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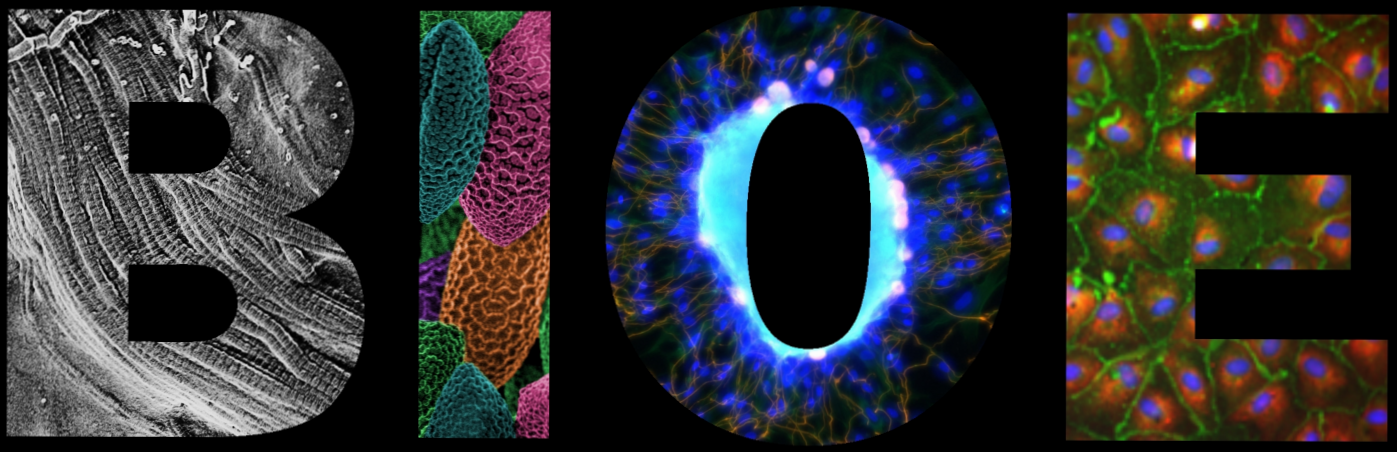
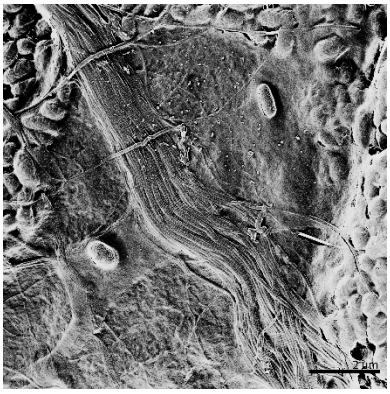
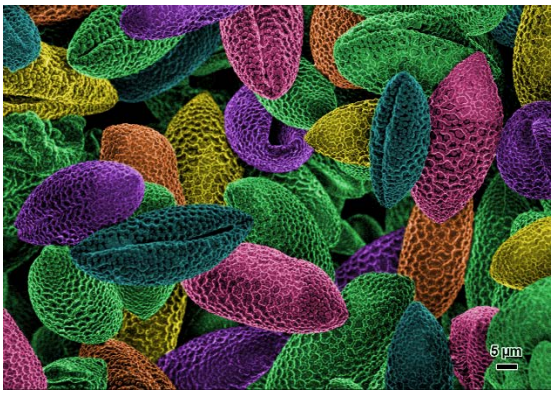


RESEARCH SYMPOSIUM

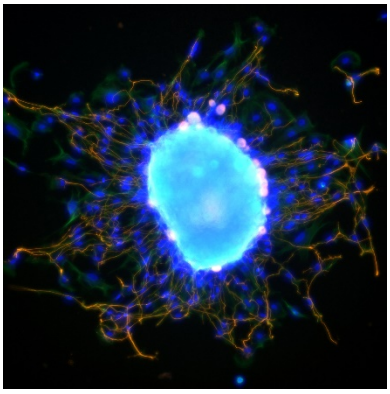
JUNE 20TH, 2018



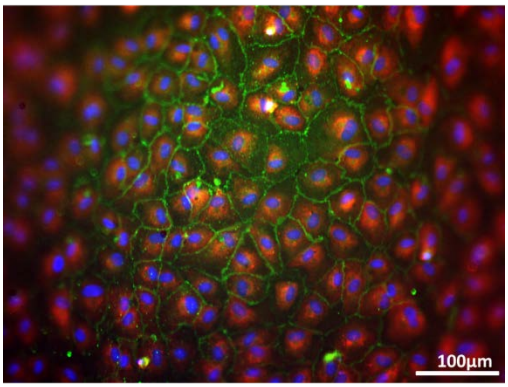
Choroid layer of the eye. Collagen fiber over a melanocyte, surrounded by melanosomes. Submitted by Ebraheim Ismail, PhD Candidate. Advisor: Jeffrey Ruberti



Pollen grains from Lilium bulbiferum spilling off the anther. Submitted by Paige Baldwin, PhD Candidate. Advisor: Srinivas Sridhar



Dissociated dorsal root ganglion neurons from rat. Submitted by Danielle Large, PhD Student. Advisor: Debra Auguste



Fluorescent HUVEC lining in a bioprinted vasculature. Stained for VE-cadherin and nuclei. (V. Lee et al., Biomaterials, 2014) Submitted by Vivian Lee, Post-doctoral fellow. Advisor: Guohao Dai

Cover design by Wen Lee

Schedule of Events

12:00 - 1:00pm **Registration, Poster Setup, and Lunch**

1:00 - 2:00pm **Welcome and Keynote Address**

Welcome
Lee Makowski, Chair of Bioengineering

Keynote Address
Eduardo Sontag, University Distinguished Professor
"Some control theory ideas in systems and synthetic biology"

2:00 - 2:45pm **Poster Session A**

2:45 - 3:30pm **Poster Session B**

3:30 - 4:45pm **Selected Student Presentations**

Zhaoran Zhang, "The attraction of rhythm: How discrete actions merge into a rhythmic pattern"

Judith Piet, "Sciatic neurectomy increases bone mechanosensitivity in aged mice"

Jeff Bouffard, "The RhoGAP SPV-1 acts through CDC-42 to regulate calcium signaling in the C. elegans spermatheca during embryo transits."

Jessica Fitzgerald, "Fabrication and Optical Properties of Dye Labeled SERRS-Encoded Au/Ag Alloy Nanoshells"

Ebraheim Ismail, "On the Elabroation of Fibrillar Collagenous Structures: A View Through the Eye"

4:45 - 5:00pm **Awards and Closing Remarks**

Eduardo Sontag
University Distinguished Professor
Department of Bioengineering
Department of Electrical and Computer Engineering
Northeastern University

Some control theory ideas in systems and synthetic biology

Abstract: Control theory and engineering has long played a major role as a technology enabler, from Watt's flyball governor to the design of sophisticated algorithms for manufacturing, robotics, aerospace guidance, or autonomous automobiles. Powering these engineering achievements is a sophisticated set of mathematical tools that allow one to analyze stability and robustness within the paradigm of nonlinear dynamical systems with controls and observations. Analogously, in the natural world, evolved principles of feedback underlie homeostatic physiological mechanisms, the interactions between the immune system and tumors or infections, and biological navigation at all scales, from bacteria to flies. In this talk, I will discuss some examples of how control theory can help provide systematic approaches toward the construction and analysis of synthetic genetic and enzymatic circuits that might be embedded in bacterial and other delivery systems for applications such as bioremediation, chemical threat detection, or chemotherapy.

Biography: Dr. Eduardo Sontag's major current research interests lie in several areas of control and dynamical systems theory, systems molecular biology, cancer and immunology, and computational biology. He received an undergraduate degree in mathematics from the University of Buenos Aires in 1972, and his Ph.D. at the University of Florida in 1977. From 1977 to 2017, he was at Rutgers, The State University of New Jersey, where he was a Distinguished Professor of Mathematics as well as a Member of the Graduate Faculty of the Department of Computer Science and the Graduate Faculty of the Department of Electrical and Computer Engineering, and a Member of the Rutgers Cancer Institute of NJ. In addition, Dr. Sontag served as the head of the undergraduate Biomathematics Interdisciplinary Major, Director of the Center for Quantitative Biology, and Director of Graduate Studies of the Institute for Quantitative Biomedicine. In January 2018, Dr. Sontag was appointed as a University Distinguished Professor in the Department of Electrical and Computer Engineering and the Department of Bioengineering at Northeastern University.
Sontag has authored over five hundred research papers and monographs and book chapters in the above areas. He is a fellow of IEEE, AMS, SIAM, and the International Federation of Automatic Control. He was awarded the Reid Prize in Mathematics in 2001, the 2002 Bode Prize and the 2011 Control Systems Field Award from the IEEE, the 2002 Board of Trustees Award for Excellence in Research from Rutgers, and the 2005 Teacher/Scholar Award from Rutgers.

Poster Session A

1 Mahsa Sadeghian
3 Max Winkelman
5 Ian Zuzarte
7 Suzanne Stasiak
9 Shravani Kakarla
11 Deepak Agrawal
13 Kamran Poorbahrami
15 Wen Lee
17 Xin Sun
19 Jenifer Winters
21 Sabah Nobakhti
23 Claudia Isern Blasco
25 Seyed Mohammad Siadat
27 Yao Wang
29 Yasmeen Farra
31 Boting Li
33 Anh Phong Tran
35 Danielle Large
37 Kevin Moulton
39 Diana Kim
41 Dongyang Yi
43 Mehrnaz Mojtabavi
45 Miguel Angel
47 Alexander Grath
49 Biel Roig-Solvas

Poster Session B

2 Shijie Yan
4 Ada Vernet Crua
6 Armin Vedadghavami
8 Diana Bernal-Franco
10 Yaoshen Yuan
12 David Medina Cruz
14 Amissi Sadiki
16 Ian Harding
18 Paige Baldwin
20 Taylor Dorsey
22 Sowmya Mannava
24 Tengfei He
26 Vivian Lee
28 Lorena Baranda
30 Arvind Mohan
32 Vineel Kondiboyina
34 Lauren Cole
36 Samuel Polio
38 Peter Bartosik
40 Carolyn Lee-Parsons
42 Shikhar Mehta
44 Donald M. OMalley
46 Rachel Horenstein
48 Zafer Dogan

Mathematical modelling of enzymatic modification-based logic gates

Deepak K Agrawal[1], Sagar D Khare[2], *Eduardo D Sontag*[1,3]

[1]Department of Electrical and Computer Engineering, Northeastern University, Boston, MA [2]Department of Chemistry and Chemical Biology, Rutgers University, Piscataway, NJ
[3]Department of Bioengineering, Northeastern University, Boston, MA

Abstract
Cell continuously responds to its environment by producing and degrading protein molecules that play a significant role in metabolic reactions. These reactions are often performed by transcriptional networks that use logical operations, determining the rate of protein production and how they are used downstream to control the production of other proteins. This resulted in several simple and complex synthetic biological circuits using transcriptional networks to demonstrate proof-of-principle for biological computation. However, transcriptional base circuits often operate at a slow time scale that ranges from hours to days thereby limiting the construction of more complex biological devices. To achieve a faster computation that is not rate-limited by transcription and translation reactions, an alternative paradigm is the design of circuits utilising post-translational modification mediated by enzymes.
Here, we present mathematical models of protease enzyme-based biological logic gates that use post translated synthetic proteins. Because we used post-translationally responsive and controllable enzyme, these logic gates operate at a time scale of minutes to hours. For a proof-of-principle, we design and model OR and XOR gates that utilise quenched fluorescent protein system and can be activated upon cleavage by Tobacco Etch Virus (TEV) protease as the output. Theoretical analysis indicates all the elements of the gates can be built using simple biochemical reactions. From the reactions, we build ordinary differential equation (ODE) models that are analysed and numerically integrated using parameters fitted from experiments or available in the literature. We investigate the operation of these gates through analysing the stability of equilibria and optimising their response considering a practical set of parameters. Using this, we have shown how these gates can be implemented. These new architectures may allow researchers to mimic the operation of complex transcriptional pathways.

Keywords: logic gates, enzyme, protease, mathematical modelling.

Targeted PARP inhibitor nanotherapy for breast cancer treatment

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[1]Department of Bioengineering, Northeastern University, Boston, MA

[2]Department of Physics, Northeastern University, Boston, MA

[3]Department of Health Sciences, Northeastern University, Boston, MA

[4]Department of Pharmacology and Toxicology, Michigan State University, East Lansing, MI

Abstract
PARP inhibitors, such as Talazoparib, selectively target cancerous cells that exhibit defective DNA repair pathways. However, these oral drugs are generally well tolerated alone and must be combined with DNA damaging agents to treat tumors without defective DNA repair, resulting in poor tolerability. Nanoparticle formulations may address this by bypassing the first-pass metabolism of oral drugs while preferentially accumulating in tumors through leaky tumor vasculature. Nanoparticles may also be actively targeted to tumors by conjugating moieties, such as antibodies, that recognize overexpressed markers on the tumor cells to enhance delivery to the disease site.

Here we studied the pharmacokinetics and pharmacodynamics of NanoTLZ, its utility as a monotherapy in a BRCA1 deficient model, and its ability to sensitize Talazoparib insensitive cells to radiation *in vitro*. We further describe development of fluorescently-labeled, targeted NanoTLZ (T-NanoTLZ) and *in vivo* efficacy in combination with radiation therapy in a PARP inhibitor-insensitive model. Pharmacodynamics indicated PAR suppression in tumors within 30 minutes with levels remaining significantly lower than control levels up to 72 hours after a single treatment. Characterization after the addition of a fluorescent probe and anti-EpCAM indicated no significant changes in physicochemical properties. T-NanoTLZ showed higher cell uptake than NanoTLZ as assayed by confocal microscopy and flow cytometry. NanoTLZ in combination with radiation proved to be an effective combination *in vitro* though this efficacy did not translate with T-NanoTLZ *in vivo*. NanoTLZ as a monotherapy was more effective and less toxic than free Talazoparib in a model that is inherently sensitive to the drug.

Keywords: nanomedicine, targeted therapy, cancer treatment

The Synthesis and Characterization of Bimetallic Nanoparticles Made by Bacteria for Biomedical Applications

Lorena Baranda Pellejero[1,2], David Medina Cruz[1], *Thomas J. Webster*[1]

[1] Department of Chemical Engineering, Northeastern University, Boston, MA

[2] Department of Chemical Engineering, Universitat Rovira I Virgili (URV), Tarragona, Spain

Abstract

Bimetallic nanoparticles show novel electronic and optical properties compared to their monometallic counterparts, presenting multiple applications in catalysis and electrochemistry. However, the potential of bimetallic nanoparticles as therapeutic agents, such as antimicrobial agents, has been barely studied. This lack of knowledge together with the urgent need of alternatives to antibiotics for treating bacterial infections proves the relevance of this study.

Physiochemical protocols are the common routes to produce these bimetallic nanoparticles, however, they are full of drawbacks such as the production of toxic by-products and need of functionalization. Thus, a green synthetic approach based on the use of living bacteria for the synthesis of CdSe and ZnSe bimetallic nanoparticles is proposed.

Bacteria are cultured in media that is inoculated with both sodium selenite (Na_2SeO_3) and cadmium chloride (CdCl2)/ zinc nitrate (ZnNO3) as metallic precursors for the nanoparticles. Using a detoxification process, bacteria can reduce metallic salt ions dissolved in elemental metallic nanoparticles. They can later be purified by disruption of the cell membranes.

TEM characterization shows the intracellular formation of spherical bimetallic nanoparticles with a rather broad nanoparticle size distribution. An important feature of these nanoparticles is the presence of a natural coating made of biomolecules coming from the bacteria, which makes them biocompatible. The composition of this coating is studied by EDX. Moreover, the reaction is monitored by absorbance, showing the impact of the presence of different metallic ions in the bacterial growth. In a near future, the antibacterial properties of these nanoparticles against Gram-positive and Gram-negative bacteria together with their cytotoxicity will be explored.

To sum up, the present study involves the synthesis of bacteria-mediated bimetallic nanoparticles as one possible candidate for fighting antibiotic resistant bacterial strains. Furthermore, this green approach has avoided the common disadvantages of tradition synthetic routes.

Keywords: Green synthesis, Bacteriogenic Synthesis, Bimetallic Nanoparticles, Antibacterial Agents.

