Analysis of Gastric Volume Changes
Why modelling?

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MRI Gastric Emptying Data

- 12 subjects in cross-over design
- Isocaloric meal bolus: albumin (alb) or lipid (lip)

![Graph showing gastric content volume over time for 12 subjects in a cross-over design, comparing albumin (alb) and lipid (lip) treatments.]
**Definition**

\[ \text{Content} = \text{Meal} + \text{Secretion} \]
Gastric "Emptying"?

**Definition**

Content = Meal + Secretion

- Content = Meal + Secretion
- Only sees meal
- Blind to secretion
- Measures radioactivity clearance
- Curves go down: “emptying”
Gastric "Emptying"?

**Definition**

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- Content = Meal + Secretion
- Only sees meal
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- Measures radioactivity clearance
- Curves go down: “emptying”

- Content = Meal + Secretion
- Only sees content
- Cannot separate meal/secretion (?)
- Measures content clearance
- Curve can go up: “change”
Use averaged curves to qualitatively assess curve shapes.
Averaging curves

How-To
Use averaged curves to qualitatively assess curve shapes
What is wrong with error bars?

How-Not-To

Standard errors bars in time series are eye candy for the reviewer. They tell the wrong story.

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What is wrong with error bars?

Standard errors bars in time series are eye candy for the reviewer. They tell the wrong story.
Licecomb plot
Eradicate!
Capturing the essence of a time-series

A GE Curve

Time after filling (ml)
Meal volume (ml)

200
250
300
350
400
450

●
●
●
●
●
●

0 20 40 60 80 100

Not a GE Curve

Time after filling (ml)
Meal volume (ml)

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Capturing the essence of a time-series

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Capturing the essence of a time-series

A GE Curve

Not a GE Curve

\[ \approx 3 \text{ degrees of freedom} \]

\[ \text{degrees of freedom} = \# \text{ points} \]
Capturing the essence of a time-series

A GE Curve

Not a GE Curve

≈ 3 degrees of freedom
High serial correlation

degrees of freedom = # points
Low serial correlation
Standard Error

\[ SE = \frac{\text{Standard Deviation}}{\sqrt{\text{Degrees of freedom}}} \]
Standard Error

\[ SE = \frac{\text{Standard Deviation}}{\sqrt{\text{Degrees of freedom}}} \]

Only for uncorrelated data:

\[ \text{Degrees of freedom} = n - 1 \]
Capturing the essence of a time-series

Standard errors too small

Can use standard errors

3 degrees of freedom
High serial correlation

12 degrees of freedom
Low serial correlation
Take Home

With serial correlation, tests based on standard errors are wrong.
How to do statistics on time series

How-To

Use not more data from one curve than it has degrees of freedom

- Extract few (e.g. 3) uncorrelated parameters from each emptying curve
- Use standard statistics (t-test, mixed model) on the hopefully uncorrelated parameters
How to do statistics on time series

How-To

Use not more data from one curve than it has degrees of freedom

- Extract few (e.g. 3) uncorrelated parameters from each emptying curve
- Use standard statistics (t-test, mixed model) on the hopefully uncorrelated parameters

How-To

Fit a nonlinear curve with few parameters to each emptying curve
The classic: Power exponential

\[ v = v_0 \cdot e^{-\left(\frac{t}{t_{empt}}\right)^\beta} \]

Note

Power exponentials go down: Good for scintigraphic data and meal
Simple Power Exponential (Elashoff et al., 1982)

\[ v = e^{-\left(\frac{t}{t_{empt}}\right)^\beta} \]
Simple Power Exponential (Elashoff et al., 1982)

Fit Functions
- Elashoff
- PowExp

\[ v = e^{-\left(\frac{t}{t_{empt}}\right)^\beta} \]
\[ v = v_0 e^{-\left(\frac{t}{t_{empt}}\right)^\beta} \]

How-To
All points are created equal. Do fit the normalization constant \( v_0 \).
LinExp Model

Note

LinExp curves go up for $\kappa > 0$: Good for MRI and gastric content
Fit of a LinExp model to one gastric emptying curve. Quality of fit plotted for combinations of $\kappa$ and $t_{empt}$. Dark blue: best fit. Red contour: 95% confidence region.

- $\kappa$ and $t_{empt}$ compete for explaining the curve.
- Many combinations of $\kappa$ and $t_{empt}$ give good solutions.
- Curve-fitting can give a treacherously unambiguous solutions.
- Same problem for PowExp, Elashoff
Use the “best” coefficients from the fit, even these are ambiguous.

Simple

Large Variance. Often no convergence
**Ballot**

- Use the “best” coefficients from the fit, even these are ambiguous.
- Simple
- Large Variance. Often no convergence

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**Bazaar**

- Present all ambiguity plots and bargain about their weights
- Outliers are tamed by borrowing strength
- Lower variance
- Fit study. Tricks required to fit individual patients
Use the “best” coefficients from the fit, even these are ambiguous.

- Simple
- Large Variance. Often no convergence

Present all ambiguity plots and bargain about their weights

- Outliers are tamed by borrowing strength
- Lower variance

Fit study. Tricks required to fit individual patients

Nonlinear mixed model, nlme

Population fit (population pharmakodynamics)
Shrinkage: lower variance from mixed model fit

Coefficients $\kappa$ and $t_{empt}$ for $LinExp$ fit of lipid meal. Each point: one fitted emptying curve.

