OPINION ARTICLE

Energetic efficiency under stress underlies positive genetic correlations between longevity and other fitness traits in natural populations

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Abstract Evolutionary relationships among fitness traits are considered in terms of the near-to-universal scenario of stressful environments leading to a resource-deficient and hence energy-deficient world. Fitness approximates to energetic (and metabolic) efficiency under this environmental model. When fitness is high, stress resistance (reducible to oxidative-stress resistance) and metabolic stability are maximal, and energy expenditure is minimal. Rapid development should then be favored followed by a long lifespan and high adult survival. Positive associations among diverse fitness or life-history traits are expected, controlled by stress-resistant 'good genotypes'. Heterozygotes tend to show higher energetic efficiency and hence higher fitness than do corresponding homozygotes under extreme environments, and to give parallel associations among life-history traits. Energy budgets under abiotic environments are pivotal for integrative evolutionary studies of life histories in natural populations.

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Introduction: a stressed and resource deficient world

Accumulating data indicate that the abundance of organisms is principally determined by resource limitations for the young. That is, organisms have the capacity to produce many offspring but environmental stresses, especially climatic, intervene to cause nutritional inadequacy (see White 1993, 2005 for an extended data set especially in herbivorous animals). Consequently, few offspring ultimately survive and reproduce. A predominant ecological theatre occurs consisting of unstable and often extreme environments especially droughts, floods and temperature extremes, which severely restrict nutrition and hence the availability of energy to underwrite evolutionary change. Life then becomes a constant struggle not to evolve but to survive, since few offspring become adults because energy resources are normally inadequate. In this harsh unforgiving world, food of sufficient quantity and quality is nearly always in short supply (White 1993, 2005; Margulis and Sagan 2002; Parsons 2005). Therefore nature

eliminates the most unfavorable variants leaving those few that can survive, which should be stress resistant and show high fitness and energetic efficiency. An expanded discussion drawing attention to exceptions such as transient irregular outbreaks during periods of resource abundance appears in Parsons (2005).

Metabolic and physical associations between organisms are frequently ignored. However, Margulis and Sagan (2002) write ''Since each population has specific energy, carbon, nitrogen, water, spaces, and other requirements that are never fully provided for by the environment, population expansion is inevitably stressed''. Similarly, Eldredge (1999) emphasized the need to take into account matter–energy transfer processes concerned with the development and continued existence of the organism, whereby those individuals that are the most efficient energetically will survive and have the best chance to reproduce. Ecological factors therefore determine the availability of energy and hence functional responses enabling adaptation to the array of habitats of a stressed world.

This stressful scenario contrasts with ecologically artificial venues under laboratory conditions and domestication generally. For example, life expectancies of *Caenorhabditis elegans* and *Drosophila* species under field condition tend to be at least an order of magnitude less than in the laboratory (e.g. Rosewell and Shorrocks 1987; Van Voorhies et al. 2005). Evolutionary change models and studies necessarily need to emphasize adaptation under ecologically realistic views of the environment, that is those of organisms in nature (Kruuk 2004; Vermeij 2004; Parsons 2005).

Fitness, energy and metabolism under environmental stress

Stress drains energy from organisms and reduces fitness. Stress is therefore an environmental change or probe that targets energy carriers. The energy balance built by organisms in their habitats is thereby disturbed, so that energetic efficiency is reduced. The availability of energy and its interaction with stress underlies fitness, so determining the limits of adaptation of organisms.

Optimum conditions for development correspond to abiotic conditions where there is minimum energy expenditure on a fitness–stress continuum, since energetic costs increase as stresses escalate away from benign environments (Zotin 1990; Parsons 1992, 1998).

