Ketone Measurement Device

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Motivation

- Diabetes is a chronic health condition where either the pancreas does not create enough insulin or the body cannot use it effectively
  - Insulin lets sugar molecules in the bloodstream that have been broken down from consumed food into the body's cells to be used for energy
  - When there isn't enough insulin or the body stops responding to it, blood sugar builds up in the bloodstream and can lead to health problems such as heart disease and kidney disease
- Without enough insulin, the body begins to break down fat for fuel which causes a buildup of acids called ketones in the bloodstream
- High ketone levels combined with high blood glucose levels can lead to diabetic ketoacidosis (DKA), which can be life-threatening

Diabetes & Ketones

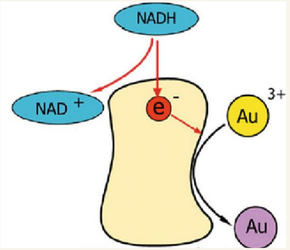
- Using enzymatic reactions, ketone levels can be measured based off the oxidation of beta-hydroxybutyrate dehydrogenase.
  - When blood containing β-hydroxybutyrate comes into contact with NAD+ in the presence of β-hydroxybutyrate dehydrogenase, the oxidation reaction is initiated. β-hydroxybutyrate in the blood is oxidized to acetoacetate, and NAD+ is reduced to NADH.
  - The amount of NADH produced is proportional to the concentration of β-hydroxybutyrate in the sample, and the oxidation of NADH to NAD+ can produce a measurable signal which is proportional to ketone concentration in the blood
- Test strips are used to collect blood samples of a minimum volume of ~0.5 uL, where most test strips use β-Hydroxybutyrate Dehydrogenase as a reagent enzyme.

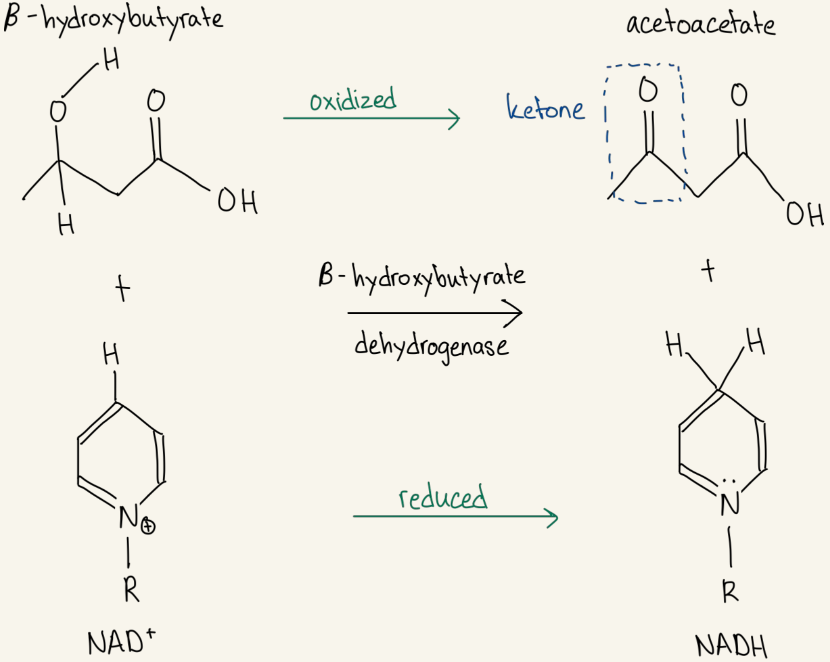
Chemistry

$$\beta\text{-hydroxybutyrate} + NAD^+ \xrightarrow{\beta\text{-hydroxybutyrate dehydrogenase}} \text{Acetoacetate} + NADH + H^+$$

$$NADH \rightarrow NAD^+ + H^+ + 2e^-$$

Gold in the electrodes facilitates electron transfer from NADH as it oxidizes back to NAD^+,

