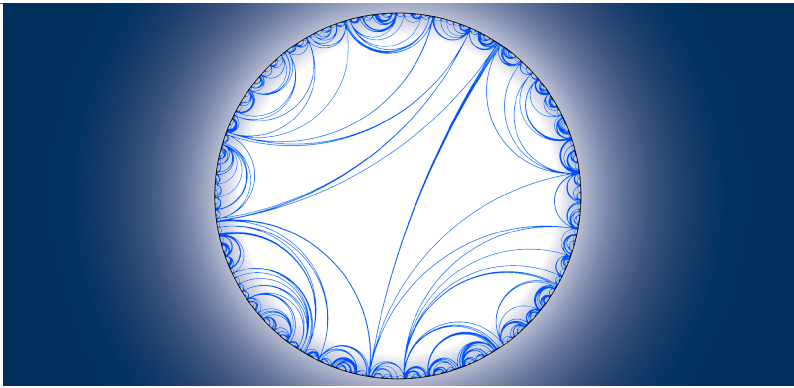




Universität Potsdam



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A Quasi-Random-Walk to model a biological transport process

Peter Keller · Sylvie Rœlly · Angelo Valleriani

Abstract Transport Molecules play a crucial role for cell viability. Amongst others, linear motors transport cargos along rope-like structures from one location of the cell to another in a stochastic fashion. Thereby each step of the motor, either forwards or backwards, bridges a fixed distance. While moving along the rope the motor can also detach and is lost.

We give here a mathematical formalization of such dynamics as a random process which is an extension of Random Walks, to which we add an absorbing state to model the detachment of the motor from the rope. We derive particular properties of such processes that have not been available before. Our results include description of the maximal distance reached from the starting point and the position from which detachment takes place. Finally, we apply our theoretical results to a concrete established model of the transport molecule Kinesin V.

1 Introduction

Amongst the many complex processes taking place in living cells, transport of cargos across the cytoskeleton is fundamental to cell viability and activity. To move cargos between the different cell parts, cells employ *Molecular Motors*. The motors are responsible for a huge variety of tasks, ranging from cell division to DNA replication and chemical transport. A subclass of such motors operate by transporting cargos along the so called cellular *microtubules*, namely rope-like structures that connect, for instance, the cell-nucleus and outer membrane. One example of such Motors is Kinesin V, common in eukaryotic cells. Due to the periodic molecular

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structure of the microtubules, the steps of Kinesin have all the same length equal to 8 nanometers, see [CC05]. Under normal conditions present in living cells, this motor performs a random walk in one dimension with a drift on the microtubule possibly stopped by detachment from the tubule. Experimental studies have led to rather detailed and successful models of the chemical processes in Kinesin V which control the movement of the motor. These chemical processes are characterized by a network of internal chemical states usually under the simplifying condition that no detachment from the microtubule is allowed. In a more realistic setting detachment is allowed. Realistic transition rates for both situations are found in [LL08].

It is possible to derive certain values like run length and time – see [LLV09] – but deriving distributional information about these quantities is much harder and usually not available.

We introduce a class of Markov Chains that formalizes the model of Kinesin with detachment. We call this new class *killed Quasi Random Walk*. It is a generalization of the usual Random Walk on the integers allowing at each position internal states on which the further movement depends. This could be seen as a so called *Markov Modulated Random Walk* or a Random Walk in a Random Environment. But we like to extend here the very well established Quasi-Birth-and-Death Process as introduced in [Neu94] (without detachment). It is a formulation of a Birth-and-Death Process in a Random Environment that uses block matrices. This perspective is especially useful for treating these processes numerically.

The term “killed” is used also for killed Birth-and-Death Processes, see e.g. [DZ05]. It reflects the fact that the process can be stopped by arriving at a cemetery state.

Our generalization enables us to derive detailed results about the spatial behaviour of a Molecule Motor, which could be applied to other processes that behave similar to Kinesin V.

The rest of the article is organized as follows. In section 2 we define the *killed Quasi-Random-Walk* and discuss shortly the tail behaviour of the process. Section 3 is devoted to the definition of the *step-process* which is the fundamental tool to prove Theorem 1 and thus to derive spatial properties of the process. Finally in section 4 we apply our theoretical results to an established model of Kinesin V.

