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Electrical fluctuations on the surfaces of proteins from hydrodynamic data

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ABSTRACT

We calculate the electrical capacitance on the surfaces of protein molecules from hydrodynamic data of the proteins. Then we estimate the electrical fluctuations (charge, voltage) through the fluctuation–dissipation theorem, which links the electrical capacitance of the system with these fluctuations. From the intrinsic viscosity of the proteins, we estimate the polarizability, which leads to knowledge of the field and dipole fluctuations. From the fitting of the capacitance, polarizability, and electrical fluctuations as a function of the molecular weight of the proteins, we report numerical equations that make it possible to estimate these physical magnitudes for a given protein, knowing the molecular weight. Charge fluctuations are in fractions of unit charge range, voltage fluctuations are in the three-mV-digit range, field fluctuations are in the two-digit mV/nm (10^6 V/m) range, and the dipole moment fluctuations range from two to three digits, times the dipole moment of the water molecule. These surface properties of proteins have not been reported before.

1. Introduction

The topic of importance of local field fluctuations in biological systems has been raised by several authors; for a review on electrical fluctuations in small systems see Ref. [1]. One way to estimate the electrical fluctuations is by knowing the electrical capacitance that emerges as a consequence of the processes or by the proper interfaces in the systems [2]. In the present study we estimate the electrical capacitance of several proteins from hydrodynamic data in order to estimate the electrical fluctuations on their surfaces. We believe these properties of the proteins have not been reported before.

It has long been inferred from a variety of experimental studies that substantial structural fluctuations occur in proteins, and that these fluctuations are essential to protein function (Careri et al. [4], Edsall [3], Weber [5]). Charged groups are extruded from the protein interior toward the higher dielectric solvent, the protein surface is often highly charged, and the dielectric properties of this interfacial region are quite different from those of the protein bulk. Simonson and Perahia [6] studied the polar fluctuations of yeast cytochrome c using nanosecond molecular-dynamic simulations in a spherical droplet of water; they found an important component of dipole moment fluctuations consisting of diffusive, mutually independent motions of the charged side chains at the protein surface.

2. The fluctuation–dissipation theorem

The time scale of the mentioned processes is in the μs–ns range; hence we can make use of the fluctuation–dissipation theorem (FDT) in the classical limit ($kT \gg \hbar\omega$ or $\omega \ll kT\hbar^{-1} = 4 \times 10^{13}$ s^{-1}) [2,7], namely

$$\left\langle (\Delta x)^2 \right\rangle^{1/2} \left\langle (\Delta f)^2 \right\rangle^{1/2} = kT, \tag{1}$$

where $\langle (\Delta x)^2 \rangle^{1/2}$ is the square root of the mean square of the spontaneous fluctuations of a quantity x, as due to the action of some random force f sensed by the environment, whose corresponding square root of the mean square of the fluctuations is $\langle (\Delta f)^2 \rangle^{1/2}$.

In order to simplify the notation we rewrite Eq. (1) as

$$\delta x \, \delta f = kT. \tag{2}$$

This equation shows a constant equilibrium between the system and the environment; when δf increases in the ambient, the system reacts in such a way as to inhibit the fluctuation of the corresponding physical quantity x and vice versa in order to maintain the product constant equal to kT. We also observe that the product $x \times f$ has dimensions of energy.

As an example of Eq. (2) we can consider in a capacitor the relation between the statistical fluctuation of charge, δq, and the corresponding fluctuation of voltage, δV, sensed by the environment,

$$\delta q \, \delta V = kT. \tag{3}$$

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Table 1
Hydrodynamic properties of proteins[a]

