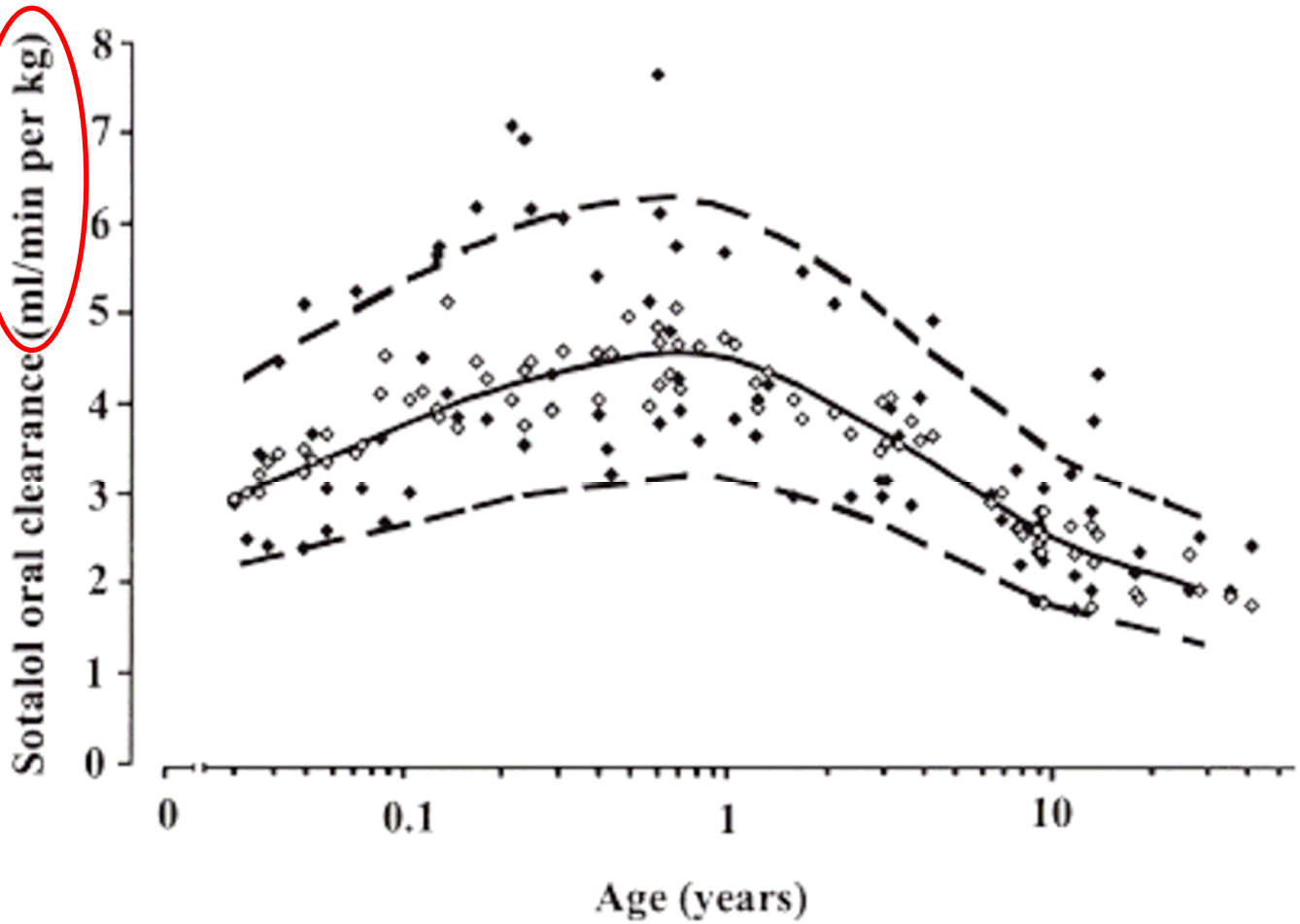
Mechanism-Based Concepts of Size and Maturity

Nick Holford
Brian Anderson

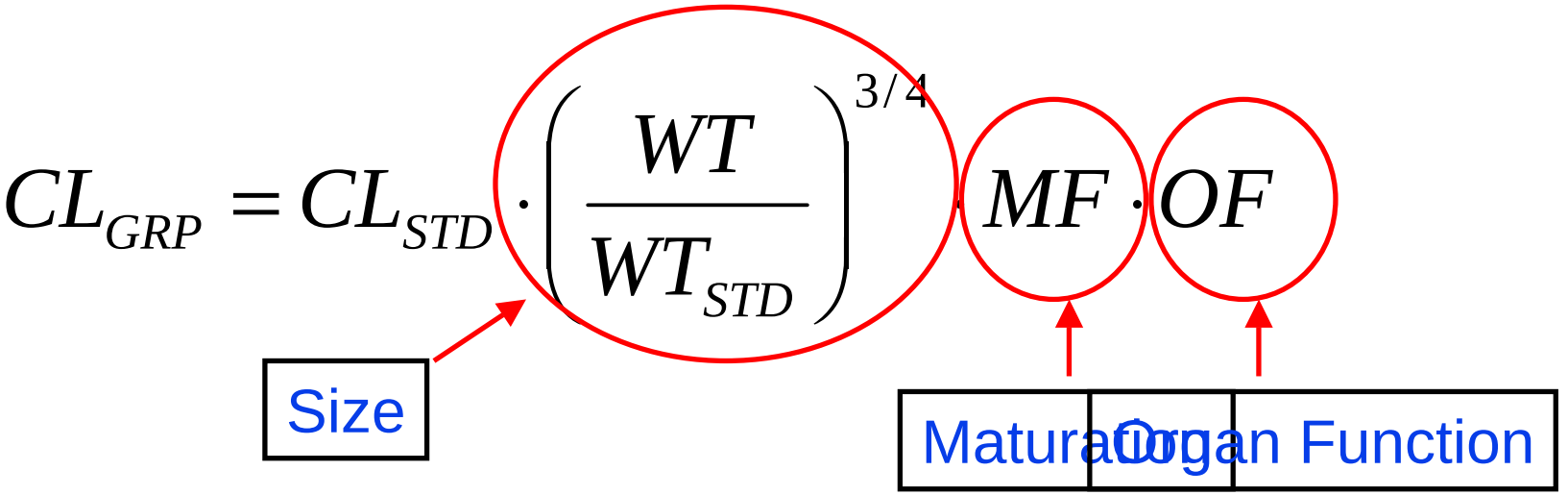
University of Auckland
Auckland, New Zealand

