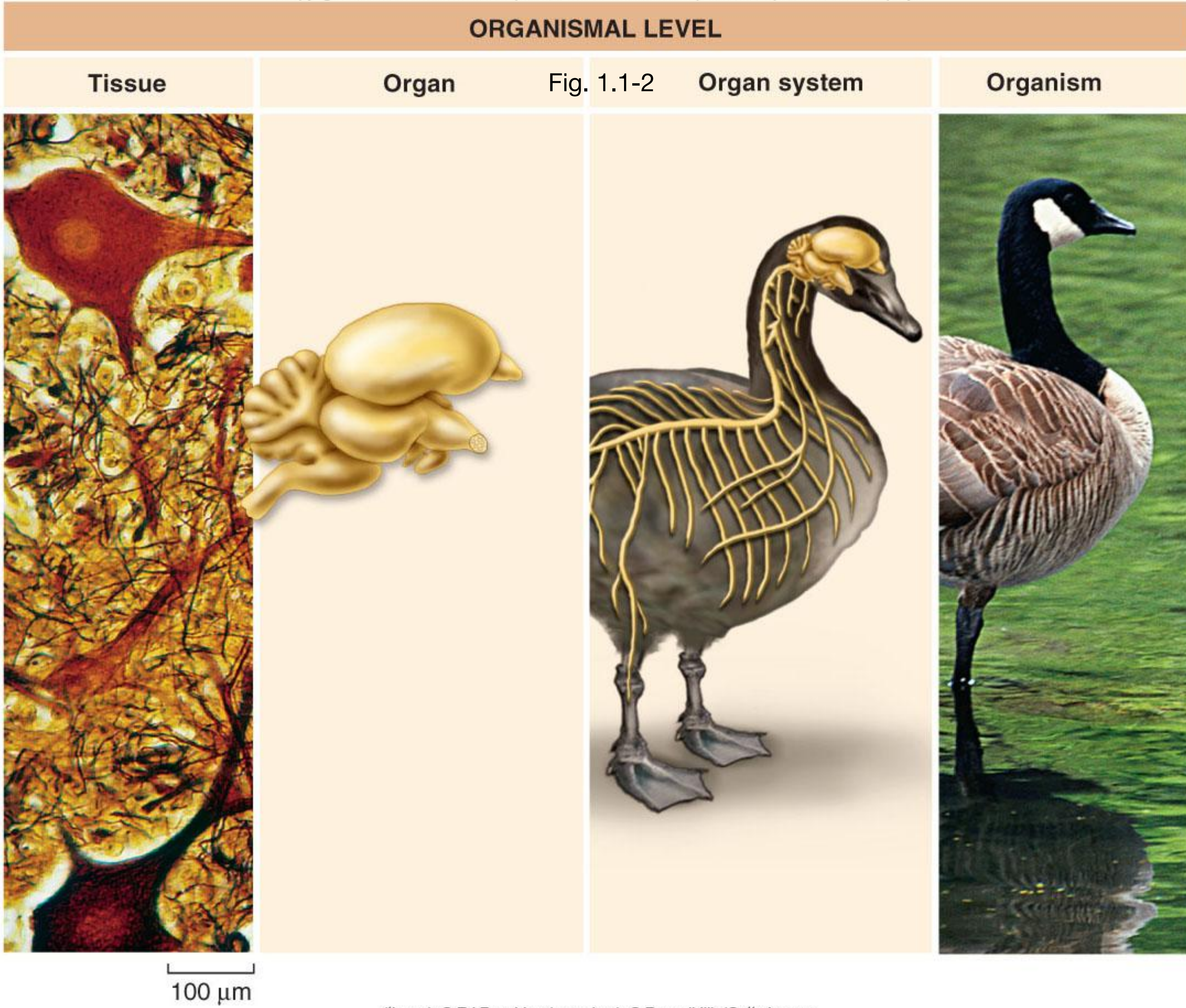
Sbl100

Biological Machines

Fig. 1.1-2


ORGANISMAL LEVEL
Tissue
Organ
Organ system
Organism
100 µm

Understanding functions of Biological systems are very very complex

Biological machines convert chemical (free) energy to mechanical work, information.

How do they work?

- What structural and chemical features are important?

- How is chemical energy utilized, converted into force, motion?

- What role is played by thermal energy and fluctuations?

- What is unique about the nano-scale: what difference does small size make?

Biological systems are very very complex, the misbalance at any level, gene or cells or tissues leads to various diseases.

Disease is a disorder or malfunction of the mind or body, which leads to a departure from good health.

Can be a disorder of a specific tissue or organ due to a single cause. E.g. malaria.

May have many causes.
Often referred to as multifactorial. E.g. heart disease.

Disease are diagnosed by a doctor analysing the symptoms (physical and mental signs).

Some common diseases are Cancer, Malaria, Dengue, AIDS, Influenza, Hepatitis A,B,C, Jaundice, Tuberculosis, Schizophrenia, Alzheimer, Parkinson, Cholera, Typhoid etc.

There are still very very severe diseases which cannot be treated so far due to lack of proper understanding which results lack of proper medicines.

