A general model for ontogenetic growth

Geoffrey B. West*†, James H. Brown†‡ & Brian J. Enquist§

* *Theoretical Division, MS B285, Los Alamos National Laboratory, Los Alamos, New Mexico 87545, USA*
† *The Santa Fe Institute, 1399 Hyde Park Road, Santa Fe, New Mexico 87501, USA*
‡ *Department of Biology, University of New Mexico, Albuquerque, New Mexico 87131, USA*
§ *Department of Ecology and Evolutionary Biology, University of Arizona, Tucson, Arizona 85721, USA*

Several equations have been proposed to describe ontogenetic growth trajectories for organisms justified primarily on the goodness of fit rather than on any biological mechanism[1–6]. Here, we derive a general quantitative model based on fundamental principles[7–9] 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 properties[10] 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 rates and the timing of life history events[2,11,12].

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:

$$B = \sum_{c}\left[N_c B_c + E_c \frac{dN_c}{dt}\right] \quad (1)$$

The incoming rate of energy flow, B, is the average resting metabolic rate of the whole organism at time t, B_c is the metabolic rate of a single cell, E_c is the metabolic energy required to create a cell and N_c 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, $N_c B_c$, 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_c, B_c, and the mass of a cell, m_c, are assumed to be independent of m remaining constant throughout growth and development.

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

$$\frac{dm}{dt} = \left(\frac{m_c}{E_c}\right)B - \left(\frac{B_c}{E_c}\right)m \quad (2)$$

Now, if $B = B_0 m^{3/4}$, where B_0 is constant for a given taxon, then

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

with $a \equiv B_0 m_c/E_c$ and $b \equiv B_c/E_c$. The 3/4 exponent is well supported by data on mammals[1,13], birds[14], fish[15,16], molluscs[17] and plants[18]. 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_c 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 allometry[7,8]. 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_t) of terminal units (capillaries) in the network: $B \propto N_t \propto m^{3/4}$. In contrast, the total number of cells, $N_c \propto m$. 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 supplied[7,8]. 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 $M = (a/b)^4 = (B_0 m_c/B_c)^4$. Thus, the variation in M among species within a taxon, where B_0 and m_c do not change, is determined by the systematic variation of the *in vivo* cellular metabolic rate, B_c, which scales as $M^{-1/4}$. Within a taxon B_0, m_c and E_c are approximately constant, so a should be approximately independent of M, whereas b ($= a/M^{1/4}$) should scale as $M^{-1/4}$. Between groups, however, a should vary, principally reflecting variations in B_0. Equation (3) can therefore be re-expressed as

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

Although equations (3) and (4) are superficially similar in structure to that of von Bertalanffy[6], 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):

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

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, $a \propto B_0$, as is confirmed by a positive correlation with B_0 (coefficient of correlation, $r^2 = 0.82$; $n = 5$; $P = 0.035$)[11]. 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 7×10^6 J Kg^{-1} (refs 11, 19), so, if $m_c \approx 3 \times 10^{-9}$ g, the energy needed to create a cell

Table 1 Values of several parameters for various organisms

Organism	a	m_0	M	Slope
Cow	0.28	33.3 kg	442 kg	1.08
Pig	0.31	0.90 kg	320 kg	1.08
Rabbit	0.36	0.12 kg	1.35 kg	1.34
Guinea pig	0.21	5 g	840 g	0.91
Rat	0.23	8 g	280 g	1.07
Shrew	0.83	0.3 g	4.2 g	0.98
Heron	1.56	3 g	2.7 kg	1.04
Hen	0.47	43 g	2.1 kg	0.72
Robin	1.9	1 g	22 g	1.03
Cod	0.017	0.1 g	25 kg	1.01
Salmon	0.026	0.01 g	2.4 kg	1.01
Guppy	0.10	0.008 g	0.15 g	1.04
Shrimp	0.027	0.0008 g	0.075 g	0.82

a, see equation (3); m_0, birth mass; M, asymptotic mass. Also shown are the negative mean values of the slopes of plots of $\ln[R(t)/R(0)]$ versus $at/4M^{1/4}$ which is predicted to have a universal value of 1; $R \equiv [1 - (m/M)^{1/4}]$ is the proportion of metabolic power devoted to growth.

