聲明

Green and Sustainable Chemistry with Microreactors

3/13/2021

楊立勔 (Barry Yang)
瑞林科技顧問公司 (Richlink Consulting Co.)
blyang55@gmail.com *0918381256*

Outline

- Flow chemistry key to green and sustainable chemistry
- Microreactor enables flow chemistry
  - Safer and greener operation, strong performance
- Impact on education and frontier R&D
- Commercial successes
- Summary

Ten Chemical Innovations That Will Change Our World

IUPAC identifies emerging technologies in Chemistry with potential to make our planet more sustainable

by Fernando Gomollón-Bel

Top Ten Emerging Technologies i
fort to more broadly promote the
chemical and related sciences a
eries that have the potential to c

Experts recruited by IUPAC s
Emerging Technologies in Chem
this article from a pool of nomi
chemists from around the glob

Flow chemistry

Chemistry International April-June 2019

Why Flow Chemistry?

- Better consistency, easier management
  - Thanks to automation and tight process control
  - Fewer opportunities for human errors
  - Unattended operation achievable and practical
- Opportunities for novel process route
  - Allow unstable or toxic intermediates to be consumed immediately upon generation, enabling synthetic routes otherwise unsuitable for batch operation
- Global leadership endorsements
  - IUPAC, FDA, US Congress

Batch vs. Continuous Flow

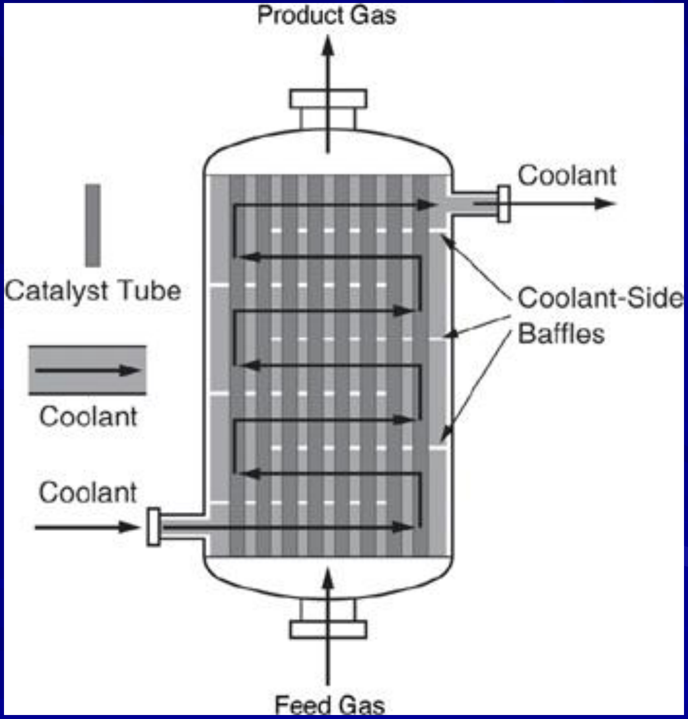
Batch Reactor, Cyclic Operation

Charge, start stirring, heat up, dose and react, cool down, stop stirring, discharge, clean up

https://en.wikipedia.org/wiki/Batch_reactor

Flow Reactor, Continuous Operation

Start up, steady operation, shut down

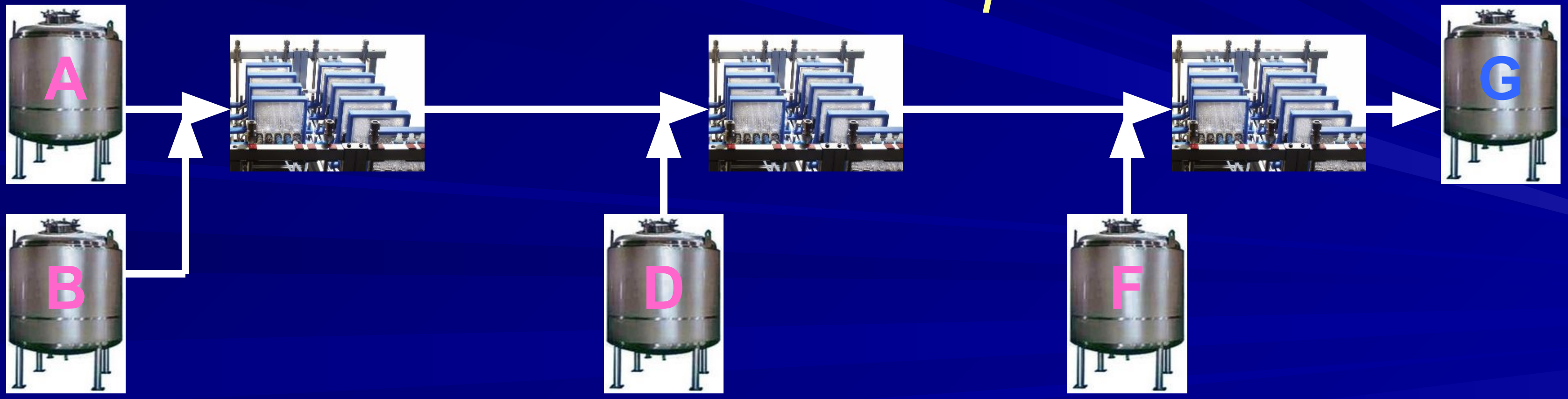


https://www.informit.com/articles/article.aspx?p=1652026&seqNum=4

Flow Process for Simplicity & Versatility

Batch Operation

Continuous Flow Operation



FDA's Draft Release, 2/2019

Quality Considerations for Continuous Manufacturing

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2019
Pharmaceutical Quality/CMC
Pharmaceutical Quality/Manufacturing Standards (CGMP)

National Centers of Excellence in Continuous Pharmaceutical Manufacturing

- H.R.4866
- Aims to limit drug shortages and spur U.S. drug manufacturing by encouraging use of continuous manufacturing in the development and approval of drugs and biologics
- FDA to designate certain universities as National Centers of Excellence in Continuous Pharmaceutical Manufacturing, which would study and recommend improvements to continuous manufacturing
- Bill passed in the House on 9/21/2020, going to the Senate next

Why Microreactor?

