one level, but would be destabilizing at another if expressed there – for example, trade-offs at the nucleotide sequence or transcription levels do not imply a trade-off at the level of phenotype [80,81]. Such accommodation and mutual "updating" [82] between levels seem crucial in evolution, culminating in ubiquitous convergence in phenotypic (e.g., metabolic) evolution, despite general lack of repeatability at the lower levels (e.g., sequence evolution).

Correspondence between control profiles of networks operating at different levels of organismal organization may determine the evolution of development that depends explicitly on reciprocal and selective interactions between levels of organization to maintain tissue and organ functioning and complementarity. Specifically, in developmental hierarchies, and in organismal accommodation of novel inputs in general, we might envision temporal transference of controls between levels of organization (see 2.4 below). Such as when entities at one level of organization are controlled by processes at another level and the distribution of such controls between levels changes in evolution of development and functioning.

1.5. Biological mechanisms behind evolutionary transference of network controls

Any mechanism that changes the distribution and directionality of node edges in a network across generations has a potential to affect the node controllability. Whether it does or not depends on the distribution of effects of other nodes within a network [35,37,58]. Correspondingly epistatic interactions that describe such context-dependency of effects should be particularly prevalent mechanism for both changing and preserving the network's controllability profile at genetic and phenotypic levels [81]. Yet, numerous other patterns and processes expressed at different levels of organization, such as degeneracy, redundancy, non-linearity, and pleiotropy can affect controllability. Fundamentally, evolution by natural selection affects evolutionary transference of network controls by favoring co-expression of consistently co-selected traits, something that lowers dependence of such co-expression on environments and increases robustness of a structure [83–85].

In sum, the controllability metric is useful because that it enables us to measure contribution of these diverse mechanisms for the transition between robustness and evolvability in a particular system. For example, even in very complex biological networks simple changes in directionality of one or a few links or internal dynamics (such as formation of feedback loops) can lead to drastic changes in controllability [58,86] with significant consequences for both current functioning and evolutionary change. These alternations determine the likelihood of transition between robustness and evolvability [3,86], but also enable characterization of a system in relation to likelihood of such transition. For example, one can compare networks in relation to the easiness by which specific structural changes (such as number of links that need to be reversed or removed) result in controllability change [39,40,87].

2. Examples

2.1. A model system: degeneracy of metabolic networks

Modularity in biochemical networks evolves readily when organisms functioning in different environments require different combinations of biochemical functions – that is when both the environment and corresponding function change in a modular fashion [88,89]. For example, the external metabolites of biochemical pathways commonly differ across environments. When a derived product of metabolic pathways is needed for an organism's persistence, but its' dietary precursor is not currently available, homeostasis coopts other reactions capable of producing this metabolite from different precursors [90–92]. This leads to evolution of degeneracy – a type of biochemical redundancy that emerges at the level of a product (Fig. 1b) [59,61,63,64].

In degeneracy, each of the biochemical modules performs distinct functions (such as adaptations to different environments), but the hubs at the intersection of these modules produce an identical product (Fig. 1b). Unlike basic and distributed redundancy, where structurally identical (e.g., duplicated and excessive) components contribute to the same function, degenerate components are structurally distinct and thus can produce different functions under different conditions [64]. For these reasons, degenerate elements increase both complexity and robustness of a biological system – dissimilar structures contribute to the same function and thus are not easily eliminated by selection on shared output [59,64,65,93]. Further, structural dissimilarity of components

that contribute to the same function potentiates future adaptations and diversification – it creates "surplus of structures for later exaptations" [61]. The cohesion of the degenerate network is maintained by the diversity of functions in different environments over different time scales (see 2.3 below). Such system is uniquely adaptable – different functions are produced in different environments [63,94] and same functions can be produced by different underlying components [59]. Network degeneracy therefore arises as a compromise between environment-specific function of each structurally distinct module and the transition between modules when the environment changes. This makes it a model system in which to study a balance between robustness and evolvability of a phenotype and the role of controllability shifts in this process.

2.2. Evolutionary shifts in controls of carotenoid networks

The evolution of carotenoid-producing network in birds provides a particularly compelling empirical example of role of control shifts in balancing robustness and evolvability. To color themselves, birds consume dietary carotenoids from the environment, metabolically convert them to various degrees into derived carotenoids which they deposit in the plumage [95]. Because birds cannot synthesize carotenoids from noncarotenoids, the evolution and diversification of their carotenoid-based colors is deterministically confined to a closed and connected biochemical space – a small subsample (about 150 compounds, less than 3%) of the global carotenoid network [96] – delimited by dietary carotenoids with which different bird species start their carotenoid metabolism ("entry points" in Fig. 1b) [97]. Depending on their ecology and physiology, different avian clades utilize different areas of this connected biochemical space over evolutionary time, with such explorations necessarily linked to the vicinity of dietary entries (Fig. 1b).

Connectedness of the avian biochemical network results in its degeneracy – production of an identical derived carotenoid through enzymatic pathways starting from different dietary carotenoids (Fig. 1b). In avian carotenoid biosynthesis these pathways comprise biochemical modules, each starting with a dietary carotenoid and linked to downstream compounds though a series of enzymatic reactions [95,98]. Biochemically redundant (i.e., degenerate) carotenoids are then expressed when any of their dietary precursors are encountered. These modules are remarkably conserved throughout avian evolution; most avian carotenoid diversification is attributed to recombination of biochemical modules, with patterns of enzymatic connectivity within each module remaining largely intact [99]. Thus avian carotenoid networks present a particularly tractable system in which distinct stable phenotypic states are linked by bridges of biochemically redundant nodes (Figs. 1b, 2d).

Degeneracy of the carotenoid network plays a key role in avian color evolution. Within species, it maintains polymorphism, conveys robustness to metabolic networks, allowing them to absorb fluctuations in dietary inputs to reliably produce required products, and facilitates close co-evolution of externally obtained carotenoids with other organismal traits, such as feather microstructure and behavioral and life history strategies [76,100,101]. Across species, degeneracy allows rapid recombination of metabolic modules and sustains biochemical elaborations [97]; across the avian phylogenetic tree the biochemically redundant nodes are hotspots of metabolic diversification [98].

In the empirical examples below, I suggest that the common cause of these effects is that degeneracy enables periodic acquisition of internal control at different levels of organization (Fig. 2). This reduces control of dietary inputs and provides bridges between diet-specific modules, thus underlying continuous evolution. Recurrent internalization of controls by external inputs empirically resolves a central question in the theory of evolution – how to reconcile developmental stability of complex phenotypes with their ability to accommodate and integrate novel inputs [84,102–104]. Although many of the ideas about the role of control shifts in this process are speculative and the subject of ongoing empirical confirmation, the examples below illustrate the general principles involved.

