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# 1 Taylor Dispersion Analysis Using Capacitively Coupled Contactless Conductivity Detector

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10

## 11 ABSTRACT

12 Taylor dispersion analysis (TDA) is a simple and absolute method to determine the  
13 hydrodynamic radius of solutes that respond to UV or fluorescence detections. To broaden the  
14 application range of TDA, it is necessary to develop new detection modes. This study aims to study  
15 capacitively coupled contactless conductivity detector (C<sup>4</sup>D) for the analysis of charged  
16 macromolecules. The detection sensitivities and hydrodynamic radii were compared for a C<sup>4</sup>D detector  
17 and a UV detector on positively or negatively charged polymers responding both to UV and C<sup>4</sup>D (poly-  
18 L-lysine and poly(acrylamide-co-2-acrylamido-1-methyl-propanesulfonate). The influence of the  
19 composition of the background electrolyte on the detection sensitivity has been studied and optimized  
20 for C<sup>4</sup>D detection. The influence of the molar mass and of the polymer chemical charge density on the  
21 C<sup>4</sup>D and UV sensitivities of detection have been investigated based on well-characterized copolymers  
22 samples of different molar masses and charge densities. The advantages and disadvantages compared  
23 to UV detection, as well as the range of applicability of C<sup>4</sup>D detection in TDA were identified. C<sup>4</sup>D  
24 detection can be an alternative method for sizing charged polymers of reasonable molar mass (typically  
25 below 10<sup>5</sup> g mol<sup>-1</sup>) that do not absorb in UV. A decline in the sensitivity of detection in C<sup>4</sup>D was observed  
26 for higher molar masses.

27 **Keywords:** Taylor dispersion analysis, contactless capacitively coupled conductivity detection,  
28 polyelectrolytes, size-based characterization

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## 33 1. Introduction

34 Taylor dispersion analysis (TDA) is an absolute method (no calibration needed) allowing the  
35 determination of the molecular diffusion coefficient ( $D$ ), and of the hydrodynamic radius ( $R_h$ ) of solutes  
36 of virtually any size in the range of 0.1-200 nm [1,2]. It can be applied to synthetic and biopolymers  
37 (such as proteins or polysaccharides) [3, 4], nanoparticles or colloids [5], and nanogels [6]. TDA is  
38 based on the dispersion of an injected band under a laminar Poiseuille flow. Its implementation in  
39 narrow bore capillaries (typically  $\sim 50 \mu\text{m}$  i.d.) presents several advantages, such as a low sample  
40 consumption (a few nL), a short analysis time, a wide range of sizing and straightforward analysis,  
41 without any sample preparation or filtration. Recently, it has been demonstrated that it is possible to  
42 retrieve from TDA data the full-size distribution of polydisperse samples (hydrodynamic radius or  
43 diffusion coefficient distributions) via an adequate data processing of the taylorgrams (called  
44 Constrained Regularized Linear Inversion) [7]. This makes this method particularly attractive, especially  
45 for the characterization of ultra-small nanoscale objects ( $< 10 \text{ nm}$ ), for which alternative sizing methods  
46 (such as dynamic light scattering) are limited by the weak signal. Moreover, TDA affords the  
47 determination of the mass-weighted distribution of the hydrodynamic radius in solution for mass-  
48 sensitive detector (as opposed to square mass-weighted for light scattering), has low sensitivity to dust,  
49 and can be performed under conditions close to those of real-life applications [8]. One limitation of TDA  
50 is the detection mode, which is limited to UV (or fluorescent) detections when performed on commercial  
51 Capillary Electrophoresis (CE) instrumentations. The development of alternative detections modes that  
52 can be used online with microscale capillaries is a key point to extent the field of applications of TDA to  
53 non-UV responding or non-fluorescent solutes. Non-UV absorbing polysaccharides can be detected by  
54 photochemical oxidation [3] but the sensitivity is relatively low with limited linear and dynamic ranges.  
55 Backscattering interferometry detection can also be used as a universal detection mode sensitive to  
56 changes in refractive index [9]. However, this detection mode lacks robustness relative to temperature  
57 changes and required a specific optical bench with adequate optical adjustment.

58 A capacitively coupled contactless conductivity detector ( $C^4D$ ) is a detector measuring the  
59 conductivity of the electrolyte passing through the detector without physical contact between the  
60 electrolyte and the electrodes. This avoids electrode passivation. Various terminologies have been used  
61 to describe  $C^4D$  principle, e.g., impedance sensor [10-13], oscillometric detector [14-17], and  
62 admittance detector [18-20].  $C^4D$  detection is relatively popular in CE [21,22], especially for the  
63 detection of small ions or underivatized amino acids including for clinical studies [23, 24]. Its application  
64 to the detection of charged polymers [25] or nanoparticles has been much less investigated in CE. To  
65 our knowledge, at that date, no article using  $C^4D$  as a detector in TDA (all solutes considered) was  
66 published. The use of conductivity detectors in liquid chromatography is generally assumed to be  
67 restricted to charged ions or to charged polymers in a conductive eluent (typically water-based  
68 electrolyte) [26]. However, Oudhoff *et al.* demonstrated that  $C^4D$  could also be used for the detection of  
69 neutral polymers in non-aqueous capillary size-exclusion electrochromatography [27] and mentioned  
70 that this detection mode appeared as an interesting alternative for non-UV absorbing macromolecules  
71 in microcapillary format (for which other detection modes such as refractive index, are not available).  
72 Even if the origin of the  $C^4D$  response in the case of neutral polymers was not clearly understood and

73 was not related to the change in viscosity associated to the polymer sample zone [27], C<sup>4</sup>D appears as  
74 a powerful versatile and universal detection mode for TDA applications in narrow bore capillaries.

75 In this work, for the first time, we aimed to investigate the use of C<sup>4</sup>D for the size-  
76 characterization of charged polymers by TDA. For that, we first investigated the use of C<sup>4</sup>D on UV-  
77 absorbing anionic and cationic polyelectrolytes to better understand how the C<sup>4</sup>D detector response  
78 changes with the solute characteristics (molar mass and chemical charge density). To better compare  
79 the two detection modes, simultaneous detection modes were performed in the same TDA run using a  
80 series of well-defined copolymer samples of various charges and various molar masses. Finally, C<sup>4</sup>D-  
81 TDA was successfully applied to a non-UV absorbing polyelectrolyte.

