

Simulation of obstacle overcoming by processive molecular motors

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Abstract: This work aims to study the dynamics of KIF1A in a noise-driven ratchet potential. KIF1A molecule is a single-headed kinesin which is specific to axonal transport in neurons. Recent studies have shown that the capability of this kind of motor to overcome an obstacle or a traffic jam that impedes the advance of a vesicle is strongly related to several neurodegenerative diseases like Alzheimer's. We model the interaction and displacement of the motor with a two state Brownian ratchet potential in two dimensions. With the numerical simulation of this model we are able to give an accurate prediction of the overcoming time of an obstacle, modelled as a Gaussian potential, as a first step towards a better understanding of the interplay between traffic dysfunctions and neurodegenerative diseases.

I. INTRODUCTION

In modern Biophysics the term “molecular motor” is referred to those molecules, typically proteins, which transduce chemical energy into mechanical work. This kind of molecules is really important for the proper functioning of the cell, and is involved in a large number of active processes [1,2]. Some typical examples of these processes are cell division, muscular contraction or vesicle transport [8].

Molecular motors are usually classified in two groups. A first group includes the so-called “*rower*” motors, which act in large assemblies like myosin that is involved in muscular contraction. The second group is known as “*porter*” motors, which are usually involved in intracellular traffic transport. These motors, such as kinesins, work either individually or in small groups [6] and are processive, that is, they perform a large number of steps before detaching from the microtubule (MT), where the motion takes place.

In this study, we focus our attention on translatory or linear motors (*porter* motors), specifically the one called KIF1A of the kinesin-3 family. We do not give a full explanation of their modelling, but rather present a generic description allowing to extract the main features of the physics involved, avoiding the biological complexity.

KIF1A is a *single-headed* plus-end kinesin which is specific to the transport of synaptic vesicle precursors in axons [4]. Trafficking conditions in neurons are extremely demanding due to the long distances that the motor has to travel (in a range from millimetres up to a few meters) being attached to the MT, the large cargoes involved and the crowded and constrained environment. In many cases the motor has to overcome roadblocks or traffic jams, and the ability to manoeuvre through these obstacles is crucial to ensure an efficient transport [4-6] and the arrival of the cargoes at their destination. The capability of travelling long distances without detaching from the MT is supported by the large number of motors available in the cell. Those motors could exert forces on a vesicle but they are limited by the liquid-like nature of the vesicle membrane. Consequently, tangential forces cannot be exerted. This implies that a large number of motors working cooperatively would not supply the ability to overcome an obstacle that impedes the advance of a vesicle, excepting if the motors make a force in the normal direction of the vesicle, where it can not be negligible [4]. Traffic dysfunctions in axons, like traffic jams, are

related to several neurodegenerative diseases like Alzheimer's [5,8].

It is singular that a monomeric (one-sided) kinesin like KIF1A could be responsible of this important task instead of a dimeric (two-sided) kinesin, which operates in a hand-over-hand mode and is more efficient than the monomeric type. Recently it has been shown that monomeric kinesins are more susceptible to work collectively and, consequently, to achieve large normal forces if the vesicle is stuck. KIF1A is self-adapted to cooperative action because of his Brownian dynamics nature. This motor operates on a two-state noise-driven ratchet mechanism and combines a strongly bound state to the MT and a weakly bound state. The weakly bound state allows the motor to diffuse freely along the MT, therefore causing the inefficiency of a single motor travelling in the filament, and it is reflected on the velocities around $\approx 0.15 \mu\text{m/s}$ and stall forces around $\approx 0.1 \text{ pN}$ obtained in single-molecule experiments [3]. Besides this is the reason whereby a group of monomeric motors is more efficient than a group of dimeric motors acting collectively. The monomeric type has a totally diffusive state and it is more receptive to modify its trajectory and overcome obstacles due to the forces exerted by other motors than the dimeric type, whose diffusive state affects only one of the two “heads” while the other “head” is attached to the MT.

