

# Pharmacotherapeutical monitoring of patients on oral anticoagulant therapy by state space models

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Slides can be downloaded from

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# Thanks

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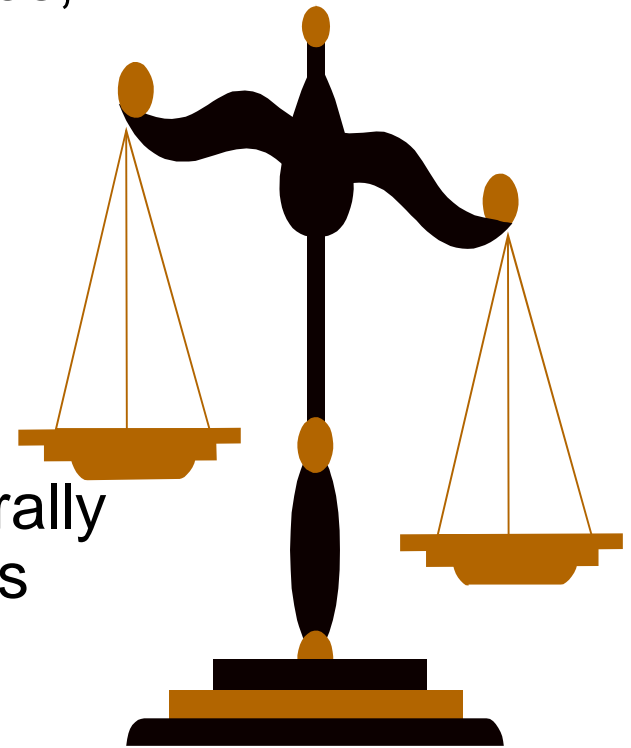
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# Outline of talk

- The medical problem
  - Oral anticoagulant therapy
  - International Normalized Ratio (INR)
  - Monitoring and quality appraisal
- Statistical methods
  - A simple mean-reversion model
  - An extended model with principles of inference
- Evaluation
  - Comparison of the two models
  - What is a good model?
  - Final thoughts / future research

# The medical problem

- Long-term oral anticoagulant therapy
  - Indications: Mechanical heart valves, atrial fibrillation, deep venous thrombosis, etc.
  - Purpose: To reduce the risk of thrombo-embolic disorders
  - A half percent of the population in the rich countries
  - The drug (e.g. warfarin) is taken orally and blocks the coagulation process
  - Adverse effects: Haemorrhage
  - Close monitoring necessary to maintain balance between risks



Monitoring and drug prescription is based on frequent measurements of *International Normalized Ratio* (INR)

$$\text{INR} := \left( \frac{\text{Patient's blood clotting time}}{\text{Mean normal blood clotting time}} \right)^{\text{ISI}}$$

- Clotting times are measured in vitro under carefully specified circumstances which constitute the *PT system*
- ISI is a standardization index which relates the current PT system to an original standard (resources depleted in 1983)

