Mass Transport and Reactions in the Tube-in-Tube Reactor

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ABSTRACT: The tube-in-tube reactor is a convenient method for implementing gas/liquid reactions on the microscale, in which pressurized gas permeates through a Teflon AF-2400 membrane and reacts with substrates in liquid phase. Here we present the first quantitative models for analytically and numerically computing gas and substrate concentration profiles within the tube-in-tube reactor. The model accurately predicts mass transfer performance in good agreement with experimental measurement. The scaling behavior and reaction limitations of the tube-in-tube reactor are predicted by modeling and compared with gas-liquid micro- and mini-reactors. The presented model yields new insights into the scalability and applicability of the tube-in-tube reactor.
INTRODUCTION

Microscale chemical synthesis in flow has advanced rapidly in recent years as a fast and effective means to discover and screen suitable reaction candidates for continuous productions.\textsuperscript{1-9} Among the many reactions studied in microchemical systems, the gas/liquid biphasic reaction is an important category.\textsuperscript{10} In order to create sufficient phase contact and increase mass transfer, a number of multi-phasic reactor configurations have been designed and tested,\textsuperscript{11} including the segmented flow microreactor,\textsuperscript{10,12-14} the packed-bed microreactor,\textsuperscript{15,16} the falling film microreactor,\textsuperscript{17,18} and the tube-in-tube reactor.\textsuperscript{19-27}

The tube-in-tube configuration uses Teflon AF-2400 tubing as a contact interface to saturate liquid streams with gas.\textsuperscript{19-27} Teflon AF-2400 is an amorphous fluoropolymer that is highly permeable to gas yet non-permeable to liquid.\textsuperscript{28} Owing to this selectivity, Teflon AF-2400 tubing has been employed as a degasser to produce gas-free liquid streams after biphasic gas/liquid reactions in segmented flow.\textsuperscript{29} The tube-in-tube design enables subsequent gas/liquid reactions while circumventing direct encounters of the two phases. This novel concept has gained much attention in the flow chemistry community as a convenient method to implement gas/liquid reactions.\textsuperscript{19-27,30}

The tube-in-tube reactor consists of a Teflon AF-2400 inner tubing and a non-permeable outer tubing (Figure 1a). The ‘shell side’ is filled with pressurized gas. The liquid stream (pure solvent or dissolved reactant) enters from the inlet of the ‘tube side’. Gas permeates through the inner wall and dissolves into the bulk of the liquid stream along the tube. A reverse configuration has also been reported in which liquid passes on the shell side and pressurized gas is on the tube side (Figure 1b).\textsuperscript{31,32}

A variety of gas/liquid reactions have been studied in the tube-in-tube reactor.\textsuperscript{19-27} For a few very fast reactions (residence time ~ 10 s) without the need for heating or heterogeneous catalysts (e.g., Grignard carboxylation using CO\textsubscript{2}), reactions occur simultaneously with gas diffusion within the tube-in-tube region.\textsuperscript{24} For most other reactions, the tube-in-tube section is only used to dissolve gas into the liquid stream, and the reaction subsequently takes place in a packed bed (catalyst cartridge)\textsuperscript{23} or a heating coil.\textsuperscript{22}
The amount of gas dissolved into flow is a key factor determining the usefulness of tube-in-tube design since the subsequent reactions are easily limited by the amount of gas loading.\textsuperscript{23,30} The dissolved gas concentration at the inlet of the tube-in-tube section is at the background level in the solvent, typically close to zero. The upper bound for the dissolved gas concentration at the outlet, $C_{\text{outlet}}$, is the saturation concentration, $C_{\text{sat}}$, determined by gas pressure and Henry’s law constant. In our model, we define the saturation fraction as $C_{\text{outlet}}/C_{\text{sat}}$, which is a dimensionless quantity independent of gas pressure. Saturation fraction is an important parameter to characterize mass transfer performance across different configurations and operation conditions.

Previous measurements of the saturation fraction of a given gas/solvent combination have required the development of inline analysis for each specific system and series of experiment to sample a range of conditions (e.g., residence time, pressure, flow rate).\textsuperscript{19,20,22-27} Predictions of gas dissolution profiles can be made simply based on transport modeling and analysis since the experimental observables are solely governed by the transport process of dissolved gas molecules across the Teflon membrane and laminar flow. Thus, such predictions offer the

\textbf{Figure 1.} (a) Conventional tube-in-tube configuration; (b) Reverse tube-in-tube configuration.
potential to reduce experimental effort and provide insight into the scaling behavior of the tube-in-tube system. Here, we present the first quantitative transport and reaction model of the conventional and reverse tube-in-tube reactors, with both analytic predictions and numerical simulations that reproduce experimental data. The model increases our understanding of the underlying transport phenomena and reaction limitations, enabling assessment of the scalability and applicability of the tube-in-tube reactor. We also compare the mass transfer mechanism and reactor performance of the tube-in-tube configuration with other gas/liquid micro- and mini-reactors (e.g., segmented flow reactors).\textsuperscript{9}

**TUBE-IN-TUBE MODEL**

Typical Teflon AF-2400 tubing has large surface area and small cross-sectional dimensions, contributing to its relatively fast gas diffusion rate across membrane and flow. The parameters for the tube-in-tube study below are based on a case study measuring hydrogen dissolution into dichloromethane (Table 1).\textsuperscript{23} The model is developed in a general framework so that other parameter values can be substituted for a particular application. It should also be noted that the model is entirely based on physical principles, and it does not contain any fitted parameters.

