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Improved Continuous Microfluidic Synthesis of Energetic Compounds

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Chemical Synthesis Methods

Batch Operation	Continuous Operation	Microfluidic Operation
High flexibility; preferred for multi-product/purpose operation, useful for a large range of reaction scale	Low flexibility; designed for a single process, not practical for development-scale production	Mid flexibility; lab and pilot scale reactor modifications are simple, reactors cannot handle all types of reaction media, useful for development to pilot plant scale
Low capital cost	High capital cost	Low capital cost
High consequence hazard; Large volumes of energetic materials being processed	High consequence hazard; large volumes of energetic materials being processed	**Low consequence hazard; µL to mL volumes of energetic materials being processed**
Reasonable scale-up from lab scale	Reasonable scale-up from lab scale – involves engineering/modeling	**Simple scale-up from lab scale**
Not suitable for unattended operation → labor intensive → high operating cost	Simple conversion to unattended operations → low operating cost	**Simple conversion to unattended operations → low operating cost**

What Types of Reactions are Good Candidates for Flow Synthesis?

Reaction Characteristics	Possible Benefit of Flow Synthesis
Pressures exceed reactor capability? Temperatures exceed reactor capability? Chemistry not compatible with reactor? Equilibrium reactions?	Likely no benefit and/or not possible
Solid precipitates? Very slow kinetics? Solid reactants or catalysts? Gaseous reactants? Homogeneous catalysts?	Possible benefits, significant technical challenges
Gas evolution in reaction? Reaction benefits from high pressure? Unstable intermediates? Fast kinetics? Highly toxic reactants or byproducts? Reactions requires or benefits from low temperature (< -10 °C)? Rapid mixing required? Highly exothermic? Over-reaction possible? Requires precise stoichiometric control?	Likely to benefit

Calabrese, G. S.; Pissavini, S. *AIChE Journal,* **2011**, *57(4)*, 828-834.

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Advantages Of Microfluidic Reactors

- Efficient heat and mass transfer
  - Highly exothermic reactions are common in energetic synthesis (nitration, oxidation, acid neutralizations, etc.). If exotherms are not properly managed, run-away reactions can occur.
  - Allow for previously “forbidden” reactions because of high level of control (high temp/pressure, concentrated products, etc.)
  - Provides non-physical mixing of reactants
- Low reactive volume (microliters to milliliters of solution)
  - Low consequence hazard
- Easy scale-up, high versatility
  - Very high throughput at lab scale (20 conditions/day)
  - Scale is increased by lengthening reactor path or including parallel reactors
  - Modular equipment for easy customization
- Low labor costs and capital depreciation
- Continuous process feedback, consistency in production
- Multiple suppliers of off-the-shelf continuous flow reactors available*
  - *Chemtrix full work stations shown as examples

Chemtrix Lab-scale Work Station

Chemtrix Kilo-scale Work Station

https://www.chemtrix.com

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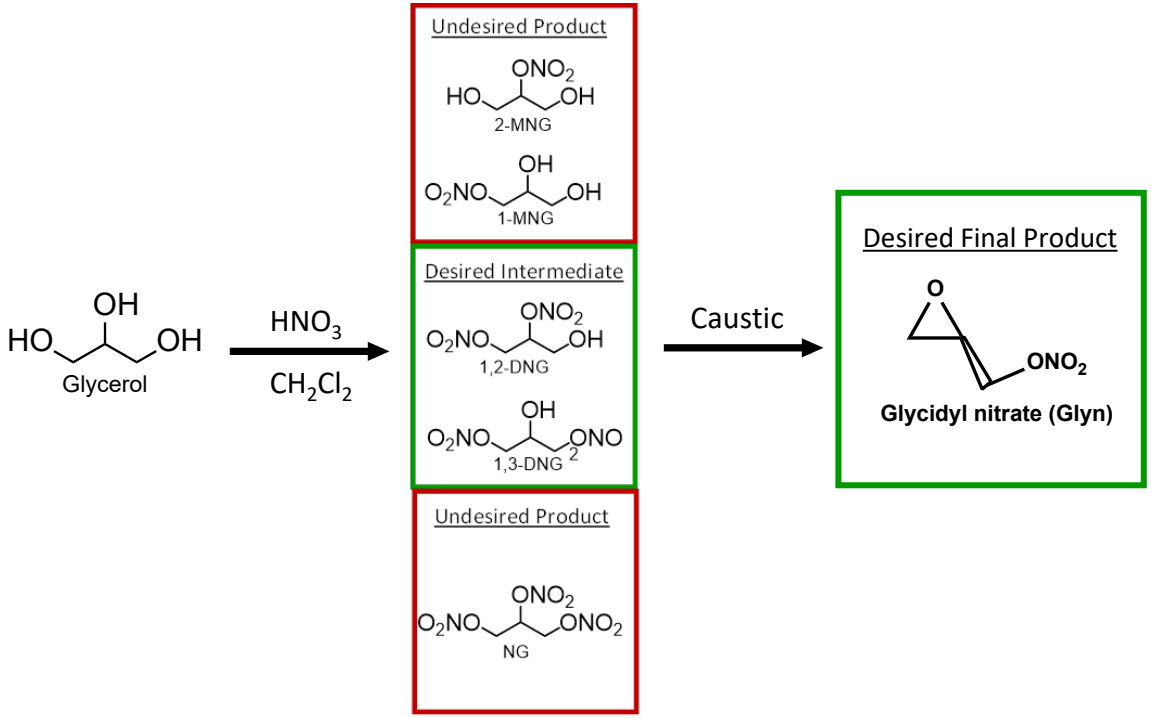
Test Case – Synthesis of Glycidyl Nitrate (GLYN)

