FEEDBACK CONTROL AT SMALL SCALES:
FOR BIOLOGY AND MEDICINE APPLICATIONS

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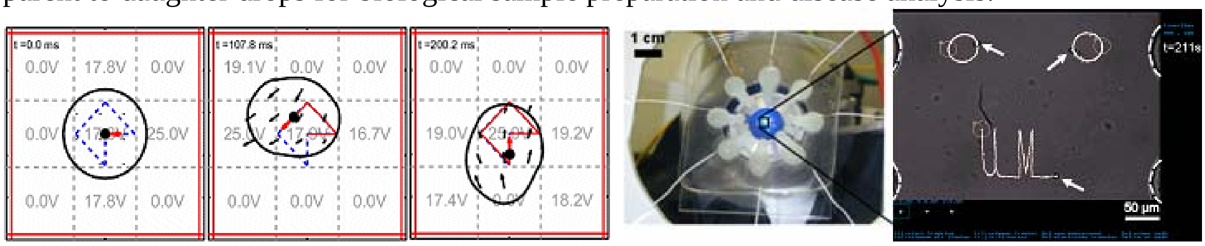
My interest is in using (feedback) control to enable new and useful biomedical systems, such as hand-held devices for accurately manipulating single cells on chip and control methods for targeting drug-coated nano-particles to deep tumors.

Feedback control is ubiquitous in *macro*-scale engineered systems (from airplanes to operational amplifiers), and in living things (from the gross organ level down even to sub-cellular processes). It allows them to achieve high performance even in complex and uncertain environments by detecting and correcting for errors as they occur. The same need for feedback control also exists for engineered micro- and nano-scale systems: they too must perform well in uncertain and complex environments. But, in broad terms and with the exception of accelerometers and atomic force microscopes, feedback control has largely not yet been developed for miniaturized engineered systems. The reason is simple: the people who do sophisticated control (control theorists) and those who make micro/nano systems overlap very little. My group lives at the intersection of these fields: we wish to develop and utilize feedback control methods to enable new and novel miniaturized systems, for biology and medicine.

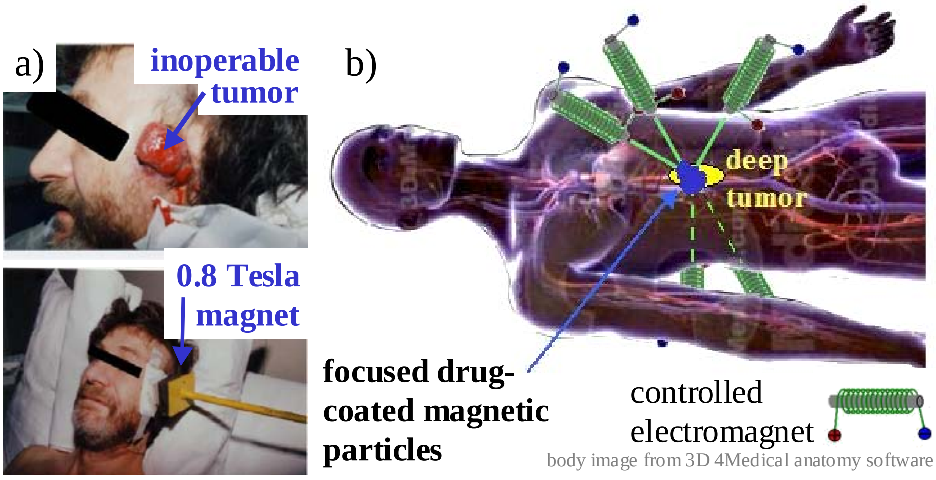
We have developed methods to precisely control micro-flows. Our methods allow precise, robust, and gentle manipulation of cells on chips to micro-meter precision in hand-held devices. This is now being developed with a company to extract cells from complex human samples (salivia, urine, blood) to present them to sensors for disease detection, in a hand-held format that nurses can carry in their pockets. Similarly, our control algorithms will allow electrowetting systems (these are systems that manipulate flows on chip by electrically modulating surface tension) to now also precisely meter liquids, to place cells on sensors, and to sort cells from parent to daughter drops for biological sample preparation and disease analysis.



Control of particles by electrowetting actuation (one particle, in simulation) and by electroosmotic flow (in our experiment using simple and cheap PDMS devices, multiple particles at once).

To do the above it was not possible to simply transfer control algorithms from macro-scale applications to the micro scale. Macro-scale control laws have been motivated by phenomena arising in aerospace, mechanical, electrical, and chemical systems. New phenomena on the micro-scale (for micro-flows especially: surface effects, moving fluid boundaries, and the combination of stochastic phenomena with continuum flows) led to the need to develop new control methodologies. It was also necessary to create the infrastructure that enables feedback control design: we had to develop models amenable to control design, had to phrase necessary device tasks (such as split this droplet accurately) as tractable mathematics questions (the split task turns out to be a shape-dependent least squares problem), had to create control algorithms to solve them, and then had to validate and demonstrate our solutions experimentally. The result is that we now have unique capabilities to control flows and objects on chips with unprecedented degrees of freedom and accuracy. This has enabled a variety of potential applications, from cleaning human samples to manipulating quantum dots.

Our next goal, which is much harder still, is to control particles in people. In particular, we want to magnetically control nano-scale particles inside the human body, for focusing chemotherapy to deep-tissue tumors. This new project is based on successful phase-I magnetic drug-delivery human clinical trials (Lubbe, Germany) but treatment is limited to tumors near the skin surface. We have defined the control problem for focusing treatment to deep-tissue tumors and will present initial modeling and control results, as well as noting the *many* challenges that remain.



A) In the phase 1 human clinical trials of our collaborator Dr. Andreas Luebbe, magnetic drug carriers can only be focused to tumors at or near the skin surface. B) Our control goal is to dynamically manipulate magnets, one against the other, to focus magnetic carriers between them to deep tissue targets.

One of the most exciting things about working in this area, between micro/nano systems, control, and medicine, is that it requires that my group really do research in all three. For example, I now have a medical student in my lab who will do animal dissections and who will study human autopsy cases at NCI. Her goal is to understand the location, depth, and shape of tumors that killed patients and that we should try to target (she is co-advised with a colleague at NIH). I will learn about animal dissections from her and she is learning about magnetic drug delivery from me. While the research questions are many, and typically any single one of them can either be a PhD thesis unto itself or be unsolvable, the key has been to define questions that are tractable but useful – an art unto itself. Interdisciplinary issues are typically those of understanding first and problem definition second: we must be able to speak the language of biologists and doctors, and must be able to explain our concepts to them in simple but accurate terms, before we can define high impact problems. In general, for commercial and societal impact, I think feedback control of miniaturized devices *must* happen before they can be included as part of complex systems because feedback is needed to allow each device to act reliably and robustly. For my own individual research group, the focus is on applications where control can enable significantly better treatment of patients (like the drug targeting example above). Put simply: my goal is to develop control methods to create systems that will dramatically improve the health of people.