Anomalous transport of subdiffusing cargos by single kinesin motors: the role of mechano–chemical coupling and anharmonicity of tether

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Abstract
Here we generalize our previous model of molecular motors trafficking subdiffusing cargos in viscoelastic cytosol by (i) including mechano–chemical coupling between cyclic conformational fluctuations of the motor protein driven by the reaction of ATP hydrolysis and its translational motion within the simplest two–state model of hand-over-hand motion of kinesin, and also (ii) by taking into account the anharmonicity of the tether between the motor and the cargo (its maximally possible extension length). It is shown that the major earlier results such as occurrence of normal versus anomalous transport depending on the amplitude of binding potential, cargo size and the motor turnover frequency not only survive in this more realistic model, but the results also look very similar for the correspondingly adjusted parameters. However, this more realistic model displays a substantially larger thermodynamic efficiency due to a bidirectional mechano–chemical coupling. For realistic parameters, the maximal thermodynamic efficiency can transiently be about 50% as observed for kinesins, and even larger, surprisingly also in a novel strongly anomalous (sub)transport regime, where the motor enzymatic turnovers become also anomalously slow and cannot be characterized by a turnover rate. Here anomalously slow dynamics of the cargo enforces anomalously slow cyclic kinetics of the motor protein.

1. Introduction
The problem of how molecular motors can operate and realize transport in such a crowded environment as cytosol of biological cells [1–3] came only recently in the limelight of attention [4–12]. Indeed, numerous recent experiments reveal that submicron particles like various endosomes and organelles, mRNA molecules, ionic channels and even smaller nanoparticles diffuse passively anomalously slow with the mean-square distance growing sublinearly in time rather than normally diffuse (linear growth) on the relevant mesoscopic time and spatial scales [4, 6, 13–30]. Molecular motors such as various kinesins are thus indispensable for delivering such and similar cargos e.g. along axons of neuronal cells [31]. In a two-state flashing ratchet model of molecular motors with position-independent switching rates it has been shown that a power stroke like operation mechanism can perfectly overcome subdiffusion slowness and result into a highly efficient normal transport characterized by mean transport velocity [10, 11]. This result is not trivial because within the simplest anomalous transport model, where the action of molecular motor on subdiffusive cargo is modeled by a constant force applied to the cargo, the cargo is always anomalously slow [4, 7]. In this anomalous transport regime the mean distance covered by cargo grows sublinearly in time, \( \langle \delta x(t) \rangle \propto t^{\alpha} \), with the same power law exponent \( 0 < \alpha < 1 \), which characterizes free subdiffusion. Also within the sub-diffusive rocking ratchet model [5, 8] the transport is anomalously slow with the same exponent \( \alpha \). The same happens also within the flashing potential ratchet model, where the potential switches either periodically, or stochastically between zero (free subdiffusion) and a spatially asymmetric periodic potential form [9]. In order to realize the normal transport in a
subdiffusive environment the trapping ratchet potential should switch between two realizations which differ by a half of the spatial period translation [10, 11]. Then, the transport can be both anomalously slow, and normal. It depends on (i) the binding strength of motor protein to the microtubule, which provides a transport highway, (ii) cargo size, (iii) the motor operating frequency, (iv) external force directed against the processive motion of the motor [10, 11], and (v) the strength of the tether or linker connecting the motor and its cargo [11]. The theory, which allows to explain this complicated interplay, is based on non-Markovian generalized Langevin equation (GLE) [32, 33] description of cytosol viscoelasticity [34–38] and its multi-dimensional Markovian embedding [36, 38].

The GLE approach has proven its utility also in describing anomalous conformational dynamics of proteins [39]. It is deeply rooted in the main principles and dynamical foundation of statistical mechanics such as dynamical theory of Brownian motion and the fluctuation–dissipation theorem (FDT) [32, 33]. Importantly, FDT must hold when a physical system is at thermal equilibrium. The approach explains the dynamical origin of both normal and anomalous Brownian motion and naturally extends beyond thermal equilibrium, which makes it most suitable to describe physical processes in living cells. Our theory explains naturally, in particular, why the power law exponent of anomalous active transport can be larger than one of the passive subdiffusion and why the power law exponent of driven anomalous Brownian motion can be larger than doubled exponent of the passive motion, as measured experimentally [6, 30]. Such experimental facts cannot be consistently explained within the previous approaches [4, 7] to anomalous transport by molecular motors, as detailed in [11]. In fact, we are developing a non-Markovian generalization of the Brownian ratchets approach to modeling of molecular motors [40–51], with a well proven utility in the case of memoryless Markovian dynamics, towards anomalous non-Markovian dynamics with long-lasting memory, which reflects viscoelastic effects in cytosol. Such non-Markovian dynamics can nevertheless be considered as a low-dimensional projection of a multi-dimensional Markovian dynamics—the idea which has a long tradition in statistical mechanics [53].

As is well known, microtubule is a periodic electrically polar structure featured by asymmetric periodic distribution of negative and positive charge densities on its surface [1, 54]. It has a spatial period $L = 8$ nm. Furthermore, the charge state of the motor protein depends on whether it is nucleotide free (no extra charges are present), either ATP, or ADP and the phosphate group $P_{i}$ are bound (three extra negative elementary charges altogether in each case), or only ADP is bound (two extra negative elementary charges). The motor binding potential energy $U(x, \zeta)$ in the electrical field of microtubule can also change accordingly, reflecting the charge distribution on the motor protein [43] and its conformational state $\zeta$, or chemical reaction coordinate [41, 46]. Being periodic in space, $U(x + L, \zeta) = U(x, \zeta)$, at fixed $\zeta$, the binding potential should, however, be spatially asymmetric, and this asymmetry can direct molecular motor in one selected direction (which can depend on the particular kind of motor) when the binding potential energy begins to stochastically fluctuate due to ATP binding, hydrolysis and dissociation of the products, repeated cyclically at random time instances. For two-headed kinesins, one of the simplest, minimal model assumptions is to consider just two spatial realizations of $U(x, \zeta)$ depending on two motor states $\zeta = \zeta_{1}$ and $\zeta = \zeta_{2}$ with the additional symmetry $U(x + L/2, \zeta_{1}) = U(x, \zeta_{2})$ (the heads are assumed to be identical and treated on equal footing) [41–45, 49]. This ensures that two subsequent half-steps of the equal length $L/2$ make one total step $L$ in the direction defined by the asymmetry of the potential, see in figure 1, therein from the left to the right. Kinesins consume one ATP molecule per one full step. Hence, the energy $\Delta G_{ATP}/2 \approx 10 k_{B} T \approx 0.25$ eV is invested into a half-step, within this model. Simplest further assumption is to characterize the switching process by one spatially-independent rate $v_{1} = v_{2}$, so that the averaged motor turnover frequency is $\nu = v_{1}/2$. A shortcoming of this approach is that it does not specify a mechanism of how the energy of ATP hydrolysis is invested into the change of $U(x, \zeta)$. Neither reflects it the back influence of the mechanical motion along microtubule on the biochemical turnovers of the motor enzyme. Nevertheless, this ratchet approach remains immensely popular for Markovian dynamics [42, 47–49, 51]. It has been generalized to anomalously operating motors in [10, 11]. However, the role of mechano–chemical coupling [41, 42, 45, 47, 52] for anomalous transport by molecular motors was not studied thus far.