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in vivo, $E_c \approx 2.1 \times 10^{-5}$ J. Taking $B_0 \approx 1.9 \times 10^{-2}$ W (ref. 11) then gives $a \equiv B_0 m_c/E_c \approx 0.25\,g^{1/4}$ per day, in good agreement with data (Table 1). Asymptotic masses, M, or equivalently b, could be predicted if B_c *in vivo* were independently known.

Equation (5) suggests powerful ways of plotting the data that reveal universal properties of growth. If the dimensionless mass ratio, $r \equiv (m/M)^{1/4}$, is plotted against a dimensionless time variable, $\tau \equiv at/4M^{1/4} - \ln[1 - (m_0/M)^{1/4}]$, then equation (5) predicts that all species, regardless of taxon, cellular metabolic rate (B_c), or mature body size (M), should fall on the same parameterless universal curve $r = 1 - e^{-\tau}$. Data for a wide variety of animals (mammals, birds, fish, crustacea) clearly show such universal properties, as illustrated by Fig. 2. We note that τ includes an adjustment for m being non-zero at birth ($t = 0$). An alternative way of exhibiting this universality is to introduce $R \equiv [1 - (m/M)^{1/4}] = 1 - r$, in which case equation (5) becomes $R(t) = R(0)e^{-at/4M^{1/4}}$. A plot of $\ln[R(t)/R(0)]$ versus $at/4M^{1/4}$ should yield a universal straight line of slope −1. The slopes for 13 species of animals are all very close to −1, their mean being -0.99 ± 0.04; see Table 1.

The quantities, r and R, have an elegant interpretation as the relative proportions of total available metabolic power (B) that, respectively, fuel maintenance and growth. To see this, note that from equation (1), relative maintenance is given by $N_c B_c/B = (B_c/B_0 m_c)m^{1/4} = (b/a)m^{1/4} = (m/M)^{1/4} = r$, independently of any other parameter. Thus, Fig. 2 represents the proportion of power devoted to maintenance and other activities plotted as a function of dimensionless time, τ. Similarly, the proportion of total metabolic power devoted to growth is $1 - r = [1 - (m/M)^{1/4}] = R$. This therefore has a universal exponentially decreasing behaviour as a function of $at/4M^{1/4}$ throughout ontogeny. Consequently, the proportion of B used for growth is the same for all species at the same stage of development, as measured relative to their asymptotic mass, M. For example, for all organisms, $R \approx 50\%$ ($R = 1 - (1/15)^{1/4} \approx 0.49$) when $m = M/15$, whereas it is around 16%, when $m = M/2$. These occur at very different temporal stages of ontogenetic development for different species. For example, at birth, a cow weighing about 40 kg ($\sim M/15$ if $M \approx 600$ kg; ref. 1), is expending about half of its metabolic power growing. After one year it has reached about half of its adult size ($m = M/2 \approx 300$ kg) and is allocating only 16% to growth. A codfish, however, almost always dies well before reaching $M/2$ ($M \approx 25$ kg; ref. 20); its maximum size is typically 6 kg ($\sim M/4$) reached at an age of around 10 years. Furthermore, it is already about 6 years old when its mass is only $M/15$ ($\sim$1.5 kg), at which stage it is still using about half of its metabolic power in continuing to grow.

For an organism with indeterminate growth, a substantial percentage of total metabolic energy is allocated to growth when its energy is integrated over its total lifespan. The lifetime allocation to growth is $E_g = \int E_c(dN_c/dt)dt = (E_c/m_c)\int(dm/dt)dt = (E_c/m_c)(m_m - m_0)$, where m_m is the maximum mass reached by the organism. As $m_m \gg m_0$ and $E_c/m_c = B_0/a$, $E_g \approx (B_0 M/a)r_m^4$, where $r_m = (m_m/M)^{1/4}$. The total metabolic energy used in a lifetime is $E_{tot} = \int B dt \approx -4(B_0 M/a)[r_m^3/3 + r_m^2/2 + r_m + \ln(1 - r_m)]$. For cod this gives $E_g/E_{tot} \approx 0.41$, so 41% of its total lifetime energy is spent on growth. For an organism with determinate growth, $r_m \approx 1$, so $E_g \approx (B_0 M/a)$. To calculate their E_{tot}, we first integrate B up to a time, t_m, corresponding to $m = (1 - \epsilon)M$ with $\epsilon \ll 1$; typically ϵ is chosen to be 0.01 or 0.05. This gives a contribution $(4B_0 M/a)[\ln(4/\epsilon) - 11/6]$. To this is added the energy used from t_m until death at $t = t_d$. Neglecting growth during this period gives

