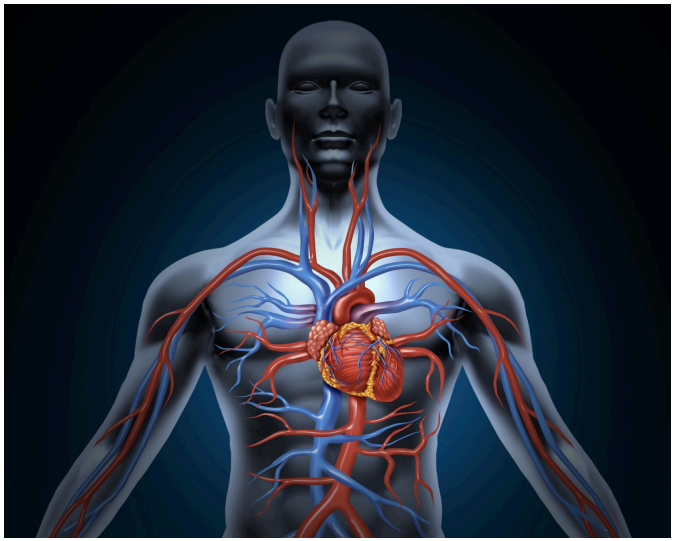
Institute of Robotics and Intelligent Systems



Microrobotics and Nanomedicine: Future Directions in Medical Robotics

Brad Nelson

Multi-Scale Robotics Lab
ETH Zurich

The MSRL Team

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Brad Kratochvil
Salvador Pane
Felix Beyeler
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Eniko Enikov
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Carmela De Marco

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Brigitte Geissmann
Karl Vollmers
Stefano Fusco
Dominic Frutiger
Sascha Stoeter
Zoltan Nagy
Didi Xu
Christos Bergeles
Franziska Ullrich
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Olgac Ergeneman
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Ninja Oess
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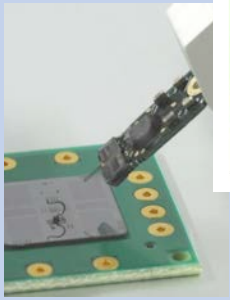
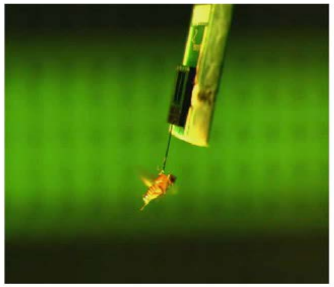
Arunkumar Subramanian
Juho Pokki
Famin Qiu
Naveen Shamsudin
George Chatzipirpiridis
Burak Zeydan

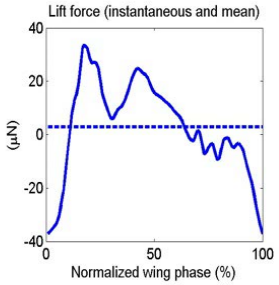
Robotics
Biomedical Engineering
MEM
Nanotechnology
Mechanical and Electrical Engineering
Computer Science
Materials
Physics
Chemistry
Medicine
Business, …

Multi-Scale Robotics Lab (MSRL)

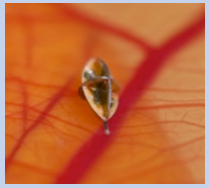
Force Sensing and Mechanobiology

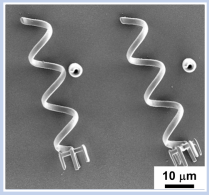


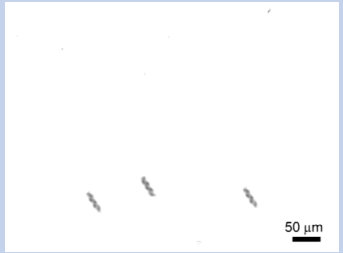


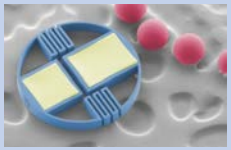


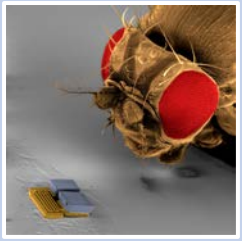
Micro and Nano Robots

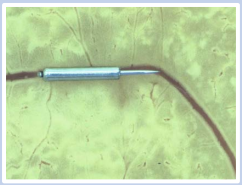




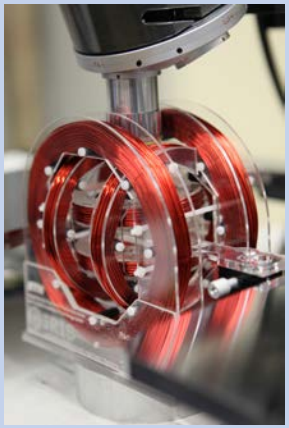


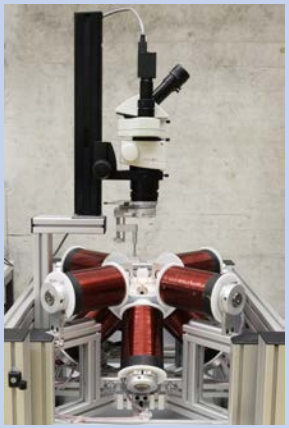




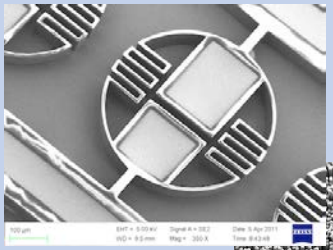


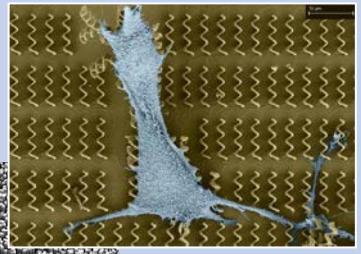
Magnetic Actuation

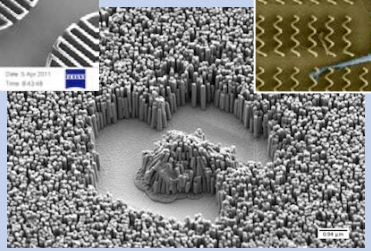




Materials and Fabrication



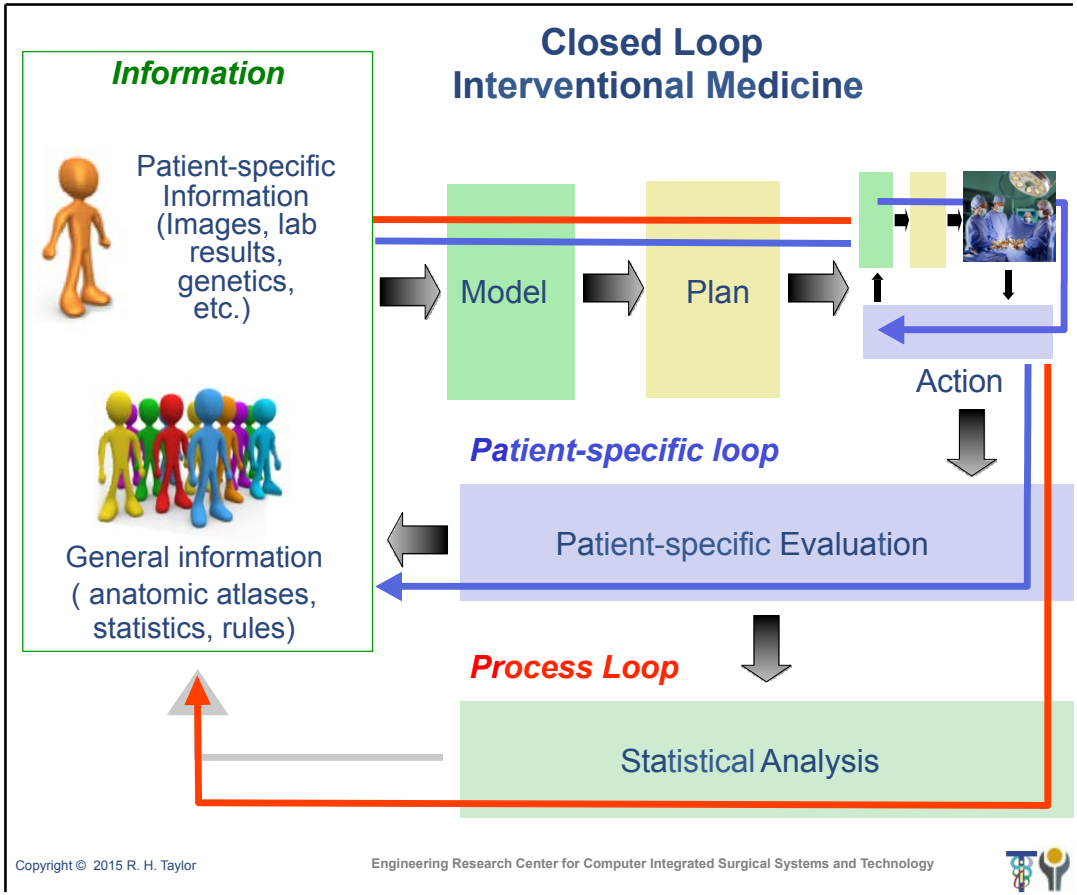




Medical Robotics

Prof. Russ Taylor of Johns Hopkins

- "A partnership between human clinicians and computer-based technology will fundamentally change the way surgery and interventional medicine is performed in the 21st Century, in much the same way that computer-based technology changed manufacturing in the 20th Century"



Surgical Robotics Landscape

Surgical Robotics (commercialized)

Orthopedics

Maxio, Perfint

Navio,
Blue Belt Technologies

MAKO, Stryker

Neurology

NeuroMate,
Renishaw

Aqurate, KB Medical

Oncology

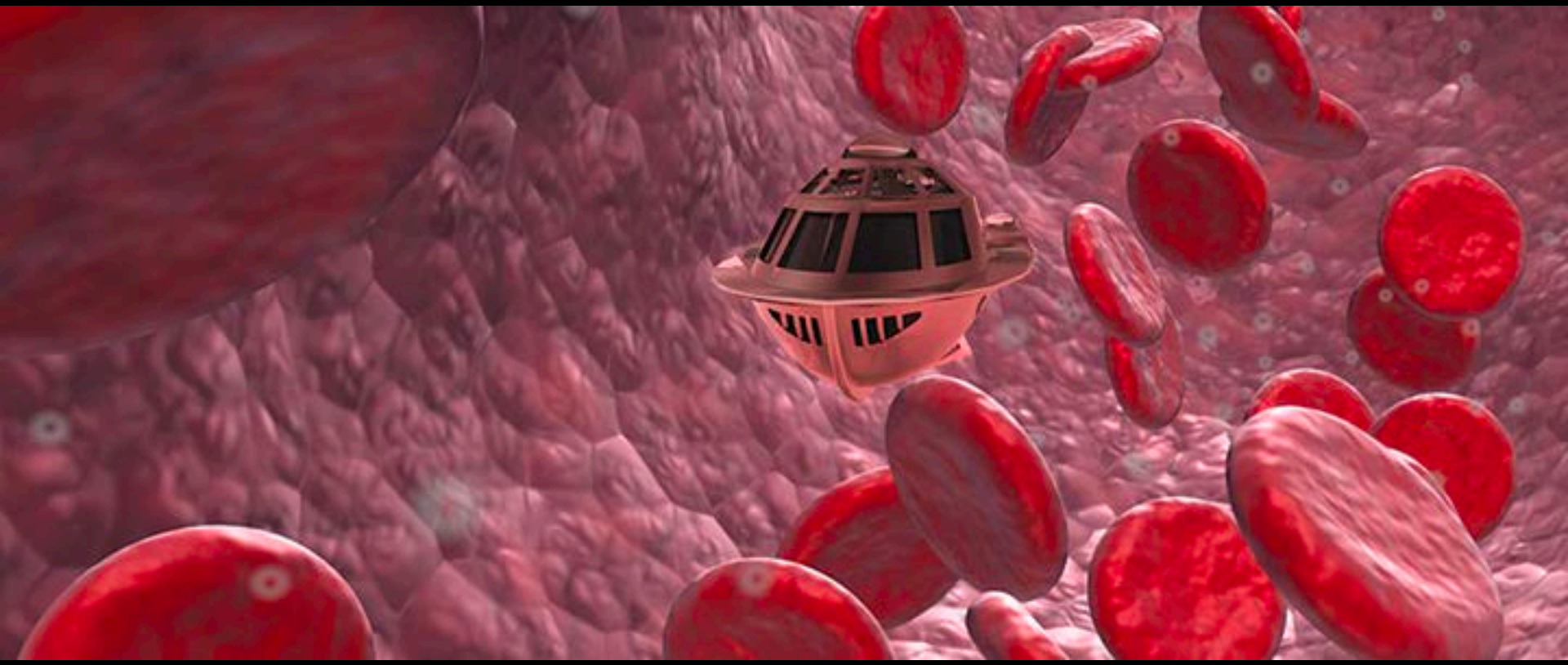
Zeus Surgical System

Gastroenterology

Da Vinci, Intuitive Surgical

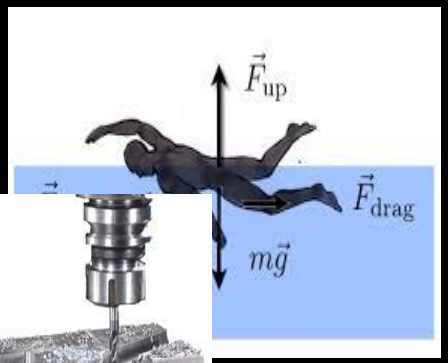
Cardiology

Magellan & Sensei,
Hanson Medical

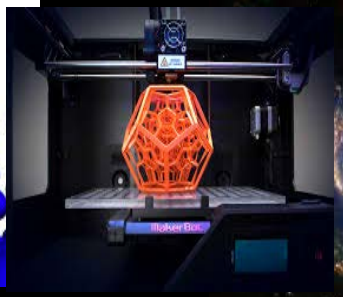


Fantastic Voyage (1966)

Physics



Fabrication



bizfi.com

Viable Business Plans

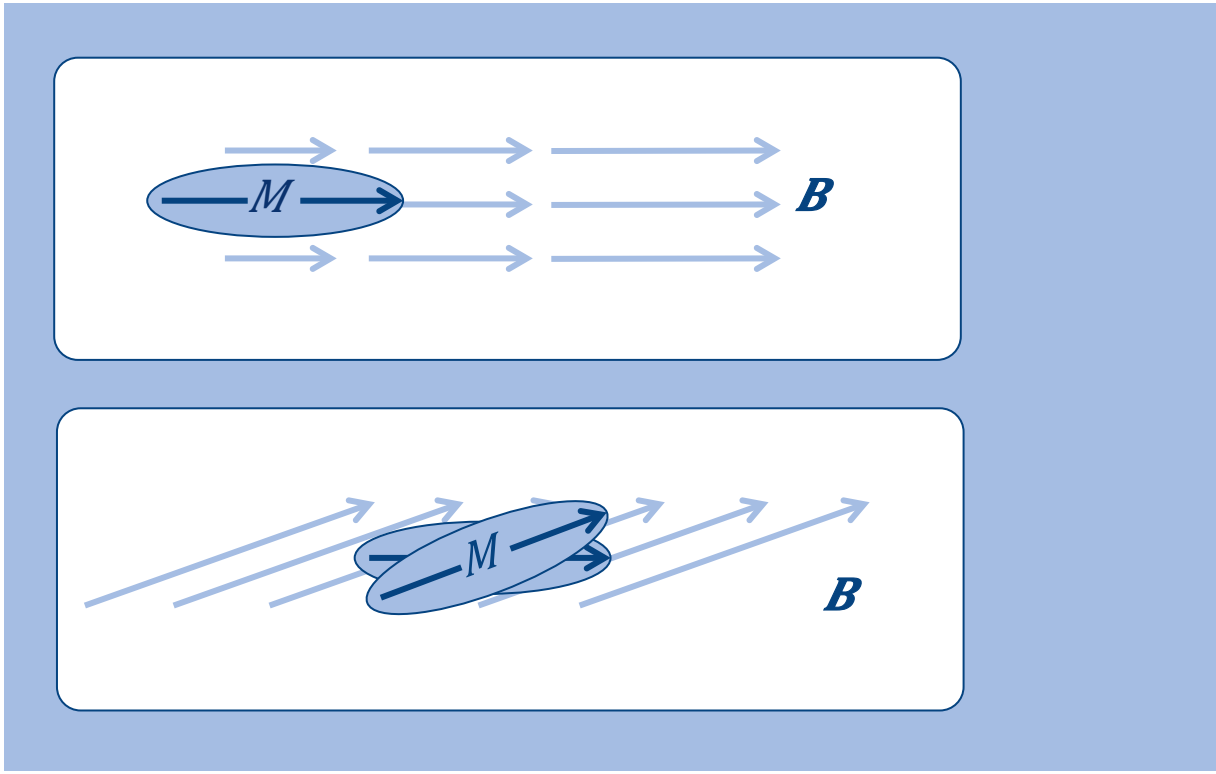
Magnetic Actuation Methods

Magnetic Force

$$\vec{F}_m = V(\vec{M} \cdot \nabla)\vec{B}$$

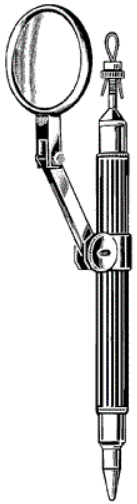
Magnetic Torque

$$\vec{T}_m = V \cdot \vec{M} \times \vec{B}$$

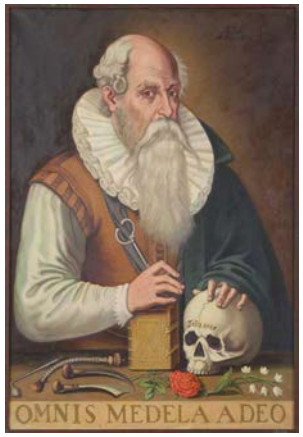


$\vec{T}_m$: Magnetic Torque [Nm]
$\vec{F}_m$: Magnetic Force [N]
V : Volume [m^3]
$\vec{M}$: Magnetization [A/m]
$\vec{B}$: Magnetic field [T]

Magnets, Electromagnets, and the Eye



Eye magnet with foreign body loop.



