



Estudio teórico de sistemas altamente asimétricos en tamaño: Distribución del Radón en cavidades alveolares.

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Theoretical Model to Estimate the Distribution of Radon in Alveolar Membrane Neighborhood

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Abstract Radon is a naturally occurring radioactive gas which tends to concentrate indoors, easily emanates from the ground into the air, where it disintegrates and emits radioactive particles. It can enter the human body through breathing or ingesting mostly water. When radon inhaled, travels through the respiratory tract to alveoli where the majority is expelled into the environment. Moreover, when ingested in water, it passes into the intestine where it is absorbed and driven from the bloodstream to the lungs; in these organs, due to differences in partial pressures, it is transported to alveoli by simple diffusion process. When radon is not removed, it decays in short-lived solid disintegration products (²¹⁸Po and ²¹⁴Po) with high probability of being deposited in biological tissues, causing DNA damage because of the densely ionizing alpha radiation emitted. We propose a semi-empirical, smooth, and continuous pair potential function in order to model the molecular interactions between radon and lung alveolar walls; we use Molecular Dynamics (MD) to determine the gas distribution in an alveolar neighborhood wall, and estimate the quantity thereof it diffuses through the alveolar membrane as a concentration function.

Keywords: Radon distribution; alveolar membrane; molecular dynamics; radon in alveoli

1. INTRODUCTION

An alveolus is a small cavity with spherical shape and an average diameter of 0.25mm. Alveoli are present in the lungs of mammals and overlay alveolar

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sacs at the end of the bronchioles terminations of the respiratory tract. They (alveoli) form the surface for gas exchange between air and blood. The walls of the alveoli are covered with alveolar epithelial and epithelial from blood capillaries. The proximity of the capillary blood with alveolar air is essential for the rapid exchange of gases. In a human, the total alveolar surface can be an area of 100-140m². Gases such as O₂, CO₂, and ²²²Ra diffuse through this wall in favor of a gradient of partial pressures: usually O₂ enters to the blood plasma and CO₂ goes out to the atmosphere. The diffusion distance between the blood plasma and the air in the alveoli is between 0.3 and 0.6 μm [3].

Within the air that reaches the alveoli, the partial pressure of O₂ (PO₂) is less than that in the atmosphere; therefore, the air enters to the alveoli by convection (inspiration). PO₂ in the blood plasma is less than that of the alveoli; hence the O₂ diffuses toward plasma through the alveolar membrane. CO₂ partial pressures are inverse to those of the O₂; therefore CO₂ diffuses across the alveolar membrane from the blood plasma to the alveolar air sac. Radon is a chemically inert and essentially non-reactive gas, like the other noble gases. It is distributed in atmospheric air at concentrations that show strong spatial and seasonal variations as they depend on meteorological parameters such as temperature, wind velocity and pluvial precipitation [10]. Radon, as any inhaled gas, is soluble in body tissues to some extent. When it is inhaled, it diffuses from the lungs to the blood and through other organs in a process governed, in part, by its relative solubility in each media [8]. In fact, the ratio of solubility in tissue to that in blood or any other medium is known as the partition coefficient. The partition coefficient of radon in blood (blood/air) is 0.43, higher than in other gases: seven times that of krypton (0.06) and more than two times that of xenon (0.18). The partition lung/blood for radon is reported to be 0.70. That means, the solubility of radon in blood is 43% of that in the air, and in lung tissue is 70% of that in the blood [9].

Alveoli are composed of a monolayer of epithelium where two cell types are distinguished: Type I pneumocytes are squamous shaped cells which cover from 95% to 98% of the alveolar surface. They have a thickness ranging from 0.1 to 0.3 μm and a diameter of 50 μm. Although they are larger than the type II, they are very thin for gases to diffuse quickly through them; this fact allows oxygen and carbon dioxide molecules dissolved in a surfactant agent pass through the intercellular spaces. Type II pneumocytes are cuboidal cells which cover from 2% to 5% of the alveolar surface. They have a diameter of 10 μm; they are smaller but thicker than Type I pneumocytes. Their main function is to synthesize and secrete a chemical substance known as surfactant substance, which is necessary for gas exchange. The cells lining the blood vessels, and which are in contact with the cells, are endothelial type (simple

plain epithelium). They have an average diameter of 8 μm and a mean wall thickness of 0.5 μm . From the erythrocyte to the alveolar space, the alveolar-capillary barrier can be distinguished as a barrier consisting of the endothelium, the basement membranes and the alveolar epithelium[1-2]. See Fig. 1.

