Some Answers to Question Set 1

Scales in biology and physics

These answers are not always complete, but they do indicate what are the important points. It is necessary to read and understand the papers. The lecture handouts are also helpful to understand what is important in the course.

Also standard biology and biochemistry textbooks can be helpful[1-3].

https://bionumbers.hms.harvard.edu/

Reminder:

- Copy and highlight (*e.g.* boldface or italics) the questions to your answer sheet.

- Give the sources of your answers. For example, if you find something on the web, give the link to the website. Give full reference to articles and books.

- Write your name and code of the course, your name, the question set, the name of the week's topic and date on each page!

- In calculations write out all units. This functions as a check that the calculations make sense.

- Write your answers using a suitable unit and with an appropriate number of significant digits. Not 0.00035mm/s ! Better to write 350nm/s !

- For liter write L rather than l since l and 1 (one) looks the same in most fonts.

- please send your answers as a ***pdf file***

- please specify references, i.e. specify where you found your answers

- please write your name in the file name

Questions Biophysics

1. How are DNA, RNA and proteins related to each other in an organism?

DNA – information storage, stable molecule, contains genes, regulatory information and other less explored functions. During cell division the DNA is *replicated*.

RNA – intermediate information storage, unstable molecule, whenever there is a need for a protein, an RNA copy of the corresponding gene is made by RNA-polymerase (*transcription*).

Proteins – the molecules that actually do the work in the body (enzymes, building material, transport, motors, detection, recognition…), proteins are made with the RNA as a template in the ribosomes (*translation*). Three bases in RNA form a codon that codes for one aminoacid, which is the building blocks of proteins.

The Central Dogma of Molecular Biology – The information flow is in the direction DNA -> RNA -> Proteins.

This is true in most cases. There are some exceptions, *e.g.* viruses that store their genome as RNA.

2. What are the relevant length scales in terms of DNA?

In genomics the relevant unit is “one base” or “one base pair”. Note that DNA has different conformations depending on its environment. B-DNA is prevalent under standard physiological conditions. It has a diameter of 2nm and a length of 0.34nm per basepair.

Each gene is roughly 1000 bases.

The human genome is about $3x10^9$ bases long organized in 23 chromosomes, the largest of which is roughly 300Mbp. There are two copies of each chromosome in each cell. The total length of the DNA in each cell is thus ~2m.

Genetic variations take place on various length scales. Single nucleotide polymorphisms refer to point mutations, *i.e.* changes in single base pairs. Structural variations are identified as important sources of genetic diversity. These are larger scale changes in the genome, spanning a wide range of size ranging from a few bases to millions of bases. For example, whole chunks of DNA are removed (deletions), displaced (translocations) or multiplied (copy number variations).

3. Give examples of relevant time scales in molecular biology? Steps per second for a motor protein? Replication speed? Cell division rate?

rate of replication 50 nucleotides / sec (eukaryotes) - many initiation sites

rate of replication 1000 nucleotides / sec (bacteria / prokaryotes)

rate of transcription ~ 100 nucleotides / sec; processivity ~ 1000bases.

rate of translation < 20 amino acids / sec (bacteria / prokaryotes)

actin/myosin: 0.1-60 um/s (variation between different classes of myosin. The group in Kalmar works with fast myosin II from skeletal muscle with speed ca 10 μm/s.

on the order of 10^3 steps / sec

kinesin/microtubules: most of them 1 um/s but there are slower ones as well.

dynein/microtubules: 1 - 7 um/s

cell division - varies a lot... nerve, muscle, liver cells normally not; in total 25 million cell division every second in the human body

bacterial cell division takes about 30 minutes

generally, days to years to never for human cells

4. What size ranges do proteins span?

The size of proteins varies widely from a few nm to 50nm.

5. How large are bacteria? Human cells? Viruses?

Bacteria are 1-10μm and lack nucleus (*prokaryotes*). Human cells belong to the *eukaryotes,* which are larger, 10μm-100μm, and have a nucleus where the DNA is stored.

