**A unique turn-off fluorescent strategy for sensing dopamine based on
formed polydopamine (pDA) using graphene quantum dots (GQDs)
as fluorescent probe**

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Abstract

A rapid, facile fluorescence sensing strategy was developed for dopamine (DA) detection based on polydopamine (pDA) formed on the surface of graphene quantum dots (GQDs). The prepared GQDs were strongly luminescent because of the aromatic planar structure. DA could self-polymerize to pDA and snap to the surface of GQDs to form a thin film in alkaline environment, leading to quenching of fluorescence due to fluorescence resonance energy transfer (FRET). With the optimized conditions, the analytical performance illustrated high sensitivity, selectivity in a wide linear range with a detection limit of 8 nM. In addition, the unique method was successfully applied for DA injection test with satisfactory labeled amount. Finally, the proposed strategy was applied for DA detection in serum, wherein accurate results were obtained.

Keywords: Dopamine detection; graphene quantum dots; fluorescent sensor; polydopamine; serum

1 **1. Introduction**

2 Carbon-based nanomaterial is a big family containing carbon dots
3 (C-Dots), graphene oxide (GO) nanoparticles, and graphene quantum dots
4 (GQDs) [1]. As a new member of carbon-based nanomaterials, GQDs
5 have inherited several merits from traditional carbon-based nanomaterials,
6 such as low toxicity, biocompatibility, and photostability [1-3]. The
7 specific excellent properties of GQD have inspired extensive studies in
8 photovoltaic devices [4], anti-cancer drug carrier [5], and especially in
9 bioanalysis [6] and cell imaging [7]. Compared with other carbon-based
10 nanomaterials, GQD is superior because of its relatively higher quantum
11 yield (QY) [3]. Recently, various studies on GQD have focused on
12 preparation and property development, while investigations on the
13 analytical applications are still very initial [6, 8]. However, fabrication of
14 special GQD that can both detect a target with specificity and indicate a
15 signal response sensitively still limits its wide application.

16 Dopamine (DA) is an important neurotransmitter that mainly exists
17 in the brain and central nervous system of mammals and transmits
18 neurosignals regarding usual movements [9]. DA also plays an important
19 role in the nervous activity, such as learning and memory [10-11]. Thus,
20 DA could act as a biomarker for various central nervous system-related
21 diseases, such as Parkinson's disease, schizophrenia, and anorexia [12],
22 by revealing the levels of health issues [13-14]. Facile and accurate

1 analysis of DA could greatly benefit the field of physiological function
2 and clinical diagnosis of special neurological diseases. In the past few
3 years, various strategies have been developed for DA detection, including
4 electrochemical methods [15-17], enzymatic methods [18],
5 photo-electrochemical sensor [19], and high performance liquid
6 chromatography [20]. However, inherent shortcomings make these
7 methods a bit difficult to satisfy the increasing requirements for simple,
8 reliable, and cost-efficient methods. Recently, fluorescent strategies for
9 detection of DA have been attracting increasing interests because of its
10 low cost, easy control, and maneuverability in biological matrixes [21-24].
11 However, with the need for a sensitive and selective DA sensor,
12 especially in complex systems (e.g. serum), the development of
13 fluorescent strategy for DA is still in its initial stage [21-23].

14 Dopamine, as generally known, tends to self-polymerize to
15 polydopamine (pDA) in alkaline environment [25-26], which is highly
16 controllable by adjusting the pH value. Interestingly, DA can snap to the
17 surface of nearly all kinds of materials to form thin, surface-adherent
18 polydopamine films [25], which have attracted extensive applications on
19 coating materials [27-31], controlled release [32], and immunoassays [33].
20 However, studies on sensitive sensors that utilize the polymerization of
21 dopamine for detection are rarely reported. GQDs prepared from
22 pyrolysis of citric acid are surface-passivated and have good fluorescence

activity [34-35]. The change in the surface of GQDs, such as assembling a thin layer, can induce FRET and quench fluorescence intensity to fabricated signal-off sensor [36]. Although some proposed sensors for dopamine detection are based on fluorescent route [21, 23], the mechanism of DA detection based on the selective polymerization of dopamine on the surface of fluorescent nanomaterials with high sensitivity and anti-interference ability in complex system remains blank.

