

Model Based Determination of Detection Limits for Proton Transfer Reaction Mass Spectrometer

Invited paper

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Proton Transfer Reaction Mass Spectrometry (PTR-MS) is a chemical ionization mass spectrometric technique which allows to measure trace gases as, for example, in exhaled human breath. The quantification of compounds at low concentrations is desirable for medical diagnostics. Typically, an increase of measuring accuracy can be achieved if the duration of the measuring process is extended. For real time measurements the time windows for measurement are relatively short, in order to get a good time resolution (e.g. with breath-to-breath resolution during exercise on a stationary bicycle). Determination of statistical detection limits is typically based on calibration measurements, but this approach is limited, especially for very low concentrations. To overcome this problem, a calculation of limit of quantification (LOQ) and limit of detection (LOD), respectively, based on a theoretical model of the measurement process is outlined.

Keywords: Detection limits; limit of quantification; limit of detection; mass spectrometry; PTR-MS.

1. WORKING PRINCIPLE OF PTR-MS

VOLATILE ORGANIC COMPOUNDS (VOCs) with concentrations (expressed as the volume ratios) down to parts-per-trillion levels (*ppt*: 1 molecule out of 10^{12} molecules), see e.g. [9, 13, 7], can be measured using a PTR-MS instrument (Proton Transfer Reaction Mass Spectrometer).

The molecules of the volatile organic compound, here symbolically denoted by M, are chemically ionized by proton transfer from H_3O^+ -ions produced in the source of the instrument, [9]:



The countrates of the resulting ions are then measured by a Quadrupol-Mass-Spectrometer. The countrates are determined at mass-to-charge ratios (*m/z*) ranging from 21 up to 500, see Figure 1.

Incidentally, also a time-of-flight mass spectrometer (PTR-TOF) may be used instead of a quadrupol mass spectrometer. Here we focus on PTR-MS.

The standard formula for determination (estimation) of the true concentration $[\text{M}]$ of M in *ppb* (1 molecule out of 10^9 molecules), say $\widehat{[\text{M}]}$, is proportional to the observed countrate of MH^+ ions at a particular mass-to-charge ratio *m/z*, see e.g. [13], and is given by:

$$\widehat{[\text{M}]} = \frac{10^9 \cdot \kappa_{\text{M}} \cdot T_{\text{H}_3\text{O}^+}}{k_{\text{M}} \cdot t \cdot g \cdot T_{m/z}} \cdot \frac{\text{countrate}_{m/z}([\text{MH}^+])}{\text{countrate}_{\text{H}_3\text{O}^+}([\text{H}_3\text{O}^+])},$$

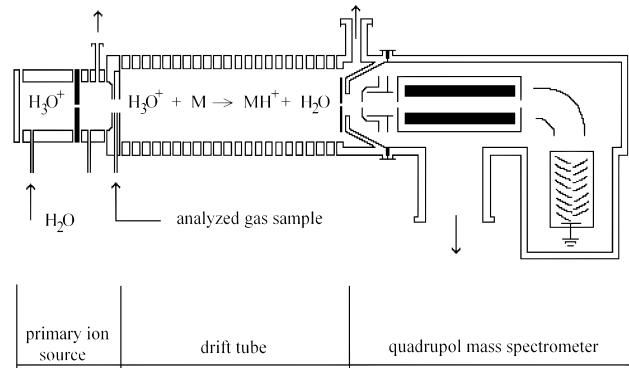


Fig. 1: Working principle of PTR-MS.

$$= \text{const}_M \cdot \frac{\text{countrate}_{m/z}([\text{MH}^+])}{\text{countrate}_{\text{H}_3\text{O}^+}([\text{H}_3\text{O}^+])}. \quad (2)$$

Here $\text{countrate}_{m/z}([\text{MH}^+])$ is the measured countrate (in cps, counts per second) of MH^+ ions detected at the mass-to-charge ratio *m/z* if the true concentration of M is $[\text{M}]$, $\text{countrate}_{\text{H}_3\text{O}^+}([\text{H}_3\text{O}^+])$ denotes the measured countrate of primary ions (H_3O^+ and its water cluster $\text{H}_2\text{O} \cdot \text{H}_3\text{O}^+$) detected at the mass-to-charge ratios 21 and 37, i.e.

$$\text{countrate}_{\text{H}_3\text{O}^+}([\text{H}_3\text{O}^+]) = IR \cdot \text{countrate}_{m/z=21}([\text{H}_3\text{O}^+]) + \text{countrate}_{m/z=37}([\text{H}_2\text{O} \cdot \text{H}_3\text{O}^+]), \quad (3)$$

where $IR = 500$ (this depends on the source of water) reflects

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the isotopic ratio of the species $\text{H}_3^{18}\text{O}^+$ and $\text{H}_3^{16}\text{O}^+$. The mass-to-charge ratio of $m/z = 37$ refers to the water cluster $\text{H}_2\text{O} \cdot \text{H}_3\text{O}^+$ (other water clusters are neglected).

Further, κ_M is a calibration constant for the compound M, k_M is the reaction constant of protonation reaction (1) for M, t is the reaction time, g is number of molecules in unit volume of sample gas, and the factors $T_{m/z}$ and $T_{\text{H}_3\text{O}^+}$ are the transmission efficiencies for MH^+ and H_3O^+ ions, see e.g. [5].

For PTR-MS, the reaction time t is represented by the drift time of precursor ions H_3O^+ within the drift tube. The calculation of the drift time is based on the standard ion mobility of H_3O^+ in nitrogen adjusted to the actual temperature and pressure in the drift tube, [18].

