BENG 186B: Principles of Bioinstrumentation Design

Lecture 16

Ion-Selective and Optical Biosensors

References

Webster, Ch. 10 (Sec. 10.3-10.6).

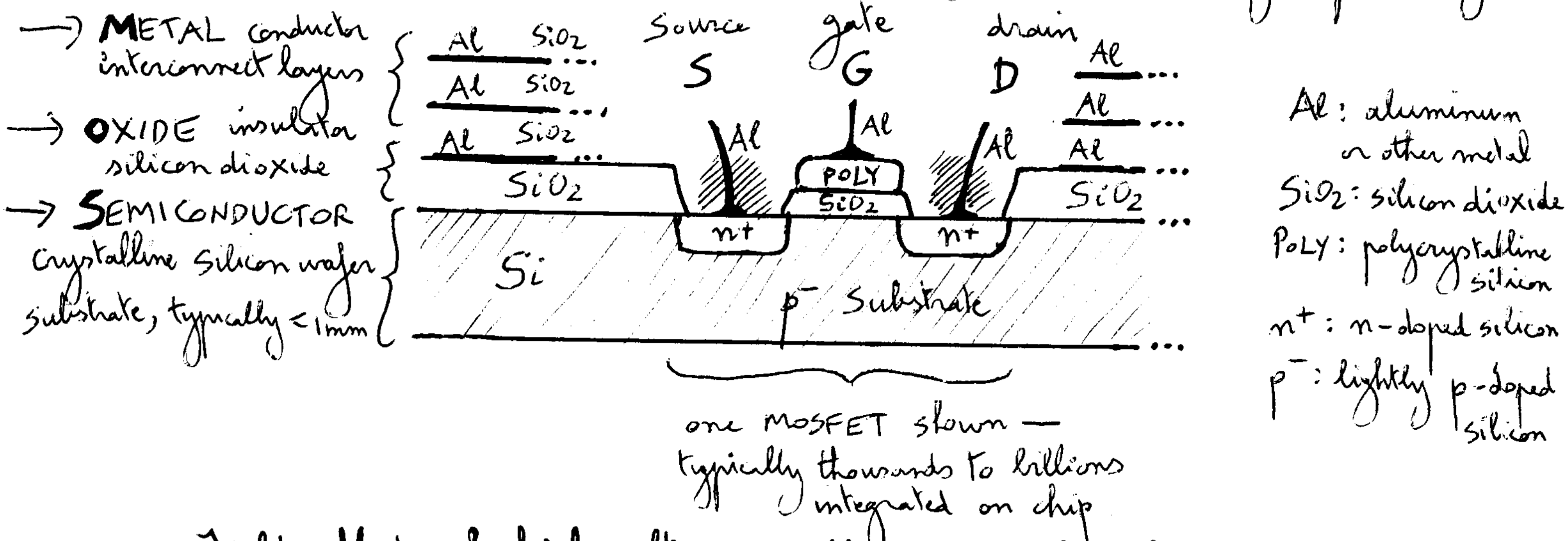
— Field-effect transistor (FET) integrated biosensors: (Sec. 10.4-5)

Compact ($\ll 1\ mm^2$) electrochemical sensors where ion-specific electrodes are formed on the gate of a FET, and concentration modulates the current or conductance of its channel.

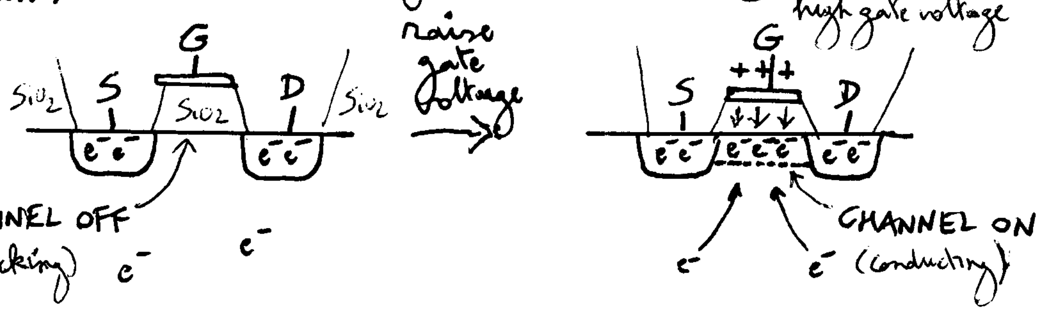
They can be integrated with standard transistor circuits on silicon microchips for automated high-throughput screening for large numbers of biomarkers with high specificity.

