Catalyst Foundation Final Report

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Summary

Neural prosthetic devices offer a means of restoring function that have been lost due to neural damage. The first part of this work investigates the design of a 15-channel low-power fully implantable stimulator chip. The chip is powered wirelessly and receives wireless commands. The chip features a CMOS only ASK detector, a single-differential converter based on a novel feedback loop, a low-power adaptive bandwidth DLL and 15 programmable current source that can be controlled via four commands. Though, it is feasible to build an implantable stimulator chip the amount of power required to stimulate more than 16 channels is prohibitively large.

Clearly there is a need for a fundamentally different approach. The ultimate challenge is to design a self-sufficient neural interface. The ideal device will lend itself to seamless integration with the existing neural architecture. This necessitates that communication with the neural tissue should be performed via chemical rather than electrical messages. However, catastrophic destruction of neural tissue due to the release of large quantities of a neuroactive species precludes the storage of quantities large enough to suffice for the lifetime of the device. The ideal device then should actively sequester the chemical species from the body and release it upon receiving appropriate triggers in a power efficient manner.

This work proposes the use of ionic gradients, specifically K^+ ions, as an alternative chemical stimulation method. The required ions can readily be sequestered from the background extracellular fluid. The parameters of using such a stimulation technique are first established by performing in-vitro experiments on rabbit retinae. The results show that modest increases (~10mM) of K^+ ions are sufficient to elicit a neural response.

The first building block of making such a stimulation technique possible is the development of a potassium selective membrane. To achieve low-power the membranes must be ultrathin to allow operation in the diffusive transport regime. One method of achieving this is to use lyotropic self-assembly, unfortunately conventional lipid bilayers cannot be used since they are not robust enough. Furthermore the membrane cannot be made potassium selective by simply incorporating ion carriers since they would eventually leach away from the membrane.

A single solution that solves all the above issues was then investigated in this work. A novel facile synwork of self-assembling receptor functionalized polymers was achieved. By combining the properties of hydrophobic and hydrophlic interactions of two polymers a triblock co-polymer was synthesized. The middle hydrophobic block is composed of biocompatible polysiloxanes and was further derivatized to posses ion recognition capabilities via pendant crown ether chains. The hydrophilic blocks were composed of

biocompatible polyoxazoline. The membrane properties were studied by self-assembling them into vesicular structures. The ion responsive properties of these polymers were then examined. These polymers also show emergent behavior, such as spontaneous fusion and shape transformation to ionic stimuli, due to the synergy between form and function.

The results from the work show that it is feasible to build a renewable chemically based neural proswork based on supramolecular architectures. However, there remains a lot of fundamental work that needs to be pursued in the future to bring the idea to complete fruition.

A Low Power Fully Implantable 15-Channel Retinal Stimulator Chip

Retinal Prostheses are being developed around the world in hopes of restoring useful vision for patients suffering from certain types of diseases like Age Related Macular Degeneration (AMD) and retinitis pigmentosa. The central component of an electrical retinal prosthesis is a wirelessly powered and driven stimulator chip, see figure 1. The chip receives commands from the outside and outputs biphasic current pulses to an electrode array placed in the retina that stimulate the remaining retinal neurons, see figure 2. The chip contains 30,000 transistors in a 0.5μm technology (3M, 2P), occupies an area of 2.3mm X 2.3mm and excluding the current sources consumes less than 2mW of power, see figure 3. The chip is powered inductively via a 125kHz power signal which is rectified to generate a ±2.5V supply. The data signal is transmitted as an amplitude shift keyed (ASK) signal on a 13.56MHz carrier. The data rate can be varied from 100kHz to 750kHz and the symbol (0 or 1) is encoded as the pulse width of the data signal. A self-biased feedback loop based single to differential converter restores the signal to full rail levels. Clock and data recovery is performed by a self-biased low-power inverter based DLL. The chip can receive four commands and each command is 16 bits long. The current amplitude, pulse duration and inter-pulse duration can be programmed by using the four commands. Figure 4 shows that the chip function is as intended, the result shown is for the chip being wirelessly powered and driving a 400μm irdium oxide electrode, the power and data coils were separated by 15mm.

