Integrated Control in Formulation
The Importance of Process Monitoring Technologies

Julian Morris

Centre for Process Analytics & Control Technology
Newcastle University & Strathclyde University, UK
www.cpact.com

Towards Integrated Control in Formulations, CPT NetPark January 17th 2019

CPACT Member Companies

Plus 12 Universities/Research Institutes

Overview of Presentation

- Setting the Scene:
  - Challenges in Formulation Product & Process Development and Production
- Measurement and Modelling Challenges
- Software (Virtual) Sensors – some Industrial Applications
- Closure

Challenges in Formulations Development and Production

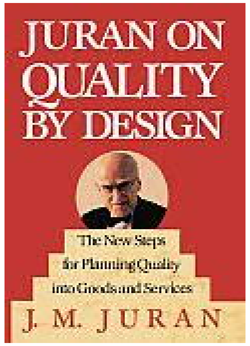
- Increasing new formulation introductions & aggressive development cycles:
  - Wider range of product forms:
    - ➢ **Reduced opportunity for generating data for analysis and modelling**
- Demands a culture-change:
  - ➢ **Products are *Complex* and *Multivariate***
  - ➢ **Processes are *Dynamic* and *Time-varying***
  - ➢ **Processes (e.g. reactions, …) are *non-linear***
  - ➢ **Products have '*Multivariate Distributions*'**
- **'Systems' Engineering:**
  - ➢ Process and Product Centric - ***6-sigma*** development & production
  - ➢ A ***system*** is the product of interacting parts. Improving the parts taken separately will not improve the whole system

CPACT

Variability and Quality by Design
Joseph Juran Edwards Deming and Walter Shewhart

Cease reliance on mass inspection to achieve quality.

Eliminate the need for mass inspection by building quality into the product in the first place.



Dr W. Edwards Deming

"Learning is not compulsory, …

…. Neither is survival"

Measurement and Modelling Challenges

Why is Measurement so Important

"You Can't Manage What You Don't Measure"
If you can't measure it, you can't improve it

Peter Drucker

"In God we trust, all others must bring data."
W Edwards Deming

We would like to Measure, Control and Optimise the ***Chemistry***, ***Biology*** and the ***Physics***

Modelling Techniques

- **Regression based modelling**
  - Multiple Linear Regression (MLR)
  - Principal Component Regression (PCR)
  - Partial Least Squares Regression (PLS)
  - ***Non-linear***
    - Non-linear PLS/PCR
    - Weighted regression
    - Fuzzy PLS/PCR
    - Gaussian Process Regression
- **Neural Networks**
  - Feed-forward neural networks
  - Inverse neural networks – inverse models
  - Fuzzy neural networks
  - Wavelet-based neural networks
  - Auto-associative neural networks
  - Mixed-nodes neural networks
  - **Recurrent (Dynamic) neural networks** – ***very powerful***
  - ....

CPACT

Process and Multivariate Data Modelling

- **Full Mechanistic Modelling is best**.
- **Empirical Modelling** using process and analytical data also provides very useful and powerful models – multivariate statistical modelling.
- **Hybrid Modelling:** the conjunction of reduced complexity mechanistic models (e.g. mass and energy balances) with process and analytical data is a very useful alternative.
- ***Transformations:*** reducing model complexity using transformations, e.g. the Arrhenius equation for the temperature dependence of reaction rates is often transformed.
  - ***Caution:*** Transformations may well be useful in process control and APC **BUT** transformations of data being used for multivariate statistical analysis and modelling can destroy the multivariate data structure and should ONLY be used with Care.
- **Data Fusion:** the integration of process measurement, process analytical and calculated data – very powerful and many methods available.

Virtual Measurement through Software Sensors: (Potential for impacting in Formulations)

- ***Soft sensors*** - known also as ***software sensors*** or ***inferential measurements*** are operators' and engineers' virtual eyes and ears.

    - Software sensors create windows into your process where physical equivalents are unrealistic or even impossible and where difficulties in measuring ***quality*** (primary) variables inevitably mean poor or no control at all:

    - e.g. reliance on lab assays/measurements leading to long measurement delays.
    - lack-of or cost-of or difficulty-of using on-line measurement technologies.
    - Reliability of existing sensors.

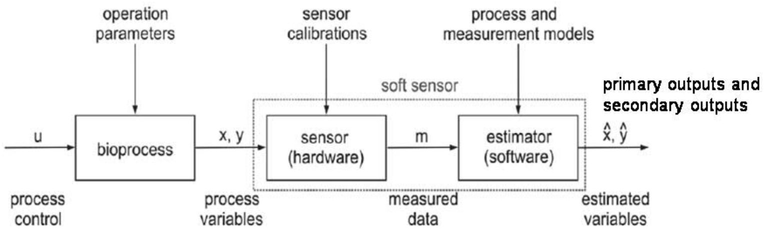
Can be Statistical (data based), Hybrid (mechanistic and data modelling), Dynamic, Non-linear and Adaptive

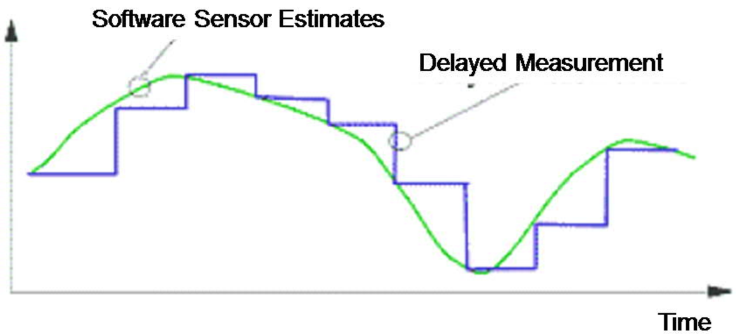
CPACT

Concepts of Software Sensors (Soft-sensors) and Inferential Measurement and Control

- In developing inferential measurement systems, the objective is to ***model the relationship*** between a primary output and secondary outputs and inputs. The model can then be used to ***generate estimates*** of the difficult to measure primary output at the frequency at which the easily measured inputs and secondary variables are measured.

  - Thus, say, instead of waiting 30 minutes for a gas chromatograph to complete its analysis, the inferential measurement system could be returning estimates of compositions every 5 minutes, using measurements of temperatures and flows:





If sufficiently accurate, the inferred states of primary outputs can then be used as feedback for ***automatic control and optimisation***.

Soft (Virtual) Sensor 'Industrial' Articles – 2006 / 2014

Industrial articles - 2006

CHEMICAL PROCESSING
LEADERSHIP | EXPERTISE | INNOVATION

MENU

Home / Articles / 2005 / Soft sensors win hard jobs

Soft sensors win hard jobs

Virtual instruments are gaining increasing roles and capabilities for closed-loop process control.

By C. Kenna Amos, contributing editor

Jan 04, 2006

Pharmaceutical MANUFACTURING

MENU

Home / Articles / 2006 / Virtual Sensors for Advanced Pharmaceutical Process Control

Virtual Sensors for Advanced Pharmaceutical Process Control

Virtual sensors allow key process variables to be monitored in real time, enabling improved process control and optimization.

By N.C. Chakrabarti, Rajesh Sahasrabudhe and Ravindra Bhuyarkar, Tata Consultancy Services, Ltd.

