Diffusion of Macromolecules across the Nuclear Pore Complex

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Nuclear pore complexes (NPCs) are very selective filters that monitor the transport between the cytoplasm and the nucleoplasm. Two models have been suggested for the plug of the NPC. They are (i) it is a reversible hydrogel or (ii) it is a polymer brush. We propose a mesoscopic model for the transport of a protein through the plug, that is general enough to cover both. The protein stretches the plug and creates a local deformation. The bubble so created (prtoein+deformation) executes random walk in the plug. We find that for faster relaxation of the gel, the diffusion of the bubble is greater. Further, on using parameters appropriate for the brush, we find that the diffusion coefficient is much lower. Hence the gel model seems to be more likely explanation for the workings of the plug.

The nuclear envelope in all eucaryotes is perforated with nuclear pores [1, 2, 3, 4, 5, 6]. Each pore has a selective filter, referred to as the nuclear pore complex (NPC). The NPC is a self-assembled, eightfold symmetric ringlike structure consisting of eight copies each of 30-50 different proteins, connecting the inner and outer nuclear membranes. It regulates the import and export traffic of proteins and has two distinct modes of transport: passive and facilitated. Passive transport is non-specific and takes place by ordinary diffusion. Colloidal gold particles with radii up to 4 nm, and generic proteins up to 50 kDa in mass, pass efficiently through the NPC in this way [7]. In contrast, facilitated translocation allows the passage of objects as large as several megadaltons. Proteins having a short amino acid sequence known as nuclear localization signal (NLS) form a complex with transportin [5] (a transporter protein rich in hydrophobic units) and are transported in this mode. The transport requires specific interactions between the translocating species and constituents of the NPC and consequently is highly selective. Gold particles of up to 32-36 nm in diameter are able to pass through some NPC if they are coated with nucleoplasmin-importin complexes [3]. This suggests that the interaction of the protein-transportin complex with NPC is essential for transport. Passage of proteins through the NPC has attracted considerable experimental and theoretical attention [8, 9, 10, 11]. According to Ribbeck and Görlich (RG) [8] the central plug of the nuclear pore is made of long diblock copolymers rich in hydrophobic phenylalanine-glycine (FG) units forming a meshwork. Only the macromolecules which can form hydrophobic contacts with the FG units are incorporated into this network and get transported. In an interesting paper,

Bickel and Bruinsma (BB) [10] point out that such a model would lead to a lower rate of diffusion. BB suggest that the central plug is a reversible polymer gel in a poor solvent and a protein in it experiences an extra noise (they call it "chemical noise") arising from the fluctuations of the FG contacts and this extra noise enhances the diffusion of the protein within the NPC. Single molecule fluorescence microscopy by Yang, Gelles and Musser [9] shows that the protein executes random walk inside the central core of the NPC. An alternate model for the plug suggests that it is not a gel but a polymer brush [12]. Surprisingly, there have been experimental support for both gel and brush models. In interesting experiments, Frey et al. [13, 14, 15] have shown that the nucleoporins form a hydrogel in vitro, offering support to the model of RG and BB. On the other hand a beautiful study by Lim et al. [16] has found that the proetins, when grafted to a surface behave like an un-cross-linked brush. Also, it is known that the interaction between the transportin and the FG residues is not just hydrophobic, but involves hydrogen bonding, electrostatic and van der Waals interactions [17, 18] and that there are extremely hydrophilic portions in between the FG units.

In the following we study a minimalistic model for the transport in the NPC. Our model is quite general, and would be applicable whether the plug is a gel or a brush. The actual values of the parameters in the model would depend on whether it is a gel or a brush. We find that the it is possible for the protein to diffuse rapidly within a reversible gel, while the diffusion would be much slower within the brush.

