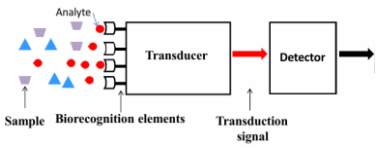
A. Biosensors

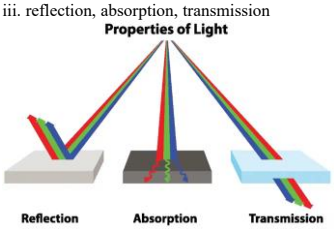
Sensor: a device that detects and responds to input (stimulus) from its physical environment.
Transducer: a more general device for converting energy from a given form into a different form



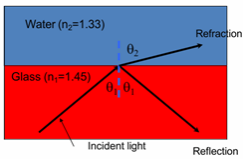
Two-component system
– Biorecognition (**bioreceptor**): facilitate specific binding to or biochemical reaction with a target
– **Transduc**tion: converts a biological binding event to a measurable transduction signal (fluorescent read out, amperometric, potentiometric)
Two-fundamental focus:
Specificity: the analyte being measured
Sensitivity: the quantity of the analyte
Sensitivity vs LOD (Limit of Detection) vs Selectivity
i. Sensitivity: Ability to discriminate between small differences in analyte concentration at a particular concentration; to respond reliably and measurably to changes in analyte concentration
Slope = sensitivity = dy/dx
ii. LOD: Minimum concentration that can be detected at a known confidence limit
LOD = 3s/m (s for standard deviation, m for slope)
iii. Selectivity: distinguish analyte from other species in the sample

B. Optical Biosensor

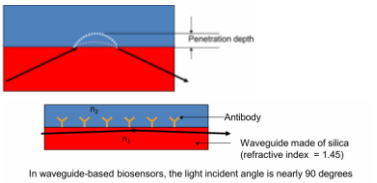
1. Sensing Interface
1) Components: Light source, Sensing interface (transducer), Optical detector
2) Properties of light:
i. travels as waves
speed: c = 3×10^{8}m/s **frequency = ν**
angular frequency = 2piν **wave length = λ = c/ν**
wave vector = k = 2pi/λ
ii. light travels in straight lines
iii. reflection, absorption, transmission



Red light: longer wavelength, higher penetration
iv. Engergy of photon **E = hν = hc/λ**
h = 6.63 x 10^{-34} Joule second
Total Engergy = Nhν Photon momentum = p = h/λ
3) Refractive Index
the speed of light = c/n (n: refractive index)
Wavelength = λ_0/n, λ_0 is the wavelength in vacuum
4) Total internal Reflection

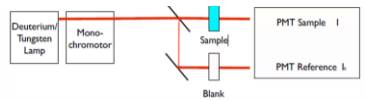


Snell's Law: $n_1 \sin(\theta_1) = n_2 \sin(\theta_2)$
Critical Angle $\theta_c = \sin^{-1}(n_2/n_1)$
Snell's law does not work when $\theta_i > \theta_c$
Substitute $\theta_2 = 90°$ to calculate the angle not enter 2
e.g: Fluorescence Microscopy, touch screen
5) **Evanescent Field (Many sensor based on)**

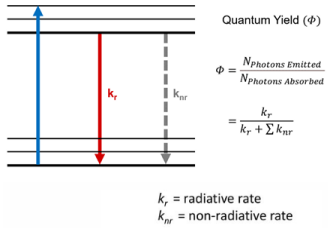


Penetration depth L_p (assuming incident angle = 90) = $\frac{\lambda_0}{4\pi\sqrt{n_1^2 \sin^2\theta_i - n_2^2}}$; λ_0 = wavelength in vacuum