## 82 **2. Material and methods**

### 83 **2.1 Chemicals**

84 The chemical structures of polyelectrolytes and their characteristics (average molar mass,  
85 nominal charge density and polydispersity index) were listed in Fig. SI-1 and Table SI-1. Poly (L-lysines)  
86 (PLL) under their chloride form at different degree of polymerization (DP): PLL20, PLL50, PLL100,  
87 PLL250 and PLL400, were provided from Alamanda Polymers (Huntsville, AL). Poly(acrylamide-co-2-  
88 acrylamido-1-methyl-propanesulfonate) (SPAM) and poly(acrylic acid-co-acrylamide) (APAM) of  
89 different molar masses were kindly provided by SNF SA (Andrézieux, France). Poly(acrylic acid) (PAA)  
90  $M_n = 3.7 \times 10^4 \text{ g mol}^{-1}$  was from Polymer sources (Canada). Polydiallyldimethylammonium chloride  
91 (PDADMAC) 20%,  $M = 4\text{--}5 \times 10^5 \text{ g mol}^{-1}$  was purchased from Sigma-Aldrich (Saint Quentin Fallavier,  
92 France).

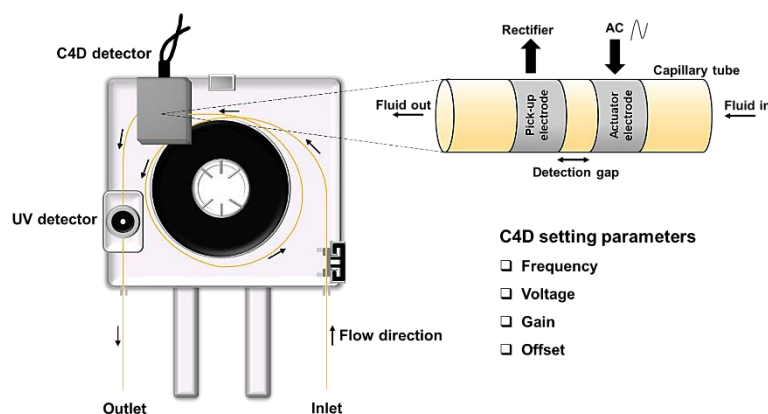
93  $\beta$ -alanine, histidine, 4-morpholinepropanesulfonic acid (MOPS),  
94 tris(hydroxymethyl)aminomethane (Tris), and sodium tetraborate decahydrate were from Sigma-Aldrich  
95 (Saint Quentin Fallavier, France). Sodium hydroxide and acetic acid were from BDH chemicals (VMR,  
96 Paris, France). Hydrochloric acid and formic acid were from Fluka (Illkirch, France) and 2,2-  
97 Bis(hydroxymethyl)-2,2',2''-nitrilotriethanol (Bis-tris) was purchased from Acros Organics (Geel,  
98 Belgium). All the electrolytes and buffer solutions were prepared using ultrapure water purified with a  
99 Milli-Q system from Millipore (Molsheim, France).

### 100 **2.2 Taylor Dispersion Analysis**

#### 101 **2.2.1 Experimental protocol**

102 All TDA experiments were performed on a 7100 CE Agilent system (Waldbronn, Germany).  
103 This system was coupled with a C<sup>4</sup>D detector from Tracedec<sup>®</sup> (Strasshof an der Nordbahn, Austria) and  
104 a built-in UV detector. Bare fused-silica capillary (Polymicro technologies, USA) of 50  $\mu\text{m}$  i.d. and 360  
105  $\mu\text{m}$  o.d. with a total length of 60 cm was used and inserted in the C<sup>4</sup>D head which is placed in the  
106 cassette as shown in Fig 1. The position of the C<sup>4</sup>D head and UV detection window are 46.4 and 51.5  
107 cm from the inlet side, respectively, which allowed for simultaneous detection from both detectors. C<sup>4</sup>D  
108 detection was performed without removing the polyimide coating, but UV detection necessitates the  
109 removal of the polyimide layer in order to achieve UV transparency.

110 The principle of C<sup>4</sup>D detection is shown on the right-hand side of the diagram in Fig. 1 and has  
 111 been fully described elsewhere [28-32]. Briefly, the C<sup>4</sup>D detector is made of two electrodes, which are  
 112 placed cylindrically around the capillary tube with a small gap between the electrodes and are  
 113 connected to an AC oscillator. The measured signal is proportional to the change in conductivity when  
 114 an analyte zone with a different conductivity from that of the BGE passes the detection gap. For  
 115 Tracedec® C<sup>4</sup>D instrumentation, different parameter settings (frequency, voltage, gain and offset) affect  
 116 the output signal and were optimized to get the best signal to noise ratio. In this work, the voltage was  
 117 set at the maximum value (0 dB). The gain was set at the maximum value without saturation of the  
 118 signal (50% or 75% depending on the conductivity of the buffer).



119  
 120 **Fig. 1.** Schematic diagram of capillary setup for Taylor dispersion analysis with C<sup>4</sup>D and UV detector  
 121 and the composition of an axial C<sup>4</sup>D system. The capillary cassette represented in this Figure is used  
 122 with the Agilent 7100 apparatus.

123 In the case of the analysis of polyanions by TDA, new capillaries were conditioned with the  
 124 following flushes: 1 M NaOH for 30 min, water for 15 min and buffer for 15 min. In the case of polycation  
 125 analysis, the inner surface of the capillary was modified by flushing a PDADMAC 0.2% m:m in water to  
 126 avoid the interaction between the polymer sample and the capillary surface. The coating procedure is  
 127 based on a previously published protocol [33] as follows: 1 M NaOH for 30 min; water for 15 min;  
 128 PDADMAC 0.2% m:m in water for 30 min; water for 15 min and buffer for 15 min. Samples were injected  
 129 hydrodynamically on the inlet side of the capillary (20 mbar, 10 s) for online detection by both detectors  
 130 ( $V_i/V_d < 1\%$ ), where  $V_i/V_d$  is the ratio of the injected sample volume to the volume of capillary from inlet  
 131 to the closest detector. TDA was performed using a mobilization pressure of 100 mbar. Between each  
 132 run, the capillary was rinsed by flushing with water for 5 min and then with buffer for 5 min. All  
 133 experiments were carried out at 25 °C.

