

## RESEARCH ARTICLE

# Plate-height model of ion mobility-mass spectrometry: Part 2—Peak-to-peak resolution and peak capacity

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In a previous work, we explored zone broadening and the achievable plate numbers in linear drift tube ion mobility-mass spectrometry through developing a plate-height model [1]. On the basis of these findings, the present theoretical study extends the model by exploring peak-to-peak resolution and peak capacity in ion mobility separations. The first part provides a critical overview of chromatography-influenced resolution equations, including refinement of existing formulae. Furthermore, we present exact resolution equations for drift tube ion mobility spectrometry based on first principles. Upon implementing simple modifications, these exact formulae could be readily extended to traveling wave ion mobility separations and to cases when ion mobility spectrometry is coupled to mass spectrometry. The second part focuses on peak capacity. The well-known assumptions of constant plate number and constant peak width form the basis of existing approximate solutions. To overcome their limitations, an exact peak capacity equation is derived for drift tube ion mobility spectrometry. This exact solution is rooted in a suitable physical model of peak broadening, accounting for the finite injection pulse and subsequent diffusional spreading. By borrowing concepts from the theoretical toolbox of chromatography, we believe that the present study will help in integrating ion mobility spectrometry into the unified language of separation science.

## KEYWORDS

drift tube, ion mobility spectrometry, peak capacity, peak resolution, traveling wave

## 1 | INTRODUCTION

In recent years, ion mobility spectrometry (IMS), both as a stand-alone technique and in combination with MS (IM-MS), has been the subject of intense research. These efforts

led to remarkable improvements in the sensitivity, versatility, and resolving power of commercial and custom-built instruments [2]. Among the many creative ways invented to harness electric forces for separating ions in gases, drift tube (DT)IMS, traveling wave (TW)IMS, trapped (T)IMS and field asymmetric waveform (FA)IMS proved to be the most successful [3,4]. The primary focus of the present study is DTIMS and DTIM-MS within the low-field limit. However, similarities between DTIMS and TWIMS allow

**Article Related Abbreviations:** DTIMS, drift tube ion mobility spectrometry; IM-MS, ion mobility-MS; TWIMS, traveling wave ion mobility spectrometry; VMD, virtual migration distance

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for occasional extension of the plate-height model to derive equations applicable for the latter technique as well.

DTIMS is a gas-phase electrophoretic method, where charged analytes are separated according to their mobilities ( $K$ ) as they drift through a gas-filled cell, propelled by a static, homogeneous electric field [5]. Mobilities are related to the mass, charge, size, and shape of ions, whereby the motion of ions is governed by two-body collisions with the neutral gas particles [6,7]. Within the low-field limit, these collisions are essentially thermal (low reduced field-strengths), making mobilities virtually independent of the applied drift voltage. In general, nonlinear effects on zone broadening are weak, and peaks converge to a Gaussian profile. Thus, plate-height models can be efficiently applied to describe DTIM separations. Having explored zone dispersion in detail previously [1], in the present study we further extend the plate-height model of IM-MS and derive suitable formulae for peak-to-peak resolution and peak capacity.

Single-peak resolving power ( $R_p$ ), the number of theoretical plates ( $N$ ), and the plate height (HETP) are highly useful indices to characterize and compare the performance of separation methods based on differential migration. However, the analyst facing a practical problem is often more interested in the actual resolution between two neighboring peaks. Peak-to-peak resolution ( $R_S$ ) is a widely employed, dimensionless measure of the extent of separation between two Gaussian peaks [8]:

$$R_S = \frac{t_2 - t_1}{2\sigma_{t,1} + 2\sigma_{t,2}} = \frac{|\Delta t|}{4\langle\sigma_t\rangle} \quad (1)$$

In Equation (1),  $t_1$  and  $t_2$  are the centroid drift times (or retention times, migration times, etc.), while  $\sigma_{t,1}$  and  $\sigma_{t,2}$  are the corresponding temporal SDs of the distributions. By employing the absolute drift time (or retention time, migration time) difference  $|\Delta t|$  and the arithmetic mean of the standard deviations  $\langle\sigma_t\rangle$ , a more concise formulation ensues. Despite the apparent similarity of the two phrases appearing in IMS literature, single-peak resolving power  $R_p$  and peak-to-peak resolution  $R_S$  should not be confused. The first is related to the sharpness of a single selected signal in the IM spectrum, often defined in a collision cross-section domain [2]. In contrast,  $R_S$  reflects separation between two adjacent peaks, influenced by both the width of the two signals as well as the distance between them.

The rationale behind Equation (1) is as follows: considering two identical Gaussians with the same area and SD,  $R_S$  will be unity when the line tangents to the closer-lying inflection points of the peaks intersect at the baseline. Unit resolution ( $R_S = 1$ ) in these cases means that each peak overlaps 4.55% of the other peak's area, while baseline res-

olution ( $R_S = 1.5$ ) results in a 0.27% overlap. The above values, however, change at constant  $R_S$  if the two peaks are not identical: the same  $R_S$  value may apply to different peak pairs with different overlap, depending on the ratio of their areas and SDs. Thus,  $R_S$  is not a direct measure of cross-contamination, and alternative functions were developed that are better suited for preparative separations and non-Gaussian peak profiles [9–11]. Although many of these functions reflect peak overlap more accurately, they are much more difficult to calculate from experimental data and have no clear advantages over Equation (1) in analytical separations, impeding their widespread application. Thus, in separation science, Equation (1) serves as a practical and universally recommended index for measuring resolution between peaks. Owing to its simplicity, popularity, direct connection to peak capacity (see later) and the fact that it served as the starting point for predictive resolution equations in chromatography and electrophoresis, we also choose Equation (1) as the basic definition to derive predictive formulae for stand-alone IMS and IM-MS.

## 2 | RESULTS AND DISCUSSION

### 2.1 | Chromatography-influenced predictive resolution equations for drift tube ion mobility spectrometry

Being a general definition and entirely descriptive, Equation (1) merely specifies the way resolution should be calculated in case an ion mobility spectrum, chromatogram, etc., is given. However, it does not help us identify underlying factors influencing resolution, nor does it help to find the optimal separation conditions. Therefore, predictive equations need to be derived that reveal the fundamental factors determining  $R_S$ , aid the optimization of separations in practice, and may estimate  $R_S$  under prescribed experimental conditions. For clarity, in resolution equations specific for a certain technique the respective separation method is indicated in the subscript of  $R_S$ .

#### 2.1.1 | Equal peak width assumption

Assuming  $\sigma_{t,1} + \sigma_{t,2} = 2\sigma_{t,2}$ , Purnell derived a predictive resolution equation for column chromatography under linear elution conditions [12]:

$$R_{S, \text{Ch}} = \frac{\sqrt{N_2} k_2 - k_1}{4(1 + k_2)} = \frac{\sqrt{N_2} \alpha - 1}{4\alpha} \frac{k_2}{1 + k_2} \quad (2)$$

In Equation (2),  $N_2$  is the plate number for the later eluting component, and  $k_1$  and  $k_2$  are the retention factors of

the respective compounds, while  $\alpha$  is the separation factor expressing intrinsic selectivity ( $\alpha = k_2/k_1$ ). The subscript in  $R_{S,Ch}$  refers to chromatography. Definitions of chromatographic parameters appearing seldom in the IMS literature are provided in the Supporting Information, Section S1.

Employing the same equal peak width assumption, but concentrating on the first peak ( $\sigma_{t,1} + \sigma_{t,2} = 2\sigma_{t,1}$ ), Knox [13] and Thijssen [14] arrived at the following formula:

$$R_{S,Ch} = \frac{\sqrt{N_1}}{4} \frac{|\Delta k|}{1+k_1} = \frac{\sqrt{N_1}}{4} (\alpha - 1) \frac{k_1}{1+k_1} \quad (3)$$

Here,  $N_1$  is the plate count for the earlier eluting solute and  $|\Delta k|$  stands for the absolute difference of retention factors.

Equations (2) and (3) are equivalent and yield the same result as Equation (1), provided the assumption of equal peak widths is satisfied ( $\sqrt{N_1}(1+k_2) = \sqrt{N_2}(1+k_1)$ ). This criterion, however, is often not met in practice, in which case Equations (2) and (3) cease to be equivalent and the choice to apply one or the other becomes arbitrary. If the second peak is broader, as in most cases,  $R_S$  values predicted by Equation (2) will be systematically lower, while those predicted by Equation (3) will be systematically higher than the reference values calculated according to Equation (1). Detailed derivations of the resolution equations presented in Sections 2.1–2.3 can be found in the Supporting Information, Section S2.

The first predictive resolution equation for DTIMS [15] was based on Equation (2), inheriting its limitations stemming from the equal peak width assumption:

$$R_{S,DT} = \frac{\sqrt{N_2}}{4} \frac{\alpha - 1}{\alpha} \quad (4)$$

Here,  $\alpha$  is defined as the ratio of ion mobilities instead of the ratio of retention factors as in chromatography ( $\alpha \geq 1$  by convention). The subscript in  $R_{S,DT}$  indicates that Equation (4) is specific to DTIM separations.

