

Thinking Outside the



Adaptive Perfusion Method to Study Drug Release from Emulsions

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Outline

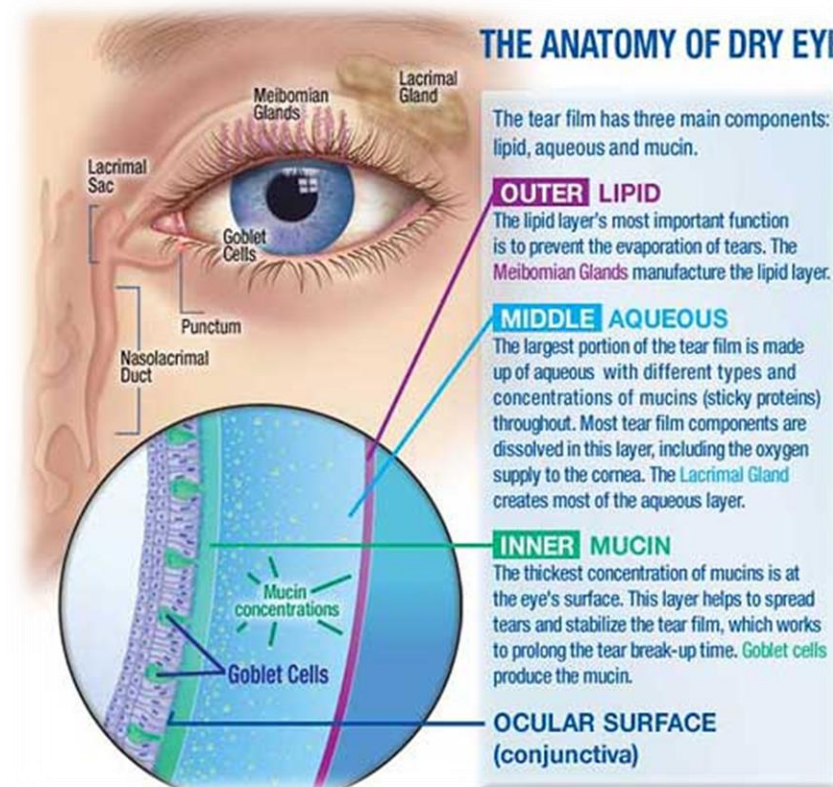
- The Problem: Drug Release from Ophthalmic Emulsions
- Inside vs. Outside the Box
- Examples

The Purpose of Studying Drug Release (IVRT)

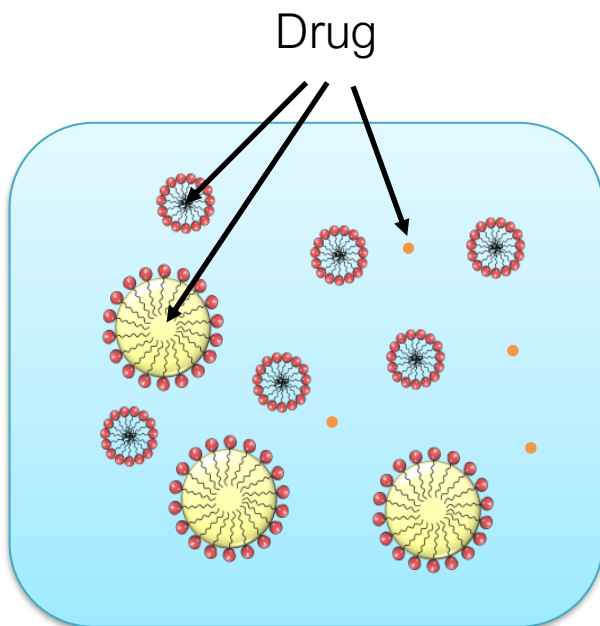
- Estimate the bioavailability (rate and extent) of drug
- Product development (formulation screening, product understanding)
- Quality control (batch-to-batch consistency)
- Bioequivalence (sameness)
- In lieu of in vivo test (IVIVC, Post-approval changes)

IVRT is not the goal, but a means to an end.

The Problem: Drug Release from Ophthalmic Emulsions



<http://www.swmeyercenter.com/tips-to-relieve-dry-eye-symptoms/>

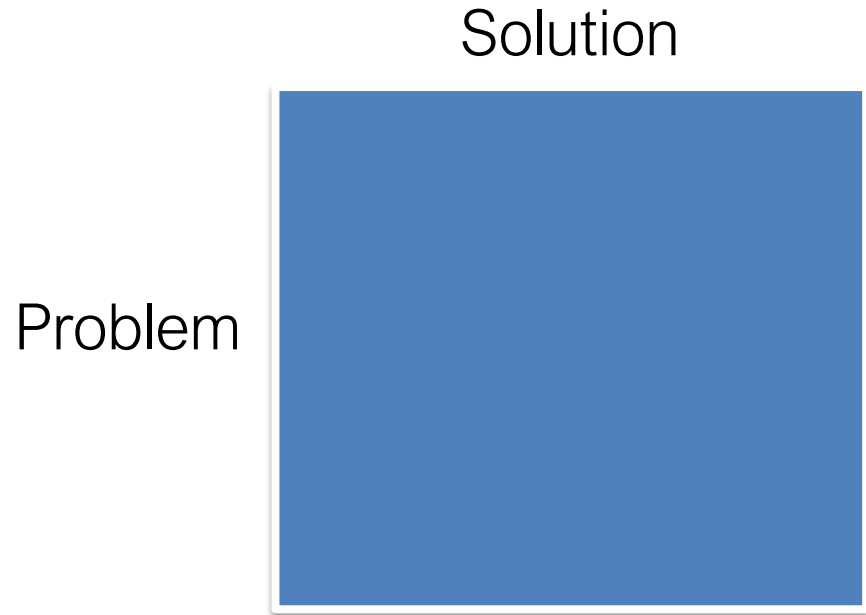


Two fundamental problems:

- Transfer kinetics
- Particle separation



Thinking inside a box:



- How to measure distance?
- How to measure weight?
- How to measure volume?
- How to measure concentration?
- How to perform dissolution for IR tablet?

Most of the time, we can do well by just thinking inside the box (the purpose of training, education)

