The Development of Chemometric Techniques for Improved Process Understanding and Reaction Optimization

Principal Investigators:
Brian Marquardt Senior Principal Engineer (206) 543-6054
marquardt@apl.washington.edu

Research Personnel:
J.P. Kirby Research Associate

Executive Summary: The purpose of this proposal involves the innovation and deployment of chemometric tools for process control and optimization. The term ‘chemometrics’ refers to a series of statistical tools that take large portions of data and extract relevant information. These tools include techniques such as Partial Least Squares (PLS) which allows a user to decompose a data matrix and build models that can be used for many different purposes such as process intensification or reaction monitoring. Chemometric analysis is typically performed with multivariate data; making it an excellent partner for most PAT instruments that use Raman, Infra-Red or Fluorescence spectroscopy. Real-time process control and optimization may be achieved by coupling the high-performance sampling and measurements capabilities of PAT tools to the rapid analysis and automation enabled by chemometrics.

Goals/Objectives:
The innovation and implementation of novel chemometric methods for process control and optimization will require in-depth evaluation of a number of data handling and analysis procedures. These will include an exploration of methods for engineering quality assurance into a system and proactively making decisions through feed-forward models. Additionally research will be undertaken to improve predictive modeling and the analysis of LIBS spectral information through high level data fusion and hierarchal modeling.

Primary Objectives:

1. Continue to develop the concept of feed-forward models for prediction of final product yield from starting materials.
2. Investigate application of high level data fusion for rapid analysis and modeling of LIBS/Raman spectral data

Budget for 2015-2016: $24,500 - Funds would support CPAC research staff to support the analytical work and supplies/travel needs for the research.

Background: Process understanding relies on optimizing three key concepts; sampling, measurement and analysis. Chemometrics is an integral component in each of these concepts from sampling statistics to background correction to predictive modeling. By applying advanced chemometric techniques, rapid improvements in understanding can be made throughout an entire process.

Background - Feed-Forward Modeling

CPAC researchers have developed a Continuous Flow Reactor system, equipped with NeSSI technology, capable of producing over 3500kg /per year from a single unit. The smart CFR system employed a multichannel Raman spectrometer to validate product quality in real-time and occupied a total footprint of $1m^3$. This smart system has demonstrated rapid optimization and quality assurance through the use of Raman, NeSSI and CFR technology. However, because measurements of product quality are performed post reaction, any issues related to reagent quality or reactor performance will result in the formation of small volumes of out of specification product. The current control mechanism for the reactor is a traditional feedback system that relies on operator input based upon assessment of reactor sensors (temperature, pressure and flow rate) and Raman chemical information. This is a non-optimal procedure that can lead to the production of small aliquots of undesirable product.

Proposed Work – Feed-Forward Modeling

We propose the development and employment of feed-forward models to certify final product yield by using the fusion of regent spectra and reactor parameters (such as T, P and F). The feed-forward model would first ensure the reagents meet a pre-determined specification before being loaded into the CFR. This approach prevents the use of counterfeit or poor quality reagents, and protects consumers from potentially harmful chemical agents. Once the reagents pass the authentication stage, the feed-forward model would employ real-time data fusion and modeling to predict final product quality. This prediction will be compared to the desired product specifications, if the prediction meets the desired specification the reagents will be released into the reactor. If the predicted yield is outside the acceptable range, the reactor conditions will be