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2. THEORETICAL MODEL

In previous works, the alveolar membrane has been modeled as a porous media through which gases diffuse [6]; this approach is in agreement with the results obtained with Scanning Electron Micrography of the alveolar region of the lungs [7]. In order to model the interaction between ^{222}Ra and a membrane, we use a potential function with tunable width and height, which allows approximating variations associated with average diameter of cells, and therefore, the width of epithelial monolayers.

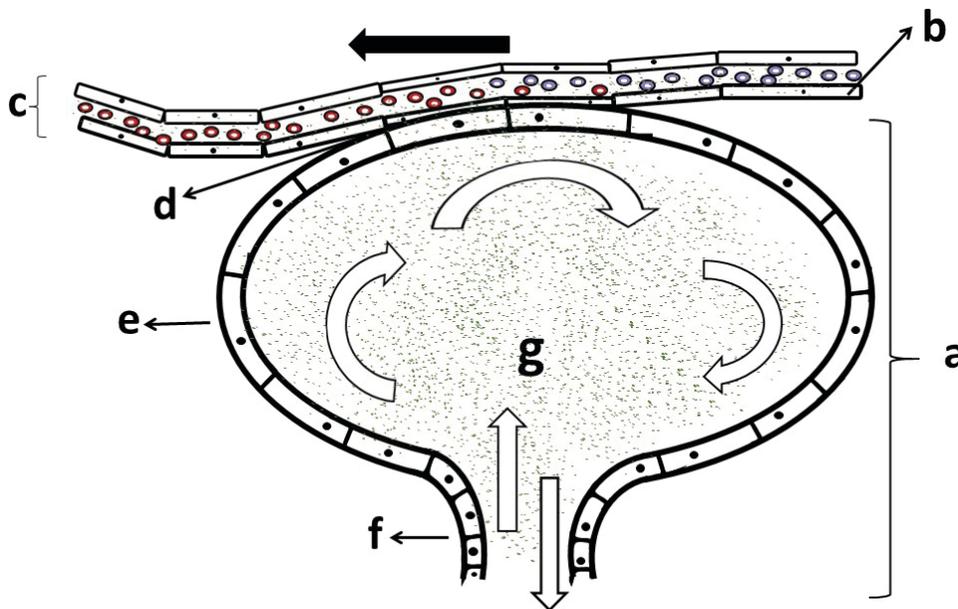


Figure 1: Radon diffusion through the alveolar-endothelial surface. (a) Transversal cut of a spherical alveolus; (b) endothelial cells of blood vessels; (c) blood vessel in contact with an alveolus, deoxygenated blood from pulmonary artery (blue) and oxygenated blood to the pulmonary vein (red); (d) alveolar-capillar; (e) squamous type I pneumocytes of the alveolar surface; (f) cuboidal type II; (g) Radon released into the alveolus. The black arrow indicates the direction of the blood flow and the white arrows show the countercurrent air flow.

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We consider a simple fluid of size $\sigma = 1$ in contact with a semipermeable membrane. The membrane is located at $z = 0$. The interaction of the membrane with the fluid particles are given by

$$\beta u(r) = 4\epsilon^* \left(\frac{u_o + (u_o + \epsilon)z^6}{4\epsilon^* + (u_o + \epsilon)z^{12}} \right), \quad (1)$$

With

$$z^* = \frac{z}{\sigma\omega'} \quad (2)$$

In the above definition, ω is the half-width, the parameter u_o is the height and is ϵ the depth of the potential function. The energy units $k_B T$, where k_B ($\approx 1.38 \times 10^{-23} \text{ Kg m}^2 \text{ s}^{-2} \text{ K}^{-1}$) is the Boltzmann constant and T is the temperature in Kelvin. This unit represents the thermal energy. The dimensionless energy parameter ϵ^* is defined by the expression

$$\epsilon^* = \frac{\epsilon}{k_B T} \quad (3)$$

The particles of the fluid can cross the membrane and occupy both sides. For a graphic description of the potential see Fig. 2.

