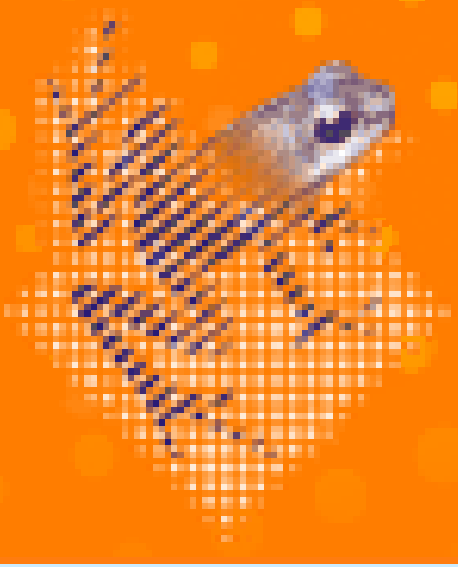


Aging and maturation as a reliability problem: The Weibull distribution and age- and maturation-adjustment functions



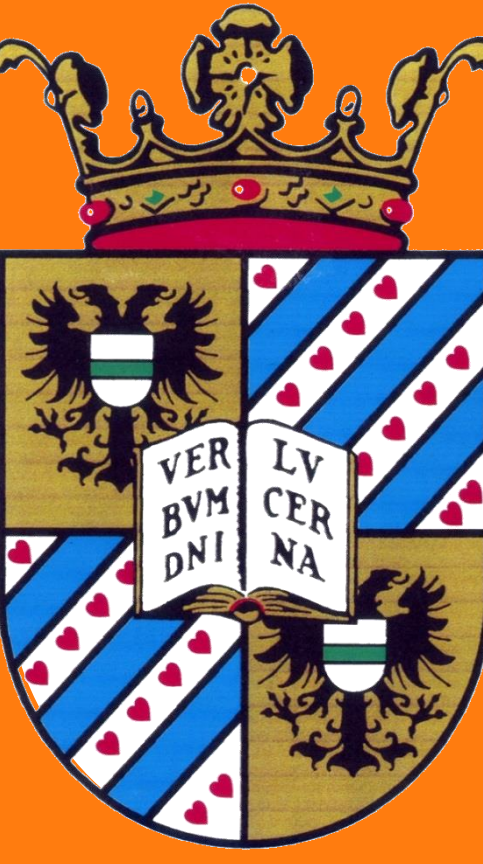
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Background and Objectives

In covariate analysis, age is often examined for its relationship with model parameters. An individual's age is informative for characteristics of physiological mechanisms which we attempt to duplicate in PK and PD models. These can be gradual changes associated with aging as well as more abrupt changes in young children associated with maturation. There is no “theory of aging” to guide model development and current approaches are empirical. There is considerable diversity in age-adjustment functions in current literature, and researchers are not often challenged as to their choices.

The purpose of this investigation is to view age-related parameters changes as a product reliability analysis. The premise is the number of functional physiological units (and thus biological function) over time after ontogenesis is analogous to the number of remaining functional products over time after manufacture.

Age- and maturation-adjustment functions

- Linear $1 + \theta(\text{age} - \text{age}_{\text{ref}})$
- Power $(\text{age}/\text{age}_{\text{ref}})^{\theta}$
- Exponential $\exp(\theta(\text{age} - \text{age}_{\text{ref}}))$
- Log-linear $1 + \theta \cdot \ln(\text{age}/\text{age}_{\text{ref}})$
- Sigmoidal Emax $\text{age}^{\theta_2} / (\text{age}^{\theta_2} + \theta_1^{\theta_2})$
- Weibull CDF** $1 - \exp(-(age/\lambda)^k)$

