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Accelerated Stability Kinetics

A Bayesian journey

.. for faster elucidation of the stability trend in Biologics

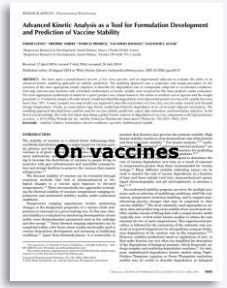
Y. Van Haelst

NCS Conference, 2022

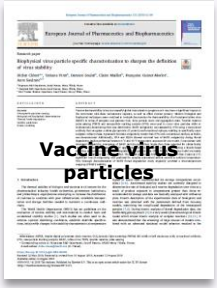
01 How it started

- A promising generalized degradation model from the Calorimetry field, translated to 'classic' stability data.
- Applied with success to vaccines stability data
- Workgroup(s) to explore applicability for ..
  - other pharmaceuticals
  - transport monitoring
  - excursion

B. Roduit et al.
Thermochimica Acta
(2014)



D. Clenet et al.
J. Pharm. Science
(2014)

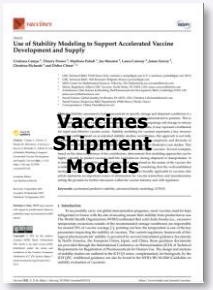


D. Clenet
EJPB
(2018)

Workgroup

A. Evers et al.
Pharmaceutics
(2022)

D. Clenet et al.
EJPB
(2018)



Campa et al.
Vaccines
(2021)

02 Advanced Kinetic Model

Reaction progress in its **differential** form ($\frac{d[A]}{dt}$ rate function) can be written as a **truncated SB** *(Sesták-Berggren)** function applicable to a wide array of reactions.

The response is standardized to a progression factor α_t between 0 and 1

Following table demonstrates how the *Sesták-Berggren* function overarches multiple kinetic models

It may be further extended for competitive and non-Arrhenius equations by using the sum of 2 SB equations (see backup slides).

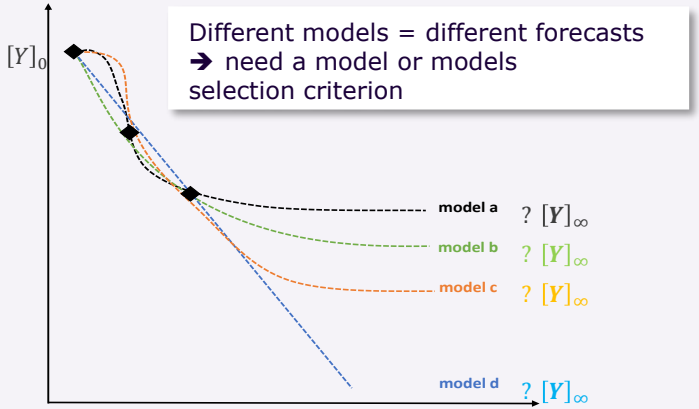
Kinetic model	Rate function	*Sesták-Berggren* function
0'th order	$d\alpha/dt = k(T)$	n = 0, m = 0 → $d\alpha/dt = k(T) * \alpha_t^0 * (1-\alpha_t)^0$
1'st order	$d\alpha/dt = k(T) * (1-\alpha)$	n = 0, m = 1 → $d\alpha/dt = k(T) * \alpha_t^0 * (1-\alpha_t)^1$
2'nd order	$d\alpha/dt = k(T) * (1-\alpha)^2$	n = 0, m = 2 → $d\alpha/dt = k(T) * \alpha_t^0 * (1-\alpha_t)^2$
n'th order	$d\alpha/dt = k(T) * (1-\alpha)^n$	n = 0, m = p → $d\alpha/dt = k(T) * \alpha_t^0 * (1-\alpha_t)^n$
Prout-Tompkins	$d\alpha/dt = k(T) * \alpha(1-\alpha)$ Autocatalytic Reaction: A + B → 2B + C	n =1, m = 1 → $d\alpha/dt = k(T) * \alpha_t^1 * (1-\alpha_t)^1$

