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UNIVERSITY OF CALIFORNIA

Los Angeles

Improved PHIP Instrumentation

A dissertation submitted in partial satisfaction
of the requirements for the degree
Doctor of Philosophy in Bioengineering

by

Jose Luis Agraz

2013

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ABSTRACT OF THE DISSERTATION

Improved PHIP Instrumentation

by

Jose Luis Agraz

Doctor of Philosophy in Bioengineering

University of California, Los Angeles, 2013

Professor Daniel Ennis, Co-chair

Professor Debio Li, Co-chair

Existing Para-Hydrogen Induced Polarization (PHIP) instrumentation relies on four factors to hyperpolarize endogenous substances externally, a static magnetic field (B_o), temperature, pressure, and software sample control. These hyperpolarized substances have enhanced magnetic resonance imaging (MRI) signals over 1000 fold, allowing for molecular imaging. We discuss the improvements in B_o generation, sample heating, sample manipulation, and software sample control to produce polarized HEP. We show that: 1) A voltage controlled voltage source, 2) A modified pinch valve, and 3) LabView software sample control developed in our laboratory doubles the HEP polarization from previous efforts.

The dissertation of Jose Luis Agraz is approved.

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University of California, Los Angeles

2013

To my wife . . .
my love & sugar-mama

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PUBLICATIONS

Improved PHIP Polarization using a Low Noise Precision Voltage Controlled Cur-

rent Source. Submitted

LabVIEW Instrumentation control software for RF Transfer para-Hydrogen Induced Polarization. Submitted

LabVIEW Finger Force Sensor Instrumentation Design. Autotest Conference Sep 2013. Schaumburg, IL

Delta-Shaped Piezoelectric Ultrasonic Motor for Two-Dimensional Positioning. Jpn. J. Appl. Phys. 47 (2008) pp. 313-318

Sequential Finger Force Associated with Fatigue. 11th World Congress of Psychology, 2002. Montreal, Canada

CHAPTER 1

History & Introduction

Cancer, Alzheimer's, heart disease, and stroke are the leading causes of death and debilitation among Americans [MM12]. These diseases are poorly diagnosed at early stages and linked with considerable morbidity and mortality [Ass12][Soc12][RGJ11]. The current gold standard for muscle ischemia, cancer, and Alzheimer's disease screening varies from a simple self exam (breast cancer) [CS11], to troponin blood level test (Heart ischemia) [TCB12], to Computed Tomography (CT) scan (ischemia, cancer, Alzheimer's disease) [SRC03][KVH07][MDF84], and the more invasive needle and excisional biopsies [NIR07]. These methods have worked in the past, but as the understanding of disease expands, these methods are becoming obsolete for earlier disease detection [AVB12][BJC12][BBR12][FMY12]. Recent studies had shown that the understanding of cell signaling or administration of basic cellular activities, may lead to the diagnosis, treatment, and in some cases the prevention of disease. Cancers such as paraganglioma and pheochromocytoma (SDH), leiomyoma, and certain cases of renal cell carcinoma are linked to the abnormal accumulation of succinate and fumarate in cells. This mechanism enables aberrations in the Krebs's cycle [CS12][BSP12][XYX12]. Similarly, high levels of succinate in a failing heart have been shown, but the quantification of this mechanism and the key to heart disease is still unknown [Tur12]. Furthermore, the earliest sign of Alzheimer's disease (AD) is the reduction of cerebral glucose, studies have suggested the glucose metabolism is shifted (among other mechanisms) to the activation of the gamma-aminobutyric acid (GABA) shunt

as alternate source of energy. This short of energy leads to the brain digesting itself [Mam12]. Ensuing studies have shown mitochondrial abnormalities in AD patients [Mor12]. Equivalently to mechanism enabling aberrations in the TCA and high levels of succinate in a failing heart quantification, the energy consumption mechanism of an AD brain changes still eludes researchers.

Thus, transforming these metabolites such as; succinate and GABA, into Magnetic Resonance Imaging (MRI) contrasting agents, through the hyperpolarization method, is a promising, safe, and minimally invasive method for disease diagnosis to the cellular level [SBB07][GAP03].

1.1 Cell Pathways, the Key to Early Disease Detection

The Krebs's cycle, also known as the tricarboxylic acid (TCA) cycle, is the a basic cell metabolic mechanism that employs a series of chemical reactions to generate energy in the form of Adenosine Triphosphate (ATP) through oxidation of biological molecules. These series of chemical reactions, also known as pathways, modify an initial molecule to form another product, to either be used as the beginning of other pathways, intermediates to a pathway, or stored in the cell. Recent studies have shown that the detection of cell pathways, may lead to the diagnosis, treatment, and in some cases the prevention of disease. Cancers such as paraganglioma and pheochromocytoma (SDH), leiomyoma, and certain cases of renal cell carcinoma are linked to the abnormal accumulation of succinate and fumarate which are part of the Krebs cycle. Succinate and fumarate are referred to as intermediates substances, and are present in all living creatures. An abnormal accumulation of intermediates indicates aberrations in the Krebs's cycle [CS12][BSP12][XYX12]. Similarly, high levels of succinate in a failing heart have been detected, but the quantification of this increase and its role in the genesis of

heart disease is still unknown [Tur12].

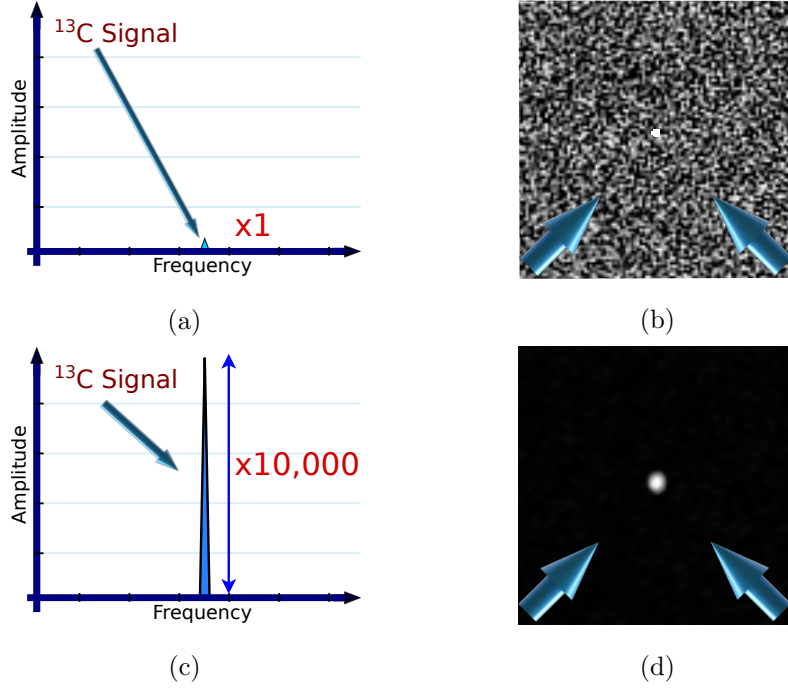


Figure 1.1: Hyperpolarized ^{13}C molecule vs. normal ^{13}C molecule signal figures: a) Frequency spectrum of a normal ^{13}C molecule signal. Very small signal amplitude at equilibrium. b) Resulting MRI image of a normal ^{13}C molecule. Signal buried in the image background noise. c) Frequency spectrum of hyperpolarized ^{13}C molecule. 10,000 times more signal amplitude. & d) Resulting MRI image of a hyperpolarized ^{13}C molecule. Large signal without image background noise[Pra08]

1.2 Hyperpolarization

The method of contrast agents hyperpolarization arose from the need of overcoming the poor Signal-to-Noise Ratio (SNR) inherent to MRI (thermal equilibrium effect). Hyperpolarization offers a unique solution to this problem skewing the thermal equilibrium effect. The hyperpolarization of molecules creates an artificial non-equilibrium distribution of excitable nuclei. Thus, increasing signal strength at multiple orders of magnitude, allowing ample signal (signal to noise

ratio, SNR) for cell metabolites real-time imaging (eq.1.1). In fact, hyperpolarization does not affect the signal intensity of water protons, but hyperpolarized molecules become a source of signal themselves [VA10]. Thermal equilibrium is defined as the alignment of spins within a magnetic field in either of two orientations, parallel or anti-parallel (Boltzmann distribution) (eq.1.2). A slightly larger proportion of spin adopts the parallel state (lower energy) and can be excited into an anti-parallel state (at body temperature, 5ppm for ^1H and 1 ppm for ^{13}C), providing the basis for MRI (fig 1.2a)[PJM06]. Unfortunately, at thermal equilibrium, a small number of excitable spins limits MRI to mostly tissue structure imaging [BG04]. Researchers have met some success increasing SNR and the ability to image beyond tissue structure, for example:

- a) Gadolinium based agents, improving T_1 contrast and repetition rate. Toxic in large amounts
- b) Increase of main Magnetic Field B_o , increases the number of excitable spins. Expensive at \$1M/Tesla
- c) Parallel imaging, multiple receiver coils, increases SNR several fold. Complicated technique and computation intensive.
- d) Cooling receiver electronics to $\sim 10\text{K}$, decreases thermal noise, thus SNR. Complicated and expensive.

Luckily, hyperpolarization increases the number of excitable spins many orders of magnitude more than any of the mentioned methods. The increase is well in excess of 10,000 fold and at a lower cost and simplicity (fig 1.2b)[BHL05]. Furthermore, using hyperpolarized substances, images are generated by looking at the hyperpolarized nuclei directly. The more the concentration, the larger the signal.

$$\text{Signal} - \text{to} - \text{Noise Ratio (SNR)} \simeq \gamma c P \quad (1.1)$$

Where γ , c , and P are the gyromagnetic ratio, concentration of the nucleus, and Polarization respectively.

$$P = \left(\frac{N^+ - N^-}{N^+ + N^-} \right) = \tanh \left(\frac{\gamma h B_o}{2k_B T} \right) \quad (1.2)$$

Where N^+ , N^- , h , B_o , k_B , and T are the number of parallel and anti-parallel spins, Planck constant, main magnetic field, Boltzmann constant, and temperature in Kelvin respectively.

The efforts to overcome thermal equilibrium leading to signal enhancement in

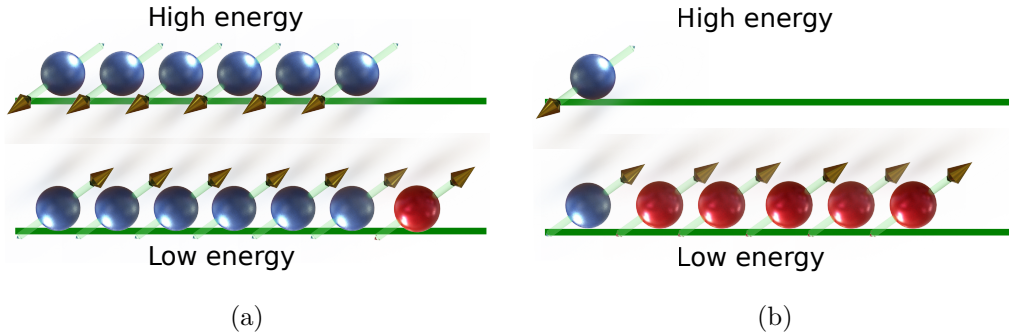


Figure 1.2: Equilibrium and hyperpolarized spin states. In the equilibrium state the Boltzmann Distribution of nuclei spin is normal, and difference between spin populations is very low, while in the hyperpolarized state it is increased up to 10^5 . The magnetic field is vertical downwards [VA10]. a) Atoms spin orientations at thermal equilibrium. Blue spins are locked and red spin is excitable. b) Atoms spin orientations at the hyperpolarized state. Blue spin is locked and red spins are excitable.

NMR began as early as the 1930's with crude experiments on paramagnetic materials. Followed by experiments on relaxation times with Cr and Ti Alum, effectively demonstrated the increase of relaxation times at a constant magnetic field, independent of the field's direction [Van40]. Finally, hyperpolarization came to life in 1953 with the theoretical discovery of the transfer of spin from a nuclei to another through cross-relaxation, effect described as the Overhauser's effect [Ove53].

Then, the Dynamic Nuclear Polarization (DNP) method was demonstrated in 1954 with experiments in magnetic susceptibility using lithium [SCS54]. DNP research continued to evolve through the 1960's leading to the discovery of the Chemically Induced Dynamic Nuclear Polarization (CIDNP) method. This method was reproduced by the disproportionation of radical pairs [WL67] [BF67]. Subsequently, Weitekamp's research work on J-coupling measurement techniques in $[1-^{13}\text{C}]$ Benzene in the early 1980's [WGP82][WGP84], led to the PASADENA (parahydrogen and synthesis allow dramatically enhanced nuclear alignment) method and the basis for PHIP. PASADENA was first proposed in 1986 [BW86] and demonstrated in 1987 by hyperpolarizing propionitrile $[\text{CH}_3\text{CH}_2\text{CN}]$, resulting in a 100-200 times increased signal [BW87]. However, unknown to most, PASADENA was first observed, but misinterpreted, by Seidler in 1983 [SBF83].

The PASADENA method is described as a proton signal enhancement, resulting from the breakdown (aided by a catalyst) (fig 1.3b) and pairwise transfer of p-H_2 (fig 1.3c) during substrate hydrogenation. Hydrogenation occurs while at magnetically inequivalent sites on the substrate molecule (fig 1.3d) within a high magnetic field [JMJ95][BW86]. Concurrently, the ALTADENA (adiabatic longitudinal transport after dissociation engenders net alignment) method, an adiabatically transfer of spin at a low magnetic field, surfaced in 1988 demonstrating hyperpolarization of ethylbenzene within a weak magnetic field [PW88]. PASADENA and ALTADENA are similar methods of hyperpolarization, but differ in the following; the PASADENA method results in a spectra with anti-phase multiplets of reaction products and introduces the fast breaking of magnetic equivalence as the hydrogenation is taken place at a high magnetic field, while ALTADENA takes place at a low magnetic field, followed by an adiabatic transfer of the hydrogenated product to the high magnetic field [KKB07]. However, heteronuclear hyperpolarization, the spin transfer from p-H_2 to other nuclei, was not demonstrated until 1987, when a new method emerged describing the moni-

toring of reaction products and the potential for much greater sensitivity [BW87] [EKD87]. Thereafter, this method was known as PHIP.

Further PHIP work was published in the early 1990's demonstrating the op-

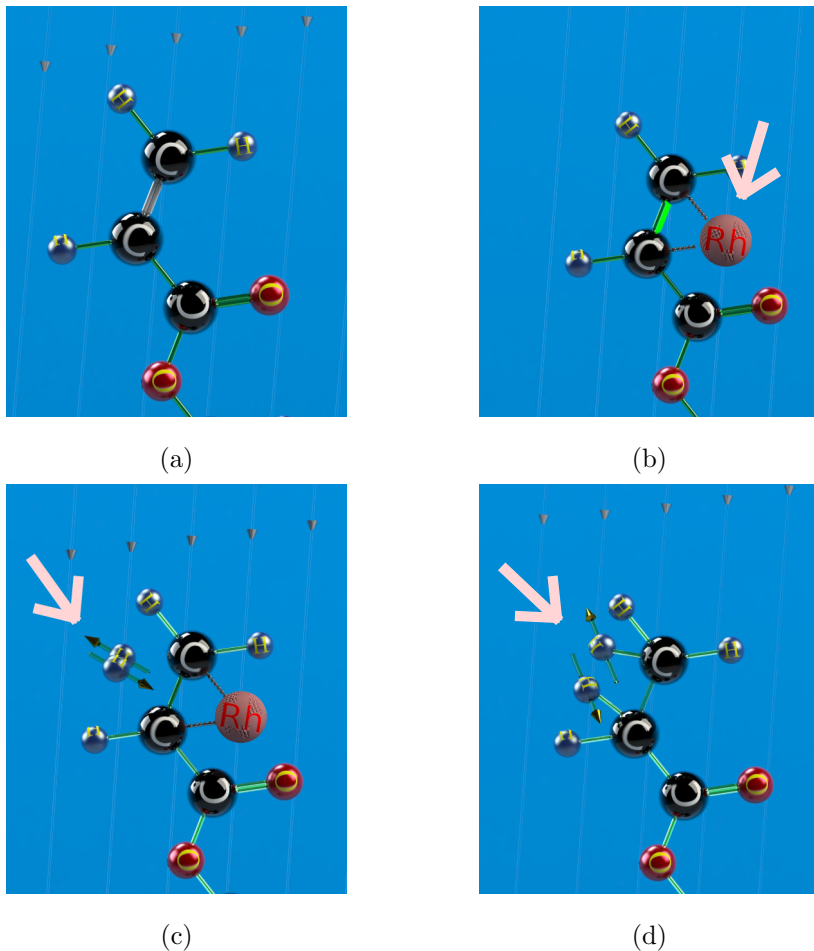


Figure 1.3: PASADENA hyperpolarization method. a) Precursor molecule with ^{13}C double bond, for example acetylene dicarboxylate. b) The weakening of precursor ^{13}C double bond by a catalyst complex (Rh). c) Precursor hydrogenation aided by the weakening of the ^{13}C double bond. d) Hyperpolarized hydrogen atoms bonded to substrate molecule

timization of spin transfer using the Insensitive Nuclei Enhanced by Polarization Transfer (INEPT) sequence. In this work, the hyperpolarization of other low γ nuclei such as; ^{29}Si , ^{15}N , ^{17}O , ^{109}Rh was proposed [JM95][DNE93] and later

demonstrated. Then, slightly more sophisticated sequences such as; the Goldman’s & Hakee’s sequences were demonstrated *in-vivo* with mild success in 1996 & 2001 [GAJ01][HNB96]. More recently, the Kadlecsek sequence had shown great simulated results, but the sequence is yet to be tested *in-vivo* [KEI10].

The PHIP method concept is based in the chemical addition of p-H₂ to a substrate or precursor molecule (gas or liquid)(fig 1.3a). This precursor is pre-loaded with a Rh catalyst complex that weakens the ¹³C double bond (fig 1.4a). The mixing of p-H₂ and the precursor occurs in a reaction chamber (fig 6.1), where a catalyst assisted hydrogenation reaction takes place, adding the two p-H₂ atoms across the carbon-carbon double bond (fig 1.4b). Then, the Rh complex dislodges. Next, the spin energy transfers from the added p-H₂ atoms to ¹³C in the newly created molecule (fig 1.4d) by irradiating the mix with microwaves (fig 1.4c). This methods results in a signal enhancement of 10,000 or more (fig 1.1)[BLA12].

Nowadays, PHIP research is reaching new limits at Cedars-Sinai Medical center with the development of a new and more stable and dependable PHIP prototype. This new development marks the firsts steps towards a clinical PHIP instrument.

1.2.1 Limitations of MRI

MRI has contributed greatly to the diagnosis and understanding of many diseases. The modality offers great soft tissue contrast, high spatial resolution, unlimited repeated measurements, and is non-invasive [IBS12][Pom09]. More specifically, MRI only allows the imaging of protons in water molecules and fats, thus, cell metabolism imaging has yet to be fully achieved using MRI. Cell metabolism imaging requires a large SNR, but MRI is restricted by *in vivo* restraints of low concentration of excitable hydrogen atoms, dielectric losses, and high costs [BCP07][BRB09].

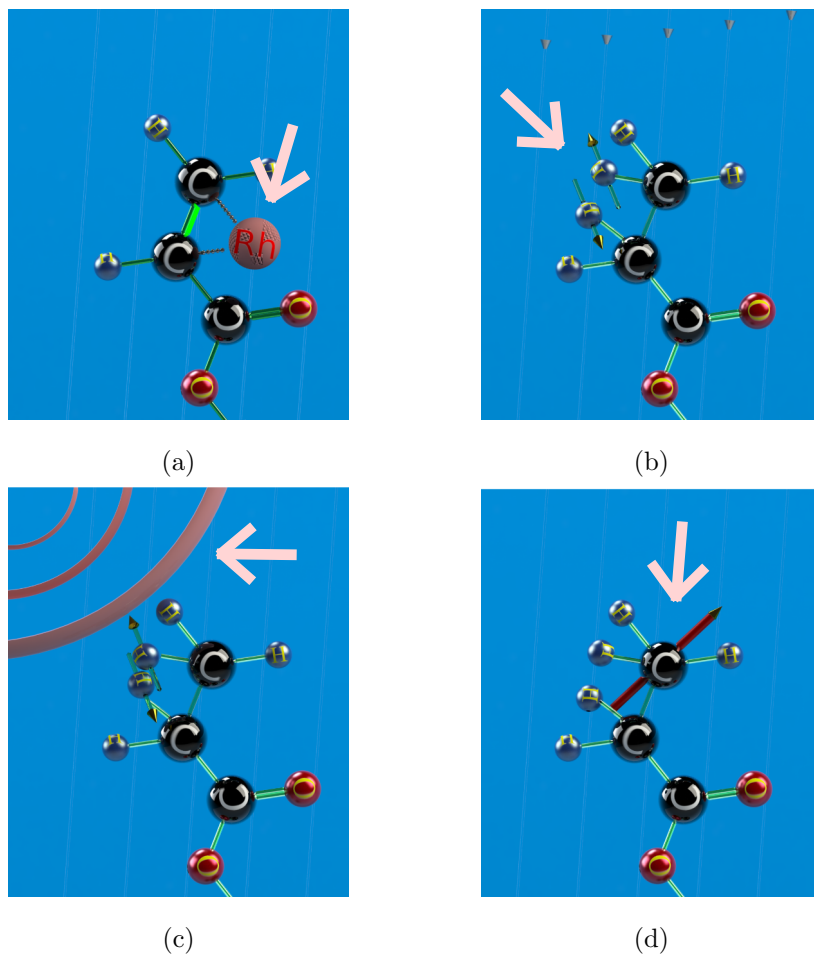


Figure 1.4: PHIP hyperpolarization method. a) ^{13}C double bond weakening by a catalyst (Rh). b) Hydrogen atoms bonded to precursor, Rh dislodged. c) Spin transfer by RF irradiation. d) Hyperpolarized ^{13}C molecule.

1.2.2 Significance of PHIP Methods

Human body anatomy and cell signaling pathways have already been explored in MRI [Bar07][Fed12][HJ12], but because of little observable molecules (order of 10^{-5}) [CAM06], poor sensitivity hinders imaging metabolic processes, and further developments have reached a plateau. Increasing the magnetic field strength provides a solution to MRI sensitivity, but at a cost of \$1M/Tesla, the increase in signal is expensive, among other technical issues such as; power deposition,

magnetic field homogeneity, and overall safety [PX12][FDJ12][KMP12]. PHIP instrumentation offers an inexpensive solution to this problem, while bringing five orders of magnitude more signal than proton imaging [HCH08]. Furthermore, PHIP provides an insight into nanochemistry and metabolics, faster imaging, and virtually none signal background noise due to the low natural abundance of ^{13}C , ^{15}N , ^{31}P [BRB09].

1.2.3 Hyperpolarization Methods

To further understand fundamental *in vivo* tissue chemical changes, it is necessary to develop a contrast agent, where molecules themselves are the source of signal and dependent on concentration and polarization level [VSC09]. There are several routes to hyperpolarization; Optical Pumping (OP), Brute Force (BF), Dynamic Nuclear Polarization (DNP), and Parahydrogen Induced Polarization (PHIP).

1.2.3.1 Optical Pumping

This method can only be used for the hyperpolarization of noble gases, such as ^3He and ^{129}Xe [VSC09] and is based on the spin exchange from laser beam photons to gas atoms by circularly polarized light. This type of polarization is used mainly for lung and sinus imaging [SCO05] (fig 1.6a).

