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Time of First Arrival in Electrochemical Collision Experiments as a Measure of Ultralow Concentrations of Analytes in Solution

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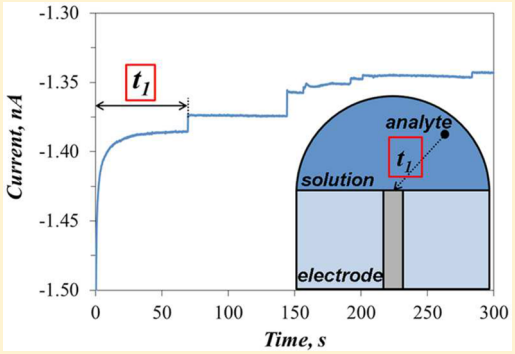
Supporting Information

ABSTRACT: In electrochemical collision experiments, the frequency of collisions of nanoparticles (NPs) with an ultramicroelectrode (UME) is a measure of the solution concentration of NPs. The time of first arrival is evaluated as a measure of ultralow (sub-femtomolar) concentration of analytes in solution. This is the time from the beginning of the experiment until the moment of observation of the first electrochemically detectable collision event. Theoretical equations are developed relating the time of the first arrival and the concentration of analyte species in solution for the cases when the species is transferred by diffusion alone and with electrophoretic migration. These equations are supported by experimental data. According to analysis of the results, the time of first arrival can be used successfully to estimate the order of magnitude of the analyte concentration with the precision of analysis being affected by the inherent stochasticity of the analyte movement and its initial position near the electrode. The use of the multiplexed parallel detection based on simultaneous measurement of a series of time of first arrival values will allow both faster and more precise determination of ultralow concentrations of analytes in solution.



Stochastic electrochemistry allows for very sensitive detection of a wide range of analytes including metal and polymer nanoparticles, emulsion droplets, carbon nanotubes, and fullerene aggregates at picomolar (10^{-12} M) and down to femtomolar (10^{-15} M) concentrations.[1−4] The developed methods of stochastic electrochemical detection are based on either the blockage of the flux of the redox species in solution by an insulating species (blocking collisions[5,6]), amplification of the electrochemical reaction (electrocatalytic amplification (ECA) collisions[7−9]), or electrolysis of the collided species (direct electrochemical detection[10−12]). In elucidation of the concentration values of analytes, the general approach is to relate the frequency of collisions to the concentration of the analyzed species. For example, when the analyte is transferred in solution by diffusion, eq 1 is used:

$$f = 4DCrN_A \quad (1)$$

where f is the frequency of collisions, D is the diffusion coefficient of the analyte species, C is its concentration, r is the electrode radius, and N_A is the Avogadro's constant.

The above equation assumes that the frequency of collisions is controlled exclusively by the rate of mass transfer of the species to the electrode, i.e., it neglects the kinetics of electrochemical detection. Kwon et al. have considered in detail the effect of finite kinetics (mixed diffusive and kinetic control) and the possibility that not every collision results in an observable signal change.[1] Later Boika et al. developed theoretical models of mass transfer of the analyzed nanoparticles (NPs) to the electrode by migration thus relating the frequency of collisions and the concentration of NPs for the case when the rate of diffusion is negligible.[6] However, in all of these examples elucidation of the analyte concentration from the frequency of collisions has one disadvantage. It is that in order to obtain the value of the collision frequency experimentally one has to record the data for a sufficiently long time. This is particularly a problem for the detection of ultralow concentrations of analytes if diffusion is the dominant mode of their mass transfer. Simple evaluation of eq 1 shows that one has to wait thousands of seconds to obtain enough data in the analysis of sub-picomolar to femtomolar (<10^{-12} to 10^{-15} M) concentrations of analytes. Thus, the use of the frequency of collisions to determine the value of concentration is disadvantageous if the analysis is to be performed rapidly in the aforementioned concentration range. Rapid detection of ultralow concentrations of explosive materials, controlled substances, disease pathogens, and pollutants is of paramount importance for our security and health.

