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INRA
SCIENCE & IMPACT

META- ANALYSIS FOR GROWTH AND SURVIVAL DATA

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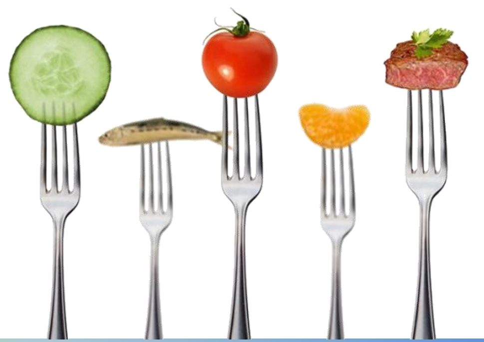
FoodMicro 2016



Introduction

- Meta-analysis enables to **re-analyse "existing" data**, generated previously by scientists working on a comparable subject.
- Since the data have been collected by different research teams, in different laboratories with different experimental set up, there is a **natural heterogeneity between studies**.
- The advantage of the meta-analysis is to take explicitly the heterogeneity due to the study and other co-variables (e.g. strain, media) into account; the **inter-study variation is quantified**.
- As a consequence, **meta-analysis enables to produce a more precise estimate of the effect of a particular treatment** than a statistical analysis where the data are pooled regardless their sources.

Key steps of meta-analysis

- Define the **objective of the meta-analysis**, the **scope** of the study: e.g. effect of thermal treatment on microbial behaviour, effect of storage conditions… etc
- Define the **criteria on which the studies will be collected**: microbial species, factors of variation, food matrix… etc
- Exhaustive **collection of studies** (e.g. peer-reviewed articles) according criteria
- Remove some of studies, if necessary, due to out-of-scope, methodology not sufficiently described, not enough data... etc
- Extract and **collect data** (store in a database)
- **Statistical analysis**
- **Interpretation of results**

Fixed or random effects

Fixed Effects Model

$Y_i = \theta + e_i$,

$e_i \sim N(0, V)$.

Random Effects Model

$Y_{ij} = \theta + \theta_j + e_{ij}$,

$\theta_j \sim N(0, \tau^2)$,
$e_{ij} \sim N(0, V)$

Study effect

The Fixed Effects **model** is a description of the studies (whole population)

The Random Effects **model** regards the studies as a sample of a larger universe of studies.

The Random Effects **model** can be used to infer what would likely happen if a new study were performed, the Fixed Effects **model** cannot (Kovalchik, 2013)

Mixed effect model: combined random and fixed effects in a model

Meta-Regression

Mixed Effects Model with a regression: **Meta-Regression**

$Y_{ij} = \theta + \boldsymbol{\beta}.\mathbf{x}_i + \theta_j + e_{ij}$,

$\theta_j \sim N(0, \tau^2)$,
$e_{ij} \sim N(0, V)$.

Study effect

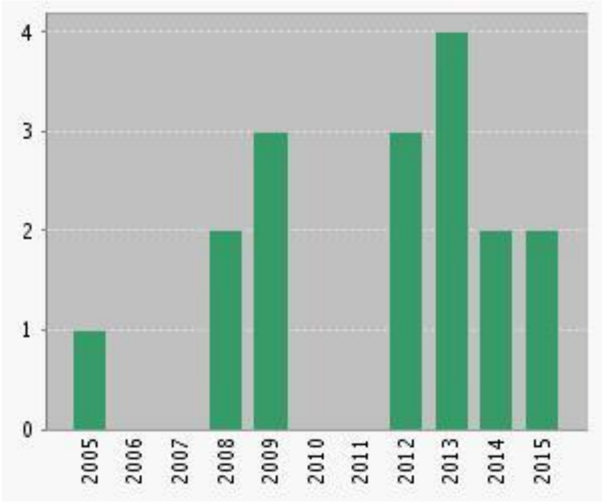
$\mathbf{X}_i$: Study-level covariates

Y_{ij} and X_i in growth
Y_{ij}: growth rate, lag time, time to achieve a microbial level
- Xi: storage temperature, pH, salt content → Quantitative factors
- Xi: food matrix, microbial species, strains → Qualitative factors

Y_{ij} and X_i in survival
Y_{ij}: D-values, time to achieve a delta log
- X_i: storage temperature, pH, salt content (stressful conditions) → Quantitative
- X_i: process factors, e.g. thermal treatment T, HPP intensity → Quantitative
- X_i: food matrix, microbial species, strains → Qualitative factors

Meta-analysis applied to growth or survival

- Articles in Web of Science
- **[TITLE:** meta-analysis *AND* (growth OR survival OR inactivation OR D-values OR lag OR resistance OR assessment)] *AND* **Topic** microbiology



