Maximal force exerted by a molecular motor

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(Received 28 June 2001; published 12 February 2002)

We consider a particle diffusing in a one-dimensional periodic lattice with arbitrary transition rates between nearest-neighbor sites. We show rigorously that the ratio of the drift velocity V to the diffusion coefficient D has the upper bound $2N/d$, where N is the number of nodes in an elementary cell and d denotes its length. Applying this result to a model of a molecular motor introduced by Fisher and Kolomeisky [Proc. Natl. Acad. Sci. USA **96**, 6597 (1999)] we show that the so called Einstein force, which sets the lower bound for the force exerted by a molecular motor, is bounded from above by $2k_BTN/d$ irrespective of the actual values of the jump rates between internal states of the motor.

DOI: 10.1103/PhysRevE.65.031905 PACS number(s): 87.16.Nn, 05.10.Gg, 05.40.−a

I. INTRODUCTION

Molecular motors are complex proteins, e.g., kinesins, myosins, or dyneins, responsible for dynamical functions of biological cells, including muscle contraction, intracellular transport, and flagellar motion. Powered by hydrolysis of ATP (adenosine triphosphate), they move along complementary protein fibers, which are made up of many identical monomers. Only microfibers comprised of polar monomers (e.g., of actin or tubulin) can contribute to transport. The tracks molecular motors move along are thus periodically modulated, asymmetric, and effectively one-dimensional structures [1,2].

An important effort toward developing a general theory of the force exerted by a single protein motor was made in a series of recent papers [3–6]. It is based on the assumption that the motion of a motor can be modeled as diffusion of a particle in a one-dimensional lattice with periodic and asymmetric transition rates. The lattice nodes correspond to different internal states and locations of a kinesin on a microtubule. A segment of a microtubule corresponds to an elementary cell of the lattice—we will denote its length as d. The number of sites in an elementary cell, N, is equal to the number of different internal states in a full mechanochemical cycle of a motor. For kinesin $d=8$ nm [1,7,8] and $N=4$ [3,4,6]. Transitions between lattice nodes are assumed to constitute a Poisson process, so the time and displacement are, respectively, continuous and discrete variables.

For such a system one can construct several quantities approximating the force exerted by the motor [3,4]. Here we will focus on the so called Einstein force F_E. It is related to the drift velocity V and the mobility b of the motor through the formula $V=bF_E$. Following the Einstein relation one has $b=D/k_BT$, where D is the diffusion coefficient of the motor, T denotes temperature, and k_B is the Boltzmann constant. Therefore F_E can be expressed simply as [3,4]

$$F_E=k_BT\frac{|\mathbf{V}|}{D}. \tag{1}$$

Using this definition Fisher and Kolomeisky [3,4] suggested that for any system with transitions restricted to the nearest-neighbor sites only

$$F_E\leqslant 2k_BT\frac{N}{d}, \tag{2}$$

which, using Eq. (1), can be written as

$$\frac{-2N}{d}D\leqslant V\leqslant\frac{2N}{d}D, \tag{3}$$

and proved it rigorously for $N=2$. In our recent paper [9] we reported a ''computer-assisted'' proof of this inequality for $N\leqslant 16$. The purpose of our present paper is to prove this hypothesis analytically for any N and arbitrary values of transition rates.

Equation (3) also sets a relation between N and an experimentally measured quantity, the randomness $r=2D/Vd$ [8,10], for it implies

$$N\geqslant 1/r. \tag{4}$$

This relation, which was originally derived only for unidirectional, N-step sequential processes [10], can be used to estimate the minimal number of steps comprising a full mechanochemical cycle [6].

As can be readily verified, the inequality (2) turns into an equality if the motor moves all the time in the same direction and all transition rates are of the same magnitude [4]. We show that this condition is not only satisfactory, but also necessary to turn (2) into an equality. This result corresponds to recent findings of Oster and Wang [11], who argue that rotary motors (e.g., F_1 ATPase rotors) are most efficient in transducing the chemical energy of ATP hydrolysis into mechanical work if the torque they generate is constant, i.e., independent of the rotation angle. A similar result was also obtained by Quian [12], who considered a continuous stochastic model for molecular motors and showed that the entropy production rate, or the dissipated heat, is minimal if the stochastic process is unidirectional and all transition rates are of the same magnitude.