Resistances to abiotic stresses tend to be correlated, for example for temperature extremes, desiccation, anoxia and ionizing radiation in *D. melanogaster*. The responses to aridity, high temperature and solar radiation differences between the north and south facing slopes of 'Evolution Canyon' Israel found in field collected *D. melanogaster* and yeast, *Saccharomyces cerevisiae*, can be interpreted in terms of oxidative stress responses (Nevo 2001; Miyazaki et al. 2003). Abiotic (physical) stresses in natural populations therefore appear reducible to oxidative stresses from Reactive Oxygen Spaces (ROS). That is, the energetic costs of abiotic stresses derive from the negative affects of ROS on fitness (Barja 2004; Criscuolo et al. 2005). Individuals with potential for a long life should therefore carry genes for resistance to ROS, which are an essential component of life in a world rich in oxygen (Hekimi and Guarente 2003). In fact, similar gene expression patterns characterize aging and oxidative stress in *D. melanogaster* (Landis et al. 2004). More broadly, oxidative stress is central in biochemical networks and the metabolic evolution of life on Earth (Falkowski 2006; Raymond and Segre 2006).

Genes conferring high stress resistance in a stressed world should promote high vitality, homeostasis, and energetic and metabolic efficiency, permitting survival to old age in the face of the multiple hazards of natural populations. For example, oxidative stress may be lower in healthy centenarians than in other aged subjects (Paolisso et al. 1998). Evolutionary changes in the rate of senescence and hence longevity should therefore depend on survival following selection for stress resistance—a more effective way of increasing longevity than direct selection on longevity itself. This is not surprising since estimates of the heritability of lifespan in *D. melanogaster* tend to be substantially lower than for survival based upon exposure to extreme environmental stresses such as desiccation. High survival therefore depends on

the effectiveness of selection for energetic efficiency to adapt to the free-radical stresses in the environments of free-living populations, both from the internal environment of organisms and their external environments. The incorporation of the ecological theatre of organisms underlies the stress theory of aging and hence of survival generally. Elsewhere I have discussed the relationship of this theory with other aging theories, which appear to be more applicable to benign environments under domestication and the laboratory (Parsons 1995, 2005).

Longevity and metabolic rate tend to be inversely correlated, so that the rate of ROS is reduced in long-lived individuals, an association often considered in term of a metabolic rate/oxidative stress theory of aging (e.g. Olshansky and Rattan 2005). But it is more appropriate to say that an energy utilization process directed towards high efficiency under resource limitations is a more fundamental evolutionary expectation (Arking et al. 2002). Not surprisingly therefore, the metabolic rate/oxidative stress theory is faced with contradictions, such as the prediction that dietary antioxidant supplementation of long-live animals should increase life expectancy or maximum lifespan, which does not appear to happen (Olshansky and Rattan 2005).

Metabolic stability, the ability of cells to resist fluctuations in steady-state concentrations within cells, is argued to be an important factor determining longevity (Demetrius 2005). Olshansky and Rattan (2005) list various molecular assessments that demonstrate the importance of cellular homeostasis and hence metabolic stability. More generally, Torres (1991) defined fitness as the distance of an individual's thermodynamic parameters from its optimum, based upon the pivotal role of ATP synthesis in energetic relationships. That is, maximum fitness corresponds to minimum energy dissipation and minimum metabolic divergence from a stable optimum. Energetic and metabolic efficiency is clearly an appropriate measure of fitness in evolutionary adaptation to the physical characteristics of specific habitats (e.g. Zotin 1990; Demetrius 2005; Parsons 2005).

Clearly, variations in energy can be related to ATP levels, so that the metabolic organization of organisms should conform with quantitative rules derived from basic physical principles (Morowitz 1992). Food input interacts with the environment to provide metabolic 'currency', which mainly involves ATP and other high-energy nucleotides (Watt 1986). From such metabolic currency pools, resources are allocated to fitness-related entities, including development and growth, maintenance, reproduction, foraging, and ultimately survival. Protein synthesis is depressed under the energetic cost of stress, so that the rate of molecular degradation becomes the key to the upper limit of survival when the stress is chronic. At these times fitness is reduced concurrently with metabolic stability.

