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Allocation of Cells to Proliferation vs. Differentiation and its Consequences for Growth and Development

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ABSTRACT A model relating the recruitment of skeletal muscle fibers from precursor cells to growth and development of the whole muscle is presented. The pattern of growth throughout ontogeny is analyzed for differences in: (1) initial number of precursor cells, (2) timing of onset of differentiation, (3) timing of offset of differentiation, and (4) differentiation rate (number of precursor cells that differentiate each cell cycle). The initial number results in a larger muscle but has no effect on relative growth rate. Later onset time and slower differentiation rate result in relatively slow growth early in ontogeny but rapid growth for most of ontogeny. A later offset time results in faster growth late in ontogeny as new fibers continue to be recruited late into ontogeny. The pattern derived from onset time and differentiation rate matches that of the precocial-altricial continuum in birds in which selection for functional ability early in ontogeny results in slow growth late in ontogeny. Methods for recognizing the different developmental parameters in the size distributions of muscle fibers are described and three empirical examples interpreted in terms of the model. *J. Exp. Zool. (Mol. Dev. Evol.) 288:219-234, 2000.*

Understanding how the genotype is translated into the phenotype is a central issue in evolutionary biology. It has long been hoped that the integration of developmental biology with evolution would help explain this process. However, developmental biology remains focused on processes at the cellular and subcellular level, whereas evolutionary biology remains focused on gene frequencies. So far, the primary thrust of this integration has been the incorporation of development into population genetics (e.g., Cowley and Atchley, '92) and the use of development genes to resolve macroevolutionary questions (e.g., Valentine et al., '96). Although important advances, neither approach opens the "black box" of how development produces adaptive variation or what implications developmental processes have for natural selection at the level of the whole organism. This paper provides an initial attempt at addressing this issue by examining how cellular processes influence growth rate and development rate of the whole organism.

Growth rate and development rate are integral components of an organism's fitness. They are the control factors underlying most life-history models (Roff, '92; Stearns, '92, Abrams et al., '96). For example, many life-history models are designed to predict either size or age at maturation, and it is growth rate that determines size and development rate that determines age at maturation (e.g., Wilbur and Collins,'73; Smith-Gill and Berven, '79; Hutchings, '93). Clearly then, it is the interaction between growth and development that determines the optimal life-history strategy (Bernardo, '93). Understanding the interaction is important not only for understanding life-history traits, but also for understanding the evolution of morphological variation as was the original hope for the concept of heterochrony (Gould, '77; McKinney and McNamara, '91). In this paper, I take a population perspective on cellular differentiation within a single tissue and develop a model of this critical interaction.

First, I must make it clear that growth and development are very different components of ontogeny even though the two terms often are treated as synonyms. Far from being synonymous, there is probably a fundamental trade-off between growth rate and development rate. Throughout this paper, growth means simply an increase in size of either a tissue or the organism as a whole.

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This can be achieved by one of three mechanisms: cellular proliferation (hyperplasia), cell growth (hypertrophy), or the addition of intercellular matrix. Of the three, cellular proliferation is generally thought to be the most important determinant of growth rate (Robertson, '59; Falconer et al., '78; Weatherley and Gill, '87; Partridge et al., '94; Stevenson et al.,'95). although cell growth is undoubtedly also critical. Both may occur at the same time, resulting in a distribution of cell sizes within a tissue. The intercellular matrix is important for some tissues (e.g., bone) but is not considered further in this paper. Development, on the other hand, refers to differentiation of cells allowing a tissue to take up its mature function. Because many cell lines lose the ability to divide once they become terminally differentiated, a trade-off between growth and differentiation rate is expected. This idea, sometimes termed the growth-differentiation balance hypothesis (Loomis,'32; Herms and Mattson,'92) has been applied to a wide range of organisms by evolutionary ecologists (reviewed in Arendt,'97). For example, Ricklefs and coworkers (Ricklefs and Weremiuk, '77; Ricklefs and Webb,'85; Ricklefs et al.,'94; Starck and Ricklefs,'98) explain the differences between altricial and precocial development of birds in terms of a growth-differentiation trade-off. Altricial species are helpless at hatching but grow quickly, whereas precocial species are able to locomote within minutes of hatching but grow slowly. Herms and Mattson ('92) use this trade-off to explain the common observation that fast-growing species of plants are usually poorly defended chemically (chemical defenses being the product of differentiated cells) whereas slow-growing species are often heavily defended.

The growth-differentiation trade-off has been an important heuristic for many evolutionary ecologists. It is, however, not a very well-defined one. Both Herms and Mattson ('92) and Ricklefs et al. ("94) describe a trade-off in terms of cellular proliferation versus cellular differentiation, but all of the empirical examples given are actually at the tissue or organism level. The result, as noted by Ricklefs et al. ('98), is that the growth-development trade-off is currently circular in structure with maturity defined in terms of variables that satisfy the trade-off. Although it seems intuitive that a trade-off between proliferation and differentiation at the cellular level should translate into a trade-off at the whole tissue or organism levels, I am aware of no attempts to model this formally. Such a translation among levels should emerge from treating tissues as a population of cells rather than from a histological or cytological perspective. The following model is one interpretation of how this might occur. It is neither the only interpretation possible, nor is it necessarily what either Herms and Mattson or Ricklefs had in mind. The purpose of this model is: to (1) define the trade-off between growth and development in a testable (noncircular) manner and (2) highlight how empirical data should be collected to test such a model.

THE MODEL

A number of tissues are likely to limit growth of the whole organism. Herms and Mattson ('92) describe the growth and differentiation of leaves as one specific example. Flowers are terminally differentiated modules in plants, and several authors have suggested that allocation of meristems for flowers may severely restrict growth (Watson, '84; Geber, '90; Bonser and Aarssen, '96). Ricklefs et al. ('94) suggest that nerves, skeletal muscle, and bones—all tissues which show no cellular division once they mature—are especially likely to limit growth in animals. I base this model explicitly on what is known about the growth and differentiation of skeletal muscle. I chose this as a model tissue because its differentiation is relatively simple, well understood (Goldpsink, '72; Koumans and Akster, '95), and empirical methods that can be applied to testing the predictions of the model already exist (e.g., Fowler et al., '80; Weatherley and Gill, '87). In vertebrates skeletal muscle makes up the bulk of an organism's mass (more than 95% in some species of fish [Weatherley and Gill, '87]), and is therefore likely to contribute strongly to whole organism growth rates. However, almost any tissue is likely to fit in the following model because, as Weatherley and Gill ('87; see also Ricklefs et al. '98) note, even constantly renewing tissues consist of terminally differentiated cells, incapable of division, derived from a population of undifferentiated cells (but see Weatherley, '90 for a contrasting opinion).