2.3. Phenotypic plasticity

What is the architecture of an organismal system that can selectively incorporate environmental inputs, translate them into functional responses, retain the most recurrent solutions over evolutionary time and express them when the inducing and current environment match? The study of phenotypic flexibility – within-generation reorganization ("updating") of adult phenotype – provides a particularly direct insight into features of a system that can non-destructively reorganize a functional phenotype in response to environmental change [105,106]. A particular challenge has been to show how previously successful functional solutions to environmental challenges are preserved and retained (i.e., internalized) to be recalled later either within a lifetime or over evolutionary time [77,107].

During each molt of life, house finches (*Haemorhous mexicanus*) are often exposed to different dietary carotenoids and, correspondingly, activate different metabolic modules of their carotenoid network to produce their feather ornamentation (Fig. 3). Biochemically redundant carotenoids, located at the intersection of diet-specific metabolic modules (Fig. 1b), assure robustness of ornament production despite annual fluctuations in the types and amounts of dietary inputs, i.e., Diet1 and Diet3 [100]. This is accomplished because greater individual experience with different dietary inputs across molts leads to wider utilization of an individual's metabolic network and, correspondingly, progressive accumulation and retention of degenerate pathways leading to the same derived carotenoids (Fig. 3). The accumulation is caused by a priming effect of previous exposure to a particular dietary carotenoid on enzyme efficiency of entire diet-specific metabolic module [100].

Although no single individual utilizes the entire species-specific metabolic network with in a lifetime [100], a diversity of dietary inputs among individuals in a population activates different biochemical modules in the network, likely assuring the cohesion of the entire network (Fig. 3). Over evolutionary time, the network degeneracy enables retention of uses and functional priming of prior generations [59,63,77], resulting in a structure that potentiates adaptations to multiple environments simultaneously, both within and between generations [61].

Thus, greater experience of functioning in this system is mechanistically linked to greater robustness of resulting traits and an increasing ability to recall and non-destructively implement previous adaptive solutions. Such "experience-related buffering" – a routine outcome of network degeneracy in many biological systems [60,108,109] – essentially amounts to acquisition of internal control over an external source-dependent system (Fig. 2). It is very likely that this mechanistic principle is central to the evolution of phenotypic flexibility in general [e.g., [110]].

2.4. Evolution of organismal integration

How can fully-grown multicellular organisms accommodate and retain novel inputs without losing functionality of already evolved structures? Framers of evolutionary theory envisioned a process – genetic assimilation – in which changes induced and controlled by the environment at the peripheries of developmental hierarchies get progressively internalized and stabilized

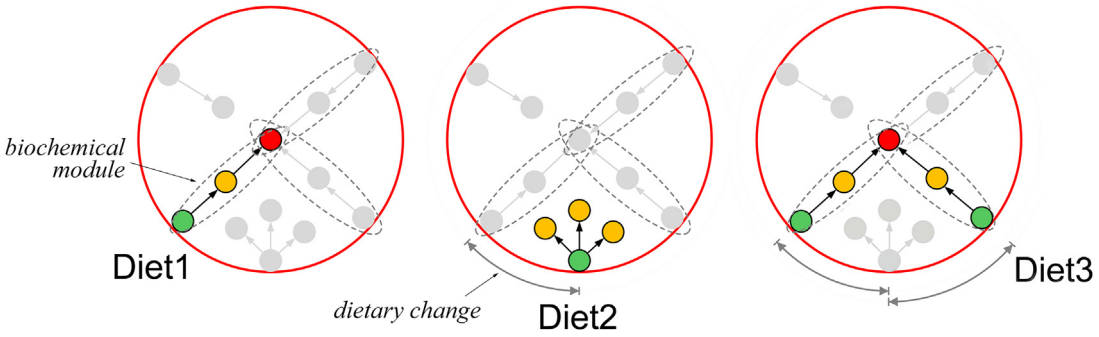

Fig. 3. Experience-related buffering in phenotypic plasticity. Exposure to different diets (green nodes) across a lifetime activates diet-specific biochemical modules or diet-dependent trait production. Some of these modules produce degenerate compounds (red nodes) located at the intersection of some of the structurally distinct modules (Diet1 and Diet3), while others do not (Diet2). Network degeneracy retains the priming and biases of preceding uses within a lifetime, and accumulate in an active network in proportion to experienced dietary change. This accumulation maintains the network cohesiveness and potentiates adaptations to multiple environments simultaneously. Modified from [100].

by regulators of existing traits [102–104,111]. Such a view of evolution as "the direction of ontogenetic accommodations of earlier generations" [112] is mechanistically accomplished by upstream traversing of developmental hierarchies by controls of environmentally-induced phenotypes – a process empirically corroborated by a number of recent studies [46,113–115].

Discordance in evolutionary rates between the levels of organization of an organism promotes the process of genetic assimilation by, first, enabling exploration and search for innovations at one level of organization without compromising current function at another [4,26], and, second, by facilitating accommodation of encountered novelties by other aspects of phenotype [103]. Thus, the process of genetic assimilation can be formalized as a progressive internalization of developmental controls of an adaptive modification, such as when trait expression lessens its dependence on the environment and different mechanisms regulate expression of the same trait across evolutionary stages in a lineage [116–118]. It follows that a definitive test of genetic assimilation requires direct assessment of two phenomena: developmental internalization of a trait's controls and the historical recurrence of the inductive environments.

In the evolution of carotenoid-producing metabolic networks, these requirements correspond to the extent of carotenoid metabolism (and thus degree of internalization of derived carotenoids) and to biochemical redundancy of some derived carotenoids that assures their longer co-evolution with other organismal components (Fig. 4). Indeed, birds repeatedly evolved the ability to integrate biochemically redundant carotenoids into their feather growth, whereas inclusion of novel carotenoids of the same molecular weight induced greater aberrations in feather growth [76]. Thus, the evolution of carotenoid ornamentation in avian lineages may be thought of as an arena for ongoing cycles of control profiles of developmental hierarchies – passing through stages of phenotypic induction by external carotenoids (source control) to progressively internalized metabolism of derived carotenoids and their integration with feather growth (internal control) and restarting when an avian lineage switches to novel dietary precursors and associated novel source controls [97].

