Statistical Monitoring of Heteroscedastic Dose-Response Profiles from High Throughput Screening

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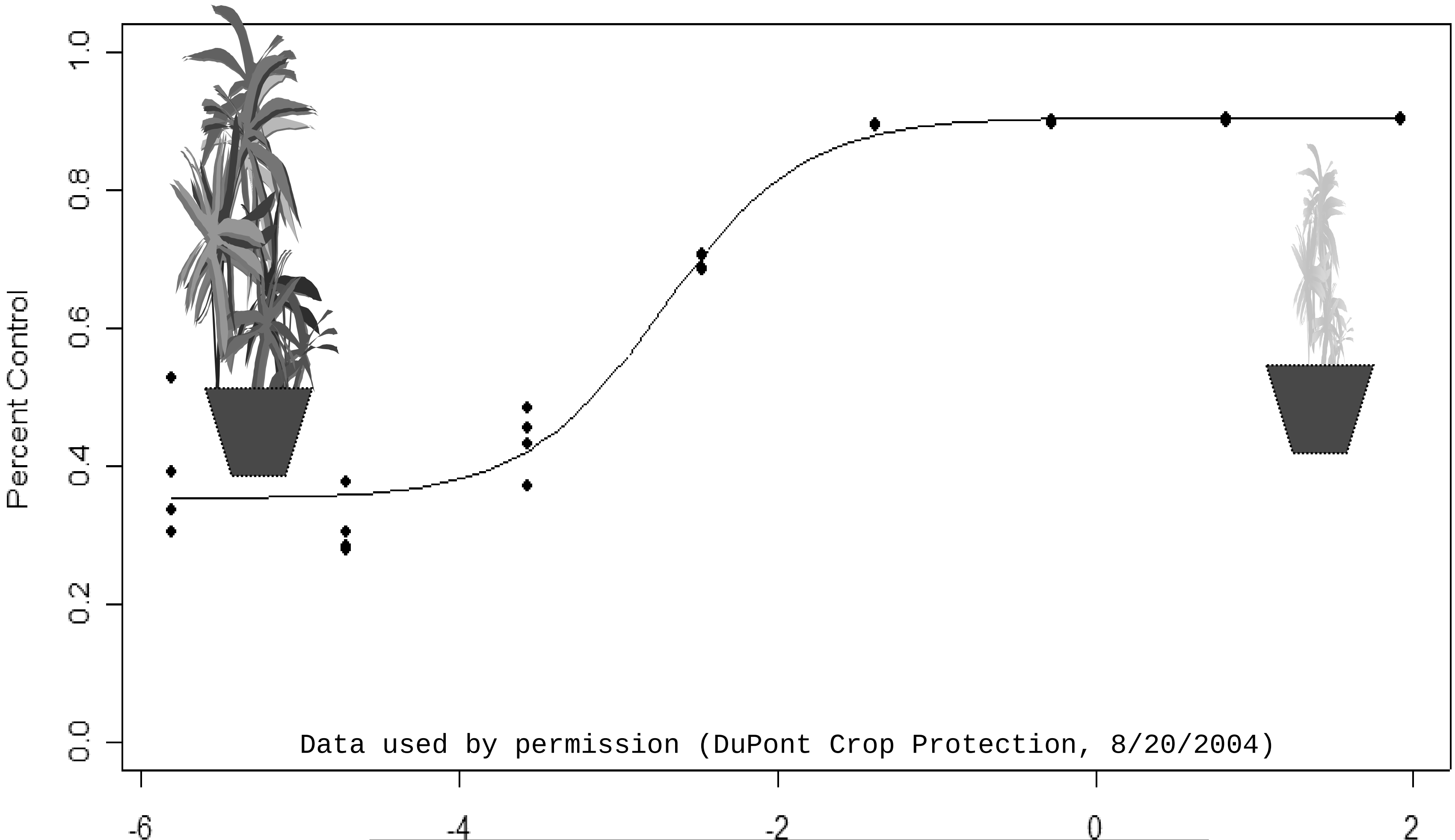
Introduction

Background and Motivation

- **High Throughput Screening (HTS): Use bioassays to test thousands of experimental compounds**
- **Bioassay quality is key to successful HTS**
- **Test commercial chemicals alongside experimental compounds to check the quality of bioassay**
- **If a bioassay experiment of the commercial chemical is undesirable for a given week, then the data generated by the HTS warrants further consideration for that run.**

Introduction

High Throughput Screening (HTS)



