Model based experimental design for accelerated small molecule stability studies

Arno Strouwen
Postdoc Statistician

Rhonda Fenwick, *Time is Now I*
Through her art, Rhonda has explored psoriasis, a chronic skin disorder she has lived with since the age of six.

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Stability studies

- Evaluate quality of drug product over time
- Determine shelf life

	Time Points (Months)				
Batch	**25C/60RH**	**30C/75RH**	**40C/75RH**	**50C**	**5C**
A	0,1,3,6,9,12,18,24	1,3,6,9,12,18,24	1,3,6	1,3	6,12,24
B	0,1,3,6,9,12,18,24	1,3,6,9,12,18,24	1,3,6	1,3	6,12,24
C	0,1,3,6,9,12,18,24	1,3,6,9,12,18,24	1,3,6	1,3	6,12,24

Accelerated Stability studies

- Store drug product at elevated conditions
  - High temperature
  - High relative humidity
- Product degrades faster
  - Model relationship between reaction rate and storage conditions
  - Use model to predict shelf life as regular storage conditions

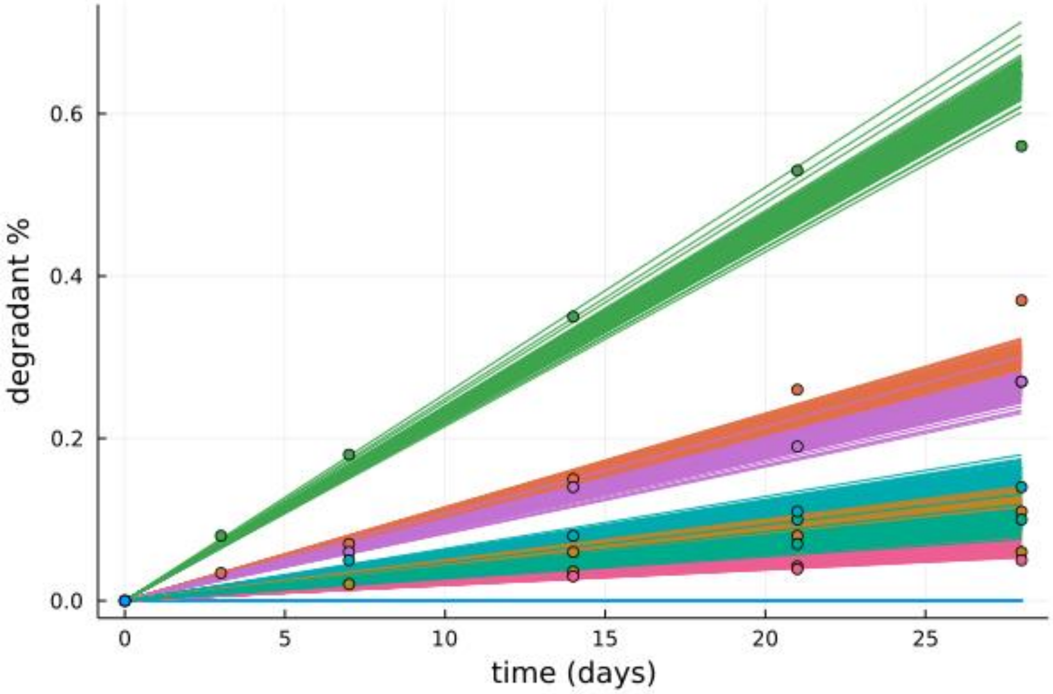
- Optimal design
  - Pick temperatures, humidities and measurement times
  - estimate the model as precisely as possible