- Metal-oxide-semiconductor field-effect transistor (MOSFET):

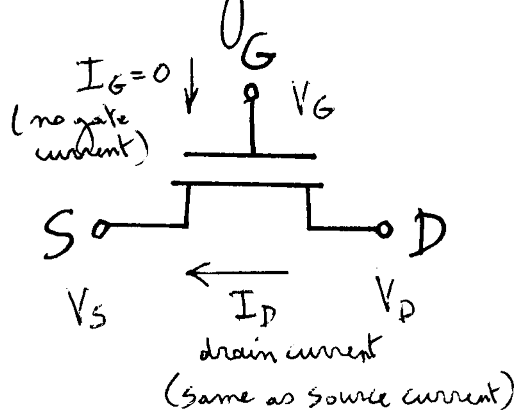
Standard transistors, fabricated in the same process, used for building amplifier circuits, digital logic, etc. for control and signal processing.



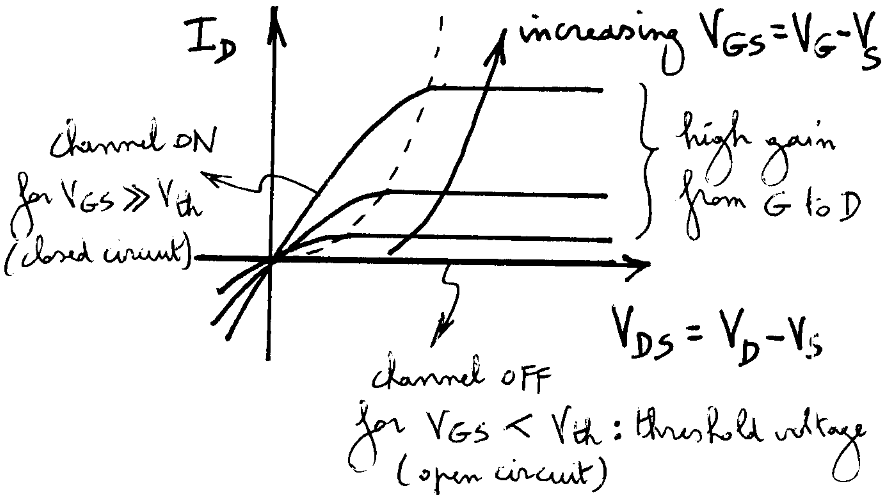
Field effect of high voltage on the gate, through the oxide, causes accumulation of electrons from the silicon on the oxide surface, creating an inversion channel of electrons conducting between source and drain:



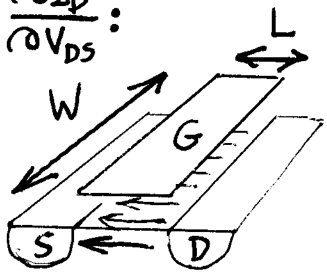
Circuit symbol:



I-V characteristics:



Simple model of channel conductance $g_{ds} = \frac{\partial I_D}{\partial V_{DS}}$:



$$g_{ds} = \frac{W}{L} \cdot \mu \cdot Q_{ox}$$

$\left[\frac{A}{V} = \frac{1}{\Omega}\right]$

μ: ELECTRON MOBILITY $\left[\frac{m^2}{Vs}\right]$

Q_{ox}: SURFACE CHARGE DENSITY $\left[\frac{C}{m^2}\right]$

W : width [μm]

L : length [μm]

$\mu \approx 0.15 \frac{m^2}{Vs}$ for n-type Si

because $I_D = \underbrace{W \cdot Q_{ox}}_{\text{charge per unit length}} \cdot \underset{\text{velocity}}{v}$