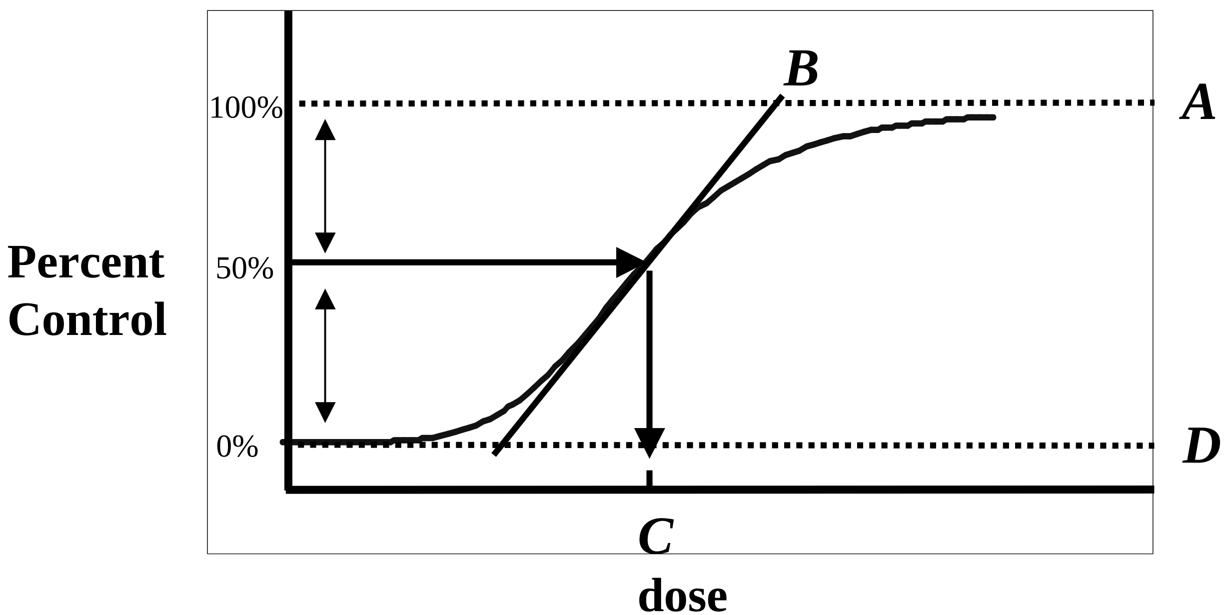
log(dose) of commercial chemical

Profile Estimation

Dose-response Model

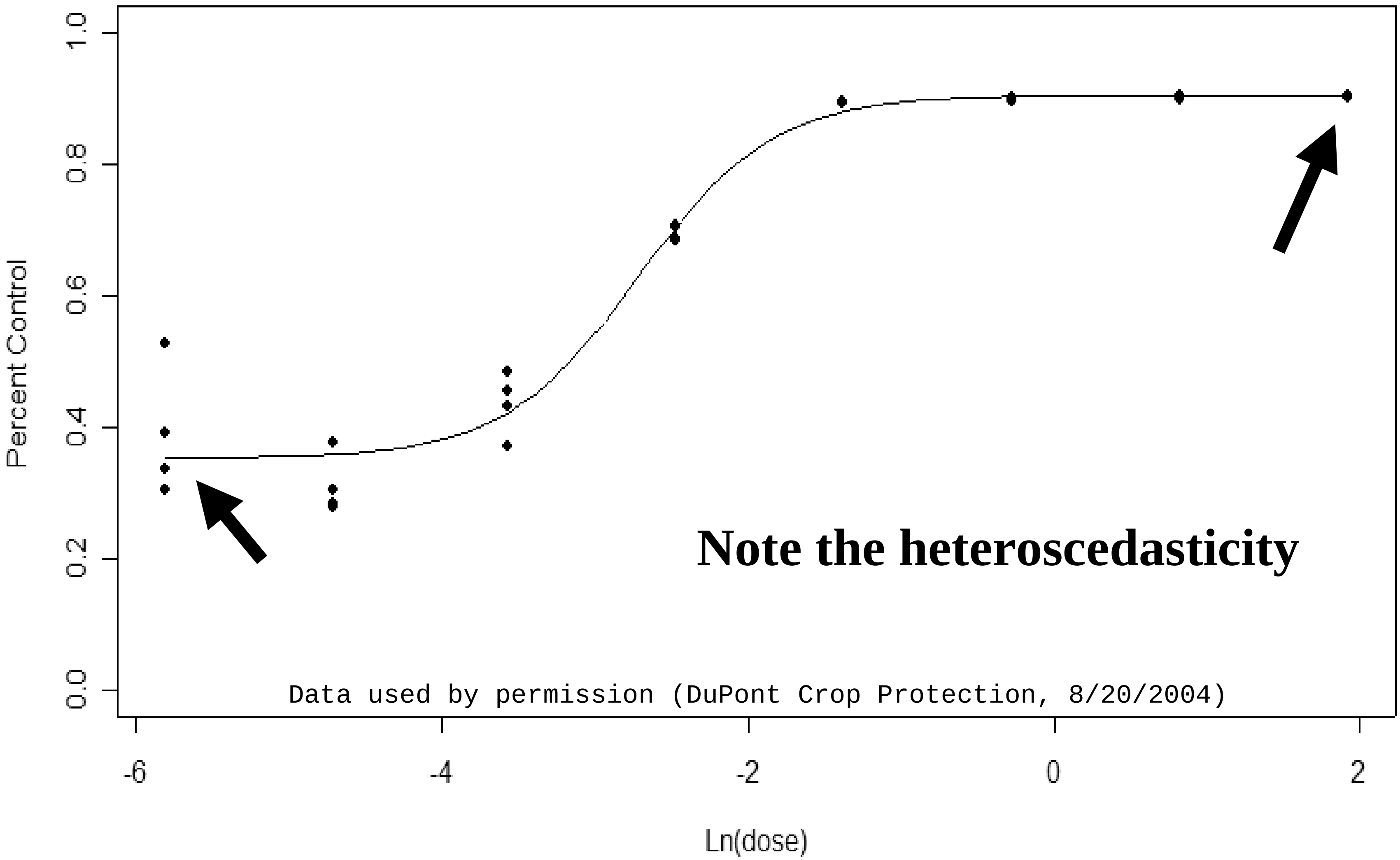
For profile i, dose j, and replication k:

$$PercentControl_{ijk} = A_i + \frac{D_i - A_i}{1 + \left(\frac{dose_{ij}}{C_i}\right)^{B_i}} + \varepsilon_{ijk}$$



