

Insight on vaccine stability based on accelerated stability data, Advanced Kinetic Modelling, and Bayesian statistics

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All data showed in this presentation are either simulated data (inspired from real stability data), or publicly available data from the literature

Vaccine stability, the 100-days challenge

The CEPI's 100-days challenge

- In 2021, the Coalition for Epidemic Preparedness Innovations (CEPI) articulated its "moonshot 100 Days Mission"
- An initiative to cut vaccine development time for new pathogens to 100 days
- ... a third of the time it took the world to deliver the first COVID-19 vaccine

Impact of the 100 days mission for vaccines on COVID-19: a mathematical modelling study



Gregory Barnsley, Daniela Olivera Mesa, Alexandra B Hogan, Peter Winskill, Andrew A Torkelson, Damian G Walker, Azra C Ghani, Oliver J Watson

Summary

Background The COVID-19 pandemic has underscored the beneficial impact of vaccines. It also highlighted the need for future investments to expedite an equitable vaccine distribution. The 100 Days Mission aims to develop and make available a new vaccine against a future pathogen with pandemic potential within 100 days of that pathogen threat being recognised. We assessed the value of this mission by estimating the impact that it could have had on the COVID-19 pandemic.

Methods Using a previously published model of SARS-CoV-2 transmission dynamics fitted to excess mortality during the COVID-19 pandemic, we projected scenarios for three different investment strategies: rapid development and manufacture of a vaccine, increasing manufacturing capacity to eliminate supply constraints, and strengthening health systems to enable faster vaccine roll-outs and global equity. Each scenario was compared against the observed COVID-19 pandemic to estimate the public health and health-economic impacts of each scenario.

Findings If countries implemented non-pharmaceutical interventions (NPIs) as they did historically, the 100 Days Mission could have averted an estimated 8.33 million deaths (95% credible interval [CrI] 7.70–8.68) globally, mostly in lower-middle income countries. This corresponds to a monetary saving of US\$14.35 trillion (95% CrI 12.96–17.87) based on the value of statistical life-years saved. Investment in manufacturing and health systems further increases deaths averted to 11.01 million (95% CrI 10.60–11.49). Under an alternative scenario whereby NPIs are lifted earlier on the basis of vaccine coverage, the 100 Days Mission alone could have reduced restrictions by 12,600 days (95% CrI 12,300–13,100) globally while still averting 5.76 million deaths (95% CrI 4.91–6.81).

Interpretation Our findings show the value of the 100 Days Mission and how these can be amplified through improvements in manufacturing and health systems equity. However, these investments must be enhanced by prioritising a more equitable global vaccine distribution.

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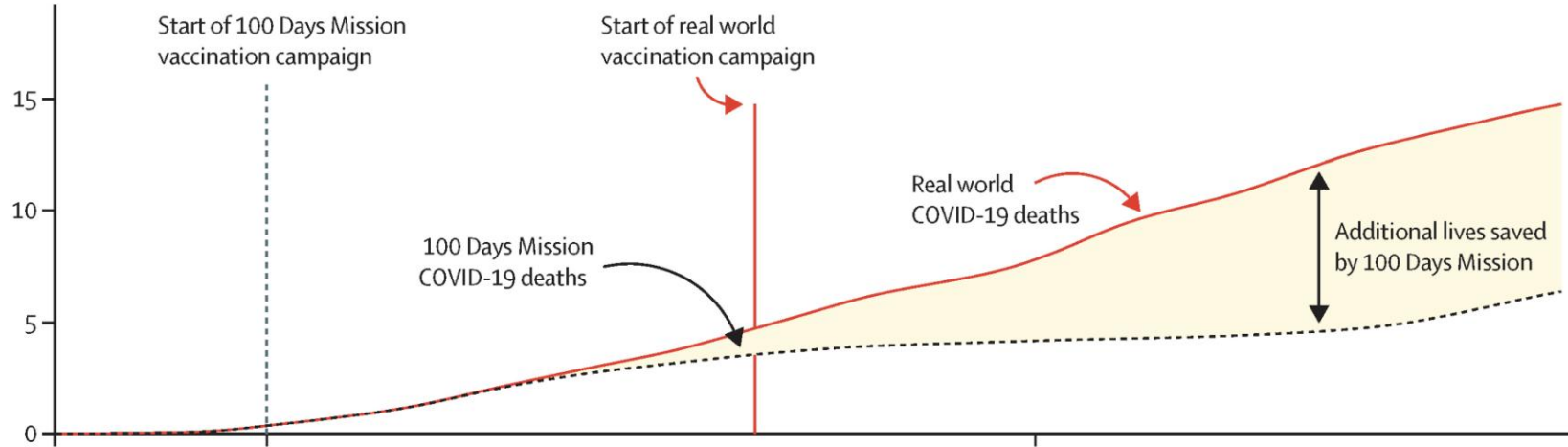
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Speed can have a major impact on death toll during a pandemic...

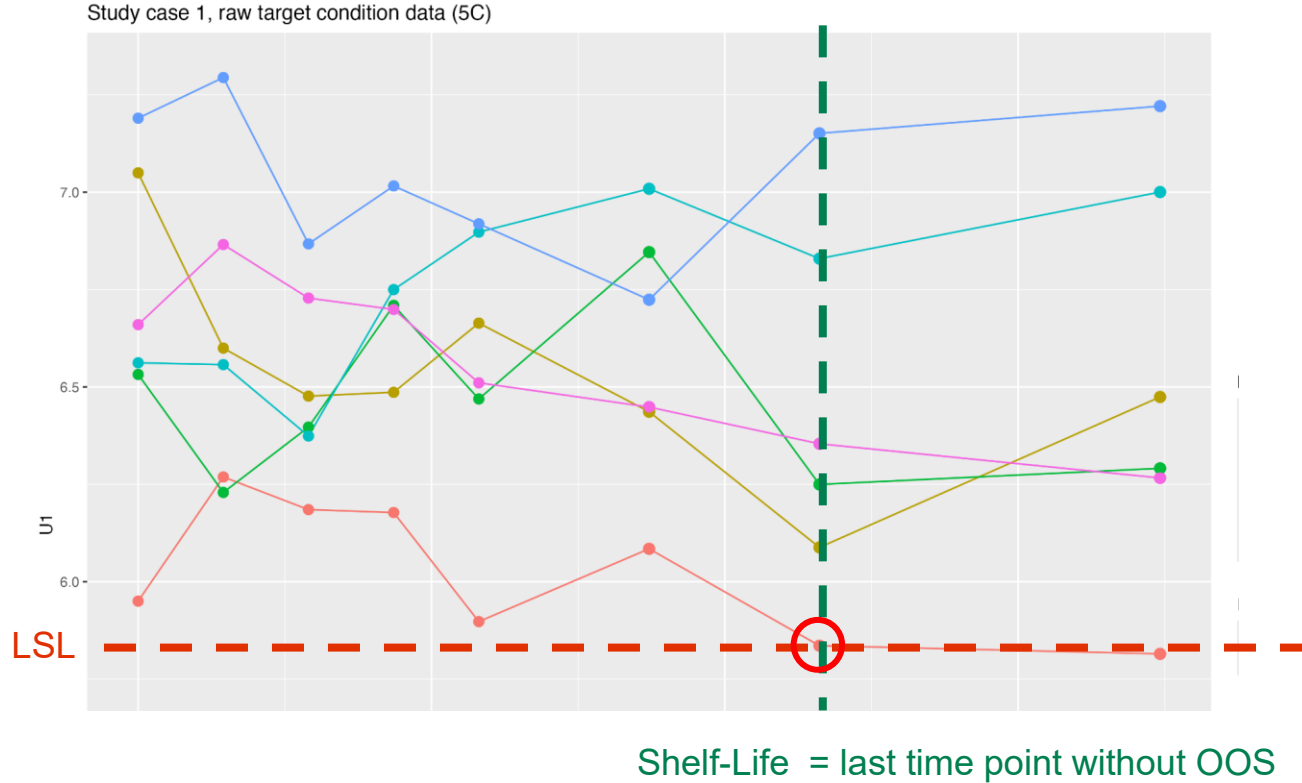


- Initiating vaccination after 100 days could have averted 8 - 33 million deaths due to COVID-19 by the end of 2021
- But in vaccine development, there is a bottleneck: **stability studies**
- To evaluate stability requires several years. In the context of pandemics, we may not have the time to wait so long
- How can we as Bayesian statisticians contribute to speed-up the stability evaluation of vaccines?

Stability analyses in the Pharma world, a long, long journey...

Compliance approach (1970 – now...)

... accepted by authorities but conceptually flawed!



Fixed batch and poolability rules (ICH Q1E, 1990 – now...)

... accepted by authorities but conceptually flawed!



Poolability rules...

