Alere™ Scientific Affairs
Clinical. Technical. Educational.

The Past, Present and Future of Blood Gas and Electrolyte Testing.

Thomas Koshy, Ph.D. Sr. Director, Scientific Affairs

September 12, 2013

Agenda

- Why Do We Measure Blood Gasses
- How Do We Measure Blood Gasses

- Why Do We Measure Electrolytes
- How Do We Measure Electrolytes

- Instrument and Devices

Why Do We Measure: ABGs

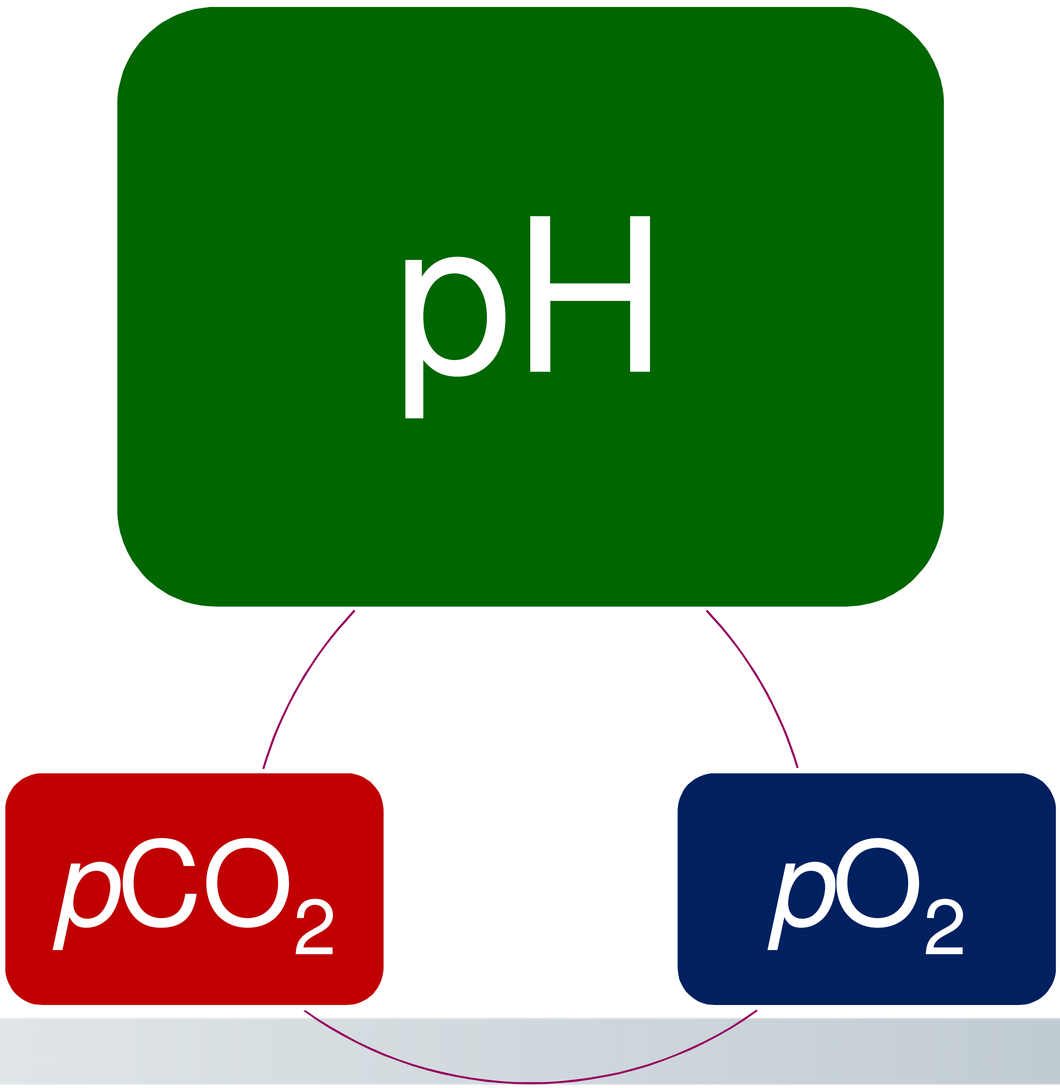
ABG data can be helpful in the differential diagnosis of:

- *Unexplained tachypnea (increased respiration) or dyspnea (shortness of breath)*
- *Unexplained restlessness, drowsiness, confusion or anxiety in bed patients or those on O_2*
- *Assessment of surgical risk*
- *Differential diagnosis of possible metabolic disturbances (i.e. sepsis, diabetic keto-acidosis)*
- *Before and during prolonged oxygen therapy and during ventilator support of patients (i.e. post-surgical recovery)*
- *Progression of cardio pulmonary disease*

Why Do We Measure: ABGs

ABG data can be helpful in the differential diagnosis of:

Chronic: *HF, Asthma, COPD* *Acute:* *Internal Trauma* *Vital Exhaustion*	*PE, Sepsis, Mental Impairment, Stroke, too many meds*	*General anesthesia is a general risk for O_2 delivery* *Imbalances O_2, pH and CO_2*	*Metabolic disturbances almost always manifest themselves in blood gasses and electrolytes*	*Before and during prolonged oxygen therapy and during ventilator support of patients (i.e. post-surgical recovery)*	*HF, COPD, pneumonia*


pH
pCO2
pO2

Why Do We Measure: pH

All enzymes and physiological processes can be affected by pH

pH extremes are incompatible with life

Adult reference range: 7.35-7.45

Why Do We Measure: *p*CO_2

- This is actually a measure of the pressure of the CO_2 dissolved in the blood.
- It represents the balance between the CO_2 produced by the tissues during respiration and the CO_2 removed by the respiratory system.
- Changes are usually due to ventilation status.
- Increases in *p*CO_2 usually result in pH decreases too.
- From *p*CO_2 and pH we can calculate HCO_3^-
- Adult reference range:
  35-45 mmHg

Why Do We Measure: pO_2

This is actually a measure of the pressure of the O_2 dissolved in the blood.

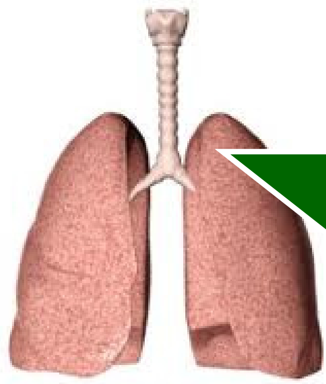
Usually linked of the ability of the lungs to oxygenate the blood

Decreases in arterial pO2 levels indicate:

- Decreased pulmonary ventilation
- Impaired gas exchange in the lungs
- Altered blood flow in heart or lungs

Adult reference range: 80-100 mmHg

pH is a Balancing Act

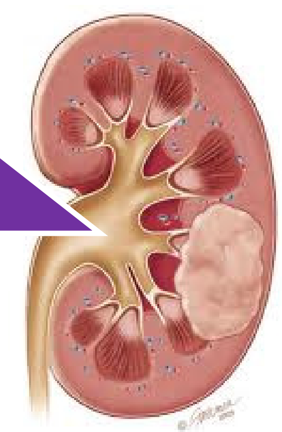


Respiratory System

- Manipulates CO_2 levels by increasing or decreasing respiratory rate.
- Faster and deeper breathing “blows off” more CO_2, raises pH
- Conversely, slower and shallower breathing retains more CO_2, lowering the pH
- This response is FAST

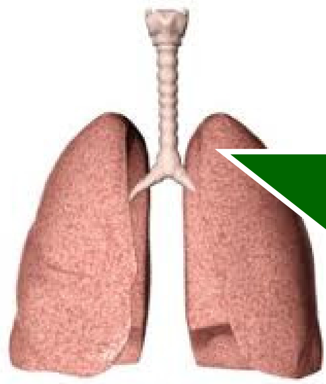
Renal System

- Regulates dissolved bicarbonate (HCO_3) produced by the kidneys.
- The kidneys also help control pH by eliminating hydrogen (H^+) ions.
- HOWEVER, this takes time, up to 24 hours



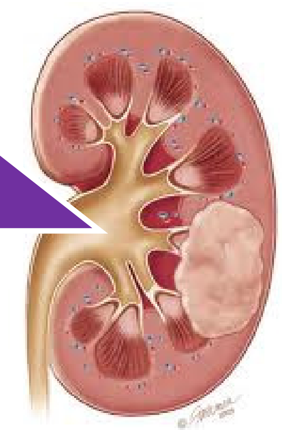
Compensation

pH balance is critical.

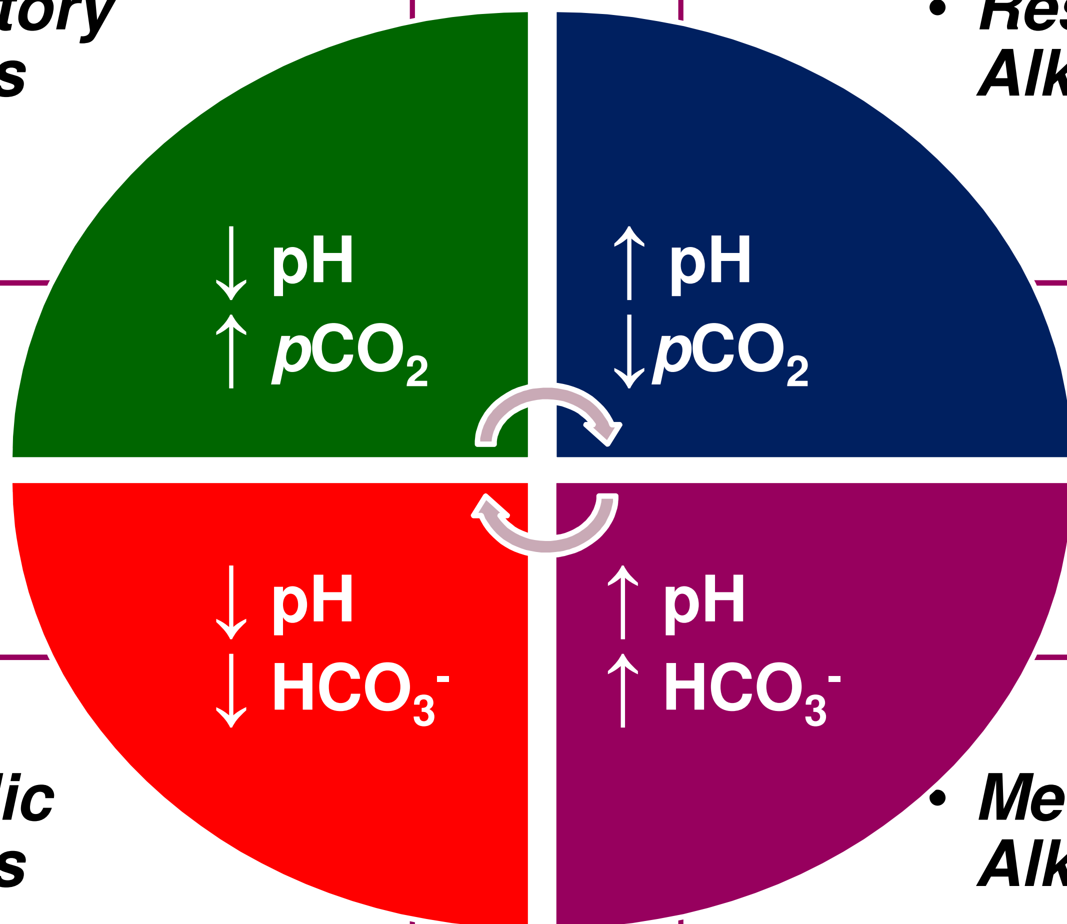


The lungs and kidneys are the primary buffer systems that work to overcome a respiratory or metabolic dysfunction

Neither system has the ability to overcompensate



- ***Respiratory Acidosis***
- ***Respiratory Alkalosis***



- ***Metabolic Acidosis***
- ***Metabolic Alkalosis***

Respiratory Acidosis:
pH < 7.35, pCO_2 > 45

Causes: Hypo-ventilation

- Depression of the respiratory center from sedatives, narcotics, drug overdose, stroke, cardiac arrest
- Respiratory muscle paralysis (spinal cord injury, Guillian-Barre, paralytics)
- Chest wall disorders (flail chest -fractured sternum or ribs , pneumothorax)
- Disorders of the lung parenchyma (CHF, COPD, pneumonia, aspiration, ARDS)
- Alteration in the function of the abdominal system (distension)

Signs and Symptoms

- CNS depression (decreased level of consciousness)
- Muscle twitching which can progress to convulsions
- Dysrhythmias, tachycardia – increased heart rate, diaphoresis (related to hypoxia secondary to hypoventilation)
- Palpitations, Flushed skin
- Serum electrolyte abnormalities including elevated K^+ (potassium leaves the cell to replace the H^+ buffers leaving the cell)

