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Spotlight

An Individual-Centered Framework For Unravelling Genotype-Phenotype Interactions

Michel Baguette,[1,2,*] Delphine Legrand,[1,3] and Virginie M. Stevens[1]

A new framework in which the multiple levels of molecular variations contribute to phenotypic variations in a complex, nonlinear and interactive way, challenges the hierarchical nature of the relationships between the genotypic and phenotypic spaces. This individual-centered framework provides new insights on the evolutionary mechanisms involved in the production of phenotypes. We propose to move this research agenda forward by combining selection experiments and functional genetics.

Genotype-Phenotype Interactions in a Population-Centered Framework

Genotype-phenotype interactions are at the heart of the theory of evolution by natural selection. The key questions are how and why genotypes and phenotypes change across generations. In his seminal book, Lewontin [1] suggested tackling this issue by considering the processes acting within the genotypic space and the phenotypic space separately. Using a population-centered approach he proposed a focus on the mean phenotypes and genotypes, (Figure 1A, P and G respectively) and on the transfer functions that modify these mean 'types', both within and between generations (Figure 1A, T1–T4). In this system, phenotypic variability is thought to be the result of three different mechanisms, that is, *genetic innovation* by mutation or recombination, *phenotypic plasticity*, the production of different phenotypes by the same genotypes under different environmental conditions, and *bet hedging*, the random production of phenotypes among offspring. Implicit in this framework is the hierarchical nature of the relationships between the genotypic and phenotypic spaces, rooted in the central dogma of molecular biology [2]. Accordingly, the relationships between both spaces are based on a cascading information transfer in which the genome is transcribed into messenger RNA, which themselves are translated into proteins; the transcription can be regulated by the epigenome according to environmental factors (Figure 1B, full arrows).

Towards an Individual-Centered Framework of Genotype-Phenotype Interactions

This population-centered framework has been recently challenged in a medical context by Ritchie *et al*. [3], who proposed that the multiple levels of molecular variations contributing to phenotypic variations could be integrated in a complex, nonlinear and interactive way (Figure 1B, broken arrows). The basic idea of Ritchie *et al*. [3] is to integrate the different types of 'omic' data, that is, genomic, transcriptomic, epigenomic, and proteomic for a more comprehensive prediction of the expression of complex traits or phenotypes. By adopting an individual-centered approach, and by going beyond the use of a single phenotypic marker, the use of this alternative framework sheds new light on the evolutionary mechanisms involved in the production of new phenotypes. Indeed, rather than looking at more or less exclusive mechanisms acting as black boxes – genetic innovation, phenotypic plasticity or bet hedging – it focuses on the functioning of the whole causality chain ranging from DNA to phenomes, through epigenomes, transcriptomes and proteomes, taking into account all the feedbacks between these compartments. Such a mechanistic approach focusing on the molecular processes implied in the emergence and maintenance of phenotypic variation will provide decisive advances in evolutionary ecology and can be considered as a real paradigm shift. Rather than considering one or another phenotypic trait, this approach provides a more convenient holistic view of the phenotype. Phenotypic traits are indeed not independent but rather, they are inter-related by architectural or physiological constraints [4], which translate into syndromes – the recurrent associations of particular values of morphological, physiological, behavioral or life-history traits under particular selection pressures [5]. Such syndromes, often associated with strong inter-individual differences (personalities, e.g., [6]), were also described at the interspecific level for example, for pollination, dispersal, or migration [7–9]. The interpretation of the functionality of these syndromes is currently hindered by the multiplicity of causes that can generate such covariations among traits: energetic, morphological, or genetic constraints can all result in the association of particular trait values. The existence of syndromes shows that particular combinations of traits could be positively or negatively selected in response to selective pressures (e.g., [5,6]). Such multivariate selection on the numerous phenotypic traits involved in syndromes would hardly be captured by the cascading information transfer linking the genotypic and phenotypic spaces in Lewontin's framework [1]. The framework of Ritchie *et al*. [3], by considering non-linear and interactive relationships (including feed-backs) among all 'omic' compartments, would be more effective at capturing the multivariate nature of selection acting on phenotypic traits. Inherent to this framework is the correlative nature of the data relating phenotypic values of traits and changes in 'omic' compartments.

