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## 1 **Modulating aqueous solution properties to optimize radiofrequency heating**

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12

13 **Exposure to a noninvasive, external radiofrequency (RF) electric field has been**  
14 **proposed for the treatment of cancer, using nanoparticles as heating agents within a tumor.**  
15 **The Kanzius Radiofrequency Hyperthermia system has been proposed for hypothermic**  
16 **therapy of cancer. Studies using this system in combination with gold and carbon-based**  
17 **nanoparticles have sparked much debate regarding the RF heating mechanisms of**  
18 **nanomaterials, especially in conductive, biologically-relevant media. Past research has**  
19 **focused on optimizing nanoparticle properties to enhance energy absorption and nano-**  
20 **localized heat, but no effort has been made to enhance the heating of highly conductive**  
21 **media by directly modulating its bulk dielectric properties. Here we show that simple**  
22 **materials, including salts, sugars, sugar alcohols, and betaines, can be used to modulate the**

1 **conductivity of aqueous solutions to optimize their heating rates. These materials are non-**  
2 **toxic, inexpensive, and **universally** available, and thus highly attractive for clinical use.**

3 Cancer is the second leading cause of mortality in the U.S. and, despite ongoing  
4 improvements in the three primary treatment modalities of surgery, chemotherapy, and radiation  
5 therapy, five-year survival for certain solid malignancies such as pancreatic and lung cancer  
6 remains profoundly low. RF-induced hyperthermia has long been investigated as a treatment  
7 modality for cancer but various clinical trials involving its use have produced mixed results<sup>1-10</sup>.  
8 One of the hallmark challenges in RF treatment of cancer is sufficiently heating a tumor to the  
9 desired temperature while sparing normal tissue, particularly fatty subcutaneous tissue that is  
10 prone to over-heating. It has been stated that tumor tissue, owing to its abnormal structure and  
11 hence increased electric conductivity, selectively heats more so than normal tissue when exposed  
12 to RF<sup>11</sup>. Separately, nanoparticles, especially gold nanoparticles, have been coupled with  
13 noninvasive RF to enhance heating and cytotoxicity<sup>12-16</sup>, generating much debate on the RF  
14 heating mechanism of nanomaterials<sup>17-23</sup>. The presence of salts, especially, in aqueous solutions  
15 and biological systems is known to affect the RF heating behavior of gold nanoparticles, but the  
16 role of salts may be “the most unresolved aspect of thermal dissipation by gold nanoparticles in  
17 RF,” according to a recent review<sup>22</sup>. Surfactant-wrapped single-walled carbon nanotubes have  
18 also been coupled with RF to enhance heating *in vitro* and *in vivo*<sup>24</sup>, similarly motivating a  
19 number of experimental and theoretical studies on nanoparticle heating mechanisms<sup>25-28</sup>. The  
20 nature of RF heating in biologically relevant materials remains poorly understood. Establishing a  
21 solid framework for RF heating in biological materials is needed not only for modeling heating  
22 behavior but also for optimization of tissue hyperthermia for therapeutic use. Here we present

1 well-defined experimental and theoretical heating curves for aqueous salt solutions that in the  
 2 future will serve as a foundation for understanding the role of salts in nanoparticle heating.

3 Macroscopic biological materials respond to electromagnetic (EM) fields as governed by  
 4 their dielectric properties, i.e., permittivity. In time-varying alternating electric fields such as  
 5 radiofrequency waves, a material's permittivity becomes a complex function as a result of the  
 6 electric polarization of the medium and is given by the equation:

$$7 \quad \varepsilon_r = \varepsilon'_r + i\varepsilon''_r = \varepsilon'_r + i \frac{\sigma}{\omega\varepsilon_0} \quad (1)$$

8 where  $\varepsilon_r$ ,  $\varepsilon'_r$ ,  $\varepsilon''_r$  are the complex, real-valued, and imaginary relative permittivities, respectively,  
 9  $i$  is  $\sqrt{-1}$ ,  $\sigma$  is the conductivity,  $\varepsilon_0$  is the relative permittivity of free space, and  $\omega$  is the angular  
 10 frequency. Dielectric materials heat when exposed to electromagnetic fields within the radio- and  
 11 microwave frequency range (3 kHz–300 GHz) and the energy absorbed by the medium is  
 12 defined by the specific absorption rate (SAR):  $\text{SAR} = \sigma E^2 / 2\rho$ . The rate of heating of a material  
 13 exposed to EM fields is then:

$$14 \quad \text{HR} = \frac{\partial T}{\partial t} = \frac{\sigma |E_{\text{eff}}|^2}{2\rho c_p} \quad (2)$$

15 where  $E_{\text{eff}}$  is the effective electric field within the sample,  $\rho$  is the mass density and  $c_p$  is the  
 16 specific heat capacity.

