

Emerging and Enabling Technologies in Membrane Separations

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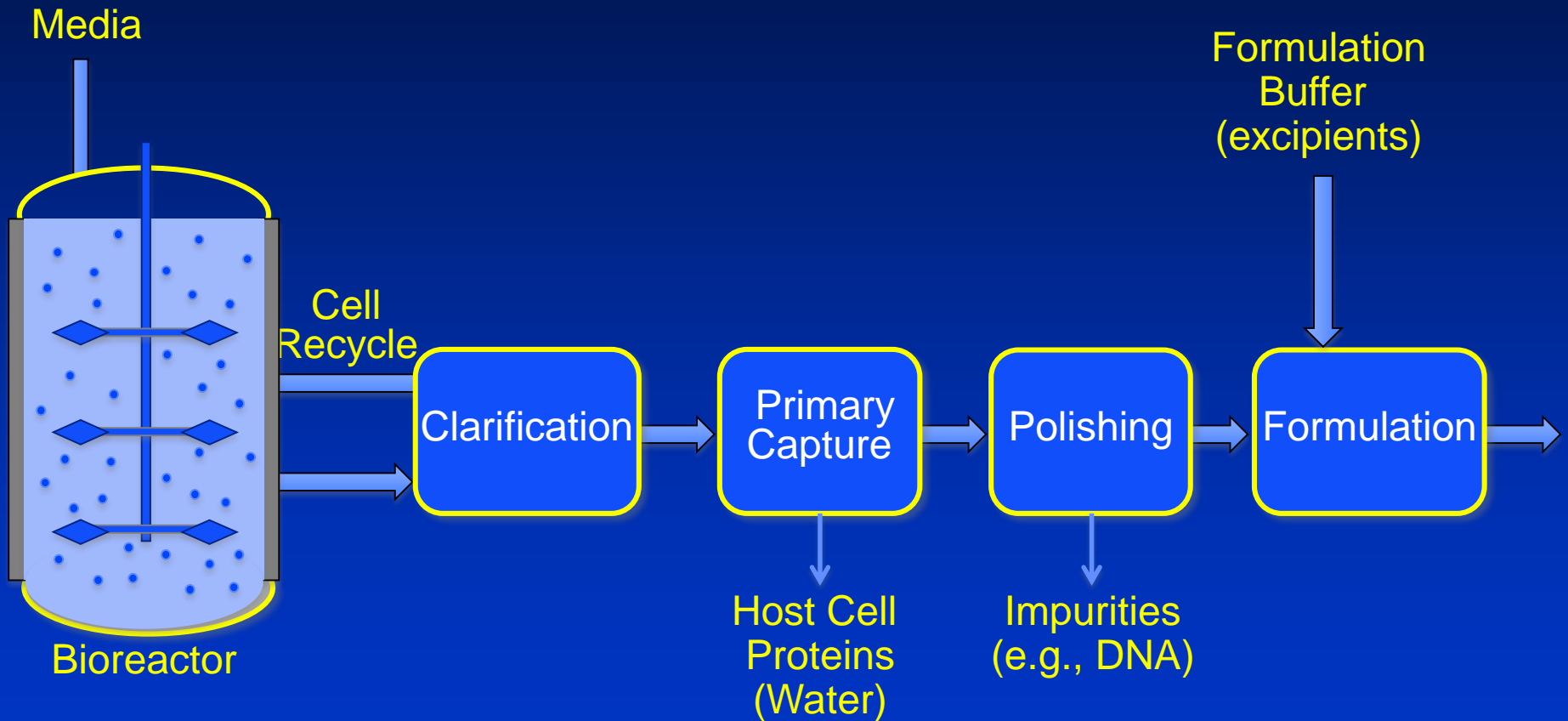
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*2nd International Symposium on Continuous
Manufacturing of Pharmaceuticals*

