# Canalization and Robustness

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## Introduction

Canalization describes the phenomenon whereby particular genotypes exhibit reduced phenotypic sensitivity or variation (i.e., increased robustness) in response to mutations and/or to environmental changes relative to other genotypes. Canalization is a variational property of genotypes: it implies a reduced potential or propensity of the phenotype, produced by this genotype, to vary in response to genetic or environmental change. The terms “canalization,” “robustness” and “buffering” are typically used interchangeably; today, “robustness” is perhaps more commonly used than “canalization.” The concept of canalization was first introduced by Conrad Hal Waddington in the 1940s; around the same time, Ivan Ivanovich Schmalhausen came up with essentially the same concept (see Books and Early History of the Canalization Concept). Their main conjecture was the existence of a special kind of stabilizing selection, so-called canalizing selection, which favors genotypes that deviate least from the trait optimum (e.g., the fitness optimum), by selecting for genetic mechanisms that suppress phenotypic variation caused by mutations (genetic canalization) or by environmental perturbations or changes (environmental canalization). The concept of canalization is closely related to the phenomenon of genetic assimilation, that is, the idea that previously hidden, cryptic genetic variants can become phenotypically expressed following an environmental or genetic perturbation and increase in frequency by selection.

## General Overviews

Early experimental evidence for the existence of canalization and genetic assimilation is reviewed in depth by Scharloo 1991, the first comprehensive review paper in the field. The review by Flatt 2005 focuses on work done after 1991. Gibson and Wagner 2000 connects canalization to the concept of variability, the propensity of a genotype to vary in response to genetic or environmental change and discuss how canalization can be detected experimentally. De Visser, et al. 2003 reviews genetic canalization and emphasizes the diverse mechanisms whereby this phenomenon can arise. Based on previous work, Meiklejohn and Hartl 2002 suggests that genetic canalization likely evolves as a correlated response to selection for increased environmental canalization. Siegal and Leu 2014 gives a modern treatment of mutational robustness and discuss its relationship with “cryptic” genetic variation, that is, genetic variation that is typically not phenotypically expressed but that can be revealed under certain conditions. Félix and Barkoulas 2015 discusses robustness from a contemporary systems biology point of view. The excellent book by Andreas Wagner (Wagner 2005) represents the most comprehensive treatment of robustness available to date; it provides a very good point of entry into the literature.

**de Visser, J. Arjan G. M., Joachim Hermisson, Günter P. Wagner, et al. 2003. Perspective: Evolution and detection of genetic robustness. *Evolution* 57:1959–1972.**

A review of genetic robustness, focusing on its evolutionary origin, proximate causes, and how to measure it.

**Félix, Marie-Anne, and Michalis Barkoulas. 2015. Pervasive robustness in biological systems. *Nature Reviews Genetics* 16:483–496.**

A modern treatment of robustness in biological systems; in particular, this paper discusses robustness from a systems biology point of view, that is, how robustness results from nonlinearities in molecular pathways and the genotype–phenotype map.

**Flatt, Thomas. 2005. The evolutionary genetics of canalization. *Quarterly Review of Biology* 80:287–316.**

A comprehensive general review of canalization; especially strong coverage of the theoretical and empirical literature that appeared after Scharloo 1991.

**Gibson, Greg, and Günter Wagner. 2000. Canalization in evolutionary genetics: A stabilizing theory? *BioEssays* 22:372–380.**

This review essay defines the process of canalization as a genetic change that results in the reduction of variability, the propensity to vary in response to genetic or environmental change; variability is contrasted with variation, which describes the actually realized differences among individuals in a population or an experiment; provides a succinct discussion of how canalization can be empirically detected.

**Meiklejohn, Colin D., and Daniel L. Hartl. 2002. A single mode of canalization. *Trends in Ecology and Evolution* 17:468–473.**

An opinion article discussing the notion that biological systems should evolve to be optimally buffered against both genetic and environmental perturbations; in particular, the authors argue that genetic canalization evolves as a correlated response to selection for environmental canalization (a phenomenon called “plastogenetic congruence”; see Computational Models of the Evolution of Robustness).

**Scharloo, Willem. 1991. Canalization: Genetic and developmental aspects. *Annual Review of Ecology and Systematics* 22:65–93.**

The first “modern” review of canalization and the phenomenon of genetic assimilation; provides a detailed discussion of Waddington’s early experiments with *Drosophila*.

**Siegal, Mark L., and Jun-Yi Leu. 2014. On the nature and evolutionary impact of phenotypic robustness mechanisms. *Annual Review of Ecology, Evolution, and Systematics* 45:495–517.**

An up-to-date review of mutational robustness and cryptic genetic variation.

**Wagner, Andreas. 2005. *Robustness and evolvability in living systems*. Princeton, NJ: Princeton Univ. Press.**

The most comprehensive treatment of robustness currently available. A special emphasis is placed on the mechanistic underpinnings of robustness as well as on the connection between neutrality and robustness.

## Books

Apart from the historical books by Waddington, Schmalhausen, Lerner, and Rendel (see Early History of the Canalization Concept), the only modern book specifically dealing with canalization and robustness is the monograph by Andreas Wagner published in 2005 (see Wagner 2005, cited under General Overviews). However, several other, more general books touch upon canalization. Hallgrímsson and Hall 2005 reviews various aspects of genetic, environmental and phenotypic variation; multiple chapters discuss canalization and how it relates to, for example, cryptic variation, genetic assimilation, and phenotypic plasticity (i.e., the ability of a single genotype to express multiple phenotypes in different environments). Schlichting and Pigliucci 1998 and West-Eberhard 2003 discuss the relationship between canalization and phenotypic plasticity. Schlosser and Wagner 2004 discusses the modular organization of organisms at various scales of organization; several chapters discuss the relationship between canalization and modularity. Similarly, the edited volume Pigliucci and Preston 2005 contains multiple chapters that discuss canalization in terms of phenotypic integration (a concept closely related to the issue of modularity), that is, the question of how phenotypic traits are integrated to make up whole organisms. Wagner 2014 contains a succinct summary of theoretical and empirical work on

canalization and how it might contribute to explain homology. Finally, Wilkins 2002 gives an authoritative treatment of evolutionary developmental biology ("evo-devo") from the perspective of developmental pathways, including a good summary of work on canalization until 2002.

**Hallgrímsson, Benedikt, and Brian Hall, eds. 2005. *Variation: A central concept in biology*. Burlington, MA: Elsevier Academic Press.**

A multi-author volume that covers all aspects of variation, the central "raw material" of evolution; several chapters discuss canalization, cryptic variation, and the relationship between canalization and plasticity.

**Pigliucci, Massimo, and Katherine Preston, eds. 2005. *Phenotypic integration: Studying the ecology and evolution of complex phenotypes*. Oxford: Oxford Univ. Press.**

An edited volume that reviews multiple facets of the genetic, physiological, and developmental integration of phenotypic characters; several chapters discuss canalization from the perspective of phenotypic integration.

