Modeling the Cell Proliferation using Compound Non-homogeneous Poisson Distribution

The Author

From the differential equations,

$$\begin{aligned}\frac{dS(t)}{dt} &= r[p_1(t) - p_3(t)]S(t) \\ \frac{dF(t)}{dt} &= r[p_2(t) + 2p_3(t)]S(t),\end{aligned} \tag{1}$$

we obtained the average cell counts of the active stem cell $S(t)$ and differentiated cells $F(t)$

$$\begin{aligned}S(t) &= S_0 \exp\Big\{rP(t)\Big\} \\ F(t) &= \int_0^t r[p_2(v) + 2p_3(v)]S(v)dv \\ &= S_0 \cdot r \cdot \int_0^t [p_2(v) + 2p_3(v)] \exp\Big\{rP(v)\Big\}dv,\end{aligned} \tag{2}$$

with $P(t) = \int_0^t [p_1(v) - p_3(v)]dv$.

We can model the stem cells and differentiated cells using the compound nonhomogeneous Poisson process as follows. Let $N(t)$ denote the number of divisions at time t. $N(t)$ is a nonhomogeneous Poisson process with rate $\lambda(t) = rS(t)$. Let X_s and Y_s be random variables such that

$$X_s = \begin{cases} +1 & p_1(s) \\ -1 & p_3(s) \\ 0 & 1 - p_1(s) - p_3(s), \end{cases} \tag{3}$$

and

$$Y_s = \begin{cases} +1 & p_2(s) \\ +2 & p_3(s) \\ 0 & 1 - p_2(s) - p_3(s) \end{cases} . \tag{4}$$

We define processes $X(t)$ and $Y(t)$ as follows

$$X(t) = \sum_{k=1}^{N(t)} X_k, \quad \text{and} \quad Y(t) = \sum_{k=1}^{N(t)} Y_k. \tag{5}$$

$X(t)$ and $Y(t)$ are compound nonhomogeneous Poisson processes. From Theorem 2.1 and Corollary of Chen and Savits (1993) (cite), the characteristic functions, expected values, and variances of $X(t)$ and $Y(t)$ are

$$
\begin{aligned}
E[e^{iuX(t)}] &= \exp\Big\{ \int_0^t \Big[e^{iu}p_2(v) - p_2(v) + e^{-iu}p_3(v) - p_3(v)\Big] rS(v)dv \Big\}, \\
E[X(t)] &= \int_0^t [p_1(v) - p_3(v)] rS(v)dv, \\
\mathrm{Var}(X(t)) &= \int_0^t [p_1(v) + p_3(v)] rS(v)dv, \\
E[e^{iuY(t)}] &= \exp\Big\{ \int_0^t \Big[e^{iu}p_2(v) - p_2(v) + e^{2iu}p_3(v) - p_3(v)\Big] rS(v)dv \Big\}, \\
E[Y(t)] &= \int_0^t [p_2(v) + 2p_3(v)] rS(v)dv, \\
\mathrm{Var}(Y(t)) &= \int_0^t [p_2(v) + 4p_3(v)] rS(v)dv.
\end{aligned} \tag{6}
$$

From the expressions of $E[Y(t)]$ and $F(t)$, it is straightforward to see that $E[Y(t)] = F(t)$.

$$
E[X(t)] = \int_0^t [p_1(v) - p_3(v)] \cdot r \cdot S_0 \exp\Big\{rP(v)\Big\}dv \tag{7}
$$

Using substitution with $q = P(v) = \int_0^v [p_1(u) - p_3(u)]du$ and $dq/dv = [p_1(v) - p_3(v)]$,

$$
E[X(t)] = S_0 r \int_{P(0)}^{P(t)} \exp\{rq\}dq = S_0 \exp\{rq\}\Big|_{P(0)}^{P(t)} = S_0 \exp\{rP(t)\} - S_0, \tag{8}
$$

since $P(0) = \int_0^0 [p_1(u) - p_3(u)]du = 0$. Thus $E[X(t) + S_0] = S(t)$.