17 Cancerous tissue, by virtue of abnormal cell growth and structure, has intrinsically  
 18 different dielectric properties than that of normal tissue<sup>11,29–32</sup>. This difference in permittivity, it  
 19 has been postulated, can be exploited to selectively heat and thus injure cancerous cells while  
 20 leaving normal tissue intact. A common mistake in interpreting equation (2), however, is to  
 21 simply equate higher conductivity with increased heating rate<sup>15,25</sup>. An external, applied electric

1 field  $E_{\text{app}}$  impinging upon an interface of two dielectric materials must obey the following  
 2 boundary condition:

$$3 \quad \varepsilon_{r,1} E_{\text{app}} = \varepsilon_{r,2} E_{\text{eff}} \quad (3)$$

4 in which it becomes apparent that the ratio of dielectric properties at the interface influences the  
 5 effective electric field within the material of interest. In the case of pure water surrounded by air,  
 6 the ratio  $\varepsilon_{r,\text{air}}/\varepsilon_{r,\text{sample}}$  is on the order of  $10^{-2}$  and the ratio is  $10^{-4}$  for normal sodium chloride  
 7 (physiologic saline) surrounded by air. In the latter case, saline is greatly polarized by the applied  
 8 electric field, thus reducing the internal effective electric field experienced by the bulk media.  
 9 Accounting for the boundary condition allows for a more precise heating rate model of a sample  
 10 surrounded by air, as is the case in the experiments reported here:

$$11 \quad \text{HR} = \frac{\sigma \left| \frac{\varepsilon_{r,\text{air}}}{\varepsilon_r} E_{\text{app}} \right|^2}{2\rho c_p} \quad (4)$$

12 where  $\varepsilon_{r,\text{air}}$  and  $\varepsilon_r$  are the absolute relative permittivities of air and the sample, respectively.  
 13 This model results in a theoretical and experimentally confirmed peak heating rate of saline  
 14 solution with concentration of 5.6 mM corresponding to a conductivity of 0.06 S/m at a  
 15 frequency of 13.56 MHz<sup>33,34</sup>. Herein we generalize this heating model to that of a large variety of  
 16 salts and show that maximal heating occurs at the same conductivity of 0.06 S/m regardless of  
 17 the atomic or molecular identity of salts.

18

## 19 **RF heating of aqueous salt solutions**

20 We measured the RF heating rates of an assortment of salts dissolved in ultra-pure water  
 21 in the concentration range 0.01–200 mM. The salts tested were NaCl, NaC<sub>2</sub>H<sub>3</sub>O<sub>2</sub>, MgCl<sub>2</sub>,  
 22 Na<sub>2</sub>SO<sub>4</sub>, AuCl<sub>3</sub>, and Na<sub>3</sub>C<sub>6</sub>H<sub>5</sub>O<sub>7</sub> (sodium citrate). Samples were loaded onto a 1.3 mL non-

1 conductive quartz cuvette and exposed to a RF field (13.56 MHz operating frequency) at 100 W  
2 generator power (Fig. 1a). Sample temperature was measured using an infrared camera and the  
3 heating rates were calculated by a least-squares linear regression of the resultant temperature-  
4 time plot (Fig. 1b). Samples were heated from 23 °C to either 27 °C or for a duration of 60 s,  
5 whichever occurred first. Over this selected small temperature range, the variation of heating rate  
6 of the solutions due to the temperature-dependence of dielectric properties is estimated to be less  
7 than 0.07%. Each salt displays a characteristic peak heating curve as a function of concentration  
8 (Fig. 2a), with salts of greater valence typically displaying peak heating at lower concentrations  
9 than salts of lesser valence.

10         The heating curves for the individual salt solutions collapse into a single curve when the  
11 conductivity of solutions is considered as shown in Fig. 2b. Peak heating occurred for all  
12 measured salts at a conductivity of 0.060 S/m. We obtained conductivity values at 13.56 MHz  
13 (RF generator operating frequency) of each sample by measuring their complex relative  
14 permittivity ( $\epsilon_r'$  and  $\sigma$ ) in the range 10 MHz–3 GHz. Of note, when measuring the relative  
15 permittivity of highly conductive solutions, electrode polarization occurs at low frequencies,  
16 which can result in significant instrument-related measurement errors, especially for  $\epsilon_r'$  [17]. We  
17 have performed the necessary corrections<sup>25</sup> and found these errors to be insignificant (<1.2% for  
18  $\sigma$  and  $\epsilon_r'$ ) for our purposes in the conductivity range studied (Extended Data Fig. 1c). The heating  
19 model of saline is thus generalized to all salts by demonstrating that the heating rate of salts is  
20 dependent on bulk conductivity regardless of specific atomic or molecular identity.