### 134 2.2.2 Theoretical aspects

135 Briefly, TDA is based on the mobilization of a sample plug in an open capillary tube under a  
 136 laminar Poiseuille flow. The parabolic velocity profile of the Poiseuille flow combined to the molecular  
 137 diffusion which redistributes the solutes along the tube's section, results in the so-called Taylor  
 138 dispersion. For a single size sample mixture, the elution profiles recorded at the detection points are  
 139 Gaussian shape [1, 2]. The band broadening resulting from Taylor dispersion is related to the temporal  
 140 variance of the elution profile,  $\sigma^2$  (in s<sup>2</sup>) which can be quantified by Gaussian fitting in the case of a

141 monodisperse sample, or by peak integration in the case of a polydisperse sample. The average  
142 molecular diffusion coefficient,  $D$  ( $\text{m}^2 \text{s}^{-1}$ ) of the solutes can be calculated using Equation (1) and  
143 transformed into the hydrodynamic radius  $R_h$  (m) using the Stokes Einstein equation (Equation (2)):

$$144 \quad D = \frac{R_c^2 t_0}{24 \sigma^2} \quad (1)$$

$$145 \quad R_h = \frac{k_B T}{6 \pi \eta D} \quad (2)$$

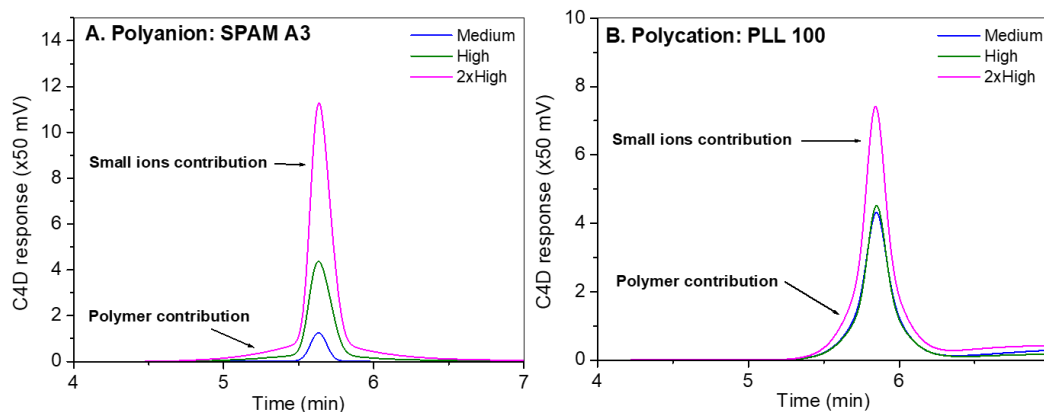
146 where  $R_c$  is the capillary radius (m),  $t_0$  is the average elution time (s),  $k_B$  is the Boltzmann constant ( $\text{Pa}$   
147  $\text{m}^3 \text{K}^{-1}$ ),  $T$  the temperature (K) and  $\eta$  the viscosity of the carrier liquid ( $\text{Pa s}$ ). Equation (1) is valid when  
148 two conditions are fulfilled. First,  $t_0$  should be much higher than the characteristic diffusion time of the  
149 solute in the cross section of the capillary, *i.e.*  $t_0 \geq 1.25 R_c^2 / D$  for a relative error ( $\epsilon$ ) on the determination  
150 of  $D$  lower than 3%. Second, the axial diffusion should be negligible as compared to convection (*i.e.*  
151 when the Péclet number  $Pe = \frac{R_c u}{D}$  is higher than 40 for ( $\epsilon$ ) lower than 3%, where  $u$  is the linear velocity  
152 ( $\text{m s}^{-1}$ ) [34]).

153 In this study, a lab-made Excel spreadsheet was used for data processing of taylorgrams,  
154 including the fitting of the elution profile by a sum of Gaussian peaks using Excel solver and the  
155 determination of the temporal variance of the polymer contribution. The multi-gaussian fitting (up to 3)  
156 allows to subtract the small ion contribution before integration of the polymer contribution to get the  
157 average diffusion coefficient and hydrodynamic radius.

### 158 3. Results and discussions

#### 159 3.1 Effect of applied frequency on the C<sup>4</sup>D signal

160 In this study, we have first optimized the applied frequency of the C<sup>4</sup>D detector on the polymer  
161 response. In C<sup>4</sup>D detection the frequency supplied to the cell has a significant impact on the  
162 performance of the detector [35, 36]. In order to obtain the highest response, the applied frequency was  
163 therefore varied using the available frequencies from the Tracdec® instrument which were noted as  
164 medium, high, and 2x high. The other operating parameters such as the gain and the offset were set  
165 constant and are indicated in the figure caption. In the case of polyanion analysis, SPAM A3 was  
166 selected to study this parameter using 100 mM histidine pH 7.68 as the mobile phase, as shown in Fig.  
167 2A. When the medium frequency was applied, the polymer could not be detected and the signal showed  
168 a taylorgram corresponding to the small ions which are present as impurities in the polymer solution.  
169 These small ions contribution can be reduced by doing dialysis against BGE without affecting the  
170 calculated  $R_h$  of the polymer (see Fig. SI-2). When a higher frequency was applied, the polymer could  
171 be detected as a broad peak even if the small ion contribution also increased in intensity. Similar results  
172 were obtained for polycation analysis (PLL100 in 8 mM Tris-Cl pH 7.4), as shown in Fig. 2B. The  
173 frequency at 2x high gave the highest C<sup>4</sup>D signals and was therefore chosen as the working frequency  
174 for the analysis of both polyanions and polycations.

