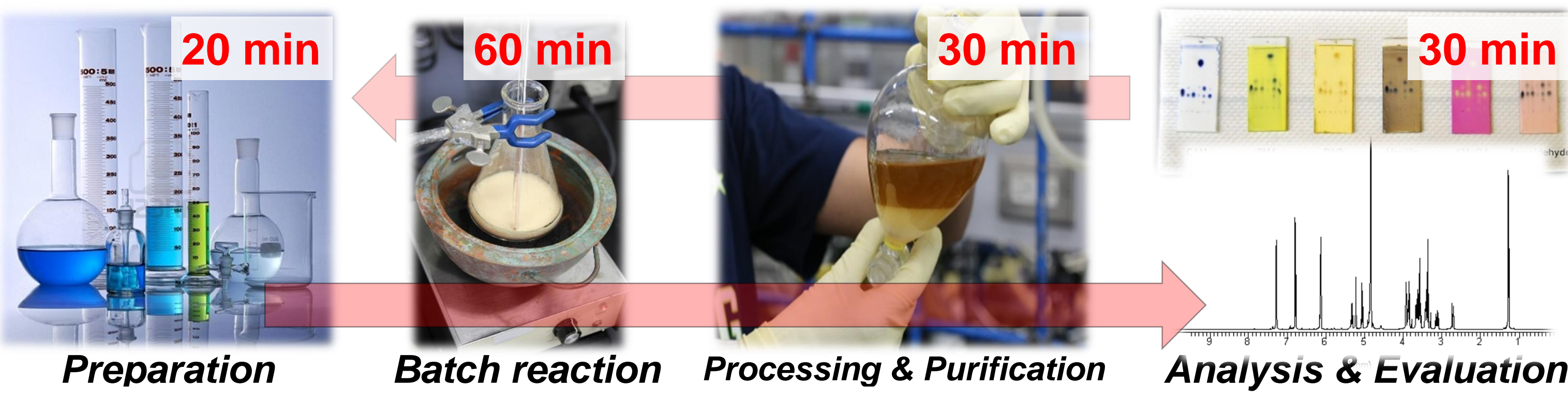




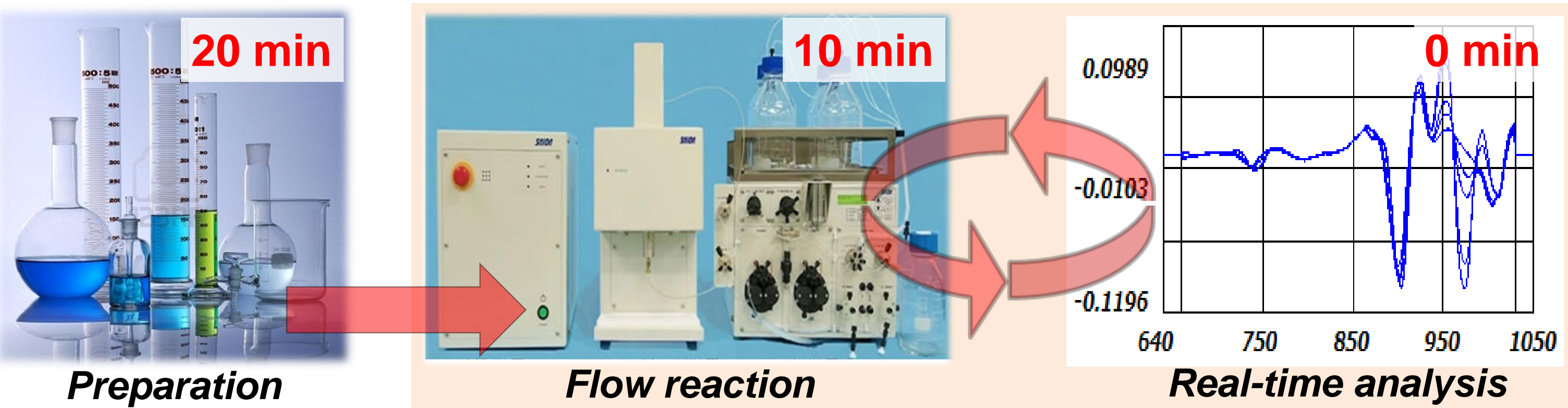
1. Introduction / Previous Works

1-1. Research Background

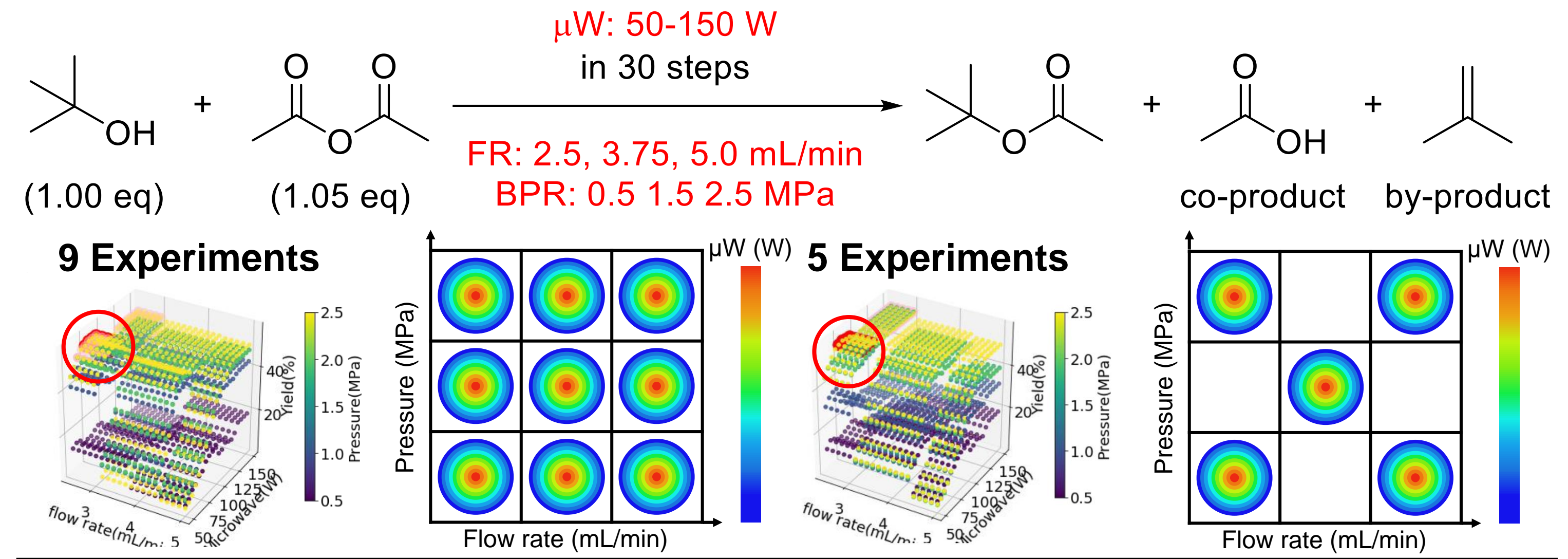
Batch reaction (Total: $N \times 140$ min)



Flow reaction (Total: $20 + N \times 10$ min)



1-3. Optimization of 3 Factors (μ W, FR, Pressure)



