Animal (2011), **5:3**, pp 439–449 © The Animal Consortium 2010
doi:10.1017/S1751731110001874

animal

A family of protein growth curves with extension to other chemical body components together with application to animal nutrition and improvement

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(Received 5 October 2009; Accepted 6 August 2010; First published online 5 October 2010)

Theory that successfully explains the magnitude and range of estimates of protein retention (PR) efficiency from the cost of turnover of existing protein indicates that conventional curves for growth description are inappropriate for protein growth. A solution to this problem is found in the consideration that the rate-limiting steps for protein synthesis (PS) and breakdown are likely to be associated with the diffusion of metabolites in and between cells. The algebraic scaling of nuclear and cellular diffusion capacity with tissue or total body protein leads to a parameterization of the primal differential equation for PR (kg/day) based on two terms representing PS and breakdown, viz.

$$PR = cQ[(P/\alpha)^{X+Z-(4/9)Y} - (P/\alpha)^{X+Z}].$$

where c *is an arbitrary constant,* Q *is the proportion of nuclei active in cell growth or division in a tissue or the whole body,* α *is the limit mass for protein (*P*, kg) in a tissue or the whole body, the power* $X + Z$ *represents the rate-limiting steps in protein breakdown and* Y *is the power of the relationship between cell volume and the amount of tissue protein. For the whole body, the contribution of the different tissues should be weighted in proportion to their PS rates with, on average,* $Y = 1/2$*. The constant 4/9 arises from the scaling of the specific diffusion rate of DNA activator precursors from nuclear dimensions and from the relationship between nuclear and cell volume. Experimental evidence on protein breakdown rate as well as protein and body mass points of inflection indicates that the range of theoretically possible numerical values of the rate-limiting powers* $X + Z = (i + 3)/9$ *for* $i = 1, 2, \ldots, 12$ *seems adequate for the description of the range of observed whole body protein and body mass growth patterns for mammals.* $Q = 1$ *represents maximal protein retention, and for* $0 < Q < 1$*, experimental evidence exists in support of a theoretical relationship between* Q *and food ingestion. The conclusion follows that some knowledge of the protein limit mass (*α*) and of the point of inflection (related to* $X + Z$*) is the main requirement for the application of the theory for description and prediction in animal nutrition and breeding.*

Keywords: protein growth curves, intake prediction, animal improvement

Implications

Growth equations are derived from basic concepts in molecular cell biology for different tissues classified as viscera, skin or bone and skeletal muscle. Their contributions can be weighted in proportion to synthesis contribution to accommodate variable body composition in the prediction of total body protein growth. Differences in point of inflection due to the type of animal or breeding improvement are accommodated by a family of curves. The deviation from maximum protein retention is quantified in terms of the proportion of growth-active nuclei (*Q*), and a relationship between *Q* and food intake is available for intake or growth prediction.

Introduction

Previous work (Roux, 2005a, 2005b and 2006) successfully explained the pronounced difference between the estimates of protein retention (PR) efficiency and protein synthesis (PS) efficiency as being due to the continuous replacement of existing protein by newly synthesized protein. Moreover, this approach allowed the algebraic derivation of theoretical retention efficiencies from the generally accepted truth in molecular biology that the rate of PS depends mainly on the

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rate of gene transcription, which in turn depends mainly on activators bound to DNA enhancers. It is, furthermore, reasonable to suppose that PS is proportional to activator concentration in the nucleus, which in turn may depend on nuclear volume due to the diffusion of activator precursors into the nucleus. The consequent hypothesis of PS proportional to nuclear volume and the scaling of nuclear volume with cell volume and hence tissue or organ size allowed the mathematical derivation of theoretical PR efficiencies for the whole body as well as constituent body tissues. These theoretical PR efficiencies could be verified by direct calculation from experimental estimates of PS and breakdown rates (PB), as well as from multiple regression procedures involving the measurement of body mass and food ingestion together with protein and fat retention.

The mathematical derivation of theoretical PR efficiencies depends, however, on an algebraic description of the relationship of the ratio PB/PS with protein mass (P), whereas for protein growth description one needs the relationship of the difference PS−PB = PR with P. The relationship between PB/PS and P is simpler than that of PS−PB as the ratio allows terms very important in the description of PB, but common to both PB and PS, to cancel. It is the primary purpose of the present communication to derive algebraic formulas from cellular diffusion considerations for terms that appear in PR = PS−PB, but which cancel in the ratio PB/PS. The secondary purpose is to show that the theoretically derived protein growth represents an adequate description of experimentally observed protein growth patterns for both the whole body and its constituent tissues.

The primal growth differential equation of von Bertalanffy (1960) can be transcribed to protein growth in the form

$$\mathrm{PR} = dP/dt = c_2P^b - c_1P^a, \qquad (1)$$

with PR measured in units of kg/day being denoted by PR, and protein measured in kg being denoted by P. Equation (1) was used for the investigation of PR efficiency (k_P) with the incorporation of turnover (Roux, 2005a, 2005b and 2006), without attention to deriving or assuming particular values of a and b. Instead, a relationship between k_P and $a - b$ was formulated for which it was found that for total body protein $a - b \leqslant 2/9$, with equality at maximum PR. This is in contradiction to the difference $a - b = 1$ for the logistic or the monomolecular, to $a - b = 1/3$ for the von Bertalanffy (1960) curve on the basis of a surface and volume argument and to $a - b \to 0$ for the Gompertz, which can be derived from equation (1) for $a = 1$ and $b \to 1$ Hence, the conclusion follows that an argument based on the quantification of PR efficiency with the incorporation of protein turnover renders all the best known members of the Richards (1959) family of curves inappropriate for protein growth description. It therefore seems worthwhile to investigate what sort of scaling of physiological processes can characterize a family of curves resulting in $a - b = 2/9$ or $a - b = (4/9)Y$, with Y representing the power in the relationship between cell volume and total protein in different tissues (Roux, 2006). In this endeavor, care is taken to bring into consideration the basic rate-limiting steps in the control of PS and breakdown involving gene transcription and the diffusion of metabolites. Furthermore, the need to characterize a whole family of curves is indicated by the necessity to use the Richards' (1959) family of growth curves in investigations of body mass growth (Gaillard *et al.*, 1997). Applicability considerations also suggest that the effect of deviation from maximum PR should be taken into consideration in such a way that it can be quantified in relation to food intake.

