Received: 15 August 2017 | Revised: 4 March 2018 | Accepted: 12 March 2018

DOI: 10.1111/jfs.12473

ORIGINAL ARTICLE

WILEY Journal of Food Safety

Rapid detection of *Salmonella* spp. using magnetic resonance

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Abstract

The globalization of the world's food trade calls for rapid and accurate detection of foodborne pathogens to ensure safety of foods for human consumption, to prevent outbreaks and management of foodborne infectious diseases. Currently, commercial detection methods for pathogenic microbials require multiple days for sample-to-answer results. In this study, we demonstrated a highly sensitive and rapid detection of a microbial pathogen using Molecular Mirroring (M^2) technology and Lab-in-the-Box system based on nuclear magnetic resonance that works rapidly and efficiently for the detection of *Salmonella*. This technology detected *Salmonella* at 1 cfu/reaction in water. In tuna, the M^2 technology detected 1 cfu/g with 5 hr of enrichment and analysis with a T_2 signal of 342 ms. In addition to sensitive detection and minimal enrichment, this methodology detected pathogens from inhibitory mediums. Therefore, this technology can be widely applied to other fields such as environmental monitoring, public health and safety, national security, and medical diagnosis.

Practical applications

The combination of molecular biology and nuclear magnetic resonance technology represents a novel, rapid, sensitive, and highly specific methodology for the detection of *Salmonella* spp. in tuna compared to standard conventional methods. Practical applications of the M^2 technology have been tested with human samples, animal samples, and food samples to detect microbial pathogens before and after food processing, thus is ideal to protect public health and to ensure food safety. Furthermore, this biosensor analytical technology can be applied to almost any medium or target of interest in the field of food safety, clinical diagnostics, and biosurveillance.

1 | INTRODUCTION

Due to the globalization of the world's food trade, food has become a major pathway for human exposure to potential pathogenic microbials that enter at many points along the value chain (Godfray et al., 2010). Food trade increased in value from 438 billion USD in 1998 to 1.06 trillion USD in 2008, growing faster than production itself (Ercsey-Ravasz, Toroczkai, Lakner, & Baranyi, 2012). Thus, tracking and detecting microbials especially pathogenic bacteria in foods back to their sources pose challenges to producer, processor, distributor, and consumer of food alike. In addition, clinicians and epidemiologists are frequently confronted with diagnostic and treatment uncertainty of patients with potential foodborne infectious diseases at the point of care.

Rapid and accurate detection of foodborne pathogens is essential for public health biosurveillance to prevent foodborne infections and ensure the safety of foods (Cabello, Godfrey, Buschmann, & Dölz, 2016; Collignon, 2013; Devaraj & Weissleder, 2011; López-Campos, Martínez-Suárez, Aguado-Urda, & López-Alonso, 2012; Mangal, Sangita, Satish, & Ram, 2015). Detection methods of microbials have improved over time. Generally speaking, culture-based tests are being substituted by faster and more sensitive culture-independent diagnostic tests such as antigen-based assays and Polymerase Chain Reaction (PCR) panels (Huang et al., 2016). However, these tests are used mainly in the public health laboratories not readily available for practitioners in the industry and clinical fields (Huang et al., 2016).

Salmonellosis is one of the most common and widely distributed foodborne diseases worldwide. It is caused by the *Salmonella* bacteria and is associated with significant morbidity and mortality (Alakomi & Saarela, 2009; Chalker & Blaser, 1988; Coburn, Grassl, & Finlay, 2007). Every year, it is estimated that 1 out of 10 individuals become infected due to *Salmonella*, resulting in 33 million deaths per year (World Health Organization (WHO), 2016). The most recent analysis of epidemiologic data on foodborne disease outbreaks in the United States indicated that *Salmonella* was the most common bacterial etiologic agent

resulting in foodborne illness, accounting for 140 (57%) of the outbreaks attributed to bacteria (Centers for Disease Control and Prevention [CDC], 2014). This emphasizes the importance of *Salmonella* monitoring and testing (Rodríguez-Lázaro et al., 2007). However, based on Food and Drug Administration (FDA) standards to detect 1 cfu in 25 g of sample, the assay requires 5 days for isolation and confirmation (Naravaneni & Jamil, 2005; Swaminathan & Feng, 1994).