2 A Killed Quasi Random Walk

2.1 The continuous time random model

A simple Random Walk (RW) on Z is a (time-homogeneous) continuous time Markov Chain with values in a space of *positions*, such that the allowed jumps (or displacements) are only to direct neighbouring positions. As generalisation, a Quasi RW is a Markov Chain with values in the product state space $Z \times M$ with $M := \{1, 2, \dots, m\}$, where, to the first *position* component as before, one adds a second component which specifies in which *internal state* the process is at each position.

A killed Quasi Random Walk (short kQRW) is a Quasi RW $X := (X_t)_{t \geq 0}$ with an additional trap or cemetery state, denoted by Δ . So the state space E of a kQRW

is of the form:

$$E := \{\Delta\} \cup (Z \times M) = \{\Delta\} \cup \{(z, i) : z \in Z, i \in \{1, 2, \dots, m\}\}.$$

The following definition precises the type of dynamics we are looking at:

Definition 1 Let $X := (X_t)_{t \geq 0}$ be a continuous time Markov Chain with values in the state space E defined as above. If its infinitesimal generator has the following structure

$$Q = \begin{pmatrix} 0 & 0 \\ R_{\Delta}^{(c)} & S^{(c)} \end{pmatrix}$$

where $S^{(c)}$ is a block tridiagonal (infinite) matrix of the form

$$S^{(c)} := \begin{pmatrix} \ddots & & & & & \\ & A & A_+ & 0 & & \\ & A_- & A & A_+ & & \\ & 0 & A_- & A & & \\ & & & & \ddots & \end{pmatrix},$$

with A_-, A, A_+ $m \times m$ -matrices, Γ_c the nonnegative m -dimensional vector $\Gamma_c := -(A_- + A + A_+) \mathbf{1}^\top$ and $R_{\Delta}^{(c)} := (\dots, \Gamma_c, \Gamma_c, \Gamma_c, \dots)$, then X is called a *killed Quasi Random Walk*.

(The notation $\mathbf{1}$ holds for the vector with all entries equal to 1).

To illustrate this definition we refer to fig.1, where gray circles encode collections of states and white circles are single states. Analogical arrows between gray circles denotes a collection of transitions. There it gets clear that the subgenerator matrix A quantifies the transitions between the internal states at each position $z \in Z$, independently of z . We refer to this property as *spatial homogeneity* of the chain. On the other hand the nonnegative matrices A_- and A_+ determine the one-step transition rates of a change of *position* to the left or to the right. For the sake of simplicity we assume throughout the article that μ , the initial distribution of X , is concentrated on position zero.

It is noteworthy that a distinct object, called Quasi Random Walk too, already appeared in the very different context of Monte Carlo Methods, see e.g. [HOS00].

2.2 The discrete time random model

Similarly to Definition 1, we define a *discrete time killed Quasi Random Walk* as a Markov chain associated to a transition matrix P of the form

$$P = \begin{pmatrix} 1 & 0 \\ R_{\Delta}^\top & S \end{pmatrix}, \quad (1)$$

where S is again an infinite block tridiagonal matrix as below composed by non-negative matrices A_{-1}, A_0, A_{+1} such that $A_{-1} + A_0 + A_{+1}$ is an irreducible substochastic matrix. The discrete time version of the vector Γ is then defined as $(Id - (A_{-1} + A_0 + A_{+1})) \mathbf{1}^\top$.

Clearly, the embedded Markov Chain of a continuous time kQRW is a *discrete time kQRW*. We will use the embedded chain in the next section to get information about the spatial motion of a kQRW before killing.

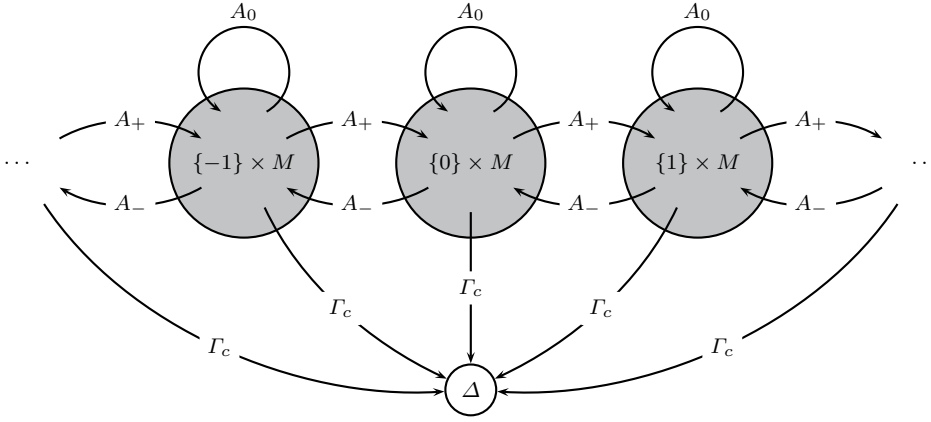


Fig. 1 Schematic transition graph of a killed Quasi Random Walk.

