

# 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

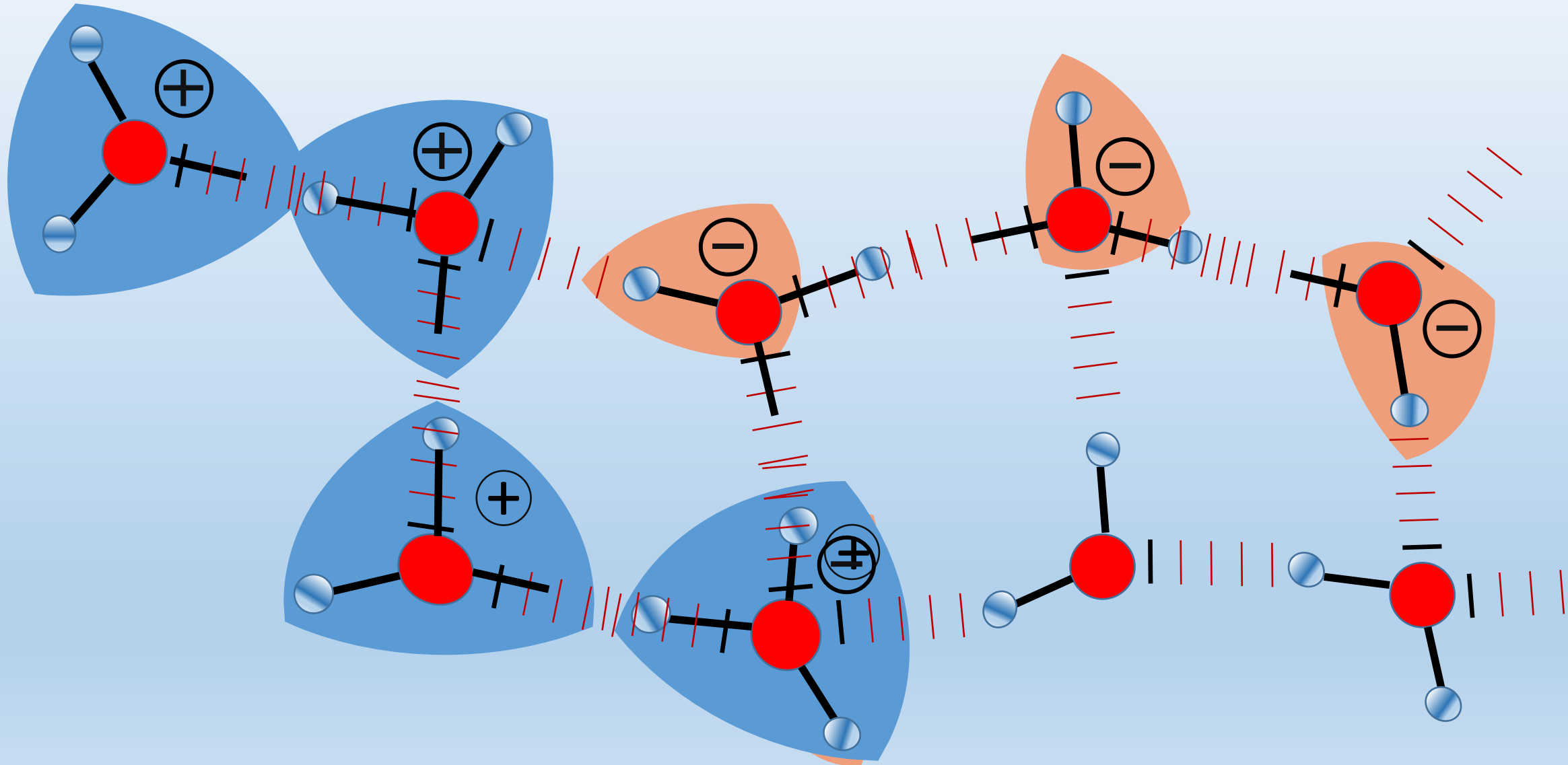
- Is the concentration of hydrogen ions in extracellular fluid (ICF) small, large, huge or minuscule?
- Why is maintaining  $H^+$  concentration within narrow limits much more important than maintaining strict concentrations of let's say iodine or zink<sup>1</sup>?
- Is it more accurate to speak of  $H_3O^+$  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

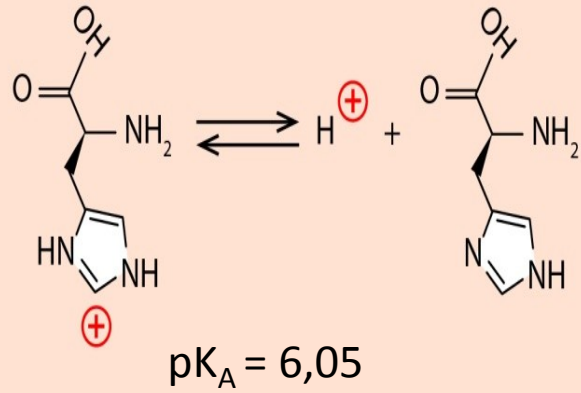
- Concentration of  $H^+ = [H^+] \sim 1\,000\,000x \ll [Na^+]$  – minuscule
- Maintaining pH within tight limits is important because of very large reactivity of  $H^+$  and its effect on the conformation of many macromolecules, especially proteins.
- Hydrogen bond – special type of weak chemical bond created by  $H^+$ ; it binds  $H_2O$  molecules together  $\rightarrow$  liquefaction of water
- $pH_{\text{plasma, Norm}} \approx 7,4 > 7,0 \rightarrow$  alkaline pH  $\rightarrow [OH^-] > [H_3O^+]$

# Dynamics of $\text{H}_3\text{O}^+$ and $\text{OH}^-$ movement in water

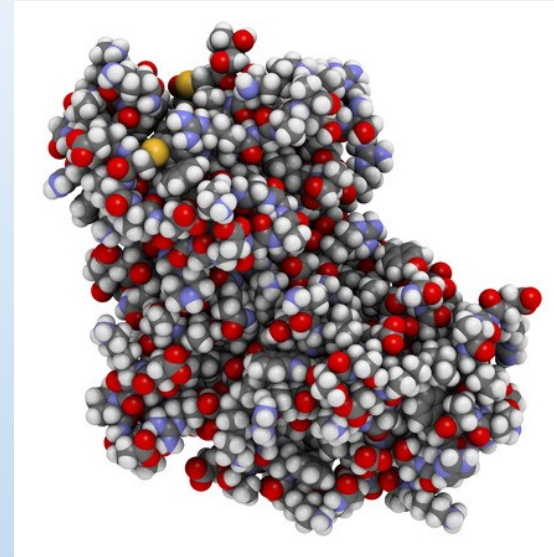
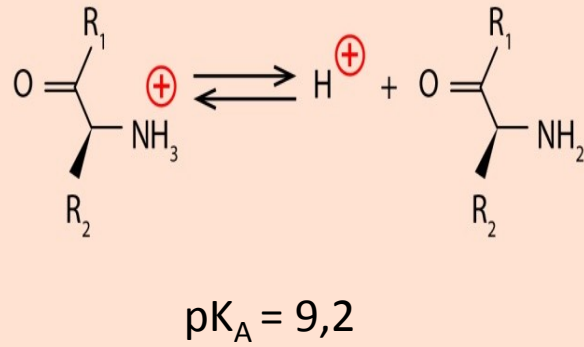


# Amino-acid charge and protein conformation

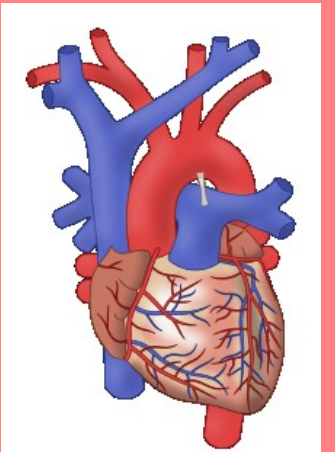
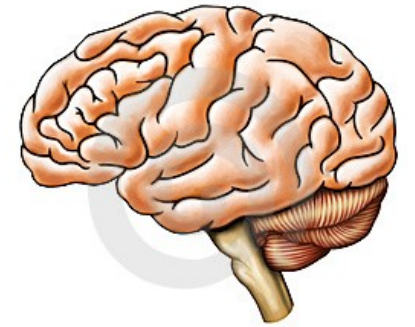
Histidine side chain



Amino terminus



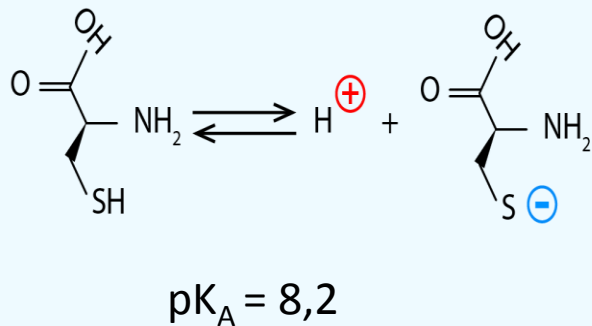
Crucial organs:



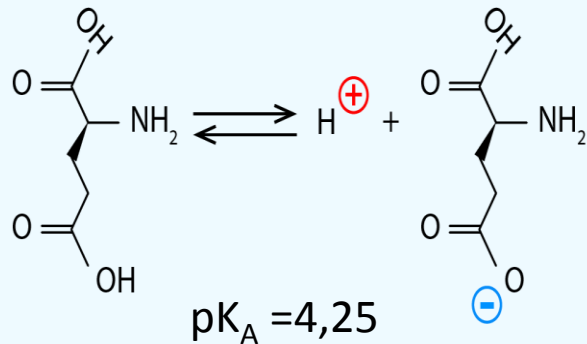
Conformation change

Dysfunction

Cysteine:



Glutamic acid:



# pH definition and its consequences

- Would you remember how pH is defined?
  - And what are rules of calculating with logarithms? E.g.  $\log(A \times B) =$
  - 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?<sup>1</sup>
  - 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

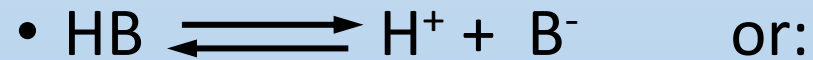
- $\text{pH} = -\log_{10}([\text{H}^+])$
- $\log(\text{AB}) = \log(\text{A}) + \log(\text{B})$
- $\text{H}^+$  concentration increasing twice:  $[\text{H}^+]_{\text{New}} = 2[\text{H}^+]_{\text{Old}}$
- From the pH definition and the logarithm calculation rules:  
$$\text{pH}_{\text{New}} = -\log([\text{H}^+]_{\text{New}}) = -\log(2 \times [\text{H}^+]_{\text{Old}}) = -\log(2) + (-\log([\text{H}^+]_{\text{Old}})) =$$
$$= -0,3 + \text{pH}_{\text{Old}}$$
- ➔ Therefore: If  $\text{H}^+$  concentration doubles:  $\text{pH}_{\text{New}} = \text{pH}_{\text{Old}} - 0,3$
- When  $[\text{H}^+]_{\text{New}} = 1/10 \times [\text{H}^+]_{\text{Old}}$  :  $\text{pH}_{\text{New}} = -\log(1/10) + (-\log([\text{H}^+]_{\text{Old}})) =$   
$$= +1 + \text{pH}_{\text{Old}}$$
 . If  $[\text{H}^+]$  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:



- 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:

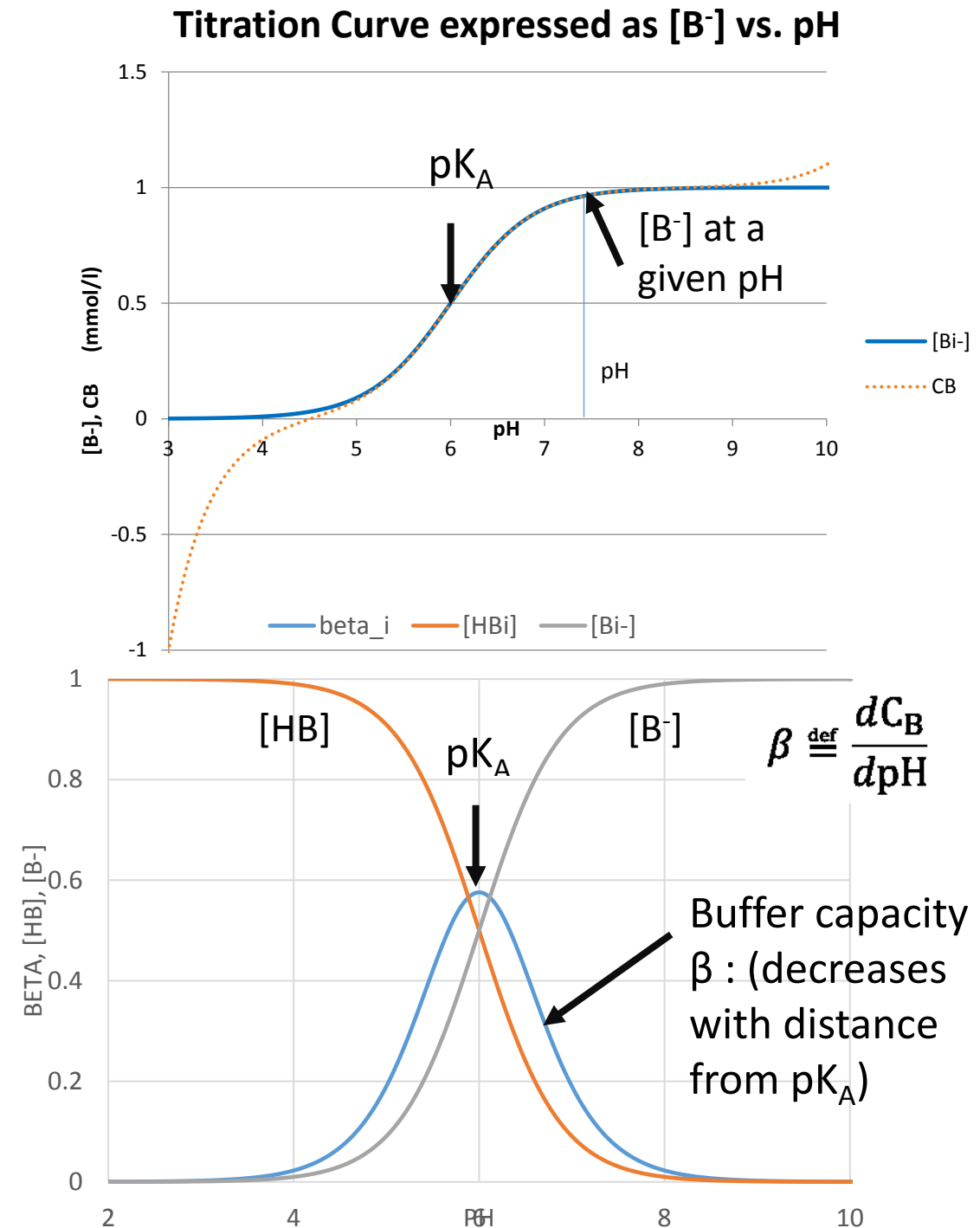
$$pH = pK_A + \log_{10} \frac{[B_i^-]}{[HB_i]}$$

- $[HB]$  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  $\beta$ .
- 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  $\downarrow[B^-]$ ,
- At alkalic pH, there is  $\downarrow[HB]$
- *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?*

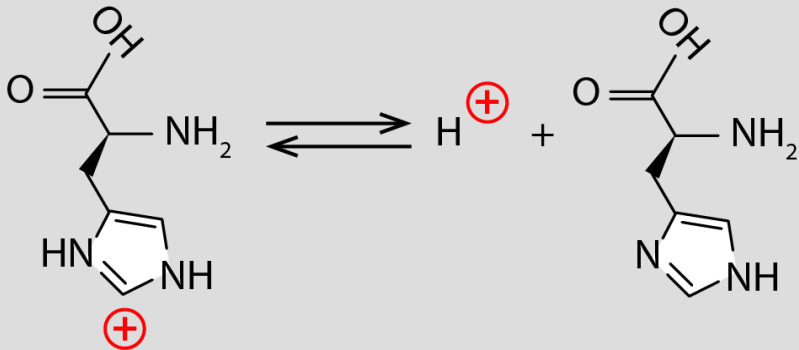


# Protein Buffers

- 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



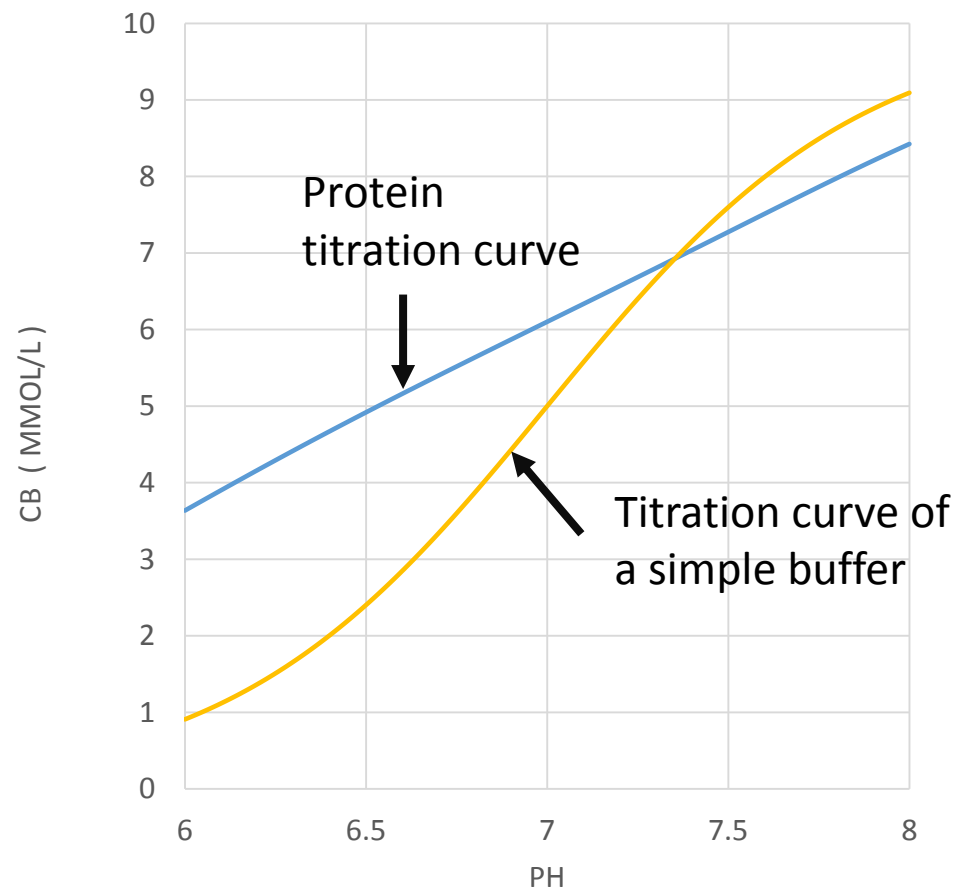
Tab:  $pK_A$

$pK_9$	$pK_{15}$	$pK_{10}$	$pK_{13}$	$pK_{11}$	$pK_8$	$pK_{12}$	$pK_7$	$pK_5$	$pK_3$	$pK_1$	$pK_2$	$pK_{14}$	$pK_{16}$	$pK_6$	$pK_4$
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

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

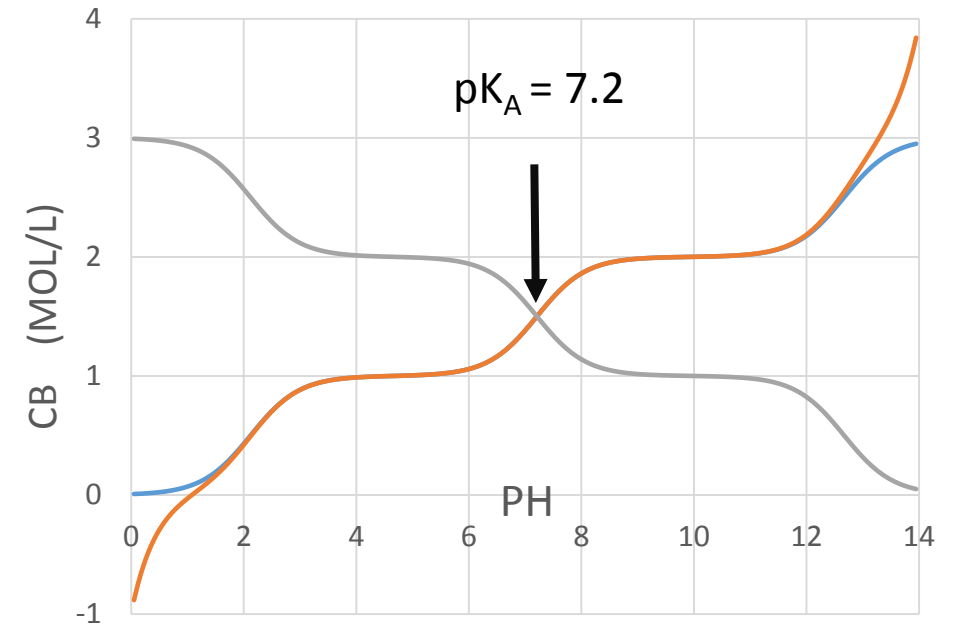
...ins in the albumin molecule (ordered)

# Protein Buffers



# Phosphate Buffer

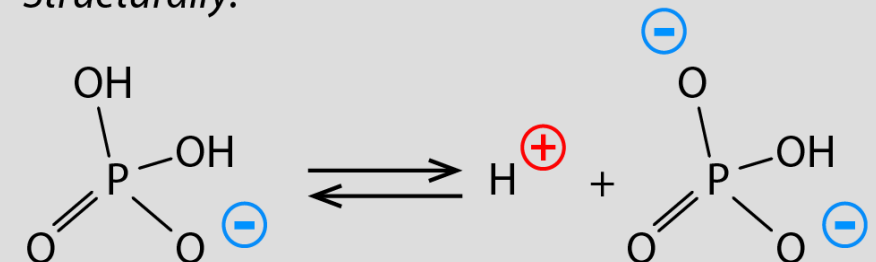
- Principal intracellular buffer
- Incl. phosphate residues of DNA
- The 2<sup>nd</sup> dissociation step is important, having  $pK_A = 7.2$



Phosphate



Structurally:



# Bicarbonate Buffer



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

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

$$pH = pK_A + \log \frac{[\text{HCO}_3^-]}{s * p\text{CO}_2}$$

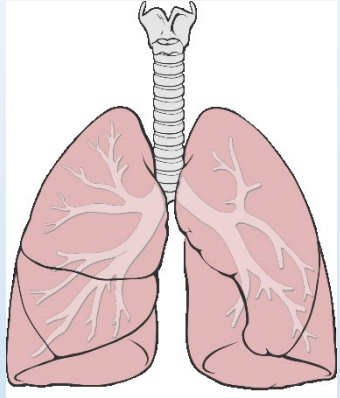
Substituting numerical values (for  $p\text{CO}_2$  in kPa) :

$$pH = 6,1 + \log \frac{[\text{HCO}_3^-]}{0,22 * p\text{CO}_2}$$

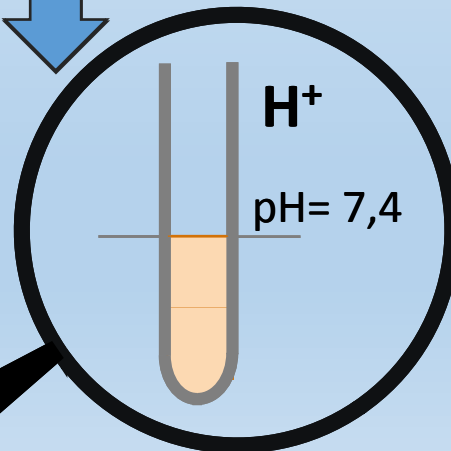
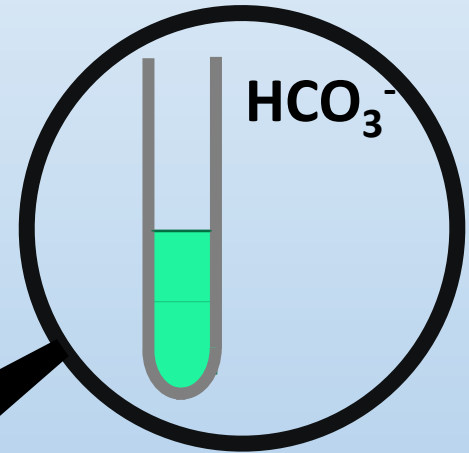
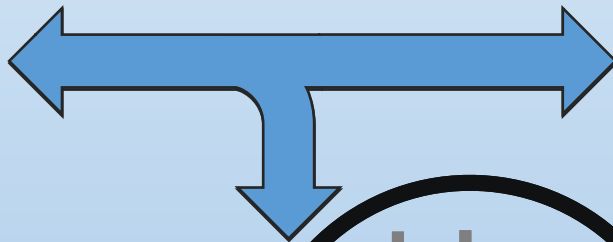
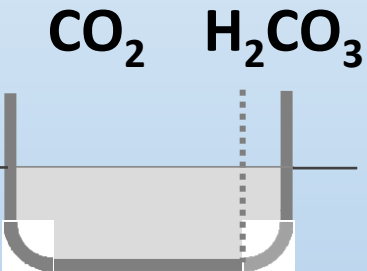
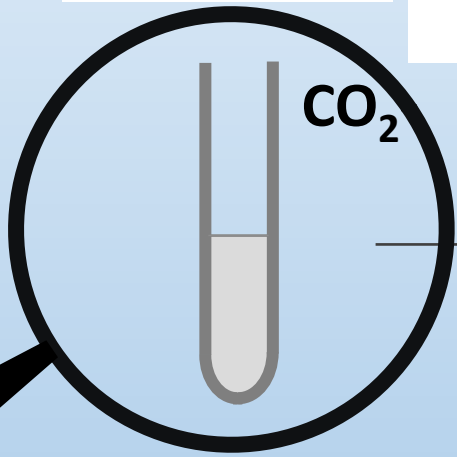
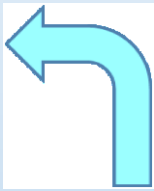
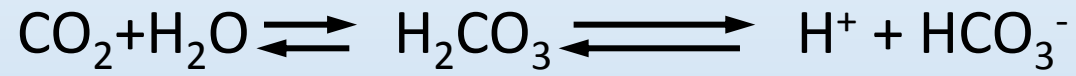
*Question for straight-A students:*  $pK_A$  of the bicarbonate buffer is 6.1. This is quite off the physiological  $pH = 7.4$ . Does this lower the buffer capacity of bicarbonate buffer?



# Bicarbonate Buffer



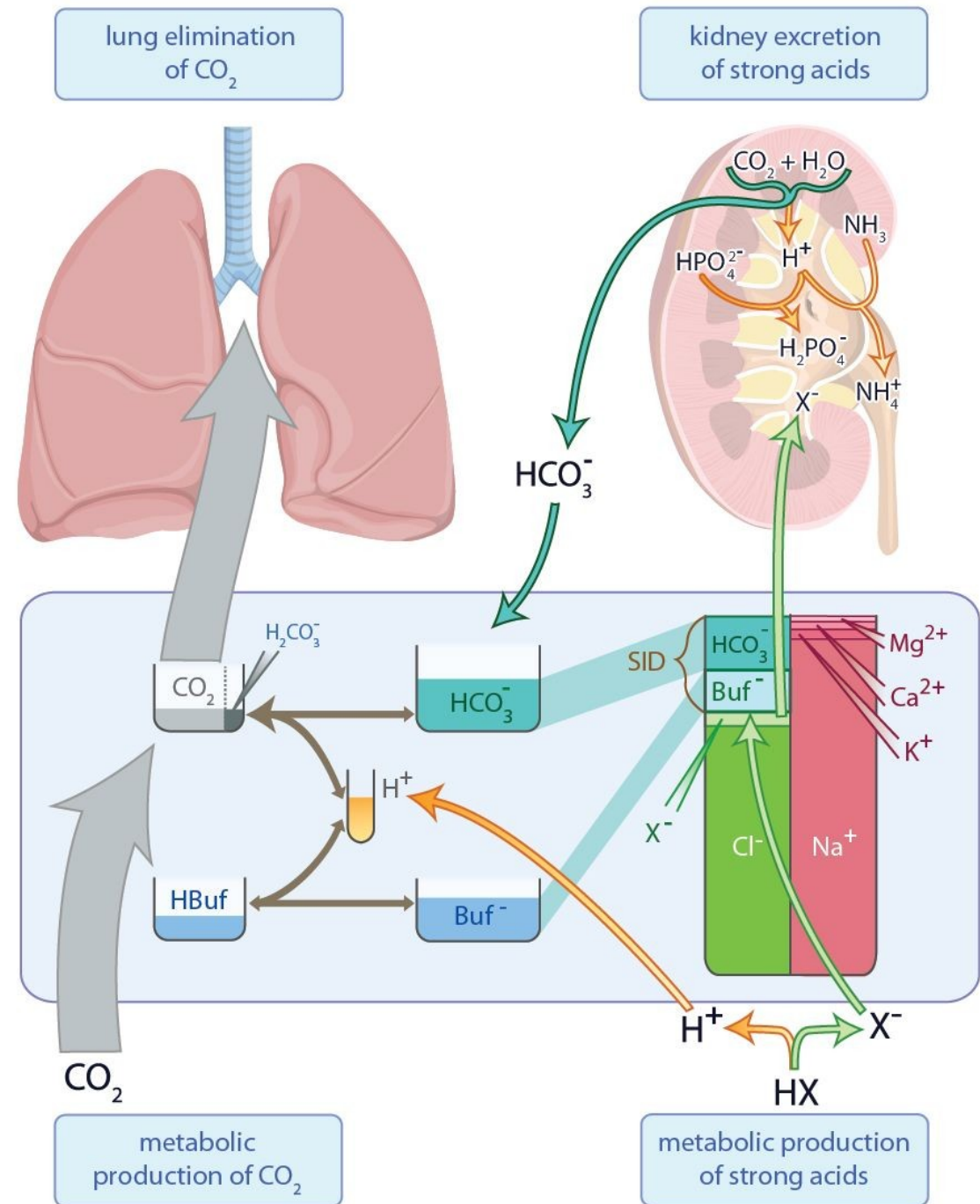
Possible depiction of reaction equilibria (as described by Henderson-Hasselbalch equation):



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  $\text{CO}_2$ 
  - Thus  $\text{pCO}_2$  can be easily regulated.  $\text{CO}_2$  behaves as an open system
- Other flows and the relationship with concentrations of other ions (electro-neutrality) are depicted in the figure:



# Bicarbonate Buffer

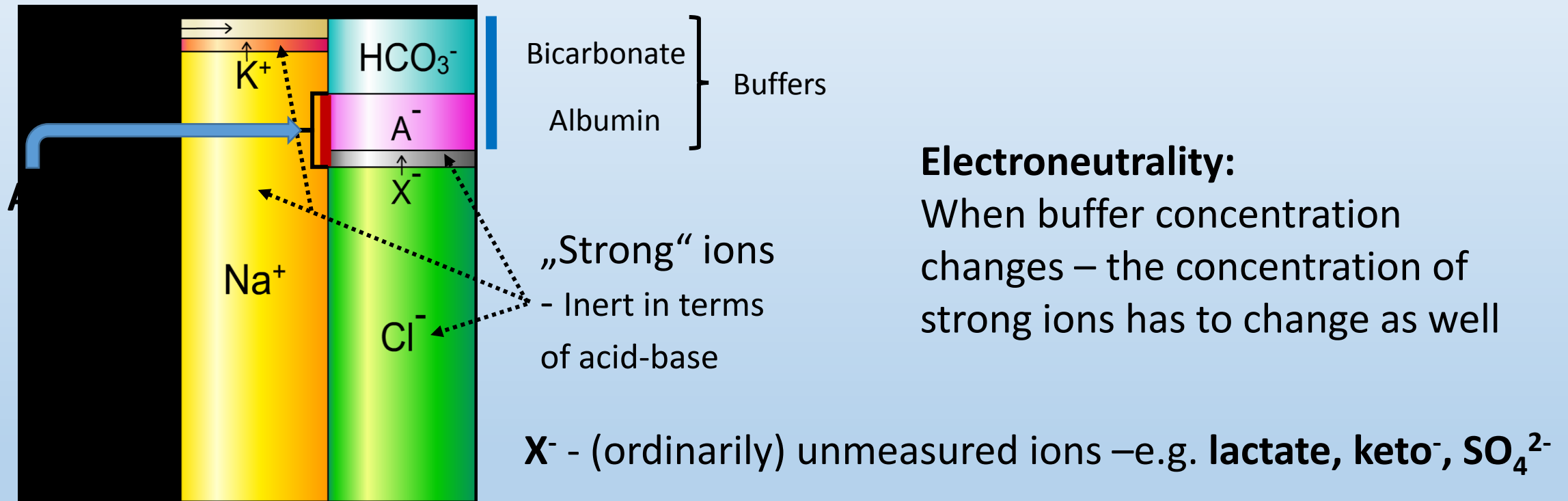
- It is the **principal buffer in terms of longer-term regulation** of  $H^+$  balance in the body.
- Lungs – regulate  $pCO_2$
- Kidneys – regulate the level of  $HCO_3^-$  in blood plasma and excretion of  $H^+$

	Primary Disturbance	When $H^+ = 40 \text{ nmol/L}$	Compensation
<b>Respiratory Acidosis</b>	$\uparrow pCO_2$	Reacts to the right - $\uparrow H^+$	Kidneys - $\uparrow HCO_3^-$ , $\uparrow BE$
<b>Metabolic Acidosis</b>	$\downarrow HCO_3^-$ (or $\uparrow \uparrow \uparrow H^+$ )	Reacts to the right when primary cause $\downarrow HCO_3^-$ (Reacts to the left when primary cause $\uparrow \uparrow \uparrow H^+$ ) –end result - $\uparrow H^+$	Lungs - $\downarrow pCO_2$
<b>Respiratory Alkalosis</b>	$\downarrow pCO_2$	Reacts to the left - $\downarrow H^+$	Kidneys - $\downarrow HCO_3^-$ , $\downarrow BE$
<b>Metabolic Alkalosis</b>	$\uparrow HCO_3^-$	Reacts to the left - $\downarrow H^+$	Lungs - $\uparrow pCO_2$

# Base Excess - BE

- Base Excess – a very precise measure of metabolic disturbances (and metabolic compensations)
- Underlying logic: Lungs regulate  $p\text{CO}_2$ . This regulation does not influence the total concentration of base forms of buffers.
- By definition: When  $\text{pH} = 7,4$  (norm) and  $p\text{CO}_2 = 5,3$  kPa (norm), then  $\text{BE} = 0$  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 ( $\text{H}^+$ ) when  $\text{BE} = 0$  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  $p\text{CO}_2$

# System of Buffers and Electroneutrality



## Electroneutrality:

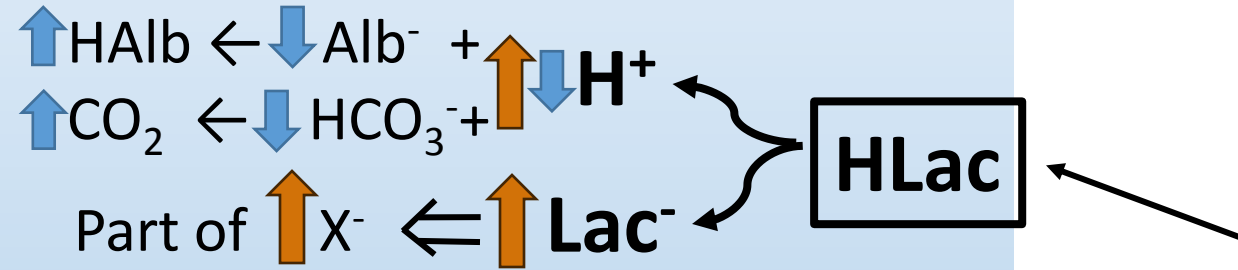
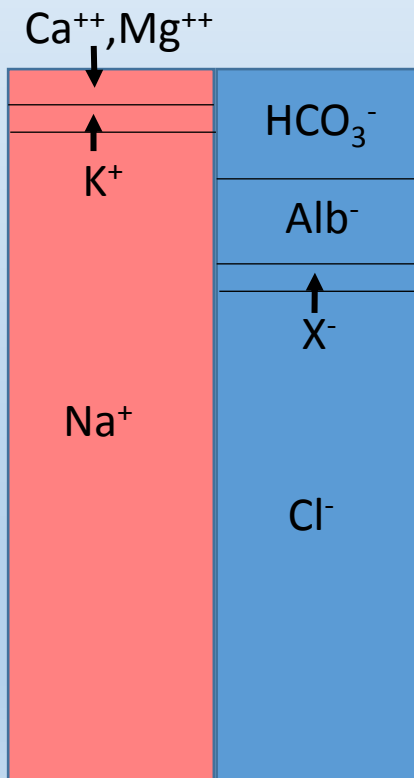
When buffer concentration changes – the concentration of strong ions has to change as well

$$\underline{AG = Anion\ gap = Na^+ + K^+ - Cl^- - HCO_3^-}$$

Parameter used in differential diagnosis of metabolic acidoses

# System of Buffers and Electroneutrality 2 – Example

**Runner in High Tatra:**  
Production of **lactic acid** in muscles







# Acid-base Balance Disturbances

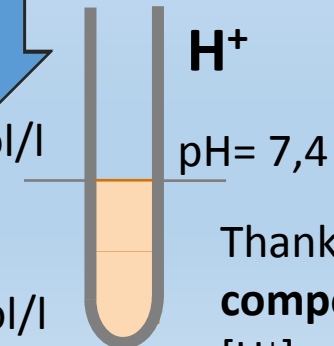
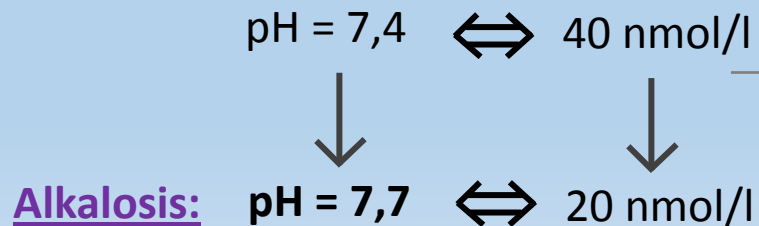
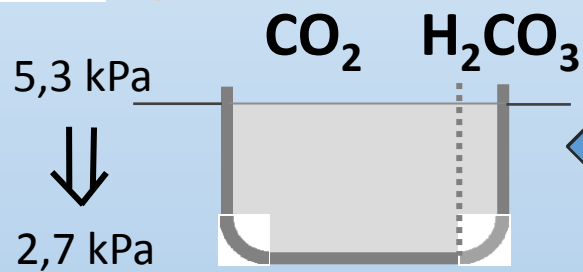
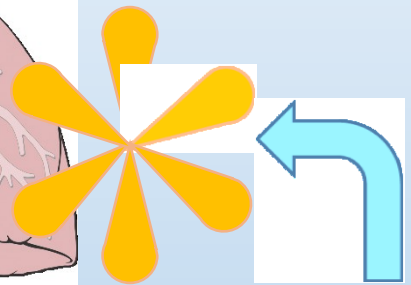
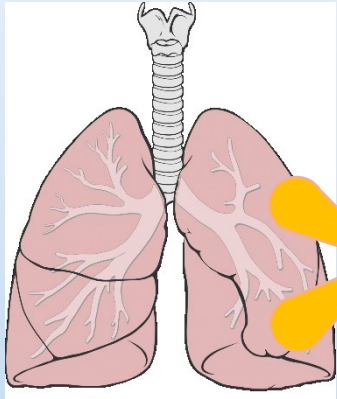
= Pathophysiology of ABB

# Respiratory Disturbances and their Compensation



# Respiratory Alkalosis and its Compensation

Cause:  
Hyperventilation



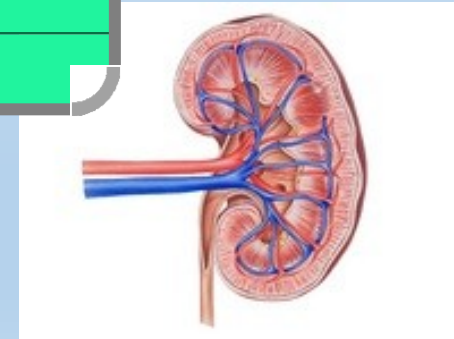
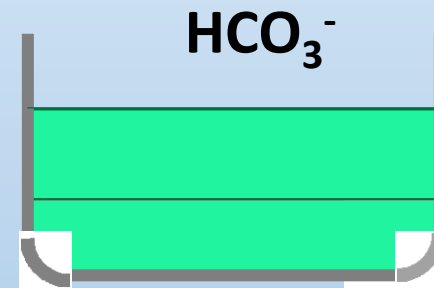
$\text{H}^+$   
 $\text{pH} = 7,4$

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

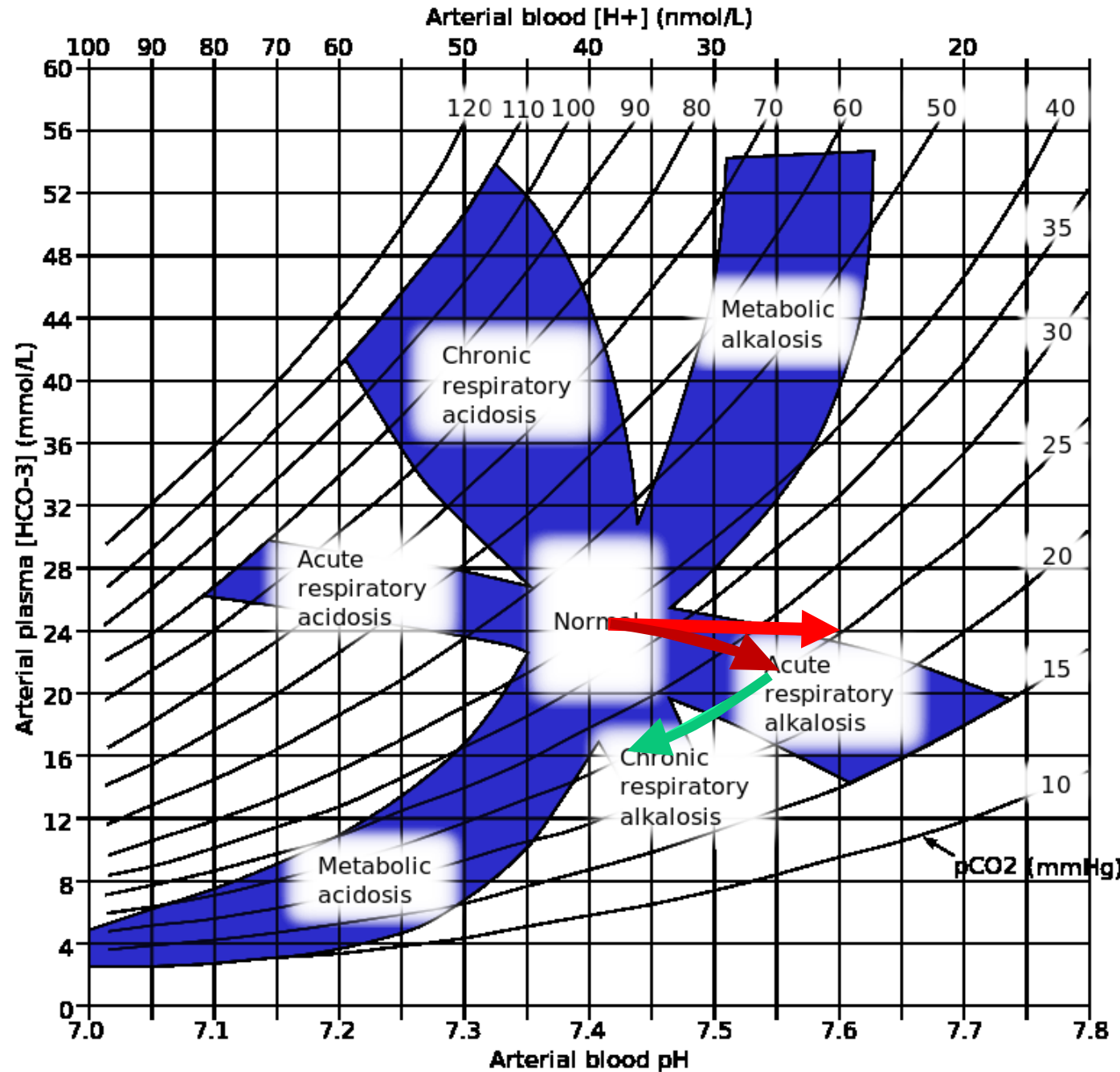
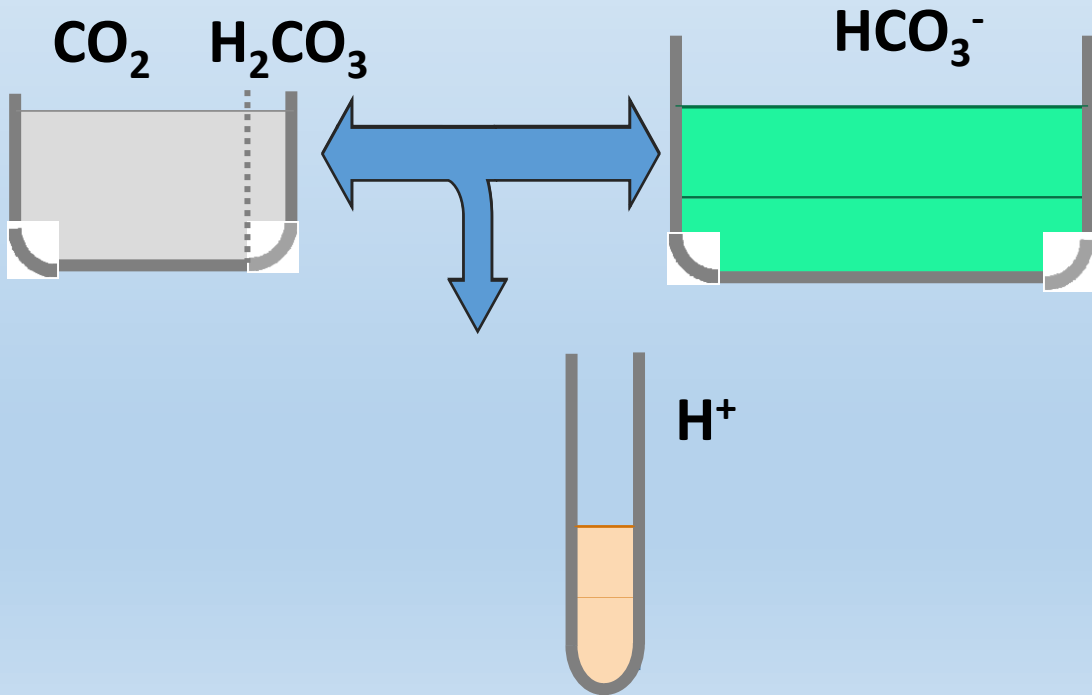
Kidney (metabolic) compensation:

*Takes 2-3 days to develop*

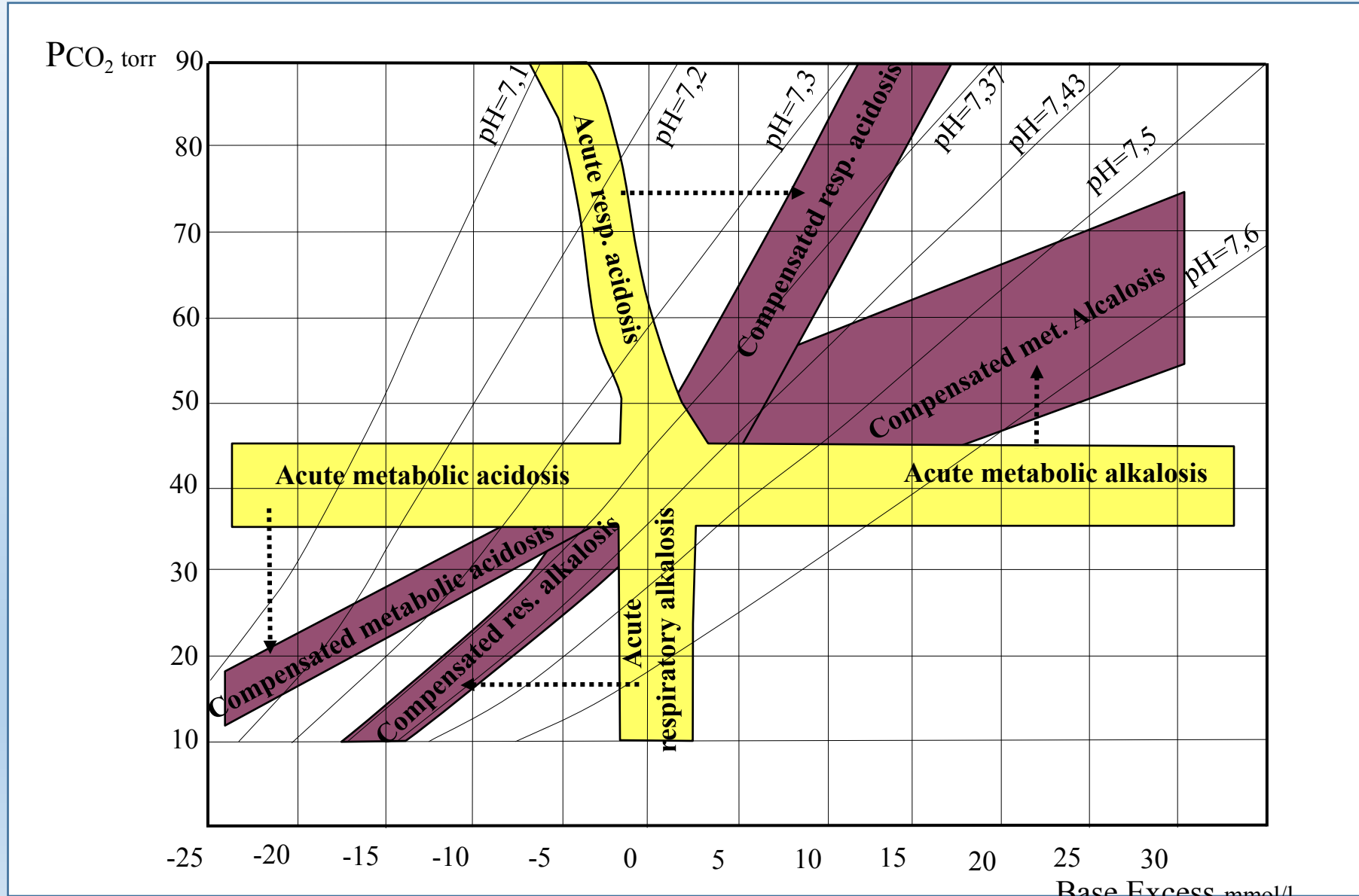
Kidneys excrete less  $\text{H}^+$  and more bicarb.  
= less bicarbonate returns to blood



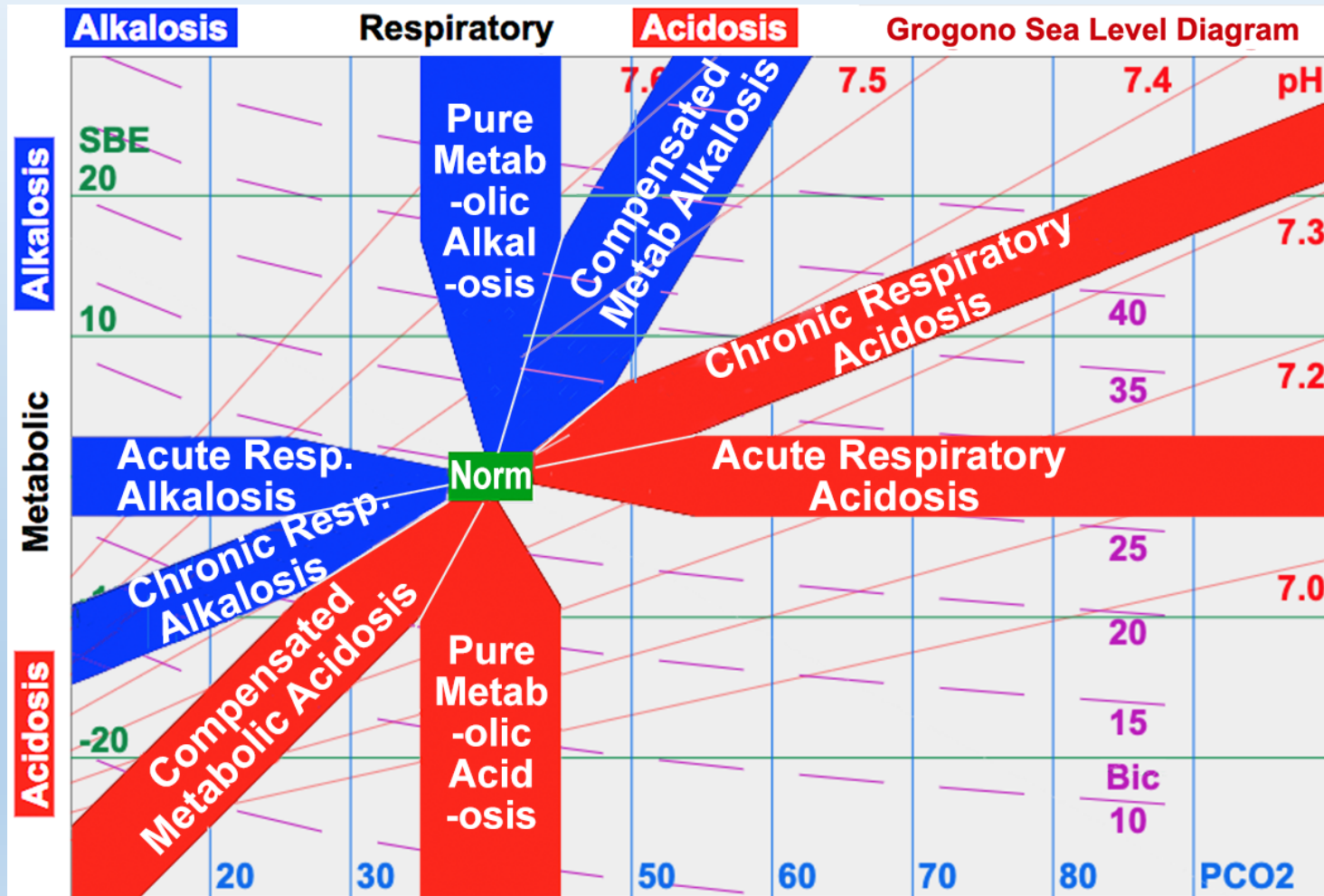
# Compensation Diagrams



# Compensation Diagrams 2



# Compensation Diagram pCO<sub>2</sub> vs BE – Different



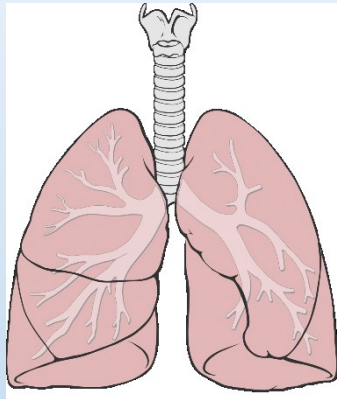
# “Boston” Rules for Diagnosing ABB Disturbances

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		$(pCO_2)_{EXPECTED} = 1.5 * [HCO_3^-] + 8$ <p>or</p> $\Delta pCO_2 = 1.2 * \Delta [HCO_3^-]$
	Alkalosis		$(pCO_2)_{EXPECTED} = 0.7 * [HCO_3^-] + 20$ <p>or</p> $\Delta pCO_2 = 0.6 * \Delta [HCO_3^-]$
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



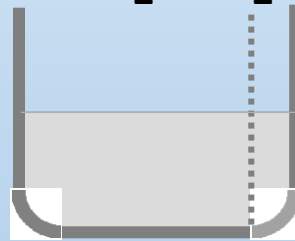
Cause: Hypoventilation

Part of global respiratory insufficiency (insufficiency type II)

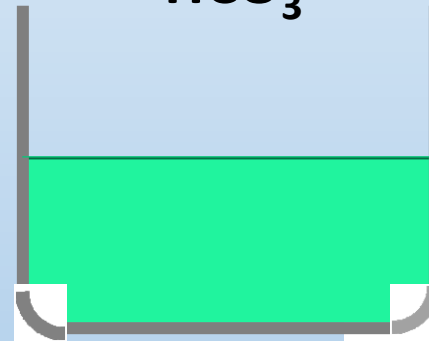


10,6 kPa  
↑  
5,3 kPa

CO<sub>2</sub> H<sub>2</sub>CO<sub>3</sub>



HCO<sub>3</sub><sup>-</sup>



Acidosis:

pH = 7,7

⇌ 80 nmol/l

↑  
pH = 7,4

⇌ 40 nmol/l



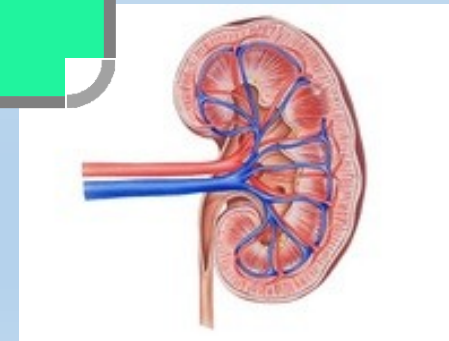
H<sup>+</sup>

Thanks to the **compensation** the [H<sup>+</sup>] and pH return closer to norm

Kidney (metabolic) compensation:

*Takes 2-3 days to develop*

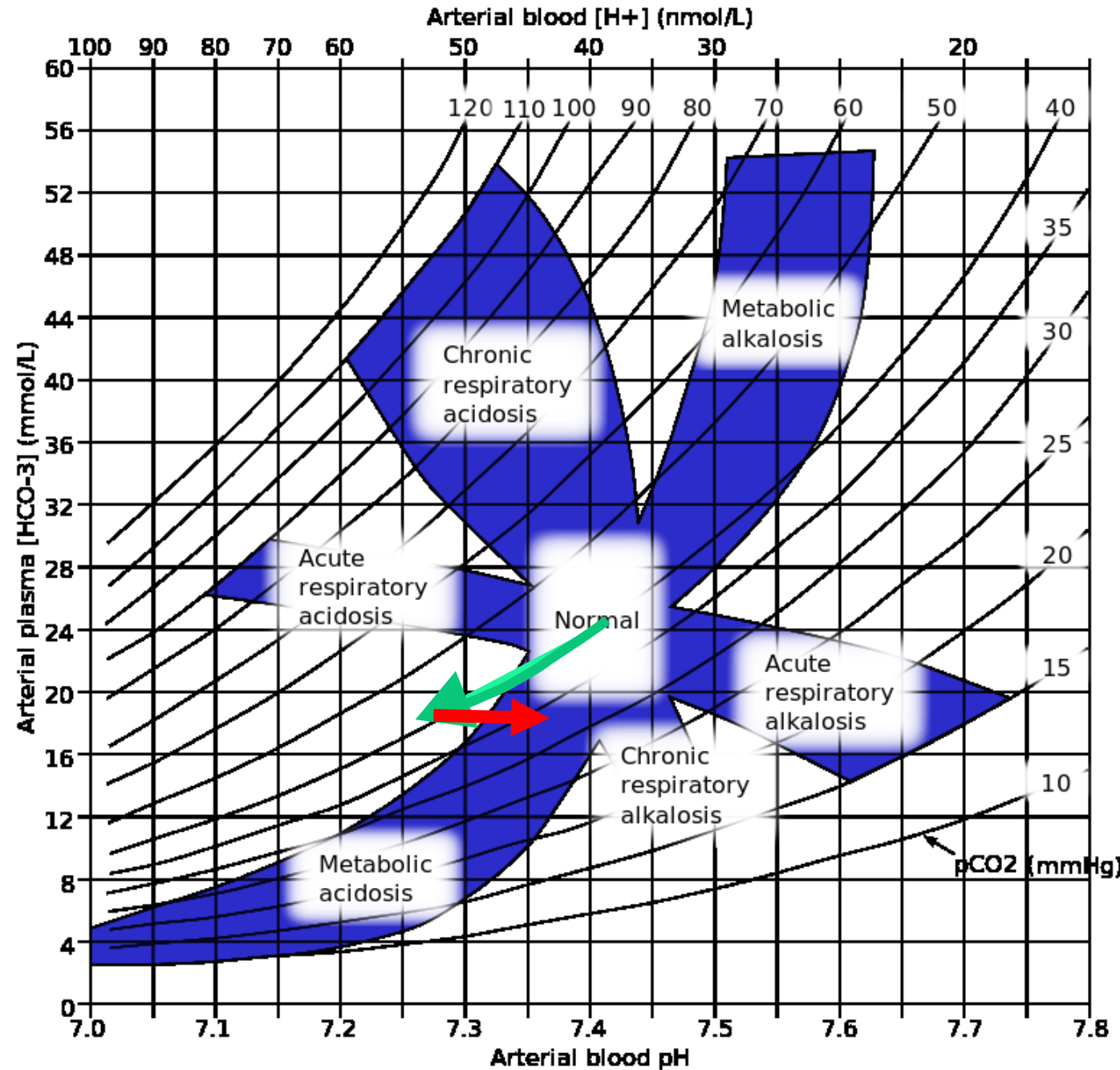
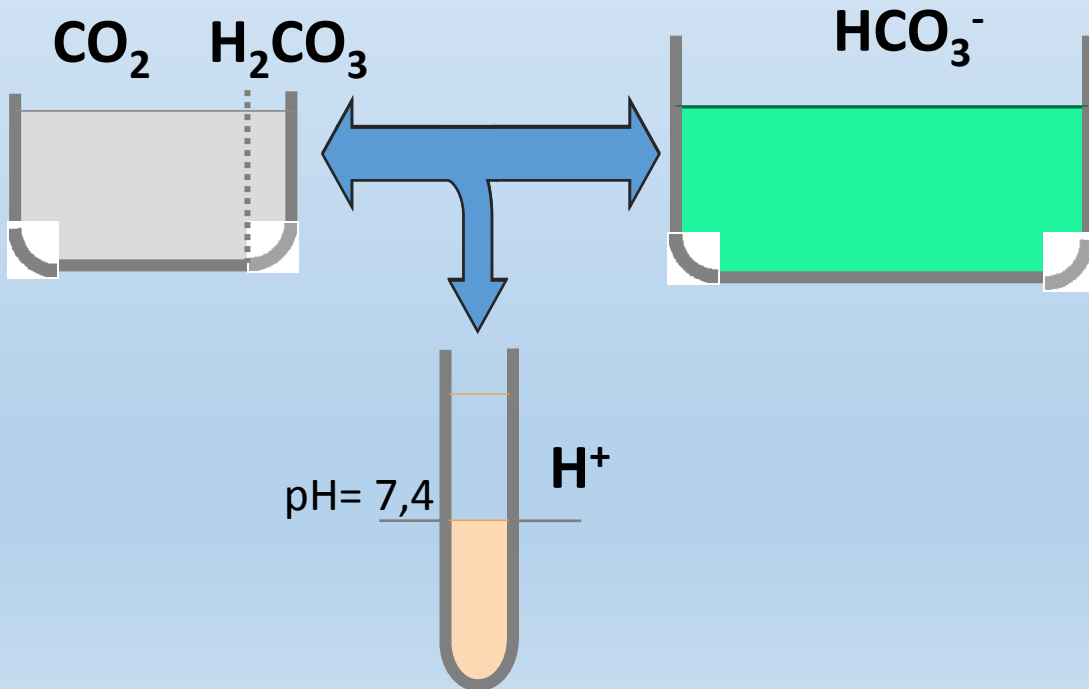
Kidneys excrete **more H<sup>+</sup>** = returning **more bicarbonate into blood**



# Metabolic Disturbances and their Compensation

# Metabolic Acidosis- Compensation Diagrams

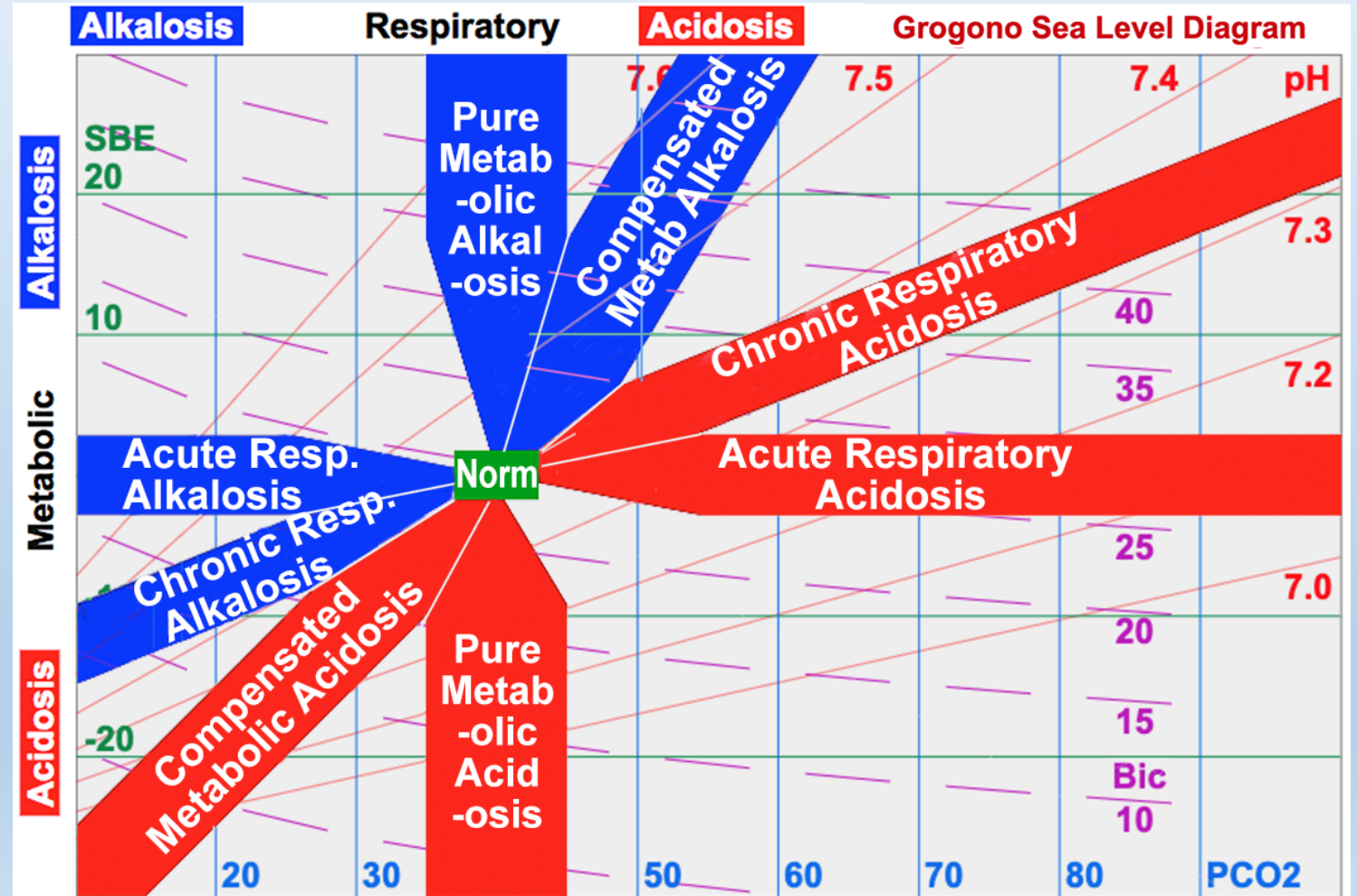
Respiratory compensation generally develops faster than the metabolic disturbance itself, thus the division into acute and chronic disturbances is missing in diagrams focused more clinically.





# Metabolic Acidosis – Compensation Diagrams

Try to draw the beakers using your memory only and add corresponding arrows illustrating acute and chronic metabolic acidosis into the diagram (full respiratory compensation develops in about 10 h)



# 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):

$$\text{pH} = 7,4 \pm 0,04$$

$$\text{pCO}_2 = 5,3 \text{ kPa}$$

$$\text{pO}_2 = 13,3 \text{ kPa}$$

- Calculated by the machine:
- $[\text{HCO}_3^-] = 24 \text{ mmol/l}$ 
  - *calculated using HH equation*
- $\text{BE} = 0 \text{ mEq/l}$ 
  - *Base Excess, Hb concentration is needed for the calculation.*

# Case study No. 3

- 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
  - pO<sub>2</sub> = 8.0 kPa
  - pCO<sub>2</sub> = 10.6 kPa
  - HCO<sub>3</sub><sup>-</sup> = 38 mmol/L
  - BE = 12 mmol/L



What kind of acid-base disturbance do we deal with?  
Is this an acute or 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  $p\text{CO}_2$  in the inspired air

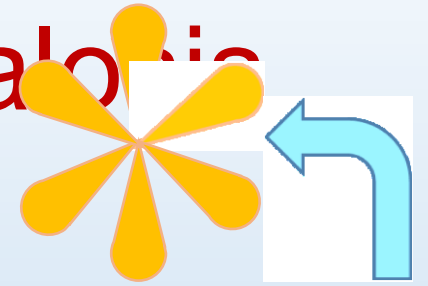
# Case Study No. 2

- 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
  - pO<sub>2</sub> = 13.4 kPa
  - pCO<sub>2</sub> = 4.1 kPa
  - HCO<sub>3</sub><sup>-</sup> = 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



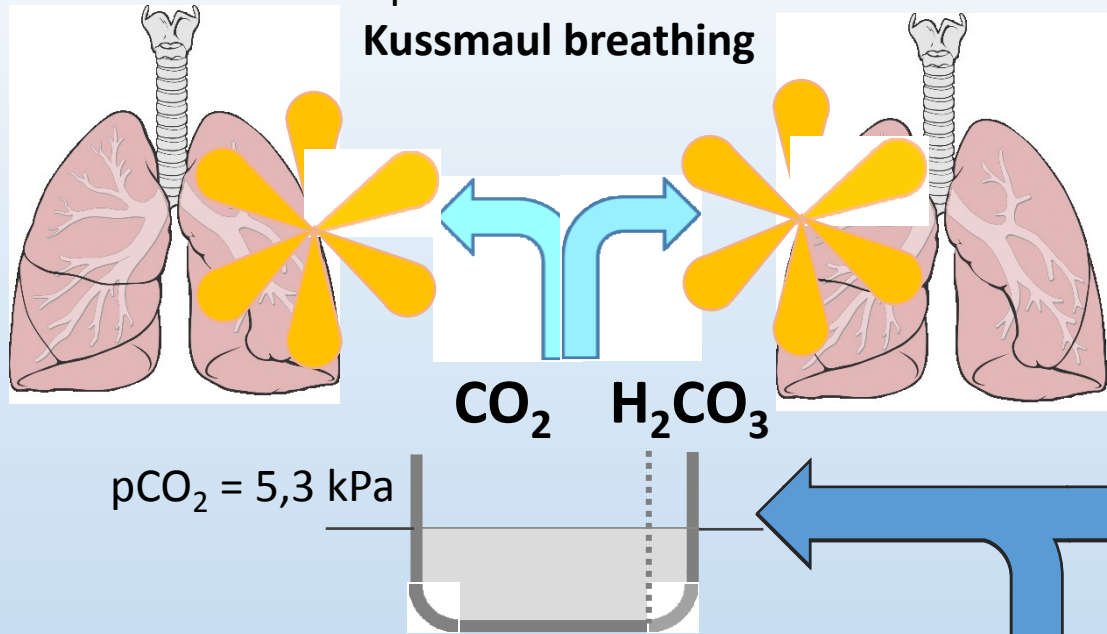
## Hyperventilation

- 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



Hyperventilation as a compensation of acidosis:

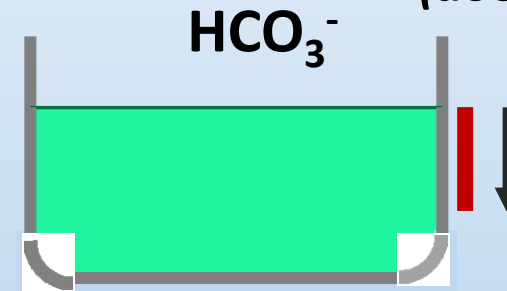
Kussmaul breathing



# Metabolic Acidosis 1 + Compensation

$$\uparrow \text{AG} = \text{Na}^+ + \text{K}^+ - \text{Cl}^- - \downarrow \text{HCO}_3^-$$

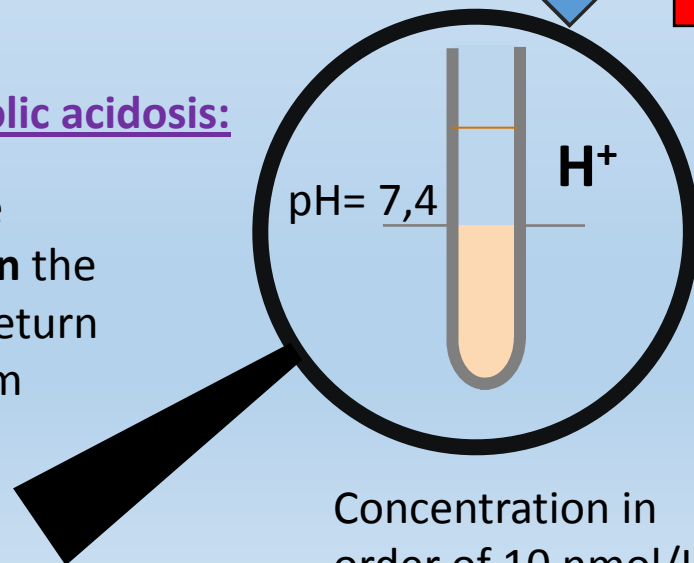
(does not include X<sup>-</sup>)



→ ↑AG is equivalent to ↑X<sup>-</sup>

compensated metabolic acidosis:

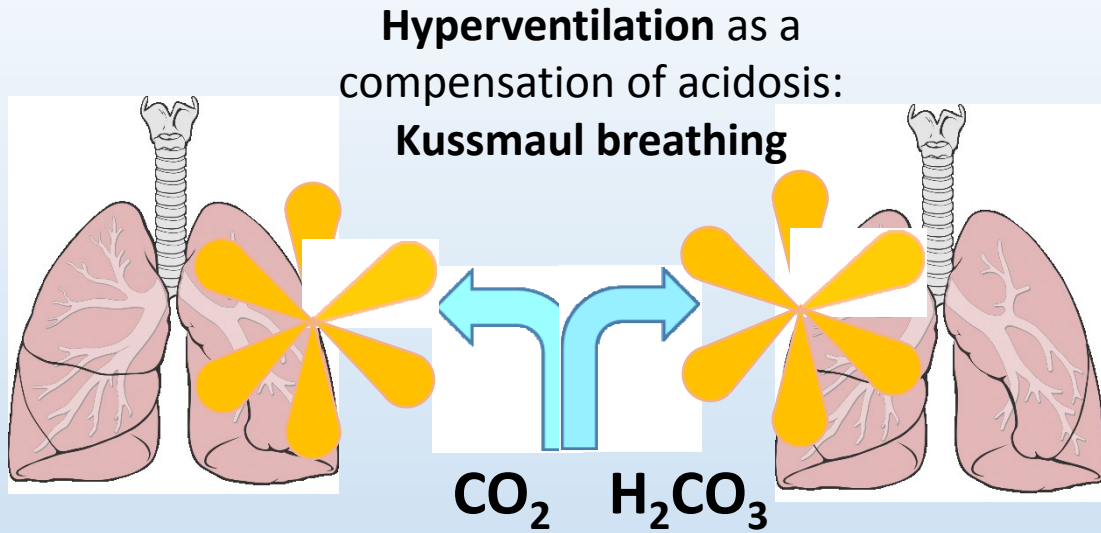
Thanks to the **compensation** the [H<sup>+</sup>] and pH return closer to norm



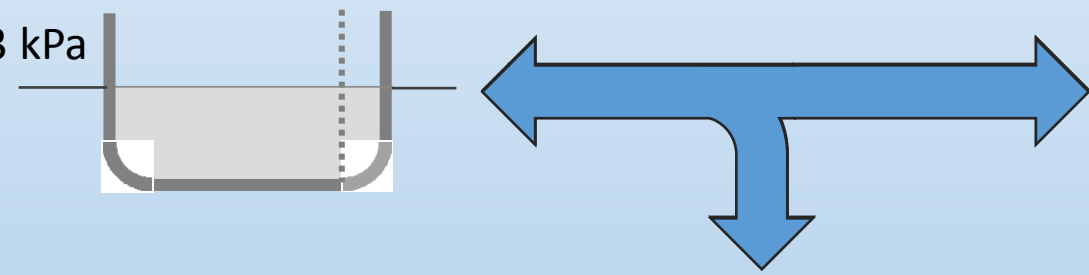


# Metabolic Acidosis 2 + Compensation

$$AG = Na^+ + K^+ - Cl^- - HCO_3^-$$

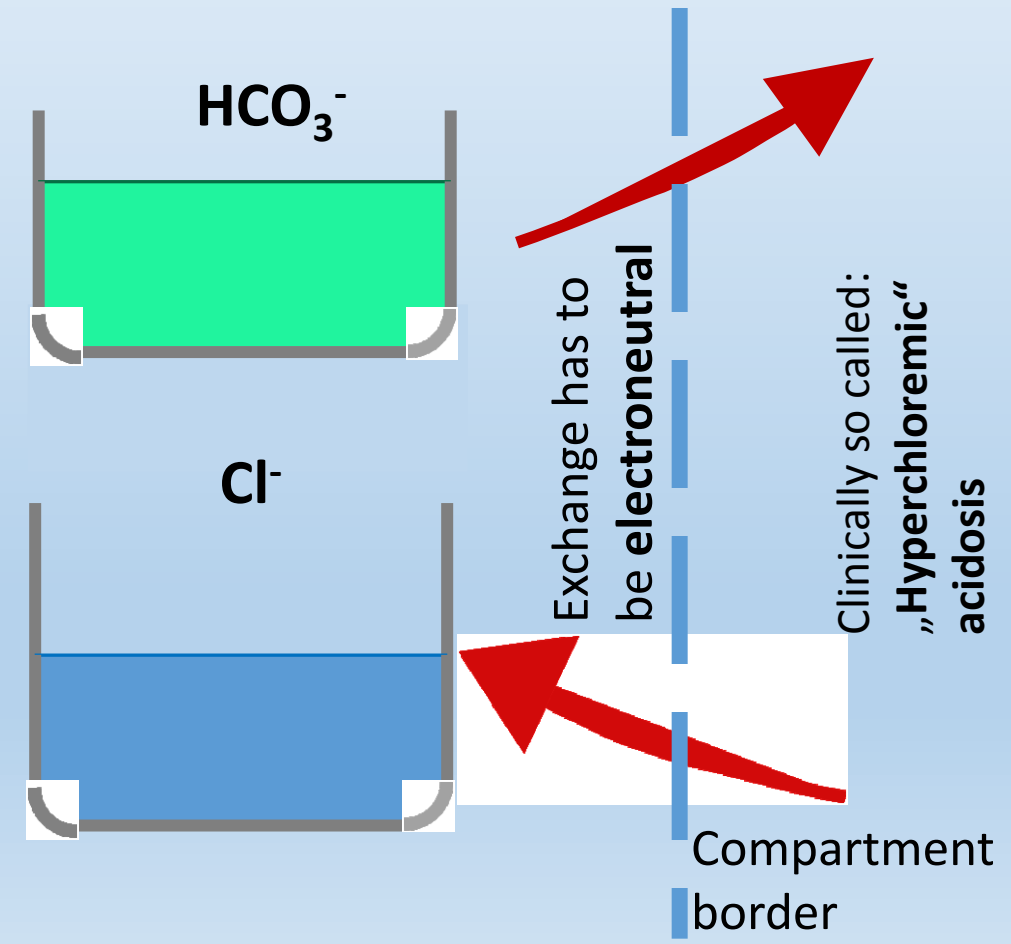
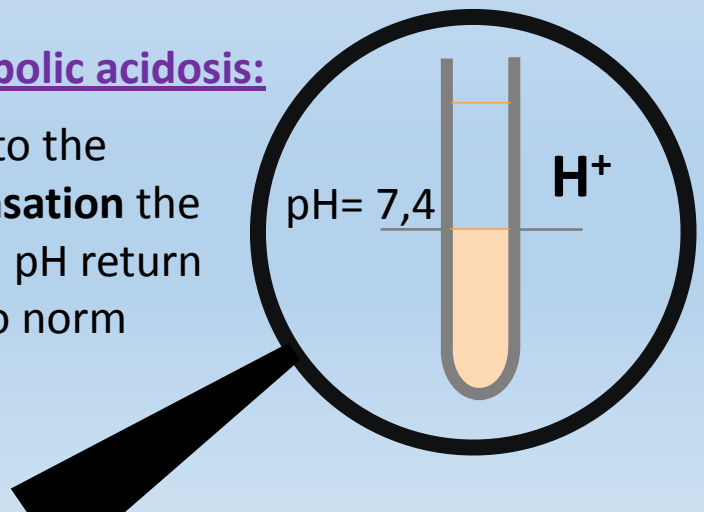


$pCO_2 = 5,3 \text{ kPa}$



## compensated metabolic acidosis:

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



# Case Study No. 1

- 38 yo female, DM 1<sup>st</sup> 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<sup>-1</sup>, HF 112 min<sup>-1</sup>, 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
pO <sub>2</sub>	12.8 kPa
pCO <sub>2</sub>	2.8 kPa
HCO <sub>3</sub> <sup>-</sup>	8 mEq/L
Glc	15 mmol/L
Na <sup>+</sup>	148 mEq/L
K <sup>+</sup>	5.5 mEq/L
Cl <sup>-</sup>	110 mEq/L
Positive acetone in urine	

# 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

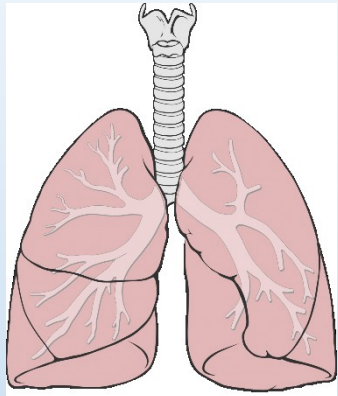
- Through intestines
  - Diarrhea
  - Fistulas and stomias
- Through kidneys (loss of regulation)
  - So called Renal tubular acidoses
  - Renal failure (can have  $\uparrow$ AG)

The difference in common strong ions reflects  $\downarrow$   $\text{HCO}_3^-$   
E.g.  $\uparrow$   $\text{Cl}^-$  (instead of the bicarbonate)-  
so called „hyperchloremic acidoses“  
(Or there can be e.g.  $\downarrow$   $\text{Na}^+$  or..)  
**AG (anion gap) is normal!**

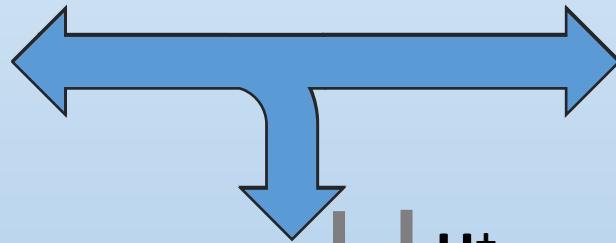
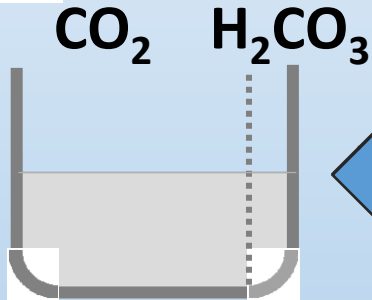
# Exercise – Metabolic Alkalosis

- 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

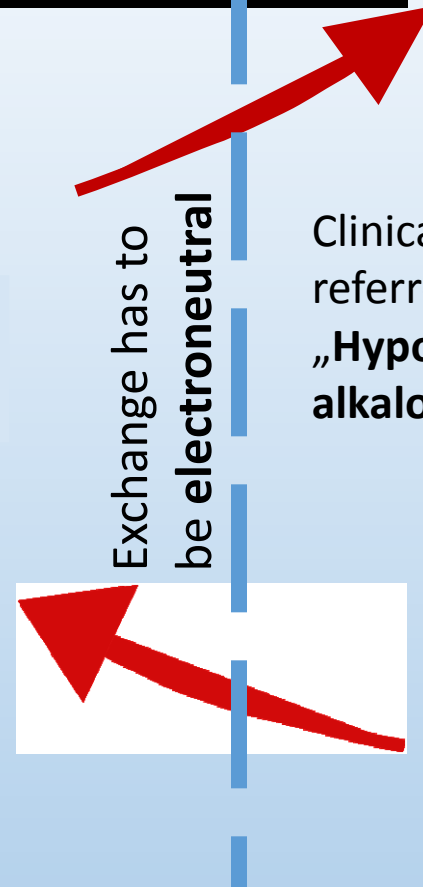
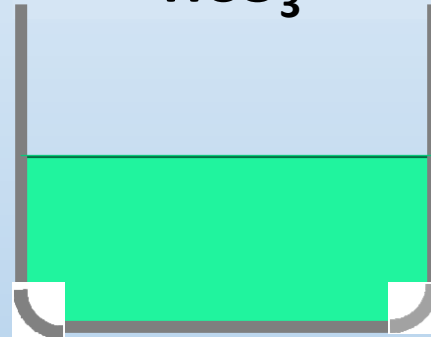
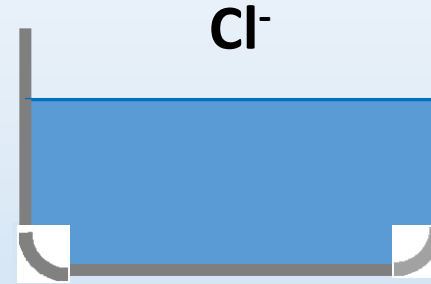


Compensation of metabolic alkalosis by hypoventilation is limited by hypoxia



$H^+$   
pH= 7,4

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



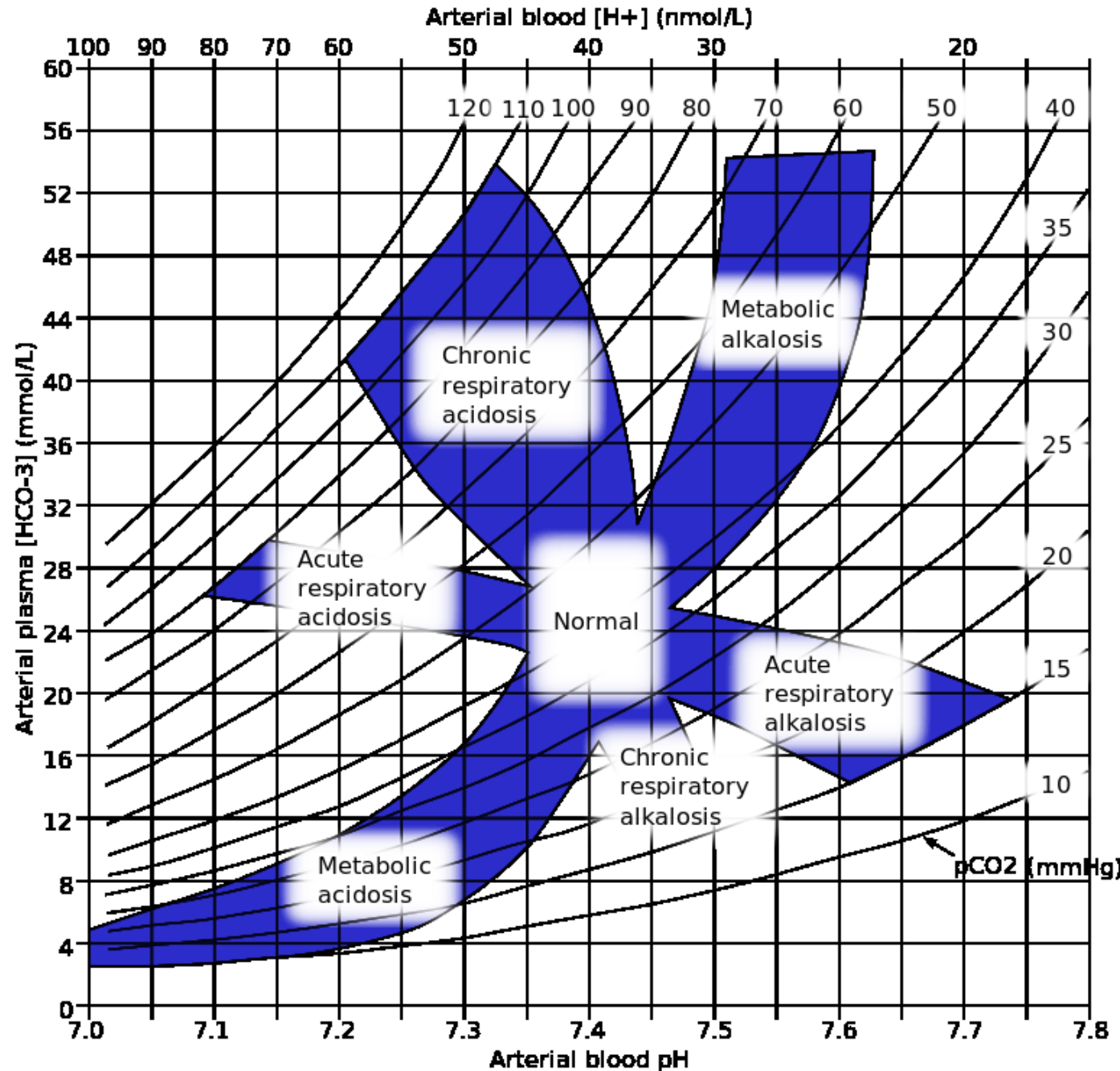
Exchange has to be **electroneutral**

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

Compartment border (e.g. stomach mucosa)

# Compensation of metabolic alkalosis

- Try to deduce the beakers and the arrows in the compensation diagram yourself.
- Min 2 minutes



# Possible Causes of Metabolic Alkalosis

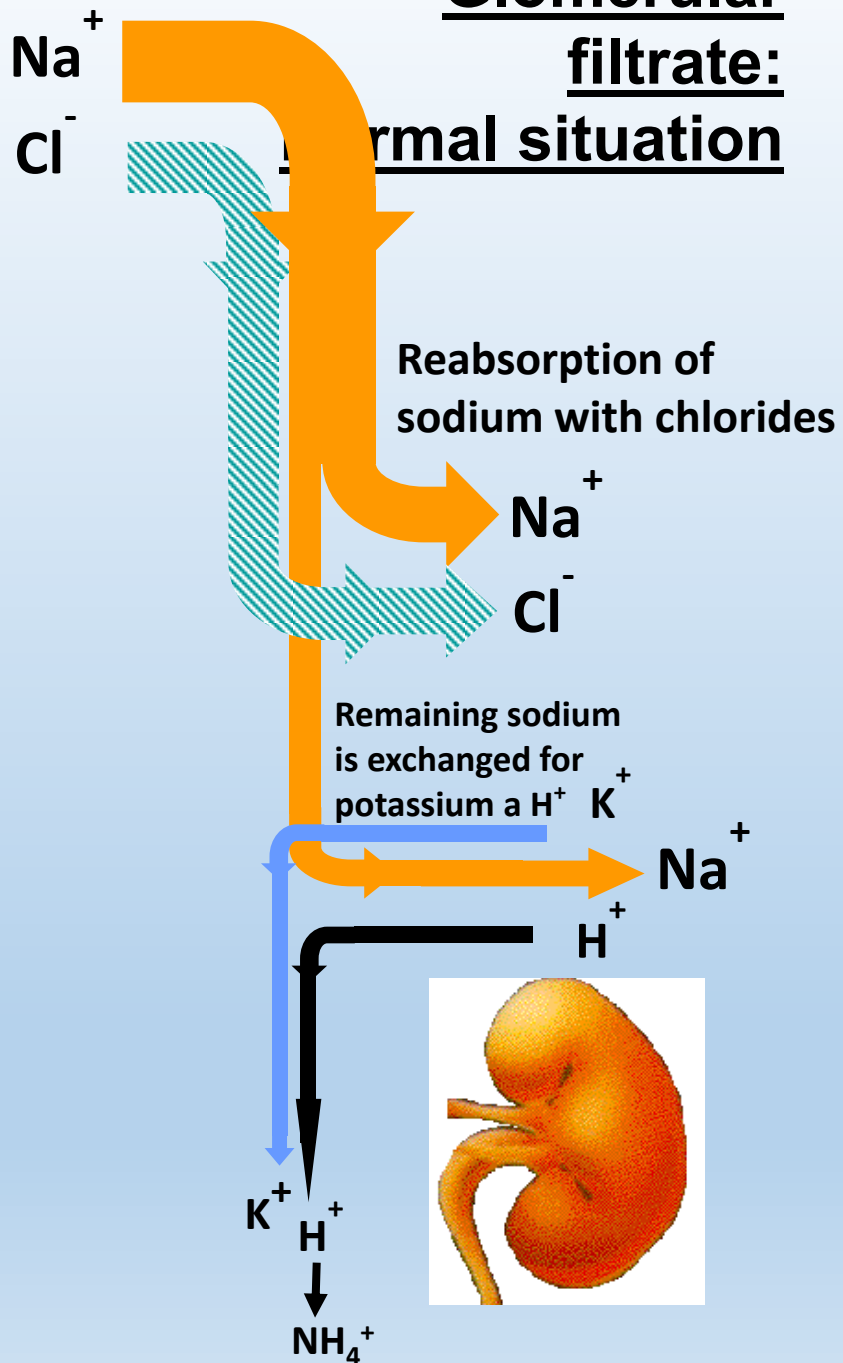
- Loss of acid by vomiting
  - ↑  $\text{HCO}_3^-$  produced by stomach into the blood (when  $\text{H}^+$  is secreted into the lumen).
- Increased renal  $\text{HCO}_3^-$  production/ increased urine  $\text{H}^+$  secretion
  - Hyperaldosteronism
  - So called Bartter syndrome
- Liver failure (↓ production of urea from  $\text{NH}_4^+$  - the reaction would be acidifying)
- Non-adequate infusion of bicarbonates/ Ringer lactate.

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

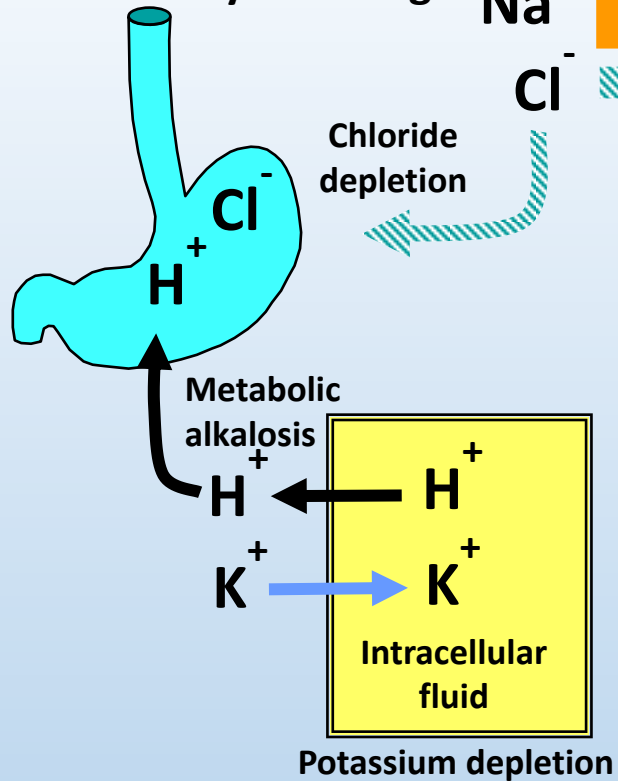
- Clinically important!
- After profuse vomiting, **hypochloremic metabolic alkalosis** develops
- Under normal circumstances, kidneys should regulate and produce only slightly acidic or alkaline urine.
- Instead, kidneys can worsen the alkalosis
- See next slide:



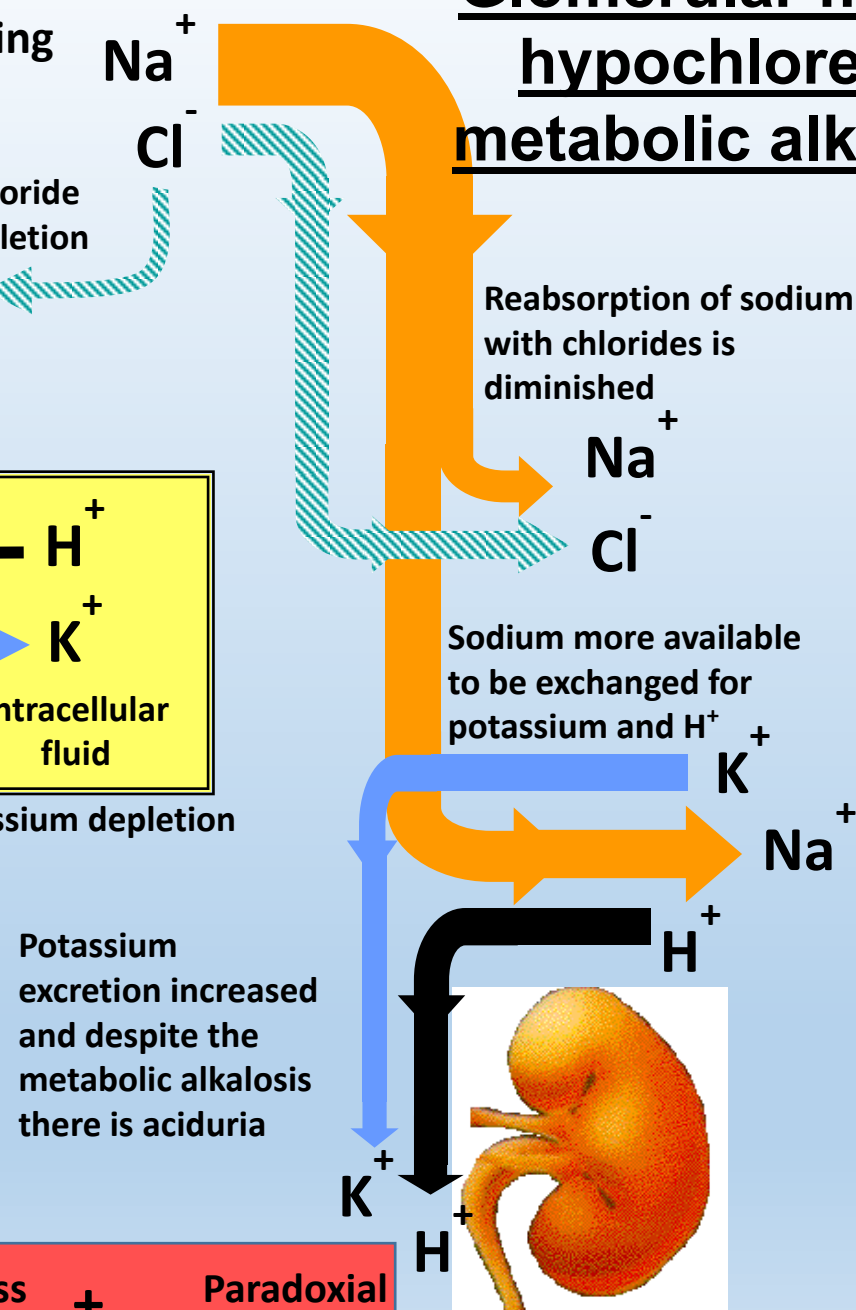
**Glomerular filtrate:**  
**Normal situation**



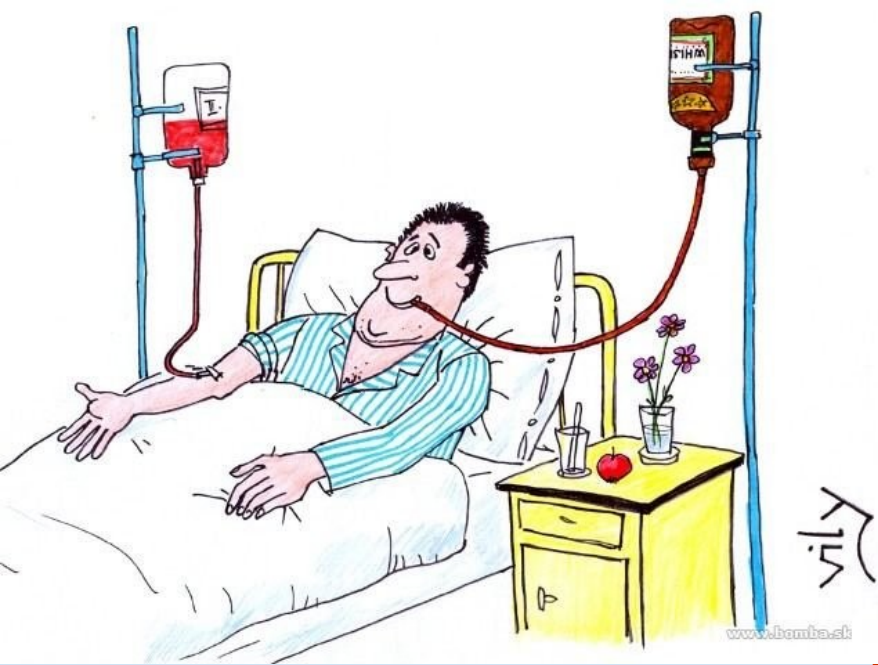
Primary cause: Loss of  $Cl^-$  and  $H^+$  by vomiting



**Glomerular filtrate:**  
**hypochloremic metabolic alkalosis**



Increased loss of potassium + Paradoxical Aciduria



# Clinical Examples of ABB Disturbances

# Summary

1. Physiology and chemistry  
H<sup>+</sup>, pH, buffers, buffers  
incorporated into metabolism,  
HH equation, electroneutrality
2. Disturbances divided into  
respiratory and metabolic
3. Clinical examples and  
causes

	Primary disturbance	Compensation
<b>Respiratory acidosis</b>	↑pCO <sub>2</sub>	Renal - ↑HCO <sub>3</sub> <sup>-</sup> , ↑BE
<b>Metabolic acidosis</b>	↓HCO <sub>3</sub> <sup>-</sup>	Pulmonary - ↓pCO <sub>2</sub>
<b>Respiratory alkalosis</b>	↓pCO <sub>2</sub>	Renal - ↓HCO <sub>3</sub> <sup>-</sup> , ↓BE
<b>Metabolic alkalosis</b>	↑HCO <sub>3</sub> <sup>-</sup>	Pulmonary - ↑pCO <sub>2</sub>

Thank you for your  
attention