Theoretical background: Flow chemistry calculations

Introduction

In a continuous flow system a chemical reaction is carried out with a continuous supply of substrate and reagents. The basic principle of a continuous flow system is shown schematically in Figure 1. In this (commonly used) setup two flows (denoted as Flow A and Flow B) are pumped into the microreactor. After being combined, they start reacting. When the combined flows reach the end of the microreactor, a third flow is introduced to stop the reaction. This is called the quenching flow, and is denoted as Flow Q.
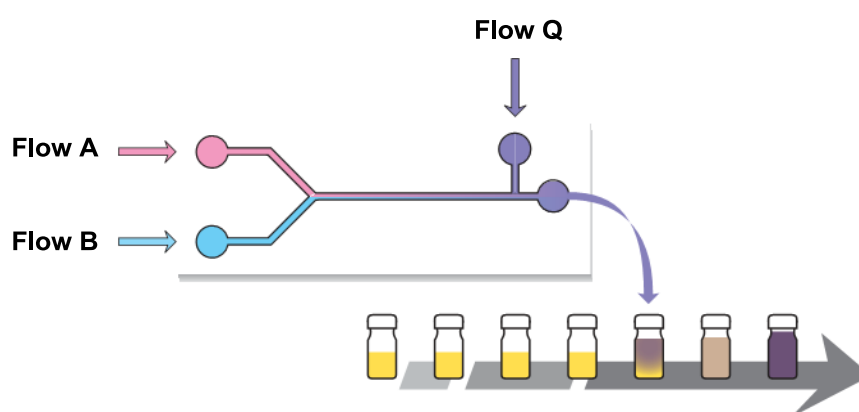

Figure 1: Schematic representation of a continuous flow setup.

In this setup, all three flow rates are adjustable, as well as the temperature of the microreactor. By varying flow rates, it is possible to adjust the reaction time and the molar ratio between substrate and reagent. The reaction temperature is adjusted separately by a temperature controller.

Parameter approach

It has been shown empirically that when conducting continuous flow experiments, it is often most convenient to approach an experiment by its reaction parameters. These parameters can be divided into *input parameters* (reaction time, reaction temperature, molar excess ratio), *intrinsic parameters* (microreactor volume, concentrations of the used solutions) and *output parameters* (flow rates, microreactor temperature) (Table 1).

Table 1: Flow chemistry parameters with their respective symbols.

Input	*Intrinsic (system specific)*	*Output*
Reaction time (t_R)	Concentration flow A (c_A)	Flow rate A (ϕ_A)
Reaction temperature (T)	Concentration flow B (c_B)	Flow rate B (ϕ_B)
Molar excess ratio B/A ($ME_{B/A}$)	Concentration flow Q (c_Q)	Flow rate Q (ϕ_Q)
Molar excess ratio Q/B ($ME_{Q/B}$)	Stoichiometric ratio B/A ($S_{B/A}$)	Microreactor temperature (T)
	Stoichiometric ratio Q/B ($S_{Q/B}$)	
	Microreactor volume ($V_{\mu R}$)	

