Forthcoming in Biology & Philosophy

Everything in Moderation or Moderating Everything? Nutrient balancing in the context of evolution and cancer metabolism

Abstract

While philosophers of science have marginally discussed concepts such as 'nutrient', 'naturalness', 'food', or the 'molecularization' of nutrition, they have yet to seriously engage with the nutrition sciences. In this paper, I offer one way to begin this engagement by investigating conceptual challenges facing the burgeoning field of nutritional ecology and the question of how organisms construct a 'balanced' diet. To provide clarity, I propose the distinction between nutrient *balance* as a property of foods or dietary patterns and nutrient *balancing* as an evolved capacity to regulate nutrient intake. This distinction raises conceptual and empirical issues, such as what properties constitute this capacity and whether they are the same in all organisms. Additionally, while scientists use the term 'balancing', its intension and extension need further clarification. Based on the literature, the properties of external nutrient detection, internal sensing of nutrient levels, and organismal regulation could provide a basic recipe for nutrient balancing. Next, using an evolutionary lens, I examine nutrient acquisition in some prokaryotes, slime molds, simple multicellular eukaryotes, and in the quirks of multicellular metabolism to raise questions about the origins and universality of balancing. Finally, I build on this explication of balance and balancing by considering how obesity and cancer might respectively elucidate problems of organismal nutrient imbalances versus disrupted cellular nutrient balancing.

Keywords: Nutrient balance, nutrient balancing, nutritional ecology, evolution, multicellularity, cancer metabolism

Introduction

Several recognized subfields exist in the philosophy of the life sciences, e.g., philosophy of biology, medicine, immunology, microbiology, neuroscience, and oncology. However, the nutrition sciences have not received such dedicated attention. The general interest in the 'philosophy of food' (Curtin and Heldke 1992; Telfer 1996; Kaplan 2012; Borghini and Engisch 2022) has largely involved ethics (Chadwick 2000; Singer 2009; Sandler 2014; Thompson 2015; Chignell, Cuneo, and Halteman 2016), aesthetics (Korsmeyer 2002; B. C. Smith 2007; Scruton 2010), or the sociological and political factors influencing food research (Nestle 2007; Orland and Spary 2012; Scrinis 2013). Some have attempted to bring epistemology and philosophy of science to bear on concepts such as 'nutrient' (Cardenas 2016), 'naturalness' (Chadwick 2000; Siipi 2013), 'food' (Borghini and Piras 2021; Borghini et al. 2021), the 'molecularization' of nutrition (Ströhle and Döring 2010), as well as historical debates in the life sciences (Bognon-Küss 2019), the use of evidential standards (Jukola 2019a, b) and how to communicate scientific uncertainty (Folker et al. 2008; Folker and Sandøe 2008). While all important questions, they leave aside many conceptual and empirical challenges facing the nutrition sciences. One overarching aim of this paper is to show why nutrition should be further examined by philosophers of the life sciences.

As there are many ways to engage with the nutrition sciences, one perhaps obvious place to start would be with the notoriously difficult question: what constitutes a healthy diet? The medical sciences have approached this through epidemiological and controlled studies (whether in animals or humans), either to understand nutrient deficiencies or to suggest possible dietary compositions (Willett 1994; Katz and Meller 2014; Cena and Calder 2020; Hall 2020). However, the dizzying complexity involved in demonstrating that a given nutrient, let alone nutrient ratios, foods or so-called 'balanced' dietary patterns reliably produce health outcomes remains a perennial obstacle (Hoffmann 2003; Jacobs and Tapsell 2008; Ioannidis 2013, 2018; Mozaffarian and Forouhi 2018; Ludwig et al. 2018). I suggest that a more fruitful way into this debate would be to analyze a distinct, yet related, biological question: *how do organisms control food intake to construct a 'balanced' diet?* Promising approaches to this question are being articulated thanks to decades of evolutionary and experimental research in the field of 'nutritional ecology' and the unifying framework called 'nutritional geometry' (Simpson and Raubenheimer 1993, 2012). As we will see, this framework provides ways to measure and model how organisms navigate their nutritional environments, which, in turn, offers insights into how dietary variations impact health outcomes.

This research program, while promising, brings forth a series of conceptual and empirical challenges that can benefit from philosophical analysis. For instance, nutritional

ecology forces us to consider whether and how organisms display an evolved capacity to *regulate* their food intake in ways that ensure health and/or survival (Simpson and Raubenheimer 2012; Simpson et al. 2015). But how should 'balance' and 'regulation' be operationalized and tracked? And can we attribute this capacity to *all* organisms? For instance, 'balance' could track many things, such as getting enough nutrients or avoiding excesses, or it could be quantified through inputs and outputs in an energy equation—an old view still hotly debated (Hall et al. 2012; Hall and Guo 2017; Raubenheimer and Simpson 2019; Minderis et al. 2021; Ludwig et al. 2021). Balance might even suggest the platitude of eating 'everything in moderation', still generally promoted by nutritionists (Sizer and Whitney 2020) and public health researchers (Mente and Yusuf 2018). Moreover, while balance appears central to nutrition sciences[1], it raises an obvious question: "Balanced with respect to what—and when during the life course?" (Simpson et al. 2015, p. 18). Despite its centrality, the concept of 'balance' remains imprecise, if not entirely muddled.

This paper thus contributes to addressing three conceptual/empirical problems regarding how nutritional ecologists attribute this regulatory capacity to diverse organisms. First, to help explicate and operationalize[2] basic concepts, I propose the distinction between nutrient *balance* as a property of foods or dietary patterns and nutrient *balancing*[3] as an evolved biological capacity to regulate nutrient intake (section 1). This distinction helps specify what is at stake in developing a biological framework for nutrition while raising new questions, such as how balancing is linked to specific biological outcomes (such as fitness), what properties constitute balancing, and how they differ between organisms. After discussing some philosophical issues with the use of optimality models in this field, I propose that a definition of balancing based on the literature should include the ingredients of *detection* of external nutrient availability, internal *sensing* of nutrient levels, and directional *regulation* (matching of intake with usage).

With its intension more precisely delimited, I ask whether the extension can be clarified by situating balancing within evolutionary history (section 2). What is at stake, for

[1] Descriptions of a 'healthy diet' in nutrition textbooks present 'variety', 'moderation', 'calorie control', and 'adequacy' as aspects distinct from 'balance' (Sizer and Whitney 2020). Yet, each of the former can be reduced to balance, and a 'healthy diet' is quite often simply equated with a 'balanced diet' (see throughout (Ross et al. 2014)). Hence, balance, even if often vaguely defined or undefined, is arguably the central organizing concept.

[2] While some degree of conceptual 'imprecision' could facilitate the integration of research agendas (Neto 2020), it is nevertheless still clear that precision has benefits – e.g., avoiding ambiguity and/or producing fruitful generalizations. This is generally what the tradition of philosophical explication has in mind (Carnap 1963; Brun 2016) and I broadly see my project as an example of this.

[3] Some qualitative research investigating concepts in healthcare settings similarly distinguishes between 'balance' as a state and 'balancing' as a process (Lipworth et al. 2011). However, this focuses on how these terms are used by patients and healthcare workers rather than how they are operationalized in a biological context.

instance, in attributing this capacity to orangutans, locusts, and slime molds, let alone humans in our complex social-cultural milieu (Raubenheimer and Simpson 2020)? While the variety of species investigated may suggest the universality of balancing, some aspects of how nutrient acquisition works in prokaryotes, slime molds, and simple multicellular eukaryotes raises questions over whether balancing originated *before or thanks to* the multicellular constraints and inhibitions on nutrient intake and metabolism (Chantranupong et al. 2015; Bich et al. 2019). Tracking the evolutionary history of balancing allows me to pose new questions for nutritional ecology, e.g., whether balance is regulated externally or internally, what is being balanced, the mechanisms for achieving this regulation and their evolutionary significance (section 3).