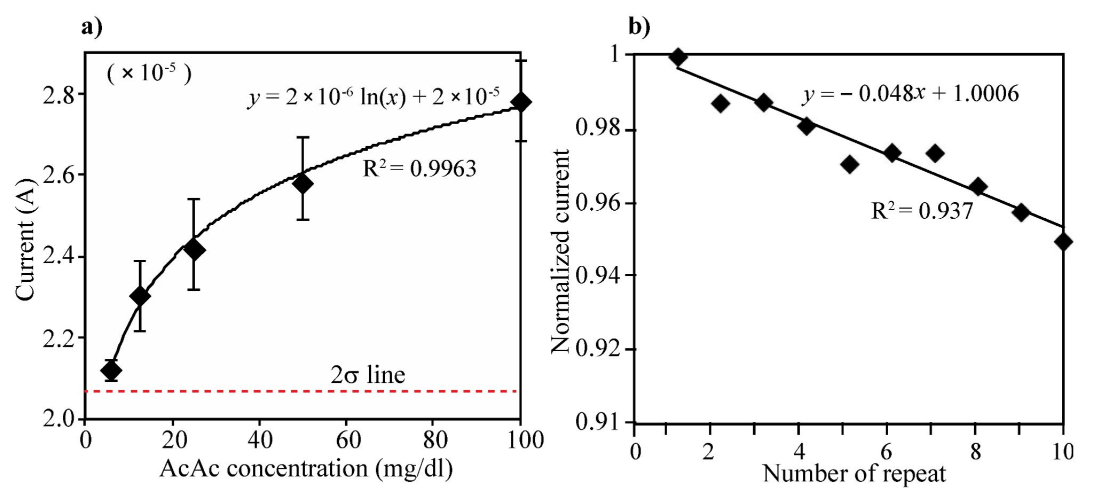


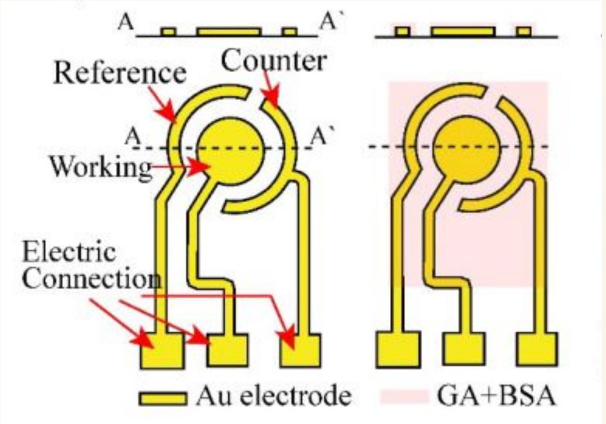


Concentration Levels:

Normal ketone blood level: <0.6 mmol/L
Slightly high: 0.6<x<1.5 mmol/L
DKA risk: 1.6<x<3 mmol/L
DKA: >3 mmol/L

Electrode and Biosensor Calibration

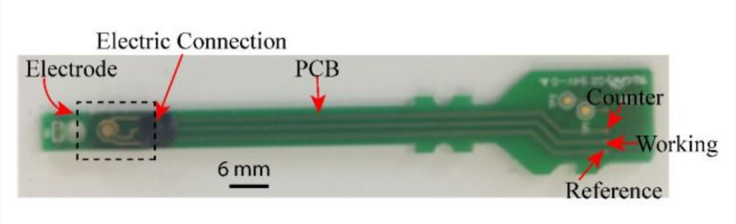




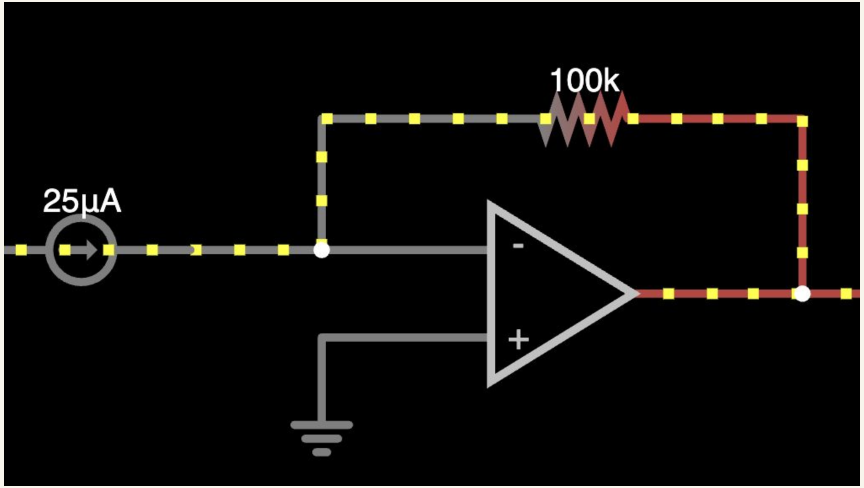
Estimated current from working electrode:

30 mg/dL AcAc = 3 mmol/L AcAc = 3 mmol/L B-HB

→ DKA: >3 mmol/L B-HB= 25 μA



Transimpedance Amplifier

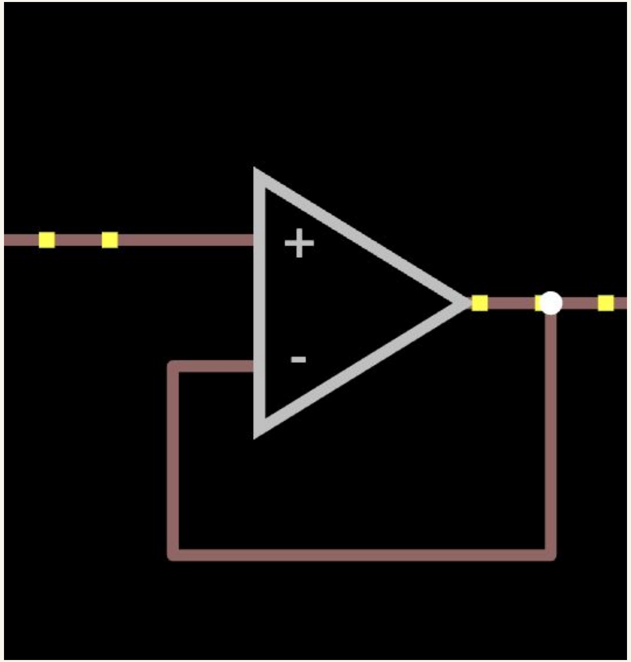


- Converts input current into voltage
- Assume 25uA for minimum threshold for DKA