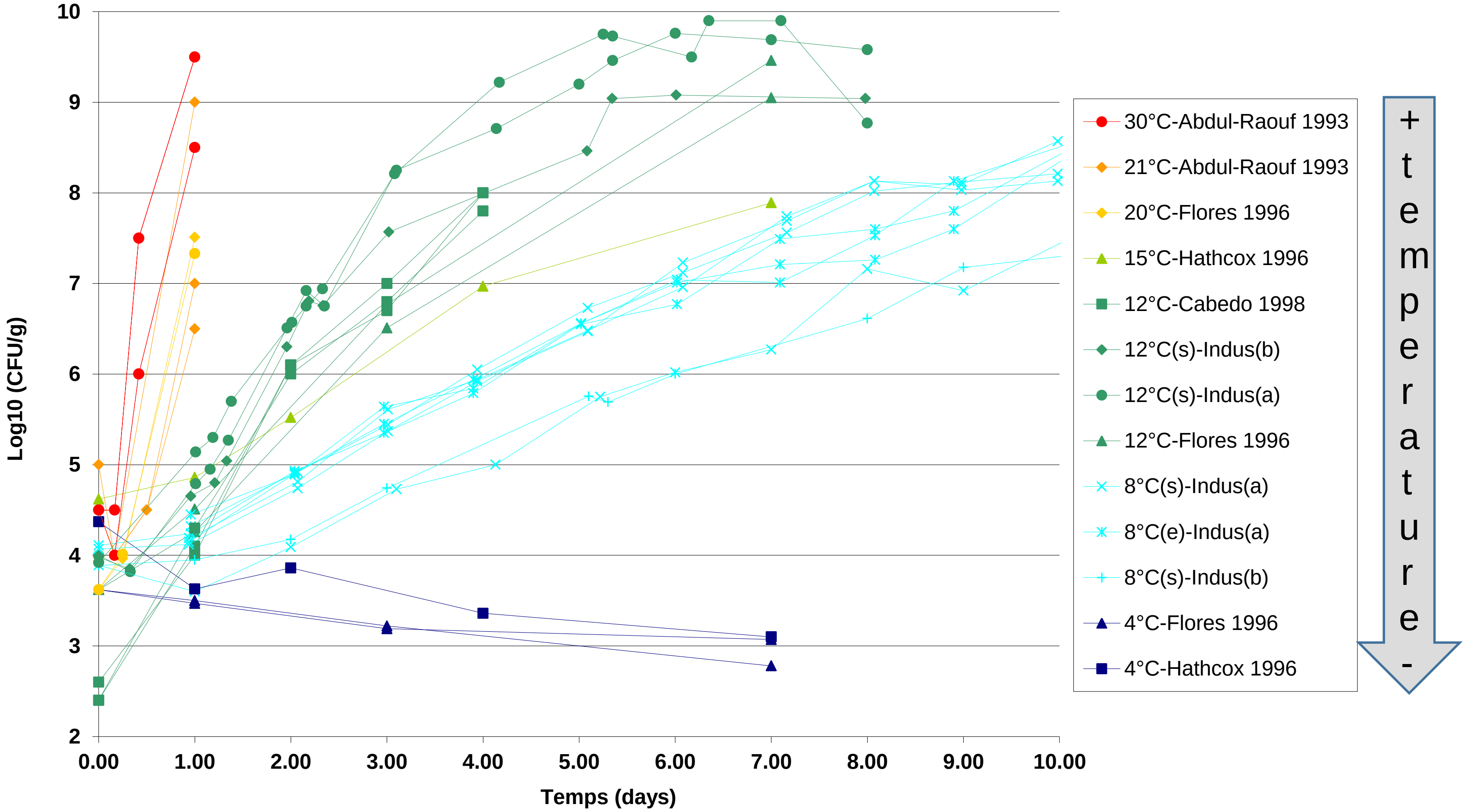
Only few articles (17):
- relatively recent in the food microbiology area
(≠ medical area)

Focus on:
- inactivation, decontamination
- antibiotic resistance (recent trend)

