Growth and Physiological Parameters for Canine Pharmacokinetic Models.

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Introduction

Mathematical combination of *in vitro* (biochemical and cell culture) results with information such as total blood volume (V_{bl}) and fractional tissue perfusion (fQ_j), metabolic tissue volumes (V_j - such as liver, kidney, intestinal tissue) and excreta flows can allow prediction of drug disposition in the whole animal and improve experiment design prior to completion of whole animal studies. In the case of animals where multiple strains or breeds are of interest, the availability of strain or breed-specific anatomic and physiological models allow more accurate prediction of systemic concentrations achieved by dosing, and promote design of more appropriate dosing regimens where whole animal or breed specific experimental data is unavailable. The primary value of using a physiologically-based pharmacokinetic model (PBPK model) over a simpler compartmental model is in the application of accurate compartment volume and flow limitations to transport equations which bound the model to feasible solutions. Available information on biochemical transporters and metabolic activities measured *in vitro* can be combined with anatomic and physiological parameters for the whole animal to estimate unmeasured or unknown transport rates, but may also be used to dissect existing pharmacokinetic data sets. For instance, a volume of distribution (Vd) can be obtained by rapid blood sampling following intravenous (IV) injection, but is of little value for predicting the fate of rapidly distributed substances that are metabolized to active substances which interact pharmacologically with specific tissues. In such cases *in vitro* experiments with red blood cells (RBCs), plasma, cultured cells or other tissue preparations are needed for further elucidation of the fate and interactions of a chemical introduced into the animal.

Drug effects are generally proportional to target tissue [$C_j(t)$] and receptor concentrations [RX_j]. An injected drug is distributed to the tissues by blood flows (Q_j) and enters tissues in proportion to permeability-driven extraction ($\varepsilon_j \sim P_m S$) and partitioning parameters (R_j). Tissue weights - assumed equivalent to volumes (V_j) - are essentially dilutional parameters applied to distributed masses of drug [$M_j(t)$] to obtain target tissue $C_j(t)$, with partitioning (R_j) and metabolic coefficients (k_e) modifying dilution in a typical PBPK model equation:

$$C_j(t) = \frac{M_j(t)}{V_j} \qquad M_j(t) = V_j\left(\frac{dC_j}{dt}\right) = \varepsilon_j Q_j(C_p - C_j/R_j) - k_e C_j V_j$$

The sections which follow summarize and fit to standard growth models available information on such organ volumes and physiological flows for experimental dogs - primarily beagles. Models for extrapolation from *in vitro* metabolism results to beagles and other breeds are illustrated.

Whole Body and Organ Growth

No single publication to-date has compiled all of the data or derived parameters needed to characterize the whole body, organ, and fluid volume growth of any canine breed. Multiple data sources must be combined via growth and mass balance models to provide satisfactory anatomical / physiological characterization of any breed. The beagle is the most commonly used canine test subject and is best characterized by available studies. A monograph edited by Andersen (1970) provides good anatomical and histological information for the beagle but little physiological information.

Studies published since Brown et al. (1997) were used with allometric body and organ growth functions for beagles from publications of Deavers et al. (1971, 1972), Trieb et al. (1978), Romsos et al. (1981) and Choi et al (2011) to derive updated growth models. Deavers et al. (1972) and Trieb et al. (1978) used relatively simple allometric functions to model organ growth data. More accurate fits to several organ weights can be achieved with logistic or Gompertz models. Extension to other breeds and a wider population distribution requires scalable models and variance measures. A combination of Gompertz models (see Roth et al., 1998) for whole body weight (BW) and BW-dependent allometric equations for organ growth are derived here and compared to several data sets (**Figures 1** and **2**, **Table 1**). The Gompertz model has two principle advantages over other growth models : (1) it includes kinetic information on the maximal growth rate (β) and age-dependent deceleration rate (α), as well as (2) allowing the maximum weight (W_{max}) and population variability to be predicted with only α, β, and a "birth weight" (W_0) which does not need to be the actual weight at birth, but simply the earliest measurement or estimate available. Skeletal growth is the primary determinant for overall morphology and body weight in canines, allowing scaling between breeds (Chase et al., 2002; Garsd et al., 1981; Hawthorne et al., 2004; Helmink et al, 2000; Salomon et al., 1999). The volumes of the thoracic cavity and skull limit growth of almost all organs, while the strength of the skeleton limits muscle development. Growth maturity is achieved in all breeds by 40 - 52 weeks of age. The maximum growth rate $(dBW/dt)_{max}$ was in the range of 0.13-0.17 * BW/week for all breeds. With the exception of the thymus, organs exhibit monotonic increases in volume with increasing BW. Scalability is achieved by driving organ weight (V_j) with relative body weight ($W(t)/W_0$). Allometric equations for Beagle organ weights have been modified here to allow prediction of organ weights for other dog breeds where no published measurements exist.

