Communication

Nutritional Trade-Offs in *Drosophila*

Juliano Morimoto *

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Nutritional Trade-Offs in *Drosophila*

Short title: Nutritional Trade-Offs in Flies

Juliano Morimoto [1,2]

[1] Institute of Mathematics, School of Natural and Computing Sciences, University of Aberdeen, Fraser Noble Building, Aberdeen, UK AB24 3UE

[2] Programa de Pós-graduação em Ecologia e Conservação, Universidade Federal do Paraná, Curitiba, 82590-300, Brazil

Simple Summar: Animals regulate nutrient intake to meet physiological needs, but no single diet optimises all traits, creating the potential for "nutritional trade-offs." This study analysed how different protein-to-carbohydrate (PC) ratios affect traits in the fruit fly *Drosophila melanogaster* using data from the Geometric Framework of nutrition. Three nutrient regions were identified: low PC ratios (e.g., 1:8) that support longer lifespans but hinder growth and reproduction, high PC ratios (e.g., 1:1) that enhance development, body mass, and male reproduction but reduce lifespan, and intermediate PC ratios (1:1 to 1:8) maximise female reproduction and larval survival. These findings highlight trade-offs between lifespan and reproduction, suggest metamorphosis may help balance nutrient needs across life stages, and point to potential genetic conflicts between males and females over metabolic traits. This research advances our understanding of how animals respond to their diets to optimise specific traits, addressing key questions in evolutionary biology and health.

Abstract: Animals often regulate their nutrient intake according to physiological needs. There is evidence that different traits require specific nutrient blends, and that animals cannot always maximise all traits with a single diet ('nutritional trade-offs'). However, we still do not have a clear understanding of which traits might be involved in nutritional trade-offs. I compiled data from the Geometric Framework of nutrition literature on the ratio of protein and carbohydrates that maximise (best PC ratios) or minimise (worst PC ratios) several larval and adult traits in *Drosophila melanogaster*. Best and worst PC ratios clustered into three regions in the protein-carbohydrate nutrient space: (1) Low PC ratios (1:8 or higher) are best for lifespan but worst for growth or reproductive traits; (2) High PC ratios (1:1 or lower) are best for adult body mass, male reproduction and larval developmental time but worst for lifespan; (3) Intermediate PC ratios (between 1:1 and 1:8) are best for female lifetime egg production, female reproductive rate and larval survival. These findings support lifespan-reproduction nutritional trade-offs, highlight the potential for metamorphosis to solve nutritional trade-offs across life stages, and the potential for intralocus sexual conflict to emerge over the expression of metabolic genes.

Keywords: dipterans; energy metabolism; gene expression; comparative nutrition

Introduction

Animals acquire nutrients to subsidise their metabolic demands, but the quantity and ratio of these nutrients vary [1–4]. When animals cannot acquire nutrients in the quantity and ratio for all traits, there is the potential for conflict whereby animals need to balance their nutrient intake to maximise one trait at the expense of another (i.e., "nutritional trade-offs") [5–7]. Previous research has uncovered evidence to support the concept of nutritional trade-offs between reproduction and lifespan and reproduction and immune traits [5–13] and between reproductive traits that contribute to different sexual selection episodes [14–16] (see also [17]). Thus, there is a general assumption that

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nutritional trade-offs are ubiquitous and could play an important role in shaping animal nutrition and evolution.

However, previous work has largely studied nutritional trade-offs among only a limited number of traits (usually two or three), with few exceptions (see e.g., [18]). For example, the landmark paper by Lee et. al. [6] used the Geometric Framework of nutrition (GF) to comprehensively assess how the ratio of protein and carbohydrate (PC ratio) in diets modulated lifespan, reproductive rate, and lifetime egg production in female *Drosophila melanogaster.* Likewise, Maklakov et. al. [7] studied PC ratio effects on the expression of three traits (lifespan and two reproductive traits) in each sex of the cricket *Teleogryllus commodus*. These examples are representative of the wider literature (e.g., [10,12,14–16,19–21] and references therein) and continue to stimulate new studies that uncover insights into animal nutritional ecology in both basic and applied sciences [22–25]. Yet, it is also important to step back to try and unify our knowledge in a more general context to gain a proper overview of nutritional trade-offs across multiple traits within and between species [10,26]. In this regard, there is unmatched advantages to the work in model organisms like *Drosophila melanogaster* for which nutritional effects have been mapped across several traits in high resolution using the GF. By compiling what we know about *D. melanogaster* responses to diet from GF studies – which to my knowledge has never been done – we will gain the much-needed general insight about nutritional trade-offs that will help us interpret current knowledge and guide future work.

