

Lecture 4: Amino Acids

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Fall 2003

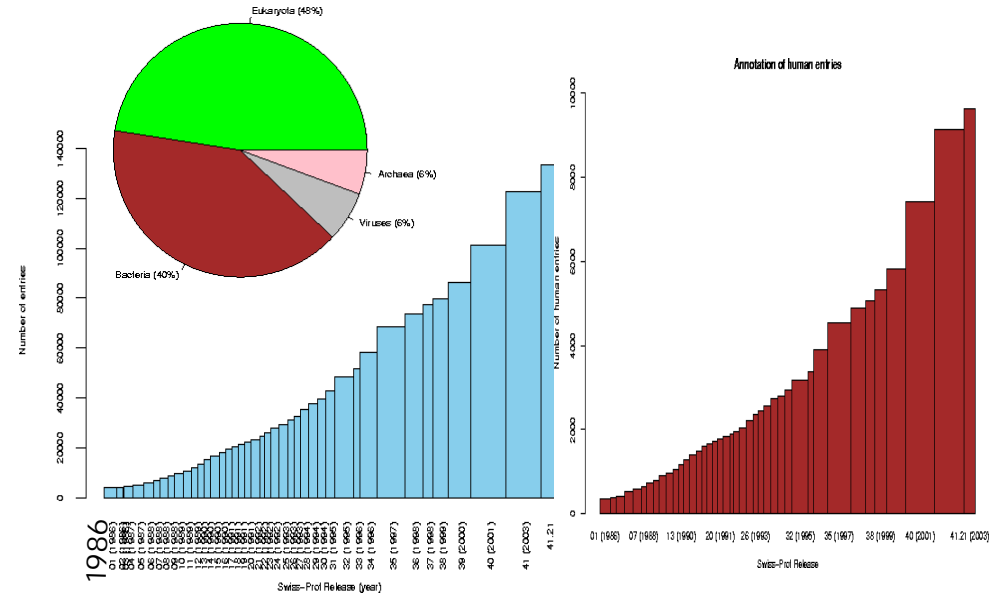
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Proteins are the “workhorses” of the cell

- Enzymes** - catalyze chemical reactions
- Regulatory proteins** - control physiological function
- Transport proteins** - move substances around/between cells
- Storage proteins** - provide a reservoir for a substance
- Motor proteins** - endow cells with capability of movement
- Structural proteins** - create and maintain biological structure
- Protective proteins** - active role in cell defense or protection
- Exotic proteins** - have specialized adaptive functions

And all this with just 20 amino acids and some post-translational modifications!

Swiss-prot database: How many proteins? From where?

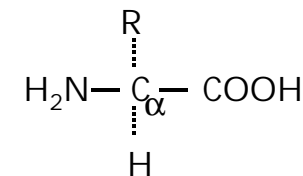


Use <http://us.expasy.org> to get to swiss-prot database

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Amino Acids

- Proteins are **polymers** of amino acids (AAs)
- There are **20 standard AAs**
- Four features of AAs structure
 - alpha carbon** (H attached)
 - a **carboxyl group** (acidic)
 - an **amino group** (basic)
 - R group** (variable)
- The **R group differentiates** 19 of the 20 AAs (Pro is the exception)



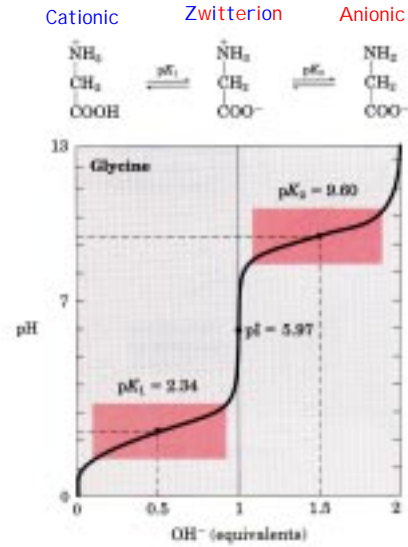
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Gly Titration (R group -H)

- Similar to the titration of a monoprotic acid;
- Isoelectric point (pI) where net charge = 0; thus, no migration in an electric field;

$$pI = \frac{(pK_1 + pK_2)}{2}$$

- pI lies midway between the two pKa values that indicate the protonation & deprotonation of the **isoionic** form.



