Lecture of November 26: Chapter 14, *in vivo* Biology, Lattice Model of Crowding and Osmosis

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Math Preamble: the Stirling approximation

In Physics, the Stirling approximation (SA) is usually written

$$lnN! \sim NlnN - N,$$

where N is a really large integer.

A more exact version is

$$N! \sim N^N e^{-N}(2\pi N)^{1/2}, \qquad (5.70)$$

Three IMPORTANT POINTS:

1. In general, when using the SA to derive a mathematical relation, the whole (5.70) should be used
2. However, the book often uses $N! \sim N^N$, which is not completely correct, but can lead to the correct relation.
3. It its recommended that you use the approximation $N! \sim N^N$ near or at the last step of a derivation, and as a ratio, say $\frac{(N+K+r)!}{(N+K)!} \sim (N+K)^r, N, K \gg r$

Crowding Effect on Binding

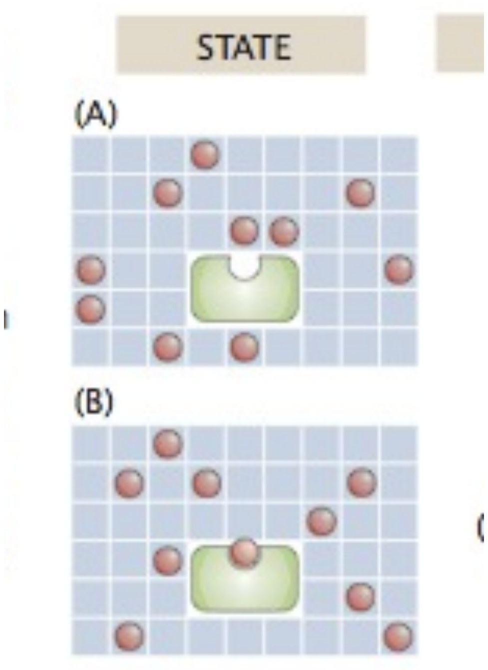


Figure 6.4 Binding with **no crowding**

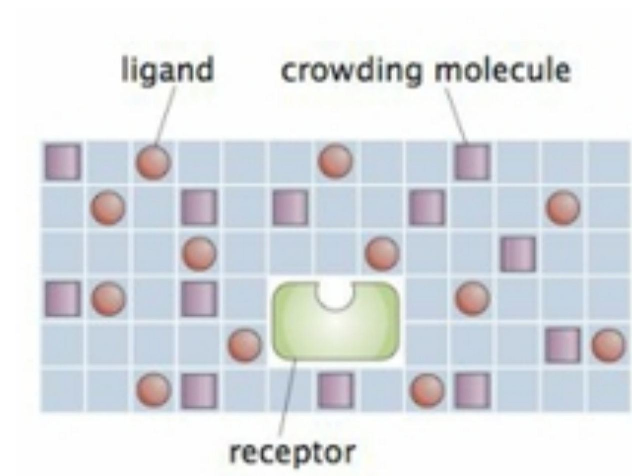


Figure 14.9 Binding with crowding Molecules

Binding without Crowding

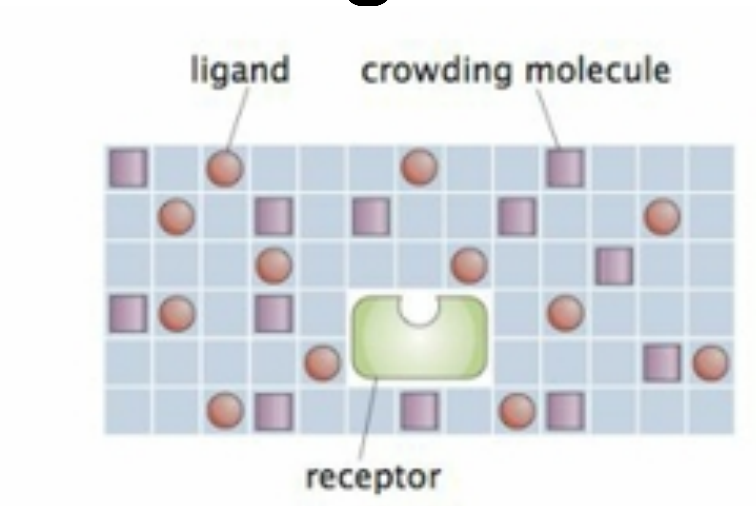
$$Z(L,\Omega) = e^{-\beta L \varepsilon_{sol}} \frac{\Omega!}{L!(\Omega - L)!} + e^{-\beta \varepsilon_b} e^{-\beta (L-1)\varepsilon_{sol}} \frac{\Omega!}{(L-1)![\Omega - (L-1)]!}. \tag{6.14}$$