Finally, apart from having a direct application in the theory of molecular motors, inequality (3) is interesting *per*

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se, for it implies that a nonvanishing drift in an arbitrary one-dimensional diffusive Poissonian system imposes a lower bound for the dispersion.

As relation (3) is supposed to be valid for any period N and arbitrary choice of transition rates, to prove it one should be able to represent V and D as functions of the transition rates. Once such a representation has been found, the task of proving inequality (3) reduces to a purely algebraic problem. General methods of expressing V and D in a nonequilibrium system were found by Derrida [13] and Claes and Van den Broeck [14]. One problem with these solutions is that they are relatively complex and we did not find a way to employ them to prove (3) for *arbitrary N*.

In our recent paper [15] we proposed a different approach, and using it we were able to express V and D in terms of a few multivariate polynomials such that each of their terms can be represented as a directed graph [9]. As we shall see, this representation turns out to be crucial to our proof, as it enables one to reduce the original problem to a graph-counting one.

The paper is organized as follows. In Sec. II we present a mathematical definition of the model. Section II contains the proof of Eq. (3), and Sec. IV is devoted to the discussion of our results. Finally, in the Appendix we clarify some technical details of the proof.

II. MODEL

We consider a one-dimensional lattice with its sites located at x_n, $n \in \mathcal{Z}$. At time $t=0$ we put a particle at site $x_0=0$. The particle can then jump between the nearest-neighbor lattice sites. Transitions are assumed to represent a continuous (Poisson) process in time governed by the master equation

$$\frac{\partial P(n,t)}{\partial t} = k^+_{n-1}P(n-1,t) + k^-_{n+1}P(n+1,t) - (k^+_n + k^-_n)P(n,t), \tag{5}$$

where $P(n,t)$ denotes the probability of finding the particle at site x_n at time t and $k^\pm_n \geqslant 0$ are the (constant in time) transition rates from a site x_n to $x_{n\pm1}$. We assume that the system is periodic in space with a period $N \geqslant 1$ and a lattice constant $d>0$, i.e., for each n there is

$$k^+_n = k^+_{n+N}, \quad k^-_n = k^-_{n+N}, \tag{6}$$

$$x_{n+N} - x_n = d. \tag{7}$$

We do not demand that the distances between consecutive lattice sites, $x_{n+1}-x_n$, should be all equal to each other. Our goal is to prove Eq. (3) for any choice of k^+_n and k^-_n

III. PROOF OF EQ. (3)

The diffusion coefficient D remains unchanged and the drift velocity V changes its sign under the mirror-reflection symmetry corresponding to exchanging k^+_j with k^-_{-j}. Using this natural symmetry we thus conclude that each of the two relations in Eq. (3) implies the other one. Therefore we will restrict our consideration to the case $V \geqslant 0$ and prove only that

$$V \leqslant \frac{2N}{d} D. \tag{8}$$

In accordance with the findings of Ref. [15],

$$V = \frac{d(P_+ - P_-)}{c_1}, \tag{9}$$

$$D = \frac{d^2(P_+ + P_-) - 2c_2V^2}{2c_1}, \tag{10}$$

where

$$P_+ \equiv \prod_{j=0}^{N-1} k^+_j, \quad P_- \equiv \prod_{j=0}^{N-1} k^-_j, \tag{11}$$

and c_1, c_2 are polynomials given by

$$c_l = \sum_{\{\gamma^+_j\},\{\gamma^-_j\}} \prod_{m,n=0}^{N-1} (k^+_m)^{\gamma^+_m} (k^-_n)^{\gamma^-_n} \psi_l(\{\gamma^+_j\},\{\gamma^-_j\}), \tag{12}$$

where

$$\gamma^\pm_m \in \{0,1\}, \tag{13}$$

$l \in \{1,2\}$, and $\psi_l(\{\gamma^+_j\},\{\gamma^-_j\}) = 0$ if at least one of the following conditions is satisfied:

$$\sum_{m=0}^{N-1} (\gamma^+_m + \gamma^-_m) \neq N - l, \tag{14}$$

$$\gamma^+_m = \gamma^-_m = 1, \quad \exists\, m, \tag{15}$$

$$\gamma^+_m = \gamma^-_{m+1} = 1, \quad \exists\, m; \tag{16}$$

otherwise, $\psi(\{\gamma^+_j\},\{\gamma^-_j\}) = 1$. The functions $\psi_l(\{\gamma^+_j\},\{\gamma^-_j\})$ are a type of characteristic function that eliminates from Eq. (12) any combination of exponents $\gamma^\pm_m$ which does not satisfy conditions (14)–(16). It can be shown that c_1 consists of N^2 and c_2 of $N^2(N^2-1)/12$ terms, so even for moderate values of N these polynomials are quite complicated.