## The INR/ISI system

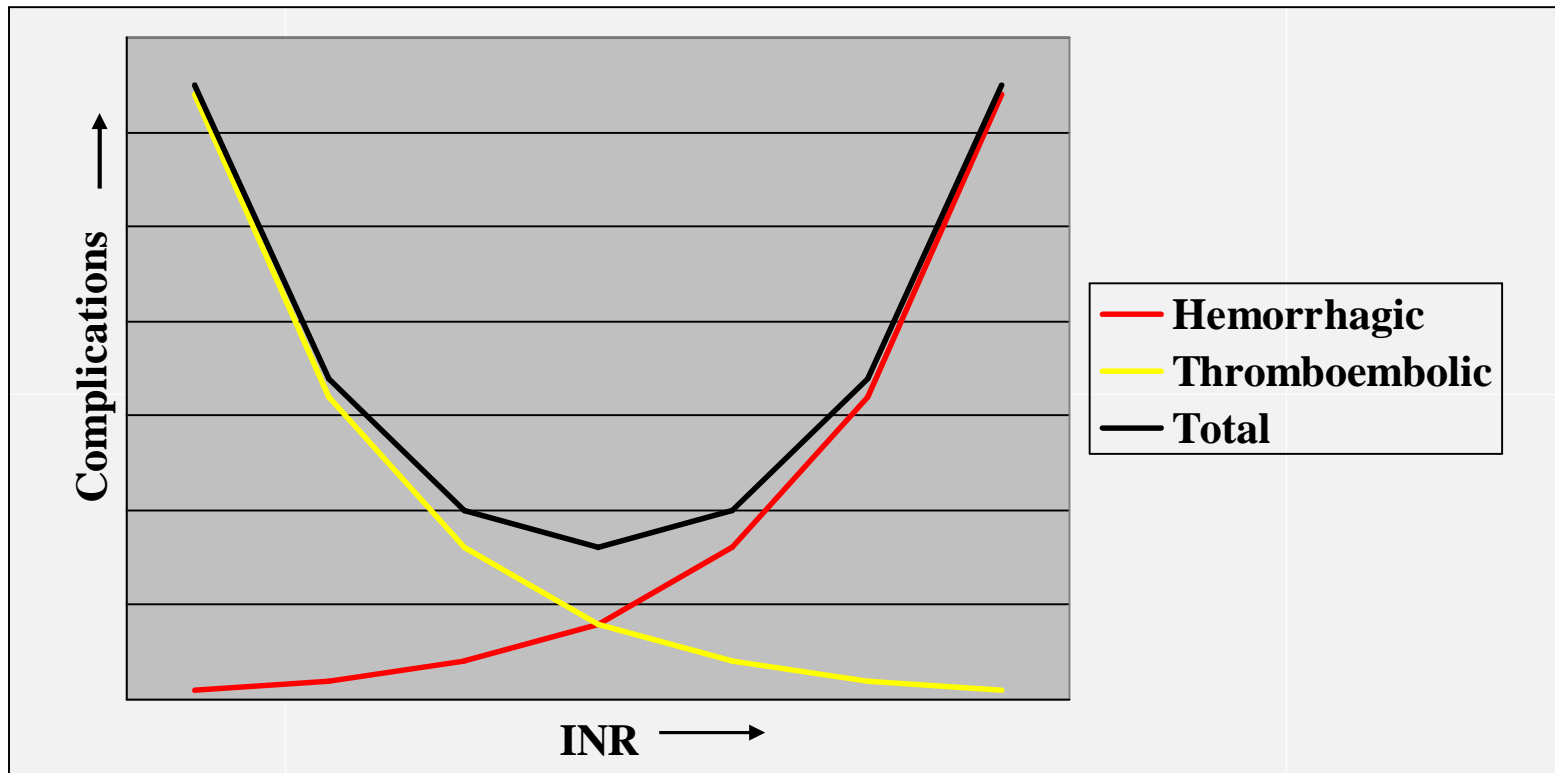
- is recommended as a global standard by the World Health Organization (WHO)<sup>1</sup>
- has some serious drawbacks<sup>2</sup>, but is the best available
- can still be considerably improved<sup>3</sup>

1. WHO Expert Committee on Biological Standardisation. Guidelines for thromboplastins and plasma used to control oral anticoagulant therapy. *WHO Technical Report Series* 1999;889:64-93.
2. Attermann J. Monitoring oral anticoagulant therapy: Measuring coagulant activity. *PhD thesis*. Department of Biostatistics, University of Aarhus, Denmark; 2000.
3. Attermann J. Inaccuracy of INR measurements and suggestions for improved WHO guidelines for calibration of reference preparations - a statistical study. *Journal of Thrombosis and Haemostasis* 2003;1:537-44.