2.5. Macroevolutionary trends

How do external components of traits get reliably incorporated into the phenotype and stabilized over evolutionary time scales to produce long-term trends? What compensates for unpredictability and contingency in these components? One of the most striking resolutions of this problem is found in evolutionary trends of carotenoid coloration in birds. Not only must carotenoids be obtained with diet to initiate their metabolism and their availability and diversity fluctuates widely, but dietary carotenoids also are some of the most unstable chemical compounds that degrade rapidly with routine UV and oxygen exposure [101 and references therein]. Indeed, environmental fluctuations and biochemical instability limit the evolution of carotenoid-based displays and lead to evolution of strategies that compensate for such instability [101]. Yet, occasionally, these environmentally-derived compounds acquire enough predictability to evolve complex and lineage-specific colorful displays and intricate associations with other aspects of the phenotype. The difference between these outcomes is related to acquisition of biochemical redundancy (Fig. 1b) that enables internalization of control of dietary inputs in a taxa's enzymatic network [101].

Fundamental dependency on dietary carotenoids strongly constrains evolutionary elongation of multi-step metabolic pathways needed for color elaboration in birds, because linear pathways are fully controlled by the source node, regardless of their length (Figs. 1a, 2a). Networks with only source controls are, thus, highly vulnerable to failure (network vulnerability measures the propensity for disruption in network function by deletion of any one of the existing compounds [119]). This is why avian carotenoid networks are twice more vulnerable to crucial link failure compared to plant networks of the same size and complexity [97] – in plant networks, the incoming edges are not controlling since plants, unlike birds, can metabolize carotenoids from non-carotenoids.

On average, avian clades gain and lose new dietary inputs (and thus new source controls) every 2–4 million years and such high lability of source inputs severely constrains the time for evolution of the metabolic elaboration that depends on them [97]. Correspondingly, there are no avian species that depend on a single dietary precursor (and thus are completely controlled by a single source input) and yet show metabolic elongation of their plumage carotenoids longer than two reactions away from a dietary precursor [97]. Instead, avian carotenoid evolution is driven by periodic encounters of biochemically redundant carotenoids (Fig. 1b), located at the intersection of diet-specific modules, that decrease controllability of dietary inputs [97,98]. Gains and losses of these redundant compounds produce evolutionary cycles of elaboration and collapse in avian carotenoid coloration (Fig. 5). In degenerate network, failure to encounter a redundant node constrains a lineage's metabolic exploration to the immediate biochemical vicinity of their dietary carotenoids (that is to one functional module), whereas gains of redundant nodes result in sustained elongation of metabolic pathways (because several structurally and functionally distinct modules that sustain such elaboration are unlikely to be lost at the same time). Therefore,

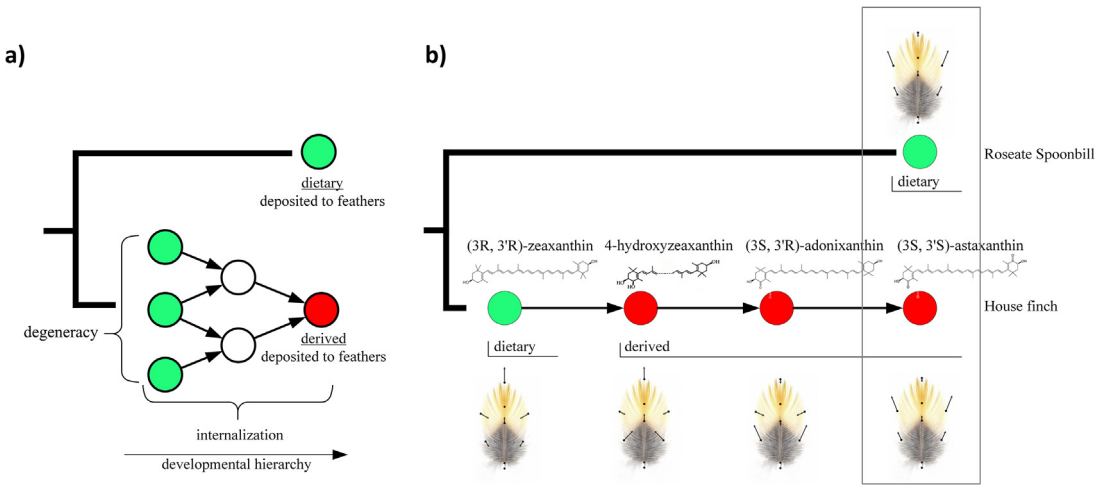

Fig. 4. Developmental shifts in controls. **(a)** Species can deposit either dietary (green circles) or biochemically modified (red circles) carotenoids (that pass through intermediate carotenoids – white nodes) in their feathers. Extent of biochemical conversion is a measure of organismal internalization, whereas degeneracy assures recurrence of some derived carotenoids. **(b)** Some of the most internalized carotenoids (e.g., astaxanthin) in one species (the house finch – lower node – multiple steps of metabolic conversions, each associated with feather modification shown below) are dietary in another (the roseate spoonbill – the upper node) allowing assessment of carotenoid effects on feather structure in relation to degree of internalization of its metabolic controls. Modified from [76].

