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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.

Keywords

Chemical Exchange Saturation Transfer; Pulsed CEST MRI; Shaped pulses; Pulse design; Iopromide; Salicylic acid; Genetic algorithm

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 (ω). Diamagnetic CEST agents, naturally occurring molecules without metal ions, have an exchangeable pool of protons typically at 7 ppm (approximately 900 Hz at 3 T magnetic field strength) from bulk water [1–3], and have an exchange rate typically 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

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[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 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 $\omega = 2\pi/L$, where ω is the angular frequency. The Gaussian waveform was given the flexibility to adjust the width (σ), center (c), and the maximum power (Table 1).

$$S(t) = \frac{a_0}{2} + \sum_{n=1}^{n=5} a_n \cos(n \cdot t \cdot \omega) + \sum_{n=1}^{n=5} b_n \sin(n \cdot t \cdot \omega) \quad (1)$$

$$f(t, c, \sigma) = e^{-\frac{(t-c)^2}{2\sigma^2}} \quad (2)$$

The two objectives were set up to minimize (1) the normalized $(1 - M_{s(+\omega)\text{noex}}) - (1 - M_{s(+\omega)})$, where $M_{s(+\omega)}$ is the signal at the resonance frequency of the labile pool, $M_{s(+\omega)\text{noex}}$ represents the signal at the same offset frequency without chemical exchange, and (2) the reciprocal of the area under the CEST spectrum (Fig. 1). These objectives were selected because strictly evaluating the difference between the peaks from the first criteria, which will maximize the CEST peak, led to broadening of the peaks or truncation artifacts in the

CEST spectra by the GA's attempt to increase the CEST signal at one offset frequency, and therefore frequently did not produce the desirable solution. This problem was mitigated by including an objective to minimize the reciprocal of the area under the curve of the CEST spectra. The optimizations by the GA were constrained to duty cycles (DC) (Eq. (3)) of no more than 50% and no more than 90%. We used these two values to account for different MRI hardware capabilities at sites where this method could be implemented. These constraints were achieved by applying a penalty when the ratio of the pulse duration to interpulse delay exceeded the restriction. For example, in the case of the 50% duty cycle, the pulse duration can be 50 ms; unless the delay time is 50 ms or more, the saturation scheme would be highly penalized and rejected. The same restriction is also placed on the 90% duty cycle scheme. Thus, the solution found by the GA cannot exceed the maximum duty cycle prescribed.

The constraints used in this work for the pulse length, delay, and saturation time might result in a discontinuous function, which is problematic to optimize using standard fitting algorithms. However, the MOGA has proven to be robust under such conditions because it allows for multiple initial guesses to the optimal values of the parameters that simultaneously minimize the area under the curve for the z spectra and maximize the CEST effect. Additionally, the average power was restricted to keep the solution from exceeding the average power of a CW pulse of the same duration. The maximum pulse power was set to 1.5 μT due to clinical scanner restrictions (Table 1). The two-pool plus MT simulations were optimized using $\text{GA}_{\text{Fourier}}$ at 50% duty cycle with the same power and pulse restrictions as shown in Table 1. The pulse parameters and simulation output for two-pool plus MT will be referred to as $\text{GA}_{\text{Fourier+MT}}$.