- Safer and greener operation
  - Intrinsically safe, less waste
- Performance upgrades
  - Process intensification
  - Higher yield, reduced needs for purification
- Shorter time to commercial operation
  - Accelerated process R&D, optimization, and scale-up
- Lower cost
  - Reduced R&D and scale-up costs, lower OPEX

Safe Operation Tied to Reactor Volume

Batch Reactor

Reactor size up to 15,000 L

Hold-up ~10,000 L

Assuming 2 days per cycle, annual “throughput” ~1,800 ton

https://en.wikipedia.org/wiki/Batch_reactor

Microreactor

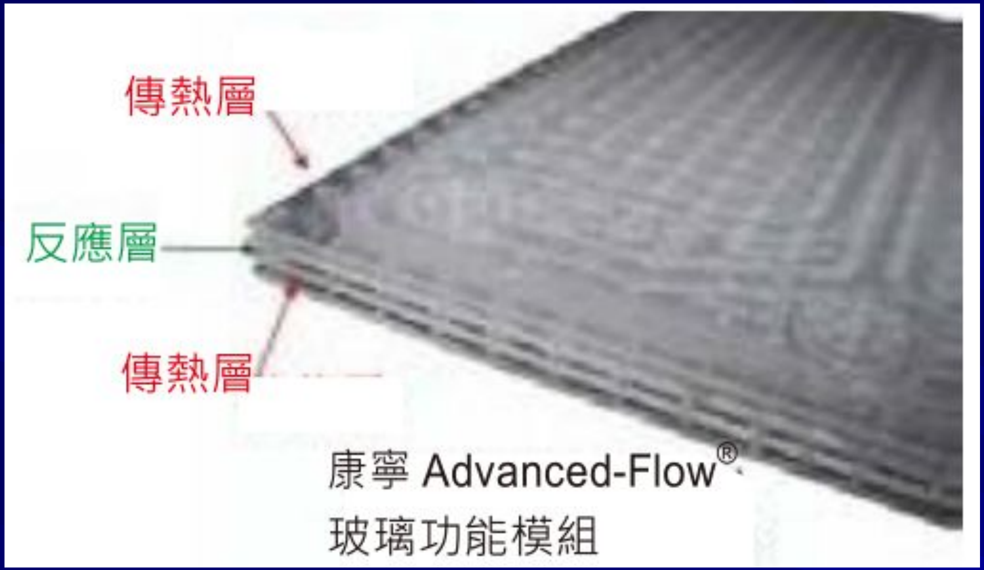
Corning G4

Hold-up ~2.5 L (assuming 10 plates at 0.25 L per plate)

Annual throughput 2,000 ton

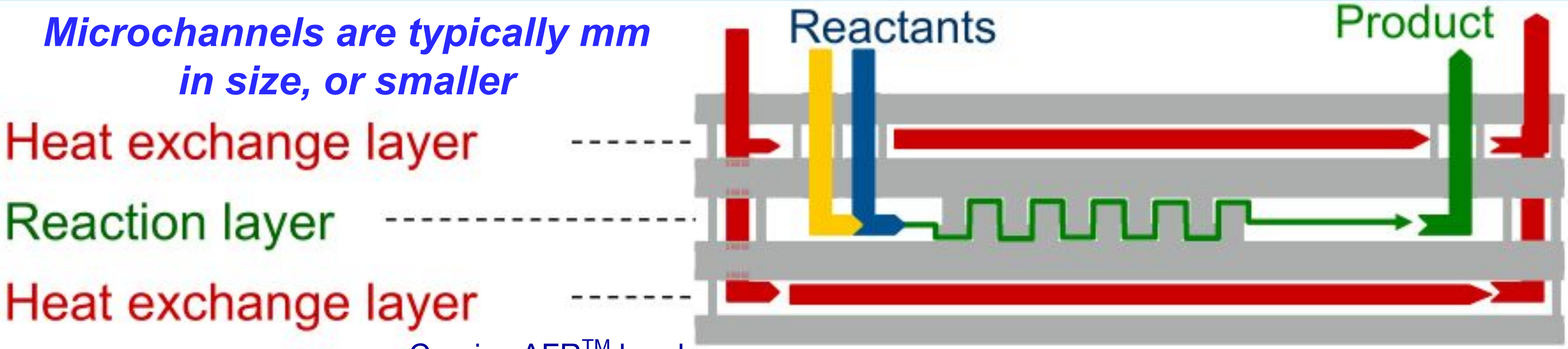
Corning AFR™ G4

Microreactor Fundamentals
- Excellent Temperature Control



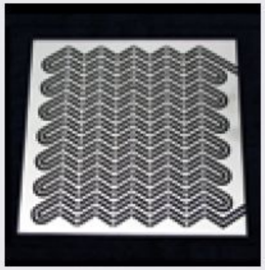
vs.