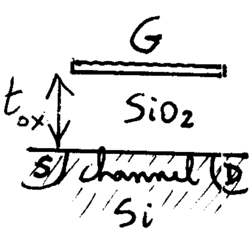
and $v = \mu \cdot \underset{\text{electric field}}{E} \cong \mu \cdot \frac{V_{DS}}{L}$ for small V_{DS}

$$Q_{ox} = C_{ox} \cdot (V_{GS} - V_{th})$$

Q_{ox}: $\left[\frac{C}{m^2}\right]$

C_{ox}: CAPACITANCE AREA DENSITY $\left[\frac{F}{m^2}\right]$

V_{th}: THRESHOLD VOLTAGE [V]



$C_{ox} = \frac{\varepsilon_0 \cdot \varepsilon_r}{t_{ox}}$

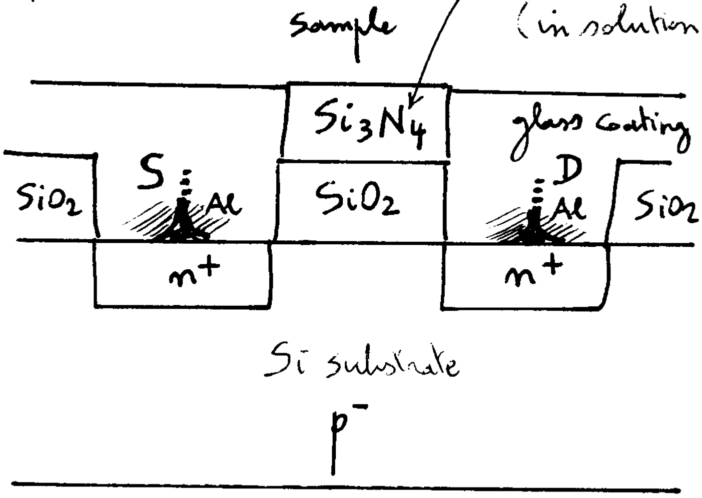
$\approx \frac{3.5\,10^{-11}\,\frac{F}{m}}{t_{ox}}$ for SiO_2

$$\Rightarrow g_{ds} = \frac{W}{L} \cdot \mu C_{ox} \cdot (V_{GS} - V_{th})$$

$V_{th} \approx 0.7V$ typical

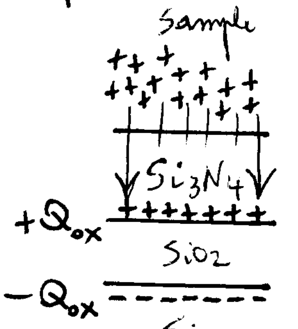
- Ion-sensitive field-effect transistor (ISFET): (Sec. 10.4)

effectively the same as a MOSFET, but with the gate polysilicon removed and replaced with an ION-SENSITIVE MEMBRANE:



- Silicon nitride Si_3N_4 is sensitive to pH, selectively passing H^+ ions.
- Other membranes are selective to other ion types.

The net ion charge diffusing through the membrane is approximately proportional to the ion concentration in the sample:



Q_{ox}: Surface charge density $\left[\frac{C}{m^2}\right]$

$$Q_{ox} \approx k \cdot [H^+]$$

$$\left[\frac{C}{m^2}\right] \quad \left[\frac{C\,\ell}{mol\, m^2}\right] \quad \left[\frac{mol}{\ell}\right]$$

