Transcranial Ultrasonic Neuromodulation of the Mesolimbic Dopamine System: Towards Push-Button Hedonism

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Abstract

Direct electrical stimulation of specific deep brain regions including the mesolimbic system has been shown to produce compulsive self-stimulation behavior in a range of mammals including humans. Transcranial focused ultrasound has been demonstrated to produce cortical neuromodulation in humans, although the mechanism remains unknown. The field of HIFU ablative surgery now routinely uses phased arrays of transducers to electronically steer an ultrasonic focus, at power levels two orders of magnitude higher than required for neural activation. Techniques from acoustic microscopy provide a convenient non-invasive way to determine both skull thickness and speed of sound in the corresponding skull region, so that the phase corrections needed to achieve transcranial focusing can be quickly ascertained without the need for CT data and simulation.

Development boards with entry-level FPGA chips (e.g. Xilinx Spartan 6) can be used for multichannel burst generation with more than adequate phase accuracy (< 0.7 degrees of phase error at 500 kHz). Low output impedance Class D amplifiers using an integrated GAN half bridge per channel can then amplify the phased FPGA logic level outputs to a 600 Vpp bipolar RF signal to drive small size medium-power ultrasonic transducers to stimulate deep brain regions and thereby safely and non-invasively produce compulsive self-stimulation of pleasure centers in human subjects.

Introduction

Reports abound in early literature on the dramatic effects of direct electrical stimulation of deep-brain septal and hippocampal regions by physically implanted electrodes. In many studies subjects, including humans, with electrodes implanted in these "pleasure centers" would activate them compulsively, self stimulating at rates of several hertz or more and continuing the self stimulation to the point of metabolic exhaustion [Olds1958, Lilly1958, Delgado1969, Moan1972, Portenoy1986].

Although these results are compelling, the attendant difficulties, expense and risks of transcranial electrode implantation mandate a search for alternative less invasive neurostimulation modalities capable of safely generating comparable experiences of pleasure at the press of a button.

Recent results report that focused ultrasound can modulate the activity of the primary somatosensory cortex in humans [Legon2014]. Additionally, results from the ablative neurosurgical literature demonstrate that phased arrays of high powered ultrasound transducers (HIFU) can precisely target deep brain areas, with spatial resolution similar to that of implanted electrodes and at power levels two orders

of magnitude higher (1000 W/cm^2) than needed for neurostimulation [Hynynen1998,Clement2000].

Finally, results from the ultrasonic imaging literature indicate how both skull thickness and speed of sound in the skull, parameters which both must be determined for the phase correction of ultrasound applied transcranially, can be easily and inexpensively determined to a sufficient accuracy [WangJing2013].

As for the apparatus, a very low cost implementation of a phased array transcranial ultrasound stimulator is feasible. Low-end FPGA chips permit low cost phase accurate pulse generation with 48 or more channels, MOSFET based digital amplifiers offer a low cost means of powering transducer arrays, and the transducers themselves can be conventional medium-power PZT.

Development and deployment of this hedonic technology, which extends the promise of the abolition of human suffering, can be seen as an urgent ethical imperative [Pearce2008, Pearce2015].

Direct electrical stimulation of the brain

Although no longer fashionable, in the late 1950s and early 1960s experimental work in direct electrical stimulation of the mammalian brain was conducted by a number of pioneers using implanted electrodes. Current levels were typically on the order of several milliamperes and pulse durations microseconds in length, with these brief pulse trains repeated on the order of 100 Hz.

Olds and Milner showed that rats would cross an electrified floor grid in order to each a lever which when depressed would briefly supply a small current to a set of electrodes implanted in the rhinencephalon or parts of the hypothalamus [Olds1958]. Remarkably, to reach the self-stimulation lever the rats would endure a higher voltage shock from the electrified floor grid than they would tolerate to reach food when they were hungry. These experiments made it very clear that electrical brain stimulation could be highly motivating, and Olds concluded: "Roughly, we may say that the motive to self-stimulate appears to be (in some cases) at least twice as strong as the motive of a 24 hour hunger drive." [Olds1960]

Lilly conducted extensive experiments to map the brains of monkeys, investigating electrode implantation in about 500 locations in a number of subjects [Lilly1960] and unexpectedly discovered that the brain regions in which electrical stimulation was rewarding (regions for which self-simulation was voluntarily commenced and continued by the simian subject) far exceeded in volume those areas for which stimulation was aversive (i.e. regions where the subject would behave so as to terminate stimulation of those areas). In certain regions, self-simulation was so compelling to the animal that they would continue to self-stimulate for as long as they remained physically able to continue: "One outstandingly exceptional region has been found, probably in the basal tegmentum of the mesencephalon. In this region each train excited muscle contractions over the whole body. The monkey learned to use these contractions to obtain mechanical resonance with the trigger and could reach 18 triggerings per second for brief periods in bursts. After each such burst of activity his hand fell of the trigger and he would bark, in an "inquiring" fashion, pause, and start another burst. He worked, in this pattern, to complete exhaustion and sleep after 20 hours and 200,000 trains." [Lilly1960]

Although studies involving implanted electrodes in humans are not as numerous as for other mammals, being generally confined to patients with medical conditions including psychosis, epilepsy and movement disorders, there exist a number of published results demonstrating human compulsive self-stimulation behaviors similar to those seen in the earlier animal experiments.

