Computer assignment 1:
Depletion forces

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1 Introduction

The concept of depletion forces is an example of how abstract theoretical modelling can be used to explain direct physical behaviour on a nanometer scale. It does so by adopting the concept of entropy and entropic forces, and applies them into a biological context – namely in the context of dilute solutions. Although the context is not completely necessary for the conclusions to hold, it holds high historical significance, and can particularly be used to explain how larger molecules submerged in a dilute solution can be affected by smaller molecules through forces occuring when the so called *depletion zones* of the larger molecules overlap. In a practical context the concept can also be used to explain even parts of the so scientifically distant procedure of wine purification, where the concept is utilized in order to filter unwanted particles from the wine itself. [1].

The depletions zones that are modellized do in essence construct the space where the center of the smaller molecules (in an ideal, symmetrical model) can't reach, and make up the basis for how attractive forces can arise due a greater volume being accessible to the smaller particles, thereby shifting the states of maximal entropy. [2]

2 Modelling depletion forces

Maximizing entropy can be said to be equivalent to minimizing the *free energy* in a system. In a system with N small balls (smaller molecules) of radius r, and one larger ball (larger molecule) of radius R, in a cavity of some shape. The cavity can then be imagined to be surrounded by a shell of thickness r through which the center of the other balls cannot reach. As a consequence, when the surface of the large molecule comes into a distance of $D < 2r$ from the boundary, the depletion zones will overlap, causing an effective entropic force to act upon the system, driving the molecule towards the boundary. Additionally, the effect will likewise cause an attraction between larger objects in general within the system, so that *two* larger molecules similarily would be driven together.

The probability density for a given microstate in our system can be written as

$$\rho_N(\mathbf{r}_1, \ldots, \mathbf{r}_N) = \frac{e^{-\beta U(\mathbf{r}_1,\ldots,\mathbf{r}_N)}}{Q} \tag{2.1}$$

where Q is the partition function. This implies that the average force on

a particle at position $\mathbf{r}_1$ can be described by the negative gradient

$$\mathbf{f}(\mathbf{r}_1) \equiv \langle \nabla_1 U \rangle = -\frac{\int d\mathbf{r}_2 \ldots d\mathbf{r}_N \left(\nabla_1 U \right) e^{-\beta U(\mathbf{r}_1, \ldots, \mathbf{r}_N)}}{\int d\mathbf{r}_2 \ldots d\mathbf{r}_N e^{-\beta U(\mathbf{r}_1, \ldots, \mathbf{r}_N)}} \tag{2.2}$$

as a direct effect of the definition. This must in turn be equivalent to stating that

$$\mathbf{f}(\mathbf{r}_1) = kT\nabla_1 \ln \rho(\mathbf{r}_1). \tag{2.3}$$

This we know since $\nabla_1 \ln \rho(\mathbf{r_1})$ can trivially be rewritten as $\frac{\nabla_1 \rho(\mathbf{r}_1)}{\rho(\mathbf{r}_1)}$, which would render the exact same result as in eq. (2.2) once we realize that we have to multiply by a factor β^{-1} to achieve identity, since Q is nothing but a constant and will not be affected by the differentiation.

To establish how the free energy in our system then depends on the position of the big molecule, we can through various assumptions assert the following:

$$D \equiv R_s - R - r_0 \tag{2.4}$$

$$f(D) \approx -\frac{\partial F}{\partial D} = ckT\frac{\partial V}{\partial D} \tag{2.5}$$

Here F is the free energy of the system whereas D is a constant describing the distance between the big ball and the center of the cavity, made up of the constants for the radius of the cavity (assumedly spherical) R_s, the radius of the ball, R, and the distance between the *center* of the ball and the center of the cavity, r_0. $c = N/V$ in turn acts as a parameter for the concentration of small balls within the system. V describes the volume of the cavity, and is here assumed to be roughly the same as the volume that is available to the smaller balls.

For a flat boundary, i.e. a box rather than a sphere as a cavity, the area of where the depletion zones of the big ball and the boundary meet can be given by

$$\frac{\partial V_{ov}}{\partial D} = -A(D) \tag{2.6}$$

where V_{ov} is the overlapping volume.