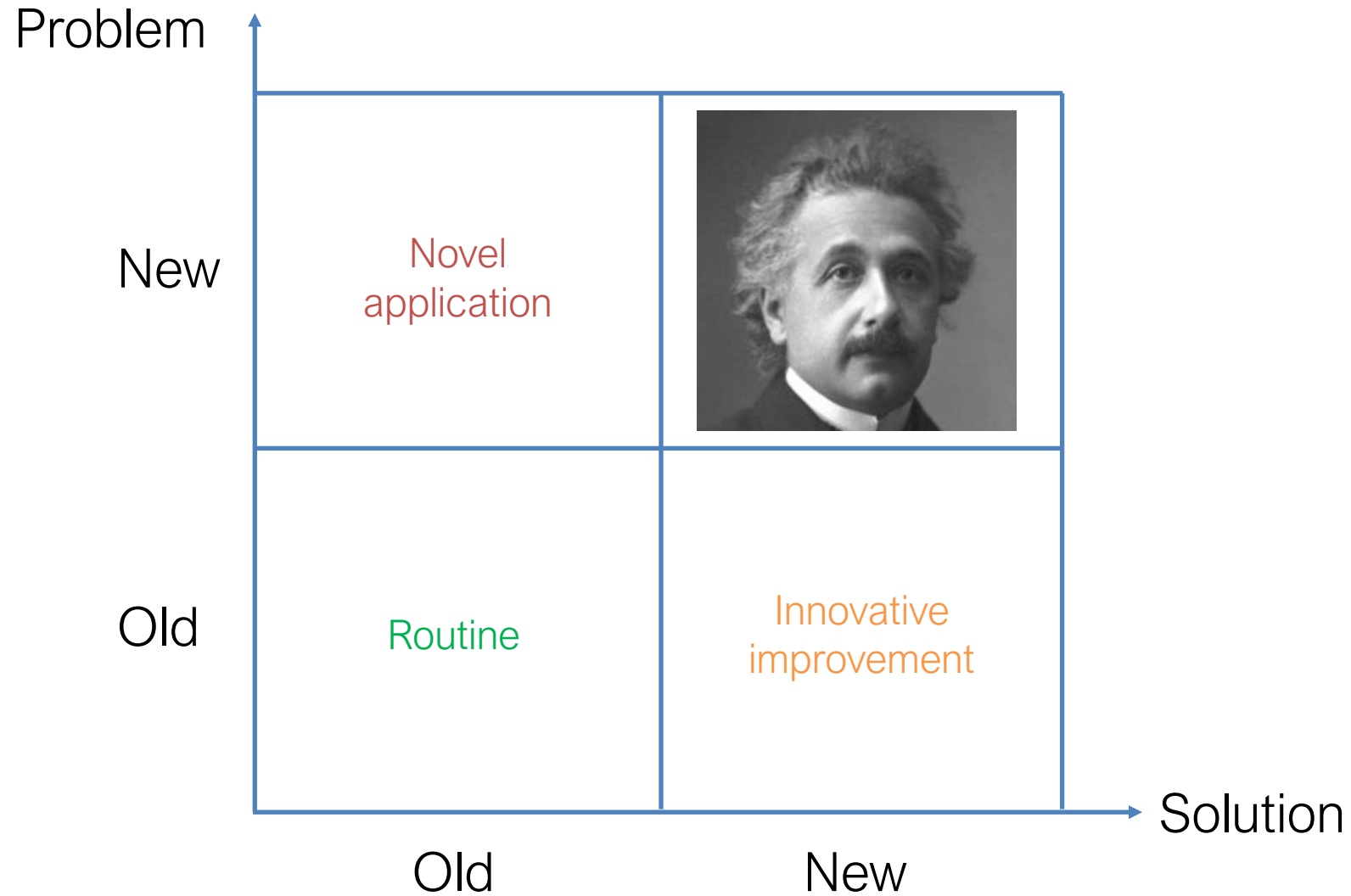
Solution

Problem

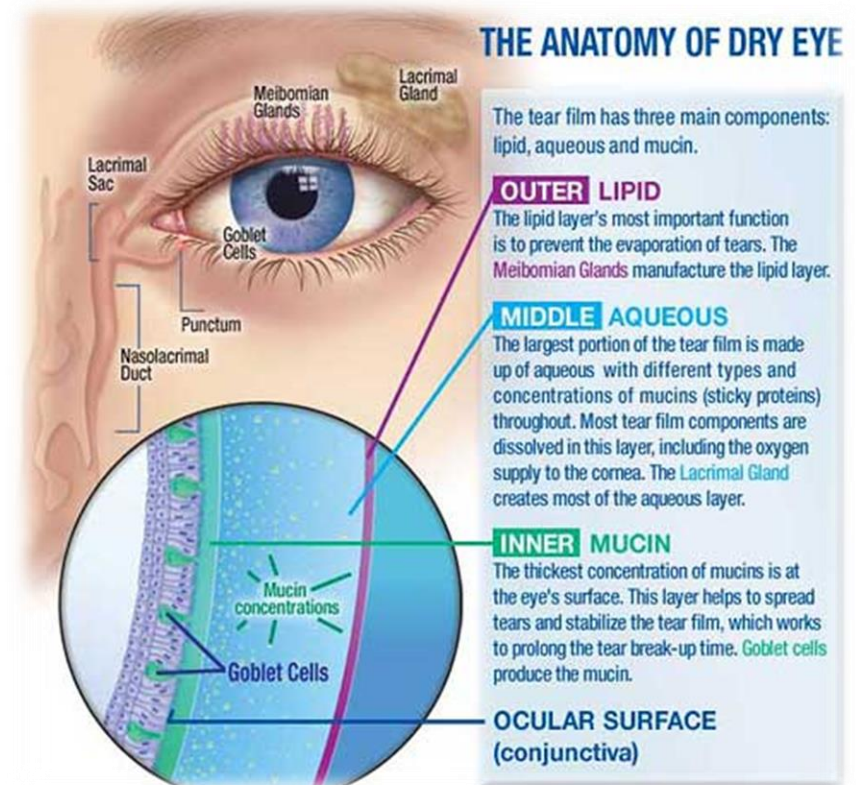


How to measure drug release
from emulsions?

