

Biochemistry

Code: SCI2035/CHE2006



2017/2018

Period 2

Contents

GENERAL INFORMATION	5
INTRODUCTION	6
READINGS.....	6
ATTENDANCE REQUIREMENT	7
ASSESSMENT	7
<i>Presentation</i>	7
<i>Resit</i>	8
COURSE COORDINATORS AND STAFF INFORMATION.....	9
OVERVIEW OF MEETINGS, LECTURES AND DEADLINES.....	10
TASKS.....	11
TASK 1. HYPERVENTILATION, A STRANGE FORM OF SUFFOCATION?.....	13
TASK 2. SICKLE CELL BLOOD	14
TASK 3. LEMONS TO RULE THE WAVES	16
<i>When rat poison becomes an anti-thrombotic agent</i>	17
TASK 4. GOT MILK?	18
TASK 5. THROMBOSIS – A BUILT-IN TIME BOMB	19
TASK 6. WOULD YOU LIKE SOME WOOD PULP IN YOUR SHREDDED CHEESE?	20
TASK 7. TURBO-DESIGN	22
TASK 8. THE MYSTERY OF THE SEVEN DEATHS	24
TASK 9. FACE THE FATS.....	25
<i>'Lorenzo's oil'</i>	26
TASK 10. IT'S TIME TO REPLICATE	27
<i>Do-it-yourself baby construction box</i>	27

General Information

Introduction

Biochemistry is defined as ‘the study of the molecules of living things’. But knowledge about structures and properties of these intrinsically inanimate molecules only provides a static picture of living cells. It does not answer the most important question: how do these molecules confer the remarkable combination of characteristics we call life? That is, how can a living organism be more than the sum of its lifeless parts? Therefore, a more appropriate definition of Biochemistry is that it describes, in molecular terms, the structures, mechanisms and chemical processes shared by all organisms, and provides organizing principles that underlie life: the molecular logic of life. These principles can be summarized as:

- All living organisms build macromolecules from the same kind of rather simple small molecules (monomeric subunits)
- The structure of a macromolecule determines its specific biological function
- Each genus and species is defined by its distinctive set of macromolecules

Aim and approach

As an introduction to various basic concepts in biochemistry and molecular biology, this course aims to communicate fundamental principles governing structure, function and interactions of biological molecules to students encountering biochemistry for the first time. The course is meant to lead to an increased appreciation of the science of biochemistry and will prepare students to enter more detailed courses on biochemistry and molecular biology to finally allow entrance to various Master programmes in the life sciences. The major objectives are:

- To communicate fundamental principles governing structure, function and interactions of biological molecules to students encountering biochemistry for the first time.
- To increase appreciation of the science of biochemistry.
- To study the synthesis and degradation of large biomacromolecules like proteins, lipids, polysaccharides and nucleotides.
- To create deeper understanding of the basic principles of enzyme catalysis and inhibition.
- To prepare students to enter advanced courses that require more detailed biochemistry knowledge and to allow entrance to various Master programmes in the life sciences.

Readings

In addition to the main course book other books may be helpful in studying learning goals from the cases. Many of those are available in the UCM Reading Room and/or in the library at the FHML (UNS50). Students are encouraged to use these additional books or other sources of information.

- *Biochemistry* by J.M. Berg, J.L. Tymoczko, and L. Stryer (8th ed.) – W.H. Freeman
- *Biochemistry* by R.H. Garrett & C.M. Grisham (5th ed.) – Brooks/Cole, Cengage Learning
- *Lehninger Principles of Biochemistry* by D.L. Nelson & M.M. Cox (6th ed.) – W.H. Freeman
- *Molecular Biology of the Cell* by B. Alberts, *et al.* (6th ed.) – Garland Science
- ...

This list of books is far from complete. You are encouraged to use whatever sources that help you to find the answer to the learning goals; varying from books to scientific publications, from youtube-videos to lectures or

documentaries. Some books or sources may be more appropriate to answer certain questions than others. Let the learning goals guide your study process.

Attendance requirement

The attendance requirement for the 11 tutorial meetings is 85%. You are allowed to miss two regular tutorials without further consequences. If you miss more meetings, you will have to apply for an additional assignment (request forms are available via the Student Portal). In order to qualify for an additional assignment you have to have valid reasons for all missed sessions. If you don't meet the attendance requirement, you are not eligible for a resit. You automatically fail the course if you miss over 30% of the scheduled meetings.

The presentation session in the sixth week of the course is mandatory and is not considered one of the regular tutorial meetings to which the 85% attendance requirement applies.

Although the attendance for lectures is not mandatory, the content adds to the pre- and post-discussions in the tutorial group meetings. Therefore, the content of the lectures is considered part of the examination.

An inspection hour for the exam will be scheduled within 10 working days after the results of a written examination are published. The inspection hour is not mandatory. In case you do not feel the need to attend (for whatever reason) then feel free.

Assessment

This course contains three elements of assessment:

1. a written exam consisting of open questions and multiple choice (65% of the overall course grade);
2. a presentation on a biochemical topic (35% of the overall course grade); 1 or 2 students per presentation – for more information, see below;
3. bonus and minus points for your participation in the tutorial meetings (insufficient/fail = -0.5, sufficient/good = 0, excellent/distinguished = +0.5) – the bonus or minus points will be added to the exam grade (to a maximum grade of 10,0).

These elements of assessment serve the purpose of assessing all learning objectives (content/knowledge and skills/competencies) of the course; the essay questions in the exam function to cover the breadth of the field, and the presentation allows you to demonstrate your acquired expertise.

Presentation

The presentation assignment during the course gives you an opportunity to discuss, develop and elaborate on a biochemical topic (2 students per presentation), with a maximum of 5 presentations in one tutorial group. We provide you with a list of topics from which you can choose. You can also come up with your own topic, but make sure to check with your tutor on the appropriateness of the topic. You are free to pick any topic within biochemistry that has your interest, but keep in mind that it has to be an academic presentation, including more than just a summation of facts as stated in the literature. In addition to that, you should move beyond the contents of the course. You are encouraged to come up with your own approaches and solutions to a biochemical problem.

