

# Nanoparticle-enhanced electrical impedance detection and its potential significance in image tomography

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**Abstract:** The conductivity and permittivity of tumors are known to differ significantly from those of normal tissues. Electrical impedance tomography (EIT) is a relatively new imaging method for exploiting these differences. However, the accuracy of data capture is one of the difficult problems urgently to be solved in the clinical application of EIT technology. A new concept of EIT sensitizers is put forward in this paper with the goal of expanding the contrast ratio of tumor and healthy tissue to enhance EIT imaging quality. The use of nanoparticles for changing tumor characteristics and determining the infiltration vector for easier detection has been widely accepted in the biomedical field. Ultra-pure water, normal saline, and gold nanoparticles, three kinds of material with large differences in electrical characteristics, are considered as sensitizers and undergo mathematical model analysis and animal experimentation. Our preliminary results suggest that nanoparticles are promising for sensitization work. Furthermore, in experimental and simulation results, we found that we should select different sensitizers for the detection of different types and stages of tumor.

**Keywords:** EIT, nanoparticle sensitizer, tumor detection, EMF analysis

## Introduction

Bioelectric impedance measurement is a biotechnical detection method that is proving to be a safe way to determine the electrical properties of tissues inside the human body.<sup>1,2</sup> It is a noninvasive, inexpensive method that provides rich functional information. The technology can also extract pathology information on the cellular level. It measures the changes in electrical properties of body tissue before the tissue becomes fully cancerous, and thus may predict the formation of tumors.<sup>3,4</sup> Electrical impedance tomography (EIT) is a technology that uses bioinformation to visualize conductivity distribution and changes anywhere that the structures of tissue lesions show no changes, and thereby accomplishes the function of imaging them.<sup>5,6</sup> However, a major challenge in electrical impedance measurement is accuracy of data capture. Commonly, researchers address this by improving the electrode model, enhancing the function of the system circuit, and changing the reconstruction method for the visualization. The signal-to-noise ratio from biological tissue is low. This is a fundamental problem for signal processing. With the development of molecular imaging and biomedical nanotechnology, various nanoscale sensitizers have been developed. Many imaging tools, such as MRI, CT, and ultrasound, use sensitizers to increase signal strength and improve diagnostic accuracy and results.<sup>9,10</sup> Accordingly, we propose a specific sensitizer that could play an important role in EIT. We attempt to use the sensitizer to more clearly distinguish

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between healthy and lesion tissues' electrical characteristics, to improve the quality of EIT imaging and realize more successful application of EIT to clinical diagnosis.

In this study, we describe an approach for enhancing EIT image quality by using nanoparticles. The approach is characteristic of studies on the application of nanomaterials in the biomedical field, specifically by changing tissue impedance with nanoparticles for their extreme electrical properties, as used in physics investigations. It has been reported that the fluorescence, adsorption, and magnetic properties of nanoparticles have been applied to improve the sensitivity of diagnostic medical examinations.<sup>11-13</sup> We introduce a novel method to increase the detectable differences between normal tissues and tumors in a convenient, fast, low-cost, and minimally invasive way. Furthermore, the approach could similarly provide targeted sensitizers for the different infiltration locations of tumors. We propose that the method described here can be used for the early diagnosis and investigation of superficial cancers such as skin cancer and breast cancer.

## Principle and theoretical demonstration

### Mathematical model

The method of bioelectrical impedance measurement involves measuring the potential ( $\Phi$ ) on the body surface while injecting a small safe electrical current into the human body through electrodes to get the impedance information indirectly. Concurrently, an electromagnetic field is formed in the active area. The mathematical model for such a problem is the following Laplace equation and boundary conditions:<sup>14</sup>

$$\nabla \cdot \sigma \nabla \Phi = 0; \quad (1)$$

with a forced boundary condition:

$$\Phi = \Phi_0; \quad (2)$$

and with a Neumann boundary condition:

$$\sigma \frac{\partial \Phi}{\partial n} = -J, \quad (3)$$

where  $\sigma$  is the conductivity,  $\Phi_0$  is the boundary potential, and  $J$  is the injected current density.