Size, Age and Clearance
How Not to Do It!



Laer S, Elshoff JP, Meibohm B, Weil J, Mir TS, Zhang W, et al. Development of a safe and effective pediatric dosing regimen for sotalol based on population pharmacokinetics and pharmacodynamics in children with supraventricular tachycardia. J Am Coll Cardiol. 2005;46(7):1322-30.

A Mechanism Based Model

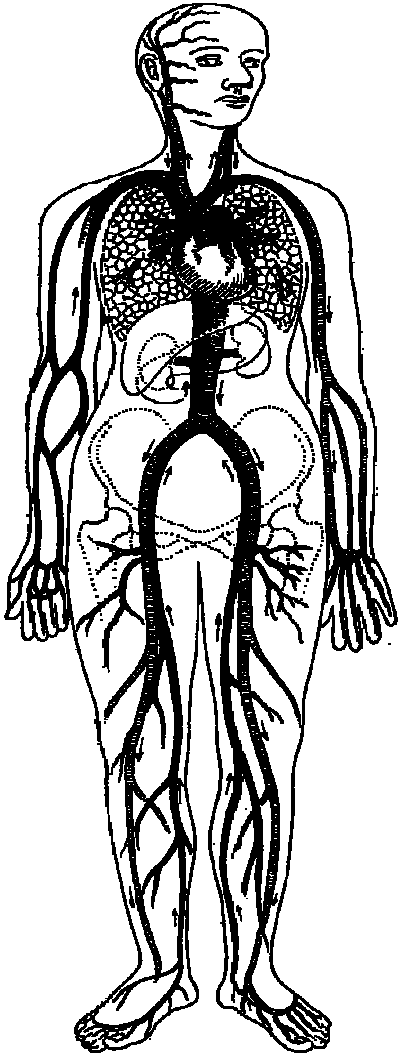


CL_{GRP}=Group clearance CL_{STD}=Population standard clearance

WT =Total Body Weight WT_{STD}=Standard weight e.g. 70 kg

Tod M, Jullien V, Pons G. Facilitation of drug evaluation in children by population methods and modelling. Clin Pharmacokinet. 2008;47(4):231-43.

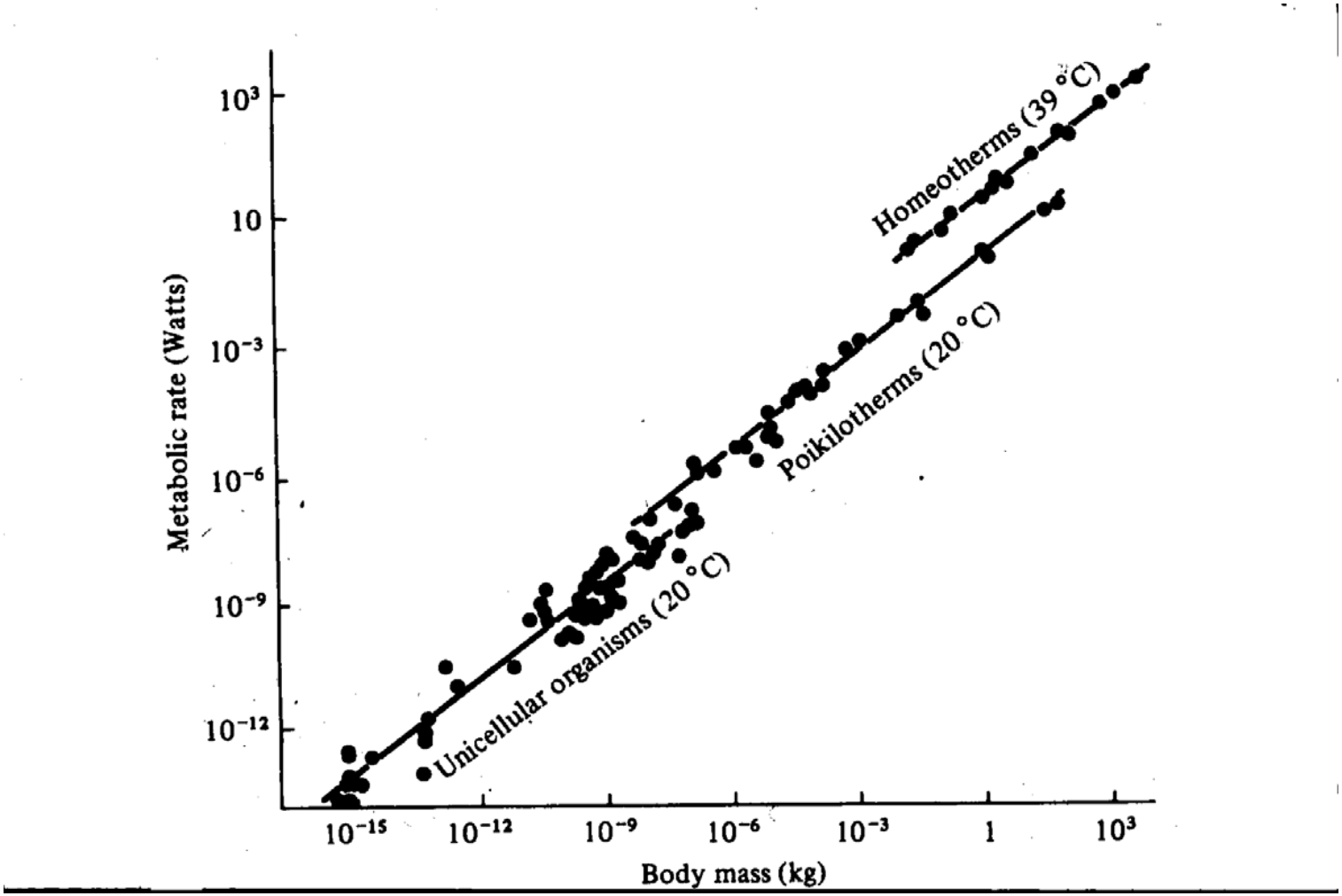
Theoretical Foundation for Allometric Scaling
Fractal Geometry



