The (ongoing) problem of relative growth

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Differential growth, the phenomenon where parts of the body grow at different rates, is necessary to generate the complex morphologies of most multicellular organisms. Despite this central importance, how differential growth is regulated remains largely unknown. Recent discoveries, particularly in insects, have started to uncover the molecular-genetic and physiological mechanisms that coordinate growth among different tissues throughout the body and regulate relative growth. These discoveries suggest that growth is coordinated by a network of signals that emanate from growing tissues and central endocrine organs. Here we review these findings and discuss their implications for understanding the regulation of relative growth and the evolution of morphology.

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Introduction

"*The problem of differential growth is a fundamental one for biology, since, all organic forms, save the simplest . . . are the result of differential growth, whether general growth which is quantitatively different in the three planes of space, or growth localized at certain circumscribed spots*". So wrote Julian Huxley at the beginning of his book, *Problems of Relative Growth* [1]. Huxley, along with D'Arcy Thompson a generation before him [2], recognized that morphological diversity is dominated by variation in body proportion, and that body proportion is in turn produced through differential growth of the body's constituent parts. Consequently, if we are to understand the evolution of morphology, we need to identify the developmental mechanisms that regulate differential growth. Nevertheless, Huxley notes "*But the subject has received little consideration*"; unfortunately, this statement has remained true for much of the eighty-five years since it was written.

With the rise of developmental physiology, we are starting to discover how the growth of structures is coordinated throughout the body. In this review, we outline recent work that has begun to elucidate the developmental regulation of relative growth, and propose foci of research that will better help us solve the vexing problem of how growth is integrated across traits to produce a properly proportioned adult, even in the face of environmental variation. As much of this new research uses insects as models, we draw on these organisms heavily to illustrate our points. However, the problem of relative growth is of the widest biological relevance, and so we also employ non-insect examples where possible.

Allometry and differential growth

As Huxley observed in *Problems of Relative Growth*, apart from simple spherical or amoeboid organisms, the form of all multicellular organisms is generated through differential growth among body parts. This is most apparent in the exaggerated morphological traits males use to compete for females, such as those observed in stalk-eyed flies and horned beetles. Indeed, Huxley used the exaggerated claw (chela) of the male fiddler crab, *Uca pugnax*, to illustrate his most important contribution to the field of morphometrics: the allometric equation $y = bx^k$ (Figure 1). This equation describes the scaling relationship between covariation in the size of trait y (typically a focal trait of interest) and trait x (typically the whole body) through ontogeny. While Huxley dismissed b (the intercept) as being biologically unimportant (although see [3]), he recognized that k, the allometric coefficient, captures the growth rate of y relative to x. He further argued that the allometric coefficient is constant, at least within each growth cycle (e.g. larval instar), such that a plot of log y against log x generates a straight line of slope k, the *constant differential growth-rate*, and intercept log b; that is log$y$ = log$b$ + k log$x$. Thus a plot of log(*chela mass*) against log(*body mass*) for male fiddler crabs at different points in ontogeny generates a straight line with a slope 1.62 for the first phase of growth and 1.26 for the second phase of growth (Figure 1, [1]). When the allometric coefficient is <1 or >1, trait y grows disproportionally slower or faster relative to trait x, a condition called *heterogony*. In contrast, when the allometric coefficient is 1, the two traits grow at the same rate, or proportionally, a condition called *isogony*.

