Bioinorganic Chemistry:
The Good, the Bad, and the Potential of Metals

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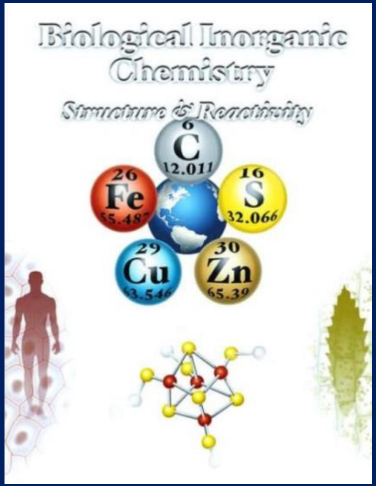
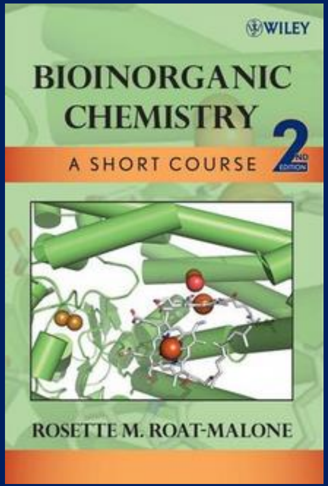


Biological Inorganic Chemistry:
Structure & Reactivity

I. Bertini, H. B. Gray, E. I. Stiefel, and J. S. Valentine



Bioinorganic Chemistry:
A Short Course
Second Edition

Rosette M. Roat-Malone

Professor Arthur D. Tinoco

- Bioinorganic Chemistry Professor
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Course Resources

1. **Literature**
   - Two main textbooks
   - Supplementary textbook chapters
   - Research articles

2. **Website**
   - http://uprrpbioinorganicchemistry.weebly.com/

     - Software links will be provided here

Course Lectures

1. Combination of traditional lecture notes and powerpoint slides for visual aid

2. Lecture slides will be made available on course website

3. Lectures may deviate from textbook therefore attendance is **IMPORTANT**

4. Follow student interactive pedagogy

Grading Scheme

The course is designed as a very informative overview of Bioinorganic Chemistry. Your grades will be distributed over different components to maximize your opportunity to do well in the course.

Assignments:	**25%/20%**
Assessments (2):	**45%/50%**
Activity Project:	**25%/25%**
Participation:	**5%/5%**
	100%

Introduction to Bioinorganic Chemstry

Bertini et al. Ch. 1, Ch. 2 (p. 7-12), Ch. 5 (p. 57-61)

What is Bioinorganic Chemistry?

Branch of chemistry that elucidates the structures and reactivities of metal ions and metal-based biomolecules and the roles they play in biological systems both beneficial and detrimental.

- Life strongly depends on the function of small molecules, proteins, and nucleic acids often in conjunction with metals.

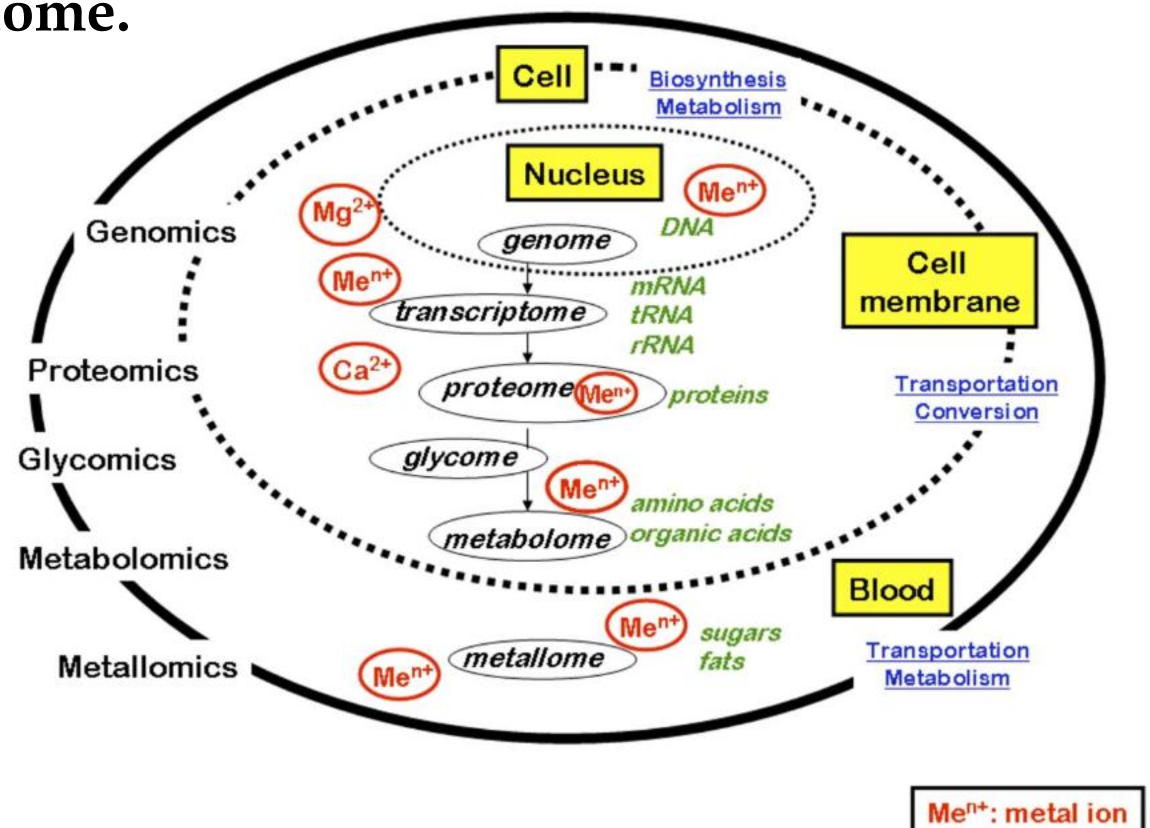
- One of the greatest challenges of the 21st century is deducing specific gene sequences as they code for the employment of certain elements (metals and nonmetals) for biomolecular mechanisms.