Moving from Patterns to Processes

We propose to move this research agenda forward by combining selection experiments and functional genetics. To

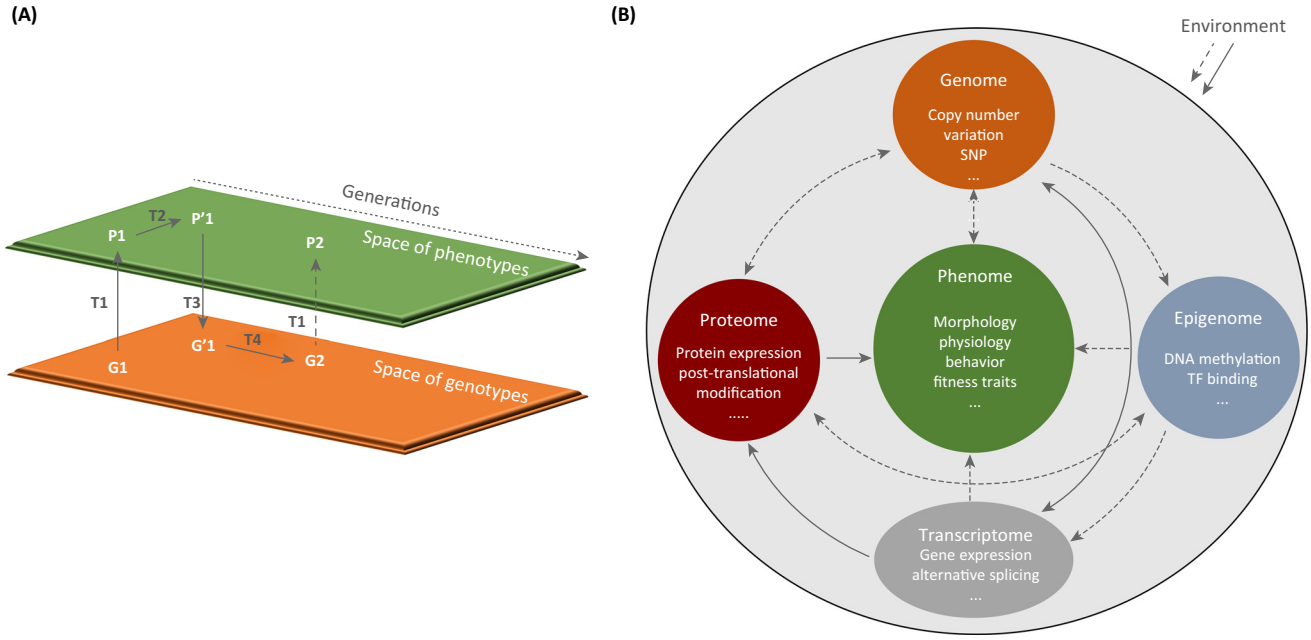

Figure 1. The two frameworks of genotype-phenotype interactions. (A) Population-centered genotype–phenotype interactions according to Lewontin's framework [1]. Abbreviations: G, mean genotype; G1, mean genotype at time t; G2, mean genotype at time t+1; P, mean phenotype; P1, mean phenotype at generation time t; P2, mean phenotype at generation time t+1; T, transfer functions. T1 and T3 are epigenetic functions that relate both spaces, being respectively the set of relations controlling the distribution of phenotypes resulting from the ontogeny of various genotypes in various environments (T1, e.g., seasonal polyphenism), and the set of relations producing genotypes from the phenotypes after transformations in the phenotypic space (T3, e.g., parental effects). T2 encapsulates the transformation of the phenotypic array in a population within a generation that results from natural selection, mating and dispersal in space and time. T4 is the phenomenology of genetics including random elements that allows the prediction of the probability distribution of genotypes in the next generation given an array of parental genotypes. Modified from [1]. (B) Individual-based genomics–phenomics interactions according to Ritchie's framework [3]. Full arrows: the hierarchical framework based on the central dogma of molecular biology [2]. Broken arrows: the alternative, hypothetical framework proposed by Ritchie *et al*. [3]. Abbreviation: TF, transcription factors. Ritchie *et al*. [3] provide a review of the analytical methods that are available to analyze multi-omics data sets, by implementing either meta-dimensional analyses (in which all scales of data are combined simultaneously to identify complex, meta-dimensional models with multiple variables from different data types), or multi-staged analyses (in which the analyses are divided into multiple steps to find associations first between the different data types, then subsequently between these associations of data and the phenotypic traits of interest). Modified from [3].