This is one of the primary goals of this paper to clarify how the bidirectional mechano–chemical
coupling affects the previous results [10, 11] obtained for the viscoelastic medium. We consider a simplest popular model of kinesins with spatially- and $\Delta G_{\text{ATP}}$-dependent transition rates $\nu_{1,2}(x)$ reflecting mechano–chemical coupling of the translation motion of the motor protein and its conformational cyclic dynamics [41, 42, 45]. Below we show that the most results of the previous work not only remain valid, but also look very similar for the correspondingly adjusted parameters. Even more important, our present more realistic setup allows to address the following question of fundamental importance: can enzyme turnovers in a crowded interior of living cell be always characterized by a turnover rate? Or maybe, they can become anomalously slow, i.e. the number of turnovers can grow only sublinearly in time under the (back) influence of the subdiffusing cargo, in the case of molecular motors. In such a case, the motor enzyme turnovers cannot be characterized by any rate anymore. The most surprising novel result of this paper is that this is indeed the case, if the amplitude of the binding potential $U_b$ becomes larger than about 20 $k_B T_\text{r}$, i.e. a characteristic energy derived from the hydrolysis of one ATP molecule. We address also the stochastic energetics of molecular motors [41, 42, 46, 60]. Here, a profound difference emerges with the thermodynamic efficiency of the anomalous flashing ratchet motors [10, 11]. In the considered more realistic model, it is essentially larger, and we will discuss the reasons why. Most surprisingly, in the regime of anomalous motor turnovers thermodynamic efficiency can reach transiently 70%, for a realistic $U_b = 25 k_B T_\text{r}$. This is at odds with common intuition which is still reluctant to recognize the power of FDT and its implications for the stochastic transport on nano- and meso-scales. In addition, we also consider an anharmonic model for the tether connecting the motor and the cargo by taking into account its maximally possible extension length. The present model encompasses the previous harmonic tether model [11] as a limiting case used for comparison.

2. The model and methods

We start from considering subdiffusive overdamped 1d dynamics of a motor with radius $a$, and a generalized spatial coordinate $y$. It is subjected to both the viscous Stokes friction with friction coefficient $\eta$, and the corresponding thermal random forces $\xi(t)$ and $\xi_{\text{mem}}(t)$ of the environment at temperature $T$, which are completely characterized by their autocorrelation functions

$$\langle \xi(t) \xi(t') \rangle = 2k_B T \eta \delta(t-t'), \quad \langle \xi_{\text{mem}}(t) \xi_{\text{mem}}(t') \rangle = k_B T \eta_{\text{mem}} \left| t - t' \right|. \quad (1)$$

The above relations express the second (classical) FDT by Kubo [32, 33], which has a very important physical content. Namely, at thermal equilibrium the energy loss due to the friction is completely compensated by the energy gain from the thermal stochastic force serving as a ‘stochastic lubricant’. Without it the motion would stop due to the frictional losses. However, beyond thermal equilibrium there emerges an overall heat flux to the environment, even in the absence of a temperature gradient. Minimizing this heat flux one can arrive at the best thermodynamic efficiency of transport. This is a very important point: there is no need to minimize the friction, contrary to a popular belief, but rather try to stay most closely to the thermal equilibrium, in order to minimize the heat losses.

Furthermore, the cargo is coupled to the motor with coordinate $x$ by an elastic tether or linker for which we use a finitely extensible nonlinear elastic (FENE) model [55] with coupling energy

$$U_{\text{inc}}(r) = -\frac{1}{2} k_L r_{\text{max}}^2 \ln \left( 1 - r^2/r_{\text{max}}^2 \right), \quad (3)$$

where $r = x - y$, and $k_L$ is an elastic coupling constant. For a small extension, $r \ll r_{\text{max}}$, $U_{\text{inc}}(r) \approx (1/2) k_L r^2$, recovering harmonic spring model, and the maximal extension length is $r_{\text{max}}$. The motor is also characterized by a Stokes friction with friction coefficient $\eta_m$ and the corresponding thermal force $\xi_{\text{m}}(t)$ obeying FDT (1) with $\eta \to \eta_m$. It moves in the binding potential $U(x, \zeta(t))$ which depends on the motor conformation $\zeta(t)$. Altogether

$$\eta_{\text{m}} \dot{x} = -\int_0^t \xi_{\text{mem}}(t-t') \dot{y}(t') \, dt' \quad - \frac{k_L(y-x)}{1 - (y-x)^2/r_{\text{max}}^2} + \xi_c(t) + \xi_{\text{mem}}(t), \quad (4)$$

$$\eta_m \dot{\zeta} = \frac{k_L(y-x)}{1 - (y-x)^2/r_{\text{max}}^2} - \frac{\partial}{\partial x} U(x, \zeta(t)) - f_0 + \xi_{\text{m}}(t), \quad (5)$$

where $f_0$ is an external loading force applied directly to the motor (for harmonic linker, $r_{\text{max}} \to \infty$, it is the same as to apply it to the cargo).

If the cargo is not coupled to the motor ($k_L \to 0$), the fractional memory friction $\eta_{\text{mem}}(t) = \eta_0 t^{-\alpha}/\Gamma(1-\alpha) \quad 0 < \alpha < 1$, with fractional friction coefficient $\eta_0$ leads to subdiffusion of cargo, $\langle \Delta y^2(t) \rangle \approx 2D_0 t^\alpha/\Gamma(1+\alpha)$, at sufficiently large times $t \gg \tau_\text{m} = (\eta_0 \eta_m)^{\alpha/(1-\alpha)}$. Subdiffusion is characterized by the fractional diffusion coefficient $D_0 = k_B T/\eta_0$. Initially, for $t \ll \tau_\text{m}$ diffusion is, however, normal, $\langle \Delta y^2(t) \rangle \approx 2D_0 t$, with $D_0 = k_B T/\eta_\text{c}$. For all times in this model [56],

$$\langle \Delta y^2(t) \rangle = 2D t E_{1-\alpha,2} \left[ -\left[ t/\tau_\text{m} \right]^{1-\alpha} \right], \quad (6)$$

where $E_{\alpha,b}(z) = \sum_{n=0}^{\infty} z^n/\Gamma(an+b)$ is the generalized Mittag–Leffler function. For the coupled motor and cargo, in the limit of infinitely rigid harmonic linker $k_L \to \infty$, $r_{\text{max}} \to \infty$ one can exclude explicitly
(see discussion in [11]) the cargo dynamics and consider anomalous dynamics of the motor alone, characterized by the Stokes friction $\eta_m + \eta_i$, and the same memory friction. This would provide a generalization of the model studied in [10]. We consider here, however, a more general model.

