Oxygen in the blood

I. SIMPLE MODEL OF HEMOGLOBIN

Haemoglobin is a large molecule with 4 sites where molecules like O_2, CO_2 and CO can bind with binding energies $\varepsilon_{O_2} \approx 2\varepsilon_{CO_2} \approx 0.8\varepsilon_{CO}$. Let $s_i = 1$ when site i is occupied and $s_i = 0$ when site i is empty. We assume that each of the adorption positions on the hemoglobin molecule are equivalent and indistinguishable.

(a) What is the total binding energy of the oxy-haemoglobin (o-Hgb) system?

The hemoglobin molecule can exchange O_2 with reservoirs (lung and tissue) where there is a certain temperature and concentration of O_2 fixing the chemical potential μ of O_2 in that reservoir.

(b) Write down an expression for Gibbs sum for O_2 in a hemoglobin molecule. Explain the symbols and the limits of the sums.

(c) What is the probability, $P(1)$, that one, and only one, O_2 molecule is adsorbed onto a hemoglobin molecule?

(d) What is the probability, $P(4)$, that exactly 4 O_2 molecules are adsorbed on a hemoglobin molecule?

(e) Plot $P(i)$, $i \in [1, 4]$ as a function of $\lambda = \exp(\mu/kT)$. Choose the parameters you find useful.

II. PAULING'S MODEL OF HEMOGLOBIN

In addition to the site binding energy in the simple model Pauling included a cooperative effect that can be expressed as a bond with energy δ between occupied sites. The total binding energy of the oxy-haemoglobin (o-Hgb) system can be expressed:

$$E = \varepsilon \sum_{i=1}^{4} s_i + \frac{\delta}{2} \sum_{i=1}^{4} \sum_{j \neq i} s_i s_j \tag{1}$$

(f) Write down an expression for Gibbs sum.

(g) Plot $P(i)$, $i \in [1, 4]$ of the Pauling model as a function of $\lambda = \exp(\mu/kT)$.

III. OXYGEN TRANSPORT IN THE BODY

Oxygen in the air meets the human blood in our lungs. The diffusive flow of oxygen from the air in the lungs to the blood is driven by a difference in chemical potential

$$\Delta\mu = \mu_{air} - \mu_0 = kT \ln\left(\frac{P_{air}}{P_0}\right),$$

where P_{air} is the partial pressure of O_2 in the air and μ_0 is the chemical potential of oxygen in the blood when leaving the lungs.

- The partial pressure of O_2 in the blood, P_0, is thus not a real pressure, but a practical unit related to the chemical potential of the oxygen in the blood.

- We will assume that $\Delta\mu$ is constant irrespective of P_{air}. The blood contains haemoglobin (Hgb) which has a large capacity to store oxygen.

- We will assume that in the lungs the haemoglobin is in chemical equilibrium with the blood. Therefore the amount of oxygen stored in each Hgb molecule, $\langle N \rangle$, is a function of the chemical potential of oxygen, P/P_0: $\langle N_{P/P_0} \rangle = f(P/P_0)$.

- As blood gets transported from the lungs we assume that no oxygen is lost from the haemoglobin until it is delivered to tissue somewhere in the body (muscles, inner organs, brain and heart...).

- The amount of oxygen transported to the tissue per unit volume blood is thus

$$c_{O_2} = \langle N \rangle c_{Hgb}.$$

- When the blood reaches the capillaries in the tissue we assume that the Hgb delivers oxygen to the tissue until Hgb is in equilibrium with the tissue.

(h) Show that the Gibbs factor for one single binding site occupied can be written as

$$x = \exp\left(-\frac{\varepsilon - \mu}{kT}\right) = \frac{P}{P_0}\exp\left(-\frac{\varepsilon - \mu_0}{kT}\right) \tag{2}$$

(i) Calculate the partition function, probabilities for occupation numbers $N=0$ to 4 and show that the the mean occupation number is:

$$\langle N_{P/P_0} \rangle = \frac{x + 2x^2 y + 3x^3 y^3 + 4x^4 y^6}{1 + x + x^2 y + x^3 y^3 + x^4 y^6}, \tag{3}$$

where $x = \exp(-(\varepsilon - \mu)/kT)$, which is a function of P/P_0, and $y = \exp(-\delta/kT)$

(j) Use the data in appendix to find reasonable values for the parameters $(\varepsilon - \mu_0)/kT$ and δ/kT. Hints: Plot as function of P/P_0 and use the initial values $\delta = 0$ and $(\varepsilon - \mu_0)/kT = 1$. Explain why these are reasonable initial guesses. If you have skipped the statistical derivation, you can use Eq. (3) directly.

(k) Find an expression for the amount of oxygen delivered to the tissue per unit volume of blood when the concentration of hemoglobin in the blood is c_{Hgb}.

(l) Normal oxygen concentration in peripheral tissue (muscles at rest, brain, liver...) is $P_t/P_0 = 0.4$ where P_0 is taken to be the partial pressure of oxygen in the lungs at sea level. Hard-working muscles can have concentration levels as low as $P_t/P_0 = 0.15$.

Plot Δc_{O_2} as a function of relevant parameters and explain what can be learnt about oxygen uptake, transport and release.

(m) Determine (from diffusive equilibrium) oxygenation of Hgb in the lungs as function of altitude. Plot the amount of oxygen delivered to muscles at rest $(P_t/P_0(z = 0) = 0.4)$ as function of altitude. Can tissue be in a resting state above 8000 m? (This is the so-called death zone. https://en.wikipedia.org/wiki/Death_zone. Do not discuss the general observations of the death zone, but discuss your model results.)

(n) Assume that genetic engineering has made it possible to produce penta-Hgb: a haemoglobin with 5 sites that have the same binding and cooperative energies as in equation (**??**) where the sums go to 5 (instead of 4). Add a fifth site to you Hgb model and compare penta-Hgb to normal Hgb.

Study the effect of 1) increasing the (normal, 4 site) haemoglobin concentration in blood by 25% and 2) increasing the number of binding sites in each haemoglobin molecule to 5. Which method of blood doping is better suited for the body to function in the death zone?

Appendix A: Data

Experimental data for oxygen uptake in Haemoglobin. P0 is the partial pressure of oxygen in blood at sea level.

% P/P0	<N> per Hgb
9.7341396e-01	3.8486807e+00
7.5003238e-01	3.7113320e+00
6.7355438e-01	3.6082383e+00
5.9560115e-01	3.4707610e+00
5.3468901e-01	3.2902720e+00

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4.8731507e-01    3.0667714e+00
4.3731293e-01    2.8002877e+00
3.8638122e-01    2.4736220e+00
3.5197545e-01    2.1383283e+00
3.1576518e-01    1.8030488e+00
2.8331207e-01    1.4935677e+00
2.5424215e-01    1.2270841e+00
2.2816359e-01    9.6919984e-01
2.0482930e-01    7.8871090e-01
1.8110994e-01    6.3403465e-01
1.5058577e-01    4.1061976e-01
1.0912061e-01    2.3033080e-01
7.5554339e-02    1.3607942e-01
4.0958982e-02    6.7855029e-02
2.3249914e-02    2.5386201e-02
1.4468577e-02    1.7229557e-02
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