Understanding Hematopoietic Stem Cell Mobility Pattern through Mathematics

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Once, Alexander Maximow, a great visionary in hematopoiesis, wrote:

> ... [U]nder the influence of stimulation, they [hemocytoblasts, aka stem cells] can be mobilized and become transformed into free, wandering ... elements. ... (Maximow [1924]).

Alexander Maximow was the first scientist who offered the idea of circulating stem cells. Normally, in bone marrow, hematopoietic stem cells can be found. Some percentage of these cells continually escapes of bone marrow and circulates in peripheral blood. The occurrence of hematopoietic stem cells in circulation was experimentally established afterward (Goodman and Hodgson [1962]; Cronkite [1997]). Some molecules with different cellular targets and different biologic activities may help to increase the motion of stem cells. The treatments of the molecules (e.g. endotoxin (Vos *et al.* [1972]; Cline and Golde [1977]), proteases (Vos *et al.* [1972]; Feher and Gidali [1987]), vaccines (Monette *et al.* [1972]), Epo crude preparations (Quesenberry *et al.* [1979]), polymethacrylic acid (Vos *et al.* [1972]), poly I-C (Quesenberry *et al.* [1979]; Mangalik and Robinson [1978]) etc.) can also help to increase the motion, especially the circular motion of bone marrow derived stem cells. In fact, they trigger the mobilization of stem cells from bone marrow. Early studies showing the process of mobilization was quite uncertain. Later, it was certified about the several important conclusions on stem cells and also demonstrated that stem cells can be forced out of bone marrow. The studies established that the mobilizable population from bone marrow is much bigger than the circulating population (Rubin *et al.* [1977]; Fliedner [1998]). Another study concluded that half-time of circulating population is $T^{1/2}$ =1-2 hours (Dorie *et al.* [1979]). The time is very short compared with all other leukocytes movement time. The circulating stem-cell population may be doing balance with bone marrow stem-cell population (Gerhartz and Fliedner [1980]). It was also

recorded that the kinetics of mobilization (i.e., speedy or delayed mobilization (Vos *et al.* [1972])) of stem cells are different and may be varied for one study to another. However, several studies concluded about faster revival after transplantation of mobilized cells (Korbling *et al.* [1995]) or about the fate of mobilized cells held true under a new experimental illumination (Wright *et al.* [2001]; Abkowitz *et al.* [2003]). Although the above studies demonstrated the type of circulation of stem cell and trafficking of circulation of stem cell from bone marrow, it is not clear about the path and pattern of circulation like one dimensional movement or two dimensional movements etc. Mathematics has helped us learn how a cell moves (Brokaw [1990]; Dembo [1989]) and can also count molecules in its environment (Berg and Purcell [1977]). Mathematical models of stem cell movement can significantly alter the way we think about and the type of study. The models can also help us to understand the kinetics of stem cell movement. Here, we discuss the mobility pattern of stem cell by using four mathematical models, which are – one dimensional random walk (1D RW) model; random walk lattices model; two dimensional random walk (2D RW) simulation; two-dimensional circular walk (2DCW) movement, three dimensional random walk (3D RW) simulation and left-right rotational movement.

Random walk movement (1D RW) model can be implemented when a series of stem cells move. The directions are randomly decided for the stem cell movement. Oftentimes the random walk is indexed by the natural numbers such as X0, X1, X2 and also some walks take their steps at random times with the position Xt as $t > 0$. If a stem cell can take one dimensional random walk, it may progress through forward or backward movement (Fig. 1A). Let k be the number of equal steps along a line, say a right step takes h_1 probability and a left step takes h_2 probability, k_1 and k_2 be the number of steps for moving right and left of stem cell, then the relation among them is $h_1 + h_2 = 1$ and $k_1 + k_2 = k$, we can find the probability of taking k_1 steps of stem cell if it moves to the right direction, and we can take $\binom{k}{k_1}$ number of steps for right and left direction. tion. Here $\binom{k}{k_1}$ is nothing but a binomial coefficient, so $P(k_1) =$

$\left[\frac{(k_1+k_2!)}{k_1!\,k_2!}\right] h_1^{k1}h_2^{k2}$ [here, k! is factorial; P is the probability]. We can also find the steps to the right and left in terms of mean, and can be written as $\langle k_1\rangle = hk \langle k_2\rangle = k - \langle k_1\rangle = k(1 - h_1) = h_2k$. Likewise, the variance can be shown as $\sigma_{k1}^2 = \langle k_1^2\rangle - \langle k_2^2\rangle = k\, h_1\, h_2$, and the root mean-square(rms) deviation can be shown as $= \sqrt{kh_1h_2}$.