The presentation should be theoretically informed. You do not have to explain basic concepts discussed in the course, since you are presenting to students from your own discipline. However, don't take all background knowledge for granted!

Format of the presentation

Every group has 20-25 minutes for the presentation, including questions and group discussion. A computer and beamer will be available.

The presentation should contain at least the following items:

- Introduction
 - Introduction of research question/hypothesis
 - Explanation of context and relevance
- State of the art
 - Overview of current research and findings as presented in the literature
- Discussion
 - Possible solutions (as provided in the literature or thought of by the students)
- Conclusion(s)
- Group discussion (presenters lead the discussion)

Assessment of the presentation

The assessment of the presentation will be based on:

- The quality of the introduction (are you able to explain the context and relevance of your research question in such a way that the audience has enough insight to understand the context and reasons for your topic?)
- The quality of the presentation of the problem (are you able to explain the problem and capable of explaining why the solutions you provide are the best solutions?)
- The handling of questions/discussion (are you able to answer questions and discuss the problem?)
- The delivery of the presentation (quality of slides, speaking posture, etc.)

The presentation should be theoretically informed. You do not have to explain basic concepts discussed in the course, since you are presenting to students from your own discipline. However, don't take all background knowledge for granted!

The tutor will assess the presentations, supported by a second assessor. Students will prepare and present in teams of 2. The presentation is the result of a cooperation. In this case, both students are expected to present. Keep in mind that you will receive a group grade for this assignment. Your tutor will assess the final product; s/he cannot evaluate whether you divided the work equally. It is your own responsibility to assure each team member invests approximately the same amount of work. The coordinators and tutors of the course reserve the right to deviate from the group grade in the case of individual students demonstrably not taking their responsibility regarding preparation and contribution to the group effort.

Resit

Students who initially fail the course, but who have complied with the compulsory attendance requirement and took part in all of the assessment during the course, are eligible for one resit.

The overall grade for this course consists of a grade for the written exam (65%) and a grade for the presentation (35%). The resit serves the purpose of lifting your overall grade to sufficient/above 5.5. It does not replace the overall grade. Hence, the resit can be either on the exam OR the presentation. In case of a

resit, you will have to redo that part of the assessment for which you received the lowest grade. In case of redoing the presentation, you can either redo the original presentation, incorporating the feedback you received, or choose a new topic and prepare a totally new presentation. Beware that a resit for the presentation automatically changes this form of assessment into an individual assessment, even if all members of the presentation-team have to redo the presentation.

In order to receive a grade for the exam you will have to do a serious attempt at passing the exam. If it is not deemed a serious attempt you will not receive a grade and you will not qualify for a resit. The same thing holds for the presentation. If it is not deemed a serious attempt you will not receive a grade and you will not qualify for a resit.

Course coordinators and staff information

Questions or issues regarding the course content and e.g. assessment should first be discussed with the tutorial group and tutors. Those questions can also be discussed with the coordinators, but preferably during or directly after the lectures. Please note that the coordinators will not reply to individual e-mails that could have been dealt with during tutorial group meetings or during lectures.

Coordinators

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Overview of meetings, lectures and deadlines

week	meeting	topic	comments
1	Lecture		
	Tutorial group meeting 1	Introduction course Pre-discussion Task 1 – Hyperventilation	
	Tutorial group meeting 2	Post-discussion Task 1 Pre-discussion Task 2 – Sickle cell blood	
2	Lecture		
	Tutorial group meeting 3	Post-discussion Task 2 Pre-discussion Task 3 – Lemons to rule the waves	
	Tutorial group meeting 4	Post-discussion Task 3 Pre-discussion Task 4 – Got milk?	
3	Lecture		
	Tutorial group meeting 5	Post-discussion Task 4 Pre-discussion Task 5 – Thrombosis - a built-in time bomb	
	Tutorial group meeting 6	Post-discussion Task 5 Pre-discussion Task 6 – Would you like some wood pulp...?	declare presentation topic to tutor
4	Lecture		
	Tutorial group meeting 7	Post-discussion Task 6 Pre-discussion Task 7 – Turbo-design	
	Tutorial group meeting 8	Post-discussion Task 7 Pre-discussion Task 8 – The mystery of the seven deaths	
5	Lecture		Monday November 27th 2017: Deadline questions Q&A meeting – send via e-mail to c.reutelingsperger@maastrichtuniversity.nl
	Tutorial group meeting 9	Post-discussion Task 8 Pre-discussion Task 9 – Face the fats	
	Tutorial group meeting 10	Post-discussion Task 9 Pre-discussion Task 10 – It's time to replicate	
6	Lecture	Part of this lecture is a Q&A-session – <i>questions should be sent via e-mail to the lecturer at least one week prior to this session. Questions should be phrased exact, unambiguous, and to the point.</i>	
	Tutorial group meeting 11	Post-discussion Task 10	
	Mandatory meeting	Presentations	
7	Exam		

Note that this is a preliminary schedule. Please check your schedule on MyUM and the announcements on the Student Portal on a regular basis.

Tasks

Task 1. Hyperventilation, a strange form of suffocation?

A group of students gathers in a lecture room at UCM, awaiting the start of the new period. They have all chosen to participate in the Biochemistry course, and they have high expectations. The background of the students is very different and some of the students are therefore a little nervous. For instance Teun, Ton and August do not have an extensive chemistry background, and fear that the course will be mainly focussed on chemistry. On the other hand there are some students who lack a solid base in biology, and hope that therefore the course will not focus too much on biology.