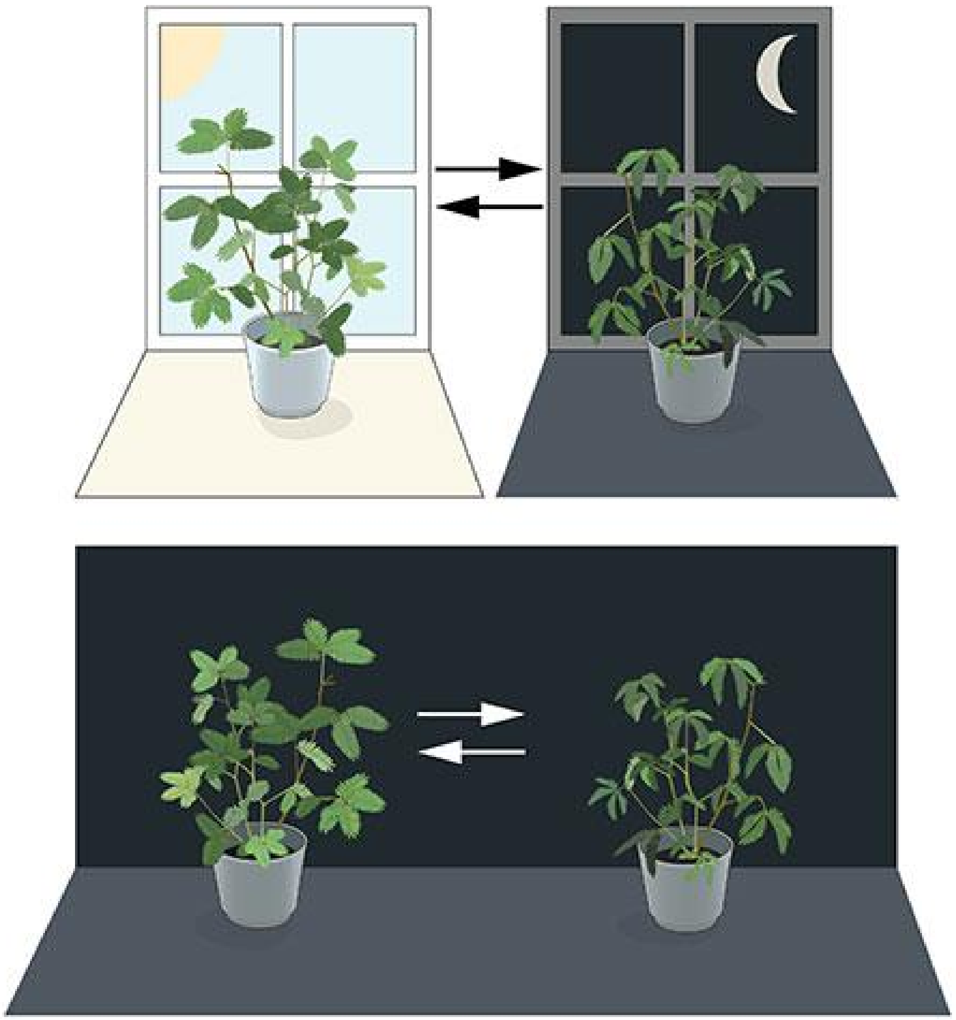
Speciality of Our Inner Clock

With utmost precision, our inner clock adapts our physiology to the dramatically different phases of the day.

The clock regulates critical functions such as behavior, hormone levels, sleep, body temperature and metabolism.

Our wellbeing is affected when there is a temporary mismatch between our external environment and this internal biological clock, for example when we travel across several time zones and experience "jet lag".

There are also indications that chronic misalignment between our lifestyle and the rhythm dictated by our inner timekeeper is associated with increased risk for various diseases.



In 18th century, Jean Jacques d'Ortous de Mairan studied mimosa plants, and found that the leaves opened towards the sun during daytime and closed at dusk.

He wondered what would happen if the plant was placed in constant darkness. He found that independent of daily sunlight the leaves continued to follow their normal daily oscillation (Figure).

Plants seemed to have their own biological clock.

The leaves continue to follow their normal daily rhythm, even without any fluctuations in daily light.

2017 Nobel Prize in Physiology or Medicin

Jeffrey C. Hall, Michael Rosbash and Michael W. Young

molecular mechanisms controlling the circadian rhythm

Circadian rhythms control when we're at our peak performance physically and mentally each day, keeping our lives ticking in time with Earth's day/night cycle

living organisms, including humans, have an internal, biological clock that helps them anticipate and adapt to the regular rhythm of the day. But how does this clock actually work?

Using fruit flies as a model organism, this year's Nobel laureates isolated a gene that controls the normal daily biological rhythm.

They showed that this gene encodes a protein that accumulates in the cell during the night, and is then degraded during the day.

Summary of findings

- circadian rhythm, originating from the Latin words circa meaning "around" and dies meaning "day".
- circadian rhythms play in coordinating our lives with Earth’s day, controlling everything from your metabolism to the timing of sleep.
- Young’s lab recently identified a prevalent mutation in a human clock gene, cryptochrome 1, that lengthens the cellular clock and makes it difficult to get to bed before midnight.
- This inherited “night owl” gene is estimated to be pretty common, found in nearly 1 out of 75 of us.
- Those who have a natural “night owl” tendancy – delaying school start times by even just one hour can significantly improve academic performance.