For each duty cycle, the $\text{GA}_{\text{Fourier}}$ optimization was performed at three different offset frequencies of 350, 640, and 1280 Hz at seven exchange rates (k_{ex}) of 50, 100, 200, 400, 600, 800, and 1000 Hz for a total of 42 different combinations. The 350, 640, and 1280 Hz offsets were selected to allow experimental results from ammonium chloride, iopromide, and salicylic acid to be compared to simulation results. For iopromide, the parameters that closely represent the CEST effect at 4.2 ppm (approximately 530 Hz at 3 T) were selected to be optimized. $\text{GA}_{\text{Fourier+MT}}$ and GA_{Gauss} were optimized at 50% duty cycle for the following conditions: 350 Hz offset with k_{ex} of 200 Hz, 640 Hz offset with k_{ex} of 800 Hz, and 1280 Hz offset with k_{ex} of 800 Hz. GA_{Gauss} was further evaluated at additional exchange rates of $k_{\text{ex}} = 50, 100, 200, 400, 600,$ and 1000 at an offset of 640 Hz. The best solution from the Pareto-optimal set was selected based on the maximum % CEST effect calculated from (Eq. (4)) where $M_{s(-\omega)}$ represents the signal at the opposite saturation frequency relative to water, and M_0 is the signal at 2000 Hz saturation frequency. The GA was performed using parallel computation on four cores for 50 generations with a population of 200. The $\text{GA}_{\text{Fourier}}$ results at 50% duty cycle were compared against a standard Gaussian pulsed CEST scheme with 1.5 μT peak power and 0.76 μT average power at 50% duty cycle (50 ms single pulse duration (τ_{pulse}) with 50 ms interpulse delay (τ_{delay})), GA_{Gauss} , and 1 μT CW. The standard Gaussian pulsed CEST scheme will be referred to as $\text{Gaussian}_{\text{standard}}$. $\text{GA}_{\text{Fourier}}$ at 90% duty cycle (90 ms single pulse duration with 10 ms interpulse delay), was compared against $\text{Gaussian}_{\text{standard}}$ also at 90% duty cycle and a 1 μT CW saturation pulse. $\text{GA}_{\text{Fourier+MT}}$ results were compared to $\text{Gaussian}_{\text{standard}}$ and CW saturation.

$$DC = \frac{\tau_{\text{pulse}}}{\tau_{\text{pulse}} + \tau_{\text{delay}}} \quad (3)$$

$$\% \text{ CEST effect} = \frac{M_{S(-\omega)} - M_{S(+\omega)}}{M_0} \quad (4)$$

2.4. Experiments using optimized pulsed CEST parameters

The phantoms consisted of 15 mL of ammonium chloride (pH 5.0), iopromide (pH 6.4), and salicylic acid (pH 7.1) at 100 mM concentration in PBS. Phantoms to mimic the MT pool were made by adding 3% agar by weight to another set of phantoms with the same conditions as listed above [33]. The exchange rates were measured using the RL-QUEST method [30]. The exchange rate will be reported in the following format: k_{ex} = exchange rate (95% confidence interval). The adjusted R^2 value was used to evaluate the goodness of fit. The optimized pulses for $\text{GA}_{\text{Fourier}}$, GA_{Gauss} , and $\text{GA}_{\text{Fourier+MT}}$ at $k_{\text{ex}} = 200$ Hz at 350 Hz saturation frequency offset, $k_{\text{ex}} = 800$ Hz at 640 Hz saturation frequency offset, and $k_{\text{ex}} = 800$ Hz at 1280 Hz saturation frequency offset were programmed onto a Siemens 3 T Skyra MRI system and CEST spectra were collected using the GA optimized parameters on phantoms. Images were acquired at room temperature using a four channel flexible coil followed by turboFLASH acquisition with the parameters as listed: TR = 460 ms, TE = 2.16 ms, FA = 15°, acquisition matrix = 64×64 , FOV = 9 cm², in plane resolution = 1.4 mm², 2 cm slice thickness. The saturation pulses were applied from −2000 Hz to 2000 Hz relative to water in increments of 20 Hz for a total of 11 min 40 s per data set. The experiment was repeated using Gaussian_{standard} pulsed saturation and CW saturation methods under the same experimental conditions. A rectangular pulse of duration 999 ms with 1 ms delay was repeated for a total of 3 s. A CEST spectrum was generated by plotting the normalized signal intensity against the saturation frequency offset. The B0 inhomogeneity was adjusted by centering the CEST spectrum in post processing, and the CEST effect was calculated following (Eq. (4)).