Upconverting Nanoparticles for in vivo Flow Cytometry

Peter Bartosik, Jessica Fitzgerald, *Mark Niedre*

Department of Bioengineering, Northeastern University, Boston, MA

Abstract

Early detection and enumeration of rare circulating tumor cells in the blood stream is necessary to identify cancer metastasis at an early stage. Common fluorescent labels have previously been used to optically detect circulating tumor cells using a custom-built in vivo flow cytometry system, with sufficient sensitivity. Although sufficient at detecting brightly labeled cells, dimly labeled cells can go undetected due to the presence of background tissue autofluorescence which may mask the fluorescence signal from weakly labeled cells. Upconverting nanoparticles are a unique type of fluorescent label which emit light at a shorter wavelength than the light used to excite them. The unique phenomenon of photon upconversion increases the spectral separation between the excitation and emission light by several hundred nanometers. This greater spectral separation leads to an improved effectiveness at filtering out background autofluorescence and thereby increasing the sensitivity of the in vivo flow cytometry system at detecting labeled cells. The goal of this project will be to assess the biocompatibility and feasibility of using lanthanide-doped NaYF4 upconverting nanoparticles to effectively label, detect and enumerate circulating tumor cells in the blood stream of a mouse. MDA-MB-231 human breast andenocarcinoma cells will be labeled with upconverting nanoparticles and injected into the blood stream of a mouse. A custom-built in vivo flow cytometry system, consisting of a 980 nm excitation laser, shortpass dichroic mirror and emission filter and a photomultiplier tube detector, will be used to detect the presence of any labeled cells in the ventral tail artery.

Keywords: biophotonics, nanoparticles, fluorescence

Paving the way for metabollic engineering of anticancer alkaloids of *Catharanthus roseus* by characterizing protein families that mediate the action of Gibberellin, a hormone that regulates plant developmental processes

Diana Bernal-Franco[1,2], Madison Belyea[2], Deborah Pano[2], Erin Cram[1], *Carolyn Lee-Parsons*[1,2]

[1]Department of Bioengineering, Northeastern University, Boston, MA

[2]Department of Chemical Engineering, Northeastern University, Boston, MA

Abstract

As part of its defense response, *Catharanthus roseus*, commonly referred to as the Madagascar periwinkle, produces valuable alkaloids such as vinblastine and vincristine, which are used as cancer chemotherapeutics. *C. roseus*, however, minimizes the production of these defense chemicals because, as all plants do, *C. roseus* optimizes its energy and resources by returning to growth once the attack is over. In this study we characterize molecular mechanisms that regulate growth developmental processes of *C. roseus*, to lay the foundation needed to engineer *C. roseus* secondary metabolism to increase the output of the valuable anticancer alkaloids. Gibberellins (GA) are plant hormones that regulate processes such as stem elongation, germination, dormancy and flowering. DELLA proteins mediate GA action by targeting a wealth of other proteins and transcription factors. Some of the targets of DELLA are proteins from the Indeterminate Domain (IDD) family of proteins. In this study we identified all the members of the DELLA and IDD protein families in *C. roseus* using bioinformatic analyses on *C. roseus* genomic assembly. Then we cloned most of the identified proteins using standard molecular biology cloning strategies, and we characterized the interaction between proteins of these families using yeast-2-hybrid assays, a widely used technique to determine if two proteins interact using yeasts. We found that IDD and DELLA families comprise several proteins in *C. roseus*, and we identified IDD proteins that interact with DELLA proteins. These results improve our understanding of *C. roseus*' developmental processes, which is critical in developing an optimal production of *C. roseus* valuable alkaloids.

Keywords: Matabollic engineering, *Catharanthus roseus*, vinblastine, vincristine, anti-cancer.

Engineering plant metabolism for the production of pharmaceutical compounds

Lauren Cole[1], Samuel Breselge[2], Diana Bernal-Franco[3], Erin Cram[1,2], *Carolyn Lee-Parsons*[1,3,4]

[1]Department of Bioengineering, Northeastern University, Boston, MA

[2]Department of Biology, Northeastern University, Boston, MA

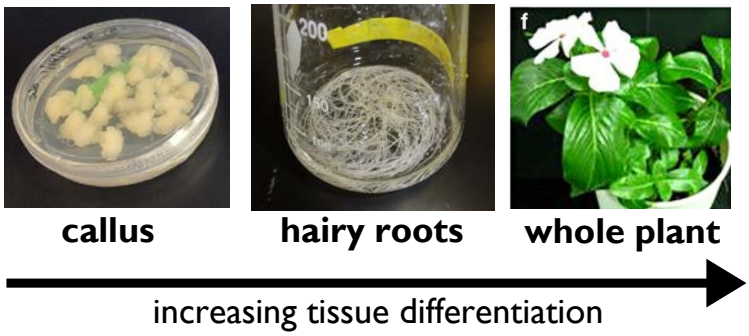
[3]Department of Chemical Engineering, Northeastern University, Boston, MA

[4]Department of Chemistry & Chemical Biology, Northeastern University, Boston, MA

Abstract

Plants are the source of many useful natural products or specialized metabolites, including pharmaceuticals, nutraceuticals, flavors, pigments, and fragrances used in the pharmaceutical, food, and cosmetic industries. Our research: i) investigates the regulation of the biosynthesis of pharmaceutical compounds from medicinal plants, and ii) develops and engineers cell and tissue cultures derived from these plants to overproduce these compounds. For example, we are investigating the *Catharanthus roseus* plant, which is the source of two costly alkaloid compounds used in anti-cancer therapies. Using hairy root cultures as a platform for investigation of alkaloid biosynthesis, we use genetic engineering techniques to alter the expression of key genes and then study the effects of those changes to better understand the regulation of the pathway. The vision of our research is to increase production in order to reduce the cost and meet the demand for these critical drugs.

Keywords: medicinal plants, specialized metabolism, plant tissue cultures, metabolic engineering



The RhoGAP SPV-1 acts through CDC-42 to regulate calcium signaling in the *C. elegans* spermatheca during embryo transits.

Jeff Bouffard[1], Alyssa Cecchetelli[2], Coleman Clifford[2], Kriti Sethi[3], Ronen Zaidel-Bar[3,4], *Erin J. Cram[2]*

[1]Department of Bioengineering, Northeastern University, Boston, MA
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[3]Mechanobiology Institute, National University of Singapore, Singapore
[4]Department of Cell and Developmental Biology, Sackler Faculty of Medicine, Tel-Aviv University, Israel

Keywords: actomyosin contractility, calcium signaling, RHO-1/RhoA, CDC-42/Cdc42

Abstract: Biological tubes are essential components of many animal bodies. Proper regulation of contractility in these tubes is vital for many life processes. The spermatheca, a 28-cell contractile tube in the nematode *C. elegans* reproductive system, provides a powerful model for studying tubes in living, intact, adult animals. During embryo transits spermathecae stretch significantly with oocyte entry, remain distended for a regulated time coincident with eggshell formation, and finally initiate coordinated cellular contractions, expelling the egg. Spermathecal contractility is controlled by calcium and RHO-1/RhoA signaling. These two pathways, featuring highly conserved proteins, control actomyosin contractility in many other biological contexts, suggesting mechanisms at work in the spermatheca potentially represent fundamental biological responses to deformations of biological tubes.

The RhoGAP SPV-1 was previously shown to regulate spermathecal contractility via RHO-1/RhoA. *spv-1* mutant spermathecae contract immediately upon oocyte entry, generating faster embryo transits and misshapen eggs. Although spermathecal contractions require calcium, SPV-1's role in calcium signaling was unknown. We examined this using time-lapse microscopy of embryo transits expressing the calcium sensor GCaMP. We found *spv-1* mutants exhibit rapid onset of calcium signaling upon oocyte entry, and elevated calcium levels throughout embryo transits. SPV-1 has RhoGAP activity toward RHO-1/RhoA and CDC-42/Cdc42. We found constitutively active (CA) RHO-1/RhoA alters embryo transit timing without recapitulating mutant calcium signaling, while CA CDC-42/Cdc42 recapitulates mutant calcium signaling aspects without altering embryo transit timing. This work uncovered previously unknown roles for SPV-1 and CDC-42/Cdc42 as calcium signaling modulators. Ongoing work seeks effectors downstream of CDC-42/Cdc42 that regulate calcium signaling.

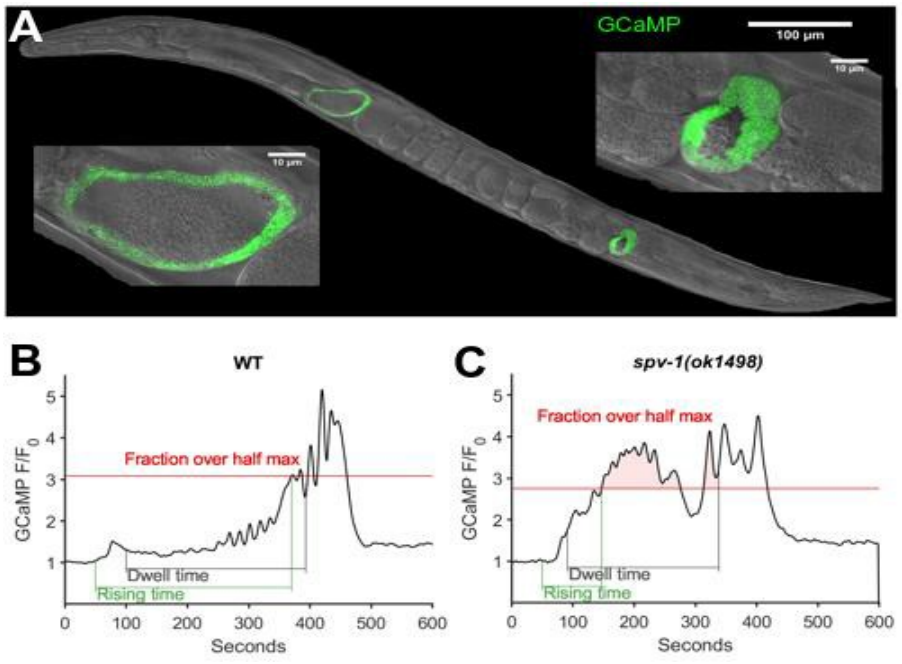

Figure legend: (A) A *C. elegans* nematode with spermathecae expressing GCaMP. The left spermatheca contains an embryo, the right spermatheca is empty. (B) Calcium signaling during a wildtype embryo transit. Embryo enters at 50s, exits at 530s.(C) Calcium signaling during a *spv-1* mutant embryo transit. Embryo enters at 50s, exits at 498s.

Comparison of oxygen saturation estimation methods for low-cost pulse oximeter prototypes in transmission and reflection modes

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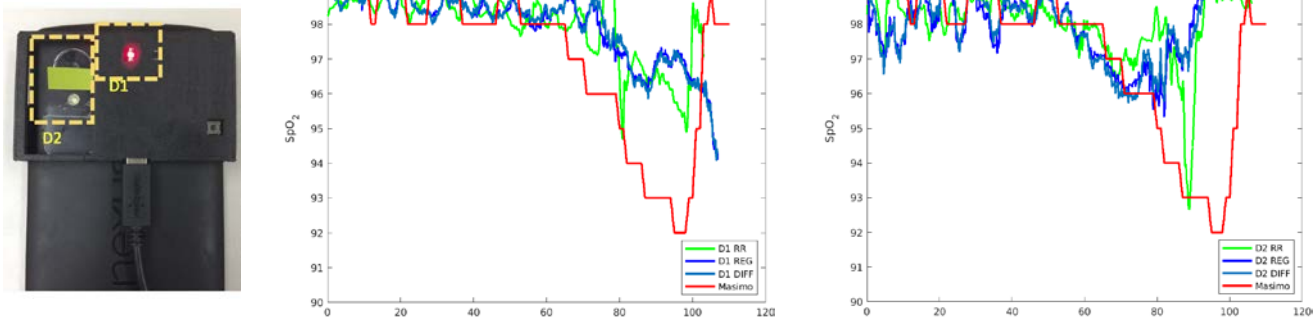
[2]Athinoula A. Martinos Center for Biomedical Imaging, MGH, 149 13th Street, Charlestown, MA 02129

Abstract

Pulse oximeter (PO) has been widely used to measure the level of peripheral oxygen saturation (SpO_2). Recently, there has been an increased interest in designing low-cost POs for resource-poor regions. Due to the dramatically reduced cost, new POs typically produce less robust raw optical signals, thus it is important to revisit the PO signal processing algorithms. The conventional methods of estimating SpO_2 rely heavily on estimating the pulsatile and non-pulsatile components of the data. It is based on the following basic principle: Blood absorbs more light at (R)ed-wavelengths and less light at infrared(IR) wavelengths, and only the arterial blood pulsate in the tissue contributing to the pulsation of emergent light intensity. Hence, it possible to measure changes in SpO_2 using optical means. In Fig. 1a, our recently developed PO devices are shown; one gathering data in reflection mode (D1), and one gathering data in transmission mode (D2). In this study, we compared three different SpO_2 estimation methods; 1) RR, which uses straightforward ratio-of-ratio definition, 2) REG, which uses the normalized derivatives of R and IR data to compute the slope of a regression line (known to correlate with SpO_2), and 3) DIFF: where the mean of the absolute derivative of the data are used to produce the pulsatile measurement. Here, we report a comparison of three methods with data acquired from D1 and D2 and compared against Masimo Rad87 PO as a reference device. Note that all three methods reveal the drop in SpO_2. However, differences in terms of stability are significant compared with the conventional methods. Therefore, further study of these techniques is necessary to understand the limitations of low-cost POs to achieve clinical grade PO stability.

Keywords: Pulse oximeter, optical devices, spectroscopy, oxygen saturation estimation.



a) b) c)

Figure 1 a) Pictures of our prototype devices: a paper filter covering half of the field of view of the mobile phone camera (D2), and a Bluetooth wireless oximeter board (D1), b) Comparison of estimation methods of SpO_2 during a breath holding experiment b) reflection mode, c) transmission mode.

Engineer 3D Brain Microvascular Network Directly from Human Pluripotent Stem Cells

Taylor B. Dorsey[1], *Guohao Dai*[1]

[1]Department of Bioengineering, Northeastern University, Boston, MA

The overall goal of this project is to create 3D brain microvascular networks for *in vitro* blood brain barrier (BBB) tissue models. The BBB is comprised of brain microvasculature endothelial cells (BMECs) known for their tight junctions and barrier functions. Current *in vitro* BBB models are largely simplistic in nature and are unable to capture the inherent *in vivo* tissue complexity which include 3D environment and fluid flow through vasculature. Cell source for tissue models is also a concern. To overcome these limitations, human pluripotent stem cells (hPSCs) derived BMECs offer an alternative. Previously, stem cells have been successfully differentiated toward vascular ECs expressing tight junctions, but their ability to form 3D vascular network is still limited. Here, we have successfully developed a method to directly differentiate hPSCs into BMECs while simultaneously creating 3D vascular networks without complicated steps of cell differentiation, isolation and reconstruction. In short, hESCs carrying the VE-Cadherin promoter driven mOrange reporter were seeded into 3D fibrin gels and differentiated towards the vascular lineage. We observed spontaneous formation of vascular networks (**Figure 1A**) and open lumen structures (**Figure 1B**). The vasculature stained positive for vascular marker, CD31, and BMEC tight junction protein, ZO-1 (**Figure 1C**). Overall, we have developed a method to create BMEC vascular networks in 3D directly from hPSCs and our observations suggest this network can be perfused. Ongoing studies include evaluating our BMEC differentiation protocol within a microfluidic device to introduce interstitial flow and ultimately achieve network perfusability. Overall, hPSC derived 3D perfusable BMEC networks will improve BBB tissue models for personalized medicine, drug screening and research into neurovascular diseases.

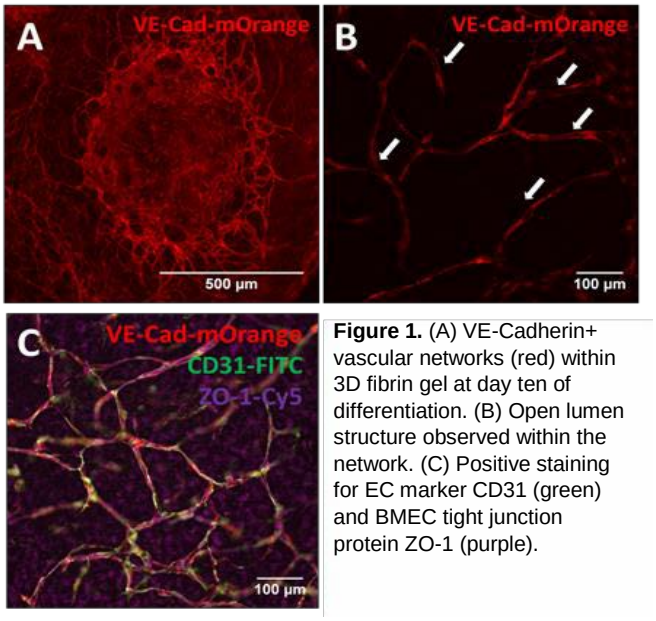


Figure 1. (A) VE-Cadherin+ vascular networks (red) within 3D fibrin gel at day ten of differentiation. (B) Open lumen structure observed within the network. (C) Positive staining for EC marker CD31 (green) and BMEC tight junction protein ZO-1 (purple).