For the binding potential, we consider the same model of piecewise linear asymmetric potential with amplitude $U_0$, spatial period $L$, and the maximum dividing the spatial period in the ratio $1:p$, with $p = 3$, as in [11], see in figure 1. Similar models are well-known and widely used [43, 44].

Important distinction between different further models possible occurs on the level of intrinsic enzyme dynamics $\zeta(t)$. The chemical coordinate $\zeta(t)$ must be cyclic, with the cycle driven preferably in one direction (rotation of the ‘catalytic wheel’ [50, 57]) by the free energy $\Delta G_{ATP}$ released from the reaction of ATP hydrolysis $\text{ATP} \leftrightarrow \text{ADP} + \text{P}_i$ kept out of the thermodynamical equilibrium (shifted to the right) by maintaining out-of-equilibrium concentrations of reactants. One of simplest related cycles involves four discrete states (figure 2, left) [45]. The ratio of the product of the (pseudo-first order) rates (one assumes that ATP, ADP, and P$_i$ molecules are abundant with their concentrations kept constant) of the counter-clockwise transitions to the product of rates in the clockwise transitions must be equal $\exp[\Delta G_{ATP}/(k_B T)]$ [58, 59]. In the case of two-headed kinesins, it should be applied to each head, with the rates which are position-dependent (mechano–chemical coupling), which would make already a rather complicated model. The simplest possible drastic reduction accounting for the mechano–chemical coupling in the case of head-over-head motion of kinesins, a so-called two-state cycle [42, 45, 58], is shown in the right part of figure 2. One considers only two states and two realizations of the binding potential, $U_1(x)$ and $U_2(x)$, obeying the additional symmetry $U_i(x + L/2) = U_i(x)$, with each transition accounting for a half-step (one head moves, another remains bound). The corresponding rates must be not only periodic in space, $\alpha_i(x + L) = \alpha_{i,2}(x)$, $\beta_{i,2}(x + L) = \beta_{i,2}(x)$, but also share additional symmetries, $\alpha_i(x + L/2) = \beta_i(x)$ and $\alpha_2(x + L/2) = \beta_i(x)$. For a two-cycle it also must be:

$$\frac{\alpha_1(x)\beta_2(x)}{\alpha_2(x)\beta_1(x)} = \exp\left[\frac{\Delta G_{ATP}}{k_B T}\right], \tag{7}$$

for any $x$, which can be satisfied, e.g., by choosing

$$\frac{\alpha_1(x)}{\alpha_2(x)} = \exp\left[\left(U_1(x) - U_2(x) + \Delta G_{ATP}/2\right)/(k_B T)\right],$$

$$\frac{\beta_1(x)}{\beta_2(x)} = \exp\left[\left(U_1(x) - U_2(x) - \Delta G_{ATP}/2\right)/(k_B T)\right]. \tag{8}$$

The total rates

$$\nu_1(x) = \alpha_1(x) + \beta_1(x),$$

$$\nu_2(x) = \alpha_2(x) + \beta_2(x)$$

of the transitions between two energy profiles must satisfy

$$\frac{\nu_1(x)}{\nu_2(x)} = \exp\left[\left(U_1(x) - U_2(x)\right)/(k_B T)\right] \tag{10}$$

at thermal equilibrium. This is condition of the thermal detailed balance, where the dissipative fluxes vanish both in the transport direction and within the conformational space of motor, at the same time [41, 42]. It is obviously satisfied for $\Delta G_{ATP} \approx 0$. Notice that if to choose $\nu_1 = \nu_2 = \text{const}$, the latter condition is not possible to satisfy.

We still have some freedom in choosing various models for $\alpha_1(x)$ or $\alpha_2(x)$. The rate $\alpha_i(x)$ corresponds to the reactions of ATP binding and hydrolysis considered as one lump reaction. It is reasonable to assume that this rate is constant, $\alpha_i(x) = \alpha_i$ within some $\pm \delta/2$ neighborhood of the minimum of potential $U_i(x)$ and is zero otherwise. Correspondingly, the rate $\beta_i(x) = \alpha_i$ within $\pm \delta/2$ neighborhood of the minimum of potential $U_i(x)$. Given these assumptions we have:

$$\nu_1(x) = \alpha_i(x) + \alpha_i(x + L/2) \exp\left[-\left(U_1(x) - U_2(x) + \Delta G_{ATP}/2\right)/(k_B T)\right],$$

$$\nu_2(x) = \alpha_i(x) \exp\left[-\left(U_1(x) - U_2(x) + \Delta G_{ATP}/2\right)/(k_B T)\right] + \alpha_i(x + L/2). \tag{11}$$

Furthermore, if we choose $\delta = L/2$ (for the given model of binding potential with $p = 3$), then ATP binding to the motor and its hydrolysis can occur, in principle, anywhere on microtubule with the same rate. This is a reasonable assumption from the biophysical point of view, which lends a further support for our model choice. It is easy to grasp that this model can give results very similar to the ratchet model with spatially independent rates $\nu_1 = \nu_2 = \alpha_i$ [11] for a sufficiently large $\Delta G_{ATP}$ and the potential amplitude $U_0$ having a similar value.
approximately the motor turnover frequency which is nearly independent of $x$. This provides a possibility to compare the studied model with the model in [11], if to choose the other parameters appropriately.

### 2.1. Energetics of the motor

In equations (4) and (5), $R_{m}(t) := \eta_{m} \dot{x}(t) - \xi_{m}(t)$, $R_{c}(t) := \eta_{c} \dot{y}(t) - \xi_{c}(t)$, $R_{\text{mem}} := \int_{0}^{t} \eta_{\text{mem}} (t - t') \dot{y}(t')dt' - \xi_{\text{mem}}(t)$ describe total environmental forces (defined for convenience with the minus sign). The sum of the averaged works done by these forces, $\Delta Q_{m}(t) = \int_{0}^{t} \langle R_{m}(t') \dot{x}(t') \rangle dt'$, $\Delta Q_{c}(t) = \int_{0}^{t} \langle R_{c}(t') \dot{y}(t') \rangle dt'$, $\Delta Q_{\text{mem}}(t) = \int_{0}^{t} \langle R_{\text{mem}}(t') \dot{y}(t') \rangle dt'$ presents the total heat exchange of the mechanical degrees of freedom of the motor protein and cargo with the environment, $\Delta Q(t) = \Delta Q_{m}(t) + \Delta Q_{c}(t) + \Delta Q_{\text{mem}}(t)$. At thermal equilibrium, $\lim_{t \to \infty} \Delta Q(t)/t = 0$, i.e. overall heat exchange is absent on average. Beyond thermal equilibrium, $\Delta Q(t) > 0$ describes the heat transfer to the environment or heat losses.