Proposition 1. *For a fixed t, $X(t)/S(t) \xrightarrow{p} 1$ and $Y(t)/F(t) \xrightarrow{p} 1$ as $S_0 \to \infty$.*

Proof. Let $\mu_{x_t} = S(t)$ and $\mu_{y_t} = F(t)$. Using Taylor's expansion,

$$
\begin{aligned}
E\Big[e^{iu\frac{X(t)}{S(t)}}\Big] &= \exp\Big\{ \int_0^t \Big[e^{i\frac{u}{\mu_{x_t}}}p_1(v) - p_1(v) + e^{-i\frac{u}{\mu_{x_t}}}p_3(v) - p_3(v)\Big] rS(v)dv \Big\} \\
&= \exp\Big\{ \int_0^t \Big[\Big(1 + \frac{iu}{\mu_{x_t}} + o(\mu_{x_t}^{-1})\Big)p_1(v) - p_1(v) + \Big(1 - \frac{iu}{\mu_{x_t}} + o(\mu_{x_t}^{-1})\Big)p_3(v) - p_3(v)\Big] rS(v)dv \Big\} \\
&= \exp\Big\{ \frac{iu}{\mu_{x_t}} \int_0^t [p_1(v) - p_3(v)] rS(v)dv + o(\mu_{x_t}^{-1}) \int_0^t [p_1(v) + p_3(v)] rS(v)dv \Big\} \\
&\to \exp\Big\{iu\Big\},
\end{aligned} \tag{9}
$$

$$
\begin{aligned}
E\Big[e^{iu\frac{Y(t)}{F(t)}}\Big] &= \exp\Big\{\int_0^t \Big[e^{i\frac{u}{\mu_{y_t}}}p_2(v) - p_2(v) + e^{2i\frac{u}{\mu_{y_t}}}p_3(v) - p_3(v)\Big]rS(v)dv\Big\} \\
&= \exp\Big\{\int_0^t \Big[\Big(1+\frac{iu}{\mu_{y_t}} + o(\mu_{y_t}^{-1})\Big)p_2(v) - p_2(v) + \Big(1+\frac{2iu}{\mu_{y_t}} + o(\mu_{y_t}^{-1})\Big)p_3(v) - p_3(v)\Big]rS(v)dv\Big\} \\
&= \exp\Big\{\frac{iu}{\mu_{y_t}}\int_0^t [p_2(v)+2p_3(v)]rS(v)dv + o(\mu_{y_t}^{-1})\int_0^t [p_2(v)+2p_3(v)]rS(v)dv\Big\} \\
&\to \exp\Big\{iu\Big\}.
\end{aligned} \tag{10}
$$

$\square$

Proposition 2. *For a fixed t, as $S_0 \to \infty$,*

$$
\frac{X(t)-S(t)}{\sqrt{Var(X(t))}} \xrightarrow{D} N(0,1), \tag{11}
$$

and

$$
\frac{Y(t)-F(t)}{\sqrt{Var(Y(t))}} \xrightarrow{D} N(0,1). \tag{12}
$$

Proof. Let $\sigma_{x_t} = \sqrt{Var(X(t))}$ and $\sigma_{y_t} = \sqrt{Var(Y(t))}$. Using Taylor's expansion,

