Scientiae Radices, **3**(1), 30-52 (2024)

Review

SciRad SCIENTIAE RADICES

Artificial Intelligence-Powered Pulse Sequences in Nuclear Magnetic Resonance and Magnetic Resonance Imaging: Historical Trends, Current Innovations and Perspectives

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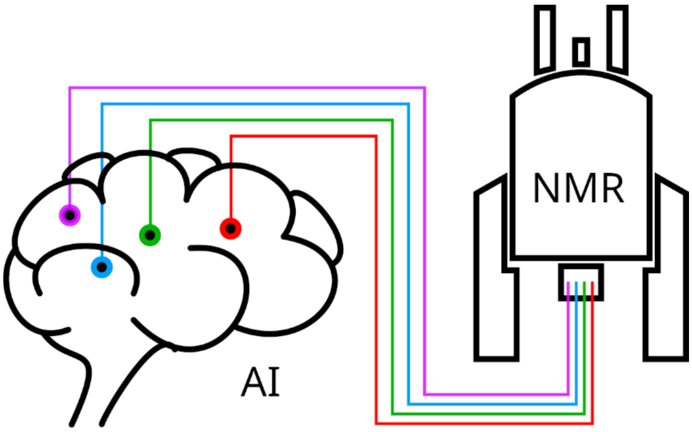

Abstract: This review article explores the historical background and recent advances in the application of artificial intelligence (AI) in the development of radiofrequency pulses and pulse sequences in nuclear magnetic resonance spectroscopy (NMR) and imaging (MRI). The introduction of AI into this field, which traces back to the late 1970s, has recently witnessed remarkable progress, leading to the design of specialized frameworks and software solutions such as DeepRF, MRzero, and GENETICS-AI. Through an analysis of literature and case studies, this review tracks the transformation of AI-driven pulse design from initial proof-of-concept studies to comprehensive scientific programs, shedding light on the potential implications for the broader NMR and MRI communities. The fusion of artificial intelligence and magnetic resonance pulse design stands as a promising frontier in spectroscopy and imaging, offering innovative enhancements in data acquisition, analysis, and interpretation across diverse scientific domains.

Keywords: Artificial Intelligence, Machine Learning, Evolutionary Algorithm, Artificial Neural Network, Nuclear Magnetic Resonance, Magnetic Resonance Imaging, Pulse Sequence, Shaped Pulse

Received: 2024.02.21
Accepted: 2024.03.22
Published: 2024.03.27
DOI: 10.58332/scirad2024v3i1a04

Introduction

In recent times, rapid advancement of artificial intelligence (AI) has become increasingly evident, revolutionizing various domains such us engineering, science, and daily routines. Notably, numerous review articles have surfaced discussing AI applications in magnetic resonance, particularly focusing on data processing, structure elucidation through the nuclear magnetic resonance spectroscopy (NMR) spectra, and magnetic resonance imaging (MRI) pattern recognition [1–6]. Recently, special issues of the *NMR in Biomedicine* [7] and *Bioengineering* [8] journals were specifically devoted to AI methods applied to magnetic resonance techniques. Despite the insights provided by these articles, the topic of AI-assisted generation of shaped pulses or pulse sequences remains largely unexplored in the existing reviews.

AI is a broad term first proposed in 1955 by John McCarthy [9,10]. According to McCarthy AI is, in general, 'the science and engineering of making intelligent machines, especially intelligent computer programs' [11]. This phenomenological, umbrella definition encompasses a wide variety of computational techniques, including Machine Learning (ML). ML is designed especially to find patterns and abstract knowledge from a limited number of examples (or trials) and apply them to new problems. AI allows for solving problems too complex for human mind to fully comprehend. Most of the AI techniques rely on stochastic optimization methods over vast parameter space which makes them superior to deterministic optimization algorithms. There is, however, no precise direction or paradigm in AI research. To cite Nils Nilson, one of the founders of the AI science, 'there is wide disagreement in the field about what AI is all about' [12]. For readers seeking a comprehensive exploration of the subject, the textbook by Russell and Norvig serves as an invaluable resource [13].

In this review I will focus on two prominent AI subfields that have been used in radiofrequency (RF) pulse sequence generation for several decades and in the last few years gained the strongest interest in the field, namely Evolutionary Algorithms (EAs) and Artificial Neural Networks (ANNs). Both belong to Machine Learning (ML) techniques.

To introduce the reader to nuclear magnetic resonance let us first consider an object that contains atomic nuclei of non-zero spin placed in a static magnetic field B_0. This external magnetic field causes a small magnetization of the object that arises from the separation of the energy states of the magnetically active nuclei. In an equilibrium, non-disturbed state, this secondary magnetization remains parallel to the B_0 (further referred to as the z-axis, following standard convention). Subsequently, a short pulse of electromagnetic field denoted as B_1^+ within a certain RF range is generated to perturb the equilibrium state, temporarily altering the orientation of the magnetization. The spontaneous return to the thermodynamic equilibrium includes a decaying precession of the magnetization at the nucleus-specific frequency (the Larmor frequency), giving rise to the electromagnetic field B_1^-. The effect of generation of the Larmor Frequency is called nuclear magnetic resonance. The B_1^- field induces an electric current alternating at the same frequency in the coils surrounding the object. The registered electric signal in the form of Free Induced Decay (FID) corresponds to the electromagnetic response of the spin population. When the frequency spectrum of the FID of a chemical sample is of interest, it pertains to Nuclear Magnetic Resonance Spectroscopy (NMR). Alternatively, when the spatial configuration or density map of the spin population within an object is assayed, the technique is called Magnetic Resonance Imaging (MRI). By replacing the single excitation pulse by a sequence of variously modulated pulses accompanied by the B_0 field alteration (magnetic field gradients) additional information about the spin system could be encoded in the FID and subsequently recovered by the data processing. Development of new pulse sequences that encode such additional information constitutes an essential field of NMR and MRI research [14].