The constant k_M and the transmission coefficients $T_{m/z}$ and $T_{\text{H}_3\text{O}^+}$ are known for several compounds, for an overview see e.g. [19]. For simplicity, in this paper we consider as a typical value $k_M \approx 2.0 \cdot 10^{-9} \text{ cm}^3 \cdot \text{particles}^{-1} \cdot \text{sec}^{-1}$, and $T_{\text{H}_3\text{O}^+}/T_{m/z} \approx 1$, respectively.

Note that $[M]$ is used to denote the true concentration of the compound M which is estimated by the PTR-MS measurements, i.e. we assume that $[M]$ is (known or unknown) constant (non-stochastic term). Further, $\widehat{[M]}$ is used to denote the estimated concentration of M, based on the measurements, and as such it is a random variable (stochastic term).

It is important to emphasize that the probability distribution of $\widehat{[M]}$ functionally depends on the true concentration $[M]$, on the level (concentration) of the background noise, say $[N]$, and the time-span of the PTR-MS measurements (here we assume common dwell time τ for count-measurements of the primary ions as well as of the MH^+ ions).

1.1. Determination of concentration based on PTR-MS measurements

A typical set of parameters for PTR-MS measurements is given in Table 1¹, see also [16].

For this setting an observed countrate $\text{countrate}_{m/z}([\text{MH}^+])$ of 184.8 cps leads to an estimated concentration of $\widehat{[M]} = 1 \text{ ppb}$.

2. DETECTION LIMITS

Determination of detection limits is critical in meeting the needs of analytical science. Data users must understand the limitations of reporting the analytical data measured down to

¹Amount of substance is a standards-defined quantity that measures the size of an ensemble of elementary entities, such as atoms, molecules, electrons, and other particles. The number of particles (molecules) in unit volume of sample gas, denoted by g , could be derived by the following considerations: The amount of sample gas, measured in *moles*, in the volume V is given by the ideal gas law as $n = p \cdot V / (R \cdot T)$, where p is the absolute pressure (e.g. 2.4 mbar = 240 Pascal), V is the volume (here $V = 1 \text{ cm}^3$), R is the universal gas constant ($8.314472 \text{ J} \cdot \text{mol}^{-1} \cdot \text{K}^{-1}$) and T is the absolute temperature (e.g. 323 K). A typical amount of sample gas in unit volume $V = 1 \text{ cm}^3$, measured in *moles*, is then $8.9371 \cdot 10^{-8} \text{ mol} \cdot \text{cm}^{-3}$. The number of particles in volume V is $g = n \cdot N_A$, where $N_A = 6.0221415 \cdot 10^{23} \text{ mol}^{-1}$ is Avogadro constant. So, typically there are $5.3818 \cdot 10^{16}$ *particles* in 1 cm^3 .

Table 1: Typical values of PTR-MS parameters: κ_M - calibration constant; k_M reaction rate constant; t - reaction time; g - number of particles in unit volume ($V = 1 \text{ cm}^3$) of sample gas; const_M - total (summaric) constant; $\text{Mean}(\text{countrate}_{\text{H}_3\text{O}^+}([\text{H}_3\text{O}^+]))$ - mean countrate of the precursor ions counts (counts per second).

PTR-MS setting/parameter

| | |
|---|----------------------|
| κ_M | ≈ 1 |
| $k_M [\text{cm}^3 \cdot \text{particles}^{-1} \cdot \text{sec}^{-1}]$ | $2.0 \cdot 10^{-9}$ |
| $t [\text{sec}]$ | $1.01 \cdot 10^{-4}$ |
| $g [\text{particles} \cdot \text{cm}^{-3}]$ | $5.4 \cdot 10^{16}$ |
| $T_{\text{H}_3\text{O}^+}/T_{m/z}$ | ≈ 1 |
| $\text{const}_M [\text{ppb}]$ | $9.2 \cdot 10^4$ |
| $\text{Mean}(\text{countrate}_{\text{H}_3\text{O}^+}([\text{H}_3\text{O}^+])) [\text{cps}]$ | $1.7 \cdot 10^7$ |

their detection limits in order to minimize the risk of making poor decisions, see [15]. The typical measures for detection limits are the limit of quantification (LOQ) and the limit of detection (LOD), respectively. Roughly speaking, LOQ represents a concentration at which quantitative results can be reported with a high degree of confidence. LOD is the lowest concentration (quantity) of a substance that can be distinguished from the absence of that substance (blank analyte). It is important to emphasize that the detection limits (determined for specific measured substance) strongly depend on the possible background noise.

The standard method for determination of the detection limits is typically based on calibration series (statistical approach).

2.1. Limit of quantification (LOQ)

Unfortunately, there is no unique and unambiguous definition of LOQ, for more details and further discussion see the Appendix 1. In this paper LOQ is understood (in accordance with other interpretations) as such minimal increase of concentration (i.e. difference of true concentrations) that the observed (measured) values of concentrations can be attributed to distinct concentrations of the substance with a high degree of confidence.

In other words, the limit of quantification of a given substance M with its true concentration $[M]$, is such minimal concentration, say $\text{LOQ}_{[M]}$, that concentration measurements at $[M]$ and at $[M] + \text{LOQ}_{[M]}$, respectively, can be attributed to distinct concentrations of the substance with high degree of confidence.

