A test of diversifying selection for a trait from within and between species genotypes and phenotypes

*Thibault Latrille***¹** *, Mélodie Bastian***²** *, Théo Gaboriau***¹** *, Nicolas Salamin***¹ 1 Université de Lausanne; 2 Université de Lyon**

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[@phylogenetrips](mailto:thibault.latrille%40ens-lyon.org?subject=) [thibault.latrille@unil.ch](mailto:thibault.latrille%40ens-lyon.org?subject=)

• Is a trait neutrally evolving or under selection? • If not neutral, is the trait changing too fast or too slow? • At which scale, between or within species variations? • How to compute variations, and how to normalize it?

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Trait evolution between and within species

case of *F*ST; BOX 1). The value of *Q*ST for a neutral quantita-

Ana Catalán, *^{.t.1} Adriana D. Briscoe,[‡] and Sebastian Hö variance in the trait (rather than at a specific locus in the trait α specific locus in the trait α Ana Catalán, *.t.1 Adriana D. Briscoe,⁺ and Sebastian Höhnat.8.**.1 Population Genetics. Individuals for this study were collected from and extensive structure structure structure existed among populations ($\mathcal{F}_{\mathcal{A}}$ D epartment of Evolutionary Biology, Evolutionary Biology Centre (EBC), \mathcal{L} and \mathcal{L} and \mathcal{L} and \mathcal{L} model in the case of dichotomous characters. New models, alán, *^{,+,1} Adriana D. Briscoe,⁺ and Sebastian Höhna^{+,§,}**,¹

How fast should evolve a neutral trait? \mathcal{L} , and if the traits are additive, and if the traits \mathbf{P} Fst for any trait (Spitze 1993). neutral expectation are considered evidence of selection www.pnas.orgcgidoi10.1073pnas.0507648103 PNAS **April 4, 2006** vol. 103 no. 14 **5425–5430** \blacksquare \mathbf{I} of the orthoclusters. In conclusion, we found that drift is the dominant evolution, we found that driving generation, we found that driving generation, we found that driving generation \mathbf{I} expression evolution in tissue in Heliconius. Nevertheless, the higher proportion of genes evolving under direction of genes evolving under direction of genes evolving under direction of genes evolving under directional t character, discuss interpretations of its parameters, and provide conducts \mathcal{L} \blacksquare

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Q_{ST}– F_{ST} comparisons: evolutionary and ecological insights from genomic heterogeneity $U = H$ Comparisons: Avolutionary U **to the accumulation of random-neutral changes and evolution by** application in the letter openful v **for genetic relatedness and identifies patterns of expression vari**significantly associated with a independent equation \mathbf{I} $\mathsf{U}\Pi$ accounted for by natural selection. This approach is conservative because it attributes maximum among-population variation to

Tuomas Leinonen¹, R. J. Scott McCairns¹, Robert B. O'Hara² and Juha Merilä¹ **ation that are affected by natural selection. To identify genes** uomas Leinonen', R. J. Scott McCairns', Robert B. C This approach was applied to *Fundulus heteroclitus*, a teleost α fish widely distributed along the α tributed along the α

Multivariate Q_{st}–F_{st} Comparisons: A Neutrality Test for the Evolution of the G Matrix in Structured Populations **funduvalue** χ_{st} r_{st} comparisons. A is evidence for local adaptation to this clinal variation in tempertrality Test for the Evolution of $\; \; \; \; \;$ $\; \; \;$ $\begin{bmatrix} 1 & 1 & 1 \end{bmatrix}$ which small selection selection pressures showledge pressures showledge pressures showledge the effects of effects

Neutral and adaptive variation in gene expression

Andrew Whitehead*† and Douglas L. Crawford‡

ica, where there is a change of 1°C per degree latitude or 12.5°C

 M is generated in identifying in identifying in identifying only if α

that we predicted affects the evolution of gene expression.

likely represents both genetic and other random biological

Guillaume Martin, *, +,1 Elodie Chapuis *, + and Jérôme Goudet * have also provided lessons for the design of future *Q*ST*–F*ST comparisons. Methods based on $\mathbf{H} = \mathbf{H} \cdot \mathbf{H} \cdot \mathbf{H} = \mathbf{H} \cdot \mathbf{H} \cdot \mathbf{H}$ $S^{*,*}$ and Jerome Goudet* **Phylogenetic Comparative Analysis: A Modeling**