Our strategy is simple. We shall consider the subset of the parameter space $\{k^-_0, \ldots, k^-_{N-1}, k^+_0, \ldots, k^+_{N-1}\}$ for which the velocity V assumes a given value and try to find in it the point $(\tilde{k}^-_0, \ldots, \tilde{k}^-_{N-1}, \tilde{k}^+_0, \ldots, \tilde{k}^+_{N-1})$ at which the diffusion coefficient D attains the smallest value. We will show that at such a point $\tilde{k}^-_j = 0$ for all j. It will then suffice to prove Eq. (8) only for this restricted parameter subspace, and this can be carried out explicitly.

First of all notice that, if $k^+_j = 0$ for some j, then $V \leqslant 0$ and Eq. (8) is satisfied trivially, for the diffusion constant D is nonnegative by definition. Henceforth we shall thus restrict our consideration to the case

$$k_j^+ > 0, \quad \forall\, j. \tag{17}$$

Suppose, for a while, that except for k_0^+ and k_0^-, all other transition rates are fixed. Definitions (12) and (13) imply that c_1 and c_2 are linear in k_0^- and k_0^+, while Eq. (15) ensures that none of their terms contains both k_0^- and k_0^+. In other words,

$$c_1 = w_1^+ k_0^+ + w_1^- k_0^- + w_1^0, \tag{18}$$

$$c_2 = w_2^+ k_0^+ + w_2^- k_0^- + w_2^0, \tag{19}$$

where $w_l^\pm \equiv \partial c_l / \partial k_0^\pm$ and $w_l^0 \equiv c_l|_{k_0^\pm = 0}$ are some multivariate polynomials in $k_1^-, \ldots, k_{N-1}^-, k_1^+, \ldots, k_{N-1}^+$, independent of k_0^- and k_0^+ $(l = 1,2)$. For example, for $N=3$ there is $w_1^+ = k_2^- + k_2^+ + k_1^+$, $w_1^- = k_2^- + k_1^- + k_1^+$, $w_1^0 = k_1^- k_2^- + k_1^- k_2^+ + k_1^+ k_2^+$, $w_2^+ = w_2^- = 1$, and $w_2^0 = k_1^- + k_2^- + k_1^+ + k_2^+$. Condition (17) guarantees that

$$c_1 > 0, \quad w_1^0 > 0. \tag{20}$$

Let us now vary k_0^+ and k_0^- in such a way that $V(k_0^-, k_0^+) = \text{const}$. This means that

$$dV = \frac{\partial V}{\partial k_0^-} dk_0^- + \frac{\partial V}{\partial k_0^+} dk_0^+ = 0, \tag{21}$$

which, in turn, implies

$$dD = \left(\frac{\partial V}{\partial k_0^+} \right)^{-1} \left(\frac{\partial D}{\partial k_0^-} \frac{\partial V}{\partial k_0^+} - \frac{\partial D}{\partial k_0^+} \frac{\partial V}{\partial k_0^-} \right) dk_0^- . \tag{22}$$

Using Eqs. (9), (18), and (20) we find that $\partial V / \partial k_0^+ > 0$ and

$$\begin{aligned} \frac{c_1^5}{d^3} \left(\frac{\partial D}{\partial k_0^-} \frac{\partial V}{\partial k_0^+} - \frac{\partial D}{\partial k_0^+} \frac{\partial V}{\partial k_0^-} \right) &= w_1^0 P'_+ P'_- (c_1)^2 + [P'_+ (w_1^- w_2^0 \\ &\quad - w_1^0 w_2^-) + P'_- (w_1^+ w_2^0 \\ &\quad - w_1^0 w_2^+)](P_+ - P_-)^2, \end{aligned} \tag{23}$$

where $P'_+ \equiv \Pi_{j=1}^{N-1} k_j^+ = P_+ / k_0^+$ and $P'_- \equiv \Pi_{j=1}^{N-1} k_j^-$. In the Appendix we show that