$$\mathbf{V = -I_{in}R}$$

$$V = -(25\mu A)(100k\Omega) = -2.5\ V$$

Unity Gain Buffer

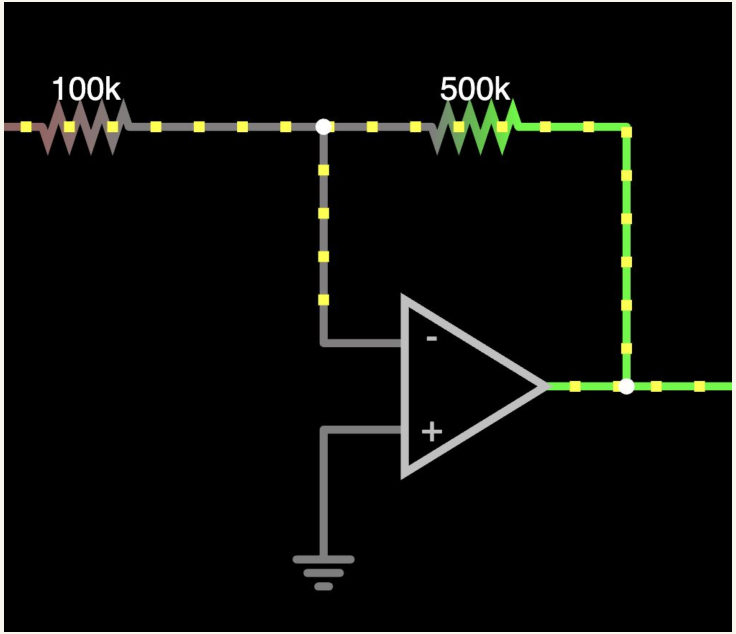


- Isolates circuit sections
- Boosts weak signals
- Gain = 1

$$\mathbf{V_{out} = V_{in}}$$

$$Z_{in} = \infty, Z_{out} = 0$$

Inverting Amplifier



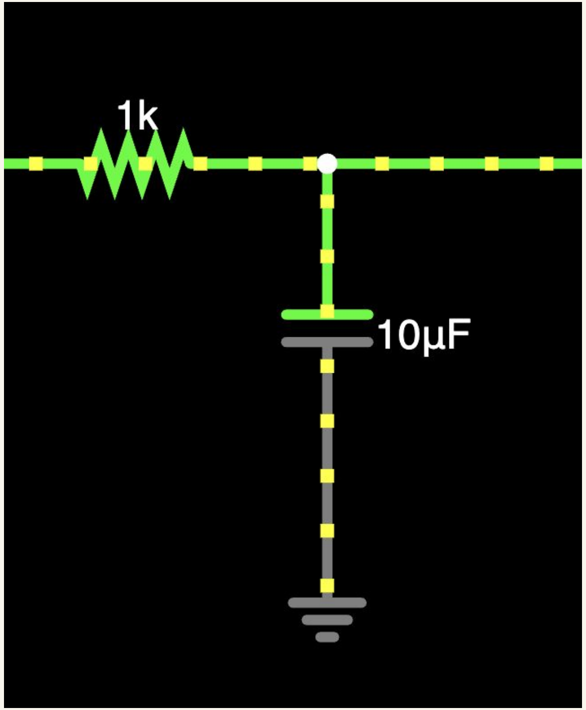
- Constant amplifier producing a negative output voltage
- Negative gain

$$\mathbf{V_{out} = -(R_f / R_i)\, V_{in}}$$

$$V_{out} = -(500k\Omega/100k\Omega)(-2.5V)$$

$$V_{out} = 12.5\ V$$

Low Pass Filter



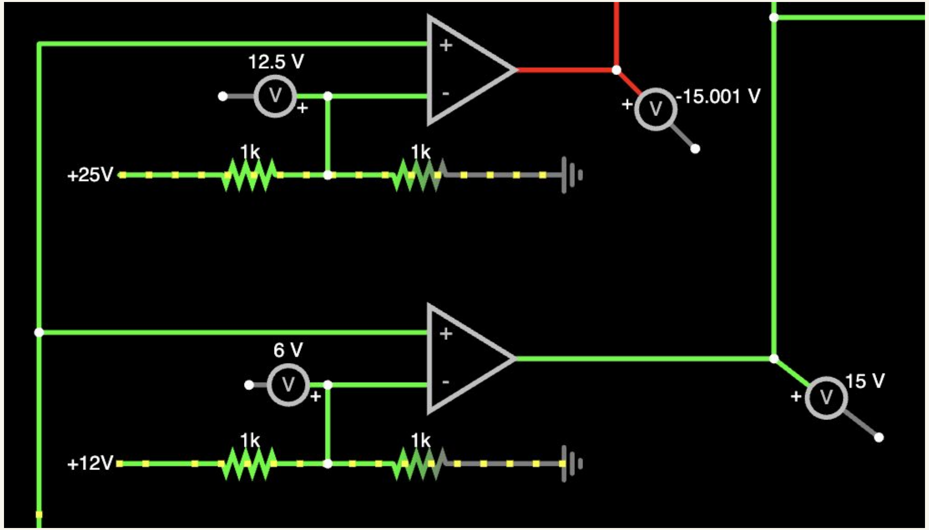
- Allow lower frequency signals to pass
- Block higher frequency signals to reduce noise

