Intra-maxillary Drug delivery and Bio-sensing via Dental Implant and its considerations

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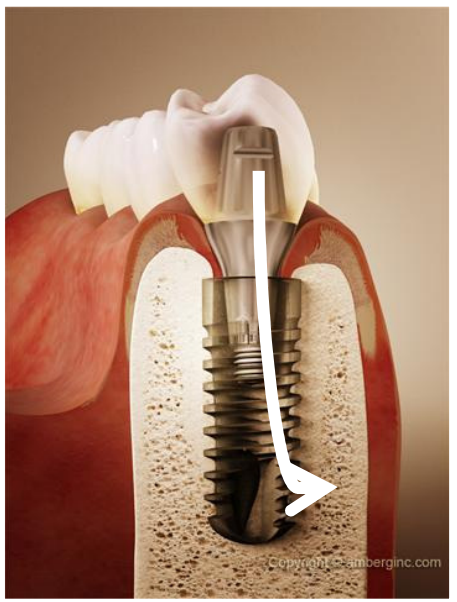
TAIPEI TECH

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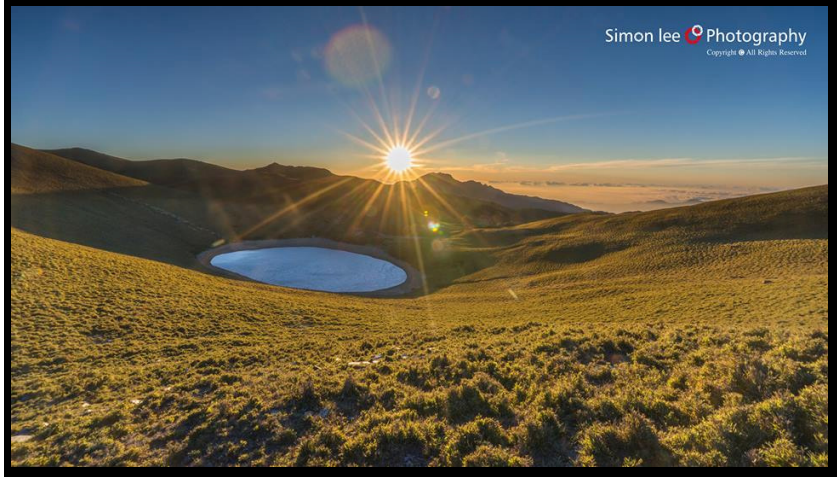
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  - (1) Drug delivery module
  - (2) Bio-sensing module
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  - (1) Glucose monitoring
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  - (3) Canine model for insulin therapy
- **Discussions & Special considerations:**
  - (1) Engineering
  - (2) Medical
  - (3) Dental

Current situation

- **Geriatrics:** The aging population as people > **65 years** in **Taiwan** has reached to **10.7%** in **2010**, and will approach to **20.1%** in **2025**
- **Geriatrics: (1)** Dentistry, **(2) C**ritical + **C**hronic care
- **Medical monitoring and therapeutics:**
  - (1) Non-invasive: BP, HR, RR monitoring + Oral tab
  - (2) Invasive → (A) Blood monitoring + (B) Injections into blood

- **Diabetes Mellitus (DM):**
  - (1) Triad: DM + CAD + Renal disease
  - (2)
    - MDII: (**4** One-touch blood sugar + **4** insulin injections) / Day
    - IVII: (**12** One-touch blood sugar + **12** insulin injections) / Day
- **Pain origins from invasive procedures:**

Drug → **Blood** (**Macromolecule**: cannot pass through GI tract)

(1) Mucosal + (2) dermal barriers

Proteins, functional polymers, etc.

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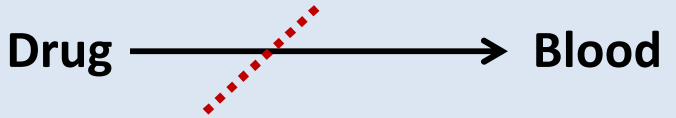
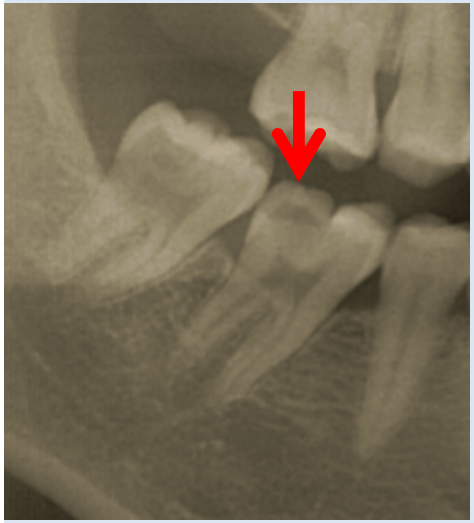


(1) Mucosal + (2) dermal barriers

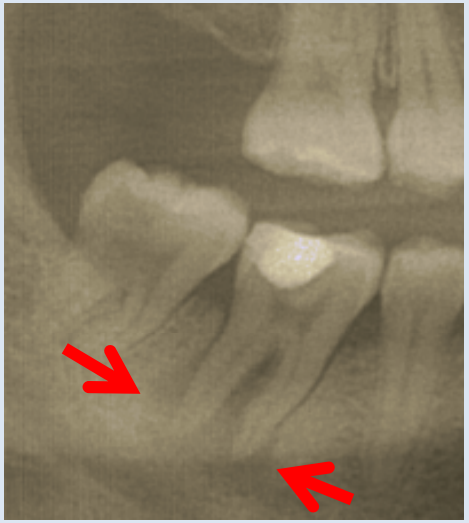
Thinking about molecular delivery in dentistry ?

Intra-bony molecular slowly releasing:

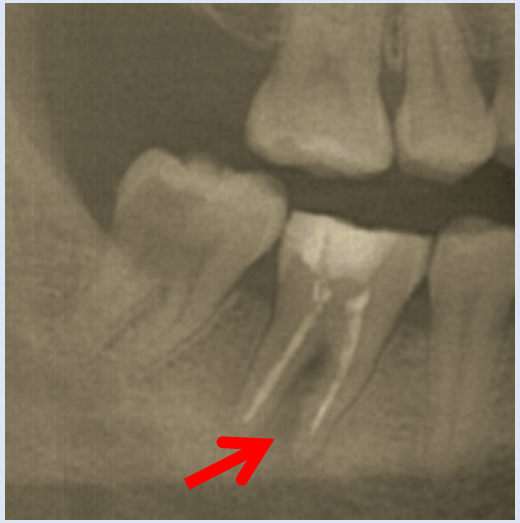
calcium hydroxide/iodoform paste (Vitapex ®) Application



2012. 10. 22
#46: Deep caries
s/p reversible pulpitis
IRM indirect capping



2015. 01. 16
#46: Apical lesion
s/p pulpitis; Pus (+)
Endodontic treatment



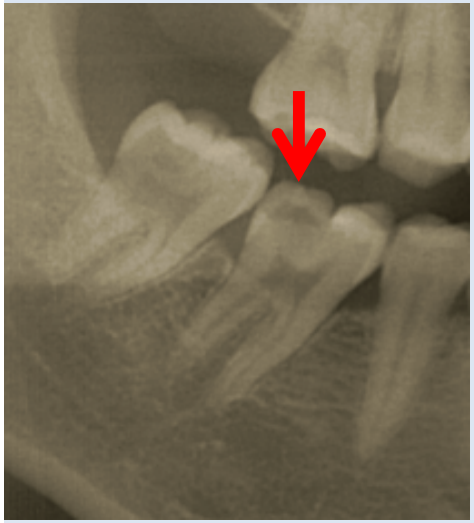
2015. 07. 16
#46: Apical lesion
s/p pulpitis; Pus (-)
Calcium hydroxide RCT

