Miniaturizacija naprav v kemijskem inženirstvu

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Fakulteta *za kemijo in kemijsko tehnologijo*
Raziskovalna skupina za mikroprocesno inženirstvo

Vsebina

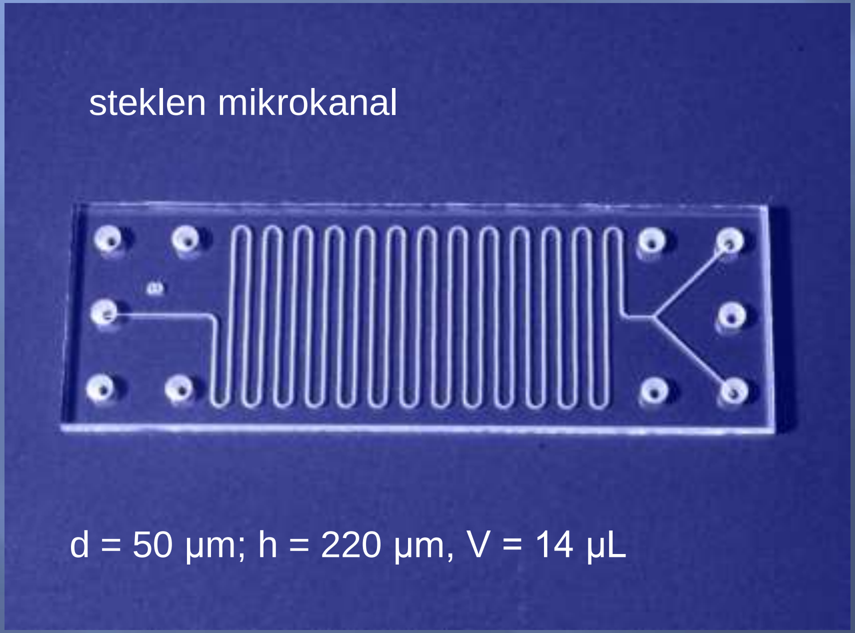
- Uvod
  - Miniaturizirane naprave, mikroreaktorska tehnologija
  - Osnovne prednosti miniaturiziranih naprav
  - Področja uporabe
- Miniaturizacija naprav v kemijski industriji in biotehnologiji
  - Mikrobioreaktorji
  - Primeri uporabe v biokatalitskih procesih
- Smernice razvoja

Mikrostrukturirane naprave – nova prelomnica v znanosti in tehniki

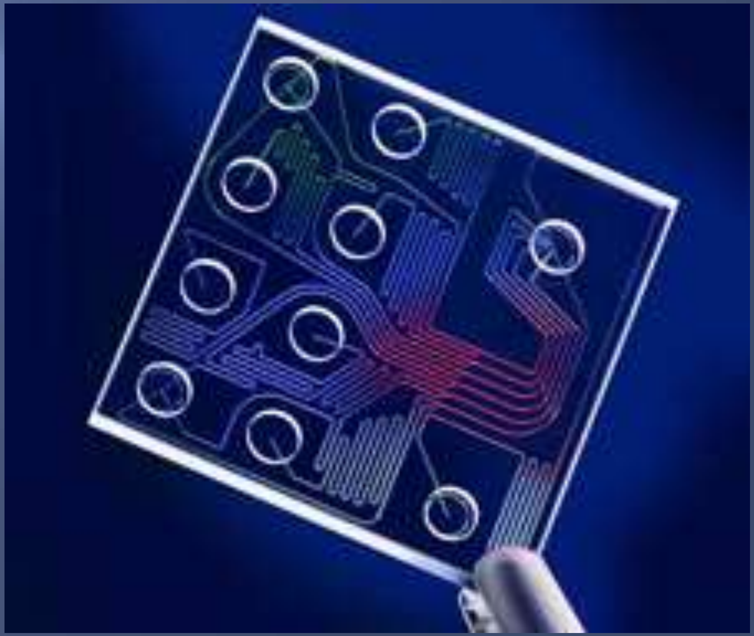
Mikrofluidne naprave

Mikroreaktorji

Lab-on-a-chip



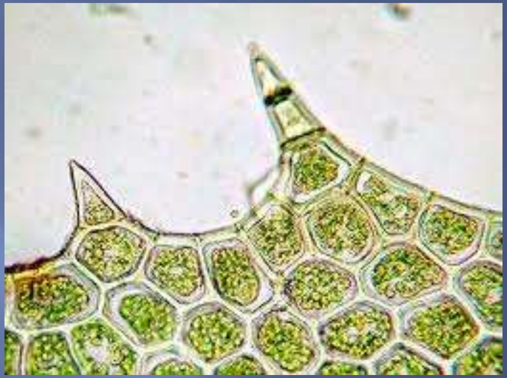
Micronit Microfluidics BV

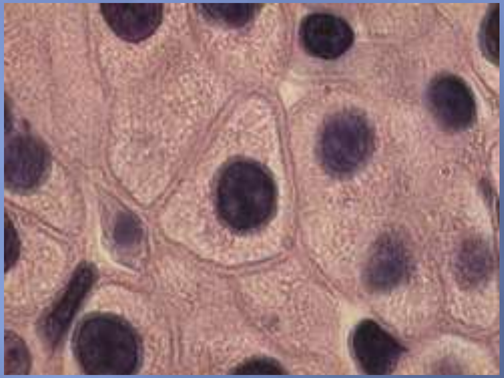


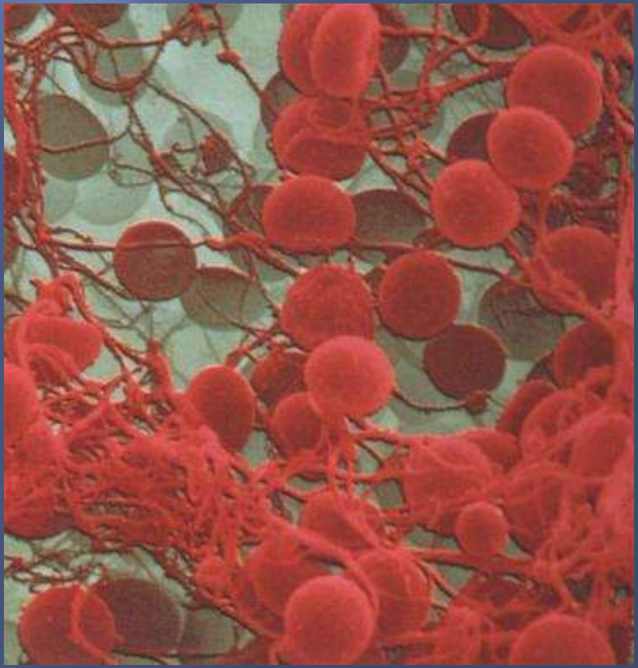
Lab-on-a-chip sistem: Agilent Technologies

Miniaturizacija – zakaj?

Narava

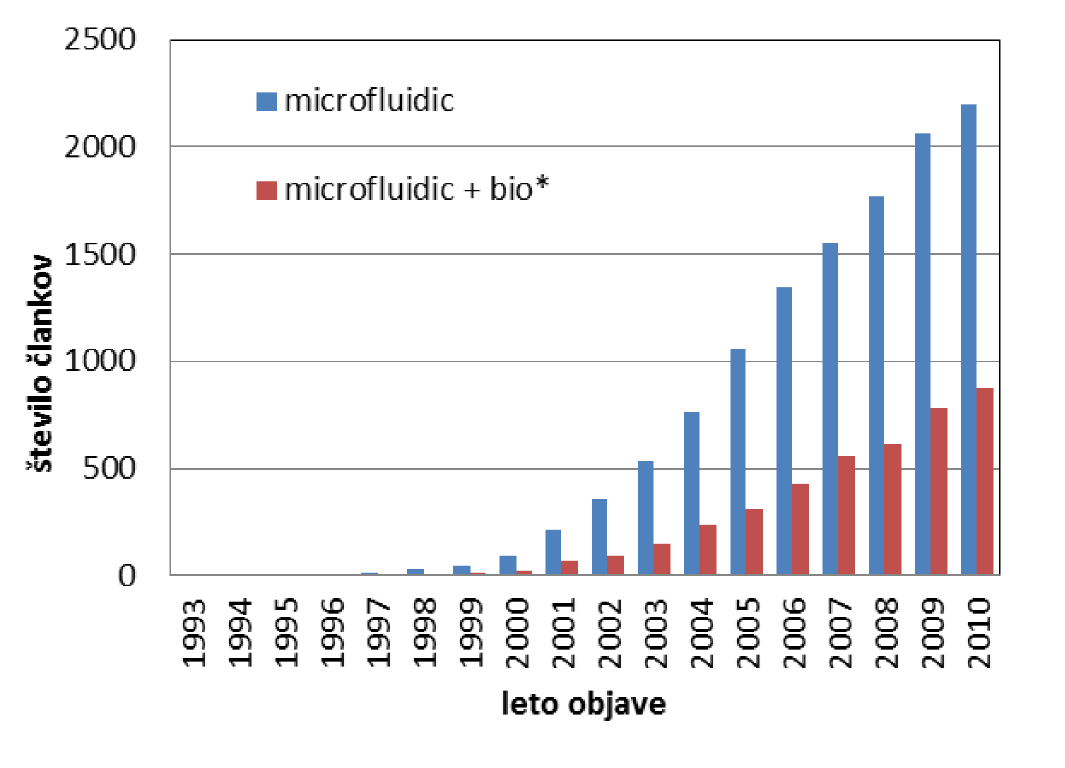


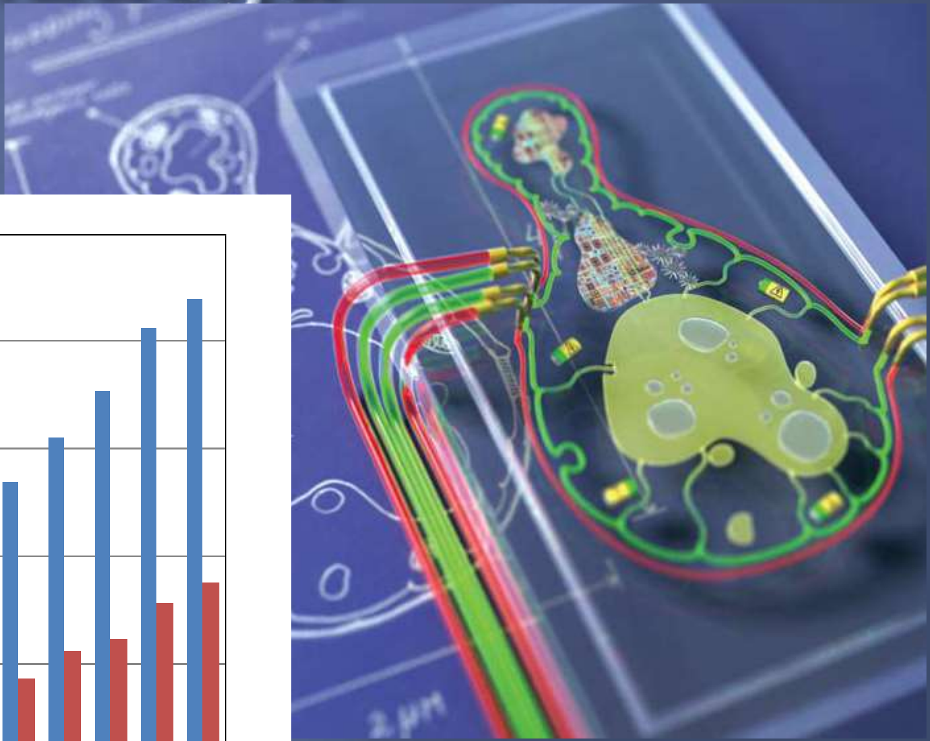




Miniaturizacija

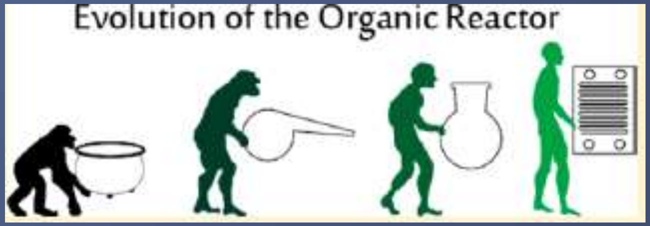
Znanost





- 1997 – prva mednarodna konferenca o mikroreaktorski tehnologiji (IMRET), prihodnje leto že 12.
- 2010: na FKKT UL prvo mednarodna tematska konferenca „Vpeljava mikroreaktorske tehnologije v biotehnologijo“ (IMTB)

Mikrofluidne naprave



Nova paradigma v kemijskem inženirstvu

Zgodovinski mejniki:

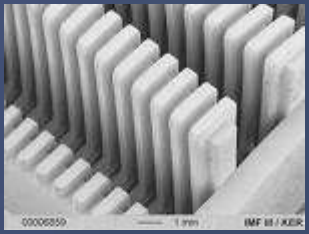
- 1986 – patentiran prvi mikroreaktor: bivša Nemška demokratična republika
- 1989 – razvit prvi mikro toplotni izmenjevalec: Forschungszentrum Karlsruhe
- 1995 – prva delavnica o mikroreaktorski tehnologiji v Mainzu

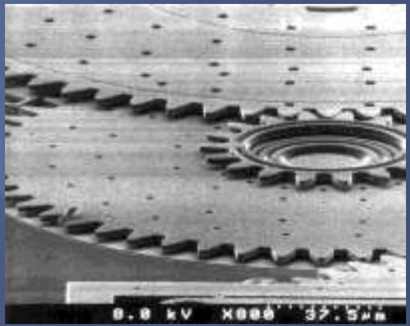
Ehrfeld Mikrotechnik BTS, Mainz

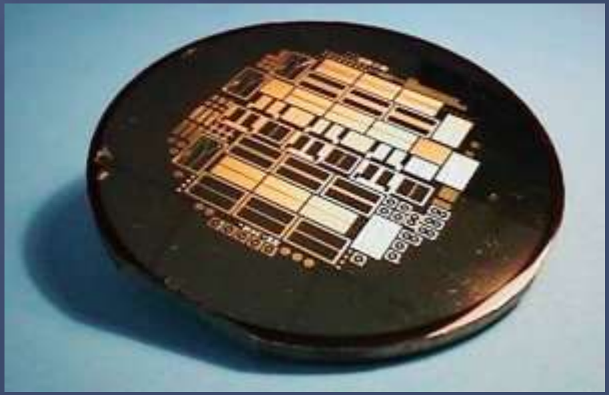
Miniaturizacija bioreaktorske tehnike

Mikroreaktorji

- iz različnih materialov: silicij, steklo, kvarc, polimeri (PDMS, PMMA) in kovine
- izdelani s pomočjo tehnik, ki so razvite na področju mikroelektronike
  - fotolitografija
  - jedkanje (izotropno, suho, elektrokemijsko,...)
  - LIGA (litografija, elektroforming, kalupiranje)
  - laserske tehnike
  - mikrolaminacija tankih kovinskih slojev







Prenos v industrijo

V ZDA in Aziji od konca prejšnjega stoletja proizvodni procesi na osnovi MRT

Chemical & engineering news, 2005:
"Vsa večja kemijska in farmacevtska podjetja se ukvarjajo z mikroreaktorsko tehnologijo."

Clariant: Competence Center in MicroReaction Technology (2004)
Sigma-Aldrich: CPC lab system (2004)
Degussa: Project House on Process Intensification (2005)
Johnson & Johnson Pharmaceutical R&D: uporaba MRT za razvoj novih procesov
Bayer, GlaxoSmithKline, Pfizer, Novartis, Lonza...

100 ton/leto proizvodnja zdravila Naproxcinod v Linzu od l. 2009; podjetje: NicOx, razvil DSM v sodelovanju s Corning Inc.

Ključne prioritete za trajnostno proizvodnjo –"zeleno" inženirstvo

Key green engineering research areas: results of the brainstorming and prioritization exercises

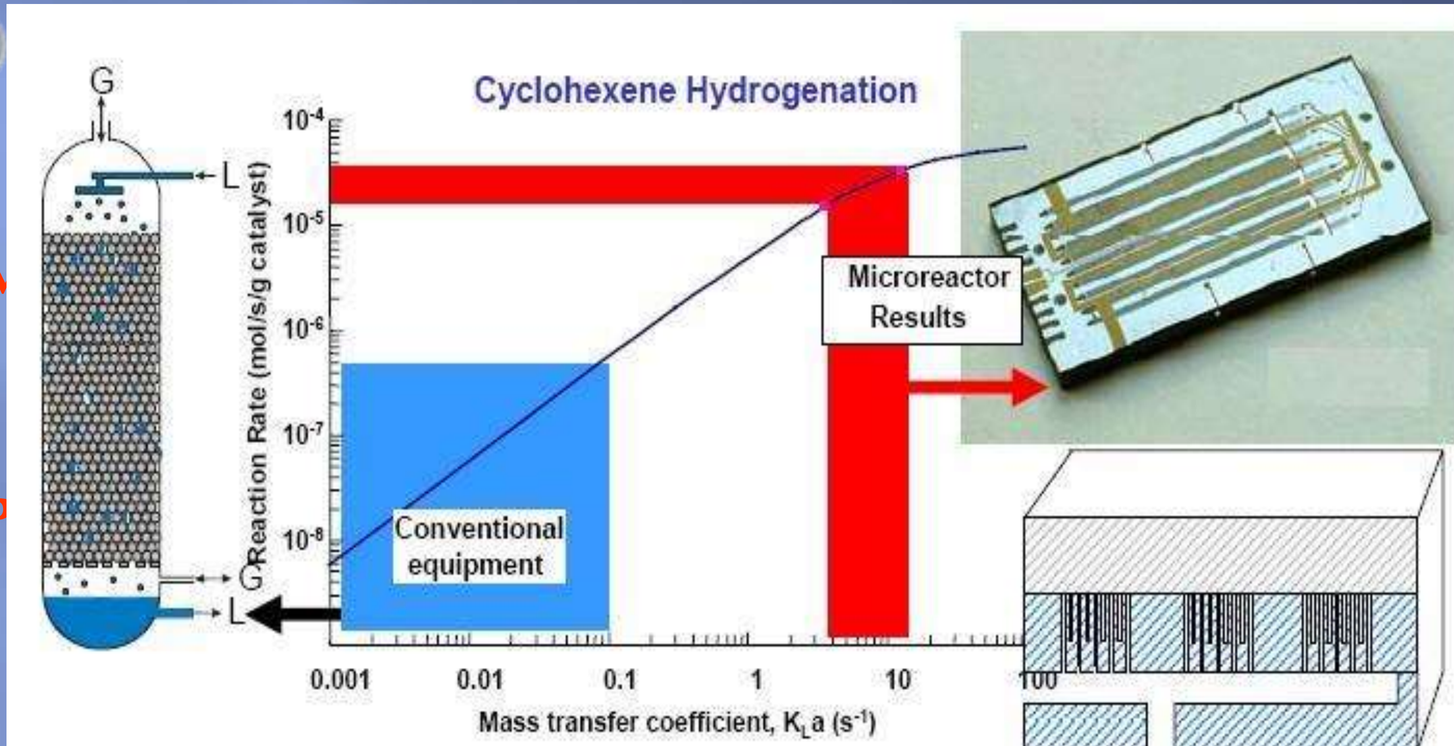
Rank	Main Key Areas	Sub-areas/aspects	Votes
1	Continuous Processing	Primary, Secondary, Semi-continuous, etc.	12
2	Bioprocesses	Biotechnology, Fermentations, Biocatalysis, GMOs,	11
3	Separation and Reaction Technologies	Membranes, crystallizations, etc.	11
4	Solvent Selection, Recycle and Optimization	Property modeling, volume optimization, recycling technologies, in process recycle, regulatory aspects etc.	10
5	Process Intensification	Technology, process, hybrid systems, etc	9
6	Integration of Life Cycle Assessment (LCA)	Life cycle thinking, Total Cost Assessment, carbon / eco-footprinting, Social LCA, streamlined tools	4
7	Integration of Chemistry and Engineering	Business strategy, links with education, etc.	4
8	Scale up aspects	Mass and energy transfer, Kinetics, and others	3
9	Process Energy Intensity	Baseline for pharmaceuticals, estimation, energy optimization	1
10	Mass and Energy Integration	Process integration, Process Synthesis, Combined Heat and Power, etc	0

Vir: Key Green Engineering Research Areas for Sustainable Manufacturing: A Perspective from Pharmaceutical and Fine Chemicals Manufacturers

Concepción Jiménez-González,[*,†] Peter Poechlauer,[‡] Quirinus B. Broxterman,[§] Bing-Shiou Yang,[⊥] David am Ende,[∥] James Baird,[¶] Carl Bertsch,[□] Robert E. Hannah,[■] Phil Dell'Orco,[○] Henk Noorman,[●] Sandy Yee,[△] Raf Reintjens,[§] Andrew Wells,[▲] Viviane Massonneau,[▽] and Julie Manley[▼]