Industrial articles - 2014

CHEMICAL PROCESSING
LEADERSHIP | EXPERTISE | INNOVATION

MENU

Home / Articles / 2014 / Consider Robust Inferential Sensors

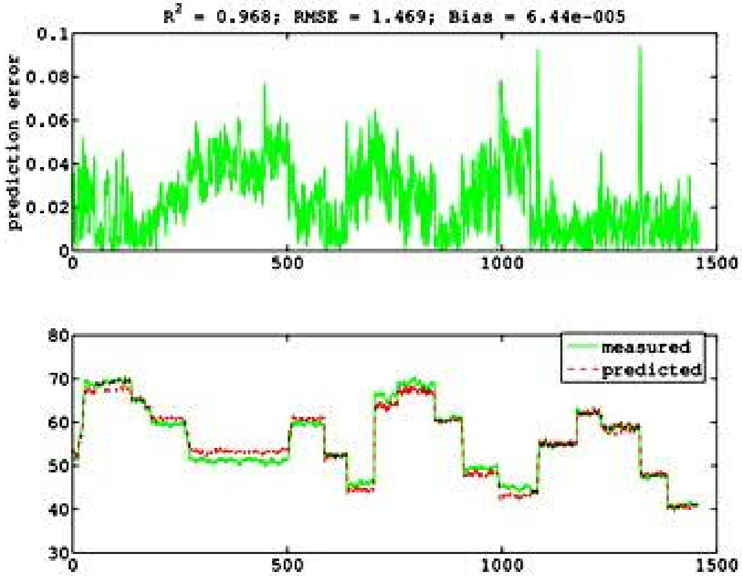
Consider Robust Inferential Sensors

Easier-to-develop-and-maintain sensors offer significant benefits for chemical processes

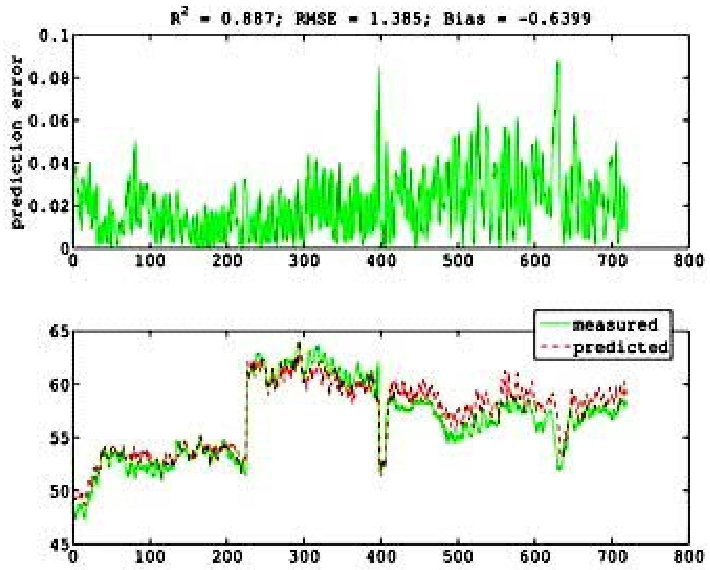
By Arthur Kordon, Kordon Consulting, LLC; and Leo Chiang, Zdravko Stefanov and Ivan Castillo, The Dow Chemical Company

Oct 02, 2014

Robust Inferential Models at Dow Chemicals (2014)



Calibration set for GT1 model
Predictions from model closely matched measured values

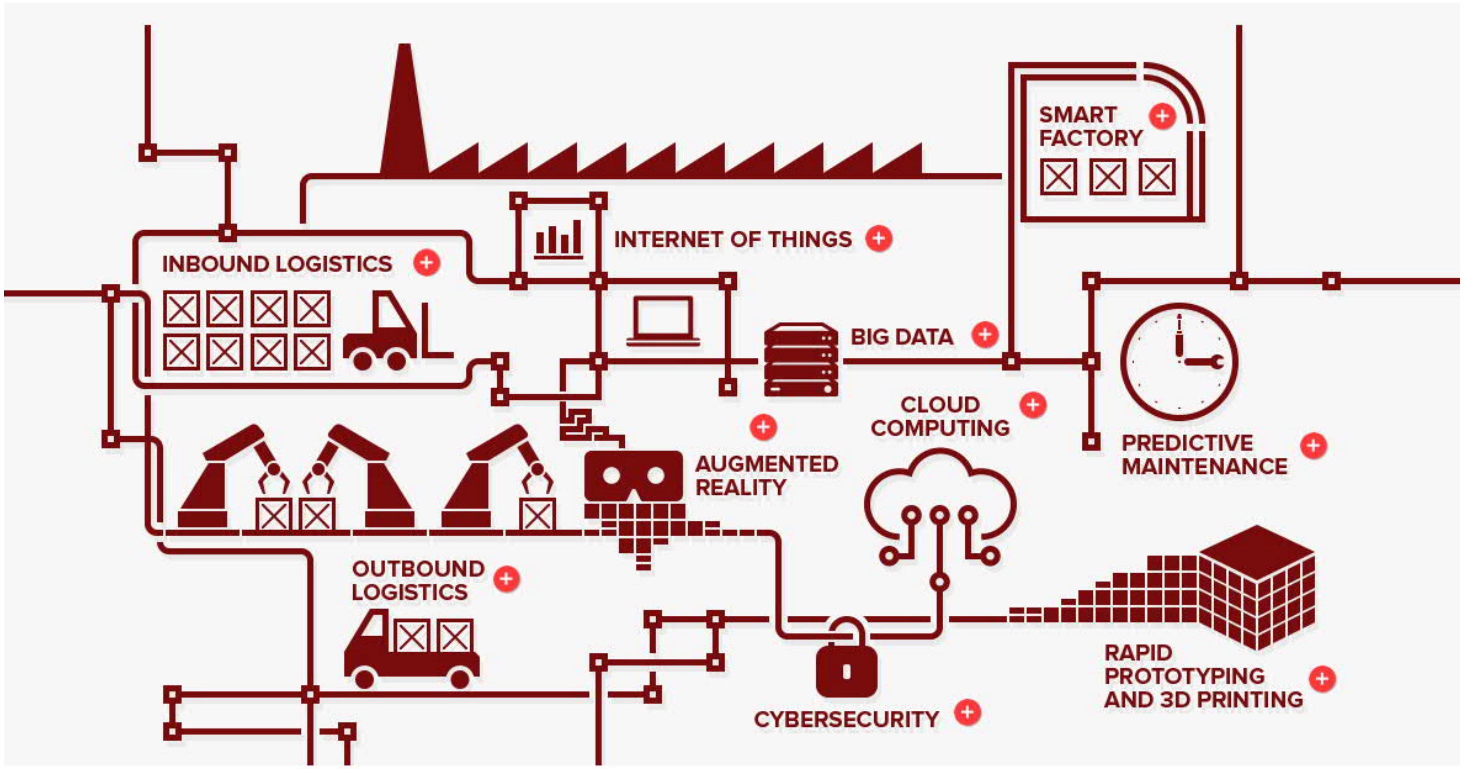


Validation set for GT1 model
Model consistently provides accurate predictions.

From: Arthur Kordon (Kordon Consulting, ex DOW), Leo Chiang, Zdravko Stefanov and Ivan Castillo Consider (DOW Chemical Company), Robust Inferential Sensors (Easier-to-develop-and-maintain sensors offer significant benefits for chemical processes), Chemicals Processing, Oct 2nd 2014

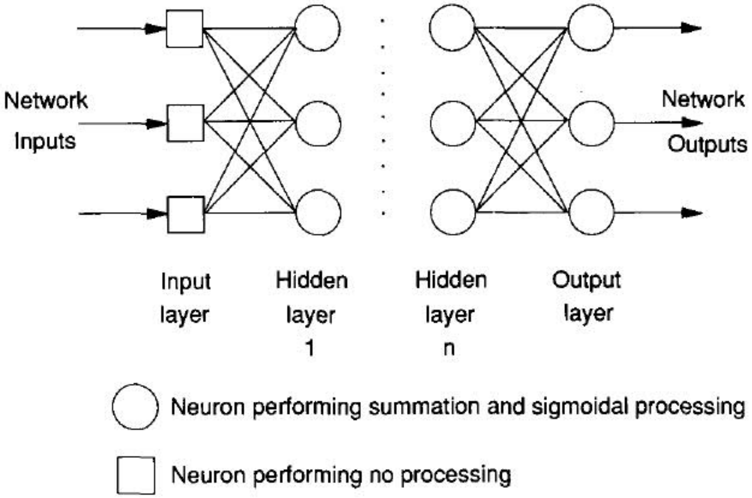
Industrie 4.0 - Smart Factory's and Virtual Sensors

- Software (Virtual) sensor systems provide new opportunities for the collection of physical, chemical and biological data measurements enabling predictions of future process behaviour to be made.