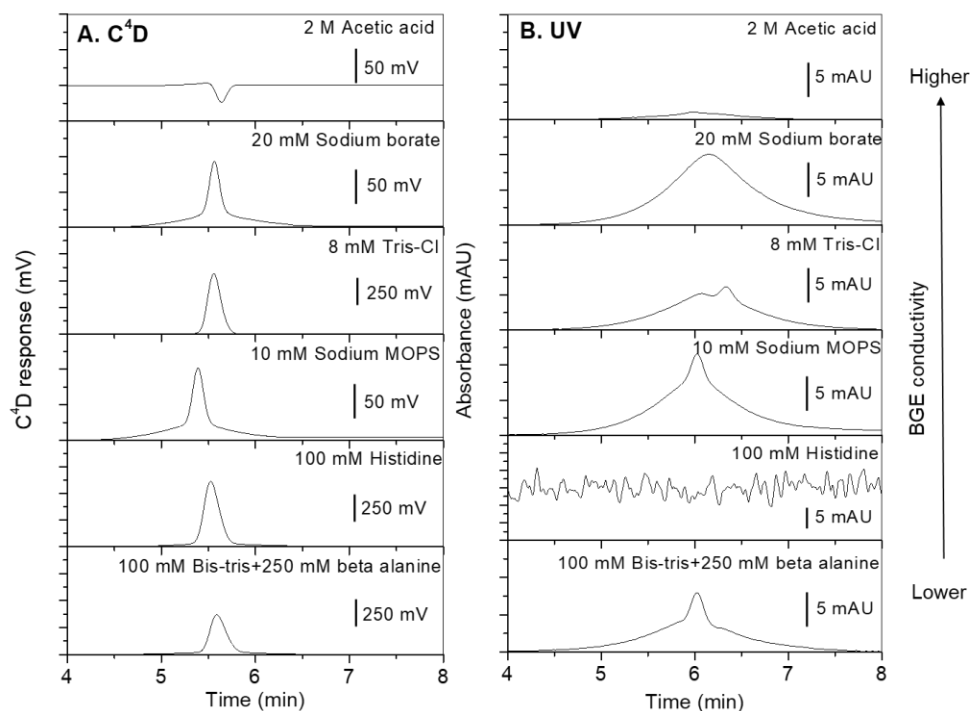


175

176 **Fig. 2.** Taylorgrams with C<sup>4</sup>D detection of polyanion SPAM A3 (A) and polycation,  
 177 PLL 100 (B) at different C<sup>4</sup>D applied frequency. Experimental conditions for polyanion: fused silica  
 178 capillary of 60 cm total length (46.4 cm to C<sup>4</sup>D detector, 51.5 cm to UV detector) x 50 μm i.d. Eluent:  
 179 100 mM histidine (pH 7.68, ionic strength 2.276 mM, conductivity 114 μS cm<sup>-1</sup>). Capillary  
 180 preconditioning: Flush with water for 2 min followed by BGE for 3 min. Sample injection: 20 mbar, 10 s  
 181 (0.6% of the capillary volume to the detector). Polymer samples: all polymers at 5.0 g L<sup>-1</sup> in the eluent.  
 182 Mobilization pressure: 100 mbar. C<sup>4</sup>D parameters: Blue line; frequency: medium, voltage: 0 dB, gain:  
 183 75%, offset: 0, Green line; frequency: high, voltage: 0 dB, gain: 75%, offset: 0, Pink line; frequency: 2x  
 184 high, voltage: 0 dB, gain: 75%, offset: 0. Experimental conditions for polycation: PDADMAC coated  
 185 capillary, 60 cm total length (46.4 cm to C<sup>4</sup>D detector, 51.5 cm to UV detector) x 50 μm i.d. Eluent: 8  
 186 mM Tris-Cl (pH 7.4, ionic strength 6.7 mM, conductivity 661 μS cm<sup>-1</sup>). Capillary preconditioning: flushing  
 187 DI for 2 min followed by BGE for 3 min. Injection: 20 mbar, 10 s (0.6% of the capillary volume to the  
 188 detector). Mobilization pressure: 100 mbar. C<sup>4</sup>D parameters: Blue line; frequency: medium, voltage: 0  
 189 dB, gain: 50%, offset: 20, Green line; frequency: high, voltage: 0 dB, gain: 50%, offset: 20, Pink line;  
 190 frequency: 2xhigh, voltage: 0 dB, gain: 50%, offset: 20.

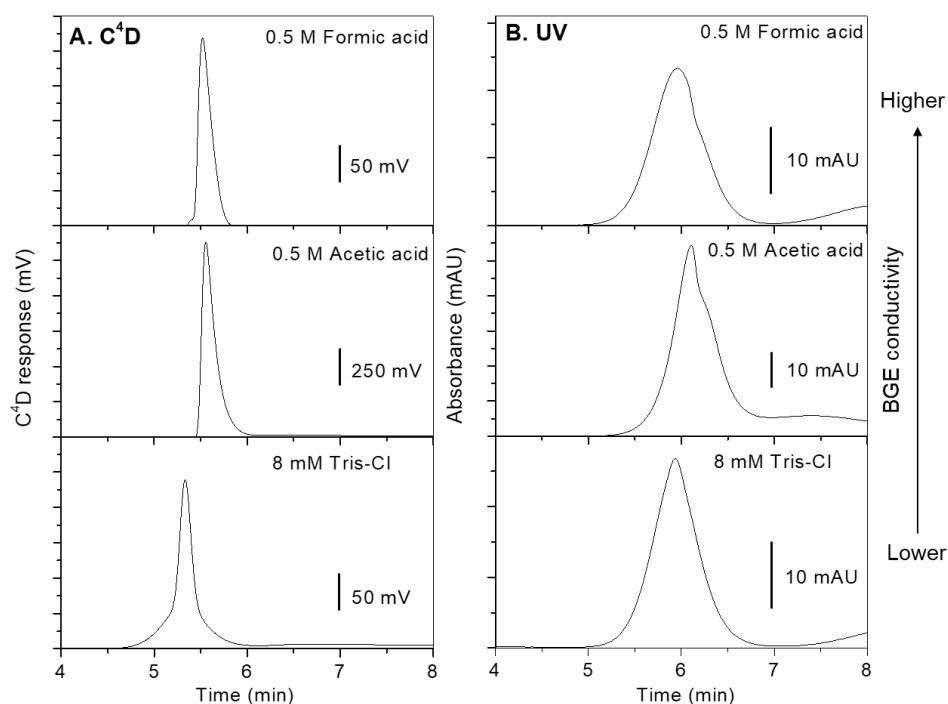
### 191 3.2 Effect of the background electrolyte

