Modeling the Cell Proliferation using Compound Non-homogeneous Poisson Distribution

The Author

1 Model

The evolution of the average cell counts of the active stem cell, $S(t)$, and differentiated cells, $F(t)$, is described by the following differential equations

$$\begin{aligned}\frac{dS(t)}{dt} &= r[p_1(t) - p_3(t)]S(t), \quad S(0) = S_0,\\ \frac{dF(t)}{dt} &= r[p_2(t) + 2p_3(t)]S(t), \quad F(0) = 0,\end{aligned} \tag{1}$$

where $r > 0$ and $p_1(t), p_2(t), p_3(t) > 0$ and $0 < p_1(t) + p_2(t) + p_3(t) \leq 1$ for any $t > 0$. The solutions of the differential equations are given by

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

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

We model the stem cell and differentiated cell counts using the compound nonhomogeneous Poisson process as follows. Let $N(t)$ be a nonhomogeneous Poisson process with rate $\lambda(t) = rS(t)$. Given a sequence of arrival times $S_1, S_2, S_3, \ldots$, the pairs of random variables $(X_1, Y_1), (X_2, Y_2), (X_3, Y_3), \ldots$ are independent with the following marginal distributions

$$(X_k, Y_k) = \begin{cases} (+1, 0), & p_1(S_k) \\ (0, +1), & p_2(S_k) \\ (-1, +2), & p_3(S_k) \\ (0, 0), & p_4(S_k) \end{cases},$$

where $p_4(t) = 1 - p_1(t) - p_2(t) - p_3(t)$. First, we define two compound nonhomogeneous Poisson processes, $X(t)$ and $Y(t)$, as follows

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

Next, we define the stopping time τ (when the stem cell count reaches 0) by

$$\tau = \inf\{t > 0 : X(t) = -S_0\}.$$

Under assumption $\mathbb{P}(\tau < \infty)$ the counts of stem cells and differentiated cells are modelled by processes $S_0 + X(t \wedge \tau)$ and $Y(t \wedge \tau)$, respectively.

2 Some Observations

From Theorem 2.1 and Corollary to Proposition 2.2 of Chen and Savits (1993) (cite), the characteristic functions, expected values, and variances of $X(t)$ and $Y(t)$ are given by

$$\begin{aligned}
\mathbb{E}[e^{iuX(t)}] &= \exp\left\{\int_0^t \Big[\left(e^{iu}-1\right)p_2(v)+\left(e^{-iu}-1\right)p_3(v)\Big] rS(v)dv\right\},\\
\mathbb{E}[X(t)] &= \int_0^t [p_1(v)-p_3(v)]rS(v)dv,\\
\mathbb{V}(X(t)) &= \int_0^t [p_1(v)+p_3(v)]rS(v)dv,\\
\mathbb{E}[e^{iuY(t)}] &= \exp\left\{\int_0^t \Big[\left(e^{iu}-1\right)p_2(v)+\left(e^{2iu}-1\right)p_3(v)\Big] rS(v)dv\right\},\\
\mathbb{E}[Y(t)] &= \int_0^t [p_2(v)+2p_3(v)]rS(v)dv,\\
\mathbb{V}(Y(t)) &= \int_0^t [p_2(v)+4p_3(v)]rS(v)dv.
\end{aligned} \tag{2}$$

Differential equations (1) immediately tell us that

$$\mathbb{E}[X(t)] = \int_0^t [p_1(v)-p_3(v)]rS(v)dv = \int_0^t dS(v) = S(t)-S_0,$$

or $\mathbb{E}[S_0+X(t)] = S(t)$. Similarly,

$$\mathbb{E}[Y(t)] = \int_0^t [p_2(v)+2p_3(v)]rS(v)dv = \int_0^t dF(v) = F(t).$$

Moreover, when the initial number of stem cells is large, for any fixed time point t the both stochastic processes are close to their expected values. More specifically, we have the following two limit results.