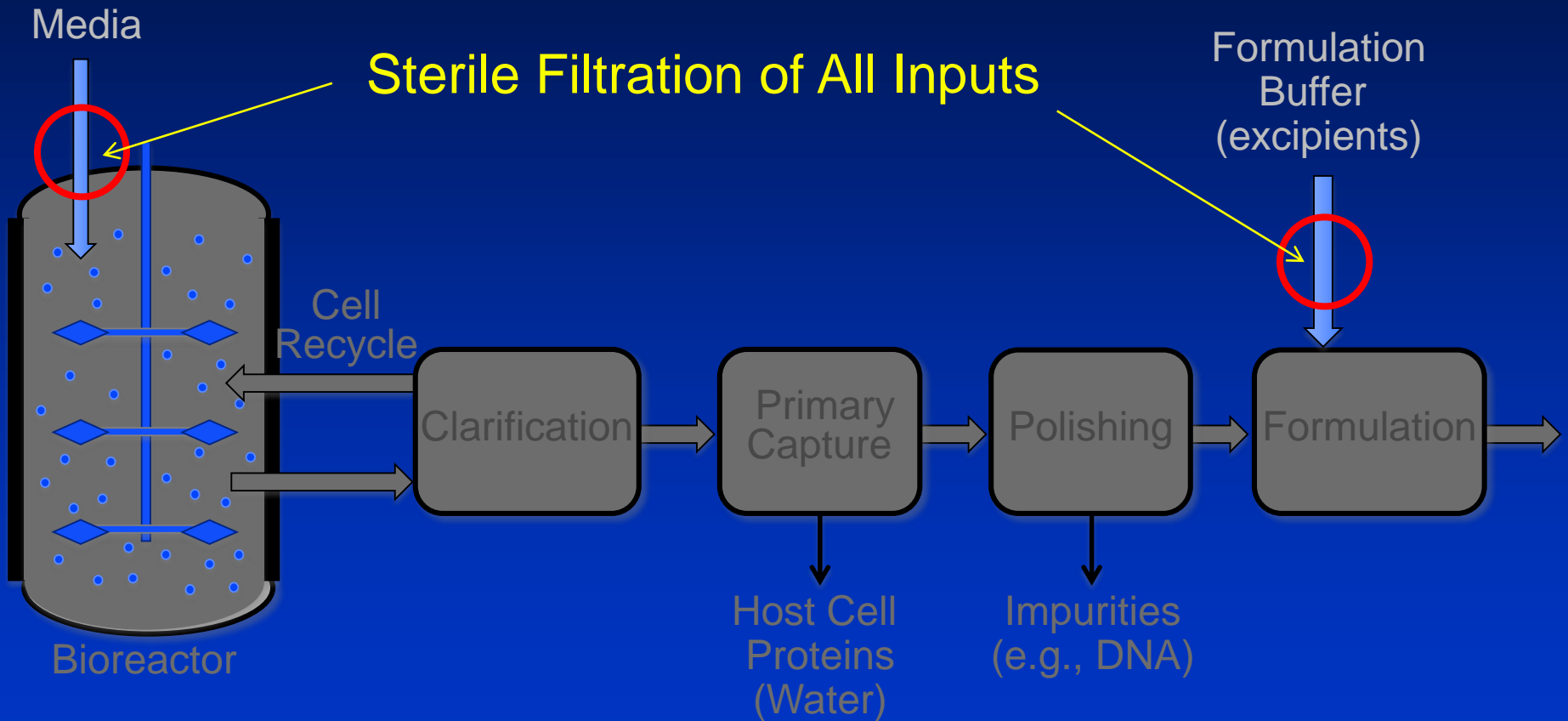
*Cambridge, MA
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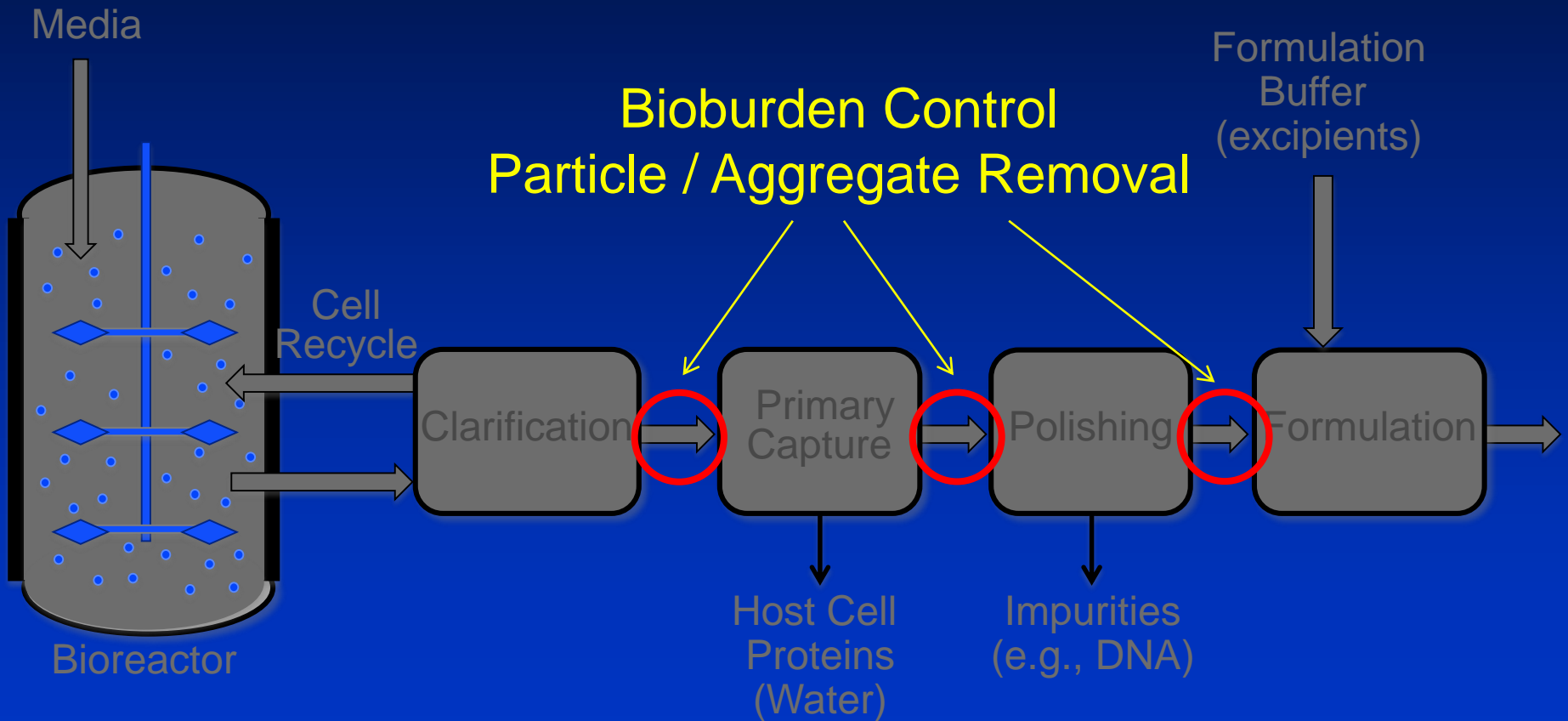
Continuous BioProcess