A little later, after the first lecture has started Ton feels rather dizzy and suddenly faints. He is just caught by August, who lays him down on the floor. August reports that Ton was breathing very strangely and fast. This may be an indication that Ton was hyperventilating. Teun takes out a small plastic bag, and they force Ton to breath into the bag for a little while. Slowly he recovers, although a splitting headache remains. After a sip of water and some rest, Ton has sufficiently recovered and the lecture can continue.

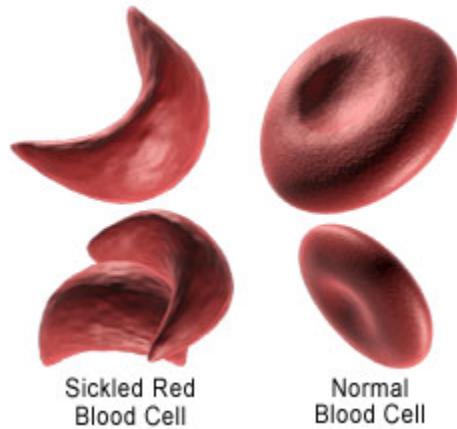
In this first lecture the teacher explains that both biology and chemistry are equally important for the biochemistry course, and that nobody needs to get stressed about their background. It is important to understand the biochemical principles, and that memorising exact and detailed structures or functions by heart is not the goal of this course. In stead, it is more important to think like a biochemist, and to solve various problems in this way, using basic, not too difficult, chemistry and biology. So there was actually no reason to be too nervous about the course at all.

Then the lecture continues on the topic of buffers, acids and bases, which is an important topic for all biochemists.



Task 2. Sickle cell blood

Sickle cell disease has been known to the peoples of Africa for hundreds of years. In Western literature, sickle cell disease was first described by the Chicago physician, James B. Herrick, who noted in 1910 that the blood of one of his patients from the West-Indies showed serious anaemia: only half the normal number of red cells was present. Many of these cells were sickle shaped.



After this first description of sickle cell disease, it took nearly 45 years of research to reveal the molecular basis of this disorder. Important to note that collaboration between physicians and chemists was essential as becomes clear from the following conversation between Dr. Linus Pauling, a renowned chemist who had been doing innovative research elucidating the structure of different proteins, and Dr. Bill Watson, a paediatric haematologist:

Linus: "*Haemoglobin appears to have a number of interesting structural properties.*"

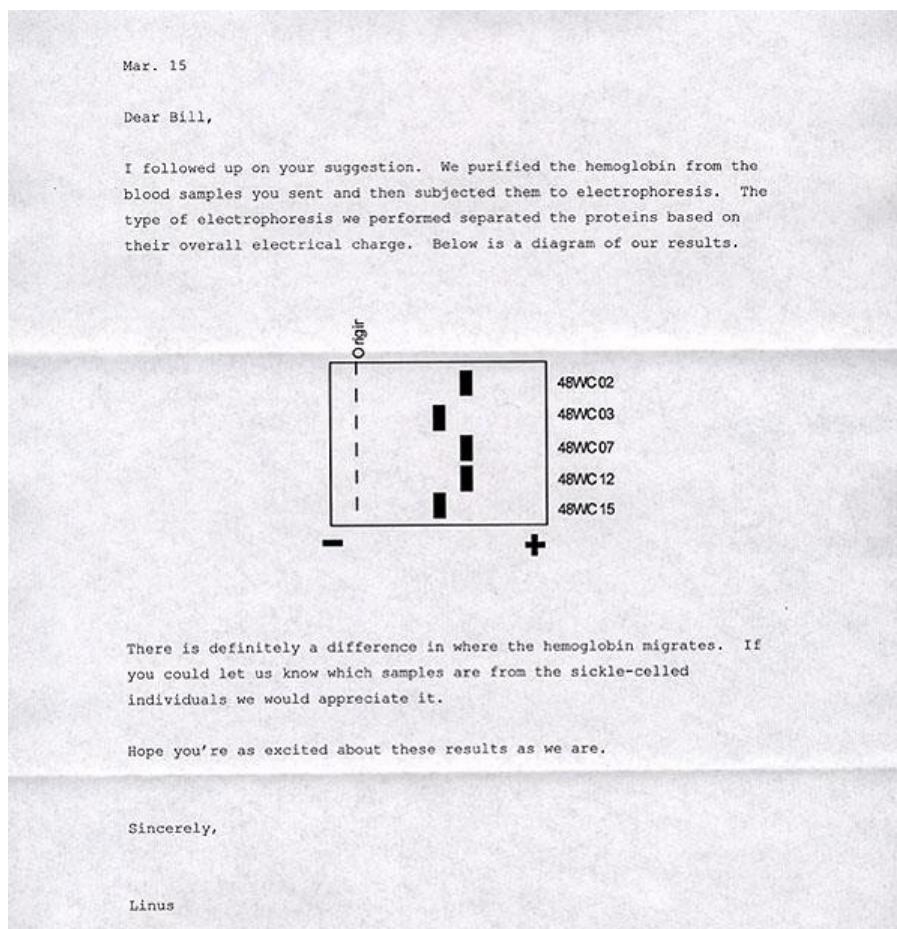
Bill: "*Linus, have you considered studying haemoglobin from individuals suffering from different forms of anaemia?*"

Linus: "*I'm not very familiar with anaemia. I thought that anaemia was a condition in which the body simply made fewer red blood cells. Is there any indication that there is a difference in the haemoglobin?*"

Bill: "*Until a few months ago I would have told you no, but a young medical student recently observed that blood from individuals with sickle cell anaemia transmits light differently than normal blood. He further noticed that if you take a tube of blood from a sickle-cell patient and allow it to sit undisturbed for a while, the cells at the bottom of the tube will become sickled, while those at the top of the tube retain their normal shape. After he shook up the tube, the sickled cells returned to their normal shape. I was thinking that this may be due to some difference in the structure of their haemoglobin and that low oxygen concentration is the factor that is causing the cells to sickle.*"

Linus: "*It definitely seems worth looking into. If you could send me some blood samples, I could try a couple things when I get back to the lab and let you know what I find out.*"

A few weeks later, Dr Watson received the following letter:



Eagerly Dr. Watson reached for his lab notebook and saw that the samples labelled 48WC03 and 48WC15 originated from patients who had been diagnosed with sickle cell anaemia. The other samples served as controls.

