

VENOM!

a gallery lab experience at Arizona Science Center

ABOUT VENOM!

BACKGROUND INFORMATION FOR TEACHERS

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Framing New Pathways to Medical Discovery for Families, Students and Teachers

About **VENOM!**

A Gallery Lab Experience at Arizona Science Center

Target Grades 4th – 6th grade

Overview

Venom! is a 45-minute, facilitator-led gallery laboratory activity during which students learn about the complex nature and structure of proteins. It illustrates the fact that form is critical to function with these molecules which are essential to life. Students participate in a hands-on activity where they learn to assemble a 2-D protein from individual amino acids using models. Finally, participants will fold their 2-D protein into a specific 3-D shape that, if they are successful, will fit a receptor, just like a lock and key. They learn about the huge numbers of configurations possible of proteins and their components.

Pre- and post- activities help prepare for the **Venom!** program and also reinforce or extend key concepts of the lab.

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What is the Lab?

Students are informed that they will be learning about proteins found inside cells. Specifically, students are told that they will be learning about a specific kind of protein found in scorpion venom.

Students learn that proteins are made of smaller building blocks called amino acids.

Given a set of instructions, and using a building set called Zoobs (that represent amino acids), students assemble a 2-D protein called a polypeptide. This protein is found in scorpion venom.

Once the 2-D proteins (polypeptides) are built, students are told that some proteins fold together to create a unique 3-D shape, and that this kind of folding is constantly occurring inside every cell of our body.

Given another set of instructions, students work in groups to fold the 2-D polypeptide into a 3-D protein. This is the shape of the protein found in scorpion venom.

Examples of 3-D proteins shapes found in human cells are shown to students on a screen. Given a few hints, students try to guess what kind of protein they are seeing.

Once all students have finished assembling their 3-D protein, they learn how proteins interact with receptors found on cells, in a lock and key fashion. In the case of the scorpion venom protein they created, it (like a key) latches onto the muscle cell receptor of a cricket (lock), and blocks the passage of chloride ions (which are important for mobility) from passing through the cell. The result of this lock and key behavior results in paralysis of the cricket, and thus, food for the scorpion.

Students are then given model cell receptors and test their 3-D protein model of scorpion venom to see if they successfully fit, like a lock and key.

Students are told that real proteins contain many amino acids, which means they can fold in a multitude of ways. This makes it challenging for scientists to figure out a proteins true 3-D shape. To help them solve the mystery, scientists rely on computers to help them organize data, in a field called bioinformatics.

Students learn that scorpion venom, while harmful in some ways, may be useful in treating cancer. Therefore scientists are very interested in studying this, and all kinds of proteins, to see if they may be helpful in treating illness and disease.

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Concepts

Proteins are complex molecules inside each cell of our body and perform many different functions.

Proteins are macromolecules made of amino acids.

Proteins fold into unique 3-D shapes that bind to other molecules in our cells, like a lock and key.

Proteins can be helpful and harmful to cells and our bodies.

Listen for These Naïve Notions

Students know little about cells. They may confuse atoms and cells; molecules and atoms.

They have trouble visualizing particles.

Cells are attributed properties of multi-cellular organisms, including psychological properties.

Students may know translation is part of protein synthesis and enzymes are proteins but cannot say which molecules are products of which cellular processes.

Students confuse things that are organic and inorganic, dead or formerly alive, organic but not moving. Cells may not be perceived as “alive.” Venom might be confusing.

The term “protein” may connote red meat.

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Objectives

Participants assemble proteins from individual amino acids using models.

Participants fold their 2D protein into a specific 3D shape that will fit the venom receptor.

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Arizona Science Standards

Grade 5

S1C1PO1	S1C3PO4	S2C2PO1
S1C2PO1	S1C4PO1	S2C2PO3
S1C2PO5	S1C4PO2	S2C2PO5
S1C3PO1	S1C4PO3	S3C2PO1

Grade 6

S1C1PO3	S1C3PO1	S2C2PO2
S1C2PO1	S1C3PO6	S2C2PO3
S1C2PO5	S1C4PO5	S4C1PO7

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College and Career Ready ELA Standards

Grade 5:

SL.5.1.	SL.5.3.	L.5.4.
SL.5.2.	SL.5.4.	L.5.6.

