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Micromixing

Quantitative Characterization of Micromixing Based on Uniformity and Overlap**

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Micromixing is "interpenetration" of solutions by molecular diffusion and field-induced differential mobility of molecules;[1,2] it is neceessary for any homogeneous reaction to occur. In macroreactors, micromixing occurs after macromixing (breaking macrovolumes of solutions into microvolumes by mechanical agitation).[3–6] In microreactors, where mechanical agitation is technically difficult,[7] micromixing can be a sole means of mixing.[8,9] Better mixing is associated with better uniformity of reactant distribution through the reactor and greater spatial overlap of the reactants. Therefore, the characterization of micromixing requires a quantitative parameter that takes into account both the uniformity and the overlap. Multiple quantitative measures for macromixing have been developed and comprehensively reviewed over decades.[3–6] They all are stochastic functions that are not applicable to micromixing, which is driven solely by the deterministic processes of diffusion and/or differential mobility. Measures of micromixing, such as coefficient of variation, quantitative overlap, and some empirical functions, do not take into consideration both the uniformity and the overlap.[10–12] Herein, we introduce nine axioms of micromixing that must be satisfied by any qualitative attribute of the quality of micromixing and design a satisfying quantitative attribute, which we term "micromixing extent" (ME). ME takes into account both the uniformity of reactant distributions through the reactor and the spatial overlap of the reactants; it changes from zero (for no mixing) to one (for complete mixing). Importantly, ME is a general quantitative measure that can be applied to all types of mixtures that are created solely by diffusion and/or differential mobility for which distributions of the solutes through the reservoir can be calculated. For example, we use ME to characterize the quality of micromixing in a capillary microreactor, a type of reactor in which good-quality mixing is difficult to achieve.[13] Our approach for characterization of the quality of micromixing can be used for the optimization of mixing in microreactors by simply maximizing the value of ME.

Considering the generality of our approach and its applicability to reacting and non-reacting molecules, we use terms "solute" and "reservoir" instead of "reactant" and "reactor", respectively. We also use the words mixing and micromixing interchangeably.

In micromixing, the exact solute distributions through the mixture can be easily calculated using deterministic equations.[14] The present work was inspired by the insight that the knowledge of solute distributions creates the foundation for a quantitative description of the quality of micromixing based on the uniformity and the overlap. We first discuss the uniformity and the overlap using common sense. In general, the goal of micromixing is to achieve as homogeneous a molecular "amalgamation" of mixed solutes as possible. In an ideal mixture, every solute uniformly fills the entire volume of the reservoir, and the uniformity is a sufficient property to describe the quality of mixing. This is not the case if mixing is non-ideal, as illustrated in Figure 1a. In Figure 1a1 and Figure 1a2, two solutes are mixed in ways that keep their uniformity of distributions identical. However, it is clear that the mixing is better in Figure 1a2 owing to a better overlap of the two solutes. On the other hand, the overlap on its own is inadequate to describe mixing; two solutes may be completely overlapping but have poor mixing if the solutes have non-uniform concentration distributions. Figure 1b illustrates situations in which the solutes overlap throughout the reservoir, but the mixing quality is different as a result of variations in uniformity. The uniformity is greater for the blue solute in Figure 1b2 than in Figure 1b1, resulting in superior mixing in Figure 1b2.

Given that the quality of micromixing depends on both the uniformity of solute distributions and the spatial overlap of the solutes, our goal was to design a quantitative attribute that ranges from zero to one and describes the quality of micromixing using both criteria. This attribute should be defined by the distributions of solutes throughout the reservoir or, in other words, by the dependence of solute concentrations on their spatial positions in the reservoir at any given time. We coin the term "micromixing extent" (ME) to name this attribute.