**Schlichting, Carl D., and Massimo Pigliucci. 1998. *Phenotypic evolution: A reaction norm perspective*. Sunderland, MA: Sinauer.**

A book on phenotypic evolution from the perspective of phenotypic plasticity and reaction norms (i.e., sets of phenotypes produced by genotypes in response to environmental change); in particular, the authors discuss the relationship between plasticity and canalization.

**Schlosser, Gerhard, and Günter P. Wagner, eds. 2004. *Modularity in development and evolution*. Chicago: Univ. of Chicago Press.**

An excellent introduction to "modularity" in evolutionary developmental biology; multiple chapters discuss how the modular organization of organisms is related to the phenomenon of canalization.

**Wagner, Günter P. 2014. *Homology, genes, and evolutionary innovation*. Princeton, NJ: Princeton Univ. Press.**

A comprehensive treatment of the homology concept in developmental evolution; the author discusses canalization in the context of how it might contribute to the origin and identity of novel body parts and characters.

**West-Eberhard, Mary Jane. 2003. *Developmental plasticity and evolution*. Oxford: Oxford Univ. Press.**

A comprehensive overview of phenotypic plasticity and the role of the environment in shaping phenotypes; West-Eberhard discusses the relationship between plasticity, canalization, cryptic variation and Waddington's concept of assimilation (see Cryptic Variation, Genetic Assimilation, and Accommodation.

**Wilkins, Adam S. 2002. *The evolution of developmental pathways*. Sunderland, MA: Sinauer.**

A very good book about the field of "evo-devo": the intersection of developmental biology, molecular genetics, and evolutionary biology; the author provides a succinct summary of work on canalization and genetic assimilation up to 2002.

## Early History of the Canalization Concept

The three most important historical works in the development of the canalization concept are the books Waddington 1940, Schmalhausen 1949, and Waddington 1957. Waddington 1940 defines the notion of canalization and illustrates it with the

"epigenetic landscape," an early pictorial and metaphorical representation of the genotype-phenotype map, and with "chreods," which represent developmental trajectories or pathways. Schmalhausen 1949 develops, independently of Waddington, the concepts of canalization (referring to it as "autoregulation"), canalizing selection (calling it "stabilizing selection"), and genetic assimilation (Schmalhausen's "autonomization"). The best known of the three books is Waddington 1957: in *The Strategy of the Genes*, Waddington more fully develops the notion of epigenetic landscapes and summarizes empirical support for canalization and assimilation. Waddington 1942 introduces the idea of "genetic assimilation" and how it relates to canalization; similarly, Waddington 1957 connects the concepts of canalization, assimilation, and canalizing selection. Rendel 1967 reviews early evidence for canalization and assimilation; after Waddington 1940, Schmalhausen 1949, and Waddington 1957 and before the modern treatment by Andreas Wagner (Wagner 2005, cited under General Overviews), this was the main reference on the subject. Riedl 1987 was one of the pioneering works in promoting a more organismal approach to evolutionary biology, including notions of robustness and canalization.

**Lerner, I. Michael. 1954. *Genetic homeostasis*. Edinburgh, UK: Oliver and Boyd.**

In this book Lerner develops the concept of "genetic homeostasis," which is essentially synonymous with "canalization"—his main thesis is that canalization is due to heterozygosity, whereas homozygosity (e.g., due to inbreeding) causes developmental instabilities.

**Rendel, James M. 1967. *Canalisation and gene control*. London: Logos.**

A short book summarizing the early experimental work on canalization, including Rendel's own work on the invariance of scutellar bristle number in *Drosophila*. This book is the main reference on canalization after Waddington's and Schmalhausen's books.

**Riedl, R. 1987. *Order in living organisms*. New York: Wiley.**

This book pioneered a developmental approach to evolutionary biology and also discussed canalization and robustness as a factor shaping macroevolutionary patterns.

**Schmalhausen, Ivan I. 1949. *Factors of evolution: The theory of stabilizing selection*. Philadelphia: Blakiston.**

In this major book, Schmalhausen develops, in parallel to and independent of Waddington, the concepts of canalization (which he calls "autoregulation"), canalizing selection (which he calls "stabilizing selection") and genetic assimilation (which he calls "autonomization"). Reprint: 1986. Chicago: Univ. of Chicago Press.

**Waddington, Conrad H. 1940. *Organisers and genes*. Cambridge, UK: Cambridge Univ. Press.**

In this important historical book Waddington develops his theory of canalization and the concepts of "epigenetics" (i.e., developmental processes in general, contrary to today's meaning of the term) and the "epigenetic landscape" (i.e., a metaphorical picture of development and the genotype–phenotype map).

**Waddington, Conrad H. 1942. Canalization of development and the inheritance of acquired characters. *Nature* 150:563–565.**

This paper develops the concepts of canalization and genetic assimilation and their interrelationship.

**Waddington, Conrad H. 1957. *The strategy of the genes: A discussion of some aspects of theoretical biology*. London: Allen and Unwin.**

In this highly influential book Waddington provides a full development of his ideas on the “epigenetic landscape” and summarizes early evidence for the phenomena of canalization and assimilation. In view of contemporary “evo-devo” and systems biology this book is remarkably prescient in its vision. Reprint: 2014. Abingdon: Routledge.

## Biographical Sketches of Waddington, Schmalhausen and Lerner

Slack 2002 provides a brief sketch of the life and work of Conrad Hal Waddington; a more detailed treatment is given by Hall 1992. Levit, et al. 2006 portrays Schmalhausen and his body of work. Hall 2005 provides a biographical sketch of Lerner’s life and revisits his book on genetic homeostasis.

**Hall, Brian K. 1992. Waddington’s legacy in development and evolution. *American Zoologist* 32:113–122.**

A short biography of Conrad Hal Waddington and an excellent overview of his work and conceptual ideas.

**Hall, Brian K. 2005. Fifty years later: I. Michael Lerner’s *Genetic Homeostasis* (1954)—A valiant attempt to integrate genes, organisms and environment. *Journal of Experimental Zoology Part B: Molecular and Developmental Evolution* 304B:187–197.**

A biographical sketch of Michael Lerner and a retrospective of his 1954 book.

**Levit, Georgy S., Uwe Hossfeld, and Lennart Olsson L. 2006. From the “modern synthesis” to cybernetics: Ivan Ivanovich Schmalhausen (1884–1963) and his research program for a synthesis of evolutionary and developmental biology. *Journal of Experimental Zoology Part B: Molecular and Developmental Evolution* 306B:89–106.**

A rather detailed overview of the life and work of Ivan Ivanovich Schmalhausen and his famous 1949 book *Factors of Evolution: The Theory of Stabilizing Selection* (Philadelphia: Blakiston).

**Slack, Jonathan M. W. 2002. Conrad Hal Waddington: The last Renaissance biologist? *Nature Reviews Genetics* 3:889–895.**

A succinct summary of the life and work of Waddington.

