Acid-base chemistry and its disturbances

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System of the presentation

- Difficult subject?
- Gradual steps → good understanding, building on what I already know
- Active learning:
  - Slide with questions to solve – give it time, try to find solutions by yourself
  - Minimum time is below
  - Answers – mostly next slide
- Why active learning?
  - Greater joy and interest (in the end)
  - Deeper knowledge
  - Remembering longer

  ➔The extra effort pays off

Acid-base Chemistry and Physiology Refresher

(hopefully)

Hydrogen ions

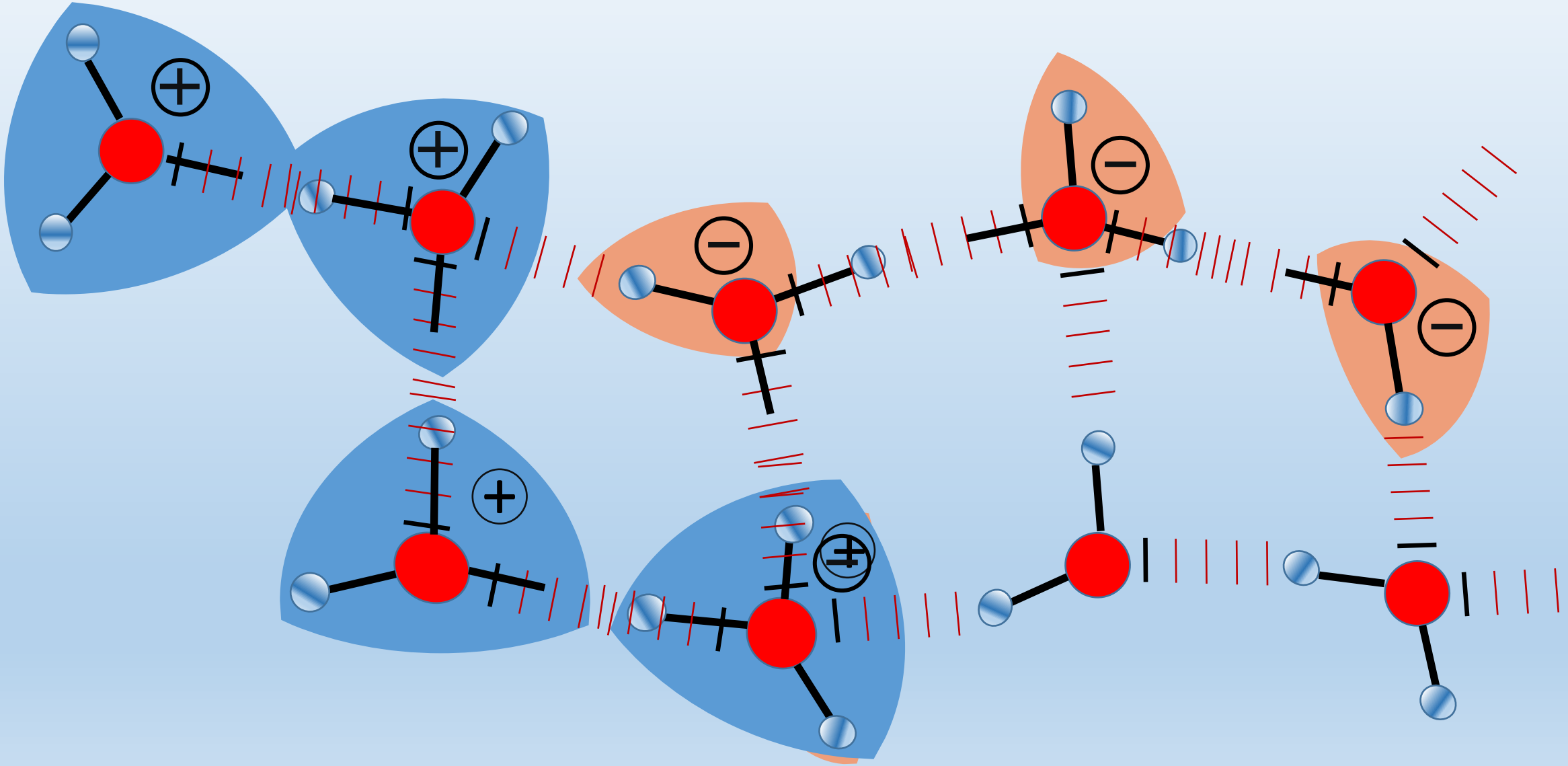
- Is the concentration of hydrogen ions in extracellular fluid (ICF) small, large, huge or minuscule?
- Why is maintaining H^+ concentration within narrow limits much more important than maintaining strict concentrations of let's say iodine or zink[1]?
- Is it more accurate to speak of H_3O^+ or H^+? Why?
- What is a hydrogen bond (H bond)?
- Is there more H_3O^+ or OH^- in plasma under physiological conditions?
- Minimum time: 2 min

1.Hint: Focus on properties of certain biomolecules as well as properties of water itself.

Hydrogen ions

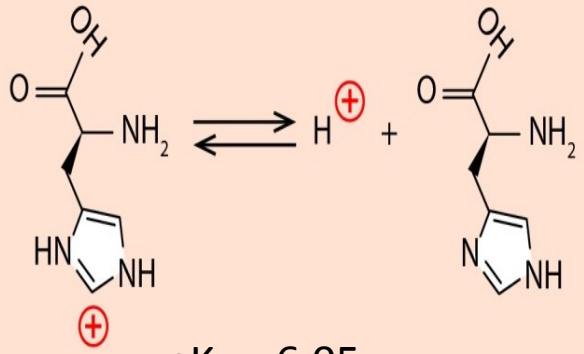
- Concentration of H^+ = $[H^+]$ ~ **1 000 000x** << $[Na^+]$ – minuscule
- Maintaining pH within tight limits is important because of very large reactivity of H^+ and its effect on the conformation of many macromolecules, especially proteins.
- Hydrogen bond – special type of weak chemical bond created by H^+; it binds H_20 molecules together →liquefaction of water
- $pH_{plasma,Norm} \approx 7,4 > 7,0 \rightarrow$ alkaline pH → $[OH^-] > [H3O^+]$

Dynamics of H_3O^+ and OH^- movement in water



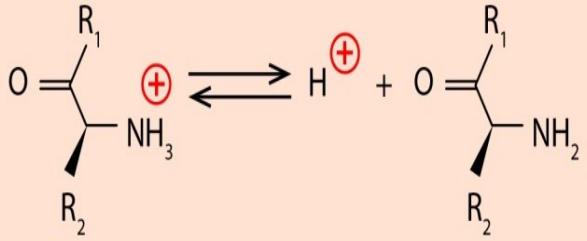
Amino-acid charge and protein conformation

Histidine side chain



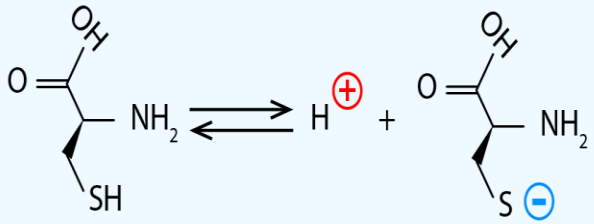
$pK_A = 6,05$

Amino terminus



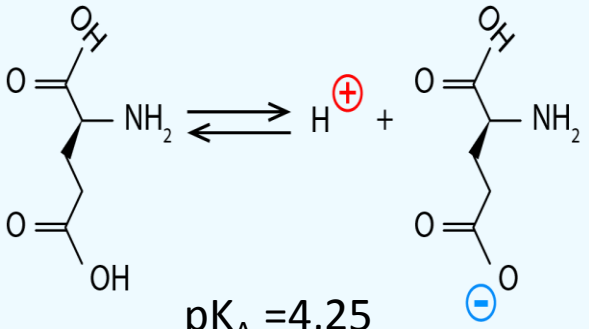
$pK_A = 9,2$

Cysteine:

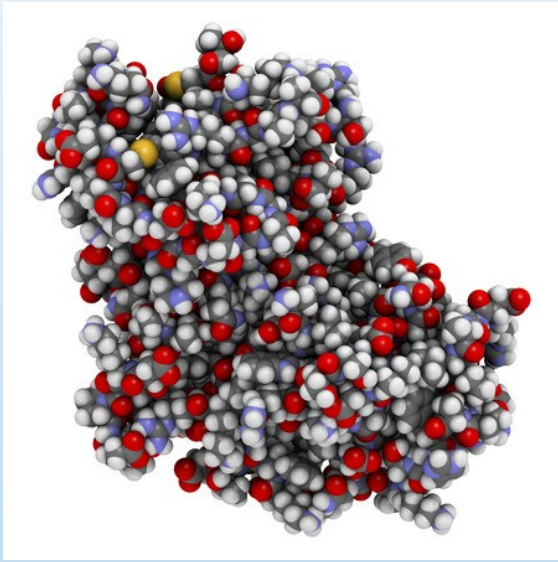


$pK_A = 8,2$

Glutamic acid:



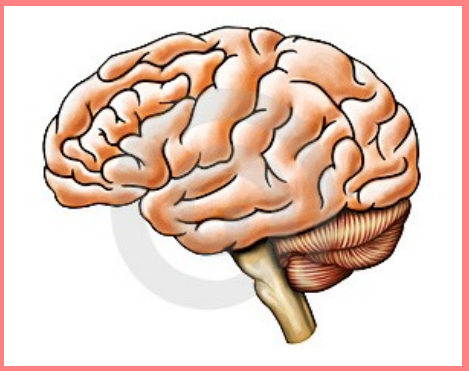
$pK_A = 4,25$

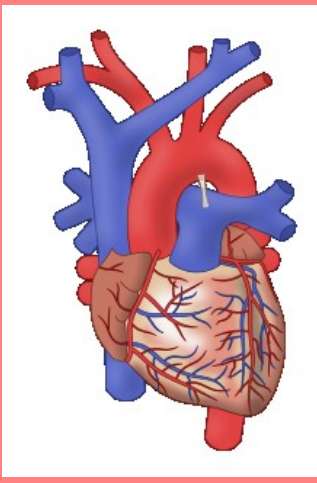


Conformation change

Dysfunction

Crucial organs:





pH definition and its consequences

- Would you remember how pH is defined?
- And what are rules of calculating with logarithms? E.g. log(A x B) =
- Try to figure out what these rules imply for the pH behavior: For instance, when H^+ concentration (denoted as $[H^+]$) increases two times, how does pH change?[1]
- How does pH change, when the H^+ concentration decreases 10x?
- *For straight-A students: How does pH change, when $[OH^-]$ increases 2x?*

- Minimum time: 3 minutes or until completion of all tasks.

- 1) You might find it helpful to know that $\log_{10}(2) = 0.3$

pH definition and its consequences - solution

- $pH = - \log_{10}([H^+])$
- $\log(AB) = \log(A) + \log(B)$
- H^+ concentration increasing twice: $[H^+]_{New} = 2[H^+]_{Old}$
- From the pH definition and the logarithm calculation rules:

$pH_{New} = - \log([H^+]_{New}) = - \log(2 \times [H^+]_{Old}) = - \log(2) + (- \log([H^+]_{Old}) =$

$= -0,3 + pH_{Old}$

➔Therefore: If H^+ concentration doubles: $pH_{New} = pH_{Old} - 0,3$

- When $[H^+]_{New} = 1/10 \times [H^+]_{Old}$: $pH_{New} = - \log(1/10) + (- \log([H^+]_{Old}) =$

$= +1 + pH_{Old}$. If $[H^+]$ decreases ten times, pH goes up by 1.

Buffers

- What are buffers and what their effects in a solution are?
- How do buffers influence pH change, when acid or base is added?
- What does pK_a of a simple buffer denote?
- For straight-A students: Can you write down the mass action equation of a simple buffer?
- Which pH does render a single substance buffer most effective?