21

## 22 **Enhancing RF heating of ionic solutions**

1 From the generalized RF heating curve for salts, it is apparent that an increase in material  
2 conductivity does not monotonically increase heating rate. Peak heating for aqueous media  
3 occurs at a conductivity of 0.060 S/m, beyond which addition of conductive material will  
4 decrease heating rate. Indeed, this was shown using metallic and semiconducting carbon  
5 nanotubes, though this behavior was not yet well understood<sup>27</sup>. Blood and body fluids are present  
6 on the far right of the curve with conductivities of 1.1 and 1.5 S/m, respectively, at 13.56 MHz<sup>35</sup>.  
7 Intra- and extra-cellular environments of cells have similarly high ion content. Therefore,  
8 increasing the heating rate of body tissues under RF energy would require *diluting* existing ionic  
9 content, a task not readily performable or tolerated *in vivo*.

10 An alternative approach presented herein is to introduce neutral, water-soluble materials  
11 called kosmotropes that, when added to an ionic aqueous solution, serve to decrease conductivity  
12 and thus increase RF heating rate of the solution. Kosmotropic (“structure-forming”) materials  
13 preferentially interact with water solvent molecules and form hydrogen bonds to water that are  
14 stronger than the water-water hydrogen bonds, thus stabilizing the water network<sup>36</sup>. Glycerol,  
15 propylene glycol, ethylene glycol, and methanol are examples of kosmotropes that are used as  
16 anti-freeze agents; in nature, sugars such as trehalose and sucrose act as cryo-protective agents  
17 when present in high concentrations in flora and fauna. Biotechnologists commonly use  
18 dimethylsulfoxide as their cryoprotectant agent of choice to reduce cellular damage by ice when  
19 freezing cells for long-term storage. Marine life, such as seagrasses, use a wide variety of  
20 kosmotropic materials, such as sugars, sugar alcohols, and zwitterions to maintain osmotic  
21 balance in the rapidly changing salinity of seawater<sup>37</sup>. Quaternary ammonium compounds called  
22 betaines, also in high concentrations, allow bacteria to survive in highly ionic environments. For  
23 example, glycine betaine is used by *E. coli* to counteract the effects of low pH and high urea

1 concentrations in the urinary tract<sup>38</sup>. In stabilizing the water network, these materials can also  
2 reduce ion mobility, a property we exploit to reduce the conductivity of highly ionic solutions  
3 thereby increasing their heating rate accordingly. To our knowledge, this is the first time that RF  
4 heating rates of aqueous solutions have been modulated in this way.

5         To perform the experiment, we measured the RF heating rates and complex permittivities  
6 of a number of kosmotropes (Fig 3a) dissolved in phosphate buffered saline (PBS), a biologically  
7 iso-osmolar solution with similar conductivity (1.15 S/m) to blood and body tissues. The  
8 kosmotropes tested were sucrose, maltose, glucose, ethylene glycol, propylene glycol, glycerol,  
9 sorbitol, glycine, sarcosine, glycine betaine, and dimethylsulfoxide. Kosmotrope solutions in  
10 PBS were prepared and appropriately diluted from concentrated stock PBS (10x PBS containing  
11 90 g/L NaCl, 1.44 g/L KH<sub>2</sub>PO<sub>4</sub>, and 7.95 g/L Na<sub>2</sub>HPO<sub>4</sub>) to maintain equivalent final ionic  
12 concentrations in all solutions. RF heating rates and complex permittivity were measured in the  
13 same fashion as the salt heating experiments described above. We found that all of the  
14 kosmotropic materials tested decreased the conductivity of PBS and increased its heating rate in  
15 a concentration-dependent manner as shown in Fig. 3b. Propylene glycol outperformed all other  
16 materials at every concentration studied, increasing the heating rate of PBS by 490% when added  
17 at a concentration of 500 mg/mL. On average, PBS heating rate increased from 0.028 °C/s to  
18  $0.034 \pm 0.001$ ,  $0.052 \pm 0.001$ , and  $0.112 \pm 0.004$  °C/s at kosmotrope concentrations of 100, 250,  
19 and 500 mg/mL, respectively. Regardless of concentration, kosmotrope-PBS solutions heat  
20 similarly to salt solutions of the same conductivity, according to the same heating model when  
21 exposed to the RF field.