| Parameters                              | Symbols | Values          |
|-----------------------------------------|---------|-----------------|
| Teflon AF-2400 Tubing Inner Radius (mm) | $R$     | 0.3             |
| Teflon AF-2400 Tubing Wall Thickness (mm)| $H$     | 0.1             |
| Teflon AF-2400 Tubing Length (m)       | $L$     | 0.5             |
| Residence Time (s)                     | $t$     | 1 - 20          |
| Flow Rate (mL/min)                     | $Q$     | 0.4 – 8.5       |
| Gas                                     |         | H$_2$           |
| Solvent                                 |         | DCM             |

We consider steady state mass transfer in an axial symmetric geometry. The flow field is fully-developed with a parabolic velocity profile. As a first step, we consider solely mass transfer with
no reactions. The species conservation equation for dissolved gas in the liquid flow then takes the form (all variables are described in Table 2):

\[ 2U(1-\frac{r^2}{R^2}) \frac{\partial C_i}{\partial z} - D_i \frac{\partial^2 C_i}{\partial z^2} = D_i \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial C_i}{\partial r} \right). \]  

(1)

The first term on the left hand side is axial convection, and the second term is axial diffusion. The term on the right hand side is radial diffusion. The conservation equation is a version of the Graetz problem, describing steady-state diffusion-controlled transport from a surface into a pressure-driven tubular flow. \(^{33}\) The boundary conditions are set by the physical system. The concentration of gas on the shell side, effectively a compressed gas chamber, is set by the partial pressure of gas \((P_0)\) and temperature,

\[ C_{i,o} = \frac{P_0}{RT}. \]  

(2)

| Symbols | Parameters | Values | Units |
|---------|------------|--------|-------|
| \(U\)   | average speed of flow | 0.025 – 0.5 | m·s\(^{-1}\) |
| \(r\)   | radial position | 0 – 0.3 | mm |
| \(R\)   | inner radius | 0.3 | mm |
| \(z\)   | axial position | 0 – 0.5 | m |
| \(L\)   | tube length | 0.5 | m |
| \(C_i\) | gas concentration in solvent | 0 – 0.04 | mol·dm\(^{-3}\) |
| \(C_{i,mem}\) | gas concentration in membrane | 0 – 0.4 | mol·dm\(^{-3}\) |
| \(C_{i,o}\) | concentration of gas phase (at 10 bar) | 0.4 | mol·dm\(^{-3}\) |
| \(D_i\) | diffusivity of gas in solvent | \(11.5 \times 10^{-9}\) | m\(^2\)·s\(^{-1}\) |
| \(k_{mem}\) | mass transfer coefficient of gas in membrane | \(2.45 \times 10^{-5}\) | m·s\(^{-1}\) |
| \(K_H\) | Henry’s law constant for gas with solvent | 9.98 | - |

Table 2. List of Variables and Values Used in the Model

At the Teflon AF-2400 membrane interface to the liquid \((r = R)\), the flux of dissolved gas molecules across the membrane equals the flux into the liquid:
\[ D_i \frac{\partial C_i}{\partial r} \bigg|_{r=R} = k_{mem} \cdot (C_i,0 - C_{i,mem} \bigg|_{r=R}) . \]  

(3)

In addition, the concentration of dissolved gas in the membrane at the gas/liquid interface, \( C_{i,mem} \bigg|_{r=R} \), is related to that in the liquid at the interface, \( C_i \bigg|_{r=R} \), through the Henry’s law constant, \( K_H \),

\[ \frac{C_{i,mem} \bigg|_{r=R}}{C_i \bigg|_{r=R}} = K_H . \]  

(4)

Finally, axial symmetric geometry implies that there is no flux across the center line of the system,

\[ \frac{\partial C_i}{\partial r} \bigg|_{r=0} = 0 . \]  

(5)

In order to delineate the important parameter combinations controlling the performance of the tube-in-tube reactors, we performed a scaling leading to the following form of the dimensionless mass conservation equation (eq 1):

\[ Pe(1-\eta^2) \frac{\partial \Theta}{\partial \zeta} - \frac{\partial^2 \Theta}{\partial \zeta^2} = \frac{1}{\eta} \frac{\partial}{\partial \eta} (\eta \frac{\partial \Theta}{\partial \eta}) . \]  

(6)

The dimensionless variables are summarized in Table 3.

| Dimensionless Group | Expression | Magnitude | Definition |
|---------------------|------------|-----------|------------|
| \( Pe \)            | \( \frac{2UR}{D_i} \) | \( 10^4 \) | Peclet number, the ratio of diffusion time scale over convection time scale |
| \( \eta \)         | \( \frac{r}{R} \) | \( 0 - 1 \) | dimensionless radial position |
| \( \zeta \)       | \( \frac{z}{R} \) | \( 0 - 10^3 \) | dimensionless axial position |
| \( \Theta \)    | \( \frac{C_i K_H}{C_{i,0}} \) | \( 0 - 1 \) | dimensionless concentration |
When feasible, it is generally beneficial to find an analytic solution to the governing equations before embarking on numerical simulations. Analytic solutions offer physical insight into the governing mass transport processes and often allow simple calculations useful in planning experiments. Several simplifications are made to facilitate the analytic solution. First of all, the Peclet number \((Pe)\) is on the order of \(10^4\), which implies that convection dominates over diffusion and that axial diffusion can then be neglected relative to axial convection. Moreover, the quantity of most interest is the average concentration of dissolved gas along axial position, especially its value at the outlet (i.e., \(C_{\text{outlet}}\)). To this end, we perform a velocity-weighted average of concentration, \(C_{ib}\),

\[
C_{ib}(z) = \frac{\int_A C_i v_z dA}{\int_A v_z dA} = \frac{\int_{r=0}^{r=R} 2U \left(1 - \left(\frac{r}{R}\right)^2\right) \cdot C_i \cdot 2\pi rdr}{\pi R^2 U}.
\]  

