INTEGRATING MACROECOLOGY AND QUANTITATIVE GENETICS: EVOLUTION OF BODY SIZE AND BRAIN SIZE UNDER ISLAND RULE

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Abstract: Island rule proposes that a negative correlation between ancestral body size in continents and the descendent body size in islands exists, and this pattern have been widely studied in a macroecological and comparative perspectives. However, there are doubts about what mechanisms underlie body size evolution in islands. Here we review methodological and theoretical framework on evolutionary quantitative genetics, showing their application on body and brain size evolution in islands, using *Hippopotamus* dwarfism as example. In our analyses we started by generating 10,000 combinations of model parameters (generation time, effective size and heritability) and tested by Mutation-Drift Equilibrium model if body size dwarfism is a consequence of neutral drift or directional selection. We found that 99.9 % of simulations rejected neutral model. Then, we estimated the strength of directional selection necessary to differentiate the island species and found that a relatively low proportion of population (0.01 - 0.2%) should be selectively killed to decrease body size. Our results also showed that one unit decrease in body size would increase, on average, fitness by 4% in each generation, so directional selection is a plausible explanation to island rule. Finally, we also simulated the evolution of brain size of dwarfed *Hippopotamus* as a consequence of body size evolution alone. Our estimates of Expected Brain Size (EBS = 484 ± 64 cc) were larger than the observed brain size (equal to 380 cc), which suggests the need to estimate directional selection acting on brain size independently of body size evolution. This supports the overall idea that brain size reduction is advantageous in island environments under a scenario reduction in resources, due to the high energetic budget of brain. Our analyses using evolutionary quantitative genetic support that Island Rule as a parsimonious adaptive explanation for the reduction in brain and body sizes and illustrates how to couple evolutionary analyses at population level to better understand macroecological patterns.

Keywords: adaptive evolution; ecogeographic rule; evolutionary genetics; island dwarfism; microevolution.

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INTRODUCTION

The study of diversity patterns in islands have a long history in ecology and evolution, since Darwin and Wallace's time (Whittaker & Fernández-Palacios 2007). More recently, MacArthur and Wilson's (1967) equilibrium theory became an almost paradigmatic approach to understand richness on isolated systems such as island, in which the equilibrium of colonization and extinction rates due to isolation (*i.e.*, distance to source pool) and area determine the number of species in short ecological times. However, increasing time scale requires thinking about local richness being also driven by speciation processes that increase the number of species after colonization (Lomolino 2000). These new species evolve in a new environment, under distinct selection processes and demographic scenarios that allow strong effects of stochastic processes, and may thus display many particular traits and adaptations in several ecological, behavioral and morphological traits (van der Geer *et al.* 2011).

In this context, Island Rule is one of the most famous evolutionary patterns proposing that there is a body size shift after colonization and leading subsequently to a speciation process (Foster 1964, Lomolino 1985). In general, it is possible to observe a negative correlation between initial body size (*i.e.*, in the mainland or continent) and relative reduction of body size in the new species or subspecies arising in the island. In other words, a large-bodied species will tend to reduce its body size (dwarfing), whereas a small-bodied ancestor will tend to lead to a larger new species (gigantism) in islands (Lomolino 1985, 2005). Several papers tried to explain this pattern at a macroecological scale, by correlating body size shifts from potential ancestors in continents and their descendant in islands with biotic and abiotic island characteristics (Lomolino *et al.* 2012, 2013, McClain *et al.* 2013). In general, gigantism is explained as a consequence of changes in biotic interactions, for example relaxed competition or predation pressures that reduce mortality and, consequently, allow larger abundances and age at maturity, leading to larger body size. On the other hand, dwarfing as a consequence of natural selection favoring small bodies in resource-poor islands due to higher intraspecific competition initially reducing population abundance and increasing fitness for lower individual growth rates and lower maturity age (Palkovacs 2003).