22         From equation (4), it is clear that heating rate can also be manipulated by altering heat  
23 capacity and density. For example, we found that lithium chloride displayed peak heating rates of



1 0.37, 0.67, and 1.21 °C/s when dissolved in pure water, 70% ethanol, and pure ethanol,  
 2 respectively (Fig. 3d). The increase in peak heating rate with increasing ethanol content  
 3 corresponds to decreases in heat capacity, density, and  $\epsilon_r'$  of the solvent. Although systemic  
 4 administration of pure ethanol would not be physiologically tolerated, direct injection of ethanol  
 5 into tumors is already used therapeutically in hepatic arterial chemo-embolization, which could  
 6 be coupled with RF hyperthermia therapy.

### 7 **Modeling RF heating behavior**

8 Thus far we have compared the theoretical model to experimental measurements not only  
 9 for the conductivity at which peak heating occurs in a given aqueous solution, but also the  
 10 general shape of the curve and found excellent agreement between the two when sample  
 11 temperature is properly accounted for. We have not, however, made direct comparisons between  
 12 theoretically predicted and experimentally measured heating rates. For that comparison, all  
 13 variables in equation (4) must be measured. Unfortunately, it is notoriously difficult to measure  
 14 the external electric field when the field strength is extremely strong as it is in our experiments.  
 15 Attempts to measure the field with a voltage probe have led to rapid (< 1 second) overheating  
 16 and subsequent damage of the probe, even at an RF generator power of 10 W. Instead, we  
 17 estimate  $E_{\text{app}}$  by fitting the heating rate model to the salt heating data in Fig. 1b. This calculation  
 18 requires a further adjustment for the effective electric field term to account for sample holder  
 19 geometry<sup>39</sup>:

$$20 \quad E_{\text{eff}} = \frac{1}{1 + N \left( \frac{\epsilon_r}{\epsilon_{r,\text{air}}} - 1 \right)} E_{\text{app}} \quad (5)$$

21 where  $N$  is the polarization tensor,  $\epsilon_{r,\text{air}}$  is the relative permittivity of air, and  $E_{\text{app}}$  is the applied  
 22 electric field in air. The polarization tensor depends upon the dimensions of the sample and is

1 approximately 0.596 in the case of our cylindrical cuvette<sup>40</sup>. Note that in the limit where the two  
2 materials are geometrically infinite plane layers,  $N$  is equal to 1 and  $E_{\text{eff}}$  reduces to equation (3).  
3 We fit equation (2) with the geometry-adjusted expression for  $E_{\text{eff}}$  shown in equation (5) to the  
4 heating rate (HR) and complex permittivity ( $\sigma$  and  $\epsilon_r$ ) values, using  $E_{\text{app}}$  as the fit parameter.  
5 The heating rate model fit is indicated by the solid line in Fig. 2b. The angular frequency  $\omega = 2\pi f$   
6 corresponds to the 13.56 MHz operating frequency of the RF generator and  $\rho$  and  $c_p$  are  
7 estimated to be equal to the values of pure water at 25 °C. Using these parameters, we calculate  
8  $E_{\text{app}}$  to be 0.49 MV/m at 100 W operating power. Although this value appears to be very large, it  
9 is necessary to achieve the heating rates reported. The same heating rate model can be applied to  
10 the 13.56 MHz RF system reported by Liu, *et al.*, who reported a maximum temperature increase  
11 of only 0.7 °C over an RF exposure period of 10 min (0.00117 °C/s). Based on the sample  
12 dimensions given, we estimate  $N$  for this system to be 0.673 and calculate  $E_{\text{app}}$  to be 30.3 kV/m,  
13 in excellent agreement with the electric field strength estimated by the authors from low power  
14 measurements<sup>34</sup>.

15         Prior studies with the Kanzius RF generator by our group utilized a power settings of  
16 900-1000 W<sup>13,21,24,27,41</sup>, compared to 100 W in the study described above. The reason for the  
17 reduction in power is to minimize the effects of the aforementioned temperature-dependence of  
18 permittivity, in which the heating rate itself would change as the sample material increased in  
19 temperature. To further evaluate this phenomenon, we additionally measured RF heating rates  
20 of salt solutions at 900 W from 25 °C to 70 °C, or for a duration 120 seconds, whichever  
21 occurred first, similar to the experimental conditions we have reported previously. Under these  
22 conditions, we measured heating rates as fast as 3.98 °C/s, corresponding to a rise in sample  
23 temperature from room temperature (~25 °C) to over 60 °C over a RF exposure period of only

1 ten seconds. Over this large temperature range, the temperature-dependence of dielectric  
2 properties of salt solutions cannot be ignored. Due to this effect, peak heating occurred at lower  
3 concentrations (Fig. 4a) and lower conductivity, 0.038 S/m (Fig. 4b), compared to 0.060 S/m at  
4 100 W.

