NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

Get a Chemical Clue:

The Biochemistry of Macromolecules

by

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Learning Objectives

- Explain how the structure of water relates to its polarity and its importance for life.
- Categorize macromolecules as carbohydrates, lipids, proteins, or nucleic acids based on their chemical structures.
- Illustrate how carbon, nitrogen, oxygen, and phosphorus are incorporated into macromolecules.
- Discuss links between the structures of macromolecules and their biological functions.

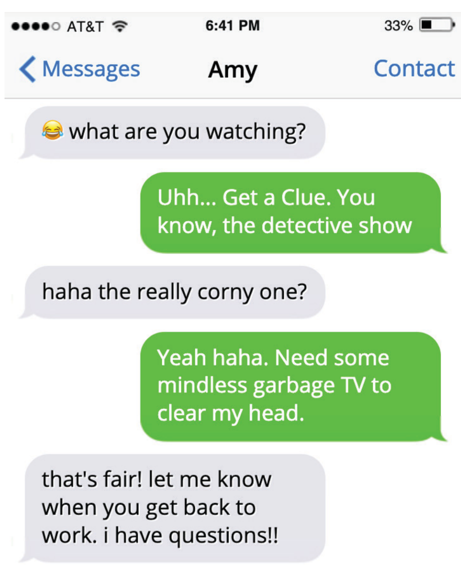
Part I – Procrastination

Miriam paused Netflix and set her laptop aside. Her phone had just gone off, buried somewhere in the nest of blankets she had made on her dorm room bed.

It was a text from her best friend, Amy: *hey are you studying right now?*

Miriam glanced guiltily over to where her biology notes were strewn across her desk. She really should be studying. The last couple of biology lectures had been about macromolecules and Miriam really didn't get it. All those chemical structures just looked like random letters and lines to her. Nothing made any sense. She had been planning to review her notes so she could go to her professor's office hours and not seem totally clueless. But the more she had reviewed, the more clueless—and frustrated—she had felt, until eventually, she'd tossed her notes aside and given in to the temptation of her guilty pleasure TV show.

I'm taking a break, she texted Amy back.



Miriam shoved her phone under her pillow with a sigh. She pulled her blanket over her head and turned her attention back to her laptop. Okay, so maybe the show was kind of silly. But she bet that Detective Doubtkey would have no trouble telling a lipid from a carbohydrate …

Miriam didn't mean to fall asleep, but her bed was cozy, and it had been a long week. She dreamed she was standing in a dingy room. Not just any dingy room, she realized, noticing the ancient couch and floor littered with empty takeout boxes. Miriam would recognize it anywhere. This was the set of *Get a Clue*, the dilapidated studio apartment from which the eccentric yet brilliant Detective Doubtkey ran his private sleuthing business.

A dim light was shining through a cracked-open door. Miriam drifted towards it. In the room beyond, a bright spotlight illuminated a paper-strewn desk and a peeling wall, as well as the back of the unmistakable figure of Detective Doubtkey in his iconic black trench coat.

"There *must* be some kind of clue!" he declared in a dramatic stage-whisper as Miriam approached. "I'm so close to working out the key!"

"What a weird dream," Miriam murmured. A little louder she said, "Uh… the key to what?"

Detective Doubtkey whipped around to face her. "The key to identifying different biological macromolecules!"

Over his shoulder, Miriam got a good look at the wall. It was covered with taped-up drawings of chemical structures, all of which had been scrawled upon wildly in red pen.

"Oh no," she said, horrified. "This is some weird *nightmare!*"

