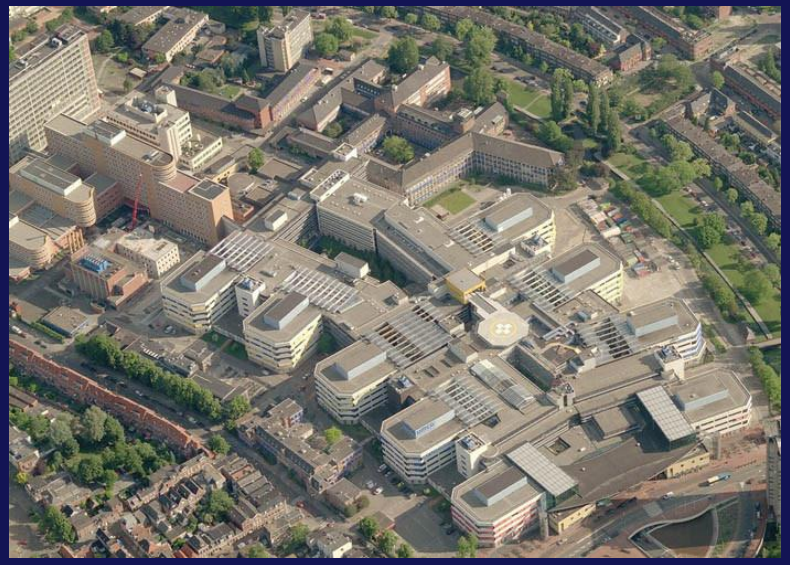
Universitair Medisch Centrum Groningen

Current approaches to covariate modeling

Douglas J. Eleveld,
Ph.D., Assistant Professor

University of Groningen, University Medical Center Groningen,
Department of Anesthesiology, Groningen, The Netherlands



Notes

- My background is in anesthesia, so I use that terminology
- I will assume that you are interested PK/PD modeling, because that's where covariate modeling is used
- I will tend to use NONMEM terminology

Why are we modeling anyway?

Data → Modeling → Applications

Clinicians and Pharmaceutical industry want guidance about how much drug to give for some intended drug effect outcome.

You modeling job is to produce a mathematical model which other people can used to guide drug dosing and reason about physiological mechanisms.

We want to understand nature!

Compartmental pharmacokinetics

We are concerned with biological systems, but we don't fully understand the relevant mechanisms. Even if we did, we probably don't have sufficient computing power to make accurate predictions

So we simplify the physiological system into compartmental models

This simplifies the mathematics and makes them solvable on computer and simple enough to visualize and reason about.

Individuals are represented by collections of compartments of varying volumes, elimination clearance and inter-compartmental clearances.

Covariates

We can create models without covariates:

$$V1 = V1_{ref} \cdot \exp(\eta 1)$$
$$CL = CL_{ref} \cdot \exp(\eta 2)$$

These generally perform poorly.

Using information from the individuals studied nearly always improves the models. For example, using an individuals weight (WGT) can be done as:

$$V1 = V1_{ref} \cdot (WGT/70) \cdot \exp(\eta 1)$$
$$CL = CL_{ref} \cdot (WGT/70)^{0.75} \cdot \exp(\eta 2)$$

Covariates are whatever someone decided to write down about the individuals when performing the study

Covariate types

Some are discrete

Sex, control/placebo vs. treatment, smoker, …

Some are continuous

Age, weight, height, BMI, …

Some are approximations

Lean-body-mass or Fat-free-mass (equation),
Creatinine Clearance (Cockcroft-Gault Equation), …

Covariate errors

Actually, *for their use in compartmental models*, all covariates are just approximations.

Subject can lie about smoking, drinking, habits or drug compliance

Even precise covariates may be in error *for their use*…

- For an abstract compartment, weight ∝ volume
- For biological systems, weight ∝ volume is only approximate
  - Density is not uniform across all individuals and sizes
- Different tissues have varying degrees of pharmacological impact
  - Hydrophilic or lipophilic drugs?

Consider a small person with huge, wet dreadlocks. Do you take the weight of the dreadlocks into account in anesthesia dosing?

Covariate structures (continuous)

Linear

$$factor = (A \cdot COV)$$
$$factor = (A + B \cdot COV)$$

Exponential

$$factor = \exp(A \cdot (COV - COV_{ref}))$$

Power

$$factor = (COV / COV_{ref})^{A}$$

Log-linear

$$factor = 1 + A \cdot \log(COV / COV_{ref})$$

Sigmoid

$$factor = COV^{A} / (COV^{A} + B^{A})$$

COV_{ref} is sometimes median but a standardized value is better

BEWARE WHEN COV=0 for power (**A**<0), log-linear, models !!!