exemplify this approach, a putative workflow based on the framework detailed in Ritchie *et al*. [3] and aimed at investigating the molecular mechanisms involved in syndromes, could be the following: a first step would be the characterization of as many syndrome-related traits as possible, using large individual sampling, followed by the statistical investigation of their relationships. From this network of traits, it would be possible to identify a key trait combination, recurrent across individuals. The second step would be selection experiments that would target for and against this trait combination to establish divergent selection lines. Samples would be collected along these lines from generation to generation at fixed time intervals and submitted both to extensive phenotyping and to genomic, epigenomic, transcriptomic and proteomic analyses. Changes in these 'omic' profiles during the selection experiments would provide a first list of molecular determinants associated with phenotypic changes. In a third step, the exact roles of candidate determinants could be further investigated by means of functional (epi)genetics, either in the organism under investigation or in related model species. In a fourth step, this functional approach could be validated by testing the consequences of a breakdown of the imposed selective pressure in samples of individuals. In case of organisms with sexual reproduction, individuals would be allowed to mate freely after multiple generations with selection, and changes in targeted (epi) genetic factors would be investigated. This procedure would provide more insights into the molecular basis and on the relative roles of genetic differentiation and/or phenotypic plasticity. The final product would be the characterization of the most significant molecular

processes underlying the evolution of syndromes – *a molecular pedigree of evolutionary changes*. Together, the conjunction of a thorough phenomic characterization recommended by Ritchie *et al*. [3], the carefully designed selection experiments and the joint exploration of the "omic" compartments by functional methods would provide an excellent opportunity to illuminate the complex relationships between the genotypic and the phenotypic spaces that have fascinated evolutionary biologists since the publication of Lewontin's seminal book [1].

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[1]Station d'Ecologie Expérimentale, CNRS USR 2936, F-09200 Moulis, France
[2]Muséum National d'Histoire Naturelle, UMR 7205 ISYEB, F-75005, Paris, France
[3]Earth and Life Institute, UCL BRC, B-1348, Louvain-la-Neuve, Belgium

*Correspondence: baguette@mnhn.fr (M. Baguette).

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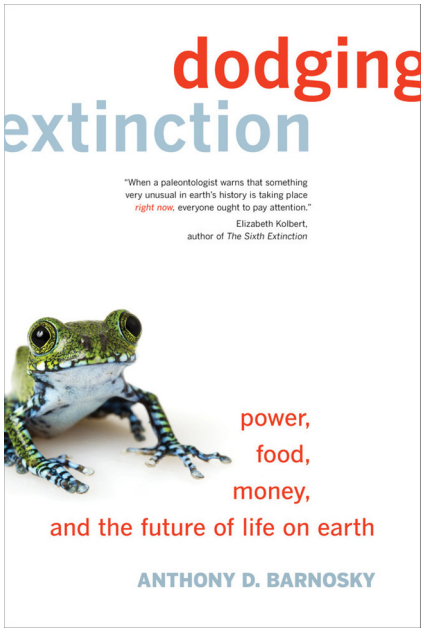
References