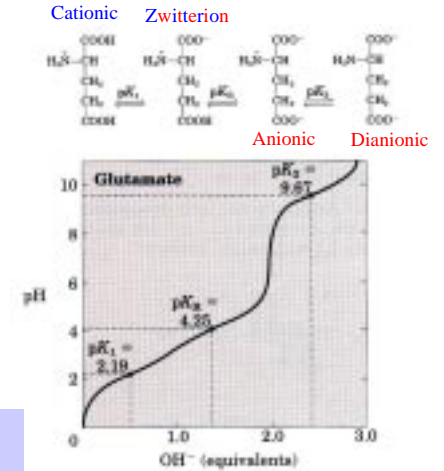
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Glu Titration (R group: -(CH₂)₂-COO⁻)

Glutamic acid = Glutamate

$$pI = \frac{(pK_1 + pK_2)}{2} = \frac{(2.19 + 4.25)}{2} = 3.22$$

What would be the physiological state?



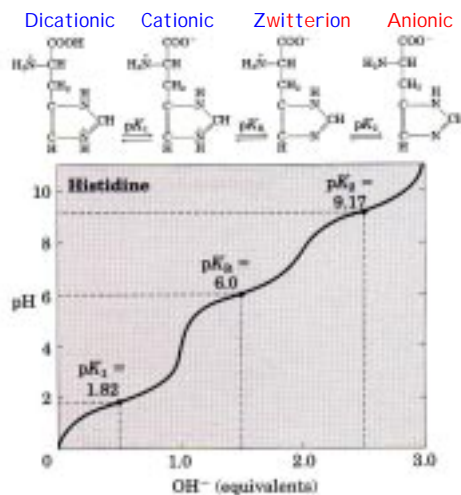
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His Titration

- Only AA with physiological buffering power;

$$pI = \frac{(6.0 + 9.17)}{2} = 7.59$$

Charged R groups are extremely important in the structure and function of proteins.

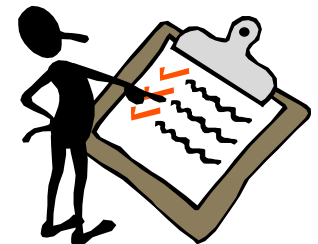


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AA Classification

20 common amino acids: differ in *size, shape, charge, hydrogen bonding capability, hydrophobicity & chemical reactivity*

- Non-polar (hydrophobic)
- Charged polar
 - Negative
 - Positive
- Uncharged polar



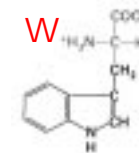
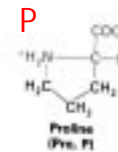
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A	Alanine	A lanine
V	Valine	V aline
L	Leucine	L eucine
I	Isoleucine	I soleucine
M	Methionine	M ethionine
F	Phenylalanine	F enylalanine
P	Proline	P roline
W	Tryptophan	No easy way!
G	Glycine	G lycine
S	Serine	S erine
N	Asparagine	asparagi N e
T	Threonine	T hreonine
Y	Tyrosine	t Y rosine
Q	Glutamine	Q -tamine
C	Cysteine	C ysteine
H	Histidine	H istidine
D	Aspartic Acid	aspar D ic acid
E	Glutamic Acid	glu E -tamic acid
K	Lysine	hi jK -lysine
R	Arginine	R ginine

You need to know:
 Structure of A.A.
 pKa's of C, N, R groups
 Name, 3 letter & 1 letter code
 Chemical nature of side groups
 hydrophobic
 polar uncharged
 charged (acid, basic)

Non-polar Amino Acids (hydrophobic)

Amino acid	Three-letter code	One-letter code	R group
Glycine	Gly	G	-H
Alanine	Ala	A	-CH ₃
Valine	Val	V	-CH(CH ₃) ₂
Leucine	Leu	L	-CH ₂ -CH(CH ₃) ₂
Isoleucine	Ile	I	-CH(CH ₃)-CH ₂ -CH ₃
Methionine	Met	M	-CH ₂ -CH ₂ -S-CH ₃
Proline	Pro	P	See below
Phenylalanine	Phe	F	-CH ₂ -C ₆ H ₅
Tryptophan	Trp	W	See below



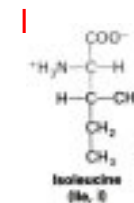
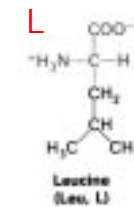
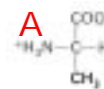
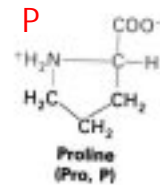
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Proline; Pro; P

- Side chain bonded to C α and N;
- Imposes rigid restraints on the rotation of the N-C α peptide bond;
- Dramatically influences protein structure;
- Proline **specifies bends and turns** in polypeptide chains.