(7)

Here, \(v_z\) stands for axial flow velocity, which is a parabolic function of \(r\). \(U\) is the average liquid velocity. In the dimensionless form:

\[
\Theta_{ib}(\zeta) = \int_{\eta=0}^{\eta=1} 4(1 - \eta^3) \Theta_i \eta d\eta.
\]  

(8)

The axial gradient of \(\Theta_{ib}\) is determined by the overall mass transfer coefficient \(k_i\),

\[
\frac{d\Theta_{ib}(\zeta)}{d\zeta} = -\frac{2k_i}{U} (\Theta_{ib}(\zeta) - 1).
\]  

(9)

\(k_i\) combines the contributions from flow \(k_{i,fl}\) and membrane \(k_{i,mem}\):

\[
\frac{1}{k_i} = \frac{1}{k_{i,fl}} + \frac{1}{k_{i,mem}}.
\]  

(10)

\(k_{i,mem}\) is obtained from membrane permeability data.\(^{28}\) \(k_{i,fl}\), the mass transfer coefficient associated with radial transport in the flow, is defined by the Sherwood number, \(Sh\),

\[
Sh(\zeta) = \frac{2k_{i,fl}}{D_i} \left. \frac{\partial \Theta_i}{\partial \eta} \right|_{\eta=1} \left. \frac{\partial \Theta_{ib}}{\partial \eta} \right|_{\eta=1} - 1.
\]  

(11)

Using a two-compartment approximation model\(^{34}\), the mass transfer mechanism can be divided into two regimes along the axial direction: the entrance region (where a thin boundary layer grows and mass transfer resistance is relatively small), and the fully-developed region (where boundary layers grow thick enough to merge, and the mass transfer coefficient becomes a
constant). By solving for $Sh(\zeta)$ in the entrance and fully developed regions respectively, we obtain:

\[
Sh = 1.357\zeta^{-\frac{1}{3}}Pe^{\frac{1}{3}} \quad \text{(entrance region)}
\]

\[
Sh = 3.657 \quad \text{(fully developed region)}.
\]

The boundary between the two compartments is determined by equating eqs 12 and 13, which yields:

\[
\zeta = 0.051Pe.
\]

For more details about the analytic derivation, please refer to the Supporting Information.

Based on the $Sh$ number, the mass transfer resistance of the membrane and the flow can then be compared. $k_{i,\text{m}}$ rapidly decreases in the entrance region, until it reaches a constant value of $7.0 \times 10^{-5} \text{ (m/s)}$ in the fully developed region. On the other hand, $k_{i,\text{mem}}$ remains a constant at $2.2 \times 10^{-4} \text{ (m/s)}$. The inverse of the mass transfer coefficient represents the mass transfer resistance, which is additive as shown in eq 10. Therefore, along the length of the tube, the mass transfer resistance of the flow gradually increases until it becomes greater than that of the membrane, although the two values still remain on the same order of magnitude. Consequently, neither resistance can be neglected in a quantitative analysis. Moreover, since the membrane resistance is not dominant in the overall mass transfer resistance, the decrease of membrane thickness alone will not result in significant enhancement in the mass transfer performance.

With $Sh(\zeta)$ known, eq 9 can be integrated in two consecutive sections to yield $\Theta_{ib}(\zeta)$, which can subsequently be converted into $C_{ib}(z)$, i.e., the velocity-averaged bulk concentration as a function of axial position. Its value at the outlet corresponds to the saturation fraction measured experimentally. By performing calculations over a range of residence times, we can obtain saturation fractions as a function of residence time.

In order to evaluate the analytic solutions and justify the assumptions made, we performed finite element numerical simulations with COMSOL Multiphysics 4.2 by directly solving the governing mass balance, eq 1, along with its boundary conditions, eqs 3-5, without any a priori simplification. The numerical simulations generated detailed three-dimensional concentration profiles as a function of both radial and axial positions. The strong convective nature of the problem ($Pe \sim 10^4$) necessitated the use of a refined mesh with a total number of $5 \times 10^4$ elements.
The reactor geometry used in numerical simulations is shown in Figure 2a. The tube-in-tube section is sandwiched between a pre-entrance section and a post-exit section. The pre-entrance section represents the tube typically connected to the tube-in-tube unit and ensures that the velocity field is fully-developed (i.e., a steady parabolic velocity profile has been established) before entering the tube-in-tube section. The post-exit section has no mass transfer or reaction so that the boundary condition at the outlet, no axial concentration gradient, is satisfied. To the right is the Teflon AF membrane, which is exposed to pressurized gas on the right hand side boundary. The two-dimensional scheme rotates into a three-dimensional tubular configuration around the symmetry axis.