The general reasoning to obtain Equation (4) is as follows: the time the ions need to traverse an empty drift cell in perfect vacuum (i.e., the analogue of chromatographic void time) is negligibly short compared to the actual drift time in gas-filled cells (equivalent of retention time). Therefore, retention factors in DTIMS are virtually infinite, meaning that the chromatographic migration factor  $k_2/(1+k_2)$  is essentially unity and may be neglected. Although the resulting formula is useful, the above argument is not justified by physical models and may be misleading: it implies that IMS is a chromatography-like process with retention playing a central role. Instead, IMS is a gas-phase electrophoretic process where convective flow or partition between stationary and mobile phases are

absent. Thus, void time and retention (factors) cannot be interpreted in relation to this technique.

To circumvent the shortcomings of the above reasoning that stem from physical differences between the techniques, we may instead concentrate on more abstract, general aspects of differential migration processes and utilize the concept of virtual migration distances (VMDs), developed by Rathore and Horváth [16]. VMDs reveal analogies between separation methods and the equivalence of separation parameters across techniques. In this system, the equivalent of the chromatographic migration factor is the electromigration factor, which in case of DTIMS—electrophoretic process in the absence of bulk flow—equals 1. The equivalent of the chromatographic retention factor is the electrophoretic velocity factor, which is infinitely large in DTIMS, analogously to condensed-phase zone electrophoresis without electroosmotic flow. Thus, obtaining Equation (4) from Equation (2) appears justified based on this concept. For the detailed description of VMDs, the interested reader is referred to the seminal publication [16]. The equivalent separation parameters mentioned above together with respective VMDs are summarized in the Supporting Information, Table S1.

### 2.1.2 | Equal plate number assumption and exact solutions

A generally more valid assumption for close-lying peaks in isocratic elution chromatography and DTIMS is that of equal plate numbers. Assuming  $N_1 = N_2 = N$ , Karger obtained the following equation for chromatography [17]:

$$R_{S,Ch} = \frac{\sqrt{N}}{4} \frac{|\Delta k|}{1+\langle k \rangle} = \frac{\sqrt{N}}{4} \left( 2 \frac{\alpha - 1}{\alpha + 1} \frac{\langle k \rangle}{1 + \langle k \rangle} \right) \quad (5)$$

In Equation (5),  $\langle k \rangle$  is the arithmetic mean of the retention factors.

An exact solution requiring no assumption on the width of peaks or the plate number was derived by Said [18,19] and Suematsu and Okamoto [20] by introducing an effective average plate number corresponding to a hypothetical analyte, defined as:

$$N_{avg} = \left( \frac{\langle t_R \rangle}{\langle \sigma_t \rangle} \right)^2 \quad (6)$$

Here,  $\langle t_R \rangle$  is the arithmetic mean of the two retention times, while the denominator contains the arithmetic mean of the peaks' temporal SDs. In practice, the ratio of  $N_1$  and  $N_2$  is generally close to unity, in which case the arithmetic [19,21] or geometric mean [22] of the plate numbers serve as sufficiently good approximation for  $N_{avg}$ . The

**TABLE 1** Corresponding predictive resolution equations for chromatography and drift tube ion mobility spectrometry

Chromatography	Drift tube ion mobility spectrometry	Assumption	Reference and name
$\frac{\sqrt{N_1}}{4} (\alpha - 1) \frac{k_1}{1+k_1}$	$\frac{\sqrt{N_1}}{4} (\alpha - 1)$	$\sigma_{t,1} + \sigma_{t,2} = 2\sigma_{t,1}$	Knox-Thijssen [13,14]
$\frac{\sqrt{N_2}}{4} \frac{\alpha-1}{\alpha} \frac{k_2}{1+k_2}$	$\frac{\sqrt{N_2}}{4} \frac{\alpha-1}{\alpha}$	$\sigma_{t,1} + \sigma_{t,2} = 2\sigma_{t,2}$	Purnell [12]
$\frac{\sqrt{N}}{4} \left( 2 \frac{\alpha-1}{\alpha+1} \frac{\langle k \rangle}{1+\langle k \rangle} \right)$	$\frac{\sqrt{N}}{2} \frac{\alpha-1}{\alpha+1}$	$N_1 = N_2 = N$	Karger [17]
$\frac{\sqrt{N_{avg}}}{4} \left( 2 \frac{\alpha-1}{\alpha+1} \frac{\langle k \rangle}{1+\langle k \rangle} \right)$	$\frac{\sqrt{N_{avg}}}{2} \frac{\alpha-1}{\alpha+1}$	No assumption (exact) <sup>a</sup>	Said [18–20]
$\frac{\sqrt{N_{geo}}}{4} \left( 2 \frac{\alpha-1}{\alpha+1} \frac{\langle k \rangle}{1+\langle k \rangle} \right)$	$\frac{\sqrt{N_{geo}}}{2} \frac{\alpha-1}{\alpha+1}$	Empirical <sup>b</sup>	–

<sup>a</sup> $N_{avg} = (\langle t \rangle / \langle \sigma_t \rangle)^2$ , the effective average plate number.

<sup>b</sup> $N_{geo} = \sqrt{N_1 N_2}$ , that is, the geometric mean of the two plate numbers.

resulting exact predictive equation for  $R_S$  is very similar to Equation (5):

$$R_{S,Ch} = \frac{\sqrt{N_{avg}}}{4} \frac{|\Delta k|}{1 + \langle k \rangle} = \frac{\sqrt{N_{avg}}}{4} \left( 2 \frac{\alpha - 1}{\alpha + 1} \frac{\langle k \rangle}{1 + \langle k \rangle} \right) \quad (7)$$

The only difference is the presence of  $N_{avg}$ . The term in parenthesis reflects the relative velocity difference of the analytes.

Equation (7) reveals the influence of fundamental separation parameters on resolution, does not suffer from the shortcomings of Equations (2) and (3), and yields the same  $R_S$  values as Equation (1) in all cases, irrespective of the ratio of peak widths or plate numbers. Therefore, we may choose it as the basis of a more accurate formula for DTIMS:

$$R_{S,DT} = \frac{\sqrt{N_{avg}}}{2} \frac{\alpha - 1}{\alpha + 1} \quad (8)$$

Here,  $N_{avg}$  is calculated according to Equation (6), using drift times ( $t_D$ ) instead of retention times. Inheriting the above-mentioned advantages of Equation (7), Equation (8) appears as a suitable choice for a predictive resolution equation in DTIMS. Table 1 provides a concise overview of resolution equations for chromatography along with the analogous formulae for IMS.

Figure 1 compares the performance of chromatography-influenced predictive resolution equations for DTIMS, highlighting their trueness under a broad range of settings. Figure 1a portrays the situation with equal plate numbers assumed for the two separands.  $R_S$  values predicted by equations based on the equal peak width assumption (red and yellow traces) show increasing deviation from the true  $R_S$  with growing values of  $\alpha$ , that is, as the distance between the peaks in the ion mobility spectrum increases. Although the experimentally most relevant region is that

of close-lying peaks where  $\alpha$  is relatively low, the results clearly indicate the limitations of the equal peak width assumption. Figure 1b represents a different setting: the ratio of the two peaks' temporal width is swept between 1 and 1.5, while  $\alpha$  is held constant at 1.05. As the second peak becomes broader relative to the first, equations based on various assumptions show increasing systematic deviation. Meanwhile, the exact equation (based on Said's formula for chromatography) successfully predicts the true value of  $R_S$  in the entire range. The empirical formula, where  $N_{avg}$  is approximated by the geometric mean of the two plate numbers, yields results sufficiently close to the true value. Thus, it proves to be a good alternative in practice. It is worth mentioning that the green trace reproduces the true value at exactly one point: Where the peak width ratio equals the value  $\alpha = 1.05$ . At this point,  $N_1$  equals  $N_2$  and the assumption the equation is based on is satisfied.