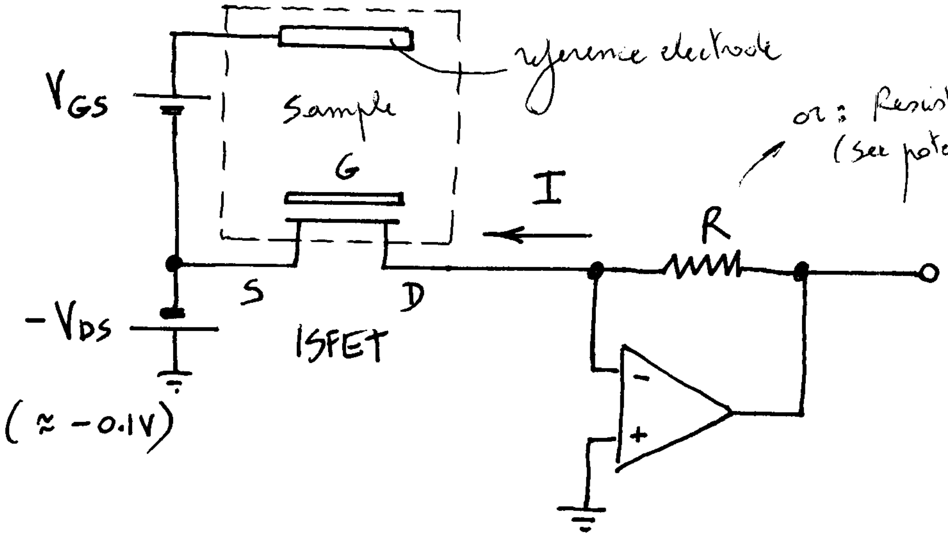
$$\Rightarrow g_{ds} \approx \frac{W}{L} \cdot \mu \cdot k \cdot [H^+]$$

(or another ion concentration)

→ measured with a Wheatstone bridge,

or a POTENTIOSTAT at a constant small ($V_{ds} \ll V_{th}$) voltage bias:

ISFET with potentiostat biasing:



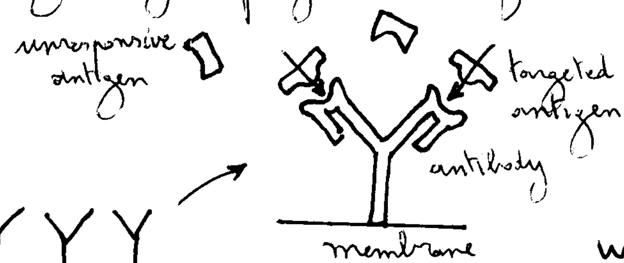
or: Resistive "T" for greater sensitivity (see potentiostat, Lecture 15)

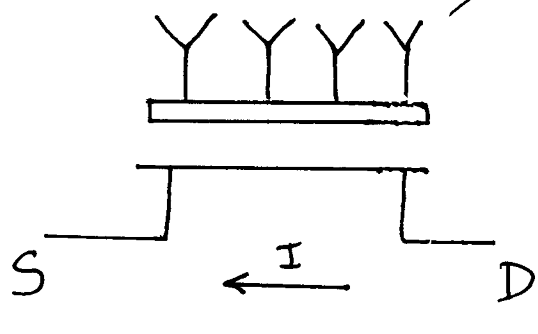
$$V_0 = R \cdot I$$
$$\approx R \cdot g_{ds} \cdot V_{DS}$$

and $g_{ds} \approx \frac{W}{L} \mu k \cdot [H^+]$

- Immunologically sensitive field-effect transistor (IMFET): (Sec. 10.5)

A special ISFET where the membrane is impermeable to ions, but is coated with antibodies for specific antigen detection, or coated with antigens for specific antibody detection:





works for targeted CHARGED antigens

$$\Rightarrow \quad g_{ds} \approx \underbrace{\frac{W}{L} \mu k \cdot 2}_{\text{2 binding sites per antibody}} \underbrace{[A^+]}_{\text{antigen concentration}}$$

Arrays of various antibody labeled IMFETS integrated with MOSFET amplification and selection circuits allow for high-throughput pathogen detection on a single microchip.

– Optical biochemical transducers : (Sec. 10.3, 10.6)

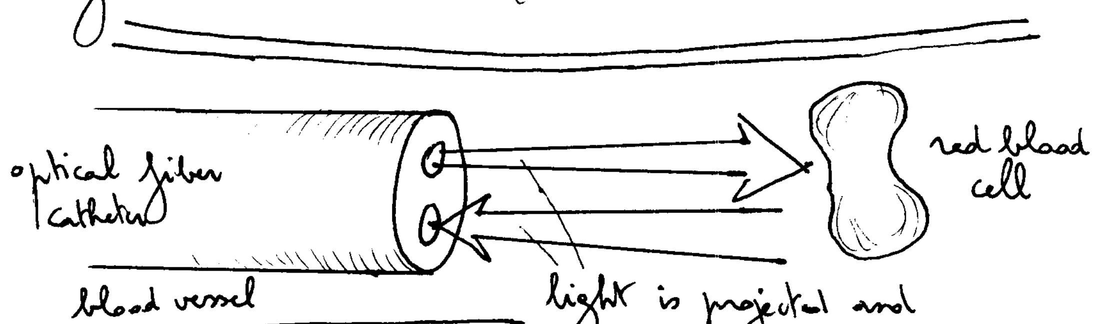
measure optical absorption, reflection, or fluorescence specific to a biochemical compound, at a specific wavelength.