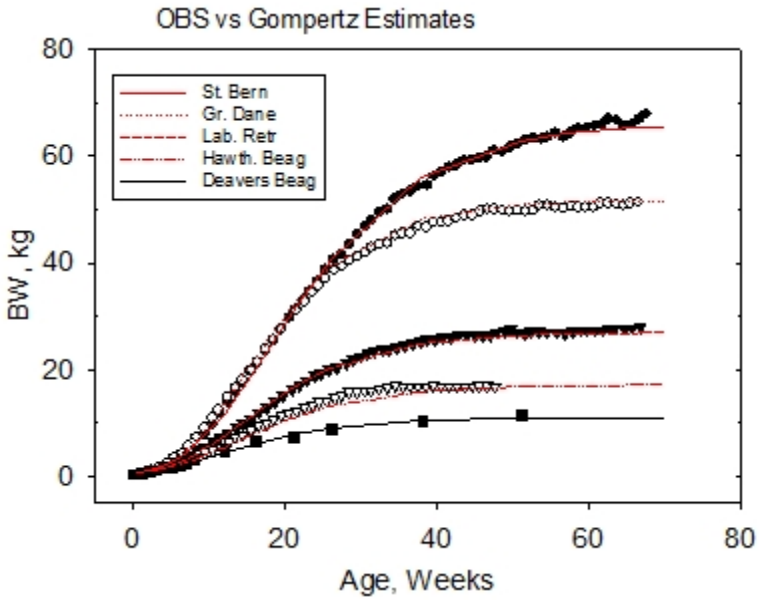

Figure 1 Gompertz functions fitted to body weights of multiple dog breeds reported by Hawthorne et al. (2004) and Deavers et al.(1972). birth weights and other model parameters for each breed are listed in Table 1.

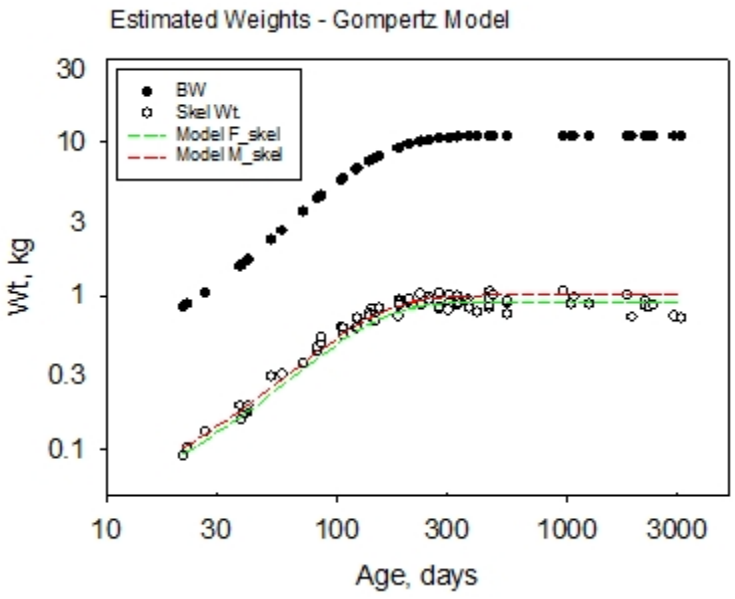

Figure 2 Example of organ volume simulation - skeleton weights predicted on the basis of the gompertz body weight model and parameters derived from regression analysis of age; body weight; skeleton weight data from Garsd, (1981) ; Salomon, (1999).

Growth is generally nutrient dependent (modeled in Roth et al., 1998). One tissue that does not reach a limiting volume with excess nutrient is storage, or white fat. Most dogs used for experimental purposes are fed a fixed ration of 300-500 g chow per day, with periods of minimal exercise. With this feed restriction, adipose tissue volume in beagles reaches a steady-state of 8 - 22 % of BW at maturity, but can rise above 40 % under *ad libitum* feeding (Ishioka et al., 2002). This is unlike the situation in rodent experiments, where animals are fed *ad libitum*, or the similar situation for human populations, where food consumption is not constrained and adipose tissue volumes may continue to expand towards obesity with age.

