Nano-based Dynamically Diluted Brain Interface

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Introduction

In this paper, we are proposing a new type of invasive brain-computer interface - "Nano-based dynamically diluted brain interface" (NDDBI), which will not require surgical operation. Instead, it will leverage methods used in Nano-medicine for delivering nanoparticles to certain areas of the human body and techniques developed in positron emission tomography for studying distribution of neuro-mediators in the brain. NDDBI can be used for novel brain to machine interfaces (BMI) which can provide new ways for mental performance enhancements, provide new therapies for brain trauma, drug obsession as well as treat neurological disorders such as Autism and Parkinson's disease. The current methods like injecting electrodes and syringe-injectable electronics might require surgical operations or does not provide a clear way to remove electronics from brain tissue if something goes wrong. Unlike those approaches, NDDBI provide a way to establish temporal two-ways wireless brain computer interface which will dissolve over the time of a few hours. This ability to dissolve is important advantage of NDDBI over to current BMI methods.

NDDBI uses metallic (gold, platinum, etc.) and magnetic nanoparticles coated with neurotransmitters such as: noradrenaline, dopamine (dihydroxyphenylalanine), or a precursor such as L-DOPA to target specific cells in the brain. The unique optical, magnetic, and chemical properties of nanoparticles will be used for laser induced thermal excitation of neurons. Also those particles will serve for contrast enhancement, increased sensitivity and better spatial, and temporal information, across MRI, PET, SPECT, and ultrasound multi-functionality and multi-modal imaging. It has been demonstrated that nanoparticles a few nanometers in diameter can cross the blood-brain barrier to reach various parts of the brain [1-2]. In addition, neurotransmitters bind to receptors of specific neural cells; providing a mechanism to selectively attach nanoparticles to certain cell types.

Once specific cells in the brain are targeted using nanoparticles, NDDBI can selectively activate sections of the brain by controlling neuron firing with IR light or ultrasound. Nanoparticles can be heated by external infrared light (or ultrasound) focused on a certain part of the brain. Light heating of a neuron on a fraction of a degree will reduce neural membrane polarization, which will lead to changes in neuron firing [3, 4]. To achieve this with NDDBI, multiple beams are positioned around the head and focus on one region, which leads to better localization and reduce intensity of light exposure. In this process a "warm" spot is created, while delivering a small amount of light into the tissue.

NDDBI includes the ability to leverage nanoparticles as a contrast agent for EEG/EMG/FMRI recordings [5,6,7]. Injecting nanoparticle agents coated with neuromodulators will enhances detection of brain activity from targeted regions. The nanoparticles serve as an interface between the brain tissue and computer.

We call this interface "Dynamically Diluted Brain Interfaces" referring to the processes of washing out of nanoparticles from the body. This process depend on types of nanoparticles but has been demonstrated taking from 2 to up to 17 hours [8]. Thus NDDBI will not stay in the body permanently and will be cleansed out of the body in a few hour.

NDDBI will allow enhance brain processing power by interfacing with external cyberinfrastructure. In addition, it will provide a new way to treat a variety of disorders associated with brain pathology. NDDBI can be used to activate parts of the brain that impact growth and neuronal plasticity and therefore it is a new tool for the treatment of traumatic brain injuries. NDDBI can even lead to new therapeutic approaches to treat drug addiction and diseases such as schizophrenia, autism, or tumor lesions that have functional effects on the pain perception process.

Currently, we are in the process of developing simulation environment which will allow to perform Computer Aided Design and Modeling of proposed approach.