Let $[M]_1 < [M]_2$ are two distinct concentrations of the substance M. Then the limit of quantification for concentration $[M]_1$ is defined as $\text{LOQ}_{[M]_1} = [M]_2 - [M]_1$, where $[M]_2$ is such concentration of the compound M that

$$\frac{\text{Std}(\widehat{[M]}_1) + \text{Std}(\widehat{[M]}_2)}{\text{Mean}(\widehat{[M]}_2) - \text{Mean}(\widehat{[M]}_1)} = \frac{1}{k}. \quad (4)$$

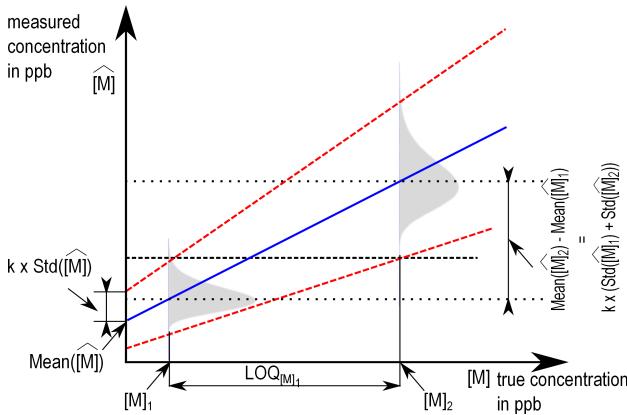


Fig. 2: The definition of the limit of quantification (LOQ) is illustrated. The solid line represents the mean value of the probability distribution of the measured signal $\text{Mean}(\widehat{[M]})$, the dashed lines represent the values $\text{Mean}(\widehat{[M]}) \pm k \cdot \text{Std}(\widehat{[M]})$.

Here, k denotes the select (pre-specified) constant (in this paper, we consider the value $k = 3$), $\text{Mean}(\widehat{[M]})$ and $\text{Std}(\widehat{[M]})$ denote the mean value and the standard deviation of the random variable $\widehat{[M]}$, respectively. For more details see Figure 2.

2.2. Limit of detection (LOD)

The limit of detection is the lowest quantity of a substance (compound M) that can be distinguished from the absence of that substance within a stated confidence limit. In general, the limit of detection depends on the particular compound M and on the probability distribution of the observable noise measured with blank analyte (i.e. in absence of compound M).

Throughout this work, the following interpretation will be used: The limit of detection, say LOD_M , is a specific value in the true concentration domain. The LOD_M equals to such concentration $[M]$ of the compound M, that its measured value $\widehat{[M]}$ is with probability of 99% above the 99%-percentile of the probability distribution of the noise measured with blank analyte, i.e. with $[M] = 0$, see Figure 3.

Notice that LOD_M is by definition equal to zero if the (background) noise is absent.

References to alternative definitions of LOD and a detailed explanation of the standard statistical approach based on the calibration experiment with normal (Gaussian) measurement errors can be found in the Appendix 1.

3. MODEL-BASED DETERMINATION OF DETECTION LIMITS FOR PTR-MS

3.1. Probability model of PTR-MS measurements

The measured counts at a single mass-to-charge ratio follow a Poisson distribution for PTR-MS, see [5, 17, 6, 10].

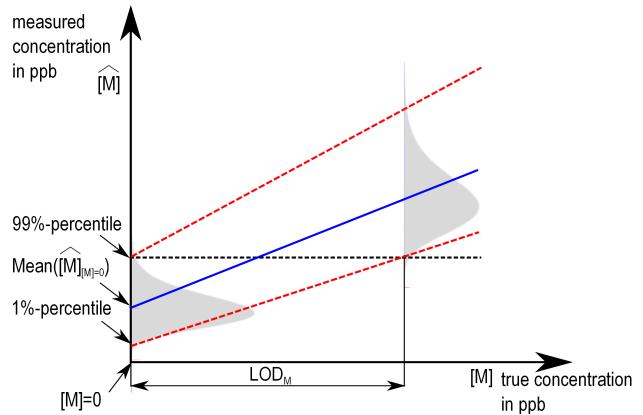


Fig. 3: The definition of the limit of detection (LOD) is illustrated. The solid line represents the mean value of the probability distribution of the measured signal $\text{Mean}(\widehat{[M]})$, the dashed lines represent the 99%-percentile and 1%-percentile of the measured signal, respectively. The mean value of the probability distribution of the concentration measurements of the blank analyte is denoted by $\text{Mean}(\widehat{[M]}_{[M]=0})$. The LOD definition indicates the true concentration for which the 1%-percentile of the measured signal is equal to the 99%-percentile of the measured concentration of the blank analyte.

Based on the formula (2) we will assume that the theoretical model for probability distribution of $\widehat{[M]}$ is proportional to the ratio of two independent Poisson-distributed random variables, $\tau \cdot \text{countrate}_{m/z}([\text{MH}^+])$ and $\tau \cdot \text{countrate}_{\text{H}_3\text{O}^+}([\text{H}_3\text{O}^+])$ (i.e. counts per dwell time τ) with the parameters $\lambda_{m/z}^\tau([M])$ and $\lambda_{\text{H}_3\text{O}^+}^\tau([\text{H}_3\text{O}^+])$ which depend on the true values of $[M]$ and $[\text{H}_3\text{O}^+]$, respectively. So, we have

$$\tau \cdot \text{countrate}_{m/z}([\text{MH}^+]) \sim \text{Poisson}(\lambda_{m/z}^\tau([M])), \quad (5)$$

$$\tau \cdot \text{countrate}_{\text{H}_3\text{O}^+}([\text{H}_3\text{O}^+]) \sim \text{Poisson}(\lambda_{\text{H}_3\text{O}^+}^\tau([\text{H}_3\text{O}^+])). \quad (6)$$

Under stable measuring conditions it is quite natural to assume that $\lambda_{m/z}^\tau([M]) = \tau \cdot \lambda_{m/z}([M])$ and $\lambda_{\text{H}_3\text{O}^+}^\tau([\text{H}_3\text{O}^+]) = \tau \cdot \lambda_{\text{H}_3\text{O}^+}([\text{H}_3\text{O}^+])$.