"OPTRODES" (optical electrodes) but without the mess of interface electrochemistry!

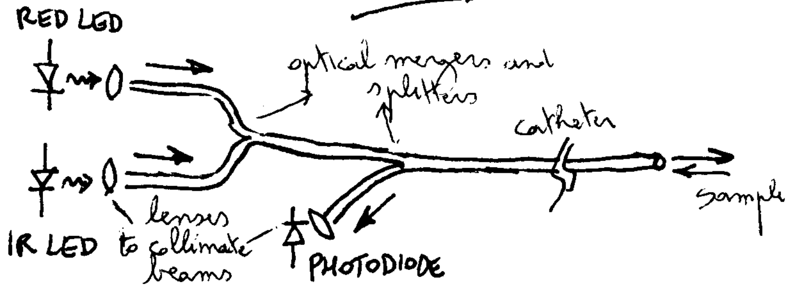
ADVANTAGES :
- no redox reactions
- high-density integration and small form factor (thin optical fiber as catheter)
- no electrical shock hazards
- no crosstalk or interference of electrical instrumentation

DISADVANTAGES :
- sensitivity to ambient light
  → chop the source and the signal synchronously to remove ambient components
- possible photobleaching can damage tissue
  → reduce light levels

• Chemical fibrosensors : (Sec. 10.3)

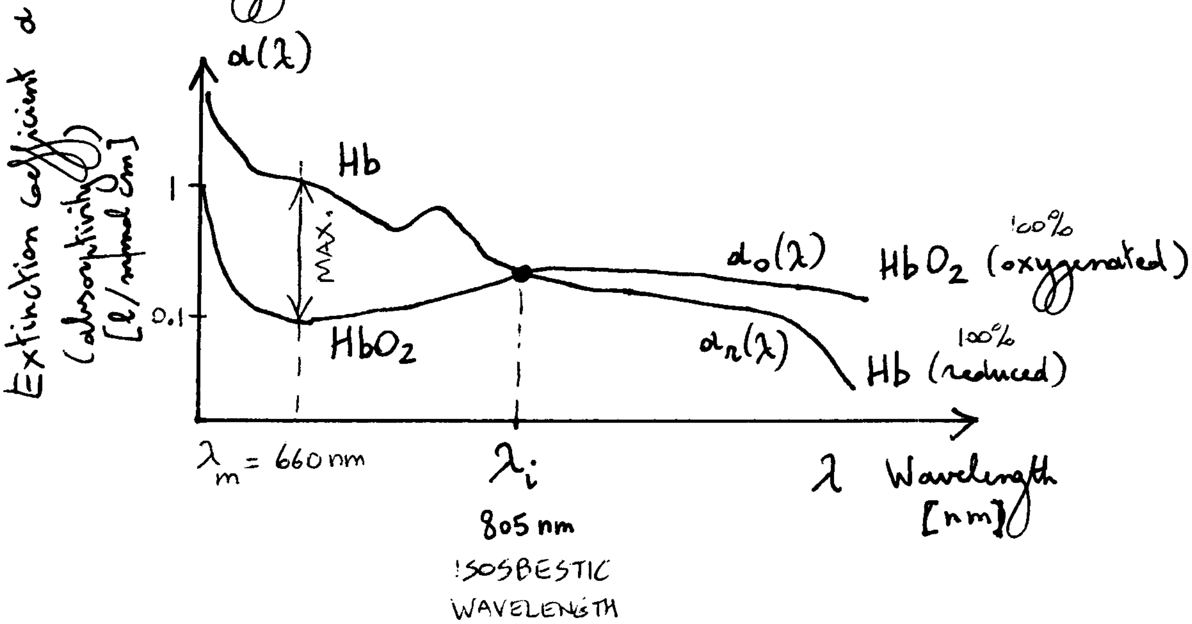


light is projected and received in the same narrow cone for high angular selectivity and high collection efficiency