2.3 The lifetime – or killing time – of the process

We always assume in this article that Δ is the only absorbing state of the system. It is reachable, because the vector $\Gamma^{(c)}$ contains at least one non zero entry due to the fact that $A_- + A + A_+$ is a *subgenerator*. Nevertheless, since the state space E is infinite, it is not immediate that τ_Δ , the time to reach Δ , usually called *killing time* or absorption time, is almost surely finite. In fact, because of the spatial homogeneity of the dynamics, τ_Δ does not depend on the last position the process visited before killing. Thus, by *lumping* (see e.g. [KS76]), it is equal to the killing time of a much simpler *reduced model*, obtained by ignoring the position coordinates, as in fig. 2.

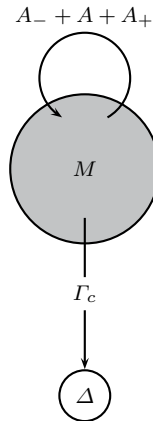


Fig. 2 Reduced killed Quasi Random Walk.

The law of τ_Δ is given explicitly in the following

Lemma 1 *The distribution of the killing time τ_Δ of a kQRW with initial law μ satisfies*

$$P(\tau_\Delta \in dt) = \mu \exp((A_- + A + A_+)t) \Gamma_c^\top dt. \quad (2)$$

This lemma is simple to prove using the phase type calculus introduced in [Neu94]. This method also allows to characterize the tail behaviour of τ_Δ .

Proposition 1 *Let $X = (X_t)_{t \geq 0}$ be a kQRW and let λ be the eigenvalue with biggest real part of the $m \times m$ -matrix $A_{-1} + A_0 + A_{+1}$. Then λ is indeed a real number and the tails of the killing time $\tau_\Delta = \inf \{t \geq 0 : X_t = \Delta\}$ satisfy:*

$$\exists K > 0 : P(\tau_\Delta > t) \stackrel{t \rightarrow \infty}{\approx} K \exp(-\lambda t) + o(\exp(-\lambda t)). \quad (3)$$

Moreover, the constant number K is explicitly given by

$$K = \mu v,$$

where v is the right eigenvector of A associated to λ .

Proof Perron-Frobenius Theory implies that λ is a real number. The remaining part of the proof can be found in [Neu94], Theorem 2.3.1. It is based on a result on non negative irreducible matrices, see e.g. [Sen06], chapter 1, Theorem 1.2.

Proposition 1 underlines that it is exponentially unlikely for the process X to be alive at large time t . Indeed, the eigenvalue λ dominates the long time behaviour of the system and is the experimentally most easily measurable time scale.

3 Spatial behaviour of the kQRW

In this section, we analyse spatial characteristic structure of the paths of a kQRW. For this reason it will be enough to consider its embedded Markov Chain, denoted by $X = (X_n)_{n \geq 0}$, which is – as already remarked – a discrete time kQRW.

3.1 The step process associated to a discrete time kQRW

Though we are especially interested in properties of the *position* coordinate we would like to factor out some irrelevant internal states of M . But one can not drastically reduce the state space of the kQRW by considering only its first coordinate, because the image of the process after projection would not be Markovian anymore. One then constructs a new process on a smaller state space having the nice property that every transition encodes a step from one position to another of the original kQRW (before killing). To restrict the state space accurately, we introduce structurally important (not necessarily disjoint) subsets of the set M :

Definition 2 Let $(X_n)_{n \geq 0}$ be a discrete time kQRW on $E = (Z \times M) \cup \{\Delta\}$ with transition matrix $P = (p_{k,l})_{k,l \in E}$. We define two (sub)sets of internal states in the following way:

1. *Arrival from the left:*

$$M^l := \{i \in M : \exists j \in M : p_{(-1,j),(0,i)} > 0\}$$

2. *Arrival from the right:*

$$M^r := \{i \in M : \exists j \in M : p_{(1,j),(0,i)} > 0\}.$$

Any subset of E of the form $\{z\} \times M^l$ or $\{z\} \times M^r$ is called an *arrival set* and its elements *arrival states*.

