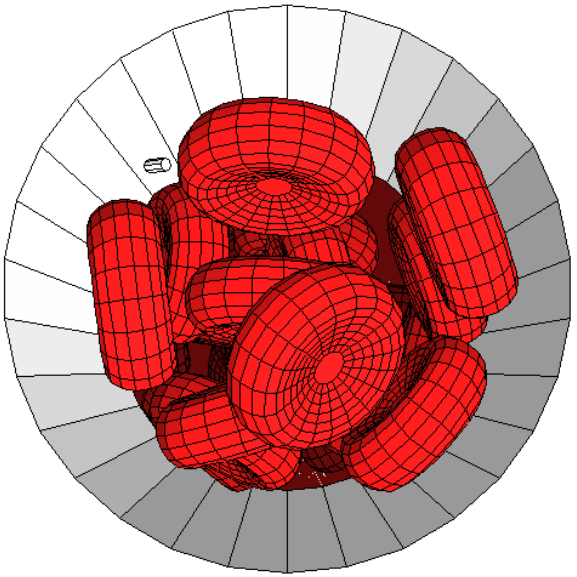
Swarms of Microscopic Devices:
Applications to Biology and Medicine

Tad Hogg
HP Labs



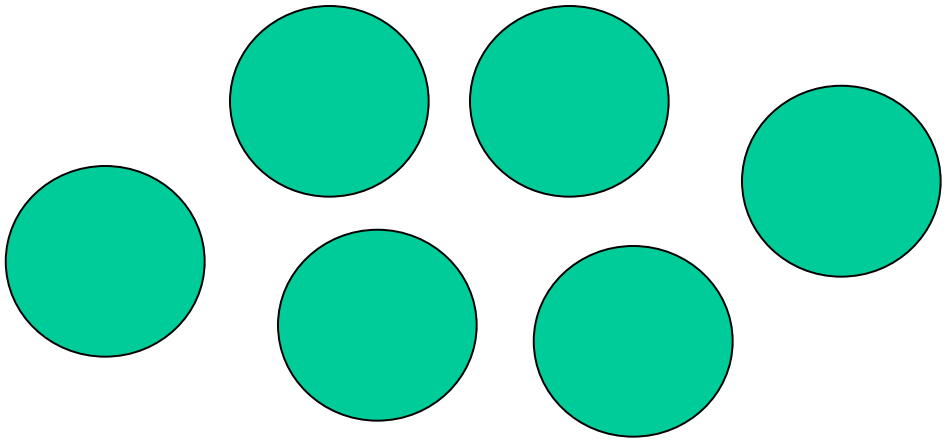
with
Phil Kuekes, Zhiyong Li, Irene Gabashvili (HP Labs)
Arancha Casal (while at Stanford Medical School)
Adriano Cavalcanti (Unicamp Univ of Campinas, Brazil)
Kristina Lerman, Aram Galstyan (USC/ISI)
David Sretavan (UCSF)
Matt Green, Cornwall Lau, Sarah Milne, Dinakar Muthiah
with Maria-Rita D'Orsogna, Dejan Slepcev, Andrea Bertozzi (UCLA/IPAM)

molecular electronics & swarms

- molecular electronics
  - eventually make tiny "eyes" and "hands"
- focus on group behavior
  - large numbers of devices
  - each with limited capability

  } swarm
- evaluate applications prior to fabrication
  - e.g., for biology and medicine
  - analysis tools including microphysics
  - suggest useful hardware trade-offs

swarm of microscopic devices



10^4 – 10^{12} devices

novel applications from activity of group

not any single device

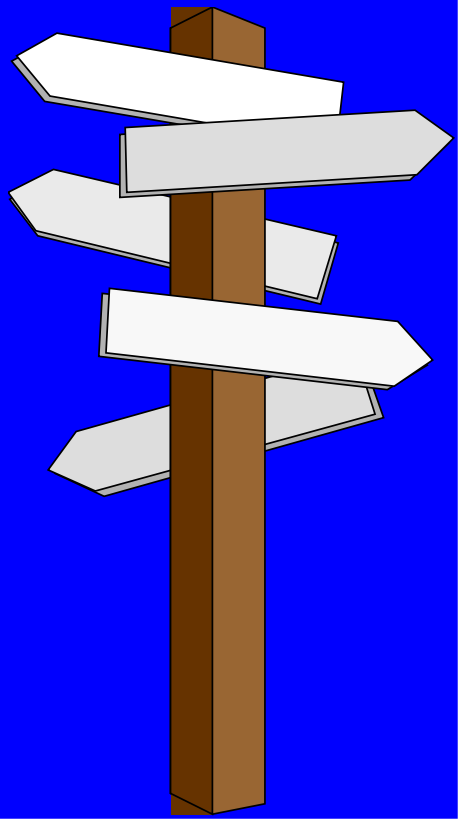
each device: size about 1 micron, mass about 10^{-12} gram
with molecular electronic components

system design challenge:
reliable, useful group behavior
in microscopic environments

- low Reynolds number fluid flow
- chemical diffusion
- Brownian motion

molecular electronics & applications

- microscopic devices
  - based on molecular electronics
- applications
- swarm-based control



size

- atom (~0.1nm)
- large molecule (~1-10nm)
- virus (~10^2nm)
- bacteria (~10^3nm)
- complex cell (~10^4nm)

} component, e.g., switch

} machine, e.g., computer

conventional semiconductor switches & CPU's
100-1000 times larger

molecular devices

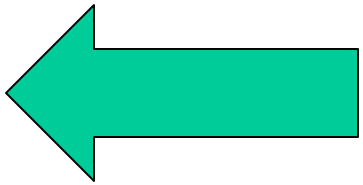
- vision vs. reality
- plausible capabilities

vision

- Feynman, 1959
  - "There's Plenty of Room at the Bottom"
- precise placement of atoms
  - covalent bonding (strong)
  - easier design than weakly bound molecules
    - cf. protein folding
- enable better devices
  - computers
  - material strength/weight (e.g., 50x that of steel)
  - catalysts, sensors, ...

reality

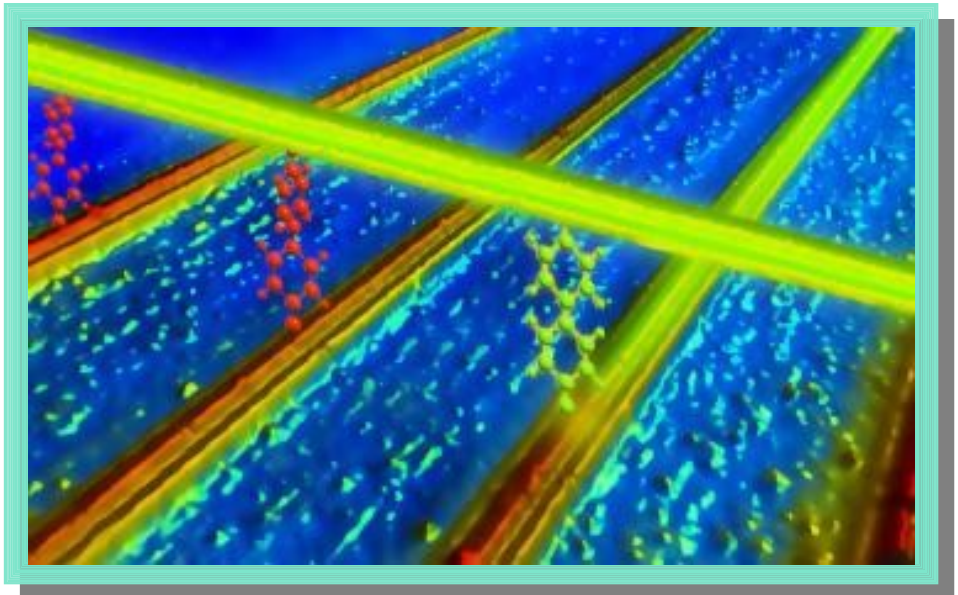
- Atomic Force Microscope (AFM), etc.
  - move, bond single atoms on surfaces
  - a long time to get many!
- programmable bacteria
    - cf. yeast for making bread
  - produce proteins, some logic
  - slow, limited material properties
- self-assembled molecular structures
  - weak bonding on patterned substrates
  - large numbers, with defects



http://www.hpl.hp.com/research/qsr/

crossbar architecture

- molecular switches between nanowires
  - use for memory & logic
  - can connect to larger circuits for I/O
    - demultiplexer



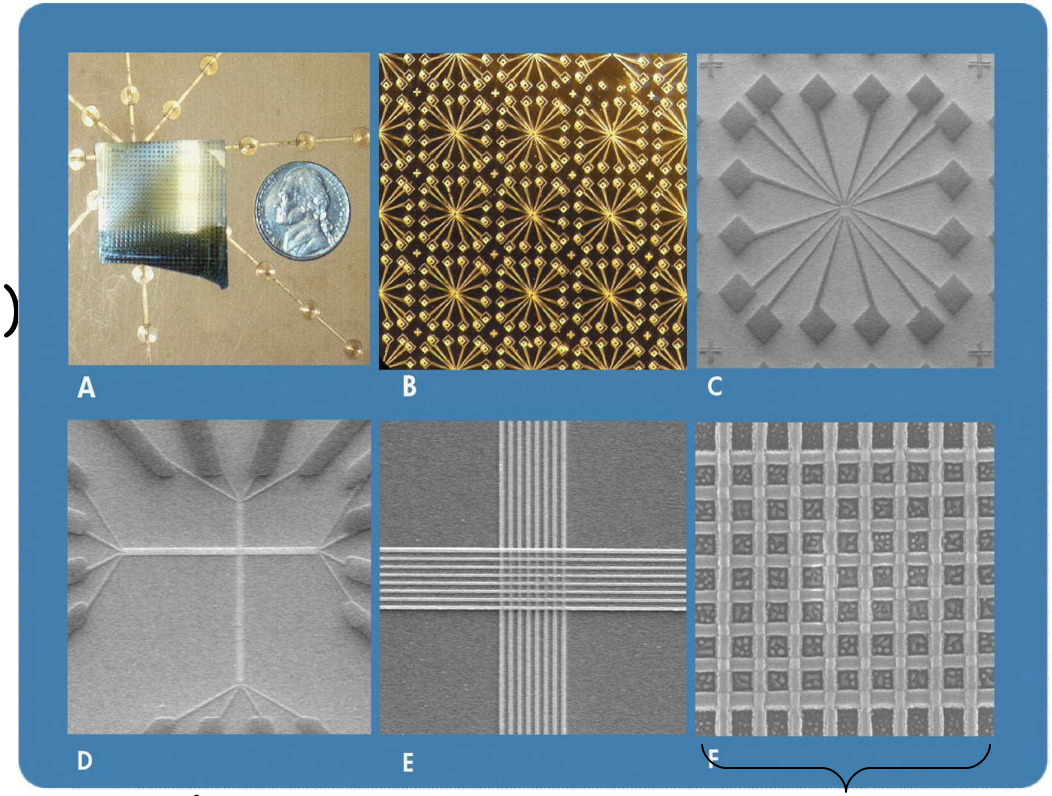
artist's conception
of molecular crossbar
(~10 nanometers)