Considering that finite element method (FEM) has the advantage of building a model for an object in any shape and of handling inhomogeneous material properties; it is adopted here to solve the EIT's problem mentioned above.

The equivalent variation of the Laplace formula (Equation 1) is:

$$F(\Phi) = -\frac{1}{2} \int_v \Phi \nabla \cdot \sigma \nabla \Phi dv = \min. \quad (4)$$

when the sensitizer is injected into tissue, the conductivity  $\sigma$  changes. We put  $\sigma'$  into Equation 4 to replace it:

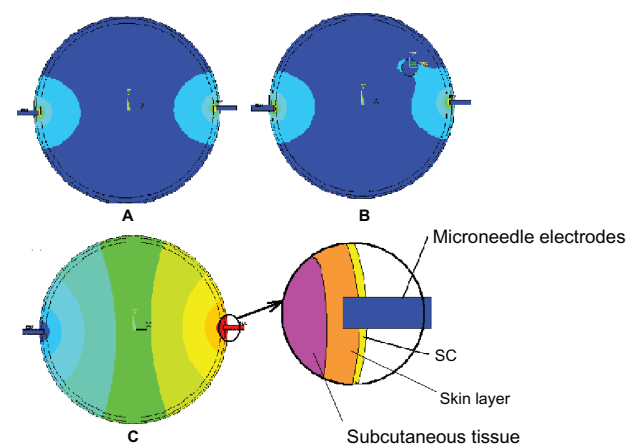
$$F(\Phi) = -\frac{1}{2} \int_v \Phi \nabla \cdot \sigma' \nabla \Phi dv = \min \quad (5)$$

$$\sigma' = \frac{k_1 \sigma + k_2 \sigma_s}{2}, \quad (6)$$

where  $\sigma_s$  is the conductivity of the sensitizer, and  $k_1$  and  $k_2$  are the size weights of the tissue and the additive amount of sensitizer. It is obvious that the potential ( $\Phi$ ) changes after  $\sigma$  is changed.

### Simulation and analysis

We used finite element analysis software ANSYS (v 9.0; ANSYS Inc., Canonsburg, PA, USA) to perform electromagnetic field (EMF) analysis of the impedance measurement. We considered two spherical EMF models. One was the model without tumor, shown in Figure 1A, and another was with tumor in the subcutaneous tissue, shown in Figure 1B. The organism body is simplified in the models, consisting of three layers: the outer skin (the stratum corneum [SC]) with high impedance, the skin layer, and the subcutaneous layer in which foreign matter is embedded. In Figure 1, microneedle electrodes are designed to penetrate the skin layer through the SC, which is composed of living cells that predominantly consist of liquid and is an electrically conducting tissue

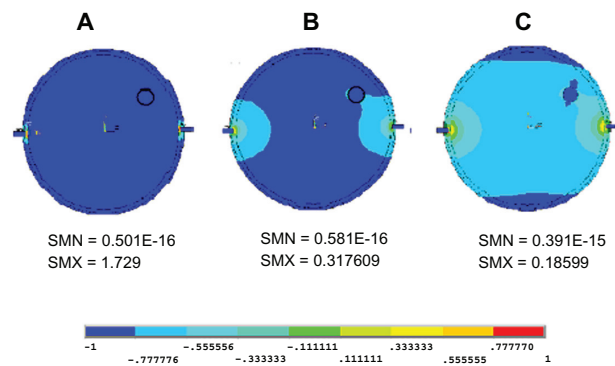


**Figure 1** The solution of electrical field strength. (A) is the solution of the model without a tumor; (B) is the solution of the model with a round tumor in the tissue; (C) is the electric potential of the degree-of-freedom solution. **Abbreviation:** SC, stratum corneum.

comparable to an electrolyte, in order to reduce the measurement uncertainty due to the high impedance of the SC. Figure 1C shows the electric potential of degree-of-freedom solution. The excitation voltage imposed in the model is 1 V. In Figure 1C, we can see that the solution of the electrical field distribution can be obtained by ANSYS software. Compared with Figure 1A, Figure 1B shows cancerous tissue is distinguishable from normal tissue in the electric field pattern due to its difference in electric properties from normal tissue.