Treatment (while identifying and treating the underlying cause)

- Physically stimulate the patient to improve ventilation
- Vigorous pulmonary therapy (chest percussion, coughing and deep breathing, inspirometry, respiratory treatments with bronchodilators)
- Mechanical ventilation to increase the respiratory rate and tidal volume
- Reversal of sedatives and narcotics
- Antibiotics for infections
- Diuretics for fluid overload

Metabolic Acidosis: pH < 7.35, HCO_3^- < 22

Causes: Increased H^+, excess loss of $HCO3^-$

- Overproduction of organic acids (starvation, ketoacidosis, increased catabolism)
- Impaired renal excretion of acid (renal failure)
- Abnormal loss of HCO_3^- (diarrhea, GI disorders)
- Ingestion of acid (salicylate overdose, oral anti-freeze)

Signs and Symptoms

- Rapid breathing. The body is blowing off CO_2 to reverse the acidosis
- CNS depression (confusion to coma)
- Cardiac dysrhythmias (elevated T wave, wide QRS to ventricular standstill)
- Electrolyte abnormalities (elevated K^+, Cl^-, Ca^{2+})
- Flushed skin (arteriolar dilitation)
- Nausea

Treatment (while identifying and treating the underlying cause)

- $NaHCO_3^-$ (sodium bicarbonate) based on ABGs only and with caution
- IV fluids and insulin for DKA (Diabetic Ketoacidosis)
- Dialysis for renal failure
- Antibiotics, increased nutrition for tissue catabolism
- Increased cardiac output and tissue perfusion for low CO_2 states
- Rehydrate, monitor intake & output
- Treat dysrhythmias, support hemodynamic and respiratory status

Respiratory Alkalosis: pH > 7.45, $pCO_2 < 35$

Causes: Alveolar Hyper-ventilation

- Psychogenic (fear, pain, anxiety)
- CNS stimulation (brain injury, alcohol, early salicylate poisoning, brain tumor)
- Hypermetabolic states (fever, thyrotoxicosis – increased thyroid)
- Hypoxia (high altitude, pneumonia, heart failure, pulmonary embolism)
- Mechanical overventilation (ventilator rate too fast)

Signs and Symptoms

- Heachache
- Vertigo
- Numbness of fingers, toes, and lips, and twitching of arms
- Tinnitus (ringing in the ears)
- Electrolyte abnormalities (decreased Ca^{2+}, K^{+})

Treatment (while identifying and treating the underlying cause)

- Sedatives or analgesics
- Correction of hypoxia (possible diuretics, mechanical ventilation to also decrease respiratory rate and decrease the tidal volume)
- Antipyretics for fever
- Treat hyperthyroidism
- Breathe into a paper bag (breathe a bit more CO_2) for hyperventilation from acute anxiety only

Metabolic Alkalosis: pH > 7.45, HCO_3^- > 26

Causes: Loss of H^+ or increased HCO_3^-

- Loss of K^+ (diarrhea, vomiting)
- Ingestion of large amounts of bicarbonate (antacids, resuscitation)
- Prolonged use of diuretics (distal tubule lose ability to reabsorb Na^+ and Cl^- therefore NaCl); Ammonia is in the urine and then binds with H^+

Signs and Symptoms: similar to the disease process

- Diaphoresis
- Nausea and Vomiting
- Increase neuromuscular excitability (Ca^{2+} binds with protein)
- Shallow breathing (respiratory compensation)
- EKG changes (increased QT, sinus tachycardia)
- May also see confusion progressing to lethargy to coma
- Electrolyte abnormality (decreased Ca^{2+}), normal or decreased K^+, increased base excess on the ABG

Treatment (while identifying and treating the underlying cause)

- Replace potassium (KCl) losses in 0.9% NaCl (rehydrates and increases HCO_3^- excretion)
- Diamox (acetazolamide, increases HCO_3^- excretion)
- Monitor neurologic status, re-orient, seizure precaution, monitor intake & output

How Do We Measure pH?

How Do We Measure….pH?

TM

- Max Cremer discovers that a potential develops between two liquids of different pH on opposite sides of a thin glass membrane

1906

- First glass pH electrodes are developed but…..

1909

- Arnold Beckman adds an amplifier to better detect the signal and develops the first “acid-o-meter”

1934

Image taken from http://beckman-foundation.com

The pH Electrode

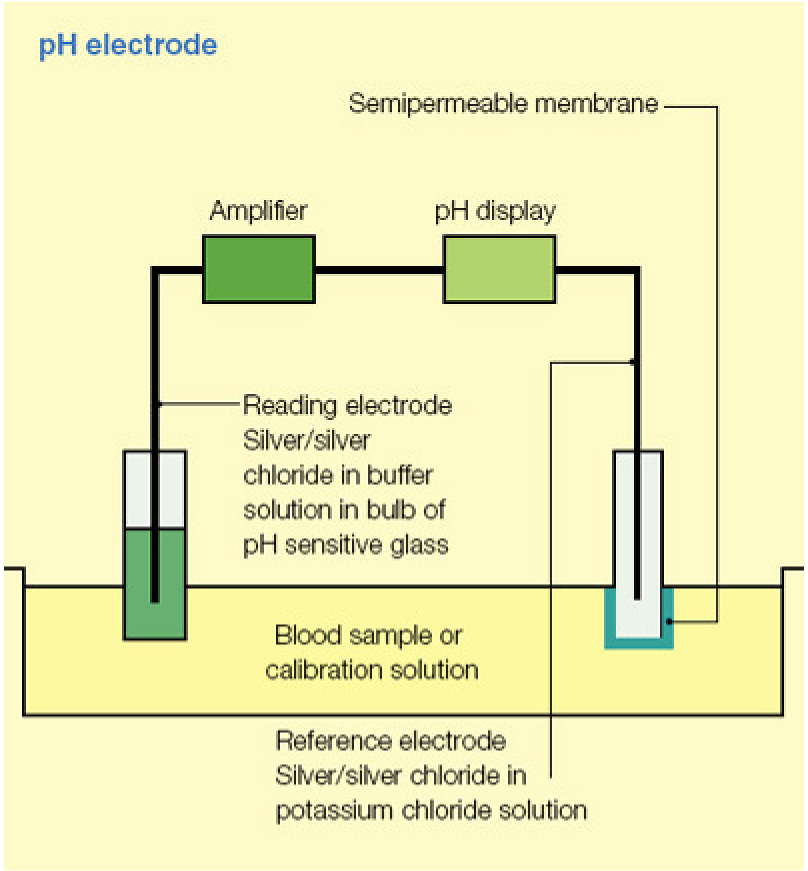
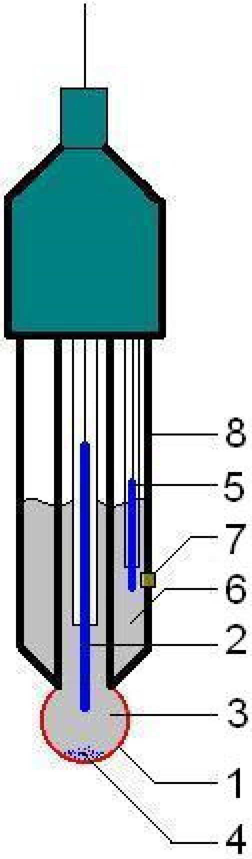


Image taken from Anesthesia UK. www.frca.co.uk



1. Sensing electrode, a bulb of pH sensitive glass
2. Internal electrode, usually silver chloride
3. Internal solution
4. AgCl precipitate
5. Reference electrode
6. Reference internal solution
7. Junction with studied solution, usually made from ceramics
8. Body of electrode, made from non-conductive glass or plastics.

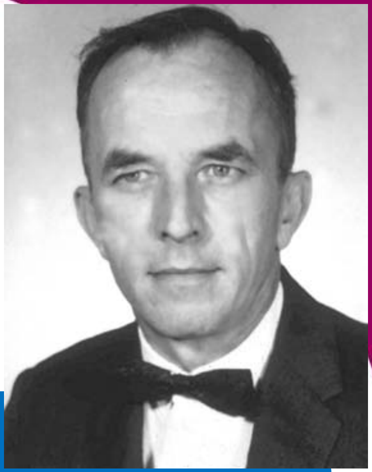
Image taken from (gasp!) Wikipedia

The pCO_2 sensor: 1954

Stow and Randall[1], covered a Beckman pH glass electrode with a cellophane membrane soaked in deionized water and then covered with a thin Teflon (gas permeable) sheet, both kept in place by a rubber band.

Severinghaus and Brandley[2] discovered that $NaHCO_3$ rather than DIW as internal electrolyte optimizes the sensor construction for a specific application (pCO_2 range) and the available pH sensor (specific pH range).

Some sensors are optical using a color change in response to the pH change



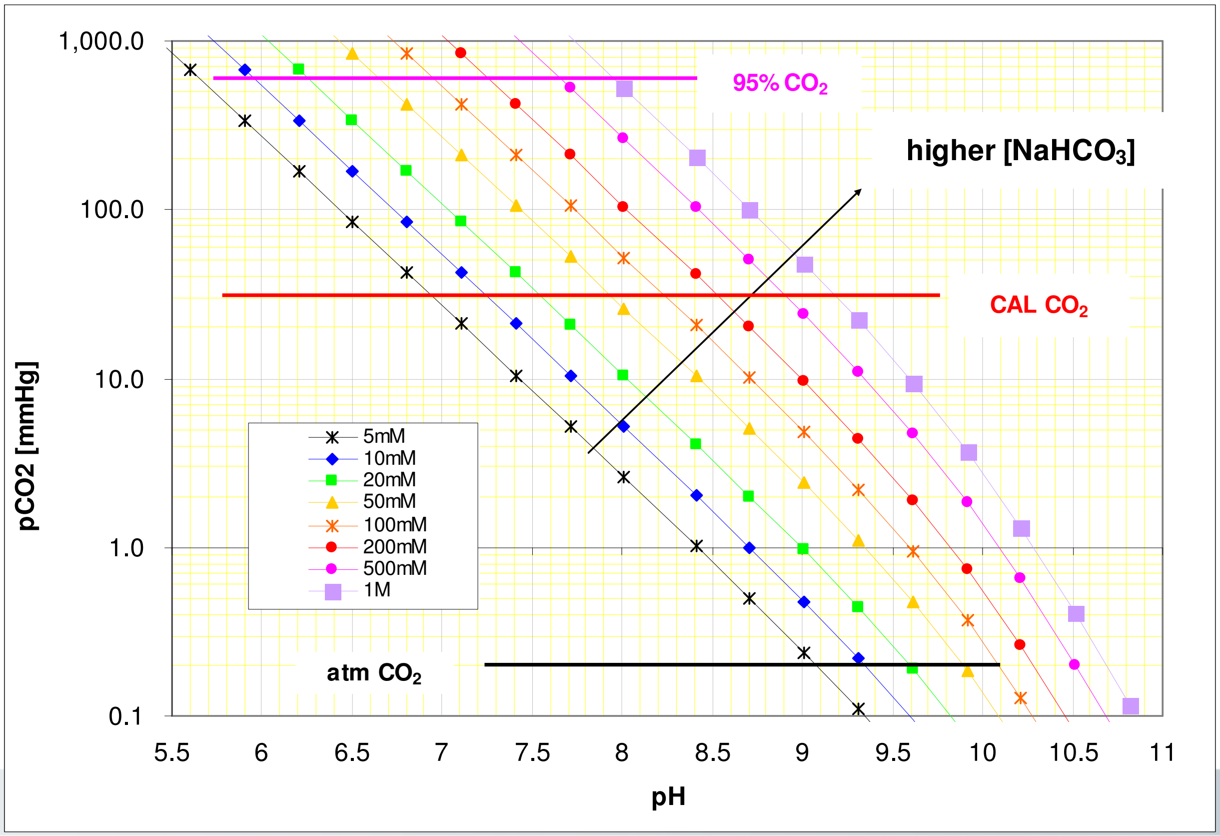
R. W. Stow. From J.W. Severinghaus. J Appl Physiol 2004;97:1599-1600

1. Arch.of Physical Medicine and Rehabilitation (1957), **38:**646-650
2. J.Appl. Physiol., (1958) **13**:515-520

Severinghaus pCO_2 sensor

$H_2O + CO_2 \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^- \rightarrow 2H^+ + CO_3^{2-}$

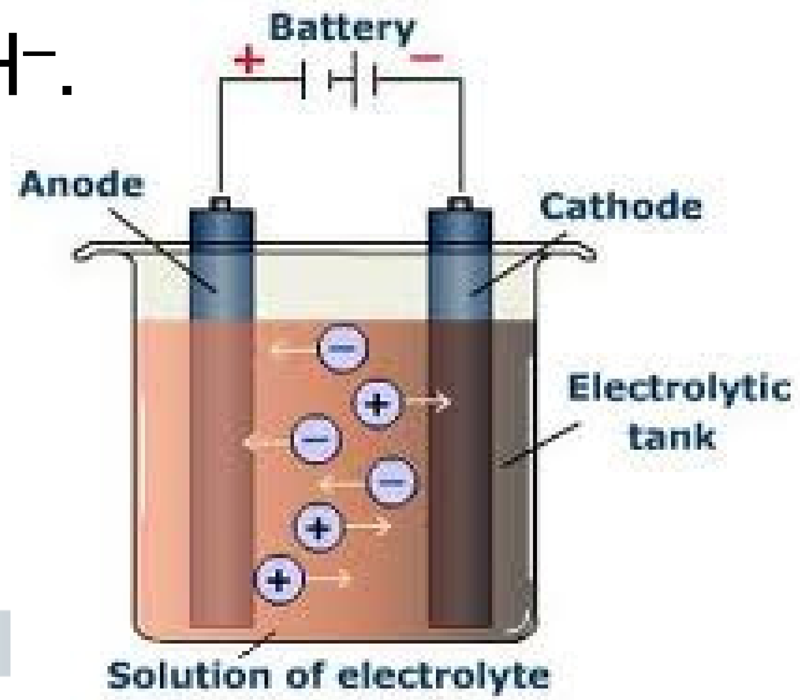
$H_2O + CO_2 + NaHCO_3 \rightarrow H_2CO_3 + NaHCO_3 \rightarrow Na^+ + H^+ + 2HCO_3^- \rightarrow 2H^+ + CO_3^{2-}$



John W. Severinghous
Am. Soc. Anesthesiologists

The *p*O2 sensor: 1897?!?