Nerve cells can be exceptionally long, a meter or so.

Viruses - 50..500nm.

6. What techniques from physics and engineering can be used to probe biology at the relevant scales? Think for example about optics, microtechnology, acoustics, electrostatics, magnetism, particle beams.

Acoustics – ultrasound imaging, acoustophoresis

Wavelength of electrons (10keV) --- ~10 pm

Wavelength of X-rays --- < nm

Wavelength of visible light --- ~ 500nm (green)

Resolution of TEM/SEM – atomic

Resolution of STM/AFM -- atomic

Resolution of SNOM – ~10 nm

Resolution of diffraction limited optical microscopy – typically ~□/2 or 200nm

Microfabrication (UV-lithography etc) -- ~μm

Nanofabrication (EBL, FIB, NIL etc) -- ~10nm

7. (*) Assume a 1μm sized spherical bacterial spore suspended in water at room temperature. What time would it take for this spore on average to diffuse distances of 1μm and 1m, respectively? Same question for a typical protein. Same question for a typical virus.

Diffusion in x, y, z directions is independent. To diffuse a given distance takes shorter time if we do not care about the direction. Therefore, for three-dimensional diffusion we have

$$\left\langle r^2 \right\rangle = \left\langle x^2 \right\rangle + \left\langle y^2 \right\rangle + \left\langle z^2 \right\rangle = 3 \cdot 2Dt = 6Dt$$

Stokes-Einstein relation gives (with f = the viscous drag; $F_{drag} = f\,v$)

$$D = \frac{k_B T}{f} = \frac{k_B T}{6\pi\eta a}$$

$$\Rightarrow t = \frac{\left\langle r^2 \right\rangle}{6D} = \frac{\left\langle r^2 \right\rangle 6\pi\eta a}{6k_B T} = \pi \frac{\left\langle r^2 \right\rangle \eta a}{k_B T}$$

With typical numbers for water at 25°C we have

$$k_B T = 4 \cdot 10^{-21} J [= kgm^2 s^{-2}]$$
$$\eta = 1 \cdot 10^{-3} kgm^{-1} s^{-1}$$
$$\Rightarrow t = \pi \frac{\langle r^2 \rangle \eta a}{k_B T} = \pi \frac{1 \cdot 10^{-3} kgm^{-1} s^{-1} 10^{-6} m 1m^2}{4 \cdot 10^{-21} kgm^2 s^{-2}} \left(\frac{\langle r^2 \rangle}{1m^2} \right) \left(\frac{a}{1\mu m} \right)$$
$$\Rightarrow t = 785 \cdot 10^9 s \left(\frac{\langle r^2 \rangle}{1m^2} \right) \left(\frac{a}{1\mu m} \right) = 25000 years \left(\frac{\langle r^2 \rangle}{1m^2} \right) \left(\frac{a}{1\mu m} \right) = 785 ms \left(\frac{\langle r^2 \rangle}{1\mu m^2} \right) \left(\frac{a}{1\mu m} \right)$$

The results are summarized in the table below for proteins, virus and bacteria. It is clear that diffusion is effective for sample transport only at small distances on the order of a μm.

KEY: (1) WRITE OUT ALL UNITS!

(2) CHECK YOUR RESULTS WITH DIMENSIONAL ANALSYSIS. IF THE UNITS IN THE ANSWER DO NOT MAKE SENSE, YOU KNOW THAT YOU HAVE DONE SOMETHING WRONG IN YOUR CALCULATIONS.

(3) WHEN COMPARING DIFFERENT SIZE SCALES IT IS VERY USEFUL TO NORMALIZE THE KEY PARAMETERS AS ABOVE. FOR OUR CASE IT MAKES IT EASY TO SEE WHAT RESULTS WE OBTAIN FOR DIFFERENT VALUES OF *r* AND *a*.

