# MEM Therapeutic Systems (MEMTS)

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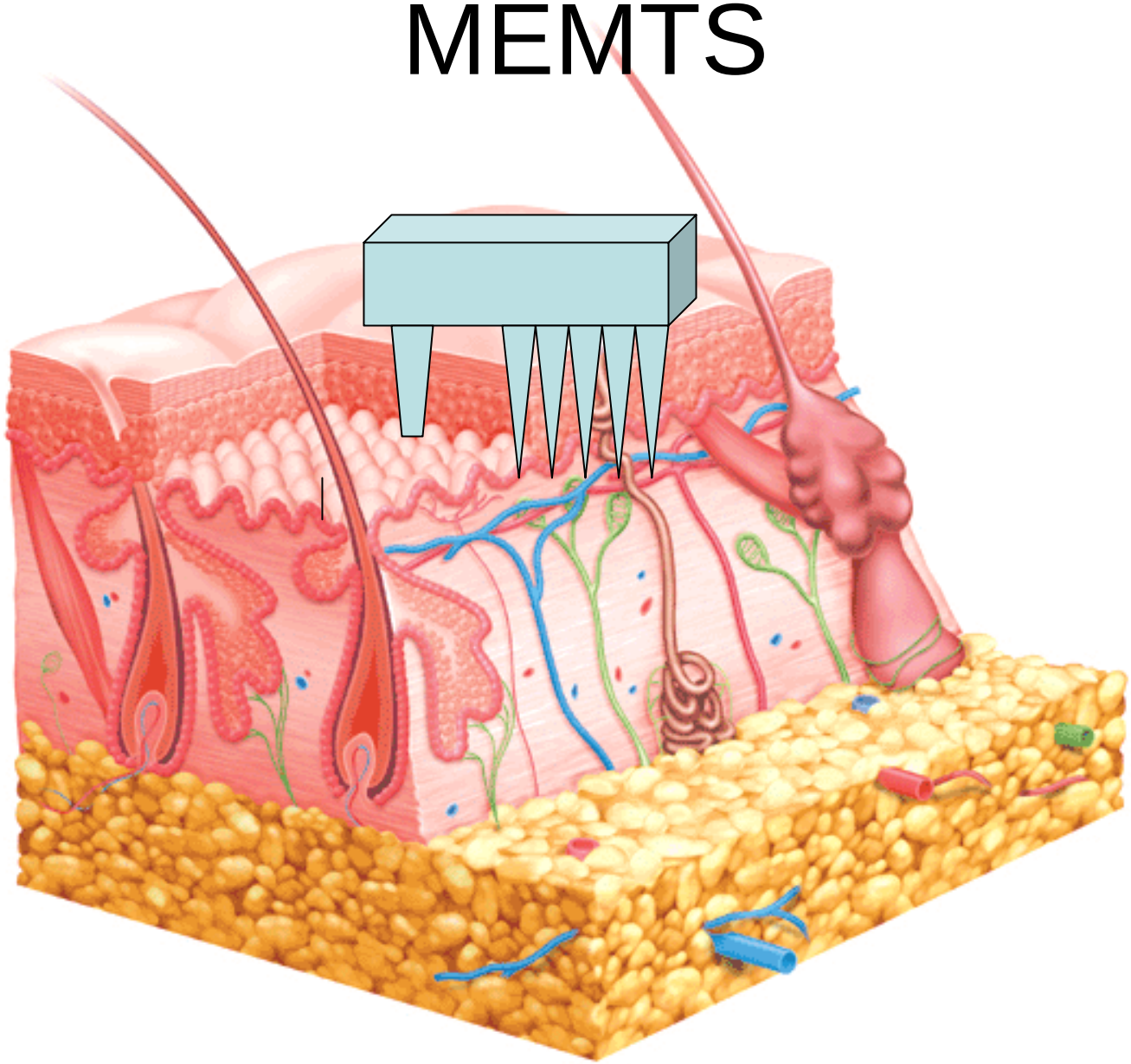
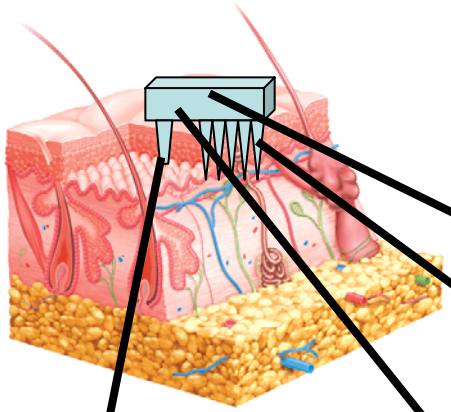
# Outline

- Clinical Relevance
- Pharmacokinetic Interactions
- MEMTS Performance
- Biochemical Sensor
- Transdermal Microneedle
- Micropump
- Manufacturing Process
- Summary

# MEMTS



# MEMTS Layout



micropump

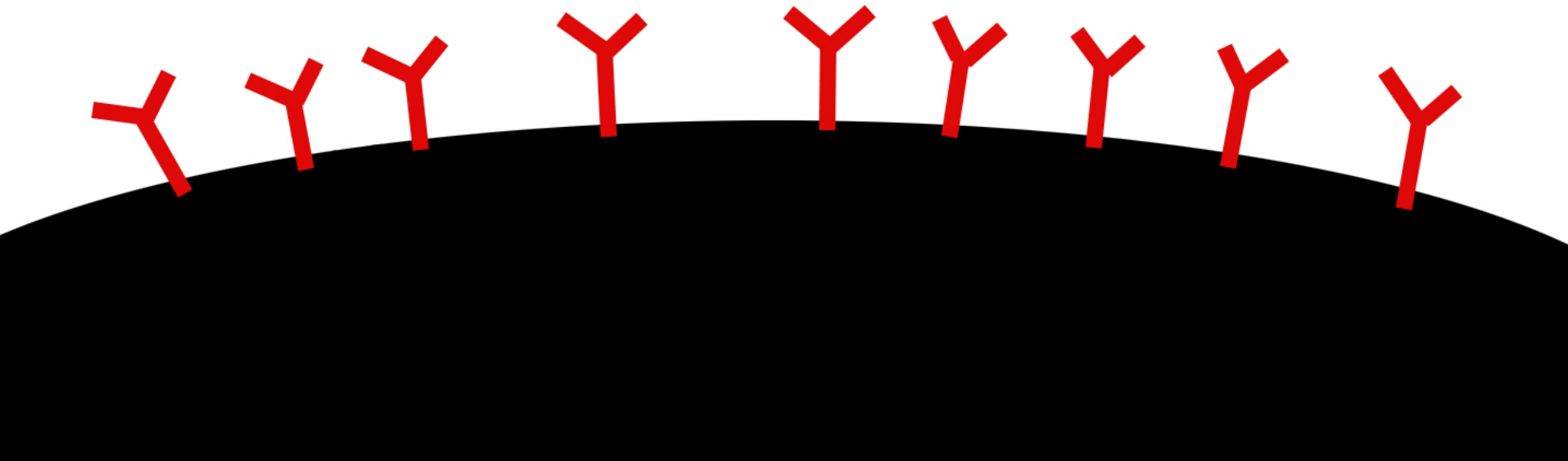
Signal processor and electronics

Wire bonding

Detection needle

Dispensing Microneedles

# Pharmacokinetic Interactions



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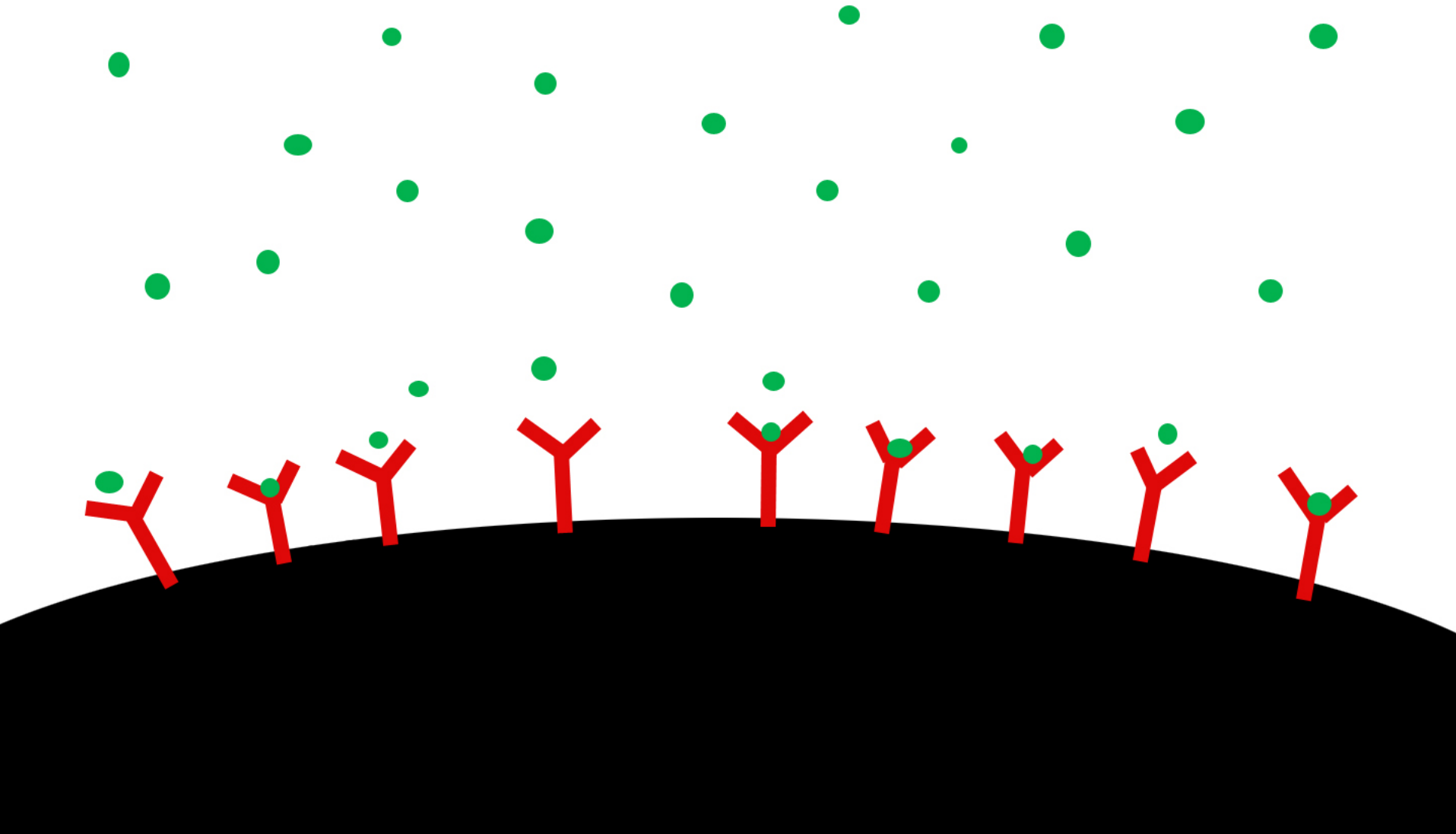