Grade 6:

SL.6.C.1

SL.6.4.

L.6.6.

SL.6.3.

L.6.4.

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Next Generation Science Standards

Science and Engineering Practices

(2-PS1-2)

(2-PS1-3)

(5-PS1-1)

(3-LS3-1)

(3-LS3-1, 3-LS4-2)

(K-2-ETS1-2)

(K-2-ETS1-1)

(4-LS1-1)

(4-LS1-2)

Disciplinary Core Ideas Grades 2-3

PS1.A: (5-PS1-1)

LS4.D: (2-LS4-1)

(K-2-ETS1-1)

LS1.A: (4-LS1-1)

ETS1.A: (K-2-ETS1-1)

ETS1.B: (K-2-ETS1-2)

LS3.B: (3-LS3-1)

(K-2-ETS1-1)

Cross Cutting Concepts Grades 2-3

(2-PS1-2)

(3-LS3-1)

(K-2-ETS1-2)

(3-5-ETS1-1)

(2-PS1-1)

(3-LS4-4, 4-LS1-1, 4-LS1-2)

(3-LS4-3)

(5-PS1-1)

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Learning Progressions

Basic Functions (3-5)

Deriving Energy from Food

- From food, people obtain fuel and materials for body repair and growth.

Coordination

- The brain gets signals from all parts of the body telling it what is going on there. The brain also sends signals to parts of the body to influence what they do.

Basic Functions (6-8)

Deriving Energy from Food

- For the body to use food for energy and building materials, the food must first be digested into molecules that are absorbed and transported to cells.

Defense

- Thinking about things as systems means looking for how every part relates to the others. The output from one part of a system (which can include material, energy, or information) can become the input to other parts. Such feedback can serve to control what goes in the system as a whole.

Coordination

- Interactions among the senses, nerves, and brain make possible the learning that enables human beings to predict, analyze, and respond to changes in their environment.

Basic Functions (9-12)

Defense

- The human body is a complex system of cells, most of which are grouped into organ systems that have specialized functions. These systems can best be understood in terms of the essential functions they serve for the organism: deriving energy from food, protection against injury, internal coordination, and reproduction.

Coordination

- Communications between cells is required to coordinate their diverse activities. Cells may secrete molecules that spread locally to nearby cells or that are carried in the bloodstream to cells throughout the body. Nerve cells transmit electrochemical signals that carry information much more rapidly than is possible by diffusion or blood flow.
- Some drugs mimic or block the molecules involved in communication between cells and therefore affect operations of the brain and body.

Strand maps for chemical reactions with predictions and explanations

Across Grades 6 – 8

- Important concepts about matter that are thought to be required to understand chemical reactions

Laboratory experiences in life sciences

Grades 1 – 13

Modeling is concerned with capturing key relations among ideas rather than surface appearance

Grades K – 8

- We can learn about the world through modeling

Arguments use reasoning to connect ideas and data

Grades K – 8

- We can learn about the world through argument

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Brief Background Information

Proteins are very complex biological molecules (macromolecules) found in every cell of our body.

Proteins are even smaller than cells.

There are an estimated 100,000 different kinds of proteins in every cell.

Proteins make up the structures of the cell and are produced by the cell.

Proteins are made up of chains of 20 kinds of building blocks, called amino acids, which are put together in a very specific order. Different sequences of amino acids create different kinds of proteins.

When folded, chains of amino acids become 3-D proteins.

Proteins have very complex 3-D shapes.

The shapes of proteins give them their function inside the cell.

Due to the large amounts of amino acid sequences and the complicated way proteins fold to give them their distinctive shapes, scientists use computers to help them manage data and track how different proteins fold. This is part of the field of study called **bioinformatics**.

Scientists continue to do extensive research into understanding the structure and function of proteins.

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Extended Background Information for Teachers

What is a protein? Of all the molecules found in living organisms, proteins are the most important. Proteins are the biological workhorses that carry out vital functions in every cell. They may be enzymes, cellular signals, and antibodies. The name, protein, is derived from the Greek word *prôtos*, meaning “primary” or “first rank of importance” and with good reason. These are the most abundant components within a cell. More than half the dry weight of a cell is made up of proteins.