With increasing complexity of the spin system under consideration or amount and type of information to be extracted the development of dedicated pulses or pulse sequence might be challenging due to the multidimensionality of the parameter space under consideration. This is where the new AI approaches find their niche. As said before, most of the AI models perform stochastic optimization over large parameter sets. Contrary to typical analytical approach, where a crucial step is to understand *how to solve* the problem, the AI methodology is rather to find *which model will solve the problem on its own*. Such paradigm shift has proved to be successful in many areas of magnetic resonance research, as will be shown throughout this review.

To visualize the ongoing growth of the interest of the scientific community in the AI-supported RF pulse design the number of articles on the topic published per year as well as the cumulative article count over the time were presented on Chart 1. Approximately exponential growth is clearly visible with a significant shift from the artificial evolution approach towards the artificial neural networks. Additionally, the timeline of the most important articles is shown on Fig. 1.

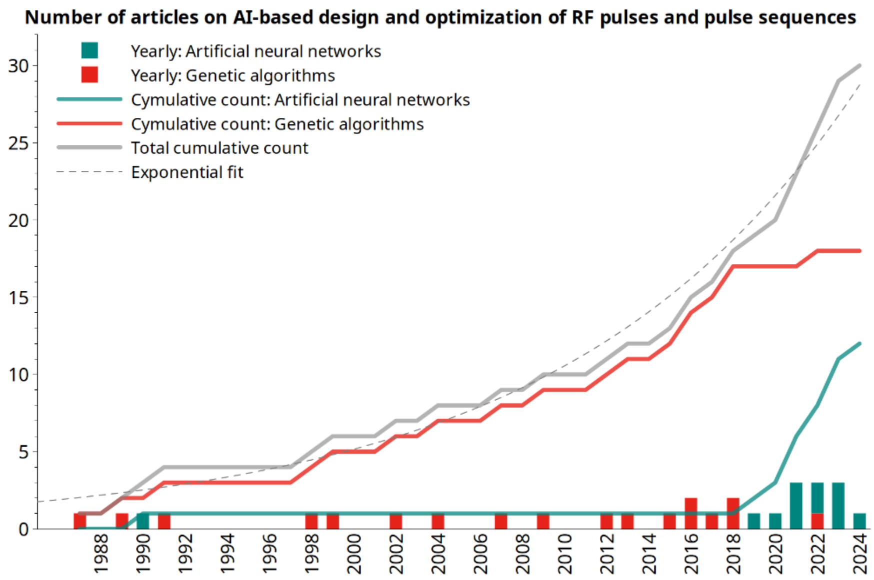

Chart 1 The number of original research articles on AI-supported design and optimization of RF pulses and pulse sequences for MRI and NMR applications. Bars represent the number of articles per year, solid lines the cumulative count over the years, dotted grey line is an exponential fit to the total count data. The green and red colors correspond to the main AI technique used in each article, GA or ANN respectively. The articles on GENETICS-AI were included in the ANN article count as the software heavily depends on the deep neural networks.

Evolutionary Algorithms

Overview the Evolutionary Algorithm concept

Evolutionary algorithms are computer optimization methods inspired by the ideas of Darwinian evolution model. Let us consider an abstract multidimensional problem where an optimal yet unknown solution is expected to exist. A set of candidate solutions that are arbitrarily far from the anticipated optimal one are then generated. By solutions, we mean a mathematical structure (*e. g.* a set of numbers, alphanumeric string, matrix, tensor) that encompasses a set of parameters or values that correspond to the multidimensional problem. During the evolutionary search pairs of the candidate solutions are *mated* and the *offspring* is generated. Each offspring solution inherits some properties of each parent. Moreover, random mutations are introduced to the parameters of the offspring to diversify the search space. Subsequently, a selection procedure is employed to determine which members of the new generation meet the predefined fitness criteria. The best individuals are retained for the next round of the optimization process, and this cycle continues until the desired solution criteria are met or the limit of generations or computation time is reached (Fig. 2) [13,15]. Genetic algorithms (GAs) are subset of evolutionary algorithms in which the parameters of the individual solutions are encoded into a one-dimensional chain of genes typically in the form of numeric of alphanumeric string [13].