Genomics ⟷ Proteomics ⟷ Metabolomics

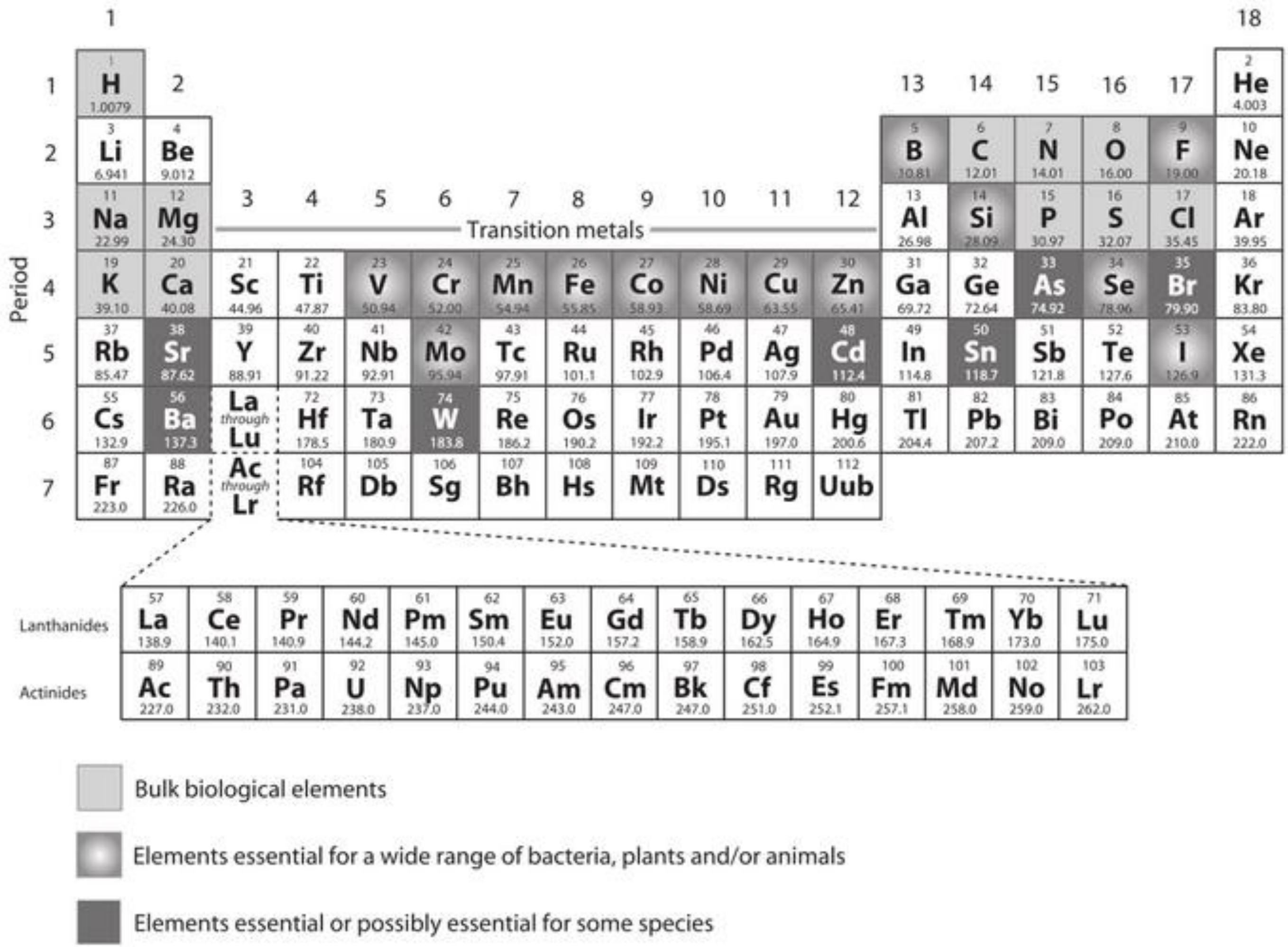
Metallomics

What is Bioinorganic Chemistry?

Every facet of the "omics" world (discipline that studies different components of a living organism) is affiliated with the metallome.



Elements important to life.



Elements important to life.

- **C, H, N, O, P, S provide the building blocks for major cellular components (proteins, nucleic acids, lipids-membranes, polysaccharides, and metabolites).**

- **>30 elements are essential for most species to function**
  - **Essential does not mean high abundance**

The elements **C, N, O, H, Ca, P, K, and S** comprise nearly 97% of the human body (dried weight). But we can not survive with just these elements.

Table 1-1 Most Abundant Elements in the Human Body[a]

Element	Dry Weight (%)
C	61.7
N	11.0
O	9.3
H	5.7
Ca	5.0
P	3.3
K	1.3
S	1.0
Cl	0.7
Na	0.7
Mg	0.3

[a]Calculated from Frieden, E., *Sci. Am.* 227(1), 54–55 (1972).

Functional Roles of Elements in Biology

- Charge Balance and Electrolytic Conductivity: Na, K, Cl
- Structure and Templating: Ca, Zn, Si, S **Ti**
- Signaling: Ca, B, NO
- Brønsted Acid-Base Buffering: P, Si, C, H
- Lewis Acid-Base Catalysis: Zn, Fe, Ni, Mn
- Electron transfer: Fe, Cu, Mo
- Group Transfer (CH_3, O, S) : V, Fe, Co, Ni, Cu, Mo, W
- Redox Catalysis: V, Mn, Fe, Co, Ni, Cu, W, S, Se
- Energy Storage: H, P, S, Na, K, Fe