Org. Process Res. Dev. 2011, 15, 900–911

[†]GlaxoSmithKline, Sustainability and Environment, 5 Moore Drive, Research Triangle Park, North Carolina, United States
[‡]DSM Pharmaceutical Products, St.-Peter -Strasse 25, 4021 Linz, Austria
[§]DSM Innovative Synthesis B.V., P.O. Box 18, 6160 MD Geleen, The Netherlands
[⊥]Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, Connecticut 06877-0368, United States
[∥]Pfizer Inc., Chemical Research and Development, Pfizer, Groton, Connecticut 06340, United States
[¶]AstraZeneca, Essential Safety, Health and Environment, Alderley Park, Macclesfield, U.K.
[□]Eli Lilly and Co., Chemical Process Research and Development, Lilly Technology Center, Indianapolis, Indiana, United States
[■]GlaxoSmithKline, Sustainability and Environment, 1 Franklin Plaza, Philadelphia, Pennsylvania, United States
[○]GlaxoSmithKline, Research and Development, Upper Merion, Pennsylvania, United States
[●]DSM Biotechnology Center PO Box 425, 2600 AK Delft, The Netherlands
[△]Johnson & Johnson, EHS2 Compliance and Environmental Affairs, Global Pharma, 200 Tournament Drive, Horsham, Pennsylvania 19044, United States
[▲]AstraZeneca, Pharmaceutical Development, Bakewell Road, Loughborough, U.K.
[▽]Merck MSD Manufacturing, Z.I de Blavozy 43700 Saint Germain Laprade, France
[▼]ACS Green Chemistry Institute, 1155 Sixteenth Street, NW, Washington, DC 20036, United States



Izboljšan prenos toplote

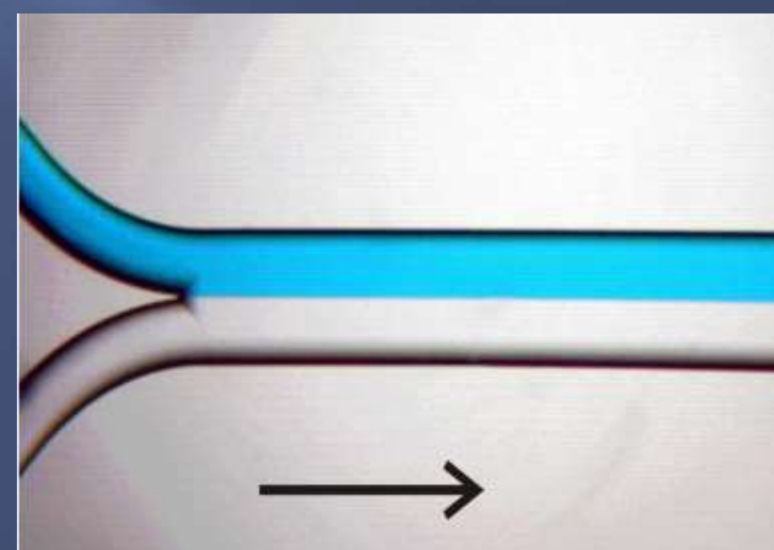
- *U do 25.000 W/m^{2}K*

Izboljšan prenos snovi

- *časi pomešanja v mikromešalnikih v milisekundah*

Kontrolirani hidrodinamski pogoji

- *večinoma laminarni tokovi*



Osnovne prednosti mikroreaktorjev in mikrostrukturiranih naprav

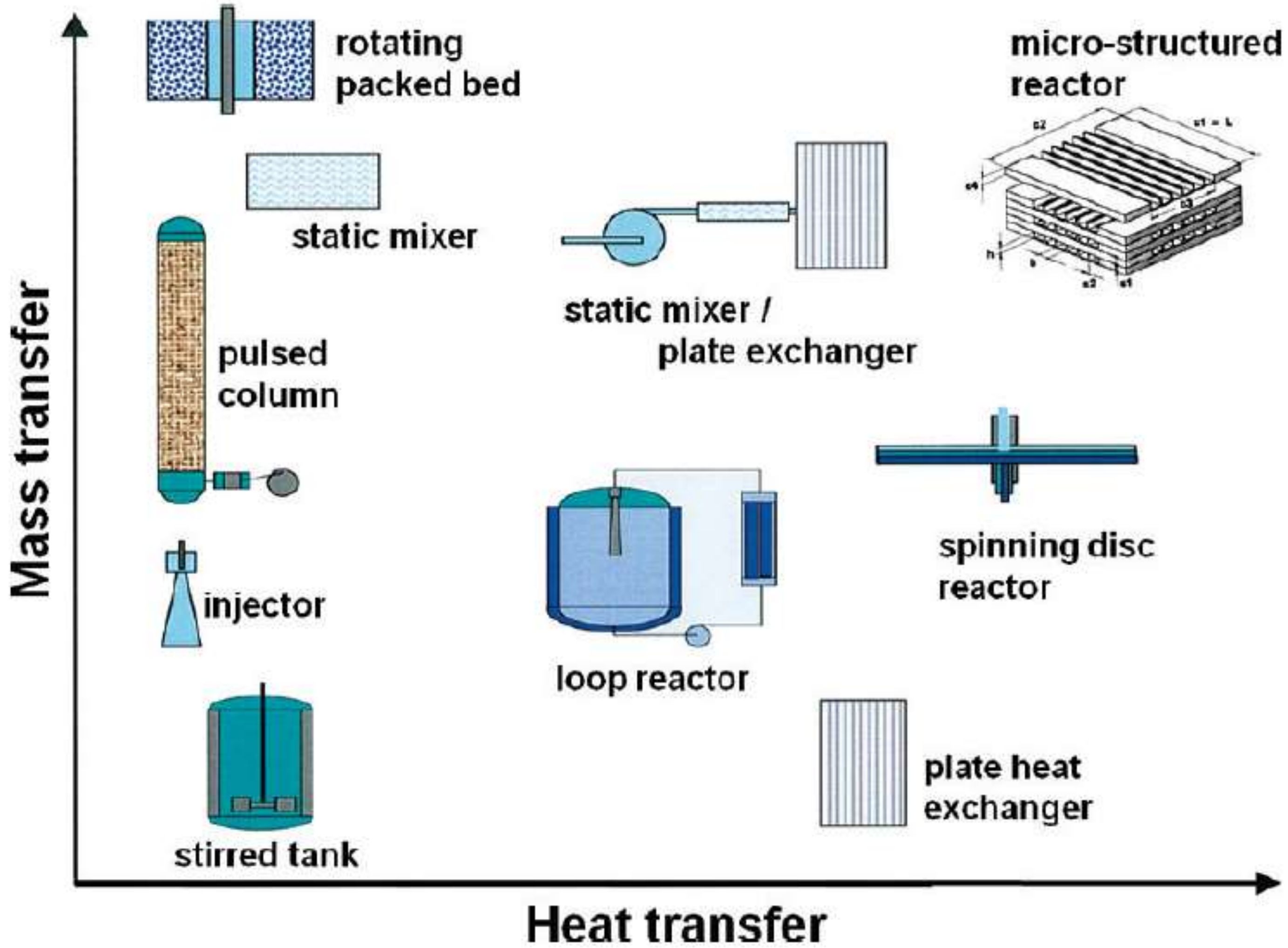


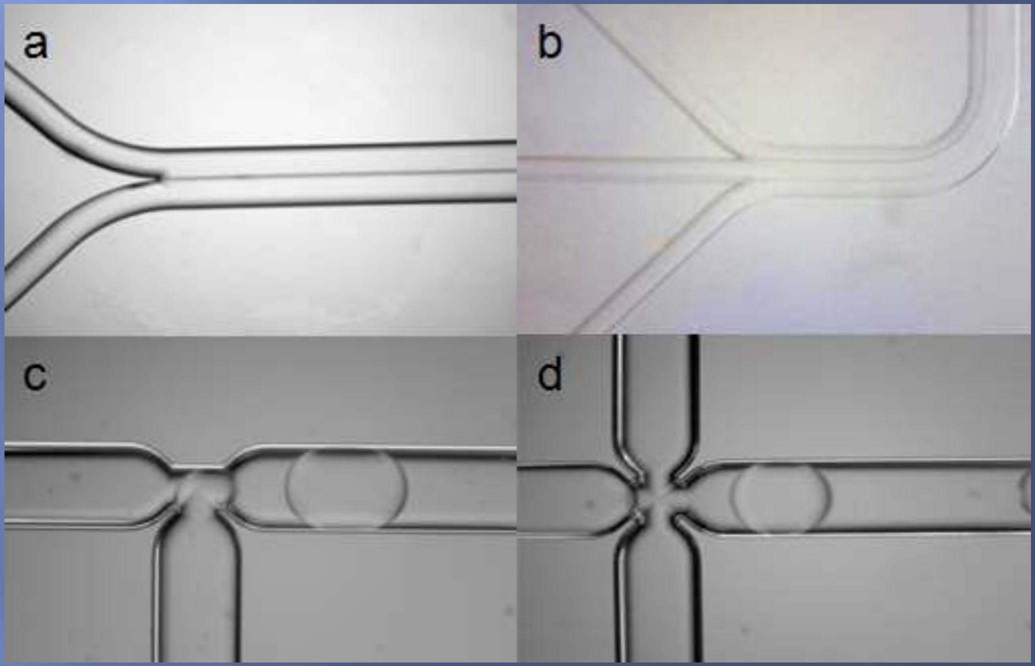
Figure 8. Benchmarking of microreactor. Adapted from the work of Jenck and Burille.[98]

Microstructured Reactors for Multiphase Reactions: State of the Art

Madhvanand N. Kashid and Lioubov Kiwi-Minsker*

Ind. Eng. Chem. Res. **2009**, *48*, 6465–6485

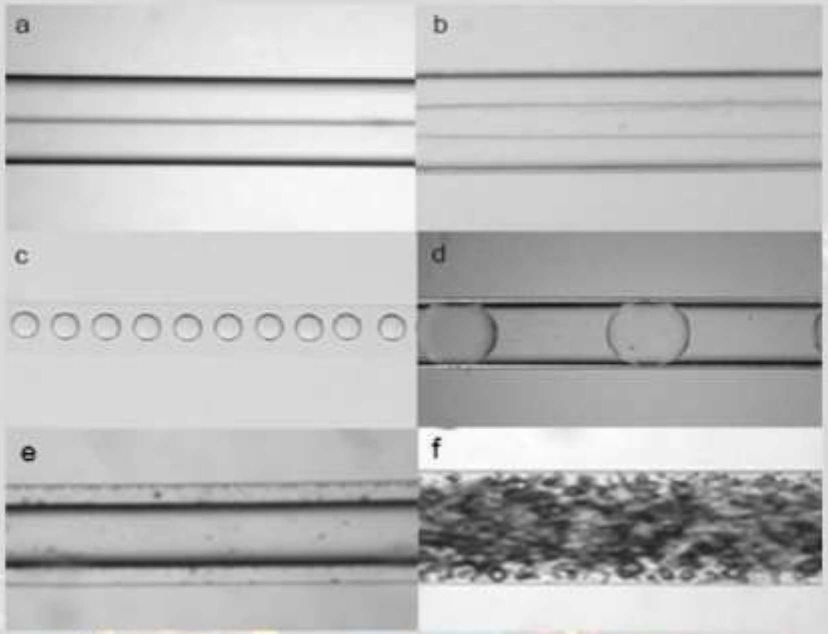
Tokovni režimi:
tok nemešljivih kapljevin



Različne geometrije kanalov vodijo v različne tokovne režime večfaznih sistemov.

Poleg tega pomembne še: sestava faz, površinska napetost, omočljivost in hrapavost površin, razmerje pretokov faz,...

Tokovni režimi: tok nemešljivih kapljevin



by Polona Žnidaršič-Plazl

f

Fig. 3. Typical flow regimes of multiphase flow within microchannels: a) parallel flow of two immiscible fluids; b) immiscible fluids in three parallel flows with two interfaces; c) droplet flow; d) Taylor flow; e) annular flow and f) dispersed flow.

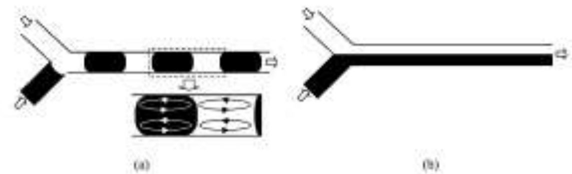


Figure 4. Stable flow patterns that can be achieved in the liquid–liquid flow capillary microreactor: (a) slug flow, (b) stratified (parallel) flow.

bursting of fluid from one channel to the other at a higher pressure drop in the case of countercurrent flow limits their applications.

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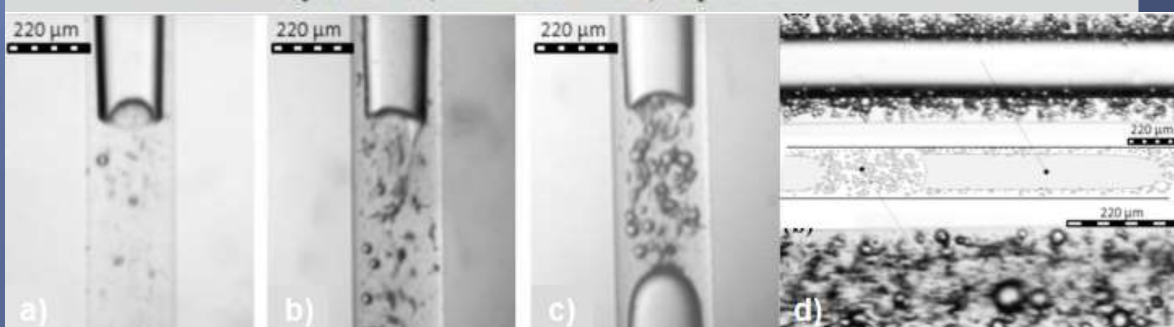
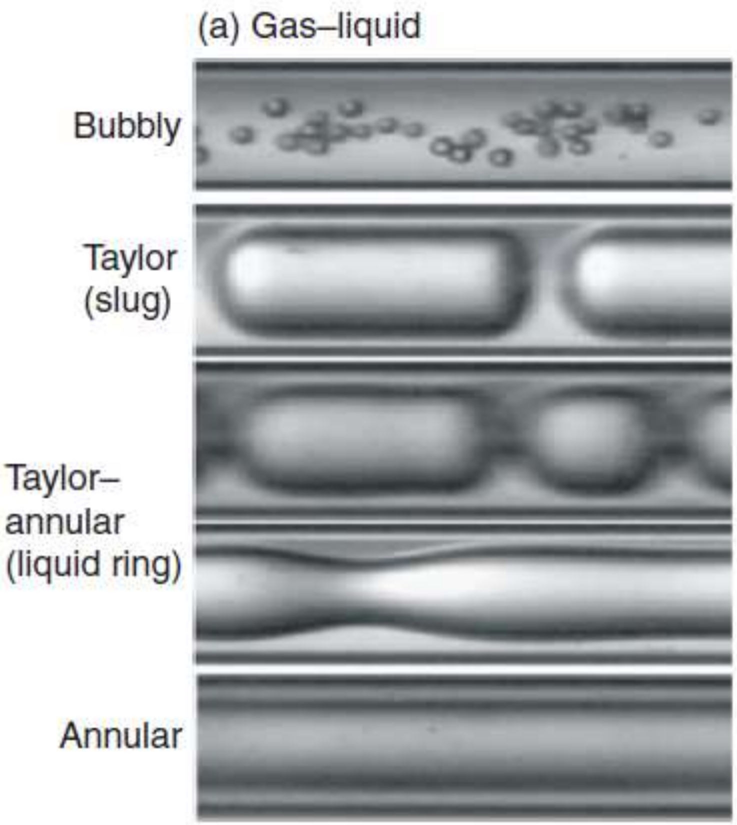


Tokovni režimi: plin/kapljevina



Serizawa A, Feng Z and Kawara Z (2002)
Experimental Thermal and Fluid Science, 26: 703-714.

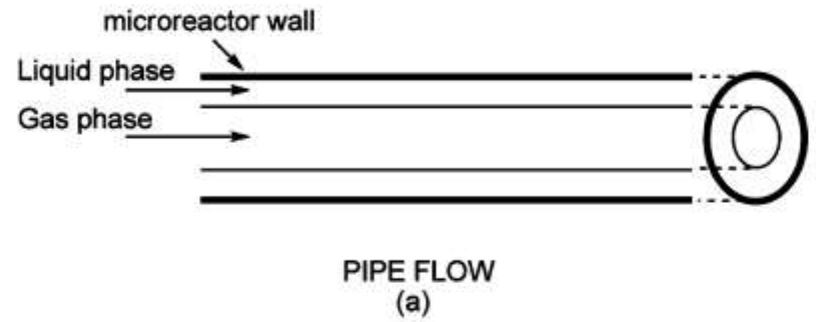


Figure 7. Pipe flow diagram.[71]

Microstructured Reactors for Multiphase Reactions: State of the Art

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Multiphase microfluidics: from flow characteristics to chemical and materials synthesis