3. Results

3.1. GA optimization of new saturation pulse shapes and parameters

Table 2 summarizes the CEST parameters derived from the $\text{GA}_{\text{Fourier}}$ optimization for each offset frequency and exchange rate. Each $\text{GA}_{\text{Fourier}}$ pulse was optimized in 2.5 h, while the GA_{Gauss} pulses were optimized in 1.25 h. Larger variations in pulse length and interpulse delay were observed for cases between exchange rates of 50, 100, and 200 Hz across the three saturation offsets compared to exchange rates between 400 and 1000 Hz. In all cases, $k_{\text{ex}} = 50$ Hz required the shortest pulse lengths compared to the other exchange rates. A decrease in power was observed for $k_{\text{ex}} = 1000$ Hz at 350 Hz offset. Interestingly, when the duty cycle was restricted to be between 50% and 90%, the optimal parameters had an average duty cycle of 76% (Table 3).

Shown in Fig. 2 are representative GA_{Fourier} pulse shapes derived for optimizing the CEST effect with an offset of 640 Hz at different exchange rates at 50% and 90% duty cycle. Even though the GA was given the flexibility to take intricate shapes, the output from the optimization most frequently described a smooth, slowly varying curve, where the average power was close to that of a CW pulse of the same duration. The smooth curve is not surprising because these pulses have favorable spectral characteristics. At times the GA did produce waveforms that had higher frequency modulations. However, many of these pulses resulted in artifacts in the CEST spectra and caused difficulty when detecting the peak of interest. The pulse parameters and waveforms that caused such artifacts were manually eliminated from the list of practical solutions.

The GA was also applied to optimize Gaussian pulse shapes and to take into account the effect of MT (Table 4). The average power for a single pulse derived for GA_{Gauss} are very similar to $Gaussian_{\text{standard}}$, but was found to be optimal with longer pulse duration and interpulse delay. $GA_{\text{Fourier+MT}}$ at 350 Hz offset found an optimal solution with higher maximum and average power and length of a single pulse duration compared to the two pool simulations using GA_{Fourier} without MT.

3.2. Simulations of CEST MRI

3.2.1. Comparison between GA_{Fourier} , $Gaussian_{\text{standard}}$, and CW saturation—

The optimized GA_{Fourier} pulsed CEST parameters and pulse shapes were then used to simulate a two pool model. The % CEST effect was calculated for each exchange rate and saturation offset frequency (Fig. 3). In all cases, the CW saturation resulted in greater % CEST effect compared to the pulsed CEST saturation schemes, and the GA_{Fourier} pulses achieved greater % CEST effect compared to the $Gaussian_{\text{standard}}$ pulses. At $k_{\text{ex}} = 50$ Hz with 50% duty cycle, the GA_{Fourier} parameters achieved between 75% and 82% contrast of the CW saturation, whereas the $Gaussian_{\text{standard}}$ pulses achieved approximately 40% contrast of the CW saturation. At 90% duty cycle, the GA_{Fourier} pulses achieved between 76% and 88% contrast of the CW saturation, whereas the $Gaussian_{\text{standard}}$ pulses achieved approximately 64% contrast of the CW saturation. For both the $Gaussian_{\text{standard}}$ and CW saturation schemes, the maximum % CEST effect occurred at $k_{\text{ex}} = 200$ Hz for all offset frequencies. However, the GA_{Fourier} pulses had the maximum CEST effect occur at $k_{\text{ex}} = 400$ Hz for offsets of 350 and 640 Hz at 50% and 90% duty cycle (Fig. 3).

The maximum CEST contrast (~18%) for all simulations occurred when the exchange rate was 200 Hz, which is approximately double the contrast observed at the maximum ($k_{\text{ex}} = 1000$ Hz, ~10% CEST) and minimum ($k_{\text{ex}} = 50$ Hz, ~10% CEST) exchange rates simulated (Fig. 3). Pulse parameters at an offset frequency of 1280 Hz and $k_{\text{ex}} = 100$ Hz are similar between the GA_{Fourier} pulses and $Gaussian_{\text{standard}}$ pulses at 50% duty cycle in terms of pulse lengths and delays (Table 2). The differences are between the maximum and average power derived from the pulse shape, where the $Gaussian_{\text{standard}}$ pulse has 1.5 μT and 0.73 μT , and GA_{Fourier} pulse has 1.12 μT and 1.0 μT respectively. In this case, the GA_{Fourier} pulse method achieved 2.5% greater CEST effect compared to the $Gaussian_{\text{standard}}$ waveform (Fig. 3C).