Of course, the pattern proposed as "island rule" (*i.e.*, the negative and continuous trend between body size shifts and the original size of the ancestors) and its underlying ecological and evolutionary mechanisms are not uncontroversial, due to several conceptual and methodological issues (*e.g.* Meiri *et al.* 2006, 2010, Raia *et al.* 2010). For instance, Meiri *et al.* (2010) showed that although there is evidence for dwarfing in mammals, gigantism is much less supported. A recent comparative analysis by Faurby & Svenning (2016) also supported island rule driving dwarfing from large mammals, especially if recently extinct species due to anthropogenic effects are included in the analyses. Thus, despite the controversy about generality of patterns and their underlying processes, dwarfing processes are usually specta-cular in some proboscideans and artiodactyls lineages (see van der Geer *et al.* 2011). Also, island rule seems to hold for primates (Bromham & Cardillo 2007, Montgomery 2013) and may explain dwarfing in at least one hominid species (the case of *Homo floresiensis*; see Diniz-Filho & Raia 2017). On the other hand, despite smaller support as part of the island rule, gigantism is mainly registered for some rodents and insectivorous groups (see van der Geer *et al.* 2011).

Island rule has been mainly investigated in a comparative macroecological context, by model-ing body size shifts in several species against predictors related to island resources and assemblage patterns (*e.g.*, Lomolino *et al.* 2012, 2013). This approach is important to find general drivers of body size shifts and show that these shifts are adaptive in a correlative context. More refined approaches focused on fewer better known species and scenarios and used empirical regression analyses to detect allometric trends under alternative models of body size growth along ontogeny (*e.g.*, Weston & Lister 2009, Kubo *et al.* 2013). However, these better known species can be also investigated in a more populational, microevolutionary context (see Barton & Turelli 1989, Manly 1985). For instance, because the processes inferred at macroecological level are clearly adaptive and imply in directional selection driving body size evolution in islands, several

important questions arise in this context, including: is natural selection strong enough to generate body size divergence in a relatively short time scale of isolation? Is the isolation enough to counteract the effect of migration? Isn't possible that purely stochastic phenomena, such as genetic drift and other processes related to founder effects, explain body size shifts in some particular situations? How other ecological and life-history traits can evolve correlated with body size shifts, or how such traits can actually constraint body size evolution?

The questions pointed out above can be at least in part answered using several evolutionary quantitative genetics tools, based on models originally developed in the 1970-1980's (see Barton & Turelli 1989, Lynch & Walsh 1998, Manly 1985). The evolutionary quantitative genetics models can be a further advance in respect to allometric scaling analyses because of their theoretical background from population genetics and more mechanistic approach to detect evolutionary processes driving body size evolution. Here we briefly review the theoretical and methodological basis of such models and show their application on understanding how natural selection could drive patterns of body size and brain size evolution in the context of island rule.

MATERIAL AND METHODS

We use as case study the differentiation between the dwarf and recently extinct *Hippopotamus lemerlei* from Madagascar and its presumed ancestor, a generalized mainland large-bodied form, *Hippopotamus amphibious* (see Weston & Lister 2009, van der Geer *et al.* 2010). These two island and mainland species weight between 274 – 393 kg and between 1200 – 2000 kg, respectively, so average values of 330 kg and 1600 kg were used for the analyses. We used a simulation approach in which 10,000 random values of model parameters were randomly sampled and combined, allowing to explore robustness of our interpretations (see Diniz-Filho & Raia 2017, Monteiro & Gomes-Jr 2005). In general, for both body size and brain size we used a mean standard deviation σ of 0.1 at ln-scale (ranging between 0.08 and 0.12) within popular-tions, which is equivalent to a mean

coefficient of variation of 10% at original scale. The proportion of variation attributable to additive genetic effects is estimated by the heritability's h^2, which is usually relatively high for morphological traits and are allowed to vary here between 0.6 and 0.9 (Lynch & Walsh 1998, Manly 1985). The colonization scenarios were expressed basically by two parameters: (1) the time for divergence (t, in generations), set here to vary between 1,000 and 10,000 generations, and (2) the effective population size Ne, which was set to vary between 100 and 10,000 (which would be roughly equivalent to a population size ranging from 400 to 40,000, by considering the mean effective size tends to be ¼ of population size, see Palstra & Fraser 2012). An R-script for performing the analyses shown below are available from the authors upon request (R Core Team, 2017).