Keywords: Pluripotent stem cell differentiation, 3D tissue models, vascular engineering

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Fabrication and Optical Properties of Dye Labeled SERRS-Encoded Au/Ag Alloy Nanoshells

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Abstract

Since Fleischmann first discovered the phenomenon of enhanced Raman signals from adsorbed pyridine on roughened Ag surfaces in 1974, surface-enhanced Raman scattering (SERS) has been used as an ultrasensitive vibrational spectroscopic technique to detect molecules on or near the surface of plasmonic nanostructures, greatly extending the role of standard Raman spectroscopy. More recently, this technique has been used to design novel nanoprobes or "SERS tags" that combine metallic nanostructures and specific organic Raman reporter molecules. In this paper, we report the fabrication, optical properties and SERS efficiency of a new family of SERS tags comprised of silica nanoparticles ca. 150 nm in diameter with an $Au_{0.5}Ag_{0.5}$ alloy shell ca. 25 nm in thickness.

Raman reporter dye molecules were chemically and/or physically adsorbed onto the surface of the SiO_2@$Au_{0.5}Ag_{0.5}$ nanoparticles which were then coated with an Ag layer. Compared to the monometallic Au and Ag nanoshells with same diameter core and shell thickness, the Au/Ag alloys show an excellent enhancement in Raman intensities. Binding studies with polymer microspheres are also described as a demonstration of the potential of these bright dye-labeled SERRS-encoded tags for high-throughput screening flows. Binding studies with polymer microspheres are also described. These microspheres are commonly used as standards and controls in flow cytometry measurements, as well as solid supports for multiplexed molecular measurements. The combination of SERS tags with flow cytometry for analyzing blood and other cell types in clinical samples provides improved multiplexing capability, offering a significant advantage over conventional flow cytometry methods. The bimetallic SERS tags, which present a stronger enhancement in Raman intensities compared to the monometallic tags can be potentially used for multiplex characterization of small molecule metabolites in biological systems.

Keywords: Core-shell nanoparticles, SERRS encoded, dye labeled, optical properties

Aortic Biomechanics in Aging Female Mice

Yasmeen Farra[1], *Chiara Bellini*[1]

[1]Department of Bioengineering, Northeastern University, Boston, MA

Abstract

Cardiovascular disease is the leading cause of death worldwide, and cardiovascular health is strongly linked to overall health and longevity. Aging significantly increases the risk of developing cardiovascular complications, although the risk factors differ between men and women. Due to the mechanical nature of vascular function, comprehensive biomechanical phenotyping of the vasculature is needed to fully describe the sex-dependent mechanisms underlying cardiovascular aging.

C57BL/6 female mice aged to 80-88 weeks were used as an animal model of aging. The ascending and descending portions of the thoracic aorta were characterized using a custom biaxial device. The *in-vivo* loading conditions of the proximal aorta were replicated through combined cyclic pressurization and axial extension. The experimental data were used to estimate key parameters of tissue mechanics.

Average values for outer diameter, wall thickness, and *in-vivo* axial stretch in the aortic tissues were 1359 μm, 124 μm, and 1.44, respectively in the ascending thoracic aorta, and 1028 μm, 99 μm, and 1.41 in the descending thoracic aorta. These results indicate a decrease in the axial stretch in the aged female mouse aorta in comparison with that of a healthy, young mouse. It has been reported that axial stretch maintained along the aorta *in-vivo* is a strong indicator of vascular health, while stiffening and reduction of axial stretch is exhibited with disease. Therefore, the results of this work suggest that aging is correlated with degenerated vascular mechanics.

Keywords: Aging, Aorta, Biaxial testing, Biomechanics, Cardiovascular

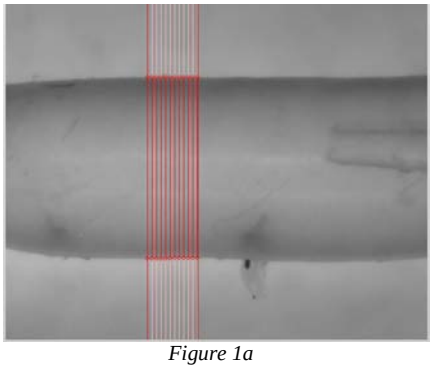

Figure 1a

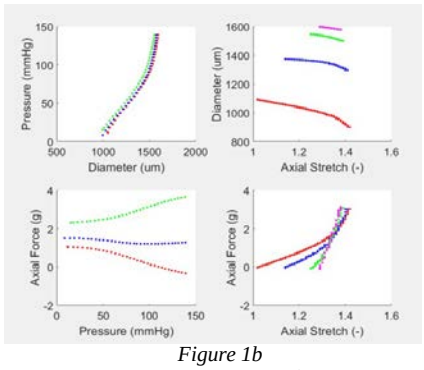

Figure 1b

Figure 1: Results of Pressure vs. Diameter and Force vs. Length mechanical testing of a descending thoracic aorta (DTA) of mouse B3. *1a* shows the pressureized DTA in testing. *1b* exhibits the resulting plots (starting from top left, clockwise) pressure vs. diameter; diameter vs. stretch; force vs. stretch; and force vs. pressure.

Directly reprogramming human dermal fibroblasts into functional endothelial cells via the overexpression of ETV2 and Sox17

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Abstract

Generating functional endothelial cells (ECs) is valuable for cardiovascular regenerative medicine and tissue engineering applications. Current methods to create ECs are limited and inefficient, and genetic engineering shows promise in circumventing these challenges. Fibroblasts are an easily obtainable, abundant cell type. Therefore, we propose to directly reprogram fibroblasts into patient-specific functional ECs (rECs) by the overexpression of ETV2 and Sox17, transcription factors that are critical in the development of vasculature. Thus, patient-specific rECs can be generated in high quantities for use in vascular tissue engineering and regeneration.

Adult human fibroblasts were transduced with lentiviral vectors coding for ETV2 and Sox17. At 13 days after their induction, $CD31^+$ rECs were isolated using magnetic-activated cell sorting and cultured further for molecular and functional assays. Expression of EC-specific markers were evaluated by qRT-PCR and immunofluorescent staining. Low-density lipoprotein (LDL) uptake, a hallmark of ECs, was also evaluated. Human umbilical vein endothelial cells (HUVECs) were used as a positive control, while fibroblasts were used as a negative control.

The overexpression of ETV2 and Sox17 greatly upregulated several endothelial-specific markers, including VE-cadherin, FLT1, and CD31. The rECs were also immunostained for these proteins, which showed an intricate network of VE-cadherin and CD31 that resembled HUVECs. rECs were capable of uptaking LDL to the same extent as HUVECs.

In summary, this data demonstrates that the simultaneous induction of ETV2 and Sox17 is able to drive the direct reprograming of fibroblasts into endothelial-like cells capable of performing select endothelial functions. More functionality assays will be conducted to further evaluate how well they are able to emulate typical ECs. In addition, a defined methodology will be developed in order to optimize the reprogramming process.

Keywords: Direct reprogramming, endothelial cells, genetic engineering

Characterization of Elite Adolescent Sports Participation on Increased Risk for Developing Cam Morphology

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Abstract

Cam-type femoroacetabular impingement (FAI) is defined as an abnormal bony growth at the femoral head, characterized by an aspherical shape. This atypical morphology is prevalent in adults who participated in specific sports (hockey, basketball, soccer) at an elite level during adolescence. Previous studies have shown that cam-morphology develops in athletes before skeletal maturity, but the etiology and mechanism remain unknown. We hypothesize that altered hip joint loads associated with certain sports cause a mechanoadaptation response that leads to cam-morphology. To address this hypothesis, we recruited elite male adolescent athletes (ice hockey, basketball, and dance) and adolescents without elite participation in a sport.

The use of Inertial Measurement Units (Opal IMUs, APDM, Inc.) to measure hip angles was validated in a gait lab with standard motion capture techniques. The methodology was applied to pervasively measure hip motion during sports practice (elite athletes) and during typical daily activities (non-elite athletes). The IMUs were secured on the thighs and the sacrum. The relative acceleration magnitude and orientation between the thigh and pelvis were determined using quaternion operations.

Results indicate that elite athletes had significantly larger magnitudes and variabilities in relative acceleration magnitude in comparison to elite dancers and controls. In addition, basketball players had significantly larger variabilities in relative acceleration magnitudes in comparison to ice hockey players. Preliminary orientation results indicate that hockey players are in flexion for the majority of practice and use a smaller range of motion compared to dancers or controls. Monitoring hip motions in an athlete's natural environment provides a more complete view of hip motion history that cannot be obtained in laboratory settings. Capturing the full extent of hip motion is important for determining etiology of cam-morphology in specific sports.

Keywords: cam-type femoroacetabular impingement, IMUs, pervasive motion capture

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The Efficient And Cost-Effective Removal Of Heavy Metal Ions From Water Using Nanoparticles And Both Living Bacteria And Bacterial Biomass

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Abstract

Industrial processes, agricultural activities, household, commercial and medical products, as well as sediments, are potential sources of heavy metals such as mercury (Hg), cadmium (Cd) and chromium (Cr). They are considered persistent, bioaccumulative toxins. For instance, mercury persists in the environment by cycling back and forth between the air and soil surface, all the while changing chemical forms. These elements will never be removed from the environment; they will be just moved to other locations and eventually buried under sediments.

Many approaches have been used to efficiently remove them from the environment. Nanotechnology has risen as one of these potential methodologies, using nanostructures to bind heavy metal ions to them. Besides, nanotechnology can be combined with living organisms is a chance to enhance the removal of metallic ions from the environment. In this research, both bacterial biomass and living bacterial were used to remove mercury, cadmium, and chromium from contaminated water, through accumulation within the biomass or a detoxification processes generating non-toxic nanomaterials, respectively.

Therefore, here we present an efficient method to remove heavy metals from water using bacterial biomass and living bacteria, with no production of toxic by-products, in a cost-effective and environmentally-friendly process.

Keywords: Heavy Metals, Bacteria, Green-Synthesis, Nanoparticles

On the Elabroation of Fibrillar Collagenous Structures:
A View Through the Eye

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Abstract

The role of collagen in tissues and its utilization in research has been of great interest in the recent years. Yet the understanding of how collagen is organized still eludes the scientific community. Collagen being the main load-bearing protein, our lab's overarching hypothesis is that extensional strain is a fundamental factor in the alignment of collagen structures by lowing the energetic barrier for assembly in the direction of stretch. A necessary factor influencing strain-induced alignment is the molecular crowding of collagen. This thesis seeks to test that human corneal fibroblasts (HCF) crowd collagen monomer juxtacellularly such that cell-achievable extensional strain can promote organized fibril elaboration via flow induced crystallization. Molecular crowding occurs intracellularly for the formation of actin, microtubules, and nucleic acids.

HCF are cultured *in vitro* in the presence of ascorbic acid for 4-weeks to develop a cornea-like construct. Quick-freeze/deep-etch electron microscopy (QFDE) is utilized to show that molecular crowding of collagen is occurring juxtacellularly, and to calculate the concentration of the crowded region.

In conventional TEM "void" regions are observed between fibroblasts and the collagenous matrix surrounding them; but it is indiscernible what molecules may exist in that region. Using the QFDE we anticipate finding a highly dense area of collagen monomer, hyaluronic acid, proteoglycans, and other molecules. In previous experiments a collagen concentration of 15 mg/ml was enough to allow for flow induced crystallization. We expect to calculate a similar concentration in the juxtacellular region. Completion of this work will provide crucial insight into a basic mechanism influencing growth and formation of collagenous tissues. Future paths would include *in vivo* analysis during development for evidence of crowding and to test *in vitro* constructs with various macromolecules, modelling *in vivo* environments.

Keywords: Human Corneal Fibroblasts, Collagen, Macromolecular Crowding, Quick-Freeze/Deep-Etch, TEM

A 3D Printing Approach to Extensional Flow-Induced Crystallization of Type I Collagen

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Abstract

Collagenous tissues consist of organized, hierarchical structures occurring from the nanoscale up to the whole tissue level. However, full alignment of lab-engineered collagenous tissue from the nanoscale level up has not yet been achieved. Utilizing a 3D printing approach, we are scaling up extensional flow-induced crystallization of concentrated collagen monomers to efficiently create highly aligned Type I collagen structures. Using parameters from previous research, a formula was derived to generate a model of a 3D printing nozzle. Computational fluid dynamics software was used to generate the model with the required extensional strain rate and flow rate. A syringe-nozzle design, allowing for direct implementation of the design into a syringe-pump, was created in SolidWorks. Model simulations demonstrate the desired extensional flow pattern along the length. Fluid particles displayed a linear relationship between their velocity and the hyperbolic length, implying a constant extensional strain rate (~0.7024 s^{-1}). Temperature simulations show that heat exchange (relevant to collagen polymerization) is limited to small increases in temperature (~1-3°C) of the bio-ink due to the relatively high flow rate. Hence, the incoming bio-ink temperature is of greater significance. In conclusion, a testable model for 3D printing highly aligned monomeric collagen has been scaled up from previous work, based on the application of pure extensional strain. This research provides a method for collagenous substrate manufacturing with applications in repair and replacement of deteriorated tissue such as injured/diseased tendon, cornea and extracellular matrices. Current studies are undergoing: concentration of bovine Type I monomeric collagen via dialysis and turbidity assays to determine the conditions under which monomeric Type I collagen polymerizes to generate a suitable bio-ink.

Keywords: Type I Collagen; 3D Printing; Tissue Engineering

Functional Characterization of Sox17-Mediated Endothelial Cells

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Abstract

Arteries and veins not only display clear anatomical differences but also exhibit distinct molecular profiles. Sox17 is a transcriptional regulator that is known for its role in endoderm, cardiac, and hematopoietic differentiation as well as contributing to arterial differentiation in a developing embryo. Its functional role to mature arterial vessel maintenance is less well understood.

To investigate, we developed a doxycycline-inducible system of the Sox17 gene. Transduction and over-expression in human umbilical venous endothelial cells (HUVECs) with Sox17 leads to reconstitution of all the known arterial markers, suggesting Sox17 is a key regulator of adult arterial EC phenotypes. Importantly, Sox17 induces the expression of multiple families of molecules (Notch, Ephrin, Connexins, PDGF) that may confer signals from ECs to smooth muscle cells (SMCs) to regulate SMC phenotypes in blood vessels. Future studies involve direct co-culture of Sox17-HUVECs and SMCs in static and flow conditions.

A potential intercellular effect by Sox17-mediated "arterial" ECs on SMCs and other supporting cells can have profound impact in the therapeutic arena. Currently, saphenous veins grafts (SVGs) along with internal thoracic artery grafts (ITAGs) are frequently used in coronary artery surgeries. However, SVGs suffer higher failure rates than ITAGs, i.e. 50% SVG failure after 10 years with half of the remaining grafts suffering some type of occlusion. A tissue-engineered vessel composed of cells better adapted molecularly and phenotypically towards arterial physiological conditions can not only become a more abundant graft source but also potentially circumvent the patency issue.

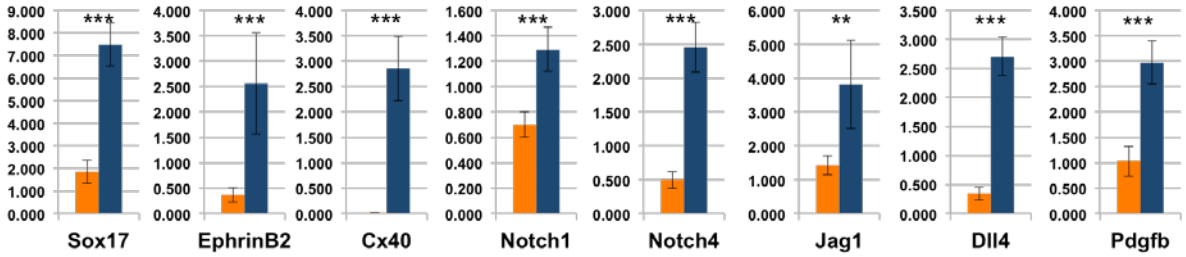

Figure 1. Gene expression levels of HUVECs transduced with Sox17 lentivirus and activated with 200ng/mL of doxycycline for two days. Doxycycline-treated HUVECs are compared to that of non-doxycycline-treated. GAPDH served as endogenous control. n=3, Student's *t*-test, **P*<0.05, ***P*<0.01, ****P*<0.001.

