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A Survey on Random Walk-Based Stochastic Modeling in Eukaryotic Cell Migration with Emphasis on its Application in Cancer

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Abstract

Impairments in cell migration processes may cause various diseases, among which cancer cell metastasis, tumor angiogenesis, and the disability of immune cells to infiltrate into tumors are prominent ones. Mathematical modeling has been widely used to analyze the cell migration process. Cell migration is a complicated process and requires statistical methods such as random walk for proper analysis. In this study, we reviewed the studies conducted on the random walk-based stochastic modeling of the eukaryotic cell migration. This statistical modeling can open some perspectives on more detailed modeling approaches and ultimately lead to more comprehensive knowledge about the biophysical and biochemical foundations of cell migration process.

INTRODUCTION

The Eukaryotic cell migration, a complicated process, which is highly regulated by molecular pathways, plays a significant role in organogenesis and tissue development. Most cells demonstrate oriented or random migration in vitro, although they may have been extracted from tissue composed of immobile cells [1]. Cell migration disorders in developed organisms are mostly associated with impairments, such as cancer cell metastasis, immune diso-rders, and wound healing deficiency. Particularly in cancer, cell migration depends on the incidences of specific mutations [2] where extensive movement occurs in metastatic cells [3]. In addition, some studies have indi-cated that patients developing tumors with the elevated levels of tumor-infiltrating cytotoxic T lymphocytes have improved response to the treatment. In this regard, one of the main goals of cancer immunotherapy is to control tumor-immune system interactions [4].

The leading studies on cell migration process are focused on fibroblasts, keratinocytes, and myoblasts. Despite some differences in the migration process of various eukaryotic cells, studies have revealed basic similarities in the mechanisms involved in morphogenesis, wound healing, immune response, and cancer cell metastasis [5]. The quantification of these similarities and differences helps in categorizing and modeling of the process. These models predict the migration properties and help in understanding the speed of cell motion-dependent processes, such as metastasis, the characteristics of an optimum migration behavior for effective interaction between lymphocytes and infectious cells and tumor, and the migration ability of tumor cells considering the spatial heterogeneity of tumor.

At present, mathematical modeling and numerical simulations are abundantly applied as complementary to in vitro investigations. Despite the perpetual necessity of experimental approaches for understanding biological processes, in silico experiments can complement these assays by limiting the measuring space and reducing the experiment cost [6–8].

The main advantage of in silico computational models is the simultaneous analysis of several dependent variables that presently seems unatt-ainable experimentally. The evaluation of the relationships of systems' variables, in spite of non-linear dynamics, facilitates more compreh-ensive and accurate analyses of experimental observations. In addition, mathematical models can identify key parameters, determining the ultimate behavior of the system and suggest the most precise experiments for system assessment [9].

The processes associated with cell migration are in-

fluenced by several closely related factors such as extracellular matrix, tissue architecture, and different cell characteristics. These factors determine the ultimate mode of cell movement in an integrative manner [10]. The time-lapse microscopy of living cells, followed by the applicat-ion of image processing algorithms, conventionally introduces a typical cell migration study. The image processing procedure is initiated with the application of image preprocessing algorithms to enhance signal-to-noise ratio and improve image quality. The application of the algorithms generally depends on the type of applied microscopy technique. The next step is to track the cell migration path and quantitatively estimate cell motility behavior using image processing software and tools [11]. The methods may include particle tracking techniques relied on image segmentation algorithms [12,13], fitting particle path curve to an evolving model, and minimizing the relevant energy functions [14], as well as the estimation of cell prospect using the posterior density function of cell states derived from Monte Carlo sampling methods [15]. The procedure terminates by recording cell spatial coordinates over the time and quantifying cell motion based on reconstructed trajectories. Accordingly, a set of parameters and quantities such as speed, rotation angle, and distance traveled can be derived for inferential data analysis [11]. At present, various software tools are available for digital image processing where some of them implement algorithms adapted for the analysis of migrating cells.

Cell movement is a stochastic process and the derivation of its descriptive parameters requires a clear discrimination of stochastic patterns relied on the rules governing random models, such as random walk. This field of applied mathematics is increasingly used to model biological systems, in particular in ecology (animals' movement) and pathophysiology (cell movements, particularly to form blood vessels and metastasis). The main advantage of random walk models is its ability to differentiate migration characteristics through intuitive data by which different cell migration mechanisms can be better understood [16].