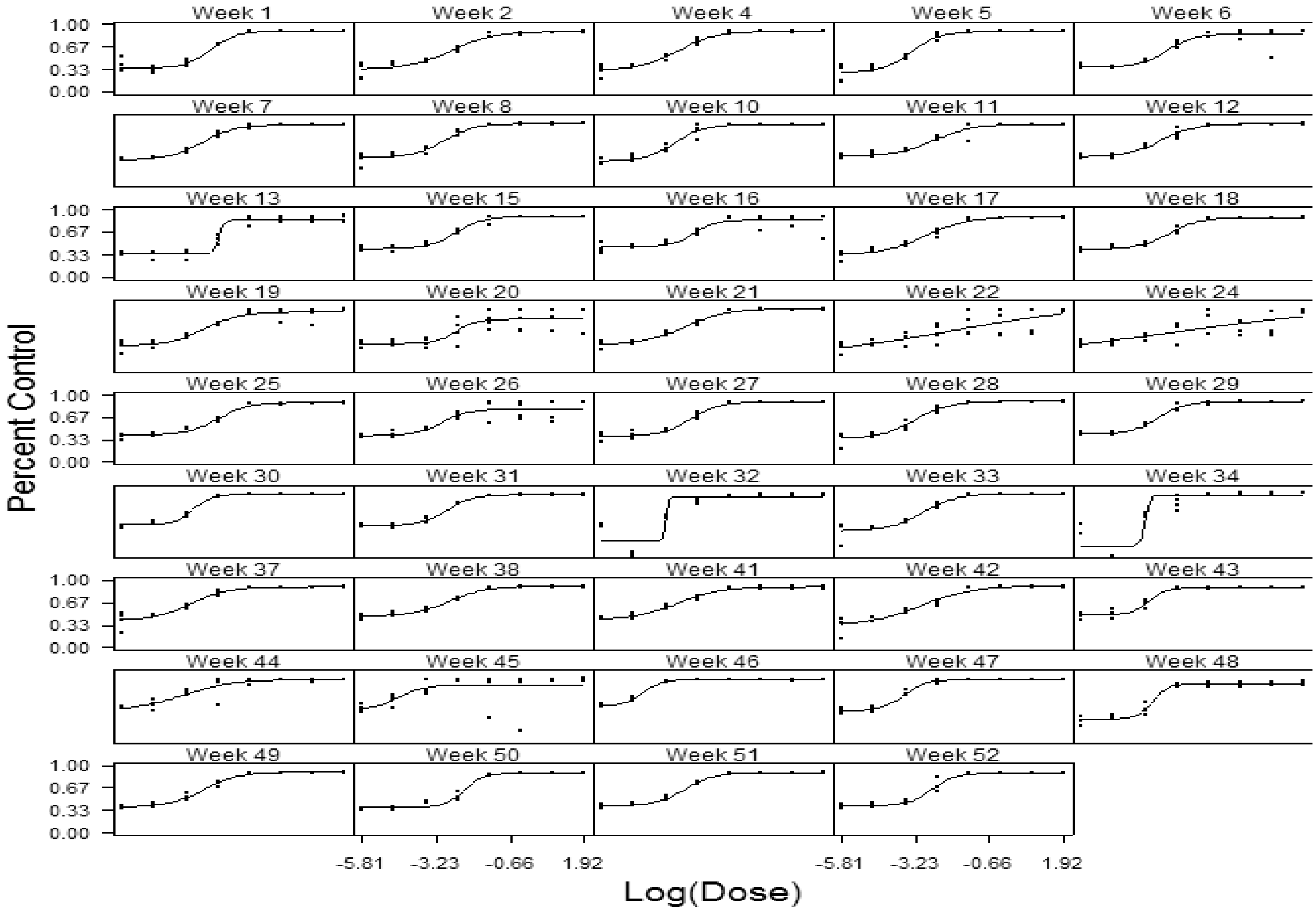
Profile Estimation

Estimated Mean Profile for Week 1



Profile Estimation

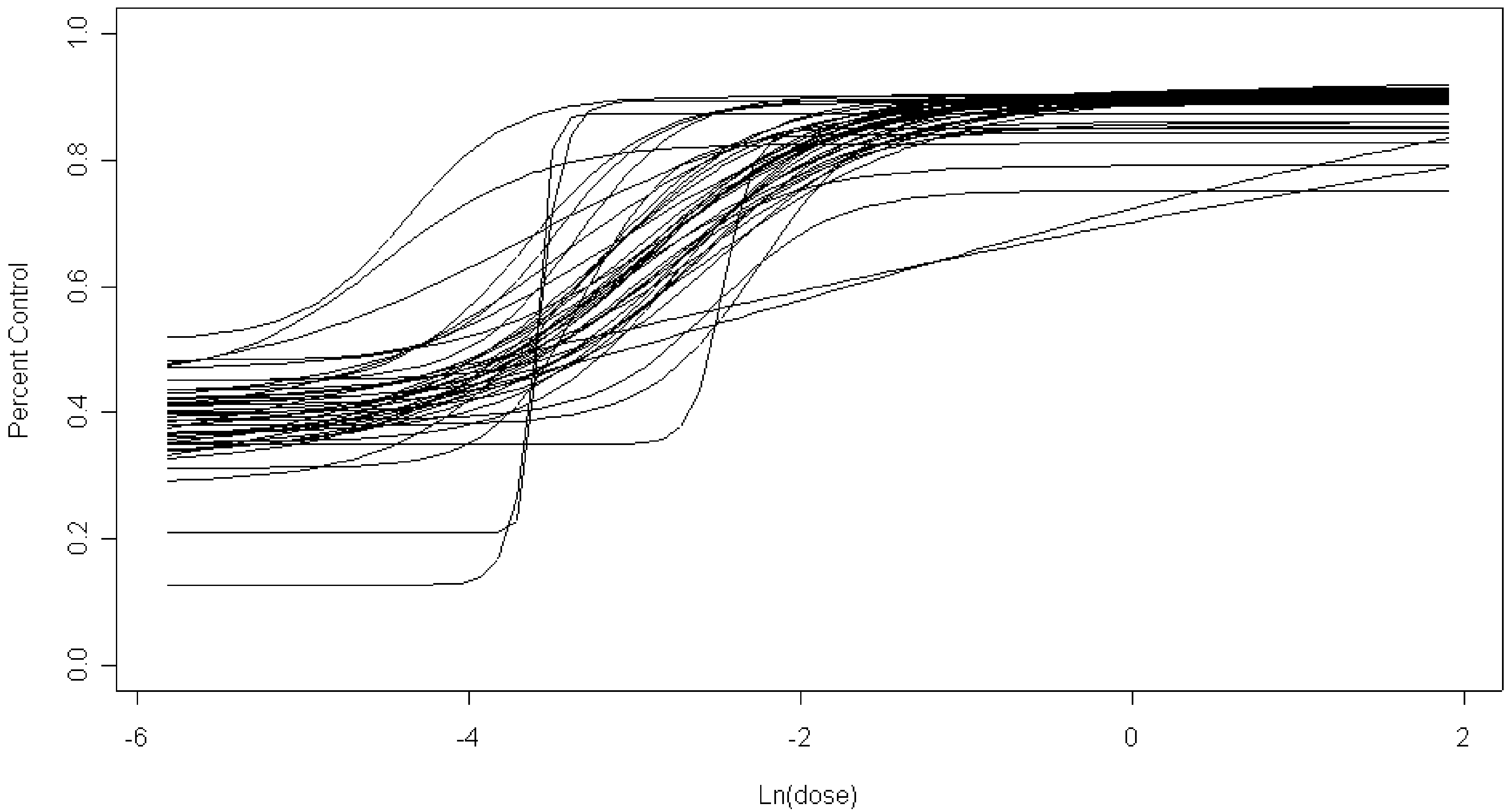
44 Estimated Mean Profiles



Data used by permission (DuPont Crop Protection, 8/20/2004)