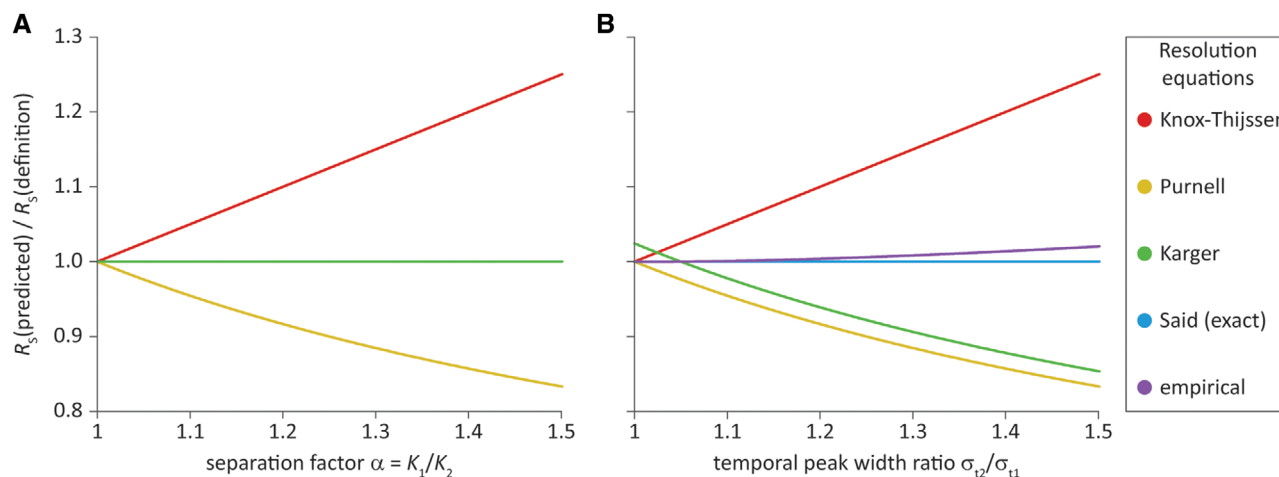
## 2.2 | Resolution equations for drift tube ion mobility spectrometry from first principles

Starting from Equation (1), it can be shown that  $R_S$  depends on the number of theoretical plates and the relative velocity difference ( $\delta_v$ , nonnegative by definition) of the analytes [23]:

$$R_S = \frac{|\Delta t|}{4\langle \sigma_t \rangle} = \frac{\sqrt{N_{avg}}}{4} \frac{|\Delta t|}{\langle t \rangle} = \frac{\sqrt{N_{avg}}}{4} \frac{|\Delta v|}{\langle v \rangle} \equiv \frac{\sqrt{N_{avg}}}{4} \delta_v \quad (9)$$

In Equation (9),  $v_i$  is the average velocity of the  $i$ th analyte zone through the separation field, defined as  $v_i = L/t_i$ . As each analyte migrates through the same conduit (tube, column, etc.) with length  $L$ ,  $|\Delta t|/\langle t \rangle$  equals  $\delta_v$ . Although in stand-alone DTIMS, zone electrophoresis or column chromatography under isocratic conditions the analytes





**FIGURE 1** Comparison of chromatography-influenced resolution equations for drift tube ion mobility spectrometry. Peak-to-peak resolution  $R_S$  calculated according to the various predictive resolution equations for DTIMS. Equations are color coded, and the names refer to the respective chromatographic equations they derive from; in the empirical formula (purple trace),  $N_{\text{avg}}$  is approximated by the geometric mean of  $N_1$  and  $N_2$  (see Table 1). Calculated  $R_S$  values are divided by the exact value of  $R_S$  as defined in Equation (1), that is, a value of 1 represents perfect agreement. As  $\alpha = 0$  leads to zero  $R_S$ , the plotted functions are not defined at this point. (A) Trueness of predicted  $R_S$  as a function of  $\alpha$ , the ratio of ion mobilities. In these calculations, equal plate counts were assumed for the two components ( $N_1 = N_2$ ); owing to the normalization of  $R_S$  values the absolute number of plates is indifferent. The exact and empirical equations would coincide with the green trace. (B) Trueness of predicted  $R_S$  as a function of the temporal peak width ratio  $\sigma_{t,2}/\sigma_{t,1}$ . The ratio of plate numbers changed according to the peak width ratio ( $N^{1/2} \sim 1/\sigma_t$ ). In the calculations,  $\alpha$  was fixed at 1.05, corresponding to 5% difference in mobilities. For calculating the green trace (equal plate number assumption),  $N_2$  was used when the two plate counts differed

migrate at constant velocity, there is no need to assume constant velocity to arrive at the above formula. In DTIMS,  $\delta_v$  is the ratio of the difference and the arithmetic mean of two drift velocities, and as such, adopts values in the range  $0 \leq \delta_v < 2$ . Although cases with one of the analyte zones being stagnant or the velocity vectors pointing to opposite directions are interesting on their own merit, due to their irrelevance to standard DTIMS these are not considered here in relation to  $\delta_v$ . In Equations (5) and (7),  $\delta_v$  is expressed using retention factors and the separation factor,  $\alpha$  being inherited by the corresponding equations for DTIMS. Instead of relying on chromatographic parameters stemming from an analogy-driven approach, this section aims to utilize first principles and relate  $\delta_v$  to fundamental parameters of IMS itself. We may look at  $\delta_v$  as the operational selectivity describing the relative behavior of two analytes in a separation.

In DTIMS, the drift velocity  $v_d$  of ions is directly proportional to their mobility  $K$ , the proportionality factor being the drift field  $E_D$ . Thus, from Equation (9) applicable to various differential migration processes, we arrive at the following expression for DTIMS:

$$R_{S,\text{DT}} = \frac{\sqrt{N_{\text{avg}}}}{4} \frac{|\Delta K|}{\langle K \rangle} \quad (10)$$

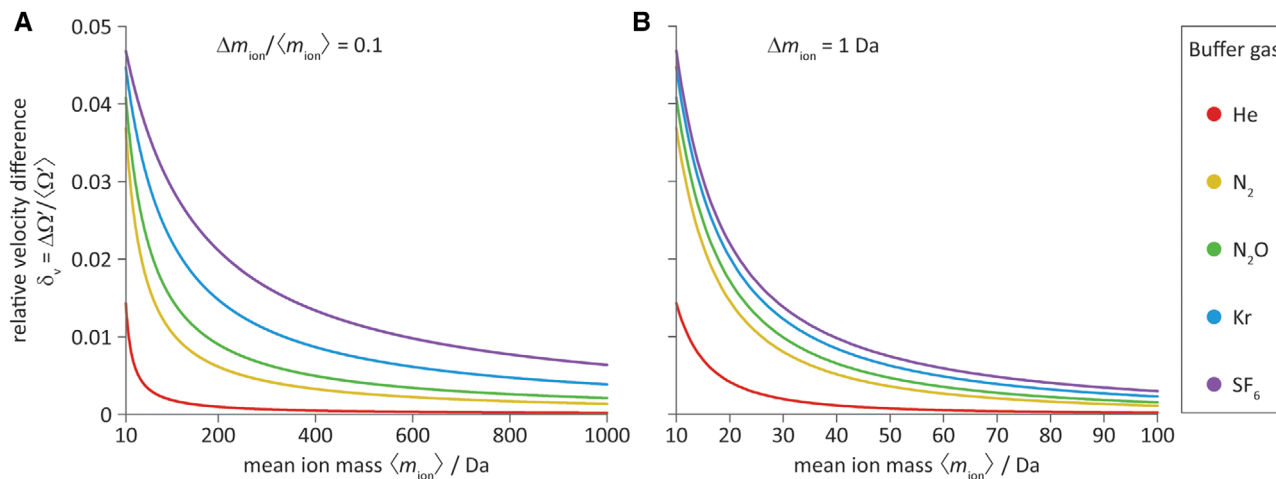
This formula is very similar to its well-known counterpart for zone electrophoresis, the main differences being

the appearance of gas-phase ion mobilities instead of their condensed-phase analogues, and the absence of an equivalent for the electroosmotic flow [24,25]. By employing the relation  $\alpha = K_1/K_2$  [15], Equations (8) and (10) can be shown to be equivalent, providing a mutual validation. Equation (10) is exact as no assumption about peak width or plate numbers was required for the derivation, and clearly shows how  $R_S$  can be improved in practice. Besides the possibility of increasing the number of theoretical plates, which concerns instrument development to a great degree, one may try to influence the relative mobilities of the two analytes through altering the separation conditions.