Third, I suggest that the balance-balancing distinction can also be clarified by considering what it means for the evolved capacity to regulate intake to 'go wrong' (Matthewson and Griffiths 2017) (section 4). While nutritional ecology has primarily been applied to conditions with apparent links to nutritional *imbalances*, such as obesity (Simpson and Raubenheimer 2005; Gosby et al. 2014), a complementary, yet more direct route for understanding diseases linked to nutrient *balancing*, particularly on the cellular level, may be found in cancer. This latter perspective may open new avenues of research into the area of tumor metabolism (Cantor and Sabatini 2012), which has so far received minimal attention by philosophers of cancer (Bertolaso 2016; Vineis et al. 2017; Plutynski 2018; Strauss et al. 2021). The concluding section gathers these questions and suggests lines for future research.

Ultimately, by analyzing philosophical and scientific issues in how nutritional ecology reformulates a central problem in nutrition science, this paper illustrates the utility of bringing philosophy of the life sciences to bear on nutrition.

1. From nutrient balance to balancing as a biological capacity

As mentioned above, instead of focusing on the traditional question of whether a 'balanced' diet can be defined in terms of specific dietary components (e.g., some mix of fruits, vegetables, grains, meats, dairy, etc.), dietary patterns (e.g., 'Mediterranean' or 'Paleo' diets), or caloric intake and expenditure, my suggestion is to consider a distinct question: what are the challenges facing a scientific framework that tracks how 'balanced' intake may reflect organismal regulatory biology? Researchers in nutritional ecology claim that a 'balanced'[4] intake of nutrients is not simply a fortuitous accident of organisms finding the right nutrients in the right quantities, but is instead "actively abetted by regulatory behavior of the animal"

[4] Tangential to this, some philosophers question whether 'balance' is a useful concept in the ecological sciences (for instance (Cooper 2001)). As we will see, 'balance' has a rather specific meaning in nutritional ecology.

(Raubenheimer and Simpson 2016). To clarify this claim, I propose to distinguish between nutrient *balance* as a property of foods/meals and nutrient *balancing* as an evolved biological capacity to regulate the intake and utilization of nutrients: nutrient balance (defined below) is achieved through nutrient balancing. As I will discuss, while these concepts are used by researchers in this field, their intension and extension could be more explicit. As such, a philosophical explication of balancing will help clarify whether there are any specific properties or traits which could delineate this evolved capacity, and from there, how widely this concept can be applied. In short, the balance-balancing distinction specifies what is at stake in asking whether animals have "evolved regulatory mechanisms that ensure ingestion of a balanced diet" (Simpson and Raubenheimer 2012, p. 16).

1.1. Mapping the multidimensional nature of nutrition: operationalizing concepts

While experiments probing the organismal capacity to compose 'balanced' diets date back to the early 20th Century (Davis 1934; Richter et al. 1938; Rozin 1976), the 'nutritional geometry' framework developed within nutritional ecology in the past 30 years provides sophisticated ways to clarify the balance-balancing distinction (Simpson and Raubenheimer 1993; Raubenheimer and Simpson 1997; Simpson and Raubenheimer 2012; Raubenheimer and Simpson 2016, 2020). On a general level, this framework aims to experimentally test how or whether individuals of a given species 'select' foods (and nutrients) in specific ratios that promote survival and/or reproduction. They thereby operationalize 'balance' in terms of an optimal intake requirement or target: the ratio of macronutrients[5] as a percentage of caloric intake, e.g., 2 parts carbohydrates to 1 part protein, which produces the most biological benefit (typically 'Darwinian fitness'[6], but other outcomes are tracked – see subsection 1.2). It is with respect to this intake target that foods and dietary patterns are judged as '(im)balanced'.

As shown in Figure 1, there is a sweet spot whereby a specific macronutrient ratio (slightly more carbohydrates than protein) results in *optimal* fitness outcomes. This represents one optimal intake target or 'balanced' diet for this organism (in this case locusts). However, what is considered an 'optimal' food combination can vary relative to developmental history (Lee et al. 2012), life stage, level of activity, sex- and age-specific rates of growth, and other factors (Simpson and Raubenheimer 2012). As I discuss below, such variations often entail trade-offs in terms of optimizing one biological outcome at the expense of another.

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[5] Their focus is primarily on *macronutrient* ratios (proteins, carbohydrates, and fats) since these appear to produce the strongest links to health outcomes, but in theory their model can include any nutrient component (such as micronutrients or minerals), whole foods or dietary patterns (Raubenheimer and Simpson 2016, 2019).

[6] In their work, these authors broadly operationalize 'Darwinian' or evolutionary fitness in terms of rates of growth/development and the probability of surviving to a reproductive stage, which are then combined into a general 'performance index' (Simpson and Raubenheimer 2012, p. 32).

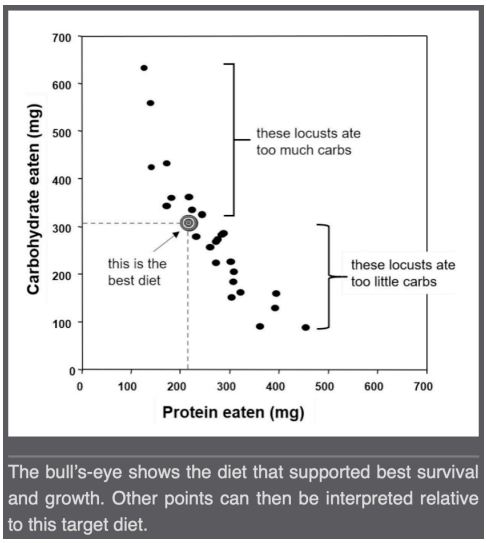

Figure 1. The ratio of protein to carbohydrate intake and its effects on growth and survival in locusts (reproduced from (Raubenheimer and Simpson 2020)).

Now, to achieve this target organisms can eat 'balanced' foods, which already reflect this ratio (e.g., 2:1 carbohydrate-protein), or 'complementary' foods (Simpson and Raubenheimer 2012). With the latter, organisms combine foods that are individually higher/lower in specific nutrients so that their mixture approaches the target. How this is achieved reflects differing nutritional needs. For example, specialists that require a narrow range of foods ('food selectors') generally seek and select already balanced foods, whereas generalists ('diet composers') face more complexities in finding and composing complementary foods into a balanced diet (Galef 1996). In each case, however, as the food in question varies in composition and as organismal demands change over time, we can track the benefits of an intake ratio that is optimized with respect to a given strategy.[7]

Thus, this framework tracks how individual foods, and their combinations into meals and dietary patterns, serve as the nutritional paths leading organisms towards or away from a fitness-promoting target of a 'balanced' diet. By varying the nutritional environment experimentally, scientists can observe how nutrient ratios produce specific outcomes. One way to show this is by tracking the costs of eating imbalanced ratios (also seen in Figure 1). This involves experimentally restricting organisms, such as locusts, to foods with differing macronutrient ratios and then allowing them to eat *ad libitum* until they molt and become

[7] While it may seem that specialists need only focus on energy intake instead of dietary composition, various studies have shown this to be inaccurate. Even if what is balanced is distinct or less complex (e.g., prioritizing fat instead of protein), and even if specialists are more sensitive to excesses than generalists, specialists still seem to seek a target intake ratio of specific nutrients (Simpson and Raubenheimer 2012, pp. 124–130).

adults[8] (Behmer et al. 2001; Raubenheimer and Simpson 2020). When faced with suboptimal choices, such as non-complementary imbalanced foods, organisms exhibit compromises or trade-offs. One is to overconsume one nutrient at the expense of others, e.g., locusts overconsume high-carbohydrate, low-protein foods until they reach their protein target, which increases feeding time, delays their development, and, beneath their exoskeleton, increases adiposity. One the other end, overeating on high-protein foods can result in being too lean, less energetic, and less likely to reach adulthood.

The key finding (observed in many species, humans included) is that locusts exhibit a strong protein appetite and are more willing to overeat carbohydrates to obtain enough protein (Simpson and Raubenheimer 2012).[9] Moreover, there are species-specific differences in terms of *which* nutrient is prioritized and the ecological factors influencing a given trade-off. The strength of nutrient appetites and the ratios comprising a given intake target will also vary across physiological, developmental, epigenetic, and genetic timescales (Raubenheimer et al. 2012). This has even led researchers to explore the effects of nutrient balance on longevity (Simpson et al. 2015). At least for fruit flies and mice, they appear to live longer not because they eat less food, as many studies on calorie restriction claim (Sohal and Forster 2014), but because of the ratio or *balance* of ingested nutrients (Solon-Biet et al. 2014, 2015). By tracking how different health outcomes, such as longevity vs. reproduction, reflect distinct 'nutritional optima' (Solon-Biet et al. 2015), these studies provide a more precise answer to the question: balanced, with respect to what?