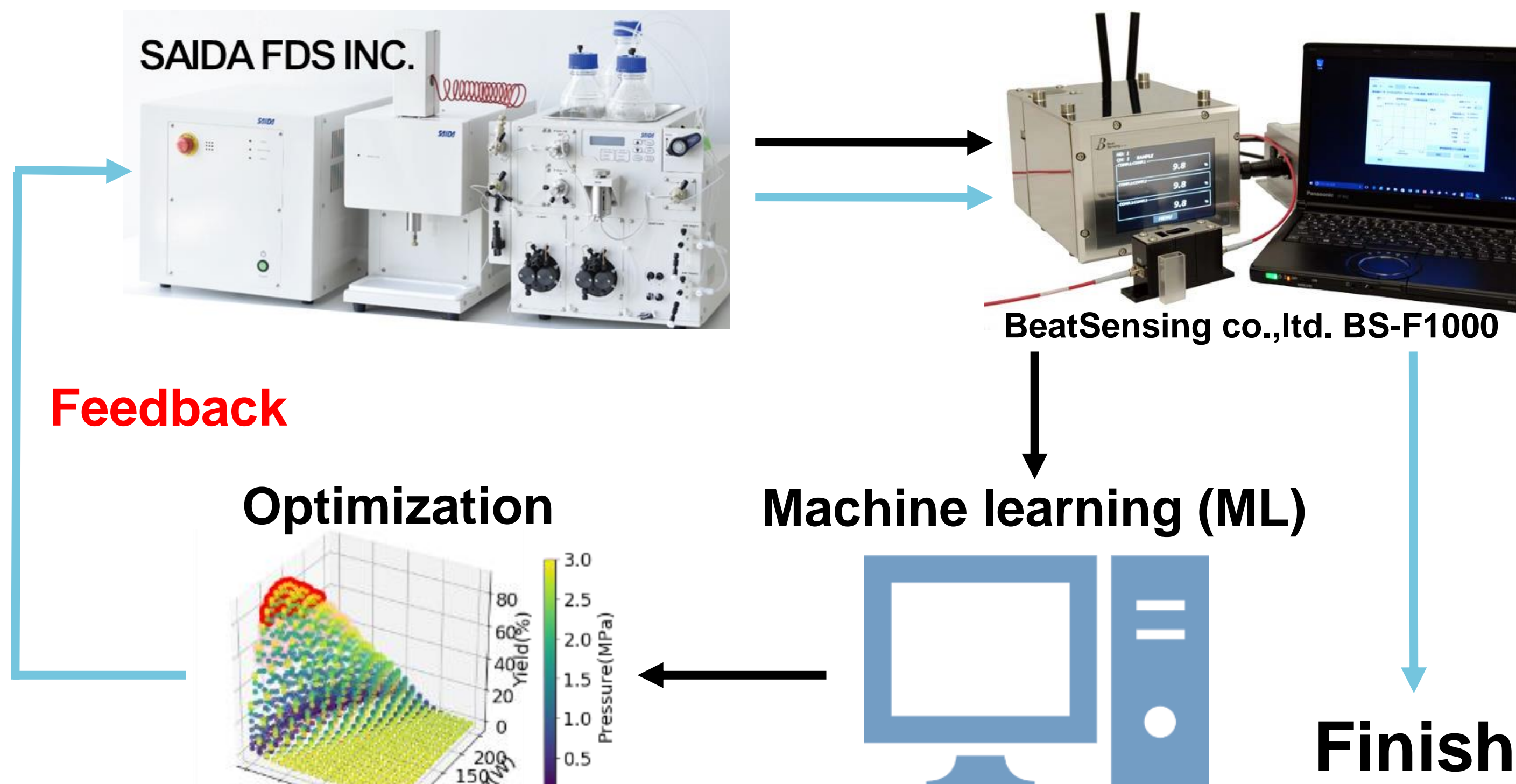
| No. of Exp. ^a | μ W (W) ^b | Temp. (°C) ^c | Flow rate (mL/min) ^b | Pressure (MPa) ^b | Yield (opt. / mea. ^d) (%) | RRMSE ^f (%) |
|--------------------------|--------------------------|-------------------------|---------------------------------|-----------------------------|---------------------------------------|------------------------|
| 9 | 76 | 215 | 2.5 | 2.5 | 56.0 / 57.0 (63.3) ^e | 1.75 |
| 5 | 76 | 215 | 2.5 | 2.5 | 56.0 / 57.0 (63.3) ^e | 1.75 |

^a Without threshold. ^b Predicted by random forest with logistic function. ^c Outlet temperature. ^d Determined by NIR analysis. ^e Determined by GC analysis using TC-17 column. ^f Relative roots mean square error.