From figure 2 in the lecture provided (see [2]), we can therefore establish that the distance h, between the area A and the boundary of the ball, as

well as the auxillary distance α, between the center of the ball and A can be described as

$$h = 2r - D$$
$$\alpha = R - r - D.$$

It follows that

$$\alpha^2 + a^2 = (R + r)^2 \Leftrightarrow a^2 = 4rR + 2(r - R)D - D^2 \qquad (2.7)$$

from pure trigonometrics, which gives us the sought-after area A. Inserted into eq. (2.5) we then get that

$$f(D) = -ckT\pi \left[4rR + 2(r - R)D - D^2 \right] \qquad (2.8)$$

when $D \in [0, 2r]$, and otherwise 0. Assuming further that $F(2r) = 0$ is a boundary condition, integrating for the free energy renders

$$F(D) = \int_D^{2r} f(D') \, \mathrm{d}D' = ckT\pi \left[4rRD' + (r - R)D'^2 \right]_D^{2r}$$
$$= ckT\pi \left[8r^2R + 4(r^3 - r^2R) - \frac{8}{3}r^3 - 4rRD - (r - R)D^2 + \frac{D^3}{3} \right]$$
$$= ckT\pi \left[4r^2R + \frac{4}{3}r^3 - 4rRD - rD^2 + RD^2 + \frac{D^3}{3} \right]$$
$$= -ckT\pi(2r - D) \left[2r \left(R + \frac{r}{3} \right) - D \left(R - \frac{r}{3} \right) - \frac{D^2}{3} \right] \qquad (2.9)$$

as a final expression.

In a spherical cavity however, the area of interest is instead given by $A = 2\pi h(D)(R_s - r)$. In this case one can from geometric analysis establish that

$$(R + r)^2 - (R_s - r)^2 = (R - r + D - h)^2 - (R_s - r - h)^2 \Leftrightarrow$$
$$0 = 4Rr - D^2 - 2RD + 2Rh + 2rD + 2Dh - 2R_sh \Leftrightarrow$$
$$h = \frac{D^2 + 2RD - 2rD - 4R}{2(R + D - R_s)}.$$

When then factorized and inserted into eq. (2.5), the force is given by

$$f(D) = -ckT\pi \frac{(2r - D)(2R + D)(R_s - r)}{R_s - R - D} \tag{2.10}$$

whereas correspondingly, the free energy is given through integrating. By first doing a polynomial long division, it can be noted that our expression within the brackets can be rewritten as

$$D - (2r - R - R_s) + \frac{2rR + 2rR_s + R^2 - R_s^2}{R_s - R - D}.$$

Integrating this with respect to D simply results in

$$-2r^2 + 2rR + 2rR_s - \frac{D^2}{2} + D(2r - R - R_s) +$$

$$+ (2r - R_s + R)(R_s + R)\frac{\ln(R_s - R - D)}{\ln(R_s - R - 2r)}$$

which can be factorized into something that, when accounting for our prefactors in the free energy expressions, results in

$$F(D) = -ckT\pi(R_s - r)\left[(2r - D)\left(R_s + R - r + \frac{D}{2}\right) + \right.$$

$$\left. + (2r - R_s + R)(R_s + R)\ln(\dots)\right]. \tag{2.11}$$

Notably, the logarithm is of the form

$$\ln\frac{R_s + d}{R_s + c} = \ln\frac{1 + \frac{d}{R_s}}{1 + \frac{c}{R_s}} = \ln(\dots) - \ln(\dots)$$

that is ideal for Taylor expanding in R_s^{-1}. When doing so, we see that the logaritmic expressions simplify to

$$\ln(\dots) - \ln(\dots) = \frac{1}{R_s}(2r - D) + \frac{1}{2R_s^2}(2r - D)(2r + 2R + D) +$$

$$+ \frac{1}{R_s^3}(2r - D)(4r^2 + 2Dr + 6Rr + D^2 + 3RD + 3R^2)$$

where insertion into what we have, while letting R_s tend towards infinity, reveals that this energy too acts as the free energy for the flat boundary.