Optical pumping is currently use for the following studies; MRI of the lungs (fig 1.5), Perfusion, Ventilation, Diffusion studies in emphysema diagnosis, Functional MRI (which exploits the solubility and lipophilic properties of Xe), and Blood oxygenation measurements (by exploiting Xe binding to Hemoglobin) [MEC02].

Hyperpolarized gases are generally delivered through inhalation for lung imaging, but there has been some great success delivering gases through intravenous injection, enabling blood-flow measurement and perfusion imaging. Duhamel in 2001, diluted Xe in 0.15 ml of a lipophilic carrier and injected the solution in a

rat's carotid. The result was a 10 to 15 times more signal than proton imaging with an in-plane image resolution of $900\ \mu\text{m}$ per pixel. No brain damage resulted for 1 to 2 solution injections [DCG01]. Shortly after, higher increases in signal (30 times) were obtained using $3\mu\text{m}$ microbubbles with encapsulated ^3He , resulting in T_1 relaxation time of 90 seconds [VEJ01]. More interestingly, ^{129}Xe Biosensors used for void body structures imaging, have shown signal increases comparable to PHIP and DNP at 10,000 times. A ^{129}Xe Biosensor is defined as trapped Xe atoms in molecular cages that bind the desired target. A cage is composed of cryptophane-A cage, a linker, and a targeting moiety, this cage may be an antibody or ligand that enables detection of a specific analyte (fig 1.6b) [SLH06].

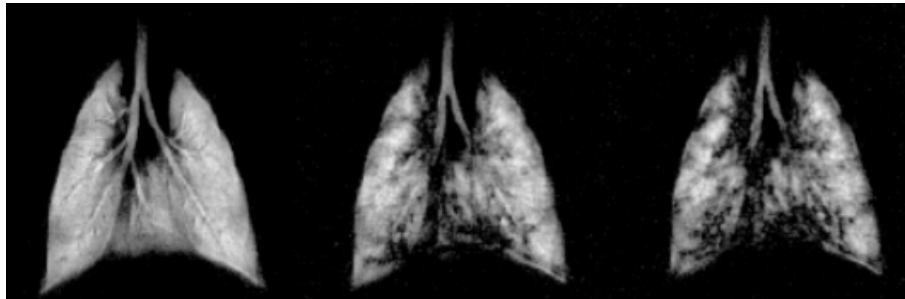


Figure 1.5: Hyperpolarized ^3He lung images at 1,7, and 15ms echo times [MEC02]

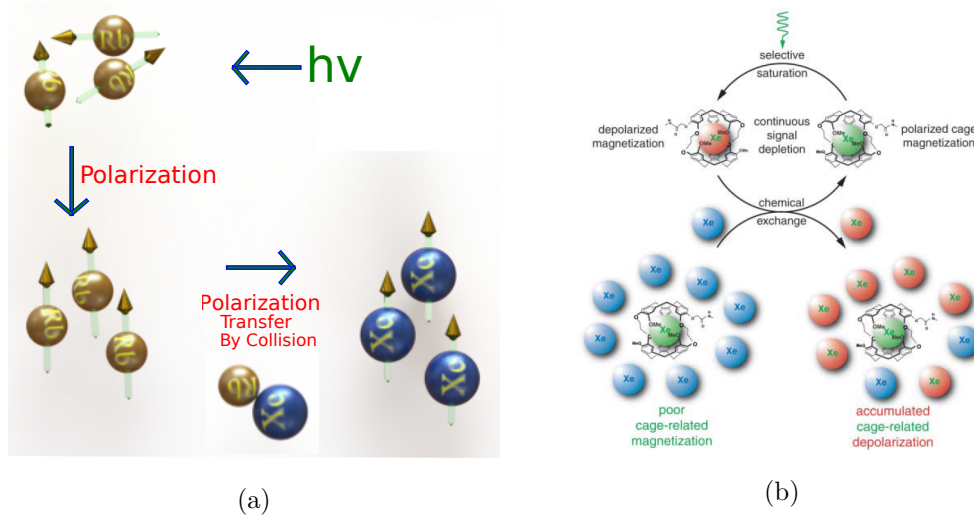


Figure 1.6: Optical Pumping hyperpolarization. a) Optical Pumping polarization of Rb by photons bombardment and lastly spin transfer from Rb to Xe by nuclei collision. b) Saturation of biosensor-encapsulated Xe (green) and chemical exchange with the free Xe (blue) allows accumulation of depolarized nuclei (red) [SLH06].

1.2.3.2 Brute Force (BF)

Quantum Relaxation Switch or BF hyperpolarization, is a difficult method to implement due to the extreme conditions required and removal of relaxation switches [VSC09]. BF hyperpolarization is achieved by applying high field and ultra low temperature conditions, where relaxation switches are necessary (O_2 , $^3He/^4He$). In addition, BF is an alternative to optical pumping for the production of hyperpolarized noble gases at high fields and low temperatures (fig 1.7) [TKF11]. However, BF is limited by the selection of hyperpolarizable gases [BRB09][KOO05]. Unfortunately for BF, the method is not practical. For example, polarization can be increased 1000 times for ^{13}C while immersed in 4K temperature at a 20 Tesla field. Then, after quickly bringing the molecule 310K in a 1.5 T MRI scanner, the signal produced is actually lower than using 1H imaging [VB12].

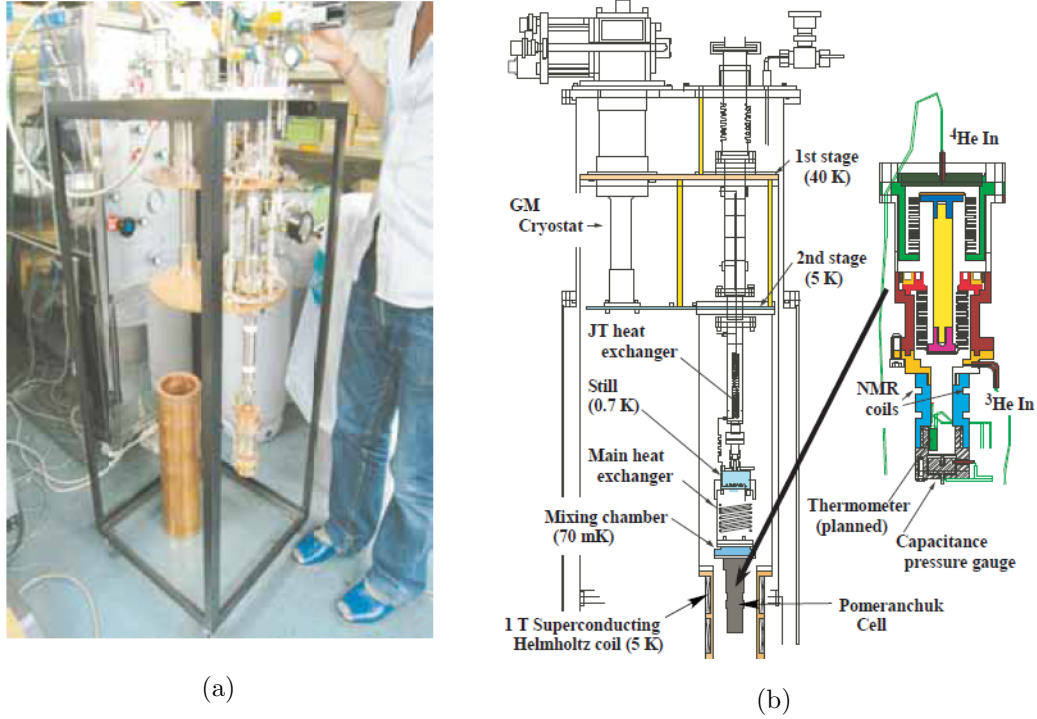


Figure 1.7: Brute Force instrumentation as used by Tanaka. a) Cryofree $^3\text{He}/^4\text{He}$ dilution refrigerator, KOBE10 μ , b) KOBE10 μ schematic, showing the Pomeranchuk cell and 1-T superconducting Helmholtz coil [TKF11]

1.2.3.3 DNP

This hyperpolarization method is based on the Overhauser effect [Ove53][BM54]. Where, the polarization is transferred from unpaired electrons coupled to nuclei through irradiation at or near the Electron Paramagnetic Resonance (EPR) frequency (fig 1.9a & 1.9b) [VB12]. This method is performed at low temperatures and at a high magnetic field (9T) to maximize polarization [BFH03]. Once the spin transfer is complete, the sample is warmed up with superheated water [BRB09] and delivered. Nonetheless, DNP has taken over 50 year to become an useful tool for reasearcher, this is mainly due to problems with the required high frequency RF, the making of an efficient double resonator, and price [Pra08].

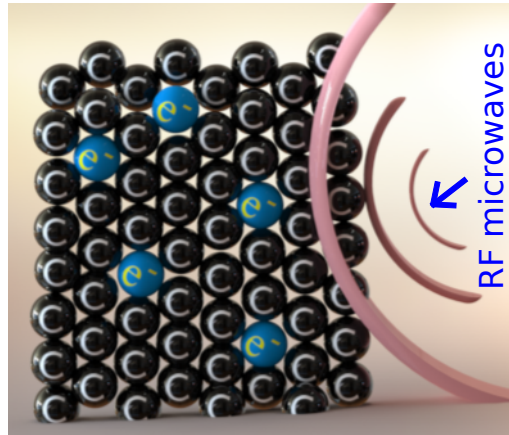


Figure 1.8: Solid material with Carbon atoms and unpaired electrons being painted with RF microwaves

The following are the steps for DNP hyperpolarization [VB12]:

1. **Sample Preparation:** Mixing of molecules labeled with a low γ nuclei (^{13}C) and solvent.
2. **Sample Transfer:** Sample is exposed to low temperature and high field to obtain high electron polarization
3. **Spin Transfer:** Frozen sample is painted with microwaves, transferring polarization to the nuclear spins.
4. **Sample Dissolution:** Rapid solid sample thawing to obtain an injectable solution. The dissolution results in small polarization loss.
5. **Sample Delivery:** Sample injection and fast imaging before relaxation to the thermal equilibrium

DNP and metabolic imaging: There has been remarkable developments in DNP metabolic imaging by exploiting the Warburg effect [GHC09]. More specifically, the hyperpolarization of Pyruvate. Pyruvate is the simplest of the alpha-keto acids and the key for several metabolic pathways. However, pyruvate is not

the only endogenous molecule hyperpolarized. As of 2011, researchers had hyperpolarized an additional 10 molecules; $[1-^{13}\text{C}]$ Ethyl pyruvate, $[1-^{13}\text{C}]$ Lactate, ^{13}C -Bicarbonate, $[1,4-^{13}\text{C}_2]$ Fumarate, $[2-^{13}\text{C}]$ Fructose, $[1-^{13}\text{C}]$ Ketoisocaproate, $[5-^{13}\text{C}]$ Glutamine, $[1-^{13}\text{C}]$ Glutamate, $[1-^{13}\text{C}]$ Urea, and $[1-^{13}\text{C}]$ Acetate, with polarization ranging from 7 to 40% [JPK09][BBG11][Pra08].

The following are some of the most remarkable research in metabolic imaging using DNP:

Metabolic pathways: In 2007 bicarbonate was found routinely in skeletal muscle, kidney, and vasculature. However, later studies at 3T found Alanine primarily in skeletal muscle and liver, while pyruvate, lactate, and bicarbonate concentrations were relatively high in the vasculature and kidneys (fig 1.9b) [KYW07].

Tumors: In 2006-08, Golman (fig 1.9a) and Chen had proven that by injecting hyperpolarized pyruvate (^{13}C), elevated levels of lactate were found in tumors, demonstrating the feasibility of studying cancer metabolism *in-vivo* using hyperpolarized ^{13}C and MRI. Thus, establishing a path for early stadiation and monitoring of the response to treatment [GZL06][CAC07][Pra08]. Same period, Gallagher demonstrated that pH tissue can be image with hyperpolarized bicarbonate ($\text{H}^{13}\text{CO}_3^-$). The study showed that the average tumor interstitial pH was significantly lower than the surrounding tissue, leading the way to image pathological processes that are associated with alterations in tissue pH, such as cancer, ischaemia, and inflammation (fig 1.10)[GKD08]. Gabellieri also found a remarkably long relaxation time of ^{15}N labeled choline, suggesting that hyperpolarized ^{15}N choline shows great potential as a target molecule for studying tumor metabolism [GRL08].

Cardiac metabolism: In 2008, Golman demonstrated that cardiac metabolic

imaging with hyperpolarized 1- ^{13}C -pyruvate is feasible. The changes in concentrations of the metabolites within a minute after injection can be detected and metabolic maps constructed (fig 1.11)[GPM08]. More specifically, Goldman found that the bicarbonate level in the myocardium is indicative of ischemic. Where level being lower or absent in the areas where ischemia was present. This is due to a decreased activity of pyruvate dehydrogenase (PDH) ^{13}C -CSI maps of lactate, alanine, bicarbonate and pyruvate from a pig heart obtained pre- and post-45-min occlusion [Pra08].

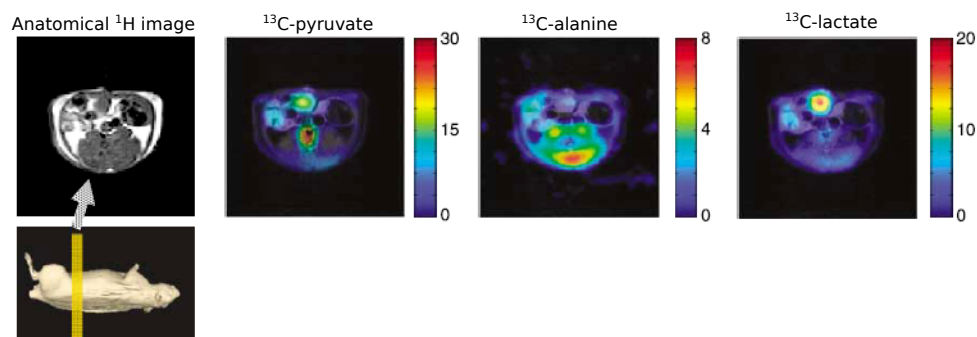
1.2.3.4 SABRE

This method achieves polarization of molecules without a direct hydrogenation of a precursor, or chemical modification. Rather, polarization is achieved by a temporary association of p- H_2 and a metal complex. This method is performed at low magnetic fields and room temperatures [AAA09][LAB12].

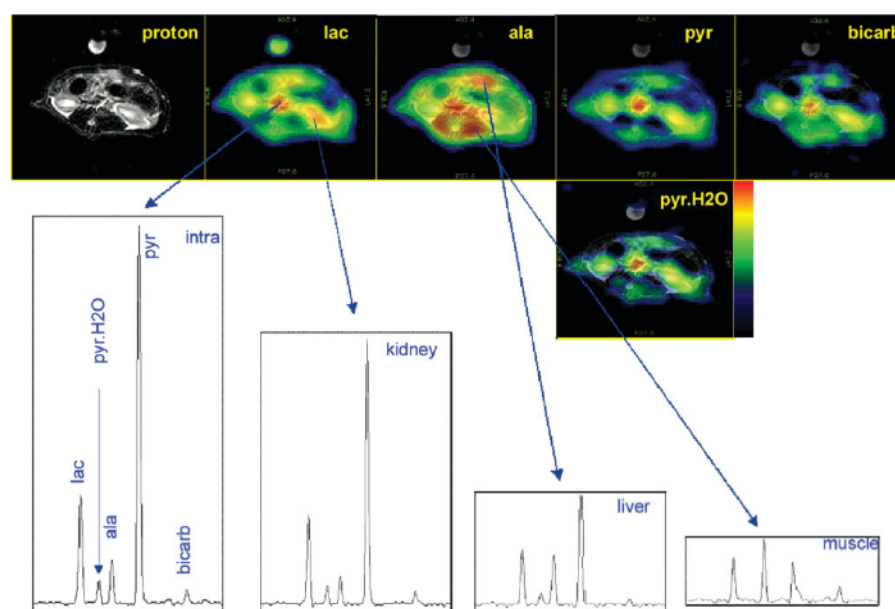
1.2.3.5 PHIP

PHIP is our target hyperpolarization method. The polarization process takes place in a low B_0 as follows: The precursor (for example fumaric acid) is pre-loaded with a Rh-complex as a catalyst, effectively weakening the carbon double bond. Next, the p- H_2 is mixed with the precursor in the reaction chamber. The reaction chamber is kept at temperature (40-60°C) and pressure (2-7 bar). Once the mixture is in the chamber, hydrogenation takes place. This is where the two hydrogen atoms are chemically added across the carbon double bond. Then, the result is the target product (for example succinate acid). The transfer of spin, or hyperpolarization, from the two attached hydrogen atoms to the ^{13}C atom in product happens when the product is exposed to a RF sequence (for example, the Goldman Sequence) that enables the polarization transfer [BLA12][HCH08]. The

product is then delivered intravenously for *in vivo* imaging (fig 1.12). Moreover, the PHIP method is cheap, an easier technique to implement, continuous flow is possible, but there is a limited number of candidate molecules, and the filtering of the toxic Rh catalyst complex are difficult problems to overcome [Pra08].



(a)



(b)

Figure 1.9: DNP Studies. a) Transversal ^1H -NMR image and simultaneously NMR signal from pyruvate, lactate, and alanine. P22 tumor tissue is indicated by the highest signal for lactate. b) Metabolite maps and individual spectra for lactate, alanine, pyruvate, and bicarbonate, in kidney, liver, and skeletal muscle. Highest signal appears red, while weakest appears black [GZL06][CAC07]

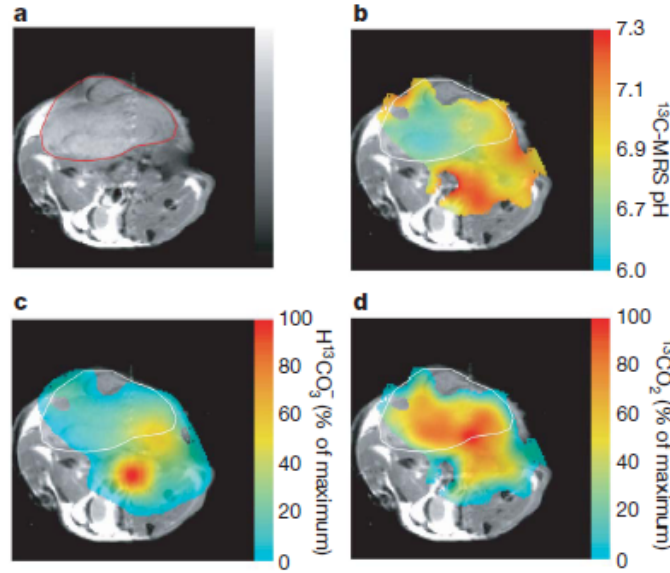


Figure 1.10: Imaging of tumor pH in vivo. a) Transverse proton magnetic resonance image of a mouse with a subcutaneously implanted EL4 tumor. b,c) pH map of the same animal d) voxel intensities in ^{13}C chemical shift images acquired ,10 s after injection. The tumor margin in b, c and d is outlined in white [GKD08]

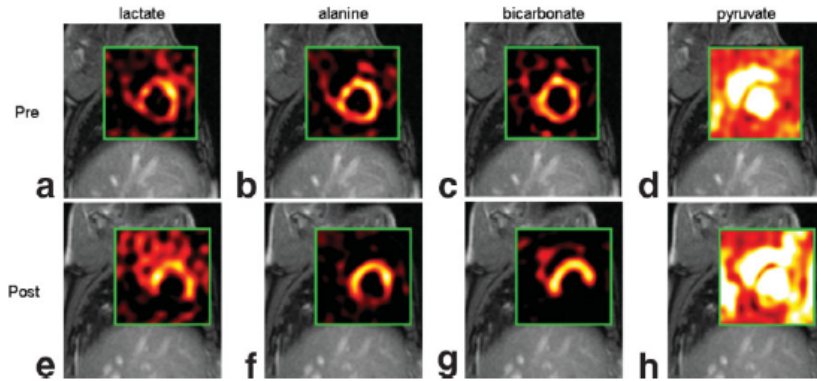


Figure 1.11: CSI maps from a pig obtained pre- (top row) and post-45-min occlusion (bottom row). The three metabolite maps of lactate (a,e), alanine (b,f) and bicarbonate (c,g) together with the injected ^{13}C -pyruvate (d,h) [GZL06]

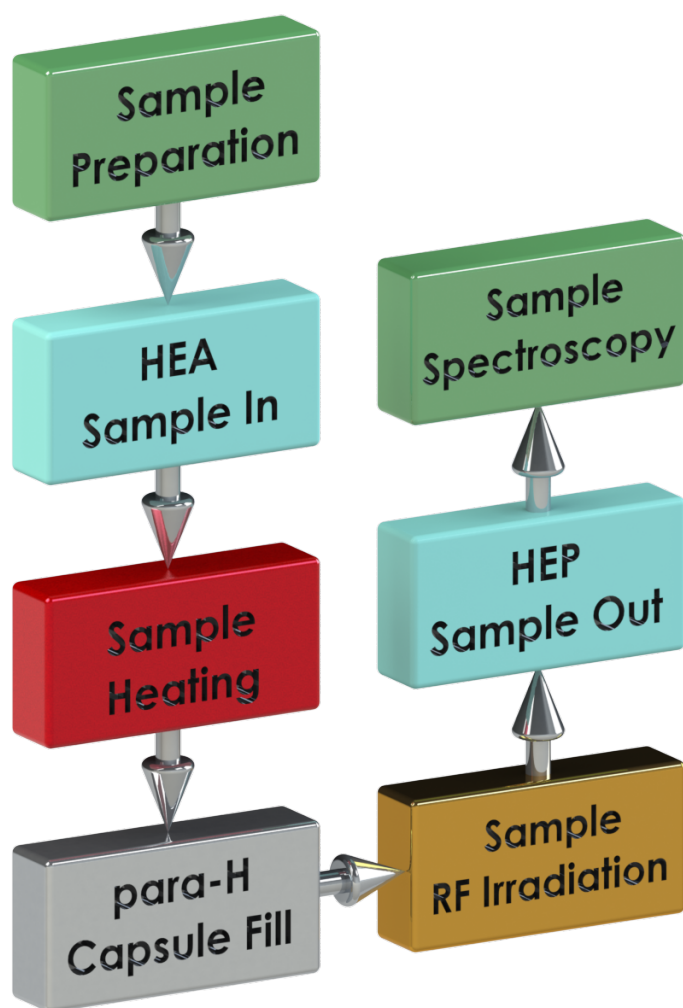


Figure 1.12: PHIP process block diagram

CHAPTER 2

PHIP Instrument Software

Hyperpolarization is a method that provides a strong enhancement of the Magnetic Resonance Imaging (MRI) signal and allows the acquisition of images from nuclei other than protons [VA10]. The hyperpolarization of cell metabolites is key to their imaging due to the 30,000 to 100,000 signal amplitude increase after hyperpolarization [NB97][HCH08][BCP07], but hyperpolarizing a metabolite is not a trivial process. Hyperpolarization of metabolites leads to a number of new challenges. LabVIEW, a high level graphical programming language efficiently adapts to hyperpolarization process challenges and allows for a more natural intuitive man-machine interaction than text based languages [Ham10][JW95]. Furthermore, as hyperpolarization of metabolites difficulties arise, LabVIEW's hardware control versatility and easy to program Graphical User Interface (GUI) [Ert03], reduce costs [BMN01] associated with the hyperpolarization process automation. In reviewing the literature, no LabVIEW software applications in para-Hydrogen Induced Polarization (PHIP) instrumentation has been published.