5 In general, peak heating occurs when the medium's real and imaginary permittivities,  $\epsilon_r'$   
6 and  $\epsilon_r''$ , respectively, are equal. Both are frequency- and temperature-dependent. For this reason,  
7 we cannot fit the heating rate model described by equations (2) and (5) as was done for the  
8 heating and permittivity data at 100 W. Instead, we use temperature corrections<sup>42-44</sup> for the  
9 conductivity, permittivity, density, and heat capacity of saline solutions to calculate the  
10 instantaneous heating rates of saline for any given temperature and concentration. The calculated  
11 heating curves at 25, 45, and 70 °C given an estimated applied electric field of 1.53 MV/m are  
12 shown in Fig. 4b as a function of solution conductivity at 25 °C. These results show that the  
13 average heating rates measured over the temperature range 25–70 °C are similar to the  
14 instantaneous heating rates at 45 °C. Other authors have also reported fast heating rates (~1.3  
15 °C/s) that similarly necessitate high electric field strengths<sup>45</sup>.

16

## 17 Discussion

18 RF-induced hyperthermia has gained interest as a compelling treatment modality for  
19 cancer. Although knowledge of tissue dielectric properties has accumulated in the past few  
20 decades, the behavior of RF heating of biological materials has been not been well characterized  
21 and has posed a significant barrier against therapeutic optimization of this potential treatment  
22 modality. *In vitro*, prior studies have characterized the heating behavior of saline solutions alone.  
23 Here, we have generalized that theoretical heating model to a diverse assortment of salts and

1 shown that the RF heating behavior is determined by the dielectric and thermal properties of the  
2 bulk solution independent of the atomic or molecular identity of the salt. With well-defined  
3 experimental and theoretical peak heating curves, we have shown that the heating behavior of  
4 aqueous solutions in a RF field is calculated with a relatively simple model even over large  
5 temperature ranges once geometry and temperature-dependent properties are well accounted for.

6         The heating rate model predicts peak heating to occur at a specific bulk medium  
7 conductivity for a given frequency as opposed to a monotonic increase with conductivity, a  
8 misconception sometimes encountered in the literature. Beyond this peak heating conductivity,  
9 heating rate decreases due to the diminished effective field strength within the sample. At 13.56  
10 MHZ, the dielectric properties of biological systems exceed this peak heating value and thus  
11 preclude the practice of adding more salts or polar materials, as this addition would actually  
12 decrease the heating rate of the medium. To achieve increased heating rates in physiologic  
13 materials, we propose the use of kosmotropes such as propylene glycol, sucrose, and glycine  
14 betaine, which are a class of molecules that stabilize water structure and decrease the  
15 conductivity of highly ionic solutions. We have shown that kosmotropes can be added to  
16 physiologic media to increase the heating rate of biologically relevant aqueous solutions in a  
17 concentration-dependent manner. In converting this technique into a clinical application, an  
18 adequate method for tumor-targeted delivery of these materials will need to be identified. One  
19 possibility includes percutaneous arterial injection into the local tumor vasculature, similar to the  
20 well-known and **clinically available** technique of arterial chemo-embolization. The human body,  
21 however, is complex dielectric with many tissue interfaces, therefore the effects of kosmotropes  
22 on the RF heating rates of *in vivo* tissues will need to be investigated. Most of the substances  
23 tested here for RF heating enhancement are widely available, inexpensive, and considered safe

- 1 when ingested in moderate quantities, making them highly attractive for clinical use. We believe
- 2 that with further understanding of suitable kosmotropes the availability of RF-induced
- 3 hyperthermia can become a treatment universal and not limited by the cost of “designer” drugs.

## 1 **Materials and Methods**

### 2 **Sample preparation**

3           Aqueous salt solutions were prepared in high-resistivity water (18.2 M $\Omega$ /cm) using a  
4 number of monovalent (KCl, LiCl, NaBr, NaCl, NaC<sub>2</sub>H<sub>3</sub>O<sub>2</sub>, NaI, NaNO<sub>3</sub>), divalent (BaCl<sub>2</sub>,  
5 CaCl<sub>2</sub>, MgCl<sub>2</sub>, Na<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>SO<sub>4</sub>), and trivalent salts (AuCl<sub>3</sub>, GdCl<sub>3</sub>, Na<sub>3</sub>C<sub>6</sub>H<sub>5</sub>O<sub>7</sub>, and Na<sub>3</sub>PO<sub>4</sub>) at  
6 concentrations varying from 0.001 mM to 2 M. For kosmotrope experiments, 1 mL of  
7 concentrated PBS containing 90 g/L NaCl, 1.44 g/L KH<sub>2</sub>PO<sub>4</sub>, and 7.95 g/L Na<sub>2</sub>HPO<sub>4</sub> was added  
8 to a known mass of kosmotrope material, followed by dilution to 10 mL to ensure equal ion  
9 concentration across all samples. Kosmotrope materials (sucrose, maltose, trehalose, glycerol,  
10 propylene glycol, ethylene glycol, glycine betaine, dimethylsulfoxide) and all salts were obtained  
11 from Sigma-Aldrich in high purity (>98 %) and used as received.