$$p_{bound} = \frac{e^{-\beta \varepsilon_b} \frac{\Omega^{L-1}}{(L-1)!} e^{-\beta (L-1)\varepsilon_{sol}}}{\frac{\Omega^L}{L!} e^{-\beta L \varepsilon_{sol}} + e^{-\beta \varepsilon_b} \frac{\Omega^{L-1}}{(L-1)!} e^{-\beta (L-1)\varepsilon_{sol}}}. \tag{6.17}$$

$$p_{bound} = \frac{(L/\Omega) e^{-\beta \Delta \varepsilon}}{1 + (L/\Omega) e^{-\beta \Delta \varepsilon}}, \tag{6.18}$$

Figure 6.4 Binding with **no crowding**

Crowding Effect on Binding: Ligand and Crowding Molecule are the same size



- We begin by calculating the partition function $Z = \sum_E g(E) e^{-\beta E}$
- $g(E)$ is the multiplicity (number of microstates) of states with energy E

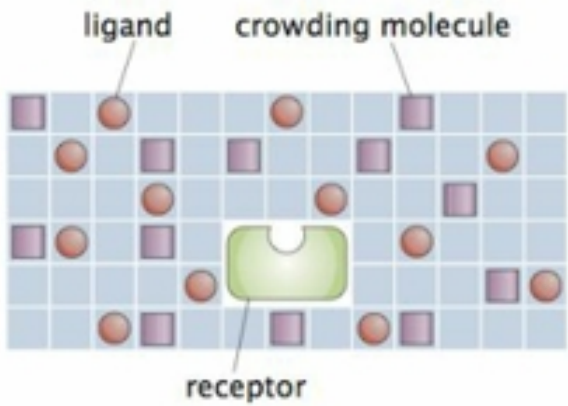
Definition:

- Ω is the number of lattice
- L is the number of ligands
- C is the number of crowding molecules

The multiplicity is the a function of Ω, L and C

$$g(\Omega, L, C) = \frac{\Omega!}{L!\,C!\,(\Omega - L - C)!}$$

Crowding Effect on Binding: Ligand and Crowding Molecule are the same size



all L **ligands** on lattice

$$Z = g(\Omega, L, C)e^{-\beta L \varepsilon_L^{sol}} e^{-\beta C \varepsilon_C^{sol}}$$

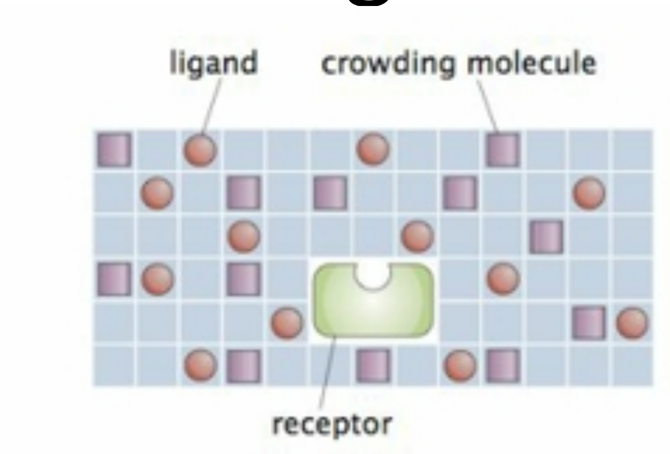
$$+g(\Omega, L-1, C)e^{-\beta(L-1)\varepsilon_L^{sol}} e^{-\beta C \varepsilon_C^{sol}} e^{-\beta \varepsilon_b}$$