In the flashing ratchet model, where the biochemical cycle kinetics of the motor and its coupling to the potential flashes are not explicitly considered, the averaged energy transduced by the potential flashes is $E_{\text{in},1}(t) = \int_{0}^{t} \langle \dot{U}(\delta, t') \rangle dt' \delta(t')$, which is equal to the averaged sum of the binding potential jumps at the transition points $U_{1} \to U_{2} \to U_{1} \to ...$. The averaged mechanical work done by the motor against the external load $f_{0}$ is $W_{\text{use}}(t) = \int_{0}^{t} \langle \delta \dot{x}(t') \rangle dt'$. In such a model, the energy balance is $E_{\text{in},1}(t) = \Delta Q(t) + W_{\text{use}}(t)$. It entirely neglects the back coupling of the potential fluctuations to the biochemical cycle of the motor, i.e. the energy transferred back to the motor and the ATP energy source, which drives the whole machinery. Such a coupling is simply not explicitly considered. Hence, thermodynamic efficiency within such a treatment is

$$R_{\text{th},1}(t) = \frac{W_{\text{use}}(t)}{E_{\text{in},1}(t)}. \quad (12)$$

It becomes constant for a sufficiently large $t$, in the case of normal transport, where both $E_{\text{in},1}(t) \propto t$, and $W_{\text{use}}(t) \propto t$. However, it algebraically decays to zero, $R_{\text{th},1}(t) \propto 1/t^{\delta - \alpha_{E}}$, in the case of anomalous transport, $\langle \delta \dot{x}(t') \rangle \propto t^{\delta - \alpha_{E}}$, both in the case of a periodic potential modulation [56, 61], and for potential-independent flashing rates [10, 11].

In the absence of external load, $f_{0} = 0$, $R_{\text{th},1}(t) = 0$, i.e. all the input energy is eventually dissipated as heat. However, something useful is yet done. Namely, the cargo is transferred on some distance $d(t)$. Different Stokes and generalized efficiencies have been defined to characterize the energetic performance of motors in such a situation, for a memoryless friction [62–64]. However, the notion of Stokes efficiency becomes even more ambiguous for viscoelastic environment [56]. For this reason, a transport delivery efficiency has been introduced in [10]. It is the ratio of the mean velocity $v(t) = d(t)/t$ of the cargo delivery to the mean number ($N_{\text{turn}}(t)$) of motor enzyme turnovers made for this within the two-state reduction, i.e. any transitions $1 \to 2 \to 1$, or $2 \to 1 \to 2$, make one cycle. Then

$$D(t) = \frac{d(t)}{tN_{\text{turn}}(t)} = \frac{d(t)}{t}. \quad (13)$$

The definition (12) is the only possibility to define thermodynamic efficiency in the case of ratchet models, which do not specify the mechanism of mechano–chemical coupling. Within these models, the process $\zeta(t)$ is considered as a driver which provides the input energy unidirectionally, i.e. without feeling any feedback [60]. However, within the considered model the energy can flow in both directions, and the potential fluctuations just provide an intermediate step. The energy supply is provided by a pool of ATP molecules, which is characterized by the out-of-equilibrium chemical potential difference of the reaction of ATP hydrolysis $\Delta G_{\text{ATP}}$ [41, 42, 46]. Hence, it is reasonable to define the input energy as $E_{\text{in},2}(t) = \Delta G_{\text{ATP}} N_{\text{turn}}(t)$ [41]. Then, the thermodynamic efficiency is

$$R_{\text{th},2}(t) = \frac{W_{\text{use}}(t)}{\Delta G_{\text{ATP}} N_{\text{turn}}(t)}. \quad (14)$$

The idea is clear: each turnover of the catalytic wheel requires energy of the hydrolysis of one ATP molecule, in accordance with the main principles of the nonequilibrium thermodynamics applied to the biochemical cycle kinetics [58, 59]. One expects that $R_{\text{th},2}(t) > R_{\text{th},1}(t)$. This is because a part of the energy $E_{\text{in},2}(t)$ can be given back to the motor, its intrinsic degree of freedom. For example, it can be recuperated in the backward synthesis, $\text{ADP} + \text{P} \to \text{ATP}$. This feature is entirely beyond the simple ratchet models with spatially independent rates, which do not take properly into account such a mecha–chemical coupling. However, this definition is also not quite precise. As a matter of fact, one ATP molecule is only consumed if a cycle is accomplished in the counterclockwise direction in the left diagram of figure 2. Moreover, it is recuperated if the cycle is completed in the clockwise direction. Therefore, for the two-state cycle depicted in the right diagram of figure 2, to correctly calculate consumption of ATP molecules we should count $p_{1}\Delta G_{\text{ATP}}/2$ with $p_{1} = (\alpha_{1} - \beta_{1})/(\alpha_{1} + \beta_{1})$ for the transition $U_{1} \to U_{2}$, and $p_{2}\Delta G_{\text{ATP}}/2$ with $p_{2} = (\beta_{2} - \alpha_{2})/(\alpha_{2} + \beta_{2})$ for the transition $U_{2} \to U_{1}$. The correspondingly calculated input energy is denoted as $E_{\text{in},3}(t)$, and the thermodynamic efficiency as $R_{\text{th},3}(t) = W_{\text{use}}(t)/E_{\text{in},3}(t)$ [41]. Obviously, since $E_{\text{in},3}(t) < E_{\text{in},2}(t)$, $R_{\text{th},3}(t) > R_{\text{th},2}(t) > R_{\text{th},1}(t)$. However, in a regime, where the catalytic wheel rotates overwhelmingly in one direction (like in the Michaelis–Menthen
treatment of enzymatic reactions, where the backward rotation is entirely neglected), the distinction between $R_{th,3}(t)$ and $R_{th,3}(t)$ becomes negligible. By the same token, one can modify the definition of the delivery efficiency in equation (13) by replacing $(N_{turn})$ with the averaged number of ATP molecules hydrolyzed. However, the difference between the both definitions exists only beyond the Michaelis–Menthen description of the motor kinetics.

2.2. Markovian embedding and numerical method

Following the already well-established methodology of Markovian embedding of [5, 36, 38] we approximate the power-law memory kernel $\eta_{mem}(t)$ by a sum of exponentials