1. Lewontin, R.C. (1974) *The Genetic Basis of Evolutionary Changes*, Columbia University Press
2. Crick, F. (1970) Central dogma of molecular biology. *Nature* 227, 561–563
3. Ritchie, M.D. *et al.* (2015) Methods of integrating data to uncover genotype–phenotype interactions. *Nat. Rev. Gen.* 16, 85–97
4. Houle, D. *et al.* (2010) Phenomics: the next challenge. *Nat. Rev. Gen.* 11, 855–866
5. Laughlin, D.C. and Messier, J. (2015) Fitness of multidimensional phenotypes in dynamic adaptive landscapes. *Trends Ecol. Evol.* 30, 487–496
6. Sih, A. *et al.* (2004) Behavioral syndromes: an ecological and evolutionary overview. *Trends Ecol. Evol.* 19, 372–378
7. Fenster, C.B. *et al.* (2004) Pollination syndromes and floral specialization. *Ann. Rev. Ecol. Evol. Syst.* 35, 375–403
8. Stevens, V.M. *et al.* (2014) A comparative analysis of dispersal syndromes in terrestrial and semi-terrestrial animals. *Ecol. Lett.* 17, 1039–1052
9. Dingle, H. (2014) *Migration: The Biology of Life on the Move.* (2nd edn), Oxford University Press

Book Review

The Most Inconvenient Truth

Jeffrey C. Nekola[1,*]



In the spring of 1902, Mont Pelée on Martinique stirred to life and the citizens of Saint-Pierre began to worry about their restless neighbor only 10 km away. However, municipal leaders refused to act; the island was in the midst of general elections with socialists poised to take control from right-wing politicians. Because Saint-Pierre was the main center of conservative voters, the governor – anxious to keep his cronies in power – put off evacuation until after polling on May 11. On May 2, Mont Pelée erupted, sending an incandescent pyroclastic flow directly towards Saint-Pierre. Within minutes the entire city and all but three or four of its 30 000 citizens had perished.

Anthony Barnosky in '*Dodging Extinction*' details a similar peril facing humanity. However, the magma filling the metaphoric volcano sitting over our global village – the size of the ever-growing human population and its insatiable requirements for energy and other resources – is never mentioned. As a result Barnosky conveniently chooses to ignore the growing body of work in human macroecology [1–4]. From these a convincing case can be made that humanity exceeded the sustainable carrying capacity for Earth around 1980 when there were only 4.5 billion people and *per capita* levels/extraction of arable land, freshwater, wild fisheries, wood-based building materials, phosphate, and petroleum peaked [1]. The current size of the human population is now 7.2 billion, with 2050 projections being raised continually from 9.5 billion (circa 2012) to 11.5 billion (summer 2015). Even if we were able to maintain current generation rates of 16 terawatts/year, and we take the now-abandoned estimate of 9.5 billion humans, this level of energy production will only provide those people with a Ugandan standard of living [2]. If we wish to live at current Chinese levels we will need to increase energy production by more than fourfold. Current US levels will require a 15-fold increase.

Where will this additional energy come from? According to Barnosky, conservation and renewable sources will be up to the task. Yet the inconvenient truth – as Barnosky himself points out – is that conservation will free-up only 10% of the energy needed to avoid a Third World existence. And, are the remaining renewable sources really without ecological cost, as his book suggests? Milton Friedman famously stated: 'there is no such thing as a free lunch', and, inconveniently, hydropower leads to a loss of riparian and riverine biodiversity, and currently represents the largest single anthropogenic source of methane, a potent greenhouse gas [5]. Wind farms already lead to the deaths of 5 million migrating birds per year [6]. Even solar cells come at an ecological price: the 2008 agreement between the Renewable Energy Corporation and HydroQuebec to make 'carbon neutral' solar cells at their Bécancour plant [7] never considered the requisite loss of terrestrial biodiversity and