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Steady State Distribution of Molecular Motor Ensembles

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***Abstract*— Directed transport of intracellular cargo is predominantly carried out by nanoscale bio-mechanical agents called molecular motor proteins. Often, multiple motors with same or different mechano-chemical properties team up to transport cargoes inside cells. In this article we analyze the behavior of homogeneous multi-motor ensembles and prove the existence of a transient state in the state space describing the various configurations for a two-motor ensemble. We further show that the various motor configurations for such an ensemble have a unique steady state probability distribution, implying that such a system possesses a degree of robustness. Results of this nature can be extended to ensembles containing higher number of motors, with the associated steady state distributions providing insights into possible mechanisms employed by motors while transporting a common cargo.**

1. INTRODUCTION

Molecular motors such as kinesin and dynein are the main effectors of intracellular transport and facilitate the directed motion of cargoes inside the cell. The transport occurs over directed polymerized lattices called microtubules. It is known that multiple motors, often of the same or different type, work in groups to enable both unidirectional and bidirectional transport over large distances *in vivo* [1]. Disruptions in intracellular traffic, often caused by impaired molecular motor behavior, are known to hamper healthy cellular environment and cause a host of ailments including neurodegenerative disorders [2], [3]. Therefore, deciphering the fundamenltals of motor protein functionality is crucial towards the goal of adressing maladies caused by impaired motor behavior.

Single motor protein behavior can be well characterized by its probabilities of stepping, detachment and reattachment as it traverses along the microtubule filament. Exprimental estimates of these probabilities have been made possible by controlled experiments using optical tweezers [1], [4], which along with enhancement using modern control mechanisms [5], [6] hold potential towards probing molecular motors with higher precision and fidelity. Well established single motor models informed by experiments have enabled theoretical models that describe transport of common cargo by multiple motor proteins. Existing models describing transport by teams of motors have utilized different approaches such as mean-field theory [7], Monte-Carlo simulations [8] and Master Equations [9]. Materassi and co-workers in [10] employed master equations to show that an ensemble of motors carrying a cargo can be efficiently analyzed by modeling it as a Markov chain governed by a suitable stochastic matrix. The model was further instaniated for kinesin motors and quantities of biological interest such as average velocity and runlength were obtained.

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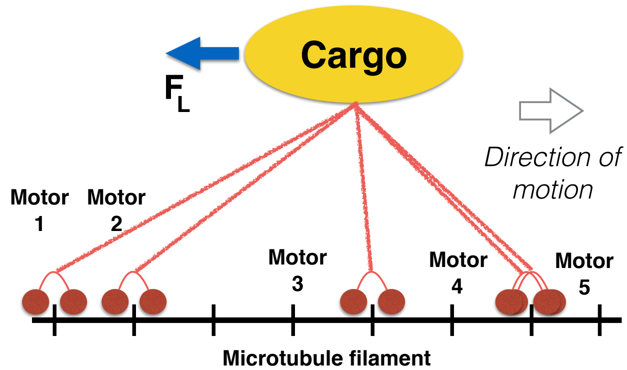

Fig. 1. Representation of an ensmeble of five motors carrying a cargo. F_L is the load force acting on the cargo in the direction opposing the cargo motion. The microtubule filament is modeled as a series of locations spaced $8\ nm$ apart.

We capialized on the modeling principles used in [10] and examined the Markov matrix to prove that the state space of the associated Markov chain contains at least one transient state. Furthermore, we show that the various configurations of the motors carrying a common cargo behave according to a unique steady state distribution. In our analysis, we have restricted our attention to an ensemble of two kinesin motors, but the results can be applied for ensembles containing higher number of motors with same or different mechano-chemical properties as well.

In the next section, a brief description of the model for multiple motors carrying a cargo is provided.