Model

- First order kinetics
- Arrhenius

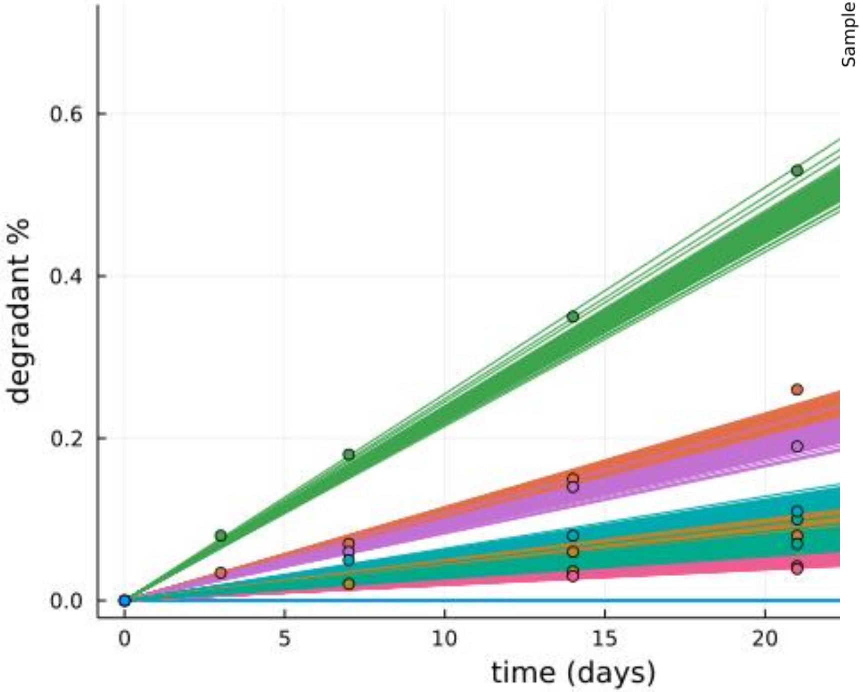
```
@model function fit_degradation(α,temps,hums,times)
    R = 8.31446261815324

    log_k~ Uniform(0.0,150)
    k = exp(log_k)
    E_T ~ Uniform(0.0,100_000.0)
    E_RH ~ Uniform(0.0,10.0)
    σ ~ Uniform(0.0,1.0)

    for j in eachindex(temps)
        T = temps[j]
        RH = hums[j]
        for i in 1:length(times[j])
            α[j][i] ~ Normal(k*exp(-E_T/(R*T) + E_RH*RH)*times[j][i], σ)
        end
    end
    return nothing
end
```