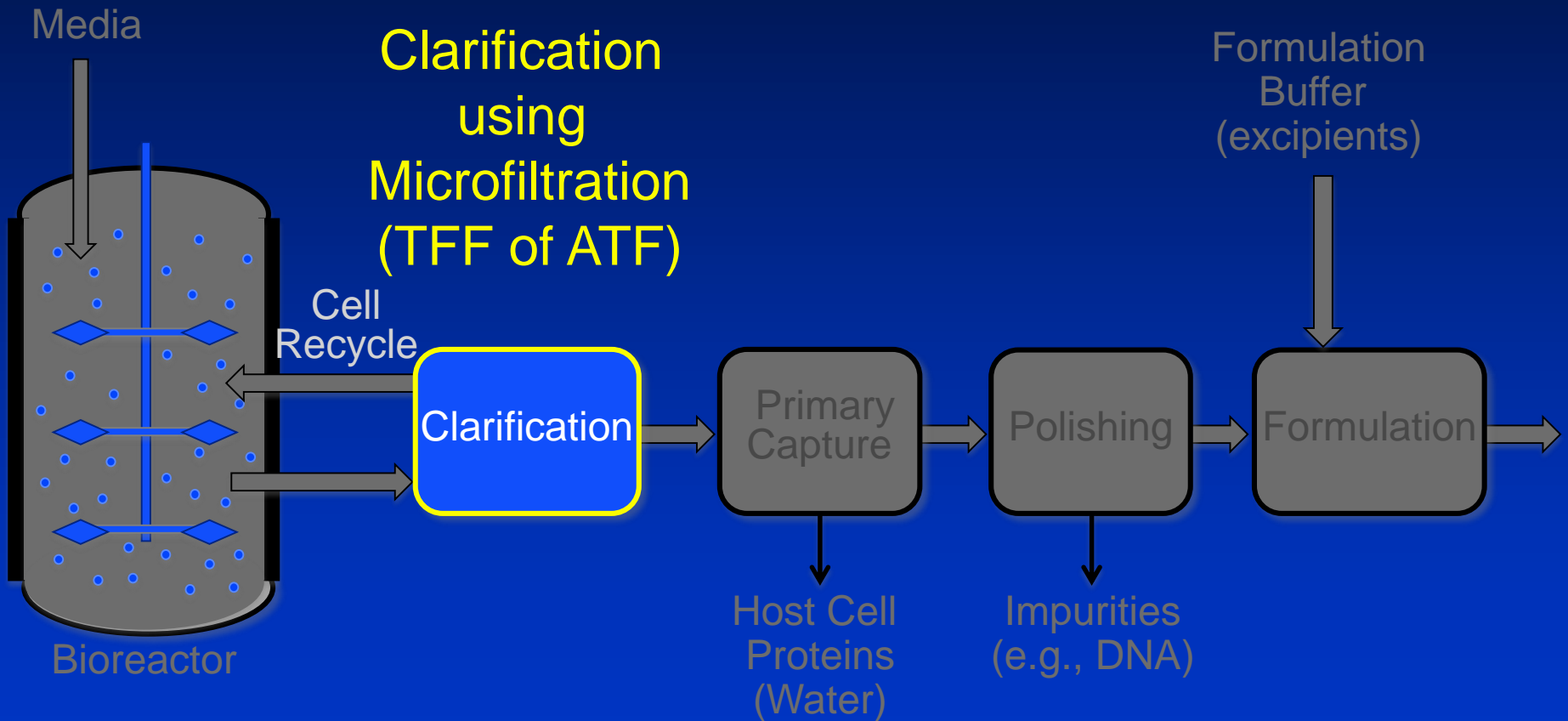
Membranes in Bioprocessing



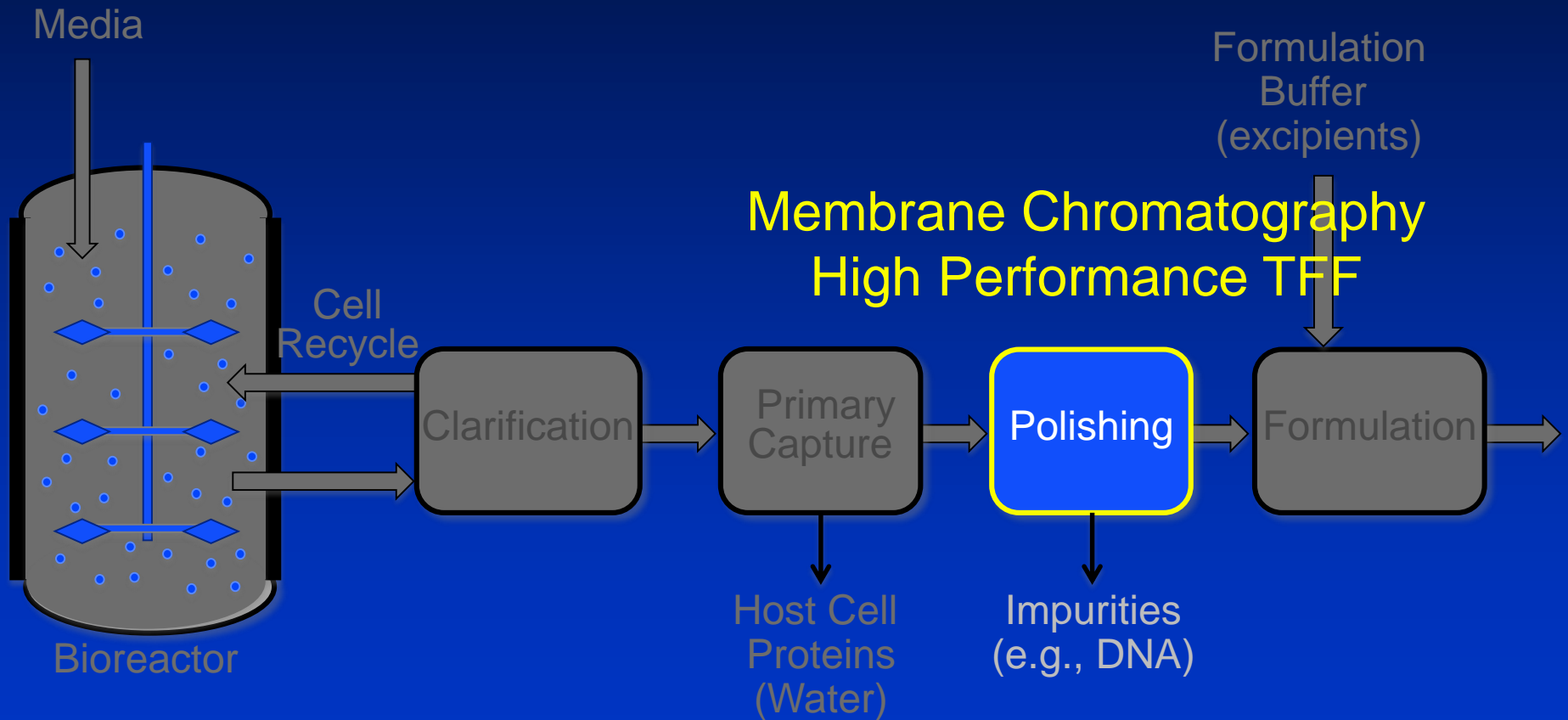
Membranes in Bioprocessing