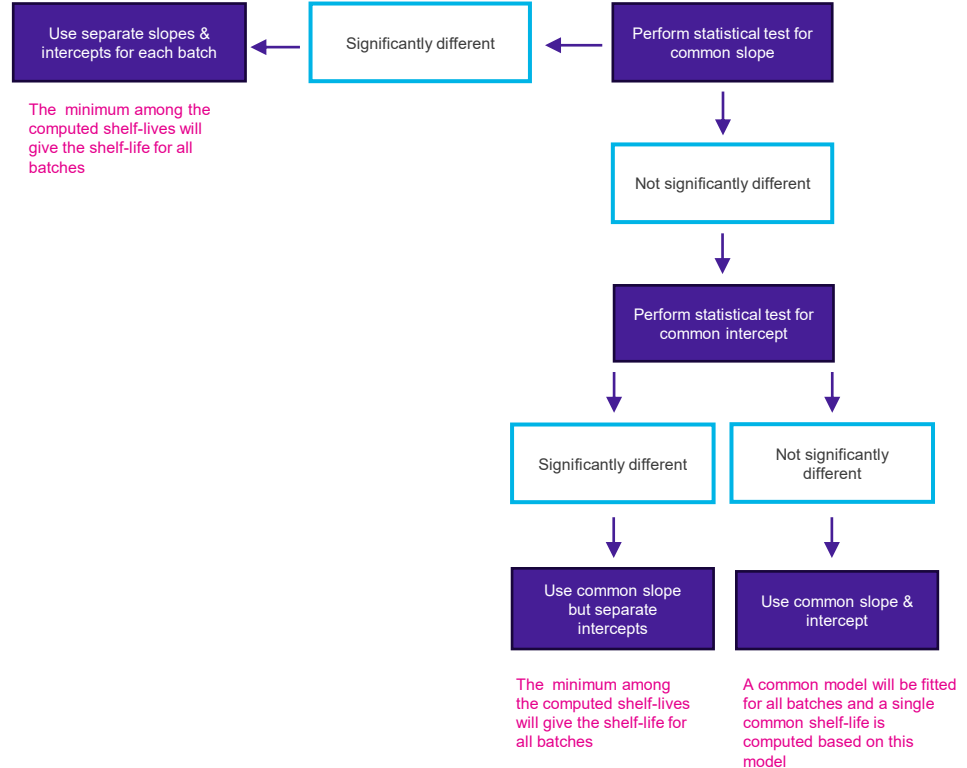
$$y_{ij} = \beta_0 + \text{Time} \times \beta_1 + \varepsilon_{ij}$$

$$y_{ij} = \beta_0 + \beta_{1j} + \text{Time} \times \beta_2 + \varepsilon_{ij}$$

$$y_{ij} = \beta_0 + \beta_{1j} + \text{Time} \times (\beta_2 + \beta_{2j}) + \varepsilon_{ij}$$

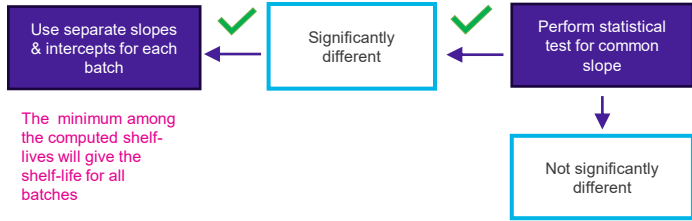
SL = "...the earliest time at which the 95% confidence limit for the mean intersects the proposed acceptance criterion. "

- Current ICHQ1E for "fixed batches"



Fixed batch and poolability rules (ICH Q1E, 1990 – now...)

... accepted by authorities, but conceptually flawed!

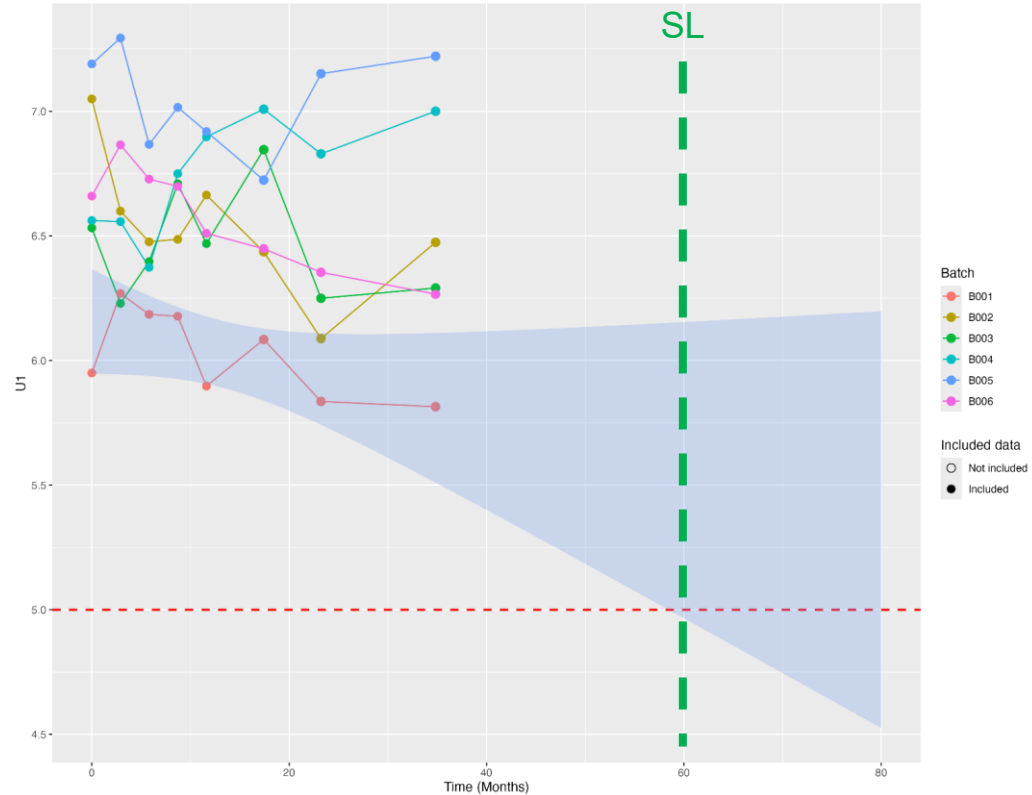


$$y_{ij} = \beta_0 + \beta_{1j} + \text{Time} \times (\beta_2 + \beta_{2j}) + \varepsilon_{ij}$$

SL = "...the earliest time at which the 95% confidence limit for the mean intersects the proposed acceptance criterion."

- Current ICHQ1E for "fixed batches"

Fix-batch approach with poolability rules



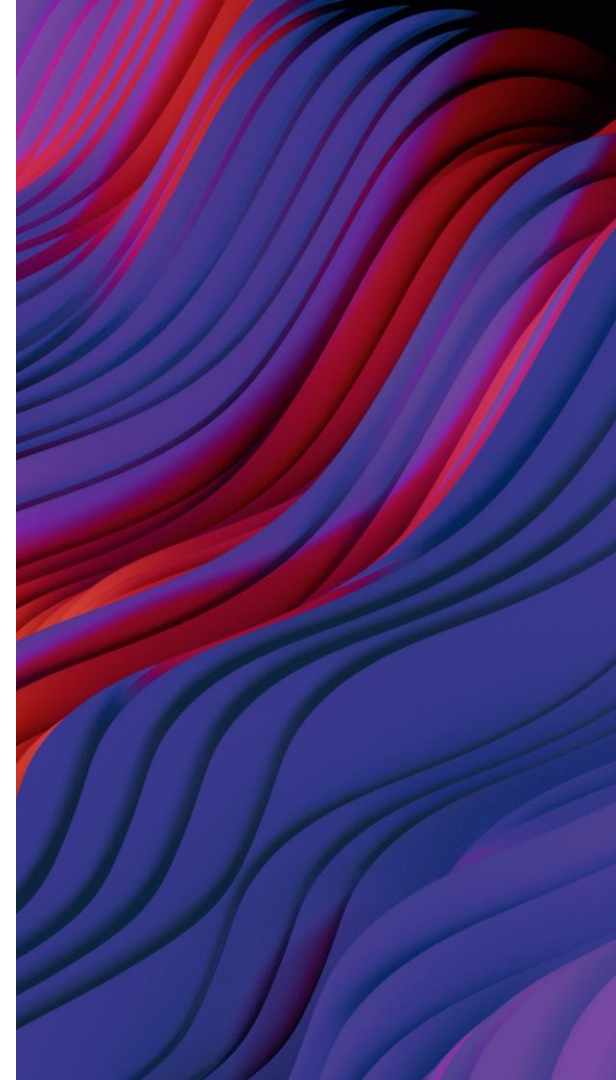
Fixed batch and poolability rules (ICH Q1E)

Limitations with shelf-life evaluation as proposed in Q1E!