Model fit

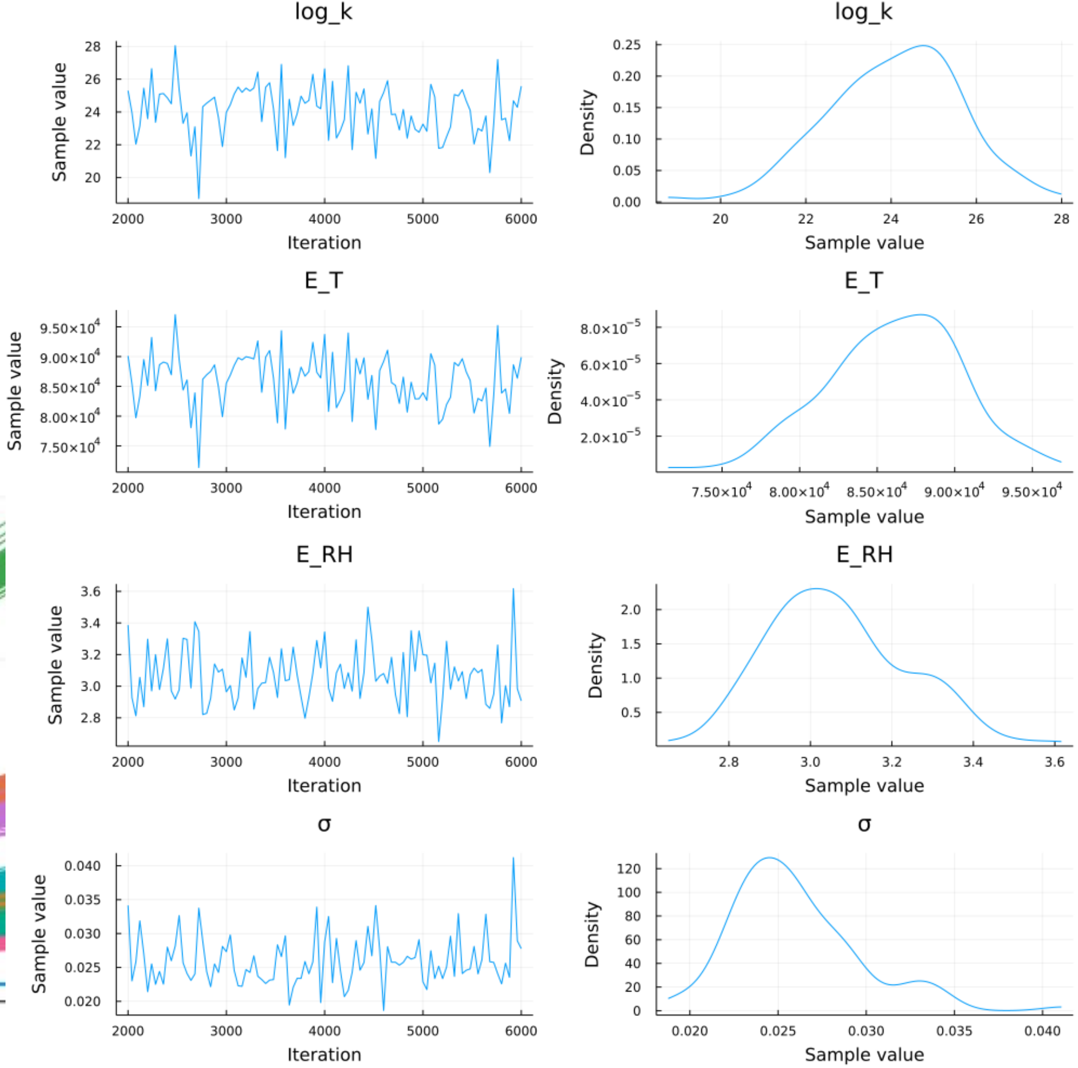


0°C, 1%
65°C, 50%
65°C, 75%
55°C, 75%
65°C, 11%
65°C, 28%
55°C, 29%

Model fit



degradant %
0.6
0.4
0.2
0.0
0
5
10
15
20
time (days)



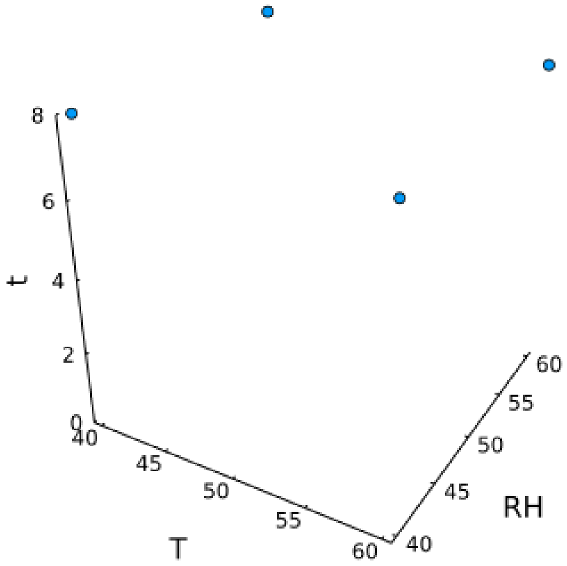
log_k
Sample value
Iteration
Density
E_T
E_RH
σ

Model based design of experiment

- Fisher information matrix
  - Related to inverse of covariance matrix of model parameter estimates
  - Determinant of FIM related to hyper-volume of covariance matrix
  - $FIM(\theta, x) = \sum_{i=1}^{n} \frac{\partial y(\theta,x)_i'}{\partial \theta} \Sigma^{-1} \frac{\partial y(\theta,x)_i}{\partial \theta}$
  - Informally: data must be sensitive to the model parameter values
- But FIM depends on the model parameter values
  - Bayesian experimental design
  - Average out FIM over prior distribution