2016. 01. 26
#46: Apical lesion
s/p pulpitis; Pus (-)
New bone formation

38 Y/O male, Personal History: Smoking(+), Past history: Nil

Intra-bony molecular slowly releasing:

calcium hydroxide/iodoform paste (Vitapex ®) Application



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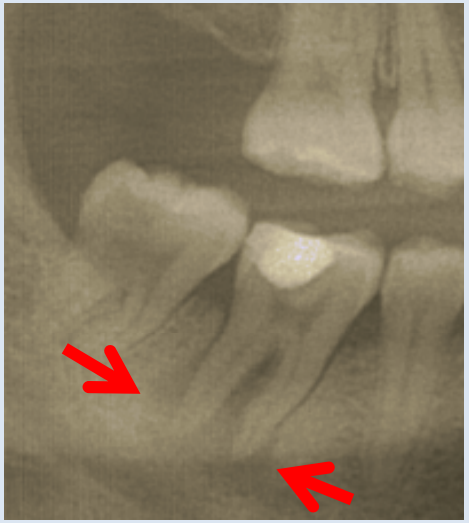

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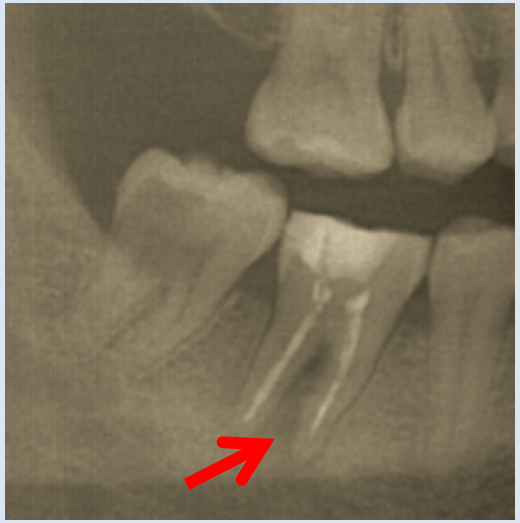
s/p pulpitis; Pus (+)
Root canal treatment



2015. 07. 16
#46: Apical lesion
s/p pulpitis; Pus (-)
Calcium hydroxide RCT

2016. 01. 26
#46: Apical lesion
s/p pulpitis; Pus (-)
New bone formation

Notice: Periodontal ligament (PDL) exists, Patient felt mild pain as paste delivery

Hint: For dentists, intra-bony molecular delivery is more than possible, or even familiar

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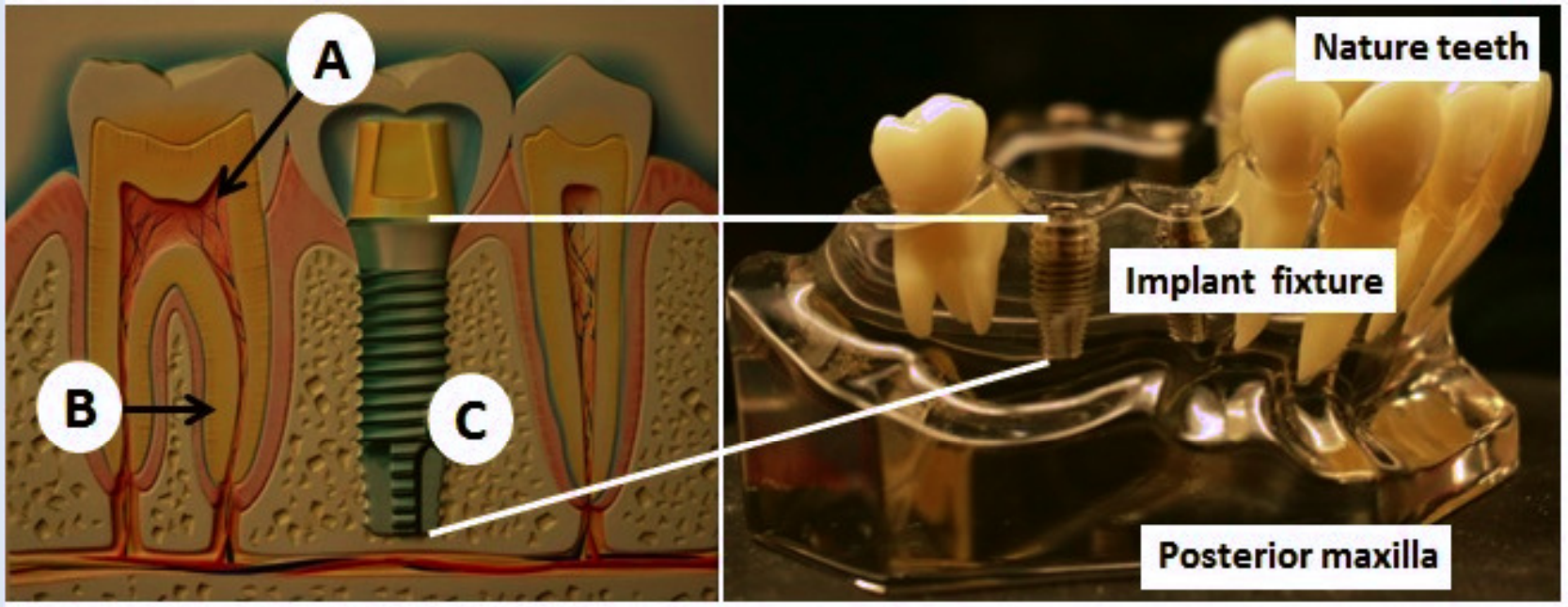
Dental implant & Pain origins



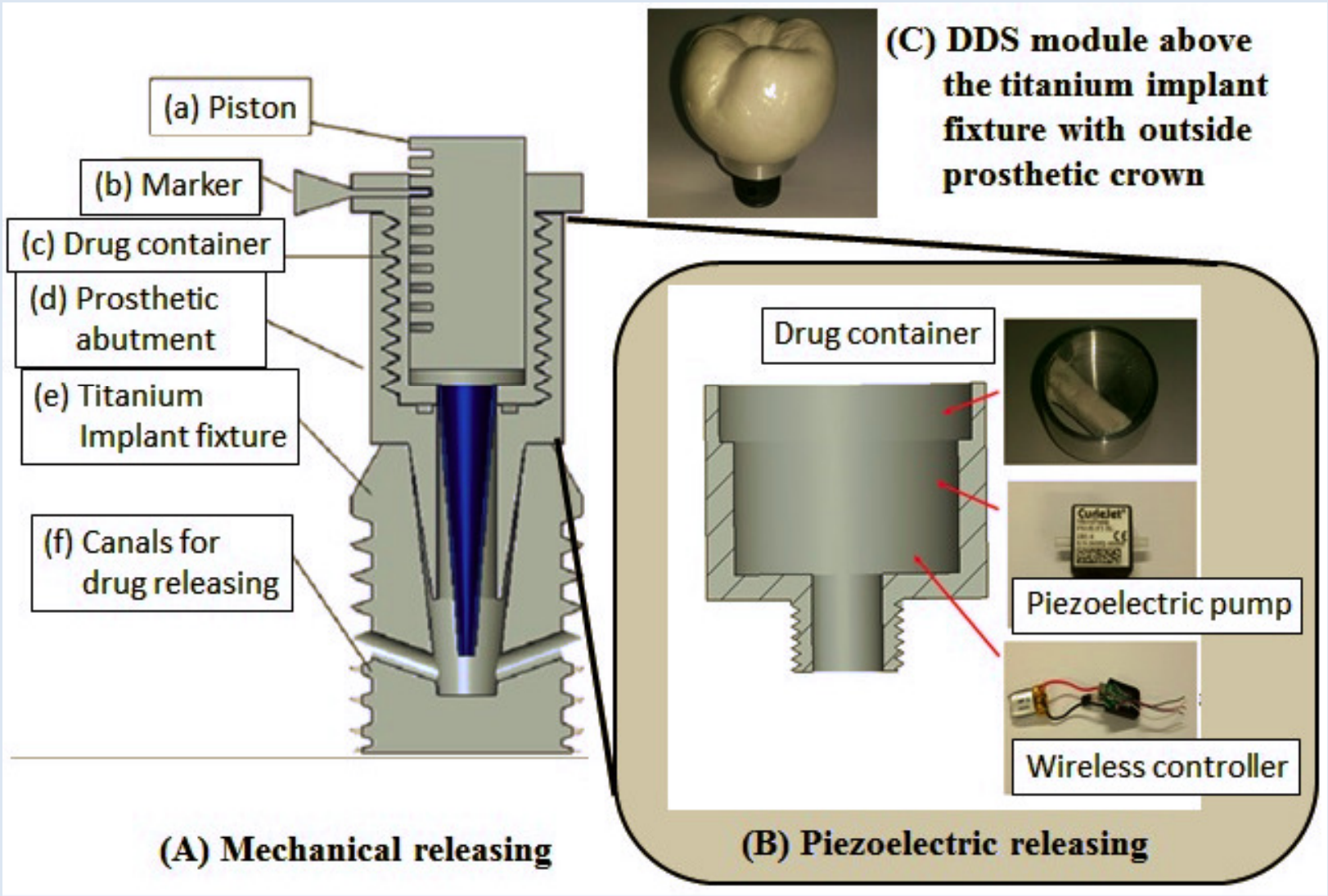
1. **Traditional pain origins: (A)** Pulp, **(B)** Periodontal ligament (PDL) ⟶ **(C)** Dental implant