$L - 1$ **ligands** on lattice, 1 **bound ligand**

All C **crowders** on lattice

$$g(\Omega, L-1, C) = \frac{\Omega!}{(L-1)!\, C!\, (\Omega - L - C + 1)!}$$

Crowding Effect on Binding: Ligand and Crowding Molecule are the same size

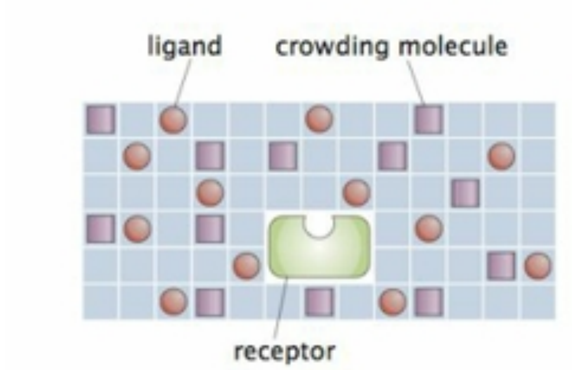


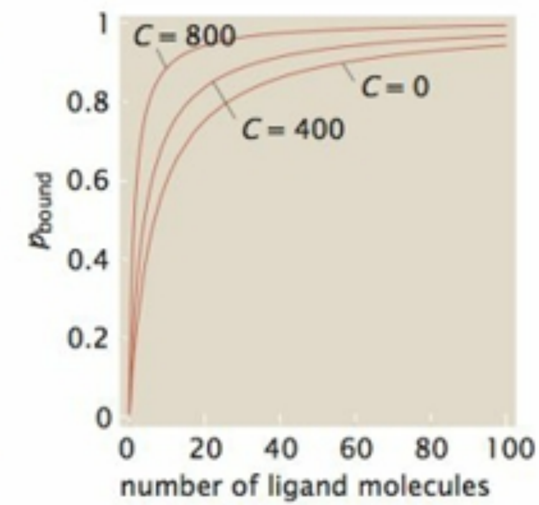
$$P_{bound} = \frac{1}{1 + \frac{g(\Omega, L, C)}{g(\Omega, L-1, C)} e^{\beta(\varepsilon_b - \varepsilon_L^{sol})}}$$

Assume Ω, L and C are large

$$\frac{g(\Omega,L,C)}{g(\Omega,L-1,C)} = \frac{(L-1)!(\Omega-L-C+1)!}{L!(\Omega-L-C)!} = \frac{\Omega-L-C}{L}$$

Crowding Effect on Binding: Ligand and Crowding Molecule are the same size





$$P_{bound} = \frac{1}{1 + \frac{\Omega - L - C}{L} e^{\beta \Delta \varepsilon}}$$

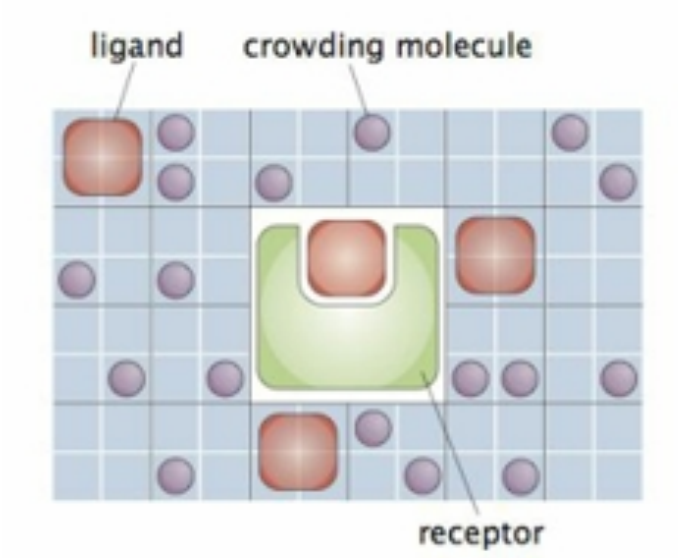
$$\Delta \varepsilon = \varepsilon_b^{sol} - \varepsilon_L^{sol}$$

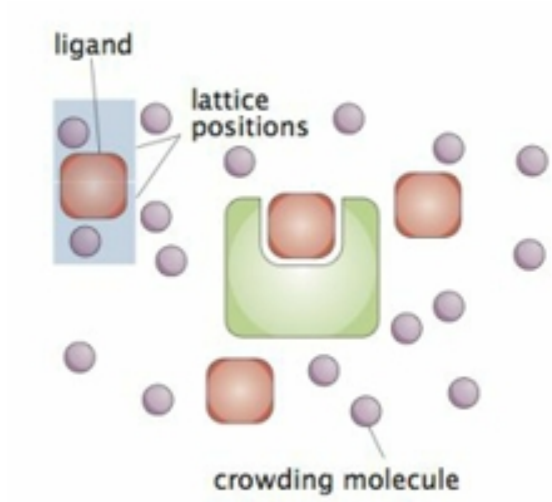
This can be written:

$$P_{bound} = \frac{1}{1 + \frac{c_0 - c_L - c_c}{c_L} e^{\beta \Delta \varepsilon}}$$

c_0 is a reference concentration; c_L is the ligand concentration, and c_c is the crowder concentration.