Examples in growth

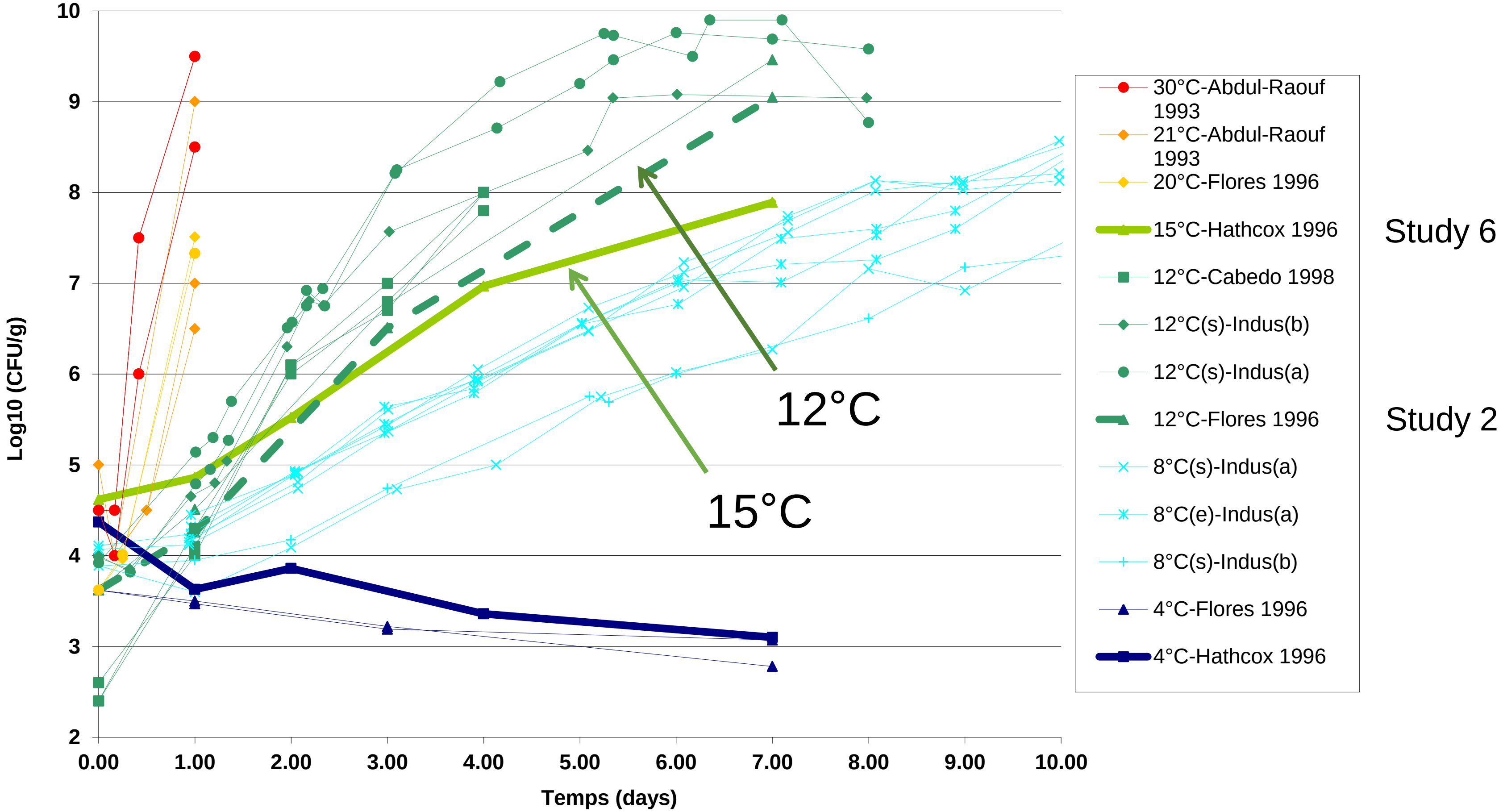
Meta-regression applied to growth

- Adapted from Vialette et al. Risk Anal. 2005, Vol 25, pp 75-83.