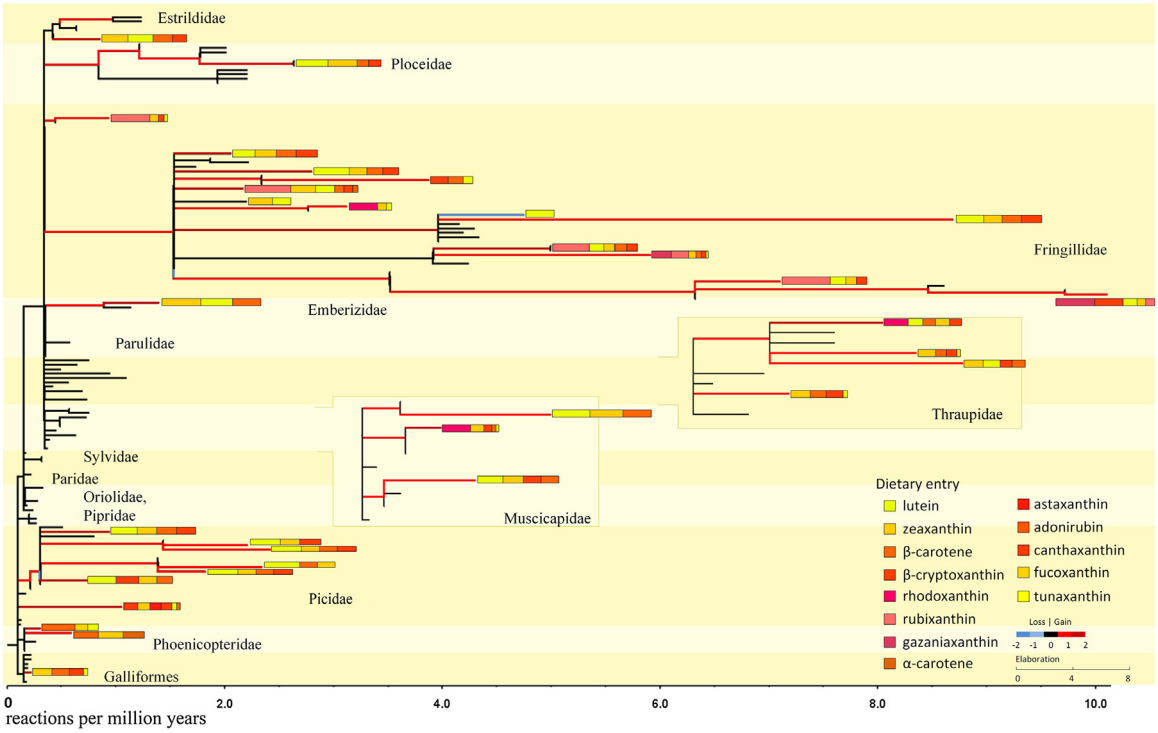

Fig. 5. Network degeneracy and associated gains of biochemically redundant carotenoids sustain metabolic elaboration in birds. Shown is avian phylogenetic tree scaled to the rate of carotenoid evolution (biochemical reactions/my). Branch length is zero in most species (and thus merged with the trunk of phylogenetic tree). Rectangles at nodes of species that showed accelerated rates of metabolic evolution (longer branches) show the length of elaboration (in reactions between dietary and plumage carotenoids) partitioned by the number of diet-specific modules (different color) that contribute to it. Fifty three out of 54 evolutionary transitions from accelerated ancestral to accelerated descendant rate were associated with the gain of additional pathway from a dietary carotenoid. All 69 cases of the network collapse or rate stasis were associated with the failure to gain an additional pathway from a new dietary carotenoid. Modified from [97].

in this case, evolution of one adaptation is sustained by evolution of another adaptation, providing an empirical example of the link between adaptation and continuing evolution.

The probability of encountering a biochemically redundant node is a function of the distribution and frequency of such nodes on the biochemical landscape accessible for an evolving lineage of birds. The rarity of such nodes in the vicinity of some dietary entry points accounts for stasis in carotenoid ornamentation in some ecological lineages of birds, whereas a high density of redundant nodes produces exceptional carotenoid diversification in others [97]. For example, every edge (e.g., one enzyme reaction) in the network area occupied by cardueline finches is associated with a gain of a biochemically redundant node [Fig. 10 in [97]] producing both exceptionally elaborated and robust carotenoid plumage coloration in this subfamily.

Because biochemically redundant carotenoids are located at the intersection of diet-specific metabolic modules, periodic acquisition of these compounds produces phenotypic convergence

between phylogenetically distant and ecologically distinct species (Fig. 1b). Such periodic convergence is a hallmark of avian color evolution – patterns of structural connectivity and degeneracy of a biochemical network explain most of the variance in avian carotenoid diversification [94,97,98]. Such convergence further illustrates that internalization of network controls mechanistically reconciles local adaptations within diet-specific modules with continuous evolution across modules (Figs. 1b, 2d).

3. Fundamental assumption and outstanding questions

The evolutionary importance of controllability shifts is based on the assumption that the topology of a network evolves faster than its dynamics or flux [27,120–123]. Two observations are particularly illustrative in this respect. First, there is a striking contrast between low controllability of simple hierarchical networks of microorganisms with large population sizes and streamlined metabolic functions [124,125] and high controllability of complex multicellular organisms with small population sizes [126–128]. Such a difference arises from the presence of internal loops in regulatory networks of multicellular organisms, e.g., when activity of transcription factors is regulated by reciprocal feedbacks. In such systems, the links between the internal loops assume control of the system as whole [129]; corresponding transitions between phenotypic states are formed by either regulatory feedbacks or accumulation of random organization in regulatory networks.

Second, is the extent to which internal dynamics of a network corresponds to its structure. Modeling studies predict that current dynamics of functioning should override any historical constraints on the network structure [19,120]. Indeed, the frequent metabolic convergence and corresponding erasure of ecological and historical effects in metabolic networks support this conclusion [97], as does an empirical study of correspondence between structure and flux in carotenoid network in a bird species [130]. Yet, the pervasive degeneracy of complex biochemical networks, such as seen in the global avian network, should weaken purifying selection against its individual components, regardless of their fitness impact and this should limit concordance between structure and function of a network. Clearly, more empirical studies, especially of multicellular organisms with small effective population sizes are needed to test this assumption empirically.

A system is controllable when it can be driven from an arbitrary initial state to a specified final state in a finite time [35]. As such, controllability has immediate relevance to the predictability of evolution. For example, network degeneracy and associated changes in control profiles discussed here, might explain ubiquitous convergence at phenotypic and metabolic levels despite essentially unknown historical convergence at the sequence level [131]. Further, the controllability concept helps identify network space inaccessible for evolution, either because of structural limitations or when some theoretically possible internal edges are associated with detrimental changes in fitness and thus are not observed [132]. Another promising direction is functional characterization of control nodes to assess the probability of transition between stable phenotypic states that are central to the processes of development and evolution.

The striking parallelism in the role of degeneracy and associated shifts in control profiles in reconciling robustness and evolvability at vastly different evolutionary scales – from phenotypic plasticity to developmental accommodations to macroevolutionary trends – suggests that it might be one of the most general phenomena in development and evolution (Badyaev, ms). This principle might empirically illustrate the pattern envisioned by Dobzhansky [133] and Schmalhausen [102], formalized by Maynard Smith [1] and since then empirically and conceptually corroborated by others [4,28,134,135] that two requirements must be fulfilled for evolution to occur – 1) historical continuity of a deterministic network that links past and present functional associations of its components and 2) survivability of intermediate steps. The organismal systems that satisfy these requirements have to combine functionality and evolvability, and I suggest here that evolutionary cycles in controls is a central aspect of this process.