II. MODEL FOR KIF1A DYNAMICS

The aim of this work is to develop an efficient simulation of a single KIF1A motor moving in alongside a MT which has a transversal barrier that the motor has to overcome. In order to model a single particle traveling around a MT with a two-state ratchet potential, we have used some approaches that have been proved really predictive for this kind of situations. The model is based on the Langevin equation

$$\lambda \frac{dx_i}{dt} = -U(x_i, k_i) - F\delta_{1i} + \zeta_i(t), \quad (1)$$

where $i=1$ for a single particle, k_i is a discrete stochastic variable that labels the two internal states of the motor, λ is a friction coefficient, $U(x_i, k_i)$ is a potential that describes the attached and detached states, $F\delta_{1i}$ is an external force and $\zeta_i(t)$ is a Gaussian white noise with autocorrelation

$$\langle \zeta(t)\zeta(t') \rangle = 2k_B T \lambda \delta_{ij} \delta(t - t') \quad (2)$$

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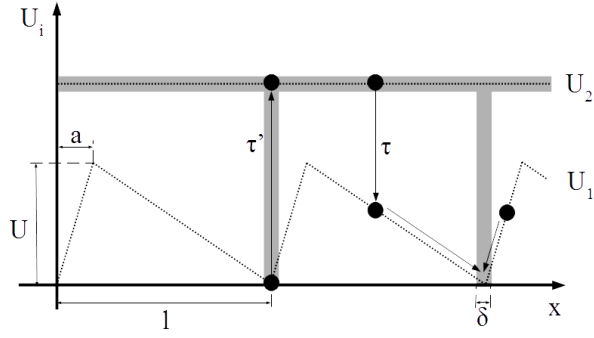


FIG 1. Representation of the two-state ratchet mechanism for KIF1A. U is the height of the potential, l is the period, a is the asymmetry parameter and δ is the region where the motor is excited to the detached state. Average excitation and decay rates of the motor in the potential U_1 and U_2 are respectively, τ' and τ . Gray zones indicate where the transitions are allowed. Small circles do not indicate the effective size of the motor, which is comparable to l but typically smaller.

We define a generic potential $U(x, k_1)$ (for simplicity U_1 state) like a sawtooth potential plotted in FIG. 1 which defines the strongly bound state (attached), and a flat potential $U(x, k_2)$ (for simplicity U_2 state) which defines the weakly bound state (detached). The friction coefficient λ is equal for both of the states. When the motor is in the attached state it perceives the effect of the U_1 potential and a white noise. If the motor captures an adenosine triphosphate (ATP) molecule, it switches to the detached state and notices only the white noise effect. It is remarkable that the motor can capture an ATP molecule only in a small neighbourhood δ around the U_1 potential minimum ($\delta \ll l$) after a typical mean time $1/\tau'$. KIF1A will return to the attached state after a lifetime of $1/\tau$. Motors excite and decay stochastically, with exponential distributed times with average values $1/\tau'$ and $1/\tau$ [4]. Due to the asymmetry of the sawtooth potential the motor will go ahead with more probability than going backwards.

The model has an important parameter that is worth to taking into account, which is the ratio $\beta = \tau/\tau'$.

A. Simulation of the motor dynamics in one dimension

Even though the aim of this project is to study the properties of a MT with a barrier as an obstacle, and how a single molecular motor like KIF1A could circumvent it, it is suitable to start from the simplest case: a motor in one dimension without barrier. This will be a way to ensure that the simulation is working properly. It has been considered a 1D lattice with the potential showed in Fig. (1), and Eq. (1) can be integrated numerically with the stochastic Euler algorithm

$$x(t + \Delta t) = x(t) - \frac{1}{\lambda} \frac{dU(x(t))}{dx} \Delta t - \frac{F}{\lambda} \Delta t + R\sqrt{2D\Delta t}. \quad (3)$$

Where D is the diffusion coefficient $D = \frac{k_B T}{\lambda}$ and it is the same for both potentials U_1 and U_2 , the integrating time step must be sufficiently small to make sure that the diffusion term and the deterministic velocity term are of the same order, R is a random Gaussian variable with average equal to