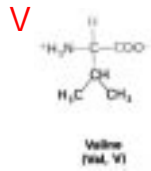
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Simple Aliphatics

Alanine; Ala; A
 Valine; Val; V
 Leucine; Leu; L
 Isoleucine; Ile; I

- Branched Chain Amino Acids
- Only alkyl chains (i.e. C's and H's);
- Hydrophobic (repel H₂O); Form part of hydrophobic core
- Although no reactivity they promote protein folding (Ala, Leu --> α -helix; Val, Ile --> β -sheet);
- Ala: best substitution for minimal structural and functional impact;
- Staggered rotamer conformation.



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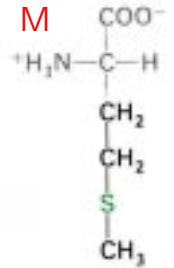
Staggered vs. not-staggered



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Methionine

- Thioether sidechain
- Little chemical reactivity
- Special in that it is first amino acid in a polypeptide chain

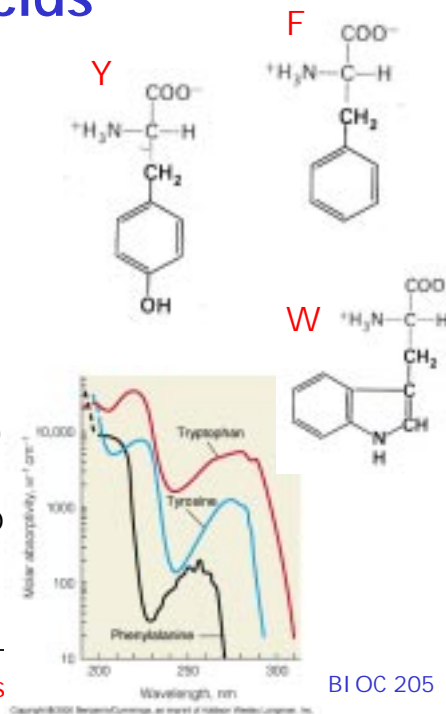


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Aromatic Amino Acids

Phenylalanine; Phe; F
Tyrosine; Tyr; Y
Tryptophan; Trp; W

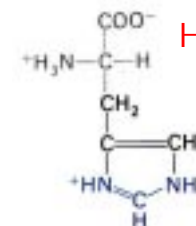
- Less abundant (especially Trp);
- Phe most abundant
- Conjugated π electron clouds confer aromatic character;
- Have **ultraviolet**; can be used to quantitate proteins (absorption at 280 nm)
- Presence of hydrophilic groups (Tyr O & Trp NH) permits partial solution exposure on protein surface
- Tyr can ionize at high pH (pKa = 10.5)-- therefore its has **polar characteristics**



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Charged Polar Amino Acids

Amino acid	Three-letter code	One-letter code	R group
Lysine	Lys	K	-CH ₂ -CH ₂ -CH ₂ -CH ₂ -NH ₂
Arginine	Arg	R	-CH ₂ -CH ₂ -CH ₂ -NH-C(NH ₂) ₂
Histidine	His	H	-See below
Aspartic acid	Asp	D	-CH ₂ -CO-OH
Glutamic acid	Glu	E	-CH ₂ -CH ₂ -CO-OH

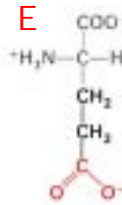
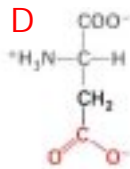


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Acidic Residues

Glutamic Acid; Glu; E
Aspartic Acid; Asp; D

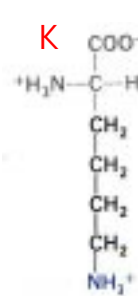
- Differ by one methylene unit;
- Deprotonated at neutral pH (pKa = 3.9-4.1);
- Can serve as **nucleophiles** in chemical reactions;
- Love to bind metal ions, especially Ca²⁺ & Mg²⁺;
- **H-bond donors and acceptors**;
- Chemically reactive (form ester linkages that can be reduced);
- Impart electrostatic properties to proteins: charge charge interactions with substrates, other proteins, etc.