Covariate structures (Discrete)

Binary covariates are relatively straightforward

$$factor = 1 + A \cdot COV$$
$$factor = \exp(A \cdot COV)$$

In NONMEM, sex is often coded as M1F2 (male=1, female=2)

$$factor = 1 + A \cdot (M1F2 - 1)$$
$$factor = \exp(A \cdot (M1F2 - 1))$$

allows females have different parameters than males

By extension, the same process applies to multilevel covariates

Significant covariates

Models with and without covariate models are "nested".

The absence of a covariate relationship being a special case.

$$factor = 1 + A \cdot (M1F2 - 1)$$

If **A**=0 results in clearly worse model fit compared to **A**≠0 then we conclude data supports different parameter male/female.

NOTE: This is conditional on the rest of the model structure!

Significance is usually based on likelihood ratio tests or information theoretic criteria (include bias-correction for number paramaters)

- Δobjective function follows $\chi 2$-distribution with *k* degrees of freedom
- Akaike information criterion (AIC)
- Bayesian information criterion (BIC)

Some comments on AIC/BIC

AIC is frequently misused in PK modeling studies

"…model with the lowest AIC is selected as the final model."

AIC is an information-weighting criteria quantifying the relative information loss going from model A to model B.

AIC is NOT a selection criteria!

A very good resource:

Model Selection and Multi-Model Inference: A Practical Information-Theoretic Approach

Kenneth P. Burnham, David R. Anderson

BIC is sometimes used as well but its assumptions are not well-suited for biological sciences (but its not horrible either)

- BIC assumes the true model is low-dimensional
- BIC assumes the true model is one of the models considered

Covariate: Weight

Weight is probably the most widely applied covariate.

Its importance is implicit in how we often describe drug dosing on a per kg basis.

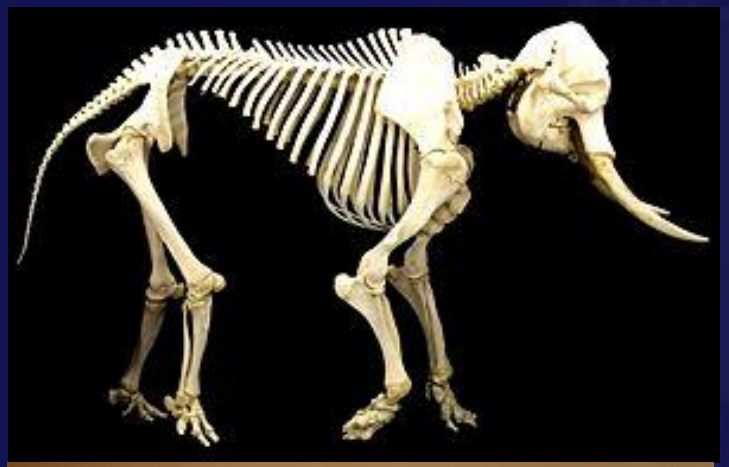
In the past, weight was only included as a model parameter covariate if its inclusion resulted in a significant improvement in model fit. Thus in in low-information situations some parameters would even be independent of weight.

This practice, has slowly been replaced with assuming parameters scale linearly with weight.

More recently, allometric scaling has been broadly applied.

Allometric scaling

- Allometry is the study of body size to diverse biological characteristics
  - Noticeable patterns emerge when considering living organisms of varying sizes and scales
  - The patterns are often not linear. Why is that? What are the rules governing the patterns?
- Allometric scaling and its role in biological sciences has a long history



The important contribution of West et al.

West et al. found that assuming

1. Space-filling hierarchical branching network
2. Invariance of terminal branches
3. Energy required to distribute resources is minimized

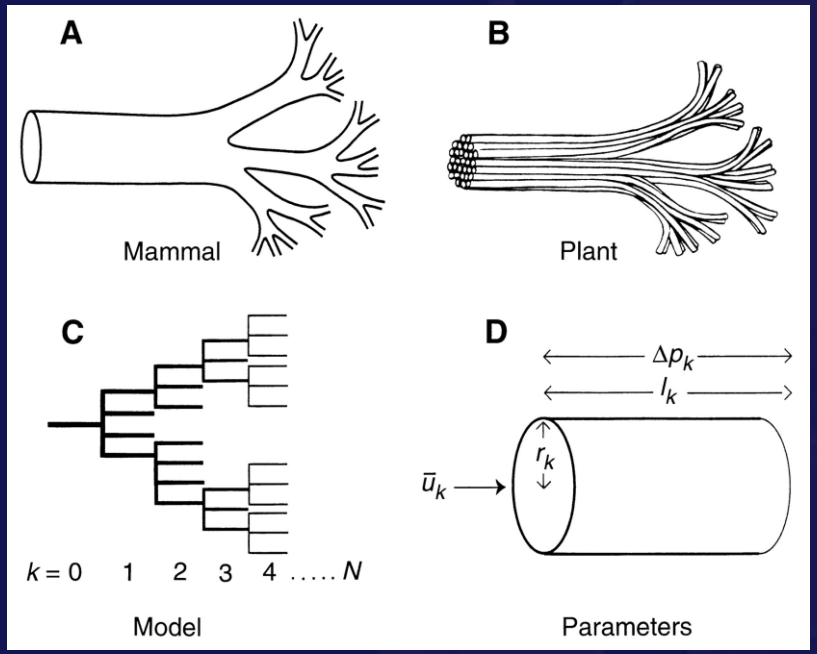
results in many characteristics scale to size to power multiples of ¼