0 and variance equal to 1. The main parameters used in this model are realistic values obtained in the literature [4,5,3,10] and are shown in Table 1. The parameter β gives information about the time that a motor has to wait to capture an ATP molecule at the minimum potential compared with the time that the motor is traveling in the U_2 diffusive state. A $\beta = 0$ state indicates that there is a high ATP concentration in the environment and the dwell time is negligible. This case is studied and compared in this 1D simulation, however in the following sections it is only analysed the $\beta \neq 0$ case.

| Parameter | Value |
|-----------------------|----------------------------------|
| Periodicity | $l=8$ nm |
| Asymmetry parameter | $a=0.2l$ nm |
| Excitation region | $\delta=0.02l$ nm |
| Excitation rate | $\tau' \leq 250$ s ⁻¹ |
| Decay rate | $\tau=250$ s ⁻¹ |
| Diffusion coefficient | $D=20$ nm ² /ms |
| Potential maximum | $U=20k_B T$ |

TABLE 1. Values for the main parameters for the simulation of KIF1A motor. All values are completely realistic except for the asymmetry parameter a , which is difficult to extract from experiments. This parameter reduces the velocity of the motor and its value has been adjusted in order to simulate the real skills of the motor.

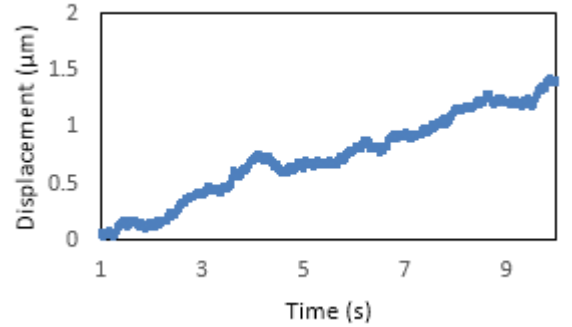


FIG 2. Displacement of the KIF1A motor along the ratchet potential.

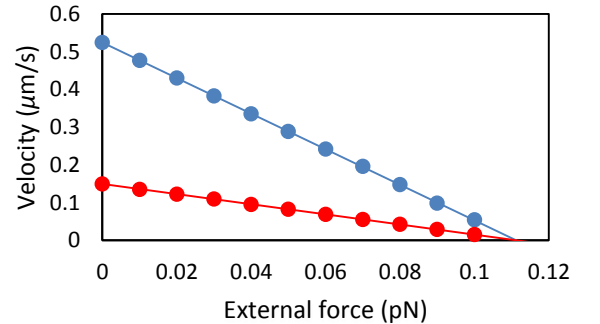


FIG 3. Representation of the Velocity-Force curves for $\beta = 0$ (Blue) and $\beta = 2.5$ (Red). The stall force of a single motor is ≈ 0.1 pN. The statistical error is comparable to the size of the dot.

Iterating the equation (1) we obtain a stochastic achievement of the KIF1A motor trajectory in different conditions of external load. In Fig. (2) it can be seen the

advance of the motor, verifying that the asymmetry of the sawtooth potential, together with the fact that there is a region where the velocity is negative, only makes the advance more slow. Checking the truthfulness of the simulation we have represented the average velocity in terms of the external force.

The results in Fig. (3) are consistent with the ones reported in the literature [5,8].

B. Simulation of the motor dynamics in two dimensions

The validity of the results obtained in the one dimension case let us keep on with the simulation and introduce the second spatial coordinate, thus creating a two-dimensional surface. In consequence, the potential form has to change adapting to the surface. The potential reproduced in Ref. [9], adapts to a two-dimensional oblique Bravais lattice with primitive vectors \mathbf{a}_i , $i = 1,2$, forming an angle $\theta > 0$, which is modelling the MT structure.