3.2.2. Comparison between GA_{Fourier} and GA_{Gauss} , $Gauss_{\text{standard}}$, and CW

saturation—The Gaussian waveform was optimized using the GA under the same conditions as the Fourier series. The GA_{Gauss} achieved higher % CEST effect compared to $Gauss_{\text{standard}}$ pulsed saturation methods at the majority of the exchange rates at 640 Hz offset. At $k_{\text{ex}} = 100$ Hz, the two Gaussian pulsed methods showed a comparable CEST effect in simulations. Overall, GA_{Fourier} performed better than both Gaussian saturation methods (Fig. 4).

3.3. Experimental CEST MRI studies

CEST spectra were collected using CW saturation and pulsed CEST methods using parameters and pulse shapes optimized for GA_{Fourier} , GA_{Gauss} , and $Gauss_{\text{standard}}$ at 50% duty cycle on phantoms of 100 mM ammonium chloride, iopromide, and salicylic acid. Additional CEST spectra were collected using GA_{Fourier} and $Gauss_{\text{standard}}$ at 90% duty cycle (Fig. 5). For each phantom the exchange rate was measured to be $k_{\text{ex}} = 155$ (98, 206) Hz for ammonium chloride ($R^2 = 0.979$), $k_{\text{ex}} = 701$ (683, 720) Hz for iopromide ($R^2 = 0.999$), and $k_{\text{ex}} = 880$ (497, 1262) Hz for salicylic acid ($R^2 = 0.929$). In all cases, the CW saturation method achieved the greatest CEST effect, followed by pulsed CEST methods optimized using the GA. At 50% duty cycle, the GA_{Fourier} pulses showed an improvement of 3.3%, 2.4% and 2.7% for ammonium chloride, iopromide, and salicylic acid phantoms, respectively compared to the $Gauss_{\text{standard}}$ pulses. For ammonium chloride and salicylic acid phantoms, the improvement in GA_{Gauss} over $Gauss_{\text{standard}}$ was less than 1%. The GA_{Gauss} saturation scheme performed as well as GA_{Fourier} with less than 1% difference for iopromide. Using a 90% duty cycle, an improvement of 5.6%, 2.8%, and 5.8% was observed for GA_{Fourier} pulses compared to $Gauss_{\text{standard}}$ for ammonium chloride, iopromide, and salicylic acid, respectively. In general, the simulations predicted greater % CEST than what was experimentally achieved. However, the difference in the % CEST values between the GA_{Fourier} pulses and $Gauss_{\text{standard}}$ were consistent for both simulation and experimental data at approximately 3% (Tables 4 and 5).

The phantom experiment was repeated by adding 3% agarose by weight to phantoms of 100 mM ammonium chloride, iopromide, and salicylic acid. The representative pulse shapes and parameters are shown in Table 4 and Fig. 6. The pulse shapes derived for $GA_{\text{Fourier+MT}}$ show that they are also smoothly varying curves similar to pulses shown in Fig. 2 for a simple two pool model. For ammonium chloride, the $GA_{\text{Fourier+MT}}$ and $Gauss_{\text{standard}}$ both achieved comparable CEST effect, 5.9% and 6.0% respectively. For iopromide and salicylic acid the $GA_{\text{Fourier+MT}}$ resulted slightly improved CEST effect of 5.5% and 4.2% respectively compared to $Gauss_{\text{standard}}$ which achieved 4.8% and 2.3%. As expected, CW saturation achieved the highest CEST effect for all cases.

