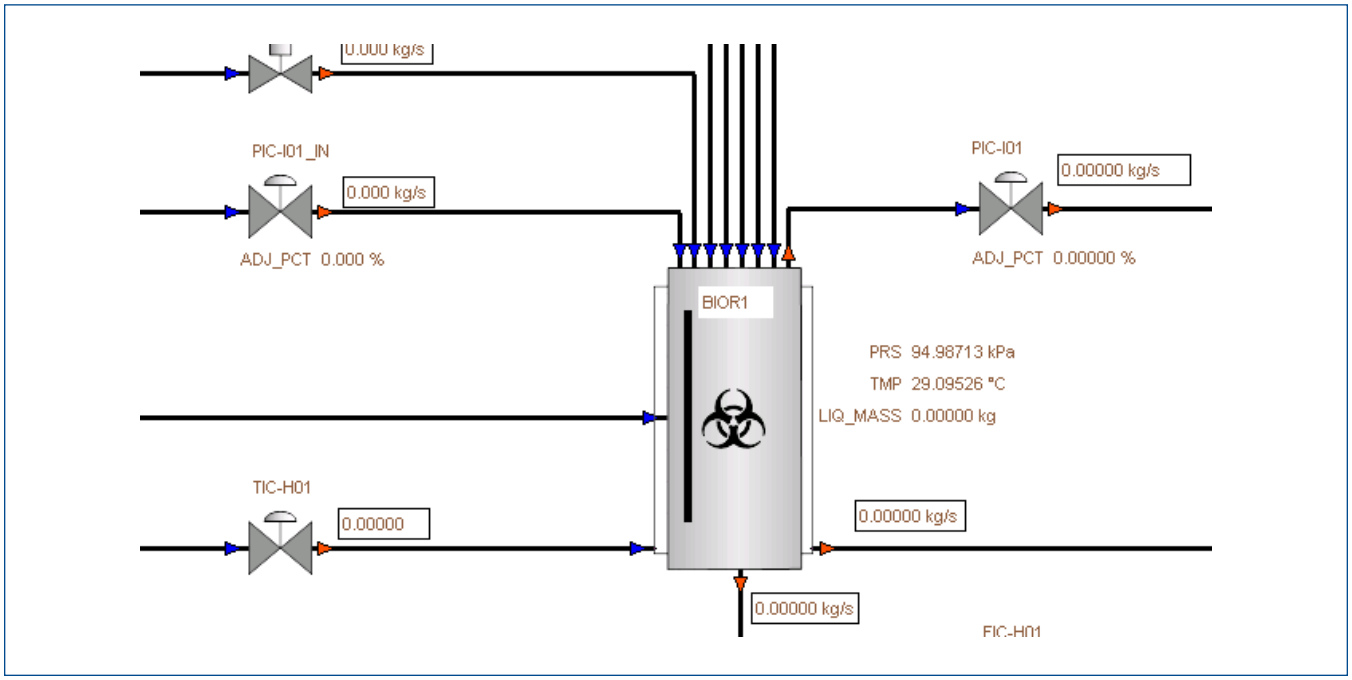
Mimic™ Advanced Modeling Objects - Bioreactor



- Intuitive unit operation modeling
- Supports continuous, batch, semi-batch or any combination of reactor modes
- Accelerates control system testing, operator training, and technology transfer
- Matches product development lab data to the reaction kinetics
- Delivers analytical data through virtual experimentation to aid in process discovery and repeatability

Introduction

The Mimic Bioreactor Modeling Object is a rigorous first-principles, dynamic model of a bioreactor or fermenter designed for high-performance simulations for operator training, automation system testing, and operations and process improvement.

The Bioreactor Modeling Object is an add-on to the Mimic Advanced Modeling Objects package that includes sophisticated modeling objects into the Mimic Simulation Studio modeling palette. These objects can be used on Mimic systems for application software testing, operator training, and process or operation improvements.

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Benefits

Intuitive unit operation modeling

This modeling object comes with modeling infrastructure that makes the development of accurate models quick and easy. The default setup of the model is for the most sophisticated case of a bioreactor with mammalian cell cultures used today for most new biologics (highly complex proteins), but the equation parameters can be adjusted to model fermenters that use yeast cells (ethanol), fungal cells (antibiotics), and bacterial cells (less complex proteins).