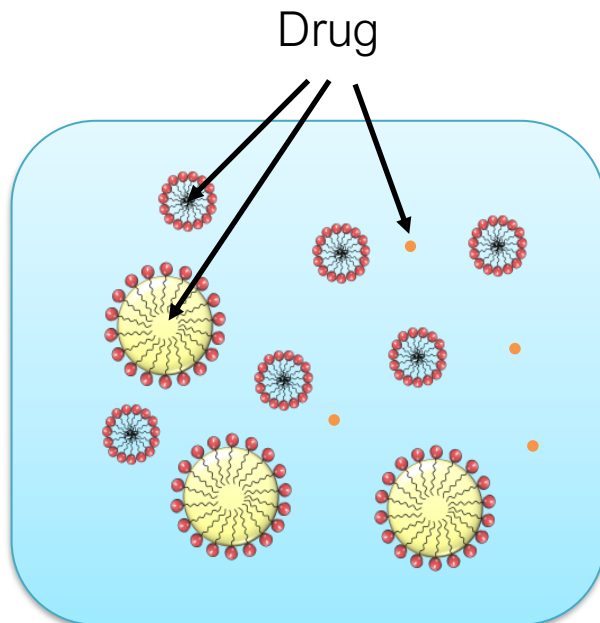
Thinking outside a box: New vs. Old



The Problem: Drug Release from Ophthalmic Emulsions



<http://www.swmeyercenter.com/tips-to-relieve-dry-eye-symptoms/>

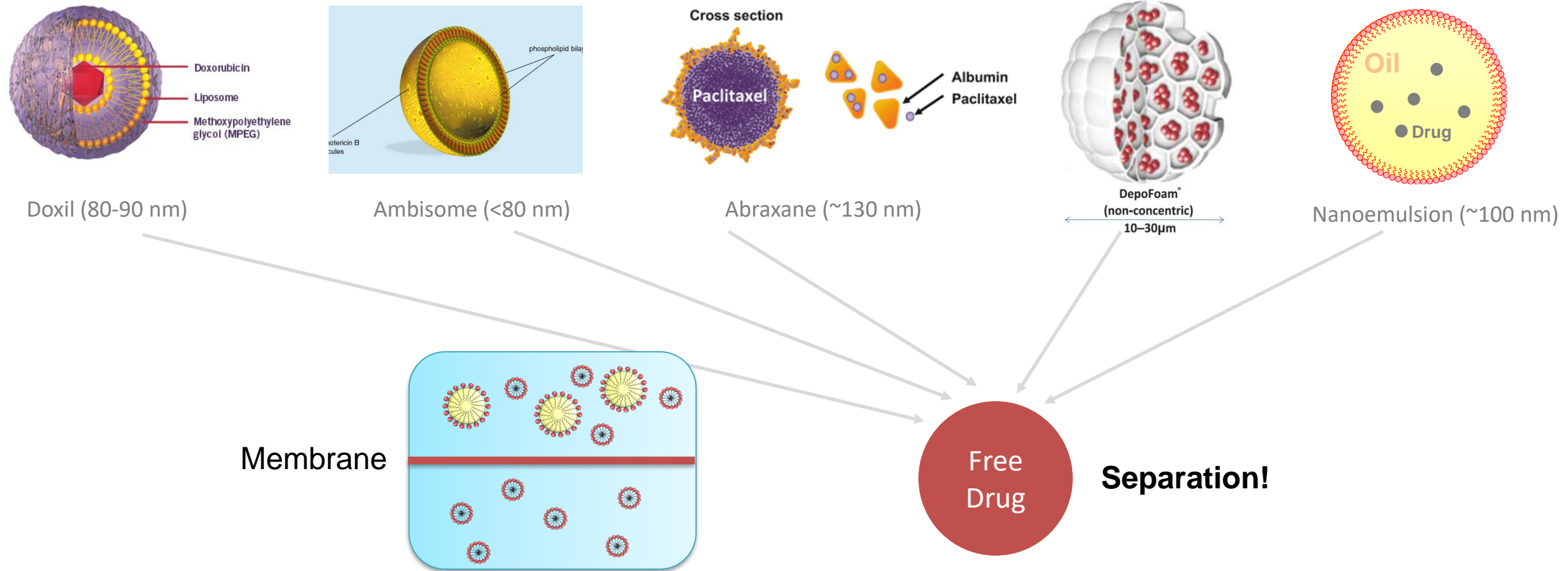


Two fundamental problems:

- Transfer kinetics (old problem, new solution)
- **Particle separation** (new problem, old solution)

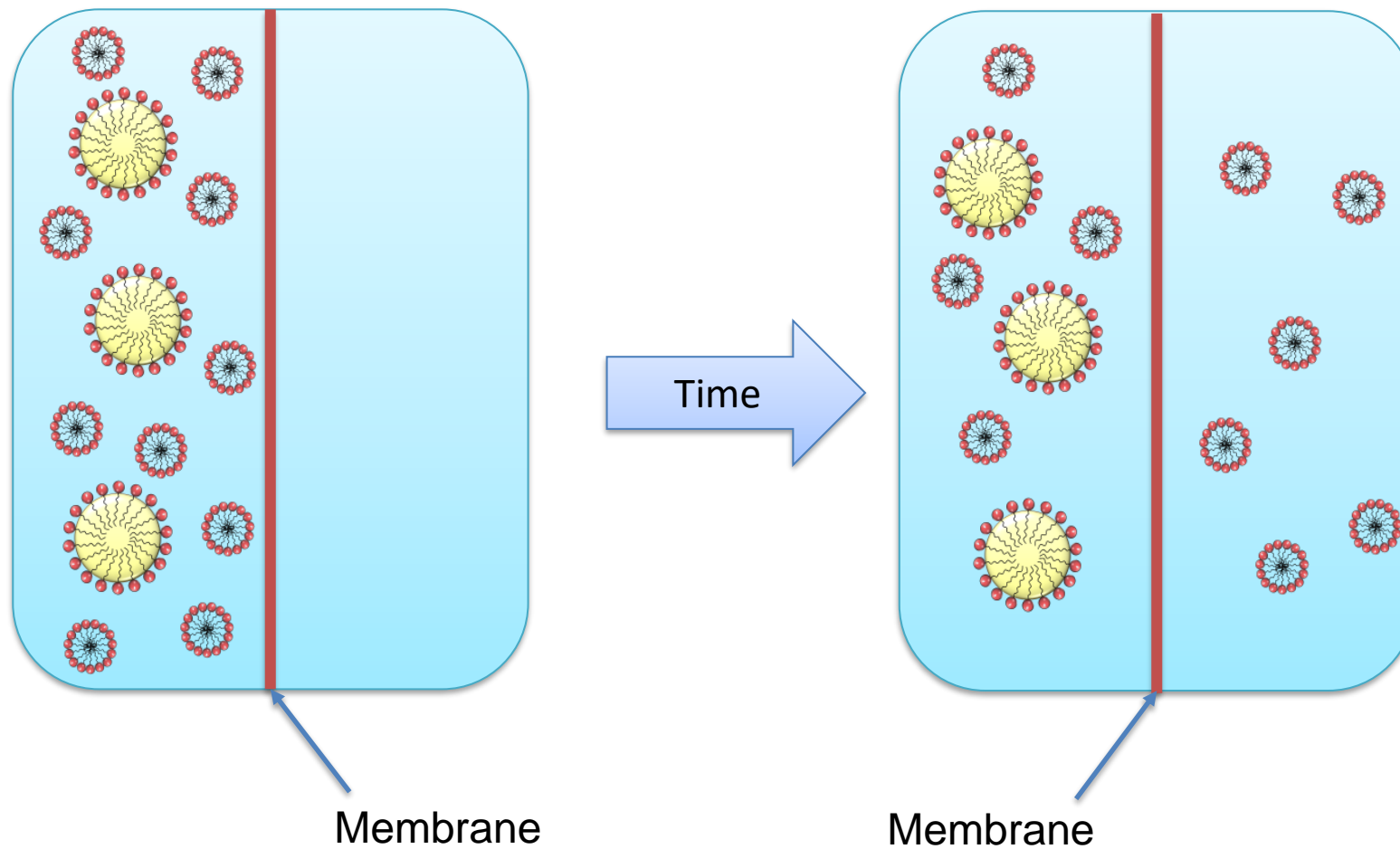
A new separation problem in IVRT...

The problem: particle separation that triggers release



The first step towards analysis drug release from dispersed systems, such as liposomes, suspensions, micelles and emulsions, is the “separation of free drug”. Common approach uses dialysis membrane, which can become rate-limiting and severely impact IVRT method’s discriminatory power.

