**INTRODUCTION**

The benefits of simulated moving bed (SMB) or multicolumn continuous chromatography (MCC) for increasing the productivity of separations have been known for over 60 years. When compared with single column batch systems, MCC offers:

- Smaller columns: lower adsorbent volume
- Higher throughput: operation at “overload” conditions with high purity and recovery
- Process flexibility: adjustable column number, size and configuration to suit feed and adsorbent properties and run time requirements
- Continuous operation

Gottschlich and Kasche described an MCC process for mAb Protein A capture in 1996 (1). With the recent development of hundreds of therapeutic mAb candidates, steady increase in upstream titer, and current high cost of manufacture, the Protein A capture step has become a primary target for MCC process improvement.

One major challenge for achieving maximum productivity is driving mAb adsorption to the full static binding capacity of the resin as fast as possible while maintaining high recovery. MCC makes this possible by including multiple columns in the capture zone, which allows recovery of the breakthrough fraction from the first column on one or more columns connected downstream. Several processes and detailed models have been described for optimizing MCC Protein A capture, with wide variation in predicted and realized productivities (2–5). Much of the variation can be attributed to differences in the assumptions used for the models (e.g. mAb titer, adsorbent and hydrodynamic properties of the resin, residence and regeneration times).

**Residence Time**

The productivity of a Protein A capture process is driven by residence time. The chart shows the theoretical productivity achieved from an MCC process at different mAb feed titer, assuming 100% yield and no constraints on the process parameters.

Gains in productivity are observed as residence times decrease, and are most dramatic at feed titers above 3 g/L.

In practice, three interdependent factors constrain the ability to achieve low residence times with maximum productivity.

- Constraints on residence time:
  1. Limitation of flow velocity due to pressure drop through the columns.
  2. Dynamic binding capacity limitations due to mass transfer characteristics of the adsorbent.
  3. Process time constraints due to insufficient number of columns.

**Process Development**

We have taken an experimental approach to optimize productivity using single column binding data, a simple Excel-based modeling tool, and small-scale MCC.

1. Determine dynamic and static binding capacities of the Protein A adsorbent; single column breakthrough analysis for DBA, saturation binding for SBC.
2. Model MCC process at various configurations (e.g. number of columns, zone flow pattern).
3. Test process models and optimize parameters using bench top MCC instrument (Octave 10 System).

**CONCLUSIONS**

1. Optimal productivities with high-titer mAb feedstocks were obtained using a lab-scale 8-column MCC Protein A capture process at 0.5 min residence time with 3 columns in the capture zone. For example, 97 g/L resin was achieved with high purity and recovery using Toyopearl AF rProtein A HC resin. This value represents 86% of the modeled productivity, but lower pressure and longer residence time.

2. Optimal performance at low residence times requires adsorbents having high DBC and low pressure drop and MCC equipment that accommodate multiple process parameters. Both of these considerations will be important to maximize process economy at production scale at any feed titer.

**References**