In addition to variation in relative size that occurs through ontogeny, size also varies among adult individuals within a population or species, and among species themselves. Here, the scaling relationship between y and x can also be captured by the allometric equation, but the relationships
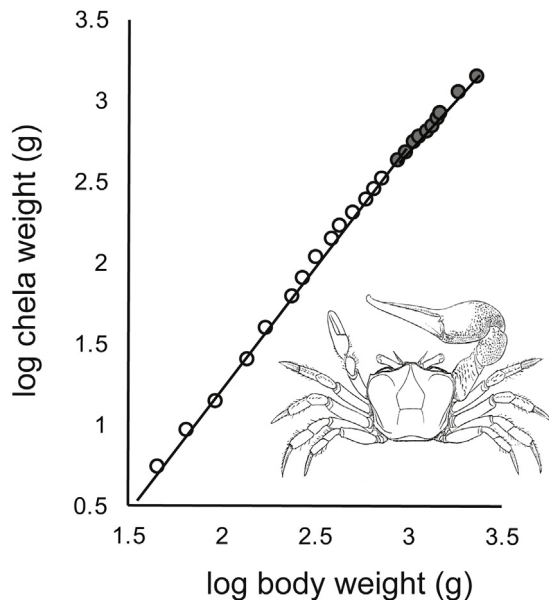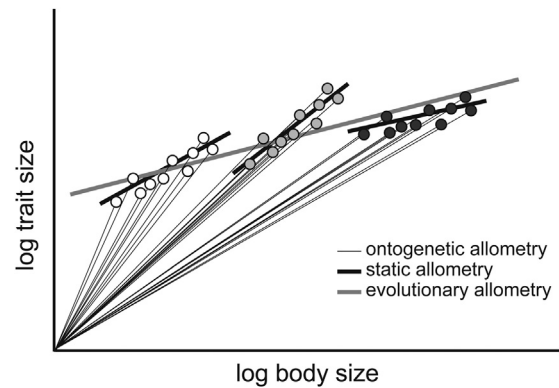
Ontogenetic allometry of chela size against body size in the fiddler crab *Uca pugnax*. Open points are the first phase of growth (slope = 1.62). Closed points are the second phase of growth (slope = 1.26). Data from [1]. Image from [87].

The relationship between ontogenetic, static and evolutionary allometry. The thin black lines are the *ontogenetic allometry* between body and trait size. These end at the final adult body and trait size (circles). The thick black line shows the *static allometry* between body and traits size among adults in a population or species. Each species is represented by a different colored circle (white, gray or black). The thick gray line shows the *evolutionary allometry* between body and trait size among species. Note that each static allometry represents a different category of morphological scaling; the population of open circles exhibit a hyperallometric relationship, gray circles illustrate isometry, and black circles reflect hypoallometric scaling.

are called *static allometry* and *evolutionary allometry*, respectively. Nevertheless, for all allometries, the two traits have the same relative size when $k = 1$, regardless of overall size (i.e. the traits change size in constant proportion to one another). When $k > 1$, trait y becomes disproportionally larger relative to trait x as size increases, whereas when $k < 1$, trait y becomes disproportionally smaller as the size of x increases. Because of the generality of these effects on overall shape, the term heterogony has been replaced by *hyperallometry* ($k > 1$) and *hypoallometry* ($k < 1$), and isogony has been replaced by *isometry*. Technically *allometry* refers to any condition that is not isometric, but recently it has come to refer to scaling relationships in general [4], and will be used in this way here. Further, the concept of allometry has been expanded beyond the morphological to include the relationship between body size and biochemical, physiological and ecological processes, such as metabolic rate, the cost of locomotion, or population density. There is a rich literature exploring these scaling relationships, many of which can also be modeled using the allometric equation [5–7].

Ontogenetic, static and evolutionary allometries describe different, but related, relationships (Figure 2). An ontogenetic allometry describes the relative size of traits throughout the growth of an individual. In as much as the purpose of ontogeny is to generate a correctly proportioned adult, the ontogenetic allometry describes how this is achieved. A static allometry describes the relative size of traits, among individuals at the same developmental stage (typically adult), within populations, species or other biological groups. The static allometry is generally thought of as the 'proper' scaling relationship for the group. Evolutionary allometries describe the pattern of evolutionary divergence in relative trait size among these same biological groups. Static and evolutionary allometries have been the subject of extensive recent research, and this work has been widely reviewed [4,8–11,12••,13], so will only be touched on here. In contrast, while the pattern of ontogenetic allometries has been well studied (e.g. [14–20]), the developmental mechanisms that regulate differential growth remain poorly understood. It is variation in these mechanisms among individuals, revealed as variation in the length and slope of ontogenetic allometries, that generates static allometries, and it is evolved changes in these mechanisms that produce the patterns revealed through evolutionary allometries.

The utility of the allometric equation to describe differential growth lies in the observation that differential growth-rates remain constant for prolonged periods of development. Huxley provided many examples of linear ontogenetic allometries between different trait pairs, including the chela and body size of male fiddler crabs, tail and body length in mice, face and cranium length in dogs, and stem and root weight in various plants [1]. Huxley initially considered the allometric equation to be a consequence of the multiplicative nature of growth, that is, the notion that traits grow exponentially, and he argued that the equation approximated a general law of