Proteins are used to support the skeleton, control senses, move muscles, digest food, defend against infections and process emotions. Without proteins, the cells in our bodies would not be able to perform biochemical reactions fast enough to sustain life. (<http://www.nature.com/horizon/proteinfolding/background/importance.html>)

Proteins come in all shapes and sizes. They can be:

- round (like hemoglobin)
- long (like collagen)
- strong (like spectrin c which protects erythrocytes - the cells that carry oxygen from the lungs to our tissues - from the powerful shearing forces they’re exposed to)
- elastic (like titin, which controls muscle stretching and contraction).

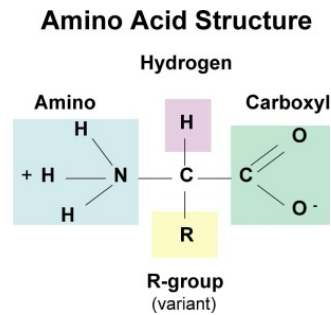
You are what you eat

Proteins can be found in the food we consume. Our body takes the proteins we eat and breaks them down into their smaller parts (monomers) called **amino acids**. Once digested, the amino acids are put back together to create new and different proteins the body needs. You can think of the amino acids as beads on a bracelet. You could take the bracelet apart and put it back together in a different order to get a new bracelet.



Proteins are a linear sequence of amino acids. In the picture below, the bracelet on top can represent a protein we take in when we eat food. The bracelet on the bottom would represent the new protein that was constructed by stringing the amino acids back together in a different order. These two proteins would have very different properties and functions in the body.

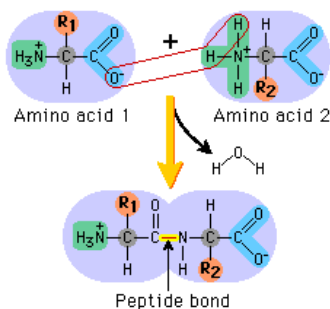
What is an amino acid?



There are 20 naturally occurring amino acids. All amino acids have the same basic structure: an amino group, a carboxyl group and a hydrogen atom but differ due to the presence of a side-chain (known as R). This side-chain varies dramatically between amino acids. Depending on the nature of the side-chain, an amino acid can be hydrophilic (water-attracting) or hydrophobic (water-repelling), acidic or basic; and it is this diversity in side-chain properties that gives each protein its specific character. What is remarkable is that the more than 100,000 proteins in our bodies are produced from a set of only 20 amino acids.

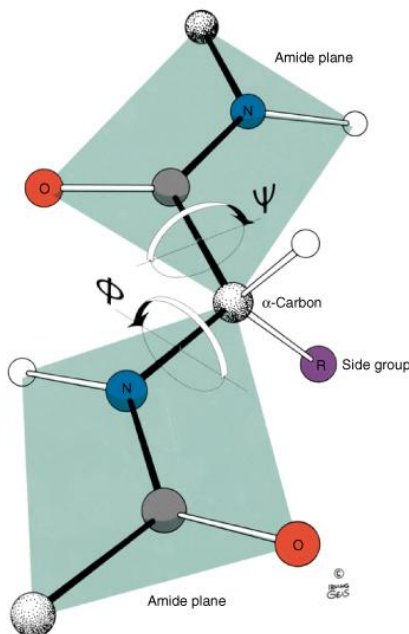
(<http://www.nature.com/horizon/proteinfolding/background/importance.html>).

<http://mwsu-bio101.ning.com/profiles/blogs/what-are-carbs-lipids-and>



Amino acids connect together to make proteins via a **peptide bond**. A peptide bond is a covalent bond that is formed between two molecules when the carboxyl group of one amino acid reacts with the amino group of another amino acid, releasing a molecule of water (known as a condensation reaction). The resulting CO-NH bond is called a peptide bond, and the resulting molecule is an **amide**.

