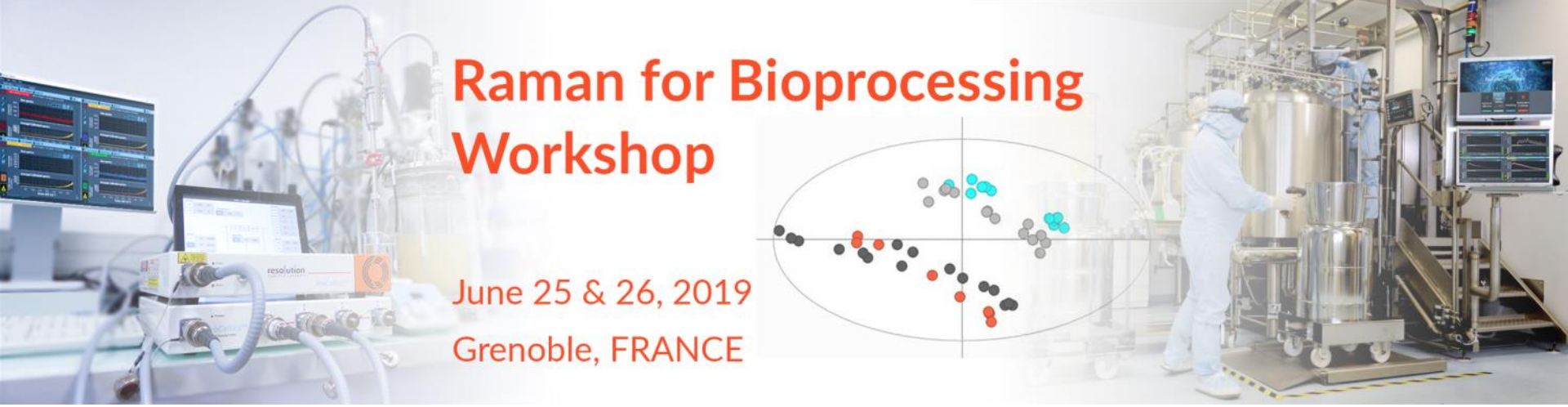
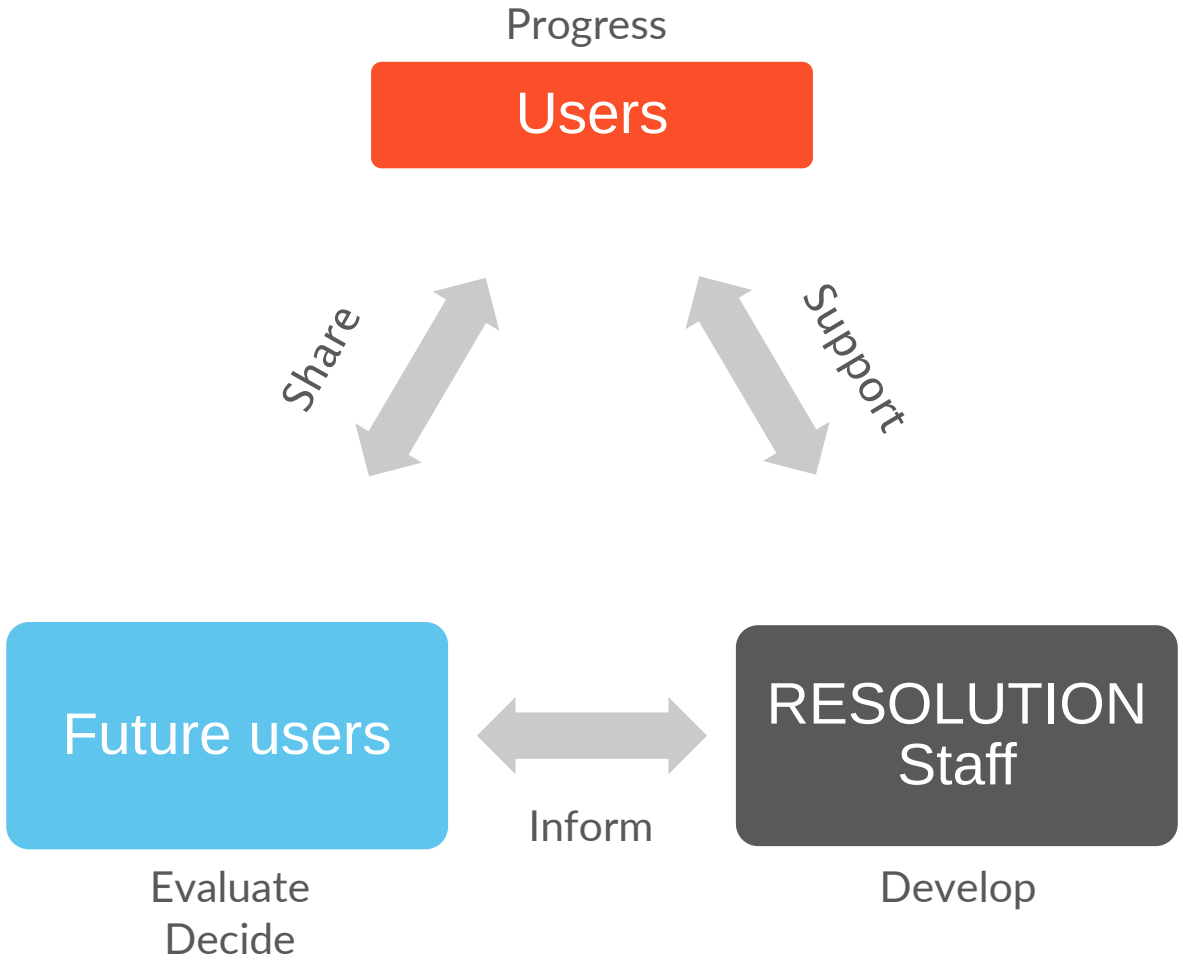


