

Anexo

Documentos comprobatorios



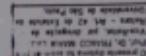
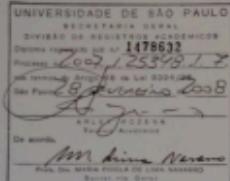
Documento 1: Diploma de Doutorado.



Documento 2: Diploma de Mestrado.



Documento 3: Diploma de Curso de Ciências Biológicas.



Documento 4: Diploma de Curso de Ciências Moleculares.



**Milner Centre for Evolution
Department of Biology & Biochemistry**

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1 November 2016

To whom it may concern

I hereby express my endorsement of the contents of the final scientific report regarding the research activities developed by Diogo Amaral Rebouças Melo during the tenure of his Research Internship Abroad Grant (BEPE-FAPESP number 2015 /21811-9), developed under my supervision from 11/05/2016 to 11/09/2016. Diogo also worked under my supervision in a Global Research Scholarship Fund from 11/03/2014 to 30/05/2014. As described in the report, this internship allowed Diogo to familiarize himself with multiple QTL mapping techniques, as well as developing new applications of existing regression models. Diogo also worked on the FAPESP project number 2013/50409-8, which is related to his PhD, being instrumental to the design of a new genotyping array specific for this project. Please feel free to contact me if you require further information.

Sincerely,

A handwritten signature in black ink, appearing to read "Jason B. Wolf".

Jason B. Wolf



PRINCETON
UNIVERSITY

Section D: Human Resources Department
Human Resources & Diversity & Inclusion Department
5 University Avenue, Princeton, NJ 08544-5264
Tel: 609-258-3200
Fax: 609-258-3201
Diversity@princeton.edu

Dr. Diego Melo
Universidade de São Paulo
Departamento De Genética E Biologia Evolutiva
São Paulo, São Paulo, Brazil

March 3, 2020

Dear Dr. Diego Melo:

I am pleased to offer you an appointment as a Postdoctoral Research Associate in the Lewis-Sigler Institute for Integrative Genomics as part of Princeton's Presidential Postdoctoral Research Fellow Program. The program is intended to recruit young and supportive leading early-career scholars who will contribute to the University's scholarly excellence and enhance its diversity.

You will receive 100% full-time salary well to \$51,074 paid monthly. You will also receive an annual research grant of \$25,000 and up to \$2,000 for a computer. The computer will be assigned to the property of the University and shall be returned to the department at the end of your appointment. Moving expenses or mileage will be报销, up to a maximum of \$5,000 for relocation from international and U.S. west coast locations, and up to a maximum of \$3,000 for relocation from all other U.S. locations (exceeding the IRS required 50-mile job site travel).

Your appointment will be for one year and may start between July 1, 2020 and September 1, 2020, with the possibility of renewal for a second year assuming satisfactory performance. We will need a written acceptance of this offer to complete the formalities of your appointment. We will write such acceptance to you as soon as possible, and in any case no later than March 1, 2020. Please reply to the e-mail containing this offer letter to accept this appointment and include a signed copy of the last page as an attachment.

This offer is contingent upon completion of all requirements for the PhD. If the PhD is not completed by September 1, 2020, then this PIREA appointment offer is no longer valid.

All Postdoctoral Research Associates in the social sciences, natural sciences, and engineering are required to complete a course in Research Conduct and Research (RCR). Our policy for RCR training can be found at <http://www.princeton.edu/univ/proc/policy-and-procedures/mandatory-research-conduct-and-research>; contact Kara Dehmlöv, Director, Genome Database, Lewis-Sigler Institute for Integrative Genomics, for details.

Final approval of your appointment is contingent upon successful completion of a background check. Information about that process will be shared with you once we have received your acceptance of our offer. Upon acceptance of your appointment, we will receive a package of benefit information from the Office of Human Resources. Our benefit package provides that postdoctoral employees earn two vacation days per month. You will be compensated for any unused vacation time at the end of your appointment up to a limit of 30 days. Please refer to <http://www.princeton.edu/univ/proc/policy-and-procedures/mandatory-research-conduct-and-research> for policies relevant to postdoctoral appointments, and to <http://www.princeton.edu/univ/proc/policy-and-procedures/mandatory-research-conduct-and-research>.

Princeton University is required to verify that you are eligible for employment under the Immigration Reform and Control Act of 1986. Information on what you must do to prove U.S. citizenship or permanent residence status that authorizes you to work is included within this letter and will also be sent to you along with the formal letter of appointment from the Dean of the Faculty upon acceptance of this offer.

We hope for the good fortune of welcoming you to the Lewis-Sigler Institute for Integrative Genomics, and we have no doubt that you will find Princeton to be a collegial and intellectually stimulating environment.

Sincerely,

Karen Heilman

cc: Julian Ayres, Assistant Professor of Ecology and Evolutionary Biology and the Lewis-Sigler Institute for Integrative Genomics.

Michael Levine, Andrew B. Murray '12 Professor in Genetics, Professor of Molecular Biology and the Lewis-Sigler Institute for Integrative Genomics; Director, Lewis-Sigler Institute for Integrative Genomics.

Kara Dehmlöv, Director, Genome Database, Lewis-Sigler Institute for Integrative Genomics.

Iain Frazee, Deputy Dean of the Faculty

Karen Heilman, Associate Dean for Academic Affairs

Alice Sonnewald, Assistant Dean of Academic Affairs

Documento 6: Comprovante de bolsa de Pós-Doutorado.

FUNDAÇÃO DE AMPARO À PESQUISA DO ESTADO DE SÃO PAULO
 TERMO DE OUTORGA E ACEITAÇÃO DE BOLSAS NO PAÍS

PROCESSO 2019/06559-6

Pelo presente instrumento, a Fundação de Amparo à Pesquisa do Estado de São Paulo, com sede na Rua Pio XI, nº 1500, Alto da Lapa, São Paulo, Capital, inscrita no CNPJ/MF sob o nº 43.828.151/0001-45, doravante denominada OUTORGANTE, por meio de seu Conselho Técnico-Administrativo, nos termos do Artigo 14, letra "b", da Lei Estadual nº 5.918, de 18 de outubro de 1960, concede ao(s) OUTORGADO(S), a seguir qualificado(s), Bolsa para a realização do Projeto de Pesquisa a seguir especificado, nas instalações e com o apoio da INSTITUIÇÃO SEDE, de acordo com as especificações, cláusulas e condições descritas a seguir e nos Anexos, que passam a ser parte integrante deste Termo.

1. OUTORGADOS

1.1 BOLSISTA: Diogo Amaral Rebouças Melo
 CPF: 329.212.298-89
 RG: 350021107-SSP/SP

1.2 ORIENTADOR/SUPERVISOR: Gabriel Henrique Marroig Zambonato
 CPF: 989.457.267-72
 RG: 116197229-IFP/RJ

2. Correspondência

2.1 BOLSISTA: Rua Caraíbas 544 - 122B, Perdizes, São Paulo/SP, CEP 05020-000
 diogro@usp.br

2.2 ORIENTADOR/SUPERVISOR: Rua Fidalga 953 - casa 10, Pinheiros, São Paulo/SP, CEP 05432-070
 gmarroig@usp.br

3. Instituição Sede: Instituto de Biociências/IB
 Universidade de São Paulo/USP

4. Projeto de Pesquisa: Arquitetura genética do crânio de mamíferos

5. Linha de Fomento: Programas Regulares / Bolsas / No País / Pós-Doutorado

6. Área/Subárea: Genética
 Genética Quantitativa

7. Coordenação: Biologia I

8. Período da vigência: 01/07/2019 a 30/06/2021

9. Relatórios Científicos: 10/07/2021

10. Prestações de Contas: 10/07/2021

FUNDAÇÃO DE AMPARO À PESQUISA DO ESTADO DE SÃO PAULO

TERMO DE OUTORGA E ACEITAÇÃO DE BOLSAS NO PAÍS

PROCESSO 2014/26262-4

Pelo presente instrumento, a Fundação de Amparo à Pesquisa do Estado de São Paulo, com sede na Rua Pio XI, nº 1500, Alto da Lapa, São Paulo, Capital, inscrita no CNPJ/MF sob o nº 43.828.151/0001-45, doravante denominada OUTORGANTE, por meio de seu Conselho Técnico-Administrativo, nos termos do Artigo 14, letra "b", da Lei Estadual nº 5.918, de 18 de outubro de 1980, concede ao(s) OUTORGADO(S), a seguir qualificado(s), Bolsa para a realização do Projeto de Pesquisa a seguir especificado, nas instalações e com o apoio da INSTITUIÇÃO SEDE, de acordo com as especificações, cláusulas e condições descritas a seguir e nos Anexos, que passam a ser parte integrante deste Termo.