192 The background electrolyte (BGE) is also an important parameter which can affect the detector  
 193 response, the noise and the peak profile. It is worth noting that the C<sup>4</sup>D response in TDA is not the  
 194 same as the one obtained in CE due to the absence of electric field in TDA. The C<sup>4</sup>D response is  
 195 expected to be directly related to the change in conductivity between the polymer zone and the BGE  
 196 zone. For an injected polymer solution having the BGE as a matrix, it could be theoretically expected  
 197 that the BGE conductivity is only impacting the background conductivity signal and not the polymer  
 198 response itself. Various BGE compositions (6 BGE for polyanions, and 3 BGE for polycations) were  
 199 tested with all details about their compositions given in Table SI-2. The choice of the BGE has been  
 200 performed based on typical buffer used in C<sup>4</sup>D for CE (e.g. histidine or acetic acid) or the well-known  
 201 low conductive buffers (also called the goods buffers, such as MOPS) or in UV-CE (e.g. sodium borate  
 202 or TRIS-Cl buffers). The signal profiles obtained for SPAM A10 polyanion are displayed in Fig. 3. The  
 203 20 mM sodium borate pH 9.2 and the 10 mM MOPS sodium pH 7.2 buffers provided the highest signal  
 204 for the polymer with a symmetrical peak shape in both C<sup>4</sup>D and UV detectors. Sodium MOPS was  
 205 retained for the rest of the study for polyanion analysis because of the lower LOD compared to sodium  
 206 borate buffer (0.10 g L<sup>-1</sup> versus 0.27 g L<sup>-1</sup> for SPAM A10). We can also notice that the signal contribution  
 207 of the small ions is more important in C<sup>4</sup>D than in UV, relatively to the charged polymer contribution  
 208 (see Fig. 3). As for polycation analysis, the BGE that gave the highest response for PLL (DP 250) with  
 209 a symmetrical peak shape was 8 mM Tris-Cl buffer pH 7.4, as shown in Fig. 4.



210

211 **Fig. 3.** Taylorgrams of SPAM A10 in different BGE with C<sup>4</sup>D (A) and UV (B) detections. Experimental  
 212 conditions: fused silica capillary of 60 cm total length (46.4 cm to C<sup>4</sup>D detector, 51.5 cm to UV detector)  
 213 x 50 μm i.d. Eluent: as indicated in each figure. Mobilization pressure: 100 mbar. Capillary  
 214 preconditioning: Flush with water for 2 min followed by BGE for 3 min. Sample injection: 20 mbar, 10 s  
 215 (0.6% of the capillary volume to the closest detector). Sample: SPAM A10 at 5.0 g L<sup>-1</sup> in the eluent. UV  
 216 detection at 200 nm at 25°C. C<sup>4</sup>D parameters: Acetic acid as BGE, frequency: 2x high, voltage: 0 dB,  
 217 gain: 50%, offset: 100. Sodium borate as BGE, frequency: 2x high, voltage: 0 dB, gain: 50%, offset: 40.  
 218 Tris-Cl as BGE, frequency: 2x high, voltage: 0 dB, gain: 50%, offset: 30. MOPS sodium as BGE,  
 219 frequency: 2x high, voltage: 0 dB, gain: 50%, offset: 25. Histidine as BGE, frequency: 2x high, voltage:  
 220 0 dB, gain: 50%, offset: 5. Bis-tris+β-alanine as BGE, frequency: 2x high, voltage: 0 dB, gain: 50%,  
 221 offset: 5.



222



223 **Fig. 4.** Taylorgrams of PLL250 in different BGE with C<sup>4</sup>D (A) and UV (B) detections. Experimental  
 224 conditions: PDADMAC coated capillary, 60 cm total length (46.4 cm to C<sup>4</sup>D detector, 51.5 cm to UV  
 225 detector) x 50 μm i.d. Eluent: as indicated in each figure. Mobilization pressure: 100 mbar. Capillary  
 226 preconditioning: Flush with water for 2 min followed by BGE for 3 min. Injection: 20 mbar, 10 s (0.6%  
 227 of the capillary volume to the closest detector). Sample: PLL250 at 3.0 g L<sup>-1</sup> in the eluent. UV detection  
 228 at 200 nm at 25°C. C<sup>4</sup>D parameters: Formic acid as BGE, frequency: 2xhigh, voltage: 0 dB, gain: 50%,  
 229 offset: 170. Acetic acid as BGE, frequency: 2xhigh, voltage: 0 dB, gain: 50%, offset: 75. Tris-Cl as BGE,  
 230 frequency: 2xhigh, voltage: 0 dB, gain: 50%, offset: 35.

### 231 3.3 Effect of polyelectrolyte charge density on C<sup>4</sup>D response

232 Fig. 5 displays the variation in the C<sup>4</sup>D and UV responses as a function of the chemical charge  
 233 density  $f$  for the SPAM family at constant injected mass concentration.  $f$  is defined as the molar content  
 234 of sulfonated monomer in the SPAM polymer and was varied from 10% to 100%. It should be noted  
 235 that, as expected, no signal could be detected with the polyacrylamide ( $f=0$ ), due to the lack of  
 236 charge/conductivity of the polymer. All the corresponding Taylorgrams are gathered in Fig. SI-3. Fig. 5A  
 237 clearly shows that the C<sup>4</sup>D response first increases linearly with  $f$  before levelling off. On the contrary,  
 238 in UV detection (Fig. 5B), the signal almost remains constant on the whole  $f$  range. The UV response  
 239 relative to the mass concentration depends on both the absorbance of the amide and the sulfonated  
 240 functional groups. The charged repeating unit should absorb more than the neutral one but since the  
 241 charged repeating unit also weighs more than the neutral one, both effects should compensate, at least  
 242 partially. To better explain the C<sup>4</sup>D response, it is necessary to express the conductivity signal as the  
 243 difference in conductivity between the eluent and the polymer zone. This difference in conductivity  
 244 corresponds to the conductivity of the polymer chain  $\kappa_{\text{polymer chain}}$  including the contribution of the polymer  
 245 counterions  $\kappa_{\text{polymer counterions}}$ :

$$246 \quad \Delta\kappa = \kappa_{\text{polymer zone}} - \kappa_{\text{BGE}} = \kappa_{\text{polymer chain}} + \kappa_{\text{polymer counterions}} \quad (3)$$