Profile Estimation

44 Estimated Mean Profiles – overlaid



Profile Estimation

Variance Function Model

General Variance Function Model:

$$Var(y_{ijk}) = \sigma_i^2 g(z_{ij}, \beta_i, \theta_i)$$

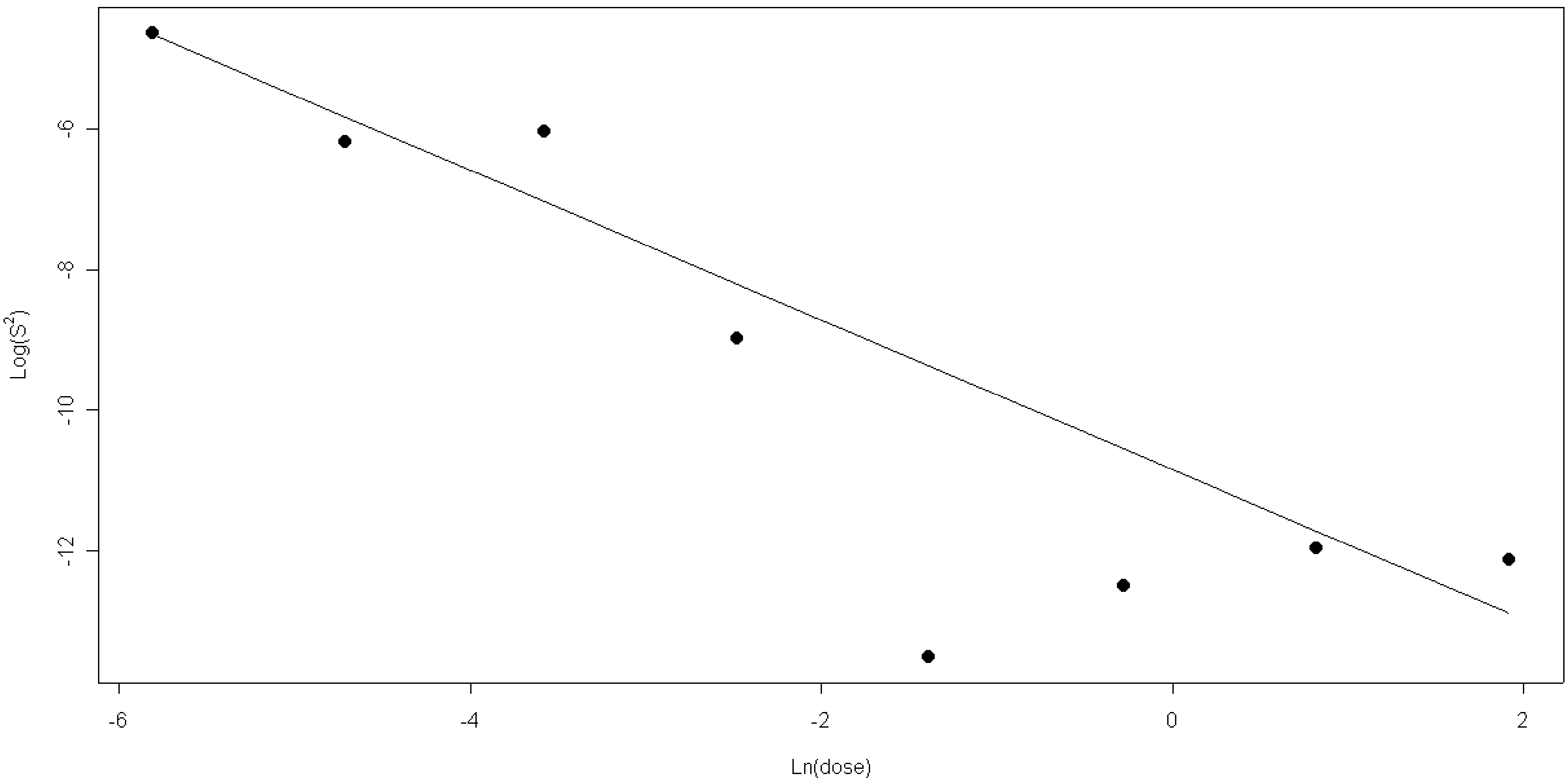
(Davidian and Carroll, 1987)

Can be written as a Generalized Linear Model (GLIM):