$$CL_{GRP} = CL_{STD} \cdot \left(\frac{WT}{WT_{STD}} \right)^{3/4}$$

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

Predictions Match Observations
18 Orders of Magnitude



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

Table 3 Examples that support the proposal that CL scales allometrically within humans

Drug	N	Age	Weight (kg)	Allometric coefficient	95% confidence interval	CV	Reference
Propofol	270	2–88 years	Range 12–100	0.76			(66)
Propofol	22	3–17 months	Range 8.3–12.5	0.61	0.38, 0.84	19.7%	(150)
Busulfan	24	3 months–16 years	Mean 23.8 Range 7.1–62.6	0.74	0.59, 0.90	10.7%	(45)
Phenytoin	322	18.4 SD 17.3 years 3 data sets (*a*) 29.5 SD 15.2 years (*b*) 6.05 SD 3.95 years (*c*) 1.33 SD 0.62 years	 (*a*) 54.4 SD 16.7 (*b*) 22.9 SD 11.6 (*c*) 11.8 SD 2.07	0.63	0.58, 0.67	3.7%	(63)
Oxycodone	39	6 months–7 years	Mean 16.3 Range 8–43	0.87	0.64, 1.10	13.3%	(151)
Pyrimethamine	89	1 week–14 years	Range 3–59	0.53	0.47, 0.59	5.8%	(34)
Sulfadoxine	89	1 week–14 years	Range 3–59	0.64	0.58, 0.70	4.8%	(34)
Methotrexate	49	6 months–17 years	Mean 30.56 Range 7.46–80	0.88			(152)
Valproate	225	0.1–14 years	Mean 31.3 Range 4–74	0.72	0.66, 0.77	4.2%	(153)
Sotolol	76	0.03–17 years	Mean 16 (SD 17.1)	0.58	0.42, 0.74	14.4%	(154)

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Size and Body Composition

- Fat Free Mass (FFM)
  - weight, height and sex
  - Janmahasatian et al. 2005

$$CL_{GRP} = CL_{STD} \cdot \left(\frac{PNWT}{WT_{STD}} \right)^{3/4} \cdot MF \cdot OF$$

- Predicted Normal Weight (PNWT)
  - FFM + Ffat*(WT – FFM)
  - Duffull et al. 2004

Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44(10):1051-65.
Duffull SB, Dooley MJ, Green B, Poole SG, Kirkpatrick CM. A standard weight descriptor for dose adjustment in the obese patient. Clin Pharmacokinet. 2004;43(15):1167-78.

How to Describe Clearance Maturation?

- Theory
  - Should be close to zero at conception
    - CL will appear during development in utero
  - Should reach adult values around age 20