Keywords: arteriovenous, Sox17, endothelial cells, smooth muscle cells

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Targeted Drug Delivery to Combat Chemotherapy-Induced Peripheral Neuropathy

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Abstract

Chemotherapy-Induced Peripheral Neuropathy (CIPN) is a painful and dose-limiting side effect of commonly administered chemotherapeutics. CIPN is known to present in distal nerve endings first, often designated as a "stocking-and-glove" distribution. As the clinical incidence of CIPN is up to 90%, the early termination of chemotherapy and/ or low quality of life are consequences faced by many cancer patients. This matter is of increasing significance, as over a million patients survive cancer in the United States annually and upwards of 15 million new cases of cancer are expected by 2020. Therefore, there is an urgent, unmet need to engineer therapeutics that prevent or attenuate symptoms of CIPN. Evidence of damage, as well as dysfunction, within dorsal root ganglia (DRG) neurons of the peripheral nervous system has been noted during the onset of CIPN symptoms. Sensory receptors unique to DRG peripheral neurons, such as the transient receptor potential villanoid 1 (TRPV1), have also been implicated in the sensory pathway of neuropathic pain. Antagonists of the TRPV1 receptor have shown promise *in vivo* in reduction of pain severity. Further, the reactive oxygen species scavenger TEMPOL and the calpain inhibitor acetyl-calpastatin have demonstrated promise in resolving symptoms of peripheral neuropathy and efficacy against motor neuron death from neurodegenerative diseases *in vivo,* respectively. Thus, we propose a pain-attenuating liposome (PAL) for TRPV-mediated delivery of TEMPOL and acetyl-calpastatin to peripheral neurons. Preliminary experimentation with non-functionalized fluorescent liposomes composed of DOPC-DiD-DSPE-PEG-COOH (94.8:0.2:5 mol%) have demonstrated endocytosis by intact DRGs. Future work aims to synthesize, characterize, and evaluate the efficacy of a TRPV1-targeted PAL for the treatment of CIPN in breast cancer tumor model.

Keywords: drug delivery, chemotherapy-induced peripheral neuropathy, targeted therapy

Effect of Exercise on Bone Health in Kids Aged 8-9 Years

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Abstract
Obesity has reached epidemic proportions around the world. One in every six children in the United States is obese. It has been observed in various studies that when adjusted for weight, obese children have lower bone mineral content (BMC) and bone mineral density (BMD), which may explain their high rates of fracture. BMD is an areal estimate and does not take into account the effect bone thickness. Bone mineral apparent density (BMAD=BMC/Area$^{1.5}$) is a volumetric estimate and has been recommended for assessing bone density in children.

The objective of this study was to evaluate the effect of a 9-month physical activity intervention on BMC, bone area, and BMAD of children based on their pretrial weight class (healthy weight and obese). Participants included obese (n=148) and healthy weight (n=203) preadolescents (8-9 years old). Their world body bone mineral density (BMC), area, and bone mineral apparent density were recorded using dual X-ray absorptiometry (DXA).

Obese children had a higher total BMC ($p<0.001$) than healthy weight children but when adjusted for their weight BMC was lower in obese children compared to healthy weight children ($p<0.001$) in both pre-trial assessments. Interestingly, pre-trial and post-trial whole body BMAD of obese children was higher than healthy weight children irrespective of adjustment by weight ($p<0.001$). Nine months of exercise significantly increased BMC ($p<0.001$) and area ($p=0.006$) in both obese and healthy weight, but had no effect on BMAD. BMAD increased more in healthy weight children than in obese children in both the exercise and non-exercise groups ($p=0.017$). The change in BMAD and BMC due to exercise within weight groups was not significantly different from each other ($p=0.53$ and $p=0.54$). Therefore, due to exercise, the increase in the bone mineral content and area for healthy weight and obese children is similar but there is no significant change in the volumetric density.

In summary, obesity is 8-9 year olds results in bones with higher BMC, area, and BMAD compared to healthy weight bones. Exercise increases BMC and area but not volumetric density (BMAD) in both healthy and obese children. The greater increase in BMC and BMAD over the 9 months in healthy weight compared to obese children indicates a slower rate of bone mass accrual, which may have implications for bone health during skeletal growth.

Keywords: Obesity, BMAD. Exercise

Tuning the Degradation Rate of Elastic PEG-PCL-DA Hydrogel using MMP-cleavable Linkers

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Abstract

We previously synthesized a visible light crosslinked, single-network, biodegradable hydrogel, polyethylene glycol-co-polycaprolactone diacrylate (PEG-PCL-DA), with high elasticity and flexibility for bioprinting [1]. Although the 'blank slate' property of synthetic materials makes it biocompatible, the encapsulated cells were trapped inside the hydrogel, and were unable to reorganize and produce its own matrix. The ideal cell-laden scaffold needs to grow and reorganize with biochemical and mechanical cues from its environment. We hypothesize that adding binding sites will improve cell adhesion and motility. In addition, inserting MMP-cleavable linkers between polymer molecules will allow the cells to degrade the scaffold as they replace it with their secreted matrix proteins.

Synthesis and characterization of PEG-PCL-DA copolymer was reported in our recently published study [1]. Human bone marrow derived mesenchymal stem cells (hMSCs) were stained with CellTracker Green CMFDA dye and suspended in media. The hMSC suspension was mixed with sterilized PEG-PCL-DA polymer solutions, MMP-cleavable peptides (KCGPQG↓IWGQCK) and Matrigel to obtain a precursor solution consisting of 5-20% (w/v) polymer, 0-2 mM peptide, 5% (v/v) Matrigel, 0.5% (w/v) LAP with a final cell density of 1.0 x 10^6 cells/ml. The precursor solution was loaded into cylindrical molds and photo-crosslinked for 30 seconds to create cylindrical cell-laden hydrogel constructs. Cell spreading over time was observed using fluorescent microscopy.

We observed a decrease in stiffness of the hydrogels as the concentration of MMP-cleavable peptides increase. At day 2, rapid degradation was apparent in the hydrogels containing 5% polymer and 2mM peptide; the cells were spread out and a significant number of cells detached from the scaffold. On the other hand, in the control hydrogels containing no peptides, the cells were fully encapsulated and no significant spreading was observed.

Keywords: Tissue engineering, Michael addition reaction, Poly(ethylene glycol) (PEG) hydrogel functionalization

Reference: [1] C. Xu, W. Lee, G. Dai, Y. Hong, *ACS Appl. Mater. Interfaces* **2018**, *10*, 9969.

3D Bio-Printed Model of Brain Tumor Microenvironment with Vasculatures

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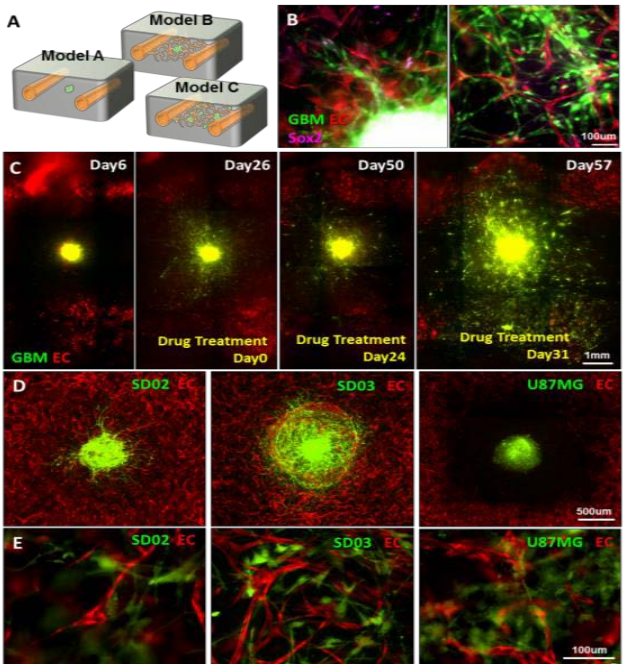
Abstract

Glioblastoma multiforme (GBM) is a highly invasive brain tumor and exploits microvessels to migrate and invade. Studying the perivascular invasion/migration may enable new possibilities in GBM treatment. However, investigating cell-cell/cell-molecular interactions in tumor microenvironments has been restricted due to the lack of proper 3D study models that can recapitulate the aggressive invasion and perivascular interactions of GBM. In this study, we created GBM-vascular niche models through 3D bioprinting to investigate tumor behaviors in various conditions.

We have developed three different GBM-vascular models using patient-derived GBM cells, vasculature endothelial cells (ECs), mural cells, and various hydrogels (Fig. 1A). We performed long-term drug treatment on Model A and observed pre-treatment aggressive invasion (~Day26), initial regression responding to drug (~Day50), and development of therapeutic resistance and resumed tumor invasion (~Day57) (Fig. 1C). In Model B and C, cell behaviors of patient-derived GBMs (SD02 & SD03) were compared with traditional cell line (U87MG). Three GBM types presented distinctive patterns of tumor invasion and EC-interactions (Fig. 1D&E). SD02 had a spiky invasion pattern with less co-localization with vasculatures; SD03 showed the most perivascular migration; U87MG spheroids caused the death of neighboring endothelial cells (Fig. 1D); however, the EC death was significantly reduced in the scattered single cell form (Fig. 1E).

Our GBM-vascular niche models recapitulate GBM hallmarks including cancer stemness (Fig. 1B), tumor type-specific invasion patterns, and drug responses with therapeutic resistance. The models have a great potential in testing patient-specific tumor behaviors under chemo-/radio-therapy conditions and consequentially helping to tailor personalized treatment strategy.

Keywords: Glioblastoma multiforme, tumor model, vascular model, tissue engineering, bioprinting



Hyaluronic acid-based extracellular matrix for cartilage tissue engineering

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Abstract

The limited self-regeneration capacity of cartilage tissue necessitates strategies for rebuilding tissue defects[1]. Recently, an interconnected macroporous scaffold displayed its ability to increase transportation of cellular nutrients and waste during cell culture[1,2]. This scaffold is composed of cryopolymerized hyaluronic acid, a naturally-derived polysaccharide envolved in multiple cellular activities and wound healing processes, making it an attractive material for cartilage defect tissue engineering[1].

6% Hyaluronic acid glycidyl methacrylate(HAGM) based cryogels were created via 0.8% substitution with alpha-Acryloyl-omega-carboxy succinimidyl ester poly(ethylene glycol) integrin binding peptide-sequence-Glycine 4 times-Arginine-Glycine-Aspartic acid-Serine(ACRL-PEG-G4RGDS) peptides for enhancing cell adhesion. Primary bovine chondrocytes were isolated, purified and seeded on prepared HAGM cryogels dropwise at 20×10^6 cells/ml for experimental groups, also embedded at the same cell density in 6% HAGM hydrogels for control groups during photopolymerization with no addition of ACRL-PEG-G4RGDS peptides **(Fig 1A)**. Over 12 days of culture, HAGM cryogel maintained more viable cells than HAGM hydrogels **(Fig 1B)**. Moreover, from the observation of DNA content assay, HAGM cryogel with added peptides better maintained an equilibrium number of cells throughout culture compared to HAGM hydrogels **(Fig 1C)**. Furthermore, cells cultured in HAGM cryogel produced more glucosaminoglycans (GAGs) than HAGM hydrogels **(Fig 1Di&1Dii)**. Together, these results suggest transportation of high-molecular weight solutes is higher in HAGM cryogel than HAGM hydrogel. Ongoing work aims to integrate HAGM cryogel-based cell culture with a cartilage defect model and more flexible peptide functions such as self- cleavability within cryogels.

Keywords: Cryogel, hyaluronic acid, primary chontrocyte 3D culture, cartilage tissue engineering.

Reference: [1]Han+, International Journal of Biological Macromolecules 2016; [2]Bencherif+, Biomaterials 2008;

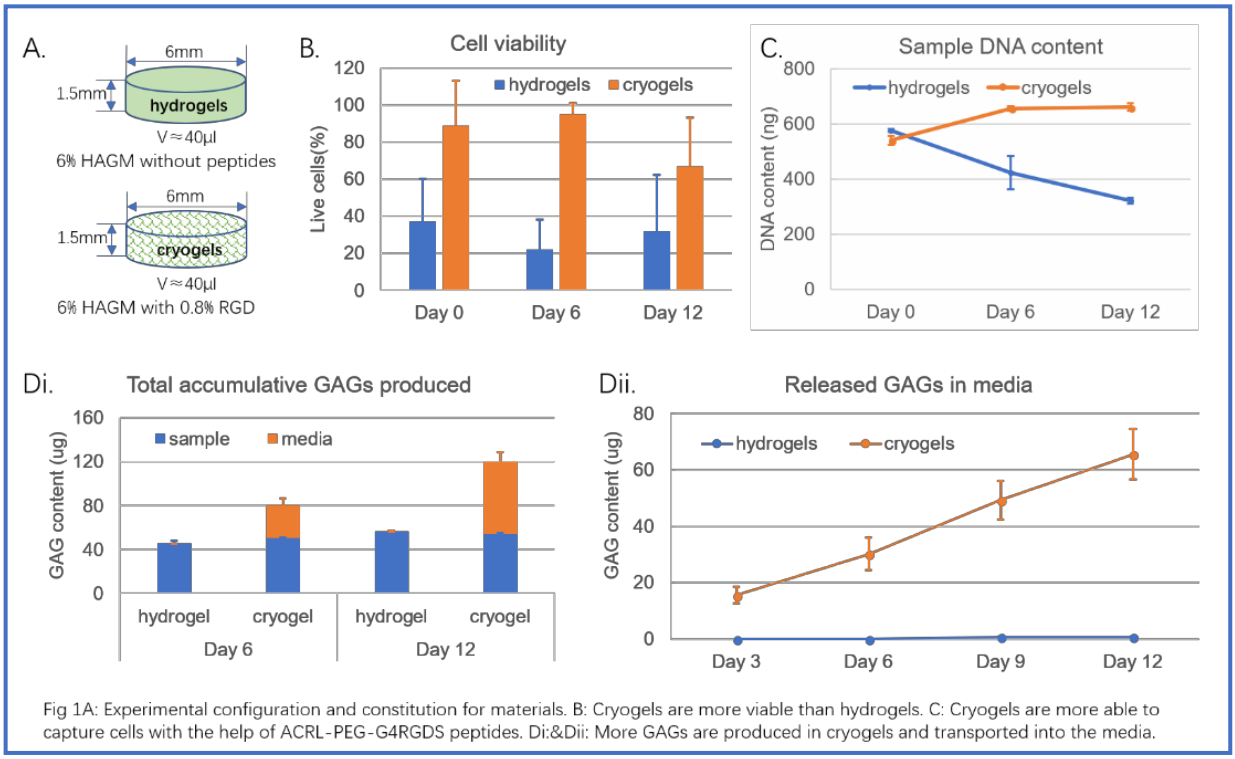

Fig 1A: Experimental configuration and constitution for materials. B: Cryogels are more viable than hydrogels. C: Cryogels are more able to capture cells with the help of ACRL-PEG-G4RGDS peptides. Di:&Dii: More GAGs are produced in cryogels and transported into the media.

Signal Processing Approaches for Diffuse in vivo Flow Cytometry

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Abstract

Enumeration of rare circulating tumor cells (CTCs) is of high interest in preclinical cancer research, since CTCs correlate with metastatic progression, response to treatment and overall survival in can-cer. We recently developed a new instrument – "Diffuse in vivo Flow Cytometer" (DiFC) - for fluores-cence detection of labeled CTCs in small animals. Briefly, as moving cells pass through the DiFC field of view, transient fluorescence 'peaks' are detected on two optode channels.

The broad goal of this project is to develop new methods to process DiFC fluorescence signals to achieve, i) high detection sensitivity of circulating cells, and ii) very low probability of false detections. To achieve this, background noise models and probability models for the cell DiFC signals were first developed for individual channels. Second, we employed a 'matched filtering' technique which de-tects model waveforms in DiFC data. Waveform templates were generated from Monte-Carlo simula-tions of the DiFC system and modeled both speed and depth of moving cells. Third, a joint-probability model was developed for coincidence detection of cells moving between the DiFC optodes. This al-lowed us to minimize false detections, better reject false positives, and determine direction of cell travel.

This approach achieved false alarm rates of zero for control animals with no circulating cells. Valida-tion on phantom model produced detection accuracy of ~95%. Matched filtering significantly improved detection signal to noise ratios, and provided speed and depth information of detected cells. We plan to extend this work to other model systems, animals and potentially humans in the future.