2. MATHEMATICAL MODEL

The linkage between the tail and motor-heads of a single motor protein is modeled as a hookean spring when stretched, having rest length l_0 and stiffness K_e (see [10] for model description). The motor exerts a force F on the cargo while transporting the cargo along the microtubule and can take a forward step as long as the force is less than its stalling force F_S. The microtubule filament is modeled as a series of equally spaced locations, with one or more motors being possibly attached to a given location. To represent multiple motors on the microtubule, the notion of absolute configuration Z is used in [10] to encode the number of motors attached to a given microtubule location. Since microtubule filaments are typically several microns in length and therefore much longer than the average processivity of molecular motors (hundreds of nanometers), Z is a bi-infinite sequence. For example, the absolute configuration for the section of microtubule in Figure 1 is $Z = [... \ 1\ 1\ 0\ 0\ 1\ 0\ 2 \ ...]$. When a motor in the configuration Z steps forward, detaches from or reattaches to the microtubule, a new configuration Z' is attained. Assuming $\lambda_Z(Z', Z)$, the probability rate of transition from Z to Z', is known then it is possible to define an infinite dimensional Markov Model (see [11], [12] for description). However, the infinite dimension of the model makes it unsuitable for an exact analysis, thereby making the solution for the Master Equation intractable.

To tackle the issue, a projection of the infinite dimentional model to a finite dimensional model is obtained in a way that preserves the Markov property. It is primarily due to the distance between the vanguard (forward most) and rearguard (rear most) motor being bounded (see [10] and [13] for details). It allows for the projection of the absolute configuration Z to a *relative configuration* σ, which contains information of the locations of all the motors in an ensemble relative to the rearguard motor. Thus the relative configuration for the ensemble in Figure 1 can be symbolically represented by $\sigma = M|M|||M||MM$, where M denotes motor at a location and $|$ denotes distinct locations. The rate of transition between relative configurations σ and σ', denoted by $\lambda_\sigma(\sigma', \sigma)$, can be computed from the rate of transition between absolute configurations $\lambda_Z(Z', Z)$ (see [10] and [13] for details). The probability of the system being in relative configuration σ' at $t + \Delta t$ given that it is σ at t is represented by $P_\sigma(\sigma', t+\Delta t|\sigma, t)$. For small Δt, we denote $P_\sigma(\sigma', t+\Delta t|\sigma, t) = \lambda_\sigma(\sigma', \sigma)\Delta t$. Knowing the rates $\lambda_\sigma(\sigma', \sigma)$, the probability $P_\sigma(\sigma, t)$ of the system having relative configuration σ at time t can be shown to satisfy the Master Equation $\frac{\partial}{\partial t} P_\vartheta(\vartheta, t) = \sum_{\vartheta' \in S} \nu_\vartheta(\vartheta, \vartheta') P_\vartheta(\vartheta', t) - P_\vartheta(\vartheta, t) \sum_{\vartheta' \in S} \nu_\vartheta(\vartheta', \vartheta)$,where S is the finite set of relative configurations.

Let $S = \{\sigma_1, \ldots, \sigma_n, \sigma_{n+1}\}$. Here, $\sigma_{n+1} = \phi$ denotes the configuration where none of the motors in the ensemble are attached to the microtubule i.e. cargo is lost. Let $P_i(t)$ be the probability of the ensemble being in the configuration σ_i at time t and $P(t) = [P_1(t), \ldots, P_n(t), P_{n+1}(t)]$. In [10], the probability vector $P(t)$ is shown to satisfy,

$$\frac{d}{dt} P(t) = \bar{\mathbf{\Gamma}} P(t) \tag{1}$$

where $\bar{\mathbf{\Gamma}} \in \mathbf{R}^{(n+1)\times(n+1)}$. Solving for $P(t)$, $P(t) = e^{\bar{\mathbf{\Gamma}}(t-t_0)} P(t_0) = \bar{\mathbf{J}} P(t_0)$, where $P(t_0)$ denotes the probability vector at initial time t_0 and $\bar{\mathbf{J}} \in \mathbf{R}^{(n+1)\times(n+1)}$. In order to arrive at a non-trivial distribution in [10], the probability is conditioned on at least one motor remaining engaged to the microtubule. It reduces the dimension of S from $n+1$ to n with the dynamics of the system now being described by $\frac{d}{dt}P(t) = \mathbf{\Gamma} P(t)$,where $\mathbf{\Gamma} \in \mathbf{R}^{n\times n}$. Thus $P(t) = \mathbf{J} P(t_0)$ with $\mathbf{J} \in \mathbf{R}^{n\times n}$.