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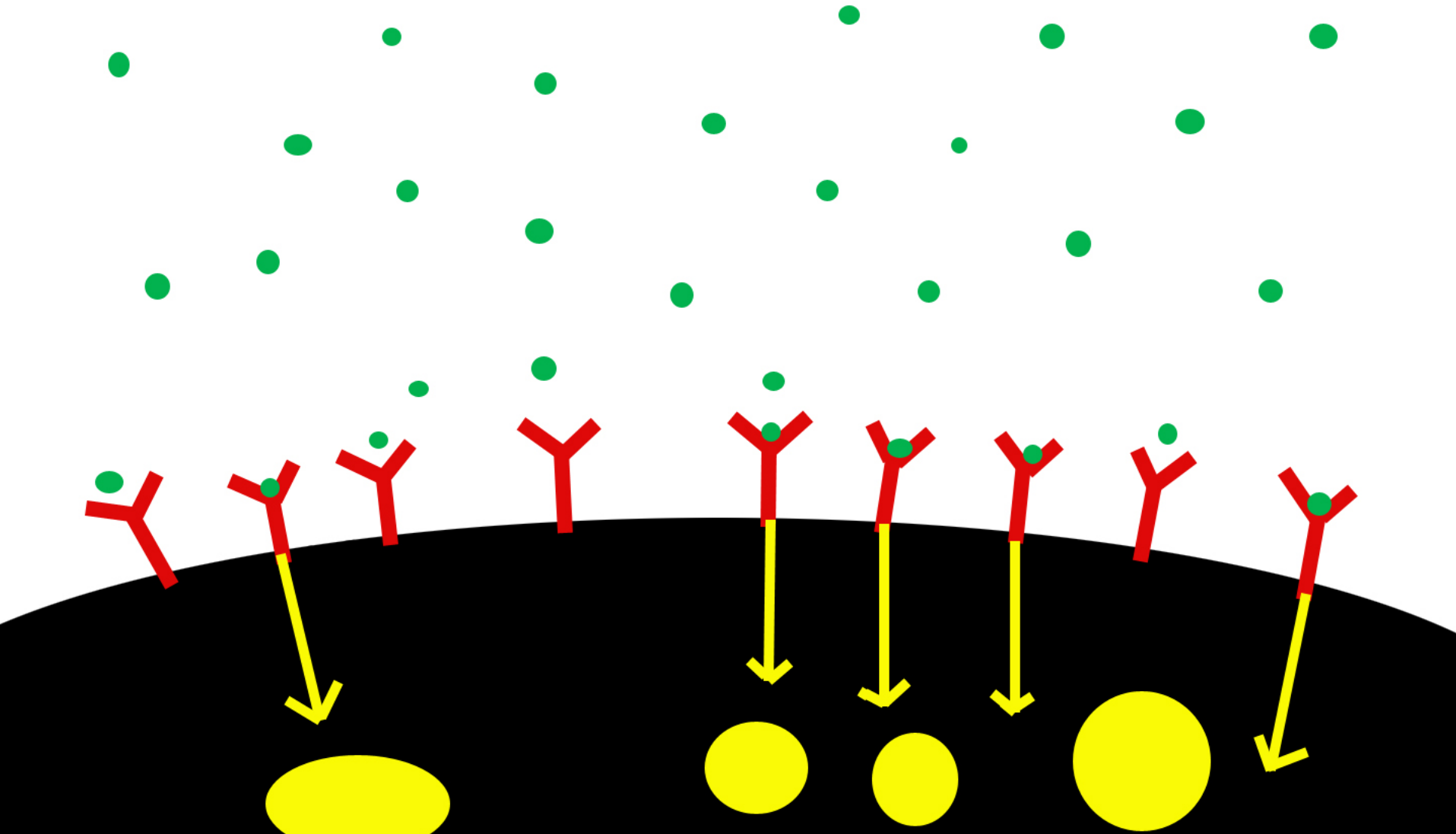

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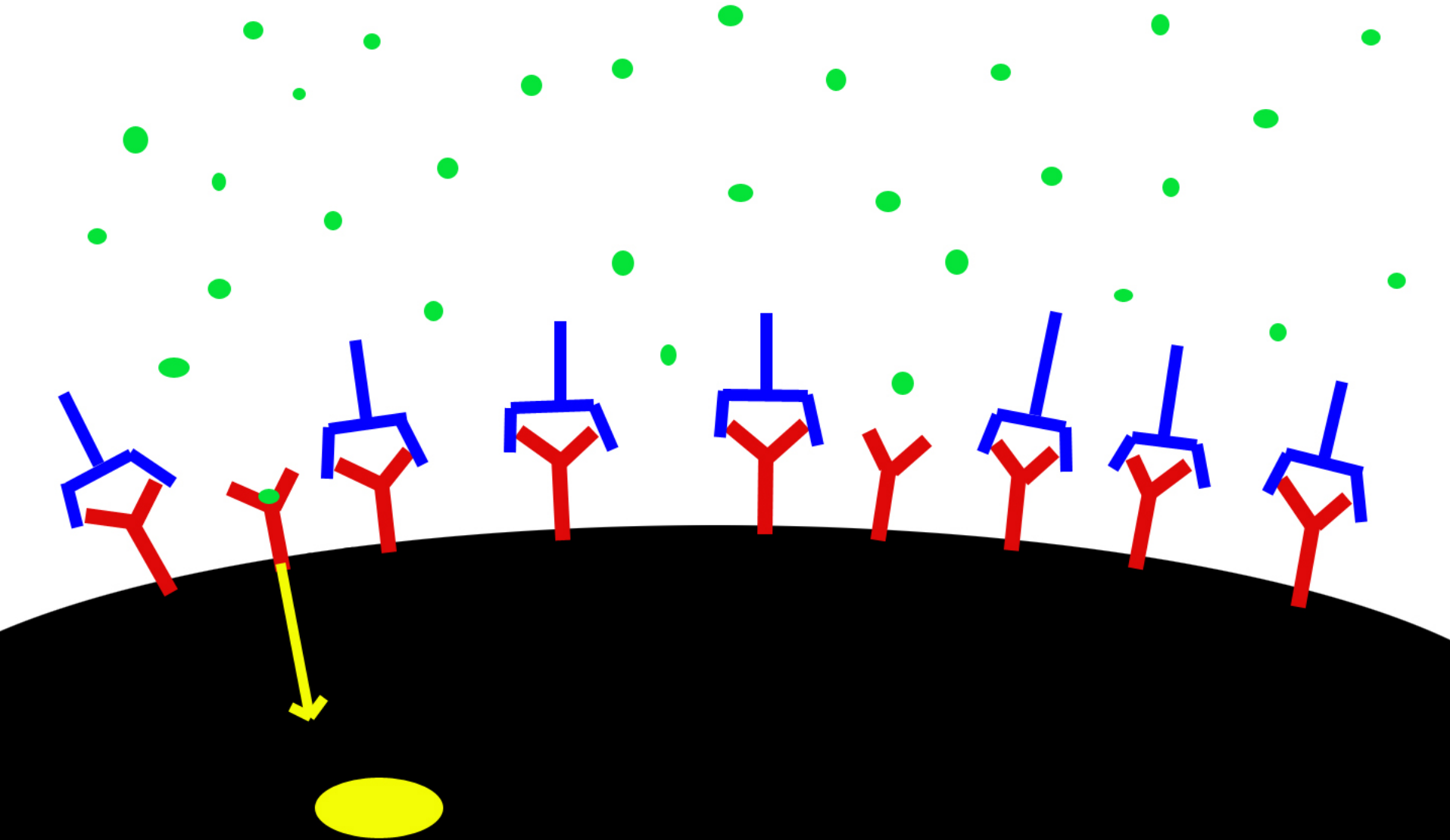

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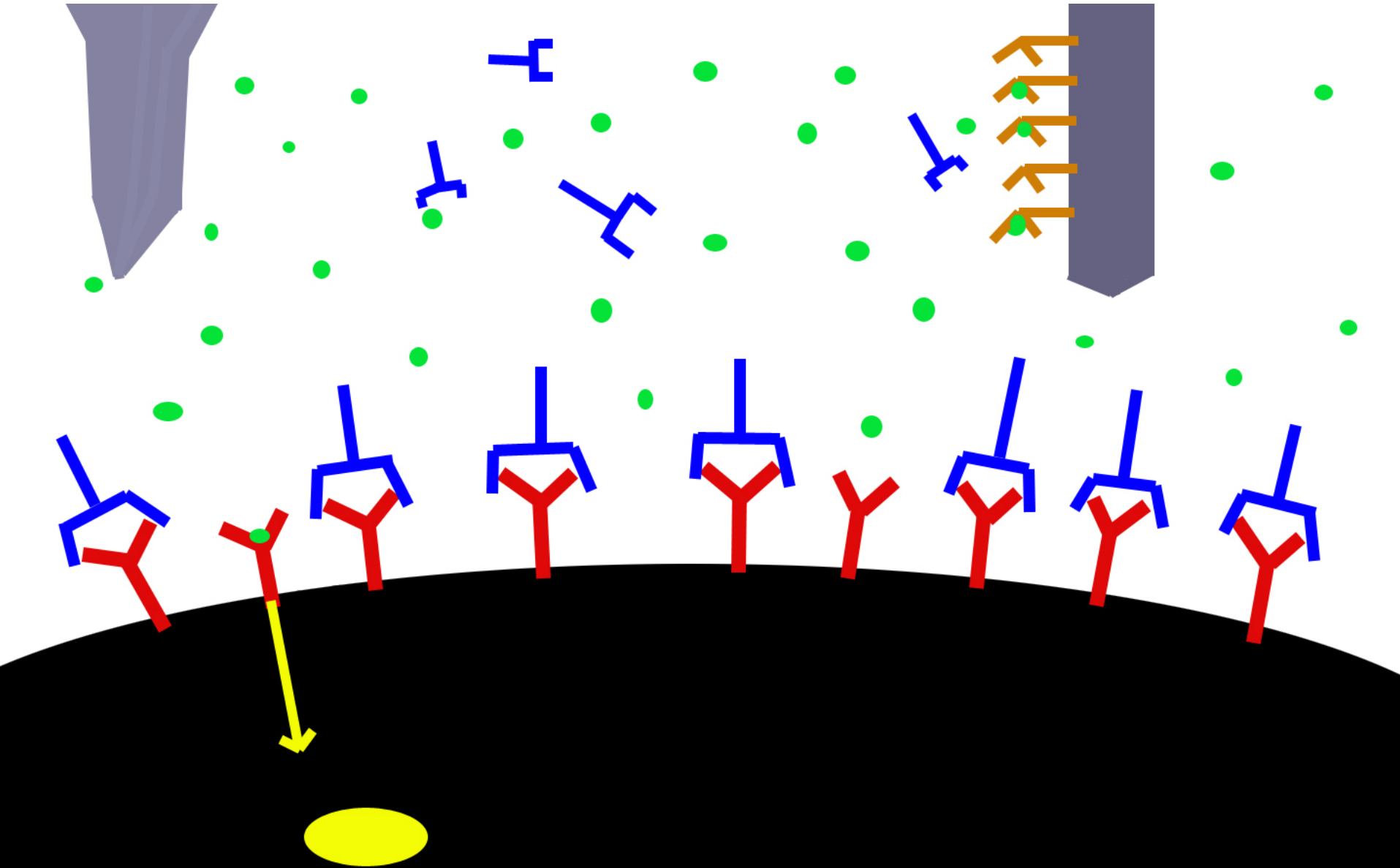