These findings offer an important challenge to the tendency to equate the notions of 'balanced' and 'optimal/healthy' diets. While nutritional ecology aims to determine whether a specific nutrient ratio is balanced (as defined above), its framework ultimately undermines the view that there is *one* optimal diet, either for a species or an individual. Instead, as intake targets can vary throughout the life course and reflect changing needs, as well as physiological and ecological trade-offs, the focus is on *how organisms optimize nutrient ratios for distinct biological or health outcomes*, such as reproductive functions, longevity, immune

[8] Further support can be found in the old tradition of experimentally altering organisms, e.g., removing part of a rodent involved in nutrient regulation and observing whether/how food preferences change to redress this ablation (Richter and Eckert 1937; Abrams et al. 1949; Leshem et al. 1999).

[9] There are various reasons for why these researchers have chosen to focus on *nutrient* ratios instead of *energy* (or caloric) balance, which has been common in traditional ecological models, such as optimal foraging theory. One reason is that while overall energy intake may be a limiting factor for what is consumed in some cases, this fails to explain why organisms (whether specialists or generalists) overeat some foods/nutrients rather than others, such as when making trade-offs in suboptimal food environments or when they are inefficient in digesting or utilizing certain nutrients (Raubenheimer et al. 2009). Focusing only on calories thus risks confounding maximizing specific macronutrients with maximizing energy.

function, sickness behaviors, body composition, etc. (Simpson and Raubenheimer 2012; Solon-Biet et al. 2014). 'Balance' is thus relative to a given outcome at a given time and environment.

Next, the notion that organisms actively 'defend' an intake target and thereby exhibit the *capacity to balance intake* based on their evolved appetites for specific nutrients is studied in different ways. First, rather than restricting organisms to balanced/imbalanced foods, researchers allow them to freely ingest complementary foods. Under these conditions, locusts and other species consistently compose diets targeting an optimal or fitness-promoting ratio, as in Figure 2 (a) (Raubenheimer and Simpson 1997; Raubenheimer et al. 2012). A second test is to observe whether balancing occurs in organisms that can seemingly survive on anything and thus have no apparent need to balance intake (Raubenheimer and Jones 2006). For instance, when confined to imbalanced foods and then offered a variety, even extreme generalists like cockroaches (Figure 2 (b)) alter their food choices in a way that redresses these imbalances and thus behave like so-called "nutrient-seeking missiles" (Raubenheimer and Simpson 2020, p. 37). Likewise, caterpillars that were subjected to nutrient imbalances early in life, e.g., protein deprivation, not only altered their developmental program (towards heavier pupae) but also showed distinct preferences for foods with higher protein content, both of which helped to mitigate the effects of the imposed imbalances (Lee et al. 2012).

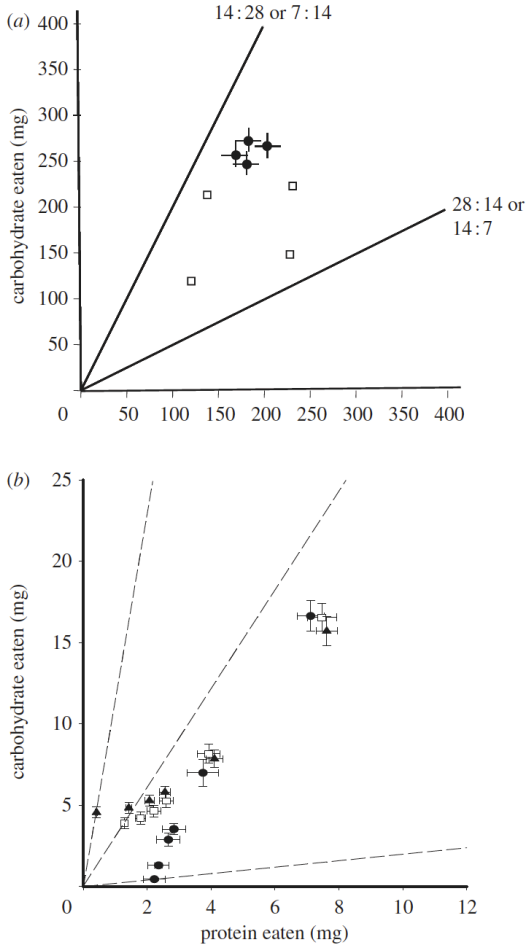

Figure 2. Two examples demonstrating regulation towards an intake target. In (a), the dark circles depict the results of locusts altering the amounts of given food pairings (represented by the lines or 'rails' indicating distinct nutrient ratios of proteins to carbohydrates) and converging on a target. The open squares show what would be expected if the locusts were *not* balancing. In (b), cockroaches were initially confined to one of three imbalanced foods (represented by the dotted lines/rails) and then given free choice of all three. The shapes represent groups of cockroaches starting from these distinct imbalanced foods, and the subsequent series shows their cumulative intake over time. By combining these foods, each group of cockroaches redressed their respective imposed imbalances and converged on the same target ratio (reproduced with permission from (Raubenheimer et al. 2012)).

Despite ambiguous results in early experiments (Galef 1991), similar findings have been reproduced in organisms as diverse as slime molds, Mormon crickets, wolf spiders, mice, cats, dogs, orangutans—and humans, at least in short-term studies—all of which are not only capable of composing diets that support their biological fitness, but can also eat to redress deficiencies, whether in the lab or the wild (Raubenheimer and Simpson 2020). As I will discuss below, the case of slime molds is interesting as it suggests ancient roots of this capacity (Dussutour et al. 2010), though it is unclear whether this constitutes 'nutrient

balancing' as observed in these other species. Nevertheless, this body of research suggests that what might appear to be anarchic or accidental feeding behaviors reflects evolved strategies for achieving balanced, i.e., fitness-supporting, nutrient intakes.

As a whole, the multidimensional framework of nutritional geometry proffers one way to incorporate 'appropriate' levels of complexity beyond single nutrient/component analyses (such as calories) while helping to isolate those interactions most strongly influencing a given outcome (Simpson and Raubenheimer 2012, p. 8; Raubenheimer and Simpson 2019). By studying how nutrient interactions (e.g., protein-carbohydrate ratios) affect organismal properties in varying environmental conditions and across life stages, this framework promises to integrate the numerous details concerning the nutritional requirements of the few species focused on by human or animal nutritionists with the unifying generalizations across multiple species coming from evolutionary biology and ecology.

1.2. Clarifying assumptions and specifying the intension of 'nutrient balancing'

As this framework holds such promise, the challenges it faces require further analysis. One could analyze the assumptions made by the 'optimality models' (Potochnik 2009) used in this framework which, as we saw, propose to link the phenotypic trait of balancing with fitness.[10] For instance, this research is clearly placed within an evolutionary context such that natural selection plays some causal role in the evolution of balancing:

> "If we assume that the nutritional responses of animals, including regulation to an intake target, rules of compromise, and postingestive regulation, have been fashioned by natural selection, it follows that an animal that achieves its intake target will enjoy maximal Darwinian fitness (or put another way, will suffer minimal fitness costs)" (Simpson and Raubenheimer 2012, pp. 20–21).[11]

Following Bolduc & Cézilly (2012), we might specify the key claims of the optimality model that nutritional ecology assumes: there is a behavior being observed (non-random, regulated food intake), this behavior is optimized in terms of the ratio of nutrients that maximize 'fitness' (or minimize costs), and this is done on various times scales and in specific ecological

[10] I thank an anonymous reviewer for highlighting this issue.