Methods and Results

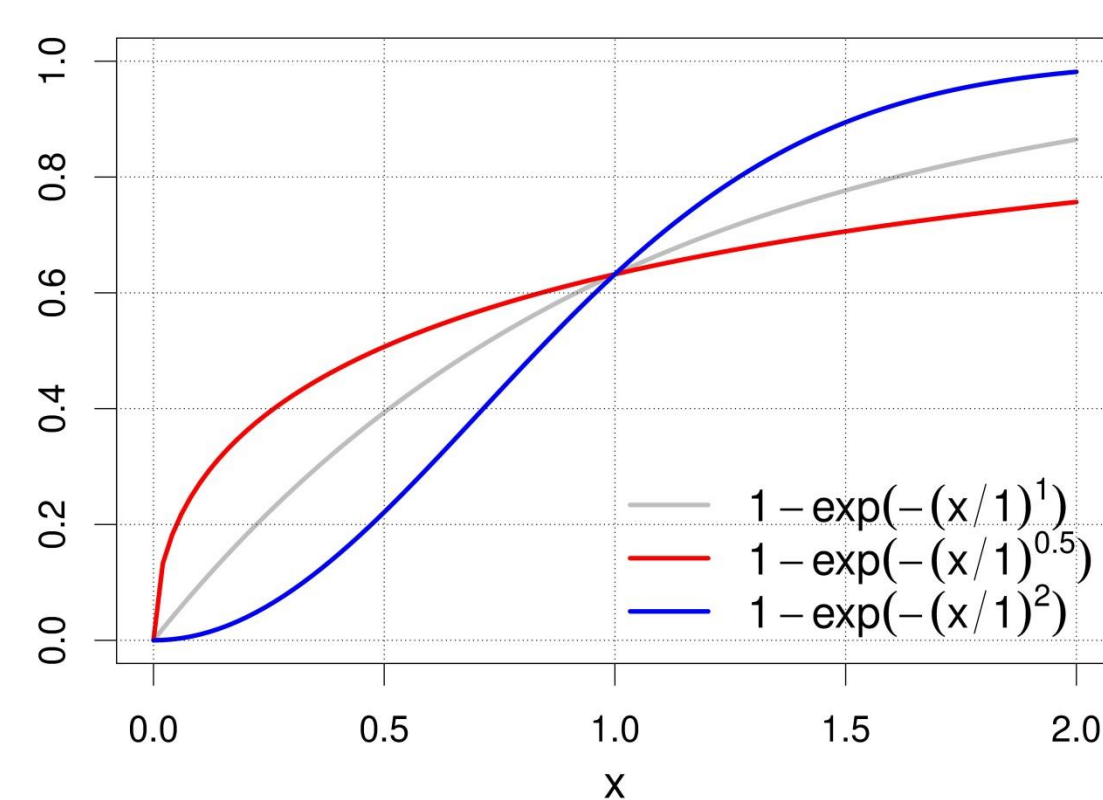
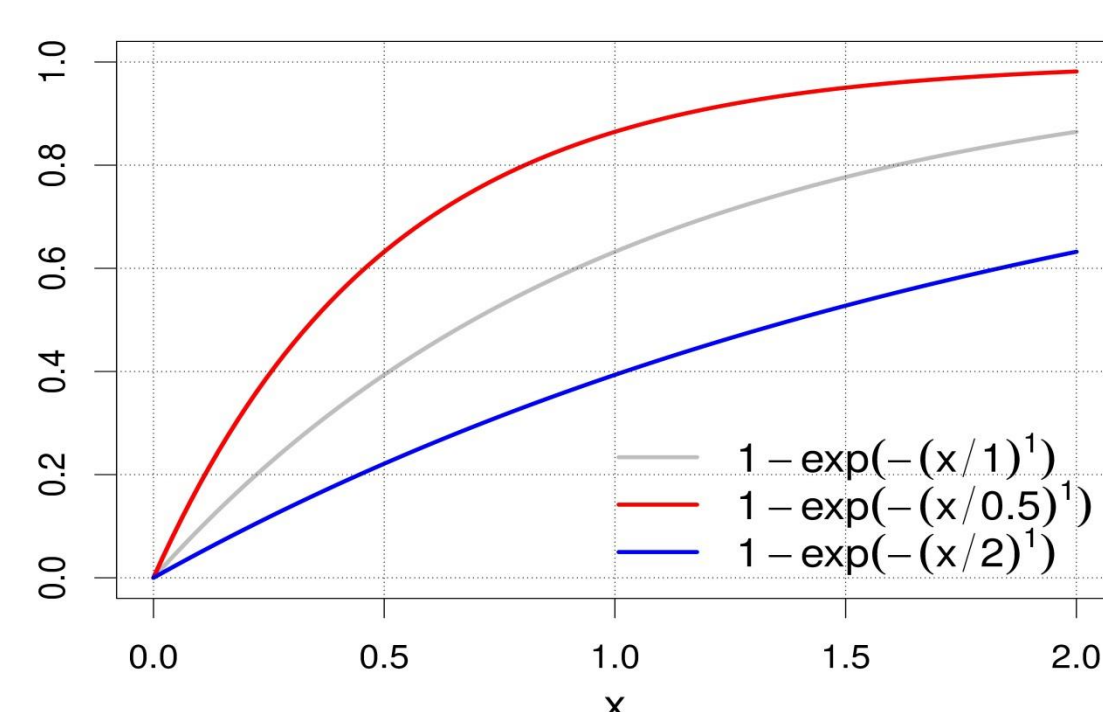
Methods

