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Internal degrees of freedom in a thermodynamical model for intracell biological transport

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Abstract

The mechanism for intracell transport based on the 1D motion of certain proteins along the cytoskeleton microtubular fibres, substantiated by recent experimental biological research, is analysed from the perspective of a non-equilibrium thermodynamical model which incorporates an internal protein degree of freedom. The role of resonances between internal and external length scales in the mechanism functioning is succintly analysed from the perspective of the cell-biological potentialities of the model. Copyright © 1998 Elsevier Science B.V.

The experimental facts that life sciences have to deal with are often too complex when an elementary (or reductionist) approach is adopted. These types of approaches are anyway illuminating when essential energetic ingredients are correctly captured by some *thermodynamical* model, and valid analyses are tried on it, with the purpose of a better comprehension and appreciation of those complex facts.

We will call attention here on a type of statistical mechanical models which are currently being pushed forward in the recent (bio-)physical literature as thermodynamical model engines with plausible cell-biological significance [1–9]. To this end, we will start with some considerations on the (meso-)scales involved in intracellular transport processes. Then we will shortly discuss the biological facts which give support to the energetics and dynamics involved in the particular transport mechanism under study, so providing motivation for the introduction of an additional "motor"-protein internal degree of freedom in the description. After that, some preliminary numerical results on the model will be shown and perspectives for future research will briefly be analysed.

Cells are relatively small: their linear size scale covers a range from 2 to 20 microns. It has been argued that this range is bounded below and above quite naturally; the sizes of the biomolecules considered as essential for life certainly impose a lower bound. Upper bounds, however, can display an interesting relation to cellular metabolic rates. In particular, the metabolic rates give a time scale τ which, through the Ernst–Einstein relation

$$\tau \sim \frac{d^2}{D}, \tag{1}$$

provides a characteristic length scale d, where D is the diffusion coefficient. Whenever $3d$ diffusion processes are the dominant intracell transport mechanisms, like in prokariotic cells, as linear size increases by a factor of 10, the metabolic rythm is

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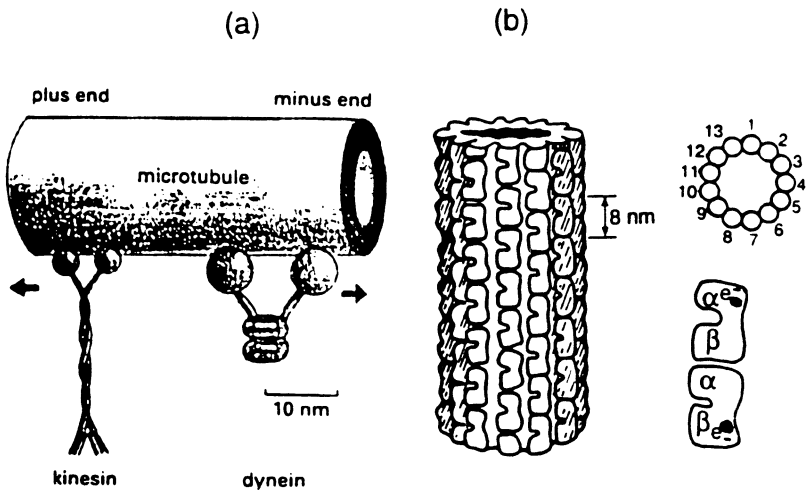

Fig. 1. (a) Textbook schematic representation of kinesin and dynein bound to the microtubular fibre; (b) Microtubule structure, cross section and two neighbouring dimers.

delayed by a factor of one hundred. It seems then intuitive that in more developed (and so more complex) cells, like eukariots, intracellular transport mechanisms cannot exclusively be based on 3*d* diffussion processes.