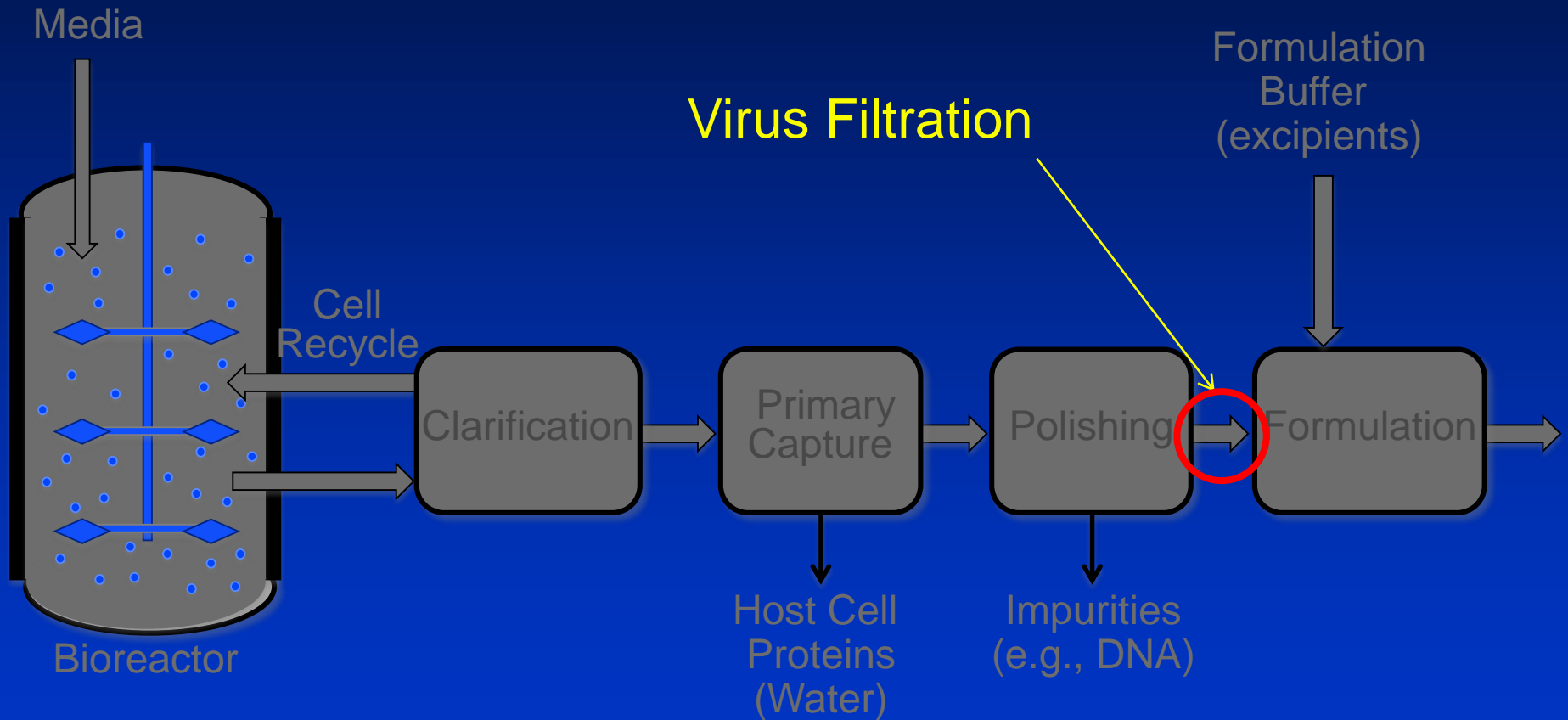
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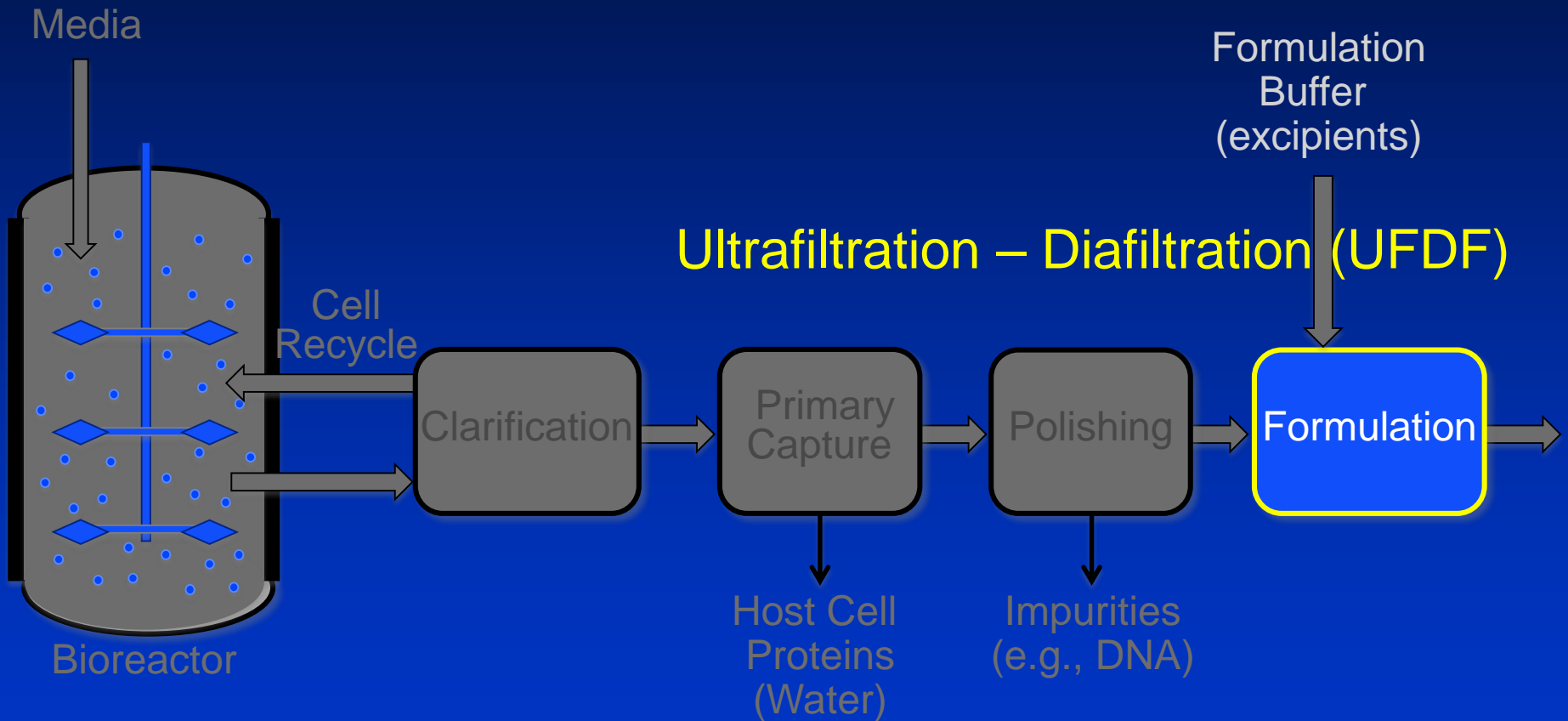
Membranes in Bioprocessing