The position of the motor in the surface is denoted as $\mathbf{r} = x\mathbf{e}_x + y\mathbf{e}_y$ and the position of the nodes $\mathbf{R}(n_1, n_2) = n_1\mathbf{a}_1 + n_2\mathbf{a}_2$, where n_1 and n_2 are integer numbers. The primitive vectors of the lattice are:

$$\begin{aligned} \mathbf{a}_1 &= l_1\mathbf{e}_y \\ \mathbf{a}_2 &= l_2(-\sin\theta\mathbf{e}_x + \cos\theta\mathbf{e}_y) \end{aligned} \quad (4)$$

Where l_1 and l_2 are the periodicities for the primitive directions respectively, and $\theta = 80^\circ$. The reciprocal basis obtained are

$$\begin{aligned} \mathbf{q}_1 &= 2\pi \frac{\mathbf{a}_2 \times \mathbf{e}_z}{|\mathbf{a}_1 \times \mathbf{a}_2|} = \frac{2\pi}{l_1}(\cot\theta\mathbf{e}_x + \mathbf{e}_y) \\ \mathbf{q}_2 &= 2\pi \frac{\mathbf{e}_z \times \mathbf{a}_1}{|\mathbf{a}_1 \times \mathbf{a}_2|} = -\frac{2\pi}{l_2}(\csc\theta\mathbf{e}_x) \end{aligned} \quad (5)$$

Once the reciprocal basis is set, it has to be proposed an adequate potential, this potential will be asymmetric and periodic in the primitive directions. The one chosen is $U = V_1 + V_2$ with V_1 and V_2

$$V_i(x, y) = V_0[\sin(\mathbf{q}_i \cdot \mathbf{r}) + \mu_i \sin(2\mathbf{q}_i \cdot \mathbf{r})] \quad (6)$$

Where V_0 is the amplitude of the chosen potential and $\mu_i \in [0, \frac{1}{2}]$, $i = 1,2$ are the asymmetry parameters for the primitive directions. For illustrative purposes the potential is represented in Fig. (4).

Assuming the validity of this assumptions we have to determine the value of the periodicity l_2 , and the asymmetry parameters μ_1 and μ_2 . KIF1A travels along a microtubule that is made of 13 protofilaments, which means that the motor has to overcome 13 potential peaks in the transverse direction to make a full turn around the MT. Dividing the perimeter of the filament over the number of potential peaks $l_2 = \frac{2\pi r}{N}$, the periodicity of the transversal coordinate can be easily calculated. The value of the MT radius is between 12 nm and 12.5 nm, then $l_2 \sim 6$ nm. The asymmetry parameter of the

parallel coordinate μ_1 can be calculated imposing only one dimension y in the proposed potential. We know that the periodicity of the parallel y direction of the MT is $l_1 = 8$ nm. Therefore, making $x = 0$ and $y \neq 0$ the value of the asymmetry parameter μ_1 which reproduces better the results obtained in the one-dimensional case for $\beta = 2.5$ is 0.23.

In order to obtain the value of the asymmetry parameter of the transversal coordinate μ_2 , we have focused on some experimental results that give the value of the pitch of a single motor in absence of an external force. Simulating the dynamics of the KIF1A motor along the 2D potential, with the values of the parameters obtained above, for different values of the asymmetry parameter we can obtain the total displacement in X and Y directions. The pitch P is the distance that the KIF1A motor has to travel in the parallel direction in order to complete a full turn in the transversal direction of the MT. Using the X, Y displacements calculated before, the total angle spanned is $\alpha = \arctan\left(\frac{X}{Y}\right)$. By using this angle and the radius of the MT it is possible to calculate the pitch

$$P = 2\pi r \cotan(\alpha) \quad (7)$$

These results are shown in Table (2) where it can be seen the relation between the pitch and the μ_2 parameter. Experimental results give a value of the pitch for a single monomeric kinesin of 300 nm approximately [8]. This model shows that the asymmetry parameter that simulates this result is $\mu_2 = 0.07$. This result gives a value for the parallel and transversal velocities of $v_Y = (0.149 \pm 0.001) \mu\text{m/s}$ and $v_X = (-0.036 \pm 0.001) \mu\text{m/s}$.

| Pitch (nm) | Asymmetry parameter μ_2 |
|------------|-----------------------------|
| 433 | 0.05 |
| 348 | 0.06 |
| 306 | 0.07 |
| 254 | 0.08 |
| 230 | 0.09 |
| 215 | 0.10 |
| 191 | 0.11 |

TABLE 2. Values of the pitch for different transversal asymmetry parameters. The statistical error of the pitch values is about 10% of its value.