RESULTS

Neutral divergence between populations and species

We started our analyses by testing if divergence between the two populations or species in islands and continents could be explained by genetic drift alone (a neutral model). We compared the mean body sizes of *H. lemerlei* and *H. amphibious* using Lande's (1977) expansion of the constant heritability model that can be generalized into Turelli's *et al.* (1988) Mutation-Drift Equilibrium (MDE) model. Under these models, the expected population divergence under neutral evolution is given by:

$$F = S^2 \, Ne \, / \, \sigma^2 \, t \, h^2$$

(equation 1)

where S^2 is the variance among populations, given by the squared difference between the means (in this case of two species or populations) and Ne is the effective population size. If this F-value is not significant (assuming 1 and infinite degrees of freedom), the difference between the two means can be assumed to be due to neutral evolution (*i.e.,* no adaptation), whereas a significant F-value indicates that directional selection better explains the phenotypic difference.

Applying equation 1 to *Hipopotamus* data showed that in 99.9% of the simulations the F-value was

significant, so that neutral dynamics is not a parsimonious explanation for the divergence between the two species. Neutral dynamics was significant in a few particular combinations of very low effective population size with long time for divergence (Figure 1) (*i.e.*, even if Ne < 500, neutral divergence is a plausible explanation in only 97.8% of the simulations).
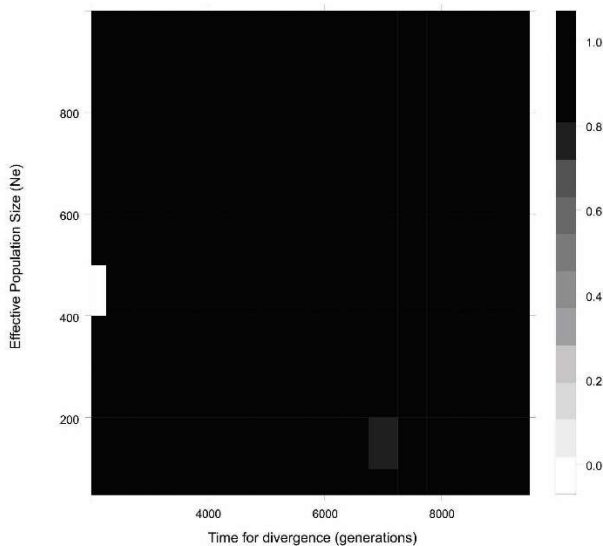
Figure 1. Proportion of simulations rejecting neutral evolution, for distinct combinations of time since divergence in generations (t) and effective population size (Ne). Values close to 1 (darker tone) indicates that this combination of parameters more frequently rejects neutral evolution.

Directional selection

As we rejected neutrality based on MDE model, we further used Lande's (1976) model to evaluate the strength of selection that is necessary to differentiate the mean values of the two species on a logarithmic scale (z) over a given time interval. In this model, selection is modeled by:

$$b = \pm \left[-2 \ln \left\{ (2\pi^{-0.5} \ (z / \sigma h^2 \ t)\right\}\right]^{0.5}$$

(equation 2)

The equation 2 models directional selection by truncation, so the b value is the number of standard deviations in a normal distribution of phenotypes necessary to displace ancestral distribution towards the new species (in this case, by a dwarfing process). So, a 1-P-value under the normal distribution associated with the b value gives the proportion of a population that selecti-

vely does not reproduce, per generation, to drive the differences between the two means (*i.e.* the selective mortality).

The distribution of b values for the divergence between the two *Hipopotamus* species in the simulations was strongly left skewed (Figure 2), peaking around 3.0. This corresponds to a 1-P-value equal to 0.1%, with confidence intervals between 0.01% and 0.2%, so a very small proportion of large-bodied individuals should have been killed in each generation to drive the divergence in body size.

