

Supporting Information

Design of dynamic trajectories for efficient and data-rich exploration of flow reaction design spaces

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Derivation of Equation (3)

From the definition of instantaneous residence time, τ_I , and under the assumption of plug flow:

$$V = \int_{t-\tau}^t \frac{V}{\tau_I(\theta)} d\theta \quad (2)$$

By canceling the volume, V , and taking the derivative w.r.t. time (using the Leibniz rule for the derivative of the integral):

$$0 = \frac{1}{\tau_I(t)} \frac{d}{dt}(t) - \frac{1}{\tau_I(t-\tau)} \frac{d}{dt}(t-\tau) \quad (S.1)$$

$$0 = \frac{1}{\tau_I(t)} - \frac{1}{\tau_I(t-\tau)} \left(1 - \frac{d\tau}{dt}\right) \quad (S.2)$$

By rearranging one obtains the equation for the time variation of the effective residence time, τ :

$$\frac{d\tau}{dt} = 1 - \frac{\tau_I(t-\tau)}{\tau_I(t)} \quad (3)$$

Model details for the determination of $K_{y_k}^{max}$

In order to find the values of $K_{y_k}^{max}$ to be used in Equation (5), an extensive parametric analysis was performed, by considering reactors similar to the one used in the experiment. The reactor can be schematised as a series of a CSTR (mixing chamber) operating at ambient temperature (as it is isolated from the heated part) and a tubular reactor modelled as a laminar flow reactor (LFR) with dispersion. The model follows the scheme reported in Figure S.1. The inlet concentration of each species, total flowrate (and consequently the instantaneous residence time), and reactor temperature change in time according to some given profile.

A mass conservation equation for each chemical species describes the variation in concentration along the reactor coordinate and during the experiment time. It is assumed that the density is constant and uniform, while temperature changes happen instantaneously over the entire reactor length.

We define the following dimensionless quantities:

$$\hat{t} = \frac{t}{\tau_I^0}, \quad \hat{x} = \frac{x}{L}, \quad \hat{c}_i = \frac{c_i}{c_{tot}^0} \quad (S.3)$$

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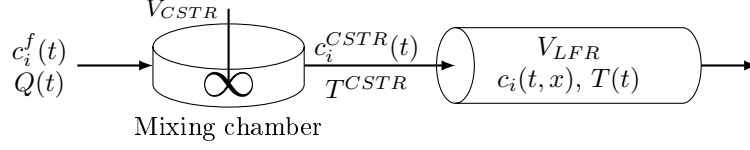


Figure S.1: Scheme of the modelled system.

as the dimensionless time, position (in the tubular reactor), and concentration respectively, where t is the physical time, τ_I the instantaneous residence time, $\tau_I^0 = \tau_I(t=0)$, x the physical position, L the tubular reactor length, c_i the concentration of species i , $c_{tot}^0 = \sum_i c_i^f(t=0)$, and c_i^f the feed concentration of species i . The instantaneous residence time is referred to the tubular reactor, thus it is equal to $V_{LFR}/Q(t)$. The transport equation for concentration inside the LFR are rendered dimensionless to yield:

$$\frac{\partial \hat{c}_i}{\partial \hat{t}} = -\frac{1}{\hat{\tau}_{LFR}} \frac{\partial \hat{c}_i}{\partial \hat{x}} + \frac{1}{\hat{\tau}_{LFR}^2 Pe_{mol}^0} \frac{\partial^2 \hat{c}_i}{\partial \hat{x}^2} + \sum_j^{NR} \nu_{ij} Da_j^0 \exp\left(\epsilon_j^0 \left(1 + \frac{1}{\hat{T}}\right)\right) \prod_k^{NC} (\hat{c}_k)^{\alpha_{kj}} \quad \hat{t} > 0, 0 < \hat{x} < 1 \quad (\text{S.4})$$

where NC is the number of species involved, NR the number of reactions considered (modelled as power law), $\hat{\tau}_{LFR} = \tau_I(t)/\tau_I^0$ the dimensionless residence time in the LFR, Pe_{mol}^0 the molecular Peclet number, ν_{ij} the stoichiometric coefficient of species i in reaction j , Da_j^0 the Damköhler number of reaction j , $\epsilon_j^0 = E_{a,j}/RT_0$ the dimensionless activation energy of reaction j , $T_0 = T(t=0)$, $\hat{T} = T(t)/T_0$ the dimensionless temperature, and α_{ij} the reaction order of species i in reaction j . The following definitions are used:

$$Pe_{mol}^0 = \frac{192 \mathcal{D} \tau_I^0}{d_t^2}, \quad Da_j^0 = \tau_I^0 k_j(T_0) (c_{tot}^0)^{\sum_k^{NC} \alpha_{kj} - 1} \quad (\text{S.5})$$