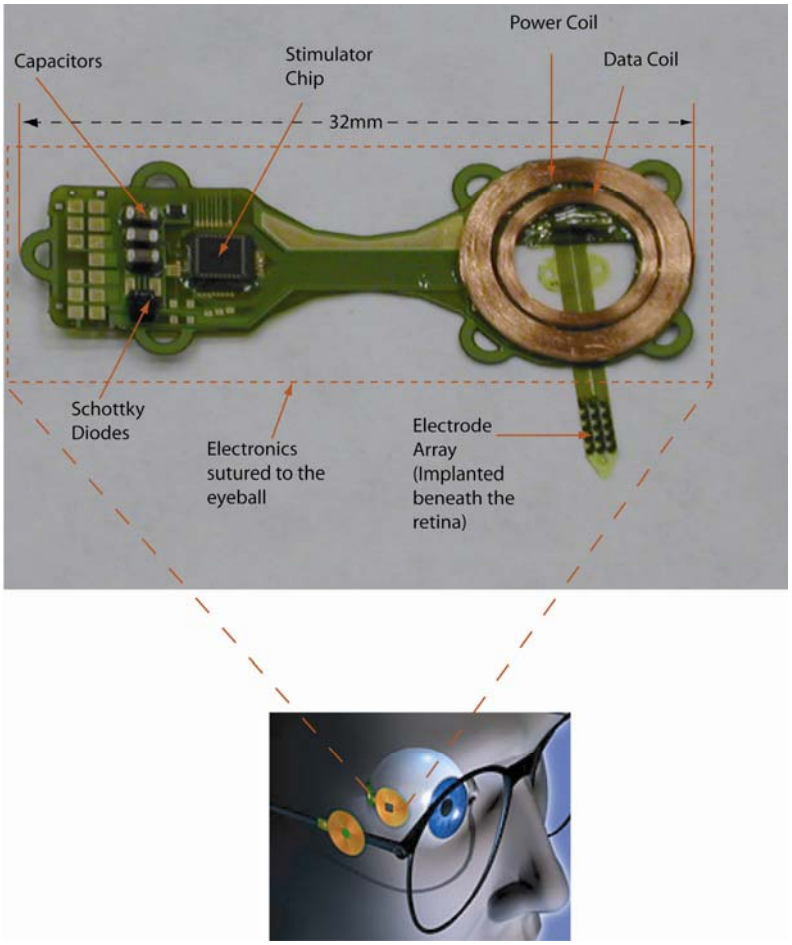

Figure 1: Schematic representation of the minimally invasive ab-externo approach. The transmitter coils are placed outside on a pair of eyeglasses and the receiver coils and the stimulator chip are placed on the eyeball. The electrode array is placed in the subretinal space through a scleral flap