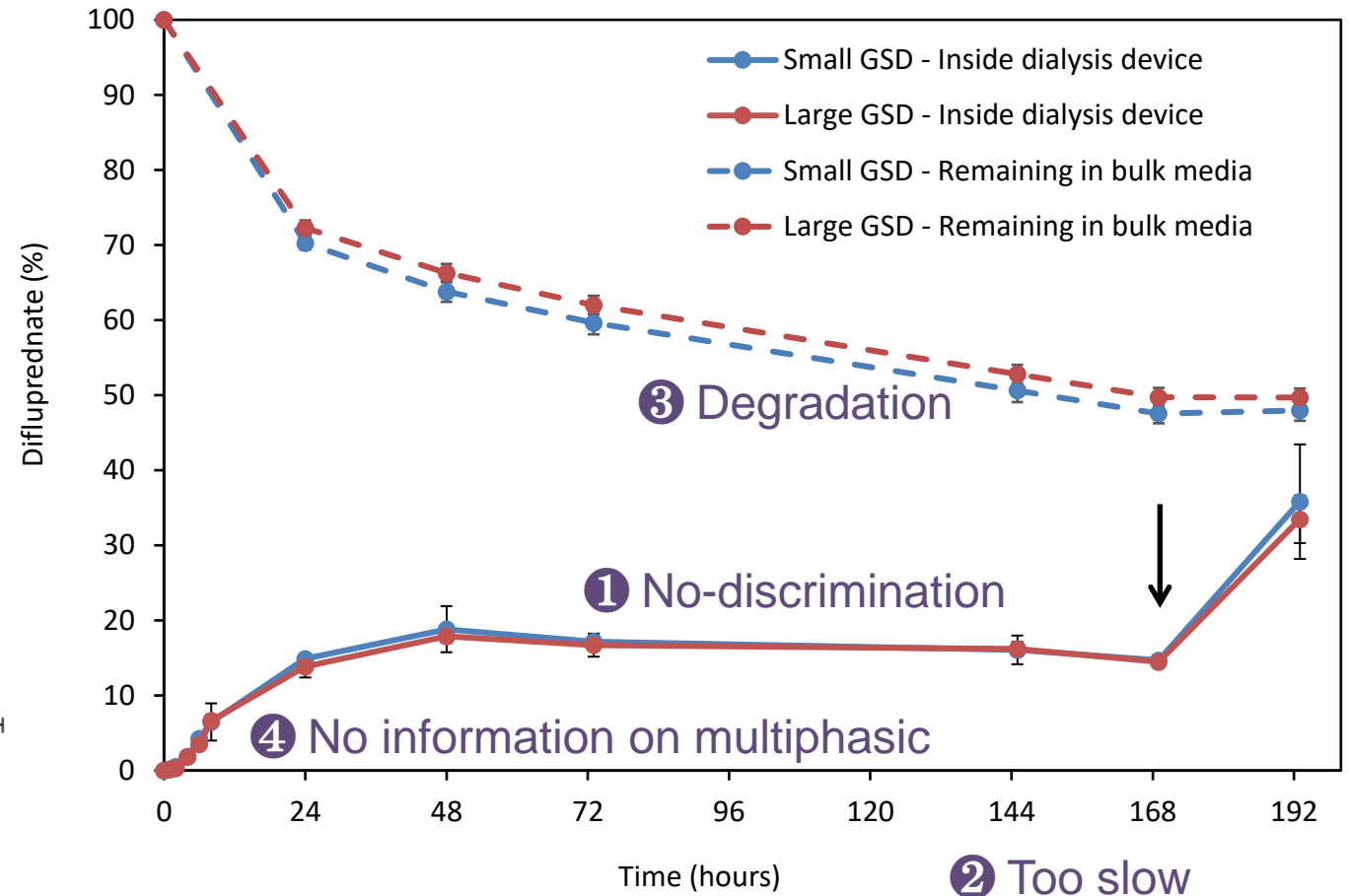
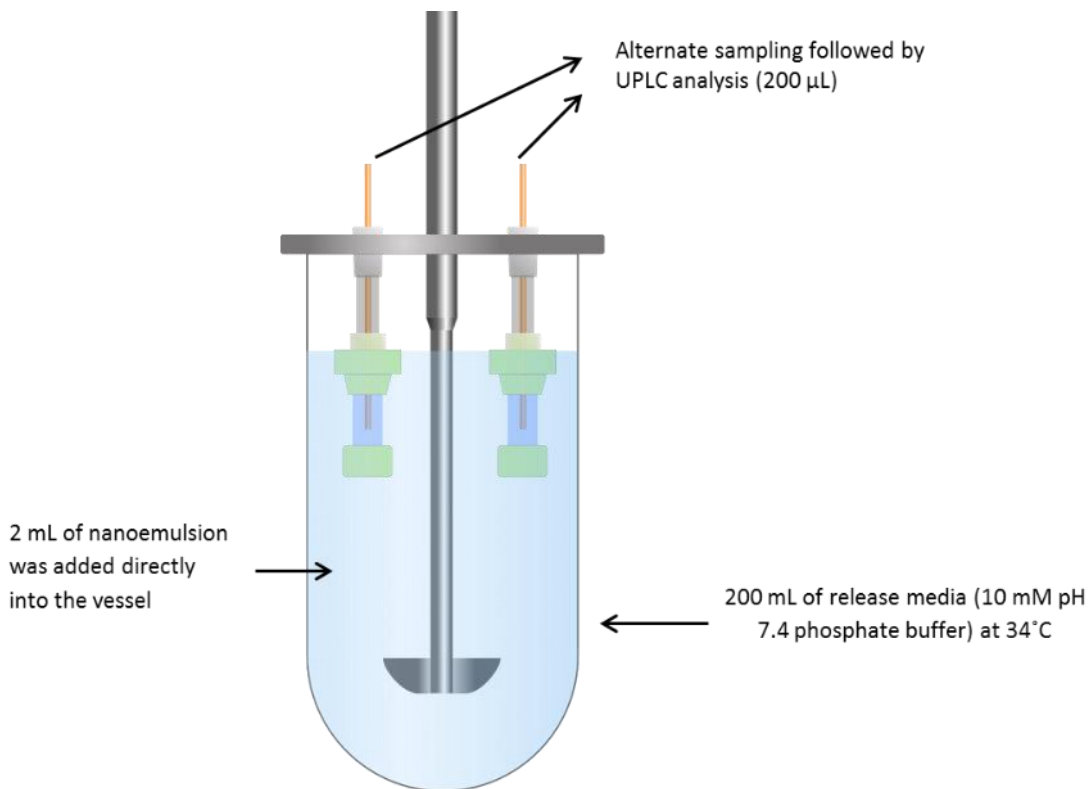
Drug release of nanoparticle: usual way



- Driven by concentration gradient: High to Low
- Membrane transfer may become a rate-limiting step

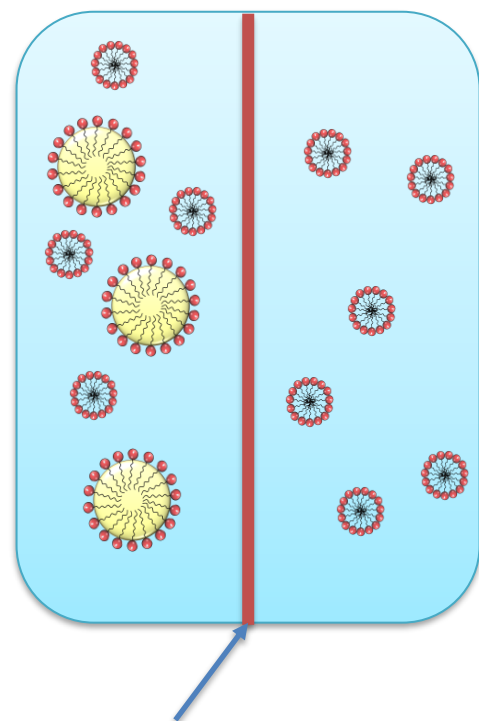
IVRT by (Reverse) Dialysis: A Typical Example

USP 2 with Reverse Dialysis

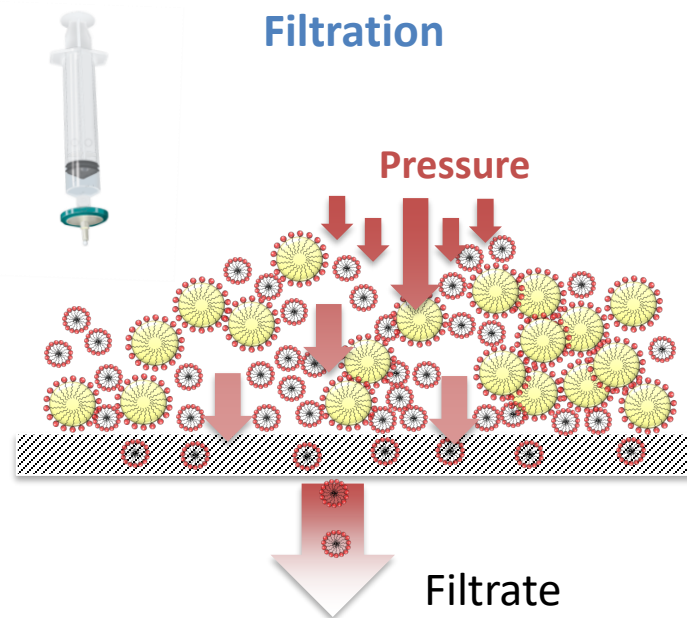


How can we solve it?