For reaction: $A \rightarrow B$

$$progression\ factor\ (of\ \text{degradation})$$
$$\alpha_t = 1 - \frac{[Y]_t - [Y]_\infty}{[Y]_0 - [Y]_\infty}$$

truncated $(\mathbf{SB})\ differential\ (rate)\ equation$:
$$\frac{d\alpha}{dt} = f(\alpha, t, k, n, m) = \boldsymbol{k(T)} \times (1-\alpha_t)^n \times \alpha_t^m$$

$$thermodynamic\ link:$$
$$\boldsymbol{k(T)} = g(T, \%RH, etc..)$$
(reaction constant in function of Temperature, humidity, etc…)



* B. Roduit et al. (2014), cfr 01 How it started

02 Advanced Kinetic Model

Beware it is a rate function

No antiderivative for $(1-a)^n a^m$

Challenge:

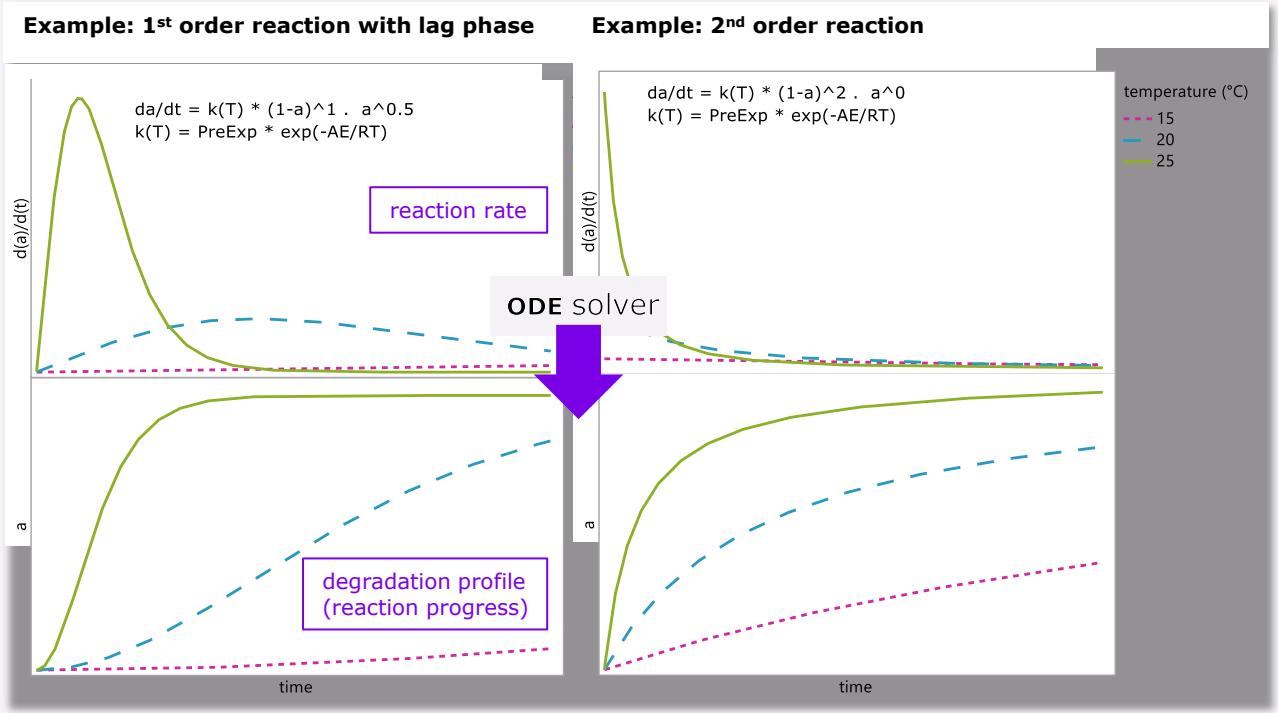
- → must be integrated numerically using an ODE solver
- → Numerical 'precision' of the ODE solver is not trivial

Benefit:

.. When numerical integration is a necessity.. forecasts where temperature and humidity vary over time become easy.

Numerical integration creates opportunities for:

- predicting impact of temperature excursion
- modeling in function of shipment data loggers



03 On to Bayesian

- A promising generalized degradation model from the Calorimetry field, translated to 'classic' stability data
- Ap
- W

Ok, approach works* …. what's NEXT ?