## Environmental Canalization, Plasticity, and G × E

Environmental canalization can be defined as the insensitivity of a genotype’s phenotype to environmental change relative to other genotypes (Flatt 2005). The notion of environmental canalization is closely related to the concept of phenotypic plasticity—that is, any type of environmentally (nongenetically) induced phenotypic variation. Environmentally canalized genotypes are less sensitive to environmental changes (i.e., less phenotypically plastic; e.g., with more shallow reaction norms) than other, more sensitive (i.e., more plastic; e.g., with steeper reaction norms) genotypes. The limiting case of maximal environmental canalization (relative to other more sensitive genotypes) implies that, for a given trait, the genotype exhibits no phenotypic plasticity at all (e.g., has a flat reaction norm of zero slope). Since genotypes differ in the amount of environmental canalization versus phenotypic plasticity, genetic variation in the degree of environmental canalization implies the existence of genotype by environment interactions (G × E; Flatt 2005). In quantitative genetics one can distinguish between macro- and microenvironmental variation, with macroenvironments (e.g., temperature, food) being experienced by many individuals within the same macroenvironment, whereas microenvironments represent random phenotypic changes or errors of development that are specific for a given individual within a particular macroenvironment. Accordingly, one can distinguish between macro- and microenvironmental canalization (Flatt 2005).

Not all authors agree on the conceptual connection between environmental canalization and phenotypic plasticity (i.e., treating them as a flip side) since plasticity itself can be a mechanism that provides robustness with respect to fitness: however, while it is true that plasticity can lead to robustness, this is only valid if plasticity at one level, or for one trait (e.g., body size), causes robustness at another level or for another trait (e.g., fitness itself). The papers Debat and David 2001 and Flatt 2005 and the chapters Dworkin 2005 and Stearns 2014 clarify the conceptual relationship between environmental canalization and phenotypic plasticity. The first analytical, population genetic theory papers that address the evolution of environmental canalization are Gavrilets and Hastings 1994 and Wagner, et al. 1997; the authors find that (micro-) environmental canalization (i.e., reduced developmental noise) can evolve readily under stabilizing selection.

**Debat, Vincent, and Patrice David. 2001. Mapping phenotypes: Canalization, plasticity and developmental stability. *Trends in Ecology and Evolution* 16:555–561.**

A very helpful review of the conceptual and terminological connections between canalization, plasticity, and developmental stability; includes a helpful discussion of these concepts in terms of quantitative genetic sources of variation.

**Dworkin, Ian. 2005. Canalization, cryptic variation, and developmental buffering: A critical examination and analytical perspective. In *Variation: A central concept in biology*. Edited by Benedikt Hallgrímsson and Brian K. Hall, 131–158. Burlington, MA: Academic Press.**

A good discussion of the relationship between canalization and plasticity in terms of partitioning variation and reaction norms.

**Flatt, Thomas. 2005. The evolutionary genetics of canalization. *Quarterly Review of Biology* 80:287–316.**

This review clarifies the commonly misunderstood relationship between phenotypic plasticity and (micro- and macro-) environmental canalization; the paper argues that environmental canalization represents a special kind of genotype by environment interaction.

**Gavrilets, Sergey S., and Alan Hastings. 1994. A quantitative model for the evolution of developmental noise. *Evolution* 48:1478–1486.**

The first mathematical analysis of the effect of selection on developmental noise, suggesting that stabilizing selection can decrease developmental noise and thus increase microenvironmental canalization.

**Roff, Derek A. 1997. *Evolutionary quantitative genetics*. New York: Chapman & Hall.**

Excellent summary of the field of evolutionary quantitative genetics; clearly defines and briefly discusses the concept of canalization and the relationship of environmental canalization and plasticity.

**Stearns, Stephen C. 2014. Evolution of reaction norms. In *The Princeton guide to evolution*. Edited by Jonathan B. Losos, 261–267. Princeton, NJ: Princeton Univ. Press.**

This book chapter explains the fact that plasticity and (genetic) canalization are not opposites (e.g., plastic reaction norms can be genetically canalized) but that environmental canalization is the flip side of phenotypic plasticity. Similar arguments are made by Flatt 2005.

**Wagner, Günter P., Ginger Booth, and Homayoun Bagheri-Chaichian. 1997. A population genetic theory of canalization. *Evolution* 51:329–347.**

The first population genetic treatment of the evolution of canalization; one of the main conclusions is that environmental canalization can evolve readily under many circumstances.

## Genetic Canalization, Epistasis, and G × G

Genetic canalization can be defined as the phenotypic insensitivity of a specific single- or multilocus genotype to mutation or changes in genetic background relative to other genotypes (Flatt 2005). Thus, genetic canalization represents an epistatic phenomenon; it implies the presence of gene by gene (G × G) interactions, where allelic substitutions with a potential for phenotypic change in some genetic backgrounds are phenotypically expressed to a different degree in other genetic backgrounds (Flatt 2005). This also sometimes called “buffering” or “canalizing” epistasis. The reviews Flatt 2005 and Hansen 2006 provide good introductions to genetic canalization and the literature in this field; the edited volume Wolf, et al. 2000 gives an excellent overview of epistasis in general. The computational study by Andreas Wagner (Wagner 1996) was the first to suggest that natural selection can shape the variational properties of genotypes. The theoretical work by Günter Wagner (Wagner, et al. 1997) demonstrates that, under stabilizing selection, the conditions for the evolution of genetic canalization are somewhat restrictive since stabilizing selection removes the source of selection pressure selecting for genetic canalization (i.e., genetic variation) more rapidly than canalization can be selected for; nonetheless, genetic canalization can evolve under stabilizing selection (for general overviews of the evolution of genetic canalization, see Flatt 2005 and Hansen 2006). Somewhat counterintuitively, however, Hermisson, et al. 2003, using a different, more general model of gene interactions find that stabilizing selection can also lead to the opposite: de-canalization (i.e., increased sensitivity of a genotype to mutations). Hermisson and Wagner 2004 shows that epistasis can lead to the release of previously hidden genetic variation but that this can happen even without de-canalization. In a similar vein, Hansen and Wagner 2001 shows that increased variability of mutant phenotypes might be a general feature of epistatic systems, suggesting that the release of previously cryptic variation—due to a major mutation as compared to wild-type—cannot be taken as evidence for the wild-type being genetically canalized.

**Flatt, Thomas. 2005. The evolutionary genetics of canalization. *Quarterly Review of Biology* 80:287–316.**

A comprehensive review of genetic canalization, its proximate mechanisms, and its evolution; discusses that genetic canalization is manifestation of G × G interactions.

**Hansen, Thomas F. 2006. The evolution of genetic architecture. *Annual Review of Ecology, Evolution and Systematics* 37:123–157.**

An excellent overview of epistasis, genetic canalization, and evolvability in the context of genetic architecture and the genotype–phenotype map.

