Journal of Theoretical Biology 430 (2017) 78–85

Contents lists available at ScienceDirect

Journal of Theoretical Biology

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

Evolvability and robustness: A paradox restored

Christine Mayer*, Thomas F. Hansen

Department of Biosciences, CEES, EvoGene & CEDE, University of Oslo, PB 1066, Blindern, 0316 Oslo, Norway

ARTICLE INFO

Article history:
Received 29 March 2017
Revised 26 May 2017
Accepted 10 July 2017
Available online 11 July 2017

Keywords:
Evolvability
Robustness
Genotype–phenotype map
Neutral network
Pleiotropy
Boolean network

ABSTRACT

Evolvability and robustness are crucial for the origin and maintenance of complex organisms, but may not be simultaneously achievable as robust traits are also hard to change. Andreas Wagner has proposed a solution to this paradox by arguing that the many-to-few aspect of genotype–phenotype maps creates neutral networks of genotypes coding for the same phenotype. Phenotypes with large networks are genetically robust, but they may also have more neighboring phenotypes and thus higher evolvability. In this paper, we explore the generality of this idea by sampling large numbers of random genotype–phenotype maps for Boolean genotypes and phenotypes. We show that there is indeed a preponderance of positive correlations between the evolvability and robustness of phenotypes within a genotype–phenotype map, but also that there are negative correlations between average evolvability and robustness across maps. We interpret this as predicting a positive correlation across the phenotypic states of a character, but a negative correlation across characters. We also argue that evolvability and robustness tend to be negatively correlated when phenotypes are measured on ordinal or higher scale types. We conclude that Wagner's conjecture of a positive relation between robustness and evolvability is based on strict and somewhat unrealistic biological assumptions.

1. Introduction

Evolvability and robustness are both thought essential for the origin and maintenance of complex, well-adapted organisms (Conrad, 1990; Kauffman, 1993; Gerhart and Kirschner, 1997; Wagner, 2005), but these two properties conflict as evolvability depends on the ability to generate new potentially adaptive phenotypes through mutation while robustness depends on the ability to maintain the same phenotype in the face of mutation. The easier it is to change the phenotype through genetic change, the more evolvable and less robust is the genotype. This creates a paradox for the evolution of complex phenotypes.

Andreas Wagner (2008) proposed an ingenious solution to this paradox. He argued that the paradox originated in thinking about evolvability and robustness as properties of the genotype. In this case, the two properties indeed conflict. His resolution of the paradox was to consider evolvability and robustness not as properties of the genotype, but as properties of the phenotype. A phenotype may be realized by a number of different genotypes, which then forms a neutral network (Fontana et al., 1993; Kauffman, 1993; Schuster et al., 1994; Gruener et al., 1996; Fontana, 2002), also called a genotype network by Wagner (2011) and Payne and Wagner (2014). By defining phenotype evolvability as the number of different phenotypes that can be generated through mutations of any member of the corresponding neutral network, and phenotype robustness as the average probability that the phenotype will not change through mutation of a member of the corresponding neutral network, Wagner argued that phenotypes with large, connected neutral networks could be both robust and evolvable, because they would have many neighbors at the same time as most mutations would leave them unchanged.

Wagner (2008) confirmed the general possibility of a positive correlation between phenotype evolvability and robustness in simulation studies in which the phenotypes were secondary structures of RNA and the associated neutral networks were sets of nucleotide sequences that generated the same secondary structure. Wagner (2005, 2012) and Payne and Wagner (2014) discuss other examples in which robustness facilitates evolvability including protein folding and transcription-factor binding, while Ebner et al., (2002), Aldana et al., (2007), Lesne (2008) and Draghi et al., (2010) have made similar arguments.

Here we explore the generality of these findings and discuss properties of the genotype–phenotype map (GP map) that generate either a positive or a negative relation between evolvability and robustness. We are using a general abstract representation of genotype–phenotype maps in which the genotype and the phenotype are represented by Boolean variables connected through Boolean operators. We demonstrate that both positive and negative relations between evolvability and robustness are possible de-

---

* Corresponding author.
E-mail address: christine.mayer@ibv.uio.no (C. Mayer).

http://dx.doi.org/10.1016/j.jtbi.2017.07.004
0022-5193/

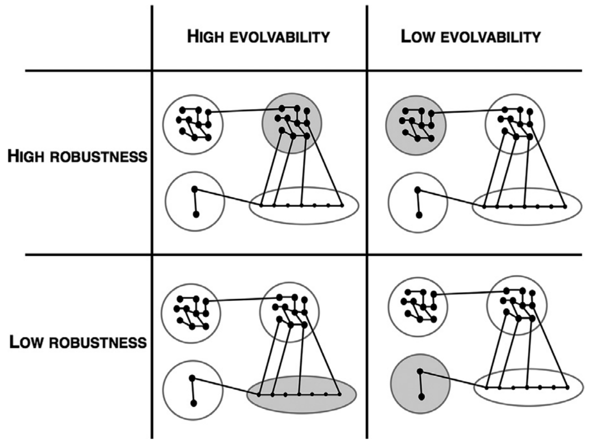

Fig. 1. How evolvability and robustness may vary across phenotypes within a GP map. The black dots represent genotypes with lines representing possible mutations, and the circles represent phenotypes. In each quadrant evolvability and robustness are assigned to the focal phenotype colored in grey. Evolvability is the number of phenotypic neighbors, and robustness is the fraction of mutations that do not leave the phenotype. Note how all combinations of phenotype evolvability and robustness are possible.

pending on the logical structure of the map. Initially we follow the definitions of Wagner (2008) closely, but later we relax some of the inherent assumptions and debate whether they are biologically reasonable.