### 12 **Electrical characterization**

13           Complex permittivity measurements were taken using an Agilent 85070E high-  
14 temperature coaxial dielectric probe (Agilent Technologies, Santa Clara, CA) connected to an  
15 Agilent E4991A impedance analyzer to extend the frequency range of the probe down to 10  
16 MHz. Four-point calibration (open, short, 50 ohm load, low-loss capacitor) of the impedance  
17 analyzer was performed prior to each measurement session. Three-point probe calibration of the  
18 probe (air, short, water) was performed periodically between samples and a single-point  
19 calibration (air) was performed between every sample to eliminate signal drift. For  
20 measurements, 600  $\mu$ L of sample was loaded onto the probe and approximately 400 logarithmic  
21 data points were acquired across the frequency range 10 MHz–3 GHz with each measurement  
22 performed in triplicate in rapid succession to avoid probe drift. We found no difference between  
23 loading a small amount of sample onto probe and immersing the probe into a plastic beaker

1 containing 20 mL of sample. Additionally, for each sample in the 900 W experiment, static  
2 solution DC conductivity was measured ten times using either an InLab 731 or 741 conductivity  
3 probe (Mettler Toledo, Columbus, OH), depending on the conductivity of the sample and the  
4 measurement range of each probe (data not shown). DC conductivity measurements were in  
5 agreement with AC conductivity measurements performed using the impedance analyzer at  
6 13.56 MHz.

### 7 **Radiofrequency heating**

8 A variable power Kanzius External RF (13.56 MHz) Generator System (ThermMed,  
9 LLC, Erie, PA) was used to heat aqueous solutions. A high-voltage RF field is generated in the 8  
10 cm air gap between the transmitting and receiving heads of the RF-field generator. For aqueous  
11 experiments, samples were placed in a 1.3 mL quartz cuvette on a non-conducting Teflon holder  
12 mounted on an adjustable rotary stage at ambient temperature and open to air. The cuvette was  
13 placed 8 mm from the transmitting head of the RF-field generator and exposed to the high-  
14 voltage RF field at 100 or 900 W generator power. Sample temperatures were recorded using an  
15 infrared camera (FLIR SC 6000, FLIR Systems, Inc., Boston, MA) approximately every 0.17 s.  
16 At 100 W, samples were heated from ambient temperature ( $\sim 23$  °C) to 27 °C or for a duration of  
17 60 s, whichever occurred first. At 900 W, samples were heated from ambient temperature to 70  
18 °C or for a duration of 120 s, whichever occurred first. Heating rates were calculated by fitting a  
19 linear regression to the temperature versus time plot of each sample for the duration of RF  
20 exposure.

21

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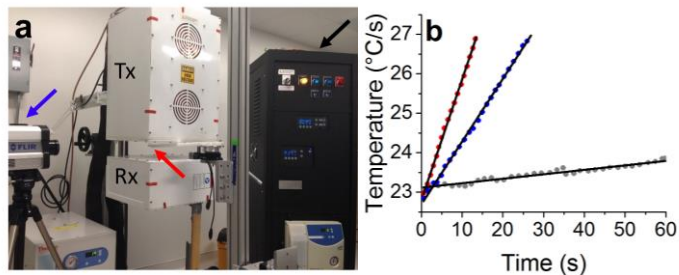
## 8 **Author Contributions**

9 N.C.L. collected and analyzed data and wrote the paper; N.C.L., S.J.C., L.J.W., and S.A.C.  
10 designed the salt heating study; N.C.L. and A.R.B. designed the kosmotrope study; J.C.H. was  
11 involved in data analysis and manuscript editing. All authors discussed the results and  
12 commented on the manuscript.

## 13 **Author Information**

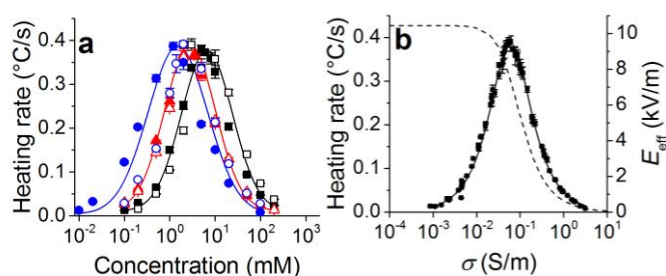
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15 report no conflicting financial interest. Correspondence and request for materials should be  
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18 reflect the views of the National Science Foundation.