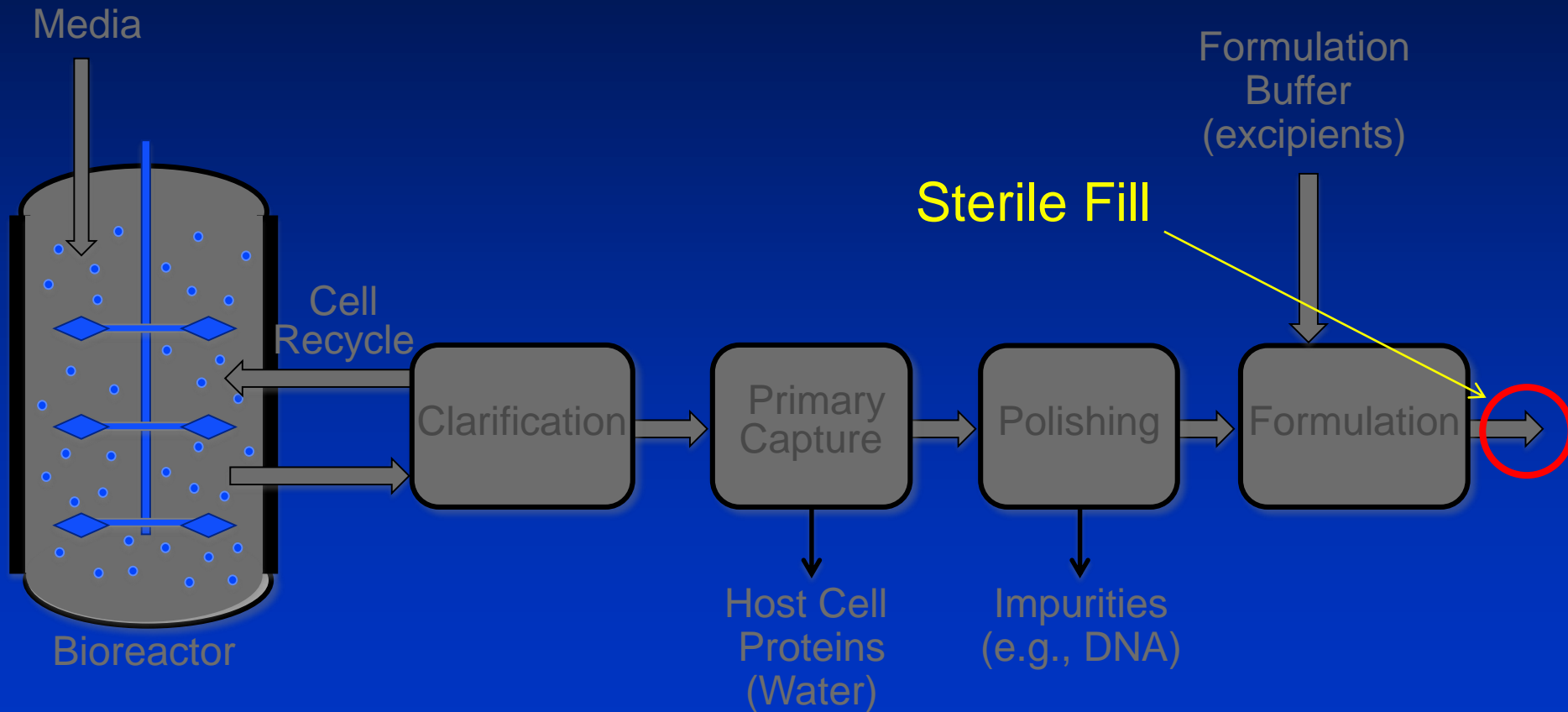
Membranes in Bioprocessing



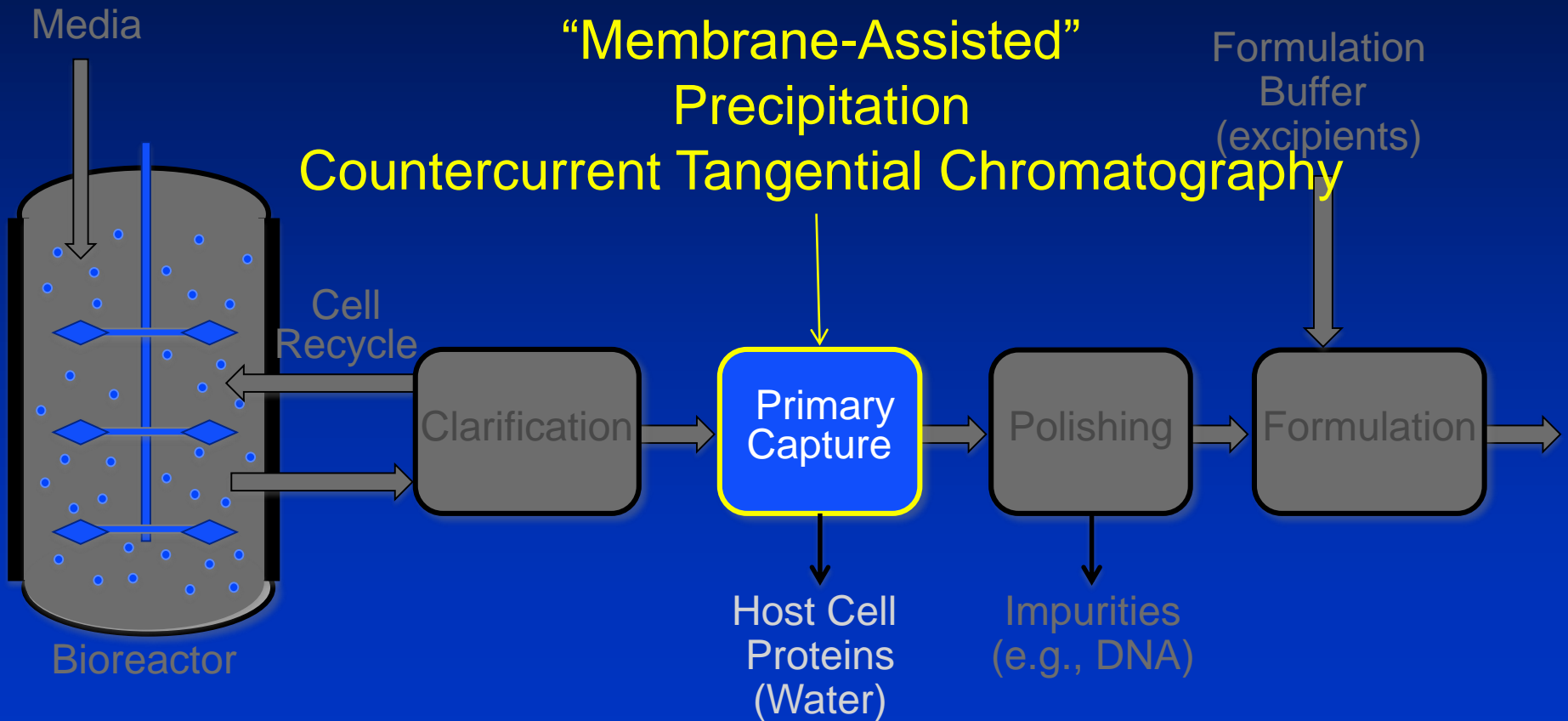
Membranes in Bioprocessing



Membranes in Bioprocessing



Membranes in Bioprocessing



Normal Flow Filtration

- **Continuous Processing**
 - Likely to be achieved by switching between modules arranged in parallel configuration
- **Challenge – need for high capacity**
 - Minimize membrane area, reduce switching frequency (sterility)
- **Current Approach**
 - Combination of pre-filter and sieving membrane
 - Depth filter media with multiple components



Membrane Chromatography

- **Continuous processing**
 - Flow through-mode (impurity removal) done using parallel arrangement (single-use)