- GLYN is the precursor for poly(glycidyl nitrate) PGN, an energetic binder of significant interest for insensitive munitions

- Highsmith method: conversion of glycerol to glycidyl nitrate (theoretically least expensive synthesis route)

- Challenges:
  - Two step process, first low pH nitration then high pH caustic ring closure (technical and compatibility challenges)
  - Highly exothermic process (including glycerol nitration and acid neutralization)
  - Targeting intermediate nitrated product (requires precise controls to achieve reasonable yield)
    - Hazardous biproduct (nitroglycerin) requires additional care to balance to both maximize target yield while minimizing hazards



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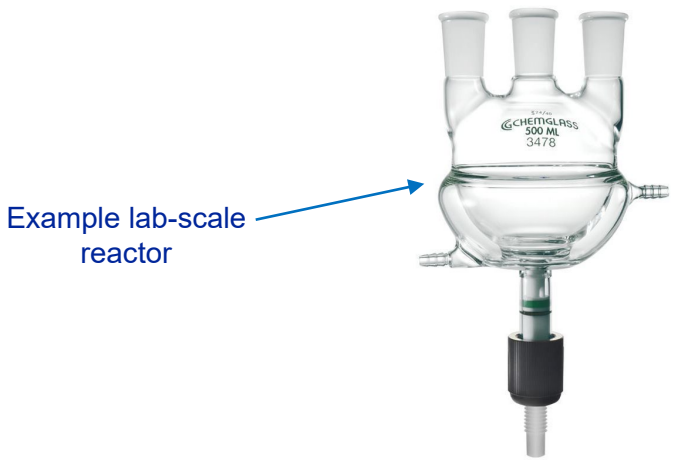
GLYN Synthesis Methods

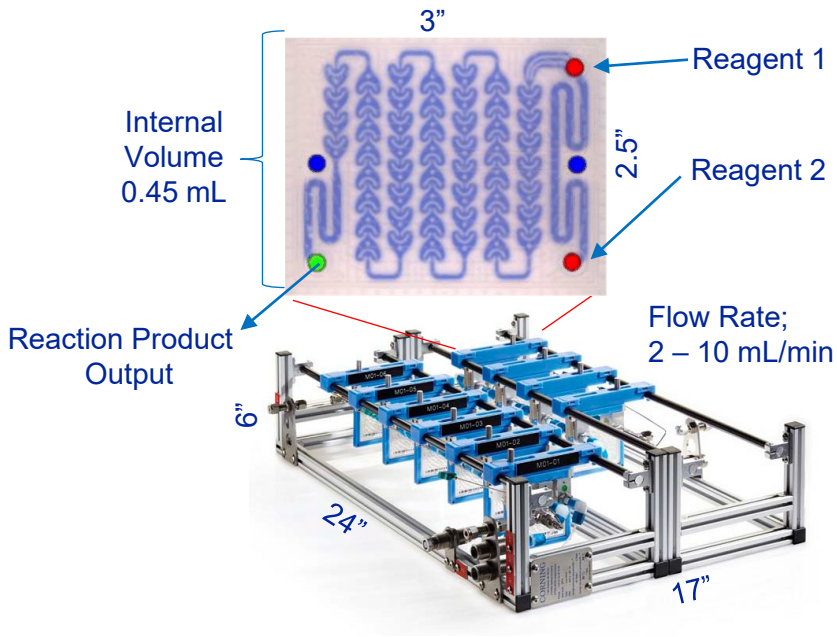
Legacy GLYN Synthesis Process

Attended batch reactions conducted by R&D scientists using large scale laboratory glassware (5 & 22L Reactor).