# Basic dose-response relationships; only qualitatively known

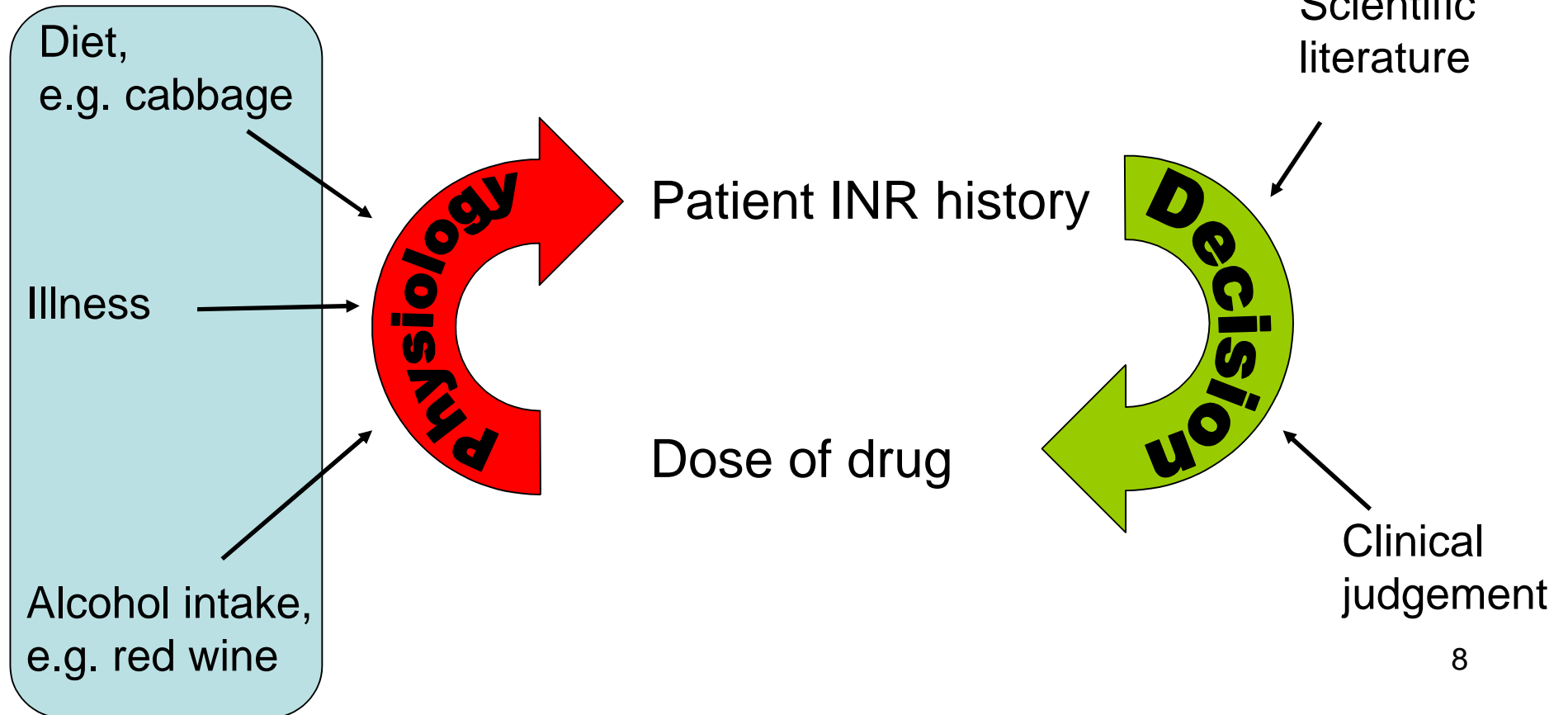
Warfarin dose  $\uparrow$   $\longrightarrow$  INR  $\uparrow$

and



# Monitoring of anticoagulant therapy is an iterative process

Patient-specific interactions with dose-INR relationship



# Self management of anticoagulant therapy<sup>1</sup>

The patient is the real expert in her dose-response relationship.