In the next section we limit our attention to two motors carrying a common cargo and show that, under the condition of one motor in the ensemble carrying the cargo remaining engaged to the microtubule, the state space S contains at least one transient state and that as $t \to \infty$, a unique steady state probability $P(t)$ is reached.

3. STEADY STATE DYNAMICS

In this section we establish existence of transient states and a unique steady state probability distribution in the state space of relative configurations of a cargo carried by multiple motors . The total number of motors in the ensemble $\bar{m} = 2$. We establish results motivated from the underlying biology and structure of the probability transition matrix $\mathbf{J}$. The Markov matrix $\mathbf{J}$ described in the previous section can be arranged in the form as shown in (2),

$$\mathbf{J} = \begin{pmatrix} \mathbf{A} & \mathbf{B} \\ \mathbf{0} & \mathbf{C} \end{pmatrix}, \tag{2}$$

where, $\mathbf{A} \in \mathbb{R}^{m\times m}, \mathbf{B} \in \mathbb{R}^{m\times(n-m)}, \mathbf{C} \in \mathbb{R}^{(n-m)\times(n-m)}, \mathbf{0}$ is a zero matrix of appropriate dimensions. Here, $\mathbf{A}$ is a column stochastic matrix and is the transition matrix of a subset of S. The state space S can be split into two disjoint sets $S_1 = \{\sigma_1, \sigma_2, \cdots, \sigma_m\}$ and $S_2 = \{\sigma_{m+1}, \cdots, \sigma_n\}$ such that $S = S_1 \cup S_2$ and it is possible to transition from S_2 to S_1(i.e., $\mathbf{B} \neq \mathbf{0}$) but it is not possible to transition from S_1 to S_2. Thus, $\mathbf{A}$ is the transition matrix of the Markov chain associated with the states S_1. The arrangement of the matrix $\mathbf{J}$ in the form of (2) is enabled by Theorem 1. First we present a few definitions.

Definition 1 (Irreducible Markov Chain)**.** An irreducible Markov chain is such that if for any $\sigma_i, \sigma_j \in S$, there exist $n \in \mathbb{N}$ such that $(\mathbf{J}^n)_{i,j} > 0$, that is, it is possible to reach any state from any other state in finite hops.

Definition 2 (Aperiodic Markov Chain)**.** An aperiodic Markov chain is the one where each state is aperiodic. The period of a state $\sigma_i \in S$ is defined as $d(i) := gcd\{n \geq 1 | (\mathbf{J}^n)_{i,i} > 0\}$. If $d(i) = 1$ then the state is said to be aperiodic.

Definition 3 (Recurrent and Transient State)**.** A state $\sigma_i \in S$ is said to be recurrent if the chain returns to state σ_i with probability 1 in a finite number of steps given that it started from σ_i, otherwise it is said to be transient.

Definition 4 (Steady State Distribution)**.** The right eigenvector π of the probability transition matrix $\mathbf{J}$ corresponding to the eigenvalue 1 is said to be a steady state distribution, that is, it satisfies $\mathbf{J}\pi = \pi$.

Definition 5 (Limit Distribution)**.** A vector π satisfying $\lim_{n\to\infty} \mathbf{J}^n = \pi\mathbf{1}^{'}$ is said to be the limit distribution of $\mathbf{J}$, where $\mathbf{1}$ is a vector of all ones of appropriate dimensions.

Theorem 1. *Given a cargo attached to $\bar{m} = 2$ motors and subjected to opposing load force F_L, there exists at least one transient state $\sigma_i \in S$.*

The first row of $\mathbf{B} \neq \mathbf{0}$ as detachment events of the molecular motors from the microtubule have non zero probability. Hence, sum of each column of $\mathbf{C} < 1$. The Gershgorin theorem leads to $|\rho(C)| < 1$ implying that the states associated with $\mathbf{C}$ are transient states. Thus, transition probabilities of all transient states are clubbed into $\mathbf{C}$. All the recurrent states correspond to $\mathbf{A}$. This justifies the structure of $\mathbf{J}$ as shown in (2).