Associations between fitness traits and stress

Development rate and longevity

The comments above can be extended to diverse fitness or life-history traits commencing with development.

Fast developing insect larvae should be able to cope best with metamorphosis, which is a time of crisis of oxygen stress in the developing embryo (Hilliker et al. 1992). In other words, this is a time of strong selection for energetic and metabolic efficiency to counter the damaging effects of ROS (see Hekimi and Guarente 2003). Translation into high stress resistance of adults should follow directly from this selection process. In the context of the stress theory of aging, rapid development should be a forerunner of a long life *in the hostile environments of free-living populations*, whereby fitness components in the young and old should be correlated. Events in adults should therefore be viewed in the context of events in the preceding developmental stage, especially in *Drosophila* and other holometabolous insects where there is a clear demarcation from developmental to adult forms (Parsons 1996, 2004; Arking 1998).

Unfortunately, much data on relationships between development time and longevity come from experiments carried out under the benign environments of laboratory populations, often after periods of artificial selection, which lead to genotypes not occurring in natural populations.

Such genotypes are likely to be at a disadvantage when exposed to the environments of natural populations. Conclusions from such data sets are difficult to summarize and often contradictory. Useful experimental material should come from strains tested as soon as possible following their introduction into the laboratory especially where some background ecological knowledge exists. Furthermore, severe stresses should be used in the laboratory so that there is substantial mortality during development. Taking into account these restrictions, there is some very limited evidence for an association between rapid development, high larva-to-adult survival and a long life in experiments with the insects *D. buzzatii*, *D. melanogaster* and the water strider, *Gerris buenoi* (see Parsons 1996, 2004 for summary). In addition, Vorburger (2005) finds that recently collected clones of the aphid, *Myzus persicae*, with shorter development times tend to have larger body sizes, fecundities and offspring. Furthermore, estimated fitnesses of clones tend to be correlated with ecological success in the field. That is, positive genetic correlations tend to occur among these life-history traits. However, extrapolations beyond these insect examples are needed especially to mammals, under the extreme stress scenario.

Finally, turning to an example wholly from the wild in birds, Mauck et al. (2004) found a positive correlation between early hatching and early breeding success with longevity in a 40-year demographic study of Leach's storm-petrel, *Oceanodroma leucorhoa*. Survival during development is therefore an important predictor of both breeding success and the achievement of a long life, and could be related to low basal metabolic rate, an expected concomitant of high stress resistance. Such valuable long-term data sets are rare and difficult to obtain, but are essential when considering evolutionary patterns in natural populations. Much more remains to be done across taxa and environments.

Heterozygosity and diverse fitness traits

Extreme-environment heterosis involving temperature-sensitive and correlated enzymes has been proposed from time to time, and early data

are surveyed in Parsons (1971). In natural populations there is now increasing evidence that heterozygosity levels tend to be positively correlated with high fitness, especially for enzyme loci influencing metabolism and contributing to the amount of energy available for development and growth. This association is most obvious under extreme abiotic stress when energetic demands from the environment are high, especially when the energy from resources is limited at times of nutritional inadequacy. Heterozygotes tend to have lower energy requirements than homozygotes especially under extreme conditions, so they should have the potential to develop and reproduce under a wider range of environmental conditions than do the corresponding homozygotes as found in blue mussels, *Mytilus edulis* (Myrand et al. 2002). Koehn and Bayne (1989) argue that the better performance of heterozygotes under stress derives from their reduced energy expenditure for maintenance metabolism, and furthermore the rate of protein recycling falls with increasing allozyme heterozygosity (see also Mitton 1993). Metabolic stability and hence fitness are therefore associated with heterozygosity. A recent field example comes from the aphid, *M. persicae*, where fitness increased significantly with heterozygosity at seven microsatellite loci used to distinguish field-collected clones (Vorburger 2005).