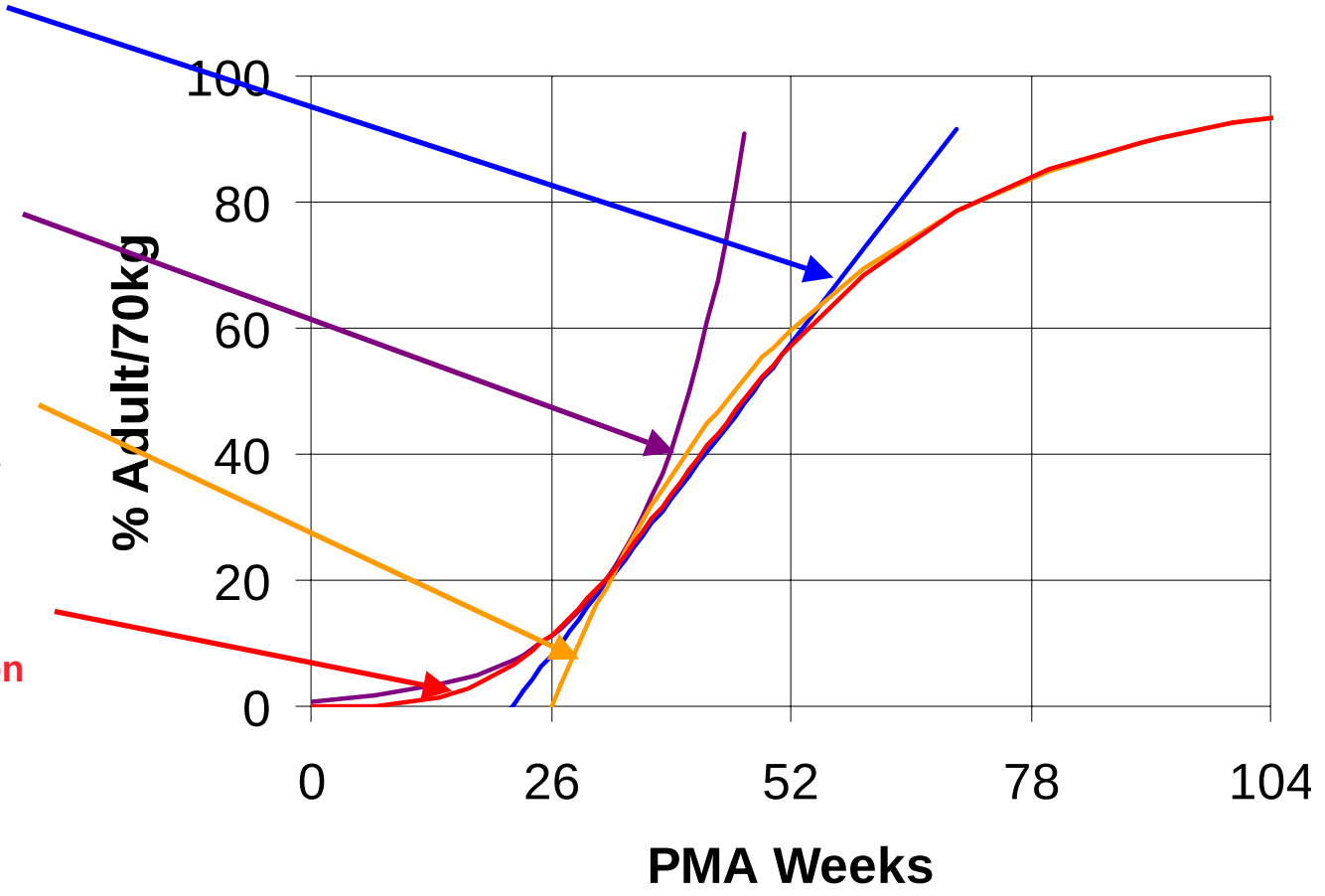
- Observations
  - Slow changes after premature birth
  - Rapid changes around time of normal gestation
  - Slow change in older children

Which Age?

- Post-natal age (PNA)
  - Does not account for *in utero* maturation
- Post-menstrual age (PMA)
  - On average 2 weeks longer than biological age
- Post-conception age (PCA)
  - The biological age but not widely recorded