1. OUTORGADOS

1.1 BOLSISTA: Diogo Amaral Reboucas Melo

CPF: 329.212.298-89

RG: 350021107-SSP/SP

1.2 ORIENTADOR/SUPERVISOR: Gabriel Henrique Marroig Zambonato

CPF: 009.457.267-72

RG: 116197229-IFP/RJ

2. Correspondência

2.1 BOLSISTA: A/C Diogo Melo, Rua Sousa Reis 153 - ap 71, Vila Indiana, São Paulo/SP,
 CEP 05686-080
 diogro@usp.br

2.2 ORIENTADOR/SUPERVISOR: Rua Fidalga 953 - casa 10, Pinheiros, São Paulo/SP, CEP 05482-070
 gmarroig@usp.br

3. Instituição Sede: Instituto de Biociências/IB
 Universidade de São Paulo/USP

4. Projeto de Pesquisa: Estimativas Diretas de
 Parâmetros Evolutivos Via Análise de Loci de Traços
 Quantitativos

5. Linha de Fomento: Programas Regulares / Bolsas / No País / Doutorado

6. Área/Subárea: Genética
 Genética Quantitativa

7. Coordenação: Biologia II

8. Período da vigência: 01/04/2015 a 31/03/2018

9. Relatórios Científicos: 10/03/2016, 10/03/2017, 10/04/2018

10. Prestações de Contas: 10/03/2016, 10/03/2017, 10/04/2018

11. Entrega da Ata de Defesa: 15/10/2018

FUNDAÇÃO DE AMPARO À PESQUISA DO ESTADO DE SÃO PAULO
 TERMO DE OUTORGA E ACEITAÇÃO DE BOLSAS NO EXTERIOR

PROCESSO 2015/21811-2

Pelo presente instrumento, a Fundação de Amparo à Pesquisa do Estado de São Paulo, com sede na Rua Pio XI, nº 1500, Alto da Lapa, São Paulo, Capital, inscrita no CNPJ/MF sob o nº 43.828.151/0001-45, doravante denominada OUTORGANTE, por meio de seu Conselho Técnico-Administrativo, nos termos do Artigo 14, letra "b", da Lei Estadual nº 5.918, de 18 de outubro de 1980, concede aos OUTORGADOS(S), a seguir qualificado(s), Bolsa para a realização de Projeto de Pesquisa a seguir especificado, em Instituição no Exterior, com o apoio da INSTITUIÇÃO SEDE, de acordo com as especificações, cláusulas e condições descritas a seguir e nos Anexos, que passa a ser parte integrante deste Termo.

1. OUTORGADOS

1.1 BOLSISTA: Diogo Amaral Reboucas Melo

CPF: 329.212.298-89

RG: 350021107-SSP/SP

1.2 ORIENTADOR/SUPERVISOR: Gabriel Henrique Marroig Zambonato

CPF: 989.457.267-72

RG: 116197229-IFP/RJ

2. Correspondência

2.1 BOLSISTA: A/C Diogo Melo, Rua Sousa Reis 153 - ap 71, Vila Indiana, São Paulo/SP, CEP 05686-080
 diogro@usp.br

2.2 ORIENTADOR/SUPERVISOR: Rua Fidalga 953 - casa 10, Pinheiros, São Paulo/SP, CEP 05482-070
 gmarroig@usp.br

3. Instituição Sede: Instituto de Biociências/IB
 Universidade de São Paulo/USP

4. Instituição no Exterior: University of Bath
 Bath
 Inglaterra

5. Projeto de Pesquisa: Estimativas Diretas de Parâmetros Evolutivos Via Análise de QTL

6. Linha de Fomento: Programas Regulares / Bolsas / No Exterior / Bolsa Estágio de Pesquisa no Exterior / BEPE - Doutorado

7. Área/Subárea: Genética
 Genética Quantitativa

8. Coordenação: Biologia II

9. Período da vigência: 11/04/2016 a 10/09/2016

10. Relatórios Científicos: 30/10/2016

11. Prestações de Contas: 30/10/2016

Termo de OutorgaProcesso 2014/01694-9

O Conselho Técnico-Administrativo da Fundação de Amparo à Pesquisa do Estado de São Paulo, doravante denominada OUTORGANTE, usando das atribuições que lhe compete o Artigo 14, letra "b" da Lei Estadual nº 5.918, de 18 de outubro de 1960, e de acordo com as especificações, cláusulas e condições descritas a seguir nos Anexos, que são parte integrante deste Termo, concede:

OUTORGADO	Diego Amaral Rebolledo Melo CPF: 329.212.298-89
Orientador/Supervisor	Gabriel Henrique Marroig Zamborato CPF: 989.457.267-72
Instituição	Instituto de Biociências/IB/USP
Unidade de Fomento	Bolsas Concedidas como Meio Obrigatório em Auxílios / Treinamento Técnico
Projeto	Elaaboração de um Pacote em R para uso em pesquisa de genética quantitativa
Área	Genética
Grande Área	Genéticas Biológicas
Sub-área	Genética Quantitativa
Vigência	01/03/2014 a 28/02/2015
Relatório Científico até	28/02/2015

Observações

- Concessão improrrogável.
 - Vinculado ao Auxílio à Pesquisa - Projeto Temático 2011/14295-7.
-

Termo de Outorga

Processo 2012/20180-0

O Conselho Técnico-Administrativo da Fundação de Amparo à Pesquisa do Estado de São Paulo, doravante denominada OUTORGANTE, usando das atribuições que lhe confere o Artigo 14, letra "b" da Lei Estadual nº 5.918, de 18 de outubro de 1960, e de acordo com as especificações, cláusulas e condições descritas a seguir nos Anexos, que são parte integrante deste Termo, concede:	
OUTORGADO	Diego Amaral Rebolledo Melo CPF: 329.212.298-89
Orientador/Supervisor	Gabriel Henrique Marroq Zamborato CPF: 989.457.267-72
Instituição	Instituto de Biociências/IB/USP
Unidade de Fomento	Bolsas Concedidas como Meio Operacional para Auxílios / Treinamento Técnico
Projeto	Técnicas comportacionais em genética quantitativa.
Área	Biologia Geral
Grande Área	Ciências Biológicas
Sub-area	Outra Subárea Biologia Geral
Vigência	01/11/2012 a 31/10/2013
Relatório Científico até	30/01/2014

Observações:

- Vinculado ao Auxílio à Pesquisa - Projeto Temático 2011/14295-7.

Termo de Outorga

Processo 2010/04497-9

O Conselho Técnico-Administrativo da Fundação de Amparo à Pesquisa do Estado de São Paulo, doravante denominada OUTORGANTE, usa das atribuições que lhe confere o Artigo 14, letra "b" da Lei Estadual nº 5.918, de 18 de outubro de 1960, e de acordo com as especificações, cláusulas e condições descritas a seguir nos Anexos, que são parte integrante desse Termo, concede:	
Outorgado	Diego Amaral Rebonatto Melo CPF: 329.212.298-89
Orientador/Supervisor	Gabriel Henrique Marroig Zamborlin CPF: 989.451.267-72
Instituição	Instituto de Biociências/IB/UFPB
Unidade Fomento	Programas Regulares / Bolsas / No País / Mestrado
Projeto	Evolução Morfológica e Morfobiologia
Grande Área	Ciências Biológicas
Área	Genética
Sub-área	Genética Quantitativa
Vigência	01/08/2010 a 29/02/2012
Relatório Científico até	10/07/2011, 10/03/2012

Observações

- Concessão improrrogável.