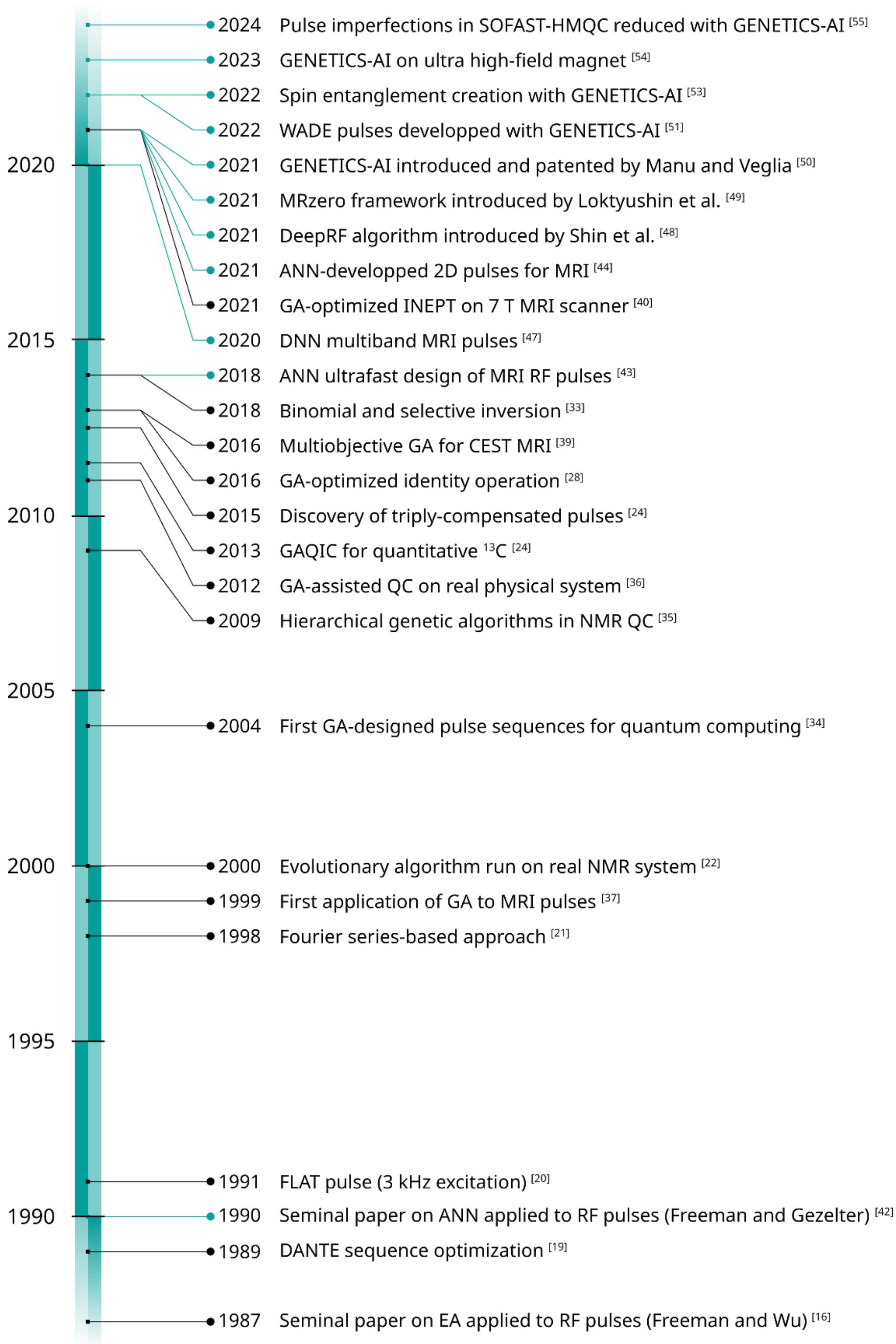

Fig. 1. The timeline summarizing most important articles cited in this review. The black or blue connector colors correspond to the main AI technique used in each article, GA or ANN respectively. The articles on GENETICS-AI were included in the ANN article count as the software heavily depends on the deep neural networks.

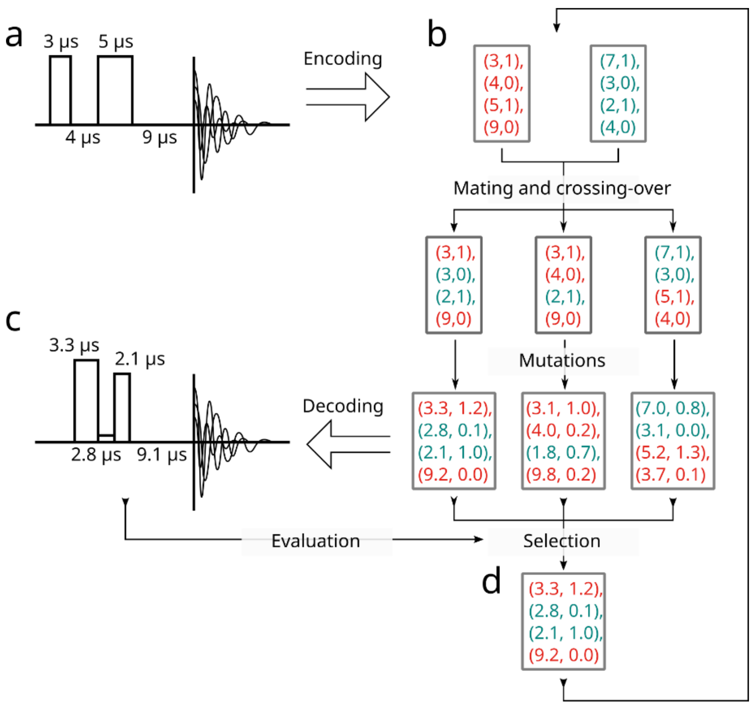

Fig. 2. A schematic description of an example pulse sequence optimization using GA: a) starting point sequences are encoded to numbers using some chosen algorithm (in this example the pulse durations and amplitudes are stored in array); b) arrays are 'mated' to produce offspring with mixed genes of the parents, additionally mutations are applied to the offspring genes to broaden the searched space; c) the newly generated arrays are decoded to the pulse sequences which are subsequently tested for performance (either by simulation of by physical spectrum registration); d) the best individuals are selected for the next iteration and the cycle repeats.

Evolutionary Algorithms in NMR pulse sequence development

The interplay between artificial intelligence and magnetic resonance traces its roots back to the 1987 seminal paper by Freeman and Wu [16]. The authors laid the theoretical groundwork for applying Darwin's ideas of evolution to the problem of pulse sequence optimization. They began by considering a general case of a sequence comprising several radiofrequency pulses interspersed with delays. The durations of these delays and pulses, as well as of the pulse phases, were conceptualized as *genes*. The pulse sequences were allowed to *evolve* in the sense that from a given sequence a set of *offspring* was generated by introducing small distortions to the genes (mutations). Subsequently, the excitation profile of each new sequence was computed using Bloch equations. The spectrometer operator was then allowed to choose, according to some pre-defined principles, one sequence to become a new parent. A proof-of-concept search for a solvent peak suppression sequence was conducted. Remarkably, within 11 generations of Darwinian evolution the well-known binomial signal suppression sequence (1:3:3:1, [17] emerged [16] In subsequent works, the authors applied the same principles to the optimization of the pulse widths of the DANTE [18] sequence [19] and self-focusing selective pulses with steady excitation profiles spanning over at least 3 kHz (coined as FLAT pulses, Fig. 3) [20].