Red points: Each emptying curve fitted individually.
Shrinkage: lower variance from mixed model fit

Coefficients $\kappa$ and $t_{empt}$ for LinExp fit of lipid meal. Each point: one fitted emptying curve.

Red points: Each emptying curve fitted individually

Green points: Nonlinear mixed model fit
Larger overshoot for lipids!

Coefficients $\kappa$ and $t_{empt}$ for $LinExp$ fit

- **Albumin**
  - Type of fit: Balloting
  - Data points

- **Lipid**
  - Type of fit: Bazaar
  - Data points
Definition

Content = Meal + Secretion

- Only sees content
- Cannot separate meal/secretion
- Content clearance

Definition

Content = Meal + Secretion

- Sees concentration
- Can separate meal and secretion
- Meal and secretion clearance

Re-analyzed data from: Götze, Treier, Fox, Steingötter, Fried, Boesiger, Schwizer (2009): The effect of gastric secretion... Neurogastroenterol Motil
Pentagastrin-induced secretion

- pgs: pentagastrin; plc: placebo
- Pentagastrin infusion switched off after 60 min
Gastric emptying is a pharmacodynamic problem

**Definition**

Content = Meal + Secretion: $\nu_c = \nu_m + \nu_s$

\[
\frac{d\nu_m}{dt} = -k_a \cdot \nu_m
\]

- Exponential emptying (boring, but quite good fit for meal)
Gastric emptying is a pharmacodynamic problem

**Definition**

Content = Meal + Secretion: $v_c = v_m + v_s$

$$\frac{dv_m}{dt} = -k_a \cdot v_c + k_b \cdot v_s(t)$$

- Secretion inhibits meal emptying; $k_b = \text{inhibition strength}$.  
- Resulting curve is “interesting”
Gastric emptying is a pharmacodynamic problem

**Definition**

Content = Meal + Secretion: \( \nu_c = \nu_m + \nu_s \)

\[
\frac{dv_m}{dt} = -k_a \cdot \nu_c + k_b \cdot \nu_s(t)
\]

- Secretion inhibits meal emptying; \( k_b = \text{inhibition strength} \).
- Resulting curve is “interesting”
- Model is too simple: does not include pentagastrin action

**Take Home**

Learn from pharmacodynamics: Model mechanisms, not curves
Population PD fit

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In Model 3, the data of the placebo arm are fitted together with the pentagastrin branch. For the placebo arm, we assume that the infusion dose is zero; we do not have to include a separate grouping parameter (plc/pgs) for this arm, because the missing infusion is the only difference between the groups. If different dose had been used, the model would directly give a dose-response curve.

From the raw data curves in Fig. 5 on page 9, one can see that pentagastrin infusion increases emptying times. We take this into account by including an additive term $k_{sm} \cdot v_{sec}$ into equation (8) modelling gastric emptying proportional to secretion in addition to meal volume dependence. This choice is worth discussing and should be compared to alternatives.

$$\frac{dv}{dt} = -k_m \cdot v_m + k_{sm} \cdot v_{sec} \quad (8)$$

$$\frac{dP_1}{dt} = -k_a \cdot P_1 \quad \text{pgs 1st comp} \quad (9)$$

$$\frac{dP_2}{dt} = -k_a \cdot P_2 + k_a \cdot P_1 \quad \text{pgs 2nd comp} \quad (10)$$

$$\frac{dv_{sec}}{dt} = -k_b \cdot v_{sec} + k_a \cdot P_2 + k_m \cdot v_m \quad \text{Secretion} \quad (11)$$
Thanks to

- MRI technical: Reto Treier, Andreas Steingötter (ETH)
- MRI medical: Oliver Götze, Mark Fox (USZ)
- Christoffer Tornøe, author of nlmeODE (PKPD)
- Keeping it together: Werner Schwizer (USZ)
\[ \frac{dv_m}{dt} = -k_m \cdot v_m + k_{sm} \cdot v_{secr} \] meal  

\[ \frac{dP_1}{dt} = -k_a \cdot P_1 \] pgs 1st comp  

\[ \frac{dP_2}{dt} = -k_a \cdot P_2 + k_a \cdot P_1 \] pgs 2nd comp  

\[ \frac{dv_{secr}}{dt} = -k_b \cdot v_{secr} + k_a \cdot P_2 + k_{ms} \cdot v_m \]
LinExp $\kappa$ by $v_0$
LinExp $v_0$ by $t_{empt}$
PowExp \( t_{empt} \) by \( \beta \)
Serial correlation

![Graph showing auto-correlation (r) vs. time difference (min)]

- Auto-correlation (r)
  - 0.0
  - 0.2
  - 0.4
  - 0.6
  - 0.8
  - 1.0

- Time difference (min)
  - 20
  - 40
  - 60
  - 80

![Graph showing factor for effective standard error vs. time difference (min)]

- Factor for effective standard error
  - 2
  - 4
  - 6
  - 8

- Time difference (min)
  - 20
  - 40
  - 60
  - 80

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