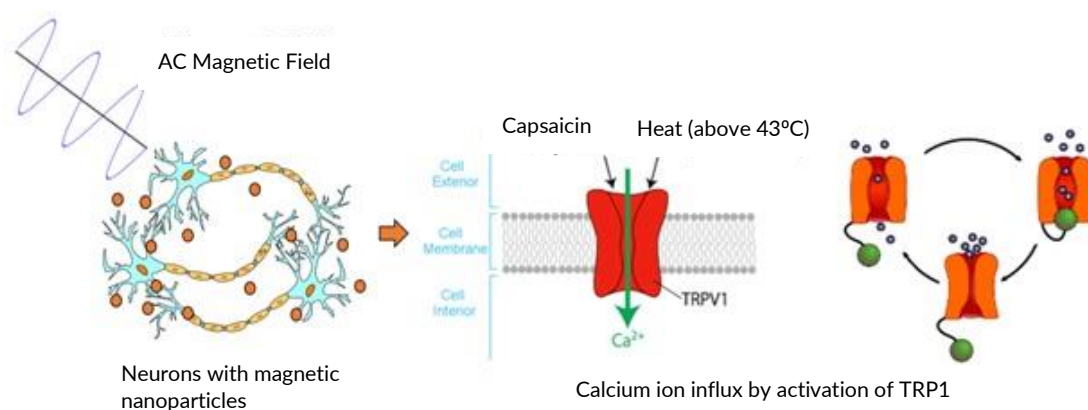


## Nano Actuation: Using Magnetic Nanoparticles and AC Magnetic Fields in Neurological and Biomedical Applications

Nano actuation can be defined as actuation of a specific action using a nanoscale object with or without the input of an external force acting on it.

Conventional neuron stimulation by external stimuli is carried out using embedded electrodes within the brain tissue. However, a new methodology has been recently proposed by MIT researchers, which involves using magnetic nanoparticles and AC magnetic fields with frequencies between 100 kHz – 1 MHz to stimulate neurons.

Researchers have demonstrated calcium ion influx in neurons after injecting 22 nm sized magnetic nanoparticles into brain tissue and exciting the neurons by activating heat-sensitive capsaicin receptors (transient receptor potential cation channel subfamily V member 1 : TRPV1) using an external AC magnetic field i.e. nano-magneto thermal excitation.



**Figure 1.** Calcium ion influx in neurons by magnetic nanoparticles nano actuation. Neurons are excited by activating heat-sensitive capsaicin receptors (TRPV1) using an external AC magnetic field.

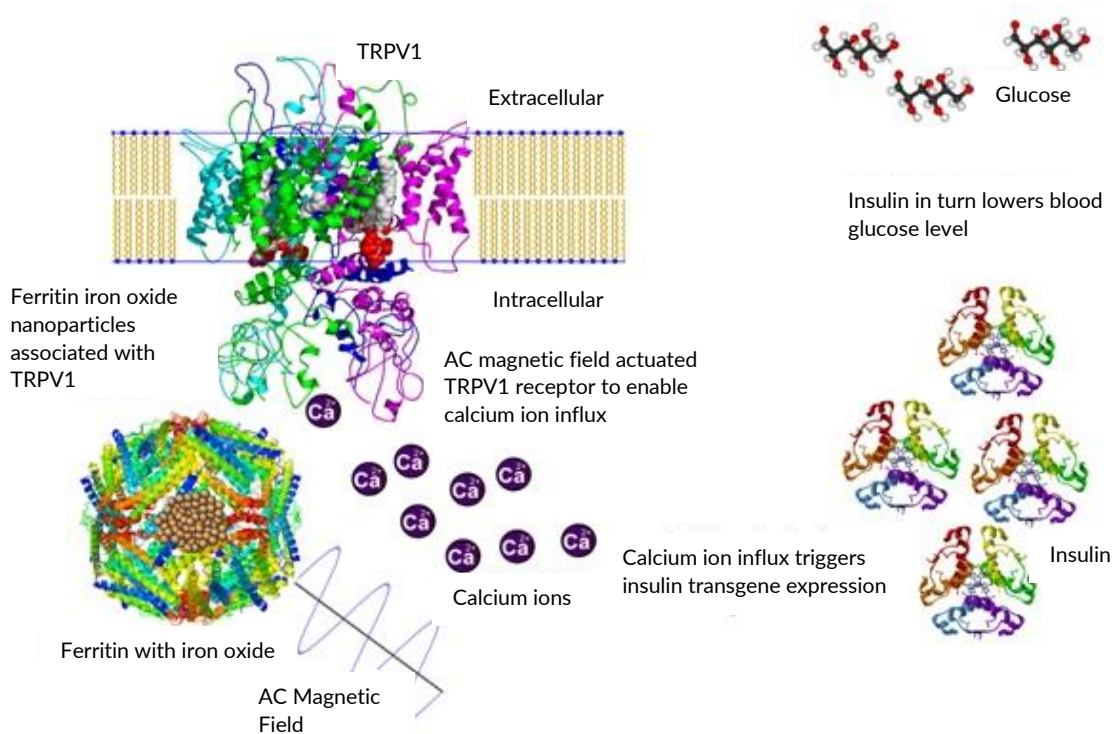
Magnetic nanoparticles localized within the target region due to their surface functionalization remained there for weeks. This allowed the researchers to re-heat the magnetic nanoparticles, leading to repeated long term nano-magneto thermal excitation of neurons using non-invasive AC magnetic fields.

TRPV1 is involved in the recognition and regulation of temperature and is also responsible for the sensation of nociception. Nociceptive neurons produce sequences of action potential in reaction to stimuli which helps to study brain circuitry. Repeated stimulus of TRPV1 would result in desensitization of the receptor resulting in alleviation of pain i.e. a potential analgesic treatment.