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

Proof. Using formulas (2) and the first-order Taylor's expansion for the exponential function $e^{iu/S(t)} = e^{iu/(S_0\exp\{rP(t)\})}$ we get

$$\begin{aligned}
\mathbb{E}\Big[e^{iu\frac{S_0+X(t)}{S(t)}}\Big] &= e^{iuS_0/S(t)}\exp\left\{\int_0^t \Big[\left(e^{iu/S(t)}-1\right)p_1(v)+\left(e^{-iu/S(t)}-1\right)p_3(v)\Big] rS(v)dv\right\}\\
&= e^{iuS_0/S(t)}\exp\left\{\int_0^t \Big[\Big(\frac{iu}{S(t)}+o\left(S_0^{-1}\right)\Big)p_1(v)+\Big(-\frac{iu}{S(t)}+o\left(S_0^{-1}\right)\Big)p_3(v)\Big] rS_0\exp\{rP(v)\}dv\right\}\\
&= e^{iuS_0/S(t)}\exp\left\{\frac{iu}{S(t)}\int_0^t [p_1(v)-p_3(v)]rS(v)dv + o(1)\right\}\\
&= e^{iuS_0/S(t)}\exp\left\{\frac{iu}{S(t)}\mathbb{E}(X(t)) + o(1)\right\}\\
&= \exp\left\{\frac{iu}{S(t)}[S_0+\mathbb{E}(X(t))] + o(1)\right\}\\
&\to \exp\{iu\},
\end{aligned}$$

as $S_0\to\infty$. Thus, $[S_0+X(t)]/S(t) \xrightarrow{D} 1$, and, therefore, $[S_0+X(t)]/S(t) \xrightarrow{P} 1$. Similarly, we get the convergence for $Y(t)$. $\square$

In the same fashion a stronger, Central Limit Theorem–type results can also be obtained.

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

$$\frac{S_0 + X(t) - S(t)}{\sqrt{Var(X(t))}} \xrightarrow{D} N(0,1),$$

and

$$\frac{Y(t) - F(t)}{\sqrt{\mathbb{V}(Y(t))}} \xrightarrow{D} N(0,1).$$

Proof. Let $\sigma_{x_t} = \sqrt{\mathbb{V}(X(t))}$. Using the second-order Taylor's expansion we have

$$\begin{aligned}
\mathbb{E}\Big[e^{iuX(t)/\sigma_{x_t}}\Big] &= \exp\left\{\int_0^t \Big[\Big(e^{iu/\sigma_{x_t}} - 1\Big)\, p_1(v) + \Big(e^{-iu/\sigma_{x_t}} - 1\Big)\, p_3(v)\Big] rS(v)dv\right\} \\
&= \exp\left\{\int_0^t \Big[\Big(\frac{iu}{\sigma_{x_t}} + \frac{i^2u^2}{2\sigma_{x_t}^2} + o\left(\sigma_{x_t}^{-2}\right)\Big)p_1(v) + \Big(-\frac{iu}{\sigma_{x_t}} + \frac{i^2u^2}{2\sigma_{x_t}^2} + o\left(\sigma_{x_t}^{-2}\right)\Big)p_3(v)\Big] rS(v)dv\right\} \\
&= \exp\left\{\int_0^t \Big[\Big(\frac{iu}{\sigma_{x_t}} + \frac{i^2u^2}{2\sigma_{x_t}^2} + o\left(S_0^{-1}\right)\Big)p_1(v) + \Big(-\frac{iu}{\sigma_{x_t}} + \frac{i^2u^2}{2\sigma_{x_t}^2} + o\left(S_0^{-1}\right)\Big)p_3(v)\Big] rS_0 \exp\{rP(v)\}dv\right\} \\
&= \exp\left\{\frac{iu}{\sigma_{x_t}}\int_0^t [p_1(v) - p_3(v)]rS(v)dv + \frac{i^2u^2}{2\sigma_{x_t}^2}\int_0^t [p_1(v) + p_3(v)]rS(v)dv + o(1)\right\} \\
&= \exp\left\{\frac{iu}{\sigma_{x_t}}[S(t) - S_0] + \frac{i^2u^2}{2\sigma_{x_t}^2}\mathbb{V}(X(t)) + o(1)\right\}.
\end{aligned}$$

Therefore, as $S_0 \to \infty$ we have

$$\mathbb{E}\Big[e^{iu\frac{S_0 + X(t) - S(t)}{\sigma_{x_t}}}\Big] = \exp\left\{-\frac{u^2}{2} + o(1)\right\} \to e^{-\frac{u^2}{2}}.$$

Again, the convergence for $Y(t)$ can be shown in a similar way. □

3 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, $E[(N(t))^2] = E[(X(t))^2] + E[X(t)Y(t)] + E[(Y(t))^2]$.