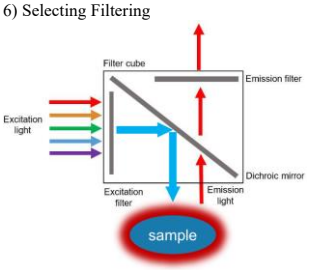
Many waveguide/optical fiber-based biosensors rely on evanescent field
2. Spectrometry
Beer-Lambert law: T=I/I$_0$=10^-αL=10^-εcL
α : absorption coefficient ; L: solution's path length(cm); ε : molar extinction coefficient; c: concentration(mol/L); I$_0$: original light intensity; I: light intensity after sample
Absorbance = A = -log10 (I/I$_0$) = αL = εcL
Sometimes, absorbance is expressed in "OD"
OD=1: 10 times attenuation (10% light passing through); OD=2: 100 times attenuation (1% light passing through); OD=: 1000 times attenuation (0.1% light passing through)
3. **Fluorescence** Spectroscopy
1) Fluorescence excitation: absorption of light
Ads: High contrast, fluorescence can be incited by specific biological or physical process.

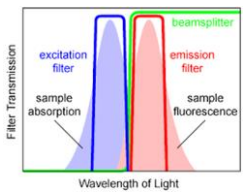


Fluorescence–ground state to singlet state&back.
Phosphorescence -ground state to triplet state&back
Both are radiative transitions, emission of photons from an electronically excited state
Energy of emitted radiation is less than that of absorbed radiation because a part of energy is lost due to vibrational or collisional processes. Hence the emitted radiation has longer wavelength (less energy). This peak distance is called ***stokes shift.***
2) Fluorescence lifetime (FLT): the time a fluorophore spends in the excited state before emitting a photon and returning to the ground state.
Radiative decay rate: k_r
Non-radiative decay rate: $k_{nr} = k_1 + k_2$
$d[S_1]/dt = -(k_r + k_{nr})[S_1]$
$[S_1] = [S_1]_{initial} \exp(-(k_r + k_{nr})t)$
3) **Quantum Yield: Φ= kr/(kr+knr) = krτs**
Where τs: the lifetime of S1 state. τs = 1/(kr+knr)

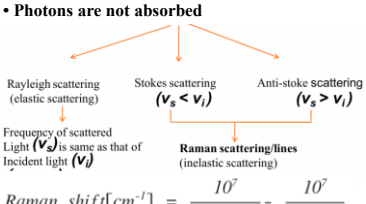


Brightness= ε x Φ, molar extinction coefficient (ε)
Factors affects: Internal inversion, quenching, intersystem crossing rate, temperature, solvent, pH, Energy Gap Law.
4) Applications: Environmental Monitoring, Medical Diagnostics, DNA Squenching, GeneticAnalysis
5) Fluorescence Emission Process: Excitation of a fluorophore through the absorption of light energy; A transient excited lifetime with some loss of energy; Return of the fluorophore to its ground state, accompanied by the emission of light.
6) Selecting Filtering



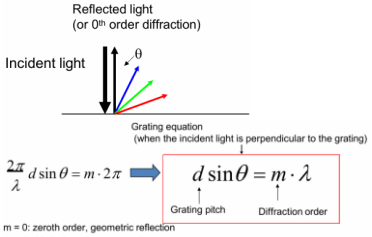


Excitation Filter Range: a little higher than the initial wavelength to the peak wavelength of excitation filter
Dichroic Mirror Wavelength: the peak wavelength of excitation to the peak of emission filter
Emission Filter Range: the peak of emission filter to the end of emission filter
Dichromatic mirror allows light of emission wavelength to pass through, while light of the excitation wavelength is reflected. So the line of it is low when the line of emission is high.
Ratio of covered area by detector= $a^2/4\pi r^2$
(the area of sphere's surface)
4. Raman Spectroscopy
Based on scattering of light; the sample is irradiated with a coherent source, typically a laser beam.
• Photons are not absorbed