I is presented and analysis are presented by the present present by the present by the present I subdivided into many partially isolated subpopulations. $\mathbf 1$ $\mathbf 1$ $\mathbf 2$ $\mathbf 3$ $\mathbf 3$ $\mathbf 3$ $\mathbf 4$ $\mathbf 5$ $\mathbf 7$ $\mathbf 8$ $\mathbf 8$ $\mathbf 9$ $\mathbf 1$ \mathbf μ_{up} demes under study. In the case of adaptive population r dontive Evelution *FIST of ST of ST or Lines* Manuscript received August 20, 2007 Lomparative Analys AA IPPIOUSH TOI TRUPLITY DTOIGHOIL Phylogenetic Comparative Analysis: A Modeling. Δ *mence substantials dentition* Γ *production* Altaiysis: A Modelling the h individuals in gene expression was not directly ascertained, all (See *Keeper and 2 months*) for 2 months. According to 2 mont \mathbf{H} **Approach for Adaptive Evolution Phylogenetic Comparative Analysis: A Modeling Approach for Adaptive Evolution**

 \mathbf{y} yet, because traits of \mathbf{y} Marguerite A. Butler and Aaron polygenic traits in wild point \mathbb{R}^n at existing method based on comparisons of \mathbb{R}^n **Marguerite A. Butler^{*} and Aaron A. King[†]** 41), and accommon environment minimizes to a common environment minimizes \mathcal{A} \mathcal{L} is the variation in generation in generation in generation in generation is generated.

Levolution Drift and Direction realms ϵ example, for example, for example, for ϵ medicine and conservation biology in the conservation of the conservation of the particular interest is determining to what degree population differentiation is caused by selection is caused by selection in the selection of $\mathsf{B} \mathsf{r}$ is adaptively versus $\mathsf{B} \mathsf{r}$ is an B neutral and selective patterns of population differentiaal Selection Are the Fvolu with state state interes. The state in ference in the state in the state in the state in
. The state in the s Forces Drivina Gene Expression Diveraence in Eve framework. **Example 19 Brain Tissue of Heliconius Butterflies** populations (G) covariance matrices by MANOVA. A simple pattern is expected under neutrality: D ¼ **Drift and Directional Selection Are the Evolution** the proportionality coefficient. This pattern is tested using Flury's framework for matrix comparison the importance of the test for the sizes of the sizes the sizes the sizes the size P_{1} stin P_{2} from P_{3} and P_{4} and P_{5} estimates of mean square matrices of means P_{4} and P_{5} great in a promise to rigorous in the property selected to result the selection of the Solid Cale assay many local pure it is generally and the pure that it is generally agreed to the sense of the sense of the **Enrres Driving Gene Expres** mental condition of the studies sources of variation. Although raising animals at one common **The Set of Sectional Selection Are the Evolutionary | The Section Selection Are the Evolutionary | The Section Selection Set Sections Are Sections Are Set Sections Are Set Sections Are Set Sections Are Set Sections Are Se** by-environment interactions. Thus, heritable differences due to Forces Driving Gene Expression Divergence in Eye and **Technik And Chief Lyonge** *Submitted November 26, 2003; Accepted August 19, 2004; Electronically published November 16, 2004*

such as body size and intelligence \mathcal{L} and intelligence \mathcal{L}

Conflict of interest statement: No conflicts declared.

specific requirements.

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 $\sqrt{3}/12$

 σ / τ

model of continuous trait evolution. We apply this model to identify expression pathways under neutral, stabilizing, and

plicit models, to test the models against data using maximum-like-

1991; Harvey and Rambaut 2000; Martins et al. 2002).

are thus qualitatively different from, and more general than, p and p and p and p and p and p

LA quantitative tramew \mathbf{r} represenced in annon <u>levolutionary history o</u> $\frac{1}{2}$ tive general that has a additive general that $\frac{1}{2}$ brk for characterizing fh finds that according the mammalian gene expre methodische petite expre heterogeneous, or mixed) when it is occurring on a set of traits. This method also provides a rigorous and quantitative framework for disentangling the effects of different selection regimes and of drift on the evolution of the G matrix. We discuss practical requirements for the proper application of our test in lifionary history of \mathbf{r} model, the variation in a trait has little biological effect§ and is a quantitutive numework io valution w history of mom $\mathsf{E}\mathsf{V}\mathsf{U}\mathsf{U}\mathsf{U}\mathsf{U}\mathsf{U}\mathsf{U}\mathsf{I}\mathsf{U}\mathsf{U}$ in a train in a traition in a traiti pairwise *F*ST estimates ranging from 0.01 to 0.24 (all statistically significant, *P* 0.05). The neighbor-joining tree (Fig. 1) supports p rial actuituis thus populations, which show a break populations, p \mathbf{b} evolutionary history of mammalian gene expression | distance (Mantel test, 1,000 permutations: *P* 0.024, *r* 0.65). | | | A quantitative framework for characterizing the $\begin{array}{ccc} \hbox{if} & \hbox$ m alian gene expression internative and n \mathbf{B} study and the evolution. However, none of the popular methods of the popular methods of the popular methods of