The time series analysis of cell trajectories provides quantitative data for the reconstruction of cell-specific motility models. Such macroscopic models of cell behavior with the microscopic properties of cellular dynamics, such as cytoskeletal changes, cell contraction forces, and the dynamics of adhesion molecules, define the systems biology of cell motility [17].

The Simple Random Walk Model (Diffusion Equation)

The Brownian motion is the foremost example of a random process (Figure 1a), which follows the simple random walk rules. In the simplest case, a particle in one-dimensional space can move from the origin with the same probability of left to right and right to left motions, where its displacement, Δx, is constant in constant discrete time intervals. In this model, particle movement does not depend on its previous and current positions, as well as on time; thus, the average displacement after time T is zero. Hence, to define a significant variable for the amount of displacement, the mean squared displacement (MSD) of the particle after a walk of N steps is a more suitable statistical quantity [18]. The quantity is calculated using the following formula:

$$R^2(\tau) = \lim_{t\to\infty}\langle\left(X(t+\tau) - X(t)\right)^2\rangle \qquad (1)$$

where $|X(t+\tau)-X(t)|$ is the particle displacement between two steps in the time series, t is the total time of the walk, and τ is the time interval between the successive steps [19]. MSD indicates the average walker distance from the original position as a function of t [20].

For a simple random walker model, we have $R^2(\tau)=2Dn\tau$, where D is the diffusion constant and n is the spatial dimension [18]. Noting that the evaluation of statistical variables in a complex set of random walkers leads to the spatiotemporal continuity of non-random variables. Such continuous processes are expressed by diffusion models derived from Brownian motion [21]. Specifically, Einstein in 1905 demonstrated that the random motion of particles at microscopic levels can perfectly express the inter-relationship between macroscopic parameters, such as diffusion coefficient, viscosity, and temperature [22,23].

The simple random walk model has repeatedly been used as one of the simplest random models of cell migration. Although this model provides a naive expression for cell migration, it is satisfactory in some cases to express cell migration aspects and diffusion processes using the pure random walk model. For example, the organization of human mesenchymal stem cells on nanotopographical surfaces can be simulated on the basis of a simple random walk model. The results of such stimulations predict the regular and irregular cellular organizations for low and high cellular densities, respectively [24].

Generalization of Simple Random Walk Model

In most cases, the movement of individual cells is not attributed to the simple random walk behavior. In

such cases, the evaluation of MSD function results in a more generalized equation, which is as follows:

$$R^2(\tau) = \lim_{t\to\infty} \langle \left(X(t+\tau) - X(t)\right)^2 \rangle \propto \tau^{\alpha} \qquad (2)$$

In this generalized model, the diffusion phenomenon is categorized on the basis of the parameter α. When MSD is the linear function of time (α = 1), we obtain the normal diffusion characteristic. If α>1, the process is called super-diffusion (rapid diffusion), whereas α<1 represents sub-diffusion (slow diffusion) phenomena [25].

In addition to MSD, velocity autocorrelation function is studied as another statistical average to investigate the random walk characteristics as defined elsewhere [26]:

$$C_V(\tau) = \lim_{t\to\infty} \frac{\langle V(t+\tau)V(t)\rangle}{\langle V^2(t)\rangle} \qquad (3)$$

This function indicates the correlation between the velocity time series of a particle with its time-shifted version. The function is expected to exponentially decrease by the amount of time shift interval(τ). Regarding cell migration, the function indicates how long the cell moves in a certain direction without a significant change in velocity. For the simple random walk model, the function has non-zero value only when τ = 0, as the successive steps in this model are independent [20].

In addition, the probability distribution and density functions indicate the possible values of discrete and continuous random variables, respectively. The probability density functions of variables, such as velocity, step length, and angular displacement, are some other statistical functions, and their behaviors can be interpreted as different characteristics for the random walk model of cell motilities. In the pure random walk model, it is presumed that the distribution of step length and consequently cell speed follow a normal (Gaussian) distribution or take a constant value, whereas cell migration does not confirm the simple assumption in several cases.