Whenever the original kQRW changes position it arrives at an *arrival set*. The next position change leads to an *arrival state* of a neighbouring position and so on. Thus each trajectory of a kQRW can be decomposed into transitions between arrival states of neighbouring positions, see fig. 3.

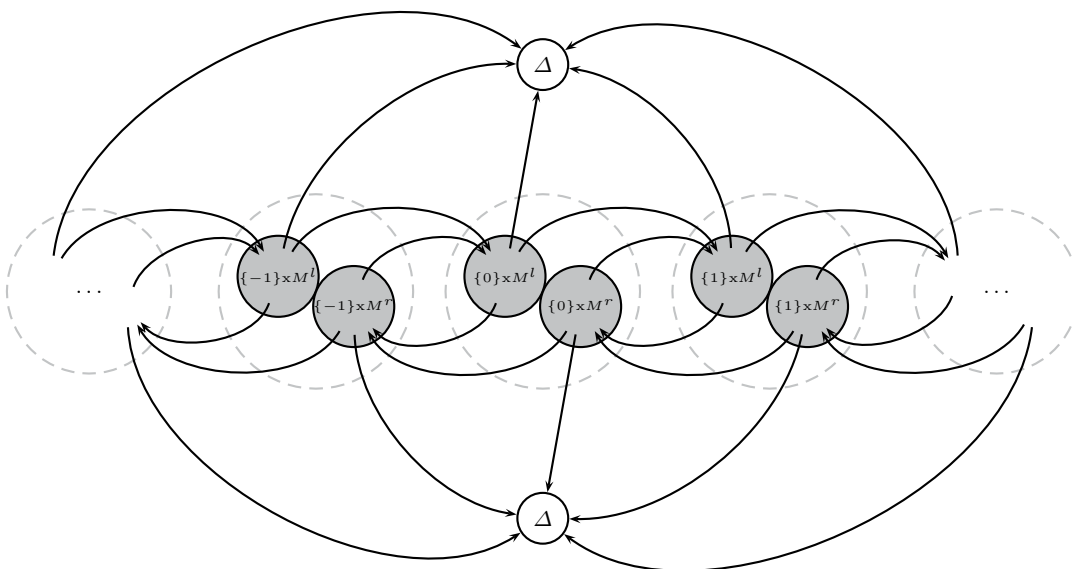


Fig. 3 The step process associated to the original kQRW. (The absorbing state Δ appears here twice only for graphical reasons).

Let us now describe the dynamic of the new process called *step process* which describes the jumps between the positions via arrival states.

Definition 3 Let $X = (X_n)_{n \geq 0}$ be a discrete time kQRW on $E = (Z \times M) \cup \{\Delta\}$ defined by three matrices A_{-1}, A_0 and A_{+1} as in (1). We define a new kQRW called *step process* and denoted by $Z = (Z_n)_{n \geq 0}$ on the restricted state space

$$\underline{E} := (Z \times (M^l \cup M^r)) \cup \{\Delta\} \subset E$$

via three new matrices $\underline{A}_{-1}, \underline{A}_0$ and \underline{A}_{+1} as follows.

The internal transition matrix vanishes: $\underline{A}_0 := 0$.

For $i, j \in M^l \cup M^r$

$$(\underline{A}_{-1})_{ij} := P(\tau_{l,j} < \infty | X_0 = (0, i))$$

and

$$(\underline{A}_{+1})_{ij} := P(\tau_{r,j} < \infty | X_0 = (0, i))$$

where

$$\tau_{l,j} := \inf \{n \geq 0 : X_n = (-1, j)\} \text{ and } \tau_{r,j} := \inf \{n \geq 0 : X_n = (+1, j)\}.$$

The associated block tridiagonal matrix is denoted by \underline{S} .