Skeletal muscle is organized into large, multinucleated cells called muscle fibers. These fibers contain the mature proteins (actin, myosin, and their associated proteins) that perform the primary function of skeletal muscle, contraction resulting in locomotion. Muscle fibers can further differentiate into a number of fiber types, each with specific contractile characteristics (Goldspink, '72). However, for the purposes of this model I do not consider this form of differentiation. Rather,

muscle fibers are treated as a single, generic type. Muscle fibers are terminally differentiated and do not undergo mitosis. They are, however, capable of increasing in size through ontogeny until a stable "adult" size is reached. Because muscle fibers do not divide themselves, new fibers must be derived from another type of cell, presumptive myoblasts (PMB's), which are not capable of performing the mature contractile function of muscle fibers. Thus the model tissue consists of two cell types with the following characteristics:

Presumptive myoblasts, which divide at each cell cycle to produce either:
1. two new muscle fibers with probability d, or
2. two new presumptive myoblasts (with probability 1-d)

Muscle fibers, which grow 1 arbitrary unit each cell cycle, and perform the mature function of the muscle tissue

The term d can be viewed as an index of differentiation rate, with d=0 being no differentiation and d=1 being maximal differentiation (all PMBs divide to produce muscle fibers). Note that d need not remain constant throughout ontogeny. Ontogeny consists of 20 time units (cell cycles) in this model. At each time unit, the number of muscle fibers in the smallest size class (size class 1) becomes $2d\ N_{PMB}$, where N_{PMB} is the number of PMB at the previous time. The population of PMBs increases by $2(1\text{-}d)N_{PMB}$. Growth of fibers is assumed to be continuous so that all fibers advance one size class each cell cycle. This is a simplification of muscle development. In reality, PMBs differentiate to form myoblasts, which are themselves post-mitotic. Several myoblasts then fuse to form what eventually becomes a myofiber (Koumans and Akster, '95). Incorporating the fusion of myoblasts into the model simply reduces the number of fibers produced per PMB by a constant fraction. Because this does not alter the qualitative results of the model, I chose to ignore these further complications of myogenesis. Presumptive myoblasts are very small compared to muscle fibers, and thus contribute negligibly to size in muscles. This may not be true for other tissues. For example, Loomis ('32) describes plant growth as having three phases: cell division, cell growth, and cell differentiation. As such, precursor cells determine growth both by cell number and cell size, but differentiated cells neither divide nor grow. There are many ways in which this particular aspect of growth-differentiation can be modelled, which only highlights the necessity for more models such as this one. Because I compare results derived from this model to empirical data for muscle growth, I assume that precursor cells do not contribute to total tissue size. Thus I estimate muscle size as:

$$\Sigma\ (\text{cross-sectional area of fibers in a size class})\ (\text{no. of fibers in that size class}).$$

Muscle size is assumed to be proportional to the size of the whole organism. As such, growth of the muscle is used as an estimate of whole organism growth rate.

Development is not explicitly modelled, but muscle function is assumed to be a function of fiber age and size. Function may be directly proportional to size in mature muscles (so that 10 fibers of size class one are equivalent to 1 fiber of size class ten), but this is unlikely to be true in growing muscle as small, young fibers have not accumulated as much protein as large, old fibers (Ricklefs et al., '98). This means that 10 fibers of size class one are less efficient than 1 fiber of size class ten, and a muscle consisting predominately of small fibers will be less "developed" than one consisting of larger fibers.

Several models similar to the one just described exist in the literature. Most notable are Arkebauer and Norman ('95) and Granier and Tardieu ('98), both relating cellular proliferation to growth patterns in leaves, and Morris and Cowan ('95) on growth of the retina in embryonic chicks. However, these models are descriptive, relating the recruitment of differentiated cells to patterns of growth, given static parameters or those reflecting environmental influences. Their goal is proximate, to relate known mechanisms to measurable parameters within tissues. My goal is to relate these proximate developmental mechanisms to potential evolutionary change and suggest possible adaptive consequences of these changes. To do this, we must extend these cellular models to incorporate parameters that are likely to change over evolutionary time.

My interpretation of Ricklefs and Weremiuk ('77, and implied in Ricklefs and Webb, '85) is that differences in growth rate are due to differences in the proportion of cells allocated towards proliferation versus those allocated towards differentiation. Allocating more precursor cells towards proliferation (small d in terms of this model) results in rapid growth and slow development, whereas allocating more cells for differentiation

(a large d) results in slow growth but rapid early development. This is not, however, the only developmental parameter that is likely to affect growth rate. Atchley and Hall ('91) describe five "developmental units" which have the potential to affect morphological evolution. Described here relative to muscle development these parameters are: (1) number of initial precursor cells, (2) time of onset of differentiation, (3) rate of cell division, (4) fraction of PMBs dividing to produce fibers, and (5) rate of cell death. My interpretation of Ricklefs corresponds with factor 4. Inspired by Weatherley et al. ('88), who found that relative body size when fiber recruitment stops may also contribute towards differences in whole body growth, I also add (6) time of offset of differentiation. In this model, I explicitly examine four of these six factors:

1. Initial number of PMB.
2. Onset of differentiation: Age at which recruitment of muscle fibers starts. Differentiation begins at different times in ontogeny, prior to which all PMBs produce two new PMBs (d = 0). At the age of onset, d becomes a constant.
3. Rate of differentiation: In this model, rate of differentiation is determined by d, the proportion of the PMB population allocated toward differentiation at each cell cycle. Initially, I assume d is constant throughout recruitment, but this assumption is dropped later.
4. Offset of differentiation: Age at which recruitment of new muscle fibers stops. At some point, PMBs stop dividing into new muscle fibers, perhaps because the tissue has run out of PMBs, or it may be controlled independently of the number of PMBs still available. Once recruitment ceases, all further growth is derived from an increase in the size of muscle fibers rather than an increase in muscle fiber number.

I chose not to model the other two developmental parameters: mitotic rate and cell death. I did not model the former because, in the context of this model, a difference in mitotic rate reduces simply to comparing individuals at different ages (i.e., a faster mitotic rate results in more cell cycles per unit time). Note, however, that this is only true if the growth of individual fibers is proportional to the mitotic rate of presumptive myoblasts. Because the concentration of DNA remains constant throughout growth of muscle fibers and the extra DNA appears to be derived from satellite cells (Ricklefs et al., '98), growth of fibers probably is proportional to mitotic rate in muscles, although this may not be true for other tissues. Cell death is likely to be important in tissues where sculpting is critical for morphology (especially bone or skin). Recent work suggests that apoptosis may be important in some muscles (McClearn et al., '95), but incorporating cell death must wait until we know more about its role in muscle growth.

Each of the four parameters acts independently of the other three (i.e., the value of any one parameter has no qualitative effect on the behavior of any other). This fact was not intuitively obvious at first for differentiation rate, because d affects the shape of the frequency distribution of fiber sizes (see Results). I therefore simulated all other factors with several values of d. Because the value of d had no qualitative effect on how the other factors behaved, I report results for initial PMB number, onset, and offset for d = 0.2 only. When not being varied themselves, the other three factors were set at n=10 for initial number of PMBs, onset time at the second cell cycle (start = 2), and offset time at the eleventh cell cycle (stop = 11). The parameter spaces examined were: (1) an initial number of PMBs from 10 to 100, (2) onset time from the second to the tenth cell cycle, (3) rate of differentiation from 0.1 to 0.9, and (4) an offset time from the eleventh to the nineteenth (penultimate) cell cycle.

RESULTS

Growth in this model consists of two phases: (1) a "recruitment phase," during which growth is due to both hyperplasia and hypertrophy and (2) a "post-recruitment phase," after offset when no new fibers are being recruited and growth is due to hypertrophy of fibers. These phases must be kept in mind while comparing results because the characteristics of the distribution of muscle fiber sizes is different in each phase.

