Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Supporting Information

Automated platforms for reaction self-optimization in flow

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Table SI-1: References of the latest developments on self-optimization automated platforms.

Item	Title	Full authors list	Reference	Variables	Reaction	Algorithm	Analysis	Automation
1	Intelligent routes to the controlled synthesis of nanoparticles	S. Krishnadasan, R. J. C. Brown, A. J. deMello and J. C. deMello	Lab Chip, 2007, 7, 1434–1441	Flowrates, temperature	Synthesis of CdSe nanoparticles	SNOBFIT	Inline UV cell	LabVIEW, Matlab
2	An Automated Microfluidic System for Online Optimization in Chemical Synthesis	J. P. McMullen, K.F. Jensen	Org. Process Res. Dev., 2010, 14 (5), 1169–1176	Equivalents and residence time	Knoevenagel condensation	Nelder-Mead Simplex , SNOBFIT , steepest descent	HPLC	LabView, Matlab
3	An Integrated Microreactor System for Self-Optimization of a Heck Reaction: From Micro- to Mesoscale Flow Systems	J. P. McMullen, M. T. Stone, S. L. Buchwald, K. F. Jensen	Angew. Chem. Int. Ed. 2010, 49, 7076 – 7080	Equivalents and residence time	Heck	Nelder–Mead Simplex Method	HPLC	LabView, Matlab
4	Self-Optimizing Continuous Reactions in Supercritical Carbon Dioxide	Parrot, A. J., Bourne, R. A., Akien, G. R., Irvine, D. J. and Poliakoff, M.	Angew. Chem. Int. Ed. 2011, 50 (16), 3788 –3792	Temperature, pressure, flowrate	Methylation in supercritical CO2	Super modified Simplex	Online GC	Matlab
5	Automated Multitrajectory Method for Reaction Optimization in a Microfluidic System using Online IR Analysis	J. S. Moore and K. F. Jensen	Org. Process Res. Dev. 2012, 16, 1409−1415	Temperature and residence time	Paal−Knorr	Steepest descent, conjugate gradient, conjugate gradient + Armijo	Online IR	LabView , Matlab
6	Organic Synthesis: March of the Machines	Steven V. Ley, Daniel E. Fitzpatrick, Richard. J. Ingham, and Rebecca M. Myers	Angew. Chem. Int. Ed. 2015, 54, 3449 – 3464	Temperature, residence time, concentration, equivalents of two reagents	3D heterogeneous catalytic reaction, 5D Appel reaction	Modified Simplex	Flow IR	Internet-based
7	Self optimizing synthetic organic reactor system using real-time in-line NMR spectroscopy	V. Sans, L. Porwol, V. Dragone, L. Cronin	Chem. Sci., 2015, 6, 1258	Concentrations and residence time	Imine formation	Modified Nelder-Mead Simplex	Flow-NMR	LabView
8	Automatic discovery and optimization of chemical processes.	Houben, C. & Lapkin, A. A.	Curr. Opin. Chem. Eng., 2015, 9, 1–7	REVIEW	REVIEW	REVIEW	REVIEW	REVIEW

Table SI-1: References of the latest developments on self-optimization automated platforms (Cont.)

Item	Title	Full authors list	Reference	Variables	Reaction	Algorithm	Analysis	Automation
9	Machine-Assisted Organic Synthesis	Prof. Steven V. Ley Daniel E. Fitzpatrick Dr. Rebecca M. Myers Dr. Claudio Battilocchio Dr. Richard. J. Ingham	Angewandte Chemie Int Ed, 2015, 54 (35), 10122-10136	REVIEW	REVIEW	REVIEW	REVIEW	REVIEW
10	Feedback in Flow for Accelerated Reaction Development	Brandon J. Reizman and Klavs F. Jensen	Acc. Chem. Res. 2016, 49, 1786−1796	Discrete and continuous variables	Suzuki–Miyaura	(DoE)-based adaptive response surface (D-optimal, G-optimal)	LC/MS	LabView , Matlab
11	Optimizing the Heck−Matsuda Reaction in Flow with a Constraint-Adapted Direct Search Algorithm	Daniel Cortés-Borda, Ksenia V. Kutonova, Corentin Jamet, Marina E. Trusova, Françoise Zammattio, Charlotte Truchet, Mireia Rodriguez-Zubiri, and François-Xavier Felpin	Org. Process Res. Dev. 2016, 20, 1979−1987	Catalyst loading, residence time, equivalents	Pd catalysed Heck–Matsuda	Constraint-adapted Nelder-Mead	Off-line GCMS	Matlab
12	Self-optimisation of the final stage in the synthesis of EGFR kinase inhibitor AZD9291 using an automated flow reactor	Nicholas Holmes, Geoffrey R. Akien, A. John Blacker, Robert L. Woodward, Rebecca E. Meadows and Richard A. Bourne	React. Chem. Eng., 2016, 1, 366-371	Equivalents, residence time, temperature	Synthesis of N′-methylnicotinamide; Amide coupling+elimination	SNOBFIT vs Central Composite Design (DoE)	Online HPLC, offline LC-MS	Matlab
13	A Novel Internet-Based Reaction Monitoring, Control and Autonomous Self-Optimization Platform for Chemical Synthesis	Daniel E. Fitzpatrick, Claudio Battilocchio, and Steven V. Ley	Org. Process Res. Dev. 2016, 20, 2, 386-394	a) 3D: temperature, concentration, residence time; b) 5D: temperature, residencetime, equivalents (2), concentration	Nitrile oxidation to amide, Appel reaction to fomr bromides from alcohols	SIMPLEX	Online Mass Spec	Internet-based
14	Online monitoring and analysis for autonomous continuous flow self-optimizing reactor systems	D. C. Fabry , E. Sugiono and M. Rueping	React. Chem. Eng., 2016, 1, 129-133	REVIEW	REVIEW	REVIEW	REVIEW	REVIEW

Table SI-1: References of the latest developments on self-optimization automated platforms (Cont.)

