

Bioelectronics

Timo Streule, 13.07.2019
tstreule@student.ethz.ch

General

Formeln

$$\text{Circle: } U_{\text{circle}} = 2\pi r, A_{\text{circle}} = \pi r^2$$

Constants:

$$h = 6.626 \times 10^{-34} \text{ Js} = 4.135 \times 10^{-15} \text{ eV s}, \quad \hbar = \frac{h}{2\pi}, \quad hc = 1.986 \times 10^{-25} \text{ J m}$$

$$\epsilon_0 = 8.85 \times 10^{-12} \text{ As/Vm}$$

$$\mu_0 = 4\pi \times 10^{-7} \text{ N/A}^2$$

$$k_B = 1.38 \times 10^{-23} \text{ J/K} = 8.617 \times 10^{-5} \text{ eV/K}$$

$$q = 1.602 \times 10^{-19} \text{ C}, \quad m_e = 9.109 \times 10^{-31} \text{ kg}, \quad m_p = 1.672 \times 10^{-27} \text{ kg}$$

$$F = 96485 \text{ C/mol} \text{ (Faraday)}, \quad R = N_A k_B = 8.314 \text{ J/mol K} \text{ (Ideal gas constant)}$$

$$N_A = 6.022 \times 10^{23} \text{ particles/mol}$$

$$0^\circ\text{C} = 273.15 \text{ K}$$

Einheiten

Druck

$$1 \text{ Pa} = 1 \text{ N/m}^2 = 1 \text{ J/m}^3 = 10 \text{ g/cm}\cdot\text{s}^2$$

Induktivität

$$1 \text{ H} = 1 \text{ Vs/A} = 1 \Omega \text{ s}$$

Power

$$1 \text{ W} = 1 \text{ J/s} = 1 \text{ VA}$$

electron volt

$$1 \text{ eV} = 1.602 \times 10^{-19} \text{ J} = 23.06 \text{ kcal/mol}$$

Charge

$$1 \text{ C} = 1 \text{ As}$$

Energy

$$1 \text{ J} = 1 \text{ kg m}^2/\text{s}^2 = 1 \text{ Nm} = 1 \text{ VAs} = 1 \text{ CV} = 1 \text{ Ws}$$

Good to know

Power in dB

$$10 \log_{10} \frac{I}{I_0}$$

Intensity

$$I = \frac{\text{avg. Power (P)}}{\text{area (A)}} \left[\frac{\text{W}}{\text{m}^2} \right]$$

avg. Power

$$P = \frac{\text{avg. Work in cycle (\overline{W})}}{\text{cycle (T)}} \left[\text{W} = \frac{\text{kg m}^2}{\text{s}^3} \right]$$

(avg.) Work

$$\overline{W} = \int_{\text{cycle}} \frac{1}{\text{cycle}} \cdot \vec{F} \cdot \vec{x} \, dt \quad [\text{J} = \text{Ws}]$$

mass m vibrates with an amplitude a along x -axis:

$$\vec{x}(t) = a \sin(\omega t) \cdot \vec{e}_x, \quad \omega = 2\pi f = 2\pi/T, \quad \vec{F}(t) = m \ddot{x}(t)$$

NuS

Induktivität

$$u(t) = L \frac{di_L}{dt} \quad \bullet \quad U(s) = sL I_L(s)$$

Konduktivität

$$i(t) = C \frac{du_C}{dt} \quad \bullet \quad U(s) = \frac{1}{sC} U_C(s)$$

Transformator

$$u_1 = L_1 \frac{di_1}{dt} - M \frac{di_2}{dt}, \quad M: \text{mutual inductance}$$

LCR-Schwingkreis

$$\omega_0 = 2\pi f_0 = 1/\sqrt{LC}$$

Laplace

$$\lambda u(t) + \mu v(t) \quad \bullet \quad \lambda U(s) + \mu V(s)$$

$$u(at), a > 0 \quad \bullet \quad \frac{1}{a} U\left(\frac{s}{a}\right)$$

$$u(t-t_0) \quad \bullet \quad e^{-st_0} U(s)$$

$$e^{-at} u(t) \quad \bullet \quad U(s+a)$$

$$(-t)^n u(t) \quad \bullet \quad U^{(n)}(s)$$

$$u^{(n)}(t) \quad \bullet \quad s^n U(s) - \dots - u^{(n-1)}(0)$$

$$t^n \quad \bullet \quad \frac{n!}{s^{n+1}}$$

$$e^{-at} \quad \bullet \quad \frac{1}{s+a}$$

$$te^{-at} \quad \bullet \quad \frac{1}{(s+a)^2}$$

1 Biosensors

1.1 Label assay vs. label-free

Label assay (sandwich):

non-specific binding:

Label-free assay (OWLS):

other interactions that could happen, except the angle binding.

1.2 Rules of Chemistry and Physics

Bracket notation

indicates concentration $A + B \xrightleftharpoons[k_{-1}]{k_1} AR$

equilibrium constant

$$K = \frac{k_{-1}}{k_1} = \frac{[A][B]}{[AR]}$$

affinity constant

$$K_a = 1/K$$

cont. flowing cell

$[AR] \sim q * \text{signal}, q = \text{const}$

$[R] \sim R_0 = \text{initial receptor density}$

1.3 Sensitivity and Specificity

Sensitivity

true positive rate (% of correctly identified +)

Specificity

true negative rate (% of correctly identified -)

Compensate Sensitivity through LOD.