- ⚠️ • Rely on **fixed batch** analyses with **poolability rules**.
Does not represent future batches variability
- ⚠️ • Suggests that product shelf-life can be estimated from (at least) 3 batches, and by calculating at the earliest the 95% CI of the worst-case batch, intersecting the specification limit(s).
BUT the worst batch observed among (at least) 3 batches is unlikely to represent future batches

Manufacturer inclined to use the minimum recommended number of batches

- Linear regression:
In some cases, non-linear trends may occur, especially with Biologics and vaccines (out of scope of current ICH Q1)



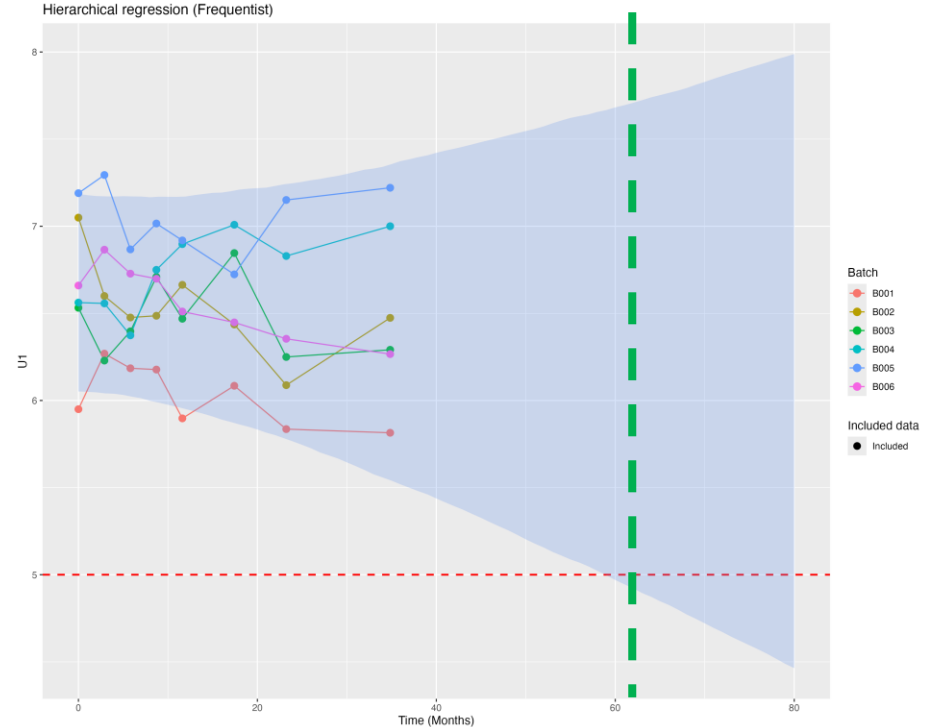
Random Batch approach (frequentist, ICH draft of... 2025!)

Also termed hierarchical regression, or mixed model... How does it apply to stability?

- Batches considered as a sample from the population of all batches
- No poolability test necessary, information from all batches is used for the estimation of a common model
- More realistic shelf-life is obtained

$$Y = \underbrace{\beta_0 + \beta_1 X}_{\text{fixed part}} + \underbrace{b_0 + b_1 X}_{\text{random part}} + \varepsilon$$

$N(0, \sigma_{intercept}^2)$ points to b_0
 $N(0, \sigma_{slope}^2)$ points to b_1
 $N(0, \sigma_{\varepsilon}^2)$ points to ε



SL

Random Batch approach (Bayesian)

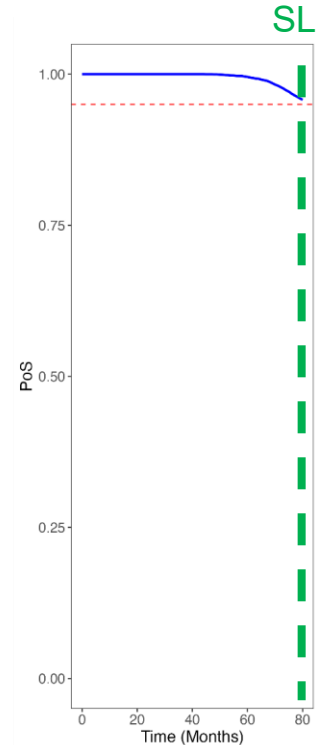
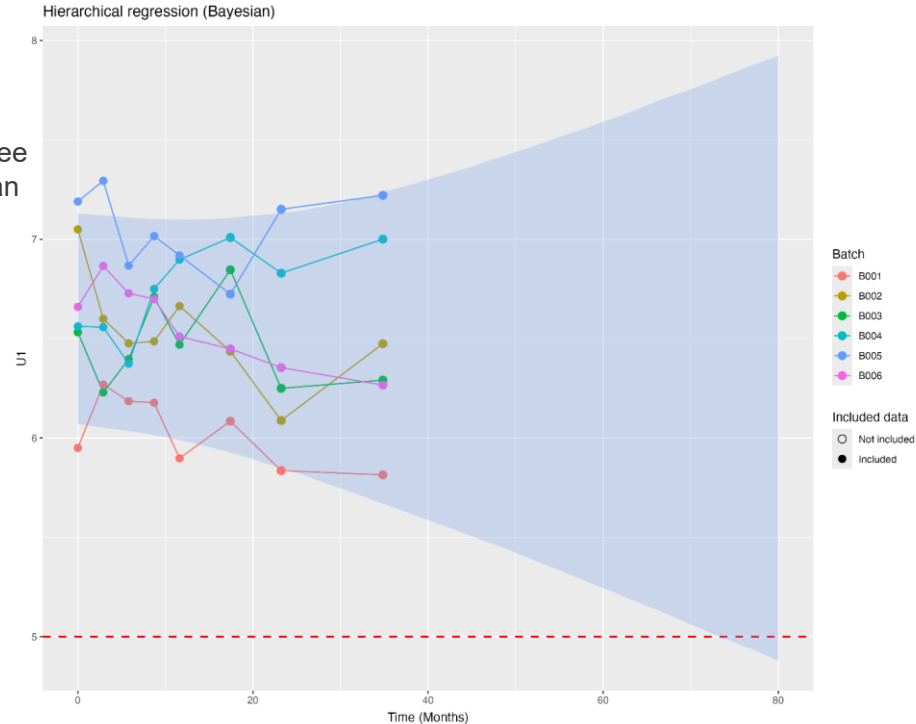
Hierarchical models, can be implemented either with frequentist or via **Bayesian statistics**

Allow to speak in terms of probabilities to meet the specs

Instead of fixing the confidence level, see how it evolves with the Time, to make an informed decision