The concentration of dissolved gas, \( C_i(r, z) \), is calculated as a function of radial and axial coordinates. The velocity-weighted averaged concentration of dissolved gas, \( C_{ib}(z) \), is then obtained as a function of axial position (eq 7). The value of \( C_{ib}(z) \) at the outlet is \( C_{\text{outlet}} \), which is equivalent to the saturation fraction when divided by \( C_{\text{sat}} \). A series of gas concentration profiles and saturation fractions can then be computed for different residence times. Figures 2b and 2c are snapshots of gas concentration profiles at different residence times as obtained from the numerical solution. Solvent flows in from the inlet without any dissolved gas, while the right hand side boundary of the membrane is in equilibrium with the compressed gas, with the saturation concentration \( C_{\text{sat}} \). For a shorter residence time (Figure 2b), solvent flows through rapidly, such that the gas is only able to permeate into the region near the membrane without fully penetrating the bulk of the liquid. The saturation fraction is thus relatively low (60%). For a longer residence time (Figure 2c), the gas molecules have sufficient time to penetrate throughout the liquid and near full saturation is achieved (saturation fraction = 98%).
RESULTS AND DISCUSSION

Model Verification

Analytic solutions and numerical simulations were performed under the same operation conditions as the experiments\textsuperscript{23} to determine the saturation fraction of hydrogen dissolved in DCM as a function of residence time (Figure 3). The predictions obtained from the two different approaches are within 2\% difference of each other, supporting the approximations used in deriving the analytic solution. The analytic approach is less computationally demanding, and it provides insights into the distinction between two mass transfer compartments, namely, the entrance region and the fully-developed region. On the other hand, numerical simulations yield detailed three-dimensional concentration profiles inside the reactor, and can be extended to alternative reactor configurations and systems with reactions, as is demonstrated below.
Our modeling results are also in good agreement with experimentally measured saturation values. Figure 3 compares model predictions with both the digital bubble counter measurements and the conventional glass burette measurements, according to the work of O’Brien et al. In addition to reproducing experimental results, the simulations have the advantage of providing detailed concentration profiles inside the reactor, which are not accessible experimentally. The three-dimensional concentration profiles elucidate reactant distributions as a result of the mass transfer characteristics of the tube-in-tube configuration. Such physical insights are helpful in predicting scaling up behaviors of the tube-in-tube reactor.

Scale-up Behavior:

In continuous flow chemistry systems, production can be increased by a longer operation time, but that approach is typically only applicable for small amounts. In order to scale up, the production rate must be increased, which is proportional to the volumetric flow rate and the product concentration in flow. The concentration of product is limited by the saturation concentration of gas in the liquid phase, as is subsequently discussed in the context of reactions in the tube-in-tube reactor. Here in this section, we focus on the scaling-up of the volumetric flow rate, $Q$, without sacrificing mass transfer performance.
The volumetric flow rate is dependent on three variables:

$$Q = \frac{(\text{Cross sectional area}) \times (\text{Tube Length})}{\text{Residence Time}}.$$  \hspace{1cm} (15)

In order to increase the volumetric flow rate, we can (i) decrease residence time, (ii) increase tube diameter, and (iii) increase tube length. We examined each of the three factors separately while keeping the other two constant. For comparison, the three approaches will depart from the same base case: residence time = 10 s, tube diameter = 6 mm, tube length = 1 m, \(Q = 1.7\) mL/min. Unless otherwise specified, we limit our discussion in the laminar flow regime \((Re < 2,000)\).

(i) Decrease residence time: Decreasing residence time shortens the time for gas permeation. When the residence time decreases from 10 s \((Q = 1.7\) mL/min) to 1 s \((Q = 17\) mL/min), the saturation fraction plummets from 98% to 35% (Figure 4). Thus, decreasing residence time is not an appropriate approach to scale up.

(ii) Increase tube diameter: As mass transfer in the tube-in-tube reactor is dominated by the diffusion process across the radial dimension, increasing the radial dimensions will lead to a proportional increase in mass transfer resistance, which compromises the mass transfer performance. For example, when the tube inner diameter increases from 0.6 mm \((Q = 1.7\) mL/min) to 3 mm \((Q = 42.5\) mL/min) and the membrane thickness increases proportionally, the saturation fraction drops from 98% to 32%.

(iii) Increase tube length: If the tube length is increased, the mass transfer performance will not be compromised as mass transfer resistance (determined by radial dimensions) and residence time are both invariant. Hence, the saturation fraction remains the same (Figure 4). The trade-off is a prohibitively high pressure drop, since \(\Delta P \propto Q^2\) for laminar flow. The flow ultimately turns turbulent at flow rates beyond 14 mL/min, leading to an even larger pressure drop. For example, at a flow rate of 50 mL/min, 30 m of Teflon AF tubing is needed. At the same time, the pressure drop reaches 130 bar, which is beyond the pressure rating for the tube and impractical for most applications.\(^{35}\)
Figure 4. Comparison of different approaches to scaling up (Green triangle: increasing tube length while parallelization; Blue diamond: increasing tube inner diameter; Red square: decreasing residence time.)

One way to reduce pressure drops is to parallelize the unit with multiple shorter strands instead of using one long tube. With the goal of controlling pressure drops below 1 bar, at 50 mL/min, 6 tubes with individual length of 5 m are needed. The Reynolds number is also effectively decreased after parallelization such that the flow remains laminar for all flow rates within the range of 50 mL/min. This approach achieves the production goal, but at a cost of approximately USD$5,000 for Teflon AF-2400 at the current price. A compact way of realizing a parallelized tube-in-tube system would be to seal a bundle of Teflon AF-2400 tubes in a wider impermeable tube, similar to constructions used for bundled heat exchangers and hollow fiber dialyzers. Securely sealing a bundle of thin Teflon tubes within an outer shell and evenly distributing the flow across multiple tubes could be potential engineering challenges.

