APPLICATION NOTE
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PRECISION IN EVERY DROP: PERFECT GRAVIMETRIC FEEDING WITH LUCULLUS® SOFTWARE

Rowin Timmermans (rowin.timmermans@securecell.ch), Securecell BV,
Luca Guerrini (guerriniluca06@gmail.com), **Javi Fuentes Izquierdo** (javi@octarinebio.com), Octarine Bio

Introduction

Being able to supply fresh medium to live cultures in bioreactors and fermenters is a common requirement in biotechnology applications. In particular, fed-batch, chemostat, perfusion, and repeated-batch processes rely on feeding for successful execution. The most often employed solution for feeding medium to a bioreactor is a pump rotating at a fixed or variable speed, either stand-alone or integrated with the bioreactor controller.

The drawback of using pumps for this purpose is a lack of accuracy. This can be partially corrected by performing a pump calibration before the start of the process. Still, even the most precise pump calibration is only helpful to a limited extent due to the following phenomena:

- When the pump tubing is autoclaved (connected to a bioreactor), the properties of the tubing change significantly because of the harsh conditions inside the autoclave.
- Once the pump is in operation, liquid displacement gradually decreases over time due to the stretching of the tubing, caused by continuous pump action.

To address these limitations and improve the accuracy of the supply of fresh medium, gravimetric feeding has emerged as a robust alternative.

Gravimetric feed principle

This approach relies on real-time mass measurements to directly quantify the amount of liquid delivered and helps to overcome the inherent variability introduced by tubing deformation and time-dependent changes in pump performance. Gravimetric feeding is used in those cases where a high degree of accuracy is required for feeding the bioreactor. The accuracy and precision of the balance are critical, as the measurements of the weight of the feed solution by the balance are the basis for correcting the feed pump setpoint. Such a setup is commonly referred to as a **gravimetrically corrected feed**, or in short, a gravimetric feed. The following is required to set up a gravimetric feed (Figure 1):

- A device with an inbuilt/programmed feedback mechanism, capable of making the necessary calculations for gravimetric feed control at a relatively high frequency. Some bioreactor controllers have this capability, but most often a computer with SCADA software is employed for this purpose, such as Lucullus®.
- A pump for administering the feed solution to the bioreactor. It can be either a pump integrated into the bioreactor controller or an independent, stand-alone pump.
- A balance for measuring the feed weight, preferably with high precision.
- Both the pump and the balance must be physically connected to the device in charge of the gravimetric feed control, to allow for data exchange between these devices. For gravimetric corrections to be as effective as possible, it is necessary to collect the balance measurements and correct the pump setpoint at a relatively high frequency.

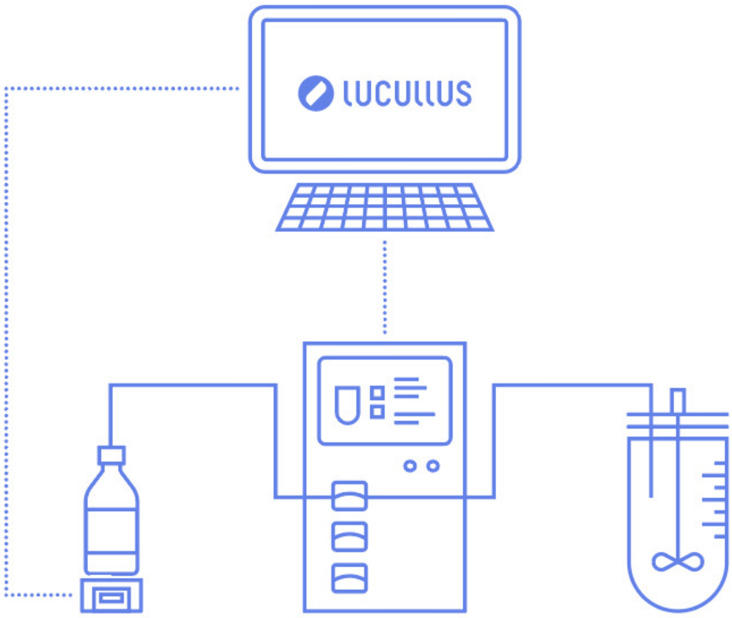

Figure 1: Schematic of a gravimetric feed setup. The icon on the top represents the computer with Lucullus® software, the icon on the bottom left represents the bottle with feed solution on a balance, the icon on the bottom right represents the bioreactor, and the icon on the bottom center represents the bioreactor controller. The solid line represents the tubing, which connects the feed bottle to the bioreactor. The dotted lines represent the cable connections between the Lucullus® computer and the balance and bioreactor controller, which allows Lucullus® to communicate with these two devices.

The following steps describe the working of the gravimetric feed control principle in more detail, assuming that the gravimetric feed is controlled by Securecell's SCADA software Lucullus®:

1. Lucullus® activates the feed pump (*pmp_feed_sp*), based on the desired feed rate (*Feed_rate_target*) set by the operator (constant feed, linear feed, exponential feed, or profile-based feed).

2. Lucullus® collects measurements from the balance that measures the weight of the feed solution at a relatively high rate, which is defined by the operator.

3. Lucullus® calculates the actual feed rate (*Feed_rate_calc*), based on two consecutive balance measurements (bal_t, bal_{t-1}), at an interval (*dt*) set by the operator (typically 1 – 10 minutes):

   $$\text{Feed\_rate\_calc} = \frac{(bal_t - bal_{t-1})}{dt}$$

   The exact duration of the interval has to be carefully tuned: if the interval is too short, inaccuracies of the balance readings will have a relatively big effect on the calculated feed rate; if the interval is too long, the feed pump may be off target longer than desired.

4. Lucullus® compares the actual feed rate with the desired feed rate and calculates a gravimetric feed correction factor (*GFCF*) based on that:

   $$\text{GRCF} = \frac{\text{Feed\_rate\_target}}{\text{Feed\_rate\_calc}}$$

   When the pump doses the feed exactly as desired, the feed correction factor will have a value of 1. If not, the value will be either smaller than 1 (the pump feeding too much) or larger than 1 (feeding too little).

5. The correction factor is used to adjust the pump speed to attain the desired feed rate:

   $$\text{pmp\_feed\_sp}_t = \text{FCF} \cdot \text{pmp\_feed\_sp}_{t-1}$$

6. Steps (2) – (5) are repeated at the interval (*dt*) set by the operator, if the feeding of the bioreactor must last (also set by the operator).