To explore the latter option in more detail, let us utilize the fundamental low-field ion mobility equation and relate  $K$  to quantities more closely associated with the ion structure and characteristics of the collision complex [6,7,26,27]:

$$K = \left( \frac{18\pi}{\mu k_B T} \right)^{1/2} \frac{ze}{16N\Omega} = C \frac{z}{\Omega\sqrt{\mu}} \quad (11)$$

In Equation (11),  $\mu$  is the reduced mass of the ion–neutral collision complex,  $k_B$  is the Boltzmann constant,  $T$  is the temperature of the buffer gas (within the low-field limit ions are assumed to be in thermal equilibrium with the gas),  $z$  is the ionic charge state,  $e$  is the elementary charge,  $N$  is the buffer gas number density, and  $\Omega$  is the rotationally averaged collision integral (herein collision cross-section),



**FIGURE 2** The influence of reduced mass difference on selectivity in drift tube ion mobility separations. (A) Relative velocity difference  $\delta_v$  of ion pairs with identical collision cross-sections and nonidentical masses (mimicking isotopologue separations), plotted as a function of the mean ion mass. Colors encode representative buffer gases, ranging from the lightest (He) to the heaviest (SF<sub>6</sub>) gas applied in practice. The relative mass difference of the ion pairs  $\Delta m_{\text{ion}} / \langle m_{\text{ion}} \rangle$  was held constant at 0.1. (B) Analogous  $\delta_v$  versus  $\langle m_{\text{ion}} \rangle$  plot showing the effect of a constant absolute mass difference. Instead of keeping the relative mass difference fixed as on the left, the absolute mass difference of the ions was held at 1 Da, resulting in a more rapid drop of  $\delta_v$  with increasing ion mass. Note the difference between the ion mass ranges on the two plots. For brief overview, the buffer gases used in the calculations with their rounded standard atomic/molecular weight in Da: He 4; N<sub>2</sub> 28; N<sub>2</sub>O 44; Kr 84; SF<sub>6</sub> 146. In the calculations, all stable isotopes/isotopologues of the buffer gas atoms/molecules were considered, weighted with their relative abundances

an effective area related to the target size for the ion-neutral pair and the efficiency of momentum transfer upon collision [28].  $\Omega$  values reflect the ions' size and shape and are independent of instrument geometry or measurement conditions within the low-field limit, serving as comparable molecular descriptors [29,30]. Dimensionless factors, physical constants, and experimental parameters that are the same for all species can be expressed by a single integrated constant  $C$ , highlighting the dependence of  $K$  on three analyte-related quantities:  $z$ ,  $\mu$ , and  $\Omega$ . These can be combined to yield the charge- and reduced mass-normalized collision cross-section  $\Omega'$ , defined as [31]:

$$\Omega' = \frac{\Omega\sqrt{\mu}}{|z|} \quad (12)$$

Ultimately, DTIMS separates gas-phase ions according to their  $\Omega'$  values. Thus, employing  $\Omega'$  (defined here as a positive quantity) we may reformulate Equation (10) to obtain the following expression for DTIMS:

$$R_{S,\text{DT}} = \frac{\sqrt{N_{\text{avg}}} |\Delta\Omega'|}{4 \langle\Omega'\rangle} \quad (13)$$

The above solution is exact and relates  $\delta_v$  to the  $\Omega'$  values of the analytes in the given buffer gas, which are characteristic to the ion-neutral complex and can potentially be stored in databases. Thus, Equation (13) is accurate and

practical, has a high predictive potential, and reveals how  $\delta_v$  can be influenced in DTIM separations, addressed in detail in the following subsections.

### 2.2.1 | The influence of the reduced mass on selectivity

The dependence of  $\Omega'$  on  $\mu$  enables analysts to optimize conditions for separations concerning ions with nonidentical masses, such as the separation of isotopes or isotopologues in stand-alone IMS. The larger the mass of the gas particles compared to the masses of the two ions, the larger the relative difference between the  $\mu$  values of the respective collision complexes will be (provided the ion masses differ). Thus,  $\delta_v$  may be tailored and  $R_S$  consequently improved by the adjustment of the buffer gas atomic/molecular weight for the separation of lighter ions with different masses [32,33].

Figure 2 explores in detail how differences in  $\mu$  can be exploited to influence selectivity in DTIMS. To study the effect of reduced mass difference on  $\delta_v$  independently of other influencing factors,  $\Omega$  and  $z$  were assumed to be identical, the absolute values being irrelevant. Although kinetic theory [34,35] and some experiments [33] suggest that isotopologues may have extremely small differences in their  $\Omega$  values, for practical purposes the assumption of identical  $\Omega$  remains generally valid [36,37]. The two plots in

Figure 2 depict  $\delta_v$  for analyte pairs with nonidentical masses as a function of their mean mass  $\langle m_{\text{ion}} \rangle$ . The colors represent various buffer gases, ranging from the lightest (He) to the heaviest ( $\text{SF}_6$ ) gas applied in practice. It is apparent that  $\delta_v$  decreases rapidly with increasing  $\langle m_{\text{ion}} \rangle$ , and that heavier gases lead to improved selectivity. The heavier the gas relative to the ions, the larger  $\delta_v$  will be for isotopologues. In Figure 2a, the relative mass difference of ions  $\Delta m_{\text{ion}}/\langle m_{\text{ion}} \rangle$  was kept constant at 0.1. For an ion pair with 10 Da average mass, it means 1 Da absolute difference, that is, 9.5 and 10.5 Da for the two species; for a pair with 100 Da mean mass, the difference is 10 Da. With the gas particles becoming heavier, the reduced mass of each collision complex approaches the mass of the respective ion. Consequently, for any given value of  $\langle m_{\text{ion}} \rangle$ ,  $\delta_v$  converges to  $\Delta(m_{\text{ion}}^{1/2})/\langle m_{\text{ion}}^{1/2} \rangle$  (corresponding uniformly to roughly 0.05 in Figure 2a) as the mass of the gas particles increases. It is apparent that for heavy ions the aforementioned convergence of  $\delta_v$  is very slow, and the values remain low under experimentally feasible conditions ( $m_{\text{gas}} < 150$  Da). In Figure 2b, the absolute mass difference between the members of each ion pair was fixed at 1 Da. Thus,  $\Delta m_{\text{ion}}/\langle m_{\text{ion}} \rangle$  decreases with increasing mean ion mass, and  $\delta_v$  drops even more rapidly as the analytes become heavier. Note the difference between the range of  $\langle m_{\text{ion}} \rangle$  values chosen in the two plots. The above analysis did not involve gas mixtures, but the presence of multiple gas isotopes/isotopologues were considered [36,38]. Despite the simplicity of the model, the main trends and strategies to exploit differences in ion mass to improve  $\delta_v$  could be revealed.

### 2.2.2 | The influence of the collision cross-section and the ionic charge state on selectivity

As the ratio of the  $\Omega$  values for two ions may also depend on the buffer gas composition, the effect of different buffer gases [39–41] and gas-phase modifiers [42,43] on selectivity have been extensively studied. Altering the ratio of  $\Omega$  values through changing or doping the buffer gas potentially enables the analyst to tailor selectivity in (low-field) IM separations, with particular relevance to isomer separations. However, in comparison to more flexible chromatographic and condensed-phase electrophoretic separations where selectivity can be influenced by tuning a myriad of parameters and conditions over a broad range, the possibilities in IMS are more restricted, and the resulting effects are less striking. It should also be mentioned that the choice of buffer gas can affect the plate count as well by influencing the absolute value of transport properties [1,2,44], which is important as  $R_S$  depends on both  $N_{\text{avg}}$  and  $\delta_v$ .

Arguably the most important application of IMS and IM-MS is the separation of isomers, where differences in  $\Omega$  represent the only aspect of selectivity. As  $\mu$  is the same for isomeric species, Equation (13) can be simplified (assuming the two analytes have the same charge):

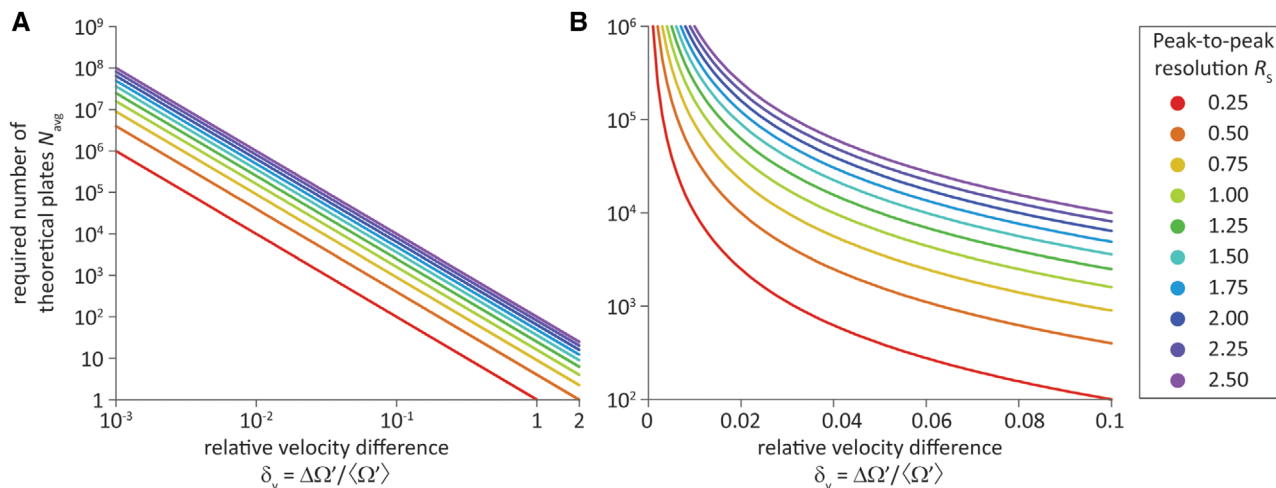
$$R_{S,\text{DT}} = \frac{\sqrt{N_{\text{avg}}}}{4} \frac{|\Delta\Omega|}{\langle\Omega\rangle} \quad (14)$$

Equation (14) is very similar to that proposed by Dodds et al. [45], the only difference being the appearance of  $N_{\text{avg}}$ , the effective average plate number defined according to Equation (6). Equations (13) and (14) can also be utilized to calculate the number of theoretical plates required to achieve certain  $R_S$  for a given analyte pair, as shown in Figure 3. The plots highlight the intertwined influence of resolving power (expressed by  $N_{\text{avg}}$ ) and selectivity (expressed by  $\Delta\Omega'/\langle\Omega'\rangle$ ) on the ultimately achieved peak resolution in DTIMS. In general,  $R_S = 0.75$  is required to readily distinguish two peaks, whereas  $R_S = 1.5$  marks baseline separation by convention. As cutting-edge high-pressure DTIMS instruments may achieve plate numbers on the order of  $10^5$  [2], separating isomers with roughly 0.5–1% collision cross-section difference represents the current limit of this technique.