Axel Günther†[a] and Klavs F. Jensen[b]
Lab Chip, 2006, **6**, 1487–1503 | 1487

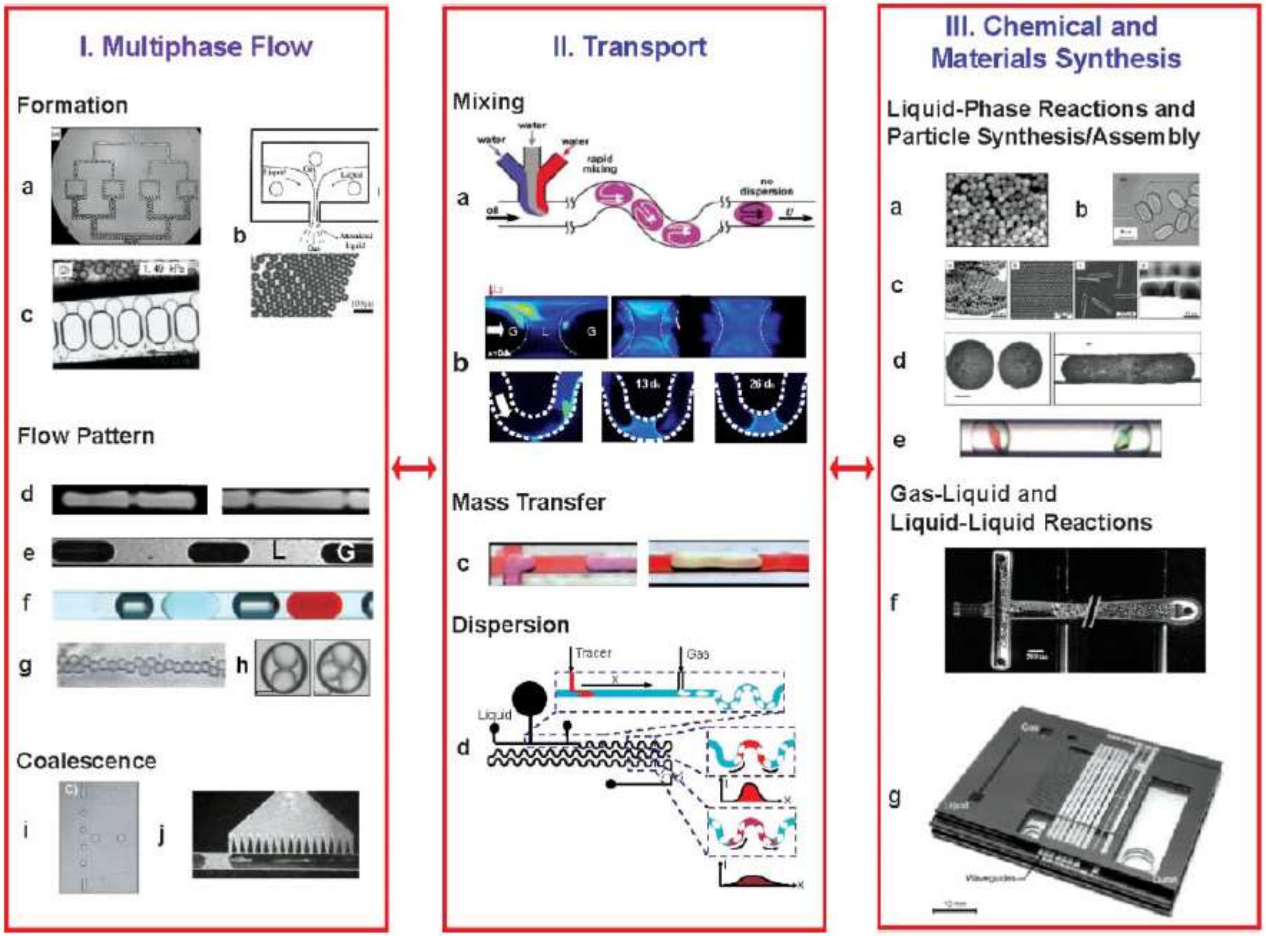


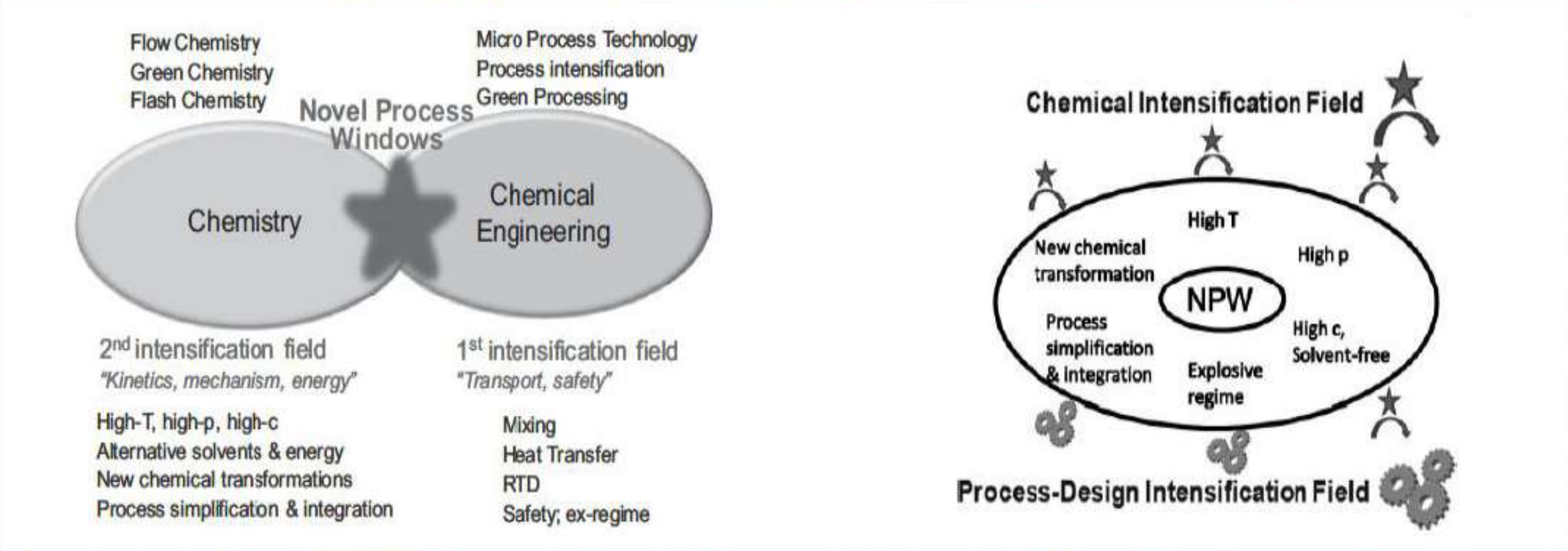
Fig. 1 Overview with representative studies of multiphase flow characteristics, I, in multiphase microfluidic networks, their relation to transport processes, II, and applications to chemical and materials synthesis, III. Studies include the formation of multiphase flow patterns by breakup into droplets, slugs and bubbles (I-a–c),[42–45] the characterization of liquid–liquid (I-d,g,h),[46,47] gas–liquid (I-e) and gas–liquid–liquid flows (I-f),[17] and merging multiphase flows by the action of capillary forces in combination with electrostatic (I-i)[48] or pressure fields (I-j). Multiphase transport processes relate to mixing enhancement in liquid–liquid (II-a)[15] and gas–liquid flows (II-b), liquid–liquid mass transfer enhancement (II-c)[28,49] and reduced axial dispersion in gas–liquid flows (II-d).[50,51] Crystallization, synthesis and assembly of nano- and microparticles (III-a–e)[32,36,37,52,53] have bee demonstrated along with multiphase reactions (III-f,g).[21,27] (Image (II-c) is the mirror image of the original so that all flows are from left to right.)

Intenzifikacija procesov

1. The transport intensification field → given by the miniaturization of flow dimensions.

2. The chemical intensification field → refers to using highly intensified and typically harsh process conditions.

3. The process design intensification field (besides the transport and chemical intensification).

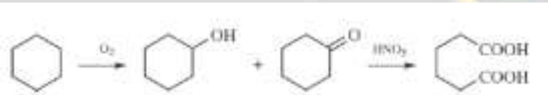


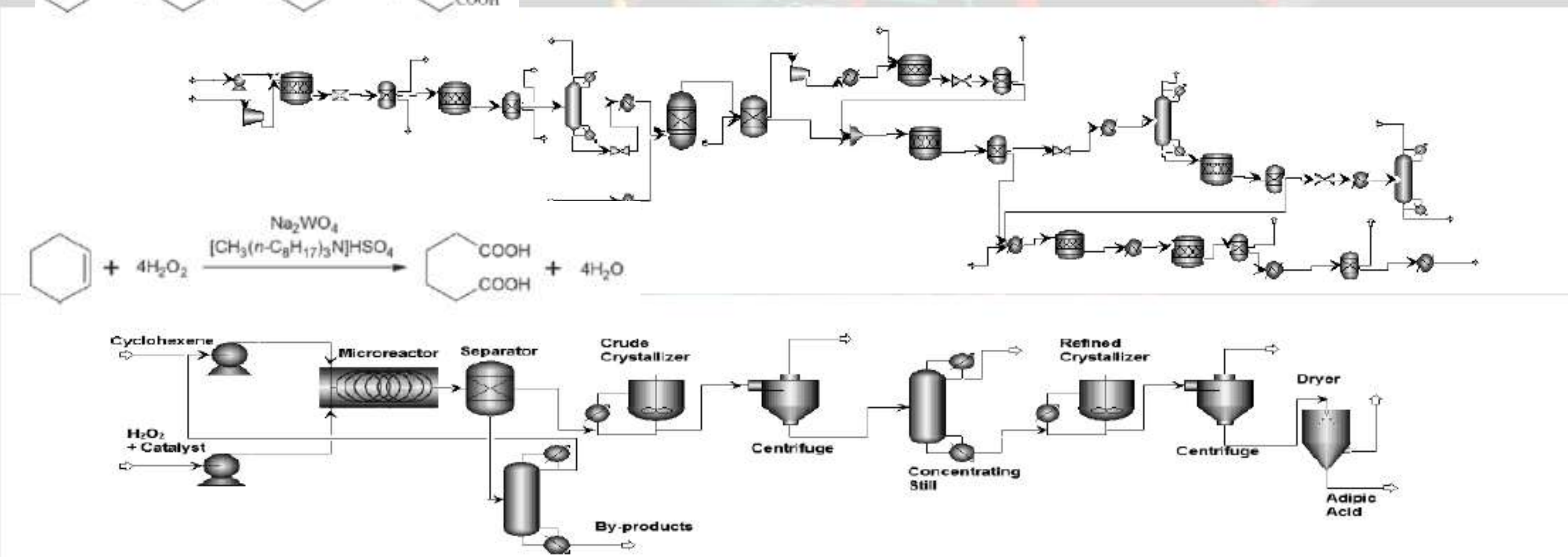
Hessel, et al., Potential Analysis of Smart Flow Processing and Micro Process Technology for Fastening Process Development: Use of Chemistry and Process Design as Intensification Fields (2012), 1184-1204.

3. The process design intensification field

- In this field we differ the following effects:

- Effect of reaction to simplify processes → this effect is very new in literature;
  → one example: production of adipic acid where the proces was simplified by applying of a microreactor.





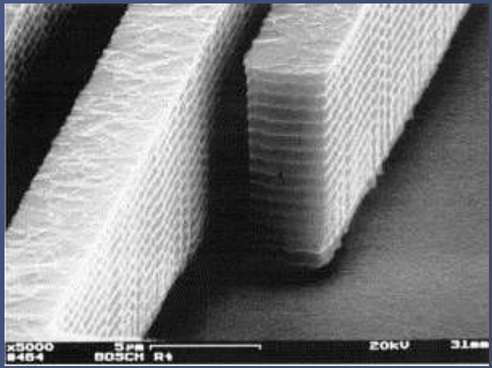
Hessel, et al., Potential Analysis of Smart Flow Processing and Micro Process Technology for Fastening Process Development: Use of Chemistry and Process Design as Intensification Fields (2012), 1184-1204.

Fig. 4. Commercial vs. simplified process of adipic acid production.

Osnovne prednosti mikroreaktorjev in mikrostrukturiranih naprav

Prednosti v uporabi

- Hitrejši prenos rezultatov raziskav v proizvodnjo
- Hitrejši začetek proizvodnje pri nižjih stroških
- Enostavnejši prenos v večje merilo
- Okolju prijazna proizvodnja



Prednosti v obratovanju

- Kontinuirno obratovanje
- Boljši nadzor
- Večja fleksibilnost
- Varnost

Področja uporabe mikroreaktorjev in mikrostrukturiranih naprav

Razvoj procesov – organska sinteza:

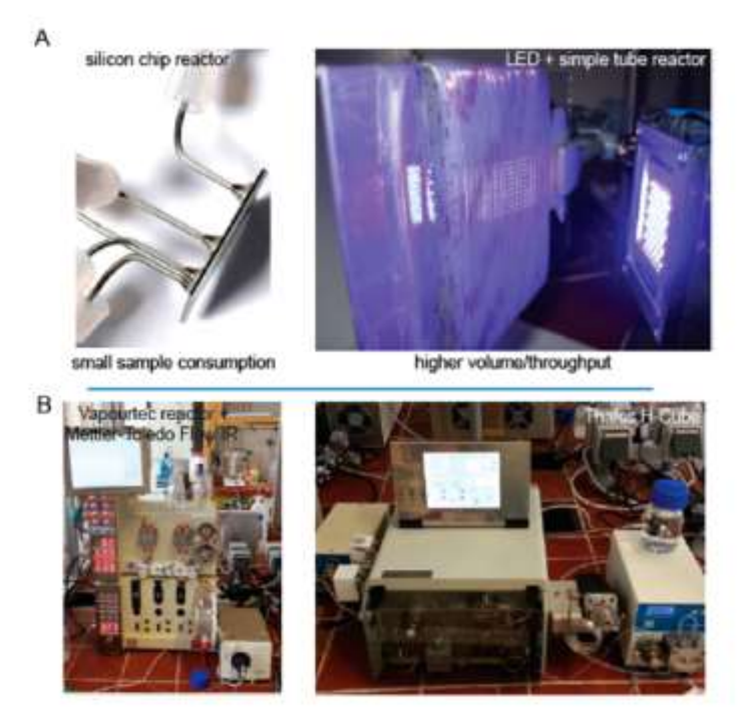


Figure 1. Flow reactors used in our groups: (A) reactor modules from simple tubing to silicon chips; (B) turn-key systems.

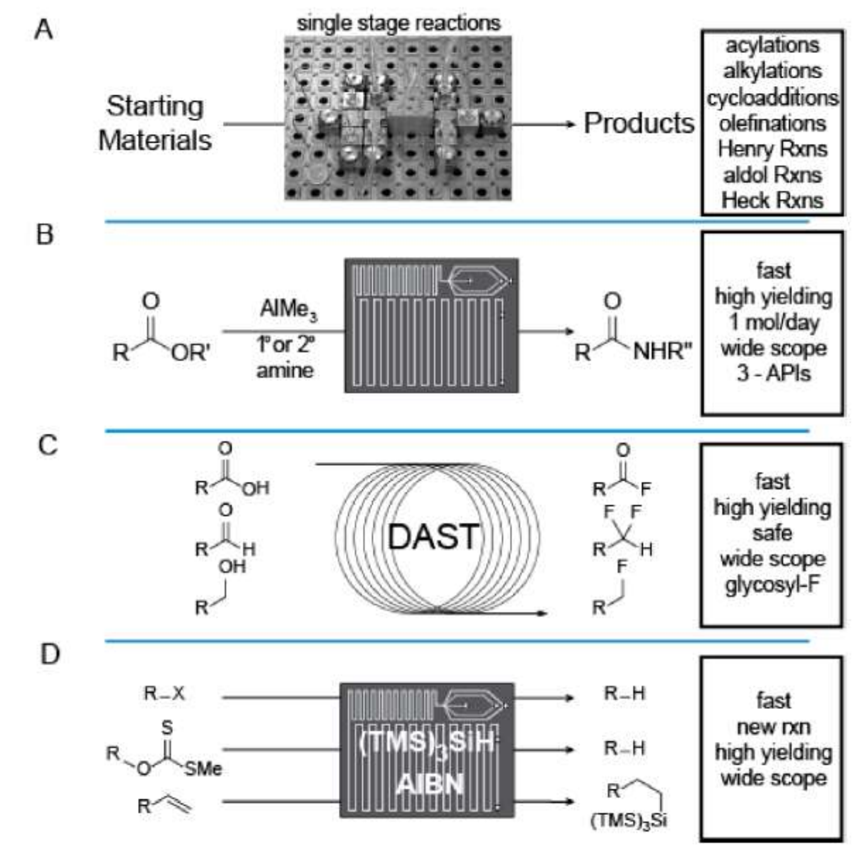


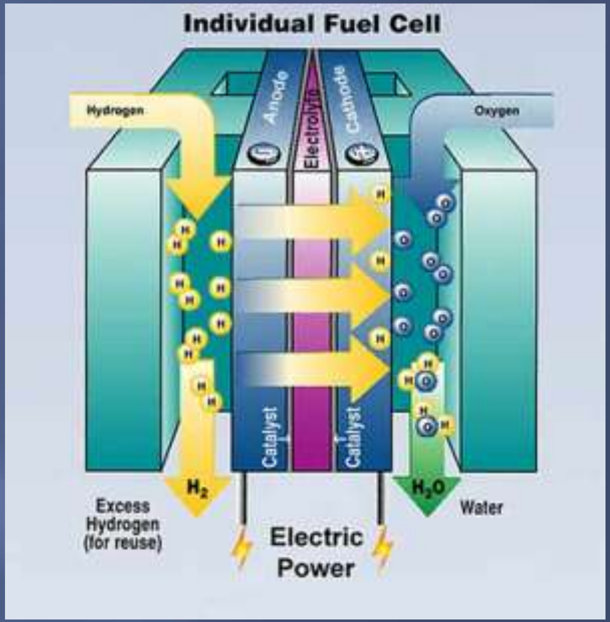
Figure 2. Early single-stage reactions performed in flow: (A) demonstration that a wide range of reactions could be run in flow; (B) safe amide formation using trimethylaluminum; (C) safe, continuous use of DAST; (D) reductions and hydrosilylations using tris(trimethylsilyl)silane.

D.T. McQuade, P.H. Seeberger: J Org. Chem., 78, 6384-6389 (2013).

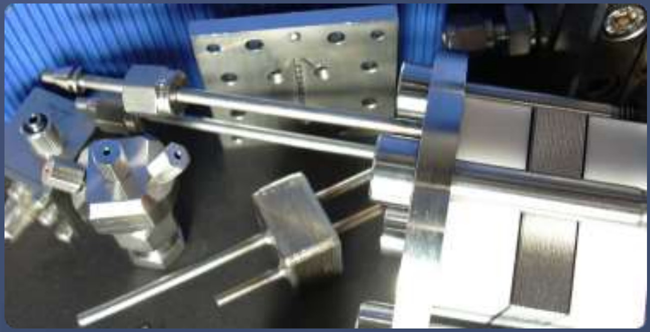
Področja uporabe mikroreaktorjev in mikrostrukturiranih naprav

Področja uporabe mikroreaktorjev in mikrostrukturiranih naprav

- Novi viri energije
  - Gorivne celice
  - Proizvodnja biodizla



- Avtomobilska industrija
  - Katalitski pretvorniki
  - Pretvorniki saj v dizelskih motorjih
  - Klimatske naprave
  - ...

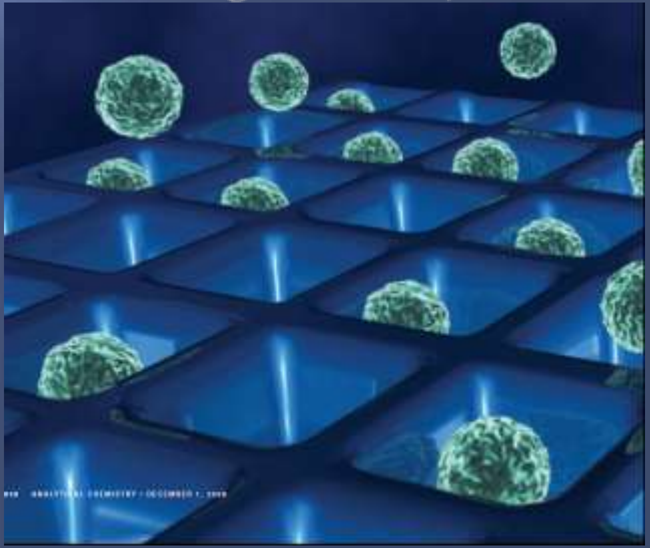


- Varovanje okolja
  - *In-situ* uničevanje onesnaženja
  - Distribuirana proizvodnja kemikalij
  - Čiščenje vode, pitna voda iz morja
  - ...
  - Integrirana proizvodnja – manj odpadnih produktov

Področja uporabe mikroreaktorjev in mikrostrukturiranih naprav

- Medicina
  - Hemodializa
  - Sinteza zdravil/dostava
  - Osebna diagnostika
  - ...

- Biologija, molekularna biologija
  - Omogočen študij posameznih celic (proteomika, genomika)
  - Visokozmogljivostni presejalni testi
  - Miniaturiziran PCR
  - ...



- Analitika biomolekul
  - Analiza nukleinskih kislin, proteinov...
  - µTAS

Multiphase flow microfluidics for the production of single or multiple emulsions for drug delivery ☆

Chun-Xia Zhao *

Advanced Drug Delivery Reviews xxx (2013) xxx–xxx

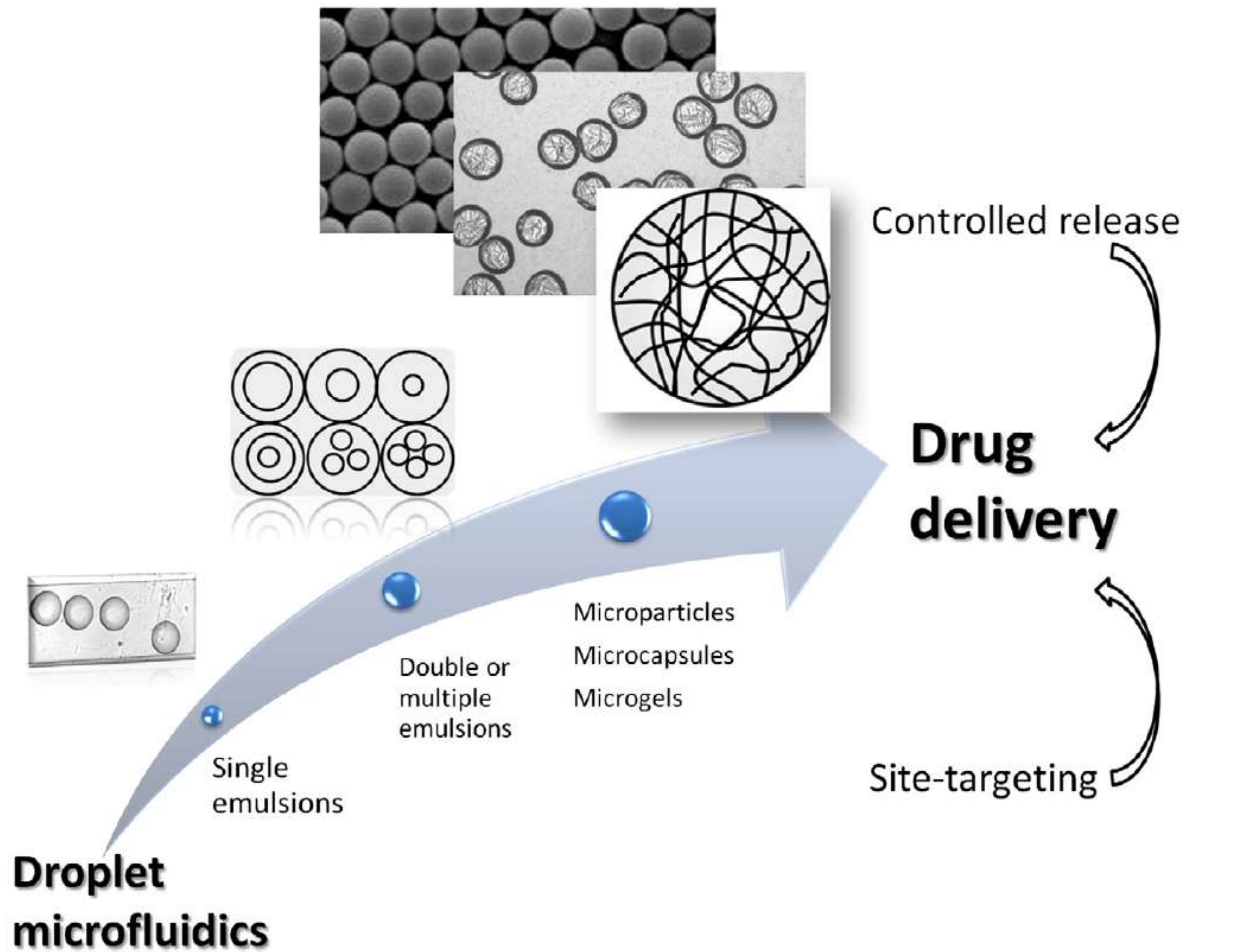


Fig. 1. Multiphase flows for the production of single and double emulsions, and micromaterials (microparticles, microcapsules and microgels) for drug delivery.