**** cfr. 01. How it started***

.. A CMC Statistician playground ☺

Optimal stability design
(!) In nonlinear systems, the optimal design points (Temp, Time) depend on the expected curve ➔ Need some prior knowledge

Occasional 'local optimum' problem
(?) What to do when nonlinear regression gets 'stuck' on a local optimum. ➔ use prior experience to choose better starting values

Building a 'stability' platform knowledge
can we use previous stability lessons learned to drive future developments in a formalized way ? The Bayesian paradigm: using previous knowledge to drive our knowledge in early development.

B. F
Therm
(2014)

Technology
(2014)

(2018)

A. Evers et al.
Pharmaceutics
(2022)

Internal / drafts

03 On to Bayesian

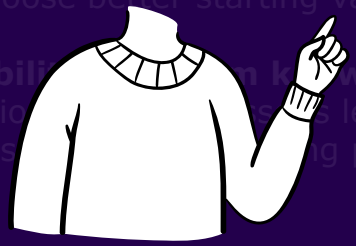
- A promising generalized degradation model from the Calorimetry field, translated to 'classic' stability data
- Ap
- W

Ok, approach works …. what's NEXT ?

… A CMC Statistician playground ☺

.. And for other reasons

When n models near equally good ➔ choosing = biasing
Bayesian model averaging has a way of accounting model choice in its model uncertainty statistics (credibility intervals etc.…)



I think we should explore Bayesian

(!) In nonlinear systems the optimal design points (Temp, Time) depend on the expected

(?) What to do when nonlinear regression gets 'stuck' on a local optimum. ➔ use prior experience to choose better starting values

Building a 'stabili … m k…wl…
can we use previo… s learned to drive future developments in a formalized way ? The Bayes… g previous knowledge to drive our knowledge in early development.

B. F… Therm… (2014)

Technology (2014)

(2018)

A. Evers et al. Pharmaceutics (2022)

Internal / drafts

04 Bayesian Advanced Kinetic Model

.. An opportunity to extend our least-squares model

… a CMC Statistician playground ☺

$$y(t) = y_0(batch) + [y_\infty - y_0 - y_0(batch)] \times \alpha(t) + \epsilon$$

$$\alpha(t) = \int_{[t=0,\ \alpha=a_0+a_0(batch)]}^{t} \frac{d\alpha}{dt}$$

$$\frac{d\alpha}{dt} = C \times \begin{bmatrix} (1-f) \times & e^{-\frac{Ea_1}{R}(\frac{1}{T}-\frac{1}{T_0})} & (1-\alpha)^{n_1}\alpha^{m_1} \\ + \quad f \times & e^{-\frac{Ea_2}{R}(\frac{1}{T}-\frac{1}{T_0})} & (1-\alpha)^{n_2}\alpha^{m_2} \end{bmatrix}$$

- principal model
- occasionally used extensions

occasionally used extensions

a_0: to model residual amount of degradant at time zero (for autocatalytic processes)

$y_0(batch)$: to model batch-to-batch variability in intercepts

$a_0(batch)$: to model batch-to-batch variability in degradants at time zero

$$[y_0(batch) \quad a_0(batch)] \sim N\left([0 \quad 0], \begin{bmatrix} \sigma^2_{y_0(batch)} & 0^* \\ 0^* & \sigma^2_{a_0(batch)} \end{bmatrix}\right)$$

$$\epsilon = \epsilon_{repeats} + \epsilon_{analysisrun} \sim N\left([0 \quad 0], \begin{bmatrix} \sigma^2_{repeatability} & 0 \\ 0 & \sigma^2_{analysisrun} \end{bmatrix}\right)$$

$\epsilon_{analysisrun}$= when stability samples are grouped in different analysis days and the between-analysis-run effect for the measurement method is non-trivial.