In this paper we investigate the possibility of using the time of first arrival (TFA, also known as the first-passage time), instead of frequency of collisions, as a measure of an ultralow concentration of analyte in solution. TFA is the period of time from the beginning of an experiment until the moment of recording by an instrument of the first measurable signal

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corresponding to the collision of an analyte species with an electrode surface. Once the species arrives by diffusion and/or migration to the electrode surface and collides with it, a change in the measured electrochemical signal is observed. Thus, by observing the change in the electrochemical signal one can determine when the species arrives at the electrode and, since TFA is proportional to the distance traveled by the species, our hypothesis is that one should be able to relate TFA to the analyte concentration in solution. The use of TFA as the measure of concentration can speed up the analysis time considerably and potentially allow evaluation of ultralow concentrations of analytes (~attomolar values, $\sim 10^{-18}$ M). The theory of the first-passage processes is developed well and a monograph can be recommended on general subject.[13] However, to the best of our knowledge, no one yet attempted to apply the knowledge of TFA to the analysis of stochastic electrochemical events, i.e., collisions. The data presented in this paper include the results of experiments supported by theoretical simulations. Here we consider only how one can relate TFA of analyte species to the value of its concentration in solution and we assume that no other complications exist, i.e., the collision is fruitful and no kinetic limitations are observed. The experiments include the study of TFA as a function of analyte concentration for the cases when the dominant mode of analyte mass transfer is migration (blocking collisions) and diffusion (ECA collisions measured based on the open-circuit potential changes). Theoretical data include the results of the simulations based on random-walk (Einstein[14]) and Langevin[15] models. Our findings indicate that one can estimate the concentration of the analyte species based just on one measurement (i.e., TFA). However, because of the inherent stochasticity of the mass transfer, the precision of such analysis is limited to the order of magnitude of the concentration value. The outlook on the future of the TFA analysis is also considered.

EXPERIMENTAL SECTION

Materials and Instrumentation. All chemicals were ACS grade and were not purified additionally before the experiments. The NPs used in experiments were either synthesized or purchased. Pt NPs were prepared and characterized according to the previously reported procedure from our group.[16] Unfunctionalized polystyrene (530 nm or 1 μm diam.) particles were purchased from Bangs Laboratories, Inc. (Fishers, IN; catalog numbers PS03N and PS04N). These spheres were supplied in aqueous solutions containing sodium dodecyl sulfate and sodium azide. To remove the unwanted chemicals, the spheres were washed by centrifugation with water before experiments. All solutions were prepared using water from Millipore Reagent grade purification system (Millipore, Bedford, MA). Ferrocenemethanol was purchased from Alfa Aesar (Ward Hill, MA), potassium chloride from Fisher Scientific (Hampton, NH), and anhydrous hydrazine solution from Sigma-Aldrich (St. Louis, MO).

UMEs were constructed by sealing metal microwires (Pt or Au) in borosilicate glass according to well established procedures. Before experiments they were polished using alumina particle suspensions (Buehler, MicroPolish II, 0.3 μm particle diameter) and then cleaned further by dipping the ends into piranha solution (1:3 H_2O_2 (conc.)/H_2SO_4 (conc.) by vol) for about 5−10 s.

Electrochemical measurements were performed using CH Instruments potentiostats, models CHI920c and CHI630. The electrochemical cell was custom-made from glass and had four openings (three for electrodes and one for injecting of particles). All experiments were done without the removal of dissolved oxygen.

Experiments. Blocking collisions[6] were used to evaluate the time of first arrival by migration. In these experiments large polystyrene beads were used as an analyte species (530 nm or 1 μm in diameter), so the contribution of diffusion to their mass transfer was minimal and, therefore, neglected. Besides the beads, the solution also contained 2 mM ferrocene methanol and 1 mM potassium chloride. The potential applied to the UME corresponded to the steady-state oxidation of FcMeOH (450 mV vs Ag|AgCl|KCl(sat.)) and lead to the formation of an electric field in solution. Since the beads are negatively charged (they were used in our previous work[6]), they migrated toward the UME and blocked the flux of the redox species upon collision with the electrode surface. This resulted in observation of collision events.