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15	Optimizing Chemical Reactions with Deep Reinforcement Learning	Zhenpeng Zhou , Xiaocheng Li, and Richard N. Zare	ACS Cent. Sci., 2017, 3 (12), 1337–1344	Flowrate, pressure, voltage	Pomeranz−Fritsch, Friedländer synthesis, ribose phosphate synt., DCIP + ascorbicAcid, nanoparticles	DRO, CMA-ES, SNOBFIT, Nelder-Mead	Online Mass Spec	n/a
16	Self-optimisation and model-based design of experiments for developing a C–H activation flow process	A. Echtermeyer, Y. Amar, J. Zakrzewski, A. Lapkin	Beilstein J. Org. Chem. 2017, 13, 150–163.	Temperature, time, equivalents of acid and catalyst	Pd-catalysed C–H activation reaction of 1 resulting in the formation of an aziridine 2	Model based DoE + Multiobjective Active Learning (MOAL)	Inline UV cell+online GC	Matlab
17	Photoredox Iridium−Nickel Dual-Catalyzed Decarboxylative Arylation Cross-Coupling: From Batch to Continuous Flow via Self-Optimizing Segmented Flow Reactor	Hsiao-Wu Hsieh, Connor W. Coley, Lorenz M. Baumgartner, Klavs F. Jensen, and Richard I. Robinson	Org. Process Res. Dev. 2018, 22, 542−550	Temperature, residence time, organic bases	Photoredox dual-catalyzed decarboxylative arylation cross-coupling	(DoE)-based adaptive response surface (D-optimal, G-optimal)	HPLC	Matlab
18	An Autonomous Self-Optimizing Flow Reactor for the Synthesis of Natural Product Carpanone	Daniel Cortés-Borda, Eric Wimmer, Boris Gouilleux, Elvina Barré, Nicolas Oger, Lubna Goulamaly, Louis Peault, Benoît Charrier, Charlotte Truchet, Patrick Giraudeau , Mireia Rodriguez-Zubiri, Erwan Le Grognec, and François-Xavier Felpin	J. Org. Chem., 2018, 83 (23), 14286–14299	Temperature, residence time, equivalents	Synthesis of natural product Carpanone, Multistep synthesis	Custom, based on Nelder-Mead and golden section search methods	Online HPLC or in-line NMR	Matlab
19	Machine assisted reaction optimization: A self-optimizing reactor system for continuous-flow photochemical reactions	K. Poscharny, D. Fabry, S. Heddrich, E. Sugiono, M. Liauw, M. Rueping	Tetrahedron, 2018, 74 (25), 3171-3175	Flowrates	Photochemical reaction, [2 - 2] photocyclization reaction of benzophenone and furan	Modified Simplex	FlowIR	LabVIEW, Matlab
20	Enhanced process development using automated continuous reactors by self-optimisation algorithms and statistical empirical modelling	Mohammed I.Jeraal, NicholasHolmes, Geoffrey R.Akien, Richard A.Bourne	Tetrahedron, 2018, 74, (25), 3158-3164	Flowrates (3), temperature	Claisen-Schmidt condensation between acetone and benzaldehyde to form benzylideneacetone	SNOBFIT	HPLC	Matlab

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21	Machine learning meets continuous flow chemistry: Automated optimization towards the Pareto front of multiple objectives	Artur M.Schweidtmann, Adam D.Clayton, NicholasHolmes, EricBradford, Richard A.Bournec, Alexei A. Lapkin	Chem. Eng. J. 2018, 352, 277-282	Case1) esidence time, equivalents, concentration, temperature; Case 2) Four parameters for N-benzylation	Case 1) SNAr; Case 2) N-benzylation	Thompson Sampling Efficient Multi-Objective (TSEMO)	HPLC	Matlab
22	OpenFlowChem – a platform for quick, robust and flexible automation and self-optimisation of flow chemistry	Nikolay Cherkasov, Yang Bai, Antonio José Expósito and Evgeny V. Rebrov	React. Chem. Eng., 2018, 3, 769-780	Flowrates (3)	Nitrobenzene hydrogenation, alkyne hydrogenation	SNOBFIT	Online GC	LabVIEW
23	Precise Polymer Synthesis by Autonomous Self-Optimizing Flow Reactors	Maarten Rubens, Jeroen H. Vrijsen, Joachim Laun, and Tanja Junkers	Ang. Chem, 2019, 58 (10), 3183-3187	Flowrates	Synthesis of polymers with precise weight distribution	Custom, specifically designed to optimize the average molecular weight to a predefined target under optimal reaction conditions	Online SEC (Size exclusion chromato graphy)	LabVIEW
24	Reconfigurable system for automated optimization of diverse chemical reactions	Anne-Catherine Bédard, Andrea Adamo, Kosi C. Aroh, M. Grace Russell, Aaron A. Bedermann, Jeremy Torosian, Brian Yue, Klavs F. Jensen, Timothy F. Jamison	Science, 2018, 361, (6408) 1220-1225	3-5 variables	C-C and C-N cross-coupling, olefination, reductive amination, nucleophilic aromatic substitution (SNAr), photoredox catalysis, and a multistep sequence.	SNOBFIT	HPLC, IR, Raman, MS	LabVIEW, Matlab