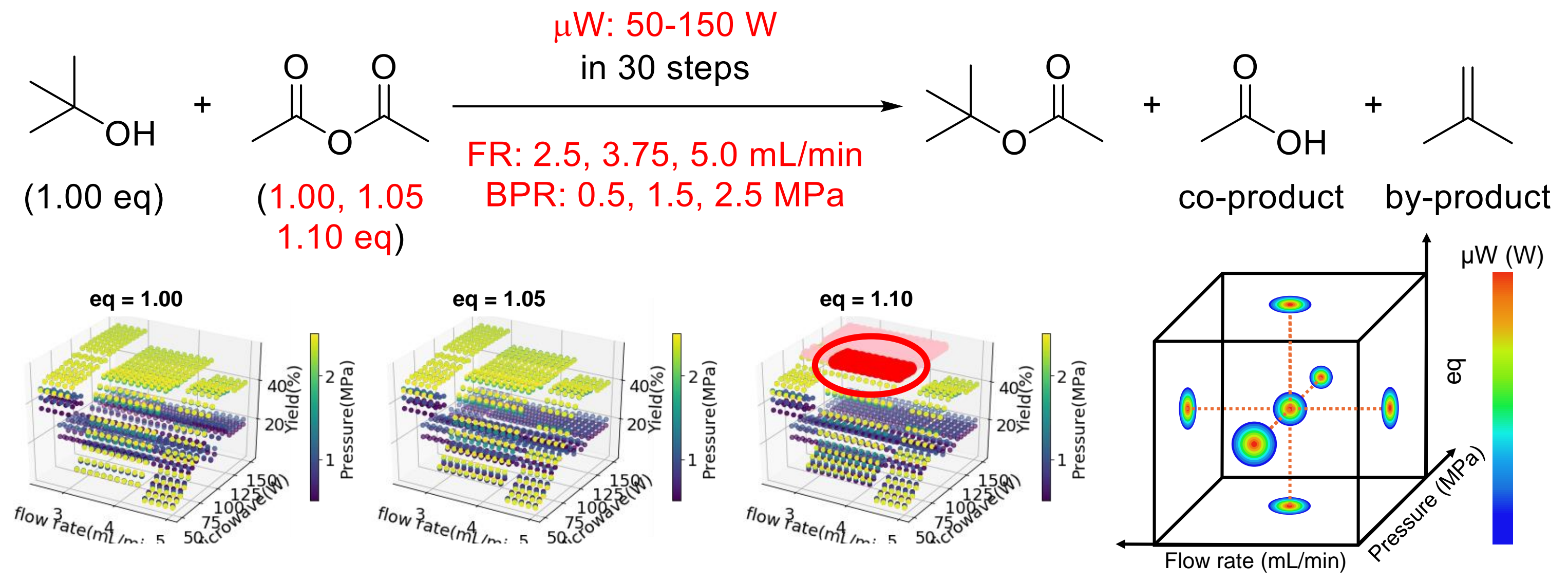
1-2. Optimization of Continuous Variables by ML

Microwave-assisted flow reaction

In-line analysis by NIR



1-4. Optimization of 4 Factors (μ W, FR, Pressure, eq)

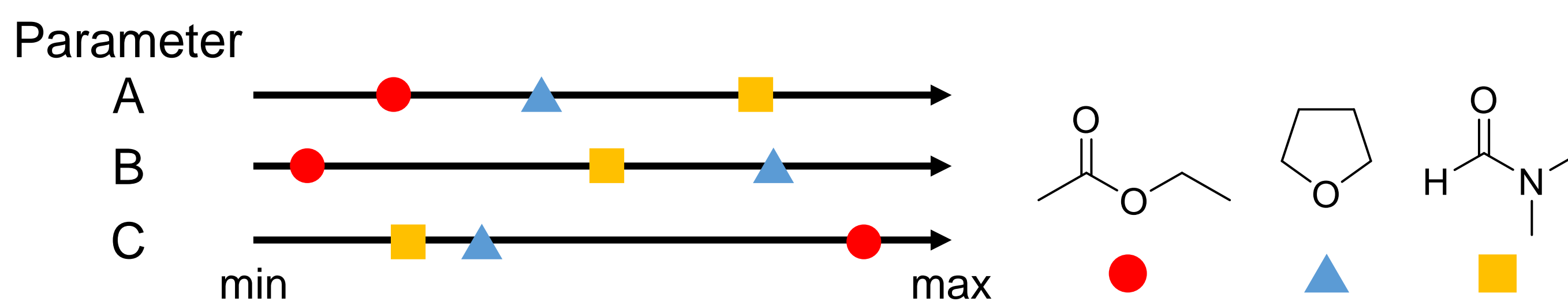


| No. of Exp. ^a | μ W (W) ^b | Temp. (°C) ^c | Flow rate (mL/min) ^b | Pressure (MPa) ^b | eq ^b | Yield (opt. / mea. ^d) (%) | RRMSE ^f (%) |
|--------------------------|--------------------------|-------------------------|---------------------------------|-----------------------------|-----------------|---------------------------------------|------------------------|
| 7 | 92 | 209 | 3.2 | 1.5 | 1.10 | 56.1 / 52.2 (59.0) ^e | 7.47 |

^a Without threshold. ^b Predicted by random forest with logistic function. ^c Outlet temperature. ^d Determined by NIR analysis. ^e Determined by GC analysis using TC-17 column. ^f Relative roots mean square error.