The parameters $\lambda_{m/z}^\tau([M])$ and $\lambda_{\text{H}_3\text{O}^+}^\tau([\text{H}_3\text{O}^+])$ represent the mean values of the random variables measuring counts of the MH^+ ions at m/z and the precursor ions H_3O^+ (and its water cluster) during the dwell time τ . The parameters $\lambda_{m/z}([M])$ and $\lambda_{\text{H}_3\text{O}^+}([\text{H}_3\text{O}^+])$ are the intensity parameters of the Poisson distributed random variables measuring counts of the ions during the unit time of $\tau = 1 \text{ sec}$.

If the detected counts of the MH^+ ions at m/z are affected by the independent background noise with the constant intensity parameter $\lambda_{m/z}^N = \lambda_{m/z}^N([N])$, where $[N]$ is the true concentration of the noise measured at m/z independent of the concentration $[M]$, then we get

$$\lambda_{m/z}([M]) = \lambda_{m/z}^S([M]) + \lambda_{m/z}^N, \quad (7)$$

where $\lambda_{m/z}^S([M])$ is the mean intensity of the detected counts exclusively due to the concentration $[M]$ of the substance M.

The intensity parameters $\lambda_{m/z}^\tau([M])$ and $\lambda_{H_3O^+}^\tau([H_3O^+])$ can be (in a natural way) estimated by the observed counts during the dwell time τ . For Poisson distributed random variable, the mean value is equal to its intensity parameter, and the standard deviation is equal to the square root of this parameter.

The distribution of the ratio of two independent Poisson distributed random variables was derived by Arendacká *et al.* in [1], where the exact analytic expressions for cumulative distribution function (cdf) as well as for the mean and the variance was given.

As the countrate $countrate_{H_3O^+}([H_3O^+])$ of precursor ions is typically large, $\lambda_{H_3O^+}([H_3O^+]) \approx 1.7 \cdot 10^7$ cps, then for a known value of $\tau \cdot \lambda_{H_3O^+}([H_3O^+])$ and for fixed dwell time τ the approximate formulas for mean and standard deviation of the measured concentrations $\widehat{[M]}$ are given by

$$Mean(\widehat{[M]}) \approx const_M \cdot \frac{\lambda_{m/z}([M])}{\lambda_{H_3O^+}([H_3O^+])}, \quad (8)$$

$$Std(\widehat{[M]}) \approx const_M \cdot \frac{\sqrt{\lambda_{m/z}([M])}}{\sqrt{\tau} \cdot \lambda_{H_3O^+}([H_3O^+])}. \quad (9)$$

For large concentrations $[M]$ the distribution of the random variable $\widehat{[M]}$ can be well approximated by a normal and/or log-normal distribution, respectively, for more details see [1].

3.2. PTR-MS measurements with the blank analyte

In order to characterize the distribution of measurements with the blank analyte the following experiment was performed: Dry, filtered room air (i.e. a mixture of $N_2 \sim 80\%$, O_2 and $CO_2 \sim 20\%$) was measured using a PTR-MS with a dwell time of one second for each ion. At most of the m/z , no signal should be visible since there is no compound included in the sample which could raise a signal. Nevertheless, ions beside H_3O^+ may come from the source and rise a signal or contaminations within the tubing system may arise.

Table 2 reports the mean countrates of 41 independently repeated measurements of blank analyte measured at selected m/z with a possible explanation of the noise source (either the explained (identified) contaminations as well as their assumed origin, or the unexplained (unidentified) contaminations of the sample and/or tubing system).

For example, at m/z 59 most probably some acetone is measured (mean countrate is 24 counts). According to the proton transfer reaction, nitrogen as well as carbon dioxide should not be protonated since their proton-affinity is lower than the one of water. Nevertheless, since at the drift tube an electric field is applied, this reaction as well as a charge transfer may take place.

Table 2: The mean countrates of 41 PTR-MS measurements with blank analyte measured at selected m/z . The symbol "?" was added to indicate possible explanation.

| m/z | mean countrate | assumed origin |
|-------|----------------|------------------------------------|
| 21 | 66511 | H_3O^+ -isotope |
| 22 | 26 | H_3O^+ -isotope |
| 23 | 0.1220 | unexplained noise |
| 24 | 0.0732 | unexplained noise |
| 25 | 0.1220 | unexplained noise |
| 26 | 0.0732 | unexplained noise |
| 27 | 0.8537 | unexplained noise |
| 28 | 142 | ?: charged N_2 |
| 29 | 16788 | ?: protonated N_2 |
| 30 | 24778 | NO^+ |
| 31 | 150 | NO^+ -isotope |
| 32 | 340500 | O_2^+ |
| 33 | 1563 | O_2^+ -isotope, methanol |
| 34 | 1721 | O_2^+ -isotope, methanol-isotope |
| 37 | 257500 | $H_2O \cdot H_3O^+$ |
| 38 | 365 | $H_2O \cdot H_3O^+$ -isotope |
| 39 | 1021 | $H_2O \cdot H_3O^+$ -isotope |
| 44 | 43 | ?: charged CO_2 |
| 45 | 606 | ?: protonated CO_2 |
| 46 | 121 | main core ions |
| 47 | 178 | main core ions |
| 55 | 35 | $(H_2O)_2 \cdot H_3O^+$ |
| 59 | 24 | ?: acetone contamination |

3.3. Determination of LOQ

Based on (4) the limit of quantification $LOQ_{[M]}$ is defined as a solution of the equation

$$\frac{Std(\widehat{[M]}) + Std(\widehat{[[M] + LOQ_{[M]}]})}{Mean(\widehat{[[M] + LOQ_{[M]}]}) - Mean(\widehat{[M]})} = \frac{1}{k}, \quad (10)$$

with the selected constant $k = 3$.