Random Walks with Non-Gaussian Step Length Distributions

Walker step length can follow the desired distribution function. New assumptions for the distribution function of random walk steps can result in super-diffusion or sub-diffusion phenomena, irrespective of steps correlation. In contrast to the classic random walk with a normal distribution with finite variance, Levy walk has Levy flight distribution function with infinite variance. The distribution function reduces with the power law $f_\mu(l) \sim l^{-\mu}$ (1<μ<3), where l is the step size. Evidently, although long steps are significantly less than short ones, they are relatively much more frequent than the normal distribution (Figure 1b). Levy walk is considered a scale-free random walk, as the power law distribution of step length shows similar behaviors in different spatial scales [27]. In addition, the scale-free nature provides special functionalities as a characteristic of several biological phenomena, such as fractal pattern in human blood vessels [28].

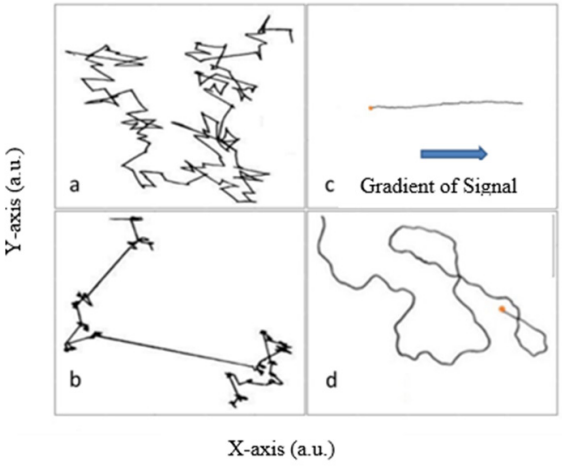

Figure 1: Schematic View of Walker Trajectories in (a) a Pure Random Walk, (b) Levy Walk, (c) Biased Random Walk, and (d) Persistent Random Walk.

It was suggested that lymphocytes motility into the brain does not follow Brownian statistics but can be described satisfactorily on the basis of the generalization of Levy walks. The model captures run and pause phases observed in lymphocytes motility. Such migration enables cells to identify rare far goals with more than 10-fold efficiency; compared to Brownian motion, this migration strategy is similar to that of monkeys and marine predacious [29].

In addition, the motility of hydra cells is super-diffusion, with non-Gaussian velocity distribution in both ectodermal and endodermal tissues. The diffusion of hydra cells can be explained as a correlated type of anomalous diffusion using Tsallis statistics [30,31].

In addition to Gaussian and Levy distributions, other statistical distributions have also been used to express the specificity of cell migrations; for instance, the migration of normal and tumor melanocyte cells in mice demonstrates a transition from a normal diffusion (α = 1) to super-diffusion (α>1) without a long-time angular persistence. The non-Gaussian velocity distribution of the cells introduces a

q-Gaussian model of migration and simulation of cell trajectories. The model perfectly reproduces the displayed transition phenomenon [17]. Moreover, the migration study of normal and tumor epithelial cells derived from Madin-Darby canine kidney (MDCK) cell line revealed the diffusion anomaly of the cells. The evaluation of the cell speeds indicated that velocity proportions generated a q-Weibull distribution, an extension of the Weibull distribution accounted for Tsallis distribution function:

$$p_{qw}(x) = p_0 \frac{r x^{r-1}}{x_0^r} \exp_q\left[-\left(\frac{x}{x_0}\right)^r\right] \qquad (4)$$

where the q-exponential expression ($\exp_q(x)$) equals to $[1+(1-q)x]^{\frac{1}{1-q}}$. Podesta et al. showed that the cell density variations result in the alternation of the shape parameters of the distribution (r and q) in a way that the distribution function inclines to Maxwellian distribution as the density of the cells increases [32].

Biased Random Walk Model

The directionality of locomotion in response to factors, such as the mechanical properties of the environment and the concentration of particular chemical compounds, is one of the vital characteristics of some eukaryotic cells [33–35]. Such migration is characterized on the basis of the non-uniform distribution of steps orientation [27]. Chemotactic movement, the most stated example of this migration pattern, can be found in specific types of eukaryotic cells (Figure 1c) [33,36–38]. For instance, experimental assessments indicated that the chemo-taxis of neutrophils in three-dimensional culture systems supported the predictions of the biased random walk (BRW) model for this migratory behavior [39]. The evaluation of B-cells› chemotaxis revealed that the highest chemotactic responses correspond to the medium gradient of chemokines, and thus, the autocorrelation function showed slower decrease than gentle and rigorous gradients [40].

