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Short Communication

Comparison of electrical conductivities of various brain phantom gels: Developing a 'brain gel model'

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ABSTRACT

The use of conducting gels to mimic brain and other tissues is of increasing interest in the development of new medical devices. Currently, there are few such models that can be utilized at physiologic temperatures. In this work, the conductivities of agar, agarose and gelatin gels were manipulated by varying NaCl concentration from 0–1 mg/ml. The AC conductivity was measured at room and physiological temperatures (37 °C) in the 100–500 Hz frequency range. Conductivity (σ) was nearly independent of frequency but increased linearly with NaCl concentration and was higher at physiological temperatures in these gels. A formula for predicting conductivity as a function of NaCl concentration was derived for each gel type. The overall goal is to develop a 'brain gel model', for studying low frequency electrical properties of the brain and other tissues at physiological temperatures.

1. Introduction

Conductivity (σ) is one of the main factors affecting the choice of a surrogate material for studying the electrical properties of the brain or the effect of electric fields on the central nervous system [1–6].

In this short communication, we report the AC conductivities of three materials: gelatin, agar and agarose. Conductivities of these gels doped with NaCl to match the average conductivity of brain tissue [7–9] are reported here for room (22 °C) and physiological (37 °C) temperatures, as a function of frequency in the 100–500 Hz range, and as a function of NaCl concentration. Based on the measured data, equations that can be used to estimate the conductivities of these gels at 22 °C or 37 °C as a function of NaCl concentration are derived. These gels possess distinct properties uniquely suitable for use as brain mimicking gels, and were chosen mainly because of their moldability and the ability to manipulate their conductivity, for applications where tissue conductivity is the main factor that needs to be mimicked. A more detailed discussion of the relative merits and demerits of these gels for use as brain surrogates is presented in the discussion section, and reviewed in literature in references [10–13].

This report is intended to be a database of conductivity for these gels, contributing towards standardization of phantom preparation techniques for in vitro experiments for various biomedical applications including microwave tomography or electrical impedance tomography (EIT). For example, in the microwave frequency range, and in near-field settings, as used in microwave tomography, electromagnetic signals are extremely sensitive to the physical and dielectric properties of the medium [14]. Accurate knowledge of the conductivity of the biological medium is critical for reconstructing images and obtaining reproducible results. The conductivities of agarose and gelatin at the frequencies and temperatures reported here have not been compiled in literature previously. The equations derived for predicting agar, agarose and gelatin gel conductivities based on NaCl concentration, frequency and temperature are also not available in literature, and their availability may assist in the preparation of appropriate brain phantoms that are mechanically stable at room and physiological temperatures. This short communication fills a gap in the literature by reporting measured conductivity values and providing equations for predicting conductivity of agar, agarose and gelatin gels as a function of frequency and NaCl concentrations at room and physiological temperatures.

The frequency values studied here are comparable to those of high frequency electroencephalography (EEG), epilepsy research and seizure abatement research [15–18]. Additionally, this frequency range is relevant in the newly developing areas of electrochemotherapy and electrical impedance sensing (EIS) in neuronal cell cultures [18,19]. Studies have reported human brain conductivity values of 0.1–0.45 S/m for gray matter and 0.18–0.3 S/m for white matter [7–9]. Over the 100–500 Hz range the conductivity values vary little compared to frequencies less than 100 Hz or greater than 500 Hz [8,20]. The study of electromagnetic signals with even the simplest geometry of phantom materials is very complex [14]. The gel recipes studied here were designed to have conductivities in the same range as that of a human

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brain, averaged assuming a homogenous and isotropic geometry and composition of brain tissue. The data provided here is intended for use in short term experiments that require a simple in vitro model with known dielectric properties. These gel recipes can also be utilized to prepare other tissue phantoms with desired conductivities.

2. Materials and methods

Research grade granulated agar was obtained from Fisher Scientific, (CAS 9002-18-0, Pittsburg, Pennsylvania, USA). Pure powdered agarose was obtained from Acros Organics, (CAS 9012-36-6, Thermo Fisher Scientific, New Jersey, USA). Saline solutions were prepared by adding NaCl (99.8% purity Sigma St. Louis, Missouri, USA), to de-ionized (DI), ultrafiltered water at 85–90 °C with a conductivity of 5.62 micro S/m, to reach concentrations of 0 to 1 mg/ml. Gel powder was then added to achieve the desired gel concentration (1.2% by weight). The solution was stirred using a magnetic stir bar and poured into 50 ml polypropylene corning tubes with a diameter of 2.1 cm, and allowed to cool at room temperature. They were then placed in a water bath at ~39 °C for a few hours to achieve uniform temperature throughout the gel.