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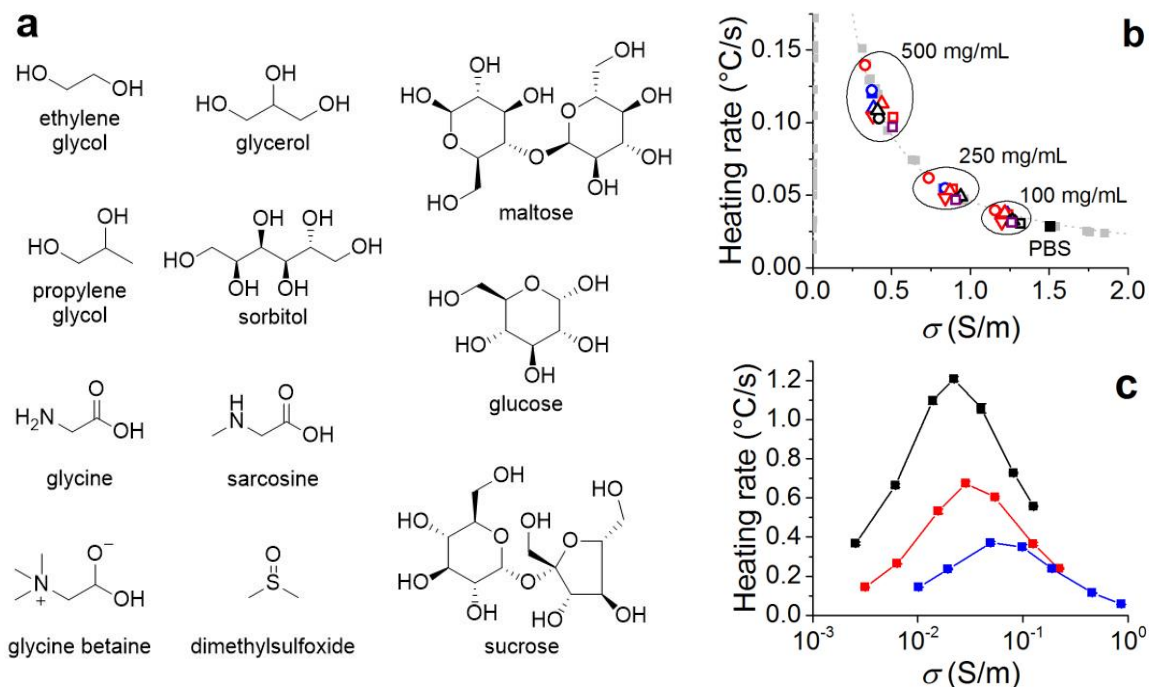
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3 **Figure 1 | Experimental setup for the RF-Induced heating of aqueous solutions.** a, The non-  
 4 invasive Kanzius RF system. A radiofrequency (13.56 MHz) generator (black arrow) is used to  
 5 generate a high-voltage electric field between the transmitting (Tx) and receiving (Rx) heads. An  
 6 infrared camera (blue arrow) is used to record the temperature of the sample (red arrow). b,  
 7 Temperature plots for 0.1 (grey), 1 (blue), and 10 mM (red) NaCl solutions. Least-squares linear  
 8 regressions (solid lines) are used to calculate RF heating rates. Insert displays the IR camera  
 9 view of the sample.



10

11 **Figure 2 | RF heating of salt solutions.** a, Concentration-dependent heating at 100 W of  
 12 monovalent (black; NaCl - ■, NaC<sub>2</sub>H<sub>3</sub>O<sub>2</sub> - □), divalent (red; MgCl<sub>2</sub> - ▲, Na<sub>2</sub>SO<sub>4</sub> - △), and  
 13 trivalent salts (blue; AuCl<sub>3</sub> - ●, Na<sub>3</sub>C<sub>6</sub>H<sub>5</sub>O<sub>7</sub> - ○). b, Conductivity dependence of heating rates (■)  
 14 and effective electric field (dashed line). Black line indicates heating rate model fit described by  
 15 equations (2) and (5). Heating rates reported are averages of three replicates with error bars  
 16 indicating SEM.



1

2 **Figure 3 | Modulating solution properties to optimize RF heating. a**, Kosmotrope structures.

3 **b**, Kosmotropes enhance the heating rate of PBS (■) in a concentration-dependent manner.