Octarine Gravimetric Feed Operation

The Lucullus® Operations team at Securecell specializes in process automation and has successfully implemented gravimetric feed correction solutions at various customer sites in the past. Recently, the Lucullus® user Octarine Bio (Octarine), based in Copenhagen, the Danish capital, contacted Securecell with a request to set up a gravimetric feed for one of their processes.

Octarine is a world-leading synthetic biology company that specializes in cell-factory engineering and precision fermentation. This enables Octarine to design custom-made microbes, producing a wide array of bio-based ingredients by fermentation, such as textile dyes, skincare ingredients, health supplements, and many other new and innovative products (for more information, visit octarinebio.com).

During a customer project, a dedicated Operation (process recipe) was programmed in Lucullus® for executing the gravimetric feed corrections and tested at Octarine using live cultivations. Based on the results of these first tests, the Operation was stepwise improved, eventually leading to a solution that generated the desired results.

Materials and Methods

The following equipment was used for executing the processes with a gravimetric feed at Octarine (Figure 2):

- Computer with Lucullus® software installed (version 23.0.0, Basic + Control license)
- A 2 L bioreactor from Getinge (1 L working volume)
- A Livit Flex bioreactor controller (Dual configuration) from Getinge
- A BCA12201-1S model balance from Sartorius (0.1 g precision)
- A BCE42021-1S model balance from Sartorius (0.01 g precision)

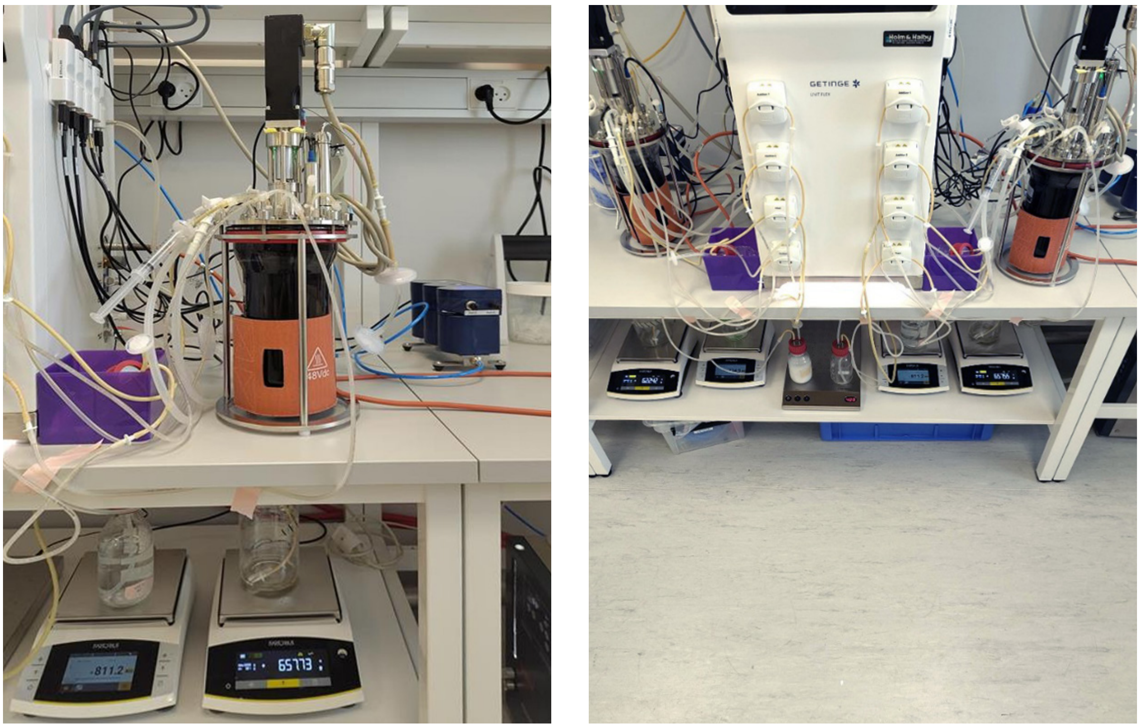

Figure 2: Experimental setup at Octarine, consisting of the bioreactor connected with the Livit Flex controller (Getinge) and a balance (Sartorius), used for measuring the weight of the feed solution.

Results and Discussion

Strategy for feeding exponentially

A key requirement for Octarine's process was to feed exponentially, as indicated by the formula below:

$$F(t) = F0 \cdot e^{K \cdot t}$$

F(t) stands for the feed rate (g/h) at any given time **t** (h), **F0** is the initial feed rate (g/h) and **K** the exponential feed coefficient (h^{-1}). Values for F0 and K were provided by Octarine (confidential).

One of the resources available in Lucullus® proved very valuable to meet this requirement: a so-called Logical Device called the Exponential Ramp. The Exponential Ramp is used specifically for the purpose of continuously calculating values for **F(t)**, based on user-defined values for **F0** and **K**, with the option to start calculations at any desired point in time during the process.

One of the main challenges that was addressed was feeding exponentially, while simultaneously applying corrections to the feed pump setpoint. This was resolved by incrementing the feed pump setpoint with discrete steps, at a user-defined interval (feed cycle). A disadvantage of this solution in its elementary form was that the cells would be systematically underfed (Figure 3).