A chronicle of Raman Bioprocessing

Christophe BONNEVILLE, PhD – President

resolution
spectra systems

Why a workshop about Raman for bioprocessing?



Why a workshop about Raman for bioprocessing?

Conference	Number of talks dealing with Raman		
	2017	2018	2019
IFPAC	5	10	9
ESACT	1	-	5
Bioprocessing Summit Europe	-	3	3

Hot topic but talks generally provide:

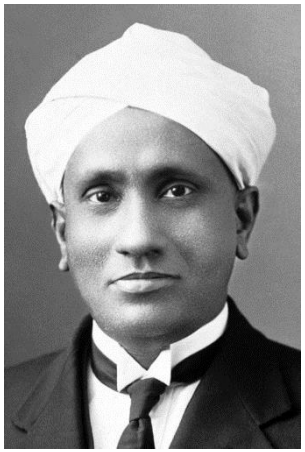
- Short redondent explantations about Raman fundamentals
- Results of user cases with very few explanations about the followed way
- No emphasis on problems to be fixed
- Lack of vision of the future

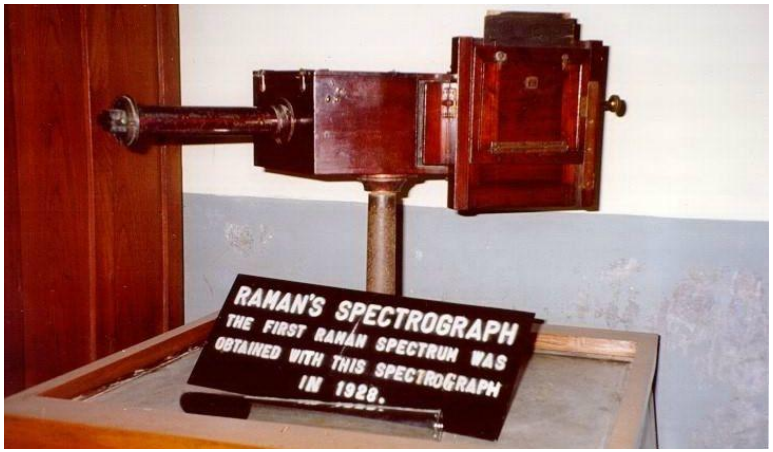
During this 2-day workshop:

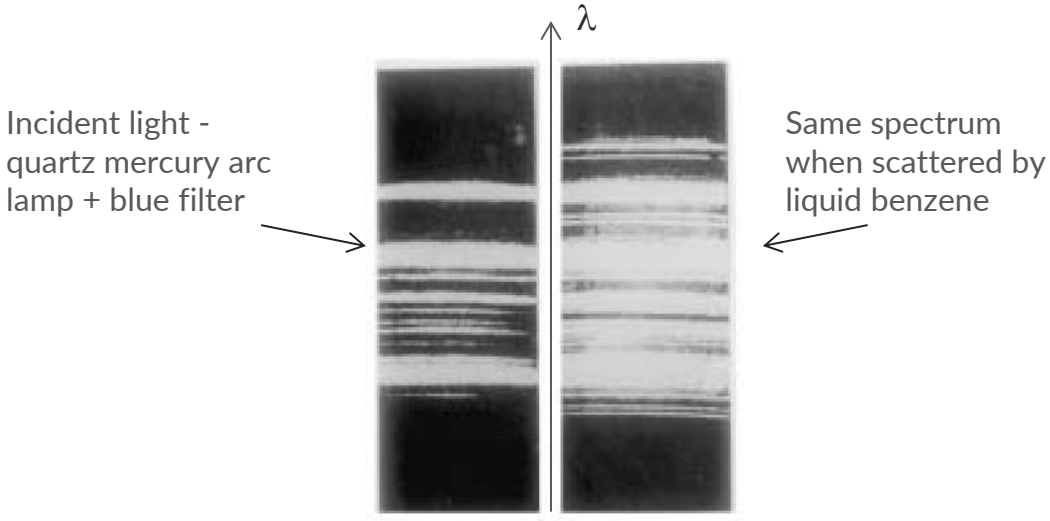
- Deeper fundamentals about Raman and chemometrics
- Detailed and transparent user cases
- Tips and tricks to progress smoothly
- Think about the future

A chronicle of Raman for bioprocessing

1930 Sir Chandrashekhara V. Raman
Nobel Prize in Physics





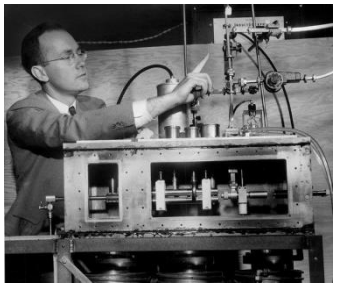


Courtesy of the Raman Research Institute, Bangalore.

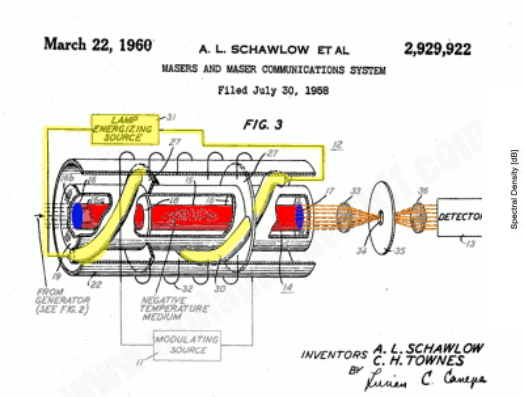
A chronicle of Raman for bioprocessing

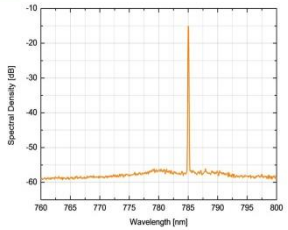
1930 Sir Chandrashekhara V. Raman Nobel Prize in Physics

1960 & 1969 LASER and CCD invention



Dr. Townes shared his Nobel with Nikolai G. Basov and Aleksandr M. Prokhorov for the invention of the **LASER**





Willard S. Boyle, left, and George E. Smith pose in the Bell Labs with a camera using their **CCD** invention, 1974