4. Discussion

In this study, a genetic algorithm (GA) was used to optimize pulsed CEST parameters. Previous reports have optimized limited numbers of experimental variables for saturation pulse shapes, and required multiple simulations and experiments to be performed before obtaining the optimized solution for pulsed CEST methods. Here, we applied a GA to

simultaneously optimize multiple pulsed CEST parameters. The optimized parameters were then used to collect data with phantoms using a 3 T Siemens Skyra MRI system, to confirm the predictions made by simulations.

CEST pulse parameters were optimized using the GA using a Fourier series at 50% and 90% duty cycle for a range of offset frequencies and exchange rates (Tables 2 and 3). The total saturation time was not included as a variable but was set to 3 s. CEST steady state may not be reached for all imaging conditions, however, our goal was to optimize the CEST saturation conditions within our constrained time frame for clinical applications. The output parameters derived from the GA_{Fourier} at $k_{\text{ex}} = 50$ Hz for 50% duty cycle are similar to pulsed CEST parameters previously evaluated for amide proton transfer (APT) experiments, where a train of 20 ms Gaussian pulses at 50% duty cycle with an average power of $0.6 \mu\text{T}$ showed desirable CEST effects [15].

At 50% duty cycle, the optimal average power for GA_{Fourier} approaches nearly $1 \mu\text{T}$ for exchange rates 400 Hz and above for all offsets. The $1 \mu\text{T}$ restriction was set in place to ensure all pulses can be implemented on a 3 T Skyra MRI system without exceeding the SAR restrictions. As an exception, the average power was relatively low at $k_{\text{ex}} = 1000$ Hz at 350 Hz offset saturation frequency. The decrease in the power is thought to be due to insufficient saturation of the labile pool when $k_{\text{ex}} > \omega$, which does not fall within the slow-to-intermediate exchange rate, and an increase in power does not increase the CEST effect. Interestingly, when the duty cycle was allowed to increase to a maximum of 90%, all evaluated saturation offsets and exchange rates had a duty cycle of $\sim 80\%$. Previous work has suggested that having a higher duty cycle would provide better CEST contrast [9]. In this case, the GA was able to derive solutions that achieved maximum CEST contrast without using the highest duty cycle within the experimental constraints. Additionally, this suggests that the average power of each individual pulse plays a larger role in improving the CEST contrast over the average power of the entire saturation duration.

The pulse parameters along with the corresponding pulse shape for each offset frequency and exchange rates were used to simulate CEST experiments. The CW saturation method clearly achieves the best saturation among the three methods. In comparing the $Gaussian_{\text{standard}}$ to the GA_{Fourier} pulses, the optimized GA_{Fourier} pulses achieved better % CEST effect under all conditions in simulation. The similarity of the single pulse duration and interpulse delay between the GA_{Fourier} and the $Gaussian_{\text{standard}}$ pulses at 640 Hz saturation offset at $k_{\text{ex}} = 100$ Hz follows previously published work, which emphasized the effect of average power on CEST spectra [6]. Under these conditions, pulse shapes are both smoothly varying but there is a difference in the average pulse power, $1.0 \mu\text{T}$ and $0.76 \mu\text{T}$ for GA_{Fourier} pulses and $Gaussian_{\text{standard}}$, respectively, which is likely to have contributed to the difference in % CEST (Fig. 3). Here, we have demonstrated that the GA_{Fourier} is able to optimize the pulse CEST shapes, and thus also the average power, to maximize the CEST effect. To further evaluate GA optimization for pulsed CEST parameters, a saturation scheme using a train of Gaussian waveforms was also optimized. As shown in Fig. 4, the GA_{Gauss} performed better than the $Gauss_{\text{standard}}$ in simulations, however, both GA_{Fourier} and CW achieved higher % CEST, hinting that giving the GA additional flexibility in the pulse shape could be beneficial.

The simulation results were further validated by phantom studies using the shaped pulses. The GA_{Gauss} had minimal improvement over $Gaussian_{\text{standard}}$ in phantoms of ammonium chloride and salicylic acid, but showed better performance for iopromide with comparable results to GA_{Fourier} . Overall, even while allowing the GA to optimize a Gaussian waveform, using the flexibility of the Fourier series seems to have an advantage over restricting the pulse shapes, and the GA_{Fourier} performed equivalent or better than GA_{Gauss} for the parameters tested in this study. Additionally, even though a standard Gaussian waveform is available on most clinical scanners, the optimized Gaussian waveform derived via GA have modified σ and center values, and would have to be programmed and implemented onto the scanner in the same manner as the GA_{Fourier} waveforms.