High kinetic energy (HiKE) IMS [46], FAIMS [47], or its recent variation, field asymmetric time-of-flight (FAT) IMS [48], exploit energetic hyperthermal collisions in high fields and the resulting dependence of  $K$  and  $\Omega$  on the reduced field strength to influence selectivity. Although this approach is effective and orthogonal to that of changing the buffer gas, it transcends the boundaries of linear low-field IMS and therefore not discussed further.

There is little playing field for the analyst to influence  $z$  selectively, but its effect is important to understand and predict  $R_S$  for ions having the same  $m/z$  but different mass and charge, such as various oligomers. In the discussion above, the separation of isotopologues, isomers and oligomers serve as representative examples. In most analytical problems, especially those concerning stand-alone IMS, it is the combined effect of  $\mu$ ,  $\Omega$ , and  $z$  that needs to be evaluated in relation to selectivity, as expressed by the single parameter  $\Omega'$  in Equation (13).

As a final remark to Section 2.2, in relation to Equations (10), (13), and (14), we shall briefly address the possibility of predicting selectivity in DTIMS relying solely on theoretical approaches. First, state-of-the-art computational methods are capable of generating correct structural models for gas-phase molecular ions of ever-increasing complexity. Second, two-body interactions governing separation in IMS are much more amenable to computational treatment than many-body encounters determining retention in chromatography [49]. If the aforementioned



**FIGURE 3** Number of theoretical plates needed for achieving defined resolution between two peaks in drift tube ion mobility spectrometry. (A) Double-log plot showing the effective average number of plates  $N_{\text{avg}}$  required to reach defined  $R_S$  values as a function of the analytes' relative velocity difference  $\delta_v$ . It is worth mentioning that  $\delta_v$  adopts nonnegative values below 2 in drift tube ion mobility separations, but values close to this theoretical upper limit are of little practical relevance.  $R_S = 1.5$  corresponds to baseline separation; an  $n$ -fold increase in  $R_S$  requires an  $n^2$ -fold increase in  $N_{\text{avg}}$ . (B) Single-log plot highlighting the most relevant and experimentally accessible region. Most separations in practice concern analyte pairs with  $\delta_v < 0.1$ . At present, state-of-the-art high-pressure linear DTIMS instruments may achieve theoretical plates on the order of  $10^5$

suitable ion structures are available,  $\Omega$  and  $K$  can be calculated in a variety of buffer gases with satisfying accuracy [50–55]. Thus, with increasing computational power and further progress of theoretical methods, the prospect of predicting selectivity in DTIMS entirely computationally, at least for simpler systems, does not seem far fetched.

### 2.3 | From stand-alone ion mobility spectrometry to ion mobility-mass spectrometry

In our analysis so far, we implicitly assumed that ion drift related post-cell effects—the analogues of extra-column factors in chromatography—are absent. This may be true for stand-alone IMS (although detector rise time is still important), but is not entirely valid in IM-MS where ions may traverse ion funnels, ion guides, and mass analyzers before reaching the detector. The residence time of ions in these post-cell compartments adds to their net drift time  $t_D$ , the sum being the total arrival time  $t_A$ . As mobility-based separation does not take place in many of these post-cell compartments, their presence affects the calculation of  $R_S$ .

Post-cell effects on  $R_S$  can be incorporated into the expression of plate numbers, as shown below. Let us adopt the dimensionless factor  $F$  from [1] as the fraction of non-separative transport time  $t_{\text{NS}}$  in relation to the total arrival

time  $t_A$ :

$$F = \frac{t_{\text{NS}}}{t_A} = \frac{t_{\text{NS}}}{t_S + t_{\text{NS}}} \quad (15)$$

In Equation (15),  $t_A$  was divided into a separative part  $t_S$  during which ions are separated according to their mobilities, and into a nonseparative part  $t_{\text{NS}}$  with no separation taking place, that is,  $t_{\text{NS}}$  is assumed to be the same for any two neighboring species. In general, residence time of ions in the mobility cell and the exit funnel (if present) amount to  $t_S$ , while  $t_{\text{NS}}$  comprises the residence times in post-cell compartments under high vacuum. Such explicit categorization of compartments is physically justified. First, pressure and temperature across a mobility cell and the corresponding exit funnel are uniform because no conductance limit is present between them. It means that ion mobilities are left unchanged and  $\delta_v$  is the same in these compartments, even if the absolute velocities may differ (low-field conditions are assumed). Second, additional separation of two neighboring ion clouds in ion guides, etc., following the drift region is not very significant, especially if the ions have identical or similar  $m/z$  ratios. Therefore, employing  $\Delta t_{\text{NS}} = 0$  for these compartments introduces a negligible error in the calculations. Using  $F$ , we can define the apparent plate number for DTIM-MS:

$$N_{\text{app}} = \left(\frac{t_A}{\sigma_t}\right)^2 (1 - F)^2 = \left(\frac{t_S}{\sigma_t}\right)^2 \quad (16)$$



The numerator of  $N_{\text{app}}$  correctly accounts for those compartments only where mobility separation takes place.

Because in compartments not contributing to separation  $\Delta t_{\text{NS}}$  is zero in our assumption,  $\Delta t_{\text{A}}$  appears equal to  $\Delta t_{\text{S}}$ . Thus, by substituting  $t_{\text{A}}$  instead of  $t_{\text{D}}$  into Equation (1), the general expression for  $R_{\text{S}}$  in the presence of post-cell compartments can be obtained:

$$R_{\text{S}} = \frac{\Delta t_{\text{A}}}{4\langle\sigma_{\text{t}}\rangle} = \frac{\langle t_{\text{S}}\rangle}{4\langle\sigma_{\text{t}}\rangle} \frac{\Delta t_{\text{S}}}{\langle t_{\text{S}}\rangle} = \frac{\sqrt{N_{\text{app}}}}{4} \delta_{\text{v}} \quad (17)$$

Here,  $N_{\text{app}}$  is the effective average plate number corrected with  $F$  according to Equation (16). Since  $\delta_{\text{v}}$  in the mobility cell and the respective exit funnel is the same, the DTIM-MS specific predictive equation for  $R_{\text{S}}$  appears as:

$$R_{\text{S,DT}} = \frac{\sqrt{N_{\text{app}}}}{4} \frac{|\Delta\Omega'|}{\langle\Omega'\rangle} \quad (18)$$

## 2.4 | Peak-to-peak resolution in traveling wave ion mobility separations

In this section, we aim to find a predictive resolution equation for TWIMS [56,57] by extending the approach employed for DTIMS before. The main difference between the two techniques concerns selectivity and  $\delta_{\text{v}}$ . Although in DTIMS drift velocities are directly proportional to  $K$ , in TWIMS this dependence is nonlinear and cannot be traced back to first principles [58]. Hence, Equation (10) and subsequent formulae derived from it are not applicable to the latter method.

A widely applied solution to the above problem is to transfer TWIM separations from their fundamental temporal dimension into the collision cross-section domain, that is, accounting for the altered selectivity by including its effect into a modified  $\Omega$ -based definition of  $N$  or  $R_{\text{p}}$  [45]. This approach has several advantages, but ultimately blurs the clear distinction between two independent aspects of peak resolution: plate count/resolving power and  $\delta_{\text{v}}$ . The method-specific, rather arbitrary modification of fundamental definitions ( $N$  and  $R_{\text{p}}$ ) also leads to some dissonance between this approach and the unified theoretical toolbox of separation methods [8].