Protein (source)	PDB	f_0 (10^{-8} g/s)	f/f_0	f (10^{-8} g/s)	$\bar{v}$ (cm^3/g)	$[\eta]$ (cm^3/g)	Molecular weight	Hydration ($g_{H_2O}/g_{protein}$)
Pancreatic trypsin inhibitor (bovine)	4pti	2.346	1.321	3.099	0.718	3.83 [25]	6,670	0.86
Cytochrome c (equine)	1hrc	2.848	1.116	3.178	0.715	2.50 [26]	11,990	0.24
Ribonuclease A (bovine)	7rsa	2.954	1.290	3.210	0.703	3.30 [27]	13,600	0.73
Lysozyme (hen)	6lys	2.968	1.240	3.680	0.703	3. [20,32]	13,800	0.57
Myoglobin (sperm whale)	1mbo	3.218	1.170	3.765	0.745	3.25 [27]	16,600	0.35
Adenylate kinase (porcine)	1ake	3.474	1.167	4.055	0.740	2.96[b]	21,030	0.41
Bence Jones REI (human)	1b6d	3.558	1.156	4.113	0.726	2.55[b]	23,020	0.35
Chymotrypsinogen (bovine)	2cga	3.582	1.262	4.521	0.721	2.8 [28,29]	23,660	0.71
Trypsin (bovine)	1tpo	3.604	1.187	4.278	0.727	2.93[b]	23,890	0.47
Elastase (porcine)	1est	3.644	1.214	4.424	0.730	3.14[b]	24,600	0.53
Carbonic anhydrase (human)	2cab	3.758	1.053	3.957	0.729	2.76 [30]	27,020	0.12
Subtilisin novo (B. amyloliq.)	1sup	3.790	1.181	4.476	0.731	2.91[b]	27,630	0.47
Superoxide dimutase (bovine)	2sod	4.041	1.132	4.575	0.729	2.64[b]	33,600	0.23
Carboxypeptidase A (bovine)	1cps	4.106	1.063	4.365	0.733	2.50[b]	35,040	0.14
Phosphoglycerate kinase (yeast)	3pgk	4.554	1.377	6.271	0.749	4.73[b]	46,800	1.04
Concanavalin A	1con	4.747	1.299	6.167	0.732	4.11[b]	54,240	0.64
Hemoglobin, oxy (equine)	1hho	5.168	1.263	6.517	0.750	3.60 [32]	67,980	0.74
Malate dehydrogenase (porcine)	1mld	5.287	1.344	7.106	0.742	4.27[b]	73,900	1.00
Alcohol dehydrogenase (porcine)	1axe	5.427	1.208	6.556	0.750	2.23[b]	79,070	0.37
Lactate dehydrogenase (dogfish)	6ldh	6.551	1.273	8.340	0.740	3.80 [31]	141,000	0.77

[a] Measured data from Ref. [23] except $[\eta]$.
[b] Calculated with Eq. (11) using for ν the formalism of Ref. [24], knowing the shape dimensions of the molecules reported in Ref. [23].

3. Relation between capacitance and electrical fluctuations

We can define the capacitance as

$$C = \frac{\delta q}{\delta V} \quad \Rightarrow \quad \delta q = C\,\delta V. \tag{4}$$

From Eqs. (3) and (4) we obtain the following relations:

$$C = \frac{(\delta q)^2}{kT}, \quad \delta V = \left(\frac{kT}{C}\right)^{1/2}, \quad \delta q = \left(kT\,C\right)^{1/2}. \tag{5}$$

These relations have already been used for several authors in various situations see; Refs. [8–12].

4. Relation between friction coefficient and capacitance

Hubbard and Douglas [13] developed a simple and accurate method of estimating the translational hydrodynamic friction on Brownian particles of arbitrary shape. The Brownian friction coefficient f takes the form

$$f = 6\pi\,\eta C, \tag{6}$$

where C is the equivalent to the electrostatic capacitance of the particle in units where the capacitance of a sphere equals its radius and η is the fluid viscosity. They arrived at this result by angular averaging of the Oseen tensor [14–17]. The connection between hydrodynamic and electrostatic properties was also recognized by Zhou [19–21], from the fact that the Oseen tensor, i.e., the Green function for the Navier–Stokes equation, when orientationally averaged, is proportional to the Green function for the Laplace equation. In this way Zhou obtained the same Eq. (6). To calculate the charge and voltage fluctuations, we make use of the hydrodynamic data for proteins reported in Ref. [23]. In Table 1, f_0 was calculated using the equation given also in Ref. [23], namely

$$f_0 = 6\pi\,\eta r_0 = 6\pi\,\eta\left(\frac{3M\bar{v}}{4\pi\,N_A}\right)^{1/3}, \tag{7}$$

where r_0 is the radius of an anhydrous spherical particle having the same mass and partial specific volume, $\bar{v}$, as the protein under consideration, N_A is Avogadro's number, and M is the molecular weight. Knowing f_0, we can calculate f from Table 1, and from Eq. (6), we determine C; see Table 2. With the knowledge of C, using Eq. (5) we determine the voltage, δV, and charge fluctuations, δq.