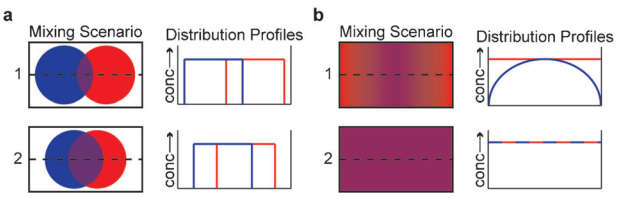

Figure 1. Graphical illustration of mixing red and blue solutes in a two-dimensional reservoir. a) Scenarios 1 and 2 have equal uniformities but different overlaps. b) Scenarios 1 and 2 have equal overlap but different uniformities. The corresponding concentration distribution profiles are shown next to each mixing scenario.

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To deduce a suitable mathematical definition of ME, we first developed a set of axioms that the definition must satisfy in order to comply with the common-sense understanding of molecular mixing. We define nine such common-sense axioms, which are summarized and graphically illustrated in Table 1. Axiom 1 demands that a maximum value of ME = 1 be only achieved when all solutes are distributed uniformly through the entire volume of the reservoir; this is the case in an ideal mixture. Axiom 2 demands that the minimum value of ME = 0 be achieved when the volume in which all solutes are present at the same time is equal to zero. Intuitively, there is an infinite number of ways in which solutes can be mixed to lead to the minimum ME = 0. Axiom 3 demands that ME does not depend on the multiplication of any concentration distribution by any non-zero constant. This axiom makes ME independent of the absolute values of solute concentrations but dependent on their concentration profiles, which makes ME a function of the mixing procedure only. Clearly, this requirement is essential for axiom 1 to be satisfied; otherwise solutes that are uniformly distributed throughout the reservoir but with different concentrations could not have ME = 1. Axiom 4 demands that ME of any set of solutes be less than or equal to that of any subset of the same solutes. This axiom originates from the understanding that increasing the number of solutes can only complicate their mixing. Axiom 5 is related to axiom 4; it demands that adding a new solute with a concentration distribution identical to that of a solute that is already present does not change ME. The need for such an axiom is obvious if we consider that the added solute could be identical to one which is present with the same distribution. In such a case, the addition of a solute would be identical to multiplying the concentration profile of this solute by a constant greater than 1 (see axiom 3). Axiom 6 demands that the diffusion of solutes with identical diffusion coefficients in a closed reservoir leads to improved ME. This axiom follows from our fundamental understanding that diffusion is a natural mechanism of mixing. If the diffusion coefficients are equal, the uniformity increases as the reagents diffuse throughout the reservoir, and the spatial overlap also increases as the solutes diffuse towards each other. The combined effect of improved uniformity and overlap leads to an increase in ME. If the diffusion coefficients are greatly different, a solute with a large diffusion coefficient can temporarily diffuse away from the location of solutes with low diffusion coefficients, thus potentially leading to a temporarily decreased overlap and ME. This phenomenon is illustrated in Figure S1 in the Supporting Information. Axiom 7 demands that ME does not change during hydrodynamic transfer of solutes if there is no diffusion, differential mobility, or flow through the solute boundaries. In the corresponding illustration in Table 1, a highly ordered structure is shown on the left; on the right, this structure is destroyed by hydrodynamic mass transfer, producing a complex pattern. This axiom again follows from the definition of micromixing that it is driven by the nonstochastic processes of diffusion and/or differential mobility. In mathematical terms, axiom 7 requires that ME be an integral of motion. Axiom 8 states that when the concentration profiles of all solutes are composed of rectangular shapes, with the concentration being either zero or a nonzero constant (a single constant for a single solute), ME can be determined from the quotient of the volumes occupied by all the solutes and the total volume of the reservoir. Axiom 9 demands that ME vary with the void volume of the reservoir. It should be noted that, in general, the boundaries of the reservoir are not physical but virtual (see examples below). In qualitative terms, by extending the volume of the reservoir without changing the solute distributions, the solutes occupy a smaller part of the total volume, resulting in a decrease in uniformity and ME. The nine deduced axioms were used for finding a suitable mathematical definition of ME.