[11] Similarly: "We are confident that millions of years of natural selection have equipped animals with a physiology that is well qualified to estimate their own nutrient requirements" (Simpson and Raubenheimer 2012, p. 19). And: "How the animal allocates these nutrients is critical to fitness, and as a result natural selection has fashioned animal physiology to achieve a favorable strategy for investing its nutritional 'income' across its various requirements" (2012, p. 20).

conditions. One could ask whether these claims commit this field to some form of adaptationism (empirical, methodological, etc. (Orzack and Sober 2001; Lewens 2009)), or whether 'balancing' constitutes a distinct functional unit to be selected for (Galef 1991). While still largely appealing to adaptationist explanations, the fact that nutritional ecologists also describe how various factors, e.g., predation during specific life stages, food availability and varying nutrient content, nutrient-nutrient interactions, etc., may pose constraints onto whether/how balancing is achieved would suggest that 'selection dynamics' play some causal role in the evolution of balancing without necessarily excluding non-selective factors.

Relatedly, we might assess the challenge of measuring fitness effects. For instance, what is being measured when it is claimed that organisms that hit their nutrient targets typically maximize 'fitness' (or minimize its costs)? In many studies, there seems to be more emphasis on 'performance' outcomes (e.g., growth, longevity, metabolic status, body composition, etc. (Solon-Biet et al. 2014, 2015)) than on reproductive *success*, which is often measured via a proxy, e.g., egg production in female fruit flies (Lee et al. 2008). While some studies broadly track reproductive outcomes, e.g., in crickets (Maklakov et al. 2008) and fruit flies (Camus et al. 2017), it remains an open question of whether or how heritable variations in balancing (within and across species) influence differential reproduction. In some sense, nutritional ecology may thus more closely track contributions to health or survival than Darwinian fitness *per se*, possibly due to the immense difficulty of measuring the latter in the wild. It is unclear to what degree this poses a serious problem for this field, except in delimiting what it claims to measure.

Setting aside fitness measures, clarifying the very capacity that is supposed to be fitness-enhancing may help address the issue of *what* is naturally selected. For instance, I proposed that we distinguish nutrient *balance* and *balancing*. In this context, *balance* captures the species-specific, individually variable, and temporally varying ratios of nutrients that optimize organismal 'fitness' (or another outcome), and *balancing* captures an evolving set of traits allowing organisms to achieve these ratios. While researchers use the term 'nutrient balancing' (Raubenheimer and Simpson 1997; Cohen 2001; Mayntz et al. 2009; Dussutour et al. 2010; Johnson et al. 2013; Chen et al. 2018), or nutrient 'selection' (Richter et al. 1938; Vivas et al. 2003; Roberts et al. 2018), the inclusion criteria for what constitutes this capacity, and what does not, are often left implicit. Instead, this capacity and its potential mechanisms of realization are mainly inferred from correlations between nutrient ratio variations and

biological outcomes. This creates the conceptual challenge of clarifying the precise conditions that determine whether an organism exhibits balancing.

We might thereby investigate whether there are properties or traits that can translate these 'non-random feeding behaviors,' or the capacity to 'regulate' intake to a target, into more precise terms to better determine what this capacity is and how widely it can be applied. For instance, throughout this research it is claimed that various organisms, from bacteria to mammals, display species-specific capacities to *detect* key nutrients in foods (e.g., using taste receptors on appendages, tongues, and the gut), that (eukaryotic) cells have pathways to *sense* their nutritional state (e.g., energy intake or deficits) and can communicate this state to other cells, and that various organisms systemically *regulate* nutrient intake and allocation in a way that matches internal states with external availability (Simpson and Raubenheimer 2012, chap. 3). Some organisms can further fine-tune this directional feeding through learned associations (Raubenheimer et al. 2012). As I will discuss, the regulation aspect seems crucial as it raises the question of how much of a nutrient to ingest (i.e., when to *stop* ingesting). Thus, building on the mechanistic descriptions of distinct aspects of balancing provided by nutritional ecologists (Simpson and Raubenheimer 2012), one way to explicate this concept would be to restrict its intension to specific biological traits (which are realized through species-specific mechanisms):

- *Detection* of specific nutrients in the environment or in 'foods' (external 'tasting'),
- *Sensing* of an internal nutritional state (on cellular or systemic levels),
- *Regulation* of intake (and allocation, absorption, excretion) within a target range relative to changing needs and functional abilities (physio-behavioral 'matching').

Specifying the conditions for balancing to occur provides one way to delimit what balancing is (its intension) based on what is implicit in this research. These are the biological traits that made the evolution of 'balancing' possible. A focus on these traits reflects how nutritional ecology builds on older traditions in physiology that study how organisms maintain functional integrity amidst nutritional changes through notions like homeostasis, allostasis, negative feedback, etc. (Raubenheimer et al. 2012). This explication also suggests that there are species-specific regulatory mechanisms on 'lower' levels that realize the three traits mentioned above. The confluence of these three traits might then explain how the regulatory task of attaining and maintaining an intake target amidst external or internal nutritional challenges, i.e., *balancing*, is achieved at the organismal level (Raubenheimer et al. 2009), and can thus be tracked across different timescales.

From here, the utility of this explication can be assessed in terms of its ability to generate new questions, e.g., are these traits shared in all organisms and are they realized in the same way? How might 'balancing' differ across the tree of life? In the next section, I will use this explication to clarify the concept's extension and to question whether balancing, so defined, is "universal among all animals" (Raubenheimer and Simpson 2020, p. 30) or even all organisms (Simpson and Raubenheimer 2012, p. 36).

2. Nutrient acquisition in evolutionary context

Starting from a biological perspective, we can assume that the ability to obtain specific nutrient ratios that support growth and survival has an evolutionary history. In other words, since the capacity of 'balancing' appears to exist *across* species, we can ask whether and how it has evolved. In this section, I ask whether the extension of 'balancing' is or should be limited to some branches on the tree of life. To better reflect multiple stages in evolution, and thereby offset the tendency to focus on 'charismatic vertebrates' (O'Malley and Dupré 2007; Titley et al. 2017), I analyze nutrient acquisition in prokaryotes, slime molds, and simple multicellular organisms before evaluating the significance of nutrient *inhibition* in multicellular metabolism (Chantranupong et al. 2015; Palm and Thompson 2017). I argue that while all organisms have evolved ways to adapt to nutrient fluctuations such that achieving nutrient *balance* may optimize survival or fitness (Efeyan et al. 2015), it is unclear whether this is universally realized via the aforementioned ingredients of *balancing*.

2.1. Prokaryotes, nutrient detection, and resource exploitation

Starting with some prokaryotes, the challenges of nutrient variability and scarcity required the evolution of ways to detect and respond to overall nutrient concentrations and the presence of specific nutrients in their surroundings (Shi et al. 2021). Some bacteria, such as *Escherichia coli*, evolved the means to couple this nutrient detection to motility pathways via chemotaxis: nutrient presence triggers counterclockwise rotation of the flagella ('smooth' swimming), whereas nutrient absence triggers an alternation between this and clockwise rotation, resulting in a random 'tumble' towards higher nutrient concentrations (Sourjik and Wingreen 2012). In prokaryotes, whether motile or not, this tracking of external nutrient detection is coupled to basic mechanisms for sensing internal levels of metabolites, e.g., those involved in nitrogen assimilation such as PII proteins (Chantranupong et al. 2015). As these metabolite pools appear to be closely regulated (Ferenci 2007) and are sensitive to starvation (Shi et al. 2021), this might suggest a rudimentary capacity for nutrient balancing. However, while the cell cycle of bacteria can be adjusted in response to external triggers and internal

processes to maintain cell-size homeostasis (Adiciptaningrum et al. 2016), it remains an open question as to whether these organisms are matching intake with changing needs or are just exploiting favorable conditions *in which they are being 'balanced'*.

For instance, when nutrients are plenty, bacteria typically approach them, ingest, and replicate within ecological constraints; as nutrients are depleted or waste products accumulate in the milieu, replication slows or ends; and when nutrients are scarce, they tumble towards higher concentrations or reduce metabolic activity and enter quiescence (Shi et al. 2021) – only to be rapidly reactivated when nutrients are reintroduced (Neumann et al. 2021). Some degree of monitoring this *differential* between external and internal nutrient levels is thus likely to favor survival and replication, but the chief constraints on nutrient intake and motility reactions, and a given foraging strategy, seem to be imposed *externally* by nutrient availability (Wang and Levin 2009; Stocker 2012). Also, while scarcity can induce population-level mechanisms to control unbridled bacterial proliferation, e.g., triggering cell death (Engelberg-Kulka et al. 2006), this still leaves the issue of how prokaryotes respond to the *presence* of nutrients, since nutrients must be present to be balanced. Do these organisms stop ingesting when a target is reached, even when nutrients are plenty, or simply stop when resources run out?