Here, we provide a solution that is mathematically equivalent to the one mentioned above, but adheres to the general formalism of separation science. To obtain the desired formula for TWIMS, a suitable expression for  $\delta_{\text{v}}$  needs to be found and substituted into Equation (9). In general, the following power function is employed for collision cross-section calibration in TWIMS, that is, to describe the dependence between  $\Omega'$  and the ion transit time (post-cell

effects being neglected) [31,59]:

$$\Omega' = A(t_{\text{D}})^B \quad (19)$$

In Equation (19),  $t_{\text{D}}$  is the transit time of ions through the TWIMS cell, while  $A$  and  $B$  are parameters that depend on experimental conditions.  $A$  and  $B$  are determined experimentally during the general collision cross-section calibration process using suitable calibrants [60,61]. Employing this semiempirical relation to express  $\delta_{\text{v}}$  and the notation  $1/B = \gamma$ , the predictive resolution equation for TWIMS appears as:

$$R_{\text{S,TW}} = \frac{\sqrt{N_{\text{avg}}}}{4} \frac{(\Omega'_2{}^\gamma - \Omega'_1{}^\gamma)}{\langle\Omega'^\gamma\rangle} \quad (20)$$

The subscript in  $R_{\text{S,TW}}$  indicates the TWIMS specificity of Equation (20). The exponent  $\gamma$  accounts for the altered selectivity in TWIM separations. In DTIMS  $\gamma$  equals 1, while in TWIMS it generally exceeds unity in practice, with clearly favorable consequences to  $\delta_{\text{v}}$  and  $R_{\text{S}}$ . Besides determination through calibration, this factor may be estimated theoretically for close-lying peaks under certain assumptions. As an illustrative example, for symmetric triangular waveforms  $\gamma$  adopts a value of 2 if the maximum ion velocity is much lower than the wave velocity [58,62].

As of today, no complete analytical description of ion motion in TWIMS cells operated with discretely stepping potential waves is available, making the technique dependent on suitable calibrants for most applications. However, a detailed model for hypothetical smoothly moving waves has been developed [62], marking a significant step toward the ultimate goal of TWIMS theory: an exact equation derived from first principles, describing the universal relation between  $K$  and the ion velocity. Once such description is available, it will be possible to place selectivity on entirely theoretical foundations in TWIM separations.

## 2.5 | Peak capacity in ion mobility separations

Having addressed peak-to-peak resolution, we may build on these findings and explore peak capacity ( $P_{\text{C}}$ ) in IM separations.  $P_{\text{C}}$  was conceived originally by Giddings for elution chromatography [63], but may be readily transferable to other differential migration methods owing to the abstract mathematical nature of the concept.  $P_{\text{C}}$  represents the maximum number of resolved peaks that can be fit into the separation window, for example, chromatogram, electropherogram, or ion mobility spectrum. It reflects the hypothetical case when peaks are ideally distributed,

meaning that  $R_S$  is the same for any two neighboring peaks within a single dimension of the separation window. Although the exact value of  $R_S$  may be chosen arbitrarily, in general it is defined to be 1 or 1.5 for practical reasons: values lower than unity would express significant peak overlap, whereas values higher than that of baseline separation would correspond to the suboptimal utilization of the time window with unoccupied spaces between peaks. In addition to the predefined value of  $R_S$ ,  $P_C$  depends on two factors: The width of the peaks and the actively utilized size of the separation window. The narrower the peaks and the larger this window, the higher the peak capacity. Due to nonideal, often random distribution of peaks in real separations, the number of resolved components in reality is merely a fraction of this number as shown by Poisson statistics [64,65]. Thus,  $P_C$  may be viewed as an estimate of the total number of resolvable components, serving as a comprehensive measure of the overall separation performance.  $P_C$  is arguably the most suitable index to compare separation methods: electrophoretic techniques may generate extremely high plate counts, but the separation window in these methods is rather narrow in comparison to chromatography, both in the liquid and the gas phase. For this reason, it is essential to obtain a suitable model for peak capacity in IMS.

As mentioned above, the maximum number of resolved peaks  $n$  in the separation window depends on the peaks' temporal width ( $\sigma_t$ ), the desired resolution between them ( $R_{S,fix}$ , the subscript referring to the fixed, predefined nature of this parameter), as well as on the breadth of the window spanning from the first to the  $n$ th peak [66]:

$$\frac{dn}{dt_D} = \frac{1}{4R_{S,fix}\sigma_t(t_D)} \quad (21)$$

$$\int_1^n dn = \frac{1}{4R_{S,fix}} \int_{t_{D,1}}^{t_{D,n}} \frac{dt_D}{\sigma_t(t_D)} \quad (22)$$

Here,  $\sigma_t(t_D)$  emphasizes the potential variation of the peak width across the separation window as a function of the drift time. From Equation (22), one can obtain the mathematical definition of peak capacity in its general integral form [67]:

$$P_{C,def} = n = 1 + \frac{1}{4R_{S,fix}} \int_{t_{D,1}}^{t_{D,n}} \frac{dt_D}{\sigma_t(t_D)} \quad (23)$$

To highlight the dependence of  $P_C$  on the plate count, Equation (23) can be rewritten using  $N = (t_D/\sigma_t)^2$ , where  $N$

may also be a function of  $t_D$ :

$$P_{C,def} = 1 + \frac{1}{4R_{S,fix}} \int_{t_{D,1}}^{t_{D,n}} \frac{\sqrt{N(t_D)}}{t_D} dt \quad (24)$$

The way  $N$  and  $\sigma_t$  depend on  $t_D$  is central to the peak capacity problem. Solving Equation (23) or (24) to yield the desired expression for  $P_C$  requires the explicit form of  $N(t_D)$  or  $\sigma_t(t_D)$  be known. In the following sections, two approximate solutions based on well-known assumptions borrowed from chromatography, as well as an exact solution derived from a suitable physical model for peak broadening in DTIMS, will be presented.

### 2.5.1 | The constant plate number assumption

Assuming that  $N$  is the same for each analyte and independent of  $t_D$ , that is,  $\sigma_t(t_D) = t_D(N)^{1/2}$  where  $N$  is constant, the solution of Equation (24) is straightforward and yields the following expression:

$$P_{C,N} = 1 + \frac{\sqrt{N}}{4R_{S,fix}} \int_{t_{D,1}}^{t_{D,n}} \frac{1}{t_D} dt = 1 + \frac{\sqrt{N}}{4R_{S,fix}} \ln \frac{t_{D,n}}{t_{D,1}} \quad (25)$$

In Equation (25),  $t_{D,1}$  and  $t_{D,n}$  correspond to the first and last peak, respectively, while the subscript of  $P_{C,N}$  implies that  $N$  was assumed to be constant. It is worth mentioning at this point that none of the peak capacity-related equations presented so far is specific for IMS. Upon changing  $t_D$  to  $t_R$ , Equation (25) becomes identical to the simple formula for isocratic elution chromatography [63,66,67].

From the inverse proportionality between  $K$  and  $t_D$  in DTIMS, or  $K$  and  $t_A$  in DTIM-MS, a more revealing formula arises that is specific for the aforementioned technique:

$$P_{C,N,DT} = 1 + \frac{\sqrt{N}}{4R_{S,fix}} \ln \frac{K_1}{K_n} \quad (26)$$

The error stemming from ignoring the mobility-independent contributions to  $t_A$  in DTIM-MS is negligible.  $\Omega'$  may also be used to express the ratio of drift and arrival times, resulting in the following practical expression for DTIMS and DTIM-MS:

$$P_{C,N,DT} = 1 + \frac{\sqrt{N}}{4R_{S,fix}} \ln \frac{\Omega'_n}{\Omega'_1} \quad (27)$$

For separations utilizing the traveling wave technique, Equation (27) can be modified according to Equation (19) and employing the notation  $1/B = \gamma$ :

$$P_{C,N,TW} = 1 + \frac{\sqrt{N}}{4R_{S,fix}} \gamma \ln \frac{\Omega'_n}{\Omega'_1} \quad (28)$$

Equation (28) makes it apparent that for the same ratio of  $\Omega'$  values and same  $N$ —defined based on the temporal or spatial SD of peaks, not on their width in a  $\Omega$ -space— $P_{C,N}$  will be higher for TWIMS than for DTIMS by the factor  $\gamma$  (neglecting the constant 1 on the right-hand side). Practical values of  $\gamma$  normally fall in the range between 1.5 and 2 [60,61]. Owing to the nonlinear dependence of  $t_D$  on  $\Omega'$ , the time window in a TWIM separation will be broader in relation to the  $\sigma_t$  of peaks than in an analogous DTIM separation. Consequently, the TWIM spectrum will be capable of encompassing more resolved components provided  $N$  is the same.