The potential distribution is the most important data used for image reconstruction in EIT. Based on the theoretical demonstration above, the potential varied with the resistance change. In our EMF simulation, three kinds of materials with different electrical properties were considered as sensitizers injected into normal tissue to change its conductivity. The three substances were ultra-pure water, normal saline, and gold nanoparticles. Ultra-pure water will enhance the impedance of tissue due to its high conductivity ( $5.5 \times 10^{-6} \text{ S} \cdot \text{m}$ ), and normal saline will increase the conductivity of tissue, as it is rich in  $\text{Na}^+$  and  $\text{Cl}^-$ . We view gold nanoparticles as good conductors with low conductivity. Figure 2 shows the electrical-field model's simulation results after the different sensitizers were added to biological tissue. Here, we suppose they can be uniformly distributed in tissue and that the final conductivity can be obtained by Equation 6.

Shown in Figure 2, the electric field distribution clearly changed with the sensitizers. In particular, the ultra-pure water and nanoparticles deeply influenced the electrical properties of both normal and cancerous tissue. This result shows it is possible to improve the diagnostic accuracy rate by using the sensitizers.



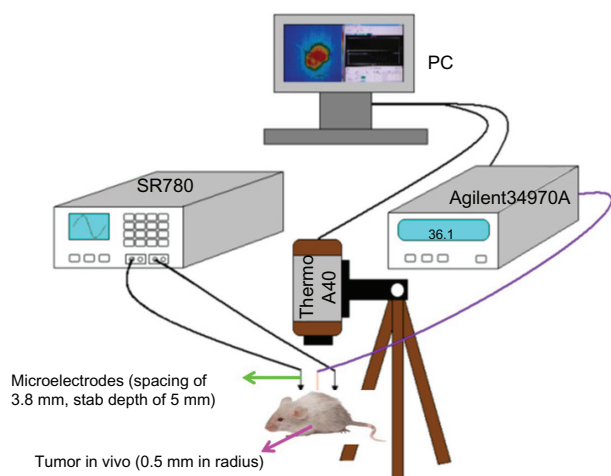
**Figure 2** The sensitizing effects of different subjects. (A) is the EMF distribution of the ultra-pure water model; (B) is the EMF distribution of the normal saline model; (C) is the EMF distribution of the gold nanoparticle model.

**Abbreviations:** SMN, solution minimum; SMX, solution maximum; EMF, electromagnetic field.

## Proof-of-concept experiment

We performed electric impedance measurement experiments in vivo of mice with tumors to confirm numerical results. The experimental system (Figure 3) consisted of a user-interface computer, a dynamic signal analyzer with two measurement channels (SR780), microelectrodes, and the temperature-monitoring equipment. As the electrodes penetrated the outermost layer of skin, the excitation source played a direct role in the subcutaneous tissue. This direct incentive and the sensitizers in this experiment may cause changes in the heat of the subcutaneous tissue. Based on this conjecture, real-time temperature measurements using thermocouples and the infrared thermal-imaging analysis were used to clarify the thermal changes.