The path for a stem cell permitted during a random walk which can be restricted to the space of a point lattice can be described as random walk lattices model. During the process, lattice is a set of linked horizontal and vertical [for 2D+] line fragments, each passing between adjacent lattice points which are regularly spaced (Fig. 1B). Lattice path is a series of points P0, P1,…,Pn with n > 0, such that each Pi is a web point and Pi + 1 is acquired by offsetting one unit east/west or one unit north/south) (Weisstein [2010]).

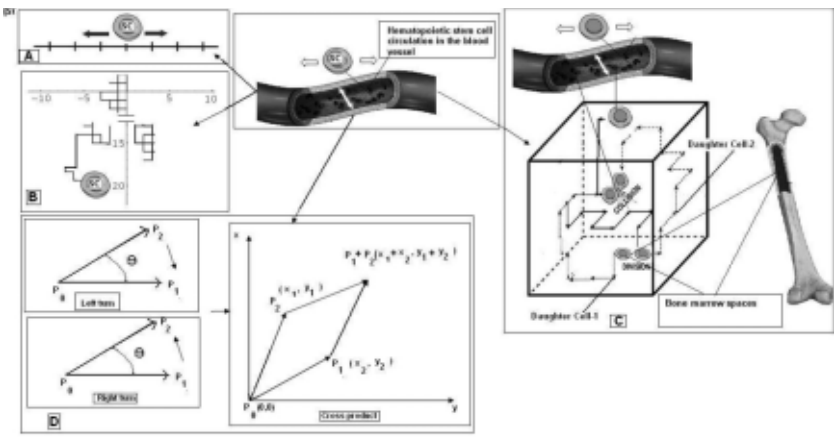

Fig. 1 – Different mathematical models to understand the stem cell mobility pattern. Stem cell is denoted as SC. (A) 1D random walk model proposed by Jones. (B) Path created during 2D walk on a point lattice (lattice not shown) as described by Weisstein. (C) Three dimensional random walk model proposed by Cheng. It shows the cell division occurs in bone marrow space which is a three dimensional random walk category. Sometime hematopoietic stem cell collision occurs in the blood vessel. (D) Left-right rotational movement model (Left turn, right turn and cross product $P_1 \times P_2$).

Another model is the two dimensional random walk (2D RW) model. Actually, moving a stem cell will usually stop for a period of time before continuing on its walk, or it may divide, followed by walks of both daughter cells. This model can be implemented during such situation. Lee *et al.* [1995] tracked individual EC motion experimentally in 2D – average cell speed, duration of time remaining stationary, and average direction changes were determined for use as parameters in simulations. Lee describes that this distinct system provides another approach to continuous models that use normal and partial differential equations to describe the dynamics of systems evolving in space and time (Lee *et al.* [1995]). This distinct model can be used to describe movements of individual stem cells rather than looking at entire populations of cells. We can calculate the possible 2D orientation of stem cell also using vectors. If, say, k is the number of two dimensional vectors for random orientations, then all vectors movements for k arbitrary directions make an angle θ, where θ varies in [0,2π] range in a complex plain and k step can be shown as

$$Z = \sum_{j=1}^{k} e^{i\theta_j}$$

Now calculating its absolute square

$$|z|^2 = \sum_{j=1}^{k} e^{i\theta_j} \sum_{m=1}^{k} e^{-i\theta_m} = \sum_{j=1}^{k} \sum_{m=1}^{k} e^{i(\theta_j - \theta_m)} = k + \left\langle \sum_{\substack{jm=1 \\ m \neq j}}^{k} e^{i(\theta_j - \theta_m)} \right\rangle$$

So we can write the above expression as

$$\left\langle |z|^2 \right\rangle = k + \left\langle \sum_{\substack{jm=1 \\ m \neq j}}^{k} e^{i(\theta_j - \theta_m)} \right\rangle$$

If we consider the distribution values of the displacement (θ_j, θ_m) of the stem cells (both positive and negative direction movement can be possible), their average (expected) is zero.