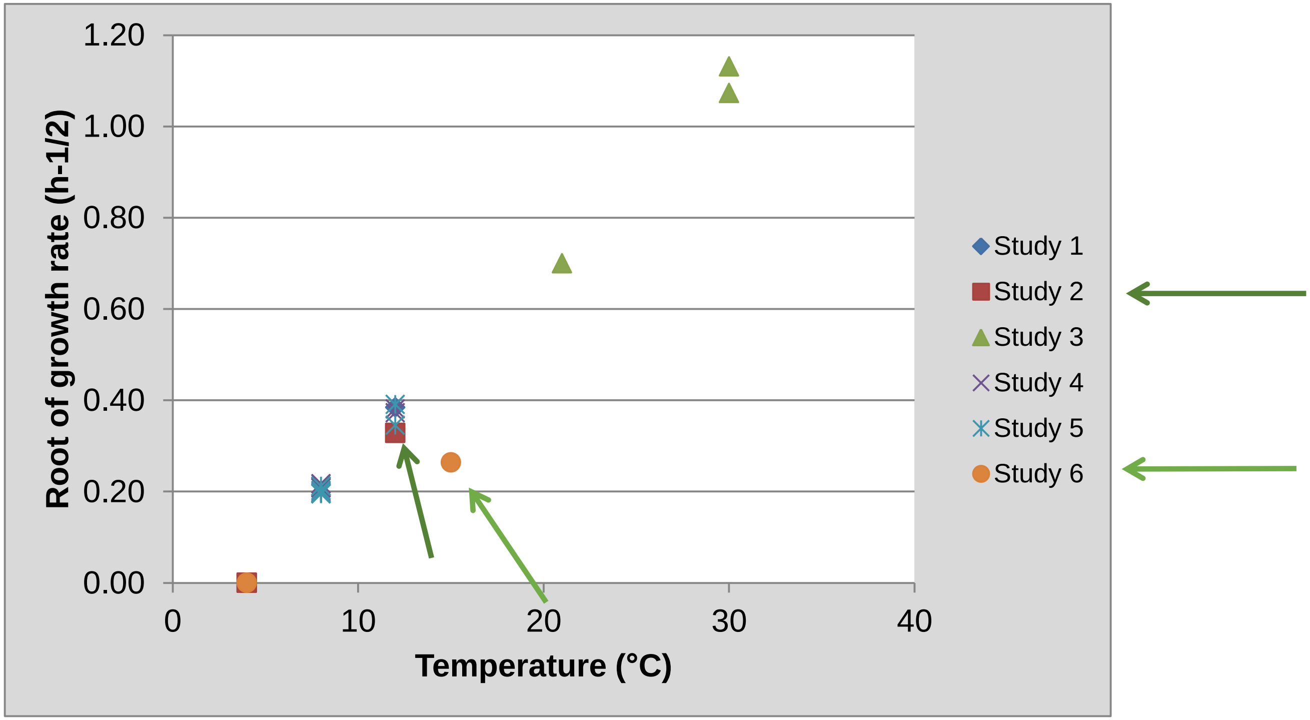
Meta-regression applied to growth

- Adapted from Vialette et al. Risk Anal. 2005, Vol 25, pp 75-83.



Meta-regression applied to growth

- Growth rates vs temperature, per study



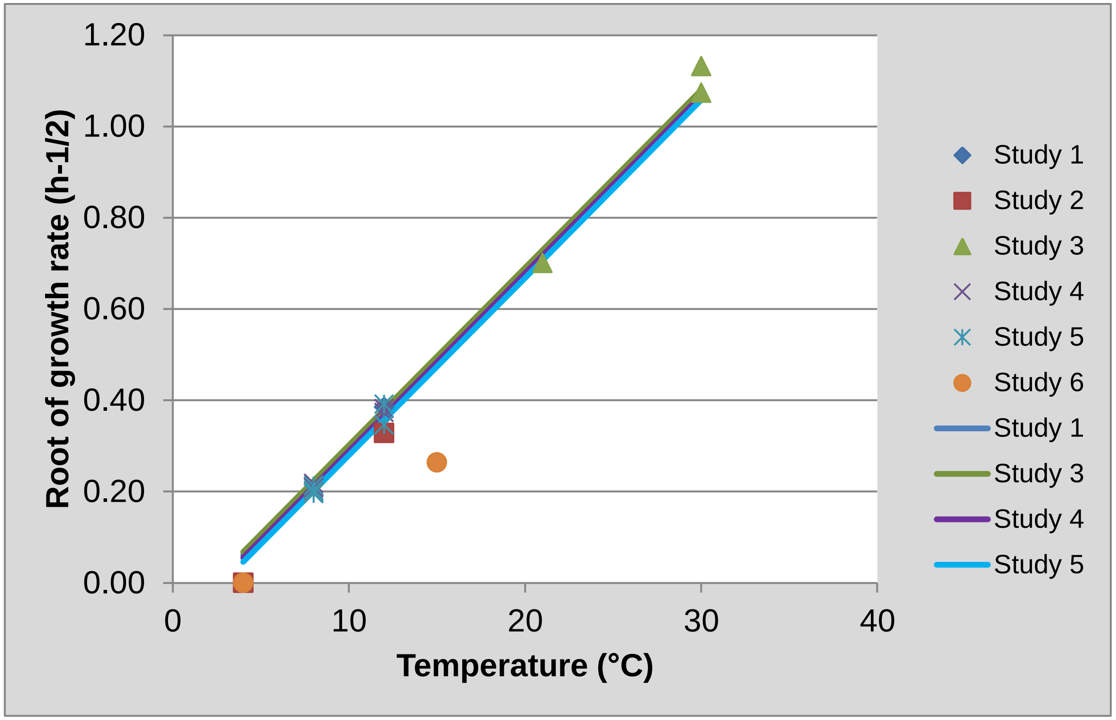
$$\sqrt{\mu_{ij}} = \sqrt{\mu'_{opt}} \times \sqrt{\gamma(T)_i} + a_j + \varepsilon_{ij}$$