$$Var(y_{ijk}) = e^{\theta_{0,i} + \theta_{1,i} \log(dose_{ij})}$$

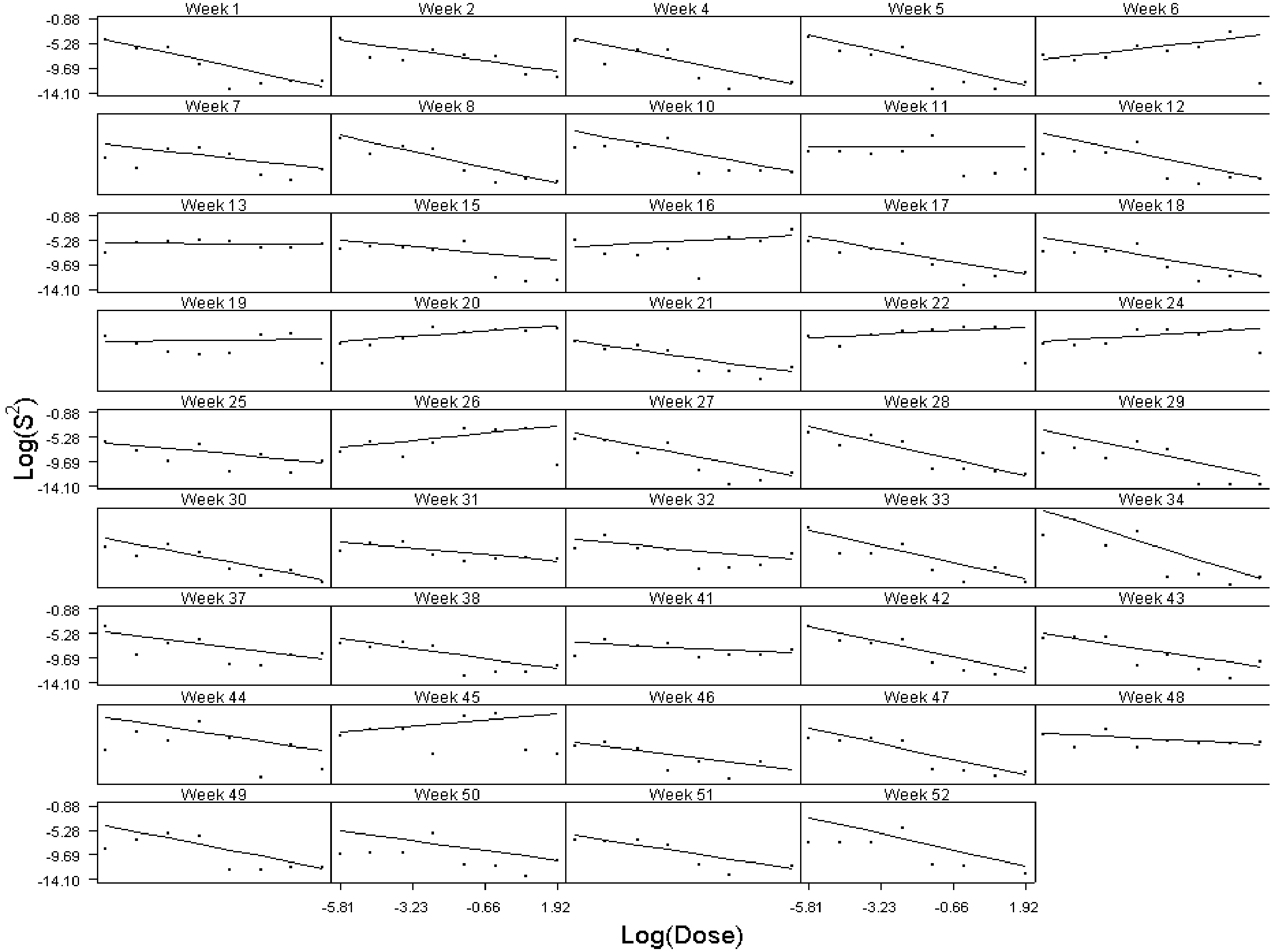
Variance Profile Estimation

Estimated Variance Profile for Week 1



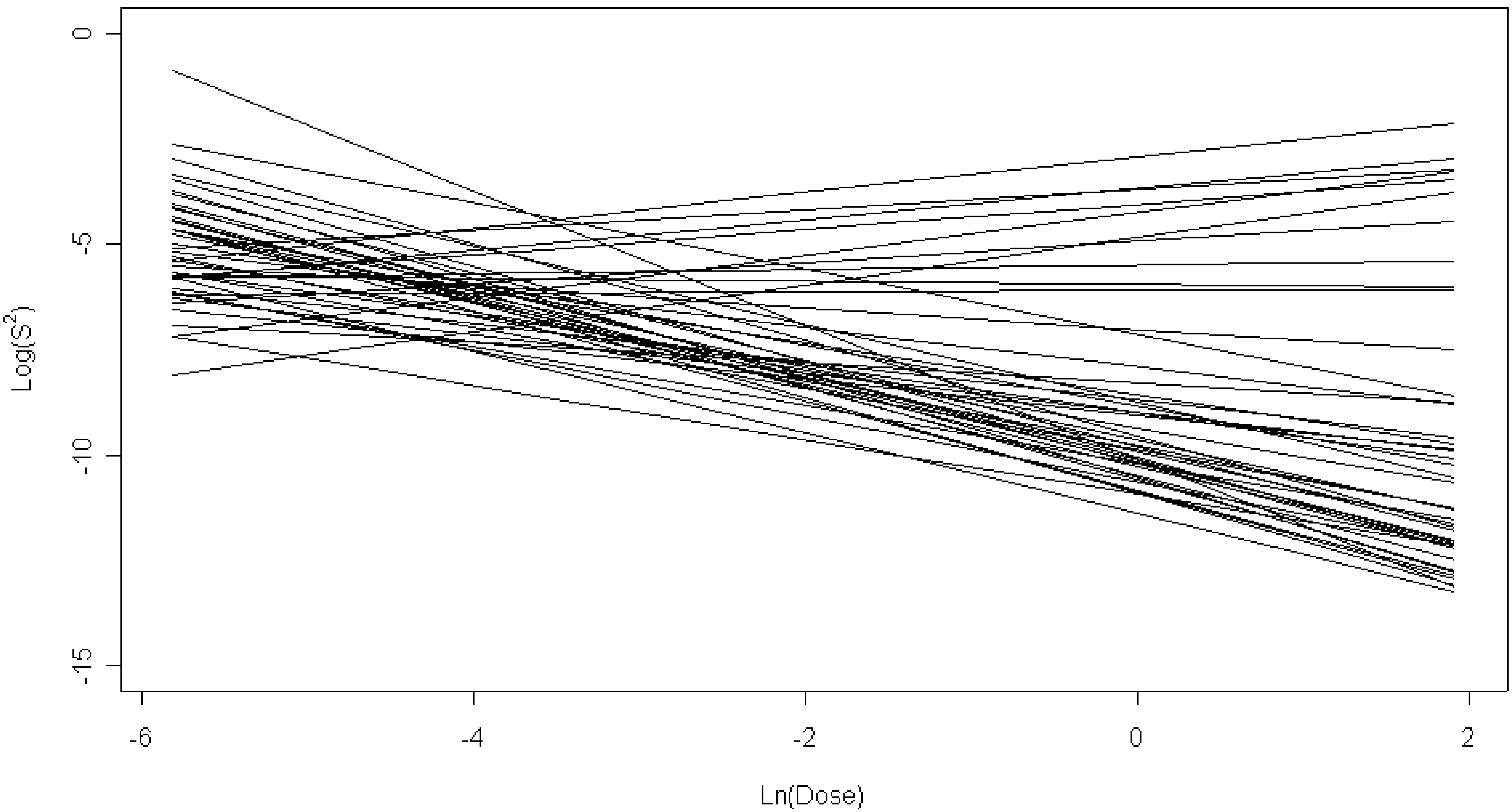
Variance Profile Estimation

44 Estimated Variance Profiles



Variance Profile Estimation

44 Estimated Variance Profiles – overlaid



Control Charts

<u>Goal</u>: Establish in-control model parameters for subsequent continuous bioassay monitoring