Taylor dispersion is assumed, \mathcal{D} is the molecular diffusivity, d_t the LFR diameter, and k_j the kinetic constant of reaction j .

The PDE in Equation (S.4) has the following boundary conditions (Danckwerts):

$$\frac{\hat{c}_i - \hat{c}_i^{CSTR}}{\hat{\tau}_{LFR}} - \frac{1}{\hat{\tau}_{LFR}^2 Pe_{mol}^0} \frac{\partial \hat{c}_i}{\partial \hat{x}} = 0 \quad \hat{x} = 0 \quad (\text{S.6})$$

$$\frac{\partial \hat{c}_i}{\partial \hat{x}} = 0 \quad \hat{x} = 1 \quad (\text{S.7})$$

The required CSTR concentration is computed from the ODE:

$$\frac{d\hat{c}_i^{CSTR}}{d\hat{t}} = \frac{1}{\hat{\tau}_{LFR}} \frac{V_{LFR}}{V_{CSTR}} \frac{\hat{c}_i^f - \hat{c}_i^{CSTR}}{\partial \hat{x}} + \sum_j^{NR} \nu_{ij} Da_j^0 \exp\left(\epsilon_j^0 \left(1 + \frac{1}{\hat{T}^{CSTR}}\right)\right) \prod_k^{NC} (\hat{c}_k^{CSTR})^{\alpha_{kj}} \quad \hat{t} > 0 \quad (\text{S.8})$$

The initial condition for both the LFR and CSTR is given by the solution of the steady problem at time $t = 0$. The transient solution for some given functions $c_i^f(t)$, $\tau_I(t)$, and $T(t)$ was obtained via the finite difference method, using second-order discretisation schemes for the space derivatives in Equation (S.4) and its boundary conditions. After running the transient simulation, the input reconstruction method described in the manuscript was used to compute the conditions of equivalent systems at steady state and fifty random points were chosen for the evaluation of the steady-state profiles.

The sinusoidal functions were chosen for the three parameters. The simulations were repeated 10 000 times varying the values of Pe_{mol}^0 (range $1 \times 10^1, 2 \times 10^2$), Da_j^0 (range $3 \times 10^{-12}, 6 \times 10^6$), and ϵ_j^0 (range 2,32), together with the parameters describing the sinusoidal variations. The 10 000 simulations were run in parallel and required approximately 9 hours on a 40-core (Intel Xeon Gold 6148 2.4 GHz), 187 GB RAM computer. The kinetic schemes considered were those of the type $(A + B \rightarrow C, C + B \rightarrow D)$, and

($A + B \leftrightarrow C + D$), where in both cases C was the product of interest. All reactions were considered to be elementary (unitary reaction order for reactants). The yield of C w.r.t. A was selected as objective function for the comparison between dynamic and steady simulations. In all simulations the ratio between the CSTR and LFR volumes V_{LFR}/V_{CSTR} was kept constant and equal to 12.3, while the CSTR temperature to a constant value of 298.15 K. The tube diameter was 1 mm and the molecular diffusivity was $10^{-9} \text{ m}^2 \text{ s}^{-1}$ (typical of liquids).