Supports continuous, batch, semi-batch or any combination of reactor modes

The Bioreactor object provides a dynamic model of a batch bioreactor or fermenter with or without an agitator and sparge and can also model continuous biological reactions including startup and shutdown. Reactor materials and heat transfer are completely configurable, supporting the use of single use, glass or stainless steel vessels.

Accelerates control system testing, operator training, and technology transfer

Biological kinetics is orders of magnitude slower than chemical kinetics. Bioreactors and fermenter batches generally take days or weeks to complete. The use of speedup factors is an essential aspect of modeling these processes. The Bioreactor object can run 1000 times real time so that a 10-day batch is completed in 15 minutes. Instead of waiting for days to see the effect of changes in operational, process, and control system conditions, the model provides complete batch profiles and scenarios in a matter of minutes.

Matches product development lab data to the reaction kinetics

Many pharmaceutical manufacturers either have incomplete of highly proprietary equations for kinetics. General purpose biological kinetic equations for the effect of operating conditions on cell growth rate and product formation rate enable the user to readily match existing profiles of cell and product formations without the use of proprietary kinetics.

Delivers analytical data through virtual experimentation to aid in process discovery and repeatability

Besides testing configurations and training operators, the Bioreactor model can be used to do a design of experiments (DOE) and explore “what if” scenarios to track down the causes of variability. Process repeatability is a foremost concern for manufacturers in the beverage, food, and drug industries. If the bioreactor model matches the change with time of process inputs and process outputs, the model can be used to rapidly explore scenarios. By varying kinetic parameters, sequences, and setpoints, the correlations between process inputs and selected process outputs can be studied with data analytics. Principal component analysis (PCA) and Projection to Latent Structures (PLS) can be used to identify the major contributors to batch repeatability. These tools can potentially lead to the online diagnosis of bad batches.

Product Description

The Mimic Bioreactor Modeling Object was designed to help pinpoint operational, equipment, process, and control system problems, leading to a better understanding by operators and engineers.

The features of the object designed for easy and effective use include:

- Dynamic mass balance calculation of cell culture media/ broth (liquid mass balance) based upon feed streams, drain streams, sparge, and evaporation and bubble effect.
- Dynamic mass balance calculation of Overhead (gas mass balance) based upon overlay stream, vent stream and evaporation and bubble from media effect.
- Dynamic energy balance calculation based upon media temperature, feed streams heat, cell metabolic heat, jacket heat transfer to bioreactor, and evaporation heat loss.
- Dynamic media component mass balance calculation based upon feed streams, cell growth, reaction and utilization, mass transfer of dissolved gases, and evaporation or condensation.
- Dynamic mass transfer calculation for oxygen and carbon dioxide between bubbles, media and cells, based upon concentrations, agitator, bioreactor pressure, and gas velocity, with optional user proprietary relationship overrides.

- Cell growth and product formation based upon Michealis-Menten Kinetics with tunable rate factors and override factors for user proprietary data relationships or algorithms.
- pH and temperature kinetic effect based of the media and reaction to acid or base additions based upon the Convenient Cardinal model.
- Overlay stream inlet for inert gases injected in the vessel headspace for pressure control and to allow extraction of gas products. The Overlay gas vents through a vapor stream out.
- Sparge stream outlet with gas components from the Sparge dissolved and metabolized in the media or carried into the Overlay with exit on the vapor stream out.
- Agitation control for stirring the media with the appropriate effects for the mixing of the Sparge gasses and the principle reaction rate.
- Reaction speedup controls of 10 to 1000 times faster than real time.

Configuration

The Bioreactor Object is based upon the Vessel Advanced Modeling Object and incorporates the Bioreaction parameters as an extension of that object. Other unit operations, such as valves, pumps, or compressors, can be added to replicate the actual plant physical design.

While the default setup of the model is for the most sophisticated case of a bioreactor with mammalian cell cultures, the equation parameters can be adjusted to model fermenters that use yeast cells (ethanol), fungal cells (antibiotics), and bacterial cells (less complex proteins). The option also exists to interface external calculations of maximum specific growth rate or maximum specific product formation rate or any of the contributing individual rate factors associated with an operating condition (pH, temperature, inhibiting or limiting component concentrations). The model will predict the concentrations of dissolved gases, sugars (glucose), amino acids (glutamine), inducers, inhibitors (ammonia and lactate), precursors, live cells, dead cells, and product in the broth of fermenters and the media of bioreactors.

