A general model for ontogenetic growth

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Several equations have been proposed to describe ontogenetic growth trajectories for organisms justified primarily on the goodness of fit rather than on any biological mechanism1–5. Here, we derive a general quantitative model based on fundamental principles6–9 for the allocation of metabolic energy between maintenance of existing tissue and the production of new biomass. We thus predict the parameters governing growth curves from basic cellular properties10 and derive a single parameterless universal curve that describes the growth of many diverse species. The model provides the basis for deriving allometric relationships for growth and the timing of life history events2,11,12.

Ontogenetic development is fuelled by metabolism and occurs primarily by cell division. Incoming energy and materials from the environment are transported through hierarchical branching network systems to supply all cells. These resources are transformed into metabolic energy, which is used for life-sustaining activities. During growth, some fraction of this energy is allocated to the production of new tissue. Thus, the rate of energy transformation is the sum of two terms, one of which represents the maintenance of existing tissue, and the other, the creation of new tissue. This is expressed by the conservation of energy equation:

\[ B = \sum_i N_i B_i + E_i \frac{dN_i}{dt} \] (1)

The incoming rate of energy flow, \( B \), is the average resting metabolic rate of the whole organism at time \( t \), \( B_i \) is the metabolic rate of a single cell, \( E_i \) is the metabolic energy required to create a cell and \( N_i \) is the total number of cells; the sum is over all types of tissue. Possible differences between tissues are ignored and some average typical cell is taken as the fundamental unit. The first term, \( N_i B_i \), is the power needed to sustain the organism in all of its activities, whereas the second is the power allocated to production of new cells and therefore to growth. \( E_i \), \( B_i \), and the mass of a cell, \( m_i \), are assumed to be independent of \( m \) remaining constant throughout growth and development.

At any time \( t \) the total body mass \( m = m_N \), so equation (1) can be written as

\[ \frac{dm}{dt} = \left( \frac{m_i}{E_i} \right) B - \left( \frac{B_i}{E_i} \right) m \] (2)

Now, if \( B = B_m m^{3/4} \), where \( B_m \) is constant for a given taxon, then

\[ \frac{dm}{dt} = am^{3/4} - bm \] (3)

with \( a = B_m E_i / m_i \) and \( b = B_i / E_i \). The 3/4 exponent is well supported by data on mammals13,14, birds15,16, fish13,17, molluscs18 and plants19. Although some mammals may show fluctuations around 3/4-power scaling owing to ‘growth spurts’ (ref. 1), the 3/4 exponent describes the overall allometry of \( B \) from birth to reproductive maturity. For altricial birds, hatchlings are supplied with a store of metabolically inert water which is expended during growth, and when this is taken into account in relating \( N_i \) to \( m \), \( B \propto m^{3/4} \) (ref. 14).

Recently, a model was developed for understanding the 3/4 exponent and, more generally, the ubiquitous 1/4 power occurring in biological allometry20,21. It is based on the premise that the tendency of natural selection to optimize energy transport has led to the evolution of fractal-like distribution networks. The 3/4 exponent was shown to be related to the scaling of the total number (\( N_i \)) of terminal units (capillaries) in the network: \( B \propto N_i \propto m^{3/4} \). In contrast, the total number of cells, \( N_i \propto m \). Thus, the reason for the different exponents of \( m \) in the two terms on the right-hand side of equation (3) is that the network constrains the total number of supply units (capillaries) to scale differently from the total number of cells supplied21. This imbalance between supply and demand ultimately limits growth. If the exponents were the same, then \( dm/dt \neq 0 \) and organisms would continue to grow indefinitely. We therefore have a fundamental explanation for the origin of determinate growth in which an asymptotic maximum body size (\( M \)) is reached. This occurs when \( dm/dt = 0 \), giving \( M = (a/b)^{3/4} = (B_m m_i/b_i)^{3/4} \). Thus, the variation in \( M \) among species within a taxon, where \( B_0 \) and \( m_0 \) do not change, is determined by the systematic variation of the in vivo cellular metabolic rate, \( B_i \), which scales as \( M^{-3/4} \). Within a taxon \( B_0 \), \( m_i \), and \( E_i \) are approximately constant, so \( a \) should be approximately independent of \( M \), whereas \( b = (a/M^{3/4}) \) should scale as \( M^{3/4} \). Between groups, however, \( a \) should vary, principally reflecting variations in \( B_i \). Equation (3) can therefore be re-expressed as

\[ \frac{dm}{dt} = am^{3/4} \left( 1 - \left( \frac{m}{M} \right)^{3/4} \right) \] (4)

Although equations (3) and (4) are superficially similar in structure to that of von Bertalanffy22, they differ significantly in that they are derived from basic principles so that the parameters governing growth, \( a \) and \( b \), are directly calculable from fundamental cellular parameters.