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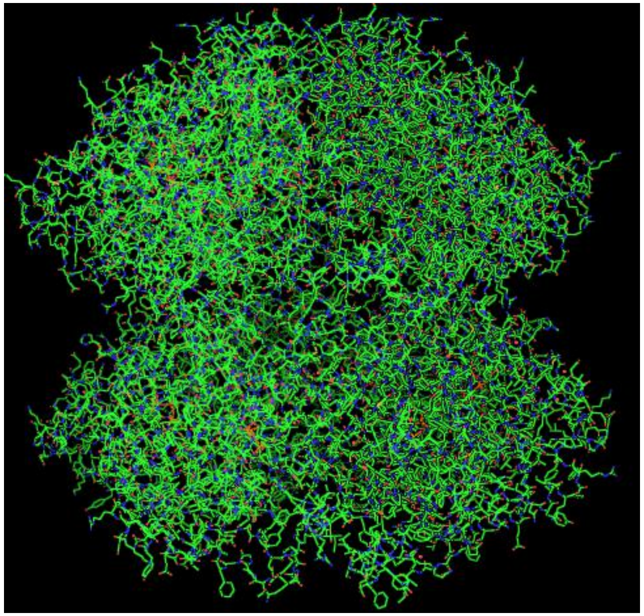
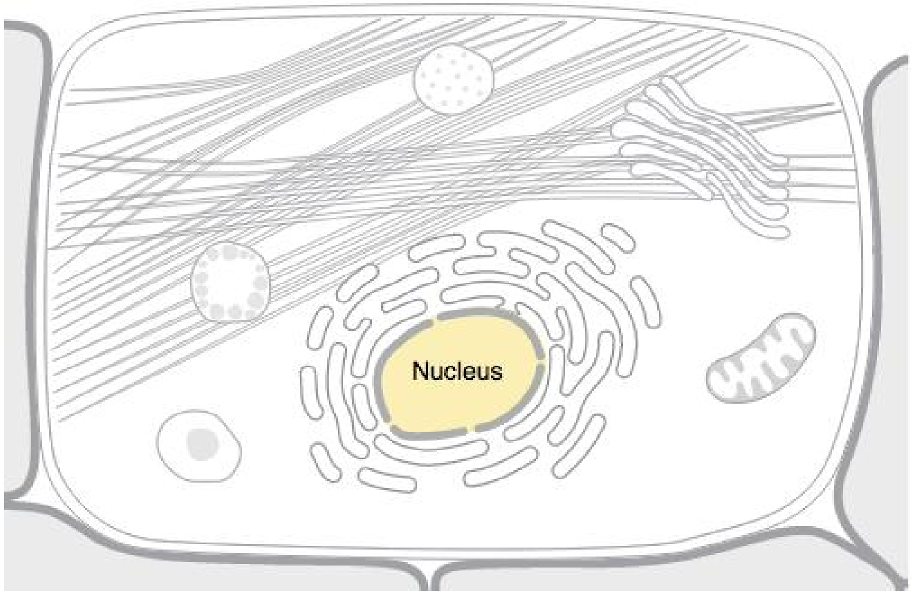
Biological Machines

Jeffrey Hall , Michael Rosbash and Michael Young discovery

PER, the protein encoded by period, accumulated during the night and was degraded during the day. Thus, PER protein levels oscillate over a 24-hour cycle, in synchrony with the circadian rhythm.