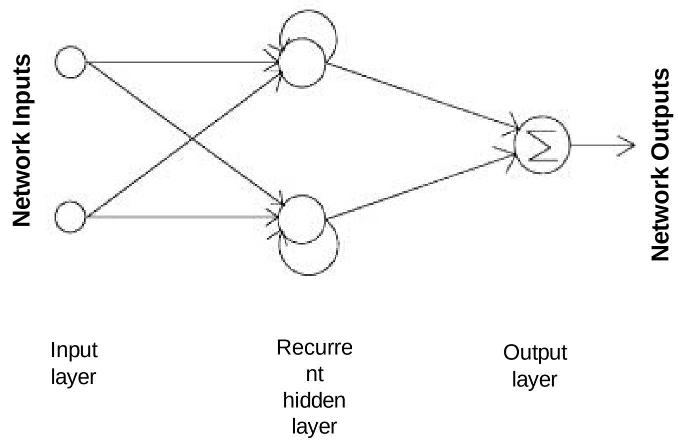


Non Linear Modelling - Neural Networks

- Whilst many artificial neural network architectures have been proposed, one structure has been predominant; that is the ***feed-forward artificial neural network***. A feedforward neural network is made up of interconnected neuron-like elements, termed nodes, organised in layers whereas a ***dynamic (recurrent) network*** has inbuilt recurrence within each node and is arguably the most powerful nonlinear empirical modelling approach.

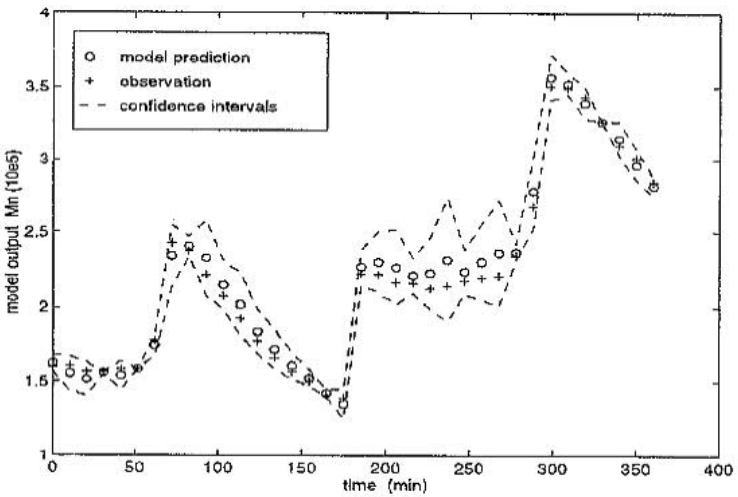


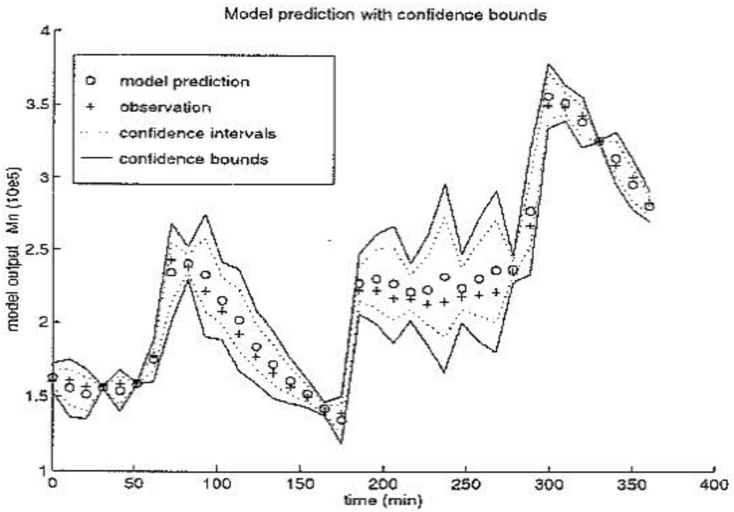
Feed-forward Neural Network



Dynamic (Recurrent) Neural Network

Confidence Intervals & Confidence Bounds for Non-linear Models (Application to MMA Polymerisation Reaction)





➢The fitness-for-purpose of a neural network model is determined by two factors. Firstly, the ability of the network to predict an output and secondly, the distribution of the training data. The ability of a neural network to predict future events can be described using confidence intervals (eg Student's t-distribution).

➢The accuracy of a neural network model is also intrinsically linked to the distribution of the training data. Where a prediction is made in a region where the training data is sparse, the confidence bounds should be wide indicating less reliability in the resulting prediction, in contrast to a region where the training data is dense.

R. Shao, J. Zhang, E B. Martin, A J. Morris, Novel approaches to confidence bound generation for neural network representations, Artificial Neural Networks, Fifth International Conference on Neural Networks, 7-9 Jul 1997

R. Shao, E. B. Martin, J. Zhang and A. J. Morris, Confidence Bounds for Neural Network Representations, Computers Chem. Engng, Vol. 21, Suppl., pp. S1173-S1178, 1997

Is Your Model Useful?

- George (G.E.P) Box often used to say ***"All models are wrong but some are useful"***.
- To analyse historical data the models are usually empirical:
  - regression, data mining (deep learning, neural networks, decision trees, etc.) or latent, eg PCA, PLS, PCR.
- Whether the model is "useful" depends on 3 things:
- The objectives for the Model:
  - Passive ⇒ Classification. Software sensors / Inferential Measurements, Process monitoring (MSPC)
  - Active ⇒ Process analysis, Optimisation, Control
- The nature of the data used to build the model: Historical operating data or data from DoEs
- The regression method used to build the model:
  - Machine Learning, Classical regression ⇒ Passive applications
  - Latent Variable Models (PLS) ⇒ Passive or Active applications

Courtesy John F MacGregor, Empirical Models for Analyzing "BIG" Data – What's the Difference?

Back to the Future

Software Sensors (Soft-Sensors)
and
Inferential Measurement & Control

The *'Original'* Version of Industrie 4.0 Virtual Sensors?

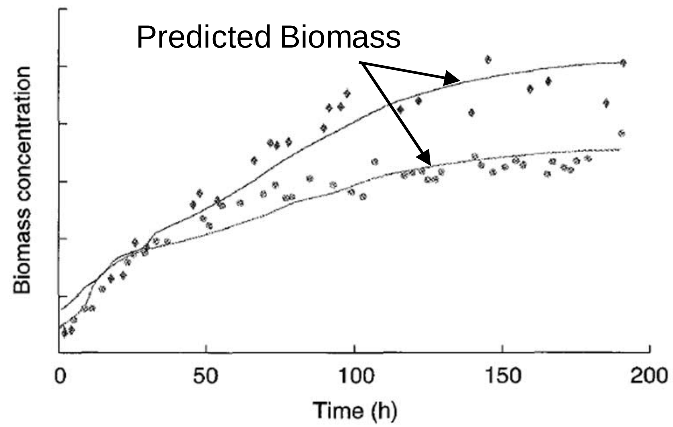
CPACT

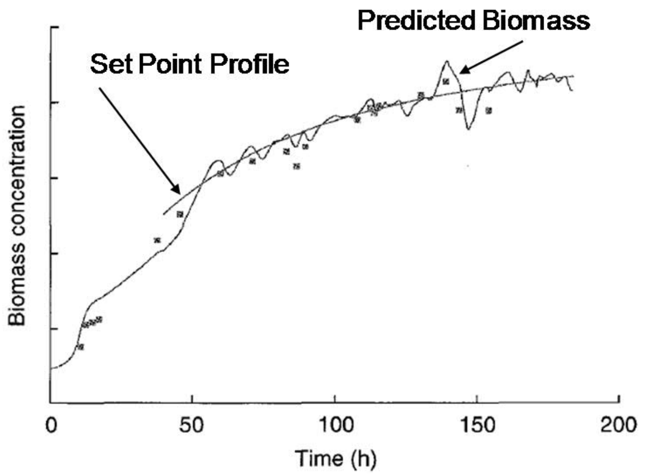
The Early Days at Newcastle (1985 - 1992)

- The research and industrial application of adaptive inferential measurement techniques and software sensors (soft-sensors) started in Newcastle in 1985/1986.
  - Guilandoust, M.T and A.J Morris, (1985), Adaptive Inferential Control of processes with slow measurement rates, Proc. 36th Canadian Chemical Engineering Conference, Calgary Canada.
  - Guilandoust, M.T., Morris, A.J. and Tham, M.T., (1987), "Adaptive Inferential Control", Proc. IEE, Part D, Control Theory and Applications, Vol 134, 3, pp 171-179, May 1987.
  - Montague, G.A., Morris, A.J. and Tham, M.T., (1988), “Application of On- Line Estimation Techniques to Fermentation Processes”, Proc. American Control Conference, pp 1129-1134, Atlanta, USA.
  - Tham, M.T., Morris, A.J. and Montague, G.A., (1989), “Soft-Sensing: A solution to the problem of measurement delays”, Chem. Eng. Res. Des., Vol. 67, pp 547-554.
  - Tham, M.T., Montague, G.A., Morris, A.J., and Lant, P., (1991), "Soft- Sensors for Process Estimation and Inferential Control", Journal of Process Control, 1, pp 3-14.
  - Montague, G.A., Morris, A.J. and Tham, M.T. (1992). "Enhancing bioprocess operability with generic software sensors", Journal of Biotechnology, 25, pp 183-201.