Further, we assume that the measurement device (PTR-MS) was properly calibrated, i.e. the calibration constant κ_M is such that the mean of the measured concentration $\widehat{[M]}$, adjusted for the noise, is an unbiased estimator of the true concentration $[M]$, i.e.

$$Mean(\widehat{[M]}) - [N] \approx [M], \quad (11)$$

or equivalently,

$$Mean(\widehat{[M]}) \approx [M] + [N], \quad (12)$$

where $[N]$ denotes the mean concentration of the background noise measured at given m/z .

Then, from (10), and by using the results (8), (9), and (12), we obtain $\text{LOQ}_{[\text{M}]}$ as a solution to the equation

$$\text{LOQ}_{[\text{M}]} = \frac{3 \cdot \alpha}{\sqrt{\tau}} \left(\sqrt{[\text{M}] + [\text{N}] + \text{LOQ}_{[\text{M}]}} + \sqrt{[\text{M}] + [\text{N}]} \right). \quad (13)$$

where $\alpha = \sqrt{\text{const}_M / \lambda_{\text{H}_3\text{O}^+}([\text{H}_3\text{O}^+])}$. For typical PTR-MS setting, as given in Table 1, we get $\alpha \approx 0.074$.

Alternatively, the limit of quantification can be computed as

$$\text{LOQ}_{[\text{M}]} = \lambda_{m/z}(\text{LOQ}_{[\text{M}]}) \cdot \frac{\text{const}_M}{\lambda_{\text{H}_3\text{O}^+}([\text{H}_3\text{O}^+])}, \quad (14)$$

where the intensity parameter $\lambda_{m/z}(\text{LOQ}_{[\text{M}]})$ is given as a solution to the equation

$$\begin{aligned} \lambda_{m/z}(\text{LOQ}_{[\text{M}]}) = & \frac{3}{\sqrt{\tau}} \left(\sqrt{\lambda_{m/z}([\text{M}]) + \lambda_{m/z}(\text{LOQ}_{[\text{M}]})} \right. \\ & \left. + \sqrt{\lambda_{m/z}([\text{M}])} \right). \end{aligned} \quad (15)$$

The above mentioned algorithms for computing $\text{LOQ}_{[\text{M}]}$ could be written as a few command lines in standard software packages. (e.g. MATLAB), see the Appendix 2.

As noted above, the limit of quantification depends on the compound M, on its true concentration $[\text{M}]$ (useful signal), on the concentration of the background noise $[\text{N}]$, and on the dwell time τ . In order to emphasize this dependence we will alternatively use the notation

$$\text{LOQ}_{[\text{M}]} = \text{LOQ}_{[\text{M}], [\text{N}]}^\tau. \quad (16)$$

3.3.1. Example

Let the true concentration of the compound M is $[\text{M}] = 0 \text{ ppb}$, the mean (true) concentration of the background noise N measured at given m/z is $[\text{N}] = 0 \text{ ppb}$, and the selected dwell time is $\tau = 1 \text{ sec}$. Then, based on the equation (13), we get the limit of quantification

$$\text{LOQ}_{[\text{M}]} = \text{LOQ}_{[\text{M}] = 0, [\text{N}] = 0}^{\tau=1} = 0.05 \text{ ppb}. \quad (17)$$

3.3.2. Example

Let the true concentration of the compound M is $[\text{M}] = 0 \text{ ppb}$, the mean concentration of the background noise N measured at given m/z is $[\text{N}] = 0.13 \text{ ppb}$, and the selected dwell time is $\tau = 1 \text{ sec}$. Then, based on the equation (13), we get the limit of quantification

$$\text{LOQ}_{[\text{M}]} = \text{LOQ}_{[\text{M}] = 0, [\text{N}] = 0.13}^{\tau=1} = 0.208 \text{ ppb}. \quad (18)$$

Notice, that the same values of the limit of quantification $\text{LOQ}_{[\text{M}]}$ can be computed using equations (14), (15), and (7):

3.3.3. Example

Let the true concentration of the compound M measured at given m/z is $[\text{M}] = 0 \text{ ppb}$ with $\lambda_{m/z}([\text{M}]) = \lambda_{m/z}^S([\text{M}]) + \lambda_{m/z}^N = 1848 + 24 = 1872 \text{ counts}$ (i.e. with the mean value of the background noise $[\text{N}] = 0.13 \text{ ppb}$), and the selected dwell time is $\tau = 1 \text{ sec}$. Then, based on the equation (13), we get the limit of quantification

$\lambda_{m/z}^N = 0 + 24 = 24 \text{ counts}$ (i.e. with the mean value of the background noise $[\text{N}] = 0.13 \text{ ppb}$), and the selected dwell time is $\tau = 1 \text{ sec}$.

Then, based on the equation (15), we get

$$\lambda_{m/z}(\text{LOQ}_{[\text{M}]}) = 38.4 \text{ counts}, \quad (19)$$

and finally, from (14), we get

$$\text{LOQ}_{[\text{M}]} = 0.208 \text{ ppb}, \quad (20)$$

what is in agreement with the results of the Example 3.3.2.