In summary, therefore, the purpose of the present communication is to present protein growth equations derived from fundamental concepts in molecular cell biology for the whole body as well as four constituent protein pools or tissues classified as viscera, skin or bone and skeletal muscle. Different values of the parameters of the primal growth differential equation associated with equation (1) are shown to characterize members of a family of protein growth curves with a variety of forms that allow description of the diversity of observed growth patterns. The deviation from maximum PR is quantified in terms of the proportion of growth-active nuclei (Q), and a relationship between Q and food intake is derived for intake or growth prediction. To realize the possibility of intake prediction, a description of fat growth can be derived from a power relationship between body fat and protein. An illustration of the fitting of a protein growth curve is given on data from the literature in Table 5. Notation is summarized in Appendix. Additional descriptions of fat retention and intake prediction are explicated in Tables A3, A4 and A5 of an online appendix available on the Animal website (Roux, 2010).

Theory and methods

Quiescent and active nuclei

A quiescent cell can be described as not being involved in growth or division, although other functions generally may continue as usual. By extension, a quiescent nucleus is defined as one that does not contribute to an increase in cell mass or cell division, that is, a nucleus for which the associated synthesis (PS) and breakdown (PB) rates of protein are equal (i.e. PS = PB). In contrast, an active nucleus can be defined as one that contributes to an increase in cell mass or number (i.e. PS > PB).

Let α be the amount of body or tissue protein at maturity, so that (P/α) can be regarded as the degree of protein maturity. For a quiescent nucleus, I assume that PS = PB $\propto (P/\alpha)^X$, with the sign $\propto$ meaning 'proportional to.' The power X represents the rate-limiting step in breakdown rate and it is possibly unequal to zero to allow for changes in breakdown control associated with age or size due to genetic, diet or other factors. It can also be assumed that the number of nuclei (nn) in a tissue scales with protein amount proportional to a power Z, $nn \propto (P/\alpha)^Z$. With all nuclei in a tissue in the quiescent state, PS and PB will scale as

$$\mathrm{PS} = \mathrm{PB} = c(P/\alpha)^{X+Z}, \qquad (2)$$

Table 1 *The WB or SM powers* X + Z *associated with different rate-limiting steps without and with IS for protein breakdown rate together with inflection points from equation (9)*

Lines	Rate-limiting steps	X	$X+Z$	$X+Z$ (decimal)	Inflection points* WB ($Y=1/2$)	Inflection points* SM ($Y=1$)
	Without IS					
1	Specific diffusion capacity	−2/9	4/9	0.444	0.044	0.000
2	Specific surface area	−1/9	5/9	0.556	0.100	0.027
3	Constant per DNA unit	0	6/9	0.667	0.161	0.084
4	Diffusion capacity	1/9	7/9	0.778	0.220	0.149
5	Surface area	2/9	8/9	0.889	0.274	0.210
6	Protein mass	1/3	1	1.000	0.323	0.266
	With IS					
7	Adding 2/3 to line 1	4/9	10/9	1.111	0.366	0.317
8	Adding 2/3 to line 2	5/9	11/9	1.222	0.405	0.362
9	Adding 2/3 to line 3	6/9	12/9	1.333	0.440	0.401
10	Adding 2/3 to line 4	7/9	13/9	1.444	0.472	0.437
11	Adding 2/3 to Line 5	8/9	14/9	1.556	0.500	0.469
12	Adding 2/3 to line 6	1	15/9	1.667	0.525	0.498

WB = whole body; SM = skeletal muscle; IS = intercellular signaling.
*The inflection point is in terms of protein maturity (Pl/α); *X*, the power representing the rate-limiting step in protein breakdown associated with a single nucleus; *Y*, the power in the relationship between cell volume and the amount of protein in a tissue or the WB; *Z*, the power in the relationship between the number of nuclei and the amount of protein in a tissue or the WB.

with *c* a constant of proportionality and PS and PB measured in kg/day.

In general, whole body or skeletal muscle $nn \propto (Pl/\alpha)^{2/3}$, that is, $Z = 2/3$ (Roux, 2006). To accommodate tissues with multinucleate cells, like muscle, a DNA unit will be defined as having a mass of $Pl/nn \propto (Pl/\alpha)^{1/3}$. For tissues with mononucleate cells, a DNA unit will be identical to a cell. It follows that the diameter of a whole body or skeletal muscle *DNA* unit will scale $\propto (Pl/\alpha)^{1/9}$, surface area $\propto (Pl/\alpha)^{2/9}$, and from Fick's law the diffusion capacity is proportional to surface/distance $= (Pl/\alpha)^{2/9}/(Pl/\alpha)^{1/9} = (Pl/\alpha)^{1/9}$. Hence, specific diffusion capacity for a DNA unit is proportional to $(Pl/\alpha)^{1/9}/(Pl/\alpha)^{1/3} = (Pl/\alpha)^{-2/9}$, with specific surface area being proportional to $(Pl/\alpha)^{2/9}/(Pl/\alpha)^{1/3} = (Pl/\alpha)^{-1/9}$.

Control of breakdown rate

For the purpose of growth description, it is perhaps important to distinguish between quantitative and qualitative control. Qualitative control would refer to the control of the breakdown of different types of protein, whereas quantitative control refers to the total amount of degraded protein. The total degradation rate would therefore be dependent on the concentration of the elements of the degrading system, which consists of lysosomes as well as a pathway inside the cytoplasm often adjacent to plasma or other membranes. It is therefore logical to expect that total protein breakdown would be related to cell or DNA unit mass, surface area or diffusion capacity. The scaling of the different possibilities for the rate-limiting step in breakdown rate (equation 2) is given in Table 1. They follow directly from the preceding discussion on DNA unit scaling. The whole body or skeletal muscle power *Z* is assumed to be equal to 2/3 (Roux, 2006). In line 1 (Table 1), it is assumed that the rate-limiting step for breakdown rate is proportional to the specific diffusion capacity for each DNA unit, that is, to $(Pl/\alpha)^{-2/9}$, so that $X = -2/9$ and $X + Z = 4/9$ for total specific diffusion capacity. The argument for the derivation of lines 2 to 6 in Table 1 is analogous to that for line 1.