Since that time the literature and industrial applications of software sensors has exploded and more recently has been ***‘re-invented’*** as a ‘Virtual Process Analytical Technology (PAT) tool’.

Enhancing Fed Batch Fermentation Controllability (circa 1990)





- Biomass estimation test data sets from two commercial scale fermentation runs with SmithKline Beecham.
- Different sugar feed-rates resulted in different levels of biomass concentration.

- The performance resulting from controlling biomass in a closed loop (by variation of sugar feed) to a set point profile predetermined by the fermentation technologists.
- Reasonable set-point tracking is observed when the loop is closed 40h into the fermentation, and good disturbance rejection following an air flowrate disturbance at 130h is also observed.

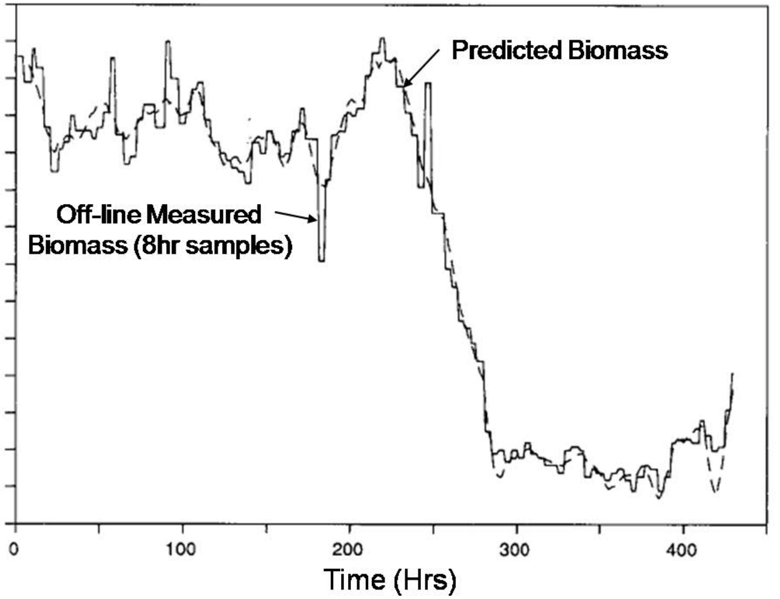
Montague, G & J. Morris, Neural-network contributions in biotechnology, Tibtech Aug 1994, 12, 312-324

Acknowledgements to: SmithKline Beecham

The Joint Marlow Foods – ICI Myco-Protein 140,000L Continuous Bioreactor at Billingham (circa 1990)

- In 1996 Marlow Foods in a joint venture with ICI used a fermenter from their single-cell animal feed programme and with Marlow Foods commissioned a 140,000L air-lift fermenter for myco-protein production at the ICI site at Billingham.

Adaptive Software Sensor Biomass Predictions

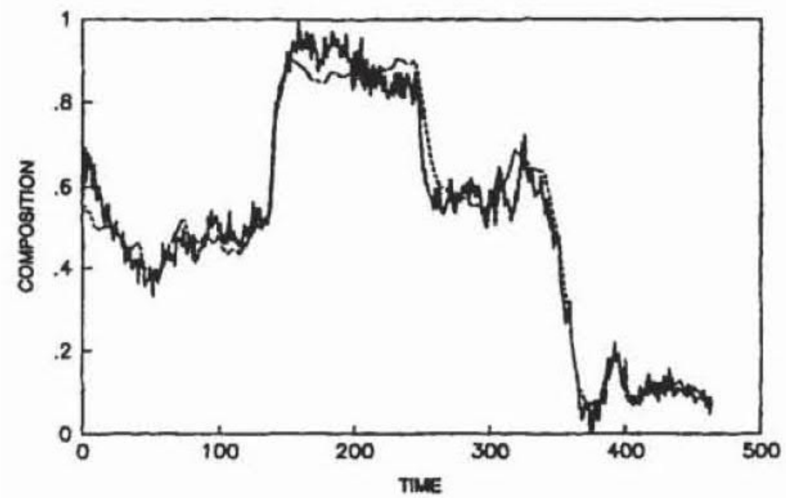


Ming T. Tham, Gary A. Montague, A. Julian Morris, and Paul A. Lant, Soft-sensors for process estimation and inferential control, J. Proc. Conttol, 1, (1991) 3-14

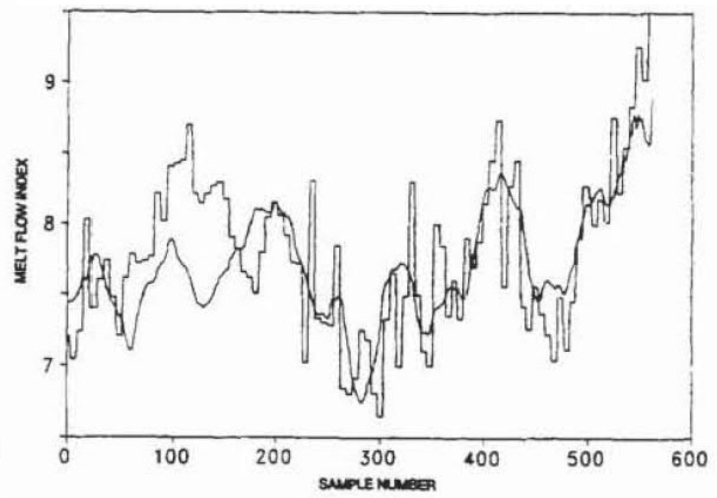
G.A. Montague, A.J. Morris & M.T. Tham, Enhancing bioprocess operability with generic software sensors, Journal of Biotechnology, 25 (1992) 183-201

Acknowledgements to: Marlow Foods and ICI Biologics

Adaptive Inferential Soft Estimation Applications: Industrial Demethaniser and Polymer Melt Flow Index



Dynamic inferential estimation for the regulation of top product composition in an industrial Demethaniser using reflux flow. The analyser delay was 20 min and process variables overhead vapour temperature, reflux flow rate, column feed rate measured every 5 min. Top tray liquid temperature was not available.



Melt Flow Index versus Lab Measurement. Neural Network inputs were reactor feed rate, coolant flow rate and hydrogen concentration above the reacting mass at 10 min intervals.