New Results

Follow this preprint

Reassessing the modularity of gene co-expression networks using the Stochastic Block Model

Diogo Melo, Luisa F. Pallares, Julien F. Ayroles

doi: <https://doi.org/10.1101/2023.05.31.542906>

This article is a preprint and has not been certified by peer review [what does this mean?].



Abstract

Finding communities in gene co-expression networks is a common first step toward extracting biological insight from such complex datasets. Most community detection algorithms expect genes to be organized into assortative modules, that is, groups of genes that are more associated with each other than with genes in other groups. While it is reasonable to expect that these modules exist, using methods that assume they exist a priori is risky, as it guarantees that alternative organizations of gene interactions will be ignored. Here, we ask: can we find meaningful communities without imposing a modular organization on gene co-expression networks, and how modular are these communities? For this, we use a recently developed community detection method, the weighted degree corrected stochastic block model (SBM), that does not assume that assortative modules exist. Instead, the SBM attempts to efficiently use all information contained in the co-expression network to separate the genes into hierarchically organized blocks of genes. Using RNA-seq gene expression data measured in two tissues derived from an outbred population of *Drosophila melanogaster*, we show that (a) the SBM is able to find ten times as many groups as competing methods, that (b) several of those gene groups are not modular, and that (c) the functional enrichment for non-modular groups is as strong as for modular communities. These results show that the transcriptome is structured in more complex ways than traditionally thought and that we should revisit the long-standing assumption that modularity is the main driver of the structuring of gene co-expression networks.

Competing Interest Statement

The authors have declared no competing interest.

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Genomics

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Documento 13: Artigo: Melo, D., Pallares, L. F., Ayroles, J. F., 2023. Reassessing the modularity of gene co-expression networks using the Stochastic Block Model.. <https://doi.org/10.1101/2023.05.31.542906>.

New Results

Follow this preprint

Saturating the eQTL map in *Drosophila melanogaster*: genome-wide patterns of cis and trans regulation of transcriptional variation in outbred populations

Luisa F. Pallares, Diogo Melo, Scott Wolf, Evan M. Cofer, Varada Abhyankar, Julie Peng, Julien F. Ayroles

doi: <https://doi.org/10.1101/2023.05.20.541576>

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Revision Summary

Abstract

Decades of genome-wide mapping have shown that most genetic polymorphisms associated with complex traits are found in non-coding regions of the genome. Characterizing the effect of such genetic variation presents a formidable challenge, and eQTL mapping has been a key approach to understand the non-coding genome. However, comprehensive eQTL maps are available only for a few species like yeast and humans. With the aim of understanding the genetic landscape that regulates transcriptional variation in *Drosophila melanogaster*, we developed an outbred mapping panel in this species, the *Drosophila* Outbred Synthetic Panel (Dros-OSP). Using this community resource, we collected transcriptomic and genomic data for 1800 individual flies and were able to map *cis* and *trans* eQTLs for 98% of the genes expressed in *D. melanogaster*, increasing by thousands the number of genes for which regulatory loci are known in this species. We described, for the first time in the context of an outbred population, the properties of local and distal regulation of gene expression in terms of genetic diversity, heritability, connectivity, and pleiotropy. We uncovered that, contrary to long-standing assumptions, a significant part of gene co-expression networks is organized in a non-modular fashion. These results bring the fruit fly to the level of understanding that was only available for a few other organisms, and offer a new mapping resource that will expand the possibilities currently available to the *Drosophila* community. This data is available at DrosophilaeQTL.org.

Competing Interest Statement

The authors have declared no competing interest.

Subject Area

Genomics

Supported by Chan Zuckerberg Initiative

Documento 14: Artigo: Pallares, L. F., Melo, D., Wolf, S., Cofer, E. M., Varada, V., Peng, J., Ayroles, J. F., 2023. Saturating the eQTL map in *Drosophila melanogaster*: genome-wide patterns of cis and trans regulation of transcriptional variation in outbred populations.. <https://doi.org/10.1101/2023.05.20.541576>.

New Results

 Follow this preprint

From GWAS to signal validation: An approach for estimating genetic effects while preserving genomic context

Scott Wolf, Varada Abhyankar, Diogo Melo, Julien F. Ayroles, Luisa F. Pallares
doi: <https://doi.org/10.1101/2023.03.09.531909>

This article is a preprint and has not been certified by peer review [what does this mean?].



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Subject Area

Genetics 

Supported by **Chan Zuckerberg Initiative** 

Abstract

Validating associations between genotypic and phenotypic variation remains a challenge, despite advancements in association studies. Common approaches for signal validation rely on gene-level perturbations, such as loss-of-function mutations or RNAi, which test the effect of genetic modifications usually not observed in nature. CRISPR-based methods can validate associations at the SNP level, but have significant drawbacks, including resulting off-target effects and being both time-consuming and expensive. Both approaches usually modify the genome of a single genetic background, limiting the generalizability of experiments. To address these challenges, we present a simple, low-cost experimental scheme for validating genetic associations at the SNP level in outbred populations. The approach involves genotyping live outbred individuals at a focal SNP, crossing homozygous individuals with the same genotype at that locus, and contrasting phenotypes across resulting synthetic outbred populations. We tested this method in *Drosophila melanogaster*, measuring the longevity effects of a polymorphism at a naturally-segregating cis-eQTL for the *midway* gene. Our results demonstrate the utility of this method in SNP-level validation of naturally occurring genetic variation regulating complex traits. This method provides a bridge between the statistical discovery of genotype-phenotype associations and their validation in the natural context of heterogeneous genomic contexts.

Competing Interest Statement

The authors have declared no competing interest.

Documento 15: Artigo: Wolf, S., Abhyankar, V., Melo, D., Ayroles, J. F., Pallares, L. F., 2023. From GWAS to signal validation: An approach for estimating genetic effects while preserving genomic context.. <https://doi.org/10.1101/2023.03.09.531909>.

RESEARCH ARTICLE

Characterizing the landscape of gene expression variance in humans

Scott Wolf , Diogo Melo , Kristina M. Garske , Luisa F. Pallares ,
Amanda J. Lea , Julian F. Ayroles 

¹ Lewis-Sigler Institute for Integrative Genomics, Princeton University, Princeton, New Jersey, United States of America, ² Department of Ecology and Evolutionary Biology, Princeton University, Princeton, New Jersey, United States of America, ³ Friedrich Miescher Laboratory of the Max Planck Society, Tübingen, Germany, ⁴ Department of Biological Sciences, Vanderbilt University, Nashville, Tennessee, United States of America, ⁵ Child and Brain Development, Canadian Institute for Advanced Research, Toronto, Canada

✉ These authors contributed equally to this work.

* dmelo@princeton.edu (DM); jayroles@princeton.edu (JFA)



Abstract

Gene expression variance has been linked to organismal function and fitness but remains a commonly neglected aspect of molecular research. As a result, we lack a comprehensive understanding of the patterns of transcriptional variance across genes, and how this variance is linked to context-specific gene regulation and gene function. Here, we use 57 large publicly available RNA-seq data sets to investigate the landscape of gene expression variance. These studies cover a wide range of tissues and allowed us to assess if there are consistently more or less variable genes across tissues and data sets and what mechanisms drive these patterns. We show that gene expression variance is broadly similar across tissues and studies, indicating that the pattern of transcriptional variance is consistent. We use this similarity to create both global and within-tissue rankings of variation, which we use to show that function, sequence variation, and gene regulatory signatures contribute to gene expression variance. Low-variance genes are associated with fundamental cell processes and have lower levels of genetic polymorphisms, have higher gene-gene connectivity, and tend to be associated with chromatin states associated with transcription. In contrast, high-variance genes are enriched for genes involved in immune response, environmentally responsive genes, immediate early genes, and are associated with higher levels of polymorphisms. These results show that the pattern of transcriptional variance is not noise. Instead, it is a consistent gene trait that seems to be functionally constrained in human populations. Furthermore, this commonly neglected aspect of molecular phenotypic variation harbors important information to understand complex traits and disease.