$$w_1^- w_2^0 \geqslant w_1^0 w_2^- , \tag{24}$$

$$w_1^+ w_2^0 \geqslant w_1^0 w_2^+ . \tag{25}$$

Consequently,

$$\frac{dD}{dk_0^-} \geqslant 0. \tag{26}$$

Therefore, for any $k_0^+, k_0^- > 0$ there exists $\tilde{k}_0^+ > 0$ such that $V(k_0^-, k_0^+) = V(0, \tilde{k}_0^+)$ and $D(k_0^-, k_0^+) \geqslant D(0, \tilde{k}_0^+)$.

Applying the same reasoning in turn for sites $j = 0, \ldots, N-1$ we conclude that for any particular choice of transition rates $k_0^-, \ldots, k_{N-1}^-, k_0^+, \ldots, k_{N-1}^+$ there must exist non-negative numbers $\tilde{k}_0^+, \ldots, \tilde{k}_{N-1}^+$ such that

$$V(k_0^-, \ldots, k_0^+, \ldots, k_{N-1}^+) = V(0, \ldots, \tilde{k}_0^+, \ldots, \tilde{k}_{N-1}^+),$$

$$D(k_0^-, \ldots, k_0^+, \ldots, k_{N-1}^+) \geqslant D(0, \ldots, \tilde{k}_0^+, \ldots, \tilde{k}_{N-1}^+).$$

It thus suffices to prove Eq. (8) only in a particular case where all k_j^- vanish. Assuming $k_j^- = 0, \forall\, j$ we arrive at

$$c_1 = P_+ \sum_{j=0}^{N-1} \frac{1}{k_j^+}, \tag{27}$$

$$c_2 = P_+ \sum_{j=0}^{N-2} \sum_{l=j+1}^{N-1} \frac{1}{k_j^+ k_l^+}, \tag{28}$$

and $P_- = 0$. Finally, by using Eqs. (9) and (10) this implies

$$\begin{aligned} V - \frac{2N}{d} D &= d P_+ \frac{2N c_2 P_+ - (N-1)(c_1)^2}{(c_1)^3} \\ &= s \left[2N \sum_{0 \leqslant j < l < N} \frac{1}{k_j^+ k_l^+} - (N-1) \left(\sum_{j=0}^{N} \frac{1}{k_j^+} \right)^2 \right] \\ &= -s \sum_{0 \leqslant j < l < N} \left(\frac{1}{k_j^+} - \frac{1}{k_l^+} \right)^2 \leqslant 0, \end{aligned} \tag{29}$$

where we used a shorthand notation $s \equiv d(P_+ / c_1)^3 > 0$. Not only does this inequality complete the proof of Eq. (8), but it also tells us that V/D assumes its maximal value $2N/d$ if and only if all k_j^- vanish and all k_j^+ are positive and equal to each other.

IV. CONCLUSIONS

We have rigorously proved that the maximal value of the Einstein force F_E is $2k_B TN/d$, where N is the number of distinct internal states (conformations) of a motor protein in a full mechanochemical cycle, d denotes the segment length of a microtubule, T is the temperature, and k_B is the Boltzmann constant. We showed that this maximal value is attained if and only if all transitions are unidirectional and of the same magnitude. We also showed that the randomness r satisfies the relation $r > 1/N$.

Although our approach is valid for any value of N and an arbitrary choice of transition rates, it still refers to a simplified situation. First, we assumed that the motion of a motor protein can be reduced to diffusion of a Brownian particle on a linear chain of lattice nodes, and other topologies deserve at least equal attention [2,16–19]. Second, we assumed that the transitions constitute a Poisson process. Although this hypothesis is confirmed by recent experiments on myosin [20], it is well known that transition rates with other probability density functions may lead to completely different upper bounds for F_E [3–6,19]. Third, our formula depends on N, which is not known exactly. Finally, we consider a single motor, while many real protein motors work collec-

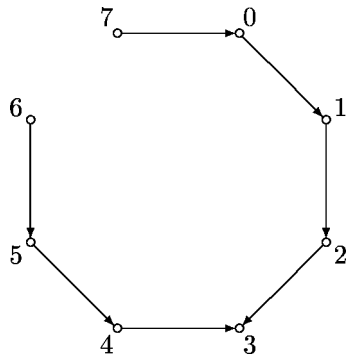

FIG. 1. The graph corresponding to a term $h_1(6,3)=k_0^+k_1^+k_2^+k_4^-k_5^-k_6^-k_7^+$ of c_1 $(N=8)$.

tively [1,2]. Nevertheless, the force calculated using all these approximations (4.3 pN) agrees quite well with the experimental value of the stalling force F_s for kinesin (different experimental techniques yielded $F_s \sim 4-8$ pN [1]). Further work is, of course, required to clarify the relevance of the above-mentioned problems.