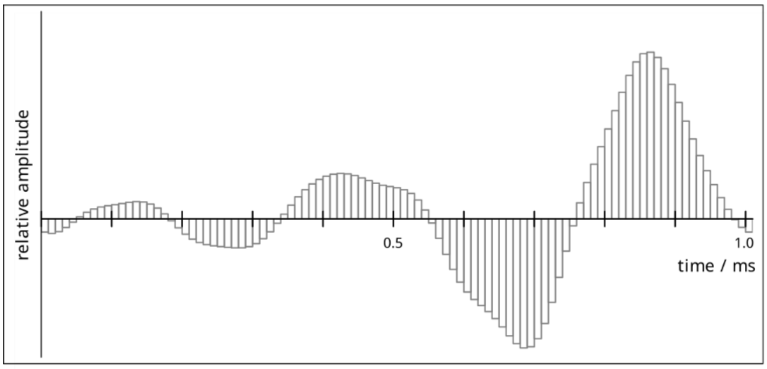

Fig. 3. An example FLAT pulse of Wu and Freeman generated by genetic algorithm. It results in high-fidelity, over 3 kHz excitation profile. The chart was generated based on the Fourier series coefficients given in [20].

In 1998 the topic was pushed forward by Lunati et al., who employed a stochastic, evolution-inspired optimization method to design selective RF pulses. They decided to avoid the black-box approach in which the shaped pulse is encoded as a series of points over the time-phase-amplitude space and the search is performed blindly, without any care about the real hardware limitations. Instead, the pulse shape (amplitude and phase) was represented as time-dependent coordinates on XY plane and defined by the following Fourier series:

$$w_x(\tau) = 2\pi \left\{ \sum_{n=0}^{Np} [A_n \cos(2\pi n\tau) + B_n \sin(\pi n\tau)] \right\}$$

$$w_y(\tau) = 2\pi \left\{ \sum_{n=0}^{Np} [C_n \cos(2\pi n\tau) + D_n \sin(\pi n\tau)] \right\}$$

where w_x and w_y are time (τ) dependent pulse amplitude on x and y axes. The sets of A_n, B_n, C_n and D_n Fourier coefficients form a search space for in silico evolutionary search. The use of Fourier series guarantees more physical, smooth and continuous pulse profile. For each candidate pulse shape, the excitation profile was computed using Bloch equations and the fitness was estimated. This led to the discovery of several new low-power, band-selective pulses with excitation profiles similar to the BURP pulse family [21].

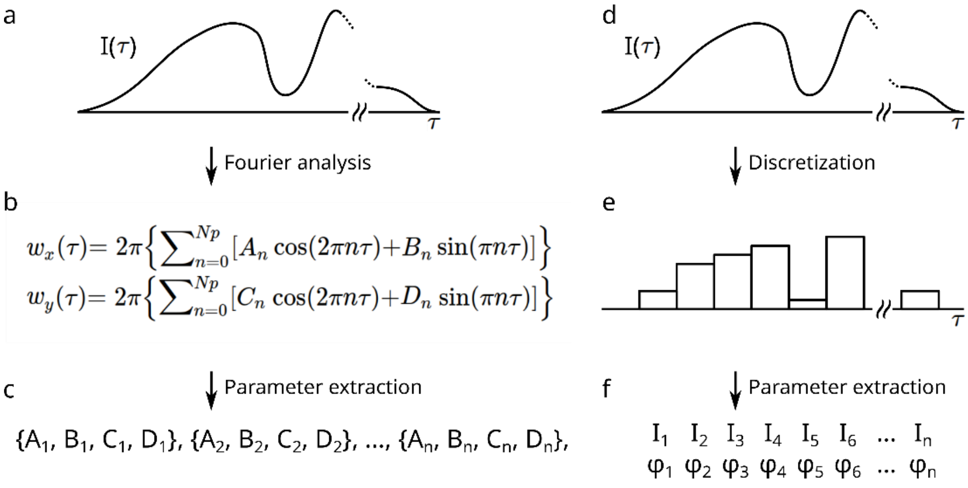

Fig. 4. Comparison of the Fourier series-based and black-box approaches to the pulse shape optimization. In the Fourier series approach the shaped pulse (a) is approximated by a Fourier series (b). The Fourier coefficients (c) are then subject to evolutionary optimization. In the black-box approach the same shaped pulse (d) is discretized (e). This leads to a set of amplitude/phase parameters (f) that are used for the optimization step.

Contrary, in 2000 Gray and Maxwell encoded the pulse shape directly as a time-dependent list of phase-amplitude pairs. Theoretically, such notation could encompass full sequence of pulses within a formal shaped pulse. The genetic algorithm optimization using 50 agents evolving over 50 generations was run on a real NMR spectrometer instead of theoretical calculation based on Bloch sphere. During each evaluation of the fitness function a physical spectrum of a sample containing 255 mM sodium trimethylsilyl 2,2,3,3-tetradeutero-propionate (TSP) in 1:2 water/DMSO was acquired. Three different tasks for the optimization were tested. The first aimed to maximize the DMSO/water signal ratio, effectively suppressing the water signal while preserving the DMSO resonance. The second experiment sought to maximize the ratio of TSP to water signals. Finally, the third experiment aimed to maximize the TSP signal relative to the sum of the water and DMSO signals. Although this evolutionary approach yielded pulse sequences with satisfactory single signal suppression properties, the simultaneous suppression of both H_2O and DMSO peaks was relatively poor [22].