**Hansen, Thomas F., and Günter P. Wagner. 2001. Modeling genetic architecture: A multilinear theory of gene interaction. *Theoretical Population Biology* 59:61–88.**

In this paper the authors show that increased variability of mutants relative to wild-type is a generic property of epistatic systems; this implies that the reduced variability of the wild-type relative to the mutants cannot be taken as prima facie evidence for the wild-type being canalized.

**Hermisson, Joachim, Thomas F. Hansen, and Günter P. Wagner. 2003. Epistasis in polygenic traits and the evolution of genetic architecture under stabilizing selection. *American Naturalist* 161:708–734.**

An important paper showing that stabilizing selection can—instead of selecting for increased genetic canalization—also lead to de-canalization, that is, render the genotype more sensitive to mutations; this is opposite to the conclusion of Wagner, et al. 1997 and illustrates that the expected outcomes can depend critically on the model of gene interaction used.

**Hermisson, Joachim, and Günter P. Wagner. 2004. The population genetic theory of hidden variation and genetic robustness. *Genetics* 168:2271–2284.**

This paper demonstrates that release of cryptic variation implies epistasis or G × E but does not imply a breakdown of canalization. This finding was important because, in the classical literature from the mid-20th century, the release of cryptic genetic variation was taken as direct evidence for the canalization of the wild-type.

**Wagner, Andreas. 1996. Does evolutionary plasticity evolve? *Evolution* 50:1008–1023.**

This paper introduces the first computational model for the evolution of genetic canalization, here confusingly called "evolutionary plasticity." It is the first of what became a cottage industry using gene regulatory network models of the MacCulloch-Pitts type to study the evolution of genetic architecture.

**Wagner, Günter P., Ginger Booth, and Homayoun Bagheri-Chaichian. 1997. A population genetic theory of canalization. *Evolution* 51:329–347.**

The first theoretical population genetic treatment of the evolution of genetic canalization under stabilizing selection; the main result of this paper is that the conditions for the evolution of genetic canalization under stabilizing selection tend to be rather restrictive since stabilizing selection is more efficient in removing genetic variation than it is selecting for canalization.

**Wolf, Jason B., Edmund D. Brodie III, and Michael J. Wade, eds. 2000. *Epistasis and the evolutionary process*. Oxford: Oxford Univ. Press.**

An excellent overview of epistasis; contains several chapters discussing genetic canalization.

## Phenotypic Landscapes, Configuration Space Models, and Canalization

A useful theoretical framework for understanding both environmental and genetic canalization are various mathematical models of the genotype–phenotype relationship. To our knowledge, the first study that conceptualized canalization and robustness as a features of the genotype-phenotype map was Andreas Wagner's 1996 computational model of gene regulation (Wagner 1996). In this paper, he showed that mutational robustness can evolve and that it can be understood as convergence toward "flat" regions of the genotype–phenotype map. A similar point was made by Van Nimwegen, et al. 1999, which uses abstract combinatorial space models to argue that evolution drives populations toward regions of high robustness, even without selection. Sean Rice developed the concept of the "phenotypic landscape," a surface that defines the phenotype as a function of underlying environmental and/or genetic factors (Rice 1998). Development is represented by interactions among these factors that determine the shape of the landscape; the height of the landscape represents a measure of a phenotypic trait. The different contour lines of the landscape represent different values of the trait, with the trait value being the same along the same contour line. The spacing between the contour lines indicates the slope of the surface and provides a measure of the degree to which underlying factors translate into phenotypic variation; the curvature of the landscape depends on the degree of non-additive (G × G and/or G × E) interactions. Points of minimal slope along a given contour are the points of maximum canalization for a given trait. For an overview of this framework see Rice 2004; mathematical details can be found in Rice 1998 and Rice 2002.

**Rice, Sean H. 1998. The evolution of canalization and the breaking of von Baer's Laws: Modeling the evolution of development with epistasis. *Evolution* 52:647–656.**

This paper develops the mathematical machinery of phenotypic landscapes and provides a model of canalization and de-canalization.

**Rice, Sean H. 2002. A general population genetic theory for the evolution of developmental interactions. *Proceedings of***

***the National Academy of Sciences of the United States of America* 99:15518–15523.**

This paper generalizes the framework developed in Rice 1998.

**Rice, Sean H. 2004. *Evolutionary theory: Mathematical and conceptual foundations*. Sunderland, MA: Sinauer.**

Excellent introduction into evolutionary theory; contains a chapter on developmental evolution that summarizes the “phenotypic landscape” framework.

**Van Nimwegen, Erik, James P. Crutchfield, and Martijn Huynen. 1999. Neutral evolution of mutational robustness. *Proceedings of the National Academy of Sciences of the United States of America* 96:9716–9720.**

In this paper the evolution of mutational robustness was modeled using combinatorial configuration spaces rather than continuous models of gene effects. The authors argue that neutral evolution (i.e., without selection) would drive populations to points of maximal robustness.

**Wagner, Andreas. 1996. Does evolutionary plasticity evolve? *Evolution* 50:1008–1023.**

The first paper that conceptualized canalization and robustness as a feature of the genotype–phenotype map based on a computational model of gene regulation.

## Population and Quantitative Genetic Theory of Canalization

To our knowledge, the first mathematical result that showed that natural selection does not necessarily lead to the survival of the fittest genotype but instead can select for a less fit but more robust genotype was provided by the theoretical chemists Peter Schuster and Jörg Swetina (Schuster and Swetina 1988). Their treatment was based on a mathematical framework that originated in the origin-of-life theory of Manfred Eigen but is mathematically equivalent to the continuous mutation-selection models of James Crow and Motoo Kimura. Wagner, et al. 1997 provides the first comprehensive theoretical treatment for the evolution of canalization under stabilizing selection, using population genetics theory. The authors establish that, while (micro-)environmental canalization can evolve relatively easily, the conditions for the evolution of genetic canalization are more restrictive: genetic canalization only evolves under weak to moderate levels of stabilizing selection. Gavrilets and Hastings 1994 (cited under Environmental Canalization, Plasticity, and G × E) also studies how stabilizing selection can favor the evolution of microenvironmental canalization, buffering against “developmental noise.” In 1997 Martin Nowak and colleagues published a brief note suggesting that natural selection can increase “genetic redundancy,” a mechanism that might contribute to robustness. Hermisson, et al. 2003 shows that, using a more general model than that of Wagner, et al. 1997, stabilizing selection can actually lead to the opposite of genetic canalization, namely de-canalization (i.e., an increased sensitivity to the phenotypic effects of mutations). This illustrates that the evolutionary outcome of selection for canalization depend critically on the models being used; different models make different assumptions about the details of gene interactions. Theoreticians have also studied the evolution of canalization without stabilizing selection, for instance, directional selection (Hansen, et al. 2006) and fluctuating selection (Kawecki 2000; Le Rouzic, et al. 2013). Proulx and Phillips 2005 introduces a general model that can integrate any form of (e.g., genetic, environmental, developmental) perturbation against which canalization might evolve. It is clear from the references discussed here that, from a theoretical point of view, the evolution of canalization is a conceptually and technically very complex issue and that the field has, at least for the most part, not yet managed to settle on a few general principles. For example, there seems to be no simple, clear-cut relationship between the different modes of selection and their effects on the evolution of canalization (also see Computational Models of the Evolution of Robustness).