Microchannels are typically mm in size, or smaller



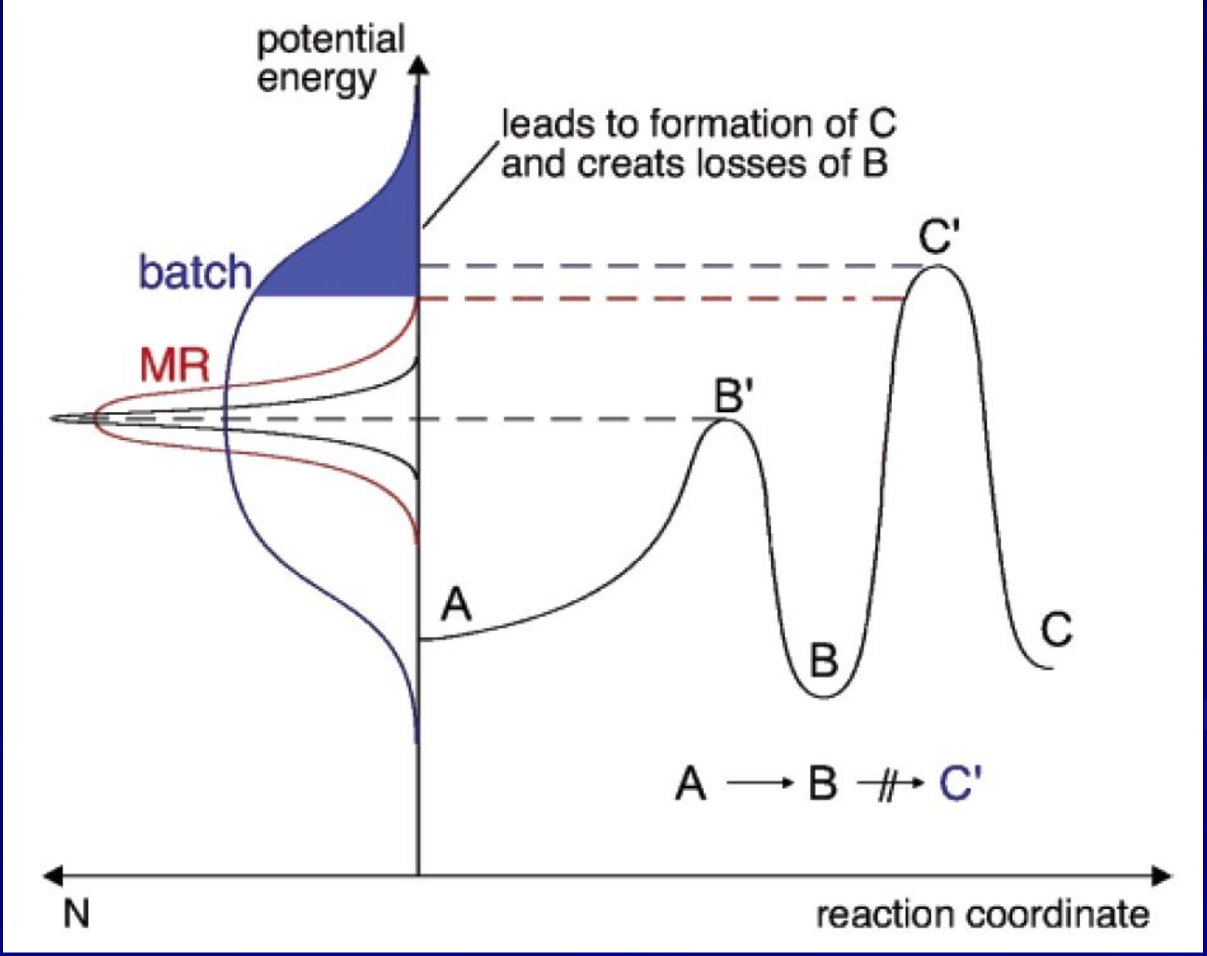
Corning AFR™ brochure

Comparison of Heat Transfer Performance

Table 2. Comparison of heat-transfer performance of different heat-exchanger (HEX) reactors.					
Reactor	Silicon Carbide Plate HEX Reactor	High-Temperature Alloy Microchannel HEX Reactor	Glass Plate HEX Reactor	Stainless Steel Plate HEX Reactor	Standard Batch Reactor
					
Heat-Transfer Coefficient, *U*, W/m^2-K	7,500	1,500	600	2,500	400
Residence Time	Few minutes	Few minutes	Few minutes	Few minutes	Few hours
Ratio of Surface Area to Volume, m^2/m^3	2,000	2,000	2,750	400	2.5
Heat Exchange Capacity, kW/m^3-K	15,000	3,000	1,650	1,000	1

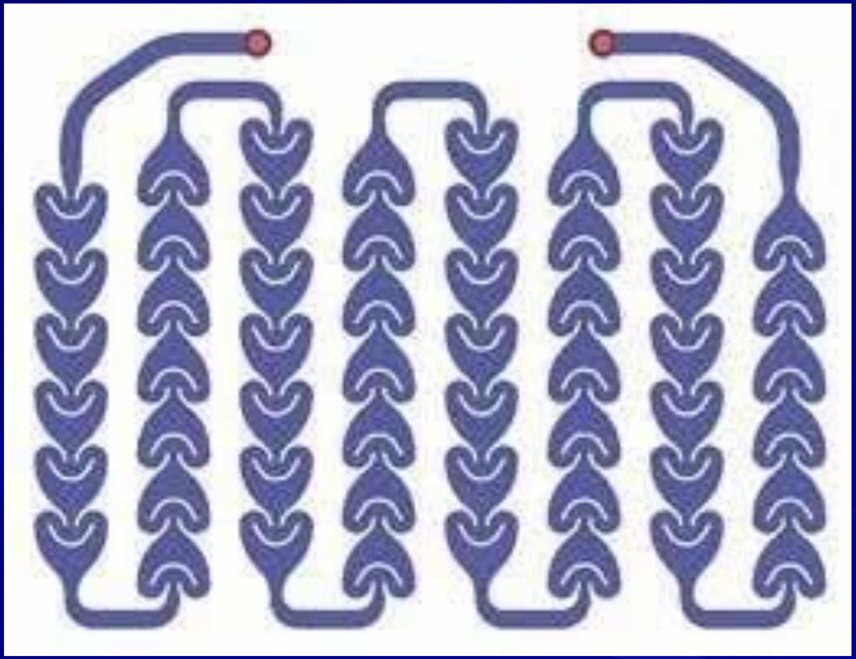
C. Gourdon, Selecting Process-Intensified Equipment, CEP, March 2020, 29