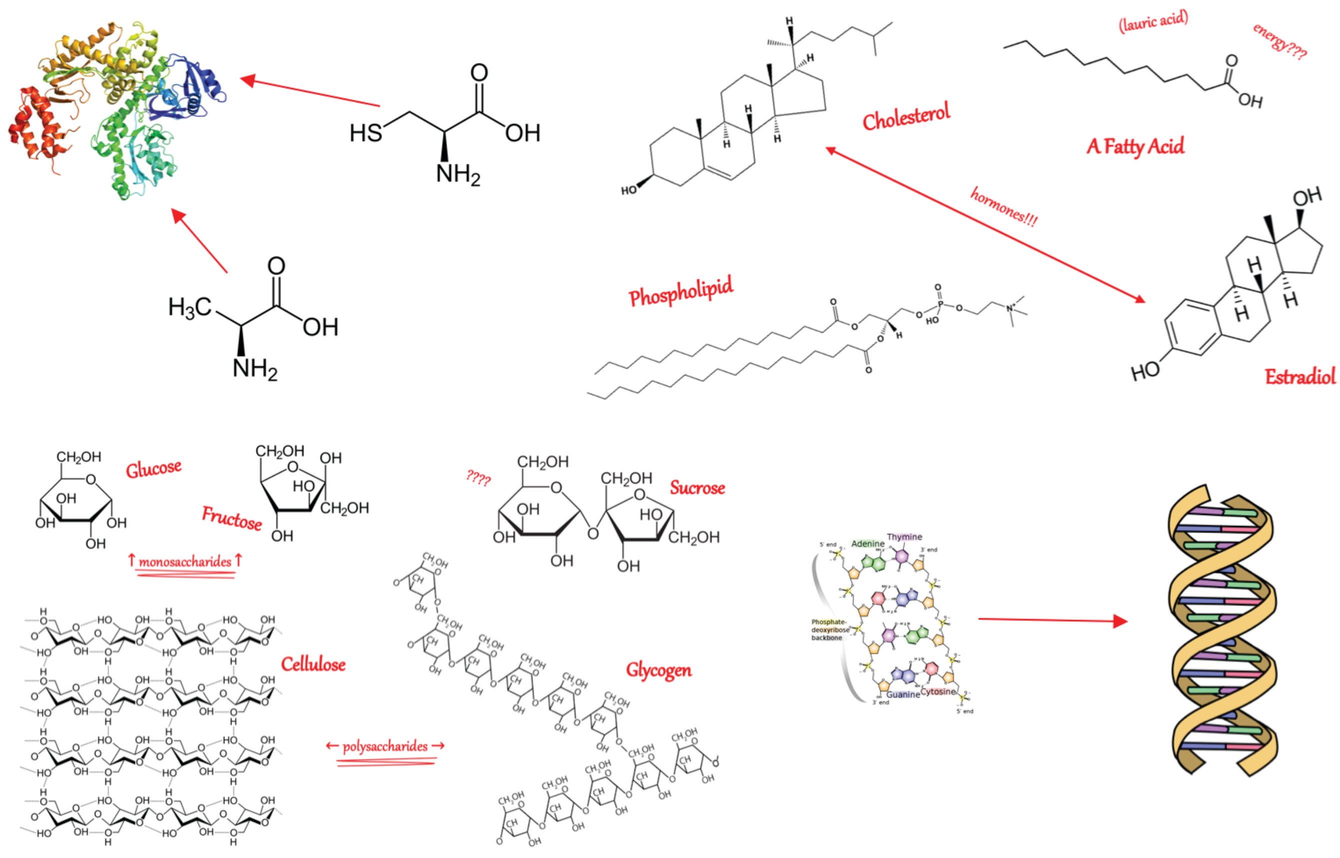


Figure 1. Detective Doubtkey's diagram.

"It's hopeless," Detective Doubtkey monologued, face bathed in shadow. "My greatest failure. I will have to live with this defeat for the rest of my days."

Oh my gosh, Miriam thought. This was *just* like the story arc back in Season 3 when the detective lost his confidence after he failed to find the crucial piece of evidence in a high-profile case. Those episodes had been so bad, the show had nearly gotten canceled.

She took a deep breath. "Okay," she said, "I totally understand how frustrating this is, but is this whole… wall thing… really necessary?"

"Yes!" The detective slammed a hand against the wall and turned to face her. "It's *important!* Macromolecules are the basis for *all living things!* How can we understand biology if we can't understand the basic building blocks of life?"

"I have a hard time with this stuff too." Miriam pulled a chair up to the desk and sat down. "Why don't we take a moment and think about what we already know?"

Task 1.1. Take a look at the image of Detective Doubtkey's wall of molecules (Figure 1). What do you understand? What confuses you? Note down anything confusing in the space below or on the diagram itself.

Task 1.2. Without looking at your class notes, write down as much information as you can recall about each type of macromolecule in the table below. Compare your answers with others in your group.

Lipids	*Carbohydrates*
Proteins	*Nucleic Acids*

Part II – Water and Polarity

Task 2.1. As you read the following passage, circle the correct word out of each bolded pair of words in parentheses.

Miriam shuffled through the pages of notes on the detective's desk. "Let's see… what do all these chemical structures tell us?" She pointed to the letters; the Cs, Ns, Os, and Hs connected by lines. "We know that molecules are made of atoms of different elements. Like carbon, oxygen, hydrogen, nitrogen, phosphorus…"

"That's obvious," said Detective Doubtkey brusquely. After a moment, he admitted, "But important. The chemical properties of those elements can give molecules **polarity**."

"Right! We talked about that in class." Miriam grabbed the pen lying on the desk and began doodling on a scrap of paper (Figure 2).

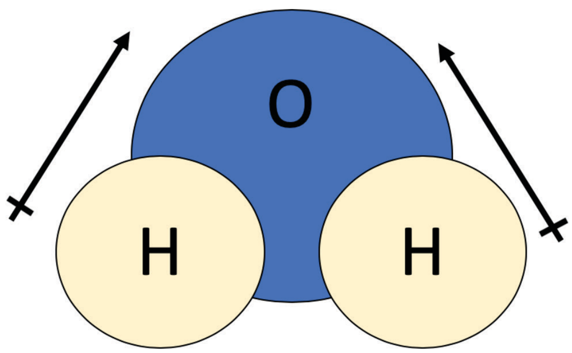


Figure 2. Polarity of a water molecule.

"I remember drawing this in my biology notes," she said. "In this water molecule, oxygen is **(more / less) electronegative** than hydrogen. The electrons in the molecule spend more time around the oxygen atom than they do around the hydrogen atoms. So, the oxygen becomes negatively charged, while the hydrogens are positively charged. The bond between them is a **(polar / non-polar) bond**." She frowned. "I don't remember why that was important, though."

Detective Doubtkey snatched up Miriam's doodle. "This! This is it! Water!"

Miriam looked at him blankly.

"Molecules dissolve other molecules with similar polarity. Water is polar thanks to its two polar bonds and its bent shape, which means the positively-charged hydrogen atoms are on the opposite side of the molecule from the negatively-charged oxygen atom. So…"

"So polar molecules dissolve in water and non-polar ones don't," said Miriam. "I remember now! That's why polar molecules are called **(hydrophilic / hydrophobic)** and non-polar molecules are called **(hydrophilic / hydrophobic)**. I guess it must be pretty important to know whether a molecule dissolves in water or not!"

