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# Decoding the Ice-Water Energy Paradox in the DW-MRI Phantom for Tumors: Targeting Thermodynamics, Kinetic and Structural Molecular Mechanisms Commentary

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**Abstract** Diffusion-weighted imaging (DWI) and the apparent diffusion coefficient (ADC) are diagnostic tools widely used to detect solid tumors and monitor therapy response. The ice-water calibration phantom has led to more accurate and reproducible DWI and ADC diagnostics by reducing intra- and inter-vendor dispersion, independent of field intensity (1.5 - 3 Tesla). The ice-water calibration phantom method is based on the idea of thermal equilibrium. The discovery of exclusion zone (EZ) may deeply change such understanding. This paper highlights how thermodynamic, structural and kinetic results of the EZ paradigm may help to explain the ice-water energy paradox and cement our understanding of the ice-water phantom and its application in the diagnosis of solid tumors and other complex diseases.

***Keywords:*** *exclusion zone, solid tumors, DWI, ADC*

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## 1. Introduction

Diffusion-weighted imaging (DWI) and the apparent diffusion coefficient (ADC) are diagnostic tools widely used to detect solid tumors and monitor therapy response. DWI uses the motion of water (i.e., water protons) to gauge tissue integrity [1], whereas ADC helps to elucidate diffusion and relaxation effects over image contrast, accounting for the fact that diffusion in biological tissues is complex and reflects different mechanisms [2,3]. DWI and ADC spare patients of the deleterious effects of ionizing radiation, allow precise diagnoses without contrast–even of small mesenchymal or epithelial tumors–and provide functional insights for interpreting tumor metabolism (i.e., metabolomics) [4].

A breakthrough by Chenevert and others based on the ice-water calibration phantom has led to more accurate and reproducible DWI and ADC diagnostics through reduced intra- and inter-vendor dispersion, independent of field intensity (1.5 - 3 Tesla). [5,6] The method, which has been very successful, is based on the idea of thermal equilibrium. The discovery of exclusion zone (EZ) may deeply change such understanding. The aim of this paper is to highlight how thermodynamic, structural and kinetic results of the EZ paradigm may help to explain the ice water energy paradox and cement our understanding of the ice-water phantom [7] and its application in the diagnosis of solid tumors and other complex diseases [8,9].

## 2. The Ice-Water Phantom

As described by Chenevert, "the method for preparing the ice water phantom consists of filling five tubes with distilled water (four at phantom corners and one in the center) as the diffusion medium standard, and one tube with a sucrose solution (9 gm sucrose/30 mL water) to provide diffusion contrast. [5] The six tubes are filled and sealed at phantom fabrication using a two-step process: (step 1) prime the phantom with ice water for 10 min for an initial rapid cool-down of the water tubes from room temperature, and (step 2) add ice to replenish the relatively large volume of ice melted during step 1, then let the phantom equilibrate for an hour before scanning. Once filled and equilibrated, the ice-water bath surrounded the measurement tubes with a temperature controlled, high thermal capacity environment" (Figure 1).

It is proposed that, "once thermal equilibrium is achieved, the ice water-based phantom offers inherent thermal control over an extended interval (several hours) to test/calibrate one or multiple MR systems. [6] For optimal accuracy in diffusion determination, the temperature of a fluid needs to be determined and controlled as diffusion coefficients are known to vary by 1.7-3.2%/°C near room temperature". At thermal equilibrium just above 0°C, the diffusion coefficient of water is known to be 1.1 x $10^3$ $mm^2/s$ [6].

## 3. The Ice-Water Energy Paradox

Interestingly, water does not always freeze at 0°C. In fact, pure water at sea level, under standard conditions, can sometimes freeze well below 0°C. Such water, often referred to as "super cooled", exhibits one of the many unusual properties, or quirks, of water that have been increasingly explored over the last decades. Principal among these is the quasi-crystalline state of water known as exclusion zone (EZ) described by Pollack [7].