Although it was known half-a-century ago that certain proteins are involved in a mechanism of 1D transport which uses the pathways expanded by the cytoskeleton microtubular fibres, it has not been up to these last 10 years that it has been understood to the extent of its biophysical modellisation. The mechanism we are speaking about is also believed to be directly related to transport of information in the nerve system functioning [10]. The proteins which carry over the chemicals along the microtubules are referred to in the biological literature as *Molecular Motors* (Fig. 1) (kynesins, dyneins; etc.) Their motion is significantly directional, an observation which is at the origin of nice discussions in recent works [2–4,8,9,11,12] where some relevant non-equilibrium statistical mechanical questions have been addressed.

Before entering into the thermodynamical modellisation, it is important for what follows an understanding of what the biological experimental evidence indicates on the energetics of the macromolecules involved, a point on which there is nowadays some literature available [13–16], though acceptedly much remains to be understood in this respect.

(i) These proteins have two motor domains referred to as "heads"joined by a chain (see Fig. 1).
(ii) These two heads interact with the microtubule by forming temporarily bound states and receive energy via an ATP hydrolysis cycle which plausibly alters the binding energetics.
(iii) Due to the polarisation state of the structural blocks (α- and β-tubulin) forming the microtubule, the binding states of the two heads are different.

In assuming (ii) and (iii), we follow the proposed interpretation by Rosenfeld et al. [16] of their experimental results.

Focussing attention on (ii), a single-particle Langevin dynamical model, with a superimposed timescale which modulates the fluctuations and a characteristic length scale imposed by the periodic microtubular substrate, has allowed the statistical mechanical analysis of the protein transport along microtubules concluding that "Under (colored noise) non-equilibrium conditions, directional transport characterises the steady-state of the dynamics, provided the periodic substrate interaction (motor-microtubule) posses spatial asymmetry" [2].

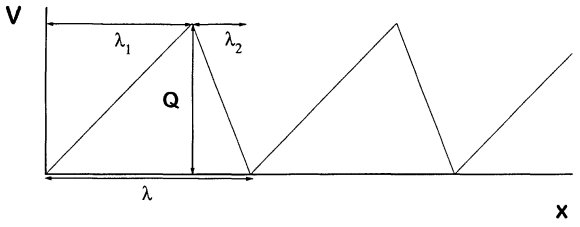

Fig. 2. Simple motor-microtubule interaction potential $V(x)$, introduced in [2]. The microtubular lattice unit is λ and the potential maxima of height Q occur at $\lambda_1 + n\lambda$ with n integer.

The timescale which modulates temporal fluctuations is determined by the hydrolysis cycle, which is in turn controlled by the ATP local concentration (energy reservoir), while the length scale is set up by the microtubular lattice unit λ (about 8 nm.).

Observation (iii) not only provides a plausible origin to the necessary asymmetry of the motor-microtubule interaction, but also suggests that this asymmetry influences the protein motion by acting on *two* degrees of freedom which evolve cyclicly among two different binding states. This makes sensible the question on the role of an additional protein internal degree of freedom.

The question we pose when introducing into the model this internal degree of freedom is that of its influence (if any) on the efficiency and characteristics of the mechanism functioning. A simple way to insert this ingredient into the above-mentioned Langevin dynamical model is to modelling the molecular motor as a dimer where two heads are (linearly or not) coupled. This is for sure a rough approximation to the "flexibility of the dimerisation segment which allows the relative rotation of the heads" [16], but it permits a fast view on the role played by the internal stresses which add a new length scale into the model. The idea of a mismatched structure altering the transport in a stoschastic ratchet was independently introduced in [9,17] in relation with the directionality of the motion. Thermal fluctuations versus resonance robustness are going to determine the overall functioning of these brownian dimers moving on asymmetric periodic substrates in non-equilibrium conditions which are induced by the time-scale of hydrolysation, and which so efficiently converts chemical energy into available work. Our aim is to analyse a very simple thermodinamical model, that is, to capture the essential and relevant energetics of this problem; by no means we pretend to present a realistic biological model.