OPEN ACCESS

Citation: Wolf S, Melo D, Garske KM, Pallares LF, Lea A, Ayroles JF (2023) Characterizing the landscape of gene expression variance in humans. PLoS Genet 19(7): e1010833. <https://doi.org/10.1371/journal.pgen.1010833>

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Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: <https://doi.org/10.1371/journal.pgen.1010833>

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Data Availability Statement: Code for reproducing all analyses and figures, along with a walk-through, is available at github.com/ayroles-lab/expression-variance-code. All relevant data are within the paper and its [Supporting Information](#).

Author summary

Gene expression variance, or the variation in the level of gene expression within a population, can have significant impacts on physiology, disease, and evolutionary adaptations. While the average level of gene expression is typically the focus of research, the variation

Morphological integration during postnatal ontogeny: implications for evolutionary biology

Alex Hubbe,^{PhD^{1,2}}, Fabio A. Machado,^{PhD³ }, Diogo Melo,^{PhD⁴ }, Guilherme Garcia,^{PhD⁵}, Harley Sebastião,^{PhD⁶}, Arthur Porto,^{PhD^{4,7}}, James Cheverud,^{PhD⁸}, Gabriel Marroig,^{PhD⁹}

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²Departamento de Oceanografia, Instituto de Geociências, Universidade Federal da Bahia, Bahia, Brazil

³Department of Integrative Biology, Oklahoma State University, Stillwater, Oklahoma, United States

⁴Lewis-Sigler Institute for Integrative Genomics, Princeton University, Princeton, New Jersey, United States

⁵Departamento de Genética e Biologia Evolutiva, Instituto de Biociências, Universidade de São Paulo, São Paulo, Brazil

⁶Department of Biological Sciences, Louisiana State University, Baton Rouge, Louisiana, United States

⁷Center for Computation and Technology, Louisiana State University, Baton Rouge, Louisiana, United States

⁸Department of Biology, Loyola University Chicago, Chicago, Illinois, United States

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Abstract

How covariance patterns of phenotypes change during development is fundamental for a broader understanding of evolution. There is compelling evidence that mammalian cranium covariance patterns change during ontogeny. However, it is unclear to what extent variation in covariance patterns during ontogeny can impact the response to selection. To tackle this question, we explored: (a) the extent to which covariance patterns change during postnatal ontogeny; (b) in which ontogenetic stages covariance patterns differ the most; and (c) the extent to which the phenotypic covariance pattern at different ontogenetic stages can be explained by the same processes determining additive genetic covariance. We sampled the postnatal ontogenetic series for both marsupials and placentals. Within each ontogenetic series, we compared covariance matrices (P -matrices) at different ontogenetic stages. Furthermore, we compared these P -matrices to two target matrices: adult P -matrix and an additive genetic covariance matrix (G -matrix). Our results show that for all ontogenetic series, covariance patterns from weaning onward are conserved and probably shaped by the same processes determining the G -matrix. We conclude that irrespective of eventual differences in how selection operates during most of the postnatal ontogeny, the net response to such pressures will probably not be affected by ontogenetic differences in the covariance pattern.

Keywords: development, G-matrix, P-matrix, Marsupalia, Placentalia

Developmental processes change the amount and distribution of morphological variation through time [Mitteroecker & Bookstein, 2009; Zelditch et al., 2006]. Not surprisingly, this is well documented for the mammalian cranium (Archey, 1984; Coleman et al., 1994; Goswami et al., 2012; Hallgrímsson et al., 2009; Mitteroecker & Bookstein, 2009; Mitteroecker et al., 2012; Nonaka & Nakata, 1984; Sydney et al., 2012; Zelditch, 1988; Zelditch & Carmichael, 1989; Zelditch et al., 1992, 2006)], which is a common model system for investigating the evolution of complex structures [e.g., Goswami (2006); Haber (2015); Machado et al. (2018)]. Yet, there is little evidence on how these documented differences along ontogeny would affect evolution.

Since natural selection is contingent on the availability and organization of morphological variation (Lande, 1979; Lande & Arnold, 1983), differences in the amount and structure of variation across life history stages can affect how populations respond to selection (Wasserman et al., 2021). For example, consider a scenario in which a pair of traits are associated (i.e., high integration *sensu* Olson & Miller, 1958) in the

juvenile phase, but in the adult phase, these traits are much less integrated [Figure 1; e.g., Sydney et al. (2012)]. If selection operates on a single trait at the juvenile stage, evolutionary responses will be aligned with the major direction of variation of juveniles, leading to a correlated response in the second trait, even in the absence of trait association in the adult phase. Furthermore, in this scenario, the reconstruction of selection using the adult stage would suggest that selection is acting on multiple traits simultaneously, while in fact, it is acting on a single trait earlier in development. Conversely, if the covariance patterns are relatively stable throughout ontogeny, selection would produce evolutionary responses that are similar across ontogenetic stages. Therefore, understanding how the variance is distributed on different ontogenetic stages can provide further insight about how complex phenotypes might evolve in response to natural selection. This knowledge has also broader implications since complex phenotypes play, for instance, an important role in ecological interactions (Assis et al., 2022; Saccheri & Hanski, 2006), and population's extinction risk (Forster et al., 2022).

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Are cats less stressed in homes than in shelters? A study of personality and faecal cortisol metabolites



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ABSTRACT

Personality is defined by characteristics of individuals and describes and accounts for temporally stable patterns of affect, cognition and behaviour traits. The study of cat behaviour and personality can minimize potential problems in the relationship between cats and their owners and decrease abandonment and maltreatment. People generally adopt animals according to the individual's appearance, age or sex. Personality assessments can help make adoptions successful by identifying ideal subjects for potential owners. A personality assessment called "Meet Your Match" (MYM), developed by the American Society for the Prevention of Cruelty to Animals (ASPCA) and validated for our cat sample was used in this study. To evaluate stress, we measured faecal cortisol metabolites (FCMs) of cats in shelters and after adoption. In an effort to improve adoption and cat adaptation in new homes, our goals were 1) to evaluate the relationship between personality and cortisol levels; 2) to confirm if MYM assessment is consistent through situations; and 3) to investigate how moving from the shelter to the owners' homes affects FCM levels. The subjects for our first goal were 53 sheltered cats. For the second and the third goals, we followed 15 of the original 53 after the adoption. No correlation was found between personality dimensions (agreeableness $p = 0.878$; openness $p = 0.141$; extraversion $p = 0.942$) and FCM levels. MYM assessment was consistent through different localities. There was a slight, but significant ($p = 0.0072$), decrease of FCM levels at owners' home. However, most subjects ($n = 11$) did not present changes that were significantly different from zero. Our study underlined the usefulness of the MYM personality assessment and confirmed a lack of correlation between personality and cortisol levels in cats. It is a further step towards incorporating a more objective approach to the adoption process in shelters to improve the pairing of humans and cats.

1. Introduction

Personality research ranges from invertebrates (Carere et al., 2018) to primates (Freeman and Gosling, 2010). Definitions of personality point to those characteristics of individuals that describe and account for temporally stable patterns of affection, cognition, and behaviour (Siegford et al., 2003; Gosling, 2008; Uher, 2011; Gartner and Weiss, 2013; MacKay and Haskell, 2015). Research in animal personality joined efforts to unravel the dimensions that compose each species' personality traits. Human personality, for example, is composed of five dimensions as shown in the Five Factor Model (John and Srivastava, 1999). Being the most popular pets in households, dogs and cats are also being studied (Jones and Gosling, 2005; Gartner and Weiss, 2013). Most studies are based on surveys with caretakers and focus on

personality measurements, genetics and the relationship between personality and its health effects in captive and confined individuals (Gartner, 2015). Recent studies have investigated cat personality dimensions (Gartner and Weiss, 2013; Gartner et al., 2014; Kaleta et al., 2016; Bennett et al., 2017; Ha and Ha, 2017; Litchfield et al., 2017) and, so far, have unfolded a number of them, such as affection, energy, sociability and curiosity (Gartner, 2015).