$$volume = k \cdot mass^{1}$$

$$time = k \cdot mass^{1/4}$$

$$power = k \cdot mass^{3/4}$$

$$rate = k \cdot mass^{-1/4}$$



West GB, Brown JH, Enquist BJ. A general model for the origin of allometric scaling laws in biology. Science. 1997 Apr 4;276(5309):122-6.

The important contribution of West et al.

West et al. provided theory which "binds" the exponents of many characteristics together in a single unified theory of *size*

Cardiovascular			Respiratory		
Variable	Exponent		Variable	Exponent	
	Predicted	Observed		Predicted	Observed
Aorta radius r_0	3/8 = 0.375	0.36	Tracheal radius	3/8 = 0.375	0.39
Aorta pressure Δp_0	0 = 0.00	0.032	Interpleural pressure	0 = 0.00	0.004
Aorta blood velocity u_0	0 = 0.00	0.07	Air velocity in trachea	0 = 0.00	0.02
Blood volume V_b	1 = 1.00	1.00	Lung volume	1 = 1.00	1.05
Circulation time	1/4 = 0.25	0.25	Volume flow to lung	3/4 = 0.75	0.80
Circulation distance l	1/4 = 0.25	ND	Volume of alveolus V_A	1/4 = 0.25	ND
Cardiac stroke volume	1 = 1.00	1.03	Tidal volume	1 = 1.00	1.041
Cardiac frequency Ω	-1/4 = -0.25	-0.25	Respiratory frequency	-1/4 = -0.25	-0.26
Cardiac output $\dot{E}$	3/4 = 0.75	0.74	Power dissipated	3/4 = 0.75	0.78
Number of capillaries N_c	3/4 = 0.75	ND	Number of alveoli N_A	3/4 = 0.75	ND
Service volume radius	1/12 = 0.083	ND	Radius of alveolus r_A	1/12 = 0.083	0.13
Womersley number ω	1/4 = 0.25	0.25	Area of alveolus A_A	1/6 = 0.083	ND
Density of capillaries	-1/12 = -0.083	-0.095	Area of lung A_L	11/12 = 0.92	0.95
O_2 affinity of blood P_{50}	-1/12 = -0.083	-0.089	O_2 diffusing capacity	1 = 1.00	0.99
Total resistance Z	-3/4 = -0.75	-0.76	Total resistance	-3/4 = -0.75	-0.70
Metabolic rate B	3/4 = 0.75	0.75	O_2 consumption rate	3/4 = 0.75	0.76

Applying West et al. allometric scaling to PK

For compartment with weight (of the compartment) of *CWGT*, then:

$$V = V_{ref} \cdot \left(\frac{CWGT}{CWGT_{ref}} \right) \qquad CL = CL_{ref} \cdot \left(\frac{CWGT}{CWGT_{ref}} \right)^{0.75}$$

But we don't know CWGT! If we assume that the weight of each compartment grows isometrically with weight (constant percentage) then:

$$\frac{CWGT}{CWGT_{ref}} = \frac{WGT}{WGT_{ref}}$$

Thus, for a 70-kg reference:

$$size = \frac{WGT}{WGT_{ref}}$$

$$V = V_{ref} \cdot size \qquad CL = CL_{ref} \cdot size^{0.75}$$

West et al. and multi-compartment PK models

The usual approach is to extend these properties in a straightforward manner to multiple compartments.