	Radius	t (r~1μm)	t (r~1m)
Proteins	5nm	4ms	125 years
Virus	50nm	39ms	1250 years
Bacteria	500nm	393ms	12500 years

8. (**) A dolphin swims in the sea at a leisurely speed of 2m per second. For this problem, assume laminar flow conditions. Once it stops moving it fins how far does it coast? How long does it have to wait until its speed has fallen to 10% of the initial speed? Repeat the calculations for a bacterium like *E. coli,* which typically swims with a speed of 20μm s^{-1} while rotating its flagella.

For the sake of simplicity, assume both the dolphin and the *E. coli* are spheres with radii 1m and 1μm as well as that their density is that of water.

Making the gross simplification that Stokes drag can be used in both cases we now have (Newton 2nd & Stokes drag):

$$ma = \sum_i F_i = F_{drag} = -fv = -6\pi\eta r v$$

$$\Leftrightarrow \frac{dv}{dt} = -\frac{6\pi\eta r}{m} v$$

$$\Leftrightarrow \frac{dv}{v} = -\frac{6\pi\eta r}{m} dt$$

$$\Rightarrow \int_0^t \frac{dv}{v} = -\int_0^t \frac{6\pi\eta r}{m} dt$$

$$\Leftrightarrow \ln v(t) - \ln v_0 = -\frac{6\pi\eta r}{m} t$$

$$\Rightarrow t = \tau \ln \frac{v_0}{v(t)}, \tau = \frac{m}{6\pi\eta r}$$

$$\Rightarrow v(t) = v_0 e^{-t/\tau}$$

The time to reach a specified velocity is thus given by

$$t_{final} = \tau \ln \frac{v_0}{v_{final}}$$

Typical numerical values that apply for *E. coli*

$$r = 10^{-6} m$$

$$\rho = 1000 kgm^{-3}$$

$$\eta = 10^{-3} kgm^{-1}s^{-1}$$

$$\Rightarrow \tau = \frac{m}{6\pi\eta r} = \frac{\frac{4\pi}{3}\rho r^3}{6\pi\eta r} = \frac{2\rho r^2}{9\eta} = \frac{2 \cdot 1000 kgm^{-3}(10^{-6} m)^2}{9 \cdot 10^{-3} kgm^{-1}s^{-1}} \left(\frac{r}{1\mu m}\right)^2 = \left(\frac{r}{1\mu m}\right)^2 222 \cdot 10^{-9} s$$

For bacterium the time to go from v_0=20mm/s to v_{final}=2μm/s is thus

$$t_{final} = \tau \ln \frac{v_0}{v_{final}} = 222 \cdot 10^{-9} s \ln \frac{20\mu m/s}{2\mu m/s} = 0.5\mu s$$

and for the dolphin

$$t_{final} = \tau \ln \frac{v_0}{v_{final}} = \left(\frac{1m}{1\mu m}\right)^2 222 \cdot 10^{-9} s \ln 10 = 6 \, days$$

To calculate the distance traveled during the slow down phase we integrate *v(t)dt* from *t=0* to t_{final} at the final speed.

$$s(t=\infty)=\int_{t_0=0}^{t=\infty} v(t)\,dt=\int_{t_0=0}^{t=\infty} v_0 e^{-t/\tau}dt=\left[-v_0\tau e^{-t/\tau}\right]_{t_0=0}^{t=\infty},\ \tau=\frac{m}{6\pi\eta r}$$

$$s(t=\infty)=v_0\tau=1\cdot10^{-6}ms^{-1}222\cdot10^{-9}s\left(\frac{r}{1\mu m}\right)^2\left(\frac{v_0}{1\mu m s^{-1}}\right)$$

$$s(t=\infty)=222\cdot10^{-15}m\left(\frac{r}{1\mu m}\right)^2\left(\frac{v_0}{1\mu m s^{-1}}\right)$$

One atom is 1Ångström = 10^{-10}m. In other words, the bacteria stop immediately. They stop within one millionth of their total length. If one would scale up this situation to us, we would stop within a micron.