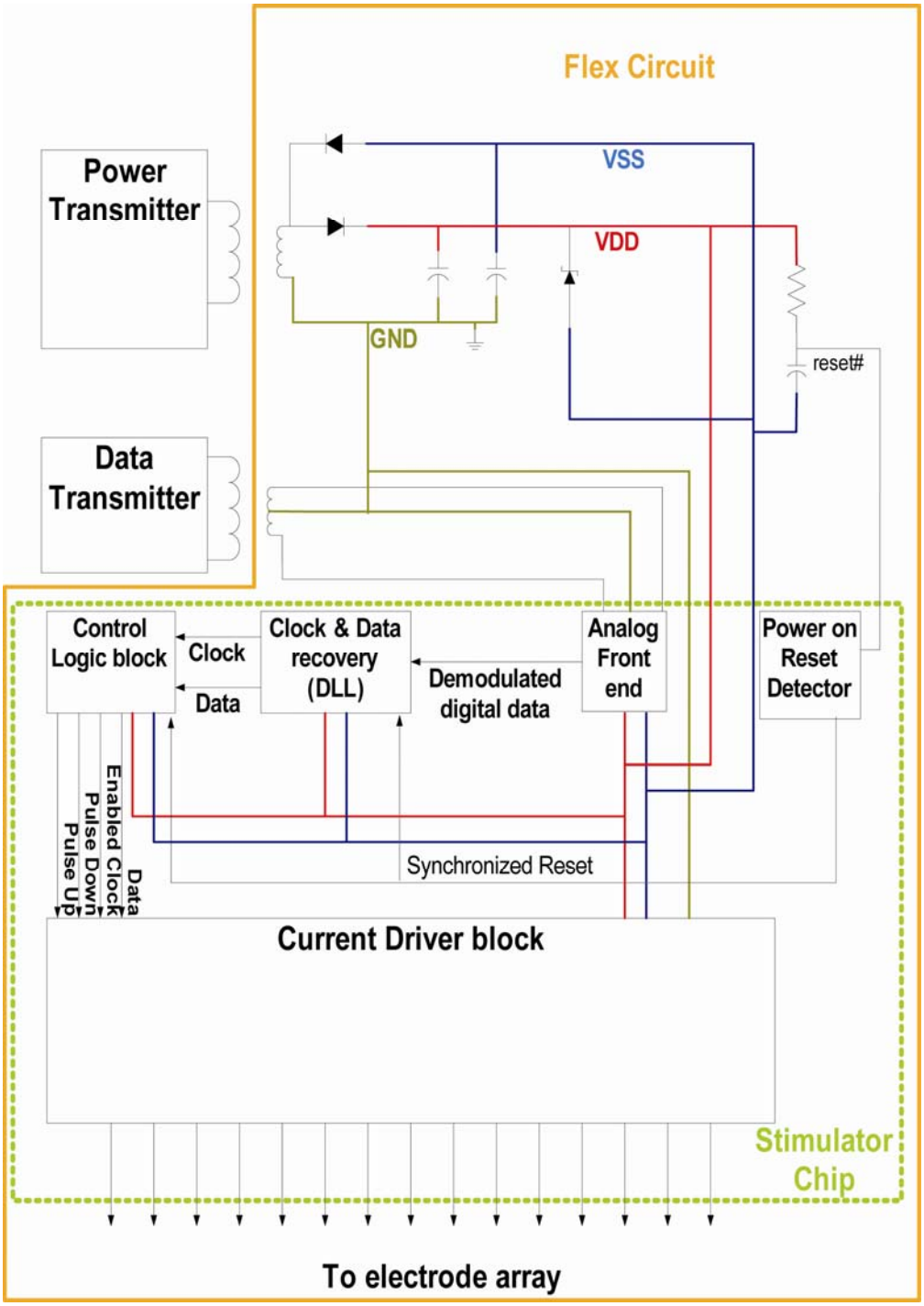

Figure 2: Architectural overview of the current retinal implant. The blocks that correspond to the stimulator chip are outlined in green. The chip receives data and power through two separate inductive links, demodulates the signal, recovers the data and the clock and outputs biphasic current pulses upon receiving the appropriate commands