The mice in the experiments were inoculated with tumors at their right armpits, and these locations were injected with the same volume of the sensitizers described. We measured the signal at 50 kHz, at 25°C. Sensitizers in this experiment were ultra-pure water, normal saline, and nano-TiO<sub>2</sub> (which has electrical conduction properties similar to those of nanogold). Laboratory mice were female BALB-C mice, aged about 6 to 8 weeks, and purchased from the Laboratory Animal Platform of Tsinghua University, Beijing, China. The animal experiment was approved by the Ethical Committee of Tsinghua University, Beijing, China. First, the breast cancer model in mice was built. EMT60 breast tumor cells were provided by the Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Beijing, China. We cultured the cells in an RP-MI 1640 serum medium containing 10% fetal bovine, and kept them in a 5% CO<sub>2</sub> incubator at 37°C. The 0.25% trypsin and PBS were used for passage. First, some mice were inoculated with diluted breast cancer cells cultured in vitro, beneath the skin of the right axilla. When the tumor size grew to 1.5–2.0 cm in diameter, the mice were killed through neck dislocation, and tumor tissues were taken out. Well-grown masses were selected and ground to make a single cell suspension. We counted the cancer cells under a microscope and adjusted its concentration to  $9 \times 10^4/\text{mL}$ . This solution was injected into mice under the axillary, with 0.2 mL for each mouse. These tumors, with good growing conditions and a short growth cycle, were grown to about 0.5 mm in radius as suitable experimental models, and then the breast cancer model was completed. Each mouse received 0.02 mL of sensitizer; measurements before injecting sensitizers were treated as the control group. The experimental results are shown in Figure 4. The TiO<sub>2</sub> nanoparticles used for the present experiments are commercially available and were directly purchased from Nachen S&T Ltd, Beijing, China. The 0.02 g/mL TiO<sub>2</sub> nanoparticle aqueous solution was injected as the nanosensitizer.



**Figure 3** The schema of the measurement system. The experimental system consists of a user interface computer, a dynamic signal analyzer with two measurement channels (SR780), microelectrodes, and the temperature-monitoring equipment.

The green lines in the graphs represent the original sample without sensitizer at two different orders of magnitude in Figure 4A and B, respectively. The experimental data were collected 30 seconds after the injection of the pharmaceutical. We believe that this was the best time for measurement – by that time the sensitizer had been able to spread evenly in the tissue. The four different color lines in the figures correspond to the impedance of tissues with different sensitizers.

The resulting data were compared to obtain the effects of the sensitizers. Ultra-pure water (UPW) enhanced the impedance of tissue; nano-TiO<sub>2</sub> and normal saline reduced the impedance by different amounts. We selected the experimental data at the 10 kHz frequency level for analysis: the impedance contrast of normal tissue and tumor ( $r = \text{normal tissue impedance/tumor impedance}$ ) were calculated:  $r_{\text{nano}} = 13.3\%$ ,  $r_{\text{original}} = 38.6\%$ ,  $r_{\text{saline}} = 24\%$ , and  $r_{\text{UPW}} = 49.1\%$ . The smaller

the  $r$ , the greater the difference in the impedance of normal tissue and tumor, indicating that the signal could be more easily detected. We saw that nano-TiO<sub>2</sub> could significantly change the impedance of healthy tissue compared to that of the tumor, a crucial factor in enhancing the accuracy of the EIT image.

These results show that the proposed system improved the impedance measurement, giving a higher signal-to-noise ratio for EIT images.