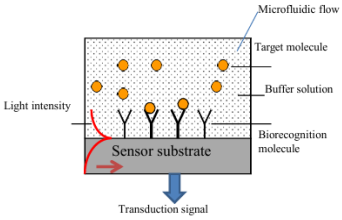


$Raman\ shift[cm^{-1}] = \frac{10^7}{\lambda_{ex}[nm]} - \frac{10^7}{\lambda[nm]}$

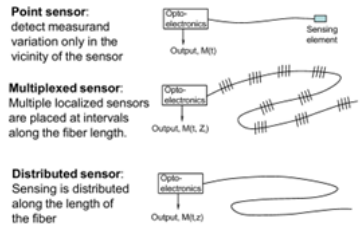
Scattering: intrinsic molecular effect which provides another way to study energy levels
Blue sky effects: Lower wavelength light has more scattering
Rayleigh scattering (elastic): Photon energy does not change; leaves the molecule in the same state
Raman scattering (inelastic): Stokes lines are those in which the photon has lost energy to the molecule, ν0−νt; Anti - Stokes lines are those in which the photon has gained energy from the molecule, ν0 +νt
Raman spectroscopy studies the frequency change of Light due to the interaction with matter
4. Optical Detector
1) Spectrometer, Monochromator, CCD, CMOS2)
Dispersion of Grating: difference in the angle of diffraction per unit change in wavelength



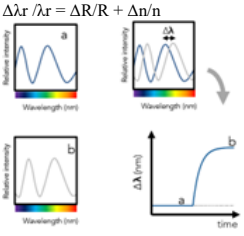
The smaller d, or the higher #groove density, the higher dispersion, higher spectral resolution
3) Resolving Power or Resolution of Grating
R = mN = λ/△λ
m = i: ith order diffraction pattern; △λ: smallest difference can be detected
5. Label Free Biosensors
Analyte has different RI than that of environment (such as water, buffer, air); RI change before and after a binding event at sensor surface.



1) Ads: No labeling involved; Direct sample measurement with minimal treatment or modification; No sample excitation; Low sample volumes needed; Potential rapid detection
2) Applications: Fiber and waveguide, Optical microcavity (Fabry - Perot cavity, ring resonator); Surface plasmon resonance (SPR) (metal film and nanoparticle); Interferometer; Photonic crystals
3) Fiber Optics Biosensor
Ads: Many choices commercially available; Inexpensive; Easy surface functionalization; Compatible with catheters or endoscopes for in vivo biosensing; Sensing and light delivery in one device; Compact size; Multi-functional; Remote accessible
Bottom Line for sensing: ***You have to have access to the evanescent field***



Point: detect only one
Multiplexed: detect different location
Distributed: detect the same thing, but provide loca
Resonance wavelength change due to changes in radius ΔR or refractive index Δn:
Δλr /λr = ΔR/R + Δn/n

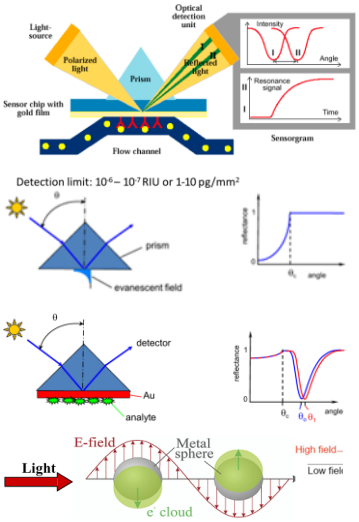


6. Resonator Biosensor
Longer interaction length → better detection limit
1) Disads: light passes the waveguide only once; Device size is large; large surface is needed, large sample quantity
2)Effective Length

$$L_{eff} = \frac{Q\lambda}{2\pi n}$$

λ: wavelength, n: resonator refractive index
Q: resonator quality factor (Q-factor)

Calculate Leff: λ = 1 μm, n=1.45, Q = 10^6 & Q = 10^8
λ-input wavelength; Pon-refractive index
3)Plasmon: The collective motion of electrons in metal relative to ion background is called"plasmon"
Surface Plasmon Resonance Sensing
•Fixed wavelength light, in a fan-shaped form, is directed at the sensor surface and binding events are detected as changes in the particular angle where SPR creates extinction of light.