New GLYN Synthesis Process

Remote microfluidic continuous flow reactor. Example of Dow Corning AFR shown below.



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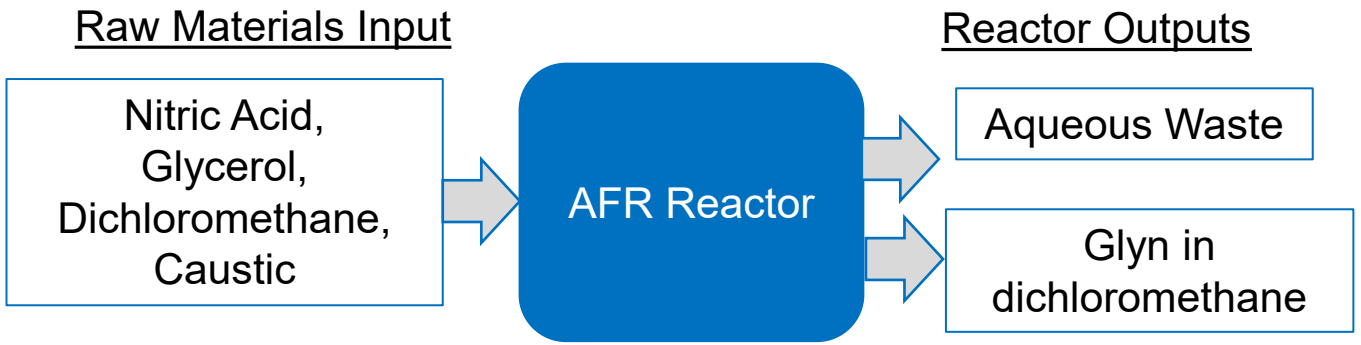
Continuous Synthesis of GLYN

High Level Process Overview - Target



Safety Advantages

- Small reactive volume (<20mL)
- Unattended process
- Greatly improved heat transfer compared to batch reactions
- No mechanical stirring
- Direct isolation of reaction product into appropriate storage vessel/locker

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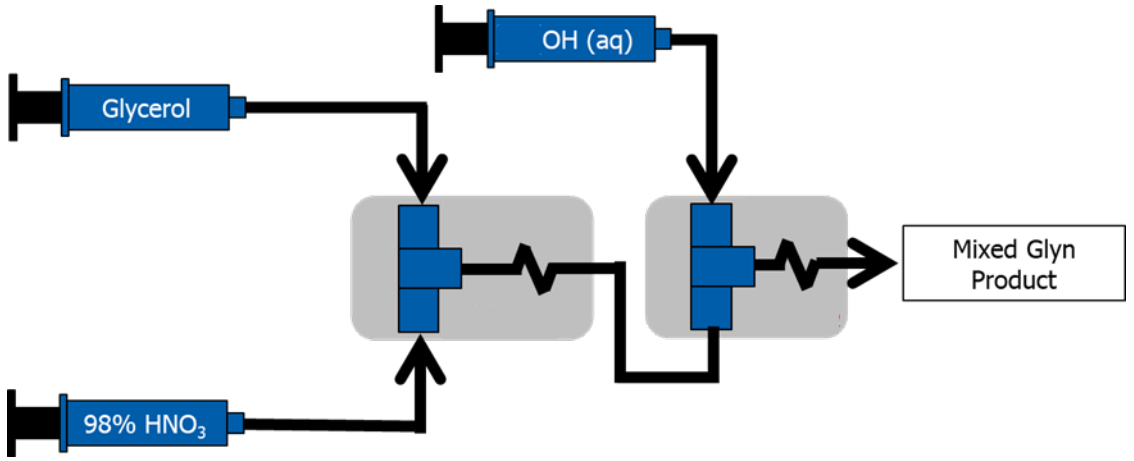
Simple Prototype Reactor Design