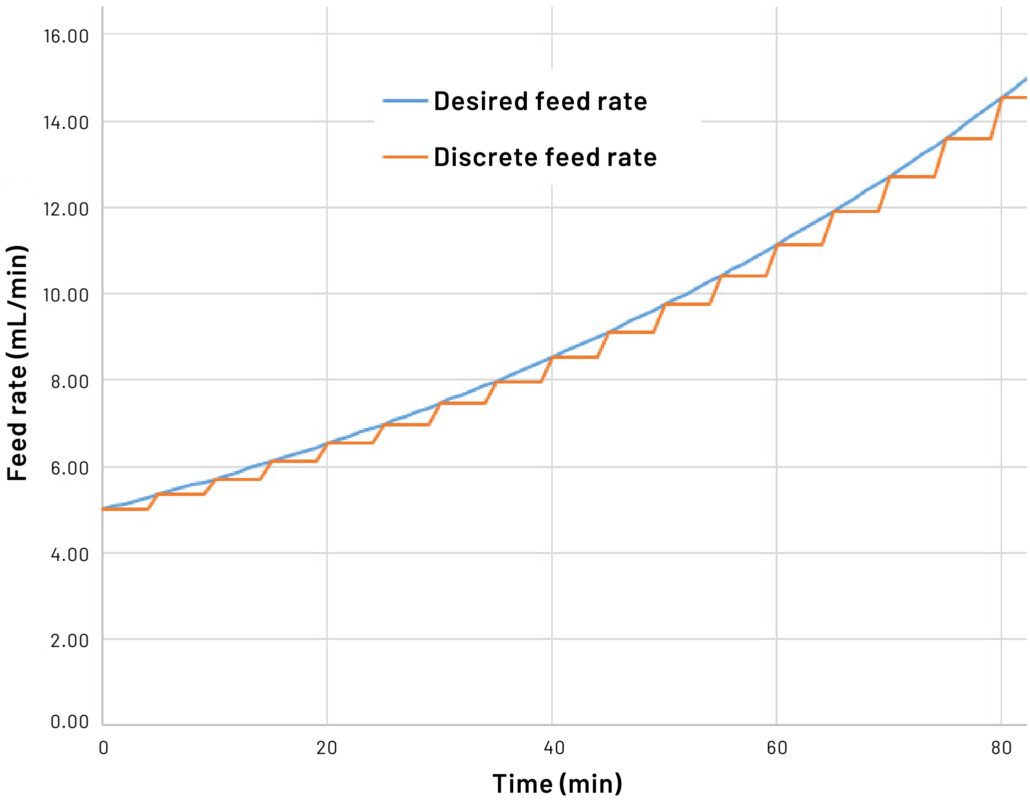

Figure 3: Example of the desired feed rate (exponential function, indicated in blue) compared to the elementary form of the discrete feed rate (stair profile, indicated in red). The discrete feed is incremented each time a full feed cycle has been completed (one feed cycle lasts 5 minutes in this example). Only at the start of each feed cycle, the discrete feed provides enough feed solution to the bioreactor. However, as time passes during a feed cycle, the discrete feed gets more and more behind the desired feed rate, until the feed cycle has been completed and a new feed cycle starts. Over a longer period, this leads to significant underfeeding of the culture.

The systematic underfeeding by the elementary discrete feed solution was corrected by programming two Exponential Ramps in Lucullus® instead of just one (both using the same values for feed parameters F0 and K, as provided by Octarine). During execution of a process, the second Exponential Ramp starts later than the first Exponential Ramp, with a delay equal to the duration of exactly one full feed cycle. This allows Lucullus® to calculate a corrected discrete feed rate for a certain feed cycle (Table 1), by taking the average of the desired feed rate at the beginning of that feed cycle (Exponential Ramp 2) and the desired feed rate at the end of that feed cycle (Exponential Ramp 1)(Figure 4).

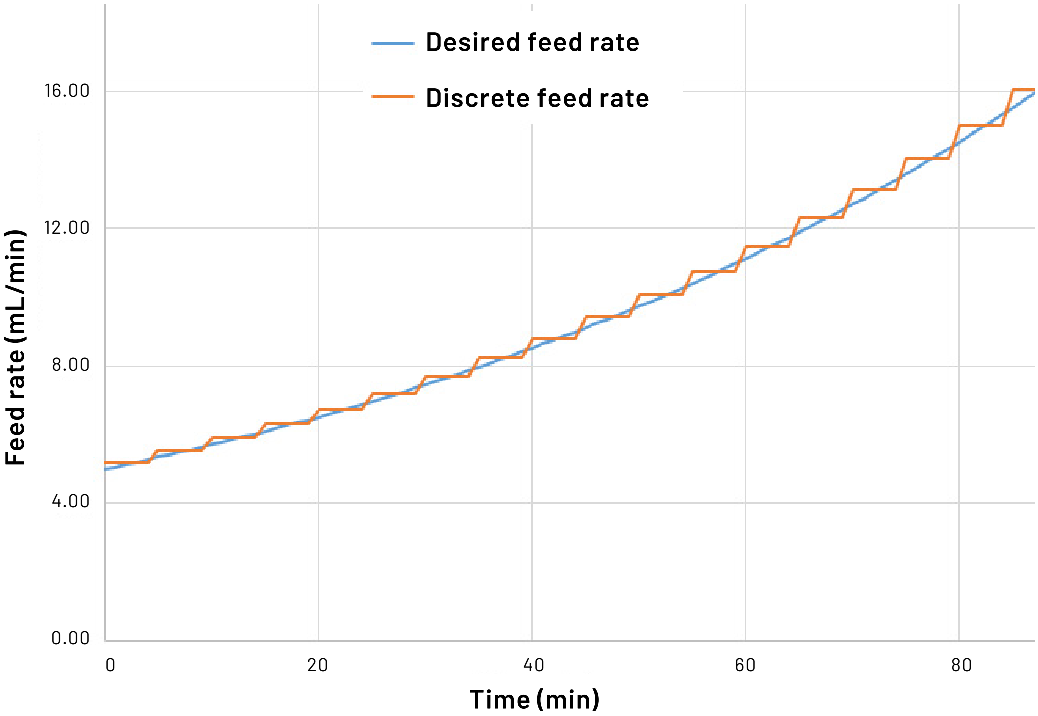

Figure 4: Example of the desired feed rate (exponential function, indicated in blue) compared to the improved form of the discrete feed rate (stair profile, indicated in red). The discrete feed is incremented each time after a full feed cycle has been completed (one feed cycle lasts 5 minutes in this example). In this case, the discrete feed has been corrected to prevent underfeeding: at the start of each feed cycle, the discrete feed provides a bit more feed solution than intended, whereas at the end of each feed cycle, the discrete feed provides a bit less feed solution than intended. This results in the amount of feed solution being dosed throughout one complete feed cycle being very close to the intended target.

t	F_1	F_2	F_av	F_dis
min	g/min	g/min	g/min	g/min
0	5.00			
1	5.07			
2	5.14			
3	5.20			
4	5.27			
5	5.34	5.00	5.17	5.17
6	5.42	5.07	5.24	5.17
7	5.49	5.14	5.31	5.17
8	5.56	5.20	5.38	5.17

9	5.64	5.27	5.46	5.17
10	5.71	5.34	5.53	5.53
11	5.79	5.42	5.60	5.53
12	5.87	5.49	5.68	5.53
13	5.95	5.56	5.75	5.53
14	6.03	5.64	5.83	5.53
15	6.11	5.71	5.91	5.91
16	6.19	5.79	5.99	5.91
17	6.27	5.87	6.07	5.91
18	6.36	5.95	6.15	5.91
19	6.44	6.03	6.23	5.91

Table 1: Example of the calculation of the corrected discrete feed rate. Parameter **F_1** represents the desired feed rate based on the exponential feed equation, which is calculated by Exponential Ramp 1 in Lucullus®. Parameter **F_2** is identical to **F_1**, except that it is calculated by Exponential Ramp 2 in Lucullus® and is started with a delay equal to a complete feed cycle (5 minutes in this example). Parameter **F_av** represents the calculated average feed rate, based on feed rates **F_1** and **F_2**. Parameter **F_dis** represents the (corrected) discrete feed rate, based on feed rate **F_av**. Note that the feed pump in this example would be activated at 5 minutes, e.g., one full feed cycle after the start of the Exponential Ramp 1 (Figures 5 and 6).