Thus, using the technique of protein electrophoresis, it could be demonstrated that the haemoglobin from patients with sickle cell disease was different than that of healthy people. This made sickle cell disease the first disorder in which an abnormality in a protein was known to be at fault. In 1956, Vernon Ingram, John A. Hunt, and Antony O. W. Stretton sequenced sickle haemoglobin and showed that a glutamic acid at position 6 was replaced by a valine. Using the known information about amino acids and the codons that coded for them, they were able to predict the mutation in sickle cell disease. This made sickle cell disease the first genetic disorder for which the molecular basis was known.

Task 3. Lemons to rule the waves

When visiting the VASA museum in Stockholm, people become easily astonished by the flawless craftsmanship of the creators of impressive warships in the 16th and 17th century. Heroic stories, juiced up by the scenery containing the original and quite impressive 17th century steel canons are told... but make no mistake, sailors in those days hardly ever died from the impact of an occasional canon ball. No, they died *en masse* from a cause quite different than steel balls.



When exploring the Saint Lawrence River in 1536, several men were afflicted by a peculiar disease, which was called scurvy. Jacques Cartier, joining the expedition, gave a vivid description of the symptoms:

[...] some did lose all their strength, and could not stand on their feet [...]. Others also had all their skins spotted with spots of blood of a purple colour: then did it ascend to their ankles, knees, thighs, shoulders, arms and neck; their mouth became stinking, their gums so rotten, that all the flesh did fall off even to the roots of the teeth, which did almost all fall out."

from C. Creighton (2014) A History of Epidemics in Britain. Volume 1. Cambridge University Press

In 1753, the Scottish physician James Lind first described the means of preventing scurvy, in his book "Treatise on Scurvy":

"Experience indeed sufficiently shows that as greens or fresh vegetables, with ripe fruits, are the best remedies for it, so they prove the most effectual preservatives against it."

J. Lind (1757) Treatise on Scurvy. 2nd ed. Millar, London

His advice to include lemon juice in the diet of sailors was adopted only forty years later by the British Navy. Interesting fact: James Lind's experiments represented the world's first clinical trial.

The problem described above and the solution suggested by the Scottish physician has everything to do with a post-ribosomal modification of one of the most abundant body proteins.

When rat poison becomes an anti-thrombotic agent

If you have been diagnosed with an unwanted blood clot, a medication named warfarin (coumarin) may be prescribed as part of your treatment to prevent further blood clots. Warfarin prevents the formation of functional clotting factors by competing with vitamin K in the liver. How does vitamin K help in the synthesis of clotting factors?



Task 4. Got milk?

Feng is a Chinese student who is doing an internship at the Department of Gastroenterology. He works together with Frank, a very sporty Dutch guy. Frank drinks a large milkshake with extra proteins, carbohydrates and fruit every day. When he offers Feng a milkshake, Feng kindly refuses because he knows he is lactose intolerant and he forgot his enzyme pills.

Frank's curiosity is aroused. What do the enzyme pills exactly do? Are they harmful to the body? If no, can't Feng take a pill every morning so as to be able to drink milk ad libitum every day? Where do the pills work and why?

Lactose is one of many enzymes of the human body. Enzymes are mandatory for life because in their absence many reactions would progress at very low rates.

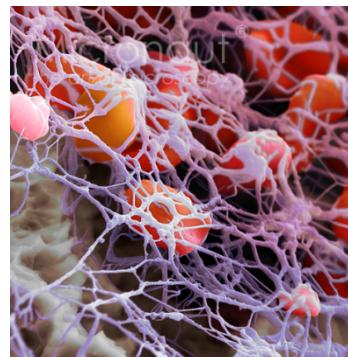
Hydrogen peroxide (H_2O_2) for example can be harmful to cells. Once formed, H_2O_2 slowly decomposes into water and oxygen. In the presence of catalase, however, it is rapidly converted. Catalase has one of the highest turnover numbers of all enzymes. One catalase molecule can convert millions of H_2O_2 molecules per second.

The reactions between enzymes and their substrates have been studied extensively by scientists. Insights in enzyme kinetics have led to the notion that inhibition of enzymes may be a powerful strategy to treat diseases.

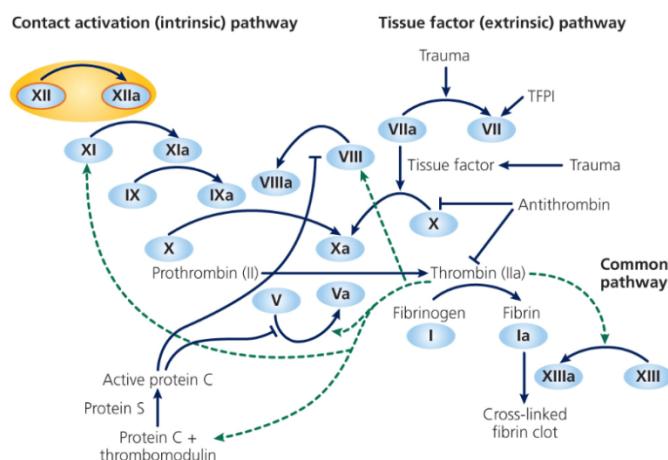
Task 5. Thrombosis – a built-in time bomb

Blood has a very important function in the human body. It transports oxygen, nutrients, and waste products. Blood is pumped round by the heart and flows through an extensive system of blood vessels. In case of blood loss, for example due to an injury, it is of crucial importance that the blood clots.