A classical sigmoidal curve (see Supplementary Information) is obtained from integrating equation (4):

\[ \left( \frac{m}{M} \right)^{3/4} = 1 - \left( 1 - \left( \frac{m_0}{M} \right)^{3/4} \right) e^{-a/M^{3/4}} \] (5)

Here, \( m_0 \) is the mass at birth (\( t = 0 \)). In Fig. 1 we plot some examples of \( m \) versus \( t \) for four very different animals and fit the data using equation (5). Values of \( a \), \( m_0 \) and \( M \) for these and several other species can be found in Table 1. Consistent with our predictions, \( a \) varies only modestly within a taxon, whereas across taxa, \( a \propto B_i \), as confirmed by a positive correlation with \( B_0 \) (coefficient of correlation, \( r^2 = 0.82 \); \( n = 5 \); \( P = 0.035 \))21. Perhaps more significantly, the magnitudes of \( a \) and \( b \) can be independently determined from fundamental parameters of the cell. The energy content of mammalian tissue has been measured to be about \( 7 \times 10^9 \) J kg\(^{-1} \) (refs 11, 19), so, if \( m_i \approx 3 \times 10^{-9} \) g, the energy needed to create a cell

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<th>Table 1 Values of several parameters for various organisms</th>
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a, see equation (3); \( m_0 \), birth mass; \( M \), asymptotic mass. Also shown are the negative mean values of the slopes of plots of ln(\( R/R_0 \)) versus ln(\( M/M_0 \)) which is predicted to have a universal value of 1; \( R = [1 - (V/V_i)^{3/4}] \) is the proportion of metabolic power devoted to growth.
Four typical examples of fits to growth curves (solid lines) using equation (5). For definition of growth parameter $a$, see equation (3). $M$, asymptotic mass; $m_0$, birth mass.

**Guinea pig**

$a = 0.200$

$M = 840$

$m_0 = 5$

**Guppy**

$a = 0.104$

$M = 0.15$

$m_0 = 0.008$

**Hen**

$a = 0.502$

$M = 2,050$

$m_0 = 43$

**Cow**

$a = 0.276$

$M = 442,000$

$m_0 = 33,333$

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**Figure 1** Four typical examples of fits to growth curves (solid lines) using equation (5). For definition of growth parameter $a$, see equation (3). $M$, asymptotic mass; $m_0$, birth mass.
For fish with external fertilization, and organisms, more than half of their metabolic power at birth is used for growth. For a cow that lives for 20 years, we obtain $E_t/E_{tot} \approx 1\%$. On the other hand, growth accounts for almost 10% of its total metabolic energy expended before maturity.

$R$ is maximal at birth, where $R(0) = 1 - (m/M)^{1/4}$. If $m/M < 1/16$, then $R(0) > 1/2$, so, for the vast majority of organisms, more than half of their metabolic power at birth is used for growth. For fish with external fertilization, and organisms, more than half of their metabolic power at birth is used for growth. The point of inflection, where growth rate is maximal (at $t_d = 0$), occurs when $m = (3/4)^{4}M \approx (1/3)M$ at which point $dN/dt = (27/256)aM^{1/4}$ and $R = 1/4$, independent of $M$. For some indeterminate growers this is never reached and growth continues to accelerate throughout life. On the other hand, for a 1 kg determinate growing mammal this gives $dN/dt \approx 6$ g per day, in agreement with data.

Three important points need clarification. The first is cell replacement. Throughout ontogeny cells are dying and being replaced by mitosis. The power required for this is included in $E$. Throughout ontogeny cells are dying and being replaced by mitosis. The power required for this is included in $E$. The second point is the difference between determinate and indeterminate growth. Once such organisms reach their age for first reproduction and there is no need during growth to modify the above equations to reflect energy allocation to reproduction. After maturation, reproduction is assumed to be fuelled by metabolic scope where metabolic rate is increased severalfold above the resting level to fuel activities such as thermoregulation and migration, as well as reproduction.

