Several microbubble ultrasound contrast agents (UCA) have been recently introduced to allow imaging blood perfusion in the microvasculature. Microbubbles exhibit strong linear and nonlinear response to incident ultrasonic beams that can be utilized to increase the contrast-to-tissue ratio (CTR). If successful, this will lead to functional ultrasonic imaging methods. This increased interest in UCA imaging has heightened the need for specialized imaging methods for improving both the sensitivity and specificity to the agent. For most microbubble UCAs, the nonlinear behavior of the bubbles led to several imaging methods with improved CTR by rejecting the linear tissue response. These developments have already led to the introduction of specialized imaging methods for UCAs such as pulse inversion (PI) and contrast phase sequence (CPS) imaging. Methods like PI and CPS provide elegant solutions to this problem by utilizing sequences of two or more pulses with specified phase and amplitude relationships. The fundamental tissue component can be cancelled by appropriately combining the echoes from these pulses. Impressive results in a range of significant clinical applications have already been achieved with these methods. However, the goal of imaging very small concentrations of UCA at the microvasculature level has not yet been achieved. This is largely due to sensitivity to motion and loss of signal to noise due to cancellation of the (dominant) fundamental component.

In order to mitigate some of the limitations of multi-pulse imaging, we have investigated the applicability of an input-output system identification model based on the 2nd order Volterra filter (SoVF) to pulse-echo ultrasound. The objective was to develop a robust method to separate the linear and quadratic components from pulse-echo data without the need for multiple transmit pulses. Furthermore, we aimed to establish that the quadratic component contains “all” the sum and difference frequency interactions and not just harmonic interactions. This has the advantage of preserving all the spectral components resulting from the UCA activity throughout the visible spectrum and not limit it to the second harmonic (SH) generation. In the presentation, we describe the SoVF and discuss its applicability to acoustic wave propagation in tissue media. In addition, we describe algorithms for obtaining the coefficients of the linear and quadratic kernels from ultrasound pulse-echo radio frequency (RF) imaging data. Finally, we give illustrative examples from imaging experiments of UCA in flow phantoms as well as in vivo data. Comparisons with established methods such as SH and harmonic PI are also presented and discussed.