2. **Bone quality:** { **Maxilla:** Type III + Type IV ⟶ Rich of **bone marrow** within **blood pool**
   Mandible: Type I + type II
   1. Cushion for injections 2. Avoid from thrombosis

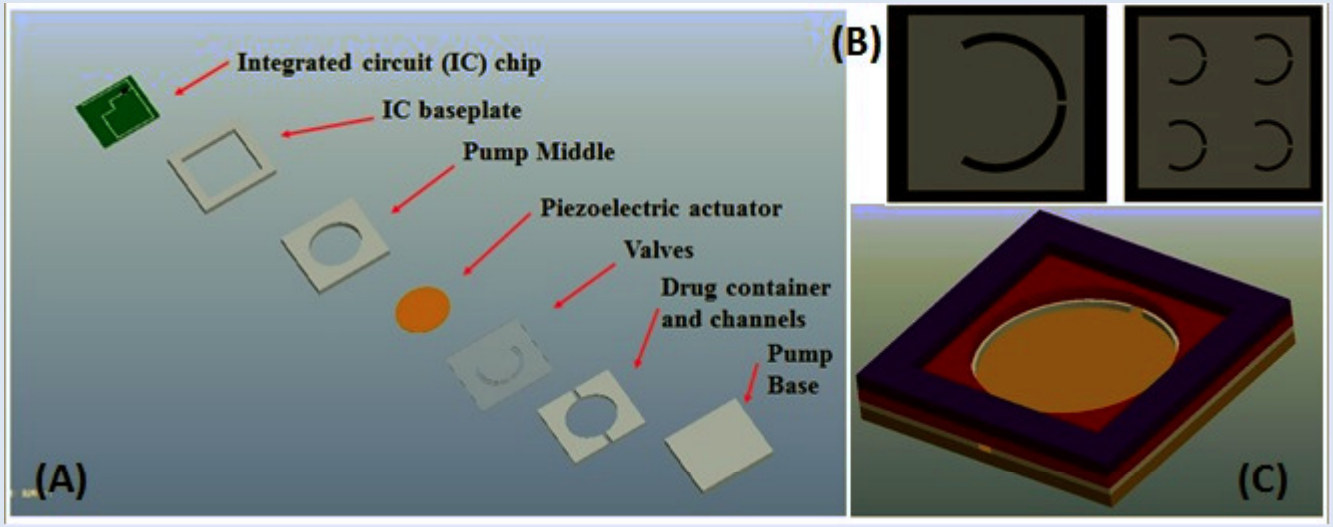
3. **Bicon® Implant system:** Absence of screw threads between:
   (A) prosthetic abutment (B) Implant fixture

4. **Implant supported (1)** Drug delivery module, and **(2)** Biosensor module

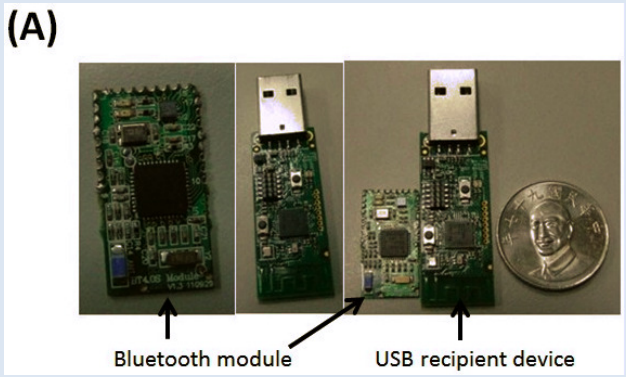
(1) Drug delivery module



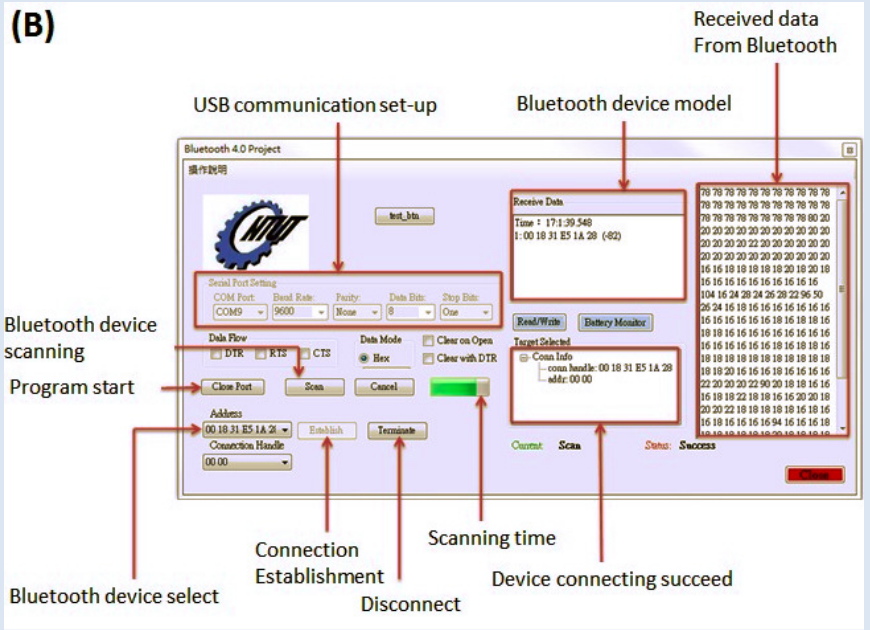
Piezoelectric micro-pump design & Bluetooth 4.0



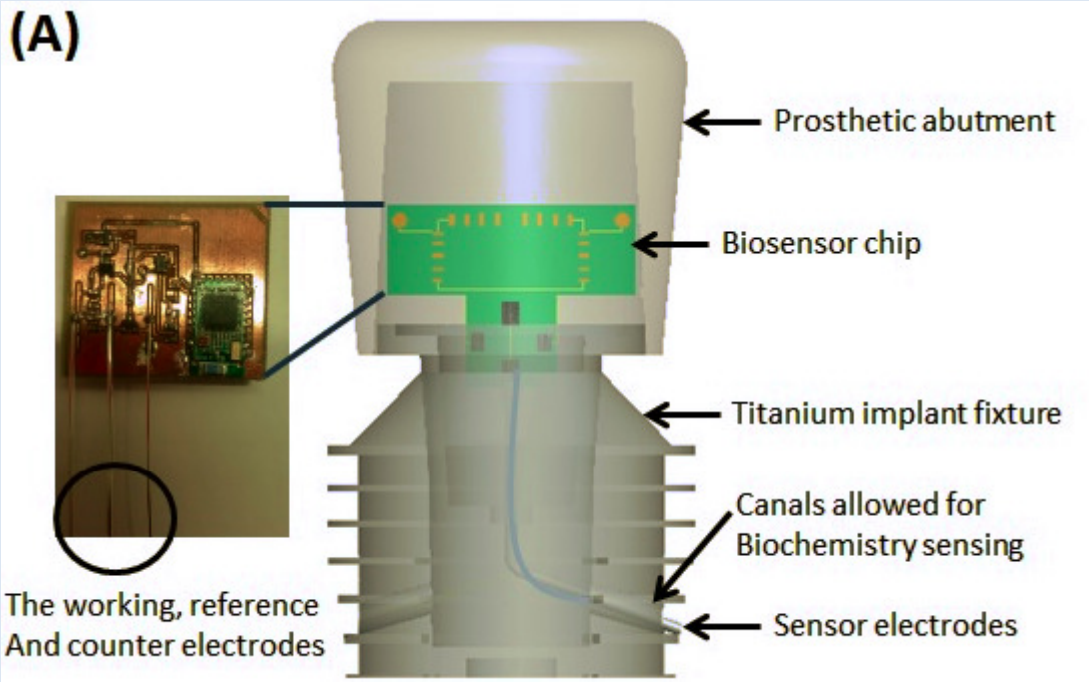
Structure of the piezoelectric pump including valves inside