To obtain lines 7 to 12, PB regulation by paracrine or intercellular signaling is assumed in addition to the rate-limiting steps indicated in lines 1 to 6, in such a way that the magnitude of the effect on PB in a DNA unit is proportional to the total number of nuclei in a tissue. Lines 7 to 12 can then be obtained by increasing *X* in lines 1 to 6 by 2/3, the power in the relationship $nn \propto (Pl/\alpha)^{2/3}$. The inflection points in Table 1 will be discussed later .

For cells classified as viscera, skin or bone, separate values obtained from Roux (2006) indicate that $Z \neq 2/3$. Hence, different but analogous tables of both *X* and *Z* will have to be constructed for them on the basis of $Z = 5/6$ (viscera) or $Z = 1/2$ (skin or bone; see Tables A1 and A2 in Roux (2010)).

Protein synthesis

In the same way as protein breakdown, the control of PS can be differentiated into qualitative and quantitative control. Qualitative control refers to the composition of synthesized proteins that is mediated by the initiation of transcription by promoters. Quantitative control, with reference to the rate of PS, mainly depends on activators bound to DNA sequences called enhancers. Generally, the control of the rate of PS would therefore depend on activator concentration in the nucleus (Roux, 2005a). Activator precursors will have to diffuse into the nucleus. Let *nv* denote nuclear volume. The nuclear surface will scale proportionally to $(nv)^{2/3}$ and nuclear diameter to $(nv)^{1/3}$. Then, from Fick's law, diffusion rate into the nucleus will be proportional to the concentration gradient and diffusion capacity, with specific diffusion capacity = (surface/distance)/volume $= [(nv)^{2/3}/(nv)^{1/3}]/nv = (nv)^{-2/3}$. Assume that for

activator precursors the signaling cascade through the cytoplasm always contains such a number of steps that the activator precursor concentration in the cytoplasm does not vary with cell size. On the basis of this premise, it is reasonable to accept that the concentration gradient of activator precursors will be invariant with cell size and hence with time. Then, if activator lifetime is also constant during growth, activator concentration will be proportional to specific diffusion capacity (Roux, 2005a):

$$[\text{activator}] \propto (nv)^{-2/3}. \quad (3)$$

It can be assumed that the rate of PS depends essentially on the rate of gene transcription (Latchman, 2005). It is also reasonable to expect that the specific rate of gene transcription would be proportional to the concentration of activators bound to enhancers. Analogous to hormone-binding kinetics (Darnell *et al.*, 1990), this activator–enhancer complex concentration would, in turn, be proportional to activator concentration. The rate of gene transcription per nucleus will then be determined by the activator concentration in equation (3) (Roux, 2005a). Furthermore, age- or size-related effects (age or size changes $\propto (P/\alpha)^X$), as in equation (2), are also applicable to all nuclei. Then for the total rate of PS (kg/day) with all nuclei ($nn \propto (P/\alpha)^Z$) in a tissue activated by a cascading effect obtained from hormonally mediated growth factors bound to receptors on the cell surface, it follows from equation (3) (Roux, 2005a and 2006) that

$$\text{PS} \propto (P/\alpha)^{X+Z}(nv)^{-2/3}. \quad (4)$$

From Teissier (1941), it generally holds for mammalian cells that nuclear volume is proportional to cell volume (cv), such that $nv \propto (cv)^{2/3}$. If it is assumed that cv is related to a power Y of the P/α of a tissue, such that $cv \propto (P/\alpha)^Y$, equation (4) becomes

$$\text{PS} = c(P/\alpha)^{X+Z-(4/9)Y}. \quad (5)$$

The constants c in equations (2) and (5) are equal, since at maturity $(P/\alpha) = 1$ and PS = PB.

The assumptions used in the derivation of equation (5) do not seem to allow a gradient of responses for an active nucleus. For differential growth in a tissue, it is therefore assumed that the differential protein growth response elicited by hormonal control is obtained by variation of the proportion of active nuclei in a tissue. Let Q denote the proportion of active nuclei in a tissue. Then, from the addition of active (equation 5) and quiescent nuclei (equation 2), a tissue will have a total synthesis rate of

$$\text{PS} = c[(1-Q)(P/\alpha)^{X+Z} + Q(P/\alpha)^{X+Z-(4/9)Y}]. \quad (6)$$

Protein retention

Since PR = PS − PB, the equation for PR (kg/day) can be obtained from the difference between equations (6) and (2):

$$\text{PR} = cQ[(P/\alpha)^{X+Z-(4/9)Y} - (P/\alpha)^{X+Z}]. \quad (7)$$

PR can be taken to be equal to the differential dP/dt, which will allow equation (7) to be regarded as a differential equation that can be solved for P, the amount of protein in a tissue. The differential equation associated with equation (7) does not have an analytic solution for all powers of (P/α). Values for the powers of (P/α) for which analytic solutions exist, together with the solutions, are published in Reiss (1989). For example, for $X + Z = 1$ the solution of equation (7) is

$$P = \alpha\{1-[1-(P_0/\alpha)^h]\exp -kt\}^{1/h}, \quad (8)$$

(von Bertalanffy, 1960) with P_0 representing the amount of protein in a tissue at time zero, $h = (4/9)Y$ and $k = ch(Q/\alpha)$. Equation (7) has to be solved numerically for values of $X + Z$ for which no analytic solution exists.

The cellular or physiological basis of protein growth parameters

Note that a cellular or physiological basis exists for all the parameters of equations (7) and (8). The limit or mature protein mass in equations (2) and (4) can be shown to arise from the relationship between PS and PB described by the parameterization of equation (1), namely $\alpha = (c_2/c_1)^{1/(a-b)}$ (Roux, 2005a). The explanation of the power of the whole body breakdown rate $X + Z$ is encompassed in Table 1. The constant 4/9 arises from the scaling of the specific diffusion rate of activator precursors from nuclear dimensions and from the relationship between nuclear volume and cell volume. The parameter Y is the power of the relationship between cell volume and amount of tissue protein. The number of multinucleate muscle cells does not increase after birth, so that $Y = 1$ for skeletal muscle (Roux, 2006). On the basis of DNA–protein relationships, it is derived by Roux (2006) that $Y = 1/3$ for mononucleate cells on average, with $Y = 1/6$ for viscera and $Y = 1/2$ for both skin and bone. For the whole body, the contribution of the different tissues should be weighed in proportion to their PS rates. On average, $Y = 1/2$, approximately, for the whole body (Roux, 2006).