 $\frac{1}{2}$ and $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ isomorphism. $\lim_{t \to \infty}$ Crient, noss syvonoru, jeren Kerstin Lindblad-Toh, 1.5 Wilfried Haerty, 6 Federica di Palma, 6.7 and Aviv Regev $4.8.9$ μ lohnson ¹ Rond B. Cummings ^{1,3} No σ joinison, beryr b. Curininings, and due to drift and migration10,11. In cases in which *Q*ST ≈ *F*ST, requires being able to detect a statistically significant enny Chen. '^{,∠} Ross Swofford.' Ieremy Johnson ecological pressures (30). Recent studies suggests (30). tersun Lindbiad-Ton, m willfied Haerty, medel Thus, the spatially separated groups appear to follow indepen-Jenny Chen,1,2 Ross Swofford,¹ Jeremy Johnson,¹ Beryl B. Cummings,1,3 Noga Rogel,⁴ V original indblad T ob 1.5 Wilfried Haerty 6 Loderica di Dalma 6.7 and Aviv Degay $4.8.9$ Kerstin Lindblad-Toh,^{1,5} Wilfried Haerty,⁶ Federica di Palma,^{6,7} and Aviv Regev^{4,8,9} $\frac{1}{1}$ is the species compared are not independent: to independent to independent to independent to independent to indepen a greater or lesser extent they share a common evolution- $\frac{1}{2}$ of $\frac{1}{2}$ method based on $\frac{1}{2}$ \mathfrak{so}_k beryf b. Cummings, \wedge inoga rogel, figure

mulation and phyloger heterogeneous selection for the trait, i.e., selection for traits Qst is very low with the sampling designs typically possiblein empirical studies (O'HaraandMerila 2005), \sim source that \sim KEYWORDS Brownian motion; natural selection; stabilizing selection; Ornstein–Uhlenbeck; RevBayes directional selection. We further demonstrate novel applications of this model to quantify the extent of stabilizing selection on a generation, parameterize the distribution of each generation of each generation level, and detect deleter sion levels in expression data from individual patients. Our work provides a statistical framework for interpreting expression nonulation and phylogens population and priyiogent In his seminal article introducing the method of independent contrasts, Felsenstein (1985) recognized two proach we demonstrate allows one to explore more detailed hypotheses and to utilize \mathbf{r} and the information content of com- $\mathsf{pre}\mathsf{score}$ sets than existing methods. Moreover, the use of a model succ

Modelling (mean) trait evolution between species

An optimal value for the trait. *Ornstein-Uhlenbeck (OU) process.*

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Different optimal value for the trait,

Pitfalls of modelling (mean) trait evolution between species

[1]Silvestro *et al* (2015); [2]Copper *et al* (2016); [3]Hansen & Martins (1996)

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• OU process can be favored a neutral trait [1,2] \rightarrow Selection but it's not. **• Brownian process can be favored for trait under diversifying selection[3]** $\begin{array}{c}\n\begin{array}{c}\n\text{Stabilizing selection} \\
\hline\n\text{An optimal value for the 100\text{m}m} \\
\hline\n\end{array}\n\end{array}\n\quad\n\begin{array}{c}\n\text{Diversifying selection} \\
\hline\n\end{array}\n\end{array}\n\begin{array}{c}\n\text{Diversifying selection} \\
\hline\n\end{array}\n\end{array}\n\begin{array}{c}\n\text{Diversifying selection} \\
\hline\n\end{array}\n\end{array}\n\begin{array}{c}\n\text{Diversifying selection} \\
\hline\n\end{array}\n\begin{array}{c}\n\text{Different optimal value for the 100\text{$

Stabilizing selection An optimal value for the trait. *Ornstein-Uhlenbeck (OU) process.*

Neutral trait Random walk of the trait *Brownian process*

Diversifying selection Different optimal value for the trait, changing along the phylogeny. *Shifted OU process.*

Trait

Quantitative-genetics across populations. \rightarrow How to adapt Q_{ST} - F_{ST} methods across species?

 \rightarrow How to adapt McDonald & Kreitman test $(d_N/d_S > p_N/p_S)$ for trait changes along a phylogeny?

Contrast polymorphism

\rightarrow What is the expected rate of evolution for a neutral trait?