The transition vector to the absorbing state Δ is given by:

$$(\underline{L})_i = P(\tau_\Delta < \tau_{r,j} \text{ for all } j \in M^l \cup M^r | X_0 = (0, i)).$$

The random time $\tau_{l,j}$ (resp. $\tau_{r,j}$) is the first time of position change to the left (resp. to the right) from the position 0 to the arrival state j . Therefore the step process has the property that with every transition the position is changed. In the application to molecular motors, it reflects the position change behaviour as it would be observed in an experiment.

Let us now compute explicitly the transition probabilities of the step process.

Proposition 2 *Let $X = (X_n)_{n \geq 0}$ be a discrete time kQRW on $E = (Z \times M) \cup \{\Delta\}$ defined by three matrices A_{-1}, A_0 and A_{+1} as in (1). The passage times $\tau_{l,j}$ (resp. $\tau_{r,j}$) from the position 0 to the left (resp. to the right) arrival state $j \in M^l$ (resp. $j \in \cup M^r$) satisfies:*

$$P(\tau_{l,j} < +\infty | X_0 = (0, i)) = e_i (Id - A_0)^{-1} R_j^\top, \quad (4)$$

where e_i is the i -th unit vector and R_j is the vector of transition rates between the arrival states at position 0 and the state j at position -1 (resp. $+1$).

Proof We have that

$$\begin{aligned} P(\tau_{l,j} = n | X_0 = (0, i)) \\ &= P\left(\bigcap_{m=1}^{n-1} X_m \in \{0\} \times (M^l \cup M^r), X_n = (-1, j) | X_0 = (0, i)\right) \\ &= e_i A_0^{n-1} R_j^\top. \end{aligned}$$

The matrix A_0 is substochastic, thus its spectral radius is strictly less than one and the von Neumann series can be applied, i.e.

$$P(\tau_{l,j} < +\infty | X_0 = (0, i)) = \sum_{n \geq 1} e_i A_0^{n-1} R_j^\top = e_i (Id - A_0)^{-1} R_j^\top.$$

□

Remark 1 It is important to note that the same procedure to construct a *discrete time* step process can be carried out in *continuous time*. But then the transition times between position changes are no more exponential. Thus the resulting continuous time step process is no more Markov but *Semi-Markov* and the above defined step process is its embedded Markov Chain.

In all the considerations we left out the initial condition. There is no reason that the initial condition of the original kQRW should be concentrated on the arrival sets only. It is therefore necessary to transform it in a new initial condition for the step process. This can be simply done in the same way as for the computation of the transition probabilities of the step process, by setting the arrival states of position zero absorbing and calculating the probabilities to arrive at any such state before the first position change.

3.2 Run length and maximal position of the kQRW

The step process is a tool to compute some spatial properties of the original kQRW process.

Theorem 1 *Let X be a discrete time kQRW and Z its associated step process according to Definition 3 with initial distribution $\underline{\mu}$ (concentrated on position zero).*

(i) *The run length of X , equal to the total number of position changes before killing and denoted by L , is equal to $\sigma_\Delta - 1$ where σ_Δ is the killing time of Z . Therefore its distribution satisfies*

$$P(L = k) = \underline{\mu}(\underline{A}_{-1} + \underline{A}_{+1})^k \underline{\Gamma}^\top.$$

(ii) *The last position of X before killing, $X^\dagger := Z_L$, admits the distribution*

$$P(X^\dagger = z) = \underline{\mu}(\text{Id} - \underline{S})^{-1} \Gamma_z^\top$$

where $\Gamma_z := (\dots, 0, \underline{\Gamma}, 0, \dots)$ has vanishing entries except at the position z where it is equal to $\underline{\Gamma}$.

(iii) *The maximal position ever attained before killing, denoted by X^* , is distributed like*

$$P(X^* = k) = \begin{cases} (1 - p_{k+1})p_k & k \geq 1 \\ 1 - p_1 & k = 0 \end{cases}$$

with $p_k = \underline{\mu}((\text{Id} - \underline{S}^-)^{-1} C)^k \mathbf{1}^\top$ where \underline{S}^- is equal to \underline{S} with all entries set to zero for positions greater than zero and C is the block matrix with vanishing blocks except \underline{A}_0 at the position $z = 1$.

Proof (i) The distribution of σ_Δ can be computed in a similar way as (2).