In addition, spatial constraints affect the coordinated According to the average dynamics of single cells in the colonies of HeLa cells and its dependence on spatiotemporal heterogeneity associated with growth geometry, Muzzio et al. suggested that cell mobility was achieved by a concerted mechanism. In this mechanism, two limiting elements with a random walk and ballistic motion ($\alpha>1$) participate to form a BRW migration. The directional biases in single cell motion influence the dynamics of the two-dimensional colony development and their specific characteristics [44].

Furthermore, the experimental findings revealed a migration tendency of cells toward the stiffness gradient of the extracellular matrix. However, different assays confirmed the increased directional persistence of migrating cells with increasing matrix stiffness [45,46]. On performing random walk-based simulations, Novikova et al. uncovered that the net flow of the cells is the conclusive outcome of the persistence subordination of matrix stiffness [47].

Persistent Random Walk

In the pure random walk model, step orientation, as well as turning angles, is considered to be independent of the trajectory in each step. In more realistic models, the natural attitude of the cell to preserve the last step's orientation is specified by the non-uniform distribution functions of turning angles [27].

Signaling pathways lead to the formation or destruction of cytoplasmic appendages (lamellipodia and filopodia) in the cell migration process mainly by the activation or deactivation of factors associated with the formation of actin filaments organization in the different areas of the cell membrane. The local activity of protein network involved in cell motility discovers the mechanism of the directional persistency of the cell migration through responding to local mechanical (through cell matrix adhesions) and chemical signals, as well as branching new appendages of the older ones. This branching proposes a positive feedback mechanism by which migration occurs persistently in the absence of any external signal (48–50). As assumed in the persistent random walk (PRW; also called correlated random walk), the cell persists in its direction of motion in some timescales, whereas displays a type of random movement along its trajectory in longer time scales (Figure 1d) [51]. Consequently, in the MSD diagrams, a continuous change from a more ballistic behavior ($\alpha>1$) for shorter time intervals to Brownian motion pattern ($\alpha=1$) for longer time distance is observed [52,53].

Notably, because of this discrepancy in different time lags, in cell migration studies, sampling time intervals may influence the results of statistical analyses of the obtained time series. Rosser et al. (2013) used a stochastic model to study the distribution of velocity and turning angles found from different sampling intervals. The results showed that changing time intervals considerably changes the above quantities up to several orders of magnitude [54].

The motion of several individual cells can be evaluated on the basis of the PRW model. In this regard, several efforts were made to model the involved mechanisms to elucidate the dependence of two consecutive steps in a random motion. Several models

cover the cell membrane fluctuations as a stochastic factor and actin network orientation as a persistence factor. For instance, Caballero et al. showed that the direction of cell motion is predictable using a statistical analysis derived from the dynamics of cytoplasmic appendages. The developed model indicated that asymmetry in the fluctuations of membrane protrusions was sufficient to predict the data obtained from the motion called biased PRW [55].

Furthermore, a model was developed by Cooper et al. (2012) on the basis of cell excitability and plasma membrane retention to describe the mechanism of the directional persistence of the cells employing a zigzag model of the consecutive formation of the protrusion. Considering the spatial limitation of cell membrane after pseudopod formation, as well as the excitation memory in the area of older pseudopod, their model could reproduce experimental data on cell migration. In addition, comparison of the predictions of this model with the experimental data indicated that the pseudopod formation was a non-Markovian process influenced by the dynamics of older pseudopodium [56].

Another model was proposed to survey the physical basis of the migration of amoeboid cells, such as Dictyostelium, and the epithelial cells of MDCK as well. In this model, the accumulation of actin polymerization inhibitors in the tail end of the cell acts as the operant of forwarding persistent motion. In addition, the density fluctuations of these molecules along with membrane drops and rises are considered as the random factors, influencing the directionality and reorientation of the cell. The combination of the stochastic turns and directional motions resulted in the anomalous diffusion (super-diffusion) of the cells in signal-absent conditions [57,58]. Furthermore, the analysis of the probability distribution of the angles between pseudopods illustrates another method to develop a stochastic model for the mechanism of cell mobility inspired from the correlated random walk. For example, a Monte Carlo simulation is proposed that incorporates the proportion of the number of pseudopods bifurcating from the older ones to the number of randomly formed de novo protrusions, pseudopodium's directional alteration (left to right and vice versa), their angular separation, and the angle variance [59].