In this paper, we proposed a unique, selective, and sensitive signal-off fluorescence strategy for DA detection. The GQDs prepared from pyrolyzed citric acid [34-35] were used as fluorescent probes. In the absence of DA, GQDs generate a bright fluorescence with excitation at a given wavelength in an alkaline buffer solution. When DA is added, DA would be adsorbed on the surface of GQDs and becomes pDA through the self-polymerization effect of DA in alkaline condition. The formed pDA could generate a thin layer on the surface of GQDs and result to an efficient fluorescence quenching of GQDs through FRET. Based on the fluorescence quenching, the amount of DA can be effectively monitored easily and inexpensively, as shown in Scheme 1.

2. Experimental section

2.1. Materials and reagents

Citric acid was purchased from Tokyo Chemical Industry Co., Ltd. Dopamine (DA), ascorbic acid (AA), uric acid (UA) were purchased from

1 Sigma. All reagents were of analytical grade and used as received. The
2 water used throughout experiments was purified by Millipore system. The
3 reaction buffer used in this system was Tris-HCl consisting of 10 mM
4 Tris-HCl (pH = 9.5).

5 2.2. Preparation of GQDs

6 GQDs stock solution was prepared from the pyrolyzed citric acid
7 (CA) according to the reported literature [34] with minor modification. In
8 a beaker, 2g CA was heated at 200°C for 30min, and the colorless CA
9 solids turn gradually into orange liquid to gain GQDs. Then, the orange
10 liquid was moved to 100mL 10 mg mL⁻¹ NaOH solution slowly, stirring
11 was needed to make the solution homogeneous. Finally, the pH value of
12 GQDs was adjusted to be 8.0. The obtained GQDs solution was used as
13 stock solution and stored at 4°C when not used.

14 2.3. Assay procedures

15 Various amounts of DA solutions were prepared using Tris-HCl (pH
16 = 9.5); mixed 270 µL DA solutions with 30 µL GQDs together and stirred
17 well; heated the mixture at 60°C for 90 min. Immediately, fluorescence
18 measurements were taken.

19 2.4. Apparatus and measurement.

20 All fluorescence measurements in this study were operated by a
21 Cary Elipse Fluorescence Spectrophotometer (Agilent Technologies,
22 Australia). The sample cell was a 350 µL quartz cuvette. The excitation

1 wavelength and emission wavelength were 390 nm and 465 nm
2 respectively. Both the excitation and emission slits were set at 5 nm.
3 Transmission electron microscopy (TEM) images were collected with a
4 JEOL JEM-1400 Microscope. X-ray photoelectron spectroscopy (XPS)
5 was surveyed using an ESCALAB 250XI electron spectrometer (Thermo,
6 USA). The ultraviolet visible (UV-vis) spectrum was obtained by
7 ultraviolet and visible spectrophotometer (UV-2450, Shimadzu, Japan).
8 The fourier transform infrared spectroscopy (FTIR) spectrum was
9 performed on Nicolet Avatar 360 spectrometer.

10 **3. Results and discussion**

11 **3.1 Feasibility study**

12 First, the optical properties of GQDs were examined by determining
13 the UV-vis absorption and fluorescent spectra, as shown in Figure 1. The
14 prepared GQDs displayed an obvious absorption peak at 365 nm ascribed
15 to π - π^* transition of C=C in the UV-vis spectrum [37]. The fluorescence
16 excitation and emission spectra presented in Fig. 1A show that maximum
17 excitation and emission wavelength are 390 and 465 nm, respectively. As
18 displayed in Fig. 1B, the emission wavelength of GQDs was stable, with
19 the excitation wavelength ranging from 300 nm to 420 nm, illustrating its
20 excitation-independent fluorescent property.

21 The feasibility for the proposed sensors for DA detection was
22 confirmed by the obtained UV-vis spectra and fluorescent images for

1 different concentrations of DA in the solution. Fig. 1C reveals that the
2 absorption value decreased regularly with the increase in DA, suggesting
3 that DA could decrease the absorption value through some special
4 function. Furthermore, the relationship between DA concentration and
5 response signals was tested through the brightness of GQDs at various
6 concentrations of DA under a UV lamp, as shown in the insert of Fig. 1C.
7 The results showed that the blue fluorescence of GQDs was gradually
8 reduced with the increase of DA concentration in the solution. Moreover,
9 the results suggested that the addition of DA can effectively quench the
10 blue fluorescence of GQDs, specifically allowing the accurate detection
11 of DA in real samples.