Last, but not least, our proof implies that a nonvanishing drift in an arbitrary one-dimensional diffusive Poissonian system imposes the lower bound for the dispersion.

ACKNOWLEDGMENT

Support from the Polish KBN Grant No. 2 P03B 119 19 is gratefully acknowledged.

APPENDIX: PROOF OF EQS. (24) AND (25)

The mirror-reflection symmetry, as described at the beginning of Sec. II, maps Eq. (24) onto Eq. (25) and vice versa. Therefore, it suffices to prove only one of them, say Eq. (25).

To prove Eq. (25) we need a more detailed description of the dependence of polynomials c_1 and c_2 on the transition rates $k_j^{\pm}$, $j=0,\ldots,N-1$. A convenient description is provided by a graphical representation [9], where each term of c_l, $l=1,2$, which is of the form $\Pi_{j=0}^{N-1}(k_j^-)^{\gamma_j^+}(k_j^+)^{\gamma_j^-}$, corresponds to an oriented graph spanned on a (regular) polygon with N nodes labeled $0,\ldots,N-1$. The graph is constructed in such a way that whenever $\gamma_j^-=1$ we draw an arrow from node j to $j-1 (\mathrm{mod}\ N)$, and whenever $\gamma_j^+=1$ we draw an arrow from j to $j+1 (\mathrm{mod}\ N)$. Conditions (13)–(16) imply that there is a one-to-one correspondence between the terms of c_l, $l=1,2$, and the set of all graphs drawn according to the following rules: (1) Draw all but l sides of the polygon; (2) replace each drawn side with an arrow in such a way that for each node there is at most one arrow starting at it. The first step is associated with conditions (13), (14), and (16), while the second step is related to condition (15). An example of a graph corresponding to a term $k_0^+k_1^+k_2^+k_4^-k_5^-k_6^-k_7^+$ of c_1 for $N=8$ is given in Fig. 1.

Note that, by definition, if an arrow is drawn along a side $(j,j+1)$ in a clockwise direction (which corresponds to a term k_j^+), the preceding side $(j-1,j)$ must be either empty or occupied by another arrow pointing clockwise (k_{j-1}^+). Similarly, a counterclockwise arrow starting at a node j (corresponding to k_j^-) must be followed by either an empty side or a side occupied by another counterclockwise arrow (k_{j+1}^-). Therefore in each term of c_l, $l=1,2$, there are exactly l empty bonds interlaced with exactly l nodes that are not the source of an arrow. Consequently, each term of c_1 is uniquely given by specifying two nodes: one, say m, such that the side $(m,m+1)$ is empty and the other one, say s, which is not a source of an arrow. In the example depicted in Fig. 1, $m=6$ and $s=3$. We will denote such a term by $h_1(m,s)$. Clearly,

$$h_1(m,s) \equiv \prod_{j=m+1}^{s-1}{}' \ k_j^+ \prod_{j=s+1}^{m}{}' \ k_j^- , \tag{A1}$$

where Π' denotes a special product defined so as to take into account the periodic nature of a polygon:

$$\prod_{j=n}^{m}{}' \ k_j^{\pm} \equiv 1, \quad \text{if } m+1 \equiv n (\mathrm{mod\ N}); \tag{A2}$$

otherwise,

$$\prod_{j=n}^{m}{}' \ k_j^{\pm} \equiv \begin{cases} \displaystyle\prod_{j=n}^{m} k_j^{\pm}, & n \leq m, \\ \displaystyle\prod_{j=n}^{N-1} k_j^{\pm} \prod_{j=0}^{m} k_j^{\pm}, & n > m, \end{cases} \tag{A3}$$

