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Design and optimization of pulsed Chemical Exchange Saturation Transfer MRI using a multiobjective genetic algorithm

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ABSTRACT

Pulsed Chemical Exchange Saturation Transfer (CEST) MRI experimental parameters and RF saturation pulse shapes were optimized using a multiobjective genetic algorithm. The optimization was carried out for RF saturation duty cycles of 50% and 90%, and results were compared to continuous wave saturation and Gaussian waveform. In both simulation and phantom experiments, continuous wave saturation performed the best, followed by parameters and shapes optimized by the genetic algorithm and then followed by Gaussian waveform. We have successfully demonstrated that the genetic algorithm is able to optimize pulse CEST parameters and that the results are translatable to clinical scanners.

1. Introduction

Chemical Exchange Saturation Transfer (CEST) MRI gains informative contrast by applying a radio frequency (RF) saturation pulse at the MR frequency of exchangeable protons on an endogenous or exogenous contrast agent followed by fast image acquisition of bulk water. The chemical exchange between saturated proton pools of the agent and bulk water causes a detectable change in the water signal, which is referred to as CEST contrast. CEST MRI data typically consists of multiple images, where the RF saturation pulse is applied at a different offset frequency (relative to water) to create a CEST spectrum.

Achieving efficient CEST contrast requires the protons to be within the slow-to-intermediate exchange regime, where the exchange rate (k_{ex}) of a labile proton of the agent is less than its offset frequency from water ($\Delta\omega$). Diamagnetic CEST agents, naturally occurring molecules without metal ions, have an exchangeable pool of protons typically at $\leqslant$7 ppm (approximately 900 Hz at 3 T magnetic field strength) from bulk water [1–3], and have an exchange rate typically $\leqslant$1000 Hz [4]. These agents include endogenous CEST compounds that contain amine, amide, hydroxyl and imino functional groups [3,5] and exogenous compounds such as iopromide (Ultravist ®), iopamidol (Isovue ®) [6–9], and salicylic acid [10]. The rate of proton exchange depends on the physiological environment such as pH and temperature [2,4]. Due to this relationship, the change in bulk water signal can be related to environmental changes *in vivo* [3].

There are two general methods of applying RF saturation pulses to the labile proton pool of the agent: continuous wave (CW) saturation and pulsed RF saturation. With CW saturation, a long rectangular pulse of constant amplitude is applied. For pulsed RF saturation, a train of short shaped RF pulses are applied to saturate the labile pool [11]. CW saturation provides effective saturation, however, it is not always possible to use CW saturation due to limitations on the hardware duty cycle as well as Specific Absorption Rate (SAR) restrictions [12,13]. Additionally, there are situations where it may be advantageous to use pulsed CEST methods. For example, pulsed CEST experiments with short saturation periods interleaved with data acquisition have been shown to have improved temporal resolution and decreased loss of the CEST effect under short T1 relaxation conditions [14]. In addition, pulsed CEST MRI can be sensitized to the signal of slowly exchanging protons [15].

CEST contrast is complex and depends on multiple experimental parameters [13,16]. The optimization of CW saturation is a two-dimensional optimization problem, in which the pulse duration and the RF power need to be optimized [11]. On the other hand, the optimization of pulsed CEST MRI is a multidimensional problem. For example, the optimization of a pulsed CEST experiment using a Gaussian waveform is a six-dimensional problem with

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the following variables: (1) maximum power, (2) total saturation time, (3) single pulse duration, (4) interpulse delay, (5) center of the Gaussian pulse, and (6) width of the Gaussian pulse. The last two variables, the center and the standard deviation of the Gaussian pulse determine the shape of the RF saturation pulse. This is important because the shape of the applied saturation pulse itself will also contribute to the overall CEST effect observed. In addition to Gaussian [11–13], a number of waveforms have been previously used in pulsed CEST MRI studies, including e-burp [17], Gaussian, Fermi [18] and d-SNOB [19]. Additionally, advice on how to select waveforms has also been provided [20].

The optimizations of pulsed CEST parameters and to generate the best CEST effect has been previously investigated [11–13,21]. However, many pulsed CEST applications predefine the saturation pulse shapes to have a Gaussian line shape or a simple variation of a Gaussian line shape in which the power, saturation time, and duty cycle are optimized. The Gaussian line shape is a natural pulse shape to select for pulsed CEST MRI because it has favorable characteristics in the spectral domain with minimal off-resonance artifacts and side bands. However, there is potential to further improve pulsed CEST by customizing the RF pulse shape and other parameters for specific characteristics of the labile pool of interest, which may lead to RF pulses that are not Gaussian-shaped.