Some credit Marie Colinet Fabry from Switzerland with inventing the technique of extracting foreign particles with magnets in 1624. (pictured to the left is her husband Wilhelm Fabry www.fabry-jahr.de)

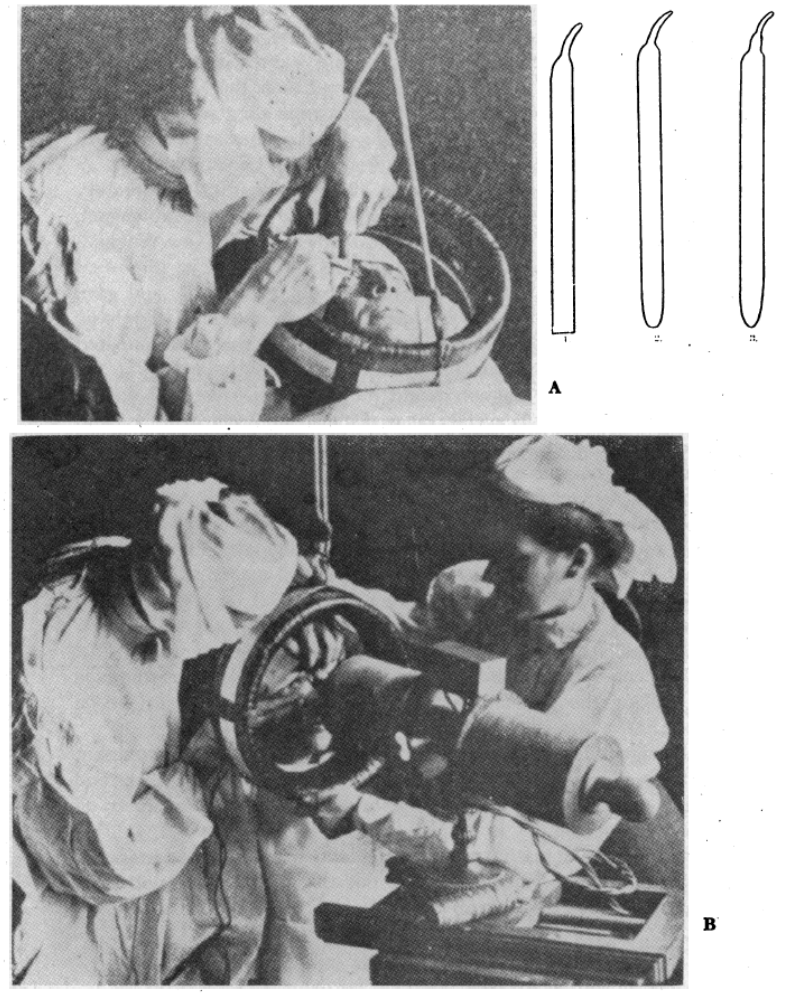


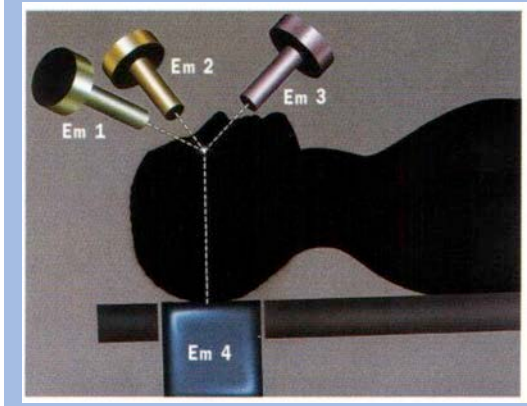
FIGURE 1. GIFFORD'S MODIFICATION OF THE JURNITSCHEK MAGNET
A: Used with Gifford's design of extra cores; B: used in combination with a Haab magnet (giant) (Ophthalmic Record).

M.F. McCaslin, "An Improved Hand Electromagnet for Eye Surgery," *Transactions of the American Ophthalmological Society*, 1958.

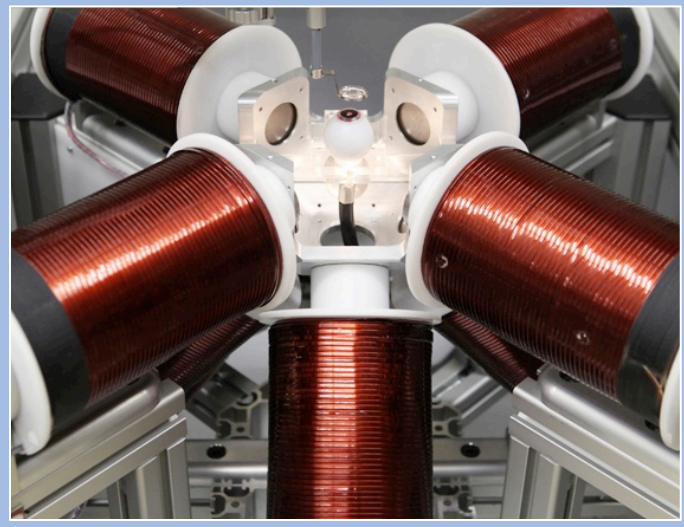
Charles D. Kelman, MD

Magnetic Phacofly for cataract surgery, 1974

- Place magnetic bead inside eye lens
- Electromagnetic system spins the bead
- Spinning bead liquefies the lens nucleus



The Octomag: An Electromagnetic Manipulation System



- Linear superposition of magnetic fields and gradients

$$\mathbf{B}(\mathbf{P}) = \sum_{e=1}^{8} \mathbf{B}_e(\mathbf{P}) = \sum_{e=1}^{8} \tilde{\mathbf{B}}_e(\mathbf{P}) i_e$$

$$\mathbf{B}(\mathbf{P}) = \begin{bmatrix} \tilde{\mathbf{B}}_1(\mathbf{P}) & \cdots \tilde{\mathbf{B}}_8(\mathbf{P}) \end{bmatrix} \begin{bmatrix} i_1 \\ \vdots \\ i_8 \end{bmatrix} = \mathrm{B}(\mathbf{P})\boldsymbol{I}$$

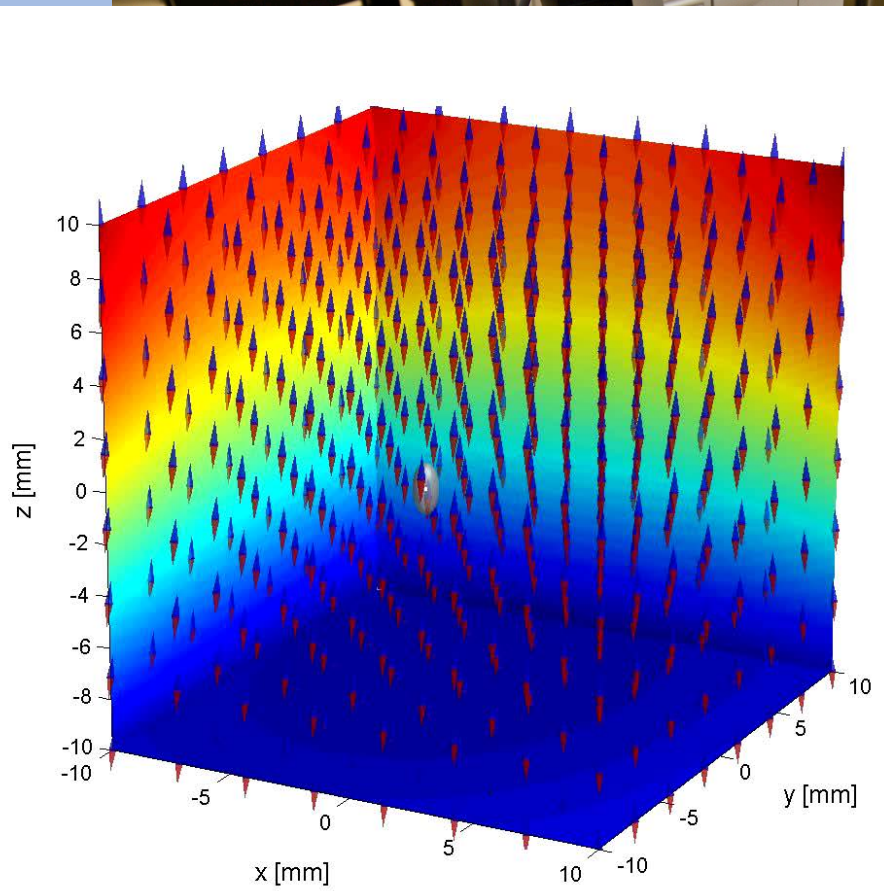
- Torque and force generation

$$\begin{bmatrix} \mathbf{T} \\ \mathbf{F} \end{bmatrix} = \begin{bmatrix} Sk(\mathbf{M})\mathcal{B}(\mathbf{P}) \\ \mathbf{M}^T \mathcal{B}_x(\mathbf{P}) \\ \mathbf{M}^T \mathcal{B}_y(\mathbf{P}) \\ \mathbf{M}^T \mathcal{B}_z(\mathbf{P}) \end{bmatrix} \begin{bmatrix} i_1 \\ \vdots \\ i_n \end{bmatrix} = \mathcal{A}_{T,F}(\mathbf{M}, \mathbf{P})\boldsymbol{I} \qquad \boldsymbol{I} = \mathcal{A}_{T,F}(\mathbf{M}, \mathbf{P})^{\dagger} \begin{bmatrix} \mathbf{T}_{des} \\ \mathbf{F}_{des} \end{bmatrix}$$

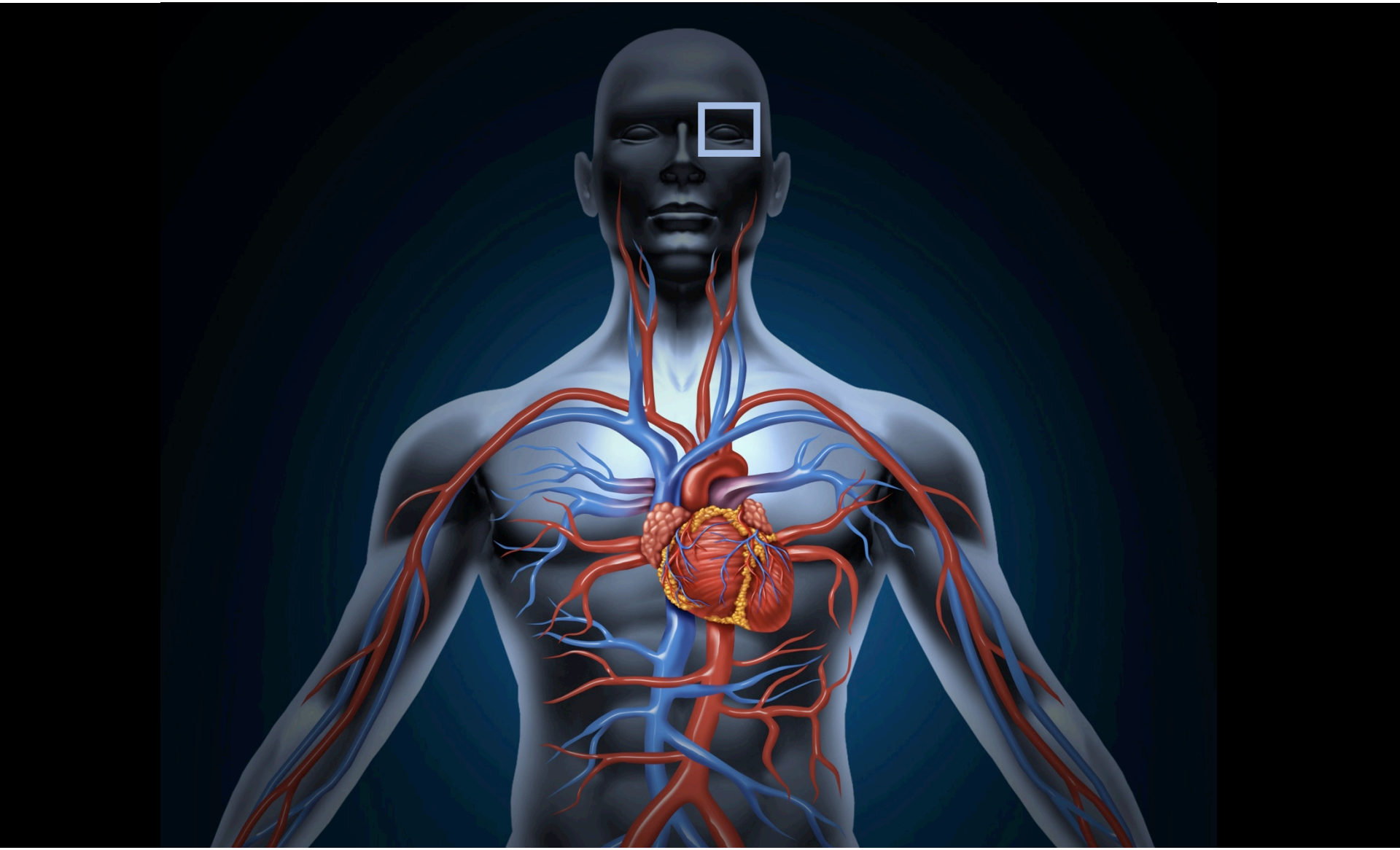
- Fields up to 40 mT
- Gradients up to 1 T/m

M. Kummer, J.J. Abbott, B. E. Kratochvil, R. Borer, A. Sengul, B.J. Nelson, "OctoMag: An Electromagnetic System for 5-DOF Wireless Micromanipulation", IEEE Trans. Rob., (26) 6, 2010