2.1 LabView Software

The LabVIEW software provides a graphical application development environment developed by NI in 1986 for Apple Macintosh. LabVIEW is composed of several sub-tools targeted at making the development and prototyping of instrumentation applications very simple, flexible, and efficient [AK98]. This prototype was developed with software flexibility in mind, allowing for easy and intuitive

changes to its graphical code. This makes LabVIEW a very versatile tool for hyperpolarization research purposes.

2.1.1 Signal Acquisition

The signals acquired in this project are; *Temperature*, *Pinch Valve Status*, *Gases Pressure*, and *B₀ Current*. These signals were acquired through two data acquisition boards. First, the NI PCI-6221 with two 16-bit analog outputs and 24 digital I/O lines (Dev1) and the NI PCIe-6351 with 16 analog inputs and 24 digital I/O lines (Dev2). Dev1 controls and acquires data from pinch valve and VCCS controllers. Dev2 controls fan heaters and RF output sequence and acquires gas pressure data. Once the signals were acquired, the data was available to LabVIEW for further analysis and software front panel (SFP) presentation.

2.1.1.1 Temperature Recording

The hyperpolarization of metabolites is temperature dependent. Thus, every circuit board designed in our lab and installed in the PHIP prototype comes with a temperature sensor. In total, there are six temperature sensors installed throughout the prototype box. In order to minimize signal noise, the temperature data acquired was further processed by LabVIEW using a Butterworth low pass digital filter with a cut off frequency at 100 Hz.

2.1.1.2 Pinch Valve System

The control of sample and gas flow was accomplished using modified Cole-Palmer 12VDC two-way normally closed solenoid pinch valves. A disposable $\frac{1}{4}$ " OD tubing was used for the sterile manipulation of gas and sample throughout the system (fig 2.1a). Each pinch valve was controlled and monitored using Dev1 through a controller circuit designed in our lab. This controller was designed to minimize

pinch valve heating and stray magnetic fields.

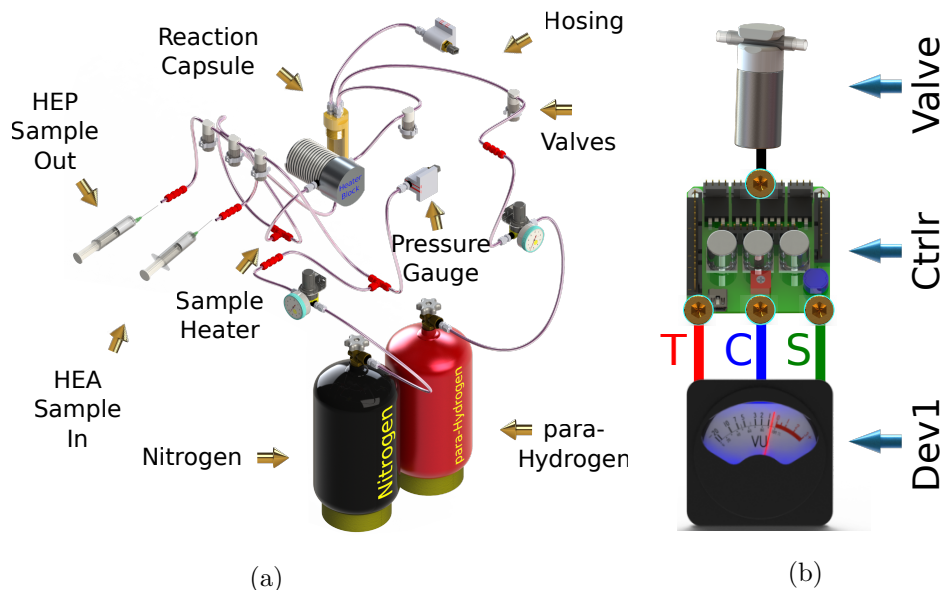


Figure 2.1: Pinch Valve and disposable $\frac{1}{4}$ " OD tubing instrument setup. The Cole-Palmer pinch valves were modified to increase pinch force to allow performance up to 8 bar. The Pinch Valve controller board (Ctrlr) was designed in our laboratory. This board measures temperature, monitors the status & controls the pinch valve, while minimizing stray magnetic fields and valve over heating. a) Pinch valve, disposable hosing, and pressure sensors system rendering. b) Pinch Valve setup. Pinch Valve controller board (Ctrlr). Valve Control input (Blue C) & Status output (Green S), and Temperature output (Red T)

2.1.1.3 Gases Pressure Recording

The Honeywell MLH150PGL06B gas pressure sensor was used to monitor nitrogen, hydrogen, and reaction chamber gas pressures. This pressure sensor is an all metal amplified sensor with temperature compensation with a range of 0 bar to 10 bar.

2.1.1.4 B_o Current Recording

The hyperpolarization of a ¹³C based metabolite is sensitive to shifts in the ¹³C resonance frequency, or Larmor Frequency (eq.2.3). Therefore, the monitoring of the hyperpolarization solenoid's magnetic field (B_o) is of the utmost importance. Exciting a metabolite sample with an incorrect RF sequence frequency will lead to poor polarization results. The Larmor Resonance Frequency is measured indirectly through a voltage measurement provided by a current controller board (designed in our laboratory). Moreover, the voltage data (V) is collected using Dev2 (fig 2.2a).

The derivation of the Larmor Frequency is as follows:

1. The current (I) flowing through the solenoid is given by Ohm's Law (eq.2.1)
2. The solenoid's B_o is given by eq.2.2
3. The ¹³C Larmor Frequency is given by eq.2.3
4. Inserting eq.2.1 into eq.2.2 and its result into eq.2.3, leads to the Larmor Resonance Frequency (ω) eq.2.4

$$I = \frac{V}{R} \quad (2.1)$$

Where V is the voltage and I is the current

$$B_o = \mu * n * I \quad (2.2)$$

Where B_o is the solenoid's magnetic field strength, μ is the permeability in air, n is the turn density, and I is the current

$$\omega = -\gamma * B_o \quad (2.3)$$

Where ω is the Larmor Frequency in radians, γ is ¹³C gyromagnetic ratio, B_o is the solenoid's magnetic field magnitude.

$$\omega = -\gamma * \mu * n * \frac{V}{R} \quad (2.4)$$

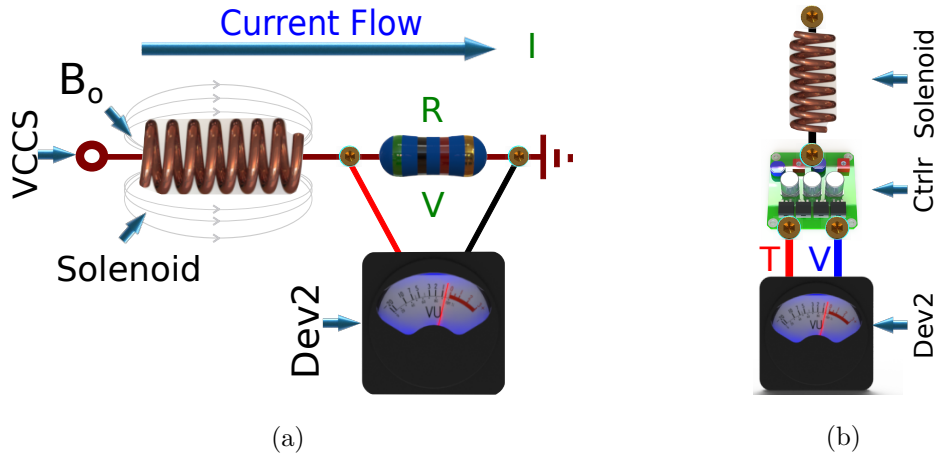


Figure 2.2: Voltage Controlled Current Source (VCCS) board (Ctrlr). This board was designed in our laboratory and provides the solenoid with a stable current source. In addition, the board produces two voltage outputs, temperature and a voltage proportional to the current flowing through the solenoid. a) Setup for indirectly measuring the Larmor Frequency ω through a voltage (V) measurement using Dev2. b) Voltage recording setup. Solenoid and Current controller board (Ctrlr), Voltage output (Blue V) and temperature (Red T)

2.1.2 Signal Generation

The signals generated in this project are H_2 and ^{13}C sequences. These signals are produced by Dev2's two 2.86 MS/s analog outputs. The output waveforms are sequences built in advance and stored in Technical Data Management Streaming (TDMS) file format for later retrieval [Ins12]. The main program reads these TDMS files and when instructed, sends the data to the output antennae in the instrument's reaction mix capsule. The TDMS file contains data on the sequence's sampling rate, waveform amplitudes and length. The sequences shape and length is dictated by the type of hyperpolarizing sequence used (Goldman, Hakee, Kadlec, etc) [GAJ01][HNB96][KEI10].

2.2 Software Design

In this PHIP instrument prototype, we have used LabVIEW as a platform for acquiring, controlling, and processing data leading to the hyperpolarization of metabolites.

2.2.1 Software Structure

The software structure of the PHIP instrument prototype is shown in fig ??.

With 46 controls and 36 indicators on the SFP, the program is too large for linear programming. Instead, the program is event driven, allowing for more efficient program execution. Each button and knob control on the SFP is linked to an event. When a button or knob is changed by the user, an event is triggered executing different program sections. If no event is triggered, the event timer times out at 100ms and collects Gases Pressure, B_o Voltage Drop, and instrument Temperature data. The events available are Start Experiment, individual Pinch Valve control, and Tab Control Setup. At time out, the following events are available; Gases Pressure, B_o voltage drop and Instrument Temperature.

1. Start Experiment: The GUI developed using LabVIEW allows for control over timing on every pinch valve. Simmer time (sample heating), number of line purges, RF sequence execution timing, experiment time range, RF sequence used, and RF feedback.
2. Gases Pressure: The optimal hyperpolarization of a metabolite is dependent (among other parameters) on pressure. Thus, when the event timer times out, the software collects voltage data from pressure sensors connected at the N_2 and p- H_2 tanks, and reaction chamber using Dev1. The data is then

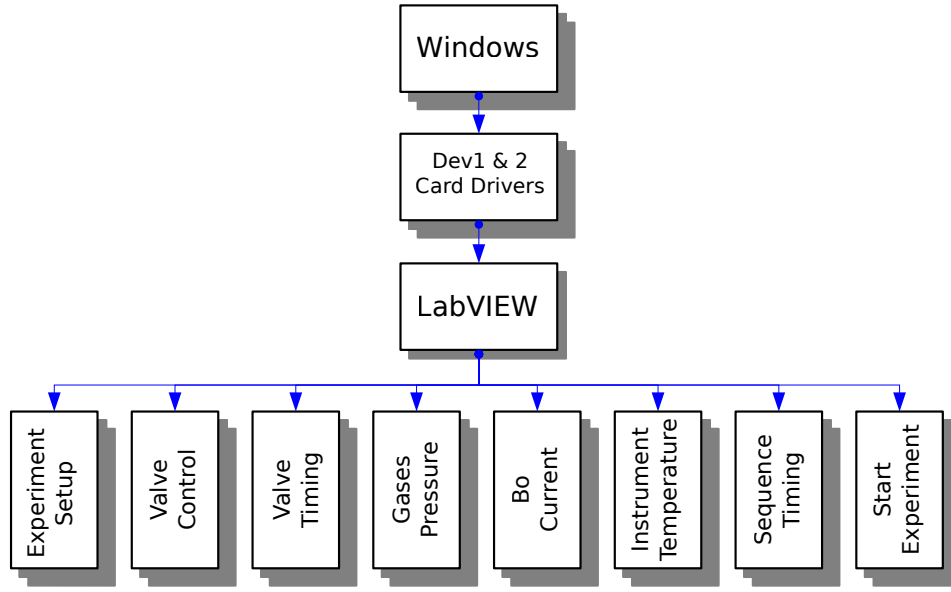


Figure 2.3: PHIP Instrument software structure

displayed in a graph on the SFP. This results in data collection at 10Hz.

3. B_o Voltage Drop: The spin transfer from $p\text{-H}_2$ to ^{13}C nuclei is dependent on exciting the nuclei at the proper Larmor Frequency (ω). Thus, when the software event timer times out, the software collects voltage data from the current controller board designed in our laboratory using Dev2 (fig 2.2). Then, the software calculates the current through the solenoid, the ω for the given current (eq.2.3), and displays the results in a graph on the SFP.
4. Instrument Temperature: In order to obtain a precursor full hydrogenation during the hyperpolarization process, the instrument environment temperature needs to be between 40°C to 60°C . Using Dev1, the software collects data from six different parts in the instrument. Five pinch valve controller boards and a current controller board developed in our laboratory has a temperature sensor. These sensors provide temperature data from inside the instrument box. When the event timer times out, the data is collected and displayed on a graph on the SFP.

5. Hyperpolarization Experiment Software Structure: A metabolite hyperpolarization experiment begins by heating up the sample and filling up the reaction capsule with p-H₂. Next, the sample is pushed into the reaction capsule and a previously chosen RF sequence applied. Then, the sample is pushed into an external vial and the lines purged (fig 2.4).

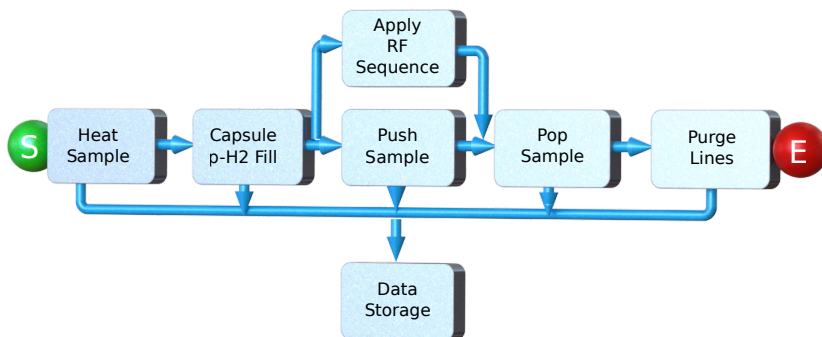


Figure 2.4: PHIP method experiment software structure. from Start (S) to End (E)

- (a) Heating sample: Heating sample or simmer time. This is the time the sample need to reach proper hyperpolarization temperature.
- (b) Purging Lines: Number of line purges do be done using p-H₂ gas after every experiment.
- (c) H₂ Gas Fill: The injection of H₂ gas into the reaction capsule for precursor hydrogenation.
- (d) Push Sample: The sample is pushed into the reaction chamber.
- (e) Apply RF Sequence: The RF sequence used to irradiate the sample in the reaction chamber.
- (f) Pop Sample: Once the sample has been polarized, the sample is pushed out of the reaction chamber into a vial.
- (g) Data file: Data on simmering time, pinch valves timing, RF sequence used, gases pressure, B₀ current, temperature, and number of purges is

stored in a TDMS file for later analysis.

6. SFP: A LabVIEW front panel is composed of controls and indicators. Controls simulate instrument input devices and supply data to the program. Indicators simulate instrument output devices and display data, using either plots or LED's. The combination of controls and indicators provides the user with an intuitive GUI. This SFP is composed of four sections; Pinch Valve Indicators, Experiment Timing Setup, a series of various controls and indicators in a Tab Control setup, and a System Status Bar (fig 2.5).

- (a) Pinch Valve Indicators: These indicators display the on/off status of the Pinch valves.
- (b) Experiment Timing Setup: This section contains all the timing controls for the hyperpolarization of a metabolites, such as; sample simmer time, pinch valve switching, RF Sequence start time, number of p-H₂ purges, and experiment length.
- (c) Tab Control Setup: This control style is the most efficient way to include a large number of individual controls and indicators in a small space. The Tab Control works by displaying a set of tabs for different sets of controls and indicators. In this case, the Tab Controls consists of nine tabs: Individual Controls-Pinch Valve control, RF Feedback-graphs the RF sequence sent to the reaction capsule, Output Wave-Selects a RF sequence to irradiate a sample, Pressure Plots- Graphs gases pressure, Analog Pressure- Uses dial indicators to show pressure, Temperature Plot- Graphs temperature throughout the instrument, B₀ Current-graphs the current flowing through the solenoid, Sequences-Selects the RF sequences to hyperpolarize a sample.
- (d) System Status Bar: This indicator displays the status of the software as a task executes.

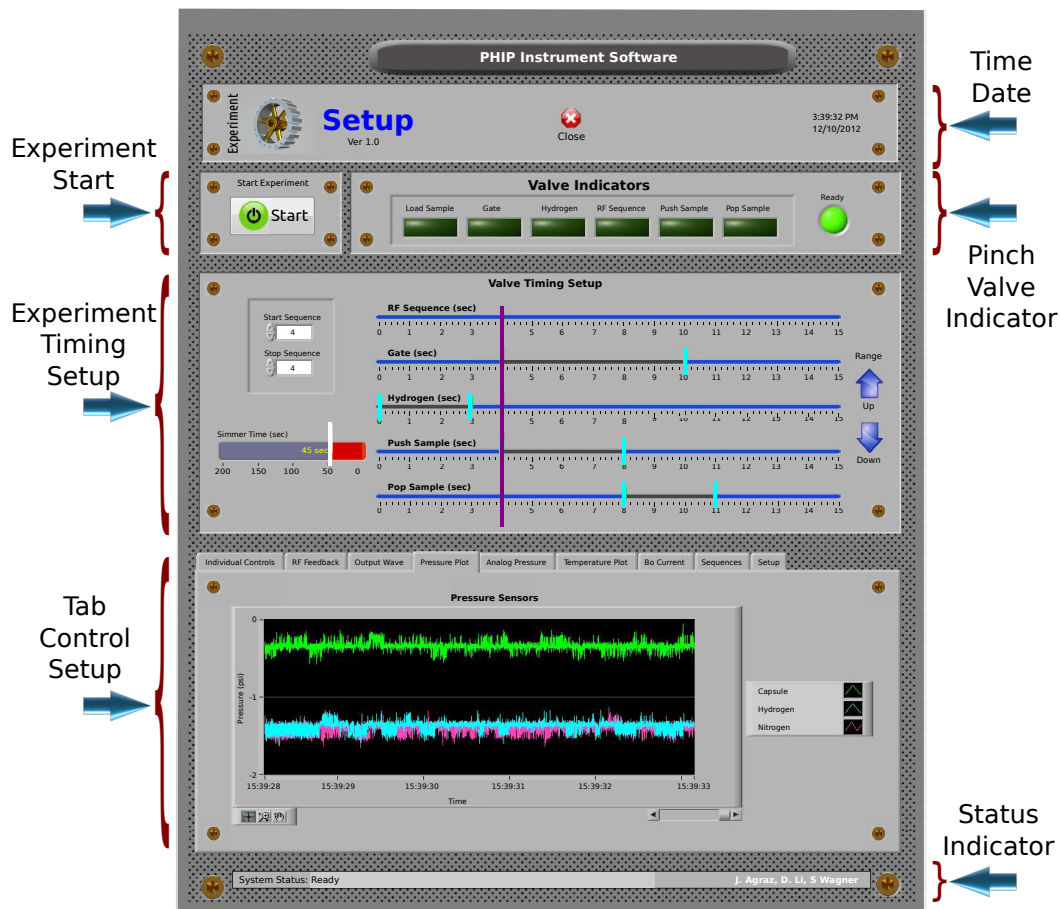


Figure 2.5: PHIP Instrument LabVIEW Front Panel. Blue labels point to the panel's four different sections: Pinch Valve Indicators, Experiment Timing Setup, TabControl Setup, and Status Bar

2.2.2 Experiment

In order to verify the above method, five different tests were performed: Pressure, Temperature, RF Sequence, and Experiment Timing. a) Pressure: The p-H₂ and N₂ gas pressure readings on the SFP were compared against a reference analog pressure gauge installed at the tanks' pressure regulator. b) Temperature: the six temperature readings on the SFP were compared against an Agilent 34411A multimeter using a 1K Ω Resistance Temperature Detector (RTD) with 4-wire connection. c) RF Sequence Delivery: The delivery of the sequence by Dev2 was

validated by placing an oscilloscope at the RF coil and verifying the waveform multiple amplitudes, frequency, and length. d) Experiment Timing; a p-H₂ and N₂ gas tanks were set to 2 bar, a 10ml water sample in a syringe was prepared. The Experiment Timing controls for sample heating, pinch valves, and RF sequence were setup as in fig 2.5. Then, the Start Experiment button on the SFP was pressed and the sample injected in the instrument. Next, the sample automated manipulation was timed with a timer and visually checked for proper on/off pinch valve sequence.

2.2.3 Results

These results are only intended to be a rough validation of the hardware and software, as the PHIP Instrument’s pressure sensor and clock timing are more accurate than the reference sensors used. Pressure: The N₂, p-H₂, and reaction chamber gas pressures readings on the SFP were compared to a reference analog gauge. The reading were taken from 0 to 5 bar in 0.5 bar increments. The three pressure experiments resulted in an average of ± 0.2 bar nonlinearity with respect of the reference. However, the instrument’s pressure sensors [Hon12] have a Honeywell pressure sensor used has a $\pm 0.25\%$ full scale accuracy and a 2% total error over a -40 °C to 125 °C range. Temperature: The six temperature sensors [Ins00] showed at $\pm 0.5^\circ\text{C}$ nonlinearity and a maximum $\pm 2.1^\circ\text{C}$ difference between readings. The large difference between readings is caused by thermal Eddy currents between sensors and the RTD used as reference. Experiment Timing: The pinch valve sequence was measured with a hand held timer to $\pm 100\text{ms}$ resolution, resulting in a maximum deviation of $\pm 300\text{ms}$. Sequence Delivery: The RF sequence was validated by measuring the RF irradiation with a secondary coil connected to an oscilloscope. As expected, the radiated output was slightly lower in amplitude due to a loss transmission between the two antennae, but showed the right frequency and timing.

2.2.4 Conclusion

The use of LabVIEW to control PHIP instrumentation has strong potential for aiding in the maximum polarization levels of different metabolites with high reliability and at an affordable price. In addition, the use of LabVIEW for the automation of metabolite hyperpolarization improves the instrument accuracy, shortens development time, and decreases hardware costs. The operational test shows that the LabVIEW-based hyperpolarization instrumentation system is stable and reliable, crucial aspects for metabolite hyperpolarization.

CHAPTER 3

PHIP Instrument B_o Stability Control

Para-Hydrogen Induced Polarization (PHIP) is a method applied to cell metabolites to enhance the magnetic resonance imaging (MRI) signal, allowing for molecular imaging [VA10][NB97][HCH08][BCP07]. The current flow generating a static magnetic field (B_o) in a PHIP instrument has been discussed previously, but in most instances attention has been directed towards the manual control of current flow using a voltage controlled voltage source (VCVS) and feedback from Hall sensors placed near the solenoid generating B_o [HCH08][GAJ01][PB11][HCH09]. The current flow produced by a VCVS often shows inherent changes in current stability [AK04][Dem0x], which is observed as noise. This noise often changes rapidly such that manual corrections become insufficient, altering the B_o and changing the nuclear resonance frequencies. In turn, this negatively affects the maximum polarization achieved.

Voltage controlled current sources (VCCS), generally known as current sources, are the foundation of electronic circuit design. They provide the basic current and voltage conditions for electronic circuits to operate. Originally, current sources were designed using resistors, however, due to size limitations, temperature instability, and manufacturing variations, their use resulted in poor accuracy and stability [Lin05]. In 1958, engineers at Crystalonics Inc developed the current regulator diode (CRD) [LMH95], a small single component that produces constant current flow regardless of changes in power supply voltage [Jea62a][Jea62b]. Then, in 1964, Robert Wildlar developed precision current source references which led

to the $\mu\text{A}702$ design [Fai86], the first commercial monolithic operational amplifier (Op Amp) [Wid65] [Rob98][Lee07]. The development of quieter and more stable current sources continues to this day, culminating with the development of the high-stability, laser-trimmed, thin-film resistors [SAG11][BP12], which allow for current source designs with excellent initial accuracy, a very low temperature coefficient, and an ultra-low noise level. These developments have been incorporated in the design of one of today's best voltage reference ICs, the Maxim MAX6126 (the device used in this VCCS design), a device with a wide operational temperature range, ultra low noise & temperature compensation, high accuracy, and force/sense outputs [Int12][Lin05].