1.3.1 Limit of Detection (LOD)

(Sensitivity)

Limitation by non-specific binding (NSB) \rightarrow noise at zero analyte

LOD

$$LOD = 3 \cdot \text{noise} / \frac{dS}{d[A]}$$

$$S_{LOD} = S_0 + 3 \cdot \text{noise}$$

LOD for intensity/signal

$$LOD_{NSB} = \langle I_{NSB} \rangle + 3 \sigma(I_{NSB})$$

Lowest detectable intensity

$$\frac{\langle I_{POI} \rangle}{LOD_{NSB}} = 1 \quad (POI: \text{proteins of interest})$$

Detectable #proteins $N\# = \frac{\Gamma}{m_{\text{protein}}} \quad [\Gamma] = \text{pg/mm}^2$ detection limit

2 Optical Microscopy

2.1 Reflection and Refraction

Law of Reflection

$$\theta_{\text{inc}} = \theta_2$$

Law of Refraction

$$\frac{n_{\text{inc}}}{n_2} = \frac{\lambda_0/\lambda_{\text{inc}}}{\lambda_0/\lambda_2} = \frac{\sin \theta_2}{\sin \theta_{\text{inc}}} \quad \text{for } \theta_{\text{inc}} < \theta_c$$

Total reflection

$\sin \theta_c = n_2/n_{\text{inc}}$ always total if $n_{\text{inc}} < n_2$

Paraxial approx.

$$\theta \approx \sin \theta \approx \tan \theta, \quad \theta \ll 1$$

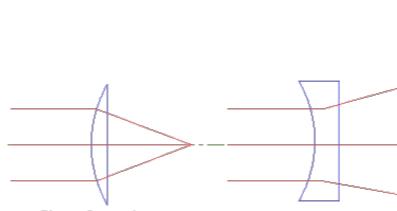
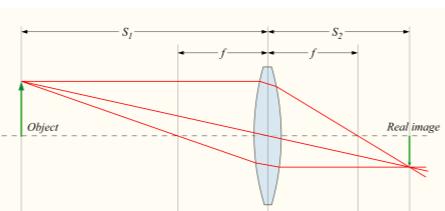
Thin lens approx.

$$R \ll S_o, S_i$$

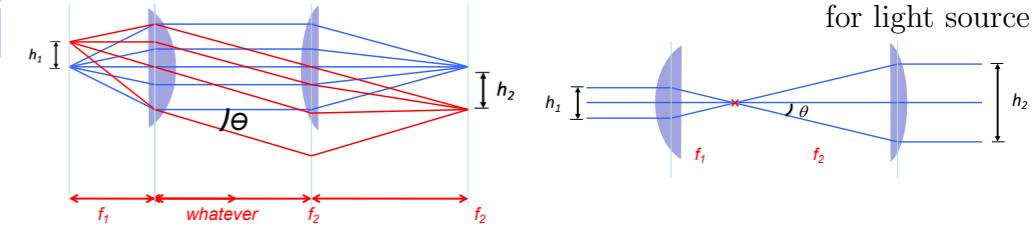
Lens makers formula

$$\frac{1}{S_o} + \frac{1}{S_i} = \frac{1}{f} = \frac{n_{\text{lens}} - n}{n} \left(\frac{1}{R_1} - \frac{1}{R_2} \right)$$

2.2 Ray Tracing



2.2.1 Simple Microscope



Magnification

$$M = h_2/h_1 = f_2/f_1 \quad * \text{ since } h_1 = f_1 \sin \theta$$

2.2.2 Beam Expander



for light source



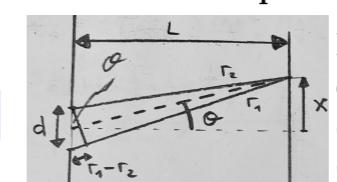
(Objective lens)

Camera: $(M = f_{\text{tube}}/f_{\text{obj}})$

(Tube lens)

2.3 Fundamental Limits of Lenses & Resolution

Due to a finite aperture will points presented as the PSF (point-spread).



First zero occurs at: $\theta \approx \sin \theta \approx 1.22 \frac{\lambda_0}{d}$

d: radius of the aperture

- $\sin \theta \approx \tan \theta = x/L$

- $r_1 - r_2 = d \cdot x/L$

maximum of the one is on the minimum of the other curve (FWHM)

$$\Delta r \approx f \sin \theta \times M \approx 1.22 \frac{\lambda_0 f}{D} \times M = 0.61 \frac{\lambda_0 n}{NA} \times M$$

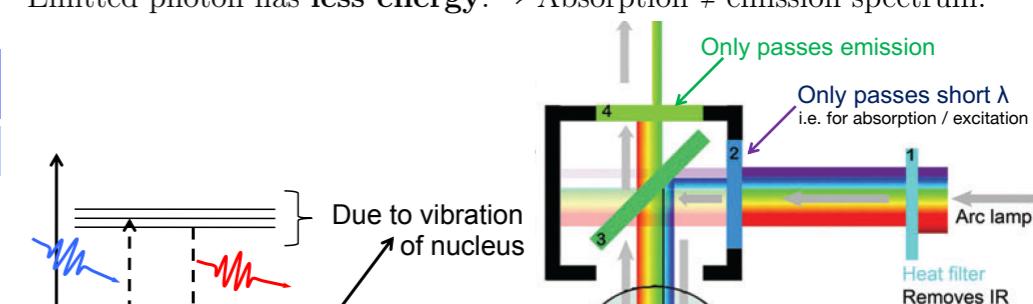
Resolution

Numerical Aperture

$$NA = n \sin \theta \approx n \frac{D}{2f} \quad n: \text{refractive index, } D: \text{aperture size of lens, } f: \text{focal length of lens}$$

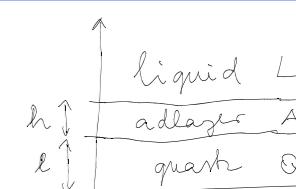
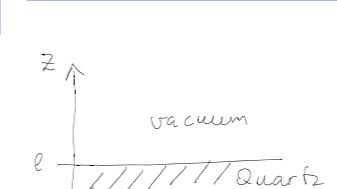
2.4 Fluorescence Microscopy

Emitted photon has less energy. \rightarrow Absorption \neq emission spectrum.



3 Mechanical Sensors

3.1 Viscoelastic media



3.1.1 Crystal with thickness l

Resonance frequency $\omega_n = n \cdot \omega_0 = n \cdot \frac{\pi}{l} \sqrt{\frac{\mu_Q}{\rho_Q}}$ [rad/s]

char. wavelength $\lambda = 2l/n$

3.1.2 Elastic plate in water

Resonance frequency $\omega_n = n\omega_0 + \Delta\omega_n$

frequency shift $\Delta\omega_n = -\sqrt{n} \sqrt{\frac{\rho_L \eta_L \omega_0}{2}} \frac{1}{l \rho_Q}$, η_L : viscosity

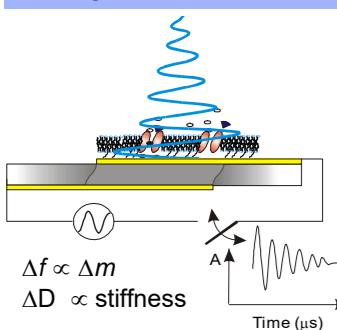
3.1.3 Elastic plate in water with adlayer

In fact is the *resonance frequency* dependent on the adlayer height.