Electrocatalytic amplification collision experiments based on measurement of open-circuit potential (OCP) changes[9] were used to study the time of first arrival by diffusion. In these experiments Pt NPs (~20 nm in diameter) were used as the analyte species. The solution also contained 15 mM hydrazine in 5 mM phosphate buffer at pH 7. Collisions of diffusing Pt NPs with a gold UME surface lead to the change in the OCP values thus allowing determination of the time of first arrival. Since no faradaic current flows in the system upon NP collisions, in this case, there is no contribution of migration to the NP mass transfer.

Numerical simulations. Simulations discussed in this paper were done using two models: the first one was developed in Multiphysics software (COMSOL, Sweden) and the second one was written in Visual Basic. All relevant equations, including the boundary and initial conditions, are described in the Supporting Information. In short, the Multiphysics model was based on Langevin's approach to treating diffusion,[15] while the model written in Visual Basic adhered to Einstein's treatment of random walks and diffusion.[1,14] It should be noted that the two models showed quite similar results. Thus, the results obtained with Multiphysics are presented in this paper.

RESULTS AND DISCUSSION

In our recent work,[6] we showed that the frequency of NP collisions (NP arrival rate by migration, diffusion rate being negligible) can serve as a good measure of the NP concentration in the bulk solution: for concentrations down to the order of 10−50 fM, where one can observe several hundred collisions in a thousand seconds. Thus, relating the collision frequency and the particle concentration is very convenient when analyzing systems in the aforementioned concentration range. However, once the concentration of the analyte species decreases substantially (especially below 1 fM), one gets at best a couple of collision events during the same 1000 second period. This is shown in Figure 1 where the frequency of collisions (calculated as the number of collisions observed during a thousand second period) is plotted vs the concentration of particles in solution. Thus, analysis of very low concentrations of analytes (attomolar−sub-femtomolar) can definitely be a lengthy process if one uses the frequency of collisions as the measure of analyte concentration. Therefore, in this paper we propose to use a new parameter, time of first

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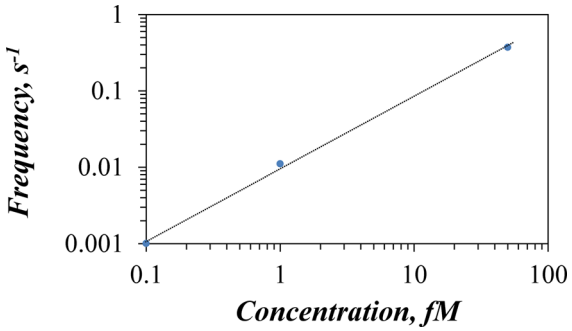

Figure 1. Frequency of blocking collisions of carboxylated polystyrene beads (530 nm diameter) with 5 μm Pt UME in 2 mM FcMeOH, 1 mM KCl. Potential applied to the UME corresponded to the steady-state oxidation of FcMeOH. Concentrations of the beads were 0.1, 1, and 50 fM, and the corresponding collision frequencies were 0.001, 0.011, and 0.37 s^{-1} (calculated as the number of collisions in a 1000 s period).

arrival (TFA), to estimate the concentration of analytes in very dilute solutions.