Keywords: Circulating Tumor Cells, In vivo Flow Cytometry, Joint Probability Model, Matched Filter-ing.

Synthesis and Characterization of Biogenic Selenium Nanoparticles with Antimicrobial Properties Made by Staphylococcus aureus, Methicillin-resistant Staphylococcus aureus (MRSA), Escherichia coli and Pseudomonas aeruginosa.

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Abstract

Antimicrobial resistance is a global concern that affects more than two million people each year. Therefore, new approaches to kill bacteria are needed. One of the most promising methodologies may come from metallic nanoparticles, since bacteria may not develop a resistance to these nanostructures as they do for antibiotics. While metallic nanoparticle synthesis methods have been well studied, they are often accompanied by significant drawbacks such as cost, extreme processing conditions, and toxic waste production. In this work, we explored the environmentally safe synthesis of selenium nanoparticles, which have shown promise in killing bacteria. Using Escherichia coli, Pseudomonas aeruginosa, Methicillin-resistance Staphylococcus aureus (MRSA) and Staphylococcus aureus, 90-150 nm average diameter selenium nanoparticles were synthesized using an environmentally-safe approach. Nanoparticles were characterized using transmission electron microscopy (TEM) energy dispersive X-ray spectroscopy (EDX) to determine the chemical composition, and ICP-MS to validate chemistry. Nanoparticles were also characterized and tested for their ability to inhibit bacterial growth. A decay in bacterial growth after 24 hours experiment was achieved against both Staphylococcus aureus and Escherichia coli at biogenic selenium nanoparticle concentrations from 25 to 250 µg/mL and showed no significant cytotoxicity effect against human dermal fibroblasts (HDF) cells for 24 hours. Bacteria were able to synthesize selenium nanoparticles through the use of different functional structures within the organisms, mainly enzymes such as selenite reductases. Therefore, biogenic selenium nanoparticles made by bacteria represent a viable approach to reduce bacteria growth overcoming the drawbacks of synthetic methods that employ toxic chemicals.

Keywords: Biogenic, Bacteria, Selenium, Nanoparticles, Antibacterial

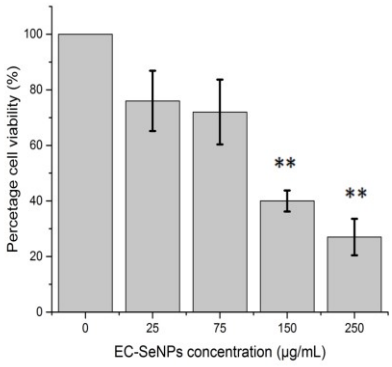

Figure 1. Effect of selenium nanoparticle made by Escherichia coli on Escherichia coli. The values represent the mean ± standard deviation, N = 3. * p<0.01, ** p<0.005

Fabrication of a fast fiber scanner for fluorescence microendoscopy

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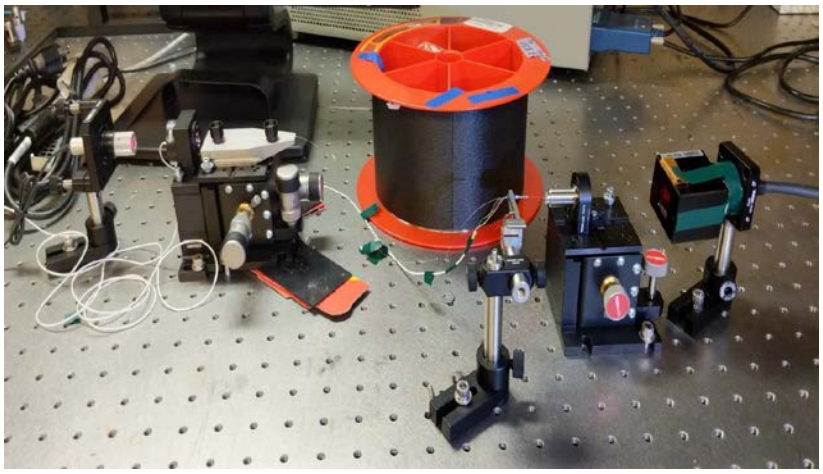
Abstract

Fiber optic scanning microendoscopy enables fluorescence microscopy deep within the body. These devices are essentially miniature laser scanning microscopes for linear (confocal or wide-field) and nonlinear (multiphoton) imaging applications. We present simple methods to fabricate a low-cost miniature fiber scanning microendoscope probe with specifications that promise video rate imaging applications.

Keywords: *In-vivo* imaging, microendoscopy, PZT, Fiber Optic



The experimental setup

New Class of Two Dimensional Nanopores for Single-Molecule Detection

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Abstract

Nanopores are promising biosensors for single-molecule detection. They are generally classified into two groups: solid-state and biological (mainly protein-based). After fabricating sub -10 nm diameter pore by focusing an electron beam on an ultrathin membrane, and immersion in two buffer baths such that the pore is a sole liquid junction between the two chambers, application of a small voltage across the membrane results in an electric field that threads polymers such as DNA through the nanopore. This results in a transient drop in the ion current, which is used to probe electrically and/or optically structural features in the polymer.

Generally, solid-state matrices, such as silicon-nitride, provide a more physically robust framework for hosting a nanopore, and further allow experiments under experimental conditions in which lipid membranes or protein channels may not be chemically compatible with. The quest to find an atomically thin membrane that can provide superior spatial resolution along with high mechanical stability has introduced two dimensional (2D) materials such as Graphene, GO, MoS_2, WS_2, and BN as second generation solid-state nanopores.

Herein, we investigate novel solid-state nanopores based on new 2D materials known as MXenes. MXenes are a family of 2D transition metal carbides, nitrides, and/or carbonitrides that are produced by selective removal of A layer atoms from layered ternary MAX phases, where M is a transition metal, X is carbon and/or nitrogen, and A is Aluminum. Nanopore is fabricated in a free-standing 2D membrane after transfer of MXene flake on a pre-fabricated 200nm hole in silicon nitride. Our preliminary data shows that MXenes provide high mechanical robustness, long-time stability, and low-noise ionioc currents through the pore for single molecule detection. This study provides the basis for application of MXenes as potential materials for second-generation solid-state nanopores.

Keywords: Nanopore, Nanotechnology, Two-dimensional Materials, MXenes

Novel Site-specific Photo-cleavable Protein Conjugates

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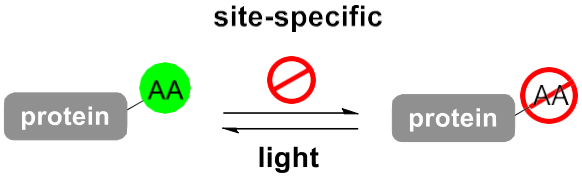
Abstract

Spatial and temporal control are hallmarks of complex biological systems. As such, methods to control the 'on' and 'off' states of biomolecules via reversible modifications are highly desirable. Cleavage of protein conjugates, particularly by bioorthogonal stimuli, is critical for many applications. Therefore, our lab has recently developed a novel method for installing photo-cleavable switches into proteins using transglutaminase (TGase, EC 2.3.2.13) to incorporate amine-containing photolabile groups on substrate glutamine residues via a transamidation reaction. Unlike previous non-specific approaches, our chemo-enzymatic method allows photo-cleavable groups to be installed into proteins in a site-specific manner. We have demonstrated installation of numerous chromophores into proteins in high yield using various transglutaminase isoforms. Subsequently, we have shown that these chromophores are removed upon photolysis to restore native protein. This reversible process is often referred to as photo-caging. Our newly developed strategy offers exceptional flexibility; the amine-containing chromophore can be tunable for various wavelengths of light (UV, multiphoton, etc.) and, additionally, TGase isoforms with broader and tailored activity can be explored.

Light as a bioorthogonal trigger offers unprecedented temporal and spatial control, and therefore the use of photo-cleavable chemistry is envisioned to be of great utility for bioengineering. For example, our method will find broad applications for biological probes, fusion proteins, antibody drug conjugates (ADCs), controlled drug release systems, photo-medicine, and photo-printing. An additional application of this reversible strategy is the installation of a payload that can be released simultaneously with a protein drug.



Keywords: photo-release • transglutaminase • protein conjugate • site-specific • photo-cleavable

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Multiscale characteristics of bone toughness

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Abstract

At the nanoscale, bone is a composite of collagen and mineral crystals. Alterations in quantity/quality of the collagen and mineral affects the porosity, tissue mineral density and matrix elasticity at the micro-scale and strength and toughness at the whole bone level. Considering the relationship between the strength and toughness, it is also believed that the elastic modulus is positively correlated to the amount of mineral in bone and therefore, fracture toughness should be primarily affected by the bone mineral content and distribution. Genetically altered mouse models of bone pathology allow us to examine how molecular defects affect the bone toughness.

We generated crack resistance curves in notched three-point bending experiments on femur to characterize the crack initiation, propagation and fracture toughness for each bone. We measured the degree of mineralization with quantitative backscattered scanning electron microscopy and the elastic modulus with nanoindentation of the embedded tibiae. Mineral to matrix ratio was measured with thermogravimetric analysis, crystal size with wide angle x-ray diffraction (both on humerus) and mineral composition by Raman spectroscopy of the embedded tibiae.

We found that the degree of mineralization, the elastic modulus, and fracture toughness varied significantly across bone models. Modulus was not correlated to the amount of mineral between and within the groups. Crystal size was not correlated to the degree of mineralization nor the tissue elastic modulus. This project research helps for better understanding of the main contributors to bone toughness by examining a wide range of material characteristics in mouse models of bone pathology.

Keywords: Bone, Fracture toughness, collagen, Mineral

The Failure of Packeting Routing between Auto-Associative Networks in Aging Brains

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Abstract

Many kinds of cognitive decline are observed in aged humans including cognitive slowing, word retrieval failures, working memory/encoding deficits and impoverished language. While these losses have varied etiologies, from "normal" aging to Alzheimer's disease, all are at heart neurocomputing failures. Human brain mapping (fMRI) studies have suggested that brain nodes are increasingly disconnected with age and pathology, but there are few neural-circuit level details on why many cognitive processes are failing. However, a theoretical analysis based upon auto-associative network theory (AAN-T) can draw connections between, and help explain, these diverse pathologies.

White matter damage is often invoked to explain cognitive slowing, while amnestic syndromes are more associated with synapse-loss and neuronal death. But these and other deficits might be more fundamentally attributed to impaired packet-routing between AANs. AANs (a type of attractor network) enable pattern recognition/completion and categorization to support many kinds of cognitive performance. They also fit well with recursive anatomical features found throughout mammalian neocortex. But in order for AAN-based memory and language operations to work, patterns (packets) must be routed from node to node in some coherent fashion. Moreover, these packets must "find" correct target AANs within a vast neocortical landscape comprised of about 20 billion neurons. One solution to this problem is a "broadcast" model where specific modalities or types of representations are communicated widely to potential target nodes/AANs. Routing failures, within the context of the broadcast model, can help explain symptoms of both normal aging and certain neurodegenerative syndromes.

Keywords: neurons, computation, aging, imaging, networks

Generating High Quality Tetrahedral Meshes of the Human Head and Applications in fNIRS

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Abstract

Developing triangular and tetrahedral meshes is essential to many neuroimaging analyses. Tetrahedral meshes, in particular, are routinely used in trans-cranial magnetic stimulation (TMS) and trans-cranial direct current stimulation (tDCS) to evaluate brain damages and study major brain disorders. These tetrahedral mesh representations are also used in electroencephalography (EEG) in the monitoring of brain activites. Physical deformations can be simulated on tetrahedral mesh models of the head to assist neurosurgeon in the study of traumatic brain injuries (TBI) and surgical planning. Tetrahedral mesh models are used to calculate light propagation inside the head using finite-element (FD) and mesh-based Monte Carlo methods in fNIRS. Tetrahedral meshes also present important advantages over a voxelated and octree representations namely in the ability to represent curved shapes without terraced boundaries, the applicability in finite element analyses, and the control over the mesh density.

We report an easy-to-use and automated MATLAB workflow "brain2mesh". It can robustly and rapidly generate multi-layered tetrahedral meshes for the human head from a segmented dataset. A surface-based mesh generation approach based on the meshing toolbox Iso2Mesh is used to ensure the conformity of the tissue boundaries and to allow for fine control of the mesh quality and density. This meshing toolbox can process the outputs of most neuroanatomical analysis tools by handling probabilistic or multi-labeled segmentations, and surface models in some specific cases. Two mesh examples are shown in Fig. 1(a)-(b) and the forward modeling of light propagation on a mesh model is shown in Fig. 1(c) using steady-state mesh-based Monte Carlo simulations (MMC).

Keywords: tetrahedral mesh generation, light propagation in tissues, brain meshing, fNIRS.

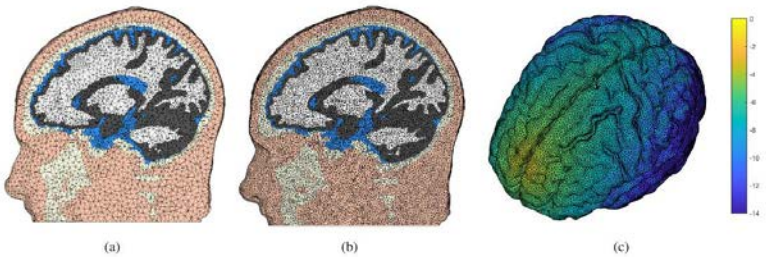

Fig. 1. (a) A coarse mesh of 599,073 tetrahedral elements, (b) a denser mesh of 2,335,398 tetrahedral elements of a 40-44 years-old [9], and (c) the fluence on the grey matter surface resulting from a steady-state mesh-based Monte Carlo (MMC) simulation at 670 nm from a pencil beam illumination at the Fz position (on a log-scale).

Sciatic neurectomy increases bone mechanosensitivity in aged mice

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Abstract

With aging, bone mechanosensitivity is reduced, leading to osteoporosis. We hypothesize that we can utilize the synergistic effect of remodeling and mechanoadaptation to restore mechanosensitivity.

In 20 months-old C57BL/6 female mice, we induced remodeling through sciatic neurectomy of the right limb. On day 5, the right tibiae were subjected to uniaxial loading for 2 weeks (9N load, 100 cycles/day, 3 days/week, 1s rest). Left limbs were kept intact as contralateral controls. Fluorescent labels were injected for dynamic histomorphometry. Following sacrifice on day 5 or 19, μCT images of the tibiae were analyzed for cortical cross-sectional parameters (10 μm resolution). Significance was tested with one-dimensional Statistical Parametric Mapping (using 1-sample t-tests, compared to contralateral control). Sections cut in the midshaft were used for endosteal and periosteal histomorphometry, with each cross-section divided into quadrants for analysis. Significance was tested with 2-sample t-tests (treated versus contralateral tibia).

Tibial cross-sectional area was not different 5 days following neurectomy, but histomorphometry indicated reduced endosteal bone formation on the medial and posterior surfaces. 19 days following neurectomy, the cross sectional area and bone formation were significantly reduced. Bone formation from loading at 9N was not detectable on micro-CT images, but histomorphometry indicated small, but significant, bone formation in specific regions. When neurectomy and loading were combined, the cross sectional area increased and bone formation increased in nearly all quadrants.

These results demonstrate that the synergistic effect of remodeling and loading can significantly increase the mechanoadaptive response in old bones. These data suggest that neurectomy induces remodeling that provides cortical bone with a pool of responsive cells to mediate adaptation.