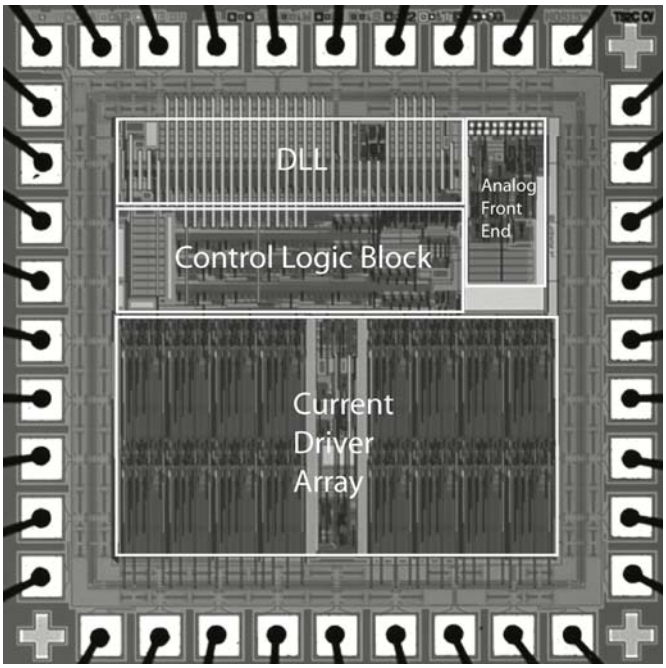

Figure 3: Microphotograph of the complete stimulator chip, the chip has a total area of 5.612 mm^2 and contains approximately 30,000 transistors

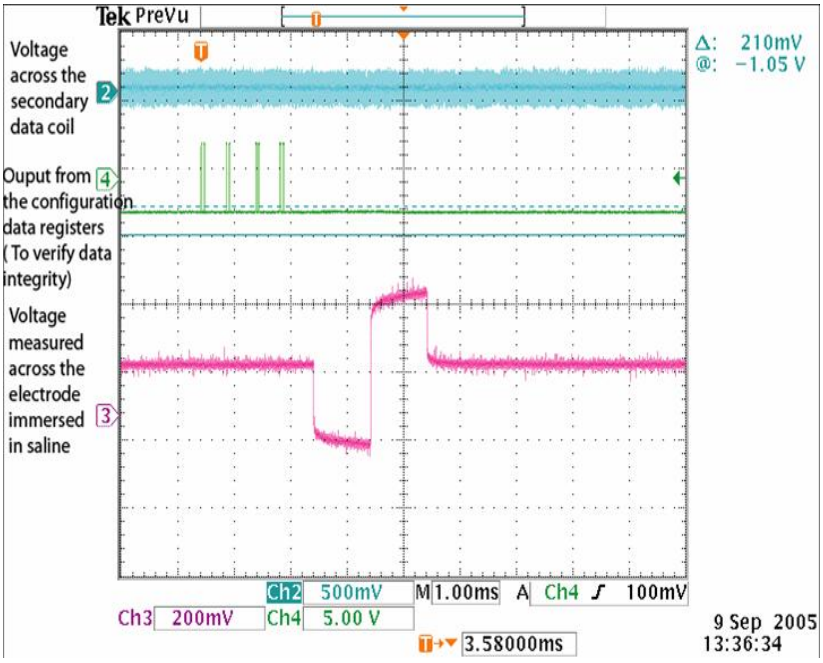

Figure 4: Output of the wirelessly driven and powered stimulator chip driving an electrode immersed in saline. The separation between the primary and secondary coils are 15mm.

Stimulation of Rabbit Retinal Ganglion Cells by altering K^+ Ion Gradients: Dose-Response Curve

Purpose: Current neural prosthetic devices use electrical stimulation to excite the neural tissue of interest. Electrical stimulation, though easy to implement is not the most effective method of neural stimulation. Common issues with electrical stimulation method are lack of focal stimulation, bio-toxicity and high power requirements. We are investigating the use of small focal application of increased extracellular concentration of potassium as an alternative to electrical stimulation.

Methods: Single-cell recordings were made from the axons of ganglion cells with an in vitro rabbit retinal preparation. The ganglion cells were stimulated over the optical receptive field with a multibarrel micropipette which contained various concentrations of KCl (0-40mM) in an osmotically balanced NaCl solution (~300 mOsm). The micropipette solutions were ejected by using a mulitchannel pressure ejector (PM8000, MDI Systems). All solutions contained Azure B to enable visualations of the solution being ejected. Pulse durations of 30-100msecs were used, see figure 5.

Results: The following results were obtained from various cell types of ganglion cells that were located in the inferior, mid-peripheral retina. The control solution which contained 0mM KCl and 150mM NaCl produced no response. Solutions that contained 10-40mM produced appreciable responses, with response strength increasing with K^+ concentration. Typical response latencies were 30-60msecs after application of K^+, see figure 6a. Application of micromolar concentrations of barium (Ba^{2+}) to the bathing solution reversibly abolished the K^+-evoked responses. Receptive fields for the K^+ responses were about 500 μm in radius, see figure 6b&c.