But if it is “enough” small, the Sauerbrey approximation is sufficient.

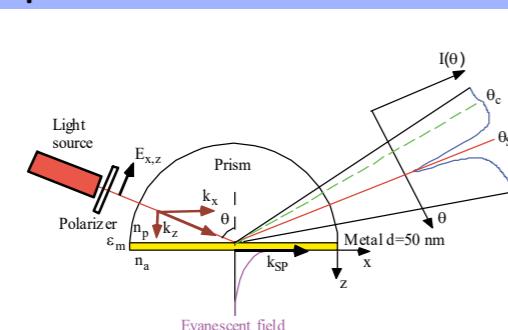
Sauerbrey eq. $\Delta f_n = 2\pi\omega_n = -n \frac{\Delta m}{C} \quad C = \frac{\sqrt{\rho_Q \mu_Q}}{2f_0^2} = 17.7 \text{ ng/cm}^2 \text{Hz}$

3.2 QCM-D vs. SPR techniques



$$\Delta m = -\frac{C}{n} \Delta f_n$$

$$\text{LOD}_{\text{QCM}} = C \cdot \delta f \approx 1 \text{ ng/cm}^2$$



$$\Delta m = d \frac{n_{\text{protein}} - n_{\text{buffer}}}{dn/dc}$$

$$\text{LOD}_{\text{SPR}} = C \cdot \delta\theta \approx 0.1 \text{ ng/cm}^2$$

3.3 QCM: Quartz Crystal Microbalance

Resonance condition $f = \frac{nv}{\lambda} = \frac{nv}{2t}$

Dissipation $D = \frac{1}{\pi f \tau}, \tau: \text{time until } \frac{U_{\max}}{e}$

Modeling of the QCM-D response in air / aqueous solution:

$$\begin{aligned} G &= G' + jG'' & \eta: \text{viscosity} (= \frac{G''}{\omega}), \mu: \text{elasticity} (= G'), \\ &= \mu + j2\pi f \eta & \rho: \text{density}, d: \text{thickness} \end{aligned}$$

3.4 Strain Gauge

Resistive strain g. $\frac{\Delta R}{R} = k \frac{\Delta l}{l} = k \epsilon, \epsilon: \text{Strain}, k: \text{Gauge factor}$

Capacitive strain g. $C = \epsilon_0 \epsilon_r \frac{A}{d}, (\text{displacement: } d \rightarrow d + \Delta d)$

4 Fluorescent Probes

4.1 Fluorescence Statistics

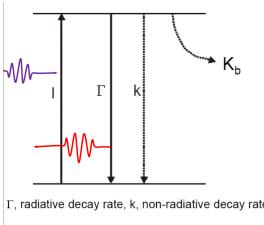
Photobleaching: A fluorescent molecule can emit a limited #photons by excitation before it irreversibly converts to a non-fluorescent molecule.

Quant. Yield $Q = \frac{\Gamma}{\Gamma+k+K_b} \sim 0 - 98\% \quad (\text{Efficiency})$

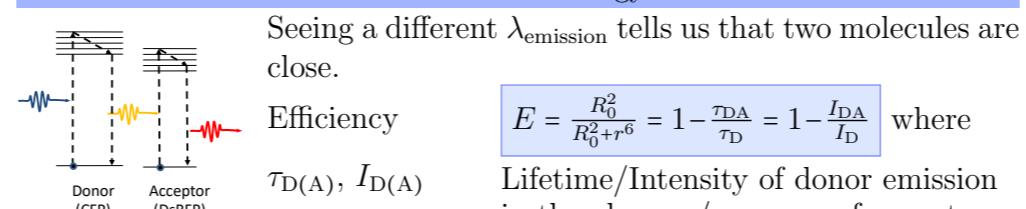
Fluorescence $\tau = \frac{1}{\Gamma+k+K_b} \sim 1 \text{ ns}$
Lifetime

Fluorescence emission is a statistical process that is characterized by exponential decays.

Molecules in excited state $\frac{dN_e}{dt} = -\left(\frac{1}{\tau_1} + \dots + \frac{1}{\tau_n}\right) N_e$



4.2 FRET – Fluorescence Resonance Energy Transfer



Seeing a different $\lambda_{\text{emission}}$ tells us that two molecules are close.

Efficiency $E = \frac{R_0^2}{R_0^2 + r^6} = 1 - \frac{\tau_{\text{DA}}}{\tau_{\text{D}}} = 1 - \frac{I_{\text{DA}}}{I_{\text{D}}}$ where

$\tau_{\text{D(A)}}, I_{\text{D(A)}}$ Lifetime/Intensity of donor emission in the absence/presence of acceptor.

4.3 Calcium Imaging

→ too slow for t dependency measurements

Calcium ion cannot be visualized/tagged directly: → Design molecules with optical properties that change upon calcium binding.

Single & dual wavelength measurements:

Concentration $[\text{Ca}^{2+}]_i = K_{\text{d,eff}} \frac{R - R_{\min}}{R_{\max} - R}$ where

for single $R \equiv F$ and $K_{\text{d,eff}} = \frac{[\text{Ca}^{2+}]_i \times (F_{\max} - F)}{F - F_{\min}}$

for dual. $R = F_1/F_2 \quad (F: \text{fluorescence})$

The binding of Ca^{2+} leads to...

- change in fluorescence **intensity** but not wavelength change
- a **shift** in excitation (and/or emission) peaks (“dual wavelength”)
- changes in fluorescent resonance energy transfer (**FRET**) & life time

4.3.1 Delivery of Calcium Indicators

Loading cells Once the molecule got cleaved (spalten), it cannot go out and gets fluorescent.

Introduce **fluoresc.** Proteins changes emission rate when Ca^{2+} binds. **proteins** or (natural) The relative change ($\Delta F/F$) in the fluorescence

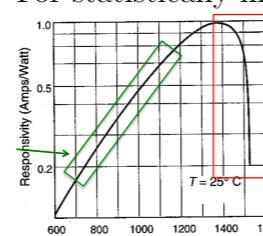
FRET proteins emission of EGFP can then be directly measured.