Theorem 2. *Submatrix $\mathbf{A}$ of $\mathbf{J}$ is irreducible and aperiodic (i.e., ergodic) and $|\rho(\mathbf{C})| < 1$.*

Theorem 3. *Consider $\mathbf{J}$ as defined in (2) such that $\mathbf{A}$ is irreducible, aperiodic (from the previous theorem) and π be its limit distribution. Then $[\pi^{'} \ \mathbf{0}^{'}]^{'}$ is the limit distribution and unique steady state distribution of the Markov chain with the transition matrix $\mathbf{J}$.*

The existence of a unique steady state distribution of the relative configurations of a cargo carried by multiple motors demonstrates that a cargo-motor ensemble is a naturally robust system. As long as the cargo remains bound to the microtubule through at least one motor the cargo-motor ensemble behaves according to a fixed distribution independent of the initial distribution.

4. CONCLUSIONS

Transport of cargo by molecular motors is modeled as a Markov chain derived from a probability master equation is analysed in this article. The steady state probability distribution of the relative configurations is proven to be unique which signifies the robustness of the intracellular transport mechanisms.

References

[1] K. Svoboda, C. F. Schmidt, B. J. Schnapp, S. M. Block *et al.*, "Direct observation of kinesin stepping by optical trapping interferometry," *Nature*, vol. 365, no. 6448, pp. 721–727, 1993.

[2] M. A. Welte, S. P. Gross, M. Postner, S. M. Block, and E. F. Wieschaus, "Developmental regulation of vesicle transport in drosophila embryos: forces and kinetics," *Cell*, vol. 92, no. 4, pp. 547–557, 1998.

[3] G. A. Morfini, Y.-M. You, S. L. Pollema, A. Kaminska, K. Liu, K. Yoshioka, B. Björkblom, E. T. Coffey, C. Bagnato, D. Han *et al.*, "Pathogenic huntingtin inhibits fast axonal transport by activating jnk3 and phosphorylating kinesin," *Nature neuroscience*, vol. 12, no. 7, pp. 864–871, 2009.

[4] L. S. Milescu, A. Yildiz, P. R. Selvin, and F. Sachs, "Maximum likelihood estimation of molecular motor kinetics from staircase dwell-time sequences," *Biophysical journal*, vol. 91, no. 4, pp. 1156–1168, 2006.

[5] S. Roychowdhury, S. Bhaban, S. Salapaka, and M. Salapaka, "Design of a constant force clamp and estimation of molecular motor motion using modern control approach," in *American Control Conference (ACC), 2013*. IEEE, 2013, pp. 1525–1530.

[6] S. Roychowdhury, T. Aggarwal, S. Salapaka, and M. V. Salapaka, "High bandwidth optical force clamp for investigation of molecular motor motion," *Applied Physics Letters*, vol. 103, no. 15, p. 153703, 2013.

[7] A. Kunwar and A. Mogilner, "Robust transport by multiple motors with nonlinear force–velocity relations and stochastic load sharing," *Physical biology*, vol. 7, no. 1, p. 016012, 2010.

[8] A. Kunwar, M. Vershinin, J. Xu, and S. P. Gross, "Stepping, strain gating, and an unexpected force-velocity curve for multiple-motor-based transport," *Current biology*, vol. 18, no. 16, pp. 1173–1183, 2008.

[9] C. W. Gardiner *et al.*, *Handbook of stochastic methods*. Springer Berlin, 1985, vol. 4.

[10] D. Materassi, S. Roychowdhury, T. Hays, and M. Salapaka, "An exact approach for studying cargo transport by an ensemble of molecular motors," *BMC biophysics*, vol. 6, no. 1, p. 14, 2013.

[11] J. L. Doob, "Markoff chains–denumerable case," *Transactions of the American Mathematical Society*, pp. 455–473, 1945.

[12] D. T. Gillespie, "Exact stochastic simulation of coupled chemical reactions," *The journal of physical chemistry*, vol. 81, no. 25, pp. 2340–2361, 1977.

[13] S. Bhaban, D. Materassi, M. Li, T. Hays, and M. Salapaka, "Emergent transport properties of molecular motor ensemble affected by single motor mutations," *arXiv preprint arXiv:1603.07999*, 2016.