3.3.4. Example

Let the true concentration of the compound M measured at given m/z is $[\text{M}] = 10 \text{ ppb}$, the mean concentration of the background noise N is $[\text{N}] = 0.13 \text{ ppb}$, and the selected dwell time is $\tau = 1 \text{ sec}$.

Then, based on the equation (13), we get the limit of quantification

$$\text{LOQ}_{[\text{M}]} = \text{LOQ}_{[\text{M}] = 10, [\text{N}] = 0.13}^{\tau=1} = 1.45 \text{ ppb}. \quad (21)$$

If we change the selected dwell time to $\tau = 10 \text{ sec}$, we get the limit of quantification

$$\text{LOQ}_{[\text{M}]} = \text{LOQ}_{[\text{M}] = 10, [\text{N}] = 0.13}^{\tau=10} = 0.45 \text{ ppb}. \quad (22)$$

3.3.5. Example

Let the true concentration of the compound M measured at given m/z is $[\text{M}] = 10 \text{ ppb}$ with $\lambda_{m/z}([\text{M}]) = \lambda_{m/z}^S([\text{M}]) + \lambda_{m/z}^N = 1848 + 24 = 1872 \text{ counts}$ (i.e. with the mean value of the background noise $[\text{N}] = 0.13 \text{ ppb}$), and the selected dwell time is $\tau = 1 \text{ sec}$.

Then, based on the equation (15), we get

$$\lambda_{m/z}(\text{LOQ}_{[\text{M}]}) = 268.6 \text{ counts}, \quad (23)$$

and finally, from (14), we get

$$\text{LOQ}_{[\text{M}]} = 1.45 \text{ ppb}, \quad (24)$$

what is in agreement with the results of the Example 3.3.4.

3.4. Determination of LOD

The limit of detection depends on the particular compound M and on the probability distribution of $\widehat{[\text{N}]}$ — the measured concentration of the background noise N, i.e. the concentration measured with the blank analyte (in absence of compound M, i.e. $[\text{M}] = 0$), which in fact depends on $[\text{N}]$, the true concentration of N, and on the dwell time τ .

In order to emphasize this dependence we will alternatively use the notation

$$\text{LOD}_M = \text{LOD}_{M, [\text{N}]}^\tau. \quad (25)$$

The limit of detection LOD_M is defined as the true concentration $[M]$ of the compound M, such that the 1%-percentile of the probability distribution of the measured concentration $\widehat{[M]}$ equals the 99%-percentile of the distribution of $\widehat{[N]}$.

Using the theoretical model based on the ratio of independent Poisson distributed random variables it is possible to calculate the exact cumulative distribution functions² as well as the required percentiles of the distributions.

To be able to do that, it is necessary to know the parameters: $const_M \approx 9.2 \cdot 10^4$, $\lambda_{H_3O^+} = \lambda_{H_3O^+}([H_3O^+]) = Mean(countrate_{H_3O^+}([H_3O^+])) \approx 1.7 \cdot 10^7$, $\lambda_{m/z}([M]) = \lambda_{m/z}^N$ as $[M] = 0$, and the dwell time τ .

In general, the mean countrate of the background noise observable at the mass-to-charge ratio m/z , i.e. the parameter $\lambda_{m/z}^N$, is unknown and should be estimated from independent experiments. For illustration, typical mean countrates of PTR-MS measurements of blank analyte (i.e. countrates of the background noise) are presented for selected m/z in Table 2.

The algorithm for computing LOD_M from the exact distribution based on the ratio of independent Poisson distributed random variables is numerically highly intensive. So, as a simple alternative, the limit of detection can be approximately computed as

$$LOD_M \approx \lambda_{m/z}(LOD_M) \cdot \frac{const_M}{\lambda_{H_3O^+}([H_3O^+])}. \quad (26)$$

where the parameter $\lambda_{m/z}(LOD_M)$ is given as the smallest solution to the equation

$$p_{0.01}\left(\lambda_{m/z}^N + \lambda_{m/z}(LOD_M)\right) = p_{0.99}\left(\lambda_{m/z}^N\right). \quad (27)$$

Here, $p_{0.99}(\lambda_{m/z}^N)$ denotes the 99%-percentile of the distribution $Poisson(\tau \cdot \lambda_{m/z}^N)$ and $p_{0.01}(\lambda_{m/z}^N + \lambda_{m/z})$ denotes the 1%-percentile of the distribution $Poisson(\tau \cdot (\lambda_{m/z}^N + \lambda_{m/z}))$ for arbitrary $\lambda_{m/z}$.

The approximate algorithm for computing LOD_M could be written as a few command lines in standard software packages, see the Appendix 2.

3.4.1. Example

Consider the LOD determination for concentration measurements of the acetone, say M, measured at the mass-to-charge ratio $m/z = 59$.

Let the estimated concentration of the background noise (i.e. blank analyte, $[M] = 0$), is characterized by the Poisson random variable with the parameter $\lambda_{m/z=59}([M] = 0) = \lambda_{m/z=59}^S([M] = 0) + \lambda_{m/z=59}^N = 0 + 24 = 24 counts$, and the selected dwell time is $\tau = 1 sec$.

²A Matlab software package for numerical computation of the cumulative distribution function as well as the mean and the variance of the ratio of two independent Poisson distributed random variables is available at <http://www.mathworks.com/matlabcentral/fileexchange/25843-poissratiocdf>.

The 99%-percentile of the distribution of measured concentration of blank analyte is calculated, based on the equation (2), as the percentile of the distribution of the ratio of two independent Poisson distributed random variables, with the parameters $\lambda_{m/z}^N = 24$ and $\lambda_{H_3O^+} = 1.7 \cdot 10^7$, multiplied by the constant $const_M$.