After designing and analyzing a number of potential mathematical constructs to define ME, we found one that incorporates both the uniformity and overlap and satisfies the nine axioms (as shown below and proven in the Supporting

Table 1: Axioms for ME and their graphic illustrations

Illustration[a]	Axiom
$ME_1 < 1$ $ME_2 = 1$	1. Maximum ME = 1 can be achieved in a single way; all solutes are distributed uniformly throughout the entire reservoir.
$ME_1 = 0$ $ME_2 = 0$	2. Minimum ME = 0 can be achieved in a variety of ways; when the solutes do not spatially overlap.
$ME_1 = ME_2$	3. ME should not depend on the multiplication of a concentration distribution by a non-zero constant.
$ME_1 > ME_2$	4. ME for all solutes should be less than or equal to ME of any of their subsets.
$ME_1 = ME_2$	5. Adding a new solute with concentration distribution identical to that of an already present solute should not change ME.
$ME_1 < ME_2$	6. Diffusion of solutes with identical diffusion coefficients in a closed reservoir leads to an increase in ME.
$ME_1 = ME_2$	7. ME should not change upon the hydrodynamic transfer of solutes without diffusion, differential mobility, or flow through solute boundaries.
$ME = (v_1+v_2)/V$, V, v_1, v_2	8. If all concentration distributions are rectangular and take a single value for a single solute, ME is the quotient of the sum of mixture volumes where all solutes are present and the total reservoir's volume.
$ME_1 = 2ME_2$	9. If empty volume is added to the reservoir without changing distributions of solutes, mixing efficiency will change in inverse proportion to the total volume of the reservoir.

[a] Illustrations 7 and 9 depict closed two-dimensional reservoirs; the two axes correspond to two spatial coordinates. All other illustrations are shown for one-dimensional mixtures; the horizontal axes correspond to a spatial coordinate and the vertical axes correspond to the solute concentration. The arrowed lines in illustration 8 indicate the respective one-dimensional volumes.

Information). Equation (1) defines ME using this mathematical construct:

$$\mathrm{ME} = \frac{1}{V}\int_V \min\left(C_1(\vec{r},t)\frac{\frac{1}{V}\int_V C_1(\vec{r},t)d\vec{r}}{\frac{1}{V}\int_V C_1^2(\vec{r},t)d\vec{r}}, \ldots C_n(\vec{r},t)\frac{\frac{1}{V}\int_V C_n(\vec{r},t)d\vec{r}}{\frac{1}{V}\int_V C_n^2(\vec{r},t)d\vec{r}} \right) d\vec{r} \quad (1)$$

where V is the volume of an m-dimensional reservoir ($m = 1,2,3$), $\vec{r}$ is a vector of the spatial coordinate, t is the time, $C_i(\vec{r},t)$ is the concentration of the ith solute as a function of $\vec{r}$ and t, and n is the total number of solutes. To satisfy axiom 4, "min" is defined as a function of $\vec{r}$ and t, and its value is equal to the smallest of the n possible values of $C_i(\vec{r},t)\int C_i(\vec{r},t)d\vec{r}/C_i^2(\vec{r},t)d\vec{r}$. Note that the integral of a function over the reservoir volume divided by the total volume of integration in Equation (1) is equivalent to the spatial average of this function. We use $\bar{C}_i$ to designate the spatial average of the concentration of the ith component. Equation (1) can thus be written in a simplified form [Eq. (2)]:

$$\mathrm{ME} = \overline{\min\left(C_1\bar{C}_1/\overline{C_1^2}, \ldots C_n\bar{C}_n/\overline{C_n^2}\right)} \quad (2)$$

Equations (1) and (2) define ME as a spatial average, thus making it a function of time only. It should be noted that the effect of $\overline{C_i^2}$ in the denominator is to normalize the effect of solutes with varying concentrations (as required by axiom 3). The mathematical proof that our definition of ME satisfies the nine axioms and the consideration of alternative definitions are presented in the Supporting Information.