MICROFLUIDIC DEVICES FOR DIALYSIS

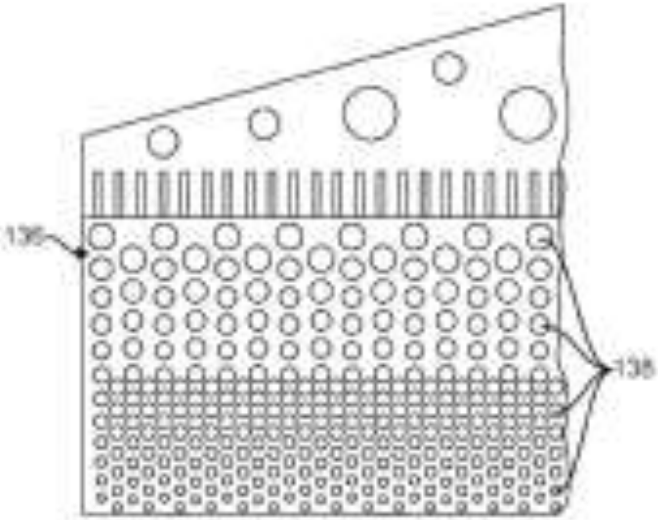


FIG. 8

(12) **United States Patent**
Browning et al.

(10) **Patent No.: US 8,419,945 B2**
(45) **Date of Patent: Apr. 16, 2013**

(54) **MECS DIALYZER METHOD**

(75) Inventors: **David M. Browning**, Portland, OR (US); **James R. Curtis**, Portland, OR (US); **Goran Nadezda Jovanovic**, Corvallis, OR (US); **Brian Kevin Paul**, Corvallis, OR (US); **Sundar Atre**, Corvallis, OR (US)

(73) Assignees: **State of Oregon acting by and through the State Board of Higher Education on behalf of Oregon State University**, Corvalis, OR (US); **Home Dialysis Plus**, Portland, OR (US)

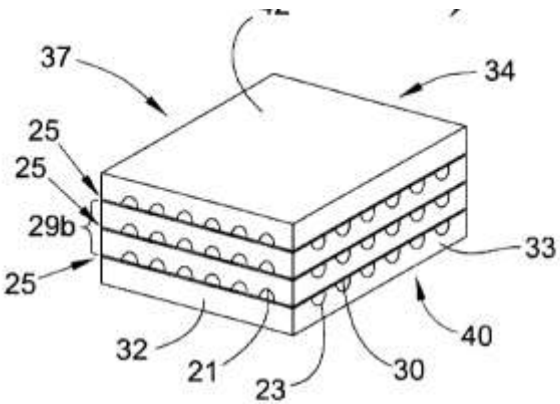


FIG. 3

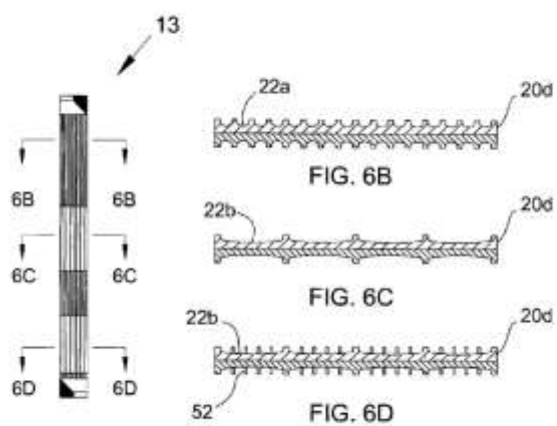


FIG. 6A

FIG. 6B

FIG. 6C

FIG. 6D

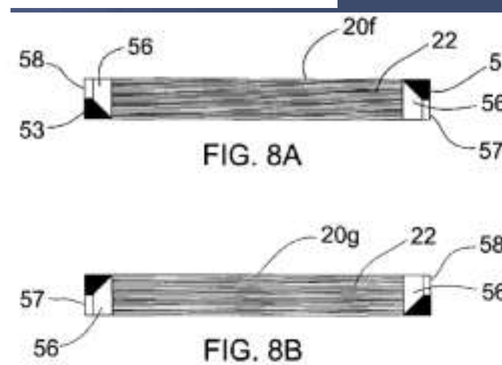
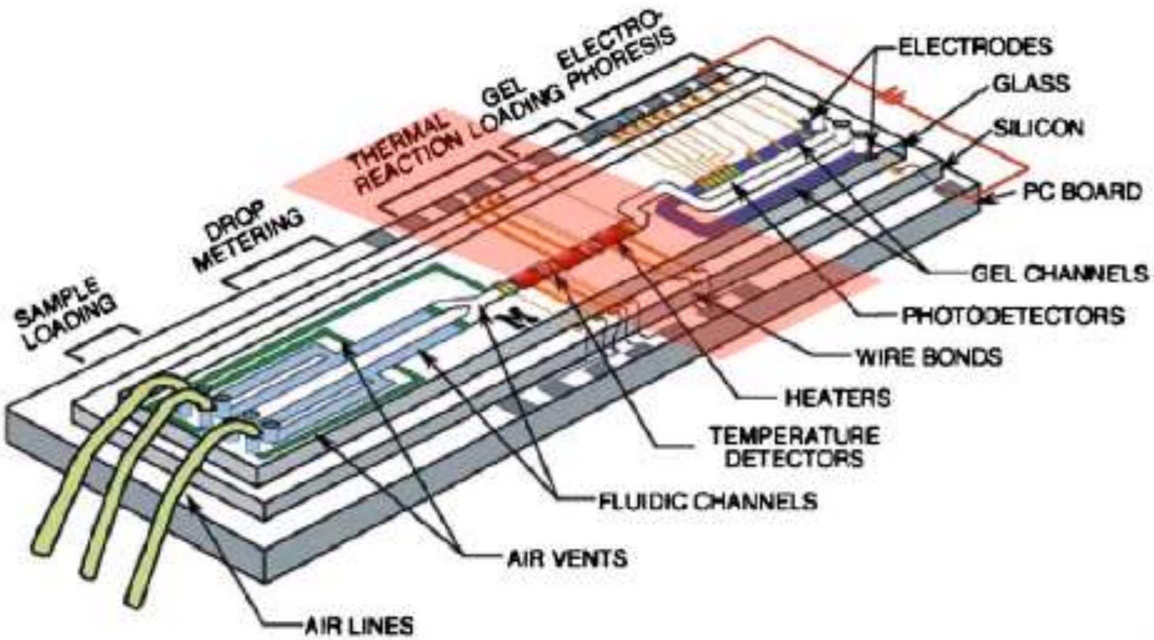


FIG. 8A

FIG. 8B

Example: DNA analysis

- Complete DNA amplification and analysis system on a chip (~1 nL sample volume)

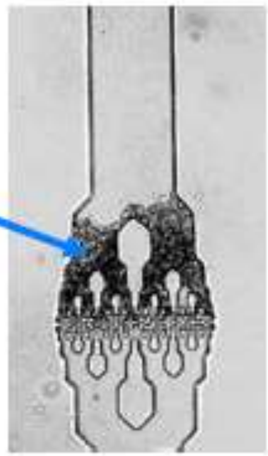


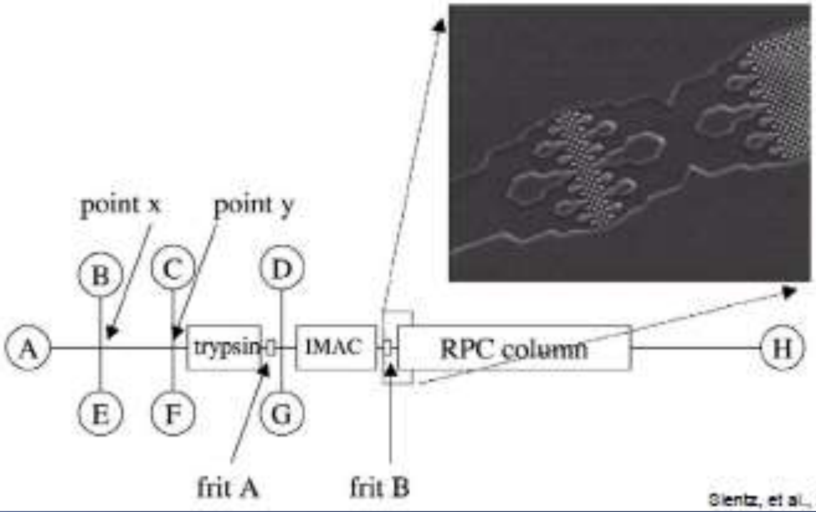
Burns, et al., Science (1998), 282, 484-487

Example: Proteomics analysis

- Complete proteomics analysis on a chip
  - Protease fragment digestion, histidine-specific separation, and capillary electrophoresis for lab-on-chip protein analysis
  - Trypsin and IDA (His-binding) immobilized on 5µm silica, loaded into channels on microreactor

Silica beads

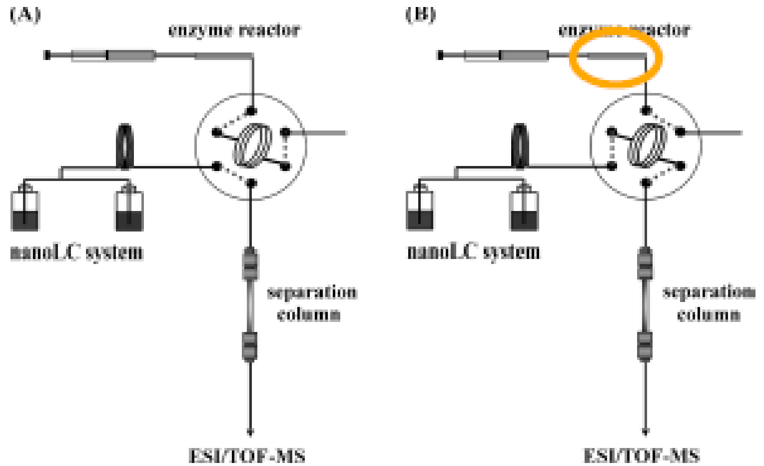




Slentz, et al., 2003, J. Chrom. A, 984, 97–107

Example: Proteomics analysis

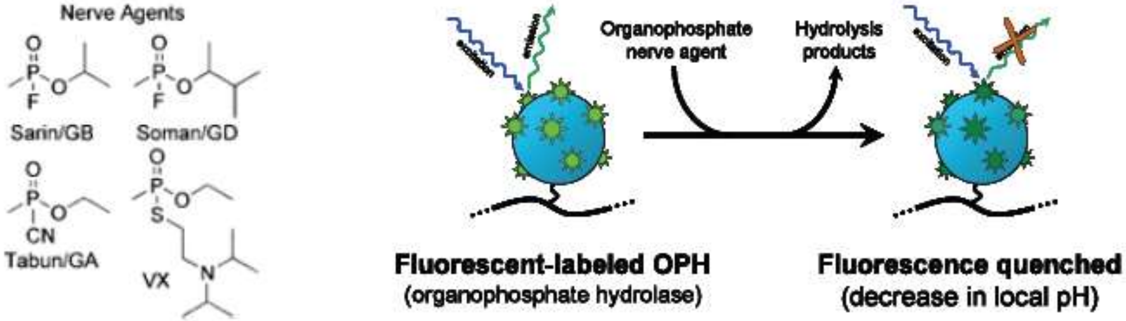
- Trypsin digestion in a pre-column capillary with porous polymer monolith
  - 95% trypsin digestion of IgG antibodies in 6 min
  - Compare 12 hr for 95% digestion in batch reaction



Krenkova, et al., 2009, Anal. Chem., 81 (5), 2004-2012

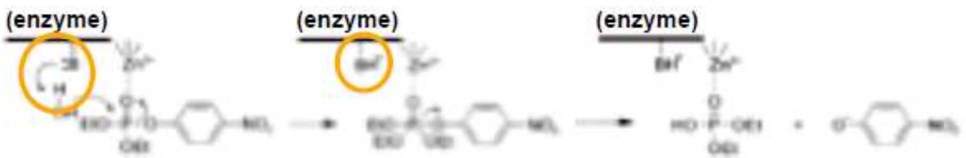
Example: Biowarfare sensor

- Detection of organophosphate chemical weapons by organophosphate hydrolase
  - Enzymatic hydrolysis of OP nerve agent (left)
  - Local pH change quenches FITC fluorescence



Burnworth, et al., Chem. Eur. J. (2007), 13, 7828-7836

- Local pH-change mechanism of sensing

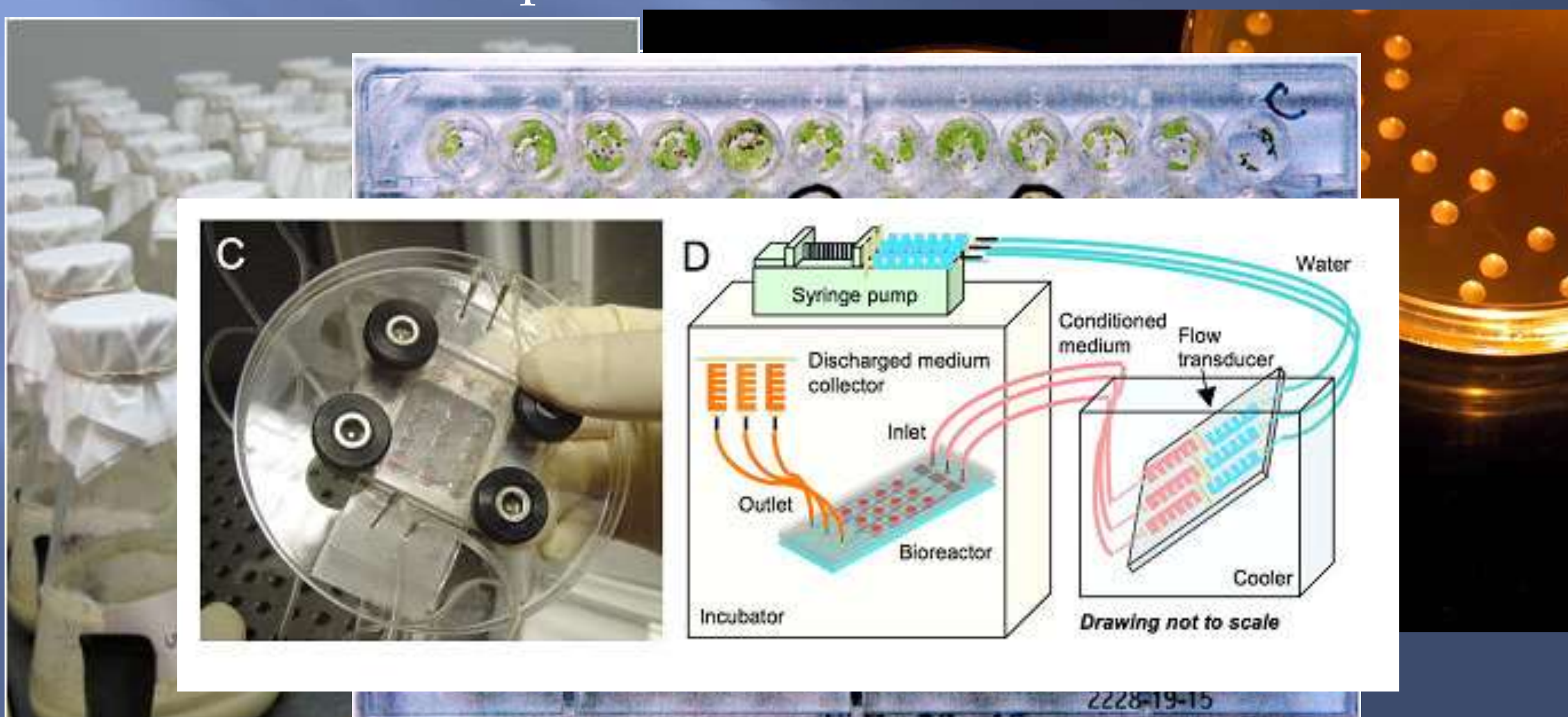


- Immobilization improves sensitivity
  - Ultra-thin monolayer reduces diffusion time and partitioning effects in enzyme layer
  - Detection of paraoxon (VX analog) demonstrated at nM levels (~3 ppb) when immobilized on quartz

Burnworth, et al., Chem. Eur. J. (2007), 13, 7828-7836

Miniaturizacija bioreaktorske tehnike

- Laboratorijsko merilo – razvoj procesov
  - erlenmajerice in petrijevke od konca 19. stoletja
  - mikrotitrske plošče od 1980



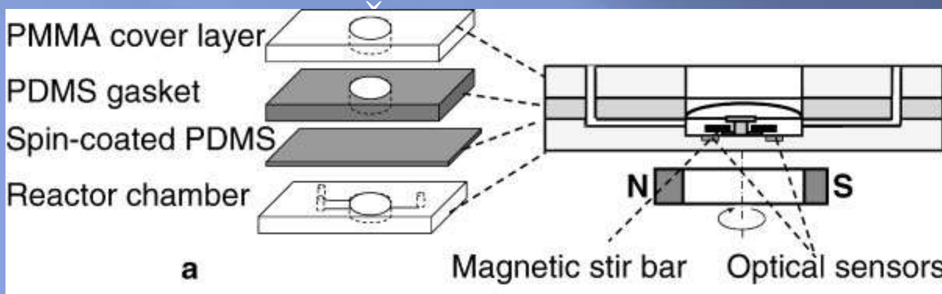
Miniaturizacija bioreaktorske tehnike

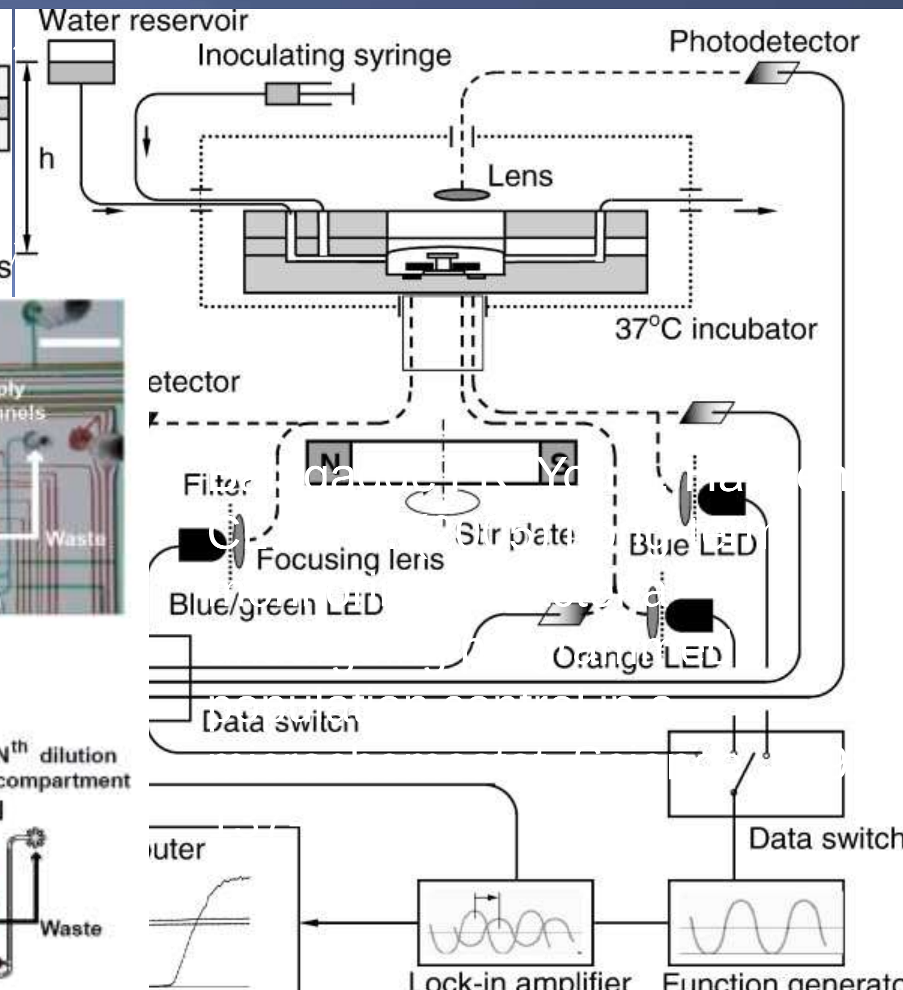
Mikrotitrske plošče – iz kombinatorne kemije