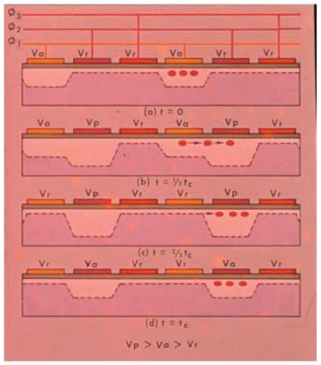
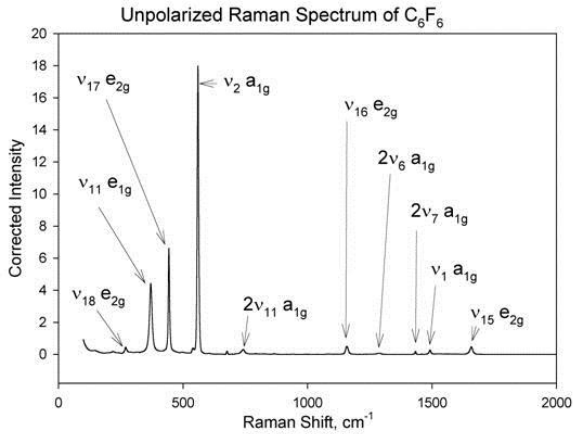


FIG. 6. (Color) The basic CCD structure.



Raman spectra of Benzene obtained thanks to a LASER and a CCD

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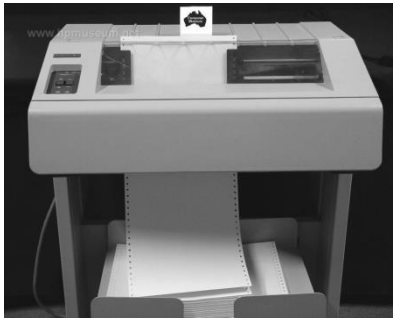
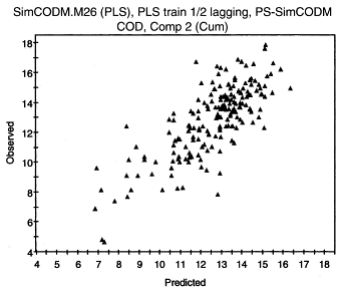
1960 & 1969	LASER and CCD invention
1970's	1st computers for instrumentation & chemometrics term invention

HP 2116A



- 1971: invention the word chemometrics by Svante Wold, Umeå Universitet, Sweden
- 1974: creation of the International Chemometrics Society (ICS)
- 1980s: first dedicated software (ARTHUR, SIMCA, and UNSCRAMBLER)



Chemometrics - Science of extracting information from chemical systems by data-driven means (multivariate statistics, applied mathematics, computer science,...) ⇔ psychometrics and econometrics.

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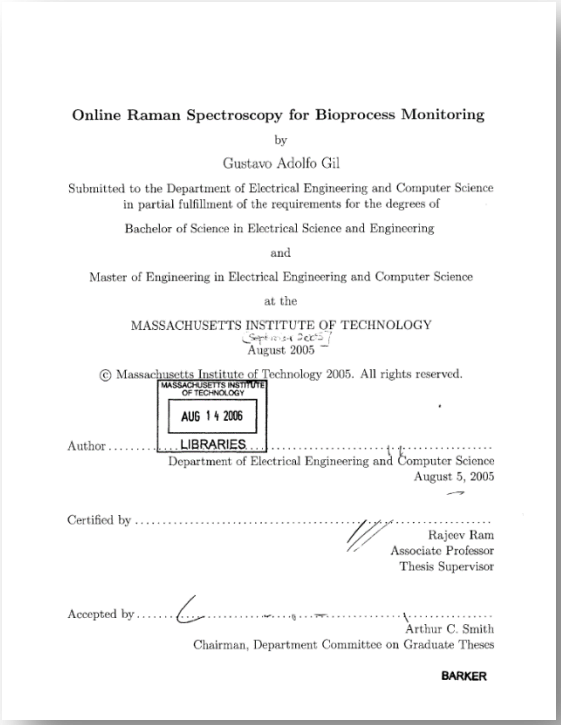

Online Raman Spectroscopy for Bioprocess Monitoring

by

Gustavo Adolfo Gil

Submitted to the Department of Electrical Engineering and Computer Science in partial fulfillment of the requirements for the degrees of

Bachelor of Science in Electrical Science and Engineering

and

Master of Engineering in Electrical Engineering and Computer Science

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

August 2005

Author .....
Department of Electrical Engineering and Computer Science
August 5, 2005