1. **<u>Variance Profile Chart</u>**
   - **Check for abnormal variances profiles**
2. **<u>Lack-of-Fit Chart</u>**
   - **Check for adequacy of model**
3. **<u>Hotelling's T^2 Chart</u>**
   - **Check for abnormal estimates of *A*, *B*, *C*, and *D***

Control Charts

Variance Profile Chart: Highlights

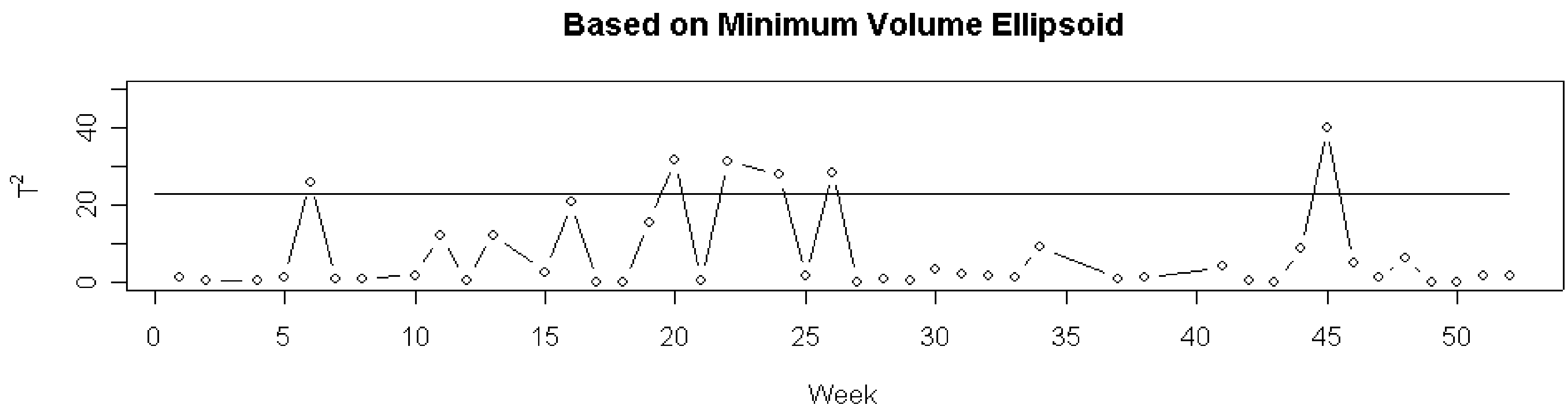
- **Need to identify abnormal values of θ_0 and θ_1**
- **However, θ_0 and θ_1 are correlated**
- **Solution: Use Hotelling's T^2 statistic**

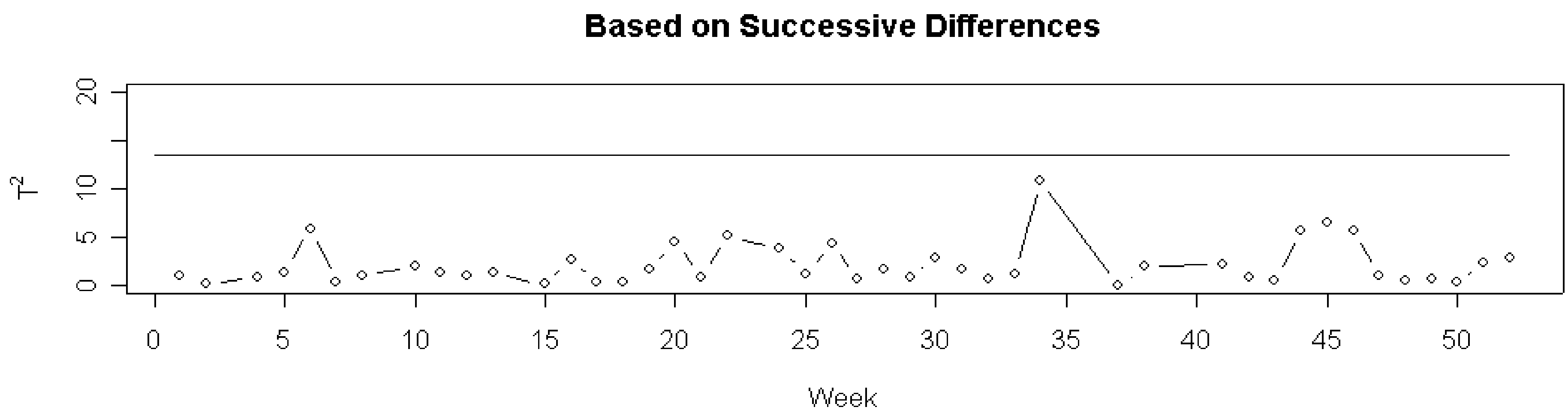
$$T_i^{\,2} = \left(\hat{\theta}_i - \hat{\mu}_\theta\right)' \mathbf{S}^{-1} \left(\hat{\theta}_i - \hat{\mu}_\theta\right) \quad \textbf{where} \quad \hat{\boldsymbol{\theta}}_i = \begin{pmatrix} \hat{\theta}_{0,i} \\ \hat{\theta}_{1,i} \end{pmatrix}$$

- **Various versions of T^2 statistic available**
- **Here we consider T^2 based on the minimum volume ellipsoid and successive differences estimator (see Williams, Woodall, Birch, and Sullivan (JQT, July 2006))**