(ii) To prove this statement we replace the unique absorbing state Δ of the step process by a countable collection $(\Delta_z)_{z \in Z}$ of absorbing states, one for each position, reachable only from position z with the probability encoded in $\underline{\Gamma}$. Therefore, defining $\sigma_{\Delta_z} := \inf \{n \geq 0 : Z_n = \Delta_z\}$ one gets

$$P(Z_L = z) = P(\sigma_{\Delta_z} < \infty)$$

which leads to the desired expression.

(iii) If the process were a simple Random Walk, i.e. $M^l \cup M^r$ reduced to a single element, the result would be simple to compute. At time 0 the maximal position is 0. Then, after some excursion to the negative positions, the process eventually reaches the position one or is being killed. But by spatial homogeneity this has the same probability as starting in some position z and waiting for the first transition to the position $z + 1$. Thus the time to reach a new maximum forms a terminating renewal process. It is terminating since absorption can occur – in finite time – while no new maximum is attained. This ensures that the maximum is almost surely finite.

For the step process we have to take $\underline{\mu}$ into consideration. Starting at time zero with a distribution $\underline{\mu}$ concentrated on position 0, delivers a new distribution on position one, once this position is attained. Once again we could set the states at position one absorbing and calculate the absorption probabilities under the

condition that Δ will not be reached. These probabilities deliver a new “initial” distribution. This distribution is given by:

$$\underline{\mu}(Id - \underline{S}^-)^{-1}C$$

by the same arguments as below. By spatial homogeneity we can repeat this procedure for every position, i.e. we get for position $z > 0$

$$\underline{\mu}((Id - \underline{S}^-)^{-1}C)^z.$$

Finally we just need to sum up the probabilities of being in a specific state at position z to obtain the desired result. \square

Remark that Statement (iii) can be easily adapted to the minimal position of the kQRW by simply exchanging the role of A_{-1} and A_{+1} .

4 Application to Kinesin V

We want to apply our theoretical results to a model of Kinesin V. Kinesin has two identical motor heads and walks in a “hand-over-hand” fashion, i.e., by alternating steps in which one head moves forward while the other one remains bound to the microtubule. Each step leads to a motor displacement of 8 nm corresponding to the lattice constant of the microtubule. These mechanical steps are rather fast and completed within 15 microseconds, see [CC05].

Kinesin exhibits tight coupling, i.e., it hydrolyzes one Adenosine triphosphate (ATP) molecule per mechanical step. After ATP has been hydrolyzed by one of the catalytic motor domains, the inorganic phosphate is released rather fast. Adenosine diphosphate (ADP) is subsequently released from the catalytic domain. When the catalytic domain of one motor head is occupied by ADP, this head is only loosely bound to the microtubule and most likely to unbind from it.

Various motor properties such as motor velocity [VSB99, CC05], bound state diffusion coefficient (or randomness parameter) [VSB99], ratio of forward to backward steps [CC05], and average run length [SVB00] were measured as a function of ATP concentration and load force. Furthermore, the motor velocity was also determined as a function of P and ADP concentration [?].

As shown in [LL07a, LL07b], all of these experimentally observed motor properties can be described quantitatively within the recently introduced network model. Aim of this section is to compute the distribution of total number of steps before detachment and the maximal distance from zero for the specific case of Kinesin V.

The model of Kinesin V, as proposed in [LLV09], is a kQRW in continuous time with $M = \{1, 2, \dots, 7\}$, start in $(0, 7)$ and comes with very simple arrival states, namely

$$z \in Z : M^r = \{5\}, \quad M^l = \{2\}.$$

The resulting step process is therefore a kQRW on $Z \times \{1, 2\} \cup \{\Delta\}$. For the transition graph, see fig. 4.

Naturally we want to use Theorem 1, but the properties in (ii) and (iii) contain infinite matrices. Therefore we need an approximation.