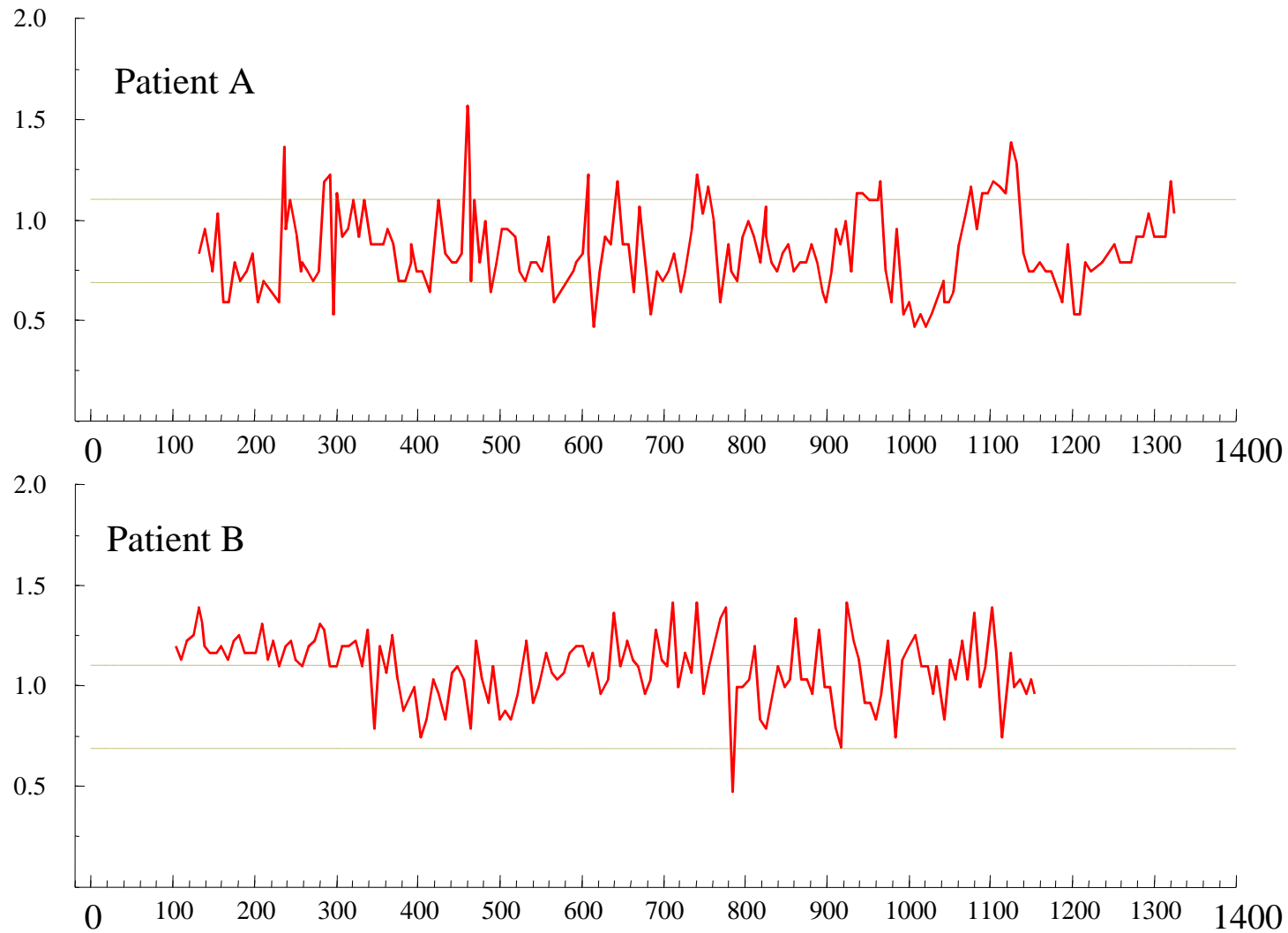
She

- performs weekly self-measurements of INR at home
- decides on dosage adjustments
- reports to the monitoring center regularly every 13<sup>th</sup> week on:
  - doses of anticoagulant medicine taken
  - INR measurements
  - complications and irregularities



1. Christensen TD, Andersen NT, Attermann J, Hjortdal VE, Maegaard M, Hasenkam JM. Mechanical heart valve patients can manage oral anticoagulant therapy themselves. *European Journal of Cardio-Thoracic Surgery* 2003;23(3):292-8.

# log(INR) vs. day since beginning of therapy for two patients on oral anticoagulant therapy



- Questions:
  - What is the "true" level of INR?
  - How should we measure quality of treatment?
  - How can we know if a patient is "out of control"?
  - How should dosing decisions be based on the patient's INR history?
- Possible answer: A statistical model!
- Problems:
  - Dose and INR are negatively correlated because patients undercompensate for interacting factors; thus dose cannot be used as an explanatory variable
  - Other (important) factors cannot be quantified
  - The "true" INR is well defined but impossible to measure; and is perhaps not the optimal guide for dosing decisions

- A simple mean-reversion model:

$$dx_t = \kappa (\theta - x_t) dt + \nu dW_t$$

$$y_t = x_t + \sigma \varepsilon_t$$

where  $x_t$  is the “true” log(INR),  $y_t$  is the measured log(INR),  $\{W_t\}$  is a standard Wienerprocess, and  $\{\varepsilon_t\}$  are iid standard normal.

This has an explicit solution which can be formulated as a linear Gaussian state space model:

$$y_k = \begin{pmatrix} 1 & 1 \end{pmatrix} \begin{pmatrix} \mu \\ \gamma_k \end{pmatrix} + v_k$$

$$\begin{pmatrix} \mu \\ \gamma_k \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & r_k \end{pmatrix} \begin{pmatrix} \mu \\ \gamma_{k-1} \end{pmatrix} + \begin{pmatrix} 0 \\ u_k \end{pmatrix}$$