In Figure 2, one can see an example of determination of the time of first arrival (t_1) for the case of an insulating sphere

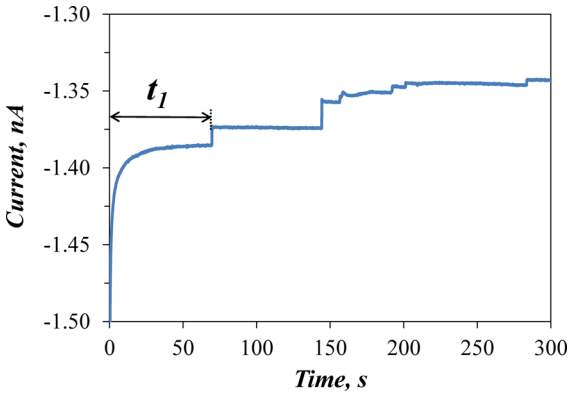

Figure 2. Chronoamperogram showing step-like features corresponding to collisions of insulating particles with the surface of 5 μm Pt electrode in 2 mM FcMeOH, 1 mM KCl solution (blocking collisions). Electrode potential was held at a value corresponding to steady-state oxidation of FcMeOH. Particle diameter 1 μm, concentration 1.45 fM. Time of first arrival (t_1) is measured from zero time until the moment of observation of the first collision event.

landing on a surface of a microelectrode (blocking collisions). TFA is defined as the time from the beginning of the experiment (the moment when the recording of the chronoamperometric curve is started) until the moment when the first collision event is observed. This approach to TFA determination is particularly suitable for cases when analyte is moving in solution predominantly by electrophoretic migration and, therefore, there is no appreciable contribution of diffusion to the analyte movement (particularly for big polymer spheres). In some cases (see Time of First Arrival by Diffusion section) TFA values determined this way included a positive error since a finite period of time passed between the moment of inserting of a UME into analyzed solution and the beginning of recording of a chronoamperogram. However, this error was not big and did not exceed a couple of seconds.

The use of TFA as an indicator of the analyte (microspheres, nanoparticles, macromolecules, etc.) concentration rests on an assumption that during this time the species travels on average the distance comparable (but not equal) to the interspecies separation (a) in solution. Equation 2 allows estimation of the interspecies separation distance; the derivation of this equation is shown in the Supporting Information:

$$a = (CN_A)^{-1/3} \tag{2}$$

where C is the species concentration and N_A is the Avogadro constant.

In Table 1 one can find typical values of the interspecies separation for very dilute solutions; these data indicate that the

Table 1. Interspecies Separation Distance, a, for Various Analyte Concentrations

C, fM (10^{-15} M)	a, μm
14.5	48.6
1.45	104.6
0.145	225.4
0.0145	485.6
0.00145 (1.45 aM)	1046.2

separation can reach values on the order of millimeters and higher and it usually exceeds the typical dimensions of microelectrodes.

Time of First Arrival by Migration. By knowing the interspecies separation distance, one can estimate TFA of the species to the electrode. A rather simple analytical expression, eq 3, can be proposed for that, which accounts for the transport of the species by migration only (thus, t_{1m}):

$$t_{1m} = \frac{4}{3}\frac{\kappa}{\mu I}(0.62a)^3 \tag{3}$$

where κ is the electrical conductivity of the solution, μ is the mobility of the analyte species, I is the faradaic current flowing through the cell, and a is given by eq 2. The product $0.62a$ represents the average distance traveled by the analyte species during the period of time equal to TFA. The derivation of eq 3 is given in the Supporting Information.

The assumption made in the derivation of eq 3 is reasonable for those experimental conditions when the rate of transport of analytes by migration is much higher than by diffusion.[5,6] One can evaluate such conditions by comparing the mass transfer rates using eq 4:

$$\frac{\nu_m}{\nu_d} = \frac{\mu E}{4D/\pi r_0} \tag{4}$$

where E is the strength of the electric field near the surface of the detector electrode having radius r_0 and D is the diffusion coefficient of the analyte species. Under the conditions observed in our typical experiments the rate of transfer of the species by migration ($\mu \sim 5 \times 10^{-8}$ m^2 V^{-1} s^{-1}, $E \sim 10^3$ V/m, $D \sim 4.4 \times 10^{-12}$ m^2/s (100 nm particle)), ν_m, is at least an order of magnitude higher than by diffusion, ν_d, for charged species 100 nm in diameter (and larger) suspended in solutions with low supporting electrolyte concentration.