$$\mathbf{H(s) = RC / (s + RC)}$$

$$w_c = 1 / RC = 1 / (1k\Omega)(10\mu F) = 100 \text{ rad/s}$$

$$f_c = w_c / 2\pi = 15.92 \text{ Hz}$$

Comparators

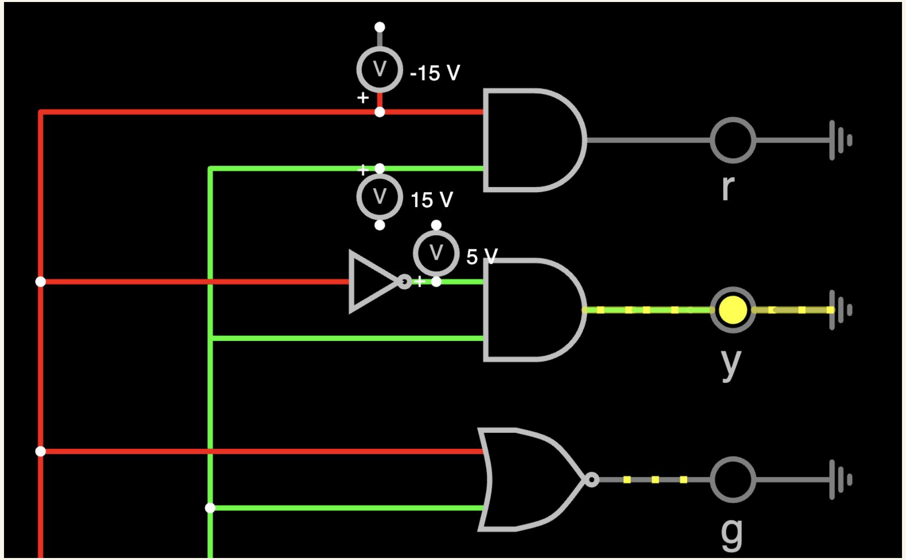


Compares the magnitudes of two voltages (V_{in} and V_{ref}) and determines which is the largest of the two

$$\textbf{out} = \{V^+ \text{ for } V_{in} > V_{ref}$$
$$\{V^- \text{ for } V_{in} < V_{ref}$$

- V_{ref} values will be adjusted based on the calibration step
- Estimated V_{ref} values: V1 = 12.5 V, V2 = 6 V

Logic Gates



CCT also sends voltage to microcontroller which outputs to alphanumeric display of ketone concentration levels