Therefore, in this study, I collated the PC ratio of diets that maximise (best) or minimize (worst) a wide range of traits in *D. melanogaster*, using my previous analytical methods to reconstruct and analyse GF landscapes [27,28]. My main goal was to characterize the potential for nutritional trade-offs by highlighting traits that have opposing responses to the same PC ratios. To achieve this, my assumption was that the *Drosophila* strains used across different studies responded were comparable. This assumption was necessary because I do not have the information of the genetic architecture of all lines in the published literature. It follows from this assumption that *Drosophila* strains respond similarly to different diets irrespective of genetic differences, which we know is not always true at least for highly inbred lines (e.g., [24]). I discuss the implications of this in the methods and discussion sections. Nevertheless, the findings of this work highlight the potential for nutritional trade-offs in *Drosophila* that will stimulate future work to uncover the causes and consequences for the ecology and evolution of this and other species.

Materials and Methods

Data

I included studies from the literature which used *Drosophila melanogaster* as model system and the Geometric Framework for nutrition as experimental design. I included studies that measure both food intake and that manipulated the macronutrient in the diet without measuring diet intake; the former approach was usually adopted by studies using adult flies while the latter, larvae. I also included studies with liquid diet that used the CAFÉ assay and studies with solid media. When possible, I used studies for which raw data was made available in the original publication. When the raw data was not available for lifespan, I used my previously validated approach to reconstruct GF landscapes to extract data that could be used to estimate PC ratios [27]. Table 1 lists the studies which were used and the traits that were studied. Raw data is provided in Data S1 in supplementary material.

Estimates of Peaks and Valleys

Using R version 4.3.2 [29], I used the Nutrigonometry models to estimate the best (peaks) and worst (valley) diets for the expression of the traits [28]. I plotted the average protein and carbohydrate estimate of peaks and valleys from different traits in the same nutrient space to aid visualisation of the potential nutritional trade-offs among traits. I estimated peaks and valleys for all studies individually and then average these estimates across different studies that measured the same trait to create a single estimates of PC ratios for the peak and valley (e.g., male lifespan in [19,30]). The best and worst PC ratio for male paternity share was estimated from [16] when males were the first (Paternity 1) or second (Paternity 2) to mate with females. I also estimated 'refractoriness' as the latency of females mated to focal male to remate with a competitor male when focal males were first to mate (i.e., which helps increase male paternity 1) and latency of previously mated females to remate with a focal male ('Latency (Remate)') when focal males were second to mate (i.e., for males to gain paternity 2) [see [16] for details]. All estimates of peak and valleys across traits were plotted in milligrams. All figures were done using the 'ggplot2' package version 3.5.1 [31]. As mentioned above, studies varied in multiple ways: genetic background of the *Drosophila* stock, diet composition (solid vs liquid), intake estimates. I therefore opted to not conduct statistical inferences as those would inevitably be biased.

Results

The distribution of peaks and valleys in nutrient space created three regions.

Region 1: High Carbohydrate, Low Protein Diets

Low PC ratios (PC ratio of ~1:8 or lower) maximised lifespan for both adult males and females as well as short-term female oviposition rate and male refractoriness (Figure 1). On the other hand, low PC ratios minimised male paternity 1, male and female adult body mass, larval developmental time and survival, and female ovariole number. Overall, low PC ratios maximise lifespan at the expense of most traits related to growth and male and female reproduction.