LSPR is size and shape dependent
1. Selective photon absorption
2. Enhancement of EM field on the nanoparticle surface

LSPR is dependent on the dielectric properties of the material, as well as the dielectric properties of the local environment that surrounds the nanoparticles.

4) Sensitivity to RI Change
with known refractive index
Resonant wavelength:
$\lambda = 2\pi r n_{eff}/m$ Rev

C. Biomedical Imaging Technologies

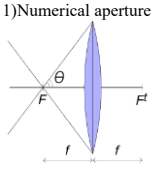
1. Applications
Magnetic Resonance Imaging, Computerised Tomography (High Resolution), X-Ray (Mostly common), Mammography, Position Emission Tomography, Ultrasound Imaging, optical imageing (No radiation, high sensitivity).
2. Photon interaction with biological tissue: Scatterd and reflected, and abosorbed, and transimitted
Extinction coefficient : $\mu_t = \mu_a + \mu_s$ (Total interaction coefficient)
The reciprocal of μ_t is the mean free path between interaction events
Scattering cross section: σ_s
Number of density: N
Scattering coefficient: total cross-sectional area for scattering per unit volume: $\mu_s = N_s\sigma_s$
3. Oxygen Saturation and Concentration
Ads of Infrared: Non-invasive, non-radiaoactive, real-time functional imaging, portable, low cost
Estimating concentration by absorption coefficients:

$$\mu_a(\lambda_1) = \ln(10)\varepsilon_{ox}(\lambda_1)C_{ox} + \ln(10)\varepsilon_{de}(\lambda_1)C_{de},$$
$$\mu_a(\lambda_2) = \ln(10)\varepsilon_{ox}(\lambda_2)C_{ox} + \ln(10)\varepsilon_{de}(\lambda_2)C_{de}.$$

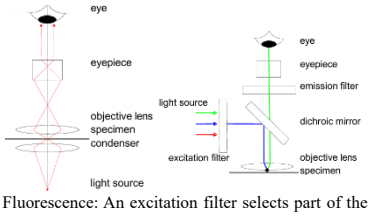
$\lambda 1$, $\lambda 2$: wavelengths; εox, εde: Molar extinction coefficients of oxy- and deoxyhemoglobin; Cox, Cde: Molar concentrations

$$SO_2 = \frac{C_{ox}}{C_{ox} + C_{de}},$$
$$C_{Hb} = C_{ox} + C_{de}.$$

Oxygenated hemoglobin absorbs more infrared light and allows more red light (660 nm) to pass through; Deoxygenated hemoglobin allows more infrared light (940nm) to pass through and absorbs more red light
4. Optical Biospy (not to take tissue put to see)
1)Numerical aperture



The numerical aperture quantifies the capability of a lens to gather light: NA = n sinθ
n is the refractive index of the medium between the objective lens and the specimen
θ is the half angle of the maximum light cone which the lens can collect.
2) Bright Field and Fluorescence Microscopy



Fluorescence: An excitation filter selects part of the electromagnetic spectrum for exciting the fluorescent materials in the specimen; Another filter is then utilized to separate the emitted light from that used for the excitation

G. Response Robertic First Responder

Due to Diffraction:
Image of a point source is not infinitely small (even at best focus).

- It is a pattern called **Airy pattern**.
- It is composed of a central spot, known as **Airy disk**, surrounded by multiple diffraction rings.
- The radius of Airy disk is:

$$d_{Airy} = 0.61\frac{\lambda}{NA}$$

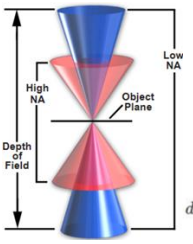
λ is the wavelenath of incident liaht.

dmin = dAiry

How to increase resolution?