5. Relation between polarizability and intrinsic viscosity

For determining the polarizability α, we use the equation given by Zhou in Ref. [19], namely,

$$\alpha = \frac{1}{3}\left(4[\eta] - V_h\right). \tag{8}$$

V_h is the hydrated volume of a molecule and is given by

$$V_h = \left(\frac{M}{N_A}\right)\left(\bar{v} + \frac{1}{\rho_h}H\right). \tag{9}$$

ρ_h is the density of hydration water in units of g/cm^3 it has been found to have a somewhat higher density than bulk water, with a value of $\rho_h = 1.104$ g/cm^3 (Bull and Breese [18]). $[\eta]$ is the intrinsic viscosity, which measures the contribution of the molecule to the viscosity of the solution in which it is dissolved [19,20]. V_h also represents the space occupied by a gram of solute at infinite dilution. In volume units the intrinsic viscosity is given by [32],

$$[\eta] = \nu V_h. \tag{10}$$

In units of (volume/g) it is given by

$$[\eta] = \frac{N_A}{M}\nu V_h. \tag{11}$$

In the former equations ν is the Simha factor [22].

6. Relations of polarizability to electric field and dipole moment fluctuations

In Ref. [7] we also gave a relation between the polarizability and electric field and dipole moment fluctuations, namely

$$\delta p = \sqrt{\alpha kT} \tag{12}$$

and

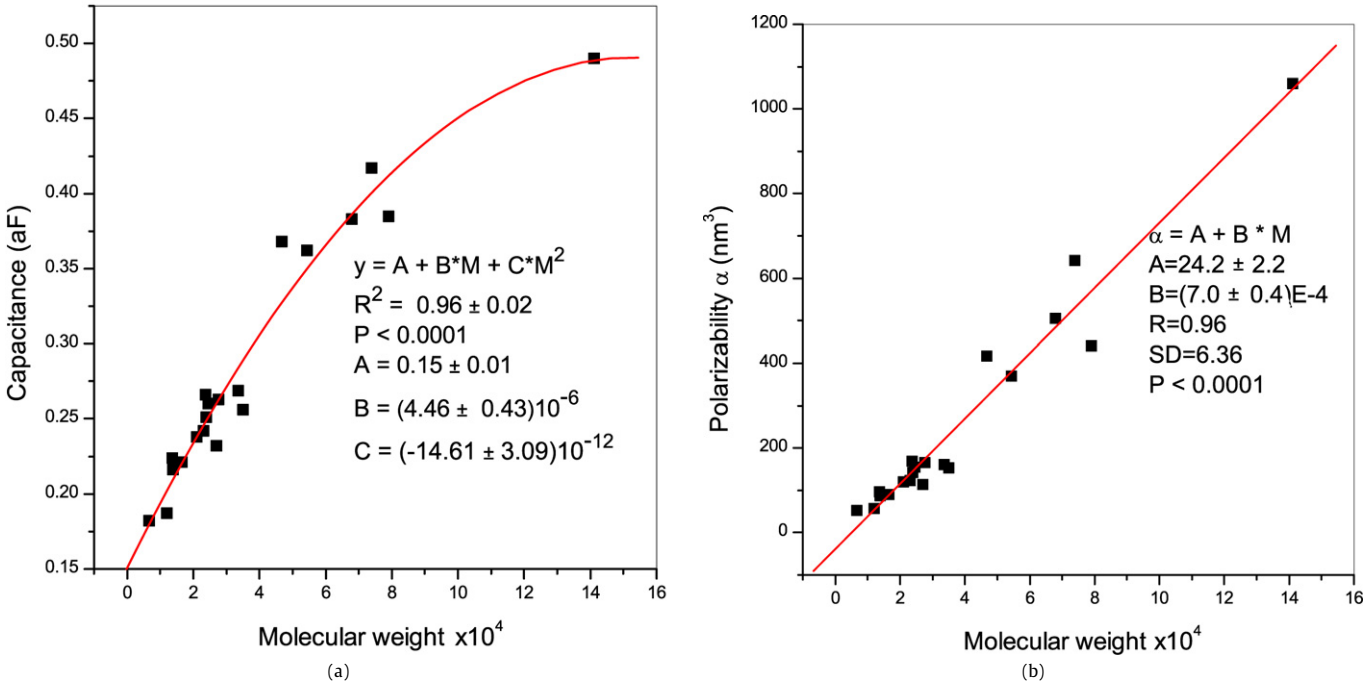
$$\delta E = \sqrt{\frac{kT}{\alpha}}. \tag{13}$$

The values of δp and δE are also reported in Table 2.