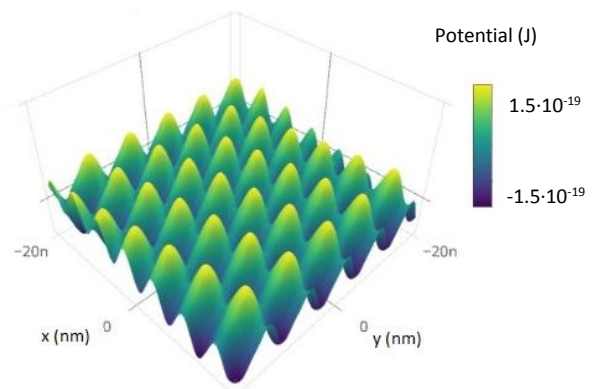


FIG 4. 2D potential with the parameters l_2 , μ_1 and μ_2 found.

III. RESULTS

Once the variables of the model are set and the simulation gives accurate and realistic results for the KIF1A motor dynamics in the MT, the obstacle can be introduced in the system.

The complex structure of a filament with a ratchet potential such as the modelled in the previous section enables the motor to advance through the parallel direction with a left biased motion in the transversal direction. This results in a helicoidal motion of the monomeric kinesin along the MT surface. This ability of twisting around a tube gives the motor a chance to avoid obstacles. Due to the left-handed biased motion, if something obstruct the parallel displacement from the kinesin, the motor will be able to surround the obstacle and keep on with the vesicle transport.

That obstacle can be a traffic jam or an inefficient kinesin obstructing other motors. A possible choice to model this type of impediment is a gaussian potential barrier in the MT surface. This barrier will be formed by a series of small gaussian potentials placed side by side along the transversal direction of the filament. The form of these small potentials is

$$G(x, y) = V_G \exp\left(-\left(\frac{(x - x_0)^2}{2\sigma_x^2} + \frac{(y - y_0)^2}{2\sigma_y^2}\right)\right) \quad (8)$$

where V_G is the gaussian height and it is 5 times larger than the ratchet potential maximum, σ_x and σ_y are the x , y width with values 1.5 nm and 0.5 nm respectively, x_0 and y_0 values are the position of the centre of each small potential barrier. Coupling the barrier with the described ratchet potential, the general form will be $U(x, y) = V_1(x, y) + V_2(x, y) + G(x, y)$. This model will consist in a 300 nm length filament with a perimeter of 75 nm with a gaussian wall placed transversally at the centre of the MT. For the simulation, the gaussian wall will adopt different values of its transversal width, from 37.5 nm, which is a half of the period, to 0 nm for the control situation. Simulating for the first time in the literature how a motor can overcome this type of barrier, the mean first passage time obtained will be shown in Fig. (5).

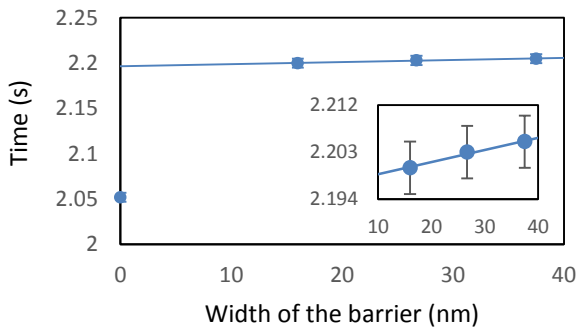


FIG 5. Representation of the average time that a motor needs to travel 300 nm in the parallel direction in front of different widths of the potential barrier.