In a range of studies Heath showed a consistent pleasurable response to stimulation of septal regions. [Heath1963] In one experiment, the subject "stimulated himself to a point that he was experiencing an almost overwhelming euphoria and elation, and had to be disconnected, despite his vigorous protests". [Moan1972]

Describing one patient with hippocampal electrodes, Heath reports: "The elevation in mood and heightened awareness involved development of a sexual motive state and in most instances, within another 5 to 10 minutes, this culminated in repetitive orgasms. Not only did the patient describe the response when questioned, but her sensuous appearance and movements offered confirmation". [Heath1972]

Delgado also demonstrated the ability to trigger euphoria in subjects through septal stimulation [Delgado1969]. In some cases, the effect was strong enough to counteract depression and physical pain [Horgan2005].

Comparable results were reported by Sem-Jacobsen: "From strong pleasure areas we have found that the patients stimulate themselves into a convulsion. In the post-ictal stage these patients were lying relaxed, smiling happily, contrary to the restless fighting frequently observed in patients after electronic treatment." [Sem-Jacobsen1960]

More recently it was observed that a human patient with a stimulating electrode implanted in the right thalamic nucleus developed compulsive self-stimulation associated with erotic sensations. Self-stimulation was so compelling that the patient developed an ulcerated fingertip from adjusting the stimulation device: "Despite several episodes of paroxysmal atrial tachycardia and the development of adverse behavioral and neurological symptoms during maximal stimulation, compulsive use of the stimulator developed. At its most frequent, the patient self-stimulated throughout the day, neglecting personal hygiene and family commitments. A chronic ulceration developed at the tip of the finger used to adjust the amplitude dial and she frequently tampered with the device in an effort to increase the stimulation amplitude." [Portenoy1986]

Remarkably, this intensely rewarding direct electrical stimulation of the mesolimbic dopamine system exhibits no tolerance. Subjects do not tire of the pleasure induced by such stimulation, which has been experimentally verified to be more rewarding than food, sex, or any of the many other indirect routes to pleasure pursed by humans.

Permanent electrode implantation in mammalian brains is relatively benign, with some subjects tolerating long-term electrode implantation for up to 14 months with no averse side effects [Delgado1955]. Nonetheless, the attendant small risks of infection and hemorrhage or glial proliferation along the the electrode tract lead us to seek an alternative modality for the stimulation of deep brain pleasure centers.

Transcranial Magnetic Stimulation

Non-invasive neurostimulation techniques exist. Development of transcranial magnetic stimulation (TMS) has shown that a magnetic field produced by a coil

positioned near the scalp can induce an electrical field in adjacent cortical regions. Provided that the magnetic flux is of sufficient magnitude (typically several tesla) and changing rapidly enough (pulse times on the order of 100 microseconds), and when the induced electric field differs in strength across a neural membrane, the change in transmembrane potentials can cause neural firing [Walsh2005].

TMS has proven itself to be a practical tool for cortical studies, and multipulse repetitive TMS (rTMS) is experimentally used for a wide range of psychiatric disorders, and has been FDA approved for the treatment of depression [Mishra2011]. However, physics prevents TMS from being practical for deep brain stimulation. It has been proven that the three-dimensional maximum of the electric field intensity will always be located at the brain surface for any configuration or superposition of TMS coils [Heller1992]. This implies that deep brain regions cannot be stimulated by TMS without far higher electric field strengths being present in cortical regions. And the presence of these higher field strengths in cortical areas necessarily causes a wide range of undesirable effects which could be avoided with a more focal stimulation technique.

In Vivo Ultrasonic Neuromodulation

Another mechanism for inducing neural activity is focused ultrasound. The stimulating effect of ultrasound on neural tissue has been known for almost a century, since the twitching of a frog's sciatic nerve was observed when stimulated at 340 kHz [Harvey1929].

Tufail et.al. were the first to report in vivo ultrasound neuromodulation in mice with a single us transducer [Tufail2010]. Yoo et.al. used us neuromodulation to both stimulate and suppress regions in somatamotor and visual areas in rabbits [Yoo2011]. A similar us signal applied transcranially to the S1 primary somatosensory cortex in human subjects was found to have both EEG and behavioral effects [Legon2014].

Sonification parameter studies have been conducted [King2013, Kim2014]. These indicate that for human neurostimulation a reasonable initial set of waveform parameters uses pulse train bursts at 500 kHz, with bursts of 360 microsecond duration repeated at 1 kHz for 500 ms. The 500 kHz frequency is near optimal for the minimization of absorption by the skull.