	$p_1(t)$	$p_2(t)$	$p_3(t)$
$X(t)$	$+1$	$+0$	-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 $p_4(t) = 0$.

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 $p_4(t) = 0$

Correction

$$\begin{aligned}
Cov(X(t), Y(t)) &= E[X(t)Y(t)] - E[X(t)]E[Y(t)] \\
&= E[(N(t))^2] - E[(X(t))^2] - E[(Y(t))^2] - E[X(t)]E[Y(t)] \\
&= \Big[(E[N(t)])^2 + Var(N(t)) - (E[X(t)])^2 - Var(X(t)) - (E[Y(t)])^2 - Var(Y(t))\Big]/2 \\
&- E[X(t)]E[Y(t)] \\
&= \Big[(E[N(t)])^2 + Var(N(t)) - Var(X(t)) - Var(Y(t)) - (E[X(t)])^2 - (E[Y(t)])^2 - 2E[X(t)]E[Y(t)]\Big]/2 \\
&\text{(rearranging terms)} \\
&= \Big[(E[N(t)])^2 + Var(N(t)) - Var(X(t)) - Var(Y(t)) - (E[N(t)])^2\Big]/2 \\
&= \Big[\int_0^t rS(v)dv - \int_0^t [p_1(v) + p_3(v)]rS(v)dv - \int_0^t p_2(v) + 4p_3(v)]rS(v)dv\Big]/2 \\
&= -\int_0^t 2p_3(v)rS(v)dv.
\end{aligned} \tag{3}$$

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 $p_1(v) + p_3(v) \leq 1$ for any $v \in (0, \infty)$, then $[p_1(v) + p_3(v)]rS(v) \leq rS(v)$. 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, $E[N(t)] = Var(N(t)) = \int_0^t rS(v)dv$).

$$\int_0^\infty rS(v)dv = r\int_0^\infty S_0 \exp\left\{r\int_0^v [p_1(u) - p_3(u)]du\right\} dv \tag{4}$$

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 $\forall u > u_0, p_1(u) - p_3(u) \leq$

$-q < 0$,

$$\begin{aligned}\int_0^v [p_1(u) - p_3(u)]du &= \int_0^{u_0} [p_1(u) - p_3(u)]du + \int_{u_0}^v [p_1(u) - p_3(u)]du \\ &\leq \int_0^{u_0} 1du + \int_{u_0}^v (-q)du \quad \text{since } p_1(u) - p_3(u) \leq 1 \forall u \\ &= u_0 - rq(v - u_0).\end{aligned} \tag{5}$$

Then,

$$\begin{aligned}\int_0^\infty rS(v)dv &= r\int_0^\infty S_0 \exp\left\{r\int_0^v [p_1(u) - p_3(u)]du\right\} dv \\ &\leq r\int_0^\infty S_0 \exp\{r(u_0 - rq(v - u_0))\}dv \\ &= r\int_0^\infty S_0 \exp\{u_0(1 + rq)\} \exp\{-rqv\}dv \\ &= S_0 \cdot r \cdot \exp\{u_0(1 + rq)\} \int_0^\infty \exp\{-rqv\}dv \\ &= \frac{S_0 \exp\{u_0(1 + rq)\}}{q} < \infty.\end{aligned} \tag{6}$$

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

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

Results from the Multivariate Characteristic Function

We model the stem cell (both viable and non-viable) and differentiated cell counts using the compound nonhomogeneous Poisson process as follows. Let $N(t)$ be a nonhomogeneous Poisson process with rate $\lambda(t) = rS(t)$. Given a sequence of arrival times $S_1, S_2, S_3, \cdots$, the 3-tuple of random variable $(X_1, Y_1, Z_1), (X_2, Y_2, Z_2), (X_3, Y_3, Z_3), \cdots$ are independent with the following marginal distributions

$$(X_k, Y_k, Z_k) = \begin{cases} (+1, 0, 0), & p_1(S_k) \\ (0, +1, 0), & p_2(S_k) \\ (-1, +2, 0), & p_3(S_k) \\ (0, 0, +1), & p_4(S_k) \end{cases}$$

where $p_4(t) = 1 - p_1(t) - p_2(t) - p_3(t)$. We define the three compound nonhomogeneous Poisson processes, $X(t), Y(t)$, and $Z(t)$, as follows