Menon Biosensors, Inc. has developed a rapid and portable nuclear magnetic resonance (NMR) biosensor system (Lab-in-the-Box, Menon Biosensors, Inc., San Diego, CA) and bioassays to rapidly detect *Salmonella*, using its core Molecular Mirroring (M^2) technology. The M^2 technology is a novel and patented approach in which iron nanoparticles are conjugated with target-specific biomarkers that mirror the target's DNA. Upon reaction, a DNA-nanoparticle complex is formed, leading to a unique magnetic resonance signal. The signal is obtained using the biosensor by measuring spin–spin relaxation time (T_2), which is correlated with the presence or absence of microorganism DNA (Menon, Newman, & Chan, 2013).

The M^2 technology was initially funded under the U.S. Department of Homeland Security and Department of Defense for biodefense applications for autonomous environmental monitoring of pathogens at key public facilities that are likely to be terrorist targets such as airports and railway stations (US Government Contract HSHQPA-05–9-0039, HDTRA1–09-C-001). Under this government contract, the system was tested and validated in the field at the Boston Metro railway and the Edgewood Chemical Biological Center (U.S. Army) to detect *Bacillus anthracis*, *Bacillus thuringiensis*, *Yersinia pestis*, and *Francisella tularensis* in aerosol and water samples in the presence of environmental interferents such as humic acid, fuel, ash, dust, and chelated iron. During validation tests, the system demonstrated 100% accuracy in blind sample detection of these targets.

In efforts to further demonstrate the capability of the M^2 technology, difficult clinical mediums were used for analysis (Yang et al., 2017). Due to the complex chemical composition and variability of blood and stool samples, both blood and stool have increased levels of assay inhibition, in comparison to other clinical mediums, such as urine (Bollard, Stanley, Lindon, Nicholson, & Holmes, 2005; Deda, Gika, Wilson, & Theodoridis, 2015; Jaschek, Gaydos, Welsh, & Quinn, 1993; Widjojoatmodjo, Fluit, Torensma, Verdonk, & Verhoef, 1992). However, the M^2 technology showed high sensitivity and specificity to detect pathogens in stool and blood (Yang et al., 2017). After developing detection methods for inhibitory samples, the detection system was validated by third-party institutions, which included assays for toxigenic *Clostridium difficile* in blood and stool and Early Mortality Syndrome-causing *Vibrio parahaemolyticus* in shrimp tissue (Yang et al., 2017).

Over the last 50 years, recent advancements have led to development of reliable culture-based techniques to detect bacterial foodborne pathogens, which are considered the "gold-standard" (Betts & Blackburn, 2009; Dwivedi & Jaykus, 2011). However, culture-based detection methods are often time-consuming, taking up to several days, due to the need for preanalytical sample processing including enrichment culture followed by isolation and biochemical and/or serological identification (Dwivedi & Jaykus, 2011; López-Campos et al., 2012; Mangal et al., 2015; Vunrcrzant & Pllustoesser, 1983). In efforts to decrease sample-to-answer time, this study demonstrates a rapid, 5-hr NMR-based approach to detect *Salmonella*, requiring minimal preanalytical sample processing (~4.5 hr) and rapid NMR detection (~0.5 hr), while maintaining high sensitivity.

2 | MATERIALS AND METHODS

2.1 | Isolation and identification of *Salmonella*

Salmonella used in this study was obtained from BHLN Technical Services, LLC (B. Olson, personal communication, June 3, 2016; BHLN Technical Services, LLC is a foreign company representative office and subsidiary of internationally renowned seafood company, Bumble Bee Seafoods. Based in Denpasar, Bali, the office coordinates operations on behalf of assignments form head office in US, while also aims to support sustainability of Indonesia fisheries). A single strain was isolated and cultured overnight in gram-negative broth at 37°C. The presence of *invA* gene was confirmed by PCR and sequencing. The cell stocks were quantified by cell-counting method using xylose lysine deoxycholate agar plates.

2.2 | Enrichment of tuna samples

Raw, packaged, *Salmonella*-negative tuna steaks were obtained from Bumble Bee's Indonesia processing plant. Tuna steaks were treated by Bumble Bee using a patented preservation process prior to packing to preserve freshness and prolong shelf life (Olson and Brinmade, 2004). Under sterile conditions, 5 g of tuna steak was added to 45 ml of Luria Broth in 250 ml baffled Erlenmeyer flasks. Flasks were then inoculated with varying concentrations of *Salmonella* and incubated at 37°C with shaking at 250 rpm. Samples were drawn after 4 hr of enrichment for cell extraction and NMR analysis.