Because of its unique properties, it has been argued that the EZ represents a fourth phase of water. The EZ consists of an ordered array of water molecules, which can form on hydrophilic surfaces and surrounds suspended particles or dissolved molecules. The EZ is energy-dependent: it grows with certain bands of electromagnetic radiation, notably the infrared (IR) band. The EZ has a negative charge and has been measured to release up to 70% of absorbed energy, which makes it a highly efficient biological battery. [7] As discussed below, it has been suggested that freezing may follow an EZ-to-ice transition. The latter would help explain an obvious ice water energy paradox: how can the increasing order needed for ice crystal formation require the removal, instead of the input, of energy? (Figure 1).

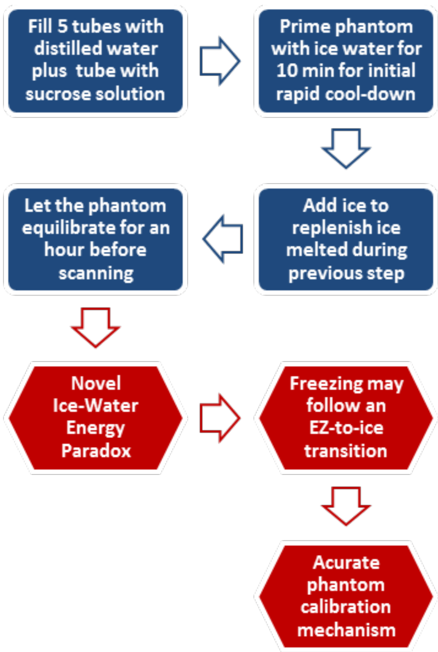


**Figure 1.** Diagram of the Ice Water Phantom Method and Exclusion Zone (EZ) Paradigm

## 4. The Exclusion Zone Paradigm

To date, scientists have explained freezing using the concept of thermal motion. The idea is that as temperature decreases, so does thermal motion. Thus, a lower temperature allows water to self-organize into ice. According to this view, higher molecular order (ice crystals) requires energy withdrawal contrary to thermodynamic expectations. Pollack and his group have recently provided an alternate explanation based on structural, thermodynamic and kinetic results that support an EZ-to-ice transition.

Structurally, both the EZ and ice comprise stacked honeycomb sheets. [7] As explained by Pollack, "during an EZ-to-ice transition, protons and planes shift because ice planes are not flat because of local attractions and repulsion". [7] "The protons insinuate themselves between any other juxtaposed oxygen pair (on adjacent planes). In this way, a positive charge glues two negative atoms. That solidifies EZ into ice". [7] "This makes sense energetically as the EZ excludes protons. Those protons constitute potential energy: positive charges separated from negative. If protons are allowed to rush back in – neutralizing the negative EZ and thereby creating ice – potential energy would get surrendered. Therefore, energy gets used for converting an ordered structured into an even more ordered structure" [7,10].

Experimental results confirm that EZ forms before ice and that the transition to the latter is accompanied by the expected "proton rush", which has been measured as a change in charge and pH as well as the simultaneous emission of IR characteristic of EZ. [7].

## 5. Conclusion

The above EZ investigations are leading to a new state of the art in water research with applications to cancer and other complex diseases. They further provide a novel window towards the understanding of the molecular mechanisms implicit in the ice-water phantom and the increased precision that it allows for the early detection of tumor response, and other diagnostic uses. [11,12,13] while positive results have been reported with other methods [10], a more comprehensive mechanistic basis for the ice-water phantom will strengthen DWI and water ADC as biomarkers capable of predicting early tumor response. Such understanding will substantiate the already high reliability in the measurement of tumor metabolism, [14,15,16] which compares favorably versus Positron Emission Tomography (PET) or (hybrid) PET/CT, as reported in the diagnosis of solid tumors of small size and varied locations. [17] Increased DWI and water ADC reproducibility and accuracy may save lives and reduce treatment and diagnostic costs. Therefore, it is essential to ascertain the role of the EZ in the freezing process and its potential implications for the ice water phantom.

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