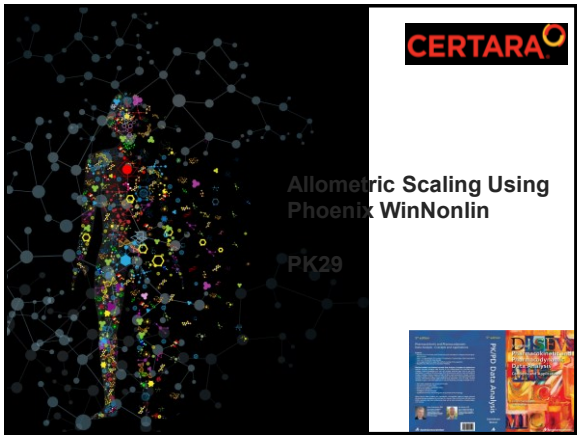


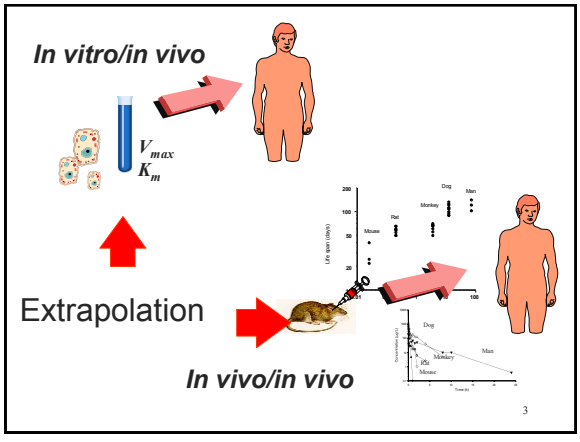
Inter-species scaling

Why scaling?

- *Select* an appropriate first dose in man
- *Predict* concentration-time course in man from animal data + variability
- *Predict* response-time course in man from animal data + variability

From what?

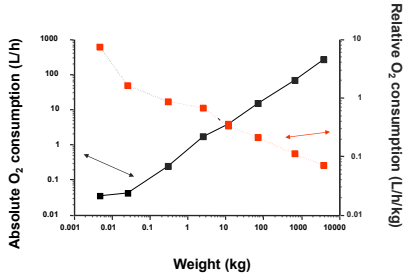
- *Effective concentrations, K_i, IC_{50}*
- *Preclinical PK data*
- *Preclinical PD/turnover data*



What is allometry?

Allometry is defined as the relationship between size (body weight, *BW*) and a physiological variable (e.g., *CL*)

Oxygen Consumption



Clusters

• Volume, organ weights, V_{ss}	~ BW^1
• Metabolic capacity, O_2, *Cl* blood flows, turnover rates	~ $BW^{3/4}$
• Physiological time, longevity, breath time, $t_{1/2}$	~ $BW^{1/4}$
• Frequencies, rate constants	~ $BW^{-1/4}$

These are empirical observations and not biological rules!

Scaling of drug and system parameters

- EC_{50} or IC_{50} correct for f_u (drug parameter)
- E_{max} or I_{max} (drug parameter)
- k_{in} (physiological parameter)
- k_{out} (physiological parameter)

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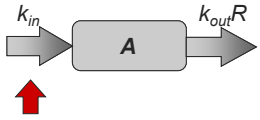
Scaling of turnover (system) parameters



$$k_{in} \propto BW^{3/4}$$

$$A_{ss} \propto BW^{1}$$

$$k_{out} \propto BW^{-1/4}$$

(Gabrielsson & Weiner, 2000)

See also e.g., Adolph, 1949

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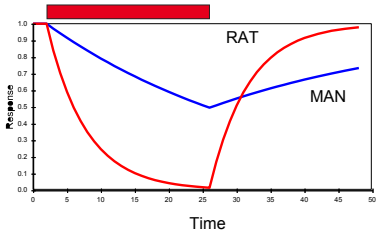
Scaling of turnover parameters



$$A_{ss} \propto BW^{1} \qquad k_{in} \propto BW^{3/4} \qquad k_{out} \propto BW^{-1/4}$$