- Volumes scale linearly with weight
- Clearance scale to the ¾ power of weight

$$V1 = V1_{ref} \cdot size \qquad CL = CL_{ref} \cdot size^{0.75}$$
$$V2 = V2_{ref} \cdot size \qquad Q2 = Q2_{ref} \cdot size^{0.75}$$
$$V3 = V3_{ref} \cdot size \qquad Q3 = Q3_{ref} \cdot size^{0.75}$$

Compartmental allometry

Another approach is to realize we know that *V* grows proportional to *CWGT* and use this for estimation of *Q2* and *Q3*, thus:

$$Q2 = Q2_{ref} \cdot \left(\frac{V2}{V2_{ref}} \right)^{0.75} \qquad Q3 = Q3_{ref} \cdot \left(\frac{V3}{V3_{ref}} \right)^{0.75}$$

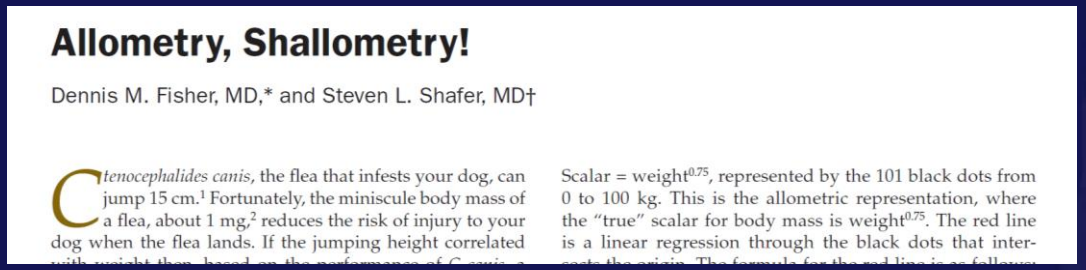
Compartmental allometry has been shown to improve model fit for propofol[1] and remifentanil[2] but it has not been widely tested.

Briefly, the approach treats *Q2* as a property of *V2*, not of the body as a whole. For example, fat as compartmental tissue:

10 kg of fat has the same PK properties (*V* and *Q*) regardless of whether it is attached to a 30kg child or a 90kg adult.

Debate: Is allometric scaling the “true” model?

There has been recent debate about allometric scaling



Allometry, Shallometry!

Dennis M. Fisher, MD,* and Steven L. Shafer, MD†

Ctenocephalides canis, the flea that infests your dog, can jump 15 cm.[1] Fortunately, the miniscule body mass of a flea, about 1 mg,[2] reduces the risk of injury to your dog when the flea lands. If the jumping height correlated

Scalar = weight$^{0.75}$, represented by the 101 black dots from 0 to 100 kg. This is the allometric representation, where the “true” scalar for body mass is weight$^{0.75}$. The red line is a linear regression through the black dots that inter-

- Of course not: In biological sciences, there are no true models!
- Yes: The assumptions of West result do the ¾ power scaling

If you don’t want to assume allometric scaling you have to argue that the structure described by West et al. does not apply, or propose a different size-scaling theory. You cant sensibly “mix-and match” exponents…

We should be trying to improve on West et al., not simply rejecting it and instead applying something else convenient or conventional

Covariate: Age

Age is often considered to covariate modeling.

There is NO theory of aging, all models are simply empirical.

In general, the rate of energetic processes decline with age?

$$CL = CL_{ref} \cdot \left(\frac{WGT}{70}\right)^{0.75} \cdot \exp\left(A \cdot \left(AGE - 35\right)\right) \cdot \exp\left(\eta\right)$$

If you (or any one, ever!!!!) will use your model for newborns, what happens when age is 0. This is important for power (**A**<0), linear, models…

Covariate: Maturation

Maturation often plays a role for children younger then 2-5 years

There is NO theory of maturation, all models are simply empirical.

Clearance organs may not be fully developed, thus clearance is lower then predicted if only allometric scaling is considered.

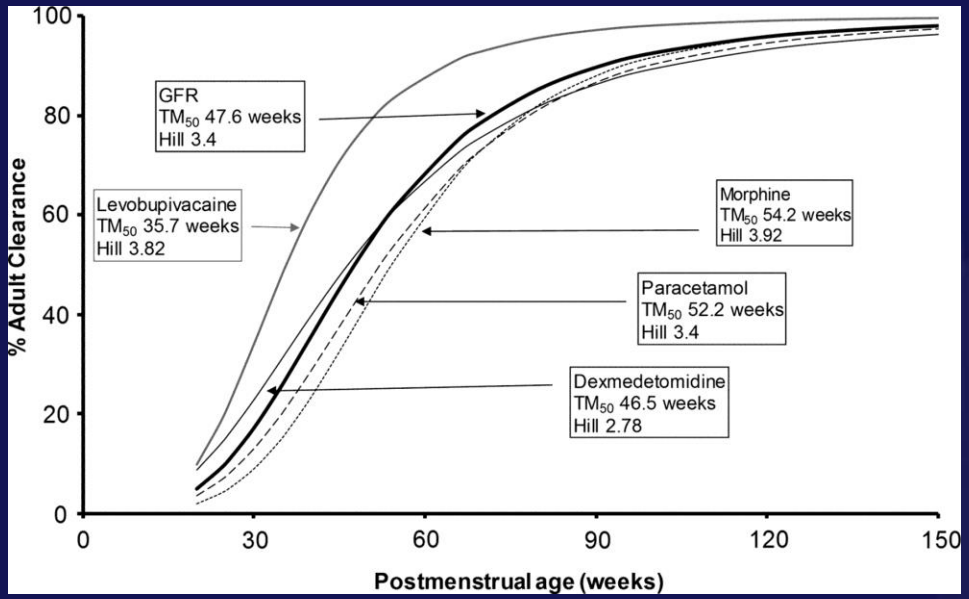
Maturation as a sigmoidal curve based on post-menstrual-age (PMA)

