MATHEMATICAL MODELING OF CELL PROLIFERATION USING STOCHASTIC PROCESSES

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Abstract. The human body is like a microsociety, in which its members are cells that reproduce by division and are organized in collaborative groups, called tissues. Each cell has a well-defined role: to send, to receive or to interpret and process extracellular signals. Another way of seeing the structure and the organization of a tissue is through random paths and actions that may occur between its cells. These random paths, similar to the Biological Brownian motion, have several possible directions. Mathematics models these possible directions with stochastic processes. Thus, tissue modeling can be done using branching processes, which can be approximated with diffusion processes, in order to apply Kolmogorov equations to compute the expected time value when a tissue reaches a certain size.

Keywords: tissue, regenerative medicine, branching process, diffusion process

Introduction
For a long time, cellular dynamics has been regarded as a deterministic process, because of the cell-cell interactions, specific information transfer and the adherence of the cells to the extracellular matrix or their organization into “in vitro” cartilage, in the case of regenerative medicine.

There are scientists who have demonstrated the stochasticity of this process. [KUPIEC, 2008, GEVERTZ et al., 2012]

The same authors argue that the process of differentiation is also a random process, because of the internal random diffusion at the molecular level. [PHU et al., 2012, MOHAMMADI et al., 2008, SOTTORIVA et al., 2010]

Using stochastic processes as an important instrument for modeling the “order in disorder” is significant, regarding the observation of the “in vitro” tissue, not only in the regenerative medicine. [ALBANO et al., 2013, CHIŞ et al., 2011], but also in studying the tumoral tissue and comparing normal cells to tumoral cells in terms of proliferation time. [CARAVAGNA et al., 2013, CAPASSO et al., 2009]

In this paper, the process of cell proliferation will be analyzed using stochastic processes. [LECCA et al., 2012, CHROBAK et al., 2012]

The goal is to create a general context for a range of studies and computational simulations in this direction.

Material and methods
Starting from the model built in [HANSON, 2007], which is a method for estimating the expected time in which a tissue doubles its size, we will try to analyze this model in a more general case when a tissue reaches a random size. [NEWTON et al., 2012]

At this point, some questions arise. Given an initial size, what is the maximum size a tissue can reach? There are many influential factors, such as cell types [BOSE et al., 2009], variation in nutrient concentrations at certain tissue layers [PERFAHL et al., 2011] or cell-cell interactions, so this question cannot be mathematically analyzed in this paper [TANAKA et al., 2010], taking into consideration that the interest here, is the evolution of cell population over time, defying some aspects, that will strongly influence the answer. [THALHAUSER et al., 2016]
Thus, the question that we will try to answer in the following part of the article is: what is the probability that a tissue reaches a random size, at a specific time.

First, a discrete model is built for the cell population, using branching processes.

Branching processes consist of particles (cells, molecules), which live for a random period of time and, at a specific moment of life or death, produce a random number of descendants.

There are processes where the appearance of new individuals happens during the life of their ancestors, called general processes. These processes describe populations of large organisms, like vertebrates or plants. The processes where the appearance of new individuals happens at the end of the ancestor life are called classical processes. These are used for modeling cell population, genes and biomolecules. In some processes, like continuum Markov processes, this distinction is irrelevant, since a descendant of a particle can be considered like an extension of the ancestor.

The evolution supposes the apparition of species. Thus, a branching process becomes hierarchically: small particles or species spread within families or other particles, which spread in turn, each current initiated by a "founder" of species.

In mathematical terms, this translates into:

Consider $X_0$, the the initial size of the population. Each individual gives birth, independently of the others, with probability $p_k$, to $k$ new individuals, where the probabilities have the propriety:

$$p_k \geq 0, k = 0,1,2,... \quad \text{and} \quad \sum_{k=0}^{\infty} p_k = 1$$

The total number of direct descendants of the initial population represents the first generation of size $X_1$. Each individual of the first generation will give birth to other individuals, according to the previous propriety and those descendants represent the second generation of size $X_2$. In general, the $n$-th generation, of size $X_n$, is composed from the descendants of the $n-1$ generation (Figure 1). Thus, a sequence of integer random variables is forming, having integer values that generates a Markov chain.