Following the above explication, balancing intake is not simply the result of external nutrient distribution but entails active *regulation* (Simpson et al. 2015) – varying intake to match changing needs and resource allocation within a target range. If 'balancing' were to apply at this stage of life, we might observe these organisms modulating when and how much specific nutrients to ingest. *E. coli* appear capable of maintaining metabolite levels within limits (Yasid et al. 2016), but 'balancing' would seem to require coordinating distinct intake receptors for specific nutrients to be ingested in ratios that reflect needs and ensure optimal growth. The question is whether their seemingly default state of ingesting when nutrients are present entails that prokaryotes cannot discriminate. Thus, while detection and minimal sensing appear present, we can ask whether regulation is specific to phylogenetically later organisms, or whether the prokaryotic ability to couple internal mechanisms to nutrient gradients (Stocker 2012), an *opportunistic resource exploitation*, is just the earliest form of balancing in this nutrient ecology.

2.2. Eukaryotes, nutrient sensing, and the nutritional revolution

While these basic nutritional strategies have allowed prokaryotes to exist and thrive for billions of years (Gould 1996), nutritional history changed when some organisms accidentally 'ate' one another. A predominant, though still contested (O'Malley 2010), theory concerning

the emergence of unicellular eukaryotes centers around an endosymbiotic event whereby an archaeal cell engulfed ('phagocytosed') a bacterium, which would later become that cell's mitochondrion (Sagan 1967; Margulis 1975; Cavalier-Smith 2002). Some of these more complex cells with organelles, such as lysosomes or vacuoles, exhibited distinct feeding behaviors[12]—such as phagocytosis ('eating'), pinocytosis ('drinking'), and autophagy ('recycling' of inner components)—and new internal pathways to coordinate this *internal consumption* of nutrients with cell growth and proliferation (González et al. 2020). "Unlike prokaryotes, stuck in a trophic niche that leads 'merely' to exogenously driven biochemical flexibility, eukaryotes begin endogenously to revolutionize the very structure of nutrition by ingesting and consuming food sources internally" (O'Malley 2010, p. 220). As we will see, internal consumption for eukaryotes can also entail external digestion: as life began feeding on life, *what* was balanced, and the mechanisms involved, became more complex.

On the one hand, cells in eukaryotic organisms evolved ways to monitor their internal supply of nutrients, such as amino acids, ammonium, and glucose, which, when sufficiently present, upregulate growth processes. This monitoring is one function of the TOR (target-of-rapamycin) signaling pathway (Chantranupong et al. 2015). On the other hand, these cells had to detect whether the energy (as ATP) output by their mitochondria was sufficient to sustain their activity and, if not, to thereby inhibit growth processes, which is one function of the AMPK (AMP-activated protein kinase) signaling pathway. These two pathways evolved crosstalk mechanisms and can inhibit one another: when TOR is active, it downregulates AMPK, and vice versa.[13] Thus, building on the basic nutrient sensing capabilities in prokaryotes, eukaryotes evolved fine-tuned pathways to "connect the status of the external world to varied intracellular processes" (Chantranupong et al. 2015, p. 70), which are still present in the cells of multicellular eukaryotes, such as humans. Some suggest that the lysosome may have been central in relaying external and internal nutrient signals to these sensing pathways and thereby contributing to nutrient balance (Mony et al. 2016).

Such general pathways, as well as those targeting specific nutrients, allowed unicellular organisms, such as yeast, to navigate their nutritional environments and to use nutrients as signals dictating optimal growth programs (Broach 2012) and thus achieve some form of "nutritional homeostasis" (Saldanha et al. 2004). This reflected the evolutionary challenge to maintain an "appropriate balance" between antagonistic pathways, such as TOR

[12] While it is possible that phagocytosis-like mechanisms were already present in some bacteria (Shiratori et al. 2019), it is nevertheless generally seen as a key eukaryotic feature.

[13] There is some evidence suggesting that AMPK preceded TOR in evolution, with the latter being a eukaryotic invention (Roustan et al. 2016).

and AMPK (González et al. 2020, p. 472). Moreover, this stage of evolution further developed the ability to upregulate survival pathways when nutrients are scarce. This partially separates growth and survival (Wahrheit et al. 2011) and slightly decouples metabolism from nutrient levels. Thus, with this eukaryotic transition, *nutrient detection* abilities were coupled with fine-tuned *nutrient sensing* pathways, furthering the evolution of nutrient acquisition.

This leads back to the geometric framework discussed above. When nutritional ecologists consider the potential mechanisms driving nutrient ratio and health interactions across species, they repeatedly focus on nutrient sensing (e.g., mTOR, AMPK, IGF-1, etc.). The hypothesis is that the mechanisms by which varying macronutrient ratios contribute to organismal health or disease appear to run through these evolutionarily conserved pathways (Levine et al. 2014; Simpson et al. 2015). Interestingly, studies also appear to support the hypothesis that mTOR and AMPK are not simply fuel gauges but are 'balance' sensors responding to variations in the *ratios* of nutrients, such as glucose and amino acids (Kwon et al. 2004; Simpson and Raubenheimer 2009). As we will see in section 4, these pathways are important for understanding whether cancers are linked to disrupted nutrient balancing.

We can now ask: is balancing observed in unicellular eukaryotes? If so, what form does it take? In fact, the ability to direct motility and growth to not only detect specific nutrients (such as carbohydrates or amino acids) but to 'select' a specific ratio of them so as to "balance their own diet" (Bonner 2010) has supposedly been observed in unicellular eukaryotes capable of living as multicellular entities, such as the slime mold *Physarum polycephalum* (Dussutour et al. 2010). To assess their capacity to balance intake, slime molds were placed under different experimental conditions. After establishing that there is a ratio of protein to carbohydrates that ensures the densest growth patterns (nutrient *balance*), Dussutour and colleagues observed that slime molds consistently altered their growth and movement to combine imbalanced foods to reach this target. Moreover, when placed in a petri dish with foods containing different ratios, slime molds regularly migrated towards those closest to their target ('balanced' foods), thus seemingly displaying nutrient balancing.

These researchers point out that this ability to 'exploit' complementary food sources in relation to growth or developmental patterns is similar to that of bacterial colonies in which "the overall pattern of growth is influenced by varying the concentration of nutrient" (Dussutour et al. 2010): plentiful nutrients drive steady or rapid growth, nutrient scarcity or dilution drives filamentous growth and foraging, and nutrient starvation can induce either quiescence or complete stasis (Broach 2012). This raises the same question as for prokaryotes concerning how external nutrient levels shape or regulate intake. While slime molds, yeast, and bacteria, all appear to benefit from nutrient 'balance', what is unclear is whether or how

intake is regulated when nutrients are present. For instance, there is the interesting observation of yeast degrading receptors for a specific nutrient even when it is abundant (probably since it is easier to get enough with fewer receptors) and upregulating receptors for rare or lacking nutrients (Séron et al. 1999). For this to constitute 'balancing', one needs to demonstrate that these adjustments are made conjointly in ways that consistently result in a specific 'balanced' intake for optimal growth. While slime molds can detect specific nutrients and appear to select and combine imbalanced foods to reach an optimal intake target (Dussutour et al. 2010), how these nutritional cues are coordinated to achieve overall nutritional regulation remains unclear. If they indeed exhibit the capacity to modulate receptors or ingestion to achieve specific targets, then given what was discussed above concerning the roles of organelles, endocytosis, and nutrient sensing pathways in eukaryotic nutrient acquisition, it is likely that these structures and pathways are involved (Mony et al. 2016; Oettmeier and Döbereiner 2019). What needs to be clarified, then, is whether there are any coordinated adjustments and constraints modulating whether or how much of a specific nutrient unicellular eukaryotes ingest, which is important for regulating intake to a target. This form of *facultative resource exploitation* may be the next evolutionary step in nutrient balancing, but two issues require further consideration.