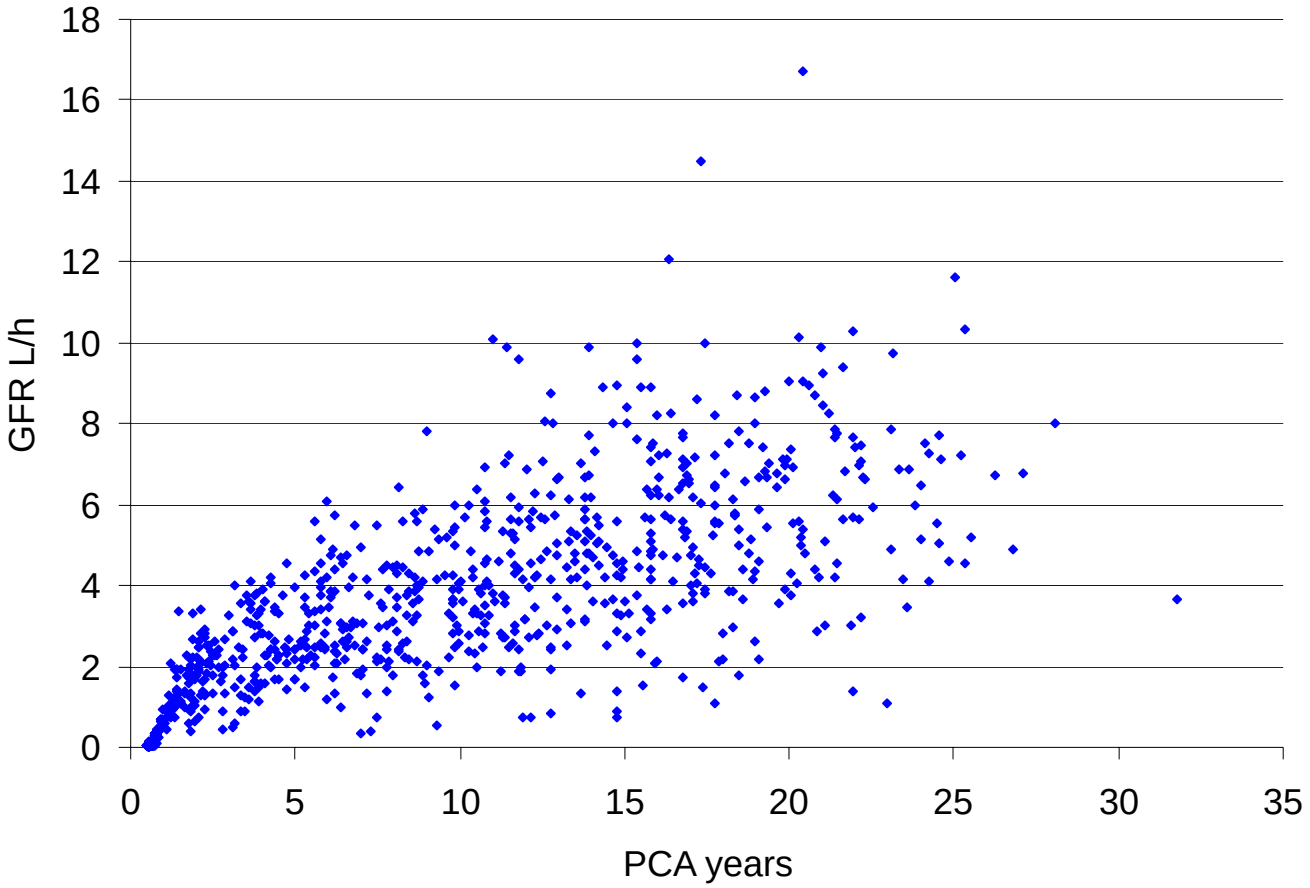
Maturation Models

- Linear increase (Linvall & Reith 2005)
  - OK for small age ranges e.g. premature neonates
- Exponential increase (Anderson 2000)
  - Premature and term OK but not adult values
- Asymptotic Exponential (Hayton 2002)
  - Term and adult OK but too fast for premature neonates
- **Sigmoid Emax (Tod et al. 2001)**
  - **Matches theory and observation across all ages**



$$MF = \frac{PMA^{HillCL}}{PMA^{HillCL} + TM_{50}^{HillCL}}$$

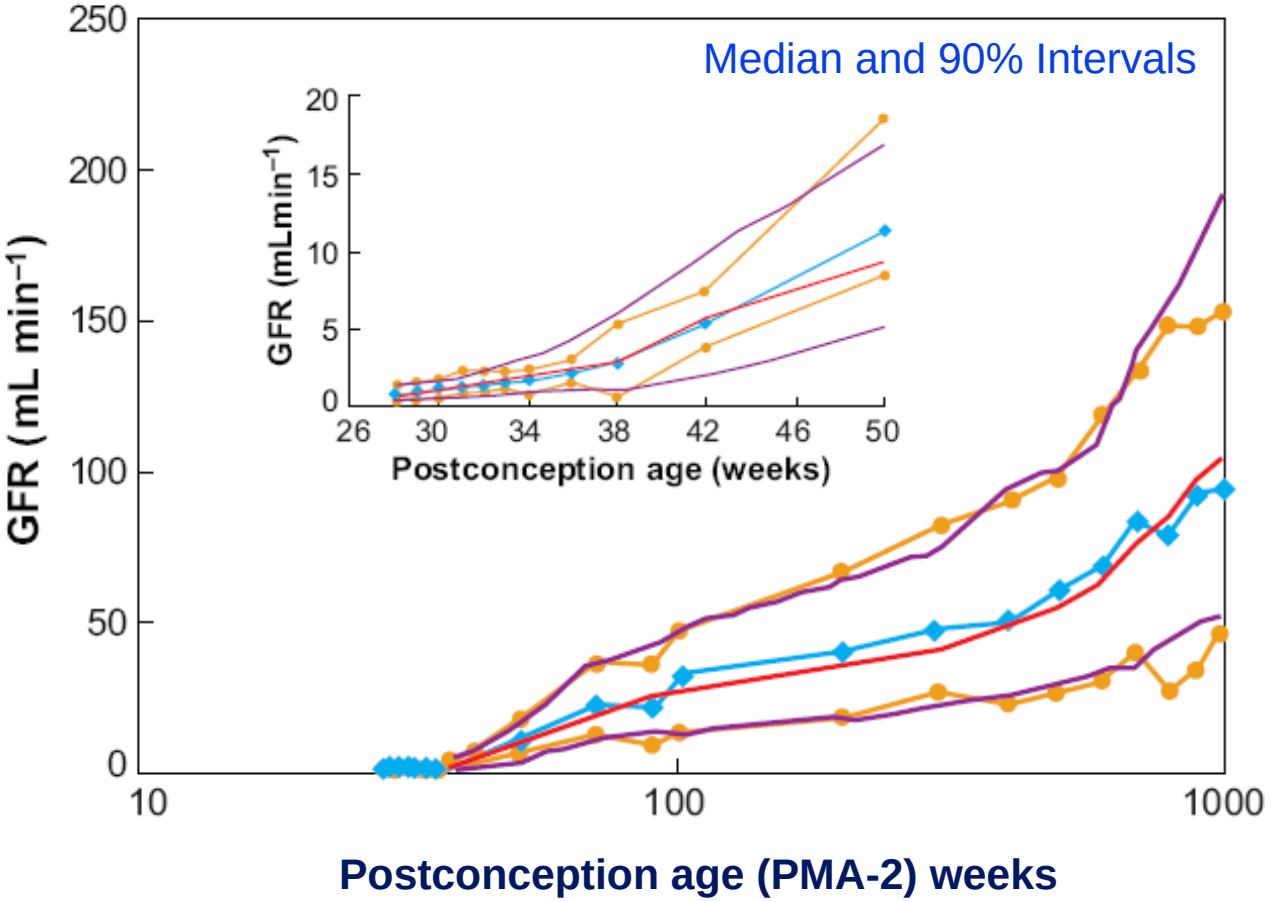
Glomerular Filtration Rate Observed Data



928 patients
26 weeks PMA to 32 y

Rhodin MM, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M, et al. Human renal function maturation – a quantitative description using weight and post-conception age. Submitted. 2008.