As complex and intricate as human-animal interactions can be (Bradshaw, 2013), potential issues in the relationship between cats and their owners — such as abandonment or mistreatment (Genaro, 2004) — can be mitigated with the aid of knowledge obtained from studies about cat behaviour and personality, the monitoring of cat populations, and educational actions (Hiby et al., 2014). Unsuccessful adoptions are a multi-causal event and are related to: aggression between cats in

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Measuring the magnitude of morphological integration: The effect of differences in morphometric representations and the inclusion of size

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The magnitude of morphological integration is a major aspect of multivariate evolution, providing a simple measure of the intensity of association between morphological traits. Studies concerned with morphological integration usually translate phenotypes into morphometric representations to quantify how different morphological elements covary. Geometric and classic morphometric representations translate biological form in different ways, raising the question if magnitudes of morphological integration estimates obtained from different morphometric representations are compatible. Here we sought to answer this question using the relative eigenvalue variance of the covariance matrix obtained for both geometric and classical representations of empirical and simulated datasets. We quantified the magnitude of morphological integration for both shape and form and compared results between representations. Furthermore, we compared integration values between shape and form to evaluate the effect of the inclusion or not of size on the quantification of the magnitude of morphological integration. Results show that the choice of morphological representation has significant impact on the integration magnitude estimate, either for shape or form. Despite this, ordination of the integration values within representations is relatively the same, allowing for similar conclusions to be reached using different methods. However, the inclusion of size in the dataset significantly changes the estimates of magnitude of morphological integration, hindering the comparison of this statistic obtained from different spaces. Morphometricians should be aware of these differences and must consider how biological hypothesis translate into predictions about integration in each particular choice of representation.

KEY WORDS: Covariance matrix, canidae, eigenvalue variance, P matrix, skull.

Symposium Article

Genomic Perspective on Multivariate Variation, Pleiotropy, and Evolution

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Abstract

Multivariate quantitative genetics provides a powerful framework for understanding patterns and processes of phenotypic evolution. Quantitative genetics parameters, like trait heritability or the G-matrix for sets of traits, can be used to predict evolutionary response or to understand the evolutionary history of a population. These population-level approaches have proven to be extremely successful, but the underlying genetics of multivariate variation and evolutionary change typically remain a black box. Establishing a deeper empirical understanding of how individual genetic effects lead to genetic (co)variation is then crucial to our understanding of the evolutionary process. To delve into this black box, we exploit an experimental population of mice composed from lineages derived by artificial selection. We develop an approach to estimate the multivariate effect of loci and characterize these vectors of effects in terms of their magnitude and alignment with the direction of evolutionary divergence. Using these estimates, we reconstruct the traits in the ancestral populations and quantify how much of the divergence is due to genetic effects. Finally, we also use these vectors to decompose patterns of genetic covariation and examine the relationship between these components and the corresponding distribution of pleiotropic effects. We find that additive effects are much larger than dominance effects and are more closely aligned with the direction of selection and divergence, with larger effects being more aligned than smaller effects. Pleiotropic effects are highly variable but are, on average, modular. These results are consistent with pleiotropy being partly shaped by selection while reflecting underlying developmental constraints.

Keywords: G-matrix, genetic architecture, genome prediction, genotype–phenotype map, horseshoe prior, QTL mapping

Individuals are composed of a complex array of traits that are interconnected through shared genetic, physiological, and developmental processes. Consequently, evolution is inherently a multivariate process, wherein suites of traits interact to determine an individual's fitness, which generates selection that cascades to the genomic level through the genotype–phenotype relationship leading to heritable changes across generations (Lande and Arnold 1983; Klingenberg

2008; Melo et al. 2016). Therefore, understanding evolutionary change in response to selection requires an understanding of the relationship between genotypic variation and multivariate traits. The quantitative genetics framework was developed to achieve this goal, historically relying on statistical measurement of genetic covariation between traits as a summary of their genetic “connectedness.” The covariances estimated using this framework can be used



The evolution of phenotypic integration: How directional selection reshapes covariation in mice

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Variation is the basis for evolution, and understanding how variation can evolve is a central question in biology. In complex phenotypes, covariation plays an even more important role, as genetic associations between traits can bias and alter evolutionary change. Covariation can be shaped by complex interactions between loci, and this genetic architecture can also change during evolution. In this article, we analyzed mouse lines experimentally selected for changes in size to address the question of how multivariate covariation changes under directional selection, as well as to identify the consequences of these changes to evolution. Selected lines showed a clear restructuring of covariation in their cranium and, instead of depleting their size variation, these lines increased their magnitude of integration and the proportion of variation associated with the direction of selection. This result is compatible with recent theoretical works on the evolution of covariation that take the complexities of genetic architecture into account. This result also contradicts the traditional view of the effects of selection on available covariation and suggests a much more complex view of how populations respond to selection.

KEY WORDS: Artificial selection, body size, cranium, experimental evolution, G-matrix, morphological integration, P-Matrix.

Evolutionary change can only occur in the presence of variation, and when dealing with complex multivariate phenotypes (consisting of multiple traits) the patterns and magnitude of genetic covariation between traits can radically influence the course of evolution (Lande 1979; Felsenstein 1988). The standing genetic covariation of a given population depends on its evolutionary history, and can be altered by selection, drift, mutation, and recombination (Turelli and Barton 1994; Jones et al. 2004, 2014). These changes in covariation, in turn, can alter how a population responds to further selection or other evolutionary processes. So, if we are to understand how populations evolve and how the current phenotypic diversity observed in nature came to be, then the

question of how genetic variation changes under various evolutionary processes becomes central to biology (Mitchell-Olds et al. 2007).

How a single trait responds to directional selection is a well-studied problem (Falconer and Mackay 1996). In general, we expect the response to selection to gradually erode genetic variation, as the many loci influencing a given trait go to fixation and, in the absence of mutation, preclude further evolutionary change (Bulmer 1971). If mutation is present and of sufficient magnitude, the variation removed by selection can be replenished and the rate of evolutionary change remains constant, at least for a time.

A theory on how directional selection and covariation interact to produce the response to selection on multiple traits was proposed by Lande (1979). This author related the standing genetic

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Insights from Systems Biology in Physiological Studies: Learning from Context

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Key Words

Physiology • Systems biology • Context • Epistasis • Top-down • Genetic background • Modularity • Interolog

Abstract

Systems biology presents an integrated view of biological systems, focusing on the relations between elements, whether functional or evolutionary, and providing a rich framework for the comprehension of life. At the same time, many low-throughput experimental studies are performed without influence from this integrated view, whilst high-throughput experiments use low-throughput results in their validation and interpretation. We propose an inversion in this logic, and ask which benefits could be obtained from a holistic view coming from high-throughput studies—and systems biology in particular—in interpreting and designing low-throughput experiments. By exploring some key examples from the renal and adrenal physiology, we try to show that network and modularity theory, along with observed patterns of association between elements in a biological system, can have profound effects on our ability to draw meaningful conclusions from experiments.

Introduction

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Low-throughput studies in experimental biology are a traditional approach in science and have been responsible for tremendous advances, from new medications to a better understanding of human behaviour. When Otto Loewi, in 1921, showed that acetylcholine was a neurotransmitter, he was using low-throughput techniques to show that one substance could perform a specific action, transmitting a message from one cell to the next [1]. Indeed, research in physiology still uses very similar approaches to identify new molecular pathways, proteins that could be targets for new drugs, mutations in genes that are good candidates for triggering diseases, and so on. Often, low-throughput studies are considered by the academic community as of higher quality when compared to high-throughput

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Modularity: Genes, Development, and Evolution

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Keywords

macroevolution, genotype–phenotype map, G-matrix, adaptive landscape, morphological integration

Abstract

Modularity has emerged as a central concept for evolutionary biology, thereby providing the field with a theory of organismal structure and variation. This theory has reframed long-standing questions and serves as a unified conceptual framework for genetics, developmental biology, and multivariate evolution. Research programs in systems biology and quantitative genetics are bridging the gap between these fields. Although this synthesis is ongoing, some major themes have emerged, and empirical evidence for modularity has become abundant. In this review, we look at modularity from a historical perspective, highlighting its meaning at different levels of biological organization and the different methods that can be used to detect it. We then explore the relationship between quantitative genetic approaches to modularity and developmental genetic studies. We conclude by investigating the dynamic relationship between modularity and the adaptive landscape and how this relationship potentially shapes evolution and can help bridge the gap between micro- and macroevolution.