Stop and Discuss: Why would it be important to know whether a biological molecule can dissolve in water or not? Discuss this with your group members. (*Hint:* what role does water play in the body?)

"Okay," said Miriam, "so we know from the water example that oxygen is very electronegative. What about other elements?"

The detective pulled out a composition journal that looked suspiciously like Miriam's biology notebook. "It says here that carbon and hydrogen are not very electronegative and form non-polar bonds with each other. Oxygen and nitrogen are the elements that really draw the electrons. When you spot those elements in a bond, it can clue you in that the bond is polar."

"Hey, you're right! It *is* like a clue!" Miriam exclaimed. "Say your clue thing!"

Detective Doubtkey narrowed his eyes. "What clue thing?"

"Your catchphrase! You know, the one you say whenever you find a really good clue? On the show?"

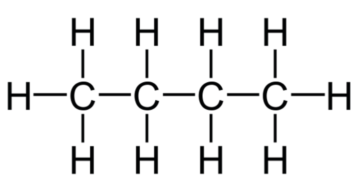
He just stared at her.

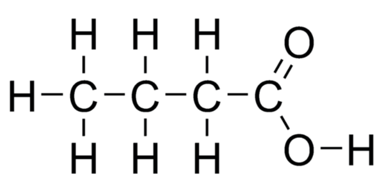
"Uh, never mind." Miriam glanced back down at the table. "Forget it."

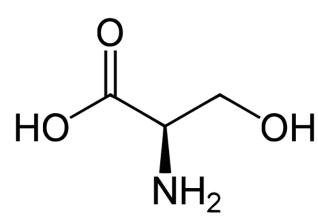
Task 2.2. Would the following bonds be polar or non-polar?

C – O	C – C	O – H	N – H
__________	__________	__________	__________

Task 2.3. Draw a circle around any hydrophilic regions of the following molecules. Draw a square around any hydrophobic regions.







Part III – Lipids

Task 3.1. Examine the structures of the lipid molecules below in Figure 3. Do you see any similarities or patterns? Discuss with your group members and take notes on the figure.

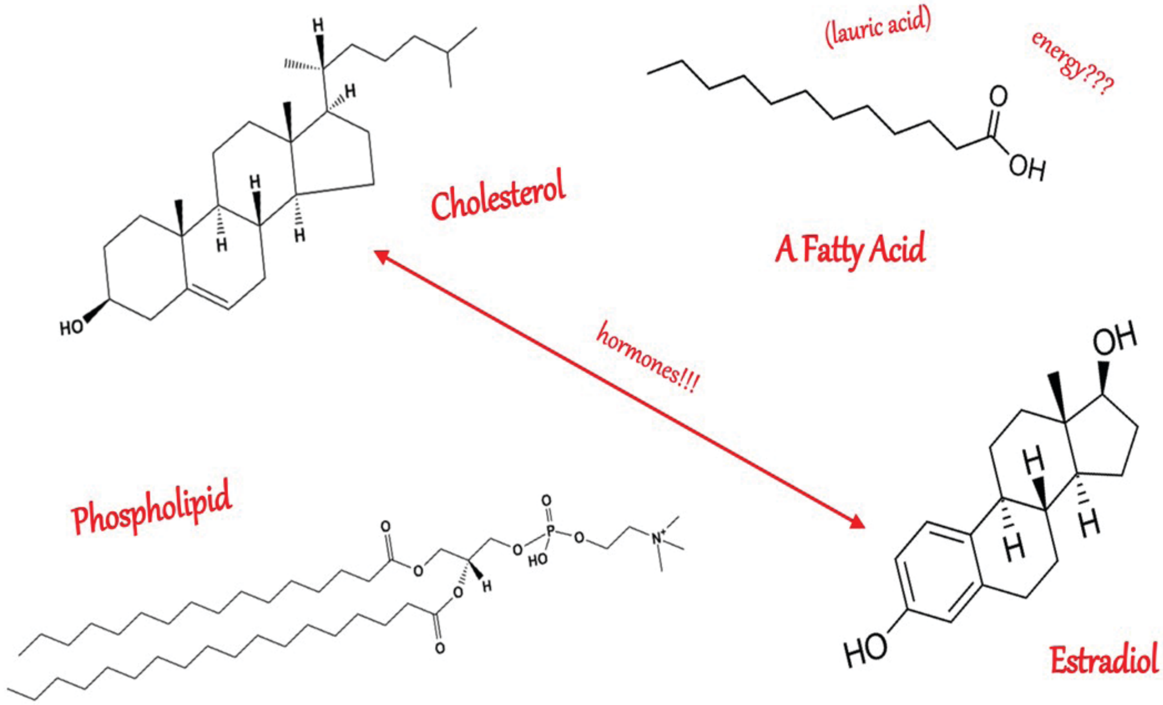


Figure 3. Lipid molecules.

"I bet we can find more clues if we look closely." Miriam got up to examine the drawings of lipids taped to the wall. "Let's see... what do these lipid molecules all have in common?"

"I got this far on my own," said Detective Doubtkey sulkily. "Lipids are easy to distinguish from other macromolecules because they have **large non-polar regions**."