http://www.hpl.hp.com/research/qsr/

molecular memory

8x8 molecular memory
HP

(image zooms in on crossbar)



crossbar architecture
self-assembled molecular switches at crosspoints

~1 micron

can also use as logic gates

"640K ought to be enough for anybody."
attributed to Bill Gates, 1981

current status

- ~ kilobit memory in ~1 micron
  - architecture also useful for logic
  - far less capable than Pentium chips
- nanoscale wires for chemical sensing
  - femtomolar concentrations
    - ~10^{12} molecules/m^3
  - mainly limited by diffusion to sensor

molecular devices

- vision vs. reality
- plausible capabilities

plausible device capabilities

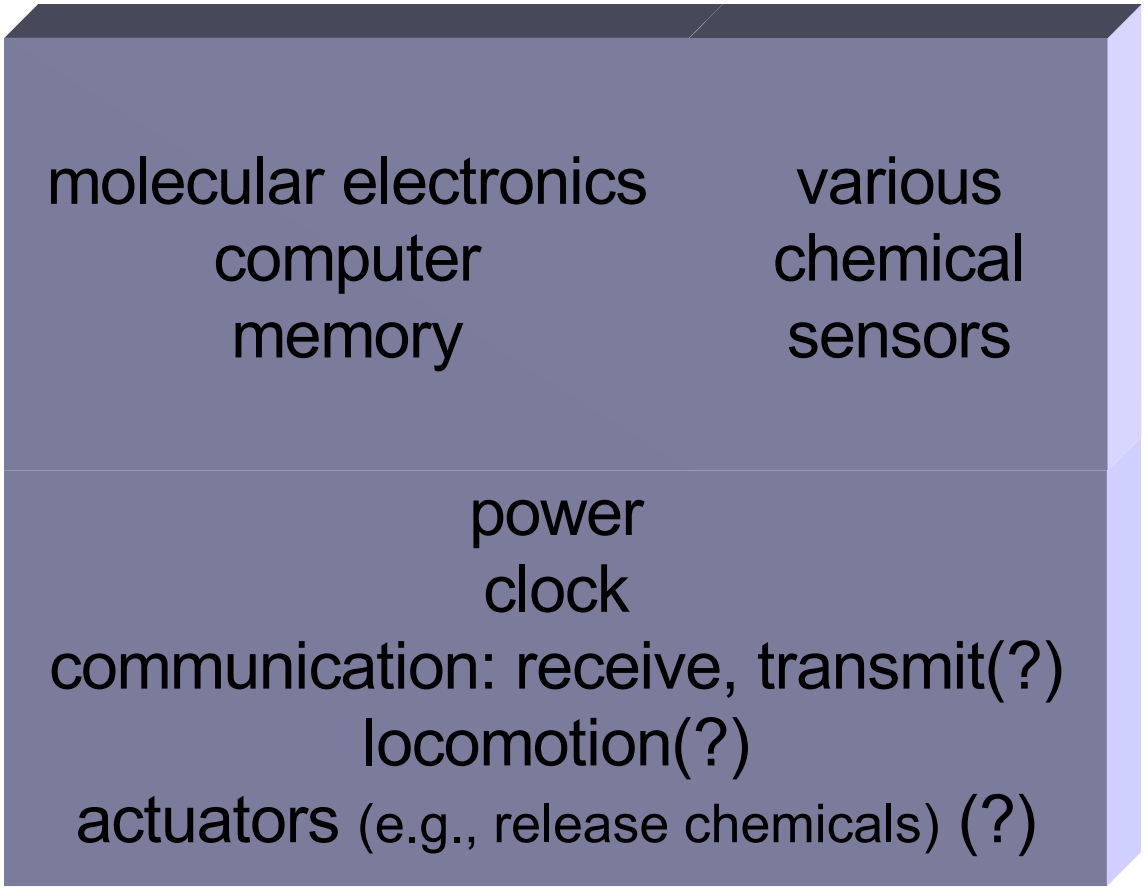
- sense
  - e.g., chemicals (femtomolar concentration)
- compute (~10^5 ops/sec)
  - e.g., pattern recognition
- possibly also:
  - move (~1mm/s)
  - communicate (~100μm)
  - act on environment
    - release chemicals
    - mechanical actions, e.g., surgery

power for 1-micron device

- 1 picowatt (pW) allows
  - ~10^5 logic operations/sec
  - communicating ~10^4 bits/sec over 100μm
    - with ultrasound
  - moving ~1mm/sec through water
- ~1000pW from glucose+oxygen in blood

- compare: 10-1000pW use by cells
  - cells are larger: ~10μm
- person at rest uses ~100 watts

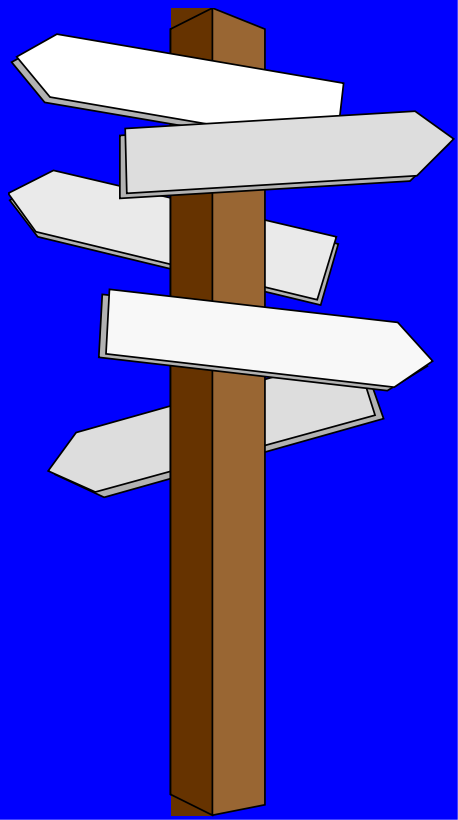
molecular electronics device



size ~1 micron

molecular electronics & applications

- microscopic devices
- applications
  - biology & medicine
- swarm-based control



preliminary engineering studies

- performance for various tasks
  - order of magnitude estimates
- using plausible values for
  - device capabilities
  - biological task environment
- simulations indicate major benefits

example applications

- monitor & manipulate bacteria biofilms
- passive diagnostics
- active monitoring
  - aid immune response
- microsurgery
  - nerve repair

for order-of-magnitude plausibility estimates:
examine key parts of overall task in simplified settings

task: study bacteria colonies

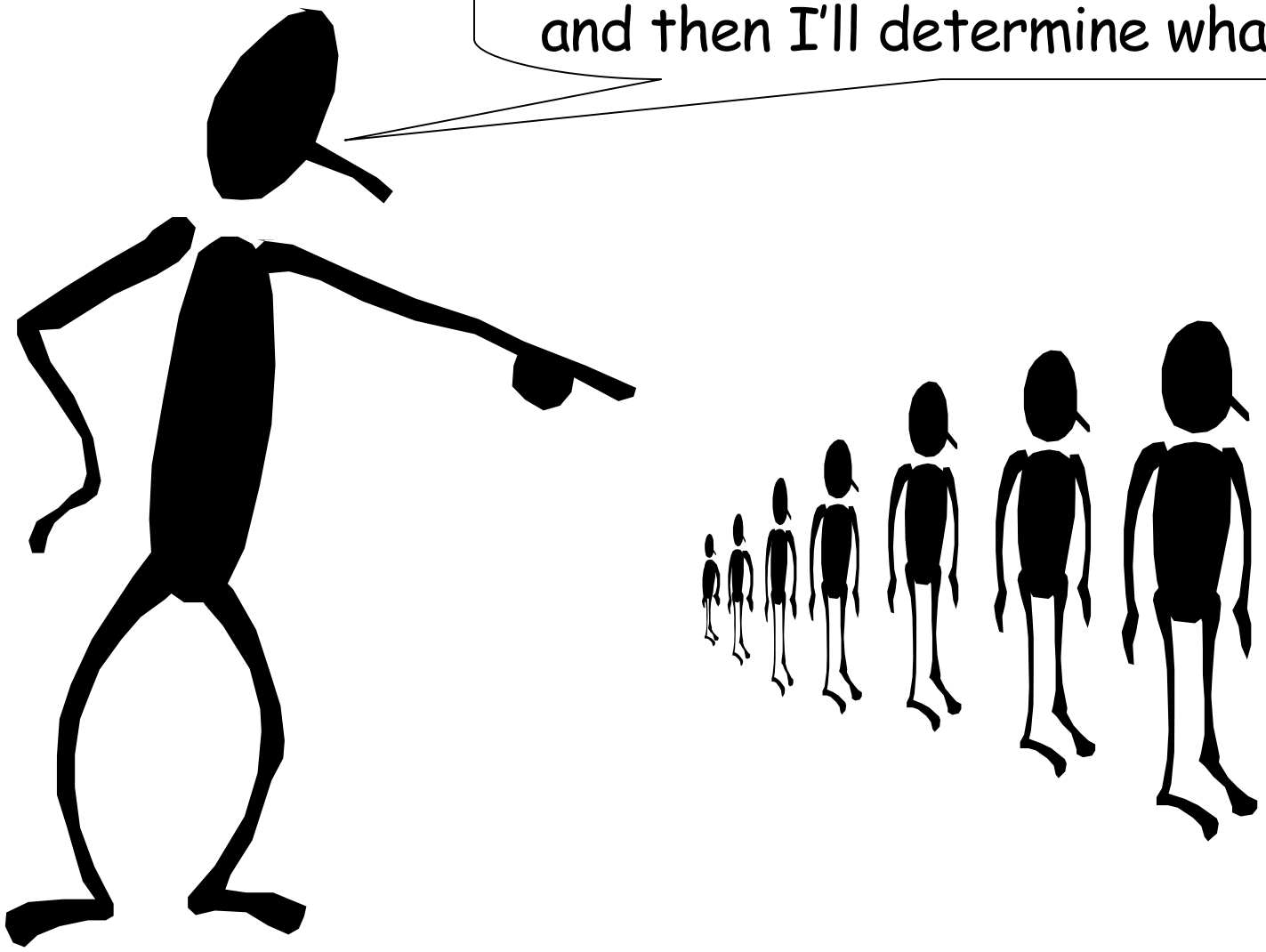
- place devices among bacteria
  - same size as bacteria
- record interesting chemicals
- later retrieve devices and download their memories
- devices could also add chemicals
  - high resolution interventions

plausibility?