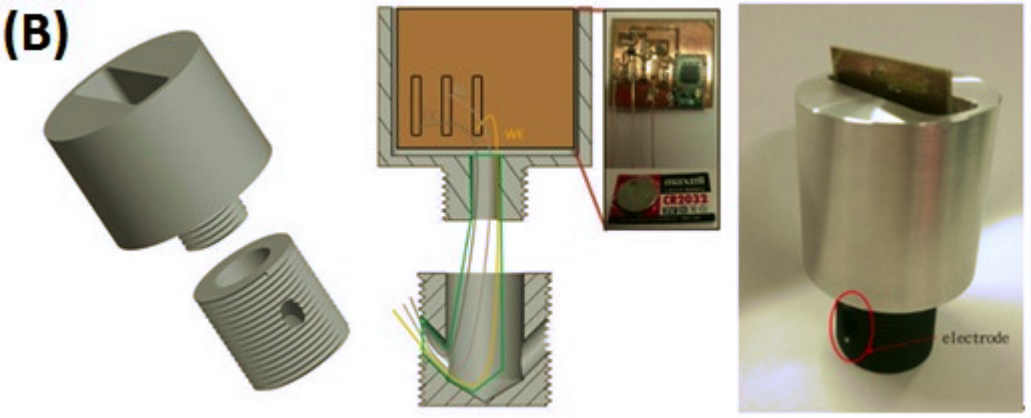


Bluetooth 4.0 module with Software interface by C++



(2) Biosensor module





Biosensor placed inside the Prosthetic abutment, including:

(1) Sensor IC
(2) Bluetooth module
(3) Power supply
(4) Extend electrodes

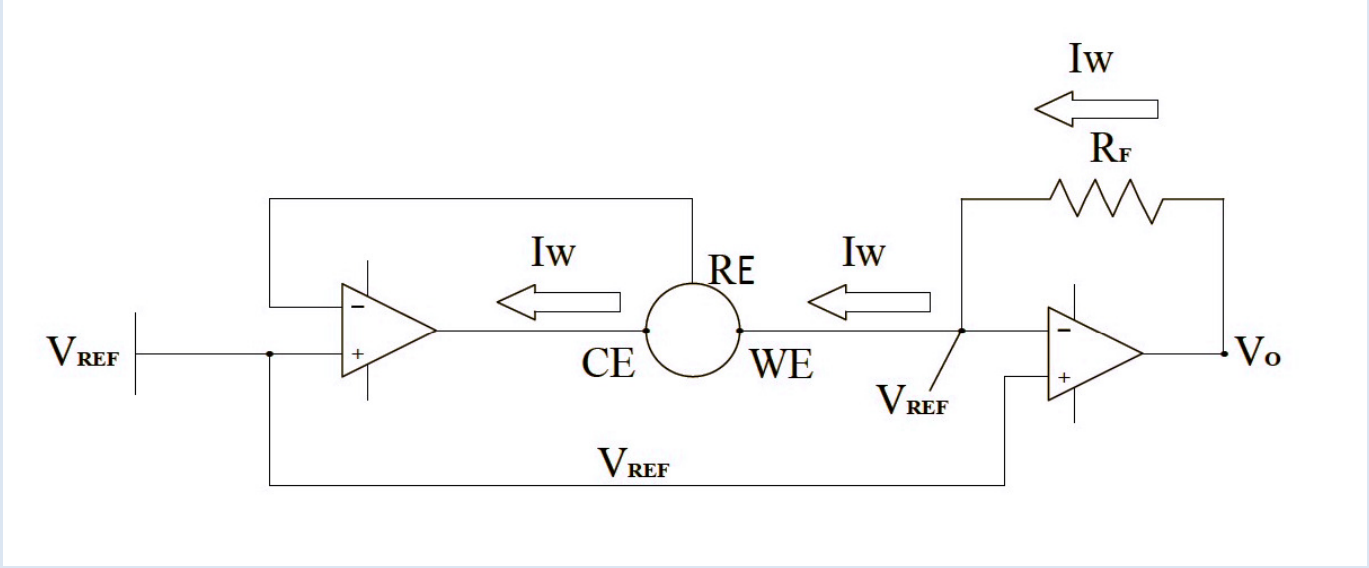
Then the set of the electrodes Extent outside the fixture by the canals, including:

(1) Working electrode
(2) Counter electrode
(3) Reference electrode

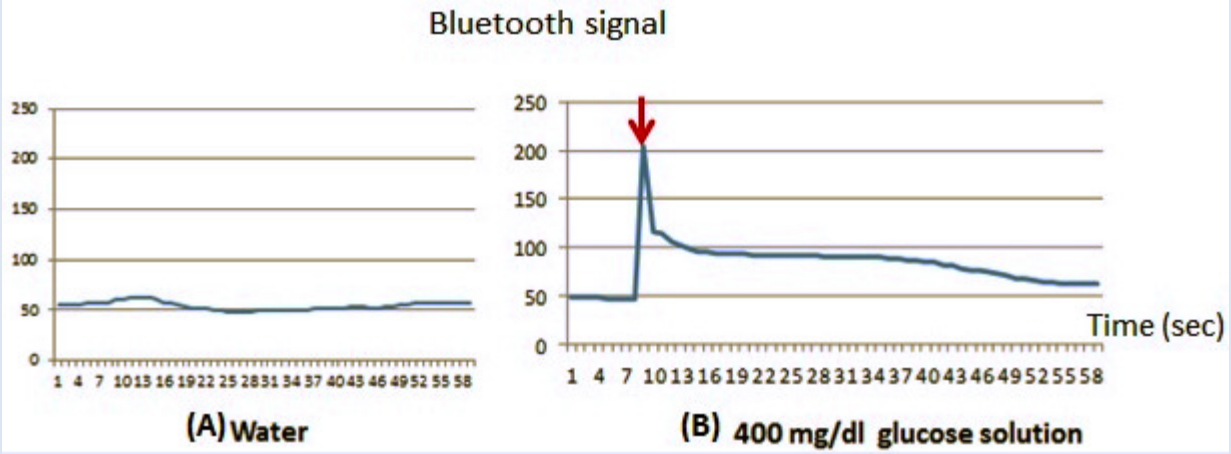
Glucose oxidase (GOD) coating & circuit design

$$\beta\text{-D-Glucose} + O_2 + H_2O \xrightarrow{\text{Glucose oxidase}} \text{D-Gluconic acid} + H_2O_2$$

GOD coated over working electrode for blood sugar sensing.



The current may change Corresponding to the Glucose concentrations.



The current changes are recorded By the bluetooth 4.0 module. And then they are transferred to outside portable device, such as computers or cell phones.