4 Kosmotropes include sugar alcohols (red; ethylene glycol - □, propylene glycol - ○, glycerol - △,

5 sorbitol - ▽), sugars (blue; maltose - □, glucose - ○, sucrose - △), amines (black; glycine - □,

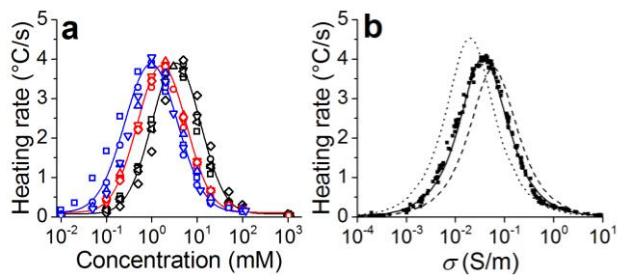
6 sarcosine - ○, glycine betaine - △), and dimethylsulfoxide (purple, □). Salt solution heating from

7 Fig. 2b is shown in grey. **c**, Heating rates of LiCl in ethanol (black), 70% ethanol (red), and

8 water (blue) at 1–100 mM. All heating rates are averages of three replicates. Error bars

9 indicating SEM are omitted for clarity in **b** but are generally smaller than symbols.

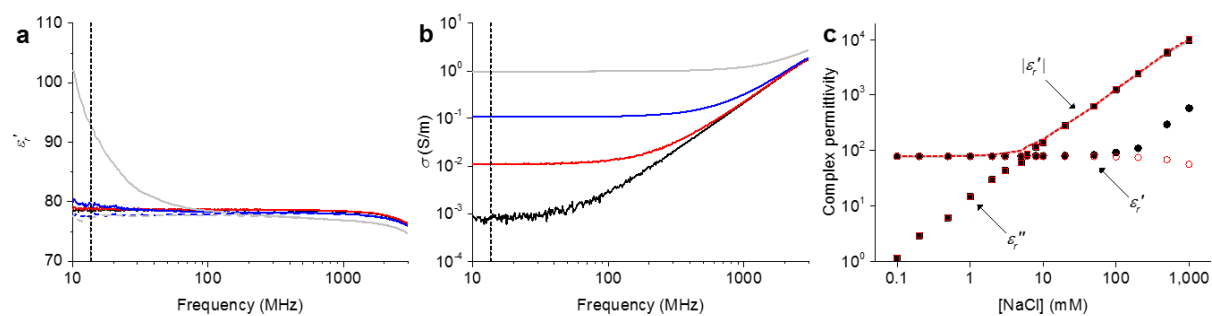
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 2 **Figure 4 | RF heating of salt solutions at high power. a**, Concentration-dependent heating at  
 3 900 W of monovalent (black; KCl -  $\square$ , LiCl -  $\circ$ , NaBr -  $\triangle$ , NaCl -  $\nabla$ ,  $\text{NaC}_2\text{H}_3\text{O}_2$  -  $\diamond$ , NaI -  $\triangleleft$ ),  
 4 divalent (red;  $\text{BaCl}_2$  -  $\square$ ,  $\text{CaCl}_2$  -  $\circ$ ,  $\text{MgCl}_2$  -  $\triangle$ ,  $\text{Na}_2\text{CO}_3$  -  $\nabla$ ,  $\text{Na}_2\text{SO}_4$  -  $\diamond$ ), and trivalent salts  
 5 (blue;  $\text{AuCl}_3$  -  $\square$ ,  $\text{GdCl}_3$  -  $\circ$ ,  $\text{Na}_3\text{C}_6\text{H}_5\text{O}_7$  -  $\triangle$ ,  $\text{Na}_3\text{PO}_4$  -  $\nabla$ ). **b**, Measured ( $\blacksquare$ ) and calculated (lines)  
 6 heating rates of saline at 25 (dotted), 45 (solid), and 70 (dashed) °C. Heating rates reported are  
 7 averages of three replicates. Error bars indicating SEM are omitted for clarity but are generally  
 8 smaller than symbols.



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**Extended Data Figure 1 | Complex permittivity of NaCl.** **a**, Real-valued permittivity and **b**, conductivity of 0.1 (black), 1 (red), 10 (blue), and 100 (grey) mM NaCl over the frequency range 10 MHz–3 GHz. Dashed blue and grey lines indicate low frequency polarization correction of real-valued permittivity of 10 and 100 mM NaCl, respectively. Dotted black line

indicates 13.56 MHz. **c**, Concentration-dependence of  $\epsilon_r'$  (circles) and  $\epsilon_r''$  (squares) for NaCl at 13.56 MHz, both measured (black) and corrected (red) values are shown. The absolute value of the relative permittivity  $|\epsilon_r|$  is indicated for measured (grey line) and corrected (dotted red line) values.