Furthermore, this research opens new opportunities within our quest to understand neurodegenerative disorders such as Parkinson's, and a possible treatment, as electrode-mediated neuron stimulation has proved effective in reducing tremors in the past. This novel non-invasive technique can provide repeated deep brain stimulation remotely and non-invasively resulting in zero damage to tissue unlike electrode implants [1].

Similarly AC magnetic field mediated nano actuation of insulin transgene expression has been demonstrated to drop blood glucose level. Green fluorescent protein- tagged ferritin protein heavy and light chain fusion led to intracellular synthesis of magnetic nanoparticles. Ferritin iron oxide nanoparticles were later attached to  $\alpha$ GFP-TRPV1.

When exposed to AC magnetic field the ferritin nanoparticles dissipate heat, which triggered calcium ion influx facilitated by TRPV1 activation. Calcium ion influx initiated transgene expression of insulin. Insulin in turn lowered blood glucose level. This nano actuation application has significant therapeutic benefits [4].



**Figure 2.** AC magnetic field exposure of ferritin nanoparticles dissipate heat, which triggers calcium ion influx facilitated by TRPV1 activation. Calcium ion influx initiate transgene expression of insulin which in turn lowered blood glucose level.

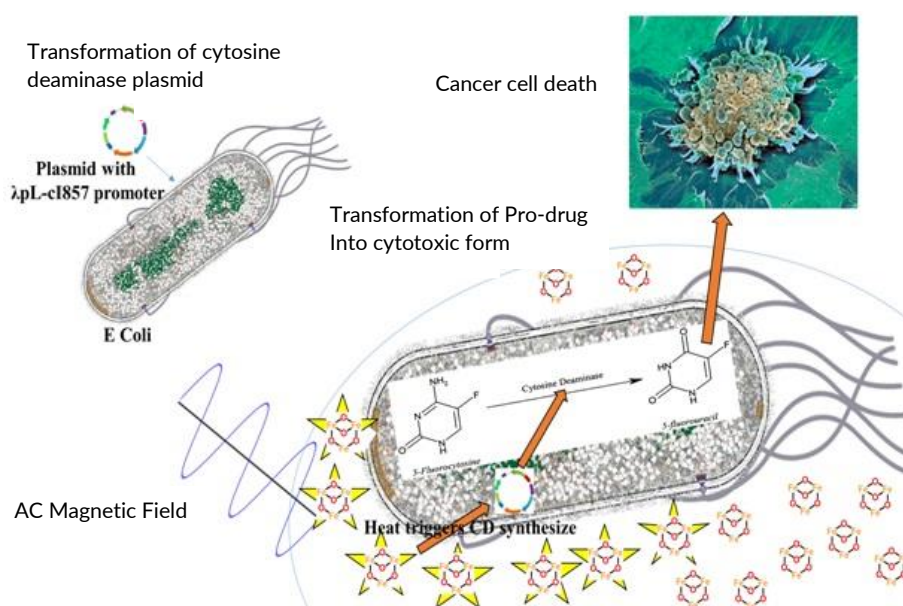
The prospect of remote actuation of magnetic nanoparticles by radiofrequency spectrum has opened up new speculations in medicine as of the above and below examples, AC magnetic field triggered drug release and actuation of biochemical pathways within cells have received significant attention in the last decade. Recent studies show successful engineering of nanoparticles with magnetite cores enclosed within a gold shell.

Magnetite nanoparticle within a gold shell has promising biomedical application due to their biocompatibility. Likewise gold shell surface functionalised with carboxylic group i.e. allows the nanoparticles to bind to enzymes. These carboxylic groups were conjugated with protease chymotrypsin (model enzyme) to demonstrate lowered enzyme activity, when nanoparticles were actuated in the presence of AC magnetic field. Nano actuation of surface functionalized nanoparticle hybrids mediated by AC magnetic field does open plenty of intracellular opportunities within the biomedical field [2].

Another vivid example would be genetically modified bacterial cells to express therapeutic enzymes under the transcriptional control of remotely actuated promoters to facilitate the transformation of non-toxic prodrugs to their cytotoxic forms. On site synthesis of enzymes offers improved constancy and regulation of enzyme activity.

Escherichia coli (E. coli) has been genetically engineered to express cytosine deaminase at elevated temperature mediated by the thermo-regulatory  $\lambda pL-cl857$  promoter which provides a thermal switch to trigger enzyme synthesis. Increased cytosine deaminase amount was detected in in vitro cultures incubated at 42°C than at 30°C and this led to improved conversion of 5-fluorouracil from 5-fluorocytosine.

These genetically modified microbes were later enclosed within alginate along with iron oxide nanoparticles. Alginate acts as an immune shield. Localised heat dissipation by iron oxide nanoparticles when exposed to AC magnetic field led to remote triggering of cytosine deaminase expression.



**Figure 3.** Localised heat dissipation by iron oxide nanoparticles when exposure to AC magnetic field led to remote triggering of cytosine deaminase expression, this in turn improve conversion of 5-fluorocytosine into 5-fluorouracil. 5-fluorouracil kills cancer cells.

AC magnetic field mediated actuation of microcapsules to enhance conversion of 5-fluorouracil from 5-fluorocytosine resulted in increased cytotoxicity within cancer cells when compared to direct chemotherapy via 5-fluorouracil. This combination of magnetic fluid hyperthermia and nano actuation of enzyme-prodrug therapy sensitize cancer cells prior to drug delivery and will improve the efficacy of the cancer treatment [3].

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