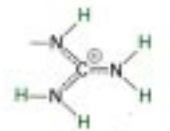
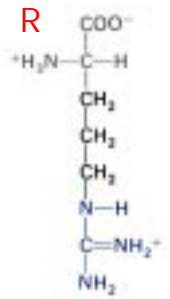
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Basic Residues

Lysine; Lys; K and Arginine; Arg, R



- Positively charged at neutral pH; lysine has a pKa ~ 10.5; arg pKa ~12); Likes protein surfaces, electrostatic interactions, especially phosphates (nucleic acids);
- Lysines are chemically reactive, NH₂ is a good nucleophile.
- Guanidinium group of arginine has three resonance forms;

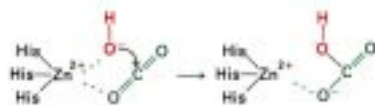
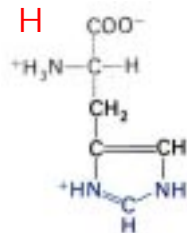


Hydrogen donor groups of arginine

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Basic Residue Histidine; His; H

- Only standard amino acid with side chain pKa near neutral pH (pKa ~ 6.0)
- Two resonance forms;
- Non-protonated N is a good nucleophile loves metals especially Zn;
- Histidine containing peptides are important biological buffers
- Involved in the active site of enzymes: can both donate and accept protons (general acid and base);
- The protonation/deprotonation reaction readily occurs at pH 7.0;
- Histidine is also aromatic, uses this with substrates

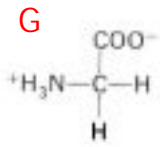


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Uncharged Polar Amino Acids

Amino acid	Three-letter code	One-letter code	R group
Serine	Ser	S	-CH ₂ -OH
Threonine	Thr	T	-CH(OH)-CH ₃
Asparagine	Asn	N	-CH ₂ -CO-NH ₂
Glutamine	Gln	Q	-CH ₂ -CH ₂ -CO-NH ₂
Tyrosine	Tyr	Y	-CH ₂ -C ₆ H ₄ -OH
Cysteine	Cys	C	-CH ₂ -SH
Glycine	Gly	G	-H

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Glycine; Gly; G



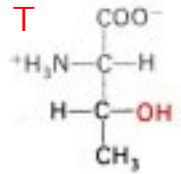
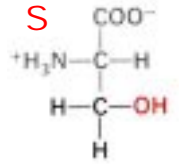
- The **simplest and smallest** amino acid (no side chain);
- Not asymmetric (no D-L);
- Can also be considered as a non-polar;
- Three unique properties:
 - Used where backbones closely approach each other
 - Can assume conformations forbidden to others
 - More flexible than others

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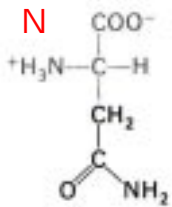
Hydroxyl Residues

Serine; Ser; S
Threonine; Thr; T

- Chemical reactivity of ethanol (pKa = 14-15);
 - Thus, proton not readily given up, **BUT** can be activated nonetheless;
- Polarity is contributed by hydroxyl. OH provides H-bonds to solvent and ligand;
- Thr has an additional asymmetric carbon;
- Important in protein surface hydration.

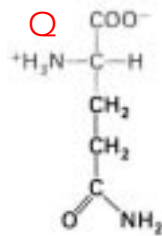


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The Amides

Asparagine; Asn; N
Glutamine; Gln; Q

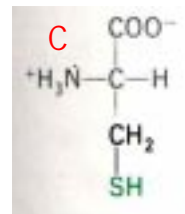
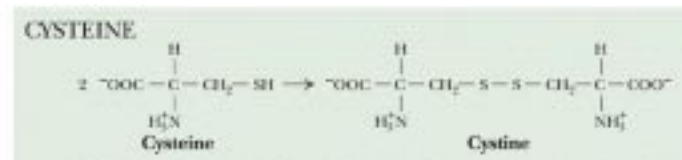


- Hydrogen bonding characteristics resembling the peptide backbone;
- Similar to acid forms;
- Chemically labile at extremes of pH;
- Most likely on protein surfaces

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Cysteine; Cys; C

- **Most chemically reactive** of all amino acid
 - susceptible to oxidation;
 - pKa = 8.5;
- Disulfide bond (cystine) stabilizes long range interactions;
- Adds stability to 3D structure.