& divergence.

 \rightarrow How to a derive a d_N/d_s ratio but for a trait instead of protein coding DNA sequences?

Phylogenetic comparative

method.

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Phylogenetic DNA evolution.

What are you familiar with?

WW

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- *V^P* : phenotypic variance.
- h^2 : heritability for the trait.
-

: covariance in mean trait value between a pair of species. • *d*: shared nucleotide divergence between a pair of species. *σ*₂ res \overline{a}

Within species variation:

Between species variation:

- cov (\bar{P}_i, \bar{P}_j)
-

When are between and within species variations equal? b = *P*¯*i, P*¯*^j* 4*d* ;
;
; ⁴*^t* · *^µ* · *^L* · *^a*² 4*t* · *µ* ies va *.* (10) **Within species variation:**

 $\frac{2}{\mathbf{W}}=\mathbf{1}.$ 4*d*

- *µ*: mutation rate per generation.
- *q*: substitution rate per generation.

• *N*e: effective population size. • σ_M^2 : effect on the trait per mutation.

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• *σ*²

 \bullet π : mutations per site between two haplotypes. **Between species variation:** $\mathbf{e}^{\mathbf{e}}$

$$
\begin{cases}\n\sigma_{\rm W}^2 \stackrel{\text{def}}{=} \frac{V_P \cdot h^2}{\pi} = \frac{4\mathcal{N}_{\rm e} \cdot \mu \cdot \sigma_{\rm M}^2}{4\mathcal{N}_{\rm e} \cdot \mu} = \sigma_{\rm M}^2, \\
\sigma_{\rm B}^2 \stackrel{\text{def}}{=} \frac{\text{cov}\left(\bar{P}_i, \bar{P}_j\right)}{4d} = \frac{\mathcal{H} \cdot \mu \cdot \sigma_{\rm M}^2}{4d \cdot \mu} = \sigma_{\rm M}^2.\n\end{cases} \Longrightarrow \sigma_{\rm B}^2 / \sigma_{\rm W}^2 = 1.
$$

Lynch (1998); Hansen & Martins (1996); Kimura (1968); Tajima (1989)

Can we test our estimate against simulated data?

• Simulator across the phylogeny under different scenarios.

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Can we test our estimate against simulated data?

THE Stabilizing selection An optimal value for the trait.

• Simulations across the phylogeny under different scenarios.

 Neutral trait No fitness function.

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Diversifying selection An optimal value for the trait, changing randomly.

Test of neutrality against simulations

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Application to brain and body size in mammals

Latrille Thibault Trait evolution at the population and phylogenetic scale $12/13$ Department of Biology and Marine Biology, UNCW Center for Marine Science, University of North Carolina Wilmington, Wilmington, NC, USA. 6Oceans Graduate School and the Oceans Institute, The University

fragmentation and sea

Department of Evolutionary Studies of Biosystems, The Graduate University of Advanced Studies,

Aitor Serres-Armero, Cynthia Steiner, Klaus-Peter Koepfli, Diane P. Genereux, Elinor K. Karlsson, Kerstin Lindblad-Toh, Tomas Marques-Bonet, Violeta Munoz Fuentes, Kathleen Foley, Wynn K. Meyer, variables nonrandomly distinguished threatened from nonthreatened species in regression ncación le

nature

down of hrain-hody aown of biam bouy sequences, especially in genes essential for viability in mice, are predominantly deleterious.

 $t,$ Alexander Kotischare t , Kara L. Topar

ZOONOMIA

Genomic information

can help predict extinc-

2012 in A genomic timesc

Nicole M. Foley et al.

FILE CONTRIBUTION OF MISTON tionships. By contrast, we observe a second a s

mammalian species.

Across 240 mammals,

species with smaller his-

genetic diversity, higher

 \mathbf{q}

more likely to be threat-

Genomic data were used

predict whether a spe-

which can be valued by

for assessing the $\mathbf{I}_{\mathbf{z}}$

risk in species lacking

 \mathcal{A}

ecological or census data.

species with smaller his-

Take home messages

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- **Use the ratio of between over within species trait variations.**
- **Normalized using nucleotide variations (i.e. divergence and polymorphism). • Not good to detect of stabilizing selection (false positives). • Good to detect diversifying selection.**
-
-

Genetic architecture of the trait and individual phenotype

- *L* is the number of loci encoding the trait.
-
-
- \bullet $G_i = \sum_{l=1}^L$

$$
\begin{array}{c}\n\mathcal{N}(0, V_E) \\
\downarrow \\
a_l \times g_{i,l} + \xi_i \\
\text{otype}\n\end{array}
$$

$$
l \in \{1, \ldots, L\}.
$$

$$
\ldots, N_e \}.
$$

Lande (1978); Lynch (1998)

 the population and phylogenetic scale

1

N^e

• $a_l \sim \mathcal{N}(0, a^2)$ is the effect of a mutation on the trait at locus • $g_{i,l} \in \{0,1,2\}$ is the genotype at locus *l* for individual $i \in \{1,1\}$. $\frac{L}{l=1} a_l \times g_{i,l}$ is the influence of genotype on the trait for individual *i*.