In 2010 Mäkelä et al. proposed a Q-INEPT-CT experiment for quantitative ^{13}C spectroscopy, utilizing the INEPT polarization transfer to increase the sensitivity. The sequence was optimized to equalize the ^{13}C signal of CH, CH_2 and CH_3 groups [23]. In 2013 Manu and Kumar further subjected the experiment to global optimization using GA. Three fitness functions were tested that focused on the shortest possible experimental time and preservation of the quantitative information in the resulting spectrum regardless of $^{1}J_{C\text{-}H}$ coupling constants. These functions varied in their treatment of the polarization transfer strengths of CH, CH_2 and CH_3 groups. In the first case (Case A), the GA was constrained to ensure possibly identical responses for all carbons. In the second case (B) the responses of CH, CH_2 and CH_3 were optimized separately. In the third case (C) only the polarization transfer of the CH_2 and CH_3 groups was considered. Finally, a family of sequences, called GAQIC sequences, were obtained. The sequence generated in the C case resulted in quantitative spectrum comparable to the Q-INEPT-CT with two-fold registration time reduction. However, they found that the best results are obtained when the CH, CH_2 and CH_3 are treated separately. Therefore, while the spectrum contained precise quantitative information, simultaneous quantification of differently substituted carbon atoms was not feasible [24].

NMR spectra obtained using pulse sequences relying on hard π and π /2 pulses often suffer from field inhomogeneity, poor pulse calibration, and offsets, particularly when a broad excitation width is required. In an effort to address these challenges, Manu and Veglia conducted a genetic algorithm (GA) search for general rotor composite pulses designed to inherently compensate for these effects. A general rotor refers to a pulse or pulse sequence that induces a rotation of a spin system in a consistent manner, irrespective of its initial state [25]. Shaped pulses with constant amplitude and phase variability, composed of 200 points underwent an artificial evolution. The selection was based on the simulated performance of the candidate solutions. After 10^4 generations the family of so-called triply compensated pulses for π and $\pi/2$ rotations was discovered. They exhibited significantly higher fidelity than hard pulses. The effectiveness of these pulses was demonstrated by applying them to solid-state magic angle spinning (MAS) spectra of ubiquitin, showcasing a nearly uniform response over a 40-60 kHz offset range [26].

The triply compensated π pulses were further exploited by Xia et al. (from the same team) to significantly enhance the intensities of 2D ^{1}H-^{15}N and ^{1}H-^{13}C HSQC, 3D TROSY-HNCA and ^{13}C-edited NOESY-HSQC experiments. The most notable enhancement was observed for the triply compensated version of ^{1}H-^{13}C HSQC (compared to the standard Bruker hsqcetgpsisp2.2 sequence) where the relative enhancement of the aromatic groups signals was up to 240% [27].

More so than for π and $\pi/2$ pulses, real-life imperfections profoundly affect the identity operation. The perfect identity operation refers to any operation that leaves a specific spin state unchanged. It is commonly employed for decupling and recoupling certain nuclei or refocusing the spin population. Typically, an even number of π pulses is applied to the spin system to perform the identity operation. However, on a real physical system, experimental imperfections strongly influence its performance, resulting in measurable differences between the initial and final spin state. Manu and Veglia demonstrated that GA specifically designed for this task can optimize phase profiles of pulses within a sequence of an even number of π pulses to achieve a robust identity operation, making it less susceptible to experimental imperfections. These identity operation subsequences were then incorporated into the transferred-echo double-resonance (TEDOR) MAS NMR experiment. The gain of sensitivity reached up to 28% for a physical sample of ^{13}C, ^{15}N labeled microcrystalline ubiquitin [28]. This and other methods for designing optimal RF pulses with the aid of GA were briefly summarized by Manu et al. [29].

Among the solvent suppression techniques, the important role is played by the binomial sequences (which are time-symmetric trains of pulses, whose nutation angles ratios reassemble the binomial coefficients: 1:1, 1:2:1, 1:3:3:1... etc.) and 'Jump and Return' (JR) sequences which utilize identity operation performed on the in-resonance solvent signal wrapped around the pulses that set the off-resonance spins perpendicularly to the z axis [17]. The excitation profile of such a sequence covers most of the desired spectrum width, excluding the unwanted solvent signal. Another classic example is gradient-based WATERGATE pulse sequence (Fig. 5) [30,31]. Contrary to presaturation, such approaches do not inherently cause removal of the exchangeable protons [32]. In 2018 Brenner et al. discovered a new family of combined binomial and JR selective inversion sequences using standard Matlab Genetic Algorithm optimization tools. The new jump-and-return sandwich (JRS) sequences proved to be of superior selectivity. For example, ten-pulse sequence had 1.5 narrower solvent inversion profile than classical W5-WATERGATE [33].

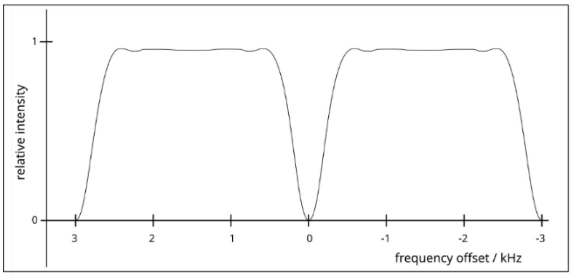

Fig. 5. Schematic excitation profile of W5 WATERGATE (based on original chart from [30])

Quantum computing on NMR system using GA-designed sequences

NMR provides a useful physical realization of the concept of quantum computing (QC). In NMR QC the spins of particular nuclei serve as qubits of a quantum computer with spin interactions facilitating information transfer and processing. The application of pulse sequence is equivalent to programming the computer. Finding appropriate pulse sequences for a given algorithm or problem to be solved constitutes a challenge in itself.

In 2004 Behrman et al. showed that GA could be successfully exploited to generate pulse sequences for NMR QC. The sequences generated by GS were shorter and more effective than the ones designed by previous authors by solving the underlying equations analytically [34]. The problem of generating pulse sequences for NMR quantum computing was later attacked by Ajoy and Kumar who developed a special class of hierarchical genetic algorithms. The genes were encoded in matrices in such a way that parameters from one row have the same hierarchy, meaning they affect the solution in a similar way. Additionally, the Darwinian model was combined with another optimizer, further enhancing the fitness of the solution. Within 20 minutes of simulation on a standard PC, candidate pulse sequences were obtained, with an estimated efficiency approximately 50% higher than those of existing sequences [35].