Herein we show that our definition of ME incorporates both the uniformity of solute distributions through the reservoir and the spatial overlap of solutes. In general, the uniformity and the overlap depend on each other and cannot be presented as two separate terms in Equation (1). However, for the two extreme cases considered below, they can be separated into two terms. In the first case, the overlap is completely excluded from consideration by having a single solute, with concentration distribution C, in the reservoir. The ME of a single solute is dependent on its distribution uniformity; accordingly, using Equation (2) for a single solute, we can define the quantitative meaning of uniformity, called quantitative uniformity [QU, Eq. (3)]:

$$\mathrm{QU} = \mathrm{ME}_{\text{single solute}} = \overline{\min\left(C\bar{C}/\overline{C^2}\right)} = \overline{C\bar{C}/\overline{C^2}} = \bar{C}^2/\overline{C^2} \quad (3)$$

The two consequent simplifications in Equation (3) are based, respectively, on two mathematical rules: the minimum of a single value is the value itself, and the average of a single value is the value itself. QU, as defined by Equation (3), ranges from 0 to 1, which is a known property of this function, widely used in mathematical statistics. QU is equal to 0 in the case of "singularity", that is, when all solute molecules are present at a single spatial point, which is experimentally unattainable. QU is equal to 1 when the concentration of the solute in every point of the reservoir is equal to the average concentration; this situation corresponds to a uniformly distributed solute. Figure S2 in the Supporting Information illustrates QU for a number of different concentration profiles.

Since the term QU is now quantitatively defined, we can consider the second extreme case, in which multiple solutes are distributed through the reservoir with the identical uniformity of $\mathrm{QU} = \bar{C}^2/\overline{C^2}$ allowing Equation (2) to be rearranged, leading to Equation (4):

$$\mathrm{ME}_{\text{identical QU}} = \mathrm{QU}\overline{\min\left(C_1/\bar{C}_1, \ldots C_n/\bar{C}_n\right)} \quad (4)$$

In deriving Equation (4), we use the mathematical rule that if each term of a series is multiplied by the same positive coefficient, the minimum of the new series is equal to this coefficient multiplied by the minimum of the original series. The second term at the right-hand side of Equation (4) defines the quantitative meaning of the overlap or simply quantitative overlap (QO), which does not include the QU term [Eq. (5)]:

$$\mathrm{QO}_{\text{identicalgtQU}_i\text{gtforgti=1,...n}} = \overline{\min\left(C_1/\bar{C}_1, \ldots C_n/\bar{C}_n\right)} \quad (5)$$

Note that this QO obtained as a degenerate case of ME is equivalent to QO recently introduced by using a different approach.[11]

Figure 2 illustrates examples of micromixing of three solutes that are characterized by identical values of $\mathrm{QU} = 0.25$ but different QO and, accordingly, different ME. Figure 2a,b demonstrates $\mathrm{QO} = 0$, as there is no volume occupied by all three solutes. The values of QO and ME become nonzero when the volume in which all three solutes are present becomes nonzero. This situation is illustrated in Figure 2c where $\mathrm{QO} = 1$, as the three solutes occupy the same volume, but $\mathrm{ME} < 1$ as the solutes do not uniformly occupy the entire volume of the reservoir. More details on QU and QO can be found in the Supporting Information.

We have shown above that, in addition to satisfying the nine axioms, our definition of ME [Eqs. (1) and (2)] accounts for both the uniformity and the overlap. Practically, to calculate ME the concentrations of all solutes must first be determined as a function of spatial coordinate for any given time, $C_i(\vec{r},t)$, which can be done by analytically solving equations of mass transfer by diffusion field-induced differential mobility of the solutes. We have found analytical solutions for a relatively complex case of a capillary micro-

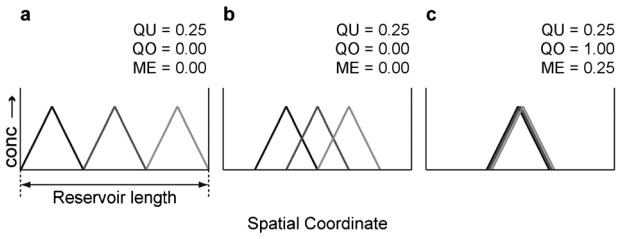

Figure 2. Graphical illustration of mixing three solutes in a one-dimensional reservoir. Quantitative uniformities are equal in every panel and between the panels. The quantitative overlap and, accordingly, micromixing extent, are zero in (a) and (b) and greater than zero in (c).