Circulation of nanoparticles through the human body

The first step to establish NDDBI is to model the amount of nanoparticles that can be administered into the human body and how they will distribute throughout the body. We are suggesting to leverage compartmental models which have been extensively developed for tracer kinetics, pharmacokinetic modeling and physiological modeling of dynamic measurements of metabolism [9, 13, and 14]. Those models can be used to simulate total mass and concentration of neurotransmitter-coated nanoparticles in different parts of human body, including specific brain regions. Dynamics of those models are constrained by physical conservation laws acting on tissue. These laws represent conservation of mass during physical transport processes such as advection in blood and diffusion of substances [9, 13, and 14].

$$\frac{dM_i}{dt} = V_i \frac{dC_i}{dt} = k_i \left[Cp - \frac{C_i}{R_i} \right] - EC_i$$

And the mass balance equation for the blood compartment is

$$\frac{dM_p}{dt} = V_p \frac{dC_p}{dt} = -\sum_i \left[k_i \frac{M_p}{V_p} \right] + \sum_i \left[k_i \frac{M_i}{R_i V_i} \right]$$

Where **"M_P**" and "**C_p**" refer to mass and concentration of nanoparticles in blood and "**M_i**" and "**C_i**" refer to nanoparticles in specific tissue.

R_i is a tissue to blood partition coefficient which is defined as the ratio of tissue chemical concentration to that of the venous outflow of the tissue when at equilibrium.

"EC_i**"** is excretion coefficient for the tissue "i". The kinetic equations describe the nanoparticle accumulation and excretion throughout different organs and bodily fluid as generally shown in Figure 1.

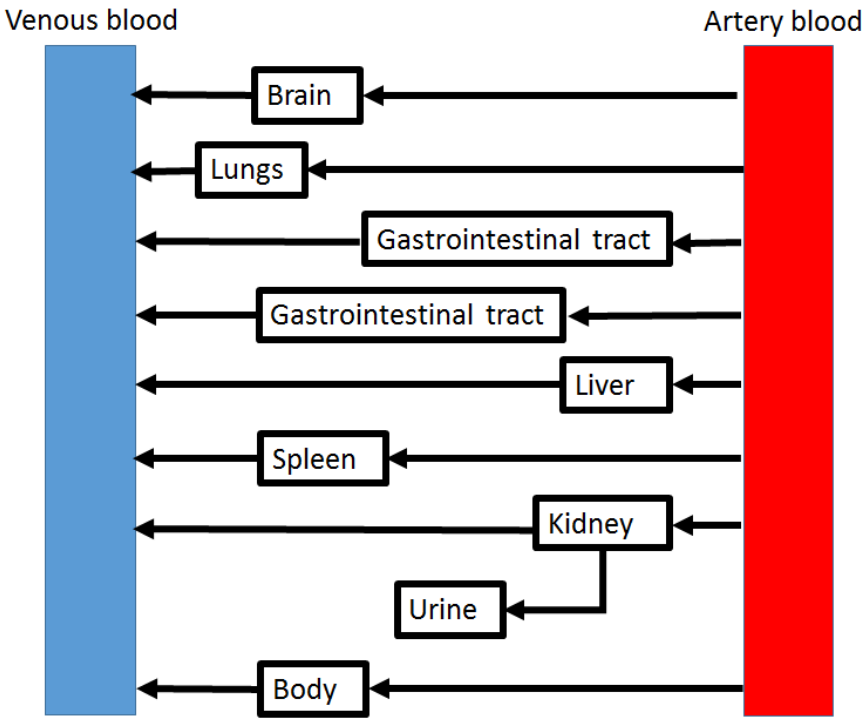

Figure 1: Nanoparticles in the blood travel from arterial side to venous side through the various organs.

"k_i" is the diffusion coefficient and can be modeled as a linear combination of parameters: $k_i = \alpha x_1 + \beta x_2 + \gamma x_3 + Const$

And depending on "*nanoparticle size*" x_1, "*zeta potential*" x_2 and "*number of neurotransmitters per surface area*" x_3. The kidney compartment is used to model how nanoparticles are washed from the body and the accumulation of nanoparticles excreted from the kidney compartment is expressed as:

$$\frac{dM_{urine}}{dt} = CL_{kidney} M_{kidney}$$

To calculate the initial values of diffusion coefficients for final estimation, the blood mass-time data can be fitted into a bi-exponential function:

$$M_i(t) = A \exp(-k_i t) + B\ exp\left[-\frac{k_i}{R_i} t\right]$$

Where *A* and *B* are the intercepts for each exponential segment of the blood mass-time curve. This equation describes the blood mass-time profile and the solution gives us the amount of nanoparticles in a specific region.