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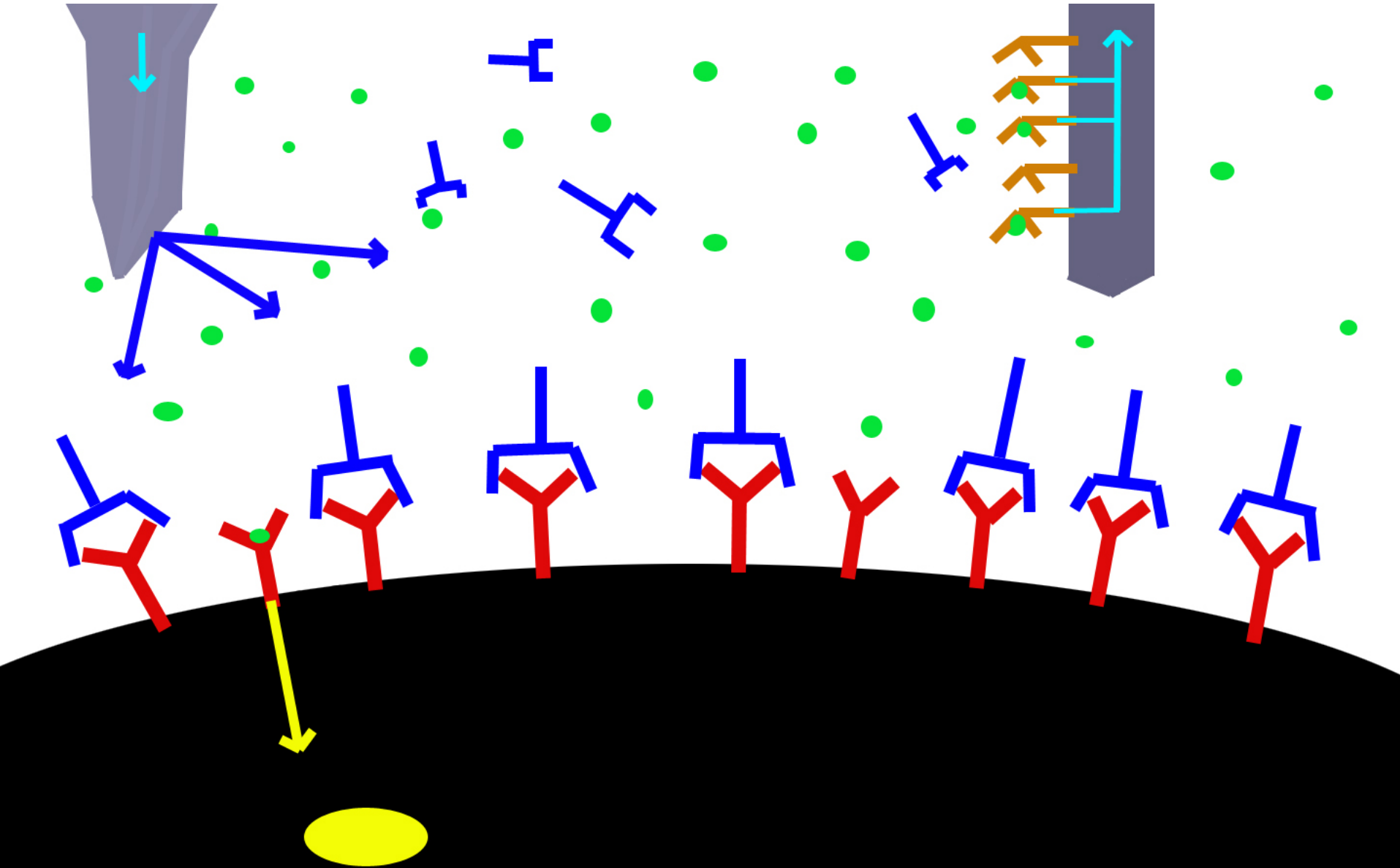

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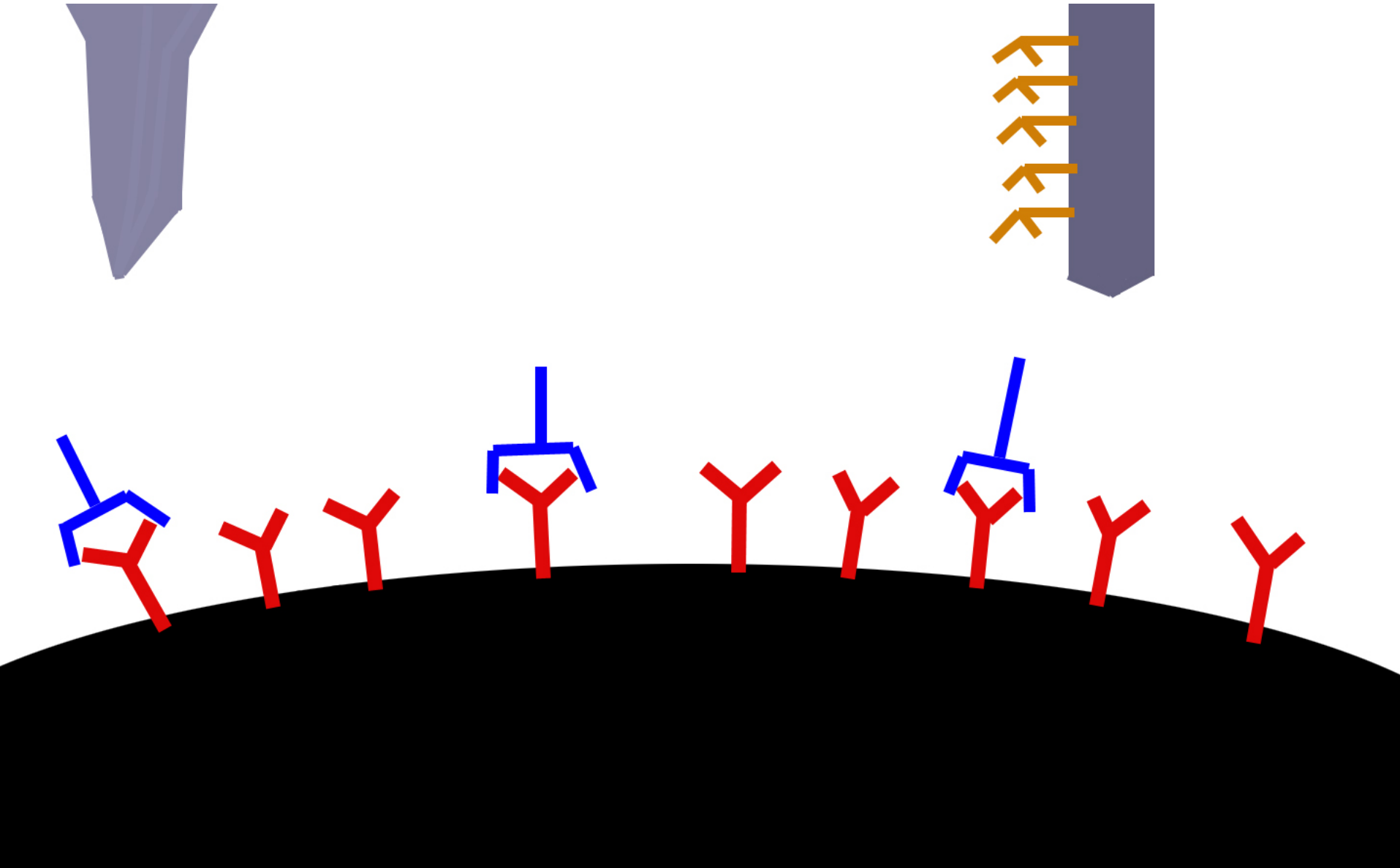
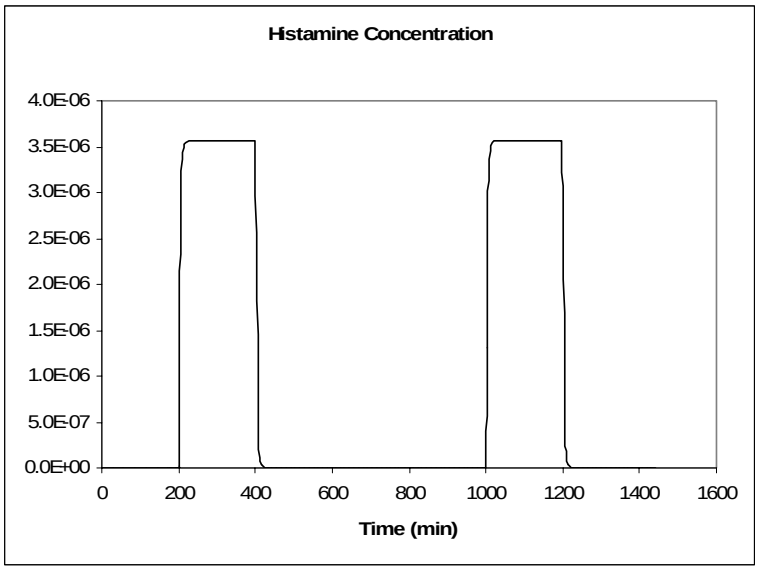
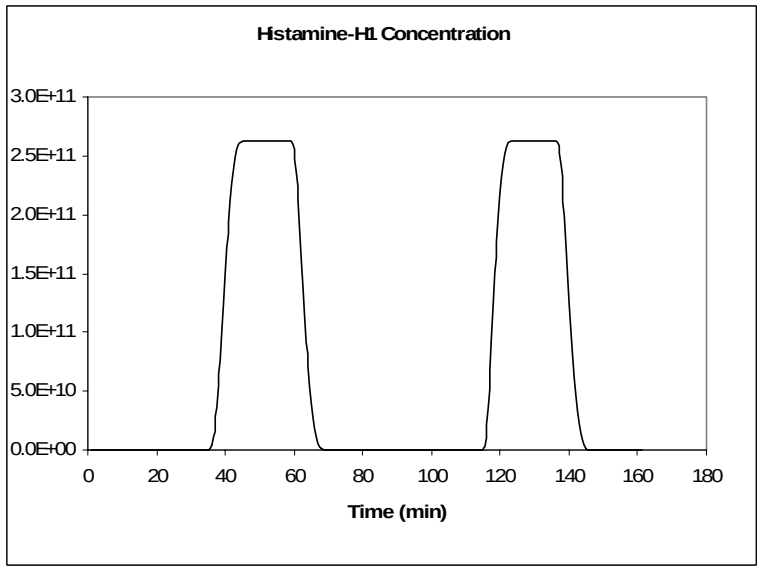


# MEMTS Performance



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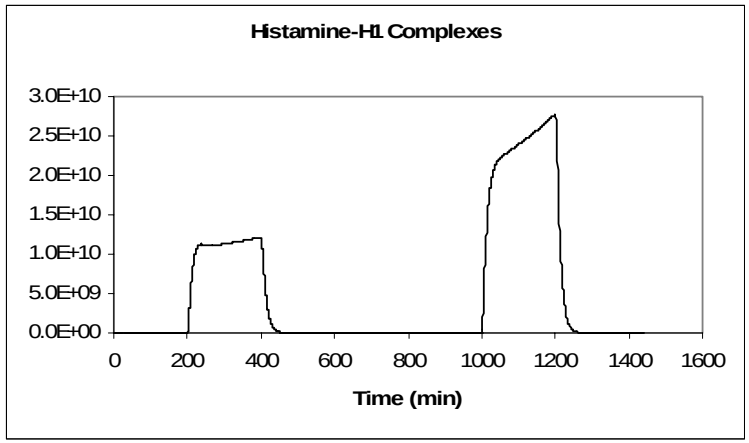
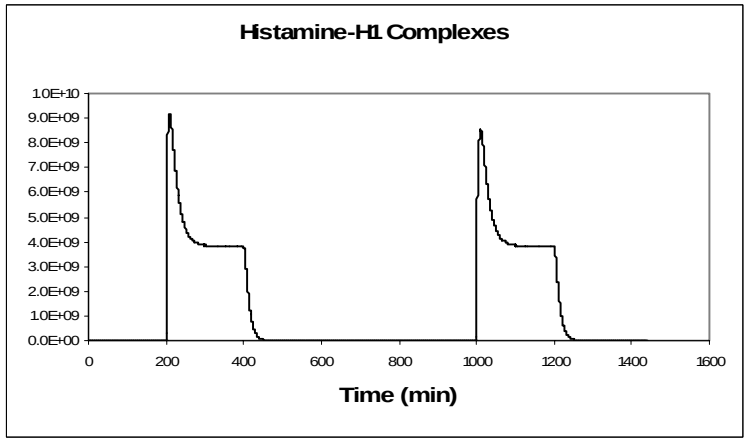
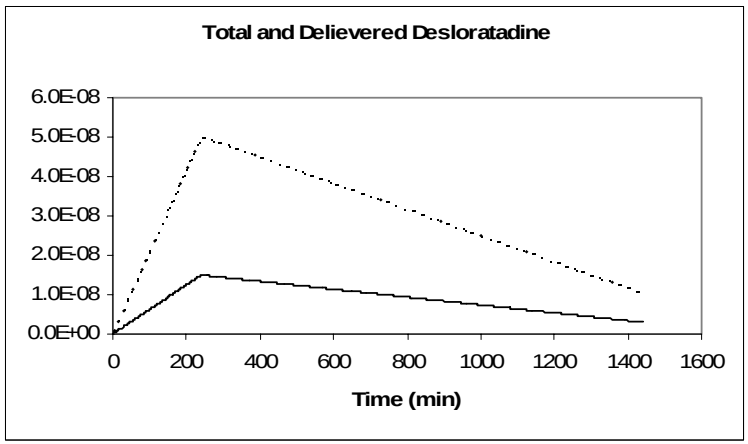
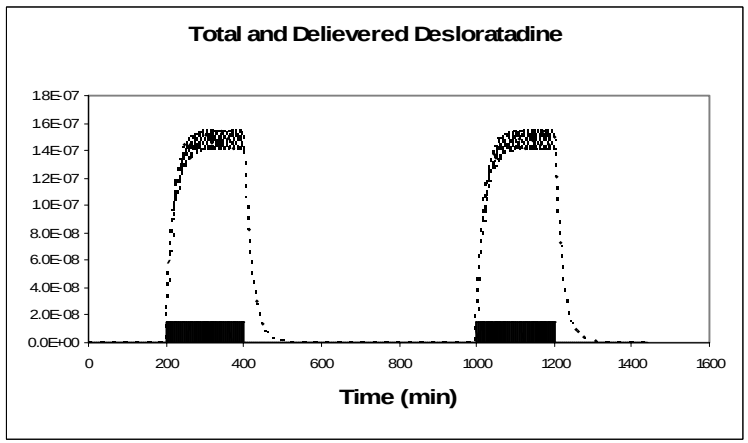