We take the pore complex to be infinitely long (end-effects neglected) and shall adopt a continuum description for the plug. We use x to denote position along the direction of the axis of the NPC. To make the problem one dimensional, we imagine the cross section of the pore to be a square, with width L_Y in the Y and height $L_Z (= L_Y)$ in the Z directions. We shall assume that the particle has a length $2R_0$ in the X direction, causes a distortion of height $\sim \alpha$ and fills the pore fully in the Y direction. Further, to simplify the analysis, we assume that periodic boundary conditions are imposed in this direction, with a period L_Y. With these, the problem is reduced to two dimensions (X and Z). The size of the distortion needed to create a cavity to accommodate the particle will be our important variable. Let $\phi(x)$ denote the height of the cavity in the Z-direction at the position x. The simplest possible expression for the energy of distortion E_{dis} would have terms quadratic in $\phi(x)$. Thus $E_{dis} = (1/2) \int_{-\infty}^{\infty} dx \left\{ \sigma \left(\partial \phi(x)/\partial x \right)^2 + k\phi(x)^2 \right\}$. The energy of interaction $E_{int} = -E_b + \int_{-\infty}^{\infty} dx Q(x - R) \left\{ (k + \Delta k)/2 \left\{ \phi(x) - \alpha \right\}^2 - (k/2)\phi(x)^2 \right\}$ of the particle at R with the plug can compensate for the distortion energy. $Q(y)$ with $y = x - R$ is a function that determines the interaction between the particle and the plug. We assume

$Q(y)$ to be a symmetric function of y, having maximum value $Q(0) = 1$. Further, we assume $Q(\pm\infty) = 0$. When the particle enters the plug it would have to break hydrophobic contacts that may be there, and the energy expenditure for that may be met by formation of new contacts of the nucleoporins with the particle. All these together is represented by a single constant E_b. Thus the energy of the system is, to within an additive constant, $E[\phi, R] = E_{dis} + E_{int}$. We refer to this as the particle on a string model for the transport, as the above expression is identical to the energy of a stretched string, which is displaced from its equilibrium position by the particle, to form a bubble. We assume overdamped, Langevin dynamics for the string and the particle, given by

$$\begin{pmatrix} \zeta & 0 \\ 0 & \zeta_p \end{pmatrix} \frac{\partial}{\partial t} \Psi(x, R, t) = - \begin{pmatrix} \frac{\delta E[\phi, R]}{\delta \phi(x)} \\ \frac{\partial E[\phi, R]}{\partial R} \end{pmatrix} + F(x, t)$$

$\Psi(x, R, t)$ is 2×1 column vector with elements $\phi(x, t)$ and R. ζ is the friction coefficient for the string and ζ_p for the particle. We shall use † to denote the transpose. $F(x, t) = (f(x, t), g(t))^\dagger$ where $f(x, t)$ and $g(t)$ are Gaussian random forces with mean zero and $\langle f(x_1, t_1) f(x_2, t_2) \rangle = 2\zeta k_B T \delta(x_1 - x_2) \delta(t_1 - t_2)$ and $\langle g(t_1) g(t_2) \rangle = 2\zeta_p k_B T \delta(t_1 - t_2)$. We define $\beta = 1/k_B T$ and denote the time of relaxation of the long wave length oscillations of the string by $\tau = \zeta/k$. A model with similar structure has been studied in the context of DNA replication by Bhattacharjee [19].