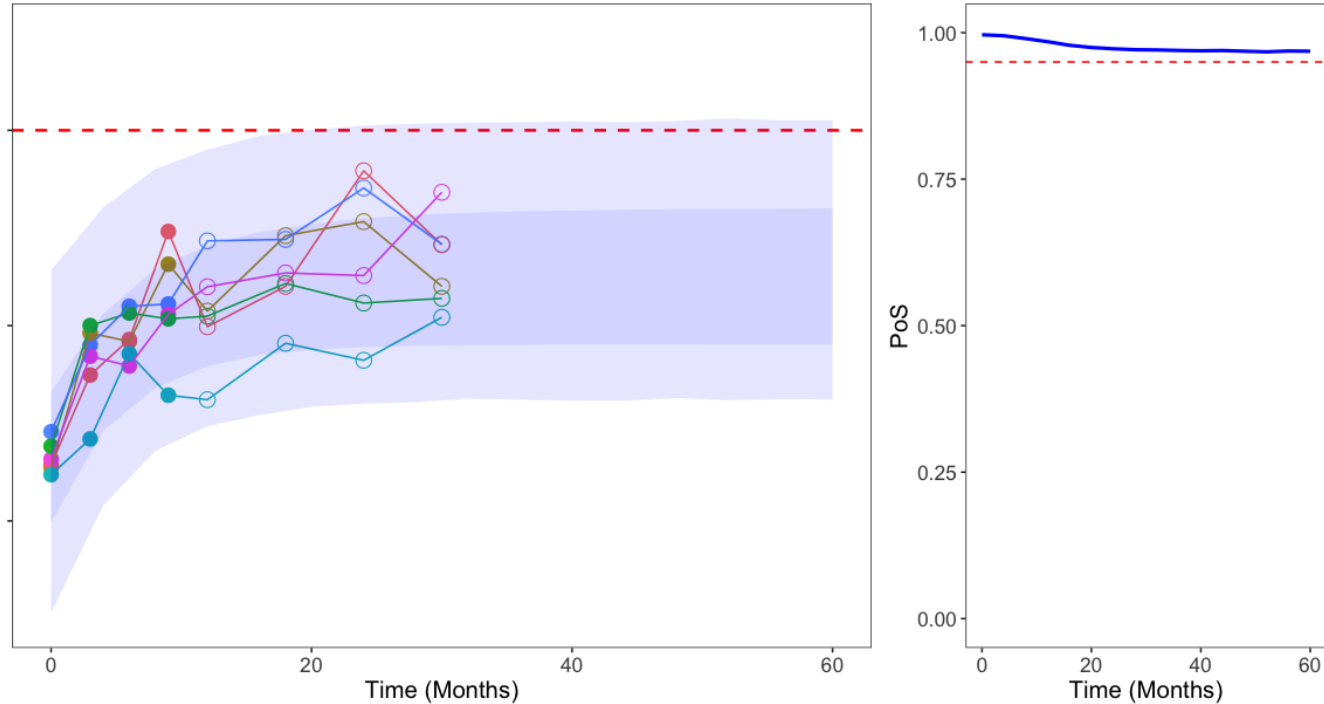
Allows to handle non-linear profiles

And many other advantages ☺

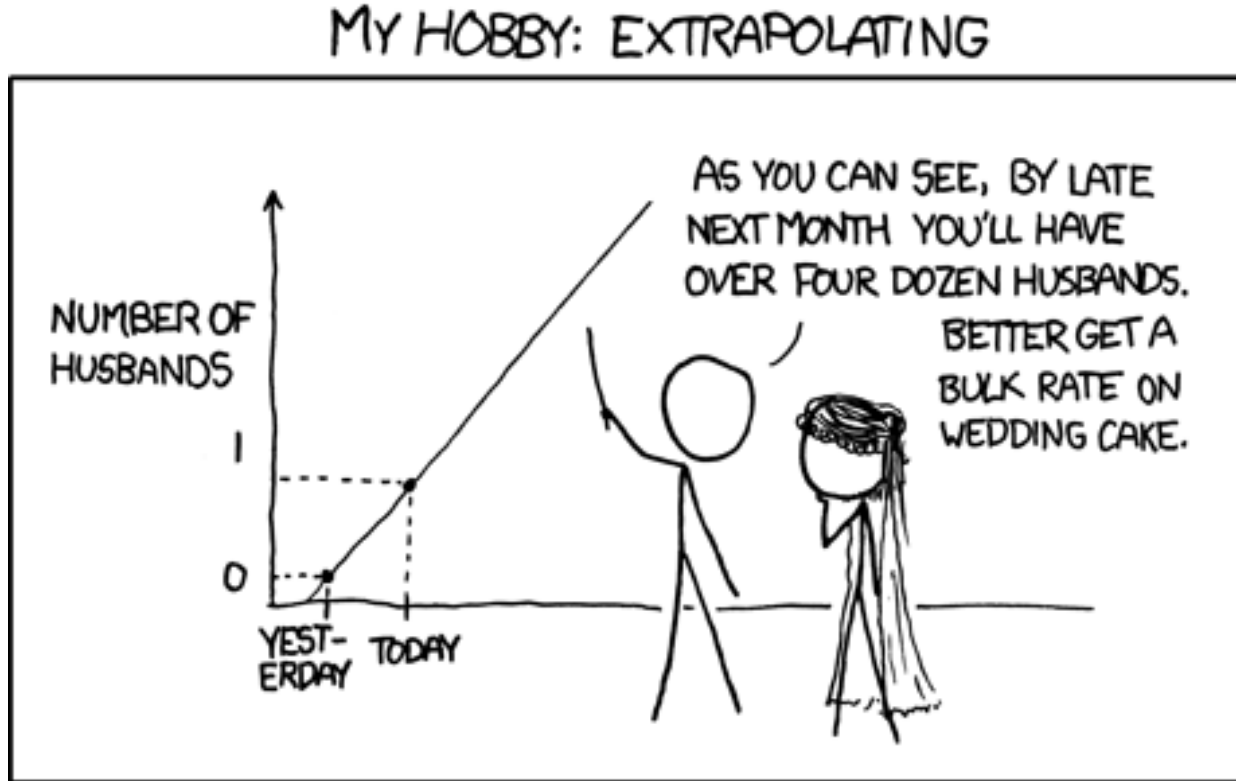


Random Batch approach (Bayesian)

Allows to fit non-linear models on long-term data (difficult with frequentist approaches)

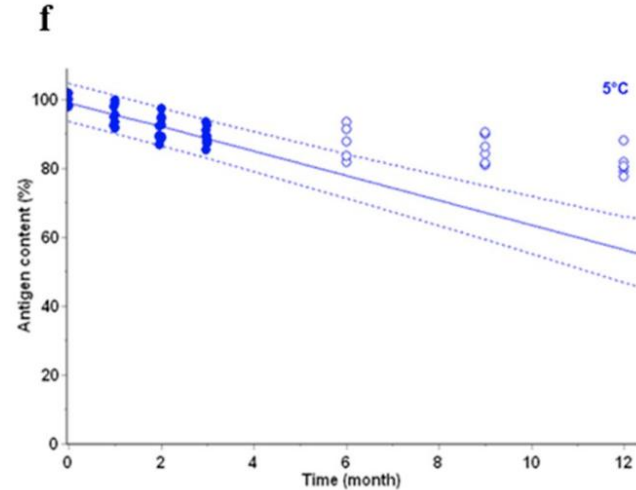
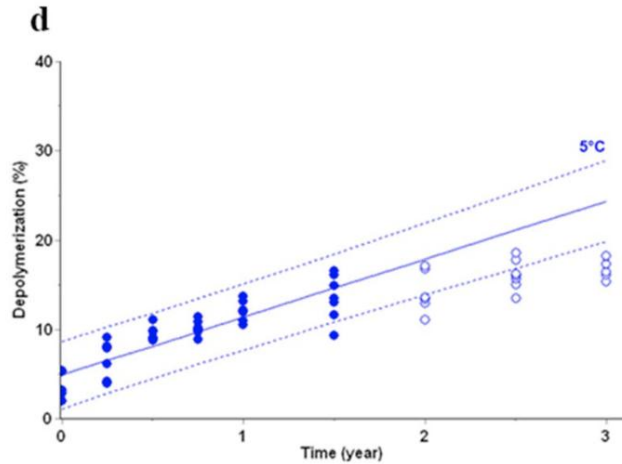


So far, we just extrapolated by extending available long-term data...



Is it possible to **really** predict?

- Hierarchical models requires to have **enough** batches stored a **sufficiently long time** to get a representative idea of the vaccine SL!
- Predictions based on long-term data may fail to describe the complex stability behaviour of vaccines, which may involve complex and multi-step reactions...
- Better to respect the limitations in projection defined in the guidance!

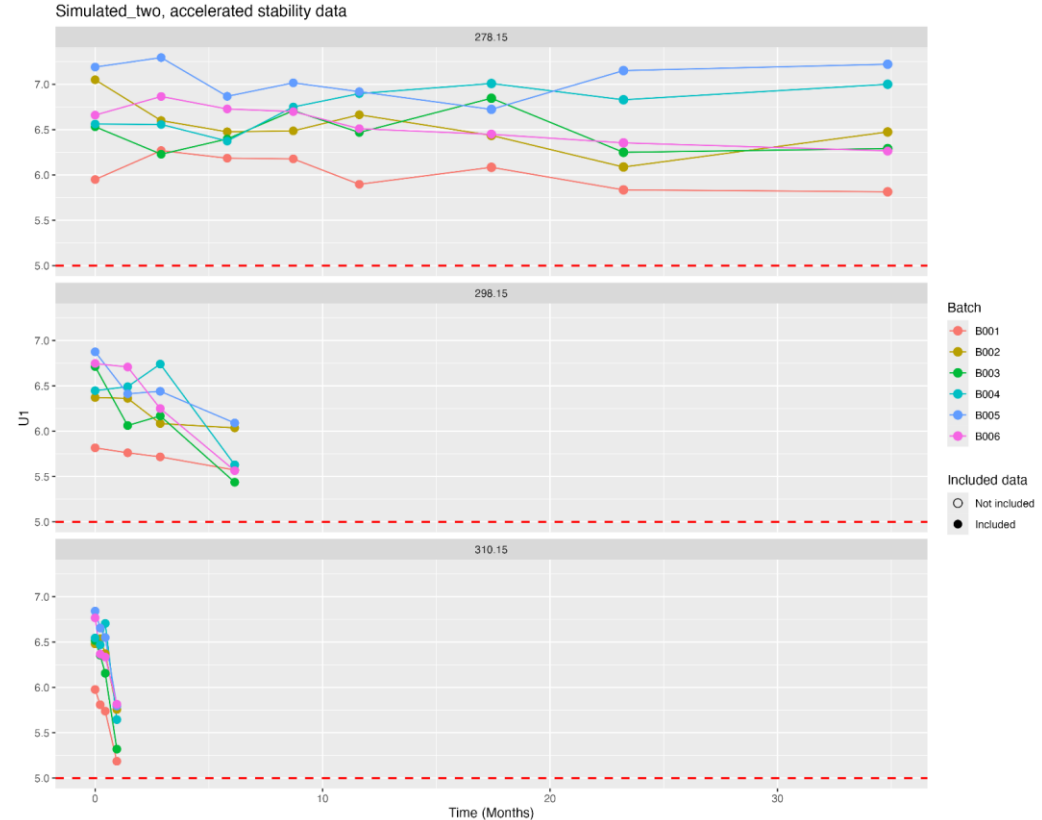


Let's consider other sources of information!

Vaccine with a linear degradation path including at higher temperatures

- 6 batches
- 3 years of data at 5 C°
- 6 months of data at 25C°
- 1 month of data at 37C°

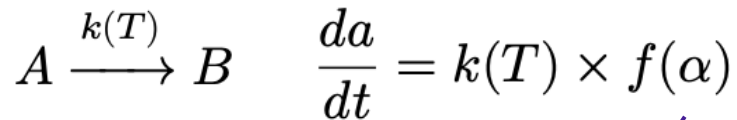
Why not including data from accelerated conditions to improve our predictions while giving early insights (ex: max 6 months of data)?