$$CL = CL_{ref} \cdot \left(\frac{WGT}{70}\right)^{0.75} \cdot \left(\frac{PMA^{A}}{PMA^{A} + M50^{A}}\right) \cdot \exp(\eta)$$

PMA is often used because maturation is not necessarily 0 at birth but is definitely 0 when PMA=0

Covariate: Maturation

Maturation of CL varies across drugs because there are different elimination mechanisms



Anderson BJ, Holford NH. Understanding dosing: children are small adults, neonates are immature children. Archives of disease in childhood. 2013 Jul 4:archdischild-2013.

Covariate testing order

This is an unsolved problem!

Many explicitly or implicitly advocate for a "shotgun approach" and forward-selection and then backward elimination.

First, forward selection:

1. Test every covariate for every parameter
2. Find the covariate relationship that best improves the model
3. If significant ($p<0.05$) then add that to the model and repeat

Next, backward elimination:

4. Remove (one-by-one) each covariate in the model
5. Find the covariate relationship that least degrades the model
6. If not significant ($p>0.01$) remove that and repeat

Covariate testing “shotgun approach”

The “shotgun approach” has some serious disadvantages

1. Multiple testing “waters-down” p-values but this is often simply ignored. Increased risk of false positive.
2. Nonsense relationships can be considered and an informal decision has to be made to include it or not
3. Co-linearity can make detecting the correct covariate difficult
    1. Age/height/weight in children
    2. Sex/FFM for adults
4. “Greedy” approach may not result in best final model

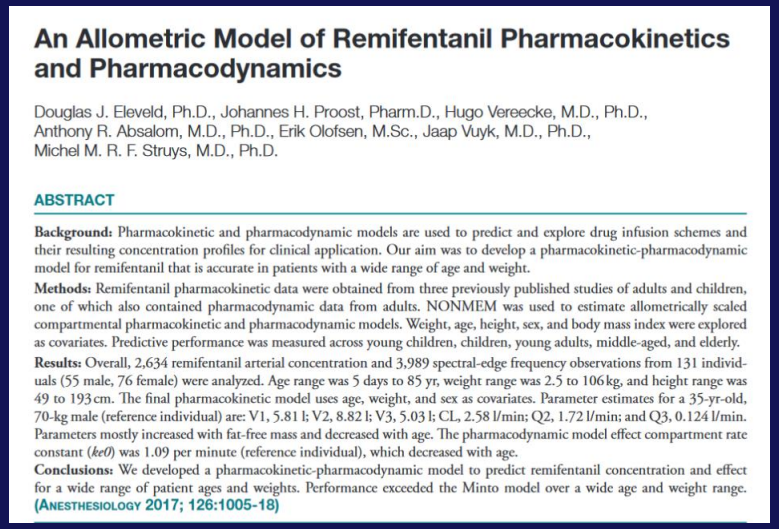
Covariate testing “mechanistic approach”

It is often better to test covariates in order of understanding of the underlying mechanisms.

1. Size
   - Simple allometric model
   - Compartmental allometry (multi-compartment models)
2. Maturation, especially on *CL*
   - if age < 5 years included in data
3. Aging
   - Especially for metabolic rated processes
4. Sex
5. Other covariates with a possible mechanistic explanation
   - If you cant even imagine a possible mechanistic explanation, maybe you should not be testing it in the model

Covariate testing “mechanistic approach”

If you want to explore different scaling methods (LBM or FFM) you have to start the *entire* process over.



An Allometric Model of Remifentanil Pharmacokinetics and Pharmacodynamics

Douglas J. Eleveld, Ph.D., Johannes H. Proost, Pharm.D., Hugo Vereecke, M.D., Ph.D., Anthony R. Absalom, M.D., Ph.D., Erik Olofsen, M.Sc., Jaap Vuyk, M.D., Ph.D., Michel M. R. F. Struys, M.D., Ph.D.