- Two-step microfluidic synthesis of Glyn demonstrated at small scale using reactor built in-house
  - Reactor operated at low-flow
  - Microfluidic-sized flow channels
  - Patented Process
- Best conditions:
  - Conversion rate similar to those seen in batch reactions



- Takeaways:
  - Reactor composed of all PTFE/PFA wetted parts could withstand both nitration and caustic conditions
  - Long nitration retention times and high acid concentrations are required to optimize DNG production
  - Neutralization of acid during caustic ring closure prone to precipitating salts – possible safety hazard
  - Batch extraction of Glyn using dichloromethane (DCM) required in work-up after sample collection

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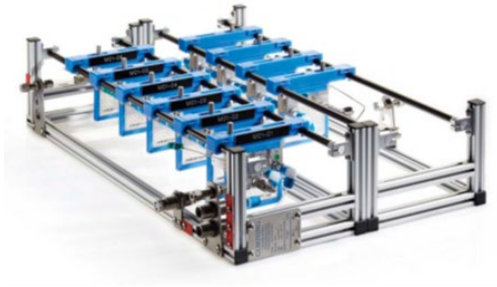
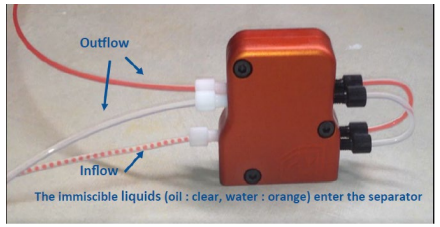
Next Steps – Improving Process Design

- Simple T-joint/tubing reactor → DOW-Corning AFR reactor
  - Advective mixers in plates decrease required residence time
  - Fully jacketed with high coolant flow for more efficient heat transfer
  - Modular design allows for quick and easy changes to reactor configuration
  - Microfluidic flow channels
  - Scaled-up versions available



- Addition of liquid-liquid in-line separators
  - In-line extraction of products into dichloromethane removes batch work-up step after product collection
  - Small internal volume
  - Scaled-up versions available



- Syringe pumps → continuous operation peristaltic pumps
  - Can be remotely operated and monitored, auto shut-off at set pressure

- Simple temperature bath → High-flow, fully enclosed heat exchange module with precise temperature control

- Addition of in-line flow sensors
  - Chemically resistant wetted parts, uses non-invasive microthermal sensing