2.3 | *Salmonella* extraction

For the *Salmonella* extraction, 25 μl of proprietary *Salmonella* capture beads were added to 700 μl aliquots of tuna enrichment broth and incubated for 30 min at room temperature with agitation on a RotoFlex shaker (Milian USA, Gahanna, OH) at 30 rpm. Samples were then placed in a magnet for 1 min to pull the beads to the side of the tube, then the supernatant was removed and discarded. Two hundred fifty microliters of wash buffer, 1× phosphate-buffered saline (PBS) pH 7 (Fisher BioReagents), was added to the beads. After briefly vortexing, the sample was placed in a magnet for 1 min and the supernatant was removed. The wash step was repeated twice. After washing, 50 μl of elution buffer, 1× Tris-ethylenediaminetetraactetic acid (EDTA) buffer pH 8 (Fisher BioRegents), was then added to the tube and heated at 95°C for 3 min. Tubes were placed back in the magnet to separate the beads and the supernatant was retained for amplification and NMR measurements.

2.4 | Nucleic acid amplification

The nucleic acid amplification targeted the *invA* gene in *Salmonella* strains, which is highly conserved among all *Salmonella* serotypes

(Galán, Ginocchio, & Costeas, 1992; Levin, 2009; Rahn et al., 1992). The *invA* gene detects all Salmonella strains while showing no detection in non-Salmonella strains (Rahn et al., 1992). Target DNA was amplified directly in water samples or whole-cell extracts by a rapid thermocycling reaction using primers targeting the *Salmonella* spp. *invA* gene (InvA1380F: 5′-GA GCG GAG GAC AAA TCC ATA-3′, InvA1671R: 5′-AT GCC CGG TAA ACA GAT GAG-3′). The nucleic acid amplification master mix contained 0.3 μM of the respective primers, 2 mM of $MgCl_2$, 200 μM of dNTPs, 5 μl of template, and 2 U of DNA polymerase in a total of 25 μl. Amplification was performed in the Lab-in-the-Box with the following cycling conditions: 40 s at 98 °C, 40 cycles of 6 s at 98 °C, and 5 s at 67 °C, and a 4 °C hold.

2.5 | NMR measurement

After nucleic acid amplification, a 100 μl mixture containing amplified product, streptavidin-coated iron nanoparticles, and phosphate-buffered saline was measured in the Lab-in-the-Box biodetector to obtain the baseline NMR T_2 signal. The tubes were placed in the Lab-in-the-Box incubator for 15 min where nanoparticles formed binaries leading to signal amplification. The mixture was then measured again in the NMR system (final T_2 signal). The resulting dT_2 was obtained by subtracting the baseline signal from each final T_2 measurement, and was used for the plots. All measurements, that is, baseline and final T_2, were performed in duplicate and averages of duplicates were used for calculations. When no target is present, uniform distribution of nanoparticles occurs resulting in lower dT_2. When target DNA is present, binary complexes of nanoparticles are formed resulting in higher dT_2.

Positive (*Salmonella enterica* subsp. *enterica* genomic DNA, ATCC 13311D-5) and negative (water) controls were included.

3 | RESULTS

3.1 | Sensitivity of nucleic acid amplification for *Salmonella* detection

The sensitivity of the *Salmonella* assay was determined by performing nucleic acid amplification followed by NMR measurements with predefined *Salmonella* doses. *Salmonella* assay showed detection at 1 cfu/reaction (Figure 1). The negative control had an average value of 1.2 ms, and the highest signal was at a dose of 10^4 cfu/reaction with a value of 771 ms. After statistical analysis, both T_2 values for 1 and 10 cfu/reaction produced a p value of <0.05, suggesting a significant difference in detection signal between 0 cfu/reaction to 1 cfu/reaction and between 1 cfu/reaction to 10 cfu/reaction; however, there was no significant difference for 10^2, 10^3, 10^4, or 10^5 cfu/reaction. The combination of both nucleic acid amplification and NMR showed high sensitivity to detect 1 cfu/reaction consistently and demonstrated quantitative capability to differentiate between 0, 1, and 10 cfu/reaction.