Conclusions: The results indicate a dose-response behaviour with the the threshold for activation at approximately 10mM. The responses to K^+ are similar in nature in regards to responses and latencies to the light-evoked responses. Blocking the K^+ evoked responses by Ba^{2+} indicates that the response may not be purely due to a Nernstian behavior but complemented by the potassium siphoning effect of the Müller cells. Additionally, it may also be due to the reversal of the glutamate pumps. The results indicate that the use of potassium is a viable alternative to electrical stimulation for the development of a retinal prosthesis.

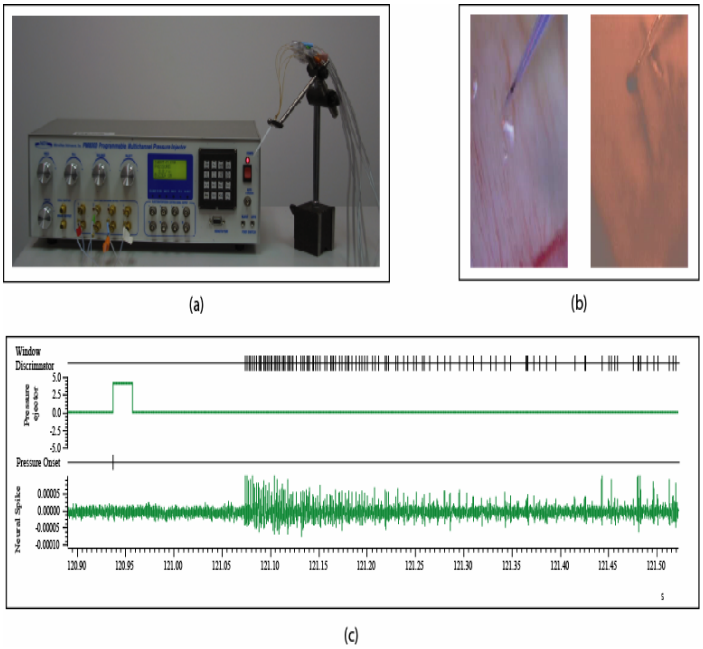

Figure 5*: a) Experimental setup used for the K+ stimulation b) Snapshots of the pipette positioned over the retina, the figure with a red shading is the pipette under red light illumination and shows the KCl solution being ejected with the dark stain caused by the Azure B dye used for visualization. The red light was used to prevent the retina from responding to the ambient light since it is known that e rabbit retinae do not respond to red light. c) Typical response to K+ stimulation. Shown is the response to concentration of 30mM KCl. The square pulse is the onset of the ejection.*