- Ludwig Danneel showed that oxygen in water is electrolyzed to form OH- at a cathode, generating a current.
- $O_2 + 2H_2O + 4e^{-} = 4OH^{-}$. It would be >50 years before his could be practically measurable.



The *p*O2 sensor: 1954-1956

- A membrane covered electrode with a platinum or gold wire (redox source) melted into a glass rod.
  - At the cathode: $O_2 + 2H_2O + 4e– = 4OH–$.
  - In the electrolyte: NaCl + OH– = NaOH + Cl
  - At the anode: Ag + Cl– = AgCl + e–.s

Leland Clark, Jr., Image taken from Am. Soc. Anesthesiologists

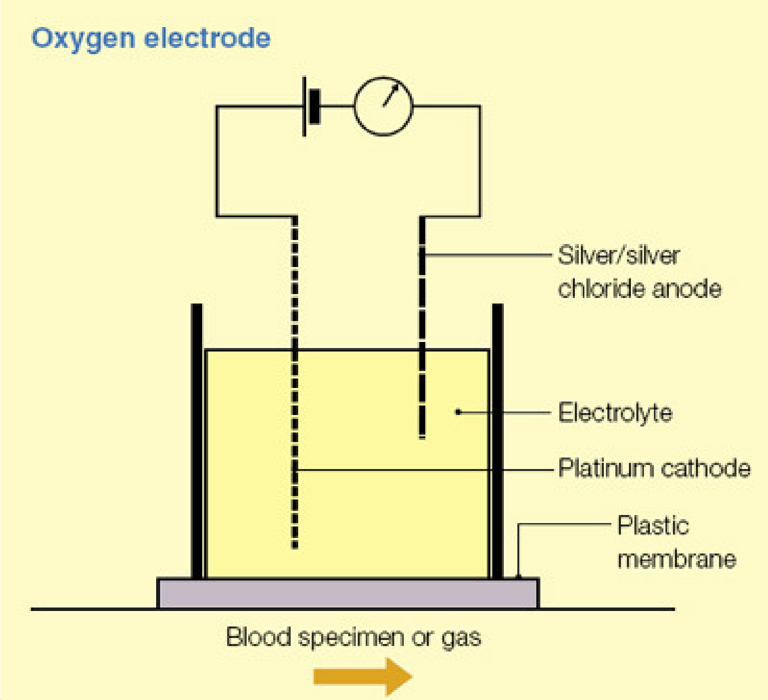


Image taken from Anesthesia UK. www.frca.co.uk

Blood Gasses

- pH
- pO_2
- pCO_2

Electrolytes

- iCa^{++}
- Na^+
- K^+
- Cl^+

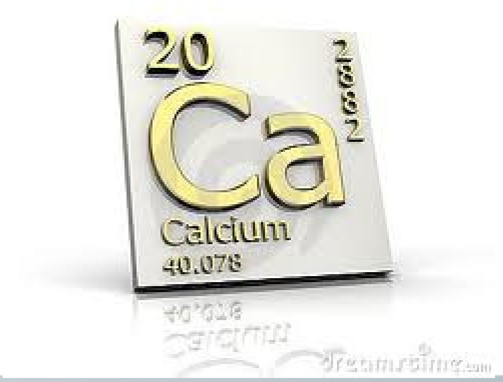
Why Do We Measure: iCa^{2+}

Calcium is essential for myocardial contraction.

Also an important 2nd messenger in regulation of many hormones: insulin, aldosterone, vasopressin, renin, etc.

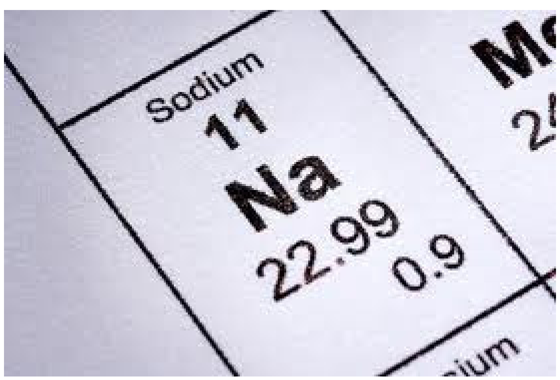
Hypercalcemia → general lethargy and can effect multiple organ systems: heart, GI muscle, kidneys, etc.

Hypocalcemia → cardiovascular disorders



Why Do We Measure: Na^+

- Sodium anions account for ~90% of the osmotic activity in plasma.
- Essential in nerve impulse transmission and muscle contraction
- Also used as a dehydration surrogate.

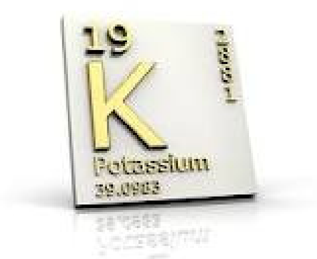


Hypernatremia →general weakness and mental confusion. Paralysis at very low levels.

Hyponatremia → less common. Cerebral dehydration can lead to bleeding, coma and death

Why Do We Measure: K^+

- Potassium is the major intracellular cation.
- Essential in
  - Regulation of neuromuscular excitability
  - Contraction of the heart and cardiac rhythm
  - Regulation of intracellular and extracellular volume and acid-base status

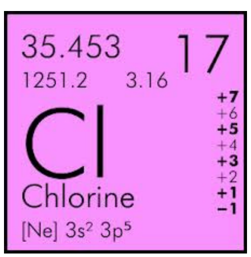


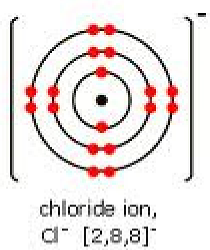
↑ Hyperkalemia → Muscle weakness, cardiac arrhythmias, possible cardiac arrest

↓ Hypokalemia → Muscle weakness (?!?), irritability, paralysis, cardiac abnormalities.

Why Do We Measure: Cl^-

- Chloride is the major intracellular anion.
- Functions with Na^+, K^+ and other cations in conduction and transport functions between cells and across membranes

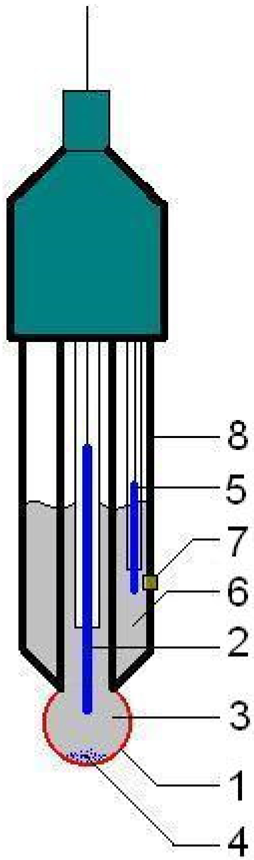




Hyperchloremia → often accompanies loss of bicarbonate or hypernatremia

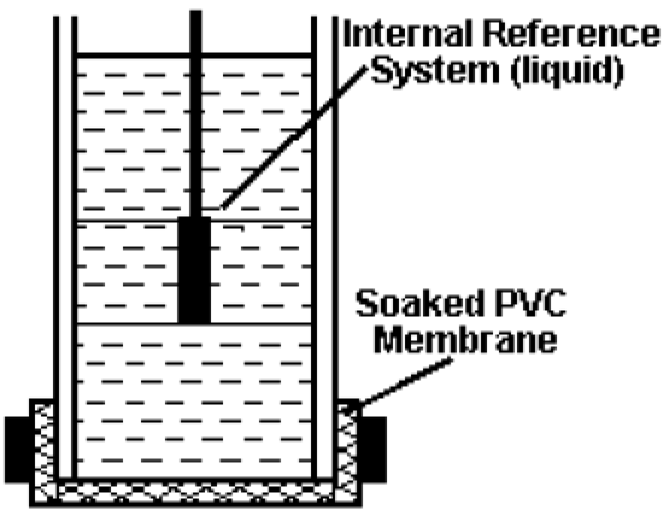
Hypochloremia → metabolic alkalosis.

How Do We Measure Electrolytes?

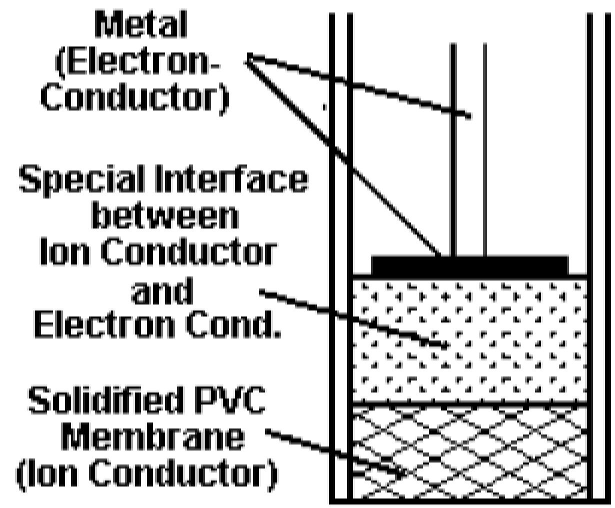


1. Sensing electrode, a bulb covered with an ion permeable membrane
2. Internal electrode
3. Internal solution
4.
5. Reference electrode
6. Reference internal solution
7. Junction with studied solution
8. Body of electrode, made from non-conductive glass or plastics.