Point of inflection

Expressed in terms of protein maturity, the protein mass at the point of inflection of equation (7) is as follows from von Bertalanffy (1960)

$$P/\alpha = [(X + Z - (4/9)Y)/(X + Z)]^{1/(4/9)Y}. \quad (9)$$

The values of P/α at the inflection point for whole body $Y = 1/2$ and skeletal muscle $Y = 1$ are given in Table 1 for the different postulated values of $X + Z$.

Experimental evidence

Evidence for the postulated values of Y

The first question that needs to be answered here is whether equation (7) with theoretical average $Y = 1/2$ for whole body protein can explain the range of experimental results recorded in the literature. Evidence in confirmation of $Y = 1/2$,

Table 2 *The WB estimates of the powers of protein breakdown rate* X + Z *together with 95% CI from regression coefficient estimates obtained by logarithmic transformation according to equation (2) on protein breakdown data from the literature*

Lines	Animals	References	$X+Z$	d.f.	s.e.	95% CI
1	Cattle	Di Marco *et al.* (1989)	0.62	3	0.051	0.46 to 0.78
2	Pigs	Reeds *et al.* (1980)	0.63	2	0.058	0.38 to 0.88
3	Rats	Goldspink and Kelly (1984)	0.74	1	0.015	0.55 to 0.93
		Weighted average (lines 1 to 3)	0.64	6	0.032	0.56 to 0.72
4	Chickens	Marumatsu and Okumura (1985)	0.98	2	0.045	0.79 to 1.17

WB = whole body.

together with $(4/9)Y = 2/9$, from PS or retention efficiency experiments for pigs, cattle and sheep as well as a weighted average from different tissues is available from Roux (2005a, 2005b and 2006). In this approach, problems with the separate estimation of a or b in equation (1) were largely ignored, with attention instead focused on estimation of the difference $a-b$.

As in the present approach, Oltjen *et al.* (1985) also modelled PR in terms of PS and PB. With reparameterization, their results provide evidence in favor of the present approach. On account of the generally high correlation between estimates of its parameters, it is difficult to obtain a direct fit to equation (1) by the conventional methods of estimation of a and b. Oltjen *et al.* (1985) circumvented the problem by using an independent estimate of protein breakdown to obtain an estimate of PS from the rat data of Enesco and Leblond (1962). By adding PB to PR to obtain PS, they effectively obtained equation (7), if $Q = 1$ is assumed. Transposed to the present notation, Oltjen *et al.* (1985) assumed $X + Z = 0.72$ and estimated $X + Z - (4/9)Y = 0.48$. Solving this gives $Y = 0.54$, near to the average value derived by Roux (2006). Oltjen *et al.* (1985) also estimated PS $\propto$ $(\text{DNA})^{0.72}$ from birth onward and PS $\propto$ $(\text{DNA})^{0.75}$ from weaning onward. Taking DNA $\propto P^{2/3}$(derivation of equation 2), this gives PS $\propto P^{0.48}$($0.48 = 0.72 \times 2/3$) as before from birth onward, but PS $\propto P^{0.50}$($0.50 = 0.75 \times 2/3$) from weaning onward. This gives $X + Z - (4/9)Y = 0.50$ and with the Oltjen *et al.* (1985) assumption of $X + Z = 0.72$, it follows that $Y = 0.50$ identical, from weaning onward, to the value suggested by Roux (2006).

Confirmation derived from experimental estimates of PS and PB for the theoretical estimates of $Y = 1$ (muscle), $Y = 1/2$ (skin or bone), $Y = 1/6$ (viscera) and 1/3 (average for mononucleate cells) is available in Roux (2006).

Di Marco *et al.* (1989) aggregately considered two protein pools: body and viscera. Body consisted mainly of skin, muscle and bone; viscera included blood, liver, digestive tract, heart and lungs. When Di Marco *et al.*'s (1989) descriptions by complex equations of body and viscera were approximated by equation (1), values of $a-b = 0.324$ for the body and $a-b = 0.078$ for the viscera were obtained in reasonable agreement to theoretical expectations of 0.296 and 0.074 derived from weighted synthesis contributions from the viscera, skin or bone and skeletal muscle (Roux, 2006).

The tenability of the derived range of theoretical $X + Z$ *powers*

An alternative approach to the estimation of parameters of equation (7) is via its components PB (equation 2) and PS (equation 6). Unless Q is known and equal to 1, equation (6) will be difficult to fit, for the same reason as equation (1). To this will be added the additional problem that, due to measurement difficulties, the available experimental observations tend to be concentrated at few points. Hence, iterative methods may fail to converge or may result in poor estimates and therefore no attempt will be made to fit equation (6). In contrast, equation (2) is easy to fit with linear regression under logarithmic transformation. This will provide valuable evidence on the tenability of the theoretically predicted values of $X + Z$ in Table 1. Estimates from equation (2) of the powers of the whole body protein breakdown rate $X + Z$ are in Table 2 and those of the powers of muscle breakdown rate $X + Z$ are in Table 3.

The confidence intervals in Table 2 for the powers of the whole body breakdown rate indicate that the mammalian observations are in agreement with the theoretical value of $X + Z = 6/9$ in Table 1, whereas the chicken value is indicated to be in agreement with values of 8/9 to 10/9.

Applied to the values of $X + Z$ for muscle in Table 3, an F-test for heterogeneity of regression coefficients indicates significance at the 0.01 level with $F = 9.81$ with 7 and 22 d.f. To get enough degrees of freedom for reliable confidence intervals of the regression coefficients, a common standard deviation from regression of 0.1558 with 22 d.f. was calculated.

Note that for muscle the significant heterogeneity F-value together with non-overlapping confidence intervals indicates that no single theoretical value of $X + Z$ in Table 1 can explain the observed values in Table 3. Instead, agreement to the whole range of values in Table 1 from lines 1 to 6 is indicated, with each estimate in Table 3 an s.e. or less away from a theoretical value in Table 1. The only difference between the well-fed rats (line 1) and the marginally malnourished rats (line 5) from the same laboratory is in the dietary protein concentration of their food, indicating that nutritional influences may cause significant differences in the observed values of $X + Z$. In contrast, the significant difference between the slow-growing well-fed rats in line 1 as well as the fast-growing rats in line 2 with the Wistar rats in line 8 suggests the importance of genetic differences in observed $X + Z$-values.