Weibull cumulative distribution

$$f(x) = 1 - \exp(-(x/\lambda)^k)$$

From reliability analysis:

- λ is the x at which 63% of failures occur
- $k < 1$ hazard decreases over time, a design flaw or quality control issue causes early failures
- $k = 0$ hazard is constant
- $k > 1$ hazard increases over time, product wears out over time



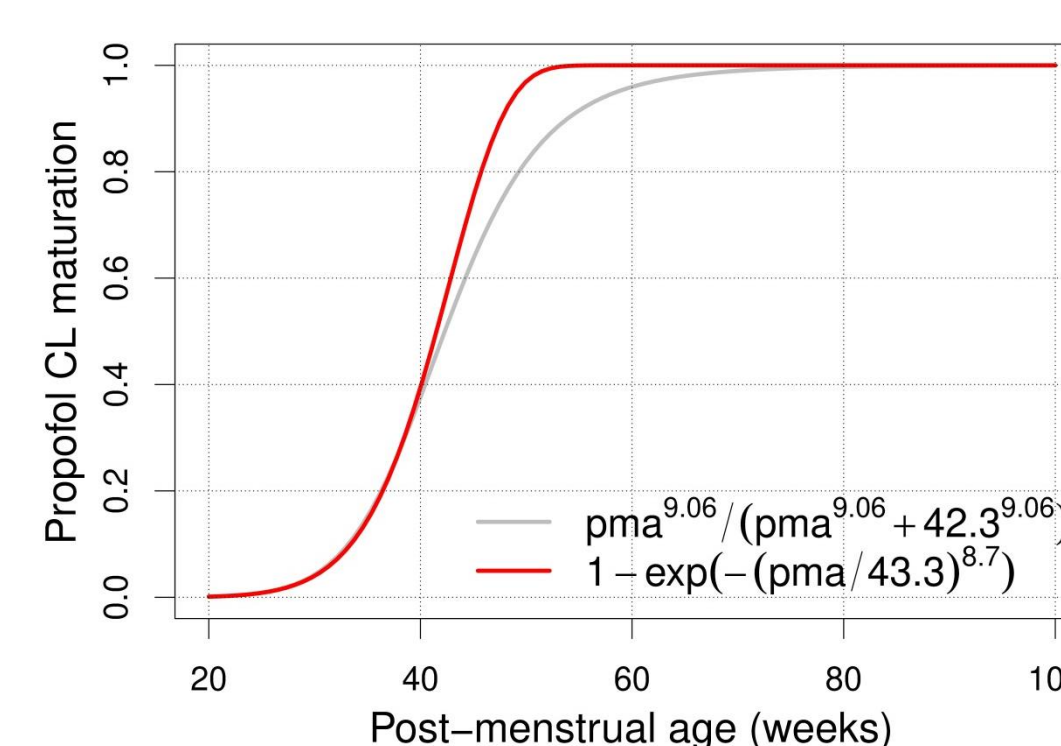
Plug-in replacement

Two PK models and datasets were chosen with a wide age-range, for Propofol¹ and Vancomycin². The age- and maturation-correction functions were plug-in replaced by the Weibull cumulative distribution function (CDF) and the model re-estimated. No model building was performed.