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Allometric Equations

$$Metabolic\ \ rate = a \cdot BW^{0.75}$$

$$Turnover\ time \propto a_1 \cdot BW^{0.25}$$

$$Y = a \cdot BW^{b}$$

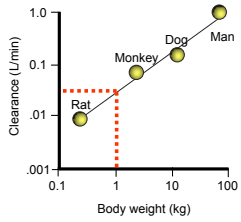
$$\ln(Y) = \ln(a) + b \cdot \ln(BW)$$

$$Cl_i = a \cdot BW_i^{b}$$

$$\ln(Cl_i) = \ln(a) + b \cdot \ln(BW_i)$$

$$V_i = c \cdot BW_i^{d}$$

$$\ln(V_i) = \ln(c) + d \cdot \ln(BW_i)$$



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Dose Scaling

$$AUC_{rat} = AUC_{man} = \frac{Dose_{man}}{Cl_{man}} = \frac{Dose_{rat}}{Cl_{rat}}$$

$$\frac{Dose_{man}}{a \cdot BW_{man}^{b}} = \frac{Dose_{rat}}{a \cdot BW_{rat}^{b}}$$

$$Dose_{man} = Dose_{rat} \cdot \left[\frac{BW_{man}}{BW_{rat}}\right]^{b}$$

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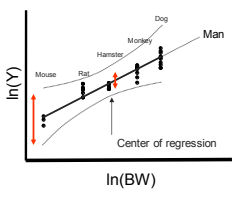
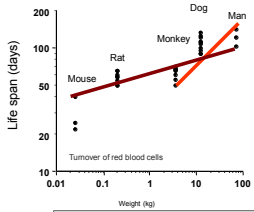
Exploring Data – BW Range is Important





$$Y = a \cdot BW^{b}$$

$$\ln(Y) = \ln(a) + b \cdot \ln(BW)$$

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Allometric Scaling – One Cmpt iv Bolus Model

$$C = \frac{D_{iv}}{V_i} \cdot e^{-\frac{Cl_i}{V_i}t} = \frac{D_{iv}}{c \cdot BW_i^d} \cdot e^{-\frac{a \cdot BW_i^{b-d}}{c}t}$$

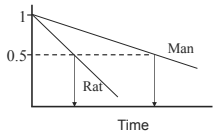
$$AUC_0^\infty = \frac{D_{iv}}{V_i} \cdot \int_0^\infty e^{-\frac{Cl_i}{V_i}t}\,dt = \frac{D_{iv}}{c \cdot BW_i^d} \cdot \int_0^\infty e^{-\frac{a \cdot BW_i^{b-d}}{c}t}\,dt$$

Physiological Time

A species dependent unit of chronological time required to complete a species independent physiological event

(half-life, aging, etc.)

Important for exposure!



Allometric Scaling Using the Dedrick Method

The thought is that small animals spend their lives at a much faster pace than larger animals. For example, smaller animals breathe faster, their heart beats faster, they move their legs faster, etc. Physiologically, if small animals have the same number of heartbeats or breaths in a given lifetime as a larger animal, then on a chronological time scale, larger animals will have slower heart beats and breaths, and the result is that smaller animals will have a shorter life expectancy.

Dedrick Plot Variables

- Kallynochrons: in 1 kallynochron, each species will clear the same volume (V) of plasma per kg BW. This assumes that Vd is directly proportional to BW. That is, the exponent of V is 1 but Cl is not equal to 1 (simple Dedrick Plot).

$$time\ scale = \frac{t}{BW^{1-b}} \qquad \text{Conc } scale = \frac{C}{Dose / BW^1}$$

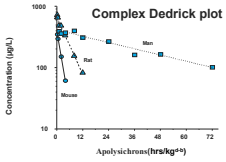
- Apolysichrons: in 1 apolysichrons, each species will clear the same volume (V) of plasma per kg BW, but the exponents for both V and Cl are not equal to 1 (complex Dedrick Plot).