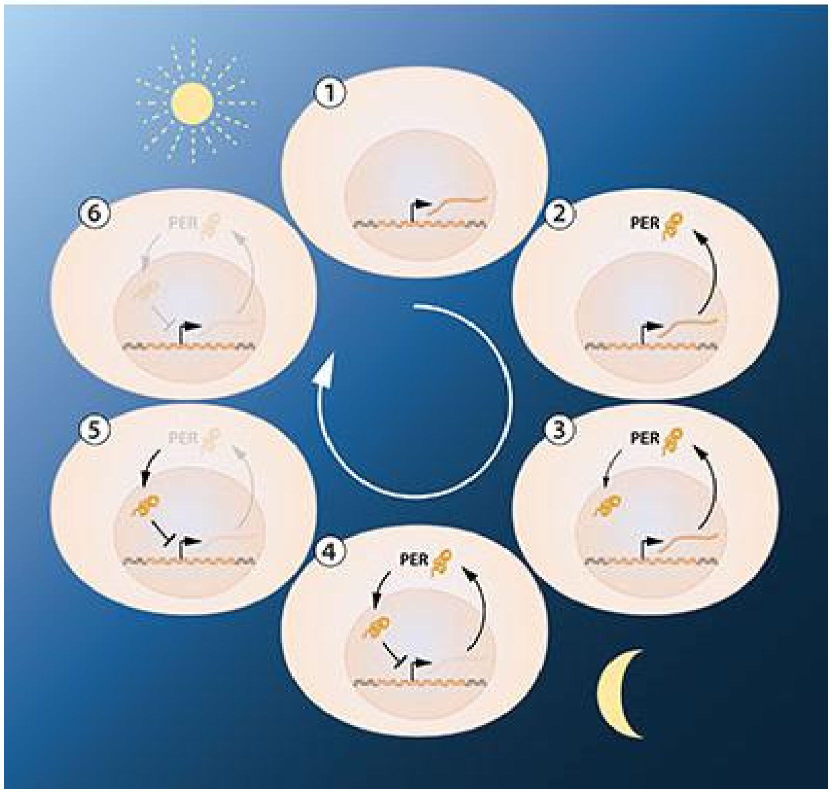


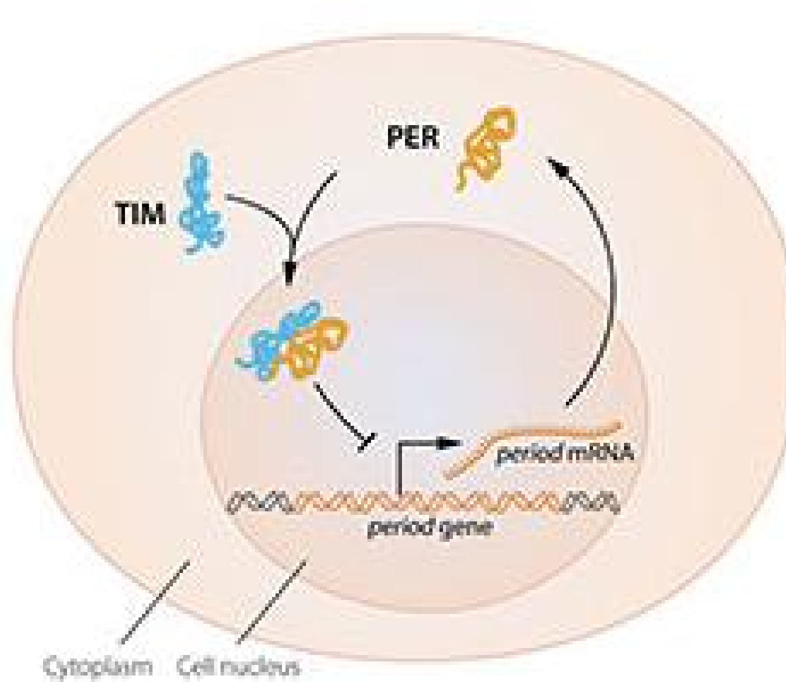


PER a protein having 1224 amino acids
They hypothesized that the PER protein blocked the activity of the period gene.

The biological cycle depends on the rhythmic formation and nuclear localization of the TIM-PER complex.

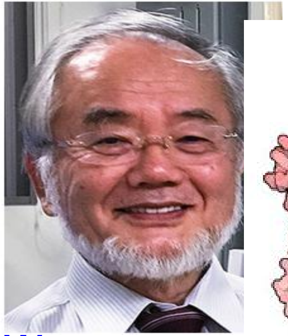
Light induces the degradation of TIM, which promotes elimination of PER.



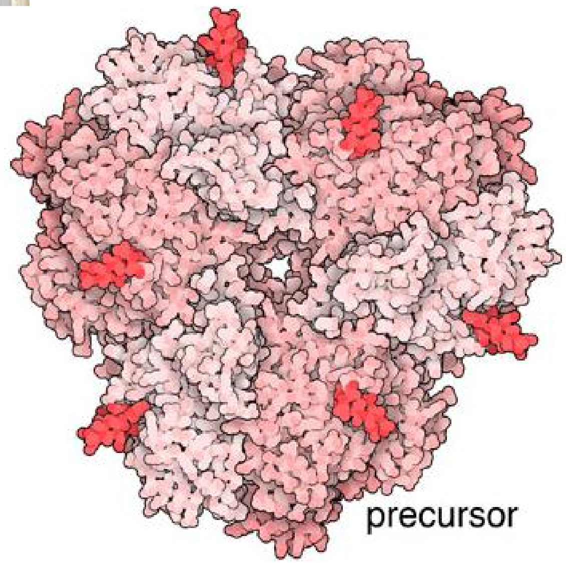


They reasoned that by an inhibitory feedback loop, PER protein could prevent its own synthesis and thereby regulate its own level in a continuous, cyclic rhythm.