Bioassays ➔ ϵ ~ LogNormal

* ***up to now either y0 batch effect or a0 batch effect has been modelled, not both together.***

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05 Bayesian Model simplification approach

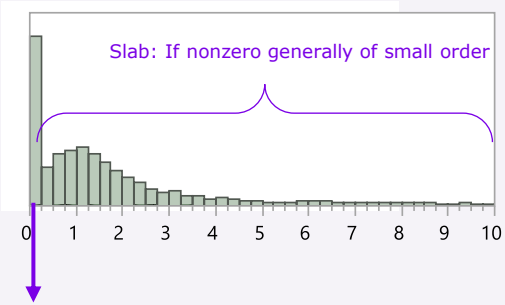
Simplification performed using peak-and-slap prior on top of a slightly informative prior.
It zeroes-out unimportant terms during the fit.

Benefits:

- no need to reiterate for all possible sub-models ➔ model 'selection' is performed in 1 go.
- No single sub-model retained? Not a problem!
  - the posterior distribution will contain the retained sub models proportional to their probability.
  - With the posterior distribution, we can build statistical intervals which will include model selection uncertainty.
  - With the posterior distribution we can visualize the median of the predictions by the models proportional to their probability… for any arbitrary point

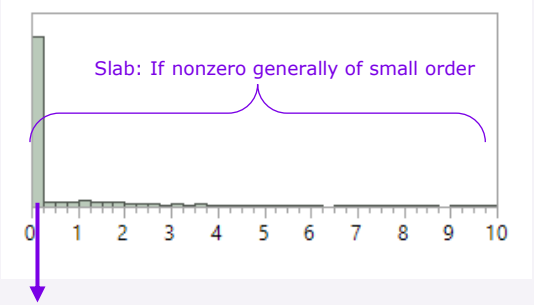
Visualization of the peak-and-slap prior :

Reaction order n_1



Peak: 20% probability to be a 'pseudo' zeroth order reaction

Autocatalytic coefficient m_1



Peak: 80% probability to have no = zero autocatalysis

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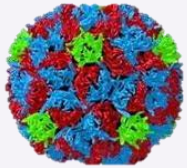
06 Case study:
Stability predictions for inactivated virus-based vaccine



Antigenicity determined by ELISA as a key stability indicating attribute for a virus-based vaccine

[#] *C. Campa et al., Vaccines* ***2021,*** *D. Clénet, Eur. J. Pharm. Biopharm.,* ***2018***

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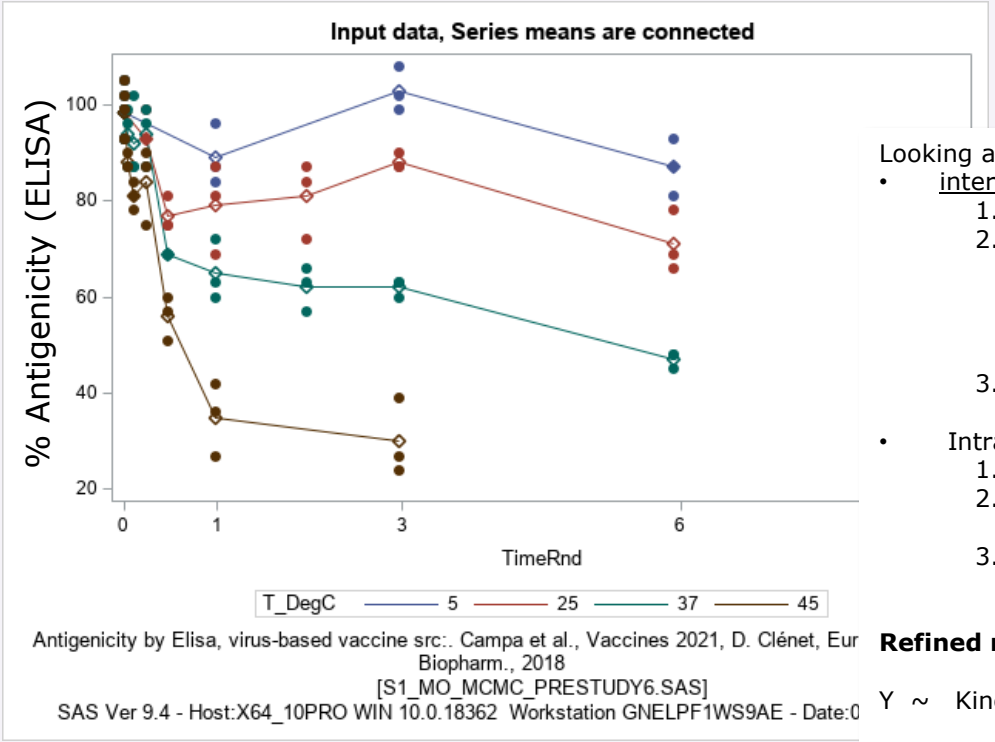
06 Case study:
Stability predictions for inactivated virus-based vaccine