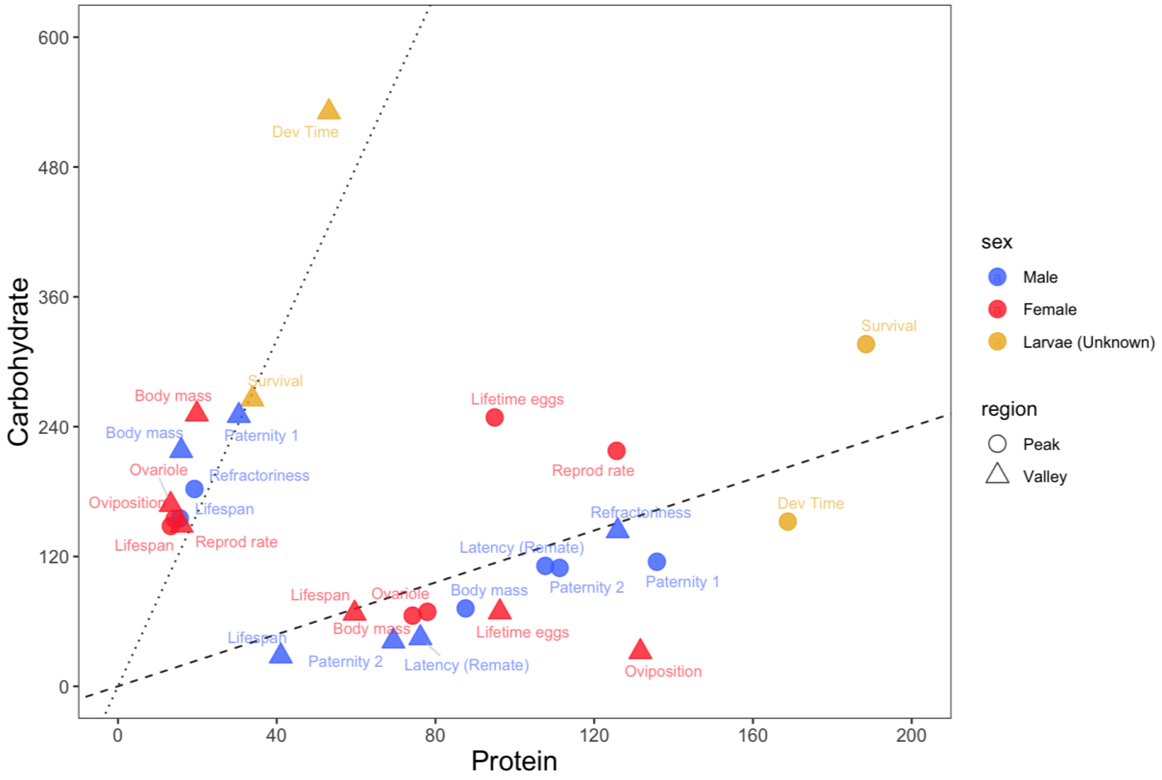

Figure 1. Nutritional trade-offs in *Drosophila*. The protein (x-axis) and carbohydrate (y-axis) estimates for the peaks (circles) and valleys (triangles) of each trait. Light blue = adult males; Red = adult females; Green = larvae. Black dashed line represents a PC ratio of 1:1.2. Black dotted line represents a PC ratio of 1:8.

Region 2: High Protein, Low Carbohydrate Diets

High PC ratios (PC ratio of ~1:1 or higher) maximised larval developmental time, adult body mass in both sexes, female ovariole number and, for diets with higher concentration of macronutrients, male paternity 2 and latency of females to remate with focal males (Figure 1). On the other hand, high PC ratios minimised lifespan in both sexes as well as short-term female oviposition rate. Male paternity 2 and latency of females to remate with focal males were also minimised in this region, but when diets had less macronutrients. Overall, high PC ratios maximised traits related to growth and reproduction at the expense of lifespan.

Region 3: Balanced Diets

Balanced diets with PC ratios between ~1:1 and ~1:3 maximised larval survival and female reproductive rate and lifetime egg production. No trait was minimised in this region (Figure 1).

Discussion

Animals must balance their nutrient intake to express fitness-related traits, which creates the potential for nutritional trade-offs among traits with competing nutritional needs [32]. Using the Nutrigonometry models on key GF studies from the *Drosophila* literature, I compiled information about the optimum PC ratio for a wide range of traits across life stages of the fly *D. melanogaster* and found a strong potential for nutritional trade-offs among traits related to lifespan, growth and reproduction. Specifically, there were three regions in protein-carbohydrate nutrient space where peaks and valleys of traits were found. Low PC ratios, which are diets richer in carbohydrates, maximised lifespan and short-term female oviposition rate but minimised all traits related to larval growth and survival, adult body mass and adult reproduction. High PC ratios, which are diets richer in protein, showed the opposite effect. Three traits were maximised at more intermediate PC ratios, namely female lifetime egg production (PC ~1:3), female reproductive rate (PC~1:2) and larval survival (PC ~1:1.5) (Figure 1). Flies are holometabolous insects and metamorphosis might help resolve nutritional trade-offs between life stages [33,34]. This is less clear within life stages and between sexes, as shown here for male and female reproductive and lifespan traits. Because males and females share the same genome, nutritional trade-offs could create the potential for intralocus sexual conflict [35–37], which might be pervasive across insects [27]. One way that intralocus sexual conflict could be resolved is through the modulation of the expression of metabolic genes in males and females [38], but we do not yet have a complete understanding of how nutritional trade-offs and sexual conflict interact to modulate organism-wide gene expression.