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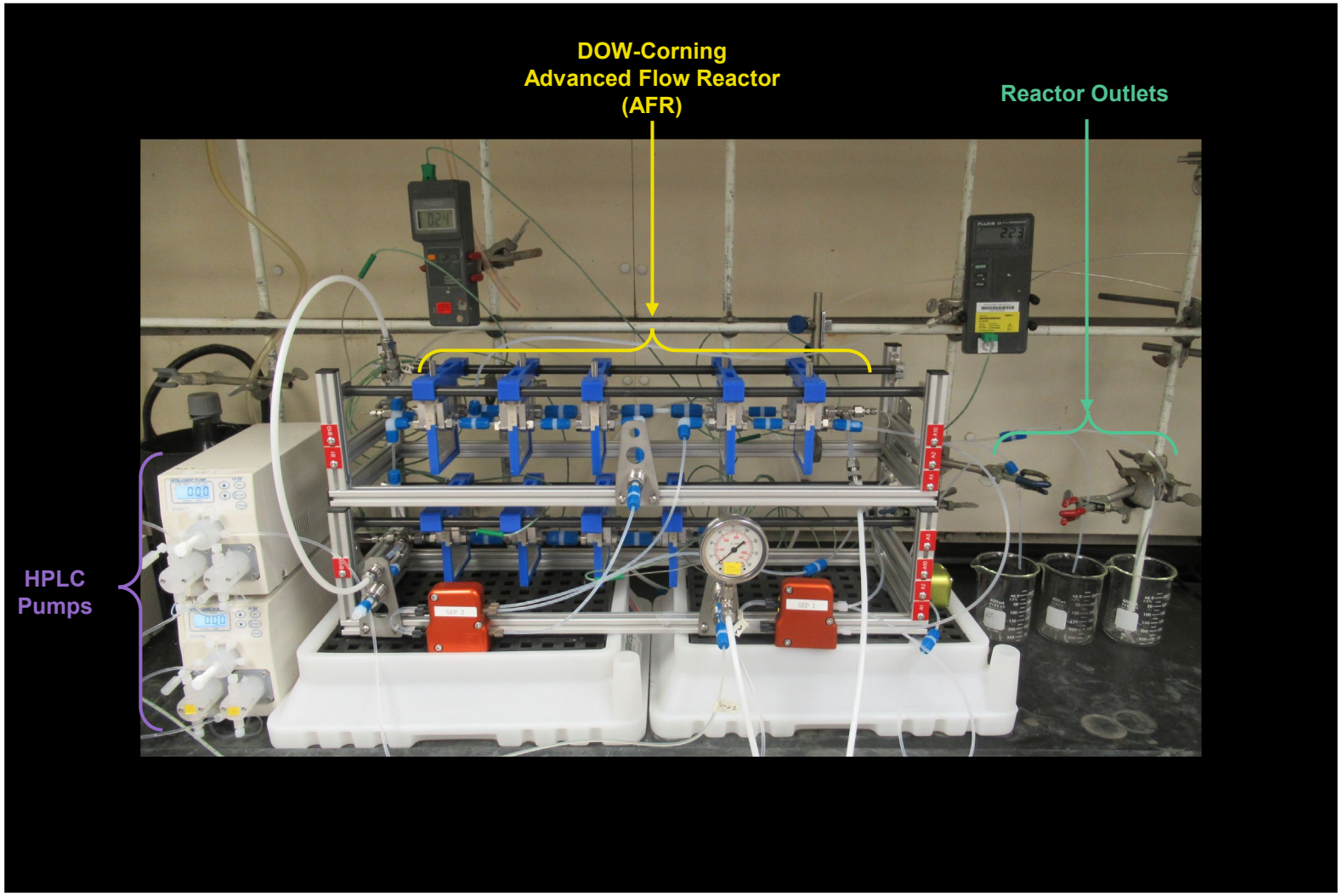
Example Reactor Setup



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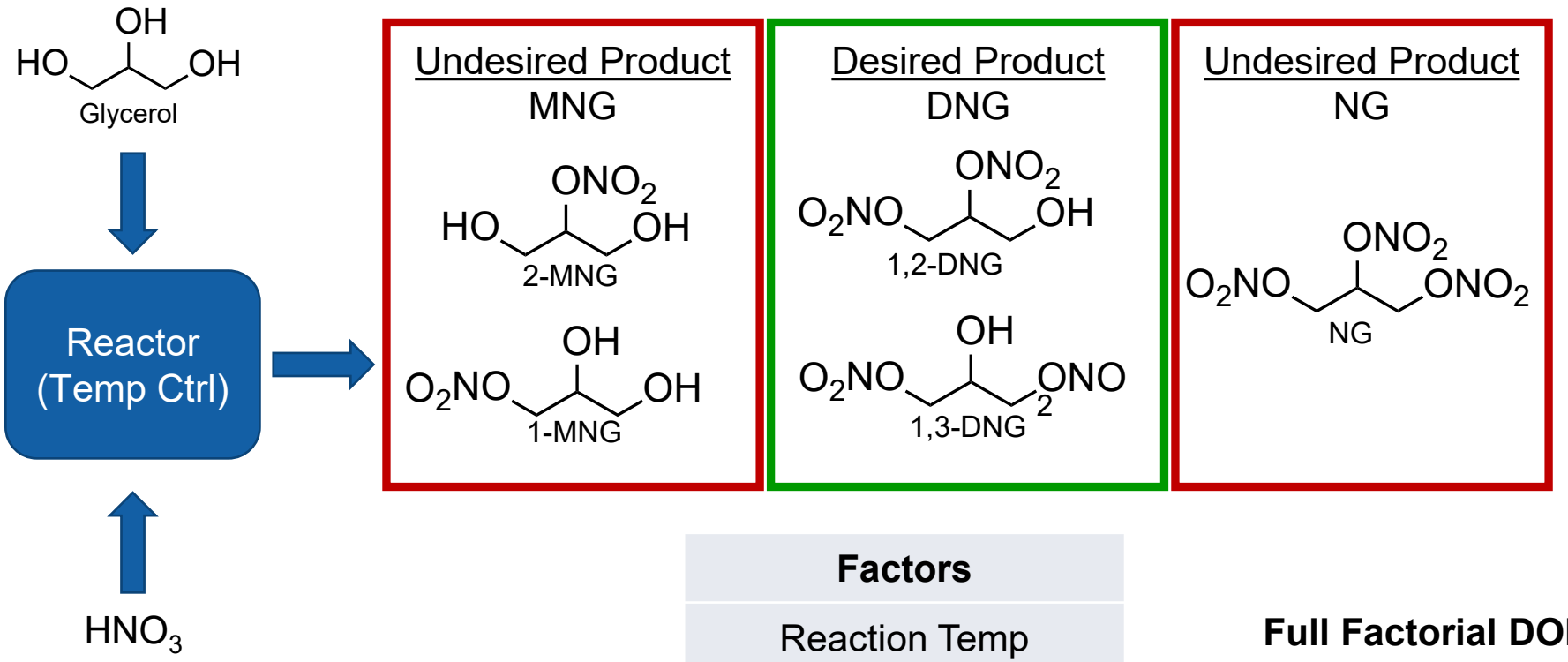
Nitration Characterization – Variables