Why $0.62a$ is the average travel distance of an analyte particle to the detector electrode can be understood considering the following. Adjacent to the electrode one can select an element of solution (such as a hemisphere) which would always contain one analyte species at all times (Scheme 1a). The volume of the hemisphere depends on the concentration of the analyte in

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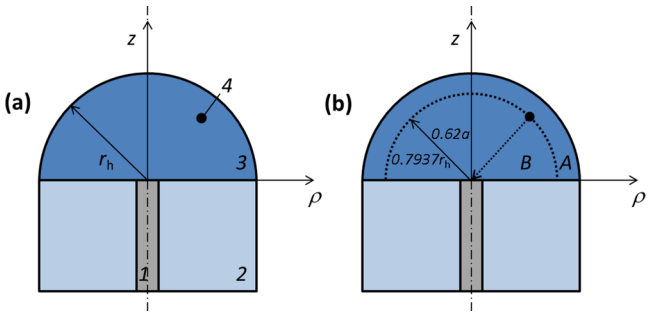
Scheme 1. (a) 1, electrode; 2, insulator (glass); 3, solution (hemisphere); 4, analyte particle and (b) solution elements A and B have the same volume. Average travel distance of the particle is indicated by the dashed arrow



solution, while the analyte particle can be present with equal probability anywhere within the hemisphere. Once the potential is applied to the electrode and the particle starts traveling to it by migration, the distance it traverses depends on its initial (random) position within the hemisphere of solution. Yet, we can define the average travel distance of the particle if we divide the hemisphere into two elements, A and B, having the same volume (Scheme 1b). Then the probability of finding the particle in either of these elements at time zero is the same, and on average the particle would travel during the experiment the distance equal to the radius of the hemisphere element B. From geometry considerations, one can easily show that the average travel distance is $\sim 0.7937 r_h$ (where r_h is the radius of the original hemisphere of solution, Scheme 1a), which amounts to approximately $0.62a$ (Table 1). It should also be noted that in these considerations we neglect the size of the particle and assume that it travels to the center of the electrode disk. Such assumptions are reasonable when the average travel distance is substantially larger than the dimensions of the electrode or the analyte. By combining eqs 2 and 3 one finds a fundamental relation between TFA by migration and the analyte concentration:

$$C = \frac{4}{3}\frac{(0.62)^3 \kappa}{\mu I N_A} t_{1m}^{-1} \quad (5)$$

Thus, by measuring TFA one can estimate the concentration of the species in solution using the above equation.

In Figure 3 one can see the comparison between the experimental and theoretical results for TFA as a function of the analyte (insulating polystyrene particles) concentration. Black error bars in this plot correspond to the standard deviation of TFA values determined from at least 10 experimental measurements. Red bars correspond to the deviation of the arrival times obtained from simulations (the details are provided in the Supporting Information). In simulations, the initial position of a particle near the electrode (position at zero time) varied as a function of the concentration of particles as well as due to the fact that this position is random. Therefore, for each value of the particle concentration one obtains a distribution of arrival times (thus, the red bars). Finally, open squares in Figure 3 correspond to the analytical solutions obtained from eq 5 using the following data: $\kappa = 1.50 \times 10^{-2}$ Ohm^{-1} m^{-1}, $\mu = 6.20 \times 10^{-8}$ m^2 V^{-1} s^{-1}, $I = 1.38 \times 10^{-9}$ A. Very good agreement between the two sets of data and the analytical expression values suggests that TFA can indeed serve as an estimate of the analyte concentration.