$$
\begin{aligned}
E\Big[e^{iu\frac{X(t)}{\sigma_{x_t}}}\Big] &= \exp\Big\{\int_0^t \Big[e^{i\frac{u}{\sigma_{x_t}}}p_1(v) - p_1(v) + e^{-i\frac{u}{\sigma_{x_t}}}p_3(v) - p_3(v)\Big]rS(v)dv\Big\} \\
&= \exp\Big\{\int_0^t \Big[\Big(1+\frac{iu}{\sigma_{x_t}} + \frac{i^2u^2}{2\sigma_{x_t}^2} + o(\sigma_{x_t}^{-2})\Big)p_1(v) - p_1(v) + \\
&\Big(1-\frac{iu}{\sigma_{x_t}} + \frac{i^2u^2}{2\sigma_{x_t}^2} + o(\sigma_{x_t}^{-2})\Big)p_3(v) - p_3(v)\Big]rS(v)dv\Big\} \\
&= \exp\Big\{\frac{iu}{\sigma_{x_t}}\int_0^t [p_1(v)-p_3(v)]rS(v)dv + \frac{i^2u^2}{2\sigma_{x_t}^2}\int_0^t [p_1(v)+p_3(v)]rS(v)dv \\
&+ o(\sigma_{x_t}^{-2})\int_0^t [p_1(v)+p_3(v)]rS(v)dv\Big\} \\
&\to \exp\Big\{\frac{iu}{\sigma_{x_t}}S(t) - \frac{u^2}{2}\Big\} \\
E\Big[e^{iu\frac{X(t)-S(t)}{\sigma_{x_t}}}\Big] &= E\Big[e^{iu\frac{X(t)}{\sigma_{x_t}}}\Big]\cdot e^{-iu\frac{S(t)}{\sigma_{x_t}}} \to e^{-\frac{u^2}{2}}.
\end{aligned} \tag{13}
$$

$$
\begin{aligned}
E\Big[e^{iu\frac{Y(t)}{\sigma_{y_t}}}\Big] &= \exp\Big\{\int_0^t \Big[e^{i\frac{u}{\sigma_{y_t}}}p_2(v) - p_2(v) + e^{i\frac{2u}{\sigma_{y_t}}}p_3(v) - p_3(v)\Big]rS(v)dv\Big\} \\
&= \exp\Big\{\int_0^t \Big[\Big(1 + \frac{iu}{\sigma_{y_t}} + \frac{i^2u^2}{2\sigma_{y_t}^2} + o(\sigma_{y_t}^{-2})\Big)p_2(v) - p_2(v) + \\
&\Big(1 + \frac{2iu}{\sigma_{y_t}} + \frac{4i^2u^2}{2\sigma_{y_t}^2} + o(\sigma_{y_t}^{-2})\Big)p_3(v) - p_3(v)\Big]rS(v)dv\Big\} \\
&= \exp\Big\{\frac{iu}{\sigma_{y_t}}\int_0^t [p_2(v) + 2p_3(v)]rS(v)dv + \frac{i^2u^2}{2\sigma_{x_t}^2}\int_0^t [p_1(v) + 4p_3(v)]rS(v)dv \\
&+ o(\sigma_{x_t}^{-2})\int_0^t [p_1(v) + p_3(v)]rS(v)dv\Big\} \\
&\to \exp\Big\{\frac{iu}{\sigma_{y_t}}F(t) - \frac{u^2}{2}\Big\} \\
E\Big[e^{iu\frac{Y(t)-F(t)}{\sigma_{y_t}}}\Big] &= E\Big[e^{iu\frac{Y(t)}{\sigma_{y_t}}}\Big]\cdot e^{-iu\frac{F(t)}{\sigma_{y_t}}} \to e^{-\frac{u^2}{2}}.
\end{aligned} \tag{14}
$$

$\square$

Covariance of $X(t)$ and $Y(t)$ when $p_4(t) = 0$

When $p_4(t) = 0 \forall t$, i.e all the stem cells can undergo further division and there is no inactive stem cell, the number of divisions equal to the sum of stem cells and differentiated cells $N(t) = X(t) + Y(t)$. For each division occurrence, the sum of stem cells and ependymal cells increases by 1 (Table 1). Then,

	$p_1(t)$	$p_2(t)$	$p_3(t)$
$X(t)$	$+1$	$+0$	-1
$Y(t)$	$+0$	$+1$	$+2$
$X(t) + Y(t)$	$+1$	$+1$	$+1$

Table 1: Change of total cell counts with each division occurrence when $p_4(t) = 0$.