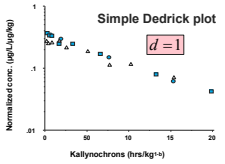
$$time\ scale = \frac{t}{BW^{d-b}} \qquad \text{Conc } scale = \frac{C}{Dose / BW^d}$$

- where

$$Cl_i = a \cdot BW_i^b \qquad V_i = c \cdot BW_i^d$$

Simple Dedrick Plot Example





$$\text{Conc } scale = \frac{C}{Dose / BW^d}$$

$$time\ scale = \frac{t}{BW^{d-b}}$$

$$AUC_0^\infty = \frac{1}{a}$$

Case Study – PK29

$$Cl_i = a \cdot BW_i^b$$

$$V_i = c \cdot BW_i^d$$

$$Cl_{di} = g \cdot BW_i^b$$

$$V_{ti} = e \cdot BW_i^d$$

$$V_c \frac{dC}{dt} = In - Cl \cdot C - Cl_d \cdot C + Cl_d \cdot C_t$$

$$V_t \frac{dC_t}{dt} = Cl_d \cdot C - Cl_d \cdot C_t$$

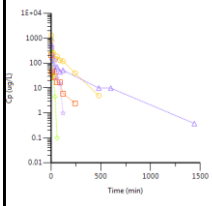
Five species (mouse, rat, monkey, dog, man) received an intravenous dose of a new compound. The body weights were 0.0020, 0.25, 3.5, 14 and 70kg, respectively.

Doses in ug

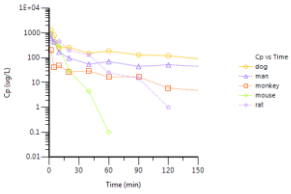
	Species	A1	Time
1	dog	6000	0
2	man	12000	0
3	monkey	200	0
4	mouse	10	0
5	rat	125	0

EDA – Plots of the Data

Plot of all data



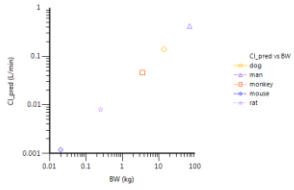
Plot of all data – times out to 150 min



Note the bi-phasic decline

NCA

Species	Cl_pred (L/min)	Vss_pred (L)
dog	0.14	13.98
man	0.42	87.95
monkey	0.05	2.74
mouse	0.00	0.01
rat	0.01	0.15



$Cl_i = a \cdot BW_i^b$

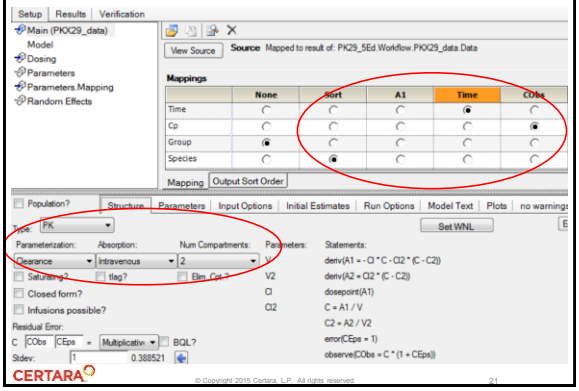
thus

$\ln(Cl_i) = \ln(a) + b$

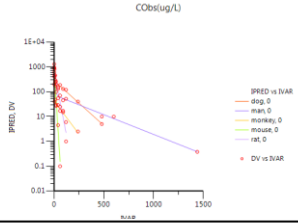
	Dependent	Units	Effect_Level	Estimate	StdError
1	Ln(Cl_pred)	L/min	int	-3.9012555	0.028889858
2	Ln(Cl_pred)	L/min	LN_BW:LN_BW	0.71719481	0.0097599217