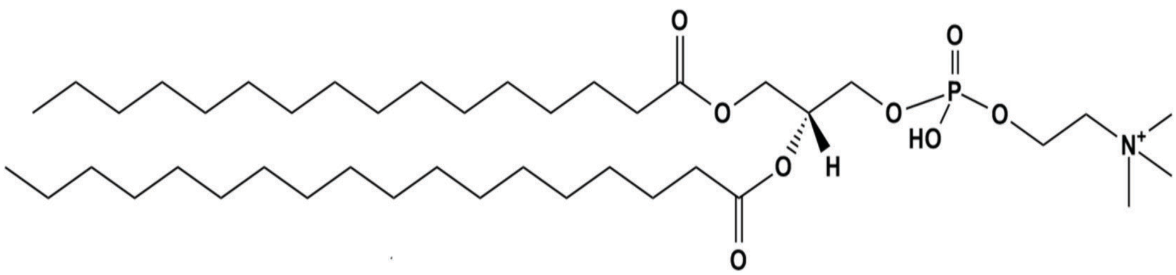
"That's why there are so many non-polar **carbon-carbon** and **carbon-hydrogen bonds**," Miriam mused. "But wait… that's weird. Some of these molecules also have polar bonds."

"Yes, but only one or two. Not enough to make the molecule itself polar."

"What about *this* molecule?" With the red pen, Miriam circled the big hydrophilic region on one of the chemical structures. She squinted at the caption. "Phospholipid… I recognize that word. But from where? What's a phospholipid?"

Detective Doubtkey shrugged. "Don't look at me. I don't know."

Task 3.2. Circle any **hydrophilic** regions in the phospholipid molecule below. Draw a square around any **hydrophobic** regions.



"One end of the molecule is hydrophobic and the other is hydrophilic…" Miriam mused. "Wait! I remember now! Cell membranes are made of **phospholipid bilayers**. All of the hydrophilic ends turn outwards to stay in contact with the water in the cytoplasm and the extracellular fluid. The hydrophobic tails bunch up in the space between, where they can stay in contact with each other and avoid the water. Forming membranes is one major function of lipids, right?"

"You know… you may be onto something," said the detective, a little hope in his voice.

Miriam beamed. "I think I'm starting to get it! Chemical structures can tell us a lot about what a molecule does, if we just take the time to think them through!"

Task 3.3. What features could you use to identify a lipid from its chemical structure? Write or draw out your answer in the space below.

Part IV – Carbohydrates

Task 4.1. Examine the structures of the carbohydrate molecules shown below in Figure 4. Do you see any similarities or patterns? Discuss with your group members and take notes on the figure.