3 Results

When running the simulation with the standard values, the results produced in fig. 1 appear. Notably, both trend lines correspond somewhat accurately to data, even though the trend line with $V_{b}ig$ omitted does not so as much as the one where it is not. Also, it is clearly seen that the limits for the simulation span between a length of 14–18 length units. This clearly corresponds to the identity $D = R_s - R - 2r$, as the values here are set to 30, 12 and 2 correspondingly, so that the depletion zones go from not overlapping at all, to overlapping completely. When the zones start overlapping, the free energy increases, since more volume is then available to the smaller spheres. During all simulations, if nothing else is noted, the amount of small balls round up to 50 specimen.
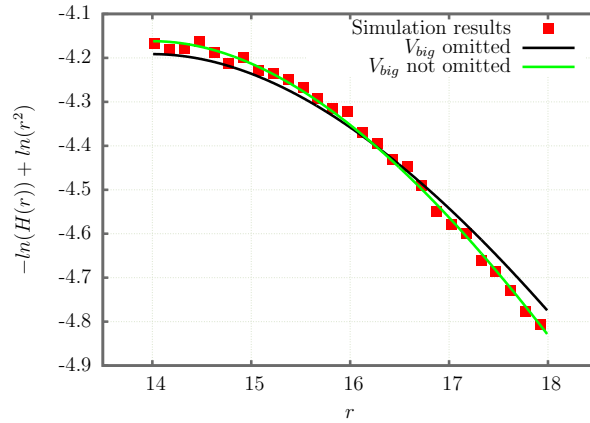

Figure 1: Simulation of depletion zone overlap effect on the free energy in a 3-dimensional cavity of spherical shape. Note that the y-axis is a similarity function that behaves like the free energy, but is not equal to it. Here it acts as a relational measure.

When the parameters are shifted somewhat however, this stability that is found in fig. 1 is lacking, both in fig. 2 and fig. 3. The system notably starts oscillating extensively whenever depletion zones overlap, whereas our approximation of ommiting V_{big} breaks down as well, particularly in the case of a bigger macromolecule. The fluctuations are a cause of the instability inherent to the dynamics of the system, occuring for example when many balls form structures next to each other.
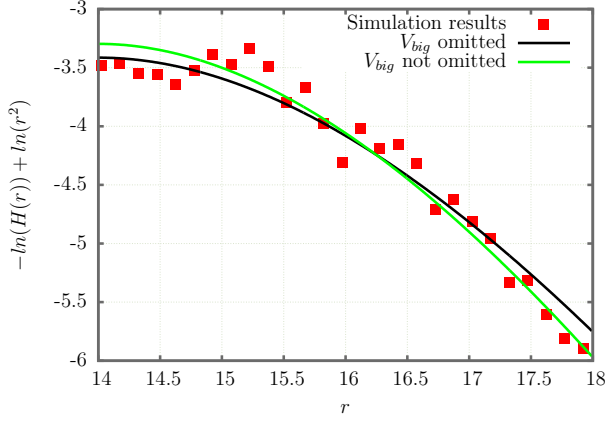
Figure 2: Simulation performed with 200 balls (cf. fig. 1 with 50 balls). Note the fluctuation behaviour as the depletion zones overlap.
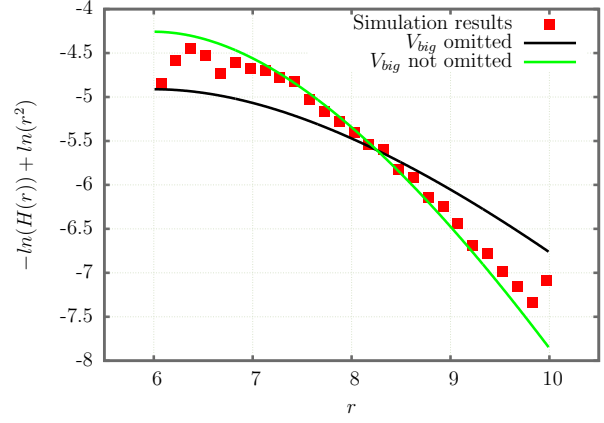

Figure 3: Bigger ball here holds a radius of 20 length units (cf. fig. 1 with radius 12). Note the depletion zone limits being changed.

The system does behave as expected, achieving a global minimum when the bigger ball is closer to the boundary. This simply is because of the fact that the smaller balls access a larger volume, and the system is thereby a subject to an increase in entropy.
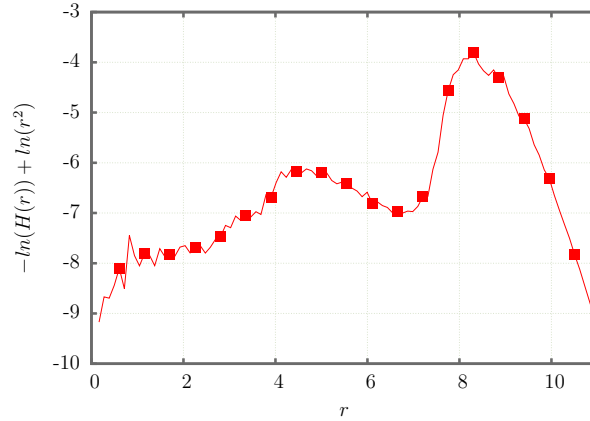

Figure 4: Potential of mean force graph for a high-density system in two dimensions. Simulation settings are $R_s = 22, R = 11, r = 1.7$, and otherwise as previously stated.