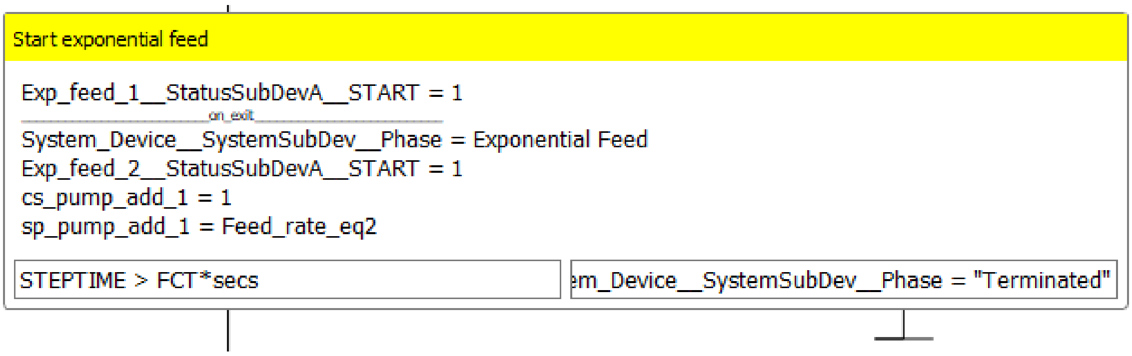

Figure 5: Activation of the Exponential Ramps 1 and 2 in the Lucullus® Operation. The start of exponential equation 2 is staggered in time by one complete feed cycle (parameter **FCT**).

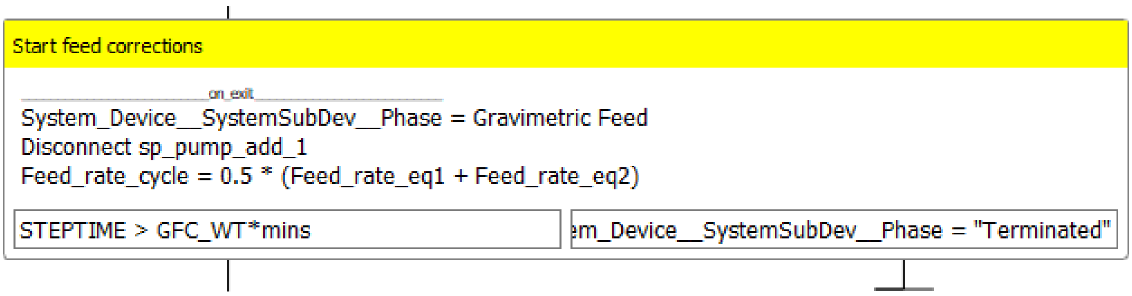

Figure 6: Calculation of the average feed rate, used to supply feed solution at a discrete rate during the next feed cycle (parameter **Feed_rate_cycle**), based on the average of the values calculated by Exponential Ramps 1 and 2.

Correcting the pump setpoint

With a solution available for adding feed solution to the bioreactor at an exponential rate with discrete steps, calculating a correction factor for the pump setpoint could be easily achieved. This is highlighted in the equation below, where parameter **Feed_rate_target** (see the section "Gravimetric feed principle") is replaced by parameter **Feed_rate_cycle** (average of the values calculated by Exponential Ramps 1 and 2).

$$GRCF = \frac{\textbf{Feed\_rate\_cycle}}{\textbf{Feed\_rate\_calc}}$$

At the start of each feed cycle, Lucullus® calculates the feed pump setpoint based on the following two inputs:

- The discrete feed rate per cycle (parameter **Feed_rate_cycle**), which is based on the average of the values calculated by Exponential Ramps 1 and 2.
- The gravimetric feed correction factor (parameter **GRCF**), calculated at the end of the previous feed cycle, which is used as a multiplication factor. Note that for the very first feed cycle, GRCF starts with a value of 1 (Figures 7 and 8).

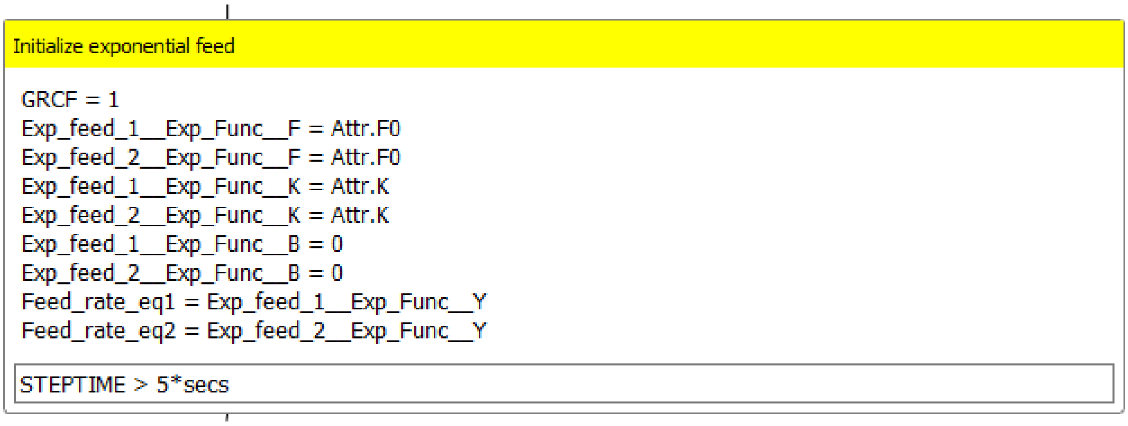

Figure 7: Initialization of the gravimetric feed correction factor (parameter **GRCF**) and the parameters **F0** and **K** for the Exponential Ramps 1 and 2.