On the other hand, multiphase gas/liquid flow reactors (segmented flow reactors on the ~ 0.1 mL/min scale and Corning Advanced Flow Reactors on the ~ 10 mL/min scale) have equally fast mass transfer rates as the micro-scale tube-in-tube reactor, and they cover a wide range of scales. Within the full range of flow rates considered here (0 – 50 mL/min), multiphase gas/liquid flow can always achieve full saturation of gas in liquid at the outlet. The mass transfer coefficient
for both the segmented flow reactors and the Corning Advanced Flow Reactors ranges between $0.1 \sim 1 \text{ s}^{-1}$ depending on operation conditions, meaning that their mass transfer time scale is $1 \sim 10 \text{ s}$. The excess gas at the outlet can be easily removed by using a settling tank or by passing pressurized gas/liquid flow through an inline degasser made from Teflon AF-2400. The resemblance between segmented flow microreactors and the Corning Advanced Flow Reactor in terms of mass transfer facilitates the scale up process.

**Reverse Tube-in-Tube Configuration:**

A reverse tube-in-tube configuration has also been introduced in which the liquid stream is on the shell side and pressurized gas is in the inner tube. We performed numerical simulation of the mass transfer performance of the reverse tube-in-tube configuration to compare with that of the original configuration. To facilitate the comparison, the same geometrical dimensions were chosen for the reverse tube-in-tube reactor as the original tube-in-tube (The inner radius of the Teflon AF tubing is 3 mm, the outer radius is 4 mm). The width of the shell side is 3 mm, which is the same as the Teflon AF tubing inner radius.

The simulation results are summarized in Figure 5. When operated at the same flow rate, the reverse configuration provides a higher gas concentration at the outlet. This is because that flowing the solvent on the shell side provides a larger cross-sectional area than on the tube side, which, at an equal volumetric flow rate, provides a longer gas/liquid contact time that enhances mass transfer. The major advantage of this configuration is its ability to directly heat or cool reactive liquid via a stainless steel outer shell. However, Teflon AF-2400 itself is not designed for prolonged or aggressive heating. A PTFE-type fluoropolymer has been reported for higher temperature applications, but the gas permeability performance of this new polymer has not been documented. Another recent investigation attempted to use the Teflon AF-2400 membrane in the reverse configuration at temperatures up to 80°C, but the temperature effect on membrane permeability and durability remains to be studied.

**Reactions in the tube-in-tube**

The above mass transfer discussion forms the foundation for studying gas/liquid reactions in the tube-in-tube reactor coupled with mass transfer. The previously published literature on the tube-in-tube reactor has focused on screening gas/liquid reaction conditions to maximize yield.
and/or selectivity.\textsuperscript{19-27,30} Industrially relevant gas/liquid reactions are typically slow, which would require heating or catalysts to be accelerated to a reasonable rate for flow applications. The tube-in-tube section affords only several seconds of residence time, and Teflon AF is not designed for heating or heterogeneous catalyst loading. Thus, in almost all cases, the tube-in-tube section is used to saturate the liquid stream with dissolved gas before reaction, and the actual reaction takes place downstream in a heating coil or packed bed.\textsuperscript{22,23}

\textbf{Figure 5.} Comparing mass transfer performance of conventional tube-in-tube and the reverse configuration. (a) Concentration profile of gas in tube-in-tube reactor; (b) 3-D visualization of tube-in-tube reactor with gas concentration; (c) Concentration profile of gas in reverse tube-in-tube reactor; (d) 3-D visualization of reverse tube-in-tube reactor with gas concentration; (e)
Comparison of saturation fraction of the two configurations. (Blue line: liquid-inside conventional configuration; Red line: gas-inside reverse configuration.)

One problem in this strategy is the amount of gas dissolved into liquid. Although gas saturation is fast (~10 s), at full saturation, the concentration of dissolved gas is only ~ $4 \times 10^{-2}$ mol/L (at a gas pressure of 10 bar), making it very likely that the dissolved gas is insufficient unless the substrate is highly diluted. Thus, it would be useful to predict the extent of gas deficiency at a given set of conditions, in order to guide experimental design. To this end, we perform numerical simulations with a newly-added reaction term, and an initial concentration ($C_0 = 0.5$ mol/L) of substrate is introduced at the inlet instead of pure solvent. It should be noted that more complex scenarios such as mixed gas, multiple substrates, multiple reactions and complex kinetics can also be modeled (e.g., hydroformylation reaction, in which a mixture of H$_2$ and CO is employed). For clarity of demonstration, a single second-order reaction between pure gas and one substrate is considered here.

For typical reactions (Figure 6a and 6b), the reaction rate is much slower than the gas permeation rate, as is the case with most gas/liquid reactions. As a consequence, reactions occur only outside of the tube-in-tube region in downstream tube sections, and the tube-in-tube region serves only to saturate the liquid stream with gas. Calculating the outlet concentration for Figure 6a and 6b reveals that the gas to substrate molar ratio at the outlet is merely 1:4, indicating that the downstream reactions will be severely gas-limited, i.e. substrate can achieve only 25% of full conversion at best (assuming 1:1 substrate to gas stoichiometry). The separation of mass transfer and reaction in a typical case means that once the flow exits the tube-in-tube region and starts to undergo reactions, gas can no longer be supplied. The low loading of gas severely limits the throughput and productivity of the tube-in-tube reactor. In a typical scenario, gas concentration in liquid can only be as high as ~ $4 \times 10^{-2}$ mol/L (at full gas saturation and a gas pressure of 10 bar), meaning that the inlet substrate concentration cannot exceed $4 \times 10^{-2}$ mol/L if full conversion were to be anticipated. Assuming that the flow rate can be scaled up to 50 mL/min (despite the engineering challenges discussed previously), the throughput is only 2 mmol/min.