Note: The dye responds *fast*, but it is *slow* to recover. Calcium dissociation rate (i.e. recovery) depends on the dye’s affinity for Calcium.

5 Detection and Noise

5.1 Signal

For statistically independent, “uncorrelated”, events we use



Poisson

$$P_{\bar{n}}(n) = \frac{\bar{n}^n}{n!} e^{-\bar{n}} \quad \bar{n}: \text{mean}$$

Signal current $\langle I_{\text{sig}} \rangle = \eta q \bar{n} / \Delta t$

Responsivity $\langle I_{\text{sig}} \rangle / P = \eta q \lambda / (hc)$

Cutoff $\lambda = 1.24/E \text{ (eV)}$

5.1.1 Fundamental Noise Sources

Noise shot $N_s = 2R\eta qB \langle I_{\text{sig}} \rangle = \langle I_{\text{shot}}^2 \rangle R, 2B \approx 1/\Delta t$

dark $N_d = 2R\eta qB \langle I_{\text{dark}} \rangle$

thermal $N_j = \langle I_{\text{Johnson}}^2 \rangle R = \sqrt{\frac{k_B T B}{R}} R$

readout $N_r = N_j + N_{\text{amplifier}}$

$$N_{\text{tot}} = N_s + N_d + N_r \quad \sigma_{\text{tot}}^2 = \sum \sigma_i^2$$

SNR curr $\text{SNR}_{\text{curr}} = \frac{\eta N_{\gamma}}{\sqrt{\eta N_{\gamma} + N_d + N_r}} \quad \eta = \text{QE} \cdot \text{absorb}$

for large numbers $\text{SNR}_{\text{shot}} = \frac{\bar{n}}{\sqrt{\bar{n}}} = \sqrt{\bar{n}} \cong \eta N_{\gamma}$

5.2 (Optical) Detectors

Photoel. effect

$$E_{\text{ph}} = hf = hc/\lambda = \phi + E_{\text{kin}}$$

incident $E_{\text{ph}} = E_{\text{binding}} + E_{\text{kin}}$ of ejected el.

Photo mult. (PMT)

$$I = \alpha (S \cdot E_{\text{ph}} n / \Delta t), S: \text{sensitivity}, N_d \uparrow$$

Choose **binning mode** (2x2, 4x4, ...) such that the pixel size of the camera fits the best the maximum pixel size.

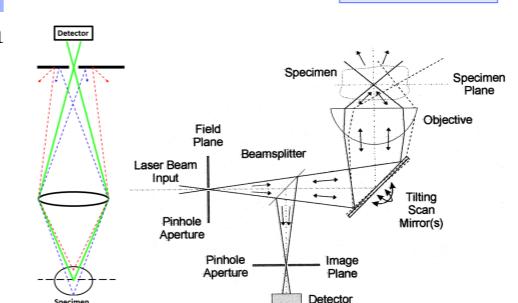
max. pixel size

$$\text{max} = 0.3 \frac{\lambda}{NA} \times M$$

5.3 Imaging Deep Tissues

Beer-Lambert's law

$$I = I_0 e^{-\mu x}$$



1st Pinhole by illumination:
→ focus the illum. to a small spot

2nd Pinhole by detector:
→ reject out of focus light
→ collect light to PMT

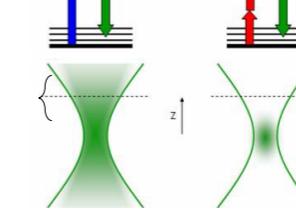
Signal and Noise (Pinhole size):
• more out of focus light → blurry
• less in-focus light → SNR↓

$$\text{Choose pinhole size } \sim \Delta r = 0.61 \frac{\lambda}{NA} \times M$$

5.3.1 2ph-Excitation

1-photon excitation: Excitation rate directly proportional to excitation light intensity

2-photon excitation: Excitation rate proportional to **SQUARE** of excitation light intensity



- + wavelength↑ → less absorbing/scattering
- + photons need to coincide in space and time to excite
- + No pinhole by detector for 2ph: Collect all the light
- low probability of occurrence i.e. inefficient
- ultra-short pulse light source needed

6 Optical Biosensors

6.1 EM

Relations:

$$c_0 = \frac{1}{\sqrt{\epsilon_0 \mu_0}} \quad k_0 = \frac{2\pi}{\lambda_0} = \frac{\omega}{c_0} = \omega \sqrt{\epsilon_0 \mu_0} \quad k = \frac{2\pi n}{\lambda} \quad n = \frac{c_0}{c} = \sqrt{\epsilon_r \mu_r} \approx \sqrt{\epsilon_r}$$

Dispersion relation $k^2 = \epsilon \omega^2 = \epsilon k_0^2 c_0^2 = k_0 \frac{\epsilon}{\epsilon_0} = k_0^2 \epsilon_r = (k_0 n)^2$

Plane waves

$$\vec{E}(\vec{r}, t) = \vec{E}_0 e^{i(\vec{k} \cdot \vec{r} - \omega t)}$$

whereby $\partial_t \hat{=} -i\omega, \partial_x \hat{=} ik_x, \partial_z \hat{=} ik_z, \partial_y \hat{=} 0$ (infinite extent)

Depth of penetration $d_p = \frac{\lambda}{4\pi} \frac{1}{\sqrt{n_{\text{inc}}^2 \sin^2 \theta - n^2}}$ (about 500 nm)

6.2 Evanescent Field Techniques

Recap

Evanescence

Always **total reflection** for $n_{\text{inc}} > n_2$

Negligible change of sensitivity compared to the size of the antibodies

6.2.1 SPR – Surface Plasmon Resonance

Plasmon

Plasmon Polariton

SPP

Dispersion relation

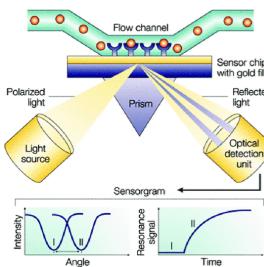
Momentum of incoming wave

quantum of an electron density wave in a metal mixture of photon (diel.) and el. dens. wave (met.) field components point in direction of propagation

$$k_{z,i}^2 = k_0^2 \epsilon_i - \beta^2 \quad i = d, m$$

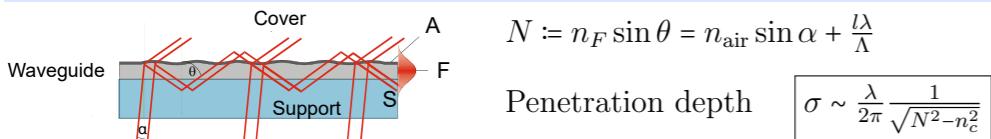
$$\beta \hat{=} k_x = \frac{\omega}{c} \frac{\epsilon_m \epsilon_d}{\epsilon_0 N}$$

where $N = \sqrt{\frac{1}{n_c^2} + \frac{1}{\epsilon_m}}$ effective refr. index of SP