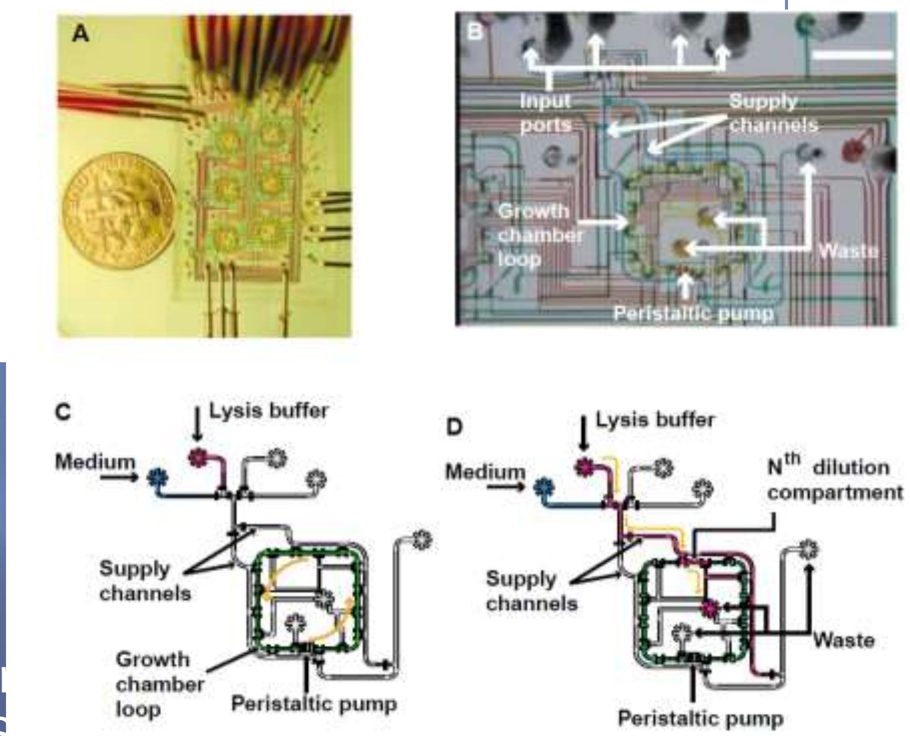
- zelo hitra izvedba bistveno večjega števila vzporednih poskusov ob manjši porabi kemikalij
- avtomatizirano neodvisno spremljanje in kontrola posameznih miniaturiziranih reaktorjev (vdolbinic)
  - optične meritve biomase
  - pH
  - pO_2
  - fluorescenca

Miniaturizacija bioreaktorske tehnike

Mikrobioreaktorji za gojenje celic





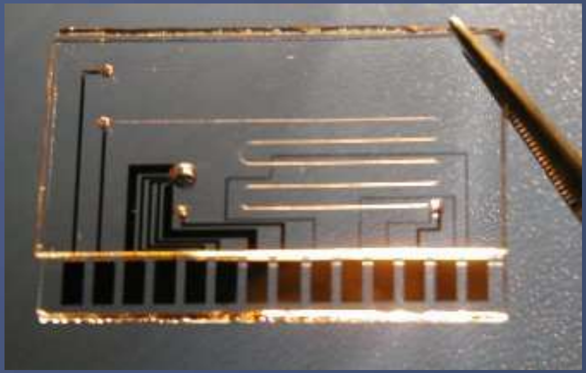


Z. Zha

A. J. Sinskey, K. F. Jensen, *Biotechnol. Bioeng.*, 2006, 93, 286-296

Encimski mikroreaktorji

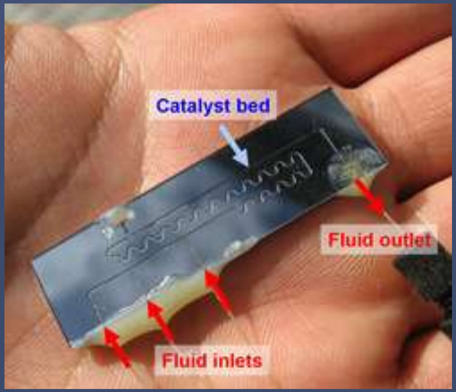
- **Analiza kemijskih spojin**
  - analiza proteinov
  - analiza nukleinskih kislin



Lab-on-a-Chip iz stekla in polimera za pomnoževanje DNA

- **Študij kinetike encimskih reakcij**
  - aktivnost in stabilnost encimov
  - presejalni testi novih biokatalizatorjev in njihovih substratov

- **Biotransformacije v mikroreaktorjih**
  - homogena in heterogena biokataliza

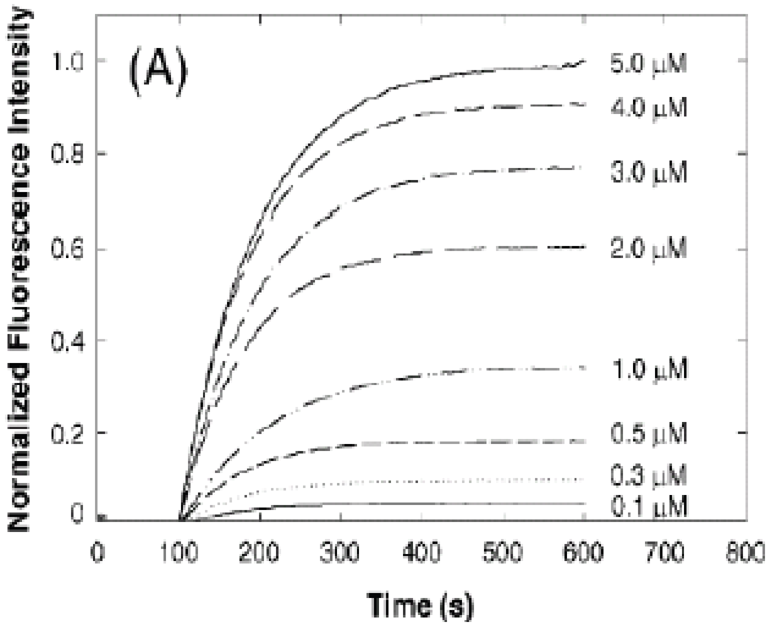


Example: Enzyme kinetics

- Experimental data successfully fitted to the Lilly-Hornby and Michaelis-Menten kinetic equations:

$$f[C_{Ao}] = \frac{C}{Q} + K_{M,app} \ln(1-f)$$

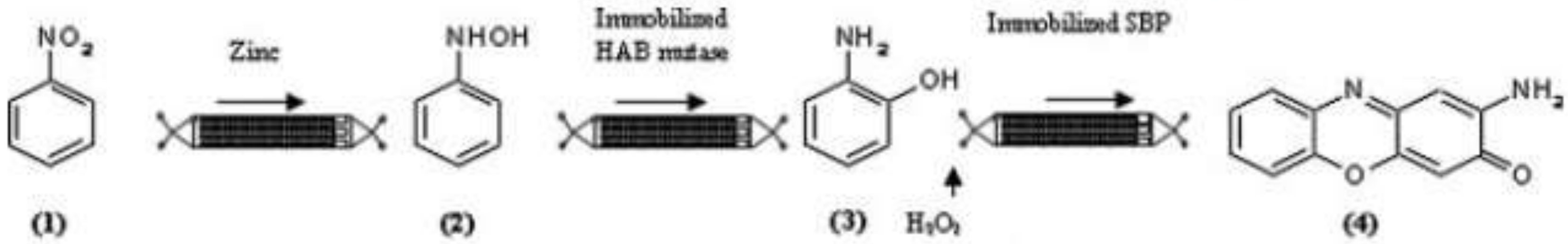
$$v = \frac{v_{\max}[S]}{K_m + [S]}$$



Seong, et al., Analytical Chemistry (2003), 75(13), 3161-3167

Example: Multi-step reactions

- Multi-step reactions handled by sequential microreactors with different catalysts



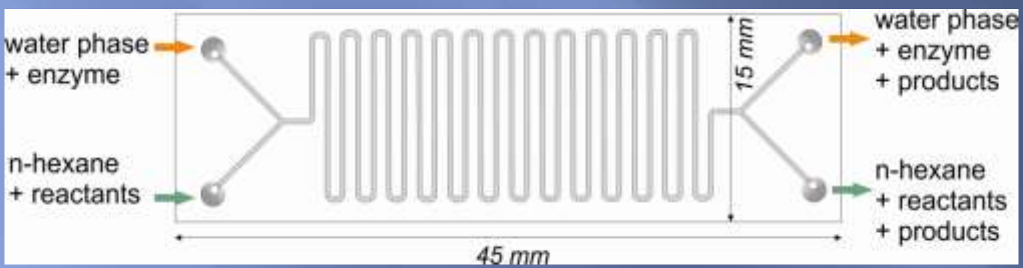
  - Metallic zinc and enzymes immobilized on silica microspheres by standard chemistries
  - Functionalized silica packed into microreactors (40mm long, 1500µm x 100µm channels)

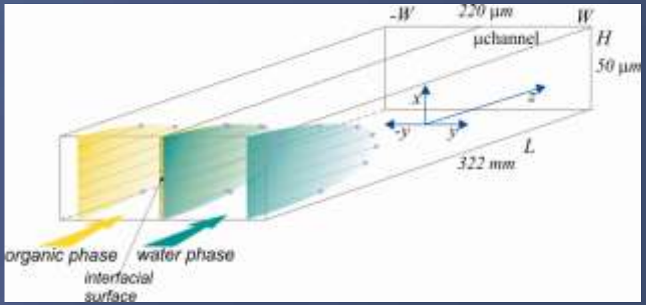
Luckarift, et al.,Biotechnol. Bioeng. (2007), 98(3), 701-705

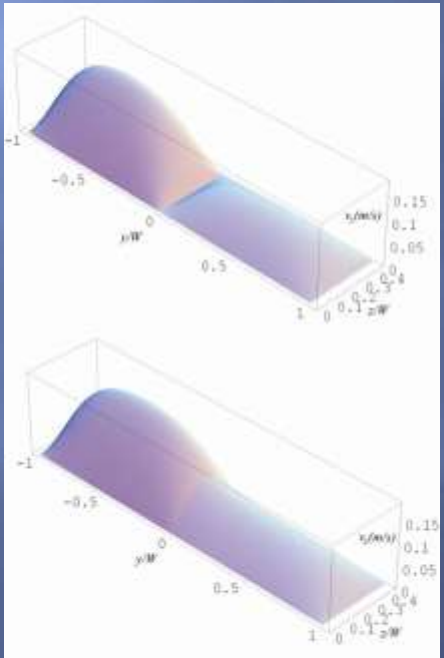
Naše raziskave z mikrofluidnimi napravami v biotehnologiji

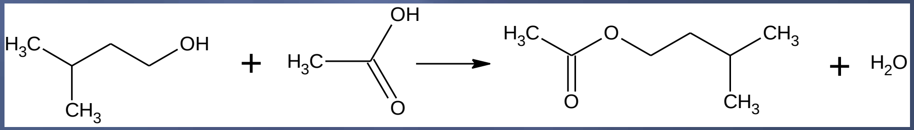
Biokatalitske reakcije v mikroreaktorjih
Ekstrakcije v mikrokanalih

Encimsko katalizirana sinteza izoamil acetata v mikroreaktorju: dvofazni sistem: voda/*n*-heksan



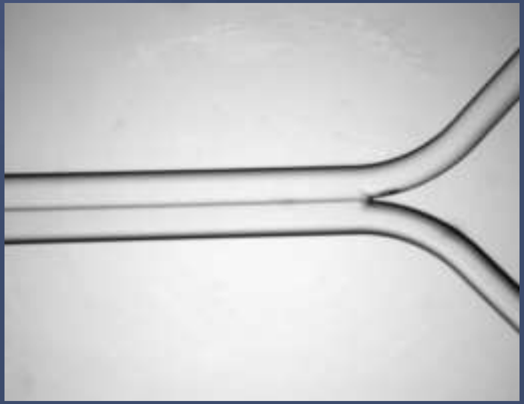




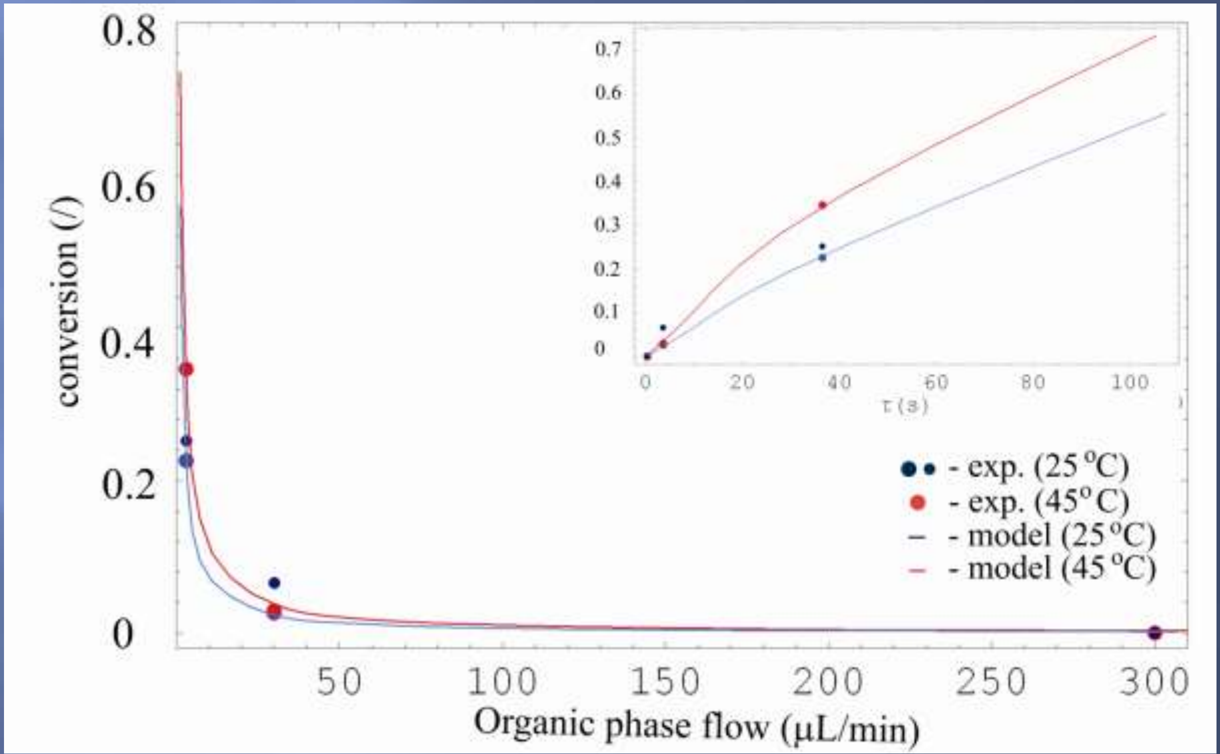


Reakcija med izoamil alkoholom in ocetno kislino v *n*-heksanu je bila katalizirana z lipazo *B* (CALB L), raztopljeno v vodni fazi

Slika na iztoku iz mikroreaktorja: pretok heksana je 30 µL/min in vode 10 µL/min.

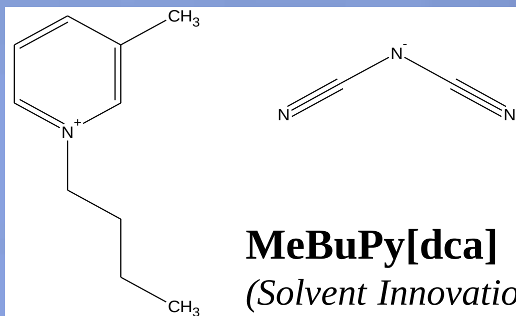


Encimsko katalizirana sinteza izoamil acetata v mikroreaktorju: dvofazni sistem: voda/*n*-heksan



Žnidaršič-Plazl P., Plazl I. *Process Biochem.*, 2009, 44: 1115-1121

Encimsko katalizirana sinteza izoamil acetata v mikroreaktorju: ionska kapljevina/*n*-heptan

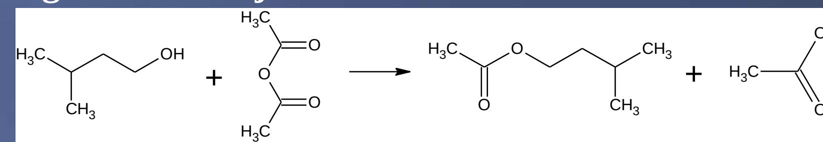


MeBuPy[dca]

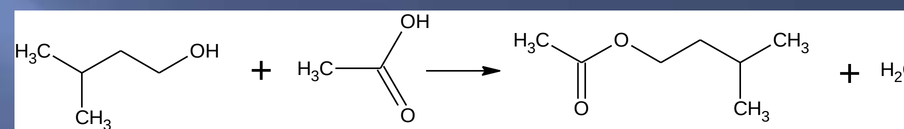
(Solvent Innovation GmbH)

mešljiv z vodo

glavna reakcija:



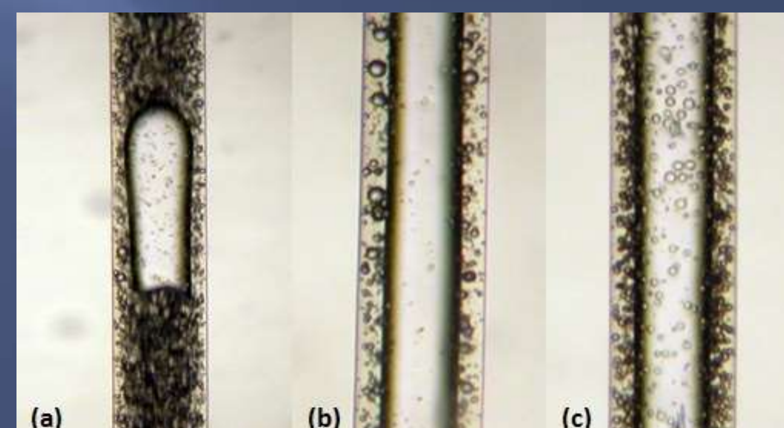
sekundarna reakcija:



heptan

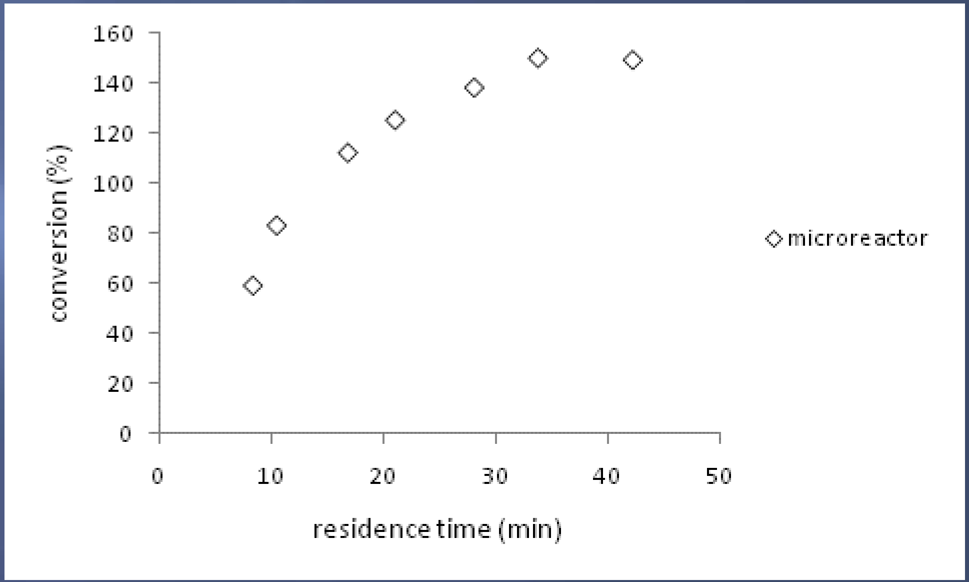
IL + lipaza B
+ anhidrid ocetne kisline

IL + lipaza B
+ izoamil alkohol



Pohar, A., Žnidaršič-Plazl P., Plazl I. *Lab Chip*, 2009, 9: 3385-3390

Encimsko katalizirana sinteza izoamil acetata v mikroreaktorju: dvofazni sistem ionska kapljevina/*n*-heptan