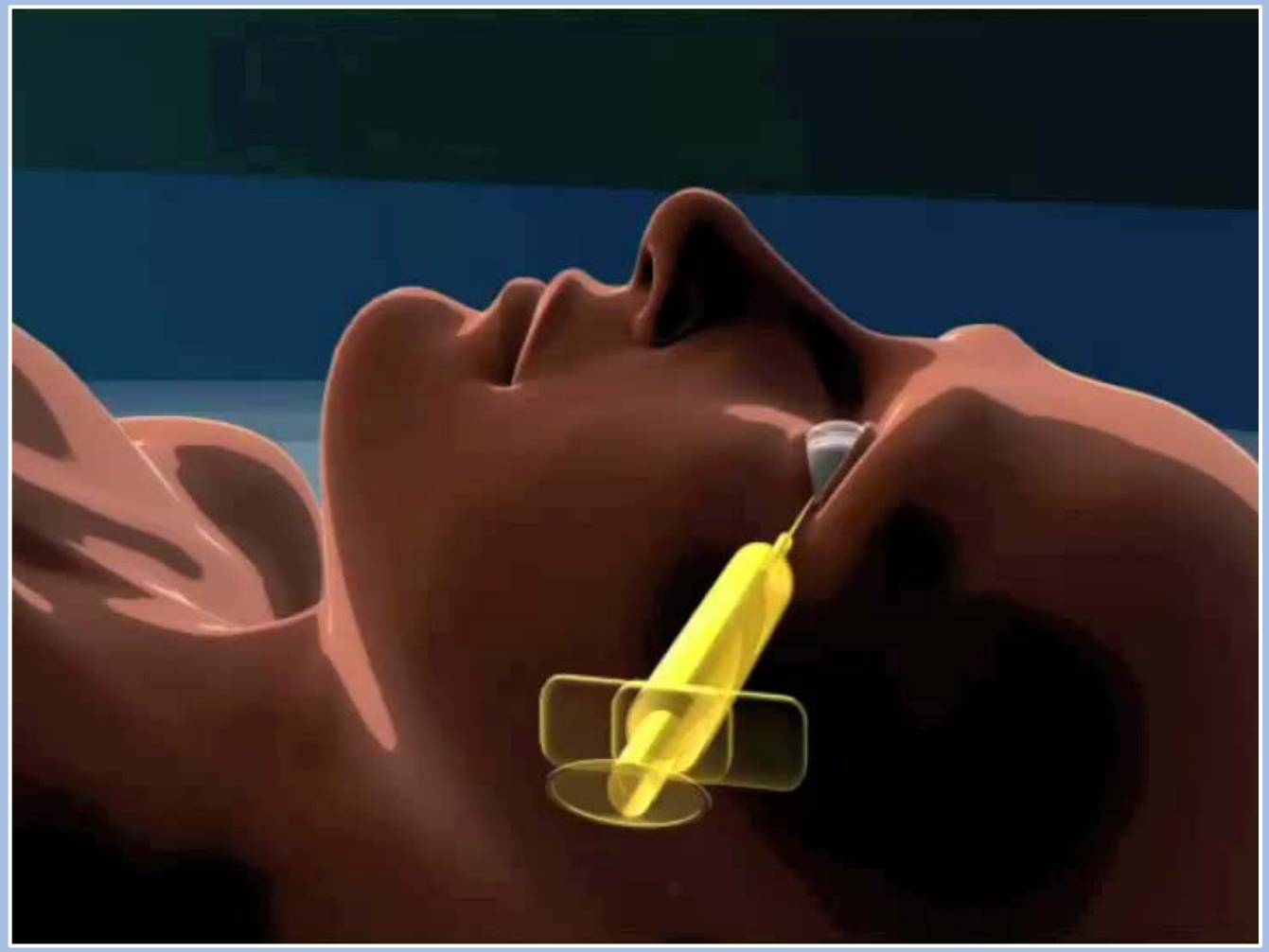
First Prototype: OctoMag



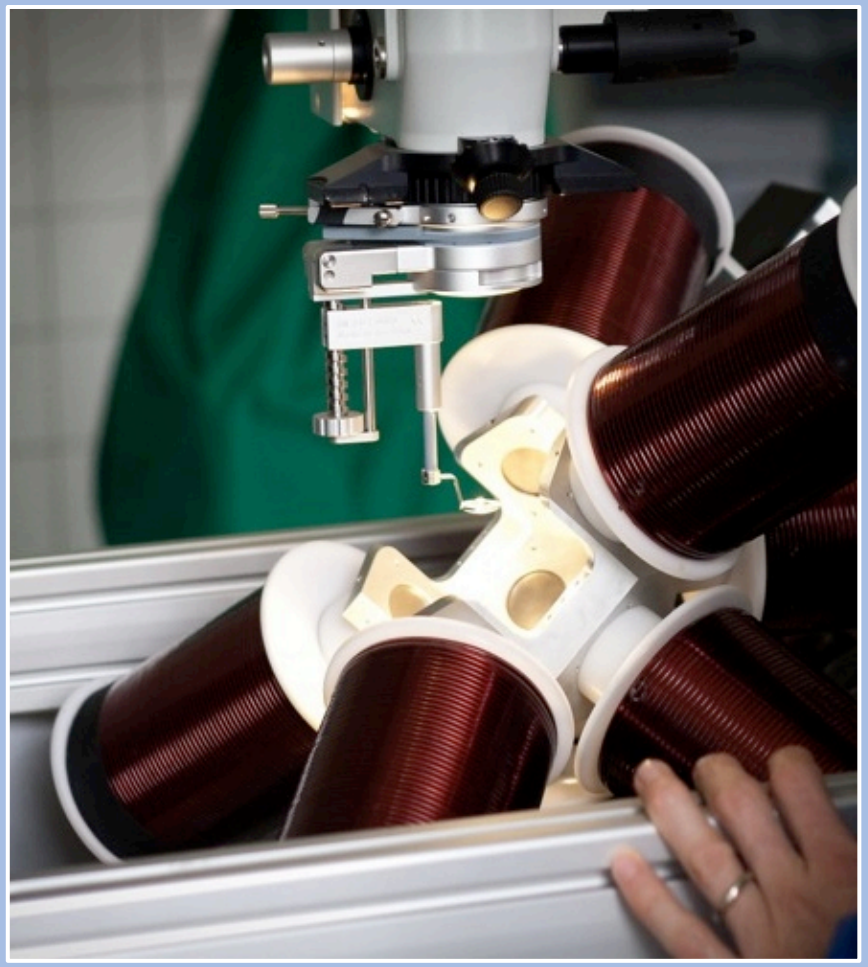
Where in the Body?

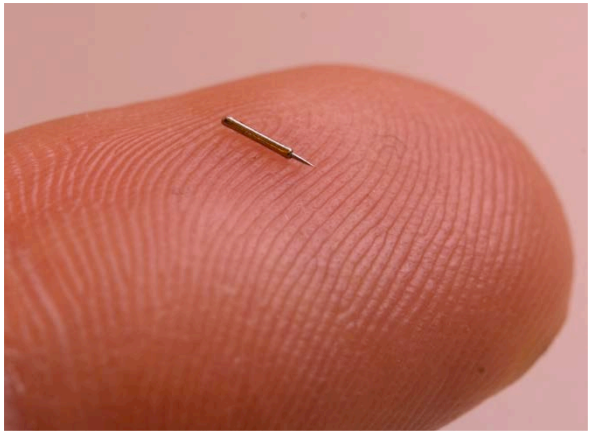


Microrobotic Drug Delivery for Retinal Therapies



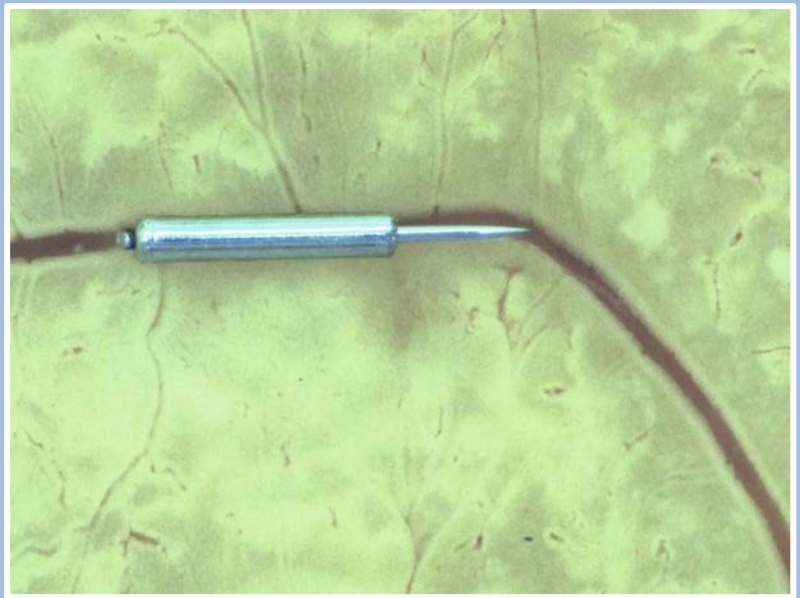
Animal Trials

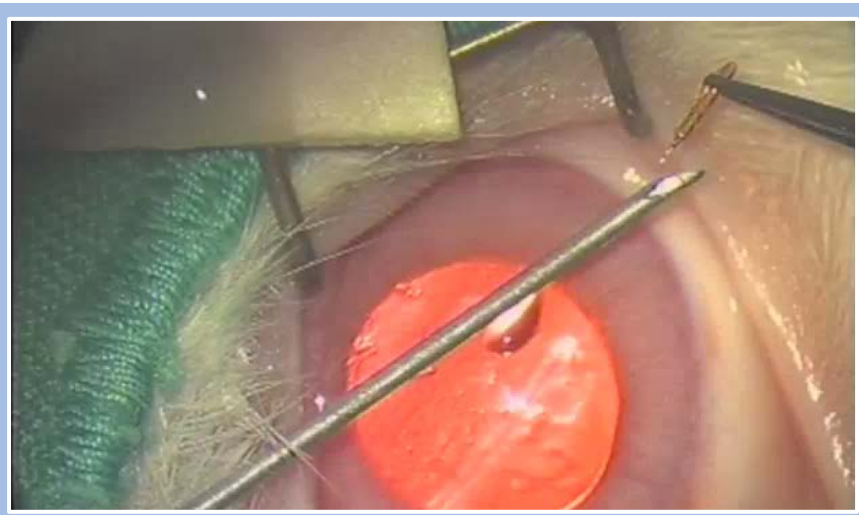




in vivo Injection and Mobility of a Microrobot

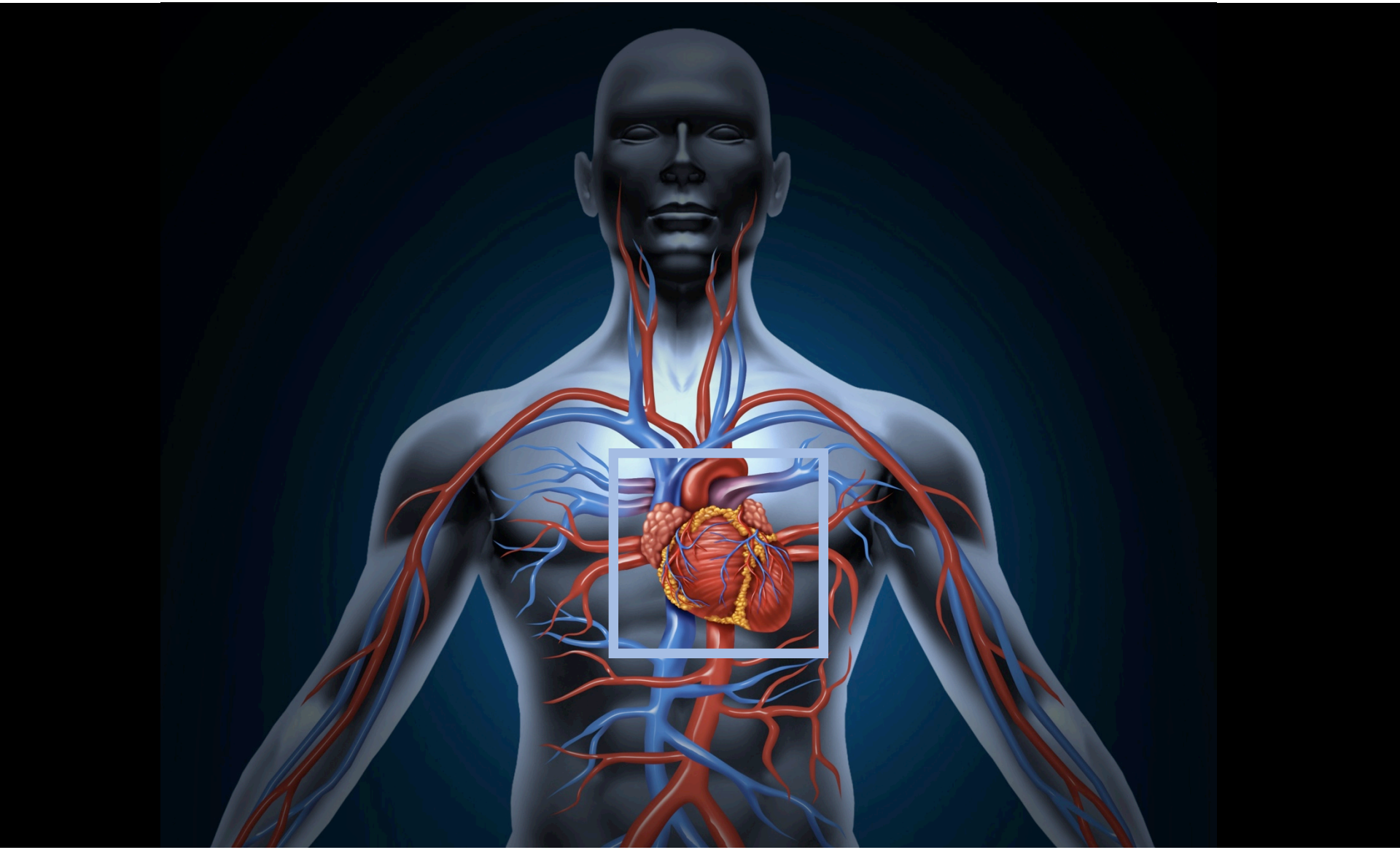
Vessel ~125µm dia.





F. Ullrich, C. Bergeles, J. Pokki, O. Ergeneman, S. Erni, G. Chatzipirpiridis, S. Pané, C. Framme, B. J. Nelson, "Mobility experiments with microrobots for minimally invasive intraocular surgery", Investigative Ophthalmology & Visual Science, Vol. 54, No. 4, April 2013, pp. 2853-63.

Other Locations in the Body



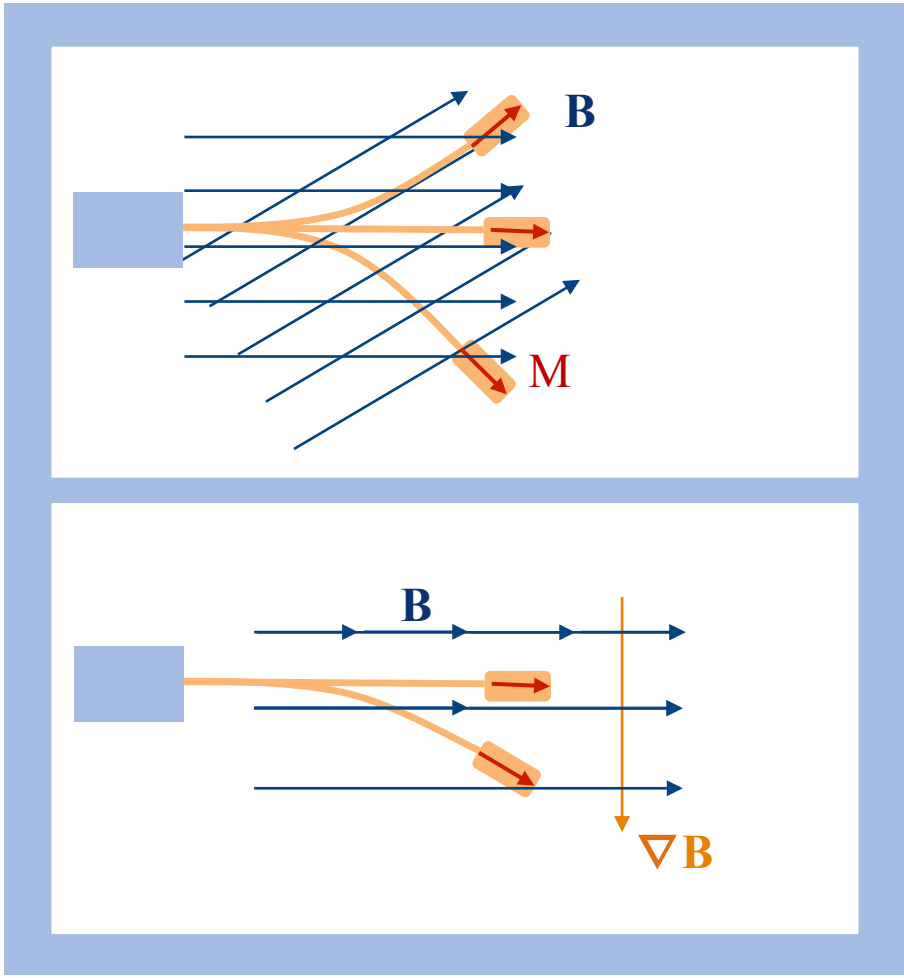
Magnetically Actuated Catheter

- Magnetic Torque

$$\mathbf{T} = \upsilon\, \mathbf{M} \times \mathbf{B}$$

- Magnetic Force

$$\mathbf{F} = \upsilon \begin{bmatrix} \frac{\partial \mathbf{B}}{\partial x} & \frac{\partial \mathbf{B}}{\partial y} & \frac{\partial \mathbf{B}}{\partial z} \end{bmatrix}^T \mathbf{M}$$



Magnetically Guided Catheters

- 1951, Hans Tillander showed preliminary experiments using a catheter with a flexible point directed by a magnetic field [1].