It should be noted that a portion of the "organ weight" and therefore, chemical residuals are contained in residual blood. Smith et al. (1972) measured these residual blood volumes in the same dogs studied by Deavers et al. (1972). Residual blood information is found with blood flows in **Table 5**.

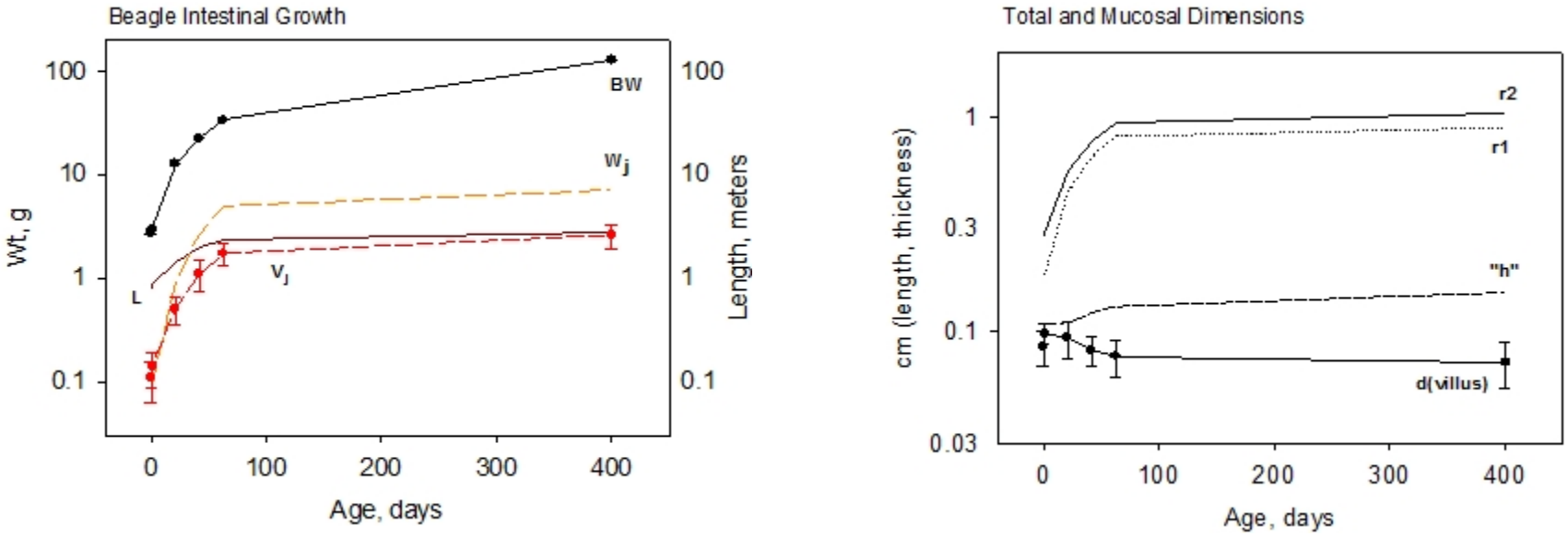

Figure 3 Observed tissue weight (V_j,●) mucosal thickness (d), predicted total thickness (h, ---), and lumen volumes (W_j, — —) of Beagle intestines (data from Paulsen et al., 2003). Note that the lumen volume quickly becomes much larger than intestinal tissue volume within the first few months of growth. Model parameters are listed in Table 2.

Internal Flows and Mass Balance

Urine and Bile Production

The majority of products of drug metabolism are eliminated via the urine and or bile, depending on the molecular weight and other species-specific metabolic determinants. In some cases the pharmacological actions of the parent drug or metabolite may alter the urine flow, partitioning and resulting concentration of excreted drug in the urine (Jeunesse et al., 2007; Nöel et al., 2013). Similar processes also occur in the bile, but biliary elimination is more difficult to measure and is consequently less-well studied than clearance and elimination of drugs in the urine (Wills et al., 1984; Pearlman et al., 1984; Beck et al., 1990).