GFR Size and Maturation

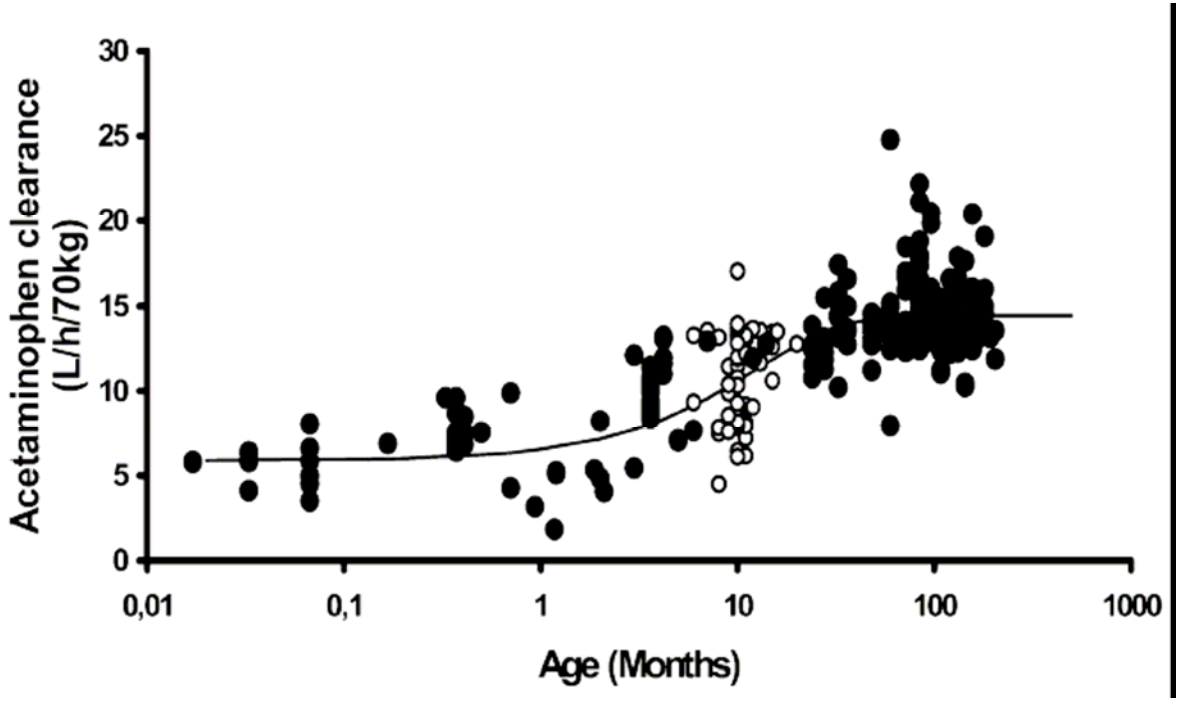


928 patients
26 weeks PMA to 32 y

CLmax= 121 mL/min/70kg
TM50 = 48 weeks PMA
Hill = 3.4

PNWT > FFM > WT
to describe size and GFR

Paracetamol Clearance

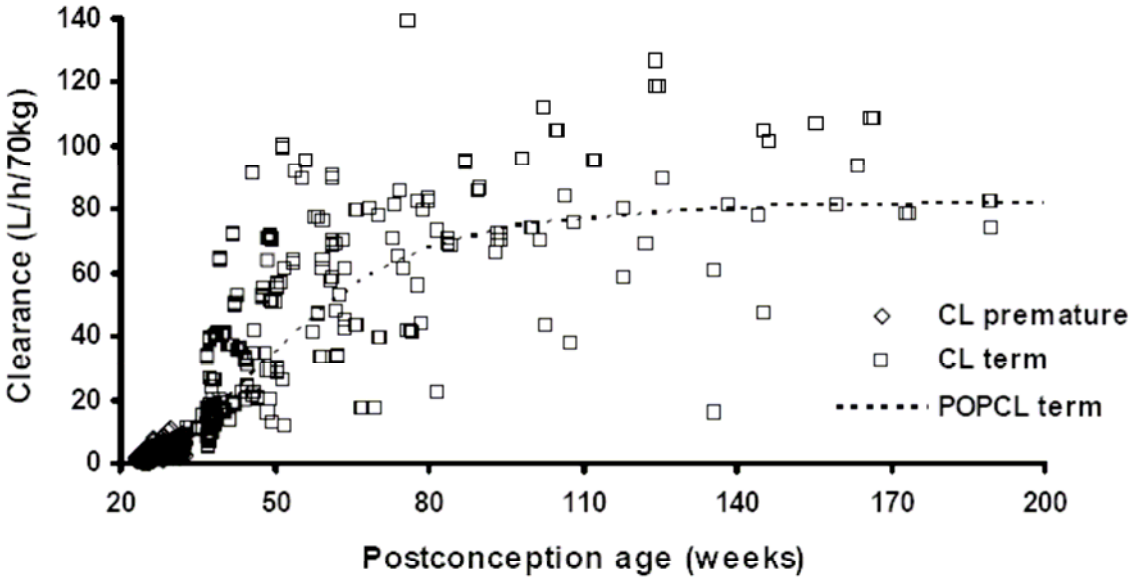


478 Neonates and Infants

CLmax= 19 L/h/70kg
TM50 = 46 weeks PMA
Hill = 3.6

van der Marel CD, Anderson BJ, van Lingen RA, Holford NH, Pluim MA, Jansman FG, et al. Paracetamol and metabolite pharmacokinetics in infants. Eur J Clin Pharmacol. 2003;59(3):243-51.