Study effect

j: study, i: data

Meta-regression applied to growth

- Growth rates vs temperature, per study: meta-regression



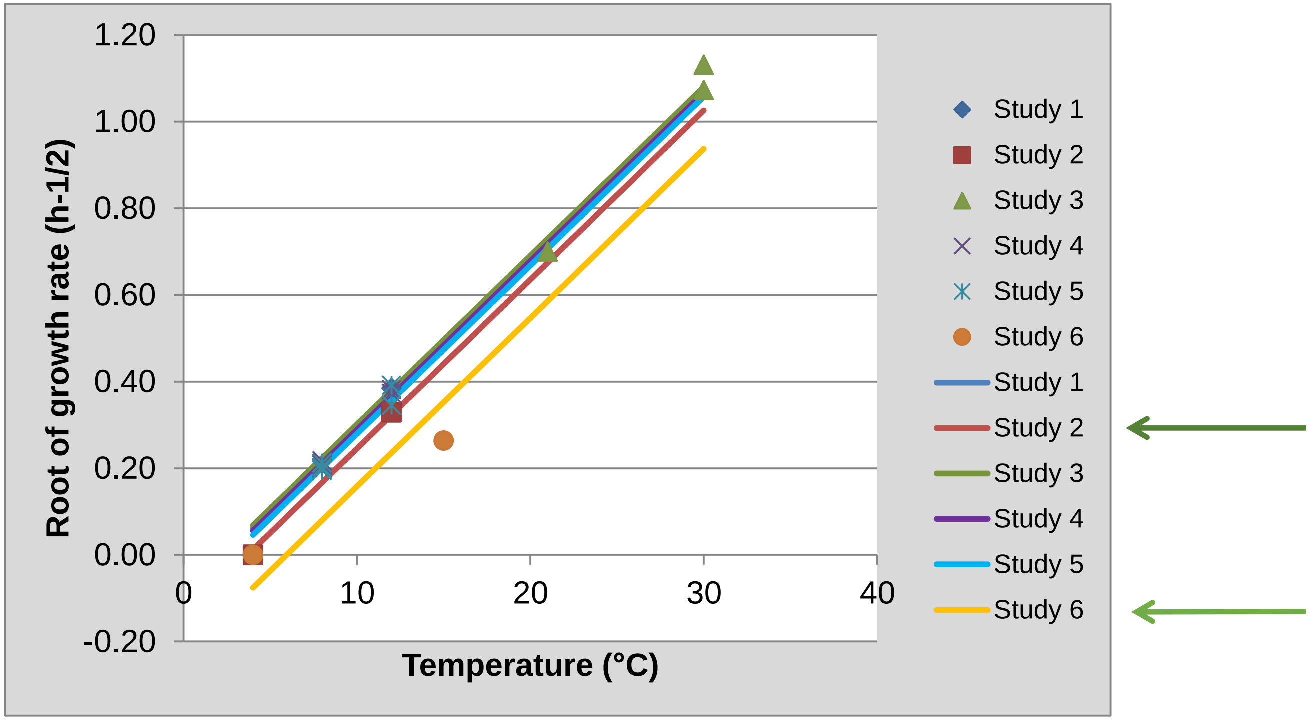
$$\sqrt{\mu_{ij}} = \sqrt{\mu'_{opt}} \times \sqrt{\gamma(T)_i} + a_j + \varepsilon_{ij}$$

Study effect

j: study, i: data

Meta-regression applied to growth

- Growth rates vs temperature, per study: <u>meta-regression</u>



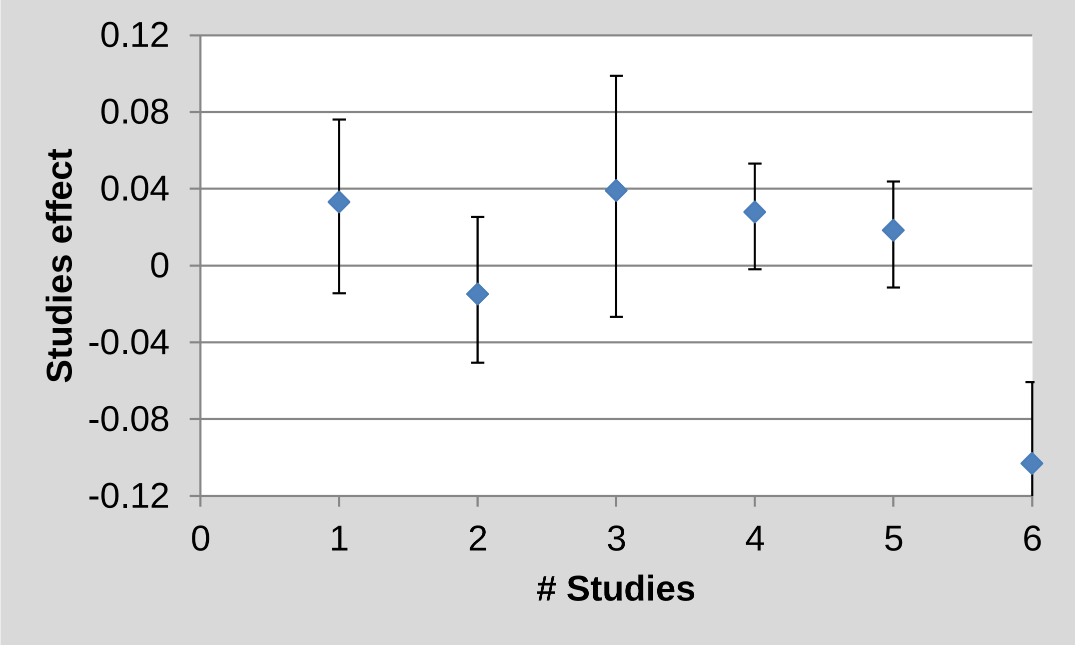
$$\sqrt{\mu_{ij}} = \sqrt{\mu'_{opt}} \times \sqrt{\gamma(T)_i} + a_j + \varepsilon_{ij}$$