The third point concerns energy allocation to reproduction in indeterminate growth. Once such organisms reach their age for first reproduction ($t_2$), a significant fraction of metabolic rate is devoted to reproduction, and the growth rate is reduced. Consider the case of oviparous organisms. Egg production can be incorporated into equation (1) by adding a term $E \cdot dN/dt$ to the right-hand side when $t > t_m$.

$$\text{Figure 2}$$

Universal growth curve. A plot of the dimensionless mass ratio, $r = 1 - R = (m/M)^{1/4}$, versus the dimensionless time variable, $\tau = (dt/4M^{1/4}) - \ln[1 - (m/M)^{1/4}]$, for a wide variety of determine and indeterminate species. When plotted in this way, our model predicts that growth curves for all organisms should fall on the same universal parameterless curve $1 - e^{-r}$ (shown as a solid line). The model identifies $r$ as the proportion of total lifetime metabolic power used for maintenance and other activities.
$m_t = m_l \Delta N_t$, is a constant fraction, $\lambda$, of body mass: $m_t \approx \lambda m_l$. Thus $E_l \Delta N_t / \Delta t \approx (\lambda E_l/t_l) N_l$. This is proportional to $N_l$ and so has the identical structure to the maintenance term, $N_l B_m$, in equation (1). Thus, the solution, equation (5), is the same after reproduction ($t > t_t$) as before ($t < t_t$), except that $B_l$ is replaced by $(B_l + \lambda E_l/t_l)$. In subsequent equations, $a$, therefore remains the same before and after $t_t$, whereas $b$ changes to $b' = (b + \lambda t_l)$. Consequently, because egg production continues throughout life, the actual asymptotic mass decreases from $M = (ab)^t$ to $M' = (ab')^t = (1 + ab')^{t-l} M$. As an example, our fit to cod data ($M' \approx 25$ kg) gives $b' \approx 1.3 \times 10^{-3}$ days$^{-1}$. To get a rough estimate for the reproductive contribution we take $\lambda \approx 10\%$ (refs 11, 21) and $t_l \approx 1$00 days and obtain $\lambda t_l = 1 \times 10^{-3}$ days$^{-1}$, giving $b' \approx 0.3 \times 10^{-3}$ days$^{-1}$. This value indicates that reproduction represents a significant portion of energy allocation. Thus, the proportion of maintenance energy allocated to reproduction relative to other activities, $E_l \Delta N_t / N_t B_m \approx \lambda + b't_l$, could be as much as a factor of 3. Consequently $M'/M = (1 + \lambda b't_l)^{-1}$ could be as small as $10^{-3}$. Thus $M \gg m_l$, so, for times before first reproduction ($t < t_t$), the solution is insensitive to $b = aM^{14}$ and growth is determined primarily by $a$. In general, separate equations operate before and after $t_t$ for most indeterminate growers, however, $t_t$ is much smaller than lifespan, $t_t \ll t_l$, so growth is well approximated by a single equation—equations (4) or (5)—for all $t$ with $b'$ (and $M'$) replacing $b$ (and $M$). These equations therefore apply to indeterminate and determinate growers with maintenance including reproduction and $M$ being interpreted as $M'$ in Table 1 and Fig. 2.

We have derived a very general growth equation from first principles on the basis of the conservation of metabolic energy, the allometric scaling of metabolic rate, and the energetic cost of producing and maintaining biomass (cells). The framework differs from recent work that has focused more on trade-offs involving producing and maintaining biomass (cells). The framework differs from recent work that has focused more on trade-offs involving producing and maintaining biomass (cells).

Supplementary information is available on Nature’s World-Wide Web site (http://www.nature.com) or as paper copy from the London editorial office of Nature.

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Hyperpolarization-activated channels HCN1 and HCN4 mediate responses to sour stimuli

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Sour taste is initiated by protons acting at receptor proteins or channels. In vertebrates, transduction of this taste quality involves several parallel pathways1−5. Here we examine the effects of sour stimuli on taste cells in slices of vallate papilla from rat. From a subset of cells, we identified a hyperpolarization-activated current that was enhanced by sour stimulation at the taste pore. This current resembled $I_h$ found in neurons and cardio-myocytes6, a current carried by members of the family of hyperpolarization-activated and cyclic-nucleotide-gated (HCN) channels8−13. We show by in situ hybridization and immunohistochemistry that HCN1 and HCN4 are expressed in a subset of taste cells. By contrast, gustducin, the G-protein involved in bitter and sweet