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

From Theorem 2.1 of Chen and Savits (1993) (cite), the characteristic functions of $\mathbf{C}(t) = (X(t), Y(t), Z(t))$ is

$$\psi_{\mathbf{C}(t)}(\mathbf{u}) = \exp\left\{ \int_0^t [(e^{iu_1} - 1)p_1(v) + (e^{iu_2} - 1)p_2(v) + (e^{-iu_1+2iu_2} - 1)p_3(v) + (e^{iu_3} - 1)p_4(v)]rS(v)dv\right\} \tag{7}$$

We use Leibniz integral rule to take the first and second derivative (using the product rule) of $\psi_{\mathbf{C}(t)}(\mathbf{u})$ with respect to u_1, u_2, and u_3, we obtain the expected values and variances of $X(t), Y(t)$, and $Z(t)$

$$
\begin{aligned}
\frac{\partial \psi_{\mathbf{C}(t)}(\mathbf{u})}{\partial u_1} &= \exp\Big\{ \int_0^t [(e^{iu_1}-1)p_1(v) + (e^{iu_2}-1)p_2(v) + (e^{-iu_1+2iu_2}-1)p_3(v) + (e^{iu_3}-1)p_4(v)] rS(v)dv \Big\} \\
&\int_0^t [ie^{iu_1}p_1(v) - ie^{-iu_1+2iu_2}p_3(v)]rS(v)dv \\
\frac{\partial^2 \psi_{\mathbf{C}(t)}(\mathbf{u})}{\partial^2 u_1} &= \exp\Big\{ \int_0^t [(e^{iu_1}-1)p_1(v) + (e^{iu_2}-1)p_2(v) + (e^{-iu_1+2iu_2}-1)p_3(v) + (e^{iu_3}-1)p_4(v)] rS(v)dv \Big\} \\
&\int_0^t [i^2e^{iu_1}p_1(v) + i^2e^{-iu_1+2iu_2}p_3(v)]rS(v)dv + \\
&\exp\Big\{ \int_0^t [(e^{iu_1}-1)p_1(v) + (e^{iu_2}-1)p_2(v) + (e^{-iu_1+2iu_2}-1)p_3(v) + (e^{iu_3}-1)p_4(v)] rS(v)dv \Big\} \\
&\Big[\int_0^t [ie^{iu_1}p_1(v) - ie^{-iu_1+2iu_2}p_3(v)]rS(v)dv \Big]^2
\end{aligned} \tag{8}
$$

$$
\begin{aligned}
\mathbb{E}[X(t)] &= i^{-1}\frac{\partial \psi_{\mathbf{C}(t)}(\mathbf{u})}{\partial u_1}\Big|_{\mathbf{u}=\mathbf{0}} = \int_0^t [p_1(v) - p_3(v)]rS(v)dv \\
\mathbb{E}[X(t)^2] &= i^{-2}\frac{\partial^2 \psi_{\mathbf{C}(t)}(\mathbf{u})}{\partial^2 u_1}\Big|_{\mathbf{u}=\mathbf{0}} \\
&= \int_0^t [p_1(v) + p_3(v)]rS(v)dv + \Big[\int_0^t [p_1(v) - p_3(v)]rS(v)dv \Big]^2 \\
\mathbb{V}[X(t)] &= \mathbb{E}[X(t)^2] - (\mathbb{E}[X(t)])^2 = \int_0^t [p_1(v) + p_3(v)]rS(v)dv
\end{aligned} \tag{9}
$$

$$
\begin{aligned}
\frac{\partial \psi_{\mathbf{C}(t)}(\mathbf{u})}{\partial u_2} &= \exp\Big\{ \int_0^t [(e^{iu_1}-1)p_1(v) + (e^{iu_2}-1)p_2(v) + (e^{-iu_1+2iu_2}-1)p_3(v) + (e^{iu_3}-1)p_4(v)] rS(v)dv \Big\} \\
&\int_0^t [ie^{iu_2}p_2(v) + 2ie^{-iu_1+2iu_2}p_3(v)]rS(v)dv \\
\frac{\partial^2 \psi_{\mathbf{C}(t)}(\mathbf{u})}{\partial^2 u_2} &= \exp\Big\{ \int_0^t [(e^{iu_1}-1)p_1(v) + (e^{iu_2}-1)p_2(v) + (e^{-iu_1+2iu_2}-1)p_3(v) + (e^{iu_3}-1)p_4(v)] rS(v)dv \Big\} \\
&\int_0^t [i^2e^{iu_2}p_2(v) + 4i^2e^{-iu_1+2iu_2}p_3(v)]rS(v)dv + \\
&\exp\Big\{ \int_0^t [(e^{iu_1}-1)p_1(v) + (e^{iu_2}-1)p_2(v) + (e^{-iu_1+2iu_2}-1)p_3(v) + (e^{iu_3}-1)p_4(v)] rS(v)dv \Big\} \\
&\Big[\int_0^t [ie^{iu_2}p_2(v) + 2ie^{-iu_1+2iu_2}p_3(v)]rS(v)dv \Big]^2
\end{aligned} \tag{10}
$$