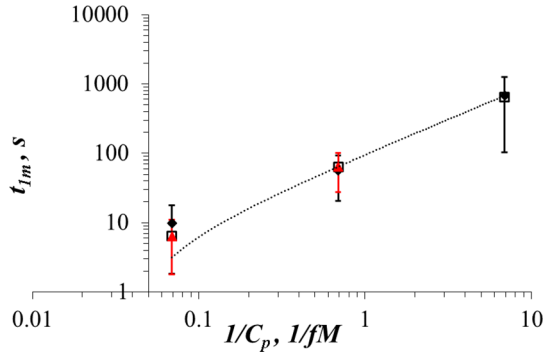


Figure 3. Time of first arrival by migration as a function of inverse particle concentration. Blocking collisions were recorded at a 5 μm Pt electrode in 2 mM FcMeOH, 1 mM KCl solution. Electrode potential was held at a value corresponding to steady-state oxidation of FcMeOH. Particle diameter 1 μm, concentration 0.145, 1.45, and 14.5 fM. Black diamonds (◆) represent experimental data with black error bars corresponding to standard deviation obtained from at least 10 measurements. Red triangles (▲) with red error bars correspond to the results of simulations. The red bar and triangle are missing for the third data point (0.145 fM) because the simulations for those conditions were going to take too long time to complete. Analytical solutions (eq 5 in the text) are given by open squares (□).

Time of First Arrival by Diffusion. When diffusion becomes the main mode of mass transport of the analyte species (i.e., when the species is not charged or the concentration of the supporting electrolyte is sufficiently high so that electrophoretic migration is negligible), one cannot use a simple eq 5 to relate the concentration of analyte to its TFA. It does not seem feasible to propose an analytical relationship similar to eq 5 for that purpose, because diffusion is a stochastic process. In the case of migration the distribution of first arrival times in Figure 3 is solely due to a random initial position of the analyte near the electrode, and eq 5 simply circumvents this problem by introducing the averaged position within the hemisphere solution element. Thus, even if the same averaged position approach is applied, one is to expect a distribution of first arrival times due to the stochasticity of diffusion. In addition, in the concentration range (~picomolar) that is amenable to the detection of individual collision events of analytes transferred by diffusion, the interspecies separation a is comparable to or even smaller than the typical dimension of the detector electrode (10 μm). This poses an additional complication to the problem of defining the travel distance of the analyte particle, since it can land anywhere on the electrode surface with the same probability, and thus even the concept of the average travel distance becomes troublesome in the case of diffusing analytes. Because of all these complications, we resorted to numerical simulations to get further insight into the idea of TFA of diffusing analyte particles.

To investigate the distribution of TFA as a function of analyte concentration, a set of numerical simulations were performed using Multiphysics software. The complete details of these simulations are provided in the Supporting Information; the results are shown in Figure 4.

These results indicate that for a given analyte concentration, the distribution of TFA values is quite large. This can be attributed both to the random position of the analyte species near the electrode surface and the random motion by diffusion. The peak values in the distributions of TFA scale linearly with

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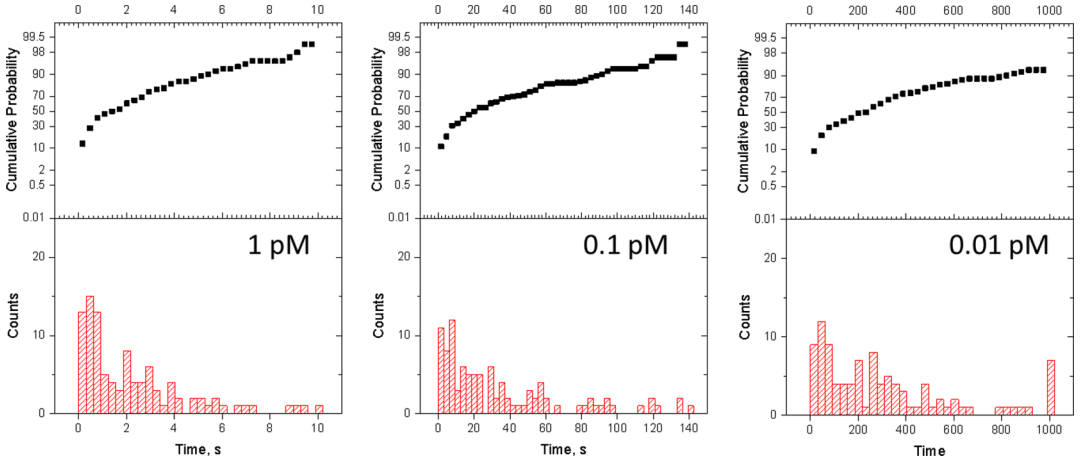