Factors
Reaction Temp
HNO_3 to Glycerol Ratio
Residence Time

Full Factorial DOE Tested
Low, Mid and High of Variables

How do the selected factors effect the concentrations of MNG, DNG, and NG?
The goal is to minimize MNG and NG while maximizing DNG.

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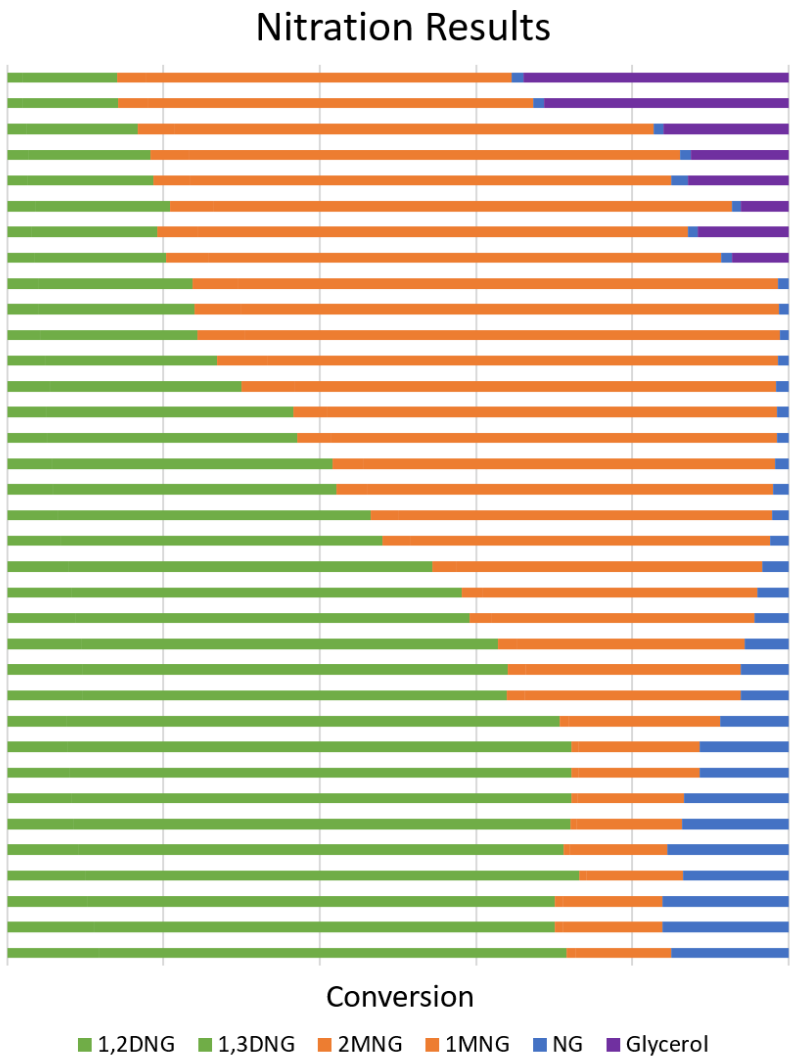
Nitration Characterization (1st Step) – Results

- **Demonstrated rapid optimization: 32 Conditions in only 2 days of testing**
- Maintained high conversion to DNG while minimizing NG side product
- Able to operate at high temperatures without fluctuations
- Short residence times (reduced more than 10X compared to in-house reactor)