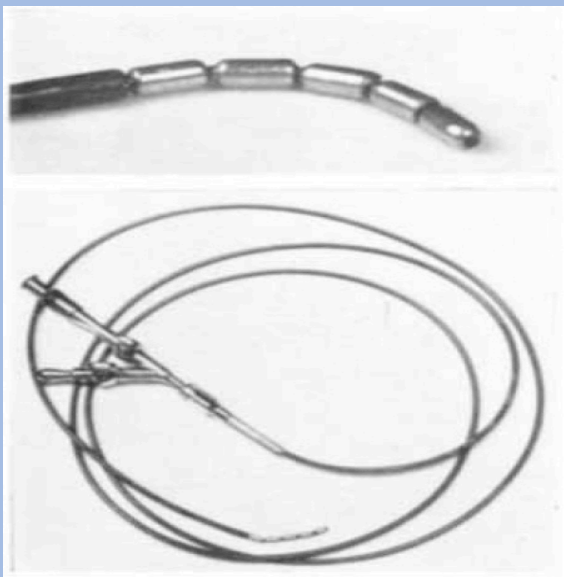


Fig. 1 (top). The point of the catheter.
Fig. 2 (below). Catheter with two-way stopcock and point.

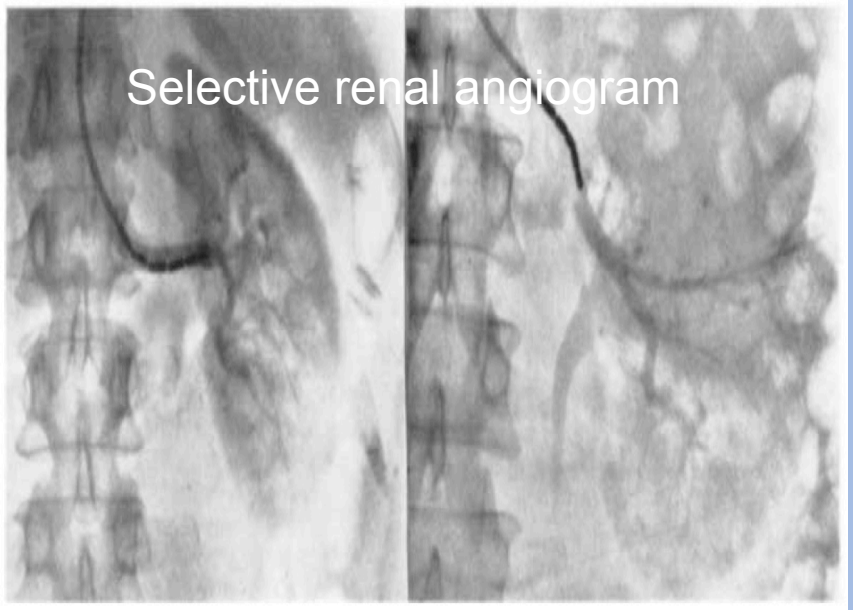


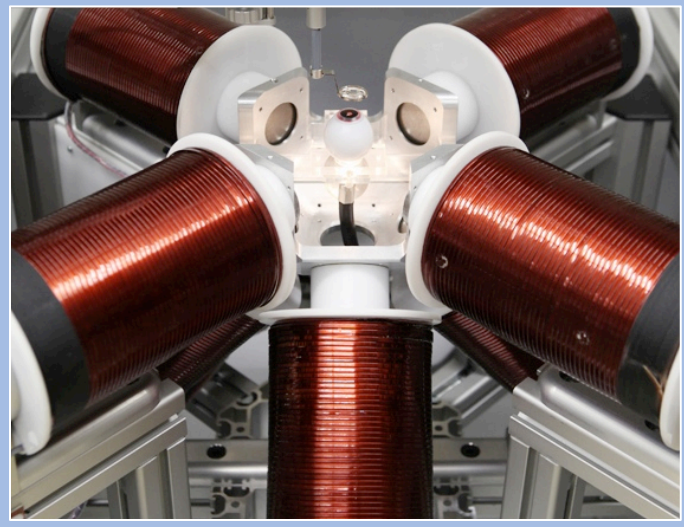
Fig. 3. Selective renal angiogram.

Fig. 4. Selective renal angiogram showing expanding process.

Adapted from H. Tillander, *Acta radiol,*1956.

[1] H. Tillander, *Acta radiol,*1951. [2] J. W. Devine et al., *Surgery,* 1953. [3] H. Tillander, *Acta radiol,*1956.

The Octomag: An Electromagnetic Manipulation System



- Linear superposition of magnetic fields and gradients

$$\mathbf{B}(\mathbf{P}) = \sum_{e=1}^{8} \mathbf{B}_e(\mathbf{P}) = \sum_{e=1}^{8} \tilde{\mathbf{B}}_e(\mathbf{P}) i_e$$

$$\mathbf{B}(\mathbf{P}) = \begin{bmatrix} \tilde{\mathbf{B}}_1(\mathbf{P}) & \cdots \tilde{\mathbf{B}}_8(\mathbf{P}) \end{bmatrix} \begin{bmatrix} i_1 \\ \vdots \\ i_8 \end{bmatrix} = \mathrm{B}(\mathbf{P})\boldsymbol{I}$$

- Torque and force generation

$$\begin{bmatrix} \mathbf{T} \\ \mathbf{F} \end{bmatrix} = \begin{bmatrix} Sk(\mathbf{M})\mathcal{B}(\mathbf{P}) \\ \mathbf{M}^T \mathcal{B}_x(\mathbf{P}) \\ \mathbf{M}^T \mathcal{B}_y(\mathbf{P}) \\ \mathbf{M}^T \mathcal{B}_z(\mathbf{P}) \end{bmatrix} \begin{bmatrix} i_1 \\ \vdots \\ i_n \end{bmatrix} = \mathcal{A}_{T,F}(\mathbf{M}, \mathbf{P})\boldsymbol{I} \qquad \boldsymbol{I} = \mathcal{A}_{T,F}(\mathbf{M}, \mathbf{P})^{\dagger} \begin{bmatrix} \mathbf{T}_{des} \\ \mathbf{F}_{des} \end{bmatrix}$$

- Fields up to 40 mT
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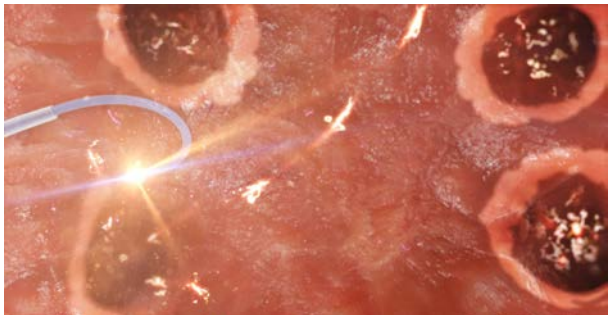
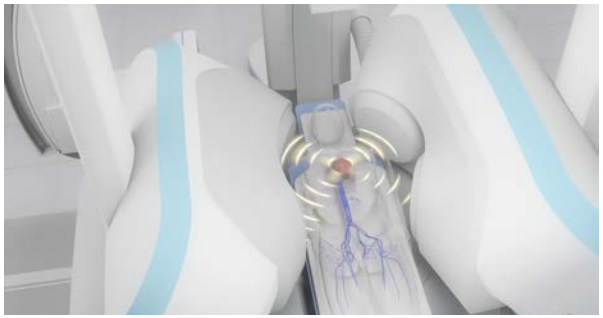
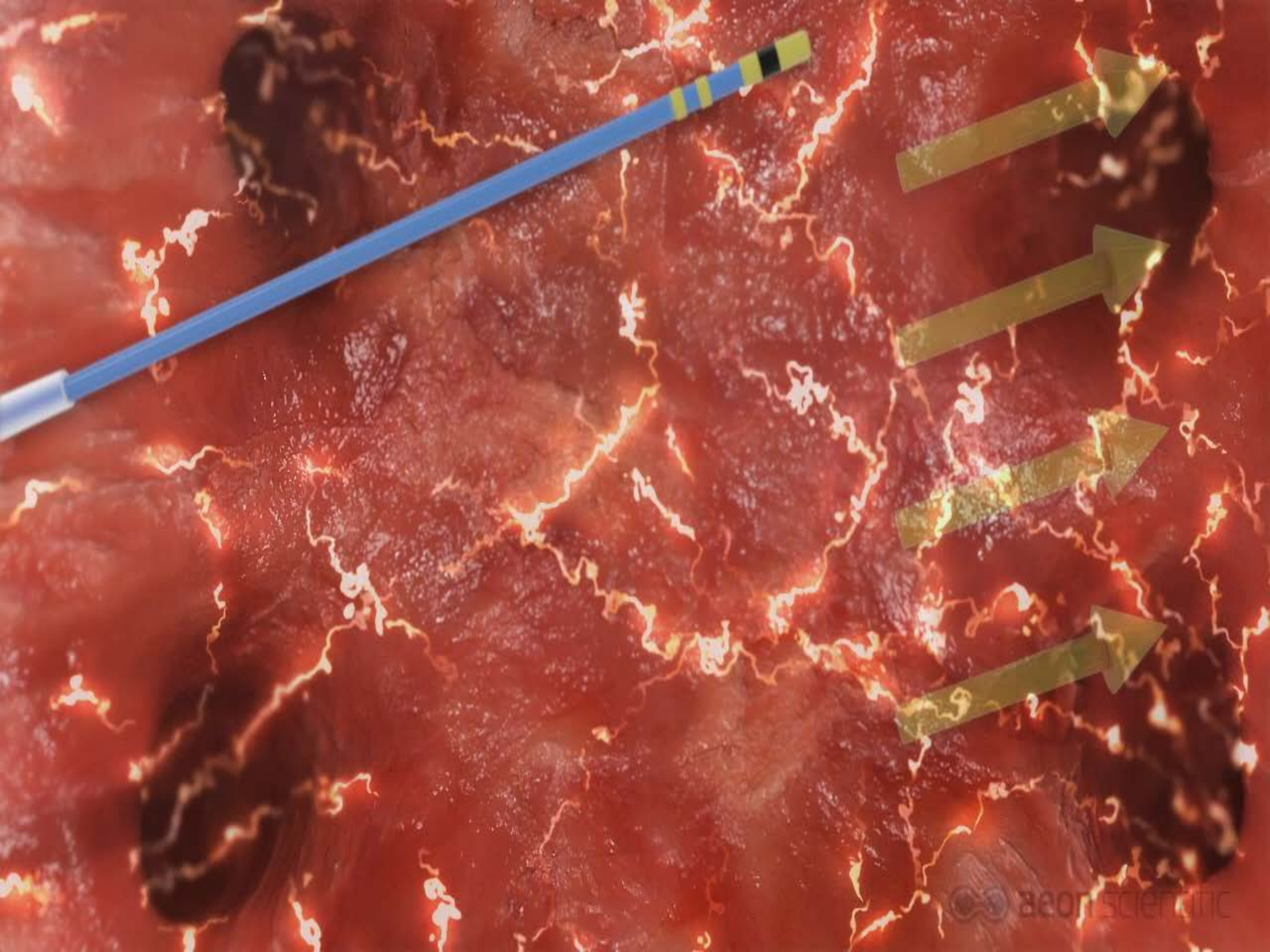
Aeon Phocus™ - Electromagnetic catheter steering system

Joystick controlled mapping and ablation

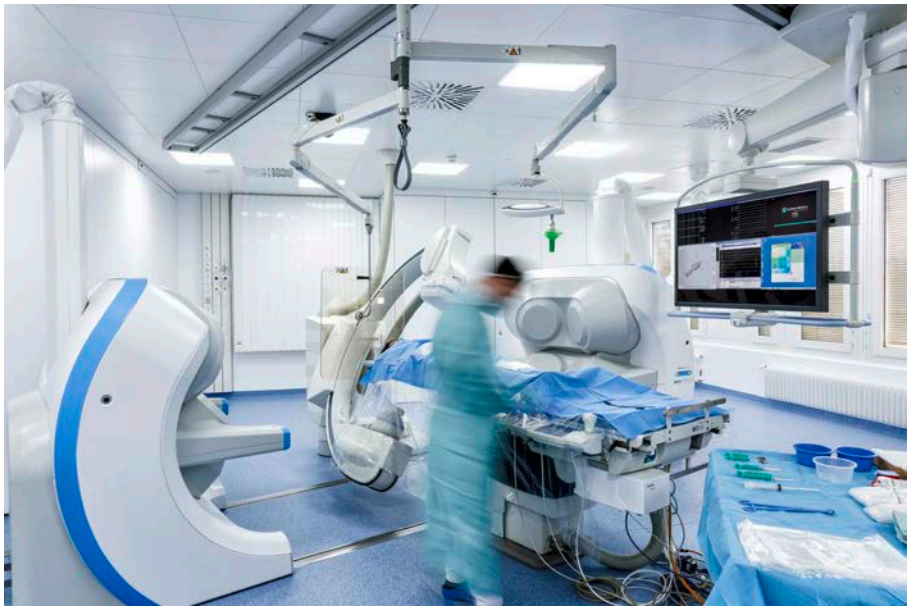





aeon scientific



First Clinical Installation of the The Aeon Phocus



Disclaimer: The Siemens angiography system shown system is a customized solution and not commercially available in all countries. Due to regulatory reasons the future availability cannot be guaranteed. Please contact your local Siemens organization for further details.

First Use in Humans (21 August 2015)

The Beginning of Medical Robotics

- **1985**
- **Memorial Medical Center Long Beach, California**
- **CT guided brain biopsy**

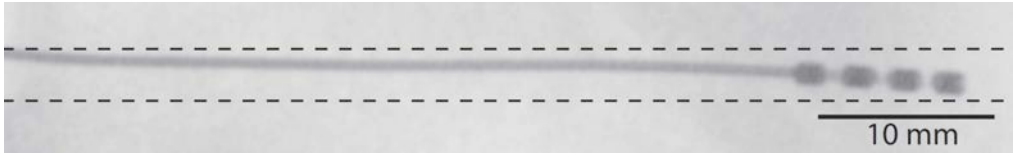
Kwoh YS, Hou J, Jonckheere EA, et al. A robot with improved absolute positioning accuracy for CT guided stereotactic brain surgery. *IEEE Trans Biomed Eng*. 1988.