Thus a=exp(-3.90) or 0.02

First We Model Each Species Separately



Then Merge the Thetas with BWs



	Species									
	dog		man		monkey		mouse		rat	
Parameter	BW (kg)	Estimate	BW (kg)	Estimate	BW (kg)	Estimate	BW (kg)	Estimate	BW (kg)	Estimate
stdev0	14.00	0.15	70.00	0.15	3.50	0.20	0.02	0.36	0.25	0.39
tvCl	14.00	0.15	70.00	0.49	3.50	0.01	0.02	0.00	0.25	0.01
tvCl2	14.00	0.57	70.00	1.84	3.50	0.00	0.02	0.00	0.25	0.17
tvV	14.00	2.39	70.00	13.68	3.50	0.00	0.02	0.01	0.25	0.18
tvV2	14.00	12.77	70.00	96.55	3.50	0.07	0.02	0.90	0.25	0.00

Perform Linear Regressions: Ln Parm vs Ln BW

$Parameter_i = \text{int} \cdot BW_i^{slope}$

thus

$\ln(Parameter) = \ln(\text{int}) + slope$

	Parameter	int	LN_BW:LN_BW	Exp_Int
1	stdev0	-1.4092041	-0.13649891	0.24433768
2	tvCl	-4.1591348	0.68090192	0.015621068
3	tvCl2	-6.0436404	1.7599038	0.0023729048
4	tvV	-2.1831946	0.74673076	0.11268098
5	tvV2	-3.4975064	1.33034	0.030272777

These will be our initial estimates for the combined species model

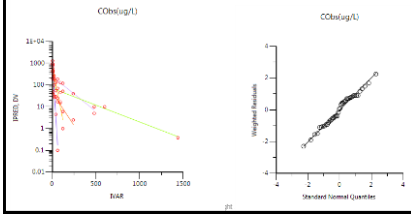
Combined Model – Use a Library Model and Edit It

```
covariate(BW)
deriv(A1 = - Cl * Cp - Cl2 * (Cp - C2))
deriv(A2 = Cl2 * (Cp - C2))

Cl = A*(BW^B)
V = C*(BW^D)
Cl2 = G*(BW^B)
V2 = E*(BW^D)

Cp = A1 / V
C2 = A2 / V2

dosepoint(A1)

error(CEps = 0.1)
observe(CObs = Cp + Cp*CEps)

fixef(A = c(0, 0.02, ))  #int Cl
fixef(B = c(0, 0.7, ))   #exponent Cl, Cld
fixef(C = c(0, 0.1, ))   #int Vc
fixef(D = c(0, 1.2, ))   #exponent Vc, Vt
fixef(E = c(0, 0.8, ))   #int Vt
fixef(G = c(0, 0.1, ))   #int Cld
```

Combined Model Fit

#int Cl
#exponent Cl, Cld
#int Vc
#exponent Vc, Vt
#int Vt
#int Cld

Parameter	Estimate	Units	Stderr	CV%
A	0.02023		0.0010744766	5.3113031
B	0.755311		0.017601136	2.3303164
C	0.0859921		0.020566234	23.916423
D	1.21174		0.021442948	1.7695997
E	0.592569		0.0404858	6.8322508
G	0.0749864		0.011944873	15.929386
stdev0	0.26685		0.028446265	10.660021



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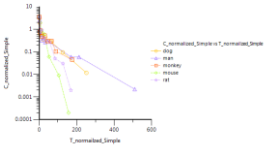
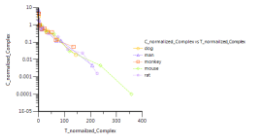
Summary

We have shown how principles of allometric scaling can be applied to simultaneously fit data from several species.

Simple Dedrick Plot
Exponent of V=1



Complex Dedrick Plot
Exponent of V not 1



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Allometric Scaling Doesn't Always Work - How Can We Identify Exceptions?

- Binding (e.g., f_u, V_c/V_{ss}, mono/multi-phasic decline)
- Cross-species metabolic differences (e.g., poly-morphism, qualitatively different *CYPs*, extra-hepatic elimination)
- Complex *Cp-t* profiles (e.g., oscillations)
- Nonlinear systems (e.g., capacity, transporters)
- Watch out for low Cl_{int} compounds
- Behavior of data in allometric and Dedrick plots

Note that for novel compounds you don't know if allometric scaling will work until the data are generated. But for analogs and structurally similar compounds of drugs that do follow allometric principles the follow-on drugs will likely do so as well.

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