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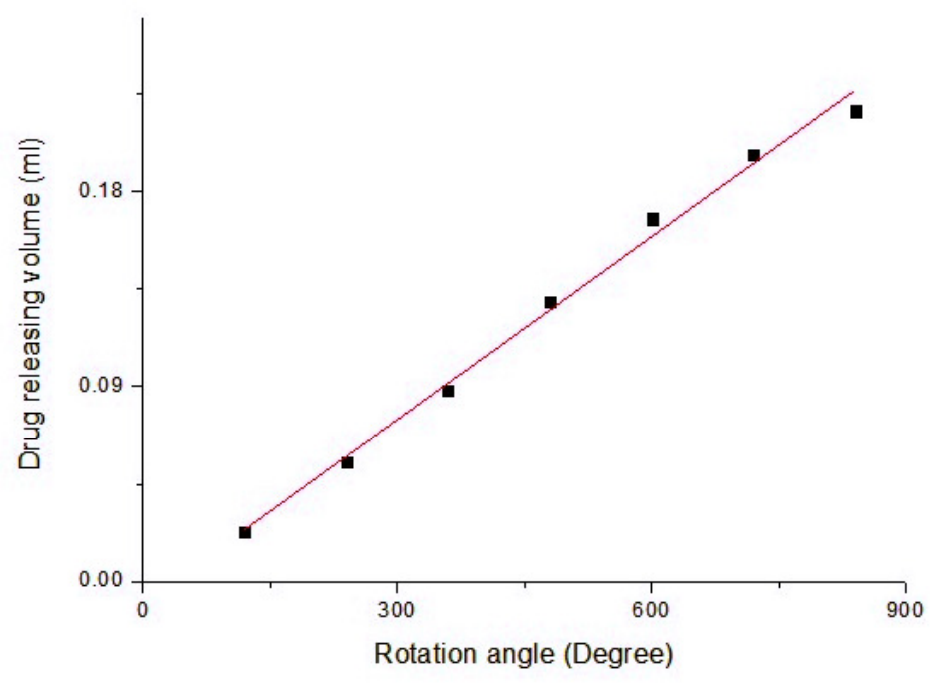
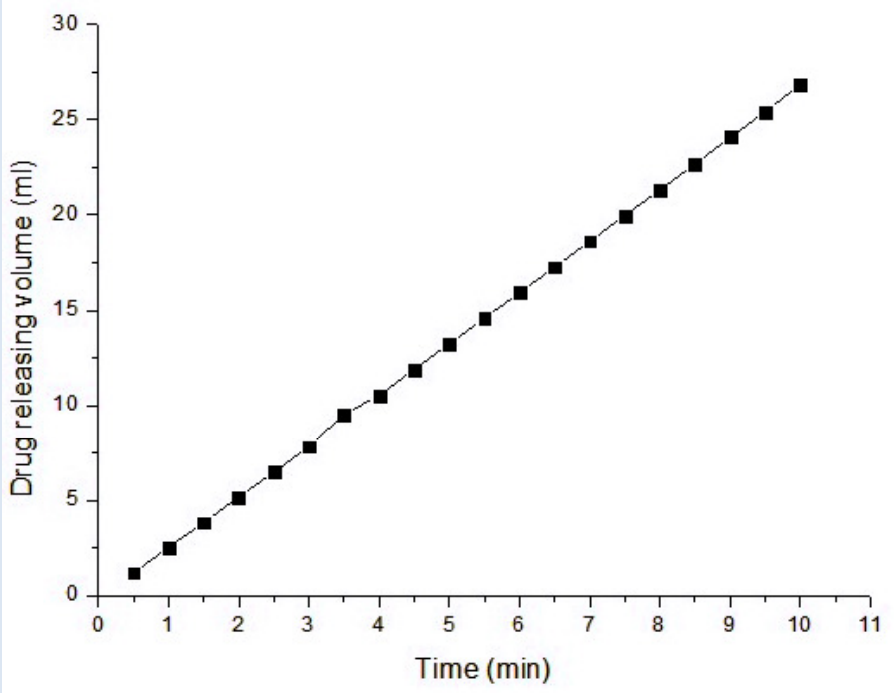
Preliminary result

Drug delivery exp.



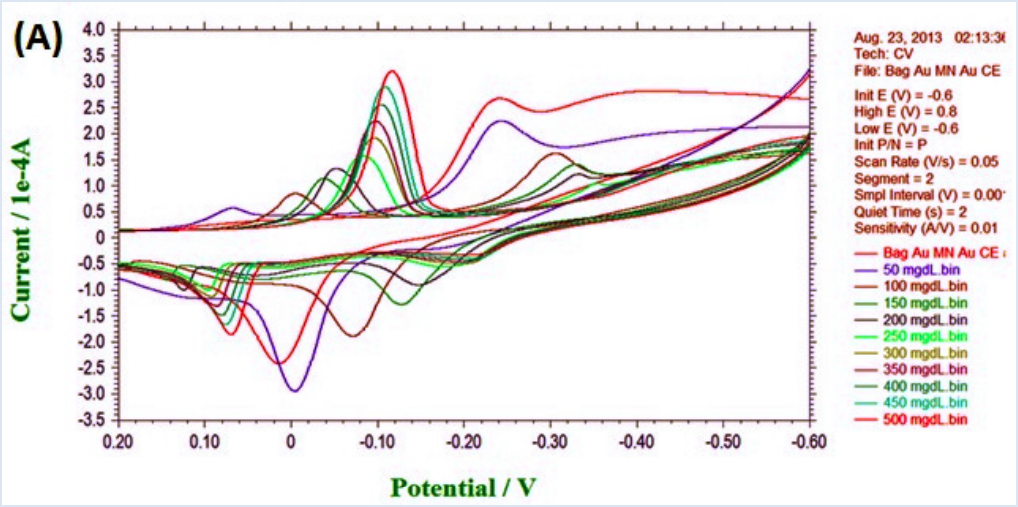
(A) Mechanical drug delivery module

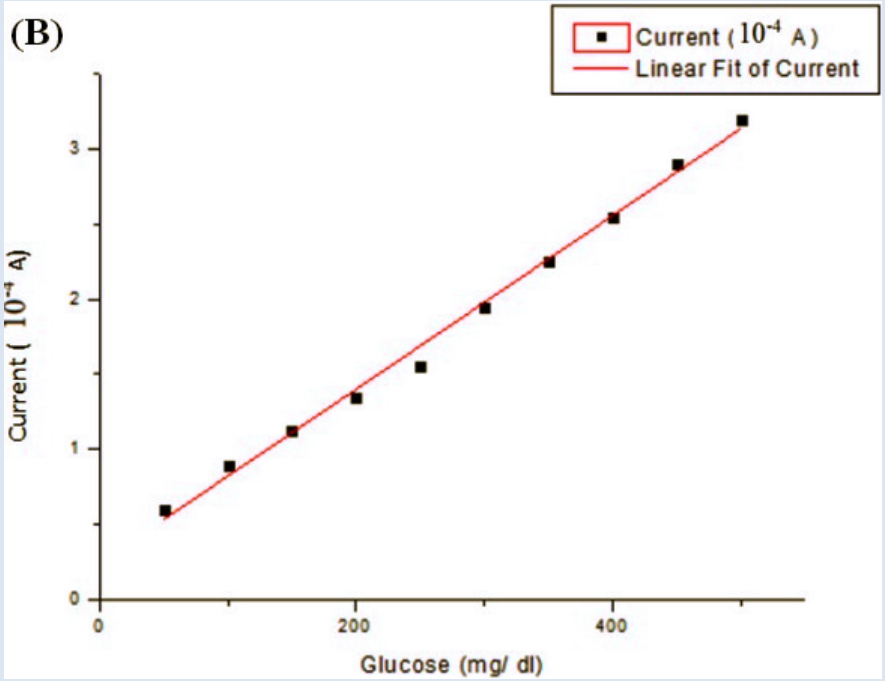


(B) Piezoelectric drug delivery module

Preliminary result

Bio-sensing exp.