In this approach, one chooses the input parameters and uses the intrinsic parameters to calculate the output parameters. The relations between the parameters are visualised in Figure 2.
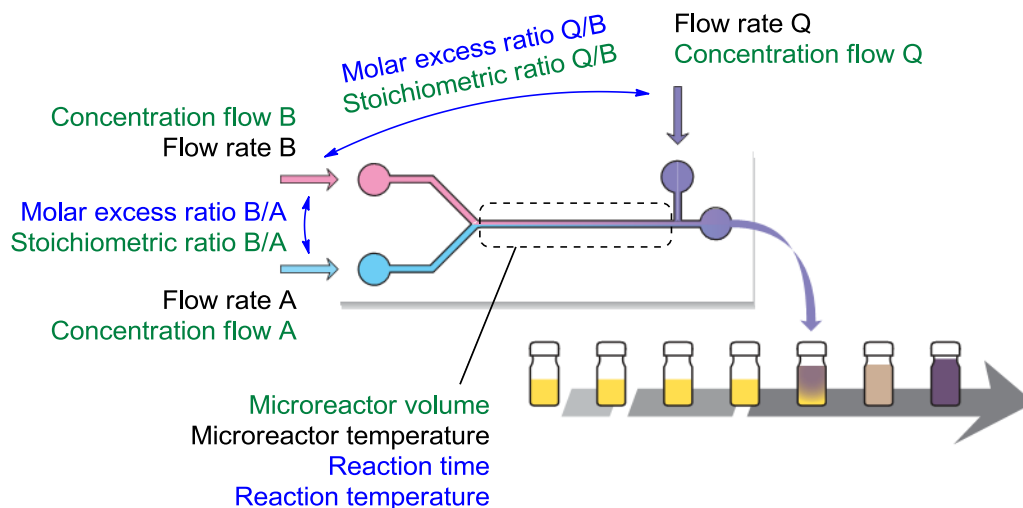
Figure 2: Flow chemistry parameters. Input = blue; intrinsic = green; output = black.

Looking at a typical, generalised continuous flow reaction as in Scheme 1, it will be obvious that it is good practice to define the ratios between reactants in a clear and unambiguous manner. Two reactions are continuously taking place: the main reaction, which forms the basis of the experiment, and the quenching reaction, which is used to destroy all leftover reagent B to stop the reaction.

Main reaction:	a A + b B	$\longrightarrow$	c C
Quenching reaction:	b B + q Q	$\longrightarrow$	r R
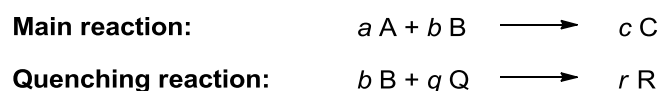
Scheme 1: Stoichiometric ratios of the main reaction and the quenching reaction.

Reactant ratio definitions

• **Stoichiometric ratios** $S_{B/A}$ and $S_{Q/B}$ are the inherent, minimum mole-to-mole ratios needed for the reaction to reach completion. In Scheme 1 it can be seen that in the main reaction a moles of A can react with a maximum of b moles of B, meaning that the stoichiometric ratio $S_{B/A}$ equals b/a. The same holds for the quenching reaction, where $S_{Q/B}$ equals q/b.

• The **molar ratio** ($M_{B/A}$ and $M_{Q/B}$) is the actually used mole-to-mole ratio (in 'batch terms': equivalents). This means that when an experiment is performed, this number signifies the actual ratio between the reactants which are continuously fed into the microreactor.

• The **molar *excess* ratio** ($ME_{B/A}$ and $ME_{Q/B}$) is defined such that a value of 1 corresponds to the stoichiometric ratio, and is calculated by dividing the molar ratio by the stoichiometric ratio (Equation 1). Varying the molar excess ratio is found to be the most straightforward way of varying the reagents ratio, since the minimal amount of reagent is used when the molar excess ratio equals 1. Concluding, for each value of a, b and q (and therefore for each reaction), the molar excess ratio gives a measure of efficiency. Using the molar excess ratio as one of the parameters in an optimisation experiments, it becomes clear immediately how efficient the reaction actually is at its optimal conditions.

$$ME_{B/A} = \frac{M_{B/A}}{S_{B/A}} \quad and \quad ME_{Q/B} = \frac{M_{Q/B}}{S_{Q/B}} \qquad \text{Equation 1}$$

Flow chemistry calculations

The calculation of the output parameters is a straightforward task, but care should be taken that all relations are taken into account. The process of determining the ultimate flow rates is most easily explained in a step-by-step manner.

Reaction and microreactor temperature

The reaction temperature is the same as the microreactor temperature, and is controlled by the temperature controller.

