

An Integrated Framework for Online Monitoring and Quality Prediction in Real-time for Batch Fermentation Processes

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Outline

- Introduction
 - Statistical process monitoring (SPM)
 - Issues in statistical monitoring of batch processes
 - Batch data organization
 - Adjustment of data lengths and trajectory alignment
- SPM and Quality Prediction:
 - Multiway PLS
 - Integration of SPM with online quality prediction
- Application to a bioprocess: Fed-batch penicillin fermentation

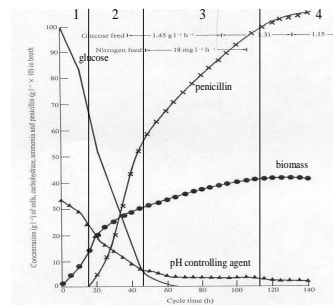
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Statistical Process Monitoring

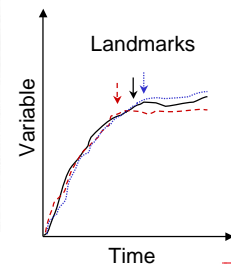
- **Statistical Process Monitoring (SPM):** Monitor process variables during or at the end of batch to detect abnormal process operation and infer unacceptable quality product
- Goal: Online implementation of SPM with quality prediction during batch progress

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Batch Process with Several Phases



Penicillin fermentation*
 *Atkinson and Mavituna, Bioengineering & Biotechnology Handbook



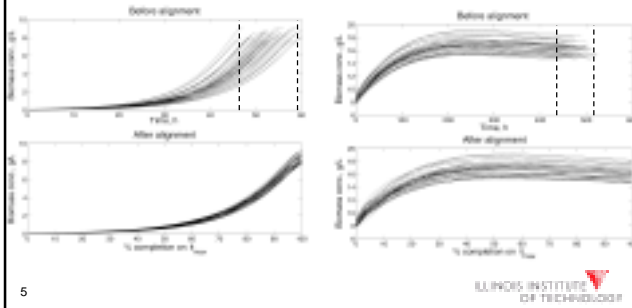
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Alignment of Variable Trajectories

Phase 1: Batch

Phase 2: Fed-batch

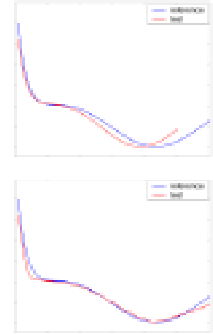
Temporal Variation



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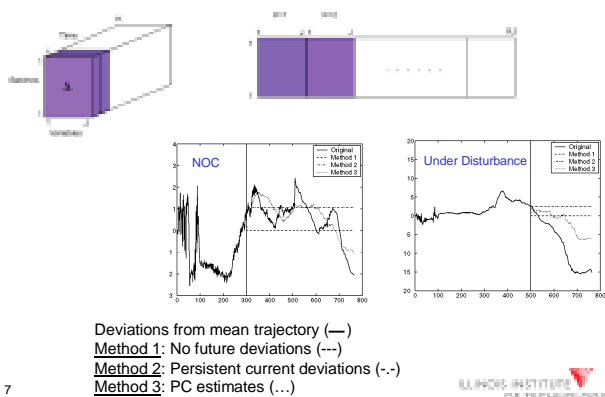
Data Alignment Techniques

- Dynamic Time Warping
 - Nonlinear dynamic programming
- Curve Registration
 - Estimate a smooth warping function by functional data analysis
- Indicator Variable (IV)
 - Re-digitize trajectories with respect to an IV
 - Smooth, monotonically increasing/decreasing, span operation range
 - MPLS for IV generation



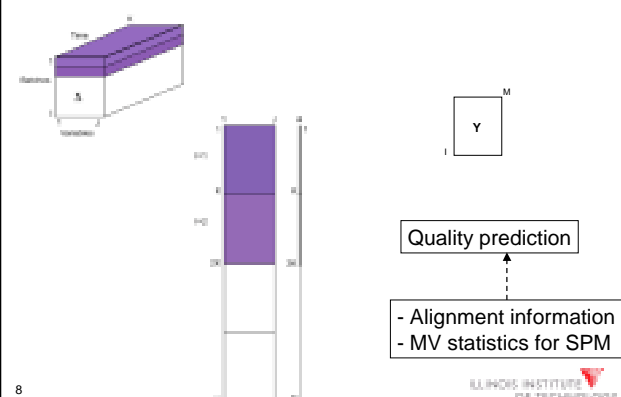
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Alternatives for Unfolding a Batch Data Array