12 3.2 Detection Mechanism

13 DA can attach onto surfaces of solids, including nanomaterials, to
14 form thin and uniform polydopamine (pDA) films. Thus, in such
15 detection process, addition of DA induces its self-polymerization forming
16 pDA, which is then be spontaneously adsorbed on the surface of GQDs,
17 and eventually form pDA/GQDs. The formed pDA films on GQDs induce
18 FRET and fluorescence quenching (the insert of Fig. 1C), which is like an
19 Hg-melamine system in the GQD solution [36]. The zeta-potential of
20 GQDs decreased from -1.62 mV to -10.82 mV and -18.37 mV when
21 $20\text{ }\mu\text{M}$ and $100\text{ }\mu\text{M}$ DA were added into GQDs solution, respectively. The
22 zeta-potential values suggested that the significant change in the surface

1 states of GQDs may be attributed to the introduction of DA forming pDA
2 with the –OH outward [7]. Furthermore, the topographical changes of the
3 formed pDA/GQDs were differentiated by AFM and TEM, as shown in
4 Figure 2. In the absence of DA, pure GQDs demonstrated an average
5 thickness of about 1.2 nm. Addition of DA caused significant
6 corrugations of GQDs and the blank mica surface, which were attributed
7 to polymerization of DA on GQDs surface and the reaction buffer. The
8 significant topographical change was accompanied by a height increment
9 of about 5 nm. The significant increase in height suggested that
10 polymerization of dopamine but not dopamine adsorption [21] occurred
11 in the proposed strategy. Similarly, the TEM image revealed that the
12 diameters of GQDs ranged from 3 nm to 6 nm. The diameters of GQDs
13 obviously increased upon reacting with DA to form pDA. Moreover, Fig.
14 2D shows that certain number of GQDs snapped to the surface of the
15 formed pDA to be a combinant.

16 FTIR spectroscopic analysis was applied to provide information on
17 the functional groups in the formation of pDA/GQDs, as shown in Fig.
18 2E. The peaks at about 1722, 1592, and 1395 cm^{-1} indicated the existence
19 of carboxyl, C=O, and C-O; whereas, the peak at 1264 cm^{-1} corresponded
20 to the epoxy group C-O [21]. The pDA had characteristic bands at 1630
21 and 1385 cm^{-1} , corresponding to aromatic C=C bonds of indole and
22 C=N-C stretching modes [38], respectively. The formed pDA/GQDs

1 illustrated the overlapping bands of pDA and GQDs at ranges of
2 1730 cm^{-1} to 1570 cm^{-1} and 1420 cm^{-1} to 1370 cm^{-1} , and offered the
3 reduced bands at 1592 , 1395 , and 1264 cm^{-1} of GQDs, which were
4 attributed to the cover effect of pDA. The addition of DA to the detecting
5 system to quench the fluorescence of GQDs through the formation of
6 pDA on the surface of GQDs was further confirmed by XPS, as shown in
7 Fig. 2F. Compared with the XPS survey spectrum of the original GQDs,
8 intense signal of N1s peaks were observed in the spectra of GQDs and
9 DA system with $50\text{ }\mu\text{M}$ and $100\text{ }\mu\text{M}$ DA, respectively. The atomic
10 percentages of N were 2.52% and 3.8% for the addition of $50\text{ }\mu\text{M}$ and
11 $100\text{ }\mu\text{M}$ DA in GQDs, respectively. Given that the samples for XPS
12 analysis were purified by dialyzing for several days to remove all possible
13 ions and small molecular residual contaminants, the observed N1s peaks
14 were attributed to the nitrogen element of pDA. The increased content of
15 N suggested that more pDA formed on the surface of GQDs which
16 eventually induced high quenching efficiency. Thus, the reduced
17 amplitude of fluorescence intensity can be applied to quantify the
18 concentration of DA.

19 3.3 Optimization of sensing conditions

20 A series of optimization experiments were performed to gain the
21 most appropriate conditions for the determination of DA, as shown in Fig.
22 S1.

3.3.1 Optimal amount of GQDs

The GQDs served as fluorescent probe in our experiments. To obtain the best fluorescence intensity, different amounts of GQDs were tested in the optimization experiments. Stock solution of GQDs was diluted in various ratios, and the corresponding fluorescence intensities for each dilution were measured. As shown in Fig. S1A, highest fluorescence values were obtained when GQDs stock solution was diluted to a ratio of 10:1. Thus, ten-fold dilution of GQD stock solution was selected as the optimum solution in the proposed strategy.