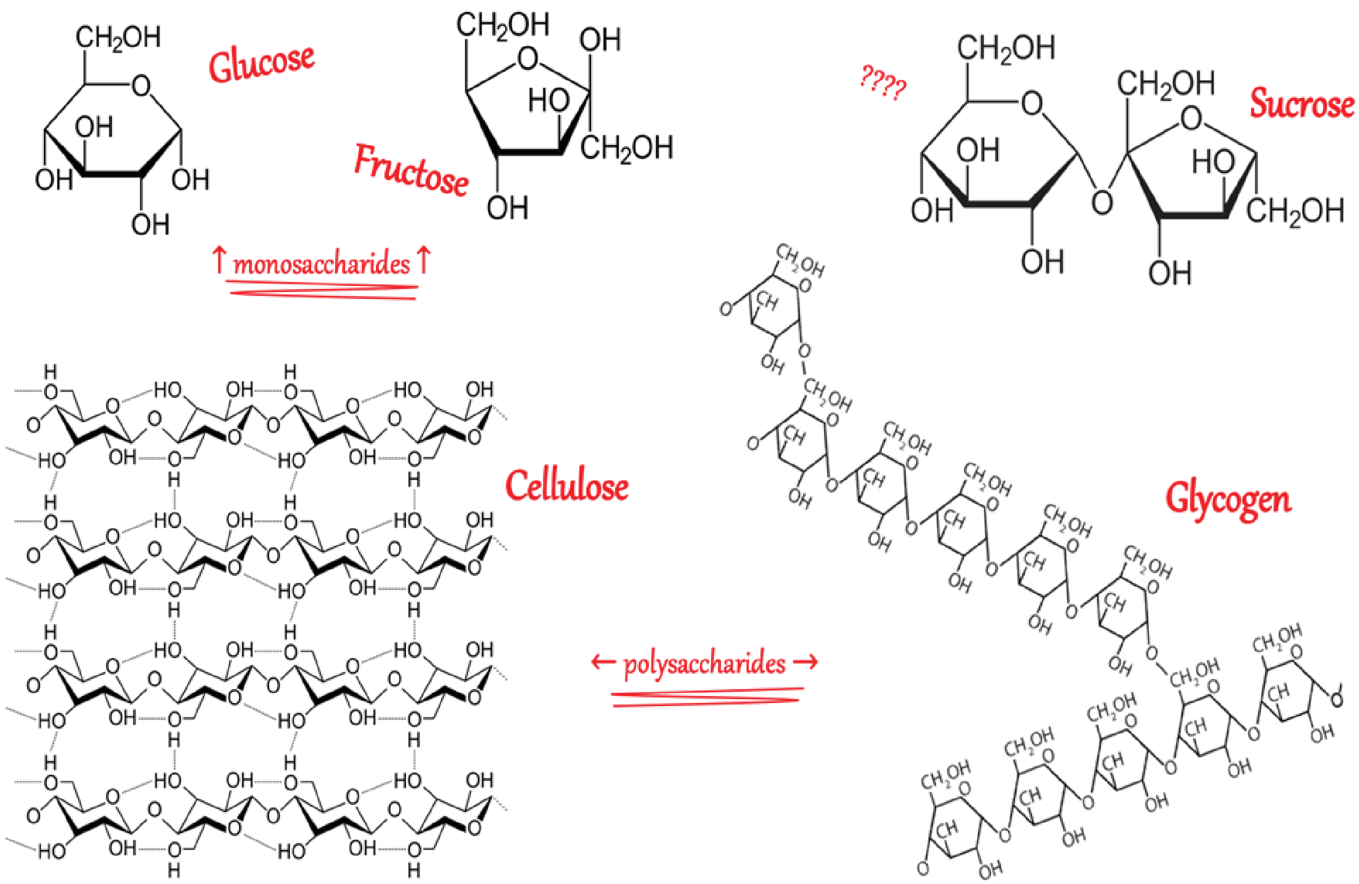


Figure 4. Carbohydrate molecules.

"I think I've already found another clue," said Miriam proudly. "Look at all these carbohydrates. They're made up of *carb*on, *o*xygen, and *hydr*ogen. Get it? Carb–o–hydrate."

Detective Doubtkey sighed. "So what? Lipids also contain those three elements."

"But these carbohydrates don't have large non-polar regions the way lipids do. There are enough polar bonds in these molecules to make them hydrophilic."

The detective raised his head. "Hmm. That's a good point."

Stop and Discuss: With your group members, compare and contrast carbohydrates and lipids. Do they have any similar functions? What do you notice about their structures?

"The names of a lot of these molecules are familiar," said Miriam. "Glucose… that's the sugar used in cellular respiration! And sucrose is table sugar, isn't it? That actually makes sense; we learned in class that one major function of carbohydrates is providing energy to the body."

"I thought fats provided energy to the body," said Detective Doubtkey. "Isn't that why exercise burns fat?"

"Fats *do* provide energy, but they're used more for long-term energy storage. Carbohydrates are more like the fuel the body is actively burning." Miriam squinted at the structures on the wall again. "Hey, wait a minute… you know how you mentioned that carbohydrates are made up of the same elements as lipids?"

"Carbon, hydrogen, and—"

"That's right! Look at all these non-polar carbon-hydrogen bonds! I remember learning that non-polar bonds have a lot of potential energy. I bet *that's* why both carbohydrates and lipids are so good at storing energy! They have the right structure for the job."

"Egads!" Detective Doubtkey leaped to his feet. "Now *that's* a clue!"

Miriam clapped her hands to her cheeks. "Aaaah, you said the clue thing!"

Stop and Discuss: What other functions do carbohydrates have, besides storing energy?

The detective seemed energized. He joined Miriam at the wall, peering closely at the drawings. "Hmm, but the mystery isn't solved yet! What about this molecule?" He jabbed his finger down on a drawing. "Cellulose. That's not an energy-providing molecule, is it?"

Miriam shook her head. "Not for humans, at least. I'm pretty sure its main job is providing structural support to plants."

"Take a closer look." Detective Doubtkey pulled a magnifying glass out of his pocket and offered it to Miriam. "Do you notice anything?"

"It's made up of a bunch of glucose molecules, hooked together." Miriam handed the magnifying glass back. "But I already knew that. We learned in class that most macromolecules are **polymers** made up of repeating subunits called **monomers**. This cellulose molecule is just a **polysaccharide** made up of glucose **monosaccharides** connected by **glycosidic linkages**."

Task 4.2. Take a look at the carbohydrate chemical structures at the beginning of this section. What do you notice about **sucrose**? What's the word for a carbohydrate made up of *two* monosaccharides?

"Here's what I *don't* get," said Miriam. "See that molecule called glycogen? It's *also* made up of bunch of glucose molecules hooked together! What's the difference between it and cellulose?"

Detective Doubtkey leaned in to inspect the drawings. "I have a hunch it has something to do with the way the glucose molecules are joined. Observe: in cellulose, the monomers are arranged in linear chains that lie adjacent to each other. This allows the -OH groups on nearby glucoses to hydrogen bond with each other, forming that net-like structure."

Miriam peered through the magnifying glass, noticing the dotted lines of hydrogen bonds between the molecules. "Huh. That makes sense, actually. All those bonds must give cellulose the strength it needs to be a good structural molecule."

"Now turn your attention to the structure of glycogen." The detective pointed to the drawing with a flourish. "See how it's *also* made up of chains of glucose molecules; except in this case, one chain branches off the other."

"Good point! I bet that means it's not as strong as cellulose is." Miriam paused a moment. "I wonder why it has *that* structure. Let me look up what glycogen does."

"If I had to guess," said Detective Doubtkey, "I'd say it's an easy way of storing glucose. Those branches provide a lot of free ends, from which a glucose molecule could detach as soon as the cell needed energy."

"Like snapping a square off a chocolate bar for a quick pick-me-up." Miriam thumbed through her notebook. "Hey, you're right! That's exactly what glycogen does. It stores energy in animal cells. Another example of molecules being perfectly suited to the jobs they do!"

"Exactly." Detective Doubtkey tucked his magnifying glass back in his pocket proudly. "Just as I am perfectly suited to being a brilliant detective."

Task 4.3. What features could you use to identify a carbohydrate from its chemical structure? Write or draw out your answer in the space below.

Part V – Proteins

Task 5.1. What are some functions of proteins in living things?

"I had a thought," said Miriam. "Glycogen and cellulose are able to perform two very different functions because polysaccharides can form two very different structures. Proteins have a *huge* number of different roles in the body! They speed up reactions, they transport other molecules, they make it possible for our muscles to move…. To perform all of these functions, proteins must be able to form a huge number of different structures."