$$
\begin{aligned}
\mathbb{E}[Y(t)] &= i^{-1}\frac{\partial \psi_{\mathbf{C}(t)}(\mathbf{u})}{\partial u_2}\Big|_{\mathbf{u}=\mathbf{0}} = \int_0^t [p_2(v) + 2p_3(v)]rS(v)dv \\
\mathbb{E}[Y(t)^2] &= i^{-2}\frac{\partial^2 \psi_{\mathbf{C}(t)}(\mathbf{u})}{\partial^2 u_2}\Big|_{\mathbf{u}=\mathbf{0}} \\
&= \int_0^t [p_2(v) + 4p_3(v)]rS(v)dv + \Big[\int_0^t [p_2(v) + 2p_3(v)]rS(v)dv \Big]^2 \\
\mathbb{V}[Y(t)] &= \mathbb{E}[Y(t)^2] - (\mathbb{E}[Y(t)])^2 = \int_0^t [p_2(v) + 4p_3(v)]rS(v)dv
\end{aligned} \tag{11}
$$

$$
\begin{aligned}
\frac{\partial \psi_{\mathbf{C}(t)}(\mathbf{u})}{\partial u_3} &= \exp\Big\{ \int_0^t [(e^{iu_1}-1)p_1(v) + (e^{iu_2}-1)p_2(v) + (e^{-iu_1+2iu_2}-1)p_3(v) + (e^{iu_3}-1)p_4(v)] rS(v)dv \Big\} \\
&\int_0^t ie^{iu_3} p_4(v) rS(v)dv \\
\frac{\partial^2 \psi_{\mathbf{C}(t)}(\mathbf{u})}{\partial^2 u_3} &= \exp\Big\{ \int_0^t [(e^{iu_1}-1)p_1(v) + (e^{iu_2}-1)p_2(v) + (e^{-iu_1+2iu_2}-1)p_3(v) + (e^{iu_3}-1)p_4(v)] rS(v)dv \Big\} \\
&\int_0^t i^2 e^{iu_3} p_4(v) rS(v)dv + \\
&\exp\Big\{ \int_0^t [(e^{iu_1}-1)p_1(v) + (e^{iu_2}-1)p_2(v) + (e^{-iu_1+2iu_2}-1)p_3(v) + (e^{iu_3}-1)p_4(v)] rS(v)dv \Big\} \\
&\Big[\int_0^t ie^{iu_3} p_4(v) rS(v)dv \Big]^2
\end{aligned} \tag{12}
$$

$$
\begin{aligned}
\mathbb{E}[Z(t)] &= i^{-1} \frac{\partial \psi_{\mathbf{C}(t)}(\mathbf{u})}{\partial u_3}\Big|_{\mathbf{u}=\mathbf{0}} = \int_0^t p_4(v) rS(v)dv \\
\mathbb{E}[Z(t)^2] &= i^{-2} \frac{\partial^2 \psi_{\mathbf{C}(t)}(\mathbf{u})}{\partial^2 u_3}\Big|_{\mathbf{u}=\mathbf{0}} \\
&= \int_0^t p_4(v) rS(v)dv + \Big[\int_0^t p_4(v) rS(v)dv \Big]^2 \\
\mathbb{V}[Z(t)] &= \mathbb{E}[Z(t)^2] - (\mathbb{E}[Z(t)])^2 = \int_0^t p_4(v) rS(v)dv
\end{aligned} \tag{13}
$$