Advanced Kinetic Modelling (AKM), some theory

Fundamentals of Thermokinetics

- Chemical decomposition of a reactant A into a product B. Can also be expressed in derivative form, with
 - t , the time
 - T , the temperature i (in K)
 - α , the reaction progress
- $k(T)$, capture the influence of the temperature on the reaction rate following the Arrhenius law
- The Reaction kinetic model is the versatile part of the story



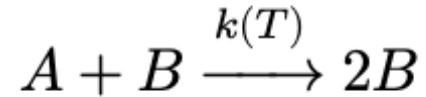
$$k(T) = A \times \exp\left(\frac{-Ea}{RT}\right)$$

$$f(\alpha) = (1 - \alpha)^n$$

$$\alpha = \frac{c_{init} - c}{c_{init} - c_{end}}$$

Autocatalytic reactions

- In many chemical reactions, the rate increases as the reaction proceeds
- As the concentration of product **B** rises, interactions between **A** and **B** become more likely, promoting further reaction
- At the start, **B** is scarce → slow reaction rate
- Once enough **B** is produced, a “**boost effect**” occurs → rapid acceleration
- As **A** is depleted, the reaction rate slows down
- This behaviour can be catch using the **Šesták-Berggren (SB) model**

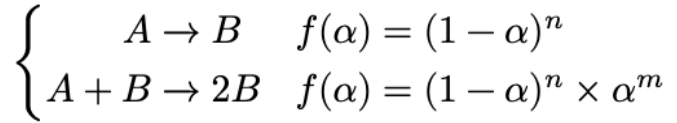


$$\frac{da}{dt} = k(T) \times f(\alpha)$$

$$f(\alpha) = (1 - \alpha)^n \times \alpha^m$$

Combined Autocatalytic-type reaction

- Sometimes, a **small amount of B is required** to start the reaction
- Without **B**, no product can form, and the **reaction cannot occur**
- **Two parallel reaction paths** to consider:
 - The first path produces initial **B**
 - Which triggers the second, **autocatalytic** path
 - A generalization that theoretically allow to **fit any reaction path** using the following (SB2):



$$\frac{da}{dt} = A \times \exp\left(\frac{-E_{a1}}{RT}\right) \times (1 - \alpha)^n +$$

$$K_{cat} \times A \times \exp\left(\frac{-E_{a2}}{RT}\right) \times (1 - \alpha)^n \times \alpha^m$$

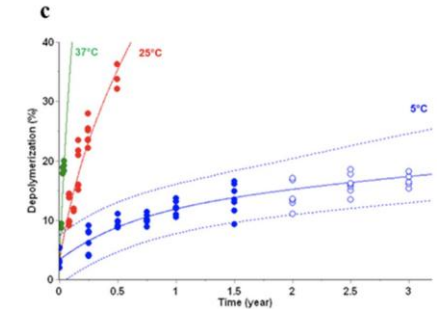
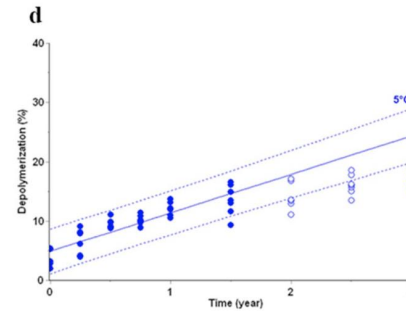
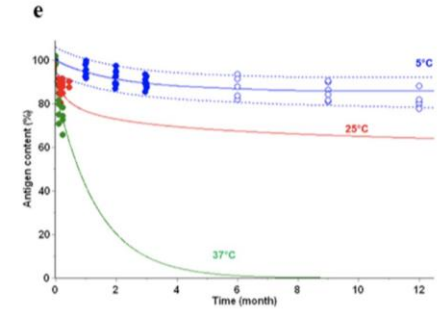
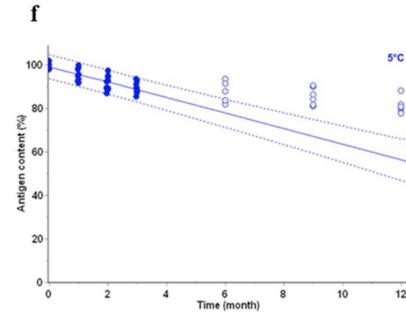
$$\frac{da}{dt} = A_1 \times \exp\left(\frac{-E_1}{RT}\right) \times (1 - \alpha)^{n1} \times \alpha^{m1} + A_2 \times \exp\left(\frac{-E_2}{RT}\right) \times (1 - \alpha)^{n2} \times \alpha^{m2}$$

Advanced Kinetic Modelling (AKM), applications

First applications: Roduit and Clénet (2014)

- This approach has been first used by **Didier Clénet** on vaccine stability data via frequentist tools
- Has been published for various vaccines (2014 -) and in the journal Nature (2023)
- Based on the resolution of the Šesták-Berggren (SB) equation via ODE solvers and optimization (AKTS)
- Confidence bounds obtained by bootstrap
- Bayesian implementation would allow **better propagation of the errors** and open the generation of probabilistics statements, very useful in stability analyses

$$\frac{d\alpha}{dt} = A_1 \exp\left(-\frac{E_{a1}}{RT}\right) (1 - \alpha)^{n_1} \alpha^{m_1} + A_2 \exp\left(-\frac{E_{a2}}{RT}\right) (1 - \alpha)^{n_2} \alpha^{m_2}$$



Recently, a nice R package developed by Francq et al.

- Frequentist / Bayesian implementation using R
- Fitted on a simplified version of the SB equation allowing to model the integrated form of the equation
- No hierarchical term included
- From Clénet et al. work, it seems the full SB equation is useful in many cases...

$$\frac{d\alpha}{dt} = A_1 \exp\left(-\frac{E_{a1}}{RT}\right) (1 - \alpha)^{n_1} \alpha^{m_1} + A_2 \exp\left(-\frac{E_{a2}}{RT}\right) (1 - \alpha)^{n_2} \alpha^{m_2}$$

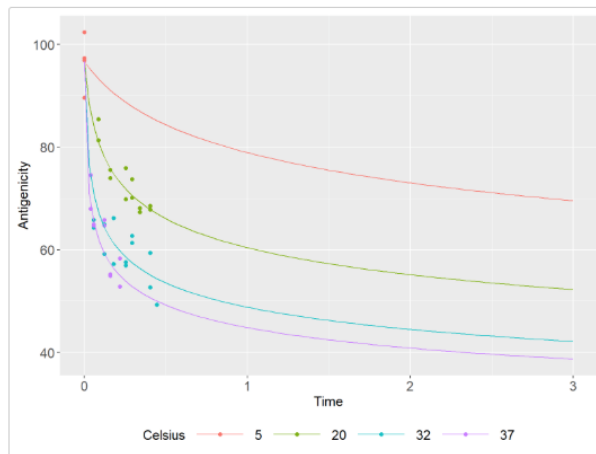
Accelerated Stability Analysis using AccelStab in R

Bernard G Francq, Ben Wells, Daniel Williams, Alex Ball

2025-03-27

```
library(AccelStab)
```

```
subdat = antigenicity[!(antigenicity$Celsius == "5" & antigenicity$time != 0),]
res = step1_down(data = subdat, y = "conc", .time = "time", C = "Celsius",
                max_time_pred = 3, temp_pred_C = 5)
step1_plot_pred(res, yname = "Antigenicity")
```



A nice Bayesian implementation by Chau et al., (2022)

- Bayesian implementation using STAN
- Fitted on a simplified version of the SB equation (Avrami-Erofeyev) and an ODE solver
- No hierarchical term included
- From Clénet et al. work, it seems the full SB equation is useful in many cases...

$$\frac{d\alpha}{dt} = A_1 \exp\left(-\frac{E_{a1}}{RT}\right) (1 - \alpha)^{n_1} \alpha^{m_1} + A_2 \exp\left(-\frac{E_{a2}}{RT}\right) (1 - \alpha)^{n_2} \alpha^{m_2}$$

AAPS PharmSciTech (2023) 24:250
<https://doi.org/10.1208/s12249-023-02695-5>

RESEARCH ARTICLE



A Bayesian Approach to Kinetic Modeling of Accelerated Stability Studies and Shelf Life Determination

Joris Chau¹ · Stan Altan² · Anneleen Burggraeve³ · Hans Coppenolle⁴ · Yimer Wasihun Kifle⁴ · Hana Prokopcova³ · Timothy Van Daele³ · Hans Sterckx⁵

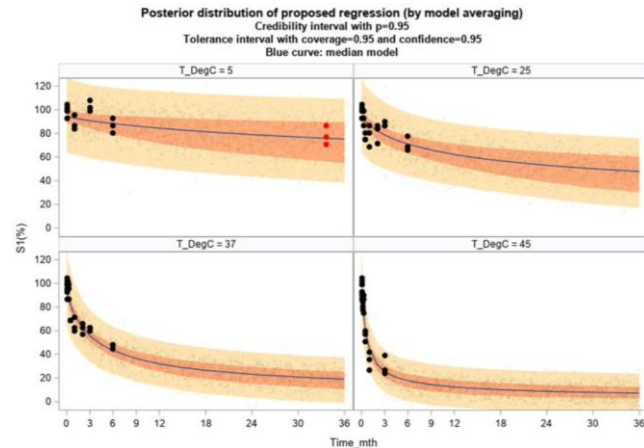
Received: 9 June 2023 / Accepted: 2 November 2023 / Published online: 30 November 2023
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Kinetic model	Differential form $f(\alpha)$	Integrated form $\alpha(t)$
Zero-order	1	kt
First-order	$1 - \alpha$	$1 - \exp(-kt)$
Second-order	$(1 - \alpha)^2$	$1 - (1 + kt)^{-1}$
Third-order	$(1 - \alpha)^3$	$1 - (1 + 2kt)^{-1/2}$
Power-law ($m = 1/2, 2, 3, 4$)	$m \cdot \alpha^{(m-1)/m}$	$(kt)^m$
Avrami-Erofeyev ($m = 2, 3, 4$)	$m(1 - \alpha)[- \ln(1 - \alpha)]^{(m-1)/m}$	$1 - e^{-(kt)^m}$
Truncated Šesták-Berggren	$\alpha^m (1 - \alpha)^n$	χ