Ion Selective Electrodes

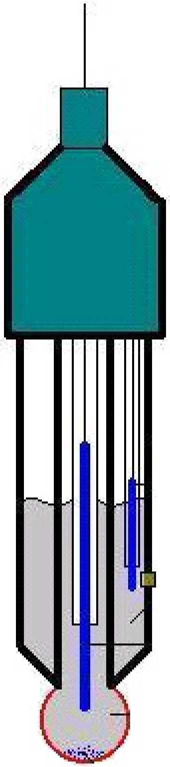


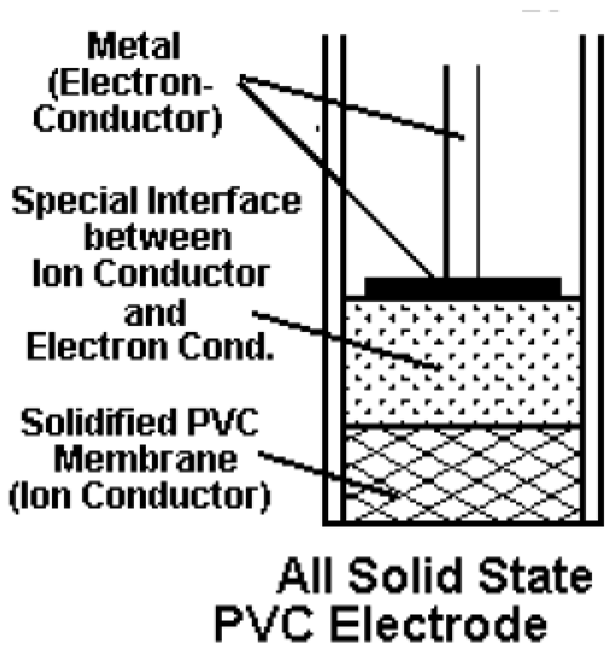
Conventional PVC
Membrane Type



All Solid State
PVC Electrode

Chris C Rundle BSc, PhD. A Beginners Guide to Ion-Selective Electrode Measurements. http://www.nico2000.net/Book/Guide1.html




Metal
(Electron-
Conductor)
Special Interface
between
Ion Conductor
and
Electron Cond.
Solidified PVC
Membrane
(Ion Conductor)
All Solid State
PVC Electrode

Benchtop Analyzers

Radiometer ABL800 FLEX®

Siemens RAPIDLab® 1200

IL GEM® Premier™ 4000

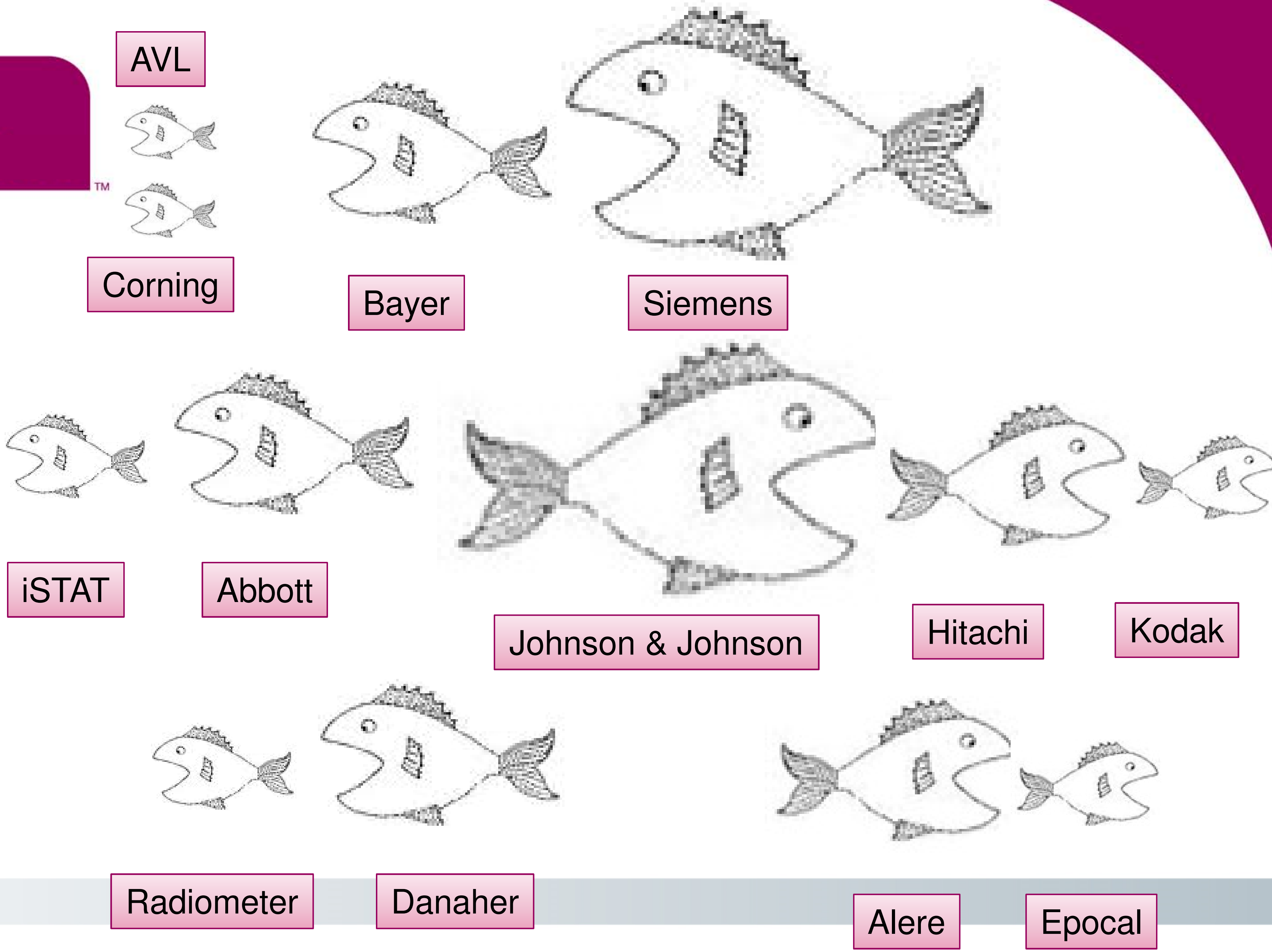
Benchtop Advancements

- Miniaturization and "cartridgization" of the electrodes.
- Small sample size
- Facilitation of the storage and re-equilibration requirements
- Alignment of the electrodes in one fluidic channel for
  - Sampling
  - Conditioning
  - Decontamination
- Data processing

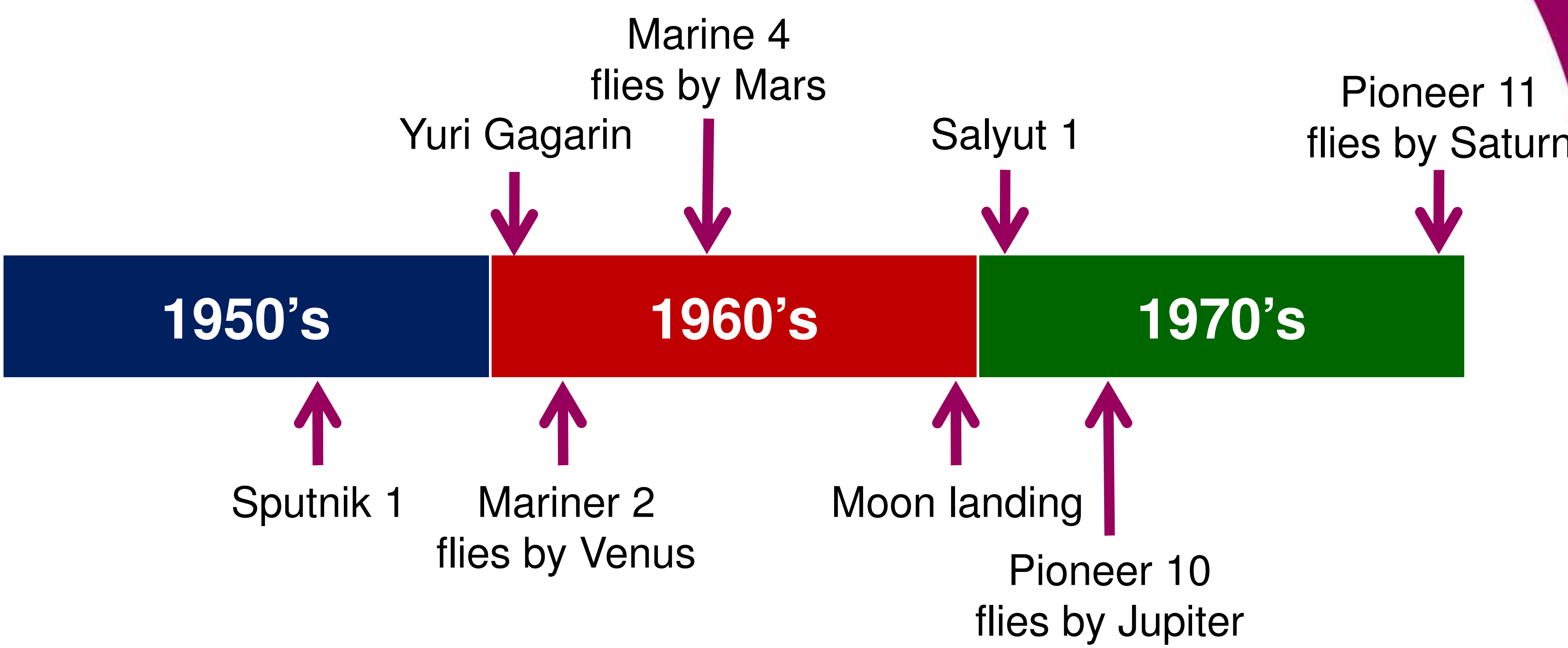
Added features on benchtops

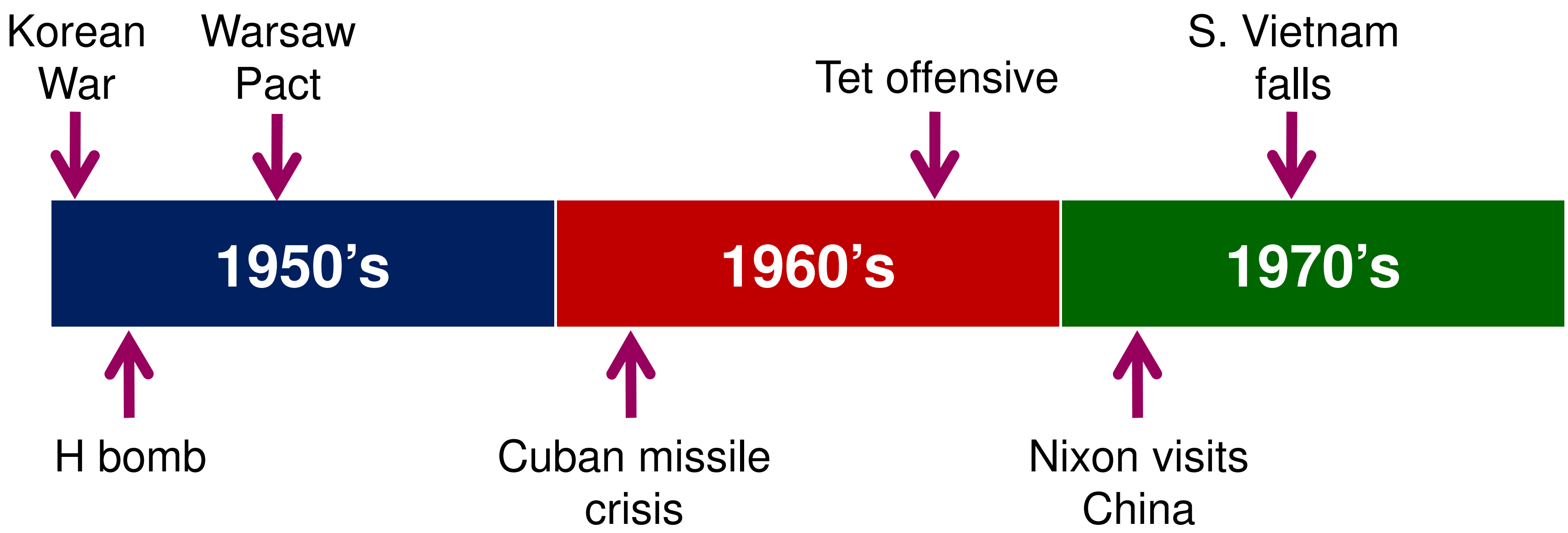
TM

- Metabolites: creatinine, BUN
- Cooximetry
- Hematology
- Small sample size
- On-board QC
- Connectivity


AVL
Corning
Bayer
Siemens
iSTAT
Abbott
Johnson & Johnson
Hitachi
Kodak
Radiometer
Danaher
Alere
Epocal

1950's	1960's	1970's


Marine 4
flies by Mars
Yuri Gagarin
Salyut 1
Pioneer 11
flies by Saturn
1950's
1960's
1970's
Sputnik 1
Mariner 2
flies by Venus
Moon landing
Pioneer 10
flies by Jupiter


Korean War
Warsaw Pact
Tet offensive
S. Vietnam falls
1950's
1960's
1970's
H bomb
Cuban missile crisis
Nixon visits China

ARPANET (Internet Predecessor)