Using the second derivatives, we also obtain the covariances

$$
\begin{aligned}
\frac{\partial^2 \psi_{\mathbf{C}(t)}(\mathbf{u})}{\partial u_1 \partial u_2} &= \exp\Big\{ \int_0^t [(e^{iu_1}-1)p_1(v) + (e^{iu_2}-1)p_2(v) + (e^{-iu_1+2iu_2}-1)p_3(v) + (e^{iu_3}-1)p_4(v)] rS(v)dv \Big\} \\
&\int_0^t [-2i^2 e^{-iu_1+2iu_2} p_3(v)] rS(v)dv + \\
&\exp\Big\{ \int_0^t [(e^{iu_1}-1)p_1(v) + (e^{iu_2}-1)p_2(v) + (e^{-iu_1+2iu_2}-1)p_3(v) + (e^{iu_3}-1)p_4(v)] rS(v)dv \Big\} \\
&\int_0^t [ie^{iu_2} p_2(v) + 2ie^{-iu_1+2iu_2} p_3(v)] rS(v)dv \int_0^t [ie^{iu_1} p_1(v) - ie^{-iu_1+2iu_2} p_3(v)] rS(v)dv \\
\mathbb{E}[X(t)Y(t)] &= i^{-2} \frac{\partial^2 \psi_{\mathbf{C}(t)}(\mathbf{u})}{\partial u_1 \partial u_2}\Big|_{\mathbf{u}=\mathbf{0}} \\
&= -\int_0^t 2p_3(v)] rS(v)dv + \int_0^t [p_1(v) - p_3(v)] rS(v)dv \int_0^t [p_2(v) + 2p_3(v)] rS(v)dv \\
Cov[X(t)Y(t)] &= \mathbb{E}[X(t)Y(t)] - E[X(t)]E[Y(t)] = -\int_0^t 2p_3(v)] rS(v)dv
\end{aligned} \tag{14}
$$

$$
\begin{aligned}
\frac{\partial^2 \psi_{\mathbf{C}(t)}(\mathbf{u})}{\partial u_1 \partial u_3} &= \exp\Big\{ \int_0^t [(e^{iu_1}-1)p_1(v) + (e^{iu_2}-1)p_2(v) + (e^{-iu_1+2iu_2}-1)p_3(v) + (e^{iu_3}-1)p_4(v)]rS(v)dv \Big\} \\
&\quad \int_0^t ie^{iu_3} p_4(v) rS(v)dv \int_0^t [ie^{iu_1}p_1(v) - ie^{-iu_1+2iu_2}p_3(v)]rS(v)dv \\
\mathbb{E}[X(t)Z(t)] &= i^{-2} \frac{\partial^2 \psi_{\mathbf{C}(t)}(\mathbf{u})}{\partial u_1 \partial u_3}\Big|_{\mathbf{u}=\mathbf{0}} \\
&= \int_0^t [p_1(v) - p_3(v)]rS(v)dv \int_0^t p_4(v)rS(v)dv \\
Cov[X(t)Z(t)] &= \mathbb{E}[X(t)Z(t)] - E[X(t)]E[Z(t)] = 0
\end{aligned} \tag{15}
$$

$$
\begin{aligned}
\frac{\partial^2 \psi_{\mathbf{C}(t)}(\mathbf{u})}{\partial u_2 \partial u_3} &= \exp\Big\{ \int_0^t [(e^{iu_1}-1)p_1(v) + (e^{iu_2}-1)p_2(v) + (e^{-iu_1+2iu_2}-1)p_3(v) + (e^{iu_3}-1)p_4(v)]rS(v)dv \Big\} \\
&\quad \int_0^t ie^{iu_3} p_4(v) rS(v)dv \int_0^t [ie^{iu_2}p_2(v) + 2ie^{-iu_1+2iu_2}p_3(v)]rS(v)dv \\
\mathbb{E}[Y(t)Z(t)] &= i^{-2} \frac{\partial^2 \psi_{\mathbf{C}(t)}(\mathbf{u})}{\partial u_2 \partial u_3}\Big|_{\mathbf{u}=\mathbf{0}} \\
&= \int_0^t [p_2(v) + 2p_3(v)]rS(v)dv \int_0^t p_4(v)rS(v)dv \\
Cov[Y(t)Z(t)] &= \mathbb{E}[Y(t)Z(t)] - E[Y(t)]E[Z(t)] = 0
\end{aligned} \tag{16}
$$