The study of blood coagulation can be traced back to about 400BC and the father of medicine, Hippocrates. Throughout the ages, scientists discovered how blood clots and it was Paul Morawitz, in 1905, who assembled coagulation factors into a scheme of coagulation, which demonstrated that in the presence of calcium and thromboplastin, prothrombin (II) was converted into thrombin (IIa), which in turn converted fibrinogen (I) into a fibrin clot. In 1944, Paul Owren discovered in a bleeding patient that a four-factor concept of clotting could not apply, and as a result factor V was discovered. This went on for a few decades resulting in the complicated clotting cascade as we know and study it today.



The cascade scheme teaches us that blood coagulation is an ingenious system of checks and balances, relying on a series of enzymatic reactions, naturally occurring anticoagulants and inhibitors. The enzymes travel in the blood as zymogens. Upon induction of blood coagulation, they become activated by enzyme action. Damage to the blood vessel wall induces coagulation and sets off an extracellular cascade involving sequential serine protease activations. The working mechanism of serine proteases is particularly interesting as they are also responsible for coordinating other physiological functions like digestion, immune response and reproduction.



Blood coagulation occurs on the surface of activated platelets. Vitamin K-dependent coagulation factors are able to bind the exposed phosphatidylserine in the outer leaflet of the plasma membrane of blood platelets. This post-translational modification of Glu to Gla residues is used as a strategy to temper hypercoagulation in thrombosis patients.

Taking a closer look at the coagulation cascade reveals that there is a delicate balance between clotting and anti-clotting. Disturbances in this balance cause problems like bleeding (haemophilia) or hyperclotting (thrombosis). Thrombosis is now termed the ‘built-in time bomb’, which strikes around half of the population 10-20 years prior to the normal, biological end of life. In the US 100.000-300.000 deaths from blood clots occur each year, which is greater than the total number of people that lose their lives each year to aids, breast cancer, and motor vehicle crashes combined.

Task 6. Would you like some wood pulp in your shredded cheese?

Polysaccharides form a large group of diverse biomacromolecules that have a wide variety of functions. For instance, mechanical strength of many organisms is based on polysaccharides: for plants in the form of lignin and cellulose, for insects and crustaceans in the form of chitin, and for humans in the form of extracellular matrix components like aggrecans (cartilage of vertebrates). Furthermore polysaccharides play an important role in the storage of energy inside organisms: from starch in potatoes and wheat to glycogen in animal species. Additionally mono-, di-, oligo-, and poly-saccharides can have a more delicate function inside multicellular organisms in the form of mucus layers for protection of soft tissue, or as signalling molecules and enzyme regulators. Sugar molecules also play an important role in recognition, e.g. the ABO blood type system. One function that has not been associated with this group of biomacromolecules is the storage of information.

Nowadays, the global food industry has exploited the myriad of polysaccharides in an almost unimaginable way. Tasty and stomach fulfilling lipids needed to be removed because of their cardiovascular risk. Sugars, as the delicious surrogates of fats, could not hold for long because of their diabetic risk and strong link with obesity. So, what keeps pre-packaged shredded cheese from clumping, low-fat ice cream creamy, and pre-made milk shakes smooth? You guessed it! Wood pulp. They call it cellulose – fibres if you want – but it's just powdered wood pulp. The industry loves this stuff: it's cheap, it helps stabilise food, lowers fat content, and increases fibre. So whenever you feel the need to eat 'real' food (and pay for it), think twice when buying the reduced-fat version of full-fat foods.

Pulp fiction and fact: Wood, cellulose and Parmesan cheese

BY JACOB HARPER | MARCH 21, 2016

OPINION

In recent lawsuits and media reports about the FDA's prosecution of a manufacturer of grated Parmesan, plaintiff's lawyers and reporters claim some Parmesan varieties have unsafe levels of certain ingredients, including "wood pulp."

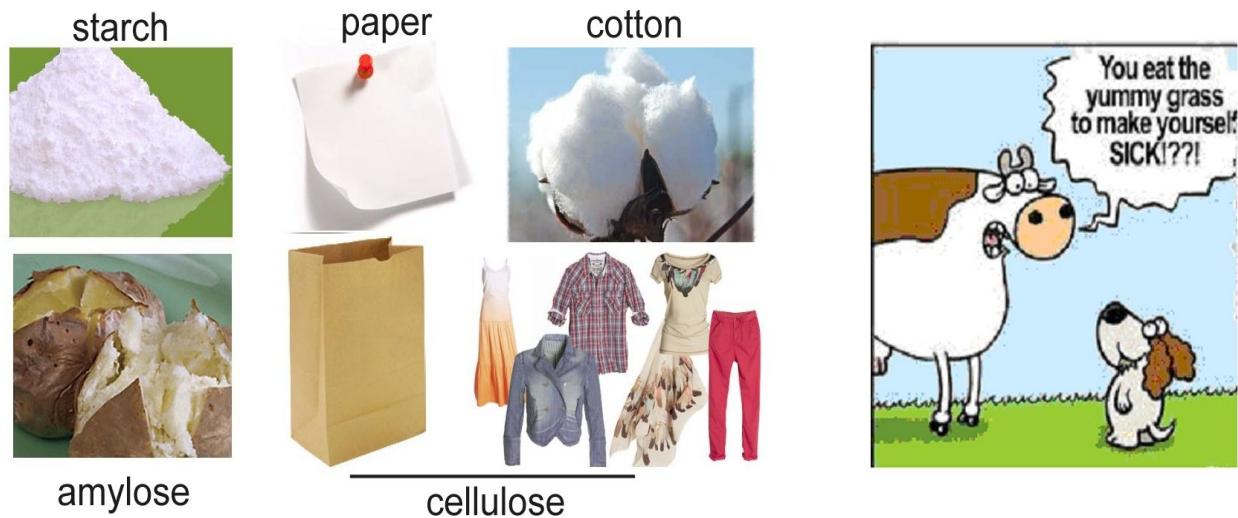


Figure 1: Ruminants and termites are able to process cellulose; we (together with most organisms) are not. How do they do that?