Launch a SPP: $0 \leq k_{||,\text{inc}} \leq k_0 n_{\text{inc}}$
must ensure $\beta = k_{||,\text{inc}} = k_0 n_{\text{inc}} \sin \theta$ $\theta \in [0, \frac{\pi}{2}]$
 $\Rightarrow n_{\text{inc}} \geq n \sqrt{\frac{\epsilon_m}{\epsilon_m + n^2}}$ $\frac{\Delta \theta}{\Delta N} \triangleq \frac{\partial \theta}{\partial N} = \frac{1}{n_{\text{inc}} \cos \theta} \approx \frac{1}{n_{\text{inc}}}$

6.2.2 OWLS – Optical Waveguide Lightmode Spectroscopy



Waves have to be in phase (constr. interference) → extremely sensitive constr. interference $0 = 2\pi m \frac{1}{\lambda} \phi_F + \phi_{FS} + \phi_{FAC}$ ϕ : phase shifts

Ansatz for 3 layer model
 $\begin{cases} \text{Cover: } C e^{-|k_z, C|(z-d_F/2)} \\ \text{Waveguide: } B e^{ik_z, F z} + A e^{-ik_z, F z} \\ \text{Support: } D e^{|k_z, S|(z+d_F/2)} \end{cases}$

Idealized adlayer $n_A = n_C + c_A \frac{dn}{dc}$

Mass calculation $M = d_A \frac{n_A - n_C}{dn/dc}$

6.3 Limitations

Above methods not usable for diagnostic purpose → NSB, LOD

Solution: diffractometric biosensors (Focal Molography)

7 Molecular Adsorption and Electron Transfer

7.1 Quantum Mechanics

Schrödinger equation $\hat{H}\psi(\vec{r}) = E\psi(\vec{r})$ where $\hat{H} = -\frac{\hbar^2}{2m} \frac{\partial^2}{\partial x^2} + V$

1D potential well $\psi(x) = \sqrt{\frac{2}{L}} \sin(k_n x)$ for $0 \leq x \leq L$

where $k_n = \frac{n\pi}{L}$, $n \in \mathbb{N}$ and $E_n = \frac{\hbar^2 k_n^2}{2m}$

1D potential barrier (tunneling) $\psi(x) = \begin{cases} Ae^{ik'x} + Be^{-ik'x} & x \leq 0 \\ Ce^{ik''x} + De^{-ik''x} & 0 \leq x \leq d \\ Fe^{ik'x} & \text{otw.} \end{cases}$

where $k' = \sqrt{2mE}/\hbar$ and $k'' = \sqrt{2m(V_0-E)}/\hbar$

transm./tunneling probability $T = \frac{F^*F}{A^*A} = Be^{-\beta d}$ with $\beta = -2\sqrt{2m(V_0-E)}/\hbar$

7.2 Electronic Transport through Molecules

Quantum conductance (1D) $G = G_0 \cdot T$ $G_0 = \frac{2e^2}{h}$, in parallel: $G = N \cdot G_0$

Tunneling probability $T = Be^{-\beta d} \propto e^{-\beta d} = (e^{-\beta NPD})^N$

1D channel current $j = -(\mu_1 - \mu_2)e v \rho_E$ $\rho_E = DOS = \frac{1}{\hbar \pi} \sqrt{\frac{2m}{E}}$

7.3 Atomic and Molecular Orbitals

Bond order: defined by difference (#electrons) divided by two
→ If the bond order is different from zero, then the bond is *stable*

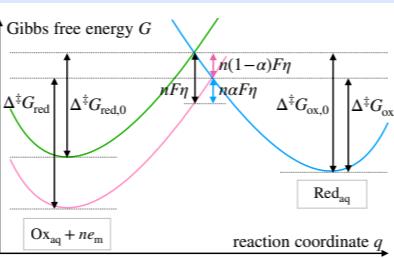
7.4 Transition State Theory

$A + B \rightarrow [AB] \rightarrow C + D$

Gibbs free energy $G = H - TS = U + pV - TS$

$pV = n_{\text{total}} RT$

7.4.1 Marcus Theory



See section 9.1.1 (Butler-Volmer)

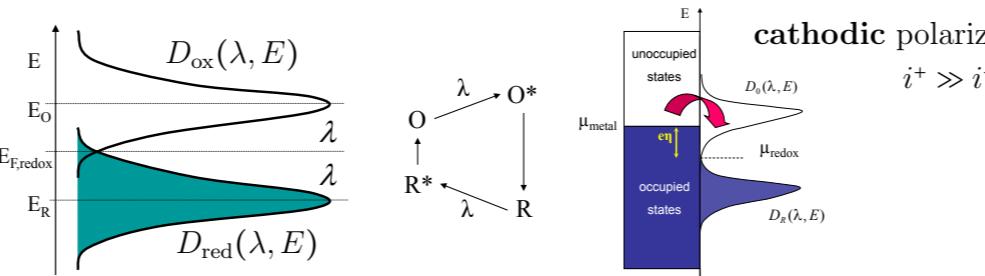
$$k_{\text{red}} = v_{\text{red}} e^{-\frac{\Delta \ddagger G_{\text{red}}}{RT}}$$

$$k_{\text{ox}} = v_{\text{ox}} e^{-\frac{\Delta \ddagger G_{\text{ox}}}{RT}}$$

$$\Delta \ddagger G_{\text{red}} = \ddagger G - G_{\text{ox,min}}$$

$$\Delta \ddagger G_{\text{ox}} = \ddagger G - G_{\text{red,min}}$$

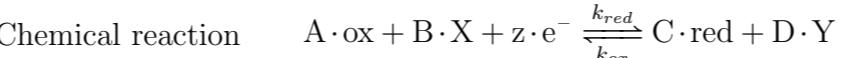
7.4.2 Gerischer's view



8 Potentiometric Biosensors

8.1 Redox Reaction

oxidation: e^- donor (*anode*) **reduction:** e^- acceptor (*cathode*)



reaction quotient $Q = \frac{a_{\text{ox}}^A \cdot a_X^B}{a_{\text{red}}^C \cdot a_Y^D}$

Standard conditions $T = 1^\circ\text{C}$, $p = 101.3 \text{ kPa} = 1.013 \text{ bar}$

"STP" $[\text{ion}] \equiv c_{\text{ion}} = 1 \text{ mol/l}$, $r = 1$ "activity coeff."