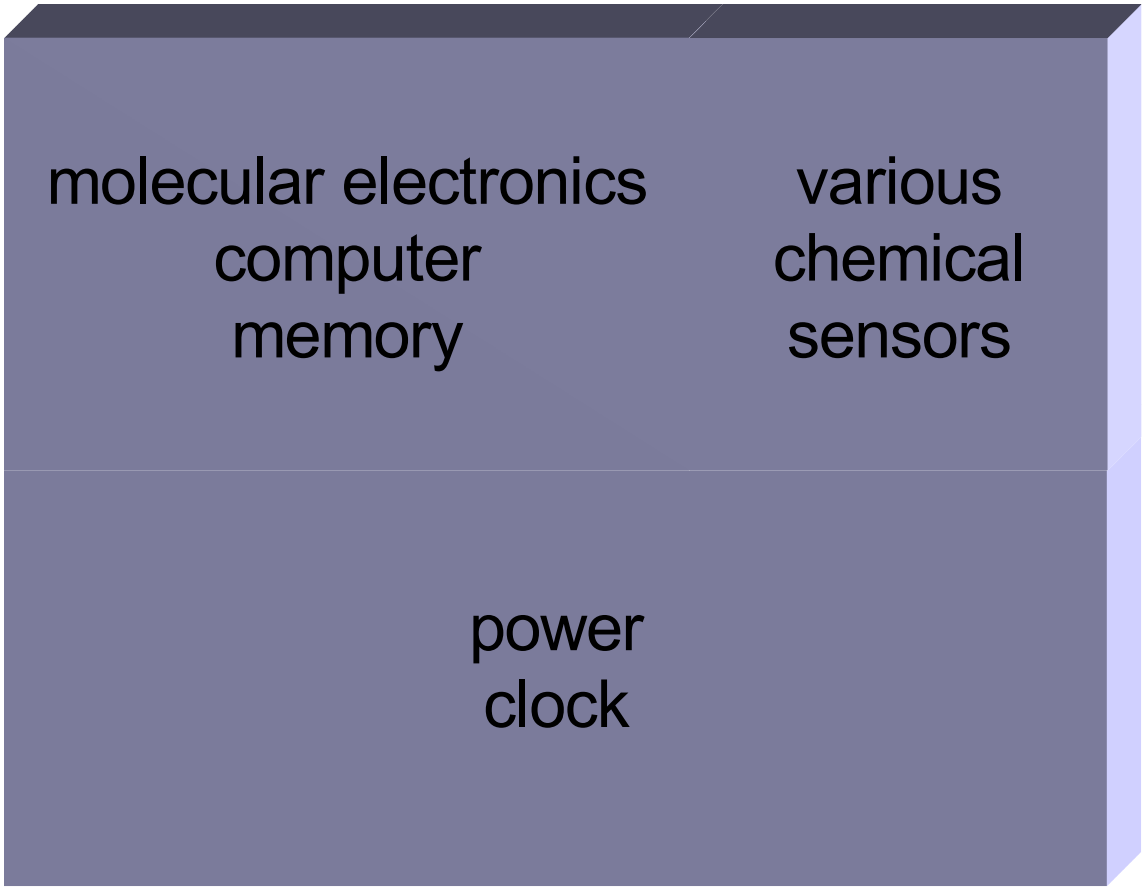
- no quantitative study yet
- e.g.,
  - interesting scenarios?
  - what chemical concentrations?
  - how long?
  - how many devices to see interesting spatial patterns?
  - …

task: high resolution sensing

- monitor for chemicals
- record interesting detections
- later retrieve devices and download their memories
- reconstruct properties of chemical sources
  - computational inference

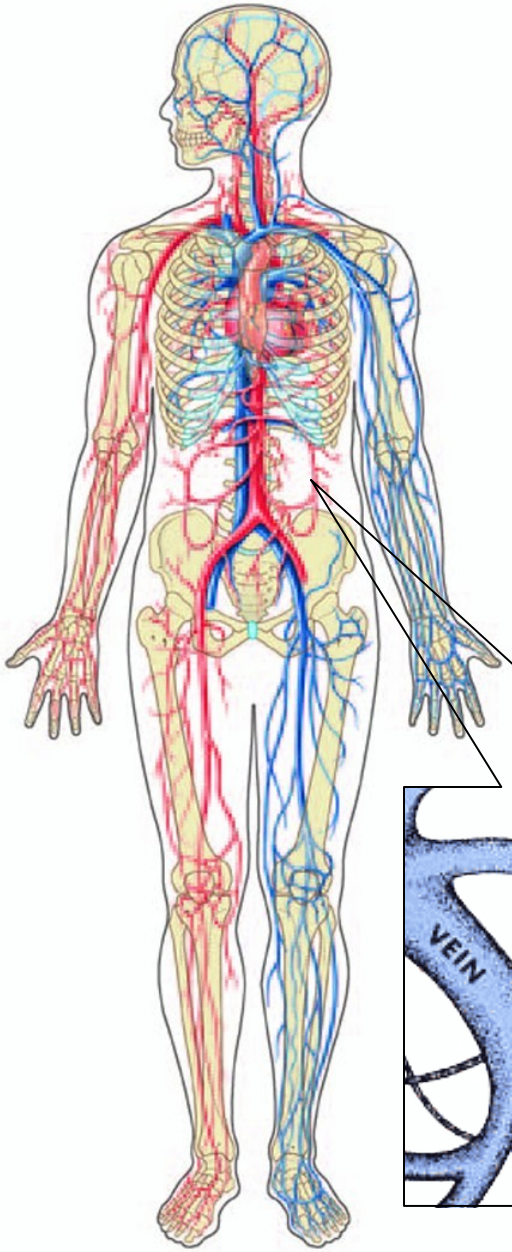

go in, look around, get out,
tell me what you found
and then I'll determine what it means

molecular electronics device



size ~1 micron

microcirculation

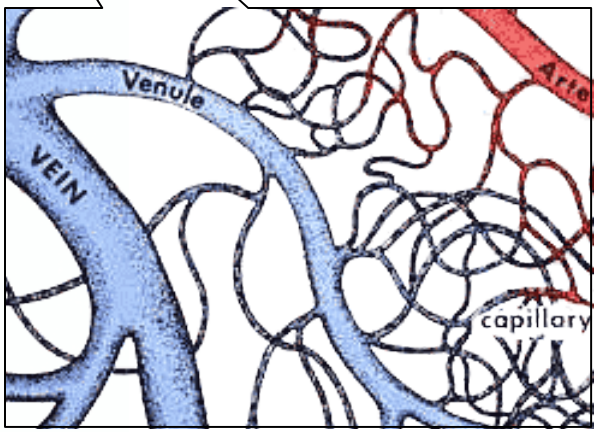


vessels <0.1mm diameter:

~10% total blood volume

~95% of ~500m^2 surface area

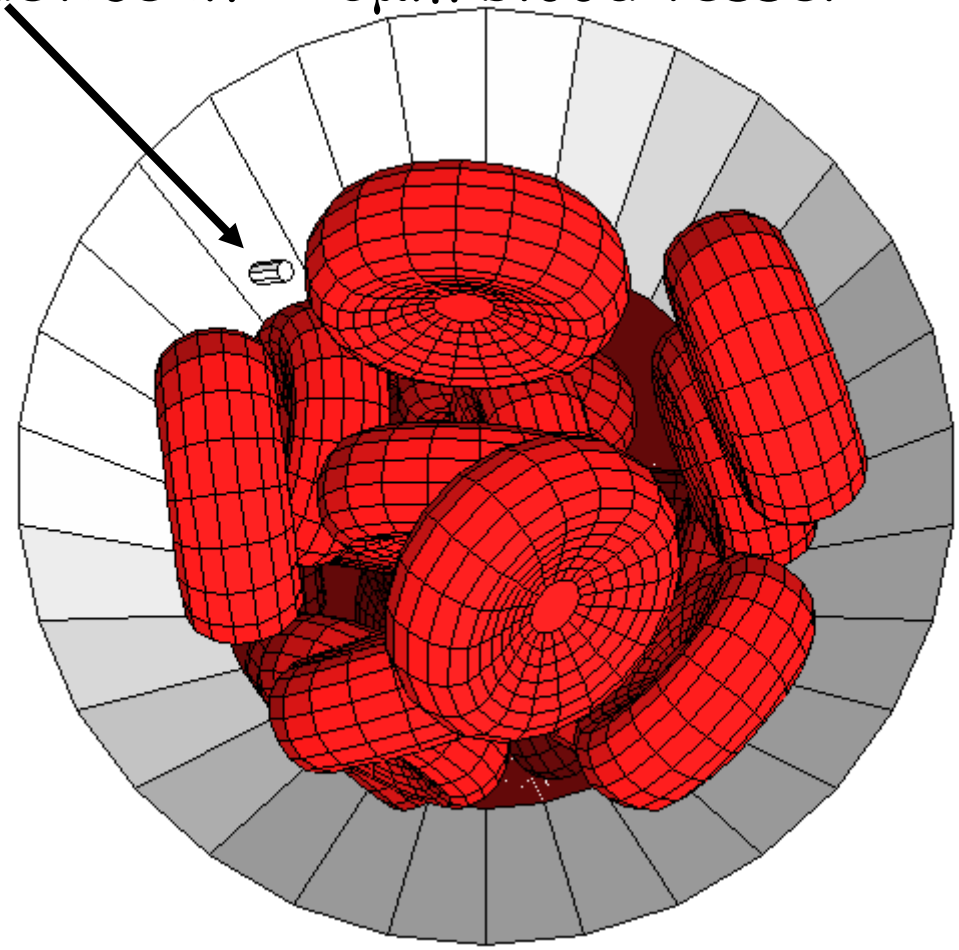
>99% of ~5x10^4 km length



small vessels
- exchange chemicals with tissue
- about 10μm diameter
- comparable to size of cells

devices within small blood vessels

schematic of one device in ~20μm blood vessel



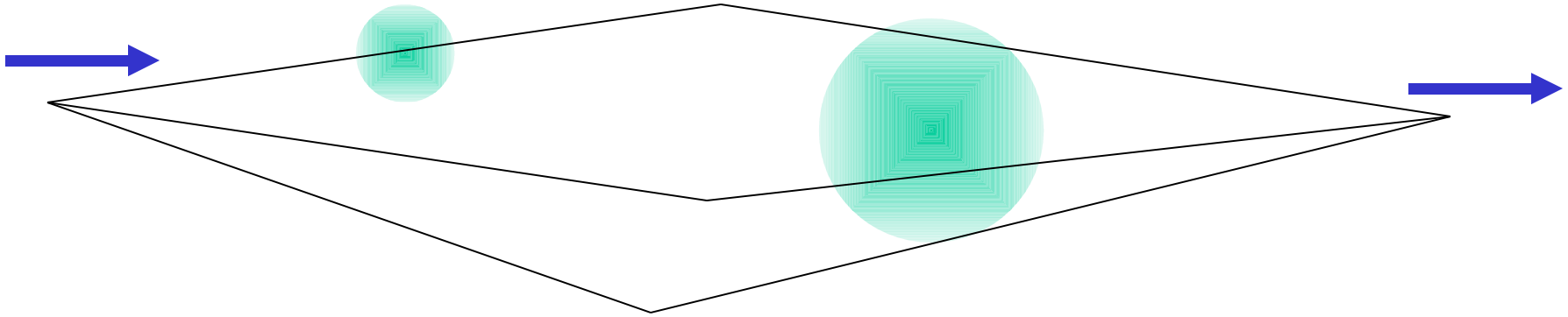
operate in moving fluid
crowded with cells
various chemicals
fractal branching geometry