SO_2 : Oxygen saturation measurement

The spectral absorptivity of hemoglobin is highly dependent on its oxygen saturation :



Beer's law of volume absorbance :

$$A(\lambda) = W \cdot L \cdot \alpha(\lambda)$$

$A(\lambda)$	W	L	$\alpha(\lambda)$
TOTAL ABSORBANCE (optical density)	Hb MOLAR DENSITY	OPTICAL PATH LENGTH	ABSORPTIVITY (extinction coefficient)
[–]	$\left[\frac{mmol}{\ell}\right]$ ·	[cm] ·	$\left[\frac{\ell}{mmol\ cm}\right]$

For Hb (100% reduced hemoglobin):

$$A(\lambda) = W \cdot L \cdot \alpha_r(\lambda)$$

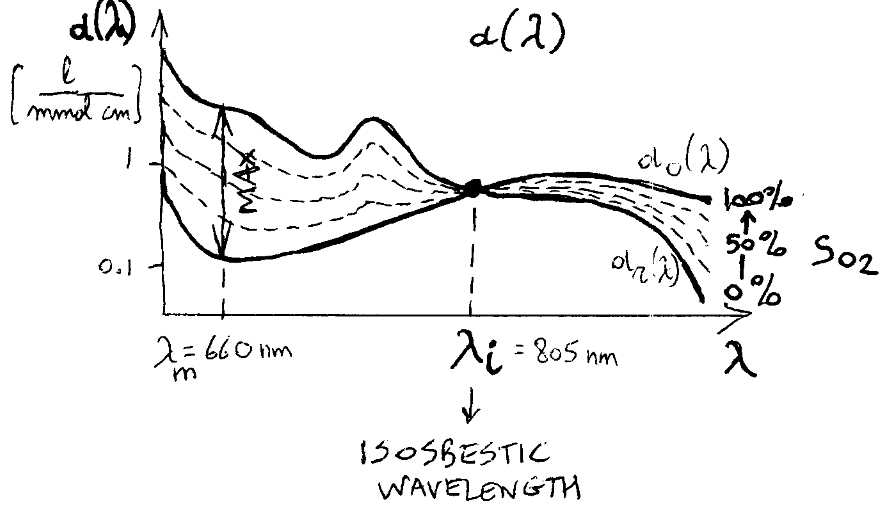
For HbO_2 (100% oxygenated hemoglobin):

$$A(\lambda) = W \cdot L \cdot \alpha_o(\lambda)$$

For a mixture C_o of HbO_2 and C_r of Hb (relative concentrations; $C_o + C_r = 1$):

$$A(\lambda) = W \cdot L \cdot \left(\alpha_o(\lambda) \cdot C_o + \alpha_r(\lambda) \cdot C_r\right)$$

$$A(\lambda) = W \cdot L \cdot \Big(\underbrace{\alpha_o(\lambda) \cdot C_o + \alpha_r(\lambda) \cdot C_r}_{\alpha(\lambda)} \Big) \qquad \begin{cases} C_o = S_{O_2} \\ C_r = 1 - S_{O_2} \end{cases}$$



At the isosbestic wavelength λ_i : $\alpha_o(\lambda_i) = \alpha_r(\lambda_i) = \alpha(\lambda_i) = \alpha_i$

$$A(\lambda_i) = W \cdot L \cdot \alpha_i$$

$$\Rightarrow A(\lambda) = \frac{A(\lambda_i)}{\alpha_i} \cdot \Big(\alpha_o(\lambda) \cdot S_{O_2} + \alpha_r(\lambda) \cdot (1 - S_{O_2}) \Big)$$

independent of W and L!