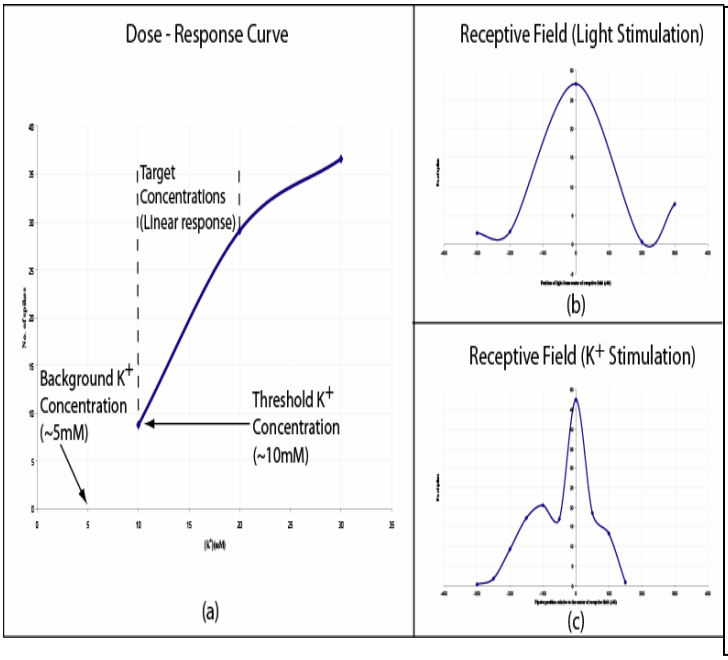

Figure 6*: a) Dose-resp-onse curve for K+ stimulation. The thresh-old is around 10mM as indicated in the graph. The target concentra-tions shows the typical range that a device employing ion stimula-tion would use. b) Stimulation by a spot of light (~100mm dia-meter). c) Stimulation by 30mM[K^+]; The recep-tive fields are qualitatively similar in size and shape for both light and potassium evoked responses. The intermediate dip in potassium evoked res-ponse maybe due to the fluid flow pattern. Overall receptive field size is 400µm for a potassium evoked response and 600µm for a light evoked response.*

Self Assembling Amphiphillic Triblock Polymers with Side-Chain Mesogens in the Hydrophobic Core for Neural Prosthetic Devices

The Boston Retinal Implant Project hopes to restore useful vision to patients who suffer from Age related Macular degeneration and reinitis pigmentosa by developing a retinal prosthesis. We have recently conducted retinal neurophysiology experiments in our lab that show that neural tissue can be effectively stimulated using potassium ions. To enable the design of a neural prosthesis using this method we have synthesized amphiphilic, poly(methyloxazoline)-poly((dimethylsiloxane-co-methyhydrosiloxane)-poly(methyloxazoline) (p(MOXA)-p(DMS-co-HMS)-p(MOXA)), triblock polymers that are functionalized with various receptor molecules via polymer analogous hydrosilylation of the ω-alkenyl substituted receptor molecule. To demonstrate feasibility we have shown here amphiphilic triblock polymers functionalized with 18-crown-6 side chains. The density of the side chain mesogens can be controlled by varying the methylhydrosiloxane content of the hydrophobic core. Vesicles formation using the electroformation process is also shown to demonstrate the self-assembling nature of these polymers, see figure 7 below

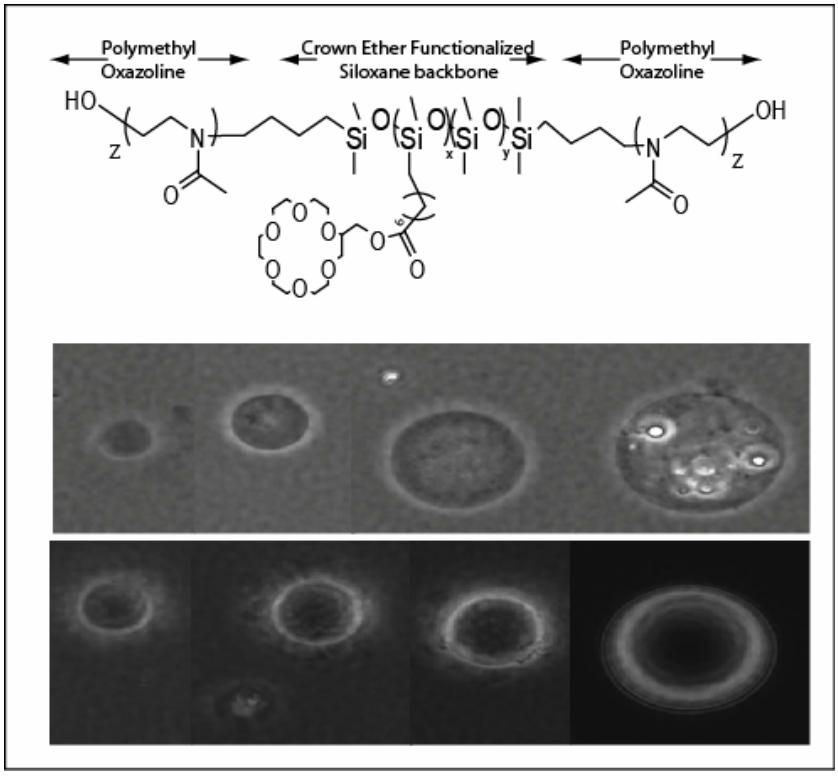

Figure 7: Self-assembling triblock copolymers functionalized with crown ethers. Pictures show the polymers self-assembled into vesicles. The top row has an 8% receptor density and the bottom a 32% receptor density.