$E[(N(t))^2] = E[(X(t))^2] + E[X(t)Y(t)] + E[(Y(t))^2]$. Since $N(t)$ is an nonhomogeneous Poisson process with rate $\lambda(t) = rS(t)$, $N(t)$ is a Poisson random variable with mean and variance

$$E[N(t)] = Var(N(t)) = \int_0^t rS(v)dv.$$

We obtain the covariance of $X(t)$ and $Y(t)$ when $p_4(t) = 0$

$$
\begin{aligned}
Cov(X(t), Y(t)) &= E[X(t)Y(t)] - E[X(t)]E[Y(t)] \\
&= E[(N(t))^2] - E[(X(t))^2] - E[(Y(t))^2] - E[X(t)]E[Y(t)] \\
&= (E[N(t)])^2 + Var(N(t)) - (E[X(t)])^2 - Var(X(t)) - (E[Y(t)])^2 - Var(Y(t)) \\
&- E[X(t)]E[Y(t)] \\
&= \Big[\int_0^t rS(v)dv\Big]^2 - \Big[\int_0^t [p_1(v) - p_3(v)]rS(v)dv\Big]^2 - \Big[\int_0^t [p_2(v) + 2p_3(v)]rS(v)dv\Big]^2 \\
&- \int_0^t 4p_3(v)rS(v)dv - \int_0^t [p_1(v) - p_3(v)]rS(v)dv \cdot \int_0^t [p_2(v) + 2p_3(v)]rS(v)dv.
\end{aligned}
\tag{15}
$$

Limit of the $X(t)$ and $Y(t)$

Show the variance of $X(t)$ and of $Y(t)$ converge as t is large.

$$Var(X(t)) = \int_0^t [p_1(v) + p_3(v)]rS(v)dv,$$

$$Var(Y(t)) = \int_0^t [p_2(v) + 4p_3(v)]rS(v)dv.$$

Since $p_1(v) + p_3(v) \le 1$ for any $v \in (0, \infty)$, then $[p_1(v) + p_3(v)]rS(v) \le rS(v)$. Then using the comparison test if $\int_0^\infty rS(v)dv$ converges then $\int_0^\infty [p_1(v) + p_3(v)]rS(v)dv$ converges

(Note that in the compound nonhomogeneous Poisson process, $E[N(t)] = Var(N(t)) = \int_0^t rS(v)dv$).

$$\int_0^\infty rS(v)dv = r\int_0^\infty S_0 \exp\Big\{r\int_0^v [p_1(u) - p_3(u)]du\Big\}dv \tag{16}$$

Assume that $p_1(u) - p_3(u)$ is a continuous function on $(0, \infty)$ and there exists $u_0 \in (0, \infty)$ such that $\forall u > u_0, p_1(u) - p_3(u) \le -q < 0$,

$$
\begin{aligned}
\int_0^v [p_1(u) - p_3(u)]du &= \int_0^{u_0} [p_1(u) - p_3(u)]du + \int_{u_0}^v [p_1(u) - p_3(u)]du \\
&\le \int_0^{u_0} 1du + \int_{u_0}^v (-q)du \quad \text{since } p_1(u) - p_3(u) \le 1 \forall u \\
&= u_0 - rq(v - u_0).
\end{aligned}
\tag{17}
$$

Then,

$$
\begin{aligned}
\int_0^\infty rS(v)dv &= r\int_0^\infty S_0 \exp\Big\{r\int_0^v [p_1(u) - p_3(u)]du\Big\}dv \\
&\le r\int_0^\infty S_0 \exp\{r(u_0 - rq(v - u_0))\}dv \\
&= r\int_0^\infty S_0 \exp\{u_0(1 + rq)\}\exp\{-rqv\}dv \\
&= S_0 \cdot r \cdot \exp\{u_0(1 + rq)\}\int_0^\infty \exp\{-rqv\}dv \\
&= \frac{S_0 \exp\{u_0(1 + rq)\}}{q} < \infty.
\end{aligned}
\tag{18}
$$

Similarly for $Var(Y(t))$, since $[p_2(v) + 4p_3(v)] \leq 4$ for any $v \in (0, \infty)$,

$$\int_0^\infty [p_2(v) + 4p_3(v)] r S(v) dv \leq \int_0^\infty 4 r S(v) dv \leq \frac{4 S_0 \exp\{u_0(1 + rq)\}}{q} < \infty.$$