# MEMTS Performance

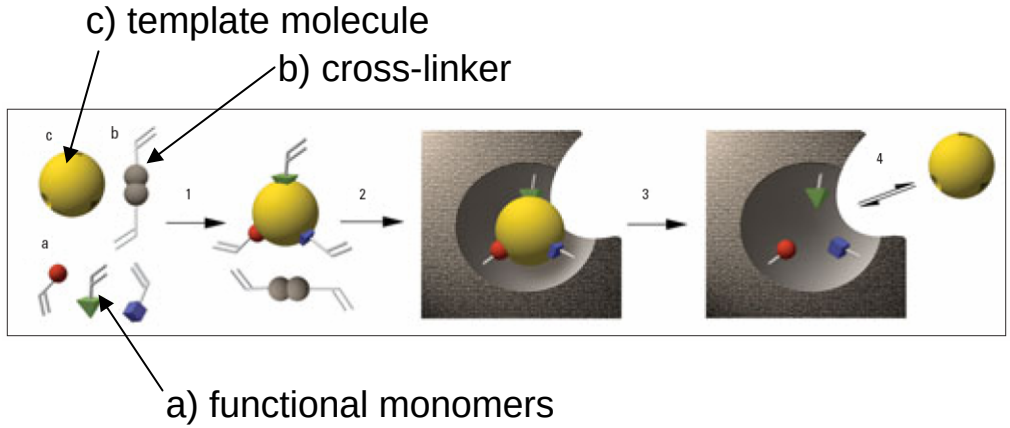
- Sensitivity Analysis
  - System performance is not compromised with detection at or below 5% histamine change (0.2μM blood-histamine)
  - Performance is insensitive to delays up to 2 minutes
  - Optimal response occurred with doses every 4 minutes
  - Duration of delivery was most efficient between 40-50% of the dose period (2 minute delivery in 4 minute release pulses)

# MEMTS Performance: Results

- The responsive delivery system elicited a better response than oral delivery, reducing the amount of allergenic interactions by an order of magnitude
- MEMTS delivery also reduced the amount of drug required by 85%

# Biochemical sensors - MIPS

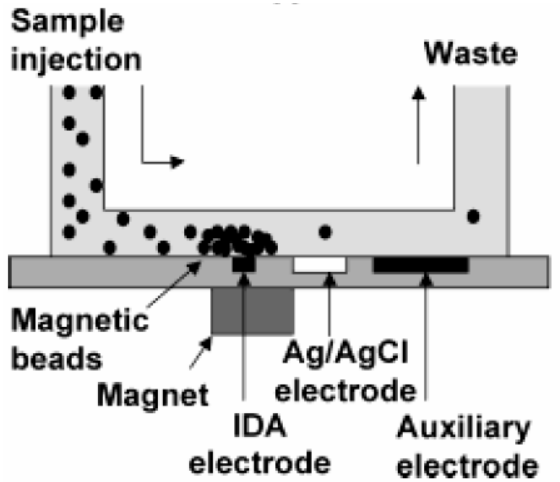
- Molecularly Imprinted Polymers (MIPs)
  - Polymer is very stiff and non-conductive
  - Polymer is washed with 100mL–2L of solvent
  - Small organic and inorganic molecules with few aromatic rings
  - Detection mechanisms: fluorescence, quartz-crystal microbalance (added mass of analyte reduces cantilever vibrational frequency), scintillation, spectral shift, proton release from polymer (pH)
- MIPS have $10^3$–$10^6$ binding sites, biological receptors have ~1.

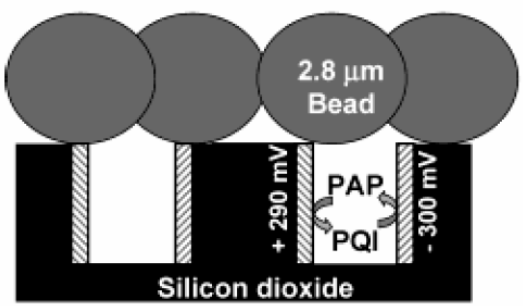


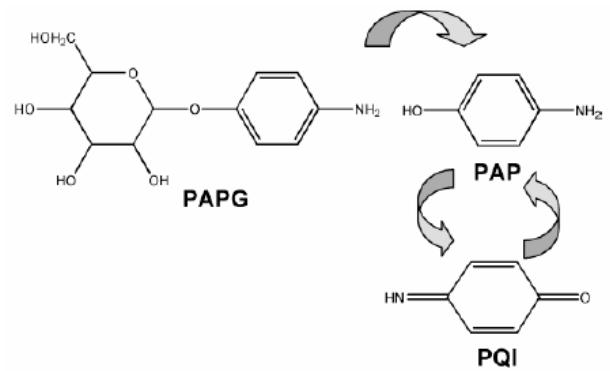

(Haupt K, Analytical Chemistry, 2003)

# Biochemical sensors – micro bead

- Bead-Based Electrochemical Detection
  - Biotin attached to rabbit anti-MS2 IgG, coupling antibody to streptavidin-coated beads
  - Potentials of +290 and -300 mV applied to two electrodes, current measured as beads injected
  - PAPG electroinactive at potential where PAP oxidized to PQI -- current proportional to antigen concentration




(Thomas JH, Analytical Chemistry, 2004)

# CNT sensor for protein detection

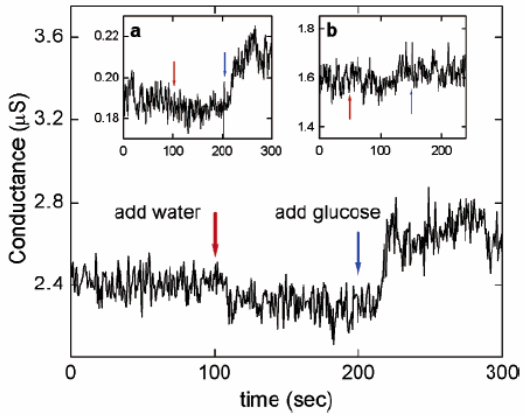
- Add antibodies to CNT surface

(Patolsky F, PNAS, 2004)

Step 1) 1% ethanol, 3-(trimethoxysilyl)propyl aldehyde for 30min; wash with ethanol; heat at 120C for 15min

Step 2) Receptors coupled to aldehyde-terminated CNT surface: 10-100µg/mL antibody; 10mM phosphate buffer containing 4mM sodium cyanoborohydride ($NaBH_3CN$)

(Unreacted CNT aldehyde surface groups passivated by reaction with ethanolamine)

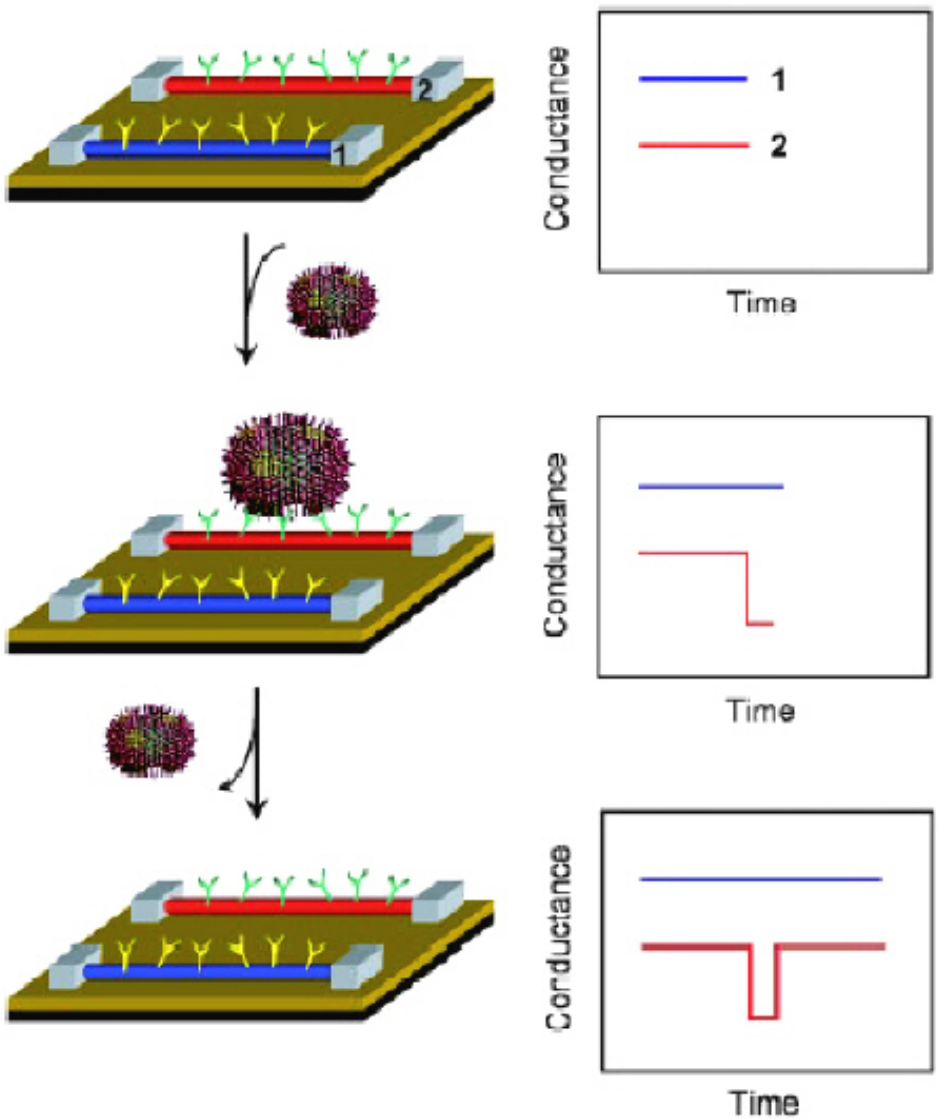


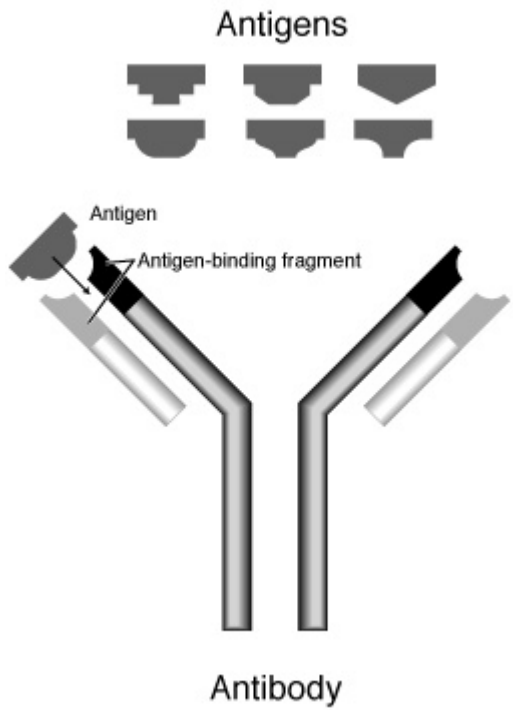

Conductance of glucose oxidase-coated SWNT increases when glucose added (Besteman K, Nano Letters, 2003)