Control Charts

Variance Profile Charts





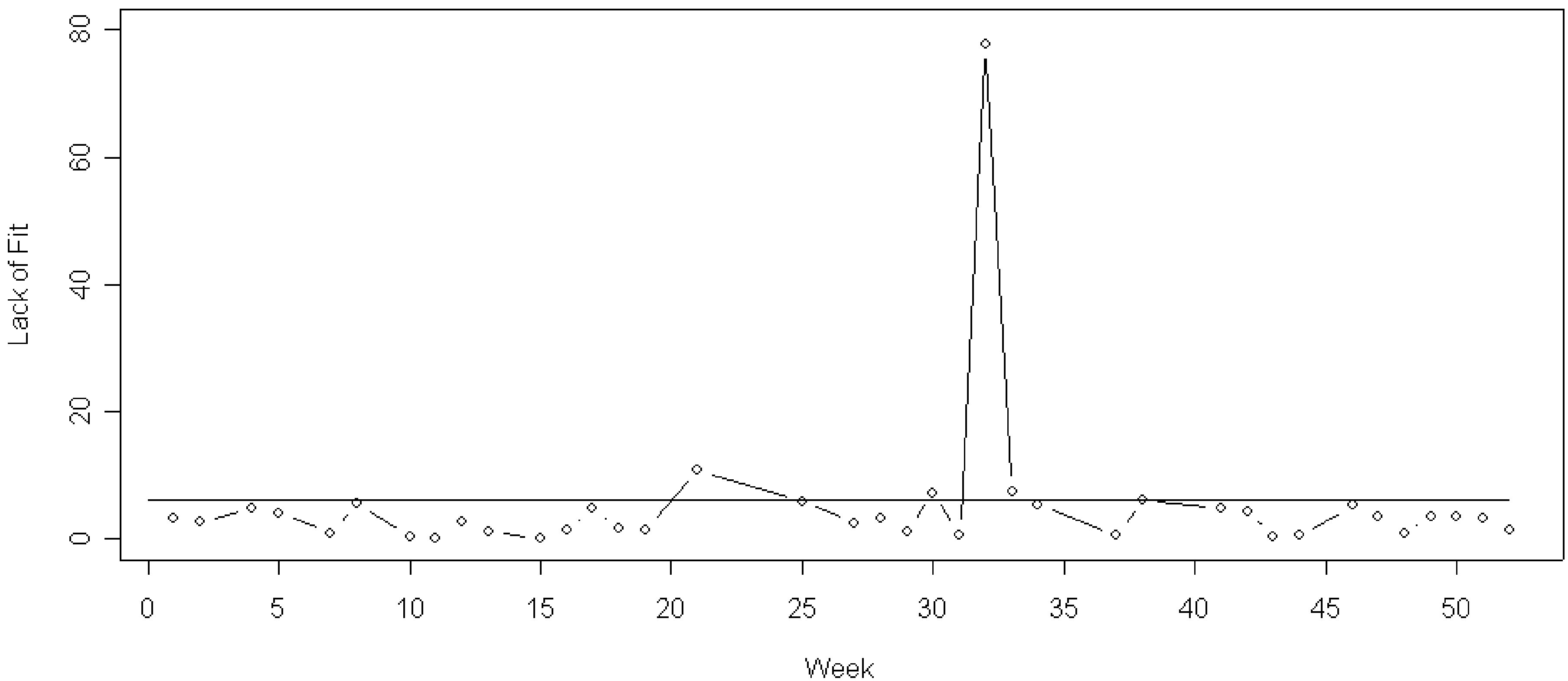
Control Charts

Lack-of-fit Chart: Highlights

- **Need to identify changes in model form**
- **For replicated data, we can calculate lack-of-fit (LOF)**
- **Problem: Heteroscedastic data**
- **Solution: Replace sums of squares with weighted sums of squares in the lack-of-fit F statistic**
- **Resulting statistic has an approximate F distribution**

Control Charts

Lack-of-fit Chart



Control Charts

T^2 Chart: Highlights

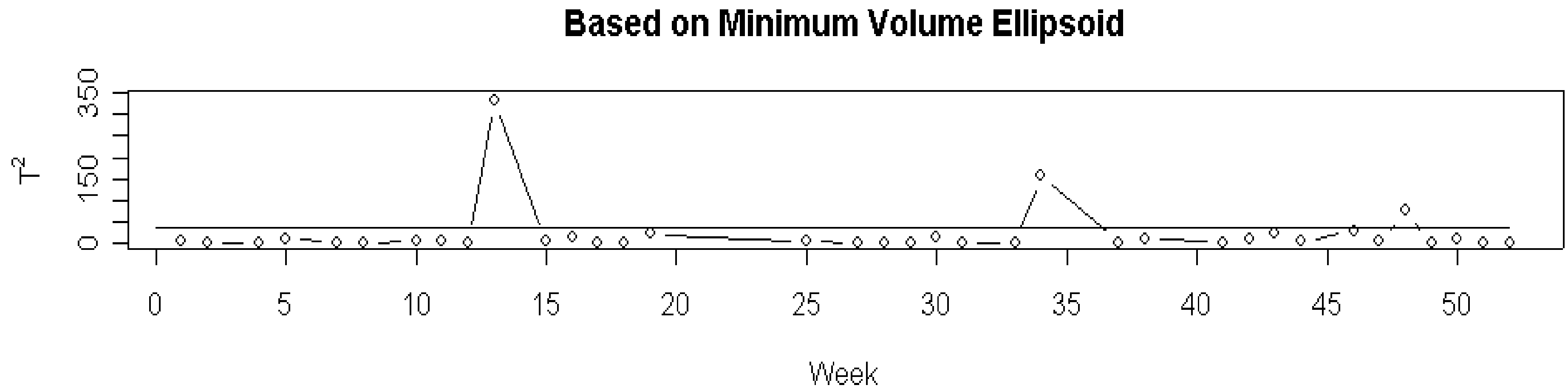
- **Need to identify abnormal estimated values of *A*, *B*, *C*, and *D***
- **However, their estimators are correlated**
- **Solution: Use Hotelling's T^2 statistic**