Food grade gelatin powder (Kroger, Cincinnati, Ohio) was procured. The preparation of gelatin samples was as described above, however, the solutions were prepared at lower temperatures of 60–65 °C and were left overnight in the refrigerator to set (0.6% by weight). At room temperature and higher, the gel did not possess sufficient mechanical strength for use as a stand-alone brain phantom. Thus the conductivity values reported here for gelatin are a few degrees lower (~21 °C) than temperatures at which measurements were made for agar and agarose gels (22–23 °C).

The gel samples were removed from the tubes, cut to a length of 7 cm and immediately placed between the electrodes in the conductivity measurement set-up (Fig. 1-A). All the gels were 2.1 cm in diameter. The temperature was measured at the center of the cylinder using a thermocouple (HH5560R, Omega Engineering Inc., Stamford, Connecticut, USA).

A 10 V AC voltage was applied across the gel at a frequency of 100–500 Hz using a waveform function generator (Agilent 33250A, Agilent Technologies, Santa Clara, CA, USA) connected in series with a digital multimeter (HP-3478A, Agilent-HP, Santa Clara, CA, USA) which was used to measure the AC current and AC voltage across the gel. AC measurements (as opposed to DC) were used, to avoid effects of polarization across the electrodes. The circuit was calibrated with multiple known resistances.

Conductivity was calculated from the resistance using Eq. (1) as follows:

$$\sigma = 1/\rho = 1/(RA/l) \tag{1}$$

where, σ is the electrical conductivity in Siemens/m, ρ is the electrical resistivity (Ohms-m), R is the electrical resistance (Ohms), A is the cross sectional area of the gel sample in m^2 and l is the length of gel sample in meters.

3. Results and discussion

Fig. 1-B shows the effect of varying NaCl concentration on the conductivities of the gels at room temperature (22 ± 1 °C). The primary contributor to conductivity in solutions is the ionic mobility of added salts through the conduction medium [21]. As a result, σ increases with

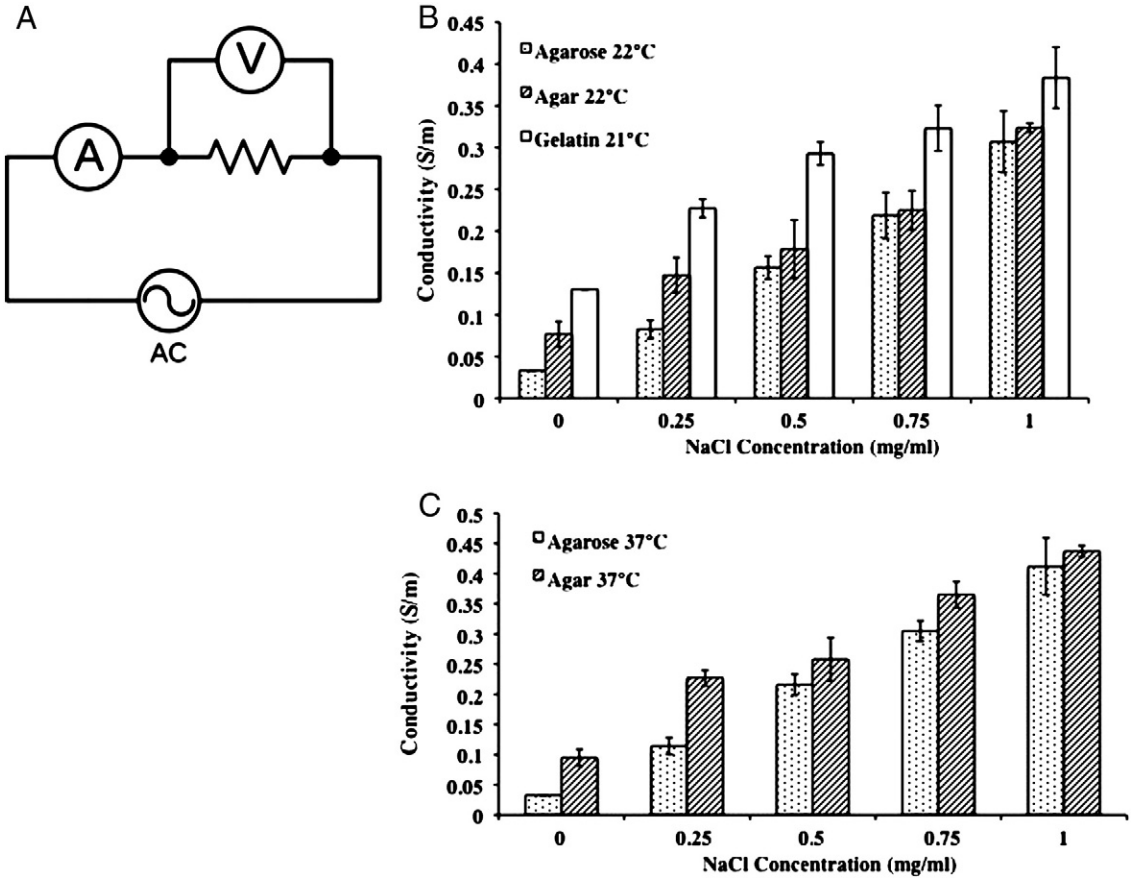

Fig. 1. (A) Circuit diagram showing the experimental set-up for the resistance measurements. (B) Conductivities of gels with increasing NaCl concentrations at room temperature at 500 Hz. The error bars represent the standard deviation (N = 3). (C) Conductivities of gels with increasing NaCl concentrations at 37 °C at 500 Hz. The error bars represent the standard deviation (N = 3).