- ANOVA (Analysis of Variance):
  - Acid ratio had by far the largest effect on glycerol nitration products, followed by temperature, with little to no effect of residence time in the region studied*
    - *Note that preliminary studies showed that a minimum residence time was required to see these effects

Sample	Temp	HNO_3/ Glycerol	Residence Time
1	Low	Low	Low
1B	Low	Low	Low
5	Low	Low	Mid
8	Low	Low	High
33	Low	Low	Low
14	Mid	Low	Mid
15	Mid	Low	Low
18	Mid	Low	Mid
21	Mid	Low	High
22	High	Low	Low
25	High	Low	Low
26	High	Low	Mid
30	High	Low	High
2	Low	Mid	Low
2B	Low	Mid	Low
3	Low	Mid	Mid
7	Low	Mid	Mid
11	Low	Mid	High
12	Mid	Mid	Low
17	Mid	Mid	Mid
19	Mid	Mid	High
24	High	Mid	Low
27	High	Mid	Mid
29	High	Mid	High
31	High	Mid	High
4	Low	High	Low
6	Low	High	Mid
9	Low	High	Mid
10	Low	High	High
13	Low	High	Low
16	Mid	High	Mid
20	Mid	High	High
23	High	High	Low
28	High	High	Mid
32	High	High	High



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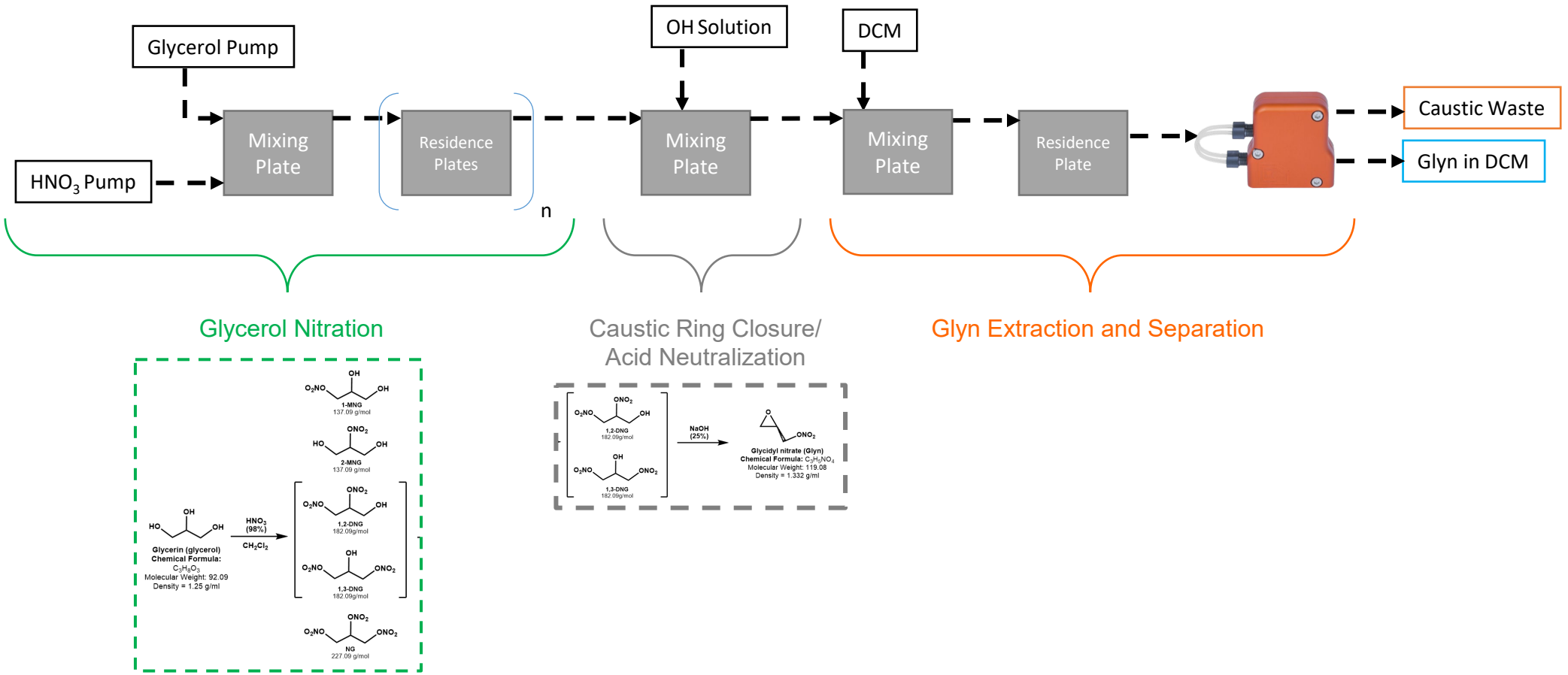
Reactor Configuration – Nitration + Ring Closure in Series