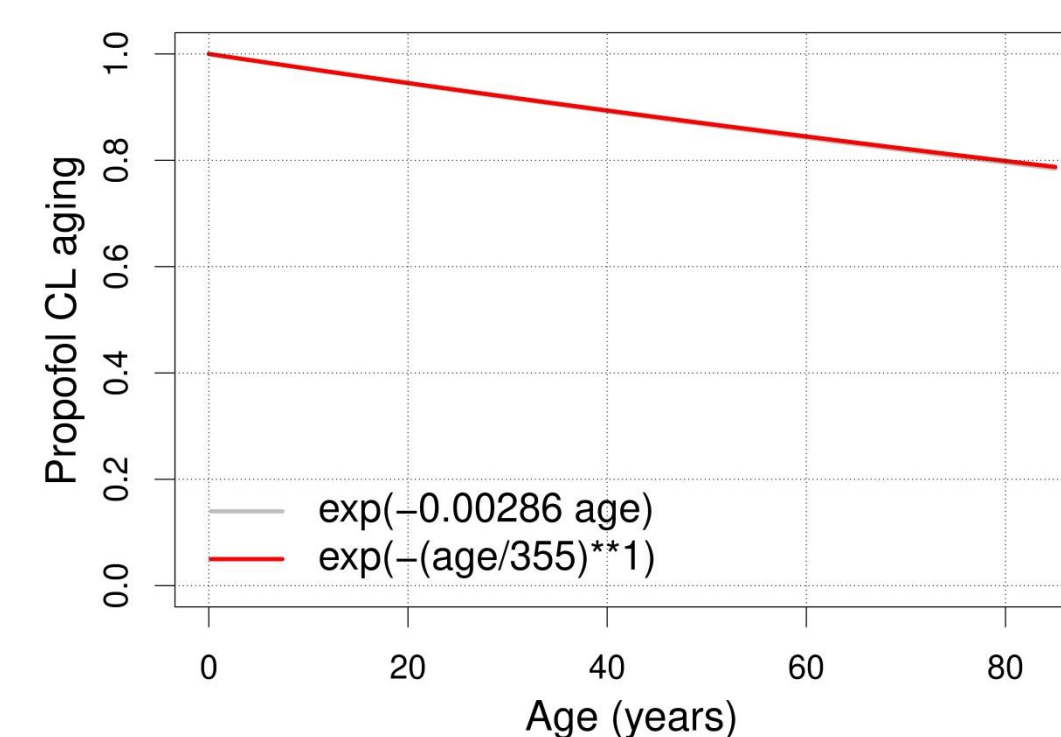
1. Eleveld DJ, Colin P, Absalom AR, Struys MM. Pharmacokinetic–pharmacodynamic model for propofol for broad application in anaesthesia and sedation. *British journal of anaesthesia*. 2018 May 31;120(5):942-59.
2. Colin PJ, Allegaert K, Thomson AH, Touw DJ, Dolton M, de Hoog M, Roberts JA, Adane ED, Yamamoto M, Santos-Buelga D, Martín-Suarez A. Vancomycin Pharmacokinetics Throughout Life: Results from a Pooled Population Analysis and Evaluation of Current Dosing Recommendations. *Clinical pharmacokinetics*. 2019 Jan 17:1-4.