Acknowledgements to: ICI Engineering and ICI Chemicals and Polymers

Prediction of Polymer Quality and Estimation of Impurity and Reactor Fouling

Case Study: Batch MMA Polymerisation

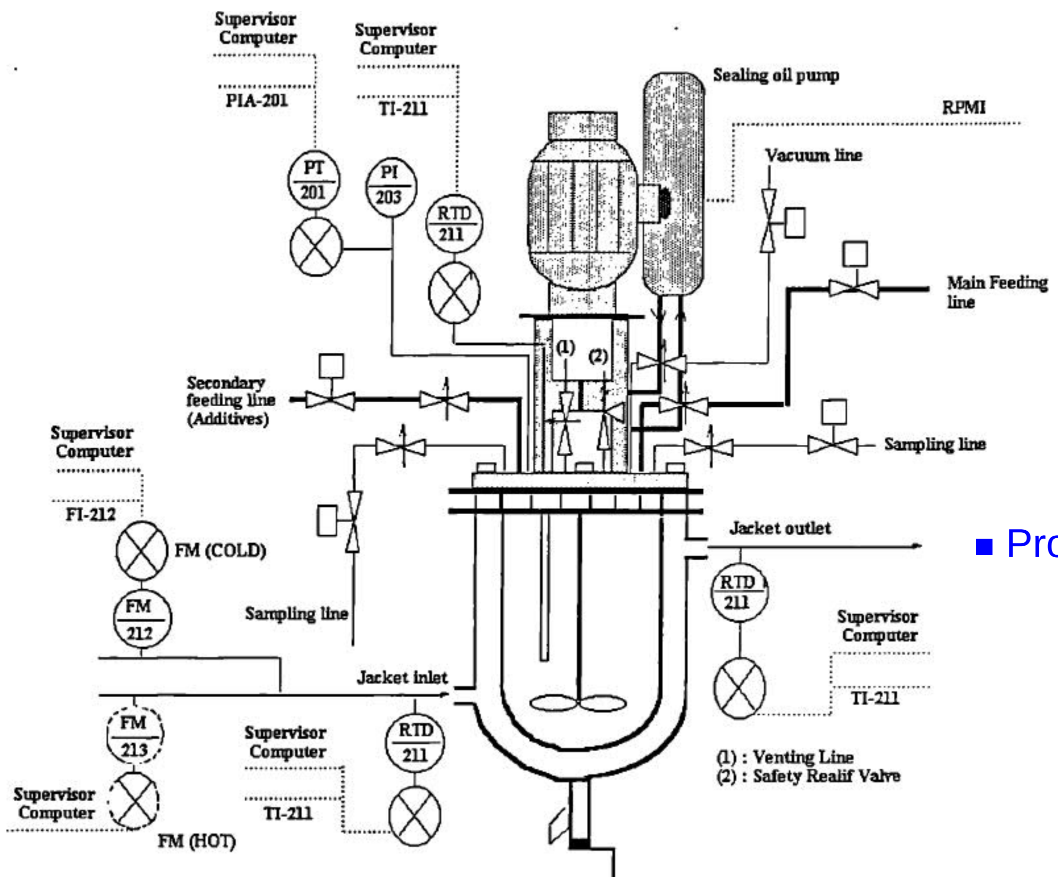
Zhang, J., Morris, A. J., Martin, E. B. and C. Kiparissides, “Estimation of Impurity and Fouling in Batch Polymerisation Reactors through the Application of Neural Networks. Computers and Chem. Engng, Vol 23, No. 3, 1999, pp 301-314.

Zhang, J., Martin, E. B., Morris, A. J. and Kiparissides, C., “Prediction of Polymer Quality in Batch Polymerisation Reactors Using Robust Neural Networks”, Chemical Engineering Journal, 69(2), 1998, pp 135-143.

Zhang, J. Martin, E. B., Morris, A. J. and Kiparissides, C. , “Inferential Estimation of Polymer Quality using Stacked Neural Networks”, Computers Chem Engng, 21, 1997, pp S1173-S1178.

CPACT

Methyl Methacrylate (MMA) Reactor
(Prediction of Weight & Number Average Molecular Weights



MMA is foundational for many acrylate polymers and is an essential co-monomer in paint, coatings, and adhesives resin formulations

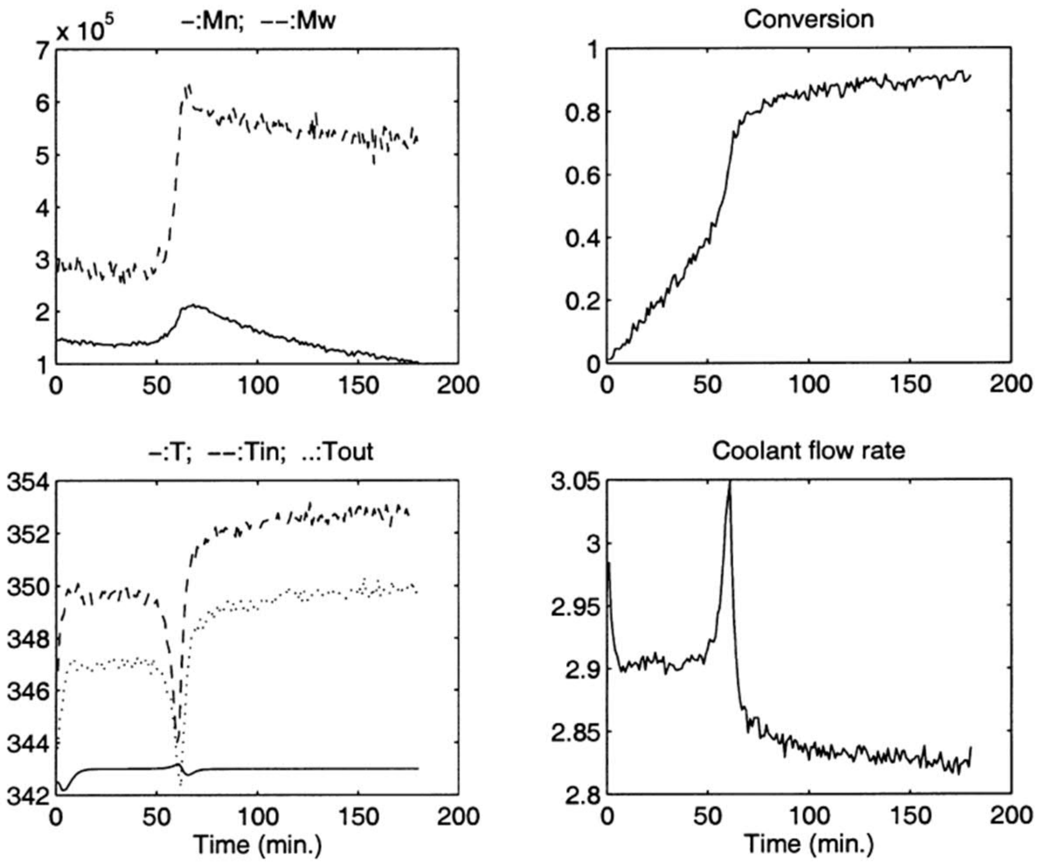
- Process measurements
  - Coolant flow rate
  - Inlet jacket temperature
  - Outlet jacket temperature
  - Monomer conversion
  - Reactor temperature

CPACT

Polymer Quality Variables and On-line Measured Process Variables

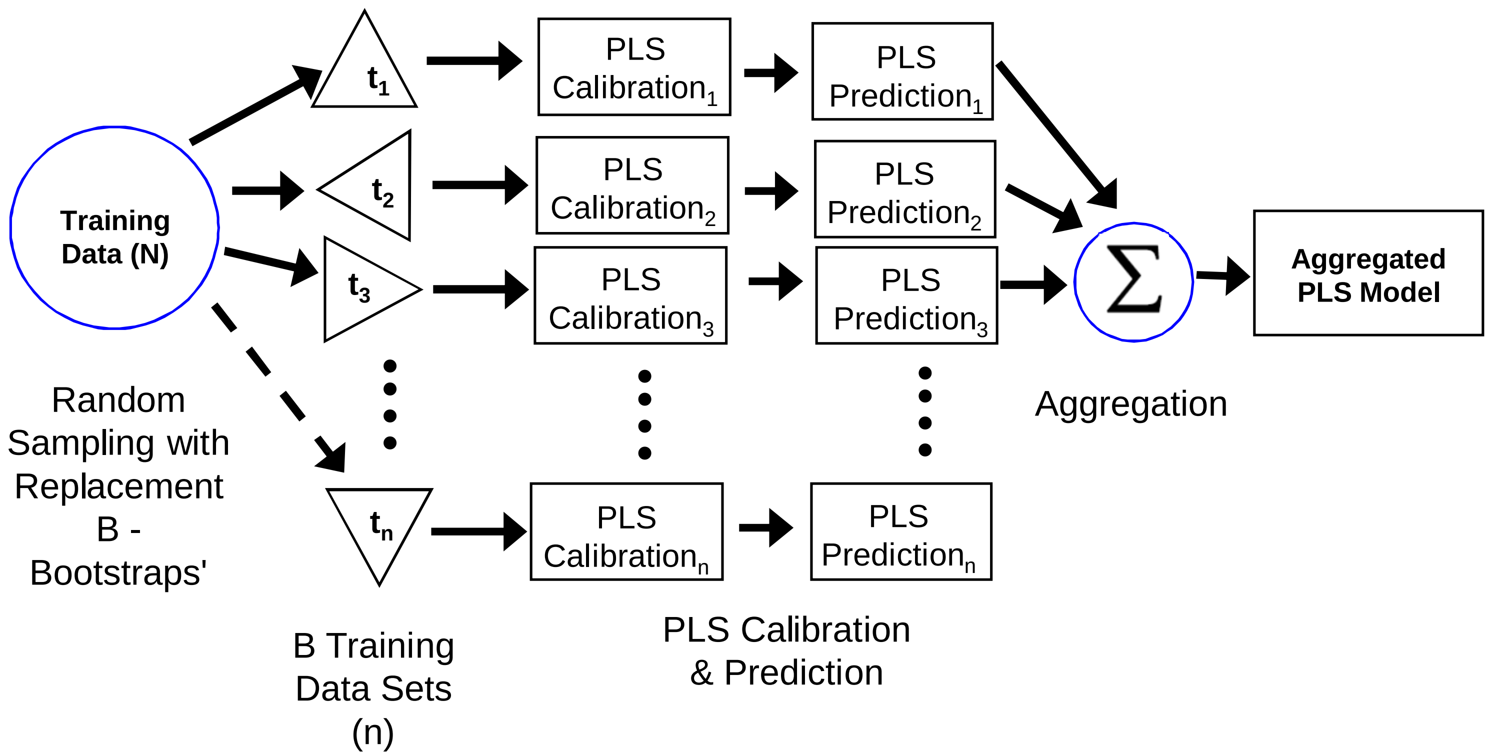
Quality (offline)