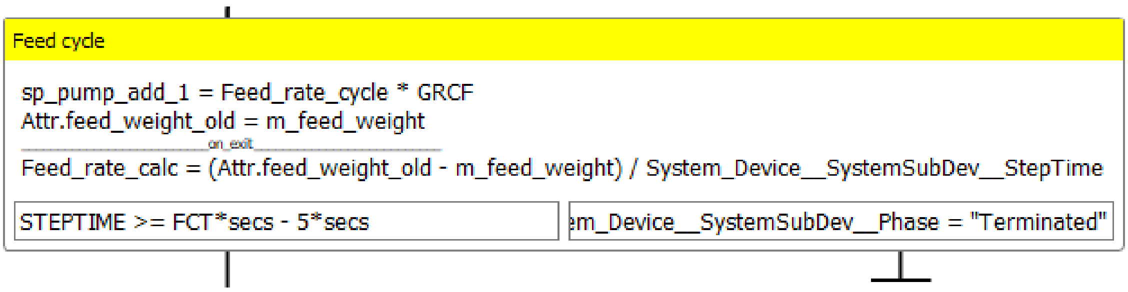

Figure 8: Calculation of the setpoint for the feed pump (parameter **sp_pump_add_1**) for the next feed cycle, based on the calculated discrete feed rate for that feed cycle (parameter **Feed_rate_cycle**) and the gravimetric feed correction factor (parameter **GRCF**). At the end of the feed cycle (parameter **FCT**), Lucullus® calculates the actual feed rate (parameter **Feed_rate_calc**), based on balance measurements captured at the start of the feed cycle and the end of the feed cycle.

The final Operation

Besides feeding as accurately as possible, other requirements by Octarine were programmed into the Operation. Combining these with the aforementioned insights and steps, the following Operation was developed (Figure 9).

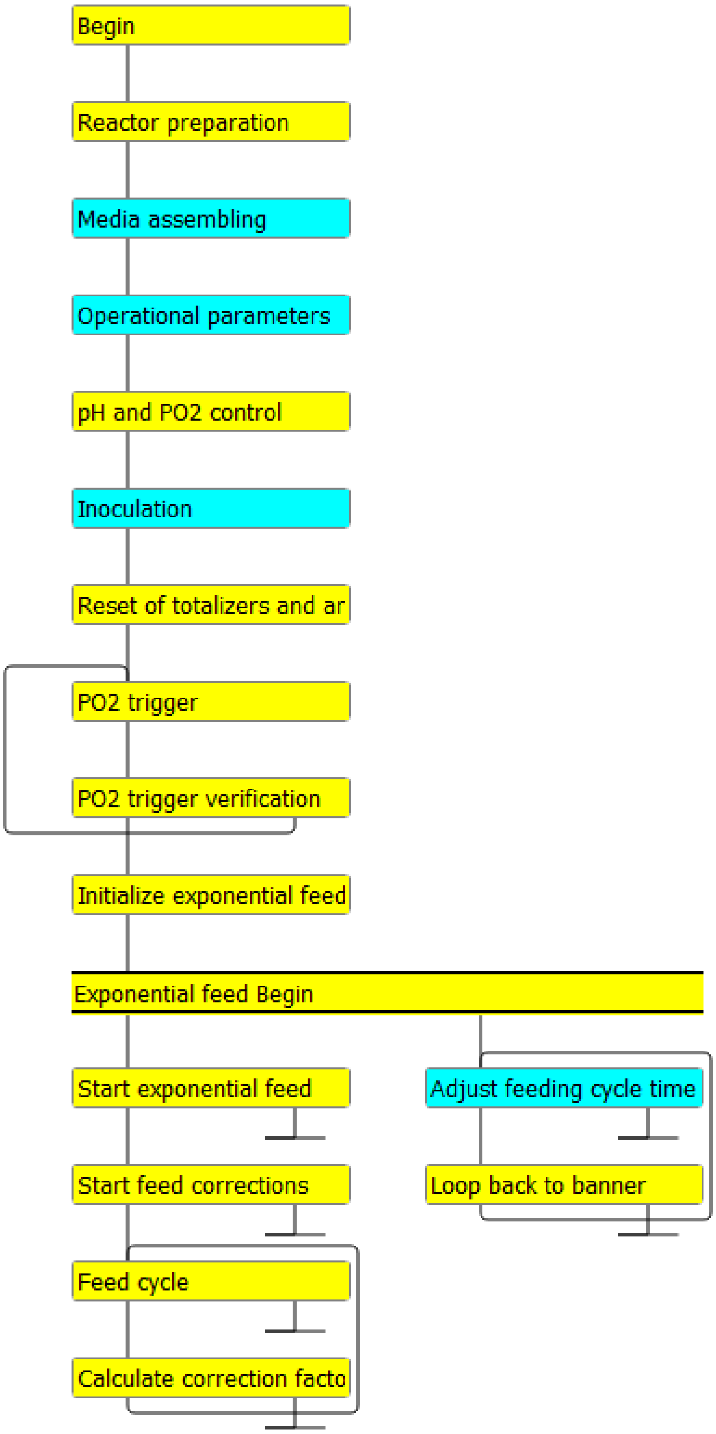

Figure 9: Overview of the final version of the complete gravimetric feed Operation. Steps with yellow headers are executed automatically by Lucullus®, whereas those with blue headers require an input from the operator before Lucullus® can proceed to the next Step. The Steps "Feed cycle" and "Calculate correction factor" are linked to each other as an endless loop, which repeats at a user-defined interval (parameter **FCT**). Note that the calculation of the gravimetric feed correction factor (parameter **GRCF**) takes place in the Step "Calculate correction factor".

Performance

Performance of the Operation was tested during live cultivations at Octarine, and the following was achieved (Figures 10 and 11).