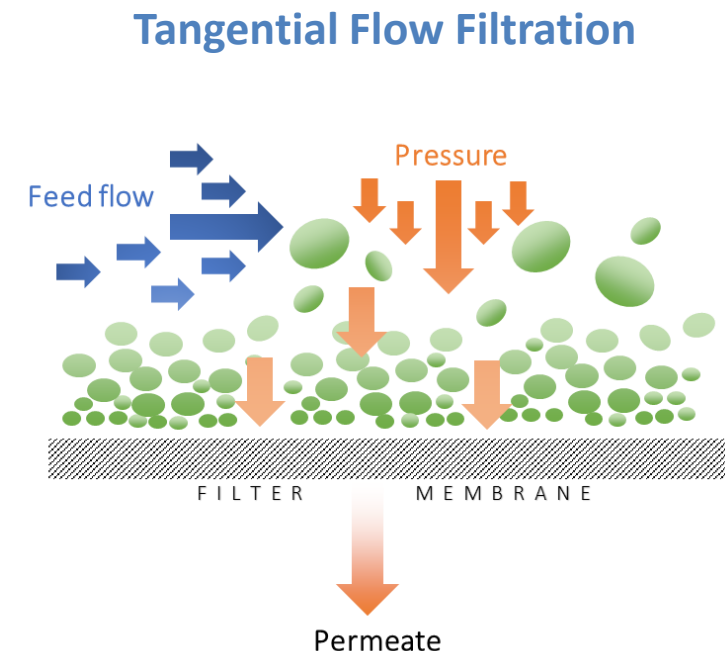
Filtration, Instead of Diffusion



Membrane



- Pressure driven
- Controllable flow by filtration
- Separation based on membrane size



- Tangential flow, thus avoiding build up at the membrane surface (swept away by flow)

TFF: old solution to old problem

- TFF is not a new technique. Widely used since 1960s in various industrial processes, e.g., de-salting, solvent-exchange, concentration.



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Complex step
proc

3 Then the solution is purified. The process, known as tangential flow filtration, is like panning for gold but removes various particles, stray lipids and the alcohol. At the end emerges the final **lipid-encased mRNA** product.

By [Jar](#)
[Dylan Monarby](#)
March 3, 2021 8:00 am ET

Different Focus in Adaptive Perfusion

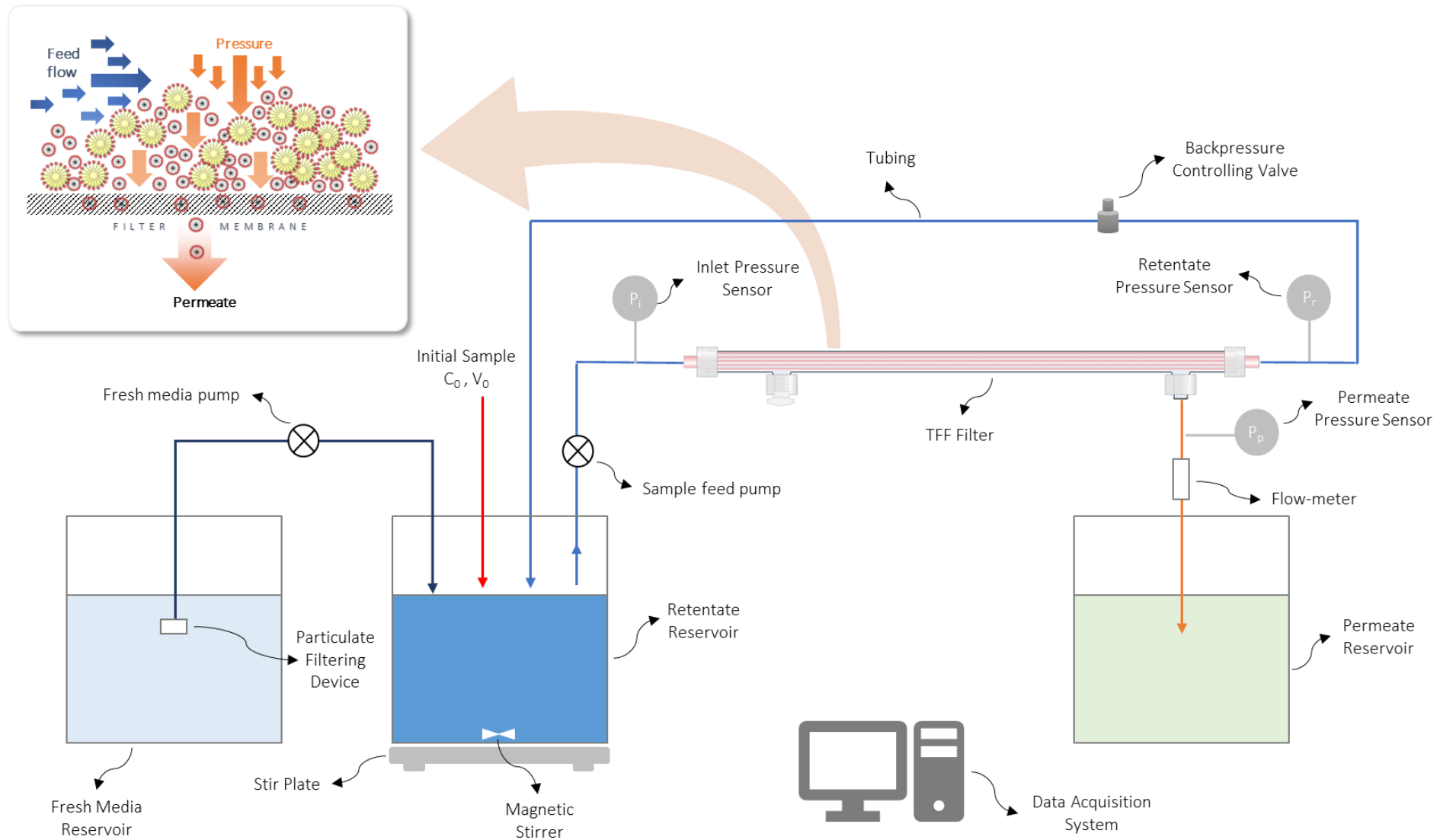
Common use:

- Only focus on retentate OR permeate
- Only focus on the extent (% recovery, purity)

In Adaptive Perfusion, goal is to obtain “Drug Release”:

- Retentate(drug remain) and permeate(drug remove)
- Rate AND Extent (how fast AND how much)

Schematic Diagram of Adaptive Perfusion



Where it begins...