Configuration parameters available for the Bioreactor allow the user to make the model function close to the actual plant bioreactor and include:

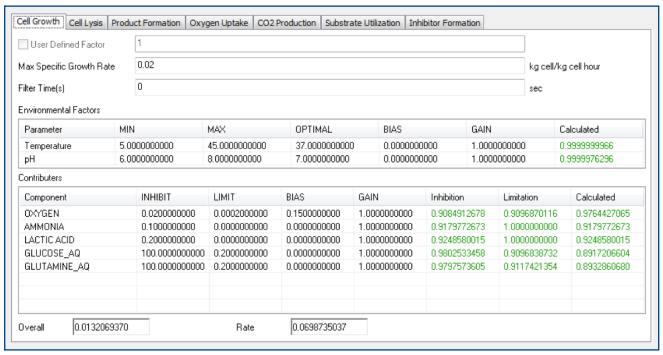
- Physical characteristics - dimensions, number of inlet and outlets, and elevations.
- Heat source type, characteristics, and links to heat instrumentation source tags in Mimic IO models.
- Agitator type, characteristics, and links to agitator control tags in Mimic IO models.
- Component set composition and kinetic effect of components.
- Kinetics parameters for each rate factor with user ability to override with proprietary data or algorithms.

The object uses ordinary differential equations for material, energy, component, and charge balances. It uses driving force equations for mass transfer between the sparge, overlay, and dissolved gases. These equations enable the object to inherently simulate the dynamics associated with disturbances, abnormal operation, transitions in continuous operations including startup and shutdown and the profiles of batch operations.

The general approach is to have the simulation match the plant in terms of key values of measured variables as they change in time. For batch processes and transitions in continuous processes there is no steady state except as achieved as a constant slope of batch profiles or continuous transitions. Key measured variables are process inputs (air and reagent flows manipulated by control loops or sequences) and process outputs (dissolved oxygen, pH, live cell concentration, dead cell concentration, and product concentration). The slopes of the profile of live cell concentration for matching cell growth rate and the profile for product concentration for matching product formation rate are critical. Process variables tightly controlled by PID loops (dissolved oxygen, pH, temperature, and pressure) will be at setpoint except for setpoint shifts and transitions. In tight control, process variability is transferred from the controlled variables to the flows manipulated by these loops. Thus, model fidelity depends more upon matching these flows to what occurs in the plant.

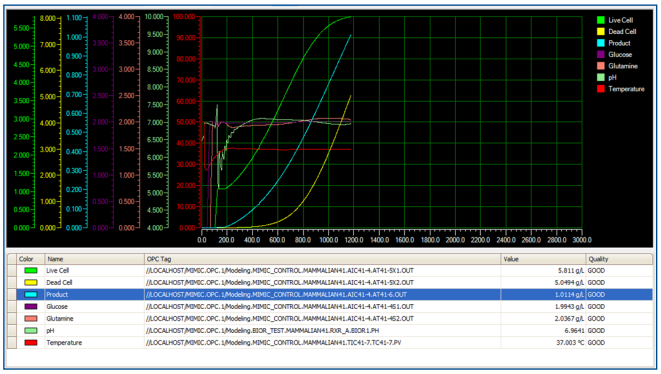
Online Kinetics Tuning

At the center of the Bioreactor object is the cell growth and product formation based upon Michealis-Menten and Cardinal Kinetics. Factor contributors and environmental factors are tunable on-line, while the Bioreactor model is running, for each rate factor in the Kinetics tab of the BIOR Kinetics tuning window.



Bioreactor View

The run time Bioreactor View provides real-time trends and profiles of the main reactor variables, delivering a deep insight into the object performance. The set of strip charts contains views for: inlet/outlet flow rates of the vessel, pressure/ temperature and vapor fraction in the reactor, vapor and liquid holdup and composition changes, reaction rate constants and reaction rates, net production and consumption, cell growth, and reactor jacket and agitator performance (if applicable).



Ordering Information

The Mimic Bioreactor Modeling Object can be added to any Mimic system by first adding the Advanced Modeling Objects - Core license.

Description	Model Number
Mimic Advanced Modeling Objects - Core	MM3-7111
Mimic Advanced Modeling Objects - Bioreactor	MM3-7142

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