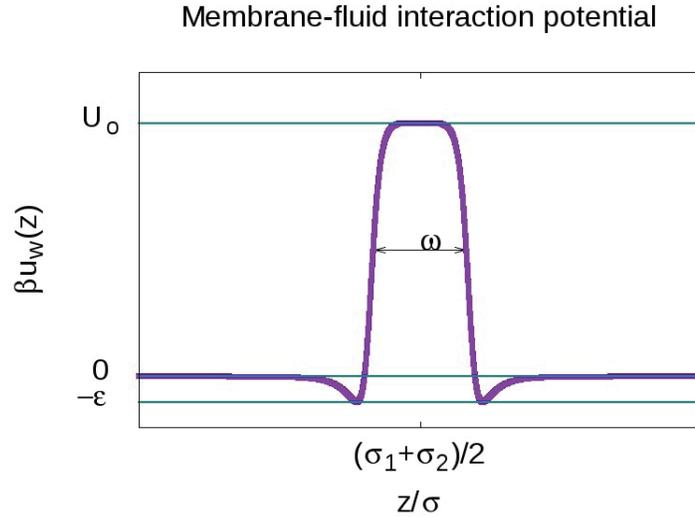


Figure 2: Radon-membrane interaction. u_o and ω are tunable parameters of the potential model.

The interaction between fluid species is modeled by a Lennard-Jones potential function, which has the mathematical form

$$\beta u(r) = 4 \frac{\epsilon}{k_B T} \left(\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right) \quad (4)$$

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The parameter values of σ and ϵ/k_B for Radon-222 chosen in this work are given by the reference [3]. The system densities and temperature correspond to gas phase and ambient conditions, approximately.

3. METHODOLOGY

Molecular dynamics runs were performed solving Newton equations with Velocity Verlet approximation. The simulation was performed with constant temperature, volume and number of particles. The general scheme of molecular dynamics algorithm requires the position at each time t . We can get the next position using the approximation

$$\bar{r}(t + dt) = \bar{r}(t) + \bar{v}(t)dt + \frac{\bar{a}(t)dt^2}{2} \quad (5)$$

We can calculate the j component of the force over the particle i by the expression

$$F_j = \sum_{i>j}^N -\nabla_j \beta u(r_{ij}) \quad (6)$$

The initial components of the particle velocity are consistent with Maxwell-Boltzmann distribution function. Subsequently, we shift all velocities, such that total momentum is zero. To ensure constant temperature in the simulation, the speed of each particle is rescaled to get the temperature desired. This is obtained by recalling that in thermodynamic equilibrium it is satisfied

$$v_\alpha^2 = \frac{k_B T}{m} \quad (7)$$

where v_α is the a component $\alpha = 1, 2, 3$ of the velocity of a given particle and m is the mass of the particle. We can use this equation to define the instantaneous temperature $T(t)$ at time t by:

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$$k_B T(t) = \sum_{i=1}^N \frac{m v_{\alpha,i}^2(t)}{N_f} \quad (8)$$

so we have an expression to instantaneous temperature. N_f is the number of degrees of freedom ($3N-3$). To match the desired temperature T , we must rescale all velocities by a factor $\sqrt{T/T(t)}$ for every integration step.

Periodic boundary conditions and minimum image were considered only in the x and y components. In the z component, infinite soft walls were imposed located at $z = \mp Lz/2$. The potential of the semipermeable wall is located at $z = 0$. The simulation box is a cube of size $Lx*Ly*Lz = 50x50x50$ in reduced units. The potential energy and the total force must be calculated for each particle-particle interaction and particle-wall interaction. The first interaction has $n(n-1)/2$ contribution terms. The second one has just n contribution terms. We have no considered cutoff distance neither cutoff-shifted potential. In the present work, we have chosen to start our run from a simple cubic lattice of size $9*9*9$ particles located at $(0,0,L/4)$. In order to establish the initial configuration we ensure that all the particles are on one side of the wall (the upper side) as it is shown in Fig. 3.