Assuming that fitness maxima are associated with high heterozygosity, associations between rapid development, high survival and a long life should occur, especially under severe environmental stresses. This genomic approach therefore gives predictions for relationships among fitness traits paralleling those emerging at the whole organism or phenomic level as already discussed. Selection for energetic efficiency in the face of the stresses to which free-living populations are exposed is the connecting link underlying this convergence.

Other fitness measures can be incorporated in principle, such as extremes of sexual ornaments and success in mating. Some biologists (e.g. Williams 1966) have suggested that preferred mates possess superior viability that is transmitted to their offspring. The choosing sex has therefore been claimed to prefer individuals carrying 'good

genes'. Wedekind (1994) has argued that sexual selection for stress resistance is important in improving the survival chances of offspring, so that 'good genes' should confer stress resistance. In any case, the energy cost from stressful environments is likely to be lowest in stress-resistant individuals, which should have low metabolic rates.

Fitness at one stage of the life cycle should therefore correlate with fitness at other stages under the extreme-stress environment model. More emphasis on energy budgets under abiotic constraints therefore seem essential for integrative studies of life-history variation, since common physiological pathways have been found to underlie life-history traits and relationships between them (e.g. Niewiarowski 2001; Parsons 2005 for summaries). In any case, adaptive change in organisms in an extremely perturbed world should be mediated via a connected metabolism (Zotin 1990; Kauffman 1993). However, some heterogeneity of correlations occurs, which is to be expected since not all populations would be in a state of energetic stress. Long-term ecological studies where stress levels in natural populations can be incorporated are a high priority.

In summary, under the stressful scenario pertaining in free-living populations, high energetic and metabolic efficiency should be associated with (e.g. Parsons 1998):

(1) high (electrophoretic) heterozygosity
(2) high stress resistance, survival, vitality, vigor and resilience
(3) high homeostasis and metabolic stability
(4) low fluctuating asymmetry
(5) rapid development
(6) high mating success
(7) improved survivorship which normally translates into a long lifespan

The expectation of positive correlations between these fitness traits contrasts with more conflicting results obtained under more benign conditions where tradeoffs can more readily develop (Parsons 2002). Basically, the above generalization reduces to stress as an environmental probe that targets energy carriers so that stress-resistant 'good genotypes' are favored.

Conclusion

Assuming the hostile environment model, there is strong selection for early reproduction, which implies selection for high energetic efficiency. A concomitant effect is increased stress resistance of adults, so that selection for rapid development translates into selection for increased lifespan. More generally, the energetic consequences of the stress theory of aging (and development) predict mainly *positive* associations among life-history traits in natural populations, in contrast with rather variable results obtained under more benign conditions. This conclusion could help to resolve interpretative difficulties apparent in studies on certain laboratory populations, and therefore is direct application when considering aging and survival in natural populations.

Fitness can be assessed at all organizational levels, but is underlain by energy at the metabolic level. Therefore, in stressed natural habitats, evolutionary adaptation is in the direction of maximizing energetic and hence metabolic efficiency from which the fitness relationships discussed in this article emerge. That is, evolutionary change might be viewed fundamentally in terms of "the new thermodynamics, which unites and integrates in a way distinct from but complementary to genetics and molecular biology, the physical and biological sciences" (Margulis and Sagan 2002). Even so, Fisher (1930) drew attention to the remarkable resemblances of the second law of thermodynamics to his fundamental theorem of natural selection, which is concerned with the genetic basis of the rate of increase of populations of organisms in their environments. Following the suggestion of one of the referees, the circle of ideas—fitness, efficiency, stability and thermodynamics—needs further explorations which are beyond the scope of this opinion paper!

Support for the establishment of links between functional and evolutionary biology, that is between the biology of proximate causations and the biology of ultimate causations is therefore becoming increasingly apparent. The energetic consequences of the stressful environments in which organisms exist are fundamental to establishing these links, here demonstrated for predictions of associations among life-history traits

under energetically limited circumstances. Incorporation into explorations of evolutionary adaptation in natural populations could be increasingly adopted.

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