All four developmental parameters affected ultimate size, but only onset of differentiation (Fig. 1) and differentiation rate (Fig. 2) show a tradeoff between growth rate and development rate. Earlier onset results in rapid initial growth (and development) but a slower overall growth rate and smaller ultimate size relative to later onset (Fig. 1). Rate of differentiation has much the same effect: rapid differentiation (large d) resulting in a rapid initial increase in muscle size, but the growth-trajectory quickly reaches an asymptote (Fig. 2). A slow differentiation rate (small d) results in slower initial growth, but a larger ulti-

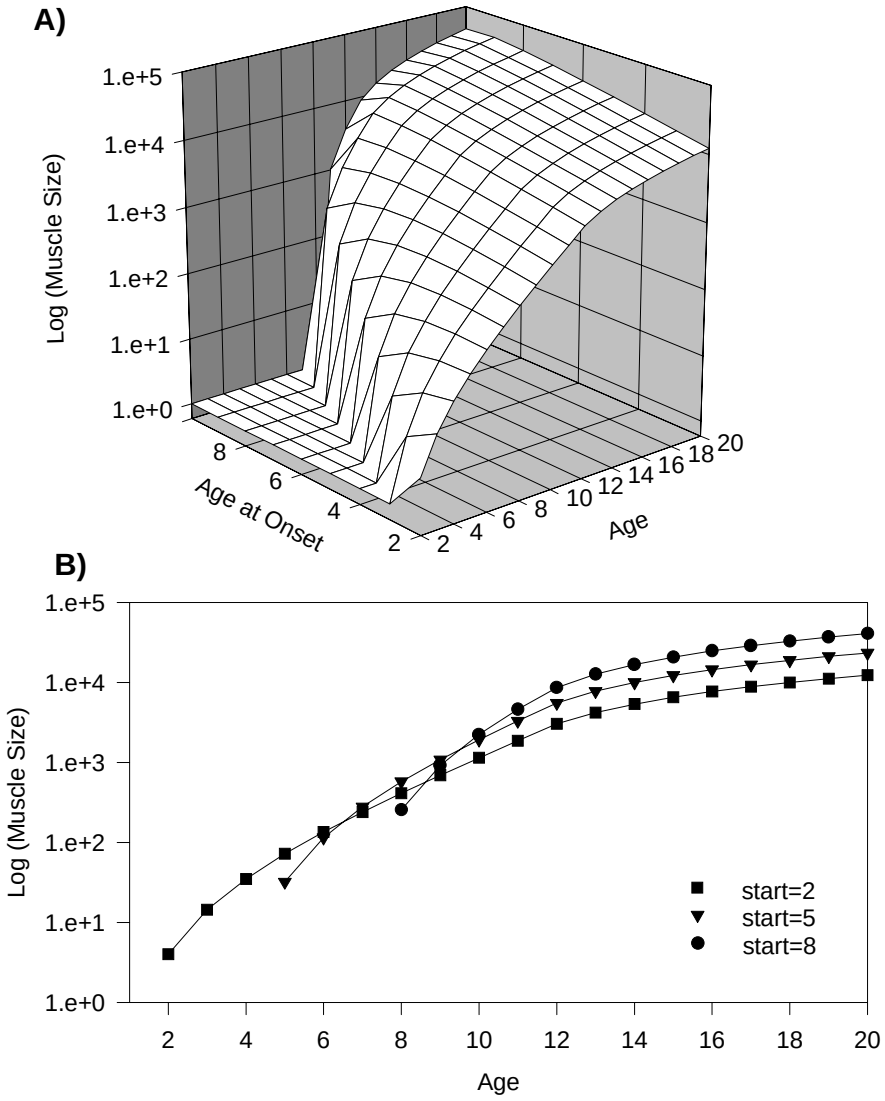

Fig. 1. Effect of onset time for differentiation on log (total muscle size) throughout ontogeny: (**A**) for the full parameter space and (**B**) cross section through the plane for three onset times. Delayed onset results in a faster overall growth rate, most of this realized lat in ontogeny. In all figures, the square represents the parameter with the slowest growth strategy, the triangle is intermediate, and the circle the fastest growth strategy. Muscle size is represented on a log scale so that relative growth rates of strategies may be compared directly.

mate size. Clearly, rapid differentiation results in a functional muscle more quickly but a smaller ultimate size and slower overall growth rate. This confirms the trend predicted in the verbal model of Ricklefs and Weremiuk ('77) and Ricklefs and Webb ('85). A slow differentiation rate and delayed onset of differentiation both result in faster overall growth rates because both build a large pool of PMBs. Because proliferation occurs at an exponential rate, it has a greater impact on growth rate than does increase in cell size, which is linear in this model. A larger initial number of PMBs results in a larger size, but no difference in relative growth rate (Fig. 3). Variation in offset time also has no effect on initial growth rate because the growth strategies do not differ at this stage. Early offset does result in a slower growth rate (when measured post-offset) but does not produce the growth-differentiation trade-off (Fig. 4).

The model offers explicit, measurable parameters that (1) distinguish fast from slow growers and (2) can be used to infer the mechanism underlying growth-rate contrasts. Empirical studies can assess differences in growth rate through phe-

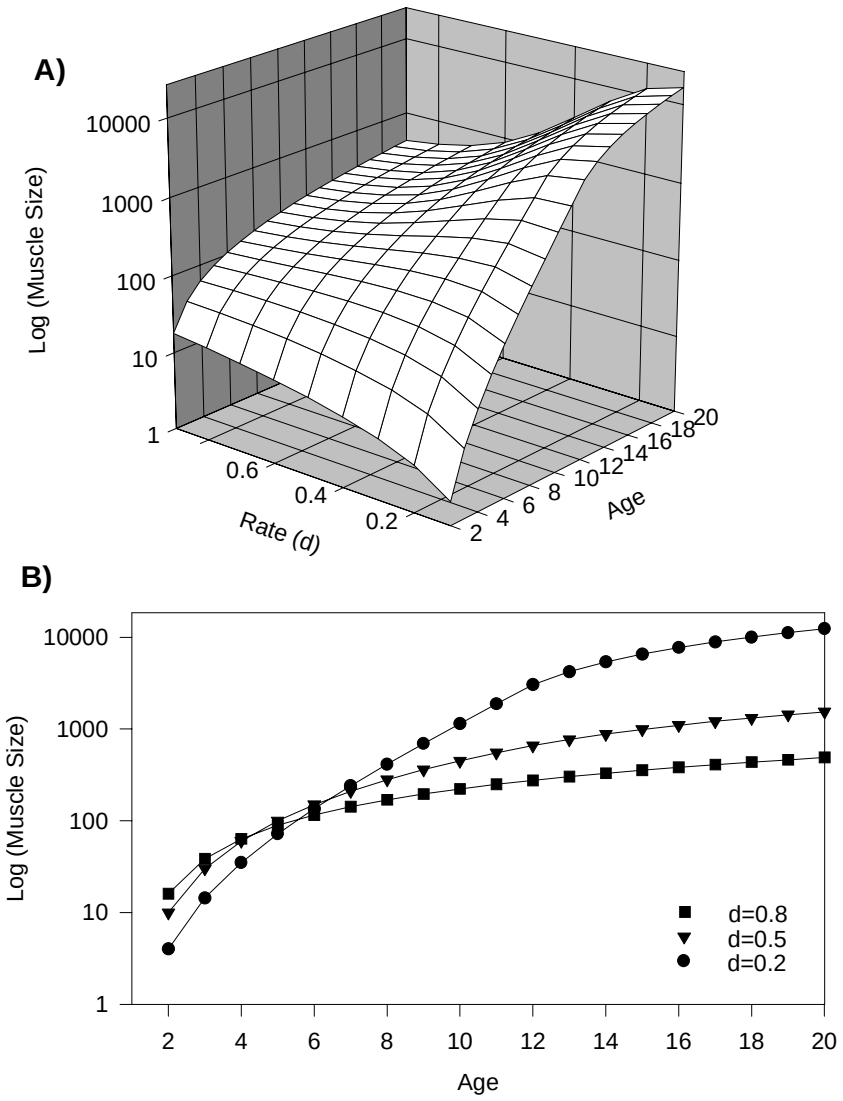

Fig. 2. Effect of changing rate (d) on log (total muscle size) throughout ontogeny. Larger d reflects a faster rate of differentiation (a greater proportion of fibers differentiate each cell cycle). (**A**) for the full parameter space and (**B**) cross section through the plane for three different rates. A slower differentiation rate results in a faster overall growth rate, most of this is realized late in ontogeny.