$$v_k \sim N(0, \sigma^2)$$

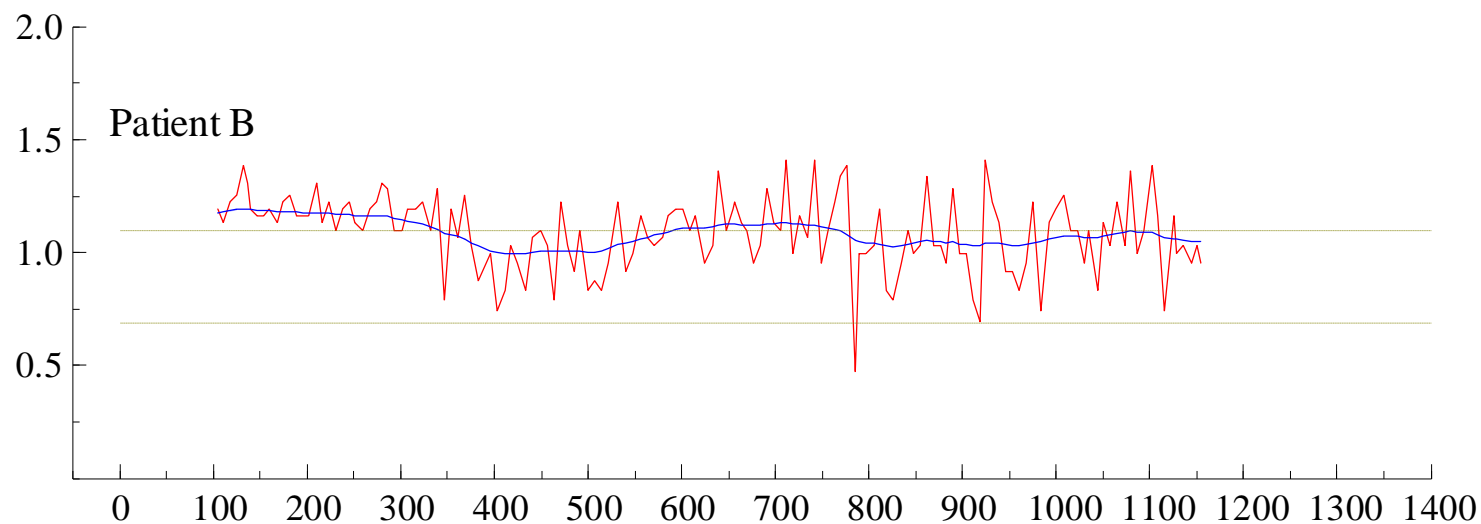
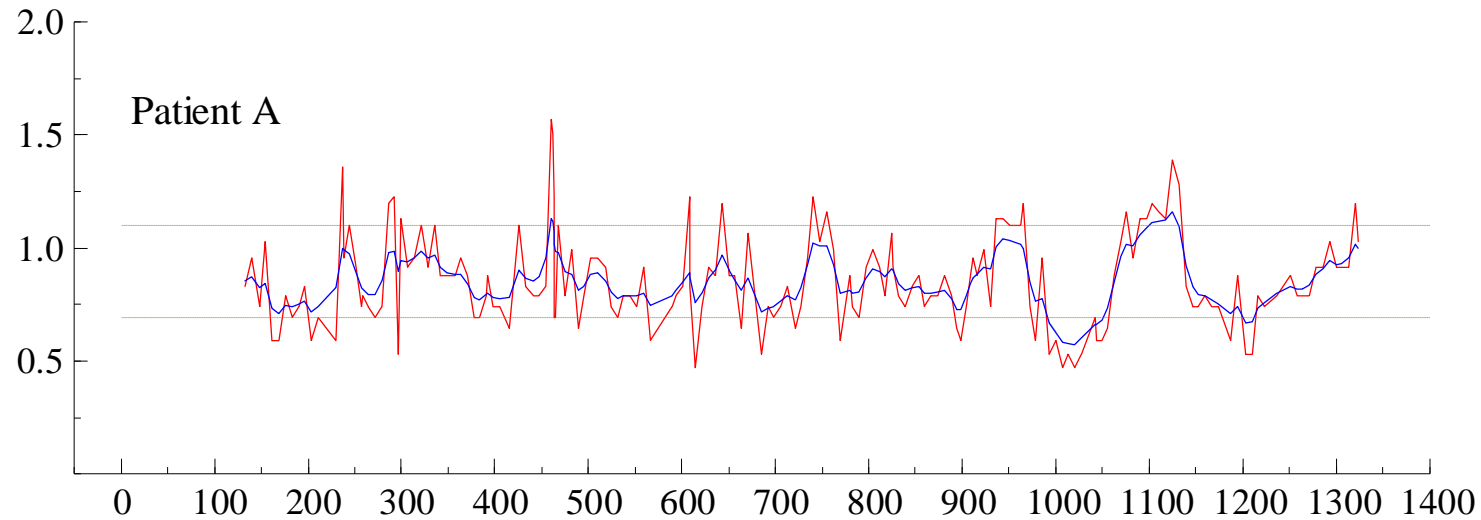
$$u_k \sim N(0, (1 - r_k^2) \nu^2)$$

$$r_k = \text{corr}(\gamma_k, \gamma_{k-1}) = \exp(-|t_k - t_{k-1}|/\rho)$$

$$\gamma_0 \sim N(0, \nu^2)$$

Can be estimated by the Kalman filter.