increasing NaCl concentrations. Gelatin showed the highest conductivity of all gels. Conductivity also increased with temperature, as expected, due to increased mobility of charge carriers. Fig. 1-C shows the conductivities of agar and agarose gels at 37 °C.

Fig. 2 shows conductivity as a function of frequency for gels with an NaCl concentration of 0.75 mg/ml. Other concentrations (not shown here) also show the same trend. In this range there was negligible dependence of conductivity on frequency, as also seen in other work [8,20].

A previous study on the effect of NaCl doping on agar gels by Bennett [22] reported the following frequency-independent relationship between conductivity and NaCl concentration c in units of grams of NaCl/mL solution volume at room temperature:

$$\sigma(\mathrm{S/m}) = 215 * c + 0.0529. \quad (2)$$

Our experiments also show a linear increase in conductivity with NaCl concentration. Linear regression analysis was done to obtain a frequency-independent regression line for estimation of conductivity of gels. The equation for agar gels at room temperature is shown below:

$$\sigma(\mathrm{S/m}) = (172 \pm 4) * \mathrm{c} + (0.0512 \pm 0.001). \quad (3)$$

Fig. 3 shows linear regression on agar gel data from this study in comparison with reference [22]. At 0 mg/ml NaCl, the conductivities nearly overlap. The discrepancy in the slope, however, may be due to the higher concentration of agar gel used here (~1.5%) [22]. A higher concentration may result in a different structural arrangement of the polymers in the gel, leading to differences in ion mobilities and hence, conductivities.

Fits to Eq. (2) were done for all of the gel data. The results are summarized in Table 1. These parameters can be used to select the phantom recipe based on desired conductivities.

Tissue surrogates should ideally be inexpensive, easy to prepare, readily accessible, and stable. Agar, agarose and gelatin are conveniently prepared by dissolution at elevated temperatures in aqueous solvent doped with NaCl, followed by cooling at room temperature and/or refrigeration. This ease of preparation cannot be achieved with several synthetic polymers. For example, polyvinyl alcohol (PVA), requires multiple freeze thaw cycles (approximately 12 h per cycle) for attaining a homogenous structure for brain phantom development [23]. This is their primary disadvantage. Hence, for short term

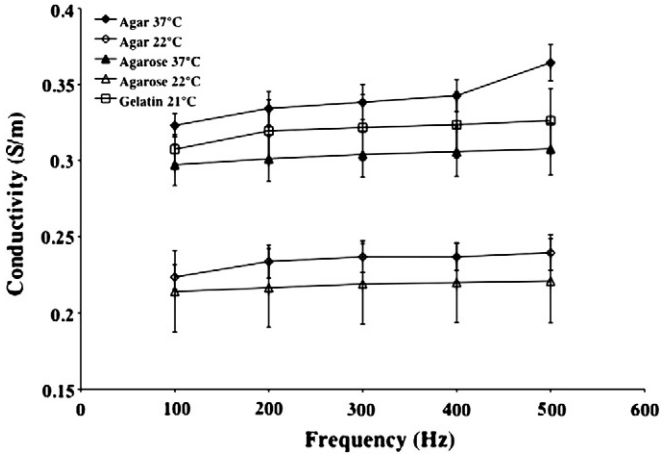

Fig. 2. Conductivities of gels as a function of frequencies between 100–500 Hz at an NaCl concentration of 0.75 mg/ml at various temperatures. The error bars represent the standard deviation (N = 3). (♦) Agar 37 °C, ( ) Agar 22 °C, (▲) Agarose 37 °C, (△) Agarose 22 °C, (■) Gelatin 21 °C.