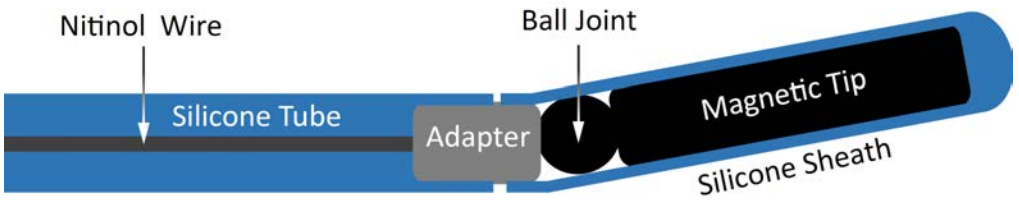
Returning to Neurosurgery

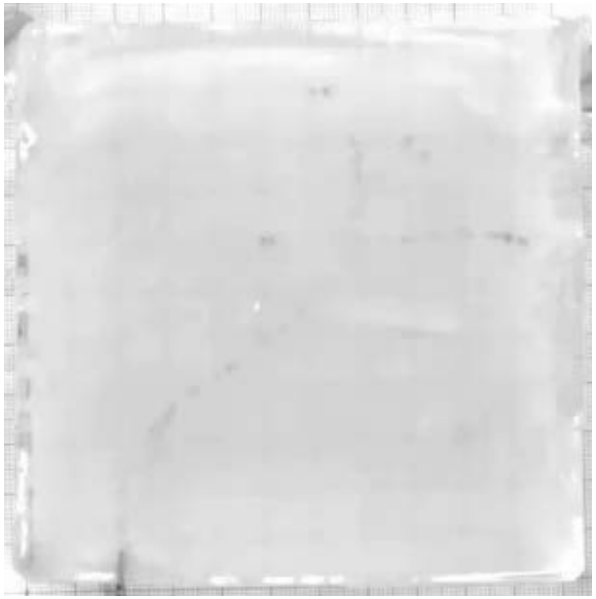
Deep Brain Stimulation Electrode insertion

Magnetically Guided DBS Electrodes

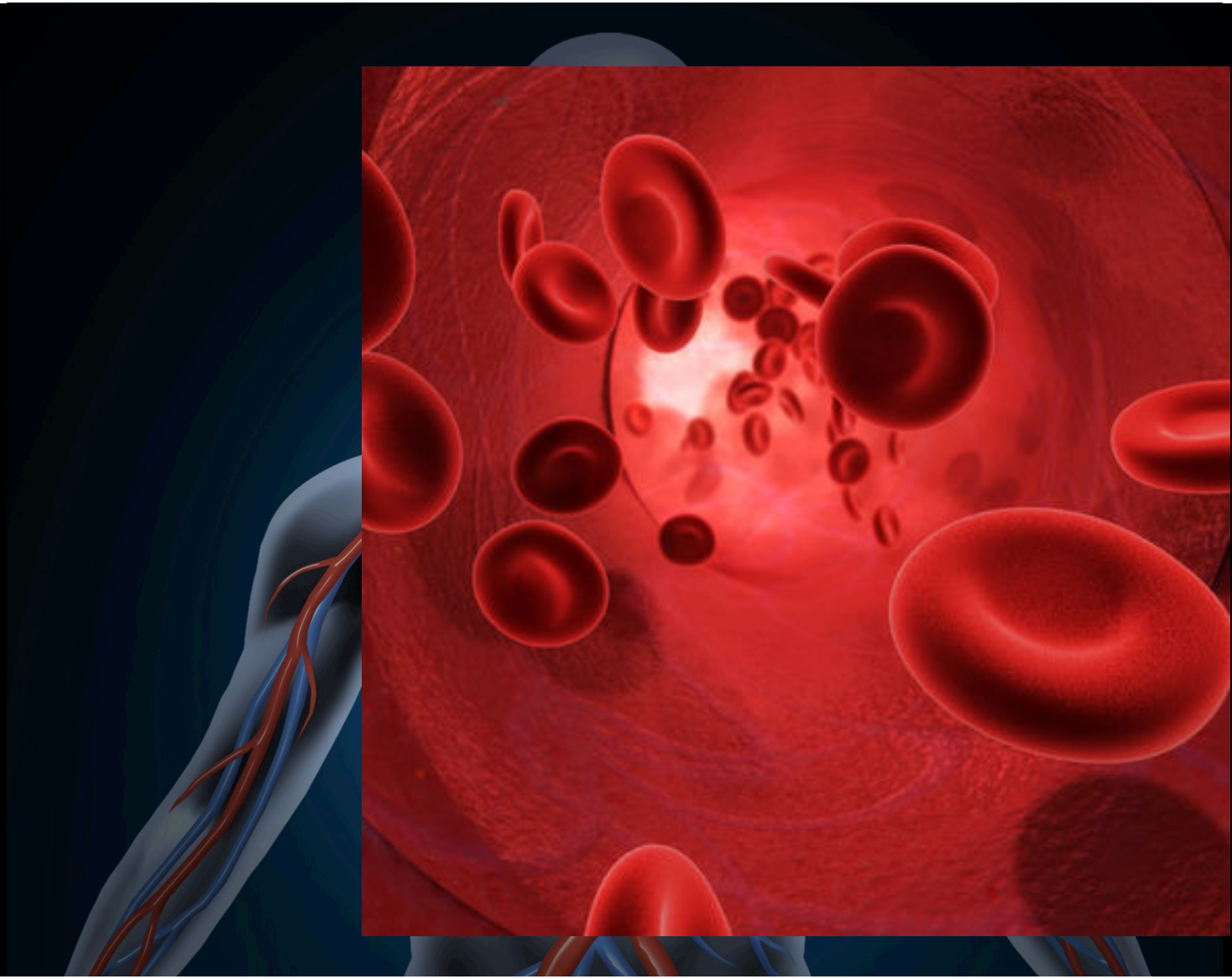
- Needle can deflect on entry
- Missed targets require multiple insertions
- Magnetic guidance allows for controlled navigation
- Magnetic torque provides continuous choice in path curvature.





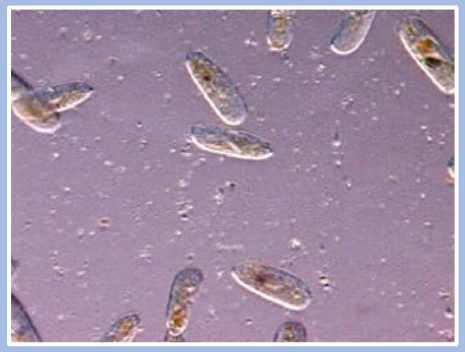


Going Smaller



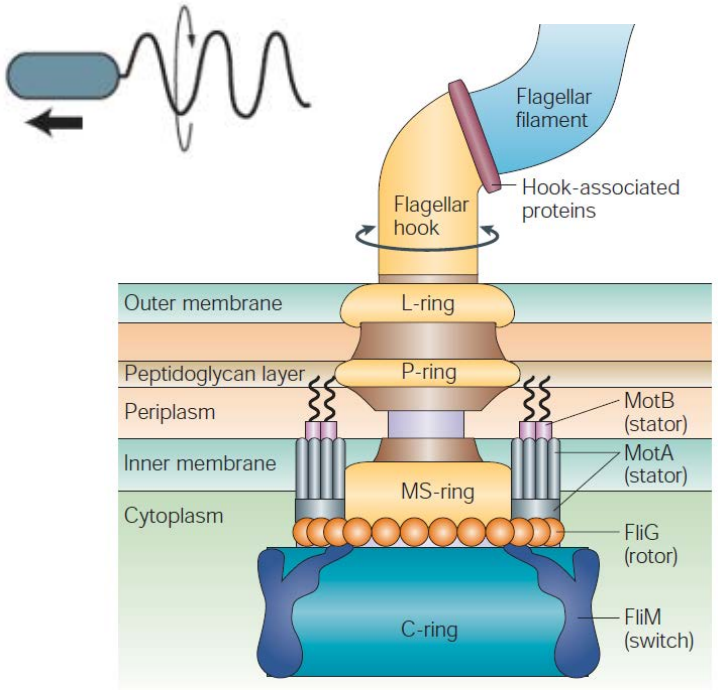
Swimming microorganisms

Paramecia, spermatazoa, cilia and flagella

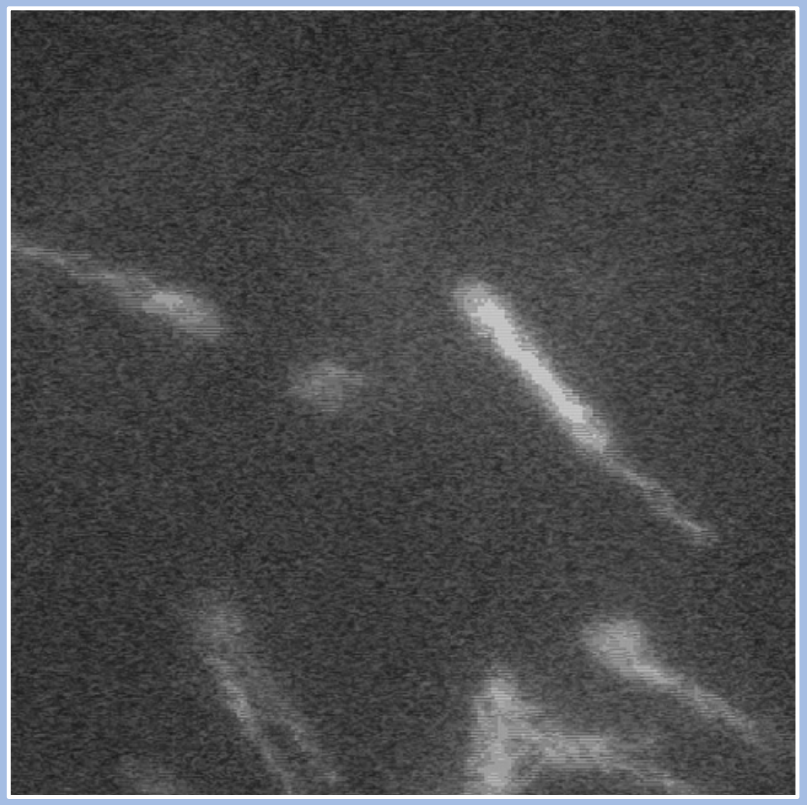


“Bacteria swim by rotating their flagellar filaments” (1973, Berg)

E. coli: “Nature’s Microrobots”

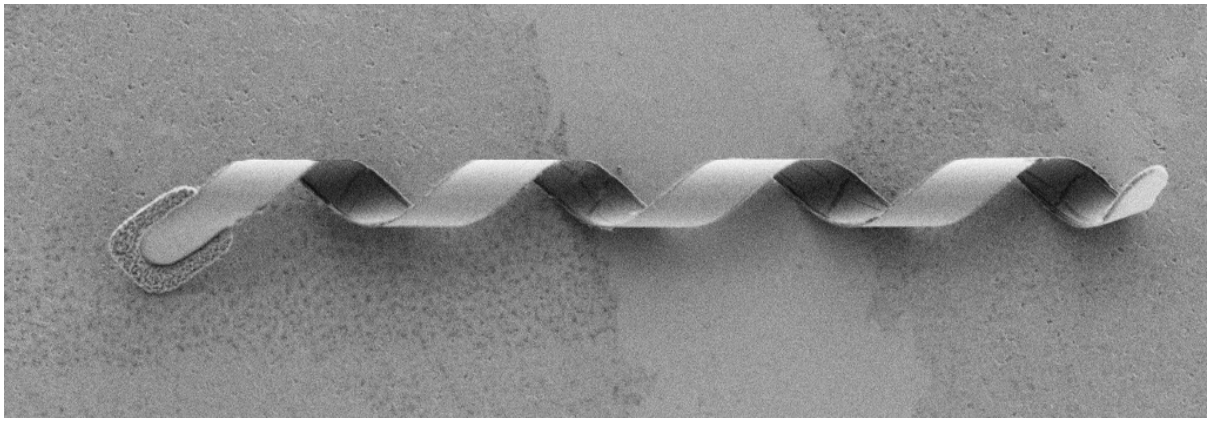


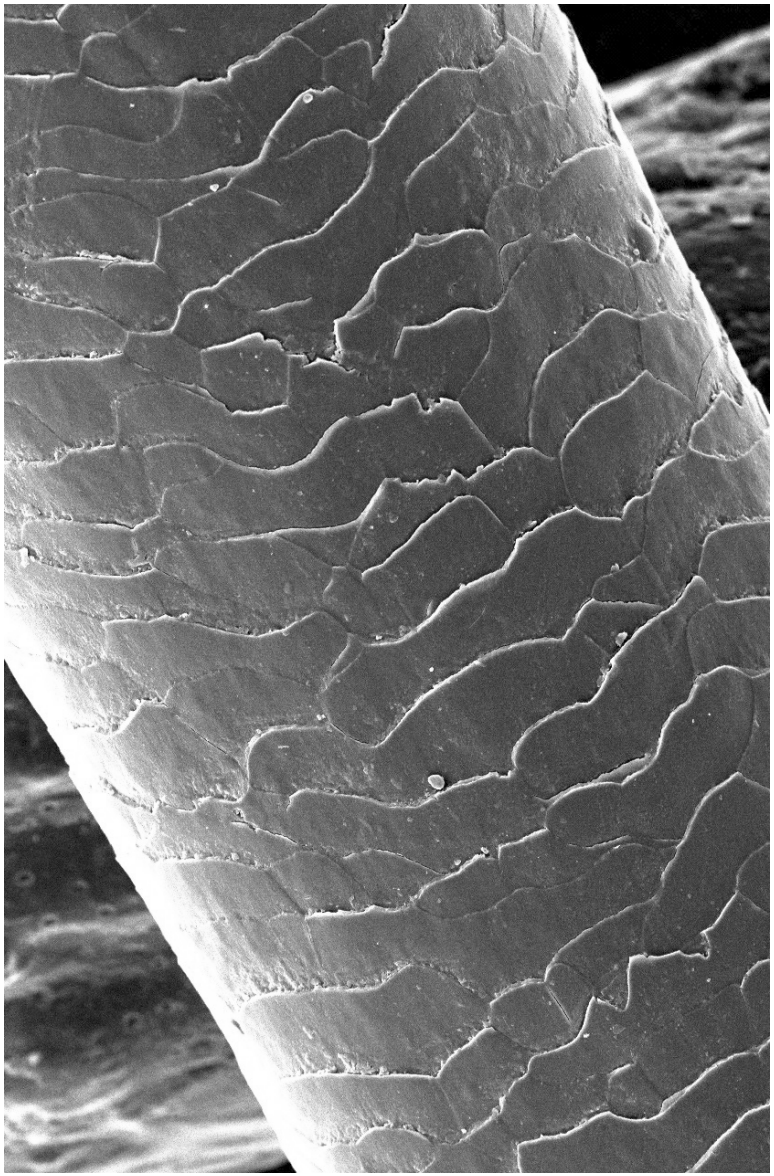
Nat. Rev. Mol. Cell Biol. 5, 1024 (2004)



H.C. Berg (Harvard University)

Artificial Bacterial Flagella (ABFs)