- Direct protein absorption to CNTs
  - Charges on protein surface exert *gating effects* or charge transfer to nanotube; changes electrical conductance of nanotube FETs.
  - Field effect induced by electron-donating/withdrawing groups; *lysine* residues on protein exterior

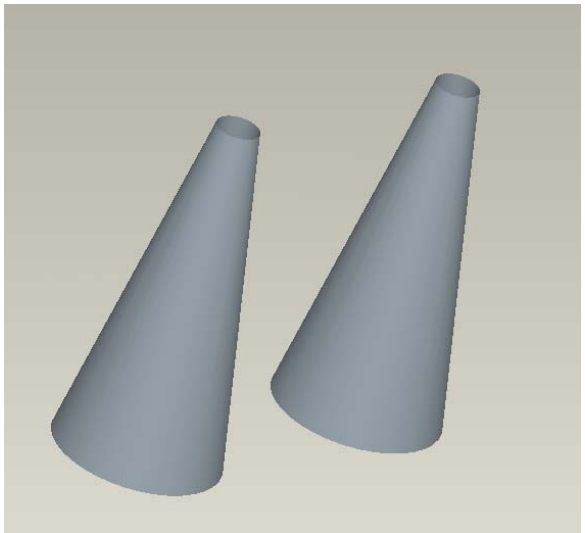
(Chen RJ, J. Am. Chem. Soc., 2004)

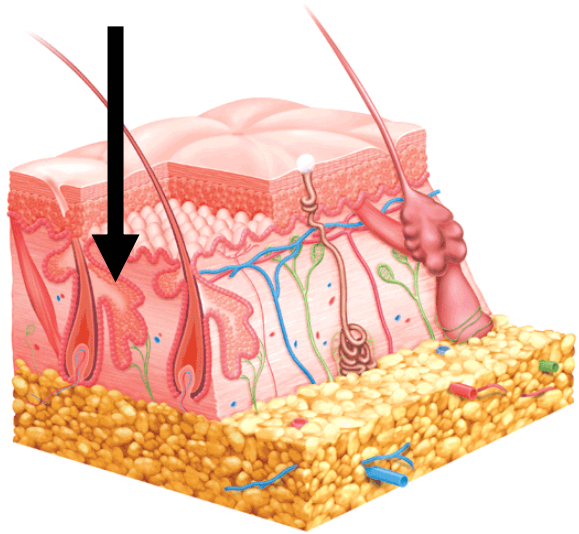
# Nanowires for detection



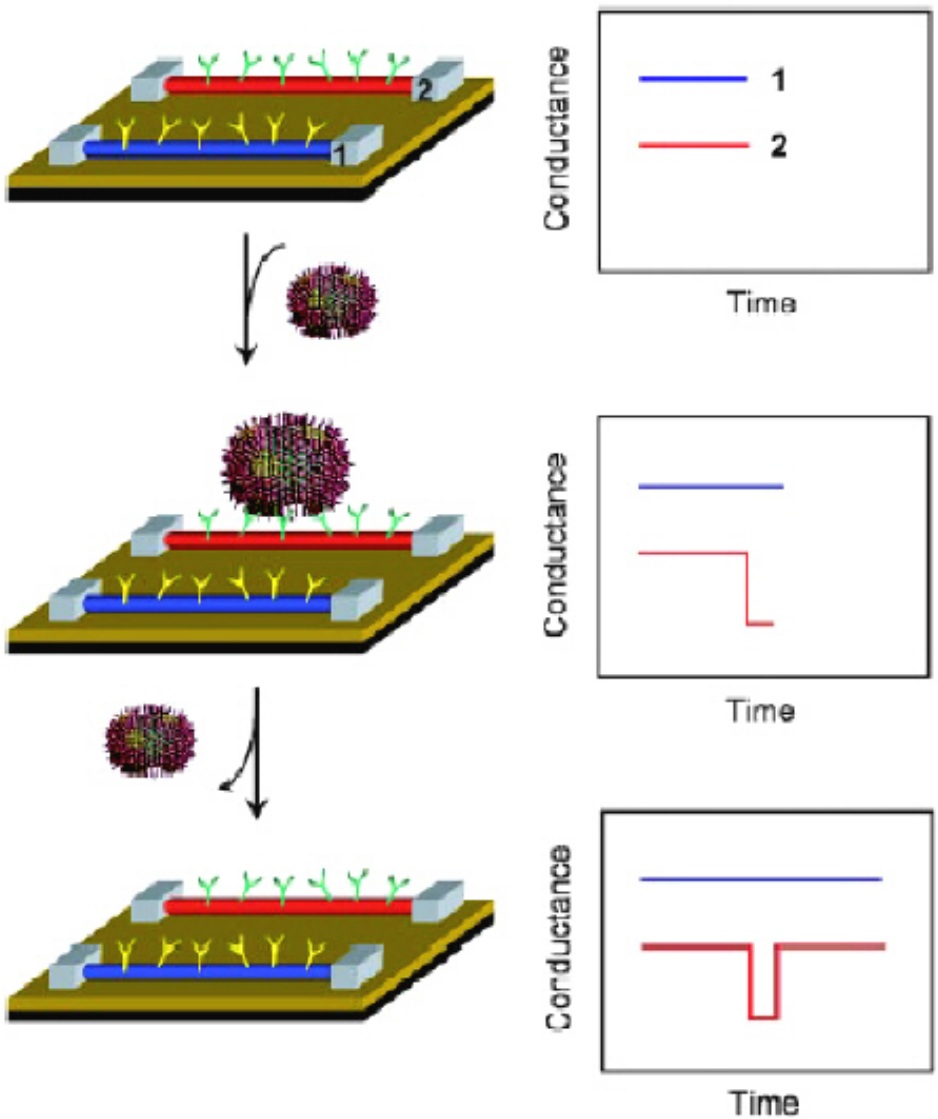
# Microneedle Array

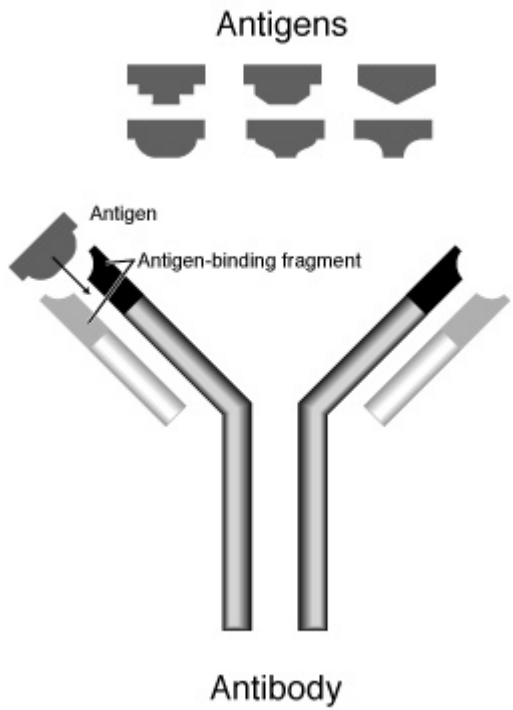




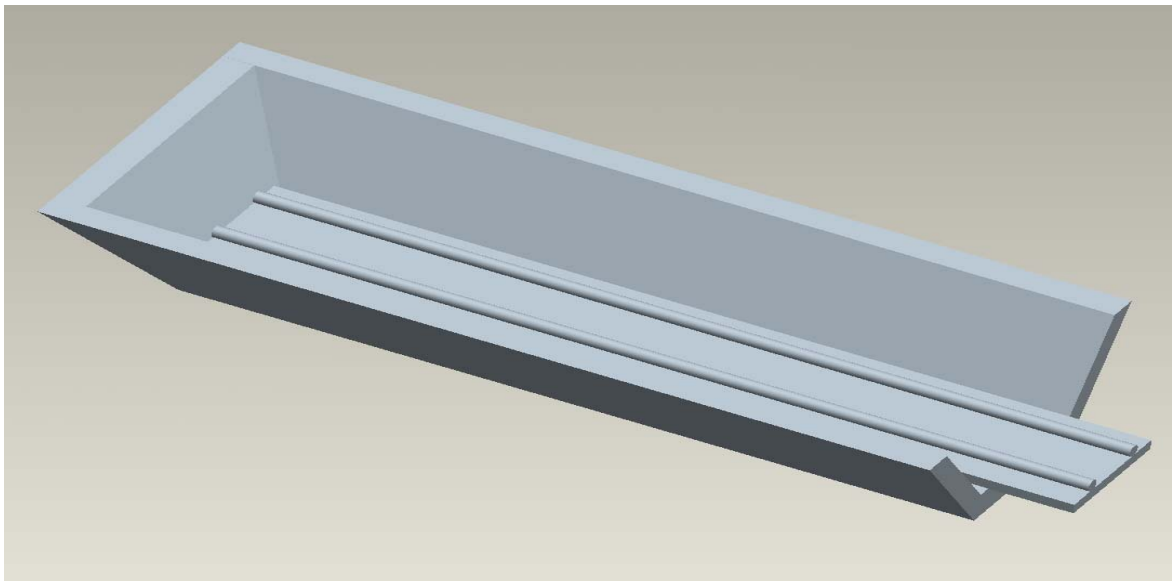
- 500 µm in length for drug delivery beneath epidermis
- 20º angle tip for skin penetration robustness
- sputtered film of biocompatible titanium coating for structural durability

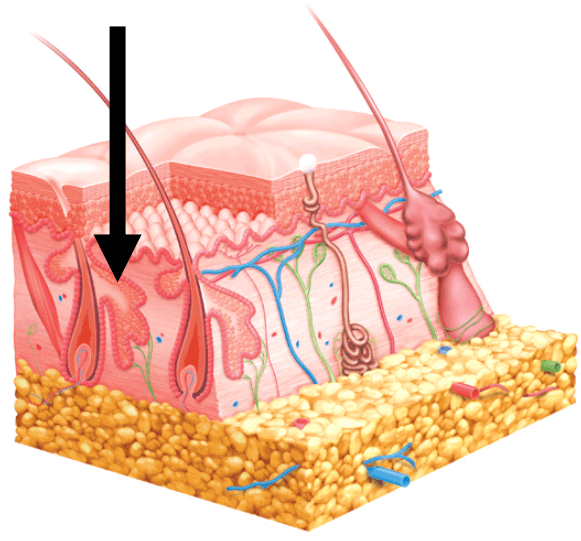
# Nanowires for detection



# Detection Needle with embedded Nanowires





- minimally invasive tip design
- embedded nanowires in trough for structural reliability
- 700 µm length to penetrate past epidermis

# Requirements for Drug Delivery Micropumps

- Flow rate – up to 100ul/min
- Self-priming – large stroke and small dead volume
- Controllability of flow rate at all time
- Drug compatibility
- No introduction of any toxic particles into the drug and vice versa
- Actuation safety
- The actuation mechanism must not damage and electrolyze the drug.
- Chip size
- Power consumption