Keywords: osteoporosis, mechanoadaptation, bone, aging

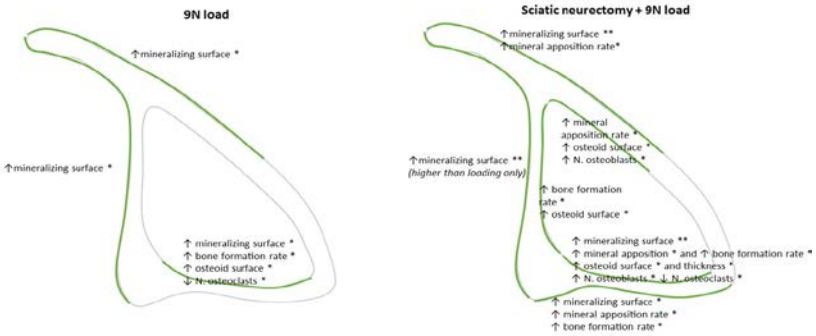

Figure 1 - Histomorphometric data, presented as a change in right tibiae, relative to contralateral controls. Student's two-sample t-tests, comparing left control tibia to right treated tibia. green line: surface of increased bone formation, compared to contralateral tibiae. * p<0.05; ** p<0.01

Computational Modeling Coupled with Imaging Techniques to Better Understand Asthma

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Abstract

Asthma is a heterogeneous chronic airway disorder that affects 334 million people worldwide. Severe asthmatics (~15% of asthmatics) are challenging to treat, as this cohort of patients do not respond well to inhaled therapeutics. Computational fluid dynamics and particle transport (CFD-PT) simulations provide unique insight on contributing factors that may lead to abnormal airflow distributions and insufficient therapeutic delivery. Here, we perform CFD-PT simulations in six subjects by coupling image-based airway geometries, measurements of segmental ventilation defect percentages (SVDP) measured from hyperpolarized ^{3}He MRI, and particle transport dynamics [1]. SimVascular (simvascular.github.io) was used to create airways from CT data and to perform the *in-silico* simulations. Respiratory resistances were incorporated as boundary conditions, matching SVDP. Following the simulations, the conducting airway resistances, R_{cond} were calculated by dividing pressure gradients by the tracheal flow rate. Following the gas simulations, 1 and 3-micron diameter particles were individually tracked by incorporation of inertial and sedimentation forces. Deposited particle concentrations (DPC) were calculated by normalizing the percent of deposited particles by the airway's surface area.

While similar between the healthy subjects, R_{cond} ranged from 1.1E-3 to 17.3E-3 $cmH_2O/mL\text{-}s$ in asthma. Extent of deposited particles also varied between the subjects, even for those within the same severity group; the severe asthmatic subject with the abnormal airway structure had 15 times greater DPC than the other severe subject.

Future efforts that incorporate a larger dataset of subjects will enable development of techniques for early identification of patients who are unable to receive adequate therapy and therefore may be ideal candidates for alternative treatment strategies.

Keywords: computational fluid dynamics (CFD), patient-specific modeling, human lung, asthma, magnetic resonance imaging

[1]Kamran, Poorbahrami, Sean Fain, David G. Mummy, Jessica M. Oakes. Aerosol Dosimetry in Asthmatic Airways: An In Silico Modeling Pilot Study. Am. J. Respir Crit. Care Med. San Diego, CA, July 2018. Podium Presentation.

Effect of Extracellular Matrix Remodeling on the Mechanical Coupling Between Human Airway Smooth Muscle Cells

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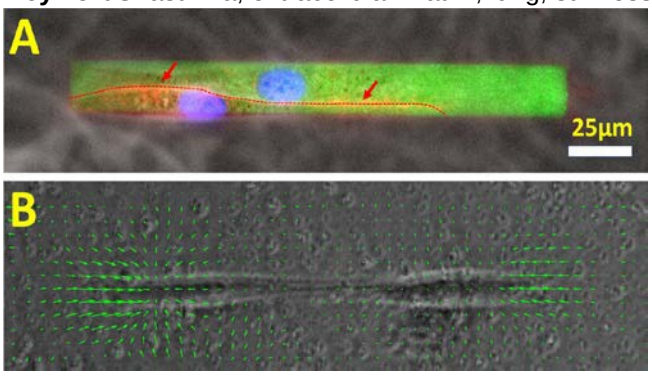
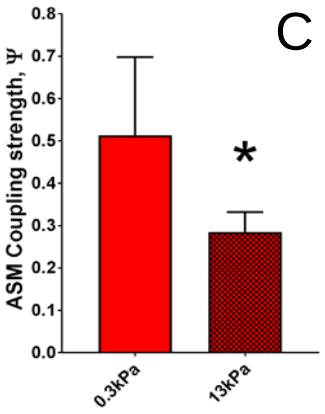
Abstract

One of the hallmarks of asthma is airway hyperresponsiveness (AHR), which is an increased sensitivity to agonists, such as allergens. The development of AHR in asthma is not well understood, but remodeling of the extracellular matrix (ECM) of asthmatic airways could play an important role. As the stiffness of the surrounding ECM changes, cells may alter how they interact with one another and the ECM via adherens junctions and focal adhesions, respectively. To study how remodeling the ECM leads to changes in connectivity, we constructed two cell pairs using micropatterning (A). We then measured the forces the human airway smooth muscle cells (HASMCs) exerted on each other and the substrate with traction force microscopy (B). We determined that as the stiffness of the ECM increases, the relative amount of force the cells exert on the neighboring cells decreases (C). We verified this by antibody staining for β-catenin and vinculin, which marked the cell-cell and cell-ECM junctions, respectively. As stiffness increased, the β-catenin present at cell-cell borders decreased significantly, while vinculin staining showed increasing signs of focal adhesions at these borders. These results indicate that as the airway ECM undergoes remodeling from a soft to stiff material, HASMC force increases and is accompanied by a change from cells exerting forces on other cells to the ECM. Understanding the consequences of altering the pathways of force transmission highlights the important, but overlooked role that the ECM remodeling plays in AHR and asthma. We plan to elucidate ways in which we can translate our findings into a treatment that focuses on the ECM and pathways of airway remodeling.

Keywords: asthma, extracellular matrix, lung, stiffness, traction force





Reconstructing Fiber Cross-sections from 1D X-ray Measurements

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Abstract

Fibrillar structures are ubiquitous in nature. Cellulose fibrils are a key component of plant and algae cell walls, while keratin and collagen fibrils give our hair, skin, tendons and bones their characteristic structure. Abnormal molecular behavior may also lead to the formation of fibrils, like the aggregation of amyloid fibrils in the brain in neurodegenerative diseases like Alzheimer's or Parkinson's. Studying the structure of these fibrils is thus of crucial importance to understand the molecular mechanisms that guide both natural processes and the progression of disease.

However, the cross-sectional arrangement of these fibers is difficult to study with most experimental techniques. Their size range, around the tens of nanometers, is too small to be adequately resolved by electron microscopy, and the inability to crystallize large enough fibril segments makes them unsuitable for crystallographic study. While X-ray fiber diffraction provides us with sub-nano scale information about the fibril's cross-section, all the 2D features of the cross-section are collapsed into a 1D curve, making the cross-section unrecoverable from just the data.

In this work we design an inverse problem framework to infer a fiber's 2D cross-section from its fiber diffraction curve. This inference is posed as a constrained non-convex optimization problem, which is efficiently solved by exploiting prior knowledge of the cross-section together with numerical and physical properties of the experimental setting. The potential of the proposed framework is shown by reconstructing the cross-section of different fibrilar structures like tobacco mosaic virus, a-beta amyloid fibers and cellulose fibrils.

Keywords: Inverse Problems, Optimization, X-ray Scattering, Alzheimer's disease, Amyloid

Femoral Growth Plate Orientation for Certain Load Conditions

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Abstract

Mechanical loads affect not only the mechanical properties of long bones but also the rate and the direction of their growth. Subsequently, loading influences the shape and ultimate functionality of these bones and their corresponding joints. Mechanical stress is a key factor in local regulation of the growth plate, which is responsible for longitudinal growth via endochondral ossification. Bone deformities of femur occur in children who experience abnormal loading on their bones during daily activities, such as in developmental dysplasia of the hip, cerebral palsy, or femoroacetabular impingement. Bone deformities can cause further problems such as early arthritis which might lead to total hip replacement and other costly procedures. Here we propose that the growth plate aligns in a direction that minimizes shear stress on its surface.

We developed an algorithm to determine orientation of the resulting growth plate under various loading conditions. The geometry of the femur was determined from an MRI of a 7-year-old boy. The algorithm determined a surface along the principle stress directions, for which shear stress is minimized. We then performed a parametric study considering various application angles of the hip contact force.

It is shown that the growth plate orientation changed significantly for 15 deg changes in anterior/ posterior placement of the joint load. This has implications for understanding changes in proximal femoral bone morphology in conditions such as anteversion, coxa valga/vara, and cam morphology, which are caused by altered growth.

Keywords: Finite element analysis, growth plate, shear stress.

Hybrid Modality Engineering: Site-Specific Modification of Proteins for Tailored Functions

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Abstract

Despite the significant advancements, protein engineering via recombinant technology (i.e., using naturally existing amino acids) cannot meet all needs. On the other hand, “hybrid modality engineering” that introduces non-canonical chemical moieties and/or scaffolds has emerged as a new fruitful approach. However, there are limited tools to modify proteins site-specifically. Towards this end, our group has been developing several chemical and enzymatic transformations that offer tailored selectivity and specificity. For example, glutamines of peptides and proteins are site-specifically modified by amines to form diverse substituted amides via a transamidation reaction catalyzed by transglutaminase (TGase). Furthermore, the N-termini of proteins are transformed to a ketone or aldehyde through a biomimetic transamination reaction using pyridoxal 5’-phosphate. This chemical handle allows for further derivatization through oxime or hydrazone formation. In addition, other amino acids, i.e., nucleophiles, can be selectively modified using orthogonal chemistries. This platform enables site-specific protein modification to insert a range of chemical moieties including affinity tags, biological probes, drugs, and fluorophores, and modulate protein properties.

Keywords: bioconjugation • site-specific • protein modification • transglutaminase • N terminus

Dynamic Tracking of Fluorescently Labeled Type I Collagen Molecules; Direct Quantification of Molecular Association with Native Fibrils

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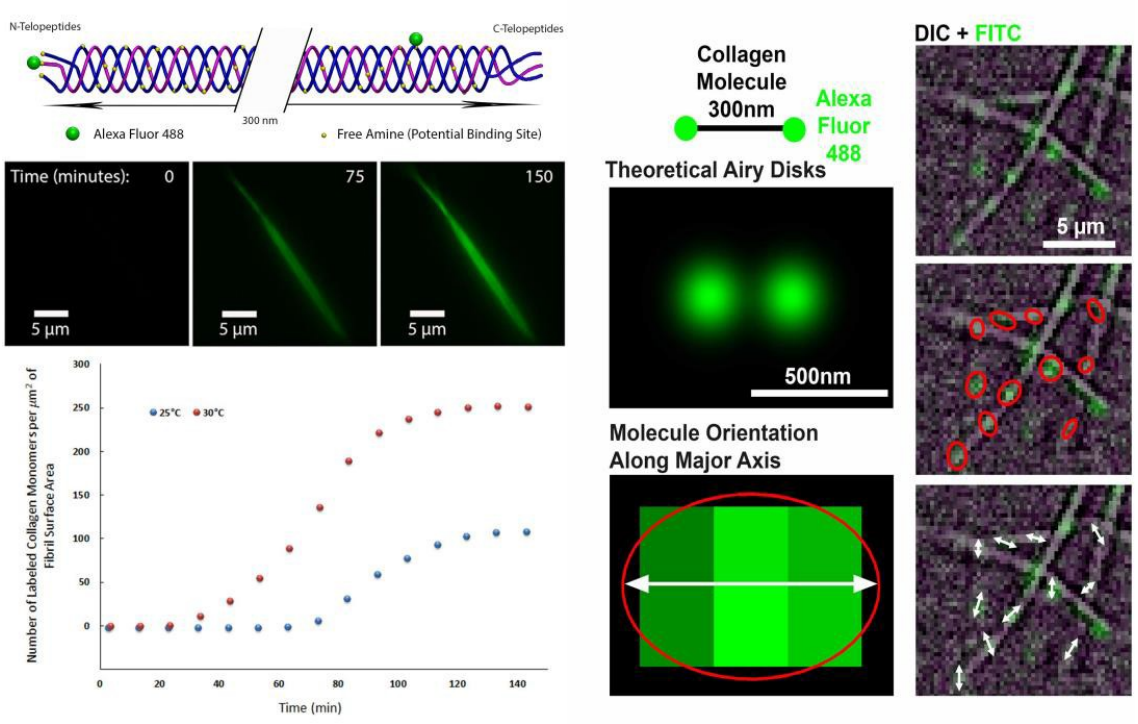
Abstract

While there are well-established theories about the formation of collagen fibrils, there are few viable hypotheses addressing the growth and remodeling of established collagenous matrix. We have hypothesized that collagen fibrils reside in a state of dynamic equilibrium with the local extracellular milieu and that this equilibrium can be altered by mechanical strain, shifting the molecular association rates, k_{on} and k_{off}, between fibrils and molecules. To test our hypothesis, we developed a robust method that will permit direct visualization of individual collagen molecular dynamics during interactions with collagen fibrils.

Type I telocollagen was tagged with ~2 fluorophores per molecule. The use of two labels permits both single molecule tracking and determination of molecular orientation. Labelling 100% of the monomers affected the self-assembly kinetics for new fibrils, but produced little discernible effect on assembled fibril morphology (D-banding). Reducing the relative number of labelled monomers to below 5% of the total number of monomers restored the self-assembly kinetics suggesting that the effect of the label can be taken into account via calibration. We then exposed native, young bovine scleral collagen fibrils, to a small concentration of labelled monomers. The incorporation rate and total accumulation (to reach equilibrium) of labelled collagen into the scleral fibrils was measured as 2.8 ± 1.2 and 4.0 ± 1.5 molecules/(μm^2/minute) and 114.3 ± 26.8 and 207.1 ± 55.4 molecules/μm^2 at 25 and 30 °C, respectively. The reaction of the monomers with the fibril surfaces produced a kinetic signature similar to *de novo* collagen assembly, with an activation energy of 12.6 kcal/mol. The results suggest that our labelled, exogenous collagen molecules dynamically associate with and incorporate into native collagen fibrils.

Keywords: Collagen Monomers, Fluorescent Labeling, Molecular Assiciation, Scleral Fibrils



Development of a Stretcher System to Study the Effect of Stretch and Substrate Stiffness on a Multicellular Ensemble of Airway Smooth Muscle Cells

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Abstract

The external mechanical environment of the airway smooth muscle (ASM) cell plays a potent regulatory role in the force that the ASM can produce, and altering the environment through matrix remodeling and stretch may affect agonist-induced calcium waves in airways. The goal of this study was to study calcium oscillations in human ASM while independently modulating the crucial mechanical aspects of the cell's physical setting. To do so, we developed a universal stretcher which translates linear displacement into planar isotropic motion **(A)**, and its unique geometry allows us to create isotropic, biaxial, or uniaxial strains, simply by changing the shape of the substrate. This tunable substrate also gives us control over extracellular matrix (ECM) stiffness and composition. In this study, we used a circle shape for isotropic strain to mimic strains felt by breathing airways, and we have confirmed that it produces a near perfect isotropic displacement field **(B)**. It sits atop an inverted microscope for live imaging calcium in patterned ASM rings, mimicking ASM organization *in vivo* **(C)**. The late Dr. Mike Sanderson has shown in precision cut lung slices that with higher doses of agonist, calcium oscillation frequency increases, and the airway constricts more[1]. Therefore, we wanted to see if ECM remodeling may affect the speed of oscillations in our airway mimics, and in fact we found that, in response to a transient stretch or agonist, calcium oscillation frequency increased significantly with matrix stiffening **(D, E)**. This suggests that ECM remodeling can trigger hyperreactivity by increasing the frequency of calcium waves for a low dose of agonist.

Keywords: Airway hyperreactivity, extracellular matrix, calcium oscillations.

References: [1]Perez and Sanderson, *J. Gen. Physiol.,* 2005.

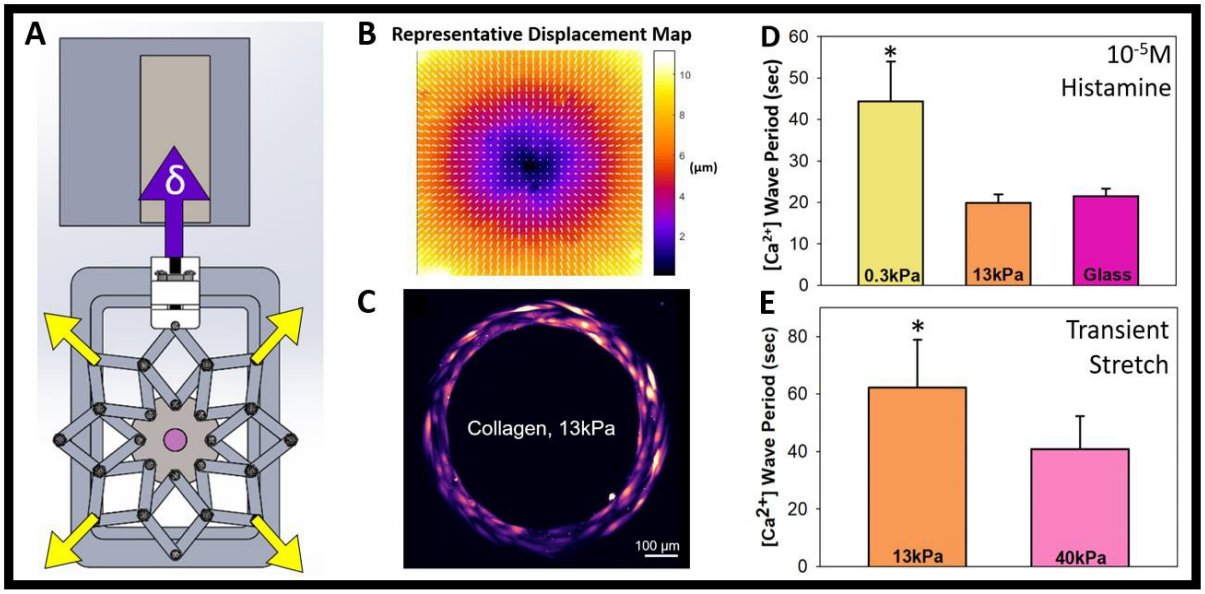

Figure 1: **(A)** Through the unique geometry of this device, linear displacment from the motor creates isotropic movement of the attached substrate. **(B)** It creates a near perfect isotropic displacement field, which is used to mimic strains felt by breathing airways. **(C)** ASM *in vivo* geometry is recreated by patterning ASM cells into rings on substrates of various stiffness and composition. The cells are loaded with a fluorecent calcium dye, which increases in intensity with increasing cytosolic calcium concentration.The frequency of calcium oscillaitons depends on environmental factors, and in response to either **(D)** a low-dose of agonist or **(E)** a transient stretch, calcium oscillation frequency increases with matrix stiffening.

