



Empirically founded genotype–phenotype maps from mammalian cyclic nucleotide-gated ion channels



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HIGHLIGHTS

- Genotype–phenotype–fitness maps are built from experimental data on ion channels.
- I focus on ion channels regulated by cyclic nucleotides, expressed in photoreceptors.
- A hierarchical series of phenotypes is considered.
- A clustering of phenotypes is observed at progressively higher integration levels.
- Magnitude and reciprocal sign epistasis, and permissive mutations are discussed.

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ABSTRACT

A major barrier between evolutionary and functional biology is the difficulty of determining appropriate genotype–phenotype–fitness maps, particularly in metazoans. Concrete perspectives towards unifying these approaches are offered by studies on the physiological systems that depend on ion channel dynamics. I focus on the cyclic nucleotide-gated (CNG) channels implicated in the photoreceptor's response to light. From an evolutionary standpoint, sensory systems offers interpretative advantages, as the relation between the sensory response and environment is relatively straightforward. For CNG and other ion channels, extensive data are available about the physiological consequences of scanning mutagenesis on sensitive protein domains, such as the conduction pore. Mutant ion channels can be easily studied in living cells, so that the relation between genotypes and phenotypes is less speculative than usual. By relying on relatively simple theoretical frameworks, I used these data to relate the sequence space with phenotypes at increasing hierarchical levels. These empirical genotype–phenotype and phenotype–phenotype landscapes became smoother at higher integration levels, especially in heterozygous condition. The epistatic interaction between sites was analyzed from double mutant constructs. Magnitude epistasis was common. Moreover, evidence of reciprocal sign epistasis and the presence of permissive mutations were also observed, which suggest how adaptive regions can be connected across maladaptive valleys. The approach I describe suggests a way to better relate the evolutionary dynamics with the underlying physiology.

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1. Introduction

Functional and evolutionary biology have long run in parallel, with relatively little exchange. Neodarwinism grew largely independently of developmental biology (Mayr and Provine, 1980), while the dichotomy between evolutionism and physiology traces back to the 'second biological revolution' of the mid-nineteenth century (Conti, 2001). In fact, very little exchange occurred

between the founding works of Charles Darwin and, say, Claude Bernard. A telling example is the different use of landscape metaphors. In the physical sciences, whose conceptual stance is maintained by functional biology, dynamical systems are often represented by energy landscapes *et similia*, with spontaneous processes viewed as tending to minimize potential or free energy. The picture is considerably different in evolutionary biology. Following Wright (1932), the evolution pathway is often described in terms of adaptive landscapes, characterized by fitness peaks and valleys plotted against genotypes or gene frequencies. Wright's suggestion was intended as a non rigorous help to grasp a population's adaptive walk through a highly multidimensional

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genotypic space (Dietrich and Skipper, 2012). However, the overall idea was much successful and gave rise to substantial theoretical work.

Such a dichotomy between energy and fitness landscapes testifies different scopes and attitudes within the main fields of biological research. The evolutionary process is rarely examined from the standpoint of the underlying physiology, whereas the latter is rarely put into an evolutionary context. However, because natural selection mostly acts on phenotypes, to fully understand how fitness depends on genotypes, one has to consider at least two components: a genotype–phenotype and a phenotype–fitness function (or map). In the absence of a better integration between functional and evolutionary biology, we do not know how to construct these maps, let alone connect them, in an empirically founded way (Alberch, 1991; Lewontin, 1974; Pigliucci, 2012; Travisano and Shaw, 2012; Waddington, 1974).

Some authors attribute the term fitness landscape to the genotype-based Wright-style landscape and the term adaptive landscape to the phenotype-based landscape originally envisioned by Simpson (Arnold et al., 2001; McGhee, 2007; Pigliucci, 2012; Simpson, 1944). Because this nomenclature is not universally adopted, I will explicitly mention whether I refer to genotype- or phenotype-based landscapes.

1.1. Theoretical landscapes

Early theoretical work made it clear that simple low-dimensional models (e.g., considering only one or a few genes) are dynamically insufficient to describe the evolution of complex systems (Lewontin, 1974). In the last four decades, models have been proposed of multidimensional landscapes based on either phenotypes (e.g., Lande and Arnold, 1983), or genotypes (e.g., Kauffman and Levin, 1987; Gavrilets, 2004). However, adequate mathematical treatment of multidimensional landscapes requires simplifying hypotheses, and different assumptions can produce very different patterns. We briefly summarize the main genotype-based landscapes. For review, see (Dietrich and Skipper, 2012; Gavrilets, 2004).