ABSTRACT

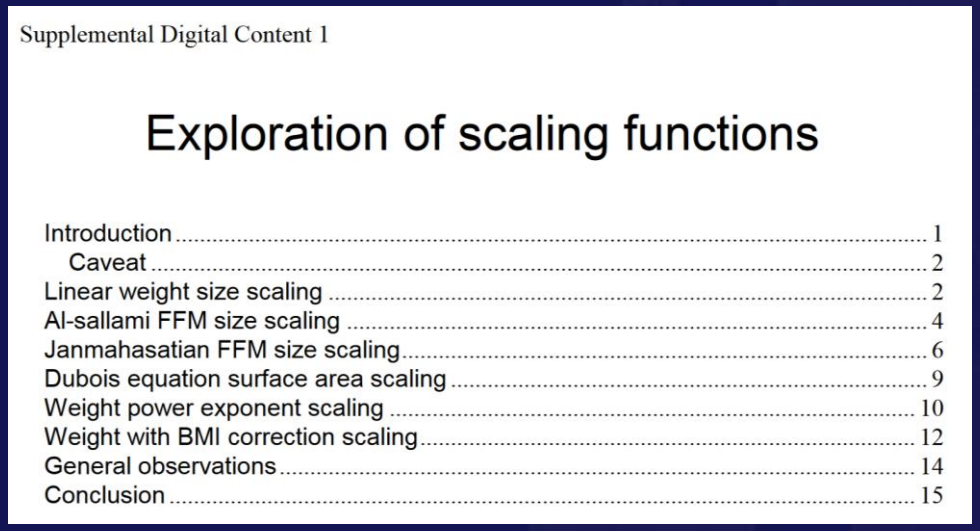
Background: Pharmacokinetic and pharmacodynamic models are used to predict and explore drug infusion schemes and their resulting concentration profiles for clinical application. Our aim was to develop a pharmacokinetic-pharmacodynamic model for remifentanil that is accurate in patients with a wide range of age and weight.

Methods: Remifentanil pharmacokinetic data were obtained from three previously published studies of adults and children, one of which also contained pharmacodynamic data from adults. NONMEM was used to estimate allometrically scaled compartmental pharmacokinetic and pharmacodynamic models. Weight, age, height, sex, and body mass index were explored as covariates. Predictive performance was measured across young children, children, young adults, middle-aged, and elderly.

Results: Overall, 2,634 remifentanil arterial concentration and 3,989 spectral-edge frequency observations from 131 individuals (55 male, 76 female) were analyzed. Age range was 5 days to 85 yr, weight range was 2.5 to 106 kg, and height range was 49 to 193 cm. The final pharmacokinetic model uses age, weight, and sex as covariates. Parameter estimates for a 35-yr-old, 70-kg male (reference individual) are: V1, 5.81 l; V2, 8.82 l; V3, 5.03 l; CL, 2.58 l/min; Q2, 1.72 l/min; and Q3, 0.124 l/min. Parameters mostly increased with fat-free mass and decreased with age. The pharmacodynamic model effect compartment rate constant (*ke0*) was 1.09 per minute (reference individual), which decreased with age.

Conclusions: We developed a pharmacokinetic-pharmacodynamic model to predict remifentanil concentration and effect for a wide range of patient ages and weights. Performance exceeded the Minto model over a wide age and weight range.

(Anesthesiology 2017; 126:1005-18)



Supplemental Digital Content 1

Exploration of scaling functions

- Without age or sex effects, surface-area scaling works best
- The best model uses allometric scaling to fat-free-mass along with corrections for age and sex

The importance of extrapolation

Please consider extrapolation when designing your models.

Regardless of where the data comes from, ask yourself these questions:

- What does my model predict for obese individuals?
- What does my model predict for children?
- What does my model predict for individuals outside my dataset?

The two most widely applied models in anesthesia, the Marsh and Schnider models for propofol, were developed in specific populations but are routinely used in different clinical situations.