2. Optimization of Solvents in Acetylation

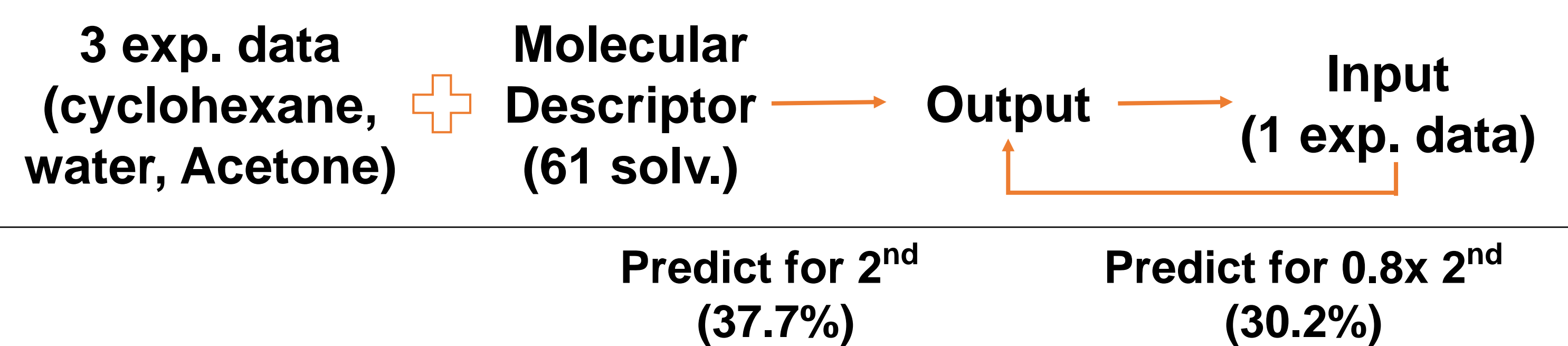
2-1. Numerous Representation of Solvents by Molecular Descriptors (5270 Parameters)



2-2. Selection of Suitable Solvents in Chemical Process (277 \Rightarrow 83 \Rightarrow 61)