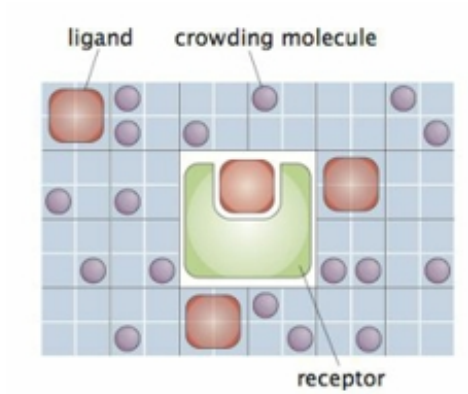
Crowding Effect on Binding: Large Ligands and Small Crowding Molecules





- It is entropically favorable for large ligand to bind
- This "force" is called a depletion force

Crowding Effect on Binding: Large Ligands and Small Crowding Molecules



all L **ligands** on lattice

$$Z = g(\Omega, L, C)e^{-\beta L \varepsilon_L^{sol}} e^{-\beta C \varepsilon_C^{sol}}$$

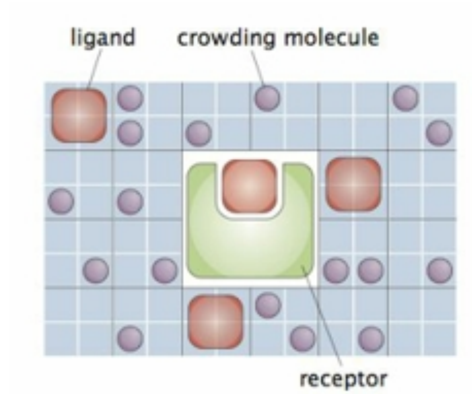
$$+g(\Omega, L-1, C)e^{-\beta (L-1) \varepsilon_L^{sol}} e^{-\beta C \varepsilon_C^{sol}} e^{-\beta \varepsilon_b}$$

$L - 1$ **ligands** on lattice, 1 **bound ligand**

All C **crowders** on lattice

$$g(\Omega, L, C) = \frac{\Omega!}{L!\,(\Omega - L)!} \times \frac{(r\Omega - rL)!}{C!\,(r\Omega - rL - C)!}$$

Crowding Effect on Binding: Large Ligands and Small Crowding Molecules

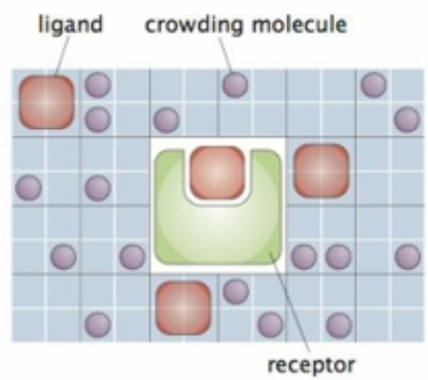


$$P_{bound} = \frac{1}{1 + \frac{g(\Omega, L, C)}{g(\Omega, L-1, C)} e^{\beta(\varepsilon_b - \varepsilon_L^{sol})}}$$

Assume Ω, L and C are large, and using Stirling approximation:

$$\frac{g(\Omega,L,C)}{g(\Omega,L-1,C)} = \frac{(L-1)!(\Omega-L+1)!}{L!(\Omega-L)!} \frac{(r\Omega-rL)!}{(r\Omega-rL+r)!} \frac{(r\Omega-rL-C+r)!}{(r\Omega-rL-C)!} = \frac{\Omega-L}{L} \frac{(r\Omega-rL-C)^r}{(r\Omega-rL)^r}$$

Crowding Effect on Binding: Large Ligands and Small Crowding Molecules



$$P_{bound} = \frac{1}{1 + \frac{\Omega - L}{L}\frac{(r\Omega - rL - C)^r}{(r\Omega - rL)^r}\, e^{\beta(\varepsilon_b - \varepsilon_L^{sol})}}$$