Ion Responsive Polymeric Vesicles

Stimuli response vesicle systems are an important subclass of self-assembling systems. These macromolecular assemblies respond to external stimuli, most commonly pH or temperature, by changing their morphology. We have recently reported receptor functionalized self-assembling triblock co-polymers. These are ABA copolymeric structures with polyoxalzoline A blocks and poysiloxane B blocks that are receptor functionalized via polymer analogous hydrosilylation of the ω-alkenyl substituted receptor molecule. By virtue of possessing supramolecular receptors, in this case crown ethers, these systems exhibit unique properties to appropriate stimuli, namely K^+ and Na^+ ions. An unexpected outcome of these polymeric systems was their tendency to coalesce under normal formation conditions without additional stimuli. When subjected to high concentrations of K^+ or Na^+ ions the coalesced vesicles rupture due to osmotic stress and then reform into microtubules. Alternatively when subjected to high concentrations of Mg^{2+} ions the vesicles rupture as in the earlier case but reform back into vesicles, see figure 8. Incorporating function as an integral part of the membrane enable these self-assembling polymeric vesicles to exhibit complex properties in response to external stimuli. We believe that such stimuli responsive systems will be useful in designing the next generation of drug delivery devices.

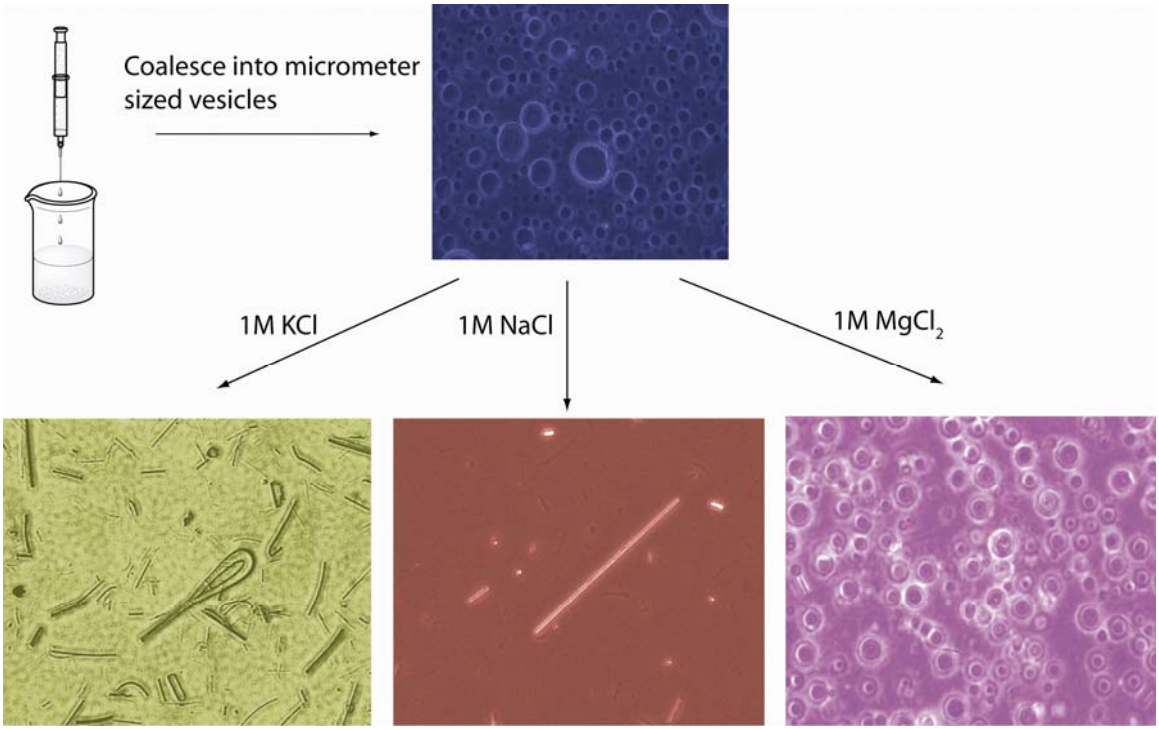

Figure 8: Shape transformations of the polymeric vesicles resulting form spontaneous fusion when subjected to various stimuli after initial rupturing due to osmotic stress. The vesicles adopt a curvy tube like configuration for KCl, a more rigid rod like configuration for NaCl and reform into spherical structure when subjected to $MgCl_2$.

Publications that resulted from the work supported by the Catalyst Foundation

Papers:

L. Theogarajan et. al "Minimally Invasive Retinal Prosthesis", Solid-State Circuits, 2006 IEEE International Conference Digest of Technical Papers (ISSCC), Feb. 6-9, 2006 Page(s):99 – 100

L. Theogarajan "A Low Power 15-Channel Retinal Stimulator Chip", Journal of Solid State Circuits (Submitted)