Morphine Clearance



449 Preterm neonates
23-32 weeks PMA
184 Full term infants
0-3 years PNA

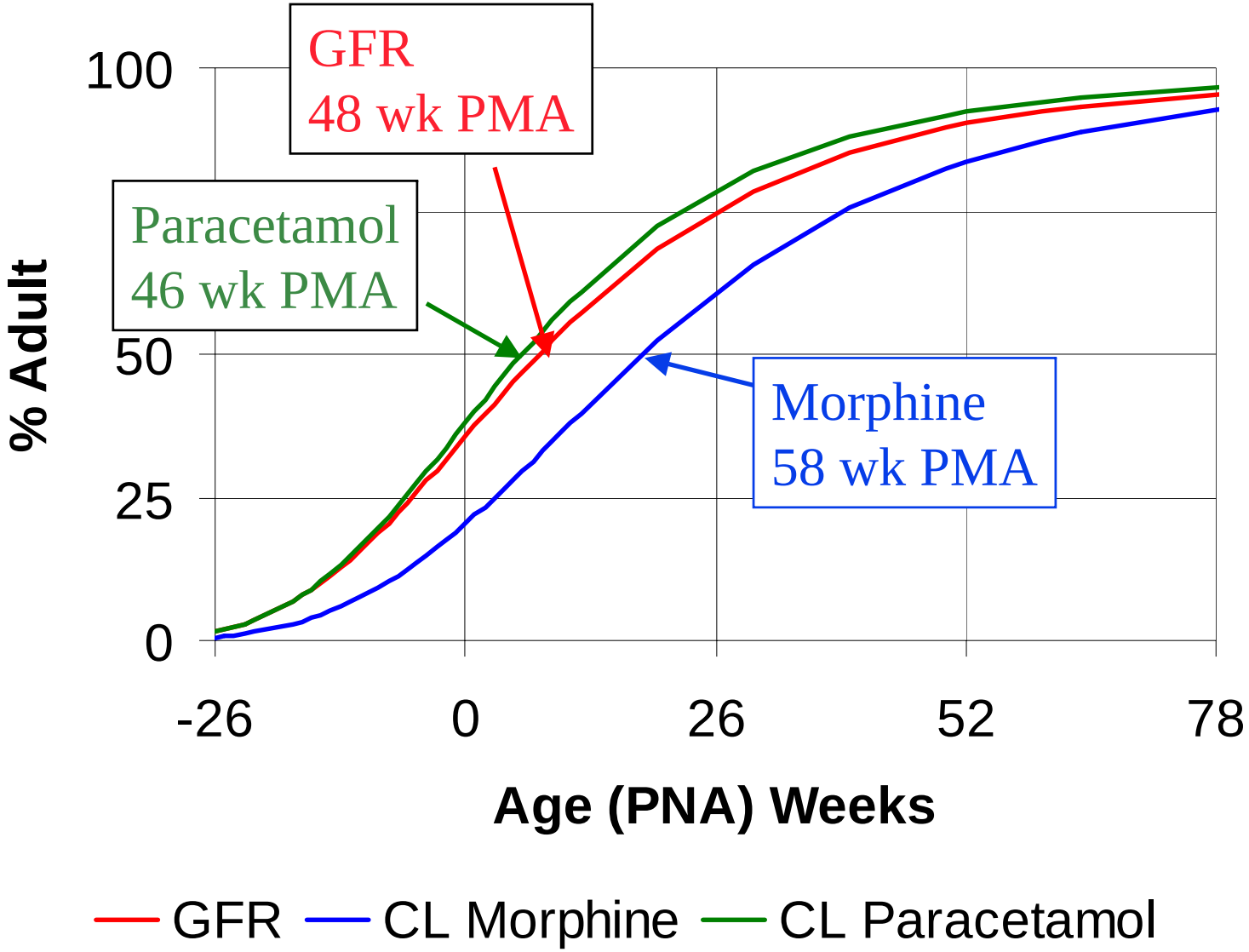
CLmax= 81 L/h/70kg
TM50 = 58 weeks PMA
Hill = 3.6

PCA=PMA-2 weeks

Anand KJS, Anderson BJ, Holford NHG, Hall RW, Young T, Barton BA. Morphine Pharmacokinetics and Pharmacodynamics in Preterm Neonates: Secondary Results from the NEOPAIN Multicenter Trial 2008.

Bouwmeester NJ, Anderson BJ, Tibboel D, Holford NH. Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. Br J Anaesth. 2004;92(2):208-17.

Renal and Metabolic Maturation



Practical Implementation

Table 5 Pediatric maintenance doses of drugs expressed as a percentage of adult dose using an allometric 3/4 power model. The neonatal estimate based on size has been reduced further by 50% to account for age-related maturational changes of clearance

Approximate age	Weight (kg)	Percentage of adult dose	Fraction of adult dose
Birth	3.2	5	1/20
2 months	4.5	13	1/8
4 months	6.5	17	
12 months	10	23	1/4
18 months	11	25	
5 years	18	36	
7 years	23	43.5	
10 years	30	53	1/2
11 years	36	61	
12 years	40	66	
14 years	45	72	3/4
16 years	54	82	
Adult	70	100	1

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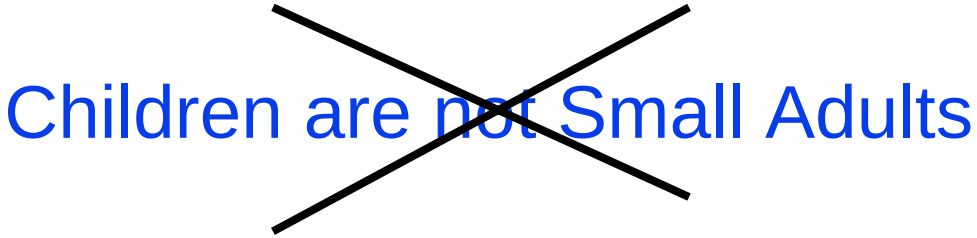
Time for an Aphorism Change



Adults are BIG Children

Children are OLD Babies

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Backup Slides

Why Estimated Allometric Coefficients are Usually Unreliable

Table 4 Imprecision of estimates of allometric coefficient for clearance (true value 0.75)

Weight distribution	5%CI	95%CI
Log normal median 70 kg, 20%CV	0.48	1.01
Log normal median 70 kg, 50%CV	0.64	0.86
Uniform 0–140 kg	0.69	0.81

Estimation was performed using NONMEM V 1.1 with the FOCE interaction method. Empirical confidence interval (CI) and CV (standard deviation/average) from parametric bootstrap distribution of 1000 replications. One hundred subjects were drawn from each weight distribution for each replication.