If the initial population is formed from a single member, i.e. $X_0 = 1$, the following relation holds, for each $n = 0,1,2,...$ :

$$X_{n+1} = \sum_{r=1}^{X_n} A_r$$

Where $A_r$, $r \geq 1$ are independent, identically distributed random variables, having the probabilities:

$$P(A_r = k) = p_k, k = 0,1,2,... \quad \text{and} \quad \sum_{k=0}^{\infty} p_k = 1$$

An important propriety, shown by Karlin Samuel and Taylor Howard, in [KARLIN, 1981] is that the probability of extinction of a population is 1 (is certain), if and only if, the expectation of the number of descendants, per individual, doesn’t exceed 1.

The branching process is then approximated with a continuous model, using diffusion processes.

A time continuous stochastic process, which verifies the Markov
propriety and has the trajectories $X(t)$ a.s.(almost sure) continuous functions in time is called a diffusion process.

Beyond their intrinsic interest, diffusion processes are major contributors to a variety of models. Many Biological phenomena are being well approximated or modeled with great reliability by diffusion processes. Examples include molecular kinetics and interaction or variations in population growth.

Let there be $\{X(t), t \geq 0\}$ a diffusion process, with $I$ a diffusion process, with $l < r$ with the possibility of being infinite ($l = -\infty$ and/or $r = +\infty$).

Figure 2. Diffusion Process
(Source: Wikipedia)

The process is regular if, starting from an interior point of $I$, any other point within $I$ can be reached with a positive probability. This property can also be expressed using the random variables hitting time. Thus, if $z \in I$, we denote $T_z$ the corresponding hitting time (meaning the random variable that represents the first moment when the process reaches the value $z$, or, if is never reached, $T_z = \infty$, by convention). The process is regular,

$$P( T_z < \infty | X(0) = x ) > 0$$

where $l < x, z < r$

A regular diffusion process satisfies the condition:

$$\lim_{h \to 0} \frac{1}{h} P(|X(t + h) - x| > \varepsilon | X(t) = x) = 0 \quad (\forall) x \in I$$

for every $\varepsilon$

Through this relation, we can understand that, on sufficiently short time intervals, there cannot be large displacements or a formalization of the propriety of continuity in trajectories of the process.

Almost all diffusion processes, which represent models of some Biological or Physical phenomena, are characterized by two main conditions, that augment the power of the above property, describing the expected variance and dispersion of the infinitesimal displacements.

Let there be

$$\Delta_h X(t) = X(t + h) - X(t).$$

then:

$$\lim_{h \to 0} \frac{1}{h} E( \Delta_h X(t) | X(t) = x) = \mu(x, t)$$

$$\lim_{h \to 0} \frac{1}{h} E[(\Delta_h X(t))^2 | X(t) = x] = \sigma^2(x, t)$$

for $l < x < r$.

The functions $\mu(x, t)$ and $\sigma^2(x, t)$ are called infinitesimal parameters of the process, in particular, $\mu(x, t)$ is called the deviation parameter, infinitesimal mean or mean of the infinitesimal displacements and $\sigma^2(x, t)$ the diffusion parameter or the infinitesimal variance.

In general, $\mu(x, t)$ and $\sigma^2(x, t)$ are continuous functions in $x$ and $t$, and a regular process usually has the variation $\sigma^2(x, t)$ positive, for $(\forall) l < x < r$ and $t > 0$.

For this diffusion model, we use backward Kolmogorov equations, in order to compute the expected time value when the tissue reaches a certain size.
Backward Kolmogorov equations characterize the random dynamic processes.

Consider \((X_t)_{t \geq 0}\) that satisfies the equation:

\[
dX(t) = \mu(X(t), t)dt + \sigma(X(t), t)dW(t),
\]

where the solution of this equation is a diffusion process, with infinitesimal deviation \(\mu(x, t)\) and infinitesimal variation \(\sigma^2(x, t)\) and \(W\) is a Wiener process (Brownian motion).