### 2.5.2 | The constant temporal peak width assumption

Let  $\sigma_t$  be constant across the whole separation window, meaning that  $N(t_D) = (t_D/\sigma_t)^2$  where  $\sigma_t$  is independent of the drift time. In this case, the solution of Equation (23) appears as:

$$P_{C,\sigma} = 1 + \frac{1}{4R_{S,fix}\sigma_t} \int_{t_{D,1}}^{t_{D,n}} dt_D = 1 + \frac{1}{4R_{S,fix}\sigma_t} (t_{D,n} - t_{D,1}) \quad (29)$$

The subscript denotes  $\sigma_t$  being a constant. Alternatively, employing  $\sigma_t = t_{D,1}/(N_1)^{1/2}$  where  $N_1$  is the plate count for the first peak, Equation (29) can be rewritten as:

$$P_{C,\sigma} = 1 + \frac{\sqrt{N_1}}{4R_{S,fix}} \left( \frac{t_{D,n} - t_{D,1}}{t_{D,1}} \right) \quad (30)$$

Equations (29) and (30) are analogous to the simple expressions derived for gradient elution chromatography [66–68]. From the general expression above we can obtain equations specific for DTIM separations:

$$P_{C,\sigma,DT} = 1 + \frac{\sqrt{N_1}}{4R_{S,fix}} \left( \frac{K_1 - K_n}{K_n} \right) \quad (31)$$

$$P_{C,\sigma,DT} = 1 + \frac{\sqrt{N_1}}{4R_{S,fix}} \left( \frac{\Omega'_n - \Omega'_1}{\Omega'_1} \right) \quad (32)$$

For TWIM separations the respective equation appears as:

$$P_{C,\sigma,TW} = 1 + \frac{\sqrt{N_1}}{4R_{S,fix}} \left( \frac{\Omega'_n{}^\gamma - \Omega'_1{}^\gamma}{\Omega'_1{}^\gamma} \right) \quad (33)$$

Thus,  $\gamma$  values exceeding unity will lead to an increase in  $P_{C,\sigma}$ .

### 2.5.3 | An exact peak capacity equation for drift tube ion mobility spectrometry based on the injection-diffusion model of zone broadening

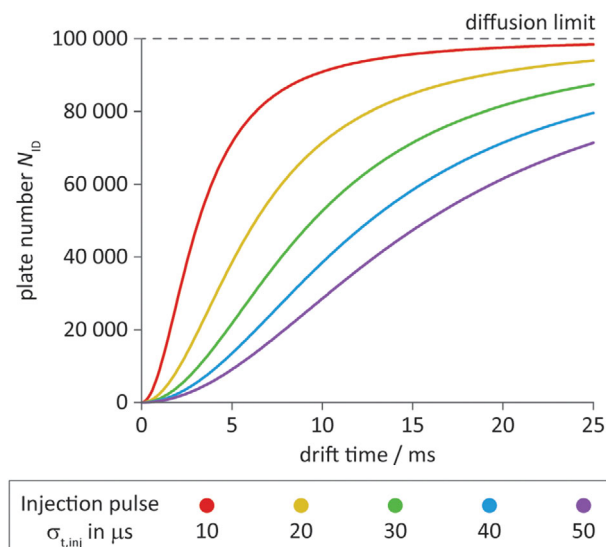
Although equations based on the constant  $N$  and the constant  $\sigma_t$  assumptions are certainly helpful, their value lies mostly in their simplicity. In DTIM separations, assuming  $N$  being the same for all species may be justified if diffusion is the dominant dispersion process and the initial spread of the injected ion cloud is negligible. On the other hand, the constant peak width assumption may be valid if  $\sigma_t$  is determined predominantly by the injection pulse-width, with subsequent diffusional broadening being negligible. In practice, however, the contributions of these two sources are generally comparable, especially under conditions where resolving power is expected to be highest [1,69]. As such, the above  $P_C$  equations have limited applicability in the experimentally most relevant cases.

To overcome these limitations and derive an exact, universally applicable  $P_C$  equation for DTIM separations, a suitable physical model of zone dispersion needs to be considered. The two major sources of peak broadening in DTIM separations are diffusion and the finite width of the injected ion packets. Being independent processes, the associated variances are additive yielding [1]:

$$\begin{aligned} \sigma_{t,ID}(t_D) &= \left( \sigma_{t,inj}^2 + \sigma_{t,diff}^2(t_D) \right)^{1/2} \\ &= \left( \sigma_{t,inj}^2 + t_D^2 \frac{2k_B T}{|z|eV_D} \right)^{1/2} = \left( \sigma_{t,inj}^2 + \frac{t_D^2}{N_{diff}} \right)^{1/2} \end{aligned} \quad (34)$$

The above variance components are analogous to those in zone electrophoresis assuming linear conditions [23,25,70]. From Equation (34), the corresponding total plate count  $N_{ID}$  can be readily calculated as:

$$N_{ID}(t_D) = \frac{t_D^2}{\sigma_{t,inj}^2 + \frac{t_D^2}{N_{diff}}} \quad (35)$$



**FIGURE 4** Systematic variation in the number of theoretical plates across a single drift tube ion mobility spectrum. Considering the finite width of the injection pulse and subsequent diffusional broadening of the ion packets, the plate count  $N_{\text{ID}}$  will appear different for each peak within a single separation at fixed drift voltage. The plate number achieved for a given analyte will depend on its drift time, which is inversely proportional to the ion's mobility. The calculations rely on the assumption that all ions have the same charge state. The diffusion limit of theoretical plates was set at 100 000 (black dashed line), corresponding to roughly 5.14 kV drift voltage for singly charged ions at room temperature. Each color-coded curve represents a different value of  $\sigma_{t,\text{inj}}$ , the temporal standard deviation associated with the injection pulse. At extremely short drift times the functions bear little practical relevance and should be interpreted carefully: For ions with very high mobilities the reduced field will inevitably exceed the low-field limit

In the above equations,  $\sigma_{t,\text{ID}}$  is the total temporal SD of a given peak, the subscript referring to the injection-diffusion physical model. Temporal variances  $(\sigma_{t,\text{inj}})^2$  and  $(\sigma_{t,\text{diff}})^2$  express the contribution of injection and diffusion, respectively. The dependence of  $\sigma_{t,\text{diff}}$ ,  $\sigma_{t,\text{ID}}$  and  $N_{\text{ID}}$  on  $t_{\text{D}}$  is shown explicitly,  $k_{\text{B}}$  being the Boltzmann constant,  $T$  the temperature of the buffer gas and ions,  $|z|$  the absolute value of the ionic charge state,  $e$  the elementary charge and  $V_{\text{D}}$  the drift voltage. Employing  $N_{\text{diff}}$ , the diffusion limit of theoretical plates, a more concise expression ensues. As  $z$  is the only analyte-specific quantity influencing  $N_{\text{diff}}$ , Equations (34) and (35) adequately describe peak broadening and the plate count for a set of ions having the same charge state. Owing to their relatively small contribution to peak broadening, space charge effects were not included into Equations (34) and (35). Figure 4 highlights the variation of  $N_{\text{ID}}$  across the separation window as a function of  $t_{\text{D}}$ . In other words, it reflects the dependence of the plate count

on the ions' mobility in a single DTIM spectrum with  $V_{\text{D}}$  and  $N_{\text{diff}}$  held constant.

Upon substituting Equation (34) into Equation (23), or Equation (35) into Equation (24), we obtain:

$$P_{\text{C,ID,DT}} = 1 + \frac{1}{4R_{\text{S,fix}}} \int_{t_{\text{D},1}}^{t_{\text{D},n}} \frac{dt_{\text{D}}}{\left(\sigma_{t,\text{inj}}^2 + \frac{t_{\text{D}}^2}{N_{\text{diff}}}\right)^{1/2}} \quad (36)$$

In Equation (36), the subscript of  $P_{\text{C,ID,DT}}$  refers again to the underlying physical model and the resulting DTIMS specificity of the formula. The solution of Equation (36) can be traced back to the following basic integral [71]:

$$\int \frac{1}{\sqrt{1+x^2}} dx = \text{arsinh}(x) = \ln\left(x + \sqrt{x^2+1}\right) \quad (37)$$

Here, arsinh is the inverse or area hyperbolic sine function (the constant of integration was omitted). Thus, the solution of Equation (36) takes the following form (step-by-step derivation can be found in the Supporting Information, Section S3):

$$P_{\text{C,ID,DT}} = 1 + \frac{\sqrt{N_{\text{diff}}}}{4R_{\text{S,fix}}} \ln \frac{t_{\text{D},n} + \left(t_{\text{D},n}^2 + N_{\text{diff}}\sigma_{t,\text{inj}}^2\right)^{1/2}}{t_{\text{D},1} + \left(t_{\text{D},1}^2 + N_{\text{diff}}\sigma_{t,\text{inj}}^2\right)^{1/2}} \quad (38)$$

An important aspect of  $N_{\text{diff}}$  is that it adopts the same value for all species within a given charge state. It is worth mentioning that—owing to similarities in the underlying mathematics—Equation (38) resembles the peak capacity equation in chromatography when extra-column band broadening is considered [72].