Another nice Bayesian implementation by Van Haelst, (2022)

- Bayesian implementation using SAS PROC MCMC
- Fitted on the full version of the SB equation
- Also Scaccia et al., 2025 (Sanofi) solved a SB2 using Bayesian stats, but few details are available
- No hierarchical term included

$$\frac{d\alpha}{dt} = A_1 \exp\left(-\frac{E_{a1}}{RT}\right) (1 - \alpha)^{n_1} \alpha^{m_1} + A_2 \exp\left(-\frac{E_{a2}}{RT}\right) (1 - \alpha)^{n_2} \alpha^{m_2}$$

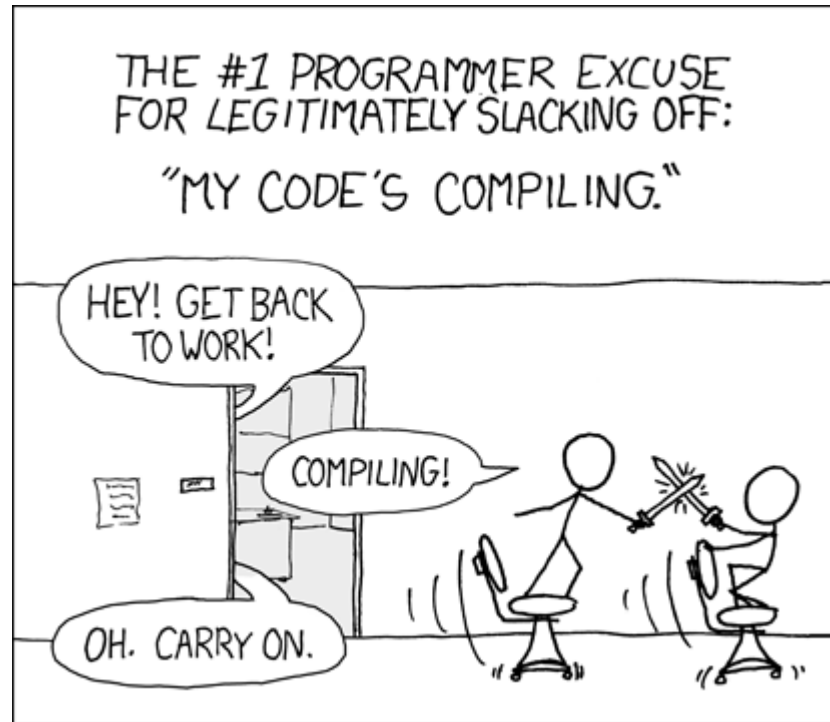


Advanced Kinetic Modelling,
bayesian implementation, a must!

Some challenges...

- From 8 to 12 parameters to estimate...
- Need to fit and to solve an ODE
- Highly correlated parameters
- Frequent chains inversion
- No 'feeling' about these parameters... Very difficult to define priors and initial values

$$\frac{d\alpha}{dt} = A_1 \exp\left(-\frac{E_{a1}}{RT}\right) (1 - \alpha)^{n_1} \alpha^{m_1} + A_2 \exp\left(-\frac{E_{a2}}{RT}\right) (1 - \alpha)^{n_2} \alpha^{m_2}$$



How to make it converge?

- Model re-parametrisation helps a lot
- ‘Good’ definition of the priors... Use literature ‘tricks’ to define n and m values (i.e., Gibson, 2021)
- Good definition of the starting values: first use a ‘Pathfinder’ approach to better identify starting values before to fit the MCMC sampler

```
mod_pathfinder <- brm(
  nlform_SB_3K,
  prior = nlprior,
  init = initss,
  data = filter(acc_data_foc, AKM_data == 1 ),
  backend = "cmdstan", algorithm = "pathfinder",
  iter = 2000, chains = 4, cores = 4)
```

- Lot of trials and errors...

```
SB1Step_b <- "vector ode_decreaseSB1Step(real t, vector y,
    real temp, real meantemp,
    real theta1, real theta2,
    real n1, real m1) {

  vector[1] dydt;

  real log_rate = log(theta1)
  - (theta2 / 8.31446261815324) * ((1 / temp) - meantemp)
  + n1 * logm(y[1])
  + m1 * log(y[1]);

  dydt[1] = exp(log_rate);
  return dydt;
}

real decreaseSB1Step(real t, real theta1, real theta2,
  real y0, real temp, real meantemp,
  real n1, real m1, real t0) {
  vector[1] y_init = [y0]';
  array[1] vector[1] y = ode_rk45_tol(ode_decreaseSB1Step, y_init, t0,
    rep_array(t, 1),
    1e-10, 1e-10, 2000,
    temp, meantemp, theta1, theta2, n1, m1);

  return y[1, 1];
}
```

```
SB2Step_w <- "
// --- helpers ---
real arrhenius(real theta, real Ea, real temp, real meantemp){
  return theta * exp((-Ea/8.31446261815324) * ((1/(temp)) - meantemp));
}

// ODE with weight w = inv_logit(wl)
vector ode_decreaseSB2Step_w(real t, vector yv, real temp, real meantemp,
  real theta1, real theta2, real theta3, real theta4,
  real n1, real m1, real n2, real m2,
  real wl) {

  vector[1] dydt;
  real y = fmin(fmax(yv[1], 1e-9), 1-1e-9); // keep y in (0,1)

  real k1 = arrhenius(theta1, theta2, temp, meantemp);
  real k2 = arrhenius(theta3, theta4, temp, meantemp);

  real comp1 = k1 * pow(1 - y, n1) * pow(y, m1);
  real comp2 = k2 * pow(1 - y, n2 + n1) * pow(y, m2 + m1);

  real w = inv_logit(wl); // in (0,1)
  dydt[1] = w * comp1 + (1 - w) * comp2;
  return dydt;
}

// integrator returning y
real decreaseSB2Step_w(real t, real theta1, real theta2, real theta3, real theta4,
  real y0, real temp, real meantemp,
  real n1, real m1, real n2, real m2,
  real wl, real t0){

  vector[1] yinit;
  yinit[1] = y0;
  array[1] vector[1] y;

  y = ode_rk45_tol(ode_decreaseSB2Step_w, yinit, t0, rep_array(t, 1),
    1e-8, 1e-8, 2000,
    temp, meantemp,
    theta1, theta2, theta3, theta4,
    n1, m1, n2, m2,
    wl);

  return y[1, 1];
};
```

Impressive results

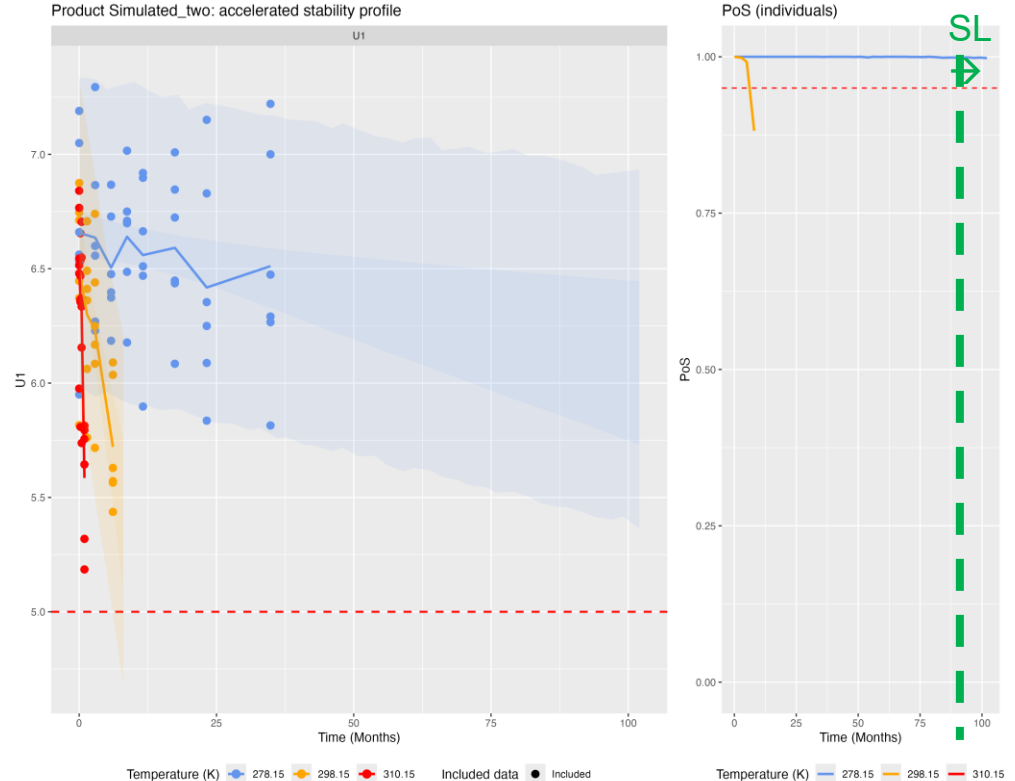
How to really extrapolate?