UNIVAC

1st computer game

Apple

1950's | **1960's** | **1970's**

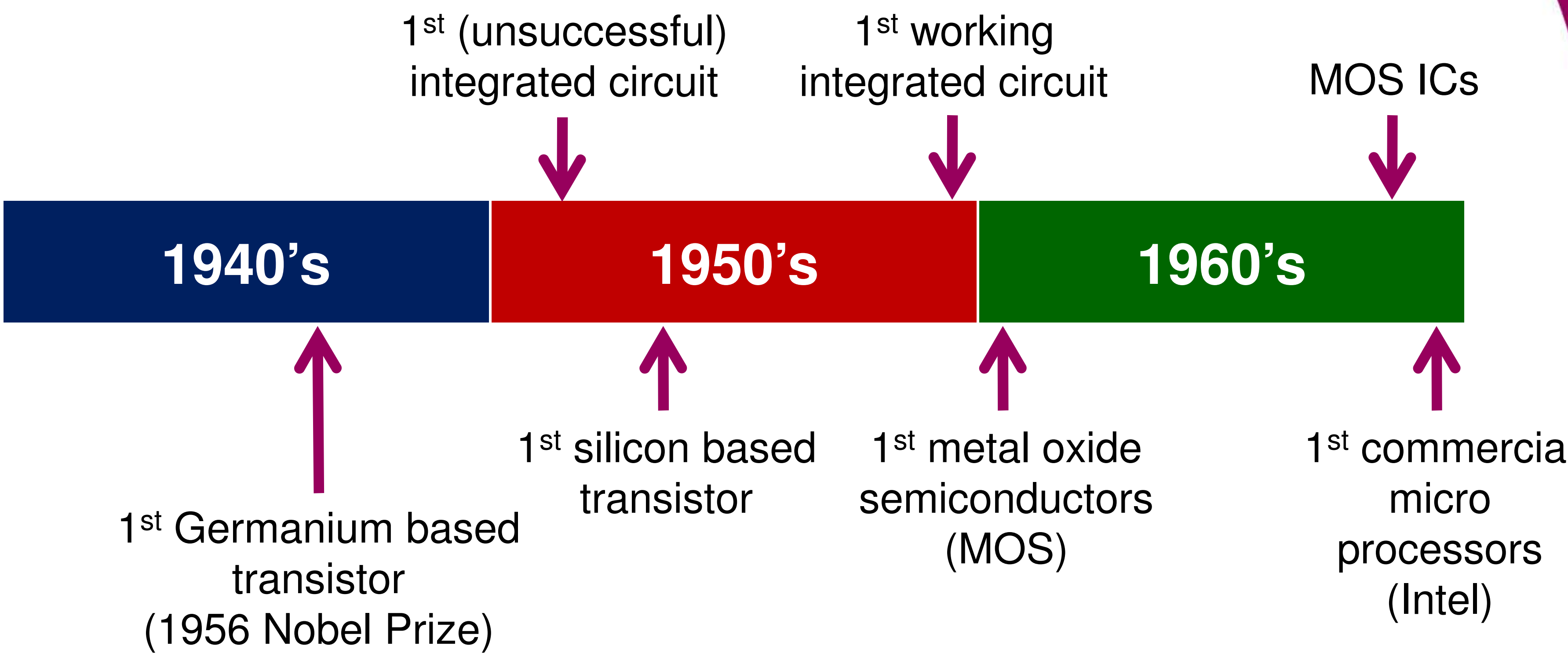
Fortran

Mouse concept

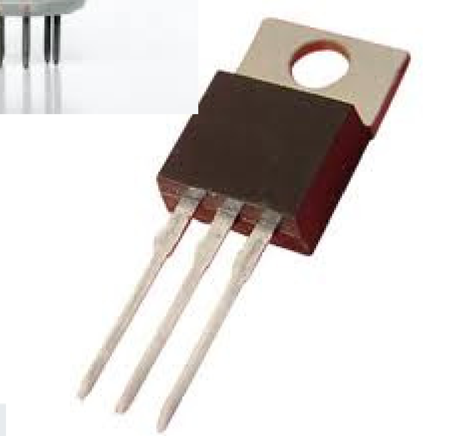
Microsoft

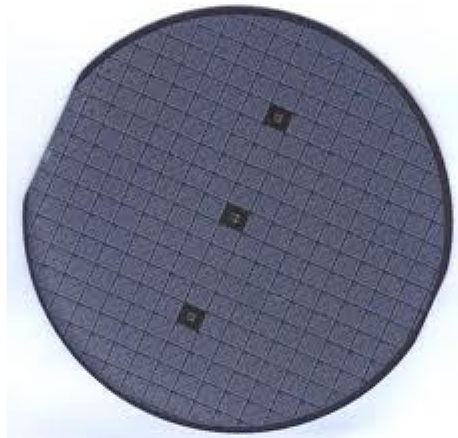
Aug 29, 1997 02:14 EDT Skynet becomes self-aware

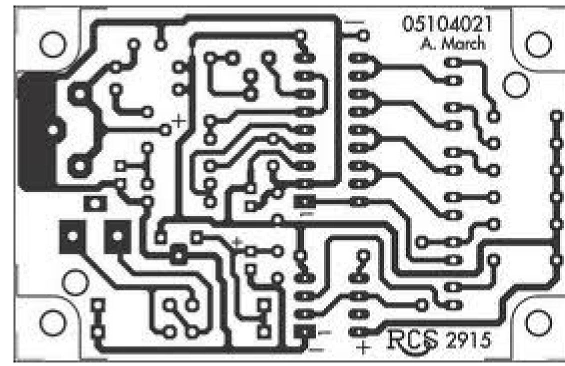
1907 Vacuum tubes (diodes, amplifiers based on vacuum tubes)
1925-1935 the first solid state devices



1940's to 1980's



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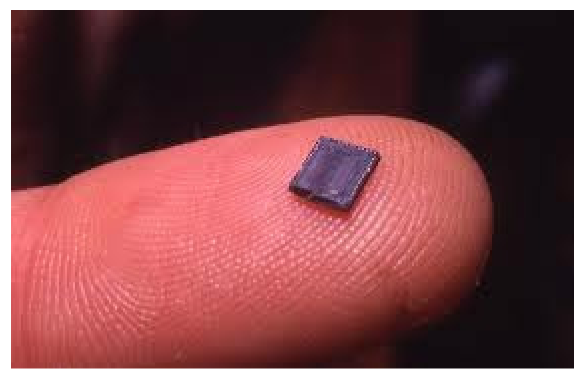
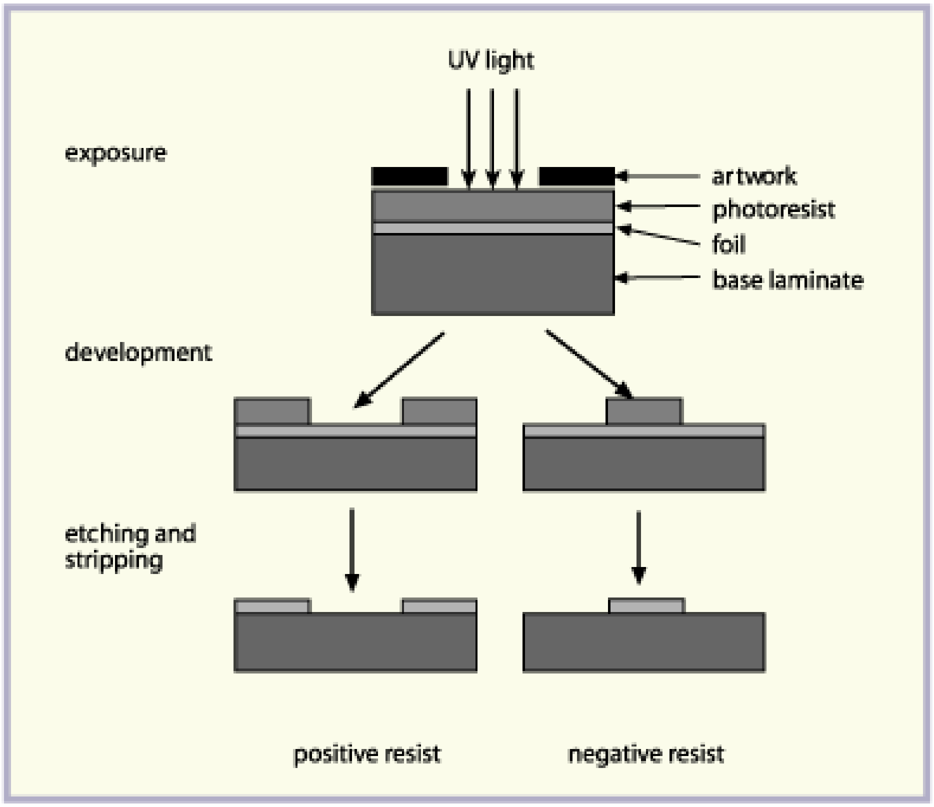


Photolithography



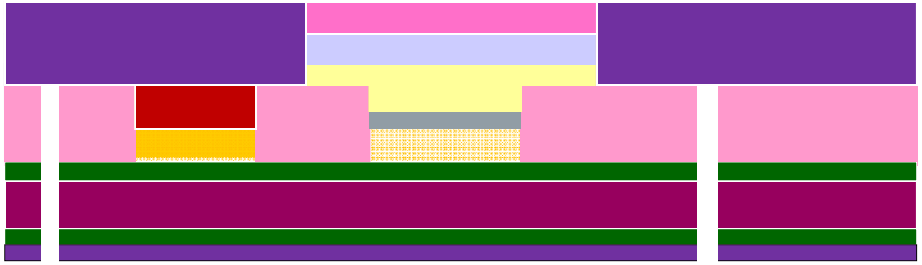
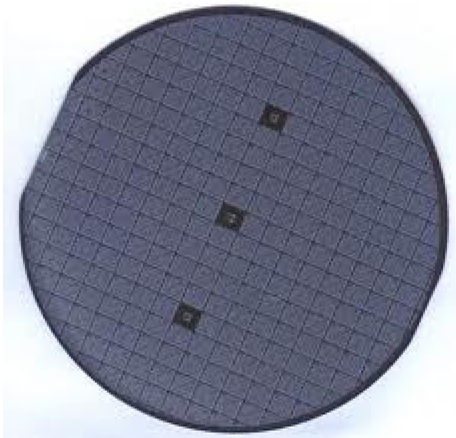
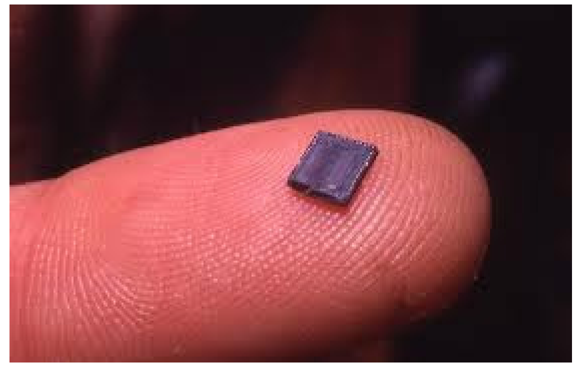


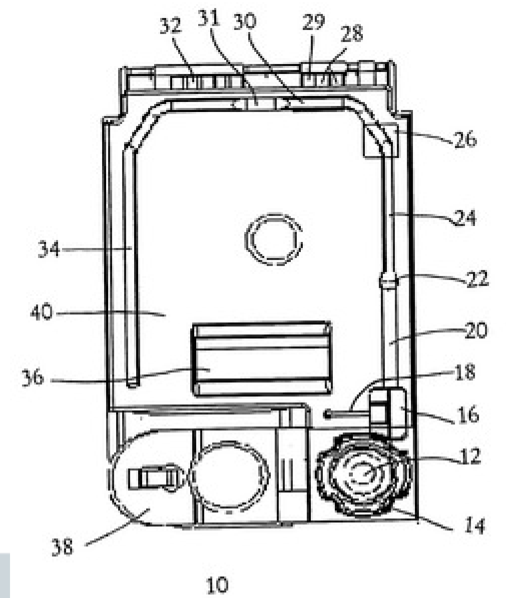
Image from http://www.ami.ac.uk/courses/topics/0224_img/index.html


i-STAT
CG8+
i-STAT
EG7+
i-STAT
6+

Imants Lauks-iSTAT in 1983







Cartridge drawing from US Patent 6,750,053 B1

iSTAT ushers in POC Testing

- No delay in results
- Faster clinical decision making
- More efficient testing/treatment processes
- No conditioning or decontamination of the electrodes

Testing Cartridges for the *i-STAT® System*: A Comprehensive Menu of Tests in a Single Platform

● Chemistries/Electrolytes ● Hematology ● Blood Gases ● Coagulation ● Cardiac Markers ■ Granted waived status for the *i-STAT 1 System with venous whole blood samples collected in a sodium or lithium heparin evacuated tube*

i-STAT Cartridges

	EC8+	CG8+	EG7+	CHEM8+	EG6+	CG4+	6+	G3+	EC4+	E3+	G	Crea	ACTk	ACTc	PT/INR	cTnI	CK-MB	BNP
Sodium (Na)	●	●	●	●	●		●		●	●								
Potassium (K)	●	●	●	●	●		●		●	●								
Chloride (Cl)	●			●			●											
TCO_2				●														
Anion Gap*	●			●														
Ionized Calcium (iCa)		●	●	●														
Glucose (Glu)	●	●		●			●		●		●							
Urea Nitrogen (BUN)/Urea	●			●			●											
Creatinine (Crea)				●								●						
Lactate						●												
Hematocrit (Hct)	●	●	●	●	●		●		●	●								
Hemoglobin* (Hgb)	●	●	●	●	●		●		●	●								
pH	●	●	●		●	●		●										
PCO_2	●	●	●		●	●		●										
PO_2		●	●		●	●		●										
TCO_2*	●	●	●		●	●		●										
HCO_3*	●	●	●		●	●		●										
Base Excess (BE)*	●	●	●		●	●		●										
sO_2^		●	●		●	●		●										
ACT Kaolin													●					
ACT Celite®														●				
PT/INR															●			
cTnI																●		
CK-MB																	●	
BNP																		●

