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# Using Normal Fat Mass to Account for Body Size and Composition

Nick Holford

University of Auckland
Auckland, New Zealand

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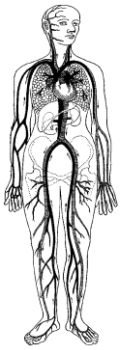
## Theoretical Foundation for Allometric Scaling



$$CL_{CHILD} = CL_{ADULT} \cdot \left( \frac{WT_{CHILD}}{WT_{ADULT}} \right)^{3/4}$$



West GB, Brown JH, Enquist BJ. The fourth dimension of life: fractal geometry and allometric scaling of organisms. Science. 1999;284(5420):1677-9.

The fundamental assumption of West's allometric theory is that all cells are similar in size and have similar energy requirements. The structure of the energy delivery system e.g. blood vessels in humans, requires a certain mass to support the delivery system as well as the target cells. This leads to the theoretical allometric scaling function with a power of ¾.

Photo shows Nick Holford (41 y 80 kg) and Sam Holford (1 y 8 kg) on Fox Glacier, NZ 1987

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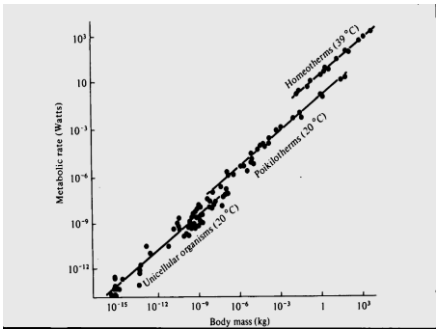
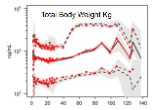
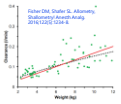
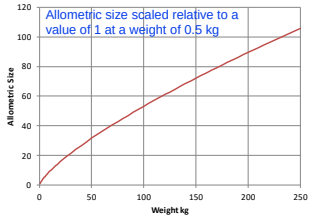
## Allometric Size Matches Observations 18 Orders of Magnitude




Peters R. The ecological implications of body size. Cambridge: Cambridge University Press; 1983.

| | | |
|---|---|---|
| Slide 4 | **Testing Allometric Theory**<br>  <br><br>N=1610<br>  <br>N=57<br>Busulfan Pharmacokinetic Parameters / Bootstrap Average / 2.5% ile / 97.5% ile / Bootstrap RSE<br>TBW Allometric exponent for CL: **0.764** / 0.733 / 0.798 / 2.3%<br>TBW Allometric exponent for V1: **1.011** / 0.871 / 1.115 / 5.6%<br>TBW Allometric exponent for Q: **0.838** / 0.734 / 0.957 / 6.7%<br>TBW Allometric exponent for V2: **0.930** / 0.885 / 0.988 / 2.6%<br>McCune JS, Bemer MJ, Barrett JS, Scott Baker K, Gamis AS, Holford NHG. Busulfan in Infant to Adult Hematopoietic Cell Transplant Recipients: A Population Pharmacokinetic Model for Initial and Bayesian Dose Personalization. Clin Cancer Res. 2014;20(3):754-63. | |
| Slide 5 | **Body Size** is the most important quantitative determinant of drug dose<br>• The **human body weight range** varies from about 500 g to over 250 kg due to both biological variability and changes over the lifespan.<br>   <br>• The **500 fold weight range** is directly translatable to predictable differences in volume of distribution and clearance | By using biologically based theory we can predict how pharmacokinetic parameters like volume of distribution and clearance will vary with size. Size is the single most important predictor of pharmacokinetic parameters based on the more than 500 fold range of body weight observed in humans. |
| Slide 6 | **Allometric Size for Clearance**<br>  <br> | The relationship between weight and clearance is non-linear. This is predictable from theory based allometry with an exponent of ¾. With weight varying 500 fold from 0.5 kg to 250 kg the equivalent allometric size varies by a factor of just over 100. |

| | | |
|---|---|---|
| Slide 7 | **Size and Body Composition**<br>• One view of body composition is to distinguish between fat mass (FAT) and fat free mass (FFM)<br>  <br>• FAT is typically around 22% of total body weight (men) and 28% (women)<br>• FFM is expected to be linked to clearance but not FAT<br>• FFM may be linked to volume but also FAT<br>http://en.wikipedia.org/wiki/Body_fat_percentage<br> | http://en.wikipedia.org/wiki/Body_fat_percentage |
| Slide 8 | **Size and Body Composition Metrics**<br>• BSA, IBW, LBW, …<br>• Predicted Normal Weight<br>• Adjusted Body Weight<br>• Adjusted Ideal Body Weight<br>• … etc<br>"Universal" – neither drug nor PK parameter specific<br>Green B, Duffull SB. What is the best size descriptor to use for pharmacokinetic studies in the obese? Br J Clin Pharmacol. 2004;58(2):119-33.<br> | There is no consistent definition of adjusted body weight when applied to children. The adult formula for ideal body weight gives negative values when used with weights and heights typical in children. Various work arounds are used e.g. based on "optimal" weight for age using WHO or CDC growth charts. |
| Slide 9 | **Normal Fat Mass**<br>• Allometric size is based only on mass<br>• Normal fat mass (NFM) is based on FFM and FAT mass normalized to the FFM equivalent using *Ffat*<br>• NFM is the mass that predicts allometric size<br>– The parameter *Ffat* is drug and parameter (CL, V) specific<br>$NFM = FFM + Ffat \cdot FAT$<br> | NFM concept first published in Anderson BJ, Holford NHG. Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokinet. 2009;24(1):25-36. |