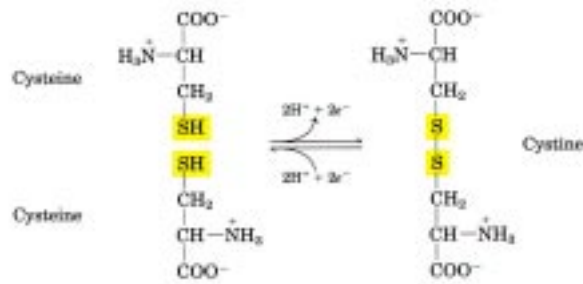
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Amino Acid Properties

Amino acids with ionizable R groups are biologically active

Disulfide Bond

Formed by oxidation of the thiol groups from two cysteines



Garrett/Grisham, Biochemistry with a Human Focus
Table 4.1

Table 4.1 pK_a Values of Common Amino Acids

Amino Acid	α-COOH pK _a	α-NH ₃ ⁺ pK _a	R group pK _a
Alanine	2.4	9.7	
Arginine	2.2	9.0	12.5 ←
Asparagine	2.0	8.8	
Aspartic acid	2.1	9.8	3.9 ←
Cysteine	1.7	10.8	8.3 ←
Glutamic acid	2.2	9.7	4.3 ←
Glutamine	2.2	9.1	
Glycine	2.3	9.6	
Histidine	1.8	9.2	6.0 ←
Isoleucine	2.4	9.7	
Leucine	2.4	9.6	
Lysine	2.2	9.0	10.5 ←
Methionine	2.3	9.2	
Phenylalanine	1.8	9.1	
Proline	2.1	10.6	
Serine	2.2	9.2	~13
Threonine	2.6	10.4	~13
Tryptophan	2.4	9.4	
Tyrosine	2.2	9.1	10.1
Valine	2.3	9.6	

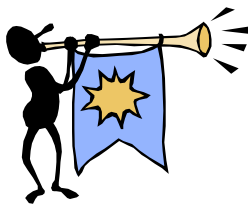
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Essential AAs

- Can not be biosynthesized;
- Must be obtained from diet

- Arg
- His
- Ile
- Lys
- Val
- Met
- Phe
- Thr
- Trp
- Leu



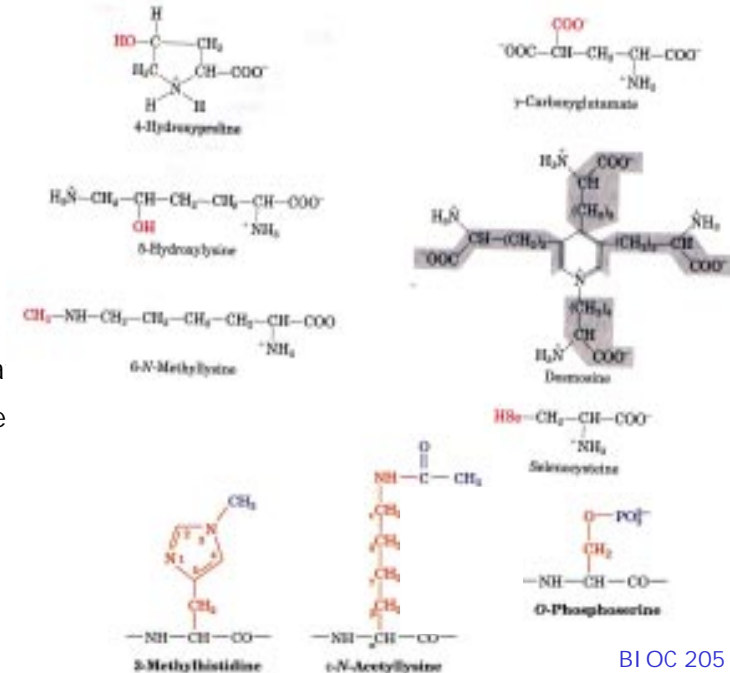
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*Essential during growth of juveniles

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Uncommon Amino Acids & Amino Acid Derivatives

- 4-hydroxyproline
- 5-hydroxylysine
- o-phosphoserine
- phosphotyrosine
- γ-carboxyglutamate
- 3-methylhistidine
- ε-N-acetyllsine



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Review

What are the four features of AA structure?

What are the pKa values for:

amino groups?

carboxyl groups?

which R groups are ionizable? What are their pKas?

What is a zwitterion?

How do you calculate the pI of an AA?

What are the structures of the 20 AAs?

How are the 20 AAs classified? Where would you find hydrophobic AAs in a protein? Where would charged groups be found?

Thinking ahead: do you think that there are many free hydrogen bond donors or acceptors in the interior of a protein?

What is an essential AA?

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