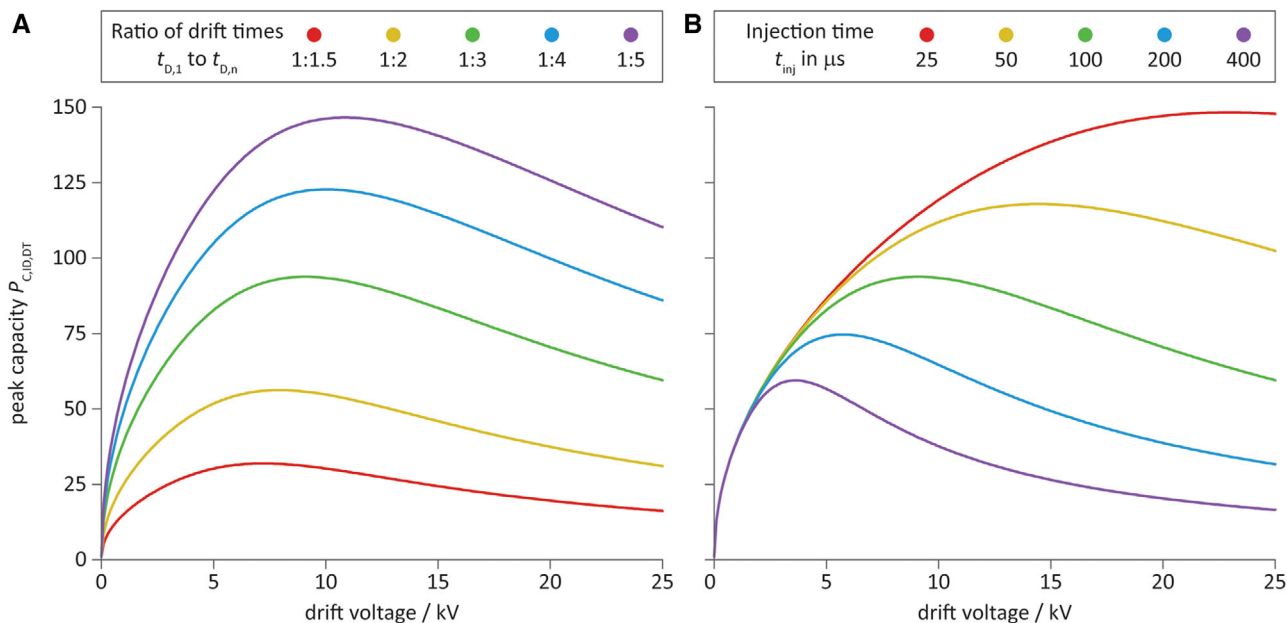
As a verification of Equation (38), the exact peak capacity equation for DTIMS, let us examine its behavior at limiting cases. If  $\sigma_{t,\text{inj}}$  is assumed to be zero (infinitesimally short injection), Equation (38) becomes:

$$P_{\text{C,D,DT}} = 1 + \frac{\sqrt{N_{\text{diff}}}}{4R_{\text{S,fix}}} \ln \frac{t_{\text{D},n}}{t_{\text{D},1}} \quad (39)$$

The subscript of  $P_{\text{C,D,DT}}$  indicates that only diffusion was considered, the initial width of the ion packet being neglected. Equation (39) is analogous to Equation (25), obtained by assuming constant  $N$  on the basis that diffusion is the dominant dispersion process.

At the other extreme,  $\sigma_{t,\text{diff}}$  is negligibly small compared to  $\sigma_{t,\text{inj}}$ . In this case, employing the Maclaurin series of arsinh( $x$ ), Equation (38) can be simplified to the following





**FIGURE 5** Peak capacity in drift tube ion mobility spectrometry based on the injection-diffusion model. Peak capacity  $P_{C,ID,DT}$  calculated according to the exact formula Equation (38) and depicted as a function of drift voltage  $V_D$ . (A) Curves are color-coded according to the drift time ratio between the first and the last peak;  $t_{inj}$  was fixed at 100  $\mu s$ . (B) Colors encode different injection times  $t_{inj}$ , varied from 25 to 400  $\mu s$  forming an equirational progression, and the drift time ratio was chosen to be 1:3. The two green curves are therefore identical. Calculations on both panels mimic real-life drift tube ion mobility separations, performed at 293.15 K in a 150 mm long drift cell using  $N_2$  or air as buffer gas at atmospheric pressure. Ions were assumed to be singly charged, and  $R_{S,fix}$  was chosen to be unity. Ion mobility of the first species was fixed at  $2.5 \times 10^{-4} \text{ m}^2 \text{ V}^{-1} \text{ s}^{-1}$ , the mobility of the last species was changed according to the defined drift time ratio

form:

$$\begin{aligned}
 P_{C,I,DT} &= 1 + \frac{1}{4R_{S,fix}\sigma_{t,inj}} (t_{D,n} - t_{D,1}) \\
 &= 1 + \frac{\sqrt{N_{inj,1}}}{4R_{S,fix}} \left( \frac{t_{D,n} - t_{D,1}}{t_{D,1}} \right) \quad (40)
 \end{aligned}$$

Details of the series expansion can be found in the Supporting Information, Section S3. The subscript of  $P_{C,I,DT}$  reflects the elimination of diffusion from the model, leaving injection the only source of dispersion considered.  $N_{inj,1}$  is the plate count for the first peak and equals  $(t_{D,1}/\sigma_{t,inj})^2$ . Equation (40) appears equivalent to Equation (30), which was obtained by assuming constant temporal peak width determined by a  $t_D$ -independent dispersion process, i.e. the duration of the injection pulse.

Figure 5 explores peak capacity in DTIMS based on the injection-diffusion model and Equation (38), highlighting the influence of the most important experimental parameters, such as the applied drift voltage  $V_D$  or the injection time  $t_{inj}$ . The latter is the actual experimentally controlled duration of the injection pulse, and the respective SD can be readily calculated using the formula  $\sigma_{t,inj} = t_{inj}/\sqrt{12}$ , assuming rectangular pulse profile [1,25]. As  $V_D$  influences both  $N_{diff}$  as shown in Equation (34), as well as the drift

time through the relation  $t_D = L_D^2/(KV_D)$ , the impact of  $V_D$  on  $P_{C,ID,DT}$  is double-edged. Although  $P_{C,ID,DT}$  depends on several factors in a complex manner shown by Equation (38), the most important trends are revealed by Figure 5. The portrayed calculations mimic real-life DTIM separations in every aspect, with  $K$  values chosen to reflect atmospheric pressure experiments. It is evident that a broader separation window may encompass more peaks (Figure 5a). In contrast to chromatography, however, the analyst has little control over this aspect of separation in DTIMS. In general, factors that efficiently increase  $N_{ID}$  across the whole spectrum also lead to higher  $P_{C,ID,DT}$ , such as employing shorter injection times as shown in Figure 5b. Albeit less obvious, the influence of the buffer gas pressure is highly important. Higher pressure leads to lower absolute mobilities, manifesting in longer drift times without altering  $\sigma_{t,inj}$  or  $N_{diff}$ . Thus, raising the pressure ultimately results in increased  $N_{ID}$  and  $P_{C,ID,DT}$  values. Similarly to resolving power or theoretical plates,  $P_{C,ID,DT}$  reaches a maximum at an optimal  $V_D$ . The positions of these maxima along the abscissa fall between the  $V_D$  values where plate counts for the first and last peak are highest (data not shown).

Being the solution of Equation (36), we may view Equation (38) as a formula accounting for the variation of the plate count across the whole DTIM spectrum. When

relying merely on resolving power and plate count, experimental conditions such as  $V_D$ ,  $t_{inj}$  or the buffer gas pressure are optimized considering a single, arbitrarily chosen component of the mixture. Peak capacity, on the other hand, enables one to optimize the separation considering the whole set of separands. Thus, it serves as a more comprehensive index of the separation performance, and a better guide for the analyst dealing with a large number of analytes simultaneously.

### 3 | CONCLUDING REMARKS

By merging appropriate mathematical concepts borrowed from chromatography with the physical principles of DTIM separations, approximate and exact equations were derived for peak-to-peak resolution and peak capacity.

In relation to peak-to-peak resolution, existing chromatography-influenced equations for DTIMS were evaluated and refined (Section 2.1). Employing resolution equations stemming from first principles, most importantly Equation (13), selectivity and relative velocity difference could be directly linked to the normalized collision cross-section of ions. Through revealing key factors influencing  $R_S$ , these predictive formulae may significantly benefit method optimization in everyday practice. Equations obtained for stand-alone linear DTIMS were also extended to DTIM-MS (Section 2.3) and TWIMS (Section 2.4). Through the factor  $\gamma$ , which reappears in expressions for peak capacity as well, Equation (20) successfully accounts for the altered selectivity in TWIM separations.

In Section 2.5, simple peak capacity equations were obtained for DTIM and TWIM separations based on the constant  $N$  and constant  $\sigma_t$  assumptions, borrowed from chromatography. As the range of applicability and validity of these approximate solutions is limited, an exact formula for peak capacity, Equation (38), was derived for DTIMS considering the injection-diffusion model of peak broadening. The peak capacity equations derived herein may prove to be especially fruitful in applications utilizing stand-alone IMS without MS analysis, and in general when dealing with extremely complex samples. In addition to making the calculation and optimization of peak capacity within a single IM separation more accurate and transparent, the equations will also benefit the estimation of overall peak capacity in multidimensional workflows incorporating DTIMS/TWIMS [65].

By further extending the plate-height model of IM-MS, the present study may also serve as a small step toward wholly integrating this emerging analytical technique into the unified language of separation science.

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### CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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