Bayesian approach:
more complex model, equating inter-series bioassay variability + LogNormality

Looking at the dataset:

- inter-series effect
  1. We observe an inter-series effect
  2. The inter-series effect appears less pronounced at lower potency values: see how the upward series effect at t=3 months is stronger in 5 and 25°C but decreases in 37°C (45ºC possibly too but difficult to assess without a 6mth measure)
  3. Series noise scaling with signal (common feature in bioassays)
- Intra-series (repeatability) effect:
  1. Substantial noise within n-plicate results
  2. Noise does not scale with potency: values at 5ºC are visually equally variable as low potency values at 3months 45ºC
  3. Intra-series noise is normal distributed

Refined model :

Y ~ Kinetic + inter-series noise + intra-series noise

$Y \sim f()_{kinetic} + Normal(0, f()_{kinetic} * RSD_{inter}) + Normal(0,\sigma_{intra})$

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Stability predictions for inactivated virus-based vaccine

Prior beliefs vs. Posterior:

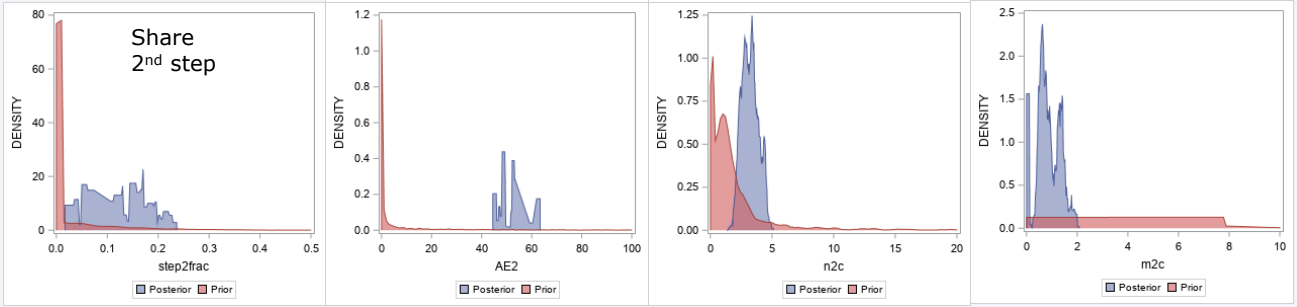
Prior settings for model simplification (peak in peak & slab):

- Prior OddsReactionOrder = 20% chance to be zero order
- Prior OddsAutocatalysis = 20% chance to have an autocatalytic part
- Prior Odds2Step = 20% chance to have a 2-step reaction

➔ Posterior Odds2Step was 100%

Step 1

Step 2



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Stability predictions for inactivated virus-based vaccine

Retained models with their posterior belief (ColPctN):

						rate/month		kCal				kCal				
			Model	$y_{(t=0)}$	$y_{(t=inf)}$	PreExp	Share(Step$_1$)	Ae_1	n_1	m_1	Share(Step$_2$)	Ae_2	n_2	m_2	rsd_{series}	sd_{repeat}
			ColPctN	P50	P50	P50	P50	P50	P50	P50	P50	P50	P50	P50	P50	P50
Step	Step1Type	Step2Type														
2Step	N.th Order	N.th Order	17.36	93.41	0.00	0.04187	88.2%	12.04	2.98	.	11.8%	45.13	2.41	.	8.16%	5.77
		Sigmoid	82.18	94.53	0.00	0.09806	84.2%	18.47	6.00	.	15.8%	50.94	3.35	0.86	8.22%	5.53
	Sigmoid	N.th Order	0.08	91.81	0.00	0.04025	88.2%	17.20	3.42	0.12	11.8%	45.13	2.56	.	6.63%	5.76
		Sigmoid	0.38	96.37	0.00	0.15302	81.6%	19.78	8.92	0.00	18.4%	48.60	3.44	1.32	7.47%	5.65

- Those are all the models that describe the data. They are all retained with their probability of describing the model in the predictions (next slide). Here, all were competitive-type equations, in agreement with the published nonlinear least squares model.