In addition to the theoretical and numerical simulations, we present comparative HEP hyperpolarization results using a VCVS & VCCS. The models described are based on transfer functions (TF), which supply the basis for finding the circuit response characteristics without solving differential equations. First, we developed the ideal VCVS & VCCS TF and impulse response to effectively demonstrating the VCCS' immunity to current flow fluctuations. Then, using Matlab we develop the VCCS' small signal model, which is estimated using the method of open-circuit time constants followed by the system's output current/input voltage ($\frac{I_o}{V_{in}}$) TF. Finally, we present the HEP hyperpolarization data showing a 50% increase in polarization using the VCCS developed in our lab.

3.1 Ideal Voltage Controlled Sources Model Development

First, we consider the current flow impulse response of an ideal VCVS & VCCS powering a solenoid (L) in the s-Domain. Then, the resulting TFs show that a VCCS is a better choice than a VCVS for generating a B_o in PHIP applications. In circuit analysis and according to Watt's law [Jim91], an ideal VCVS maintains a given voltage difference between its terminals independent of the current drawn,

while an ideal VCCS maintains a given current through its terminals independent of the voltage across its terminals. Any circuit can be modeled for analysis as a combination of voltage sources, current sources, and impedance elements. These models further simplify with the aid of Laplace transformations and TFs for circuit analysis in the s-Domain [AK04][Jim91][Rob08].

3.1.1 Ideal VCVS model

In order to obtain the VCVS circuit setup model as shown in figure 3.1a, we derive the resistor current ($i_T(t)$) with a disruptive noise (impulse pulse) in the s-Domain using Kirchhoff's law & the voltage divider rule [AK04] in equation (3.1). Then, the VCVS circuit current impulse response is evaluated in the time-Domain ($i_R(t)$), leading to equation (3.2), where L is the solenoid (40mH) and R is the current sensing resistor (1Ω). The resultant plot is displayed in figure 3.1b. The VCVS' $I_R(s)$ change exponentially in the presence of a disrupting impulse pulse, making a VCVS design a poor choice for generating a stable B_o (fig??).

$$i_T = \underbrace{i(\infty)}_{\text{Steady State}} + \underbrace{i(t)}_{\text{Current Function}} \times \underbrace{\delta(t)}_{\text{Impulse}} \quad (3.1)$$

$$\begin{aligned} \mathcal{L}\{V_R(t)\} &= V_R(s) = V_{in}(s) \times \frac{R}{sL + R} \\ I_o(s) &= \frac{V_R(s)}{R} = V_{in}(s) \times \frac{1}{sL + R} \\ I_o(s) \times (1) &= V_{in}(s) \times \frac{1}{s + \frac{R}{L}} \times \mathcal{L}\{\delta(t)\} = V_{in}(s) \times \frac{1}{s + \frac{R}{L}} \times (1) \\ \mathcal{L}^{-1}\{I_o(s) \times (1)\} &= V_{in}(t) \times e^{-\frac{R}{L}t} \\ i_o(t) \times \delta(t) &= V_{in}(t) \times e^{-\frac{R}{L}t} \\ i_T &= i(\infty) + i(t) \times \delta(t) = 1 + e^{-25t} \end{aligned} \quad (3.2)$$

Where $i(\infty)=1$ Ampere, $V_{in}=1$ Volts, $L=40\text{mH}$, & $R=1\Omega$

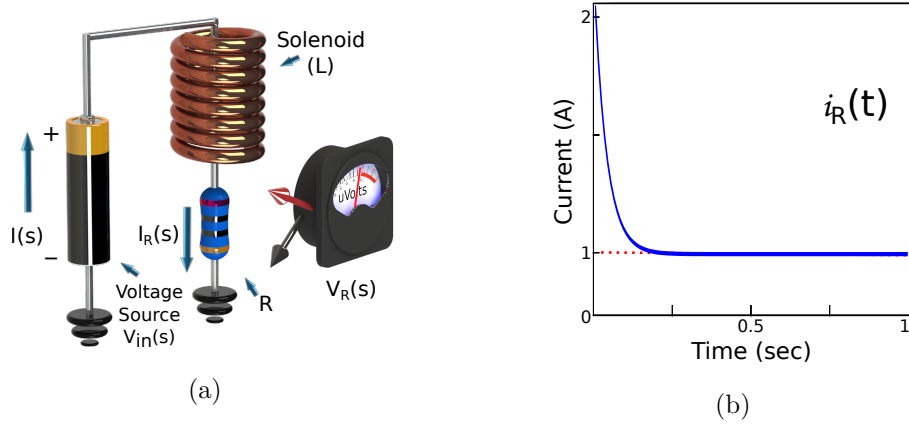


Figure 3.1: A VCVS is incapable of generating a stable current flow $I(s)$, leading to an instable B_o , while the VCCS produces a stable $I(s)$, thus a stable B_o . VCVS & VCCS transfer functions with an impulse response were developed and tested across a resistor (R). a) Ideal VCVS test setup, b) VCVS impulse response, current flow after a disruptive impulse measured at R

3.1.2 Ideal VCCS model

Similar to the VCVS derivation, the ideal VCCS circuit setup model is shown in figure 3.2a. Using Kirchhoff's law, the VCCS current flow is the same at any point in the circuit, as shown in equation (3.3), where k is a current flow constant (1 Ampere). The result plot is displayed in figure 3.2b. The VCCS' current flow is a given constant, thus an ideal VCCS' output current is immune to noise, making this design a good choice for generating a stable B_o (fig 3.2).

3.2 VCCS Model Development

We begin by describing the VCCS components: 1) An ultra high precision, ultra low noise, series voltage reference [Int12] 2) A passive low pass filter, 3) An active low pass filter, 4) A MOSFET current sink and Op Amp with negative feedback, 5) Coil filter, and 6) Measure current port (fig 3.4 & 3.3). We employ various

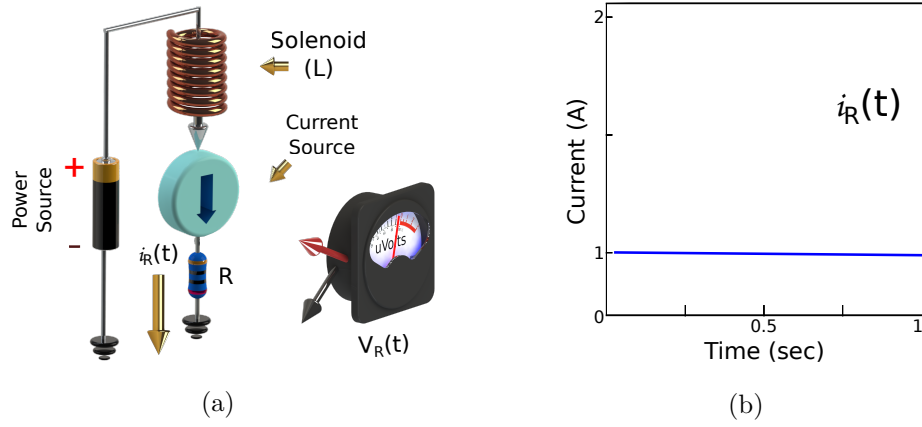


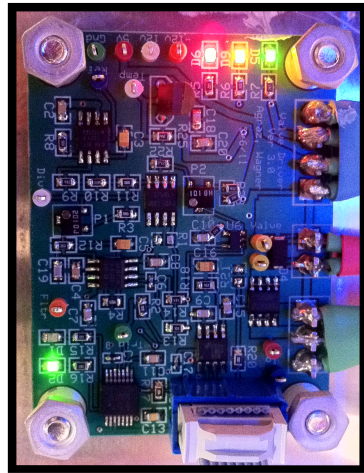
Figure 3.2: a) Ideal VCCS test setup, b) VCCS impulse response, current flow after a disruptive impulse measured at R

$$I(s) = I_L(s) = I_R(s) = \frac{k}{s}(1) \iff i(t) = k \quad (3.3)$$

Matlab toolboxes to develop the VCCS small signal model [Att99][Mou05], and consequent simulations result in the complete VCCS' input/output TF (I_o/V_{in}) shown in equation (3.4), zeros and poles are listed in table (3.1).

$$TF_{vccs} = \frac{I_o}{V_i} = \frac{TF_1(s) \times TF_2(s) \times TF_3(s)}{R_{sense}} \quad (3.4)$$

Where I_o is the current through the solenoid (V_o/R_{sense}), V_i is the voltage reference, TF_1 is the passive low pass filter TF, TF_2 is the active low pass filter TF, TF_3 is the current sink TF, R_{sense} is the current sense resistor.



Actual
Circuit

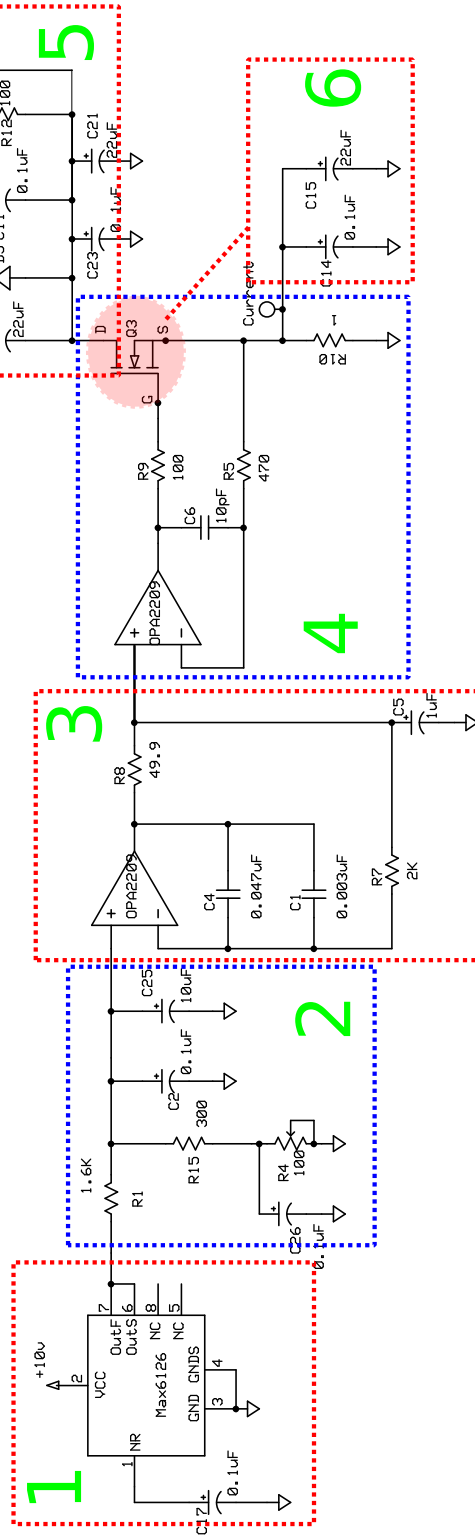


Figure 3.3: VCCS schematic. 1) Voltage reference, 2) Manual current control & passive filter, 3) Active filter, 4) Current sink, 5) Coil filter, and 6) Measure current port filter

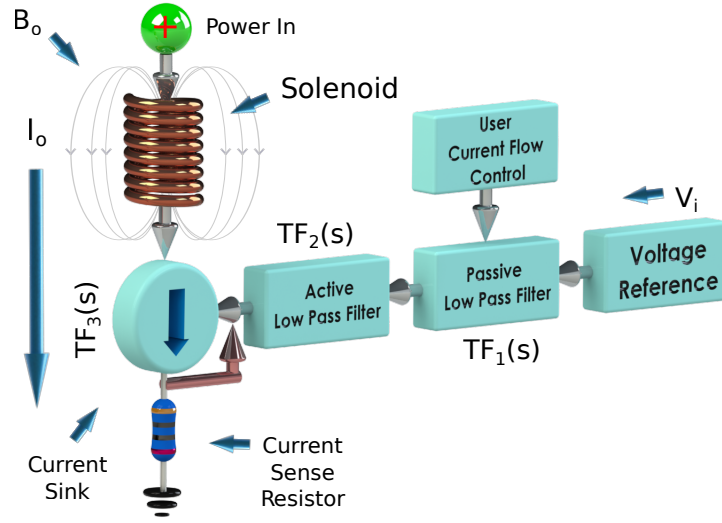


Figure 3.4: VCCS design block diagram. A TF model was developed for each circuit components. The TF_{vccs} is the product of each TF which ultimately is used to characterize I_o and B_o . The solenoid typical input power is +5V

3.2.1 Voltage reference

The voltage reference used is a Maxim integrated ultra high precision, ultra low noise, series voltage reference. This reference has an ultra low noise to $1.3\mu V_{p-p}$ from 1/10Hz to 10Hz, a ultra low drift of 3ppm/ $^{\circ}C$ with a $\pm 0.02\%$ initial accuracy [Int12].

3.2.2 Passive Low Pass Filter

The passive low pass filter serves two purposes, the design uses a ten-turn potentiometer (R_4) as a voltage divider to adjust I_o and uses a low pass filter to minimize any electronic noise pickup through cabling (fig 3.5). As shown in equation (3.5), the complete filter's TF has one zero ($130K \frac{rad}{sec}$) and two poles ($-130K \frac{rad}{sec}$ & $307K \frac{rad}{sec}$) (fig 3.5).

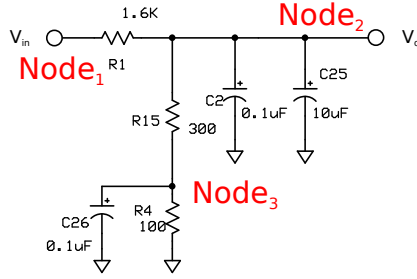


Figure 3.5: Passive Low Pass Filter

$$TF_1(s) = \frac{V_{o1}}{V_{i1}} = \frac{(s - a_z)}{(s - a_p)(s - b_p)} \quad (3.5)$$

Where $V_{i1}=V_{in}$, a_z is the equation's zero, and a_p & b_p are the equation's poles.

3.2.3 Active Low Pass Filter

The output voltage from the passive low filter is filtered by an active low pass filter, minimizing any residual noise (fig 3.5). As show in equation (3.6), this filter's transfer function has two zeros ($79 \times 10^6 K \frac{rad}{sec}$, $-0.2 \times 10^6 K \frac{rad}{sec}$) and three poles ($31 K \frac{rad}{sec}$, $-11 K \frac{rad}{sec}$, $12 K \frac{rad}{sec}$).

$$TF_2(s) = \frac{V_{o2}}{V_{i2}} = \frac{(s - a_z)(s - b_z)}{(s - a_p)(s - b_p)(s - c_p)} \quad (3.6)$$

Where $V_{i2}=V_{o1}$, a_z & b_z are the equation's zeros, and a_p , b_p , & c_p are the equation's poles.

3.2.4 Current Sink

The resulting output voltage from the active low pass filter drives the gate of a MOSFET setup as a current sink. In order to maintain control of the MOSFET drain current, an Op Amp is setup in a negative feedback configuration (fig 3.7)

[Rob08]. As shown in equation ((3.7)), the TF has three zeros ($79 \times 10^6 K \frac{rad}{sec}$, $0.2 \times 10^6 K \frac{rad}{sec}$, $31 K \frac{rad}{sec}$) and four poles ($3700 K \frac{rad}{sec}$, $-1800 K \frac{rad}{sec}$, $-3400 K \frac{rad}{sec}$, $-0.2 \times 10^6 K \frac{rad}{sec}$). Notice

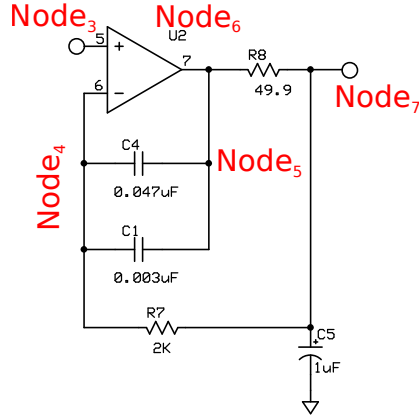


Figure 3.6: Active Low Pass Filter

that R_9 , C_6 , & R_5 provide a filter to allow for most MOSFETs without changing the circuit, D_5 provides protection for transients that may be produced by the main coil, C_9 , C_{11} lowers the resonance frequency of the main coil circuit, and R_{12} provides current drain and lower resonance frequency for the circuit

$$TF_3(s) = \frac{V_{o3}}{V_{i3}} = \frac{(s - a_z)(s - b_z)(s - c_z)}{(s - a_p)(s - b_p)(s - c_p)(s - d_p)} \quad (3.7)$$

Where $V_{i3}=V_{o2}$ & $V_{o3}=V_{out}$, a_z , b_z , & c_z are the equation's zeros, and a_p , b_p , c_p , & d_p are the equation's poles.

3.2.4.1 Power Dissipation

Power dissipation at the current sink MOSFET is a key component to the circuit stability. As power dissipation increases because of increased current or/and power supply voltage, the current flow (I_o) derates and is given by equation (3.8) [Sem06a]. For an optimal thermal noise level, the voltage drop across V_{DS} must be kept at a minimum while keeping the MOSFET operating in saturation. If the V_{DS} is too low, the power dissipation and thermal noise will be at a minimum, but may render the MOSFET useless. Using trial an error, a $V_{DS}=1V$ yields the

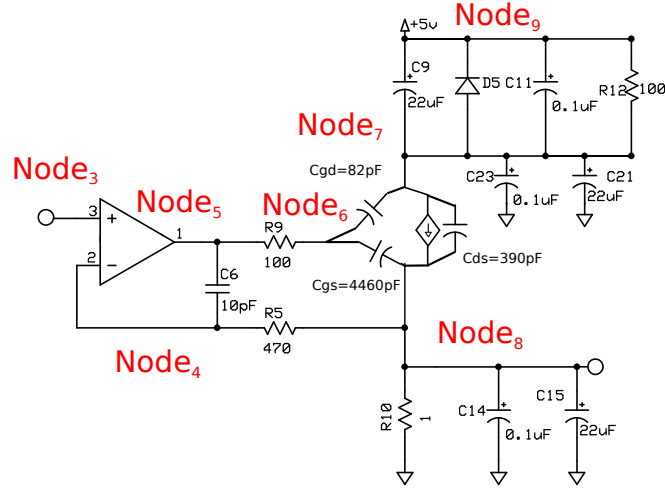


Figure 3.7: Current Sink

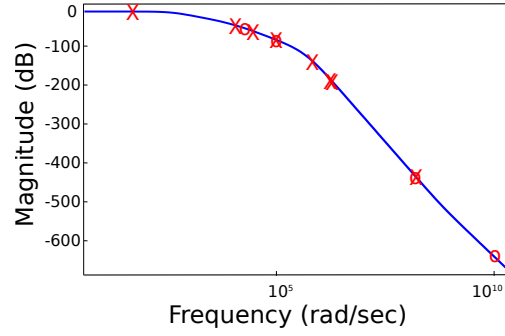


Figure 3.8: Equation (3.7) frequency response with zeros (o) and poles (x)

coolest MOSFET while keeping thermal noise below 10μV.

$$I_o = \sqrt{\frac{P_D}{R_{DSon} \times T_{jmax}}} \quad (3.8)$$

Where I_o is the current flow through the MOSFET, R_{DSon} is the ON drain-source resistance, P_D is the MOSFET's power dissipation, and T_{jmax} is the junction temperature of the MOSFET.

Table 3.1: TF_{vccs} ZEROS & POLES

	Zeros (K rad/sec)			Poles (K rad/sec)			
	a_z	b_z	c_z	a_p	b_p	c_p	d_p
$TF_1(s)$	-130	—	—	130	-307	—	—
$TF_2(s)$	79×10^6	-0.2×10^6	—	31	-11	-12	—
$TF_3(s)$	79×10^6	0.2×10^6	-31	3700	-1800	-3400	-0.21×10^6

3.2.5 Coil filter

As RF irradiate a given sample during molecular spin transfer, the rf sequence may induce a small magnetic field at B_o , causing a change in magnetic field, thus sample resonance frequency. Although, eliminating this effect completely is not feasible, by transforming the main coil into a tank circuit with a very low resonance frequency, the effect may be minimized. The resonance frequency for tank circuit is given by equation (3.9) and the bandwidth is given by equation (3.10). Since the tank circuit has a $F_c=170$ with a $BW=400\text{Hz}$, as long as the rf sequence frequency components are above $170+400/2=370\text{Hz}$, noise induced into B_o will be minimum. Note that MOSFET capacitances are ignored, as the capacitances are in the nano Farads range, thus negligible at 370Hz (fig 3.9).

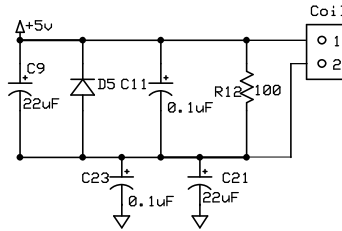


Figure 3.9: Coil filter setup

$$F_c = \frac{1}{2\pi\sqrt{LC}} \implies F_c = \frac{1}{2\pi\sqrt{40mH \times 22\mu F}} = 170Hz \quad (3.9)$$

Where L is the main coil inductance, L=40mH, and C is the total capacitance of the circuit, C=22.1μF.

$$BW = \frac{R}{2\pi L} \implies BW = \frac{100\Omega}{2\pi \times 40mH} = 400Hz \quad (3.10)$$

Where R is R₁₀=100Ω and L is the main coil, L=40mH.

3.2.6 Measure current port filter

In order to keep track of the current flow through the main coil, a 1Ω current resistor was setup to allow voltage measurements, the current is measured indirectly using Ohm's law (Fig. 3.10). Measuring the current accurately is a priority. Thus, a RC filter is setup for this purpose. The filter frequency is given by equation (3.11). However, the MOSFET's resistance across the drain-source that forms the filter is dynamic by many factor such as; temperature, input voltage, power supply, and gate length (W) [Sem02]. For a MOSFET working in the saturation region, the current through the MOSFET is given by equation (3.11), and solving for the resistance across the drain-source (r_o), r_o is given by equation (3.13). Assuming all parameters in equation (3.13) except for V_{DS} are constants, and V_{DS} design target is $1v \pm V_{noise}$, where V_{noise} was measured at 150μV. Then, by Ohm's law $r_o=1\pm150\mu\Omega$. Using equation (3.11) with $R=r_o$ and $C=22.1\mu F$, the filter frequency at the port is $F_c=7.233KHz \pm 1Hz$.