3.2 | Detection of cells in tuna with enrichment

The established *Salmonella* assay was applied to processed samples from 4-hr enriched samples with tuna and specified *Salmonella* concentrations. Based on Figure 2, the limit of detection was determined at 1 cfu/g. The lowest detected dose of 1 cfu/g had an average T_2 signal of 364 ms, while the highest signal was an average 817 ms at 100 cfu/g. There was a statistical difference between doses of 1 cfu/5g and 1 cfu/g and between 1 cfu/g and 10 cfu/g; however, there was no statistical difference between 0 cfu/g and 1 cfu/5g. The results were confirmed with three separate replicates.

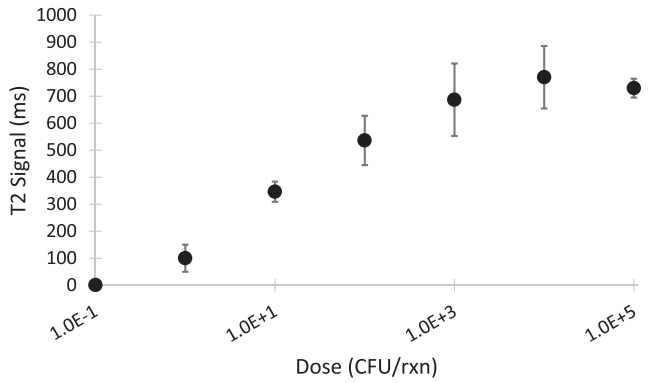

FIGURE 1 A dose-response curve of *Salmonella* using NMR analysis. Nucleic acid amplification and NMR were performed in triplicate. The *y*-axis shows the T_2 signal in milliseconds (ms). The *x*-axis plots the dose in cfu/reaction. Standard error bars were calculated based on three repeat experiments

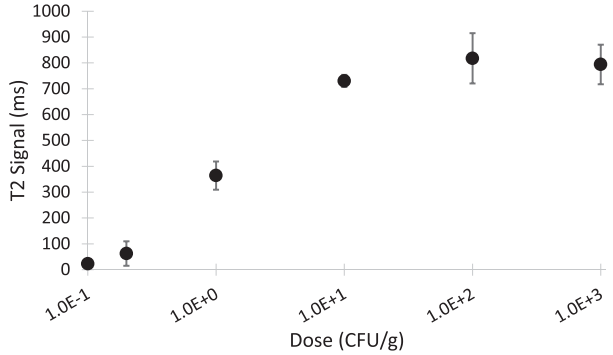

FIGURE 2 A dose-response curve of *Salmonella* using enrichment with tuna. Enrichment, nucleic acid amplification, and NMR measurements were performed in triplicates. The *y*-axis plots the T_2 signal in milliseconds. The *x*-axis indicates initial concentrations of *Salmonella* before enrichment. Standard error bars were calculated based on three repeat experiments

4 | DISCUSSION

In this study, we used the Lab-in-the-Box biodetector which combines a unique NMR detection platform with a rapid nucleic acid amplification to produce a synergistically sensitive assay. All nucleic acid detection methods require a detection platform to analyze and measure product. Many detection platforms have been used, including quantitative culture methods, DNA hybridization, gel electrophoresis, and luminescence, however, these processes either require a large enumeration of product or long incubation times (Alves, Niguma, & de Oliveira,

2015; Betts & Blackburn, 2009; Blodgett, 2010; Mangal et al., 2015; Stannard, 1997; Zhou, Zhong, Long, Han, & Liu, 2014). Alternatively, the M^2 detection platform increases the sensitivity of nucleic acid amplification by utilizing an NMR-based platform technology. As shown in Figure 1, the M^2 *Salmonella* assay has the sensitivity to detect 1 cfu/reaction with high confidence.

Nucleic acid detection is widely used in the food industry and public health laboratories. In the current study, *Salmonella* was detected at a level of 1 cfu/g of tuna with as little as 4 hr of enrichment time using the M^2 technology. Though FDA regulations require a higher sensitivity of 1 cfu in 25 g, commercial kits and FDA-approved methods for *Salmonella* detection are time-consuming, requiring more than 24 hr and up to 72 hr (Vunrcrzant & Pllustoesser, 1983), and may not elucidate problems rapidly enough to allow for appropriate remediation (Mangal et al., 2015). The M^2 technology for *Salmonella* detection is potentially more useful for rapid treatment.