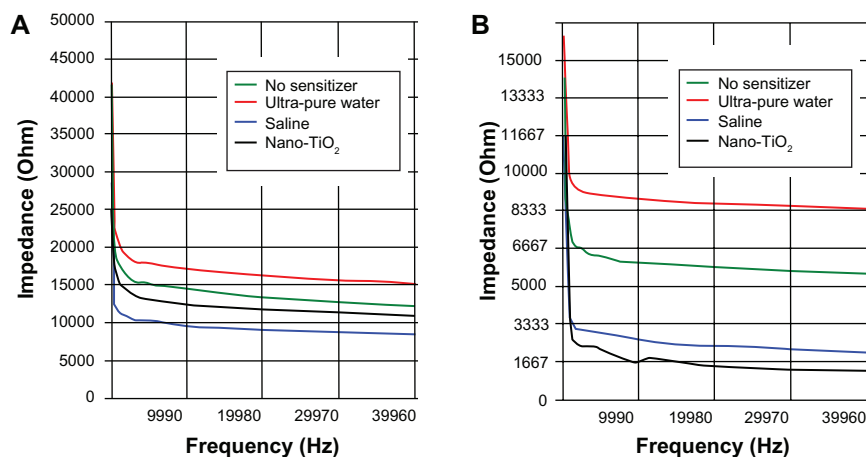
## Discussion

In this work, our approach differed in many ways from traditional methods of enhancing EIT imaging quality.<sup>15</sup> Our methodology used physical methods to change the electrical properties of biotissues to make it easier to obtain useful information effectively from noise. Following the examples of other imaging methods, such as CT, MRI, and ultrasound, we utilized the capability of certain substances (which we call sensitizers) to increase the impedance gap between the normal tissue and tumors.

We tested our method for impedance change with a mathematical-model-based simulation and animal experiments that demonstrated that the nanoparticle sensitizer could be used to enhance this type of measurement. The materials we considered influenced the electrical impedance of healthy tissue and of tumor tissue to different degrees.

## Tumor size

We wish to improve the survival rate of tumor patients by diagnosing the tumors at an early stage. Similar sets of validation simulations were conducted on tumors of different radii. There was a spherical tumor with 2 mm radius in our simulation model, located in the subcutaneous tissue.



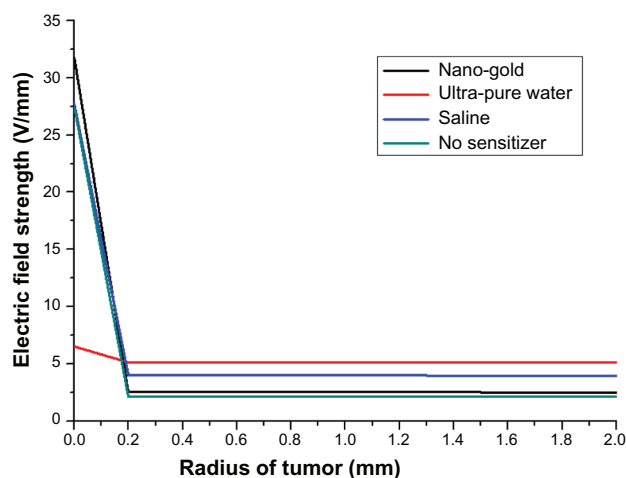
**Figure 4** The impedance of tumor and normal tissue with different sensitizers. (A) shows the experimental results for the tumor into which were injected sensitizers; (B) shows the experimental results of healthy tissue with sensitizers.

The distributions of the electric field strength in the models are shown in Figure 5 with the numerical simulation of a noise-free situation.

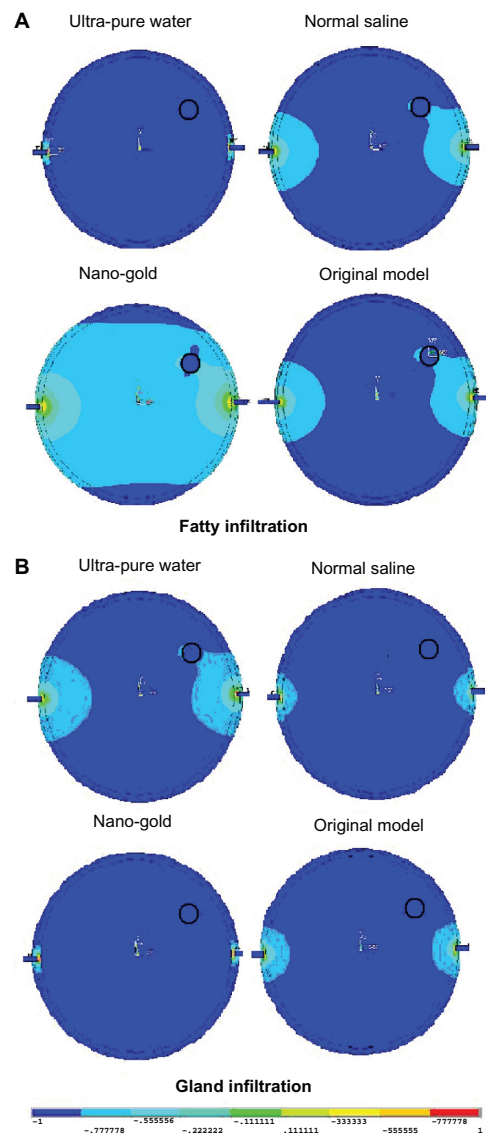
A tumor radius of 0.2 mm can be measured by using this method. Ultra-pure water narrowed the impedance of normal and abnormal tissue significantly, while nanogold had performed well at increasing the difference, as also shown by the experiments. Based on the results of the numerical simulation analysis and experiments, nanoparticles with low conduction can be used in EIT when the tumor is located in lower-impedance tissue, such as subcutaneous layers, glands, and muscle, to enhance accuracy.