1980’s to 21st century

™


i-STAT


epoc

Epocal

2002-Dr. Varlan joins Epocal

2006-epoc system launched

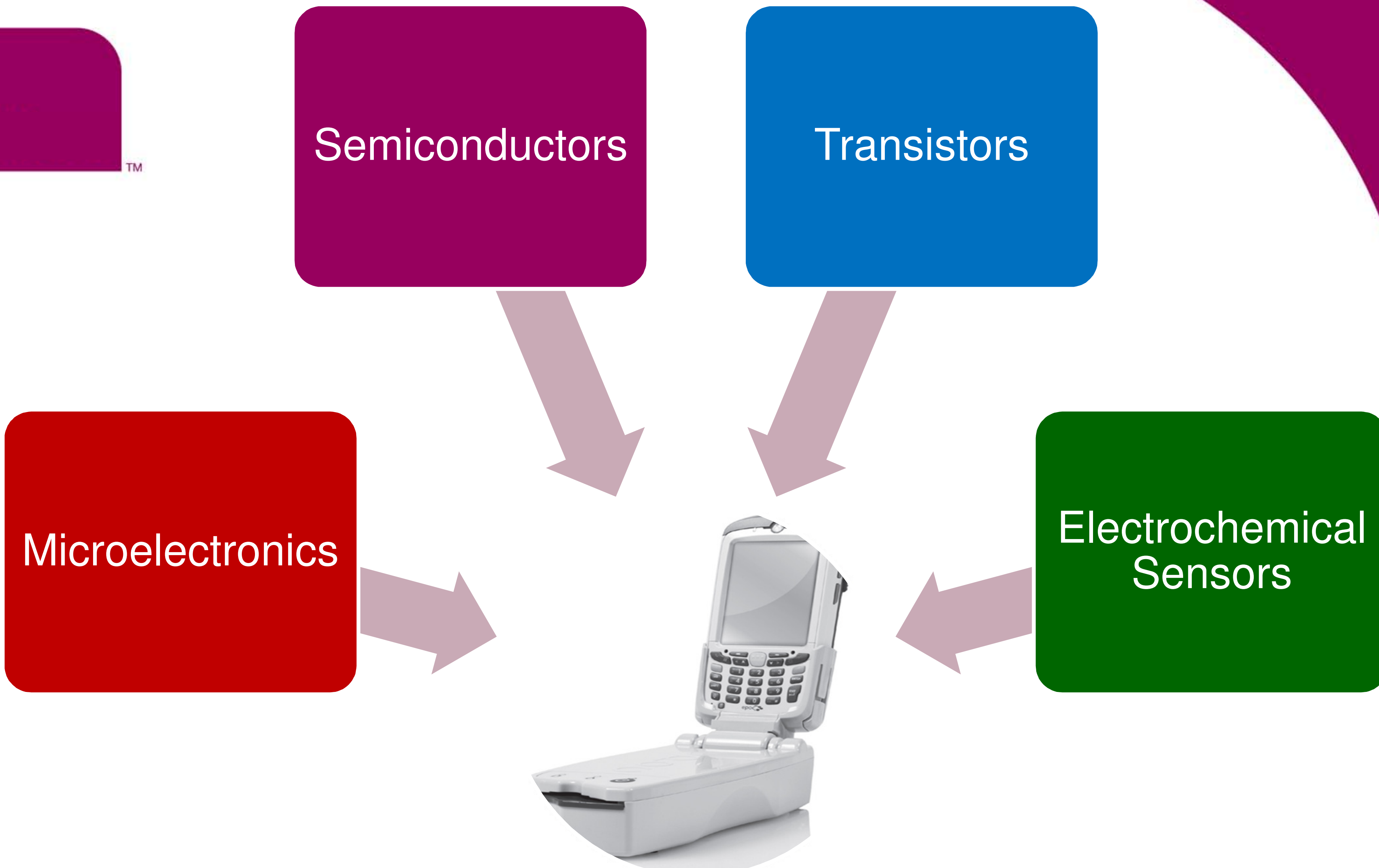
1999-Dr. Lauks leaves iSTAT

2001-Dr. Lauks founds Epocal

2011-Epocal/Alere collaboration begins

epoc®

BLOOD ANALYSIS

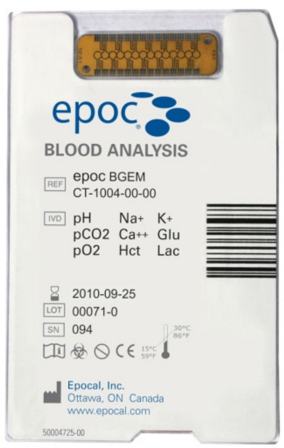

Semiconductors
Transistors
Microelectronics
Electrochemical Sensors

epoc System Components

™

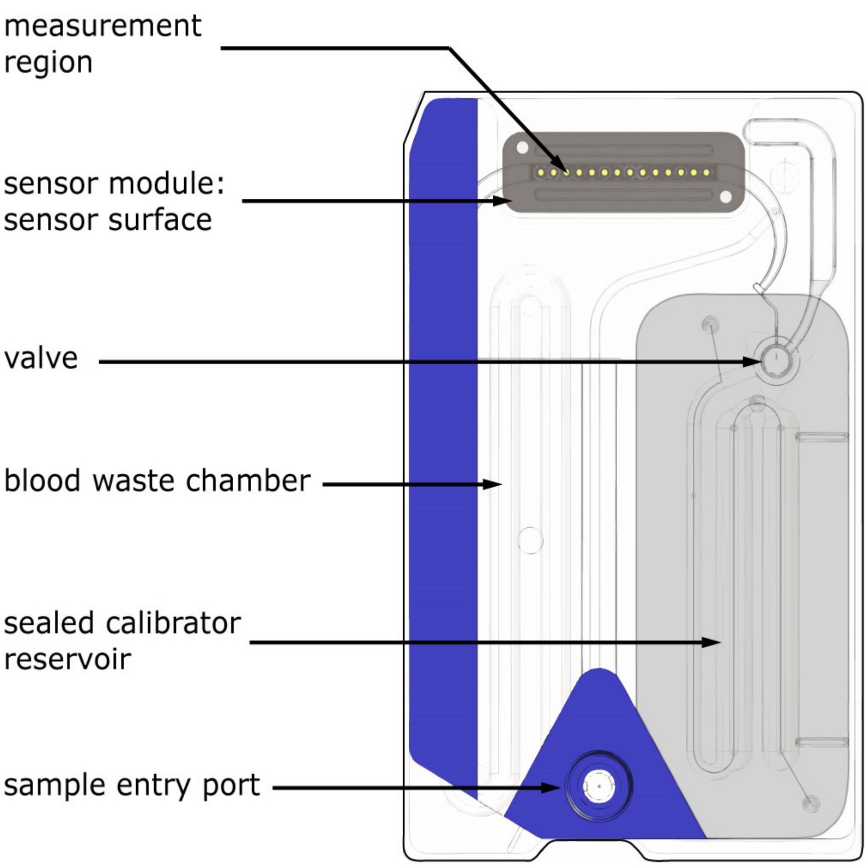
epoc®
BLOOD ANALYSIS

- epoc Host Mobile Computer
- epoc Reader
- epoc Test Card

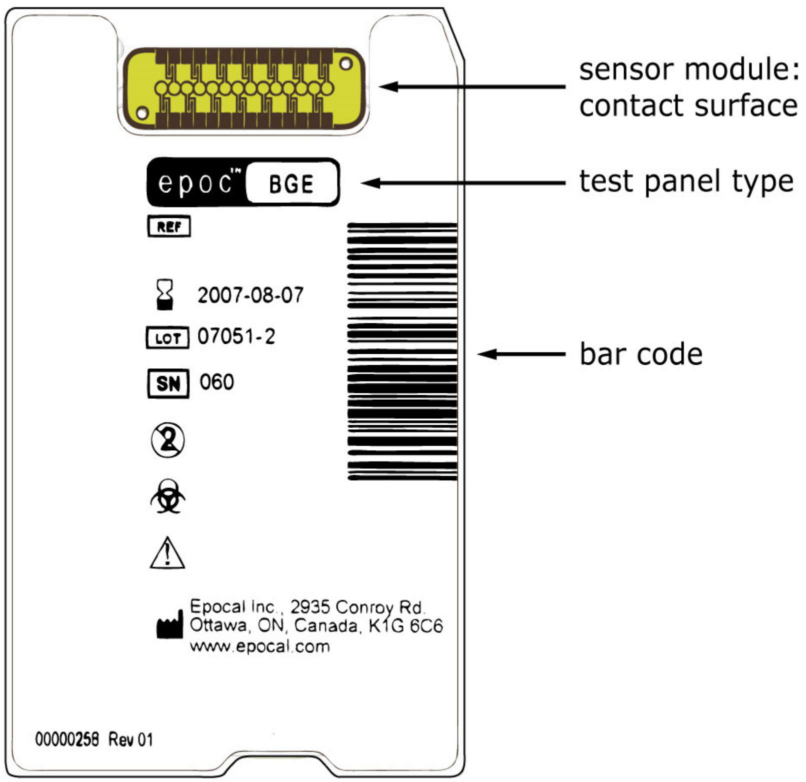


- epoc Data Manager (not shown)