8.2 Electrochemistry

Dynamic equilibrium no net charge over time ($k_1 = k_{-1}$)

Chemical potential $\mu_j = \left(\frac{\partial G}{\partial n_j} \right)_{p,T,n'}$

Equilibrium $\mu_A = \mu_B$

Chemical potential $\mu_{\text{redox}} \equiv E_{F,\text{redox}} \equiv E^*$

Equilibrium

Contact potential $\bar{\mu}_A = \bar{\mu}_B$ $\bar{\mu}_j = \mu_j^0 + z_j F \Delta \phi$

Nernst equation, $\Delta \phi$ $\Delta \phi = V_{\text{in}} - V_{\text{out}} = \frac{k_B T}{Q} \ln \left(\frac{[C]_{\text{out}}}{[C]_{\text{in}}} \right)$

$E = E^0 - \frac{59 \text{ mV}}{z} \log_{10} Q$

$E_{\text{cell}} = E_1 - E_2$ or let $E_1 \stackrel{!}{=} E_2 \rightarrow \text{pH} = \dots$

8.3 Ion-selective Electrodes (ISE)

Sensor is separated to solution through a H^+ permeable glass.

pH electrode

$$\text{pH} = -\log_{10} a_{\text{H}^+} = \frac{K' - \Delta \phi}{0.059 \text{ V}}$$

8.4 Bioenzymatic Electrodes

Find out how much substrate + X + ... $\xrightarrow{\text{enzyme}}$ product + Y + ...

Detect "a lot" X
↔ "very few" substrate was initially present

9 Amperometric Sensors

9.1 Electrochemistry

Overpotential

$$\eta \equiv \Delta \phi_{\text{appl}} - \Delta \phi^0 \equiv \phi_s - \phi_m \equiv E - E^0 \quad (\text{at } E^0 \text{ via Nernst})$$

$$\eta = 0 \quad (\text{equilibrium i.e. no net current})$$

$$1\text{st: } n \propto Q, \quad 2\text{nd: (equiv. weight) } W_{\text{eq}} = M/z$$

$$m = \frac{Q}{z F} M = \frac{I t}{z F} M = n \cdot M \quad [m] = g, [n] = \text{mol}$$

9.1.1 Butler-Volmer equation

Effect of η on barrier height G
Let ϕ_s : potential of ions in solution

ϕ_m : potential of e^- in (metallic) electrode

z : valency of oxidized species

n : #of transferred e^-

$z - n$: valency of reduced species

$$\text{transfer coeff. } \alpha \quad nF\eta = n(1 - \alpha)F\eta + n\alpha F\eta$$

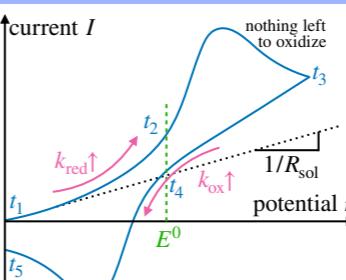
$$@\text{equi. } (\eta = 0) \quad f \equiv \frac{F}{RT} @298\text{ K} \frac{1}{25.69 \text{ mV}}$$

The Butler-Volmer equation relates what we measure (the **current**) with what we would like to determine (the **concentration** of an analyte):

Butler-Volmer

$$j = \underbrace{nFAk_0}_{j_0} (C_{\text{ox}}(0,t) e^{-\alpha n f \eta} - C_{\text{red}}(0,t) e^{(1-\alpha)n f \eta})$$

9.2 Cyclic Voltammetry



Water electrolysis High potentials/volt's

→ affects I (disturbance, bad)

9.3 Amperometric Sensors

9.3.1 Clark (Oxygen) Electrode

→ Measure O_2

- test solution $\xrightarrow[\text{membrane}]{\text{O}_2 \text{ passes}}$ Pt cathode $\xrightarrow{\text{reduction}}$ current
- Ag anode is in KCl solution (→ "enough" Cl^- for oxidation)

9.3.2 1st and 2nd Generation

analyte of interest ... $\xrightarrow{\text{redox enzyme}}$... $\xrightarrow{\text{mediator}}$... Clark Electrode

problem P1 (1st) O_2 may be consumed, when not measured

problem P2 (2nd) need to have "enough" of them

Mediator needs to be • reversible • not toxic • no side reactions

9.3.3 3rd Generation

Immobilization/fixation of a redox enzyme on electrode surface

→ free-diffusing redox mediators are not necessary

→ in vivo measurements allowed since immobilized

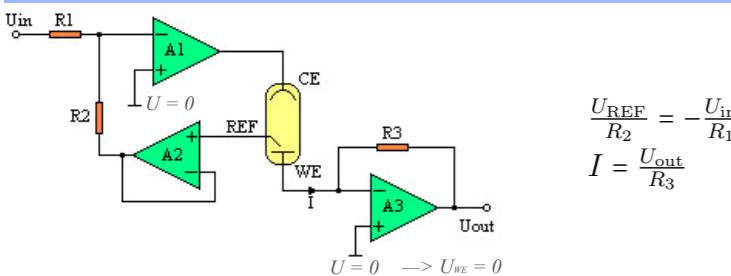
problem P3

Efficient electron transfer (Marcus theory)