Table 2
Electrical properties of proteins

Protein (source)	PDB	C		α (nm^3)	$\delta q/e_0$	δV (mV)	δE (mV/nm)	$\delta p/p_{H_2O}$[c]
		nm[a]	aF[b]					
Pancreatic trypsin inhibitor (bovine)	4pti	1.63	0.182	51.03	0.171	150.3	26.86	24.90
Cytochrome c (equine)	1hrc	1.68	0.187	60.17	0.173	148.4	24.8	27.04
Ribonuclease A (bovine)	7rsa	2.01	0.224	89.10	0.189	135.6	20.37	32.90
Lysozyme (hen)	6lys	1.94	0.216	82.35	0.186	137.9	21.17	31.63
Myoglobin (sperm whale)	1mbo	1.98	0.221	109.69	0.188	136.4	18.32	36.51
Adenylate kinase (porcine)	1ake	2.14	0.238	124.7	0.195	131.4	17.2	38.93
Bence Jones REI (human)	1b6d	2.17	0.242	116.9	0.197	130.5	17.8	37.70
Chymotrypsinogen (bovine)	2cga	2.39	0.266	128.8	0.206	124.5	16.96	39.56
Trypsin (bovine)	1tpo	2.25	0.251	139.6	0.200	127.9	16.2	41.18
Elastase (porcine)	1est	2.34	0.260	148.3	0.204	125.8	15.8	42.45
Carbonic anhydrase (human)	2cab	2.08	0.232	152.6	0.193	133.0	15.53	43.06
Subtilisin novo (B. amyloliq.)	1sup	2.36	0.263	160.5	0.205	125.1	15.2	44.16
Superoxide dimutase (bovine)	2sod	2.44	0.269	178.8	0.207	123.7	14.4	46.62
Carboxypeptidase A (bovine)	1cps	2.30	0.256	177.3	0.203	126.7	14.4	46.41
Phosphoglycerate kinase (yeast)	3pgk	3.31	0.368	446.8	0.243	105.7	9.1	73.68
Concanavalin A	1con	3.25	0.362	454.0	0.241	106.6	9.02	74.27
Hemoglobin, oxy (equine)	1hho	3.44	0.383	488.4	0.248	103.7	8.70	77.03
Malate dehydrogenase (porcine)	1mld	3.75	0.417	630.9	0.259	99.3	7.65	87.55
Alcohol dehydrogenase (porcine)	1axe	3.46	0.385	343.8	0.248	103.4	10.37	64.64
Lactate dehydrogenase (dogfish)	6ldh	4.40	0.490	1074.1	0.280	91.6	5.86	114.2

[a] $1F \equiv 8.985 \times 10^{18}$ nm.
[b] $aF \equiv attoF = 10^{-18}$ F.
[c] $p_{H_2O} = 1.84D = 6.138 \times 10^{-30}$ Cm.



(a) (b)

Fig. 1. Electrical parameters of proteins.

7. Results and conclusions

In Fig. 1a is plotted the capacitance as a function of the molecular weight, M, of the proteins. We can fit the curve by a second-order polynomial. We observe very low values of the capacitance of the proteins, C, in the range [0.18–0.5] aF, with a corresponding increase of the capacitance with the size of the molecule. In Fig. 1b we observe a linear fitting relation between the polarizability, α and M; the polarizability varies in the range [50–1100] nm^3. Corresponding to the low values of the capacitance, C, the fluctuations of charge are negligible; in units of the elementary charge the range is $[0.17–0.28]\delta q/e_0$, which could be interpreted as the probability of producing a unit charge variation in the protein. In Fig. 2a we observe exponential growth with M for these charge fluctuations. In Fig. 2b we observe the voltage fluctuations as a function of the molecular weight; these fluctuations are in the range [90–150] mV, decreasing with the size of the protein molecule. This effect was already predicted for colloidal particles and polyelectrolytes in Refs. [9,10]. We observe a good fitting of data with a first-order exponential decay curve. In Fig. 2c are plotted the field fluctuations δE versus M, showing the first-order exponential decay. These high field fluctuations are in the range [5–30] mV/nm. Finally, in Fig. 2d are plotted the dipole moment fluctuations in units of the water molecule dipole moment versus M; we observe a second-order polynomial fitting in the range $[25–115]\delta p/p_{H_2O}$. These dipole moment fluctuations are