SE=12.1%
SE=8.8%
SE=4.5%

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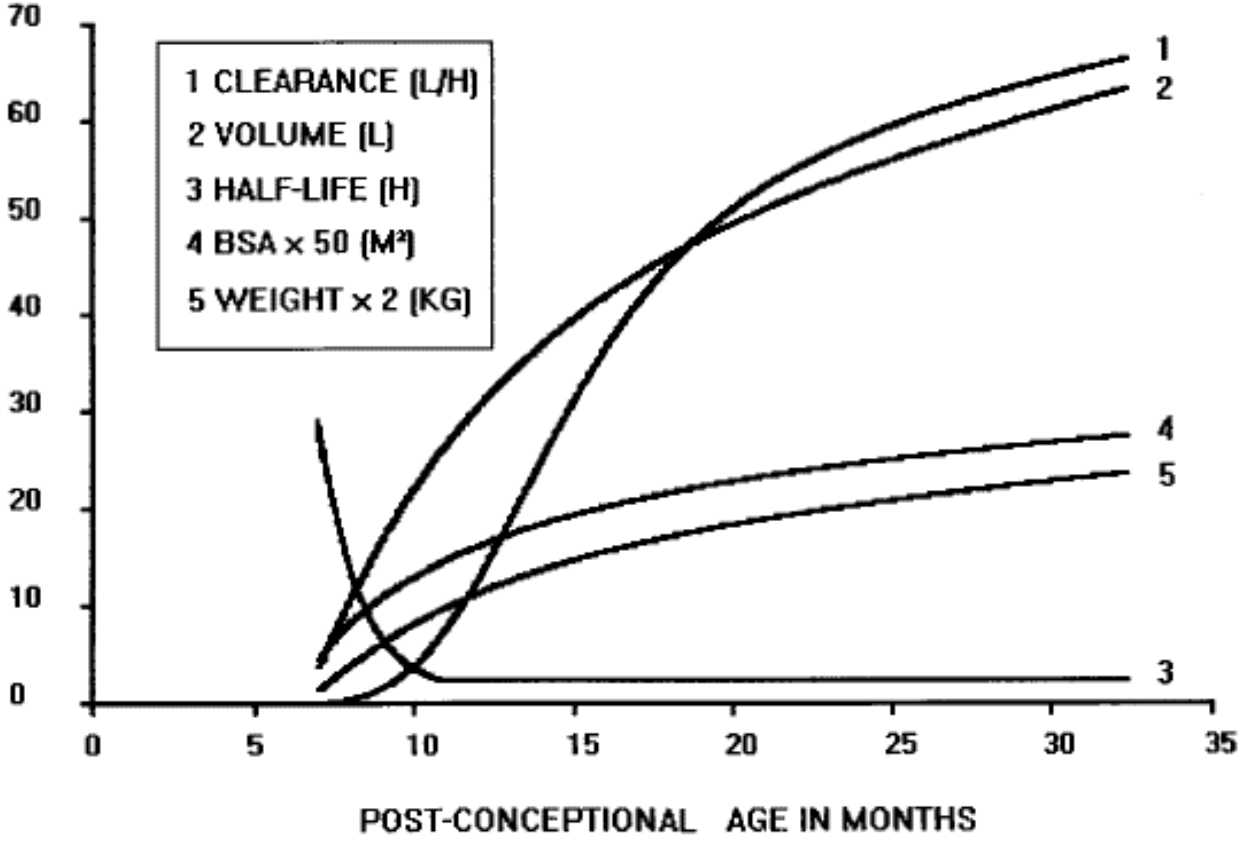
Volume of distribution

- Body composition changes with age
- Foetus spends 9 months in a swimming pool
- When babies are born they cry and pee to get rid of all the excess water!
- Volume of distribution falls after birth

Glomerular Filtration Rate

Derived from Acyclovir in Neonates



CLmax*=7.1 L/h/1.73 M^2
TM50=53.6 weeks PCA
Hill=6.17

79 subjects
0 to 2 years PNA

*=Fixed at
'normal adult value'

Tod M, Lokiec F, Bidault R, De Bony F, PetitJean O, Aujard Y. Pharmacokinetics of Oral Acyclovir in Neonates and in Infants: a Population Analysis. Antimicrob Agents Chemother. 2001;45(1):150–7.

History of Size Scaling

Table 2 Key references detailing the development of the allometric 3/4 power model

Year	Event	Reference
1637	Galileo discussed relationship of skeletal size to body mass	(8, 143)
1839	Sarrus & Rameaux propose "surface law" to French Royal Academy	
1932–1934	Brody & Kleiber establish that log (BMR) plotted against the log(body weight) produces a straight line with a slope of 3/4	(18, 19)
1931–1937	Brody & Carrel define physiological time	(144, 145)
1949	Adolph relates physiological properties in various animals to body weight	(35)
1961	Kleiber considers explanations that are based on changes in body composition with size	(24)
1970	Application of physiological time onto plasma time-concentration profiles from different species	(39)
1973	McMahon offers a structural explanation	(27)
1977	Introduction of allometric equations in pharmacokinetic parameter scaling	(146)
1983	Peters considers the ecological implications of body size	(7)
1984–1995	Comprehensive reviews about the role of allometry in pharmacokinetics	(8, 42, 147–149)
1997+	Fractal geometry to mathematically explain this allometric 3/4 power model.	(21, 23, 26, 29–31)

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