cf. artist conceptions often show much more open space

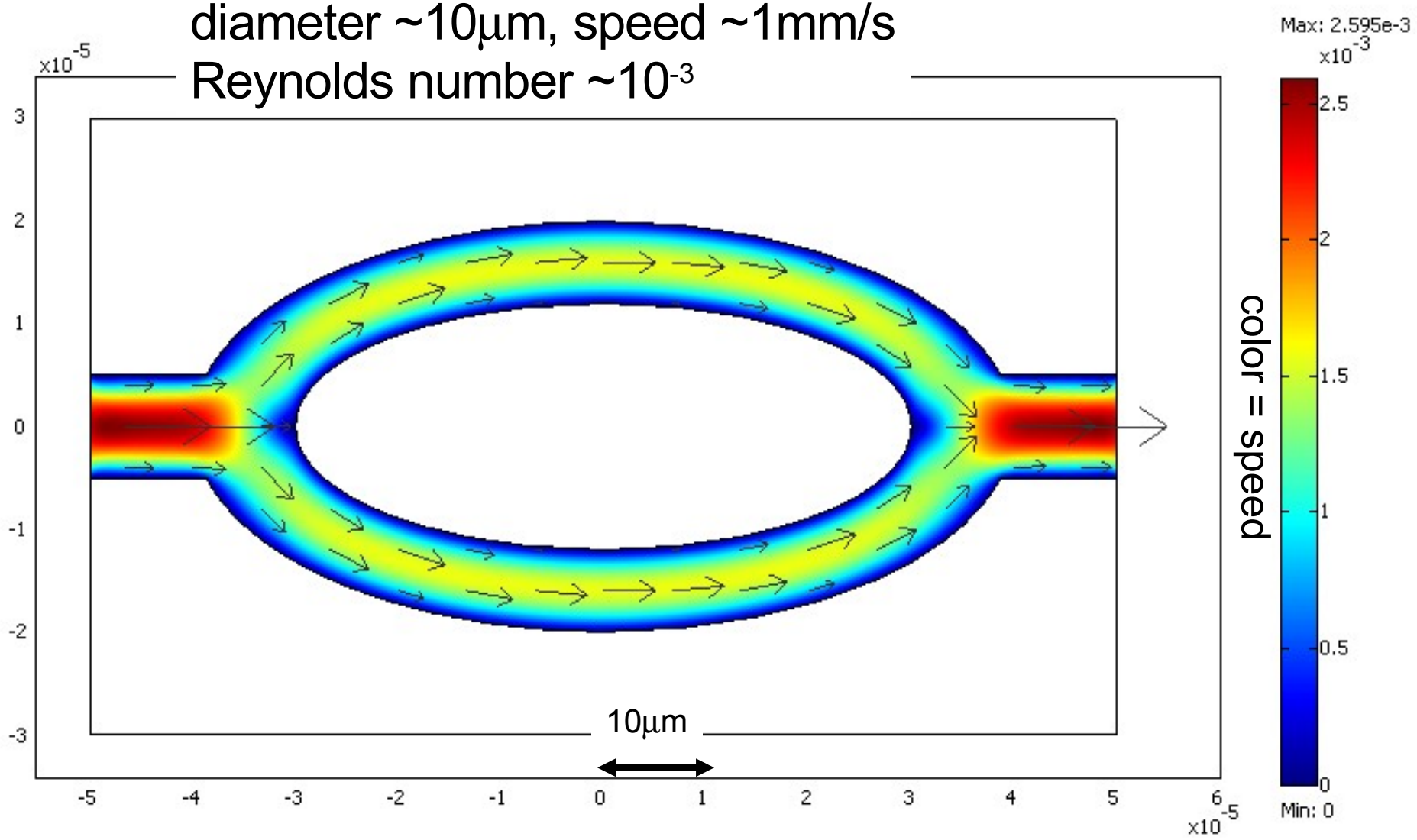
a simulation environment
A. Cavalcanti, www.nanorobotdesign.com

identify chemical source(s)

- e.g.,
  - a small or a large source?
  - one or many?
- how well can devices distinguish
  - using local sensors, clocks…

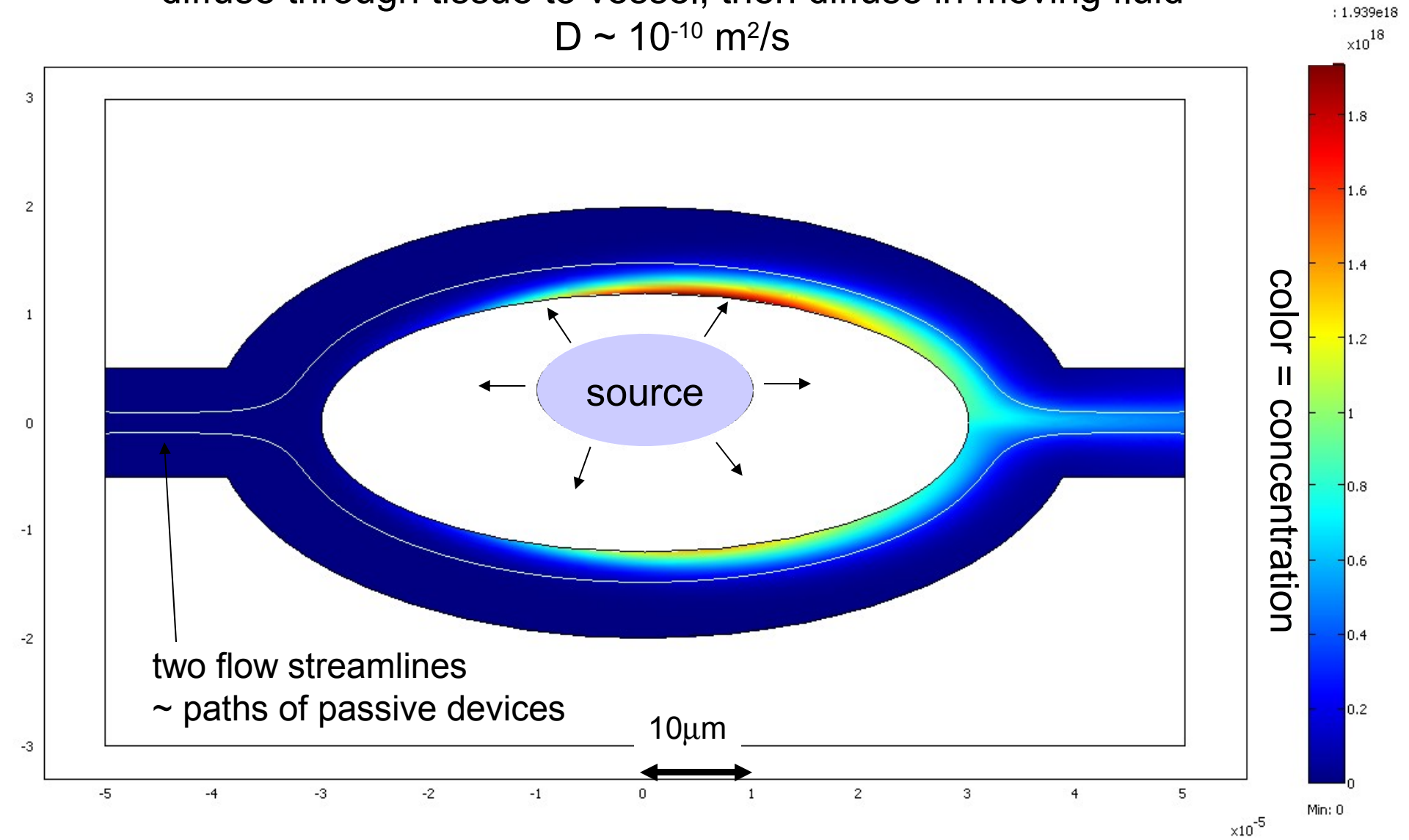


2D fluid flow in small vessels
diameter ~10μm, speed ~1mm/s
Reynolds number ~10^{-3}



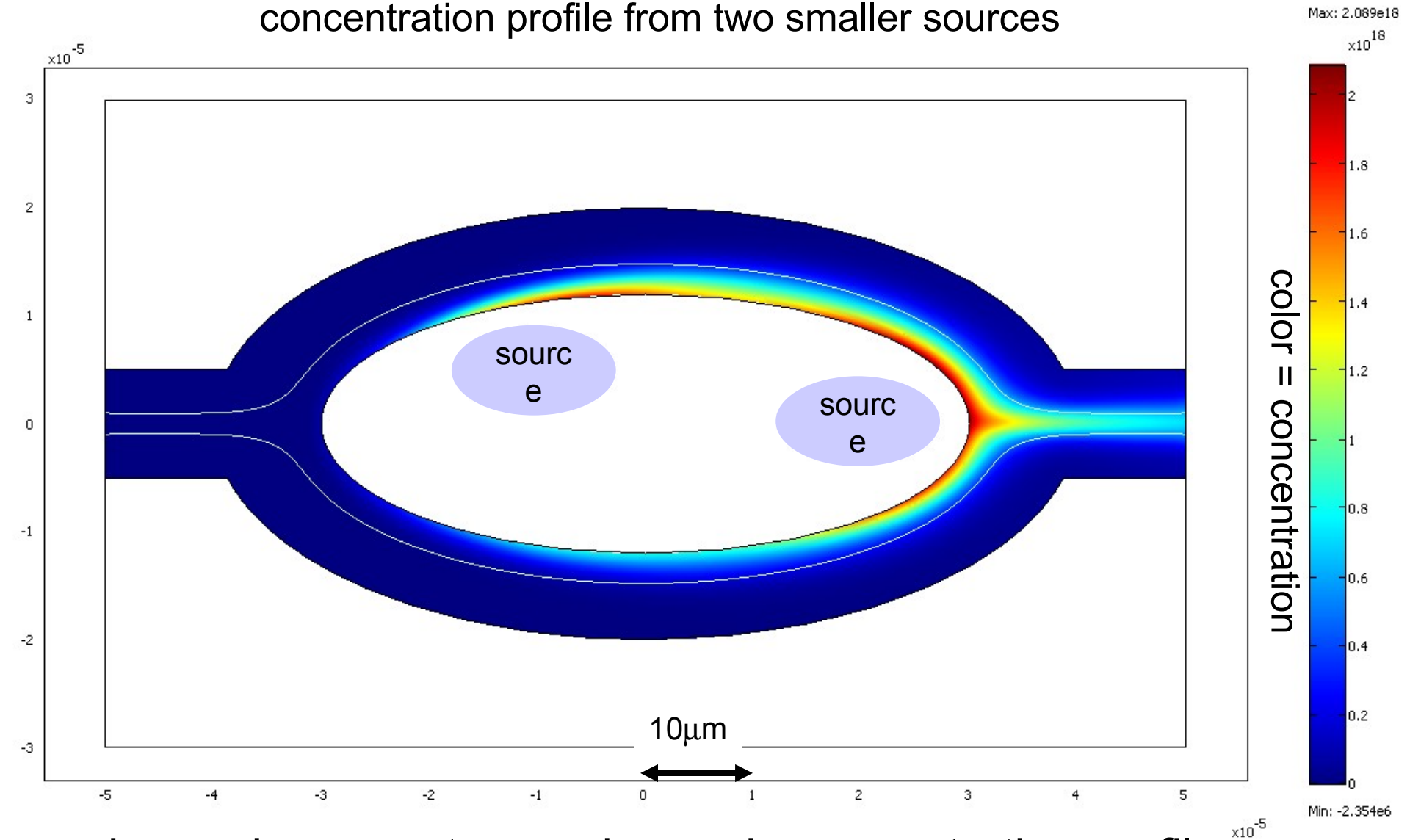
simple model: fluid and chemical, not cells in fluid