Higher Selectivity from Tighter Temperature Control



Org. Process Res. Dev. 2004, 8, 440

Static Mixer in Microreactor



Corning heart shaped static mixer

Corning AFR™ brochure, 2016

Advantages of Microreactor

- Process intensification
  - Up to100X intensification demonstrated over traditional flow reactor
- Much safer operation (intrinsic safety)
  - Minimal chemical hold-up
  - Characteristics of a flame arrester
  - Usually no moving parts (such as a stirrer) to cause mechanical breakdown, little vibration
- Higher energy efficiency
- Operating window can often be widened safely
- Process control inherently better
- Assured scale-up (numbering up)

湿法磷酸萃取净化

与全球领先的矿物工程公司Bateman的技术相比，本发明设备体积仅为其1/2000，制造成本为其1/50，开车时间由5~7d缩短到2~4min，年开工时间从不足7200h提高到8000h以上。

比较项目	本发明	Bateman技术
设备容积	100L	$200m^3$
年开工时间	>8000h	<7200h
单次清洗耗时	~2h	~20d

数据来源：“湿法磷酸萃取净化新型装备技术”成果鉴定材料（2011年），企业标定

徐建鸿, 第二届微化工研讨会, 上海, 2018

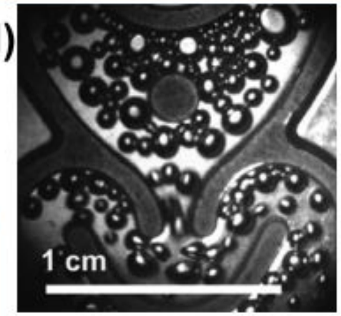
Disadvantages of Microreactor

- Limited compatibility with solid particulates
  - Particulates could cause channel clogging
    - Not suitable for reactions with heavy precipitation
    - Although recent development has successfully demonstrated processing slurries with up to 30% solid content
- Higher pressure drop
  - Due to channel size being small
- High reactor cost
  - Due to the need for fine engineering and precision manufacturing
  - But total cost to market is often much lower

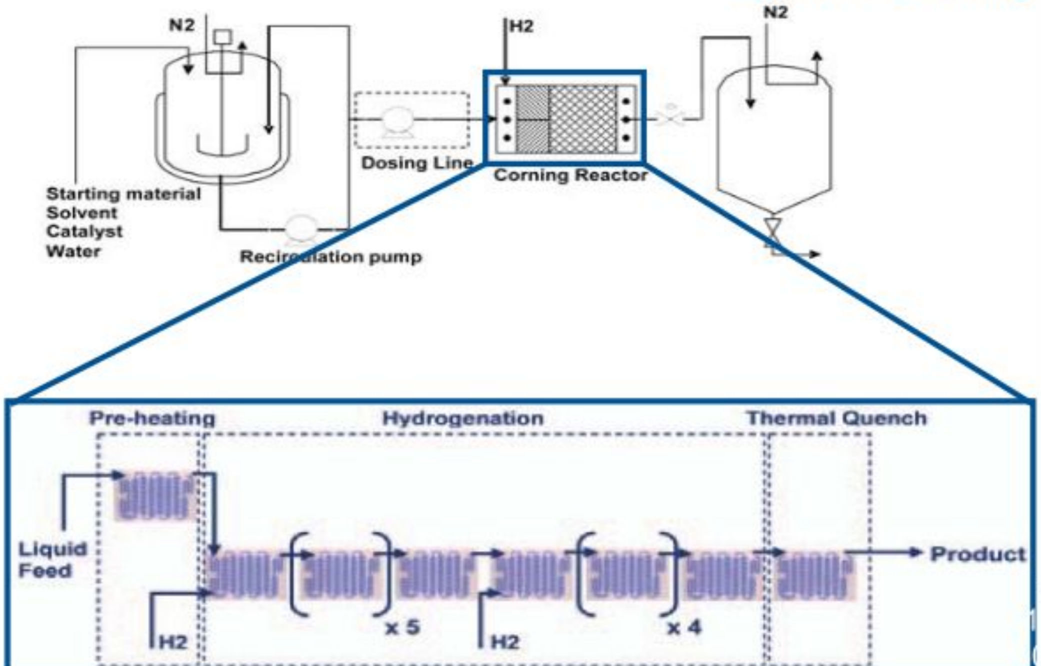
Selective Hydrogenation of Slurry in Corning AFR™ with 98%+ Conversion and Selectivity