The Isppa power levels of about 24 W/cm^2 used in human experiments [Legon2014], is well below the FDA recommended limit of 190 W/cm^2 for ultrasonic diagnostic imaging, in addition to being applied with a lower duty cycle. Tissue damage from high intensity focused us can be caused by heating, even at at power levels below which mechanically destructive cavitation occurs, yet a temperature increase is not required for neurostimulation.

The mechanism by which us causes neuromodulation is not yet understood, although there is speculation that the induced mechanical oscillations deform neuronal cell membranes, or proteins embedded therein, so as to affect ion channel kinetics in a manner that promotes depolarization [Tyler2011].

These early experiments with human ultrasonic neurostimulation have all used a single fixed-focus transducer.

However, it is abundantly clear from the extensive ultrasonic surgery literature

that apparatus to electronically steer in 3d a small focal spot of ultrasound of adequate amplitude to induce neural firing is already mature.

Phased Arrays in Ultrasonic Ablative Surgery

High intensity focused ultrasound (HIFU) has been used since at least 1971 for ablative neurosurgical treatment of movement disorders [Gavrilov1976]. High acoustic power levels (on the order of 1 kw) are used to heat localized areas of brain tissue to levels at which thermal damage by protein denaturation occurs, above 56 C. These are far higher power levels than used for us neurostimulation, where no observable thermal effects occur [Legon2014].

The electronic steering of a phased array ultrasonic focus is a long established practice in the field of ultrasonic surgery. An electronically steerable focus can be achieved by the use of a phased array of us transducers. Each transducer is powered by a separate individually controllable RF amplifier. The relative phases of the respective signals feeding the transducers are timed in such a way that the effective radiation pattern of the array is reinforced in a desired direction and suppressed in undesired directions, with compensation for distortions introduced by the skull.

Hynynen was the first to demonstrate focusing through an (ex vivo) skull with a 64 element phased array [Hynynen1998], which was later extended to a 500 element array [Hynynen2004]. Other groups have built similar research systems [Hall2006].

The maturity of this technology is signaled by the existence of a commercial available MRI-guided ultrasound surgery system (http://www.insightec.com) which has been used for treatment in humans of glioblastoma [McDannold2010] and thalotomy for essential tremor [Elias2013].

Phase Correction Techniques

The human skull impedes ultrasonic waves, strongly reflecting and scattering them in addition to changing their velocity and causing refraction.

In order to focus an ultrasonic signal transcranially, it is necessary to know (in addition to the stereotactic details of position and orientation) the skull thickness and speed of sound in the skull (sos) at that position. The sos value varies considerable with position due to bone porosity variations.

With the skull thickness and sos parameters determined, phase corrections can be applied to the ultrasonic signal to compensate for the presence of the skull.

A variety of approaches to determine skull thickness and sos parameters have been proposed in the literature. One method is to measure thickness and infer density information from data derived from a CT scan [Clement2002]. In yet another approach, MRI data is used to estimate skull thickness, and used together with the minimum of the spectrum of a reflected pulse to determine the phase correction. [White2005]. In recent us ablative neurosurgery with commercially available apparatus, the focus is interactively steered with a 3d indication of the position

of the focus made visible using MRI thermometry (TcMRgFUS).

Unfortunately, these methods either require very expensive and specialized apparatus or have other shortcomings which make their mass deployment infeasible.

However, there exists a simple low-cost approach for skull thickness and sos determination which originated in the time-resolved acoustic microscopy literature. Hanel's "double focus" technique used us focused on both the front and back surface of the skull, with the timings of the reflections together with geometry and Snell's Law to simultaneously determine the thickness and sos. [Hanel1999]. This method has been improved to utilize a phased array for virtual focusing [Wydra2013] and to also account for scalp thickness [WangJing2013].

A small linear phased array, the length of which is sufficiently small so the array remains approximately tangent to the skull, can be used together with the same experimental apparatus which powers an array of larger transducers spaced hemispherically around the skull for the deep brain stimulation. (An HP 21200B 2.5 MHz cardiac probe is suitable.)