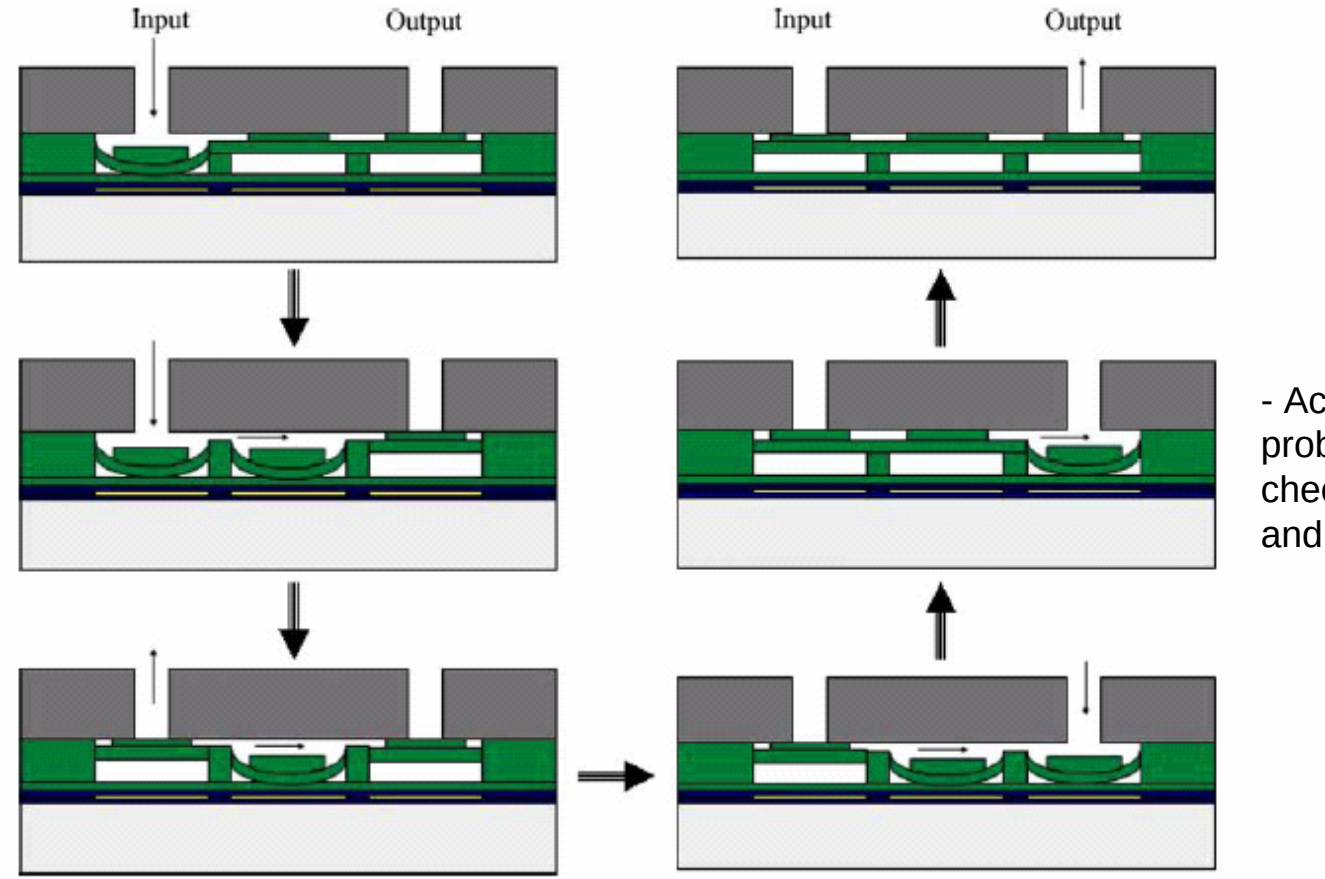
# Micro Pumps

- Mechanical Pump
  - Reciprocating type ; Tribological problem
    - Membrane type
      - Two-passive-valve micropump
      - Valve less diffuser/nozzle micropump ;Back flow problem
    - Peristaltic type
      - Reduced valve-leakage and no driven frequency limitation.
      - The actuators are not in contact with liquid.
      - The pumped volume is determined only by the features of the actuator.
  - Rotary type ; for high viscous fluid
- Non-mechanical pump

# Types of microactuation

- Electrostatic
  - Good reliability and energy efficiency
  - Small displacements
  - Non-linear input & output relationship
- Piezoelectric – preferred for medical applications
- Magnetostrictive
  - Affects drug quality, mechanical micropumps
- Thermopneumatic
  - Affects drug quality, mechanical micropumps
- Shape memory alloy

# Working principle of proposed micropump




Working principle of proposed micropump (glass ( ); Si substrate ( ); gold pads ( ); dielctric ( ); membrane ( )).

- Active membrane valves can resolve problems associated with the passive check valves, such as valve clogging and valve breaking.

# Schematics of the proposed micropump

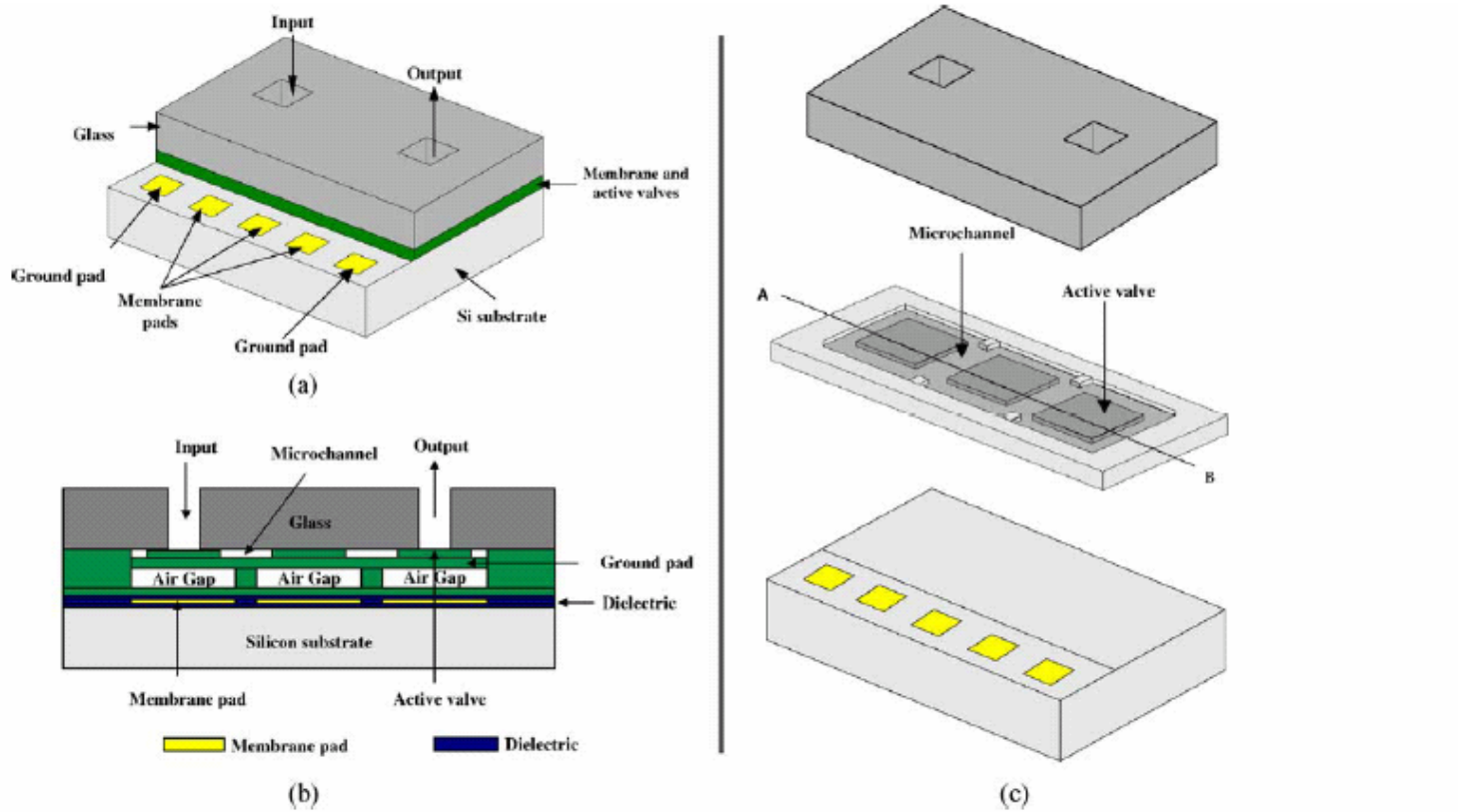
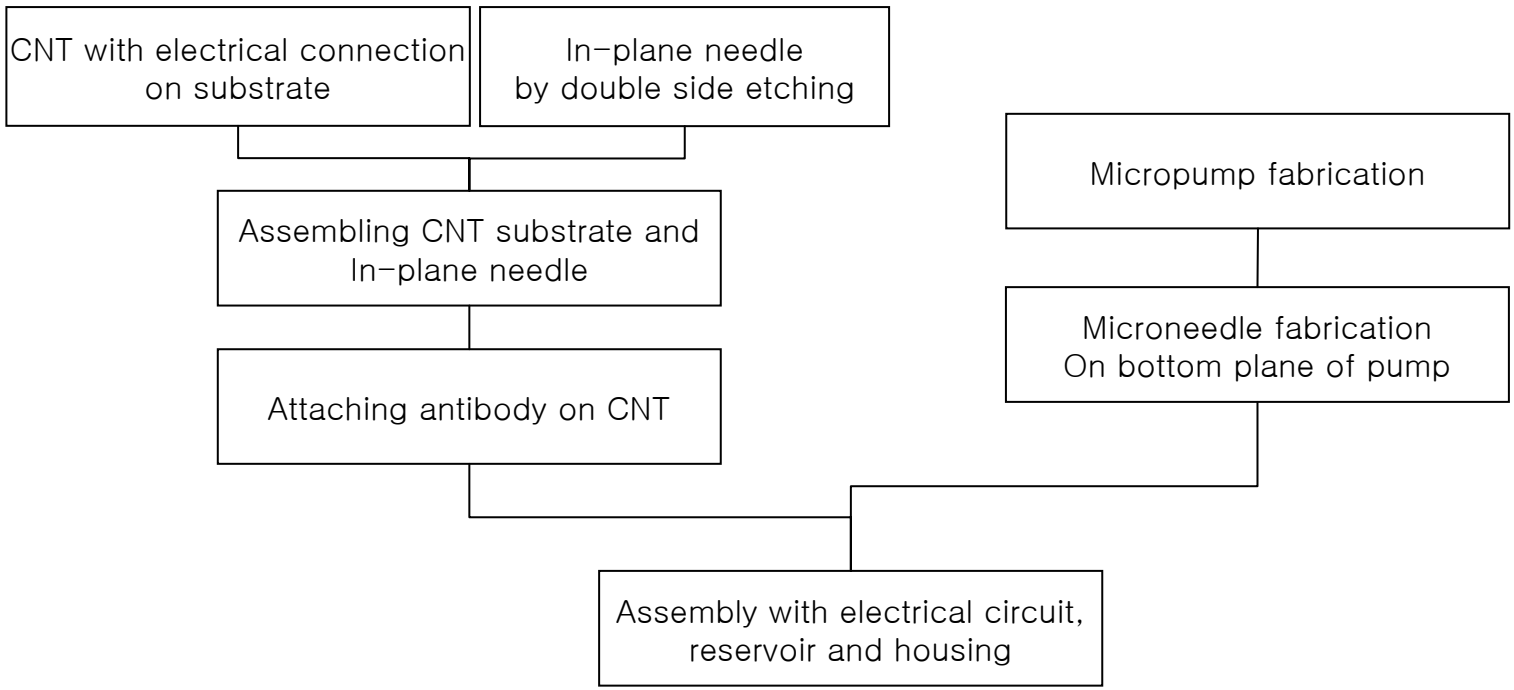
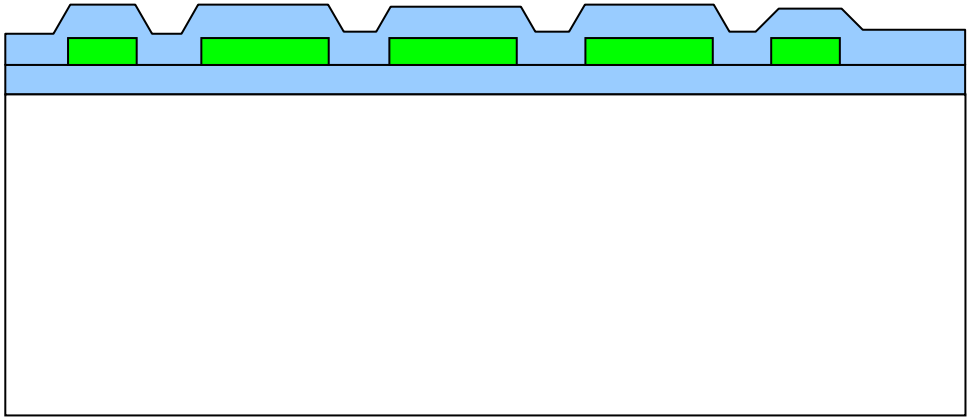



Fig. 1. (a) Three dimentional schematic of the proposed micropump (glass ( ); Si substrate ( ); gold pads ( ); membrane part ( )). (b) Three layers of proposed structure (glass ( ); Si substrate ( ); gold pads ( ); membrane ( ); microchannel ( )). (c) Cross-section of the proposed micropump (A–B view) (glass ( ); Si substrate ( ); gold pads ( ); dielctric ( ); membrane ( )).