 - Bind-and-elute configuration more challenging (“multi-column” format ?)
- **New ligands / membranes under development**
 - Higher binding capacity (less frequent replacement)
 - More robust binding (e.g., salt-tolerant ligands)
 - Multi-modal ligands with enhanced selectivity

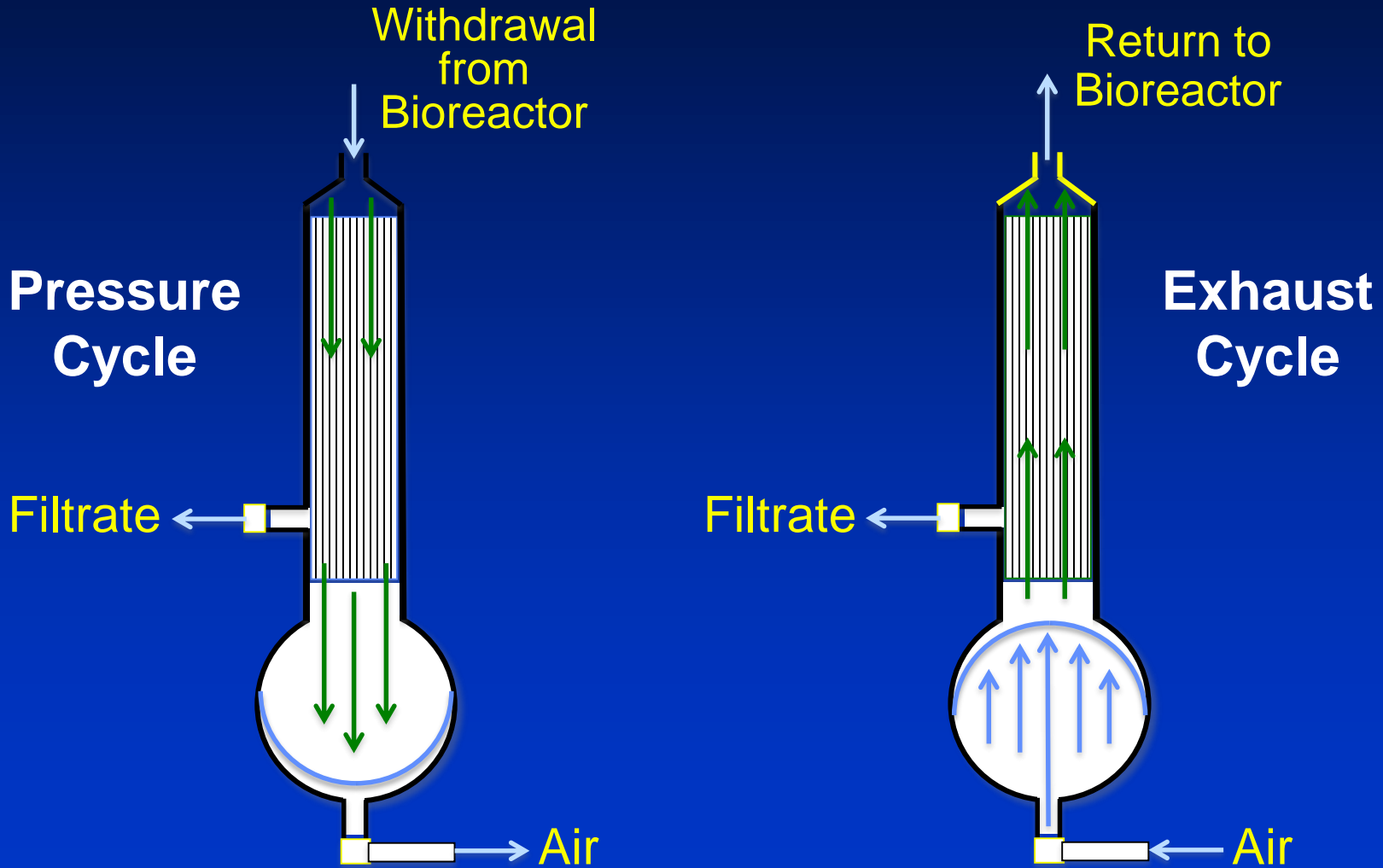


Tangential Flow Filtration

- **Challenge – new process configuration needed**
 - Current modules and process configurations were designed for batch processing
 - Need to eliminate feed recycle currently used in most TFF applications (e.g., UFDF)
- **Current Approaches**
 - Alternating Tangential Flow Filtration (ATF)
 - Single Pass Tangential Flow Filtration (SPTFF)
 - Countercurrent staging