Nanoparticles circling through the brain

Part of the nanoparticles that reach the brain will cross the blood-brain barrier. To model the amount of particles delivered through blood vessels to a certain brain region, the following equation is used:

$$N_i \sim 2\pi R_i * L_i * \exp(-k * F_i)$$

Where "N" is the number of particles in each vessel segment "i" of radius "R" and length "L", and "F" is the flow rate (dependent on segment pressure), which might vary along vessel segments. The higher the flow, the quicker particles will leave the segment thus there is less time to diffuse. "k" is the normalization coefficient, which has to be found experimentally.

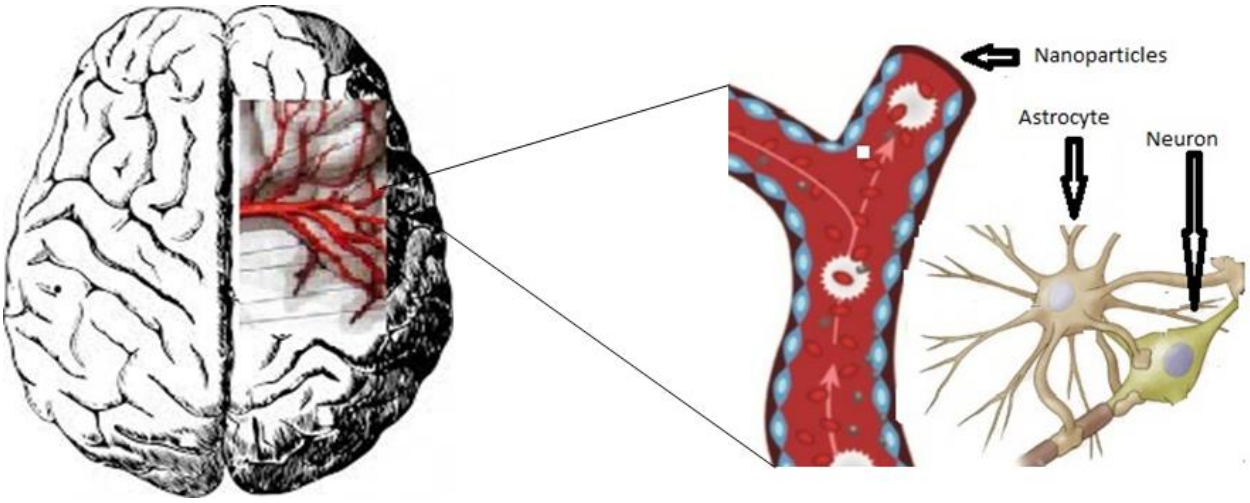

Figure 2 illustrate nanoparticle migration through vascular system of the human brain.

The nanoparticle diffusion (adoption) model [10] is described by the transport of molecules at the point of release from the vascular segment by quasi-steady reaction-diffusion equations. We assume that molecules are supplied by the existing vasculature at rate "F", diffuse into the tissue with constant diffusion coefficient "D", are uptaken by cells with rate "N_{up}", and decay-wash out of system with rate "N_{dec}". Therefore, the equations that represent total mass conservation for delivered nanoparticles can be used to model the amount of nanoparticles in a brain region close to the vessel segment "i"

$$\mathbf{0} = \boldsymbol{\nabla} * (\mathbf{D} * \boldsymbol{\nabla}\mathbf{N}) + \mathrm{F} - N_{up} - N_{dec}$$

It has been determined by several studies that nanoparticles of a few nanometers in diameter can cross the Blood Brain Barrier and get to various parts of the brain [1-2]. Simultaneously, golden or platinum nanoparticles have low chemical activity; thus, do not interfere with chemical processes in the brain.