http://www.phschool.com/science/biology_place/biocoach/translation/pepb.html

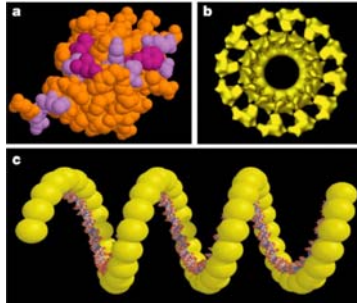
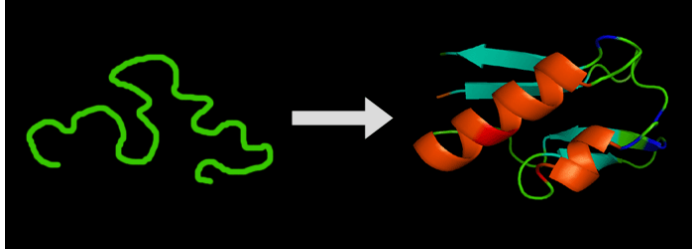


Chains of 50 amino acids are called **peptides**, 50-100 amino acids called **polypeptides**, and over 100 amino acids called **proteins**. A number of hormones, antibiotics, antitumor agents and neurotransmitters are peptides (proteins).

The chemical “backbone” of amino acids can swivel at **dihedral angles**; there are two dihedral angles per amino acid. This allows for lots of freedom of movement.

How can proteins do so much?

Since proteins can be 100's of amino acids in length, there is lots of movement and twisting (due to the dihedral angles). Proteins are able to fold spontaneously. We call the process **protein folding**.



This folding allows proteins to assume a characteristic 3-D shape. The particular shape of the protein depends on the amino acid sequence and it is the shape of the protein that gives it its specific function.

http://www.nature.com/horizon/proteinfolding/background/figs/importance_f1.html

Protein structures

Proteins can come in all shapes and sizes, from a relatively basic structure like ubiquitin (a), to complex and beautiful structures, such as the bacteriophage 29 head-tail connector (b) and bacteriophage protein (c).

Part a reproduced with permission from Hicke, L. *Nature Rev. Mol. Cell Biol.* **2**, 195-201 (2001).

Parts b and c reproduced with permission from O'Donnell, M. & Hingorami, M. M. *Nature Rev. Mol. Cell Biol.* **1**, 22-30 (2000). © Macmillian Magazines Ltd.

Protein structure levels of organization

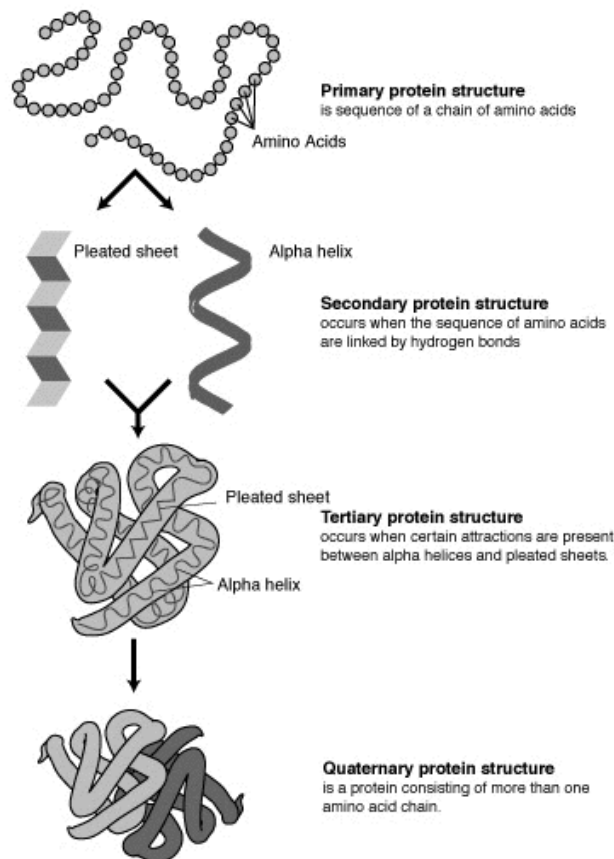
There are four levels of organization to a protein:

- Primary Sequence: linear sequence of amino acids
- Secondary structure (modular building blocks): brief intermediate form
- Tertiary structure: 3-D form
 - a- helices (alpha)
 - B-sheets (beta)
- Quaternary structure

The sequence of amino acids in a protein defines its **primary** structure. The blueprint for each amino acid is laid down by sets of three letters known as base triplets that are found in the

of three letters known as base triplets that are found in the coding regions of genes. These base triplets are recognized by ribosomes, the protein building sites of the cell, which create and successively join the amino acids together. This is a remarkably quick process: a protein of 300 amino acids will be made in little more than a minute.