Following Manly (1985), it is still also possible to calculate the selection differential S in one generation by:

$$S = \sigma \exp \left(-1/2 \ b^2\right) / \{ (2\pi)^{1/2}\}$$

(equation 3)

which, according to Matsumura *et al.* (2012), can be related to the selection gradient β describing the relationship between fitness and trait values by:

$$\beta = S / \sigma^2$$

(equation 4)

The selection gradient β is more frequently estimated in natural populations than selection differentials S, making easier to compare the minimum selection intensity necessary to differentiate the two species with previous empirical estimates (Hereford *et al.* 2004, Kingsolver *et al.* 2001, Kingsolver & Pfenning 2007, Matsumura *et al.* 2012). Moreover, because body size data for the two species are ln-transformed, this β approximates the mean-standardized gradient at the original scale, which can be interpreted as the slope of fitness against trait values.

In *Hippopotamus* data, the median selection gradient was equal to 4%, with 95% confidence interval ranging from 1.6% and 19% (Figure 3). Therefore, a reduction in one unity of the trait (in this case, in kilograms) between the two species will increase the fitness by a proportion given by about 4%, on average. As expected, the selection gradient β is related to time since divergence (see eqs. 2 and 3), with values closer to 30% of fitness increase necessary to drive the population differentiation if divergence occurred very fast, in say 1000 generations. In natural populations,
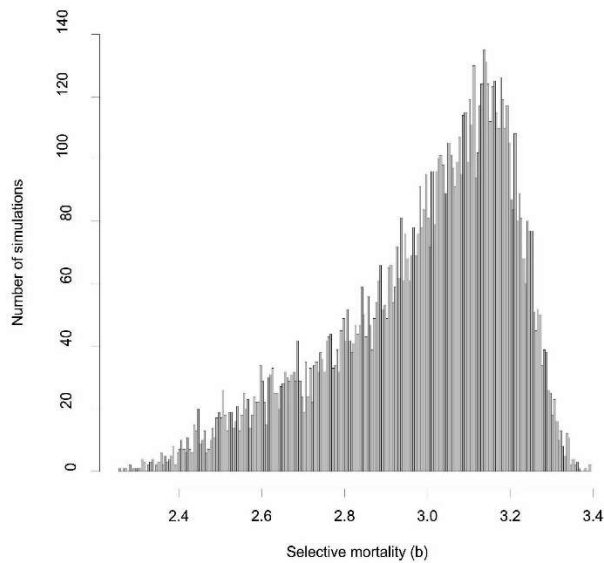
Figure 2. Distribution of selective mortality (b) from 10,000 simulations comparing the two *Hippopotamus* species, according to Lande's (1976) model.
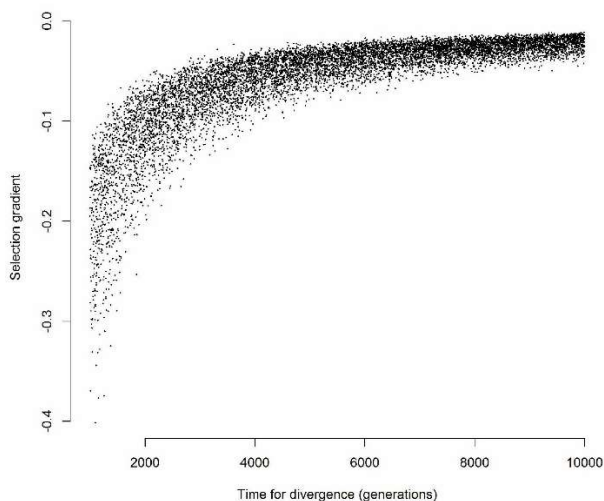
Figure 3. Relationship between intensity of selection (measured by selection gradient β that is the slope between fitness and trait values) in the 10,000 simulations analyzing divergence between the two *Hippopotamus* species. The negative values of β are due to the dwarfing process that reduces body size from the ancestral.

values of β higher than 1.0 (100%) are considered high, so a strength of selection of 4% between successive generation would be, in principle, considered very low. However, it is important to remember that this low strength would act continuously throughout a long time, by a constant selection force across generations. These selection models can be considered as overall or

mean estimates in time and higher selection strength in a few generations are mathematically equivalent to low selection strength in a higher number of generations. Raia & Meiri (2011), for instance, suggested that island evolution may be better explained by a punctuated equilibrium model, of very fast divergence after island colonization and due to strong selection pressures driving body size evolution (see also Lister 1989). However, although these possibilities are equivalent in a mathematical/statistical sense, they imply in different ecological scenarios and variation of environmental conditions throught time.