Certified by .....
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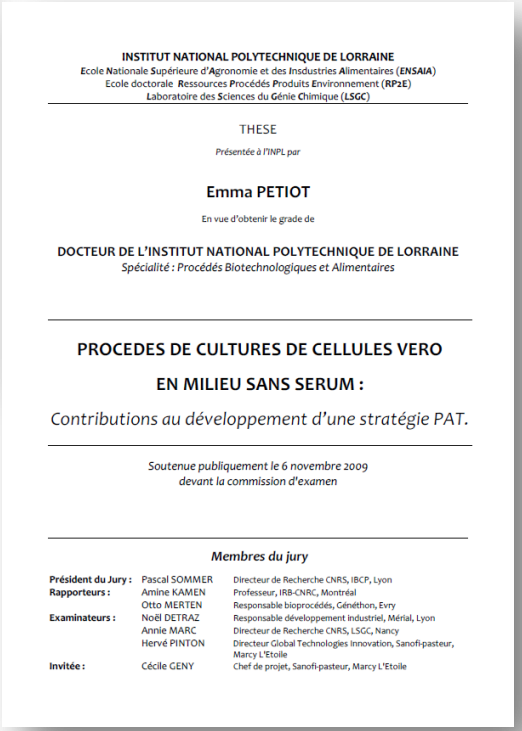

INSTITUT NATIONAL POLYTECHNIQUE DE LORRAINE
Ecole Nationale Supérieure d'Agronomie et des Industries Alimentaires (*ENSAIA*)
Ecole doctorale Ressources Procédés Produits Environnement (**RP2E**)
Laboratoire des Sciences du Génie Chimique (**LSGC**)

THESE

Présentée à l'INPL par

Emma PETIOT

En vue d'obtenir le grade de

DOCTEUR DE L'INSTITUT NATIONAL POLYTECHNIQUE DE LORRAINE
Spécialité : Procédés Biotechnologiques et Alimentaires

PROCEDES DE CULTURES DE CELLULES VERO EN MILIEU SANS SERUM :

Contributions au développement d'une stratégie PAT.

Soutenue publiquement le 6 novembre 2009
devant la commission d'examen

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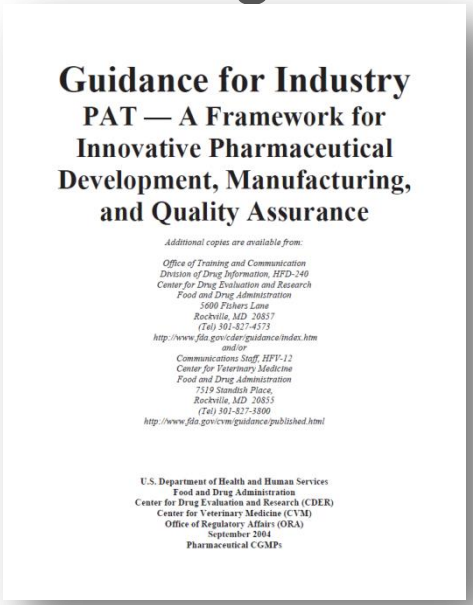

Guidance for Industry

PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

Additional copies are available from:

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U.S. Department of Health and Human Services
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September 2004
Pharmaceutical CGMPs

In the PAT framework, these tools can be categorized according to the following:

- Multivariate tools for design, data acquisition and analysis
- Process analyzers
- Process control tools
- Continuous improvement and knowledge management tools

integrated manner. The goal of PAT is to enhance understanding and control the manufacturing process, which is consistent with our current drug quality system: *quality cannot be tested into products; it should be built-in or should* ***be*** *by design.*

Thus, a focus on process understanding can facilitate risk-based regulatory decisions and innovation.