$$\Rightarrow S_{O_2} = \frac{\alpha_r(\lambda)}{\alpha_r(\lambda) - \alpha_o(\lambda)} - \frac{\alpha_i}{\alpha_r(\lambda) - \alpha_o(\lambda)} \cdot \frac{A(\lambda)}{A(\lambda_i)}$$

for any $\lambda \neq \lambda_i$

Choose λ to maximize denominator $\alpha_r(\lambda) - \alpha_o(\lambda)$
for maximum noise robustness
$\Rightarrow \lambda = \lambda_m = 660$ nm

$$\Rightarrow S_{O_2} = b - c \cdot \frac{A(\lambda_m)}{A(\lambda_i)} \quad \text{where} \quad \begin{cases} \lambda_m = 660 \text{ nm} \\ \lambda_i = 805 \text{ nm} \\ b, c \text{ are constants} \end{cases}$$

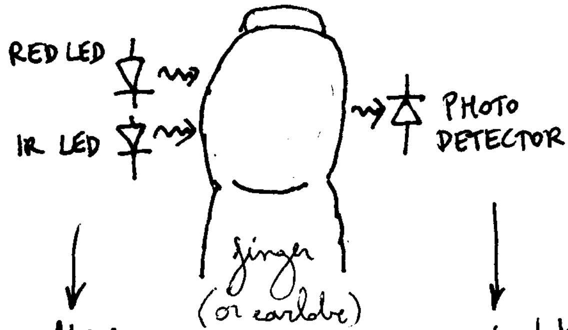
RATIOMETRIC TECHNIQUE

S_{O_2} obtained as ratio of two measurements $\Rightarrow$
insensitive to common-mode factors (W, L, ...)

• Non-invasive blood-gas monitoring: (Sec. 10.6)

S_{O_2} with PULSE OXIMETRY

Same ratiometric measurement of S_{O_2} but now non-invasively, optically through the skin, taking a ratio of tissue absorbances at two different wavelengths:



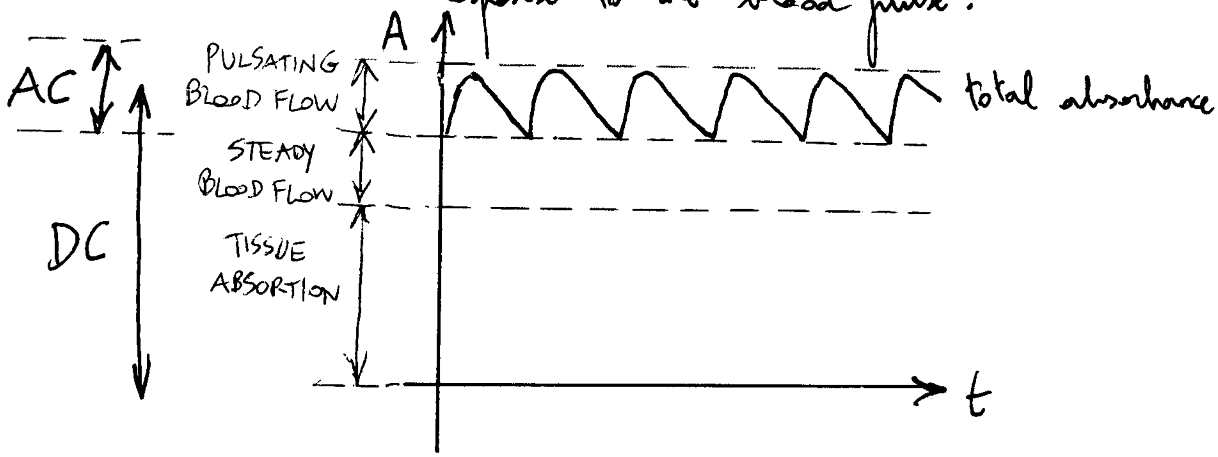
$$S_{O_2} = f\left(\frac{A(\lambda_{red})}{A(\lambda_{IR})}\right)$$

$$\approx 110\% - 25\% \frac{A(\lambda_{red})}{A(\lambda_{IR})}$$

multiplex and chop sources over time ...

... and detect the in-phase synchronous components in the output.

Use the DC responses at both frequencies to normalize the AC response to the blood pulse:



$$A(\lambda_{red}) = \frac{AC(\lambda_{red})}{DC(\lambda_{red})}$$

$$A(\lambda_{IR}) = \frac{AC(\lambda_{IR})}{DC(\lambda_{IR})}$$