The Nobel Prize in Physiology or Medicine 2016 Yoshinori Ohsumi



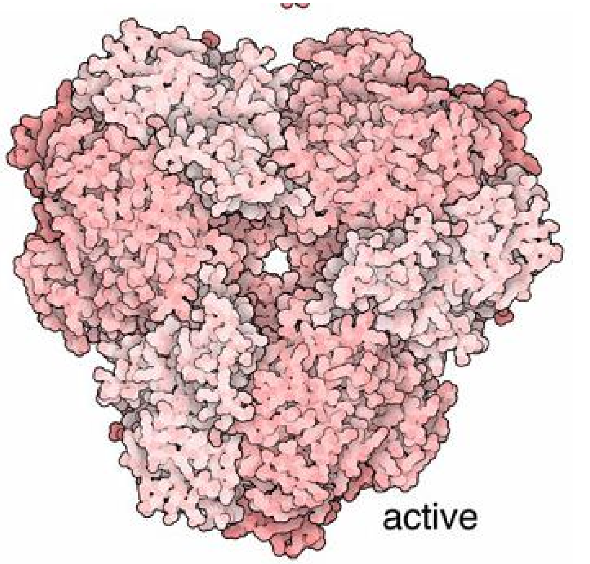
Aminopeptidase 1 and Autophagy



PDB entry 5jh9

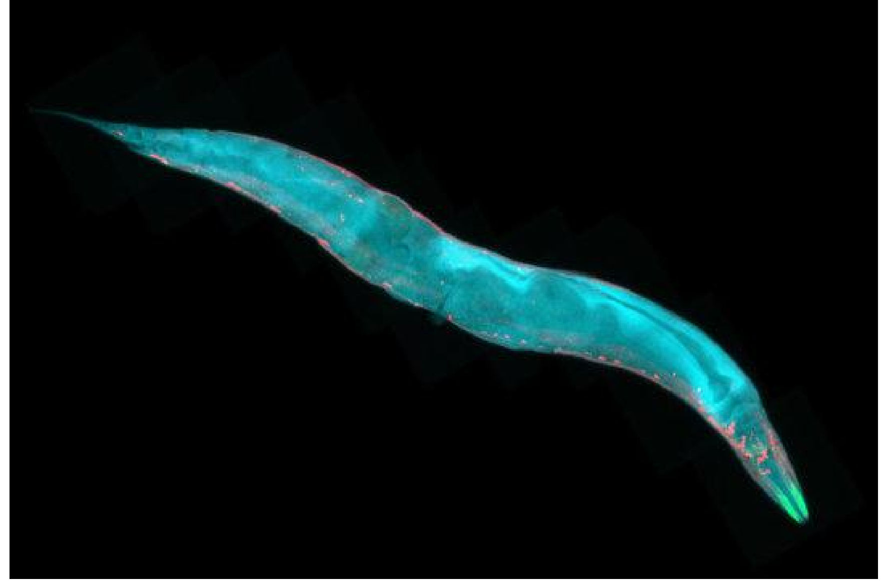
Cells are constantly changing, building new molecules when needed and breaking down others when they are finished with them.

The proteasome and exosome systems recycle biomolecules one at a time, but the cell also has a system for bulk recycling, termed autophagy. The name means “self-eating,” and that’s just what the cell does.



PDB entry 4r8f.

It packages up the waste and delivers it to its internal digestive system, lysosomes, where everything is broken down by a soup of digestive enzymes.



Researchers at the Institute of Molecular Biology (IMB) in Mainz, Germany said last month that – by studying a type of worm called C. elegans – they've made a breakthrough in understanding why humans age. They call the aging process a quirk of evolution

Their work involves identification of the genes belonging to a process called autophagy – from Greek words auto meaning self and phagy meaning devouring – a normal physiological process related to the destruction of damaged cells in the body

Biological Molecular Machines

Cells are not built in factories
They have to build themselves

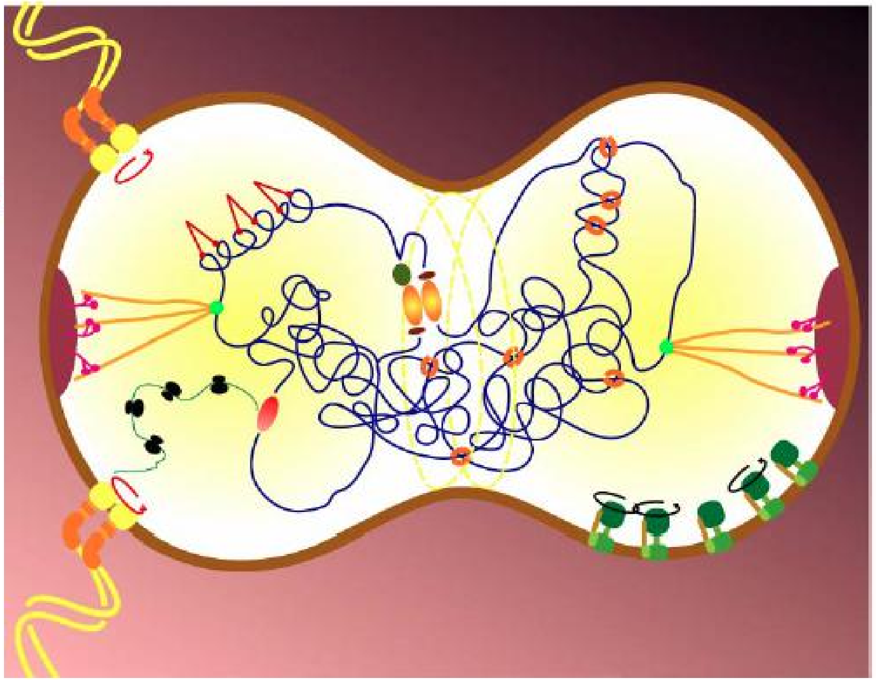
Lots of Jobs to Do:

- Getting food and fuel
- Eliminating waste
- Converting raw materials to useful stuff
- Building molecular machines
- Copying and protecting genetic information
- Repairing damage
- Dividing the cell
- Controlling and coordinating all these
- Etc.