For very fast reactions with low gas pressure (Figure 6c and 6d), the reaction is also gas-deficient due to mass transfer limitations. The gas saturation concentration is proportional to gas pressure according to Henry’s law, and the maximum pressure is limited by the mechanical
tolerance of the Teflon AF membrane. The highest gas pressure applied to the tube-in-tube reactor so far is 30 bar, and another source recommends that the maximum gas pressure in the tube-in-tube reactor not exceed 27 bar. Therefore, the dissolved gas concentration in flow is generally very low.

Both of the above scenarios (which represent almost all experimental conditions) result in gas deficiency, meaning that the supply of gas is the limiting factor in determining throughput. One solution for gas deficiency is to perform a total recycle (i.e., connecting the outlet with the inlet) over a long period of time, as proposed in previous works. Although more gas can be introduced into the reactive system after multiple passes through the tube-in-tube section, this approach essentially turns the system into batch mode rather than continuous mode.
Figure 6. Simulated reaction in tube-in-tube reactor: (a) and (b) show gas deficiency under reaction limited conditions (simulation parameters: second-order rate constant $k = 0.1 \text{ L·mol}^{-1}·\text{s}^{-1}$, $p = 30 \text{ bar}$, $c = 0.5 \text{ mol/L}$); (c) and (d) show gas deficiency caused by mass transfer limitations (simulation parameters: $k = 10 \text{ L·mol}^{-1}·\text{s}^{-1}$, $p = 10 \text{ bar}$, $c = 0.5 \text{ mol/L}$); (e) and (f) show the stoichiometric reaction condition, with fast kinetics and high gas pressure (simulation parameters: $k = 10 \text{ L·mol}^{-1}·\text{s}^{-1}$, $p = 30 \text{ bar}$, $c = 0.5 \text{ mol/L}$).

An alternative approach to eliminating gas deficiency is to use multiphase gas/liquid reactors (such as the segmented flow reactor) that have bubbles of compressed gas within the reactive liquid. In this configuration, gas is supplied as soon as it is consumed, and the excess gas can help drive reactions to completion. Heating and/or heterogeneous catalyst loading can also be easily realized by running biphasic reactive flows through a packed bed, which further enhances the rate, conversion and selectivity of a reaction.

For the tube-in-tube reactor, the only case that is not gas-deficient is the rare scenario when very fast reactions are performed under very high gas pressures (Figure 6e and 6f). One phenomenon worth noting, though, is the large radial gradient of both substrate and gas, because gradient-driven diffusion across the radius is the major transport mechanism. Dissolved gas is concentrated near the tube wall, whereas the substrate is concentrated near the tube center. As a result, the gas to substrate concentration ratio spans multiple orders of magnitude across the radial direction. The lack of mixing results in a series of localized reactions zones with highly different reaction rates and potential variation in selectivity. Moreover, it complicates the transfer of optimized reaction conditions from the tube-in-tube reactors to a larger scale reactor with different gas-liquid contacting schemes.

To enhance mixing in the tube-in-tube reactor, especially in scale-up scenarios, one approach is to increase the $Re$ number such that the flow turns turbulent. However, it also induces large pressure drops, which may challenge the mechanical strength of the Teflon AF material and lead to unnecessarily high energy consumption. Alternatively, the use of static mixers inside the tube-in-tube reactor presents the possibility to enhance radial mixing.

On the other hand, mixing does not pose problems for segmented flow microreactors or packed-bed microreactors. Sufficient convection generated by shear flow ensures good mixing within the liquid phase, and microreactor optimization results are more likely to scale.
CONCLUSIONS

We have developed a quantitative model to analyze mass transfer and reactions in the tube-in-tube reactor. Both analytic and numerical solutions closely reproduce available experimental data. With a given combination of gas/solvent/substrate, operation conditions and kinetic information, our model is able to predict detailed three-dimensional concentration profiles for all species, and such information is not accessible experimentally. The profiles in turn enable calculations of the gas saturation fraction, reaction stoichiometry, and substrate conversion. While the tube-in-tube configuration is able to saturate the solvent stream with dissolved gas, it could be limited by (i) difficulty heating or loading with catalyst particles; (ii) relatively low loading of gas, which can lead to gas deficiency and low conversion of substrate; (iii) insufficient radial mixing, complicating reaction kinetics and optimization; and (iv) challenges in transferring tube-in-tube optimization results to larger-scale reactors, due to differing contacting strategies. Nevertheless, the tube-in-tube reactor remains a convenient platform for laboratory flow chemistry experiments, and the understanding of its unique transport behavior will be helpful in future development.

ASSOCIATED CONTENT

Supporting Information. Further details regarding model identification, scaling-up calculation and reaction simulation. This material is available free of charge via the Internet at http://pubs.acs.org

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Supporting Information

for

“The Roles of Mass Transport and Reactions in the Tube-in-Tube Reactor”

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S1. Model Description

S1.1 Identification of Flow Field

When analyzing mass transfer phenomena, the general starting point is the mass conservation equation for solute (the form presented below is in cylindrical coordinate, as is the case for tube-in-tube reactor):

$$\frac{\partial C_i}{\partial t} + v_r \frac{\partial C_i}{\partial r} + \frac{v_\theta}{r} \frac{\partial C_i}{\partial \theta} + v_z \frac{\partial C_i}{\partial z} = D_i \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial C_i}{\partial r} \right) + \frac{2}{r^2} \frac{\partial^2 C_i}{\partial \theta^2} + \frac{\partial^2 C_i}{\partial z^2} \right] + R_{yi}$$  \hspace{1cm} (S1)

The left-hand side is composed of a transient term and convection terms. The right-hand side consists of diffusion terms and a volumetric source term.