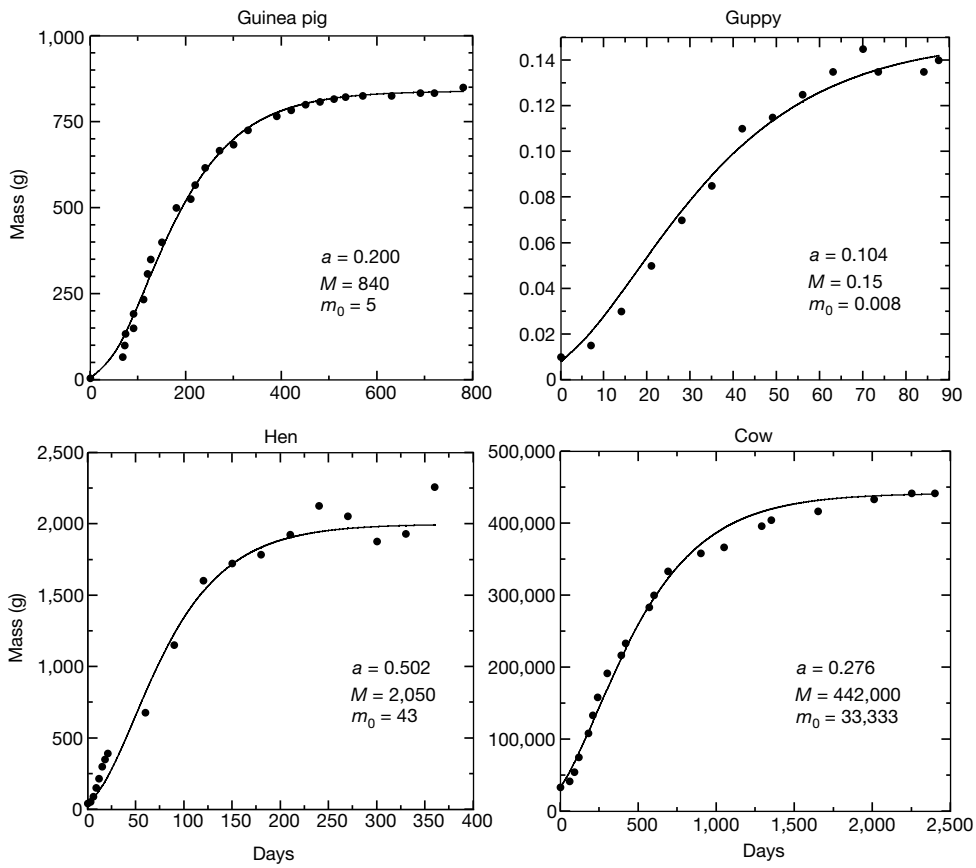

Figure 1 Four typical examples of fits to growth curves (solid lines) using equation (5). For definition of growth parameter a, see equation (3). M, asymptotic mass; m_0, birth mass.

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$(B_0M/a)b(t_d - t_m)$. Typically, $b(t_d - t_m) \gg 4[\ln(4/\epsilon) - 11/6]$ so $E_g/E_{tot} \approx b(t_d - t_m) \ll 1$. For example, for a cow that lives for 20 years, we obtain $E_g/E_{tot} \approx 1\%$. On the other hand, growth accounts for almost 10% of its total metabolic energy expended before maturity.

R is maximal at birth, where $R(0) = 1 - (m_0/M)^{1/4}$. If $m_0/M < 1/16$, 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 $m_0 \ll M$, $R(0) \approx 1$, so nearly all metabolism at hatching is used for growth. The point of inflection, where growth rate is maximal ($d^2m/dt^2 = 0$), occurs when $m = (3/4)^4M \approx (1/3)M$ at which point $dm/dt = (27/256)aM^{3/4}$ 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 $dm/dt \approx 6$ g per day, in good agreement with data[1].

