

## A Swiss Army Knife for Modern Biomanufacturing

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### Single step implementation to de-risk continuous processing

Adoption of single use (SU) technology to entire production schemes is only recently realized after decades of having disposable products available. The use of buffer and small disposable bioreactor bags were implemented early while more sophisticated or large unit operations employing SU are only recently available to complete the “disposable facility dream”. Likewise the implementation of continuous production will begin in a step-wise fashion with individual unit operations addressing the largest bottleneck or by adopting the simplest, lowest risk technology to achieve early ROI and productivity gains.

Multi-column continuous chromatography (MCC) at production scale has been an ambition of GMP facilities for some time. Implementation of MCC at large scale greatly increases productivity, particularly at the capture step where many production facilities are bottlenecked as a result of productivity gains in upstream fed-batch or perfusion systems.

### Beyond continuous batch production

MCC by itself substantially intensifies the capture process with productivity gains of nearly 3X (1). The bioprocess systems’ group of YMC has further enhanced the chromatography process by engineering a platform that not only provides a simple 2-column method for continuous capture (a patented process by YMC ChromaCon® AG) but through innovative

engineering and end-user verification has combined 4 unit operations into a single skid. Scale up of 100X has been proven by a GMP producer of biologics (1).



Figure 1: Successful scale up of 100x on 2-column continuous capture systems  
Shown: Contichrom CUBE benchtop and Contichrom TWIN LPLC GMP pilot.

A single Contichrom TWIN® LPLC System can perform:

- Batch – with an outstanding range from 0.4 to 20 LPM
- Continuous-batch capture – patented CaptureSMB® 2- column technology
- Sequential (orthogonal) polishing – pool-less 2-step chromatography
- Buffer in-line dilution (BID) – on-board in-line dilution of buffers and CIP solutions
- Single use aseptic interface – permits use in minimally classified suite

## Simple yet flexible multi-function system

Continuous, multi-column Protein A capture chromatography is shown to debottleneck the downstream purification of monoclonal antibodies. The advantages of this type of continuous process as compared to traditional single-column capture include improved resin capacity utilization, shorter processing times or reduction in resin volume, and reduction in buffer consumption, all while maintaining yields at > 98%. However, achieving these benefits comes at the expense of increased hardware complexity and investment. More complex equipment also increases risk of downtime and maintenance costs.

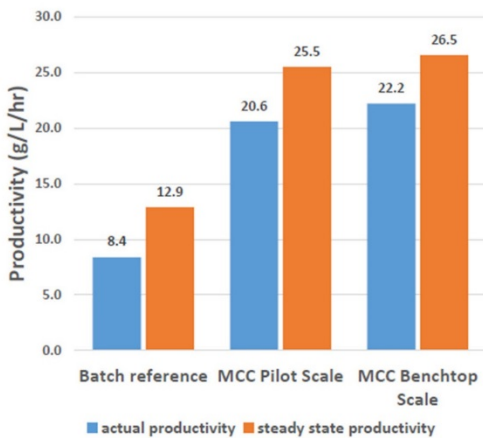


Figure 2: A 2- to 3-fold increase in productivity when using continuous capture over single-column batch (4).

While systems and processes utilizing up to as many as 8 or more columns have been reported, a simple 2-column continuous system maximizes process performance with respect to resin capacity utilization, buffer consumption, and product concentration while minimizing hardware investment and risk (2). Fewer columns significantly reduces equipment complexity simply by reducing the number of valves, plumbing, and monitoring required. Simpler hardware also means simpler operation

and automation facilitating operator understanding, equipment qualification, and process validation.

Employing continuous capture chromatography for process intensification is proven way to enhance productivity. Combining multiple functions within a single unit operation on single system, such as in-line dilution of buffer concentrate to produce point-of-use buffer for the continuous capture operation (2), not only increases productivity, it also minimizes facility footprint, increases asset utilization, and reduces costs.

## Sequential batch operation

The continuous operation of two interconnected downstream unit operations (e.g. flow through and bind-elute polishing steps) is another way to increase productivity and streamline the downstream process. Two-fold increases in productivity for continuous, sequential batch operation as compared to individual batch steps has been reported (3). In addition, operating two, connected polishing steps continuously eliminates the need for in-process hold and