Epocal's FlexCard™



TEST CARD - TOP

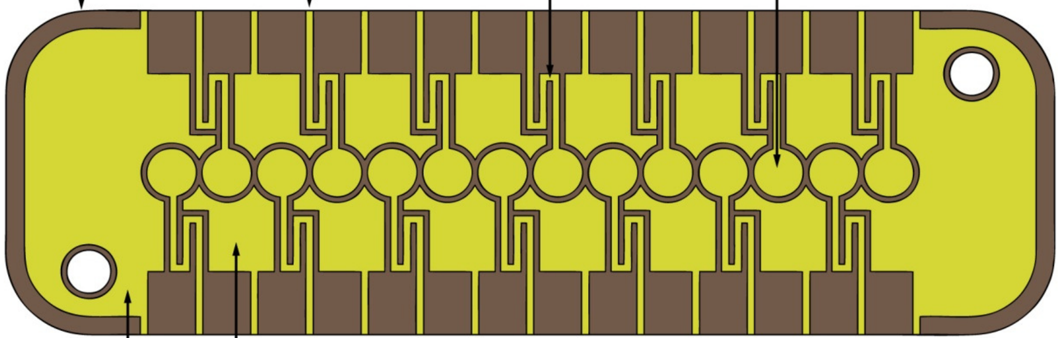


TEST CARD - BOTTOM

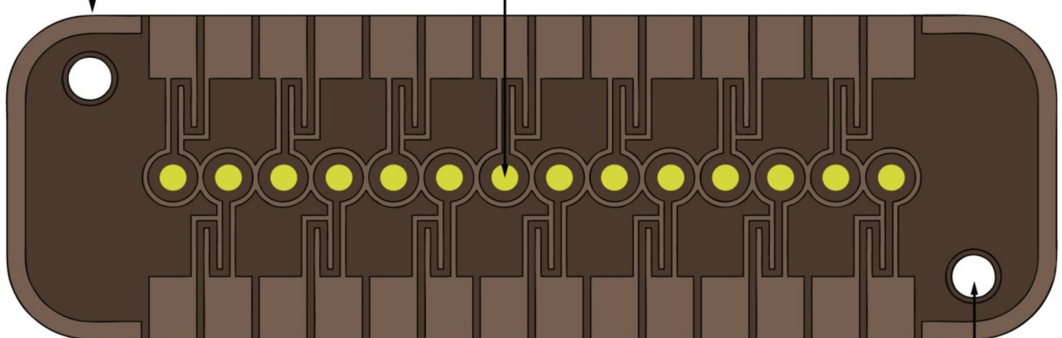
Analyte Sensor Module

Smart Card Technology™

ELECTRODE CONTACT SURFACE OF THE MODULE



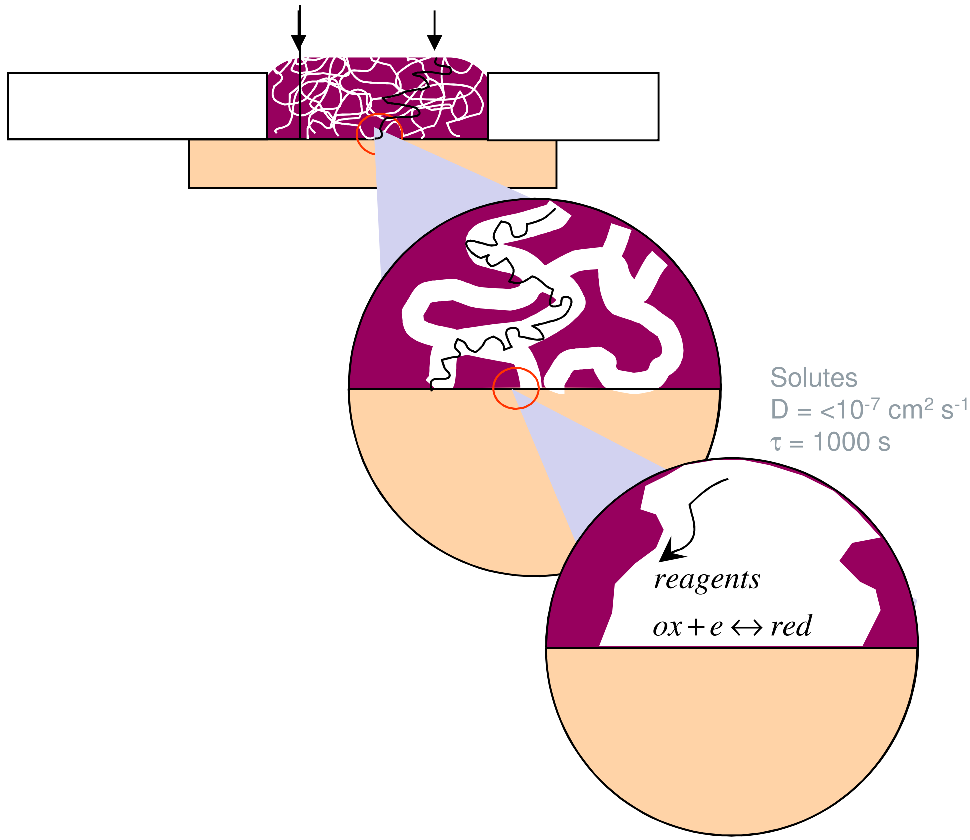
SENSOR SURFACE OF THE MODULE



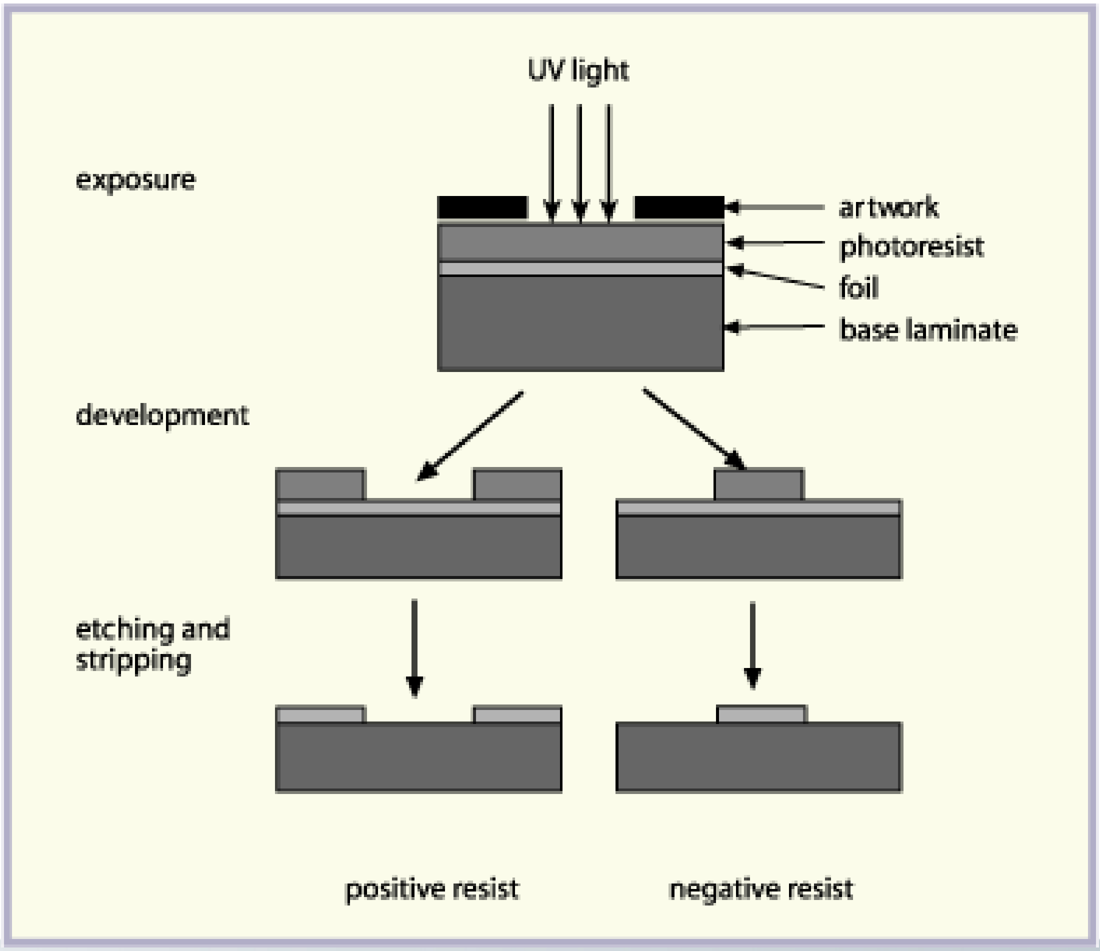
Heterogeneous Membranes

Epocal developed the concept of a heterogenous membranes with hydrophobic and hydrophilic compartments with differential gas and ion diffusion rates.

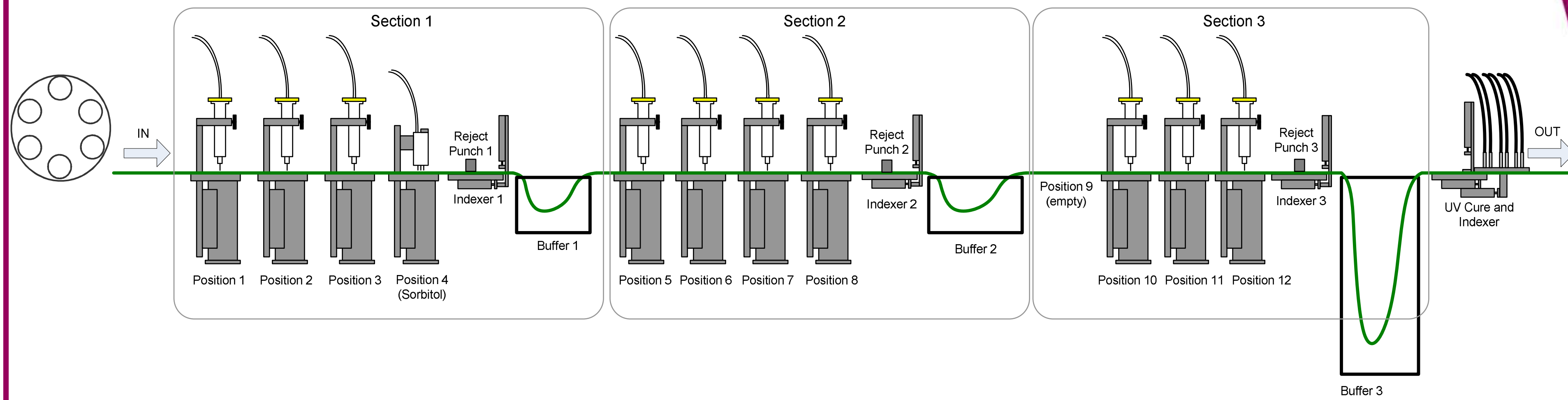
This permits dispensing materials from syringes to make sensors without resorting to costly microfabrication.

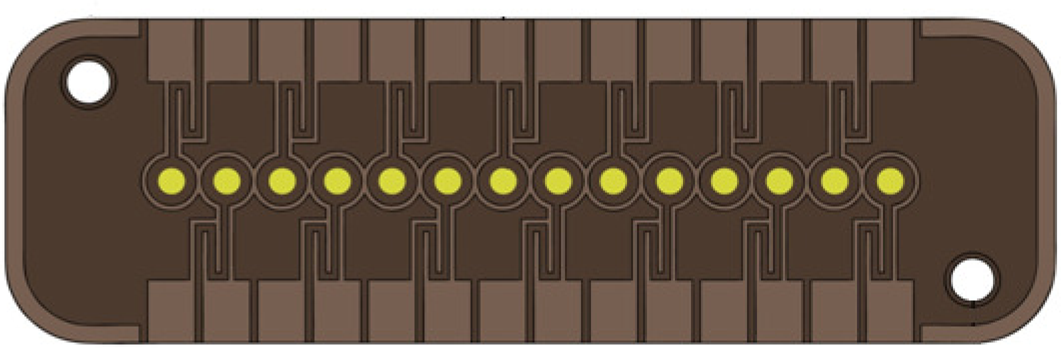


From this….

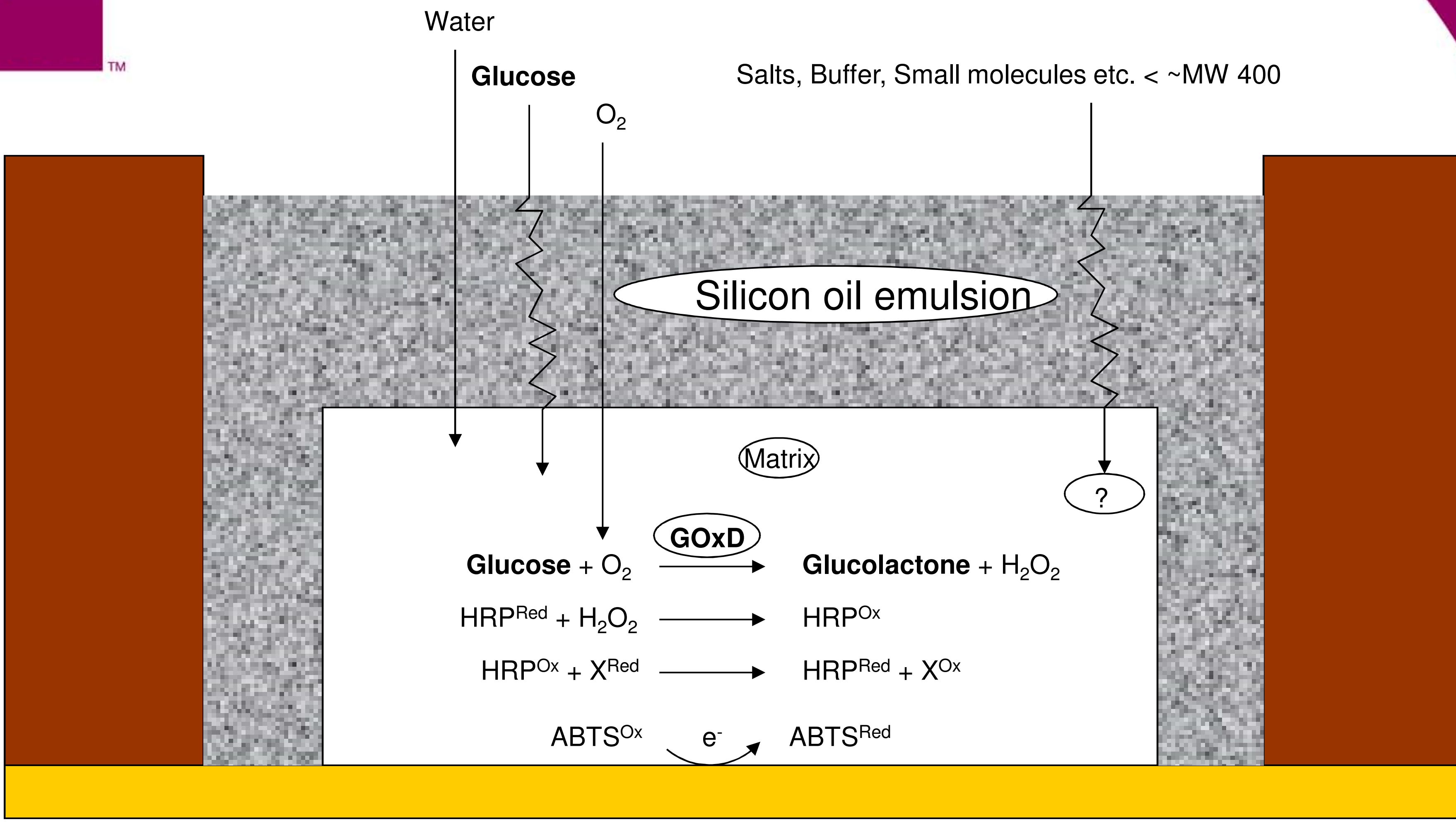

UV light
exposure
artwork
photoresist
foil
base laminate
development
etching and
stripping
positive resist
negative resist