Red LED: *and* gate

INPUT		OUTPUT
A	B	
0	0	0
1	0	0
0	1	0
1	1	1

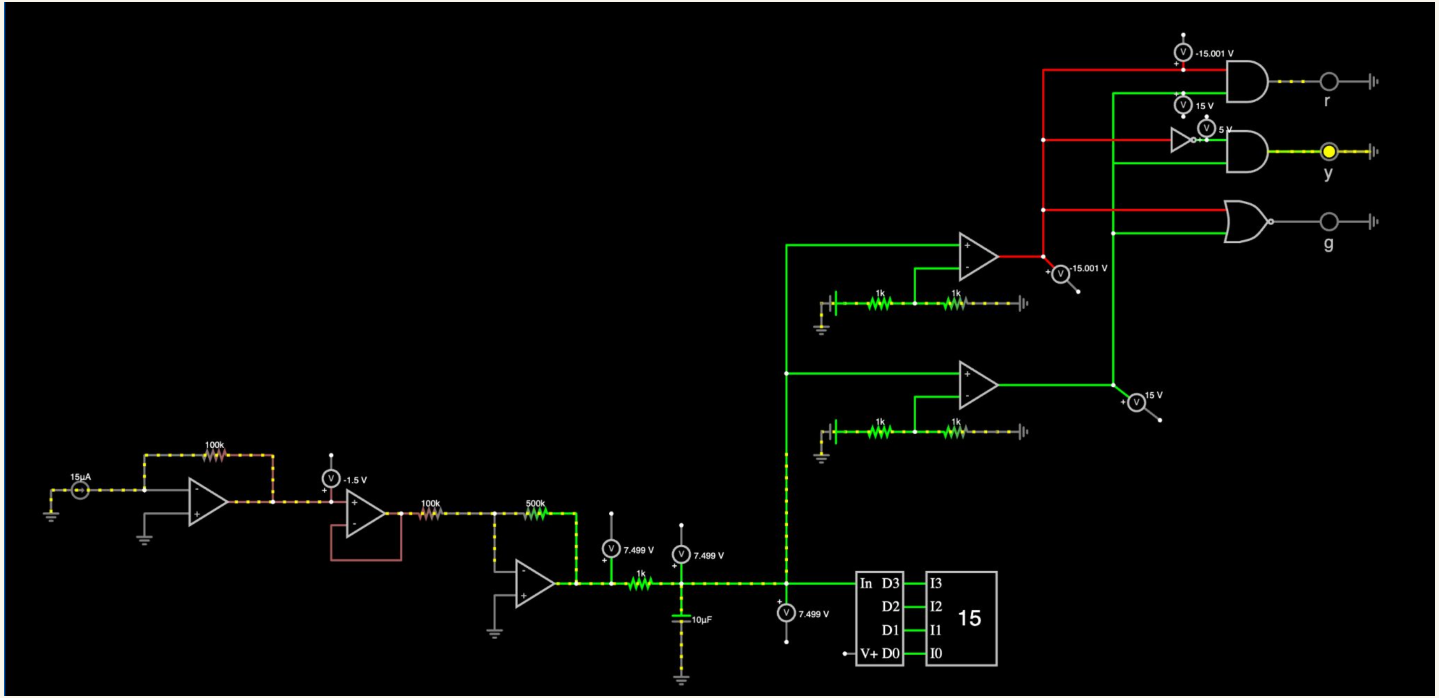
Yellow LED: *inverter* + *and* gate

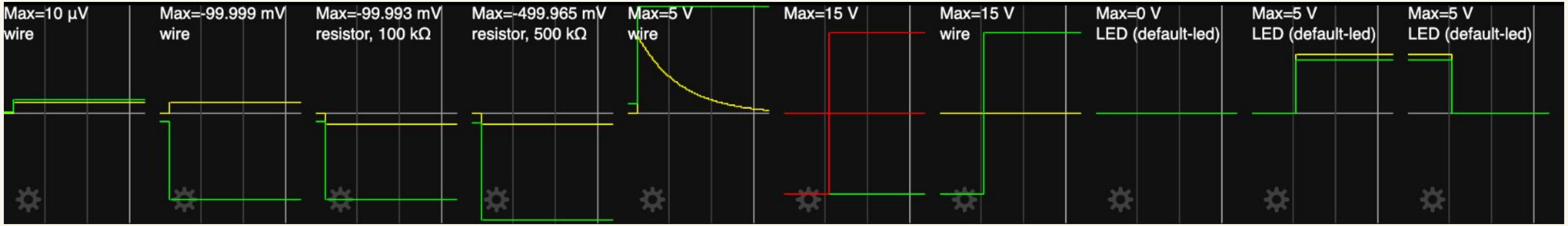
INPUT	OUTPUT
A	
0	1
1	0

INPUT		OUTPUT
A	B	
0	0	0
1	0	0
0	1	0
1	1	1

Green LED: *nor* gate

INPUT		OUTPUT
A	B	
0	0	1
1	0	0
0	1	0
1	1	0





voltage simulation of current from 1μA → 15μA

https://tinyurl.com/28qxfy3j

Limitations and Improvements

- Ensuring the device is calibrated to the relative ketone and β-hydroxybutyrate levels of the patient is critical to ensure that accuracy and relative conversions are maintained in the device's calculations
  - Ranges of abnormal ketones in blood range anywhere from **1.5 mmol/L**, to the high end of **3.0 mmol/L**, where the patient is at a serious risk of DKA
  - Appropriate calibration to the patient's normal levels would affect LED display ranges on the device to most accurately represent concern of DKA
- While a gold electrode was specified in our diagram, it's important to note that varying conductive materials used in the working electrode have different properties, and variations in conductivity, current load, and corrosion resistance across materials can all affect the ability of the electrode to transfer current and exchange electrons
- The reference voltage of 25V is quite high as a voltage source so we would need to find a battery or change it to make it work.

Global Impact

- Early detection of **diabetic ketoacidosis** (DKA):
  - For individuals susceptible to DKA, regular monitoring of ketones allows for early detection of rising concentrations of ketones in the blood, something that normal glucose monitors are unable to do
  - Blood measurement allows for current plasma ketone concentration, reducing variability in diagnostic uncertainty that would come with standard urine ketone tests, due to the need of lab processing needed for dilution factors in urine and higher salt concentrations in the sample
- Gives nutritional insight towards diet and lifestyle changes that would be aimed to reduce risk of DKA and diabetes, allowing for greater metabolic health awareness
  - Regular ketone monitoring may aid in maintaining nutritional ketosis, a state that can enhance fat metabolism, improve endurance, and support cognitive function

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