concentration of typical chemical released in response to injury or infection
diffuse through tissue to vessel, then diffuse in moving fluid
$D \sim 10^{-10}$ m^2/s



1μm devices encounter ~10 to 100 molecules while passing through vessel

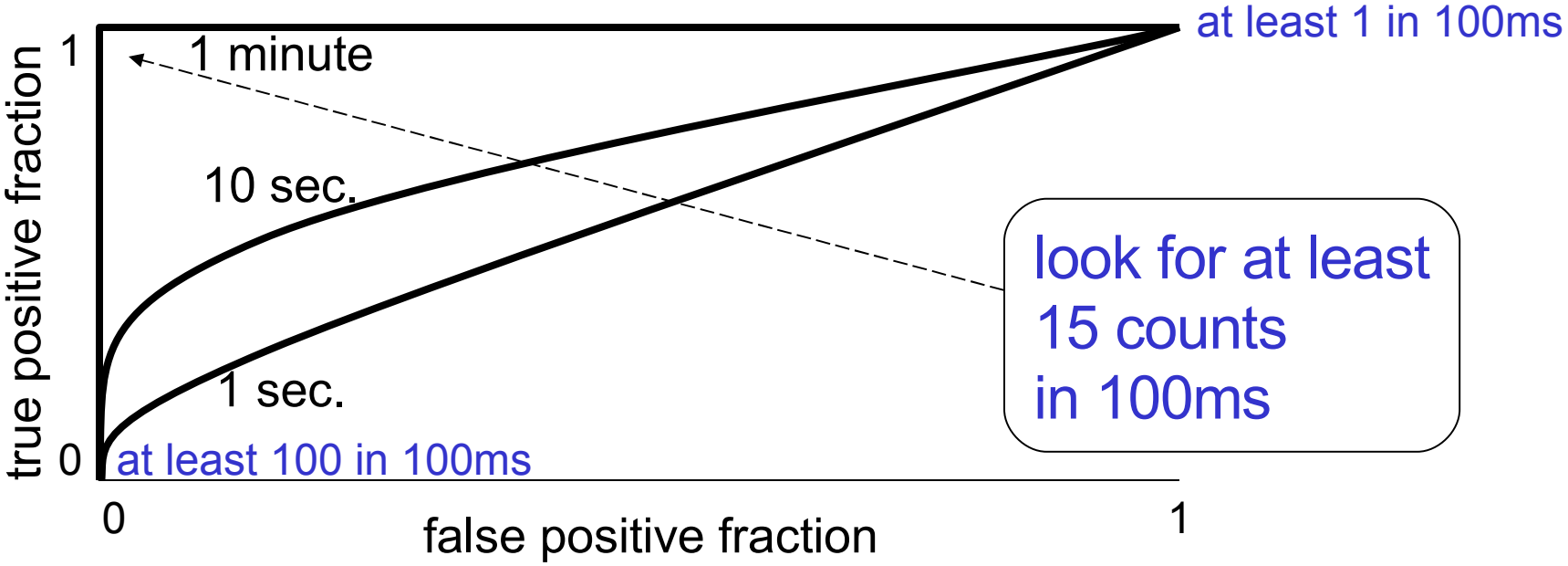
concentration profile from two smaller sources



change in geometry => change in concentration profile

inference example

one 10μm source in $1cm^3$, 10^9 sensors
typical concentration of chemical signal from injury/infection
simple inference: threshold with Poisson count distribution

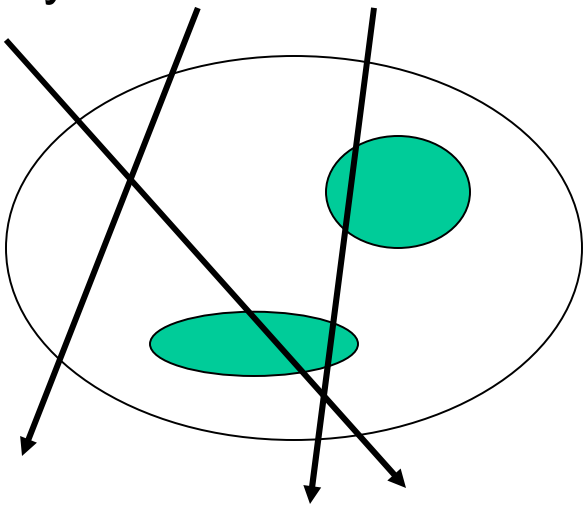


lessons: in vivo sensing

- can detect sources at 10-100μm scale
  - based on simple model
- accuracy depends on
  - chemical concentration
    - noise from Poisson statistics at low concentrations
  - background concentration
    - could be reduced using pattern recognition
      - if source gives a combination of chemicals

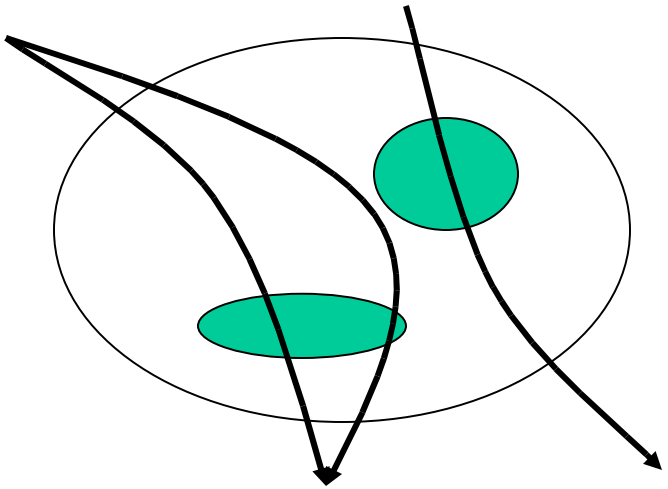
“tomography”

X-rays



known geometry
data: integral along paths
infer: structure

micro-sensors in fluid flow



unknown geometry
data: values along paths
infer: structure & geometry?

variation: external signal

- indicate tissue region of interest
  - e.g., with ultrasound
    - with ~1cm resolution
  - devices active only when signal detected
- could also mark locations near skin
  - aggregate as signal to outside

variation: stick to vessel wall

- programmable stickiness
  - improve statistics when interesting chemical events detected
    - collect counts over longer time
  - enter branches as a group
    - synchronized measures give correlations

variation: other sensors

- sensors for fluid flow
  - to infer branching, cell concentrations, …
    - low Reynolds number fluid flow
- sensors for nearby devices
  - infer spatial correlations

measure in vivo vs. in vitro?
(e.g. from blood sample)

- concentration may be high in small regions
  - but too diluted to detect when mixed throughout blood volume
- spatial patterns may be significant
  - e.g., 3 chemicals detected in same place vs. from different locations
    - appear the same when mixed throughout blood volume
- temporal patterns

task: aid immune response

- monitor for chemical signals
- follow gradient to source
- identify infectious microbe
  - patterns of chemicals
- pass info to attending physician
  - which immune cells can't do


go in, follow chemical signals,
tell me what you found
and then I'll determine what to do
release chemicals if I tell you,
get out

example: infecting bacteria

- bacteria release toxin and replicate
  - how does toxin spread to blood?
    - multiple nearby small vessels?
    - what are realistic concentration gradients?
      - measured concentrations reported in literature may be over fairly large volumes
  - with more bacteria, toxin concentration increases
- how does time to find infection compare to typical immune response?
  - innate ~minutes to hours, adaptive ~days

active response

- aggregate at chemical sources
  - to investigate nature of source
    - e.g., type of infecting bacteria
  - to act at source
- could report while still in region
  - e.g., by message passing network among devices to external communication device
  - distributed control problem (computer science)

responding to gradient

- noisy direct measurement
  - short time available while passing source
- move to wall & stick for a while
  - e.g., via random motions
- signal others nearby
- give up if measurement too noisy
  - e.g., if not very near source
  - reduces power use, but slower response

scenario

- 10^{12} devices in 5-liter blood volume
  - use about 10^{-5} of blood volume
    - compared to ~40% used by red cells
  - total mass of all robots: a few grams
- enough time to detect chemical?
  - low concentration => far past target when detected

