A device for accurate and automated injection of hyperpolarization substrate with minimal dead time and arbitrary volumes

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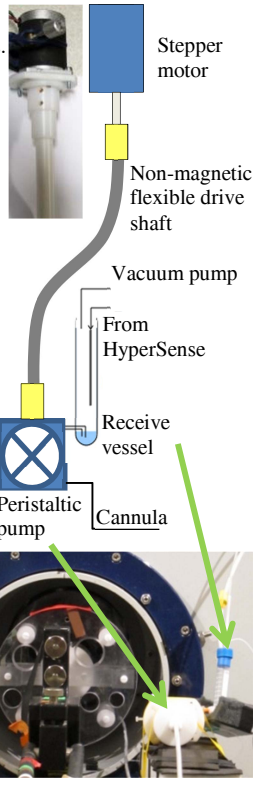
Introduction: Over recent years hyperpolarisation by dissolution dynamic nuclear polarisation has become an established technique for studying metabolism *in vivo* [1]. Temporal signal plots obtained from the injected metabolite and daughter products, e.g. pyruvate and lactate, can be fitted to compartmental models to estimate kinetic rate constants. Improvements to the model [2] and physiologically meaningful parameters can be measured by consistent and reproducible injections through automation [3]. A previously developed injection system [3] was limited in the range of volumes it could deliver and delayed the injection due to a required syringe filling step. Here we show an improved MR compatible injector that delivers faster injections (no syringe filling time) and fully controllable injection rate with arbitrary injection volume.

Figure 1: schematic of the direct drive injection system and associated images.



MR compatible automated injector: The injector consists of a peristaltic pump directly driven by a stepper motor, see Figure 1. A high torque bipolar stepper motor (578BYG621, Wantai Motor, Changzhou city, China) was connected to a plastic peristaltic pump (150 series, Williamson Pumps Ltd, Poynings, UK) by a flexible drive shaft. The drive shaft was constructed of a 4 mm phosphor-bronze shaft in a 6mm O.D. nylon tube 250cm in length (SS White Technologies Ltd, Milton Keynes, UK). This permits the ferromagnetic stepper motor to be mounted outside of the 5G line of the magnet. The stepper motor was controlled by an open source Arduino Uno v3 microcontroller (www.arduino.cc) and an in-house designed stepper motor driver circuit. Using custom designed software liquid volumes and rates could be pre-programmed for injection or withdrawal. External devices, e.g. flow diverter, are also controlled during injection. A receiving vessel and cannula were attached to the inlet and outlet ports of the pump respectively.

Method: To determine the accuracy and scalability of the injection system delivered, volumes were measured against programmed volumes in the range 0.100-10.000ml for a constant rate of 7.0ml/min. The delivered volume was measured at least three times by mass of distilled water. Before commencing the pump was calibrated by measuring the mass of water after 10 pump revolutions at 80rpm, repeated 3 times.

Once the calibrated volume had been entered into the software no further adjustments were made. A test injection was performed using hyperpolarised ^{13}C pyruvate into a glass vial mounted on a 20mm $^{13}C/^{1}H$ surface coil (a 6.7M acetate phantom was attached to the rear of the coil). The injection was programmed to deliver 1.50ml of pyruvate at 6.92ml/min, simultaneously starting with the MR acquisition sequence. The signal was localised using a 0.5ms Gaussian pulse and slice selection in a 7T small animal scanner (Bruker Avance II) withTR=1s, for 180s total duration. Integrals were measured using Topspin software (Bruker).

Results and discussion: Figure 2 shows an excellent correlation between the demand and delivered volume from 100µl to 10.000ml, r^2=1. The average difference of the demand to delivered volume was found to be 1.7% across the range and the average standard deviation for all measured volumes was 0.009ml. Pump delivery times ranged from 0.9 to 86s. For the test injection of hyperpolarised pyruvate, signal was first detected at 6s, reaches the maximum at 13s, matching the duration of the injection (see Figure 3). The data shows that the pump can be operated at arbitrary volumes between 0.100-10.00ml, volumes typically used for mice and larger rodents. For smaller volumes the internal diameter of the tubing contained within the peristaltic pump could be reduced to improve accuracy. Larger volumes are limited only by the size of the receiving vessel connected to the pump.

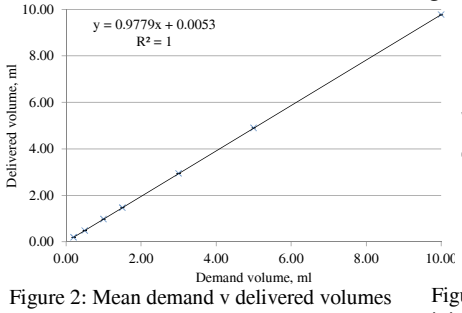


Figure 2: Mean demand v delivered volumes delivered by injector. Error bars ± 1 S.D.

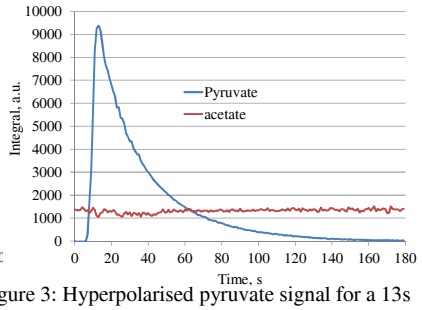


Figure 3: Hyperpolarised pyruvate signal for a 13s injection into a glass vial + acetate reference signal.

References

[1] Hyperpolarized Pyruvate Injection in Subjects With Prostate Cancer, Clinical trial NCT01229618.

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