

ADDITION AND BIOREACTOR WEIGHT CONTROLS – OPERATION MODES TO IMPROVE ACCURACY AND REPLICABILITY IN YOUR BIOREACTOR WITH BIONET BSCALE

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There are different fermentation modes in bioreactor systems: batch, fed-batch, and continuous mode. The batch mode is the simplest. The bioreactor is filled with the medium containing all the components that the organism requires to grow or produce determined biomolecules like a metabolite or protein. This fermentation mode has a production limitation: once the limiting substrate is consumed, the cells cannot continue growing, with limited productivity and low cell density.

Alternative operation strategies are the fed-batch and continuous mode. These aim to increase the cell density and productivity and are operated under open systems. The fed-batch mode implies the addition of substrate to the bioreactor, usually a concentrate solution of the limiting substrate, which overcome problems of catabolite repression if the initial concentration of the limiting substrate is too high to reach the desired cell density. The continuous fermentation is a process with a constant withdrawal of medium and a constant replacement of fresh media at an identical flow rate.

VOLUMETRIC ADDITION STRATEGY (VIA PERISTALTIC PUMPS)

The volumetric dosing system is the most common system used for the addition of acid, base, antifoam, and other substrates and fresh media in bioreactors, where peristaltic pumps are the most common choice for the supply. They are associated with a number of benefits, mainly around the fact that they do not contaminate the fluid, as only the tube has contact with the fluid. In addition, they require very low maintenance, they have high capacity of handling viscous and shear-sensitive fluids, they prevent backflow and the amount of fluid pumped per rotation is fixed.

However, as these pumps are not self-priming, the actual flow rates might sometimes have very slight deviations from the existing peristaltic pump performance curves. Moreover, the flow supplied by this type of pump is prone to drifts as the tubing becomes worn and they also require periodic re-tensioning if operated for long periods which could otherwise lead to the accumulation of fine deviations. Another problem is the variability of the rheological properties of the substrate solution. Therefore, the pump output should be measured and regularly checked especially in specific applications with critical requirements related to accuracy of pump control.

GRAVIMETRIC ADDITION STRATEGIES

For applications where the volume added to the bioreactor is critical, BIONET recommends **gravimetric control strategies** such as those behind the **BWC (Bioreactor Weight Control)** and **AWC (Addition Weight Control)** modes. These can be a very accurate method, as they use a precision scale in combination with a variable speed pump and advanced control software module.

AWC will allow the user to perform an accurate automatic addition with the addition pump based on the addition container weight change, measured with an external scale. The bottle of the substrate is on a scale which sends the value of the weight to the **ROSITA** or **MARTA** software to enhance precision on the addition pumps' flows and to enhance **weight data features**, including **visualization** and **registration** tools.

The **BWC** mode require a scale for the bioreactor be connected, and it is used for level measurement or to keep a constant weight in continuous processes. The bioreactor vessel is placed on a scale which sends the value of the weight to the **ROSITA** or **MARTA** software to enhance precision on the addition and withdrawal pumps' functioning and to enhance **weight data features**, including **visualization** and **registration** tools.

Both modes enable highly **accurate control** of added and/or removed liquids, even for long processes, as it eliminates the variability generally associated with volumetric or state variances of the tubing wearing within peristaltic pump heads or the variability of the density of the substrate solution. This renders both operation modes very interesting for process control, for high quality requirements and to improve replicability.

An example of a bioreactor configuration for the application of these modes via Bionet's bScale module is shown in Figure 1.

THE TECHNOLOGY MODULES REQUIRED: AWC AND BWC WITH BSCALE

These technological capabilities are offered by the **Plug&Play** module **bScale**, available for all Bionet's bioreactors to enable the connection of several addition bottles and bioreactor scales and the integration of their measurements in the **ROSITA** and **MARTA** bioprocess software for additional data and control features. This way, **bScale** brings both the hardware and software technological solutions to enhance **process precision** and allow weight data **visualization** and **registration** and **control capabilities** of addition and weight-associated operation strategies.

Moreover, the **bScale** module allows for the connection of several scales, from a range of scale precisions and brands used in lab and production of different precisions, allowing the operator to use their preferred or existing scale.

THE SOFTWARE REQUIRED: AWC AND BWC CAPABILITIES IN ROSITA AND MARTA

When the **bScale** is connected to the Bioreactor Control Unit and activated from the software settings screen, the Advanced Addition/Bioreactor Weight capabilities are automatically integrated into the associated **ROSITA** or **MARTA** software screens following the Plug&Play concept.

The **AWC** control functions are configured in **ROSITA** and **MARTA** by adjusting the weight parameter at the desired set point, which will then make the pump flow function according to such control loop. The pump is therefore regulated continuously and automatically to reach the set-point of flow rate selected, as a result of measuring the difference in weight of the reservoir bottle over time.

In the **BWC** configuration window, the user will also introduce the desired weight value as a set point (this time of the bioreactor), and indicate whether this is to enter a control loop with the addition pumps and/or the withdrawal pumps.

Moreover, configuration of PID values and associated alarms is also possible. Finally, the **bScale software module** enables weight **data visualization** in the various real-time tools (e.g. trend and comparative graphs) and **exportation** in .csv.

Additionally, the **AWC** and **BWC** can also be programmed under the **time-profile** or **recipe control strategies**, allowing the activation of the said controls across up to 20 time points, or upon the occurrence of a process event.

Finally, the fact that both **ROSITA** and **MARTA** have similar programming layers facilitates the **scalability** as well as the scale-down of the bioprocess even further than what the enhanced **reproducibility** already does.



Fig. 1: Set-up of an addition weight control for a fed-batch by a Bionet system, where the bottle of the substrate is placed on a scale for precise addition control and weight data visualization and registration and where the bioreactor is also placed on a scale for bioreactor weight data visualization and registration. Both will be recognized by the software via the bScale modules also shown in the picture.

REFERENCES

McNeil, B. & Harvey, L. M. (2008). Practical fermentation technology. Chichester, England: Wiley.