Research Apparatus Overview

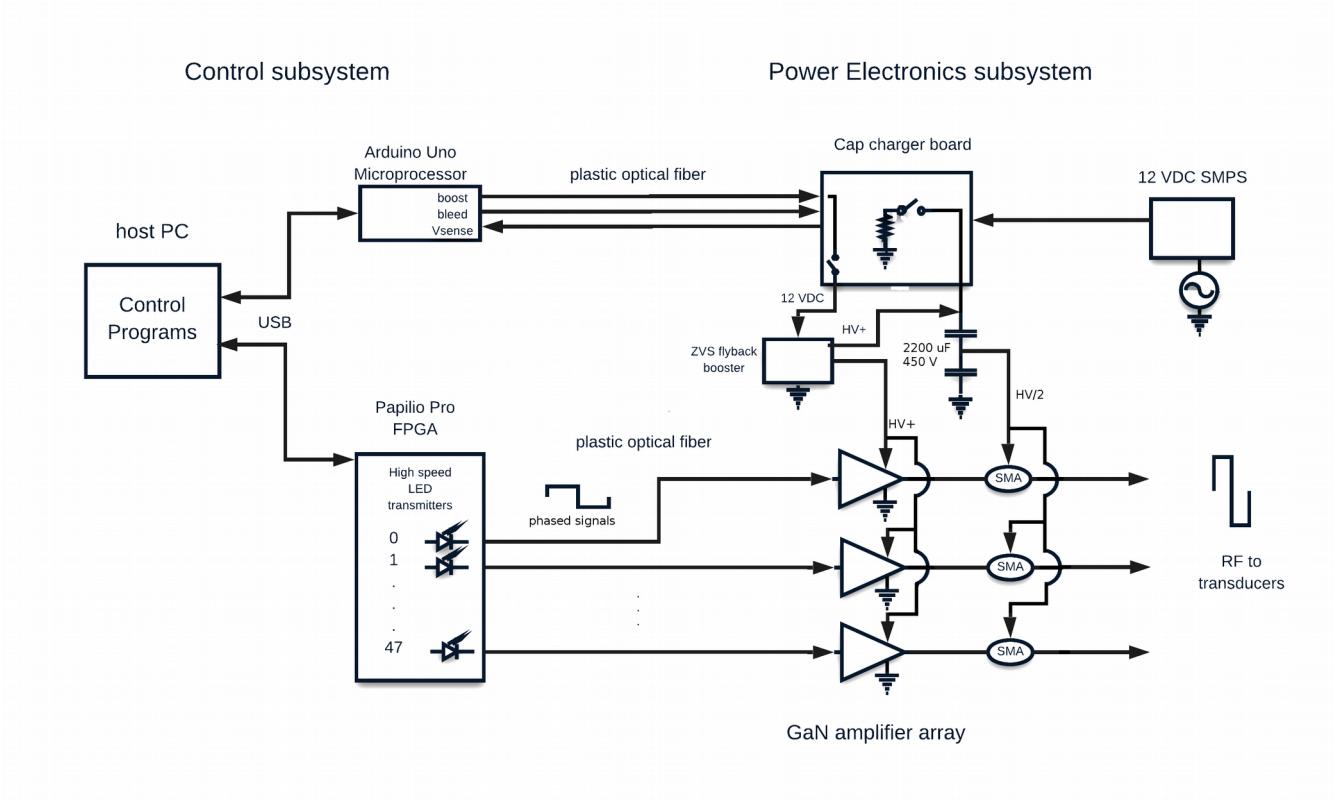

Fig.1 Pulser Mark 5 Architecture

We have designed and constructed a simple and low cost multichannel phased array ultrasonic pulser apparatus, suited for ultrasonic neuromodulation research.

Figure 1 shows a block diagram of the architecture of the latest version (Pulser Mark 5). It is superior in performance to the system of [Santos2011], and incorporates a new type of highly efficient half-bridge amplifier.

There are up to 48 channels of ultrasonic output. Waveform parameters under software control include:

Frequency (range [126,2500] kHz)
Cycles per burst (range [1,1023])
Burst repetition frequency (range [0,2] kHz)
Number of bursts (range [1,1023])

These parameter ranges include the values found to be effective for transcranial focused ultrasound stimulation in both rats [Kim2014] and humans [Legon2014].

In addition to these four waveform parameters, each channel has an associated phase delay parameter, specified in clock units of 3.90625 ns. (At a nominal 500 kHz, this is less than 1 degree of phase.) These independent phase parameters allow dynamic steering of the focal spot under software control.

The phased signal bursts are produced by an FPGA, which is controlled via a USB link by programs running on a Linux host computer. On the host side, burst parameters can be specified and a burst triggered either from the command line or with a simple GUI.

Each FPGA output channel is connected to an independent modular Class D amplifier based on a novel GaN (gallium nitride) half bridge chip, the Navitas NV6252. Each amplifier can drive a transducer with a bipolar square wave of up to +- 300 V in short burst trains.

This switching amplifier design is more power efficient and much lower cost than a standard RF power amplifier. The square wave output contains harmonics of the drive frequency, but this is acceptable for ultrasound neuromodulation applications which are not concerned with spectral purity [Gulick2015].

The amplifier high voltage rails are supplied by a pair of electrolytic capacitors. These capacitors are charged by a ZVS flyback transformer, supplied by a small DC switching power supply powered by 110 VAC mains. The capacitor voltage set point is controlled by a microprocessor, which also communicates with the Linux host via USB.

Figure 2 shows these components in a single channel version of the apparatus, without optical fiber isolation between the control and power subsystems.