In the simulation, 729 (9^3) particles were used in a $50x50x50$ (sigma units) box. The MD algorithm requires time discretization; in order to achieve system

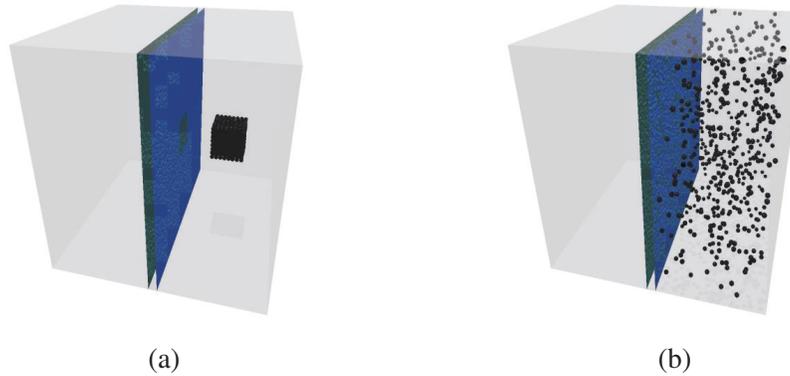


Figure 3(a): Shows the simulation initial configuration. The particles are in the upper side and the membrane is located at the middle of the box in a cubic unit cell. (b) When the systems has reached the thermodynamic equilibrium, some particles crossed toward the other side of the membrane.

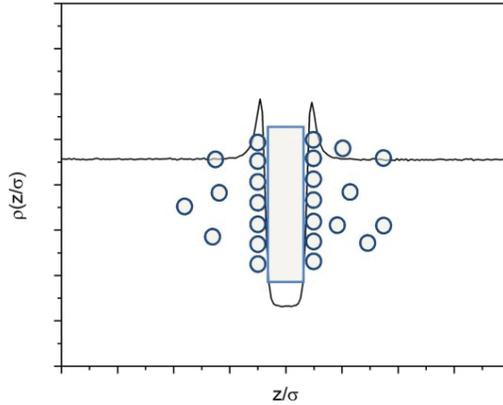


Figure 4: Schematic interpretation of the density profile in the neighborhood of the permeable membrane.

stability we found that $dt=0.01$ is the optimal parameter for discretization. The system evolves along 5×10^5 steps to ensure thermodynamic equilibrium before making statistical averages. The statistical averages were obtained in 10^7 integration steps.

The density profile of a fluid near a wall is the average number of particles located at a distance z from the wall. This average is calculated every 10 steps of integration in our work. Mathematically, this is defined by

$$g(z) = \frac{n(z)}{A \Delta z N_s} \quad (9)$$

In the above equation, A is the simulation box transversal area. The Δz parameter is the differential bin to calculate the histogram. In Fig. 4 we can see a schematic representation of this function. $n(z) / N_s$ is the ratio of the number of particles located at z to the number of samples taken in the simulation.

5. RESULTS AND DISCUSSION

The density profiles obtained at reduced temperatures $T=2$ and $T=3$ are shown in Fig.5. The kinetic energy of the particles is not enough for them to cross the energy barrier as we can see in the figure a fore mentioned. The particles remain located in the upper side ($z>0$) of the membrane.

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The results showed that the density of the particles is higher on the membrane surface than in the bulk. If we have an increment in the energy of the particles, some of them can cross the membrane. The particles in both sides are conserved, so the total density is conserved too. The density profile on the surface is higher in the two sides, even with low density.