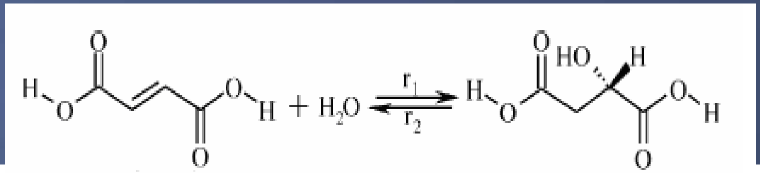


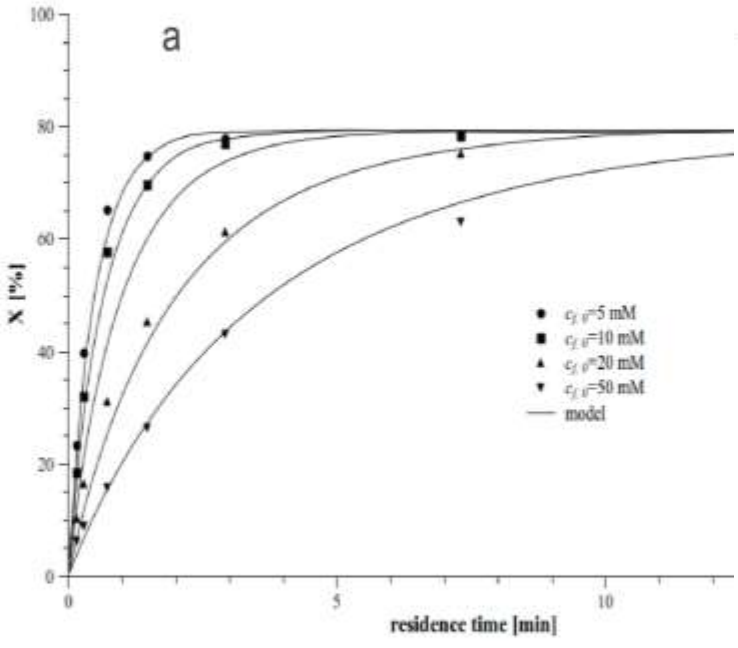
Reference	*Reaction time*	*Conversion*
Krishna et al.[23]	**72 h**	**96.4 %**
Krishna et al.[2]	**72 h**	**80 %**
Ghamgui et al.[7]	**8 h**	**64 %**
Langrand et al.[26]	**24 h**	**80 %**
Welsh et al.[25]	**48 h**	**75.8 %**
Razafindralambo et al.[24]	**24 h**	**80 %**
Romero et al.[1]	**2 h**	**192 %**
Macedo et al.[6]	**48 h**	**80 %**
This work – batch exp.	**95 min**	**149 %**
This work – microreactor	**33.8 min**	**150 %**

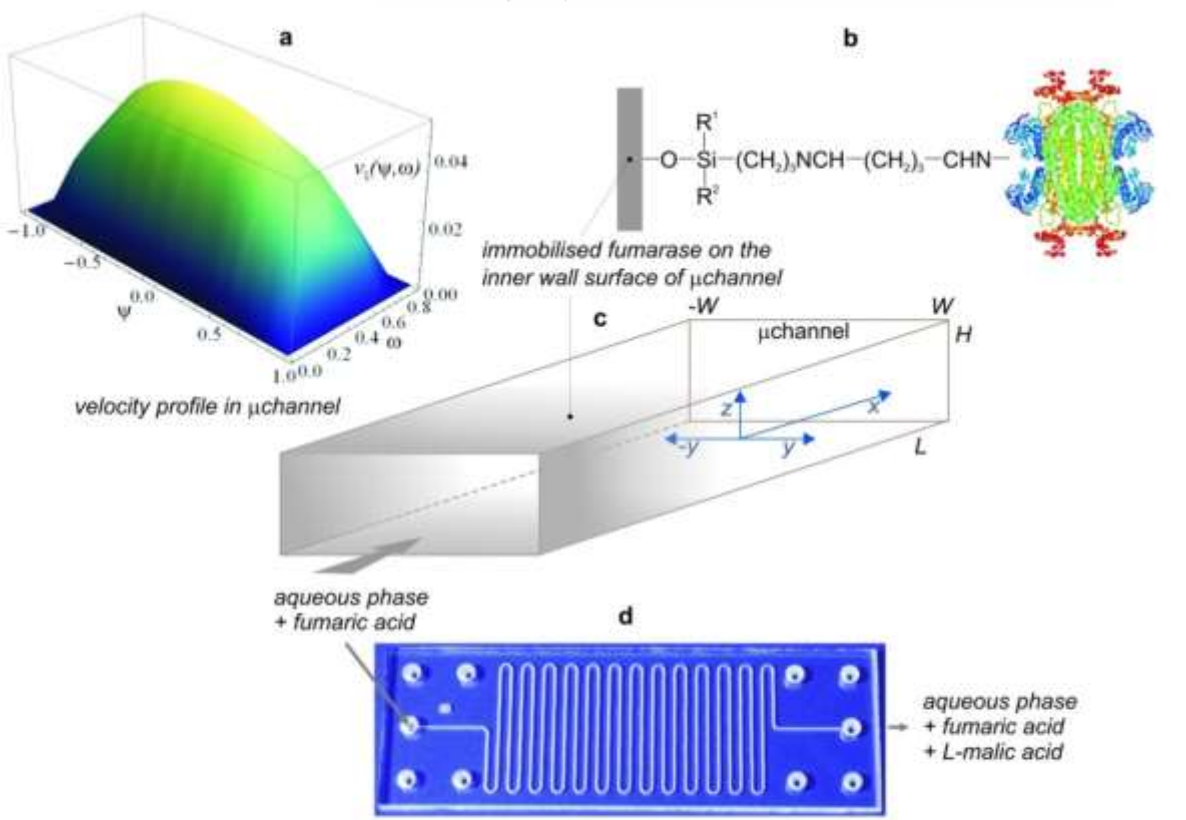
Pohar, A., Žnidaršič-Plazl P., Plazl I. *Lab Chip*, 2009, 9: 3385-3390

Kontinuirna proizvodnja L-jabolčne kisline v mikroreaktorju

z imobilizirano komercialno fumarazo

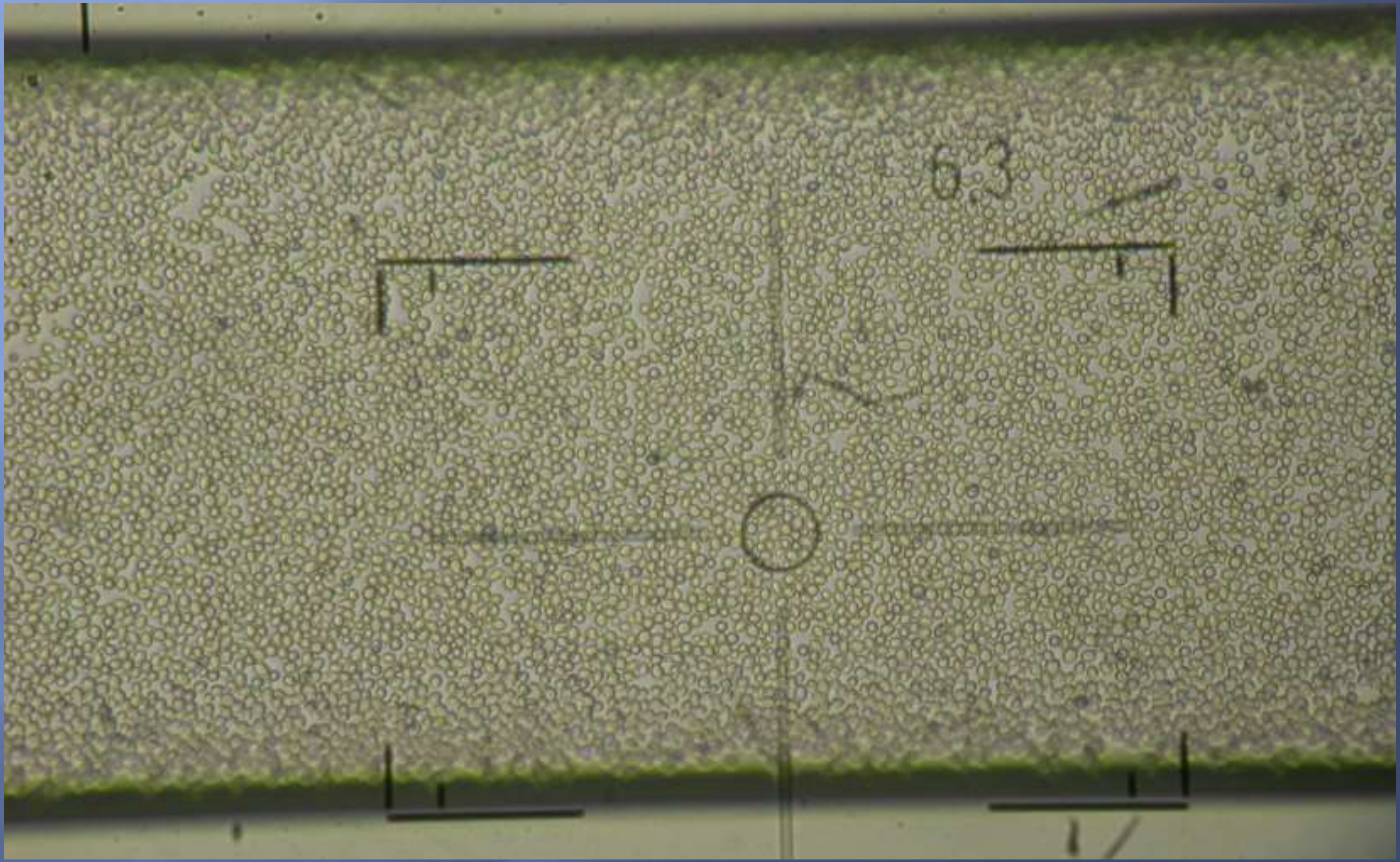






G. Stojkovič, I. Plazl, P. Žnidaršič Plazl. *Microfluid. Nanofluid.*, 2011, 10: 627-635

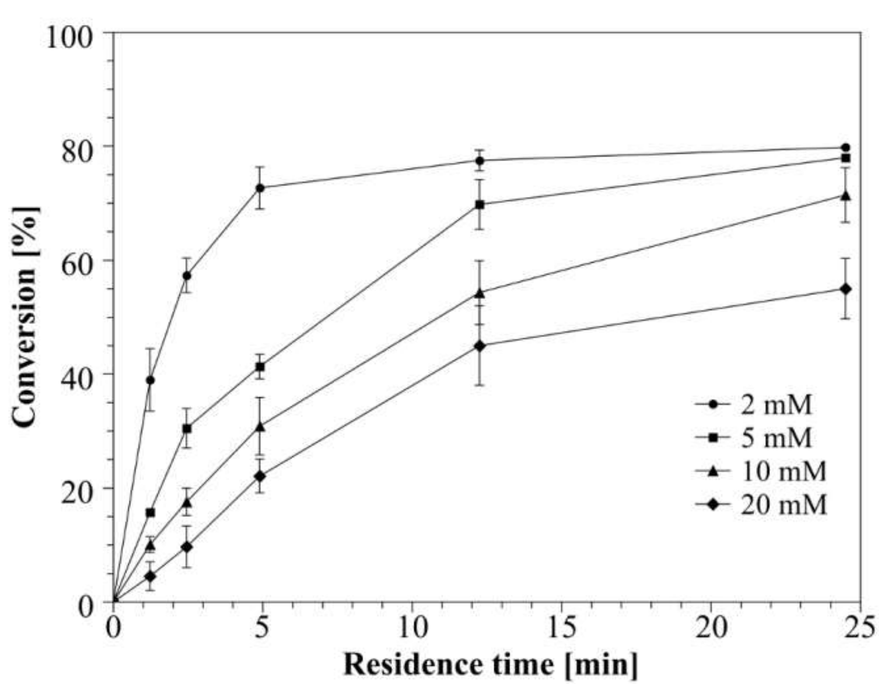
Imobilizacija kvasovk *Saccharomyces cerevisiae* v steklen mikroreaktor

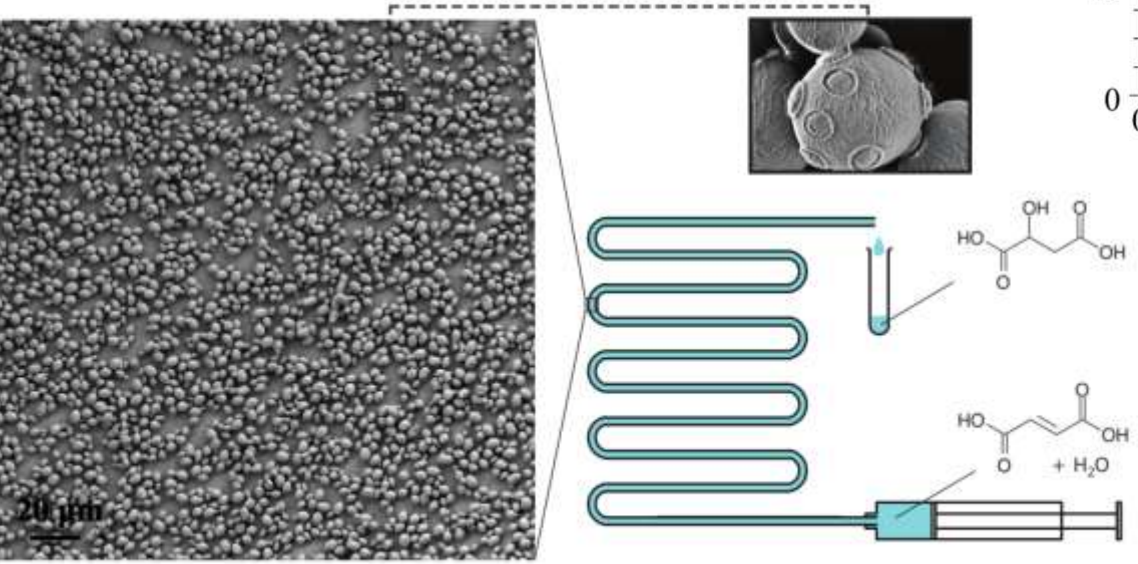


G. Stojkovič, P. Žnidaršič-Plazl, *Acta Chim. Slov.* 2010, 57:144–149

Kontinuirna proizvodnja L-jabolčne kisline v mikroreaktorju

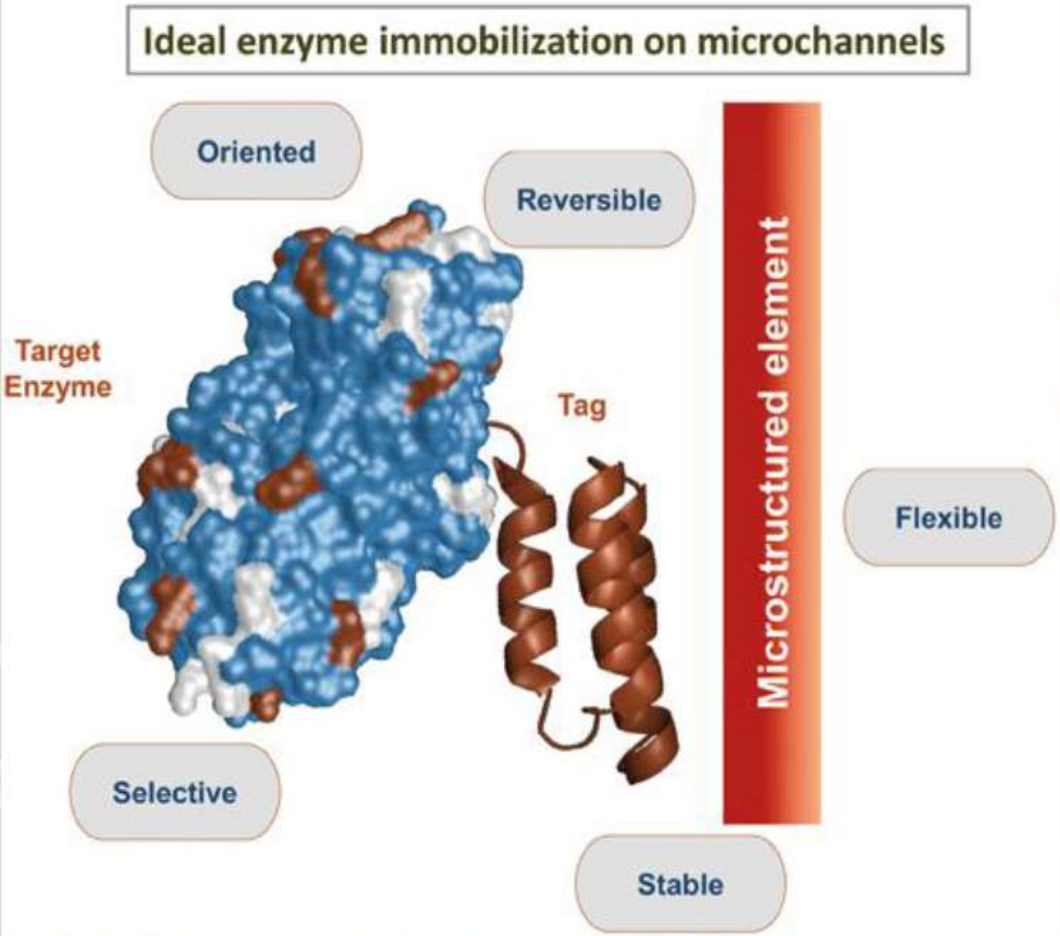
z imobiliziranimi in permeabiliziranimi celicami *Saccharomyces cerevisiae*





	Mikrobioreaktor	Laboratorijski membranski bioreaktor
Imobiliziran katalizator	*Saccharomyces cerevisiae* MZKI K86	*Saccharomyces cerevisiae* (Kvasac, d.o.o.)
Produktivnost biokatalizatorja [mmol/g_{ww} dan]	11.8	3.49
Volumetrična produktivnost [mM/dan]	646	174

Imobilizacija encimov na površino mikroreaktorjev

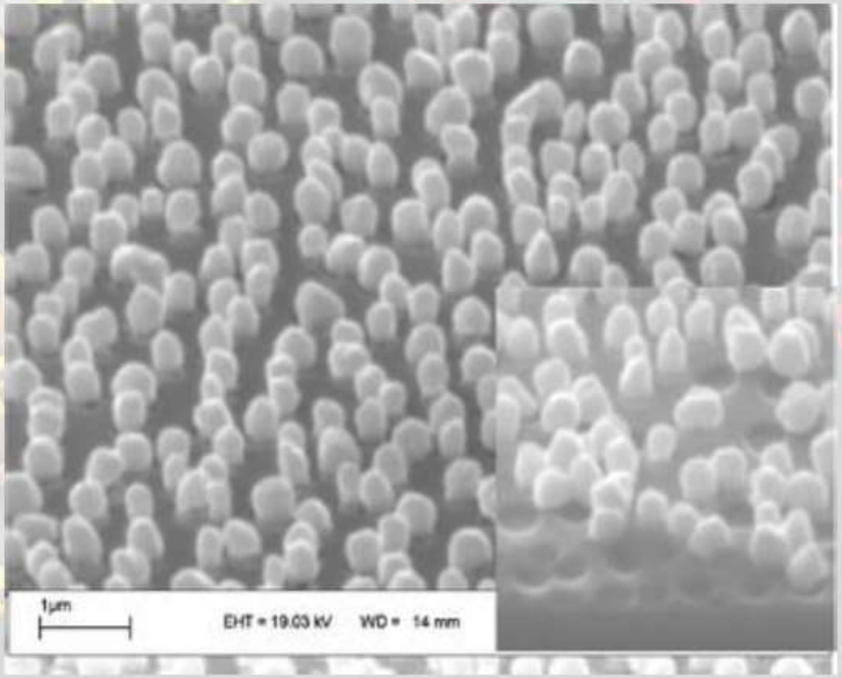


Nidetzky B, Smart enzyme immobilization in microstructured reactors (2013), 50-55.

Fig. 9. Ideal enzyme immobilization on microchannels.

Silicon dioxide pillars

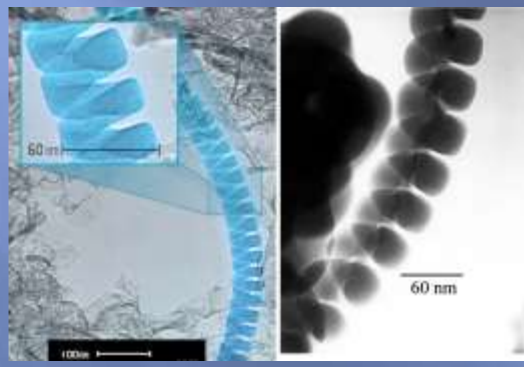
- Advantages:
  - effective for increasing the surface area;
  - have beneficial effects on flow (like a static mixer);
  - used to immobilize DNA; could be used for enzymes or other biomolecules as well.