notypic manipulation (temperature, food level, hormone treatment) or through genetic differences (among populations or species or through genetic engineering). Measuring the complete growth trajectory for an individual is labor intensive and often impractical. Moreover, sampling muscle tissue often destroys the animal, making it impossible to get a complete trajectory. Fortunately, differences in growth rate can be detected in the distribution of fiber sizes so that empirical studies do not need both an individual's growth trajectory and periodic muscle samples to compare growth strategies. Regardless of the developmental mechanism, a fast-growing individual generally has a smaller average (mean or modal) fiber size whether growth strategies are matched for size (Fig. 5A,B) or age (Fig. 6A,B) because a greater proportion of fibers are in the smaller size classes (Fig. 7A,B). But given these differences in growth rate, is it possible to distinguish what developmental parameter(s) is responsible? It turns out that each developmental parameter leaves a unique signature on the distribution of muscle fiber sizes (Table 1).

The shape of the distribution of muscle fiber sizes depends strongly on differentiation rate (the

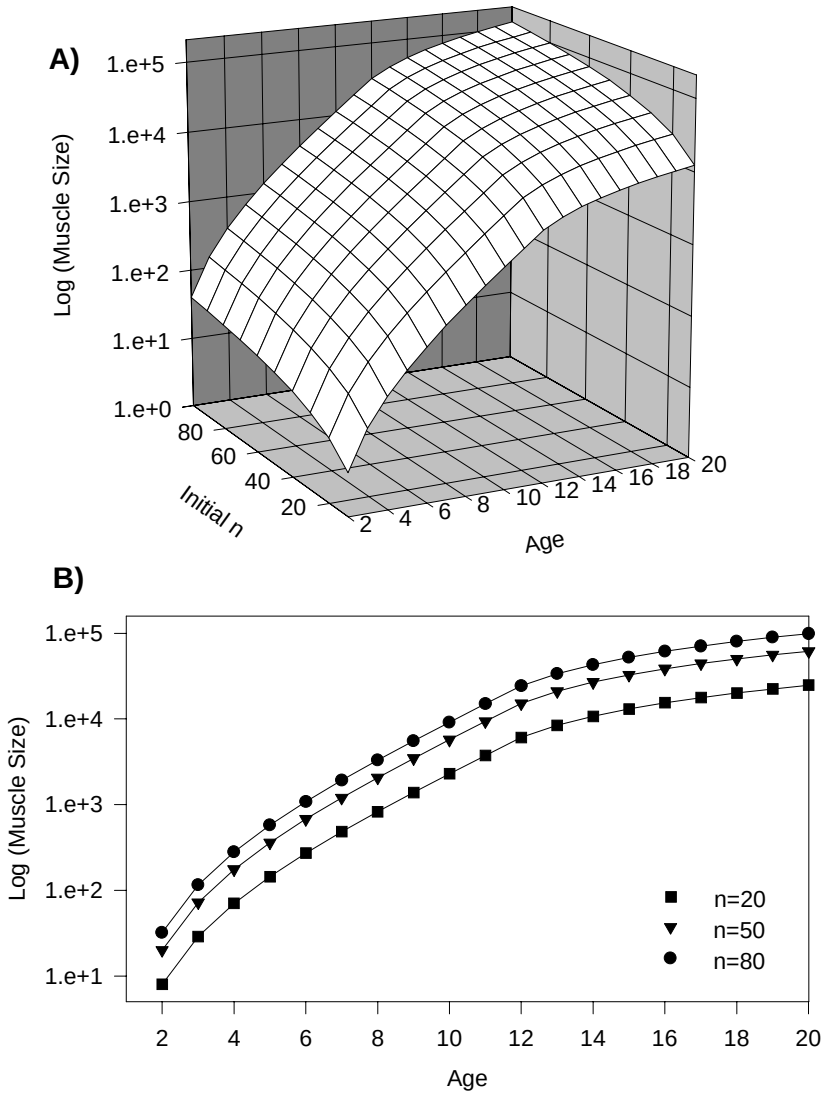

Fig. 3. Effect of changing initial number of precursor cells: (**A**) for the full parameter space and (**B**) cross section through the plane for three initial number. Note that the size lines are parallel, in (B), indicating no difference in relative growth rates.

magnitude of d). The shape of the distribution can properly be examined only during the post-recruitment phase. For large d, fibers recruited early comprise the most frequent size class, whereas for small d, fibers recruited late make up the majority of fibers. As a result, once recruitment has stopped, rapid differentiation produces a left-skewed distribution and slow differentiation produces a right-skewed distribution (Fig. 8A). However, most organisms produce a nearly normal distribution of fiber sizes (Fowler et al., '80; Weatherley and Gill, '87), which clearly is not produced by a constant d throughout ontogeny. Morris and Cowan ('95) provide empirical data that d increases throughout ontogeny in retinal cells of embryonic chicks (Morris and Cowan actually track the nondifferentiating cells, m = 1 – d, which decreases through ontogeny, their Fig. 2). If d increases throughout ontogeny, a frequency distribution nearing normal is produced (Fig. 8B). The skewed pattern still occurs (right skewed if d is on average less than 0.5, left skewed if d is on average greater than 0.5, symmetric if d averages 0.5), but it is much less pronounced. Although d has a profound effect on the shape of the frequency distribution, as already noted it does not qualitatively affect the other factors.