3.3.2 Effect of pH

To achieve a highly sensitive determination of DA using GQDs as probe, the pH values of the reacting buffer (Tris-HCl) were studied and optimized. Fig. S1B shows that varying pH values from 6.5 to 12.5 had little effect on the initial fluorescence intensity of GQDs. This result indicated that the blank values of GQDs were unified and stable. The addition of DA led to fluorescence quenching over a wide pH range. However, the quenching efficiencies of DA at these pH values were quite different. The DA had greater quenching effect in alkaline media than in acidic solution. The highest quenching efficiency was detected at pH 9.5, suggesting that this pH value was the most suitable for the proposed strategy. This result can be attributed to an enhanced polymerization of DA to pDA and its adsorption on the surface of GQDs at pH 9.5 in such

1 detecting system. Therefore, pH 9.5 was utilized for fluorescent sensing
2 strategy.

3 3.3.3 Optimal reaction temperature and dynamics study

4 The effect of temperature on the efficiency of the changes in the
5 fluorescence intensities before and after the addition of DA into GQDs
6 solution was studied. As shown in Fig. S1C, the degree of quenching
7 increased with temperature and achieved the maximum at 60 °C. In
8 addition, we studied the dynamics of the reaction at three temperature
9 levels to optimize the reaction time for detection of DA, as shown in Fig.
10 S1D. At a special temperature, the fluorescence intensity was gradually
11 quenched along the reaction time tested. The reaction rates at 50 °C and
12 60 °C were higher than that at 25 °C, while 60 °C was considered the
13 most appropriate. Furthermore, fluorescence intensity was quenched to a
14 highest extent after 100 min of reaction time. Thus, 60 °C and 100 min
15 were selected as the optimal reaction temperature and reaction time for
16 GQDs and DA, respectively.

17 3.4 Sensing performance of DA

18 3.4.1 Selectivity

19 Various common substances in plasma may interfere with the
20 accuracy of quantitative detection of DA. Therefore, the selectivity and
21 specificity of the method must be investigated. Fig. 3A shows that
22 common substances, including AA, UA, Cys, and so on, had nearly no

1 effect on the fluorescence intensity of the samples compared with the
2 blank. Conversely, DA significantly quenched the fluorescence intensity
3 of GQDs at a much lower concentration. In particular, AA and UA, which
4 have similar electrochemical properties to DA, did not affect the
5 selectivity of the proposed sensor. Furthermore, a competitive experiment
6 of the DA detection with the presence of interferences was also operated
7 to discuss the specificity of the method, as shown in Fig. 3B. It shows
8 that the changed values of the fluorescence intensities of DA and the DA
9 with presence of common molecules are similar, illustrating that the
10 existing interference did not interrupt the accurate test of DA.

11 3.4.2 Quantitative assay, reproducibility, and stability

12 Considering the appreciable quenching of fluorescence intensities of
13 GQDs brought by DA addition, the determination of DA through the
14 proposed method was assessed. The fluorescence profile for series of
15 concentrations of DA in the GQD solution with the detection conditions
16 is shown in Fig. 3C. The fluorescence of GQDs at 460 nm was highly
17 sensitive to DA, and was quenched with increasing concentration of DA.
18 The fluorescence intensity decreased when DA was increased from 0 μM
19 to 300 μM . Thus, 300 μM DA could completely quench the fluorescence
20 intensity of GQDs, illustrating that the efficiency of quenching was
21 sensitive to the concentration of DA. A plot of F_0/F versus the
22 concentrations of DA showed a non-linear relationship in the range of

1 0.01 μM to 300 μM . A linear equation ($F_0/F = 0.99526 + 0.03045 \times C_{\text{DA}}$
2 (μM)) was obtained in the DA concentration range of 0 μM to 60 μM
3 ($R=0.9977$), as shown in Fig. 3D. The limit of detection (LOD) for DA
4 was 0.008 μM based on $S/D = 3$. In addition, good precision was
5 indicated (relative standard deviation, RSD) by 2.9%, 5.4%, and 8.5% for
6 five independent detections of 0.5, 1, and 5 μM DA, respectively,
7 suggesting the excellent reliability of the proposed fluorescence sensing
8 strategy. The above results illustrated that the proposed fluorescence
9 sensor based on GQDs enabled highly favorable and accurate recognition
10 of DA in complex samples.

11 Furthermore, the stability of GQDs was investigated under
12 continuous UV irradiation and in the long term of a 6-week period, as
13 shown in Fig. S2. Upon UV irradiation at 365 nm for 150 min, a 6.7%
14 decrease in the fluorescence intensity of GQDs was observed. Moreover,
15 the fluorescence response of GQDs was stable with only a 7.8% decrease
16 at the end of 6-week period when stored in a refrigerator at 4 $^{\circ}\text{C}$. The
17 results indicated the satisfactory long term stability of GQDs.