1. In *single-peak landscape models*, natural selection and mutation play the major role (Coyne et al., 1997; Fisher, 1941; Provine, 1986). These are useful to study adaptation around a local peak (e.g., Orr, 1998), but not necessarily the global landscape, which may be more or less ‘rugged’.
2. *Neutral landscapes*. If most mutations at the molecular level are assumed to be neutral (Kimura, 1968; King and Jukes, 1969), the ensuing fitness landscape is flat. No adaptive peaks are present and genotypic divergence is determined by stochastic factors.
3. *Rugged landscapes based on NK models*. The contribution to fitness is studied of N loci, each interacting randomly with K other loci (Kauffman and Levin, 1987). As N grows, new adaptive peaks appear which outnumber those originally present in lower-dimension spaces. Moreover, as K increases, the fitness of the accessible peaks tends to fall towards the mean landscape fitness. This would limit the extent of selective optimization attainable by natural selection. The NK model assumes there is no genetic variation in the population, fitness can vary from 0 to 1 and is assigned randomly to genotypes, the interaction between loci is random and the probability of fixation does not depend on the effect of the mutation (discussed in Gavrilets, 2004; Gavrilets and Gravner, 1997).
4. *Holey landscapes*. More recent work has considered very highly-dimensional fitness landscapes (i.e. genotype-based), under assumptions complementary to those of the NK model. In particular, many diallelic loci are considered, with randomly assigned fitnesses which can only assume the values 0 and 1

(Gavrilets and Gravner, 1997). Gavrilet’s model can thus consider diploid homo- and heterozygotes, and treat more realistically some aspects of speciation (Gavrilets, 2004; Gavrilets and Gravner, 1997; Gravner et al., 2007). Under these assumptions, genotypes with similar fitnesses form quasi-neutral networks that expand throughout the genotype space and are punctuated by non-adaptive ‘holes’. Clusters of fit genotypes are connected by quasi-neutral pathways (‘ridges’) that facilitate random walk between the adaptive peaks, so that no traversal of the unfit valleys is necessary to walk through the landscape.

1.2. Difficulties with the evolutionary landscapes

None of the above models can fully describe the dynamics of the evolutionary process. Flat landscapes miss the adaptive nature of many organisms’ features. The same applies to highly multidimensional rugged landscapes based on NK-type models, characterized by a myriad of low fitness peaks. On the other hand, the NK-type models with a low dimensionality, which resemble the original Wright-style landscape, leave us with the problem of explaining the evolutionary transition between different adaptive peaks (Coyne et al., 1997; Gavrilets, 2004; Goodnight, 2012). In holey landscapes, the problem of shifting from one peak to another loses much of its relevance.

A more general criticism concerns the tenability of the basic assumptions of each model. Particularly difficult is to determine the appropriate dimensionality, and it has been suggested that the effective dimensionality of adaptive surfaces may steadily decrease during the evolutionary process (Goodnight, 2012). In low-dimensional landscapes, the Wrightian peaks and valleys would tend to reappear. Moreover, because of the difficulty of defining realistic and treatable genotype–phenotype and phenotype–fitness maps, we do not know how to unify the landscapes based on genotypes with those based on phenotypes (Pigliucci, 2010, 2012). These and other problems hamper a satisfactory unification of genotypic and phenotypic evolution as well as micro- and macroevolution (Alberch, 1991; Arnold et al., 2001; Lewontin, 1974; Pigliucci, 2010; Provine, 1986; Rice, 2012; Waddington, 1974; Wagner and Zhang, 2011). Similar criticisms have been expressed from the standpoint of evolutionary developmental biology (‘evo-devo’). In fact, understanding genotype–phenotype functions has great relevance to determine the relation between the mechanism of ontogenesis and the evolutionary changes in morphology (Carroll, 2008; Love, 2006; Müller, 2007; Pigliucci, 2010). Nonetheless, neither micro- nor macroevolution can be reduced to morphological change, and these may not leave clear traces in the fossil record (e.g., Hoekstra and Coyne, 2007). Allelic variants can produce physiological or behavioral effects which appear after birth and are not necessarily implicated in the development of form. Understanding these issues is of great importance to comprehend the physiological evolution, which is largely missed by the paleontological evidence, as well as the problem of the stability of form in geological time, which may be accompanied by ‘invisible’ physiological evolution.

1.3. Comparing theoretical and experimental landscapes

1.3.1. Landscapes in macromolecules

Theoretical work indicates that highly-dimensional protein spaces may be indeed characterized by adaptive pathways that expand throughout the sequence space and bypass the adaptive valleys, which bears some resemblance to the holey-landscape models (Babajide et al., 2001; Bastolla et al., 1999; Bornberg-Bauer and Chan, 1999; Govindarajan and Goldstein, 1997; Lipman and

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