For a more correct calculation for the dolphin, since the Reynolds number is >1000 and the flow is turbulent, i.e. the inertial effects dominate over the viscous, another expression for the drag must be used

$$F_{drag}=\frac{1}{2}\rho C_{drag}Av^2$$

where ρ=1000kg m^{-3} is the density of the water, C_{drag} ~ 1 is a drag coefficient and $A=\pi R^2$ is the cross-sectional area of the dolphin.

Critical thinking & The web

9. How many papers has JO Tegenfeldt authored? How many of these where cited by Tegenfeldt's former postdoc W Reisner? [Use ISI Web of Science]

Web of Science gives 85 hits (for "tegenfeldt jo"). The included journals differ between different databases. Some conference contributions and review papers are listed in Web of Science and not listed among the publications on the Tegenfeldt website. The latest papers may not always be listed.

Searching for just "Tegenfeldt" gives 395 papers. A closer look reveals that the earliest papers go back to 1966 and does not quite fit in the profile of Jonas Tegenfeldt. There must be more than one Tegenfeldt out there!

To find papers coauthored by Reisner and Tegenfeldt, run a search on “Reisner W” and combine the searches using AND in Search History.

Use "Cited Reference Search" and choose "Tegenfeldt jo". The result should eventually be a list of roughly 2500 publications that cite Tegenfeldt.

Then look into "Search History" where you can use boolean operations between search results! You should find that 29 of Walter Reisner's papers cite a paper coauthored by Tegenfeldt.

10. Select the five most important papers of Tegenfeldt’s!

Typically the most cited papers are the most important, but one could also argue that other criteria are more adequate:

- number of patents based on ideas presented in a paper

- number of people helped

- amount of money generated

- actual contents

- novelty

etc etc.

To see which papers are most cited, sort by “Times Cited” or press “Create citation report”.

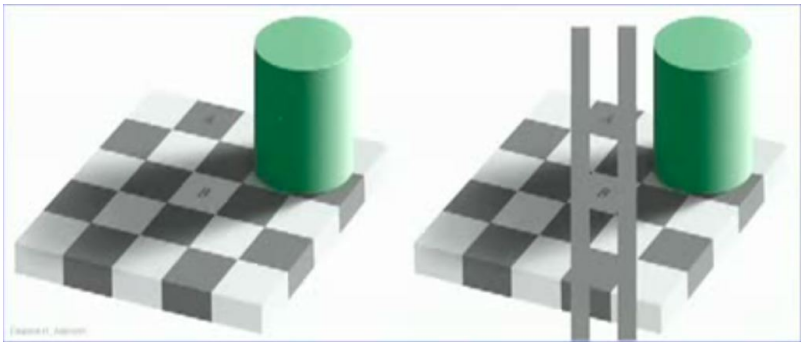
11. Tegenfeldt is the coauthor of a fair number of papers, but how many of them has he actually made a significant contribution to?

Typically the first author has the main responsibility for the paper and the last author is the senior researcher who started and/or ran the project, had the idea etc. However, sometimes the authors are listed alphabetically. Sometimes, the last author is the formal head of the lab or the one who is the formal advisor to the first author. It is difficult to say, and customs vary across disciplines. The best is to speak to the people involved. Any knowledge that you might have will quickly reveal who is in charge of the science of the project.

Some journals give clear information about the contributions of each author in terms of e.g. basic idea of the project, measurements, data analysis, provision of reagents,

writing of the manuscript. Note that simply providing money does not count, although to get the money in the first place you normally have to come up with a good project idea.

12. Seeking information on the web may appear to be easy, but how reliable are the answers you get from the web? Can you trust the web? ... your eyes?



Information and data given through ANY media carries a certain uncertainty. You can never be completely sure about what you read or even see with your own eyes.