Urine production in humans is usually proportional to the intake of water, but may increase or decrease in the presence of excess heat or other stresses. Urine production in the dog is relatively constant, except when excessive water intake is forced. Under standard laboratory conditions (STP), dogs convert about 30 % of their water intake into urine volume, with the remaining 70 % divided between exhaled water and fecal moisture, depending on dry food intake, temperature and exercise (O'Connor et al., 1975). Three newer publications measured urine production in conscious, freely moving beagles. Laroute et al. (2005) measured multiple urinary parameters in pups aged 65–68 days and adult females, age 6-9 years. Urinary output ranged from 28 mL/kg-day in puppies to a mean of 17 mL/ kg-day (~ 170 mL) in adult females. Jeunesse et al. (2007) were primarily interested in the effect of spironolactone on diuresis, but measured urine output under control as well as drug-dosed conditions. Their results ranged from 11 to 17 mL/kg-day, with a food ration of only 250 g/day. McAfferty et al. (2009) were interested in urodynamics (bladder pressure, volume per void) and implanted appropriate telemetric sensors in otherwise freely moving dogs. Their results gave a range of 16-18 mL/kg-day. A very similar experiment was performed by Nöel et al. (2013) in a telemetric study of the urodynamic effects of 5 drugs. Urine production values are listed in Table 3, with other input and outputs.

Bile Production

Information on the production of bile in canines is very limited in comparison to reports which include information on bile output in rats and humans. Pearlman et al, (1984) used bromophenol blue as a tracer for biliary elimination, and in the process measured bile output (Qbj -mL/min) in beagle test subjects, collected at 5 and 15 min intervals out to 12 hours.. This data was used to model the effect of bile flow on tracer elimination:

$$\frac{excretion\ rate}{flow} = \frac{1}{Q_{bj}} \frac{(A_{ex})_j}{t_j} = C_{bile}(t_j)$$

Bile flow (Qbj) oscillated wildly about 0.1 mL/min (6 mL/hr), but when the output of tracer (Aex) was divided by the flow, tracer elimination was found to be a concentration-dependent first-order process. Beck et al. (1990) performed a similar experiment using indomethacin as a marker of biliary elimination. Measured bile production ranged from 5 to 7 mL/hr for 14 kg beagles.

Gastric Emptying and Intestinal Transit

Stomach emptying is essentially first-order from a mathematical perspective (Read et al., 1980), and is dependent on the chemical nature and consistency of the food, with aqueous liquids containing carbohydrates and proteins emptied within 1 hour (t1/2 ~ 15 min) while digestible oils may delay emptying to 6 hours (Table 4a and Figure 6). Solid-containing meals delay emptying in proportion to the size of particles, with emptying of liquid portions of the meal at a similar rate to aqueous liquids (Hinder & Kelly, 1977). These authors reported the times for emptying of various components of mixed meal to dogs. The mixed meal was designed to study the emptying of a liquid, a digestible solid, and an indigestible solid after concurrent ingestion. The meal was comprised of 400 mL of 1 percent glucose, 50 grams of cubed liver, and 40 (7 mm) plastic spheres. The half-time for emptying of glucose was about 30 minutes ($\mathbf{k}_{\mathbf{empty}}$ = 1.38 /hr); the half-time to empty cubes was about 2 hours ($\mathbf{k}_{\mathbf{empty}}$ = 0.35/hr); none of the plastic spheres had left the stomach at 4 hours after ingestion. Oswald et al. (2015) summarized gastric emptying times (GET = T1/2) as determined by disappearance of polyethylene spheres in a test meal for 3 breeds of dogs. The mean GET ranged from 4.7 to 7.8 hr, with faster transit associated with younger (more active ?) dogs, but little difference between breeds of very different body size. This is consistent with data previously compiled by these authors, indicating little difference between species in GET despite order of magnitude differences in body size.

Transit of meal components through the intestines is initially controlled by the metering function of the stomach with feedback from the intestines (Read et al., 1982). Intestinal sensors identify carbohydrate, amino acid and fatty acid components of the meal, produce stomach-regulating cholecystokinin (CCK) in proportion to these components, with plasma CCK levels providing feedback to the stomach. The rate of emptying is therefore a dynamic process tailored to the meal components (McLaughlin, et al.,1999 ; Stephens et al., 1975). The presence of products of lipid digestion in the stomach and small intestine inhibits the release of gastrin and delays gastric emptying. The most powerful inhibitors of gastrin release are monoglycerides and fatty acids. Long-chain fatty acids exert the largest delaying effect on gastric emptying. The increase in activity per millimole parallels the activity of intestinal esterifying enzymes towards different fatty acids, and the capacity of the lymph to carry the esterified FA. The optimal chain length is 14 carbons - added myristate caused a linear decrease in $\mathbf{k}_{\mathbf{empty}}$ from 3.3/hr (control) to 1.2/hr at 10 mM potassium myristate (Hunt & Knox, 1968). Table 4a lists typical gastric emptying rates for these types of meal components, while Figure 7 shows the theoretical intestinal lumen and plasma concentration responses for each type of nutrient.