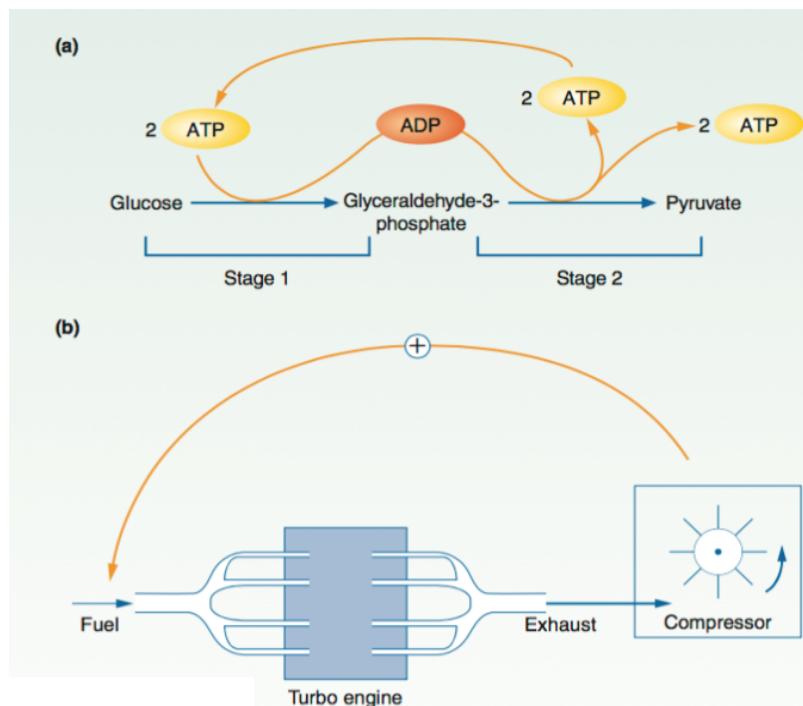


Figure 2: *Sequoiadendron giganteum* – trees growing to an average height of 50-85m (164-297ft). How are they able to stand up for hundreds of years?

Task 7. Turbo-design

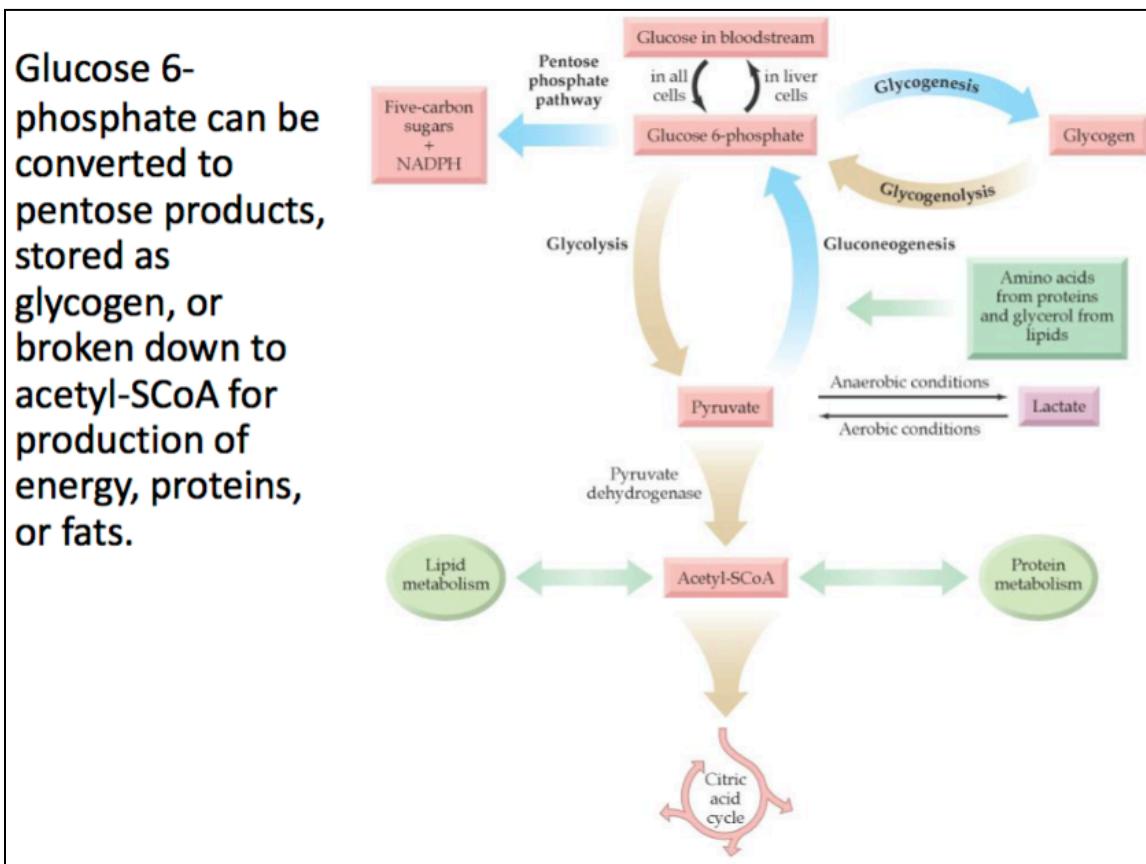
Modern species are the result of billions of years of rigorous natural selection, which has adapted organisms to their various environments. This selection process also governs the metabolic pathways that manage the biochemical transformations that sustain life. As systems biologists analysed metabolic processes, it became apparent that evolution, operating under thermodynamic and kinetic constraints, has converged again and again into a relatively small set of designs. Catabolic pathways, those that degrade organic molecules and release energy, provide an important example. These pathways typically have two characteristics: optimal ATP production and kinetic efficiency (i.e. minimal response time to changes in cellular metabolic requirements). Living organisms have optimised catabolic pathways, in part, by ‘placing’ highly exergonic reactions at the beginning of a pathway. The early “activation” of nutrient molecules thus makes subsequent ATP-producing reactions (usually near the end of the pathway) to run thermodynamically downhill. As a result, the pathway can produce ATP under varying substrate and product concentrations. The term “turbo design,” inspired by the turbo engines in jet aircraft, describes this phenomenon. A good example is glycolysis, the energy-capturing reaction pathway that converts glucose into pyruvate.