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Animal behaviour

Costly learning: preference for familiar food persists despite negative impact on survival

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Animals often rely on events in their environment that provide information (i.e. experience) to alter their future decision-making in ways that are presumed to be beneficial. Such experience-based learning, however, does not always lead to adaptive decision-making. In this study, we use the omnivorous harvestman *Heteromitobates discolor* to explore the role of past diet on subsequent food choice and survival. We first tested whether a short-term homogeneous diet (rotten crickets, fresh crickets or dog food) influenced subsequent food choice (rotten cricket versus fresh cricket). We next examine the impact of diet on survival. We found that following experience with a homogeneous cricket diet, adult harvestmen displayed a learned preference for familiar food, regardless of whether it was rotten or fresh crickets; individuals experiencing dog food were equally likely to choose rotten versus fresh crickets. We additionally found that individuals that ate rotten crickets suffered shorter survival than those that ate fresh crickets. Together, our results suggest that the diet an individual experiences can lead to maladaptive food preferences—preferences that ultimately result in reduced longevity.

1. Introduction

Early modelling of foraging behaviour focused heavily on optimality, with models that predicted an animal's behaviour based on relative costs and benefits of alternative tactics [1]. These models assumed that animals have complete information about their environment; an unlikely assumption that led to proponents arguing for the importance of incomplete information and the role of experience in leading to behavioural changes [1]. More recently, it has been contended that formal theoretical modelling can be misleading or even wrong, as it often neglects the underlying mechanisms of behaviour, including psychological mechanisms such as learning and decision rules [2,3]. Additionally, many simple models do not incorporate the spatio-temporal heterogeneity, or complexity, of natural environments [3].

Indeed, animals are known to deviate from optimal decision-making across behavioural contexts—they are impulsive, they may not behave in ways that maximize rewards, and they may value alternative options irrationally (reviewed in [2,3]). One potential explanation for how and why animals engage in non-optimal decision-making may rely, at least in part, on the fact that animals often update their decision-making based on experience, or the processing of new information [4]—they learn. Additionally, seemingly irrational behaviour observed under simplified environmental conditions may be better understood

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A case study of extant and extinct Xenarthra cranium covariance structure: implications and applications to paleontology

Alex Hubbe, Diogo Melo, and Gabriel Marroig

Abstract.—Most of the mammalian diversity is known only from fossils, and only a few of these fossils are well preserved or abundant. This undersampling poses serious problems for understanding mammalian phenotypic evolution under a quantitative genetics framework, since this framework requires estimation of a group's additive genetic variance-covariance matrix (**G** matrix), which is impossible, and estimating a phenotypic variance-covariance matrix (**P** matrix) requires larger sample sizes than what is often available for extinct species. One alternative is to use **G** or **P** matrices from extant taxa as surrogates for the extinct ones. Although there are reasons to believe this approach is usually safe, it has not been fully explored. By thoroughly determining the extant and some extinct Xenarthra (Mammalia) cranium **P** matrices, this study aims to explore the feasibility of using extant **G** or **P** matrices as surrogates for the extinct ones and to provide guidelines regarding the reliability of this strategy and the necessary sample sizes. Variance-covariance and correlation **P** matrices for 35 cranium traits from 16 xenarthran genera (12 extant and 4 extinct) were estimated and compared between genera. Results show xenarthran **P**-matrix structures are usually very similar if sample sizes are reasonable. This study and others developed with extant therian mammals suggest, in general, that using extant **G** or **P** matrices as an approximation to extinct ones is a valid approach. Nevertheless, the accuracy of this approach depends on sample size, selected traits, and the type of matrix being considered.

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Introduction

The evolution of continuous traits is critically dependent on the genetic variance available in populations. Moreover, since traits in multicellular complex organisms often are not genetically independent (due to pleiotropy, epistasis, and linkage disequilibrium), these organisms cannot be regarded as a collection of independent parts being changed by evolutionary processes. Instead, an organism must be understood as a coherent whole, with relationships described by a covariance structure. Thus, traits usually evolve in a correlated way, and to fully understand the evolution of complex structures (like the mammalian skull) we need to deal with the inheritance of such multidimensional phenotypes (Fisher 1930; Wright 1931; Lande 1979; Lande and Arnold 1983; Falconer and MacKay 1996). Quantitative genetics provides a framework with which to understand multivariate

phenotypic character evolution, and this framework has been used to study many evolutionary questions in several extant and some extinct species, from plants to vertebrates (e.g., Lande 1979; Cheverud 1984; Lofsvold 1986; Arnold 1992; Steppan 1997; Goswami 2006; Goswami et al. 2014; Hansen and Houle 2008; Webster and Zelditch 2011; Porto et al. 2013; Armbruster et al. 2014; Haber 2015). Under this framework it is fundamental to determine the additive genetic variance-covariance matrix (hereafter **G** matrix), since it interacts with evolutionary processes to determine the rate and direction of evolution (Lande 1979; Lande and Arnold 1983; Cheverud 1984).

The **G** matrix is a symmetric square matrix in which each row/column represents a phenotypic trait measured in a population. The **G** matrix describes the additive genetic variance of each trait (i.e., unstandardized measure of heritability) on the diagonal and



SOFTWARE TOOL ARTICLE

REVISED **EvoIQG - An R package for evolutionary quantitative genetics [version 3; referees: 2 approved, 1 approved with reservations]**

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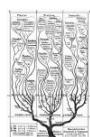
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Abstract

We present an open source package for performing evolutionary quantitative genetics analyses in the R environment for statistical computing. Evolutionary theory shows that evolution depends critically on the available variation in a given population. When dealing with many quantitative traits this variation is expressed in the form of a covariance matrix, particularly the additive genetic covariance matrix or sometimes the phenotypic matrix, when the genetic matrix is unavailable and there is evidence the phenotypic matrix is sufficiently similar to the genetic matrix. Given this mathematical representation of available variation, the `\text{EvoIQG}` package provides functions for calculation of relevant evolutionary statistics; estimation of sampling error; corrections for this error; matrix comparison via correlations, distances and matrix decomposition; analysis of modularity patterns; and functions for testing evolutionary hypotheses on taxa diversification.



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Fitness Trade-offs Result in the Illusion of Social Success

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SUMMARY

Cooperation is ubiquitous across the tree of life, from simple microbes to the complex social systems of animals [1]. Individuals cooperate by engaging in costly behaviors that can be exploited by other individuals who benefit by avoiding these associated costs. Thus, if successful exploitation of social partners during cooperative interactions increases relative fitness, then we expect selection to lead to the emergence of a single optimal winning strategy in which individuals maximize their gain from cooperation while minimizing their associated costs [2]. Such social “cheating” appears to be widespread in nature [3], including in several microbial systems [4–11], but despite the fitness advantages favoring social cheating, populations tend to harbor significant variation in social success rather than a single optimal winning strategy. Using the social amoeba *Dictyostelium discoideum*, we provide a possible explanation for the coexistence of such variation. We find that genotypes typically designated as “cheaters” [12] because they produce a disproportionate number of spores in chimeric fruiting bodies do not actually gain higher fitness as a result of this apparent advantage because they produce smaller, less viable spores than putative “losers.” As a consequence of this trade-off between spore number and viability, genotypes with different spore production strategies, which give the appearance of differential social success, ultimately have similar realized fitness. These findings highlight the limitations of using single fitness proxies in evolutionary studies and suggest that interpreting social trait variation in terms of strategies like cheating or cooperating may be misleading unless these behaviors are considered in the context of the true multidimensional nature of fitness.