13. There is still hope, though. It is possible to gain knowledge on the web, but you need to be vigilant! Give a few rules of thumb as to how to behave.

- Double-check – read multiple sources. Do they agree?

- Read established websites, journals and books. Going through a university library (website) ensures that at least some filtering has been done.

- Is it easy to find the source of the information, who is behind?

- Go to websites of the leading research groups in the field.

- Read the references.

- THINK! Does it make sense?

- Again, critical thinking involves being *critical* and *thinking*; we cannot just trust a source without understanding the reasoning behind the message. Conversely, we cannot just distrust another source without understanding why the reasoning does not make sense. Of course, from a practical point of view it might be difficult to always check what you read this way, but if something is important, one should set aside some time to critically assess the validity.

Could there be an underlying agenda?

- economic interests (Who pays for the website? Who would gain from the view that is propagated in the website? Have the researchers started a company on the idea that is presented in the paper?)

- religious interests (Creation *vs* Darwin)

- political interests (government supporters may block out data that supports the Kyoto protocol; another government may play down the risks of chemicals that can be used to sedate hostages and kidnappers…)

Note that deceit is much more common than outright lying. Often crucial information is left out that leaves the reader with the desired impression. One classical example is "Since a week, Mr NN has not drunk a drop of whiskey." Nothing is said about any alcohol problems, but reading this line of text it is easy to get the impression that Mr NN has had drinking problems.

Be aware that daily newspapers are not reliable sources of information and analyses. In the education of journalists statistics and scientific method are not emphasized. The significance of single events is often overstated and things are seldom put in perspective. Sources and raw data are often not shared making reassessment of stated conclusions difficult. Quality may vary and there does exist good journalism; nevertheless mass media does NOT reach the standards of the scientific literature.

A few questions that one can ask while reading on the web (and in other sources as well):

- Have the experiments been reproduced by other groups?

- Does it make sense? Is the story self-consistent?

- Are there references (to the scientific literature)? Do the references actually exist? Do they make sense? Are the references representative of the state of the field, or have they been carefully selected in a biased manner?

- If a specific point of view is propagated, are alternative views discussed as well?

- Are the conclusions consistent with the presented data?

Age of the document: Try to find the latest paper to obtain the most up to date interpretation. In addition, it is important to check the original paper. Many times

well-known papers are cited as standard references. However, the author might not have read the paper and might have misunderstood the contents of the paper.

Note that although you see several warning signs, it does not necessarily mean that a statement is wrong. You need not only know when a statement is false. You also need to understand why.

General rules of thumbs for identifying bad arguments and bad science can be found here:

https://en.wikipedia.org/wiki/List_of_fallacies

http://www.compoundchem.com/2014/04/02/a-rough-guide-to-spotting-bad-science/

14. Once you find the information on the web, explain how you can use it in your own work in order to comply without being considered to plagiarize?

Cite the sources; rewrite the text. Be open about the fact that it is not your own current work.

If you want to cite the exact text, use “citation marks”.

The key point is that you must not pretend that you are the source of the material.

15. Assume you are given an assignment to write a report. You realize that you already have written a similar report previously. May you simply copy sections from your original report?

This is not recommended. For scientific journals the authors normally often surrender the copyright to the publisher. As a student the actual writing is a good exercise and typically going through an old text, allows you to improve it significantly even if you were happy with it initially.

References

[1] Lubert Stryer, *Biochemistry*, 7 ed. (W. H. Freeman and Co., New York, 2010).

[2] Neil A. Campbell, *Biology*, 8 ed. (The Benjamin/Cummings Publishing Company, Inc., Menlo Park, 2009).

[3] Carl Brändén and John Tooze, *Introduction to protein structure*. (Garland Publishing, Inc., New York, 1991).

[4] Marc J. Madou, *Fundamentals of Microfabrication: the science of miniaturization*, (CRC Press LLC).