Channels, pores

Metabolic pathways

Genetic machinery

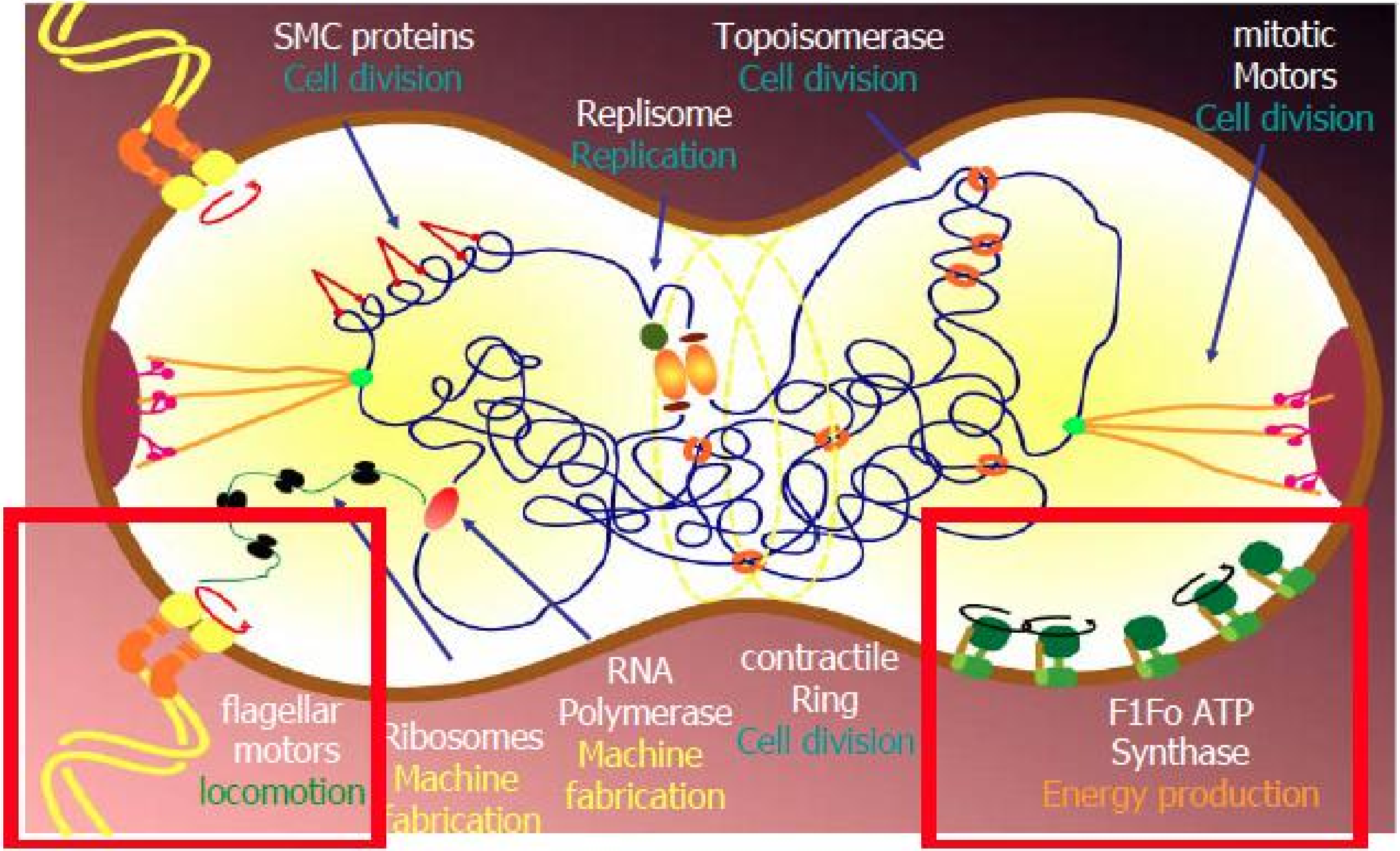


There is a machine (or system of machines) for every job

There is a system for making machines (central genetic machinery)

There is a system of coordination among the machines

Many jobs - many machines



A machine is an apparatus using mechanical power having several parts, each with a definite function and together performing a particular task.

A molecular machine, is “an assemblage of parts that transmit forces, motion, or energy from one to another in a predetermined manner”.

- Living organisms are made up of numerous biological machines which are more complex than artificially constructed machines.

- biological machines are necessary for performing life functions.