Process (online)

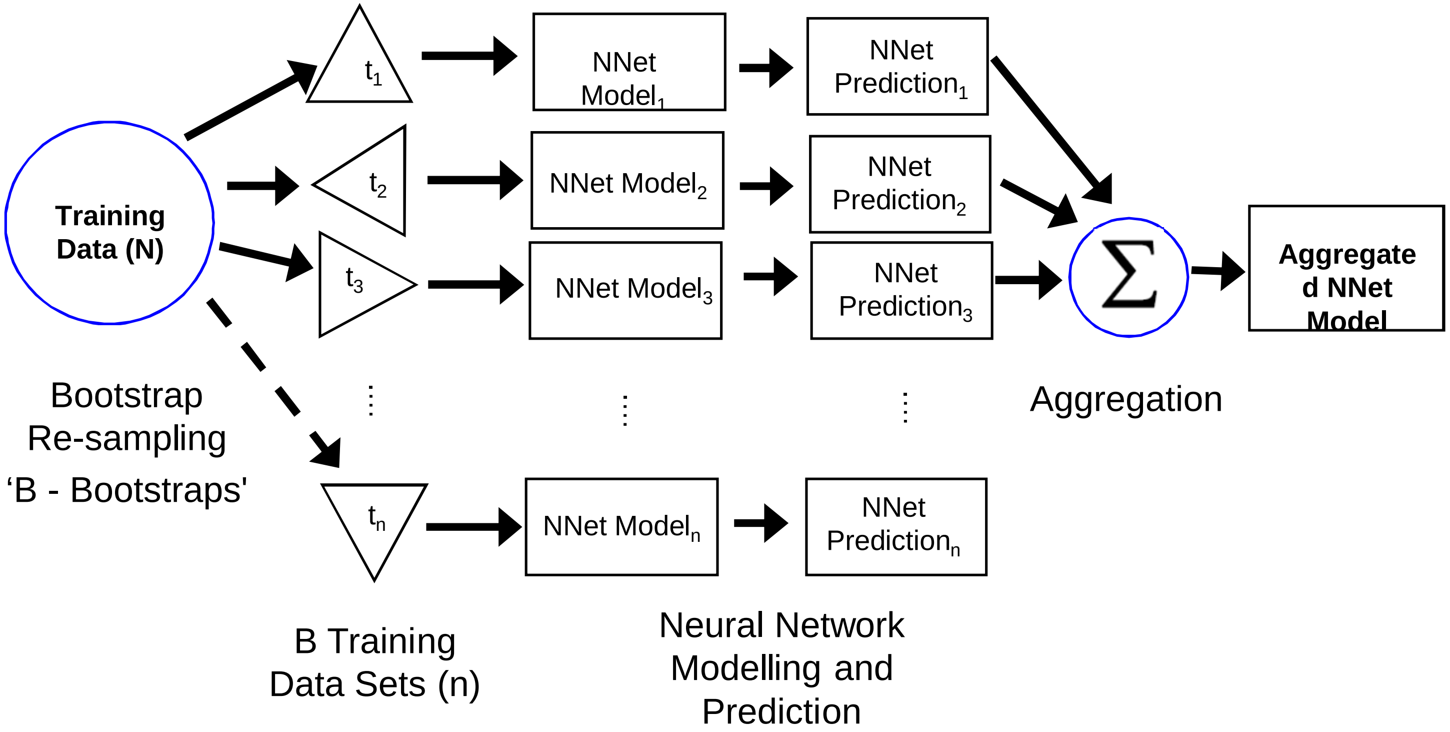


CPACT

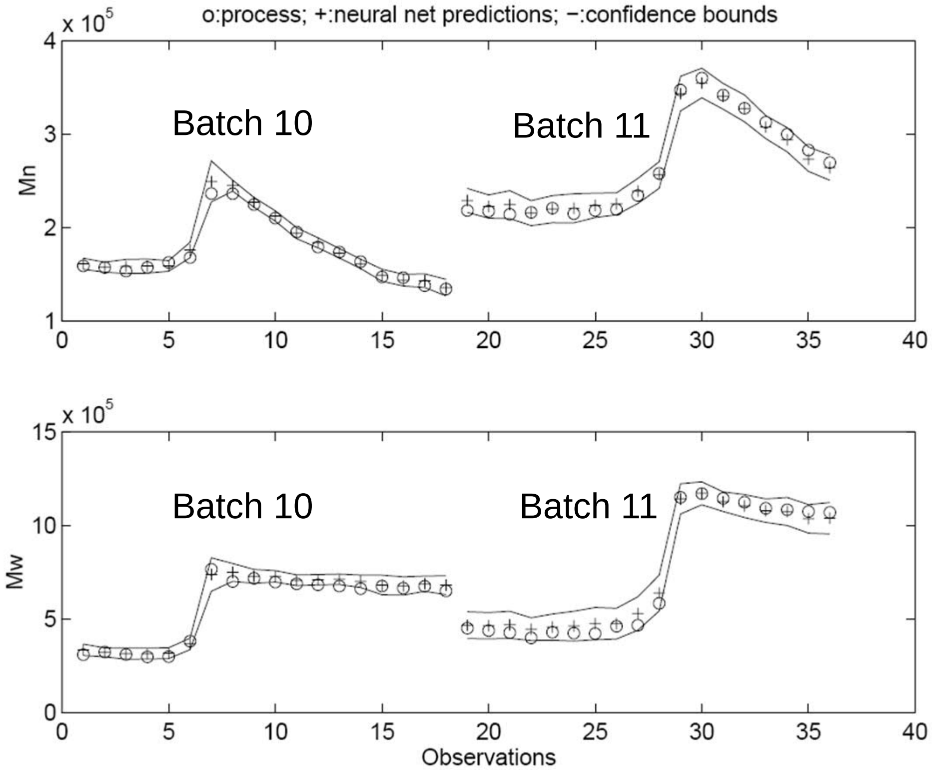
Aggregated (Stacked) PLS Regression Models



Aggregated (Stacked) Neural Network Models



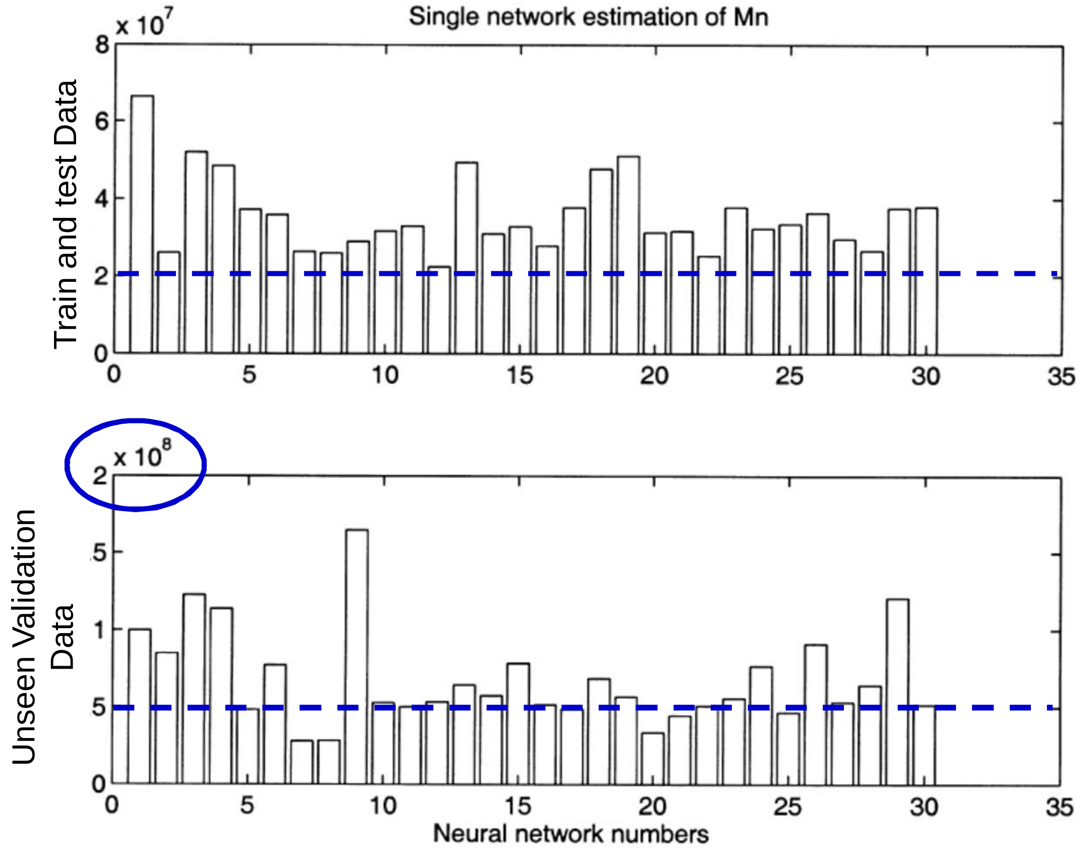
Model Predictions with 95% Confidence Bounds