log(INR) vs. day since beginning of therapy for two patients.  
Smoothed states obtained by the simple model have been added to observed values



- An extended model

$$y_k = \begin{pmatrix} 1 & 1 \end{pmatrix} \begin{pmatrix} \mu_k \\ \gamma_k \end{pmatrix} + v_k$$

$$\begin{pmatrix} \mu_k \\ \gamma_k \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & r_k \end{pmatrix} \begin{pmatrix} \mu_{k-1} \\ \gamma_{k-1} \end{pmatrix} + \begin{pmatrix} \tilde{u}_k \\ u_k \end{pmatrix}$$

$$v_k \sim q_1 N(0, \sigma^2) + (1 - q_1) N(0, C_1 \sigma^2)$$

$$\tilde{u}_k \sim q_2 N(0, "0") + (1 - q_2) N(0, \tau^2)$$

$$u_k \sim q_3 N(0, (1 - r_k^2) \nu^2)$$

$$+ (1 - q_3) N(0, C_3 (1 - r_k^2) \nu^2)$$

$$r_k = \text{corr}(\gamma_k, \gamma_{k-1}) = \exp(-|t_k - t_{k-1}|/\rho)$$

$$\gamma_0 \sim N(0, \nu^2)$$

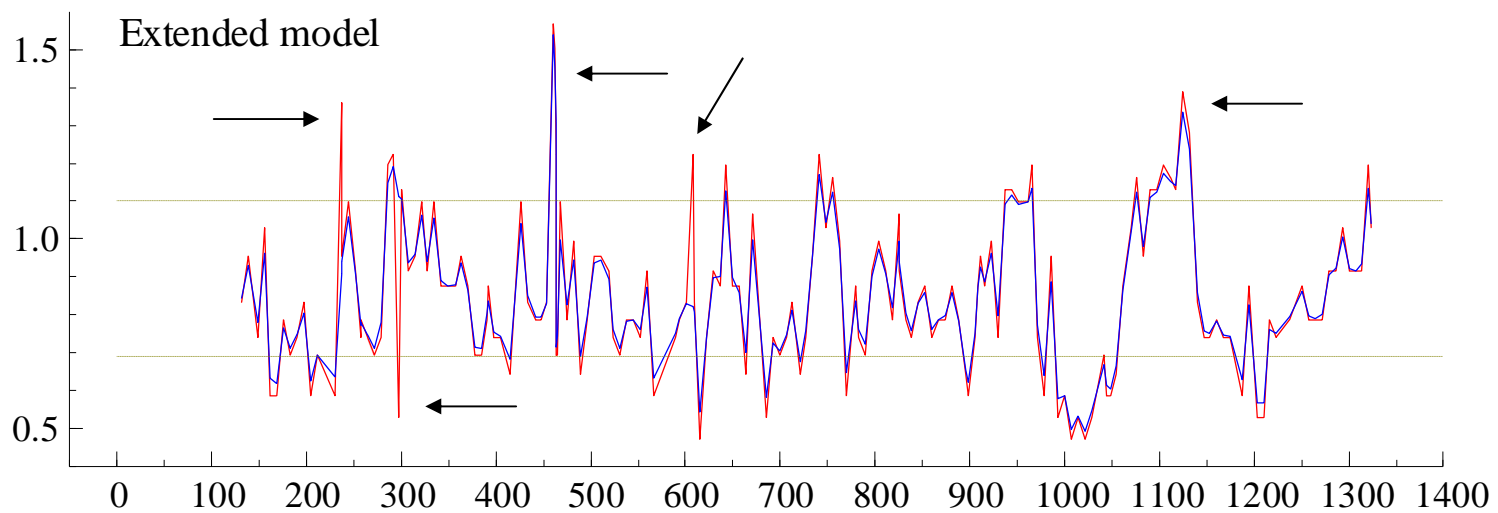
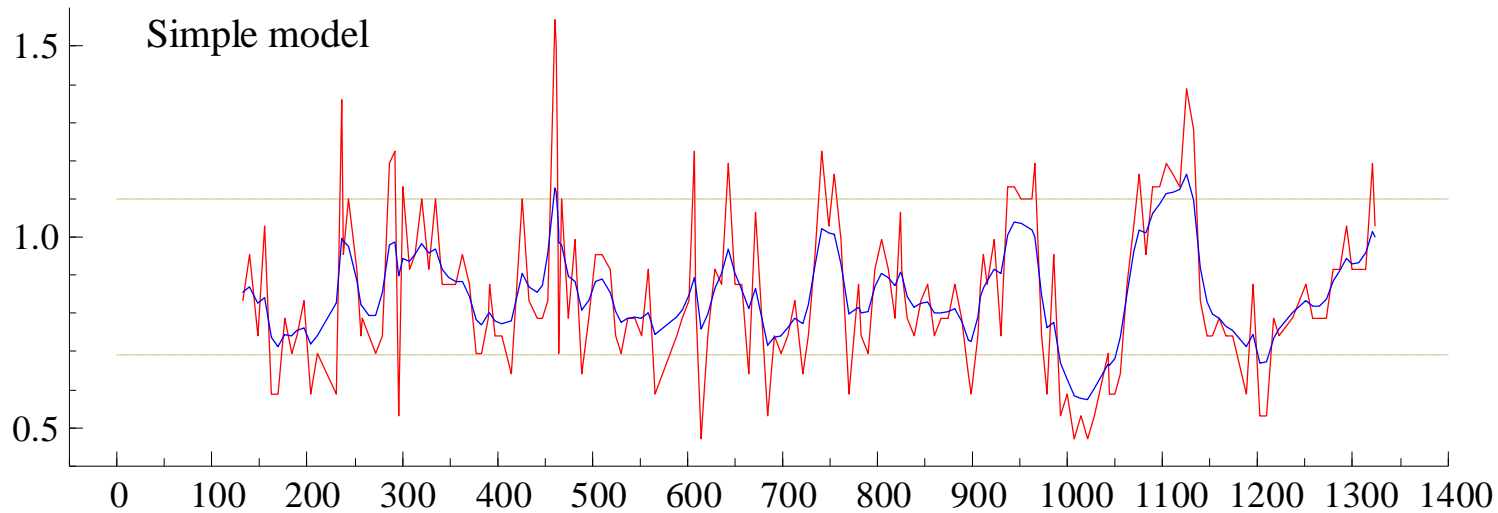
# Inference in general state space models, non-complete history:

- Extended, generalized or non-linear Kalman filtering:
  - Nonstatistical applications in the 1960s and 1970s
  - Dynamic Generalized Linear Model (West, Harrison & Migon, 1985)
- Techniques for sampling from the posterior distribution of states or disturbances:
  - Gibbs sampler (Carlin, Polson & Stoffer, 1992)
  - Numerical integration (Frühwirth-Schnatter, 1994)
  - Simulation smoother (de Jong & Shephard, 1995, 1997)
  - New simulation smoother (Durbin & Koopman, 1997, 2000, 2002)

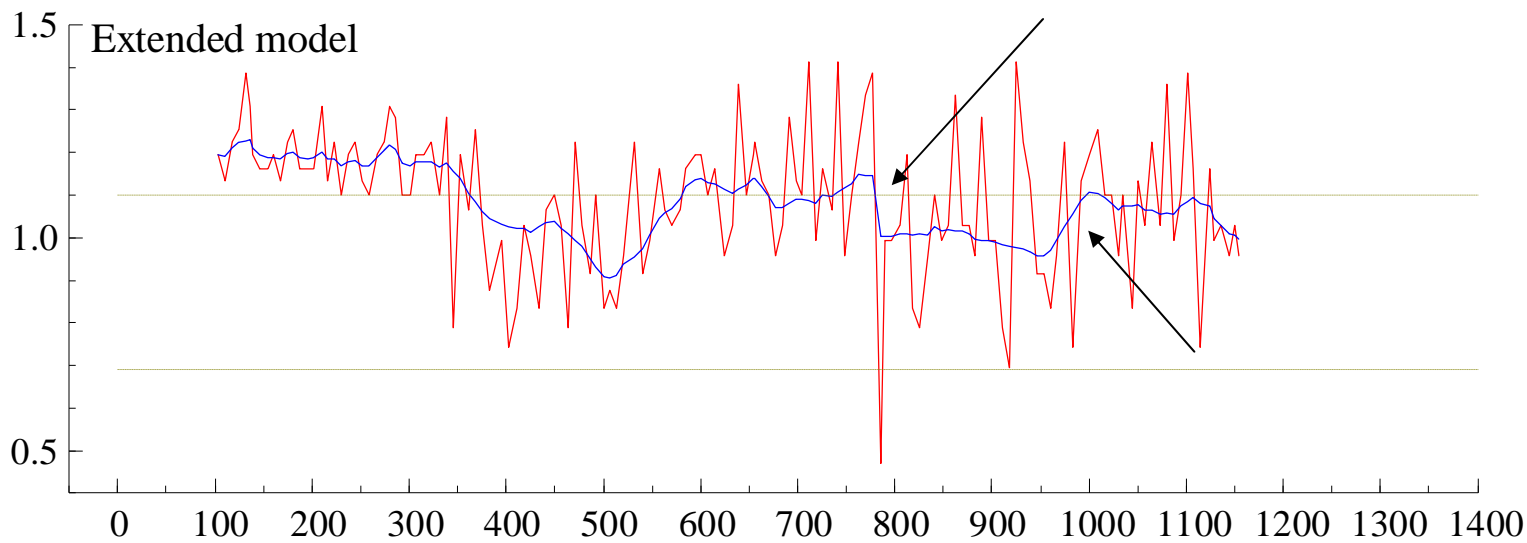
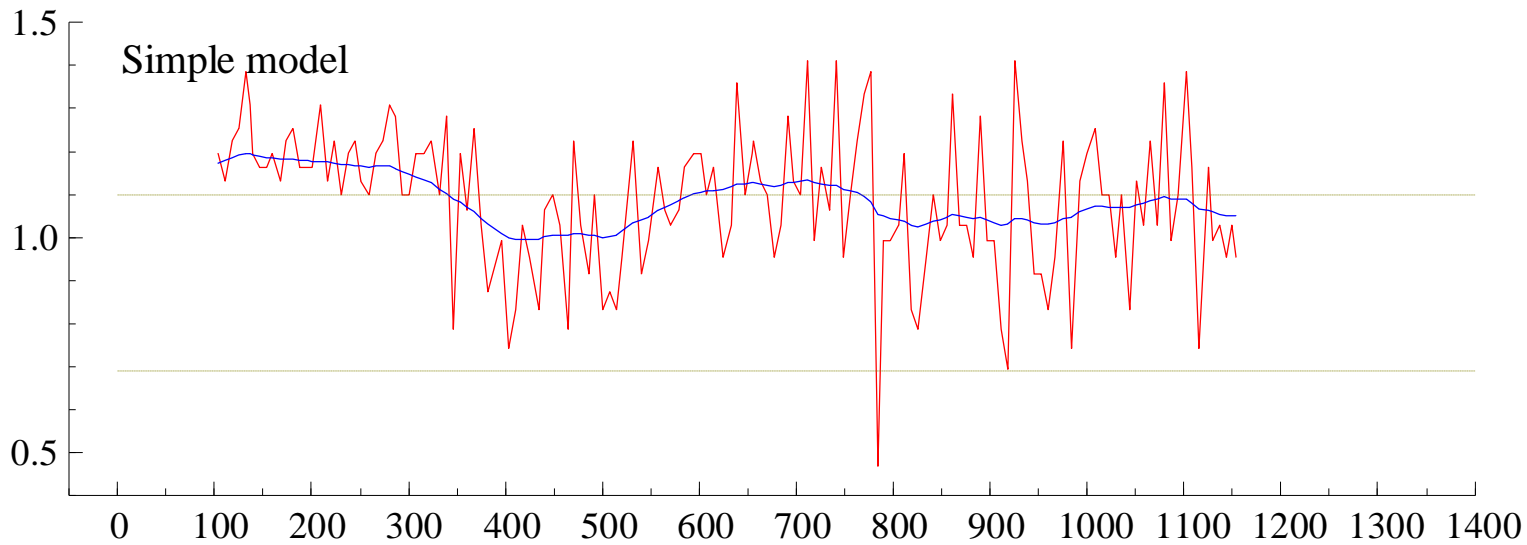
# Principles of estimation

- Linearize to obtain an approximating linear Gaussian state space model with the same mode of the posterior state as the exact model
- Use the posterior density given by the approximate model as importance density
- Sample from this density by using the simulation smoother
- Proceed with inference as usual in importance sampling

log(INR) vs. day since beginning of therapy for patient A. Smoothed states obtained by the simple and extended models have been added to observed values



log(INR) vs. day since beginning of therapy for patient B. Smoothed states obtained by the simple and extended models have been added to observed values



# Final thoughts

- How do we know if a given smoothed curve (or another statistic) is a reasonable and useful expression of a patient's "true" INR?
- Answer: We cannot know!
- The usefulness of a given statistic can be evaluated by
  - Perhaps, an experienced clinician, or, better,
  - A randomized controlled clinical trial with hard endpoints (major complications)