- Increase numerical aperture.
  - NA = $n \sin\Theta$ is upper-limited by 1 in air.
  - Use **oil-immersion** objectives $n_{oil} \approx 1.51$.
- Use shorter wavelengths.

Axial Resolution-Depth of focus



$$d_{tot} = \frac{\lambda \cdot n}{NA^2} + \frac{n}{M \cdot NA}e$$

dtot: depth of field; λ: wavelength of illuminating light; NA: objective numerical aperture; M: lateral magnification

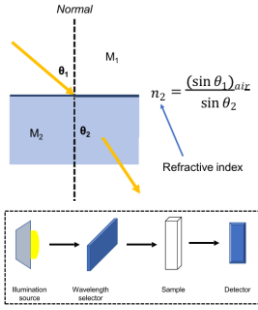
4) Photoacoustic Imaging (PAI)

Combine optical (high resolution) and ultrasound (great imaging depth) advantages. Noninvasive / No X-ray exposure.

5. Hyperspectral Imaging

Spectroscopy: Shine light to the matter, light can be reflected, absorbed, and scattered.

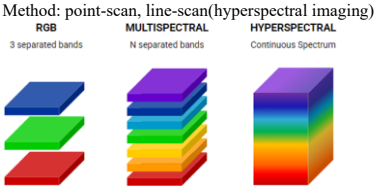
When an incidental beam passes through a medium which differ in refractive index (RI). If the medium has higher refractive index, the fraction of reflected radiation will be higher.



$$n_2 = \frac{(\sin\theta_1)_{air}}{\sin\theta_2}$$

Spectrometer measures reflectance, absorbance, etc.

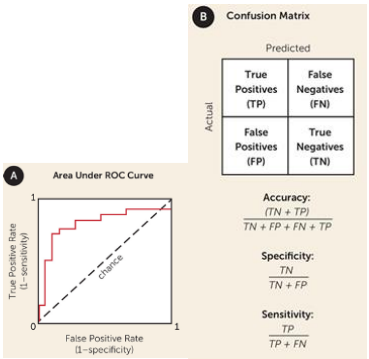
Method: point-scan, line-scan(hyperspectral imaging)



Applications: remote sensing. Imaging skin cancer and border decisions, virus screening

6. Imaging Analysis

Image processing covers four main areas: Image formation, Visualization, Analysis of image, Management of the acquired information



7. Microfluidic Optical Biochips

Biochip: a miniaturized laboratory capable of performing thousands of simultaneous biochemical reactions.

1)Technologies: Sensing chemistry, Microarray or Microfluidics, Reader and Signal processing

2)ads: sample saving, faster analysis, integration

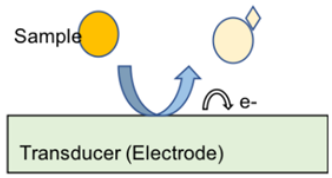
D. Smart Systems

Nano robot: The technology of creating machines or robots are close to the microscopic scale of a nanometer (10^−9 meters).

E. Electrical Biosensor

Challenges: high sensitivity, selectivity, low power

1. Electrochemical Sensor



1)Types:

Potentiometric, Amperometric, Conductometric

2) Nernst Equation

The potential of a potentiometric electrochemical cell

$$E_{cell\ potential} = E_{cathode} - E_{anode} = E_{reduction} - E_{oxidation}$$

$$E = E^\circ - \frac{RT}{nF}\ln Q \qquad E = E^\circ - \frac{0.05916}{n}\log Q$$

Q: reaction quotient; n: the number of electrons exchanged in the half-cell reaction.; E° for each cell: standard hydrogen electrode (S.H.E.), strongest oxidizing agents higher; strongest reducing agents lower .