Attaching certain neurotransmitters like dopamine, acetylcholine, or noradrenalin can allow particle to bind to certain type of cells like "dopaminergic" neurons or "acetylcholine" neurons. Dopamine and noradrenalin neurotransmitters bind to certain receptors on the cell membrane, which are specific to certain neurons, so that specific binding is achieved (Figure 3).

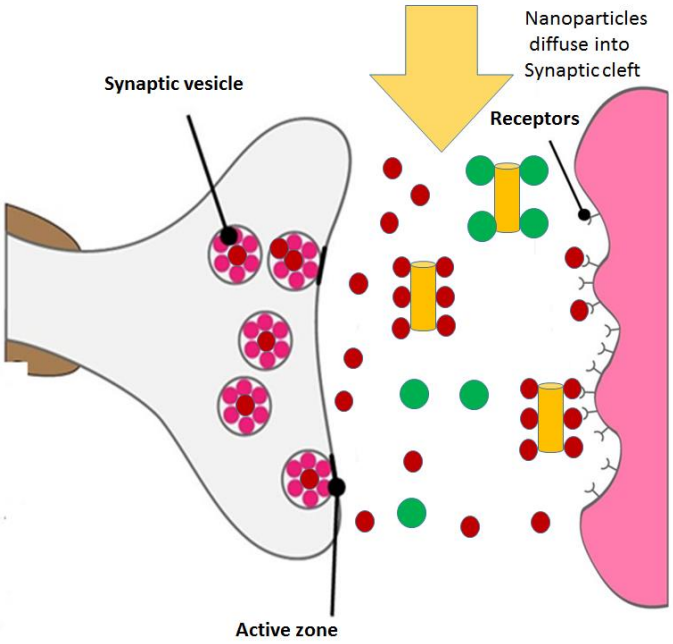

Figure 3: Neurotransmitters coated nanoparticles can reach synaptic cleft and bind specific receptors based on the coated neurotransmitters.

Activation of nanoparticles in specific brain area

Nanoparticles, which are temporally attached to specific neurons in specific parts of the brain, can be used as an interface to deliver pinpoint excitation to the particular brain regions. This is how information can be delivered into the brain. It can be achieved because nanoparticles can sense external electromagnetic fields, infrared radiation, and ultrasound, and generate heat from the resonance effect in the metallic core and/or surface Plasmon. When a nanoparticle is heated it will change the local temperature of the neuron membrane. Even the slightest temperature change can decrease membrane polarization and lead to an increase in probability of neuron firing [3-4]

We are suggesting infrared lasers because beams can be collimated to intersect in a specific area of the brain to achieve the desired intensity resulting in a lower exposure level for surrounding areas (Figure 4).

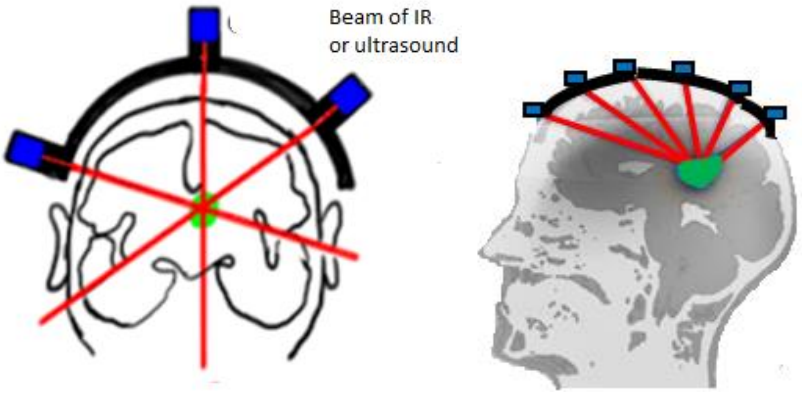

Figure 4: Leverage multiple intersecting beams to create a "hot" spot, while maintaining low intensity for each beam