The representation above shows the difference between the traveling times in a MT without any obstacle in comparison with the time with an obstacle of different width. In order to improve the interpretation of these results in Fig.

(7) and Fig. (6) there are represented the first passage time for a simulation with a half period barrier and for the free track simulation respectively.

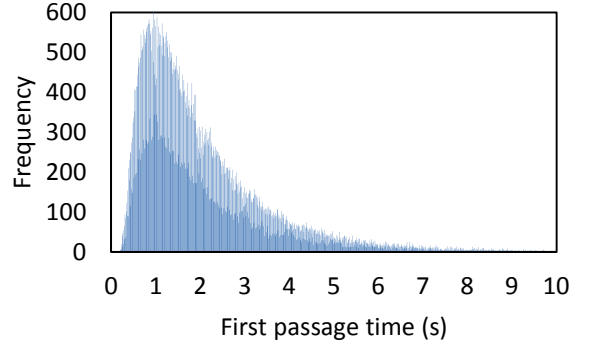


FIG 6. First passage time for a simulation with no barrier.

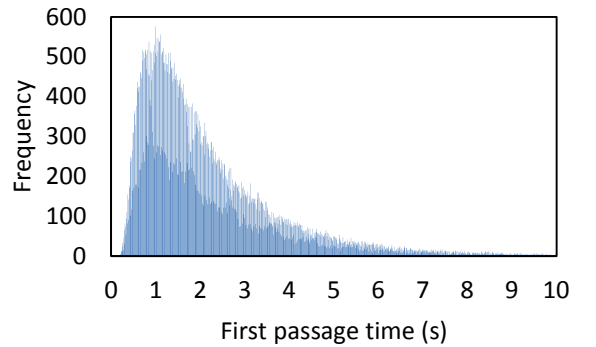


FIG 7. First passage time for a simulation with a half-period barrier.

By comparing these two graphics it can be observed that the peak of the first passage time with a half-period barrier is lower than the no-barrier, and the tail of the histogram is wider. This is due to the potential barrier, that make the motors move slower than in the no-barrier case.

To summarize, draw upon experimental results, in this work we have developed a model to describe the dynamics of the KIF1A motor along a filament with a potential barrier in order to study the behaviour of a single kinesin in demanding trafficking conditions.

IV. CONCLUSIONS

- The ideas that emerge from the analysis of the previous sections can be briefly summarized. We have developed a two-dimensional model that simulates the dynamics of a single monomeric kinesin in an impaired filament. The reduced mobility of these motors caused by obstacles in the microtubule is a possible cause of several neurodegenerative diseases. The model is based in a two-state ratchet potential solved by a Langevin equation and simulated with a stochastic Euler method, first simulating for one dimension and later extending to the two-dimensional case. Both situations have reported satisfactory results,

sustaining our hypothesis. Introducing real values obtained from experiments in some parameters of the model, we have found evidence of the effect that an obstacle causes to the KIF1A motion. The potential wall introduced is modelled as a series of gaussian potentials along the transversal direction of the microtubule. This model allows to extract information about the monomeric kinesin dynamics along a MT that is hardly accessible from experimental observation. To our knowledge this is the first time in the literature that a model which incorpores a potential barrier is simulated.

- The conclusions of this work encourage to delve into the study of monomeric kinesin motors and expand our knowledge about this topic. The results obtained could be improved by iterating more cases in the simulation, consequently reducing the statistical error of some parameters. The next logical step would be to do more realistic the traffic jam approximation and change the form of the potential barrier. An example could be if it was formed by a random distribution of single gaussian

potentials, emulating a certain number of inefficient kinesins which were obstructing the vesicle transport in axons. Another situation to take into account would be to put an external force and find the dependence of the first passage time with the external force. To conclude this study, it would be worth to mention an interesting phenomena not studied in this work such as the behaviour of a group of motors acting collectively. Such study could completely change and definitely improve our whole understanding of the axonal transport.

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