Acknowledgements

I am grateful to three referees for insightful comments that improved the paper, to Vincent Debat and Arnaud Le Rouzic for the invitation to contribute, suggestions of important references, and editorial comments, and to Renee Duckworth, Xander Posner, Erin Morrison, and Nikolay Formozov for helpful discussion. Empirical work on evolution of avian carotenoid network was funded by the grants from the National Science Foundation (DEB-0075388, IBN-0218313, and DEB-0077804) and the David and Lucille Packard Fellowship.

References

[1] J. Maynard Smith, Natural selection and the concept of a protein space, Nature 225 (1970) 563–564.
[2] W. Fontana, P. Schuster, Continuity in evolution: on the nature of transitions, Science 280 (1998) 1451–1455.
[3] C. Torres-Sosa, S. Huang, M. Aldana, Criticality is an emergent property of genetic networks that exhibit evolvability, PLoS Comput. Biol. 8 (9) (2012) e1002669.
[4] A. Wagner, The Origins of Evolutionary Innovations: A Theory of Transformative Change in Living Systems, Oxford University Press, 2011.
[5] S. Gavrilets, A dynamical theory of speciation on holey adaptive landscapes, Am. Nat. 154 (1999) 1–22.
[6] M. Huynen, P.F. Stadler, W. Fontana, Smoothness within ruggedness: the role of neutrality in adaptation, Proc. Natl. Acad. Sci. U. S. A. 93 (1996) 397–401.
[7] V. Debat, P. David, Mapping phenotypes: canalization, plasticity and developmental stability, Trends Ecol. Evol. 16 (2001) 555–561.
[8] A. Bergman, M.L. Siegal, Evolutionary capacitance as a general feature of complex gene networks, Nature 424 (2003) 549–552.
[9] H.F. Nijhout, The nature of robustness in development, BioEssays 24 (2002) 553–563.
[10] S. Bershtein, M. Segal, R. Bekerman, N. Tokuriki, D.S. Tawfik, Robustness-epistasis link shapes the fitness landscape of a randomly drifting protein, Nature 444 (2006) 929–932.
[11] J. Hermisson, G.P. Wagner, The population genetic theory of hidden variation and genetic robustness, Genetics 168 (2004) 2271–2284.
[12] Y. Kim, Rate of adaptive peak shifts with partial genetic robustness, Evolution 61 (2007) 1847–1856.
[13] L. Hadany, T. Beker, Fitness-associated recombination on rugged adaptive landscapes, J. Evol. Biol. 16 (2003) 862–870.
[14] J.L. Payne, A. Wagner, Latent phenotypes prevade gene regulatory circuits, BMC Syst. Biol. 8 (2014) 64.
[15] J.A.G.M. de Visser, J. Hermission, G.P. Wagner, L.A. Meyers, H. Bahgheri-Chaichian, J.L. Blanchard, L. Chao, J.M. Cheverud, S.F. Elena, W. Fontana, G. Gibson, T.F. Hansen, D. Krakauer, R.C. Lewontin, C. Ofria, S.H. Rice, G. von Dassow, A. Wagner, M.C. Whitlock, Perspective: evolution and detection of genetic robustness, Evolution 57 (9) (2003) 1959–1972.
[16] A.V. Badyaev, K.R. Foresman, Extreme environmental change and evolution: stress-induced morphological variation is strongly concordant with patterns of evolutionary divergence in shrew mandibles, Proc. R. Soc. Biol. Sci. Ser. B 267 (1441) (2000) 371–377.
[17] J.A. Draghi, T.L. Parsons, G.P. Wagner, J.B. Plotkin, Mutational robustness can facilitate adaptation, Nature 463 (2010) 353–355.
[18] D.A. Kondrashov, F.A. Kondrashov, Topological features of rugged fitness landscapes in sequence space, Trends Genet. 31 (2015) 24–33.
[19] A. Wagner, Robustness and evolvability: a paradox resolved, Proc. R. Soc. B 275 (2008) 91–100.
[20] A. Le Rouzic, O. Carlborg, Evolutionary potential of hidden genetic variation, Trends Ecol. Evol. 23 (1) (2008) 33–37.
[21] C. Mayer, T.F. Hansen, Evolvability and robustness: a paradox restored, J. Theor. Biol 430 (2017) 78–85.
[22] D.M. Weinreich, N.F. Delaney, M.A. DePristo, D.L. Hartl, Darwinian evolution can follow only very few mutational paths to fitter proteins, Science 312 (2006) 111–114.
[23] K.S. Sarkisyan, D.A. Bolotin, M.V. Meer, D.R. Usmanova, A.S. Mishin, G.V. Sharonov, D.N. Ivankov, N.G. Bozhanova, M.S. Baranov, O. Soylemez, N.S. Bogatyreva, P.K. Vlasov, E.S. Egorov, M.D. Logacheva, A.S. Kondrashov, D.M. Chudakov, E.V. Putintseva, I.Z. Mamedov, D.S. Tawfik, K.A. Lukyanov, F.A.