Here, we consider axial symmetric mass transfer at steady state without reaction. Therefore, the conservation equation simply becomes:

$$v_r \frac{\partial C_i}{\partial r} + v_z \frac{\partial C_i}{\partial z} = D_i \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial C_i}{\partial r} \right) + \frac{\partial^2 C_i}{\partial z^2} \right] \hspace{1cm} (S2)$$
To proceed, a priori identification of flow field inside the tube is needed. For fully-developed pressure driven flow in a cylindrical tube at low Reynolds number \((Re < 2100)\), the solution to Navier-Stokes equation yields a simple parabolic velocity profile (also known as Poiseuille flow), which reads:

\[
v_z(r) = 2U(1-(\frac{r}{R})^2), \ v_r = 0
\]

\[(S3)\]

\[
U = \frac{Q}{\pi R^2}
\]

\[(S4)\]

\(Q\) is volumetric flow rate.

To justify that the flow field has become fully-developed before entering tube-in-tube region, we note that the momentum entrance length in a tubular flow is given by:\(^1:\)

\[
\frac{L_{ent}}{R} = 1.18 + 0.112 \text{Re} \sim 10^1
\]

\(L_{ent} \sim 10R \sim 3 \text{mm}\). Since the solvent steam has travelled for much longer than 3 mm in the same tubing before entering tube-in-tube region, the momentum entrance effect should be neglected and the velocity field inside tube-in-tube region is fully-developed, i.e., invariant with axial position. Therefore, the flow inside tube-in-tube assumes constant Poiseuille velocity field.

### S1.2 Identification of material property parameters

The permeability \(\kappa\) of Teflon AF-2400 membrane is defined as:

\[
\dot{V}_{\text{STP}} = \kappa \cdot A \cdot \nabla P
\]

\[(S5)\]

Where \(\dot{V}_{\text{STP}}\) is gas volumetric flow rate through membrane at standard temperature and pressure, \(A\) is membrane area, \(\nabla P\) is pressure gradient. Because of the thinness of membrane, \(\nabla P\) can be linearized as \(\nabla P = \frac{\Delta P}{H}\), where \(\Delta P\) is the pressure drop across membrane, \(H\) is membrane thickness. Compare with the expression for gas phase mass transfer coefficient \(k_g\):

\[
\dot{n} = k_g \cdot A \cdot \Delta C_{g,i}
\]

\[(S6)\]
Where $\dot{n}$ is the gas molar flow rate through membrane, and $\Delta C_{g,i}$ is the gas concentration difference across membrane.

Using the ideal gas law (at standard temperature and pressure$^2$):

$$
V_{STP} = \dot{n} R \frac{T_{\text{standard}}}{P_{\text{standard}}} = \dot{n} R \frac{273.15 K}{1.01325 \text{ bar}}
$$

(S7)

$$
\Delta P = \Delta C_{g,i} RT
$$

(S8)

$$
k_{g,\text{mem}} = \left( \frac{T}{273.15 \text{ K}} \right) \cdot (1.01325 \text{ bar}) \cdot \frac{K}{H} = 2.45 \times 10^{-5} \text{ (m/s)}
$$

(S9)

However, it should be noted that the obtained $k_g$ is based on gas concentration, so the calculated concentration in the membrane is essentially the gas concentration in thermal equilibrium with the membrane. At the membrane/liquid interface, mass transfer coefficient should be based on the concentration of dissolved gas in liquid. Therefore, dimensionless Henry’s law constant $K_H$, which represents the saturation concentration of hydrogen in DCM, is needed for this conversion. Value of $K_H$ for hydrogen and DCM at the given temperature and pressure is not available in handbooks. We thus estimated it using the vapor liquid equilibrium database in Aspen Plus$^\text{®}$, which gives a value of 9.98.

$$
K_H = \frac{C_{g,i}}{C_{l,i}} \quad \text{(Matching concentration at gas/liquid interface)}
$$

(S10)

$$
k_i \frac{\partial C_{l,i}}{\partial x} = k_g \frac{\partial C_{g,i}}{\partial x} = k_g K_H \frac{\partial C_{l,i}}{\partial x} \quad \text{(Matching flux at gas/liquid interface)}
$$

(S11)

Therefore, $k_i = k_g K_H$, meaning that the as-obtained $k_g$ should be multiplied by $K_H$ in order to account for the partition of gas concentration between two phases.

$$
K_H = \frac{C_{g,i}}{C_{l,i}} \cdot \frac{P / RT}{x_{g/l} \cdot C_{l,\text{pure}}} = \frac{P / RT}{x_{g/l} \cdot \frac{\rho_{l,\text{pure}}}{M_{l,\text{pure}}}} = 9.98
$$

(S12)
Thus, in order to make dissolved gas concentration continuous across liquid/membrane interface to facilitate numerical simulation, the gas concentration in membrane is divided by Henry’s constant (Eqn. S10), and the gas permeability is adjusted accordingly.