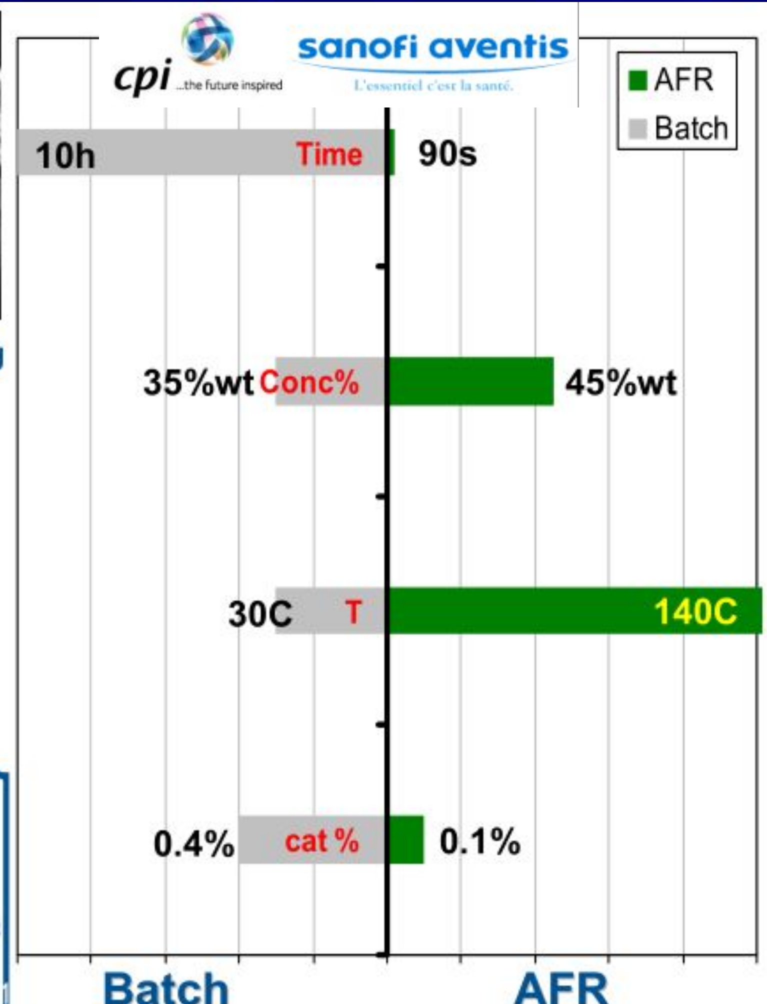
- **highly exothermic (>400 kJ/mol)**
- **~30 μm catalyst in slurry**
- **significant catalyst reduction**

Ref: Chemistry Today 27(6),
Nov-Dec (2009)