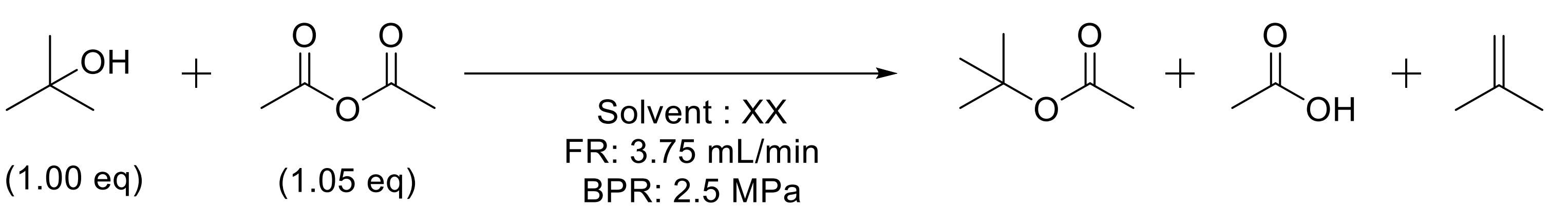
| Entry | Name | Entry | Name | Entry | Name | Entry | Name |
|-------|--|-------|----------------------------|-------|----------------------------|-------|--------------------------------|
| 1 | (2,2-Dimethyl-1,3-dioxolan-4-yl)methanol | 50 | Acetic Anhydride | 99 | Diethyl Ether | 148 | n-Propylamine |
| 2 | (E)-1,2-Dichloroethane | 51 | Acetophenone | 100 | Ethane-1,2-diol diacetate | 149 | Octamethylcyclotrisiloxane |
| 3 | (Trifluoromethoxy)benzene | 52 | Aniline | 101 | Ethanolamine | 150 | Octamethylcyclotrisiloxane |
| 4 | (Z)-1,2-Dichloroethane | 53 | Benzonitrile | 102 | Ethoxybenzene | 151 | p-Cymene |
| 5 | 1,1,1,3,3,3-Hexafluoropropan-2-ol | 54 | Benzofuran | 103 | Ethyl Ethoxypropionate | 152 | Pentadecane |
| 6 | 1,1,2,2-Tetrachloroethane | 55 | Benzylamine | 104 | Ethyl 3-oxobutanoate | 153 | Pentamethyl Phosphonic Diamide |
| 7 | 1,1,2-Trichloroethane | 56 | Bromobenzene | 105 | Ethyl butyrate | 154 | Pentane-2-ol |
| 8 | 1,2,3,4,5-Pentafluoro-6-trifluoromethylbenzene | 57 | Butoxyglycol | 106 | Ethyl propionate | 155 | Pentane-3-ol |
| 9 | 1,2-Dichloropropane | 58 | Butyl Carbonyl | 107 | Ethylbenzene | 156 | Pentane-2,4-dione |
| 10 | 1,2-Diaminoethane | 59 | Butyl Carbonyl Acetate | 108 | Ethylchloroacetate | 157 | Perfluorobenzene |
| 11 | 1,2-Dichlorobenzene | 60 | Butyl Cellosolve | 109 | Fluorobenzene | 158 | Perfluorodecalin |
| 12 | 1,2-Dimethoxypropane | 61 | Butyl Cellosolve Acetate | 110 | Furan | 159 | Propyl Glycol Ether |
| 13 | 1,3,2-Dioxathiolane-2-oxide | 62 | Furfural | 111 | Gamma-butyrolactone | 160 | Propylene Glycol |
| 14 | 1,3-Dichlorobenzene | 63 | Gamma-butyrolactone | 112 | Hexamethylcyclotrisiloxane | 161 | Pyridazine |
| 15 | 1,3-Dioxolane | 64 | Gamma-butyrolactone | 113 | Hexamethylcyclotrisiloxane | 162 | Pyridine |
| 16 | 1,3-Dioxane | 65 | Gamma-butyrolactone | 114 | Hexamethylcyclotrisiloxane | 163 | Pyrimidine |
| 17 | 1,8-Diazabicyclo[7.1.0]heptane | 66 | Gamma-butyrolactone | 115 | Hexamethylcyclotrisiloxane | 164 | Pyrimidine |
| 18 | 1-Butylamine | 67 | Gamma-butyrolactone | 116 | Hexamethylcyclotrisiloxane | 165 | Propyl Glycol Ether |
| 19 | 1-chloro-4-(trifluoromethyl)benzene | 68 | Gamma-butyrolactone | 117 | Hexamethylcyclotrisiloxane | 166 | Propylene Glycol |
| 20 | 1-Hexanol | 69 | Cyclohexanone | 118 | Hexamethylcyclotrisiloxane | 167 | Propylene Glycol |
| 21 | 1-Methoxypropan-2-ol | 70 | Cyclopentane | 119 | Hexamethylcyclotrisiloxane | 168 | Propylene Glycol |
| 22 | 1-Methylazepan-2-one | 71 | Cyclopentane | 120 | Hexamethylcyclotrisiloxane | 169 | Propylene Glycol |
| 23 | 1-Nitropropane | 72 | Decamethylcyclotrisiloxane | 121 | Hexamethylcyclotrisiloxane | 170 | Propylene Glycol |
| 24 | 1-Nitropropane | 73 | Decamethylcyclotrisiloxane | 122 | Hexamethylcyclotrisiloxane | 171 | Propylene Glycol |
| 25 | 2,2,2-Trifluoroethanol | 74 | Decane | 123 | Hexamethylcyclotrisiloxane | 172 | Propylene Glycol |
| 26 | 2,2,4,4-Tetrafluoro-1,3-dioxane | 75 | Diethylamine | 124 | Hexamethylcyclotrisiloxane | 173 | Propylene Glycol |
| 27 | 2,2,4,4-Tetrafluoro-1,3-dioxane | 76 | Diethylamine | 125 | Hexamethylcyclotrisiloxane | 174 | Propylene Glycol |