247 The conductivity  $\kappa_i$  (in S m<sup>-1</sup>) of a given charged specie  $i$  is related to its electrophoretic mobility  $\mu_i$  (in  
 248 m<sup>2</sup> V<sup>-1</sup> s<sup>-1</sup>), its effective charge  $z_i$ , its molar concentration  $C_i$  (in mol L<sup>-1</sup>) and the Faraday constant  $F$  (in  
 249 C mol<sup>-1</sup>) according to eq. (4):

$$250 \quad \kappa_i = F c_i z_i \mu_i \quad (4)$$

251 The molar concentration in charged monomer  $C_{M,1}$  (sulfonated repeating unit) in the sample zone is  
 252 related to the mass polymer concentration  $C_{m, \text{polymer}}$  according to:

$$253 \quad c_{M,1} = \frac{C_{m, \text{polymer}} f}{fM_1 + (1-f)M_2} \quad (5)$$

254 where  $M_1$  is the molar mass of a charged repeating unit (g mol<sup>-1</sup>), and  $M_2$  is the molar mass of the  
 255 uncharged repeating unit (g mol<sup>-1</sup>). The molar concentration in polymer counter-ion is equal to  $C_{M,1}$   
 256 leading to eq. (6) by combining equations (3) to (4):

$$257 \quad \Delta\kappa = (\mu_{\text{polymer chain}} + \mu_{\text{polymer counterions}}) F c_{M,1} z_1 \quad (6)$$

258 where  $\mu_{polymer\ chain}$  is the effective electrophoretic mobility of the polymer chain,  $\mu_{polymer\ counterions}$  is the  
 259 effective electrophoretic mobility of the counterions. Two regimes should be distinguished: below and  
 260 above the Manning counterion condensation threshold [37]. Below the condensation threshold,  
 261 corresponding to  $f=37\%$  for a vinylic polyelectrolyte, all the charged repeating units bare one nominal  
 262 charge ( $z_i=-1$ ) and are completely dissociated from their counterions. Above the counterion  
 263 condensation threshold, counterion condensation occurs and the effective charge per sulfonate group  
 264  $z_1$  decrease with  $f$  according to:

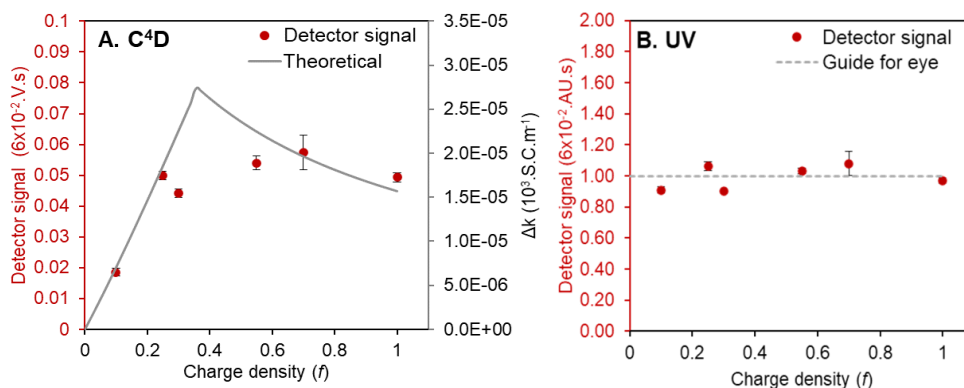
$$265 \quad z_1 = \frac{0.37}{f} \quad (7)$$

266 Therefore, the difference in conductivity is expressed as:

$$267 \quad \Delta\kappa = (\mu_{polymer\ chain} + \mu_{polymer\ counterions}) F c_{M,1} \quad \text{for } f < 0.37 \quad (8)$$

$$268 \quad \Delta\kappa = (\mu_{polymer\ chain} + \mu_{polymer\ counterions}) F c_{M,1} \times \frac{0.37}{f} \quad \text{for } f > 0.37 \quad (9)$$

269 Finally, equations (8) and (9) were plotted in solid line in Fig. 5A taking  $\mu_{polymer\ chain} = 48$  TU and  $\mu_{polymer\ counterions} = 49$  TU and by adjusting the resulting curve to the experimental point using a multiplying factor to take into account the unknown detector constant, where TU stands for Tiselius unit ( $1\text{ TU} = 10^{-9}\text{ m}^2\text{V}^{-1}\text{s}^{-1}$ ). It is worth noting that the effective charged per charged repeating unit can be experimentally determined by capillary isotachopheresis [38, 39] and followed the Manning counterion condensation theory for linear polyelectrolytes.