Those purely theoretical works were followed by physical realization of universal computation in NMR spectrometer using GA-generated pulses. Manu and Kumar used 5-bromofuroic acid, where the two aromatic protons served as a two-qubit model system. Using GA-optimized pulse sequences several quantum operations were performed. First, authors showed that single qubit rotations (SQR) (equivalent to selective nuclei excitation) are possible with a sequence composed of only nonselective hard pulses. Then the CNOT gate was developed as a basis for any kind of universal quantum computing. Finally, a creation of Bell state (a state where the two spins are maximally entangled) was achieved using a single GA-evolved sequence (compared to standard procedure that requires three separate steps) [36].

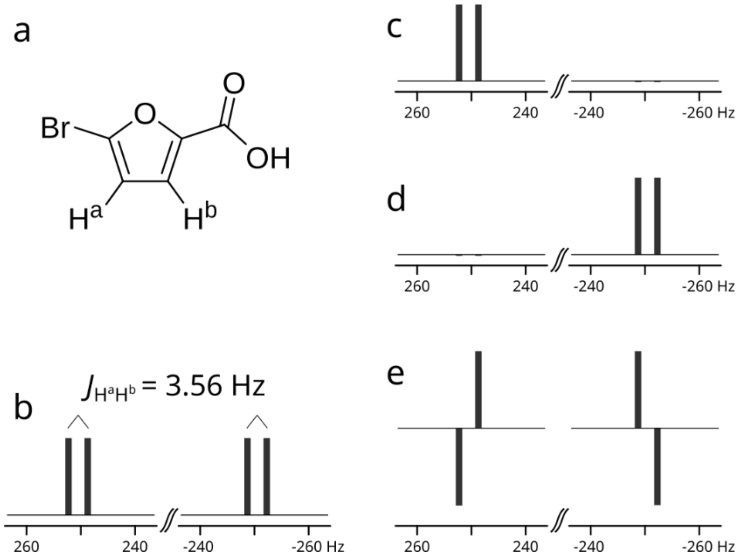

Fig. 6. Examples of quantum operations performed on real two-spin system using GA-evolved pulse sequences. a) 5-bromofuroic acid, a model two-qubit system, b) schematic representation of equilibrium spectrum, c) after single qubit rotation sequence (SQR) centered at –249.5 Hz, d) SQR centered at 249.5 Hz, e) after Bell state creation. For original spectra see [36].

Genetic Algorithms in MRI pulse sequence development

Magnetic resonance imaging (MRI) shares the physical principles with NMR. Modern MRI is a pulsed technique where the pulse shapes and pulse sequences, along with gradient control, play the vital role in designing and conducting the experiments. Thus, many of the theoretical works concerning the NMR pulse sequences are relevant to MRI researchers and vice versa. In this review the MRI section is separated for sake of clarity, not for significant physical or theoretical differences.

The first attempt to use GA-like algorithms for MRI pulse generation dates back to the 1999 article of Lunati et al. who discovered a new family of adiabatic, frequency-selective pulses with aid of simplified evolutionary optimization method [37].

In MRI the spatial selective RF pulses are used to excite (or invert) the nuclear spins inside a predefined physical area of the scanned body. The pulse and the gradient waveform that accompanies it are typically designed using the so-called *k*-space method in which the approximate RF pulse is obtained from the desired spatial excitation profile treated with the Fourier Transform (FT). Subsequent adjustments are then applied to remove artifacts in the excitation profile that arise from the non-linearity of the Bloch equations and the finite approximation of the FT. In the 2007 article, Pang and Shen used the GA for the direct generation of shaped pulses. Within 46 generations the GA yielded a $\pi/2$ pulse of significantly cleaner excitation profile than obtained by the *k*-space method. Analogously, the inversion pulse was developed within 32 generations [38].

Chemical exchange saturation transfer (CEST) is a contrasted MRI technique. It focuses on proton exchange rate in bulk water and the contrast agent. In a pulsed version of the technique the labile protons undergo saturation under the action of a series of short RF pulses. Finding the best pulse program for CEST constitutes a multidimensional optimization problem. To address it, Yoshimaru et al. proposed in 2016 a new multiobjective GA that takes into account the maximum power, average power, single pulse duration, delay between the pulses and shape of the pulse. The evolved pulse sequences gave a slightly higher CEST effect than the best sequences known to date [39].

In 2021, Somai et al. re-discovered the concept of GA-assisted optimization of pulse sequences. They used the black-box approach earlier criticized by Lunati et al. [21]. Thus, the pulse shape was encoded as series amplitude-phase points over time domain. Even though, they have taken the physical limitations of the amplifiers and RF coils into account and introduced smoothing step to the phase profile prior physical generation of the RF pulse. The verification of the proposed GA-optimization framework was performed with extensive experimental research on 7 T MRI system. The intensity of polarization transfer from proton to carbon using GA-modified INEPT sequence reached over 190% when compared to an unoptimized INEPT. Proton to nitrogen polarization transfer was as high as 160% more effective when optimized vs. unoptimized BINEPT sequences were compared. The registration of *J*-coupling artefact-free images was also demonstrated [40].

Artificial Neural Networks

Artificial Neural Networks (ANNs) are artificial structures (usually virtual, although physical realizations exist). With ANNs a complex computational task is performed by a set of functional elements that execute relatively simple mathematical operations. Those elements are arranged in such a way that the results of computations performed by some of them are passed to others as the input (Fig. 7). They might be organized in layers, groups or subnetworks, depending on the architecture of the network. The use of ANNs lies in the scope of the field of machine learning. A plethora of ANN techniques and models have been developed. Here we would like to focus on deep learning and reinforcement learning [41].