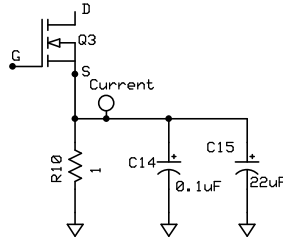


Figure 3.10: Current Sink

$$F_c = \frac{1}{2\pi RC} \quad (3.11)$$

Where C is the total capacitance of the circuit, C=22.1 μ F and R is the resistance across the MOSFET's drain-source.

$$I = K(V_{GS} - V_T)^2 + \frac{V_{DDS}}{r_o} \quad (3.12)$$

Where K is the transconductance gain, V_{GS} is the voltage across the gate and source, V_T is the threshold voltage, V_{DS} is the voltage across the drain and source, and r_o is the resistance across the drain-source

$$r_o = \frac{V_{DS}}{I - K(V_{GS} - V_T)^2} \quad (3.13)$$

3.2.6.1 Temperature Sensor

The process of full precursor hydrogenation for optimal hyperpolarization is sensitive to temperature. In our PHIP instrument design, the hydrogenation of HEA is best at 45°C. In order to monitor temperature, our design monitors the ambient temperature near by through a precision temperature sensor LM35 with a full range given by equation (5.8) [Sem00]. The output capacitance of the sensors is 50nF, a value too small to filter high frequencies at the output, thus, an additional capacitor was installed at C₂₂=1 μ F

3.3 Current Flow Noise & Long Term Drift Experiment

We compare current flow noise (i_n) from a VCCS circuit designed in our laboratory and an off-the-shelf VCVS (HY3003D-3 power supply). The experiment demonstrates how a VCVS driving a solenoid results in poorly controlled current flow (I_o), while a VCCS provides more stable I_o and predictable Larmor frequencies over short and long periods. B_o and the Larmor frequency drift (F_Δ) for i_n

3.4 Hydroxyethyl Propionate Hyperpolarization Experiment

The PHIP hyperpolarization experiment setup for producing hyperpolarized hydroxyethyl propionate (HEP) is shown in figure 3.13. The goal of the experiment was to produce hyperpolarized HEP using a VCVS and a VCCS for generating the B_o in a PHIP instrument developed in our laboratory. Then, the polarization obtained was compared for each DUT. The experiment performed for each DUT was as follows: 1) The DUT was installed in the PHIP instrument, 2) An HEA solution was prepared, 3) Each sample was run with the PHIP instrument's polarization automated process, 4) Each HEP sample was collected and its polarization measured in a 9.4T Bruker Biospin Scanner.

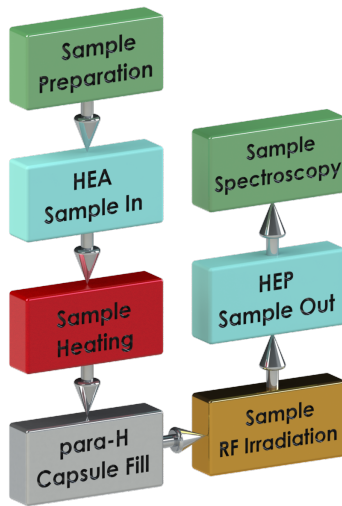


Figure 3.13: PHIP hyperpolarization process using HEP

3.4.1 HEA Solution Preparation

A 40mL solution of deuterium oxide (D_2O) was used to dissolve 10mM of Hydroxyethyl acrylate-1- ^{13}C , 2,3,3-d3 (HEA) and 2mM of Wilkinsons catalyst Rh norbornadiene bisphosphine [OWY65]. The solution yielded 26 3mL samples.

3.4.2 PHIP Instrument Polarization Process

3mL of HEA solution was inserted into the PHIP instrument and the preprogrammed Labview automation software began the polarization process. In the PHIP process as seen in figure 3.14, the sample was heated for 45 seconds to 45°. While the sample was heated, the reaction chamber was filled with 95% para-Hydrogen gas at 7 bar. Next, the sample was pushed into the reaction chamber and the HEA hydrogenated to HEP with the catalyst's aid. During the hydrogenation process, the sample was irradiated with a Radio Frequency (RF) sequence [GJA05] and the para-hydrogen spin order was transferred to the adjacent ^{13}C nuclei. Finally, the sample was ejected out of the instrument and captured in a syringe.

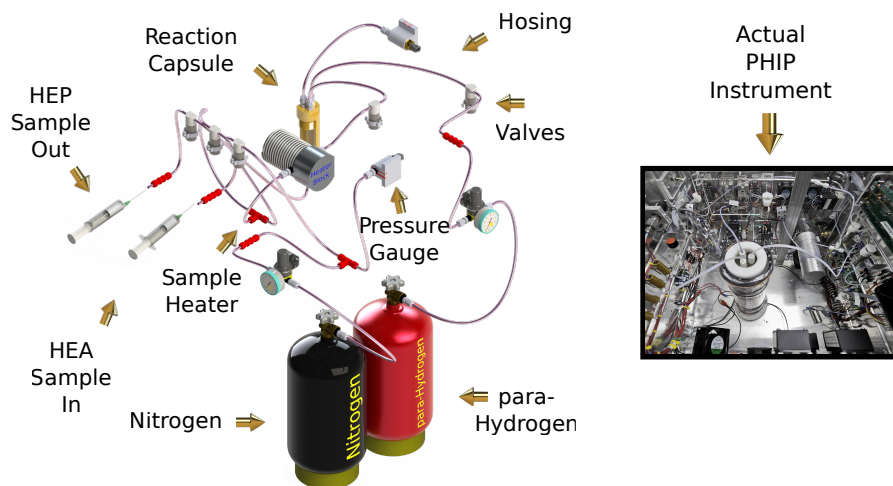


Figure 3.14: Basic PHIP Instrument rendering displaying the basic components for polarization automation. The precursor sample is introduced into the system using a syringe. Next, the sample is moved to the heater block where the temperature is raised by conduction to 45° for 45 sec. Nitrogen gas is used to transport the sample throughout the system. Then, para-Hydrogen gas is used to hydrogenate the precursor. Finally, the sample is irradiated with RF, the spin transferred, and the polarized sample ejected into a syringe.

3.4.3 Measuring HEP Polarization

The HEP sample polarization was measured with a 9.4T Bruker Biospin Scanner using a 90°hard pulse. The signal was acquired with a 20kHz spectral width at the ^{13}C carbonyl resonance frequency.

3.5 Results

Results were collected for the following; 1) TF_{vccs} model's poles & zeros and VCCS' I_o measurements at 0Hz, 2) VCVS & VCCS' i_n and i_D , 3) VCVS & VCCS' HEP polarization.

3.5.0.1 VCCS Model

As shown in Table 3.2, the model (TF_{vccs}) was solved for I_o and evaluated at V_i from 300mV to 1V, with two different loads, 1.5Ω & 4Ω . Then, the circuit's I_o measured under the same loads. $\text{TF}_{vccs}(I_o)$ data correlates with experimental data to 0.02% at 0Hz. VCCS design is characterized by the TF's dominant pole and

Table 3.2: VCCS' I_o MODEL CORRELATION UNDER DIFFERENT LOADS

V_i	TF_{vccs}	R=1.5 Ω		R=4 Ω	
		I_R	Corr	I_R	Corr
(mV)	(mA)	(mA)	%	(mA)	%
300	299.94	300.01	0.02	300.01	0.02
500	499.9	500.01	0.02	500.01	0.02
800	799.82	800	0.02	799.98	0.02
1000	999.75	999.98	0.02	999.99	0.02

damping ratio. The dominant pole (ω_d) determines the low pass filter prevalent cut-off frequency and the damping ratio (ζ). ζ describes how quickly a disturbance decays after being applied to our design. A $\zeta=1$ means short decay, while $\zeta=-1$ means a long decay. The design's complete TF shows a $\omega_d=49\text{Hz}$ & a $\zeta=0$, failing stability using the routh test [Rou77][Hur64] with four negative real roots. The passive low pass filter's TF is shown in equation 3.5 with $\omega_d=49\text{Hz}$ and a $\zeta=1$. The active low pass filter's TF is shown in equation 3.6 with $\omega_d=1.893\text{KHz}$ and a $\zeta=1$. The current sink's TF is shown in equation 3.7 with $\omega_d=296\text{Hz}$ and a $\zeta=-1$. A complete list of zeros & poles is shown in Table 3.1.

Current flow noise (i_n) was collected using the Agilent 34411A at 1.6KHz for 30 seconds. Then, B_o and the resonance frequency shifts for ^1H & ^{13}C were calculated using the BiotSavart law & the Larmor frequency equation [Has10]. The results are listed in Table 3.3 and shown in figure 3.15. The same procedure was utilized for i_D , but at 0.2Hz for 70 hrs. The results are listed in Table 3.4 and shown in figure 3.16.

Finally, a total of 26 samples for VCVS & VCCS HEP polarization were

Table 3.3: RESONANCE FREQUENCY SHIFT DUE TO i_n

	I_o	B_o	H_2		C^{13}	
	$\bar{x}$ (mA)	$\bar{x}$ (mT)	Δ (Hz)	σ	Δ (Hz)	σ
VCVS	800.7	1.801	± 31.6	19.5	± 7.97	4.9
VCCS	794.0	1.780	± 4.1	1.01	± 1.03	0.2

collected. For each sample, volume & peak area was recorded, and the peak area was calibrated by volume. Then, the mean ($\bar{x}$), standard deviation (σ), and percent polarization gain was calculated using equation (3.15), where P_{vccs} is the polarization using a VCCS and P_{vcvs} is the polarization using a VCVS. HEP

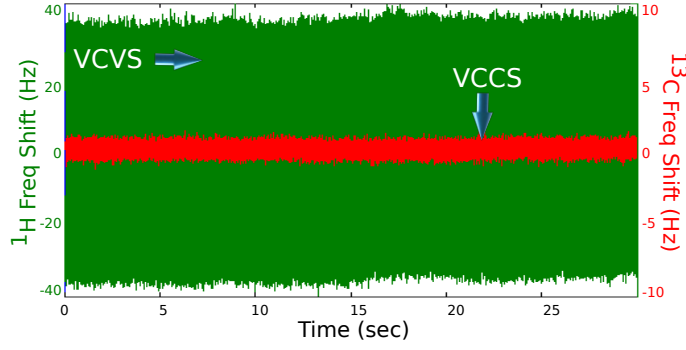


Figure 3.15: Resonance frequency shift caused by current flow noise (i_n). i_n data was captured at 1.6KHz for 30 seconds. VCVS' i_n is depicted in green, while VCCS' i_n is depicted in red

Table 3.4: RESONANCE FREQUENCY SHIFT DUE TO i_D

	I_o	B_o	H_2		C^{13}	
	$\bar{x}$ (mA)	$\bar{x}$ (mT)	Δ (Hz)	σ	Δ (Hz)	σ
VCVS	803.5	1.807	± 37.9	9.8	± 9.5	2.4
VCCS	793.7	1.785	± 1.4	0.4	± 0.3	0.1

polarization data is listed in Table 3.5 and plotted in figure 3.17.

3.6 Discussion

We have presented the results for the implementation of a VCCS for doubling the hyperpolarization of endogenous substances, more specifically, HEP. We deduced that the use of an ultra low noise, high stability voltage reference driving a current sink generates a stable I_o to 15ppm, resulting in a stable B_o for the hyperpolarization of HEP. This has led us to propose a new definition for the generation of a precision B_o for hyperpolarization applications. This new approach is fundamen-

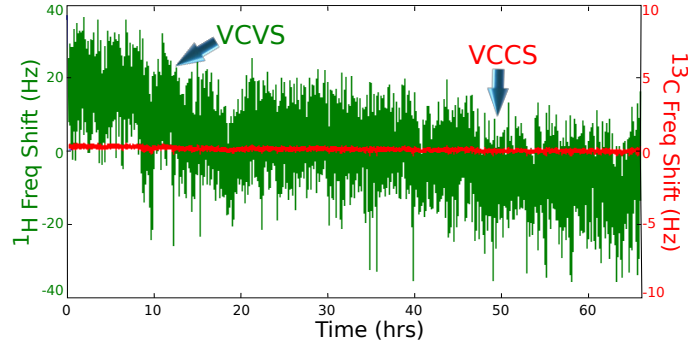


Figure 3.16: Resonance frequency shift caused by current flow long term drift i_D . i_D data was collected at 0.2Hz for 70 hrs. VCVS' i_D is depicted in green, while VCCS' i_D is depicted in red

$$\frac{P_{vccs} \times 100}{P_{vcvs}} - 100 \quad (3.15)$$

tally different from the traditional generation of B_o using VCVS devices, which does not control the flow of current.

We have calculated the TF's solutions and examined the circuit stability. Although the circuit is stable for 0Hz (where the circuit usually performs), the stability of the current sink section in the circuit begins to decrease at higher frequencies, thus the negative poles. More specifically, the instability resides at 380KHz with a 200KHz bandwidth and a peak gain of 2. Because of the dominant pole at 49 Hz, this characteristic should only affect i_n & i_D at a minimum beyond thermal and 1/f noise frequencies (≤ 1 KHz). Our definition of precision B_o generation suggests new approaches worth exploring, and more detail of circuitry optimization using TFs, board layout, & measurements on the VCCS' thermal and 1/f noise could be particularly rewarding. For example, minimizing the amount of poles and including negative feedback will produce a more efficient circuit with less components and a lower i_n & i_D . Most importantly, the circuit will be more immune to external influences such as electrical noise and temperature changes.

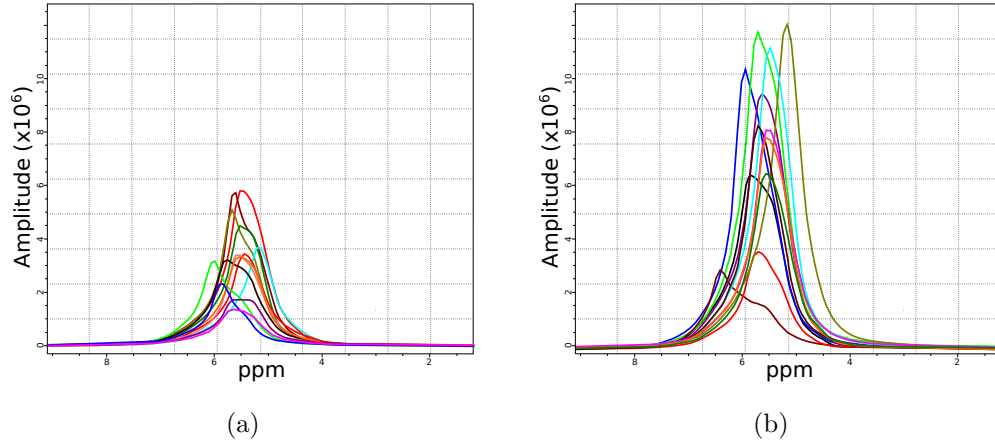


Figure 3.17: Polarized HEP spectra. a) B_o VCVS driven. b) B_o VCCS driven.

3.7 Conclusion

This paper presents a model and implementation of a VCCS for the generation of precision B_o in PHIP instrumentation. Furthermore, we show a much lower i_n and i_D and a 100% increase in HEP polarization compared to previous methods of B_o generation. The VCCS model, confirmed by experimental results with a 0.02% correlation at 0Hz, shows that i_n and i_D are principally dependent on the control of current flow. Because of the reduction in i_n and i_D , we were able to achieve higher levels of polarization. Specifically, for 10mM of HEA, 2mM of catalyst solution, and the Goldman RF sequence, the HEP polarization increased an average of 115% calculated using equation (3.15), with a minimum at 20% & a maximum of 152% from using a VCCS.

Table 3.5: HEP HYPERPOLARIZATION USING A VCVS & A VCCS

Sample Number	VCVS			VCCS		
	Peak Area A.U.	Volume mL	Peak Area A.U./mL	Peak Area A.U.	Volume mL	Peak Area A.U./mL
1	27	1.0	26	48	0.7	65
2	19	1.2	16	138	1.3	104
3	50	1.1	47	87	1.5	58
4	72	1.4	50	49	1.5	33
5	49	1.1	43	100	1.2	81
6	59	1.6	37	107	1.5	72
7	79	1.4	55	129	1.4	93
8	65	1.4	46	86	1.6	55
9	45	1.3	34	103	1.4	75
10	27	1.2	23	163	1.4	119
11	46	1.5	31	140	1.4	101
12	45	1.1	41	109	1.5	72
13	41	1.4	29	148	1.5	98
$\bar{x}$	48	1.3	37	108	1.3	79
σ	18	0.2	12	36	0.2	24

CHAPTER 4

PHIP Instrument B₀ current noise

4.1 Noise

All electronic circuits show some type of noise. This noise is produced by three random factors: 1) The motion of electrons in a material, 2) the motion of holes and electrons in a semiconductor, and 3) the diffusion of holes and electrons in a potential barrier. These random type of motion lead to three of the most notable types of noise: 1) Thermal noise, 2) Shot noise, 3) Flicker noise ($1/f$) [Lea94].

4.1.1 Thermal Noise

Thermal noise is generated by the thermal energy causing free electrons to travel randomly through a material [Lea94]. This type of noise was first found by Schottky and measured by Johnson and later an open circuit model published by Nyquist given by equation (4.1). This type of noise is also known as white noise, as thermal noise has a flat power distribution in the optical band. Thermal noise between f_1 and f_2 is simply given by equation (4.2)

$$V_t = \sqrt{4kTR\Delta f}, \text{ or } I_t = \frac{V_t}{R} = \sqrt{\frac{4kT\Delta f}{R}} \quad (4.1)$$

where k is the Boltzmanns, T is the absolute temperature, R is the resistance, and Δf is the bandwidth

$$V_t = \sqrt{4kT \int_{f_1}^{f_2} R_e(z), dx} \quad (4.2)$$

where R_e is the real part of the impedance Z , f_1 & f_2 are the start and stop frequencies.

4.1.2 Shot Noise

Shot noise is generated when current crosses a p-n junction in a semiconductor [Zie70]. This type of noise is commonly known as shot noise as the noise sounds like buck shot dropped on a metal surface. As electrons enter the junction, the diffusion of electrons and holes and their recombination results in short noise and is given by Schottky's equation (4.3). Shot noise is independent of frequency, thus it has a flat power distribution [Lea94] as shown in figure 4.1a.

$$I_{sh} = \sqrt{2qI\Delta f} \quad (4.3)$$

where I is the current through the device and q is the electronic charge constant

4.1.3 $1/f$ Noise

The current flow through the junction of two conductive materials generates noise known as contact, flicker, or $1/f$ "one-over-f noise". The noise is produced by the imperfections in the two material junctions and show as changes in conductivity. The $1/f$ noise is given by equation (4.4) and shown in figure 4.1b. This noise mainly increases at low frequencies, thus the name pink noise.

$$I_{sh} = \sqrt{\frac{K - fI^m\Delta f}{f^n}} \quad (4.4)$$

where I is the dc current, n is the degree of noise slope, K_f is the flicker noise coefficient, and m is the flicker noise exponent

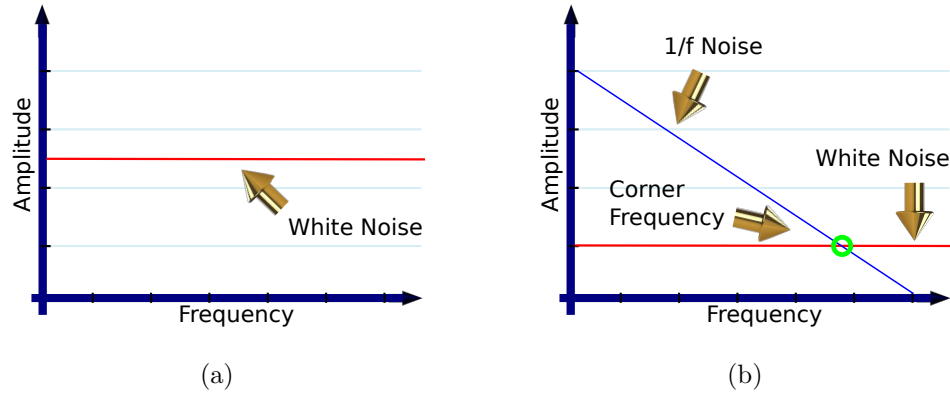


Figure 4.1: a) Shot noise basic spectra. b) $1/f$ basic spectra

4.2 VCCS Noise

In the PHIP instrument design, the most influential source of noise are $1/f$ and thermal noise. The noise data obtained will help in the hyperpolarization of future substances, as the amount of polarization interference by noise will be a known quantity.

4.2.1 Method

The VCCS designed in our lab was tested for $1/f$ and thermal noise using the Agilent 35670A spectrum analyzer. The design was characterized over expected hyperpolarization environments for future endogenous substances, at temperature from 40°C to 70°C and current from 50ma to 900ma. The four corners (extremes) spectra is shown in figure 4.2a and the average shown in figure 4.2b

The spectrum analyzer was setup as follows; 0Hz to 1.6KHz, 100 averages, and 401 points, with a -90dB equipment noise floor. Temperature was varied from 40°C to 70°C in 2°C steps, and current was varied from 50ma to 900ma in 50ma steps. The total number of data sets were $15 \times 17 = 255$ with 401 points each.