To this


Section 1
Section 2
Section 3
IN
OUT
Reject
Punch 1
Indexer 1
Buffer 1
Position 1
Position 2
Position 3
Position 4
(Sorbitol)
Reject
Punch 2
Indexer 2
Buffer 2
Position 5
Position 6
Position 7
Position 8
Position 9
(empty)
Reject
Punch 3
Indexer 3
Position 10
Position 11
Position 12
Buffer 3
UV Cure and
Indexer



Glucose sensor

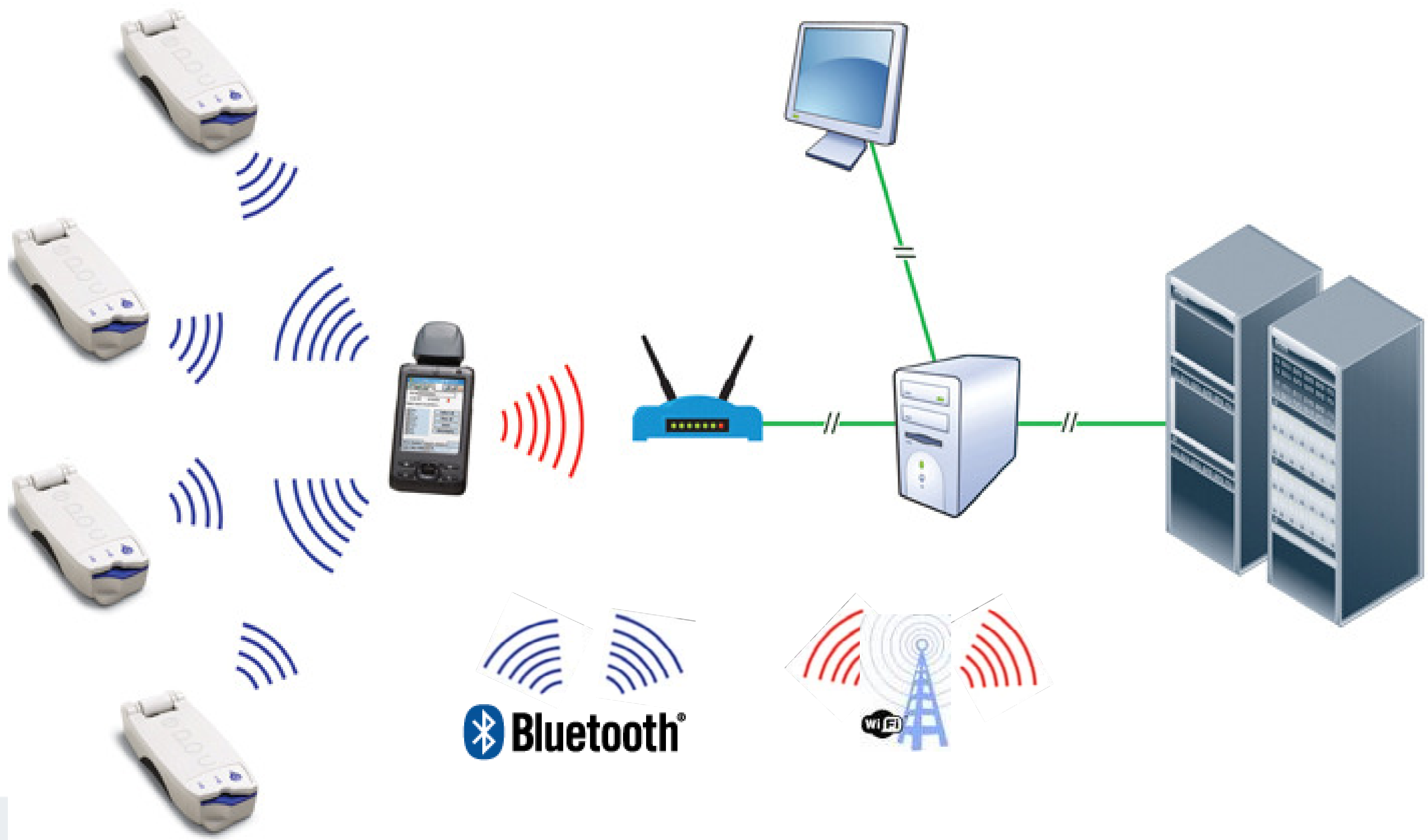


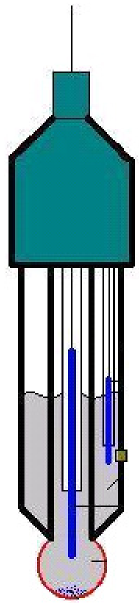
GOxD = Lactate Oxidase

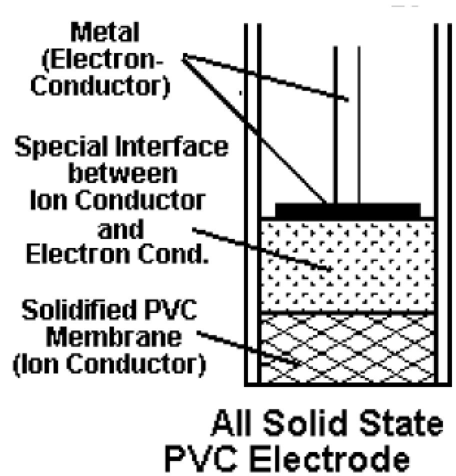
HRP = Horseradish Peroxidase

Conductometric sensor as a fluidic control

epoc Wireless Communication

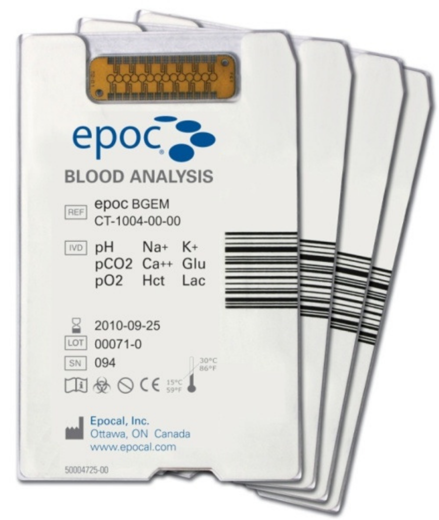




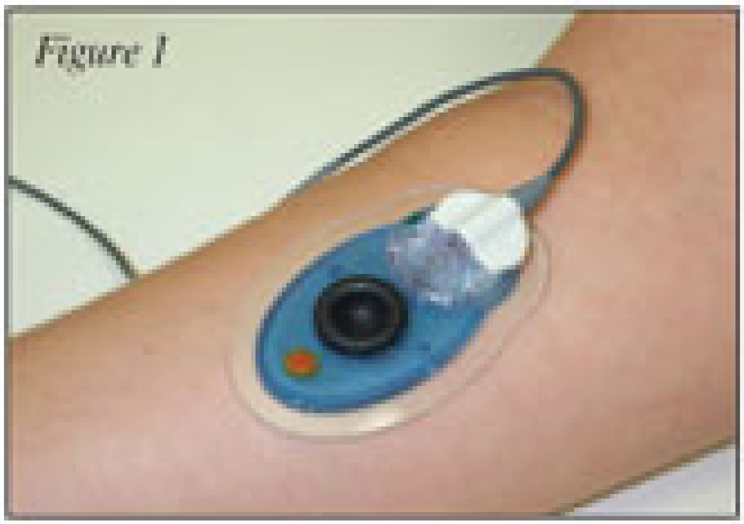


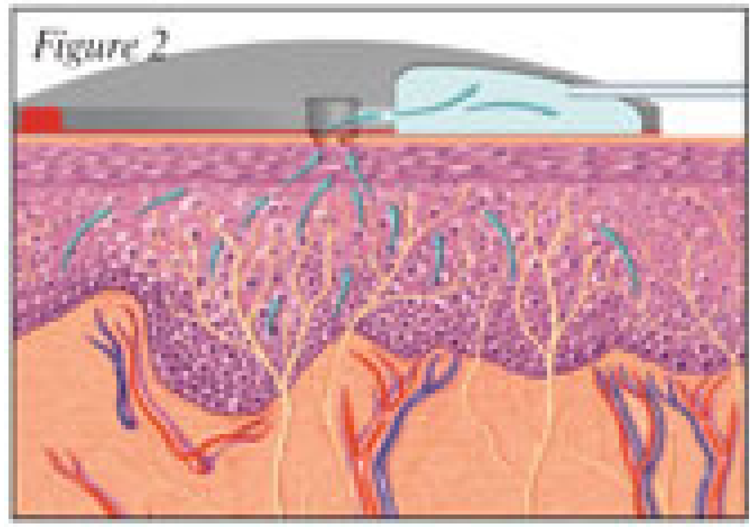
Metal (Electron-Conductor)
Special Interface between Ion Conductor and Electron Cond.
Solidified PVC Membrane (Ion Conductor)
All Solid State PVC Electrode

i-STAT CG8+
i-STAT EG7+
i-STAT 6+



epoc
BLOOD ANALYSIS
epoc BGEM
CT-1004-00-00
pH Na+ K+
pCO2 Ca++ Glu
pO2 Hct Lac
2010-09-25
00071-0
094
Epocal, Inc.
Ottawa, ON Canada
www.epocal.com



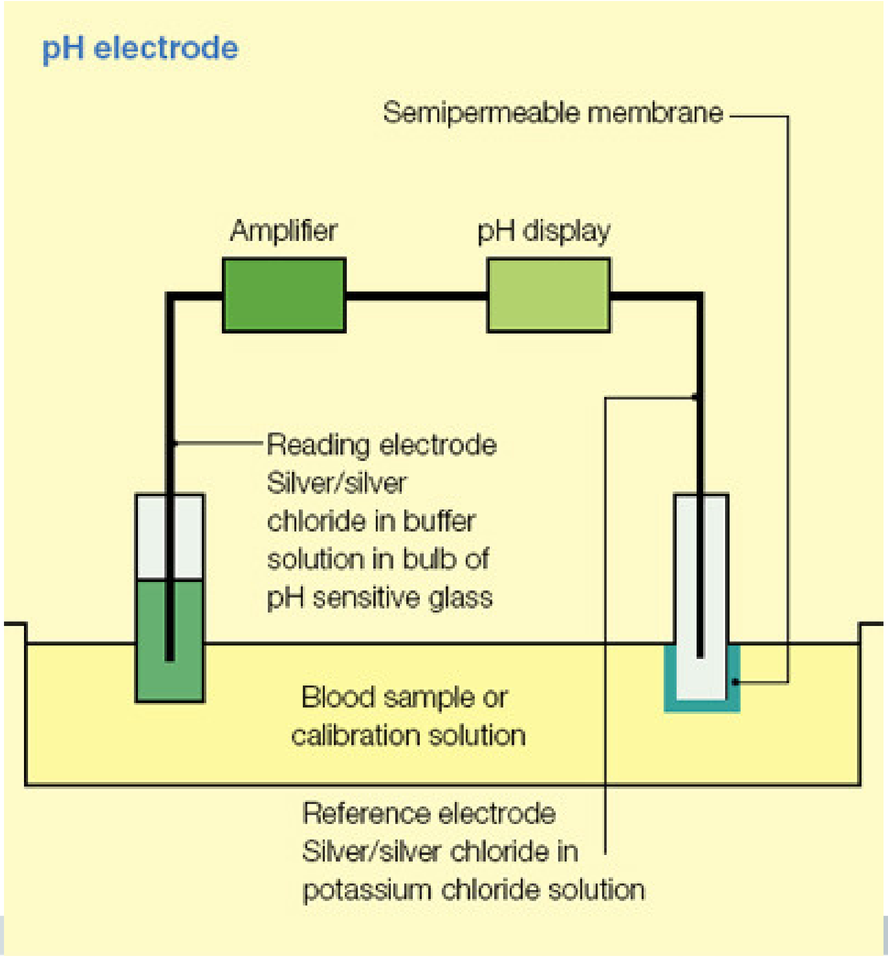


SpectRx's Real-Time Glucose-Sensing System monitors levels of glucose in transdermal fluid.

It's All About Potential

- Max Cremer discovers that a potential develops between two liquids of different pH on opposite sides of a thin glass membrane

1906



Questions?

Thank You!

Today is the youngest you'll be for the rest of your life. Act like it.