Moreover, it is shown that cellular persistence is an exponential function of speed; this general rule can be explained on the basis of a physical model of cell polarity changes along with actin network dynamics [60] and its effect on cell directional persistency. This model can predict a general phase diagram of cell trajectories, which reproduces a full range of observed migration patterns [61].

In some cell populations, a combination of simple random walk and PRW models can be used to explain cell migration properties; for example, lymphocytes migration is predictable considering such two-population models. However, the application of PRW model for exploring motile lymphocytes in lymph nodes, in general, had been confirmed experimentally [62,63], It was shown that CD^{8+} T-cells migration in non-inflamed lymph nodes does not completely comply with the PRW model. In turn, the two-population model, suggested by Banigan et al., attributes Brownian motion and variable PRW model with noise to different cell populations, and can predict the experimental statistical properties of the migration of such cells. The discrepancy between two-population model and the model proposed to describe active T-cells migration inside inflammatory brain demonstrates the discordance of statistical features related to lymphocytes migration in different tissues [29,64].

In addition, in a study on the motility of B lymphocytes in germinal centers, O'Conner et al. showed that unlike the random motion of inactive B-cells, active B-cells show biased motility and the slope of their MSD plot accepts an α-value of more than 1 [65]; this is similar to the behavior of primary blood cells, which follow the PRW migration model to reach medullary cords [66].

The capability of direction retention, inducing persistent random motion, results in some complicated behaviors in several cells. The migration behavior of an amoeboid eukaryotic cell was investigated in the absence of chemotaxis signals, and the results indicated that the cell displayed a particular model of random motion under following circumstances: long intervals of straight motion and frontward movement with zigzag steps. The motion comprises the consecutive phases of run and turn and the migrating cells have a directional memory of one step. The distribution of traveled distance and turning magnitude can be fit to an exponential function. This migration model can increase the chance of acquiring targets, compared with Brownian motion [52,67].

The physical properties of the environment influence the migration of individual cells (68). Regarding the migration of hydra cells in ectodermal and endodermal communities, Rieu et al. (2000) applied the standard statistical analyses and accordingly showed that the cell motion can be explained in both structures on the basis of the PRW model. Different diffusion coefficients were found for the two communities,

where the smaller diffusion coefficient for the endoderm indicated its more adherent structure [69].
In addition, the effect of interstitial flow on cell migration demonstrated that increased flow changes breast tumor cells to an amoeboid phenotype. The evaluation of the heterogeneity of migratory phenotypes of cells subjects to different interstitial flow intensity and ascertains other random walk characteristics for amoeboid and mesenchymal phenotypes, among them was distinct directional persistence in two mentioned migration modes [70,71].

GENERALIZED PERSISTENT RANDOM WALK

Persistent Random Walk Models with Non-Gaussian Step Length Distribution

In this generalization, the assumption of the constant or Gaussian step length has been reduced; hence, the distribution of steps length may follow an arbitrary function.
For instance, by the evaluation of the migration of human breast epithelial cells, the bimodal correlated random walk model as an alternative to the simple PRW model was proposed. This model of movement comprises two types of correlated flights with exponential distribution: a first directional phase that can be replaced by a second reorientation phase successively [6].
Additionally, while investigating the motion of T lymphocytes in lymph nodules, Fricke et al. reported that likewise Brownian motion, Levy walk is not a full descriptive model of migration. As an alternative, they suggested a correlated random walk with the peculiar distribution function of step length. The lognormal distribution function of velocities, as well as steps length, short-term directional persistence, and heterogeneity of cell mobility patterns, are main properties that enhance the proficiency of this migration pattern. The evaluation of the average velocity of studied T lymphocytes revealed that T-cells show a continuous pattern of motion, which results in the defined search strategies: cells have a relatively smaller average velocity with a heavy-tailed distribution that permits them to have few long-range steps. The velocity distribution of mentioned cells shows the most compliance with lognormal distribution with parameters μ and σ that equal to 0.48 and 0.91, respectively:

$$y = f\left(x \mid \mu, \sigma\right) = \frac{1}{x\sigma\sqrt{2\pi}} e^{\frac{-(\ln x-\mu)^2}{2\sigma^2}}$$

$$\sigma=0.91,\mu=0.48 \qquad (5)$$

The significant characteristic of the distribution is its high measures of skewness and kurtosis in contrast to the fast cells that indicate a more Gaussian-like distribution with lower amounts of skewness and kurtosis. In addition, agent-based simulations depicted that the lognormal modulated PRW has the maximum compliance with the observed efficiency of migrating T cells, following dendritic cells. This migration behavior presents a balance between the accuracy and amount of distance traveled by the cells [72]. Moreover, the findings confirm the hypothesis of migration heterogeneity among the T-lymphocyte population [64].

Persistent Random Walk of Cells as Heterogeneous Time Series

In some cases, the temporal homogeneity of cell migration properties should be considered by the models. For instance, epithelial cells may find the movement potential through a process called epithelial to mesenchymal transition that occurs in cancer cells metastasis [73,74]. To model cell migration based on time-dependent quantitative properties, one of the possible approaches is the estimation of statistical variables through time; Bayesian inference, developed in the shadow of Bayesian statistics, can be used for this propose. The Bayes theorem relates the probability distribution of a random variable without any knowledge of observations (prior distribution) to its probability distribution after the observation of the event (posterior distribution). Applying Bayesian inference method, based on Bayes theorem, the statistical properties of random variables can be updated after an initial estimate of their distribution [75]. Metzner et al., resembling the cell migration phenomenon as a random walk with time-varying statistical parameters, showed that the time dependent parameters can be estimated in consecutive steps of obtained time series using the sequential Bayesian inference method. The parameters of the migration model studied were cellular activity and persistence that showed considerable fluctuations through investigated cell trajectories. The possibility of evaluating the effect of environmental characteristics on cells motility is another result obtained using sequential Bayesian inference method [76].
In addition, it has been shown that a Bayesian inference schema can be established to evaluate the accordance between a class of random walk and the observed cell trajectories' data. Within this framework, the migration patterns of zebrafish macrophages and neutrophils showed distinct random walk models whose amounts of directional persistence were spatiotemporally modulated [77].

Anisotropic Persistent Random Walk

The PRW model cannot be considered as the best description for the motility profile of all cell species. A more comprehensive model can be developed considering generalizations, such as the heterogeneity of migration behaviors among cell population, as well as excluding the assumption of spatial isotropy in velocities of the cells. The migration pattern of fibrosarcoma cells in two-dimensional and three-dimensional cultures showed some deviations from the PRW model, among which is the non-Gaussian distribution of speeds that emerge from the heterogeneous nature of cell migration. Wu et al. suggested that two-dimensional migration statistics can be well predicted by the PRW model considering different model parameters for individual cells. However, the simulation results showed that predicting three-dimensional cell migration characteristics, additionally, requires the attribution of different persistent times and speeds to the primary and non-primary directions of movement. The anisotropic PRW model perfectly predicts the migration behavior of the cells. [78].

Reinforced Random Walk

In this model, it is assumed that the walker moves on a weighted graph. The probability of choosing the edges connected to the vertex is proportional to the weights attributed to them. In addition, after each walk through an edge, the weight may increase [79]. This weight amplification can be interpreted as the creation of a cell pathway in the extracellular matrix in such a way that the probability of cell migration in the certain direction increases. Similarly, adding the appropriate initial weight to the edges of the graph, a phenomenon such as chemotaxis can also be modeled on the basis of this type of random walk [80,81]. Angiogenesis is one of the physiological processes illustrated by this model. A mathematical model based on the theory of reinforced random walk developed by Plank et al., (2002) successfully described the migration of vascular endothelial cells in response to different angiogenesis factors. According to this model, endothelial cells initially form a spherical community in which all cells can move on a regular graph. Chemotaxis responding to vascular endothelial growth factor (VGEF) and haptotaxis responding to collagen concentration are modeled by adding proper weights to the edges of the graph, proportional to the concentration of the components [82]. Moreover, hybrid models proposed to map VEGF-depended angiogenesis consider that VEGF concentration changes in addition to modeling chemotaxis of endothelial cells using the reinforced random walk. For example, it is reported that the hybrid model was able to predict the threshold concentration required to stimulate the quiet cells for a biased motion, as well as the optimum concentration for their movement [83].