2.3. Multicellular diversity and the inhibition of intake

The first issue is that some phylogenetically later organisms still exhibit basic feeding behaviors. Organisms from the phylum Placozoa—the simplest multicellular animals, which appeared roughly 6-700 million years ago, compared to over 2 billion years for eukaryotes—appear to feed in ways resembling bacteria, protists, and some fungi: ingest when present. *Trichoplax adhaerens* uses chemotaxis to *randomly* yet preferentially direct movement towards food (typically cyanobacteria and microalgae, which are digested externally and endocytosed) and possibly certain amino acids (Smith et al. 2019; Smith and Mayorova 2019). There is clearly an ancient capacity to track the differential between external nutrient gradients and internal nutrient levels, and thus *exploit* environments that might redirect this differential to an organism's benefit.[14] But it remains plausible that organisms deploying chemotaxis, even multicellular ones like *T. adhaerens*, are directing themselves towards environments *in which they are balanced*, with intake timing and nutrient quantity regulated externally by nutrient availability, instead of controlling intake to match internal needs. One way to explain this feeding behavior in later (eu)metazoan organisms (Srivastava et al. 2008) is that balancing, or

[14] Like bacteria, *T. adhaerens* exhibits both individual and collective feeding (Fortunato and Aktipis 2019).

the traits making it possible, may have evolved multiple times in distinct lineages, with both balancing and (seemingly) non-balancing organisms appearing on the same phylogenetic branch.

This leads to the second issue, which concerns metabolism in more complex multicellular organisms where there is not only the need to respond to nutrient fluctuations and monitor intracellular energy levels, but to *coordinate* these inputs among organs and physiological systems (West et al. 2015). As most cells within multicellular eukaryotes, such as metazoans, are not in direct contact with the external environment, they evolved the capacity to sense nutrient levels within the cell and its extracellular milieu, and to communicate these levels to other cells and organs using signaling molecules, such as hormones[15], cytokines, or other growth factors: "With the onset of multicellularity, physiological processes evolved in metazoans that maintain homeostasis for the organism as a whole" (Chantranupong et al. 2015, p. 72). These molecular pathways enabled organisms to connect and coordinate intracellular sensing of nutrient levels with organismal feeding behavior and to regulate more precisely what to ingest and when.

Importantly, with this cooperation came constraint. The evolution of multicellularity brought the *cell-extrinsic* regulation of cell growth through not only cellular interactions but also intercellular space (Bich et al. 2019). This regulation of nutrient acquisition, usage, and cell growth by signaling molecules entails that cells are *instructed whether*, for instance, to turn on their survival and repair mechanisms (by upregulating AMPK) instead of growth and replication (by downregulating mTOR or IGF-1) in response to specific nutrients and, crucially, *even if nutrients are available*. This may have been a key step in the evolution of nutrient balancing as it meant that cells relinquished some of their metabolic flexibility, thereby relying on fewer nutrients for energy production and in turn developing distinct mechanisms to maintain "circulating nutrient levels within a narrow range" (Efeyan et al. 2015, p. 302). It is here that the *regulation* aspect of balancing plays a distinct role:

> "Because metazoan cells are commonly surrounded by nourishing body fluids, placing nutrient uptake under cell-extrinsic control constitutes a metabolic adaptation of multicellular animals *to prevent excessive consumption of the body's resources and to suppress aberrant proliferation*" (Palm and Thompson 2017, p. 234, emphasis added).

[15] While early forms of insulin pathways appear to exist already in some unicellular eukaryotes (Le Roith et al. 1980; Baig and Khaleeq 2020), their main function seems to be for regulating internal glucose homeostasis.

At this stage, nutrient levels are not regulated primarily through ecological constraints on autonomously living cells, but through *internal* constraints on cells competing for resources. In other words, thanks to cell-extrinsic regulation of growth, metazoans could further decouple their internal metabolic processes from environmental nutrient levels with the ability to allocate resources towards not only growth or reproduction, but also the *maintenance* of specific functions in a shared environment (Pfeiffer and Bonhoeffer 2003). This kind of regulated constraint on nutrient intake seems distinct from what we observe in unicellular organisms. While the latter can detect and select some of what they eat, the sheer presence of nutrients generally triggers opportunistic ingestion to sustain replication within ecological limits. In complex multicellular organisms, the creation of a microenvironment means that proliferation and quiescence are controlled internally and are thus decoupled from external nutrient cues. Here we see the possibility of "being quiescent in a plentiful environment" (Daignan-Fornier et al. 2021). The question is what this intake inhibition entails for the evolution of balancing: does balancing *per se* require this multicellular trait or is this just another form of balancing building on previous ones?

Future research could explore these possibilities. Does nutrient balancing, as rudimentary as it is, already exist in the exploitation of resource gradients by prokaryotes, unicellular eukaryotes, and simple multicellular organisms? If so, then nutrient balancing may be a universal capacity that evolved differently (or multiply) in different lineages and ecological conditions. Or are these early organisms just taking advantage of nutritional niches in which intake (when and how much of specific nutrients) is regulated *externally*, whereas balancing (i.e., detecting, sensing, regulating) only became possible in multicellular organisms when nutrient intake was constrained and controlled to maintain specific ranges of nutrient levels? Such testable questions become possible through this explication of nutrient balancing.

3. Using evolution to draw conceptual distinctions

Examining nutrient balancing across the tree of life suggests that in the broadest sense this concept tracks diverse solutions to the ecological constraints of nutrient variability; balancing is a function of how organisms interact with the constraints of their nutritional milieu. Whether or not balancing is coexistent with life itself, complex multicellular organisms nevertheless provided novel mechanisms by which organisms could fine-tune their

metabolism and behavior in response to these constraints. This evolutionary lens suggests a more complex recipe for balancing based on a refinement of the ingredients from section 1.2:

- Prokaryotes provided coupling mechanisms for *detecting* specific nutrients and thereby exploiting resource variations.
- Unicellular and simple multicellular eukaryotes fine-tuned their internal nutrient *sensing* or relative 'fuel gauges', which can modulate survival and allow for distinct forms of resource exploitation, possibly even balancing.
- The evolution of multicellularity, particularly in metazoans, provided an *internal regulation* of resources whereby cells are instructed whether/how much to intake, further decoupling metabolism from external cues—and clearly exhibiting balancing.

While organisms have evolved distinct strategies of balancing, such as error minimizing or nutrient maximizing (Simpson et al. 2002), there appears to be a widespread sensitivity to the *costs* of what (or how much) is ingested, with nearly all organisms responding to extremes in nutrient levels. No foods are *inherently* nutritious or noxious (Simpson and Raubenheimer 2012, chap. 5), but organisms nevertheless evolved ways to optimize nutrient intake and usage. In some organisms, these traits were further fine-tuned via appetite/taste/learning systems (Galef 1981; Provenza and Balph 1990; Simpson and Raubenheimer 2012) for species-specific and context-sensitive physio-behavioral regulation. As such, perhaps the central biological significance of balancing is in the evolution of distinct strategies to detect, select, and regulate the nutrients for growth and survival *at the least cost.* In other words, the evolution of capacities in simple organisms to detect and exploit nutrient concentrations, as well as the multicellular capacity to regulate internal resource consumption and control proliferation, may at their core reflect the challenge to navigate the trade-offs of nutrient ratios and toxicity: *obtaining the most beneficial nutrients (for a given outcome) at the least cost.*

This evolutionary lens highlights multiple distinctions concerning how nutrient scarcity and variation drove the evolution of nutrient balancing. For instance, we can distinguish the types of evolved responses to distinct ecological pressures, whether the locus of regulation for nutrient intake and usage is more exogeneous or endogenous, and whether the different foods/nutrients being balanced shape how or whether an organism exhibits balancing. Furthermore, we can specify the traits/mechanisms driving intake and allocation responses, as well as the evolutionary significance of these traits. Table 1 compiles these distinctions based on the broad characteristics found in the evolutionary lineages discussed

above. By considering these distinctions, we may better assess whether and how a given instance of responding to nutrient variation exhibits nutrient balancing.