18 3.5 Real application

19 The proposed strategy was applied to test DA injection in buffer with
20 the standard addition method and calculated the labeled amount to
21 investigate the reliability for practical application. As shown in Table 1,
22 the labeled amounts of the six different DA preparations injected ranged

1 from 92.6% to 106.8%, which satisfied the requirements of Chinese
2 Pharmacopoeia Standards. Thus, these results further suggested that the
3 proposed strategy was appropriate for real detection of DA injection.

4 Considering the complicated composition of clinical sample, the
5 proposed method was used to detect various concentrations of DA in
6 simulated serum samples prepared by adding fetal calf serum to buffer to
7 a 10% final content. As shown in Fig. 4, although the fluorescence
8 intensity of GQDs in 10% fetal calf serum was slightly lower, a similar
9 trend in change as presented in Fig. 3C was observed, wherein
10 fluorescence intensity gradually decreased when DA was increased. This
11 result suggests that the serum constituent nearly have no effect on the
12 proposed fluorescence strategy. Moreover, a calibration curve (Fig. 4B)
13 with a close slope to that of the standard solution was obtained (Fig. 4C).
14 Considering all the results, the proposed strategy could be applied to DA
15 detection in practical blood sample, which could even be expanded to
16 diagnosis and therapy of central nervous system related diseases.

17 **4. Conclusion**

18 In this work, a unique signal-off strategy for DA detection was
19 developed. Fluorescent GQDs were prepared and used as fluorescent
20 probes. The feasibility was studied by analyzing the GQDs own peaks
21 and UV spectrum characterization and proved to be a good one. The
22 quenching mechanism was proposed as FRET, which was characterized

1 through various techniques, including AFM, TEM, zeta-potential, FTIR,
2 XPS, and so on. All characterization results had more or less verified the
3 FRET mechanism in different respects. A good linear relationship
4 between DA concentration and fluorescence intensity was observed, and
5 the LOD was as low as 8 nM, which satisfies the regulatory requirements.
6 The proposed strategy exhibited high selectivity, good reproducibility,
7 and also indicated advantages of facile fabrication, simple operation, and
8 excellent stability. In addition, the proposed strategy was successfully
9 applied for DA testing in DA injection and simulated serum, achieving
10 accurate results. This design principle of signal-off fluorescence by FRET
11 from polymerized pDA for DA detection may be extended to other
12 fluorescent nanomaterials.

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Captions

Scheme 1. Illustration of the preparation of GQDs and the detection of DA.

Figure 1. (A) UV-vis absorption, fluorescence excitation and emission spectra of GQDs. (B) The emission curves of GQDs with the different excitation wavelength. (C) UV-vis absorption spectra (inset: the fluorescence images) of GQDs with different concentrations of DA.

Figure 2. The AFM (A, B) and TEM (C, D) of GQDs (A, C) and GQDs with 10 μ M DA (B, D). (E) The FTIR spectra of the GQDs, pDA and GQDs-pDA. (F) The XPS spectra of the GQDs and GQDs with different concentrations of DA.

Figure 3. (A) The fluorescence intensities of GQDs with a series of 50 μ M interfering substance, DA and blank. (B) The fluorescence intensities of GQDs with DA in the presence of 50 μ M interfering substance, mixture of interferences and blank. (C) The fluorescence response of GQDs to various concentrations of DA. (D) The calibration curve of DA detected with GQDs). Error bars represent standard deviations of measurements (n = 3).

Table 1 Detection results of DA injection based on the proposed method

Figure 4. (A) The fluorescence response and (B) the calibration

1 curve of GQDs to various concentrations of DA in 10% serum. (C) The
 2 comparison of calibration curve of GQDs to various concentrations of
 3 DA in Tris-buffer and 10% serum.

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8 Scheme 1

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Figure 1

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6 Table 1

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C_{added} (μ M)	Labelled amount (mg:2ml)	$F_0/F \pm SD$	$C_{detected}$ (μ M)	Calculated DA content (mg:2ml)	Percent of labeled amount (%)
30	20	1.91 ± 0.047	30.19	20.11	100.6
25		1.70 ± 0.015	23.16	18.52	92.6
15		1.47 ± 0.030	15.57	20.75	103.8
10		1.31 ± 0.014	10.38	20.74	103.7
8		1.23 ± 0.042	7.66	19.13	95.6
5		1.16 ± 0.019	5.34	21.35	106.8

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1 Figure 4

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