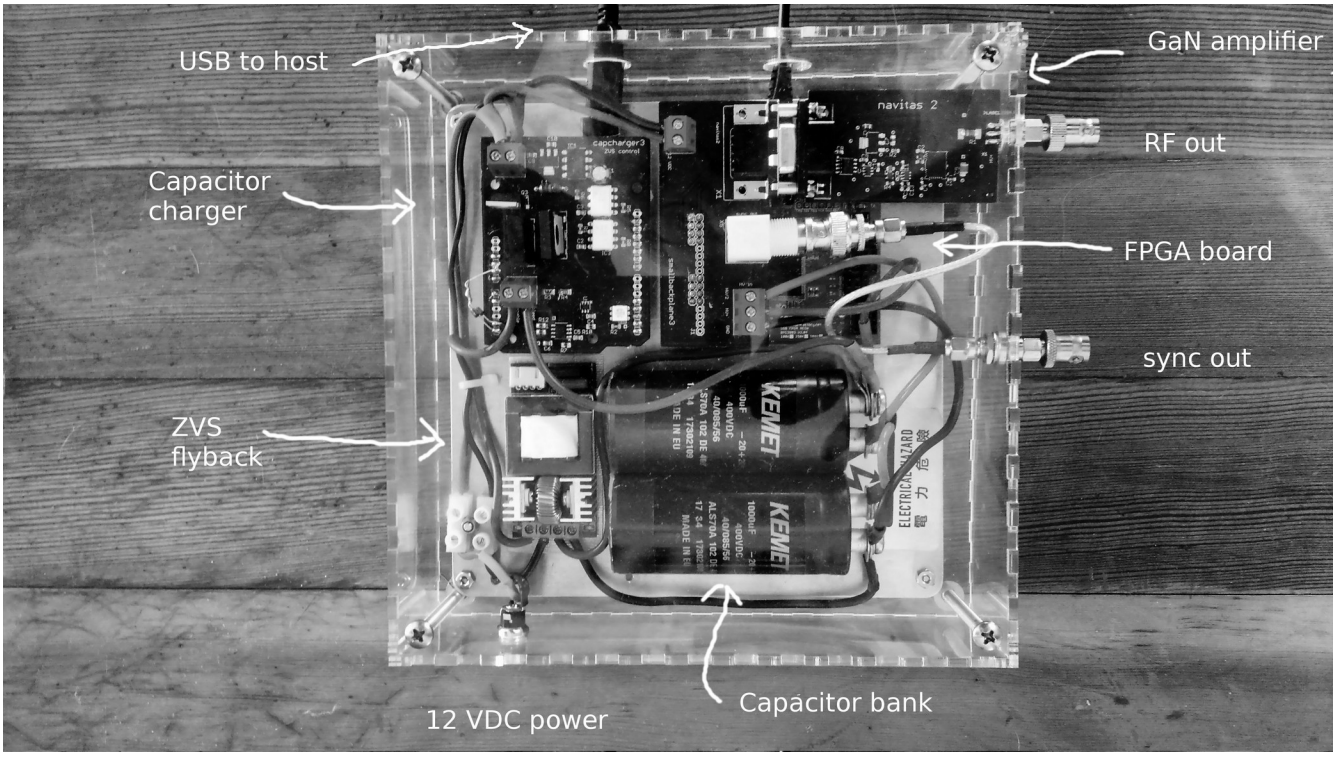

Fig.2 Single channel pulser

Due to significant amounts of EMI from the very high speed edges (200 V/ns) of the GaN FETs, in the latest version of the apparatus the FPGA signal generation and the power supply control microprocessor are in one RF shielded enclosure, and the power electronics (GaN amplifiers and capacitor power supply) are in a separate RF enclosure. These enclosures are electrically isolated and linked by plastic optical fiber.

Phased array signal generator

A Papilio Pro FPGA board is used for generation of the phased array signal, 48 channels. The Papilio is a low cost open source FPGA board with a Xilinx Spartan 6 LX9 FPGA. (http://store.gadgetfactory.net/papilio-pro-spartan-6-fpga-dev-board-with-sdram/)

Custom software for the Papilio was written in VHDL to program the FPGA for phase generation and communication with the host over USB. The VHDL source code is available HERE, and the freeware Xilinux ISE development Version 14.7 can be used to compile this code into the bit file (phasegen.bit) suitable for downloading to SPI Flash program memory on the Papilio board. No vendor-specific ip is used, except for the digital clock multiplier block. A 256 Mhz clock is synthesized.

The Papilio board has a dual channel FT2232 chip for USB communication. Channel A

is connected to the JTAG pins of the FPGA and is used for downloading the FPGA .bit file. Channel B is used for 115.2 Kbps serial communication with the Linux host computer for transmission of the waveform parameters for an output burst train, and triggering the burst.

Running on the Linux host, the phasegen.pl Perl script accepts waveform parameters on the command line, transmits these to the FPGA, and enables output of the burst. Each invocation of phasegen.pl must be preceded by call to the fpa_reset script, which reflashes the phase generation code to the FPGA, ensuring a consistent initial state. This initialization step is handled automatically by the phasegen_gui.pl script, which also provides a rudimentary GUI for control of the waveform. The GUI is useful mostly for verification of the waveform parameters with an oscilloscope, but during experimental runs the FPGA is usually controlled by programmatic invocation of the command line phasegen.pl script. Typically, phase delay parameters are calculated programatically, for example to determine delays appropriate for the circular focus of a phased array, then the phasegen.pl script is called with these computed parameters.