A. Casal et al., Nanorobots as Cellular Assistants in Inflammatory Responses, BCATS-2003

simulation study

- using plausible physical parameters
  - e.g., proteins released by tissue injury
  - typical 10^4 dalton chemokine
    - 30ng/ml near source, 0.1ng/ml background
- examine ability to find source
  - while passing in small blood vessels
  - with various local control rules

for moving sources: M. Green et al., Finding a Chemical Source in Fluid Flow, IPAM summer project 2005

simulation models computation time vs. accuracy

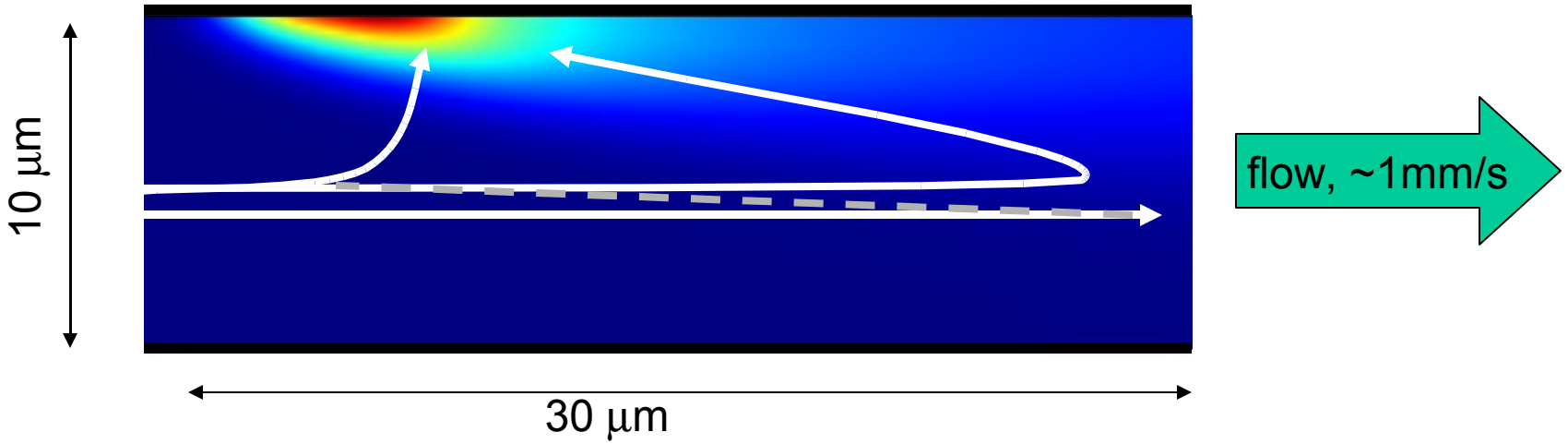
- 2D or 3D fluid flow
  - chemical diffusion in moving fluid
  - empty vessel or with cells
  - rigid or deformable cells and walls
  - …
- simple case assumes
  - objects are rigid
  - objects do not alter fluid flow

simulation study results

- ~30-90% of passing devices can find source
  - depending on geometry of source and flow
  - with plausible level of power use
- also examine false positive rate
  - based on background concentration

benefit of communication

- detect source somewhat downstream
  - much power to swim back upstream
  - vs. communicate to upstream devices



source on pipe wall, fluid flow (parabolic profile), diffusion ~300µm^2/s

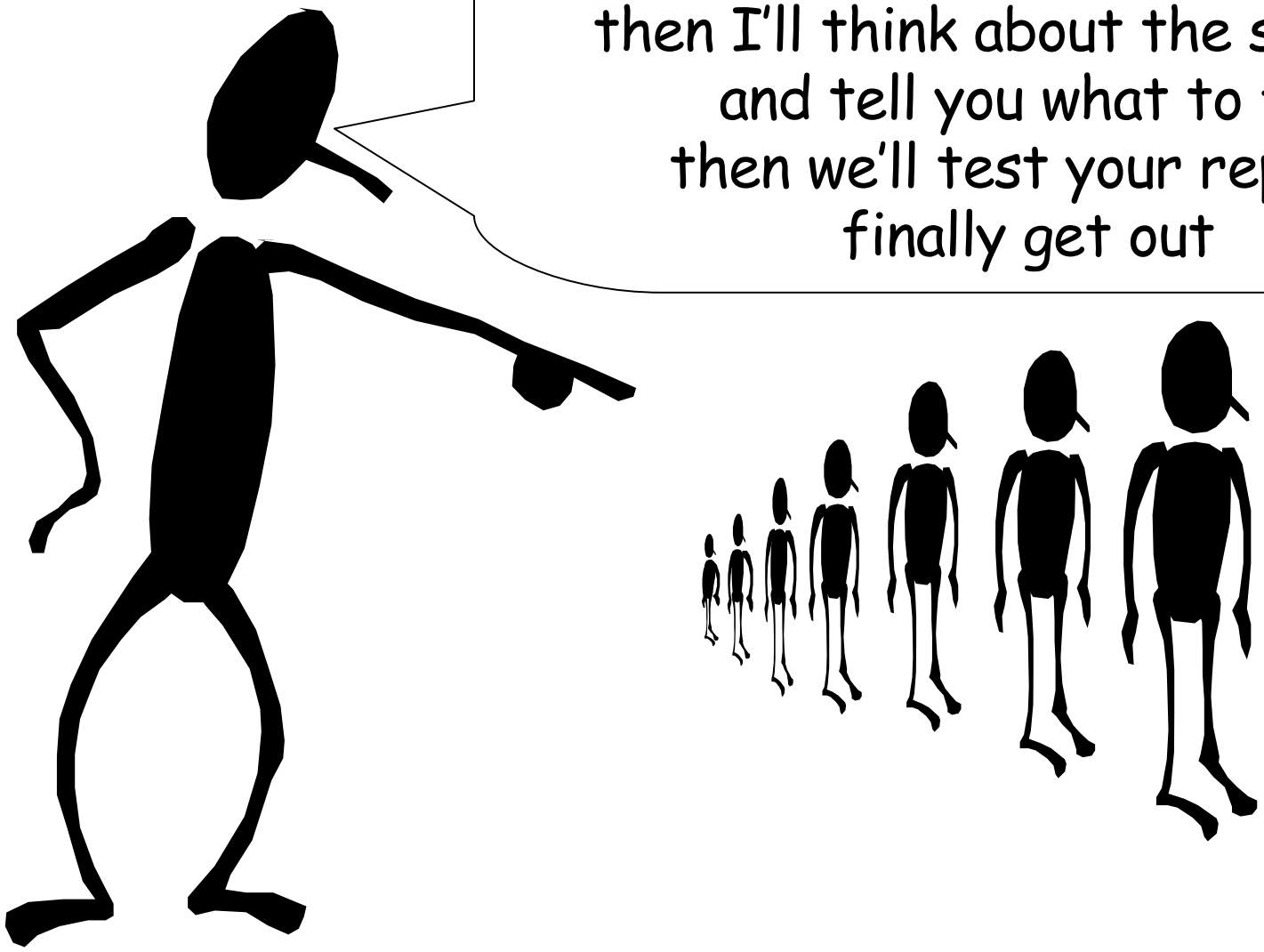
lessons: immune response

- simple control rules effective
  - redundancy from huge numbers
  - even for source size of just one cell
- possibly much faster response
  - than immune system
  - devices could act or alert physician

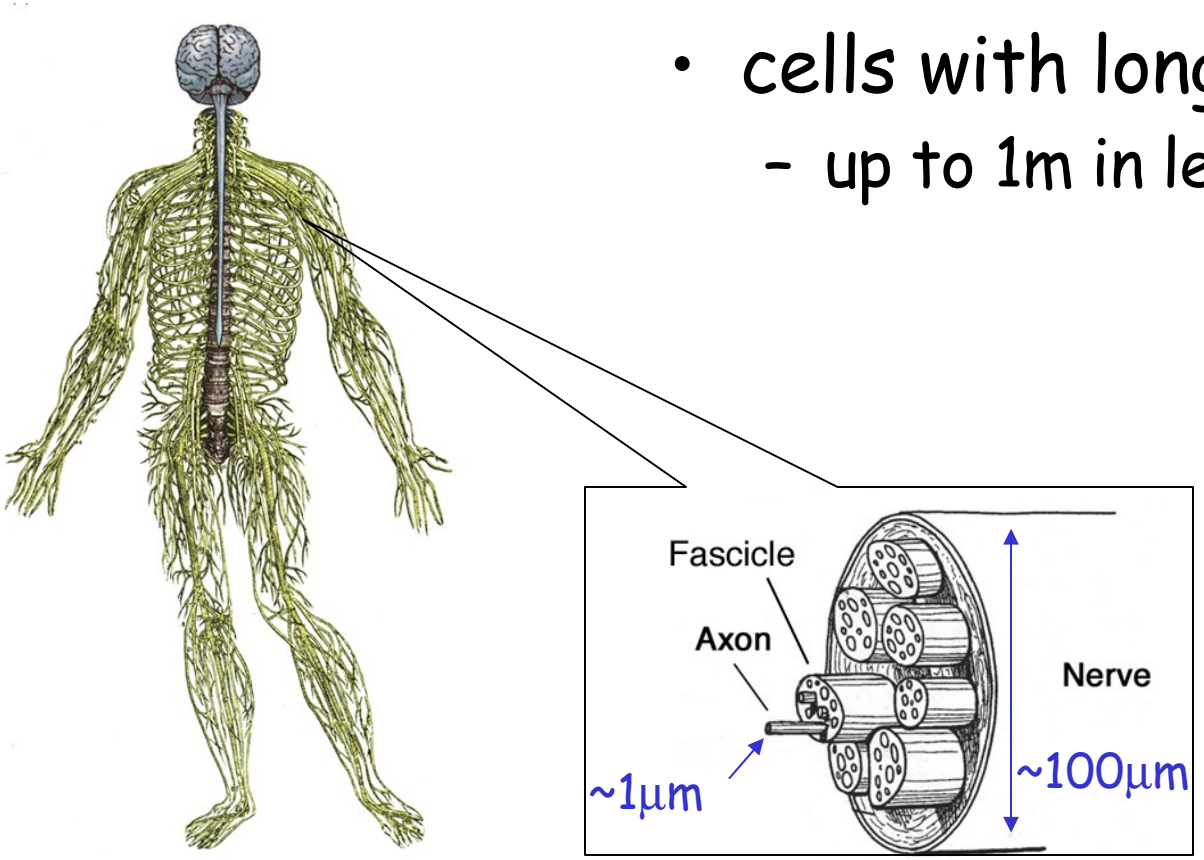
task: nerve repair

- approaches
  - regeneration via appropriate chemicals
  - repair via replacement with graft tissue