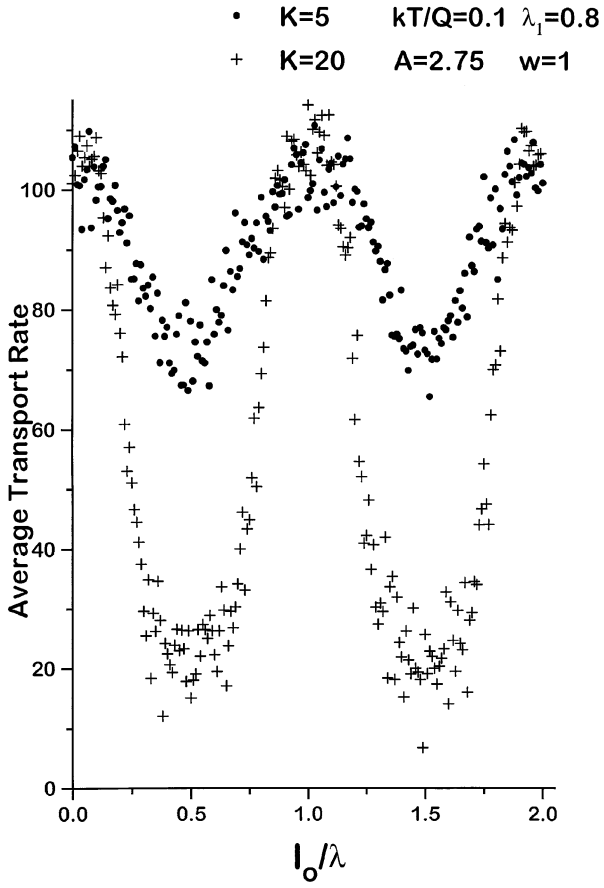

Fig. 3. Average transport rate versus internal-external legth scale ratio, l_0/λ. The other model parameters are shown.

More specifically, we consider the Langevin dynamics of the dimer $u \equiv (u_1, u_2)$ with both space and time modulation:

$$\dot{u} = -\frac{\partial \mathcal{H}}{\partial u} + A\sin(\omega t) + \xi(t), \tag{2}$$

where $\mathcal{H}(u)$ is the free energy assumed for the dimer, the periodic modulation set the time-scale $2\pi\omega^{-1}$ and $\xi(t)$ is a white gaussian noise of two independent components $\xi(t) \equiv (\xi_1, \xi_2)$ where, $\langle \xi_j(t)\xi_j(s)\rangle = 2k_{\mathrm{B}}T\delta(t-s)$, $\langle \xi_j(t)\rangle = 0$ for $j = 1, 2$. A simple

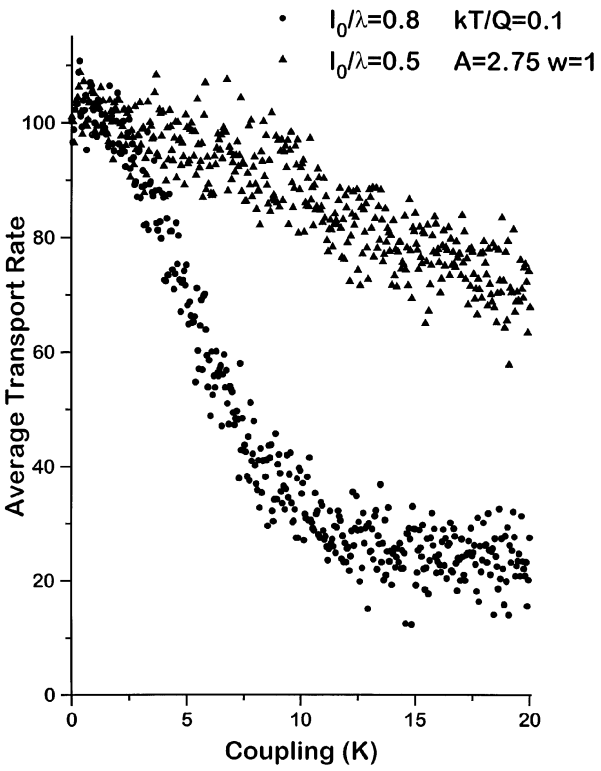

Fig. 4. Average transport rate versus coupling strength K. Two different mismatching ratios are shown.