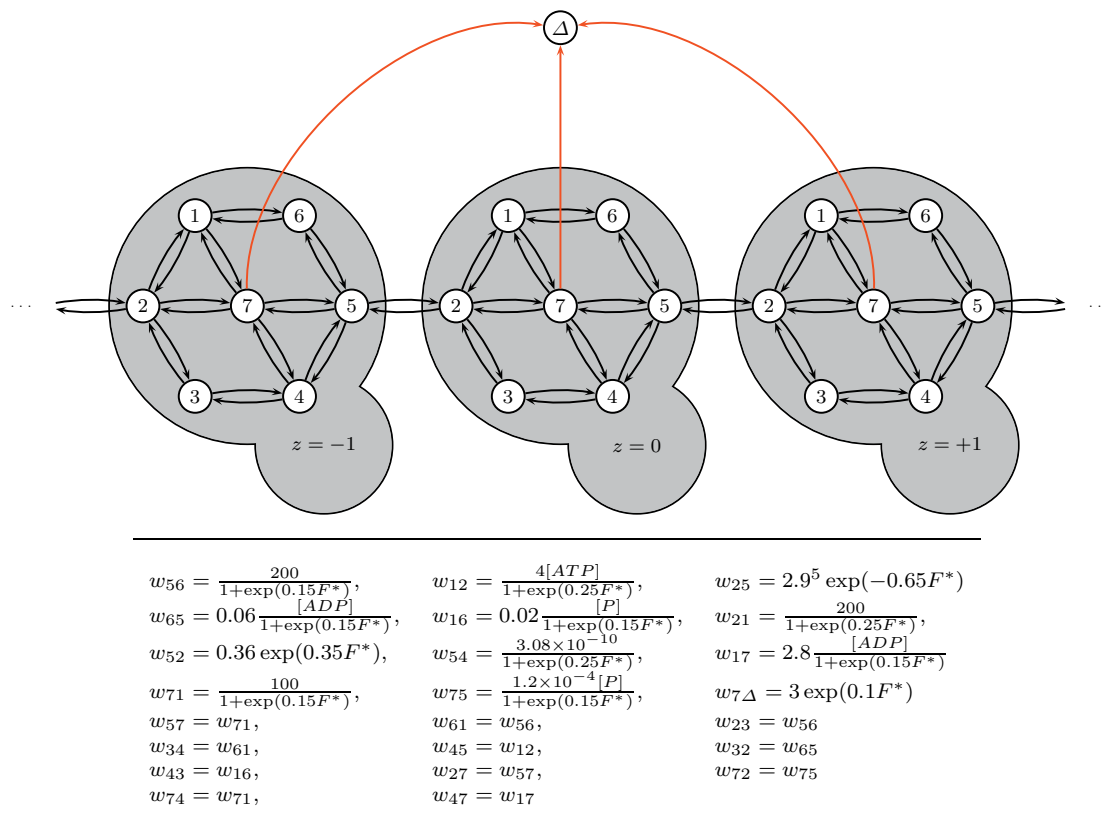


Fig. 4 A transition from i to j exists if an arrow connects them in the graph. The transition rate is denoted by w_{ij} and given below the graph. The exact values of the various parameters are given in [VLL08, LL08].

As already mentioned after Proposition 1, the probability to reach a position far away from zero shrinks exponentially fast. Thus an immediate idea to approximate is to cut the original process symmetrically and reduce the state space to

$$E_n := \{-n, -n+1, \dots, -1, 0, 1, \dots, n-1, n\} \times M \cup \{\Delta\}.$$

We also need to modify the behaviour at the boundary. Instead of moving from position $-n$ to Δ with Γ we define for this transition $\Gamma^- := \Gamma + A_{-1}\mathbf{1}^\top$ and accordingly $\Gamma^+ := \Gamma + A_{+1}\mathbf{1}^\top$ for position n . Therefore it is impossible for this new process to reach a position greater n or lower than $-n$. Indeed, the results of Theorem 1 apply also for finite number of positions and can be easily adapted. Naturally we gain the original process back, if we take the limit $n \rightarrow \infty$.

We choose for the parameters appearing in the transition rates, see fig. 4,

$$F^* = 10, [ATP] = 10\mu M, [ADP] = 0.5\mu M, [P] = 0.5\mu M.$$

It is assumed, that these parameters are constant throughout the lifetime of the kQRW, such that the Markov Chain is time homogenous.

The associated step process as introduced Definition 3 has the following numerical values (numbers are rounded):

$$\underline{A}_{+1} = \begin{pmatrix} 0 & 0.2190 \\ 0 & 0.0193 \end{pmatrix}, \underline{A}_{-1} = \begin{pmatrix} 0.6986 & 0 \\ 0.9644 & 0 \end{pmatrix}, \underline{\Gamma} = (0.0825, 0.0163)$$

and initial distribution

$$\underline{\mu}(i) := \begin{cases} 0.402471 & i = (0, 2) \\ 0.402471 & i = (0, 5) \\ 0.195058 & i = \Delta \\ 0 & \text{else.} \end{cases}$$

Note that $\underline{\mu}$ is defective in the sense that it is possible that the process gets killed before any change of position can occur and thus has a weight on Δ .