It will be interesting to study the molecular mechanisms and metabolic pathways which are up- and down-regulated when flies experience different diets. An ambitious but worthwhile goal is to create GF performance landscapes of genes and pathways using omics technologies to give us the necessary mechanistic insights of the drivers underlying nutritional trade-offs. TOR and AMPK pathways are two obvious higher level regulatory pathways to control nutritional trade-offs but what are the genes that modulate nutritional responses and trade-offs downstream of these major pathways [39–42]? My previous work has raised the possibility that the uric acid pathway modulates at least some diet- and density-dependent responses during *D. melanogaster* larval development [43], but the study lacks the high-resolution nature of GF experiments and is by no means comprehensive. Other studies have used the GF but did not gain similar level of molecular insights in either larvae (e.g., [18,20,21,44]) or adults (e.g., [6,19,30]). Molecular insights are crucial because we are now uncovering how diet composition interact with genes and their expression to modulate diet responses, growth and fitness. For example, Yurkevych et al., [45] showed changed in the expression of a wider range of genes that underpinned tolerance to high protein diets. Similarly, Francis et al., [23] showed that genetics plays a major role in diet-dependent responses in *D. melanogaster*. Likewise, Havula et al., [24] showed that genetics can strongly modulate larval development and survival, particularly in less favourable diets such as high-sugar diets. Investigating the effects of larval crowding – which is known to modulate protein availability – on *D. melanogaster* larval gene expression, I found transcriptomic-wide trade-offs across most major pathways including metabolism and immunity [46]. Similar findings were reported in *Drosophila simulans* [47]. It is possible that these transcriptomic-wide trade-offs emerge and are modulated by diets, but specifically how remains to be ascertained. Future work should take advantage of the molecular resources available for *D. melanogaster* to uncover further insights into gene-diet interactions.

Table 1. Literature that was included in this study.

Lead author	Year	Trait(s)	Stage	Sex	Strain	Reference
Lee	2008	Lifespan, reproductive rate, lifetime egg production	Adults	Females	Canton-S	[6]
Semaniuk	2018	Lifespan	Adults	Females	'IF'	[48]
Jensen	2015	Lifespan	Adults	Females, Males	Dahomey (Stuart Wigby)	[19]
Carey	2022	Lifespan	Adults	Females, Males	Dahomey (Nick Priest)	[30]
Rodrigues	2015	Adult body mass, Ovariole number	Adults	Females, Males	Outbred (Azeitão, Portugal)	[18]
Lihoreau	2016	Oviposition	Adults	Females	Canton-S	[49]
Morimoto	2016	Paternity share (P1 and P2), Refractoriness*, Latency to remate	Adults	Males	Dahomey	[16]
Kutz	2019	Developmental time, survival	Larvae	NA	Outbred (Ballina, Australia)	[44]

* There was no detectable statistical effect of diet for this trait in the original study by [16] but the trait was included here for completeness.

Even though there is growing evidence that genetics play an important role in diet-dependent responses, I assumed that the nutritional responses of the different *D. melanogaster* strains used across studies in the literature are comparable. There are not enough studies which consistently use the same genetic strain to allow for a study such as this. Therefore, the results presented here should be interpreted with caution, as there are likely unaccounted genetic effects underpinning the estimates of peaks and valleys. However, it is interesting that Havula et al., [24] reported higher larval survival variability in high-sugar diets across 196 *D. melanogaster* isolines. As shown here, this could be explained by the fact that diets with low PC ratio (i.e., sugar-rich diets) represent the worst diet for larval survival and therefore impose a much harsher developmental environment that could translate into higher variability in survival. Francis et al., [23] also found similar effect of genetic variability in more extreme (high sugar and high protein) diets. Together, these findings agree the argument I recently put forward that trait variability should increase when organisms feed in imbalanced diets [50]. This remains to be empirically tested.

Conclusions

There is strong potential for nutritional trade-offs between lifespan and traits related to growth and reproduction in *Drosophila melanogaster.* Future studies should focus on gaining mechanistic insights as in Havula et al., [24] and Francis et al., [23]. Furthermore, we need to gain a broader taxonomic understanding of how dietary responses are realised, and whether there are phylogenetic responses across taxa that can help us gain a broader understanding of how diet responses have evolved [27].

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Data S1. Raw data used in this study.

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Data Availability Statement: The data used in this paper is available as supplementary material.

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