When extrapolation goes wrong

Consider the Kataria PK model for propofol in children

The Pharmacokinetics of Propofol in Children Using Three Different Data Analysis Approaches

Bideshwar K. Kataria, M.D., Sudha A. Ved, M.B.B.S.,† Honorato F. Nicodemus, M.D.,† Gregory R. Hoy, M.D.,‡ Dawn Lea, R.N., B.S.N.,§ Michel Y. Dubois, M.D.,‖ Jaap W. Mandema, Ph.D.,# Steven L. Shafer, M.D.***

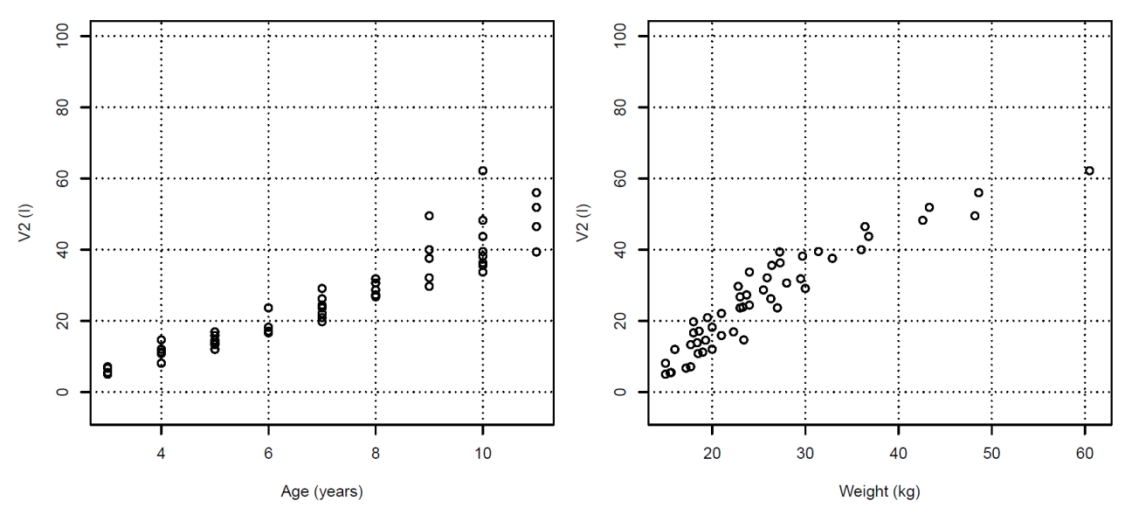
Age range 3-11 years, weight range 15-61 kg. Best fit model was:

$$V1(l) = 0.41 \cdot WGT$$
$$V2(l) = 0.78 \cdot WGT + 3.1 \cdot AGE - 16$$
$$V3(l) = 6.9 \cdot WGT$$
$$CL(l/\min) = 0.035 \cdot WGT$$
$$Q2(l/\min) = 0.077 \cdot WGT$$
$$Q3(l/\min) = 0.026 \cdot WGT$$

See anything strange here?

When extrapolation goes wrong

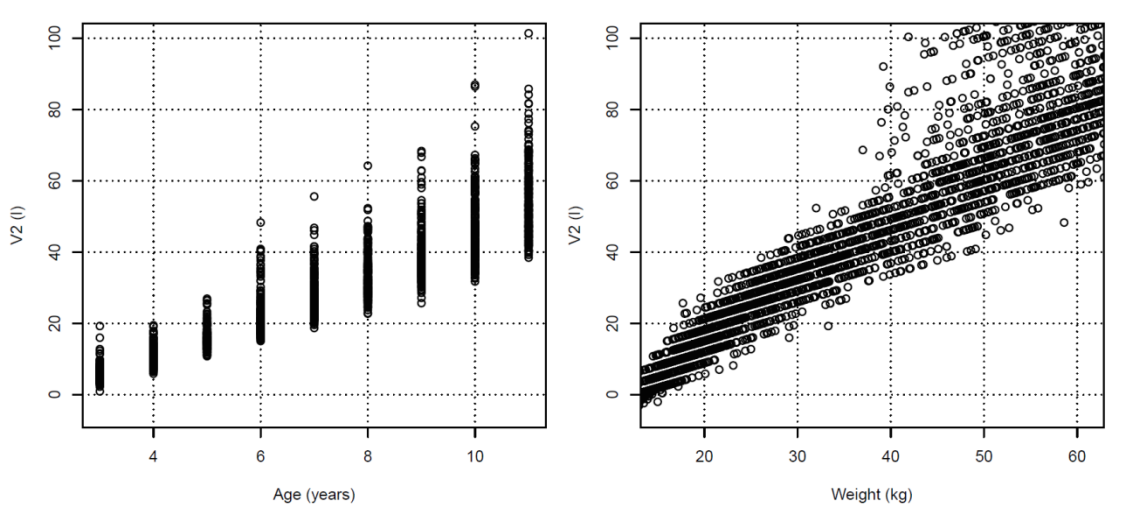
Lets look at the population typical *V2* for the individuals studied…



