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Toward a physiological explanation of juvenile growth curves

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Abstract

Juvenile growth curves are generally sigmoid in shape: Growth is initially nearly exponential, but it slows to near zero as the animal approaches maturity. The drop-off in growth rate is puzzling because, everything else being equal, selection favors growing as fast as possible. Existing theory posits sublinear scaling of resource acquisition with juvenile body mass and linear scaling of the requirement for maintenance, so the difference, fuel for growth, decreases as the juvenile increases in size. Experimental evidence, however, suggests that maintenance metabolism increases sublinearly not linearly with size. Here, we develop a new theory consistent with the experimental evidence. Our theory is based on the plausible assumption that there is a trade-off in the capacity of capillaries to supply growing and developed cells. As the proportion of non-growing cells increases, they take up more macromolecules from the capillaries, leaving fewer to support growing cells. The predicted growth curves are realistic and similar to those of previous models (Bertalanffy, Gompertz, and Logistic) but have the advantage of being derived from a plausible physiological model. We hope that our focus on resource delivery in capillaries will encourage new experimental work to identify the detailed physiological basis of the trade-off underlying juvenile growth curves.

Introduction

Juvenile animals are under intense selection to grow as fast as possible (see, e.g., Sibly & Calow, 1986), but growth slows as mature size is approached, as shown in Fig. 1 for animals that do not grow after first reproduction, the case under consideration here. The slowdown in growth must result from a trade-off or constraint. But what is the constraint? Despite decades of research, there has been no consensus on the answer to this fundamental question about life histories. Von Bertalanffy (1960) argued that growth slows because as body size increases a greater proportion of assimilated energy and biomass is allocated to maintenance including activity (catabolism) and a decreasing proportion is allocated to growth (anabolism); growth stops when all assimilation is allocated to maintenance. In Von Bertalanffy's model, metabolism scales linearly with body mass (as m^1) while assimilation scales as some fractional power of mass (e.g., as $m^{2/3}$ or $m^{3/4}$). A problem with this and some more recent theories (West *et al.*, 2001; Hou *et al.*, 2008; Moses *et al.*, 2008; Hou *et al.*, 2011) is that more than a century of empirical research shows that maintenance metabolic rate scales with an exponent less than 1 in adults and presumably something similar applies in juveniles (though cf. (Peterson *et al.*, 1999)). So a different mechanistic explanation is needed for why growth slows as animals approach mature size.

Here, we develop new theory consistent with the experimental evidence and based on a plausible physiological model. We follow earlier models in assuming that the trajectory of growth reflects the balance between inputs and outputs of energy and material resources. For simplification, we frame the model in terms of macromolecules – the organic compounds (carbohydrates, lipids, and proteins) assimilated from food and distributed around the body in the blood. These macromolecules are taken up from the blood in the capillaries and supplied to cells. Cells use these macromolecules for one of two purposes: (1) maintenance — a large fraction of them are broken down in respiration (catabolism) to produce the ATP that is used to power the work of living including activity; (2) production — some macromolecules are preserved and reassembled into new biomass. Our model is based on consideration of how the macromolecules taken up from the capillaries by cells are allocated between maintenance and production. We assume that the capacity of the capillaries to supply macromolecules is limited and that growth stops when all macromolecules are used by developed cells to maintain a steady state so that none are available for growing cells to produce new biomass. We develop the model by distinguishing between two kinds of cells:

(1) Growing cells: These cells increase in mass and divide by mitosis, so they more than replace themselves. Consequently during growth, the number of cells and the body mass, m, of