4.2.2 Results

The average thermal noise found is $125\text{nV}\sqrt{Hz}$ without noticeable changes over temperature (fig. 4.2a & 4.2b). The average over all noise found was $22.5\mu\text{V} \pm 12.5\mu\text{V}$, with the least amount noise was found at higher temperatures $10\mu\text{V}$. while the most amount of noise at low temperatures $35\mu\text{V}$ (fig. 4.3a & 4.3b). Curve fitting was done using Matlab's Lowess model with a 25 span and a quadratic polynomial, resulting in $R=0.74$. Data with larger R of 0.94 is shown in figure 4.4a & 4.4b. The calculation of the $1/f$ rms noise is given by equation (4.5). For $V_{tn}=125\text{nV}\sqrt{Hz}$, $F_c=1\text{KHz}$, $F_L=0.1\text{Hz}$, and $F_H=1.6\text{Hz}$, the $V_{n,rms}$ is given in equation (4.6), or $12\mu\text{V}_{rms}$, with a $V_{n,pp}$ given in equation (4.7), or $79.2\mu\text{V}_{pp}$

$$V_{n,rms} = V_{tn} \times \sqrt{F_c \times \ln\left(\frac{F_c}{F_L}\right) + (F_H - F_C)} \quad (4.5)$$

where $V_{n,rms}$ is the $1/f$ rms noise, V_{tn} is the thermal noise voltage, F_c is the $1/f$ corner frequency, F_L is the lower frequency of the measurement, and F_H is the upper frequency of the measurement

$$V_{n,rms} = 125\text{nV}\sqrt{Hz} \times \sqrt{1\text{KHz} \times \ln\left(\frac{1\text{KHz}}{0.1\text{Hz}}\right) + (1.6\text{KHz} - 1\text{KHz})} \quad (4.6)$$

$$V_{n,pp} = 6.6 \times 12\mu\text{V}_{rms} = 79.2\mu\text{V}_{pp} \quad (4.7)$$

where $V_{n,pp}$ is the $1/f$ noise peak to peak voltage and 6.6 is the rms to Peak-to-peak most used conversion factor

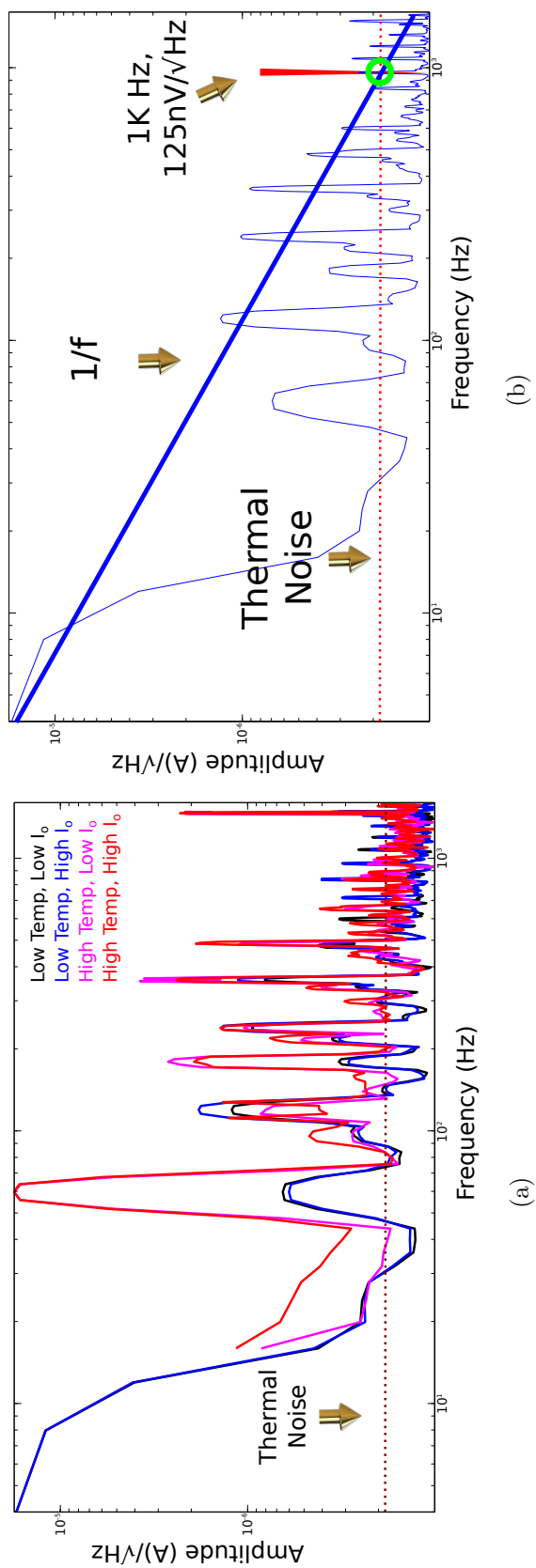
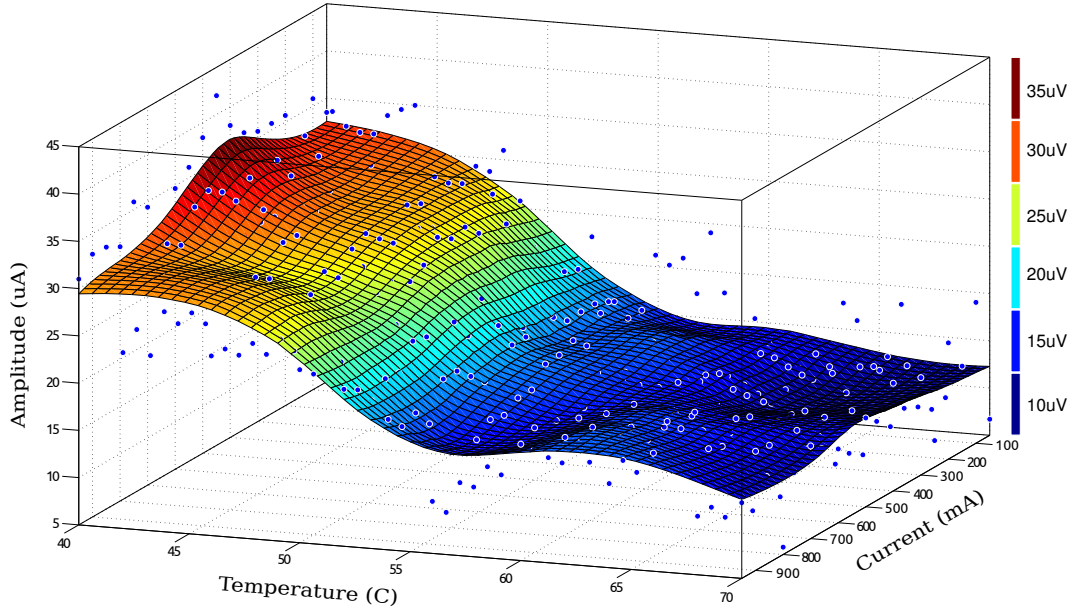


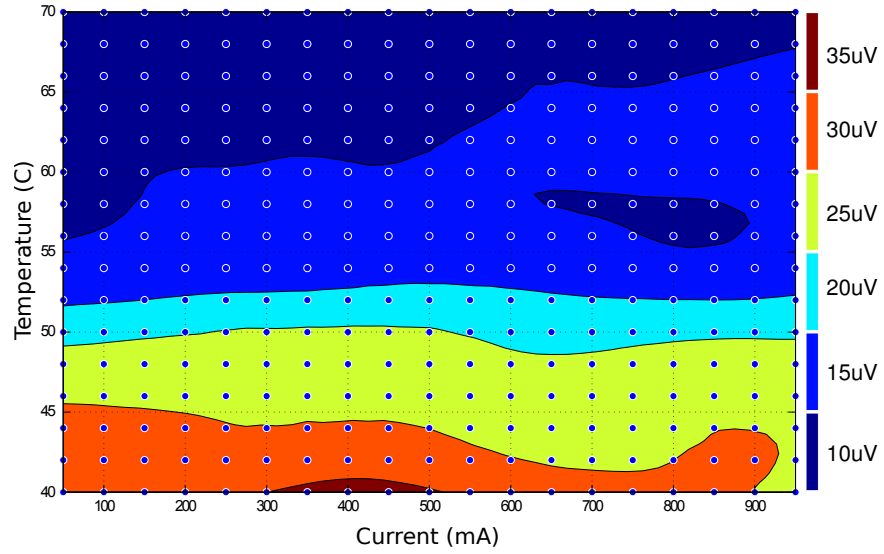
Figure 4.2: VCCS noise measured with an Agilent 35670A spectrum analyzer. a) Measured noise at the four corners; low temp & low current, low temp & high current, high temp & low current, and high temp & high current b) Average noise for all 255 data sets

4.2.3 Conclusion

Although, the measured noise is much greater than in integrated circuits (IC) for low current application, the VCCS design shows very low noise levels at high currents (1Amp). Also, the VCCS design has the capabilities of handling much larger currents with minimum design changes at virtually the same noise levels measured here. Further design improvement, such design simplicity, could come from redesigning the circuit using TF with negative feedback and lower noise levels and drift may be achieved by using digital control.

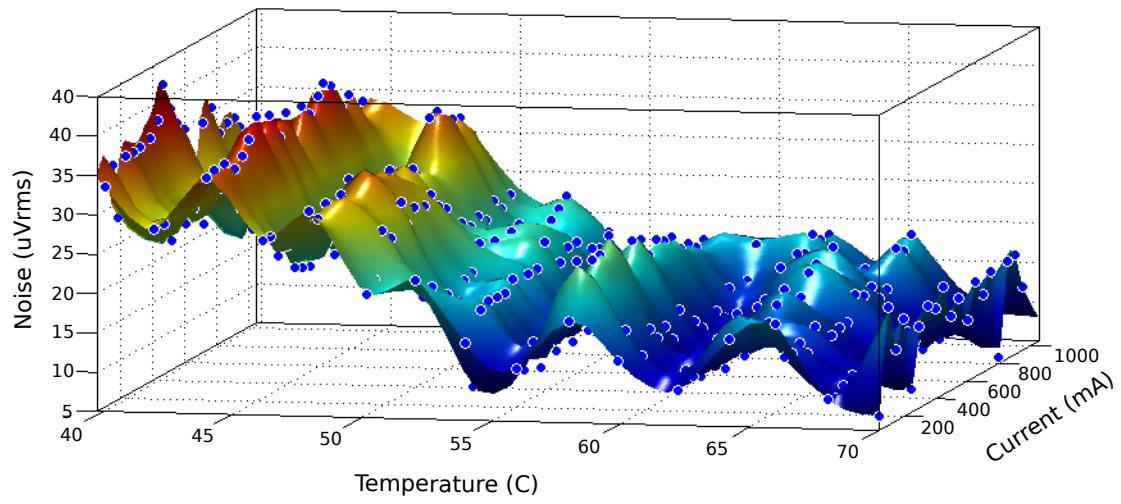


(a)

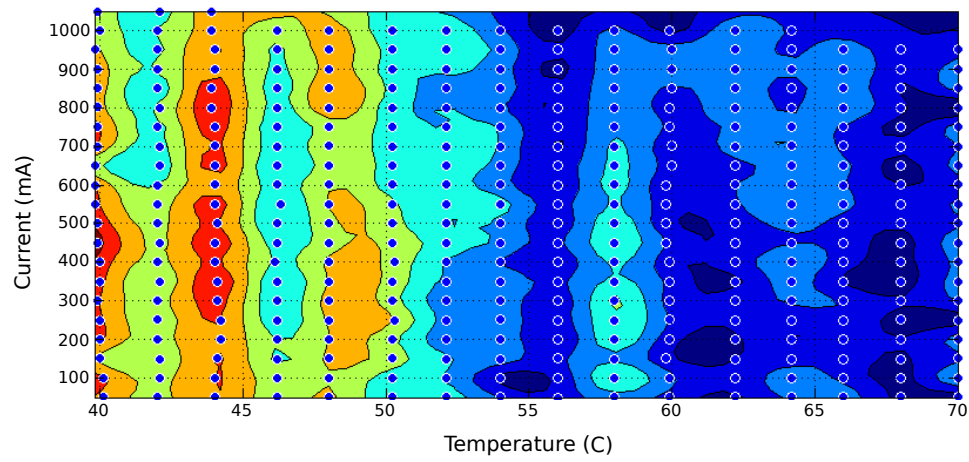


(b)

Figure 4.3: Complete VCCS noise measured with an Agilent 35670A spectrum analyzer, from 40 to 70°C and from 50ma to 900ma. Matlab plots shown use the Lowess model with a 25 span, a quadratic polynomial, and $R=0.74$. a) 3D plot, b) Countour plot



(a)



(b)

Figure 4.4: Same data as figure 4.4, but with a larger R of 0.94 . a) 3D plot, b) Countour plot

CHAPTER 5

PHIP Instrument Pinch Valve System

5.1 Pinch Valves

Pinch valves are keystone to sample management as pinch valves hold and deliver the sample from stage to stage. Off the shelf pinch valves limited to 2 bar, but we successfully modified the pinch valve design to 7 bar. The modification is based on increasing the diameter of the plastic hose while increasing the pinching force. The pinch valve was over driven with 12v, increasing the pinch force for 200ms, thereafter, the pinch valve kept the plastic hose closed with a minimum force.

5.1.1 Circuit

We begin by describing the pinch valve circuit (fig 5.1) components: 1) An ultra high precision, ultra low noise, series voltage reference [Int12], 2) Exercise valve 3) An active low pass filter, 4) A MOSFET current sink and Op Amp with negative feedback, 5) Over drive, 6) Valve feedback, and 7) Temperature sensor. In addition, we employ various Matlab toolboxes to develop the small signal model [Att99][Mou05] for the active low pass filter and current sink, and consequent simulations result in the complete input/output TF (I_o/V_{in}) shown in equation (5.1), zeros and poles are listed in table (5.1).

$$TF_{total} = \frac{I_o}{V_i} = \frac{TF_1(s) \times TF_2(s)}{R_{sense}} \quad (5.1)$$

Where I_o is the current through the solenoid (V_o/R_{sense}), V_i is the voltage reference, TF_1 is the active low pass filter TF, TF_2 is the current sink TF, R_{sense} is the current sense resistor.

Table 5.1: TF_{vccs} ZEROS & POLES

	Zeros (K rad/sec)			Poles (K rad/sec)			
	a_z	b_z	c_z	a_p	b_p	c_p	d_p
$TF_1(s)$	79×10^6	-0.2×10^6	—	31	-11	-12	—
$TF_2(s)$	79×10^6	0.2×10^6	-31	3700	-1800	-3400	-0.21×10^6

5.1.1.1 Voltage reference

The voltage reference used is a Maxim integrated ultra high precision, ultra low noise, series voltage reference. This reference has an ultra low noise to $1.3\mu V_{p-p}$ from 1/10Hz to 10Hz, a ultra low drift of 3ppm/ $^{\circ}C$ with a $\pm 0.02\%$ initial accuracy [Int12].

5.1.1.2 Exercise valve

When the Labview software sends an activate pulse to the circuit, the not gate activates the MOSFET allowing for an input voltage at the VCCS. R_2 , and C_1 are set as a low pass filter with a cut off frequency given by equation (5.3), R_1 is set to drain any lingering potential at the gate of Q_3 , as the input impedance of the MOSFET is very high, R_3 , R_9, R_{10} , R_{10} , and R_{28} are set as a voltage divider given by equation (5.3).

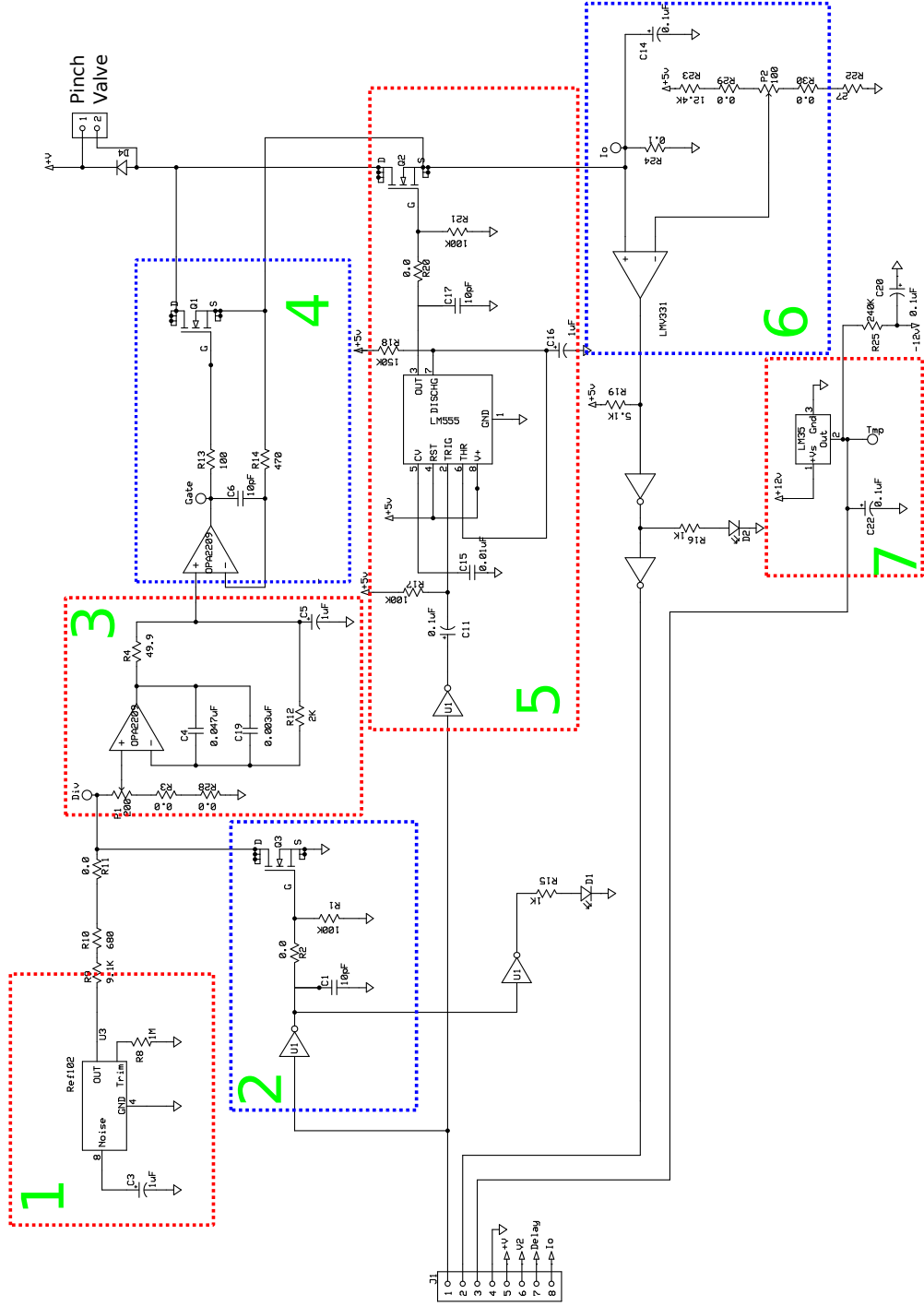


Figure 5.1: Pinch Valve Driver. 1) Voltage reference, 2) Exercise valve, 3) Active filter, 4) Current sink, 5) Over drive, 6) Valve feedback, and 7) Temperature sensor

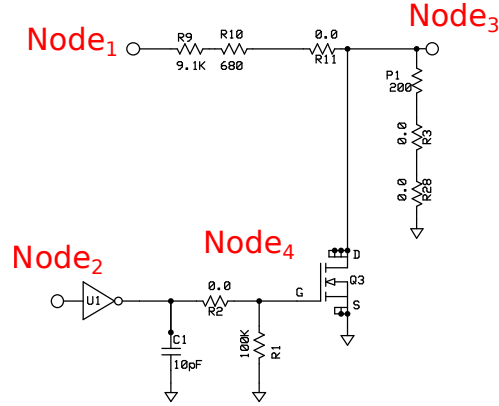


Figure 5.2: Exercise valve circuit. P₁ is use to calibrate the hold pinch valve magnetic field

$$F_c = \frac{1}{2\pi R_2 C_1}, \quad (5.2)$$

Where R₂ is in Ohms and C₁ is in Farads.

$$V_o = V_{in} \frac{R_3 + R_{28} + P_1}{R_3 + R_{28} + P_1 + R_9 + R_{10} + R_{11}}, \quad (5.3)$$

Where R & P are in Ohms. P₁ is use to calibrate the hold pinch valve state.

5.1.1.3 Active Low Pass Filter

The output voltage from the voltage reference is filtered by an active low pass filter, minimizing any residual noise (fig 5.5). As show in equation (5.4), this filter's transfer function has two zeros ($79 \times 10^6 K \frac{rad}{sec}$, $-0.2 \times 10^6 K \frac{rad}{sec}$) and three poles ($31 K \frac{rad}{sec}$, $-11 K \frac{rad}{sec}$, $12 K \frac{rad}{sec}$).

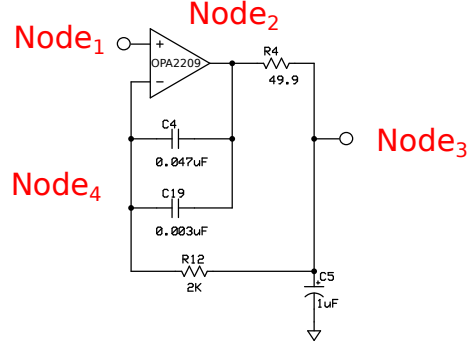


Figure 5.3: Active Low Pass Filter

$$TF_1(s) = \frac{V_{o2}}{V_{i2}} = \frac{(s - a_z)(s - b_z)}{(s - a_p)(s - b_p)(s - c_p)} \quad (5.4)$$

Where $V_{i2}=V_{o1}$, a_z & b_z are the equation's zeros, and a_p , b_p , & c_p are the equation's poles.

5.1.1.4 Current Sink

The resulting output voltage from the active low pass filter drives the gate of a MOSFET setup as a current sink. In order to maintain control of the MOSFET drain current, an Op Amp is setup in a negative feedback configuration (fig 5.4) [Rob08]. As shown in equation (5.5), the TF has three zeros ($79 \times 10^6 K \frac{rad}{sec}$, $0.2 \times 10^6 K \frac{rad}{sec}$, $31 K \frac{rad}{sec}$) and four poles ($3700 K \frac{rad}{sec}$, $-1800 K \frac{rad}{sec}$, $-3400 K \frac{rad}{sec}$, $-0.2 \times 10^6 K \frac{rad}{sec}$). Notice that R_{13} , C_6 , & R_{14} provide a filter to allow for most MOSFETs without changing the circuit, D_5 provides protection for transients that may be produced by the pinch valve coil.

$$TF_2(s) = \frac{V_{o3}}{V_{i3}} = \frac{(s - a_z)(s - b_z)(s - c_z)}{(s - a_p)(s - b_p)(s - c_p)(s - d_p)} \quad (5.5)$$

Where $V_{i3}=V_{o2}$ & $V_{o3}=V_{out}$, a_z , b_z , & c_z are the equation's zeros, and a_p , b_p , c_p , & d_p are the equation's poles.

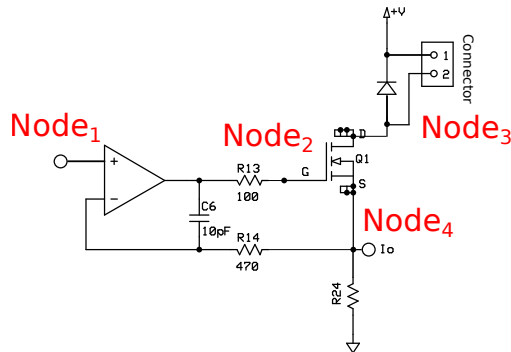


Figure 5.4: MOSFET current sink

5.1.1.5 Over Drive

The PHIP method requires pressures well above off-the-shelf pinch valves. Thus, we have developed an over drive circuit helps the pinch valve over come the additional hose thickness while keeping the magnetic field generated at the valve's solenoid to a minimum and interference with B_o . The over drive is activated when the valve is initially activated by the rise of the pulse from the instrument. The length of the over drive pulse (fig 5.5a) is given by the equation (5.6) [Sem06b] by a mono stable circuit in figure 5.5b and the current to the pinch valve controlled by the MOSFET Q_2 operating in the saturation region.

5.1.1.6 Valve Feedback

The PHIP method is in infancy and plagued with a myriad of problem. In order to verify that a valve has been successfully activated, we have developed a circuit that monitors the current drawn by the pinch valve solenoid figure (fig. 5.6). The

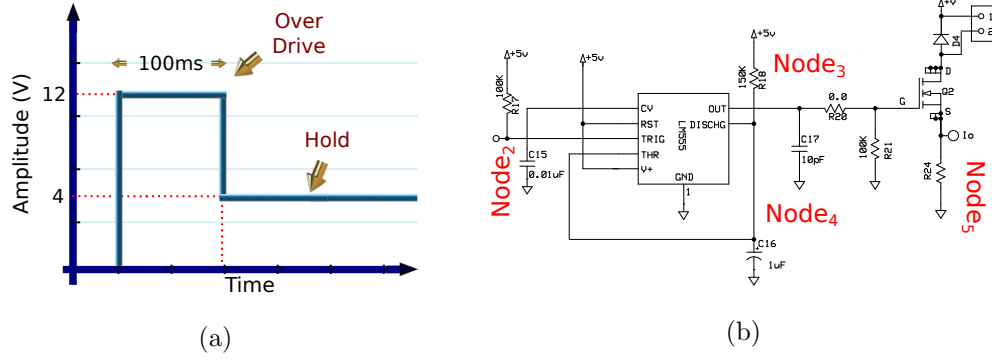


Figure 5.5: Pinch valve over drive. a) Over drive timing and b) Circuit

$$t_{pulse} = \frac{2}{3}R_{18}C_{16} \implies t_{pulse} = \frac{2}{3} \times 150K\Omega \times 1\mu F = 100ms \quad (5.6)$$

circuit requires: 1) Voltage reference, 2) Input voltage, and 3) A comparator. The Voltage reference is set by P_2 to a given voltage equivalent to an input voltage. The input voltage is the product of the current drawn by the pinch valve solenoid through R_{24} . In our design, we use the OPAMP comparator [STM11] to compare the input voltage from R_{24} to a voltage reference. A comparator is an OPAMP with its output optimized for operation in saturation. In fact, a comparator is a 1-bit analog-to-digital converter with differential analog input and a digital output [Ins01]. Once the pinch valve solenoid has been activated, the OPAMP compares the input voltage to the voltage reference, if the solenoid coil draws a given amount of current through R_{24} , then the OPAMP's output rises, signaling the instrument that the valve has been exercised as given in equation (5.7).

$$V_o = \begin{cases} 1 & \text{if } V_{input} \geq V_{Ref}, \\ 0 & \text{if } V_{input} < V_{Ref}. \end{cases} \quad (5.7)$$

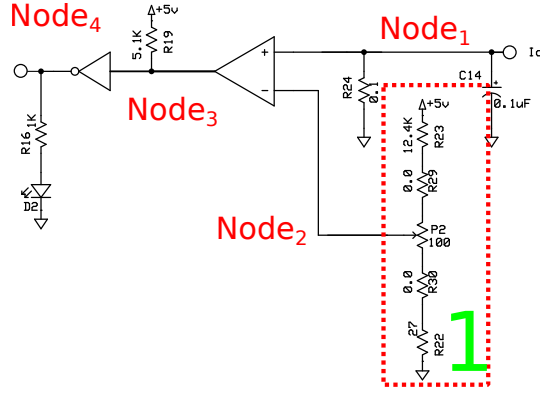


Figure 5.6: Valve Feedback circuit. 1) Voltage reference divider

5.1.1.7 Temperature Sensor

The process of full precursor hydrogenation for optimal hyperpolarization is sensitive to temperature. In our PHIP instrument design, the hydrogenation of HEA is best at 45°C. In order to monitor temperature, our design monitors the ambient temperature near by through a precision temperature sensor LM35 with a full range given by equation (5.8) [Sem00]. The output capacitance of the sensors is 50nF, a value too small to filter high frequencies at the output, thus, an additional capacitor was installed at $C_{22}=1\mu\text{F}$

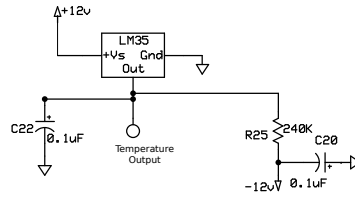


Figure 5.7: Temperature sensor circuit

$$R_{25} = \frac{-V_s}{50\mu A} \implies R_{25} = \frac{-12V}{50\mu A} = 240K\Omega \quad (5.8)$$

5.2 Pinch Valves

The PHIP method for research and clinical purposes requires a sterile environment where samples can be hyperpolarized and delivered to the target. A pinch valve with replaceable tubing provides for the sterile environment for hyperpolarization research. In our design, we use a Mechanically pinched, open frame, electric, with a fail closed, pinch valve. There are two main components to pinch valves, the body and a sleeve (fig 5.8).