A jet engine creates propulsion by mixing air with fuel to create hot, expanding, fast-moving exhaust gases, which blast out the back. Some of the air drawn in at the front of the engine is diverted into compressors, where its pressure increases substantially before flowing into combustion chambers and mixing with fuel molecules. As the burning fuel molecules expand, they flow through turbines fitted with fan blades that drive the compressors. An important feature of this process is that hot exhaust gases are also fed back into the engine to accelerate the fuel input step.



This task reveals how carbohydrate fuel is burned by living cells with the same remarkable efficiency. When cells are already well supplied with glucose, the excess glucose is converted to other forms for storage: to glycogen, the glucose storage polymer, by the glycogenesis pathway, or to fatty acids by shuttling acetyl-S-coenzyme A into the pathways of lipid metabolism rather than the citric acid cycle. When energy is needed,

glucose 6-phosphate undergoes glycolysis to pyruvate and then to acetyl-S-coenzyme A, which enters the citric acid cycle.



Heterotrophs are purely aerobic organisms, meaning they need oxygen to stay alive. Under normal conditions, there is enough oxygen to ensure sufficient energy/ATP production for cells to function. Paradoxically, in the body of aerobic heterotrophs, anaerobic metabolism still occurs. An example is when in human muscle tissue ATP is depleted fast and not enough oxygen can be provided to replenish ATP reserves. In response, acidification of the tissue occurs, which leads to an increase in oxygen release from the blood (see task 1 and 2). The low pH is caused by an alternative pathway, i.e. fermentation. When the muscle tissue gets the chance to rest, the pH of the tissue increases and is restored.

The question of course is: what is the role of oxygen in metabolism? And in absence of oxygen, what changes so that the organism/cells can still function, despite the drop in pH?

Task 8. The mystery of the seven deaths

Imagine that you work as chief Medical Officer for a major city. You investigate suspicious deaths and provide toxicology services to the county. Unfortunately it has been a busy week. In the past five days, seven people have died, all with similar symptoms. It is your job to examine the data and determine the cause of death for these seven victims.

The first victim was a 12-year-old girl. Her parents said that she was awake in the middle of the night complaining of a stuffy nose and sore throat. They gave her an extra strength Tylenol (= paracetamol) and sent her back to bed. At 7am the next morning, the parents found their daughter collapsed on the bathroom floor. An ambulance rushed the girl to a nearby hospital, where she was pronounced dead.

That same day, paramedics found the second victim unconscious on his kitchen floor after what they thought was an apparent heart attack. Sadly, the victim's brother and fiancée also collapsed later that night while the family gathered to mourn his passing. Both had taken Tylenol to help them cope with their loss shortly before collapsing; neither survived.

In the next four days, four other similar deaths were reported, all in the same neighbourhood and all with similar symptoms.

From the autopsy report:

- *Immediate cause of death was hypoxia (suffocation or lack of oxygen).*
- *Tissue sections from heart, lung, kidney, and liver all showed massive cell death.*
- *Staining with specific dyes showed major mitochondrial damage within the affected tissues.*
- *Oxygen levels in the patients' blood were approximately 110 mm Hg (normal range: 75-100 mm Hg).*

Subcellular Metabolite Analysis:

Detailed analysis of the damaged cells showed that ATP levels in the mitochondria were very low. Levels of pyruvate and acetyl coenzyme A (CoA) were normal.

You begin to suspect a malfunction of a specific cellular metabolic pathway and so you request a more detailed analysis of the sub-cellular components of the affected cells from the autopsy. The levels of key metabolites are reported below:

Average Metabolite Levels

Metabolite	Average Patient Levels	Normal Levels
Glucose	99 µM	100 µM
Pyruvate	27 µM	25 µM
NAD+	10 µM	75 µM
NADH	400 µM	50 µM

Can you develop a hypothesis about which pathway may be affected based on these abnormalities? Explain your reasoning.

Source: Michaela A. Gazdik; national centre for case study teaching in science

Task 9. Face the fats

Joe was glad to be finally home from a tiring day - first to class and then straight to his job. Now it was 8pm. Tired and hungry he threw his backpack on the floor. In the search for a meal, he found some hot pockets in the freezer and threw two in the microwave before he slumped on the couch and turned on the TV. Another one of those annoying drug company commercials! This one was about some drug called Vytorin™. As the microwave beeped that his dinner was ready, Joe watched the commercial and laughed at all of the people who resembled what they ate. He wondered...do I look like a 'Hot Pocket'?

As Joe wolfed down his dinner, he was curious. How much cholesterol was in a hot pocket anyway? He grabbed the box from the trash can and read the nutrition label on the back.

Whoa! Joe realized that one hot pocket is considered a serving so he had eaten 620 calories for dinner. Not to mention 50 mg of cholesterol. Although he had no idea if this was high or not, he figured it couldn't be good or there wouldn't be a need for a 'Lean Pocket'.

After a quick google search, Joe found the following information: "the American Heart Association and US dept. of Agriculture recommend that you limit your fat intake to no more than 30% of your daily calories, of that 30%, 10% or less of the fat calories should come from *saturated* fat. One gram of fat = 9 calories."

Fat? Saturated? Are these different than cholesterol? Joe kept on searching and started to understand a little bit about cholesterol and fats but still didn't quite get why they are so unhealthy. And if they are unhealthy, why do we need cholesterol and fat?