GaN Power Amplifiers

The 3.3 V waveform output signals of the phase generator are amplified to drive the piezoelectric transducers. As the channels differ in phase, we use a discrete amplifier per channel. The multichannel nature of the apparatus allow it to deliver a much higher power than a single channel stimulator, as the output current is in parallel across the channels.

A wide variety of ultrasound amplifier designs exist in the literature, a comprehensive review can be found in chapter 3 of [Wang2016]. Analog amplifiers (classes A, B and AB) have far lower efficiency than switched mode amplifiers such as class D, in which the output transistors operate as digital switches.

Half bridge class D topologies are popular for ultrasound amplifiers [Hall2006] [Lewis2009] and are much lower cost than standard RF amplifiers though they can only output square waves of an amplitude defined by the HV rails. The class D amplifier simply switches its output between the voltages on the HV rails. For ultrasonic neuromodulation applications, spectral purity is not essential, as long as side lobes can be minimized through appropriate phasing. For CW operation at HIFU power levels an LC tuning network on the output would be needed to filter higher harmonics, but heating due to reflected power is not a practical problem when burst trains are short as needed for neurostimulation.

Amplifiers can produce either unipolar or bipolar outputs. Unipolar outputs polarize the transducer in one direction only with a voltage swing between 0 and +HV, whereas bipolar output alternate polarities of -HV and +HV across the transducer. The latter is desirable for optimizing mechanical output of the transducer, but necessitates a more complex, bipolar, power supply design.

Earlier versions of our pulser used a Microchip MD1213 driving a TC6320 dual N- and P-channel MOSFET pair. This MOSFET pair is very common in both medical imaging ultrasound equipment (such as the Telemed LS-/tmp/gui128 beamformer) and in research [Qiu2012][Wu2013] but is limited to 100 V.

Recently developed Gallium Nitride (GaN) high electron mobility transistors have the advantages over silicon FETs of lower device loss at high switching frequency and high power density. Our amplifiers use the Navitas Semiconductor NV6252 half

bridge power IC, rated at 650 V and 6 A maximum pulsed output current. The higher voltage rating allows our apparatus to much achieve higher peak ultrasound pressures, which vary with the square of the voltage, than can lower voltage devices.

Our amplifier design is also motivated by that of [Lewis2009] who observes that the tradition of building ultrasound amplifiers with 50 ohm output impedance results in a mismatch with the impedance of typical transducers, the latter being much lower than 50 ohm. A lower impedance amplifier results in more efficient power transfer, without need for impedance matching circuitry.

The GaN half bridge is driven by dead time circuitry, adapted from the TI LMG5200EVM-01A evaluation module, to avoid shoot through. Eagle files and BOM for the amplifier are HERE.

We have used our GaN amplifiers at lower voltages to drive linear phased array probes (such as the HP21200) for phased array reflection tests, and at higher voltages to drive transducers such as the Shenzhen Hurricane Tech. TD0500KA transducer and other larger HIFU transducers.

Power Supply

Audio power amplifiers typically use mains current into a center-tapped transformer, rectified by a diode bridge, then followed by filter capacitors, to provide bipolar DC output.

Our power supply design avoids the expense and weight of a transformer, and more importantly ensures safety by limiting the total amount of energy the apparatus can deliver to that stored in pre-charged capacitors.

The HV rails of our amp are powered by a pair of electrolytic capacitors (2200uF 450V) connected in series. The midpoint of the series connection of the capacitors is wired to the shield of the SMA RF connectors powering the transducers. The amplifier switches the center connection between chassis ground and the HV+ terminal of the series capacitors to achieve bipolar output. The HV- terminal of the series capacitors is bonded to chassis ground. In operation, the transducer receives a bipolar square wave. NOTE: This means you CANNOT connect the amplifier outputs directly to test equipment such as an oscilloscope that connects cable shield to chassis ground, as the RF output connector of the amplifier is at HV/2 (half the voltage of the capacitor bank) with respect to mains ground! To connect amplifier output to an oscilloscope, use only the center terminal of the amplifier RF out connectors, and ground the probe ground to chassis ground or use a differential probe. Also, cables from the amplifiers to the transducers must be constructed so as to avoid exposing the HV/2 voltage on the connector shield, which can be hazardously high.

The capacitor bank is charged by a very efficient Zero Voltage Switching (ZVS) flyback transformer of Mazilli design. Power to the ZVS system is controlled at low frequency by a large MOSFET switched by an Arduino, which also senses capacitor bank voltage using a 16 bit I2C ADS (ADS1110). When the capacitor voltage exceeds the voltage set point, and when the system is to be shut down, the capacitor bank is discharged by using another power MOSFET to switch in a 5.6 K bleed resistor rated to 700 V and 100 W.