Consider also \(u(t, x)\) defined as the conditional expectation:

\[
u(t, x) = E[g(X(t))|X(0) = x],
\]

where \(g(x)\) is a bounded, piecewise continuous on \(I\), and \(u(t, x)\) is differentiable in \(t\) and twice differentiable in \(x\). Then, \(u(t, x)\) satisfies the partial differential equation, called backward Kolmogorov equation:

\[
\frac{\partial u}{\partial t} = \frac{1}{2} \sigma^2(x) \frac{\partial^2 u}{\partial x^2} + \mu(x) \frac{\partial u}{\partial t}
\]

with the initial condition \(u(0, x) = g(x)\), where \(u(0, x) = \lim_{t \to 0} u(t, x)\).

Mathematical modeling of cell proliferation

In [RIDLEY, 2008], the authors built a discrete model, which is then approximated by a diffusion process.

Consider \(B_i\) a branching process, where \(i = 1, 2, 3, ...\) for which there are three possible transitions on the time interval \((t, t + \Delta t)\):

\[
B_i = \begin{cases} 
0, & \text{if the cell dies} \\
1, & \text{if there is no change} \\
2, & \text{if cell divides}
\end{cases}
\]

Thus, the total number of cells changes from \(N(t)\), corresponding to time \(t\), to:

\[
N(t + \Delta t) = \sum_{i=1}^{N(t)} B_i
\]

where the difference in the number of cells is:

\[
\Delta N(t) = \sum_{i=1}^{N(t)} B_i - N(t) = \sum_{i=1}^{N(t)} (B_i - 1)
\]

Suppose that \(B_i, i = 1, 2, 3, ...\) are independent, identically distributed random variables, having the conditioned moments:

\[
E[B_i|N(t) = n] = m(n, \Delta t)
\]

\[
D^2[B_i|N(t) = n] = d(n, \Delta t)
\]

And the superior moments:

\[
E[(B_i - m(N(t), \Delta t))^k|N(t) = n] = m_k(n, \Delta t)
\]

which will be increasingly smaller, with \(k \geq 3\).

The conditional moments of changes in cell number \(\Delta N(t)\) are:

\[
E[\Delta N(t)|N(t) = n] = \sum_{i=1}^{n} E[B_i|N(t) = n] - n = n(m(n, \Delta t) - 1)
\]

and

\[
D^2[\Delta N(t)|N(t) = n] = \sum_{i=1}^{n} E[(\Delta N(t) - n(m(n, \Delta t) - 1))^2|N(t) = n] = E\left[ \left( \sum_{i=1}^{n} B_i - m(n, \Delta t) \right)^2 \right] \]

and, because \(B_i, i = 1, 2, 3, ...\) are independent, identically distributed random variables:

\[
E\left[ \left( \sum_{i=1}^{n} B_i - m(n, \Delta t) \right)^2 \right] = \sum_{i=1}^{n} E[(B_i - m(n, \Delta t))^2] = nd(n, \Delta t)
\]

Next, a diffusion process is built, which will approximate the branching process. Consider \(T\) a period of time and \(\tau = t/T\) a new time scale and let there be:

\(X(\tau) = N(\tau)/T\), since the tissue will grow
with the number of generations.

In order to have a consistent model with this scaling, the order of the expectation of state changes must be the same as that of temporal variations.

Let there be

\[ \mu(x) = \lim_{\Delta t \to 0} \frac{E[\Delta X(t)|X(t) = x]}{\Delta t} \]

and

\[ \sigma^2(x) = \lim_{\Delta t \to 0} \frac{D^2[\Delta X(t)|X(t) = x]}{\Delta t} \]

Those moments will be considered as in the Gompertz growth model:

\[ \mu(x) = \mu_1 x \ln \left( \frac{K}{x} \right) \]

and

\[ \sigma^2(x) = \sigma_1 x, \]

where \( \mu_1 \) is a constant growth coefficient, \( \sigma_1 \) is a positive constant and \( K \) is a saturation level.