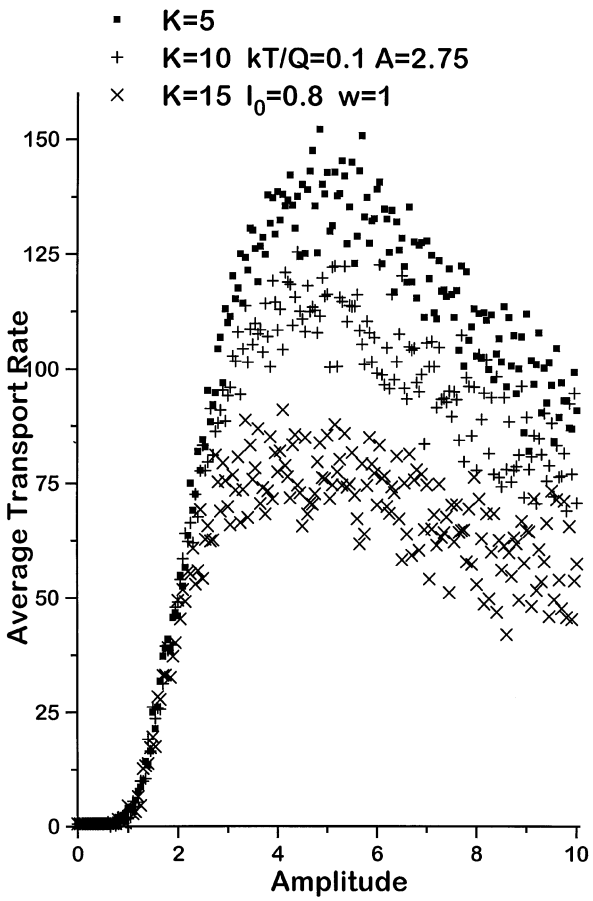

Fig. 5. Average transport rate versus amplitude of energy input (hydrolysis ATP cycle). Note the recoiling of optimal amplitude when coupling strength increases.

choice for $\mathcal{H}(u)$ is the following:

$$\mathcal{H}(u) = V(u_1) + V(u_2) + W(u_2 - u_1) \tag{3}$$

with $V(x)$ the two-parameter sawteeth potential considered in [2] (Fig. 2), and $W(y) = (1/2)K(y - l_0)^2$. As the simulation provides numerical estimates of the steady-state probability measure giving, for example, the average transport rate and other steady-state averages, it offers the opportunity to get a glance at the effects of the internal degree of freedom on mean steady-state descriptors.

Fig. 3 shows the average transport rate (number of microtubular lattice units, jumped by the two heads centre of mass, per unit time) obtained from (rough) simulations of Eqs. (2) with other parameters almost adjusted to optimality conditions. It is plotted versus the length scale set-up by the internal degree of freedom, l_0/λ. Harmonic resonances are clearly seen when $l_0/\lambda \simeq n$ (integer) enhancing transport. The delaying effect of the "out-of-resonance" condition severely affects the transport rate as indicated in Fig. 3.

The intensity K of the internal coupling influences significantly the transport rate (see Fig. 4), particularly when mismatching between length scales is present. The effect on optimal amplitude of energy input is shown in Fig. 5 for a matching of $l_0/\lambda = 0.8$ (a value compatible with the structural biochemical estimations of dynein to tubulin length ratio).

These preliminary results open up several questions on the functioning of the mechanism from a non-equilibrium thermodynamics perspective. Also, from the biological interest side, some research is needed to understand more deeply the differences between kynesin and dynein regarding the energetics of binding,

specially in connection to their opposite directional motion. For example, a clear understanding of the polarisation states (with its possible dynamics) in the microtubule could permit a better anchored analysis of this issue. The model could serve as a guide to experimental design, helping to understand what is and is not important in determining the functioning of biological molecular motors.

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