In order to ensure that the dynamic systems approximates steady-state operations, it is necessary to satisfy the pseudo-steady-state hypothesis (PSSH):

$$\frac{\partial \hat{c}_i}{\partial \hat{t}} \approx 0 \quad (\text{S.9})$$

This time derivative can be expanded by taking into account the variations of \hat{c}_i w.r.t. time, space, and design parameters (\hat{y}_k), which are only time dependent and in this case are represented by \hat{c}_i^f , $\hat{\tau}_{LFR}$, and \hat{T} :

$$\frac{\partial \hat{c}_i}{\partial \hat{t}} = \frac{\partial \hat{c}_i}{\partial \hat{t}} \Big|_{\hat{x}, \hat{y}_k} + \frac{\partial \hat{c}_i}{\partial \hat{x}} \Big|_{\hat{t}, \hat{y}_k} \frac{\partial \hat{x}}{\partial \hat{t}} + \sum_k \frac{\partial \hat{c}_i}{\partial \hat{y}_k} \Big|_{\hat{t}, \hat{x}, \hat{y}_j \neq k} \frac{d\hat{y}_k}{d\hat{t}} \quad (\text{S.10})$$

The first term on the right hand side is null because of the PSSH and the second is also null because position and time are independent variables. As one wants the PSSH to be valid for any variation of \hat{y}_k , it follows that

$$\frac{d\hat{y}_k}{d\hat{t}} \approx 0 \quad \forall k \quad (\text{S.11})$$

Alternatively, by considering the maximum value of the time variation

$$K_{y_k} \stackrel{\text{def}}{=} \max_{\hat{t}} \left(\frac{d\hat{y}_k}{d\hat{t}} \right) < K_{y_k}^{max} \quad (\text{5})$$

Experimental implementation details

The experiments were run on an automated platform controlled via an in-house software written in Python. The software allows to set the variations of the parameters of interest. In particular it can control the variations of temperature, residence time, and concentration (expressed as a ratio between the inlet concentration, $c_i^f(t)$, to the system and the concentration in the reagents stack, c_i^s). Given this information, the software computes the flowrates needed for each species and sets the pump set-points to the correct value over time. As of now the variations for parameters allowed are constant, linear, and sinusoidal. Via parallelised routines, the software controls the switch of the HPLC valve for analysis and checks continuously for pressure spikes for safety reasons (*e.g.*, clogging).

The volumetric flowrates of each species, Q_i , are computed by solving a system of algebraic equations, starting from residence time, τ_I , and concentration ratios, $c_i^R(t) = c_i^f(t)/c_i^s$. It should be noted that only $NC - 1$ concentration ratios can be given. This issue is solved by letting the software solve for the required solvent ($i = NC$) flowrate. Therefore one has:

$$\sum_i Q_i(t) = \frac{V_{LFR}}{\tau_I(t)} \quad Q_i(t) = \frac{V_{LFR}}{\tau_I(t)} c_i^R(t) \quad (\text{S.12})$$

which leads to the following flowrate for the solvent:

$$Q_{NC}(t) = \frac{V_{LFR}}{\tau_I(t)} \left(1 - \sum_{i=1}^{NC-1} c_i^R(t) \right) \quad (\text{S.13})$$

FTIR and HPLC details

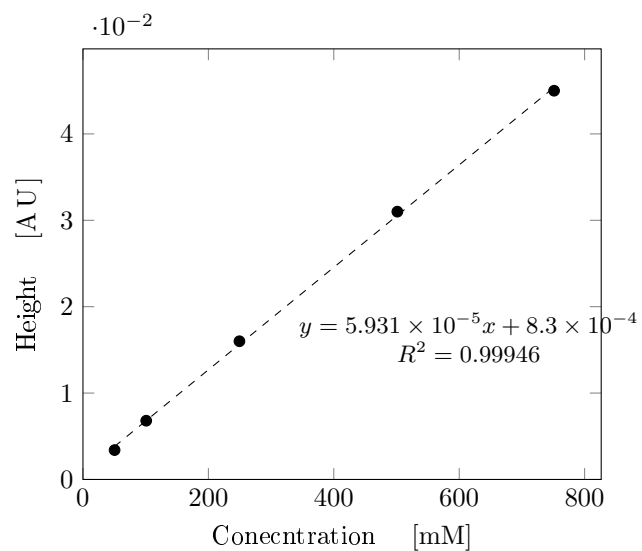


Figure S.2: FTIR calibration curve for product **3**.