Table 3 *The muscle estimates of the powers of protein breakdown rate* X + Z *together with 95% CI from regression coefficient estimates obtained by logarithmic transformation according to equation (2) on protein breakdown data from the literature*

Lines	References	Animals	Muscles	*n*	$X+Z$	s.e.	95% CI
1	Millward *et al.* (1975)	Well-fed rats	Gastrocnemius	5	0.43	0.066	0.29 to 0.57
2	Bates and Millward (1981)	Fast-growing rats	Gastrocnemius	5	0.59	0.078	0.43 to 0.75
3	Kang *et al.* (1985b)	Turkey poults	Breast	4	0.70	0.052	0.59 to 0.81
4	Kang *et al.* (1985b)	Turkey poults	Leg	4	0.81	0.056	0.69 to 0.93
5	Millward *et al.* (1975)	Malnourished rats	Gastrocnemius	5	0.83	0.054	0.72 to 0.94
6	Kang *et al.* (1985a)	Broiler chickens	Breast	4	0.89	0.066	0.75 to 1.03
7	Kang *et al.* (1985a)	Broiler Chickens	Leg	4	0.93	0.067	0.79 to 1.07
8	Siebrits and Barnes (1989)	Wistar rats	Gastrocnemius	7	0.96	0.088	0.78 to 1.14

F-test for heterogeneity: $F = 9.81^{xx}$ with 7 and 22 d.f.

Table 4 *Time trends in inflection points obtained by Knap (2000) on protein growth data for modern pigs together with the powers of protein breakdown rate* X + Z *that would result in equal inflection points from equation (9) under the assumption of* Y = *1/2*

References	Years	Improvement time rank	Inflection points	s.e.	$X+Z$ (equation 9)	$(X+Z)$ − rank
Doornenbal (1971)	1969	2	0.379	0.100	1.146	2
Tullis (1981)	1976	1	0.364	0.267	1.105	1
Noblet *et al.* (1994)	1984	3	0.385	0.072	1.163	3
Quiniou and Noblet (1995)	1990	4	0.405	0.100	1.221	4
Van Lunen (1994)	1993	5	0.462	0.056	1.409	5

Y, the power in the relationship between cell volume and the amount of protein in a tissue or the whole body.

Tables 2 and 3 do not provide any evidence for $X+Z$-values substantially above unity. With $X+Z=1$, the maximum value of the point of inflection is the Gompertz value of $P/\alpha = 0.368$ with $Y \rightarrow 0$. However, fitting a Bridges curve with a flexible point of inflection, Knap (2000) obtained values for the inflection point on modern pig protein growth data, given in Table 4, with inflection points showing an increasing trend above the Gompertz value. On the assumption of $Y = 1/2$, equivalent inflection points from equations (7) and (9) will require values of $X+Z$ substantially above unity. Consequently, the observations in Table 4 are in agreement with lines 7 to 10 in Table 1.

In evaluating the information in Table 4, it is important to realize that the 1976 population represents unimproved pigs before the initiation of modern selection programs. It therefore gets the first position in the improvement time rank. The 1969 values represent one of the first populations to be systematically selected for growth and body composition traits and therefore gets the second improvement time rank. The values for 1984, 1990 and 1993 represent pigs with greater periods of improvement from their populations of origin behind them, and therefore obtain larger time ranks. The $X+Z$ rankings represent the magnitude of the numerical values of $X+Z$. Note that the two rankings are in complete agreement. This corresponds to a Spearman's rank correlation coefficient of unity, $r_s = 1$. With $n = 5$, $r_s = 1$ is significant for a one-tailed test at the 0.01 level of significance. This means that the trend in $X+Z$ with time due to breeding improvement is not likely to be a chance event. The likely proximate cause of larger $X+Z$ values is that breeding improvement causes faster growth at more advanced ages in improved pigs compared with unimproved ones, indicating the importance of genetic influence on the point of inflection.

The general conclusion follows that Tables 2 to 4 provide substantial experimental support for the range of the theoretical values of $X+Z$ postulated in Table 1. This means that a whole range or family of protein growth curves exists for mammals given by equation (7) with postulated values of $X+Z$ like Table 1 and values of Y according to the type of tissue or whole body tissue composition.

The interpretation and estimation of Q

From equation (7), it is evident that, other things being equal, the maximum PR will occur with $Q = 1$, that is, with all nuclei in the active state. Experimental evidence for the existence of a maximum PR (PR_{max}) is summarized by Moughan (1999). In growing pigs, several hyperalimentation studies indicate that the supply of a balanced diet at a level exceeding normal *ad libitum* ingestion leads to an increased growth rate, but not an increased retention of body protein. These studies imply the operation of a maximal rate of PR (Moughan, 1999).

At present, no method exists for the direct estimation of Q. Indirect estimates have therefore been devised by Roux (2005a and 2006) to comply with the basic property of a proportion, that is, to vary between zero and one. Here, a generalization will be presented, derived from a theory developed for pigs (Kyriazakis and Emmans, 1992) that contains Roux's (2005a and 2006) formula based on intake rate as a simplification applicable to protein-limiting foods.

From equation (7), it follows that $PR = QPR_{max}$, or $Q = PR/PR_{max}$. From Sandberg *et al.* (2005), $PR = e_P(IPI - IPM)$, with IPI

indicating ideal protein (IP) intake and IPM indicating IP intake at protein maintenance when PR = 0. Kyriazakis and Emmans (1992) made the marginal efficiency of retaining IP (e_p), a function of the ratio of the metabolizable energy (ME) content (MEC, MJ/kg), to the digestible crude protein (DCP) content (DCPC, kg/kg) of the food, R (MJME/kgDCP). The proposed relationship is $e_P = \mu R$, with μ a constant and a maximum value for e_P of e_P^* when R is above a specific value R^*. With this notation, $PR_{max} = e_P^*$ (IPO−IPM), with IPO the optimal IPI when $PR = PR_{max}$. It follows that

$$Q = PR/PR_{max} = (e_P/e_P^*)(IPI - IPM)/(IPO - IPM). \quad (10)$$

Two special cases of equation (10) are of interest. The first is for protein-limiting foods when $R > R^*$ and consequently $e_P = e_P^*$, so that

$$Q = (IPI - IPM)/(IPO - IPM)$$

or for PR and PR_{max} on different levels of the same diet

$$Q = (MEI - MEM)/(MEO - MEM), \quad (11.1)$$

with MEM the ME intake at body protein maintenance and MEO the ME intake at PR_{max}, since on levels of the same diet the ratios involving IP and ME will be the same.