Excellent G/L Mixing





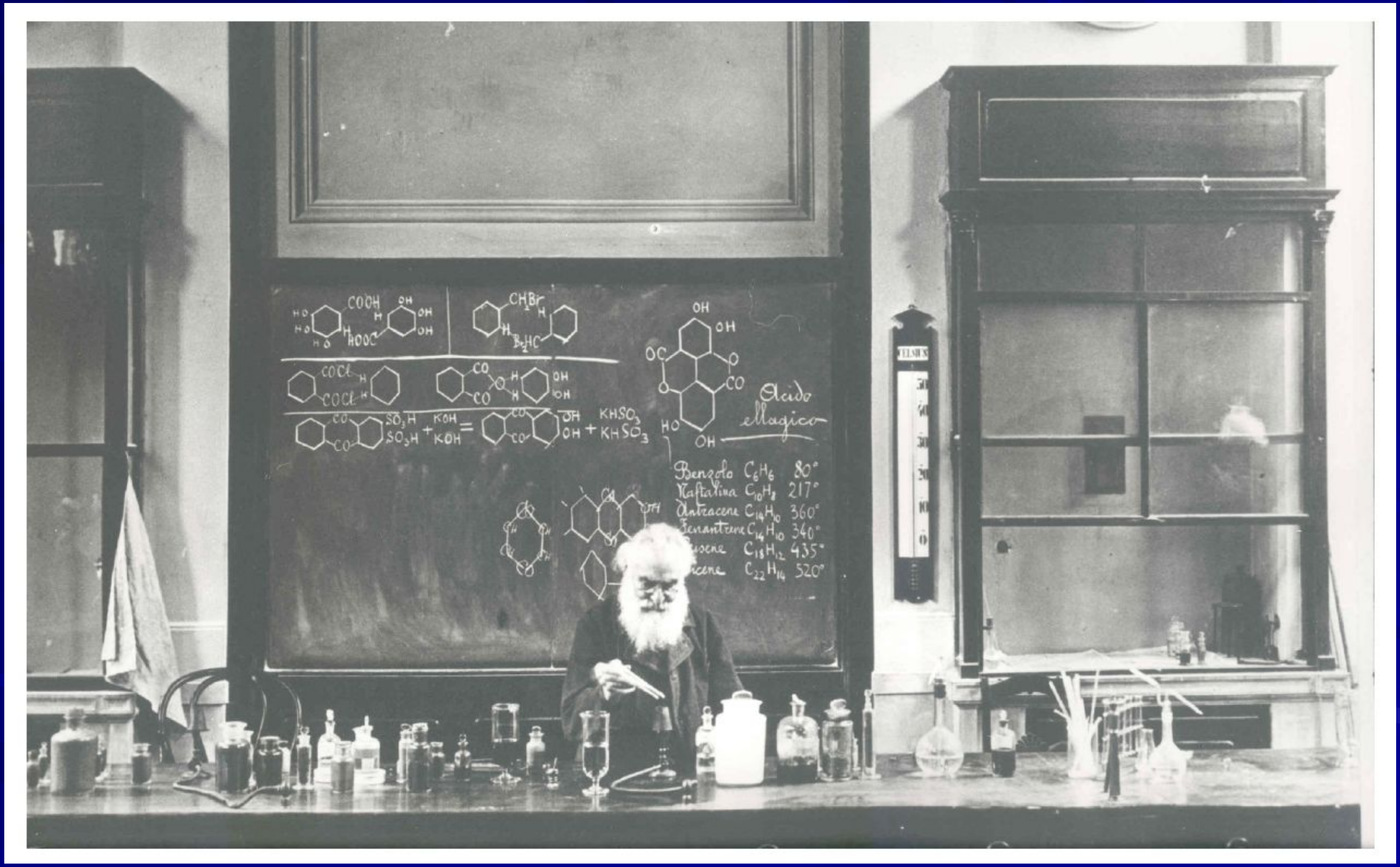
Corning AFR™ presentation, Woehl, 2010

Benefits of Microreactor

- Shorter time to market
  - Accelerated process R&D, optimization, and scale-up
- Non-traditional processing enabled
  - Practical, safer, on-site, on-demand production
  - Portable, small footprint, modular/skid design
  - Can integrate multiple operations into 1 unit
  - Dedicated device for assigned reaction, avoiding cross contamination
  - Can handle some multi-phase reactions effectively
- Overall cost reduction, greater profit
  - Reduced R&D and scale-up costs
  - Lower OPEX (higher yield, higher throughput, less solvent, less waste...)

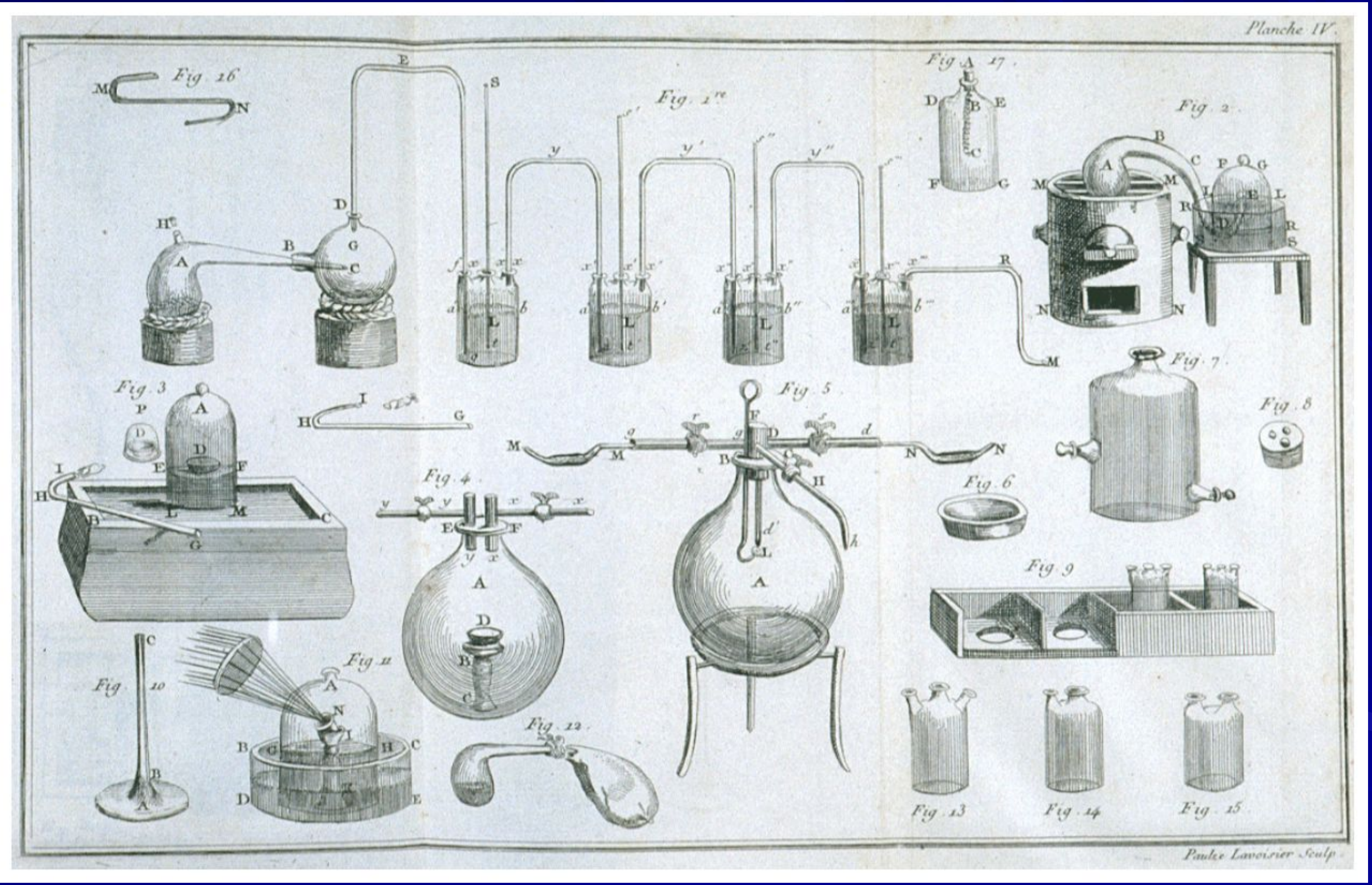
Impact on Education and Frontier R&D

Good Old Day



C. Moberg, Microreactors in Chemistry, KTH (2011)

19th Century Equipment for Synthesis



C. Moberg, Microreactors in Chemistry, KTH (2011)

20th Century Equipment for Synthesis

C. Moberg, Microreactors in Chemistry, KTH (2011)

Educational Microreactor at NCU - Corning Nebula^{TM} System

流动化学教学在欧美成为热门课程

Continuous-Flow Chemistry in Chemical Education

Daniel Blanco-Ania and Floris P. J. T. Rutjes*

Radboud University, Institute for Molecules and Materials, Heyendaalseweg 135, 6525 AJ Nijmegen, The Netherlands

Received: 20 September 2017; accepted: 25 October 2017

While continuous-flow chemistry is steadily increasing its footprint in academic research and in the manufacturing of pharmaceutical intermediates and fine chemicals, the attention for flow chemistry in educational programs is on average rather limited. This account is meant to provide a personal overview of the possibilities to address the involvement of flow chemistry in the various stages of chemical education.