Therefore

$$\left\langle |z|^2 \right\rangle = k$$

In that case, rms (root means square) distance will be

$$|z|_{rms} = \sqrt{k}$$

So, for s step size the distance becomes

$$b_{rms} = s\sqrt{k}$$

Stem cells can have circular walk, meaning that the movement is on the trajectory of the circle, where the two-dimensional circular walk (2DCW) movement can be implemented. The circular path can be represent as a simple Euclidean geometry (Thomas [1956]; Tsutsumi [1992]) consisting of those points (X_n, Y_n) in a plane which are the same distance $\left(\sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2}\right)$ from the given point called the center.

Cheng, one of the pioneer researcher from the same research group of Lee, explored the purpose of random walk model of cell motility in three dimension (Cheng *et al.* [2006]) (3D). This model supposes a highly porous scaffold which permits unrestricted motion (Fig. 1C). The algorithm for 3D motion is much related to that of 2D motion. However, it is also containing a migration index, stem cell division counter, direction persistence counter, waiting time, and varying transition probabilities to determine the new direction that a stem cell will move in after stopping, colliding, or dividing. Another feature of the model is that it added in a waiting time that a stem cell will remain stationary after colliding with another stem cell, which accounts for the tendency of stem cells to form clusters in 3D. Cell seeding in two modes is considered: uniform cell seeding throughout the 3D space, seeding with cells seeded along edges of a cylindrical portion of the entire 3D grid. The simulation runs until the cell volume fraction, $\kappa(t)$, increases to the point that all available sites are occupied by cells. In another way stem cells can move in x, y and z direction which are statistically independent and the square of the distance from the origin to the point (x, y, z) can be shown as $r^2 = x^2 + y^2 + z^2$ (Howard [1983]).

Sometime, a stem cell may move in left-right rotational direc-

tion. Movements of a stem cell may be counterclockwise (left turn), clockwise (right turn), collinear (no turn) (Fig. 1D). If we calculate cross product, in that case, $P_1 \times P_2$ can be interpreted as the signed area of the parallelogram formed by the points (0,0), P_1, P_2, and $(P_1 + P_2)$

$$P_1 \times P_2 = \det \begin{pmatrix} x_1 x_2 \\ y_1 y_2 \end{pmatrix} = x_1\, y_2 - x_2\, y_1 = - P_1 \times P_2$$

From cross product we can interpret that if $P_1 \times P_2$ is positive, then P_1 is clockwise from P_2 with respect to the origin (0,0), if cross product is negative then P_1 is counterclockwise from P_2, therefore $\vec{P_0P_1}$ is clock wise from directed segment $\vec{P_0P_2}$ with respect to their common end point P_0. Therefore, if $P_1 - P_0$ denotes the vector $P'_1 = (x'_1, y'_1)$, where, $x'_1 = x_1 - x_0$, $y'_1 = y_1 - y_0$, in the same way we can define $P_2 - P_0$.

Therefore the cross product is

$$(P_1 - P_0)\ (P_2 - P_0) = \det \begin{pmatrix} (x_1 - x_0) & (x_2 - x_0) \\ (y_1 - y_0) & (y_2 - y_0) \end{pmatrix}$$

positive result means $\vec{P_0P_1}$ is clockwise from $\vec{P_0P_2}$, and if the result is negative then $\vec{P_0P_1}$ is anticlockwise from $\vec{P_0P_2}$ (Cormen *et al.* [2009]).

We can conclude that the cell movement persists as long as the cell is alive. Cell mobilization, like bone marrow homing, is a complex biologic process which needs the orchestrated participation of several upstream regulators and downstream effectors. Copresentation of immobilized chemokines / adhesion molecules and their downstream partners presents a roadmap to hematopoietic stem cells within bone marrow by guiding their directed migration.

Currently, no model can completely describe the stem cell or tissue growth process or stem cell mobilization properly, because there are still too many unknowns regarding the process itself. Application of these models in stem cell behavior and treatment of cells as individuals can be advantageous because the complex behavior of cells can be broken down into ingredients. In the

words of Jones and Sleeman [2006]: "by modeling crucial steps as discrete processes, it is then possible to develop individual areas independently of the rest of the model". Cohen [2004] stated that caution must be used in applying models to living systems because "theoretical understanding is required as a check on the great risk of error in software and to bridge the enormous gap between computational results and insight or understanding". Until more of the basic biology is known, as well as the math to represent that biology, models will serve as fair predictors for simplified cases of stem cell dynamics and growth. Knowledge in these and other aspects of the biology of stem cell mobilization is expected to pay high clinical dividends in the future.

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