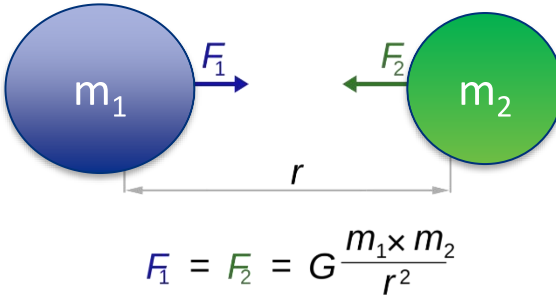
Model based experimental design

Each dot repeated 4 times

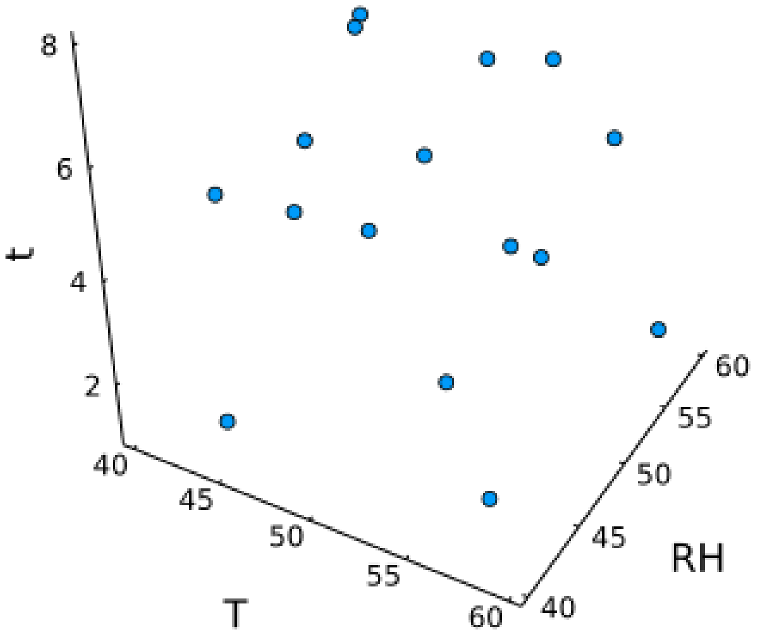


Space filling designs

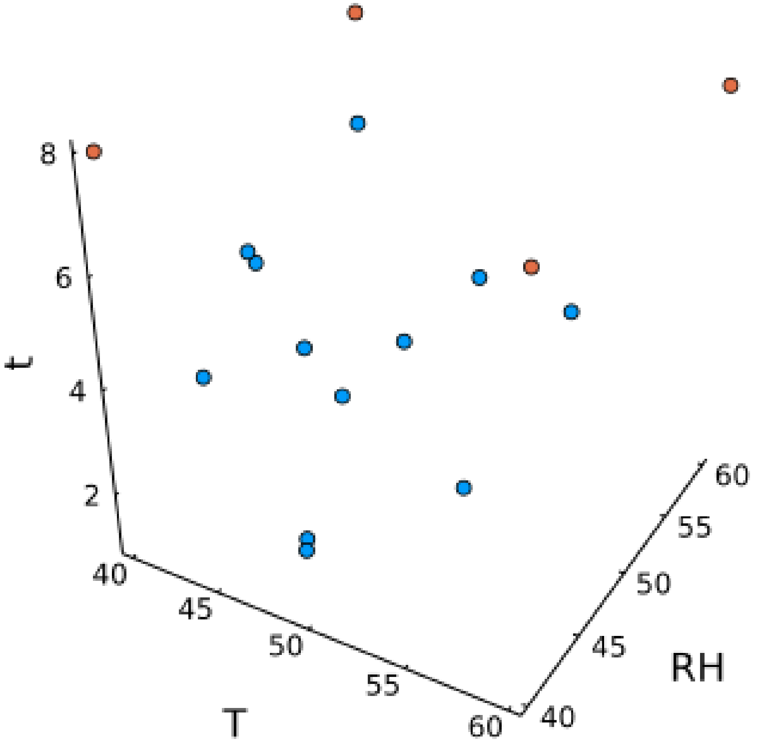
- Model free experimental design technique
- Try to spread measurements over the design space
  - Minimize sum of forces
  - $\sum_{i=1}^{N}\sum_{j=i+1}^{N}\frac{1}{r_{i,j}^2}$
- Often only a subset of factors is important
  - Do not only fill up entire design space
  - Also fill up all possible projections (MaxPro; Joseph et al 2022)
    - (T,RH,t) ; (T,RH) ; (T,t) ; (RH,t) ; (T) ; (RH) ; (t)
  - $\frac{1}{\binom{n}{2}}\sum_{i=1}^{N}\sum_{\substack{j=1 \\ j\neq i}}^{N}\frac{1}{\prod_{l=1}^{p}\left(x_{il}-x_{jl}\right)^2}$



Space filling designs



Combination Model based + Space filling



Rhonda Fenwick, *Time is Now I*
Through her art, Rhonda has explored psoriasis, a chronic skin disorder she has lived with since the age of six.

contact@arnostrouwen.com

21st October 2022