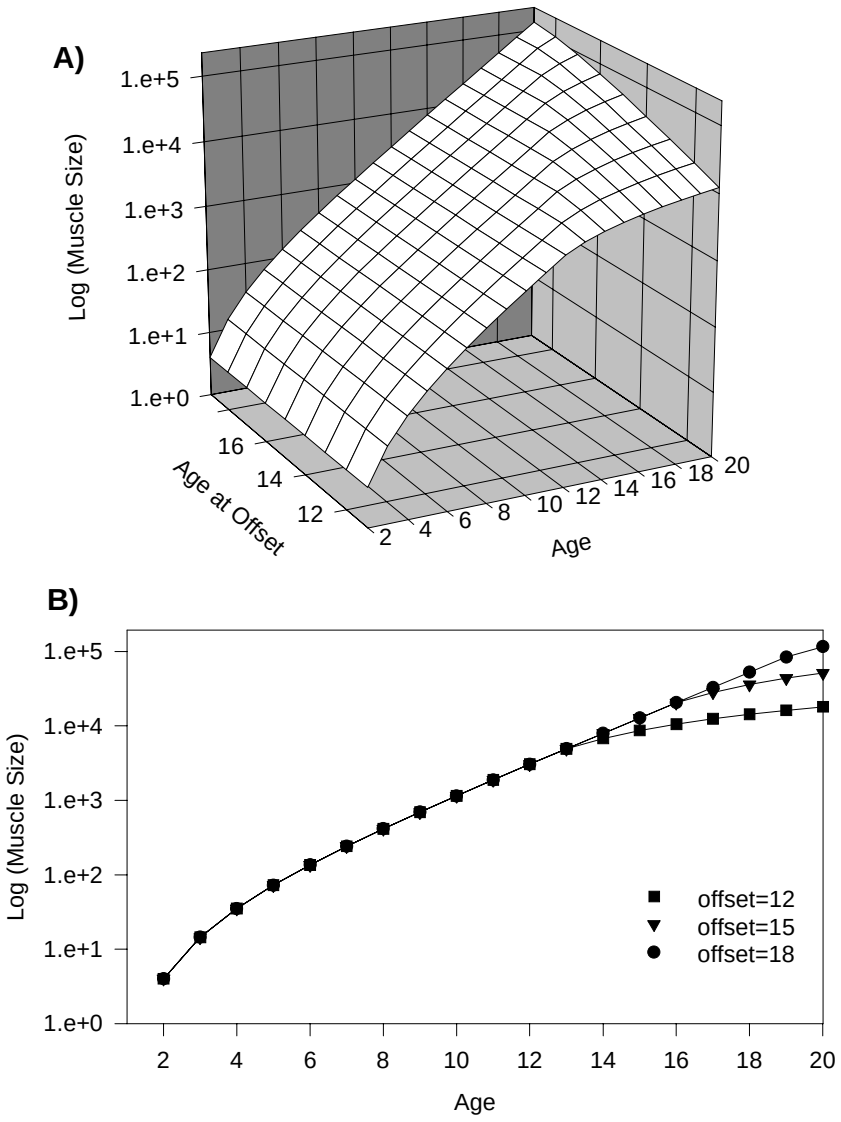

Fig. 4. Effect of changing the offset time of recruitment: (**A**) for the full parameter space and (**B**) cross section through the plane for three different stopping times. Note that offset time has no effect on most of ontogeny; it mainly affects the final size.

Differences in onset and offset can be detected by looking at the largest and smallest fiber size classes respectively. Assuming fibers all grow at the same rate, an earlier onset produces a larger maximum-fiber size when organisms are matched for age. Likewise, a later offset time result in a smaller minimum-fiber size. Neither differentiation rate nor initial number of PMBs has an effect on the range of fiber sizes. The assumption that fibers grow at a similar rate across individuals is critical in comparing maximal and minimal fiber size. This assumption is easily tested by sampling growth strategies at least twice during ontogeny, preferably post-offset so that the entire distribution of fiber sizes can be compared.

Matching growth strategies for a given age makes it easy to distinguish among differences in developmental mechanisms. However, most studies sample so that growth strategies are matched for size, not age. This intuitively seems the more appropriate comparison and is probably the one that should be used to examine the functional con-

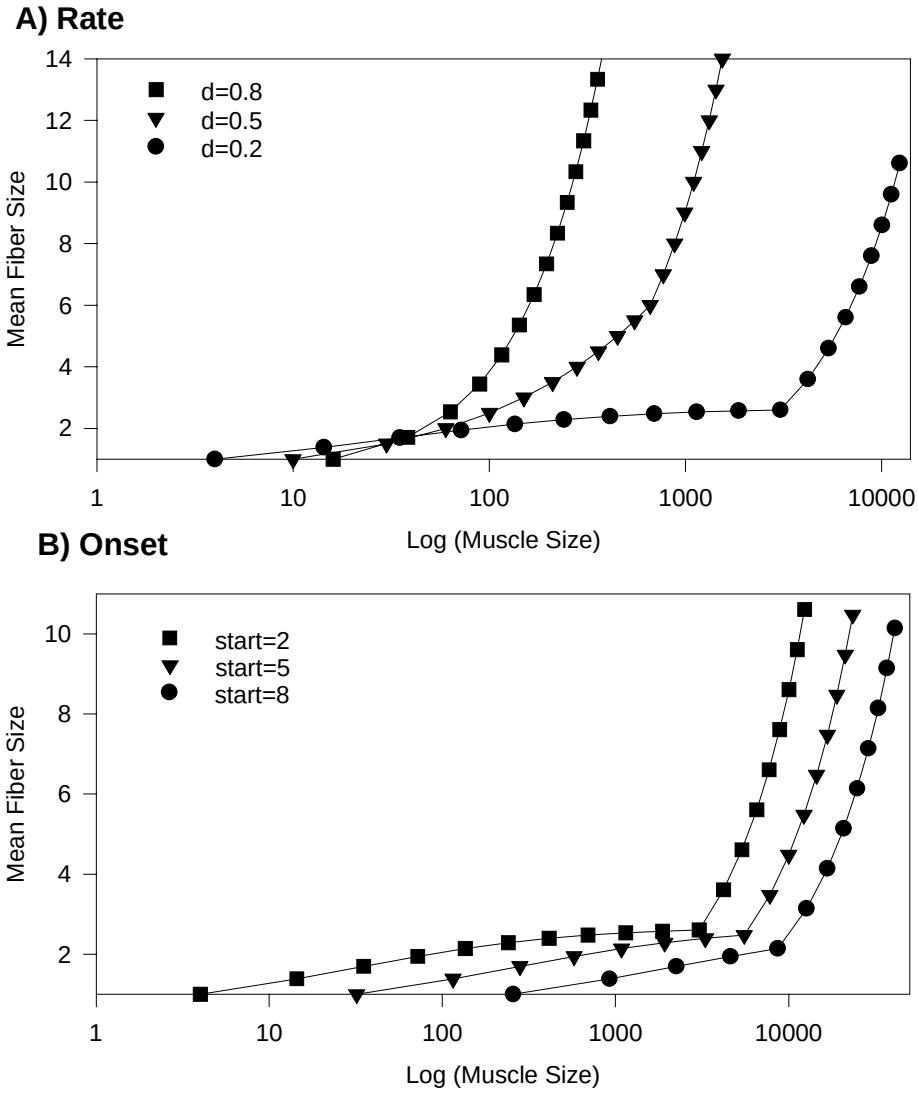

Fig. 5. Mean fiber size relative to log (total muscle size) for difference in (**A**) differentiation rate and (**B**) onset time. Note that for rate the smallest d (the fastest growth strategy) initially has the largest mean fiber size, but for most of ontogeny it has the smallest. In contrast, late onset (the fastestest growth strategy) has a smaller mean fiber size throughout ontogeny.

sequences (i.e., trade-offs) of growth strategies. The model indicates that such sampling may not be very useful for identifying the underlying developmental mechanism responsible for these differences. For example, differences in the largest-fiber size are diagnostic of changes in onset time when individuals are matched for age. Matched for size, several parameters produce a smaller largest-fiber size for a fast growth strategy (Fig. 9). Onset time has this effect throughout ontogeny (Fig. 9B), but both a small differentiation rate (Fig. 9A) and late offset time (not shown) also have this effect late in ontogeny. Depending upon when one sampled, it may not be possible to distinguish onset of differentiation from the other mechanisms when organisms are matched for size.