$$\eta_{mem}(t) = \sum_{i=1}^{N} k_i \exp\left(-\nu_i t \right), \quad (15)$$

obeying fractal scaling $\nu_i = \nu_0 / b^{i-1}$, $k_i \propto \nu_i^{\alpha}$, and introduce $N$ auxiliary Brownian particles modeling viscoelastic properties of the environment. Notice that this choice of scaling is different from the Prony series approximation in [37], where $\nu_i \propto t^{-i/\alpha}$, and $k_i$ is a constant independent of $i$. The Prony expansion can be rigorously derived from the polymer dynamics for different polymer models yielding various modelspecific $\alpha$ [65]. However, the great advantage of our fractal scaling choice is that it allows to use a much smaller number of terms in the kernel approximation and thus allows for simulations of anomalous dynamics on practically arbitrary experimentally relevant time scales [38]. This expansion allows to transform the considered non-Markovian problem into a Markovian one in the space of enlarged (by $N$) dimensionality. Then, the standard methods of the numerical solution of stochastic differential equations (SDEs), such as stochastic Euler, or stochastic Heun method, can be applied for a fixed realization of the potential $U_i(x)$. This approach allows for a highly accurate numerical integration of fractional Langevin dynamics even for a moderate $N \sim 10 - 100$ [36]. The accuracy of the kernel approximation is controlled by the scaling parameter $b$. Even for a crude decade scaling $b = 10$ expressing the idea ‘one power law time decade requires about one exponential in approximation’ it is better than 4% between two memory cutoffs, the short time cutoff $\tau_{min} = 1/\nu_0$, and the large time cutoff $\tau_{max} = b^{N-1}\tau_{min}$. For $b = 2$, the accuracy of approximation improves to about 0.01% [61]. For such a choice, the statistical errors in the numerical simulations emerging due to a finite number of the trajectory realizations $n$ will typically be larger. This is because such sampling errors scale as $1/\sqrt{n}$. Hence, for a typical $n \sim 10^3 - 10^4$, the choice of $b = 10$ suffices for the most practical purposes. It provides accuracy of several percent., which in the stochastic simulations is considered as a pretty good one.

Given the maximal time range of subdiffusion defined by $\tau_{max}$, one can always find appropriate minimal Markovian embedding dimension with the required accuracy. Since $N \sim \log_{b}(\tau_{max}/\tau_{min})$ this ensures an excellent numerical method [36, 38]. The finiteness of $\tau_{max}$ reflects finite effective viscosity $\zeta_{eff}$ of cytosol fluid which can be exponentially enhanced with respect to one of water depending on the cargo size [66–68]. Indeed, the effective friction at very large times is $\eta_{eff} = \int_{0}^{\infty} \eta_{mem}(t) dt \propto \zeta_{eff}$ and on the scaling grounds, $\eta_{u} \sim \eta_{eff} \tau_{max}^\alpha$. For $t \gg \tau_{max}$ passive diffusion of cargo becomes again normal. It is characterized by the friction coefficient $\eta_{u} + \eta_{eff}$ and diffusion coefficient $D_{c,eff} = k_B T / (\eta_{u} + \eta_{eff})$ largely suppressed with respect to one in water. With these parameters [10],

$$k_i = \nu_0 \eta_{eff} \left[ b^{i-1}/(b^N - 1) \right]. \quad (16)$$

Following [11, 38], upon introduction of $N$ auxiliary overdamped Brownian particles with coordinates $y_i$ and frictional coefficients $\eta_i = k_i/\nu_i$, the Markovian embedding dynamics reads

$$\eta_{u} \dot{x} = f (x, \xi(t)) + \frac{k_L (y - x)}{1 - (y - x)^2/\tau_{max}^2} + \sqrt{2\eta_{u} k_B T \xi_{mem}(t)},$$

$$\eta_i \dot{y}_i = -\frac{k_L (y - x)}{1 - (y - x)^2/\tau_{max}^2} - \sum_{i=1}^{N} \eta_{i} (y - y_i) + \sqrt{2\eta_{i} k_B T \xi_{i}(t)},$$

where $f (x, \xi(t)) = -\partial U(x, \xi(t))/\partial \xi - f_0$. Furthermore, $\xi(t)$ are uncorrelated white Gaussian noises of unit intensity, $\xi_i(t)\xi_j(t') = \delta_{ij}\delta(t - t')$, which are also uncorrelated with the white Gaussian noise sources $\xi_0(t)$ and $\xi_{mem}(t)$. To have a complete equivalence with the stated GLE model in equations (4) and (5) with memory kernel (15), the initial positions $y_i(0)$ are sampled from a Gaussian distribution centered around $y(0)$, $\langle y_i(0) \rangle = y(0)$ with variances $\langle (y_i(0) - y(0))^2 \rangle = k_B T / k_i$ [38].

2.2.1. Choice of parameters and details of numerics.

As in [11], we take $a_{act} = 100$ nm for the effective radius of kinesin, about 10 times larger than its linear geometrical size (without tether) in order to account for the enhanced effective viscosity experienced by the motor in the cytosol compared to its value in water. The viscous friction coefficient is estimated from the Stokes formula as $\eta_{w} = 6\pi a_{mem} \zeta_{w}$, where $\zeta_{w} = 1$ mPa · s is water viscosity. Furthermore, we use the characteristic time scale $\tau_{mem} = L^2/\eta_{w} / U_0$ to scale time in the numerical simulations with $U_0 = 10 k_B T_1$. For the above parameters, $\tau_{mem} \approx 2.94$ ms. Distance is
Table 1. Parameter sets.

| Set | $D_{b4}, \text{nm}^2 \text{s}^{-0.4}$ | $k_e, \text{pN nm}^{-1}$ | $\alpha_1, \text{s}^{-1}$ | $U_0, k_B T_\text{f}$ | $r_{\text{max}}, \text{nm}$ |
|-----|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| $S_1$ | 171 | 0.320 | 170 | 20 | $\infty$ |
| $S_2$ | 1710 | 0.320 | 170 | 20 | $\infty$ |
| $S_3$ | 1710 | 0.032 | 170 | 20 | $\infty$ |
| $S_4$ | 171 | 0.032 | 170 | 20 | $\infty$ |
| $S_5$ | 1710 | 0.320 | 170 | 20 | $80$ |
| $S_6$ | 171 | 0.320 | 170 | 20 | $80$ |
| $S_7$ | 171 | 0.320 | 170 | 20 | $80$ |
| $S_8$ | 171 | 0.320 | 170 | 20 | $80$ |
| $S_9$ | 1710 | 0.320 | 170 | 20 | $80$ |
| $S_{10}$ | 1710 | 0.320 | 170 | 20 | $80$ |