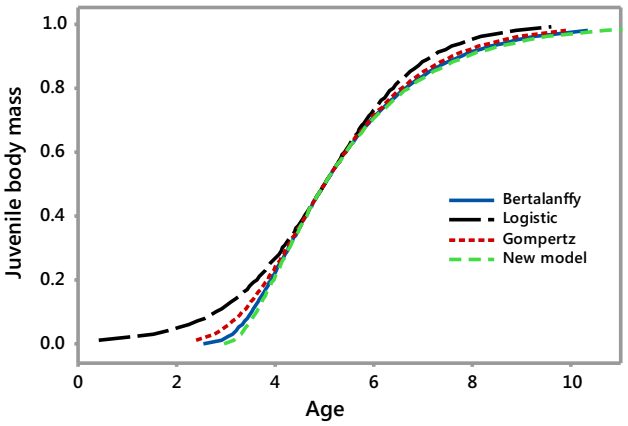

Figure 1 Juvenile growth curves used to fit growth data. Note that growth slows as mature size is approached. The Bertalanffy equation has been used most frequently, for many kinds of animals, including thousands of species of fish (www.fishbase.org), but the Logistic and Gompertz have been applied to birds (Calder 1984) and all three to reconstructions of dinosaur growth (Myhrvold, 2013). Growth curve parameters are here chosen to give the same body masses and growth rates at age 5. Note that the form of the new model derived in the text is similar to the Bertalanffy, Logistic, and Gompertz equations, but because the predicted growth curves are so similar, it is often difficult to distinguish between them using growth data alone ((Katsanevakis & Maravelias, 2008; Myhrvold, 2013; Lugert et al., 2016; Peters 1983; Reiss 1989), but see also Peterson et al. (1999)).

the juvenile animal increase. Conservation of energy and mass requires growing animals and cells to assimilate macromolecules to produce net new biomass.

(2) Non-growing, developed cells: Early in ontogeny, all cell lines divide and grow, but when the organism has matured and growth has stopped, the body contains two kinds of developed cells. Some, such as neurons and skeletal muscle cells, stop dividing and survive for the life of the animal. Others, such as epithelial, blood, and glial cells, die and are replaced. We consider the macromolecules used for turnover of cells in non-growing individuals at steady state as being used for maintenance of existing biomass.

Our analysis focuses on the delivery of macromolecules to growing and developed cells and assumes, following Reiss (1989), that over ontogeny the rate of assimilation of macromolecules into the body increases as the 2/3 power of body mass and maintenance rate as the ¾ power. Assimilation rates of multicellular animals have generally been considered to scale as the 2/3 power of body mass, both within species over ontogeny and across species (Kooijman 2010; Reiss 1989; Sibly *et al.*, 2013). In the Discussion, we consider how physiological models such as ours can be tested experimentally.

Theory

We assume that cells are arrayed in service volumes around capillaries that supply them with resources and carry away wastes. As the animal grows, the number of capillaries increases with body mass; mass at maturity is assumed to be given. In a mature, non-growing animal, the developed cells take up macromolecules from the capillaries at rates just sufficient to support maintenance respiration at steady state. In a growing animal, some cells take up macromolecules at higher rates to support biomass production and growth. To formalize, assume that each capillary supplies a service volume containing a fixed number of developing and/or developed cells, and the capillaries are invariant units which transport macromolecules at constant concentrations and constant rates.

Let:

q be the number of cells in the mature body

r be the number of macromolecules needed to build a cell

t be age of the animal in seconds

v be the flow rate of macromolecules in a capillary, macromolecules/second.

x be the proportion of cells that are fully developed, $x = m/m_\infty$ where m is juvenile body mass during growth and m_∞ is adult body mass when growth has stopped.

We require the following:

Assumption 1: The rate at which animals acquire macromolecules is proportional to $m^{2/3}$, $= am^{2/3}$ for some constant a, and the number supplied to developed cells is proportional to $m^{3/4}$, $= bm^{3/4}$ for some constant b. The remaining macromolecules are delivered to growing cells. This assumption applies at the levels of both individual capillaries and the whole organism. Only the needs of the developed cells are provided for in the mature non-growing animal, so $am_\infty^{2/3} = bm_\infty^{3/4}$, so $b = am_\infty^{1/12}$.

The total capacity of the capillaries to deliver macromolecules is the product of the number of capillaries and the flow rate of macromolecules in a capillary, v. This is equal to assimilation rate, and so, by assumption, scales as $am^{2/3}$. Assuming v does not scale with m, the number of capillaries increases as $c\ m^{2/3}$, for some constant c, and the capacity of the capillaries to deliver macromolecules $= cvm^{2/3}$, $= cvx^{2/3}\, m_\infty^{2/3}$ since $m = xm_\infty$. By Assumption 1, some of these macromolecules go to developed cells, at rate $bm^{3/4} = am_\infty^{1/12}\, x^{3/4}\, m_\infty^{3/4} = cvm_\infty^{10/12}\, x^{3/4}$. The remaining macromolecules are delivered to growing cells at rate $cvx^{\frac{2}{3}}\, m_\infty^{\frac{2}{3}}\,(1 - m_\infty^{1/6}\, x^{\frac{1}{12}})$.