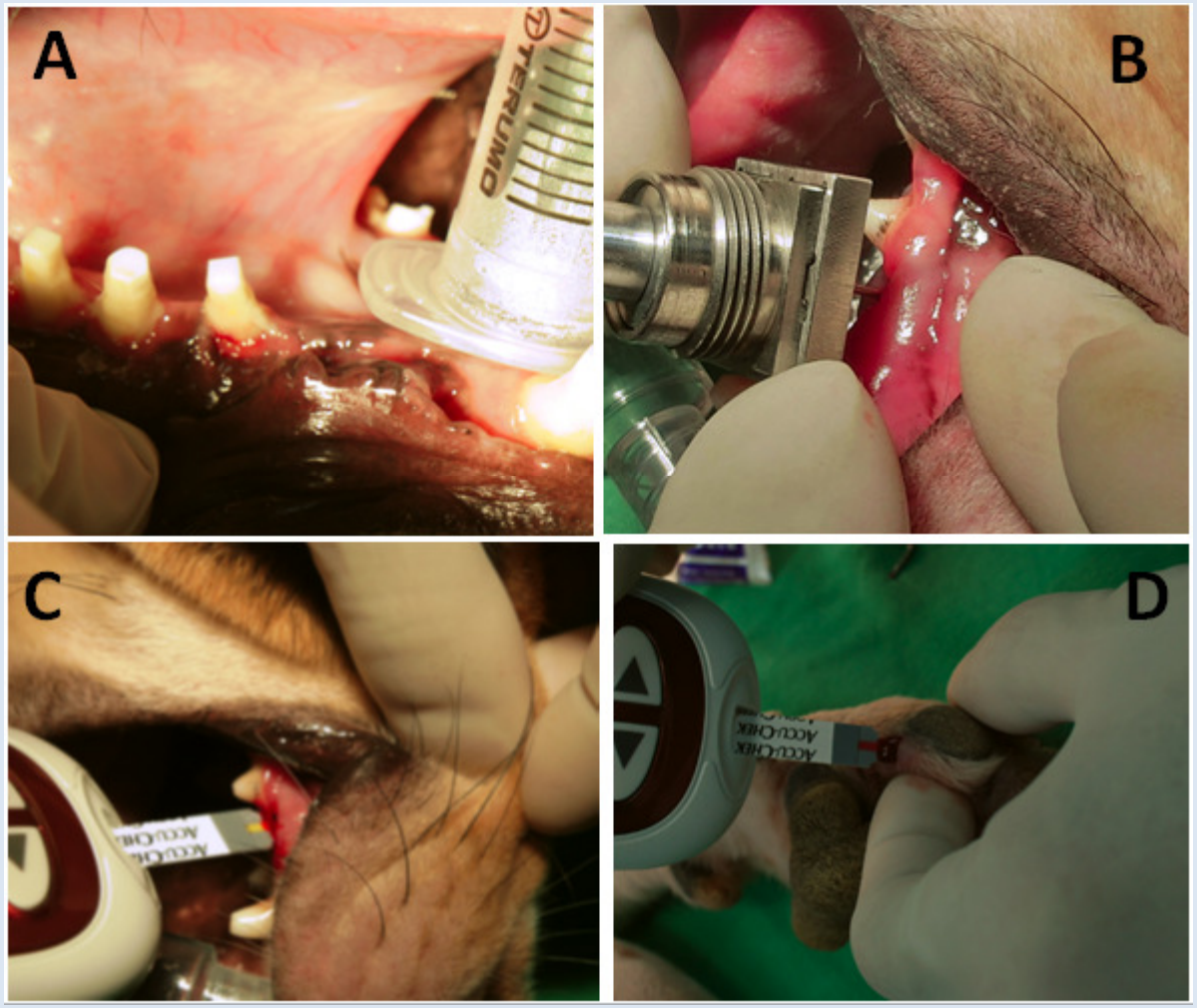
The cyclic voltammetry by different glucose concentration, sweeping From 0.2 to -0.6 V:

(A) From 50 mg/dL to 500 mg/dL.

(B) Peak value recorded and shows highly linearity, with **4 mg/dL** increasing will elevate **1 µA** of the current.

Preliminary result

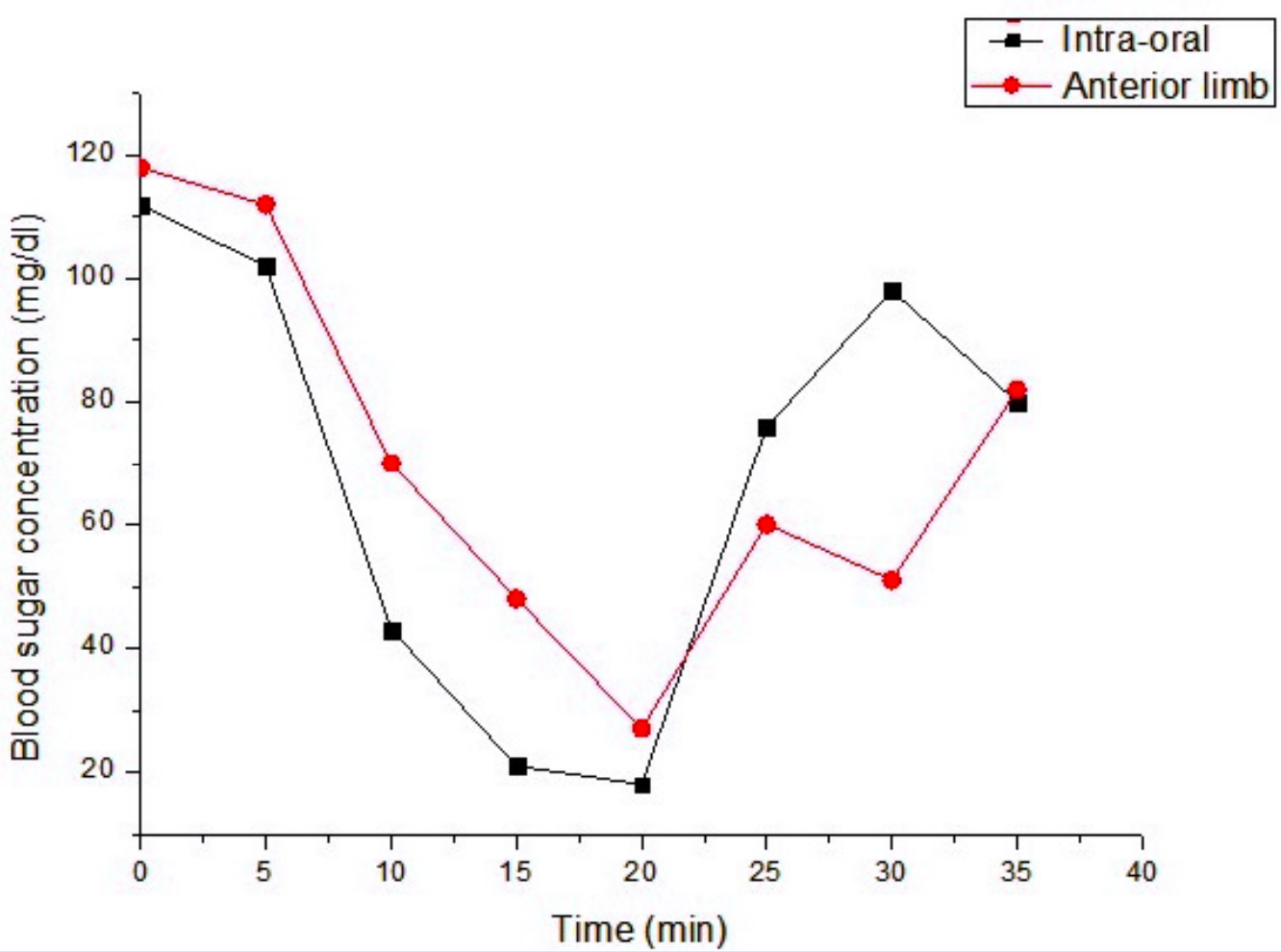
Preliminary canine study



Canine model: After 1 month of osseointegration, 2nd stage surgical exposure arranged to link the drug delivery and biosensing module. The blood sugar is monitored over intra-oral biosensor and lower limb calibration.