Equation (11.1) is identical to the estimate previously suggested by Roux (2005a). An estimate based on insulin-like growth factor (IGF) concentration in the blood is similar with (IGF) replacing ME. For energy-limiting foods when $R > R^*$ equation (10) or an ME equivalent will have to be used, with $e_P/e_P^* < 1$, equation (11.1) will overestimate Q.

The second special case of interest from equation (10) is when $R > R^*$, but the levels of IPI on the different diets are the same and equal to IPO. The last term of equation (10) then cancels so that it becomes

$$Q = e_P/e_P^* = MEI/MEO, \quad (11.2)$$

as follows from the definition of R. Experimental evidence for the validity of equation (11.2) follows from the approximate linear relationship between PR and MEI with zero intercept for pigs between 45 and 100 kg live mass and MEI of 0.7, 0.8, 0.9 and 1.0 × MEO, with approximate constant CPI, obtained by Quiniou *et al*. (1996).

For cattle (Roux, 2005b), the available evidence on the application of equation (11.1) indicates $Q = 1$ in equation (7) at *ad libitum* intake on diets adequate for maximal growth. In contrast, some evidence exists for sheep (Roux, 2005b) that either $Y < 1/2$ or $Q < 1$ at *ad libitum* intake, except for compensatory growth during realimentation after diet restriction. The application of equation (11.1) is illustrated in Roux (2005b) for cattle and sheep.

General protein growth curves for mammals

In Table 2, the average value for $X + Z$ for mammals is near to 2/3. Since none of them is significantly different from 2/3, equation (2) can be fitted for each species for PB and by calculating α according to the formulas in Roux (2005a). The constant c, calculated by assuming $X + Z = 2/3$, together with α is as follows

	α (kg)	c (kg/day)	$c/\alpha^{3/4}$
Cattle	118.6	2.071	0.0576
Pigs	28.61	0.9816	0.0794
Rats	0.0879	0.00916	0.0567.

A logarithmic regression of c on α gives a slope of 0.768 (s.e. = 0.0462), not significantly different from 3/4. Assuming a slope of 3/4, $c = 0.0638\alpha^{3/4}$ can be calculated. By the arguments leading to equation (7) and assuming (4/9)$Y = 2/9$, a fit by equation (7) to the three mammalian species becomes

$$PR(kg/day) = 0.0638\alpha^{3/4}Q[(P/\alpha)^{4/9} - (P/\alpha)^{2/3}]. \quad (12)$$

The 3/4 power assumed in equation (12) is near to a value of 0.72 ($n = 6$; s.e. = 0.017) for the mature body mass relationship calculated by Waterlow (1984) for the protein turnover of six species, from mouse to man and cattle.

The pigs of Table 2 and equation (12) have a point of inflection $P/\alpha = 0.161$ (Table 1). This is much lower than the values calculated for pigs by Knap (2000) from the Bridges equation. In contrast to equation (12), the growth data of Quiniou *et al*. (1996; Table 5) indicate a point of inflection during their period 2, which cannot be reconciled with a value of $P/\alpha = 0.161$. It therefore seems worthwhile to illustrate the fit of equation (7) on the data of Quiniou *et al*. (1996) in Table 5.

Roux (2005a) gives an example in which the fitting of power curves for the description of PB and PS gives estimates of limit or mature protein mass in agreement with the estimates from the fitting of Gompertz curves by Knap (2000). Knap's (2000) collation of data from the literature contains that of Tullis (1981) with some observations very near to maturity. The estimates obtained from Tullis (1981) are well contained within the confines of the total collection of estimates. It seems, therefore, that the somewhat premature truncation of growth records in other cases did not cause any serious bias in Knap's (2000) estimates of protein limit mass. However, Knap's (2000) limit masses show clear sex differences with averages of $\alpha = 26.4$ for castrates, $\alpha = 30.3$ for females and $\alpha = 32.9$ for males, with $n = 3$ for both males and castrates and $n = 4$ for females, on discarding an outlying male estimate of $\alpha = 38.5$. Since estimates of protein limit mass show no time trend indicative of selection improvement, these estimates can be used when estimates for specific types or breeds are unavailable or not reliable.

As estimates of PR are subject to measurement error as well as individual variability and the differences are small in the body mass range under consideration, I fitted curves to averages over all sexes, breeds and nutritional treatments. One-third of the pigs were male and two-thirds were castrates, so that limit protein mass is estimated by $\alpha = 1/3 \times 32.9 + 2/3 \times 26.4 = 28.6$ (Table 5). Protein mass is obtained by

Table 5 *The fitting of equation (7) to average protein retention and protein maturity (P/α) in four growth periods on data published by Quiniou* et al. *(1996)*

Periods	Mean body mass (kg)	PR (kg/day) (*y*-variate)	P/α (kg/kg)	(Equation 7) $(P/\alpha)^{8/9}-(P/\alpha)^{10/9}$ (*x*-variate)
1	48.1	0.145	0.269	0.0788
2	64.2	0.153	0.359	0.0819
3	79.3	0.149	0.444	0.0802
4	94.2	0.139	0.527	0.0751
			Intercept	−0.0153
			s.e.	0.0147
			Slope	2.0478
			s.e.	0.1865
			r	0.9918^{xx}
			ratio $\bar{y}/\bar{x}$	1.8544
			Q	0.8746

Q, the ratio of the total experiment protein retention (PR) to the *ad libitum* average PR.