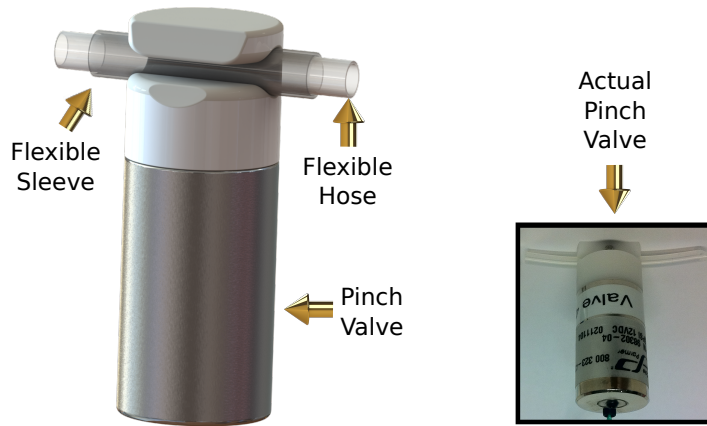


Figure 5.8: Pinch valve pressure specification increase modification by doubling the sleeve wall thickness.

5.2.1 Sleeve

The sleeve contains the flow media, or flexible hose, that isolates the flow from the environment and contamination. These are often made of variety of rubber-like elastomers such as Buna-N, butyl, neoprene, Nordel, hypalon, Viton, silicone, polyurethane, polypropylene, white butyl, and odorless and tasteless white neoprene [BAL06]. The sleeve consists of a short section of flexible hose, in our case, silicon, because this material has the best tensile strength and its particularly resistant to tearing and delaminating (fig 5.9).

5.2.2 Body

The body contains the solenoid or air pressure to compress the flexible hosing to open or close the flow [yBK90]. This type of pinch valve is referred at a direct operated or as a jacketed pinch valve. This design is the most cost effective as production is simple in comparison with hand wheel operated pinch valves, but comes with the lowest pressure rating [BAL06].

Pinch Valves Advantages

1. No direct contact with fluid
2. Simple operation
3. Light weight
4. Compact
5. Inexpensive
6. closes around suspended particles
7. Shorter actuator stroke
8. High pressure recovery factor (F_L). F_L is given by equation (5.9)

Pinch Valves Disadvantages

1. Largest particle size is half the nominal valve size
2. Capacity reduced by %20
3. When opened, adjacent pipe will not drain below centerline

$$F_L = \sqrt{\frac{P_1 - P_2}{P_1 - P_{vc}}} \quad (5.9)$$

where P_1 is the input, P_2 is the output, and P_{vc} is the fluid vapor pressure

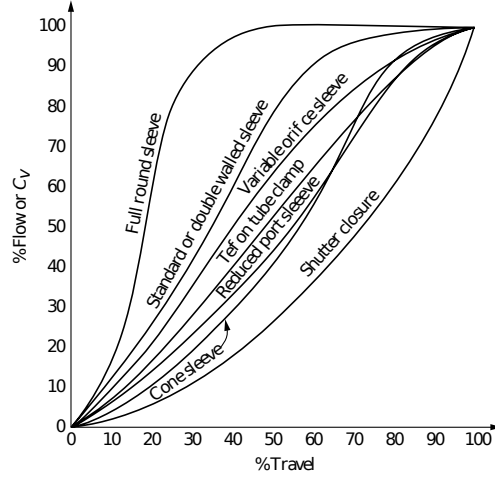


Figure 5.9: Sleeve type vs % of pinch travel [BAL06]

5.2.3 Limited Life

The life cycle of the hosing section being compressed by the pinch valve depends on the strength and wear of the flexible hosing. Mostly, when the pinch valve is activated and the flexible hosing becomes compressed, the flexible hosing tends to become stretched and fatigued, eventually, cracking and leaking [Sch63]. This problem is further worsen with the increase in temperature, drying the flexible hosing making the material more likely to crack and fail. Sleeve life in a shell and tube pinch valve operating at its maximum rated pressure is usually around a mean of 75,000 cycles with a variation of $\pm 25,000$ [BAL06].

5.2.4 Increasing pinch valve pressure specification

The PHIP method requires pressures twice the manufacturer's of 30 psi. In order to increase the pressure specification, the flexible hose wall was increased by $\frac{1}{8}$ " to $\frac{1}{4}$ " by the addition of a secondary sleeve at the pinching point. This wall thickness

increase, decreases the flow capacity by %20, increases the pressure capacity to 80psi, and increases the life time because of the shorter sleeve compression travel (fig 5.10). Since the pinch force on a silicon tubing is linearly proportional to pressure [MBP12], we deduct that the initial force to pinch the silicon hose at 30 psi is 25N, while the force to pinch the silicon hose at 60 psi is 50N.

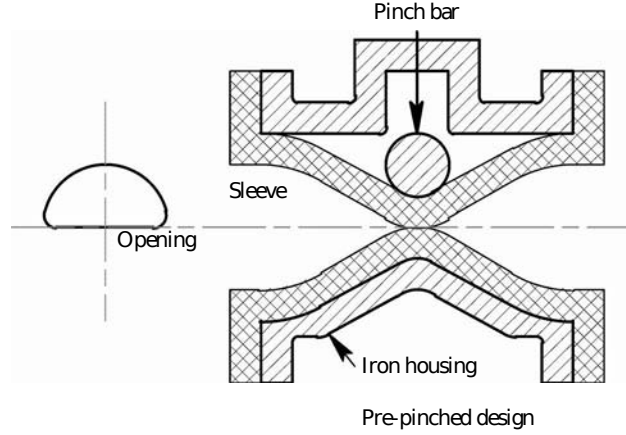


Figure 5.10: Prepinched valve typel [BAL06]

5.3 Conclusion

The addition of a sleeve to the pinch valve hosing increased the pinch valve doubled pressure capabilities. In addition, the development of an over drive pinch valve board minimized overheating, increased the valve's pinch force, and minimized stray magnetic fields generated by the solenoid.

CHAPTER 6

Mechanical Hardware

6.1 Complete Capsule

In order to hydrogenate a precursor and ultimately hyperpolarize a molecule using the PHIP method, a reaction chamber is necessary with the proper environment for hyperpolarization. The following are the required mechanical hardware components for the PHIP reaction chamber: 1) Capsule Pedestal, 2) Capsule Spacer, 3) Former Pedestal, 4) Sample Heating Block, and 5) RF Coil Former (fig. 6.1).

6.1.1 Capsule Pedestal

This pedestal made of teflon, places vertically the reaction chamber in the most homogeneous part of the B_o field (fig. 6.2).

6.1.2 Capsule Spacer

This spacer made of teflon, places horizontally the reaction chamber in the most homogeneous part of the B_o field (fig. 6.3).

6.1.3 Former Pedestal

This pedestal made of teflon keeps the B_o and RF coil formers in place in the instrument (fig. 6.4).

6.1.4 Sample Heating Block

This heating block made of aluminum acts as a heat source to increase the precursor sample temperature for optimal hydrogenation (fig. 6.5).

6.1.5 RF Coil Former

This former made of acrylic was designed to hold the RF coils for spin sequence transfer (fig. 6.6).

6.1.6 Data Aquisition cards

Two data aquisition cards were used with this instrument ad their connections listed as follows: dev 1 (fig. 6.7) & dev 2 (fig. 6.8).

6.1.7 Fan Cooling & Heating

A set of fans and heaters were used to keep reaction temperature constant as show in fig 6.9.

6.1.8 Reaction Chamber

The reaction chamber was made of polysulfone and their specifications shown in fig 6.10 & 6.11

6.2 Conclusion

The PHIP instrument was buit using the many parts shown in this chapter, such as; Capsule, predestals, formers, and heating block were designed, built, and sucessfully tested with the instrument.