Study effect

j: study, i: data

Meta-regression applied to growth

- Growth rates vs temperature, per study: meta-regression



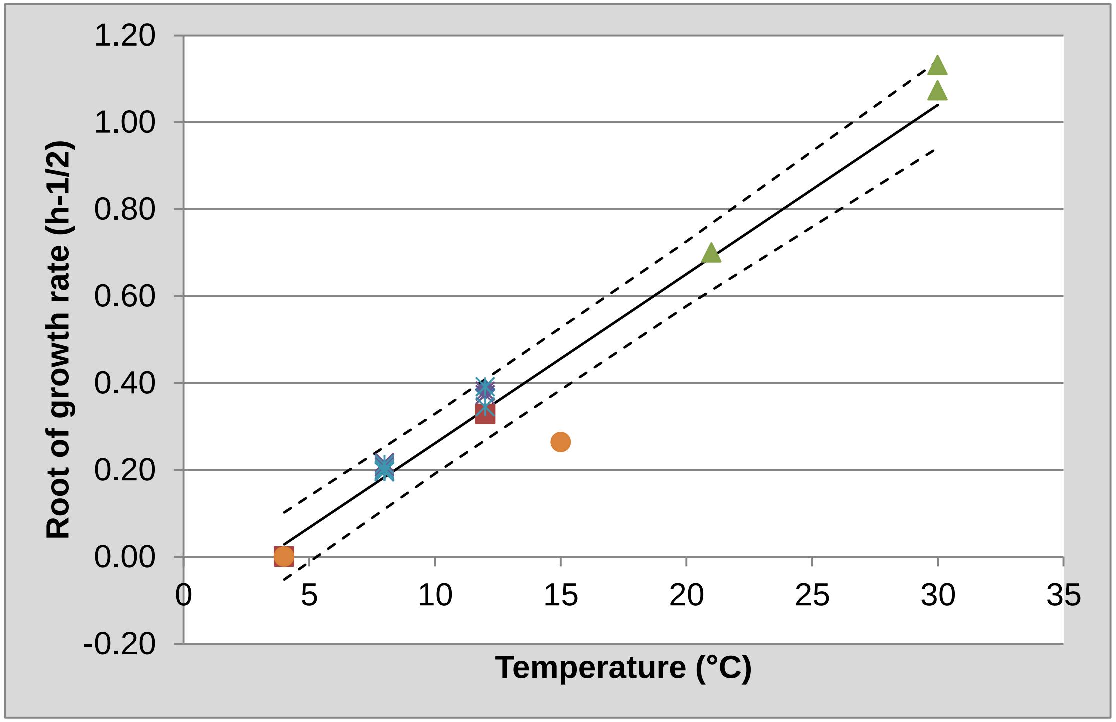
$$\sqrt{\mu_{ij}} = \sqrt{\mu'_{opt}} \times \sqrt{\gamma(T)_i} + a_j + \varepsilon_{ij}$$

Study effect

j: study, i: data

Meta-regression applied to growth

- Growth rates vs temperature, average effect: meta-regression



$$\sqrt{\mu_{ij}} = \sqrt{\mu'_{opt}} \times \sqrt{\gamma(T)_i} + a_j + \varepsilon_{ij}$$

j: study, i: data

$\sum a_j = 0$

Random effects

Random Effects Model

$Y_{ij} = \theta + \theta_j + e_{ij}$,

$\theta_j \sim N(0, \tau^2)$,
$e_{ij} \sim N(0, V)$

Co-variates

The Random Effects model regards the co-variates as <u>a sample</u> of a larger universe of co-variates.

Not only "**studies**" should be considered in the model with a random effect. Very often:

Random effect for:

- **strains**
- **food matrix and/or medium**

Fixed effect:

- Species

Choice of random / fixed depends on i) objective of the meta-analysis and ii) process of gathering data

Mixed effect model: combined random and fixed effects in a model

Examples in inactivation

Meta-regression applied to inactivation

- Ex. adapted from Diao et al. Int J Food Microbiol 174 (2014) 23–30

Objective: thermal treatment effect on inactivation of *C. botulinum* and surrogate

→ **D-values, proteolytic *C. botulinum* and *C. sporogenes* PA 3679**

911 data collected from 38 different studies, 2 species, 11 strains of *C. botulinum*