- Minimum time: 3 minutes

Buffers – Solution 1

- Buffers inhibit the pH change by binding the extra H^+ when their concentration increases (when pH falls) and releasing H^+ when $[H^+]$ decreases (pH goes up).
- They are crucial for stabilizing pH within certain range!
- Hydrogen ion and buffer react according to the formula:
- $HB \rightleftharpoons H^+ + B^-$ or:

  $HB^+ \rightleftharpoons H^+ + B$

- Reaction equilibrium concentrations can be expressed by the well-known mass action formula:

$$K_A = \frac{[H^+] * [B_i^-]}{[HB_i]}$$

- This can be expressed in the logarithmic form as well:

$$pH = pK_A + \log_{10} \frac{[B_i^-]}{[HB_i]}$$

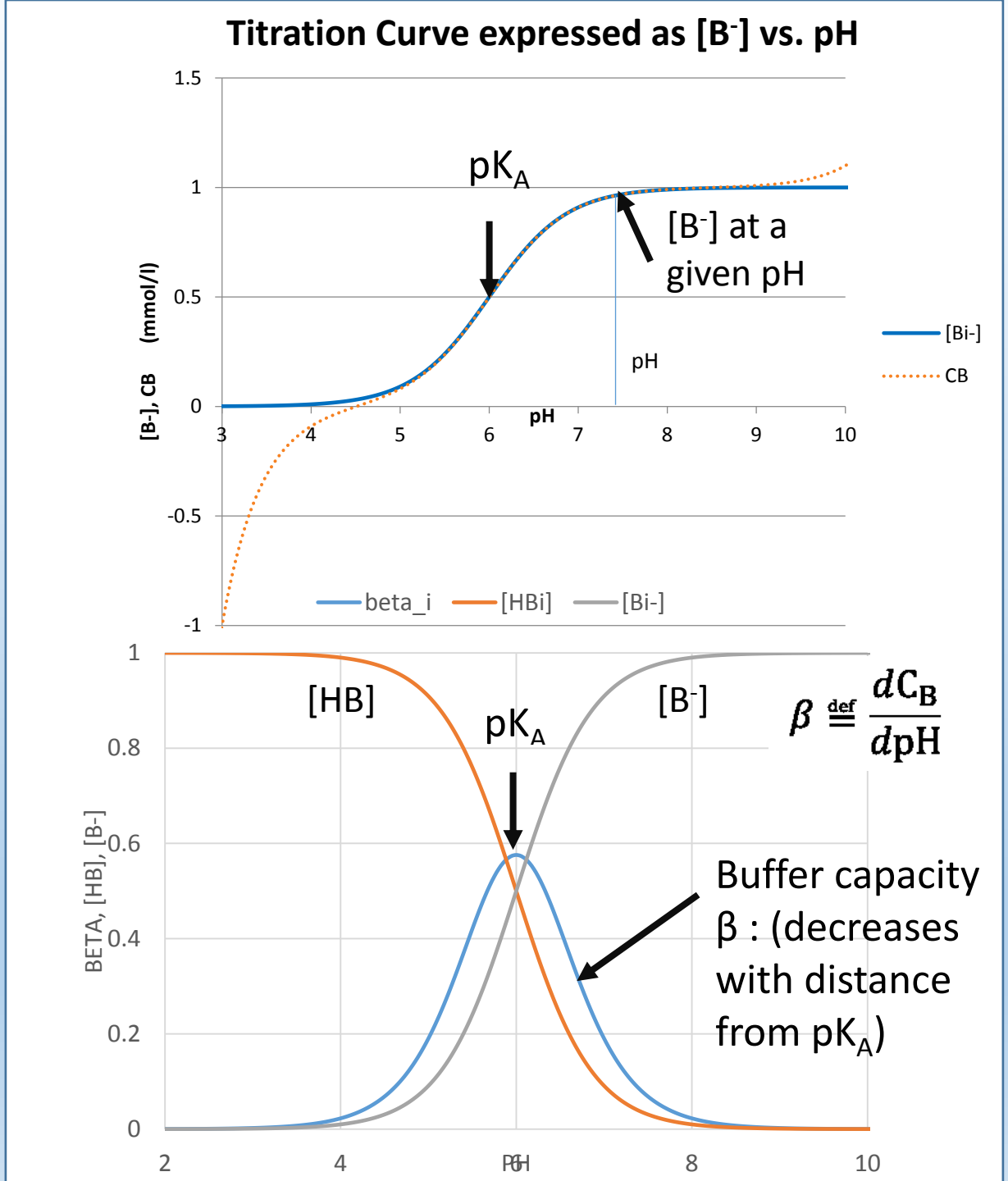
- [HB] and $[B^-]$ are in 1:1 ratio, when $pH = pK_A$

(prove this using the previous relationship)

Buffers – Solution 2

- Single-substance buffer is most effective when the pH coincides with its pK_A .
- Efficiency of a buffer at a given pH can be measured by its buffer capacity β.
- When pH and pK_A fall far, the efficiency of the buffer is constrained by the buffer component that is low in concentration.
- For instance, at acidic pH, there is ↓[B^-],
- At alkalic pH, there is ↓[HB]

- *For straight-A students: How does the [B^-]/[HB] ratio change when acid is added at pH far from its pK_A? Does it change a lot or a bit?*

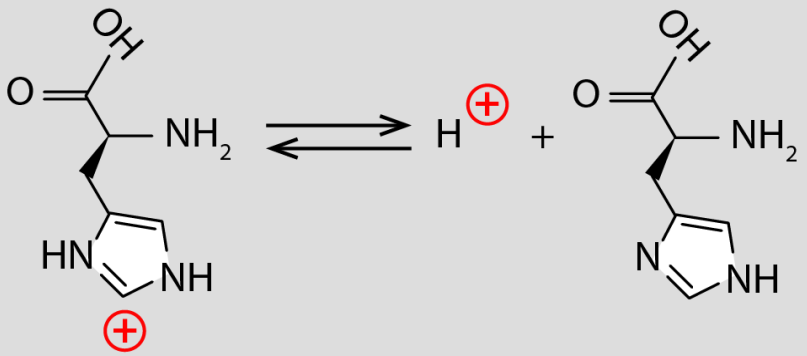


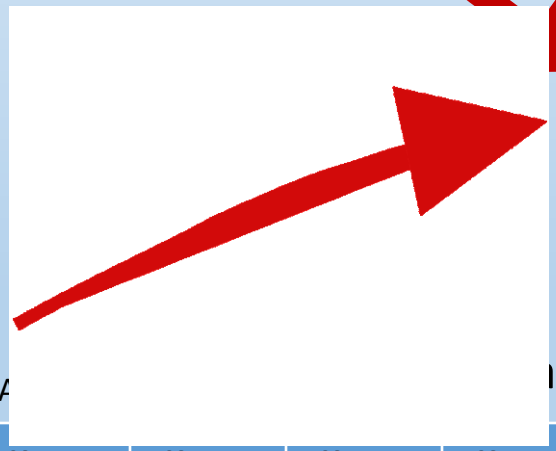
Protein Buffers

- Principal buffers in blood are:
  - **Hemoglobin!**
  - Albumin, and other proteins of blood plasma

- Key buffer residues are histidine side chains.
- pK_A's of individual histidine side chains differ significantly (influence of surrounding aminoacids)

Histidine side chain



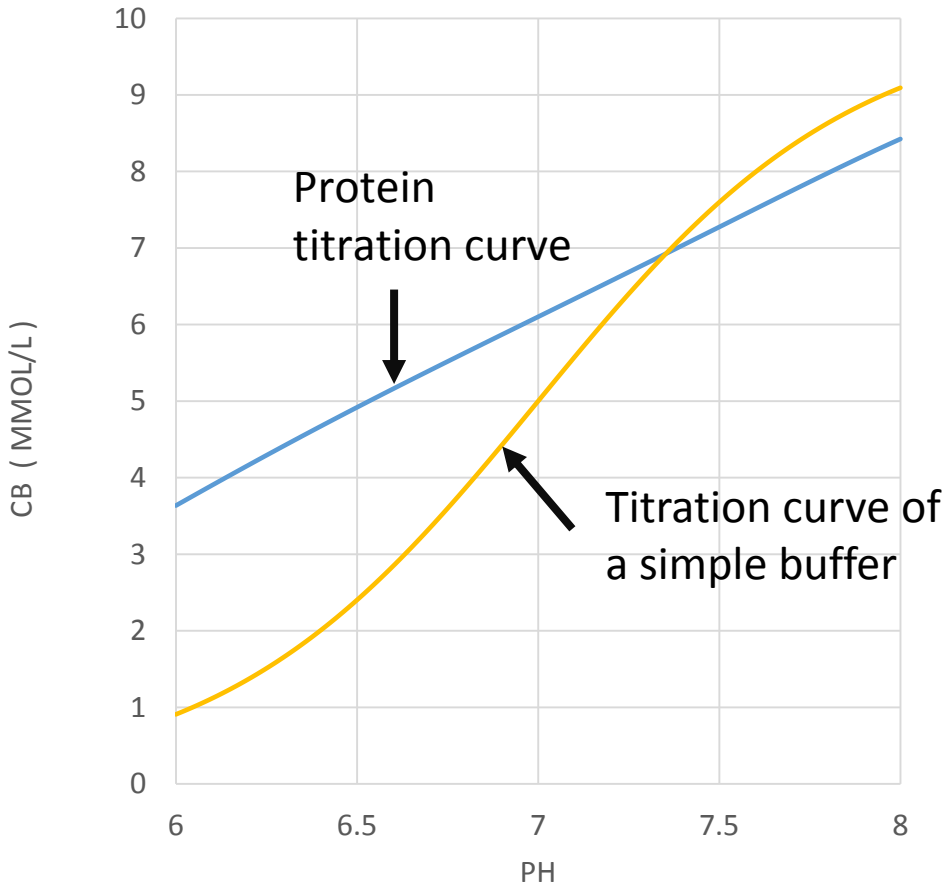


Consequence: Virtually **linear** protein **titration curve.** **Buffer capacity** is almost constant over a wide range of pH.

Tab: pK_A ... ains in the albumin molecule (ordered)

pK_9	pK_{15}	pK_{10}	pK_{13}	pK_{11}	pK_8	pK_{12}	pK_7	pK_5	pK_3	pK_1	pK_2	pK_{14}	pK_{16}	pK_6	pK_4
4.85	5.2	5.75	5.82	6.17	6.35	6.73	6.75	7.01	7.10	7.12	7.22	7.3	7.3	7.31	7.49

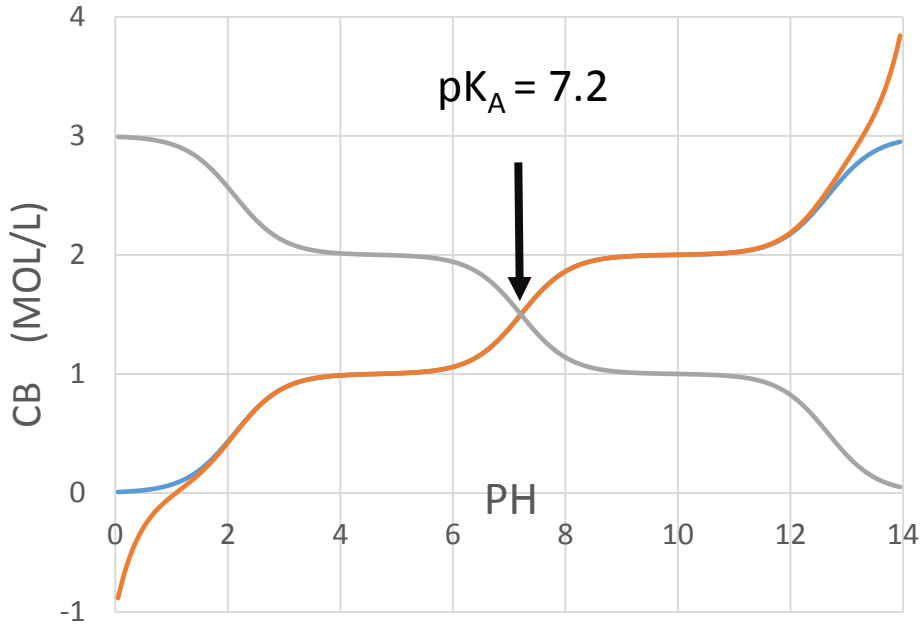
Protein Buffers



Phosphate Buffer

- Principal intracellular buffer
- Incl. phosphate residues of DNA

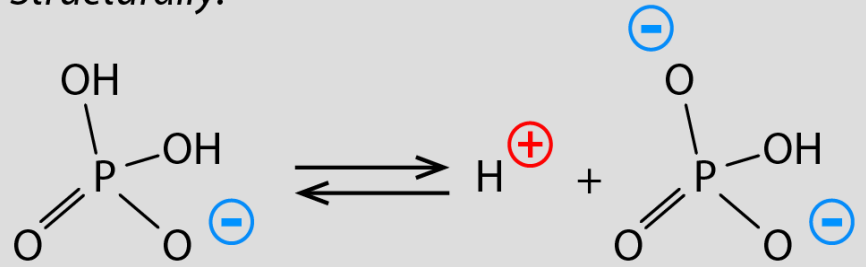
- The 2nd dissociation step is important, having $pK_A = 7.2$



Phosphate

$H_2PO_4^- \rightleftharpoons H^+ + HPO_4^{2-}$

Structurally:



Bicarbonate Buffer

$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$

Catalyzed by Carboanhydrase – present in stomach, kidneys and erythrocytes.