DISCUSSION

The model presented in this paper quantifies the verbal model of Ricklefs and Webb ('85) and Herms and Mattson ('92). A trade-off between cellular proliferation and differentiation can influence growth rate through two of the four mechanisms analyzed: rate and onset of differentiation. Rapid growth early in ontogeny limits growth later in life, but delaying recruitment of fibers allows a faster overall growth rate and larger ultimate size

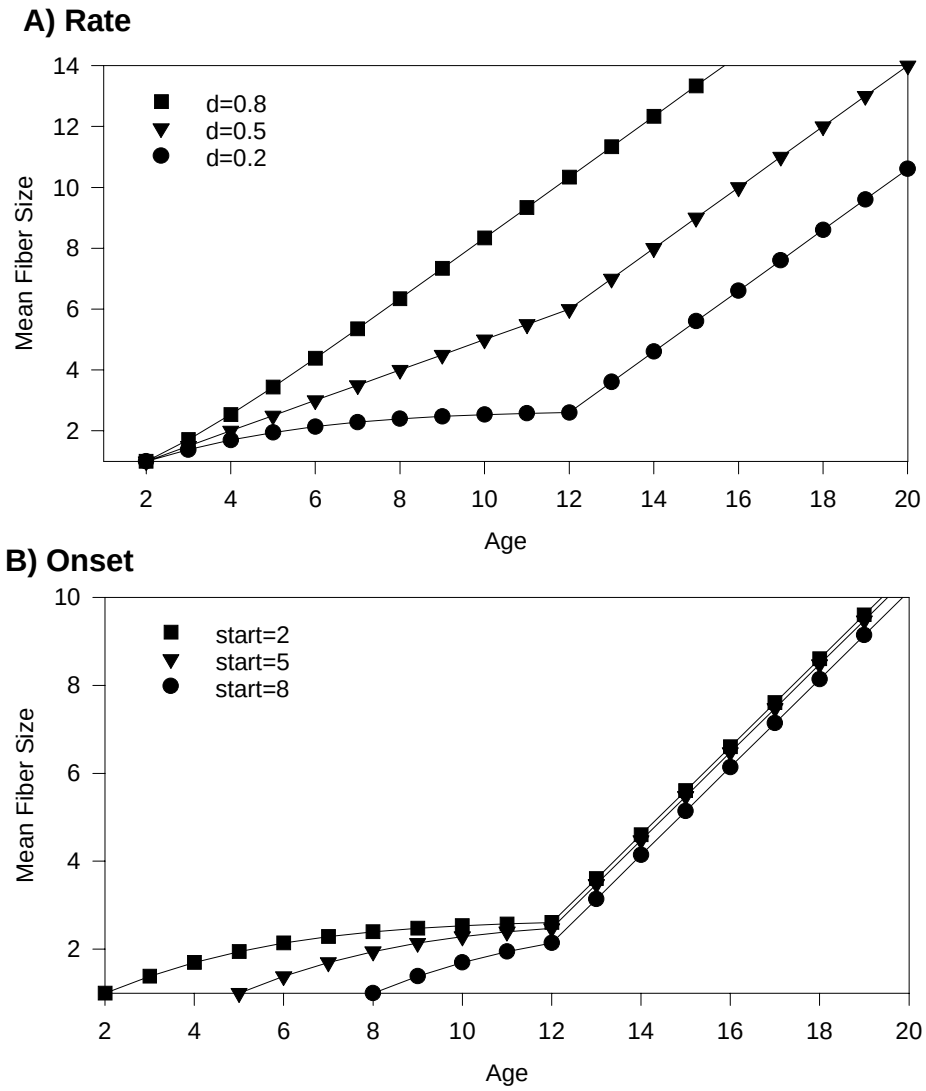

Fig. 6. Mean fiber size relative to age for (A) rate and (B) onset time. In both cases, the faster growth strategy (small d or late onset) results in a smaller mean fiber size throughout ontogeny, although this effect becomes very small for onset after recruitment of fibers stops.

(Figs. 1 and 2). This matches the pattern of growth and development described for precocial versus altricial development in birds.

The temporal trade-off between fast growth early in ontogeny versus fast growth later in ontogeny is not the only trade-off that may result. The trade-off between growth rate and development rate described by Ricklefs et al. ('94) follows directly from the temporal trade-off. As noted above, rapid growth (whether from a slow differentiation rate, delayed onset, or delayed offset) results in a smaller mean fiber size (Fig. 5). This means that, matched for size, a fast-growing organism has more young, small fibers. These fibers have had less time to accumulate contractile proteins (Ricklefs et al., '94, '98) and are thus not as efficient as the older fibers in a slow-growing individual. In addition, fibers do not pack perfectly, so that ten small fibers necessarily take up more space than one fiber with ten times the size. Because individual fibers are less mature and packing is less dense, the muscles of a fast-growing individual should be capable of producing less total force than those of a slow-growing individual when they are matched for total body size. This may explain the low swimming endurance of fast-growing fish compared with slower-growing conspecifics (Kolok and Oris, '95; Farrell et al., '97; Gregory and Wood, '98). Two other trade-offs also emerge from the perspective of this model. Many

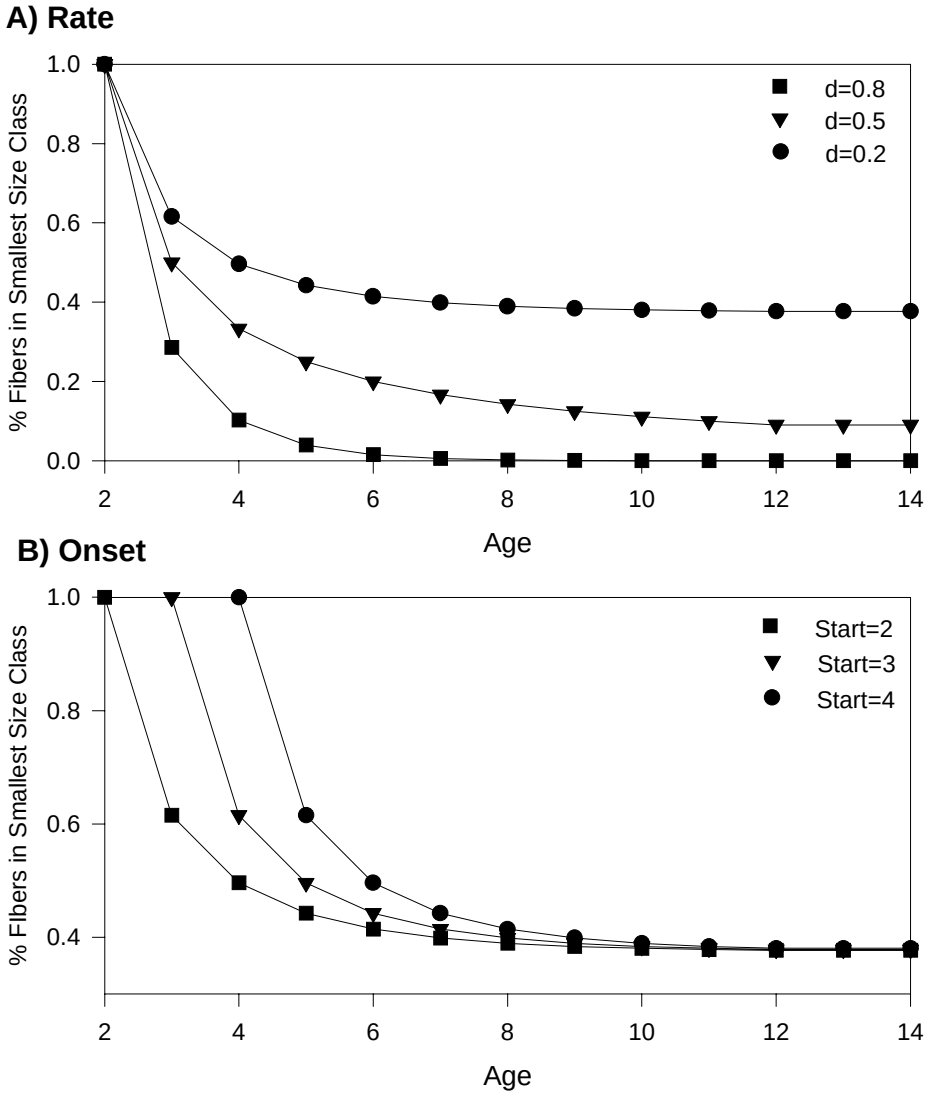

Fig. 7. Percent of fibers in the smallest size class relative to age for (**A**) rate and (**B**) onset. Note that, matched for age the faster growth strategy has a greater percentage of fibers in the smallest size class throughout ontogeny.

