Closed Loop Total Intravenous Anesthesia (TIVA) for Combat Casualty Care

- An auto-pilot for safe and effective TIVA delivery -

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NeuroWave Systems Inc. was founded in 2003.

- Our mission is to develop, manufacture, and market innovative monitoring and drug delivery devices using advanced signal processing and control system engineering for Anesthesia, Critical Care, and Military Medicine, in order to improve patient safety, outcome and quality of life.
- Our R&D programs are mainly supported through the US Department of Defense and the National Institutes of Health.

Disclosure:
- I am a salaried employee of NeuroWave
- I own stocks in NeuroWave

US Army AutoTIVA Program
**Capability Gap**

The Army’s challenge:
- Anesthesia delivery in Combat Surgical Hospitals has been traditionally handled using a drawover vaporizer that was being discontinued by its manufacturer. At the time, no replacement solution could be readily identified by the DoD.
- Gas anesthesia, while being the standard of care, also suffers from significant drawbacks in terms of logistics. Use of standard off-the-shelf anesthesia gas machines is impractical when considering fielding such units.
- Conversely, Total Intravenous Anesthesia (TIVA) was identified as the "battlefield anesthetic of the future" (Barras et al., 2005) "given its safety, simplicity, scientific nature and small logistical footprint".

**TIVA’s advantages:**
- Lower post-operative nausea and vomiting (reduced workload for post-operative care providers, lower incidence of self injury)
- Does not trigger malignant hyperthermia (difficult/impossible to treat in austere environments)
- Improved hemodynamic stability and temperature conservation
- Fast and predictable recovery and orientation
- Reduced post-operative pain
- Lower ICP
- Simple, low-maintenance equipment with small logistical footprint (no need for gas scavenging system, safe for care providers)
- Also associated with lower incidence of post-operative delirium in pediatric patients, and longer survival in cancer surgery patients
- Higher patient satisfaction

Despite the efforts invested by the Tri-service Anesthesia Research Group initiative on TIVA (TARGiT) in helping and training service personnel in the administration of TIVA, its practice is far from widespread. It is virtually non-existent in CSH and limited at higher echelons of care due to the difficulties in managing the drug delivery, and the lack of familiarity with its administration.

**NeuroWave’s Solution**

In 2010, we reached out to the Army and proposed to develop a compact intravenous anesthesia delivery support system (AutoTIVA), based on standard off-the-shelf infusion pumps.

The goal of AutoTIVA was to provide Army anesthesiologists with a tool to enable the safe and effective delivery of propofol and remifentanil, at all echelons of care, so that combat casualties may have access to the benefits of TIVA.

How?:... by developing a closed-loop propofol/remifentanil drug delivery system based solely on feedback from the brain.

- ... Autopilot/cruise controller for TIVA.
- Paradigm shift: from prescribing a dose to prescribing an effect.
- Additional advantages: reaction time, vigilance, time saving, drug optimization, protocol implementation, closing the expertise gap...

A contract was awarded to NeuroWave in 2011.
Early Research Focus

A multi-disciplinary research group (ECEM) was founded in 2001 at UBC and brought together engineers, scientists and clinicians with the goal to improve anesthesia care through automation, smart monitoring, and data analytics. In fact, an early focus was the development of a closed-loop anesthesia drug delivery system to control depth of anesthesia (auto-pilot/cruise control).

Two important technical challenges were identified and tackled very early on:

- Lack of a proper sensor technology adapted to closed-loop operation
- Lack of a method to handle patient variability within a feedback control framework
  - In other words: how can we ensure controller stability in view of patient variability?

Key Technology #1: Sensor

A new algorithm — WAVCNS — based on non-invasive EEG-processing was developed in 2000/2002 to resolve some of the limitations of the BIS, in particular:

- Use of Wavelet analysis for delay-free characterization of the patient’s state
- Deterministic (vs. interpretative) algorithms to ensure a Linear and Time Invariant (LTI) behavior

EEG montage was selected to allow for a bilateral implementation to provide independent and redundant WAVCNS values from both sides of the brain simultaneously.

- Good inter-hemispheric reproducibility, where a sustained difference over +/− 8 units is rare in patients with no known neuro-pathologies.
Key Technology #1: Sensor

- Rapid response (no calculation delay)
- LTI behavior (no switching algorithms)
- Index robustness (high level of inter-hemispheric agreement)

... makes the WAVCNS well suited for use as feedback sensor...

... and also well suited as a simple monitoring tool!

Members of the UBC research group patented the sensor technology in 2002 and licensed it to Cleveland Medical Devices (NeuroWave division).

Key Technology #2: Controller

Inter-patient variability can be readily observed by deriving PK/PD models for a given population of patients.

Leveraging the delay-free/LTI characteristics of the WAVCNS sensor, we have shown that PD parameters can be identified based simply on induction data.