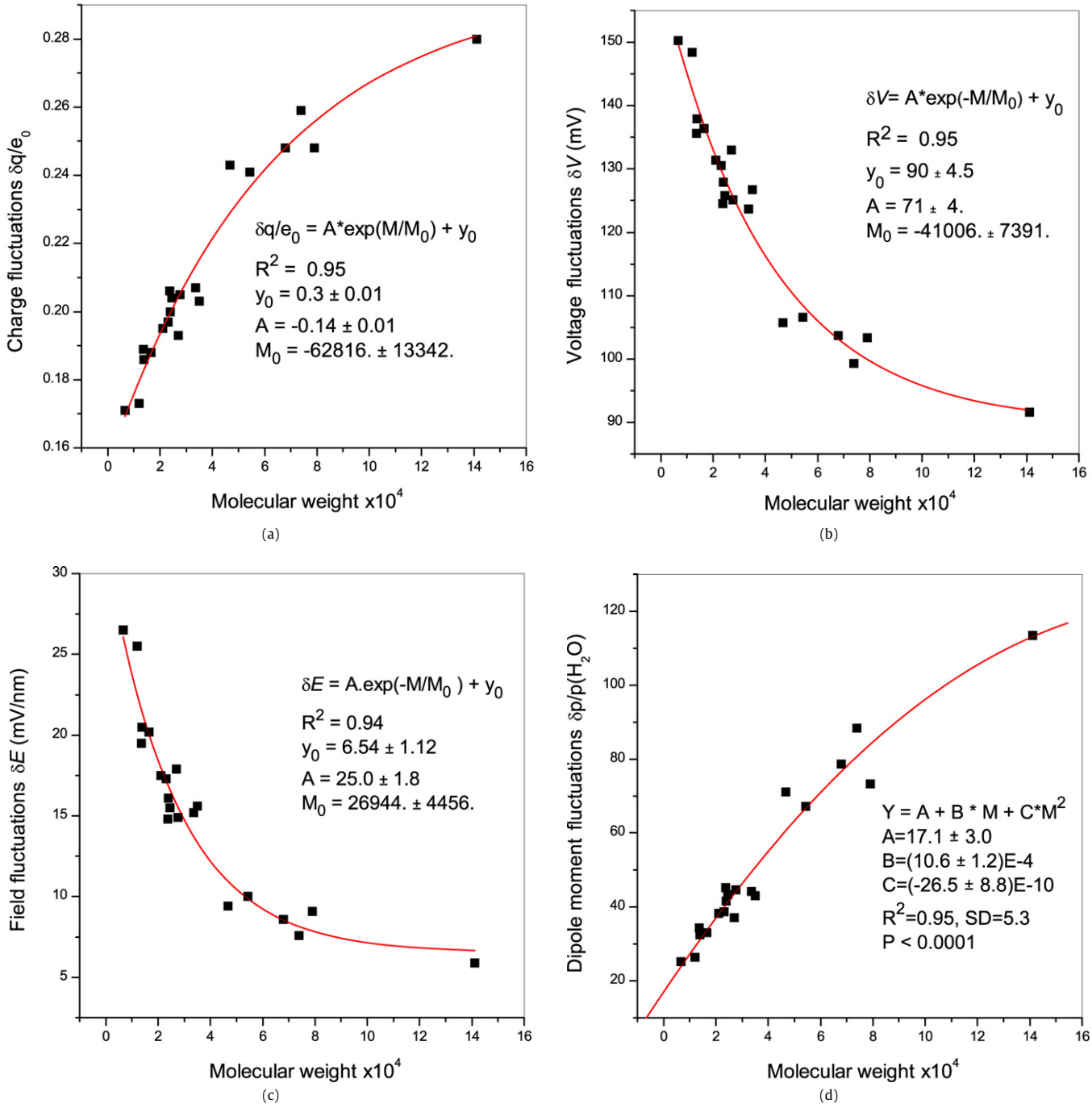


Fig. 2. Electrical fluctuations of proteins.

comparable with the mean dipole moment square root fluctuations estimated by Takashima and Asami for several proteins [33]. Although, with another mechanism than thermal fluctuations, dipole moment fluctuations have already been proved to be the cause of a molecule moving unidirectionally in an electric field of a polar periodic substrate with an average velocity on the same order as that typical of protein motors as kinesin [34]. We believe that the high dipole moment thermal fluctuations of proteins could be used in a similar way. In conclusion, using phenomenological equations (FDT), we predict high electrical fluctuations on the protein surfaces. We developed numerical equations that allow us to estimate these fluctuations for a given protein knowing the molecular weight.

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