Over the past decade, new NMR-based detection platforms have been proposed (Devaraj & Weissleder, 2011; Dias, Hussain, Marcos, & Roque, 2011; Haun, Yoon, Lee, and Weissleder, 2010; Holford, Davis, & Higson, 2012; Koh, Hong, Weissleder, & Lee, 2009; Kuila et al., 2011; Liu, Gao, Ai, & Chen, 2013; Tassa, Shaw, & Weissleder, 2011). In comparison to other NMR technologies, Menon's signal levels are more robust due to the larger T_2 signals present. Comparable NMR-based detection platforms have a low T_2 signal, usually below 100 ms (Liong et al., 2013; Shelby et al., 2016). With the Lab-in-the-Box biodetector, we observed a 4:1 signal to noise ratio in the T_2 signal across a 5-log dose range compared to competing NMR technology in which a 1.6:1 signal to noise ratio is observed in the same dose range (Liong et al., 2013; Menon et al., 2013; Shelby et al., 2016). This shows the robustness of the M^2 assay in differentiating between positive and negative samples.

In previous studies, the M^2 assay displayed rapid and specific detection in human stool and blood (Yang et al., 2017). Knowing the ability of the M^2 assay to detect pathogens in complex, inhibitory mediums, tuna was chosen as the matrix in this study. Tuna has a high-fat content leading to difficult processing and analysis (Basit, 2009; Chapela et al., 2007). However, the high sensitivity demonstrated by the M^2 *Salmonella* assay to detect 1 cfu/g provides confidence to analyze samples in a variety of inhibitory mediums.

In comparison to current standard methods of detection, NMR technology in pathogen detection is a relatively new field. Through the continual development of the M^2 technology and Lab-in-the-Box system, we have confidence to increase the sensitivity to match FDA standards with significantly lower preanalytical processing time. In our future studies, we plan to continue applying the M^2 technology and Lab-in-the-Box to a large variety of pathogens and mediums to show the robustness and sensitivity of the assay in global applications.

5 | CONCLUSION

In conclusion, we have demonstrated a highly specific, sensitive, and rapid method for the detection of a microbial pathogen using NMR. The M^2 technology and Lab-in-the-Box system offer an NMR-based pathogen detection method that works rapidly and efficiently for the detection of *Salmonella*. More importantly, we have shown that the system is capable of sensitive detection with minimal enrichment and in inhibitory mediums, thus providing results within hours rather than days. We believe that this method is an easy and efficient approach for rapid detection of foodborne bacteria that can be made available for practitioners in the food industry. Moreover, the ability for the technology to detect pathogens in inhibitory mediums can also be widely applied to other fields such as for environmental monitoring, public health and safety, national security, and medical diagnosis.

ACKNOWLEDGMENTS

The authors would like to thank BHLN Technical Services, LLC (Denpasar, Bali Indonesia) for providing tuna and strains and Scripps Clinic Medical Laboratory for providing equipment, resources, and facilities. We would also like to thank Bumble Bee Seafoods and Jan Tharp for performing a blind validation of the M^2 technology for *Salmonella* detection.

AUTHORS' CONTRIBUTIONS

All authors were involved in the interpretation of data, writing and reviewing the manuscript at various stages in the research project. PY and CW were responsible for collecting data and designing the *Salmonella* assay. PY, SH, CW, and SM were responsible for the development and maintenance of the M^2 technology. FF significantly contributed to the reviewing and editing of the manuscript.

CONFLICT OF INTEREST

This study was funded by Menon Biosensors, Inc. The *Salmonella* strain and tuna was provided by BHLN Technical Services. Scripps Clinic Medical Laboratory provided facility to handle *Salmonella*. A third-party blind validation was conducted by Bumble Bee Seafoods under the supervision of Jan Tharp, Chief Operating Officer. Bumble Bee and Jan Tharp have no conflict of interest with Menon Biosensors, Inc. The data were collected at Scripps Clinic Medical Laboratory and the corresponding author did not have access to data collection. All authors hold stock in Menon Biosensors, Inc.

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How to cite this article: Yang P, Wong C, Hash S, Fung F, Menon S. Rapid detection of *Salmonella* spp. using magnetic resonance. *J Food Saf*. 2018;e12473. https://doi.org/10.1111/jfs.12473