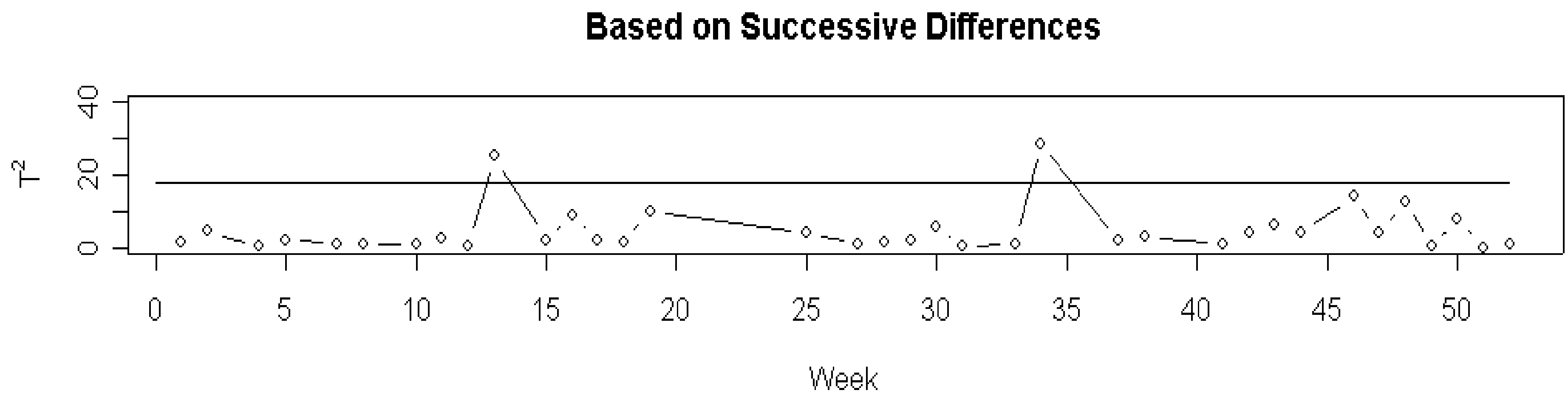
$$T_i^2 = \left(\hat{\boldsymbol{\beta}}_i - \overline{\hat{\boldsymbol{\beta}}}\right)' \mathbf{S}^{-1} \left(\hat{\boldsymbol{\beta}}_i - \overline{\hat{\boldsymbol{\beta}}}\right) \quad \textbf{where} \quad \hat{\boldsymbol{\beta}}_i = \begin{pmatrix} \hat{A}_i \\ \hat{B}_i \\ \hat{C}_i \\ \hat{D}_i \end{pmatrix}$$

- **Various versions of T^2 statistic available**
- **Here we consider T^2 based on the minimum volume ellipsoid and successive differences estimator**

Control Charts

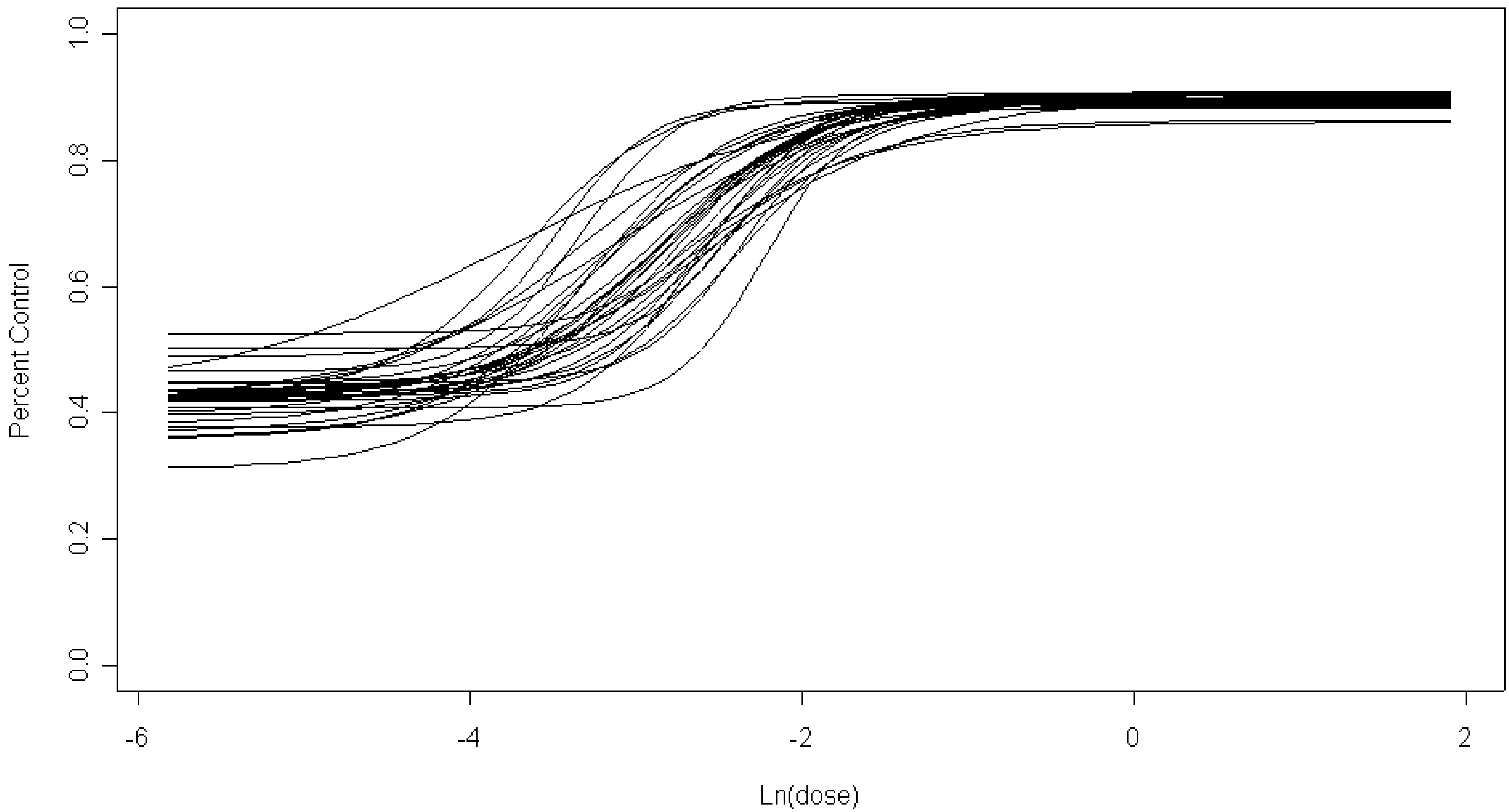
T^2 Charts





Control Charts

In-control Estimated Profiles



Conclusions

Nonlinear Profile Monitoring

- **Nonlinear profile monitoring requires 3 charts:**
  - **Variance Profile Chart**
  - **Lack-of-Fit Chart**
  - **T^2 Chart**
- **Nonlinear profile monitoring is part of the relatively new field of profile monitoring**
- **Many engineering and biological applications of profile monitoring**
- **Profile monitoring papers can be obtained upon request**

Some References

Davidian, M., and Carroll, R. J. (1987), "Variance Function Estimation" *Journal of the American Statistical Association* 82, pp. 1079-1091.

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