Do you see the problem? Probably not yet…

When extrapolation goes wrong

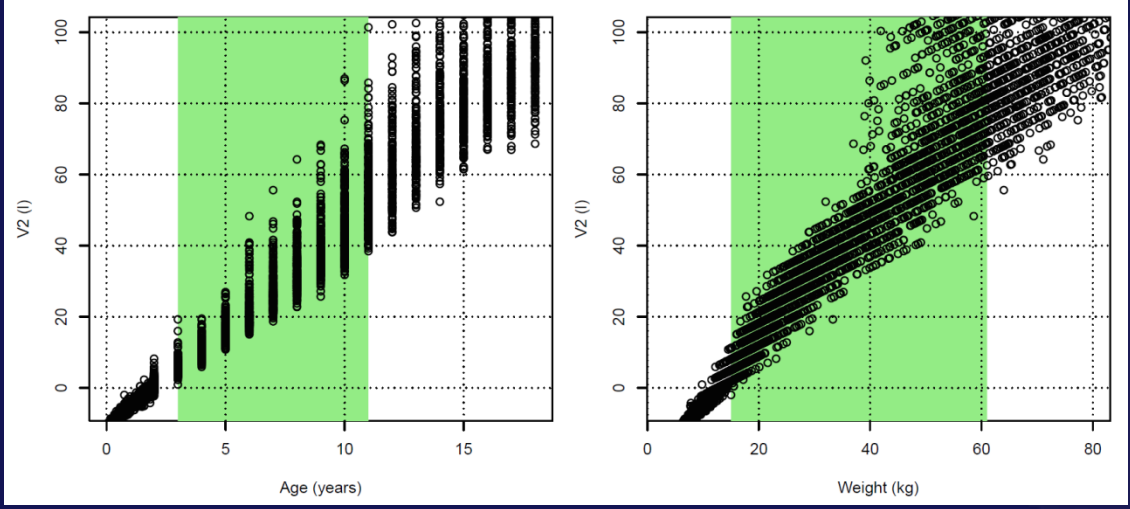
Lets look at an expanded covariate set using age and weights of children taken from NHANES[1] data



Things should start to look suspicious at the low end…

When extrapolation goes wrong

Lets extrapolate a little bit to ages 0-18 and weights 3-80 kg. The green area is the range of individuals studied.



V2 is predicted to be <0 just outside of data range!!!

When extrapolation goes wrong

Is it reasonable that a PK model developed from children 3-11 years old sometimes produces nonsense values for children 2-years old?

- What evidence would really be required to conclude that 2-year old children are really so different from 3-year old children that another PK model is needed?
- An exponential age model would have fixed this problem.
- The model development was performed with first-order (FO) method. When performed using first-order-conditional (FOCE) method this age covariate is no longer significant. Thinking about extrapolation might have avoided a false-positive covariate.

Evaluating models: Imagine it's a person

Evaluate you models honestly. Is it giving wise advice?

How can you identify a "dumb" model?

- Imagine that the model was a person and ask questions
- If you think the response is not wise try to make the model better

Consider an constant-volume model:

What dose should be given to a child? Obese?

$$V1 = V1_{ref} \qquad CL = CL_{ref}$$

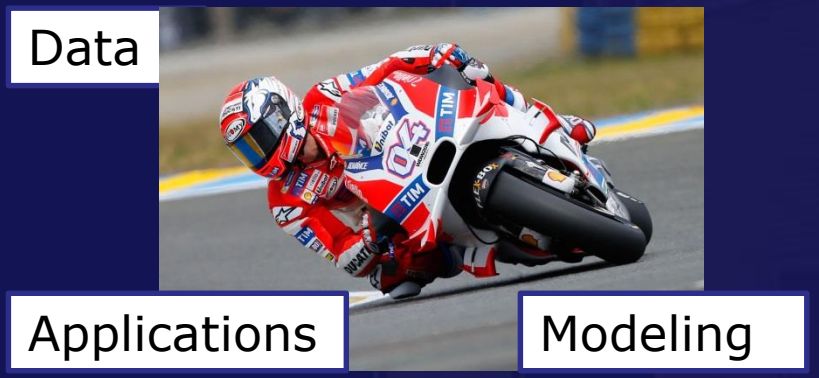
- Everyone, regardless of size, should receive the same dose and will achieve the same concentration

You probably would not take this advice from a person, so its probably not wise to take this advice from a model

Some final messages

Think about applications when making your model

- Don't have a myopic view of the meaning of your model
- All applications are outside your data
- Allometric scaling always useful



Think about physiological mechanisms when covariate testing. If you cant even imagine a mechanism, maybe you should not test it.

You don't always get the best final results by being "greedy" i.e. taking the best modification at each step. Sometimes you have to restart model building and consider a different branch.

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