Preliminary result

Preliminary canine study



Initially 5 unit of the NPH (rapid onset insulin) is performed. Then the blood sugar is monitoring every 5 minute from both intra-oral biosensing module and anterior lower Limbs for calibrations. Blood sugar debonding at 25th minute may be due to glucagon Releasing.

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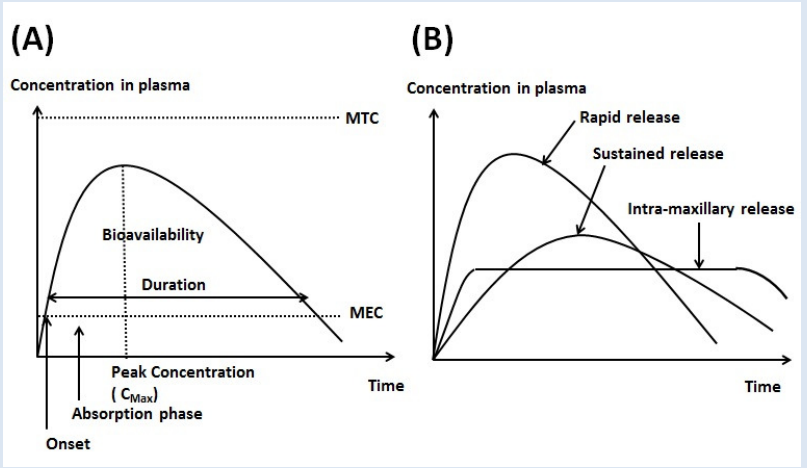
Discussions

- **Other invasive drug delivery device:**
  (1) Short-period (<2 wks): Central Venus Catheter (CVC)
  (2) Long-term: Port-A-Catheter, **dental implant supported DDS module**
- **Advantages of the implant supported DDS and biosensor module:**
  (1) Relative painless during drug delivery (vs CVP + Port-A)
  (2) Fixed by surrounding bone, avoid from component loosening, and internal bleeding (vs Port-A)
  (3) Non-invasive while drug reloading & module replaced (semi-implanted)
  (4) Lead to creative drug releasing and bio-sensing therapy: low volume and continuous (drug releasing + blood monitoring)
  (5) Free from thrombolism: Surrounding bone marrow structures
- **Diabetes Mellitus (DM):**
  As target disease due to frequently invasive therapy demanded.
  (1) Biosensor: **4 mg/dL** (+) lead to **1 μA** increasing
  (2) Drug releasing: **0.5 ml** contains **5000 units** insulin, meet **2 months** demands
- **Myocardiac infarction (MI):** **CK, CKMB** + **troponin I** continuous monitoring /5 min lasting for 1-2 months

Discussions

- **Restricts and constrains in implant supported DDS and biosensor module:**
  - (1) Drug delivery **type, volume,** and **speed** is restricted
  - (2) It is **limited** for patient with **frequently invasive procedure** demands
  - (3) **Dental** and **medical cooperation** is needed to ensure safety & efficiency
  - (4) **Frequently dental appointments** for device debridement & drug reload
- **Further improvement:**
  - (1) **Module size** & volume minimizing for practical applications
  - (2) **Enzyme polymerization** & improvement for long-term blood monitoring
  - (3) **Accuracy improvement** over IC design for further applications
  - (4) Safety concern: **drug polymerization** during releasing
  - (5) Pain evaluation experiments design



Special considerations

Engineering

(Blood sugar) (CK, CKMB)

1. **Accuracy in monitoring:** From **mg/dl** → **ng/dl**, about **10^{-6}** degree
2. **Component sealing:** Avoid infection status
3. **Size minimization:** CMOS + MEMS technology

Medical

Painless
Non-invasive

+

Continuous macromolecular delivery
Frequently blood monitoring

Geriatrics:

- **(1) Neurodegenerative disorders:** 1. Alzheimer's 2. Parkinson's disease
- **(2) Metabolic disorder:** Diabetes mellitus
- **(3) Cardiovascular disease:** Continuous CK + CKMB monitoring

Dental

Avoid from:

- **(1) Periodontitis:** Remove infective status
- **(2) Excessive occlusal loading:** Medical purpose
- **(3) Osseointegrative destructions:** Combined + selective releasing

Calcium hydroxide + iodoform

Acknowledgements

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Mucosa VS. Skin

Moist environment: Saliva flow contain → bacteria retain

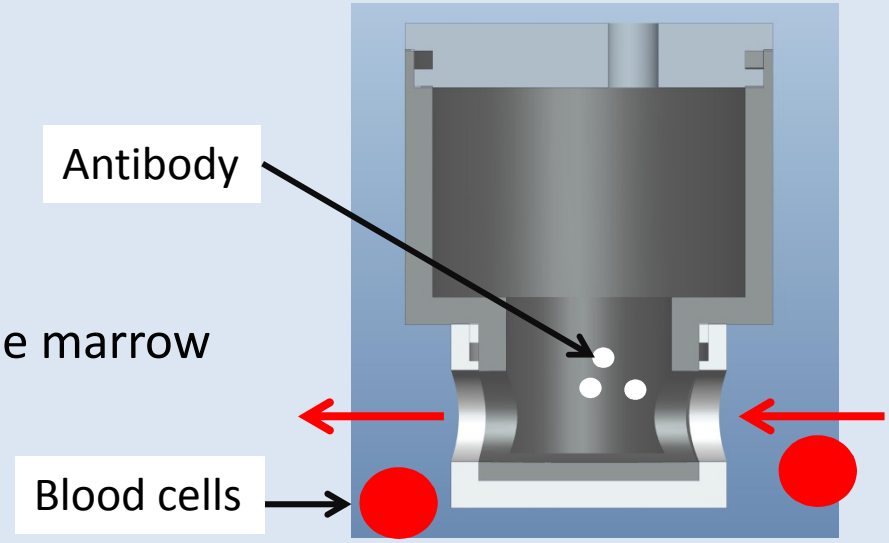
(Accumulation)

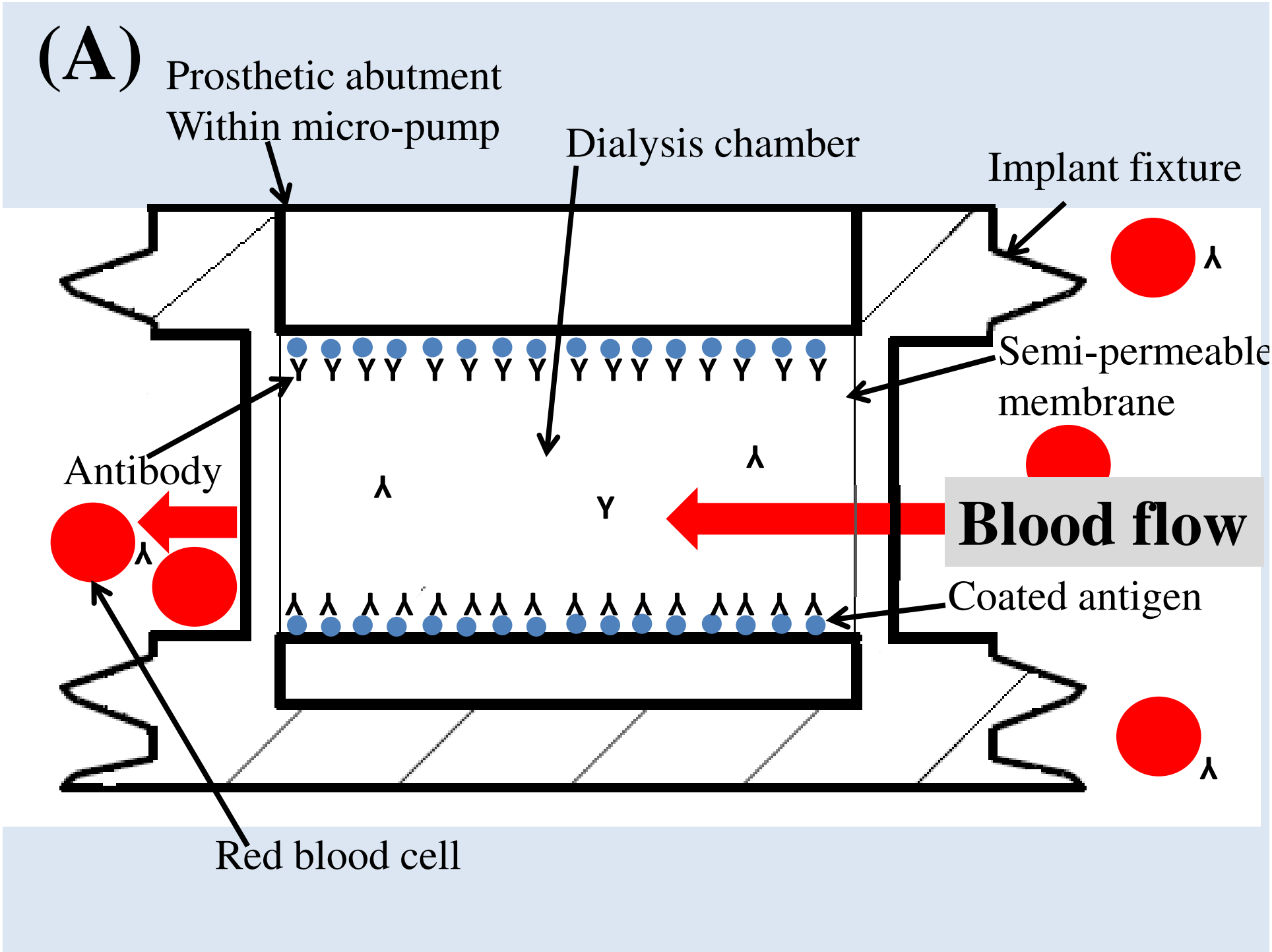
Saliva decrease (Radiotherapy origin, etc.) → Dental caries, periodontitis ↑