In deep learning, the computational elements are organized in layers. It means that some group of the elements performs their calculations simultaneously (in a functional sense) and the results of their calculations are altogether passed to another group (another layer). While the number and size of the layers vary significantly, depending on the problem to be solved, the deep learning architectures typically consist of multiple layers [13].

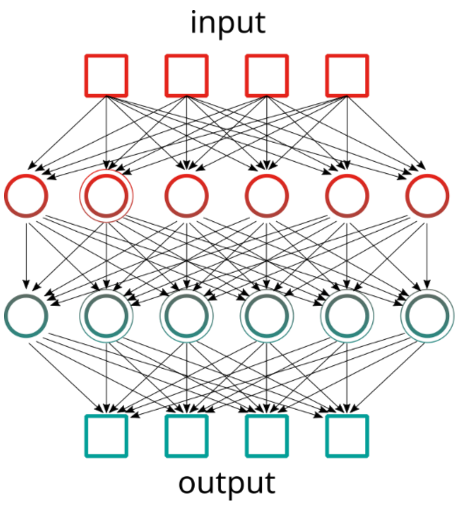

Fig. 7. Schematic representation of ANN. The input is provided to a series of computing elements. The results are subsequently passed through several layers of neurons and finally reach the output layer, where the result is returned. The existence and exact number of layers as well as the overall network architecture heavily depend on the problem to be solved and the approach taken.

In comparison to the extensive and established history of using genetic algorithms (GA) in pulse and pulse sequence generation, the utilization of artificial neural networks

(ANNs) appears to be relatively nascent. Apart from seminal work dating back to 1990 (see below), significant advancements in this field have predominantly occurred over the past decade.

The first mention of the use of ANN in the context of RF pulse design dates to the 1990 work of Gezelter and Freeman. After a brief, then-state-of-the-art description of the ANN theory, they showed proof-of-concept generation of a shaped pulse. The so-called JANUS pulse was designed to prepare antiphase magnetized multiplet directly from an equilibrium magnetization. This was intended to be further used for selective coherence-transfer experiments (INEPT, COSY) or double-quantum filtration (INADEQUATE) [42].

Following this early work, there was a significant gap in research on the topic for nearly three decades. In 2018, Vinding et al. reported the application of ANN for ultrafast design of multidimensional RF pulses for MRI purposes These pulses are particularly valuable in clinical settings, such as localized spectroscopy, where only a precisely defined, three-dimensional region of the body should be irradiated [43]. Complex irradiation patterns are often of limited practical utility due to the complexity and length of time required for calculating the necessary pulses. Using ANN, the authors reduced the calculation (or rather prediction) time to milliseconds.

In subsequent work the Vinding's team developed a convolutional neural network prediction of two-dimensional RF pulses. The tool was capable of on-the-fly designing RF pulses (within 9 ms) to excite hand-drawn areas, with compensation of subject-specific B_1^+ inhomogeneity and d B_0 offset up to 600 Hz at 7 T magnet. The method resulted in a small risk of pulse amplitude overshoot in case of $\pi/3$ pulses [44]. The pulse overshoot is a situation when a pulse amplitude momentarily reaches higher than nominal value (Fig. 8). In later investigations, the authors identified a significantly higher risk of amplitude overshoot for $\pi/2$ pulses. Consequently, the method underwent further development to address this issue without compromising its inherent advantages [45].

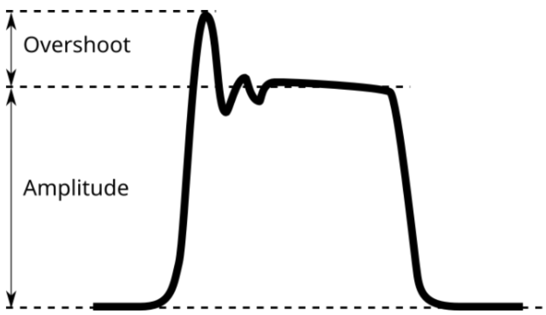

Fig. 8. RF pulse overshoot – the pulse amplitude reaches higher then expected value at the begining. (scheme based on[46]).

Shin et al. used deep reinforcement learning to design multiband RF pulses for MRI. Multiband pulses are used to excite several slices at once, speeding up the MRI data acquisition. The authors combined the DNN with greedy tree search algorithm (an optimization algorithm) to minimize the peak amplitude [47].

The ideas behind the use of deep reinforcement learning applied to the RF pulse design was further explored by the same authors. Their DeepRF algorithm was shown to be able to generate slice-selective excitation and inversion pulses, B_1-insensitive volume inversion pulses and B_1-insensitive selective inversion pulses [48].

In 2021 Loktyushin et al. introduced the MRzero framework that generates RF sequences for MRI, whose 2D excitation profile reassembled arbitrary image data. No *a priori* knowledge was required for the system to learn how to produce a sequence for a given MRI experiment. The neural network supervised learning was governed by the results of simulations based on the Bloch equations. The resulting model was then used for experiments on a phantom and volunteer's brain, confirming the ability to excite 2D areas in agreement with the provided source images [49].

In 2020 Veglia and Manu received a patent for the method for creation of RF pulses with triple compensation at a high level of fidelity. The so-called GENErator of Triply Compensated pulSes (patented as GENETICS, in later articles referred to as GENETICS-AI) is an RF pulse optimizer and generator whose mode of action heavily relies on both the neural networks and genetic algorithms. The core library of constant amplitude, variable amplitude pulses was generated by an evolutionary algorithm. Subsequently, the ANN fed with that data was trained to find optimal pulses for a given problem [50].