assuming it to be a fraction of 0.16 of live body mass (Agricultural Research Council (ARC), 1981). Table 5 shows that PR is maximum in period 2 with an approximate value of $P/\alpha = 0.359$. Table 1 indicates consonance with $X + Z = 10/9$ for $(4/9)Y = 2/9$ for whole body protein. Hence, from equation (7), one would like to fit

$$\mathrm{PR} = cQ[(P/\alpha)^{8/9}-(P/\alpha)^{10/9}]. \qquad (13)$$

This can be done by regression of PR on $(P/\alpha)^{8/9}-(P/\alpha)^{10/9}$ through the origin. To test for goodness of fit, an ordinary regression analysis was performed. The highly significant correlation coefficient of 0.9918 indicates excellent fit and the non-significant intercept indicates the acceptability of a fit through the origin. The slope through the origin is estimated by the ratio of the averages of the *y* and *x* regression variables and *Q* is the ratio of total experiment average PR to the *ad libitum* average PR. Analysis by Quiniou *et al.* (1996) suggests that *ad libitum* PR is equivalent to PR_{max} in their data. It follows that *c* in equation (13) can be estimated by 1.8544/0.8746 = 2.1203. Accepting as in equation (12) a 3/4 power relationship with α, the constant *c* becomes $c = 2.1203/(28.6)^{3/4} = 0.1714\alpha^{3/4}$. Hence, equation (13) becomes

$$\mathrm{PR} = 0.1714\alpha^{3/4}Q[(P/\alpha)^{8/9}-(P/\alpha)^{10/9}]. \qquad (14)$$

Inclusion of the term $\alpha^{3/4}$ would allow for comparison with or prediction between species, breeds or types with different limit protein masses but the same powers for (P/α) in equations (7) or (14). Such a scaling of PR with protein limit mass is, furthermore, in agreement with Taylor's (1980) genetic scaling rules in animal growth. This matter will be further discussed in Roux (2010).

Body mass evidence

Body and protein mass. Owing to the cost and measurement problems, there is far more evidence available on body mass itself than for body composition. However, body and protein mass are often strongly related during growth, so that body mass growth can be a fair indication of protein mass growth. Let *W* indicate empty body mass. Then, on average, $P \propto W^{0.89}$ for cattle (ARC, 1980), $P \propto W^{0.86}$ for sheep (ARC, 1980) and $P \propto W^{1.00}$ for pigs (ARC, 1981). Siebrits (1984) found $P \propto W^{1.09}$ for lean pigs and $P \propto W^{0.93}$ for obese pigs. Taking $P \propto W^{0.9}$, it can be shown for equation (1) that, for $a = 1$ and $b = 7/9$, there will be a shift in inflection from 0.323 for protein to 0.318 for body mass, a relative difference of 0.025. The conclusion, therefore, is that body mass growth will often give a fair indication of body protein mass growth.

Fish body mass growth. Ursin (1979) used equation (1) with body mass as a variate to describe fish body mass growth and estimated *a* and *b* together with 95% confidence limits from a detailed analysis of the growth curves of 81 fish species as

$$a = 0.83 \pm 0.06 \text{ and } b = 0.59 \pm 0.02. \qquad (15)$$

Since the fish's empty body does not contain much fat, it is assumed that $P \propto W^{1.09}$ or $W \propto P^{0.92}$ like lean pigs (Siebrits, 1984). Then $dW/dt = P^{-0.08}dP/dt$, so that substitution of *W* with $P^{0.92}$ in $dW/dt = c_4W^{0.59}-c_3W^{0.83}$ (equation 15) gives

$$dP/dt = c_2P^{0.62}-c_1P^{0.84}, \qquad (16)$$

with c_1, c_2, c_3 and c_4 as arbitrary constants. From equation (7), it follows that $X + Z = 0.84$ and $X + Z-(4/9)Y = 0.62$. Solving for *Y* gives $Y = 1/2$, or $(4/9)Y = 2/9$, in agreement with the mammalian estimates. According to Fauconneau and Arnal (1985), muscle provides a fraction of 0.22 of PS in Rainbow trout, near enough to the 0.25 fraction assumed in Roux (2006) for the derivation of $Y = 1/2$ for total body protein in mammals. Hence, equations (15) and (16) are in agreement with the theory encompassed in equation (7).

Variation in body mass growth form. Variation in body mass growth form has been investigated by Gaillard *et al.* (1997) by fitting the Richards (1959) growth curve family from birth to adulthood to 69 species of eutherian mammals. They showed

that growth form differs significantly among eutherian mammals and concluded that 'the commonly used Gompertz model can no longer be considered as the general model for the description of mammalian growth.' For each species, the inflection point was calculated according to von Bertalanffy (1960). From the inflection points, values of $X + Z$ were calculated from equation (9) and are given in Table 6, on the supposition of a fit by equation (7) with $Y = 1/2$ on the assumption of whole body $P \propto W$.

Inflection points before birth can only be accurately estimated from prenatal observations. Hence, inaccurate or unrealistic negative estimates were replaced by the best available approximate estimates of (birth mass)/(adult body mass) for the estimation of $X + Z$ in Table 6. This creates consonance between the lowest values in Table 6 and those in Table 1.

Judged by the significance of the Richards shape parameter (Gaillard *et al.*, 1997), only two estimates of $X + Z$ larger than 1.7 in Table 6 are significantly larger than the maximum value of Table 1 in line 12 at the 0.05 level and none at the 0.01 level. For a sample of 69, this is about what one would expect to occur by chance, from the definition of a type 1 error. In addition, seven of the nine outliers larger than 1.7 are rodents, either squirrels or chipmunks, known as hibernators to build up body fat to survive the winter asleep. This possibly fast increase in body fat near maturity may explain a late point of inflection in body mass, not necessarily approximately coinciding with a point of inflection in protein mass. Hence, without further evidence on whole body protein growth, the outliers in Table 6 cannot be regarded as evidence of a possible inadequacy of Table 1 in the explanation of whole body protein growth.

It is clear from equation (7) that variable values of Q will distort the observed growth pattern. The relationship of Q to nutrition is given by equation (10). Presumably, animals are customarily fed to the *ad libitum* level in growth studies. Since PR_{max} is achievable in pigs (Moughan, 1999), *ad libitum* intake on nutritious food could generally result in $Q = 1$. Hence, the assumption of approximate constancy of Q during growth from birth to maturity may be realistic for many of the growth curves of Gaillard *et al.* (1997). Overall, the evidence in Table 6 may therefore indicate that most species have $X + Z$ values according to lines 1 to 6 in Table 1, but that a significant minority has to be accommodated by lines 7 to 12. This is in agreement with the evidence in Tables 2 to 4.