	Response type	Regulatory locus	Intake Object(s)	Mechanisms	Evolutionary significance
△ **Prokaryotes**	Detection and exploitation	Partly endogeneous, reflects availability	Specific molecules or nutrients	External-internal detection, chemotaxis	Motility, replication
⌾ **Eukaryotes** (unicellular)	Detection, selection and exploitation	Increasingly endogeneous, reflects availability?	Various nutrients, simple organisms	External detection, internal sensing (fuel gauges), chemotaxis	Internal complexity, slightly decoupled survival
✤ **Simple Multicellularity**	Basic coordination, selection, exploitation	Increasingly endogeneous, reflects availability?	Simple organisms w/ varying nutrients	Fuel gauges, external/internal digestion, chemotaxis and foraging	Coordinated feeding behaviors, improved metabolic efficiency
✳ **Complex Multicellularity**	Metabolic constraint, fine-tuned coordination	Largely endogeneous, w/ decoupled metabolism	Complex organisms w/ varying nutrients	Regulated foraging, detection, inhibition and allocation	Functional coordination, nutritional trade-offs in growth, performance, survival, reproduction

Table 1. Distinctions concerning the nature, regulatory locus, nutrients/foods ingested, mechanisms of action, and apparent evolutionary significance of organismal responses to nutrient variability.

This perspective produces avenues that can benefit from philosophical investigation. First, we might analyze the evolution of eusociality whereby there appear to be layers of nutrient coordination between individuals and super-organismal units (Lihoreau et al. 2014). Does it make sense to attribute nutrient balancing to these latter units? Second, there could be important differences between *autotrophs*, generally understood as those organisms that create their own food by transforming sunlight (*phototrophs* (Tang et al. 2011)) and/or chemicals, and *heterotrophs*, or those which eat and absorb nutrients, or their fellow autotrophs (Persson et al. 2010). Is balancing the same in these categories? Do simple sponges and plants exhibit balancing or is their intake more exogenously regulated (Amtmann and Blatt 2009; Cui 2012; Shik and Dussutour 2020)? Relatedly, how does balancing differ in sessile versus mobile organisms (Zheng 2009; Saito and Uozumi 2020)? Future research would benefit from a thoroughly comparative framework of 'balancing' across species.

Until now, I only mentioned in passing that nutrient *imbalances* can have detrimental effects on organismal fitness or performance outcomes. Various philosophers and biologists have questioned whether measuring such effects in terms of fitness costs is sufficient to assess health outcomes (Stearns and Koella 2008; Méthot 2011; Kingma 2014; Giroux 2016), which I will largely set aside. Instead, I want to further test the utility of this explication by investigating the implications of disruptions to nutrient balance and balancing.

4. Disrupting nutrient balancing from without and from within

Having distinguished nutrient balance and balancing, and having investigated the evolved traits that constitute the latter capacity (detection, sensing, regulation), we should expect to see dysfunctions not only induced by nutrient imbalances but also specific to nutrient balancing. The focus in nutritional ecology has been on obesity. Below, I suggest that while obesity can help illustrate dysfunctions pertaining to nutrient *balance* from the 'outside-in', cancer is a more direct route to elucidate dysfunctions of *balancing* from the 'inside-out'.

First, obesity is generally seen as resulting from one form of imbalance – taking in more calories than expended – and increased intake may tip this balance more than reduced expenditure (Swinburn et al. 2009; Vandevijvere et al. 2015). The central question is why this occurs. Acknowledging the complex etiology of obesity,[16] nutritional ecologists suggest that one reason for the rising rates in Western societies is a mismatch between our evolved protein appetite and our energy-dense, protein-poor food environment (Simpson and Raubenheimer 2005; Gosby et al. 2014; Raubenheimer and Simpson 2019): in this environment, humans (like locusts) compromise by overconsuming energy-dense foods to gain limiting protein (for populational and experimental evidence, see (Gosby et al. 2014)). This mismatch[17] could take various forms: due to an *abnormal* environment (evolutionarily novel foods, e.g., ultra-processed or hyperpalatable foods), an *inhospitable* environment (foods lacking essential nutrients), or from a *heuristic failure* in developmental trajectories[18] (when nutritionally-deprived mothers give birth to children 'primed' for a nutrient-poor environment but are surrounded by food) (Matthewson and Griffiths 2017). While these mismatches come from distinct angles, the overarching result is caloric imbalance (Borer 2021).

Now, an individual can ingest too many calories and not become obese *due to* the 'buffering' aspects of nutrient balancing, e.g., post-ingestively upregulating metabolism, absorption, or excretion (Raubenheimer et al. 2012), thereby modulating energy expenditure. While there are costs to exceeding this balancing 'threshold', we can also observe dysfunctions to balancing even in normal or hospitable conditions (what Matthewson and Griffiths call *mechanism failures*): e.g., failures to detect nutrients in foods, defects in cellular 'fuel gauges' (mTOR or insulin signaling), or dysfunctional nutrient absorption, allocation, or storage—any of which can result in an inability to regulate intake to a target (Simpson and

[16] I set aside debates over how to define obesity and instead focus on broader issues explaining why it occurs.
[17] For a philosophical analysis of 'mismatch' and its use in nutritional ecology, see (Bourrat and Griffiths 2021).
[18] In this case, an individual could eat a 'balanced' (fitness-optimizing) diet and still develop obesity or metabolic disorders. This would dissociate, to some degree, fitness and health outcomes. However, the link to fitness can be maintained if we distinguish costs to *realized* vs. *expected* fitness (Matthewson and Griffiths 2017, p. 456).

Raubenheimer 2012). In these cases where 'internal' dysfunctions drive imbalanced intake, obesity may be a problem of both nutrient balance and balancing. Overall, however, obesity reflects organism-environment dynamics that, whatever the cause, lead organisms to ingest more than they expend (Hall et al. 2022).

At first glance, cancer also appears to be related to organismal nutritional imbalance. In attempts to explain the epidemiological associations between cancer and obesity rates, some scientists suggest that nutritional imbalances may reveal shared causal links (Marshall 2006; Font-Burgada et al. 2016; Zitvogel et al. 2017; Ringel et al. 2020). The hypothesis is that energy imbalance or 'overnutrition' may contribute to tumorigenesis through various pathways and their interactions, e.g., excess growth in adipose tissues, chronic systemic inflammation, impaired immune responses, and endocrine or hormonal disruptions. As I hinted at in section 2.2, nutritional ecologists suggest that some nutritionally-caused imbalances may disrupt cellular metabolism through the conserved nutrient sensing pathways of mTOR and AMPK (Simpson and Raubenheimer 2009). The implication is not that obesity is itself causing cancer, but that obesity and increased risk of cancer formation may share the common causes of chronic hypernutrition and its multiple downstream effects.

Now, it is important to disentangle tumorigenesis from nutritionally-caused imbalances. First, while both humans and non-human animals can develop obesity and cancer in poor or inhospitable food environments (Klimentidis et al. 2011; Raubenheimer et al. 2015; Sepp et al. 2019), it is clearly possible to consume a (fitness-optimizing) balanced diet and still get cancer from other causes (Blackadar 2016). Moreover, while hypernutrition may increase the risks for *some* human cancers, poor diets and their metabolic effects are not enough to explain why various other types of cancers occur (Calle and Kaaks 2004; Moore et al. 2014; Theodoratou et al. 2017). Thus, imbalanced dietary intake is neither a necessary nor sufficient condition for cancer formation.