LabVIEW (DISPLAY)

FLOW METER (DISPLAY)

PRESSURE MONITOR

FRESH FEED PUMP

FRESH MEDIA BOTTLE

INLET

HOLLOW FIBER

RETENTATE

BACKPRESSURE GEAR

FLOW METER (SENSOR)

PERMEATE

SAMPLE FEED PUMP

SAMPLE/ RETENTATE BOTTLE

PERMEATE BOTTLE

STIRRER

STOPWATCH

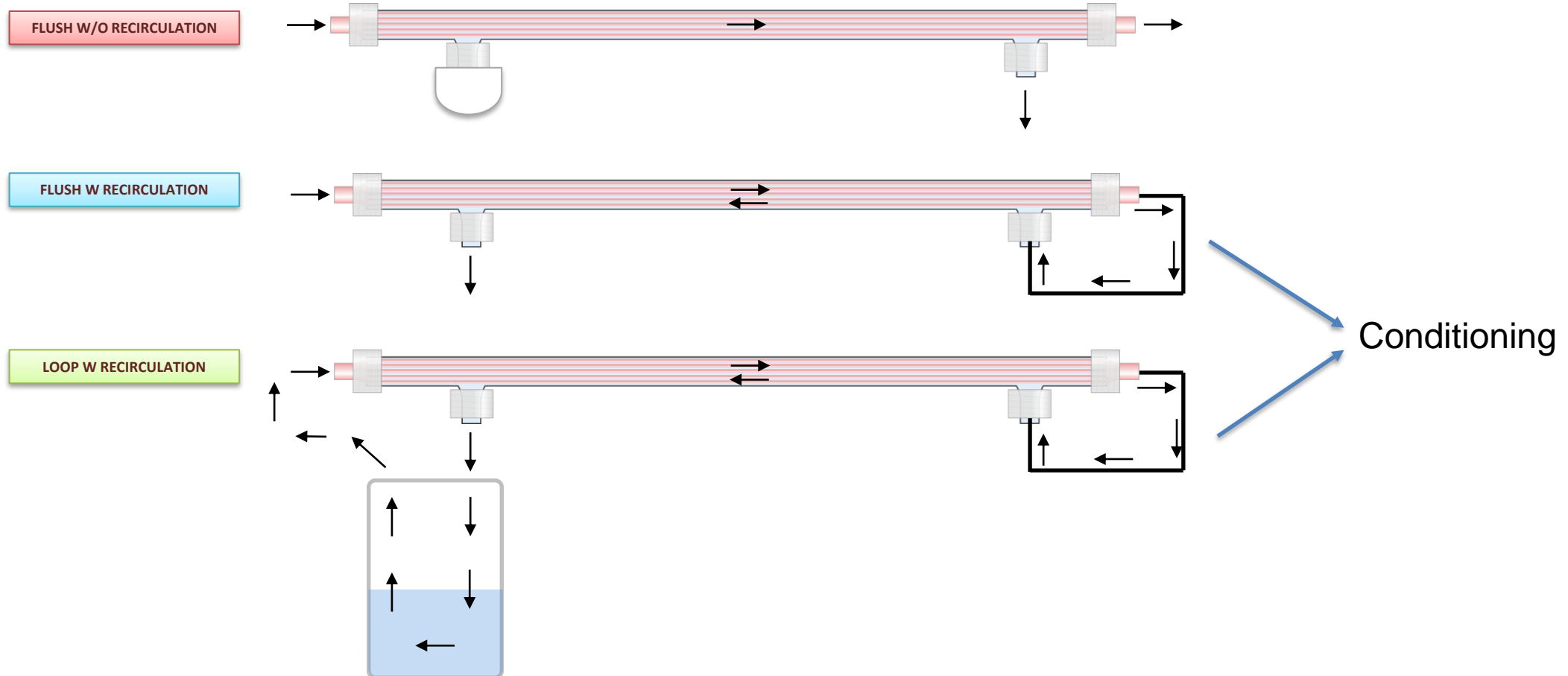
LAB 1021 LAB 102

Key Challenges (Solved)

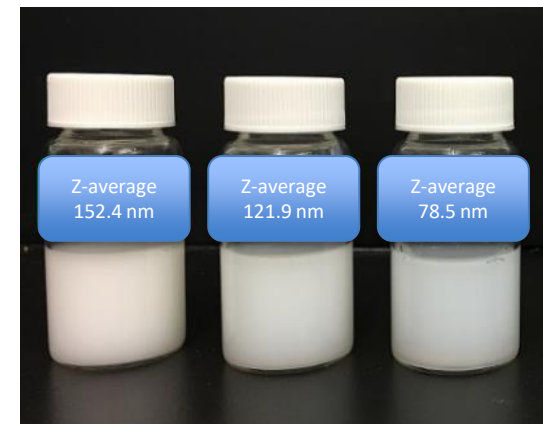
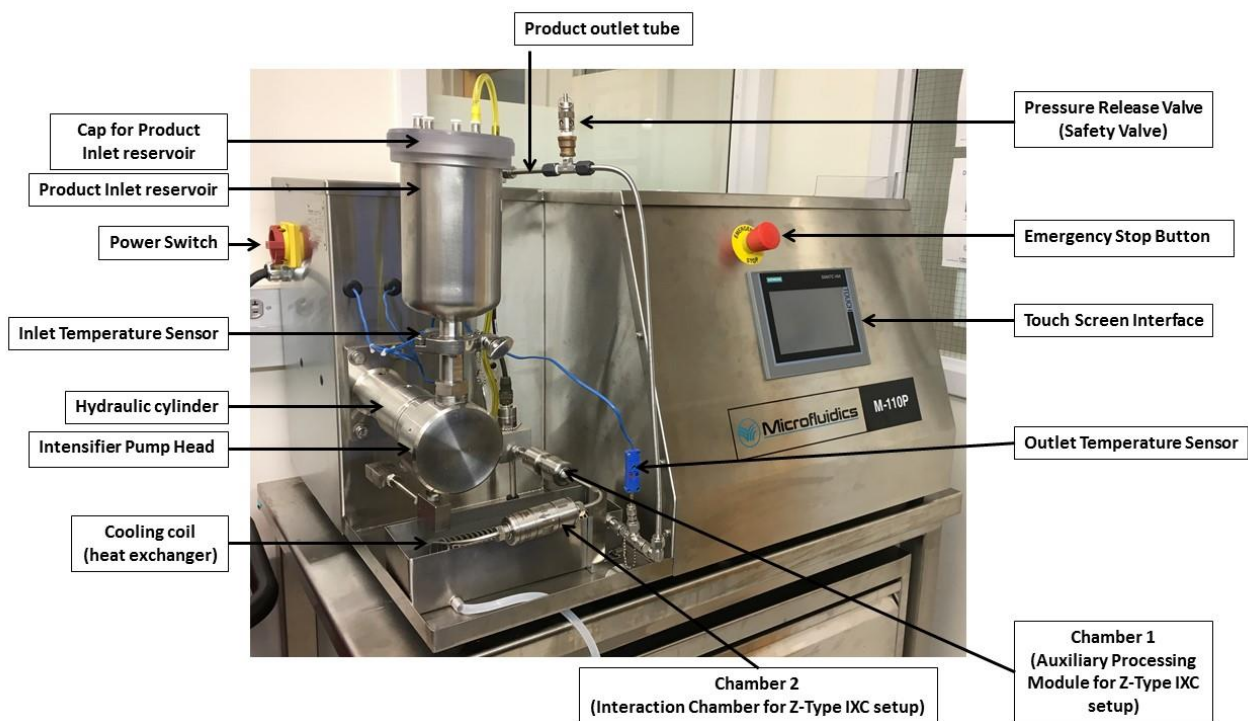
- **Reproducibility:**
 - Fiber to fiber (critical for switching fibers)
 - Run to run
- **Fouling:**
 - Performance degradation, lead to low flux -> can't see the difference between different GSD formulation
- **Discriminatory capability**

Solution: Membrane Conditioning

Both Medium and Configuration are important!!