Real time release is the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data. Typically, the PAT component of *real time release* includes

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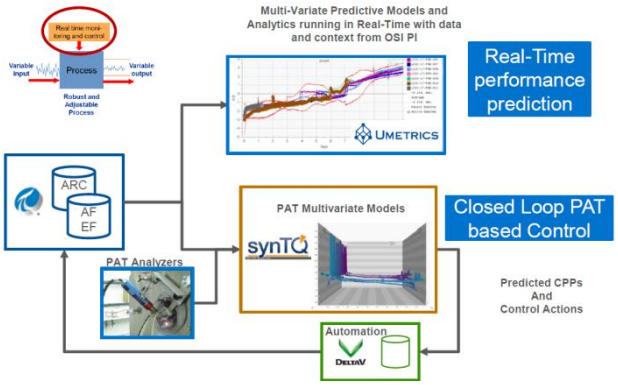
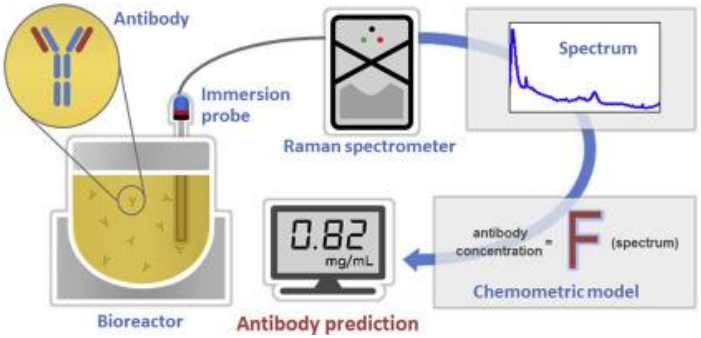


Biogen – PAT architecture

Intellicentic Consortium



CellPAT project – Sanofi Pasteur – LASIR Université de Lille

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2004	PAT FDA directive
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2015	1st cross-scale modeling

AIChE

Cross-Scale Predictive Modeling of CHO Cell Culture Growth and Metabolites Using Raman Spectroscopy and Multivariate Analysis

Brandon Berry
Cell Culture Development, Biogen Idec, Inc., 14 Cambridge Center, Cambridge, MA 02142

Justin Moretto, Thomas Matthews, John Smelko, and Kelly Wiltberger
Cell Culture Development, Biogen Idec, Inc., 5000 Davis Drive, Research Triangle Park, NC 27709

DOI 10.1002/btpr.2035
Published online December 29, 2014 in Wiley Online Library (wileyonlinelibrary.com)

3L to 2,000L… but not yet real real-time parameter quantitation!

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2015	1st cross-scale modeling
2017	1st GMP Raman analyzer

- ProCellics™
- GMP compact hardware
- Unique interface for calibration dataset management and real-time monitoring

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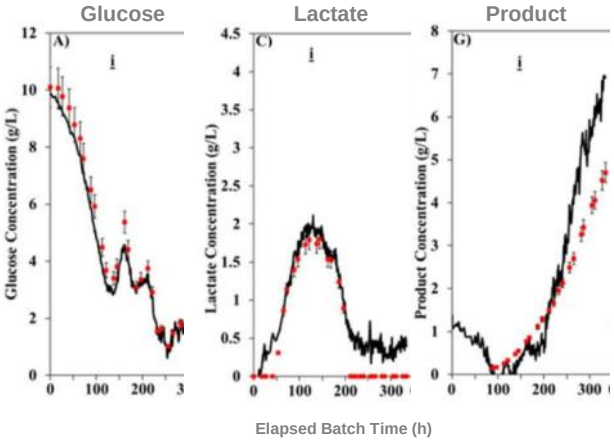
The Bioprocessing PAT world is dreaming of generic models for every processes…



(1) Webster *et al.* (2018) Development of Generic Raman Models for a GS-KOTM CHO Platform Process

Parameter	N	Latent Variables	Concentration Range	Precision	Error*
Glucose (g/L)	344	5	0.4 – 10.1	0.4	4 %
Lactate (g/L)	344	5	0 - 3.7	0.3	8 %
Product (g/L)	267	6	0 – 4.7	1.2	26 %