Equilibrium (mass action) expressed by the **Henderson-Hasselbalch equation:**

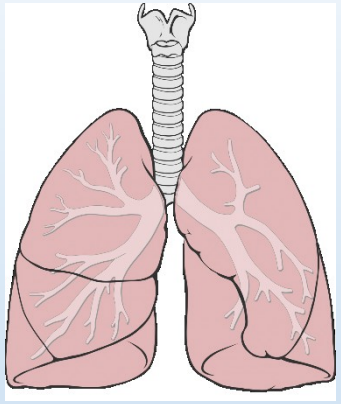
$$pH = pK_A + log\frac{[HCO_3^-]}{s * pCO_2}$$

Substituting numerical values (for pCO_2 in kPa) :

$$pH = 6{,}1 + log\frac{[HCO_3^-]}{0{,}22 * pCO_2}$$

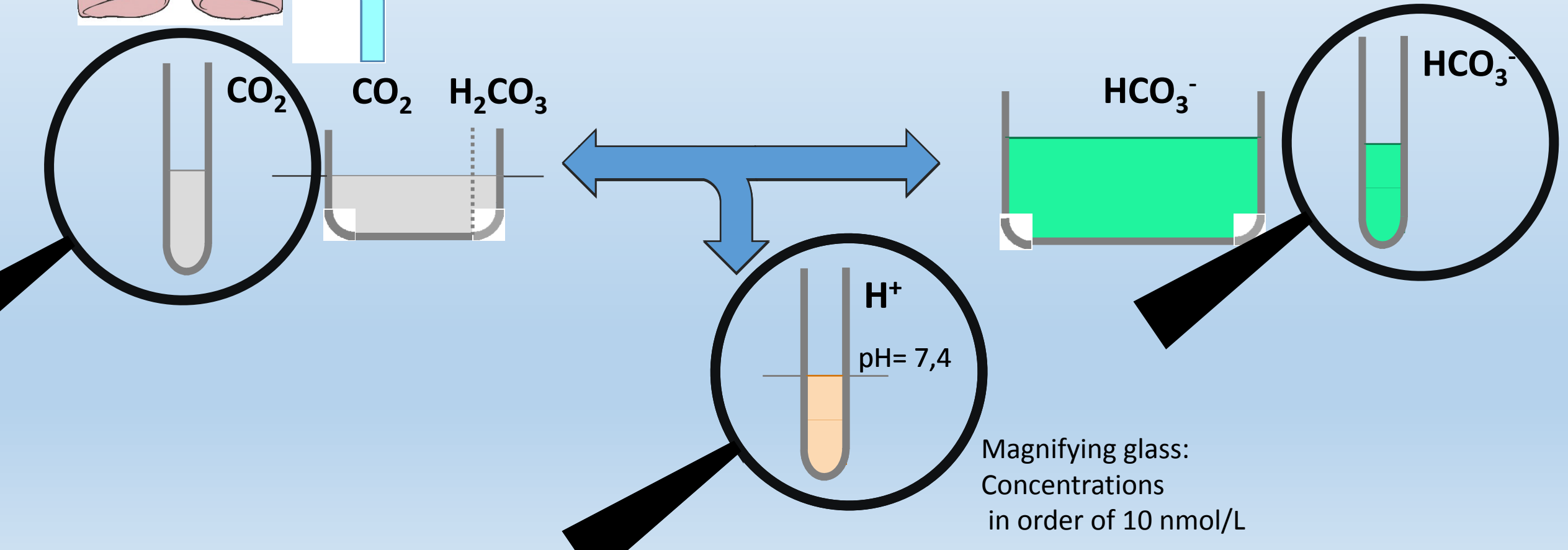
Question for straight-A students: pK_A of the bicarbonate buffer is 6.1. This is quite off the physiological pH = 7.4. Does this lower the buffer capacity of bicarbonate buffer?

Bicarbonate Buffer



Possible depiction of reaction equilibria (as described by Henderson-Hasselbalch equation):

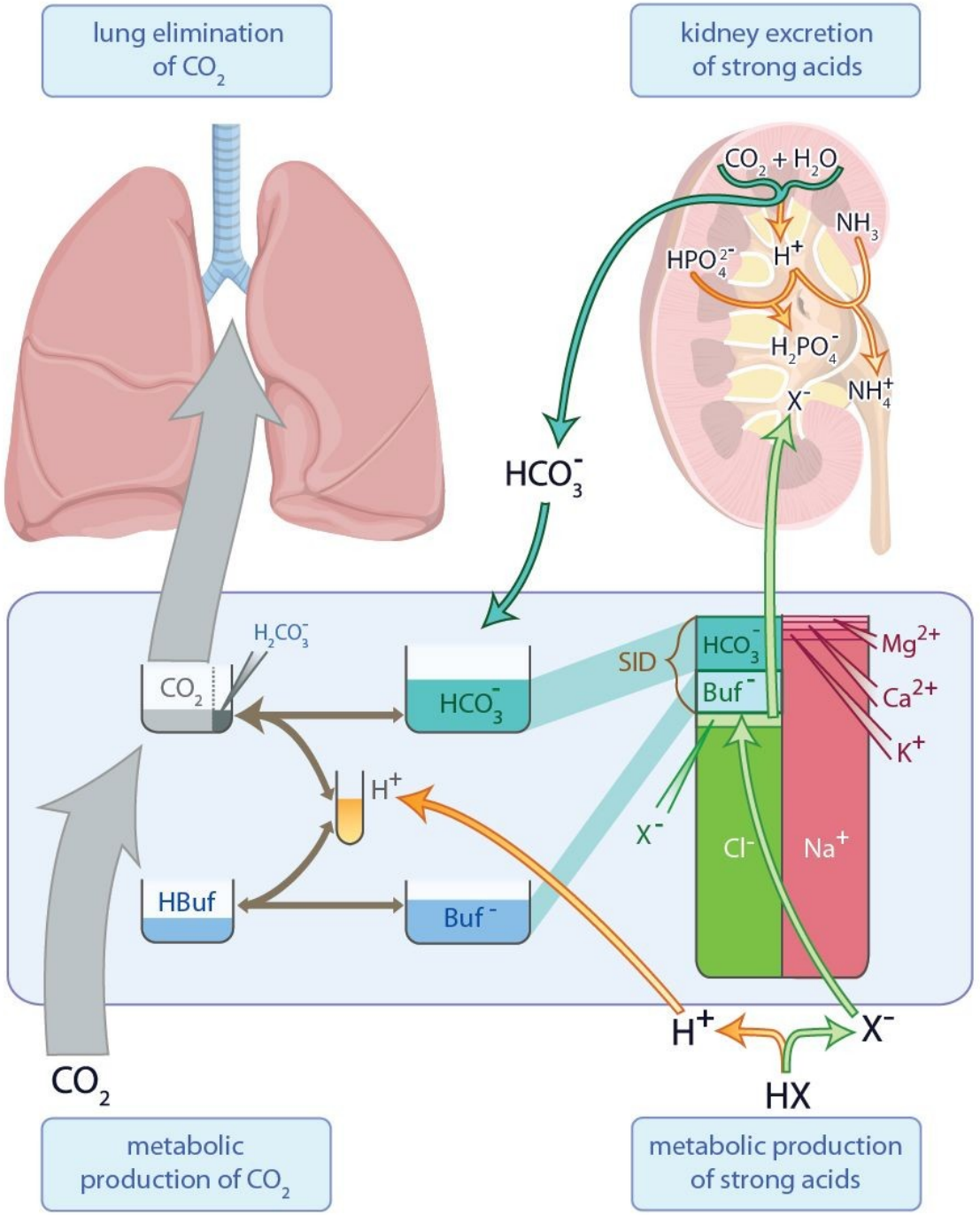
$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$



Magnifying glass:
Concentrations
in order of 10 nmol/L

Metabolism and the System of Regulating Acid-base Status

- The biggest turnover is in the system of CO_2
  - Thus pCO_2 can be easily regulated. CO_2 behaves as an open system
- Other flows and the relationship with concentrations of other ions (electro-neutrality) are depicted in the figure:



Bicarbonate Buffer

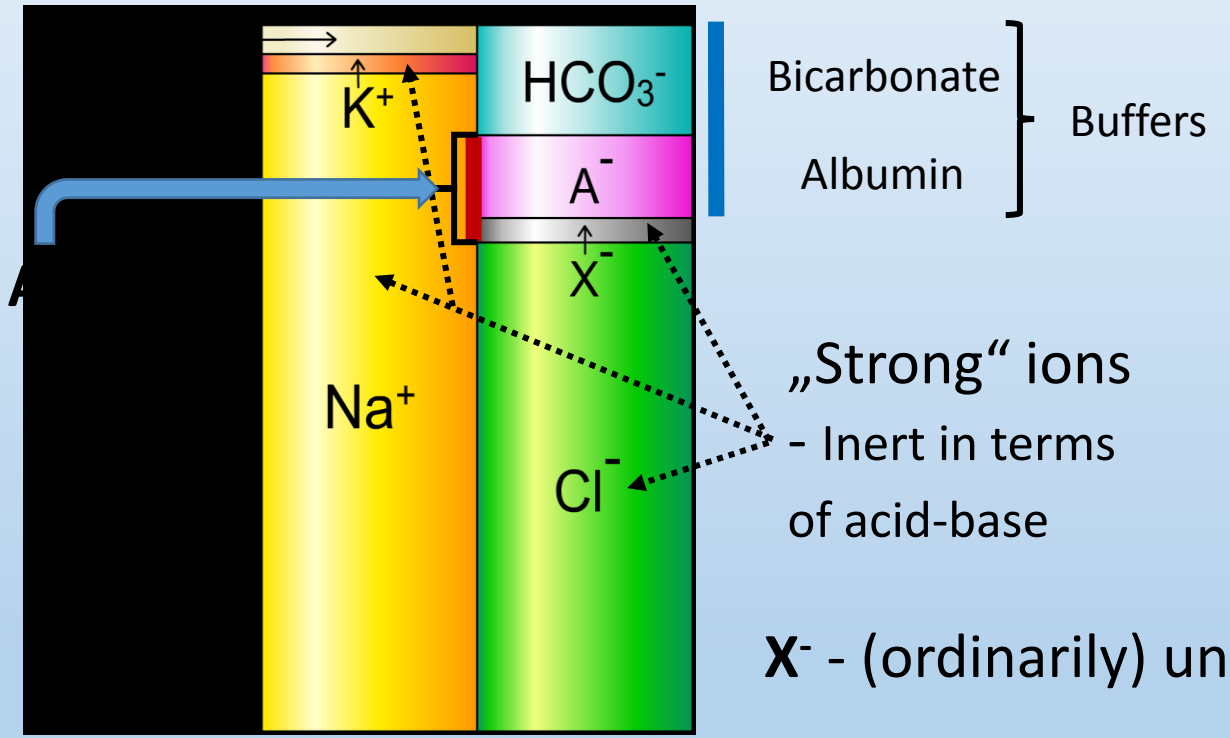
- It is the **principal buffer in terms of longer-term regulation** of H^+ balance in the body.
- Lungs – regulate pCO_2
- Kidneys – regulate the level of HCO_3^- in blood plasma and excretion of H^+

	Primary Disturbance	When H+ = 40 nmol/L	Compensation
Respiratory Acidosis	↑pCO_2	Reacts to the right -↑H^+	Kidneys - ↑HCO_3^-, ↑BE
Metabolic Acidosis	↓HCO_3^- (or ↑↑↑H^+)	Reacts to the right when primary cause ↓HCO_3^- (Reacts to the left when primary cause ↑↑↑H^+) –end result - ↑H^+	Lungs - ↓pCO_2
Respiratory Alkalosis	↓pCO_2	Reacts to the left - ↓H^+	Kidneys - ↓HCO_3^-, ↓BE
Metabolic Alkalosis	↑HCO_3^-	Reacts to the left -↓H^+	Lungs - ↑pCO_2

Base Excess - BE

- Base Excess – a very precise measure of metabolic disturbances (and metabolic compensations)
- Underlying logic: Lungs regulate pCO_2 . This regulation does not influence the total concentration of base forms of buffers.
- By definition: When pH = 7,4 (norm) and pCO_2 = 5,3 kPa (norm), then BE = 0 mmol/L
- Now, when we add 10mmol/L of acids, part of this amount reacts away with bicarbonate and part with the B- form of nonbicarbonate buffers – BE decreases to -10 mmol/L
- Conversely, taking away 15 mmol/L of acids (H^+) when BE =0 increases both the level of bicarbonate and the B- of non-bicarbonate buffers – BE increases to +15 mmol/L
- The value of BE is independent of subsequent changes in pCO_2

System of Buffers and Electroneutrality



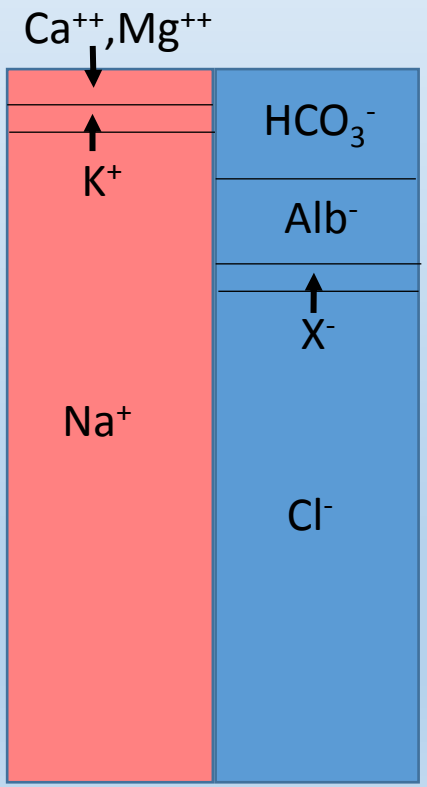
„Strong“ ions
- Inert in terms of acid-base

Electroneutrality:
When buffer concentration changes – the concentration of strong ions has to change as well

X^- - (ordinarily) unmeasured ions –e.g. **lactate, keto$^-$, SO_4^{2-}**

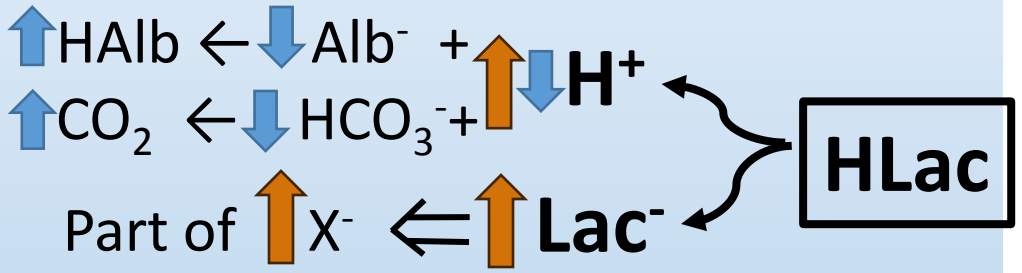
AG = Anion gap = $Na^+ + K^+ - Cl^- - HCO_3^-$
Parameter used in differential diagnosis of metabolic acidoses

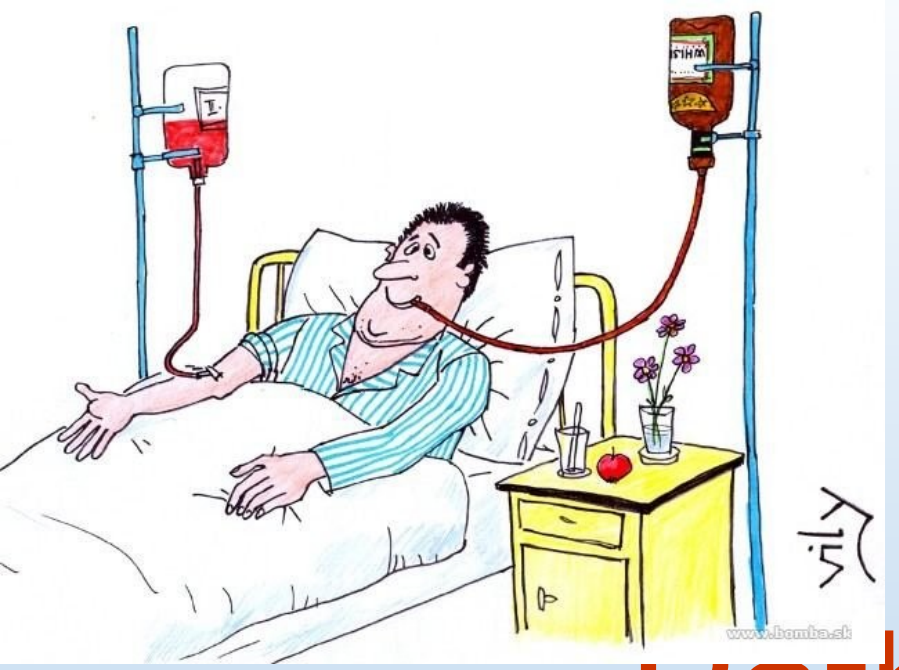
System of Buffers and Electroneutrality 2 – Example



Runner in High Tatras:

Production of **lactic acid** in muscles





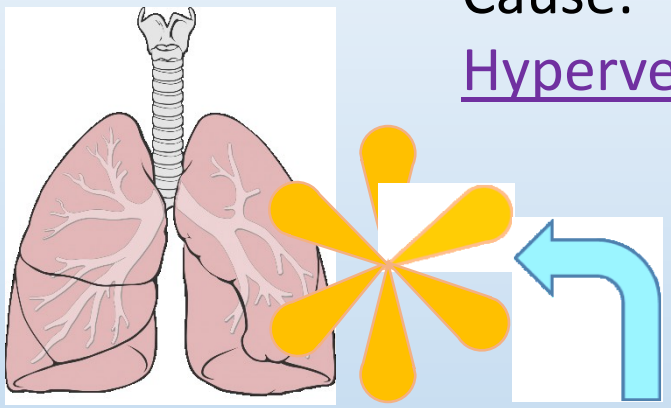
Pathophysiology of ABB disturbances + clinical examples

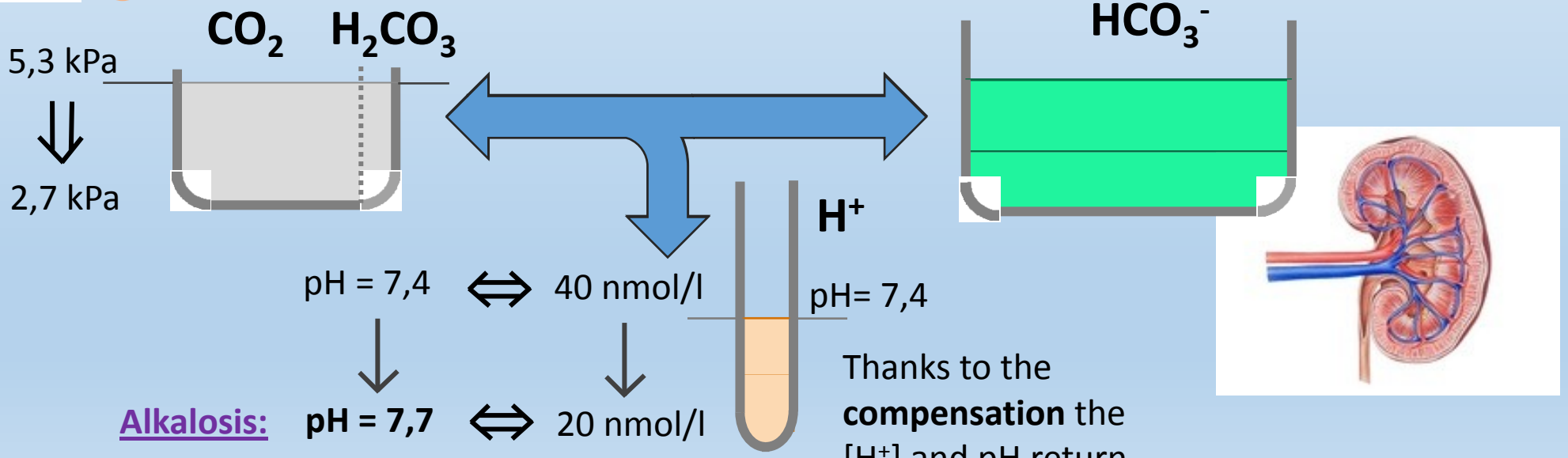
Respiratory Disturbances and their Compensation

Respiratory Alkalosis and its Compensation

Cause:

Hyperventilation





Kidney (metabolic) compensation:

Takes 2- 3 days to develop

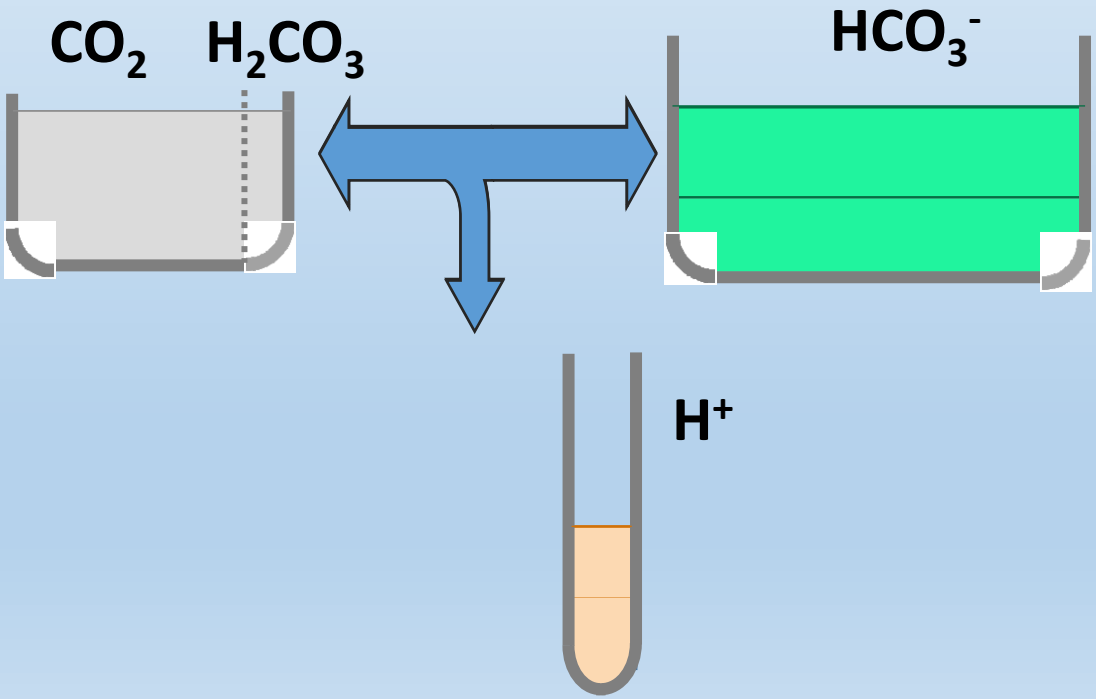
Kidneys excrete less H^+ and more bicarb.

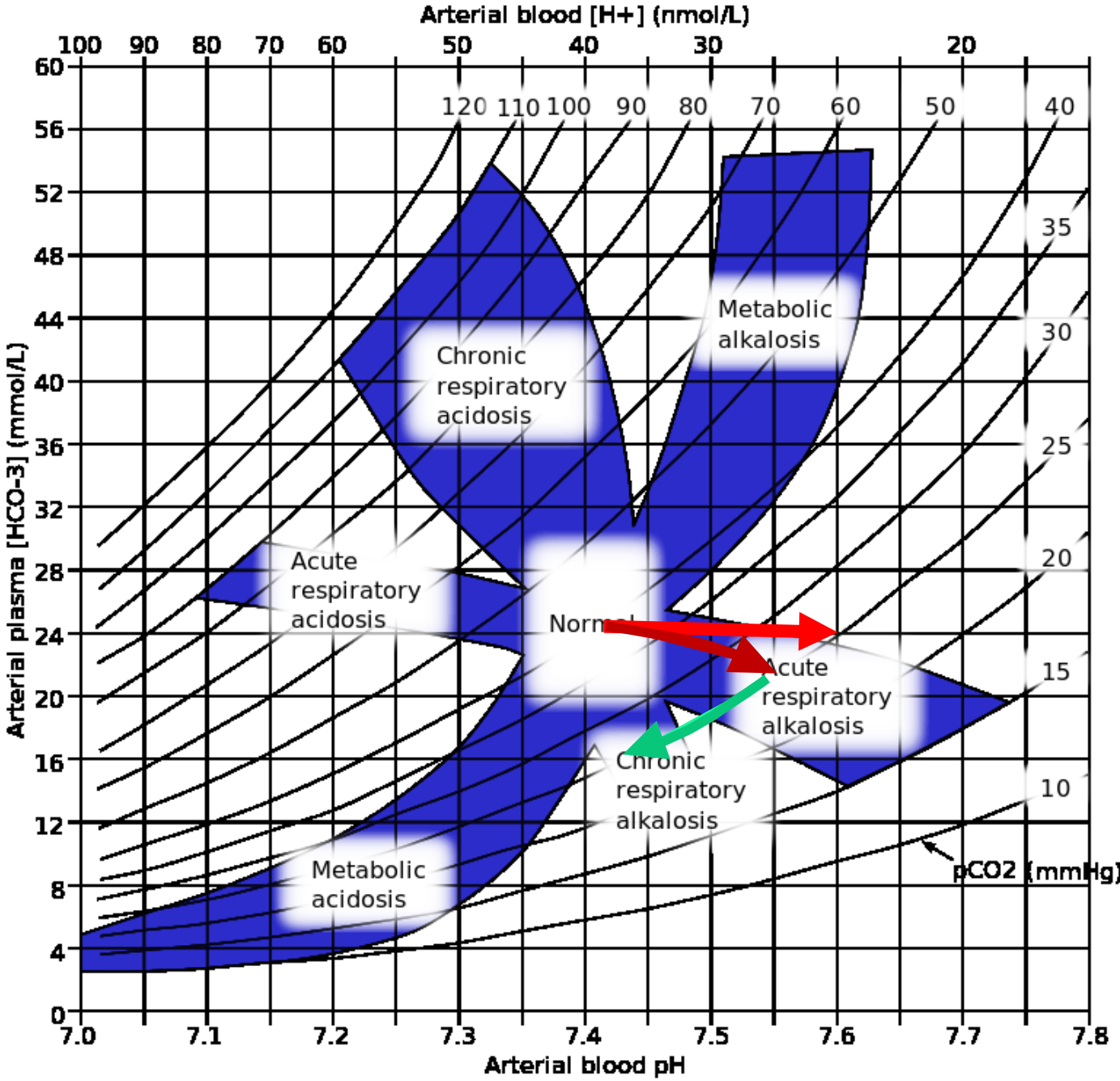
= less bicarbonate returns to blood

Thanks to the **compensation** the $[H^+]$ and pH return closer to norm

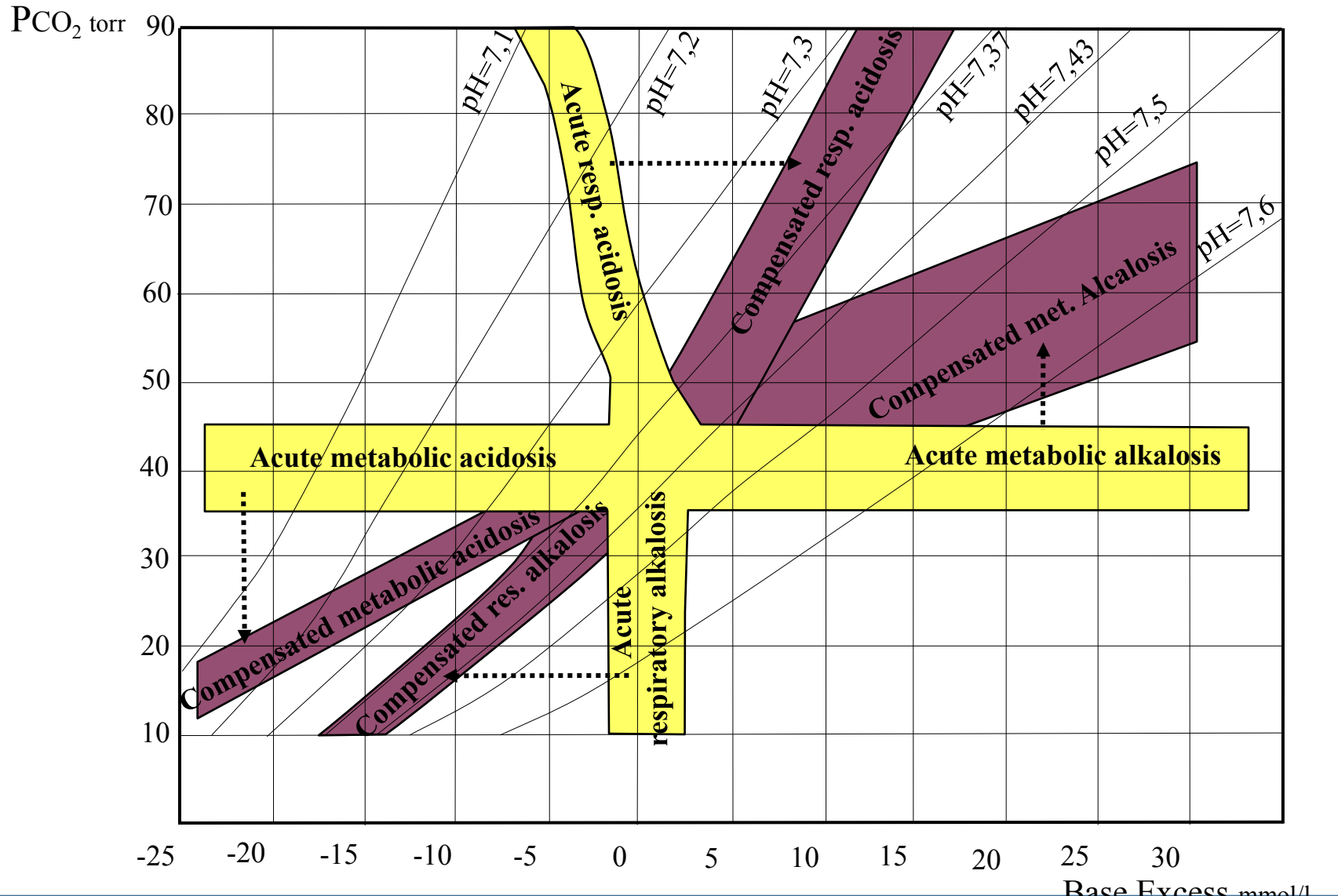
Compensation diagrams and rules

Compensation Diagrams

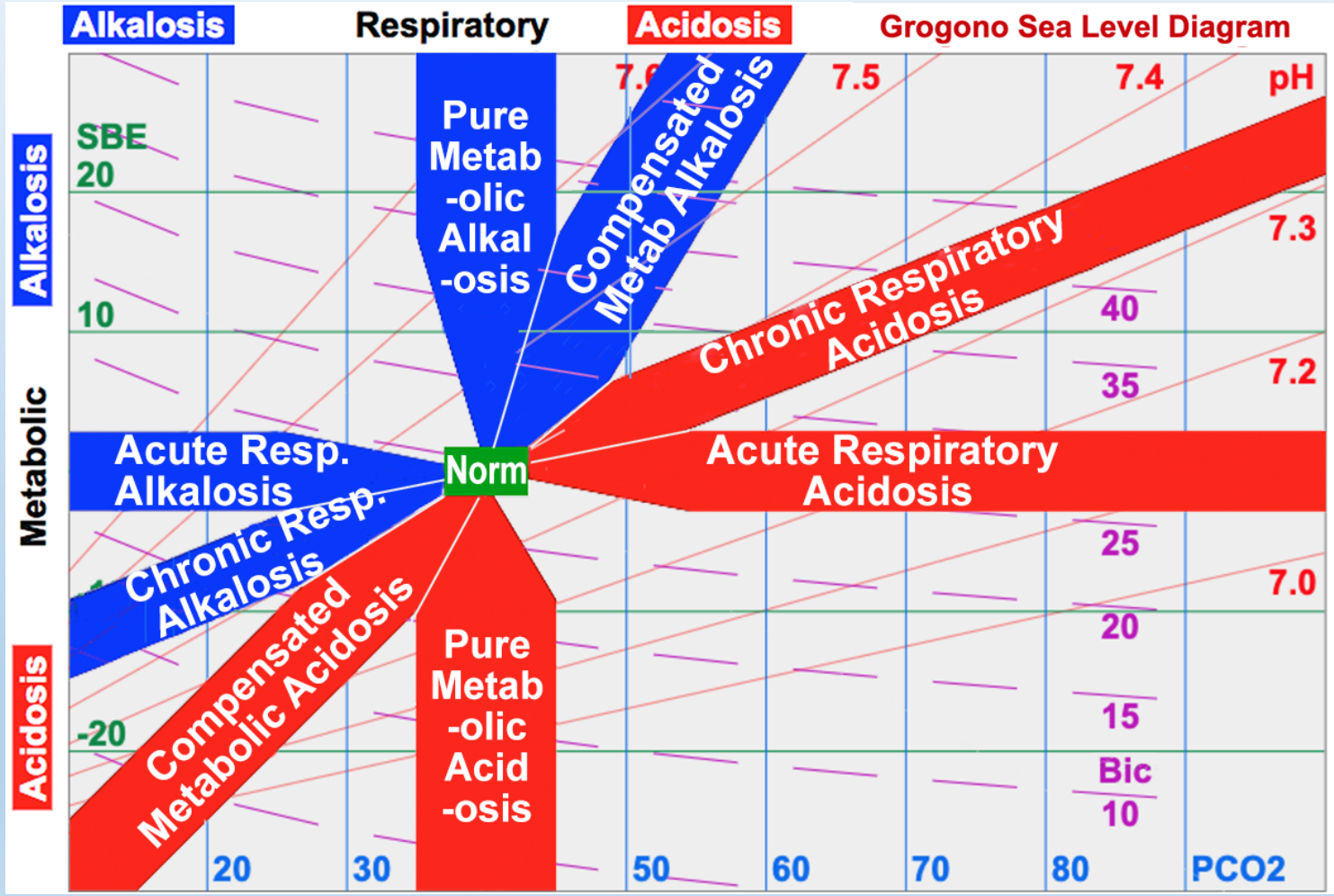




Compensation Diagrams 2



Compensation Diagram pCO_2 vs BE – Different



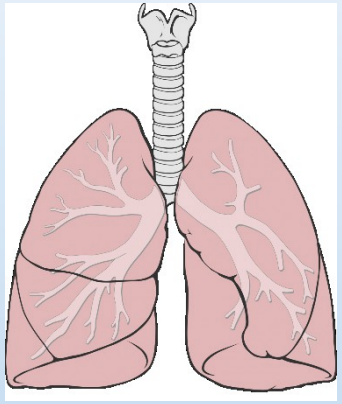
“Boston” Rules for Diagnosing ABB Disturbances

Alternative to the compensation diagrams - however, you have to remember them ☹

For straight-A students - optional: This is for pCO_2 expressed in mmHg – convert to a version in kPa (pCO_2 40 mmHg = 5,3 kPa)

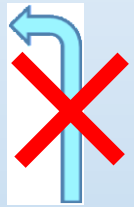
Metabolic	Acidosis		$(pCO_2)_{EXPECTED} = 1.5 * [HCO_3^-] + 8$ or $\Delta pCO_2 = 1.2 * \Delta[HCO_3^-]$
	Alkalosis		$(pCO_2)_{EXPECTED} = 0.7 * [HCO_3^-] + 20$ or $\Delta pCO_2 = 0.6 * \Delta[HCO_3^-]$
Respiratory	Acidosis	Acute	$[HCO_3^-]_{EXPECTED} = 24 + 1\left(\frac{pCO_2 - 40}{10}\right)$
		Chronic	$[HCO_3^-]_{EXPECTED} = 24 + 3.5\left(\frac{pCO_2 - 40}{10}\right)$
	Alkalosis	Acute	$[HCO_3^-]_{EXPECTED} = 24 + 2\left(\frac{pCO_2 - 40}{10}\right)$
		Chronic	$[HCO_3^-]_{EXPECTED} = 24 + 5\left(\frac{pCO_2 - 40}{10}\right)$

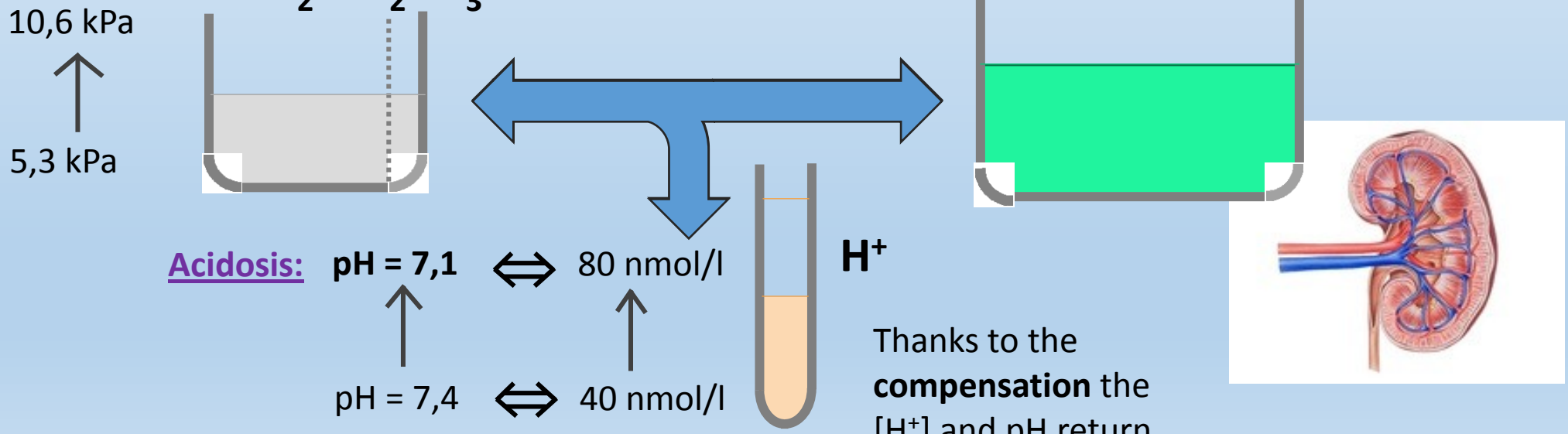
Respiratory Acidosis and its Compensation



Cause: **Hypoventilation**

Part of global respiratory insufficiency (insufficiency type II)





Kidney (metabolic) compensation:

Takes 2- 3 days to develop

Kidneys excrete **more H^+** = returning **more bicarbonate into blood**

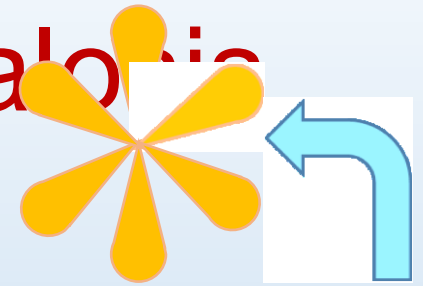
Thanks to the **compensation** the $[H^+]$ and pH return closer to norm

Case Study No. 1

- You examine a 20 YO student at the hospital admission.
- Cannot concentrate and even could not move her fingers for a brief moment (which scared her). Still feels strange pins and needles in her fingers.
- She has not been seriously ill until now, no medication
- Physical examination – normal
- SA: She has split with her boyfriend recently, had been together for 4 years. Difficult to go thru.
- Lab: pH = 7.49
  - pO2 = 13.4 kPa
  - pCO2 = 4.1 kPa
  - HCO3- = 22 mmol/L
  - BE = -1 mmol/l

What acid-base disturbance this is?
What kind of acute problem do we see here?
What would be your advise her?

Possible Causes of Respiratory Alkalosis



Hyperventilation

- A) At hypoxemia
  - High altitude disease
  - Right-left pulmonary shunting
    - And ventilation-perfusion dysbalance similar to shunt
  - With artificial ventilation
- B) Respiratory center irritation
  - Trauma, inflammation, salicylates.
- C) Panic attack

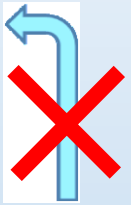
Case study No. 2

- 68 year old male comes to your ambulance.
- History of chronic bronchitis and pulmonary emphysema.
- Mild dyspnea, COVID antigen test negative
- Lab: pH = 7.31
    - pO2 = 8.0 kPa
    - pCO2 = 10.6 kPa
    - HCO3- = 38 mmol/L
    - BE = 12 mmol/L

What kind of acid-base disturbance do we deal with?
It this an acute a chronic problem?

Possible Causes of Respiratory Acidosis

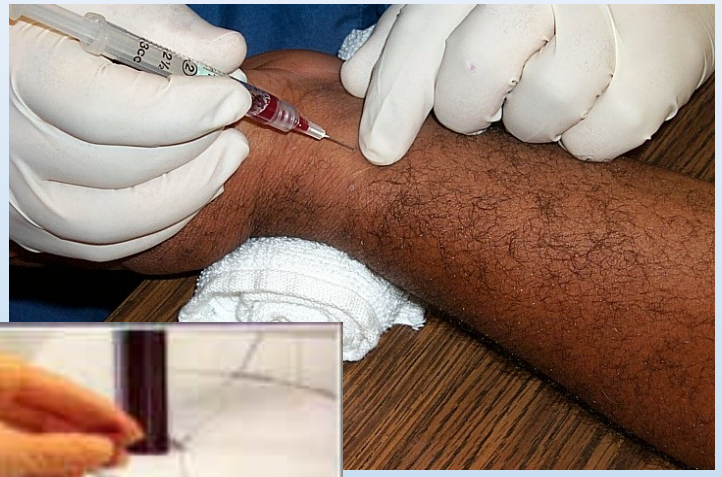
- Decreased alveolar ventilation
  - A) Respiratory center depression
    - Drugs, medicaments (e.g. opioids)
    - Damage or ischemia:
      - Trauma
      - Stroke
      - Tumor
      - Cerebral edema / increased intracranial pressure
  - B) Nerve or muscle disease
    - Myasthenia gravis
    - Polyradiculoneuritis
    - Serious obesity/ Pickwickian syndrome



- C) Lung disease
  - Restrictive diseases
    - ARDS
    - Pulmonary fibroses
  - Obstructive diseases
    - Astma
    - Tumor
    - Foreign body
  - Increase in dead space
    - Pulmonary embolism
    - Pulmonary emphysema
  - Trauma, pneumothorax, serial rib fractures
- Increased pCO_2 in the inspired air

What is Taken and Assessed?

- Blood Gases Measurement in Arterial Blood (so called „Astrup“)
- Serum electrolytes
- Concentrations of buffers (e.g. hemoglobin) and other parameters



Blood Gases Measurement – „Astrup“

Assessed by the machine (sensors = selective electrodes):

pH = 7,4 ± 0,04

pCO_2 = 5,3 kPa

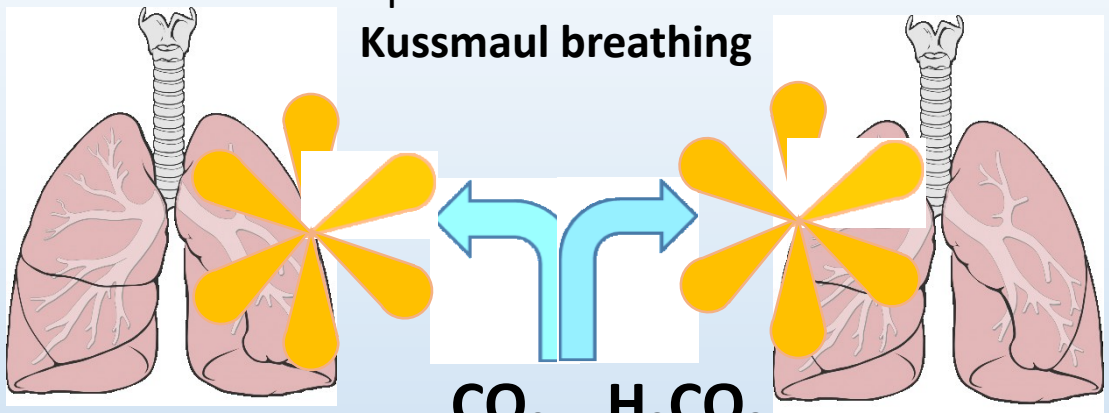
pO_2 = 13,3 kPa

- Calculated by the machine:
- $[HCO_3^-]$ = 24 mmol/l
  - *calculated using HH equation*
- BE = 0 mEq/l
  - *Base Excess, Hb concentration is needed for the calculation.*

Metabolic Disturbances and their Compensation

Metabolic Acidosis 1 + Compensation

Hyperventilation as a compensation of acidosis:
Kussmaul breathing



CO_2 H_2CO_3

pCO_2 = 5,3 kPa

HCO_3^-

AG = $Na^+ + K^+ - Cl^- - HCO_3^-$
(does not include X^-)

➔ ↑AG is equivalent to ↑ X^-

compensated metabolic acidosis:

Thanks to the **compensation** the $[H^+]$ and pH return closer to norm

pH= 7,4

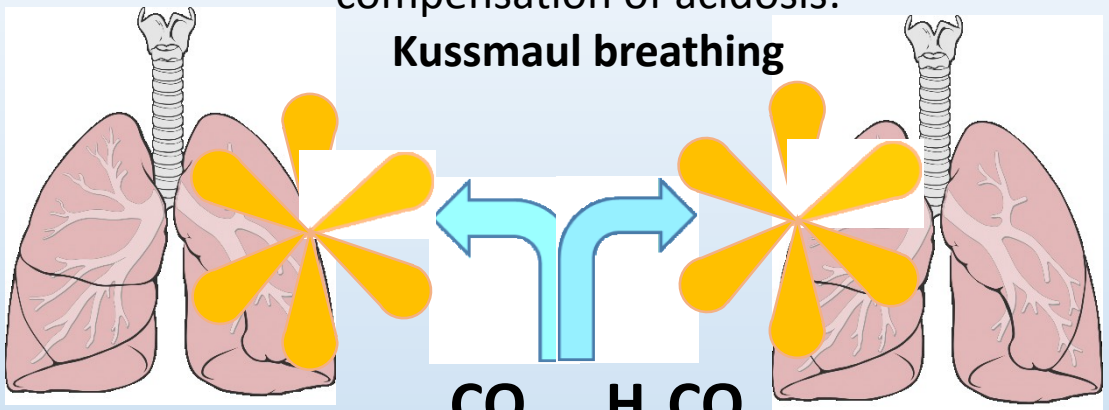
H^+

Concentration in order of 10 nmol/L

Metabolic Acidosis 2 + Compensation

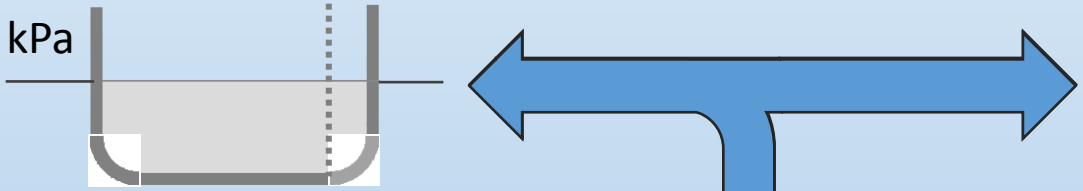
AG = $Na^+ + K^+ - \uparrow Cl^- - \downarrow HCO_3^-$

Hyperventilation as a compensation of acidosis:
Kussmaul breathing

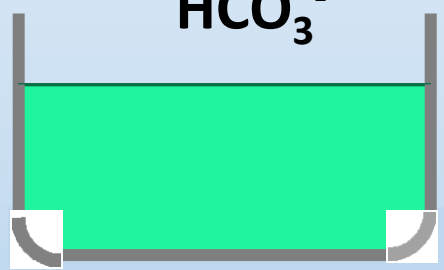


CO_2 H_2CO_3

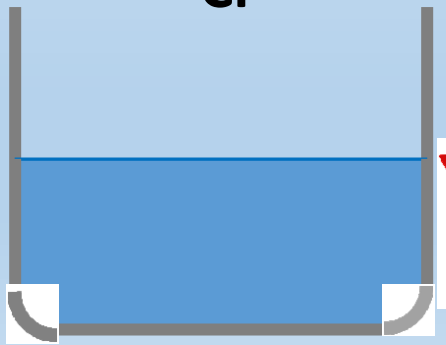
pCO_2 = 5,3 kPa

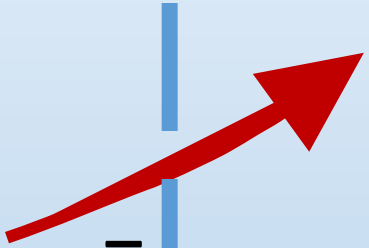


HCO_3^-



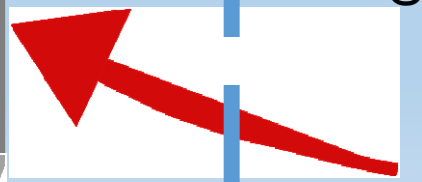
Cl^-





Exchange has to be **electroneutral**

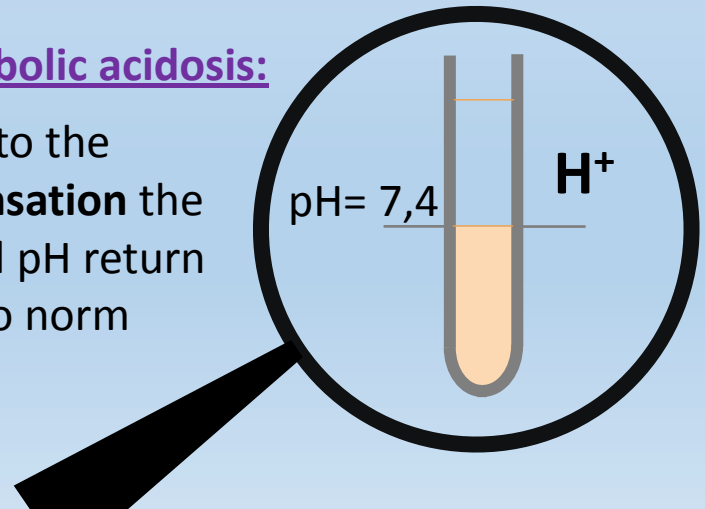
Clinically so called: **„Hyperchloremic" acidosis**



Compartment border

compensated metabolic acidosis:

Thanks to the **compensation** the $[H^+]$ and pH return closer to norm



Case Study No. 3

- 38 yo female, DM 1st type
- Chills and fever lasting several days
- She has not felt well --> not eaten much → not taken much insulin
- During admission day: Abdominal cramps, vomited several times
- Physical exam: BF 30 min^{-1}, HF 112 min^{-1}, BP 110/70 lying and 100/60 standing, 37 °C,
- Dry mucosae and fruity breath odor

What acid base disturbance do we deal with? Is it a compensated disturbance?

What else could be said about her hydration and ion concentrations?

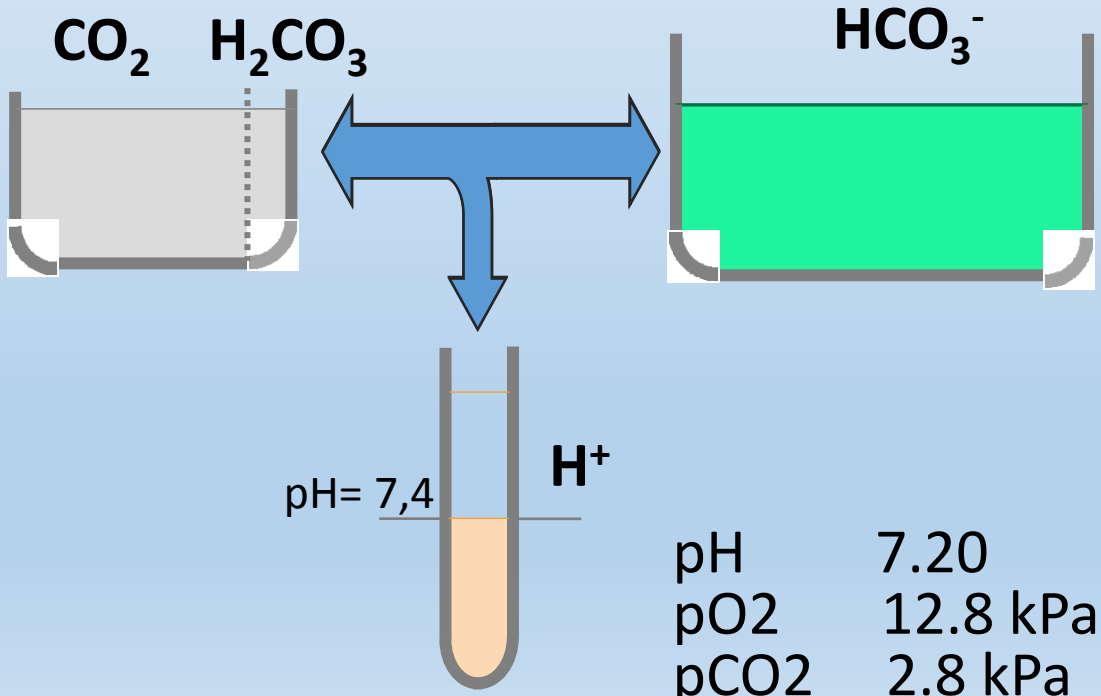
Lab:

pH	7.20
pO2	12.8 kPa
pCO2	2.8 kPa
HCO3-	8 mEq/L
Glc	15 mmol/L
Na+	148 mEq/L
K+	5.5 mEq/L
Cl-	110 mEq/L

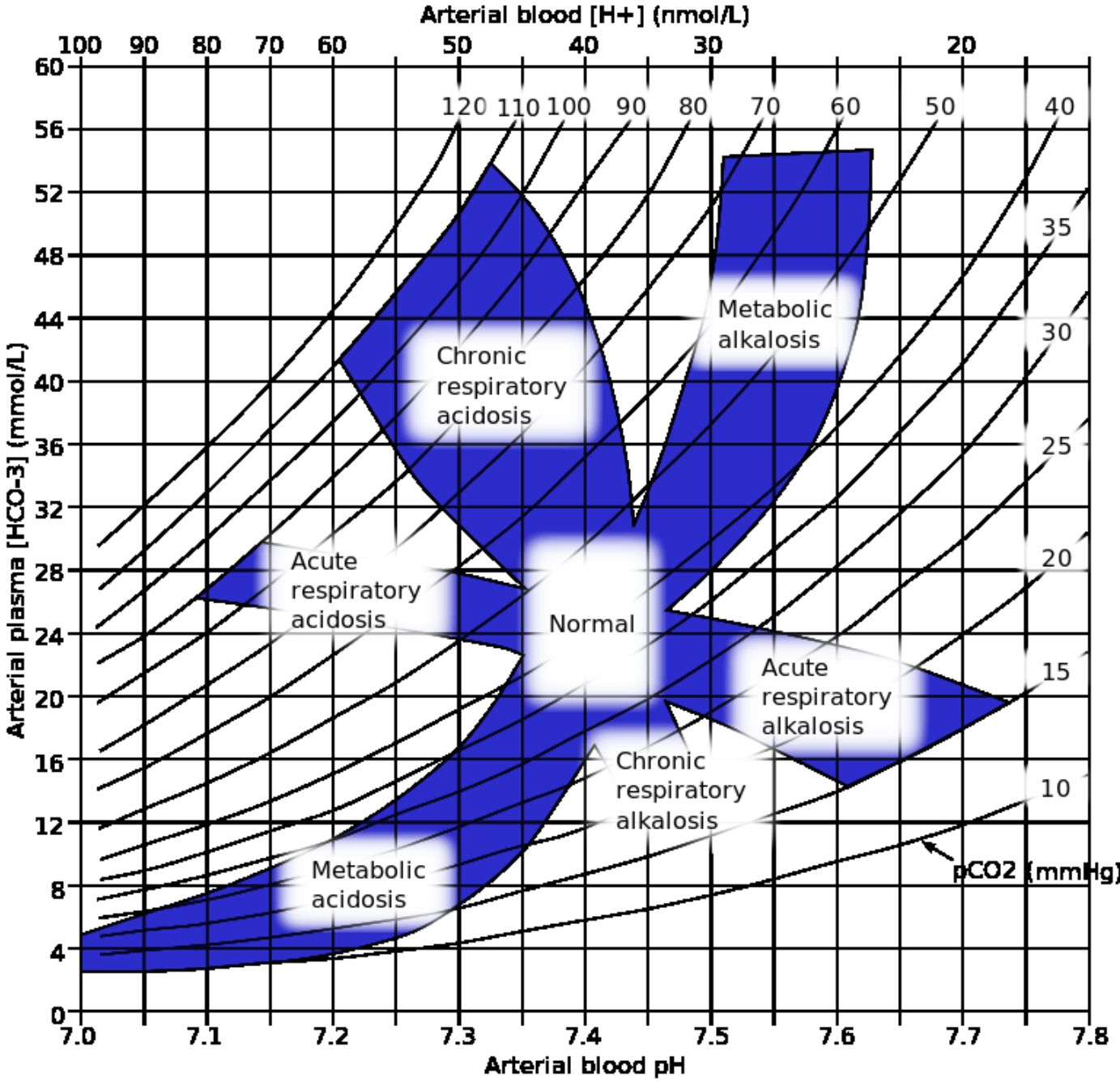
Positive aceton in urine

Metabolic Acidosis- Compensation Diagrams

Draw our patient status into the compensation diagram and model her situation with the beakers



pH	7.20
pO2	12.8 kPa
pCO2	2.8 kPa
HCO3-	8 mEq/L



Possible Causes of Metabolic Acidosis

A) Loss of bicarbonates due to increased acid buffering

- Ketoacidosis
  - Diabetic
  - Alcohol
  - Starving
- Lactic Acidosis
  - Enormous physical strain
  - Circulatory shock / systemic ischemia
- Allogenic substances
  - Salicylate poisoning

AG (anion gap) is increased!: Anion of the buffered away acid accumulates in the body.

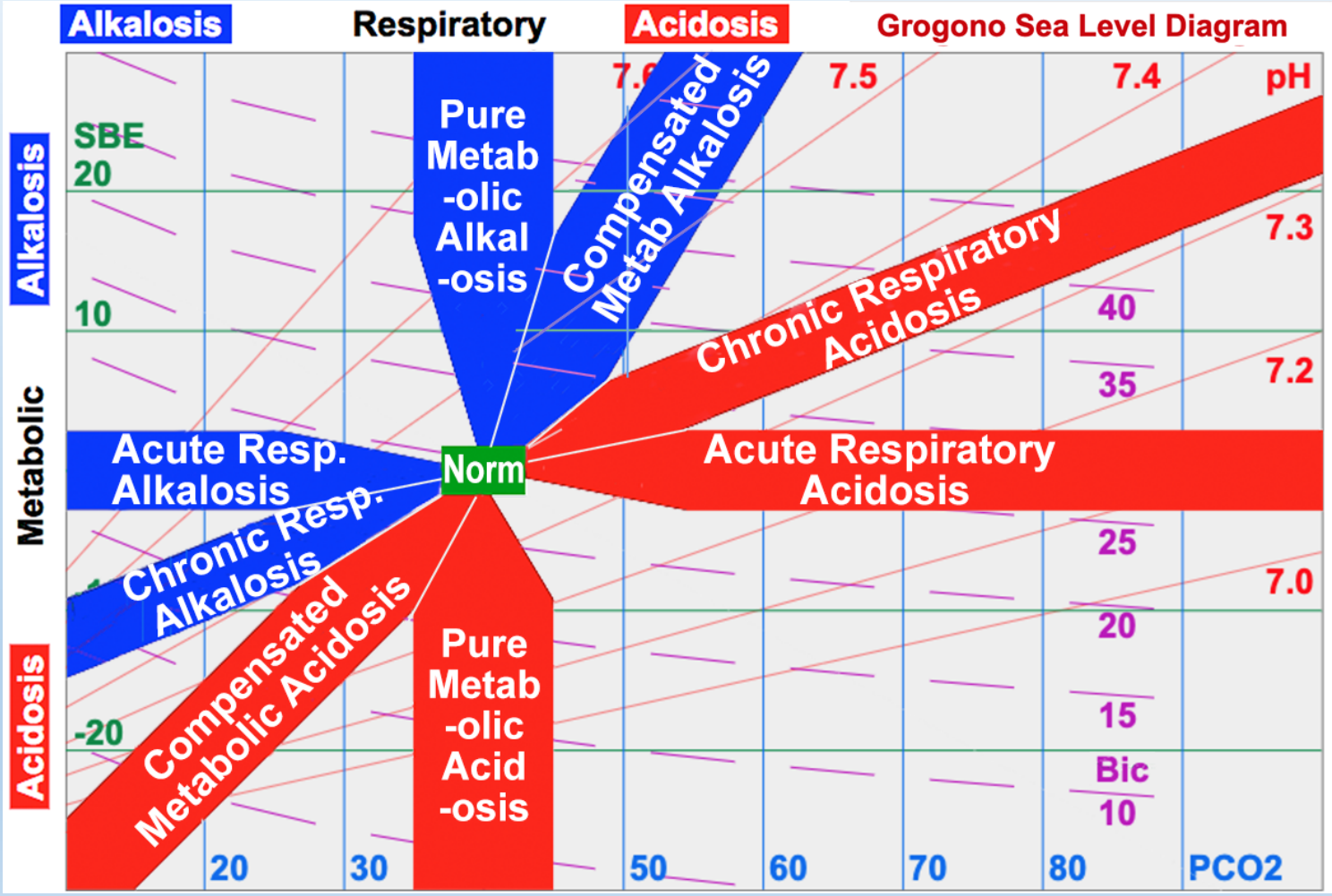
B) Loss of bicarbonates into the third space/out of body

- Through intestines
  - Diarrhea
  - Fistulas and stomias
- Through kidneys (loss of regulation)
  - So called Renal tubular acidoses
  - Renal failure (can have ↑AG)

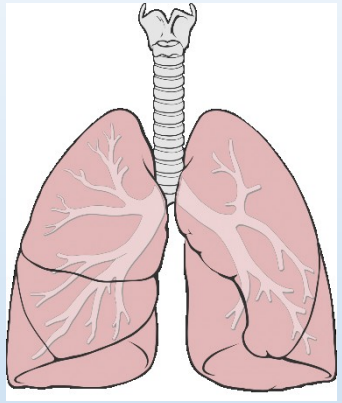
The difference in common strong ions reflects ↓ HCO_3^-
E.g. ↑ Cl^- (instead of the bicarbonate)- so called „hyperchloremic acidoses“
(Or there can be e.g. ↓ Na^+ or..)
AG (anion gap) is normal!

Exercise – Metabolic Alkalosis

- Try to derive the beaker chart of metabolic alkalosis and its compensation by yourself. (result can be checked on the next slide)



Metabolic Alkalosis + Compensation



Compensation of metabolic alkalosis by hypoventilation is limited by hypoxia

CO_2 H_2CO_3

Cl^-

HCO_3^-

H^+

pH= 7,4

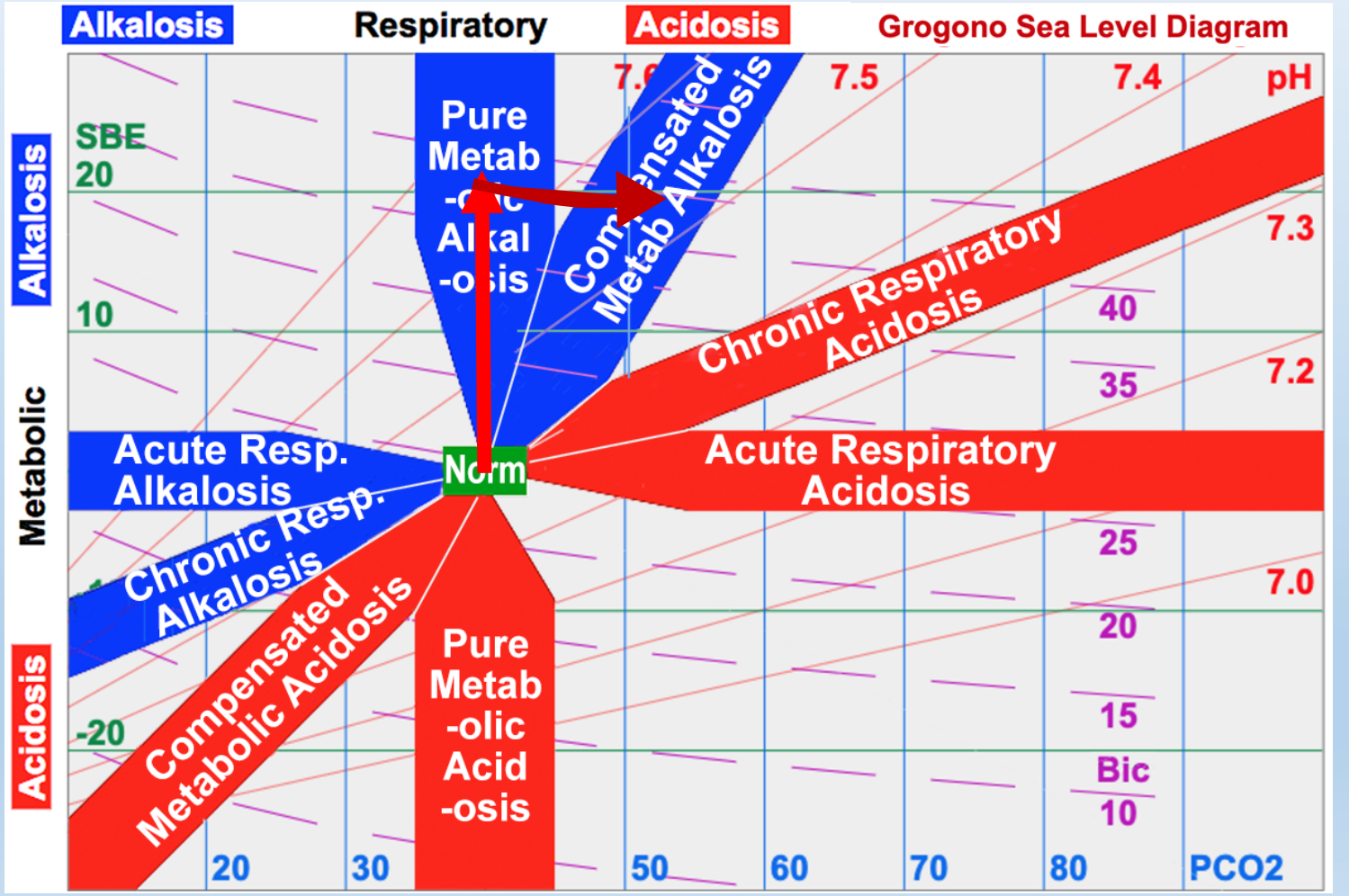
Thanks to the **compensation** the $[H^+]$ and pH return closer to norm

Exchange has to be **electroneutral**

Clinically, it is often referred to as: **„Hypochloremic“ alkalosis**

Compartment border (e.g. stomach mucosa)

Metabolic alkalosis and its compensation



Possible Causes of Metabolic Alkalosis

- Loss of acid by vomiting
  ↑ HCO_3^- produced by stomach into the blood (when H^+ is secreted into the lumen).
- Increased renal HCO_3^- production/ increased urine H^+ secretion
  - Hyperaldosteronism
  - So called Bartter syndrome
- Liver failure (↓production of urea from NH_4^+ - the reaction would be acidifying)
- Non-adequate infusion of bicarbonates/ Ringer lactate.

Pathogenesis of Paradoxical Aciduria and Loss of K^+ after Severe Vomiting

- Clinacally important!
- After profuse vomiting, **hyperchloremic metabolic alkalosis** develops
- Under normal circumstances, kidneys should regulate and produce only slightly acidic or alkaline urine.
- Instead, kidneys can worsen the alkalosis
- See next slide:

Glomerular filtrate: normal situation

Na^+
Cl^-

Reabsorption of sodium with chlorides

Na^+
Cl^-

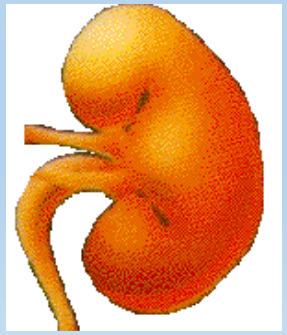
Remaining sodium is exchanged for potassium a H^+ K^+

Na^+

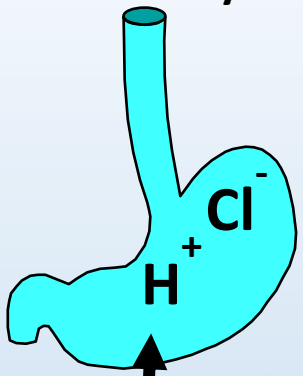
H^+

K^+ H^+

NH_4^+



Primary cause: Loss of Cl^- and H^+ by vomiting



Chloride depletion

Metabolic alkalosis

H^+ → H^+

K^+ ← K^+

Intracellular fluid

Potassium depletion

Glomerular filtrate: hypochloremic metabolic alkalosis

Na^+
Cl^-

Reabsorption of sodium with chlorides is diminished

Na^+
Cl^-

Sodium more available to be exchanged for potassium and H^+

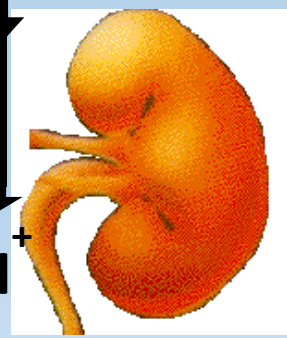
K^+

Na^+

H^+

Potassium excretion increased and despite the metabolic alkalosis there is aciduria

K^+
H^+



Increased loss of potassium + Paradoxial Aciduria

Summary

1. Physiology and chemistry

   H+, pH, buffers, buffers incorporated into metabolism, HH equation, electroneutrality
2. Disturbances divided into respiratory and metabolic
3. Clinical examples and causes

	Primary disturbance	Compensation
Respiratory acidosis	$\uparrow pCO_2$	Renal - $\uparrow HCO_3^-$, $\uparrow$BE
Metabolic acidosis	$\downarrow HCO_3^-$	Pulmonary - $\downarrow pCO_2$
Respiratory alkalosis	$\downarrow pCO_2$	Renal - $\downarrow HCO_3^-$, $\downarrow$BE
Metabolic alkalosis	$\uparrow HCO_3^-$	Pulmonary - $\uparrow pCO_2$

Thank you for your attention