Creating Anatomically Accurate Multi-layer Optical Brain Phantoms

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[2]Department of Chemical Engineering, Northeastern University, Boston, MA

Abstract

Functional near-infrared spectroscopy (fNIRS) is an emerging optical imaging technique to study brain functions, with the advantage of measuring brain activities noninvasively using safe and non-ionizing near-infrared light. Creating optical phantoms that mimic realistic brain tissue optical properties and shapes is critically important to the development of novel fNIRS imaging techniques. In this study, we designed and created an optically and anatomically mimicking multi-layered 3D silicone brain phantom for fNIRS imaging. The brain anatomy of the phantom was based on a published brain atlas derived from averages of MRI scans. Various 3D mesh generation and processing steps were applied to convert the brain segmentation to multi-layered tissue 3D mesh models, including 3 major brain tissue layers: the gray matter, cerebral spinal fluid (CSF) and the superficial layer (scalp and skull). These 3D mesh-based models of different tissue layers were 3D printed to create the negative molds for each tissue composition. Starting from the innermost layer, two-part silicone materials were first mixed with white and black pigments to simulate the desired optical properties for the specific tissue, and then mixed together for degassing and curing. The cured inner silicone phantom was then embedded inside the next outer layer mold to add the outer tissue layer, until all layers are included. Two water soluble wax spheres were embedded next to the motor and visual cortex regions using water soluble wires inside the gray matter molds before silicone injection. After casting the full brain phantom, the embedded wax spheres were dissolved with 80 ºC water. This study provides an efficient and replicable method for the fabrication of complex brain phantoms for brain function research using fNIRS.

Keywords: Brain, Phantoms, 3D Printing, Functional Near-Infrared Spectroscopy (fNIRS).

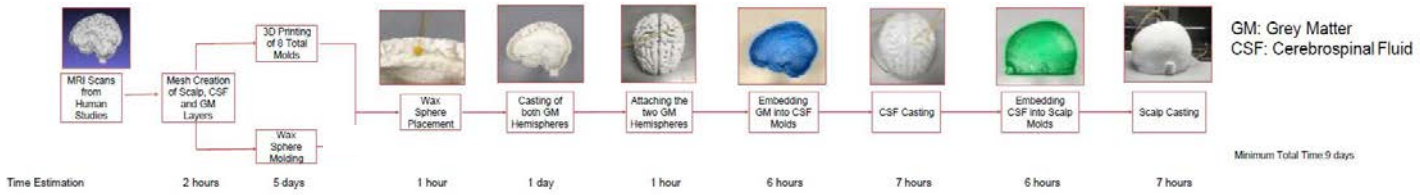

Figure 1: Phantom fabrication work-flow

A Novel Approach for the Synthesis of Metallic Nanoparticles on Top of a Tellurium Nanowire Using a Green Chemistry Approach for Biomedical Application

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Abstract

Healthcare concerns, such as antimicrobial resistance and cancer, can be addressed from a nanotechnological point of view. Current synthetic approaches for production of nanoparticles, based on physicochemical standards, are easy and straightforward. Nevertheless, there is a cost associated with these methodologies, such as the production of toxic by-products or the lack of biocompatibility of the products. Therefore, new methods are needed, and the green chemistry offers a suitable and novel answer, achieving a safe and environmentally-friendly design, manufacture and use of chemical products.

In this research, tellurium nanowires were synthesized using both a physicochemical approach (CHEM-TeNWs) and a green synthesis methodology (GREEN-TeNWs). The nanowires were characterized in terms of structure and composition and then they were compared in biocompatibility and cytotoxicity experiments with the aim to elucidate which one had an enhanced biocompatibility and anticancer properties. Then, GREEN-TeNWs were used for the synthesis of metallic nanoparticles in an easy and straightforward method with no need of reducing agent that was completed within 1 minute of reaction. Nanoparticles were characterized and the synthetic process was compared with the ones described in literature, with the aim to compare the methods in terms of chemical needed, reaction conditions and economic implications.

Keywords: Nanowires, Tellurium, Biocompatibility, Anticancer, Green

Multi-arm Avidin Nano-construct as a Cationic Carrier for Intra-cartilage Drug Delivery

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Keywords: intra-cartilage delivery, osteoarthritis, avidin, PEGylation

Osteoarthritis (OA) is a debilitating disease of joints that affects soft tissues like cartilage. Rapid clearance of drugs from joints and hinderance from highly negatively charged matrix prevents intra-cartilage delivery of therapeutics. It is critical for OA drugs to reach their cell target sites inside cartilage. We previously showed rapid and full-thickness intra-cartilage penetration of positively charged Avidin in-vivo owing to its optimal size and net charge[1-3]. Avidin when conjugated with dexamethasone (Dex)[4] suppressed cytokine induced catabolic activity significantly greater than Dex alone in a rabbit injury model. Drug loading content (DLC) in this design, however, was limited to 4 moles of Dex per mole of Avidin. Higher DLC is desirable for clinical translation such that any side-effects that may be associated with the carrier are minimized. Here, we design and characterize a new multi-arm PEG Avidin with higher DLC that can be conjugated with 8x more Dex.

10kDa 8-arm PEG amine was biotinylated and then conjugated with Avidin in 4:1 molar ratio. Avidin/biotin binding was confirmed with HABA titration, a dye that shows high absorbance on binding with biotin sites; its absorbance dropped with increasing concentration of PEG-biotin that competitively displaced HABA from biotin binding sites of Avidin. **Fig 1A** shows that HABA absorbance did not change beyond 4:1 molar ratio of PEG-biotin to Avidin as all biotin sites are then occupied by PEG-biotin. Addition of two or four moles of multi-arm PEGs per Avidin did not affect its zeta potential **(ζ)** suggesting minimum shielding of cationic charge. Its equilibrium uptake and intra-cartilage depth of penetration **(Figs 1Bi & Bii)** also remained unchanged. **Fig 1Biii** shows smudged band for 4:1 PEG-Avidin compared to Avidin confirming increase in molecular weight in coomassie blue stained gel in reverse polarity. Brown iodine staining confirms presence of PEGs. Dex was conjugated to PEG-Biotin-amine using ester linker to produce Avidin-PEG-DEX and confirmed using H-NMR (**Fig 1C**). Ongoing work includes studying its bio-efficacy using in-vitro cartilage OA model.

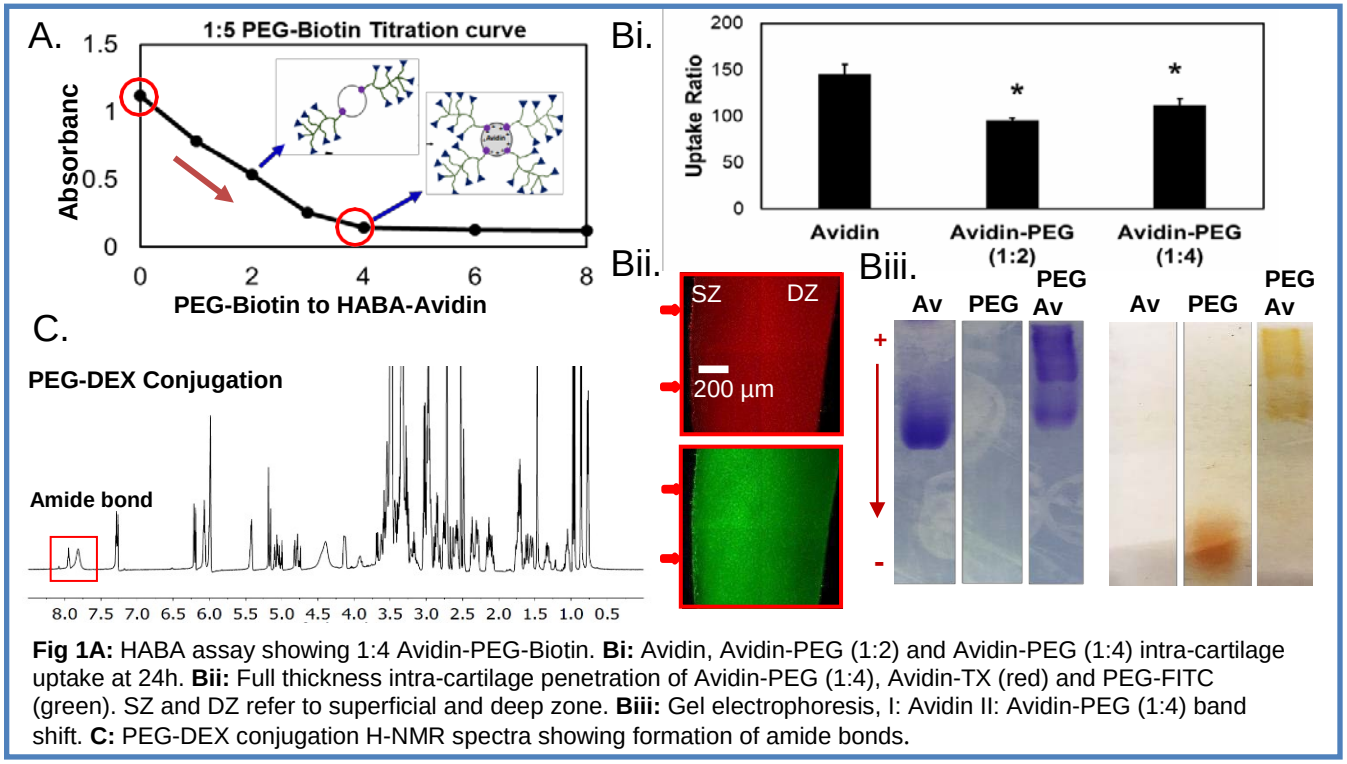

Fig 1A: HABA assay showing 1:4 Avidin-PEG-Biotin. **Bi:** Avidin, Avidin-PEG (1:2) and Avidin-PEG (1:4) intra-cartilage uptake at 24h. **Bii:** Full thickness intra-cartilage penetration of Avidin-PEG (1:4), Avidin-TX (red) and PEG-FITC (green). SZ and DZ refer to superficial and deep zone. **Biii:** Gel electrophoresis, I: Avidin II: Avidin-PEG (1:4) band shift. **C:** PEG-DEX conjugation H-NMR spectra showing formation of amide bonds.

References: [1]Bajpayee+, Biomaterials 2014; [2]Bajpayee+, J Orthopedic Research 2014; & [3]Bajpayee+, J Orthopedic Research 2014; [4]Bajpayee+, Osteoarthritis Cartilage 2016; [5]Bajpayee+, Eur Cell Mater 2017.

Engineering Optimally Charged Carriers for Targeting Negatively Charged Cartilage

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Keywords: Charge interactions, targeted delivery, peptide carriers, negatively charged tissues

Targeted delivery to cartilage remains challenging due to its dense matrix containing highly negatively charged aggrecans that prevent penetration of most macromolecules[1]. Its high negative fixed charge density (FCD), however, provides a unique opportunity for enhancing intra-cartilage penetration, uptake and retention of cationic drug carriers[2]. We recently showed that positively charged protein, Avidin, results in 400x higher intra-cartilage uptake compared to its neutral counterpart[3]. Here, we hypothesize that for a tissue of known FCD, there exists an optimal cationic charge range on carriers of given size that can enable full-depth tissue penetration and long-term retention. Inspired by Avidin's structure, we designed **C**ationic **P**eptide **C**arriers (**CPCs**, ~3000Da) with net charge varying b/w +8 & +20 and studied their transport properties in cartilage.

Steady state and effective (due to binding) diffusivities of CPCs in bovine cartilage were determined using custom transport chambers[3]. Equilibrium uptake of CPCs and their intra-cartilage retention was studied by desorbing in 1x or 10x PBS (to disrupt charge interactions) (**Figs 1A-B**). CPC+14 resulted in highest intra-cartilage uptake (~390x), full depth penetration within 24h **(Fig 1C)**, and 100% retention over 7 days (**Fig 1D**). CPC+8 had significantly lower uptake and retention, while CPC +20 was unable to reach deep zones owing to stronger binding interactions (**Fig 1C**). CPC+14 uptake reduced to 180x when cartilage FCD was depleted by 40-80% using enzymes to stimulate tissue degeneration. This uptake, however, is very high (implying 180x higher solute concentration inside cartilage than outside) confirming that CPCs can be used for targeting degenerated cartilage from mid to late stage osteoarthritis (**Fig 1E**). The work highlights that for a tissue of given FCD, there exists an optimal charge for a carrier of given size that enables full depth penetration through weak and reversible binding, and long-term retention owing to high tissue binding site density. Ongoing work includes electrical charging of drugs and contrast agents by using optimally charged CPCs to make them cartilage penetrating.

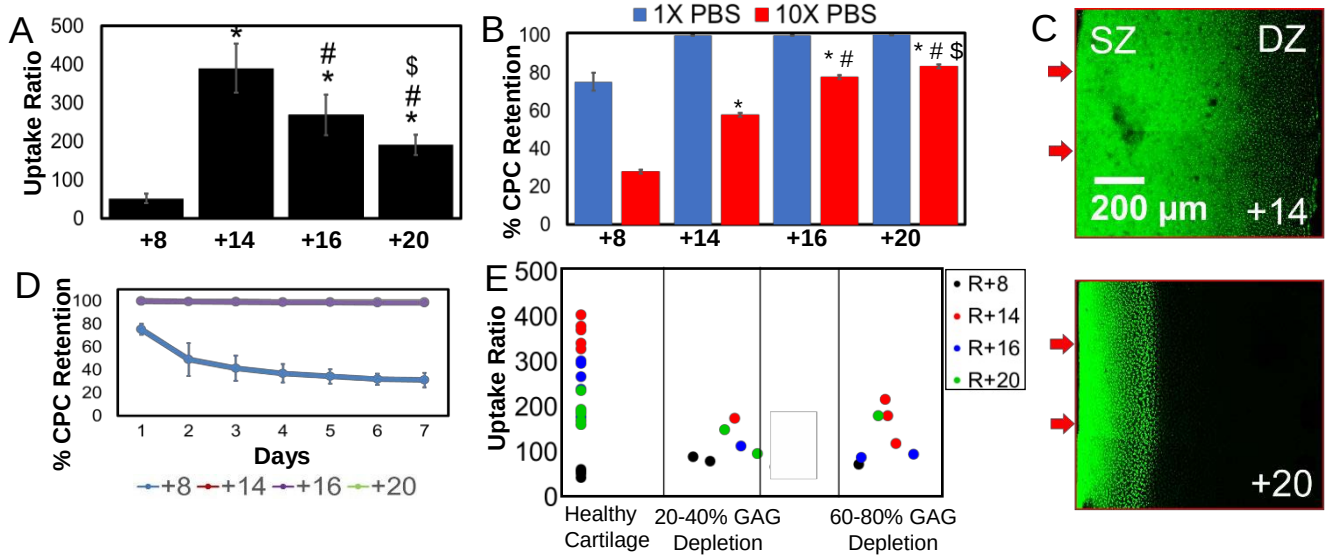

Fig 1A. Intra-cartilage uptake of CPCs over 24h **B.** % CPC retained within cartilage following 24h desorption in 1x or 10x PBS. * vs CPC +8, # vs CPC +14, $ vs CPC+16; $p<0.05$ **C.** Depth of penetration of CPC+14 and CPC+20. SZ and DZ refer to superficial and deep zone. **D.** % CPC retention within cartilage over 7 days in 1x PBS **E.** Intra-cartilage uptake of CPCs for healthy and GAG (glycosaminoglycan) depleted explants.