Heat transfer taking place in the target region of the brain can be modeled by equation [11]:

$$\frac{\partial T}{\partial t} = \boldsymbol{\alpha \nabla^2 T} + \frac{Q}{\rho C_P}\left(1 + \mathbf{10}^{-OD}\right)$$

Where first element $\boldsymbol{\alpha \nabla^2 T}$ represent heat conduction and the second $\frac{Q}{\rho C_P}\left(1 + \mathbf{10}^{-OD}\right)$ is heat from laser irradiated nanoparticles.

α - Tissue thermal diffusivity (area/time)

Q - Laser energy (power/volume)

ρ - Tissue density (mass/volume)

C_P - Tissue heat capacity (energy/mass*degree)

OD - Optical density

The tissue temperature at the "warm" spot will need to be kept at a small fraction of a single degree to keep membrane polarization and increase the probability of neuron firing.

The "warm" spot will allow for neuron firing, while using low intensity beams. In addition, leveraging different nanoparticles coated with different neuro-transmitters creates a way to specifically target different cell types. For example, golden nanoparticles connected with dopamine will provide a way to communicate with dopamine cells. Platinum nanoparticles connected with noradrenaline molecules will provide a way to communicate with other noradrenalin neurons. One advantage of this approach is that multiple neurotransmitters can be identified simultaneously by using different nanoparticles.
It has been demonstrated that nanoparticles can be contrast agents for FMRI to increase the sensitivity in measuring brain activity [2, 5, 6, and 7]. NDDBI is proposing to use neurotransmitter coated magnetic nanoparticles as a contrast agent for fMRI and EEG / EMG brain activity detection.

In NDDBI, nanoparticles are to be distributed over the neurons and within the synapses. During neural activities, the sparsely distributed nanoparticles will be detected by means of FMRI, EMG/EEG. It is expected that binding of nanoparticles to receptors will change the electric and magnetic properties of the brain tissue and enhance contrast in measured magnetic and electric signals which will be detected more effectively.

NDDBI goes a step further in extending the use of nanoparticles as a way to deliver pinpoint excitation into the brain. Neurotransmitter coated nanoparticles can provide us with a temporal interface that can operate in both directions, to activate certain brain areas, and to enhance detection of brain activity in specific regions. A crucial advantage of NDDBI is that nanoparticles will bind to a certain cell types and provide a two-way communication channel with specific neural populations in the brain.

Conclusion and medical applications

Pain management

New therapeutic protocols are another area where NDDBI is applicable.

One application is binding nanoparticles to the antinociceptive system cells and activating these cells to inhibit pain signal processing. Inhibiting pain in higher cortical centers would improve quality of life in oncology patients.

Brain trauma

Using NDDBI it might be possible to ensure the growth of neurons in a given direction (motor to the motor or sensitive to sensitive) for brain trauma patients. Therefore, neurons could re-grow in a healthy manner.

Orchestration of neural dynamics

In psychiatry, NDDBI would be useful for Autism therapy. There are a few theories that explain autistic brain mechanisms and how they give rise behavioral symptoms. Some neural models, like the iSTART model [12], describes how cognitive, emotional, timing, and motor processes that involve brain regions (prefrontal and temporal cortex, amygdala, hippocampus, and cerebellum) may interact together to create and perpetuate autistic symptoms. Those models suggest that autistic symptoms may arise from the breakdown of some brain processes. These processes include a combination of: underaroused emotional depression in the amygdala and other brain regions, learning of hyperspecific recognition categories in temporal and prefrontal cortices, and breakdowns of adaptively timed attentional and motor circuits in the hippocampal system and cerebellum (Figure 5). Therefore, it might be possible that activation of damaged brain regions during therapeutic sessions would reverse development of autistic symptoms.