It is convenient to work with dimensionless quantities, and use the original symbols themselves to denote them. Thus we change to $\beta E \to E$, $\beta E_b \to E_b$, $x/R_0 \to x$, $\phi(x)/R_0 \to \phi(x)$, $\alpha/R_0 \to \alpha$, $R/R_0 \to R$, $\beta k R_0^3 \to k$, $\beta \Delta k R_0^3 \to \Delta k$, $\sigma \to \sigma \beta R_0$, $t/\beta \zeta R_0^3 \to t$ and $\zeta_p/\zeta R_0 \to \zeta_p$. The minimum energy configuration for the system obeys the two equations $\frac{\delta E[\phi, R]}{\delta \phi(x)} = 0$ and $\frac{\partial E[\phi, R]}{\partial R} = 0$. These lead to $\sigma \frac{\partial^2 \phi(x)}{\partial x^2} - k\phi(x) - (\Delta k(\phi(y) - a) - k\alpha)Q(x - R) = 0$ and $\int_{-\infty}^{\infty} dx Q'(x - R)((k + \Delta k)\{\phi(x) - \alpha\}^2 - k\phi^2(x)) = 0$. The prime, $'$ is used to denote differentiation with respect to x. As the shape of the distortion would obviously depend on where the particle is located, it is clear that the distortion would have the form $\phi_c(y)$ where $y = x - R$. In terms of y, the first of the two equations become $\sigma \frac{\partial^2 \phi_c(y)}{\partial y^2} - k\phi_c(y) - (\Delta k(\phi(y) - \alpha) - k\alpha)Q(y) = 0$. The second equation is easily satisfied by having $\phi_c(-y) = \phi_c(y)$. Once ϕ_c satisfying these conditions is found, it may be used to get the minimum energy, $E_c = E[\phi_c(x - R), R]$. The minimum energy configuration with the particle stationary at R_b, and with the center of the distortion coinciding with R_b shall be referred to as having the bubble at R_b and this may be specified by the function $\Psi_c(x - R_b, R_b) = (\phi_c(x - R_b), R_b)^\dagger$. Movement of the bubble as a whole is described as change of $\Psi_c(x - R_b, R_b)$ by change of R_b. It is clear that this motion is translational as the energy of the system is unchanged by this movement. This causes the existence of a "zero mode" [20]. At a finite temperature, there would be fluctuations which will

cause the bubble to execute random motion. It is to be noted that the distortion and the particle can fluctuate in opposite directions and therefore R_b and R follow different dynamics. Following the methods of instanton theory [20], that has been used in a similar context [21, 22], we write the state of the system at any time as the configuration with the bubble located at R_b plus fluctuations about this configuration, which we expand in terms of the normal modes about the bubble at R_b. Thus, we write $\Psi(x, R, t) = \Psi_c(x - R_b(t), R_b(t)) + \sum_{l=1}^{\infty} C_l(t)\Psi_l(x - R_b(t))$, where $\Psi_l(x - R_b) = (\phi_l(x - R_b), J_l)^{\dagger}$ are normal modes, the equation for which will be defined later. We now substitute the above expansion into the Langevin equation and expand the RHS up to first order in $C_l(t)$. The result is $\varsigma \dot{R}_b(-\phi'_c(x - R_b(t)), 1)^{\dagger} + \sum_{l=1}^{\infty} \dot{C}_l(t)\Psi_l(x - R_b(t)) = \sum_{l=1}^{\infty} C_l(t)\left\{\widehat{L}\Psi_l(x - R_b(t)) - \dot{R}_b\Psi'_l(x - R_b(t))\right\} + F(x, t)$ where ς is a 2×2 diagonal matrix with diagonal elements 1 and ζ_p. The operator $\widehat{L}$ is defined by

$$\widehat{L}\Psi_l(y) =$$

$$\begin{pmatrix} \{-\sigma\partial^2/\partial y^2 + k + \Delta kQ(y)\}\phi_l(y) - Q'(y)\{\Delta k(\phi_c(y) - \alpha) - \alpha k\}J_l \\ -\int_{-\infty}^{\infty} Q'(y')\{\Delta k(\phi_c(y') - \alpha) - \alpha k\}\phi_l(y') + J_l\int_{-\infty}^{\infty}dyQ''(y)\left\{(k + \Delta k)/2\,(\phi_c(y) - \alpha)^2 - (k/2)\phi_c(y)^2\right\} \end{pmatrix}$$