Finally, the effect of the MT pool on GA optimization was evaluated by including an MT pool to the two-pool simulation. Experimentally, the $Gaussian_{\text{standard}}$ and $Gaussian_{\text{Fourier+MT}}$ achieved the same % CEST effect in an ammonium chloride with agar phantom. Slight improvement was observed for the iopromide and salicylic acid phantoms with agar. This may suggest that the current minimization functions set up for the GA may not be optimal for separating the CEST effect from the MT pool, especially when the CEST effect is close to the water peak. Therefore, there is potential for future work to improve the optimization.

The main limitation of the approach presented in this work is that the experimental parameters were optimized for specific offset frequencies and exchange rates. The effect of assuming the wrong exchange rate has to be evaluated in the future, but our approach took into account the entire z spectra and not only the frequency at which the saturated pool resonates. Thus we expect that the effect of saturation off-resonance with the exchanging pool will be negligible. Furthermore, the fact that the shaped pulses were designed for specific exchange rates might be used to filter pools with similar concentrations but different exchange rates. For example, Fig. 4 indicates that CW saturation results in a CEST effect of approximately 8–20% depending on the exchange rate (50–1000 Hz); on the other hand, our GA-optimized pulses resulted in CEST effects of approximately 8% for the same ranges of exchange rates, suggesting that CW and shaped pulses might be combined to design experiments resulting in CEST MR images weighted toward a range of exchange rates.

As shown in Table 2 for a 50% duty cycle the results optimized for slow exchange, $k_{\text{ex}} = 50$ Hz are quite different from faster exchange rates. A pulse designed for an exchange rate of 50 Hz at a particular offset frequency will not have optimal performance if the exchange rate is faster. This will be a challenge to select one optimal pulse shape for endogenous *in vivo* CEST MRI studies. However, there is little variation between pulse parameters for exchange rates 400 Hz and above. This indicates that it is more important to optimize pulse parameters for slower exchange rates, for applications such as APT, but *in vivo* CEST MRI studies could potentially use a more generalized pulse for faster exchange rates. Additionally, exogenous agents should be designed to have faster exchange rates in order to take advantage of the generalized pulse shapes.

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Fig. 1.

Flow chart of genetic algorithm optimization. (1) A population was comprised of a group of individuals, for which each individual was comprised a set of genes. Each gene in this case represented a CEST experiment parameter that needed to be optimized. (2) Each individual was evaluated by a fitness function, and for this study, two objective functions were used to describe the fitness function. These objectives were set up to maximize the CEST peak of the labile pool and to minimize the area under the CEST spectra. (3) One cycle through this diagram is called a generation. At each generation, mutations were coded into the genes to add variations into the population. The algorithm was performed on a population of 200 individuals for 50 generations.

Fig. 2.

Representative pulse shapes derived by the genetic algorithm at a saturation offset of 640 Hz at two duty cycles for the following exchange rates: (A and E) 100 Hz, (B and F) 200 Hz, (C and G) 400 Hz, and (D and H) 1000 Hz. t_p represents the pulse duration derived by the genetic algorithm (Tables 2 and 3). The right column are representative pulses for a 50% duty cycle, and the left column for a 90% duty cycle. In general, the curves were smooth and slowly varying. Large differences in pulses shape and pulse duration (t_p) are observed between at $k_{ex} = 100$ and 200 Hz.

Fig. 3.

Simulated pulsed CEST spectra at duty cycles 50% (A–C) and 90% (D–F) were used to calculate % CEST effect for offsets of 350 Hz (A and D), 640 Hz (B and E), and 1280 Hz (C and F) for a range of exchange rates. The simulations were carried out using pulsed CEST parameters optimized by the genetic algorithm (GA_{Fourier}), and Gaussian_{standard} pulses. The continuous wave (CW) CEST spectra was simulated at 100% duty cycle. In all cases, the GA_{Fourier} pulses had improved % CEST compared to the Gaussian_{standard} pulses.