Kondrashov, Local fitness landscape of the green fluorescent protein, Nature 533 (7603) (2016) 397–401.
[24] M. Lynch, The Origins of Genome Architecture, Sinauer Associates, Sunderland, MA, 2007.
[25] E.V. Koonin, The Logic of Chance: The Nature and Origin of Biological Evolution, FT Press Science, 2011.
[26] M. Chiang, S.H. Low, A.R. Calderbank, J.C. Doyle, Layering as optimization decomposition: a mathematical theory of network architectures, Proc. IEEE 95 (1) (2007) 255–312.
[27] R. Jothi, S. Balaji, A. Wuster, J.A. Grochow, J. Gsponer, T.M. Przytycka, L. Aravind, M.M. Babu, Genomic analysis reveals a tight link between transcription factor dynamics and regulatory network architecture, Mol. Syst. Biol. 5 (2009) 294.
[28] S. Gavrilets, Fitness Landscapes and the Origin of Species, Princeton University Press, Princeton, NJ, 2004.
[29] A. Wagner, Robustness, neutrality, and evolvability, FEBS Lett. 579 (2005) 1772–1778.
[30] S. Ciliberti, O.C. Martin, A. Wagner, Robustness can evolve gradually in complex regulatory gene networks with varying topology, PLoS Comput. Biol. 3 (2) (2007) e15.
[31] R. Albert, H. Jeong, A.-L. Barabasi, Error and attack tolerance of complex networks, Nature 406 (2000) 378–382.
[32] A. Wagner, Evolutionary constraints permeate large metabolic networks, BMC Evol. Biol. 9 (2009) 231.
[33] M. Lynch, Scaling expectations for the time to establishment of complex adaptations, PNAS 107 (2010) 16577–16582.
[34] A.V. Badyaev, Epigenetic resolution of the 'curse of complexity' in adaptive evolution of complex traits, J. Physiol. 592 (11) (2014) 2251–2260.
[35] K. Zhou, J.C. Doyle, K. Glover, Robust and Optimal Control, Prentice Hall, Englewood Cliffs, New Jersey, 1995.
[36] D.G. Luenberger, Introduction to Dynamic Systems: Theory, Models, and Applications, Wiley, 1979.
[37] Y.-Y. Liu, J.-J. Slotine, A.-L. Barabasi, Controllability of complex networks, Nature 473 (2011) 167–173.
[38] A. Moradi Amani, M. Jalili, X. Yu, L. Stone, Finding the Most influential nodes in pinning controllability of complex networks, IEEE Trans. Circ. Syst. II: Exp. Briefs 64 (6) (2017) 685–689.
[39] Z. Yuan, C. Zhao, Z. Di, W.X. Wang, Y.C. Lai, Exact controllability of complex networks, Nat. Commun. 4 (2013) 2447.
[40] C. Campbell, J. Ruths, D. Ruths, K. Shea, R. Albert, Topological constraints on network control profiles, Sci. Rep. 5 (2015) 18693.
[41] C. Zhao, W.X. Wang, Y.Y. Liu, J.J. Slotine, Intrinsic dynamics induce global symmetry in network controllability, Sci. Rep. 5 (2015) 8422.
[42] X. Liu, L. Pan, Identifying driver nodes in the human signaling network using structural controllability analysis, IEEE/ACM Trans. Comput. Biol. Bioinform. 12 (2) (2015) 467–472.
[43] S. Wuchty, Z.N. Oltvai, A.-L. Barabási, Evolutionary conservation of motif constituents in yeast protein interaction network, Nat. Genet. 35 (2003) 176–179.
[44] T. Yamada, M. Kanehisa, S. Goto, Extraction of phylogenetic network modules from the metabolic network, BMC Bioinform. 7 (2006) 130.
[45] M. Campillos, C. von Mering, L.J. Jensen, P. Bork, Identification and analysis of evolutionarily cohesive functional modules in protein networks, Genome Res. 16 (2006) 374–382.
[46] J.M. Peregrín-Alvarez, C. Sanford, J. Parkinson, The conservation and evolutionary modularity of metabolism, Genome Biol. 10 (2009) R63.
[47] H.B. Fraser, A.E. Hirsh, L.M. Steinmetz, C. Scharfe, M.W. Feldman, Evolutionary rate in the protein interaction network, Science 296 (5568) (2002) 750–752.
[48] M.W. Hahn, A.D. Kern, Comparative genomics of centrality and essentiality in three eukaryotic protein-interaction networks, Mol. Biol. Evol. 22 (4) (2005) 803–806.
[49] J. Ruths, D. Ruths, Control properties of complex networks, Science 343 (2014) 1373–1375.
[50] C. Campbell, K. Shea, R. Albert, Comment on "Control profiles of complex networks," Science 346 (2014).
[51] A.V. Badyaev, A.B. Posner, E.S. Morrison, D.M. Higginson, Cycles of External Dependency Reconcile Local Adaptation and Continuity of Evolution in Metabolic Networks, 2018, In review.
[52] H.F. Nijhout, M.C. Reed, Homeostasis and dynamic stability of the phenotype link robustness and plasticity, Integr. Comp. Biol. 54 (2) (2014) 264–275.
[53] I. Salazar-Ciudad, On the origins of morphological variation, canalization, robustness, and evolvability, Integr. Comp. Biol. 47 (2007) 390–400.
[54] G.P. Wagner, J. Zhang, The pleotropic structure of the genotype-phenotype map: the evolvability of complex organisms, Nat. Rev. Genet. 12 (2011) 204–213.
[55] G.P. Wagner, J.G. Mezey, The role of genetic architecture constraints for the origin of variational modularity, in: G. Schlosser, G.P. Wagner (Eds.), Modularity in Development and Evolution, Chicago University Press, Chicago, IL, 2004, pp. 338–358.
[56] S.C. Janga, M.M. Babu, Network-based approaches for linking metabolisim wuith environment, Genome Biol. 9 (2008).
[57] E. Borenstein, M. Kupiec, M.W. Feldman, E. Ruppin, Large-scale reconstruction and phylogenetic analysis of metabolic environments, Proc. Natl. Acad. Sci. U. S. A. 105 (38) (2008) 14482–14487.
[58] G. Basler, Z. Nikoloski, A. Larhlimi, A.L. Barabasi, Y.Y. Liu, Control of fluxes in metabolic networks, Genome Res. 26 (7) (2016) 956–968.