**Hansen, Thomas F., José M. Alvarez-Castro, Ashley J. R. Carter, Joachim Hermisson, and Günter P. Wagner. 2006. Evolution of genetic architecture under directional selection. *Evolution* 60:1523–1536.**

The authors demonstrate that, counterintuitively, canalization can evolve under directional selection, for which one would normally expect de-canalization to evolve.

**Hermisson, Joachim, Thomas F. Hansen, and Günter P. Wagner. 2003. Epistasis in polygenic traits and the evolution of genetic architecture under stabilizing selection. *American Naturalist* 161:708–734.**

This study shows that under more general conditions that those studied by Wagner, et al. 1997 stabilizing selection can under some circumstances lead to de-canalization (i.e., the evolution of increased sensitivity to mutations).

**Kawecki, Tadeusz J. 2000. The evolution of genetic canalization under fluctuating selection. *Evolution* 54:1–12.**

This study examines whether and how canalization can evolve under a regime of temporally fluctuating selection and finds that weak to moderately strong fluctuating Gaussian selection favors genetic canalization.

**Le Rouzic, Arnaud, José M. Álvarez-Castro, and Thomas F. Hansen. 2013. The evolution of canalization and evolvability in stable and fluctuating environments. *Evolutionary Biology* 40:317–340.**

A model of how evolvability and canalization evolve under different genetic architectures and selection regimes. Provides theoretical evidence that canalization evolves as a byproduct of trait evolution.

**Nowak, Martin A., Maarten C. Boerlijst, Jonathan Cooke, and John Maynard-Smith. 1997. Evolution of genetic redundancy. *Nature* 38:167–171.**

A brief note from making a qualitative argument that natural selection should be able to increase mutational robustness.

**Proulx, Stephen R., and Patrick C. Phillips. 2005. The opportunity for canalization and the evolution of genetic networks. *American Naturalist* 165:147–162.**

This paper introduces a general model for the evolution of canalization that can incorporate any form of (e.g., genetic, environmental, developmental) perturbation. The authors derive an upper bound for the strength of selection on canalization, which is approximately equal to the fitness load. Load is not only induced by relatively rare mutations but can also be due to migration, segregation, developmental noise, and environmental variance, so that each of these perturbations can strongly select for canalization.

**Schuster, Peter, and Jörg Swetina. 1988. Stationary mutant distributions and evolutionary optimization. *Bulletin of Mathematical Biology* 50:635–660.**

This pioneering contribution was the first mathematical result that demonstrated that selection can increase mutational robustness rather than the fitness of the best genotype.

**Wagner, Günter P., Ginger Booth, and Homayoun Bagheri-Chaichian. 1997. A population genetic theory of canalization. *Evolution* 51:329–347.**

The first analytical, population genetical treatment of the evolution of canalization under stabilizing selection. The paper demonstrates that under stabilizing selection environmental canalization should evolve relatively easily, whereas the conditions for the evolution of genetic canalization are much more restrictive.

## Computational Models of the Evolution of Robustness

Since the 1990s a growing body of work has been using computational and numerical simulation models to study the evolution of canalization and robustness. The first such model was published by Andreas Wagner (Wagner 1996, cited under Phenotypic Landscapes, Configuration Space Models, and Canalization), using simulations of a gene regulatory network; this paper was

among the first to show that canalization can indeed evolve by selection. Surprisingly, however, it was later found by Siegal and Bergman 2002 that—in the same model as used by Wagner—canalization can evolve even when the focal phenotype is not under any direct selection; instead, the authors found that in the model there was selection against sustained oscillations in gene expression that led to indirect selection for canalization. Wilke, et al. 2001 uses a model of "digital organisms" (i.e., a so-called artificial life model) to show that selection can favor a mutationally insensitive genotype when mutations rates are high. Finally, an important landmark paper is Ancel and Fontana 2000, which shows that genetic canalization can evolve as a byproduct of (correlated response to) selection favoring environmental canalization—in this case, equivalent with thermodynamic stability—in a model of RNA folding.

**Ancel, Lauren W., and Walter Fontana. 2000. Plasticity, evolvability, and modularity in RNA. *Journal of Experimental Zoology Part B: Molecular and Developmental Evolutions* 288:242–283.**

A computational study of the evolution of RNA secondary structure demonstrating that in response to environmental perturbations selection favors the evolution of environmental canalization and that genetic canalization evolves secondarily as a correlated response to selection. The authors introduce the term "plastogenetic" congruence to denote the correlation between environmental canalization/plasticity and genetic canalization.

**Siegal, Mark L., and Aviv Bergman. 2002. Waddington's canalization revisited: Developmental stability and evolution. *Proceedings of the National Academy of Sciences of the United States of America* 99:10528–10532.**

This paper was the first to show that canalization can evolve in model of a gene regulatory network even without any selection on canalization/robustness or the trait itself.

**Wagner, Andreas. 1996. Does evolutionary plasticity evolve? *Evolution* 50:1008–1023.**

The first numerical computer simulation study of a gene regulatory system, showing convincingly that canalization can evolve by natural selection, as had been hypothesized by Waddington and Schmalhausen.

**Wilke, Claus O., Jia Lan Wang, Charles Ofria, Richard E. Lenski, and Christoph Adam. 2001. Evolution of digital organisms at high mutation rates leads to survival of the flattest. *Nature* 412:331–333.**

The authors of this paper use computational "artificial life" models ("digital organisms") to demonstrate that under high mutation rate selection can favor a mutationally more robust genotype.