Figure 4. Distributions of TFA values by diffusion for three different analyte concentrations (1, 0.1, and 0.01 pM) obtained from COMSOL simulations. Analyte, 20 nm Pt NPs; $D = 2.15 \times 10^{-11}$ m^2/s. Electrode radius, 5 μm.

concentration thus suggesting a linear relationship between the peak value of TFA and the analyte concentration.

The data presented in Figure 4 were supported by the results of the calculations of the mean time to capture a particle released at random in a solution volume near the electrode surface. The exact details of these simulations are given in the Supporting Information. The determination of the capture time, W, is based on solving the following Poisson's equation, eq 6, subject to the Dirichlet boundary condition, eq 7:[17]

$$\nabla^2 W = -\frac{1}{D} \tag{6}$$

where D is the diffusion coefficient of the particle.

The Dirichlet boundary condition is applied to the electrode surface and defined as

$$W(\text{electrode}) = 0 \tag{7}$$

Then the mean capture time is determined numerically from the integral given below:

$$\frac{1}{V}\int\int_V\int W \, dV \tag{8}$$

The values of the mean capture time determined this way for the three concentrations, 1, 0.1, and 0.01 pM, under the conditions of Figure 4, were 1.46, 13.14, and 92.80 s, respectively. These results are in acceptable agreement with the mean TFA values (Figure 4) of 2.27, 35.09, and 307.67 s. The discrepancy between the two sets of data may be attributed to the limited number of the simulations run to obtain the data in Figure 4 (100).

We tried to investigate the validity of the discussed above simulations experimentally. In Figure 5 one can see a graphical representation of the observed relationships between the time of first arrival and the concentration of Pt NPs to the power (−1). The details of these experiments are given in the Experimental Section. The experimental data presented in Figure 5 show that the relationship between the TFA and the concentration of the species seems to be linear; however, a large scatter of the experimental data points is present and, hence, wide standard deviation bars.

Finally, the simulation results shown in Figure 4 were further normalized by multiplying the corresponding values of TFA by the factor f_N given below:

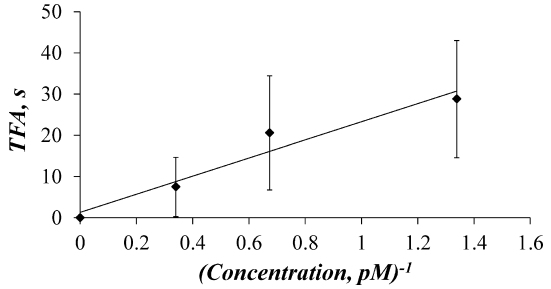

Figure 5. Relationship between the time of first arrival by diffusion and the concentration of Pt NPs in the power (−1). Experimental data were obtained from collision experiments of ∼20 nm Pt NPs with the surface of a 10 μm Au electrode in 15 mM hydrazine and 5 mM phosphate buffer solution at pH 7 (the moment of collision was determined by the change in the OCP value).

$$f_N = \frac{1}{\sqrt{2\pi}} D(CN_A)^{2/3} \frac{r_{el}}{(CN_A)^{-1/3}} = \frac{1}{\sqrt{2\pi}} DCN_A r_{el} \tag{9}$$

where $1/(2\pi)^{1/2}$ is the normalizing constant, r_{el} is the radius of the electrode, and other symbols have the same meaning as defined in previous equations.