scaled in units of $L$, elastic coupling constants in units of $U_0^2/L \approx 0.64 \text{ pN nm}^{-1}$, and forces in units of $U_0/L \approx 5.12 \text{ pN nm}^{-1}$, $\nu_0$ was chosen $\nu_0 = 100 (3.4 \cdot 10^3 / \text{s})$ yielding $\tau_{\text{min}} = 29.4$ ns, and $\alpha$ was $\alpha = 0.4$ as found experimentally in [6, 21]. Two cargo sizes were considered, large $a_c = 300 \text{ nm}$, which corresponds to the magnetosome size in [6], and a smaller one. For larger cargo, we assume that its effective Stokes friction $\eta = 6 \pi a_c \xi_w$ is enhanced by the factor of $\eta_{\text{eff}}/\eta = 3 \times 10^4$ in cytosol. Assuming that $\tau_{\text{max}} = 10\tau_{\text{min}} = 294 \text{ s}$ this yields fractional friction coefficient $\eta_{\text{f}} = \eta_{\text{eff}}/r_{\text{max}}^{1/2}$ with $r \approx 0.93$ [11], which yields subdiffusion coefficient $D_{b4} = k_B T/\eta_{b4} \approx 1.71 \times 10^{-16} \text{ m}^2 \text{ s}^{-0.4} = 171 \text{ nm}^2 \text{ s}^{-0.4}$. It is in a semi-quantitative agreement with the experimental results in [6]. Smaller cargo is characterized by $\eta_{\text{eff}}/\eta = 3 \times 10^5$ yielding $D_{b4} = 1710 \text{ nm}^2 \text{ s}^{-0.4}$, ten times larger. Furthermore, we used two values of rate constant $\alpha_1$: 170 s$^{-1}$ (fast) and 34 s$^{-1}$ (slow), in order to match approximately the enzyme turnover rates $\nu \sim \alpha_1/2$ in [11]. Accordingly, we used mostly $U_0 = 20 k_B T_\text{f}$ in simulations, although we used also two larger values of $U_0$, see table 1, in order to arrive at the thermodynamical efficiencies as large as 50% typical for kinesins [47]. Moreover, two different values for the elastic spring constant were used, $k_1^{(1)} = 0.32 \text{ pN nm}^{-1}$ (‘strong’), which corresponds to measurements in vitro [69], and a ten times softer spring $k_1^{(2)} = 0.032 \text{ pN nm}^{-1}$ (‘weak’), in accordance with recent results in [21] in living cells. For the maximal extension of linker we used $r_{\text{max}} = 80 \text{ nm}$ [1, 31], and also $r_{\text{max}} = \infty$, which corresponds to harmonic linker in [11]. The studied sets of parameters are shown in table 1.

In order to numerically integrate stochastic Langevin dynamics following to one potential realization $U_{1,2}(x)$, we used stochastic Heun method implemented in parallel on NVIDIA Kepler graphical processors. Stochastic switching between two potential realizations is realized using a well-known algorithm. Namely, if the motor is on the given surface $U_1(x)$ or $U_2(x)$, at each integration time step it can switch with the probability $\nu_1(x)\delta t$ or $\nu_2(x)\delta t$ correspondingly to another surface, or to evolve further on the same surface, where $\delta t$ is the integration time step, and $k_1,2(x)$ are given in equation (11). A particular embedding with $b = 10$ and $N = 10$ was chosen in accordance with our previous studies. Furthermore, we used $\delta t = 5 \times 10^{-3}$ for the integration time step and $n = 10^5$ for the ensemble averaging. The maximal time range of integration was $10^6$, which corresponds to 2.94 s of motor operation. $\Delta G_{\text{ATP}} = 20 k_B T_\text{f}$ was taken in all numerical simulations. We also checked that with $\Delta G_{\text{ATP}} \to 0$, the motor stops at $f_\text{f} = 0$, i.e. no directed motion and useful work can be derived from the reaction of ATP hydrolysis being at thermal equilibrium, in accordance with stochastic thermodynamics of isothermal engines [58, 59].

3. Results

3.1. Comparison of different models: similarities and the role of the tether anharmonicity

We compare first in figure 3 the results for the parameter sets $S_1, S_2, S_3, S_{4a}$ of the present model and the corresponding parameter sets $S_1, S_2, S_3, S_4$ in [11], for the ensemble averaged trajectories. One can see that almost no difference can be visually detected, both for larger and smaller cargo, stronger and weaker linker. The transport is clearly anomalously slow for $S_1$ and $S_{4a}$ always (large cargo), and it changes from normal to anomalous transport upon increase of $f_\text{f}$ in the cases $S_2$ and $S_3$ (smaller cargo). For stronger linker, the difference between the motor and cargo positions is not significant, and for this reason the cargo position is not shown in figures 3(a) and (b). For weaker linker, the difference becomes very strong in the case of large cargo, see in figure 3(d), where for $f_\text{f} = 0$ it increases up to about 170 nm, see in the figure 4(a), inset. The corresponding elastic energy becomes 111 $k_B T_\text{f}$, i.e. of the same of order as a typical energy of covalent bonds and such a linker clearly cannot sustain transport [11]. It will be disrupted. However, the linker anharmonicity starts to play a profound role when the cargo-motor distance becomes larger than about one fifth of the maximal linker extension $r_{\text{max}}$. The latter one can
be in the range between 10 nm and 150 nm for different motors [1, 31]. We consider $r_{\text{max}} = 80$ nm (10 L). Then, for a strong linker the anharmonicity does not play any essential role. We clarify its role in figure 4(a) for a weak linker and large cargo. It is seen that anharmonicity restricts the increase of the cargo-motor distance by $\approx r_{63}$ nm only. Substituting this value in equation (3) yields $U_{\text{mic}}^{(\text{max})} \approx 24 k_{B} T$. Such a linker should be able to sustain transport of large cargo, not necessarily it will be disrupted. This is an important result: even weak linkers can possibly support strongly anomalous transport of large cargos due to nonlinear effects.

In [11], we revealed a very interesting effect which can emerge due to the weakness of linker. Namely, if to reduce the turnover frequency of motor pulling large
cargo from 85 to 17 Hz (which is the case \( S_6 \) in [11]) then the motor operates normally at \( f_0 = 0 \), whereas the cargo enters temporally a super-transport regime with \( \alpha_{\text{eff}} > 1 \). A natural question emerges if this effect survives for the considered FENE model of linker. Figure 4(b) answers this question in affirmative, lending it therefore a further support with respect to possible experimental realization. The explanation of this effect is simple: when the motor is in normal regime, its distance increases linearly in time. However, for a weak linker the retardation of the cargo past the motor increases sublinearly in time, see inset in figure 4(b). This causes the effect that the mean distance covered by cargo increases super-linearly in time, although it, in fact, moves slower than motor. Clearly, in this case ‘super’-transport does not imply a faster transport at all! The cargo lags behind the normally walking motor. Interestingly, sub-transport also does not proceed necessarily slower than the normal one [70–72].

The effective transport exponents \( \alpha_{\text{eff}} \) of motor and cargo (the latter one in some cases only, where the difference is substantial) are shown in figure 5. Their behavior is rather similar to one studied in [11]. The new feature is that the difference between \( \alpha_{\text{eff}} \) of the motor and cargo for a large cargo on weaker linker becomes smaller due to nonlinear effects in elastic coupling. This is, however, what was to expect, not a surprise.

3.2. Thermodynamic efficiency: discrepancy between models

The real discrepancies between the studied model and the model in [11] appears for the thermodynamic efficiency, see in figure 6. Indeed, \( R_{\text{th},2} \) is typically essentially larger than \( R_{\text{th},1} \), and \( R_{\text{th},3} \) is slightly larger than \( R_{\text{th},2} \). The latter relative discrepancy is, however, less than 2% for the set \( S_1 \) (strongly anomalous transport) and becomes almost negligible for the set \( S_2 \) (close to normal transport), indicating that ‘catalytic wheel’ rotates overwhelmingly in one direction. Notice also that the difference between \( R_{\text{th},1} \) and the same quantity for similar parameter sets in [11] is small. This once more confirms that the ratchet models with constant, spatially independent rates provide a reasonable description of the work of molecular motors. What they, however, cannot do properly indeed is to describe thermodynamic efficiency of the motor. This is a principal shortcoming...
because simple ratchet models do not take properly the (bidirectional) mechano–chemical coupling into account. The correct definition of thermodynamic efficiency of molecular motors is one given by $R_{\text{II},3}$ and it can be essentially larger than $R_{\text{II},1}$.