We take Ψ_l to obey the eigenvalue equation $\widehat{L}\Psi_l = \lambda_l\Psi_l$. It is convenient to introduce an inner-product $(\Psi_l|\Psi_{l_1}) = \langle\phi_l|\phi_{l_1}\rangle + \zeta_p J_l^* J_{l_1}$, where $\langle\phi_l|\phi_{l_1}\rangle = \int_{-\infty}^{\infty}dx\phi_l^*(x)\phi_{l_1}(x)$. With this definition of the inner product, $\widehat{L}$ is a hermitian operator on the space spanned by Ψ_l. Further, $\partial/\partial R_b(\phi_c(x - R_b), R_b)^{\dagger} = (-\phi'_c(x - R_b), 1)^{\dagger}$ is an eigen function of $\widehat{L}$ with an eigenvalue zero, as may be easily proved by differentiating $\left(\frac{\delta E[\phi, R]}{\delta\phi(x)}\right)_{\phi_c(x - R_b), R_b} = 0$ and $\left(\frac{\partial E[\phi, R]}{\partial R}\right)_{\phi_c(x - R_b), R_b} = 0$, with respect to R_b and writing the results in the matrix form. This is the zero mode of the system. After normalizing, this mode may be written as $\Psi_0 = (-\phi'_c(x - R_b), 1)^{\dagger}/\sqrt{c}$, with $c = \zeta_p + \langle\phi'_c|\phi'_c\rangle$. Note that in the spirit of instanton approach the sum over l in the expansion of $\Psi(x, R, t)$ does not include this mode. Further, the fact that $Q(y)$ is a symmetric function, means that one can classify the eigenfunctions Ψ_l based upon the symmetry or antisymmetry of $\phi_l(y)$. If $\phi_l(y)$ is symmetric, then Ψ_l has the simple form $\Psi_l = (\chi_l, 0)^{\dagger}$, where χ_l is a symmetric eigenfunction of the operator $\left(-\sigma\frac{\partial^2}{\partial y^2} + k + \Delta kQ(y)\right)$. Further, for this case, $\lambda_l = \varepsilon_l$, where ε_l is the eigenvalue associated with χ_l, a fact we will use later.

On taking inner product of the equation involving $C_l(t)$ with $\Psi_0(x - R_b(t))$ we get $\dot{R}_b(t) = h(t) + (\dot{R}_b(t)/c)\sum_{l=1}^{\infty} C_l(t)\left\langle\phi''_c|\phi_l\right\rangle$, where $h(t) = (g(t) - \left\langle\phi'_c \mid f(t)\right\rangle)/c$. To get the simplest approximation for the diffusion coefficient for the bubble, we neglect the "string-phonon-particle scattering" (SPP) term (the last term) of the above equation involving $\dot{R}_b(t)$ and get $\dot{R}_b(t) = h(t)$. The diffusion