- swarm application:
  - "eyes" and "hands" for microsurgery

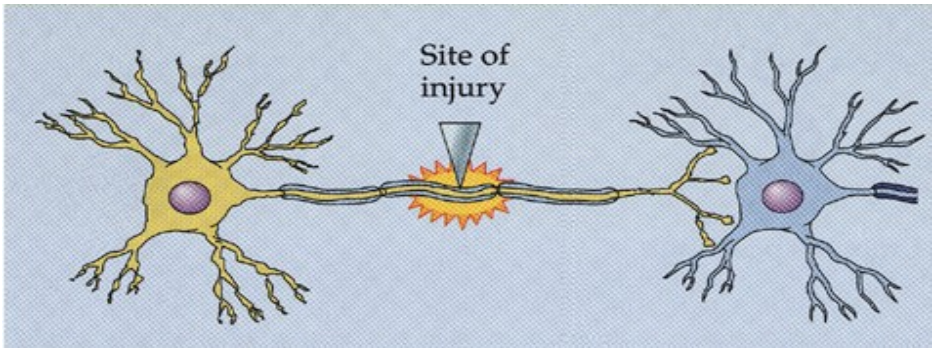

go in, find damaged axons,
tell me what you find
then I'll think about the situation
and tell you what to fix,
then we'll test your repairs,
finally get out

nervous system

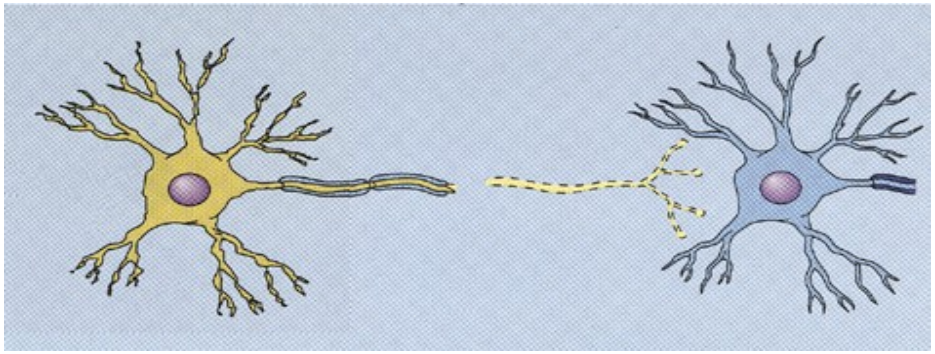


- cells with long axons
  - up to 1m in length

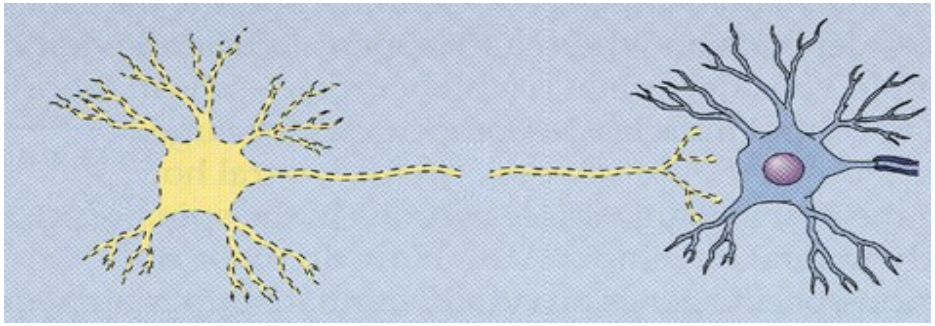
axon injury



synapses lost
(Wallerian
degeneration)



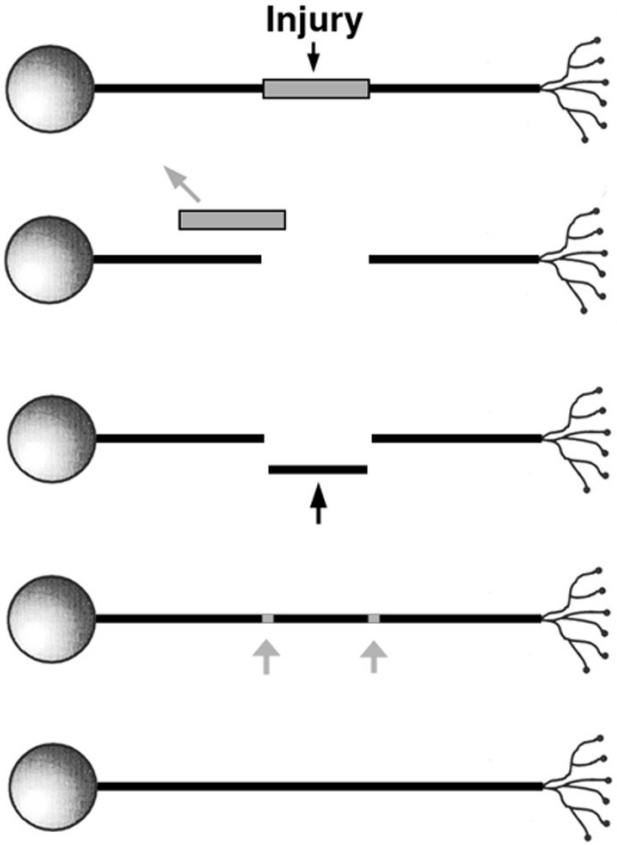
cell death



conventional approach: regeneration

- encourage axon re-growth
  - e.g., with suitable drugs
- difficulties:
  - synapses lost, neurons die
  - slow growth (~ 1mm/day)
  - wrong connections

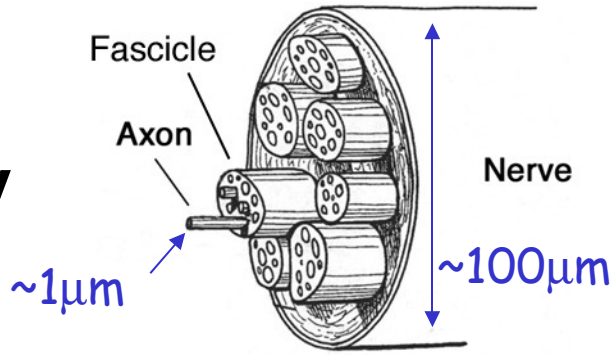
surgical repair: an alternative



- remove damaged section
  - replace with graft
- expose axons in host & graft
  - enzymes digest connective tissue
- electrofuse axon pairs
  - using voltage pulse
  - often gives functional axon

micro-neurosurgery of single axons

micro-surgery

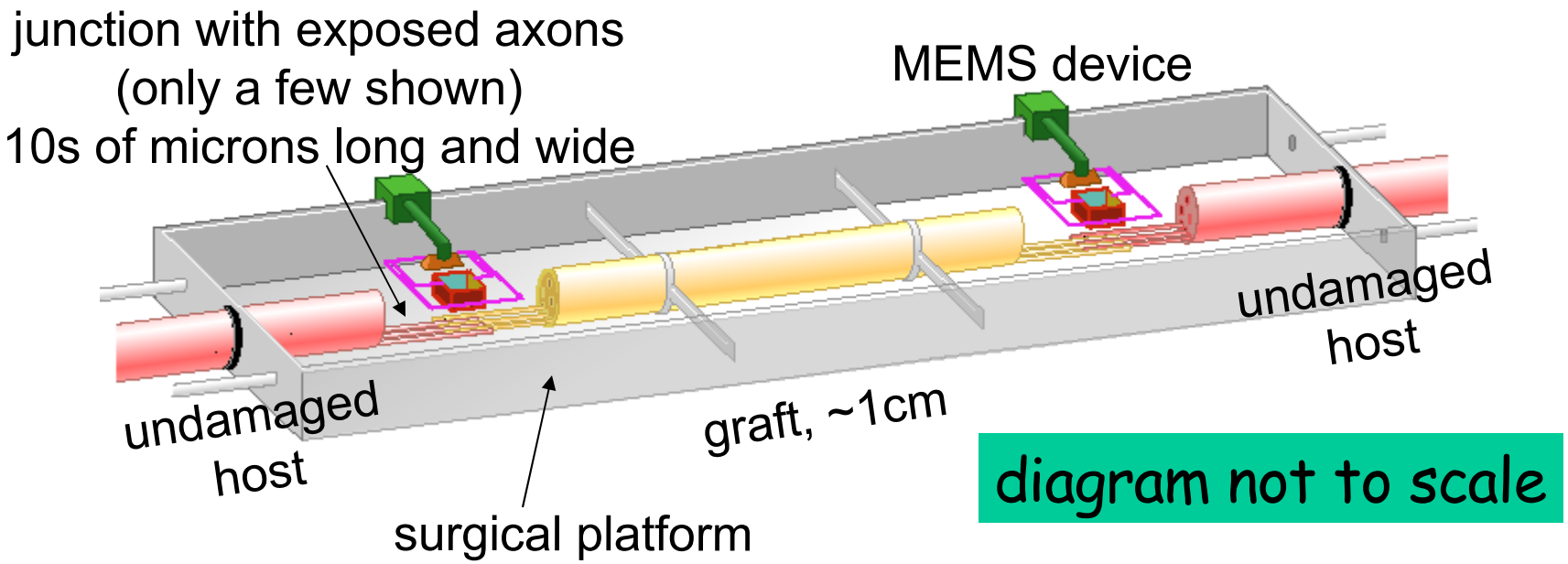


- in vitro: single axon repair demonstrated
  - with MEMS devices

- in vivo: evaluate and manipulate ~1000 axons in nerve
  - which are viable?
  - which pairs should be connected via graft?
    - e.g., connect motor to motor axons, not motor to sensor

D. Sretavan et al., *Neurosurgery* **57**:635 (2005)

nerve repair



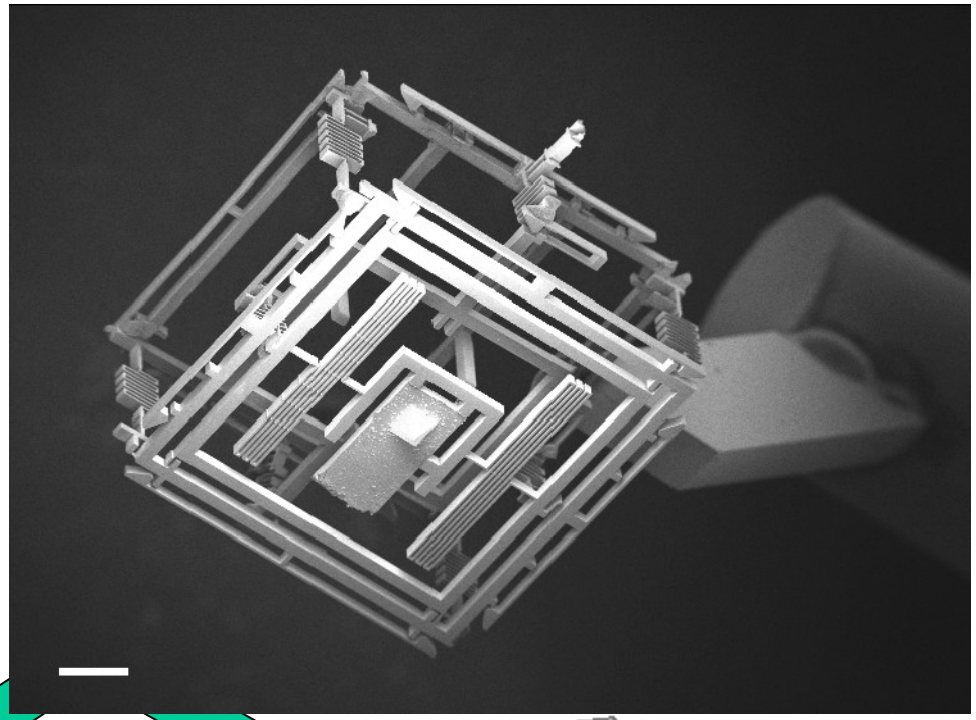
operate in fluid at lower than body temperature
reduces tissue injury