2. Amperometric biosensors

Amperes x time = Coulombs

1 Faraday = 1 mole of electrons = 96,500 coulombs

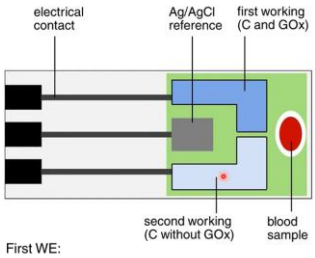
1 mole= 6x10^23

These sensors with fixed voltage

1) Glucose biosensor

$$\text{glucose} \xrightarrow{\text{GOx}} \text{gluconic acid} + H_2O_2$$

$$H_2O_2 \xrightarrow{+600\ mV} 2H^+ + O_2 + 2e^-$$



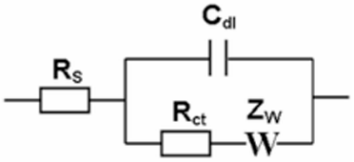
First WE:
Current from H_2O_2 (from glucose) and something else

Second WE:
Current from something else

H_2O_2 (glucose) current
= First WE − Second WE

3. Randle Circuits

a Randles circuit is an equivalent electrical circuit that consists of an active electrolyte resistance RS in series with the parallel combination of the double-layer capacitance Cdl and an impedance (Zw) of a faradaic reaction.



4. Bioelectricity

1)Passive: To measurethe electric signals produced by the activity of living tissues

Electroencephalography(EEG, brain); Electrocardiography (ECG, heart); electromyography (EMG, muscle)

2)Active: To study the effect of electric fields due to an external device on tissue

Deep brain stimulation (DBS); Functional stimulation (FES); Cardiac defibrillation (CDF)

e ≅1.602 × 10^-19 C

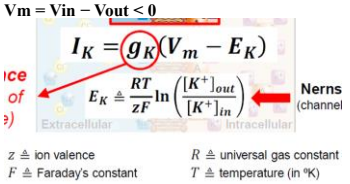
1 C= e/ 1.602 × 10^-19 ≅ 6.241× 10^18e

1 A = 1 C/s 1 V = 1J/ 1C

3) Biopotentials

Features: Threshold, All-or-none response, Intensity

Vm = Vin − Vout < 0



$z \triangleq$ ion valence $R \triangleq$ universal gas constant

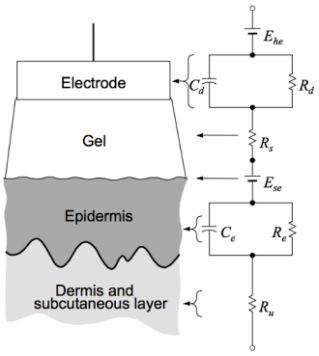
$F \triangleq$ Faraday's constant $T \triangleq$ temperature (in °K)

4) Five phases of Action Potential

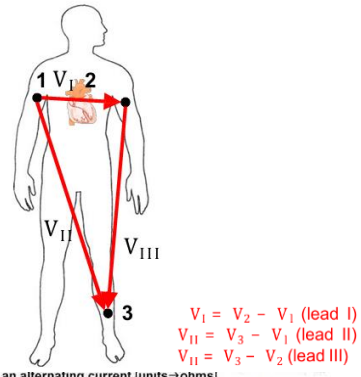
Below Threshold- Resting potential; Depolarization; Action potential; Repolarization; Hyperpolarization

5. Bioelectric Measurement

To measure EMG: First, place two electrodes on the skin surface, e.g., one of them away from the muscle to be measured; Second, measure the difference between the potentials at the electrodes: Vd = Vl − V2; Third, we have an electronic circuit (amplifier) inside the acquisition system that amplifies Vd