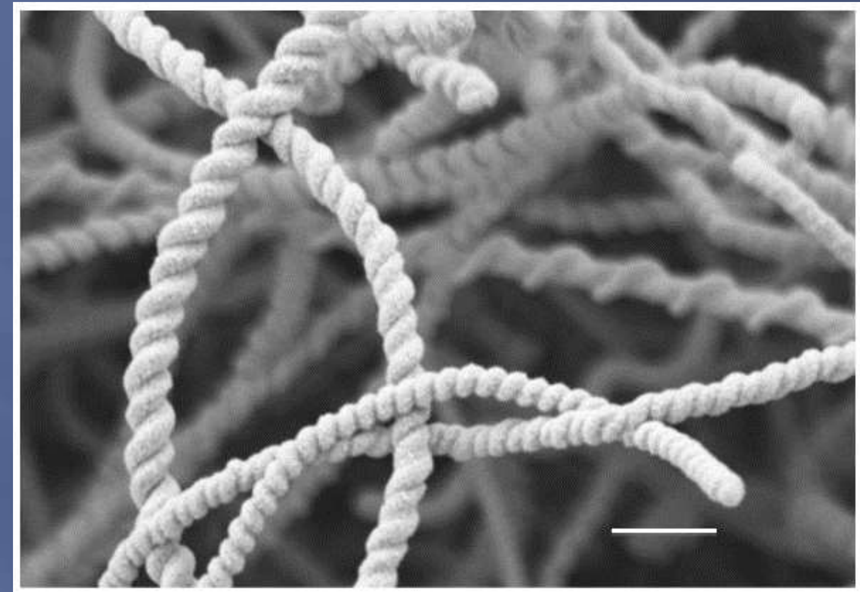


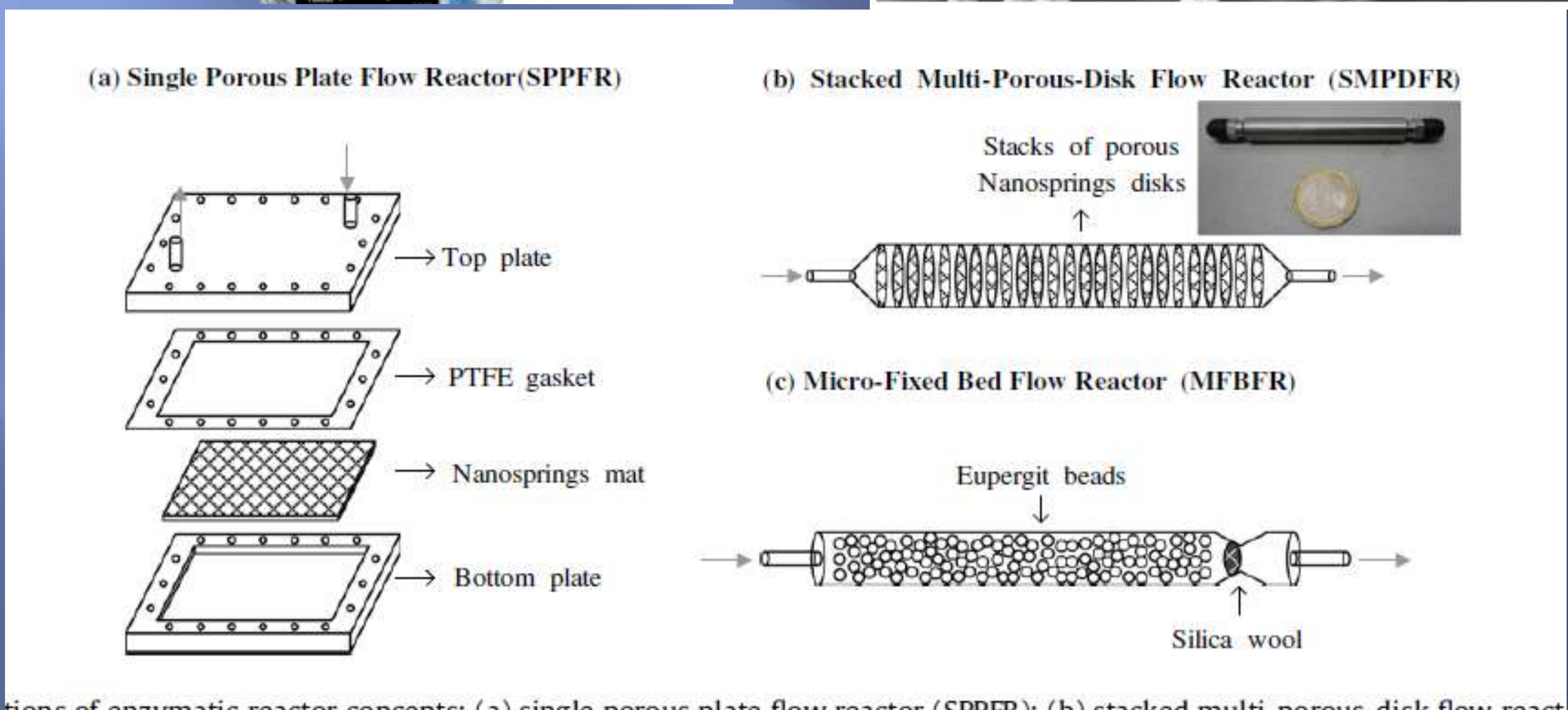
J. Mater. Chem., 2004,14, 1526-1532

Fig. 10. Silicon dioxide pillars.

Nanovzmeti


60 nm

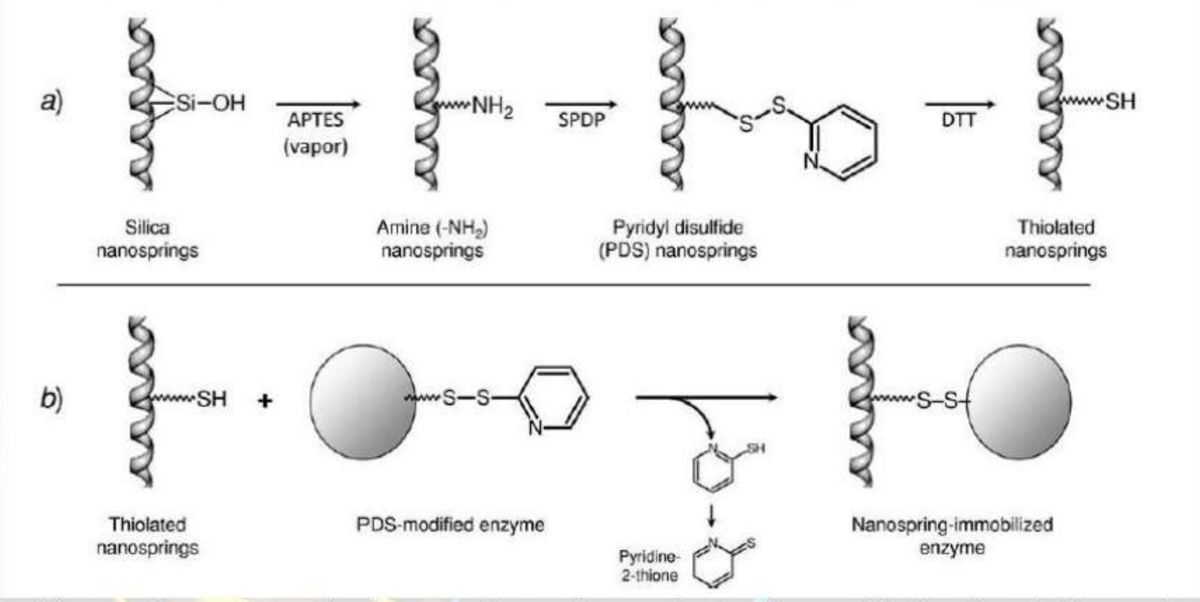



(a) Single Porous Plate Flow Reactor(SPPFR)
Top plate
PTFE gasket
Nanosprings mat
Bottom plate
(b) Stacked Multi-Porous-Disk Flow Reactor (SMPDFR)
Stacks of porous Nanosprings disks
(c) Micro-Fixed Bed Flow Reactor (MFBFR)
Eupergit beads
Silica wool
tions of enzymatic reactor concepts: (a) single porous plate flow reactor (SPPFR); (b) stacked multi-porous-disk flow react

Nanosprings supports

- Properties:

  - good supports for enzyme immobilization → increasing surface area;
  - nanosprings need to be activated by aminosilane treatment (salinization);
  - successfully applied for immobilization of *Aspergillus oryzae* β-galactosidase.

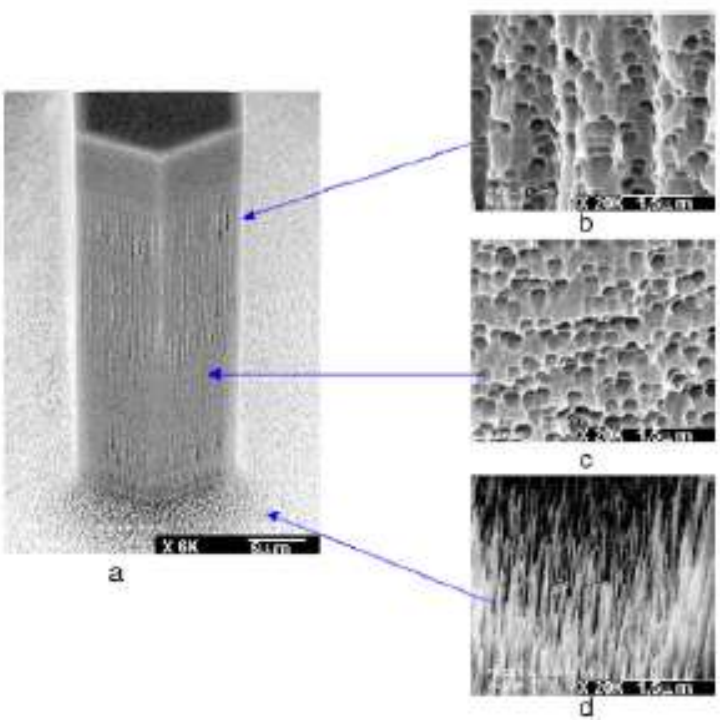


Schilke KF, et al., A Novel Enzymatic Microreactor with Aspergillus oryzae β-Galactosidase Immobilized on Silicon Dioxide Nanosprings (2010), 1597-1605.

Fig. 11. a) Activation of silicon dioxide nanosprings with thiol groups for enzyme immobilization; b) Immobilization of PDS-modified enzyme on nanosprings by covalent disulfide bonds.

Example: Nanostructures

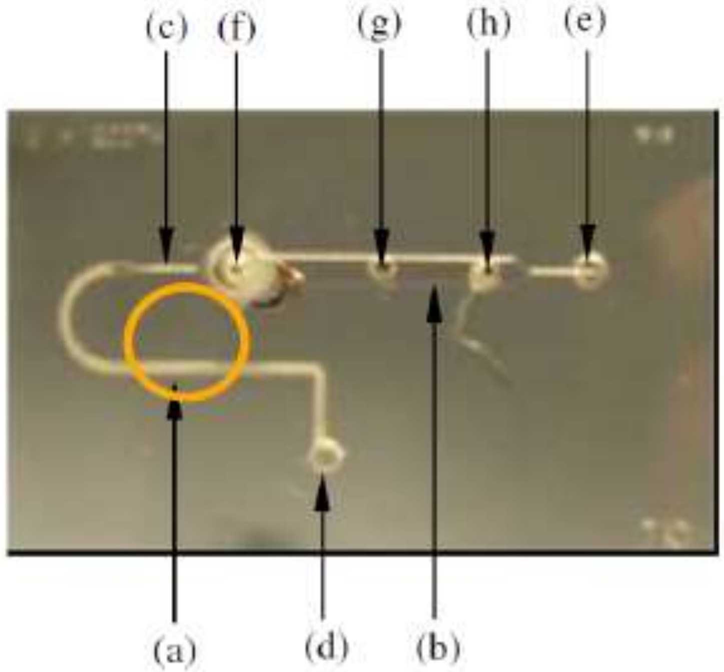
- Etching increases surface area
  - “Black silicon” created by etching of Si pillars
  - Different morphologies created by Si crystal orientation and etchant
  - >10x increase in trypsin digestion activity when immobilized on etched silicon pillars vs. native

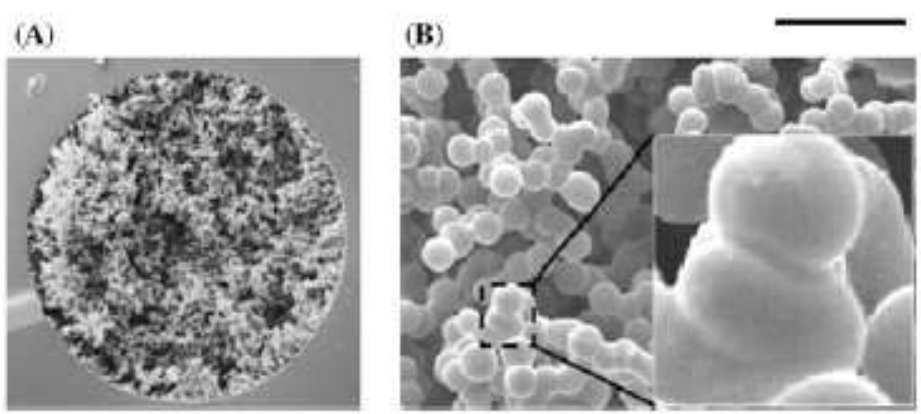


Roumanie, et al.,Chem. Eng. J. (2008), 135S, S317-S326

Examples: Nanostructures

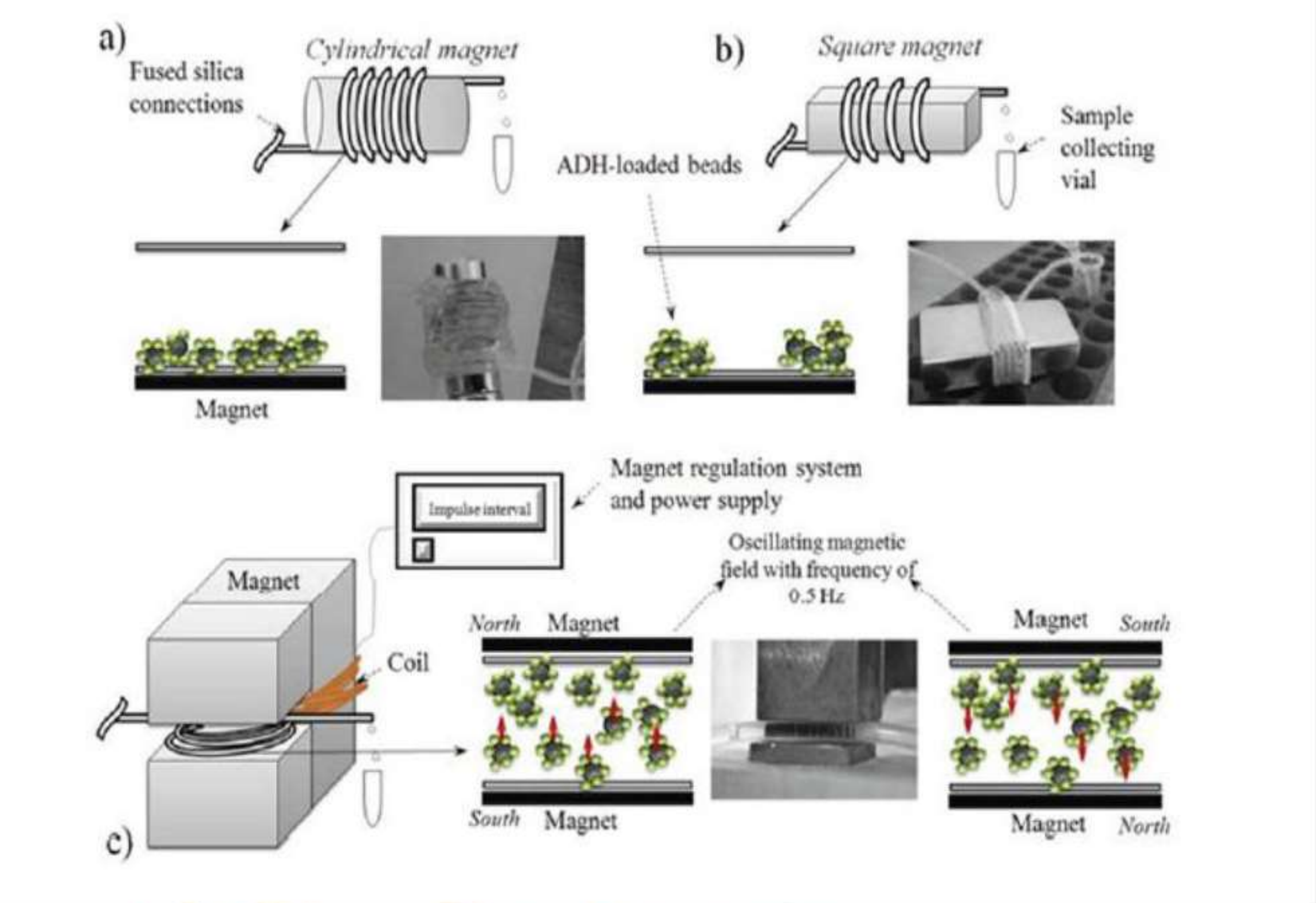
- Surface area, enzyme-loading increased by nano-/micro-scale features on surface





He, et al., Microfluidics & Nanofluidics (2010), 8, 565-573.

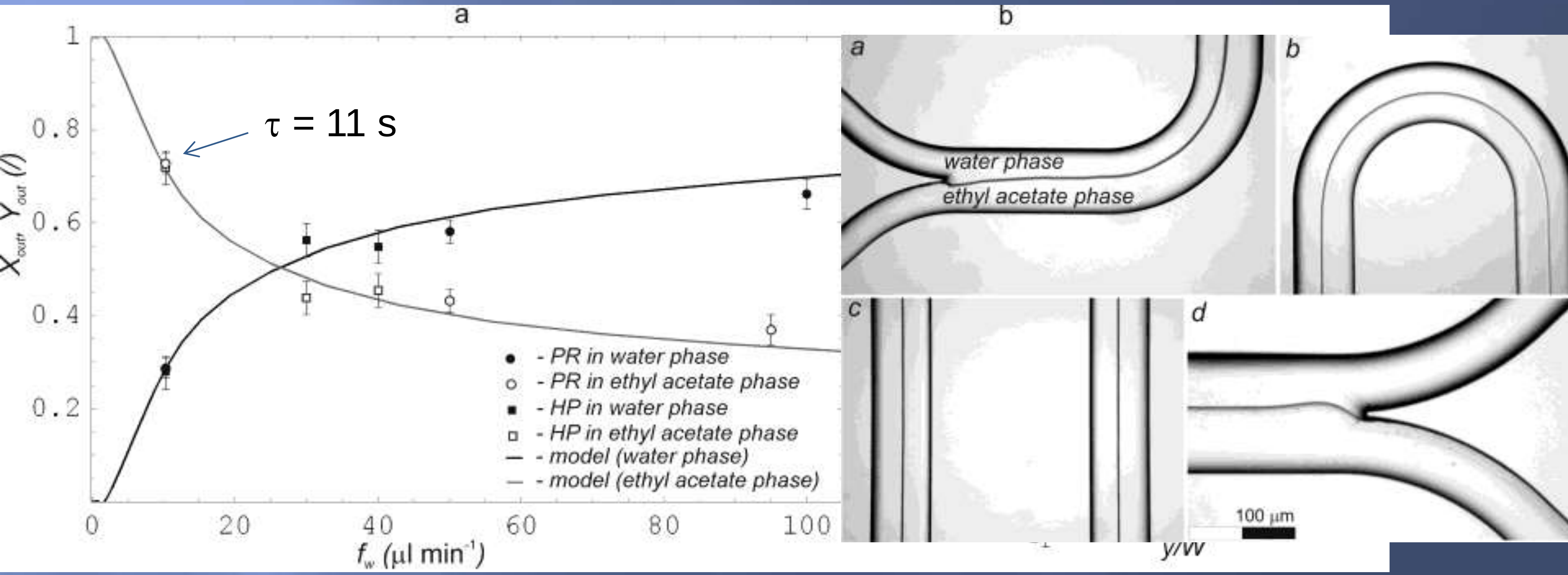
Mikrobioreaktorji z magnetnim poljem

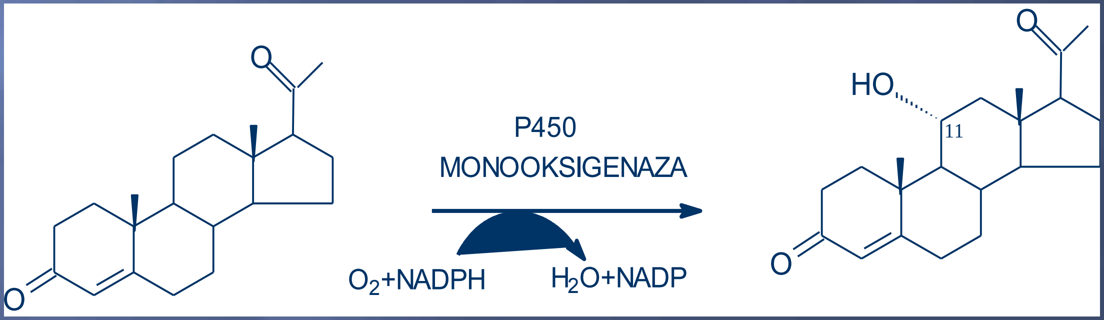


alić A, et al., NAD+ oxidation in a microreactor catalyzed by ADH-loaded MNPs (2013), 2191 - 9550.

Fig. 12. Immobilization of enzymes with magnetic nanoparticles.