Fig. 4.

Optimization of the Gaussian pulse using a genetic algorithm (GA) as a function of exchange rate (k_{ex}). The offset for the exchangeable pool was fixed to 640 Hz, while k_{ex} was varied systematically. The solid circles correspond to continuous wave saturation (CW), solid triangles is the GA-optimized Fourier series (GA_{Fourier}), solid diamond is the GA-optimized Gauss series (GA_{Gauss}), and solid squares is the standard Gauss pulse (Gauss_{standard}). The GA_{Gauss} achieved higher % CEST effect in simulations compared to the Gauss_{standard}, however, the GA_{Fourier} performed better than both Gaussian pulsed CEST schemes.

Fig. 5.

Experimental CEST spectra acquired on phantoms of 100 mM ammonium chloride, pH = 5.0, $k_{\text{ex}} = 155$ Hz (A and D), 100 mM iopromide, pH = 6.4, $k_{\text{ex}} = 701$ Hz (B and E), and 100 mM salicylic acid, pH = 7.1, $k_{\text{ex}} = 880$ Hz (C and F). The data presented in the top row was acquired using 50% duty cycle for the pulsed CEST methods. The second row was acquired at 90% duty cycle. Data acquired with the phantoms are consistent with simulations where continuous wave (CW -●-) performed the best, followed by pulses and parameters of $\text{GA}_{\text{Fourier}}$ (solid line), GA_{Gauss} (solid circles), and $\text{Gaussian}_{\text{standard}}$ (dashed line) waveform. At 50% duty cycle, both $\text{GA}_{\text{Fourier}}$ and GA_{Gauss} were compared against CW and $\text{Gaussian}_{\text{standard}}$. The GA optimized pulses performed better than the $\text{Gaussian}_{\text{standard}}$, but little difference was observed between $\text{GA}_{\text{Fourier}}$ and GA_{Gauss} for iopromide.

Fig. 6.

Experimental CEST spectra with MT acquired on phantoms of 100 mM ammonium chloride, pH = 5.0 (A), 100 mM iopromide, pH = 6.4 (B), and 100 mM salicylic acid pH = 7.1 (C) with 3% agarose. The corresponding pulse shapes derived by GA used to acquire the data are shown below (D–F). $GA_{MT+Fourier}$ achieved higher % CEST over GA_{Gauss} for iopromide and salicylic acid (B and C), but resulted in comparable % CEST effect for ammonium chloride.

Table 1

Constraints for the optimization of CEST pulse parameters using a genetic algorithm.

Parameter	Lower limit	Upper limit
Max. power (μ T)	0.5	1.5
Avg. power (μ T)	–	1
Pulse length (ms)	20	100
Pulse delay (ms)	20	100
Gaussian std	1	128
Gaussian center	1	128

Table 2

Optimized parameters of pulsed CEST experiments using a genetic algorithm for a maximum duty cycle of 50%.

<i>Saturation offset = 350 Hz</i>									
Exchange rate (Hz)	50	100	200	400	600	800	1000		
Maximum power (μ T)	0.89	1.19	1.11	1.43	1.49	1.48	0.8		
Average power (μ T)	0.57	0.83	0.72	0.92	0.96	0.96	0.54		
Pulse length (ms)	23	99	72	92	82	91	93		
Interpulse delay (ms)	28	99	73	94	85	96	99		
Duty cycle (%)	45	50	50	50	49	49	48		
<i>Saturation offset = 640 Hz</i>									
Exchange rate (Hz)	50	100	200	400	600	800	1000		
Maximum power (μ T)	1.13	1.1	1.3	1.45	1.5	1.5	1.47		
Average power (μ T)	0.78	1	0.85	0.96	0.99	1	1		
Pulse length (ms)	20	50	74	67	86	86	67		
Interpulse delay (ms)	20	51	75	68	89	89	69		
Duty cycle (%)	50	50	50	50	49	49	49		
<i>Saturation offset = 1280 Hz</i>									
Exchange rate (Hz)	50	100	200	400	600	800	1000		
Maximum power (μ T)	1.18	1.12	1.22	1.5	1.44	1.5	1.47		
Average power (μ T)	0.76	1	0.99	0.97	0.97	0.99	1		
Pulse length (ms)	20	50	95	81	82	70	80		
Interpulse delay (ms)	20	51	99	81	83	71	82		
Duty cycle (%)	50	50	49	50	50	50	49		