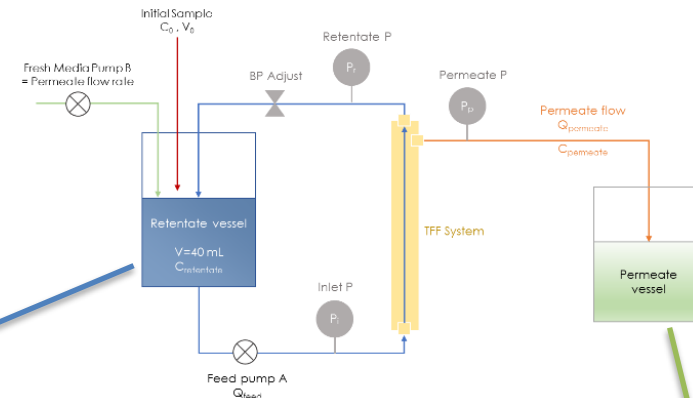


In-house Formulation with Intentionally Varied GSD



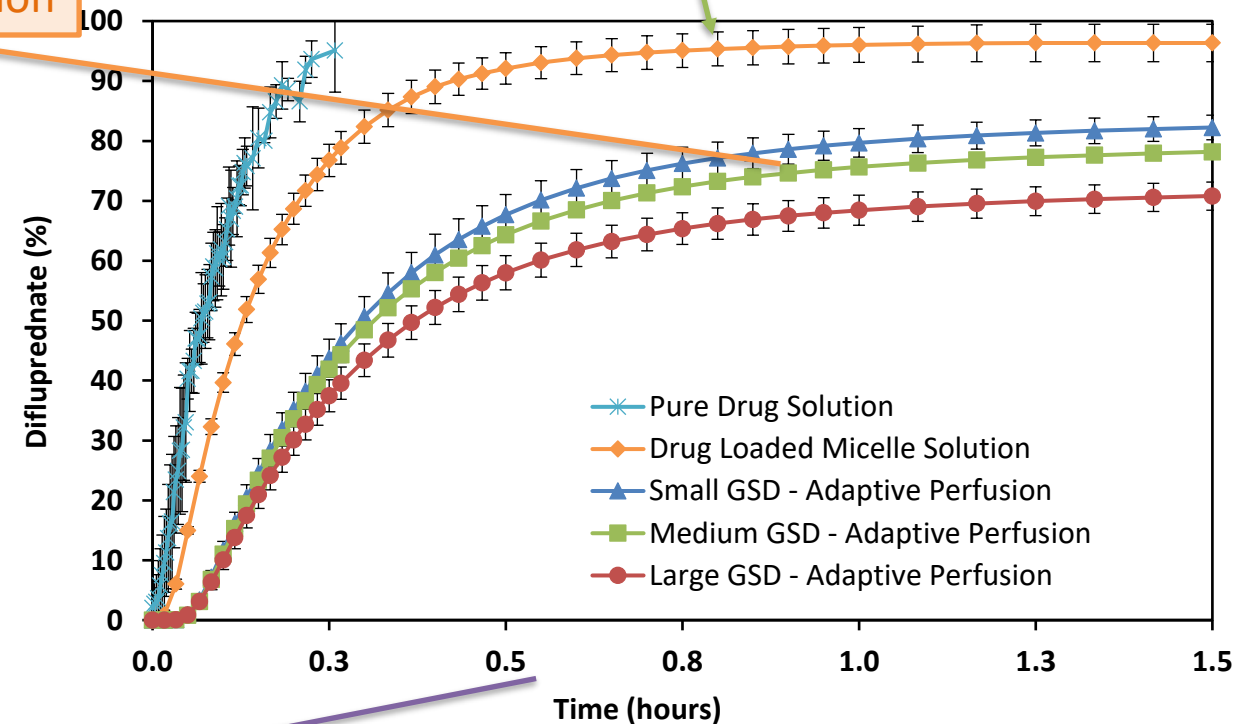
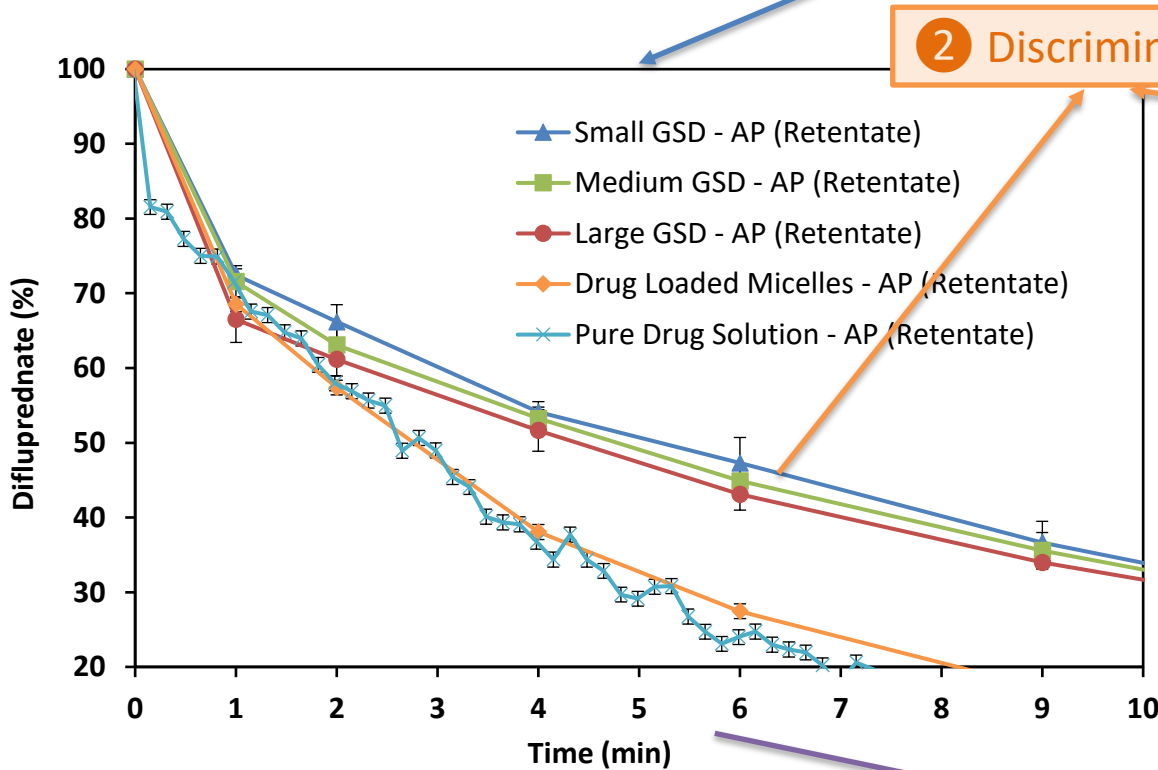
Sample	Z-Average (d.nm)	PdI
Large GSD	152.4 ± 1.3	0.181 ± 0.014
Medium GSD	121.9 ± 0.9	0.203 ± 0.010
Small GSD	78.5 ± 0.6	0.206 ± 0.008