Consider the initial size \( d \). We will try to find the moment when the tissue has the size \( g \). There is the probability that the tissue would not reach this size or, even, that it would go extinct. We define the hitting time:

\[ \tau^{(g)}(x_0, t_0) = \inf \{ t \mid X(t) = g, X(s) \in (0^+, g), t_0 \leq s < t, X(t_0) = x_0 \} \]

If \( d \) is sufficiently large, the tissue never attains this dimension, so there is the convention, for this situation, that \( \tau^{(g)}(x_0, t_0) = \infty \). Another observation is that, given the fact that we are interested in the number of cells, \( d \) is an integer.

We define, for this random variable, the distribution function

\[ R_{\tau^{(g)}}(x_0, t_0) = P[\tau^{(g)}(x_0, t_0) < t]. \]

having the density

\[ Q^{\phi}(x_0, t_0) = P[\tau^{(g)}(x_0, t_0) < \infty] = \int_0^\infty R_{\tau^{(g)}}(x_0, t_0)(t)dt. \]

If \( x_0 = d \) and \( t_0 = 0 \), then the problem consists in finding \( Q^{\phi}(c, 0) \). Consider \( u_0(x_0) = Q^{\phi}(x_0, 0) \). This function satisfies the homogeneous backward Kolmogorov equation:

\[ B_{x_0}[u_0](x_0) = \frac{1}{2} \sigma_1 x_0 u_0''(x_0) + \mu_1 x_0 \ln \frac{K}{x_0} u_0'(x_0) = 0 \]

Because we are interested in the case \( x_0 > 0 \), we can simplify and write the equivalent form

\[ u_0''(x_0) + 2 \frac{\mu_1}{\sigma_1} \ln \frac{K}{x_0} u_0'(x_0) = 0 \]

To solve this partial differential equation, we consider the change of variable \( u_0'(x_0) = y(x_0) \neq 0 \). After computing, the following equation is obtained:

\[ y(x_0) = u_0'(x_0) = (\beta_1 x_0)^{\gamma_1} x_0, \]

where

\[ \gamma_1 = 2 \frac{\mu_1}{\sigma_1} \text{ and } \beta_1 = \frac{1}{ke} > 0. \]

Thus, \( y(x_0) = \left( \frac{u_0'}{y} \right)'(x_0) = 0 \), and so:

\[ Q^{\phi}(x_0, 0) = u_0(x_0) = \frac{\int_0^\infty y(x)dx}{\int_0^\infty y(x)dx}. \]

The expectation of the moment when the cell population reaches the size \( g \) can be approximated with:

\[ T^{(g)}(d) = \frac{M^{(g)}(d)}{Q^{\phi}(d, 0)}, \]

where

\[ M^{(g)}(x_0) = \int_0^\infty t R_{\tau^{(g)}}(x_0, 0)dt \]

verifies the equation:

\[ B_{x_0}[M^{(g)}](x_0) = -Q^{\phi}(x_0, 0) \]

and the boundary conditions:
\[ M^{(g)}(0^+) = 0 \text{ and } M^g(g) = 0. \]

We denote \( u_1(x_0) = M^{(g)}(x_0) \) and, thus, the equation becomes:

\[ B_{x_0}[u_1](x_0) = -u_0(x_0). \]

By solving this equation, we obtain

\[ u_1(x_0) \text{ as a function of } u_0(x_0). \]

Considering \( x_0 = d \), the following result is obtained:

\[ T^{(g)}(d) = \frac{u_1(x_0)}{u_0(x_0)}. \]

Conclusions

Taking into consideration some general assumptions about cells, stochastic processes can model the randomness of cell division.

Basically, the tissue can be considered as a cell population and, in consequence, the studies regarding the evolution over time of a population have been applied to this particular case. The next step, in this analysis, is to consider specific conditions, translated into mathematical restrictions to this process, according to cell types, variation in nutrition, cell differentiation, and comparison between normal cells and tumoral cells or between an "in vivo" or "in vitro" tissue.

References