The genetic algorithm (GA) is a type of evolutionary algorithm that is suitable for the optimization of a large number of parameters. The GA solves an optimization problem by mimicking the process of natural selection [22,23]. In the 1980s, the GA was applied to design spectrally-selective RF pulses for magnetic resonance experiments [22]. The GA has since then been applied to design specialized pulses for a variety of MR applications [24,25]. To set up an optimization problem using a GA, it is important to have a good model that describes the system of interest. For CEST MRI, the Bloch–McConnell equations provide an excellent model that describes chemical exchange and spin dynamics within a magnetic field [26,27].

In this study, the GA was used to optimize the maximum power, average power, single pulse duration, interpulse delay, and the shape of the RF pulse as described by a Fourier series for a pulsed CEST MRI experiment [28]. The GA was also applied to optimize a pulsed CEST MR experiment using a train of Gaussian pulses as well as a three-pool model that took into account the effect of magnetization transfer (MT). This optimization was performed for a range of offset frequencies and exchange rates that are relevant for endogenous and exogenous diamagnetic CEST MRI contrast agents. Additionally, the optimization was constrained to maximum duty cycles of 50% and 90%. These duty cycles were selected based on previous publications, and to show the adaptability of the GA [11,13]. Results from the simulations using the newly derived parameters were compared to experimental studies performed with chemical solutions of ammonium chloride, iopromide, and salicylic acid.

2. Methods

2.1. Pulsed CEST simulations

A two-pool model based on the Bloch–McConnell equations was used to simulate continuous wave (CW) and pulsed CEST experiments [26]. Each RF pulse shape was segmented into 128 increments, and the magnetization was propagated at each increment. For CW saturation, the amplitude modulation of a shaped pulse was replaced with constant amplitude. A three-pool model that takes into account the effect of magnetization transfer (MT) was also used to simulate CW and pulsed CEST. The MT pool was implemented as a Super-Lorentzian lineshape with parameters described in [31,32]. All simulations were programmed in MATLAB® 2014 (Mathworks, Natick, MA), and the source code is available for download at the open science framework (https://osf.io/k8zvm) [36].

2.2. Genetic algorithm

To the best of our knowledge, this the first time that the GA is applied to optimize CEST MRI acquisitions. However, the first implementation of the GA for the design of RF pulses in NMR/MRI was reported almost thirty years ago [22]. Since then, the GA has been used in NMR/MRI for the design of pulsed gradients [33], selective excitation and inversion [34], and *k*-space trajectories [35]. Thus, an extensive literature on this method and its application to MRI is available, and we will only briefly describe the application of the GA to CEST MRI saturation pulses. Our implementation of GA in MATLAB and additional documentation is available for download at https://osf.io/k8zvm [36].

Optimization using the GA coded each CEST parameter of interest as a gene, where many genes together comprised an individual. The GA began with a group of random individuals that comprised the population (Fig. 1). Each individual had an associated cost function, which was used to evaluate and rank the individuals. The low ranking individuals were discarded, leaving the individuals with desirable characteristics. These individuals then became parents to produce the next generation of individuals, thus maintaining the population. As the generations propagated, the algorithm was programmed to induce small mutations into the genes, which allowed the individuals to evolve. This process was repeated for a set number of generations, or when minimal variation in the output solution was reached [23]. In this study, a multi-objective genetic algorithm (MOGA) was used where two competing objectives were coded in the fitness functions which evaluated the performance of the CEST parameters. With MOGA, the optimized solution is not a single individual, but rather a set of individuals known as the Pareto-optimal set. The individuals within the Pareto-optimal set had reached an optimal solution in that the solution cannot be further improved in one fitness function without causing degradation in the second fitness function [29]. All MOGA were performed in MATLAB®, using the following options: Population size = 200, Crossover fraction = 0.80, Pareto fraction = 0.35, Migration Fraction = 0.20, Generations = 50, Selection Function = Tournament, Mutation Function = Adapt Feasible.

2.3. Implementation of genetic algorithm for optimizing pulsed CEST parameters

The MOGA, simply referred to as GA from here on, was implemented using MATLAB® global optimization toolbox. The following parameters were optimized for different combinations of exchange rate and offset: (1) maximum power, (2) average power, (3) single pulse duration, (4) interpulse delay, and (5) shape of the RF pulse. The total (also maximum) saturation time was not included as a variable in this study because it depends on the time available for a scan for clinical applications, and thus, the saturation time currently used in our clinical protocol (3 s) was used for our studies. The Bloch–McConnell simulations for pulsed CEST were carried out by rounding the total saturation time to the nearest whole number of pulse duration and interpulse delay unit that would fit into the total saturation time to prevent pulse truncation. Thus it was possible for the total saturation time to be slightly less than 3 s. The shape of the RF pulse was described either by a Fourier series (Eq. (1)), referred to as $GA_{Fourier}$ from here on, or by a Gaussian waveform (Eq. (2)) referred to as GA_{Gauss}. The Fourier series was described using five harmonics where a_0, a_n and b_n represents the Fourier coefficients, L represents the period, and $\omega = 2\pi/L$,

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