Is it possible to *really* predict? Implementation of AKM with Bayesian methods

- Predictions bands achieved using all available data
- AKM fitted using a Bayesian approach, ODEs and a mix of log-normal and horseshoe priors

$$\frac{d\alpha}{dt} = A_1 \cdot \exp\left(-\frac{E_{a1}}{RT}\right) \cdot (1 - \alpha)^{n_1} \cdot \alpha^{m_1}$$

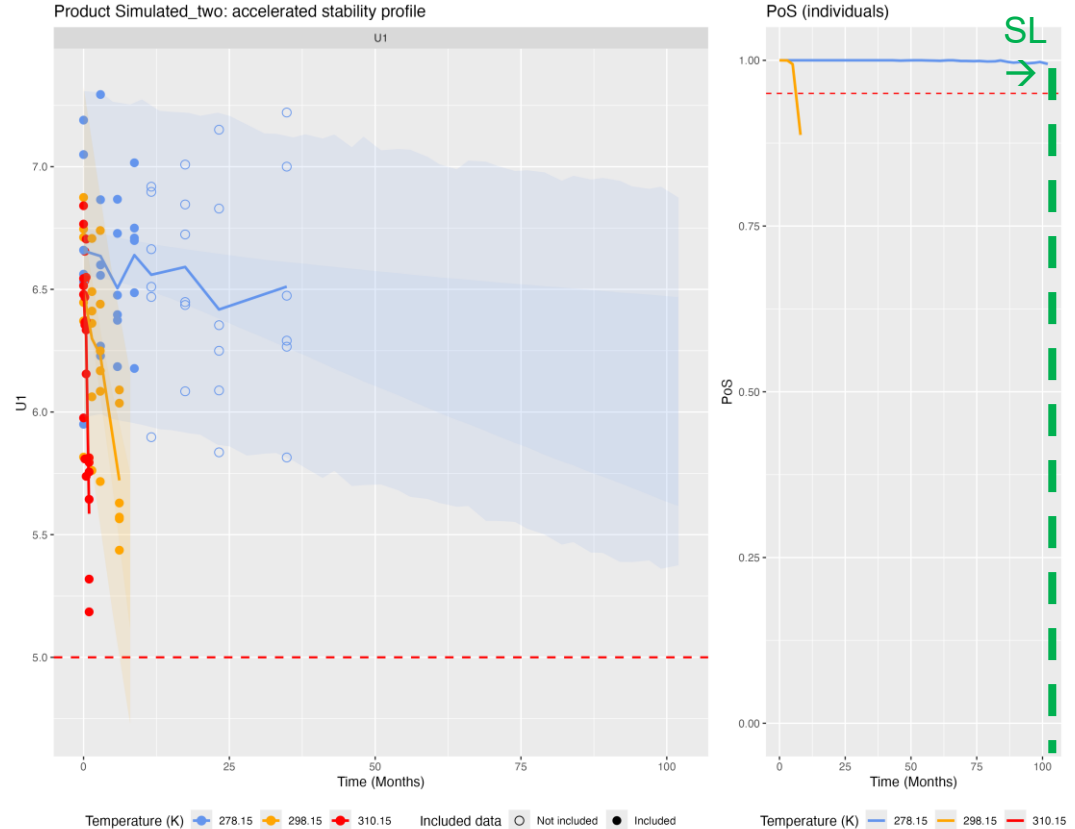
- Good agreement between projection and observations
- SL estimate based on the PoS graph (more than 100 months vs. 80 months before...)
- Hierarchical terms on A_1 and E_{a1}



How to really extrapolate?

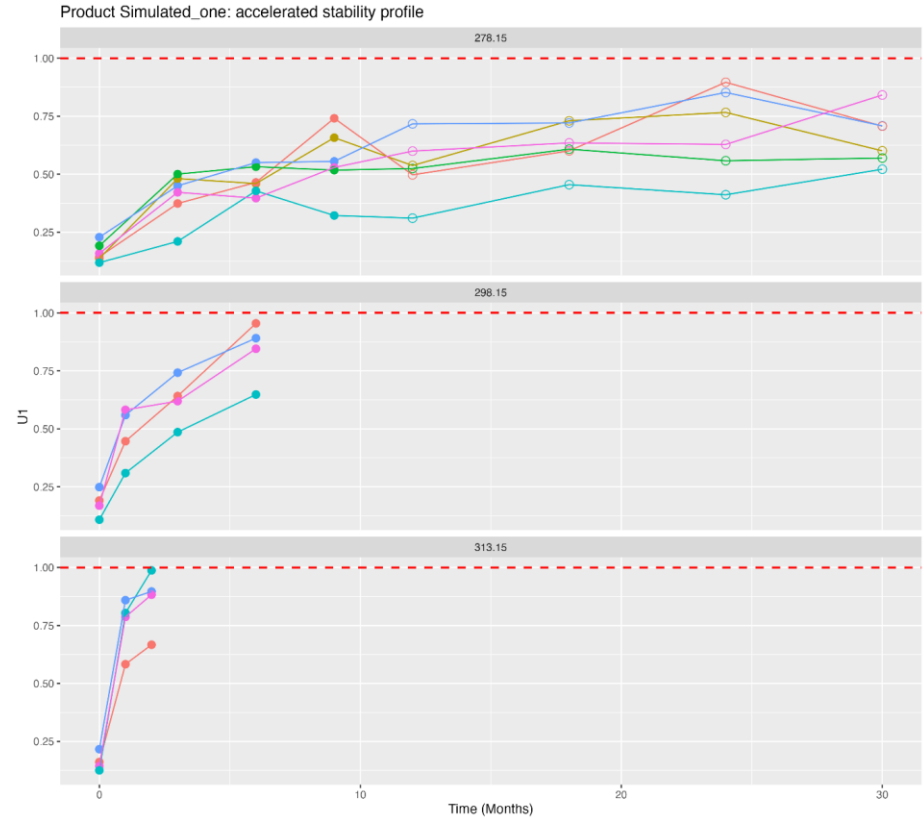
Is it possible to *really* predict? Implementation of AKM with Bayesian methods

- Predictions bands achieved using only **10 months** of data (filled circles)
- Impressive predictive capacity, the intervals are just a bit larger, underlying uncertainty of extrapolation
- Impossible if based only on the 5C data...



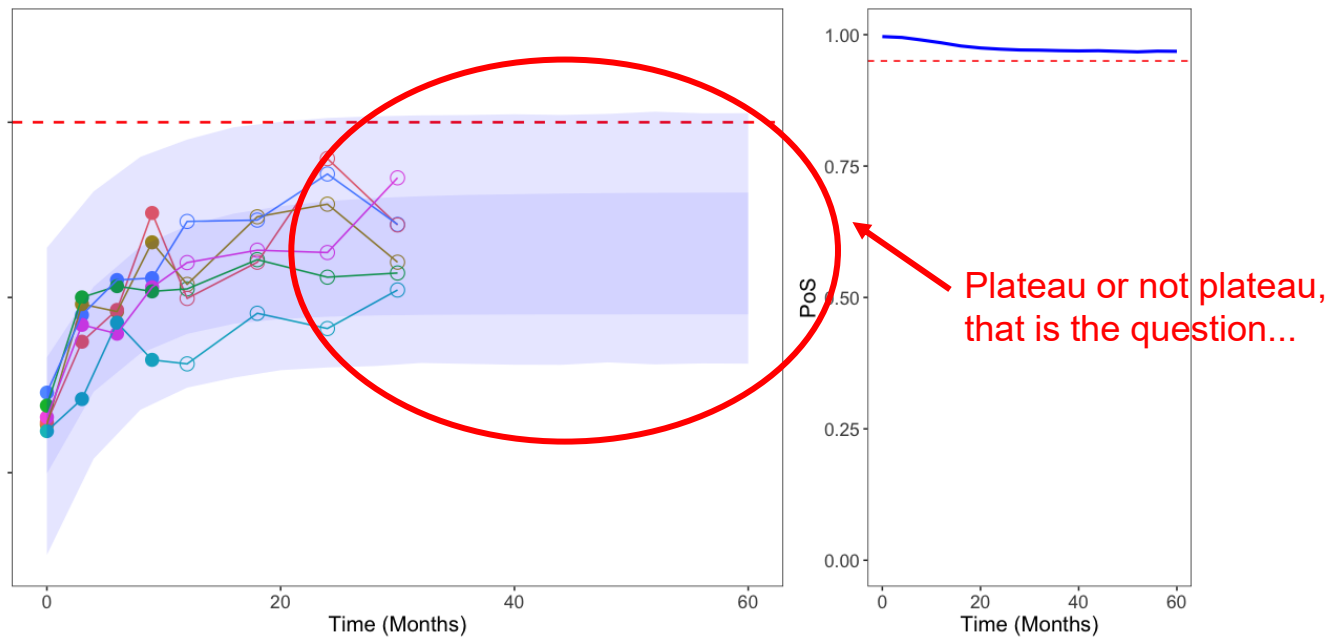
A non-linear example

- Includes 6 batches
- 30 months of data at 5 C°
- 6 months of data at 25C°
- 1 month of data at 37C°
- USL set at 1.0