coefficient is then found to be $D_0 = \frac{1}{2t} \int_0^t dt_1 \int_0^t dt_2 \langle h(t_1)|h(t_2)\rangle = c^{-1}$. One can write D_0 as a harmonic mean $D_0 = D_p D_s (D_p + D_s)^{-1}$, with $D_p = \zeta_p^{-1}$, $D_s = \left\langle \phi_c' \mid \phi_c' \right\rangle^{-1}$. It is interesting that within this approximation, D_0 is always less than D_p implying that the diffusion coefficient within the plug is less than outside, as expected [8]. To get a better approximation, one has to include the last term of the equation involving $\dot{R}_b(t)$. For this, we have to find $C_l(t)$. On taking inner-product of the equation involving $C_l(t)$ with $\Psi_l(x - R_b(t))$, and neglecting SPP scattering, we get $\dot{C}_l(t) = -\lambda_l C_l(t) + (\Psi_l \mid F(t))$, which can be solved with the condition $C_l(-\infty) = 0$ to get $C_l(t) = \int_{-\infty}^t dt_1 (\Psi_l \mid F(t_1)) \exp(-\lambda_l(t - t_1))$. One should now solve for $\dot{R}_b(t)$ and then calculate the diffusion coefficient. However, this is difficult, as the noise is multiplicative. We therefore adopt a simple minded approach in which $\dot{R}_b(t)$ on rhs is replaced by $h(t)$ to get the following equation $\dot{R}_b(t) = h(t)(1 + B(t)/c)$, where $B(t) = \sum_{l=1}^{\infty} \int_{-\infty}^t dt_1 (\Psi_l \mid F(t_1)) \exp(-\lambda_l(t - t_1)) \left\langle \phi_c'' \mid \phi_l \right\rangle$. If one further assumes that $h(t)$ and $B(t)$ are uncorrelated then the diffusion coefficient becomes $D = D_0 + \frac{1}{2tc^2} \int_0^t dt_1 \int_0^t dt_2 \langle h(t_1)h(t_2)\rangle \langle B(t_1)B(t_2)\rangle$. This is easy to calculate since the noises are delta function correlated and it becomes, $D = D_0 (1 + B/c^2)$, where $B = \langle B(t)B(t)\rangle = \sum_{l\neq 0} \left| \left\langle \phi_c'' \mid \phi_l \right\rangle \right|^2 / \lambda_l$. As $\phi_c''(x)$ is an even function of x, only ϕ_l that are symmetric will contribute in this sum. But as we saw above, they are identical with χ_l, and for them $\lambda_l = \varepsilon_l$. We can therefore write $B = \sum_l \left| \left\langle \phi_c'' \mid \chi_l \right\rangle \right|^2 / \varepsilon_l$. It is clear that one can expand the sum over l to include all l. Thus we get $D = D_0 \left(1 + \left\langle \phi_c'' \left| \widehat{G} \right| \phi_c'' \right\rangle / c^2\right)$. $\widehat{G} = \left(-\sigma \frac{\partial^2}{\partial y^2} + k + \Delta k Q(y)\right)^{-1}$ is the Green's operator. Note that in the Schrödinger operator $-\sigma \frac{\partial^2}{\partial y^2} + k + \Delta k Q(y)$, the term $\Delta k Q(y)$ vanishes at infinity. It is straightforward to calculate the diffusion coefficient for simple models of $Q(y)$. We define an enhancement factor $r = D/D_0 = \left(1 + \left\langle \phi_c'' \left| \widehat{G} \right| \phi_c'' \right\rangle / c^2\right)$. We now perform calculations for a simple model with $Q(y) = \theta(y - 1) - \theta(y + 1)$. Further, we put $\Delta k = 0$ so that the calculation becomes easy. Then one can find ϕ_c easily and obtain $E_c = -E_b + \alpha^2 \sqrt{k\sigma} \sinh(\sqrt{k/\sigma}) \exp(-\sqrt{k/\sigma})$, where E_b is the dimensionless value of the binding energy $(= E_b \beta)$. If $E_c \leq 0$, then the entry into the NPC has no activation energy (however, exit would be activated). The Green's function is $G(y, y_1) = \left(\sqrt{k/4\sigma}\right) \exp(-\sqrt{\frac{k}{\sigma}} |y - y_1|)$ so that $\left\langle \phi_c'' \left| \widehat{G} \right| \phi_c'' \right\rangle = \left(\sqrt{k/\sigma}\right) \left(1 - \exp(-2\sqrt{k/\sigma}) - 2\sqrt{k/\sigma} + 4k/\sigma\right)/8$. With these, we get $D_0 = 2\sigma/\delta$ with $\delta = (2\sigma\zeta_p + \alpha^2(\sqrt{k\sigma} - \exp(-2\sqrt{\frac{k}{\sigma}})(2k + \sqrt{k\sigma})))$ and $r = 1 + \dfrac{\alpha^2 \sqrt{\frac{k}{\sigma}} \exp(2\sqrt{\frac{k}{\sigma}}) \left(-1 + \exp(2\sqrt{\frac{k}{\sigma}}) - 2\sqrt{\frac{k}{\sigma}} + 4\frac{k}{\sigma}\right)}{2\left((-1 + \exp(2\sqrt{\frac{k}{\sigma}}))\alpha^2 \sqrt{\frac{k}{\sigma}} - \frac{2k\alpha^2}{\sigma} + 2\zeta_p \exp(2\sqrt{\frac{k}{\sigma}})\right)^2}$.