The result is a linear chain of amino acids, but this only becomes a functional protein when it folds into its three-dimensional (**tertiary structure**) form. This occurs through an intermediate form, known as **secondary structure**, the most common of which are the rod-like α -helix and the plate-like β -pleated sheet. These secondary structures are formed by a small number of amino acids that are close together, which then, in turn, interact, fold and coil to produce the tertiary structure that contains its functional regions (called domains). **Quaternary structure** is a larger assembly of several protein molecules or polypeptide chains.



<http://vls.wikipedia.org/wiki/Ofbeeldinge:Protein-structure.png>

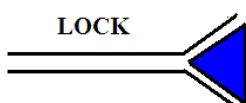
Why is a protein's 3-D structure important?

Protein Lock and Key Model

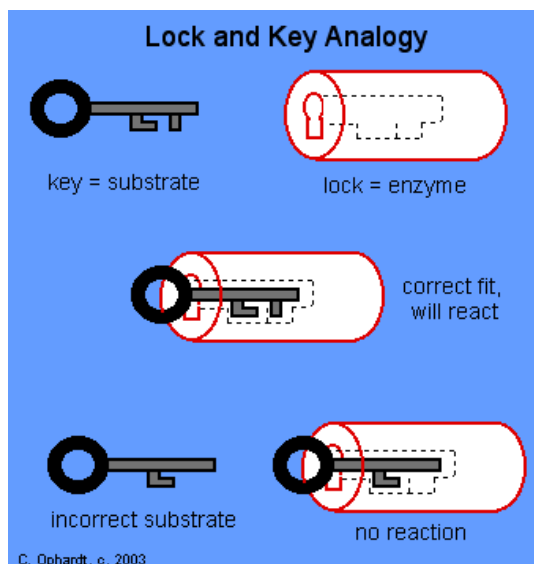
As stated before, protein molecules are very complicated. Because of interactions between atoms within the molecules, they are often bent and twisted. This complicated structure gives each protein a specific shape. Because of the shape, the molecule can interact in very specific ways with other molecules. Think of a jigsaw puzzle. There is only one piece that will fit perfectly in each spot.

One model used to describe the behavior of molecules interacting because of their shapes is the lock and key model. Below is a generic representation of a lock and key site. The lock is called an **active site** and the key is called the **substrate**. The active site is called "active" because interaction of the molecules (lock and key) in this way usually results in some chemical change or reaction.

The active site (lock) may represent a cancer-causing molecule and the substrate (blue triangle key) may represent a designer drug molecule that interacts with the cancer molecule to weaken it. If scientists can learn how to reproduce the substrates (keys) to a variety of active sites (locks) believed to cause illness, they may be able to more effectively treat or cure them.



<http://www.chemeddl.org/resources/TSTS/Gellman/Gellmanpg5-8/LockandKeyT.html>

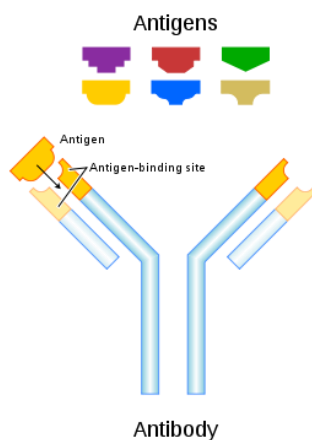


<http://www.elmhurst.edu/~chm/vchembook/571lockkey.html>

Smaller keys, larger keys, or incorrectly positioned teeth on keys (incorrectly shaped or sized substrate molecules) do not fit into the lock (enzyme). Only the correctly shaped key opens a particular lock.