S. Bibian et al., "Patient variability and uncertainty quantification in anesthesia", IFAC, 2006
We have further shown that patient variability over the study population can be mathematically described using the relative multiplicative uncertainty framework:

\[ P = P_0 + r \Delta, \text{ where } |\Delta| \leq 1 \]

\[ P = P_0 \cdot (1 + W_2 \Delta), \text{ where } W_2 = \frac{1}{r} \]

Key Technology #2: Controller

A linear, fixed controller can be shown to be mathematically stable for any patient model inscribed within the uncertainty bounds if the complementary sensitivity function does not exceed the inverse of the uncertainty weight.

Robust Stability (RS) condition:

- The controller parameters can be further optimized such that to provide the highest gain (i.e., fast reaction) without violating the RS condition.
- Mathematical proof of stability in view of patient-variability.

Dual propofol/remifentanil controller:

- The sole control of hypnosis using propofol will not provide anesthesiologists with the full benefits of automatization. In fact, dual control of hypnosis and analgesia is highly desirable.
- In 2006, we hypothesized that a controller designed for the control of the WAV (i.e., fast reaction) without violating the RS condition. This dual control concept was successfully clinically tested in France (MedSteer/Foch), Canada (iControl/UBC) and India (CLADS) over the past 10 years.
Limitations:

- We realized that infusion pumps approved for human use cannot be remotely controlled without voiding regulatory approval.
- We reached out to pump manufacturers to discuss the possibility of interfacing their pumps (or creating a specific remotely controllable pump version for the purpose of this application). Regulatory hurdles and costs were major issues.
- Another problem was the multiplicity of user interfaces, which adversely affects human factors and requires additional training.
- Hardware complexity/cabling was another weakness of the proposed solution.

A first prototype of the AutoTIVA, integrating both our WAVCNS sensor and the dual controller, was built in 2012.

In 2014, the Office of Naval Research reached out to NeuroWave to add sedation and fluid delivery to their Automated Critical Care System (ACCS) platform, a fully instrumented NATO litter designed for prolonged field care, remote operation, and long distance unmanned en-route care.

- In order to meet the Navy’s objectives, we proposed to first develop an infusion technology suitable for en-route care. More specifically, we proposed to develop a robust modular 4-channel infusion platform.
- A contract with ONR was awarded to NeuroWave in October 2014.
Key Technology #3: Infusion Pump

- Dual epicyclic gear to minimize friction and tube pull
- Geometric pumping chamber design to minimize flow pulsation at low speeds
- Twist and lock features for rapid and error-free insertion
- Pressure sensors for upstream and downstream occlusion detection
- Transparent cover to facilitate visual inspection
- 2 variants: low flow (up to 1,200 mL/hr) and high flow (up to 4,000 mL/hr)
- Flow accuracy ±5%

Bayonet-style mechanism for quick and easy cartridge insertion
- Compact enclosure houses a light stepper motor
- Lighted edge for improved usability
- Water ingress and ESD protection

Vertically Integrated Solution

We reached out to the US Army again in 2015 and proposed to add the Navy infusion technology to the previous AutoTIVA platform.

- Development work was started in late 2016

...may have the potential to revolutionize the standard of care by ensuring adequate and timely therapy delivery with improved performance in high-workload and high-stress environments.”
Regulatory Considerations

- Sensor (validity, latency/dynamics, robustness and reliability)
- Controller design (inter-patient variability considerations, conformity to the drug label, handling of non-linearities, etc.)
- Preclinical evaluation (safety, evidence of efficacy, and performance evaluation under faults conditions)
- Implementation (safety features and fallback modes, archive)
- Clinical use & usability (adequacy of training, operational transparency, simulator-based training, etc.)

Take home message
Closed-loop TIVA is both technically and clinically feasible

- The AutoTIVA concept (EEG-based dual controller for propofol and remifentanil) has been clinically validated in thousands of cases by research teams from Canada, France, and India.
- Leverages the benefits of TIVA and brain monitoring. The closed-loop function acts as a force multiplier.

The AutoTIVA is a vertically integrated solution combining 3 key technologies: brain monitoring, infusion pump, and robust controller, developed by UBC/NeuroWave.

- Fully functional pilot product optimized for manufacturability
- Regulatory approval (FDA) will be sought, as the AutoTIVA transitions to an Advanced Development program at USAMMA.

The FDA has indicated strong interest in PCLC technologies, and is being supportive of sponsors willing and capable to bring applications for review.

- Their feedback has guided our design since early on.

Funding from the US Army (Medical Research and Material Command) and the Office of Naval Research is gratefully acknowledged.

- Their critical support has been necessary to get the project moving forward.
- More than just a funding Agency, they are partners with whom we often interact to refine operational concepts, and system specifications. They will likely be our first end-users.