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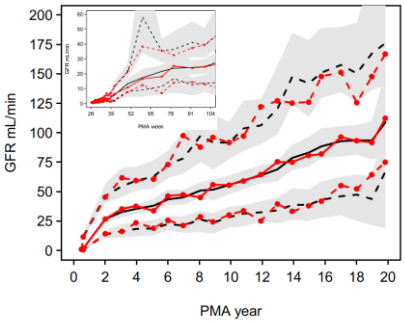
## Glomerular Filtration Rate Which Size Metric?




| Model | dOFV |
|---|---|
| allo NFM | . |
| allo FFM | 5 |
| BSA | 60 |
| linear FFM | 254 |
| linear TBW | 280 |

| *Ffat* | Estimate |
|---|---|
| GFR | 0.22 |

Rhodin MM, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M, Holford NHG. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol. 2009;24(1):67-76.



Traditional clinical practice usually scales GFR using body surface area (BSA). This is not based on sound biology. This data set is the largest collection of GFR values that has evaluated alternative size models. Theory based allometry provides the best description. There is some support for a role of fat mass as the size driver for GFR.

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## Ffat: Drug and PK Specific

| | *Ffat* Clearance | *Ffat* Volume | *LogP** | Source |
|---|---|---|---|---|
| GFR | 0.22 | - | - | Neonates-adults, n=928 (Rhodin, Anderson et al. 2009) |
| Heparin | 0 | 1 | -13.2 | Children 0.5-15 y n=64 (Al-Sallami, Newall et al. 2016) |
| Oxypurinol | 0 | 0 | -1.7 | Adult patients with gout (n=92), healthy subjects (n=12)(Wright, Stamp et al. 2013) |
| Gemcitabine | 0 | 0 | -1.4 | Adults, n=56 (Tham, Wang et al. 2008) |
| Busulfan | 0.51 | 0.20 | -0.59 | 0.1–66 years, n=1610 (McCune, Bemer et al. 2014) |
| Lithium | 0 | 0 | -0.38 | Children (n=61) (Landersdorfer, Findling et al. 2016) |
| Ionized molecule | -0.37 | -0.23 | -0.38 | Adults, n=4014 (unpublished work) |
| Ethanol | 1 | 0.39 | -0.29 | Adults, n=108 (Holford, Jiang et al. 2015) |
| Beta-blocker | 0.27 | 0 | 0.23 | Adults, n=195 (unpublished work) |
| Paracetamol | 1 | 0.78 | 0.49 | Adults, WT 73 SD 13 kg, n=189 (Allegaert, Olkkola et al. 2014) |
| Warfarin (S-) | 0 | - | 2.7 | Adults, n=456 (unpublished work) |
| Warfarin (S- and R-) | 0 | 0 | 2.7 | Adults, n=264 (Xue, Holford et al. 2016) |
| Parent<br>Metabolite | -0.76<br>-0.82 | -0.51<br>-0.48 | 2.7 | Adults, n=91 (unpublished work) |
| Dexmedetomidine | 0 | 0 | 2.89 | Adults Obese n=20, age 18-54 y, WT 94-152 kg, BMI 36-52 $kg.m^{-2}$<br>Lean n=20, age 18-60 y, WT 59-97 kg, BMI 23-30 $kg.m^{-2}$ )<br>(Cortinez, Anderson et al. 2015) |
| Propofol | 1 | 1 | 4.33 | Adults obese (n=19, age 40 SD 8.7 y,WT 106 SD 18 kg, BMI 39.7 SD 4.1 $kg.m^{-2}$) and 51 non-obese (n=51) (Cortinez, Anderson et al. 2010) |



Ethanol Ffat is for Vmax which will be proportional to clearance at a specific ethanol concentration. Dexmedetomidine FFM prediction was used to identify a reduction in clearance associated with FAT mass ("morbid obesity").

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## (Normal) Size Matters

- Allometric theory helps understand biology
- The concept of allometric size can be extended to include FFM and FAT
- NFM is a biologically based, integrated size metric for all humans