Whereas nutritional imbalances may only partially contribute to shaping what and how some cancer cells eat from the 'outside-in', we could further clarify dysfunctions in nutrient balancing mechanisms by investigating how cancers involve *problems of cellular feeding* from the 'inside out'. In support of this link, consider that the dysregulations in cell growth and proliferation observed in cancers involve a series of metabolic alterations on various biological levels throughout cancer progression (Hanahan and Weinberg 2011; Al-Zhoughbi et al. 2014; Xiao et al. 2019; Altea-Manzano et al. 2020). Moreover, the hallmark of tumor metabolism describes forms of 'reprogramming' or 'rewiring' how cells and tissues respond to, acquire, and allocate nutrients (Cantor and Sabatini 2012; Pavlova and Thompson 2016; DeBerardinis and Chandel 2016). Thus, cancers appear closely linked to cellular

dysfunctions in nutrient balancing. One way to evaluate this potential link is to see how cancer metabolism pertains to the distinct traits of nutrient balancing outlined above. From there, we can ask whether metabolic imbalances in cancer cells also *result from* disruptions to these cellular balancing pathways. The upshot is not to implicate organismal nutrition as a direct cause of these cellular metabolic changes, but to better understand how this metabolic 'reprogramming' affects how cells, and potentially organisms, eat.

Interestingly, cancer metabolism appears to involve disruptions in each of the traits of nutrient balancing, which increasingly decouples cellular and organismal nutrition: with nutrient *detection*, cancer cells exhibit mutations in the cell-extrinsic control of nutrient uptake that disconnects cellular nutrition from nutrient availability and intercellular growth signals; they redirect nutrient *sensing* by constitutively activating mTOR or using AMPK to scavenge for or recycle nutrients to survive scarcity; and they exhibit much flexibility in terms of *regulating* which fuels they seek out and when (Pavlova and Thompson 2016; DeBerardinis and Chandel 2016; Faubert et al. 2020). In advanced stages of some cancers, these cellular changes can trigger various systemic or organismal effects, which are most evident in cachexia (Al-Zhoughbi et al. 2014): the increased proteolysis, lipolysis, autophagy, and apoptosis that degrade skeletal muscles and release nutrients for tumors also induce gut barrier dysfunctions and inflammatory cytokines, even altering satiety and taste signals—all of which impairs nutrient absorption and reduces food intake (Muscaritoli et al. 2010; Argilés et al. 2014; Berardi et al. 2021). Interestingly, cachexia is typically seen as an 'energy balance disorder', yet this imbalance persists *even when* total intake is controlled, due to the multilevel disruptions in how nutrients are balanced, which confirms that it is better seen as a disruption of balancing from the inside-out. While still controversial to describe cancers as 'metabolic diseases' (Coller 2014), cancers nevertheless progressively alter how cells and tissues respond to their nutritional environment (Elia et al. 2018; Faubert et al. 2020; Altea-Manzano et al. 2020).

Further questions arise and could be clarified in light of this theoretical framework. One longstanding debate in oncology concerns whether local and systemic metabolic changes in cancer cells and tissues *precede* or *result from* some of the typical oncogenic mutations and dysregulated growth signaling observed in many cancers (Gillies et al. 2008; Kroemer and Pouyssegur 2008; Taubes 2012; Ward and Thompson 2012; Haq 2014; Devic 2016; Pavlova and Thompson 2016; Lunt and Fendt 2018; Satriano et al. 2019). The question is whether key aspects of tumorigenesis are *specific to* altered metabolism such that the latter is not just a marker of tumor growth but is one maker of it. Clarifying why, how, and when nutrient balancing is disrupted in and by cancer cells might provide some insight into whether/how

tumor metabolism plays such a central role in tumorigenesis and progression.

It would be interesting to investigate, for example, whether these cellular balancing pathways are disrupted early and consistently enough to produce predictive 'metabolic profiles' or biomarkers (Liesenfeld et al. 2013; Patel and Ahmed 2015), and whether these disruptions occur in the same way or in a specific order in all or most cancers. One could hypothesize that the disruptions occur in the 'reverse' order predicted by recent, though contested, theories of cancer (Nedelcu 2020; Lineweaver et al. 2021) such that multicellular nutrient regulation pathways are disrupted before 'eukaryotic' nutrient sensing and 'prokaryotic' nutrient detection/uptake. Relatedly, we might even consider whether cancer cells, or entire tumors, exhibit optimal foraging strategies (Amend et al. 2018). Finally, it remains an open question as to how to unify the context-dependency and heterogeneity of metabolic phenotypes and the opportunistic cellular feeding behaviors that evolve with cancer progression and metastasis (Pavlova and Thompson 2016; Faubert et al. 2020). The upshot is that nutritional ecology has much to offer oncology, and such testable questions can be raised when cancer is viewed not just in light of nutrient (im)balance but in light of nutrient balancing.

5. Concluding questions and future suggestions

Bringing these strands together, the central aim of this paper was to analyze research claiming that organisms have the capacity to navigate their nutritional environment to construct a 'balanced' nutrient intake that supports their health and survival. This already brought two interesting findings that could be further explored philosophically; one being that nutrient ratios might be more important for longevity than calorie restriction, and the other being that there is no single optimal diet, but only diets optimized for distinct outcomes. After questioning the optimality models used in nutritional ecology, I then clarified that *balancing*—defined based on the traits of nutrient detection, internal nutrient sensing, and directed regulation—is a capacity allowing for the optimization (or *balance*) of nutrient intake for different ends. While my aim was to make explicit what was already implicit in the scientific literature, the ingredients used to clarify the intension of balancing are only one possibility and could be further refined or modified based on other considerations.

Concerning this concept's extension, various questions were raised concerning when in life's history 'balancing' emerged. Viewing this capacity through an evolutionary lens, I questioned whether the rudimentary forms of nutrient acquisition in prokaryotes, unicellular eukaryotes, and even some simple multicellular organisms, are sufficient to constitute balancing, or whether this capacity only became possible through the multicellular ability to

constrain and control nutrient intake. Do prokaryotes coordinate distinct intake receptors for specific nutrients to be ingested in ratios that reflect needs and ensure optimal growth? Does this capacity differ in unicellular and multicellular eukaryotes? Eukaryotic slime molds appear to balance intake but more research is needed into the regulatory aspect whereby intake of different nutrients is controlled to achieve specific ratios. While it is possible that balancing has evolved multiple times in distinct forms, this kind of control seems most apparent with later multicellular organisms such as metazoans. Building on the above intensional and extensional analyses, philosophers may thus contribute to developing a rigorous comparative biology of balancing whereby distinctions are drawn among, for example, autotrophs and heterotrophs, mobile and sessile organisms, and even social organisms or super-organisms.

Next, I suggested that bringing the balance-balancing distinction to bear on obesity and cancer might help clarify ways in which the evolved capacity to regulate intake to a target can 'go wrong'. While obesity pertains largely to organismal nutrient imbalance coming from the outside-in, cancer may better elucidate disruptions to nutrient balancing from the inside-out through changes in cellular feeding. Going forward, bringing nutritional ecology into oncology might provide new insights concerning the possible links between nutrient balancing and the metabolic phenotypes observed in cancer formation and progression. We might even ask whether the question of attributing balancing across the tree of life could help specify in what sense, if any, cancer cells exhibit a 'reversion' to unicellular metabolic phenotypes (Trigos et al. 2017; Okasha forthcoming).

Zooming out, one issue that was mentioned in passing at the end of section 1.1 is that nutritional ecology is put forth as an 'integrative' and 'unificatory' field (Raubenheimer et al. 2009, 2012; Simpson and Raubenheimer 2012), providing a framework to unify the detailed analyses of the nutritional physiology of some species with the broad generalizations in evolutionary biology and ecology. While this field nicely illustrates the insight that nutrition "touches, links, and shapes all aspects of the biological world" (Simpson and Raubenheimer 2012, p. 2), it remains an open question as to how to integrate these historically and methodologically distinct traditions. Philosophers of science might thus further analyze this project to determine what kind of unification is involved and how to evaluate its success.

While this paper analyzed balancing in diverse species, it is important to acknowledge the epistemic challenges closer to home: "Measuring the human intake target throughout the life course remains one of the major challenges in nutrition" (Simpson and Raubenheimer 2012, p. 94). Consequently, what is being balanced by/within an organism (human or not) and the context in which this occurs require careful consideration, for which a rigorous philosophy of/in the nutrition sciences could prove useful. In the end, even if 'nutrient

balance' cannot be boiled down to specific dietary components or a universally beneficial nutrient ratio comprising *the* optimal diet, a scientifically-informed philosophical study of balance and balancing raises many questions beyond just eating 'everything in moderation'.

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