→ may be overcome by mediators

→ minimize ET distance

9.4 Three Electrode Cell

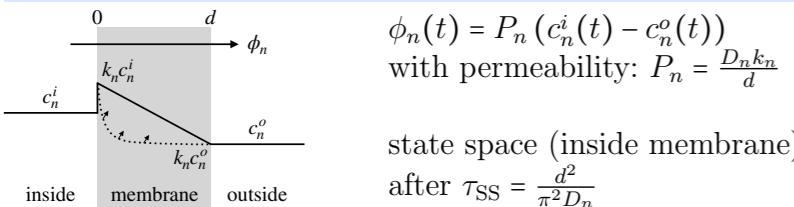


10 Membranes and Transport

10.1 Diffusion

Concentration	$c(x, t)$ [mol/l = mol/ 10^3 cm 3]
Flux	$\phi(x, t)$ [mol/cm 2 s]
Fick's law	$\phi(x, t) = -D_n \frac{\partial c_n(x, t)}{\partial x} = \phi_0$ in steady state
	D_n : diffusion coeff [cm 2 /s]
Continuity eq.	$-\frac{\partial \phi_n(x, t)}{\partial x} = \frac{\partial c_n(x, t)}{\partial t}$
e.g. Delta initial condition	$c(x, t) _{t=0} = n_0 \delta(x)$
	$c(x, t) = \frac{n_0}{\sqrt{2\pi}\sigma} e^{-x^2/\sigma^2}, \sigma = \sqrt{2D_n t}, t_{1/2} = \frac{1}{D_n} x_{1/2}^2$

10.1.1 Diffusion across membrane



10.2 Osmosis

$$\pi(x, t) = RT \sum_n c_n(x, t) \quad c_\Sigma(x, t): \text{osmolarity/total conc.}$$

Zero pressure if

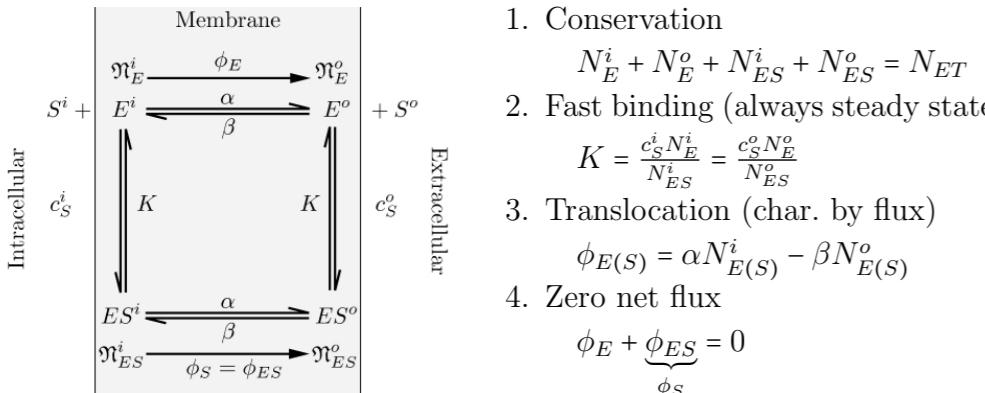
$$\pi_i - \pi_o = 0$$

$$\text{Volume of the cell } v_c(\infty) = v'_c + \frac{N_\Sigma^i}{c_\Sigma^o} \quad v'_c: \text{non-water volume}$$

10.3 Carrier mediated Transport

- Hints for their existence
- Saturation of solute trsp. (\nexists Fick's law)
- Competitive inhibiton
- Structure specificy

4-state carrier model



$$\text{Net flux out of cell } \phi_S = \frac{\alpha\beta}{\alpha+\beta} N_{ET} \left(\frac{c_S^i}{c_S^i + K} - \frac{c_S^o}{c_S^o + K} \right) \quad (\phi_S)_{\max} = \frac{\alpha\beta}{\alpha+\beta} N_{ET}$$

10.4 Ion Transport

$$\text{Continuity eq. } \frac{\partial J_n(x, t)}{\partial x} = -z_n F \frac{\partial c_n(x, t)}{\partial t} \quad z_n: \text{valency}$$

Poisson eq.

i.e.

$$\text{Nernst-Planck eq. } u_n: \text{molar mobility}$$

Debye Length
“depletion width”

Nernst Equi. Pot.

$$\frac{\partial^2 \psi(x, t)}{\partial x^2} = -\frac{1}{\epsilon} \sum_n z_n F c_n(x, t)$$

electric field potential = local charge density

$$\text{current } J_n(x, t) = -z_n F D_n \frac{\partial c_n(x, t)}{\partial x} - u_n z_n^2 F^2 c_n(x, t) \frac{\partial \psi(x, t)}{\partial x} \quad \text{diffusion of charge} \quad \text{mobility of charge in E-field}$$

$\lambda_D \approx 1 \text{ nm}$ within $\tau_r \approx 1 \text{ ns}$

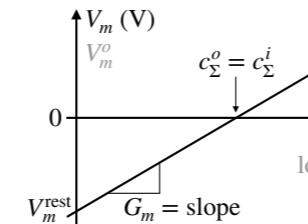
$$V_n = \frac{59 \text{ mV}}{z_n} \log_{10} Q \quad \text{with} \quad Q = \frac{c_s^o}{c_s^i}, \quad \frac{D_n}{u_n} = RT$$

$$V_K \approx -75 \text{ mV}, \quad V_{Na} \approx 55 \text{ mV}$$

$$\text{Donnan equilibrium } V_m = V_n \implies I_n = 0 \quad \left(\frac{c_s^o}{c_s^i} \right)^{\pm \frac{1}{z_n}} = e^{\frac{F V_m}{RT}} \quad +: \text{anodic}$$

10.4.1 Resting (membrane) potential

Resting $\leftrightarrow I_m = 0$



3-ion model

Resting potential

$$J_m = J_K + J_{Na} + J_o = 0$$

permeable to K, Na and some others

$$V_m^{\text{rest}} = \frac{V_K G_K}{G_{\text{tot}}} + \frac{V_{Na} G_{Na}}{G_{\text{tot}}} + \frac{V_o G_o}{G_{\text{tot}}} \quad G_{\text{tot}} \equiv G_m = \text{slope}$$

where $J_n \neq 0$ (only momentarily rest)

10.5 Active Transport

Rest is only momentarily \rightarrow maintain conc. gradients with active transport.

- Ions moving against its conc. gradient \rightarrow ATP needed
- Active pumps for $J_m = 0$ (rest) and $J_{n,in} + J_{n,out} = 0$ (quasi equilibrium).