More clearly now in the denser system, minimas apart from the origin are present, most notably around the value of 7 length units in fig. 4. Because

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of the higher density, this is assumed to correspond to the smaller balls aligning up at the boundary, preventing the larger molecule from moving there, and thereby incapacitating the system somewhat. It ought also to be possible for the balls to assume a thicker layer directly around the larger ball, as can be imagined to happen in the region < 4 length units, although sparse data makes the conclusion hard to make. It should be noted, however, that the successive decrease as can be seen in the region $r \rightarrow 0$ does not necessarily correspond to a factual decrease in free energy, but is instead the consequence of lack of data in this region. Nevertheless, it can certainly be imagined that the small balls might align so that the larger one is "locked in" in the center, and so the results might hold at least some significance, though further simulations are required to reveal the nature of this.

The barrier between the first and the second minima ought however to correspond to the additional effort needed for the macromolecule to penetrate the layer of numerous smaller balls in order to reach the boundary.

Lastly, when the shape of the cavity is changed from a circular shape towards that of an ellipsis, other dynamics appear. Since data for the free energy is harder to quantify in this case, the dynamics can instead be understood by examining the real-time illustration of the macromolecule's positions during a simulation, provided in fig. 5.
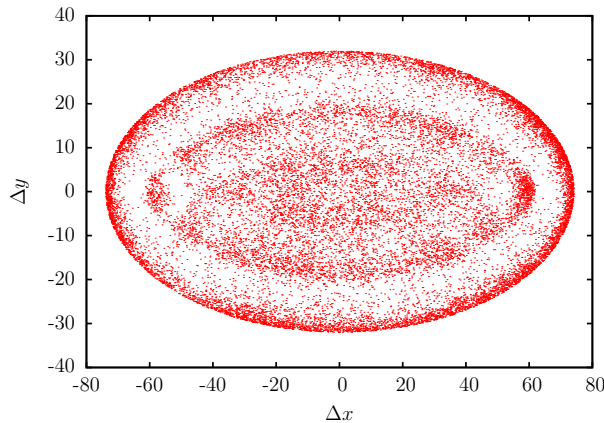

Figure 5: Position of the larger molecule in a 2D-landscape within a ellipsoidal cavity. The system is as in the previous example in a high-density configuration, where the smaller balls make up a fraction of ~ 30 % of the available volume.

Here the same behaviour which brought about the result with several minima in the previous simulation is come into display. Clearly, the larger ball has a direct bias towards some one–two boundaries within the cavity,

as well as the outer rim. As in the previous simulation, this ought to be the result of many smaller balls layering up, so that the larger ball must pass through them in order to reach the outer boundary. Notably, in the ellipsoidal extremes where $\Delta y \approx 0$ the bias for the ball to be positioned there is stronger than in other parts of the ellipsoidal boundary. This should correspond to the lack of available space to move within our two dimensions, so that the larger ball would to a higher extent be forced to move *through* the small balls in order to shift its position markedly. The collisional forces from the small ball will therefore at those extremes further prevent the ball from moving than in other cases. Indeed, because the entropical forces will push the ball towards the positions where the area of the overlapping depletion zones will be maximized, the thinner parts of the ellipsis make a natural habitat for this phenomenon. The macromolecule simply *fits* better into the edges where the zones overlap maximally.

4 Conclusions

Our results have shown that it is indeed possible to model depletionary forces through simple approximations and the concept of thermodynamics. In particular, it can be seen that a larger molecule in fact is pushed towards the boundaries of a system in correspondence with the concept of maximizing the overlapping depletion zones which forelie.

When the curvature of the boundary to a higher extent corresponds to the surface of the macromolecule, this is even more apparent, and the system will exhibit a corresponding behaviour to zones abiding to this property.

In practice, this can certainly be used in biological contexts to explain the gathering and interaction of similar-size or well-fitting proteins, and possibly further, not here analyzed, extensions of this forcing phenomenon.

References

[1] Moreno, Juan; Peinado, Rafael, *Enological Chemistry*: 325-326, Elsevier Inc, San Diego, 2012.

[2] Anna Bille, *Computer Assignment 1: Depletion forces*, Lund University, 2015.