Antivenom

One example of how scientists may use this lock and key model to help fight illness is through the development of **Antivenom**. Antivenom (more appropriately called antivenin or antivenene) is a biological product used in the treatment of venomous bites or stings. Antivenom is created by milking venom from the desired snake, spider or insect. The venom is then diluted and injected into a horse, sheep, goat or cat. The subject animal will undergo an immune response to the venom, producing antibodies, a type of protein, against the venom's active molecule. Samples of the host animal's blood are taken and the antibodies are separated out. They are then fragmented and purified by a series of digestion and processing steps. When injected into a patient, specific active sites (binding sites) on the antibody fragments bind to the venom or venom components (substrate) which circulate through the blood stream. This binding neutralizes the activity of the venoms and prevents further complications in the patient.



Antivenom is injected into the victim's blood typically via an intravenous infusion. The antibodies in the antivenom circulate in the blood and attach themselves to the toxins preventing them from causing further damage. In other words they neutralize the toxins making them harmless, but they are not able to reverse damage already done. Thus, they should be administered as soon as possible after the snake bite, but are of some benefit as long as venom is present in the body.

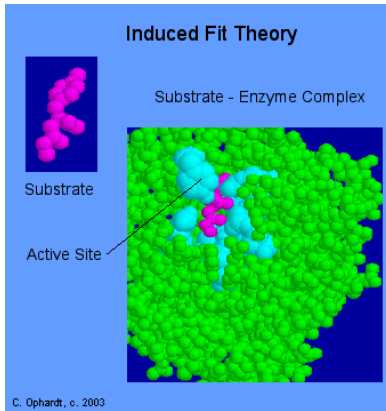
Each antibody binds to a specific antigen; an interaction similar to a lock and key

<http://en.wikipedia.org/wiki/Antibody>

Induced Fit Theory

Not all experimental evidence can be adequately explained by using the lock and key model. For this reason, a modification called the induced-fit theory has been proposed.

The induced-fit theory assumes that the substrate plays a role in determining the final shape of the enzyme and that the enzyme is partially flexible. This explains why certain compounds can bind to



the enzyme but do not react because the enzyme has been distorted too much. Other molecules may be too small to induce the proper alignment and therefore cannot react. Only the proper substrate is capable of inducing the proper alignment of the active site.

In the graphic to the left, the substrate is represented by the magenta molecule, the enzyme protein is represented by the green and cyan colors. The cyan colored protein is used to more sharply define the active site. The protein chains are flexible and fit around the substrate.

Why do scientists want to understand protein folding?

The importance of protein folding has been known for almost 50 years, but this became a major focus for pharmaceutical companies when scientists discovered that apparently unrelated diseases such as Alzheimer's disease and cancer were linked by defects in the folding of proteins. Now, protein misfolding has been identified as the cause of around 20 diseases, and is thought to occur in many ways. In one mechanism, accumulation of insoluble and toxic misfolded protein junk seems to be a key step on the way to Alzheimer's disease and prion disorders such as Creutzfeldt-Jacob disease (CJD), a form of brain damage that leads to a rapid decrease of mental function and movement. In other conditions, such as cystic fibrosis, hereditary emphysema and some cancers, misfolding leaves too little normally folded protein around to do its job. Insights into the defects that result in both these misfolding mechanisms have allowed scientists to come closer to designing successful treatments for these diseases.

<http://www.nature.com/horizon/proteinfolding/background/traating.html>

Can we predict the final 3-D protein structure knowing only its amino acid sequence?

Although it is possible to deduce the primary structure of a protein from a gene sequence, its tertiary structure cannot be determined (although it should become possible to make predictions when more tertiary sequences are submitted to databases). It can only be determined by complex experimental analyses (X-ray crystallography and Nuclear Magnetic Resonance) and, at present, this information is only known for about 10% of proteins. It is therefore not yet known how an amino-acid chain folds into its tertiary structure in the short time scale (fractions of

a second) that occurs in the cell. So, there is a huge gap in our knowledge of how we move from protein sequence to function in living organisms: the line of sight from the genetic blueprint for a protein to its biological function is blocked by the impenetrable jungle of protein folding, and some researchers believe that clearing this jungle is the most important task in biochemistry at present

(<http://www.nature.com/horizon/proteinfolding/background/importance.html>).

What do we know about protein folding?