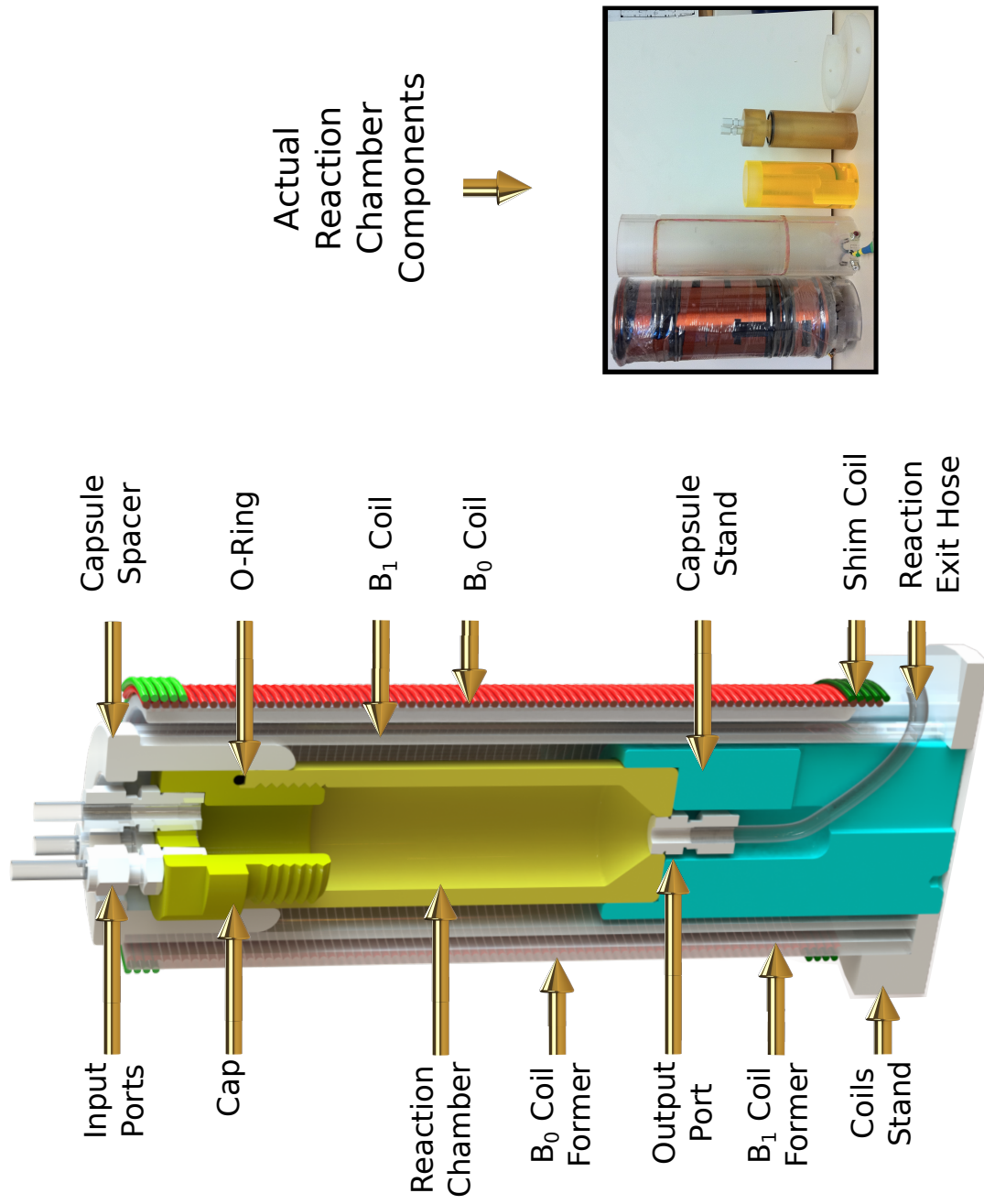


Figure 6.1: Complete reaction capsule setup

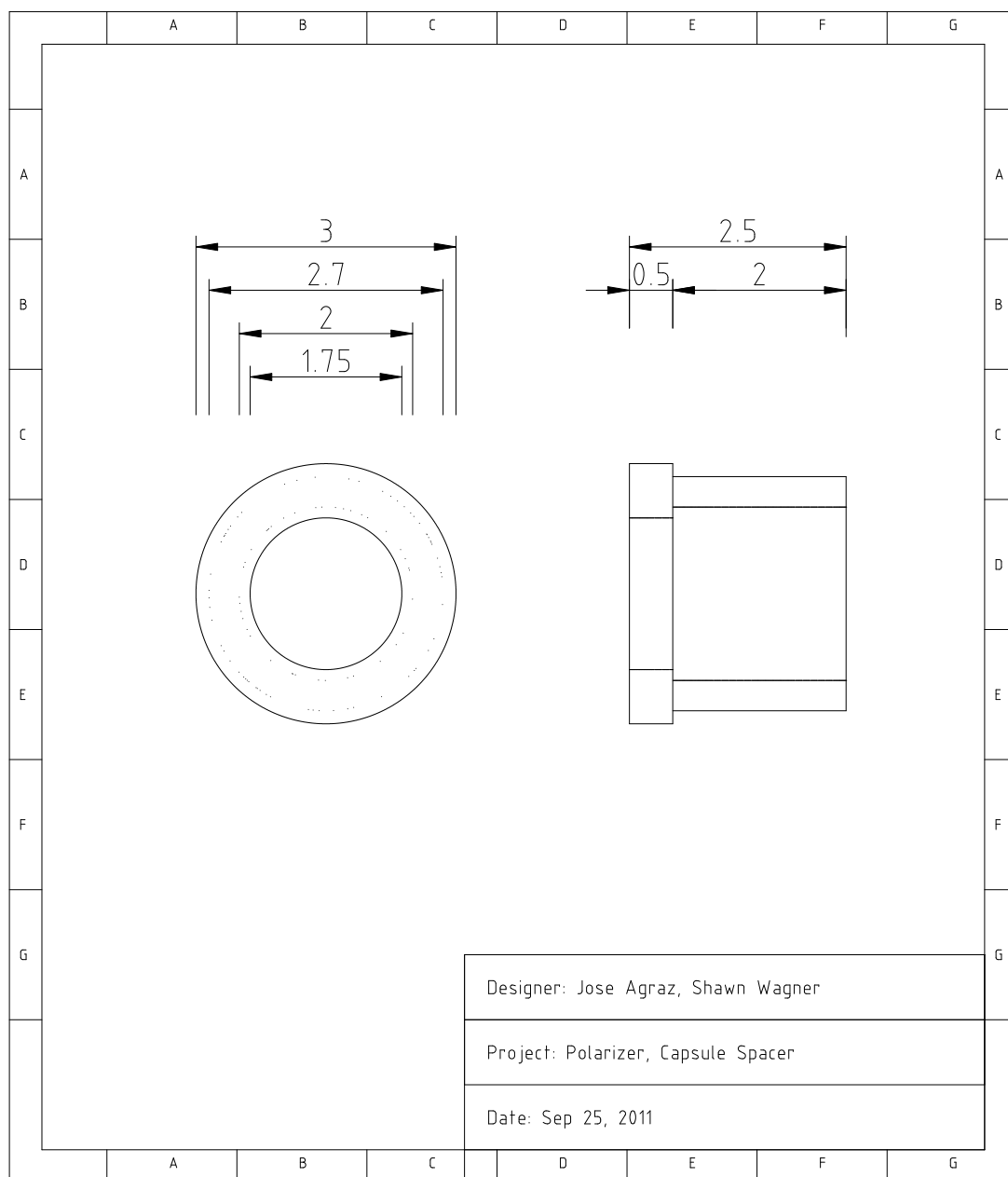


Figure 6.3: Teflon spacer between the reaction capsule and formers

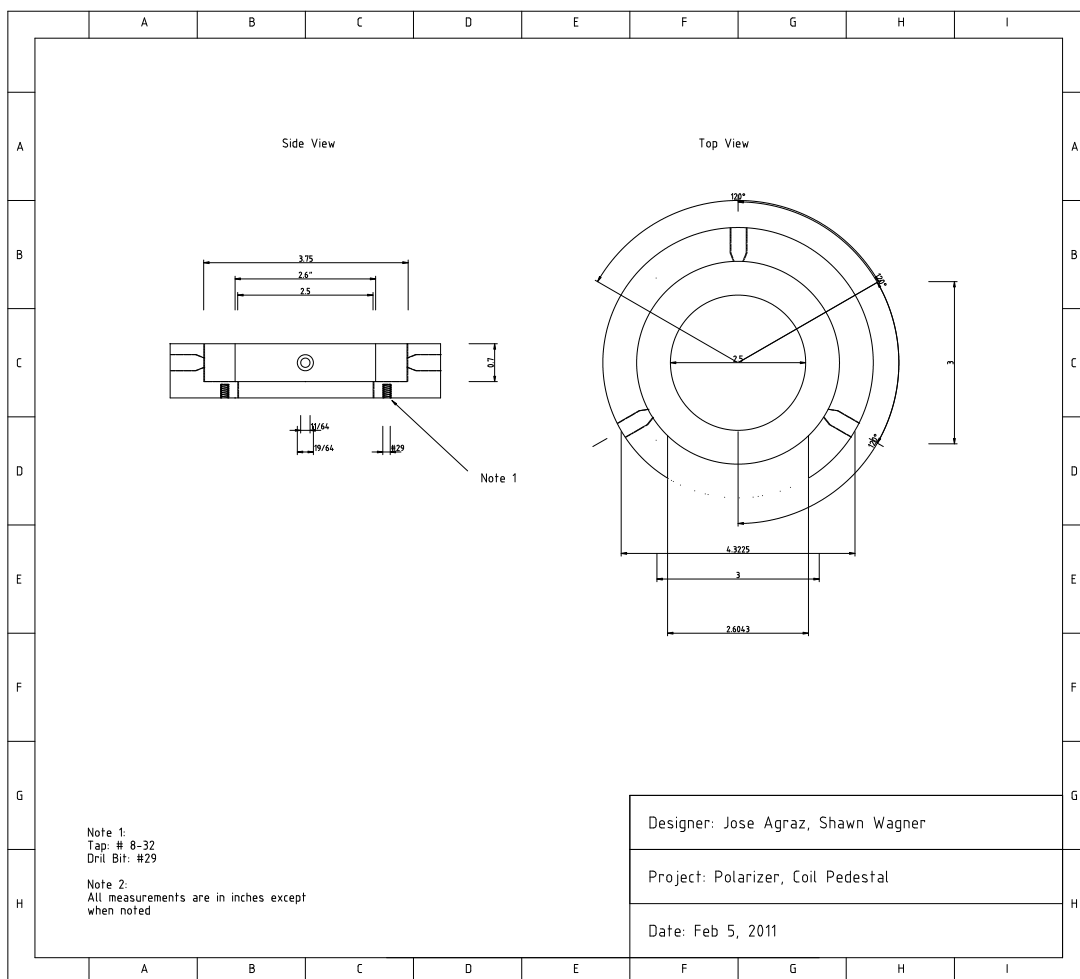


Figure 6.4: Formers pedestal

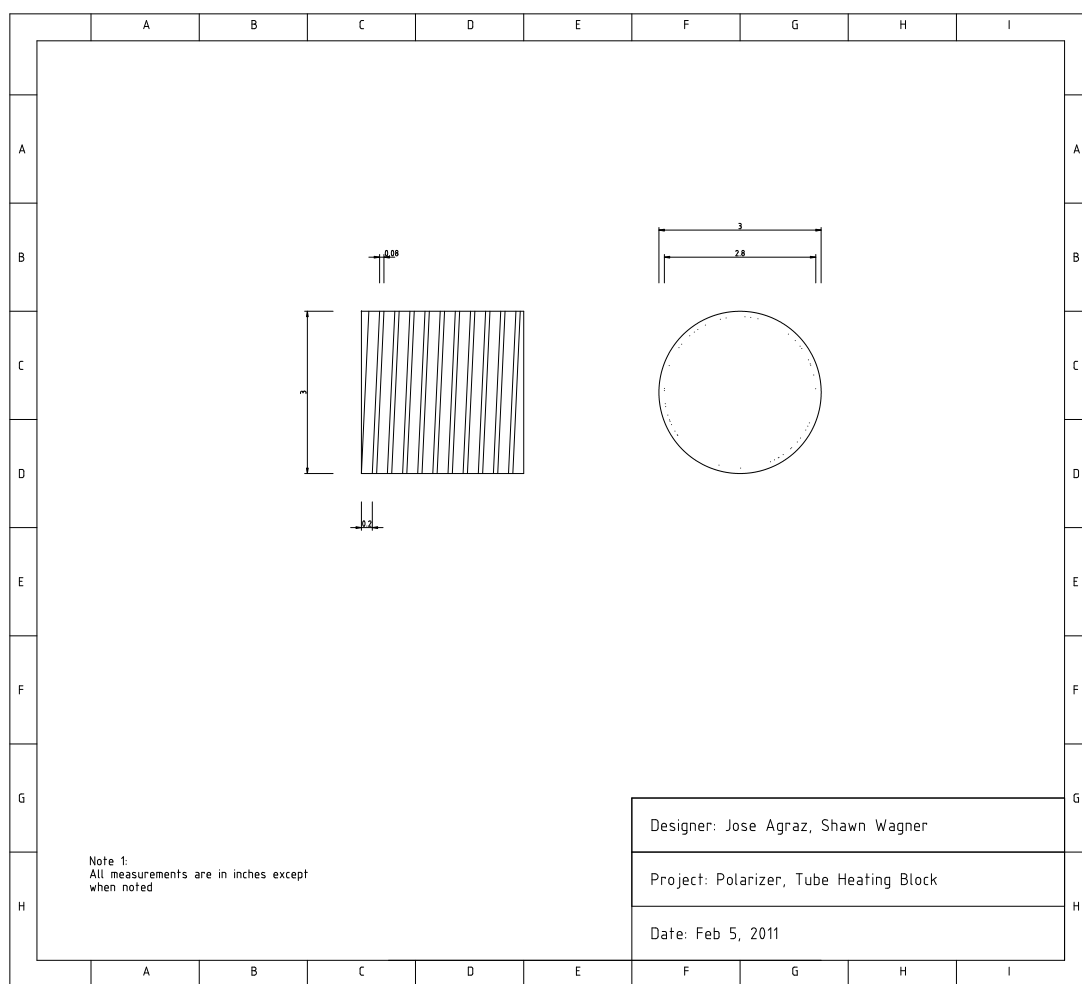


Figure 6.5: Precursor sample heating block

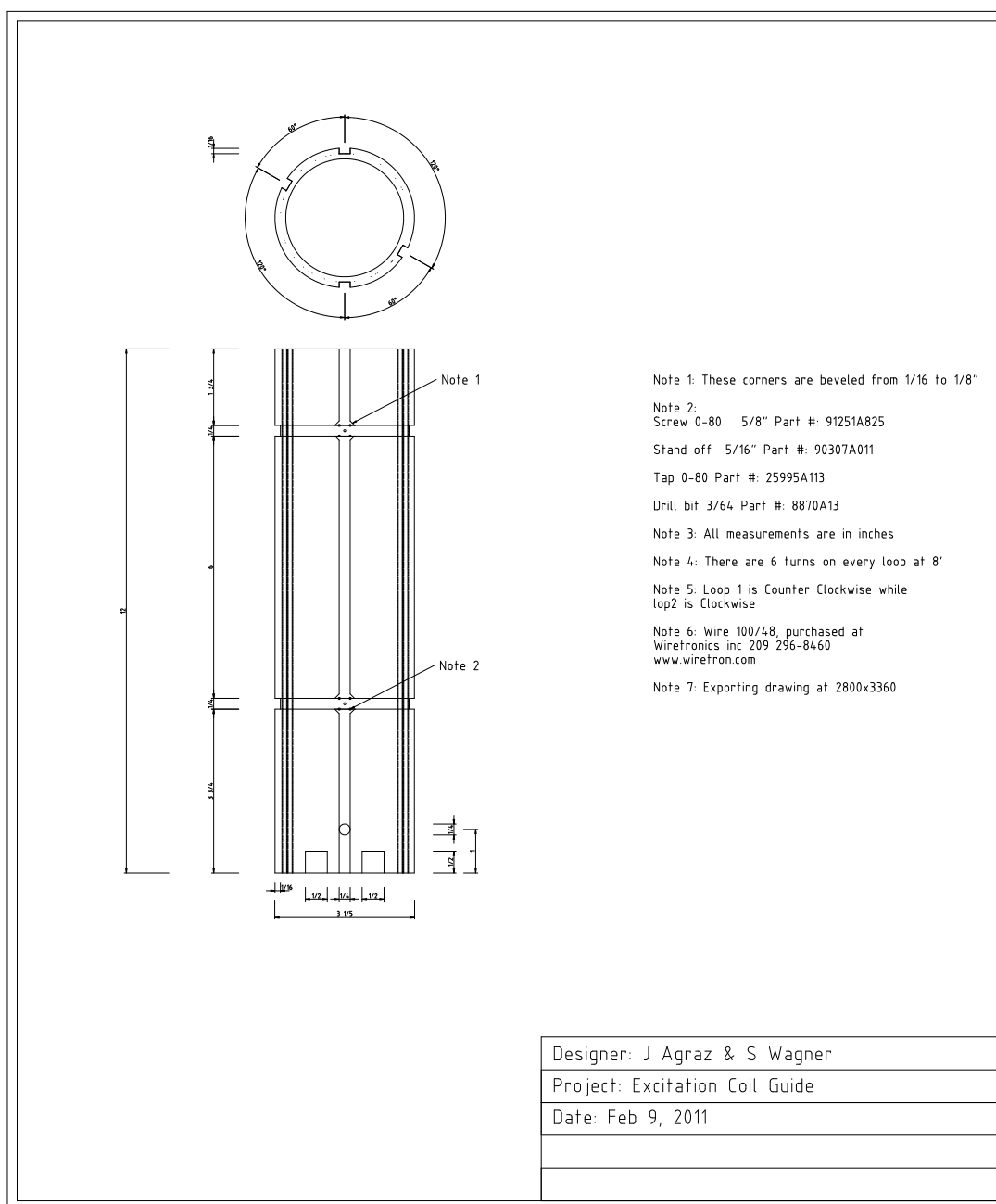
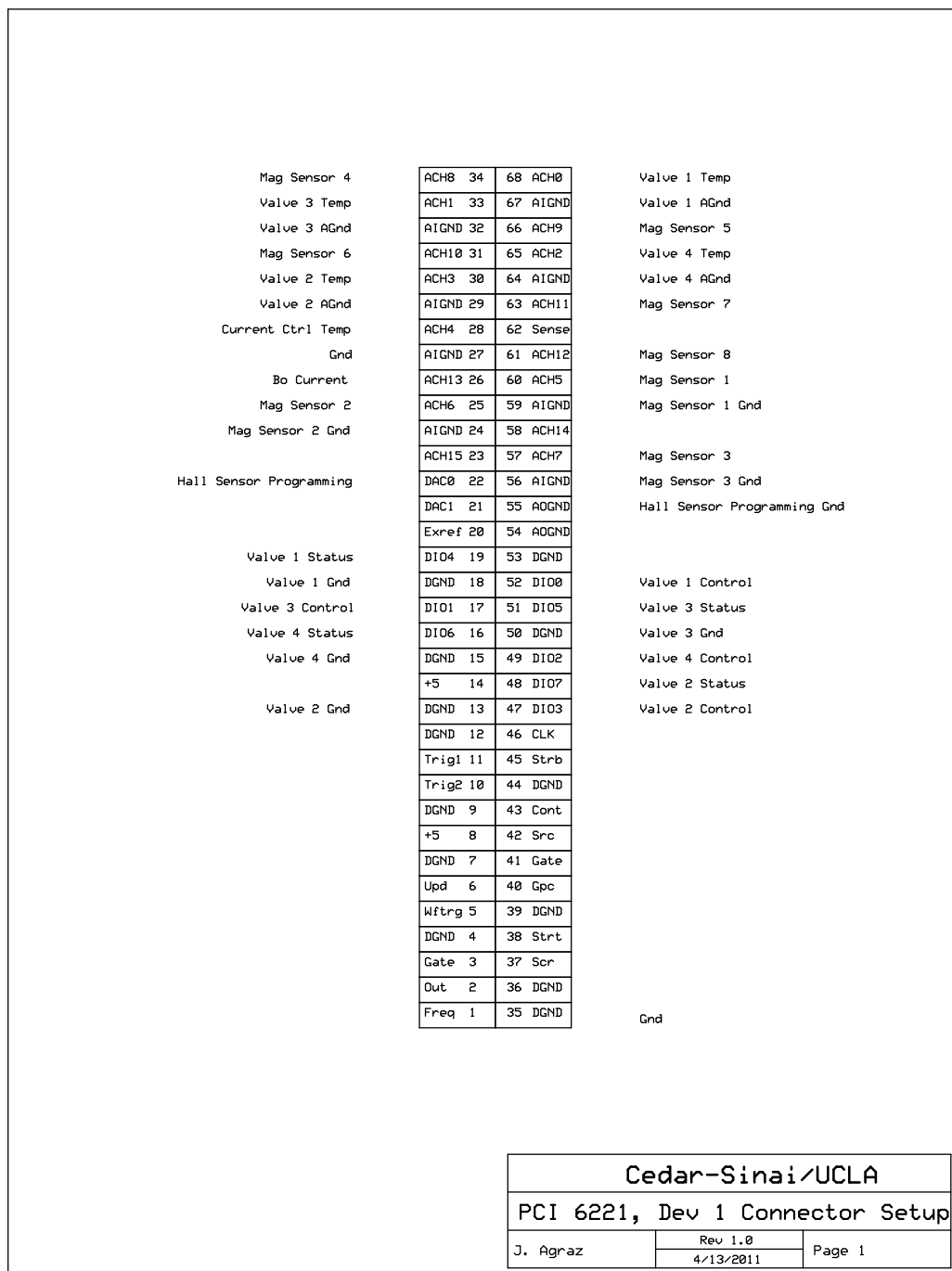
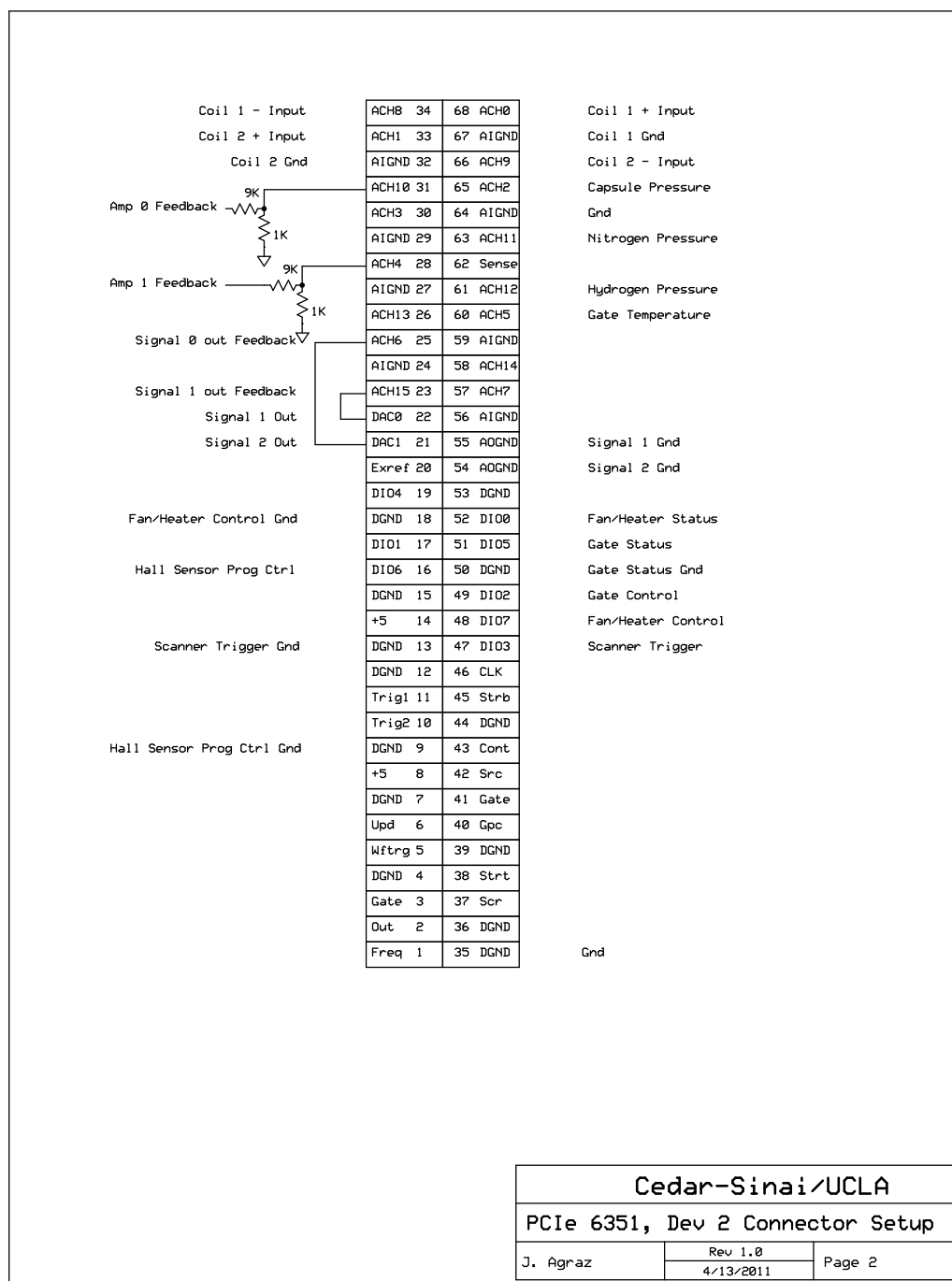


Figure 6.6: Reaction chamber RF coil former



Z:\home\jagraz\Downloads\DAQ68PinConnector.sch - Dev 1

Figure 6.7: NI DAQ Dev 1 connections



Z:\home\jagraz\Downloads\DAQ68PinConnector.sch - Dev 2

Figure 6.8: NI DAQ Dev 2 connections

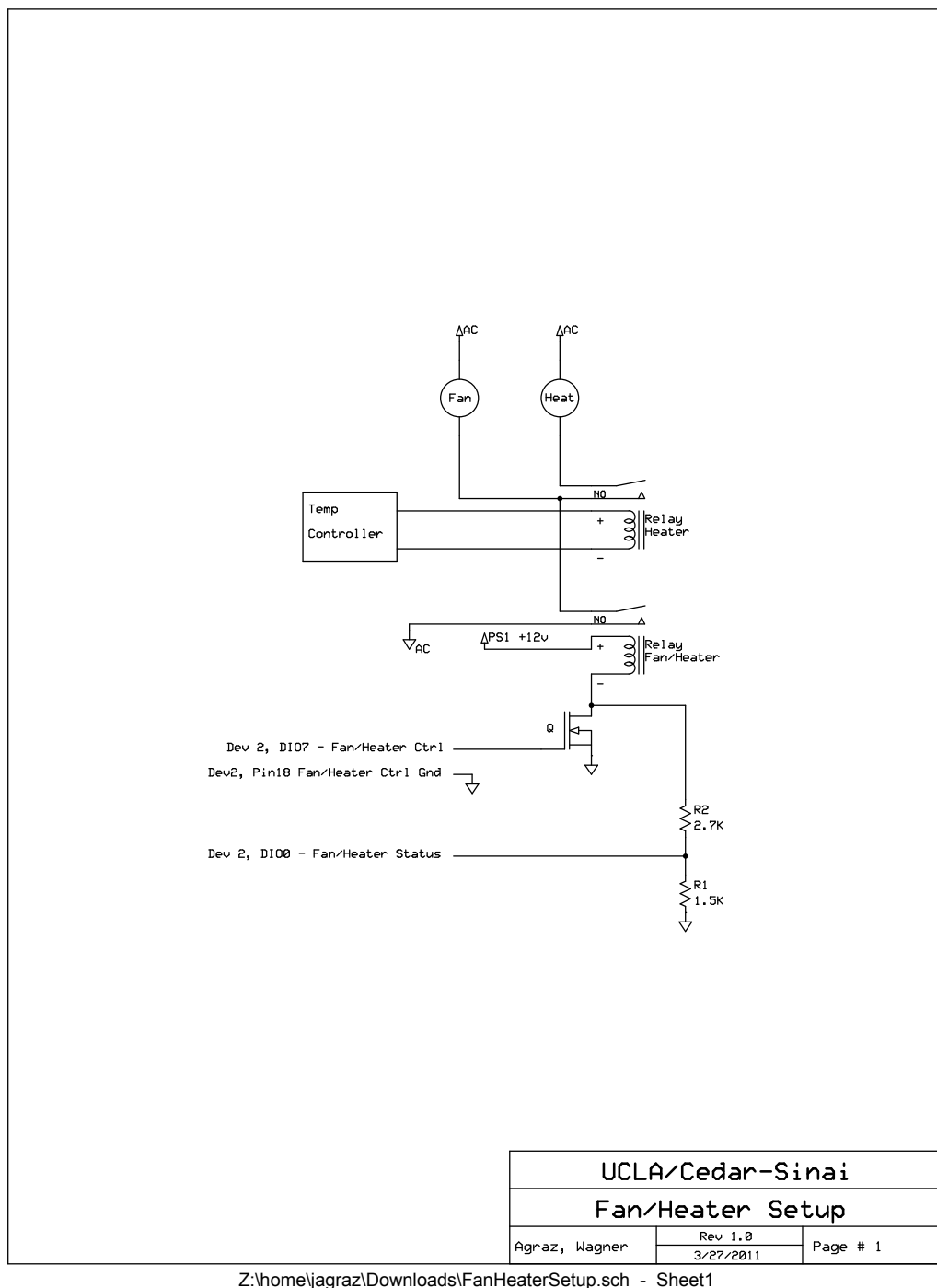


Figure 6.9: Heating and cooling fan setup

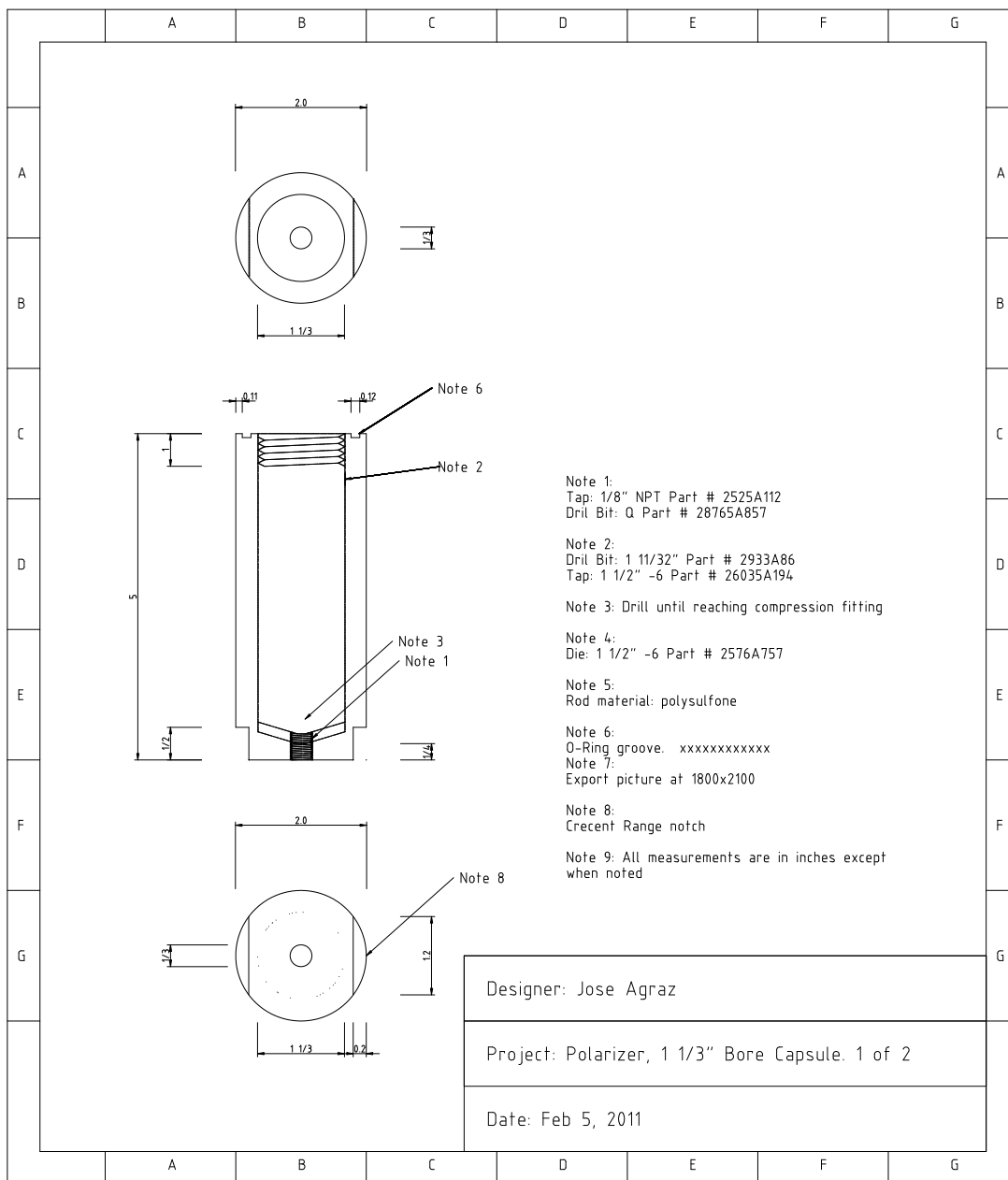


Figure 6.10: Reaction chamber main body

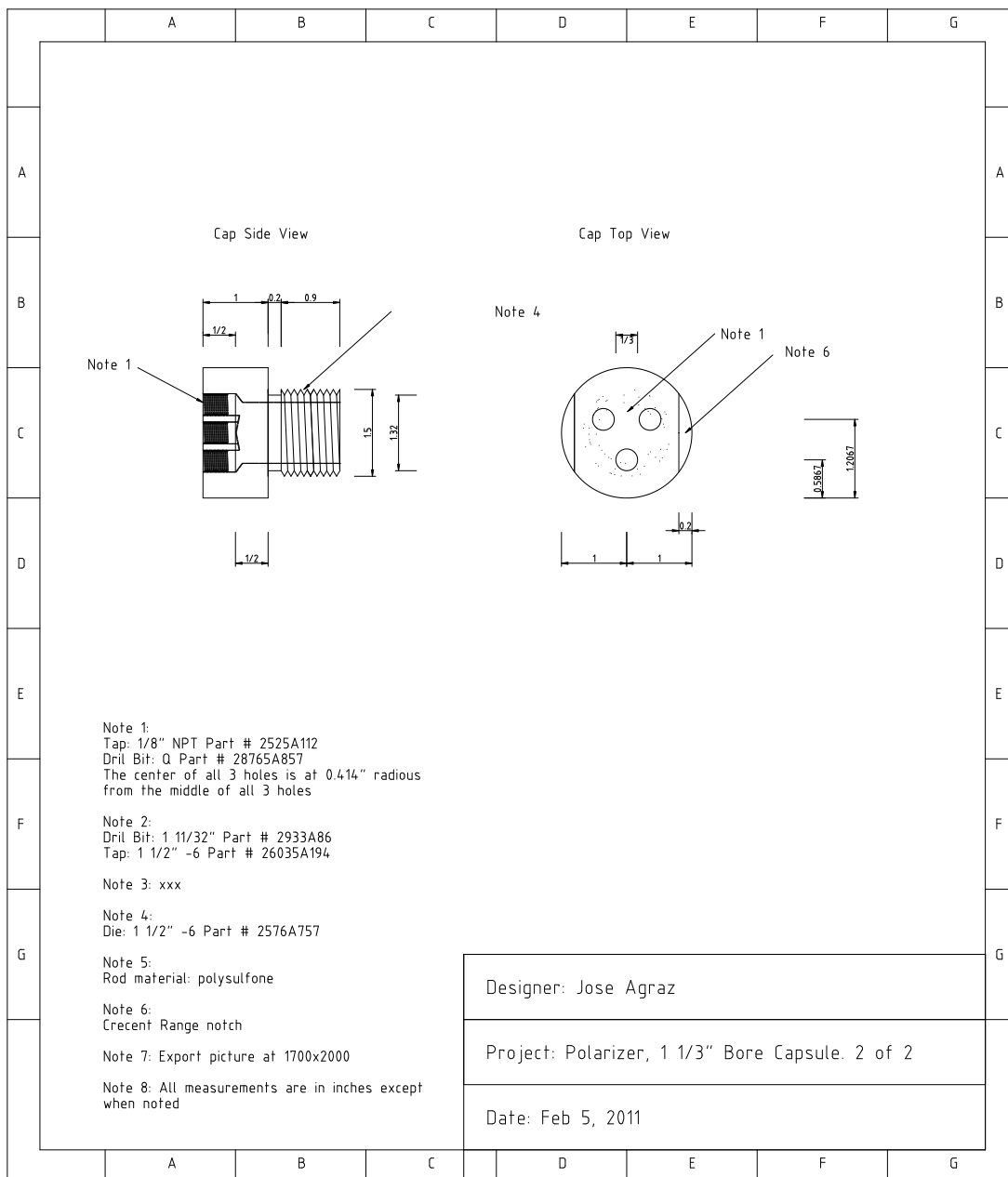


Figure 6.11: Reaction chamber capsule cap

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