## Cryptic Variation, Genetic Assimilation, and Accommodation

Waddington 1942 (cited under Early History of the Canalization Concept) introduced the concept of genetic assimilation, that is, the process whereby a trait that is initially only phenotypically expressed or produced in response to an environmental change or perturbation increases in frequency by selection acting on previously hidden (genetic and/or—possibly epigenetic—variation) and eventually becomes constitutively expressed even in the absence of the environmental stimulus. In other words, one can think of genetic assimilation as representing the evolution of an environmentally canalized (i.e., "flat," slope of zero) reaction norm, which leads to the constitutive expression of a trait independent of the inducing environment, from an initially plastic (non-zero slope) reaction norm (see Braendle and Flatt 2006; Ehrenreich and Pfennig 2016). Experimental evidence for the existence of this phenomenon is summarized by Scharloo 1991 (cited under General Overviews). A closely related concept, genetic accommodation, was introduced by West-Eberhard 2003 (cited under Books): genetic accommodation is the process whereby a novel environmentally or genetically induced phenotype becomes, via selection, either more or less plastic; thus, accommodation is an adaptive evolutionary change in the environmental regulation of a trait, as is discussed by Braendle and Flatt 2006 and Ehrenreich and Pfennig 2016. The evolution of a new (plastic or canalized) reaction norm can either proceed via an environmentally or genetically induced release of cryptic variation that selection can act upon, or via "standard" selection of segregating variation for plasticity (genotype by environment interactions; G × E). Waddington's genetic assimilation is thus a special case of genetic accommodation (Braendle and Flatt 2006; Ehrenreich and Pfennig 2016). The phenomenon of cryptic

genetic variation is reviewed by Paaby and Rockman 2014. Hermisson and Wagner 2004 shows that the release of cryptic variation is not necessarily due to de-canalization but represents a general property of systems exhibiting epistasis or G × E. This was an important finding because the release of cryptic variation, presumably due to a breakdown of genetic canalization (de-canalization), was considered to represent evidence for the robustness/canalization of the wild-type. Experimental proof that the release of cryptic variation can occur under constant mutational canalization has been provided by the laboratory of Mark Siegal in two landmark papers (Richardson, et al. 2013; Geiler-Samarotte, et al. 2016). However, an important recent finding is that genetic assimilation does not necessarily (at least not always) require the expression and selection of segregating, previously cryptic variants but that stress (e.g., heat shock) can actually induce *de novo* mutations (e.g., DNA deletions or transposon insertions) that then become subject to assimilation (Fanti, et al. 2017).

**Braendle, Christian, and Thomas Flatt. 2006. A role for genetic accommodation in evolution? *BioEssays* 28:868–873.**

A review essay that clarifies the conceptual relationship between Waddington's genetic assimilation and genetic accommodation by West-Eberhard 2003 (cited under Books), arguing that at a fundamental level they represent the same process.

**Eshel, Ilan, and Carlo Matessi. 1998. Canalization, genetic assimilation and preadaptation: A quantitative genetic model. *Genetics* 149:2119–2133.**

An early formal mathematical model of genetic assimilation.

**Ehrenreich, Ian M., and David W. Pfennig. 2016. Genetic assimilation: A review of its potential proximate causes and evolutionary consequences. *Annals of Botany* 117:769–779.**

An excellent, conceptually very clear review of genetic assimilation, genetic accommodation and their relationship.

**Fanti, Laura, Lucia Piacentini, Ugo Cappucci, Assunta M. Casale, and Sergio Pimpinelli. 2017. Canalization by selection of *de Novo* induced mutations. *Genetics* 206:1995–2006.**

An important paper showing that genetic assimilation upon heat-shock stress in *Drosophila* does not necessarily need to rely upon cryptic, already segregating variation but can actually be caused by *de novo* mutations induced by heat shock.

**Geiler-Samarotte, Kerry A., Yuan O. Zhu, Benjamin E. Goulet, David W. Hall, and Mark L. Siegal. 2016. Selection transforms the landscape of genetic variation interacting with HSP90. *PLoS Biology* 14.10: e2000465.**

An important contribution which demonstrates that the classical molecular mechanism for "buffering" the phenotype, HSP90, does not change the overall mutational robustness of the phenotype, but allows for the accumulation of cryptic variation.

**Hermisson, Joachim, and Günter P. Wagner. 2004. The population genetic theory of hidden variation and genetic robustness. *Genetics* 168:2271–2284.**

Before the publication of this paper, the release of previously hidden variation under genetic or environmental perturbation was taken as "prima facie" evidence that the increase of "cryptic" variation occurs due to de-canalization. This paper shows that this reasoning is flawed: any trait under stabilizing selection and subject to epistasis, whether initially canalized or not, will exhibit this release of cryptic variation.

**Paaby, Annalise B., and Matthew V. Rockman. 2014. Cryptic genetic variation: Evolution's hidden substrate. *Nature Reviews Genetics* 15:247–258.**

A recent up-to-date review of cryptic genetic variation.

**Richardson, Joshua, Locke D. Uppendahl, Maria K. Traficante, Sasha F. Levy, and Mark L. Siegal. 2013. Histone variant HTZ1 shows extensive epistasis with, but does not increase robustness to, new mutations. *PLoS Genetics* 9.8: e1003733.**

This was the first experimental demonstration that highly epistatic alleles lead to release of cryptic genetic variation but do not necessarily affect genetic robustness/canalization. This is an important finding since release of cryptic genetic variation was considered as direct evidence for the canalization of the wild-type.

## Classical Examples of Canalization and Assimilation

Several classical experimental examples serve to illustrate the phenomenon of canalization and genetic assimilation; most of these are reviewed and discussed in depth by Scharloo 1991 (cited under General Overviews). The majority of the early experiments were carried out in *Drosophila*. Waddington 1953 performs a selection experiment on the *Drosophila* cross-veinless mutant phenotype: in one selection line Waddington selected for flies that showed the mutant phenotype after heat shock treatment; in the other he selected for flies that did not show the phenotype after heat shock. After twelve generations, there was a 55 percent difference in the inducibility/non-inducibility of the phenotype between the two lines. In addition to these two lines, Waddington kept in each generation flies from both lines without exposing them to heat shock. In this no-heat-shock control line of the line selected for increased sensitivity, Waddington found some flies showing the mutant phenotype in the absence of heat shock. Thus, in these flies the mutant phenotype now started to appear without the inducing environmental perturbation, a clear example of genetic assimilation. This experiment was later repeated by Bateman 1959, with a similar outcome despite using a different base stock of flies. Another famous example is the experiment by Waddington 1956 on the genetic assimilation of the bithorax mutant phenotype. Dun and Fraser 1958 discovered that a mutation in the mouse decreases the mean number of whiskers on the snout, yet at the same time increases the variance. Since this variance is heritable and can be selected upon, the authors concluded that mutation is de-canalizing, leading to a release of cryptic variation on which selection can act, an inference that turned out to be flawed (see Hermisson and Wagner 2004, cited under Cryptic Variation, Genetic Assimilation, and Accommodation). A similar experiment was performed by Rendel 1959 using a fly mutant that affects the number of bristles on the scutellum.

**Bateman, K. Gillian. 1959. The genetic assimilation of four venation phenocopies. *Journal of Genetics* 56:443–447.**

An independent repetition of the genetic assimilation experiment of Waddington 1953.

**Dun, Robert B., and Alex S. Fraser. 1958. Selection for an invariant character—"vibrissae number"—in the house mouse. *Nature* 181:1018–1019.**

A classical experiment on canalization. This paper shows that the *Tabby* mutation in the mouse decreases the average number of whiskers on the snout while at the same time increasing the variance in whisker number. This variance, induced by the mutation, is heritable and can artificially be selection upon. The authors interpreted these results to mean that the wild-type is canalized but the mutant de-canalized, with the mutation uncovering previously cryptic genetic variation.