"Brilliant observation," said Detective Doubtkey. "Hmm. Why don't you follow me to the Information Station? Let's see what we can find out."

Miriam gasped. "The Information Station!" She laughed as the detective walked over to a complicated-looking computer covered in wires and blinking lights.

"My Information Station is no laughing matter," said the detective severely. "It's a state-of-the-art machine. I designed it myself to keep enemy hackers out of my private files."

"See, this is why Amy thinks your show is corny." Miriam peered past his shoulder, watching with delight as the computer booted up with a lot of unnecessary beeping. A pair of images appeared on the largest of its screens:

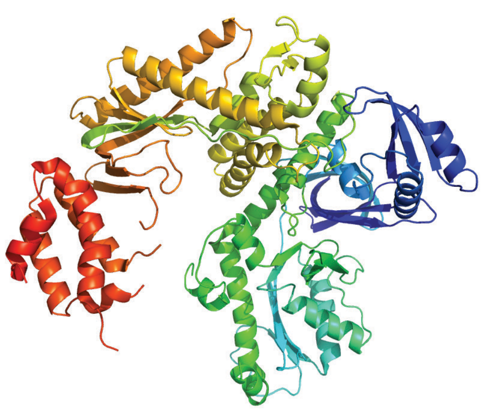


Exhibit A.
DNA polymerase 2

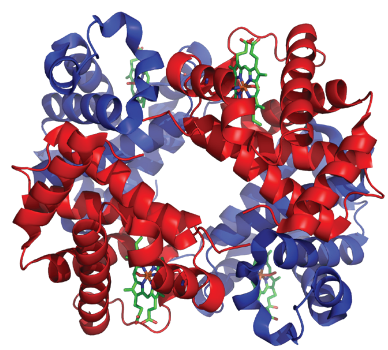
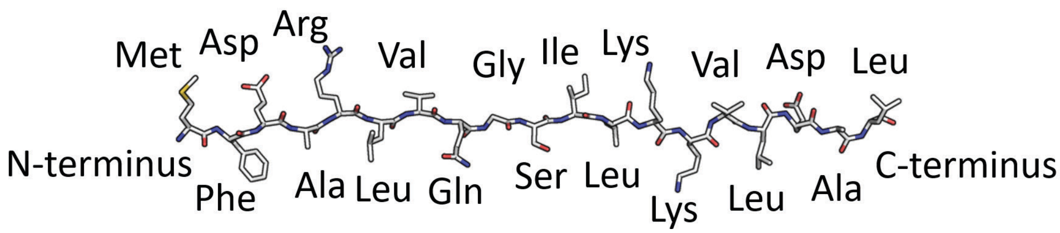


Exhibit B.
Hemoglobin

"Look at those complex shapes!" said Miriam. "No wonder proteins can perform so many functions. Each shape must be suited to a different task, the same way differently-shaped tools can be used for different purposes. But what causes the proteins to fold up like that?"

"Let's take a closer look." The detective cleared his throat. "Computer, zoom in!"



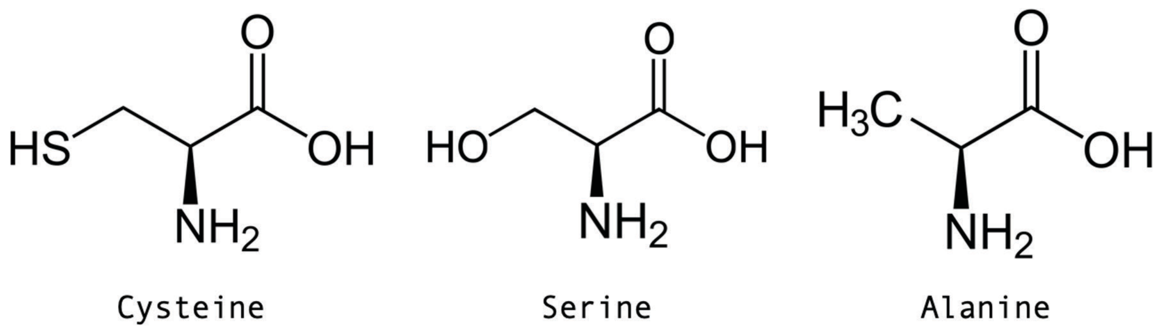
Amino Acid Chain

"It would seem that those large folded molecules are long chains of **amino acid** monomers joined by **peptide bonds**," said the detective. "The sequence of amino acids must determine the nature of the protein."

"Okay," said Miriam. "That makes sense… but that still doesn't quite explain the shape. Why aren't proteins just a long rope of amino acids? What causes all those folds?"

"Let's zoom in closer," said Detective Doubtkey. "Computer—!"

"Wait, wait—let me do it!" Miriam interrupted excitedly. "Computer, zoom in!"



"These are just three of the *twenty* different amino acids that make up proteins," Detective Doubtkey reported, reading off one of the computer's auxiliary screens.

"You know, these all look really similar," Miriam remarked. "All three of them have the same chemical groups at the bottom and on the right."

"Those must be the **amine group** with the nitrogen on the bottom and the **carboxyl group** with the O=C-OH on the right," said Detective Doubtkey. "They've got to be the same on every amino acid because that's how amino acids bond together to form a protein chain: carboxyl group to amine group."

"Makes sense." Miriam gestured to the chemical groups on the left side of the molecules. "Now *these* groups are different on each of these molecules."