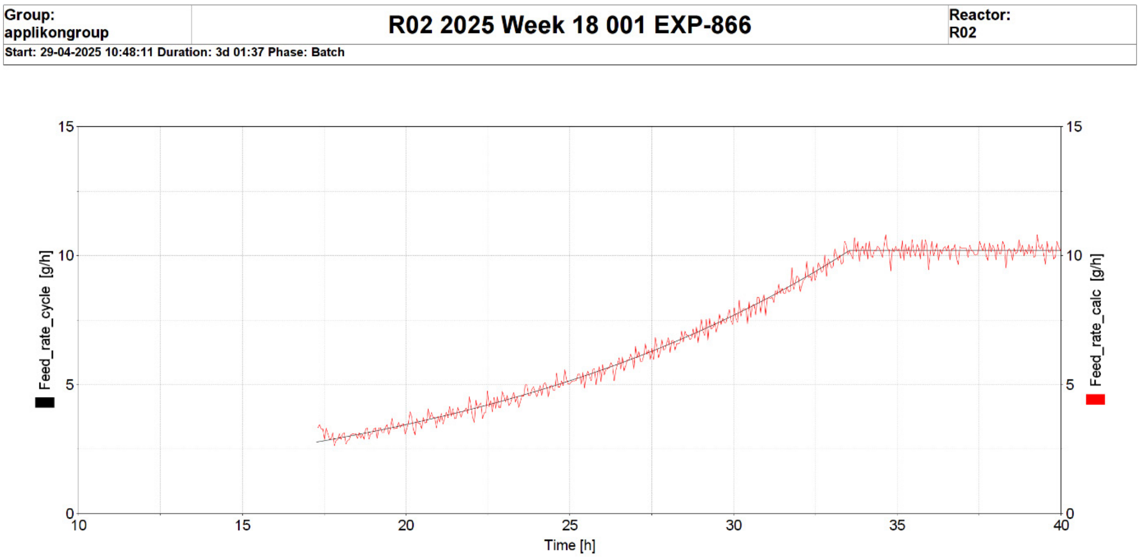

Figure 10: Performance of the gravimetric feed correction algorithm. The black curve indicates the desired feed rate (parameter **Feed_rate_eq1**) and the red curve indicates the calculated actual feed rate, based on consecutive weight measurements of the feed solution (parameter **Feed_rate_calc**). The small oscillations of the red curve are the result of continuous adjustments to the gravimetric feed correction factor (parameter **GRCF**).

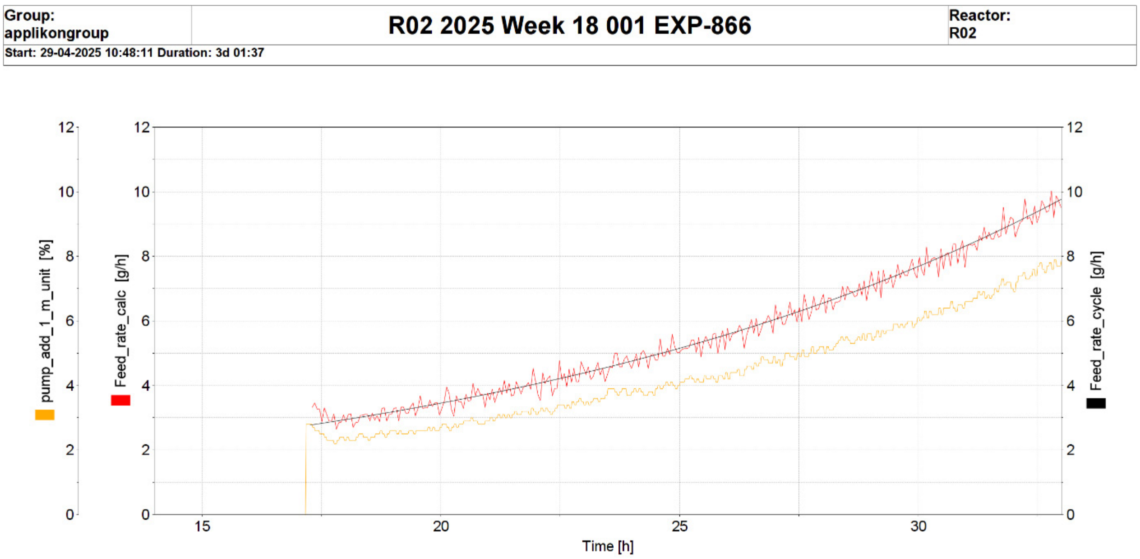

Figure 11: Comparison between a process without gravimetric feed correction and a process with gravimetric feed correction. The black curve indicates the desired feed rate (parameter **Feed_rate_cycle**) and the red curve indicates the calculated actual feed rate, based on consecutive weight measurements of the feed solution (parameter **Feed_rate_calc**). The orange curve indicates the action of a feed pump (parameter **pump_add_1_m_unit**) that is not gravimetrically corrected (calibrated before the start of the process), indicated as a % of the maximum possible pump rate. Gradually increasing deviation over time of the actual pump rate concerning the desired pump rate is not evident by observing the curve itself, but may be gleaned by monitoring the weight of the feed bottle over time.