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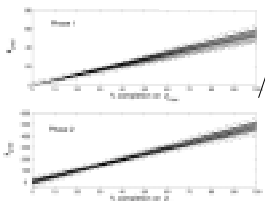
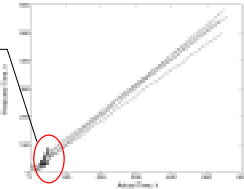
Alternatives for Unfolding a Batch Data Array



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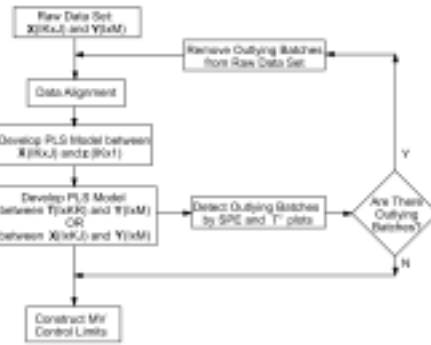
MPLS Prediction of Local Time

Discontinuity:
loss of
monotonic
increase

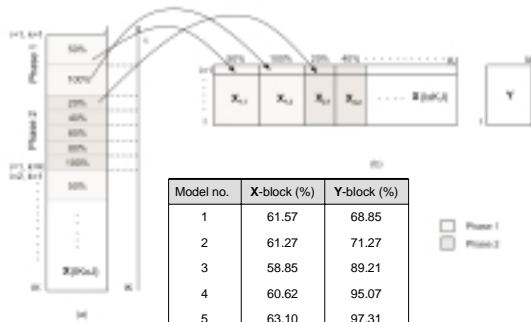


- After dividing into two phases with IV:
 - Phase 1: Batch
 - Phase 2: Fed-batch

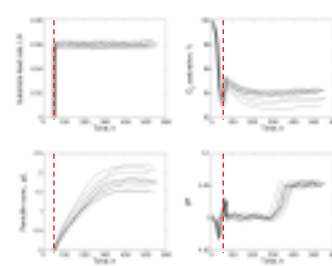
MSPM Framework Development



Integrated Framework: MSPM & Quality Prediction



Fed-batch Penicillin Fermentation



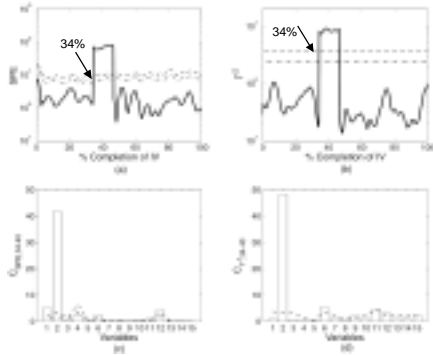
Input Variables
Feed Temperature
Feed Rate
Inflow Air Rate
Agitator Power Input
Coolant Flow Rate
Coolant Temperature

Process Variables
Culture Volume
Fermentor Temperature
Generated Heat
Concentrations of
Substrate
Dissolved Oxygen
Biomass
Penicillin
CO₂
H⁺ (pH)

Two control loops to regulate pH and temperature in the fermentor

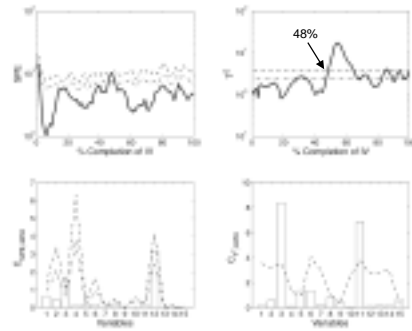
Quality Variables
Final penicillin concentration
Overall productivity
Yield of penicillin on biomass
Yield of penicillin on substrate
Amount of penicillin produced

Case 1 : Step disturbance



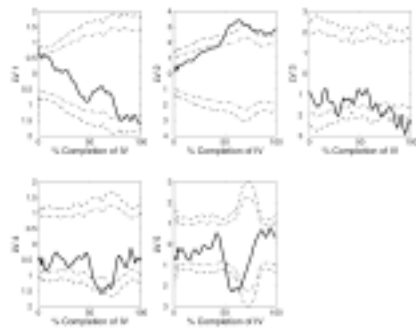
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Case 2: Drift disturbance