Ekstrakcija steroidov v sistemu mikrokanalov





progesteron

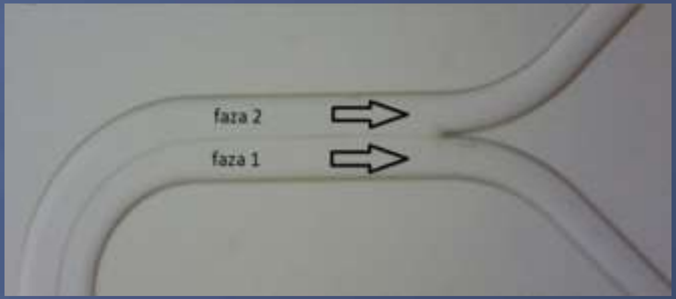
11α-hidroksiprogesteron

P. Žnidaršič-Plazl and I. Plazl. *Lab Chip*, 2007, 7, 883–889

Ekstrakcije bioloških makromolekul z dvofaznimi vodnimi sistemi

Dvofazni vodni sistemi:

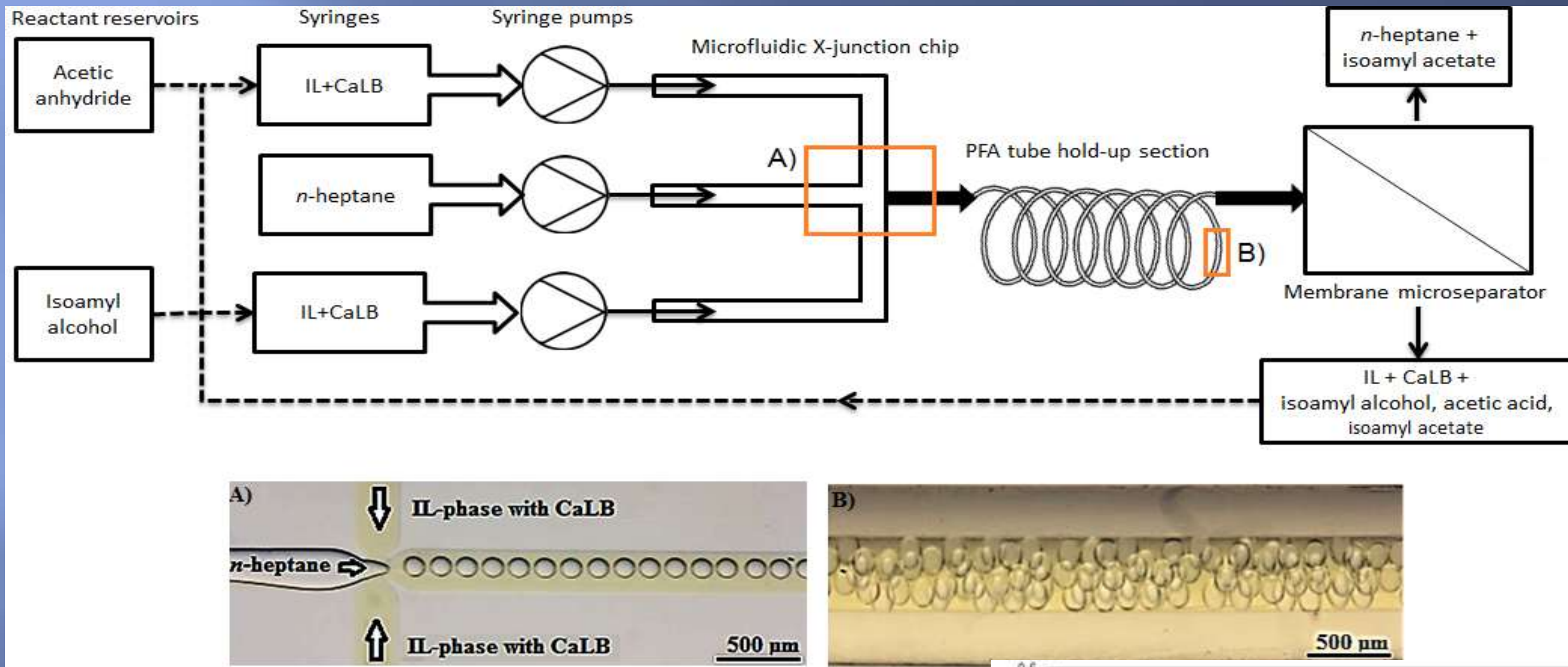
- PEG/fosfat
- ionske kapljevine/fruktoza



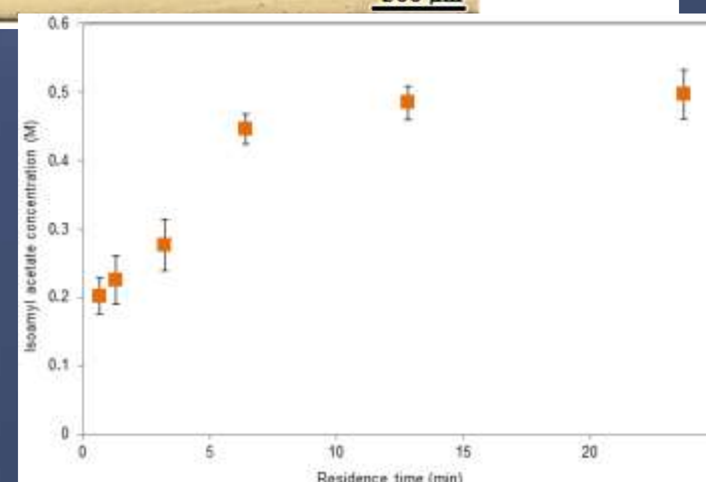
Vzporedni tok in separacija faz na izstopu

Tvorba mikro kapljic v sistemu mikrokanalov

Integracija bioprocesov

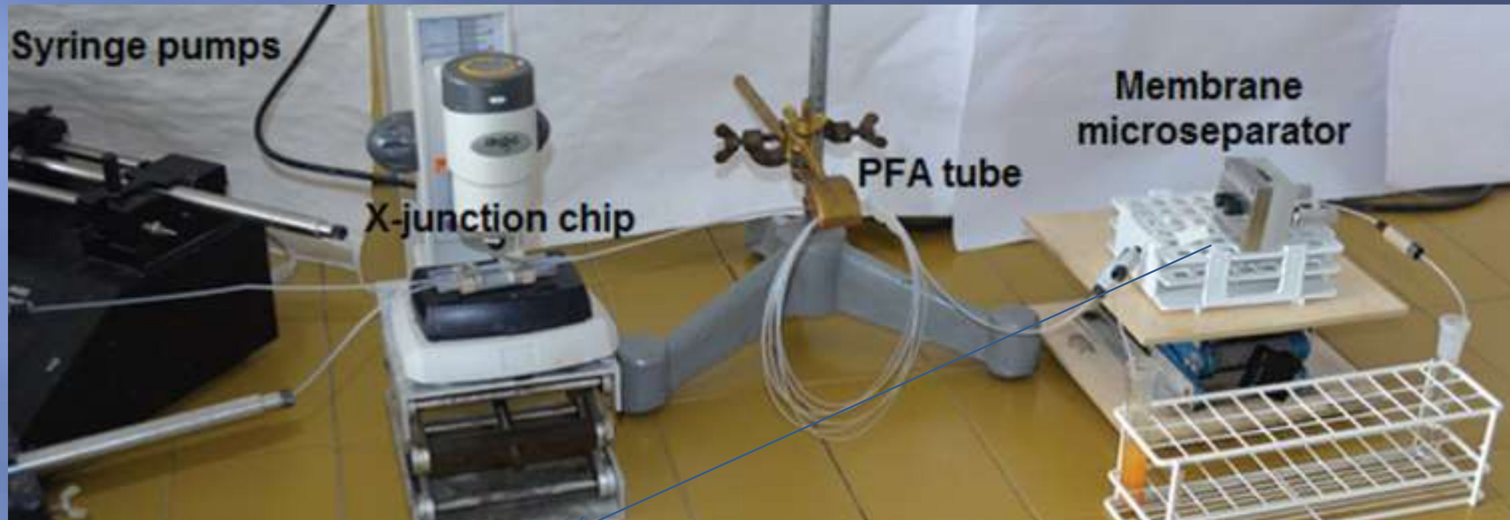


Novak U., Žnidaršič Plazl, P. *Green Proc. Synth*. **2**, 2013, 561–568

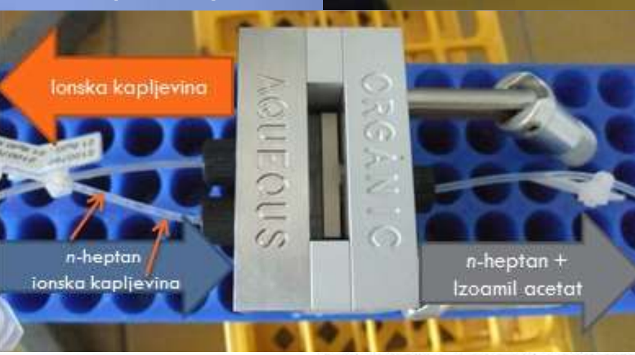


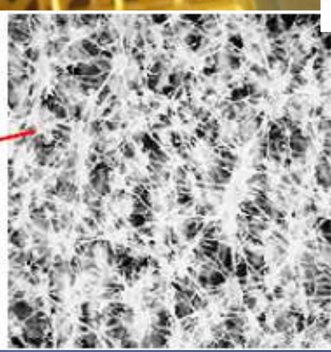
Integrated lipase-catalyzed esterification in two-phase system

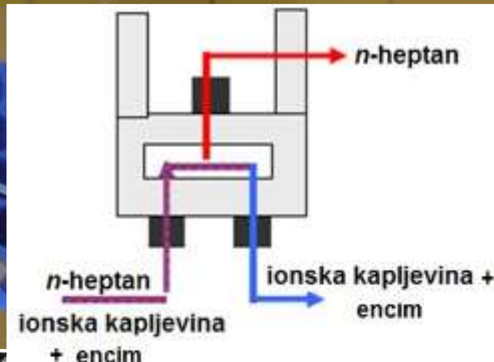
Integracija bioprocesov



Separacija faz z membanskim mikroseparatorjem







Ponovna uporaba ionske kapljevine z encimom

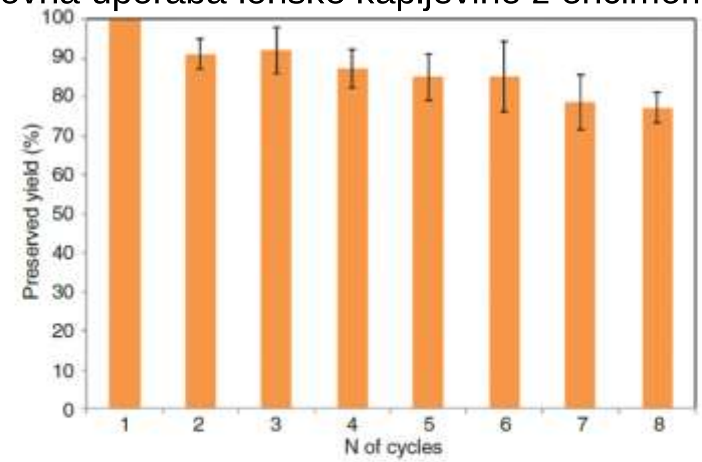
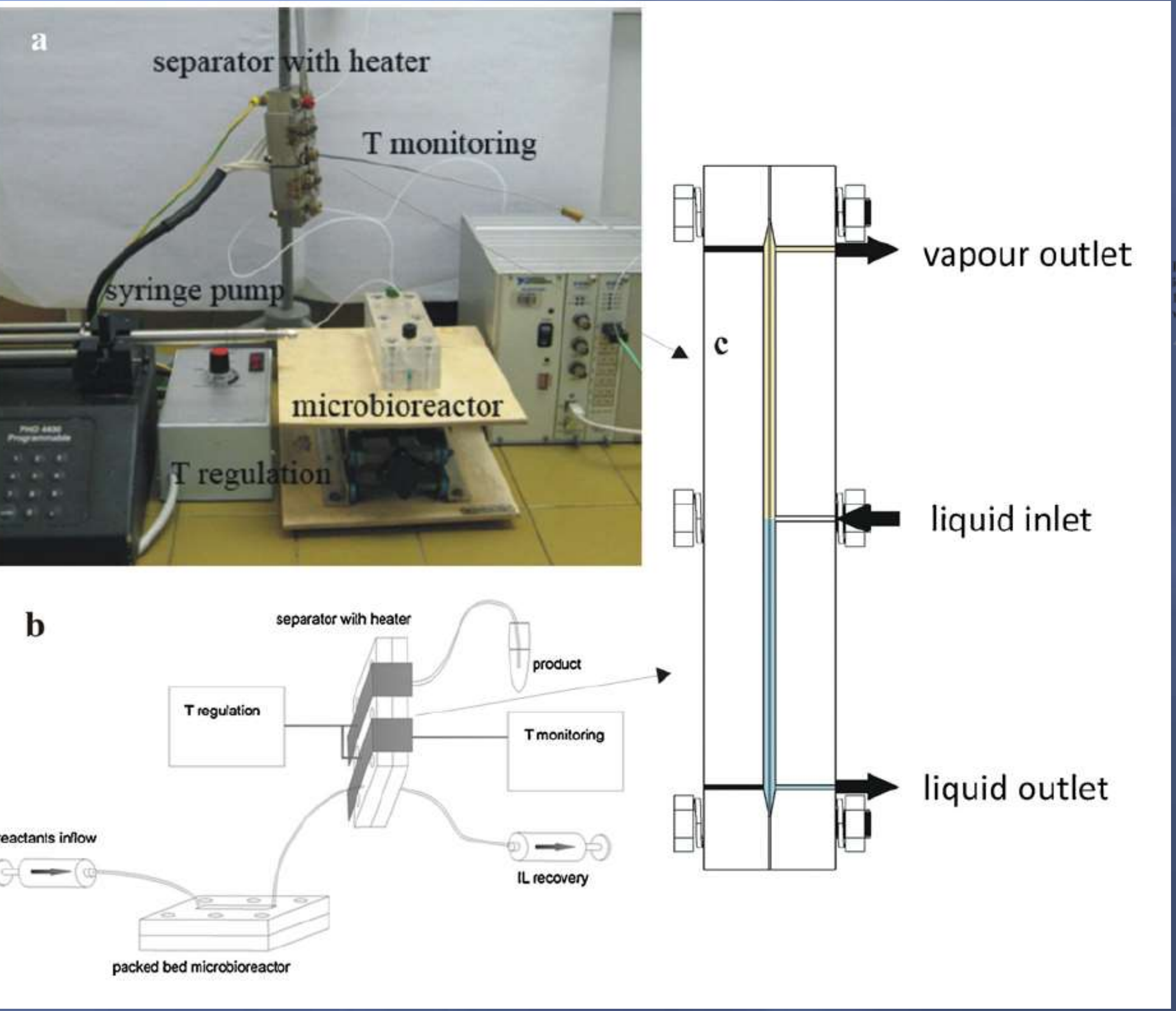
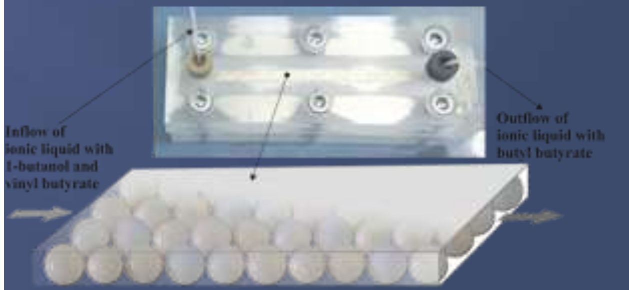


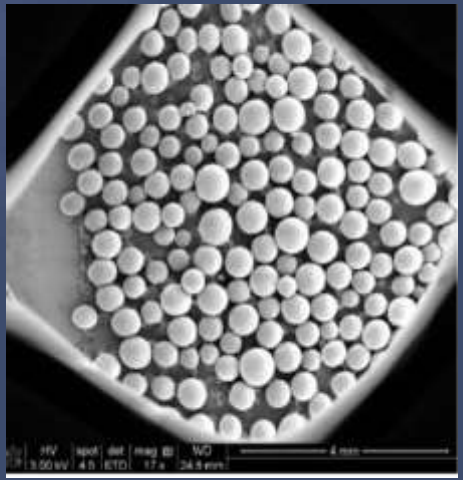
Figure 5 Preserved esterification yield considering both phases at the exit of the membrane microseparator at a retention time of 12.3 min after reuse of ionic liquid phase with dissolved CaLB. Process conditions were the same as described in Figure 4.

Novak U., Žnidaršič Plazl, P. *Green Proc. Synth*. **2**, 2013, 561–568

Integracija mikrobioreaktorja z uparjalnikom







Opis reaktorja s strnjenim slojem

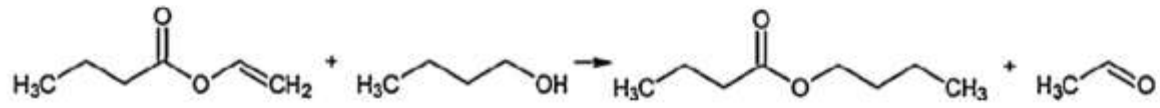
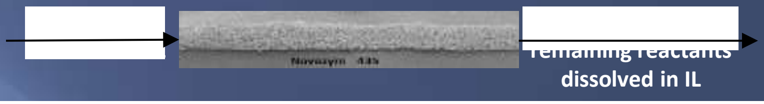


Fig. 3. From left to right are: vinyl butyrate, 1-butanol, butyl butyrate and acetaldehyde.

$$r = \frac{v_{\max}\gamma c_a(t)c_b(t)}{K_a c_b(t)(1+(c_b(t)/K_{ib})+K_b c_a(t)(1+(c_a(t)/K_{ia})+c_a(t)c_b(t)}$$



$$v\frac{dc_a(x)}{dx} - D\frac{d^2c_a(x)}{dx^2} = \frac{1-\varepsilon}{\varepsilon}(-r)$$

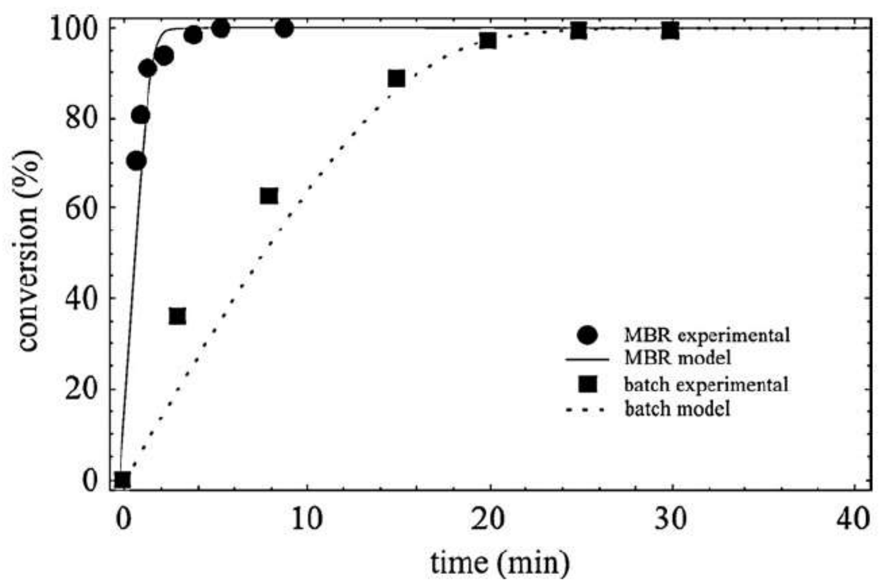
$$v\frac{dc_b(x)}{dx} - D\frac{d^2c_b(x)}{dx^2} = \frac{1-\varepsilon}{\varepsilon}(-r)$$

$$v\frac{dc_p(x)}{dx} - D\frac{d^2c_p(x)}{dx^2} = \frac{1-\varepsilon}{\varepsilon}r$$

with the following boundary conditions:

$$c_a(0) = c_{a0}; \quad c_b(0) = c_{b0}; \quad c_p(0) = 0$$

$$\frac{dc_a}{dx}(L) = 0; \quad \frac{dc_b}{dx}(L) = 0; \quad \frac{dc_p}{dx}(L) = 0$$



Zaključki

- Vse reakcije so neprimerno hitrejše od reakcij v klasičnih šaržnih procesih.
- Kontinuirno obratovanje.
- Možna separacija produktov na iztoku iz mikroreaktorja in ponovna uporaba katalizatorjev.
- Možna integracija procesov z zaključnimi procesi – ekstrakcija ipd.
- Z razvitim matematičnim modelom lahko dimenzioniramo mikroreaktorje in optimiziramo proces.

Smernice razvoja

- Razvoj mikrofluidnih naprav za:
  - Analizo celic in biomolekul, diagnostika
  - Zgodnje faze razvoja bioprocesov
  - Industrijske biotransformacije
  - Zaključne procese
  - Integracijo bioprocesov
- Razvoj cenovno dostopnih mikrofluidnih naprav za enkratno uporabo
- Razvoj novih orodij za opis procesov na molekularni ravni
- 30 % vseh novih razvitih produktov bo proizvedeno v mikroreaktorjih