Determination of flow rates

In order to relate reaction time and microreactor volume, we define the *total flow rate* (ϕ_{tot}) as the sum of *flow rate A* (ϕ_A) and *flow rate B* (ϕ_B). We can now relate both microreactor volume ($V_{\mu R}$) and reaction time (t_R) to the total flow rate as in Equation 2. The reaction solution that flows through the microreactor (volume $V_{\mu R}$) with flow ϕ_{tot}, takes time t_R to go from the start to the end of this volume.

$$\phi_{tot} = \phi_A + \phi_B = \frac{V_{\mu R}}{t_R}$$

Equation 2

To obtain values for *flow rate A and B*, we must take into account the *molar ratio between B and A* and the *concentration of solutions A and B* (c_A and c_B). These are related as in Equation 3, since by multiplying the concentration ("mmol/mL") by the flow rate ("mL/min") we get a measure of the amount of substance per unit time ("mmol/min"). For the quenching flow Q the same holds (Equation 4). We also introduce the *flow ratio between B and A* ($R_{B/A}$) and do the same for Q and B.

$$M_{B/A} = \frac{c_B \cdot \phi_B}{c_A \cdot \phi_A} \quad \rightarrow \quad R_{B/A} = \frac{\phi_B}{\phi_A} = M_{B/A} \cdot \frac{c_A}{c_B}$$

Equation 3

$$M_{Q/B} = \frac{c_Q \cdot \phi_Q}{c_B \cdot \phi_B} \quad \rightarrow \quad R_{Q/B} = \frac{\phi_Q}{\phi_B} = M_{Q/B} \cdot \frac{c_B}{c_Q}$$

Equation 4

Combining Equation 2 and Equation 3, we can isolate *flow rate A* as in Equation 5.

$$\phi_B = R_{B/A} \cdot \phi_A \quad \rightarrow \quad \phi_{tot} = \phi_A + \phi_B = \phi_A + R_{B/A} \cdot \phi_A = \left(1 + R_{\frac{B}{A}}\right) \cdot \phi_A$$

$$\phi_A = \phi_{tot} \cdot \frac{1}{1 + R_{B/A}}$$

Equation 5

Applying the same trick for *flow rates B and Q* we get Equation 6 and Equation 7.

$$\phi_B = \phi_{tot} \cdot \frac{R_{B/A}}{1 + R_{B/A}}$$

Equation 6

$$\phi_Q = \phi_{tot} \cdot \frac{R_{B/A} \cdot R_{Q/B}}{1 + R_{B/A}}$$

Equation 7

Example calculation

Suppose we want to conduct the reaction below at 55°C, with a reaction time of 1.0 min at a molar excess ratio B/A of 2.0. We set the molar excess ratio Q/B to 2.0 to make sure all leftover reagent is consumed by the quench flow.

Main reaction: $2\,A + 3\,B \longrightarrow 2\,C$

Quenching reaction: $1\,B + 1\,Q \longrightarrow 1\,R$

→ We now have *chosen* all the *input parameters* of the experiment.

The stoichiometric ratio B/A is 3/2, for Q/B this is 1. Our fictional continuous flow experiment uses three stock solutions – solution A with a substrate concentration of 0.2 M, solution B with a reagent concentration of 0.1 M and solution Q with a concentration of 1.0 M. The microreactor has an internal volume of 92 µL.

→ We now have *defined* all the *intrinsic parameters* of the experiment.

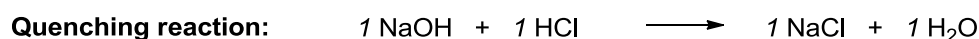With the above equations we can now *calculate* the *output parameters*:

- Calculate *total flow rate*, *molar ratios* and *flow ratios*:
  - $\phi_{tot} = \dfrac{V_{\mu R}}{t_R} = \dfrac{92\ \mu L}{1.0\ min} = 92\ \mu L/min$
  - $M_{B/A} = S_{B/A} \cdot ME_{B/A} = \dfrac{3}{2} \cdot 2.0 = 3.0$
  - $M_{Q/B} = S_{Q/B} \cdot ME_{Q/B} = 1 \cdot 2.0 = 2.0$
  - $R_{B/A} = M_{B/A} \cdot \dfrac{c_A}{c_B} = 3.0 \cdot \dfrac{0.2}{0.1} = 6.0$
  - $R_{Q/B} = M_{Q/B} \cdot \dfrac{c_B}{c_Q} = 2.0 \cdot \dfrac{0.1}{1.0} = 0.2$
- Calculate *flow rates*:
  - $\phi_A = \phi_{tot} \cdot \dfrac{1}{1+R_{B/A}} = 92\ \mu L/min \cdot \dfrac{1}{1+6.0} = 13.1\ \mu L/min$
  - $\phi_B = \phi_{tot} \cdot \dfrac{R_{B/A}}{1+R_{B/A}} = 92\ \mu L/min \cdot \dfrac{6.0}{1+6.0} = 78.9\ \mu L/min$
  - $\phi_Q = \phi_{tot} \cdot \dfrac{R_{B/A} \cdot R_{Q/B}}{1+R_{B/A}} = 92\ \mu L/min \cdot \dfrac{6.0 \cdot 0.2}{1+6.0} = 15.8\ \mu L/min$

→ We now have *calculated* all the *output parameters*.

Now just set the right temperature, set the pumps to the correct flow rates and press start!

Exercise 1 – Understanding the calculations

We want to conduct a substitution reaction (see below) in continuous flow. Solution A contains the bromide at a concentration of 0.2 M, solution B contains the sodium hydroxide at a concentration of 1.0 M and the quenching solution Q contains the hydrochloric acid at a 0.5 M concentration. The parameters we want to test are a temperature of 20°C, reaction time of 5.0 min and a molar excess ratio B/A of 1.2. Quenching of the reaction is done using a molar excess ratio of 4.0.

Main reaction: 1 R-Br + 1 NaOH $\longrightarrow$ 1 R-OH

Quenching reaction: 1 NaOH + 1 HCl $\longrightarrow$ 1 NaCl + 1 H$_2$O

    A. With an internal microreactor volume of 56 µL, calculate all three flow rates (A, B and Q) of the experiment.

    B. What happens to the flow rates if we increase the reaction time by a factor 5? Give an explanation without calculations.

    C. Suppose we run an experiment at flow rates 45.0, 20.0 and 15.0 µL/min for A, B and Q respectively. What are the reaction time and molar excess ratios ($ME_{B/a}$ and $ME_{Q/B}$)? *Hint: Equations 4 and 5 are now two equations with two unknowns.*

Exercise 2 – A real-world example

The following experimental procedure is used in the bromination of acetophenone:

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All experiments were conducted in a standard FutureChemistry B-200
FlowStart setup, using the Basic Quench Microreactor with internal
volume of 92 µL.

Solution A:   Acetophenone (233 µL, 2.00 mmol) and hydrobromic acid (33%
              in acetic acid, 173 µL, 1.00 mmol) dissolved to a total
              volume of 10 mL with 1,4-dioxane

Solution B:   Bromine (103 µL, 2.00 mmol) dissolved to a total volume of
              10 mL with 1,4-dioxane

Solution Q:   2-Methoxypropene (555 µL, 6.00 mmol) dissolved to a total
              volume of 10 mL with 1,4-dioxane
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    A. Give the reaction equation of the bromination reaction, for both main reaction and quenching reaction. From this equation, determine the stoichiometric ratios $S_{B/A}$ and $S_{Q/B}$. You might first need to figure out the reaction mechanism for the main reaction as well as for the quenching reaction.

    B. In a previous optimisation studies it was found that for this reaction optimal conditions are achieved at a molar excess ratio B/A of 1.5, temperature of 20°C and a reaction time of 40 sec. A molar excess ratio Q/B of 3.0 was used. Calculate the corresponding flow rates.

    C. When the optimised reaction (parameters of 2.B) is translated to a larger microreactor, the reagent is fully consumed and thus quenching is not needed. Calculate the microreactor volume needed for a throughput (total flow rate) of 1.0 L/min reaction mixture. Also sketch the continuous flow setup needed for this so-called preparative run.