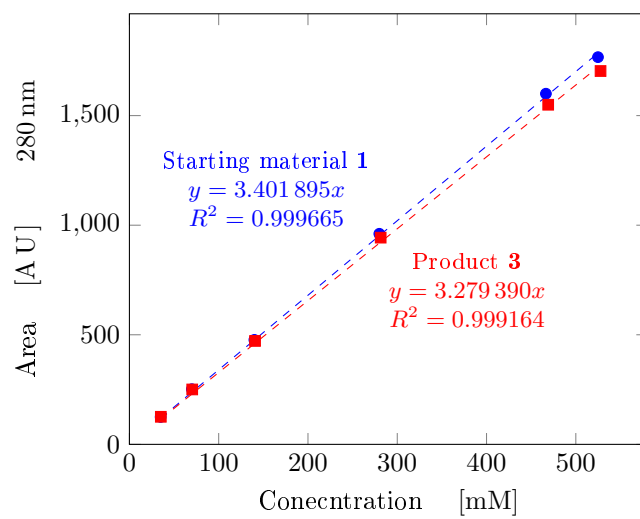


Figure S.3: HPLC calibration curve.

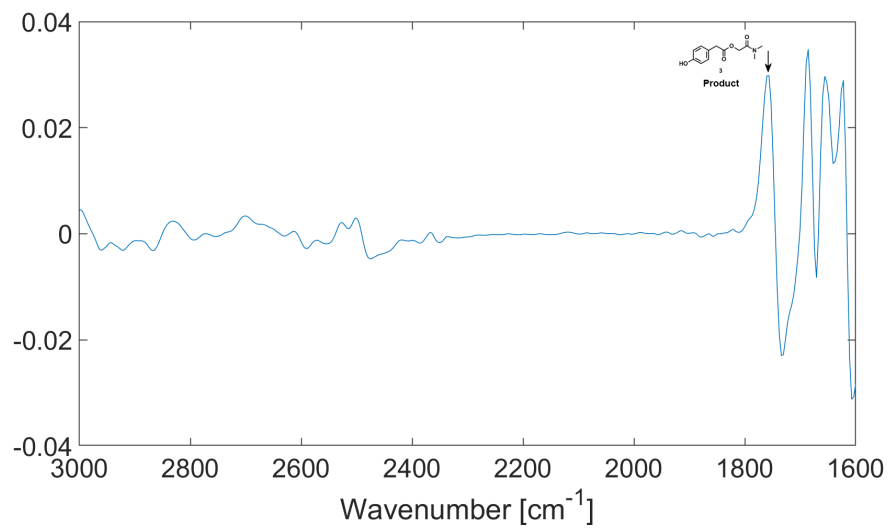


Figure S.4: Example of IR processed spectrum.

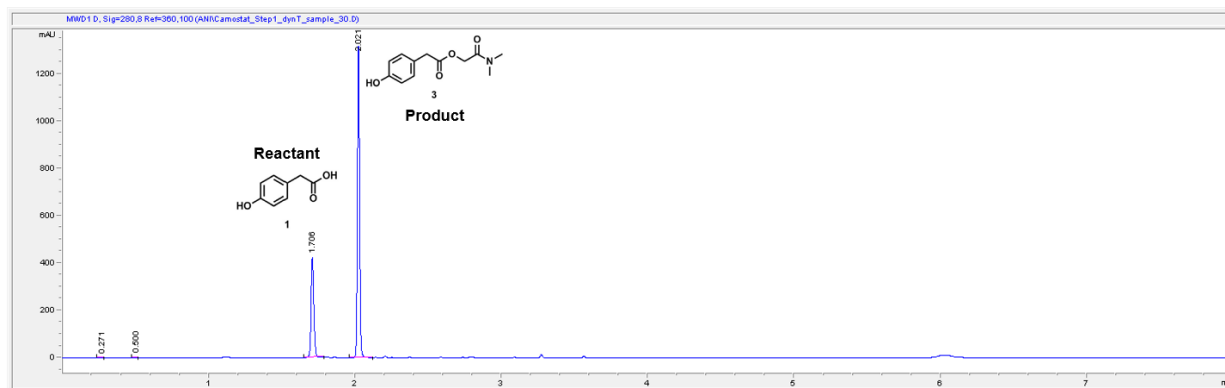


Figure S.5: Example of HPLC spectrum.