We now estimate the diffusion coefficient of the protein, assuming that the plug is a gel. As experimental information on the properties of the gel is scarce, the numbers used are only rough estimates. As the protein has size of a few nanometers, we take $R_0 = 10\ nm$, $\alpha = 10\ nm$ and $L_Y = L_Z = 30\ nm$. Temperature is taken to be 300 K. We take the diffusion coefficient of
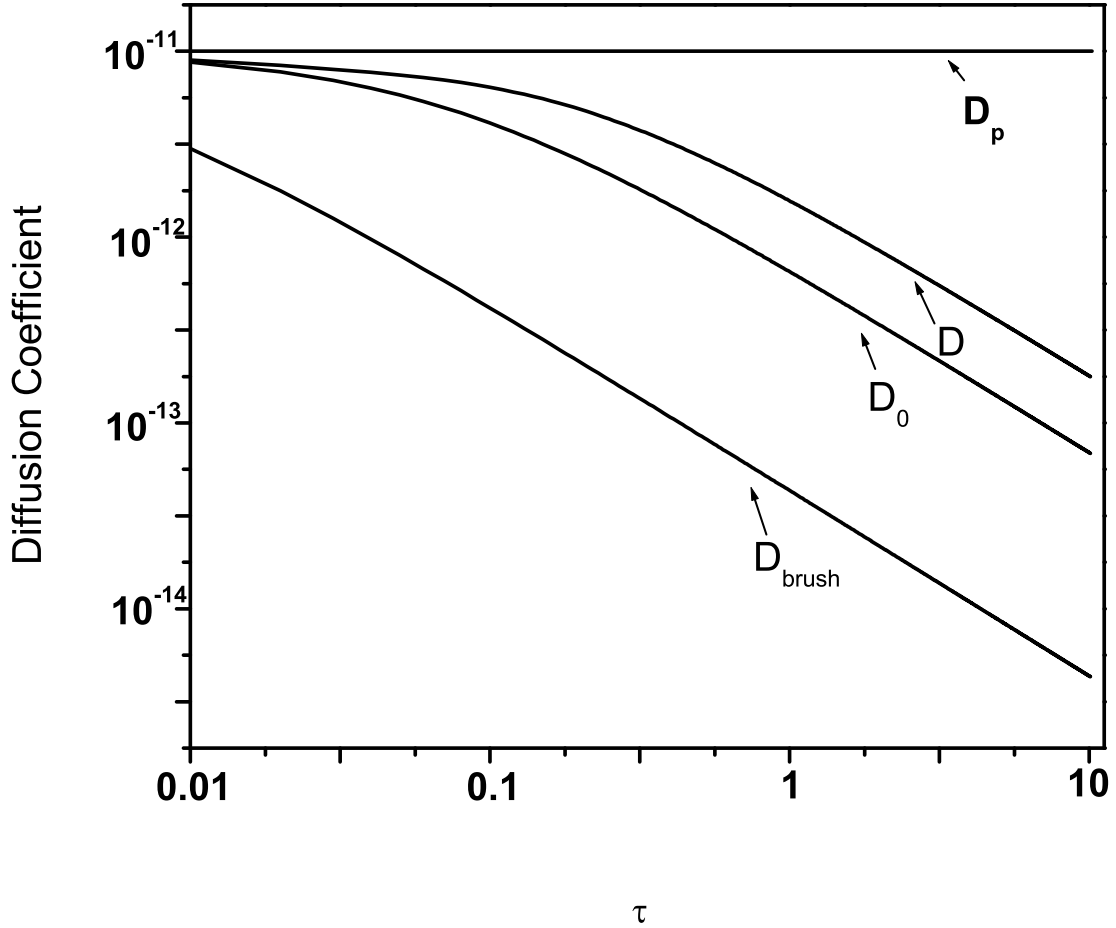
FIG. 1: Plot of the diffusion coefficient of the macromolecule against the longest relaxation time (τ). D_p is the diffusion coefficient outside the gel. D_0 and D with $\sigma = 2 \times 10^{-13} J/m$ (for the gel) and D_{brush} with $\sigma = 2 \times 10^{-15} J/m$.