Keywords: Continuous-flow chemistry, chemistry education, teaching modules, sustainable chemistry

JOURNAL OF CHEMICAL EDUCATION — Laboratory Experiment

Cite This: J. Chem. Educ. XXXX, XXX, XXX−XXX — pubs.acs.org/jchemeduc

Continuous-Flow Chemistry in Undergraduate Education: Sustainable Conversion of Reclaimed Vegetable Oil into Biodiesel

Frank A. Leibfarth,[†,‡] M. Grace Russell,[†] David M. Langley,[†] Hyowon Seo,[†] Liam P. Kelly,[†] Daniel W. Carney,[§] Jason K. Sello,[§] and Timothy F. Jamison*[,†]

[†]Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

[‡]Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, United States

[§]Department of Chemistry, Brown University, Providence, Rhode Island 02912, United States

JOURNAL OF CHEMICAL EDUCATION — Laboratory Experiment

pubs.acs.org/jchemeduc

Flow Chemistry in Undergraduate Organic Chemistry Education

Burkhard König,[†] Peter Kreitmeier,[†] Petra Hilgers,[†] and Thomas Wirth*[,‡]

[†]Institut für Organische Chemie, Universität Regensburg, Universitätsstrasse 31, D-93040 Regensburg, Germany

[‡]School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff, CF10 3AT, United Kingdom

Corning Advanced-Flow Laboratory Molecule Maker

10.26 Chemical Engineering Laboratory

Spring 2018

MIT 优秀课程

Continuous Flow Optimization

Faculty Advisor:
Klavs F. Jensen
Office: 66-542a
Phone: 617-253-4589
E-mail: kfjensen@mit.edu

Client/Internal Consultant:
Victor L. Schultz
Office: 66-507
Phone: 617-324-1896
E-Mail: schultzv@mit.edu

伍辛軍，連續流反應器技術與應用以及康寧流動化學教育平台介紹， ©2019 Corning Inc

On-demand Continuous-flow Production of Pharmaceuticals in a Compact, Reconfigurable System (MIT)

- Based on flow chemistry
- Refrigerator-size, modular-design, reconfigurable
- Demonstrated production of multiple pharmaceuticals meeting U.S. Pharmacopeia standards

Adamo et al., Science, 352, 61 (2016)

Automated High-Speed Reaction Screening (Pfizer)

- Based on flow chemistry at nano-mole scale
- 1500 experiments per day, with real-time analysis
- Powerful for reaction optimization
- Results verified at raised scales

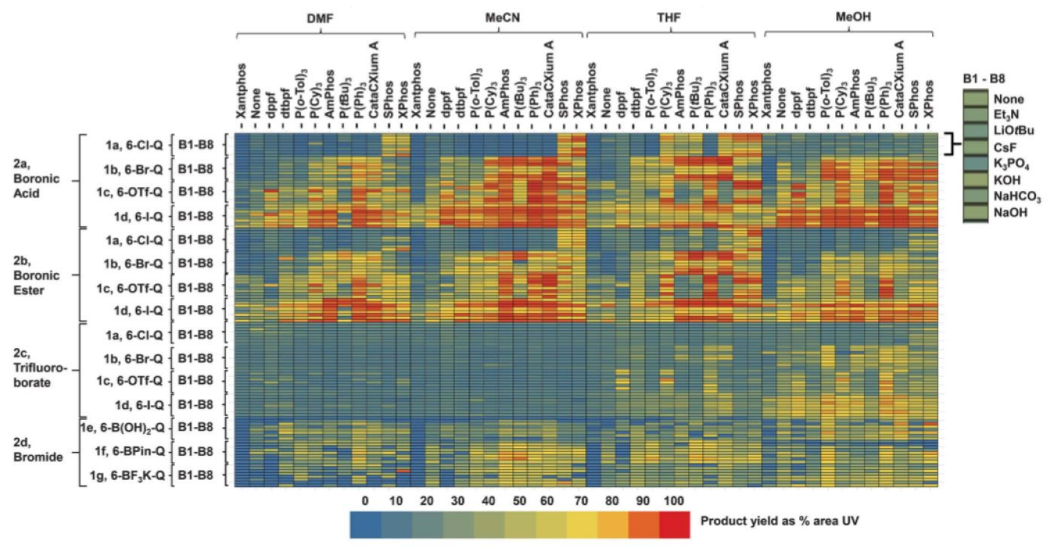


Fig. 3. Complete heatmap visualization. A total of 5760 reactions of **1a–1d** with **2a–2c**, and the reaction of **2d** with **1e–1g** evaluated across a matrix of 11 ligands (plus one blank) × 7 bases (plus one blank) × 4 solvents.