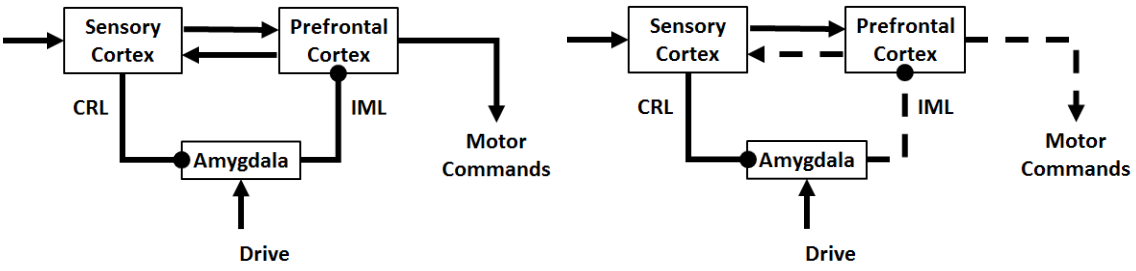

Figure 5: How activity of various part of the brain might paly role in developing autistic behaviors.

Another model explores interactions among three types of internal representations during reinforcement learning: sensory and cognitive representations through Sensory Cortex, drive representations through Amygdala, and motor representations through Prefrontal Cortex [12].
As this model suggests, sensory representations temporarily store internal representations of sensory events in working memory, while drive representations are sites where reinforcing and homeostatic cues converge to activate emotional responses.

Finally, motor representations control the read-out of actions. The two successive stages of a sensory representation are interpreted to be in the appropriate sensory cortex and the prefrontal cortex. As opposed, the prefrontal stage requires motivational support from a drive representation to be fully effective in the form of feedback from the incentive motivational learning (IML) pathway. In this model, the amygdala is interpreted as one important part of a drive representation. Amydgala inputs to the prefrontal cortex cause feedback to the sensory cortex that selectively amplifies and focuses attention upon motivationally relevant sensory events. When a drive representation like the Amygdala gets depressed, diminished activation of its outputs in response to sensory events depresses motivational inputs to the prefrontal cortex in response to emotionally important events, and hereby attenuates motivationally-appropriate signals to and from the prefrontal cortex (Figure 5: arrow lines). As a result, motivationally irrelevant events are not suppressed, and prefrontal-mediated plans and actions are insufficiently activated, which leads to development of autistic behavior. We are suggesting that it is possible to develop therapeutic procedures that will leverage nanoparticles to externaly depress or activate brain regions in response to various events. This will in turn stimulate the development of new long range connections between damaged zones. Such connections might lead to inprovement in autistic behavious, but will require extensive research.

Current progress

Currently, we are in the process of developing Computer Aided Modeling environment and 3D printing model of brain slices with embedded nanoparticles. Those 3D slices will allow to perform Computer Aided Design and Simulation of proposed laser system.

As a first step, we are building 3D model of brain slices based on Open fMRI – open raw magnetic resonance imaging datasets. This model will be used to create 3D printing of layered brain slices using various materials. We are going to create anatomically correct 3D brain model with blood vessels infused with liquids which will model human blood. Also, electrical fires are going to be embedded into the 3D printed model to imitate electric activity in the certain parts of brain.

We are starting with well adopted gellan gum and then going to proceed with other materials to have very porous brain scaffold. We are proposing to infuse porous materials with lecticans, proteoglycans that contain a lectin domain and a hyaluronic acid-binding domain. Those proteins provide unique composition of the extracellular matrix of the human brain tissue [15]. Later, we expect to infuse 3D printed model pores with cell cultures of glial cells and neurons.

Thus we will be able closely model physical properties of the brain to perform laser system testing and understand how laser beams will propagate through brain tissue and create “warm” spot.

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