## Tumor location

A prerequisite of EIT is the obvious differences in electrical characteristics between tumors and healthy tissue.<sup>16</sup> However, there are various types of normal tissue, such as glands, skin, muscle, and fat. They also have different electricity-conducting capacities. Therefore, the measurement results must be different due to different tumor-infiltrating locations. We hope that special sensitizers for different tumor-infiltrating locations can enlarge the discernible gap between normal and abnormal tissue, thus enhancing image quality. Figure 6 shows the differing electric field analysis results for different sensitizers for different tissue infiltrations. We selected the fatty infiltration model and the gland infiltration model – the tumors in fat tissue or in gland tissue. Figure 6 shows how the effect of nanogold as the sensitizer is better than other sensitizers or the original model (ie, with nothing added before measurement) in the fatty infiltration model. However, in the gland infiltration model, the results were different, and the effect of ultra-pure water was better than the other sensitizers we used. When we used the sensitizer to enhance electrical impedance detection,



**Figure 5** Different influences of sensitizers for different tumor sizes.



**Figure 6** Different influence of sensitizers for different infiltration tissues. (A) is the fatty infiltration model; (B) is the gland infiltration model.

we needed to choose different sensitizers according to which objects were being observed.

## Sensitizer-material safety and further development

Undeniably, biological diagnostic detection with nanoparticles has been under considerable development and shows great potential. But there are still some issues to explore. Safety is the most important characteristic of medical materials. We look forward to the chosen sensitizers' both achieving maximum enhancement of EIT imaging quality and meeting criteria of biological safety evaluations. Materials science and biomedical medicine are becoming more and more closely linked. The biological applications of nanomaterials have achieved much,

developed significant momentum, and shown huge potential for further development. However, the application of nanomaterials is still very limited, especially in the biomedical field; large numbers of clinical trials are needed for confirmation of the results of animal experiments. Nanomaterials are easy to move in the biological body's rapid metabolism due to their exceptionally small size, which can reduce the harm from side effects. Using nanoparticles as sensitizers in EIT technology not only increases the range of nanomaterial applications, but also improves EIT safety and effectiveness in the clinical setting.

## Conclusion

In this study, a new concept of sensitizers for EIT has been proposed for improving the signal-to-noise ratio in electrical impedance measurements. To validate the effects of different sensitizers, finite element analysis and animal experiments were conducted. We compared normal saline, nanoparticles, and distilled water as sensitizer materials, and showed that different materials have obviously different effects on the electrical properties of tissue. In addition, we believe that using nanoparticles as sensitizers in some tumor locations can more effectively enhance the quality of EIT images. Nanosensitizers have the potential to improve the accuracy of EIT technology and thus make the dream of applying EIT technology to early tumor diagnosis come true.

We believe the application of nanomaterial sensitizers to electrical impedance measurements is both a promising new technology for decreasing diagnostic uncertainty and a feasible way to attempt electrical impedance imaging in the biomedical field. Overall, more experimental and theoretical analyses are needed to demonstrate their effects in clinical applications.

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## Disclosure

The authors report no conflicts of interest in this work.

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