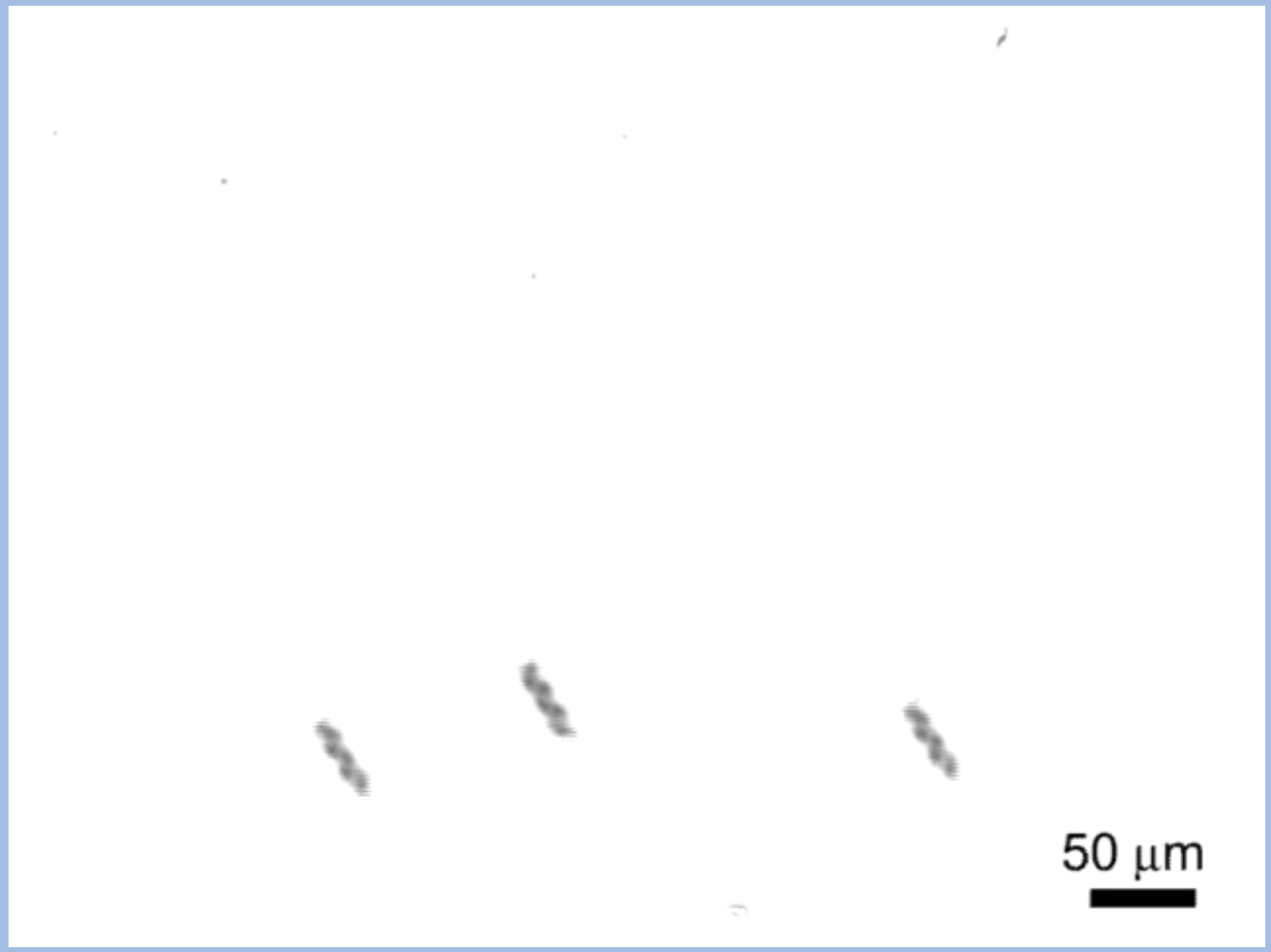




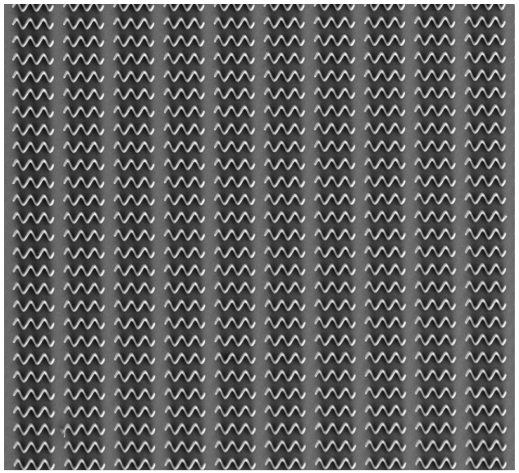
Artificial Bacterial Flagella

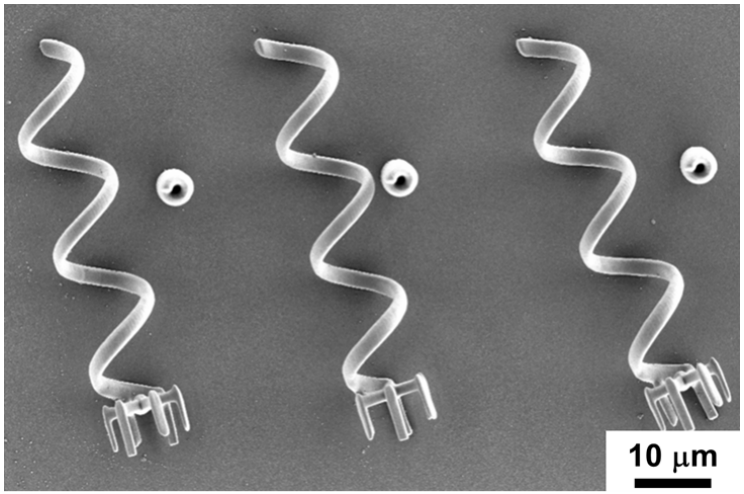
2012 Guinness Book of World Records

Synchronized Swimming



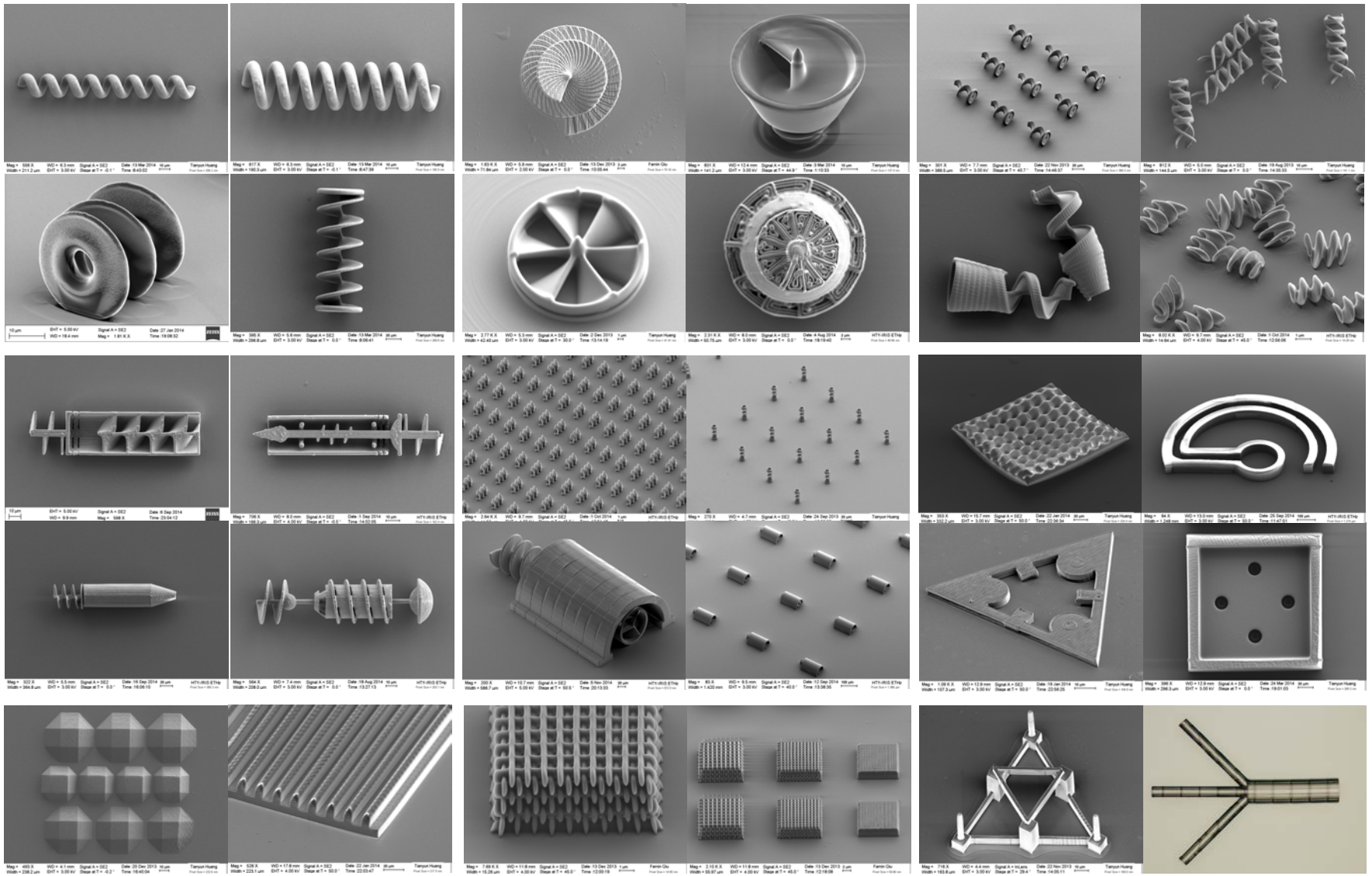
3D NanoPrinting





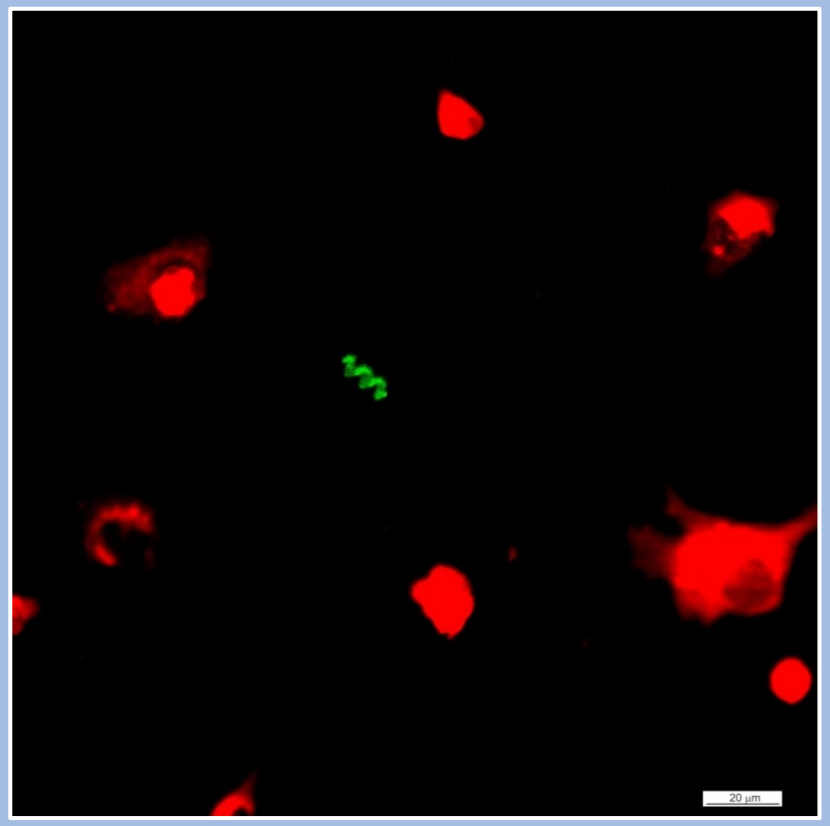
Magnetic Helical Micromachines. Fabrication, Controlled Swimming, and Cargo Transport.
S. Tottori, L. Zhang, F. Qiu, K.K. Krawczyk, A. Franco-Obregón, B.J. Nelson, *Advanced Materials*, (2012)

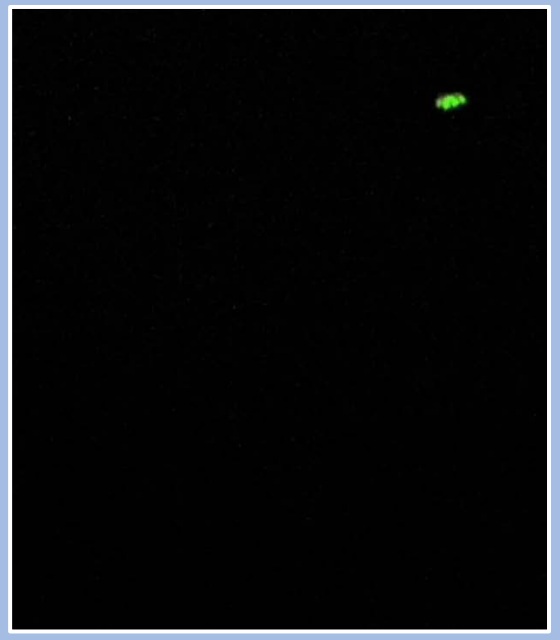
3D Nano-printed Microstructures (2μm-2000μm)



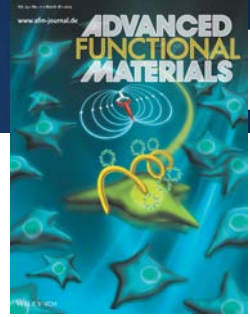
3D Printed Microtransporters: Compound Micromachines for Spatiotemporally Controlled Delivery of Therapeutic Agents. Ti.Y.Huang, M.S. Sakar, A. Mao, A.J. Petruska, F. Qiu, X.B. Chen, S. Kennedy, D. Mooney, and B.J. Nelson, *Advanced Materials*, (2015)