[59] G.M. Edelman, J.A. Gally, Degeneracy and complexity in biological systems, PNAS 98 (2001) 13763–13768.
[60] R. Frei, J. Whitacre, Degeneracy and networked buffering: principles for supporting emergent evolvability in agile manufacturing systems, Nat. Comput. 11 (3) (2011) 417–430.
[61] P.H. Mason, Degeneracy at multiple levels of complexity, Biol. Theory 5 (2010) 277–288.
[62] P.H. Mason, Degeneracy: demystifying and destigmatizing a core concept in systems biology, Complexity 20 (3) (2015) 12–21.
[63] G. Tononi, O. Sporns, G.M. Edelman, Measures of degeneracy and redundancy in biological networks, PNAS 96 (1999) 3257–3262.
[64] J. Whitacre, A. Bender, Degeneracy: a design principle for achieving robustness and evolvability, J. Theor. Biol. 263 (1) (2010) 143–153.
[65] A. Force, M. Lynch, F.B. Pickett, A. Amores, Y. Yan, J. Postlethwait, Preservation of duplicate genes by complementary, degenerative mutations, Genetics 151 (1999) 1531–1545.
[66] S. Huang, I. Ernberg, S. Kauffman, Cancer attractors: a systems view of tumors from a gene network dynamics and developmental perspective, Semin. Cell. Dev. Biol. 20 (7) (2009) 869–876.
[67] J.C. Doyle, M. Csete, Architecture, constraints, and behavior, Proc. Natl. Acad. Sci. U. S. A. 108 (Suppl. 3) (2011) 15624–15630.
[68] J. Stelling, S. Klamt, K. Bettenbrock, S. Schuster, E.D. Gilles, Metabolic network structure determines key aspects of functionality and regulation, Nature 420 (2002) 190–193.
[69] I. Peter, E.H. Davidson, Genomic Control Process: Development and Evolution, first ed., Academic Press, 2015.
[70] E.H. Davidson, D.H. Erwin, Evolutionary innovation and stability in animal gene networks, J. Exp. Zool. Part B, Mol. Dev.Evol. 314 (3) (2010) 182–186.
[71] D.H. Erwin, E.H. Davidson, The evolution of hierarchical gene regulatory networks, Nat. Rev. Genet. 10 (2009) 141–148.
[72] M. Levin, L. Anavy, A.G. Cole, E. Winter, N. Mostov, S. Khair, N. Senderovich, E. Kovalev, D.H. Silver, M. Feder, S.L. Fernandez-Valverde, N. Nakanishi, D. Simmons, O. Simakov, T. Larsson, S.Y. Liu, A. Jerafi-Vider, K. Yaniv, J.F. Ryan, M.Q. Martindale, J.C. Rink, D. Arendt, S.M. Degnan, B.M. Degnan, T. Hashimshony, I. Yanai, The mid-developmental transition and the evolution of animal body plans, Nature 531 (7596) (2016) 637–641.
[73] E. Buitrago-Delgado, K. Nordin, A. Rao, L. Geary, C. LaBonne, Shared regulatory programs suggest retention of blastula-stage potential in neural crest cells, Science 348 (2015) 1332–1335.
[74] N. King, M.J. Westbrook, S.L. Young, A. Kuo, M. Abedin, J. Chapman, et al., The genome of the choanoflagellate *monosiga brevicollis* and the origin of metazoans, Nature 451 (2008) 783–788.
[75] S.A. Newman, The developmental-genetic toolkit and the molecular homology-analogy paradox, Biol. Theory 1 (2006) 12–16.
[76] A.V. Badyaev, A.L. Potticary, E.S. Morrison, Most colorful example of genetic assimilation? Exploring the evolutionary destiny of recurrent phenotypic accommodation, Am. Nat. 190 (2017) 266–280.
[77] R.A. Watson, G.P. Wagner, M. Pavlicev, D.M. Weinreich, R. Mills, The evolution of phenotypic correlations and d̈evelopmental memory, Evolution 68 (4) (2014) 1124–1138.
[78] H. Ramsay, L.H. Rieseberg, K. Ritland, The correlation of evolutionary rate with pathway position in plant terpenoid biosynthesis, Mol. Biol. Evol. 26 (5) (2009) 1045–1053.
[79] M.D. Rausher, The evolution of genes in branched metabolic pathways, Evolution 67 (2012) 34–48.
[80] J.D. Bloom, S.T. Labthavikul, C.R. Otey, F.H. Arnold, Protein stability promotes evolvability, PNAS 103 (2006) 5869–5874.
[81] R.J. Woods, J.E. Barrick, T.F. Cooper, U. Shrestha, M.R. Kauth, R.E. Lenski, Second-order selection for evolvability in a large Escherichia coli population, Science 331 (6023) (2011) 1433–1436.
[82] R.E. Lenski, J.E. Barrick, C. Ofria, Balancing robustness and evolvability, PLoS Biol. 4 (2006) e428.
[83] G.P. Wagner, J.G. Mezey, R. Callabretta, Natural selection and the origin of modules, in: W. Callebaut, D. Raskin-Gutman (Eds.), Modularity: Understanding the Development and Evolution of Complex Systems, MIT Press, Cambridge MA, 2005.
[84] A.V. Badyaev, Origin of the fittest: link between emergent variation and evolutionary change as a critical question in evolutionary biology, Proc. R. Soc. Lond.: Biol. Sci. 278 (2011) 1921–1929.
[85] A.V. Badyaev, K.R. Foresman, Evolution of morphological integration: I. Functional units channel stress-induced variation in shrew mandibles, Am. Nat. 163 (2004) 868–879.
[86] T. Jia, Y.Y. Liu, E. Csoka, M. Posfai, J.J. Slotine, A.L. Barabasi, Emergence of bimodality in controlling complex networks, Nat. Commun. 4 (2013) 2002.
[87] X.F. Zhang, L. Ou-Yang, Y. Zhu, M.Y. Wu, D.Q. Dai, Determining minimum set of driver nodes in protein-protein interaction networks, BMC Bioinform. 16 (2015) 146.
[88] N. Kashtan, U. Alon, Spontaneous evolution of modularity and network motifs, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 13773–13778.
[89] R. Milo, S. Shen-Orr, S. Itzkovitz, N. Kashtan, D. Chklovskii, U. Alon, Network motifs: simple building blocks of complex networks, Science 298 (2002) 824–827.
[90] T. Tanaka, K. Ikeo, T. Gojobori, Evolution of metabolic networks by gain and loss of enzymatic reaction in eukaryotes, Gene 365 (2006) 88–94.