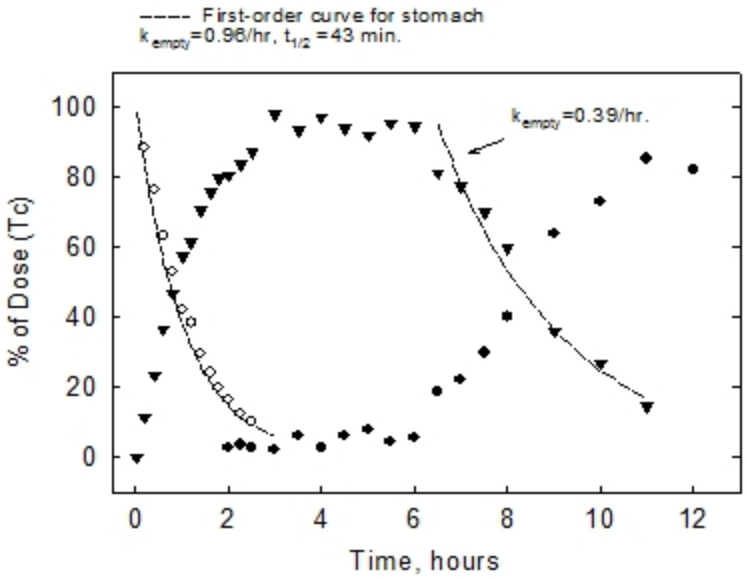

Figure 6 Gastric and intestinal emptying rate functions fitted to human subject data from Read et al.(1980). Intestinal emptying rate was derived by subtracting Cecum filling rate from cumulative gastric emptying.

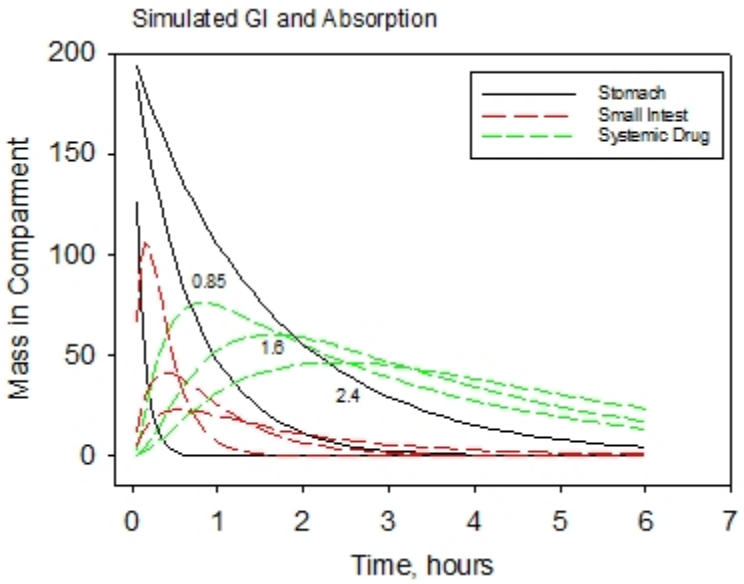

Figure 7 Simulated intestinal lumen and plasma drug concentrations based on gastric emptying rates estimated for diets of different viscosity as reported by Ehrlein and Pröve (1982). GET = 4.5, 29, 65 min.; k_{a2} = 2.0/hr k_e = 0.35/hr ; T_{int} (max) = 9, 24, 33 min ; T_{pla} (max) = marked.

Intestinal transit is less-well characterized than GET, and depends as much on activity of the migrating motor complex (MMC) as the food contents. Movement through the intestines is also dependent on consistency, but chyme is generated by mixture of food and fluid with gastric fluid, bile, and pancreatic fluid, with the last two added simultaneously with absorption of nutrients and water. Intestinal transit and consequential water absorption is inversely dependent on the amount of exercise that the animal experiences, among other factors, for a given food type. Intestinal contraction and propulsion is controlled by the MMC, which is modified by animal activity and exercise (Gruber et al., 1987). The MMC progresses through the small intestine, propelling the contents during each cycle (Scott et al., 1976, Kellow, 1996). The cycle is highly variable, ranging from 15 - 180 min in duration (Oberle & Amidon, 1987). As a consequence, intestinal transit is complex and difficult to predict except in the case of a sedentary animal - the subjects of most published experiments. Using gastric emptying rates, water absorption and lumen volumes (Wj) for intestinal segments, theoretical transit times can be estimated. These estimates are compared in Table 4b. As part of their analysis of breed-specific parameters, Oswald et al. (2015) also summarized total and large intestinal transit times (TTT and LITT). Unlike the results for gastric emptying (GET), large intestine emptying (LITT) appeared to be proportional to the size of the animal and total body weight.