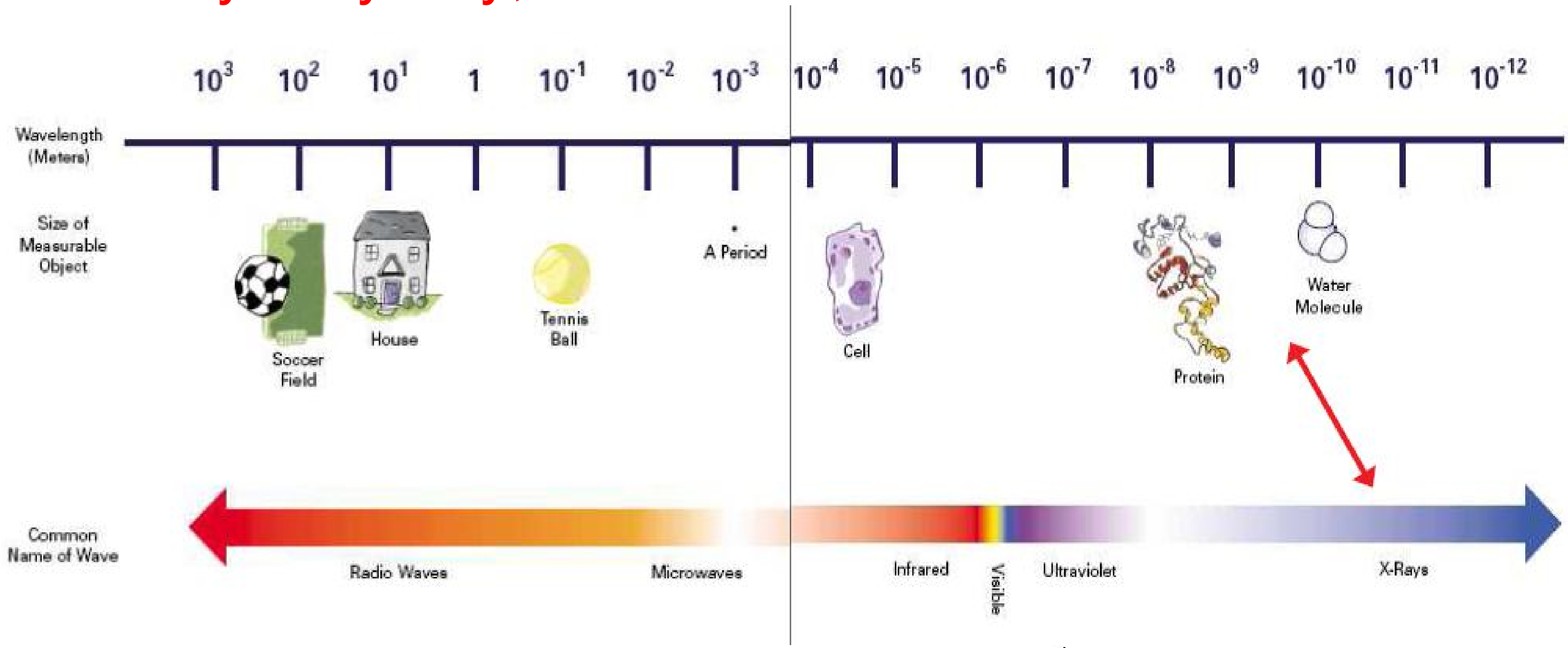
- Proteins that hydrolyze ATP perform mechanical work in the cells.

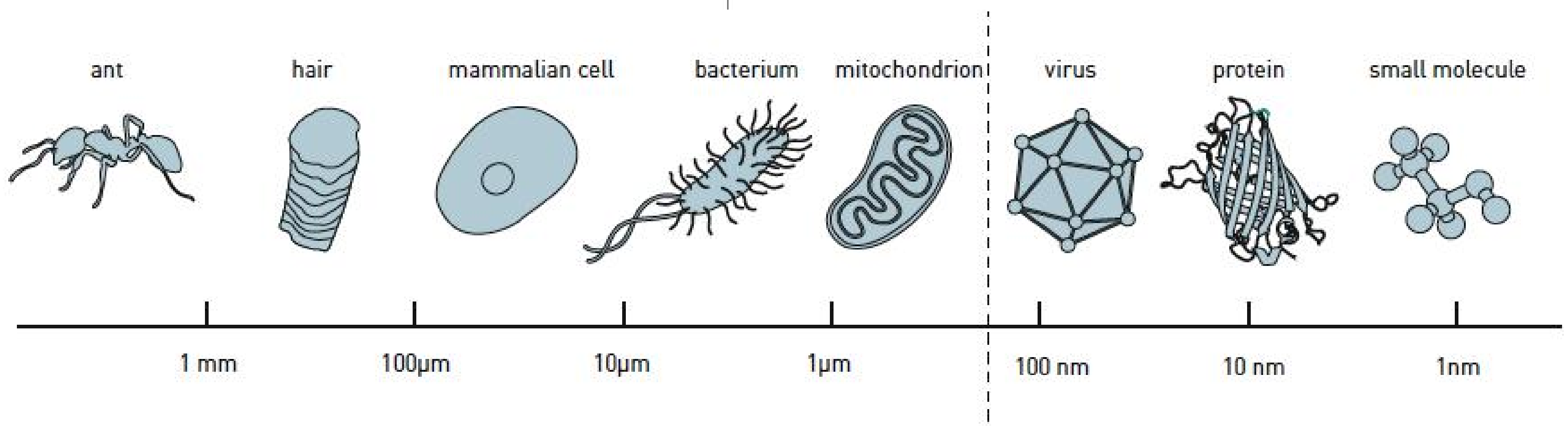
- ATP is analogous to the fuel required by engines to perform work.

- The details of life are finely calibrated.

Molecular machines are highly highly complex and we are just beginning to understand their inner workings, till date only a few have been studied sufficiently by biologists. ……. So we need great engineers

Main reason in failure of our not understanding the biological problems is because the cells, proteins, DNA are very very tiny,





Noble Prize 2017 in chemistry
For discovery of Cryo-Electron Microscopy

Jacques Dubochet University of Lausanne in Switzerland, Joachim Frank at Columbia University, and Richard Henderson at the MRC United Kingdom

The wavelength of electrons is much shorter than that of light, it can reveal much finer detail

high-resolution, 3D images to target cancer drugs and demystify the dengue, Chikungunya and Zika virus and many many more.

An example of Molecular machine: Hemoglobin

- Hemoglobin is found in the Red blood cells.

- Hemoglobin in the blood carries oxygen from the respiratory organs (lungs or gills) to the rest of the body (i.e. the tissues).