The significant differences in body protein $X + Z$ powers obtained in Tables 3 and 4 also argue against the possibility that the significantly different body mass fit of different members of the Richards family is solely due to nutrition, body composition or other environmental effects, masking the only true mammalian body protein growth curve. The alternative to a single growth curve is a family or distribution of growth curves based on Table 1. The distribution in Table 6 suggests either $X + Z = 8/9$ or slightly less likely $X + Z = 1$, from Table 1, as the median or modal values of such a distribution.

Growth of other chemical components and intake prediction By assuming power relationships between body protein and other chemical components, appropriate growth curves for these chemical components can be derived. This is illustrated for fat growth in Roux (2010), together with applications of protein and fat growth descriptions in intake prediction.

Table 6 *The distribution of values of the powers of protein breakdown rate* X + Z *estimated from the inflection points of the family of curves fitted to mammalian body mass growth data by Gaillard* et al. *(1997)*

$X + Z$ interval	*n*	Fraction
0.4 to 0.5	6	0.09
0.5 to 0.6	5	0.07
0.6 to 0.7	6	0.09
0.7 to 0.8	5	0.07
0.8 to 0.9	8	0.12
0.9 to 1.0	11	0.16
1.0 to 1.1	3	0.04
1.1 to 1.2	7	0.10
1.2 to 1.3	1	0.01
1.3 to 1.4	2	0.03
1.4 to 1.5	3	0.04
1.5 to 1.6	1	0.01
1.6 to 1.7	2	0.03
>1.7	9	0.13
Total	69	0.99

Discussion

Possible genetic, nutritional, environmental and age influences on the growth parameters $X + Z$, Y and Q

Variation in $X + Z$. The growth parameter $X + Z$ can experimentally be estimated from the power in the relationship between PB and the body component or tissue protein mass. The postulated theoretical values of $X + Z$ in Table 1 are determined by the possible rate-limiting steps associated with protein breakdown in skeletal muscle or the total body. Evidence is presented in Table 3 for the possibility of a nutritional effect on $X + Z$, and in Tables 3 and 4 for genetic effects. $X + Z$ is important in determining the inflection point in the protein growth curve. That selection for growth rate may change $X + Z$ is evident from Table 4. This suggests the influence of natural selection in the explanation of species differences (Table 6) in points of inflection determined by $X + Z$, as it may be advantageous to have fast growth coinciding with favorable seasonal effects such as temperature or food supply.

Break points. von Bertalanffy (1960) provides evidence that breaks or changes in mammalian growth curves generally occur with the onset of puberty. Changes in protein metabolism have also been observed at such a break in the growth curve by Siebrits and Barnes (1989). It follows that an estimate of $X + Z$ from equation (2) may vary according to measurements before, after or straddling the break. The estimate of Siebrits and Barnes (1989) in Table 3 is from points after the break, since very few measurements before the break were taken. Straddling the break will, in this case, lower the estimate of $X + Z$ appreciably. The possibility of

the existence of different growth curves before and after the prepubertal break needs consideration. Owing to lack of information, this possibility was ignored in the present publication.

The parameter Y. The parameter Y is the power of the relationship between cell volume and tissue protein content. Values for Y for different tissues have been derived by Roux (2006). For the whole body, the contribution of the different tissues should be weighted in proportion to their PS rates. An average $Y = 1/2$ for the whole body is given by Roux (2006), but Y may very well differ between types, breeds or species. Evidence of approximate $Y = 1/2$ exists for mammals and fish (the present communication), but more uncertainty exists for chickens or birds in general.

Variation in Q. The growth parameter Q is the proportion of nuclei active in either cell enlargement or multiplication. It can be estimated from equation (10) or its derivations, equations (11.1) and (11.2), as well as from intake and maintenance rates and diet properties. It is evident from equation (7) that a constant $Q < 1$ will merely cause a constant proportional change in PR during growth. On the other hand, a variable Q during growth may disguise the true growth form as determined by the rest of the parameters $X + Z$ and Y.

Practical utility

Perhaps the greatest practical utility of the theory developed in this study is the possibilities for intake and growth description and prediction shown in the construction of Table 5 together with Tables A4 and A5 in Roux (2010). With some information on limit masses and inflection points, fairly general equations such as equation (13) together with a fat analog are easily obtainable with the aid of Table 1 and can be adapted to specific circumstances by calculation of the constant c from available experimental observations, even at a single growth point. In contrast to the multiple points of inflection available from Table 1, the Gompertz, for example, is only applicable to the situation of a point inflection at $P/\alpha = 0.368$. Furthermore, the papers of Ursin (1979) and Oltjen *et al.* (1985) illustrate that the fitting of general equations such as equation (1) or (7) will be difficult without information on limit mass or point of inflection. Technically, this problem arises from the intra-correlation between the structural parameters of curvilinear functions.

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Appendix

A description of the most important variables, their abbreviations and their units of measurement for the prediction of body component growth and food intake

Abbreviations	Description
α	The limit or mature protein mass of the total body, body component or tissue (kg)
$\propto$	proportional to
β	The limit or mature total body fat mass (kg)
c	Arbitrary constants, sometimes with subscripts to differentiate between them
cv	Cell volume
DNA unit	The amount of protein associated with a nucleus, equal to *P*/*nn* in multinucleate tissues; identical to a cell in mononucleate tissues
F	Fat mass (kg)
FR	Fat retention (kg/day)
ME	Metabolizable energy (ME, MJ)
MEI	ME intake (MJ/day)
MEO	Optimal ME intake at PR = PR_{max}
MEM	The ME intake at body protein maintenance with PR = 0 (MJ/day)
nn	Nuclear number
nv	Nuclear volume
P	The protein mass in a tissue, body component or whole body (kg)
P/α	Protein maturity (kg/kg)
PB	Protein breakdown (kg/day)
PR	Protein retention (kg/day)
PS	Protein synthesis (kg/day)
Q	The proportion of nuclei active in cell growth or division
W	Empty body mass (kg)
X	The power associated with the DNA unit rate-limiting step in protein breakdown
Y	The power of the relationship between cell volume and tissue, body component or whole body protein amount
Z	The power of the relationship between the number of nuclei and tissue, body component or whole body protein amount