→ Provide possibility for long-term medical device placement (ex: dental implant)

Mucosal loaction: (1) Nasal, (2) Oral, (3) Anal, (4) Vaginal, (5) Urethra

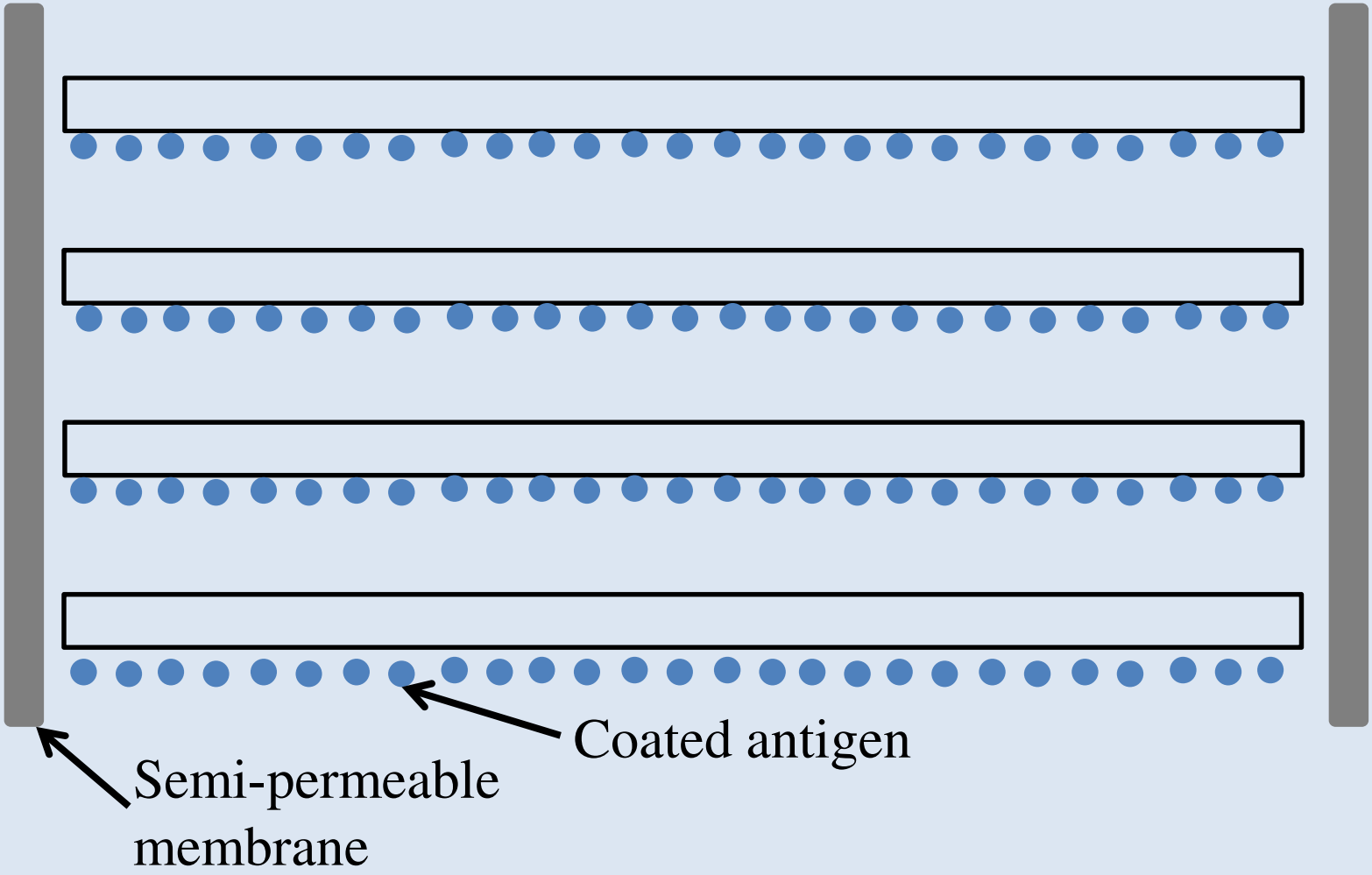
(1) Jaw bone supported
(2) The biggest cavity
(3) Well studied in Dental implant
(4) Thrombosis prevention inside bone marrow




(A)
Prosthetic abutment
Within micro-pump
Dialysis chamber
Implant fixture
Semi-permeable
membrane
Antibody
Blood flow
Coated antigen
Red blood cell

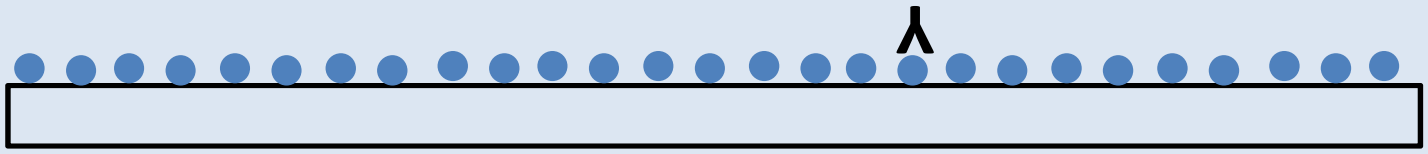
(B)

Dialysis chamber

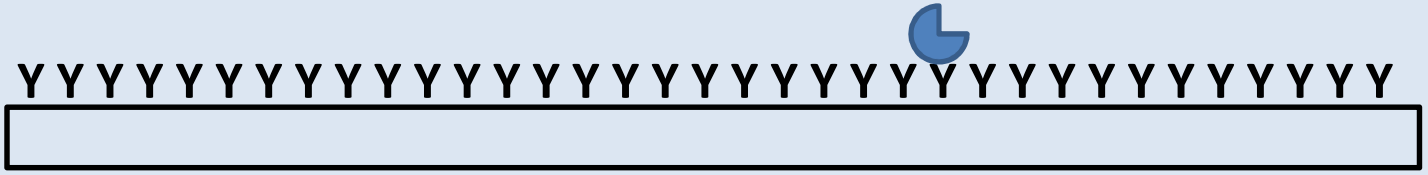


(C)

(1) Antibody trapping: **SLE**



(2) Molecular trapping: **Amyloidosis**



(3) Cellular trapping