Delivering Drugs to Individual Cells

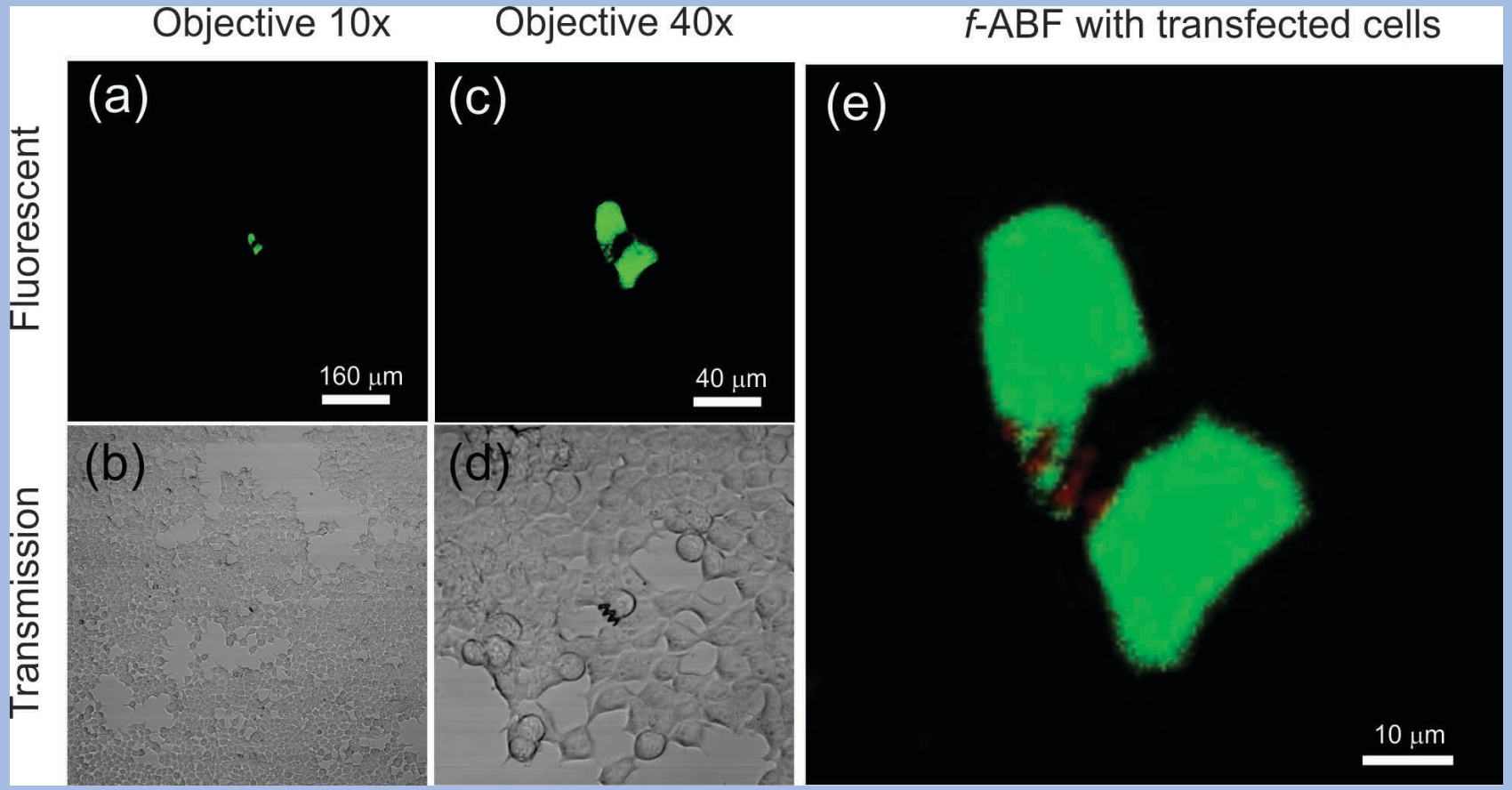




Cell Transfection and Gene Expression

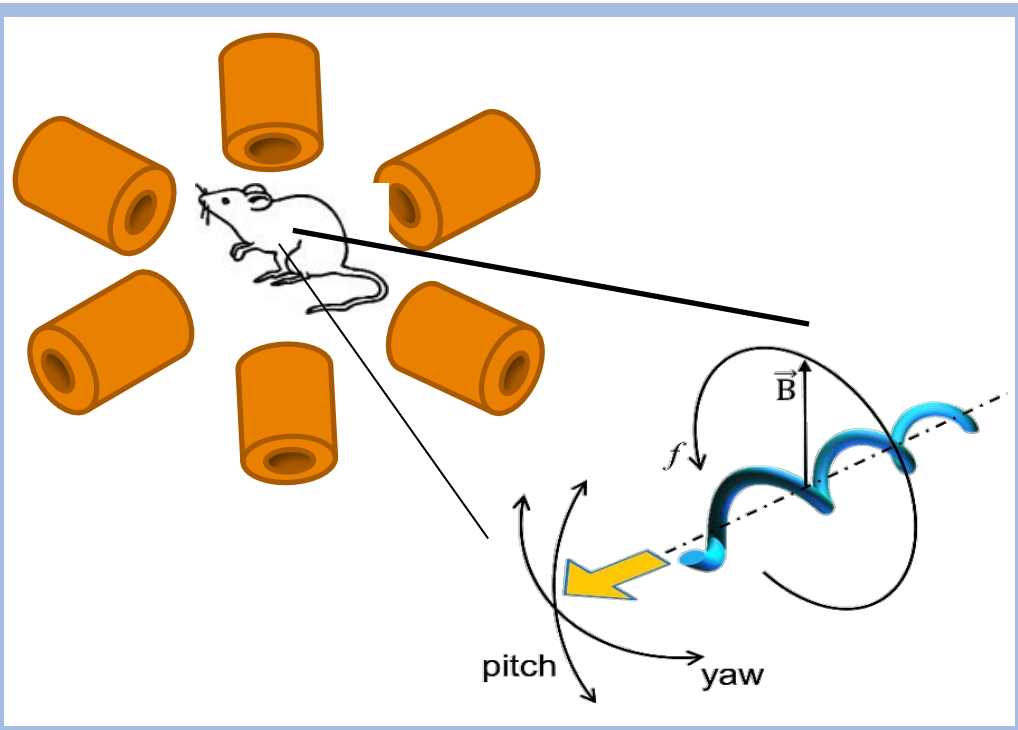


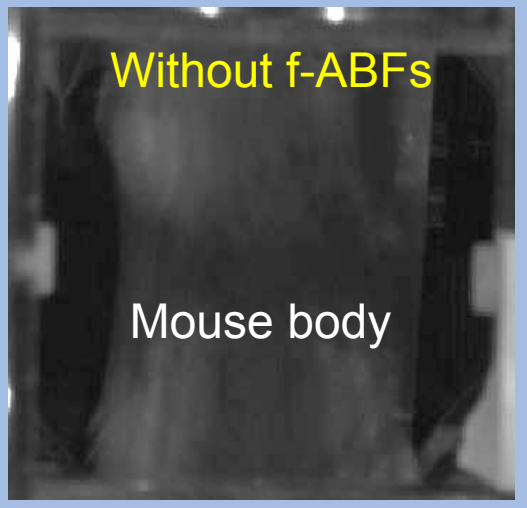
- Only targeted cells were transfected by DNA carried on ABFs
- Cells expressed the Venus protein (a Yellow Fluorescent Protein) encoded in the DNA

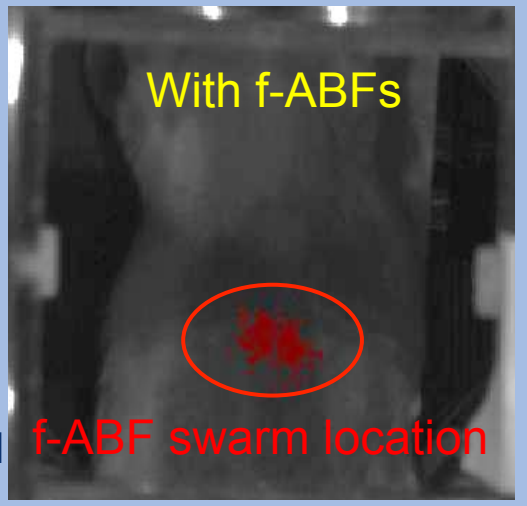


F. Qiu *et al. Adv. Funct. Mater.*, (2015)

in vivo Swimming



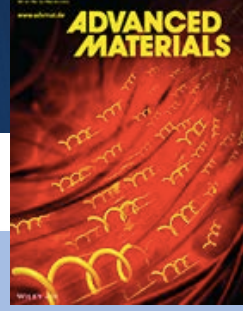


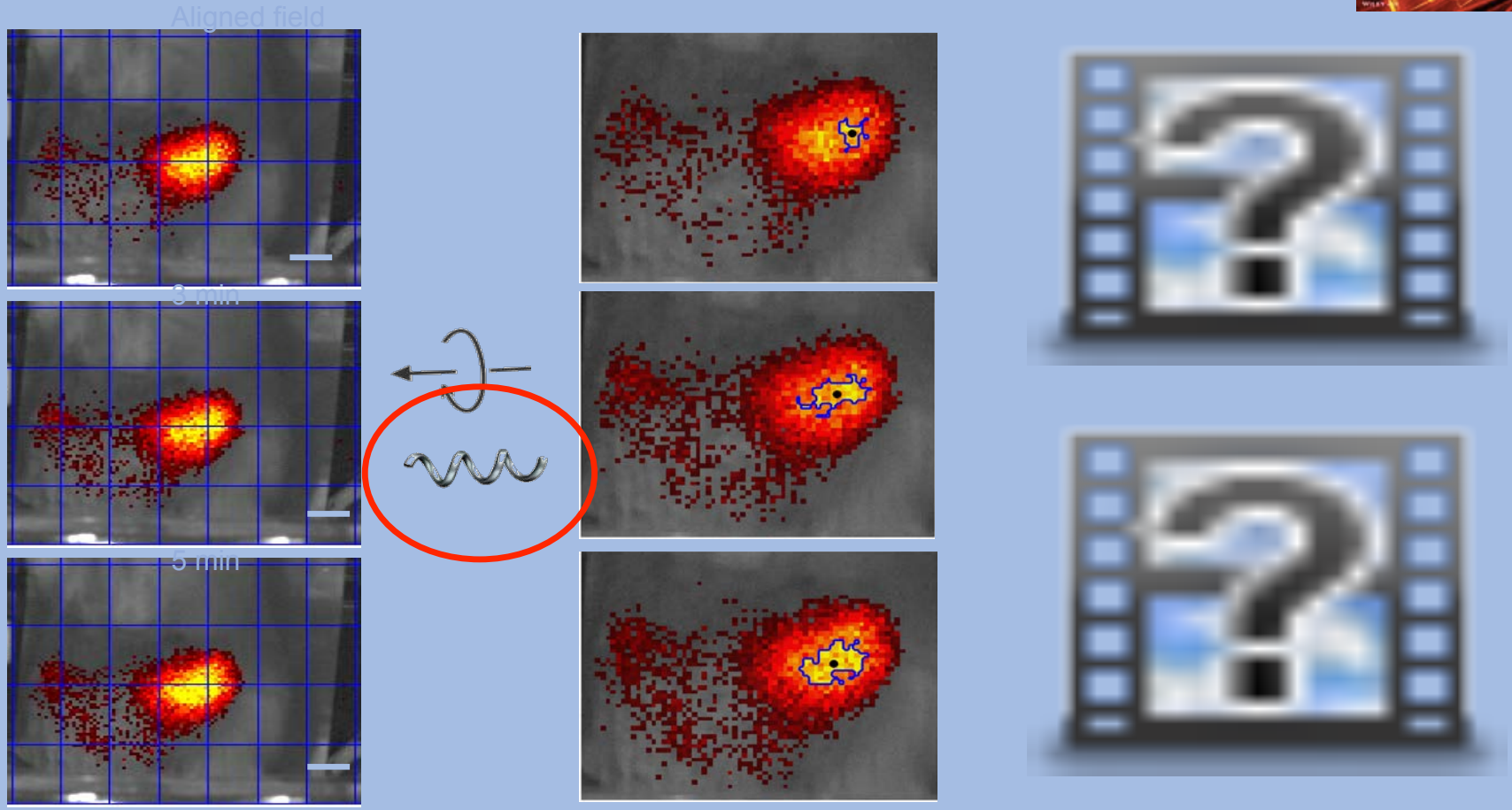


- NIR-797 dye served as a tracking probe for an *in vivo* imaging system (IVIS)
- A swarm of f-ABFs were injected into the peritoneal cavity
- The swarm was observed (the red cloud) and controllably moved

Controlled In Vivo Swimming of a Swarm of Bacteria-Like Microrobotic Flagella.
A. Servant, F. Qiu, M. Mazza, K. Kostarelos, B.J. Nelson, *Advanced Materials*, (2015)

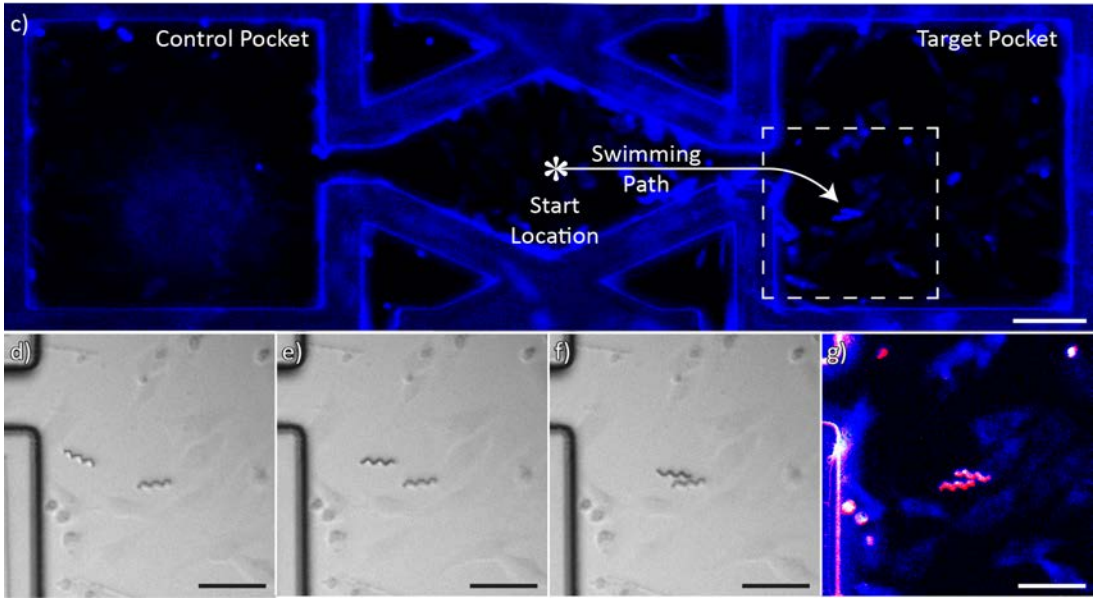
in vivo Swimming of Swarms

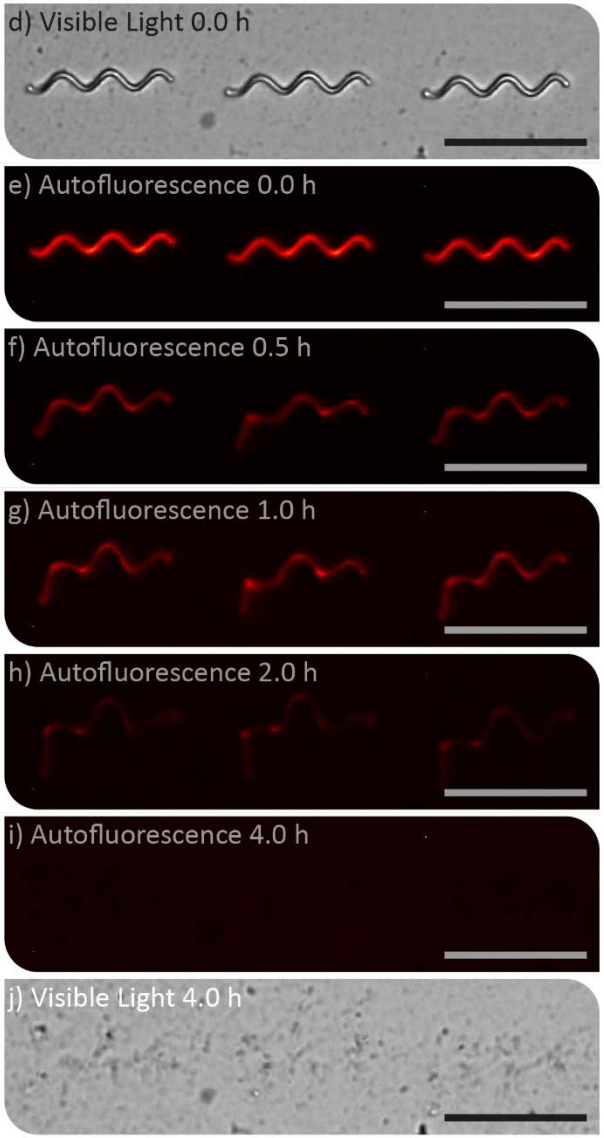




Controlled In Vivo Swimming of a Swarm of Bacteria-Like Microrobotic Flagella.
A. Servant, F. Qiu, M. Mazza, K. Kostarelos, B.J. Nelson, *Advanced Materials*, (2015)

Bioerodable Microrobots



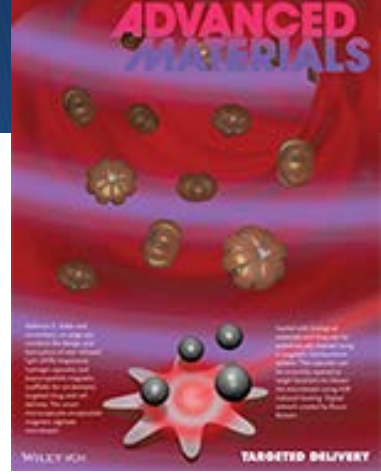


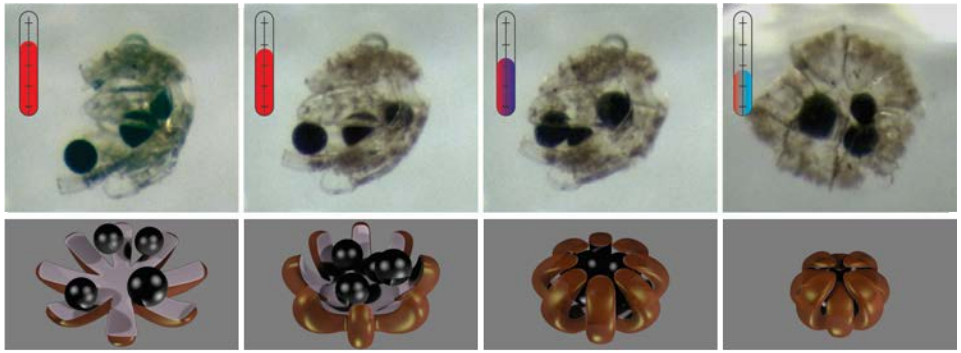
Superparamagnetic-hydrogel composite

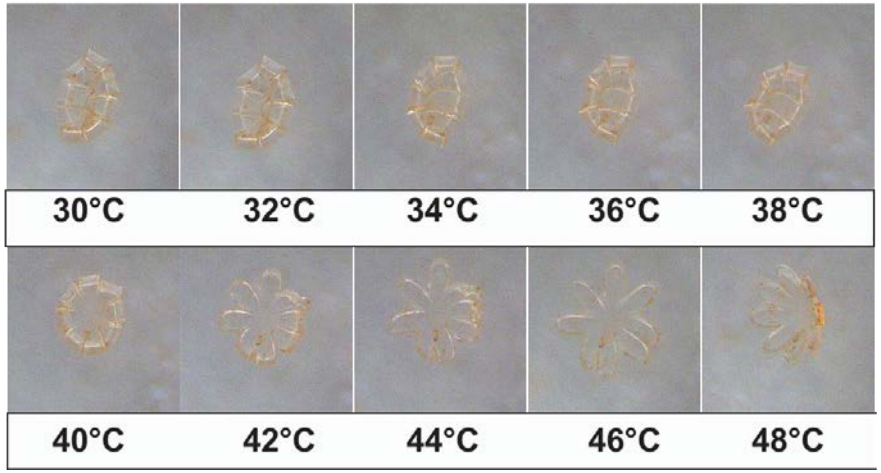
3D printable using two-photon photopolymerization