However, the normal modus operandi of linear molecular motors such as kinesins is one at zero thermodynamic efficiency ($f_0 = 0$). The work is done entirely on overcoming the dissipative resistance of the environment while relocating cargo from one place in the cell to another one. Neither potential energy of the motor, nor the potential energy of the cargo is enhanced at the end. This is very different from the work of the ionic pumps whose primary goal is to enhance the electrochemical potential of the pumped ions. The cargo delivery efficiency D exhibits the same features revealed in [10, 11], and we do not consider it in further detail in this paper, referring the readers to [11].

As a matter of fact, all the main features revealed in [10, 11] with respect to the occurrence of normal versus anomalous transport regime depending especially on the cargo size, binding potential amplitude, and motor operating frequency remain valid, being even rather close in the numerical values, if to match the parameters of both models appropriately. This confirms that the modeling route of flashing ratchets with spatially independent rates is a reasonable one.

### 3.3. Anomalously slow motor turnovers with high thermodynamic efficiency

We next wish to clarify whether this simple model can demonstrate thermodynamic efficiency as high as 50% featuring real kinesins with the stalling force about 7–8 pN [47]. To find the corresponding regime, we consider expression for the stalling force obtained in [10, 11] by fitting the numerical simulations therein:

$$f_0^{\text{stall}}(T, U_0, \nu_{\text{turn}}) \approx \frac{4}{3k_B} F_0(T, U_0, \nu_{\text{turn}})$$

with $F_0(T, U_0, \nu_{\text{turn}}) = U_0 - U_m(\nu_{\text{turn}}) T / T_r := U_0 - TS_0(\nu_{\text{turn}})$, for $F_0 > 0$, and $U_0 \approx 11.2 k_B T_r$ at $\nu_{\text{turn}} = 85$ Hz, or $a_1 = 170$ s$^{-1}$, in our case. $F_0(T, U_0, \nu_{\text{turn}})$ can be interpreted as free-energy barrier height. At $T = 0$, $f_0^{\text{stall}} \approx 4U_0/(3L)$, the result which is easy to obtain due to the piece-wise constant character of the force in the considered binding potential. Temperature reduces $F_0$ due to the entropic contribution $T S_0$, and for $F_0 < 0$, the stalling force is exponentially small. This imposes a minimal $U_0$ for molecular motors at physiological temperatures. It is about 10–11 $k_B T_r$ [11]. Equation (18) yields $f_0^{\text{stall}} \approx 6$ pN at $U_0 = 20 k_B T_r$ and $a_1 = 170$ s$^{-1}$, in agreement with numerics. It also predicts $f_0^{\text{stall}} \approx 9.43$ pN at $U_0 = 25 k_B T_r$, and $f_0^{\text{stall}} \approx 12.85$ pN at $U_0 = 30 k_B T_r$. This suggests to use $U_0$ in the range of 20–30 $k_B T_r$ to describe a realistically strong motor with larger efficiency. Simple ratchet models, which do not take properly the mechano–chemical coupling into account, may prevent the detailed consideration of such high binding potential amplitudes because they create impression that the energy of the hydrolysis of one ATP molecule may simply be not enough to fuel one catalytic cycle and to move synchronously by one spatial period at the same time. This is because the sum of the energies required to lift the potential energy of the motor in the binding potential while doing two half-steps becomes larger than $\Delta G_{\text{ATP}}$. Such an argumentation neglects, however, the fact that the energy invested in the enhancement of the motor’s potential energy can be recuperated and used again. In fact, even for $U_0 = 30 k_B T_r$ (sets $S_0$, $S_{10}$) the motor moves remarkably fast, faster than for $U_0 = 20 k_B T_r$, in absolute terms, at the end point of simulations, but yet slower for intermediate times (set $S_0$), see in figure 7.

However, the motor becomes slower for $U_0 = 30 k_B T_r$ (sets $S_0$, $S_{10}$) than for $U_0 = 25 k_B T_r$ (sets $S_1$, $S_{10}$) at the same other parameters. This slowdown results obviously because the motor turnovers become slower. The stalling force about 10 pN at $U_0 = 30 k_B T_r$ is essentially lower than one predicted by equation (18). This is because the motor turnover frequency is lower than 85 Hz. More precisely, the motor cannot be characterized by a turnover frequency anymore, at least when it pulls a large cargo, set $S_0$. Our analysis, see below, reveals that in this case the input energy $E_{\text{in},3}$ grows sublinearly in time, $E_{\text{in},3}(t) \propto t^\gamma$, $0 < \gamma < 1$, or $\langle N_{\text{turn}}(t) \rangle \propto t^\gamma$, meaning that the enzyme turnovers become anomalously slow and cannot be characterized by a frequency anymore. This is a profoundly new result: the mechano–chemical coupling can cause anomalously slow rotation of the cargo.
The corresponding enzymatic reaction cannot be characterized by a mean rate anymore! The intuition is correct in predicting that it will be difficult to perform one enzymatic cycle by hydrolyzing one ATP molecule for such a large $U_0$. However, the motor operation is still possible, and it can start to consume ATP energy sublinearly in time, with the exponent $\gamma$. Astonishingly, the motor can become thermodynamically highly efficient in this anomalous regime, see below.

With the increase of $U_0$ first to $25k_BT$, and then further to $30k_BT$; thermodynamic efficiency increases essentially indeed. For the smaller cargo, it reaches a typical experimental value of 50% and even larger already for $25k_BT$; at $f_0 \approx 6-7.5$ pN with the stalling force $f_0^{\text{stall}} \approx 9.1$ pN, see in figure 8(b). The stalling force is a bit larger than for real kinesins. However, maximal thermodynamical efficiency of about 58% is also larger, as should be for a stronger motor. Nevertheless, this simple model yields indeed realistic efficiencies and stalling forces at the same time. Moreover, our model motor can operate even in the regime of strongly anomalous transport with $\alpha_{\text{eff}} \approx 0.58$ at the thermodynamic efficiency as large as 70%, for $U_0 \approx 30k_BT$, at $f_0^{\text{opt}} \approx 8.5$ pN with stalling force $f_0^{\text{stall}} \approx 10$ pN, see in figure 8(b), set $S_7$. This is a real surprise! For the smaller cargo, the maximal efficiency becomes even larger, about 83% at $\alpha_{\text{eff}} \approx 0.92$, although this transport regime is close to normal. Anomalous subdiffusive transport regime with such a huge efficiency, over 70%, was difficult to expect a priori.