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Engineering a Microvascular Niche on a Chip

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Abstract

Understanding the influences of stem cell fate holds great potential for the advancement of tissue engineering. Recently, adult human neural stem cells (NSCs) have been observed in close proximity to blood vessels in a microenvironment designated as the neurovascular niche. This suggests that if this niche is recreated in an experimental system *in vitro* then the mechanisms of NSC self-renewal and differentiation will become better understood. Microfluidic devices have become effective tools for promoting the formation of microvasculature through endothelial cell vasculogenesis. In this study, we describe a method used to develop a 3-D microvascular network within a microfluidic device with the eventual goal of recreating the neurovascular niche. As we continue our efforts, the effects of extracellular matrix components and physical parameters on capillary formation will be quantified by evaluating the networks in their morphology (lumen size and density) and function (permeability and inflammation). Once a consistent model of the microvascular niche is developed, protocol modifications will be made to create a more accurate representation of the neurovascular niche, including the introduction of astrocytes and pericytes. NSCs will eventually be introduced and evaluated on their orientation, proliferation, and ratio of self-renewal to differentiation. From this, we hope to elucidate the role of microvasculature in NSC fate in the neurovascular niche. This will have a direct impact on developing new methods for the sustained *ex vivo* expansion of patient-specific stem cells to treat neurodegenerative diseases, as well as assist in NSC pharmacological studies.

Keywords: Microvascular Networks, Vascular Niche, Microfluidic Device, Lab on a Chip

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Distal Residues of Ornithine Transcarbamoylase Contribute to Electrostatic and Dynamics Properties of the Enzyme

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Partial Order Optimum Likelihood (POOL) is a machine learning method that predicts catalytically important residues based on the tertiary structure of the protein, with computed chemical and electrostatic properties of the residues as input features. POOL has predicted spatially extended active sites, where residues that are not in direct contact with the substrate still contribute to catalysis for many enzymes, including for ornithine transcarbamoylase (OTC). OTC is part of the urea cycle and the arginine biosynthesis pathwayO it catalyzes the reaction of carbamoyl phosphate (CP) with ornithine (ORN) to produce citrulline and inorganic phosphate. Enzyme variants were created through singleRsite directed mutagenesis and subsequently assayed for their kinetic activities, showing that predicted residues contribute to catalysis while nonRPOOLRpredicted residues do not. Solution scattering techniques and molecular dynamics (MD) simulations were used to understand if these distal residues play a role in dynamical structural changes, thus affecting catalysis from a distance. ThreeRdimensional reconstructions of the solution scattering data for wildRtype OTC and variants were generated using the programs GNOM and GASBOR from the ATSAS suite. Reconstructions of variants with mutations in distal positions show a structural rearrangement that in some cases reverses upon the addition of substrates. Principal component analysis (PCA) of the MD simulations also suggests collective movements that are consistent with solution scattering data. Therefore, in addition to electrostatic effects, these distal residues may play a role in modulating dynamics and thus contribute to the catalytic mechanism of OTC. Supported by NSF MCBR1517290

Keywords: Solution scattering, MultiRlayer active site, OTC, POOL

A Dual-grid Mesh-based Monte Carlo Algorithm Using a Coarse Tetrahedral Mesh for Ray-tracing and a Voxelated Grid for Output

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Abstract

A major challenge in the Monte Carlo method (MC) for photon migration simulation in human tissues is the high computational overhead. To accurately represent the curved boundaries in complex anatomies, voxel-based MC requires locally refined grid which leads to more computational cost. Mesh-based MC (MMC) uses triangular surfaces to improve accuracy at the boundaries without increasing the element density and therefore the speed is not sacrificed.

In this work, we propose a dual-grid MMC (DMMC) algorithm to utilize a coarsely tessellated tetrahedral mesh for ray-tracing computation and the use of an independent uniform voxelated grid for output quantity storage. It is realized that photon trajectories within the same tissue domain are independent of the discretization method. By coarsening the mesh domain while keeping the same triangular surface representation as with the conventional MMC, we can not only significantly decrease the number of ray-tracing events that need to be computed but also preserve the accuracy at the boundary. For accuracy of the output, a fine voxelated grid is independently created to store the simulation results.

We first validate the DMMC algorithm by comparing it with MMC and MCX (GPU accelerated voxel-based MC) with a fine discretization and then quantify the speed improvement by comparing DMMC using different tetrahedral mesh densities. From Fig.1(a), using only a fraction of nodes and elements, DMMC produced a solution that matches excellently with that of MMC. From Fig.1(b), nearly 2x and 3x speed improvement were observed for different scattering coefficients μ_s=1mm^{-1} and μ_s=0.5mm^{-1} respectively. The speed improvement diminishes when μ_s is high. This is because when the mean free path is significantly smaller than the average size of elements, the dominant factor that determines the ray-polygon testing computational efficiency becomes the number of scattering event rather than the mesh density.

Keywords: Biophotonics, Monte Carlo method, Turbid media.

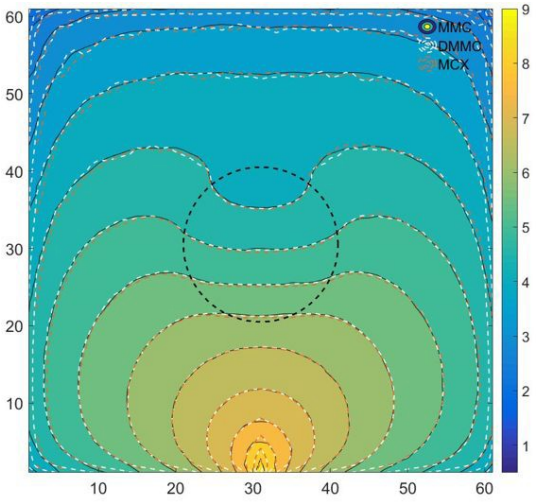
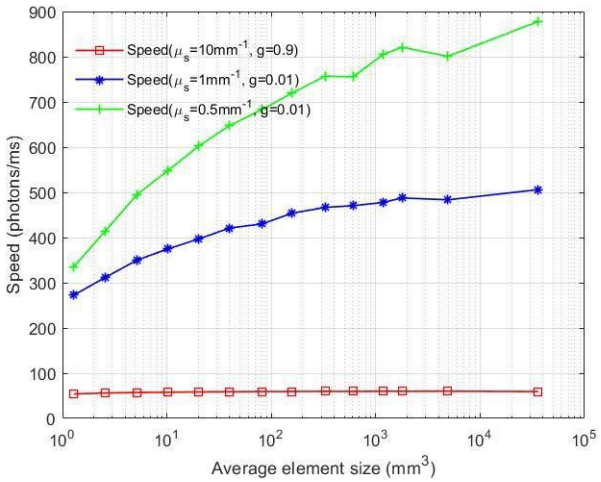


Fig. 1 (a) Comparison of DMMC with MMC and MCX



(b) Speed vs Average element size

Development of a Protocol to Investigate the Impact of E-Cigarettes on the Pulmonary and Cardiovascular Systems

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Abstract

Pervasive e-cigarette (e-cig) use is drawing concerns in the U.S., however to date little research has been conducted on its long-term health effects. E-cig devices generate fine particulates suspended in a gas (aerosols), and these aerosols have the potential to translocate into the bloodstream by crossing the epithelial/endothelial layers at the interface between alveoli and capillaries. Despite the fact that combustion does not occur, in contast to conventional cigarettes, the aerosolization process produces harmful chemical compounds including formaldehyde. In this pilot study, we demonstrated the feasibility of using ApoE$^{-/-}$ mice as an animal model to evaluate the health effects following long-term e-cig usage, compared to cigarette smoking. ApoE$^{-/-}$ mice are prone to atherscreleosis even when fed a normal chow diet. Twelve mice were divided into two experimental groups (cigarette smoke and e-cig aerosols, n=6). Each group was exposed once a day for 3 months using the InExpose system (SCIREQ Inc.). Smoke and aerosol characteristics were dynamically quantified with Engine Exhaust Particle Sizer (EEPS, TSI Inc.) and MicroDust Pro (CASELLA). Body weight and blood pressures were recorded weekly throughout the study. Following the exposure protocol, respiratory mechanics (e.g. resistance, compliance, pressuve-volume waveforms), infiltration of cells within the alveolar spaces, vascular stiffness, and signs of inflammation and remodeling (tissue histology with H&G, VVG, and Mason's Tricrome stains) were quantified in both the aorta and the lungs. Pilot study results highlighted that particle sizes are more unifiromy distributed and are larger in size for the e-cigs, compared to cigarettes. Mice exposed to cigarette smoke exhibited larger respiratory compliance and aortic stiffnesss compared to the mice exposed to e-cigarettes. Future studies will include adjusted puffing protocols as well as larger number of subjects for comprehensive evaluation on the health outcomes from e-cig exposure.

Keywords: E-cigarette, cigarette, mice, aerosol, lung mechanics, cardiovascular.

The attraction of rhythm: How discrete actions merge into a rhythmic pattern

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Abstract

It is a well-known, but nevertheless intriguing observation that humans "fall into step": When listening to music, humans spontaneously synchronize their movements to the rhythm; when the audience applauds after a concert, the clapping hands starts to synchronize into a common rhythm. But what if there is no external rhythm? The current study examined how humans spontaneously merge a sequence of discrete actions into a rhythmic pattern, and whether this change correlated with task performance.

Two experiments used a virtual throwing task, where subjects performed a long sequence of discrete trials, throwing a virtual ball to hit a virtual target as accurately as possible. In Experiment 1, subjects (n = 15) performed 11 daily sessions with 240 trials on each day (total of 2640 trials). Task performance was measured by hitting error, and continuous kinematic data of the arm trajectory across trials was collected to quantify changing rhythmicity via the inter-throw intervals and the dwell times between successive ball releases. Even though there was no instruction to perform rhythmically, results showed that variability of the inter-throw intervals decreased and dwell times shortened or disappeared with practice. The coefficient of variation of the inter-throw interval was 10%, which is only slightly higher than in rhythmic tapping synchronized to a metronome. Variability of the Poincare map of the orbit in state space decreased indicating periodicity and dynamic stability. Importantly, subjects who achieved higher accuracy in throwing also displayed a higher level of rhythmicity. In Experiment 2, two groups of subjects (n = 8 in each) performed a slightly less challenging task variation for 6 days (total of 720 trials, different target location). The discrete group was instructed to pause their arm between two successive throws while the self-paced control group did not receive any instruction about dwell time, as in Experiment 1. The self-paced group performed significantly better than the discrete group with significantly lower repeatability in their hand trajectories. These results show that subjects are spontaneously "attracted" to rhythmic solutions, even when there is no explicit need to do so. A break of the continuous flow of performance has a disrupting effect on performance, even though there may be more time to evaluate each throw and correct for errors. These findings are discussed in the context of previous neuroimaging results that showed that rhythmic movements involve significantly fewer cortical and subcortical activation than discrete movement activity and therefore may pose a more parsimonious solution.

Keywords: Rhythmic movement, periodicity, variability, stability.

Fast 3D Monte Carlo Photon Transport Simulations in Biological Tissues via Image Denoising

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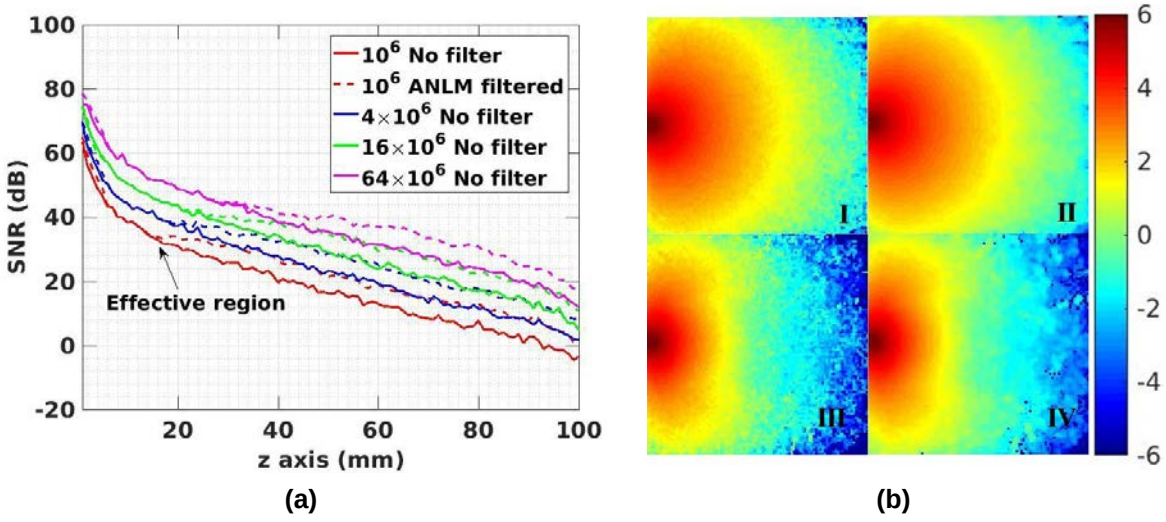
Abstract

The Monte Carlo (MC) method is widely recognized as a gold standard for modeling light propagation inside complex biological tissues. Unlike other deterministic radiative transport equation (RTE) solvers, MC generates the light distribution by launching large number of independent random trials of photon packets. As a result, stochastic noise is inherent and spatially varying depending on the number of photons arriving at a given voxel. While such noise can be reduced by launching more photons, it can result in much longer simulation run-times. It is therefore necessary to develop a signal processing technique which 1) can remove the spatially varying noise without changing the underlying light distributions, and 2) has high speed so that the overhead added by the denoising step does not exceed that of running more photons in most MC simulations. In this work, we apply a noise adaptive non-local means (ANLM) filter to noticeably improve low-photon MC simulation image quality, which is equivalent to accelerating MC simulation speed. By using graphics processing units (GPU) accelerated parallel computing, our developed GPU-ANLM algorithm is 2x faster than the previously reported GPU ANLM in literature, and 5x to 6x faster compared to the CPU version. Fig. (a) show an average signal-to-noise ratio (SNR) improvement of around 6 dB, which translates into roughly 4x speed improvement. Combined with GPU-accelerated MC photon transport simulations, GPU-ANLM filter is shown to accelerate MC biophotonic simulations for most commonly used photon numbers. Further improvement of the denoising techniques includes a rigorous study of the MC noise model and the development of deep neural network based denoisers for improved efficacy.

Keywords: Monte Carlo photon transport, graphics processing unit, denoising.



(a) **(b)**

Figure 1. (a) Comparison of the SNR (dB) across a homogeneous domain with and without filtering at various photon numbers, and (b) cross-section of the fluence (in log10) generated from running 10^6 photons in a homogeneous domain (**I**) before and (**II**) after filtering; similarly, we also show simulation outputs in a heterogeneous domain containing an absorber (**III**) before and (**IV**) after filtering.

Quantifying Movement in Preterm Infants Using Photoplethysmography

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Abstract

Movement is an important sign of infant health. However, systematic clinical study of movement and its relevance to adverse neurodevelopmental and cardio-pulmonary outcomes in preterm infants is limited because of time-consuming and subjective analysis of video or reluctance to attach additional sensors to the infant. We evaluated the hypothesis that the photoplethysmogram (PPG), routinely used for oximetry in preterm infants in the neonatal intensive care unit (NICU), can provide a reliable long-term measurement of movement, similar to or better than human raters. *Methods:* We developed a wavelet-based algorithm that detects movement signals from the PPG. In 5 infants, we compared the algorithm's performance to 3 raters, who identified movement using video and accelerometers attached to two limbs and force sensors embedded within the mattress. In an additional 13 infants, we studied the age-related changes in movement patterns revealed by the movement detection algorithm. *Results:* Comparison between our algorithm and human raters showed that the true positive rate in detecting incidences of movement was 73% and the positive predictive value was 76%. The intraclass correlation coefficient between raters was 0.39. The algorithm revealed a decline in brief movements (<5s) with increasing post-conceptional age (27.3 – 33.9 weeks). *Conclusion:* Movement can be quantified using PPG signals and can reveal maturational changes in preterm infants. *Significance:* Our movement monitoring system can be implemented using routine PPG and enables further studies of the relation between motor activity and neurodevelopmental and cardio-respiratory outcomes in preterm infants.

Keywords: Continuous wavelet transform, movement detection, photoplethysmograph, preterm infants.