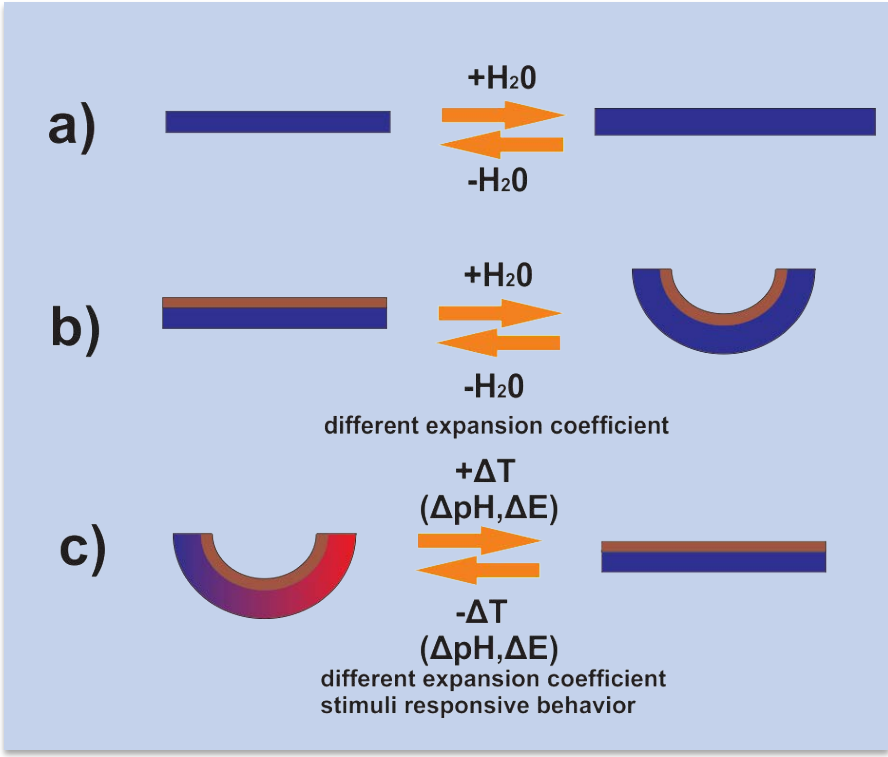
Degradable Magnetic Composites for Minimally Invasive Interventions: Device Fabrication, Targeted Drug Delivery, and Cytotoxicity Tests. C. Peters, M. Hoop, S. Pané, B.J. Nelson, and C. Hierold, *Advanced Materials*, (2016)

Hydrogel-Based Self-folding Structures



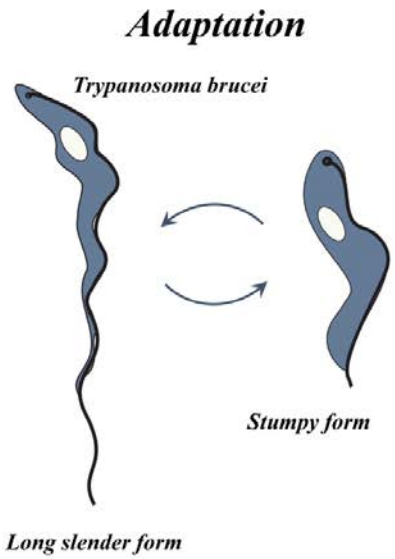


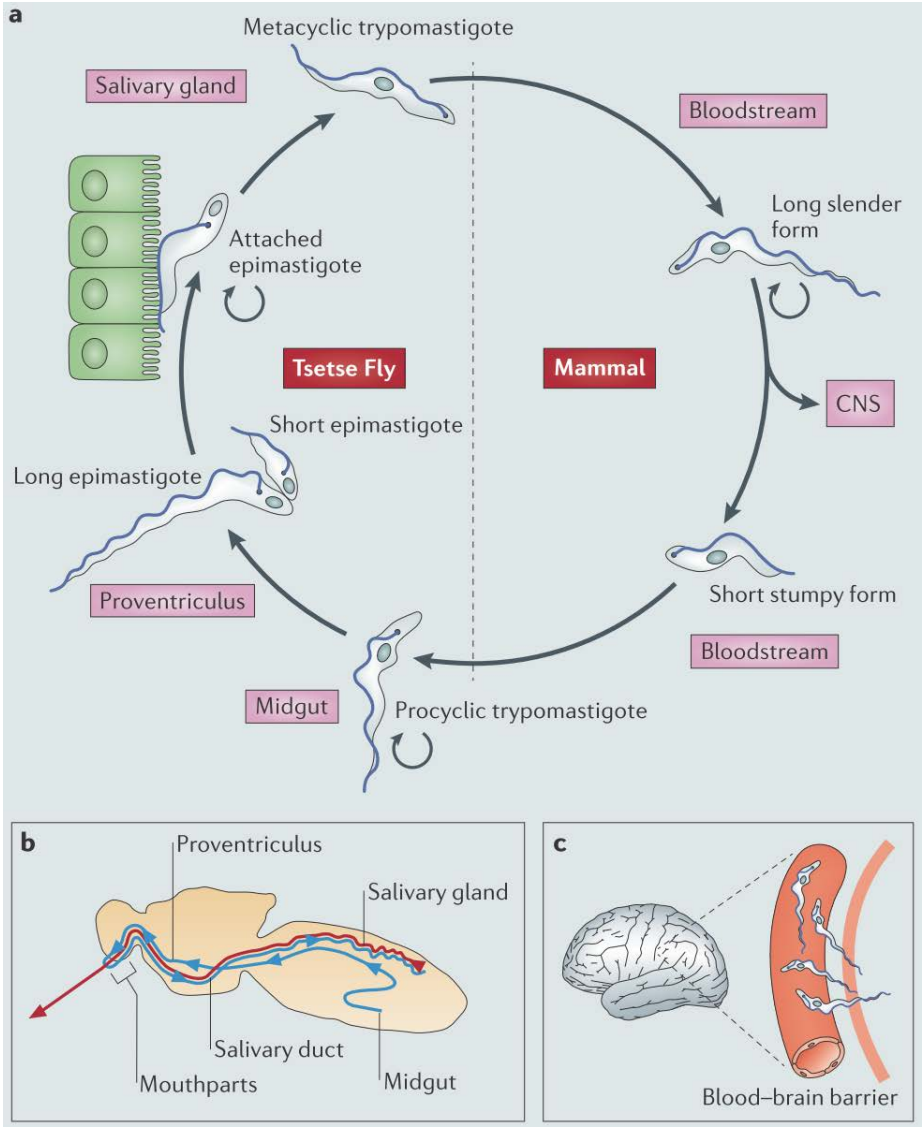




An Integrated Microrobotic Platform for On-Demand, Targeted Therapeutic Interventions. S. Fusco, M.S. Sakar, S. Kennedy, C. Peters, R. Bottani, F. Starsich, A. Mao, G.A. Sotiriou, S. Pané, . E. Pratsinis, D. Mooney, and B.J. Nelson, *Advanced Materials*, (2014)

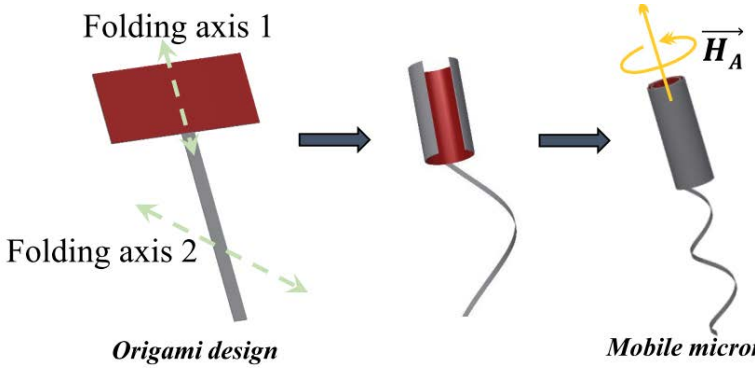
Shape Changing Microrobots: The Life Cycle of *Trypanosoma brucei*

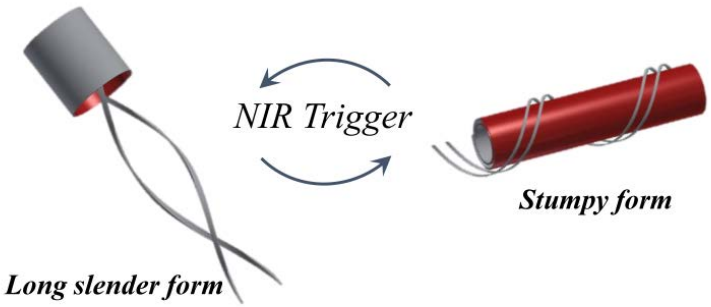


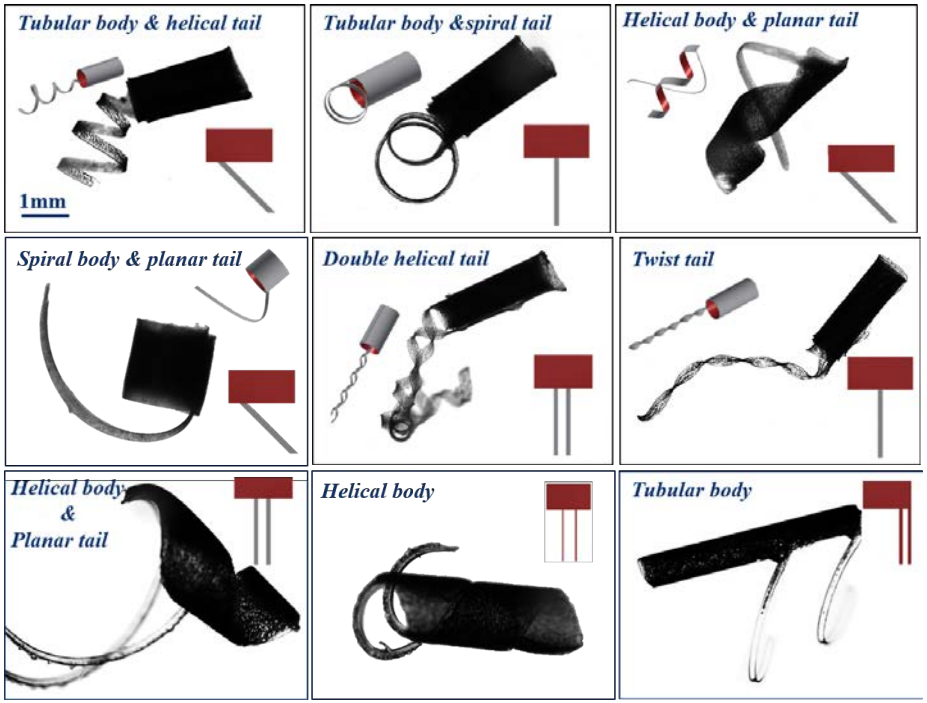


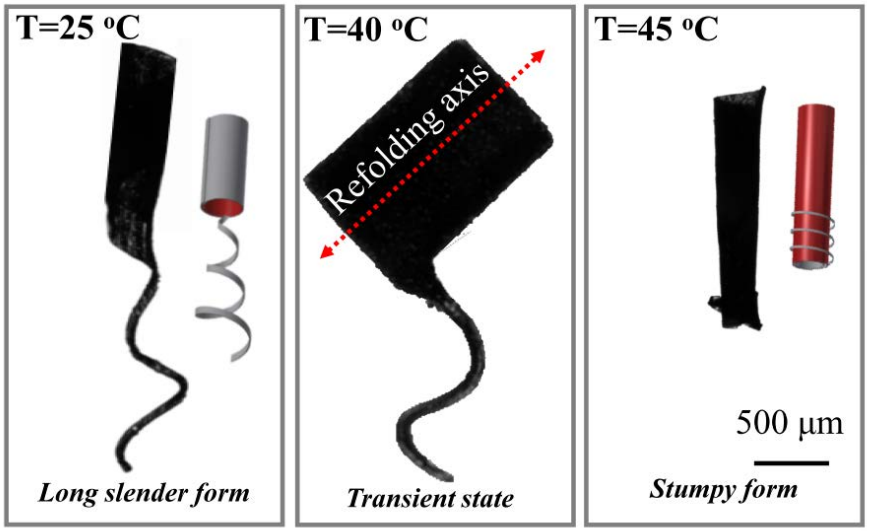
G. Langousis et al. *Nature Rev. Microbiol.* 2014

Origami Microrobots and Programmable Magnetic Anisotropy







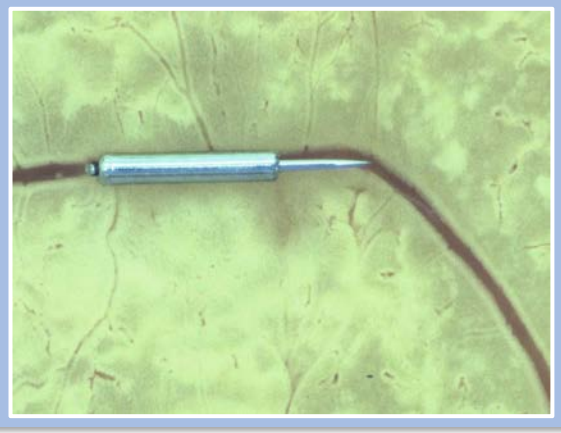


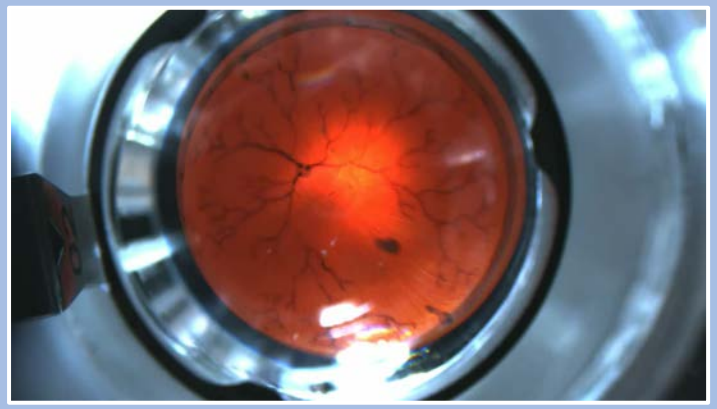
Soft compound micromachines with programmable motility and morphology, H-W Huang, M.S. Sakar, A.J. Petruska, S. Pane, B.J. Nelson, *Nature Communications*, (2016)

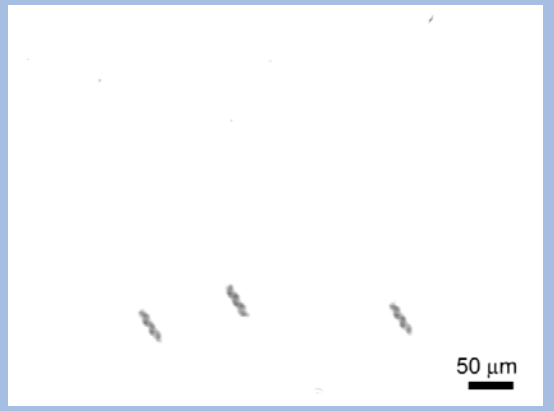
Shape Changing, Soft Microrobots

Outlook for Medical MicroRobotics

- The Micro/Nanorobotics Community has made tremendous progress in a decade
  - Power, locomotion, fabrication
  - Magnetic guidance, in particular, has progressed
  - Addressing appropriate therapies
- The potential is huge, but the timeline uncertain
- The field is in its infancy, but clinical application is on the horizon







The Need for Access to Surgery in the Developing World

- Sustainable development goals “cannot be achieved without explicitly addressing one of the most crucial needs facing the world: **a lack of access to surgery**.”
  - Shrime and Meara, Harvard Medical School, in *NYTimes*, 25 Sep 2015.

- “Nearly one-third of human disease is amenable to surgery”
  - Shrime et al. *The Lancet Global Health*, Vol. 3, Apr 2015.

- H.I.V., tuberculosis and malaria make up less than one-tenth of the global disease burden, combined.

- Surgery: “The neglected stepchild of global health.”
  - Farmer and Yim, *World J Surg*. 2008 Apr; 32(4): 533–536.

Photo from *Essential Surgery*, The World Bank 2015