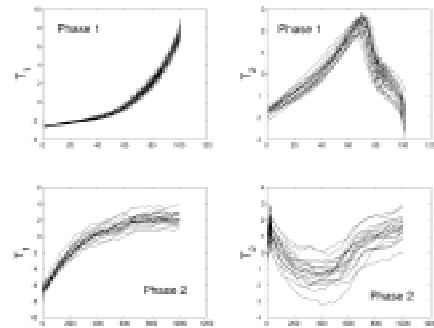
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Case 2: Linear scores



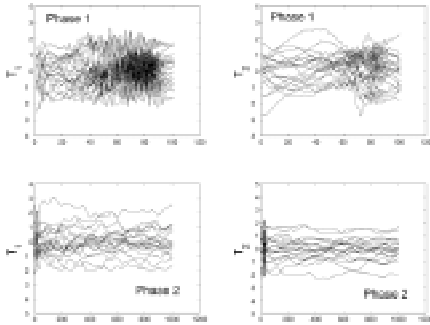
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Nonlinear scores of MPLS model



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Mean-centered scores of MPLS model

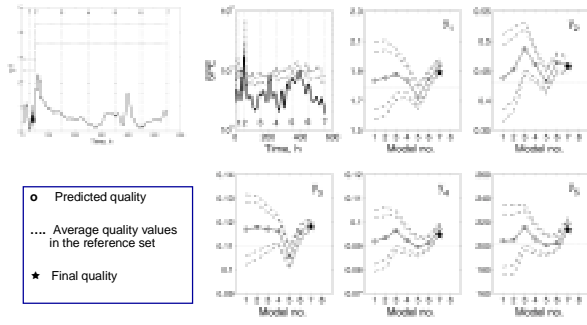


Session: 263b, 2:20pm, Friday, Nov. 8
 Room: 205, Indianapolis Convention Center



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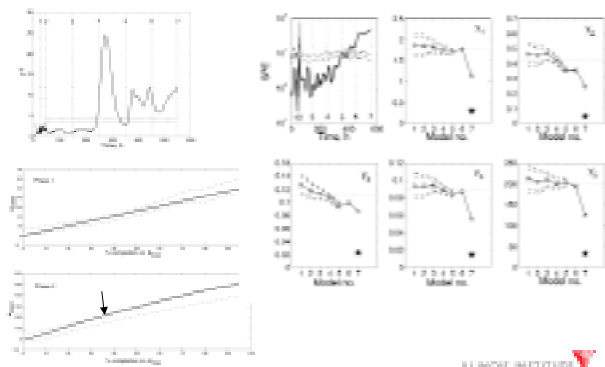
Quality Prediction: Good Batch (NOC)



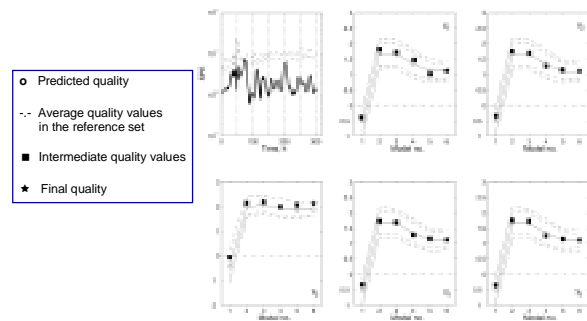
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Quality Prediction: Faulty Batch (Drift)



Online Estimation of Intermediate Quality: NOC

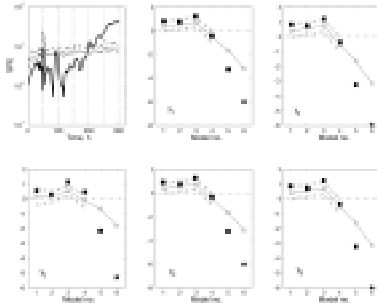


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Online Estimation of Intermediate Quality: Fault case

- Predicted quality
- - Average quality values in the reference set
- Intermediate quality values
- ★ Final quality



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Conclusions

- Real-time SPM provides opportunity for timely intervention saving a batch that may be ruined
- SPM based on variable direction provides an alternative monitoring method
 - Preserving variable direction in unfolding is advantageous:
 - ▶ No future value estimation required
 - ▶ Data alignment performed simultaneously
 - Care should be taken for discontinuities in IVs
 - Divide progress of the batch into phases
 - ▶ Divide data as batch/fed-batch phases

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Conclusions

- Online quality prediction allows early assessment
- Enhanced multivariate charting: **faster fault detection/diagnosis**
 - Detailed trend analysis and diagnosis using contribution plots with limits
- Framework suitable for integrating into a real-time supervisory knowledge-based system

Session: 291e, 10:00am, Friday, Nov. 8

Room: Illinois-Marriott

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