Propofol

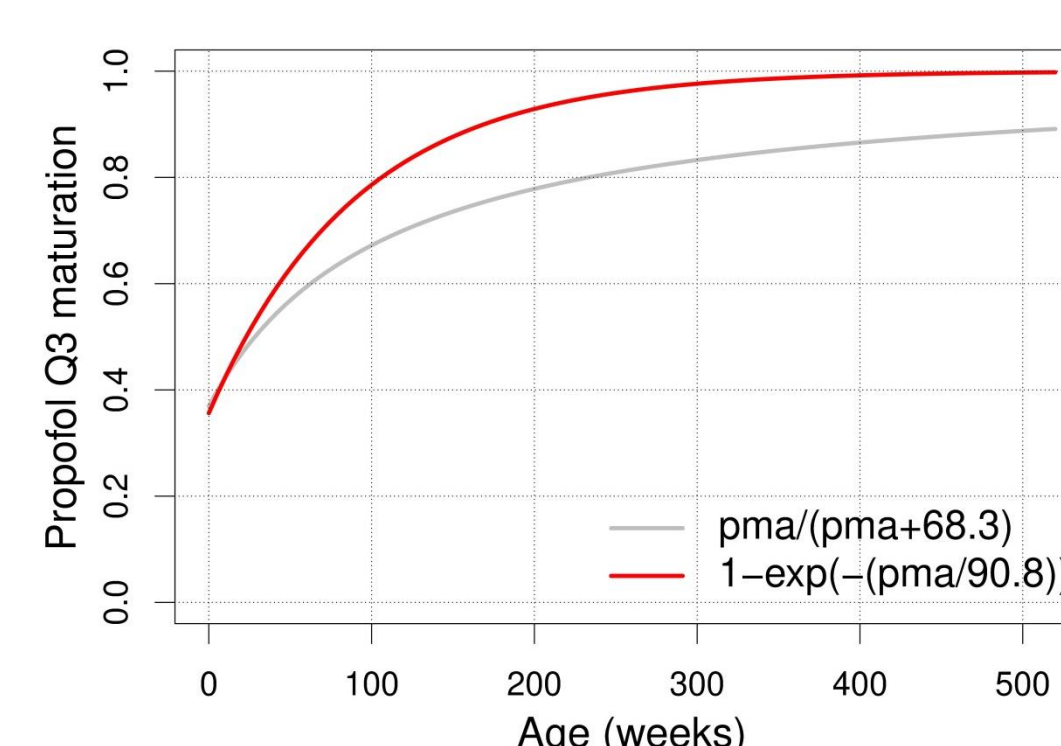
Maturation of CL shows rapid increase in hazard