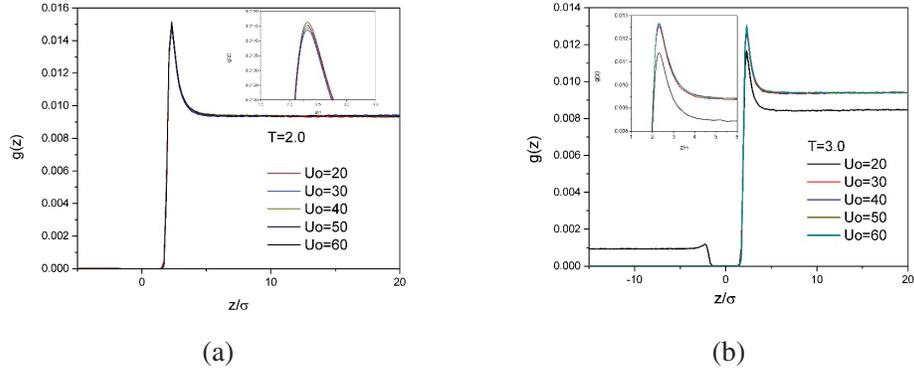


Figure 5: Radon distribution. Figure (a) shows the density profile for a system with a reduced temperature $T= 2$. The results for reduced temperature $T=3$ are shown in figure (b).

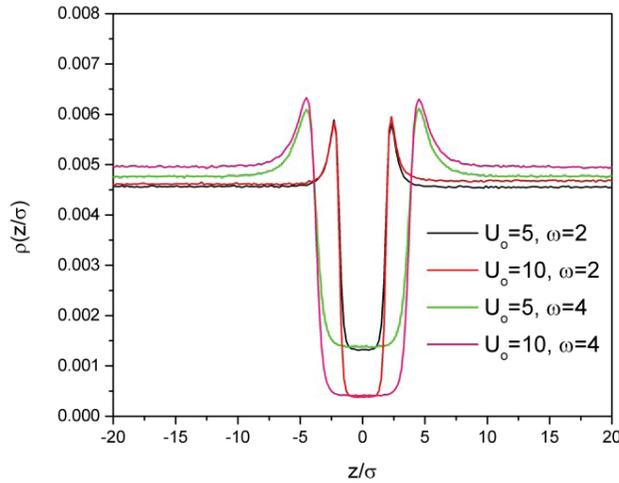


Figure 6: Radon distribution near to two membrane regions with different width. We appreciate some radon particles confined between alveolar bilayers.

In Fig. 6 we have four results for a system with width and height potential parameters. The reduced temperature is $T=5$, $U_0=5$ and 10 ; and $\omega=2$ and 4 . The kinetic energy of the particles is enough to cross the membrane, so the density of the particles in both sides is equal in the bulk. In contrast with the results previously shown, we have that radon can be confined into the alveolar membrane. This is because the particles on the membranes surface are acting like a second potential barrier, confining some particles inside the membrane.

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5. CONCLUSIONS

Our theoretical model allows the prediction of an approximate amount of radon that passes from air through alveolar membrane, which is incorporated into the bloodstream. It even predicts the amount of radon particles that are temporarily confined between the endothelium and the internal alveolar surface. These approximations are very useful in biophysical and medical contexts because it is known that the risk of developing lung diseases is directly correlated with the amount of radon that is present in tissues and, of course, the time that such particles remain between them.

Particularly, at a fixed temperature $T = 2.0$, which corresponds to the normal human body temperature, radon does not pass through the alveolar membrane even when the potential barrier is diminished; moreover, its distribution outside the membrane does not have significant changes. However, when temperature is increased, radon starts to diffuse through the membrane and some particles remain confined between alveolar monolayers. This phenomenon is attributed to the fact that many of the proteins of the alveolar wall lose structural stability when the temperature increases, making the porous surface permeable, and even increasing the membrane pores diameter. In addition, we can observe a distribution where the particles are very close to each other, both inside and outside the alveolar wall; this is explained by the fact that radon solubility decreases as temperature increases in the mucous layer covering the alveoli (whose major component is water).

In addition, we used equations (2), (3), (9), and some radon experimental parameters in order to estimate the amount of radon diffusing across the alveolar membrane. Our results showed that a portion equivalent to 33% of the initial amount is distributed near the wall, and 12% of the initial amount was confined between the alveolar monolayers.

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