- Nonlinear least squares model with wAIC based selection criterion was:

$$\frac{d\alpha}{dt} = 0.409 * \frac{1.08E8}{s}\ e^{\frac{-19.7\ kCal}{RT}}(1-a)^4 + 0.591 * \frac{1.68E31}{s}\ e^{\frac{-28.5\ kCal}{RT}}(1-a)^2$$

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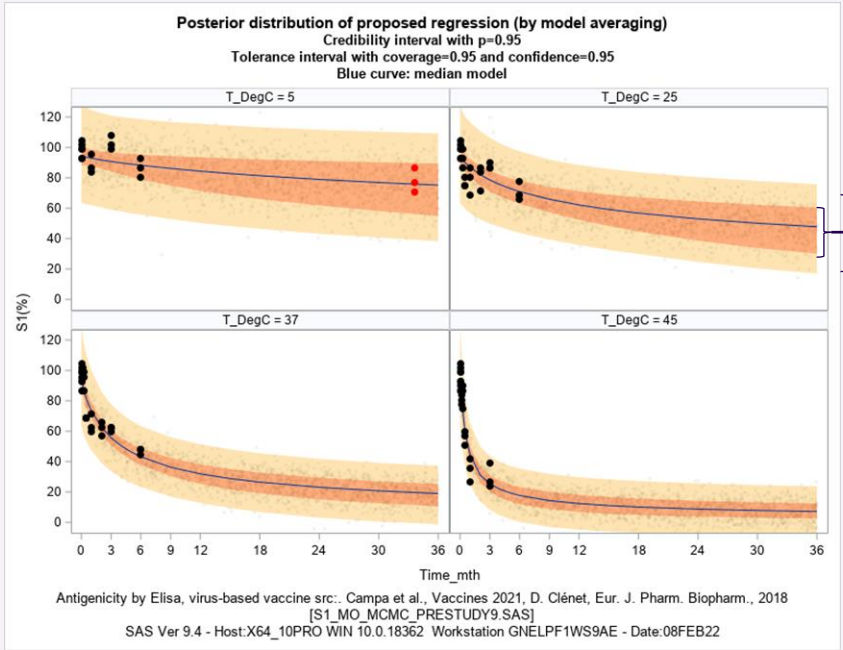
Stability predictions for inactivated virus-based vaccine

Bayesian model averaging



Credibility interval, contains 95% of most probable models

ß-γ interval (e.g., Bayesian tolerance interval) region wherein at least 95% of the population of 'future' observations are expected considering the 95% of most probable models/coefficient values

(See previous slide for considered models in this model averaging)