Correlated evolution between brain size and body size

We can also use other quantitative genetic models to investigate patterns of correlated evolution between distinct traits. For instance, there have been very interesting discussions on how brain size evolves as a response to dwarfing process under the island rule (Diniz-Filho & Raia 2017, Weston & Lister 2009). If the main explanation for dwarfing in large mammals under island rule is reducing energetic budget, then a strong reduction in brain size is also expected, by considering that cerebral tissues are quite demanding in this sense (Herculano-Houzel 2012, Montgomery 2013). On the other hand, there may be mechanical constraints related to skull shape or other directional forces that would counteract dwarfing trends. These pressures in opposite direction should be expected if dwarfing would cause loss of fitness due to loss of behavioral or cognitive abilities, that could thus counteract advantages in reducing energetic budget in resource-poor island environments.

To test correlated evolution between brain and body size, we started with the assumption that brain size is only tracking reduction in body size, without any further particular selective pressures driving brain volume reduction per se. Under this model of correlated evolution (Lande 1979), the slope of brain size reduction would be given as a function of the heritabilities of the two traits (*i.e.* brain and body size) and the genetic correlation r among them, as well as their standard deviations, by:

$$\alpha = r\left[(h_b\,\sigma_b)/(h_w\,\sigma_w)\right]$$

(equation 5)

Starting with the body size and brain size values of the ancestral species, it is possible to use this slope to calculate the Expected Brain Size (EBS) of the dwarfed island species by a simple regression model (in which the intercept of the model is given by the ancestral values along X and Y axis and the slope is α). Here we defined that phenotypic correlation between brain size and body size was equal to 0.5 ± 0.025, which is multiplied by the mean heritabilities from each simulation to estimate the genetic correlation (*i.e.*, Cheverud's conjecture of approximation of genetic from phenotypic correlations – see Manly 1985).

In the case of *Hippopotamus*, we used brain sizes equal to 380 cc and 882 cc for *H. lemerlei* and *H. amphibius*, respectively, following (Weston & Lister 2009). The values were ln-transformed and using equation 5 we determined that mean EBS across the 10,000 simulations was equal to 484 ± 64 cc, a mean value larger than the observed 380 cc in H. lemerlei (Figure 4). A similar pattern was observed by Weston & Lister (2009), and their allometric models based on ontogenetic patterns estimated EBS values varying between 456 and 544 cc for the island species.

However, as previously stated, the model described in equation 5 assumes that evolution in brain size occurred only as a correlated response to body size evolution. The patterns in Figure 4 shows that there is a bias, and observed value is much smaller than mean simulated EBS. This suggests that there may be other selective pressures driving differentiation in brain size between the two *Hippopotamus* species. Indeed, this can be explicitly investigated using multivariate extension of Lande's models (see Lande & Arnold 1983, Hansen & Houle 2008). The idea is to estimate simultaneously the selection gradient β for the two traits, accounting for the correlation between them, and to derive a vector of selection gradients β by:

$$\beta = G^{-1}\Delta Z$$

(equation 6)

where G is the genetic covariance matrix and ΔZ is the vector of differences between body and brain