$Yij = \theta + \boldsymbol{\beta}.\mathbf{x}i + \theta j + eij$

θj : $\alpha_{study} + \beta_{strain(species)} + \delta_{medium} + \eta_{pH}$

$\boldsymbol{\beta}.\mathbf{x}i$: effect of temperature (Z-values) depends on the species

Random effect of study, strain and medium

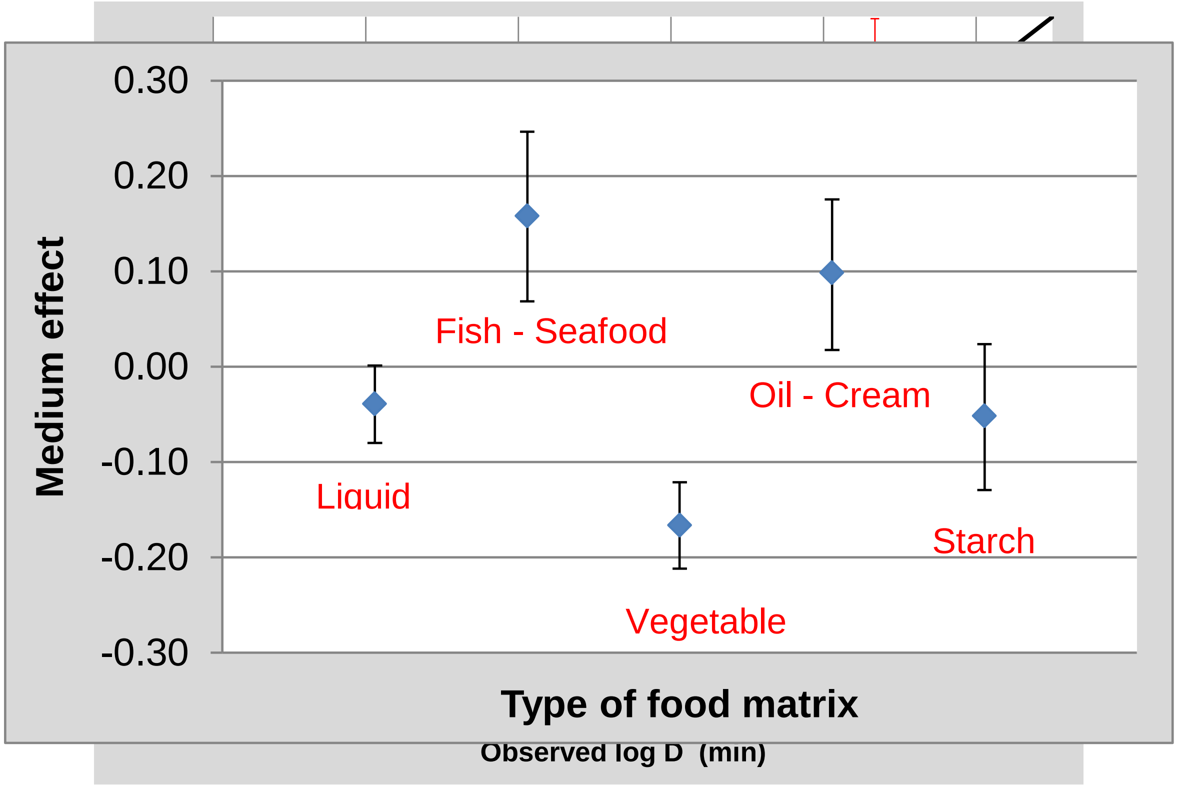
Fixed effect of pH

Hypothesis: $eij \sim N(0, V)$, V identical among the two species

→ **Hierarchical mixed effect model**

Meta-regression applied to inactivation

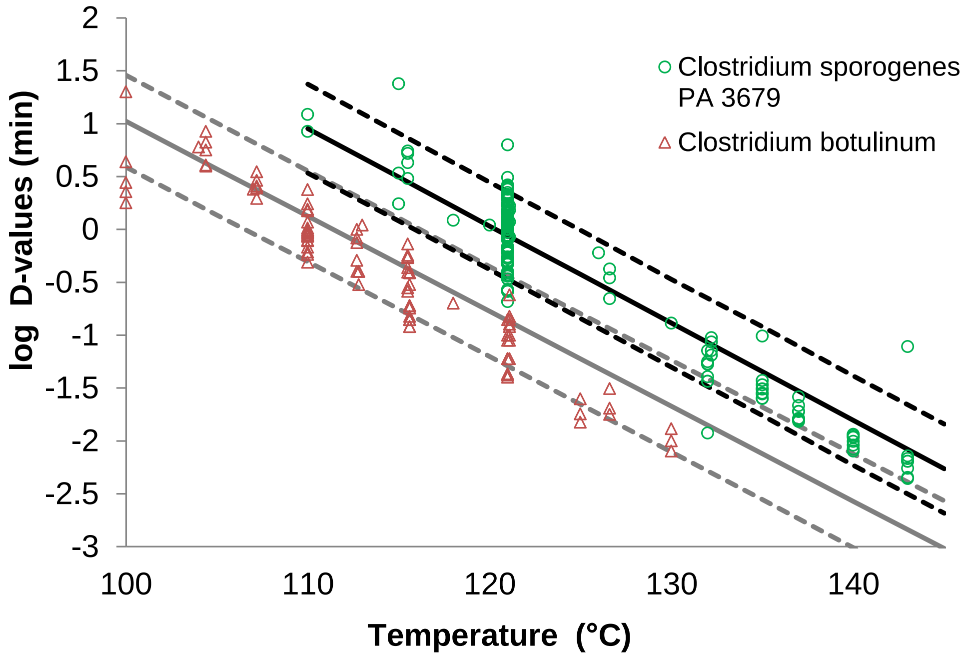
- Adapted from Diao et al. Int J Food Microbiol 174 (2014) 23–30