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 B_c, the average metabolic rate of a cell *in vivo*. If dN_c^d/dt is the cellular mortality rate, then the power required to replace cells that have died is $E_c dN_c^d/dt$. The cell death rate is proportional to the number of cells present, so $dN_c^d/dt = \gamma N_c$, where γ is the inverse lifetime of a typical cell. Thus, an amount γE_c must be contributed from B_c to replace the average cell; $b = B_c/E_c$, so γ represents that portion of b attributable to cell replacement. For a 50 kg mammal, a typical cell lives for around 2 months[10], although there is considerable variation among tissue types; thus, $\gamma \approx 0.02$ days^{-1}. Taking $E_c \approx 2 \times 10^{-5}$ J gives $\gamma E_c \approx 4 \times 10^{-12}$ W, which is comparable to $B_c = B_0 m_c/M^{1/4}$. Thus, $\gamma \approx B_c/E_c = b = aM^{-1/4}$ so, across species, the lifetime of cells increases as $M^{1/4}$. Moreover, once growth ceases, a substantial proportion of metabolism is devoted to cell replacement.

The second point is the difference between determinate and indeterminate growth. The two cases are distinguished by whether the organism reaches t_m and approaches an asymptotic size, M, before death (see Supplementary Information). From equation (5), $t_m \approx (4M^{1/4}/a)\ln[4\{1 - (m_0/M)^{1/4}\}/\epsilon]$. Except for a small logarithmic modulation, $t_m \propto M^{1/4}$, in agreement with data[2,11]. A related time is the doubling time, T, which is the time taken to increase from m to $2m$. This is given by $T = (4a/M^{1/4})\ln[\{1 - (m/M)^{1/4}\}/\{1 - (2m/M)^{1/4}\}]$, which, when $(m/M)^{1/4} \ll 1$, reduces to $T \approx (4a)(2^{1/4} - 1)m^{1/4}$, scaling as empirically observed[4,5]. Organisms with determinate growth typically reproduce only after attaining nearly asymptotic size ($m \approx M$, when $t > t_m$) (ref. 2). For them, t_m can be equated with the age to 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[11].

The third point concerns energy allocation to reproduction in indeterminate growth. Once such organisms reach their age for first reproduction (t_r), a significant fraction of metabolic rate is devoted to reproduction, and the growth rate is reduced. Consider the case of oviparous organisms[2,3]. Egg production can be incorporated into equation (1) by adding a term $E_e dN_e/dt$ to the right-hand side when $t \geq t_r$; E_e is the energy needed to create a single egg cell and N_e the number created by time t. Data from oviparous ectothermic invertebrates and vertebrates[11,21] support the assumption that, during a spawning period $\Delta t = t_s$, the mass of a clutch,