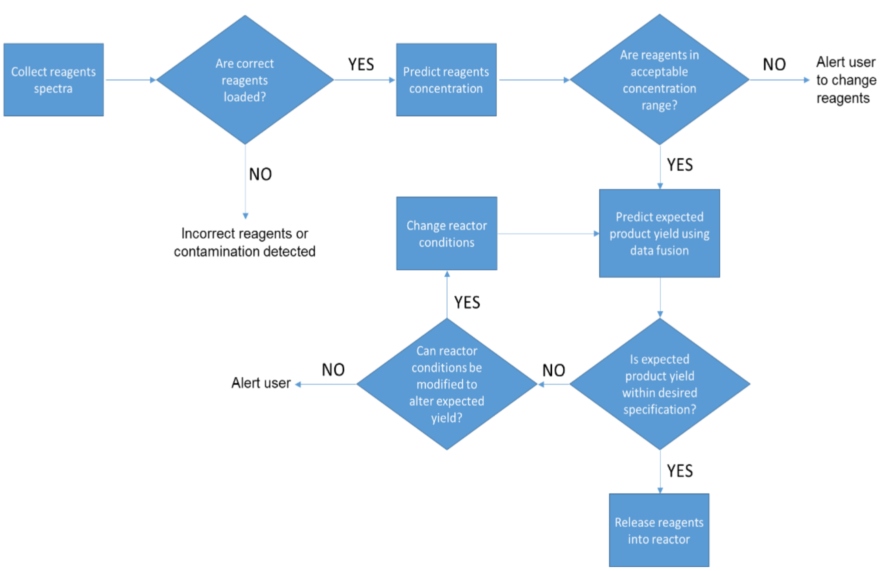

Figure 1 - Basic Outline of Feed-forward model architecture

modified to achieve the desired range in product yield. Implementation of this technology will ensure that the materials produced in the reactor meet quality specifications, furthermore this technique could be applied across any manufacturing process were information regarding raw materials can be gathered.

Background - LIBS Spectral Analysis

Recent improvements in laser technology and CCD arrays have led to a significant increase in the application of LIBS for process analysis. LIBS is an incredibly data rich technique and can be used across a wide array of industries owing to the minimal sample preparation required for analysis. The increased usage of LIBS spectra has amplified the demand for techniques and procedures for handling and analyzing LIBS spectra. Previous work by CPAC researchers has focused on preprocessing methods and techniques for the removal of information not associated with the LIBS analytical signal.

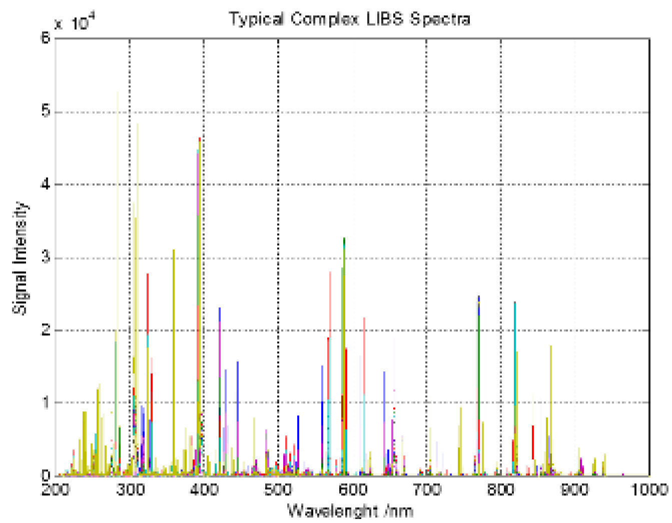

Figure 2 - Typical complex LIBS spectra

Proposed Work – LIBS Spectral Analysis

We propose to build upon previous CPAC research and harness LIBS spectra for classification and predictive modeling purposes. To achieve this goal research will be conducted to first produce methods for rapid elemental identification and quantification using LIBS spectra. Secondly high level data fusion methods will be applied to combine relevant outputs from a number of hierarchal models to fully extract all information from the LIBS. Figure 3 shows an overview of a higher order data fusion procedure. In this procedure three different models are produced using the LIBS data, each model is built using a different technique and extracts different sources of information. High level data fusion fuses the outputs of the different models together to produce a fused matrix. The newly fused matrix undergoes a final round of modeling that could be useful for numerous application including classification and quantification algorithms

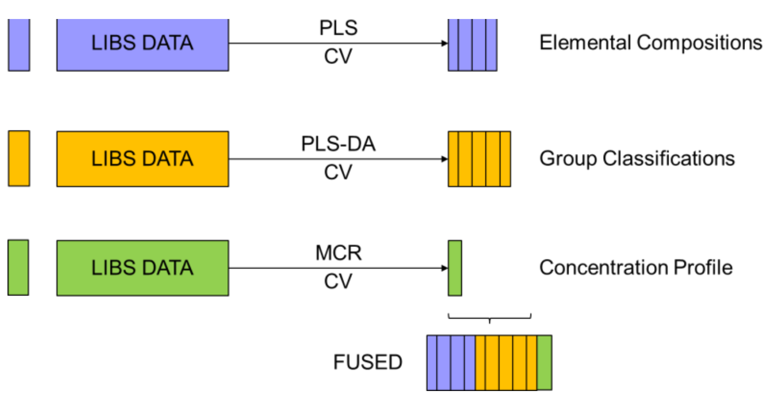

Figure 3 - High level data fusion schematic

Biographical Sketch

NAME	POSITION TITLE
Brian J. Marquardt, Ph.D. Applied Physics Laboratory University of Washington Seattle, WA 98105	Senior Principal Engineer Research Professor, Electrical Engineering