The resultant distributions are shown in Figure 6. These distributions look very similar and, since their area is equal to one, they can be regarded as the probability density functions $p(t_{norm})$ for the normalized TFA values, t_{norm}. The exact analytical expression that best describes $p(t_{norm})$ is not known to us. However, the log-normal distribution curve seems to fit these distributions quite well, as shown in Figure 7. It should be noted that the analysis of the data in Figures 4 and 6 indicates that ∼60% of all collision events is observed for $0.02 \leq t_{norm} \leq 0.2$. In this t_{norm}-range the individual distributions of absolute values of TFA do not overlap, i.e., from a single experimental measurement of TFA one can estimate the order of concentration of the analyte in solution with the probability of 60%.

CONCLUSIONS

The findings presented in this paper confirm our hypothesis that TFA can serve as a measure of concentration of a wide group of analytes: those which move in solution exclusively by diffusion or Brownian motion and those which are charged and thus can move, in addition, by migration. The data indicate that

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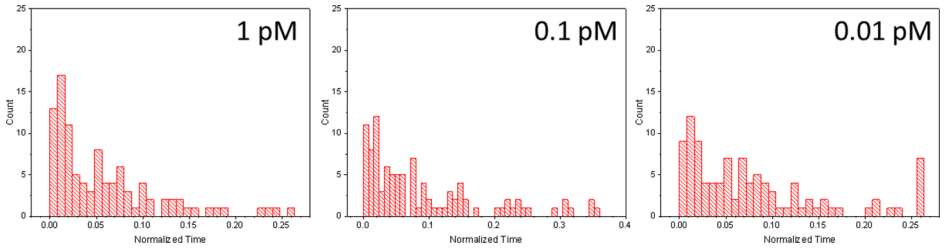

Figure 6. Distributions of normalized TFA values for three different analyte concentrations (1, 0.1, and 0.01 pM). Normalization was done by multiplying the TFA values in Figure 4 by the normalization factor f_N given by eq 9 in the text. All other parameters are the same as in Figure 4.

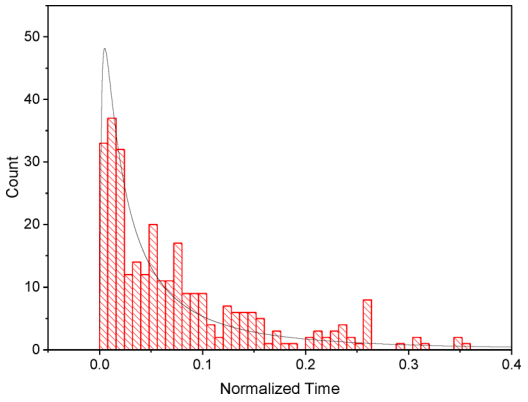

Figure 7. Fit between the log-normal distribution curve (black line) and the normalized TFA values from the three distributions in Figure 6

it should be feasible to detect analytes at concentrations down to ~0.01 fM, if the analyte is transferred by migration and ~0.01 pM, if the analyte is transferred by diffusion. The upper level of concentrations is ~1 fM and 1 pM, respectively; here it is possible to use the frequency of collisions to determine the concentration of the analyte. The very nature of a stochastic process of mass transfer, whether it is diffusion or migration, or both, takes its toll on the precision of TFA analysis: a value of TFA obtained from an experiment with a single electrode indicates an order of magnitude of the analyte concentration. Yet, the value of concentration obtained this way is still valuable in cases when the knowledge of exact concentration is not important but rather a quick estimate is required. One could envision greater benefits of concentration analysis based on TFA measurements if they are done in parallel, i.e., by using an array of individually addressable electrodes. This way one can achieve high precision and fast analysis, something that is not readily available using current technology of stochastic electrochemistry.

■ ASSOCIATED CONTENT

Supporting Information

Derivation of analytical equations for the time of first arrival and description of performed numerical simulations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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