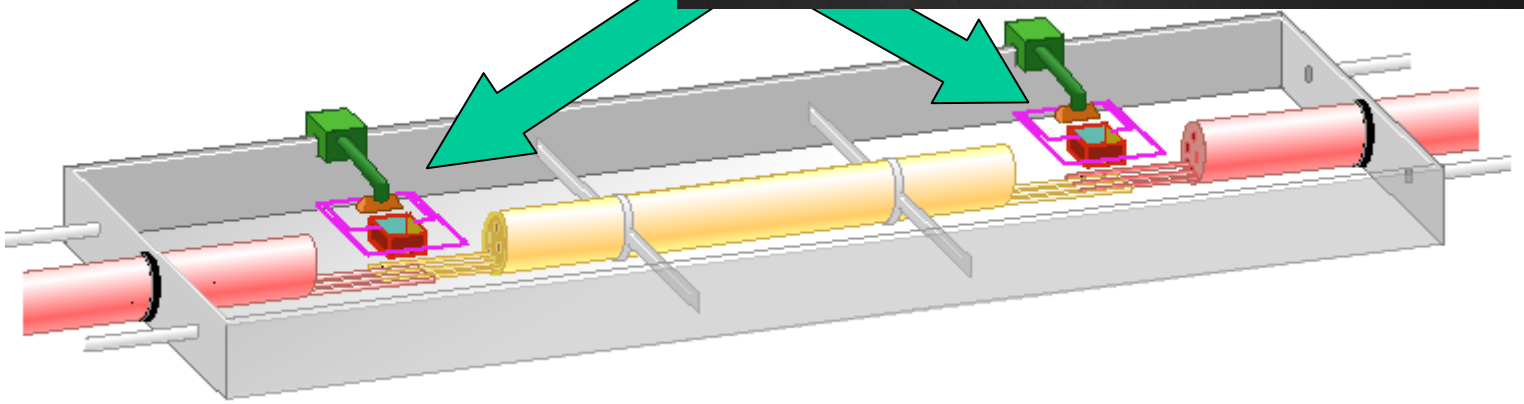
D. Sretavan, UCSF

D. Sretavan et al., *Neurosurgery* **57**:635 (2005)

MEMS microsurgery device

1mm^3 volume
view from below
axon cutter at center



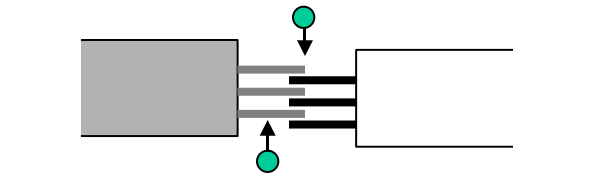


~10^4 devices

use of micron-scale devices

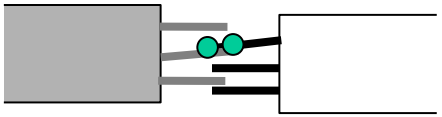
- identify axon type
  - motor, sensory
- with MEMS: signal through graft
  - to determine matching axon ends
- external CPU: which axons to fuse
- fuse axons
- with MEMS: test repairs

repair steps

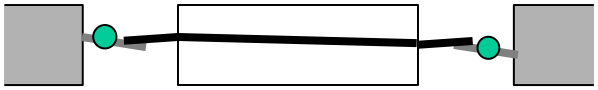


move to axons and evaluate properties
using powered and Brownian motion

map connectivity through graft
using electrical signals on axons



move and fuse axons as instructed
using electric fields or chemicals



test host – graft –host connections
using electrical signals on axons

MEMS device could twist graft to minimize average reported mismatch
e.g., twist a bit, recheck mismatch, repeat

simulation study

- using plausible physical parameters and nerve geometry
- results:
  - improved accuracy & speed
    - compared to MEMS device acting alone
  - repair time ~1 hour or less

T. Hogg and D. Sretavan, Controlling Tiny Multi-Scale Robots for Nerve Repair, Proc. of AAAI-2005

open questions: biology

- biology of nerve structure
  - how are axons organized in nerves
  - changes due to injury
- biophysics parameters
- how accurate must repairs be for acceptable functional recovery
  - e.g., plasticity to retrain after repair

computational issues

- mix scale of devices: MEMS and micron-scale
- feedback for external control by physician
  - look & report
  - act only if get signal to continue
  - collect detail info on surgery for analysis during and after procedure
  - evaluate quality of procedure

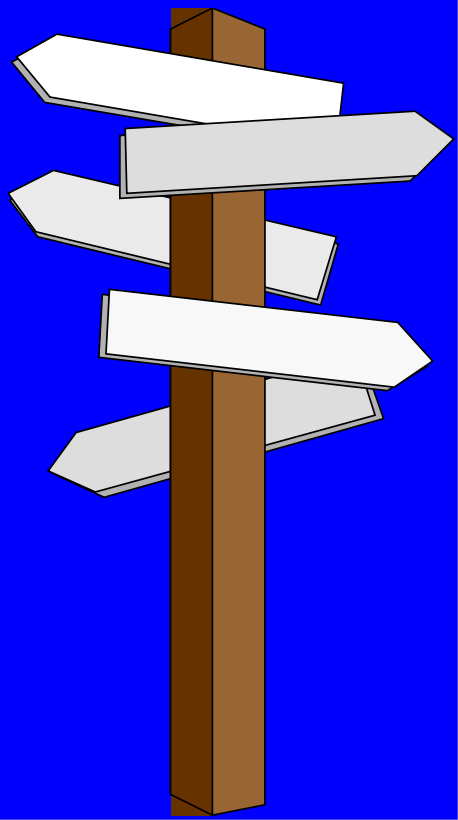
lessons: nerve repair

- general strategy:
  - use devices for detailed "look around"
  - then compute what to do
    - incorporate relevant clinical constraints
  - use devices as "tiny hands"
  - MEMS for tissue-scale manipulation
- fast & accurate treatments
- physician can monitor and control progress

T. Hogg and D. Sretavan, Controlling Tiny Multi-Scale Robots for Nerve Repair, Proc. of AAAI-2005

molecular electronics & applications

- microscopic devices
- applications
- swarm-based control



scenarios: summary

- high resolution chemical sensing
  - 10^3-10^9 devices, passive motion
- aid immune response
  - 10^9-10^{12} devices, active motion
  - act at target
    - e.g., release chemicals
- aid microsurgery
  - 10^4 devices, active motion
  - communication & electrical stimulation
  - work with larger devices

swarm behaviors

- evaluate average behaviors
  - quickly evaluate many scenarios
  - e.g., differential eqns for device states
    - coupled to physics of flow, diffusion, …
      - e.g. Galstyan et al., at SIS-2005
- simulation study for details
  - identify significant unknown biophysical parameters

novel swarm task domain

- swarm properties
  - large number of devices (up to 10^{12})
  - microscopic physics
- system context
  - swarm + larger-scale devices
    - e.g., coordinate at cell and tissue sizes
  - human "in the loop" for overall control

swarm control issues

- aggregate at interesting locations
  - ensure some response, not too much
- aggregate sensor info
  - global picture from many local measures
- manipulate environment
  - e.g., microsurgery
  - complete task without causing local injury

future work: simulations

- more realistic environment & device models
- study behavior trade-offs
  - power, sensor accuracy, speed, number of devices, fabrication difficulty
  - system performance

validation?

- difficult
  - can't yet build devices to test
  - many unknown biophysical parameters
- partial answer: robustness
  - achieve task with multiple plausible
    - device capabilities,
    - control methods, and
    - range of task parameters

future work: engineering

- forming structures
  - cf. modular robots
    - Bojinov et al., Multiagent control of self-reconfigurable robots, *Art. Intel.* **142**,99-120 (2002)
- heterogeneous devices
  - specialized for power, communication, …
  - multiple robot sizes
    - e.g., micron and millimeter (MEMS)

future work: biology

- quantify microenvironment properties
  - e.g., patterns of chemicals on cells
  - possible large scale changes?
    - e.g., signals to some immune cells changing immune system response
- safety, biocompatibility
- identify relevant medical scenarios

safety

- biocompatibility
  - time: minutes, hours, days, ….
    - depending on task
- reliable controls
  - allow for errors
    - sensor noise, broken devices,…
  - e.g., avoid too much aggregation at one area
- power: avoid excess heat load
  - e.g., too many devices active in small volume

biology questions

- tissue & vessel microstructure
- chemical sources
  - size (e.g., single cells?)
  - chemical concentrations & gradients
  - pattern recognition complexity
    - single or multiple chemicals?
    - variation in space or time?

further applications

- uses for micron-scale devices
  - research tools
  - medical diagnostics & treatment
  - environmental monitoring
- complementing current technologies
  - what are the "killer applications"?
    - possible to implement "soon"

longer term possibilities:
R. Freitas Jr., www.nanomedicine.com

when available?

- lab demonstrations
  - combining existing memory, logic, sensors

few years (if reason to do so)

- ? full system: power, surface coating, …
- commercial
  - large quantities, low costs

recap: key points

- molecular electronics
  - eventually make tiny "eyes" and "hands"
  - well-suited to biology and medicine
- opportunity for swarm control
  - large numbers, limited device capability
- evaluate usefulness prior to building
  - suitable mathematical models
  - tasks showing potential benefit

your ideas?

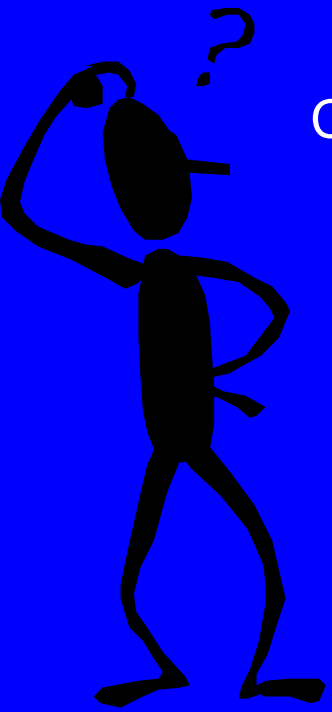
- biomedical tasks
- swarm control methods
- mathematical models

further info

Hogg & Sretavan, Controlling Tiny Multi-Scale Robots for Nerve Repair, Proc. of AAAI-2005

Cavalcanti & Hogg, Simulating Nanorobots in Fluids with Low Reynolds Number, Foresight Conference 2003

Casal et al., Nanorobots as Cellular Assistants in Inflammatory Responses, BCATS-2003



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R. Freitas Jr., www.nanomedicine.com