A non-linear example

Predictions based on **long-term** stability data – Non-linear hierarchical model



$$y_{ijk} = a_i + s_i \times e^{r_i \times t_j} + \epsilon_{ijk}$$

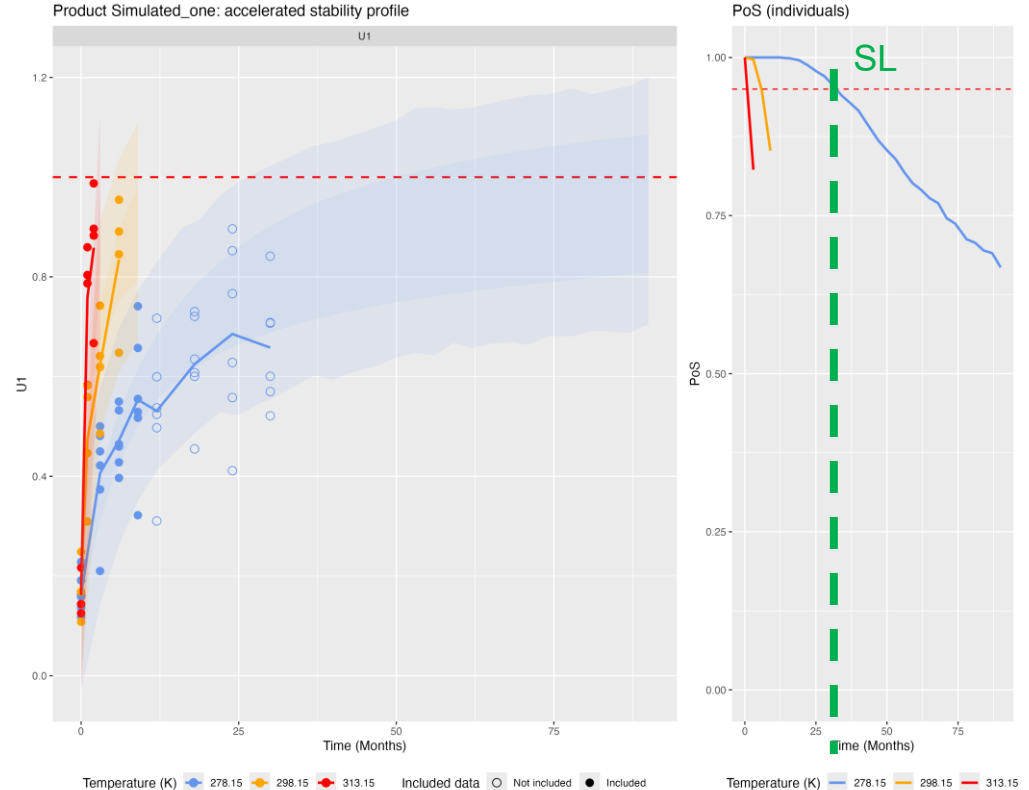
A non-linear example

Predictions based on accelerated stability data – Bayesian AKM

- Predictions bands achieved using only 10 months of data (filled points)
- AKM fitted using a Bayesian approach and ODEs
- Mix of log-normal and horseshoe priors

$$\frac{d\alpha}{dt} = A_1 \cdot \exp\left(-\frac{E_{a1}}{RT}\right) \cdot (1 - \alpha)^{n_1} \cdot a^{m_1}$$

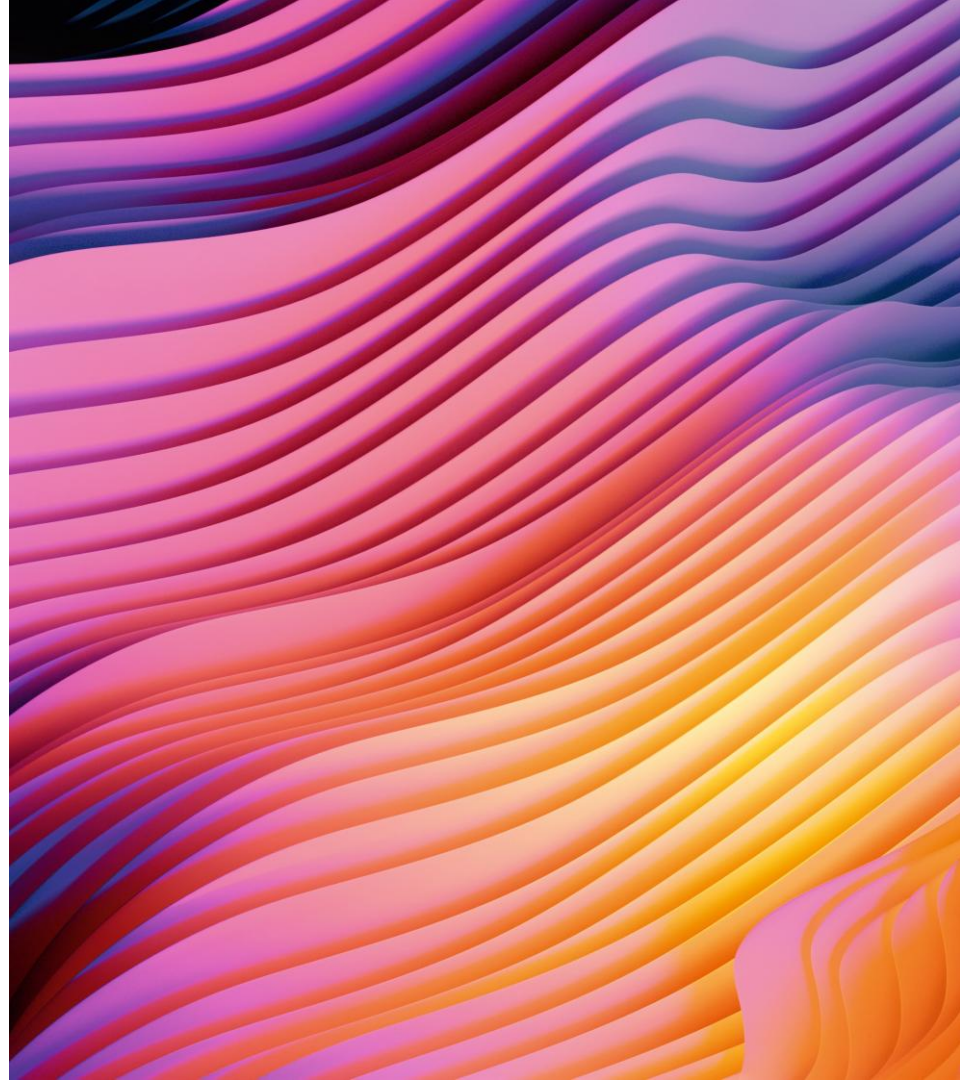
- Excellent agreement between projections and observations
- SL estimate based on the PoS graph



Next steps...

Next steps

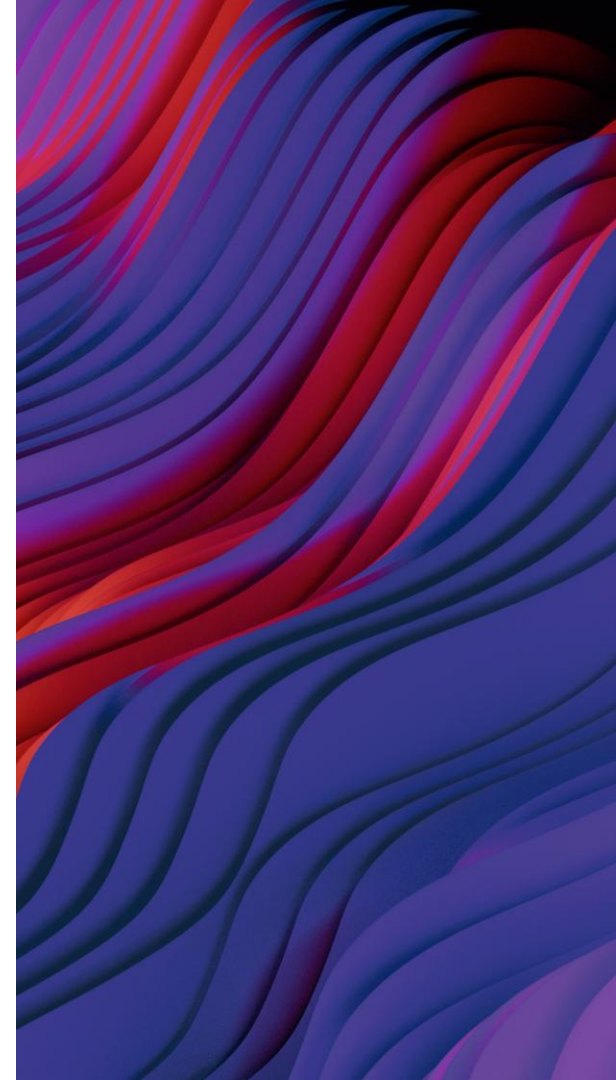
- Improve the robustness of the model fit
- Running the SB2 model remains challenging and currently incompatible with hierarchical terms
- It is not yet clear which parts of the equation would benefit most from hierarchical structure in practice
- Initiate discussion with regulators on future statistical frameworks, so far, the use of mixed models has just been cited in the most recent draft version of the ICH, there is a 20 years time lag between regulations and research ...
- All this work was carried out within the Inno4Vac consortium



Also, a big thanks to your Industrial partners from the Inno4vac consortium



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Many thanks for your
attention and your
recommendations!

Thank you धन्यवाद Děkujeme Mange
takk Vă mulțumesc Gracias Vielen
Dank شكراً Teşekkürler Děkojame jun
Спасибо Merci 谢谢 Obrigado ありがとう
ございました Cảm ơn bạn Paldies 감사합
Hartelijk dank Thank you धन्यवाद Dě
Mange takk Vă mulțumesc Gracias
Vielen Dank شكراً Teşekkürler Děkojan