

# Making the case for accurate multipoint analysis by process mass spectrometry in biological production

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## Key Words

- Fermentation
- Fermentor
- Fermenter
- Cell Culture
- Biologics
- Bioprocess
- PAT
- Bioremediation
- Proteins
- Enzymes
- Vaccines
- Process Understanding
- Process Optimization



Figure 1: Typical benchtop bioreactor.

## Introduction

### Field-Proven Technology with a Worldwide Installation Base

The use of online process analytical technology (PAT) has recently become a high-profile endeavor in the biotechnology industry. Yet, many fermentation scientists have been using Thermo Scientific™ Process Mass Spectrometers since the early 1980s to reliably monitor the composition of gas streams into and out of fermentors and bioreactors. Unfortunately, it is not uncommon for others to assume that the measurement of oxygen and carbon dioxide in the effluent is all that's required when making the first steps towards process control. They further assume that sufficient accuracy can be achieved by discrete measurement technology. Both of these assumptions are false. Firstly, the sparge gas is always variable due to external biology (people and trees) that inevitably change the input to the instrument air system and secondly, the ubiquitous twin-tower desiccant dryer systems will either absorb or regurgitate CO<sub>2</sub> depending on where they are in the regeneration cycle. Only accurate comparison of sparge gas and effluent gas can provide accurate prescreening for possible contamination. Accurate comparison is also required in order to calculate real-time information regarding culture respiration and the availability of nutrients.

### Minimum Requirements for Effective Control:

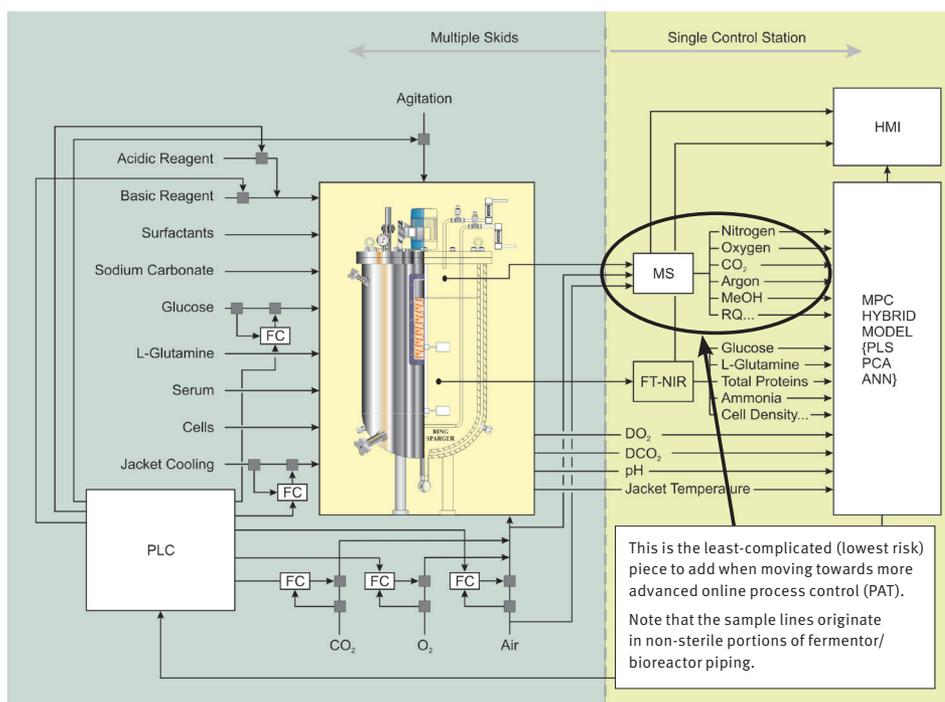
- Sparge and effluent gases must be measured
- All gas components need to be measured
- High accuracy is required to calculate meaningful metrics
- Automatic calibration of all components is essential
- Flexible analysis methods and schedules are required
- Operational simplicity and reliability
- Local support

### Magnetic Sector Analytical Performance

	N <sub>2</sub>	N <sub>2</sub>	O <sub>2</sub>	O <sub>2</sub>	Ar	Ar	C <sub>2</sub>	C <sub>2</sub>
	%mol	%mol	%mol	%mol	%mol	%mol	ppm	ppm
	Mean	St Dev	Mean	St Dev	Mean	St Dev	Mean	St Dev
Day 1	78.0807	0.0028	20.9459	0.0026	0.9337	0.0003	396.84	1.31
Day 2	78.0767	0.0023	20.9494	0.0023	0.9342	0.0003	397.46	1.25
Day 3	78.0761	0.0024	20.9500	0.0023	0.9342	0.0003	397.34	1.28
Day 4	78.0798	0.0023	20.9469	0.0023	0.9337	0.0003	396.31	1.31
Day 5	78.0777	0.0030	20.9487	0.0028	0.9339	0.0003	396.76	1.34
Day 6	78.0741	0.0023	20.9518	0.0022	0.9344	0.0003	397.47	1.27
Day 7	78.0750	0.0023	20.9512	0.0022	0.9342	0.0003	397.23	1.30

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Figure 2: Fully instrumented fermentor.



### Taking The First Steps Towards Advanced Process Control

This process diagram illustrates a fully instrumented fermentor. Both liquid and gas-phase measurements are provided to monitor a wide range of process variables in real-time. These data are fed into the advanced process control (APC) system that will often include hybrid models consisting of formal (linear) models and neural (nonlinear) network models. The APC system provides the set-points for a number of variables that include control of nutrients, amino acids, sparge content and flow, together with the traditional variables of agitation, temperature, pressure and pH. Whereas this diagram represents the ideal situation for process understanding and scale-up, there is a fair degree of cost and complexity associated with this comprehensive approach. The more common approach, since it provides significant added value with moderate cost and minimum risk, is to add a multistream mass spectrometer. The Thermo Scientific™ Prima PRO is equipped to monitor 60+ fermentors without compromising sterility. The Prima BT provides a bench-top solution for smaller scale fermentors being configured with 15 sample and 6 calibration ports. The highly precise and complete gas composition measurements provided by both models are easily incorporated into the APC system. Significant improvements in process control can be achieved very quickly - usually within a day or two of startup.

### Delivering Value During Every Stage of Product Development

The complex manufacturing processes that are inherent in biotechnology require advanced instrumentation to ensure an optimal path to the final product. Mitigating risk throughout the scale-up process is the key to increasing profits. The Prima PRO and Prima BT process mass spectrometers offer the speed and precision necessary to reliably track process dynamics, enabling timely corrective action to be taken. From research and development to creation of the final product, the Prima platform technology helps bring products to market faster, increase yields and enhance profits for a rapid return on investment.

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