Joe wondered how cholesterol is processed by the human body. What are the fates of cholesterol? And also, he encountered the terms 'good' cholesterol (HDL) and 'bad' cholesterol' (LDL). He read that high cholesterol intake can lead to hyperlipidaemia and this can lead to diseases like atherosclerosis and heart attack.

Joe figured out that low cholesterol/LDL levels in your blood help keep you healthy by preventing heart attacks and strokes. Therefore, maybe eating foods that are low in cholesterol may ultimately be able to lower your risk for these diseases.

Nutrition Facts		
Serving Size 1 piece (127g)		
Servings Per Container 2		
Amount Per Serving		
Calories 310	Calories from Fat 110	% Daily Value*
Total Fat 13g	20%	
Saturated Fat 6g	29%	
Trans Fat 0g		
Cholesterol 25mg	9%	
Sodium 630mg	26%	
Total Carbohydrate 37g	12%	
Dietary Fiber 2g	8%	
Sugars 9g		
Protein 11g		
Vitamin A 0%	• Vitamin C 0%	
Calcium 15%	• Iron 10%	
Thiamine 20%	• Riboflavin 15%	
Vitamin B12 15%	• Niacin 15%	
Folic Acid 15%	• Phosphorus 10%	
* Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:		
Calories: 2,000 2,500		
Total Fat	Less than 65g	80g
Sat. Fat	Less than 20g	25g
Cholesterol	Less than 300mg	300mg
Sodium	Less than 2,400mg	2,400mg
Total Carbohydrate	300g	375g
Dietary Fiber	25g	30g

By the time he went to bed, Joe decided he should really start paying more attention to what he ate, especially with regard to fats and cholesterol and he should exercise more. It is never too early to 'Face the Fats'.

'Lorenzo's oil'

Fatty acids are important sources of fuel because, when metabolized, they yield large quantities of ATP. Most naturally occurring fatty acids have an unbranched chain of an even number of carbon atoms, from 4-28. Unlike most fatty acids, very long chain fatty acids are too long to be metabolised in the mitochondria, and must be metabolised in peroxisomes. Adrenoleukodystrophy is a disorder of peroxisomal fatty acid beta oxidation which severely affects the myelin in the central nervous system.



Task 10. It's time to replicate

The importance of DNA replication in biology is hard to underestimate. Without DNA replication and inheritance, growth would be impossible and evolution would not occur. None of the millions of different species that exist would have originated.

DNA replication must be carried out accurately, with an efficient proofreading and repair mechanism in place for any mismatches or errors. This DNA-repair ability of a cell is vital to the integrity of its genome and thus to the normal functionality of an organism. A cell that has accumulated a large amount of DNA damage (or one that no longer effectively repairs damage), can go into i) senescence, ii) apoptosis or iii) enters a state of unregulated cell division, which can lead to the formation of a tumour that is cancerous.

DNA can be damaged by many things that surround us: chemical mutagens, ionizing radiation (nuclear energy or cosmic rays), sunlight (free radicals induced by UV-A light), industrial chemicals, polycyclic hydrocarbons found in smoke. Even the natural ageing process and respiration causes DNA damage at the rate of about 10.000 lesions/cell/day.

Despite the thousands of alterations that occur in our DNA each day, very few are actually retained as mutations thanks to highly efficient DNA repair mechanisms. The importance of repair mechanisms is highlighted by the high number of genes that are devoted to DNA repair.

Do-it-yourself baby construction box

In 1987, Japanese researchers investigated a specific gene in the *E. coli* bacteria. Surprisingly they noticed something they did not look for initially: in the bacterial genome the same short segment of DNA repeated itself. Triggered by this discovery and many experiments later they found out that the repeats are used by lots of bacteria and unicellulars as a strategy much like an immune system against invading viruses and plasmid DNA. They called it *clustered regularly interspaced short palindromic repeats* which took way too long when talking about the discovery, and thus the abbreviation CRISPR was born. Short DNA sequences from invading viruses are incorporated at CRISPR loci (spacers) within the bacterial genome and serve as 'memory' of previous infection. Re-infection triggers the complementary mature CRISPR-RNA to find a matching sequence, which provides the CRISPR-associated (Cas) nuclease the specificity to form a double-strand break at specific 'foreign' DNA sequences, thereby abolishing this foreign DNA.

Until recently gene editing in eukaryotic cells has been a difficult process (using recombinant viruses or Zn-fingers) with limited accuracy. With the powerful CRISPR-Cas technique, cutting/ligating DNA becomes easier than ever before, with special thanks to the RNA-

The screenshot shows a news article from the September 2016 issue of Nature magazine. The title is "Chinese scientists genetically modify human embryos". Below the title, a sub-headline reads "Rumours of germline modification prove true — and look set to reignite an ethical debate." The author's name, David Cyranoski & Sara Reardon, is listed, along with the publication date, 22 April 2015. A "Rights & Permissions" button is visible. The main image is a scanning electron micrograph (SEM) of a cluster of human embryos, appearing as greenish-yellow spheres against a black background. A caption at the bottom right credits "Dr. Yorgos Nikas/SPL". A small note at the bottom states "Human embryos are at the centre of a debate over the ethics of gene editing."

navigation system, allowing for highly specific gene editing. There is not a researcher that does not know this technique and it has led to a significant amount of breakthroughs (in the laboratory): removing mutations that cause diseases, cultivating crops without gluten, exterminating viruses, searching for genes that cause cancer, and many more. But this also implies a down side...

New difficult challenges arise. A valid reason to start up serious Think Tanks on the ethics and genetics of this technique. It will require some more critical thinking before we are able to walk into the hospital with a CRISPR/Cas toolbox to create our do-it-yourself baby.

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

SICKLE CELL DISEASE

Selection-free genome editing of the sickle mutation in human adult hematopoietic stem/progenitor cells

nature research
ARTICLE

doi:10.1038/nature24033

Kathy Niakan, et al.

Embryo edit makes human 'knockout'

CRISPR inactivation of gene
allows developmental study