Perera et al., Science 359, 429 (2018)

A Continuous Flow Manufacturing Facility (Novartis)

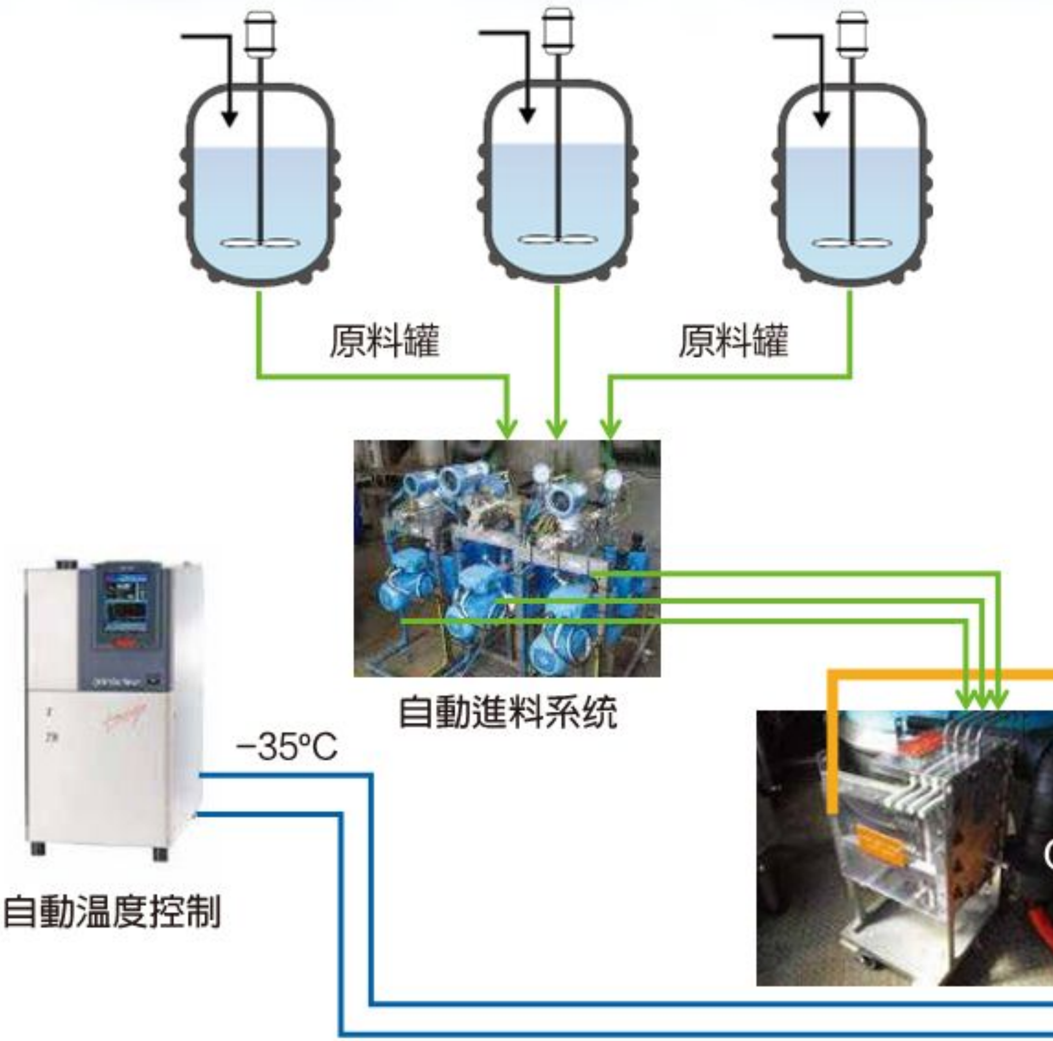
https://www.novartis.com/stories/discovery/new-drug-manufacturing-tools-change-pharma-chemistry

The Active Substance is Dried, Granulated, and Compressed into Tablets Continuously

https://www.novartis.com/stories/discovery/new-drug-manufacturing-tools-change-pharma-chemistry

Commercial Successes

案例：康寧AFR®反應器成功實現原料藥中間體cGMP生產（西班牙）



- **收率提高一倍**
  (康寧AFR®：60%，傳統攪拌釜：31%)
- **產品純度改善**
  (康寧AFR®：98-99%，傳統攪拌釜：95%)
- **工藝節能明顯**
  (康寧AFR®： -35˚C ，傳統攪拌釜：-70˚C)
- **無放大效應**
  (G4生產和G1實驗室結果完全相同；年產能放大30倍；開車一次性成功，系統運行穩定)
- **康寧AFR®工藝： 成本降低35%，投資回報期為1年**

Medichem S.A.

康寧AFR_小冊子

A Commercial Nitration Operation Using Corning G4

Continuous Production Using Ehrfeld Mikrotechnik's Miprowa Reactor

- For Shaoxing Eastlake (紹興東湖高科)
  - For a highly exothermic alkoxylation reaction
- Design capacity: 10,000 m.t./yr
  - Replacing 20+ conventional batch reactors
- Reactor core:
  - 7 m long, 40 cm wide
  - 150 rectangular reaction channels with exchangeable static mixers
- 4 ys from concept to commercial operation
- Commercial operation a huge success
  - Since 9/2016
  - Safer and greener operation
  - Lower cost, higher profit

A. Stankiewicz, The Principles and Domains of Process Intensification, CEP, March 2020, 23

150 microchannels in parallel

Converting Landfill Gas to Liquid Fuels (Velocys/ENVIA)

www.velocys.com

2 Velocys FT reactors, each with >10,000 microchannels in parallel, producing ~200 barrels of liquid fuels per day

Summary

- Continuous manufacturing based on flow chemistry is the future
  - Especially for pharmaceutical and fine chemicals industries
  - Endorsed by IUPAC, FDA, US Congress…
- Microreactor offers huge advantages for process development and production
  - Including safer and greener operations, performance upgrades, cost savings, and shorter time-to-market
  - Technology is already proven and being commercialized rapidly
- Flow chemistry and microreactors are entering college education
  - As part of chemistry lab courses