*As percentage of maximum process

…but the accuracy delivered by such models is poor

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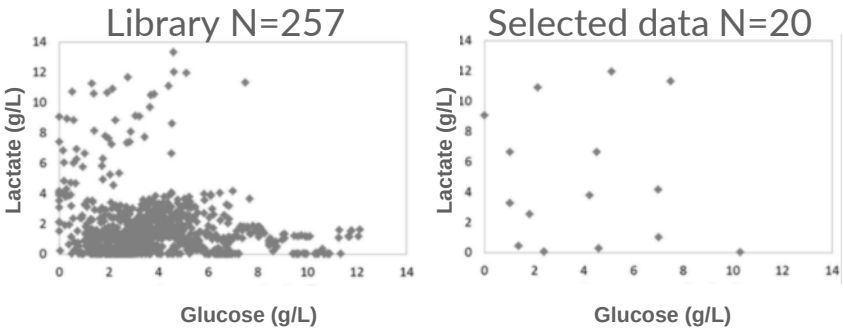
2017	Generic model trial by Lonza
2019	Local model in a large dataset…

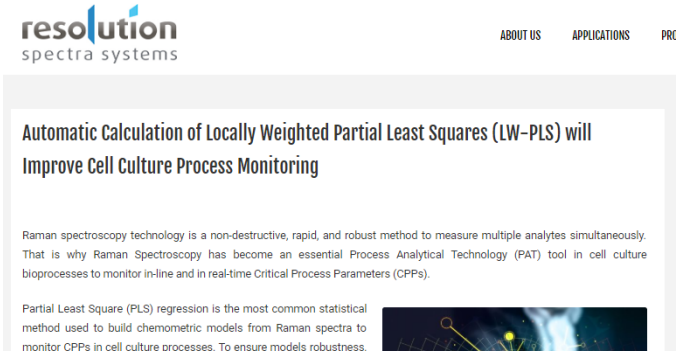
Generic dataset and local models…



Rowland-Jones *et al.* (2017), Comparison of Spectroscopy Technologies for Improved Monitoring of Cell Culture Processes in Miniature Bioreactors

Parameter	N	Latent Variables	Precision	Error*
Glucose (g/L)	20	8	0.3	3 %
Lactate (g/L)	20	6	0.3	2 %

*As percentage of maximum process



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2. Chemometric support
3. GMP support
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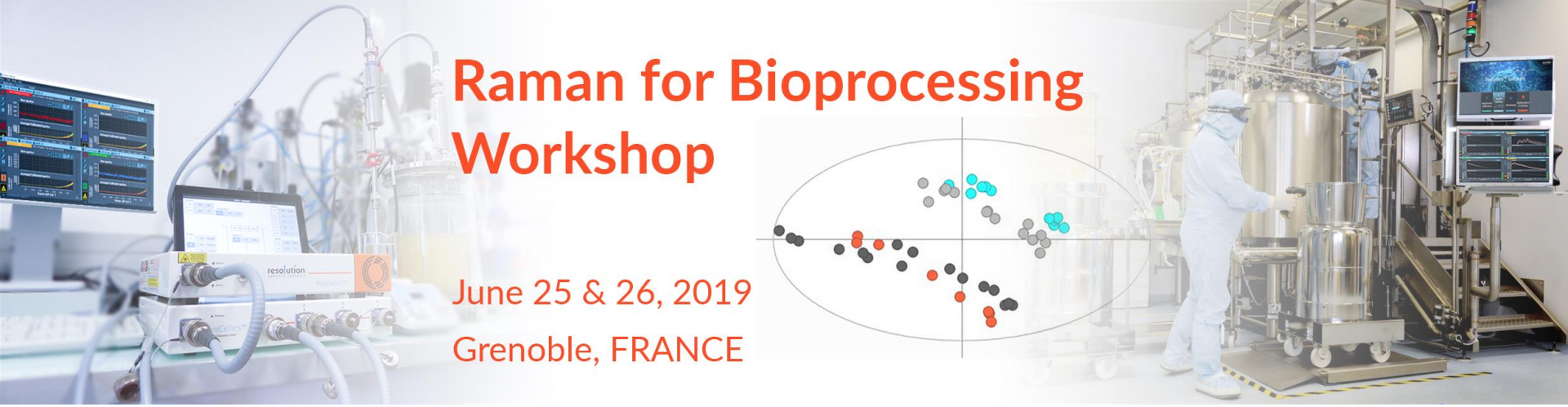
5. Training material



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