RESULTS AND DISCUSSION

Social Success in *D. discoideum*

D. discoideum live as single-celled amoebae in terrestrial habitats, but when their food is depleted, large numbers ($\sim 10^6$) of individuals aggregate to form a multicellular fruiting body [13, 14]. The fruiting body is comprised of dead stalk cells that sacrifice themselves to hold aloft a ball of viable spores. Importantly, because fruiting bodies can contain a mixture of different genotypes, this is expected to lead to selection for exploitative social “cheaters,” which in *D. discoideum* have historically been defined simply as those strains that are overrepresented in the spore population of chimeric fruiting bodies [12, 15–20]. Consistent with earlier experiments [21, 22], we found that a set of genotypes isolated from a small geographic area in North Carolina [23] showed highly significant quantitative genetic variation (i.e., among-strain variation, H^2) in the relative number of spores produced by each strain after amoebae were mixed in a 50:50 ratio and allowed to undergo chimeric development ($H^2 = 0.35$, credible interval (CI) = [0.16, 0.62]; see Figure S1). This resulted in a linear (transitive) dominance hierarchy ($t_{tri} = 0.73$, $p < 0.001$; see [24]) with clear cheaters and “losers” when defined solely in terms of spore numbers. These observations thus raise a critical question: what processes maintain such variation in apparent social success in this species?

Trade-offs Exist between Spore Size, Number, and Viability

One mechanism by which variation in social success could persist is if fitness gains during social competition are offset by inherent costs in another context (e.g., social traits expressed in a non-social context or through pleiotropic links between different social traits or social and non-social traits). Such trade-offs could potentially lead to the coexistence of diverse social behaviors, where different strategies have similar overall fitness, and hence the variation is nearly neutral and persists at mutation-selection balance [25]. It is also possible that the traits mediating social interactions are shaped primarily by selection in a non-social context, which incidentally gives rise to variation in social fitness, but only as a neutral byproduct.

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Directional selection can drive the evolution of modularity in complex traits

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Modularity is a central concept in modern biology, providing a powerful framework for the study of living organisms on many organizational levels. Two central and related questions can be posed in regard to modularity: How does modularity appear in the first place, and what forces are responsible for keeping and/or changing modular patterns? We approached these questions using a quantitative genetics simulation framework, building on previous results obtained with bivariate systems and extending them to multivariate systems. We developed an individual-based model capable of simulating many traits controlled by many loci with variable pleiotropic relations between them, expressed in populations subject to mutation, recombination, drift, and selection. We used this model to study the problem of the emergence of modularity, and hereby show that drift and stabilizing selection are inefficient at creating modular variational structures. We also demonstrate that directional selection can have marked effects on the modular structure between traits, actively promoting a restructuring of genetic variation in the selected population and potentially facilitating the response to selection. Furthermore, we give examples of complex covariation created by simple regimes of combined directional and stabilizing selection and show that stabilizing selection is important in the maintenance of established covariation patterns. Our results are in full agreement with previous results for two-trait systems and further extend them to include scenarios of greater complexity. Finally, we discuss the evolutionary consequences of modular patterns being molded by directional selection.

variational modularity | G-matrix | quantitative genetics | pleiotropy | phenotypic correlations

Modularity, the organizational pattern found in many organisms, can be defined as the tendency for some parts to be more associated with each other than with other parts of the same organism. This type of modular organization can manifest at many levels, for example, between the bases of an RNA molecule (1), in the interaction between proteins (2), or in the covariance structure of continuous morphological traits (3). In each case, the type of association is different, but the modular pattern remains (4). Traits measured on a continuous scale that covary with each other can frequently be divided into variational modules. A variational module is characterized by higher correlations between traits in the same module and lower correlations between traits of different modules.

Modularity is an important concept in understanding the evolution of many biological systems. At the individual level, tension in producing a full, coherent organism, and having each of its parts performing a separate task subject to different selective pressures and requirements, shapes the association between traits (5). At the same time, the existing pattern of association also influences the response to a given selective pressure: Traits that are associated tend to change together (6, 7). The evolutionary consequences of these correlations are twofold. On the one hand, traits that perform a common function will tend to change in an orchestrated fashion, although interfering less with traits in other modules at the same time. On the other hand, if natural selection

promotes changes in only one trait of a module, the other traits within this module will suffer an indirect selection pressure and change as well, even if this response leads to lower fitness (8). This indirect response in other traits is due to their genetic correlation with the selected trait. Understanding how traits become associated, or correlated, is therefore a central question in evolutionary biology.

The question of how modular patterns evolve in each level of complexity is still open to intense scrutiny (9–11). In morphological systems, one condition for the evolution of variational patterns is the existence of genetic variation in the association between traits in a population. Pavlicev et al. (12) have presented empirical evidence of this variation by showing the existence of relationship quantitative trait loci (rQTLs). These rQTLs are genomic regions that show variation in epistatic effects, altering pleiotropic relations and the correlation between phenotypic traits. Using this concept and the multivariate breeder's equation, Pavlicev et al. (13) proposed a simple deterministic model for the evolution of association or dissociation between two traits in response to directional and stabilizing selection.

The variational pattern of genetic associations between continuous morphological traits is expressed in the additive genetic covariance matrix, called the G-matrix (8, 14). Covariance expressed in the G-matrix is the result of the sum and interaction of genetic effects on many traits, such as pleiotropic and epistatic effects, and shared development, leading to heritable variation and covariation. This variation interacts with evolutionary processes, such as drift and selection. The multivariate breeder's equation relates a population's G-matrix with its response to a given directional selection pressure (14). Under certain conditions,

EVOLUTION

Significance

Modularity, the tendency for the parts of many biological systems to be organized into semi-independent groups, is crucial to the understanding of diversification and the interaction between a population and its environment. In particular, a population's response to selection is dependent on its modularity pattern, which, in turn, is molded by selection. How these modular patterns evolve is therefore a central question in biology. We show, using novel individual-level simulations, that directional selection is very efficient at restructuring variation and creating modular patterns in continuous traits and that stabilizing selection can maintain established patterns.

Author contributions: D.M. and G.M. designed research; D.M. and G.M. performed research; D.M. contributed new reagents/analytic tools; D.M. analyzed data; and D.M. and G.M. wrote the paper.

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Data deposition: Full simulation runs and code are available from the Dryad Digital Repository: doi.org/10.5061/dryad.3cb81. Code is also available at github.com/fem-usp/evomod. R package for analyzing results can be found at github.com/fem-usp/evomod-r.

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MODULARITY, NOISE, AND NATURAL SELECTION

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Most biological systems are formed by component parts that are to some degree interrelated. Groups of parts that are more associated among themselves and are relatively autonomous from others are called modules. One of the consequences of modularity is that biological systems usually present an unequal distribution of the genetic variation among traits. Estimating the covariance matrix that describes these systems is a difficult problem due to a number of factors such as poor sample sizes and measurement errors. We show that this problem will be exacerbated whenever matrix inversion is required, as in directional selection reconstruction analysis. We explore the consequences of varying degrees of modularity and signal-to-noise ratio on selection reconstruction. We then present and test the efficiency of available methods for controlling noise in matrix estimates. In our simulations, controlling matrices for noise vastly improves the reconstruction of selection gradients. We also perform an analysis of selection gradients reconstruction over a New World Monkeys skull database to illustrate the impact of noise on such analyses. Noise-controlled estimates render far more plausible interpretations that are in full agreement with previous results.

KEY WORDS: Adaptation, models/simulations, morphological evolution, pleiotropy, quantitative genetics, selection—natural.

The study of biological systems and its component parts, whether molecules, cells, tissues, organisms and its forming parts, and even species and their interactions, is rapidly converging to the central theme of modularity. This refers to the connections among some of the component parts of a biological system (genes or morphological traits, for example) and the lack of such associations among other parts of the same system (Olson and Miller 1958; Berg 1960; Wagner et al. 2007). The notion that interacting parts are not independent is intuitive and appears early in the history of Biology (see Mayr 1982). Therefore, modularity is quickly becoming one of the central questions in modern biology (Wagner et al. 2007; Klingenberg 2008) and a point of convergence of various specialties and areas (Mathematics, Statistics, Genetics and Genomics, Evolutionary Biology, Ecology, Biochemistry, and Physiology).