"Indeed they are. Those must be the **R groups**, which vary by amino acid."

Miriam looked thoughtful. "If proteins differ by amino acid sequence, and amino acids only differ by their R groups, then the R groups *must* be the key to different protein shapes!"

"I'll see what I can find about it." Detective Doubtkey picked up Miriam's notebook and began to flip through it, but before he could find anything, she had a realization.

"Hey, maybe it's a matter of polarity again! See how serine has a *polar* R group? That R group would be hydrophilic; it would want to be in contact with the water in the protein's environment. But alanine has a *non-polar* group that would be hydrophobic. I bet these different R groups create little hydrophobic regions and hydrophilic regions along the chain of the protein. The hydrophobic regions would fold inwards to avoid the water, while the hydrophobic regions would fold out to stay in contact with it."

"Egads!" The detective glanced up from his notes, looking impressed. "A brilliant deduction! You may be almost as clever as I am!"

"I don't know about this other amino acid, though." Miriam tapped the image of cysteine on the screen. "What's up with that sulfur atom?"

"You're in luck! I just found the page." The detective turned the notebook outwards to show her. "Cysteine is a very special amino acid. That sulfur group can bond with other sulfur groups on other cysteines in the protein, forming structures called **disulfide bridges**. Those disulfide bridges are another important contributor to stabilizing a protein's shape."

"It all goes back to chemical properties, doesn't it?" Miriam mused. "The chemical properties of amino acids determine how they will interact with each other and their environment. They also fold the protein into a specific shape, and the chemical properties of that shape allow it to do the task it was designed for."

Task 5.2. What features could you use to identify a protein from its chemical structure? What about an amino acid? Write or draw out your answers in the space below.

Part VI – Nucleic Acids

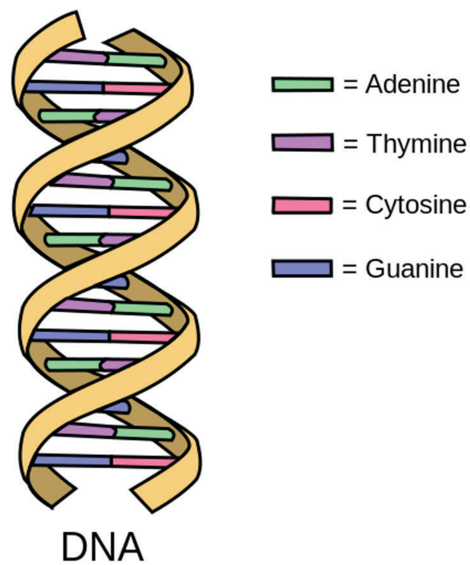
Task 6.1. What are some functions of nucleic acids in living things?

"There's one last type of macromolecule I remember from class," said Miriam. "Nucleic acids... the molecules that store genetic information, like DNA and RNA."

"Indeed," said Detective Doubtkey with a smile. "Should we make some deductions as to what the structure will be like based on what we know about the function?"

"Let's see… nucleic acids form the genetic code. The structure would need to be organized, but also flexible enough to encode every gene an organism needs."

"I concur." The detective punched a few keys on the computer's keyboard. "Let's take a look."



"I remember a little about the structure of DNA," said Miriam. "The molecule is made up of two strands of **nucleotides** joined by **phosphodiester bonds**. The sequence of those nucleotides is what forms the genetic code."

Detective Doubtkey squinted at the screen. "Are those colorful parts the nucleotides?"

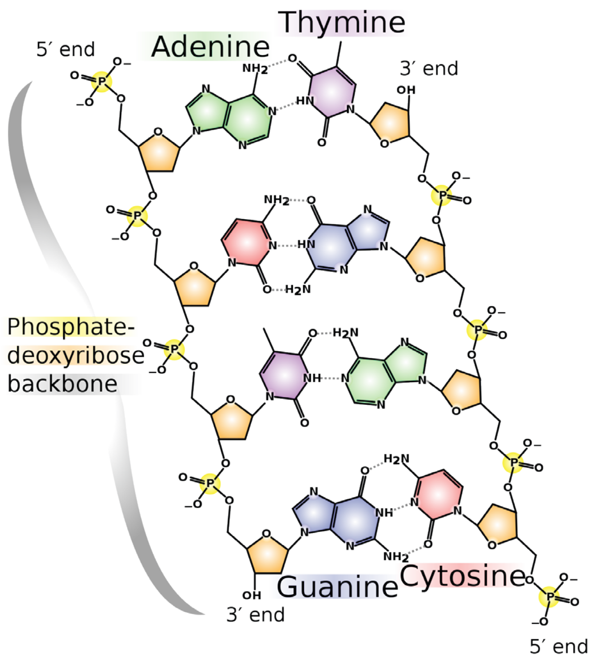
"No." Miriam frowned. "The colorful parts are **nitrogenous bases**. Each nucleotide has one of the four different nitrogenous bases, but I know they also other have other chemical groups. You just can't see them in this image. They've been drawn as that thick yellow line."

"I don't suppose you remember what the other chemical groups are?"

"No." Miriam took a moment to think. "But… I bet they're the same on every nucleotide, just like the carboxyl group and the amine group on amino acids. That way, nucleotides can form a strand with any sequence, just like amino acids can bond into a protein chain in any order."

"I'll bet you're onto something," said the detective. "But observe; the bonds *between* the single nucleotide strands to form the double helix are more specific. Adenine is always paired with thymine and guanine is always paired with cytosine. Why do you think that is?"