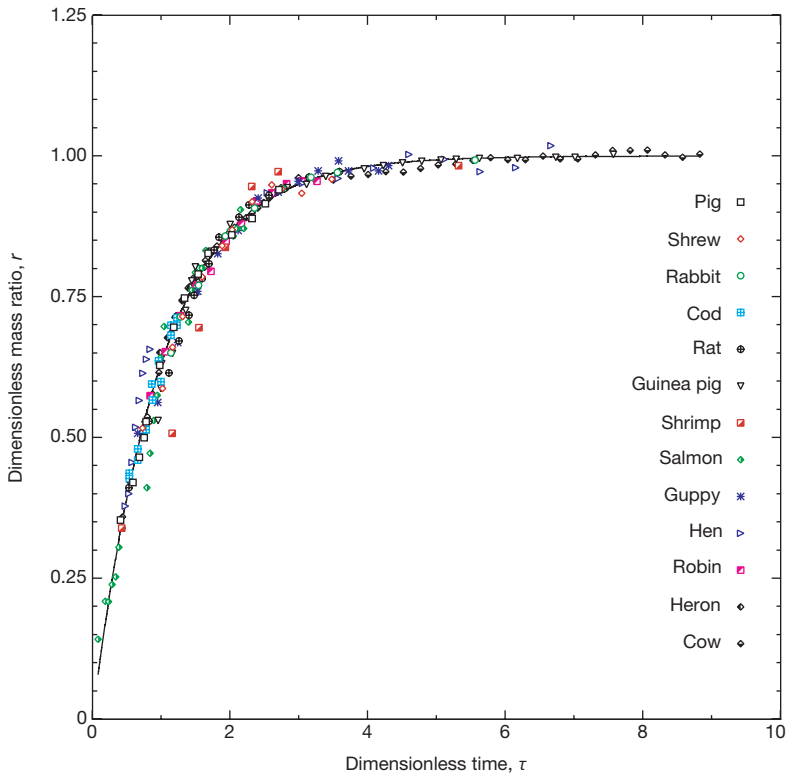

Figure 2 Universal growth curve. A plot of the dimensionless mass ratio, $r = 1 - R \equiv (m/M)^{1/4}$, versus the dimensionless time variable, $\tau = (at/4M^{1/4}) - \ln[1 - (m_0/M)^{1/4}]$, for a wide variety of determinate and indeterminate species. When plotted in this way, our model predicts that growth curves for all organisms should fall on the same universal parameterless curve $1 - e^{-\tau}$ (shown as a solid line). The model identifies r as the proportion of total lifetime metabolic power used for maintenance and other activities.

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$m_k = m_e \Delta N_e$, is a constant fraction, λ, of body mass: $m_k \approx \lambda m$. Thus $E_e dN_e/dt \approx E_e \Delta N_e/\Delta t \approx \lambda E_e m/m_e t_s$. The energy density of egg and other cells are similar, $E_e/m_e \approx E_c/m_c$, so this additional term becomes $E_e dN_e/dt \approx (\lambda E_c/t_s)N_c$. This is proportional to N_c and so has the identical structure to the maintenance term, $N_c B_c$, in equation (1). Thus, the solution, equation (5), is the same after reproduction ($t > t_r$) as before ($t < t_r$), except that B_c is replaced by $(B_c + \lambda E_c/t_s)$. In subsequent equations, a therefore remains the same before and after t_r, whereas b changes to $b' \equiv (b + \lambda/t_s)$. Consequently, because egg production continues throughout life, the actual asymptotic mass decreases from $M = (a/b)^4$ to $M' = (a/b')^4 = (1 + \lambda/bt_s)^{-4}M$. 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 $t_s \approx 100$ days and obtain $\lambda/t_s \approx 1 \times 10^{-3}$ 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, $E_e(dN_e/dt)/N_c B_c \approx \lambda/bt_s$, could be as much as a factor of 3. Consequently $M'/M = (1 + \lambda/bt_s)^{-4}$ could be as small as 10^{-2}. Thus $M \gg m$, so, for times before first reproduction ($t < t_r$), the solution is insensitive to $b = a/M^{1/4}$ and growth is determined primarily by a. In general, separate equations operate before and after t_r; for most indeterminate growers, however, t_r is much smaller than lifespan, $t_r \ll t_d$, so growth is well approximated by a single equation—equations (4) or (5)—for all t but 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 reproduction and mortality[2–4,22,23]. Our model attributes the slowing of growth as body size increases to limitations on the capacity of networks to supply sufficient resources to support further increase in body mass. Its power is demonstrated by its ability to quantitatively predict growth curves for both determinate and indeterminate growers, oviparous and viviparous species, ectotherms and endotherms, vertebrates and invertebrates (Fig. 2). The model can be extended to plants. Previously[24], a simpler version was presented for trees that included only the second term in equation (1). This was adequate largely because the first term only becomes important at large body sizes and only a small proportion of the trees had masses that approached the asymptotic value. Perhaps the most appealing and powerful feature of our model is that the parameters of the growth equation can be derived from fundamental cellular properties and predicted quantitatively from metabolic measurements that are not directly related to growth. □

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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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Correspondence and requests for materials should be addressed to G.B.W. (e-mail: gbw@lanl.gov).

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

David R. Stevens*, Reinhard Seifert†, Bernd Bufe‡, Frank Müller†, Elisabeth Kremmer§, Renate Gauss†, Wolfgang Meyerhof‡, U. Benjamin Kaupp† & Bernd Lindemann*

* *Department of Physiology, Universität des Saarlandes, D-66421 Homburg, Germany*
† *Institute for Biological Information Processing, Forschungszentrum Jülich, D-52425 Jülich, Germany*
‡ *Department of Molecular Genetics, Deutsches Institut für Ernährungsforschung, Arthur-Scheunert-Allee 114-116, D-14558 Potsdam-Rehbrücke, Germany*
§ *Institute for Molecular Immunology, GSF, D-81377 München, Germany*

Sour taste is initiated by protons acting at receptor proteins or channels. In vertebrates, transduction of this taste quality involves several parallel pathways[1–5]. 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-myocytes[6,7], a current carried by members of the family of hyperpolarization-activated and cyclic-nucleotide-gated (HCN) channels[8–13]. 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

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