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Nutritional ecology and the evolution of aging

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ABSTRACT

Considerable progress has been made in understanding both evolutionary and mechanistic aspects of biological aging, although the two areas remain poorly integrated. We suggest that a greater emphasis on ecology can help to remedy this, by focusing on the interface between biological mechanisms and the environments in which they evolved by natural selection. Among the most salient aspects of the environment relevant to aging is nutrition, and yet in the bulk of aging research nutrition is coarsely represented as dietary restriction or caloric restriction, without consideration for how specific components of diet, beyond "energy" (the undifferentiated mix of macronutrients), are driving the observed effects. More recently, it has become clear that specific nutrients (notably amino acids) and interactions among nutrients (i.e., nutritional balance) play important roles in the biology of aging. We show how a method developed in nutritional ecology, called the Geometric Framework for nutrition, can help to understand the nutritional interactions of animals with their environments, by explicitly distinguishing the roles of calories, individual nutrients and nutrient balance. Central to these models are the active regulatory responses that animals use to mediate between variation in the nutritional environment and fitness-related consequences such as lifespan and reproduction. These homeostatic responses provide a guide for researchers that can help to link the biological mechanisms with evolutionary processes in the context of a multi-dimensional nutritional environment.

1. Introduction

The almost universal phenomenon of aging is considered one of the enduring unsolved problems in biology (Dev, 2015). Broadly, the study of biological aging has clustered within two general areas (Hughes and Reynolds, 2005; Monaghan et al., 2008; Flatt and Schmidt, 2009). One sub-field applies evolutionary theory and techniques to understand how a process so detrimental to health, reproduction and survival can be reconciled with evolution by natural selection. The other is mechanistic, aiming to understand the underlying molecular, cellular and physiological processes, often in laboratory studies using experimental model systems. Although there have been significant advances over recent years both in evolutionary and mechanistic research into aging, important challenges remain. Arguably, however, none of these challenges considered separately would qualify for the list of major unsolved problems in biology (Hayflick, 2007a, b). Rather, as in other areas of life-history research, the big questions lie at the intersection of different sub-fields (Flatt and Heyland, 2011): how to reconcile the evolutionary and mechanistic theories of aging, and how to apply these theories and their reconciliation to ensure that gains in human healthspan are commensurate with gains in lifespan (Cesari et al., 2013).

Increasing attention is being focused on the question of how evolutionary and mechanistic strands of aging research can be integrated into a single framework to produce an over-arching theory of biological aging (Partridge and Gems, 2006; Flatt and Schmidt, 2009). An important, but under-represented area for addressing this challenge is the science of ecology. Ecology focuses both on the interactions that take place between organisms within ecological assemblages (broadly referred to as "community ecology", Stroud et al., 2015), and the details of how specific traits of organisms interact with biotic and abiotic aspects of the environment (sometimes referred to as "functional ecology", Calow, 1987; Raubenheimer and Boggs, 2009). Between functional and community ecology is "population ecology" (Krebs, 2015), which deals with questions regarding the distributions of populations of species in space and time. The functional-population-community ecology triumvirate is intimately associated via evolution (McLachlan and Ladle, 2011), because biological traits, such as the proximate factors influencing lifespan and the schedule of reproduction, evolve through differential success within populations in the context of community interactions (e.g., foraging and predation). Ecology therefore provides a body of theory that is essential for linking organism traits with evolution, as is recognised in the integrative field of evolutionary ecology (Fox et al., 2001; Cheplick, 2015).

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In many, if not most cases, ecology is already implicit in both mechanistic and evolutionary studies of aging. For example, the majority of experimental manipulations that generate variance in physiological responses emulate variance in the environment (e.g., dietary restriction); likewise, many of the processes that evolutionary theories of aging address are ecological — prominent among these are the risk of extrinsic mortality (Shokhirev and Johnson, 2014) and resource availability (Kirkwood, 1977). Ecology can thus provide a substantial link to bridge mechanistic and evolutionary theories if greater emphasis is placed on exploring the multi-faceted and dynamic interface between evolved mechanisms and the environment in which they operate.

The strong evidence that senescence is a real phenomenon in wild populations (e.g. Nussey et al., 2013) opens the way for a deeper integration of ecology with aging research. This has already begun, to the extent that in recent years there have appeared journal special issues dedicated to the subject (Monaghan et al., 2008; Fletcher and Selman, 2015). However, a large proportion of research into aging concerns nutrition, but the ecological aspects of the relationship between nutrition and aging remain scantly developed. In the most common model, dietary restriction, animals that are restricted in availability of macronutrients while provided sufficient micronutrients usually have extended lifespans relative to unrestricted controls (McCay et al., 1935). And yet the nutritional causes relating dietary restriction to senescence and lifespan are poorly understood. A widespread assumption is that energy is responsible, as suggested by the commonly used synonym for dietary restriction "caloric restriction" (Speakman and Mitchell, 2011). Some research, however, has implicated not calories per se, but the protein component, with particular roles for specific amino acids (Speakman and Mitchell, 2011; Fontana and Partridge, 2015). A more-detailed account of how diet impacts on aging is needed to understand the evolution of senescence, the underlying mechanisms, and the ecological contexts in which they evolved.