L. Theogarajan, S. Desai, M. A. Baldo and C. Scholz, "Versatile Synthesis of Self-assembling ABA Triblock copolymers with Polymethyloxazoline A-blocks and a Polysiloxane B-block Decorated with Supramolecular Receptors", Polymer International, 2007 (In press)

L. Theogarajan, C. Scholz, S. Desai, R. Jensen, M. Baldo and J. Rizzo "Self Assembling Amphiphillic Triblock Polymers With Side-Chain Mesogens In The Hydrophobic Core For Neural Prosthetic Devices", Polymer Preprints, 145-146, 2006

L. Theogarajan, S. Desai, M. Baldo and C. Scholz," Ion Responsive Polymeric Vesicles", Polymer Preprints, 48(2), 1040-1041, 2007

L. Theogarajan, "Supramolecular Architectures for Neural Prostheses", Ph. D Dissertation, M.I.T, 2007

Posters

L. Theogarajan, R. Jensen and J. F. Rizzo, "Stimulation of Rabbit Retinal Ganglion Cells by Altering K+ Ion Gradients:Dose-Response Curves" ARVO Poster, 2004

S.K. Kelly, M. Markova, L. Theogarajan, W.A. Drohan, G.W.Swider, B. Yomtov, J.L. Wyatt, J.F. Rizzo, "Development of a Telemetry System for the Boston Retinal Implant." Poster 3168 at The Association for Research in Vision and Ophthalmology (ARVO), May 2006.

W.A. Drohan, L. Theogarajan, S.K. Kelly, J.L. Wyatt, B.M. Yomtov, J.F. Rizzo, "Development of Retinal Implant Driver Software for Retinal Implant Project." Poster 3167 at ARVO, May 2006.

G. Swider, L. Theogarajan, W.A. Drohan, S.K. Kelly, B.M. Yomtov, J.L. Wyatt, J.F. Rizzo, "Testing and Qualification of the Boston Retinal Implant Chip." Poster 3187 at ARVO, May 2006.

D.B. Shire, M. Gingerich, S. Retterer, L. Theogarajan, S. Kelly, M. Markova, M. Raj, S. Cogan, J. Wyatt, J.F. Rizzo , "Design and Fabrication of an Ab Externo Retinal Prosthesis.". ARVO Poster 4177, May 2004.

Acknowledgements:

I would like to thank the Catalyst foundation for supporting this work. Additional support for this work was provided by the Veterans Administration, Boston. I would like to thank Prof. John L. Wyatt, Dr. Joseph Rizzo, Dr. Ralph Jensen, Prof. Marc Baldo and Prof. Carmen Scholz for their guidance and support. Luke Firmansjah, Salil Desai, Mariana Markova, Greg Swider, Milan Raj, Bill Drohan, Kaveh Milanina and Shawn Kelly for their help and suggestion on various aspects of the work.