where $0 \leq n,m \leq N-1$. In other words, for any function f defined on the nodes of the polygon, $\Pi'^{m}_{j=n} f(j)$ is a product of all $f(j)$ associated with nodes j lying between nodes n and m in the clockwise direction; however, if this would mean that all nodes should be taken into this product, then $\Pi'^{m}_{j=n} f(j) \equiv 1$. Thus, for example, $h_1(0,0)=k_1^+k_2^+\cdots k_{N-1}^+$, $h_1(0,1)=k_2^-k_3^-\cdots k_{N-1}^-k_0^-$, and $h_1(0,2)=k_1^+k_3^-k_4^-\cdots k_{N-1}^-k_0^-$. Using the polynomials $h_1(m,s)$ we can rewrite c_1 as

$$c_1 = \sum_{m=0}^{N-1} \sum_{s=0}^{N-1} h_1(m,s). \tag{A4}$$

Similarly, each term of c_2 corresponds uniquely to a graph containing exactly two empty sides and two nodes that do not start an arrow. Each term of c_2 is thus a product of the form

$$h_2(m,s;n,t) \equiv \prod_{j=m+1}^{s-1}{}' \ k_j^+ \prod_{j=s+1}^{n}{}' \ k_j^- \prod_{j=n+1}^{t-1}{}' \ k_j^+ \prod_{j=t+1}^{m}{}' \ k_j^- , \tag{A5}$$

where the order of the nodes m, s, n, and t on the polygon must satisfy the following condition: if we start moving along the nodes of the polygon in the clockwise direction, then from m we must first go to s, then to $n \neq m$, then to t, and finally return to m. This guarantees that each polynomial $h_2(m,s;n,t)$ is actually a product of exactly $N-2$ transition rates $k_j^{\pm}$.

The polynomials w_1^0, w_1^+, w_2^0, and w_2^+ satisfy the following relations:

$$w_1^0 = \sum_{m=0}^{N-1} h_1(m,0), \tag{A6}$$

$$k_0^+ w_1^+ = \sum_{m=1}^{N-1} \sum_{s=1}^{m} h_1(m,s), \tag{A7}$$

$$w_2^0 = \sum_{m=1}^{N-1} \sum_{n=0}^{m-1} \sum_{t=n+1}^{m} h_2(m,0;n,t), \tag{A8}$$

$$k_0^+ w_2^+ = \sum_{m=2}^{N-1} \sum_{n=1}^{m-1} \sum_{s=1}^{n} \sum_{t=n+1}^{m} h_2(m,s;n,t). \tag{A9}$$

Each term of the product $k_0^+ w_1^0 w_2^+$ is thus of the form $h_1(l,0)h_2(m,s;n,t)$, where $1 \leqslant s \leqslant n < t \leqslant m \leqslant N-1$ and $0 \leqslant l \leqslant N-1$. Similarly, each term of the product $k_0^+ w_2^0 w_1^+$ is of the form $h_1(l,s)h_2(m,0;n,t)$, where $0 \leqslant n < t \leqslant m \leqslant N-1$ and $0 \leqslant l \leqslant N-1$. Using the explicit form of h_1 and h_2 [see Eqs. (A1) and (A5)], one can verify that

$$h_1(l,0)h_2(m,s;n,t) = \begin{cases} h_1(n,s)h_2(m,0;l,t), & l < t, \\ h_1(l,s)h_2(m,0;n,t), & l \geqslant t. \end{cases} \tag{A10}$$

We thus see that each term of $k_0^+ w_1^0 w_2^+$ [the left-hand side (LHS), of Eq. (A10)] can be mapped onto a term of $k_0^+ w_2^0 w_1^+$ [RHS of Eq. (A10)]. This mapping is an injection: if it maps some $h_1(x_1,0)h_2(x_2,x_3;x_4,x_5)$ on some $h_1(l,s)h_2(m,0;n,t)$, then evidently $x_2 = m$, $x_3 = s$, $x_5 = t$, and for $l \geqslant t$ there is $x_1 = l$, $x_4 = n$, while for $l < t$ there is $x_1 = n$, $x_4 = l$. In each case $x_1, \ldots, x_5$ can be determined uniquely if l, s, m, n, and t are known.

The fact that Eq. (A10) defines an injection implies that $k_0^+ w_1^0 w_2^+ \leqslant k_0^+ w_2^0 w_1^+$, which completes the proof of Eq. (25).

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