Medium in which *C. botulinum* was inactivated

Meta-regression applied to inactivation

- Adapted from Diao et al. Int J Food Microbiol 174 (2014) 23–30



Inactivation in Vegetable

$$\log D_{ave} = \; Log\, D^* + \alpha_{study} + \beta_{strain(species)} + \delta_{medium} + \eta_{pH}$$

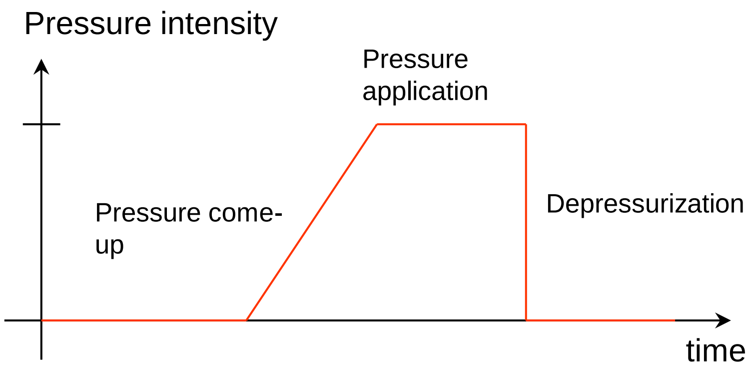
Slope (Z) depends on the species

Example in HPP inactivation

Meta-regression applied to inactivation

Many factors might influence *microbial* inactivation:

- Depending on the process application
  - Kinetics of pressurization
  - Treatment duration
  - Pressure intensity
  - Temperature (cold, mild)



- Depending on the product itself
  - Quantity of fat, pH, water activity, chemical composition

- Depending on the microorganism
  - Species, strains…
  - Physiological state

- Depending on microorganism / product (contamination route)
  - Inoculum

Meta-regression applied to inactivation

- **High Pressure Processing**

Response (Y_{ij}): Time to obtain 3 log reduction

- **Focus on three main foodborne pathogens :**
  Listeria monocytogenes, Salmonella* and *Staphylococcus aureus

- Objective : To identify which factors influence *L. mono*, Salmonella, *S. aureus* inactivation

- **54 studies, 248 data**

Meta-regression applied to inactivation

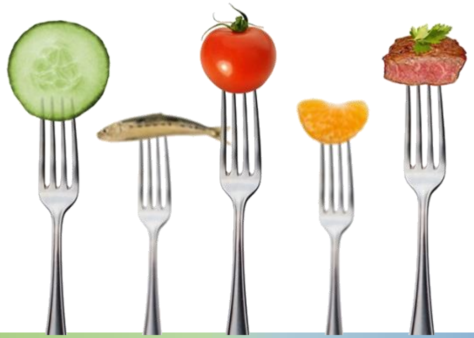
Hierarchical mixed effect model

Response (Yij): Time to obtain 3 log reduction:

- Depending on the process application
  - Kinetics of pressurization X
  - Pressure intensity ✓
  - Temperature (cold, mild) ✓
- Depending on the product itself
  - Quantity of fat, pH, water activity , chemical composition ✓
- Depending on the microorganism
  - Species, strains… ✓
  - Physiological state
- Depending on microorganism / product (contamination route)
  - Inoculum ✓

On-going work, to be published in IJFM, Guillou et al.

Conclusion



Conclusion

- Microbial growth and survival: abundant literature, many data available
- **Meta-analysis is a powerful tool to integrate data from ≠ studies**
  - Well adapted to growth, survival, inactivation → Meta-regression on µ, logD…
  - Enable to identify significant effects and to build a predictive model
- It takes **explicitly the heterogeneity due to the study into account**; the inter-study variation is quantified.
- Meta-regression is a statistical technique, based on “mixed effect model”, with or without a hierarchical structure:
  - Fixed effect factor: e.g. temperature, species…
  - **Random effect factor: e.g. studies, strains, medium….**
- Should be encouraged among the food microbiologist community: statistically robust, relatively easy to implement, **faster (less labour intensive) and cheaper than lab experiments**

Thank you!

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