The time between macromolecules arriving at growing cells is:

$$\frac{1}{cvx^{\frac{2}{3}}\, m_\infty^{\frac{2}{3}}\,(1 - m_\infty^{1/6}\, x^{\frac{1}{12}})}, \tag{1}$$

and the time required for the arrival of the r macromolecules needed for the production of one new cell

$$\frac{r}{cvx^{\frac{2}{3}}\, m_\infty^{\frac{2}{3}}\,(1 - m_\infty^{1/6}\, x^{\frac{1}{12}})}. \tag{2}$$

This delivery increases the number of developed cells by one and the proportion of the final number of developed cells by $1/q$. Since an increase in x of $1/q$ is achieved in time $\frac{r}{cvx^{\frac{2}{3}}\, m_\infty^{\frac{2}{3}}\,(1 - m_\infty^{1/6}\, x^{\frac{1}{12}})}$, it follows that:

$$\frac{\Delta x}{\Delta t} = \frac{cvx^{\frac{2}{3}} m_\infty^{\frac{2}{3}}}{rq} (1 - m_\infty^{1/6} x^{\frac{1}{12}}).$$

In the limit when $\Delta t \to 0$, we get the equation in differential form:

$$\frac{dx}{dt} = \frac{cvx^{\frac{2}{3}} m_\infty^{\frac{2}{3}}}{rq} (1 - m_\infty^{1/6} x^{\frac{1}{12}}), \quad (3)$$

or in integrated form:

$$t = -(4m_\infty^{1/2} \sqrt{x}4 + 6m_\infty^{1/3} \sqrt{x}6 + 12m_\infty^{1/6} \sqrt{x}12 + 12 \ln(1 - m_\infty^{1/6} \sqrt{x}12)) dm_\infty^{-2/3} + t_0 \quad (4)$$

where $d = \frac{cvm_\infty^{\frac{2}{3}}}{rq}$ and t_0 is a constant of integration. The predicted growth curve plotting x against t is compared with other growth curves in Fig. 1.

Discussion

We view our model as a promising start toward a mechanistic understanding of why growth slows progressively as mature body size is approached. Our model follows earlier treatments in assuming that growth slows because as body size increases a larger fraction of assimilated macromolecules are devoted to maintenance and a smaller fraction is available for growth. Our analysis differs from earlier treatments in directing attention to the trade-off between supplying growing and developed cells occurring at the level of the capillaries. The trade-off is a direct consequence of conservation of energy and matter in the form of organic macromolecules. Macromolecules taken up from capillaries and used for maintenance (respiration) are necessarily not available to growing cells. But our model does not make the unrealistic and empirically unsupported assumption of linear scaling of maintenance metabolism with body mass as in the theories of Bertalanffy (Reiss (1989) and West *et al.*, (2001); but see Moses *et al.*, (2008)). Our model is consistent with the mass and energy balance analysis of Hou *et al.* (2008), with observed sublinear non-power law scaling of assimilation rate with body mass in the growing animal, and with ¾ power scaling of respiration rate with adult body mass across species in line with Kleiber's rule. Our model produces realistic growth curves similar to those of other equations commonly fitted to data (Fig. 1).

Following earlier models, we assume that growth stops when assimilation rate is equal to maintenance rate. If as here both rates are related to body mass by power laws, it follows that the scaling exponent of maintenance has to be greater than that of assimilation rate. But how much greater? In the model presented here, the exponents of assimilation and maintenance are 2/3 and ¾, respectively, so the difference is 1/12. In the Bertalanffy and Logistic equations, the differences are 1/3 and 1, respectively. The corresponding scaling exponents for maintenance are 1 and 2, respectively. These values are greater than our value of ¾, which we consider realistic and have incorporated into the model presented here. Perhaps surprisingly, the Bertalanffy and Logistic equations, derived from assumptions similar to but less realistic than ours, produce juvenile growth curves remarkably similar to those of our model (Fig. 1).

Many aspects of growth are not addressed by our deliberately oversimplified models. Individuals grow when gain of net new biomass due to cell division and growth exceeds loss of existing biomass due to cell death, but the balance between gain and loss varies with the type of cell. Some, such as neurons and skeletal muscle, stop dividing when the animal stops growing and then survive for the duration of the lifespan. Others, such as the cells of the skin, gut, endocrine glands and the precursors of blood, connective tissue, and sperm cells, continue to reproduce throughout life (Savage *et al.*, 2007). We have been careful to distinguish between the proliferation of net new cells which results in growth of the individual, and maintenance of a steady state between cell reproduction and cell death which continues throughout life. At maturity when growth has stopped, the rate of production of new cells by mitosis has slowed to match the rate of natural cell death.