Over the past two decades the field of nutritional ecology has demonstrated across diverse taxa and contexts (e.g., lab experiments, free-living wildlife, animal production systems, companion animals) that animal-food interactions are complex, involving homeostatic regulatory mechanisms, such as appetite systems, that intricately mediate the relationships between many nutrients and their physiological impacts (reviewed in Simpson and Raubenheimer, 2012). A state-space modelling approach that has been developed to study these interactions, called the Geometric Framework for nutrition, has shown that their inclusion in empirical and theoretical studies can substantially increase predictive and explanatory power compared with studies based on a single currency, such as energy or protein (e.g., Raubenheimer, 2011; Raubenheimer and Simpson, 1993; Raubenheimer et al., 2009; Simpson and Raubenheimer, 2005, 2012; Simpson et al., 2015). The Geometric Framework has been applied in theoretical (Simpson and Raubenheimer, 2007; Simpson and Raubenheimer, 2009; Piper et al., 2011) and empirical research into aging, the latter including several insect species and one mammalian model system, C57BL6 laboratory mice (reviewed in Le Couteur et al., 2016).

Our aim in this paper is to introduce the logic of the Geometric Framework, and show in the context of experiments exploring links between nutrition, reproduction and aging how it can be used to develop a detailed understanding of the interface between the animal and its nutritional environment that could help to unify mechanistic and evolutionary theories of aging. Against this background, we discuss the ecological relevance of the caloric restriction protocol in aging research, and conclude that a broader paradigm is needed which considers the causal links between diet and lifespan to be an open-ended question. This will provide a stronger basis for integrating mechanistic and evolutionary theories of aging, and leave the way open for non-model organisms to contribute maximally to understanding biological aging.

2. The geometry of diet

We begin by showing how some core concepts in nutritional ecology are represented within the Geometric Framework. The device within this framework in which the interaction of the animal with its nutritional environment is modelled is a Cartesian space called a *nutrient space* (Fig. 1A). The two or more axes defining this space each represent a functionally important food component, for example the macronutrients protein, carbohydrate and fat. Within the nutrient space, key aspects of the environment (e.g., food compositions), the animal (e.g., current nutritional state, optimal nutritional state), and its interaction with the environment (feeding and other homeostatic responses) can be represented in common, multidimensional nutrient metrics.

Such a nutrient space representing the animal's nutritional interaction with the environment can be empirically parameterised either through captive animal experiments or observational studies in the wild, and related to various outcomes of interest, including mechanistic responses (e.g., activation of key nutrient signalling pathways and physiological markers of health and aging) and functional outcomes, such as reproduction and longevity. In this way nutritional geometry provides a template in which the animal's evolved responses to a multi-dimensional nutritional environment can reveal the links between functional outcomes and the underlying mechanisms, as we detail further in the rest of this section.

2.1. Homeostatic targets

A central tenet of nutritional ecology is that the interactions of animals with their environments are not passive, but actively guided by homeostatic systems that have evolved to produce adaptive outcomes. To model this, the nutritional states on which the animal will converge if unconstrained are represented within the nutrient space as target points or small regions. The *intake target* describes the cybernetic goal of the mechanisms regulating ingestion (Fig. 1A); physiological targets, for example the *growth target*, can similarly be described (Raubenheimer et al., 2009), but we will not consider these further in this paper.

An animal reaches its intake target through the selection of foods, and regulating how much of each is eaten. Foods are represented within the nutrient space as the ratio of the nutrients that each contains. Geometrically, this is given as the slope of a radial that projects from the origin into the nutrient space, called a *food rail*.

As the animal eats, it ingests the nutrients in the same proportion as they occur in the food, and consequently its nutritional state can be modelled as changing along the rail representing the food that it is eating - the more it eats, the further along the rail it "moves". If the rail representing a particular food intersects the intake target (i.e., contains the same ratio of nutrients that is prioritised by the animal's regulatory systems), then this food is nutritionally balanced with respect to the nutrients in the model, and by eating the right quantity of this food the animal can "navigate" directly to its intake target (e.g., Food 1 in Fig. 1A). By contrast, if the food is imbalanced then it does not on its own allow the animal to reach its target (e.g., Food 2). However, the animal can nonetheless use this food to navigate to the target, if it combines it in the diet with another imbalanced food, provided the two foods fall on opposite sides of the intake target (e.g., Food 2 combined with Food 3). Such combinations of nutritionally imbalanced foods that can be combined into a balanced diet are called *complementary* food pairings.

Importantly, regulatory targets like the intake target are not merely hypothetical constructs, but can readily be measured in laboratory studies or even in free-ranging wild animals (Felton et al., 2009a; Johnson et al., 2013; Raubenheimer et al., 2015). Experimentally, the protocol is to provide the animals with complementary food pairings and measure the point of intake on which the animal converges over a stipulated period. To ensure that this point does, in fact, represent a homeostatically regulated outcome, it needs to be statistically distinguished from a null hypothesis (Fig. 1B). This could be a mathematical expectation, for example observed intakes could be compared to the anticipated outcome if feeding were indiscriminate or random.