For dilute concentration of Ligands L << C << Ω:

$$P_{bound} = \frac{1}{1 + \frac{\Omega}{L}\left(1 - \frac{C}{r\Omega}\right)^r e^{\beta\Delta\varepsilon}}, \qquad \Delta\varepsilon = \varepsilon_b - \varepsilon_L^{sol}$$

Crowding Effect on Binding: **Small Ligands** and **Large Crowding** Molecules

$$P_{bound} = \frac{1}{1 + \frac{g(\Omega, L, C)}{g(\Omega, L-1, C)} e^{\beta\left(\varepsilon_b - \varepsilon_L^{sol}\right)}}$$

$$g(\Omega, L, C) = \frac{\Omega!}{C!\,(\Omega - C)!} \times \frac{(r\Omega - rC)!}{L!\,(r\Omega - rC - L)!}$$

$$\frac{g(\Omega,L,C)}{g(\Omega,L-1,C)} = \frac{(L-1)!}{L!} \frac{(r\Omega-rC-L+1)!}{(r\Omega-rC-L)!}$$

Limitation of Lattice Model

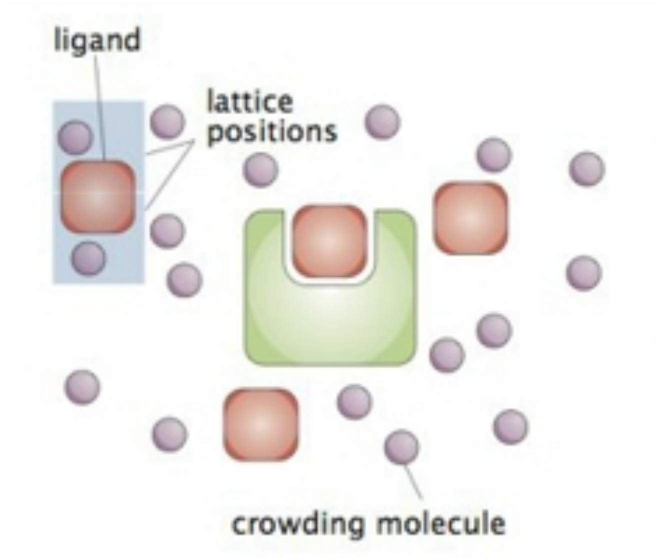


Figure 14.10: Limitations of the lattice model of crowding. This figure shows an allowed configuration for a ligand that is artificially *forbidden* in the lattice model.

Lattice Model of Osmosis

$$Z_{\text{sol}}(H,\Omega) = \frac{\Omega!}{H!(\Omega - H)!} e^{-\beta H \varepsilon_{\text{H}}^{\text{sol}}}, \qquad (14.7)$$

$$pv = G(\Omega - 1) - G(\Omega) = -k_{\text{B}} T \ln \frac{Z_{\text{sol}}(H,\Omega - 1)}{Z_{\text{sol}}(H,\Omega)},$$

$$p = -\frac{k_{\text{B}} T}{v} \ln(1 - [H]v). \qquad (14.10)$$

Assignment 8:Exercise 1

- On page 319 textbook states that for chromosomal DNA, a Kuhn length is about 300 bp
- However, this gives rather bad results.
- It is better for *in vitro* (test tube) DNA to use a Kuhn length, a = length of 1 base pair, 1 bp

Assignment 8:Exercise 2

- For N, the figure states that the separation between the two markers is 100 kb = $10^5 bp$, where we will assume (since this is chromosomal DNA) that the Kuhn length a is the length of 300 bp
- Also $N^/ a^2 = 0.5\mu m^2 \rightarrow N^/ = 50$
- Some students interpret the left figure as showing that there are 11 Kuhn length, but that’s just a schematic.
- Equation 8.36 and 8.37 must be divided by 4, otherwise it is not normalized.