reactor with sequential injections of the solutes.[15] Alternatively, the concentrations of all solutes as a function of spatial coordinates for any given time can be found numerically. Custom-made software and a numerical approach described in sections 4.2.4–4.2.6 of reference [14] were used in an example below. COMSOL, a user-friendly physics software, makes it possible to find the concentrations of solutes micromixed by diffusion even without writing differential equations.[16]

Then, the boundaries of the reservoir should be defined to allow the integration over the reservoir volume. Finally, Equation (1) is used to calculate ME. To illustrate the use of ME, we simulated two examples of the micromixing of two solutes in an open-capillary microreactor by 1) a field-induced differential mobility along the reactor axis and 2) diffusion (see the Supporting Information).

Finally, we demonstrated that ME is not only a theoretically sound parameter, but it also has a practically useful predictive property. The major reason for mixing molecules in chemistry is to facilitate efficient reaction to, for example, achieve high product yield. We thus tested if ME could be used to optimize micromixing with the goal of increasing product yield. ME was calculated for recently described experiments.[11] The experiments included mixing and hybridizing two strands of complimentary DNA inside a capillary. Briefly, the two DNA solutions were sequentially injected into a capillary by pressure pulses to form plugs with interpenetrating parabolic profiles. After injection, DNA strands mixed by transverse diffusion, and the double-stranded DNA (dsDNA) hybrid was formed. The amount of dsDNA formed was then determined, and the relative product yield was calculated.

To determine ME for these experiments, we first calculated the concentrations of the two DNA strands after mixing as functions of the position in a capillary. The calculations were performed by numerically solving the equations of mass transfer as described in sections 4.2.4–4.2.6 of reference [14]. Custom-made software, Excel with a DLL library written in Object Pascal,[17] was used for calculations (available for download from the "KCE tools" table in the Research section of www.chem.yorku.ca/profs/krylov). The output of calculations was the concentrations of the two DNA strands after mixing as functions of their position in the capillary. These concentrations were then used to calculate ME with Equation (1). For convenience, the calculation of ME was performed in the same Excel spreadsheet. The relative amount of the product was found to correlate well with ME (Figure 3), thus suggesting that ME can be used to maximize the product yield of bimolecular reactions in microreactors by maximizing ME.

To conclude, we introduced a quantitative attribute of micromixing, termed ME, that takes into account two mixing criteria: the uniformity of solute distributions through the reservoir's volume and the spatial overlap of the solutes. According to our definition, ME is a mathematical function that depends only on concentration profiles of solutes in the reservoir; therefore, this parameter is applicable to all kinds of mixtures, including liquid mixtures and solid mixtures, which are created by diffusion of field-induced differential mobility, and for which concentration profiles of solutes can be calculated. Our newly introduced approach for quantitative characterization of the quality of micromixing will allow for the optimization of micromixing by simply maximizing ME.

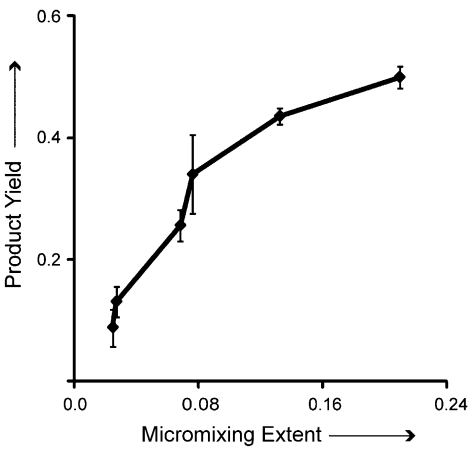

Figure 3. Dependence of product yield on ME. See text for details.

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