"It's time to find some answers." Miriam cleared her throat. "Computer, zoom in!"



"It all makes sense now that we can see the individual nucleotides!" Miriam exclaimed. "See how adenine and thymine bond together in two places, while guanine and cytosine bond in three places? They're like puzzle pieces that only fit together with each other!"

"You were also right about the other chemical groups," said Detective Doubtkey. "Each nucleotide has a **5-carbon sugar** (deoxyribose in this case, since we're looking at DNA), and a **phosphate group**. Those two groups allow the nucleotides to link up, forming the backbone we saw in the original image."

"Each of the chemical groups in a nucleotide has a role to play," Miriam observed. "The phosphate group and the five-carbon sugar hold the nucleic acid together while the nitrogenous bases form the genetic code."

Task 6.2. What features could you use to identify a nucleic acid from its chemical structure? What about a nucleotide? Write or draw out your answers in the space below.

"By Jove, we've done it!" Detective Doubtkey exclaimed. "The mystery is solved! We've identified every type of macromolecule there is!"

"Hey, we have, haven't we?" Miriam felt herself start to smile. "I just hope I can remember all this on my midterm."

"I have full confidence you will. I couldn't have done it without you." Detective Doubtkey put a hand on her shoulder. "In fact, you've showed such brilliant detective work today that I want you to become my assistant."

"*Really?* Me?!" Miriam's mouth dropped open. "Oh my gosh, of course I'll be your assistant! I always wanted to be a detective! I mean, med school would've been cool too, but—wow! Do you think I can have my own trench coat? Can I drive the Mysterymobile? Can I—?"

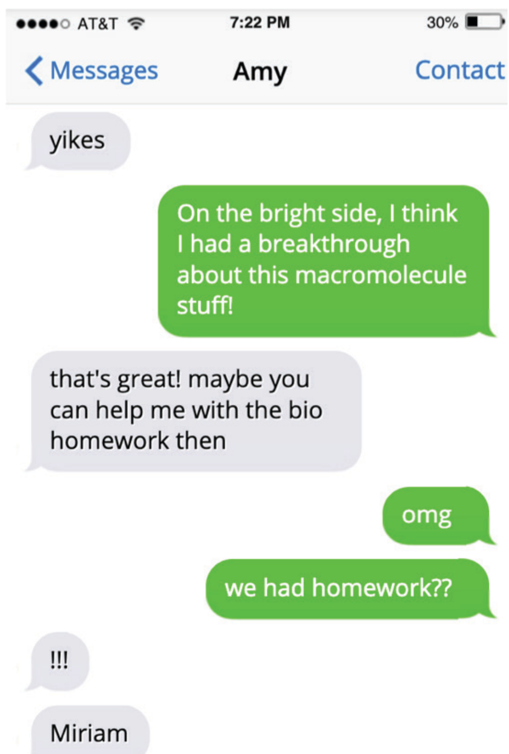
She blinked. The room was starting to fade around her…

Part VII – Epilogue

It was the sound of her cell phone going off that woke Miriam up. She dug out it out of the tangle of blankets, groggily pushing away her laptop, which was still quietly playing an episode of *Get A Clue*.

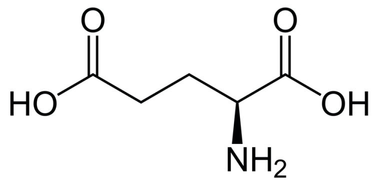
The message was from Amy: *ok I'm really gonna need you to answer I have sooo many questions*

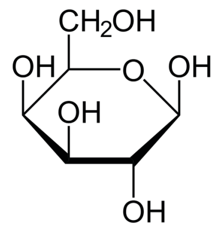
Sorry, Miriam texted back. *Fell asleep. I may have just had a dream where my test anxiety manifested as a TV character.*

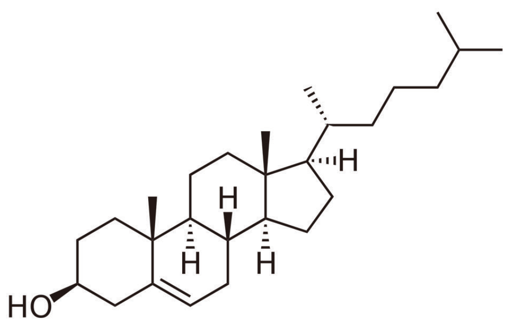


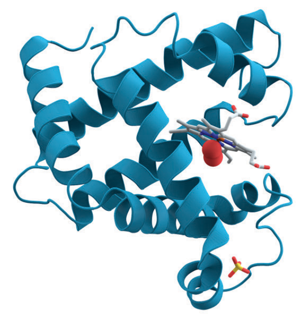
Wrap-Up Questions

Help Miriam with her homework by classifying the following compounds. Be as specific as you can!









Challenge Question

In Part IV, Miriam pointed out that all the C-H bonds clue you in that carbohydrates and lipids are both energy-storing molecules. Gram for gram, lipids store more energy than carbohydrates. If you look at the structures of triglyceride and glucose, can you think of any chemical reason why this would be?

Learning Gains

Without looking at the case or any notes, write down as much information as you can recall about each type of macromolecule. Compare your answers to the notes taken for Task 1.2.

Lipids	*Carbohydrates*
Proteins	*Nucleic Acids*

Write down any questions you still have and share this with your instructors or teaching assistants:

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Internet references accessible as of August 15, 2022.