The explanation of this paradoxical behavior reveals a profoundly new feature. Namely, the enzymatic cycling and the potential flashes occur in this case anomalously slow in time with the power law exponent $\gamma$. To understand this we plotted the time-dependence of the thermodynamic efficiencies versus time in figure 9 for the sets $S_1$ (here and in [11]), $S_7$, and $S_8$, at $f_0$ taking the values 3.07, 5.12 and 8.70 pN correspondingly (near to the maximum of efficiency versus $f_0$). For $S_1$, both $R_{\text{th,1}}(t) \propto 1/t^{1-\alpha_{\text{eff}}}$, and $R_{\text{th,3}}(t) \propto 1/t^{1-\alpha_{\text{eff}}}$, with $\alpha_{\text{eff}} \approx 0.54$ confirming that $E_{\text{th,1,3}}(t) \propto t$. However, for $S_7$ and $S_8$, $R_{\text{th,3}}(t) \propto 1/t^{\lambda}$ with $\lambda \neq 1-\alpha_{\text{eff}}$. Assuming that $E_{\text{th,3}}(t) \propto t^\gamma$ one obtains $\lambda = \gamma - \alpha_{\text{eff}}$, from which $\gamma = \lambda + \alpha_{\text{eff}}$. Hence, from the data in figure 9 we deduce that $\gamma \approx 0.62$ ($\alpha_{\text{eff}} \approx 0.556$) for $S_8$ and $\gamma \approx 0.87$ ($\alpha_{\text{eff}} \approx 0.57$) for $S_7$. The occurrence of this thermodynamically highly efficient anomalous transport regime, where both the mean transport distance and the number of motor turnovers grow sublinearly in time, but with different exponents, presents a profound result of this work, beyond recent treatment in [10, 11].

4. Discussion

In this paper, we further generalized our model of anomalous transport in viscoelastic cytosol of living cells, which is realized by various molecular motors such as kinesins. In this model, normally (in the absence of cargo) operating motor is pulling subdiffusive (if not coupled to motor) cargo on an elastic linker, or tether. Subdiffusion is described within non-Markovian GLE approach and its Markovian multidimensional embedding realization within a generalized Maxwell–Langevin model of viscoelasticity. The generalization consisted in two aspects. First, we took the mechano–chemical coupling between the motor cyclic turnovers and its translational motion into account within a variant of the model of hand-over-hand motion of kinesin which was introduced in [42, 44, 45]. It is featured by spatially-dependent rates of conformational transitions. This spatial dependence reflects biochemical cycle kinetics of the molecular motor moving in a periodic binding potential. Our particular model choice was done in accordance with a biophysically plausible requirement that ATP binding to the motor and its hydrolysis can be realized with the same lump rate $\alpha_1$ anywhere on microtubule.
This model choice allowed comparison with the ratchet model in [11], based on the same requirement, by matching $\gamma_1$ with the doubled enzyme turnover rate in [11], using other parameters the same and for $\Delta G_{ATP} = U_0 = 20 \ k_B T$. Second, we considered anharmonic linker with a maximally possible extension length within the FENE model, instead of the harmonic linker in [11]. As an important result of this study, we confirmed within the present more realistic setting all the major findings of [10, 11]. Our theory explains how the same motors operating in the same cells can realize both normal and anomalous transport of various cargos depending on the cargo size, strength of the motor (maximal loading force which depends on the amplitude of binding potential), motor operating frequency (which depends, in particular, on the ATP binding and hydrolysis rate), and the value of loading force opposing the motion.

However, an important discrepancy between the present model and the model of [11] emerges on the level of thermodynamic efficiency. Within the present model, the input energy fueling the motor operation is calculated as the energy required to accomplish biochemical cycles of the motor in the working direction by hydrolyzing ATP molecules [41, 44, 45], in accordance with the main principles of the free-energy transduction in biology [58], rather than as the energy invested into the potential flashes unidirectionally [60]. The former is less than the latter because of bidirectional coupling. This makes thermodynamic efficiency of molecular motor essentially larger than one obtains in simple ratchet models with unidirectional coupling and constant flashing rates. We showed that our model can consistently explain near to normal transport with thermodynamic efficiency of 50% in viscoelastic environment of biological cells, for realistic parameters. As a major surprise, we showed that a strongly anomalous subdiffusive transport is also possible with thermodynamic efficiencies as high as 70%.

Here we revealed a very important new feature. Namely, the biochemical enzyme turnovers can become anomalously slow, $\langle N_{\text{turn}}(t) \rangle \propto t^\gamma$, $0 < \gamma < 1$, due to the influence of viscoelastic environment, not being characterized by a turnover rate anymore. To the best of our knowledge, this is the first time when anomalous enzyme kinetics of this kind, i.e. no mean turnover rate exists, is predicted within a physical approach based on the fundamental principles of statistical mechanics [32, 33]. To reveal such a regime provides a real challenge for experimental biophysicists.

It is important to mention that the difference in thermodynamic efficiencies does not affect the major results in [10, 11] because normally such motors as kinesins are operating at zero thermodynamic efficiency just relocating cargos from one place in the cell to another one, not increasing their potential energy, or chemical potential.

Furthermore, we showed that the linker anharmonicity practically does not introduce any significant difference in the case of strong linkers with elastic constant typically used in biophysical literature [69]. However, a recent experiment [21] suggested that the elastic constant can be an order of magnitude lower in viscoelastic environment of living cells in comparison with one in water. In [11], we showed within the model of harmonic linker that the transport of large cargos is hardly possible on such a weak linker when the motor operates at a high turnover frequency of about 100 Hz. The linker should then become broken. However, in the present work we demonstrated that a weak linker can yet sustain such a transport due to strong anharmonic effects, because it is hardened upon extension. Moreover, we reaffirmed the emergence of a paradoxical regime of cargo’s supertransport with $\alpha_{\text{eff}} > 1$ on a weak linker for the motor stepping normally with $\alpha_{\text{eff}} = 1$ at a small operating frequency.

5. Summary and conclusion

Let us summarize now the major findings of this work, starting from the most surprising results. First, we revealed a novel regime of anomalously slow motor enzyme turnovers under the influence of mechanical load in viscoelastic cytosol. Such cyclic turnovers cannot be characterized by a rate. Also very unexpected, thermodynamic efficiency of the molecular motor in this anomalous regime is very high. And another surprise, the motor can pull faster, in absolute terms, a large subdiffusing cargo in this regime, than in the regime of normal turnovers characterized by rate. Second, we showed that thermodynamic efficiency is larger within the studied model featured by the position-dependent conformational transition rates and bidirectional mechano–chemical coupling, than within the ratchet model with the position-independent rates and unidirectional coupling. Third, in spite of this essential discrepancy, the both models provide very similar results in the most other aspects, if to
properly match their parameters. Fourth, we clarified the constructive role of the tether anharmonicity within a finitely extensible nonlinear elastic model.

To conclude, we hope that the further confirmation of the major results of [10, 11] in a more realistic setup of this work, as well as new results of this work, will inspire the followup experimental work, which will provide a further feedback to theoretical description of both anomalous and normal transport processes, as well as enzyme kinetics in the viscoelastic crowded environment provided by the cytosol of living cells.

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