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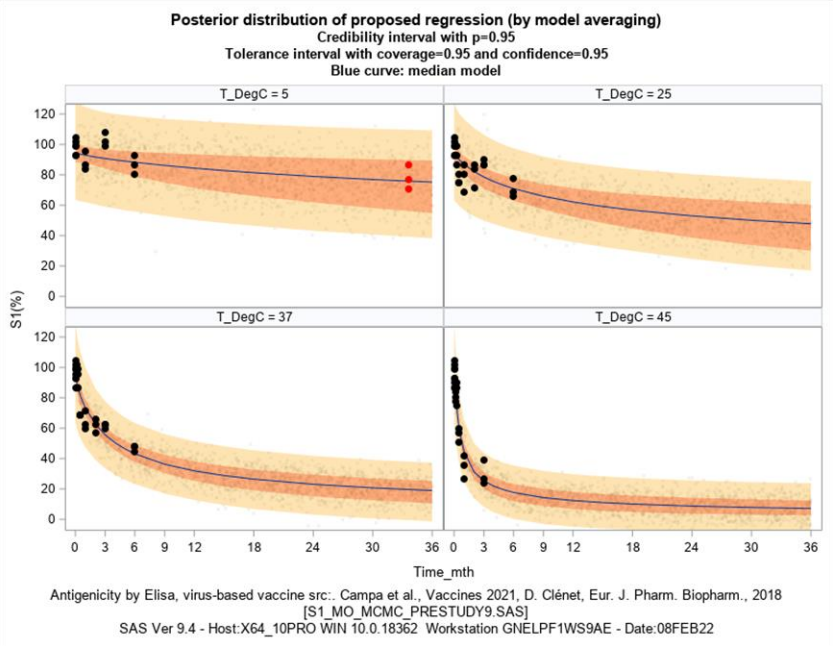
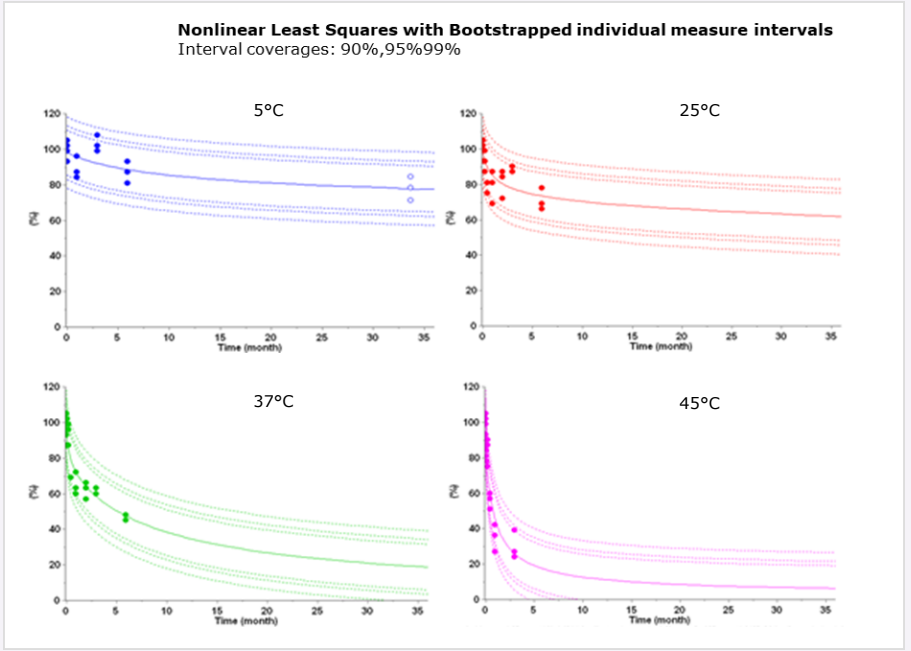
Stability predictions for inactivated virus-based vaccine

Bayesian model averaging

vs.

Nonlinear Least squares approach





Here: Difference is in the tolerance band: it narrows at low recoveries because we modeled log-normal inter-series variability. Otherwise, results are near identical to the Nonlinear Least Squares approach with bootstrapped prediction intervals.

07 What's Next ?

Where we are

"Heat map" algorithm for sensitivity analysis of model coefficients demonstrated the importance of prior knowledge for optimal (time, temperature) points

Developed Bayesian Model averaging platform

for Advanced Kinetic models

Next steps

fitting molecules to acquire platform knowledge

(interaction with scientists)