TABLE 1. The four developmental parameters modeled and their effects on frequency distribution of muscle fibers, overall growth pattens, and their associated trade-offs[1]

Developmental parameter[2]	Effect on frequency distribution	Growth pattern	Trade-offs
Initial number (larger)	None	Larger throughout, but no effect on relative growth rate	Tissue allocation
Onset of differentiation (delayed)	Largest fiber size is smaller Range of fiber sizes is smaller Smaller mean	Crossing trajectories	Mean fiber size Temporal effect
Rate of differentiation (slower)	Skew Smaller mean	Crossing trajectories	Mean fiber size Temporal effect
Offsect of differentiation (delayed)	Smallest fiber is smaller Range of fiber sizes is larger Smaller mean	Larger final size Growth faster once recruitment ceases	Mean fiber size Tissue allocation Reserve runout

[1]Effects on frequency distribution are those produced by a faster growth strategy relative to a slow strategy.
[2]Parenthetical terms describe how faster growth is achieved.

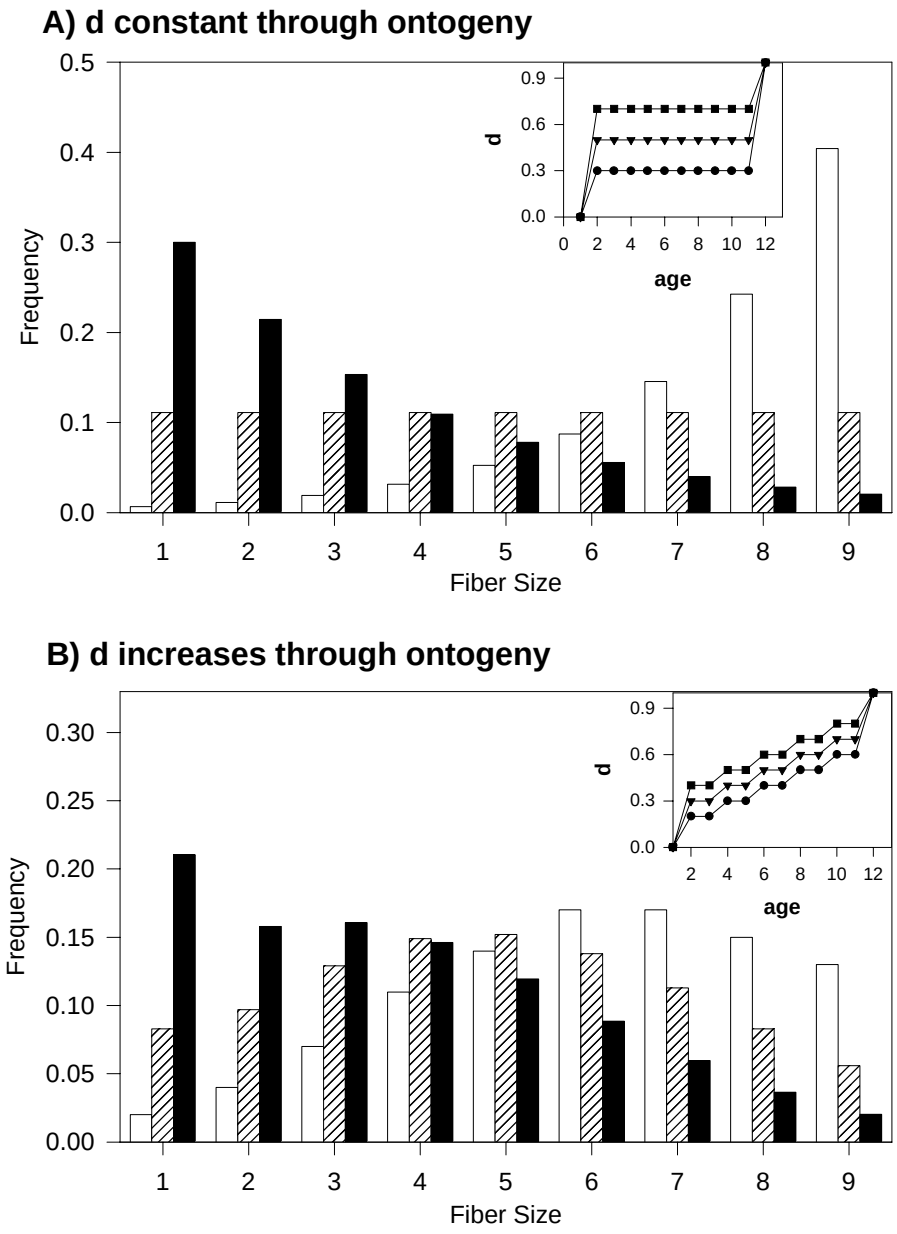

Fig 8. Effect of differentiation rate on shape of fiber-size distribution. A rapid differentiation rate (large d) results in a left-skewed distribution; a slow differentiation rate results in a right-skewed distribution. (**A**) d is constrant throughout ontogeny: open bars d = 0.7, hatched bars d = 0.5, solid bars d = 0.3. (**B**) d increases throughout ontogeny resulting in near normal distributions: open bars d averages 0.6, hatched bars d averages 0.5, solid bars d averages 0.4. Insets show how d changes throughout ontogeny, being 0 before onset and 1 after offset.

cell types can be derived from a single precursor cell and different tissues will compete for the limited supply of precursor cells (see, e.g., Nijhout and Emlin, '98). This should be especially important in determining the initial number of precursor cells. Finally, if d > 0.5 then there is a potential for using up the entire pool of precursor cell. If some precursor cells are not held in reserve, an organism is less able to repair damage that occurs later in life. Each of these trade-offs are associated with one or several of the develomental parameters modeled (Table 1). This suggests that selection to modify either growth rate or body size may occur throuth different developmental mechanisms, depending upon what trade-offs are tolerated in a specific ecological setting.

A strength of this model is that techniques already exist for testing its predictions. A number