Our model of resource limitation at the cellular level is consistent with structure and function at the level of cells, tissues, and capillary service volumes. For one example, in the epithelial tissues of skin, gut, and endocrine glands, where the cells reproduce and die at high rates throughout life, the reproducing cells occur in close proximity to the capillaries that supply the necessary macromolecules. In a mature individual, there is a steady state where half of the daughter cells remain in situ and continue to divide by mitosis, while the other half differentiate and move away from the capillary and eventually mature, die, and are sloughed off (https://en.wikipedia.org/wiki/Epithelium).

Another example is the link between cancer tumor growth and resource supply to cells through capillaries. Most cancers occur in the types of cells that continue to reproduce throughout life (see above). The tumor starts growing when normal regulation of cell proliferation is interrupted and rates of production of new cells by mitosis exceed normal rates of cell death. As expected from mass and energy balance, the growing tumor and its constituent cells have higher rates of resource uptake than non-malignant cells, because macromolecules are being used for production of new biomass as well as maintenance respiration of existing biomass. One corollary is the phenomenon of angiogenesis, in which the malignant cells recruit new capillaries that supply macromolecules to support tumor growth (de Palma *et al.*, 2017).

Like most models of the growth process, ours assumes that growth stops when all assimilated macromolecules are used to support maintenance metabolism and none are available for net new production. None of these models, however, predict the body mass at maturity. The mature body size of adult animals is the result of complex interactions among past evolutionary and contemporary physiological, developmental, and genetic processes. The diverse body sizes of extant animals have evolved by natural selection in response to interactions with the abiotic environment and other organisms (e.g., Smith *et al.* (2010)). More proximally, size at maturity is the result of regulatory mechanisms and environmental influences operating at

many levels of organization. There is an ontogenetic program, evolved by natural selection, encoded in the genome, and played out during development that targets the mature body size. Some of the regulatory mechanisms, such as mammalian growth hormone, operate at the whole-organism level. Others must operate more locally – at the level of tissues and cells – so as to coordinate growth and development and control the number and distribution of the different cell types and tissues that comprise the body. Some of this localized regulation undoubtedly involves molecular signals between the cells and capillaries such as occurs in angiogenesis. But we hypothesize that much of the regulation may be due to direct feedbacks between resource supply from capillaries and resource demands of growing and developed cells.

There should be abundant scope to extend the perspective started here to model the details of supply and demand at the level of capillaries and their service volumes. There is a need for renewed attention to how their structural and functional properties vary with whole-organism body size, both within an individual over ontogeny and across species. More elaborate models can address some of the biological details. These include the following: (a) how the fates of epithelial cells change with increasing distance from capillaries (see above); (b) how cancer tumors and exercising muscles recruit new capillaries to fuel their higher metabolic demands (Adair and Montani 2010); and (c) how imbalances in the temperature dependence of rates of biomass production and developmental differentiation affect time to maturity and adult body size in ectothermic animals (Atkinson, 1994; Atkinson & Sibly, 1997; Ashton *et al.*, 2000; Zuo *et al.*, 2012).

Tests of the model should include whether during ontogeny:

(1) Capillaries are invariant units: in particular, do their physical dimensions and flow rates remain constant over ontogeny;
(2) The number of capillaries scales sublinearly with body mass, $\propto m^{\frac{2}{3}}$;
(3) At each moment in time, a number of macromolecules, $\propto m^{3/4}$, are supplied to developed cells, and the remainder are delivered to developing cells. It would seem that the relevant macromolecules or cells could be marked and tracked using technologies such as quantum dots (Whiteside *et al.*, 2009), fluorescent dyes (Ogura *et al.*, 2011), metabolic labeling, flow cytometry or some combination thereof. Such techniques are widely used in cancer research, but surprisingly little is known about the linkages between capillary resource supply, replication and growth of cells, and regulation of whole-organism growth and development.

In sum, there is abundant scope for renewed attention to the phenomenon of ontogenetic growth and the role of physiological processes at all levels of organization.

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