size between the two species and simulated ancestral values (see below). The elements of G were derived from the genetic parameters defined above, with diagonals given by $\sigma^2 h^2$ and extra-diagonal given by the covariance calculated from the genetic correlation r from equation 5, as previously explained. In equation 6, the coefficients in the vector β are actually partial slopes of fitness on traits across the generations.
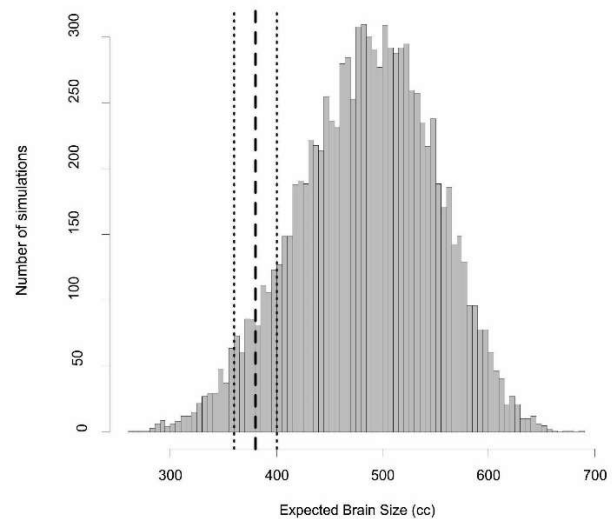
Figure 4. Expected Brain Size (EBS) based on Lande's (1979) model for correlated evolution, assuming that directional selection on body size alone drives patterns in brain size. The dashed lines indicate the observed values in *H. lemerlei*, showing that simulations tend to overestimate these observed values.

Using equation 6 shows that median β across generations for body size approximates the univariate analyses from equations 3-4 (*i.e.*, equal to about 4%), but brain size also has a mean independent slope equal to 2%. This confirms that directional selection in body size alone do not explain observed brain size patterns in *H. lemerlei* due to correlated evolution, being necessary to invoke additional forces driving brain size independently (or in addition) of those in body size. This supports the overall idea that brain size reduction is advantageous in island environments due to reduction in resources. This shows that in this case with *Hippopotamus* there are no other constraints or directional selection acting in the opposite direction (*i.e.*, avoiding or reducing the rate of dwarfing in brain size to due to potential loss of behavioral or cognitive/sensorial characteristics).

DISCUSSION

Moreover, we illustrate here a basic approach that allows a better assessment of how evolutionary mechanisms, especially directional selection, could drive population divergence between island and mainland species or subspecies, under alternative colonization scenarios with varying population size and time for divergence. With this, we tried to provide another link between pattern and processes analyses in macroecology, a demanding issue in this research field (*e.g.*, Beck *et al.* 2012, Cabral *et al.* 2017, Smith *et al.* 2008).

Our analyses using evolutionary quantitative genetic models of *Hippopotamus lemerlei*, assuming a large-bodied ancestor similar to *H. amphibius*, support that reduction in brain and body sizes can be due to directional selection under Island Rule. Of course, the critical assumption of our analyses is that dwarfing of *H. lemerlei* happened under Island Rule and that it evolved from a population of *H. amphibius* (or another related species with similar brain and body size values) that colonized Madagascar. If, for instance, the ancestral species is a larger continental species such as *H. gorgops*, which seems to be the sister species of *H. amphibius* (see Boisserie 2005), selection intensity would increase accordingly (or the selection strength estimated here would be maintained if time to divergence would be much larger). But even if historical relationship among dwarf *Hippopotamus* from Madagascar is more complex and *H. lemerlei* evolved from a much earlier already dwarfed species in the island, the logic of the process demonstrated here remains, and dwarfing process under Island Rule would still be plausible.

It is important to notice that the application of these methods to other groups of organisms, in a comparative framework, may be challenging due to lack of data and detailed colonization and divergence scenarios for island and mainland species. We used here a broad range of genetic and population parameters, as well as demographic and colonization scenarios, and used simulations to assess the robustness of our conclusions. In some cases, more data may be available and provide a more accurate evaluation of such parameters (*e.g.* Diniz-Filho & Raia 2017). In some cases, molecular data for extant species may be helpful to better establish demographic and colonization scenarios, or can be used in phylogenetic comparative analyses to provide ancestral states and other expected trait-values for island species. This would provide an interesting new and integrated research avenue in island biogeography (*e.g.*, Santos *et al.* 2016). Despite difficulties, we hope that the approach shown here stimulate other researchers to explore their data and to try to incorporate more complex factors in the model parameters or colonization scenarios to improve our understanding of insular dwarfism under more realistic evolutionary scenarios.

ACKNOWLEDGMENTS

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