11 Action Potential & Hodgkin-Huxley Model

11.1 Current Clamp

Fix current I_m and measure membrane potential V_m \rightarrow Good for observing AP (since voltage can change)

11.3 2-state ion channel model

two states

#open states

Prob. being open

Boltzmann law

close $\xrightleftharpoons[\beta]{\alpha}$ open with gate charge Q

$$\frac{dn(t)}{dt} = \alpha(\mathcal{N} - n(t)) - \beta n(t)$$

$$x(t) \approx \frac{n(t)}{\mathcal{N}} = x_\infty + (x_0 - x_\infty) e^{-t/\tau_x}$$

$$x_\infty = \frac{\alpha}{\alpha + \beta}, \quad \tau_x = \frac{1}{\alpha + \beta}$$

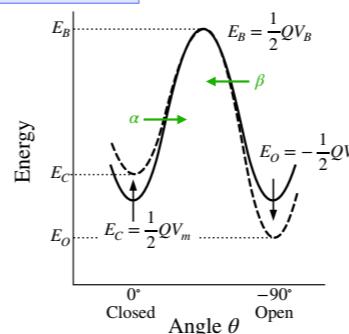
$$\alpha = A e^{(E_c - E_B)/kT}$$

$$\beta = A e^{(E_o - E_B)/kT}$$

$$x_\infty = \frac{1}{1 + \beta/\alpha} = \frac{1}{1 + e^{-QV_m/kT}}$$

$$\tau_x = \frac{1}{A e^{-\frac{1}{2} QV_B/kT}} \dots$$

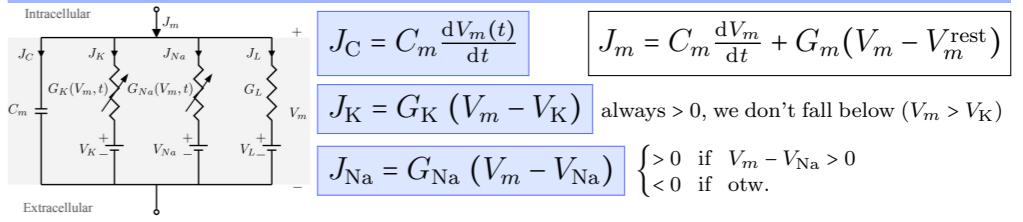
$$\dots \frac{1}{e^{\frac{1}{2} QV_m/kT} + e^{-\frac{1}{2} QV_m/kT}}$$



11.2 Voltage Clamp

Fix voltage V_m and measure the current I_m \rightarrow Good for studying membrane channel proteins (ion transport)

11.4 Circuit Model (Conductance)



$$V_K \approx -75 \text{ mV}, \quad V_{Na} \approx +55 \text{ mV}$$

$$J_m = C_m \frac{dV_m}{dt} + G_m (V_m - V_m^{\text{rest}})$$

$$J_m = C_m \frac{dV_m}{dt} + G_m (V_m - V_m^{\text{rest}}) \quad \begin{cases} > 0 & \text{if } V_m - V_{Na} > 0 \\ < 0 & \text{if otherwise} \end{cases}$$

- slow onset; decays slow
- K⁺ inactivates Na⁺ channels

\rightarrow Refractoriness (kurzzeitige AP Resistenz)
(Na⁺ channels are still inactive, $h \approx 0$)

11.5 Multiple states gate

open $n_Q(V_m, t)$

big/small $Q \rightarrow$ fast/slow dynamics

Let's write

$$[h] = n_{-Q} \text{ “slow”, } [m] = n_{2Q} \text{ “fast”, } [n] = n_Q$$

The lower T , the bigger the difference btw them.

11.6 Hodgkin-Huxley (HH) model

Experimentally you may fit the K⁺ and Na⁺ current into

$$\text{Conductance} \quad G_K(V_m, t) = \bar{G}_K n^4$$

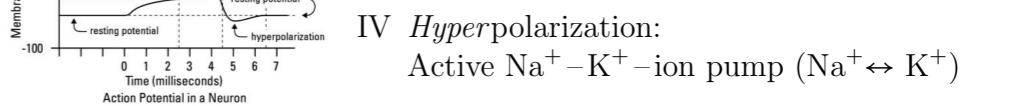
$$G_{Na}(V_m, t) = \bar{G}_{Na} m^3 h$$

Four regimes during AP:

II Depolarization: Na⁺ gate opens \rightarrow Na⁺ in

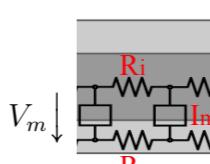
III Repolarization: K⁺ gate opens \rightarrow K⁺ out

IV Hyperpolarization:
Active Na⁺-K⁺-ion pump (Na⁺ \leftrightarrow K⁺)



11.7 Decrement-free conduction

11.7.1 Core – Conductor Model



$$R_i = r_i dz \quad \leftarrow dz: \text{per unit length}$$

$$R_o = r_o dz$$

$$I_m = k_m dz \quad \leftarrow \text{may use HH-model} \quad \text{if } 0 \rightarrow I_o = -I_i$$

$$\text{Core-Conductor eq. } \frac{\partial^2 V_m(z, t)}{\partial z^2} = (r_o + r_i) K_m(z, t) - r_o K_e(z, t)$$

$$\text{wave eq. } = \frac{1}{v^2} \frac{\partial^2 V_m(z, t)}{\partial t^2} \quad \text{with } v = \frac{W}{\Delta t}$$

$$K_e = 0 \quad v \approx \frac{K_m a}{2 \rho_i} \quad \text{for } r_i \gg r_o \quad \text{i.e. } v \propto \sqrt{a}$$

11.7.2 Cable model

– Core-Conductor with HH-model inside

Linearize (1st order) \rightarrow timescale for membrane voltage changes $\tau_m = \frac{C_m}{G_m}$

$$\text{Let } v_m = V_m + V_m^{\text{rest}} \quad \text{Let } v_m = V_m + V_m^{\text{rest}}$$

$$v_m + \underbrace{\tau_m \frac{\partial v_m}{\partial t}}_{=0 \text{ time indep.}} - \lambda_C^2 \frac{\partial^2 v_m}{\partial z^2} = r_o \lambda_C^2 K_e$$

$$\lambda_C = \frac{1}{\sqrt{g_m(r_o + r_i)}}$$

λ_C = cable length L / axon radius r_o

λ_C = cable length L / axon radius r_o

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