Develop optimal design algorithm which utilizes the platform knowledge

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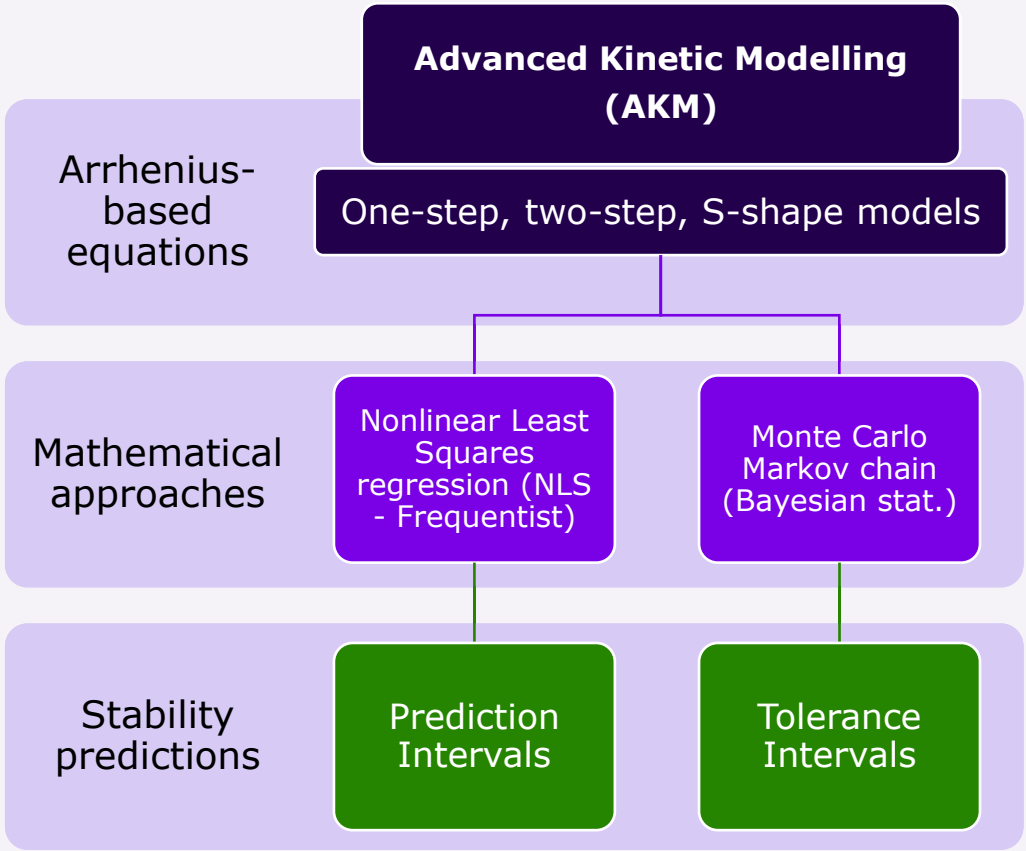
Advanced Kinetic Modelling (AKM)
Arrhenius-based equations
One-step, two-step, S-shape models
Mathematical approaches
Nonlinear Least Squares regression (NLS - Frequentist)
Monte Carlo Markov chain (Bayesian stat.)
Stability predictions
Prediction Intervals
Tolerance Intervals

Thank you

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Backup slide: Advanced Kinetic Model

Example of other models covered

Reaction Type	Complete formula (da/dt =..)	Simplified	Reaction stages
0, 1st, 2nd, 3rd, 4th order	$k_1(1-a)^{0,1,2,3,4\ldots}\ a^0 + 0(1-a)^0 a^0$	$k_1(1-a)^{0,1,2,3,4\ldots}$	$A \longrightarrow B + C$
nth order	$k_1(1-a)^n a^0$ $+0(1-a)^0 a^0$	$k_1(1-a)^n$	$A \longrightarrow B + C$
Avrami-Erofeev type (nucleation)	$k_1(1-a)^{n_1} a^{m_1}$ $+0(1-a)^0 a^0$	$k_1(1-a)^{n_1} a^{m_1}$	$A \longrightarrow B + C$
Prout-Tompkins(autocatalysis)	$k_1(1-a)^1 a^1$ $+0(1-a)^0 a^0$	$k_1(1-a)a$	$A + B \longrightarrow 2B + C$
Consecutive 1st order with autocatalysis	$k_1(1-a)^1 a^1$ $+k_2(1-a)^1 a^1$	$k_1(1-a)a + k_2(1-a)a$	$A \longrightarrow B + C$ $A + B \longrightarrow 2B + C$
Consecutive nth order with autocatalysis	$k_1(1-a)^{n_1} a^{m_1} + k_2(1-a)^{n_2} a^{m_2}$	same	$A \longrightarrow B + C$ $A + B \longrightarrow 2B + C$
Competitive 1st order	$k_1(1-a)^1 a^0$ $+k_2(1-a)^1 a^0$	$(k_1+k_2)(1-a)$	$A \longrightarrow B + C$ $A \longrightarrow D + E$
etc..	..	..	..