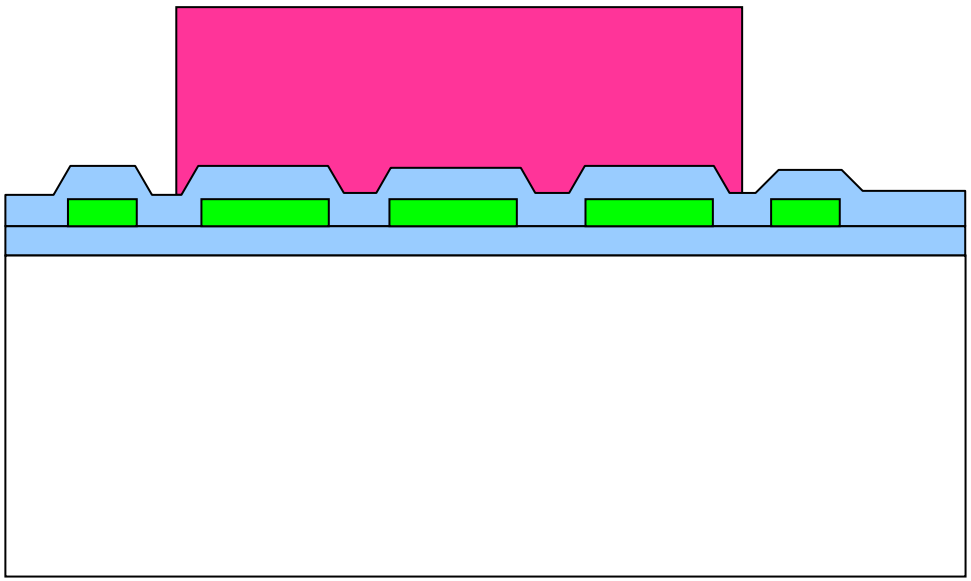
# Process Flow Chart





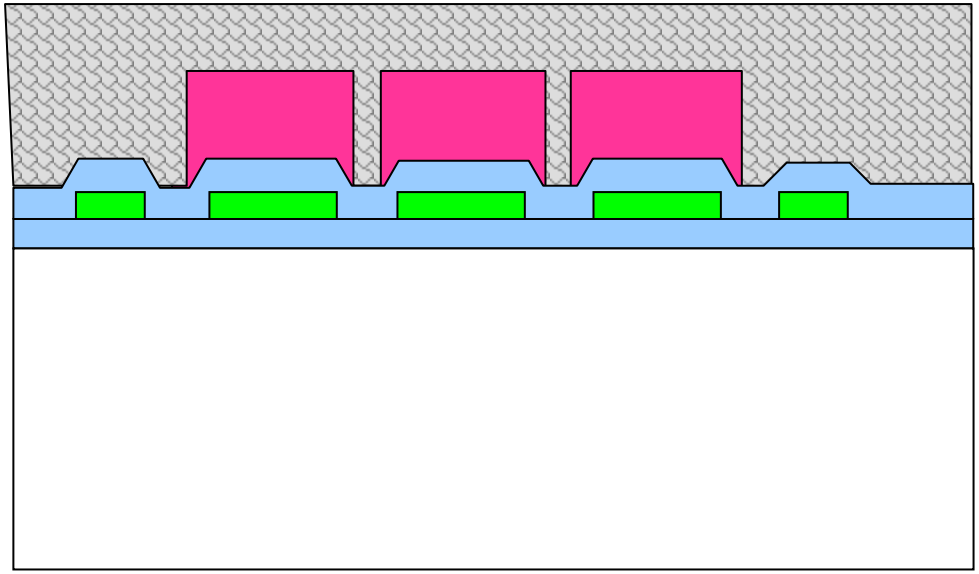
-A thin Si3N4 is deposited on the Si substrate which act as electrical insulation between pads and substrate.
-Au is sputtered and then patterned to form electrical pads.
-A thin Si3N4 is deposited and patterned. It plays the dielectric role between upper and bottom electrodes.

Si Si3N4 Au



-A 4 um thick photoresist (sacrificial layer) is deposited and patterned. Since, the next processes can affect the photoresist, it is cured in order to resist against high temperature processes

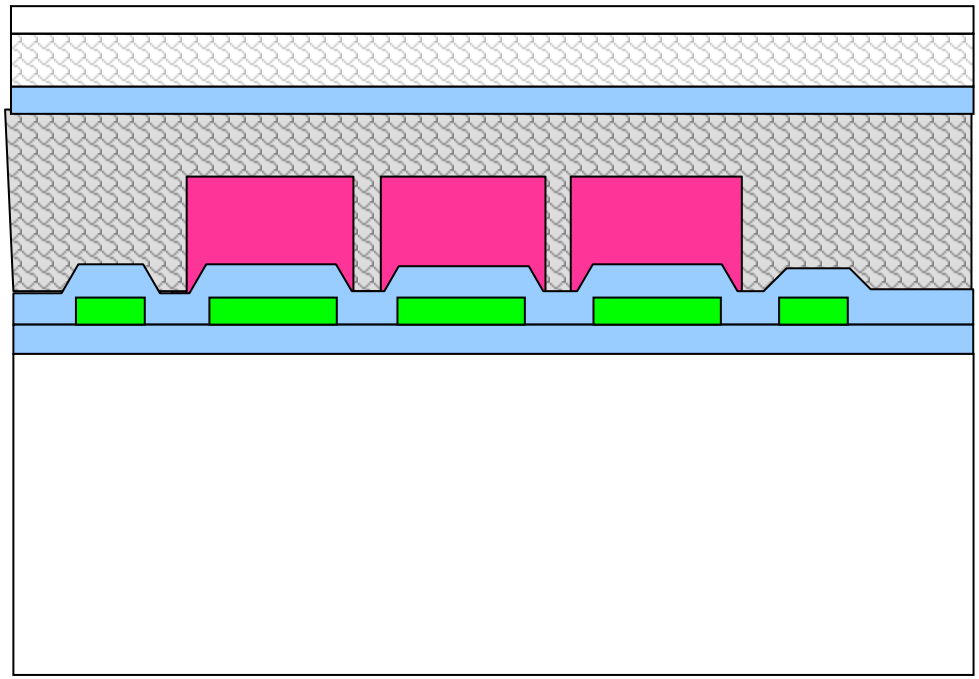
Si Si3N4 Au PR



-A 4 um thick p+ doped polysilicon is deposited, planarized, and polished

Si | Si3N4 | Au | PR

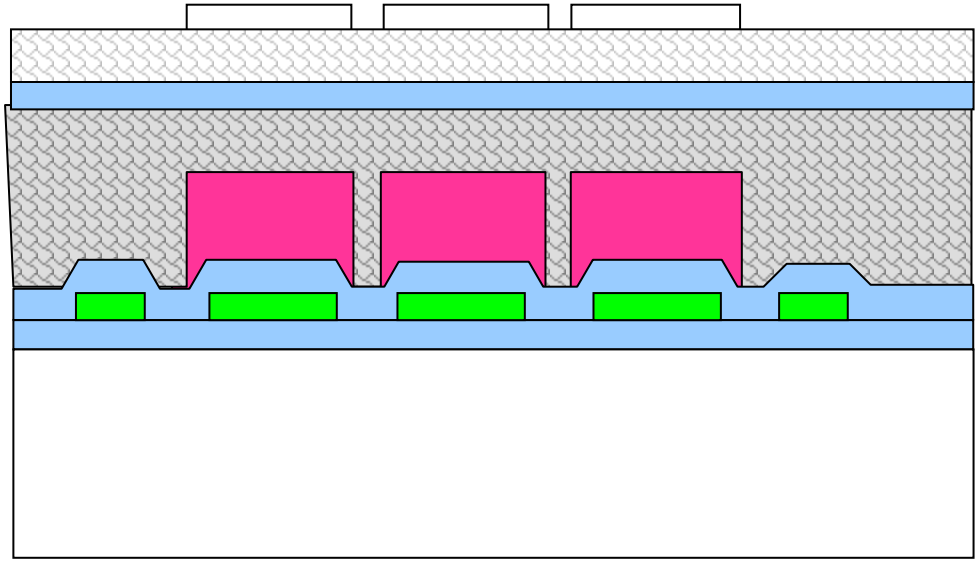
P-polySi



-poly/Si3N4/poly/ SiO2 sandwich layer is deposited. The 2 um polysilicon is the membrane thickness and the 3 um is active valve thickness. SiO2 is used as the selective anodic bonding layer and Si3N4 is used for etch-stop of the polysilicon

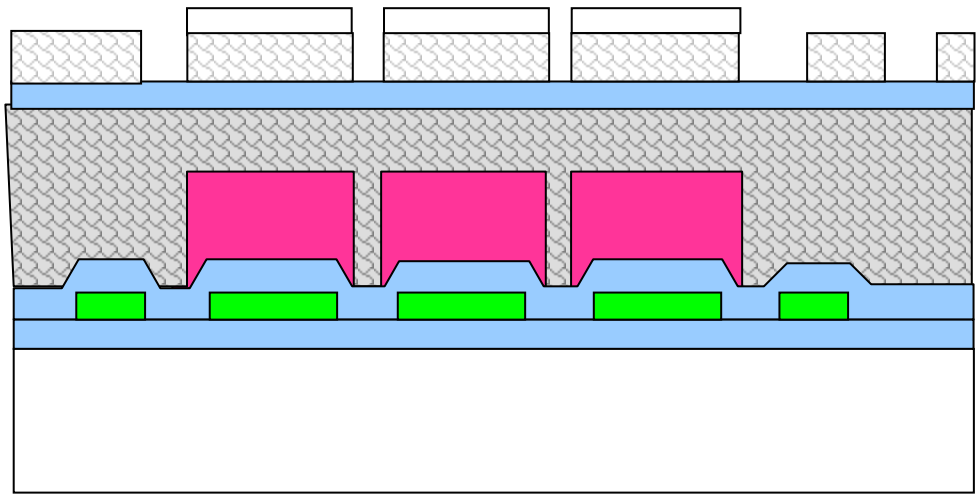
Si | Si3N4 | Au | PR

P-polySi | Poly Si



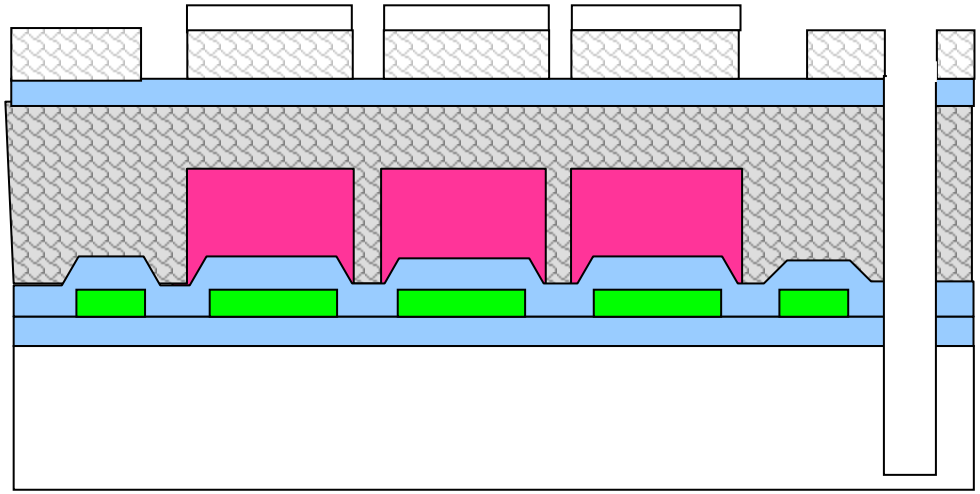
-The SiO2 is patterned to be used as the selective anodic bonding layer