In biology, several types of modules have been recognized, including (1) functional, consisting of characters or features that

act together on performing a task or function and are quasi-autonomous in relation to other functional sets; (2) developmental, which corresponds to parts of an embryo that are relatively autonomous with respect to pattern formation and differentiation, or an autonomous signaling cascade; (3) variational, composed of characters that vary together and are relatively independent of other such sets (Wagner et al. 2007).

The study of modularity is centered on statistical estimation of association among traits (Olson and Miller 1958; Berg 1960). Whether such association is measured by correlation, covariance, or distance/similarity measures, it is usually represented by matrices. Even if a particular system or network does not present a modular structure or is not being interpreted under this theory, associations among traits, parts, genes, or lineages will still be quantified by statistical association or dissociation matrices among these elements. We will focus here on correlation or covariance matrices (from now on **C-matrix**) among variables, although the

Selection Response Decomposition (SRD): A New Tool for Dissecting Differences and Similarities Between Matrices

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Abstract Genetic and phenotypic variance/covariance matrices are a fundamental measure of the amount of variation and the pattern of association among traits for current investigations in evolutionary biology. Still, few methods have been developed to accomplish the goal of pinpointing in which traits two matrices differ most, hampering further works on the field. We here described a novel method for dissecting matrix comparisons. This method is called Selection Response Decomposition and is an extension of the random skewers in the sense that evolutionary responses produced by known simulated selection vectors are unfolded and then compared in terms of the direct and indirect responses to selection for any trait. We also applied the method in diverse case studies, illustrating its potential. Both theoretical matrices and empirical biological data were used in the comparisons made. In the theoretical ones, the method was able to

determine exactly which traits were responsible for the known a priori differences between the matrices, as well as where matrices remained similar to each other. Similar support could be observed in comparisons carried on between matrices produced from empirical biological data, since reasonable and detailed interpretations could be made regarding matrix comparisons. SRD represents an excellent tool for matrix comparisons and should provide quantitative evolutionary biology with a new method for analyzing and comparing variance/covariance patterns.

Keywords V/CV matrix · Random skewers · G-matrix · Selection gradient

Introduction

Evolution in complex systems, where many traits share a common genetic basis and/or interact to perform some function together, results from the interaction between evolutionary processes and within-population patterns and magnitudes of association among traits. Genetic and phenotypic variance/covariance (G- and P-matrices) and correlation matrices are a critical quantitative measure of association among traits in a system and, therefore, play a central role in evolutionary biology (Arnold et al. 2001). This led, in the past decades, to a research program focused on estimating G- and P- matrices and comparing them among populations and/or species (Steppan et al. 2002). While some debate sparked around the subject of how to compare those matrices (Cheverud 1988; Roff 1997; Phillips and Arnold 1999; Houle et al. 2002; Cheverud and Marroig 2007), few methods were developed to pinpoint where (in which traits) any pair of matrices differ and where they remain essentially similar.

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Chapter 11

How Does Modularity in the Genotype–Phenotype Map Shape Development and Evolution?



Diogo Melo

Abstract Traits do not evolve independently, as genetic and developmental associations affect the variation that is expressed in populations and that is available for evolutionary change. In this chapter, we explore the causes and consequences of structured variation, introducing the concept of modularity, exploring some possible causes for modular organization in different levels, and, finally, discussing how the introduction of new variation can evolve.

11.1 Evolution and Variation

Hence if man goes on selecting, and thus augmenting, any peculiarity, he will almost certainly modify unintentionally other parts of the structure, owing to the mysterious laws of correlation. Darwin (1872)

Evolution proceeds by many different processes, all of which depend on the variation present in natural populations. The probability of fixation or loss of a neutral variant due to drift depends on its frequency in a population. The increase or decrease via natural selection of the frequency of an allele that has an effect on fitness depends on the standing variation in that locus. Therefore, the fate of a new variant depends on the population in which the new variant appears, whether it is neutral or not. Advantageous variants that are quite frequent may be lost in small populations, while even the smallest advantage in fitness can guarantee that a rare variant will be fixed in very large populations. In an analogous way, the change in the distribution of a phenotype in a population depends on its standing variation, and the details of this variation can profoundly alter the evolutionary process. For example, consider a hypothetical selection regime that operates as to increase the length of the left arm of the individuals in a population. Individuals that have a long left arm leave more

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Modularity and Integration

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Glossary

Developmental module Performs a specific role in developmental processes and corresponds to a set of cells, genes, or tissues that are relatively independent with respect to pattern formation and differentiation, or an autonomous developmental signaling pathway.

Evolutionary modules Sets of phenotypic elements evolving in coordinated fashion, because the elements are inherited together or because they are jointly selected.

Functional module Sets of traits or features that interact to perform some discrete function or task.

Genetic architecture Refers to the pattern of genetic effects that underlie the variation for a given set of phenotypic characters and its variational properties. A description of genetic architecture may include statements about gene and allele number, the distribution of allelic and mutational effects, and patterns of pleiotropy, dominance, and epistasis.

Genetic modules Sets of traits that are modular due to pleiotropy or linkage disequilibrium.

Genotype–phenotype map Depicts relationship between genetic variation and phenotypic variation; that is, it specifies which locus or loci affects each trait or traits.

Internal stabilizing selection Stabilizing selection due to the interaction of the phenotype with other internal characteristics of an organism, and is related to the need for

coadaptation of traits to one another rather than to the external environment.

Linkage disequilibrium The nonrandom association of alleles at different loci.

Morphological integration Refers to the cohesion or association among morphological traits that are related functionally and/or developmentally. Traits that are integrated tend to covary together, and so this results in higher correlation between these traits when compared to traits that are not integrated.

Pleiotropy A single locus affecting two or more phenotypic traits.

Quasi-independence (quasi-autonomy) A lower than average grade of connectedness, for example, the elements of modules are highly interconnected, while being less connected to other modules. This 'quasi independence' may allow one character to change without affecting others.

Quantitative Trait Loci (QTL) Refers to DNA loci that affect quantitative traits.

Variational modules Set of covarying traits that vary relatively independently of other sets of traits. The reason for this relative independence of different sets of traits, or modules, is that pleiotropic loci with effects on traits belonging to different modules are less frequent than those within modules. These modules are recognized by higher correlations between traits in the same module and lower correlations between traits of different modules.

What Is Modularity and Integration?

Biology is rapidly embracing the challenge of dealing with multidimensional hierarchical systems as a way of moving forward and addressing questions that range from the genetic basis of diseases, behavior, or morphology, the ecological structure of communities, or the evolution of any of these features. To face this challenge we need both theoretical developments and methods capable of dealing with such complexity. At the core of all this lies the concept of modularity. In Biology, modularity refers to the pattern and magnitude of association among elements in a system. This pattern emerges whenever a high connectivity between some elements in the system exists, forming modules, and at the same time these same elements are more loosely associated to other elements that compose other modules. Modularity depends on the ability of a system to organize semi-autonomous parts, or even discrete elements, into a coherent whole. Modularity can be studied at nearly every scale of biological organization; and it has been described in a variety of contexts and observed in many model systems, in a wide range of disciplines and specialties. These include proteins (Han *et al.*, 2004), genes (Litvin *et al.*, 2009), cells (Hartwell

et al., 1999; Wagner, 1996), organs (Schlosser and Wagner, 2004), and ecosystems (Montoya *et al.*, 2006).

Here, we address modularity in the context of morphological quantitative traits and discuss the influence of genetic, functional, and developmental factors at this level. In this context, different parts of organisms can behave as modules because they exhibit some degree of independence, and are internally organized, reflecting their developmental origins and functions, as we will see later (Cheverud, 1996; Klingenberg, 2004).

Most of our current understanding of character correlations and on the evolution of complex continuous traits is influenced by the concept of morphological integration (Olson and Miller, 1951, 1958). Olson and Miller (1951, 1958) coined the term morphological integration to describe high levels of phenotypic correlation within subsets of morphological traits. Today, these sets of integrated traits related functionally and/or developmentally are termed modules. In a remarkable work addressing morphological variation and correlation in plants, Raissa Berg (1960) described a similar concept known as 'correlation pleiades.' As with morphological integration, correlation pleiades are based on the presence of high levels of