By using the algorithm for computing the exact distribution function we get the value of the 99%-percentile of the distribution of the background noise, $p_{0.99}(\lambda_{m/z}^N) = 0.195 ppb$.

Further, by searching through the space of all possible parameters $\lambda_{m/z}$ of the exact distribution of the ratio of two independent Poisson distributed random variables, we find the value of the parameter $\lambda_{m/z}(LOD_M)$ such that $p_{0.01}(\lambda_{m/z}^N + \lambda_{m/z}(LOD_M)) = p_{0.99}(\lambda_{m/z}^N)$ (i.e. the 1%-percentile of the exact distribution of the measurements at the true concentration LOD_M equals to the 99%-percentile of the noise), we get $\lambda_{m/z}(LOD_M) = 28 counts$.

Then, LOD_M is given as the mean value of the exact distribution with the parameter $\lambda_{m/z}^{LOD}$, i.e.

$$LOD_M = 0.152 ppb. \quad (28)$$

For comparison, we also present result of the approximate algorithm based on (26) and (27). The 99%-percentile of $Poisson(\lambda_{m/z}^N)$ is $p_{0.99}(\lambda_{m/z}^N) = 36 counts$. By solving the equation (27) we get $\lambda_{m/z}(LOD_M) = 28$. Finally, from (26) we get

$$LOD_M = 28 \cdot \frac{const_M}{\lambda_{H_3O^+}} = 0.152 ppb, \quad (29)$$

what is in agreement with (28), the result of exact computation.

4. CONCLUSIONS AND DISCUSSION

Determination of statistical detection limits is typically based on calibration measurements, but this approach is considerably limited, especially for measurements with very low concentrations of the analyte. In general, the detection limits depend on the substance concentration (useful signal) and on the explained and/or unexplained background noise.

In this paper we have suggested a model-based determination of detection limits (LOQ and LOD) for proton-transfer-reaction mass spectrometer (PTR-MS). The assumed theoretical model for the concentration measurements of the analyte (volatile organic compound, say M) $\widehat{[M]}$ is proportional to the ratio of two independent Poisson distributed random variables, as described in Section 3. This model covers the situations when the measurement process is influenced by the presence of the background noise and respects the effect of the dwell time (i.e. the time of PTR-MS measurement).

The theoretical model-based approach assumes the exact knowledge of the parameters characterizing the noise and the measurement process by PTR-MS. In real situations, the intensity of the noise should be estimated from independent experiments.

The algorithms for computing the limit of quantification (LOQ) as well as the limit of detection (LOD) are very simple. As we have illustrated in this paper, the working algorithms for computing LOQ and LOD could be written as a few command lines in standard software packages for technical computing, as e.g. in MATLAB.

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APPENDIX 1

As mentioned above, determination of detection limits is critical in meeting the needs of analytical science. Data users must understand the limitations of reporting the analytical data measured down to their detection limits in order to minimize the risk of making poor decisions. Unfortunately, there is no unique and unambiguous definition of LOQ and/or LOD. The problem of detection limits, focused on different analytical methods and methodology, was broadly studied and analyzed in the literature, see e.g. [2], [15], [4], [14], [8], [7], [3], [5], [12], [11].

Here we shall use the statistical concept for determination of the detection limits as suggested in e.g. in [3] and [12].

Although LOD and LOQ, as presented in [3] and [12], are considered for situations when the calibration function (in the simplest cases it is the calibration line) is available, we can use this concept of LOD and LOQ also in the situations when the given theoretical model is assumed to be valid for modeling the relation between the measured concentration (in this paper denoted as $\widehat{[M]}$) and the true concentration (in this paper denoted as $[M]$).

It means that for a given true concentration, say x , we can calculate the predicted value of the measured concentration, say Y_x , together with the $(1 - 2\alpha)$ -prediction interval ($_x\gamma_1^{(\alpha)}$, $_x\gamma_2^{(\alpha)}$), i.e. with the random interval for which the relations

$$\Pr(Y_x > {}_x\gamma_1^{(\alpha)}) = 1 - \alpha, \quad (30)$$

$$\Pr(Y_x < {}_x\gamma_2^{(\alpha)}) = 1 - \alpha, \quad (31)$$

hold true. The $_x\gamma_1^{(\alpha)}$ and $_x\gamma_2^{(\alpha)}$ are the proper (lower and upper) prediction limits.

Definition of LOD. LOD is such a (true) concentration $\text{LOD}_{(0)}$ that

$$\text{LOD}_{(0)}\gamma_1^{(\alpha)} = {}_0\gamma_2^{(\alpha)}. \quad (32)$$

Definition of LOQ. LOQ for the (true) concentration x is such a minimal (true) concentration LOQ_x for which the relation

$$\frac{\text{Std}(Y_x) + \text{Std}(Y_{x+\text{LOQ}_x})}{\text{Mean}(Y_{x+\text{LOQ}_x}) - \text{Mean}(Y_x)} = \frac{1}{k}, \quad (33)$$

where k is a given constant (in the paper we consider $k = 3$), $\text{Mean}(Y_x)$ and $\text{Std}(Y_x)$ are the mean value and the standard deviation of the random variable Y_x , respectively.