Education/Training

INSTITUTION AND LOCATION	FIELD OF STUDY	DEGREE	YEARS
Ripon College	Chemistry	A.B.	1993
University of South Carolina	Analytical Chemistry	Ph.D.	1997
University of Washington	Analytical Chemistry	*Post-Doc*	1998-1999

Personal Statement

My research group has been developing remote optical sensing platforms for environmental, industrial, chemical and biological applications for over 12 years. We have extensive experience in the design and construction of robust chemical measurement instrumentation for diverse applications. My research group is a multidisciplinary team that includes chemists, engineers, oceanographers and statisticians. My group specializes in developing solutions for complex problems starting from the ideals of fundamental science through to the design and construction of measurement systems capable of deployment in extreme environments.

Appointments

2012-present Senior Principal Engineer, University of Washington, Applied Physics Lab
2009-present Research Prof., Univ. of WA, Electrical Engineering
2007-2011 Senior Res. Engineer, University of Washington, Applied Physics Lab
2000-2006 Senior Research Scientist, University of Washington, CPAC
1998-1999 Post-doc, University of Washington, CPAC
1993-1997 Research Assistant, University of South Carolina

Publications – 10 Most Relevant

1. B. J. Marquardt, Dimitra N. Stratis, D. A. Cremers and S. M. Angel, "Novel probe for Laser-Induced Breakdown Spectroscopy and Raman Measurements Using an Imaging Optical Fiber," *Appl. Spectrosc*, **52**, 9, 1148, **1998**.
2. S. M. Angel, J. C. Carter, D. N. Stratis, B. J. Marquardt, W. E. Brewer, "Some New Uses for Filtered Fiber-Optic Raman Probes: *In Situ* Drug Identification and *In Situ* and Remote Raman imaging," *J. Raman Spectrosc.*, **30**, 9, 795, **1999**.

3. P.G. Vahey, S.H. Park, B.J. Marquardt, Y. Xia, L.W. Burgess and R.E. Synovec, "Development of a Positive Pressure Driven Sub-Nanoliter Injection Technique for Micro-Fabricated Open Tubular Liquid Chromatography," *Talanta*, **51**, 1205, **2000**.
4. B.J. Marquardt*, T. Le and L.W. Burgess, "Demonstration of a High-Precision Optical Probe for Effective Sampling of Solids by Raman Spectroscopy," SPIE Proceedings, Vol. 4469, August, **2001**.
5. T. M. Battaglia, E. E. Dunn, M. D. Lilley, J. Holloway, B. K. Dable, B. J. Marquardt, K. S. Booksh, "Development of an *In-situ* Fiber Optic Raman System to Monitor Hydrothermal Vents," *Analyst*, **129(7)**, 606, **2004**.
6. B. K. Dable, B. J. Marquardt,* "Characterization and Quantitation o a Tertiary Mixture of Salts by Raman Spectroscopy in Simulated Hydrothermal Vent Fluid," *App. Spectrosc*, **60(7)**, 773, **2006**.
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8. T. Dearing, W. Thompson, C. Rechsteiner and B.J. Marquardt, "Characterization of Crude Oil Products Using the Data Fusion of Process Raman, IR and NMR Spectra," *Appl. Spectrosc.*, 65(2), 181-186, **2011.**
9. M. Roberto, S. Martin, T. Dearing, B.J. Marquardt, "Integration of Continuous Flow Reactors and in-line Raman Spectroscopy for Process Optimization", *Journal Pharm. Innov*., 7(2), 69 – 75, **2012**.
10. S. Mozharov, A. Nordon, D. Littlejohn and B. Marquardt "Automated Cosmic Spike Filter optimized for Process Raman Spectroscopy". *Applied Spectosc.*, 66(11), 1326, **2012**
11. S. Ewanick, W. Thompson, B. Marquardt and R. Bura, "Real-time Understanding of Lignocellulosic Bioethanol Fermentation by Raman Spectroscopy", *Biotechnology for Biofuels*, 6:28, **2013**
12. Brian J. Marquardt and Lloyd W. Burgess, *Optical Immersion Probe Incorporating A Spherical Lens*, US patent #'s 6,831,745and 6,977,729 issued Dec. 2004 and Dec. 2005.