For any neutral genomic region of interest, the genetic diversity (π) , the fraction of the region that are different between two randomly sampled haplotypes, is also a balance between mutations and drift $^{[1]}$:

Normalizing trait variation using polymorphism between mutation and drift[2], the additive genetic variance in the population (*V*A) is:

$$
\pi=4N_{\rm e}\cdot\mu.
$$

At the population level, we have:

 $\sigma^2_{\rm W}$

 V_A is also the phenotypic variance (V_P) multiplied by heritability (h^2) , giving:

$$
\frac{\text{def}}{=}\frac{V_{\text{A}}}{\pi} = \frac{4N_{\text{e}}\cdot\mu\cdot L\cdot a^2}{4N_{\text{e}}\cdot\mu} = L\cdot a^2.
$$

. (4)

$$
\sigma_W^2 = \frac{V_P \cdot h^2}{\pi} = L \cdot a^2.
$$

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 $\cdot \mu.$ (3)

. (5)

 $[1]$ Tajima (1989)

Evolution of mean trait value as a function of trait architecture

P is the trait mean value. If the trait is neutral and encoded by many loci, *P* evolves as Brownian process. cov (\bar{P}_i, \bar{P}_j) is the covariance in mean trait value between a pair of species^[1]:

CC-BY-SA Latrille Thibault Trait evolution at the population and phylogenetic scale 16/13 *d* = *t* · *q* = *t* · *µ.* (9)

 $^{[1]}$ Hansen & Martins (1996)

Normalizing mean trait value evolution using divergence P^1 = *N*^e \ln · *^µ* · *^L* · *^a*² *N*^e $\mathbf x$

The substitution rate per generation (q) is $[2,3]$:

For a neutral genomic region of interest, some mutations will eventually reach fixation in the population due to genetic drift $(\mathbb{P}_{\text{fix}} = 1/2N_e)^{[1]}$, resulting in a substitution.

$$
q = 2N_e \cdot \mu \cdot \mathbb{P}_{\text{fix}} = 2N_e \cdot \mu \cdot \frac{1}{2N_e} = \mu. \tag{8}
$$

For *t* generations, the genetic distance (*d*) measured as the number of substitution per site is:

$$
d = t \cdot q = t \cdot \mu.
$$
 (9)

We thus have for a pair of species:

 σ_B^2 def $=$

$$
\frac{\text{cov}\left(\bar{P}_i,\bar{P}_j\right)}{4d} = \frac{4t \cdot \mu \cdot L \cdot a^2}{4t \cdot \mu} = L \cdot a^2.
$$

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. (10)

- *n* is the number of taxa.
- *D* $(n \times n)$ is the symmetric distance matrix computed from the branch lengths and the topology of the phylogenetic tree.
- \overline{P} ($n \times 1$) is the vector of mean trait values at the tips of the tree.
- $1 (n \times 1)$ is a vector of ones.

Estimation at the phylogenetic scale

Input:

Output:

-
- $\sigma_{\rm B}^2$ is the estimated trait variance measured at the phylogenetic scale.

$$
\begin{cases} \phi = \left(\mathbf{1}^\mathsf{T} \times \mathbf{D}^{-1} \times \mathbf{1}\right)^{-1} \cdot \left(\mathbf{1}^\mathsf{T} \times \mathbf{D}^{-1} \times \bar{\mathbf{P}}\right), \\ \sigma_\mathrm{B}^2 = \frac{1}{4} \frac{\left(\bar{\mathbf{P}} - \phi \cdot \mathbf{1}\right)^\mathsf{T} \times \mathbf{D}^{-1} \times \left(\bar{\mathbf{P}} - \phi \cdot \mathbf{1}\right)}{n-1} .\end{cases}
$$

• ϕ is the estimate mean trait value at the root.

At the phylogenetic scale, the maximum likelihood estimates of ϕ and $\sigma_{\rm B}^2$ are^[1]:

(11)

 $[1]$ O'Meara *et al.* (2006)