Stochastic Langevin Equations

The application of stochastic differential equations is another approach to describe the stochastic properties of cell migration phenomenon. The stochastic Langevin equation characterizes the walker movement in a viscous environment under the influence of stochastic forces. The Ornstein–Uhlenbeck (O–U) process, as the solution of Langevin equations, is a random process evolved from Brownian motion to model the velocity of particles in the fluid as a continuous time random walker [84,85].

This O–U process incorporates two factors influencing particle velocity: the frictional resistance of a particle in the fluid proportional to its velocity and stochastic factors such as thermal noise and the random hitting from the particles around [20,84]. The applications of both the continuous and discrete representation of O–U process have been investigated in cell movement studies [86–89].

The cell motion equations derived from the Langevin equations for a Brownian particle are expressed as follows:

$$\frac{dx(t)}{dt} = v(t) \tag{6}$$

$$\frac{dv(t)}{dt} = -\hat{a}v(t) + \sqrt{\acute{a}}\,\hat{i}\,(t) \tag{7}$$

where β and α express the intensity of viscous and random forces, respectively, and ξ(t) is a random term with specified distribution. By adding an expression to the second equation, the effect of concentration gradient of chemotactic molecules can also be included. The statistical analysis of the process indicates that the two involving parameters, α and β, are in association with two cell motility parameters, namely, cell speed and persistence time [87,88].

A dynamic model proposed by Liang et al. (2011) on the basis of the experimental data from Dictyostelium cell migration could successfully depict the statistical characteristics obtained from cell trajectories. In this model, using the O–U process, two stochastic Langevin differential equations were recommended

to model the random alternative emergence of pseudopods, perpendicular and parallel with the direction of motion [90].

However, there are some inconsistencies between O–U process predictions and the mobility behavior of some cells, such as fibroblasts and keratinocytes. Eventually, cell specificity can be explained by attributing cell-specific values to the parameters included in the model. The specificity of the models indicates that the different migration modes of certain cells can be elucidated by applying relevant models where differences are considered in the values of the model parameters [91,92].

CONCLUSIONS

Due to the importance of the cell migration process, particularly in the initiation and development of diseases such as cancer, cell migration models have considerably attracted attention in recent years. The mathematical models based on stochastic processes were among the ones that showed their ability in the statistical characterization and classification of cell migration. This study aimed to describe the characteristics and potentials of different types of random walk models regarding the migration of eukaryotic cells. For this purpose, we attempted to classify modeling approaches and introduce the models' application to explain the migration process in different cells. Table 1 briefly shows the different types of the developed models.

In conclusion, studies indicated that the modeling of cell migration on the basis of the mathematical rules in stochastic processes and random walk models revealed some differences and similarities among cell migration strategies in different cell species and under distinct environmental conditions.

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CONFLICT OF INTEREST

The authors claimed that there is no conflict of interest regarding this paper.

ETHICS APPROVAL

Not applicable.

Table 1: Random-Walk Models in the Migration of Eukaryote Cells

Random Walk Model	Eukaryote Cells
Simple Random-Walk Model	Inactive B-Cells on Germinal Centers [65]
Random Walks with Non-Gaussian Step-Size Distributions	
The Q–Gaussian Random-Walk Model	Normal Melanocytes and Melanocytic Tumors in Mice [17]
The Q-Weibull Random-Walk Model	Normal Epithelial and Epithelial Tumor Cells [32]
Generalized Levy Walk	Lymphocytes in Brain [29]
Anisotropic Random-Walks	
Persistent Random-Walk Model	Lymphocytes in Lymph Nodes [63] Hydra Cells in Cellular Communities [69]
Reinforced Random-Walk Model	Vascular Endothelial Cells [82]
Biased Random-Walk Model	Chemotactic Migration of Neutrophils [39]
Bimodal Correlated Random-Walk Model	Human Breast Epithelial Cells [6]
Lognormal Modulated CRW	T Lymphocytes [72]
Persistent Random-Walk Model of Cell as a Heterogeneous Time Series	Breast Tumor Cells [76]
Anisotropic Persistent Random-Walk Model	Fibrosarcoma [78]
Stochastic Langevinequations	Dictyostelium [90] Fibroblasts and Keratinocytes [92]

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