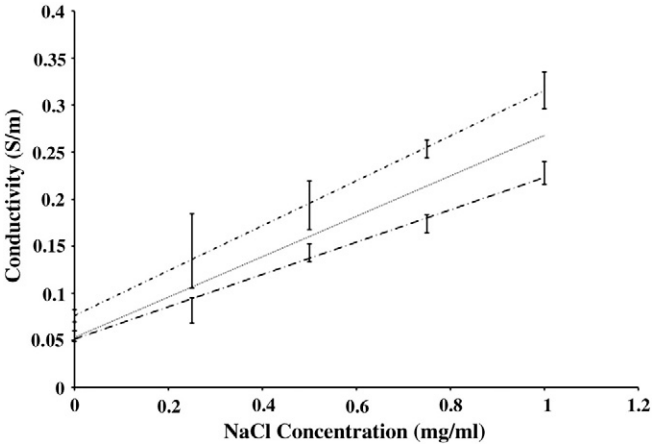

Fig. 3. Linear regression on agar gel conductivity data as a function of NaCl concentrations at room temperature (long-dashed line), physiological temperature (short-dashed line) and from reference [22] (dotted line) using Eq. (2). Note that at 0 g/ml of NaCl the conductivities from reference [22] and this study closely overlap.

experiments, PVA gels offer no added advantage over any of the other gels studied in this work, despite their high structural rigidity, low cost and long shelf life [24,25]. Another tissue surrogate, polyacrylamide gels, contract when heated to 35 °C and are better suited for drug delivery applications, than tissue phantom development [26].

Conducting experiments at 37 °C is important for accurately mimicking biological systems. Although gelatin is an excellent surrogate material at low temperatures, it disintegrates under its own weight at physiological temperatures unless very high concentrations are used, in which case it loses its structural comparability to brain tissue. This limitation is overcome by using agar or agarose, both of which possess the ability to sustain shape at 37 °C without external support. Moreover, the proton density and relaxation time of agar gels are in the range of human soft tissues. Hence, researchers studying magnetic resonance (MR) and nuclear magnetic resonance (NMR) of brain choose to use agar as a brain phantom [3,27,28]. Agar gels possess superior structural rigidity compared to agarose [29]. Agar however is relatively impure and possesses multiple charges [30]. Agarose, comparatively, is electrically neutral and of high purity. The conductivity of agarose can be completely manipulated by only controlling the added NaCl content [30]. In addition to MR research, agarose is widely used as a brain mimicking gel for infusion studies because of its structural properties [31,32]. For example, porcine brain in vivo and agarose gel have similar pressure profiles, penetration transient and drag forces associated with the advancement of a catheter into the tissue [31]. Agarose gel also mimics the brain in its ability to create a seal against the outer wall of a delivery device inserted into it [31]. Drag forces of agarose gels are within 5–10% of living human brain tissue [31,33]. Another important factor affecting the use of gels in brain mimicking applications where conductivity is important is their degree of homogeneity. Agar, agarose and gelatin have very small density fluctuations. Whereas, certain synthetic polymers such as polyacrylamide gels suffer from cluster formation and resulting

Table 1
Linear regression data for gel conductivities in the frequency range 100–500 Hz.

Gel	Temperature (±1 °C)	Slope[a]	Intercept[a]	R^2
Agar, measured	22	172 ± 4	0.050 ± 0.001	0.98
	37	239 ± 4	0.069 ± 0.004	0.99
Agarose	22	193 ± 2	0.016 ± 0.003	0.99
	37	277 ± 1	0.018 ± 0.003	0.99
Gelatin	21	172 ± 5	0.116 ± 0.002	0.97
Agar, from reference[b]	~22	215	0.053	0.99

[a] Numbers represent mean ± standard deviation.
[b] Taken from reference [22].

structural inhomogeneities, despite their excellent optical transparency and mechanical properties [34,35]. Polyacrylamides also suffer from limited shelf life, which is a few hours when exposed to air or few weeks in an airtight container [34,35]. Moreover, polyacrylamide gels are toxic and require special handling [36].

One of the limitations of brain phantom gels studied here is their homogenous and isotropic nature, a deviation from the physiological human brain. The goal of this work, however, was to prepare gels that match the *average* conductivity of the human brain for in vitro experiments at room and physiological temperatures, assuming that the brain is a homogenous medium. The results presented here are intended to be a part of intermediate experiments building towards understanding a more complex in vivo system. The biodegradability of the gels studied in this work is not a limitation for short-term experiments.

4. Conclusions

The conductivities of three brain phantom gels: agar, agarose and gelatin with different NaCl concentrations were measured at biologically relevant temperatures and at frequencies in the 100–500 Hz range.

The gel strengths were chosen so that the gels could sustain their structure at experimental temperatures without the need for a container or external support. The conductivities were found to have a direct dependence on NaCl concentration, temperature and frequency.

Gelatin was studied only at room temperature. Even at room temperature, its conductivity was comparable to agar and agarose at physiological temperatures. Conductivities increased with temperature for Agar and Agarose gels as expected. The conductivities were nearly independent of frequency in the range studied.

This work provides a method for estimation of the effect of increasing NaCl concentrations on the conductivity of gels. These results can find applications in research involving electrical properties of brain tissues using surrogate materials.

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