Process optimization

During the iterative process of programming, testing, analyzing results, and reprogramming, Securecell developed a simulation of the gravimetric feed Operation in Excel. The simulation proved to be a great help in determining the key contributing factors to a properly functioning gravimetric feed algorithm, as well as indicating suitable values for certain parameters involved in the various calculations.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	Start weight	Initial feed rate	Exp. coefficient	Offset	Time step (column A)	Balance precision	# digits	Feed Cycle Time	FCF dev. lim.		AFAC = Actual dosed Feed added per Cycle (assuming an exp. Fe			
2	W0 (g)	F0 (g/h)	K (1/h)	B (g/h)	dt (min)	Bpr (g)		FCT (sec)	FCF DL (%)		CFAC = Calculated dosed Feed added per Cycle (based on record			
3	0	3.80	0.082	0	1	0.01	2	60	3		FCF = Feed Correction Factor			
4											FCF dev. Lim. = Allowed deviation Limit for FCF			
5	Time	Desired feed rate	Averaged feed rate	Calculated feed rate	Pump setpoint	FCF	FCF corrected	Desired feed added	Actual feed added	Balance reading	Increment	AFAC	CFAC	Dosage discrepancy
6	min	g/h	g/h	g/h	g/h			g	g	g		g	g	%
12	5	3.82	3.82	4.20	3.82	0.91	1.00	0.254	0.258	-0.26	X	0.064	0.070	10.0
13	6	3.83	3.83	3.60	3.94	1.06	1.03	0.318	0.321	-0.32	X	0.064	0.060	-5.8
14	7	3.83	3.83	4.20	3.82	0.91	1.00	0.382	0.387	-0.39	X	0.064	0.070	9.7
15	8	3.84	3.84	3.60	3.94	1.06	1.03	0.445	0.451	-0.45	X	0.064	0.060	-6.1
16	9	3.84	3.84	4.20	3.83	0.91	1.00	0.509	0.516	-0.52	X	0.064	0.070	9.4
17	10	3.85	3.85	3.60	3.95	1.07	1.03	0.574	0.580	-0.58	X	0.064	0.060	-6.4
18	11	3.85	3.85	4.20	3.84	0.92	1.00	0.638	0.646	-0.65	X	0.064	0.070	9.1
19	12	3.86	3.86	3.60	3.96	1.07	1.03	0.702	0.710	-0.71	X	0.064	0.060	-6.6
20	13	3.86	3.87	4.20	3.84	0.92	0.99	0.766	0.776	-0.78	X	0.064	0.070	8.8
21	14	3.87	3.87	3.60	3.97	1.07	1.02	0.831	0.840	-0.84	X	0.064	0.060	-6.9
22	15	3.87	3.88	4.20	3.85	0.92	0.99	0.895	0.906	-0.91	X	0.065	0.070	8.5
23	16	3.88	3.88	3.60	3.97	1.08	1.02	0.960	0.970	-0.97	X	0.065	0.060	-7.1
24	17	3.88	3.89	4.20	3.86	0.92	0.99	1.024	1.037	-1.04	X	0.065	0.070	8.2
25	18	3.89	3.89	3.60	3.98	1.08	1.02	1.089	1.101	-1.10	X	0.065	0.060	-7.4
26	19	3.89	3.90	4.20	3.87	0.93	0.99	1.154	1.167	-1.17	X	0.065	0.070	7.9
27	20	3.90	3.90	3.60	3.99	1.08	1.02	1.219	1.232	-1.23	X	0.065	0.060	-7.6
28	21	3.91	3.91	4.20	3.87	0.93	0.99	1.284	1.298	-1.30	X	0.065	0.070	7.6
29	22	3.91	3.91	3.60	3.99	1.09	1.02	1.349	1.363	-1.36	X	0.065	0.060	-7.9
30	23	3.92	3.92	4.20	3.88	0.93	0.99	1.414	1.429	-1.43	X	0.065	0.070	7.3
31	24	3.92	3.92	3.60	4.00	1.09	1.02	1.480	1.494	-1.49	X	0.065	0.060	-8.1
32	25	3.93	3.93	4.20	3.89	0.93	0.99	1.545	1.561	-1.56	X	0.065	0.070	7.0
33	26	3.93	3.93	4.20	3.78	0.94	0.96	1.611	1.625	-1.63	X	0.065	0.070	6.9
34	27	3.94	3.94	3.60	3.89	1.09	0.99	1.676	1.688	-1.69	X	0.066	0.060	-8.5
35	28	3.94	3.95	3.60	4.02	1.09	1.02	1.742	1.753	-1.75	X	0.066	0.060	-8.6
36	29	3.95	3.95	4.20	3.90	0.94	0.99	1.808	1.820	-1.82	X	0.066	0.070	6.4
37	30	3.95	3.96	4.20	3.79	0.94	0.96	1.874	1.885	-1.89	X	0.066	0.070	6.3
38	31	3.96	3.96	3.60	3.91	1.10	0.99	1.939	1.948	-1.95	X	0.066	0.060	-9.0
39	32	3.96	3.97	3.60	4.03	1.10	1.02	2.006	2.014	-2.01	X	0.066	0.060	-9.1
40	33	3.97	3.97	4.20	3.92	0.94	0.99	2.072	2.081	-2.08	X	0.066	0.070	5.9
41	34	3.98	3.98	4.20	3.80	0.95	0.96	2.138	2.146	-2.15	X	0.066	0.070	5.7

Figure 12: Overview of the simulation of the gravimetric feeding, programmed in Excel.

In particular, the precision of the balance used to measure the weight of the feed solution turned out to be critical. This is especially the case at the very early stage of Octarine's process, during which time the feed rate is extremely low. During the first tests. when the gravimetric feed correction was applied, it turned out to have a deleterious effect on adding feed solution when desired feed rates were very low, causing considerable oscillations in the addition of feed solution by the feed pump, overfeeding and underfeeding the culture in turns. Using the Excel simulation, the critical factor was quickly identified: the precision of the balance (0.1 g at that time). Based on this finding, Octarine decided to purchase a new balance with a higher precision of 0.01 g to replace the balance with 0.1 g precision they had been using so far. This resulted in a dramatic improvement in properly correcting the feed pump setpoint at the early stages of the process.

As a further improvement, a parameter was introduced in the Operation, which acts as a time delay between starting the exponential feed and starting gravimetric corrections. This allows the operators at Octarine to temporarily feed the culture without gravimetric corrections during the initial stage of the exponential feed, when the pump is dosing at extremely low feed rates. The duration of this delay can be tuned by the operators, based on the experience of previous executed processes, to find the optimal moment for activating the gravimetric feed correction.

Another crucial parameter to optimizing the gravimetric correction of the feed pump is the duration of the feed cycle (parameter **FCT**). If the feed cycle duration is relatively short, small fluctuations of the feed balance measurement will have a significant impact on the calculated feed rate (parameter **Feed_rate_calc**), leading to undesired inaccuracy of the gravimetric feed correction factor (parameter **Feed_rate_calc**), which is partially based on this parameter. If the feed cycle duration is relatively long, on the other hand, the feed pump might add too little or too much feed solution for a considerable time before a correction takes place. Again, this parameter can be tuned based on the experience obtained from past processes to find the optimal value. In the case of Octarine, the value of the feed cycle was eventually set to several minutes (confidential data).