the protein outside the network to be $D_p = k_B T/\zeta_p = 10^{-11} m^2 s^{-1}$, which gives the value of $\zeta_p = 4.14 \times 10^{-10} Js/m^2$. Considering a slab of dimensions L_X, L_Y and $L_Z(= L_Y)$, the energy required to deform it by a constant amount a in the Z-direction is $L_X a^2 Y/2$, where Y is the Young's modulus. Using our equation for E_{dis} for the same situation gives $k L_X a^2/2$. Equating the two, we get $k = Y$. Y for the hydrogel formed by nucleoporins in vitro has been measured to be 2000 Pa [13]. With this value for k, to produce a deformation with $\phi = 10 \ nm$ over a length of 20 nm requires only an energy of $1.2 kJ/mol$, which is $\sim k_B T/2$. So the deformation of the gel to produce a hole of the required size requires only thermal energy. So then, why does not the particle just deform the gel and get inside? The answer must be that to get inside, it will have to break the

network. It is known that a colloidal particle of size 5 nm is not able to get into the pore [7, 10]. This means that there must be at least one hydrophobic contact to be broken to create a hole of volume $(5nm)^3$. We will take the energy of a hydrophobic contact as $5k_BT$. Therefore, to create a hole of the size of a protein, $(20nm \times 10nm \times 10nm)$, one will have to break 16 hydrophobic contacts which will require an energy of $80k_BT$. This rather large energy requirement can be compensated by the formation of roughly the same number of hydrophobic contacts between the protein and the network. We estimated σ by putting the condition that the deformation energy due to the two quadratic terms of E_{dis} have the same value for creation of a deformation of size 10 nm over a length of 20 nm. This gave σ for the gel $\sigma_{gel} = 2 \times 10^{-13} J/m$. As no experimental data on the relaxation time of the network is available, we took $\zeta = 2\ Js/m^3$, so that the long wave length relaxation time τ of the gel would be 1 ms. This seems reasonable as the gel is formed due to rather weak hydrophobic interactions among FG units. These data correspond to the following values for the dimensionless parameters: $\alpha = 1, k = 1, \zeta_p = 0.0207, D_p = 1/\zeta_p = 48.3092$. With these values, we find: The value of D_0, diffusion coefficient of the protein inside the network to be $6.51 \times 10^{-13} m^2/s$. This means that putting into the network has reduced the diffusion coefficient by roughly a factor of ~ 15, as expected[10]. The value of $r = 2.4$ and hence $D = 1.56 \times 10^{-12} m^2/s$ - noise in the gel enhances the diffusion considerably. Putting the length of the NPC to be $50nm$, this would give a residence time of 1.6 ms for the particle. This estimates a transport rate of ~ 600 proteins/second which is roughly in agreement with the experiments [8]. In Fig. 1 we have made a plot of diffusion coefficient against the relaxation time (τ) of the gel, keeping all other parameters fixed which shows that the faster is the relaxation of the gel, faster is the diffusion of the macromolecule (protein) inside it. Further, the enhancement factor, r is ~ 2 for $\tau > 1\ ms$.

What would happen if the plug were a brush? In a brush, there are no hydrophobic contacts and hence there is no network. Any contact would contribute to the elasticity of the plug and therefore, if the plug were a brush, the value of σ would be much lower. The model is easily analyzed in the limit $\sigma \to 0$, to find that $D_0 \to 0$, $r \to 1$ so that $D \to 0$. Thus the diffusion coefficient of the particle within the brush would be much lower than in the gel. To demonstrate this, we have calculated the diffusion coefficient for the case with $\sigma = \sigma_{gel}/100$ and the results are given in the Fig. 1, and it is seen that the diffusion coefficient is lowered by a factor of 1/35.

It is also interesting to compare our results with those of Zilman *et al* [23]. In their model, the greater binding energy of the particle to the FG units would enhance the transport, by retaining the particles longer in the pore. The same thing would happen within our model too. The two models are similar in that the movement of the particle is co-operative, with the contacts at the

front being formed at the same time as the contacts at the back are being broken, leading to easy motion of the particle within the NPC. However, over approach is more detailed, and is able to take care of the limit where σ is small, which as we have argued, is very important.

In summary, we have proposed a model for the transport of a protein through the NPC. We find that a reversible gel would lead to larger diffusion coefficients than the polymer brush and hence we suggest that the plug of the NPC is a gel. However, final confirmation of this needs more experimental work and simulations.

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