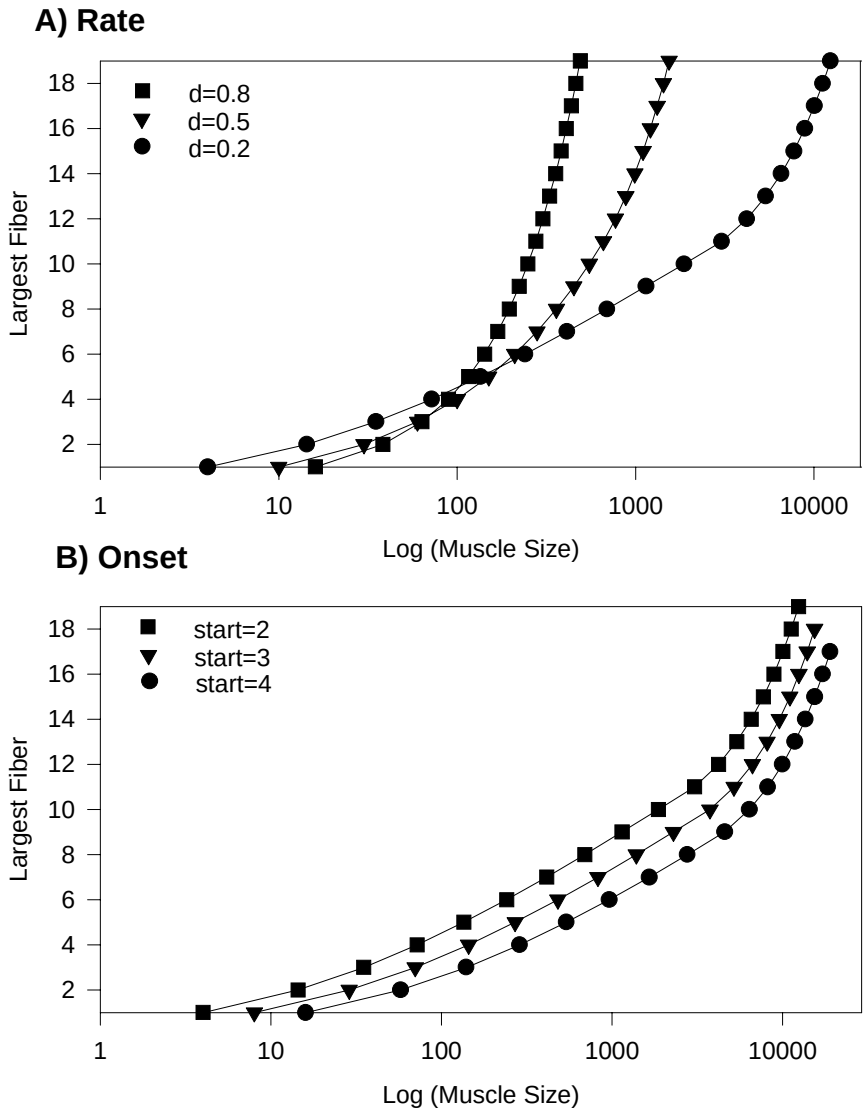

Fig. 9. Largest fiber detectable when growth strategies are matched by size for (**A**) differentiation rate and (**B**) onset time. This trait is diagnostic for onset time when strategies are matched for age. However, when matched for size the fastest growth strategy results in a smaller largest-fiber for both rate and onset time late in ontogeny.

of studies compare the distributions of muscle fiber sizes among genotypes with known differences in growth rate. The purpose of most of these studies was to determine whether fiber number or fiber size determined the growth differences. Towards this end, data were usually collected prior to the offset of fiber recruitment, before the optimal time for distinguishing among developmental parameters (Table 1). As such, the data currently published are not adequate for testing the predictions of the model. One encouraging result to emerge from these studies is that, matched for body size, the faster-growing animals all had smaller mean fiber diameters in agreement with the model (Weatherley and Gill, '84, '87; Weatherley et al., '88; Meyer-Rochow and Ingram, '93; Alami-Durante et al., '97). In addition, the model allows us to reinterpret some of the conclusions in these papers. Weatherley and Gill ('87; Weatherley et al., '88) broadly surveyed species of teleost fish and found a strong correlation between body size at which recruitment of new muscle fibers stop and the maximum body size characteristic for that species. Overall, recruitment stops when a fish reaches about 44% of its ultimate size, leading Weatherley and Gill to conclude that larger, faster

growing species continue to recruit new fibers to a larger body size than do smaller, slower-growing species. The model supports this conclusion, but these results cannot be used to infer anything about the underlying developmental mechanisms. When growth strategies are matched for size, onset time, offset time, and differentiation rate all show positive correlations among growth rate, ultimate body size, and size at which recruitment stops. In fact, all three developmental parameters produce results qualitatively similar to Figures 2, 3, and 4 of Weatherley et al. ('88). In order to infer anything about the underlying developmental mechanisms, growth strategies must be matched for age rather than size.

Fowler et al ('80) is the only study I know of where fiber recruitment is compared at both size and age. They compared the fiber-size distribution in a line of Japanese quail selected for large size at four weeks of age (the P line) with an unselected control (C) line. All muscles were analyzed post-offset, giving us a more accurate view of recruitment mechanisms. Looking at the diagrams of fiber-size distributions (Fig. 1 of Fowler et al., '80) , matched for age, the P line clearly has an earlier onset time (the maximal fiber-size class is larger) and a similar offset time (the minimum fiber size is the same). There appears to be a slight left skew for the P line implying a larger d, although this is quite small. In terms of the above model, the earlier onset and faster differentiation of the P line should result in a slower growth rate relative to the C line, but the P line has a faster total body growth rate. The apparent contradiction is resolved by recognizing differences between the P and C line in terms of tissue allocation. Although the P line grows faster overall, the muscles are disproportionately small relative to whole body mass. Muscle mass is actually smaller in the P line than in the C line when the two are matched for body mass (Fowler et al., '80; Lilja et al., '85). It appears that muscle is growing more slowly in the P line in agreement with the model.

My final example resolves an apparent contradiction in the literature. Aquaculturists have considered temperature manipulation as a potential mechanism to accelerate yield in fish because warm temperature accelerates embryonic development. Stickland et al. ('88; see also Ulsher et al., '94) confirmed that Atlantic salmon eggs maintained at warm temperatures resulted in faster embryonic development but similarly sized hatchlings (suggesting faster growth) relative to young from eggs raised at cool temperatures (the former hatching in 54 days; the latter taking 127 days). They also showed that the warm-reared hatchlings had fewer but larger muscle fibers. That is, the faster growth is due to fiber growth rather than fiber recruitment, which they contrast to Weatherley and Gill's ('87; and see above) conclusions for teleosts. The model explains this apparent contradiction because Stickland et al. ('88) were working with embryonic growth while Weatherley and Gill ('87) describe growth in juveniles and adults. The growth patterns described above show that rapid differentiation or early onset does result in faster growth early (Figs. 1 and 2) but that this is not sustained throughout most of ontogeny. The model predicts that warm-reared hatchlings are not able to sustain their rapid growth, and should ultimately produce smaller adults. If this proves true, then the model also provides a sober warning to aquaculturists. Although rearing eggs at warm temperatures accelerate embryonic development and increases the rate at which young can be produced, it results in smaller, slower-growing adults.

This model is a first step towards removing some of the circularity implicit in previous definitions of a growth-development trade-off (Ricklefs et al., '98). By describing specific underlying mechanisms and means of identifying them, a priori predictions about patterns of growth and development can be tested. Current empirical examples can be interpreted in terms of the model but are not sufficient for testing this model because of how samples have been collected. Sampling from organisms of known age is more useful in distinguishing developmental parameters (Atchley and Hall, '91) than are size-based comparisons. In addition, size distributions of fibers collected post-recruitment are more informative than those collected from individuals still actively recruiting cells. Fortunately, this is easy to do with birds and mammals (where recruitment ends soon after birth), and Weatherley et al. ('88) have determined the general size at which this occurs in fish. Finally, samples must be taken at multiple ages to confirm that fibers are growing at a similar rate across growth strategies.

Perhaps the most promising return for integrating development and evolution is a better understanding of how adaptive variation arises and evolves. However, most current attempts at integration continue to emphasize subcellular and gene level patterns in both fields. If we are to understand how cellular processes translate into variation at the level of the organism, it is criti-

cal that we develop predictive models such as this one. Studies at the gene level elucidate biochemical interactions, but if there are several developmental mechanisms for solving a given evolutionary problem, (see Cohan, '84 for an empirical example, this model for a theoretical example), then such studies can tell us little about the control of development at the level of the organism. Developmental models such as this offer new approaches for attacking current problems in functional morphology, life-history strategies, and phenotypic evolution. Several recent studies in fish suggest that swimming ability may be compromised by rapid growth (Kolok and Oris, '95; Farrell et al., '97; Gregory and Wood, '98). How does this relate to the composition of muscle fiber sizes in these fish? A trade-off between growth and development also has important implications for life-history theory (Herms and Mattson, '92). Most life-history models are concerned with body size at maturation because fecundity increases with size and risk of predation usually decreases with size. A growth-development trade-off means that not only is one's size at maturation important, but also how one got to be that size (e.g., Pigliucci et al., '97).

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