During a burst train, the voltage delivered to the transducers will decrease

slightly as the capacitor bank discharges. The capacitance can be chosen to be sufficiently large to mitigate this to any degree desired. When used with a large number of channels, the capacitor bank size should be increased to compensate for the addition of channels, to be able to maintain the same voltage drop for a given set of burst parameters.

Optoisolation

The fast edges of the high voltage output of the GaN amplifiers emits RF interference. To contain this, the power electronics (GaN amplifier array and capacitor charger) are housed in a RF shielded enclosure. This is connected to the control electronics subsystem (FPGA phase signal generator and Arduino capacitor charger controller) with an array of plastic optical fibers. The distance between the control and power electronics subsystem enclosures can be at least several meters, the fiber is inexpensive.

The phased signals' transitions which switch the amplifier must be both fast in their rise and fall times and low jitter (both intra and inter-channel) to avoid introducing phase distortion which would defocus the ultrasonic array. The optical receivers on the GaN amplifiers are Broadcom AFBR-2624 with integrated photodiodes, capable of operating at up to 50 Mbd. These are driven through 1 mm plastic optical fiber by Broadcom AFBR-1624 LEDs.

The Arduino based capacitor charger also uses plastic optical fiber to communicate with the capacitor charger board in the power electronics subsystem. An LM331 voltage-to-frequency encoder on the capacitor charger board reads cap bank voltage through a resistor divider and transmits it to the Arduino using a low cost IR LED, the Industrial Fiberoptics IF-E91A. An IF-D95T photologic detector at the Arduino end has ample bandwidth to receive the digital signal from the LM331.

Host Programs

Command line program, phasegen.pl

On the PC host side, phasegen.pl communicates via USB with the Papilio Pro FPGA board. The program phasegen.pl is a Perl script with accepts command line arguments specifying the burst parameters.

The positional command line arguments are respectively as follows. Each of these is a 10 bit integer.

1) Fundamental frequency of the ultrasound.
This is specified as half of the period of the ultrasound signal, in clock units. Each clock unit is 3.90625 ns. For example, to specify a 500 kHz frequency, which has a period of 2 microseconds, half the period is 1000 ns so the parameter would be supplied as 256 (since 1000 / 3.0925 = 256).

2) Cycles per burst.
A burst train consists of a number of bursts. This parameter the number of cycles (at the fundamental frequency) in each burst. For example, for a "one shot" emission of a single cycle, this parameter would be specified as 1. Instead of cycles per burst, the [Tyler] experiments specified a burst duration of 360 microseconds. At 500 kHz this is the same as 180 cycles per burst.

3) Burst period.
The cycles per burst gating is reset after this many cycles of the fundamental frequency.

4) Number of bursts.
This parameter specifies the number of bursts to be emitted.

5) Array of phase delays, one per channel.
Phase delays are given in clock units. The default value for all channels is zero, i.e. bursts from all channels fire synchronously. This default can of course be used for testing inter-channel jitter. After transmitting the specified parameters to the FPGA board, the burst train is triggered. If phase delay parameters for some channels are omitted, the default value of 0 is used.

Here are some further examples.
For a one shot, specify cycles per burst as 1 (to request 1 cycle) and number of bursts as 1 (to request the 1 burst, consisting of 1 cycle):

```
phasegen.pl 255 1 500 0 0 0
```

Note that the phase delays for only 3 channels were specified, all of these given as 0. The phase delays for all other unspecified channels would have the default value of 0.

For a pitch/catch echo test one typically uses more cycles per burst. For example, to emit a single burst consisting of 3 cycles:

```
phasegen.pl 255 3 500 0 0 0
```

Graphical User Interface Program, phasegen_gui.pl

The parameters to phasegen.pl are supplied in ways which suit the VHDL code, and the quirks in this make it more convenient to use a higher level interface when manually specifying burst parameters. The script phasegen_gui.pl runs a Tk GUI interface with sliders for setting the burst parameters in more convenient units. For example, the fundamental ultrasound frequency is specified in kilohertz. Figure 3 shows the phasegen_gui.pl interface.

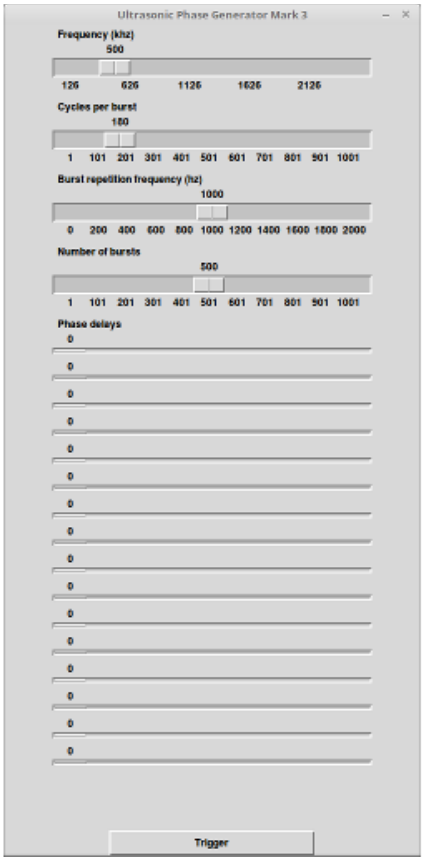

Fig.3 GUI interface

After transforming all parameters into the form expected by phasegen.pl, the phasegen_gui.pl invokes the command line phasegen.pl program, echoing the details of the parameters to stdout.