- Adding caustic treatment (ring closure) and DCM extraction/separation to AFR nitration configuration



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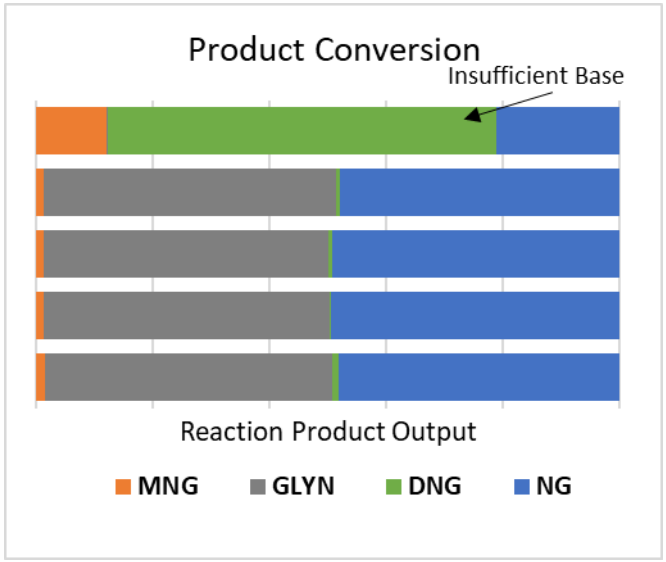
2-Step Characterization

- Low nitration flow, reactor flow near maximum
- Glyn isolated in DCM via in-line extraction
  - Low MNG/DNG contamination
- Synthesis and conversion rate lower than desired, NG content high



- Successfully synthesized and extracted Glyn in flow with low MNG/DNG contamination
- Low overall output, higher NG than desired

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Demonstration of GLYN Synthesis in Updated Configuration

- Improved reactor configuration tested (proprietary, patent in work)
- Best conditions yielded 3X higher than standard configuration
  - Only small variations in overall conversion and output in range studied
  - Greatly improved overall output, but did not significantly decrease NG (solution in work)
  - Side product contamination (can affect polymerization to PGN):
    - **No MNG detected, very small amounts of DNG in final product flow**
- Further optimization in progress
  - Expect to see higher overall yield and full conversion of DNG to GLYN
  - New reactor configuration expected to greatly decrease NG levels
- Demonstration of remote operation and larger-scale collection in progress

- Improved reactor configuration tripled production of GLYN

- Demonstrated clean output of GLYN with low levels of undernitrated product contamination

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Summary

- **Successfully designed and tested a microfluidic reactor with in-line purification and extraction system using commercially available flow modules**, including the DOW Corning Advanced Flow Reactor (AFR), continuous operation peristaltic pumps, in-line liquid-liquid phase separators and in-line flow meters
  - Configured so that pumps can flow sensors can be remotely operated and monitored
  - Currently waiting on delivery of additional hardware to remotely control flow pathways – will allow for full automation of reactor
  - No temperature fluctuations observed, clogging hazards managed, small overall volumes of nitrated products
- **Test case: GLYN Synthesis**
  - Nitration of glycerol to dinitroglycerine (DNG) was demonstrated at conversion rates comparable to batch synthesis at rates approaching kilo scale
  - Two-step/one-reactor nitration and ring closure in series, including separation of organic product stream from aqueous waste, was successful
    - **Demonstrated nearly 4X the production rate seen in original in-house reactor without extraction**
    - Further optimization in work with additional needed hardware, expect to double production rate

Demonstrated ability of modular microfluidic equipment to quickly change testing parameters and reactor configurations

Allows for rapid optimization of processes; precise control of temperature, residence time and reactant ratios allows for much greater tuning of reactions compared with traditional batch synthesis

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