This software was used for the development of novel binomial sequences – water irradiation devoid (WADE) pulses. Their mode of action is to excite as much as possible of the offset spectrum while performing the identity operation on the on-resonance frequency. The WADE pulses are of constant amplitude and phase π-shifted. In order to experimentally verify the usefulness of the WADE pulses they were incorporated into a TROSY-HSQC pulse sequence. Such modified WADE-TROSY experiments were found to have up to 70.5% higher SNR than standard Bruker trosyetf3gpsi.2 [51].

Later it was found that upon incorporation of the WADE pulses into the NOESY experiment (based on noesygpph19 from the Bruker library), a higher number of NOE crosspeaks was observed, compared to excitation sculpting (ES) NOESY spectrum. Most of the additional crosspeaks come from the H^N-H^N interactions which are invisible in standard NOESY due to fast exchange of these protons with water. The average intensity of the spectrum increased as well by a factor of about 54% (compared to ES-NOESY) [52].

The GENETICS-AI platform was used in an extensive research project, covering quantum computing, NMR and MRI [53]. In the field of QC, a model two-qubit quantum computer was prepared from $^{13}CHCl_3$. High fidelity spin entanglement between the ^{13}C and ^{1}H nuclei was achieved. For NMR applications the high bandwidth (over 40 kHz at 99.99% fidelity) π and $\pi/2$ shorter than 300 μs were reported. Extending the pulse duration to 1350 μs allowed to reach 500 kHz high fidelity bandwidth which is far from possible using rectangular pulses. Moreover, the pulses are highly resistant to the instrumental noise and pulse miscalibration. On the BB channel the GENETICS-AI-generated pulses outperformed any known to date shaped pulses reaching, for example, 750 kHz bandwidth at 1.5 ms pulse duration. In the field of MRI, the authors showed GENETICS-AI capability of generating pulses for RF inhomogeneity-compensated sin-echo (SE) sequences. These GEN-SE sequences were shown to be highly inhomogeneity-insensitive, compared to rectangular pulse-based spin-echo sequences, as tested on a phantom [53].

Recently, the usefulness of GENETICS-AI was tested on a high-field 900 MHz spectrometer. NMR experiments at high and ultra-high fields are prone to technical difficulties due to significantly longer relaxation times and problematic excitation of the high bandwidth with hard pulses or even classical shaped pulses. With use of the triply compensated pulses developed with aid of GENETICS-AI Manu et al. were able to increase sensitivity of re-engineered ^{1}H-^{15}N TROSY-HSQC spectra [54]. GENETICS-AI was also employed to enhance overcome the limited irradiation bandwidth, inadequate compensation levels and pulse imperfections in SOFAST-HMQC spectra. With the triply compensated pulses a new RAPID-HMQC experiment was developed [55].

In addition to the problem of pulse sequence generation it is worth mentioning that the lack of unified naming conventions leads to significant problems with sharing and exchanging the data on the web. Several naming proposals of the unification have been suggested yet no real standard has emerged to date. To address this problem Liang et al. used a supervised machine learning model (a random forest model) to recognize and classify a given sequence type. The model raises a flag when the encountered sequence does not belong to any earlier known type [56].

Summary and perspective

The history of AI-developed magnetic resonance pulses and pulse sequences can be traced back to the late 1970s, but until recently, progress has been fragmented, with many early works serving as proof-of-concept studies without significant follow-up. However, over the past decade, there has been a notable shift, with AI-driven search for RF pulses evolving into a comprehensive scientific endeavor for select research groups. This transition has been facilitated by the development of dedicated frameworks and software such as DeepRF, MRzero, and GENETICS-AI, which could potentially pave the way for the widespread adoption of AI-generated pulses within the NMR and MRI communities.

The growing refinement and accessibility of AI-developed pulses, coupled with software interfaces, hold the promise of integration into routine NMR and MRI experiments. This could significantly streamline data acquisition processes, enhance sensitivity and resolution, and introduce novel possibilities in experimental design. AI-generated pulses could be tailored to specific experimental requirements and sample characteristics. Real-time adaptation of pulse sequences through machine learning algorithms may provide researchers with unprecedented control and versatility in their experiments, allowing for more intricate and specialized investigations. Pushing the boundaries of sensitivity, resolution, and imaging speed will be essential for unlocking the full potential of AI-driven pulse design in magnetic resonance applications.

In recent years, a significant shift from the GA to ANN-based methods for AI-supported pulse sequence generation can be seen. Specifically, deep learning methods seem to progress towards rapid and effective generation of RF pulses for space-selective excitation in MRI. It can be expected that once those methods reach sufficient stability and replicability, they will be incorporated into the standard libraries of MRI experiments. Most possibly this will expand the available palette of diagnostic techniques. Thus, it could be predicted that at some point the AI-based pulse generation frameworks will be further developed not only by academics but also MRI manufacturers. Increase of the spatial excitation selectivity or artifact reduction might contribute to enhancing the market advantage.

It is worth to mention that while the advances in the field of NMR are significant and of high importance from a scientific and cognitive point of view, they usually touch sophisticated, cutting-edge techniques (with the historical exception for solvent-suppression). Further research should also explore the AI-based optimization of pulse sequences for routine spectroscopy. Obviously, not much is to be done to simple 1D experiments, however the refinement of 2D or 3D correlation spectra or diffusion experiments in terms of the acquisition time, resolution, artifact removal, etc. might strongly impact the NMR community. It could be predicted that future releases of the spectrometer controlling software of major spectrometer manufacturers will include AI-based tools for experiment optimization.

In conclusion, the fusion of artificial intelligence and magnetic resonance pulse design represents a promising frontier in the field of spectroscopy and imaging. By harnessing the power of machine learning algorithms, researchers have the potential to revolutionize data acquisition, analysis, and interpretation in NMR and MRI, ultimately advancing our understanding of complex biological systems and materials.

Conflict of interests

The author declares no conflict of interests.

Acknowledgements

Paulina Tokarz and Ryszard Nazarski are acknowledged for their valuable contributions through fruitful discussions and meticulous review of the manuscript.

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