**Rendel, James M. 1959. Canalization of the scute phenotype of *Drosophila*. *Evolution* 13:425–439.**

An experiment similar to that done by Dun and Fraser 1958 but with the *Drosophila* mutant *scute*, which affects scutellar bristle number.

**Waddington, Conrad H. 1953. Genetic assimilation of an acquired character. *Evolution* 7:118–126.**

Selection experiment demonstrating genetic assimilation of the cross-veinless phenotype in *Drosophila*.

**Waddington, Conrad H. 1956. Genetic assimilation of the *bithorax* phenotype. *Evolution* 10:1–13.**

Another classical and famous experiment showing genetic assimilation of the bithorax mutant phenotype in *Drosophila*.

## Modern Examples of Canalization, Assimilation, and Accommodation

One of the first modern experimental studies of canalization, using genetic tools in *Drosophila*, was conducted by Stearns and Kawecki 1994, which demonstrates that traits that are under stronger selection are also less variable, as intuitively predicted based on Waddington's qualitative argument. Also using fruit flies as a model, Gibson and Hogness 1996 uncovers the molecular mechanism underlying one of Waddington's classical experiments: Waddington had found that ether exposure can cause heritable, selectable phenotypic expression of the previously cryptic bithorax mutant phenotype. Gibson and Hogness 1996 shows that this is not simply a "phenocopy" effect but that ether treatment uncovers cryptic variation at the causative locus, *Ubx*, itself: genotypes that produce the mutant phenotype in response to ether harbor a cryptic, ether-sensitive polymorphism at Ubx that can be selected upon (genetically assimilated). Gibson, et al. 1999 provides a clear-cut experimental demonstration of the existence of cryptic genetic variation. In a famous landmark paper, Rutherford and Lindquist show that impairment of Hsp90 function in *Drosophila* leads to the release of cryptic morphological variation that can become genetically assimilated (several similar studies by the Lindquist group have subsequently been performed with fruit flies, yeast prions, and *Arabidopsis*). However, the authors' conjecture that Hsp90 might represent an adaptive "capacitor" for the context-dependent, adaptive release of hidden variation ("evolutionary capacitance") remains controversial. Elena and Lenski 2001 experimentally examines the evolution of genetic canalization in *E. coli* but fails to find that mutational effects become more canalized. Suzuki and Nijhout 2006 demonstrates that a color polyphenism in the tobacco hornworm, *Manduca sexta*, evolves via genetic accommodation in a laboratory experiment (also see Cryptic Variation, Genetic Assimilation, and Accommodation). Importantly, Fanti, et al. 2017 (cited under Cryptic Variation, Genetic Assimilation, and Accommodation) have recently demonstrated that genetic assimilation can proceed via selection of stress-induced *de novo* mutations and therefore does not necessarily require standing cryptic variation as a mechanism.

**Elena, Santiago F., and Richard E. Lenski. 2001. Epistasis between new mutations and genetic background and a test of genetic canalization. *Evolution* 55:1746–1752.**

The authors examine the effects of introducing a set of twelve mutations into an ancestral and a derived laboratory strain of *E. coli* and conclude that mutational effects in the derived background are not more canalized than in the ancestral background, suggesting that the evolved strain has not acquired genetic canalization.

**Gibson, Greg, and David S. Hogness. 1996. Effect of polymorphism in the *Drosophila* regulatory gene *Ultrabithorax* on homeotic stability. *Science* 271:200–203.**

A beautiful molecular genetic study repeating one of Waddington's classical experiments: fly genotypes that are more sensitive to treatment with ether vapor—that is, showing an increased frequency of the bithorax mutant phenotype—actually possess a polymorphism at the *Ubx* locus that confers increased sensitivity. Thus, ether treatment uncovers cryptic variation at *Ubx* that can be selected upon (i.e., be genetically assimilated).

**Gibson, Greg, Matthew Wemple, and Sylvie van Helden. 1999. Potential variance affecting homeotic *Ultrabithorax* and *Antennapedia* phenotypes in *Drosophila melanogaster*. *Genetics* 151:1081–1091.**

Experimental demonstration of the existence of potential (i.e., previously cryptic) variation in wild-type genetic backgrounds, whose effects are not normally observable but which become visible when mutants are introgressed into the wild-type backgrounds.

**Rutherford, Suzanne L., and Susan Lindquist. 1998. Hsp90 as a capacitor for morphological evolution. *Nature* 396:336–342.**

A landmark paper showing that impaired functionality of the chaperone Hsp90 in *Drosophila* causes the expression of heritable, previously cryptic morphological variation that can be selected upon and which can become genetically assimilated. However, the

authors hypothesis that Hsp90 might have evolved to serve as an adaptive “capacitor” for the conditional release of hidden variation remains highly controversial.

**Stearns, Stephen C., and Tadeusz J. Kawecki. 1994. Fitness sensitivity and the canalization of life-history traits. *Evolution* 48:1438–1450.**

The first modern genetic study of canalization: the authors measured the effects of P-element insertions on variation in life-history traits and concluded that traits more closely related to fitness are more canalized. Later it was realized that comparisons of these traits might be confounded by differences in genetic architecture (i.e., different mutational target sizes); however, this is itself a potentially confounded argument since it cannot distinguish between evolved (canalized) and “generic” genetic architecture.

**Suzuki, Yuichiro, and Frederik H. Nijhout. 2006. Evolution of a polyphenism by genetic accommodation. *Science* 311:650–652.**

A recent experimental demonstration of the existence of genetic accommodation.

## Proximate Mechanisms Underlying Canalization and Robustness

Wilkins 1997 and Hartman, et al. 2001 review the multiple mechanisms that can lead to canalization or robustness (also see General Overviews). Most generally, in terms of transmission genetics, canalization can be understood to be a consequence of G × G and/or G × E interactions (Flatt 2005, cited under General Overviews). In terms of proximate mechanisms canalization can arise from plasticity, functional (genetic) redundancy (e.g., Nowak, et al. 1997, cited under Population and Quantitative Genetic Theory of Canalization; Wilkins 1997), enzyme kinetics causing dominance (Bagheri and Wagner 2004), pleiotropy, modularity (e.g., Ancel and Fontana 2000, cited under Computational Models of the Evolution of Robustness), or as an emergent property of gene networks and biochemical pathways (see Robustness as an Emergent Property of Networks and Pathways).

**Bagheri, Homayoun C., and Günter P. Wagner. 2004. Evolution of dominance in metabolic pathways. *Genetics* 168:1713–1735.**

A theoretical model of the evolution of dominance which can be viewed as a form of phenotypic robustness to mutations.

**Hartman, John L. IV, Barbara Garvik, and Lee Hartwell. 2001. Principles for the buffering of genetic variation. *Science* 291:1001–1004.**

This review discusses canalization or buffering mainly from the perspective of gene interactions.