- It is fast (typically a couple of seconds)
- It is consistent
- It involves weak bonds (non-polar covalent) – hydrogen bonding; van der Waals;

Salt bridges

- It is mostly a 2-state system (primary and tertiary); very few intermediates makes it hard to study

What we don't know about protein folding:

- Mechanisms
- Forces
 - Relative contributions
 - Hydrophobic force thought to be critical

The challenge of bioinformatics and protein folding

Bioinformatics is the field of science in which biology, computer science, and information technology merge to form a single discipline. Over the past few decades, major advances in the field of molecular biology, coupled with advances in genomic technologies, have led to an explosive growth in the biological information generated by the scientific community. This deluge of genomic information has, in turn, led to an absolute requirement for computerized databases to store, organize, and index the data and for specialized tools to view and analyze the data. The field of bioinformatics has evolved such that the most pressing task now involves the analysis and interpretation of various types of data, including nucleotide and amino acid sequences, protein domains, and protein structures.

The challenge of attempting to simulate protein structures in computer models is a process called **protein** or **molecular**

modeling. Small proteins can have 100 amino acids, and some large human proteins can have up to a 1,000. This makes for astronomical possibilities of combinations, and trying all of them to find the correct 3-D structure requires massive amounts of computing power. For example, a 100 amino acid protein with 2 moving dihedrals, with 2 possible positions for each dihedral would equal 2^{200} conformations!

Computer simulations cannot yet solve the folding code that is hidden in the primary structure by simply calculating the molecular dynamics atom by atom, as to work through just 50 milliseconds of folding would take even the fastest computer around 30,000 years.

(<http://www.nature.com/horizon/proteinfolding/background/importance.html>).

Any realistic hope of cracking the folding code, such as to produce special designer proteins that evolution had not planned, is probably a very long way off. However, our improved understanding of the route that a protein must take from its synthesis to the correct folded form already enables us to contemplate better treatments or even cures for diseases in which proteins have departed from the correct folding route.
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Vocabulary

Atom (/ˈatəm/): the basic unit of matter, sometimes described as building blocks.

Amino Acid (əˈmēnō/ /ˈasid/): building blocks of larger molecules called proteins. The amino acids are arranged like beads on a string. There are 21 common amino acids in proteins.

Bioinformatics (ˌbīōˌɪnfərˈmatiks/): the science of collecting and analyzing complex biological data

Cell (sel/): the smallest structural and functional unit of an organism

Chlorotoxin (/ˈklɒrəˈtæksɪn/): a 36-amino acid peptide found in the venom of the death-stalker scorpion which blocks certain chloride channels in a cell.

Macromolecule (/ˈmɑːkrəˈmɒləˌkyʊːl/): A very large molecule, such as a protein, consisting of many smaller structural units linked together.

Molecule (/ˈmɒləˌkyʊːl/): a group of two or more atoms that stick together.

Polypeptide (/ˌpɒliˈpepˌtɪd/): a chain of amino acids linked together by peptide bonds.

Protein (/ˈprɔːtɪn/): molecules made from tiny building blocks called amino acids, and are a vital part of all living things. They are part of everything that happens within cells. Their main function is to heal wounds, fight infection and build muscle.

Receptor (/riˈseptər/): specialized proteins in the cell membrane that take part in communication between the cell and the outside world.

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Links and References

Experience more *Venom!* at our partner website *Ask a Biologist*:

<http://askbiologist.asu.edu/body-depot>.

<http://www.nature.com/horizon/proteinfolding/background/importance.html> (The importance of protein folding)

<http://www.nature.com/horizon/proteinfolding/background/treating.html> (Treating protein folding diseases)

<http://www.scienceteacherprogram.org/pdf/GiftOfProtein.pdf> (The Gift of Protein: Protein bracelet lesson plan)

<http://www.youtube.com/watch?v=lijQ3a8yUYQ> (Video: Protein and protein folding overview)

<http://fold.it/portal/> (Game: figuring out how to fold proteins)

http://www.chem4kids.com/files/bio_proteins.html (Kids website: Building proteins from amino acid chains)

<http://www.pbs.org/wgbh/nova/insidenova/2011/02/the-venom-chronicles-venom-faqs.html> (Information about the venom of different animals and the research being done)

<http://animal.discovery.com/tv/wild-recon/how-venom-works.html> (Different videos about the venom of different animals)

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