The run length – the total number of steps before killing – is given by Theorem 1, (i) and shown in fig. 5.

For the approximation of the last position immediately before killing we used different “cutting heights”, displayed in fig. 6, to investigate the convergence behaviour. Indeed there is no qualitative change of the plot for $n \geq 50$, which is still small for a computer.

Finally we used the same approximation procedure for the maximal position ever attained before killing and gain the plot in fig. 7. The plot is also based on $n = 50$ positions.

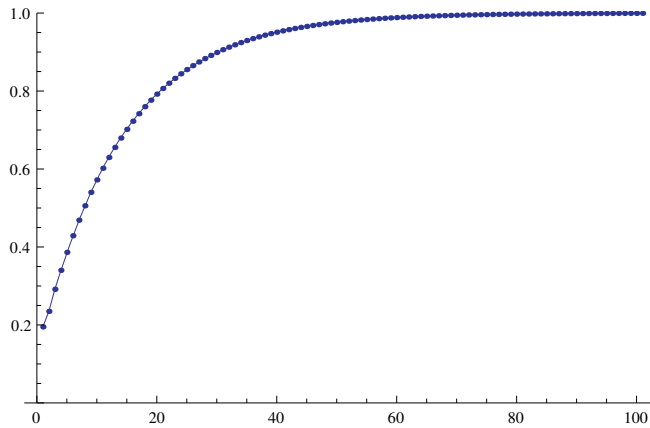


Fig. 5 Distribution function of the number of steps prior to killing.

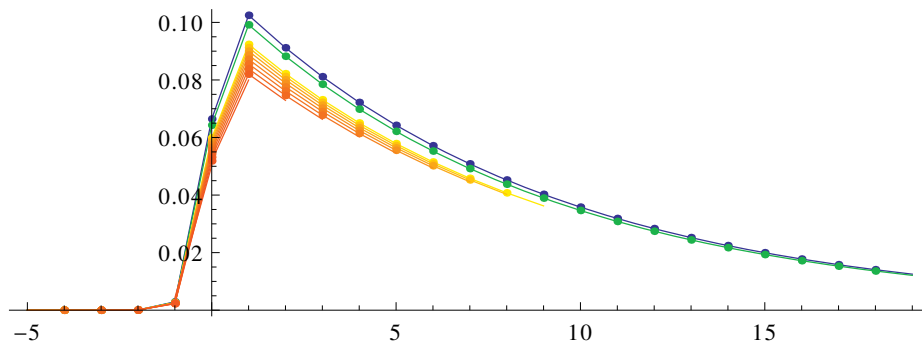


Fig. 6 Plot of the approximation of the distribution of the last position visited cutted at n for $n \in \{1, 2, \dots, 9, 10, 20, 50\}$ (from red to blue). The convergence is good, for $n > 50$ does the resulting curve not differ significantly from the blue one. The approximation introduces an error at the n and $-n$ which is not shown here.

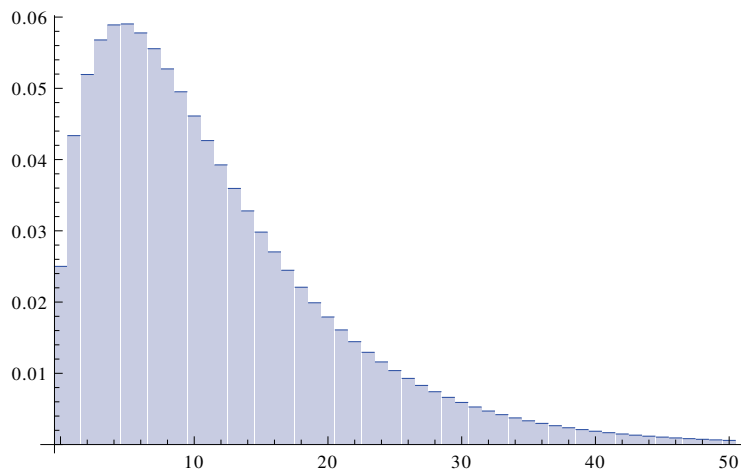


Fig. 7 Distribution of the maximal position attained prior to killing.

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