**Wilkins, Adam S. 1997. Canalization: A molecular genetic perspective. *BioEssays* 19:257–262.**

A review essay that argues that redundancy, due to the existence of paralogous genes, may be an important mechanism underlying canalization.

## Robustness as a Property of Networks and Pathways

As mentioned in the section Proximate Mechanisms Underlying Canalization and Robustness, robustness can arise from systems-level properties of genetic or biochemical networks and pathways. One of the first studies showing how robustness can arise as an emergent property of biochemical networks is Barkai and Leibler 1997. Gibson 1996 finds that threshold-dependent transcriptional regulation can lead to robustness. Von Dassow, et al. 2000 analyzes a mathematical model of the *Drosophila* segment polarity network and finds that it displayed robustness over large fractions of the parameter space, thereby demonstrating that network

structure and threshold effects can cause robustness without the need of natural selection. Andreas Wagner finds that mutational robustness cannot be explained by genetic redundancy alone (Wagner 2000). Rünneburger and Le Rouzic 2016 provides a recent example of a simulation study that examines the evolution of canalization in a gene regulatory network. This area has been reviewed by Masel and Siegal 2009 and, more recently, by Siegal and Leu 2014.

**Barkai, Naama, and Stanislas Leibler. 1997. Robustness in simple biochemical networks. *Nature* 387:913–917.**

This important study shows that simple biochemical networks of bacterial chemotaxis are robust against perturbations due the connectivity of these networks.

**Gibson, Greg. 1996. Epistasis and pleiotropy as natural properties of transcriptional regulation. *Theoretical Population Biology* 49:58–89.**

A model showing how epistasis and pleiotropy emerge as properties transcriptional regulation and that threshold-dependent transcriptional regulation can lead to buffering.

**Masel, Joanna, and Mark L. Siegal. 2009. Robustness: Mechanisms and consequences. *Trends in Genetics* 25:395–403.**

A review of the idea that robustness can arise as an intrinsic property of biological systems.

**Rünneburger, Estelle, and Arnaud Le Rouzic. 2016. Why and how genetic canalization evolves in gene regulatory networks. *BMC Evolutionary Biology* 16:239.**

A recent, individual-based simulation study examining the evolution of genetic canalization in gene regulatory networks.

**Siegal, Mark L., and Jun-Yi Leu. 2014. On the nature and evolutionary impact of phenotypic robustness mechanisms. *Annual Review of Ecology, Evolution, and Systematics* 45:495–517.**

A recent review of the mechanisms underlying mutational robustness.

**von Dassow, George, Eli Meir, Edwin M. Munro, and Garrett M. Odell. 2000. The segment polarity network is a robust developmental module. *Nature* 406:188–192.**

In this study of a mathematical model of the *Drosophila* segment polarity model the authors show unexpected levels of robustness to changes in parameter values. The effect can be traced back to the fact that these biochemical models display saturation and threshold effects that lead to robust dynamical attractors.

**Wagner, Andreas. 2000. Robustness against mutations in genetic networks of yeast. *Nature Genetics* 24:355–361.**

In this paper the author shows that mutational robustness cannot be explained by genetic redundancy alone, that is, by the presence of duplicated genes that perform the same function. The conclusion was that robustness is a network property that is not exclusively due to genetic redundancy.

## Robustness and Evolvability

Evolvability, the ability of a genotype to produce—through mutations—adaptive variants, has a somewhat paradoxical and not yet fully understood conceptual relationship to robustness. Wagner and Altenberg 1996 introduces ideas of evolvability that existed in computer science (the so-called representation problem) to evolutionary biology and suggests that modularity is one way of how biological systems can retain evolvability despite increasing complexity. Kirschner and Gerhart suggested that evolvability is

enabled through a number of systems properties that essentially boil down to mechanisms of developmental robustness (Kirschner and Gerhart 1998). The connection between certain forms of robustness and evolvability is that evolvability is expected to increase if negative pleiotropic effects of otherwise adaptive mutations are suppressed by developmental regulation or buffering, as predicted by Rupert Riedl (Riedl 1978). However, the connection between robustness and evolvability is not entirely intuitive: evolvability requires the expression of heritable phenotypic variation and thus canalization seems antithetical to the idea of evolvability. The latter argument is, of course, only true if canalization and evolvability are considered with respect to one and only one character, while in multidimensional models the relationship is more complicated. In any case, this question has engendered a large number of papers of which we can only mention a few here. Wagner 2008 shows that robustness of RNA secondary structure is correlated with mutational accessibility of alternative phenotypes and thus positively correlated with evolvability. Bloom, et al. 2006 shows a similar result for proteins. Draghi, et al. 2010 show that the relationship between robustness and evolvability is non-monotonic, meaning that it can be positive or negative depending on population structure.

**Bloom, Jesse D., Sy T. Labthavikul, Christopher R. Otey, and Francis H. Arnold. 2006. Protein stability promotes evolvability. *Proceedings of the National Academy of Sciences of the United States of America* 103:5869–5874.**

In this pioneering paper Jesse Bloom and colleagues show that the thermodynamic stability of proteins increases their evolvability.

**Draghi, Jeremy A., Todd L. Parsons, Günter P. Wagner, and Joshua P. Plotkin. 2010. Mutational robustness can facilitate adaptation. *Nature* 463:353–355.**

In this paper the authors show that the relationship between robustness and evolvability is nonlinear; depending on the specific circumstances increased robustness can either increase or decrease evolvability.

**Kirschner, Marc, and John Gerhart. 1998. Evolvability. *Proceedings of the National Academy of Sciences of the United States of America* 95:8420–8427.**

Kirschner and Gerhart were among the first to suggest that certain forms of developmental regulation and buffering could lead to higher evolvability and might even be a prerequisite of evolvability.

**Riedl, Rupert. 1978. *Order in living organisms*. New York: Wiley.**

This visionary book anticipated many ideas of developmental evolution and evolutionary systems biology. Among them is the idea that developmental constraints that prevent unconditionally deleterious side effects will actually increase evolvability.

**Wagner, Andreas. 2008. Robustness and evolvability: A paradox resolved. *Proceedings of the Royal Society of London B* 275:91–100.**

Using RNA secondary structure models, the author shows that more robust phenotypes (secondary structures) have access to a larger number of alternative phenotypes and are thus more evolvable. The paper also shows that population structure is essential for assessing the evolvability of a phenotype in addition to its variational properties.

**Wagner, Günter P., and Lee Altenberg. 1996. Perspective: Complex adaptations and the evolution of evolvability. *Evolution* 50:967–976.**

This paper introduced the notion of “evolvability” and suggests that modularity ensures evolvability of complex organisms. The paper also distinguishes “variability” (i.e., the ability to vary), measured by mutation rate and mutational variance ($V_m$), and “variation” (i.e., actual differences among genotypes). This distinction emphasizes that canalization is a variational property rather than only reflecting the amount of genetic variation in a population (which depends on many factors not related to robustness).

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