Process Measurements
Neural Network Predictions

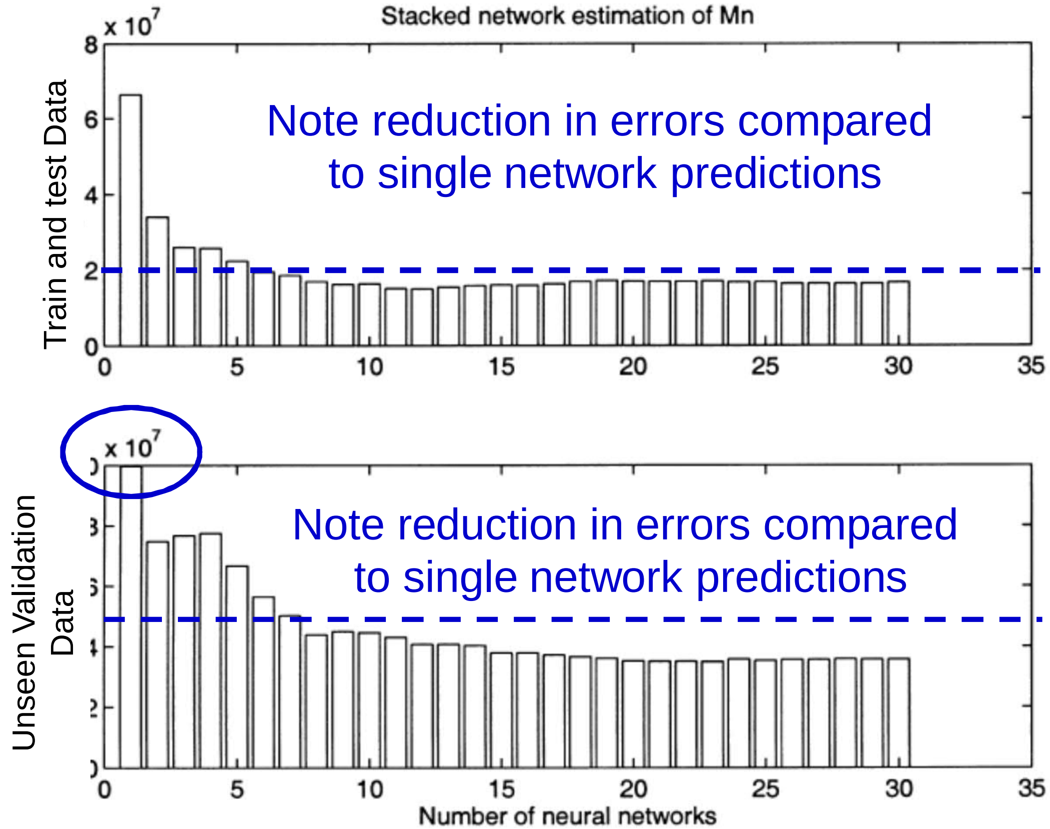
For clarity model predictions confidence bounds are plotted at 10 min intervals.