| 28 | 2,2,4,4-Tetrafluoro-1,3-dioxane | 77 | Diethylamine | 126 | Hexamethylcyclotrisiloxane | 175 | Propylene Glycol |
| 29 | 2,2-Dimethoxypropane | 78 | Diethylamine | 127 | Hexamethylcyclotrisiloxane | 176 | Propylene Glycol |
| 30 | 2,2-Dimethoxypropane | 79 | Diethylamine | 128 | Hexamethylcyclotrisiloxane | 177 | Propylene Glycol |
| 31 | 2,4-Dimethyl-3-pentanone | 80 | Diethylamine | 129 | Hexamethylcyclotrisiloxane | 178 | Propylene Glycol |
| 32 | 2,4-Dimethyl-3-pentanone | 81 | Diethylamine | 130 | Hexamethylcyclotrisiloxane | 179 | Propylene Glycol |
| 33 | 2,6-Dimethylpyridine | 82 | Diethylamine | 131 | Hexamethylcyclotrisiloxane | 180 | Propylene Glycol |
| 34 | 2-Amino-2-methylpropan-1-ol | 83 | Diethylamine | 132 | Hexamethylcyclotrisiloxane | 181 | Propylene Glycol |
| 35 | 2-Ethoxyethanol | 84 | Diethylamine | 133 | Hexamethylcyclotrisiloxane | 182 | Propylene Glycol |
| 36 | 2-Ethoxyethyl Acetate | 85 | Diethylamine | 134 | Hexamethylcyclotrisiloxane | 183 | Propylene Glycol |
| 37 | 2-Ethoxyethanol | 86 | Diethylamine | 135 | Hexamethylcyclotrisiloxane | 184 | Propylene Glycol |
| 38 | 2-Methoxy-1-(1-methoxy-2-propenyl)oxypropane | 87 | Diethylamine | 136 | Hexamethylcyclotrisiloxane | 185 | Propylene Glycol |
| 39 | 2-Methyl-1-propanamine | 88 | Diethylamine | 137 | Hexamethylcyclotrisiloxane | 186 | Propylene Glycol |
| 40 | 2-Methyl-1-propanamine | 89 | Diethylamine | 138 | Hexamethylcyclotrisiloxane | 187 | Propylene Glycol |
| 41 | 2-Methyl-1-propanamine | 90 | Diethylamine | 139 | Hexamethylcyclotrisiloxane | 188 | Propylene Glycol |
| 42 | 2-Methyl-1-propanamine | 91 | Diethylamine | 140 | Hexamethylcyclotrisiloxane | 189 | Propylene Glycol |
| 43 | 2-Methyl-1-propanamine | 92 | Diethylamine | 141 | Hexamethylcyclotrisiloxane | 190 | Propylene Glycol |
| 44 | 3,5-Dimethyl-2-butane | 93 | Diethylamine | 142 | Hexamethylcyclotrisiloxane | 191 | Propylene Glycol |
| 45 | 3,5,5-Trimethylcyclohex-2-enone | 94 | Diethylamine | 143 | Hexamethylcyclotrisiloxane | 192 | Propylene Glycol |
| 46 | 3-Methyl-2-butanone | 95 | Diethylamine | 144 | Hexamethylcyclotrisiloxane | 193 | Propylene Glycol |
| 47 | 4-Hydroxy-4-methylpentan-2-one | 96 | Diethylamine | 145 | Hexamethylcyclotrisiloxane | 194 | Propylene Glycol |
| 48 | 4-Methylcyclohexanemethanol | 97 | Diethylamine | 146 | Hexamethylcyclotrisiloxane | 195 | Propylene Glycol |
| 49 | 5-Chloropentane | 98 | Diethylamine | 147 | Hexamethylcyclotrisiloxane | 196 | Propylene Glycol |

2-3. Solvent optimization by Machine Learning



| No. of calculation | 8 | 3 |
|--------------------|----|---|
| No. of solvents | 10 | 5 |

2-4. Prediction of Better Solvents



61 Exp. + Molecular Descriptor \rightarrow 216 solv. Molecular Descriptor \rightarrow Predicted in 277 solvents

| Actual Solvent Rank | Solvent | Yield (%) | Predicted Solvent Rank | Solvent | Yield (%) |
|---------------------|-------------------------|-----------|------------------------|-----------------------------|-----------|
| 1 | Triacetin | 42.2 | 1 | Propylene Diacetate | 27.9 |
| 2 | γ -Valerolactone | 37.7 | 2 | DPMA Glycol Ether Diacetate | 48.4 |
| 3 | DMA | 34.8 | 3 | Ethylene Glycol Diacetate | 14.3 |

Training data

Test data

\checkmark Higher yielded solvent in 277 solvents