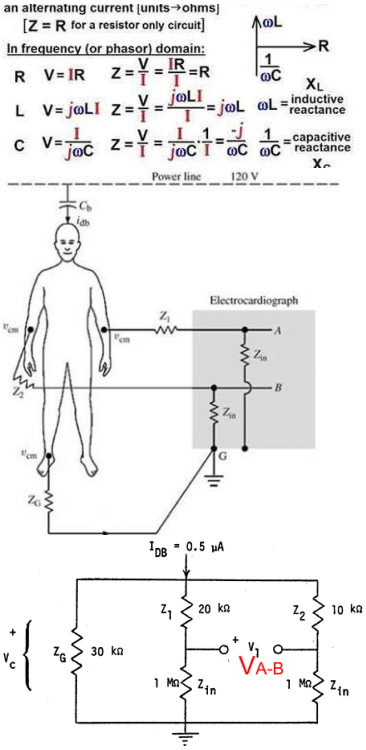
To measure ECG:



an alternating current [units→ohms]
[Z = R for a resistor only circuit]

In frequency (or phasor) domain:

R	$V = IR$	$Z = \frac{V}{I} = \frac{IR}{I} = R$		
L	$V = j\omega LI$	$Z = \frac{V}{I} = \frac{j\omega LI}{I} = j\omega L$	ωL	inductive reactance X_L
C	$V = \frac{I}{j\omega C}$	$Z = \frac{V}{I} = \frac{I}{j\omega C}\frac{1}{I} = \frac{-j}{\omega C}$	$\frac{1}{\omega C}$	capacitive reactance X_C



x dB = 20lgx

Bode: y aixs for dB; x aixs for frequency

6. Bio Amplifiers

Requirements: Biopotential amplifiers should have high input impedance i.e., greater than 10 MΩ; Output impedance of the amplifier should be low to drive any external load with minimal distortion; Gain of the amplifier is greater than x1000 as biopotentials are typically less than a millivolt; Safety: the amplifier should protect the organism being studied

Monitor power: Bluetooth's average energy is low but the peak power can be very high. Units can be damaged be current drop.

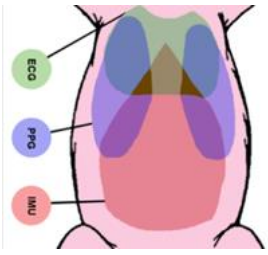
PPG: SPO_2, heart contraction; capture potential signal, mechanical movement can cause noise, but the frequency is much lower than respiration so it will not generate electrical signal. Critical freq = 60

IMU: respiratory rate

ECG: pulse propagation, sensitive to movement

The **minimum distance between two ECG** electrodes should be more than 50mm: electrodes get electrical signal potential, hence if we wanta high enough big difference, we need big distance to allow signal go through enough distance so that there is a potential decay for ECG to capture.

Best location to place implant: implantation is under skin, we want somewhere that will not make objective pain, also we want the place where signals are detectable (ECG is usually 45°).



Redundancy Reason: none of the sensors can guarantee. Sensitive to noise (ambient lighting noise/ body movement)

Duty cycle: D = PW/T × 100%

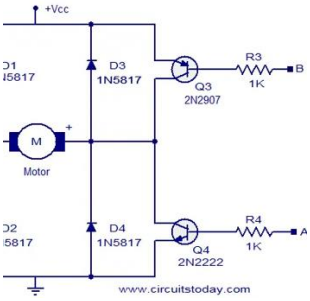
PW: Pulse width; T: Total duty cycle period

Sleep/on: waking up the device can cost extra energy; it takes time to warm up to get reliable result since turning on needs to overcome inertia

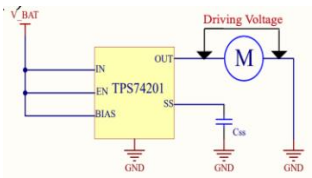
With increasing frequency the Battery Life Time drops much faster than of continuous mode: Turning on has a higher power surge. So when the frequency is very high, doing nothing but waking up consumes energy. Waking up dominates the consumption

Drug Delivery: 1 revolution = 2 linear actuation

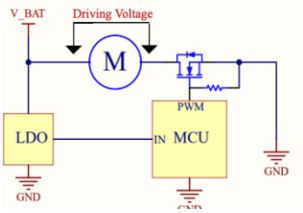
Mirror the figure:



Analog soft starter



Digital soft starter



DAC-based soft starter