Single Network Predictions of Number Average Molecular Weight

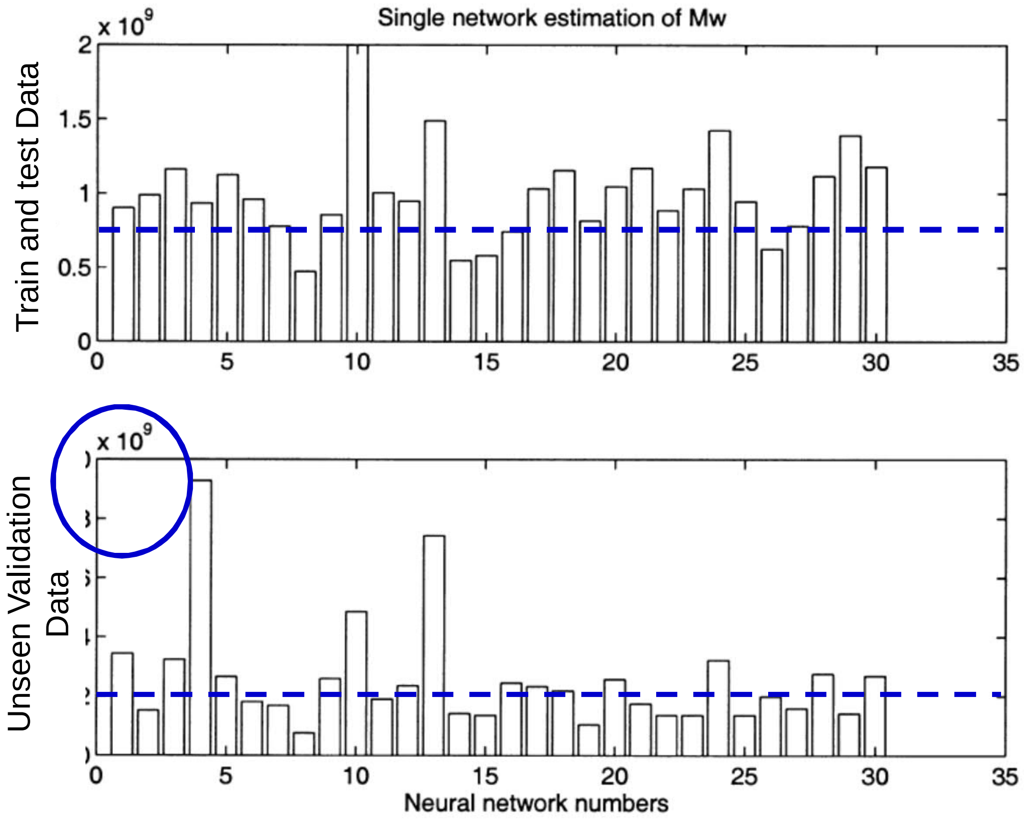


CPACT

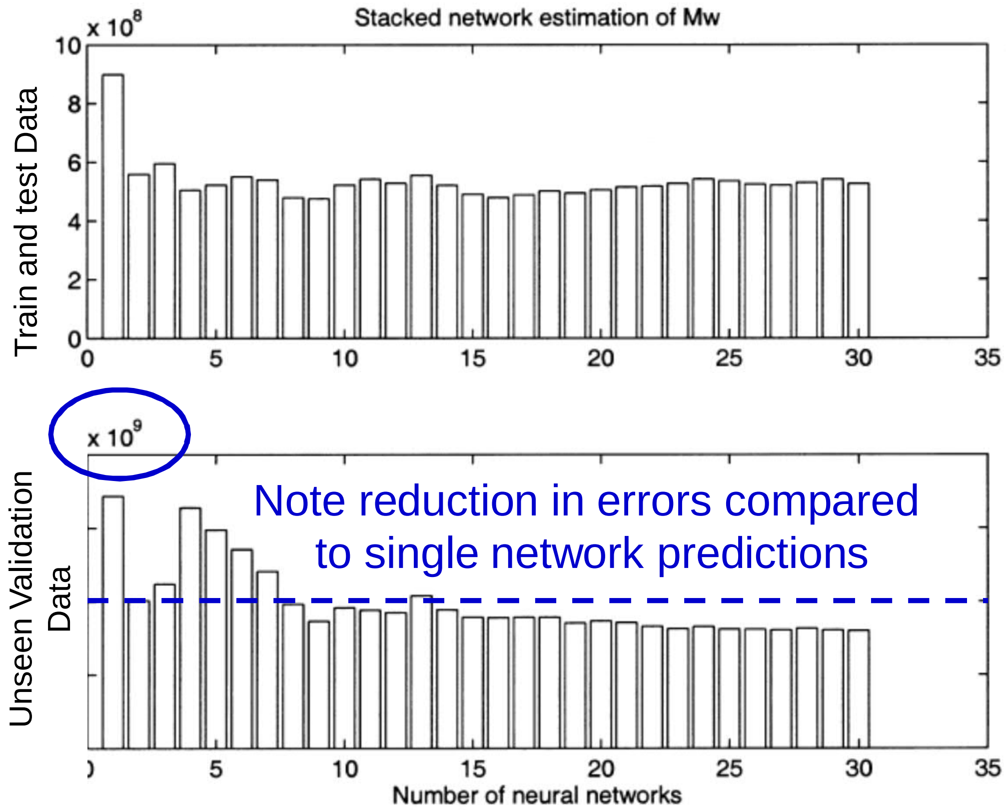
Aggregated Network Predictions of Number Average Molecular Weight



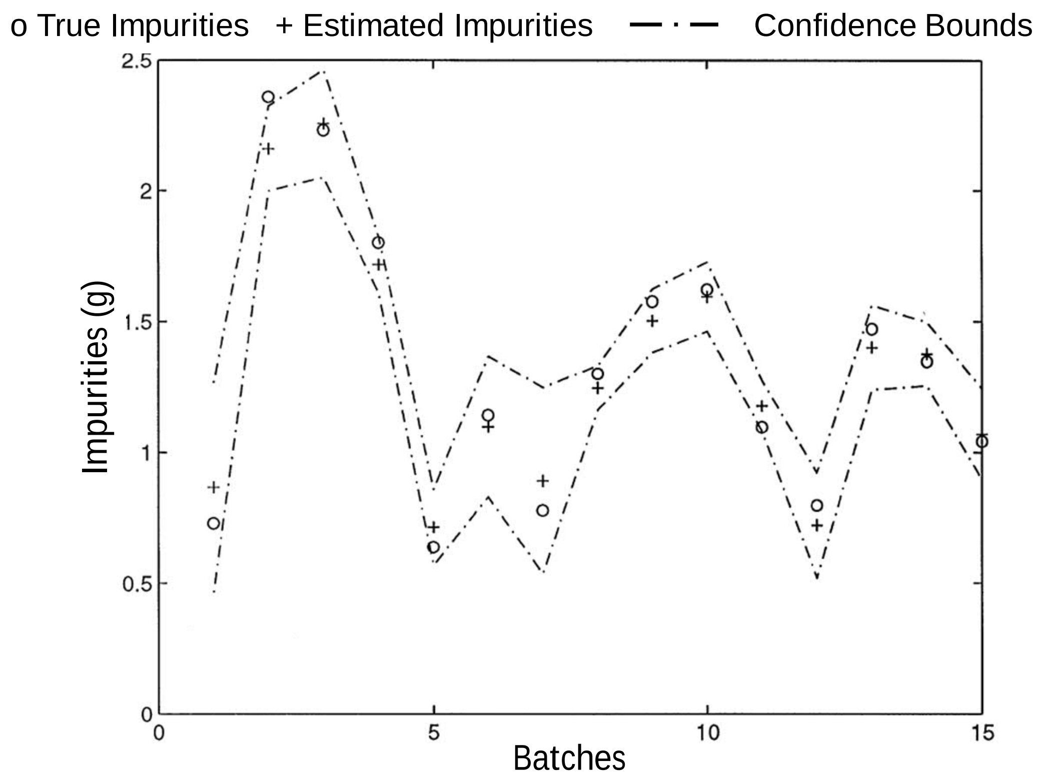
Single Network Predictions of Weight Average Molecular Weight



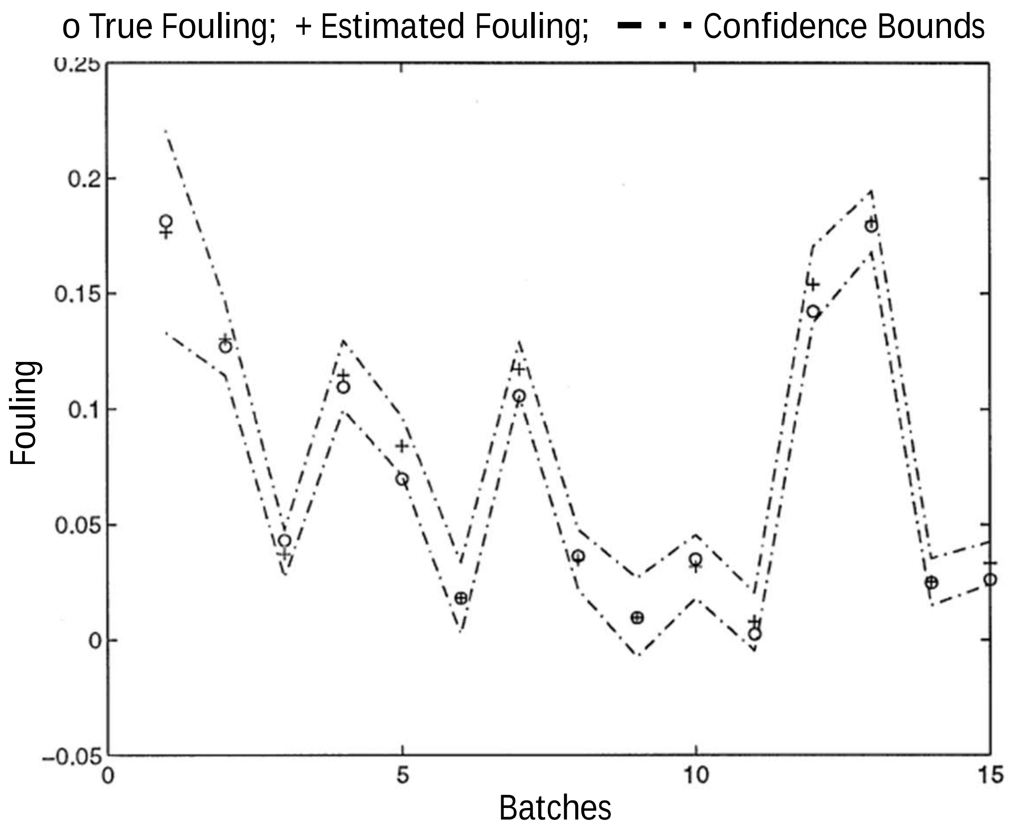
Aggregated Network Predictions of Weight Average Molecular Weight



Estimation of Reactive Impurities using Aggregated Neural Network Models



Estimation of Reactor Wall Fouling using Aggregated Neural Network Models



Closure

Its not just the Application of Process Measurement and Control Technologies

It is the COMBINED use of the appropriate process measurements along with smart modelling and smart chemometrics

for Success to be Achieved

Provide Significant Technological and Business Opportunities

- Industrial applications are much more complex than implementing ***'eight sensors'*** in a ***smart-phone*** compared to ***thousands of data points in an industrial processing***.
- ***Industrie 4.0*** and the Industrial Internet of Things (IoT) provide impetus.
- Automated systems have always produced large amounts of data which typically have been left ***'unused and unexplored'***.
    - *Software Sensors and Analytics in industrial applications can produce surprisingly fast returns on investment – e.g. the faster measurement, prediction, early-warning, etc of process and equipment failures before they happen such as production stops and lost production time to whole batches (runs).*
- *Convincing conservative chemicals, materials and pharmaceutical companies needs good business cases with predictable returns on investment*.
    - Also provides an opportunities to move from CAPEX to OPEX.

CPACT

Thankyou to Dr Dave Berry for the kind invitation

and of course you for your attention

I will be happy to answer questions

Acknowledgements: My CPACT research colleagues past and present and CPACT member companies for their R&D challenges and CASE Studies

CPACT