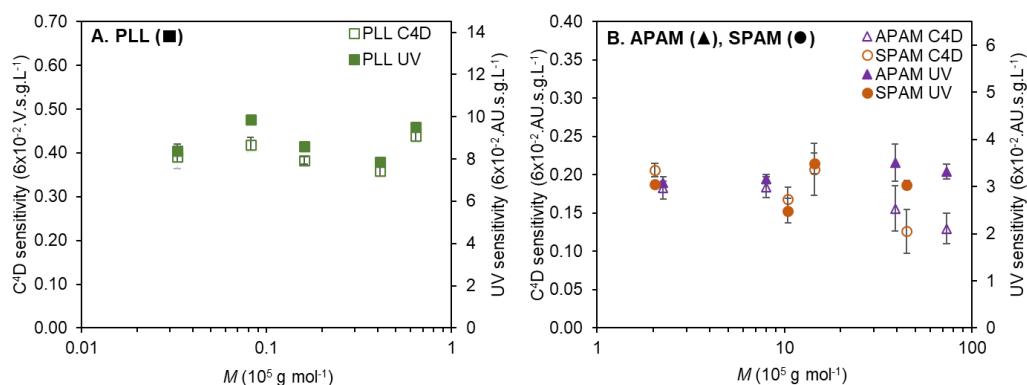


275  
 276 **Fig. 5.** Variation of experimental detection signal (peak area) of the SPAM family according to the  
 277 chemical charge density  $f$  in C<sup>4</sup>D (A) and UV (B). Experimental conditions: fused silica capillary of 60  
 278 cm total length (46.4 cm to C<sup>4</sup>D detector, 51.5 cm to UV detector) x 50  $\mu\text{m}$  i.d. Eluent: 10 mM MOPS  
 279 (pH 7.2, ionic strength 5.0 mM, conductivity 355  $\mu\text{S cm}^{-1}$ ). Mobilization pressure: 100 mbar. Capillary  
 280 preconditioning: flushing DI for 2 min followed by BGE for 3 min. Injection: 20 mbar, 10 s (0.6% of the  
 281 capillary volume to the detector). Sample concentration: 3.0 g L<sup>-1</sup> in the eluent. UV detection at 200 nm  
 282 at 25°C. C<sup>4</sup>D parameters: frequency: 2x high, voltage: 0 dB, gain: 50%, offset: 25, baseline value: 565.  
 283 The plain line in Fig. 5A represents the theoretical C<sup>4</sup>D response at constant polymer mass  
 284 concentration as given by equations (8) and (9) with a floating constant.

285 All the taylorgrams used to build Fig. 5 are presented in Fig. SI-3. They were fitted with multi-  
 286 gaussian functions (up to 3), and subtracted from the small ion contribution before integration on the  
 287 left part of the taylorgram to calculate  $R_h$  and  $D$ . Results are gathered in Table SI-3. The  $R_h$  values from  
 288 C<sup>4</sup>D detection were generally lower than the  $R_h$  values obtained by UV detection. To better understand  
 289 these discrepancies, the influence of the polymer molar mass on the C<sup>4</sup>D detection response were  
 290 further studied.

### 291 3.4 Studying the effect of molar mass on the sensitivity of detection

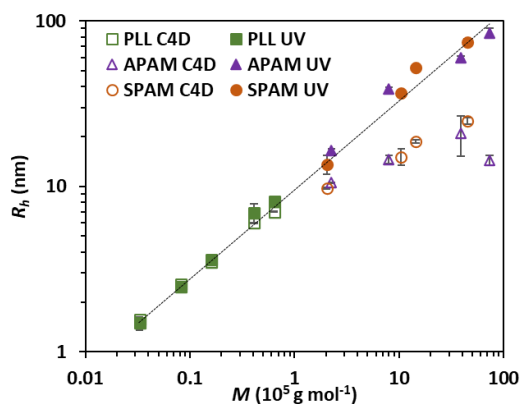
292 Different polyelectrolytes (PLL, APAM and SPAM) with different molar masses were studied to  
 293 compare the sensitivities of detection in UV and C<sup>4</sup>D, as calculated from the slope of the calibration  
 294 curves (i.e. peak area vs concentration). Fig. 6A shows that the sensitivity of detection of the PLL family  
 295 (molar mass  $M$  between  $3.3 \times 10^3$  and  $6.4 \times 10^4$  g mol<sup>-1</sup>) behave very similarly for C<sup>4</sup>D and UV detection  
 296 modes and remains almost constant on the whole range of molar mass. For APAM and SPAM families  
 297 (see Fig. 6B), the sensitivity of C<sup>4</sup>D detection tends to decrease for the highest molar masses, while it  
 298 was relatively constant in UV detection mode on the entire molar mass range. This tendency observed  
 299 only for C<sup>4</sup>D detection can explain why lower average  $R_h$  values were obtained compared to UV,  
 300 especially for the higher molar mass polymer samples. A possible explanation for this difference in  
 301 behaviour between UV and C<sup>4</sup>D detection could be a drop in the effective mobility of the polymer chain  
 302 with increasing molar mass of the polymer. Indeed, it is well-known in CE that the effective  
 303 electrophoretic mobility of synthetic polyelectrolytes decreases with increasing concentration of sieving  
 304 (entangled or unentangled) polymer solution [40]. Different regimes do exist depending on the molar  
 305 mass and polymer concentrations, but even in unentangled polymer solutions, transient entanglement  
 306 or collisions between polymer chains tend to decrease the electrophoretic mobility [41, 42]. The same  
 307 effect is expected to occur inside the polyelectrolyte zone in TDA, even in absence of sieving matrix,  
 308 above a certain molar mass and/or injected concentration. And this effect should be more pronounced  
 309 for higher molar mass polyelectrolytes due to closer entanglements between chains. In UV, since the  
 310 detection mode does not depend on the effective mobility of the polymer, this phenomenon has no  
 311 effect on the sensitivity of detection.



312  
 313 **Fig. 6.** Variation of detection sensitivity of PLL (A) and APAM or SPAM (B) according to the molar mass  
 314 ( $M$ ) in C<sup>4</sup>D and UV detection. Experimental conditions: for PLL; 0.2% wt PDADMAC coated capillary,  
 315 for APAM and SPAM; bare-fused silica capillary, 60 cm total length (46.4 cm to C<sup>4</sup>D detector, 51.5 cm

316 to UV detector) x 50  $\mu\text{m}$  i.d. Eluent: for PLL; 8 mM Tris-Cl buffer (pH 7.40, ionic strength 6.7 mM,  
 317 conductivity 661  $\mu\text{S cm}^{-1}$ ), for APAM and SPAM; 10 mM MOPS (pH 7.2, ionic strength 5.0 mM,  
 318 conductivity 355  $\mu\text{S cm}^{-1}$ ). Mobilization pressure: 30 mbar. Injection: 20 mbar, 10 s (0.6% of the capillary  
 319 volume to the closest detector). Polymer sample: 3.0 g L<sup>-1</sup> in the eluent. Capillary preconditioning:  
 320 flushing with water for 2 min followed by BGE for 3 min. UV detection at 200 nm at 25°C. C<sup>4</sup>D  
 321 parameters: frequency: 2x high, voltage: 0 dB, gain: 50%, offset: 35, 25 and 25 for PLL and APAM,  
 322 SPAM, respectively. Error bars are +/- SD on  $n = 5$  repetitions.