Blood Volumes and Flows

Total blood volume has been determined by several methods, all of which involve the dilution of a "non-absorbable" tracer which is added to the blood. Serial samples are taken to determine dilution after tracer addition. In practice, molecular tracers (dye or protein) can escape from the total blood circulation and particulate tracers (^{51}Cr - or carbon monoxide - labeled red blood cells, polystyrene nanospheres) can be trapped in tissues. As a consequence, each method requires different corrections and may give somewhat different results. Gupta et al. (1981) published canine plasma volume results which converge on two values - one associated with low sodium intake (36 ± 3 mL /kg) and one associated with high sodium intake (54 ± 3 mL/kg). When converted to blood volume (via hematocrit, HCT = 35 - 50 %)) these correspond to 50 ± 5 mL/ kg and 90 ± 10 mL /kg. The latter value (~ 9 % BW) is high compared to blood volumes in other species (4 - 6 % BW) but is comparable with results of other authors for beagles (Deavers et al., 1971; Finsterer et al., 1973 ; Green & Jackman, 1979) which average 8 % BW (80 mL/kg).
Brown et al. (1997) did not include systemic blood volumes, but did compile some residual blood volumes found in tissues of exsanguinated animals. Residual blood was measured in dogs by Smith et al. (1972). They showed, consistent with later blood pressure compliance studies (Carniero & Donald, 1977; Green & Jackman, 1979) that the lung, liver, intestines and particularly the spleen act as blood reservoirs for red blood cells resulting in a higher relative "hematocrit" for residual blood in these tissues. The residual blood values are listed in **Table 5**.

Total cardiac output (CO) and fractional organ-specific flow ($fQ_j * CO = Q_j$) distribution have been measured by soluble, non-absorbable dye (or radioactive tracer) dilution but now are generally measured using larger, radiolabeled microspheres, which are known to be trapped by arterial capillaries resulting in the distribution of flow-dependent numbers of microspheres into specific tissues fed by the aorta (Quillan & Reid, 1988). Output values obtained by these authors ranged from 124-140 mL/min-kg BW, whereas Green & Jackman obtained much lower CO values of ~ 77 mL/kg-min., using ^{133}In-transferrin as a tracer. Cardiac output and updated values of fractional organ-specific flows are listed in **Table 5**.

Body, Organ, and Fluid Volume Models with Scaling

Most growth models in the literature are either allometric - applied freely across species - or are experiment-specific, ie. they apply only to a single data set. In both of these cases the parameters provide erroneous predictions when applied to animals of different species or strains. Some model modifications can allow fitting of parameters which allow scaling over wider ranges of strain (breed) and life stage. Models which incorporate the ratio of maximum to minimum BW (W_0 / W_{max}) can provide this flexibility as long as a true maximum has been sampled and the exponential growth rate parameters are fitted to appropriately transformed weight or size data. Logistic equations generally do not include time-dependent (kinetic) growth parameters. Models which do include time dependence can also be modified with "relative time" transformation, which is primarily of value in cross-species growth modeling - not explored in this review.

Two different forms were used to fit and predict organ sizes from BW:
(1) Logistic functions, of the form $V_j\,(BW) = W_{max} / (1 + c(BW)^b)$ and (2) allometric functions $V_j\,(BW) = c(BW)^b$.
In each case use for scaling across breeds requires conversion to a relative body weight basis
($f_j = (V_j/BW)$) so that a similar relative organ size can be computed - for example

$$V_j(breed\ 2) = BW(breed\ 2)\left[\frac{V_j(beag)}{BW(beag)}\right] = \left[\frac{1}{BW(beag)}\right]\left(\frac{W_{max}}{1+c[BW(beag)]^b}\right)$$