Table 3
Optimized parameters of pulsed CEST experiments using a genetic algorithm for a maximum duty cycle of 90%.

<i>Saturation offset = 350 Hz</i>									
Exchange rate (Hz)	50	100	200	400	600	800	1000		
Maximum power (μ T)	0.61	1.02	1.16	1.2	1.44	1.46	1.47		
Average power (μ T)	0.46	0.89	0.79	0.94	0.9	0.97	0.98		
Pulse length (ms)	79	78	85	91	91	84	91		
Interpulse delay (ms)	23	23	25	28	28	39	46		
Duty cycle (%)	77	77	77	77	76	68	66		
<i>Saturation offset = 640 Hz</i>									
Exchange rate (Hz)	50	100	200	400	600	800	1000		
Maximum power (μ T)	0.94	1.01	1.12	1.39	1.47	1.44	1.48		
Average power (μ T)	0.79	0.85	0.91	1	0.99	0.92	0.97		
Pulse length (ms)	78	77	92	97	80	88	87		
Interpulse delay (ms)	23	24	27	27	27	31	31		
Duty cycle (%)	77	76	77	78	75	74	74		
<i>Saturation offset = 1280 Hz</i>									
Exchange rate (Hz)	50	100	200	400	600	800	1000		
Maximum power (μ T)	1.08	1.2	1.18	1.33	1.45	1.49	1.48		
Average power (μ T)	1	0.98	1	0.99	1	1	0.98		
Pulse length (ms)	78	95	95	94	92	98	97		
Interpulse delay (ms)	22	24	25	26	28	27	26		
Duty cycle (%)	78	80	79	78	77	79	79		

Table 4

The applications of the GA in CEST MRI. The GA has the flexibility to be used to optimize shaped pulses for particular chemical environments ($GA_{\text{Fourier+MT}}$) or within additional pulse shape constraints (GA_{Gauss}).

<i>GA_{Fourier+MT}</i>			
Offset (Hz)	350	640	1280
k_{ex} (Hz)	200	800	800
Maximum power (μT)	1.46	1.49	1.5
Average power (μT)	1	0.8	1
Pulse length (ms)	50	72	82
Interpulse delay (ms)	51	88	85
Duty cycle (%)	50	45	49
<i>GA_{Gauss}</i>			
Offset (Hz)	350	640	1280
k_{ex} (Hz)	200	800	800
Maximum power (μT)	1.09	1.47	1.49
Average power (μT)	0.62	0.74	0.75
Pulse length (ms)	64	75	89
Interpulse delay (ms)	72	78	92
Duty cycle (%)	47	49	49
Gauss std	30	26	26
Gauss center	64	64	65

Table 5
Comparison of % CEST effect between simulated (sim) and experimental (exp.) data.

Offset (Hz)	k_{ex} (Hz)	CW		GA Fourier		Gaussian	
		Sim	Exp.	Sim	Exp.	Sim	Exp.
50% duty cycle							
350	200	51.4	31.6	24.2	16.4	20	13.1
640	800	12.3	11.3	6.8	6.6	3.9	4.2
1280	800	12.6	11.4	6.9	6.7	3.9	4
90% duty cycle							
350	200	51.4	43.8	36.2	37.4	31.4	31.8
640	800	12.4	16.1	9.1	12.8	6.9	10
1280	800	12.6	22.1	10.6	18.7	7	12.9