- Biomineralization: Ca, Mg, Fe, Si, Sr, Cu, P

Reactions of biomolecules are thermodynamically driven.

1. Biochemical reactions obey the three laws of thermodynamics and typically involve the acquisition and utilization of energy

2. The spontaneity of these reactions is defined by ΔG
   - $\Delta G = \Delta G° + RT \ln Q$

   - At equilibrium, $\Delta G = 0$,
     $\Delta G° = -RT \ln K = \Delta H° - T\,\Delta S°$

   - $\Delta G° < 0$ $(K > 1)$ indicates a spontaneous reaction; exergonic reaction

But…

Many things that shape life as it exists are the actions of organisms (mainly human) which trigger kinetic processes (geological, environmental, and biological) forcing life to sustain itself far from chemical equilibrium.

Kinetics (k values) vs. Thermodynamics (K values)

Course Objectives

1. Give you a global perspective of metals in biology by understanding fundamental interactions between metals and biomolecules
2. Discuss pertinent metal binding theories
3. Explore metal binding from the context of structure, stability (quantitative), and transport
4. Present analytical tools to study metals
5. Focus on select functions of metals in biological systems
6. Look at examples of biological adaptations for metal use
7. Study the potential of metals in medicine

1. Origin of Elements

1. Origin of Elements

Protons, neutrons, electrons form → (Nucleosynthesis) → Small Elements Form

↓ Element Burning (Fusion)

Bigger Elements Form → Stars Form/Explode

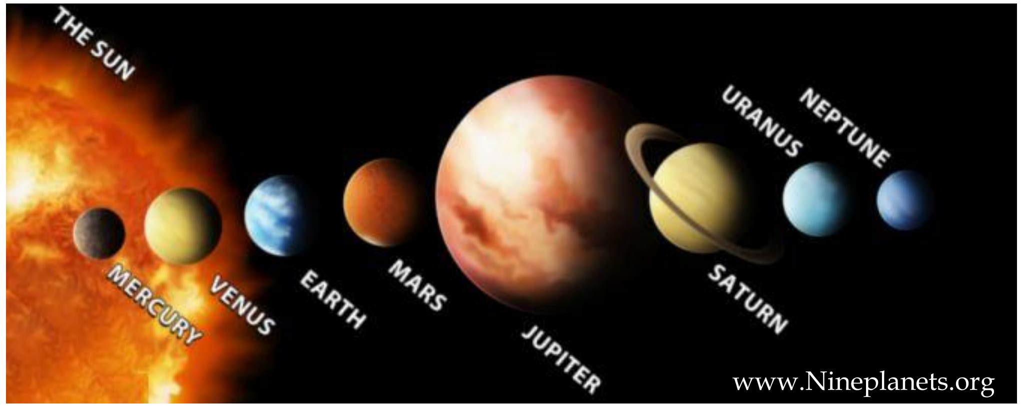
↓

Elements of Life

O, Mg, Al, Si, Fe → Terrestial formations

C,H,N,O,P,S → Living Organisms

2. O_2 Evolution on Earth helps to Sustain Life



Earth

Surface temp.: 14 °C

Atmospheric Pressure: 14.696 psi

Major Gas Composition:

CO_2 (~0.03%), N_2 (78%), O_2 (21%)

Mars

Surface temp.: -63 °C

Atmospheric Pressure: 1/100th of Earth

Major Gas Composition:

CO_2 (95.0%), N_2 (2.7%)

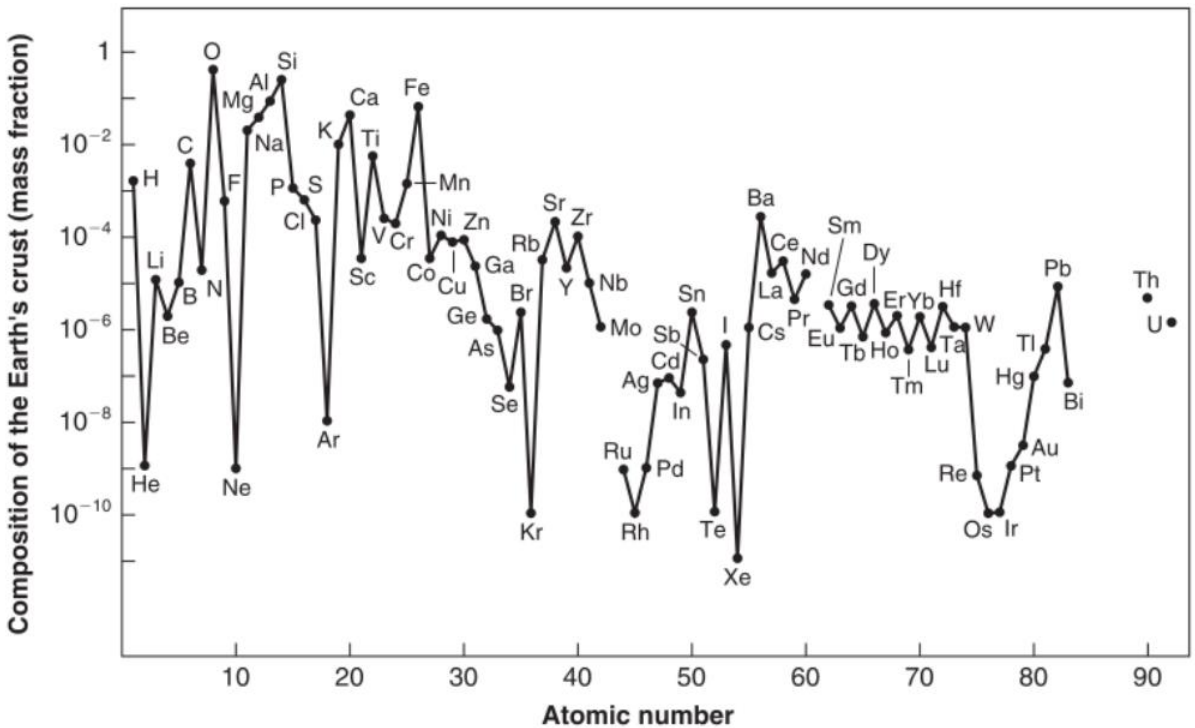
2. O_2 Evolution on Earth helps to Sustain Life

- Earth originally had a reducing atmosphere
  - Under these conditions, O_2 would be quickly reduced
    Each oxygen has an oxidation state of 0
  - CO_2 would be favored.
    Each oxygen has an oxidation state of -2
- Earth evolved into an oxidizing atmosphere
  - The rise of the biological process of O_2 evolving photosynthesis
    Higher plants, algae, and cyanobacteria engage in photosynthesis

$$6\,CO_2 + 6\,H_2O \xrightarrow{\text{Light}} C_6H_{12}O_6 + 6\,O_2$$

3. Element Abundance

A. Abundance on Earth



$$\textbf{Mass Fraction} = \frac{\textbf{Mass of the total amount of an element}}{\textbf{Combined masses of all elements}}$$

3. Element Abundance

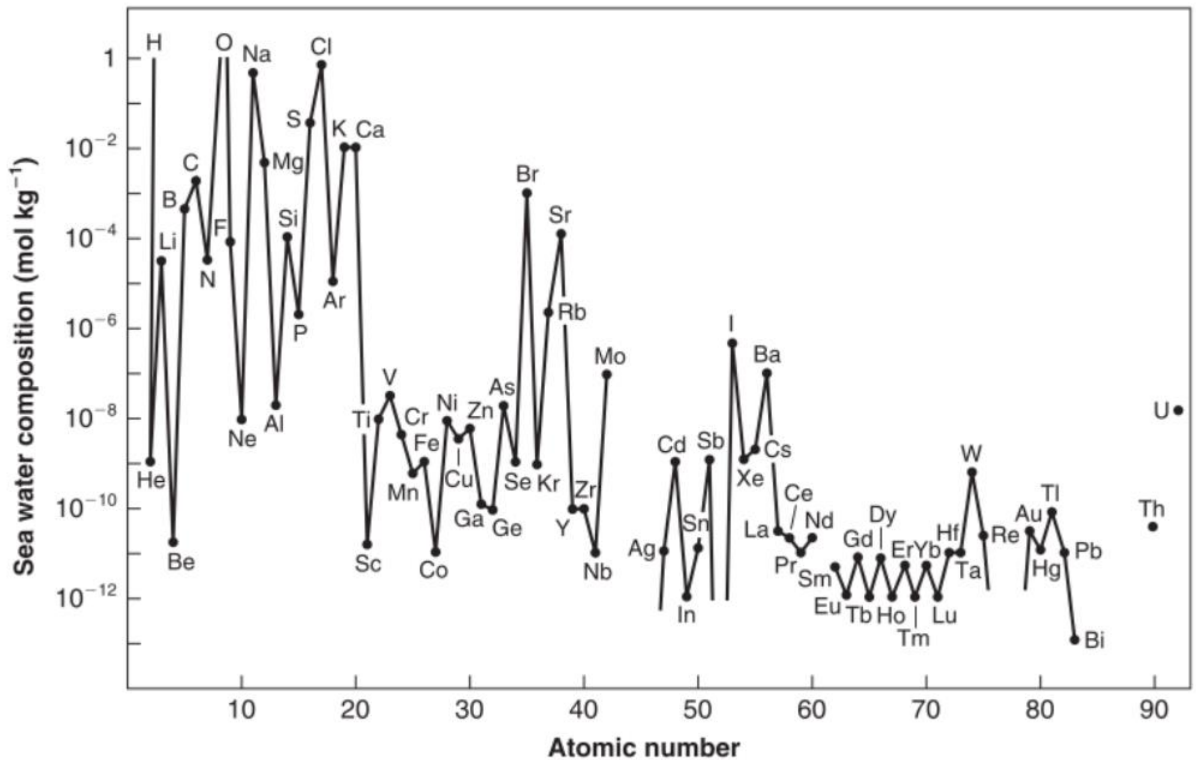
- The levels of elements on the crust are often quoted as a measure of elemental availability for biological systems

Abundance ≠ Availability

- Minimum abundance is clearly required but more importantly is the bioavailability of the element in a solid or soluble form, from which organisms can effectively utilize the element

3. Element Abundance

B. Abundance in the Oceans

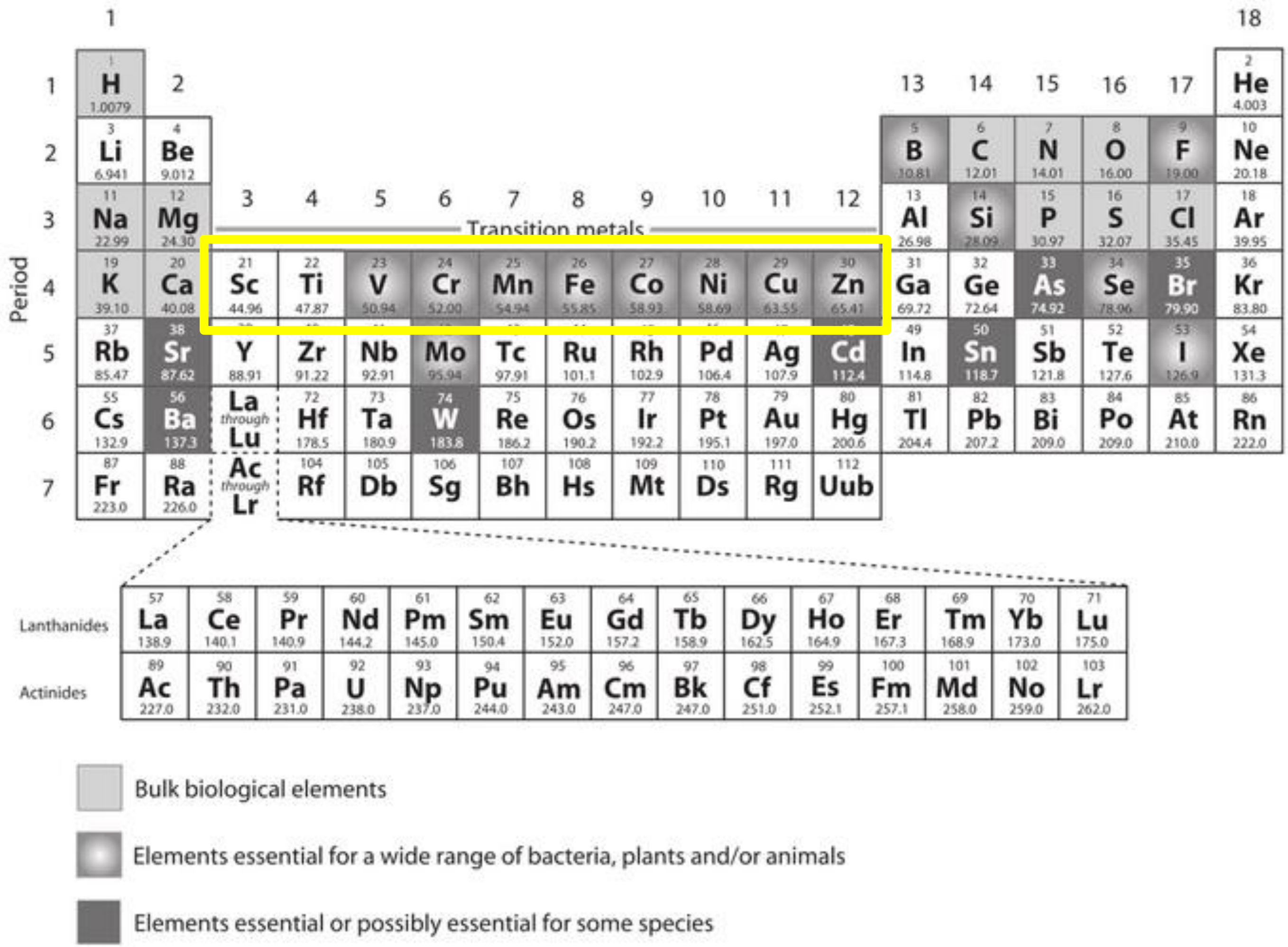


- Element abundance of the ocean is a better indicator of availability
    - Indicates relative solubility

3. Element Abundance

- Concentrations of the transition metals in oceans are relevant to the scope of our course
  - 1 st row transition elements have low but **NOT** insignificant abundance

Elements important to life.



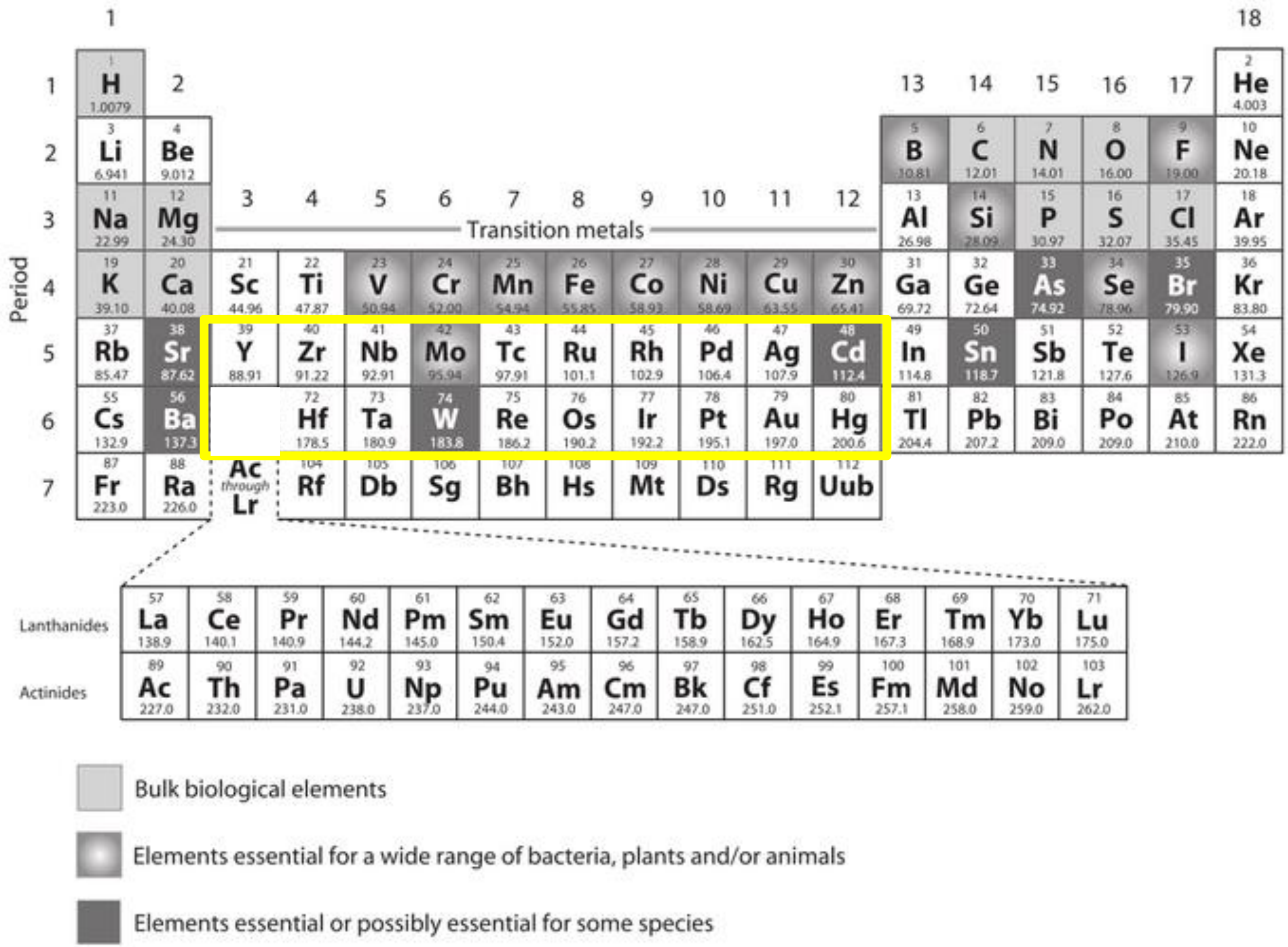
3. Element Abundance

- Concentrations of the transition metals in oceans are relevant to the scope of our course
  - 1 st row transition elements have low but **NOT** insignificant abundance
  - In 2nd & 3rd row transition periods, molybdenum and tungsten are the most abundant and are bioactive
    - Mo(VI) is the most abundant transition metal in the oceans.
    - Debate:

      Is it so prevalent because of its biological functions due to its unique chemistry?

      Or does its abundance force its way into biological use?

Elements important to life.



3. Element Abundance

– Different mechanisms must be involved in the transport of 1st row transition elements versus 2nd & 3rd row elements

- 1st row: Largely cationic di or trivalent ions (i.e. Fe(II)/Fe(III))

  Or present as organic bound complexes

- MoO_4^{2-} and WO_4^{2-} highly soluble, anionic species

4. Element Bioavailability

2 billion people worldwide suffer from malnutrition because of micronutrient deficiencies.
(World Health Organization)

Bioavailability of the elements is very important. Two main factors must be considered:

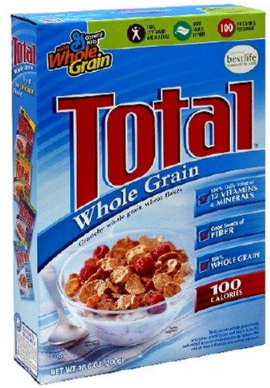
1. Prevalence in environments where life exists
   - Abundance of nickel in the Earth's core is not useful

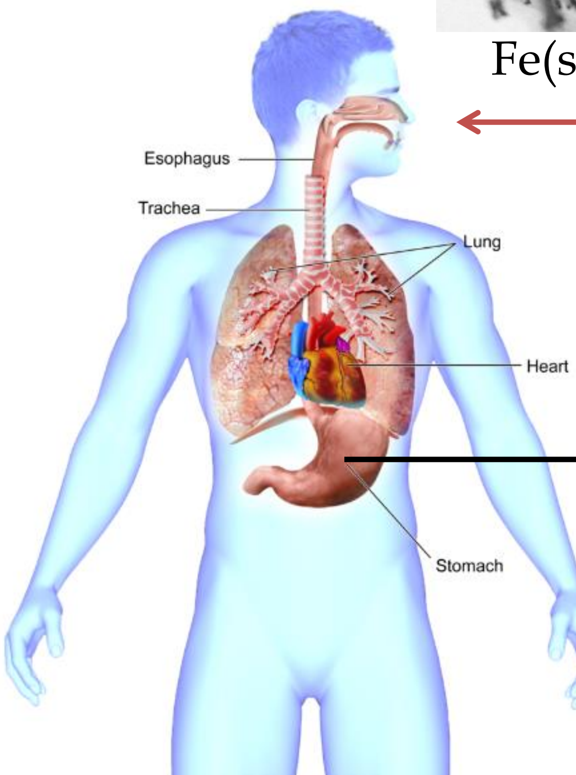
2. Formulation of the element
   - Fe_2O_3 (rust) is very abundant but not a usable source of iron because of poor solubility.
   - Harmless and stable formulations are critical
     - Bound (complexed) form of metals
     - Oxidation state
   - Able to be solubilized and absorbed

How do we get iron into our bodies?

5. Influencing Metal Solubility

Fe(s)





pH ~ 3-4 (Normal)
pH ~1-2 (Metabolism)

In the stomach, the dissolving of iron is coupled with oxidation:

$$2\ H^{+}(aq) + Fe(s) \rightleftarrows H_2(g) + Fe^{2+}(aq)$$

Fe^{2+} is bound by gastroferrin and transported to the intestines.

5. Influencing Metal Solubility

Absorption occurs in the intestine where the pH is 8.0 resulting in further oxidation:

$$Fe^{2+}(aq) \rightleftharpoons Fe^{3+}(aq) + e^-$$

At this pH, precipitation would occur:

$$Fe^{3+}(aq) + 3\,OH^-(aq) \rightleftharpoons Fe(OH)_3\,(s)$$

How much soluble Fe(III) would there be?

$$Fe(OH)_3\,(s) \rightleftharpoons Fe^{3+}(aq) + 3\,OH^-(aq)$$

K_{sp} (Solubility product) = $[Fe^{3+}][OH^-]^3 \sim 10^{-38}$ M

At pH 7.0, $[Fe^{3+}] = 10^{-38}/(10^{-7})^3 = 10^{-17}$ M **IRON IS BIOUNAVAILABLE**

5. Influencing Metal Solubility

Table V.1.
Average Relative Abundance of Selected Elements in the Earth's Crust, Sea Water, Mammalian Blood Plasma, and in Mammalian Cells or Tissue

Element	Crust (ppm)	Sea Water (μ*M*)	Blood Plasma (μ*M*)	Cell/Tissue[a] (μ*M*)
Ca	4×10^4	1×10^4	2×10^3	1×10^3
Cd	0.2	1×10^{-3}		
Co	25	2×10^{-5}	2.5×10^{-5}	
Cu	55	4×10^{-3}	8–24	~68
Fe	5×10^4	1×10^{-3}	22	0.001–10
K	3×10^4	1×10^4	4×10^3	1.5×10^5
Mg	2×10^4	5×10^4	500	9×10^3
Mn	950	5×10^{-4}	0.1	180
Mo	1.5	0.1		5×10^{-3}
Na	3×10^4	5×10^5	1×10^5	1×10^4
Ni	75	8×10^{-3}	0.04	2
V	135	0.03	0.07	0.5–30
W	1.5	5×10^{-3}		
Zn	70	0.01	17	180

[a] Approximate values based on total content rather than labile concentration.

In blood and cells, iron levels are much higher than solubility predicts.

WHY???

Iron binding by biomolecules