This is particularly easy for the allometric models, since

$V_j\,(beagle) / BW\,(beagle) = c(BW)^{(b-1)}$ and $V_j\,(breed\ 2) = BW\,(breed\ 2)\,[c(BW)^{(b-1)}]$

Tables

Table 1 - Body Weight and Organ Weight Model Parameters

Model Coefficients for Fitted Equations				
Gompertz Model (1 stage)				
Breed	"α" - growth deceleration	"β" - initial growth rate	"W0" - initial (birth) weight	W_{max} = W0*exp(β/α)
Beagle	0.114/week	0.4165/week	0.15 - 0.285 kg	11 - 17 kg
Lab. Retriever	0.107 ± 0.004	0.494 ± 0.047	0.260 - 0.45	24 - 29
Ger. Shepherd	0.106	0.488	0.400 - 0.50	26 - 30
Gr. Dane	0.120 ± 0.006	0.696 ± 0.086	0.450 - 0.90	50
St. Bernard	0.091 ± 0.007	0.469 ± 0.086	0.350 - 0.70	60 - 70
Logistic Equation and Allometric (Deavers, 1972) Parameters for Beagles				
Organ/Tissue	"a"	"b"	"x0"	Allometric
Liver	598.15	-1.44	6.35	$43.9*BW^{0.847}$
Kidney	81.9	-1.05	6.42	$11.7*BW^{0.672}$
Lung	243.6	-1.04	17.47	$14.9*BW^{0.742}$
Heart				$8.06*BW^{0.913}$
Stomach				$11.9*BW^{1.23}$
Intestine				$64.0*BW^{1.038}$
Spleen	32.03	-0.266	9.08	$4.07*BW^{0.728}$
Adrenal	2.51	-1.79	-1.56	
Ovaries	4.157	-0.970	38.86	
Brain (ref ?)	72.4	-1.20	0.825	$42.09*BW^{0.285}$
Pituitary	0.0685	-1.72	2.96	
Bone*				$0.2606*BW^{0.866}$
Muscle	Data from Andersen (1980), linear fit : V_{mus} /BW = 0.336 + 0.0173*BW			

* Allometric fit for Total Skeleton transformed from Garsd et al. (1981) Table 1, equation 1:

$\log_{10}(y) = -0.534 - 0.041x_1 + 0.886\log_{10}(BW)$ where y = total skeleton wt., grams, x_1 = 1 ♂, 2 ♀

$y = EXP[\ln(10)*(-0.534 - 0.041x_1 + (0.886/\ln(10))*\ln(BW))]$
$= 0.2606*EXP(0.886*\ln(BW)) = 0.2606*BW^{0.866}$ (males)

Table 2 - Gastrointestinal Tract Dimensions for 12 kg Dog

Segment	% Tot. GI Wt	% Tot. Intest.	* Seg. Length = (a, b) L (cm)	Seg. Length = % Tot * Tot. L	Lumen Vol (W_j) % Tot * W_{tot} ‡
Stomach	24.6	---	---	---	720 mL
Duodenum	6.7	8.87	(29, 0.67) **34**	**25** cm	63 mL
Jejunum	48.7	64.7	(212, 0.72) **217**	**183** cm	461
Ileum	3.1	4.1	(9.0, 0.45) **12**	**12** cm	29
Colon	16.8	22.3	---	**63** cm	159

* ($L = a + wt^b$) from Oswald et al., 2015, Figure 1 ‡ Intestinal Lumen (W) @ 12 kg = 712 mL

Table 3 - Water Balance, Urine and Bile Flows

Input/Output	Source	Flow	Reference
Input	Food	300-600 g/day	Frost (1989), Rotat (2015)
Input	Metabolism	0.1 - 0.6 g/kg	O'Connor (1975)
Input	Drink	1 - 10 g/kg-hr (rest vs running)	O'Connor (1975)
Output	Water Exhalation	0.5 - 7 g/kg-hr (rest vs running)	O'Connor (1975)
Output	Urine	0.5 - 0.7 g/kg-hr	Laroute (2005), Jeunesse (2007), McAfferty (2009)
Output	Bile	0.3 - 0.5 g/kg-hr	Pearlman (1984), Beck (1990)