GaN Amplifier Performance

Use of a capacitor bank as the power source switched by the amplifiers allows large HIFU transducers with high capacitance to be driven with fast rise times and negligible waveform degradation. Figure 4 shows a burst of 3 cycles of 100 Vpp square-wave unipolar output at 500 Khz into a 53 mm diameter HIFU transducer (CNIR Hurricane Tech Shenzhen Co. Ltd.), captured at 500 MSa/sec with a Rigol DS1104Z oscilloscope.

Fig.4 Burst of 3 cycles into HIFU transducer at 100 Vpp (blue)

Rise time is under 10 ns. A dummy load consisting of a 1 kΩ 1 W resistor in parallel with a 220 pF capacitor to simulate a smaller transducer results in a rise time of approximately 5 ns.

Safety Considerations

Acoustic power can be characterized by a number of metrics including spatial-peak pulse-average intensity (Isppa) and spatial-peak temporal-average intensity (Ispta). Most crucial is to limit the peak rarefactional pressure to avoid cavitation. The brief (0.5 sec) sonifications required for neurostimulation do not cause appreciable heating, which scales proportionally with duration. [Tufail2010] reports that none of the ultrasound waveforms used to stimulate mice cortex elicited a significant change in cortical temperature within 0.01 C resolution limits.

[Legon2014] used a peak rarefactional pressure of 0.8 MPa for human cortical neurostimulation. [Tufail2011] reports that “at peak rarefactional pressures < 1 MPa, ultrasound has been found effective for acutely (tens of hours up to spaced trials repeated across weeks) stimulating brain circuits without producing damage in mice as assessed by cellular, histological, ultrastructural and behavioral methods."

Ultrasonic attenuation in human cranium is approximately 13 dB/cm [Pinton2011], which for an 8 mm thick bone represents a voltage loss factor of 3.3. [Legon2014] confirms experimentally the Isppa dropped by "approximately fourfold"

when hydrated cranium was inserted into the beam path in a test tank. Attenuation in water is 0.3 dB/(cm Mhz), at 500 khz, this is 0.6 dB/cm.

We used a custom deltabot positioner to move a calibrated hydrophone (HNR-0500, Onda Corporation) which has a nominal sensitivity of 250 nV/Pa to a 3d grid of positions around the focus of a 72mm focus HIFU transducer. Results rendered using Mayavi to show pressures at the grid points are shown as Figure 5, it is clear the focus is axially elongated.

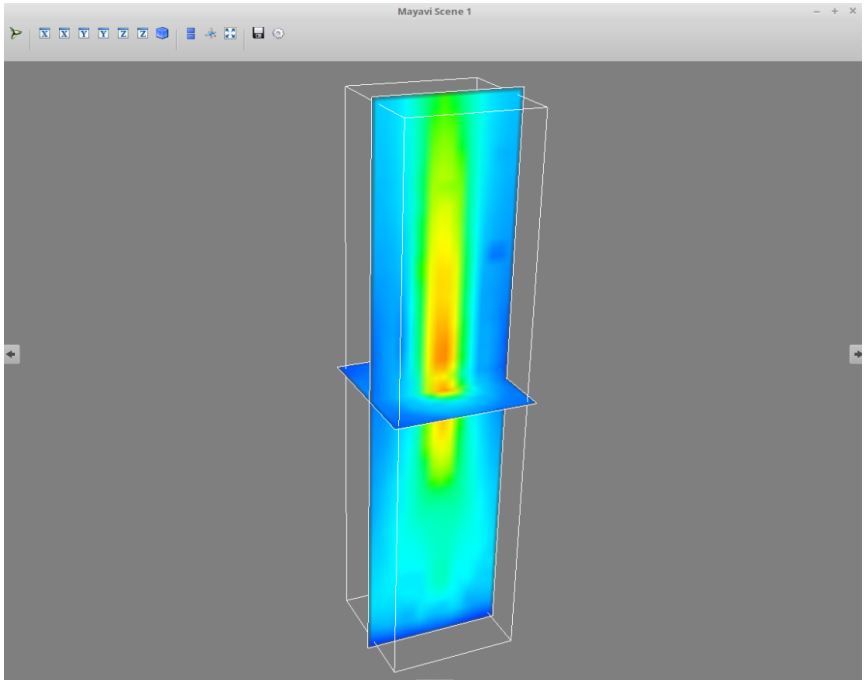

Fig.5 Focused HIFU transducer beam

At the experimentally determined focal point, an input voltage level of xxx V was necessary to achieve a peak rarefactional pressure of 4 Mpa, which would fall to the safety limit of approximately 1 Mpa after cranial attenuation.

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