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APPLICATION NOTE

HASTINGS

# Improve Fed-Batch Fermentation by Measuring Mass Flow

## How can my fermentation process yield a more consistent product?

Any biochemical process is only as consistent as the parameters that control it. What makes a fed-batch fermentation process particularly susceptible to variation is the fact that it relies on many critical parameters. With an aerobic fermentation process, temperature, $pO_2$, substrate consumption, and pH are primary critical parameters responsible for the process quality. These parameters depend on several inputs such as the substrate feed rate, heater power, agitation, aeration, and oxygen flow rate. If that's not enough to worry about, a change in one of the inputs may affect more than one critical parameter and these relationships can change throughout the different phases of fermentation. For example, during the initial phase, the oxygen flow has little effect; however during the exponential growth phase oxygen consumption rises dramatically. Suddenly the oxygen feed gas becomes a highly influential factor in the process. For a consistent fermentation process - one that produces high yield, quality product - you must continuously monitor and control the critical parameters throughout. Precise process control also enables more effective scale-up from bench-top to pilot to GMP production. This application note specifically addresses the best method for measuring and controlling the critical gas flows to a fermentation reactor.

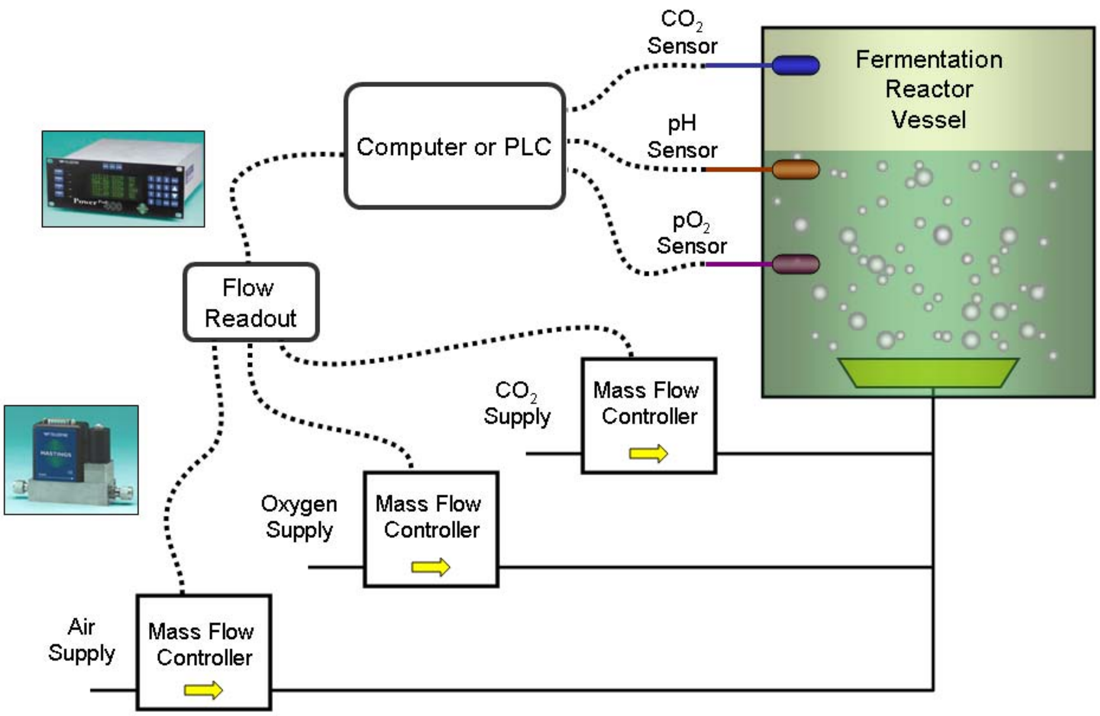
## Objectives

- ✓ To ensure accurate air, oxygen, and $CO_2$ flow to the reactor vessel
- ✓ To provide flow signals for documentation, event tracking, or flow totalizing
- ✓ To close-loop control gas flows and process sensors

## Methods

Often fermentation reactors have used manual or passive flow methods based on needle valves, venturi meters, or rotameters to set and monitor the gas flow rates. However, these passive devices are highly susceptible to errors due to temperature or pressure fluctuations which often occur due to local environmental and supply pressure conditions. Even the best of these passive flow devices can vary by over 10% in routine operation—significantly affecting the process. Further, the measurement principle for these devices is based on volumetric flow. While volumetric flow works well for incompressible liquids, such techniques for gas flow measurement are inadequate for determining the quantity delivered to the process. Alternatively, **mass flow meters** produce accurate flow measurement and are independent of pressure and temperature conditions. These instruments also provide an electronic output which can be used for regulatory documentation, event tracking, and flow totalizing.

For cases where you need to actively regulate the gas flows, **mass flow controllers** (MFCs) can be used in place of mass flow meters. MFCs measure and automatically adjust an internal control valve to maintain the flow at a commanded set point. There are two general approaches to using MFCs for process control. One approach uses time-based set point commands. Here, the flows are begun, changed, ramped, and/or stopped according to a predetermined recipe for the process. Set points are issued by a process control computer or PLC to each MFC. Another approach uses feedback from on-line process sensors such as pH, $pO_2$, or $CO_2$, to adjust the flow set points as the process progresses. An example configuration using a closed-loop approach with process sensors is shown in the figure below.




In this implementation a Flow Readout is used to interface (via RS-232) with the system's computer or PLC. The Flow Readout maintains individual set points to each of the mass flow controllers and provides other real-time functions such as event tracking, alarm status, and flow totalizing. This frees the system's computer from real-time flow monitoring and control.

The algorithm for adjusting flow rate set points in response to sensor signals is beyond the scope of this note. However, it is typical to associate the pH sensor and $CO_2$ sensor with the $CO_2$ flow; the $CO_2$ sensor with the Air flow; and the $pO_2$ sensor and $CO_2$ sensor with the oxygen flow. Systems can be operated with relatively simple one sensor to one gas flow control algorithms or with multi-input, multi-output control algorithms. But in any control scenario, the capability of the system to achieve a consistent process and resulting product requires a precise gas flow measurement.

## Instrument Selection

For the methods addressed above, gas flow measurement and control using a mass flow meter/controller has distinct advantages over relying on passive flow meters and manual needle valves. The range of flow rates required for each gas depends on the fermentation process and, of course, the volume of the reactor. For flow rates up to 500 standard liters per minute (slm) The Hastings HFC 200 Series mass flow meter/controller is recommended. Its 1% accuracy and relative insensitivity to temperature and pressure make it ideal for this application. For flow rates above 500 slm, the Hastings HFC 300 Series is recommended. The gas type, full scale flow range, fittings, and other options are specified when ordering the instrument.

The selection of a power supply/readout depends on the functionality and capabilities required. If connecting to a single MFC and analog or RS-232 interfaces are sufficient, the Hastings Power$^{Pod}$ -100 is recommended. The Power$^{Pod}$ -400 is the ideal choice when operating multiple MFCs or when sophisticated functionality (e.g. flow totalizing or gas ratio control) is required.

For Information on all Teledyne Hastings Vacuum Measurement and Mass Flow Instruments, visit our website:

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