Table 4a - GastricVolumes and Emptying Coefficients

Segment /Species	Tissue Wt. (% BW)[a]	Lumen Volume (% BW)	Gastric Secretion	k_{empty} (1/hr)[b]	Comments
Rat (S-D)					
Stomach	0.46 ± .06	(0 - 3 %)	?	1.15->0.33 (0.5 - 2 hr)	fasted--> ad libitum fed
Dog (Beagle)					
Stomach [wt = $11.9(BW)^{1.23}$]	0.8 ± 0.15	(0 - 6 %)	150 - 240 mL/hr	1.4->6.0 (30 - 7 min) 0.85 ->1.2 (50 - 34 min) 0.39- 0.35 (~ 2hr)	w/ 55 mM glucose -> saline. w/ 500 mM glucose w/ meat cubes
Human					
Stomach	0.20	1,300 mL (1.8 %)	30-700 mL/hr	1.1- 4.6 (37 - 9 min) 2.2 ± 0.9 3.3 -> 1.2 0.40	330-1250 mL sucrose-pectin. orange juice 0 --> 10 mM myristate ^{99m}Tc-olive oil

[a] Tissue weights & lumen volumes from: Deavers et al (1972), ILSI (1994), Thompson & Hollis (1958)

[b] Transit times from: Clemens & Stevens (1980), Enck et al. (1989), Hinder & Kelly (1977), Hunt & McDonald (1954), Read et al. (1980), Thompson & Hollis (1958), Weisbrodt (1969), Williams (1988).

Table 4b - Example Intestinal Flows - with Food - 12 kg dog, 845 g Total Intestine wt.

Segment	Max Velocity (cm/hr)	Max Flow[a] (mL/hr)	H_2O Absorption (mL/g-hr)[b]	Transit Time : / Segment
Duodenum	100.0	151	0.11*56 = 6.2 g	15 min
Jejunum	61	+ 0.25 hr *(+ 4 - 0.96 mL/hr) = 154	0.13*411 = 54 g	180 min
Ileum	42.3	- 2 hr *54 g = 46	0.69*26 = 18 g	41 min
Colon		- 0.69 hr*18 g = 33	0.56*63 = 36 g	5 hr +

[a] Maximum flow from previous segment + bile (duodenum) - water absorbed
Output from stomach after 6 min = (720 mL)[1- exp[(-0.35/hr)*0.1 hr] = 24.76 mL + 0.48 mL (bile)
Flow/Wj = f/Lj = 25.24 mL/63 mL = 0.4*Lj = 0.4*25 cm / 6 min = 1.67 cm/min

[b] Water absorption rates from Higgins et al. (1971), Code et al. (1960), and Cooperstein et al. (1959).

Table 5 - Blood and Lymph Parameters

Cardiac Output (CO) = 124-140 mL/min-kg BW		Total Vol = 60 (low Na) - 80 mL/kg BW	
Organ	Blood - % Organ Wt.[a]	Fraction of CO	Reference
Lung (arterial)	9.7 → 12.3 %	0.088	Quillen & Reid (1988)
Liver (arterial)		0.046	" "
Liver (portal)	12.5 → 15 %	0.168	derived
Kidney	9.75 → 12.3 %	0.173	Quillen & Reid (1988)
Mesenteric / Intestine	6.7 → 2.5 %	0.137	" "
Splanchenic / pancreas	20 → 32 %	0.054 0.029	" "
Stomach	4 → 2.3 %	0.031	" "
Muscle	2.3 → 1.2 %	0.217	" "
Skin	4.2 → 1.4 %	0.060	" "
Brain	1 %	0.020	" "
Fat		0.070	derived
Bone		0.081	(w/o vertebrae)
Thoracic Lymph Flow = 2 - 5 mL/min *in vivo* for 20 - 30 kg dog			Browse et al., 1974

[a] Equivalent to "residual" blood - data obtained primarily from Smith et al. (1972).

Table 6 - Example Hepatocellular Parameters

Species	Hepatocytes / g Liver [a]	*In Vitro - In Vivo* Scaling Factor (for whole liver volume V_{liv} (g) and reaction rate/10^6 cells)
Human	$139 \pm 25 \times 10^6$	V_{liv} (1170 - 2080 g) x 139 = 162 - 289 x 10^3
Dog	$215 \pm 45 \times 10^6$	V_{liv} (300 - 650 g) x 139 = 41.7 - 90.3 x 10^3
Rabbit	$114 \pm 20 \times 10^6$	
Rat	$117 \pm 30 \times 10^6$	V_{liv} (7.3 - 14.6) x 117 = 0.85 - 1.71 x 10^3
Mouse	$135 \pm 10 \times 10^6$	V_{liv} (1.65 - 2.2) x 135 = 222 - 297

[a] from Sohlenius-Sternbeck (2006)

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