ATF – Alternating Tangential Filtration



ATF – Alternating Tangential Filtration

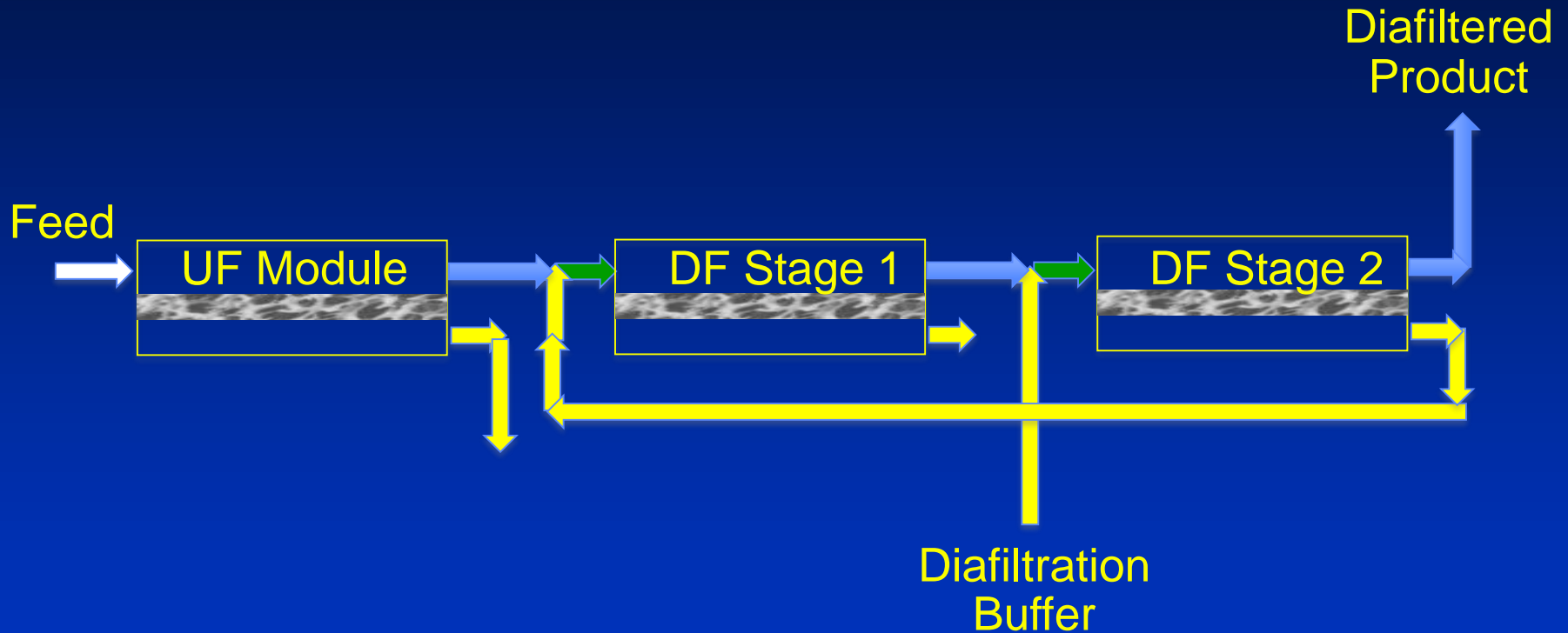
- **Flow reversal**
 - Unclogs blocked fibers, disrupts boundary layer
- **Very low flux operation**
 - Minimizes cell deposition
 - Backfiltration – in situ membrane cleaning
- **Membrane fouling remains problematic**
 - Need for new membranes specifically developed for continuous clarification with perfusion
 - Opportunities for new high performance modules

Single Pass TFF

- **Required conversion (concentration) achieved in single pass through module**
 - Specially-designed (e.g., Pall Inline Concentrator)
 - “Long” modules (e.g., modules in series)
 - Single-use systems (replace as needed)
- **Membrane fouling remains problematic**
 - Need for new membranes / modules specifically developed for long-term operation



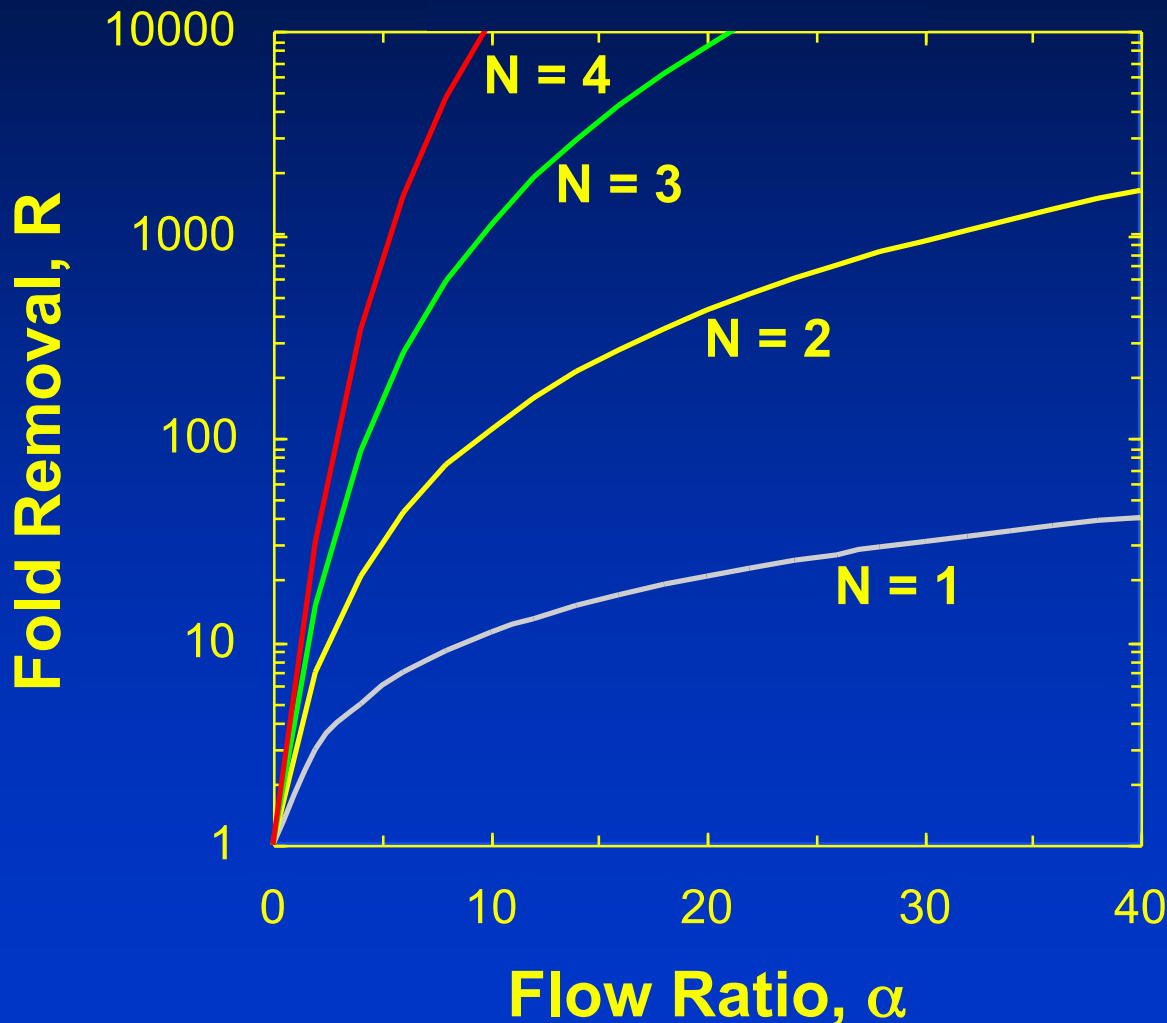
Process Configuration - Staged Diafiltration