Aging of CL shows constant hazard



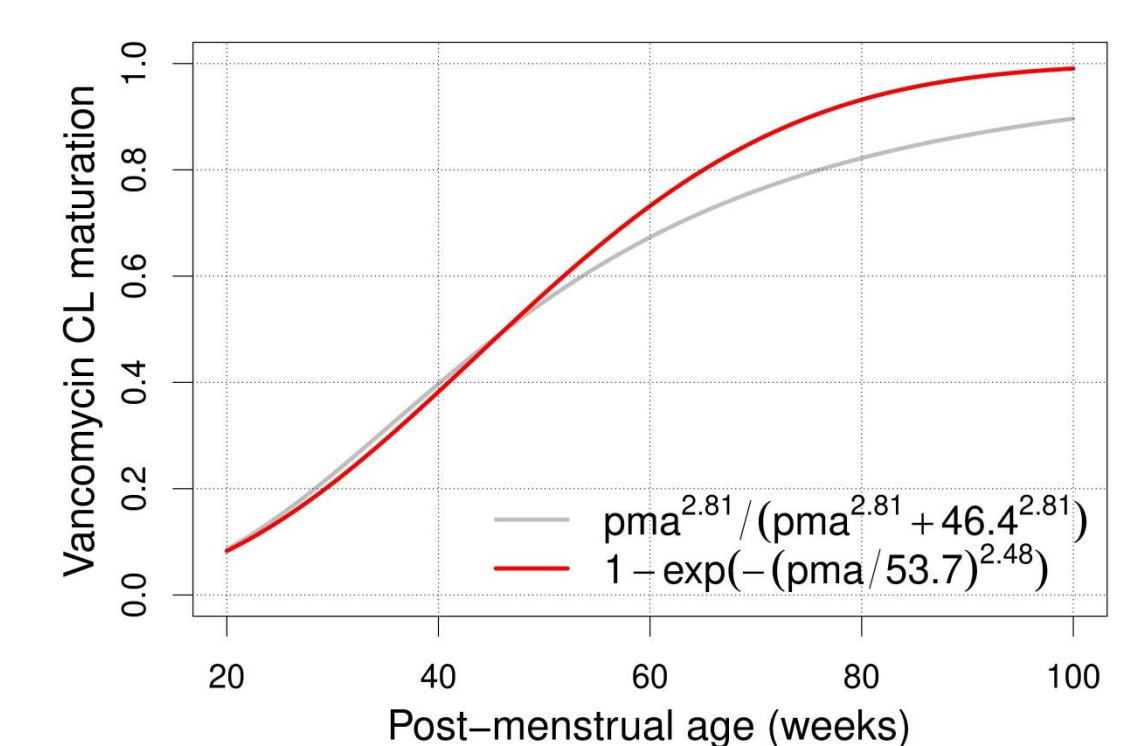
Maturation of Q3 shows constant hazard



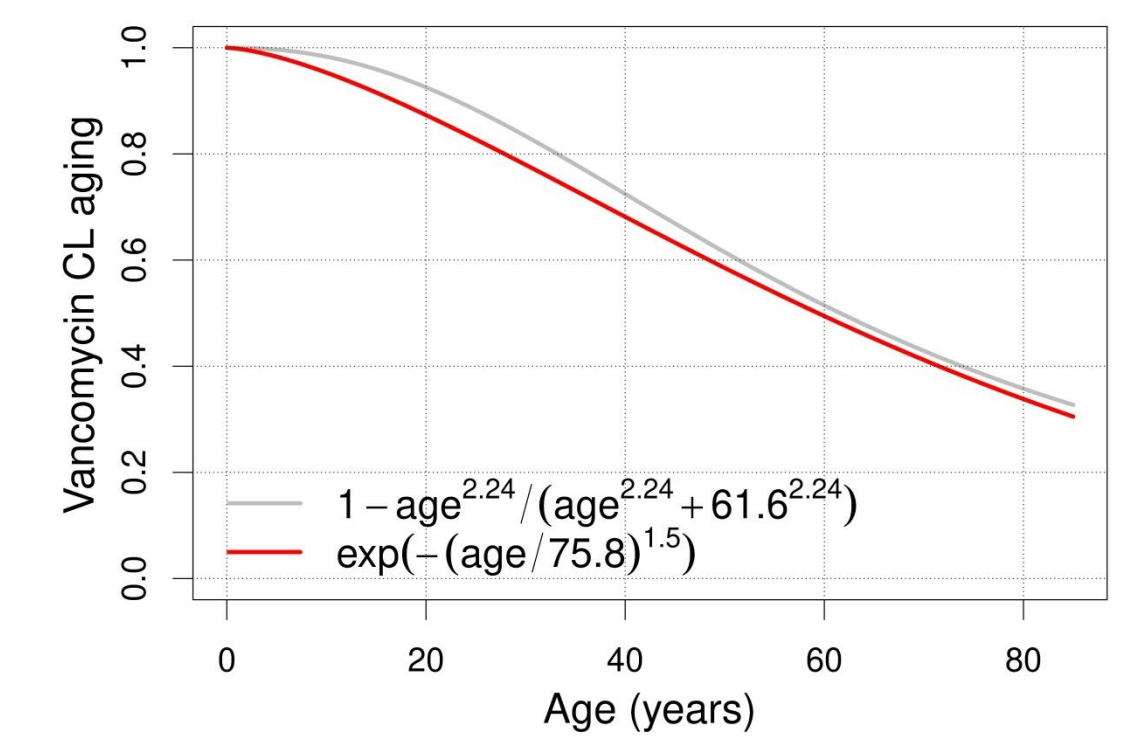
Change in objective function value 12.7

Vancomycin

Maturation of CL shows fast increase in hazard



Aging of CL shows fast increase in hazard



Change in objective function value -7.78

Conclusions

Age- and maturation-correction functions showing diverse behaviors can be modelled in a unified framework with Weibull CDF functions with only moderate impact on the final model fit, using only two (or one) parameters. Full model development would likely lead to at least similar model fit.

Covariate adjustment functions with a mechanistic interpretation should be preferred over arbitrarily chosen empirical functions to avoid “over-testing”. The Weibull CDF can be justified by the view that model parameters are macro observations of a multiple functional units that probabilistically gain (or lose) function over time according to a increasing/decreasing/constant hazard. These properties may be useful for formulating theoretical approaches to modelling aging and maturation.

Questions for future work

- What are the necessarily elements of a “Theory of aging”?
- Does aging begin at conception, birth, or after maturation? Does the delayed attainment of function due to maturation influence the age of the functional unit and its failure rate in aging?
- Does the interpretation of the function units as “capillaries” in the sense of allometric scaling influence weight scaling exponents?