In the case of having a regression line $Y_x = \beta_0 + \beta_1 x + \varepsilon_x$, $\varepsilon_x \sim N(0, \sigma^2)$ (homoscedastic case), i.e. if we have realizations y_1, y_2, \dots, y_n of independent normally distributed measurements $Y_{x_1}, Y_{x_2}, \dots, Y_{x_n}$ with equal dispersions, the predicted response of Y for a given x is

$$Y_x = b_0 + b_1 x + \varepsilon_x \quad (34)$$

with the mean value $\text{Mean}(Y_x) = \beta_0 + \beta_1 x$ and

$$b_0 = \bar{y} - b_1 \bar{x}, \quad (35)$$

$$b_1 = \frac{\sum_{i=1}^n (x_i - \bar{x}) y_i}{\sum_{i=1}^n (x_i - \bar{x})^2}, \quad (36)$$

are the least-squares estimates of b_0 and b_1 (see e.g. [12]). The upper prediction limit for blank signal ($x = 0$) is

$${}_0\gamma_2^{(\alpha)} = b_0 + t_{n-2}(1 - \alpha) \sqrt{\frac{\sum_{i=1}^n (y_i - b_0 - b_1 x_i)^2}{n-2}} \times \sqrt{1 + \frac{1}{n} + \frac{\bar{x}^2}{\sum_{i=1}^n (x_i - \bar{x})^2}}, \quad (37)$$

($t_{n-2}(1 - \alpha)$ is the $(1 - \alpha)$ -quantile of Student t distribution with $n - 2$ degrees of freedom). LOD is such a true concentration $\text{LOD}_{(0)}$ that

$$\begin{aligned} \text{LOD}_{(0)}\gamma_1^{(\alpha)} &= b_0 + b_1 \text{LOD}_{(0)} \\ &- t_{n-2}(1 - \alpha) \sqrt{\frac{\sum_{i=1}^n (y_i - b_0 - b_1 x_i)^2}{n-2}} \\ &\times \sqrt{1 + \frac{1}{n} + \frac{(\text{LOD}_{(0)} - \bar{x})^2}{\sum_{i=1}^n (x_i - \bar{x})^2}} \\ &= {}_0\gamma_2^{(\alpha)}. \end{aligned} \quad (38)$$

For a given x the proper estimate of $\text{Mean}(Y_x)$ is

$$\widehat{\text{Mean}}(Y_x) = b_0 + b_1 x, \quad (39)$$

and the proper estimate of $\text{Std}(Y_x)$ is

$$\begin{aligned} \widehat{\text{Std}}(Y_x) &= \left(\frac{1}{n-2} \sum_{i=1}^n (y_i - b_0 - b_1 x_i)^2 \times \right. \\ &\times \left. \left(1 + \frac{1}{n} + \frac{(x - \bar{x})^2}{\sum_{j=1}^n (x_j - \bar{x})^2} \right) \right)^{\frac{1}{2}}. \end{aligned} \quad (40)$$

The estimate of LOQ for given x is $\widehat{\text{LOQ}}_x$ for which

$$\frac{k}{b_1} \left[\widehat{\text{Std}}(Y_x) + \widehat{\text{Std}}(Y_{x+\widehat{\text{LOQ}}_x}) \right] = \text{LOQ}_x, \quad (41)$$

is valid. For more details see [12].

APPENDIX 2

Here we present a simplified version of the algorithms for computing the limit of quantification (LOQ) and the limit of detection (LOD). As illustrated, the working algorithms for computing LOQ and LOD are very simple and could be written as a few command lines in standard software packages for technical computing, as e.g. in MATLAB.

5.1. Computing the LOQ from concentrations

```
% Computing the LOQ from concentrations
% Example 3.3.2

% Set the PTR-MS settings
constM      = 9.2e4;
lambdaH3O   = 1.7e7;
C = constM/lambdaH3O;
a = sqrt(C);

% Set the parameters - Example 3.3.2
tau = 1;
M = 0;
N = 0.13;
MN = M + N;

% Set the function defined by eq. (13)
eq13 = inline( ...
    'sqrt(tau)*x-3*a*(sqrt(MN+x)+sqrt(MN))', ...
    'x', 'MN', 'tau', 'a');

% LOQ: the solution of eq. (13)
LOQ = ...
fzero(@(x)eq13(x,MN,tau,a),[0 5]);
```

5.2. Computing the LOQ from countrates

```
% Computing the LOQ from countrates
% Example 3.3.3

% Set the PTR-MS settings
constM      = 9.2e4;
lambdaH3O   = 1.7e7;
C = constM/lambdaH3O;

% Set the parameters - Example 3.3.3
tau = 1;
lambdaS = 0;
lambdaN = 24;
l = lambdaS + lambdaN;

% Set the function defined by eq. (15)
eq15 = inline(...
    'sqrt(tau)*x-3*(sqrt(l+x)+sqrt(l))', ...
    'x', 'l', 'tau');

% lambdaLOQ: the solution of eq. (15)
lambdaLOQ = ...
fzero(@(x)eq15(x,l,tau),[0 500]);
```

```
% LOQ: the solution of eq. (14)
LOQ = lambdaLOQ * C;
```

5.3. Computing the LOD

```
% Computing the LOD from countrates
% Example 3.4.1

% Set the PTR-MS settings
constM      = 9.2e4;
lambdaH3O   = 1.7e7;
C = constM/lambdaH3O;

% Set the parameters from the Example 3.4.1
tau = 1;
lambdaS = 0;
lambdaN = 24;
l = lambdaS + lambdaN;

% Set the function defined by eq. (27)
eq27 = ...
    inline('p99-poissinv(0.01,tau*(x+lN))', ...
    'x', 'p99', 'ln', 'tau');

% lambdaLOD: the solution of eq. (27)
p99 = poissinv(0.99,tau*lambdaN);
lambdaLOD = fzero(@(x)...
    eq27(x,p99,lambdaN,tau),[eps 100]);

% LOD: the solution of eq. (26)
LOD = round(lambdaLOD) * C;
```

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