Si | Si3N4 | Au | PR | P-polySi



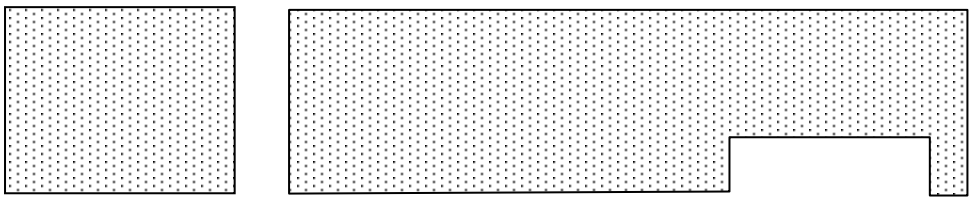
-The polysilicon is patterned. The Si3N4 is used as the mask

Si | Si3N4 | Au | PR | P-polySi | Poly Si



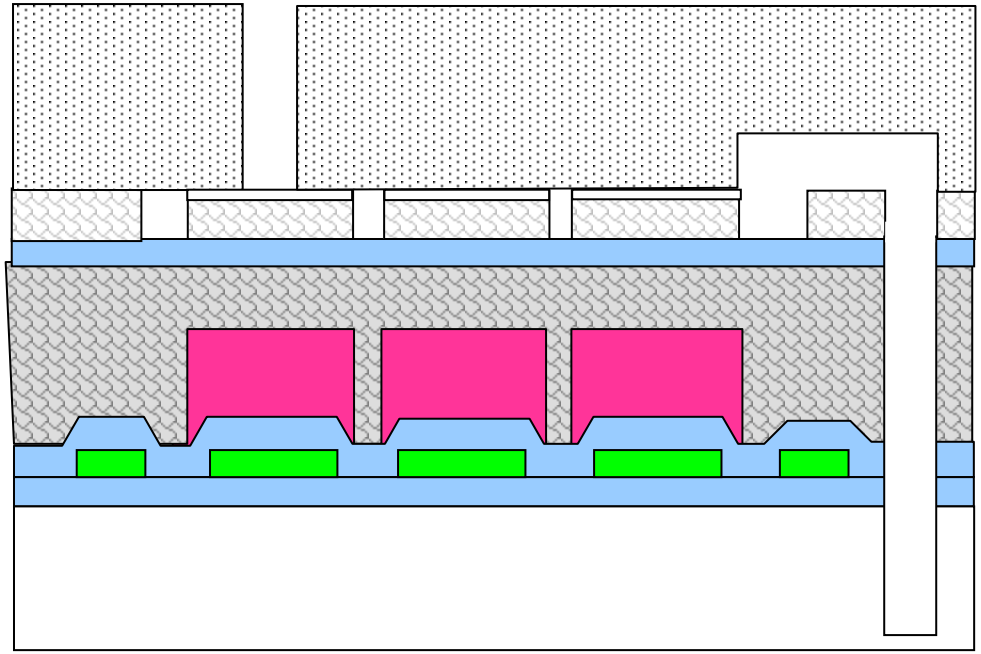
-Multi layer etchings for channel between pump and needle

Si | Si3N4 | Au | PR | P-polySi



-A hole and a groove are created in the glass substrate which are the input and output ports

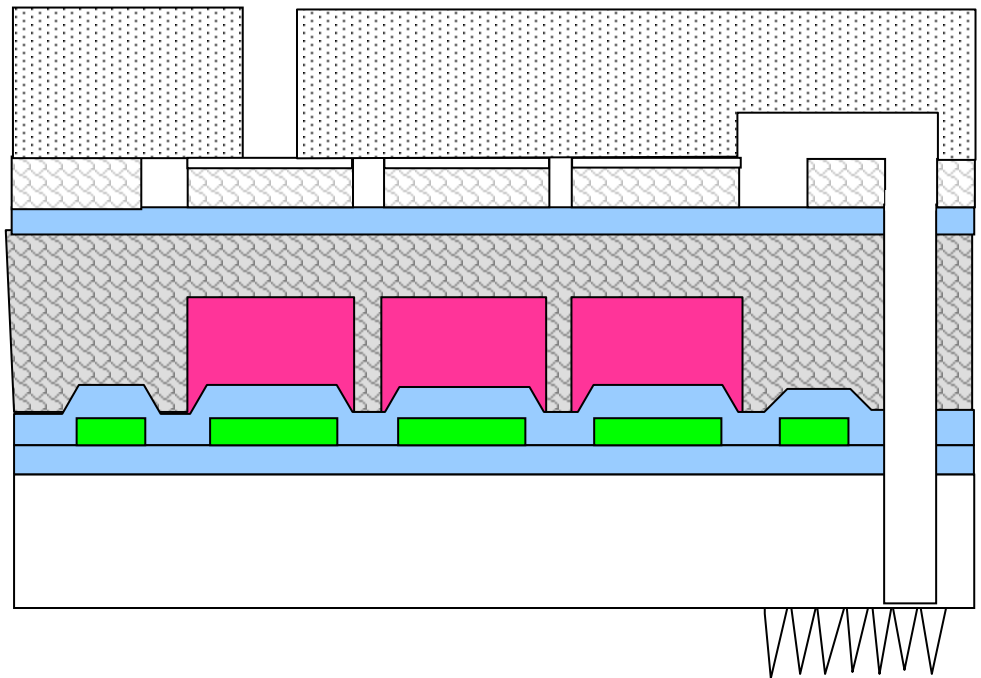
Si | Si3N4 | Au | PR | P-polySi | Poly Si | Glass



-Two substrates are anodically bonded together

Si | Si3N4 | Au | PR

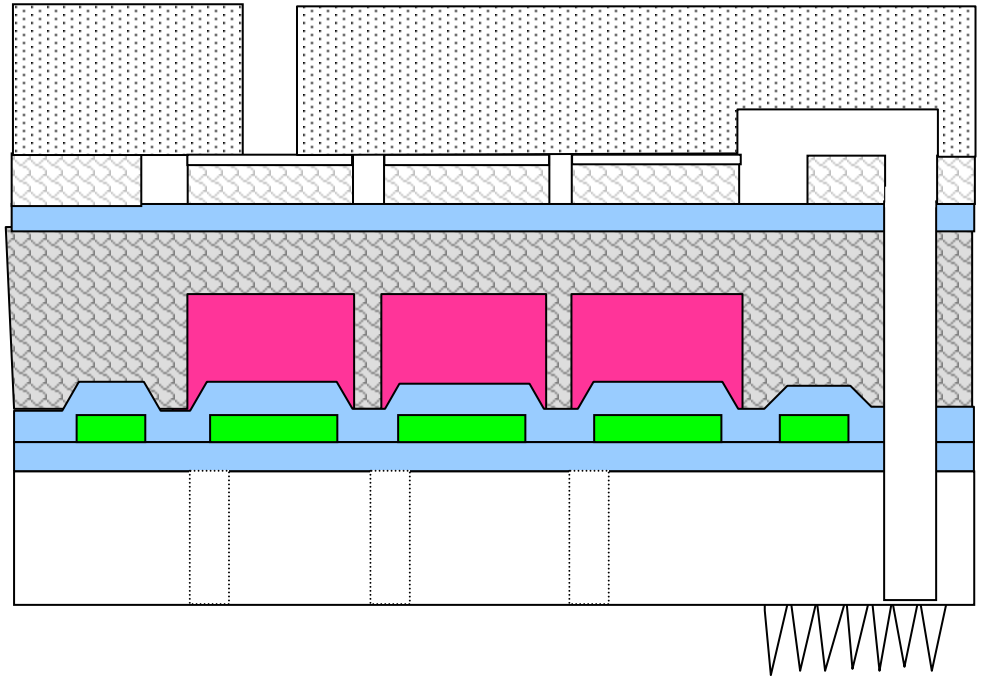
P-polySi | Poly Si | Glass



-Needles are fabricated on the bottom plane with etching processes

Si | Si3N4 | Au | PR

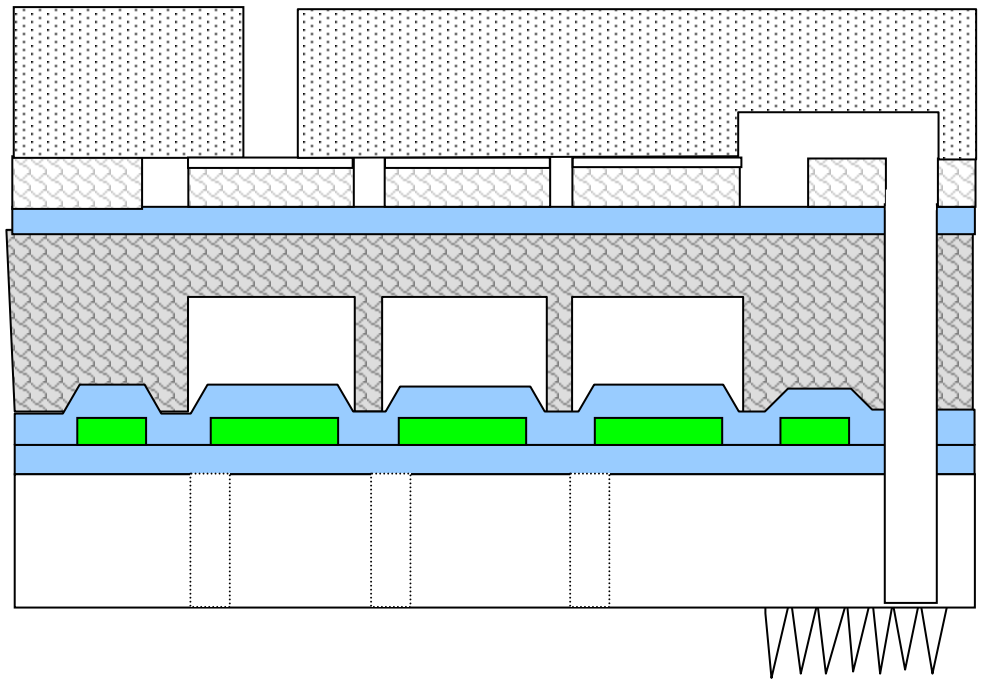
P-polySi | Poly Si | Glass



-Some holes are created on the backside of the Si substrate which will be used to remove sacrificial layer

Si | Si3N4 | Au | PR

P-polySi | Poly Si | Glass



-The photoresist (sacrificial layer) is removed. The Au and glass and Si3N4 act as the self-masking capability against the solution

Si | Si3N4 | Au | PR

P-polySi | Poly Si | Glass

# Summary

- Clinical Relevance
- Pharmacokinetic Interactions
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