[91] A.V. Badyaev, Homeostatic hitchhiking: a mechanism for the evolutionary retention of complex adaptations, Integr. Comp. Biol. 53 (2013) 913–922.
[92] D. Vitkup, P. Kharchenko, A. Wagner, Influence of metabolic network structure and function on enzyme evolution, Genome Biol. 7 (2006) R39.
[93] A.V. Badyaev, The beak of the other finch: coevolution of genetic covariance structure and developmental modularity during adaptive evolution, Philos. Trans. R. Soc. Biol. Sci. 365 (2010) 1111–1126.
[94] A.V. Badyaev, Evolvability and robustness in color displays: bridging the gap between theory and data, Evol. Biol. 34 (2007) 61–71.
[95] K.J. McGraw, The mechanics of carotenoid coloration in birds, in: G.E. Hill, K.J. McGraw (Eds.), Bird Coloration. I. Mechanisms and Measurements, Harvard University Press, Cambridge, MA, 2006, pp. 177–242.
[96] D. Umeno, A.V. Tobias, F.H. Arnold, Diversifying carotenoid biosynthetic pathways by directed evolution, Microbiol. Mol. Biol. Rev. 69 (2005) 51–78.
[97] A.V. Badyaev, E.S. Morrison, V. Belloni, M.J. Sanderson, Tradeoff between robustness and elaboration in carotenoid networks produces cycles of avian color diversification, Biol. Direct 10 (2015) 45.
[98] E.S. Morrison, A.V. Badyaev, Structuring evolution: biochemical networks and metabolic diversification in birds, BMC Evol. Biol. 16 (2016) 168.
[99] E.S. Morrison, A.V. Badyaev, Structure versus time in evolutionary diversification of avian carotenoid networks, J. Evol. Biol. 31 (2018) 764–772.
[100] A.V. Badyaev, E.S. Morrison, Emergent buffering balances evolvability and robustness in the evolution of phenotypic flexibility, Evolution 72 (3) (2018) 647–662.
[101] D.M. Higginson, V. Belloni, S.N. Davis, E.S. Morrison, J.E. Andrews, A.V. Badyaev, Evolution of long-term coloration trends with biochemically unstable ingredients, Proc. R. Soc. B 283 (1831) (2016) 20160403.
[102] I.I. Schmalhausen, Organism as a Whole in Individual Development and History, Academy of Sciences, USSR, Leningrad, 1938.
[103] M.J. West-Eberhard, Developmental Plasticity and Evolution, Oxford University Press, Oxford, 2003.
[104] J.M. Baldwin, Development and Evolution, Macmillan, New York, 1902.
[105] T. Piersma, J. Drent, Phenotypic flexibility and the evolution of organismal design, Trends Ecol. Evol. 18 (2003) 228–233.
[106] C.D. Schlichting, M. Pigliucci, Phenotypic Evolution: A Reaction Norm Perspective, Sinauer Associates, Sunderland, MA, 1998.
[107] J.A. Stamps, W.E. Frankenhuis, Bayesian models of development, Trends Ecol. Evol. 31 (4) (2016) 260–268.
[108] S.L. Rutherford, From genotype to phenotype: buffering mechanisms and the storage of genetic information, BioEssays 22 (2000) 1095–1105.
[109] J.M. Whitacre, A. Bender, Networked buffering: a basic mechanism for distributed robustness in complex adaptive systems, Theor. Biol. Med. Model. 7 (2010) 20.
[110] R.A. Duckworth, A.L. Potticary, A.V. Badyaev, On the origins of adaptive behavioral complexity: developmental channeling of structural trade-offs, Adv. Study Behav. 50 (2018) 1–36.
[111] C.H. Waddington, Evolution of developmental systems, Nature 147 (1941) 108–110.
[112] J.M. Baldwin, A new factor in evolution, Am. Nat. 30 (1896) 441–451.
[113] P.K. Diggle, J.S. Miller, Developmental plasticity, genetic assimilation, and the evolutionary diversification of sexual expression in Solanum, Am. J. Bot 100 (6) (2013) 1050–1060.
[114] D. Emera, R. Romero, G. Wagner, The evolution of menstruation: a new model for genetic assimilation, Bioessays 34 (1) (2012) 26–35.
[115] C.D. Schlichting, M.A. Wund, Phenotypic plasticity and epigenetic marking: an assessment of evidence for genetic accommodation, Evolution 68 (3) (2014) 656–672.
[116] K.L. Sikkink, R.M. Reynolds, C.M. Ituarte, W.A. Cresko, P.C. Phillips, Rapid evolution of phenotypic plasticity and shifting thresholds of genetic assimilation in the nematode caenorhabditis remanei, G3 (Bethesda) 4 (6) (2014) 1103–1112.
[117] I.M. Ehrenreich, D.W. Pfennig, Genetic assimilation: a review of its potential proximate causes and evolutionary consequences, Ann. Bot. 117 (2015) 769–779.
[118] A.V. Badyaev, K.P. Oh, Environmental induction and phenotypic retention of adaptive maternal effects, BMC Evol. Biol. 8 (2008) e3.
[119] V. Gol'dshtein, G.A. Koganov, G.I. Surdutovich, Vulnerability and hierarchy of complex networks, Cond. Matter (2004), arXiv:cond-mat/0409298v1.
[120] J. Gao, B. Barzel, A.L. Barabasi, Universal resilience patterns in complex networks, Nature 530 (7590) (2016) 307–312.
[121] D. Leitold, A. Vathy-Fogarassy, J. Abonyi, Controllability and observability in complex networks - the effect of connection types, Sci. Rep. 7 (1) (2017) 151.
[122] E.S. Morrison, A.V. Badyaev, The landscape of evolution: reconciling structural and dynamic properties of metabolic networks in adaptive diversifications, Integr. Comp. Biol. 56 (2016) 235–246.
[123] S.S. Shen-Orr, R. Milo, M. Shmoolik, U. Alon, Network motifs in the transcriptional regulation network of Escherichia coli, Nat. Genet. 31 (2002) 64–68.
[124] E. Ravasz, A.L. Somera, D.A. Mongru, Z.N. Oltvai, A.-L. Barabasi, Hierarchical organization of modularity in metabolic networks, Science 297 (2002) 1551–1556.
[125] S. Maslov, S. Krishna, T.Y. Pang, K. Sneppen, Toolbox model of evolution of prokaryotic metabolic netowks and their regulation, PNAS 106 (2009) 9743–9748.
[126] T. Osterlund, S. Bordel, J. Nielsen, Controllability analysis of transcriptional regulatory networks reveals circular control patterns among transcription factors, Integr. Biol. (Camb.) 7 (5) (2015) 560–568.
[127] S. Bernhardsson, P. Gerlee, L. Lizana, Structural correlations in bacterial metabolic networks, BMC Evol. Biol. 11 (2011) 20.
[128] M. Lynch, The evolution of genetic networks by non-adaptive processes, Nat. Rev. Genet. 8 (10) (2007) 803–813.
[129] S. Wuchty, T. Boltz, H. Kucuk-McGinty, Links between critical proteins drive the controllability of protein interaction networks, Proteomics 17 (10) (2017), 1700056.
[130] E.S. Morrison, A.V. Badyaev, Beyond topology: coevolution of structure and flux in metabolic networks, J. Evol. Biol. 30 (2017) 1796–1809.
[131] M. Lässig, V. Mustonen, A.M. Walczak, Predicting evolution, Nat. Ecol. Evol. 1 (3) (2017), 0077.
[132] J.A.G.M. de Visser, J. Krug, Empirical fitness landscapes and the predictability of evolution, Nat. Rev. Genet. 15 (2014) 480–490.
[133] T. Dobzhansky, Speciation as a stage in evolutionary divergence, Am. Nat. 74 (1940) 312–321.
[134] G.P. Wagner, And evolutionary innovation, in: Homology, Genes, Princeton University Press, Princeton and Oxford, 2014.
[135] T.N. Starr, L.K. Picton, J.W. Thornton, Alternative evolutionary histories in the sequence space of an ancient protein, Nature 549 (7672) (2017) 409–413.