Hard-Sphere Gas Model

$$p = k_B T[H](1 + x + 0.625x^2 + 0.287x^3 + 0.110x^4). \qquad (14.11)$$

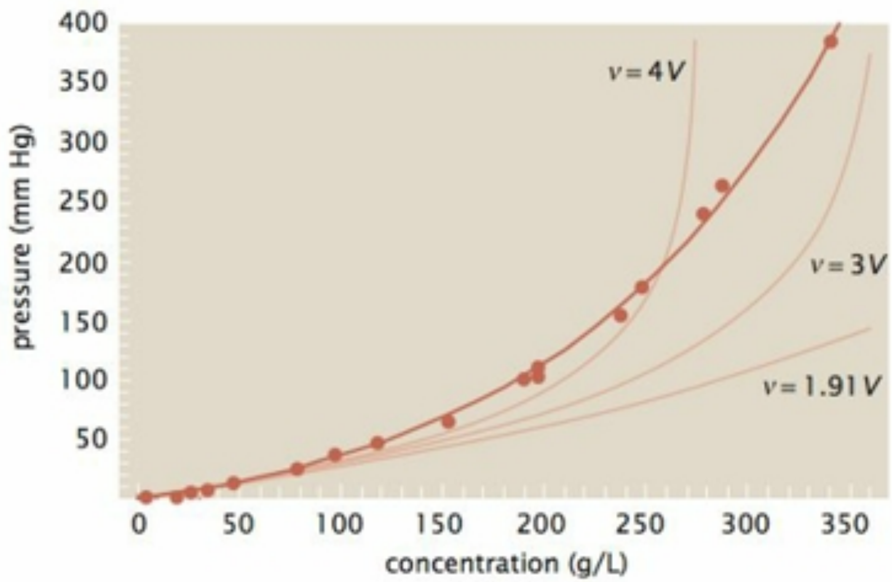


Figure 14.11: Osmotic pressure of a concentrated solution of hemoglobin at 0 °C. The filled circles are the experimental data points. The light red lines are predictions of the lattice gas, while the full red line is the pressure of a gas of hard spheres as described by Equation 14.11, with each sphere having a volume *V* corresponding to a diameter of 5.8 nm. The labels on the lines indicate the volume of a single box in the lattice model given in Equation 14.10. (Data taken from P. D. Ross and A. P. Minton, *J. Mol. Biol.* 112:437, 1977.)

Detail:

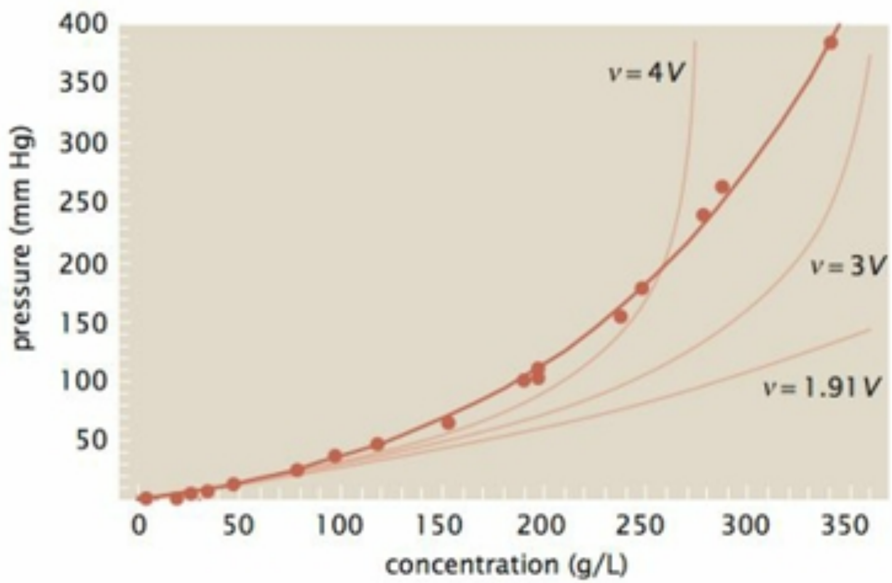
1) mass of 1 Hemoglobin, M_H = 64 000 Da
2) with V = volume of sphere of diameter 5.8 nm = $1\times10^{-25}m^3$
3) For concentration 200 g/L $\rightarrow x = V[H]\sim0.748, P\sim17000Pa$
4) Note 1 mm Hg $\sim133Pa$

Final Exam

- Chapter 5: section 5.1, 5.2, 5.4, and 5.5; assignment 5
- Chapter 6: section 6.1, 6.2 and 6.4; assignment 6
- Chapter 7: Section 7.1 and 7.2; assignment 7
- Chapter 8: Section 8.1 and 8.2; assignment 8
- Chapter 14: read all; assignment 8

Hard-Sphere Gas Model

$$p = k_B T[H](1 + x + 0.625x^2 + 0.287x^3 + 0.110x^4). \qquad (14.11)$$



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In Problem 14.3, verify that equation 14..11 is consistent with the figure caption 14.11, with V = volume of sphere of radius 5.8 nm