Future improvements

An alternative Operation was being developed for executing the gravimetric feed corrections at the same time as the Operation described in this Application Note. Testing and troubleshooting this alternative Operation had not been fully completed at the time the project at Octarine was completed. The advantage of the alternative version of the Operation is that it does not require the exponential feed to be divided into many discrete feeding steps, thereby enabling Lucullus® to increment the feed pump setpoint continuously (Figure 13). This is accomplished by integrating the calculated values for the pump setpoint, based on the exponential feed equation and the current value of the gravimetric feed correction factor, throughout one full feed cycle (parameter **FCT**), which then yields the expected decrease of the weight of the feed solution (parameter **dW_pred**) (Figure 14).

$$\mathbf{dW\_pred} = \int_{t\_FCT\_start}^{t\_FCT\_end} \mathbf{GRCF \cdot F(t) = GRCF \cdot F0 \cdot e^{K \cdot t}}$$

$$\mathbf{dW\_pred} = \frac{(\mathbf{F0 \cdot GRCF})}{\mathbf{K}} \cdot (\mathbf{e}^{t\_FCT} - \mathbf{e}^{t\_0})$$

This expected weight decrease is compared to the actual weight decrease, which is based on two consecutive balance measurements of the feed solution (weight at the start and the end of a feed cycle).

$$\mathbf{dW\_act} = (\mathbf{bal\_FCT\_start}) - \mathbf{bal\_FCT\_end}$$

The gravimetric feed correction factor is then calculated as a function of these two weight differences.

$$\mathbf{dW\_act} = (\mathbf{bal\_FCT\_start}) - \mathbf{bal\_FCT\_end}$$

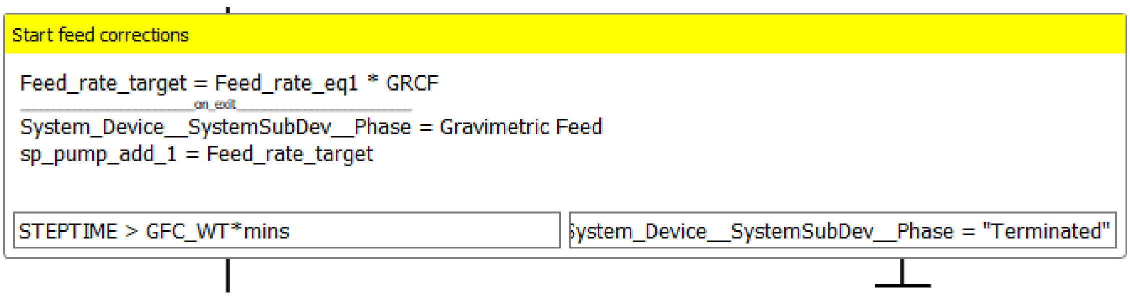

Figure 13: Calculation of the target feed rate (parameter **Feed_rate_target**), based on the values generated by the Exponential Ramp 1 (desired feed rate) and the gravimetric feed correction factor. Lucullus® is programmed to re-calculate the target feed rate continuously. The constantly increasing values of the target feed rate are assigned to the pump setpoint (parameter **sp_pump_add_1**). Note that in this alternative Operation the Exponential Ramp 2 is not used, as there is no need for it.

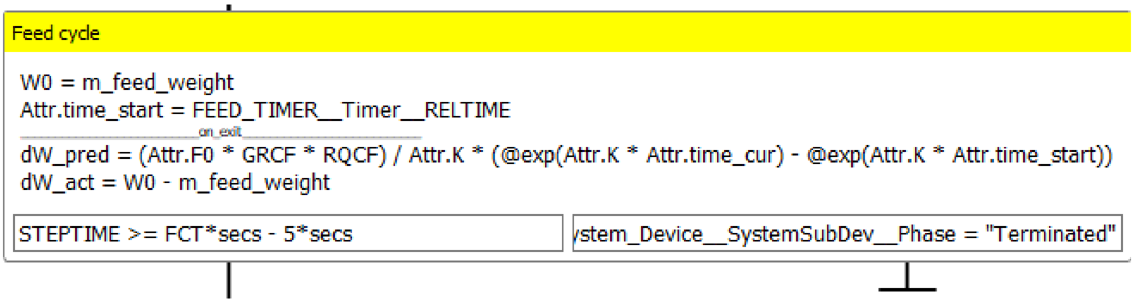

Figure 14: Calculation of the predicted weight decrease (parameter **dW_pred**), based on the gravimetric feed correction factor and the exponential feed equation integrated throughout a full feed cycle, and calculation of the actual weight decrease (parameter **dW_act**), based on balance measurements at the start and end of a feed cycle.

Future tests will have to be performed to properly assess this alternative version of the Operation and compare its performance to the original Operation. It is expected that by adjusting the feed pump setpoint continuously, feed accuracy will be even better compared to the solution where the feed pump setpoint is adjusted periodically.

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The implementation of a gravimetric feed system allows for more accurate control over the desired growth rate during fed-batch fermentations. This improves biomass yields on the carbon source, enabling the optimal or desired amount of biomass to be reached at a specific point in the fermentation. Better control over biomass formation at different metabolic stages results in a boost in product yield per unit of biomass. Furthermore, a noticeable increase in the reproducibility of the feed profile was achieved between fermentation runs. This was accomplished by eliminating the need for pump calibration and preventing operational issues related to changes in the setup, such as variations in tubing lines and feed density. As a result, the characterization of the fermentation protocol could be improved, and more systematic results were obtained, while simplifying the transfer of feeding profiles to external partners.

It was crucial to have received assistance from Securecell for programming, testing, troubleshooting and optimizing the Lucullus® Operations employed for achieving a gravimetric feed system, which functioned exactly as desired. The experience and proactive work mentality of Securecell's engineers made the difference between having a proper functioning solution within the set time constraints for this project, or not.

Conclusion

Gravimetric feed control is a very effective method for dosing feed solutions to bioreactor systems in a very precise manner, supporting the optimization of the bioreactor environment. Successfully applying gravimetrical feed control is challenging and requires equipment with the right characteristics, know-how about the key parameters involved, as well as experience with process automation.

KEY TAKEAWAYS

- The powerful process automation capabilities of Lucullus® allow for the successful implementation of advanced process control strategies, such as the gravimetrically corrected feed at Octarine.
- Valuable insights into the performance of gravimetrical feed control are gained by simulating the feeding process. It helps to determine the most important contributing factors.
- The precision of the balance plays a key role in the correct execution of gravimetric feed correction, especially when feed rates are particularly low.
- Other important parameters for optimizing gravimetrical feed control include the frequency at which the correction factor is calculated (feed cycle time) and the delay time between starting the feed pump and starting gravimetric feed corrections.

Contributor list
The gravimetric feed control regulation was developed and optimized by Lucullus® Application Specialists, Manuel Cantero, and Rowin Timmermans from Securecell, based on the requirements and feedback from Research Scientists Luca Guerrini and Javier Fuentes Izquierdo from Octarine. A special thanks to Kim Hanson and Tine Holbæk Levinsen from Holm and Halby for establishing the contact between Octarine and Securecell.

OCTARINE

Holm & Halby
TIL LABORATORIER I UDVIKLING

securecell

SECURECELL AG

In der Luberzen 29
CH – 8902 Urdorf
+41 44 732 91 00
contact@securecell.ch