- Continuous, single-pass, operation
- High solute removal due to staging + high conversion



Countercurrent Staged Diafiltration



- For $N = 1$, a flow ratio of $\alpha = 19$ corresponds to a 20-fold reduction in solute concentration
- Same flow ratio provides:

$R = 380$ for $N = 2$

$R = 7,200$ for $N = 3$

$R = 138,000$ for $N = 4$



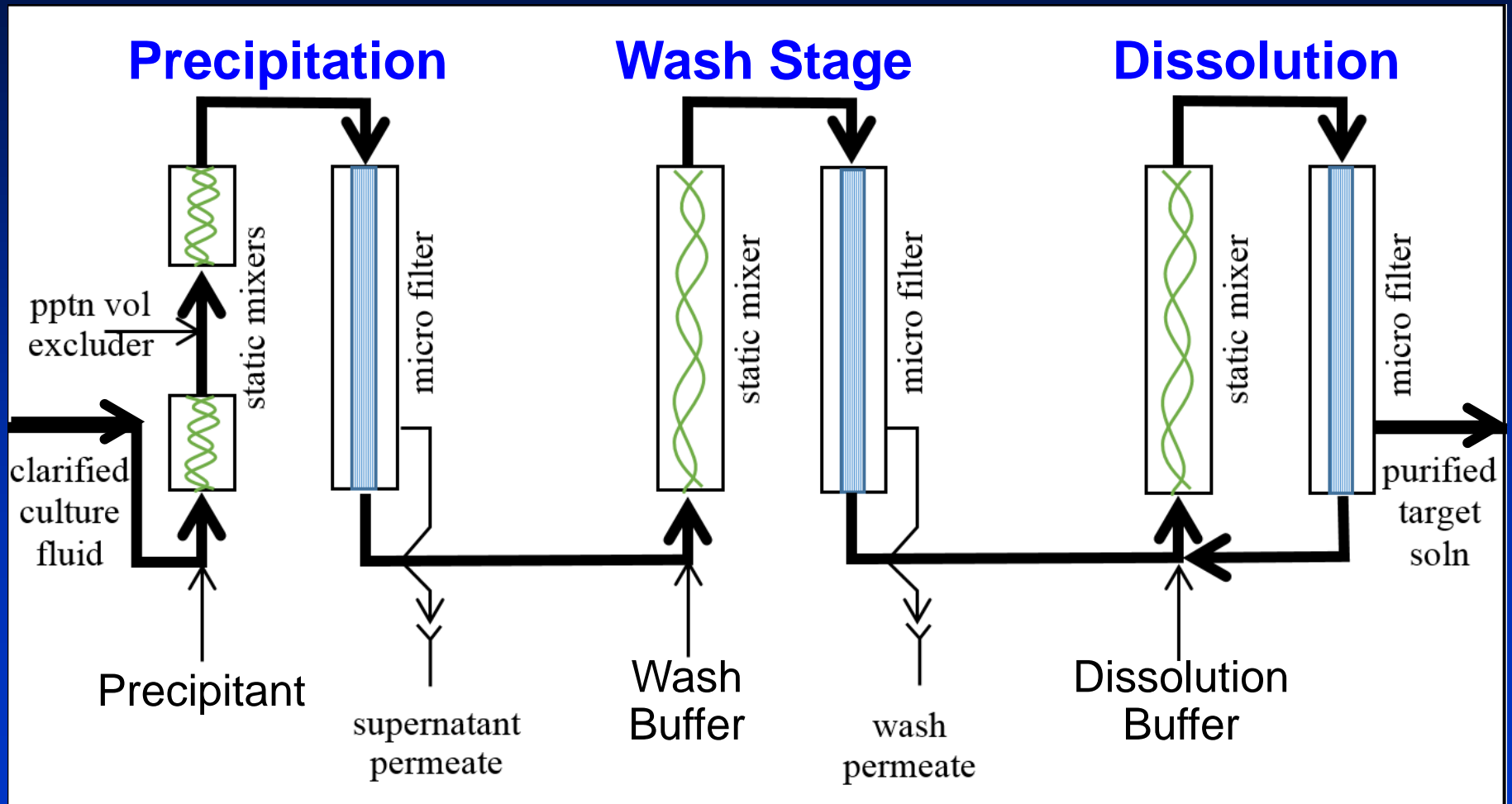
“Membrane-Assisted” Processes

- Membrane systems can be used for “fluid management” in continuous versions of classical downstream processes
 - Chromatography – flowing resin instead of packed column
 - Precipitation – washing and re-dissolution of precipitate to enhance yield and purification
- Countercurrent staging of membrane modules can significantly enhance performance

Continuous Countercurrent Tangential Chromatography (CCTC)

- Chromatographic resin (beads) flows as a slurry through a series of static mixers and hollow fiber membrane modules
 - All operations (binding, washing, elution, stripping) performed directly on the slurry
 - Hollow fiber membrane allows separation and collection of fluid phase
 - Static mixers provide residence time + uniformity
- Countercurrent staging reduces buffer and resin requirements while increasing yield

Continuous Precipitation



Membranes - Summary

- Membrane systems will play a critical role in development of continuous processes
 - Sterility barrier, virus clearance, clarification, purification, formulation
- Challenges:
 - Membranes, modules, and process configurations were all developed for batch operations
 - Efforts to develop continuous membrane processes lag those for chromatographic systems
 - Membrane fouling remains major challenge