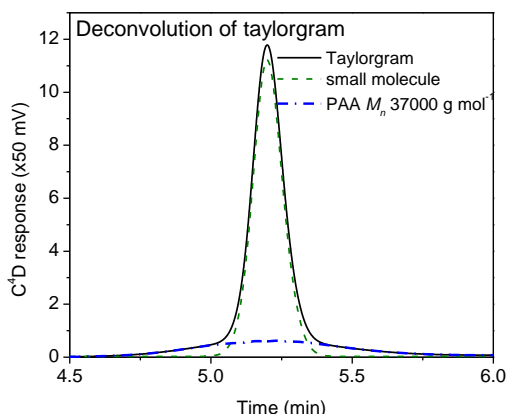
323 The taylorgrams of PLL, APAM and SPAM families at the different molar masses with both  
 324 detectors are shown in Fig. SI-4. The taylorgrams were integrated on their left part after subtraction of  
 325 the small ions contribution to calculate  $R_h$  and  $D$  (results in Table SI-2). It was found, for the PLL family  
 326 (3,300 - 64,000 g mol<sup>-1</sup>), that the UV and C<sup>4</sup>D detectors give similar average  $R_h$  values. For the APAM  
 327 and SPAM family (3 - 9 x 10<sup>5</sup> g mol<sup>-1</sup>), the UV detector systematically gave higher average  $R_h$  values  
 328 compared to the C<sup>4</sup>D detector. Fig. 7 presents a correlation plot between  $\log R_h$  and  $\log M$  for the two  
 329 detection modes and the three families of polyelectrolytes. Using UV detection (plain symbols), we  
 330 obtained a good linear correlation (in log-log scale) on the entire range of molar mass for the three  
 331 polyelectrolyte families, as recently observed, even for ultra-high molar mass APAM (up to 25 x10<sup>6</sup> g  
 332 mol<sup>-1</sup>) [43]. Using C<sup>4</sup>D detection (open symbols), the linear correlation was only obtained for molar  
 333 masses up to around 100,000 g mol<sup>-1</sup>. This difference in behavior between UV and C<sup>4</sup>D can be  
 334 explained by the decrease in detection sensitivity at high molar masses in C<sup>4</sup>D, which tends to introduce  
 335 a bias towards the lowest molar masses.



336  
 337 **Fig. 7.**  $\log R_h - \log M$  plots of both detectors for PLLs, APAMs and SPAMs. Experimental conditions as  
 338 described in Fig. 6.

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350 **3.5 Application of TDA-C<sup>4</sup>D to non-UV absorbing polyelectrolyte**



351  
 352 **Fig. 8.** Taylorgram of PAA  $M_n = 3.7 \times 10^4 \text{ g mol}^{-1}$  and gaussian fit at injected concentrations of  $3.0 \text{ g L}^{-1}$ .  
 353 Experimental conditions: fused silica capillary of 60 cm total length (46.4 cm to C<sup>4</sup>D detector, 51.5 cm  
 354 to UV detector) x 50  $\mu\text{m}$  i.d. Eluent: 10 mM MOPS sodium (pH 7.2, ionic strength 5.0 mM, conductivity  
 355  $355 \mu\text{S cm}^{-1}$ ). Injection: 20 mbar, 10 s (0.6% of the capillary volume to the detector). Mobilization  
 356 pressure: 100 mbar. Capillary preconditioning: flushing with water for 2 min followed by BGE for 3 min.  
 357 UV detection at 200 nm at 25°C. C<sup>4</sup>D parameters: frequency: 2x high, voltage: 0 dB, gain: 50%, offset:  
 358 20, baseline value: 565.

359 As an example of application to non-UV absorbing polymer, poly (acrylic acid) (PAA) was sized  
 360 by TDA-C<sup>4</sup>D. The Taylorgram of PAA  $37000 \text{ g mol}^{-1}$  is shown in Fig. 8 before and after subtraction of  
 361 the small ion contributions. The integration of the polymer contribution leads to  $R_h = 6.66 \pm 0.22 \text{ nm}$   
 362 (calculated on 4 repetitions at 2 injected concentrations,  $3.0$  and  $5.0 \text{ g L}^{-1}$ ). This value is in excellent  
 363 agreement with the  $R_h$  value obtained from the intrinsic viscosity  $[\eta]$  using eq. (10):

364 
$$R_h = \left( \frac{3[\eta]M}{10\pi N_A} \right)^{\frac{1}{3}} \quad (10)$$

365 where  $N_A$  is the Avogadro number and  $M$  is the molar mass of the PAA [33]. Eq. (10) gives  $R_h = 6.88$   
 366 nm for  $[\eta] = 222 \text{ mL g}^{-1}$  determined on the same PAA sample by capillary viscosity measurements in  
 367 the same eluent (see Fig. SI-5).

368 **4. Conclusion**

369 In this work, for the first time, TDA has been investigated using a C<sup>4</sup>D detector. The applied  
 370 frequency and BGE composition have been studied and optimized. 2x High frequency with 10 mM  
 371 sodium MOPS pH 7.2 for polyanions, and 8 mM Tris-Cl pH 7.4 for polycation were selected. The effect  
 372 of polymer chemical charge density on the C<sup>4</sup>D response was then studied. It was found that the  
 373 sensitivity of detection in C<sup>4</sup>D increases linearly with the chemical charge density up to about 37%, and  
 374 then levels off due to the onset of Manning counterion condensation. The average  $R_h$  values provided  
 375 by the UV and C<sup>4</sup>D detectors were comparable for low to moderate molar masses polyelectrolytes ( $M$   
 376  $< 10^5 \text{ g mol}^{-1}$ ). However, for higher molar masses ( $M > 10^5 \text{ g mol}^{-1}$ ), the C<sup>4</sup>D detector provided lower  
 377 average  $R_h$  values compared to UV, probably due to a drop in the electrophoretic mobility of the

378 polyelectrolyte with increasing molar masses. Therefore, C<sup>4</sup>D detection can be an alternative method  
379 for sizing low to moderate molar mass charged polymers that do not absorb in UV.

#### 380 **Credit authorship contribution statement**

381 **Chutintorn Somnin:** Investigation, Writing – original draft. **Joseph Chamieh:** Conceptualization,  
382 Supervision, Writing – review & editing. **Phoonthawee Saetear:** Conceptualization, Supervision,  
383 Writing – review & editing. **Hervé Cottet:** Conceptualization, Supervision, Writing – review & editing.

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390 copolymer samples.  
391

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# Graphical Abstract

## Taylor Dispersion Analysis Using Capacitively Coupled Contactless Conductivity Detector

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