- Hemoglobin is the protein that makes blood red.

- It is composed of four protein chains, two alpha chains and two beta chains, each with a ring-like heme group containing an iron atom.

- Oxygen binds reversibly to these iron atoms and is transported through blood.

- "Hemoglobin is a remarkable molecular machine that uses motion and small structural changes to regulate its action."

- Hemoglobin structure has been explained by Max Perutz’s 18-year quest.

- Hemoglobin uses iron within its protein structure to carry oxygen from the lungs to the rest of the body through the blood.

- The breathing required a protein channel to open for O2 to access the heme.

- The coupled change of local and quaternary conformations between oxy and deoxy forms explained the cooperativity of O2 binding.

- Some organisms like snails and crabs, on the other hand, use copper to transport oxygen, so they truly have blue blood.

- Aside from oxygen transport, hemoglobin can bind and transport other molecules like nitric oxide and carbon monoxide.

- Nitric oxide affects the walls of blood vessels, causing them to relax. This in turn reduces the blood pressure.

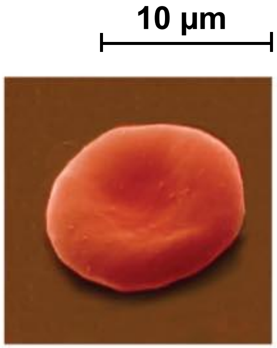
- Carbon monoxide, is a toxic gas. It readily replaces oxygen at the heme groups, forming stable complexes that are difficult to remove.

- This abuse of the heme groups blocks normal oxygen binding and transport, suffocating the surrounding cells.

Sickle-Cell Disease: A Simple Change in Primary Structure

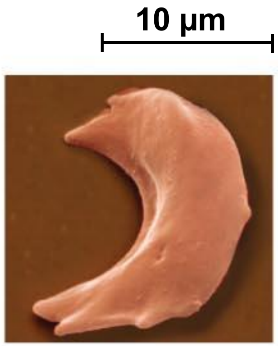
Red blood cell shape

Normal cells are full of individual hemoglobin molecules, each carrying oxygen.



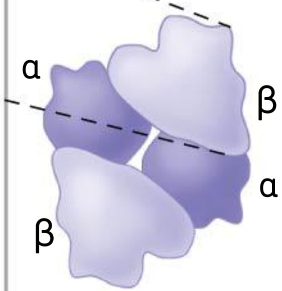
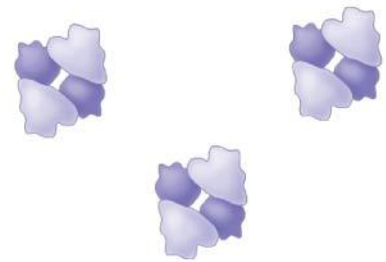
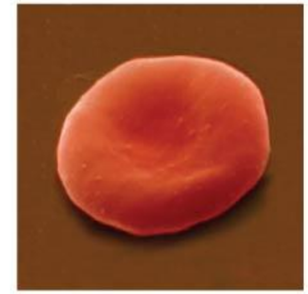
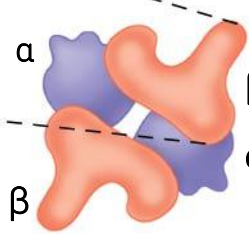
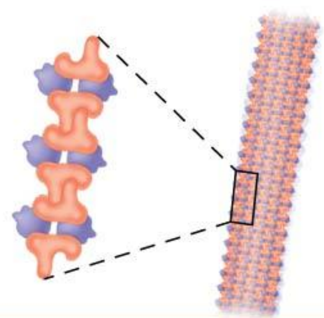
Red blood cell shape

Fibers of abnormal hemoglobin deform cell into sickle shape.



A slight change in primary structure can affect a protein's conformation and ability to function.

Sickle-cell disease, an inherited blood disorder, results from a single amino acid substitution in the protein hemoglobin, unable to transport oxygen

	Primary Structure	Secondary and Tertiary Structures	Quaternary Structure	Function	Red Blood Cell Shape
Normal	1 Val 2 His 3 Leu 4 Thr 5 Pro 6 Glu 7 Glu	 β subunit	Normal hemoglobin 	Molecules do not associate with one another; each carries oxygen. 	 5 μm
Sickle-cell	1 Val 2 His 3 Leu 4 Thr 5 Pro 6 Val 7 Glu	Exposed hydro-phobic region  β subunit	Sickle-cell hemoglobin 	Molecules crystallized into a fiber; capacity to carry oxygen is reduced. 	 5 μm

Artificial Blood

- Blood transfusions have saved countless lives.
- However, the need for matching blood type, the short life of stored blood, and the possibility of contamination are still major concerns.
- The main challenge is keeping the four protein chains of hemoglobin together, the four chains rapidly fall apart.
- To avoid this problem, novel hemoglobin molecules have been designed where two of the four chains are physically linked together. two additional glycine residues form a link between two of the chains, preventing their separation in solution.
- There are two basic approaches to constructing an oxygen therapeutic. The first is perfluorocarbons (PFC), chemical compounds which can carry and release oxygen.
- The second is haemoglobin derived from animals, or artificially via recombinant technology, or via stem cell production of red blood cells in vitro.

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