2. Theory and methods

2.1. General considerations

Wagner (2008) proposed the following definitions (rendered in our terminology):

- Genotype robustness is the number (or fraction) of mutations of a genotype that do not lead to an alternative phenotype.
- Genotype evolvability is the number of alternative phenotypes that can be generated by a single mutation of the genotype.
- Phenotype robustness is the average of genotype robustness over all genotypes within a neutral network.
- Phenotype evolvability is the number of alternative phenotypes that can be generated from the phenotype through mutation.

While genotype evolvability and robustness are negatively related almost by definition, phenotype evolvability and robustness need not be. Positive relationships can arise, as explained by Wagner (2008), if evolvable networks with many neighbors tend to be internally highly connected as illustrated in the upper-left quadrant of Fig. 1, and if networks with few neighbors also tend to have few internal connections as in the lower-right quadrant of Fig. 1. However, as illustrated by the two other quadrants in Fig. 1, inverse relationships can also arise because internally connected networks do not necessarily have many neighbors and vice versa. Some genotype–phenotype maps may also tend to generate more evolvable or robust phenotypes than others. As illustrated in Fig. 2, any combination of evolvability and robustness is possible across maps. Phenotype evolvability and phenotype robustness are thus not automatically positively related, and the relationship needs to be established on a case-by-case basis. To explore the relative occurrence of the different relationships, we will do an exhaustive investigation of all possible genotype–phenotype maps up to a certain level of complexity.

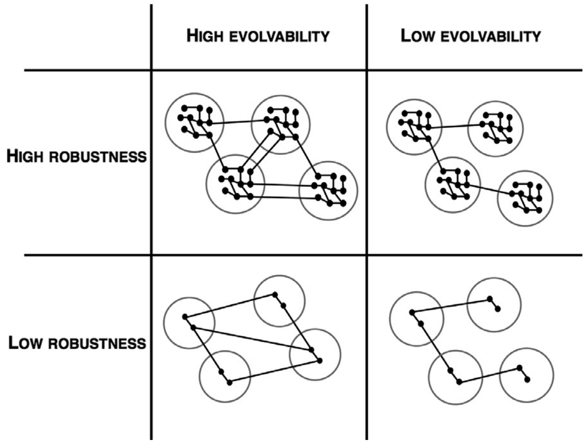

Fig. 2. How robustness and evolvability may vary across GP maps. Each quadrant shows a genotype–phenotype map with a different combination of robustness and evolvability averaged over the four phenotypes each map generates. Notation as in Fig. 1.

2.2. The Boolean genotype–phenotype map

In our model both genotypes and phenotypes are vectors of Boolean variables coded as 0 and 1, and the genotype–phenotype map is defined as a combination of Boolean logic operators. Boolean variables and functions have often been used as a convenient way of modeling genotype–phenotype relationships in the abstract, or to approximate threshold responses (e.g. Kauffman, 1969, 1993; Frank, 1999; Gavrilets, 1999; Thieffry and Romero, 1999; Ebner et al., 2002; Albert and Othmer, 2003; Espinosa-Soto et al., 2004; Quayle and Bullock, 2006; Aldana et al., 2007; Fierst and Phillips, 2015). It is also worth noting that any Boolean function or logic operator can be represented as a multilinear form in Boolean variables and are thus special cases of the multilinear epistatic model of Hansen and Wagner (2001). Here we will generate large numbers of random Boolean maps. Pleiotropy is modeled by allowing elements in the genotype vector to affect more than one element in the phenotype vector, and mutation is modeled by changing single elements of the genotype vector.

The evolvability and robustness of phenotypes generated by a Boolean genotype–phenotype map can be calculated from the following formula:

$$\mathbf{B}_{zz} = \mathbf{B}_{zg}\mathbf{B}_{gg}\mathbf{B}_{gz}, \tag{1}$$

where $\mathbf{B}_{gg}$ is a genotypic adjacency matrix where the ijth element is 1 if the ith and jth genotypes are connected by a single mutation, $\mathbf{B}_{gz}$ is a matrix where the ijth element is 1 if the genotype i is associated with the phenotype j, and 0 if not, and the matrix $\mathbf{B}_{zg} = \mathbf{B}_{gz}{}^{T}$ is thus a description of the genotype–phenotype map. The resulting symmetric matrix $\mathbf{B}_{zz}$ describes the connections of phenotypes by mutation in their corresponding genotypes. Its diagonal elements give the number of ways the corresponding phenotype can mutate into itself, and its off-diagonal elements, ij, give the number of ways phenotype i can mutate into phenotype j. The robustness of a phenotype is thus given by the corresponding diagonal element of $\mathbf{B}_{zz}$, or alternatively as a fraction by dividing this with the sum of the corresponding row (or column). The evolvability of a phenotype in Wagner's sense is the number of non-zero off-diagonal elements in the corresponding row (or column).

If we arrange the Boolean genotypes according to the value of their corresponding binary number, then the matrix $\mathbf{B}_{gg}$ has a characteristic pattern, as illustrated here for a genotype of length three: