Bioquímica Geral
RFM0004

Membranas

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Membranas

Por quê as membranas biológicas são importantes?

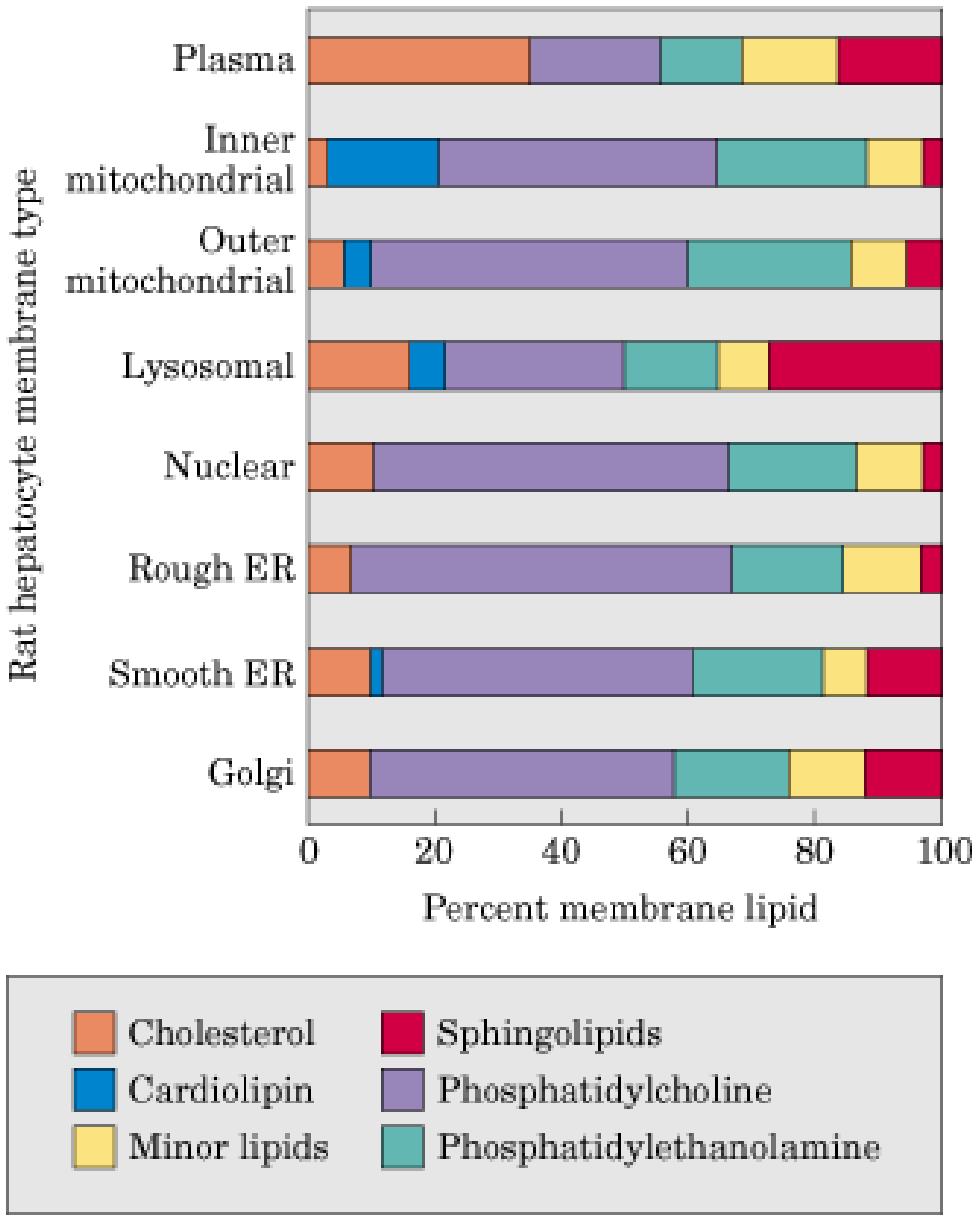
- Matriz para diversas moléculas
- Fusão e divisão
- Seletividade
- Flexibilidade

Composição da membrana

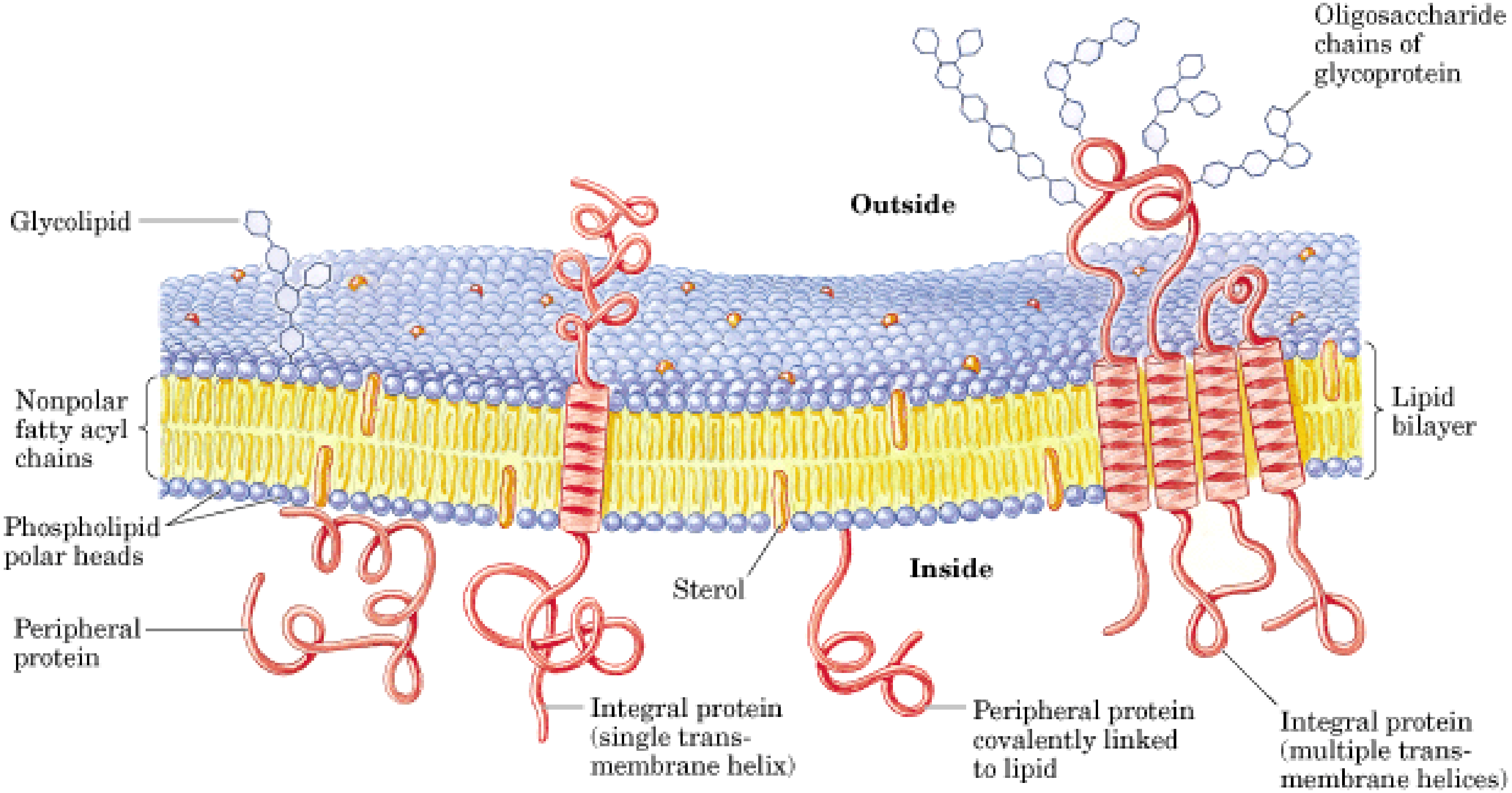
table 12–1

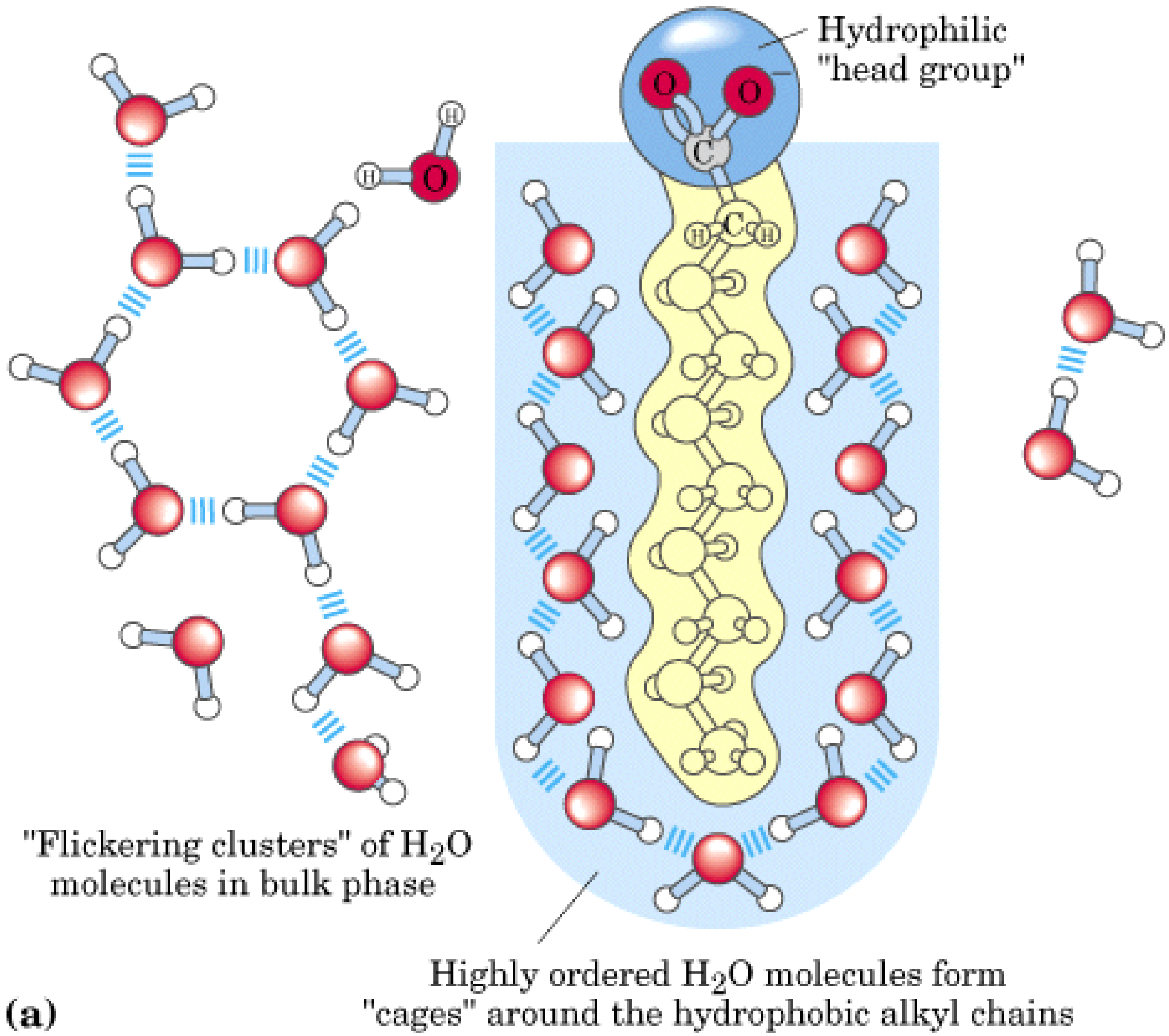
Major Components of Plasma Membranes in Various Organisms

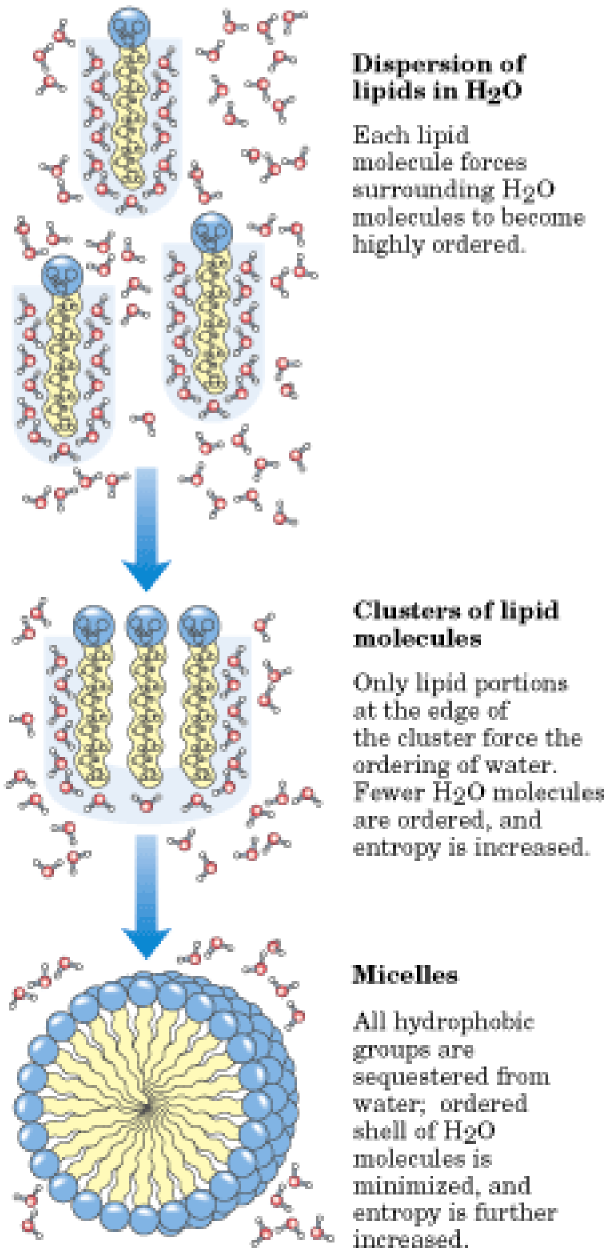
	Components (% by weight)				
	Protein	Phospholipid	Sterol	Sterol type	Other lipids
Human myelin sheath	30	30	19	Cholesterol	Galactolipids, plasmalogens
Mouse liver	45	27	25	Cholesterol	—
Maize leaf	47	26	7	Sitosterol	Galactolipids
Yeast	52	7	4	Ergosterol	Triacylglycerols, steryl esters
Paramecium (ciliated protist)	56	40	4	Stigmasterol	—
E. coli	75	25	0	—	—


Plasma
Inner mitochondrial
Outer mitochondrial
Lysosomal
Nuclear
Rough ER
Smooth ER
Golgi
Rat hepatocyte membrane type
0
20
40
60
80
100
Percent membrane lipid
Cholesterol
Cardiolipin
Minor lipids
Sphingolipids
Phosphatidylcholine
Phosphatidylethanolamine

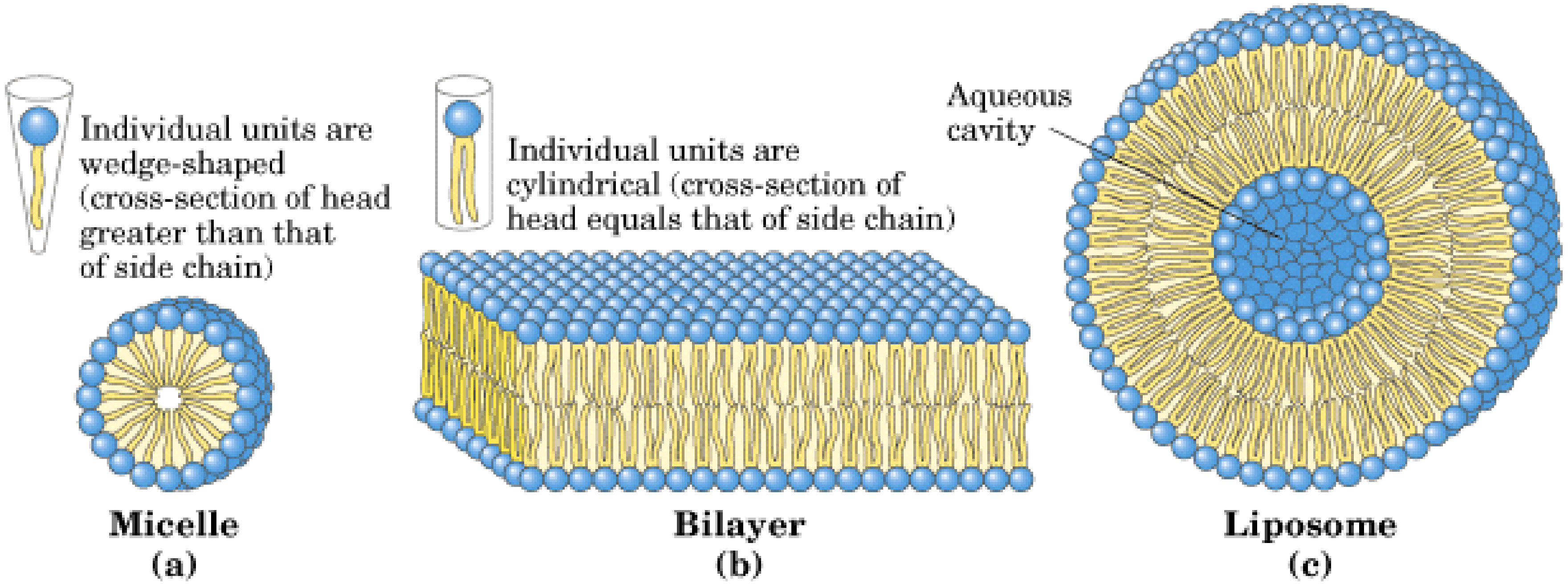
Cada tipo de membrana possui uma combinação diferente de lípídios e proteínas (e também de glicolipídios e glicoproteínas).
Mosaico fluido




Hydrophilic
"head group"
O
O
C
O
H
H
C
H
H
"Flickering clusters" of H_2O
molecules in bulk phase
Highly ordered H_2O molecules form
"cages" around the hydrophobic alkyl chains
(a)


Dispersion of lipids in H_2O
Each lipid molecule forces surrounding H_2O molecules to become highly ordered.
Clusters of lipid molecules
Only lipid portions at the edge of the cluster force the ordering of water. Fewer H_2O molecules are ordered, and entropy is increased.
Micelles
All hydrophobic groups are sequestered from water; ordered shell of H_2O molecules is minimized, and entropy is further increased.

Agregados de lipídeos anfipáticos em água



Distribuição assimétrica dos fosfolipídeos

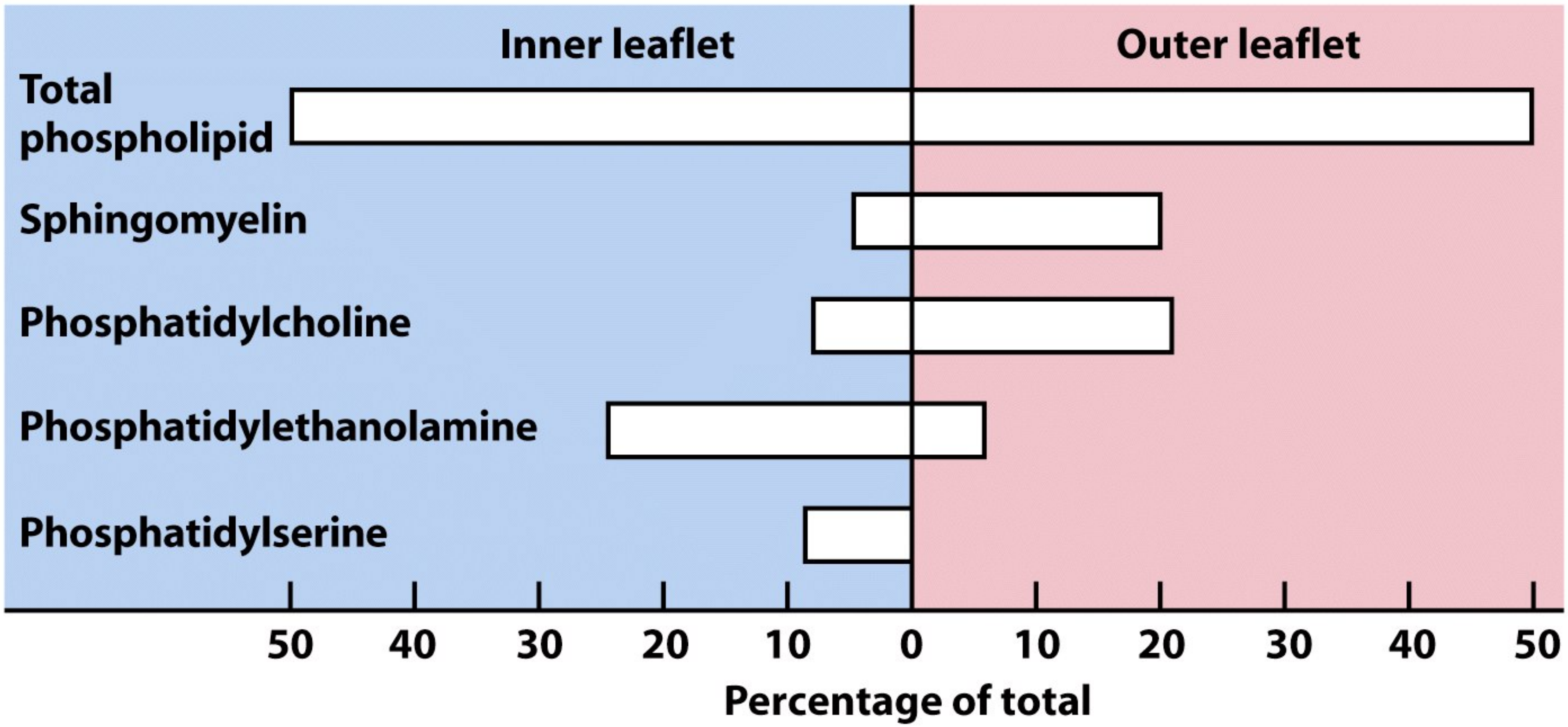


Figure 9-33 Fundamentals of Biochemistry, 2/e

Permeabilidade da bicamada

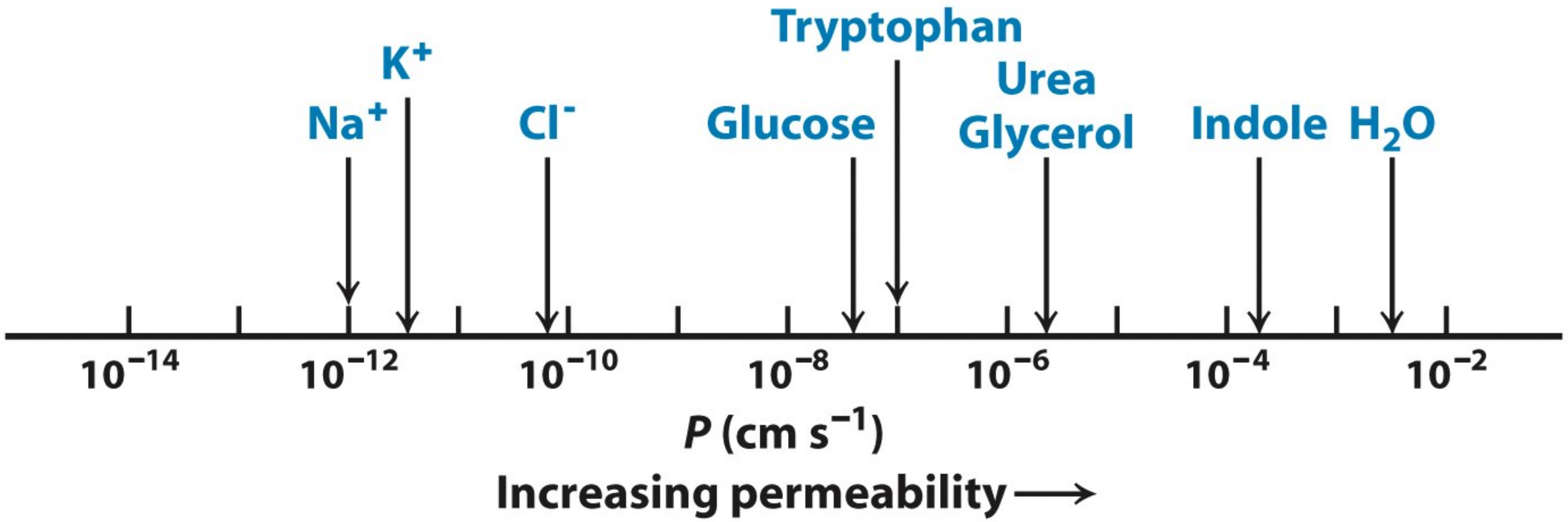


Figure 12-15
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Difusão dos lipídeos na membrana

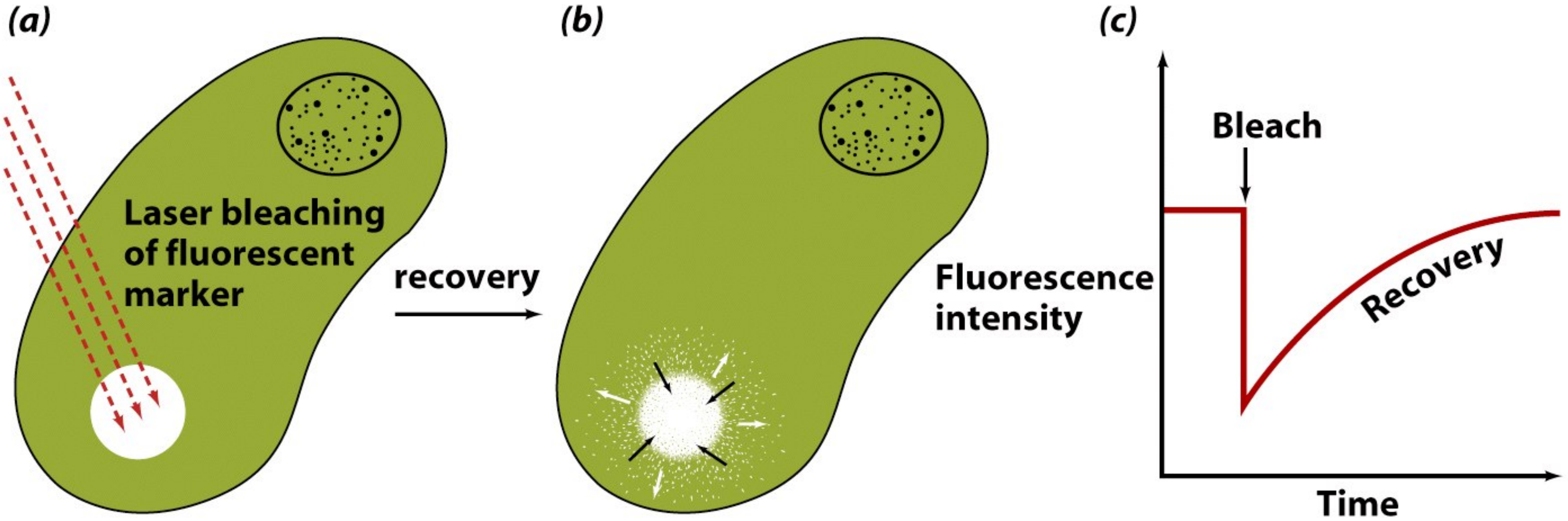
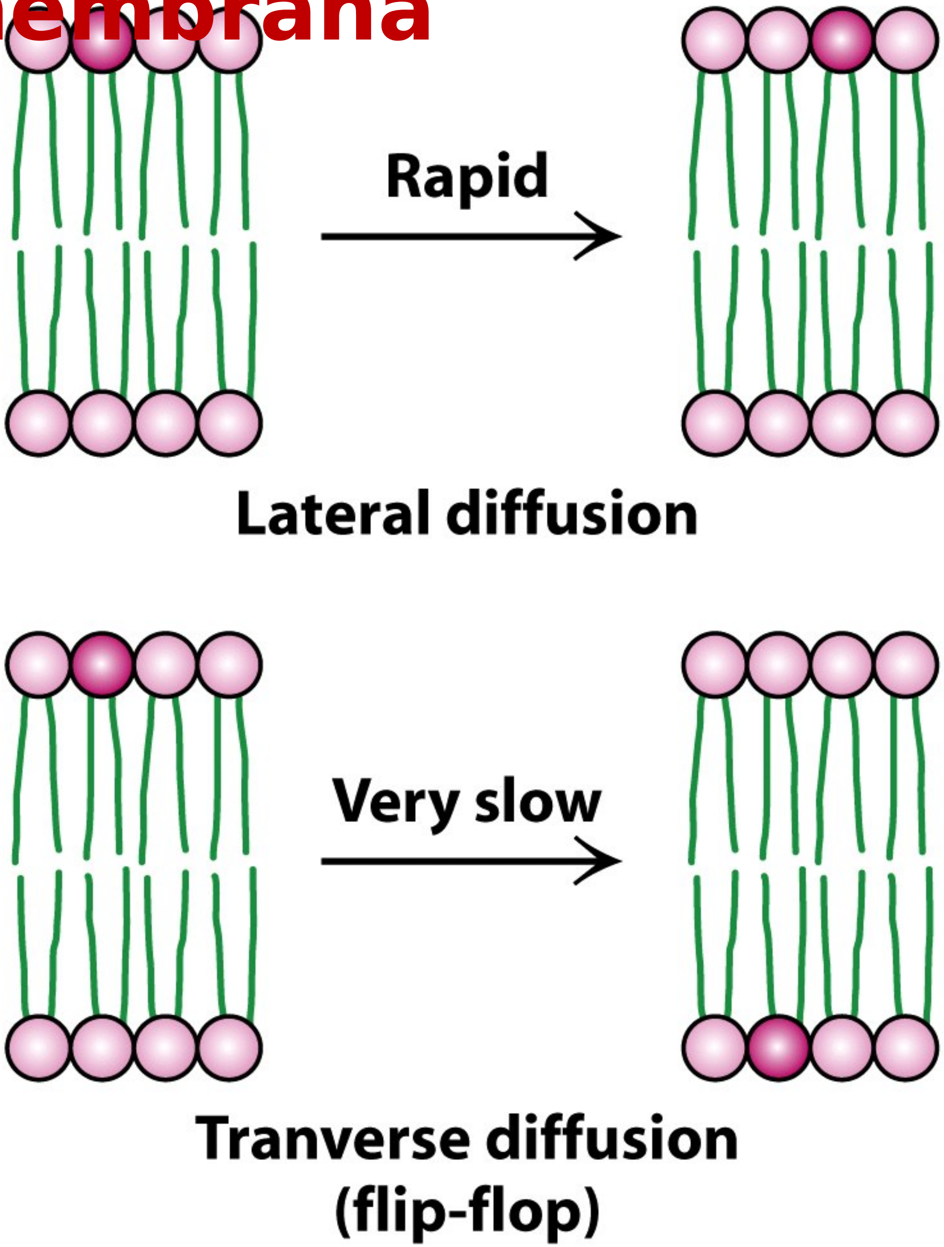


Figure 9-28 Fundamentals of Biochemistry, 2/e

Difusão dos lipídeos na membrana



Temperatura de transição

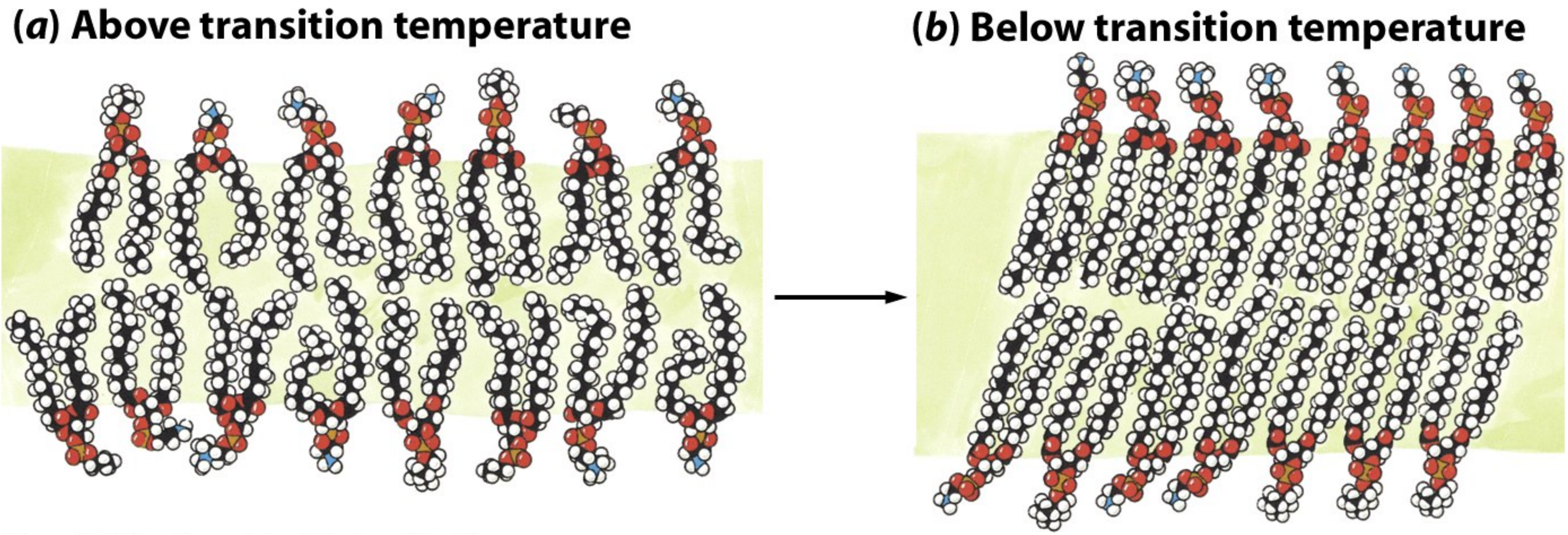


Figure 9-18 Fundamentals of Biochemistry, 2/e

Fluido

Solido paracristalino

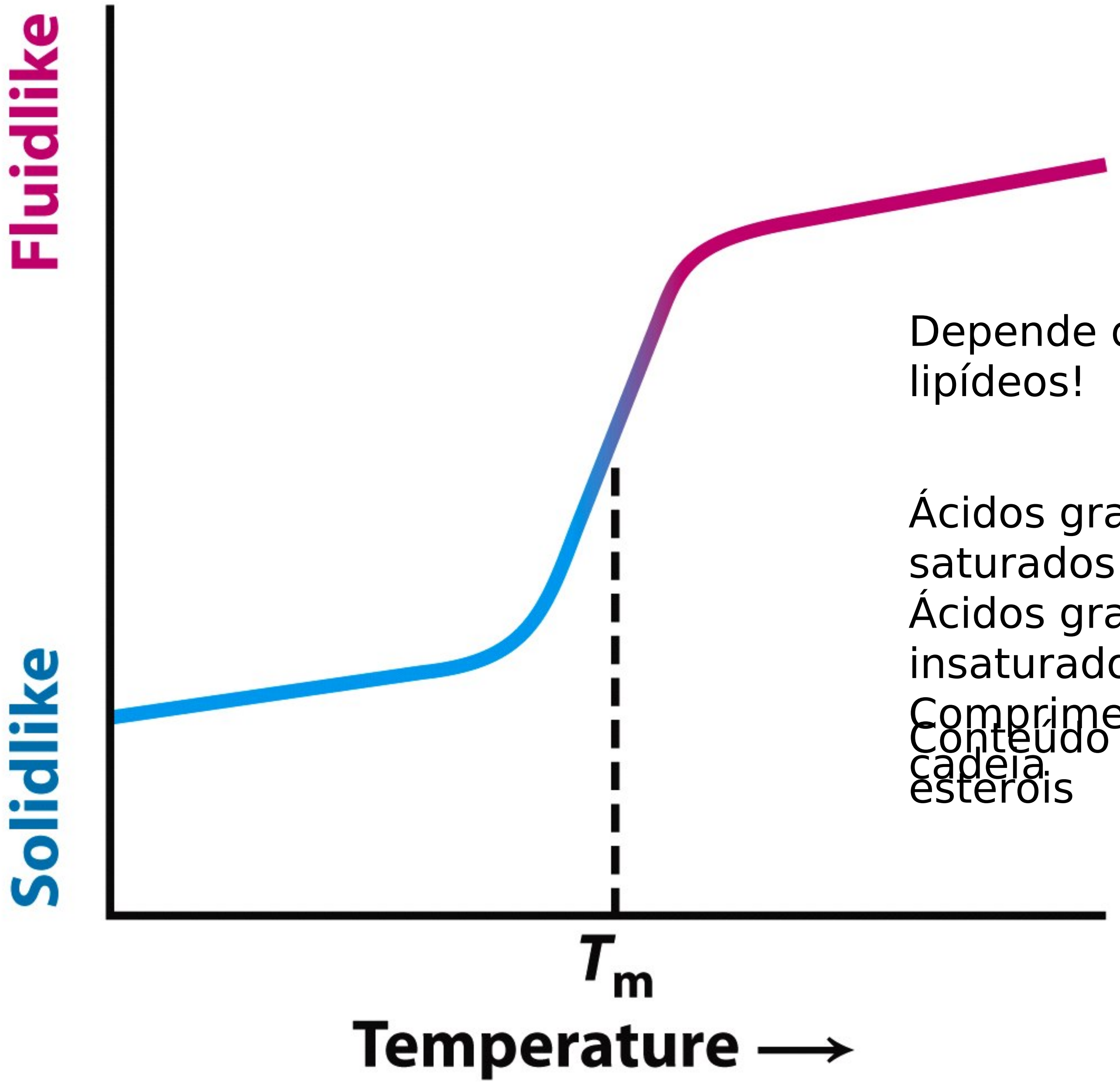


Figure 12-32
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Depende da composição de lipídeos!

Ácidos graxos saturados
Ácidos graxos insaturados
Comprimento da cadeia
Conteúdo de esteróis

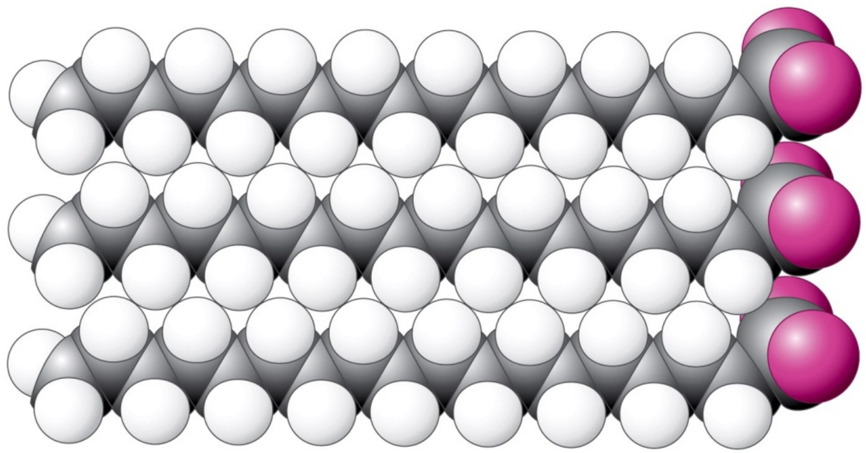

Figure 12-33a
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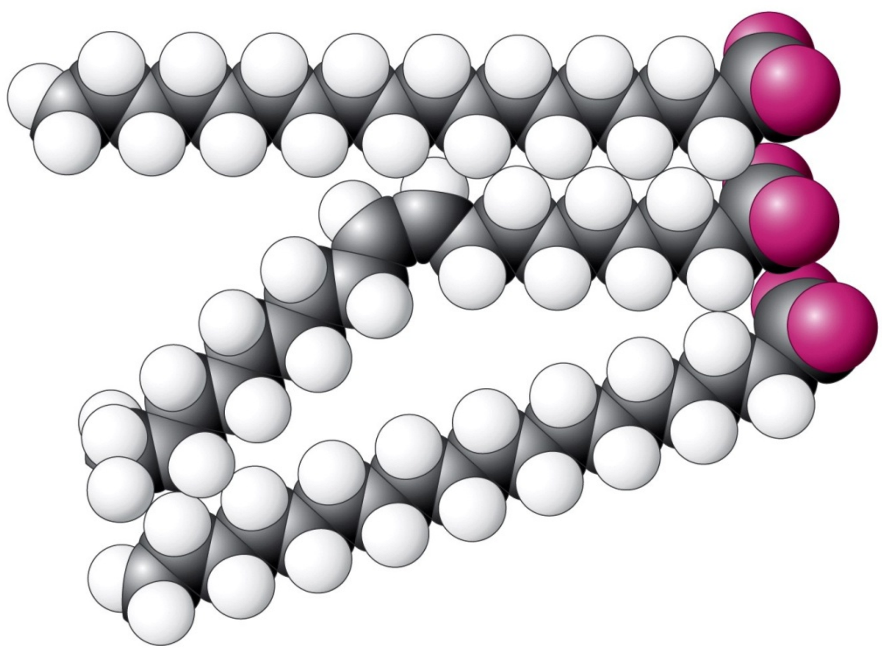

Figure 12-33b
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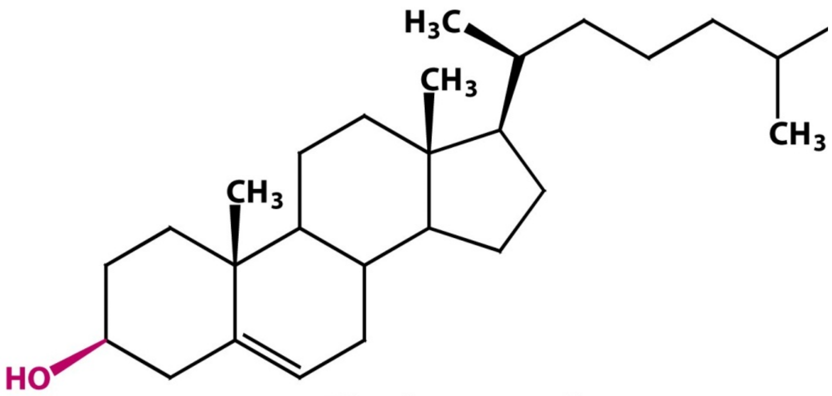
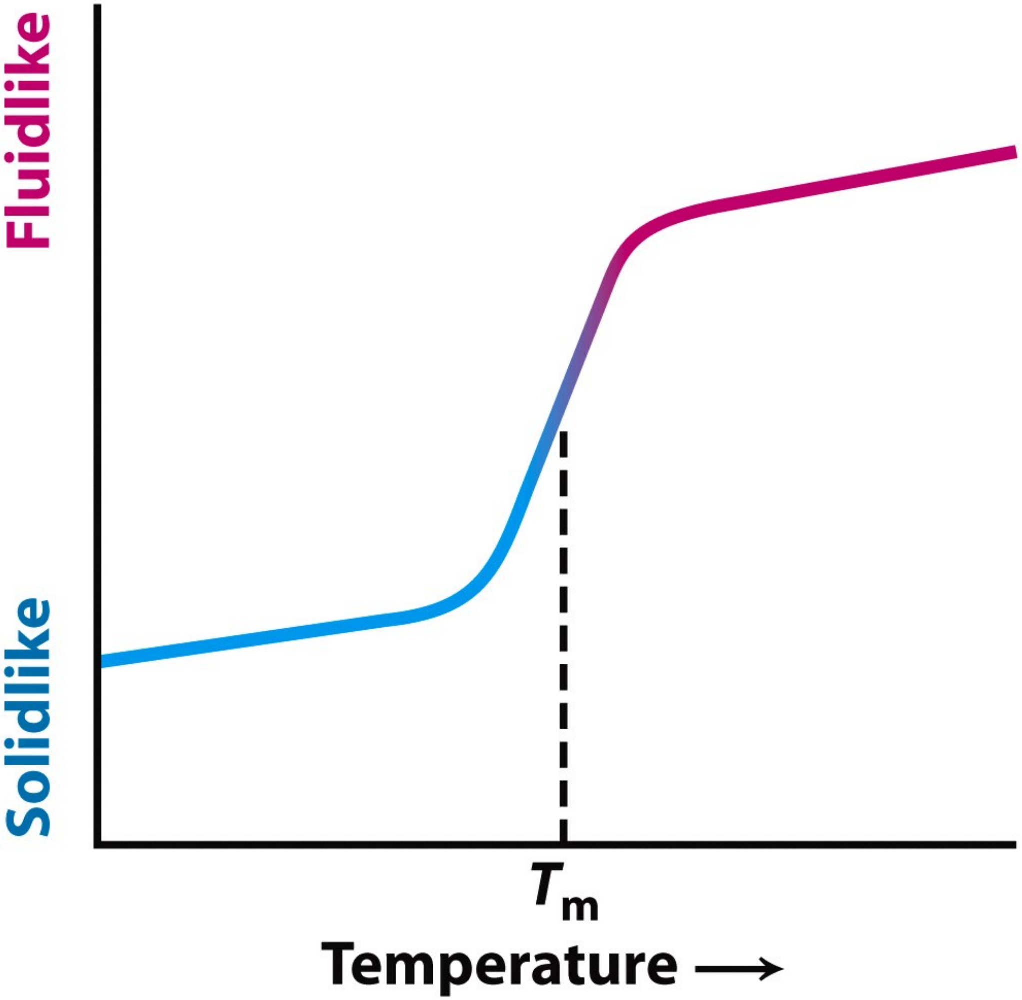
Fatty Acid Composition of *E. coli* Cells Cultured at Different Temperatures

	Percentage of total fatty acids*			
	10 °C	20 °C	30 °C	40 °C
Myristic acid (14:0)	4	4	4	8
Palmitic acid (16:0)	18	25	29	48
Palmitoleic acid (16:1)	26	24	23	9
Oleic acid (18:1)	38	34	30	12
Hydroxymyristic acid	13	10	10	8
Ratio of unsaturated to saturated†	2.9	2.0	1.6	0.38

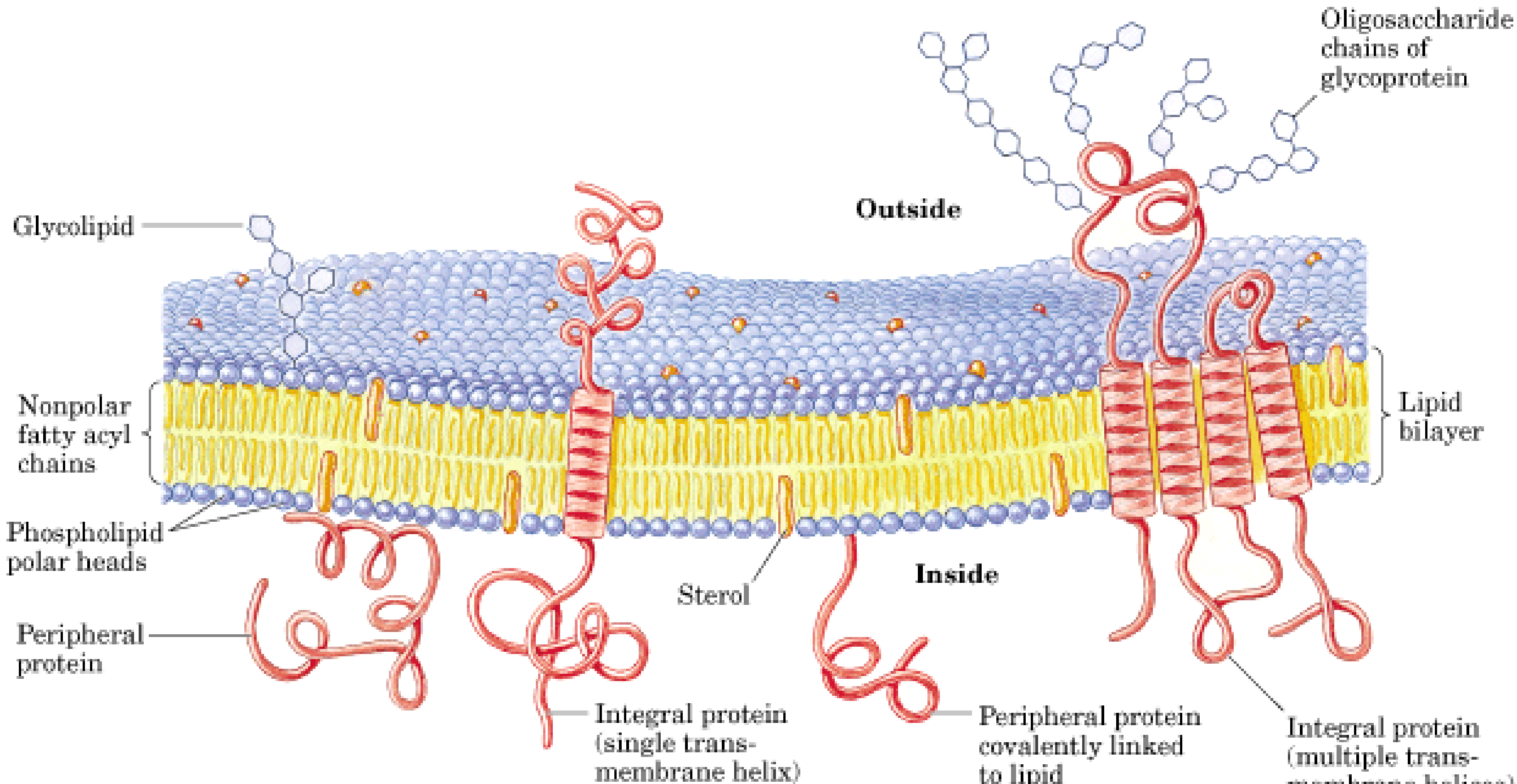


Cholesterol



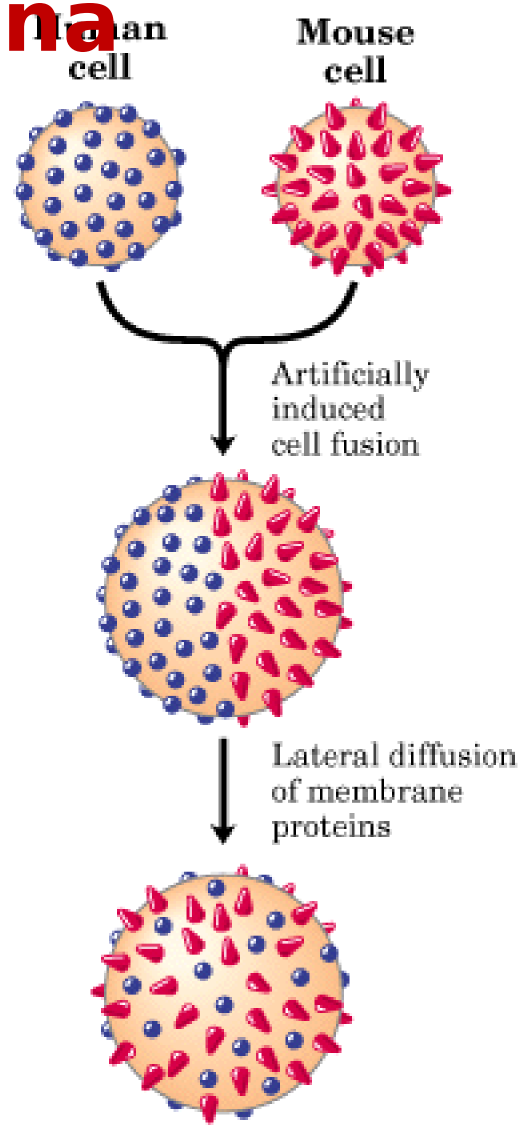
Abaixo da temperatura de transição:
aumenta fluidez – menos sujeita a transição de fase
Acima da temperatura de transição:
reduz a fluidez da bicamada

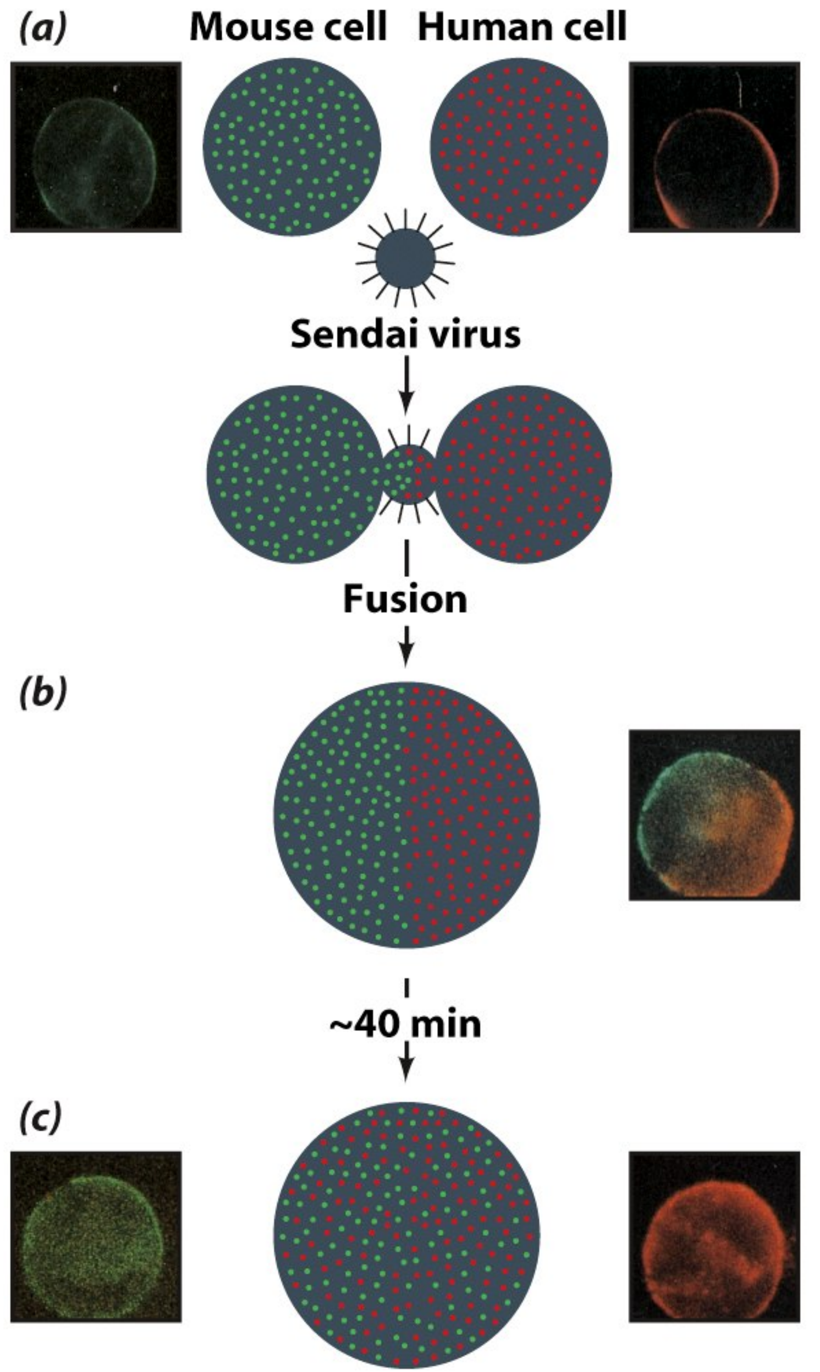
Moderam a fluidez da membrana!!!



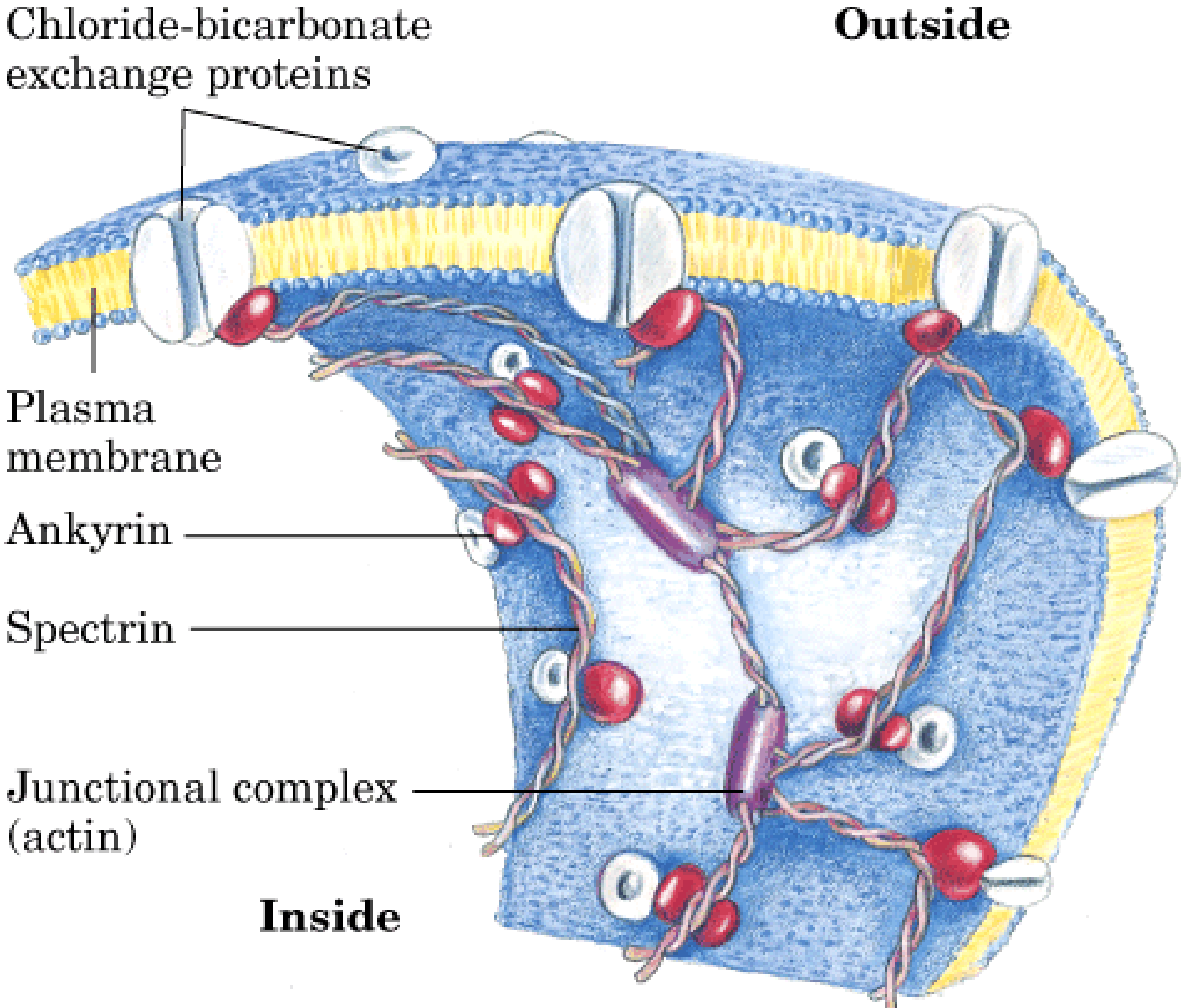
Oligosaccharide chains of glycoprotein
Glycolipid
Outside
Nonpolar fatty acyl chains
Lipid bilayer
Phospholipid polar heads
Sterol
Inside
Peripheral protein
Integral protein (single trans-membrane helix)
Peripheral protein covalently linked to lipid
Integral protein (multiple trans-membrane helices)

Difusão das proteínas de membrana

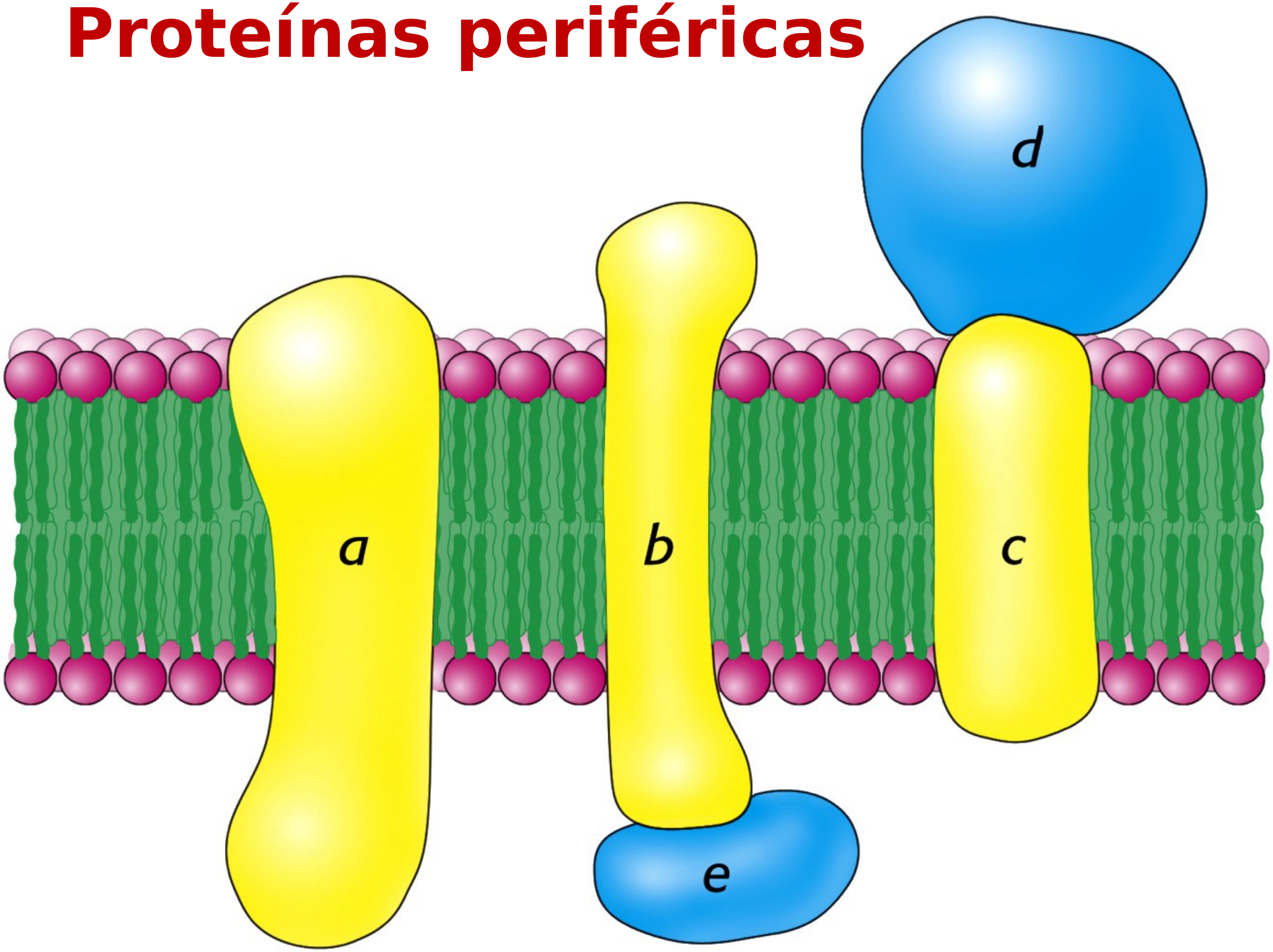



(a)
Mouse cell
Human cell
Sendai virus
Fusion
(b)
~40 min
(c)

Proteínas ancoradas a estruturas internas



Proteínas integrais de membrana
Proteínas periféricas



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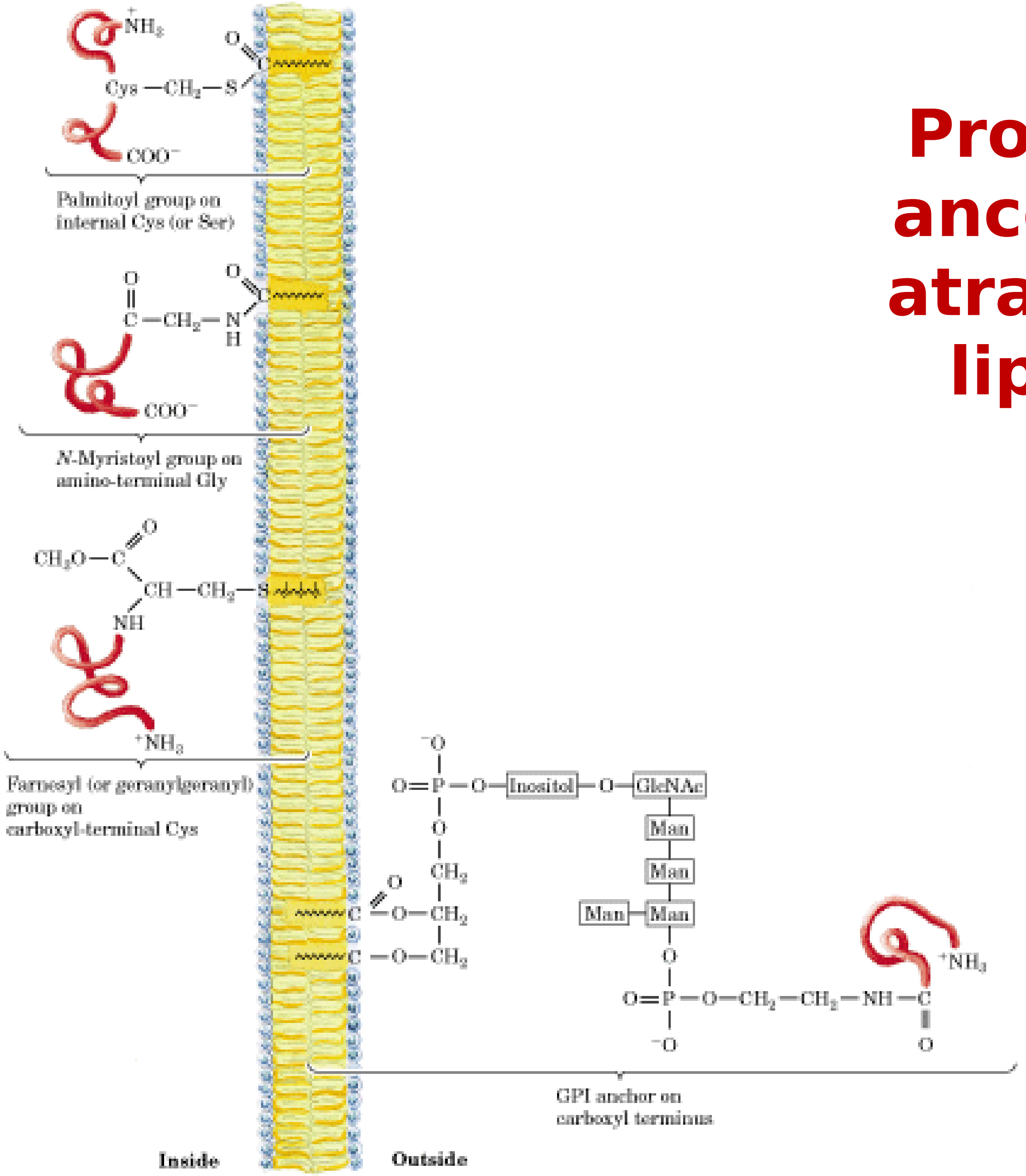
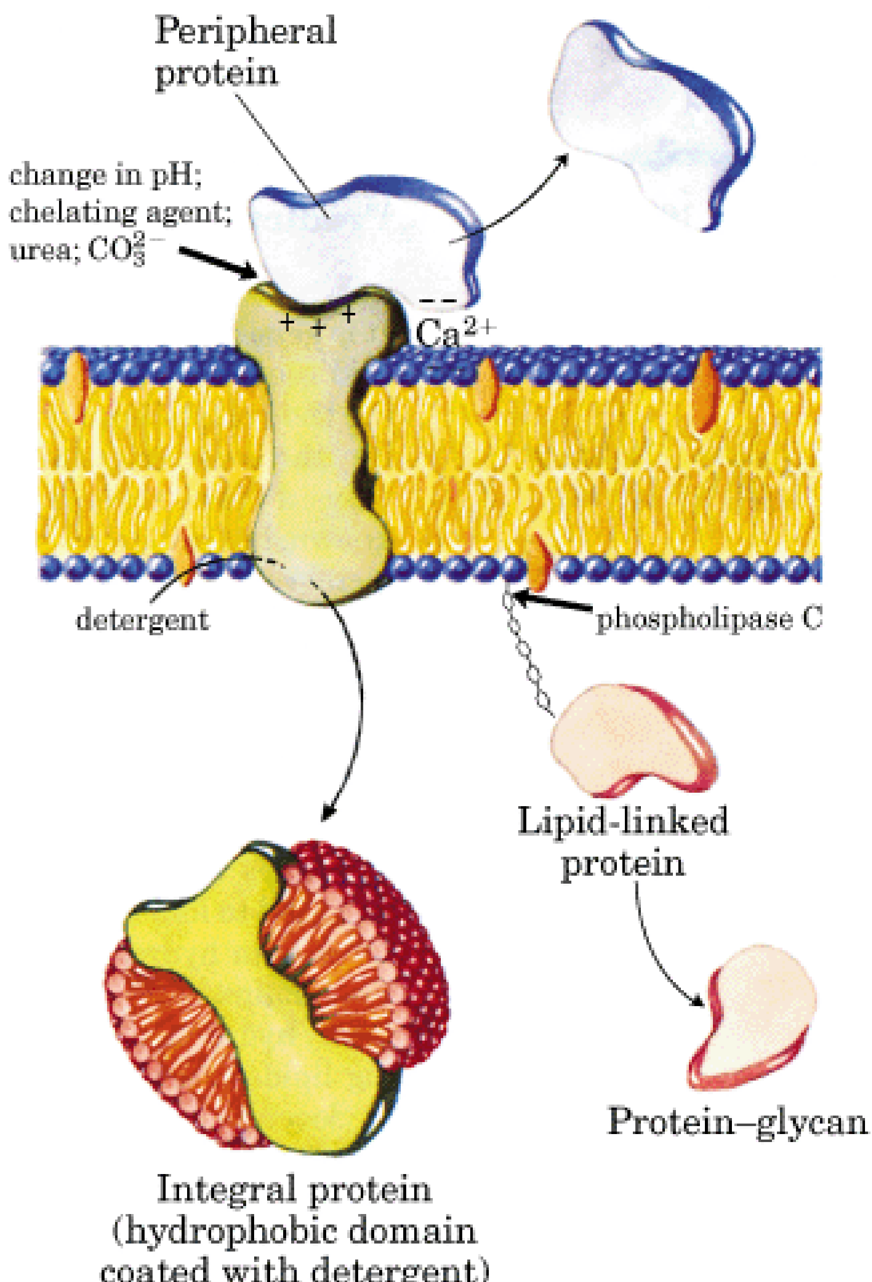
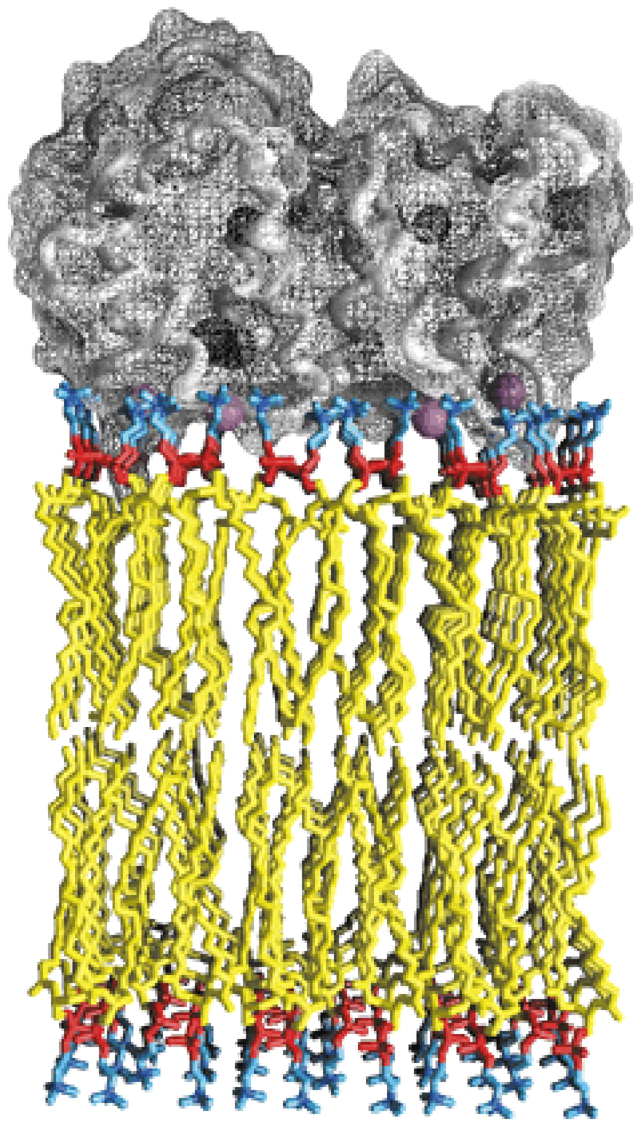
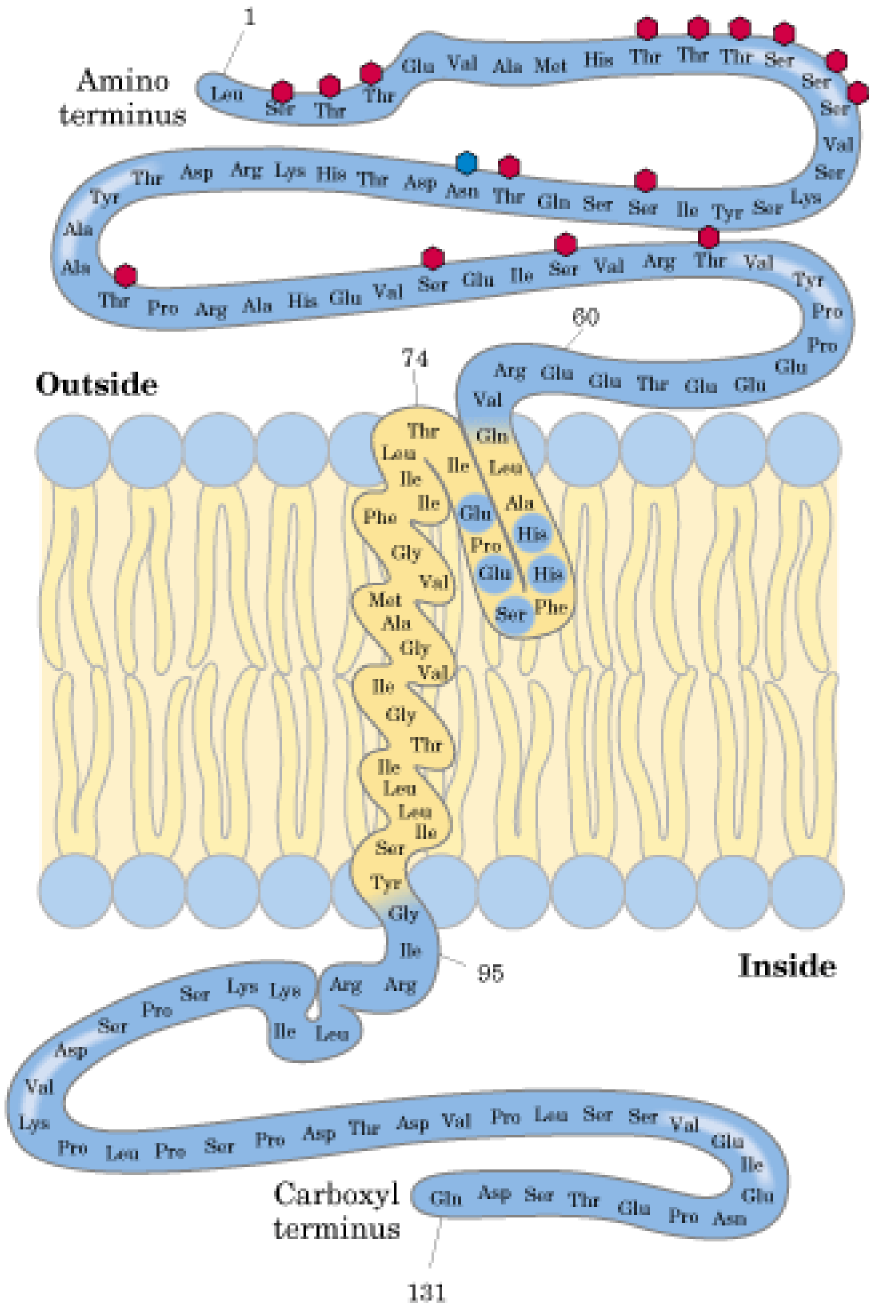
Proteínas ancoradas através de lipídios



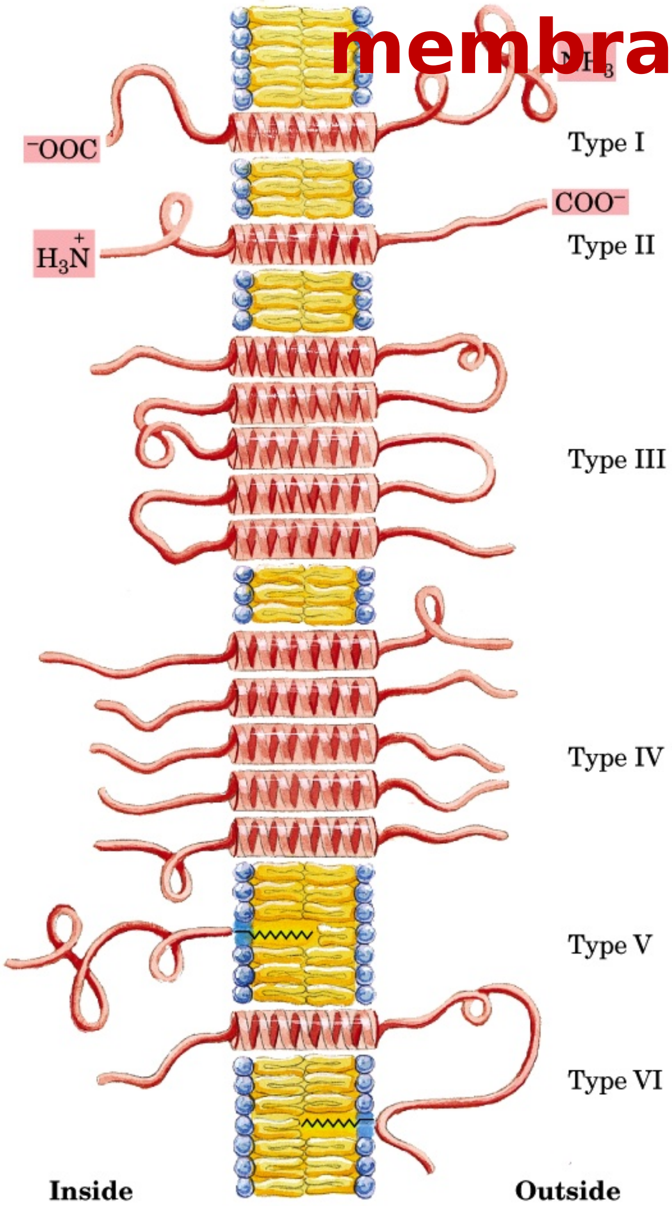

Peripheral protein
change in pH; chelating agent; urea; CO_3^{2-}
Ca^{2+}
detergent
phospholipase C
Lipid-linked protein
Protein–glycan
Integral protein (hydrophobic domain coated with detergent)





1
Amino terminus
Leu Ser Thr Thr Glu Val Ala Met His Thr Thr Thr Ser Ser Ser Val Ser Lys Ser Tyr Ile Ser Ser Gln Thr Asn Asp Thr His Lys Arg Asp Thr Tyr Ala Ala Thr Pro Arg Ala His Glu Val Ser Glu Ile Ser Val Arg Thr Val Tyr Pro Pro Glu Glu Glu Thr Glu Glu Arg Val
60
74
Outside
Gln Leu Ala His His Phe Ser Glu Pro Glu Ile Ile Leu Ile Thr Ile Phe Gly Val Met Ala Gly Val Ile Gly Thr Ile Leu Leu Ile Ser Tyr Gly Ile
95
Inside
Arg Arg Leu Ile Lys Lys Ser Pro Ser Asp Val Lys Pro Leu Pro Ser Pro Asp Thr Asp Val Pro Leu Ser Ser Val Glu Ile Glu Asn Pro Glu Thr Ser Asp Gln
Carboxyl terminus
131

Diferentes tipos de proteínas de membrana

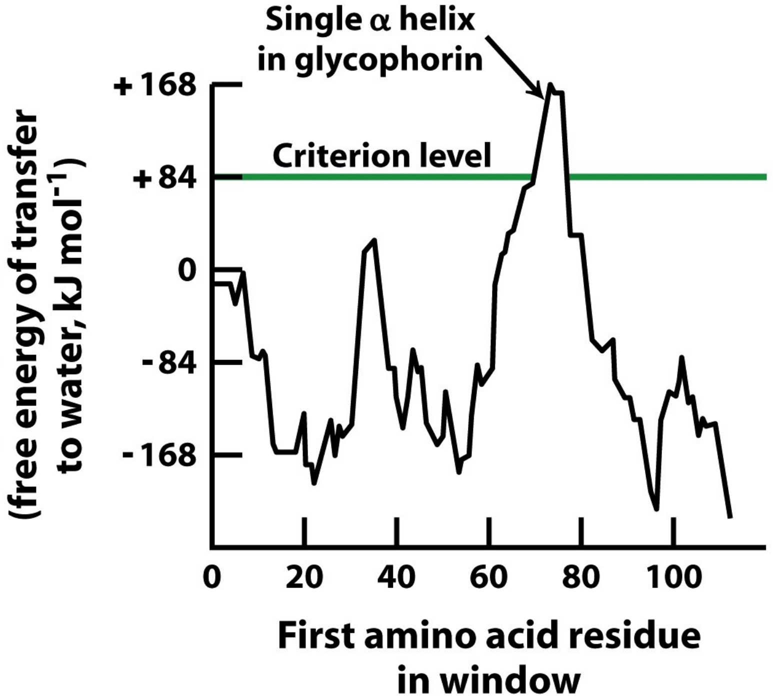


É possível prever a estrutura de uma proteína de membrana?

Índice de hidropatia

Table 12.2 Polarity scale for identifying transmembrane helices

Amino acid residue	Transfer free energy in kJ mol^{-1} (kcal mol^{-1})
Phe	15.5 (3.7)
Met	14.3 (3.4)
Ile	13.0 (3.1)
Leu	11.8 (2.8)
Val	10.9 (2.6)
Cys	8.4 (2.0)
Trp	8.0 (1.9)
Ala	6.7 (1.6)
Thr	5.0 (1.2)
Gly	4.2 (1.0)
Ser	2.5 (0.6)
Pro	−0.8 (−0.2)
Tyr	−2.9 (−0.7)
His	−12.6 (−3.0)
Gln	−17.2 (−4.1)
Asn	−20.2 (−4.8)
Glu	−34.4 (−8.2)
Lys	−37.0 (−8.8)
Asp	−38.6 (−9.2)
Arg	−51.7 (−12.3)



12-27b
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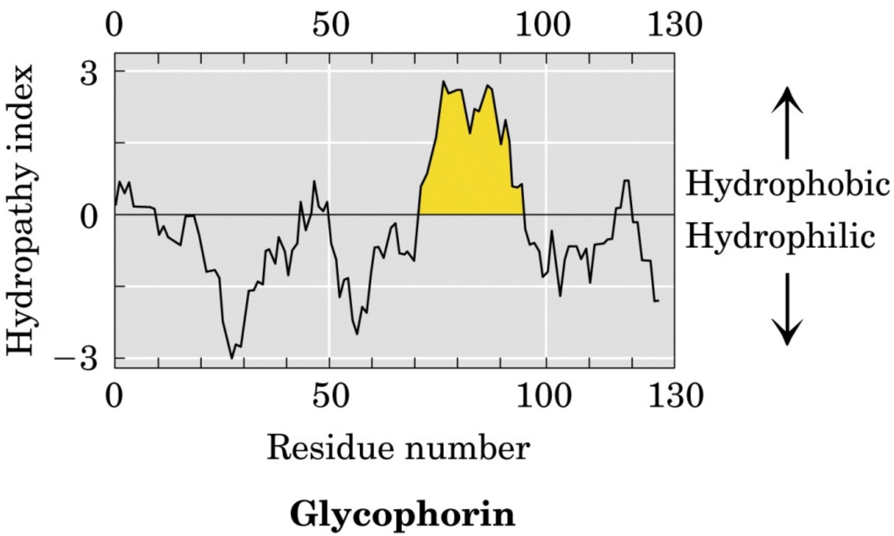
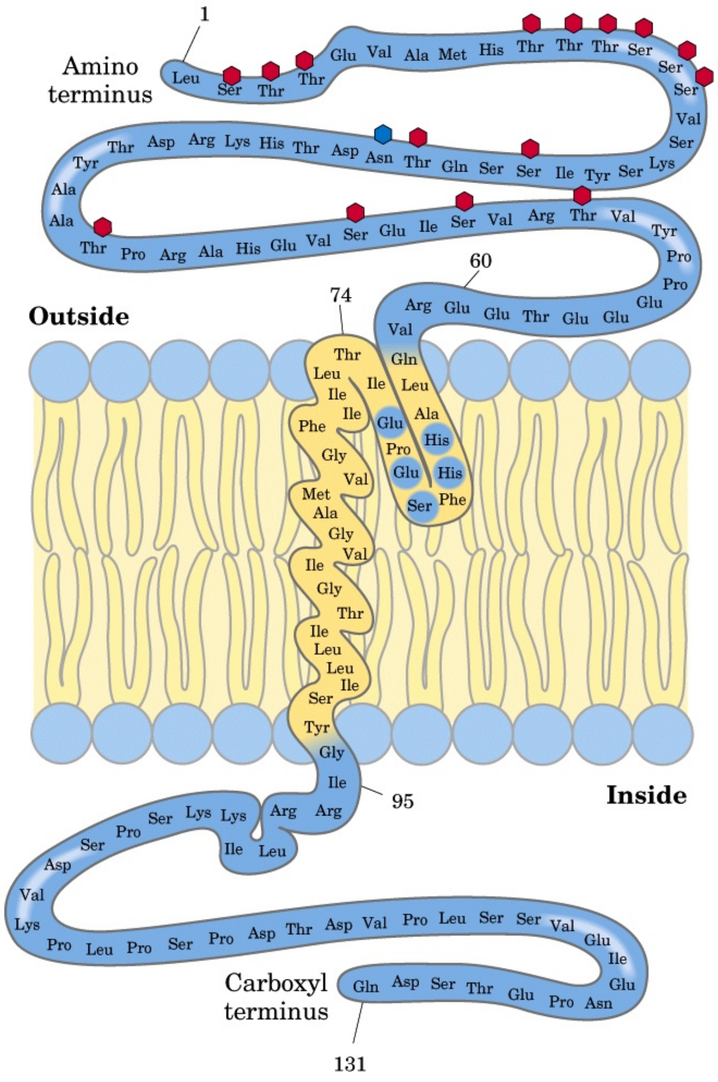
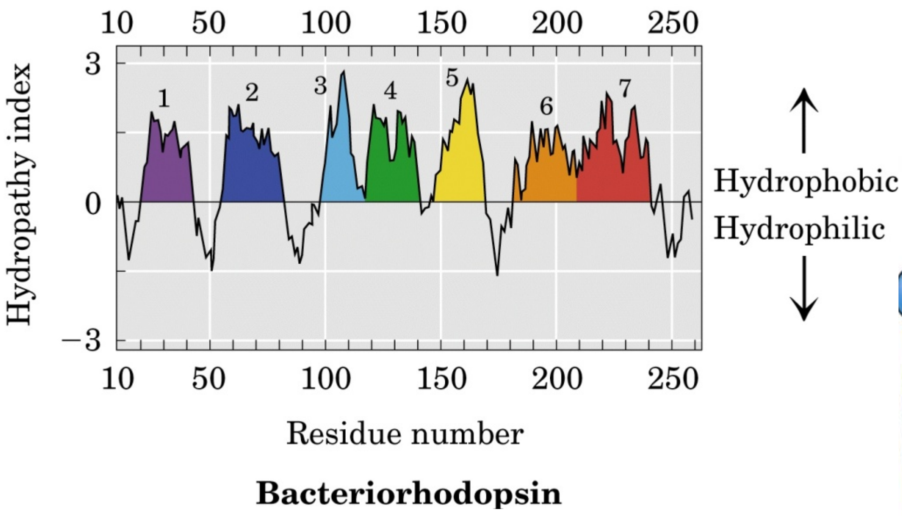
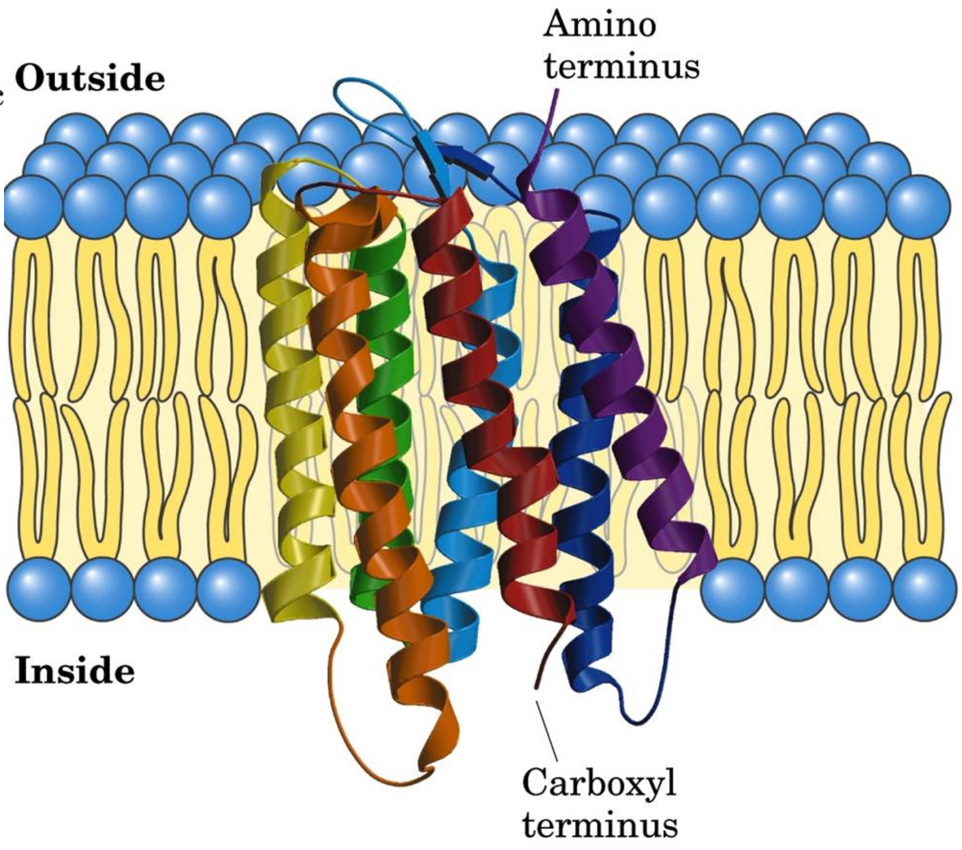
Glicoforina



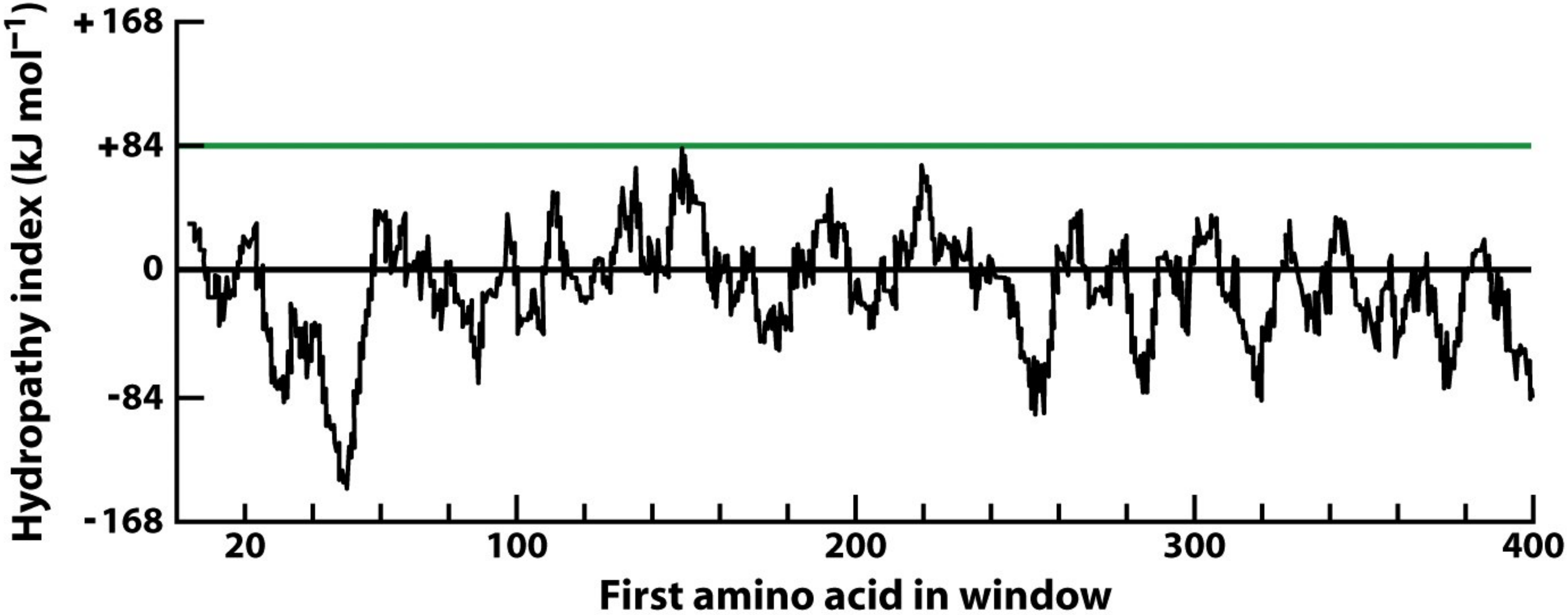


Rodopsina


10
50
100
150
200
250
3
0
−3
1
2
3
4
5
6
7
Hydropathy index
Residue number
Bacteriorhodopsin
Hydrophobic
Hydrophilic


Outside
Amino terminus
Inside
Carboxyl terminus

Proteína de membrana
Ex: porina



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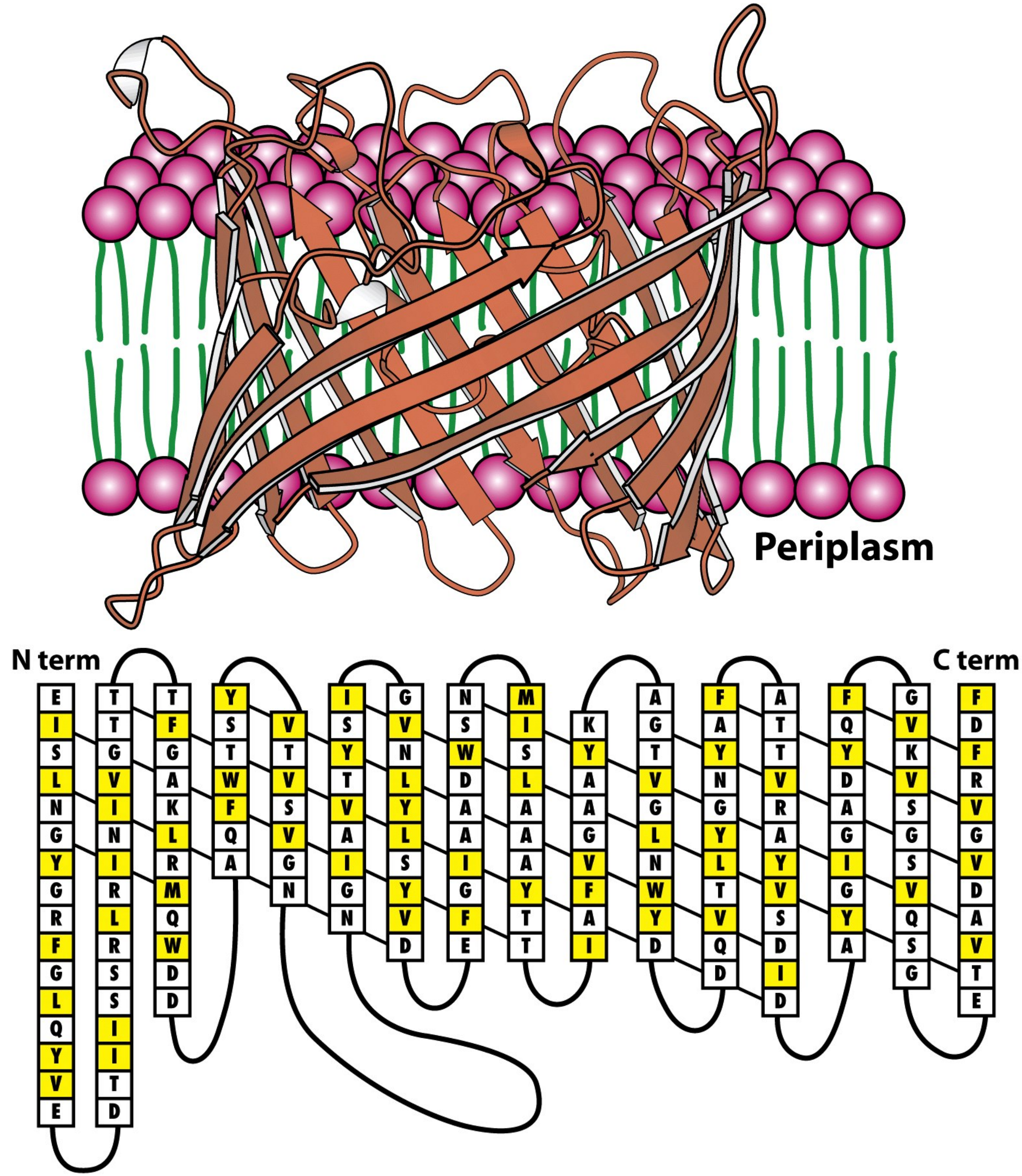
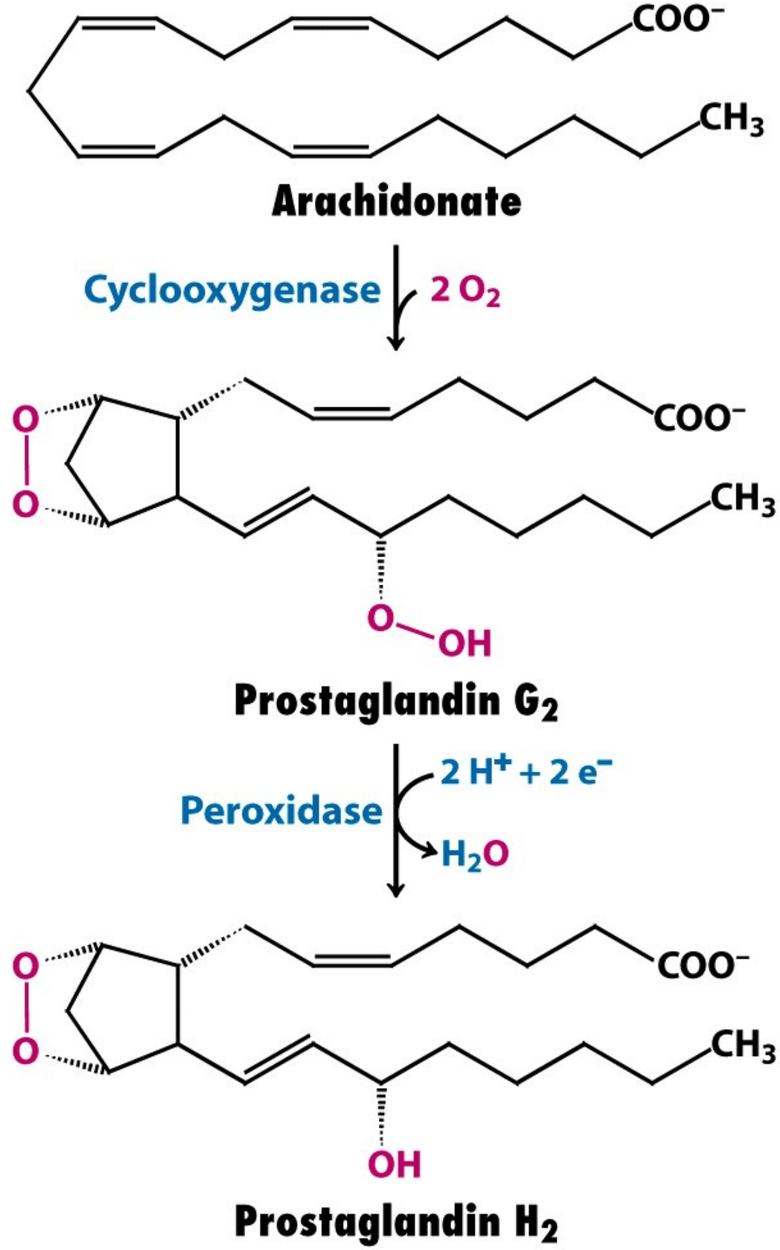

Periplasm
N term
C term
E I S L N G Y G R F G L Q Y V E
T T G V I N I R L R S I I T D
T F G A K L R M Q W D D
Y S T W F Q A
V T V S V G N
I S Y T V A I G N
G V N L Y L S Y V D
N S W D A A I G F E
M I S L A A A Y T T
K Y A A G V F A I
A G T V G L N W Y D
F A Y N G Y L T V Q D
A T T V R A Y V S D I D
F Q Y D A G I G Y A
G V K V S G S V Q S G
F D F R V G V D A V T E



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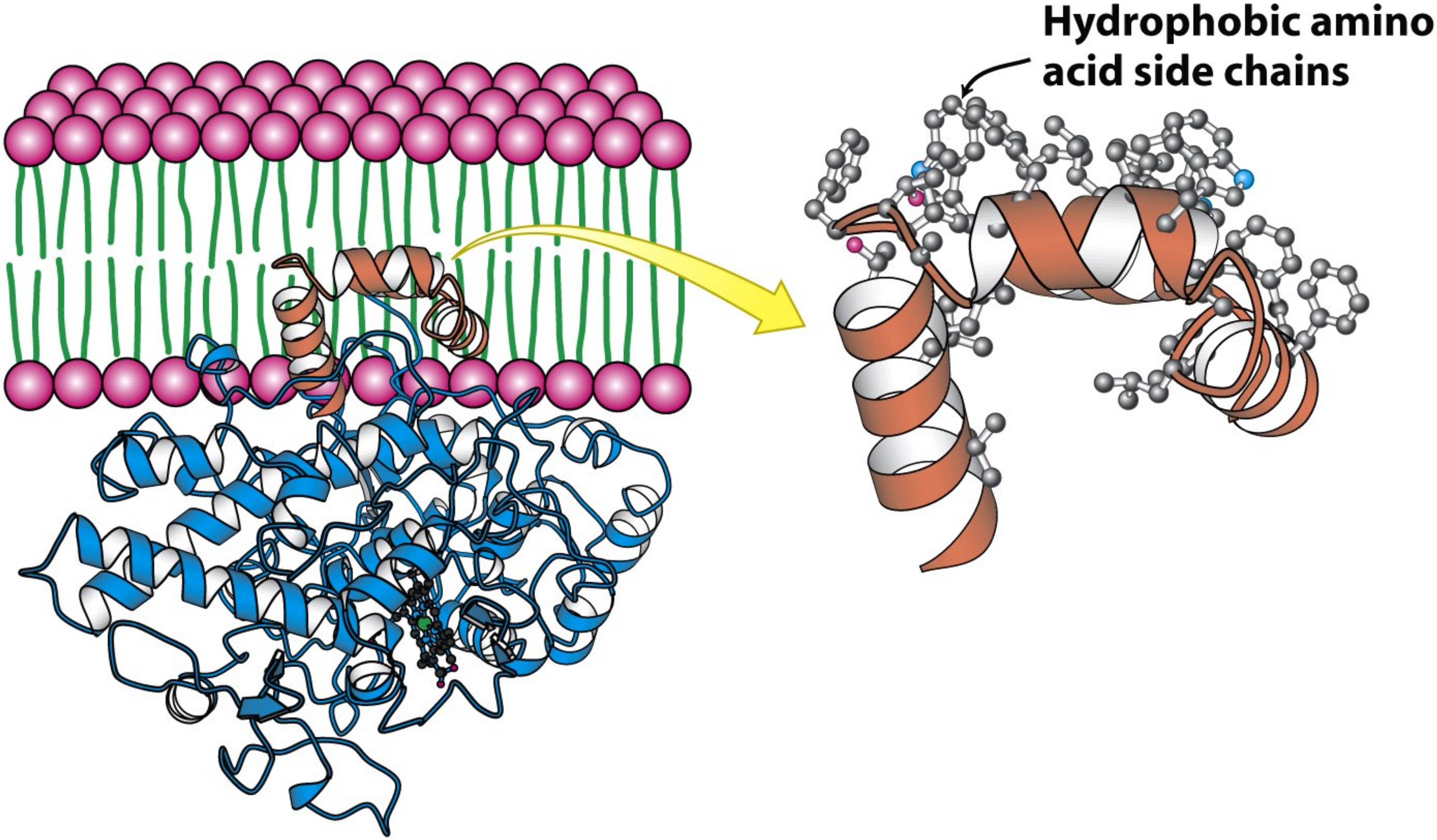

Figure 12-23
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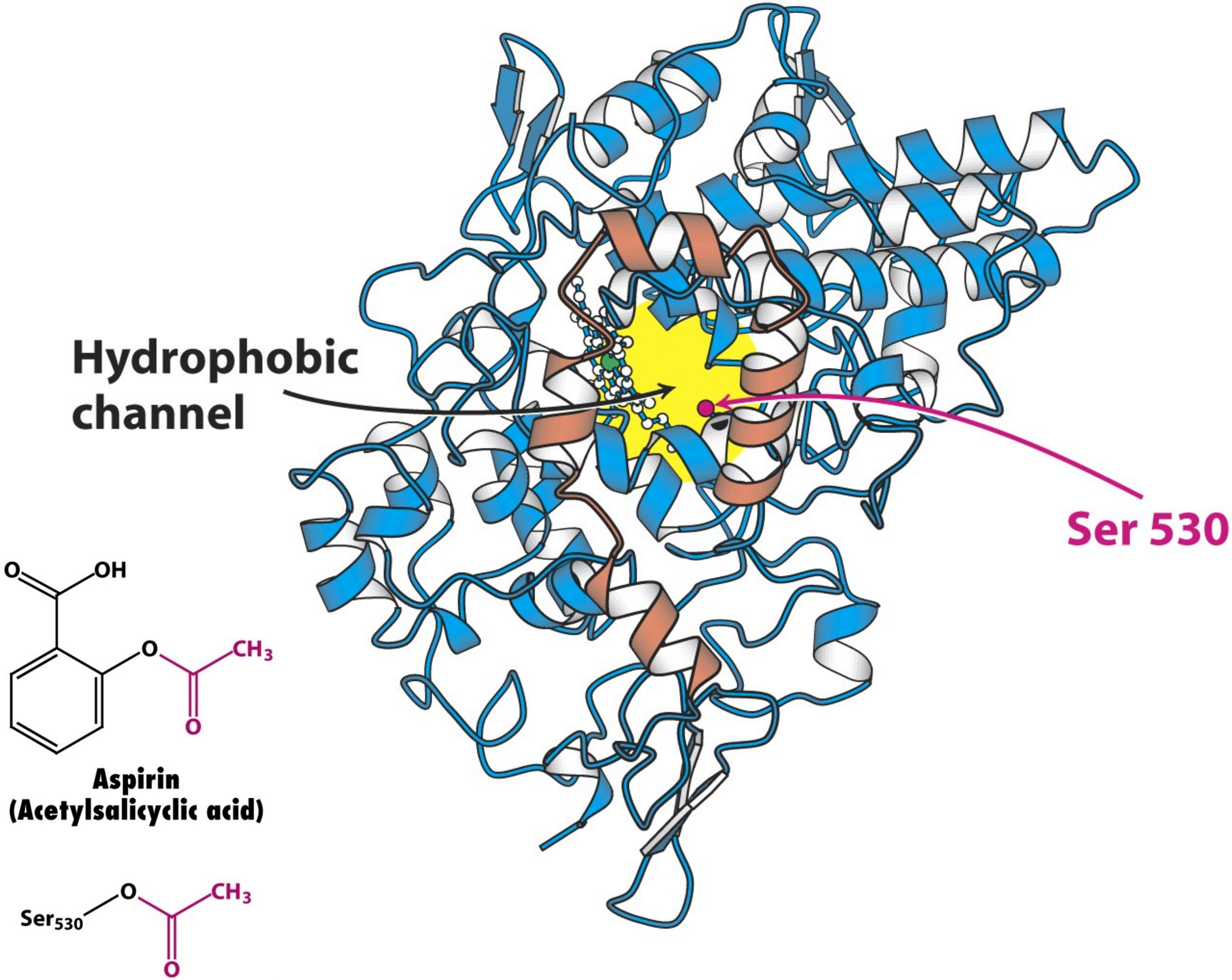

Figure 12-25
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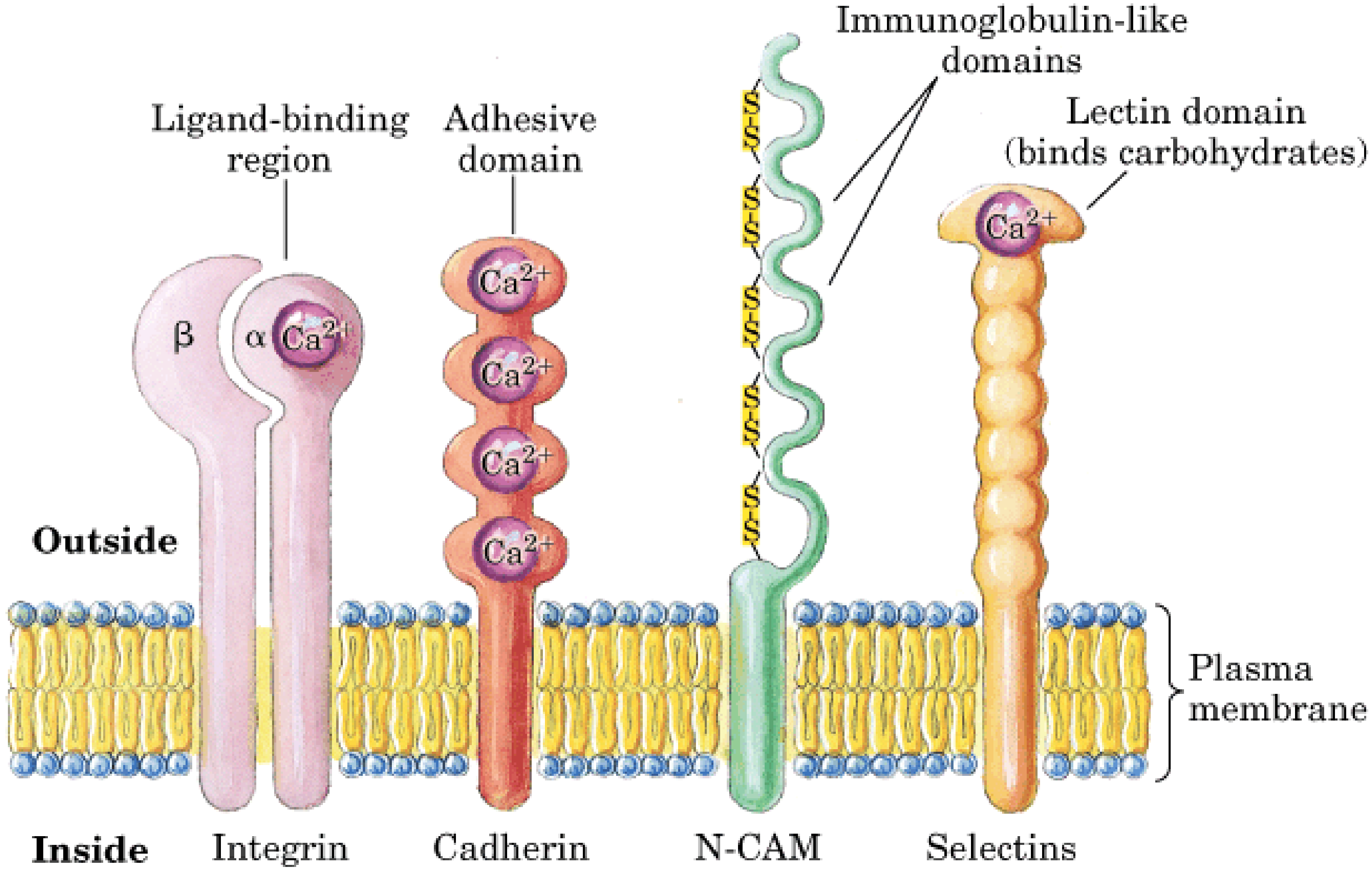
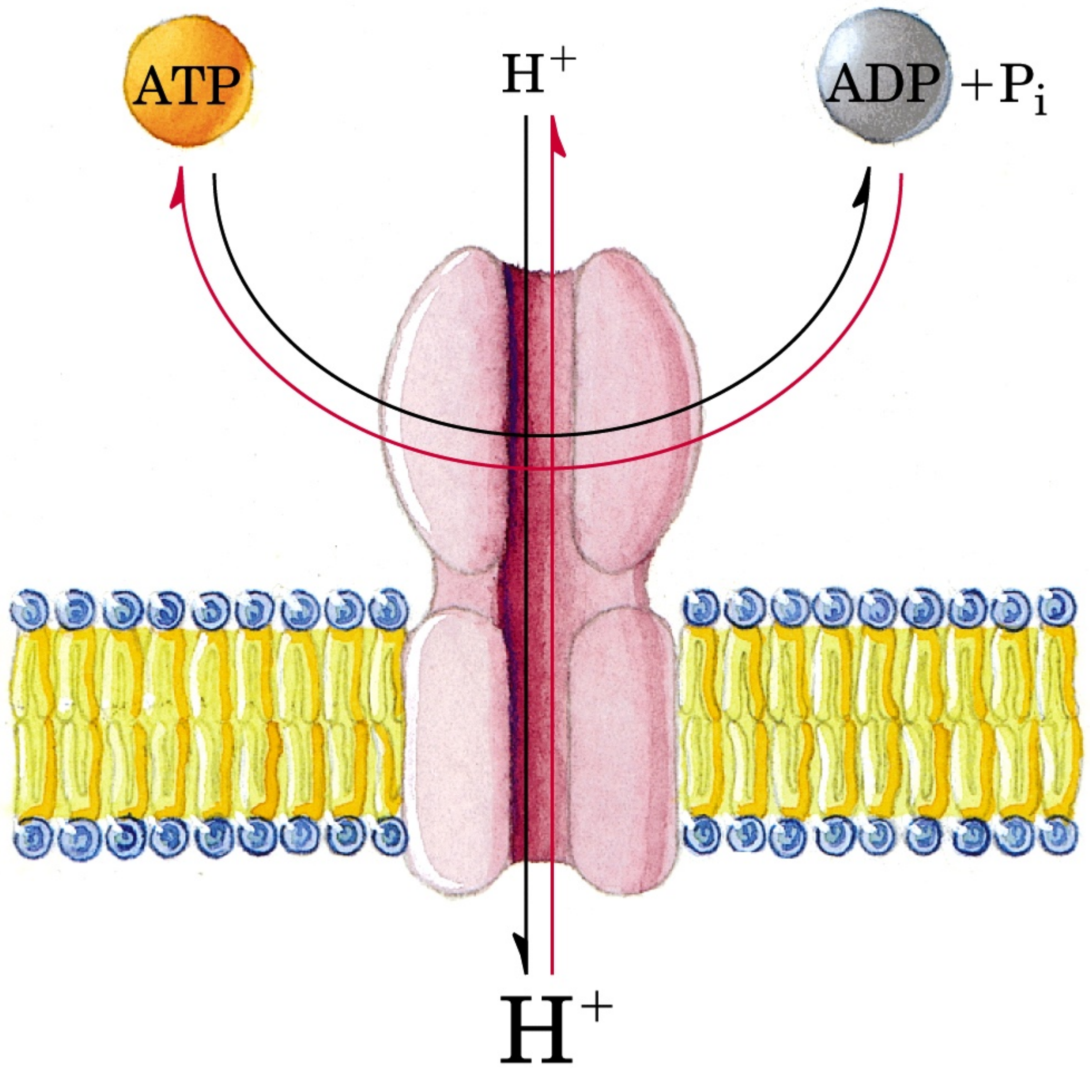
Proteínas integrais de membrana: interação célula-célula, adesão

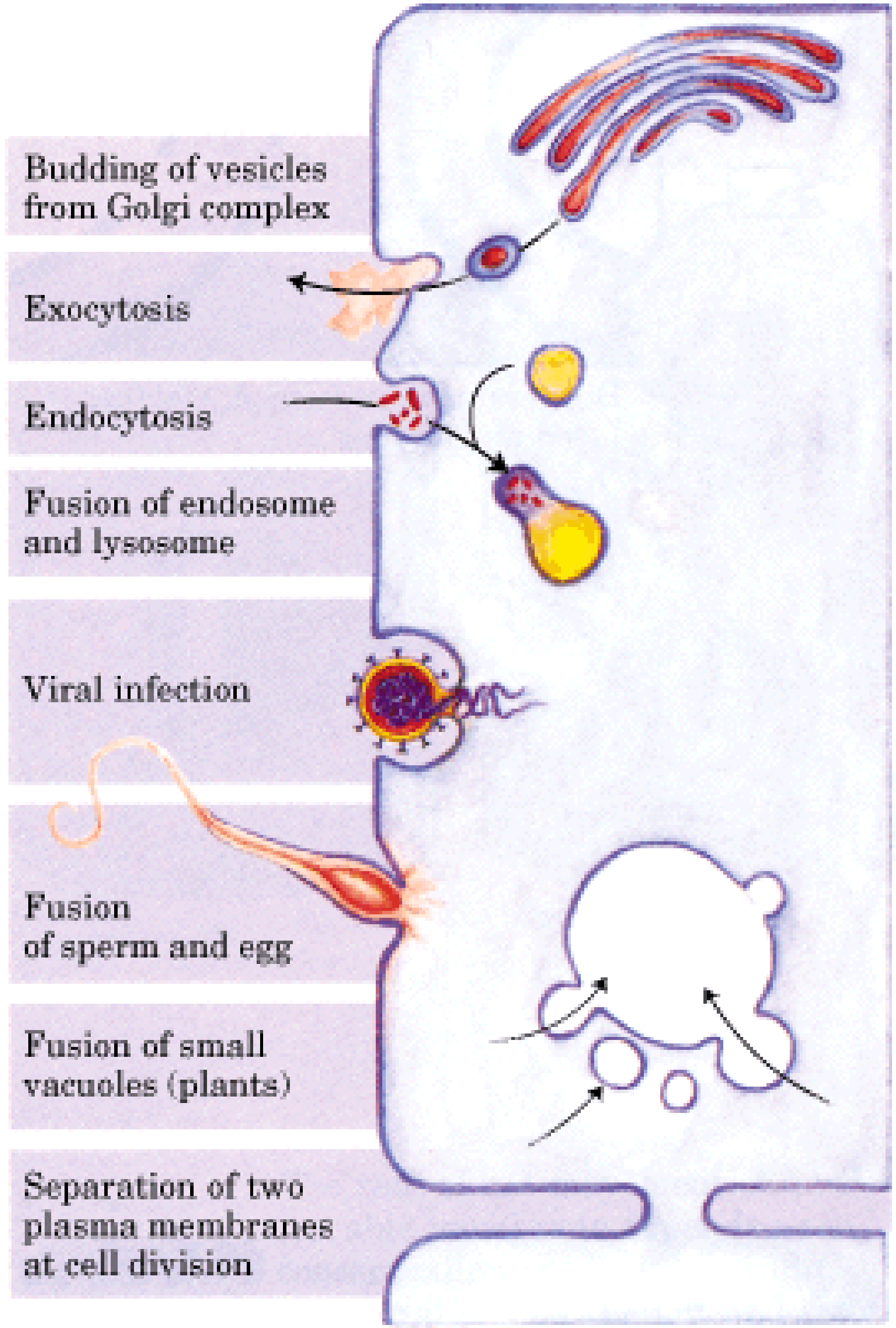


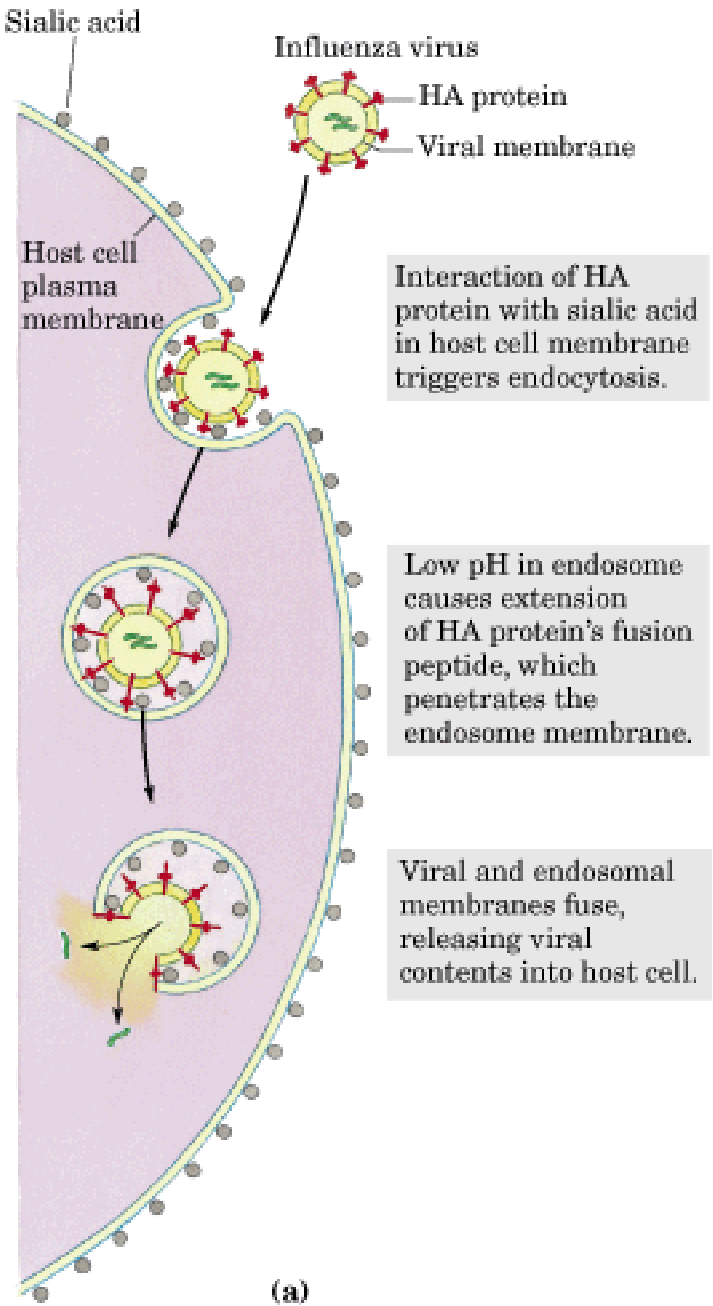
Assimetria estrutural gera assimetria funcional



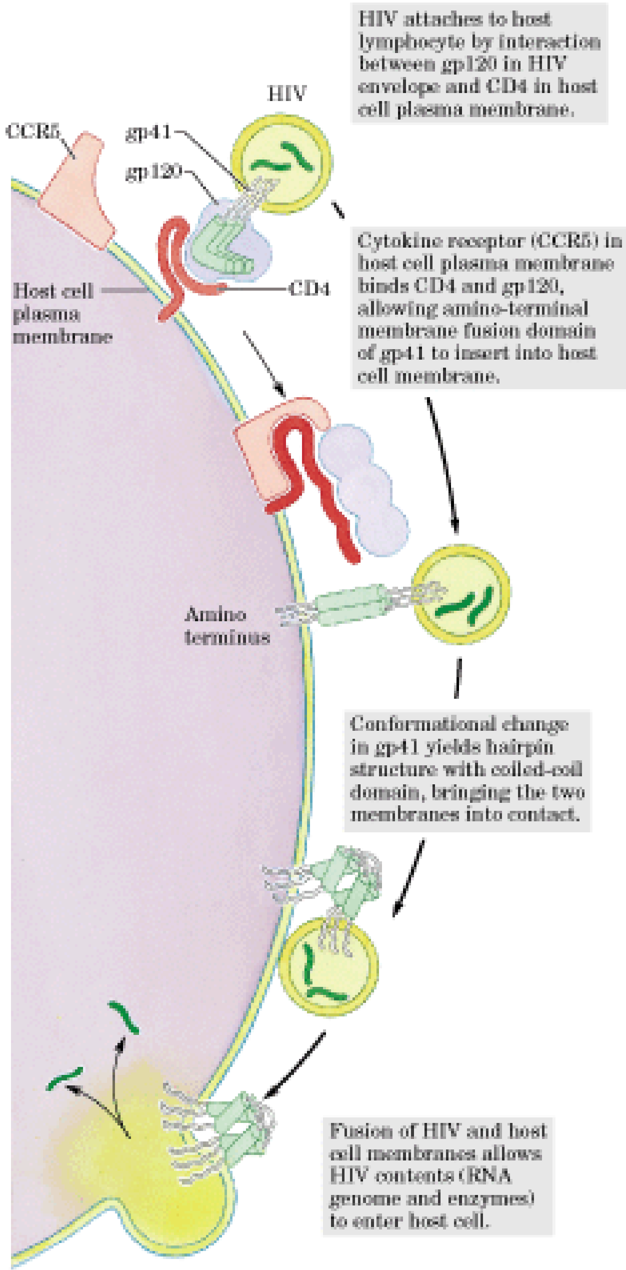
Fusão de membranas

1. Reconhecimento
2. Proximidade das superfícies – exclusão de água
3. Rompimento local da bicamada lipídica
4. Fusão = uma única bicamada contínua




Sialic acid
Influenza virus
HA protein
Viral membrane
Host cell plasma membrane
Interaction of HA protein with sialic acid in host cell membrane triggers endocytosis.
Low pH in endosome causes extension of HA protein's fusion peptide, which penetrates the endosome membrane.
Viral and endosomal membranes fuse, releasing viral contents into host cell.

(a)


HIV attaches to host lymphocyte by interaction between gp120 in HIV envelope and CD4 in host cell plasma membrane.
HIV
CCR5
gp41
gp120
CD4
Host cell plasma membrane
Cytokine receptor (CCR5) in host cell plasma membrane binds CD4 and gp120, allowing amino-terminal membrane fusion domain of gp41 to insert into host cell membrane.
Amino terminus
Conformational change in gp41 yields hairpin structure with coiled-coil domain, bringing the two membranes into contact.
Fusion of HIV and host cell membranes allows HIV contents (RNA genome and enzymes) to enter host cell.

(b)

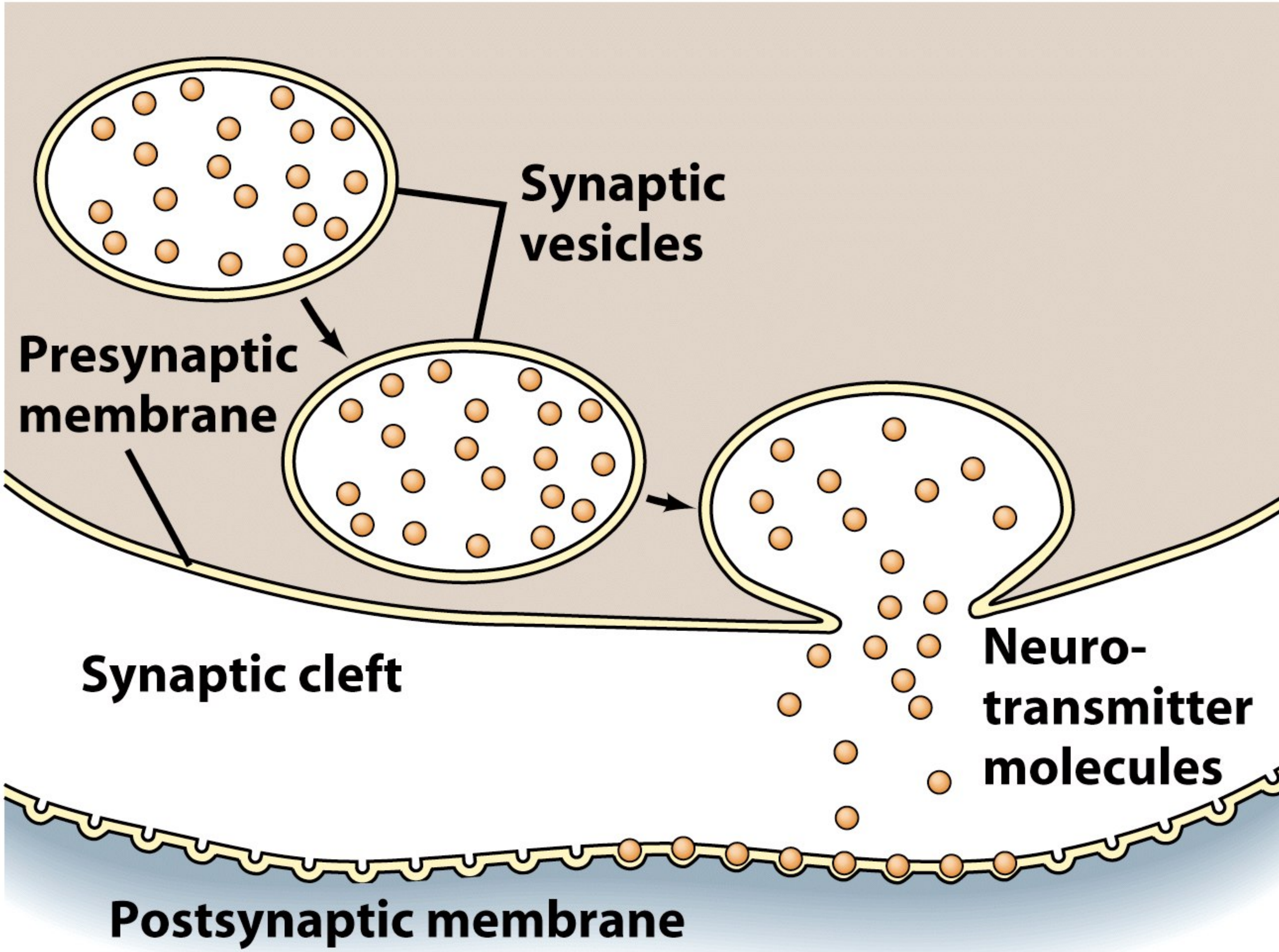
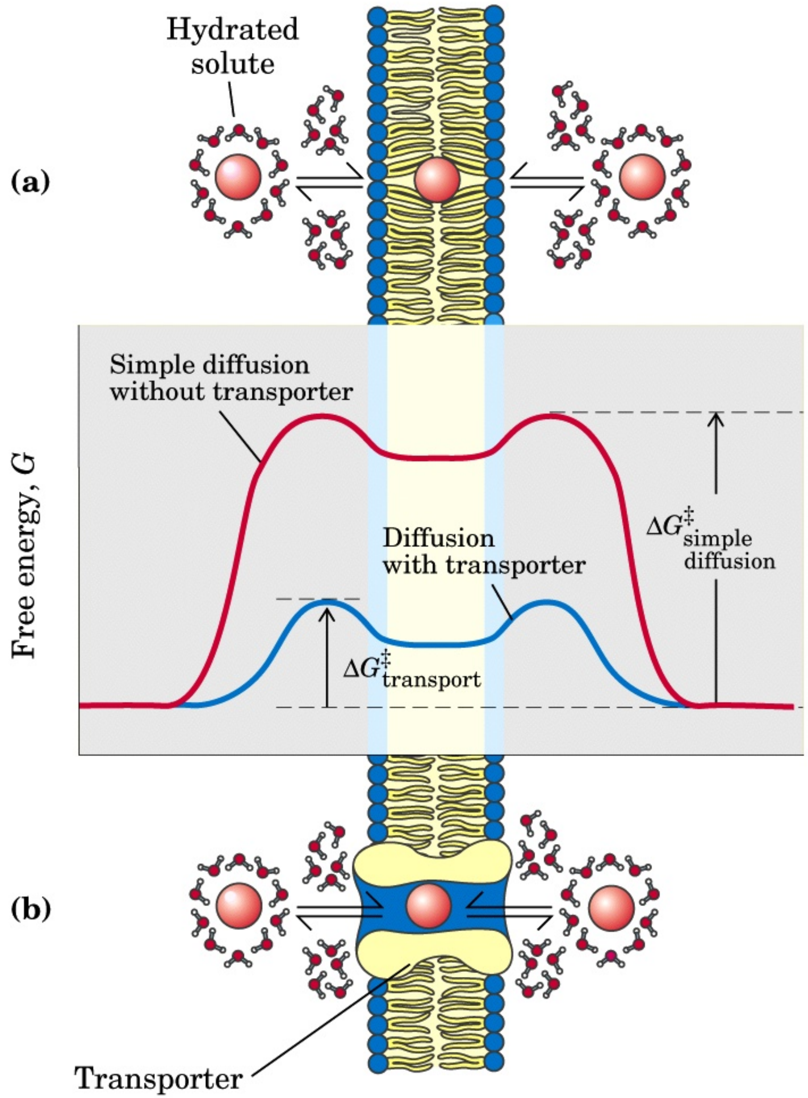
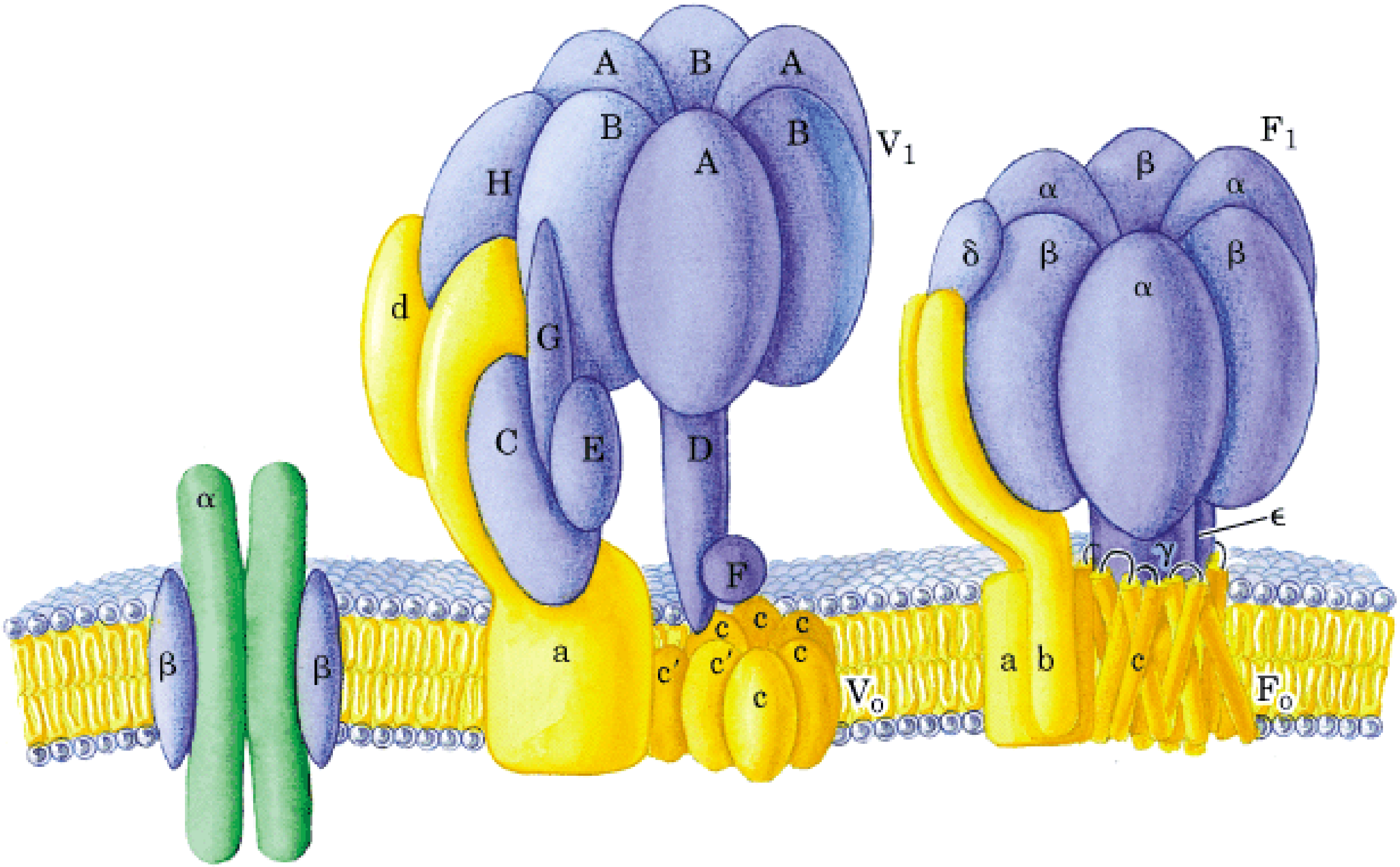


Figure 9-47b Fundamentals of Biochemistry, 2/e

Transporte através de membranas:
transportadores passivos



Transporte ativo: ATPases



P-type
(a)

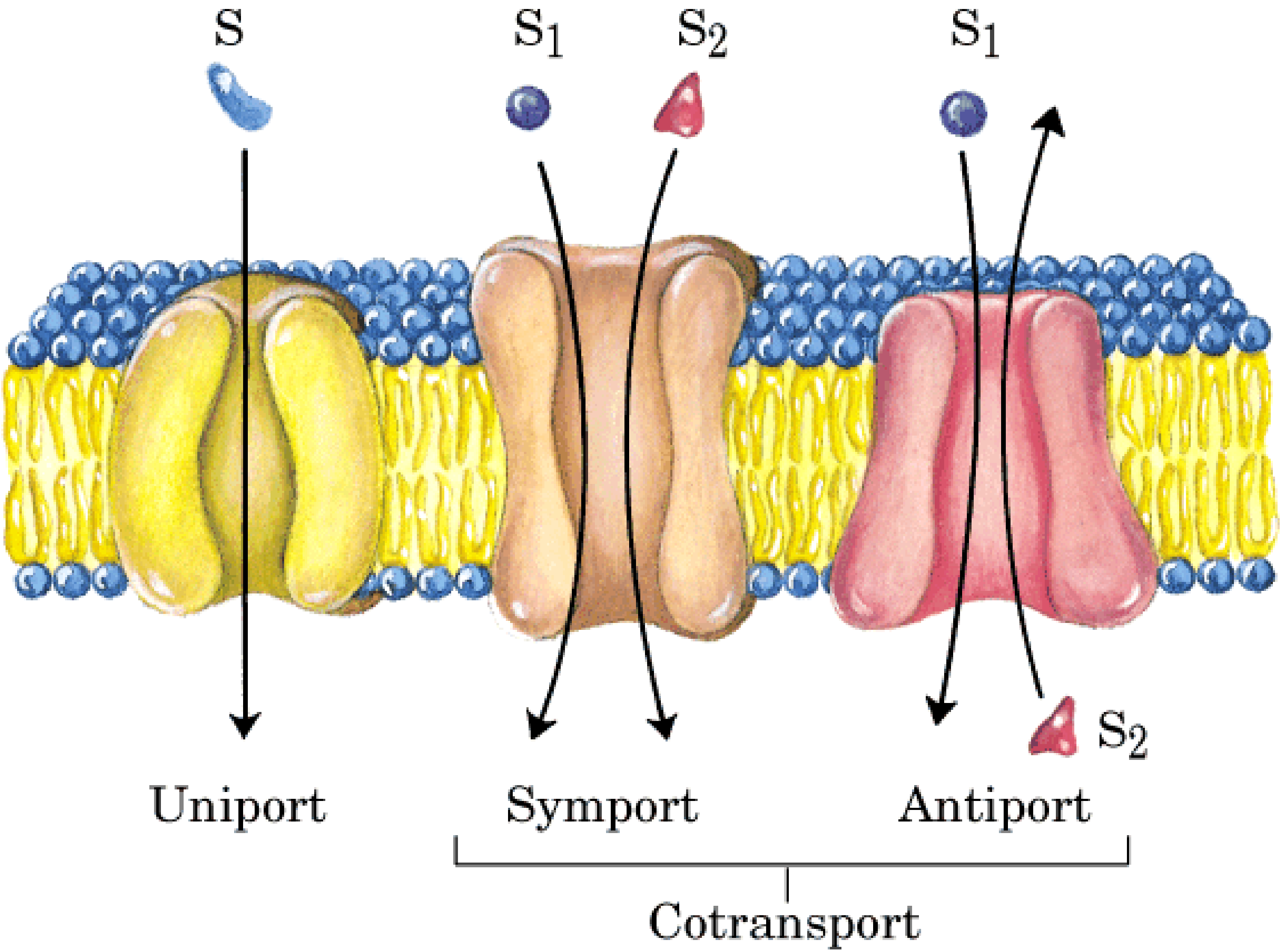
V-type
(b)

F-type
(c)

table 12–4

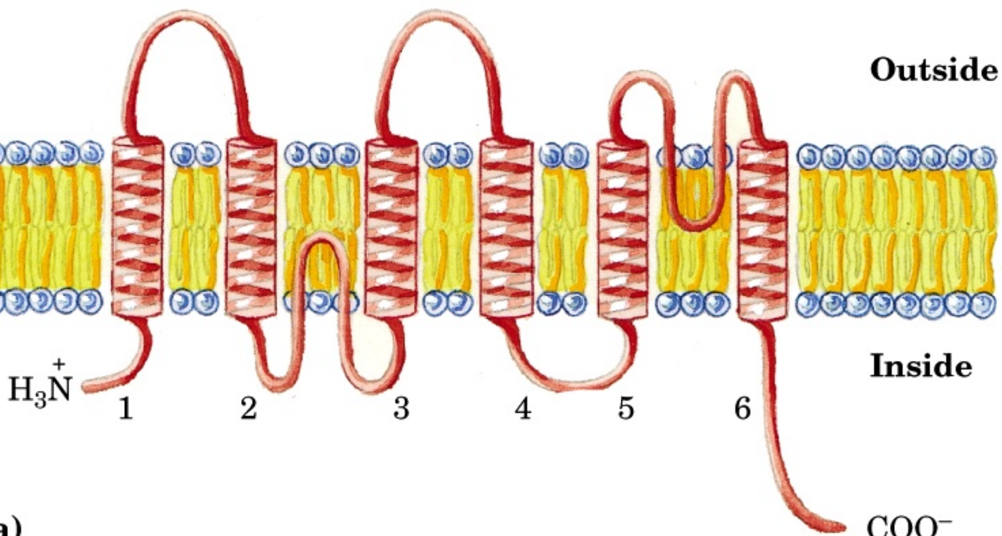
Four Classes of Transport ATPases

	Organism or tissue	Type of membrane	Role of ATPase
P-type ATPases			
Na^+K^+	Animal tissues	Plasma	Maintains low $[Na^+]$, high $[K^+]$ inside cell; creates transmembrane electrical potential
H^+K^+	Acid-secreting (parietal) cells of mammals	Plasma	Acidifies contents of stomach
H^+	Fungi *(Neurospora)*	Plasma	Create H^+ gradient to drive secondary transport of extracellular solutes into cell
H^+	Higher plants	Plasma	
Ca^{2+}	Animal tissues	Plasma	Maintains low $[Ca^{2+}]$ in cytosol
Ca^{2+}	Myocytes of animals	Sarcoplasmic reticulum (endoplasmic reticulum)	Sequesters intracellular Ca^{2+}, keeping cytosolic $[Ca^{2+}]$ low
Cd^{2+}, Hg^{2+}, Cu^{2+}	Bacteria	Plasma	Pumps heavy metal ions out of cell
V-type ATPases			
H^+	Animals	Lysosomal, endosomal, secretory vesicles	Create low pH in compartment, activating proteases and other hydrolytic enzymes
H^+	Higher plants	Vacuolar	
H^+	Fungi	Vacuolar	
F-type ATPases			
H^+	Eukaryotes	Inner mitochondrial	Catalyze formation of ATP from ADP + P_i
H^+	Higher plants	Thylakoid	
H^+	Prokaryotes	Plasma	
Multidrug transporter			
	Animal tumor cells	Plasma	Removes a wide variety of hydrophobic natural products and synthetic drugs from cytosol, including vinblastine, doxorubicin, actinomycin D, mitomycin, taxol, colchicine, and puromycin

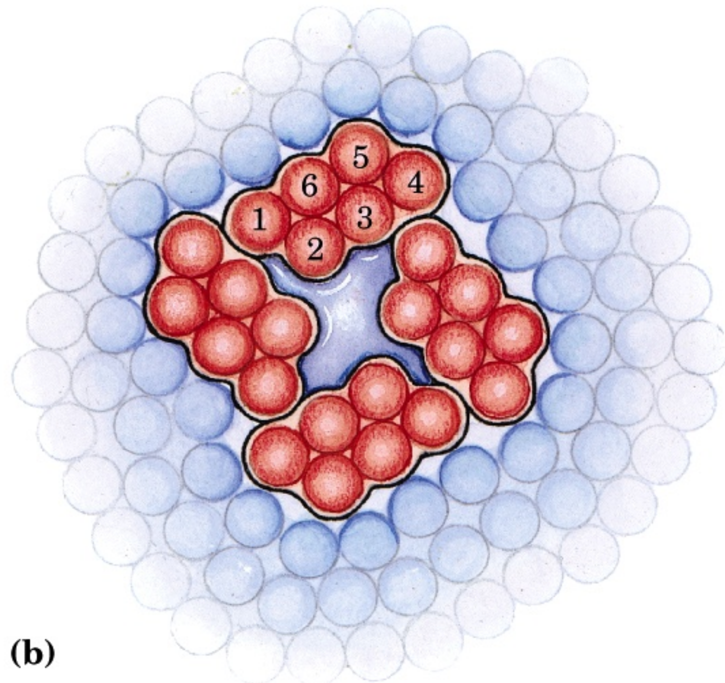


S
S1
S2
S1
S2
Uniport
Symport
Antiport
Cotransport

Transporte através de membranas:
Ex.: aquaporina



(a)



(b)

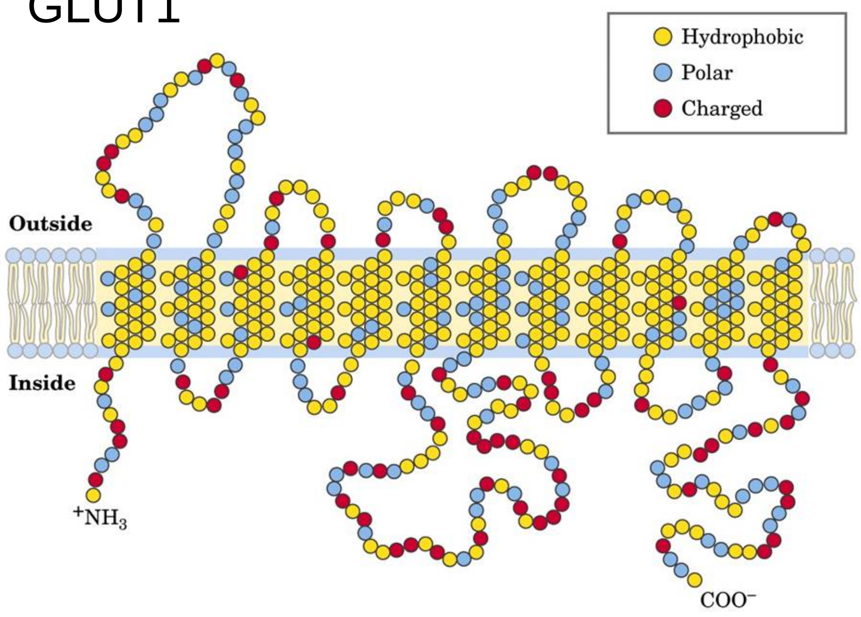
~5 x 10^8 moléculas de água por segundo

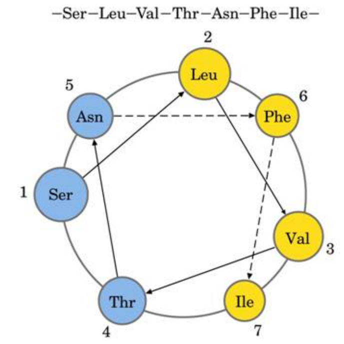
Aquaporins

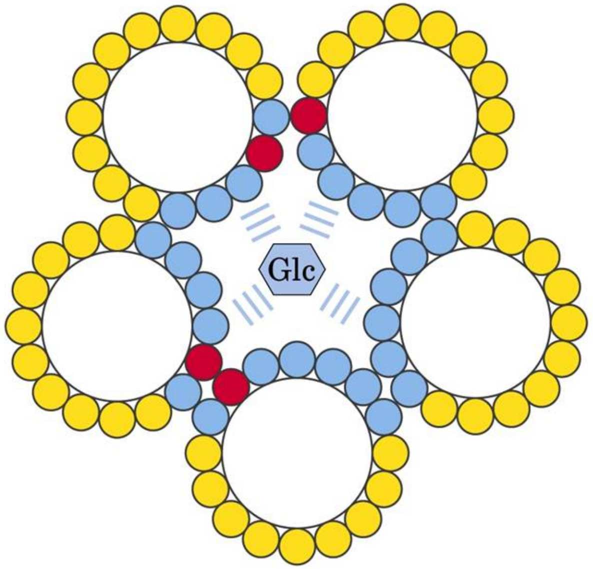
Aquaporin	Roles and location
AQP-1	Fluid reabsorption in proximal renal tubule; secretion of aqueous humor in eye and cerebrospinal fluid in central nervous system; water homeostasis in lung
AQP-2	Water permeability in renal collecting duct (mutations produce nephrogenic diabetes insipidus)
AQP-3	Water retention in renal collecting duct
AQP-4	Reabsorption of cerebrospinal fluid in central nervous system; regulation of brain edema
AQP-5	Fluid secretion in salivary glands, lachrymal glands, and alveolar epithelium of lung
γ-TIP	Water uptake by plant vacuole, regulating turgor pressure

Transporte através de membranas:
Ex.: transportador de glicose

GLUT1

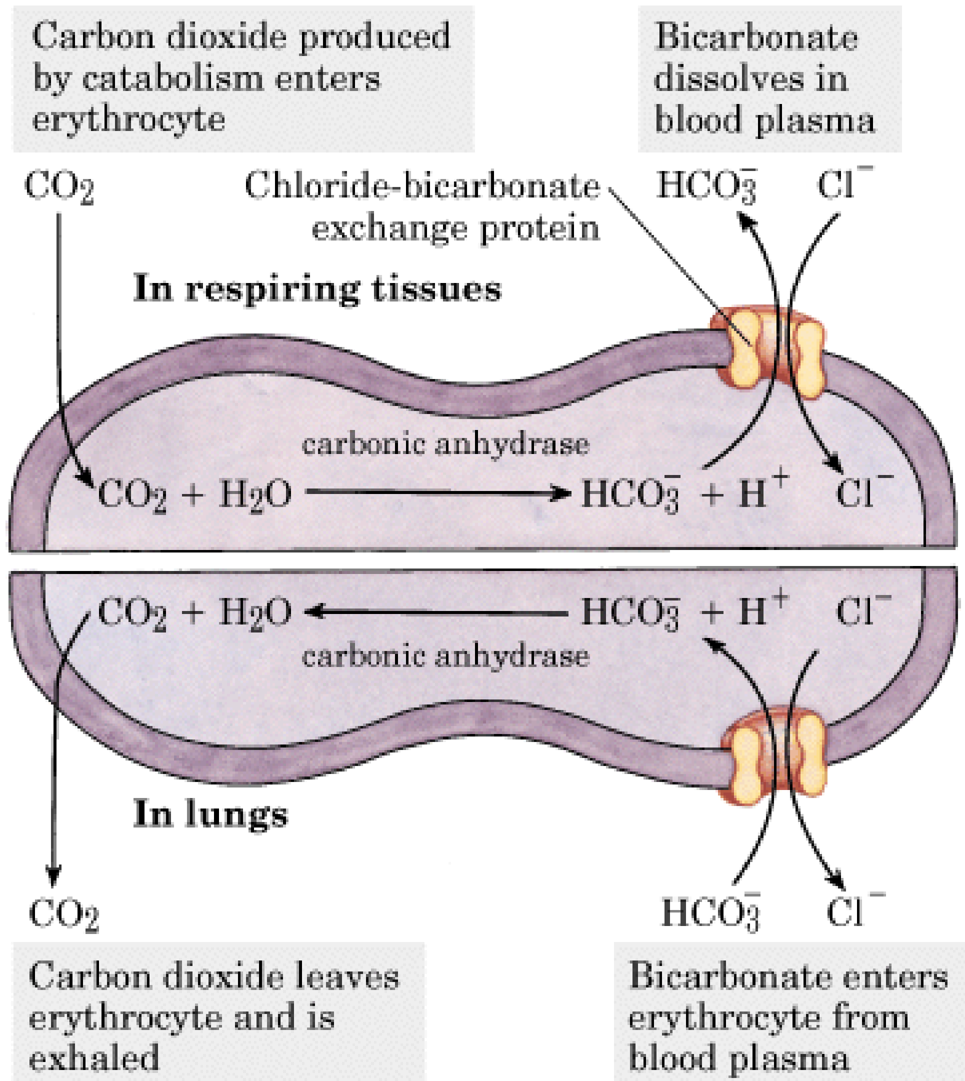






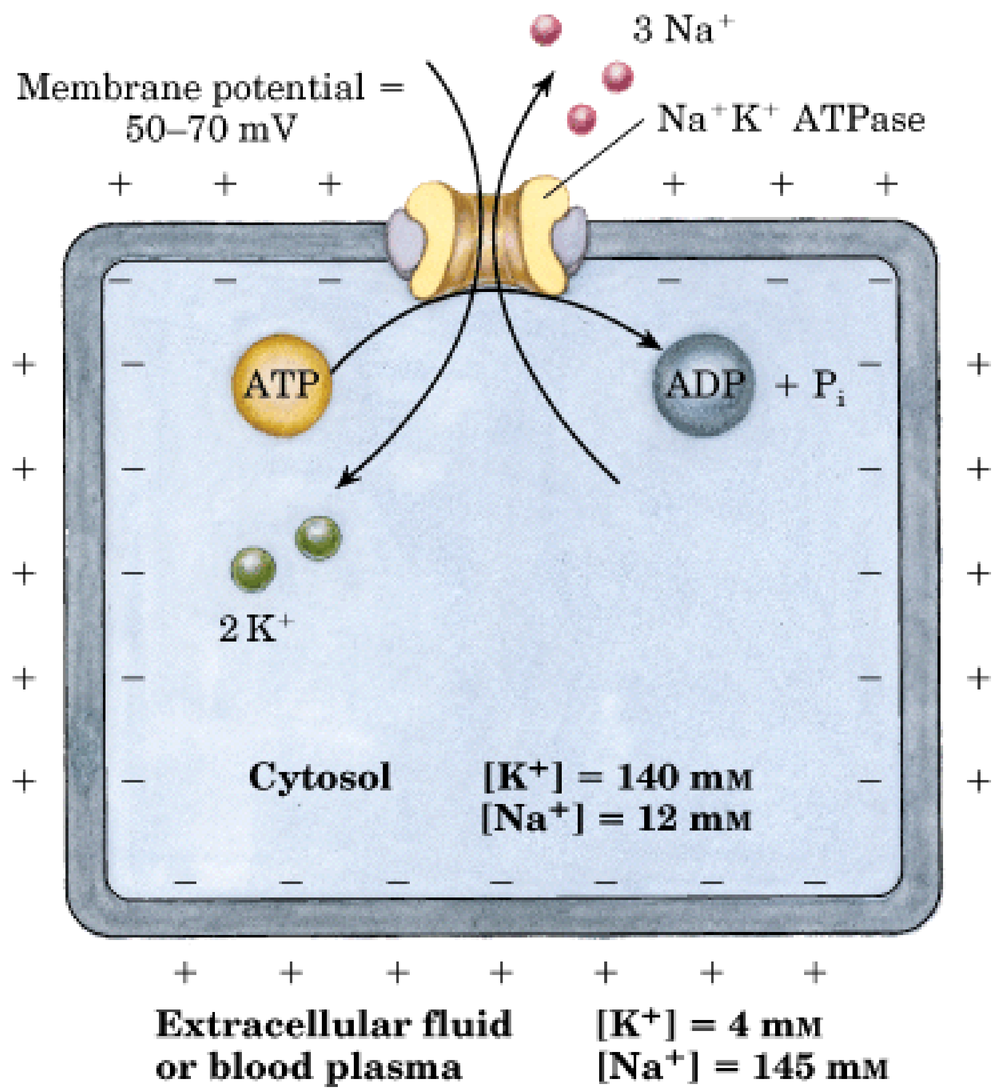
Transporte através de membranas:

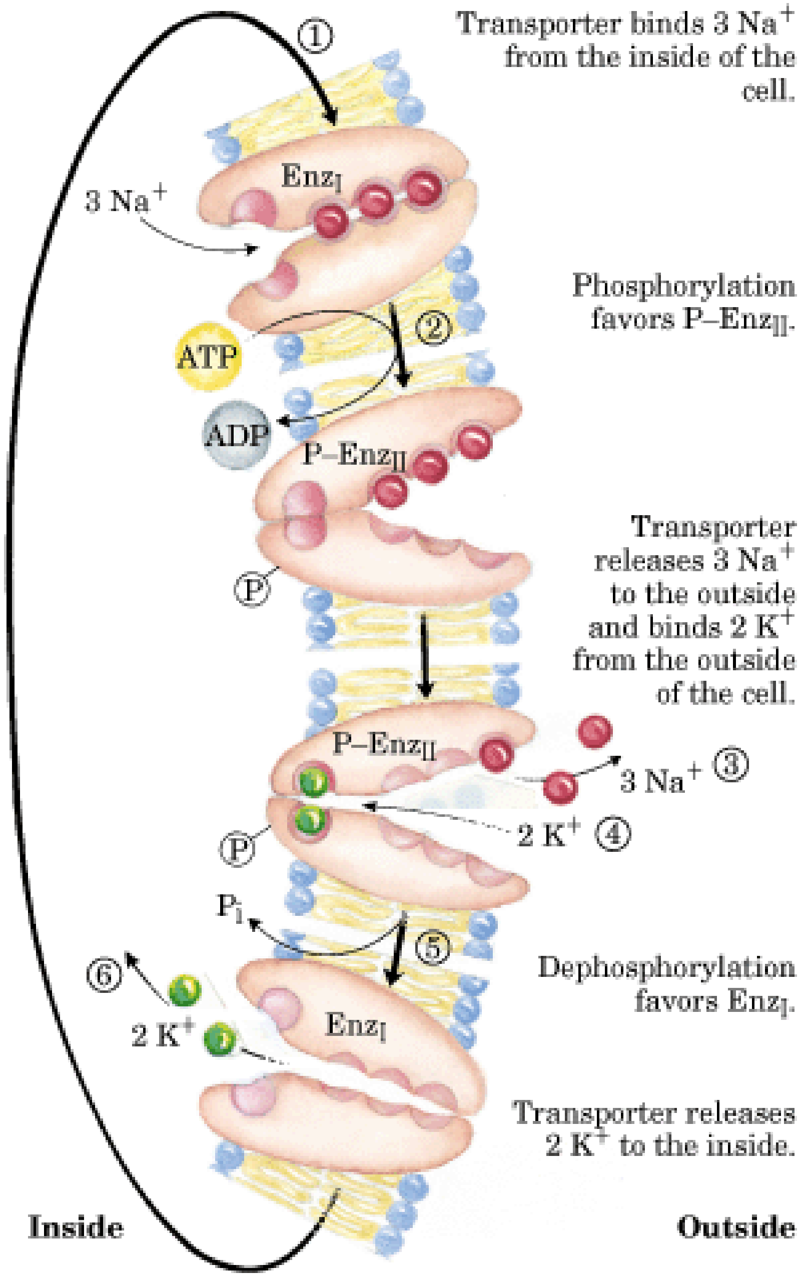
Ex.: transportador de cloreto/bicarbonato



Transporte através de membranas:

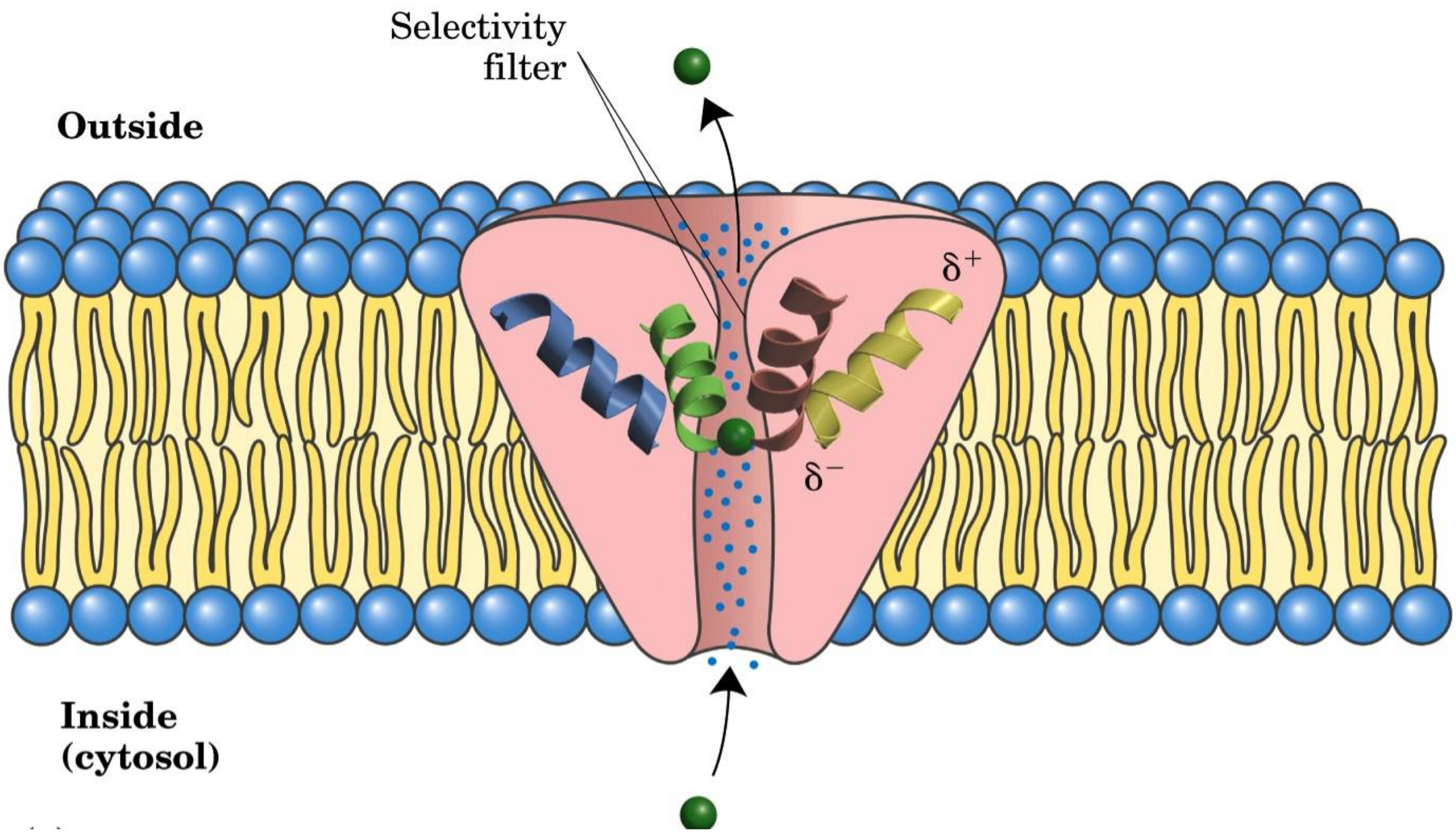
Ex.: bombas de sódio-potássio



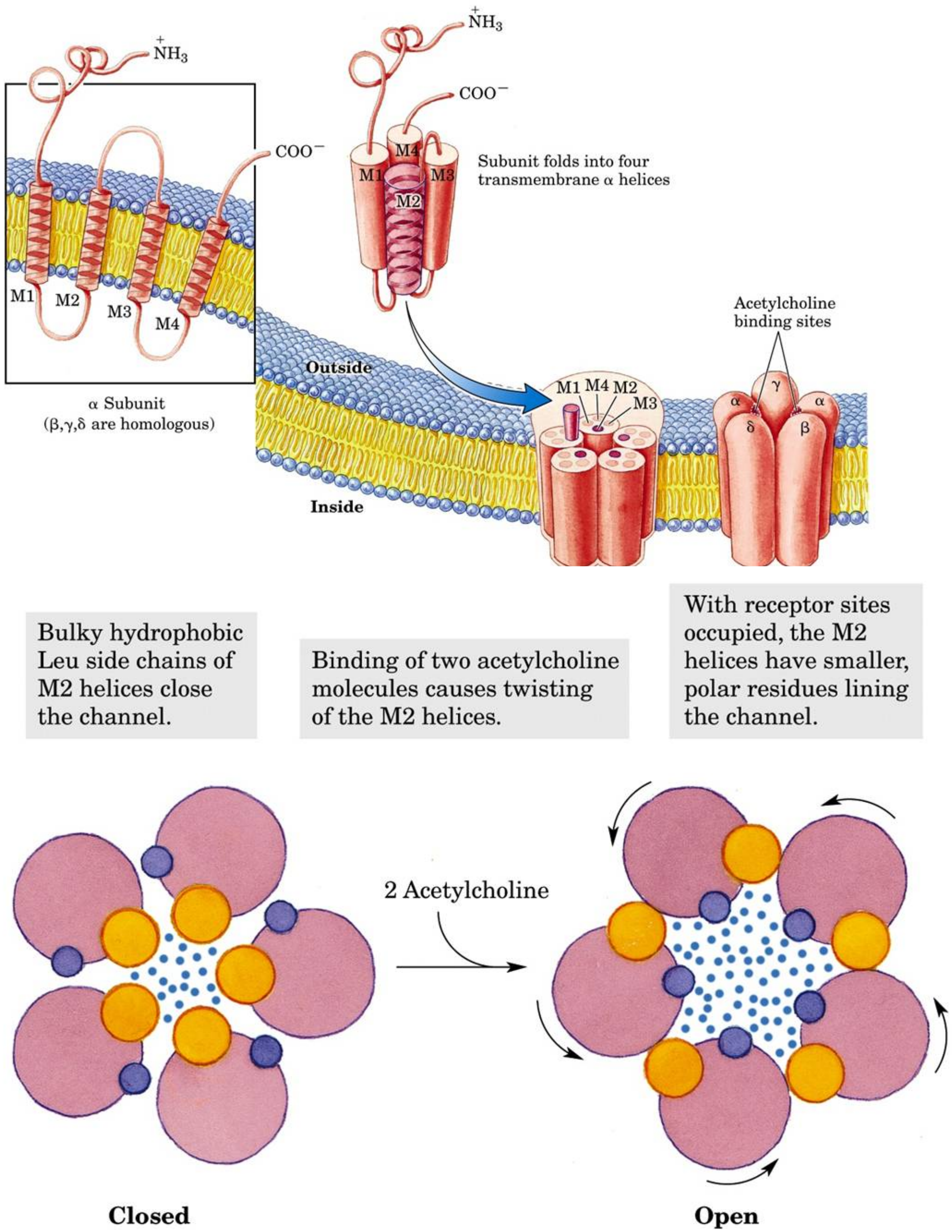


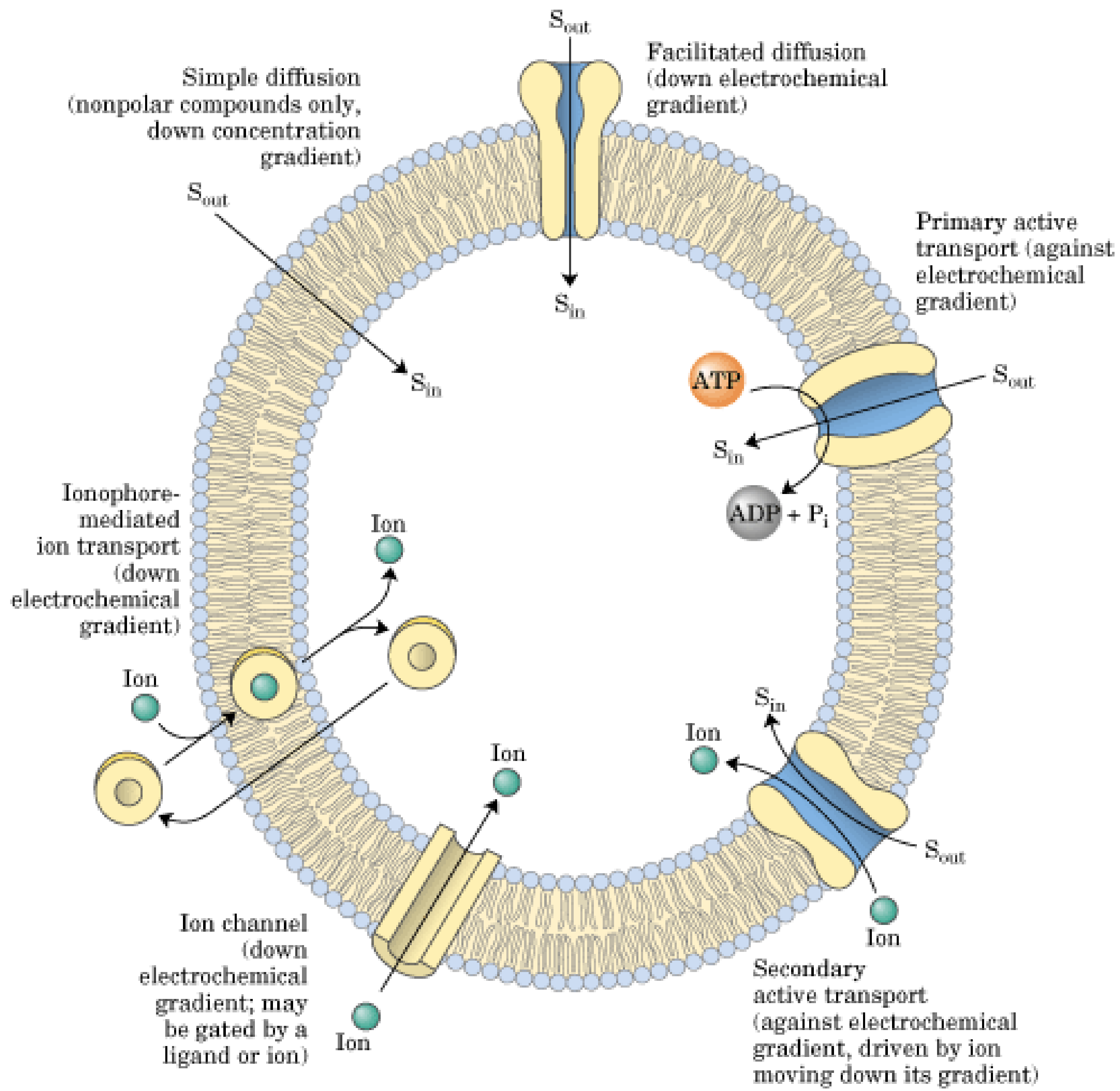
Transporter binds 3 Na^+ from the inside of the cell.
①
Enz$_I$
3 Na^+
Phosphorylation favors P–Enz$_{II}$.
②
ATP
ADP
P–Enz$_{II}$
Ⓟ
Transporter releases 3 Na^+ to the outside and binds 2 K^+ from the outside of the cell.
P–Enz$_{II}$
3 Na^+ ③
2 K^+ ④
Ⓟ
P_i
⑤
⑥
Dephosphorylation favors Enz$_I$.
2 K^+
Enz$_I$
Transporter releases 2 K^+ to the inside.
Inside
Outside

Ex.: Canal iônico de K^+



Ex.: Receptor de acetilcolina: canal dependente de ligante





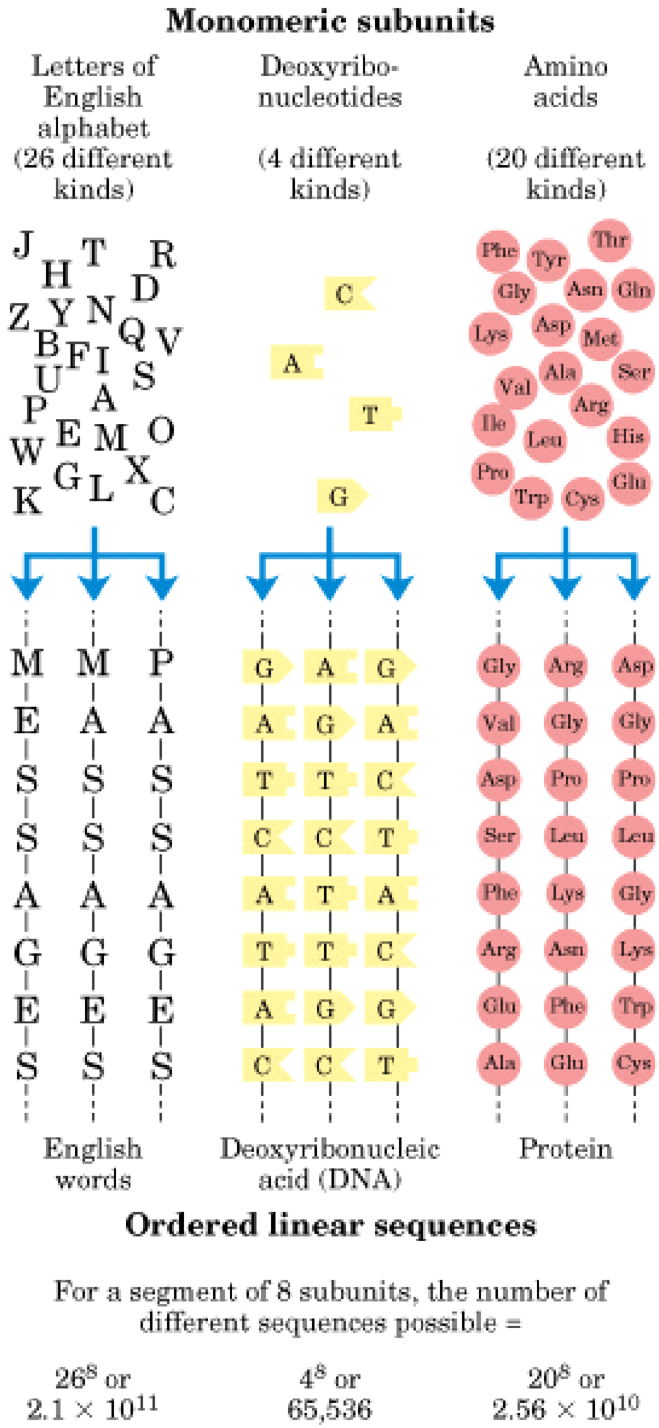
Simple diffusion (nonpolar compounds only, down concentration gradient)
S_{out}
S_{in}
S_{out}
S_{in}
Facilitated diffusion (down electrochemical gradient)
Primary active transport (against electrochemical gradient)
ATP
S_{out}
S_{in}
ADP + P_i
Ionophore-mediated ion transport (down electrochemical gradient)
Ion
Ion
Ion
Ion
S_{in}
S_{out}
Ion
Ion
Ion channel (down electrochemical gradient; may be gated by a ligand or ion)
Secondary active transport (against electrochemical gradient, driven by ion moving down its gradient)

O que é a Bioquímica?

A Bioquímica estuda, no nível molecular, as estruturas, mecanismos e processos químicos comuns a todos os organismos.

Visto que todos os seres vivos são constituídos por moléculas "inanimadas", a vida é no seu nível mais básico um fenômeno bioquímico.

Lógica molecular da vida !!!

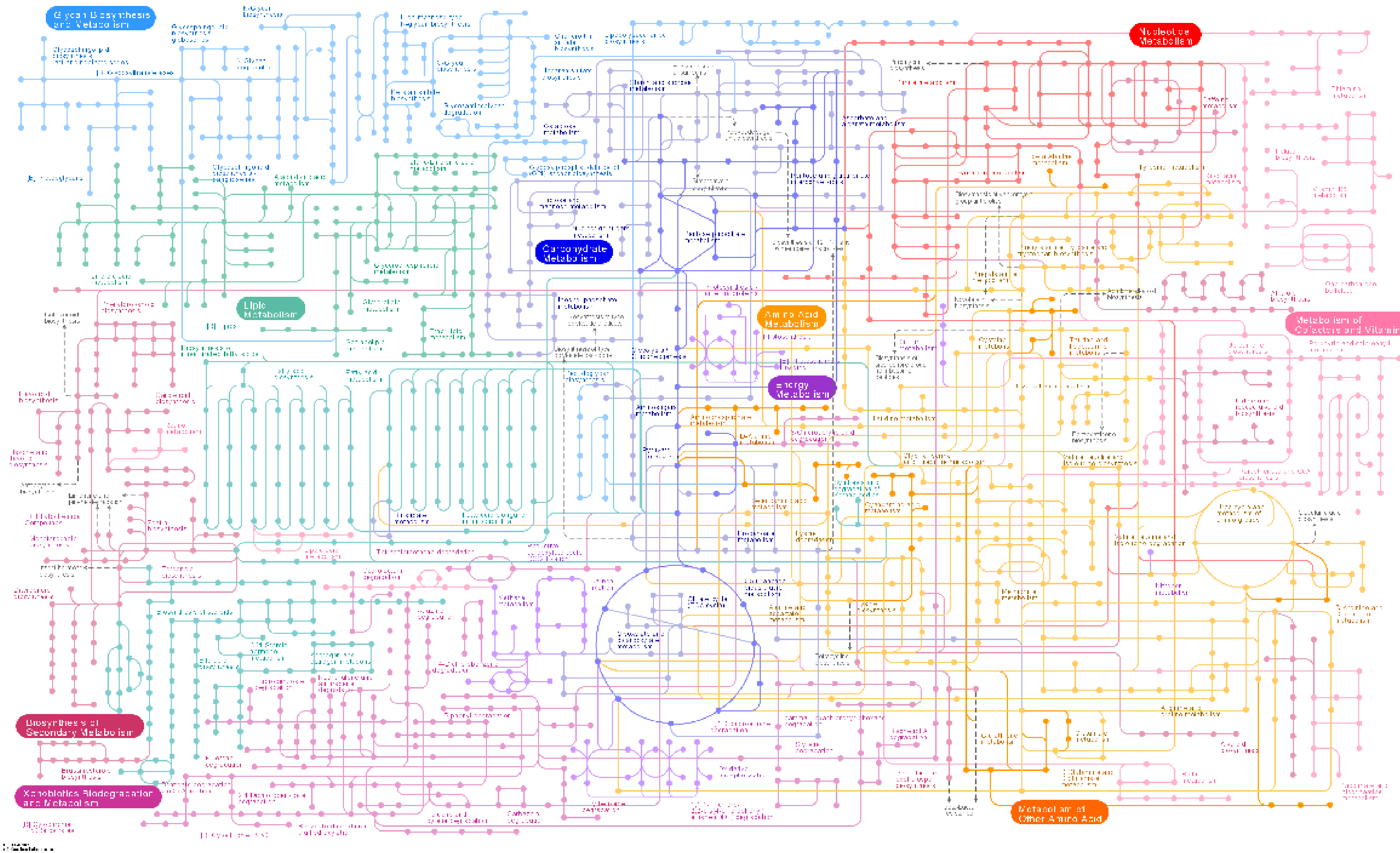


O que nós estudamos:

Interações moleculares
Água e pH
Aminoácidos e peptídeos
Proteínas
Enzimas e regulação enzimática
Carboidratos
Nucleotídeos
Ácidos Nucleicos
Lipídeos
Membranas

BIOQUÍMICA

Campo altamente INTERDISCIPLINAR



Vias de síntese e degradação das biomoléculas

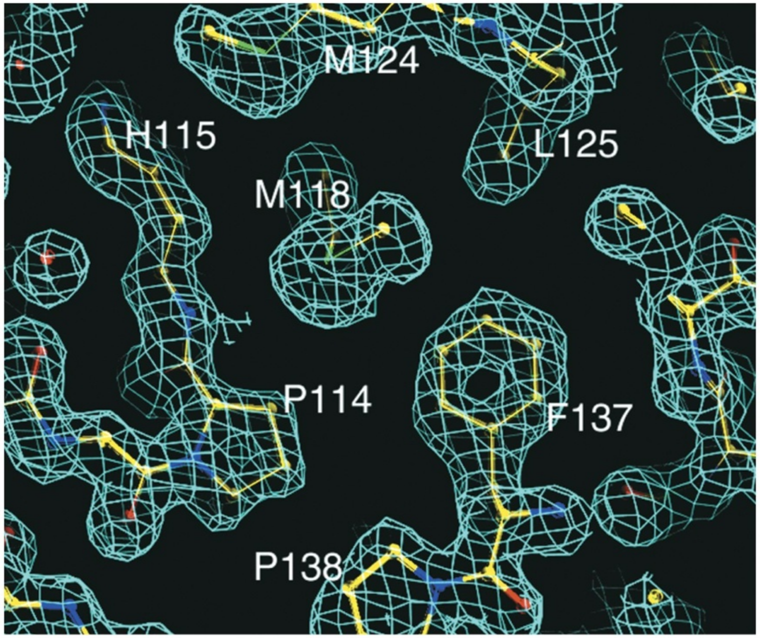


Figure 6-23 Fundamentals of Biochemistry, 2/e

Cinética
Dinâmica
Regulação

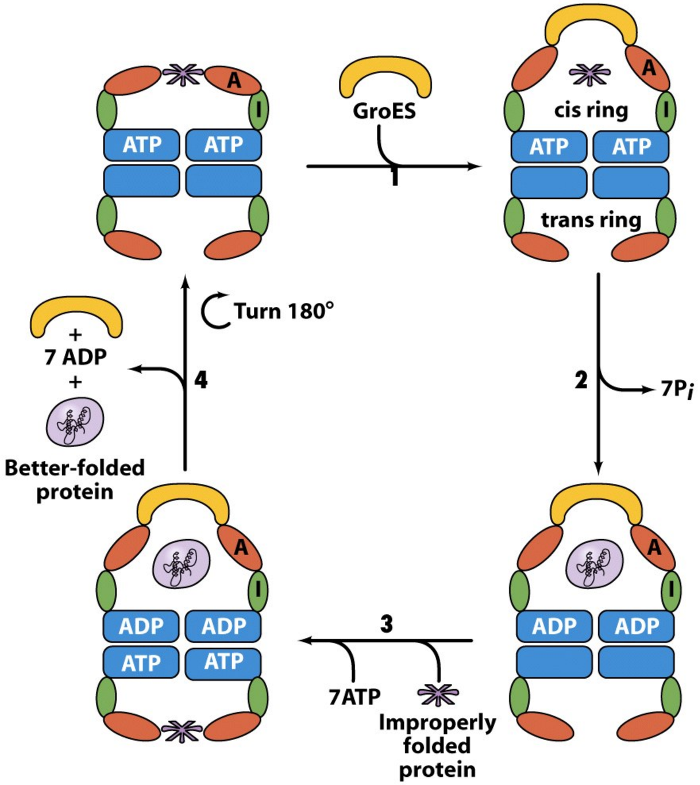
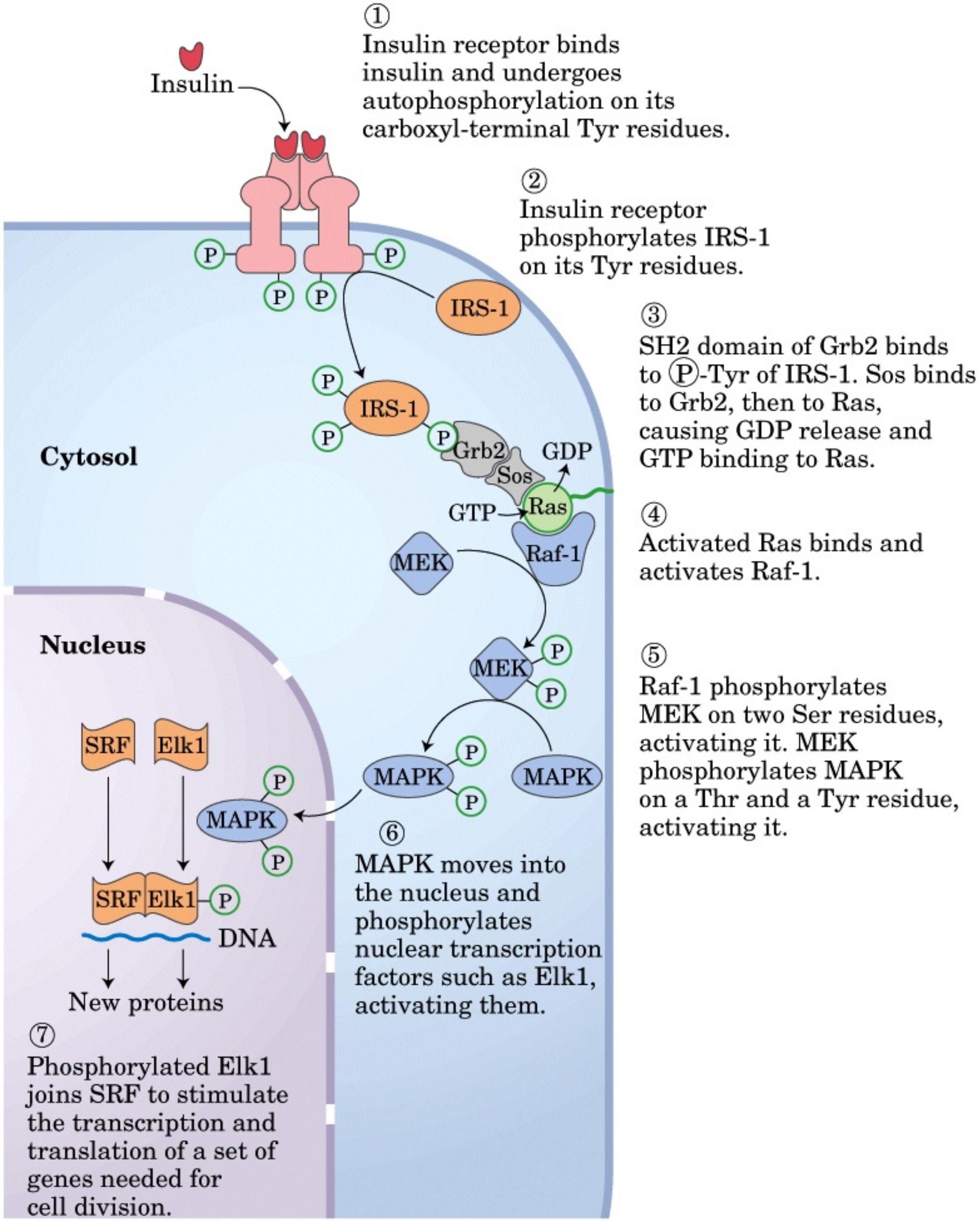


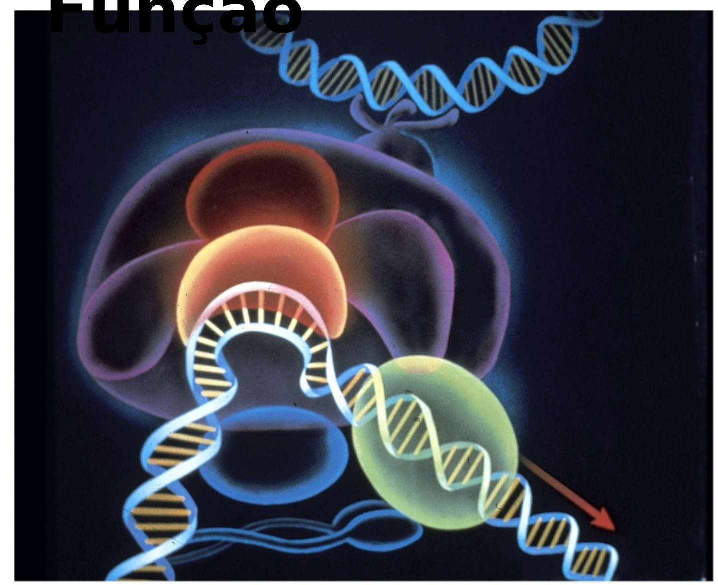
Figure 6-46 Fundamentals of Biochemistry, 2/e

Determinação de propriedades químicas, estrutura 3D e função de biomoléculas



Vias de transdução de sinal

Informação genética: Seqüência Transmissão Expressão Função

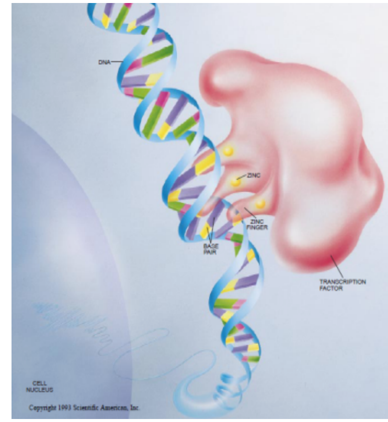


Chapter 27 Opener Fundamentals of Biochemistry, 2/e

Zinc Fingers

They play a key part in regulating the activity of genes in many species, from yeast to humans. Fewer than 10 years ago no one knew they existed

by Daniela Rhodes and Aaron Klug

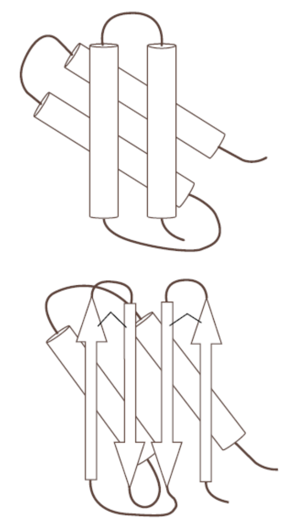


The Prion Diseases

Prions, once dismissed as an impossibility, have now gained wide recognition as extraordinary agents that cause a number of infectious, genetic and spontaneous disorders

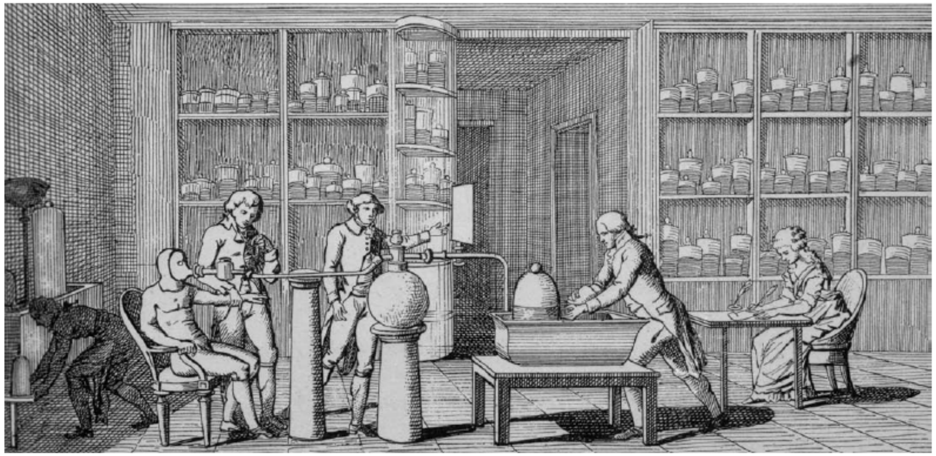
by Stanley B. Prusiner

FRED E. COHEN



DIMITRY SCHIDLOVSKY

SOURCE: Fred E. Cohen



BETTMANN/CORBIS

Eighteenth century chemist Antoine Lavoisier investigates whether exhaled breath is analogous to the fumes of a combustion engine.

HISTORY

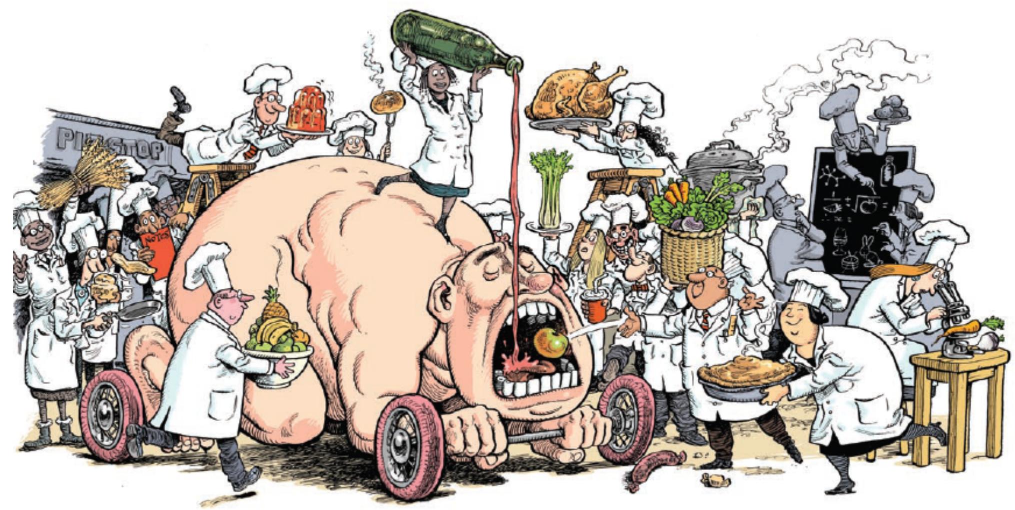
The changing notion of food

The pioneers of nutrition research determined the energy content of food and also helped to overturn misconceptions about various diseases that plagued humankind.

DIVERSITY

Of beans and genes

Several human genes involved in digestion have diverged along cultural lines. Research suggests these adaptations influence the range of foods tolerated and even certain diseases.



INTERDISCIPLINARY RESEARCH

Big science at the table

Researchers are adopting the tools of bioinformatics and pharmaceuticals to study and interpret the ever-growing body of data on the interplay between diet and genes.

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The Protein Data Bank: a historical perspective

Helen M. Berman

Rutgers, The State University of New Jersey, USA. Correspondence e-mail: berman@rcsb.rutgers.edu

The Protein Data Bank began as a grassroots effort in 1971. It has grown from a small archive containing a dozen structures to a major international resource for structural biology containing more than 40000 entries. The interplay of science, technology and attitudes about data sharing have all played a role in the growth of this resource.

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DOI: 10.1093/bioinformatics/btg309

Early bioinformatics: the birth of a discipline—a personal view

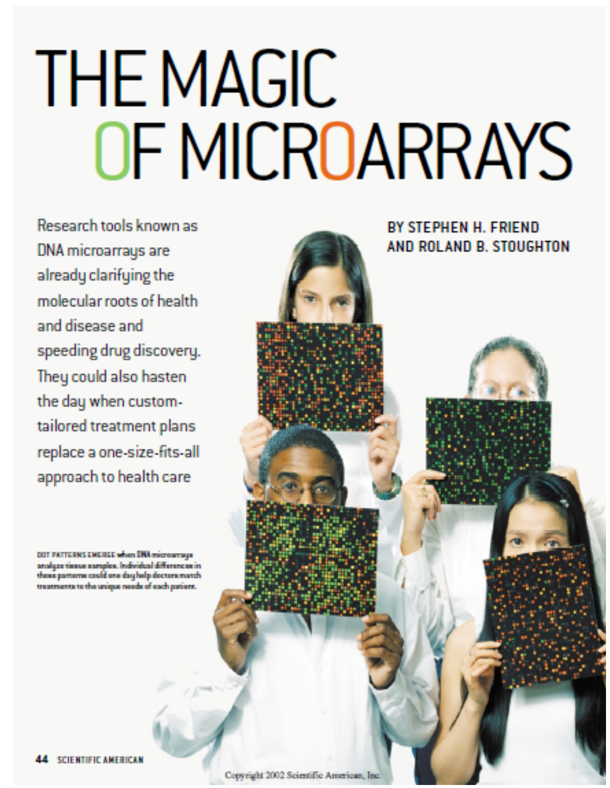
Christos A. Ouzounis[1,] and Alfonso Valencia[2]*

[1]Computational Genomics Group, The European Bioinformatics Institute, EMBL Cambridge Outstation, Cambridge CB10 1SD, UK, [2]Protein Design Group, National Center for Biotechnology, CNB-CSIC Campus U. Autonoma Cantoblanco, Madrid 28049, Spain

Review Paper

Review

What is bioinformatics? An introduction and overview



TASTE

More than meets the mouth

Certain things taste differently to different people. Why is this, and does this affect our choice of food?

I. HOOTON/SCIENCE PHOTO LIBRARY

DEVELOPMENT

Mother's milk: A rich opportunity

Research on the contents of milk and how breast-feeding benefits a growing child is surprising scientists.

HEALTH

Edible advice

Diet-related illnesses are some of the biggest killers today. Can we tailor our food intake to prevent these diseases? Large international projects are underway to find out.

WHAT FUELS FAT

The human body's ability to store energy as fat seems haywire in a world full of food. Understanding how our complex energy-regulating systems can falter and lead to obesity is revealing new ways to fight excess weight

Computational systems biology

Hiroaki Kitano

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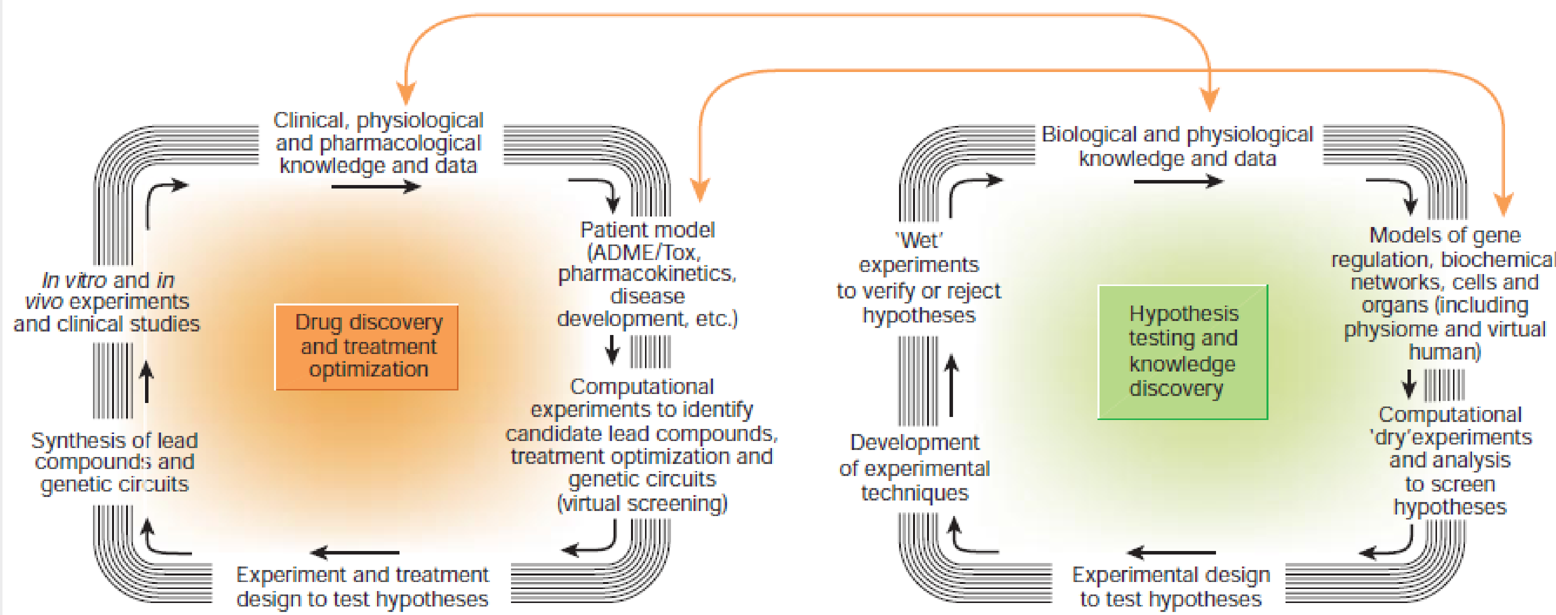
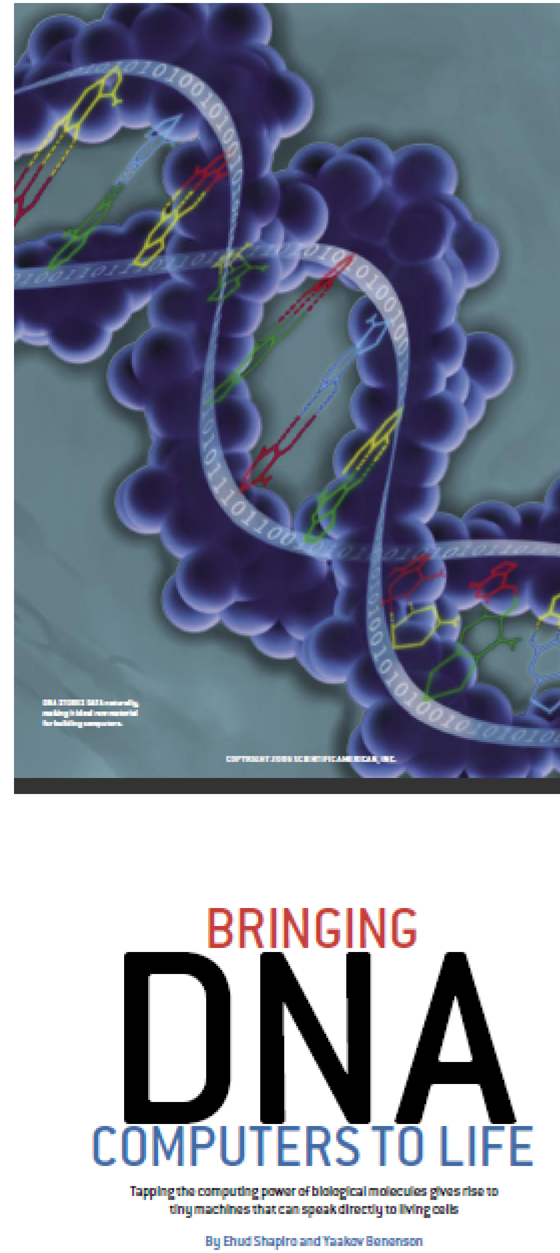


FIVE HARD TRUTHS FOR SYNTHETIC BIOLOGY

Can engineering approaches tame the complexity of living systems? **Roberta Kwok** explores five challenges for the field and how they might be resolved.

THE HYPE
A promise of unprecedented power

Nature has portrayed synthetic biologists as wielding the power to 'hack' life (right), and in its *Guide to Synthetic Biology*, the civil society organization ETC Group even likened their activity to playing God. But in reality, the field has yet to deliver much of practical use.



BRINGING DNA COMPUTERS TO LIFE

Tapping the computing power of biological molecules gives rise to tiny machines that can speak directly to living cells

By Ehud Shapiro and Yaakov Benenson

Os conhecimentos bioquímicos

NUNCA SÃO ESTANQUES!!!