Results



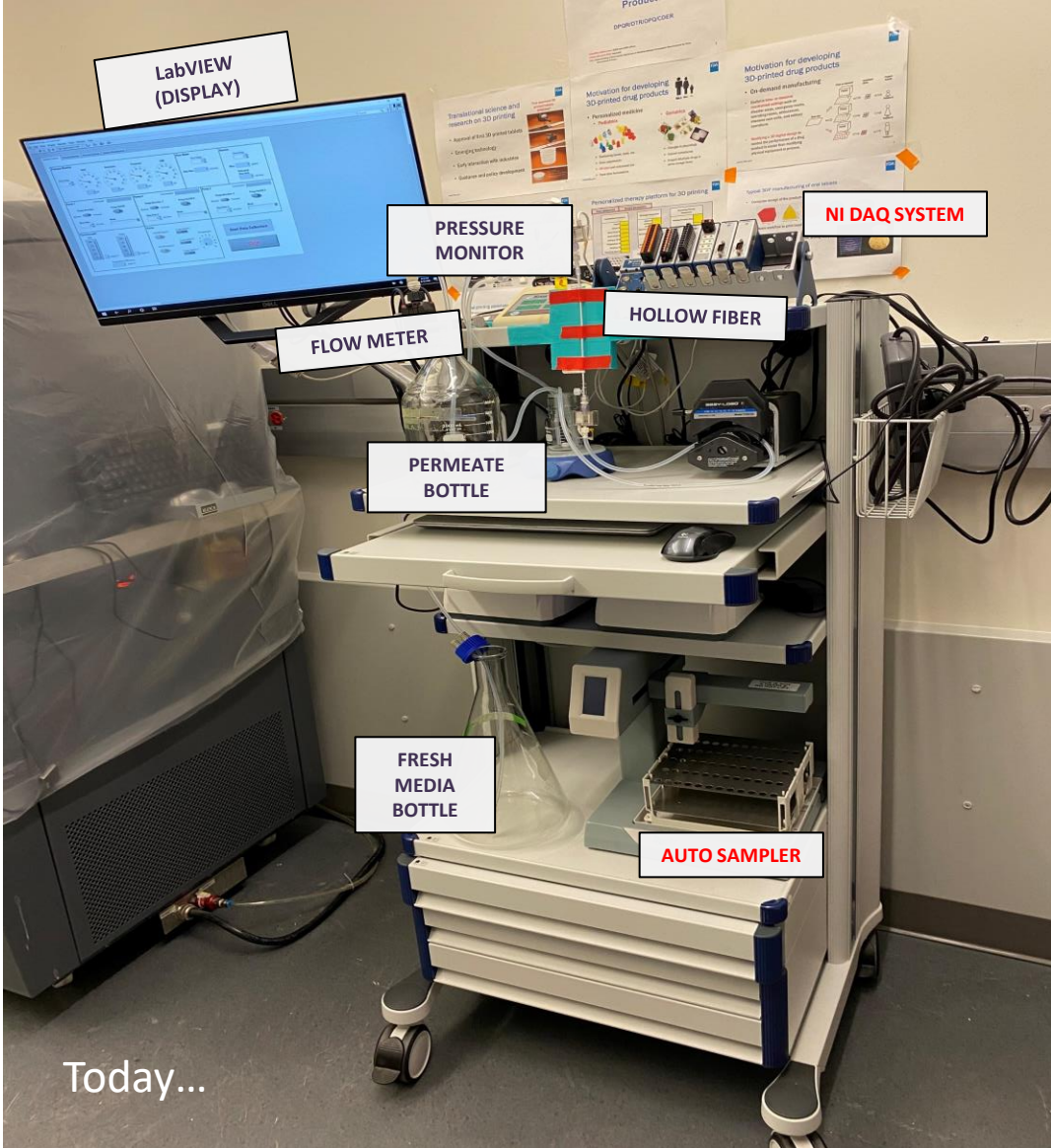
Retentate Concentration Profile (n=3)

Permeate Concentration Profile (n=3)



1 Fast

Future: A Turnkey Solution



Today...

Custom Designed Control Interface

System Startup	Pressure Reading Time Delay: <input type="text" value="0"/> Inlet: Retentate: Permeate: TMP:	Flow Meter Reading Time Delay: <input type="text" value="0"/> Flow Rate: <input type="text" value="0"/> mL/min	Backpressure Setting 												
Experimental															
Pre-Condition	Valve Control Valve 1: <input type="text" value="0"/> 4-ways switch Valve 2: <input type="text" value="0"/> 3-ways switch Valve 3: <input type="text" value="0"/> 3-ways switch Valve 4: <input type="text" value="0"/> 2-ways switch Valve 5: <input type="text" value="0"/> 3-ways switch Valve 6: <input type="text" value="0"/> 3-ways switch														
Run-time															
Re-conditioning	Balance Control Balance 1: <input type="button" value="Tear"/> <input type="button" value="Zero"/> 0.000 g Balance 2: <input type="button" value="Tear"/> <input type="button" value="Zero"/> 0.000 g	Pump Control and Calibration <table border="0"> <tr> <td style="text-align: center;">Pump 1</td> <td style="text-align: center;">Pump 2</td> </tr> <tr> <td>Initialization: <input type="button" value="OK"/></td> <td>Initialization: <input type="button" value="OK"/></td> </tr> <tr> <td>Direction: <input type="button" value="↺"/> <input type="button" value="↻"/></td> <td>Direction: <input type="button" value="↺"/> <input type="button" value="↻"/></td> </tr> <tr> <td>Flow rate: <input type="text" value="100"/> mL/min</td> <td>Flow rate: <input type="text" value="5.0"/> mL/min</td> </tr> <tr> <td>Tubing size: <input type="text" value="16"/></td> <td>Tubing size: <input type="text" value="16"/></td> </tr> <tr> <td>Calibration: <input type="button" value="Start Cal."/></td> <td>Calibration: <input type="button" value="Start Cal."/></td> </tr> </table>		Pump 1	Pump 2	Initialization: <input type="button" value="OK"/>	Initialization: <input type="button" value="OK"/>	Direction: <input type="button" value="↺"/> <input type="button" value="↻"/>	Direction: <input type="button" value="↺"/> <input type="button" value="↻"/>	Flow rate: <input type="text" value="100"/> mL/min	Flow rate: <input type="text" value="5.0"/> mL/min	Tubing size: <input type="text" value="16"/>	Tubing size: <input type="text" value="16"/>	Calibration: <input type="button" value="Start Cal."/>	Calibration: <input type="button" value="Start Cal."/>
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Calibration: <input type="button" value="Start Cal."/>	Calibration: <input type="button" value="Start Cal."/>														
Process Monitor															

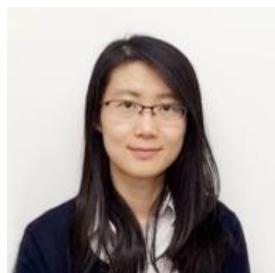
Closing Thoughts...



Thinking critically

- Old problem, new solutions;
- New problem, old solutions;
- It's all about perspectives (expand your boxes).

Acknowledgement



Yixuan Dong



Deval Patel



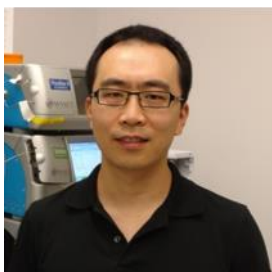
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