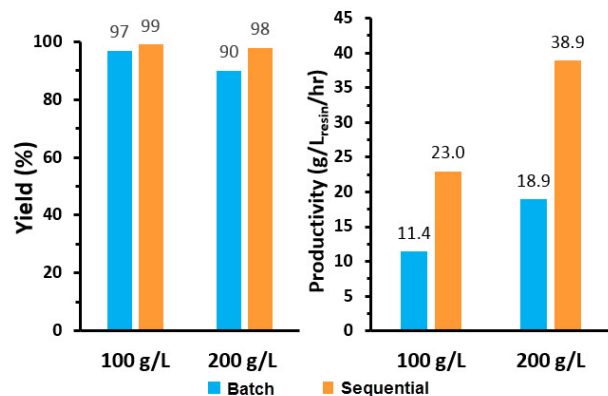


Figure 3: Data for two different loads shows a consistent twofold increase in productivity when using sequential over batch (4) while maintaining a high yield.

storage and eliminates the time associated with changeover between individual unit operations streamlining the process. Operating sequential

batch operations continuously on a two-column system, such as the Contichrom TWIN LPLC, combines two unit operations in one system, reducing the equipment footprint to maximize throughput per square foot of operating suite.

## System optimized for use in a single use, buffer concentrate environment

The Contichrom TWIN with its on-board, highly precise (+/- 1.0% accuracy) (2) buffer dilution option provides:

- Use of buffer concentrates – saves space
- Utilization of concentrated caustic – for fully automated system CIP / sanitization
- Facilitates sequential processing - creates in-line buffer for conditioning of feed between sequential two-column steps
- Significant space savings – two unit operations combined and use of concentrates further decreases tankage by 10X or more

## Single use environment enabled

A proprietary manifold by YMC Process Technologies enables the unit to automatically and aseptically manage multiple buffers, WFI and CIP from single use bags / tubing sets. This arrangement allows use of the unit in a minimally classified area – saving significant cost associated with more highly classified cleanroom production environments. The adaption to a commonly available disposable aseptic connector simplifies the interface between the single use and stainless steel components on both the upstream and downstream sides of the unit. The ingenious design and automation assures the sanitization of all system-facing surfaces prior to opening the DAC resulting in a fluid path that is never exposed to an open environment that is not sanitized.



Figure 4: A proprietary buffer, feed and CIP manifold maintains an aseptic, closed environment between single use equipment and the Contichrom TWIN.

## De-risk the continuous challenge and gain significant flexibility and productivity

Using this uniquely simple, patented design eases production implementation, validation and maintenance. The new Contichrom TWIN Enhanced Platform delivers scalable, proven cost reductions (>50% Protein A and buffer reduction) (4) significantly increased production flexibility, 2-3 fold productivity gains and the ability to combine multi-unit operations on a single skid in a single use environment. Simple design with options for multi-function enhancements de-risk the investment both in validation ease and manufacturing asset utilization / flexibility. This is truly the Swiss Army Knife for modern biomanufacturing facilities.

## Wide range in commercial production

Units with the functionalities mentioned above are now commercialized with a flow ranges of up to 20 LPM – a platform enabling small to large production lot purifications on the same system. Systems with similar features have been installed in the USA, Europe and Japan.

(1) James Angelo, John Pagano, Thomas Müller-Späth, Kathleen Mihlbachler, Srinivas Chollangi, Xuankuo Xu, Sanchayita Ghose, and Zheng Jian Li, Scale-Up of Twin-Column Periodic Counter-Current Chromatography for MAb Purification, *BioProcess International* Vol. 16(4) April 2018

(2) Daniel Baur, Monica Angarita, Thomas Muller-Spath, Fabian Steinebach and Massimo Morbidelli, Comparison of Batch and Continuous Multi-Column Protein A Capture Processes by Optimal Design, *Biotechnol. J.* 11(7)2016:920-931.

(3) Mary Jo Wojtusik, Kurt Wilner, Low Pressure Liquid Chromatography Using EcoPrime LPLC with Enhanced Buffer In-Line Dilution, *BioProcess J.*,15(3)2016:14-19

(4) James Angelo, Srinivas Chollangi, John Pagano, Daniel Baur, Kathleen Mihlbachler, Thomas Muller-Spath, Xuankuo Xu, Massimo Morbidelli, Sanchayita Ghose, Scale Up Design and Optimization for an Intensified Downstream Process Utilizing Multi-Column Operations, 255<sup>th</sup> ACS National Meeting, New Orleans LA, March 2018.

Editor's note: This technology was originally introduced by LEWA-Nikkiso America Inc. In late 2018 YMC Co., Ltd acquired the technology, manufacturing site, staff and license from LEWA. YMC now produces the Contichrom TWIN LPLC and HPLC and Contichrom CUBE instrument in the USA.



Photo: Contichrom TWIN with batch, continuous capture (CaptureSMB), buffer in-line dilution (BID) and sequential polishing capabilities. Also shown is optional single use buffer management manifold.