Furthermore, to obtain numerical solution, it is also necessary to approximate gas diffusivity $D_{g,\text{mem}}$ in membrane based on permeability $\kappa$.

\[ \dot{V}_{\text{STP}} = \kappa \cdot A \cdot \nabla P \]  
\[ \dot{n} = D_{g,\text{mem}} \cdot A \cdot \nabla C_{g,\text{mem}} \]

By using eqn. S7 and S8, we get:

\[ D_{g,\text{mem}} = \left( \frac{T}{273.15 \text{ K}} \right) \cdot (1.01325 \text{ bar}) \cdot \kappa = 2.45 \times 10^{-9} (\text{m}^2/\text{s}) \]  
\[ D_{l,\text{mem}} = D_{g,\text{mem}} K_H = 2.44 \times 10^{-8} (\text{m}^2/\text{s}) \]

Lastly, hydrogen diffusivity in DCM $D_{g,\text{liq}}$ is needed for calculation. This is again not available in handbooks, and it is thus estimated via Stokes-Einstein relation. This is a reasonable estimation due to the low aspect ratio of hydrogen gas molecule.

\[ D_{g,\text{liq}} = \frac{k_g T}{6\pi \eta R} \]

### S1.3 The two-compartment model

$Sh(\zeta)$, the dimensionless mass transfer coefficient of laminar flow, is solved for analytically in two separate regimes: entrance region and fully-developed region.
**Entrance Region:** As pure solvent stream just enters the tube, the concentration change will be confined to a thin boundary layer right next to tube wall. The velocity field near wall can be thus linearized according to Leveque approximation. For constant wall concentration boundary condition, a similarity solution could be obtained:

\[
\Theta(s) = \frac{3}{\Gamma\left(\frac{1}{3}\right)} \int_{s}^{\infty} e^{-s^3} \, dt, \quad \text{where} \quad s = \left(\frac{2}{9}\right)^{1/3} \frac{1 - \eta}{\zeta^{1/3}},
\]

\[\text{(S19)}\]

\[Sh = 1.357 \zeta^{-1/3} Pe^{1/3}\]

\[\text{(S20)}\]

**Fully-developed Region:** As mass transfer boundary later grows thicker along axial position, it disappears eventually due to confined geometry within a tube. At this point, the fully-developed region starts, which is signified by a constant \(Sh\) number. An eigenfunction expansion solution is conveniently obtained, and the eigenvalue of the slowest decaying term dictates \(Sh\) number in the fully-developed region:

\[Sh = 3.657\]

\[\text{(S21)}\]

In reality, there is a transition region between entrance region and fully-developed region that should be characterized by multiple terms of eigenfunction expansion. Here, for mathematical simplicity, we employ a two-compartment model.\(^4\) Namely, we find the boundary of two compartments by linearly extrapolating the \(Sh\) of fully developed region and entrance region:

\[Sh = 1.357 \zeta^{-1/3} Pe^{1/3} = 3.657, \quad \zeta = 0.051Pe\]

\[\text{(S22)}\]

As has been mentioned above, we assume constant concentration boundary condition (i.e., the Dirichlet boundary condition) when solving for the two compartments. The actual boundary condition at the liquid/membrane interface requires matching concentration and matching flux. In order to derive a simple analytic solution, we approximate the boundary concentration to be the Dirichlet boundary condition. Figure 2b and 2c suggest that the concentration along this boundary is relatively constant.
Both the two-compartment model and the Dirichlet boundary condition are justified by the good agreement (only within 2% difference) between the analytic solution and the numerical simulation, which does not contain any of these assumptions. Both modeling approaches are further validated by their ability to closely reproduce experimental results.

S2. Scaling up tube-in-tube reactor

When scaling up the tube-in-tube reactor, increasing length while parallelizing proves to be the most feasible approach. Figure S1 illustrates the number of parallel tubings and their individual length needed to control pressure drop within 1 bar at a given flow rate.

![Figure S1. Number of parallel tubes needed for reactor scale up](image-url)
S3. Modelling reactions in tube-in-tube reactor

Table S1 summarizes reactive systems studied in the tube-in-tube reactor. When residence time is written as a summation of two parts, the first part refers to residence time in the tube-in-tube section, the second part refers to residence time in a downstream reactor.

Table S1. Summary of Tube-in-Tube Experimental Studies

| Gas    | Reaction                     | Res. Time. | T (°C) | Catalyst         |
|--------|------------------------------|------------|--------|------------------|
| CO₂    | Grignard Carboxylation⁵      | 42 s       | R. T.  | --               |
| H₂     | Hydrogenation⁶              | 10 s + 2 min | R. T.  | Ir, homogeneous  |
|        |                              |            |        | Pd/C, heterogeneous |
| H₂     | Hydrogention⁷               | 1 min + 80 min | R. T.  | Ir, Rh, homogeneous |
| CO     | Methoxycarbonylation⁸       | 2 min + 37 min | 100    | Pd, homogeneous  |
| CO     | Hydroformylation⁹           | 1 min + 33 min | 65     | Rh, homogeneous  |
| H₂     | Heck Coupling¹⁰            | 2 min + 20 min | 120    | Pd, homogeneous  |
| C₂H₄   | Glaser-Hay Coupling¹¹       | 16 s + 25 min | 100    | Cu, homogeneous  |
| O₂     | Paal-Knorr¹²               | 1 min + 50 min | 100    | --               |
| NH₃    | Thioureas synthesis¹³       | 1 min + 50 min | 55     | --               |

Apart from modeling simple gas/liquid reactions, our method is also capable of modeling complex system with mixed gas or multiple substrates. Figure S2 demonstrates numerical modeling of a hydroformylation reaction carried out in the tube-in-tube reactor with equal
amount of H$_2$ and CO, and a hypothetical third order rate constant $k = 0.5 \text{ L}^2\text{mol}^{-2}\text{s}^{-1}$. H$_2$ and CO have different concentration profiles due to their different solubility and permeability.

**Figure S2.** Modeling multicomponent reaction in tube-in-tube reactor

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