1 CMV Level in Placenta

To study the how cmv goes through the placenta, we simplify the process by diffusion in 1 dimension, and treat the dynamic as homogeneous in other dimensions:

$$\frac{\partial c}{\partial t} = D\frac{\partial c^2}{\partial x^2} - \mu c. \tag{1.1}$$

with boundary conditions:

$$c = 0, \quad x = 0, \quad t \geq 0, \tag{1.2}$$

$$c = V_m(t), \quad x = l, \quad t \geq 0, \tag{1.3}$$

and initial condition:

$$c = 0, \quad 0 < x < l, \quad t = 0. \tag{1.4}$$

Here, c denotes the concentration of cmv. Constant D denotes the diffusion coefficient. Constant μ denotes the death rate of the cmv.

On the mother side, we consider CMV has reached equilibrium on the mother side, so we consider the the concentration of cmv is kept at a constant value.

On the infant side, we are interested in the early infection. Once a virus reaches the infant side, blood quickly wash it away.

Let us consider a simple case when clearance rate is 0 ($\mu = 0$) and $c_1(t) = V_m$, then we obtain:

$$\frac{\partial c}{\partial t} = D\frac{\partial c^2}{\partial x^2}, \tag{1.5}$$

with boundary conditions:

$$c = 0, \quad x = 0, \quad t \geq 0, \tag{1.6}$$

$$c = V_m, \quad x = l, \quad t \geq 0, \tag{1.7}$$

and initial condition:

$$c = 0, \quad 0 < x < l, \quad t = 0. \tag{1.8}$$

The solution (i.e, the concentration of the CMV across the placenta) given in the form of a trigonometrical series is

$$c = V_m\frac{x}{l} + \frac{2}{\pi}\sum_{1}^{\infty}\frac{V_m \cos(n\pi)}{n}\sin\frac{n\pi x}{l}\exp(-Dn^2\pi^2 t/l^2). \tag{1.9}$$

In fact, as long as the the clearance rate μ and diffusion coefficient D is a constant, the more general system given below also have analytic solution.

$$\frac{\partial c}{\partial t} = D\frac{\partial c^2}{\partial x^2} - \mu c. \tag{1.10}$$

with boundary conditions:

$$c = c_1(t), \quad x = 0, \quad t \geq 0, \tag{1.11}$$

$$c = V_m(t), \quad x = l, \quad t \geq 0, \tag{1.12}$$

and initial condition:

$$c = f(x), \quad 0 < x < l, \quad t = 0. \tag{1.13}$$

A change of variable $q = ce^{\mu t}$ turns (1.10) into the following form:

$$\frac{\partial q}{\partial t} = D\frac{\partial q^2}{\partial x^2}. \tag{1.14}$$

with boundary conditions:

$$q = c_1(t)e^{\mu t} = b_1(t), \quad x = 0, \quad t \geq 0, \tag{1.15}$$

$$q = V_m(t)e^{\mu t} = b_2(t), \quad x = l, \quad t \geq 0, \tag{1.16}$$

and initial condition:

$$q = f(x), \quad 0 < x < l, \quad t = 0. \tag{1.17}$$

The procedure to solve (1.14) using Fourier transform is included in appendix. Here we give the result:

$$\begin{aligned}
q(x,t) &= s(x,t) + v(x,t) \\
s(x,t) &= \frac{b_2(t) - b_1(t)}{l}x + b_1(t) \\
v(x,t) &= \sum_{n=1}^{\infty} T_n(t)\text{sin}\left(\frac{n\pi x}{l}\right) \\
T_n(t) &= \exp(-D\left(\frac{n\pi x}{l}\right)^2 t)\left(C_n + \int_0^t \exp(-D\left(\frac{n\pi x}{l}\right)^2 \tau)Q_n(\tau)d\tau\right) \\
Q_n(t) &= -\frac{2}{l}\int_0^L \partial_t s(x,t)\text{sin}\left(\frac{n\pi x}{l}\right)dx \\
C_n &= \frac{2}{l}\int_0^L (f(x) - s(x,0))\text{sin}\left(\frac{n\pi x}{l}\right)dx
\end{aligned} \tag{1.18}$$

2 Number of viruses that Entered the Infant

To obtain number of viruses that enter the infant, denoted by C, we can use the following formula:

$$C = \int_0^T D\frac{\partial c}{\partial x}\bigg|_{x=0} (\text{Surface area of placenta})\ dt \tag{2.1}$$

Now let us continue the calculation with the simple case: when clearance rate is 0 ($\mu = 0$) and $c_1(t) = V_m$ as an example. Since c given in (1.9) is a solution to the diffusion equation, we can calculate the $\frac{\partial c}{\partial x}$ by differentiating (1.9) term by term. Then the flux through the infant side is given by:

$$\left.\frac{\partial c}{\partial x}\right|_{x=0} = \frac{V_m}{l} + \frac{V_m}{l}\sum_{1}^{\infty} 2(-1)^n \exp(-Dn^2\pi^2 t/l^2), \tag{2.2}$$

Plugging into (2.1) gives:

$$\frac{DV_m}{l}\int_0^T \left(1 + \sum_{1}^{\infty} 2(-1)^n \exp(-Dn^2\pi^2 t/l^2)\right) dt$$
$$\times \text{ (Surface area of placenta) }.$$

Note that:

$$\begin{aligned}\sum_{1}^{\infty}(-1)^n \exp(-Dn^2\pi^2 t/l^2) &\leq \sum_{1}^{\infty} \exp(-Dn^2\pi^2 t/l^2) \\ &\leq \int_0^{\infty} \exp(-D\pi^2 t/l^2 x^2) dx \leq \infty.\end{aligned} \tag{2.3}$$

Since (2.3) shows the series is absolutely convergent, with some algebra, we can apply Fubini–Tonelli theorem to change the order of summation and integration.

$$\begin{aligned}&\left|\int_0^T \sum_{n=1}^{\infty}(-1)^n \exp(-Dn^2\pi^2 t/l^2)\exp(-\mu t)dt\right| \\ =&\left| -\int_0^T \sum_{k=1}^{\infty}\left(\exp(-D(2k-1)^2\pi^2/l^2 t) - \exp(-D(2k)^2\pi^2/l^2 t)\right)\exp(-\mu t)dt\right| \\ =&\left| -\sum_{k=1}^{\infty}\int_0^T \left(\exp(-(D(2k-1)^2\pi^2/l^2+\mu)t) - \exp(-(D(2k)^2\pi^2/l^2+\mu)t)\right)dt\right| \\ =&\left| -\sum_{k=1}^{\infty}\int_0^T \left(\exp(-a_1 t) - \exp(-a_2 t)\right)dt\right| \\ =&\left| -\sum_{k=1}^{\infty}\left(\frac{1-e^{-a_1 T}}{a_1} - \frac{1-e^{-a_2 T}}{a_2}\right)\right| \\ \leq&\left|\sum_{k=1}^{\infty}\frac{1}{a_1} + \sum_{k=1}^{\infty}\frac{1}{a_2}\right| \\ =&\left|\sum_{k=1}^{\infty}\frac{C}{k^2}\right| < \infty\end{aligned} \tag{2.4}$$

The total amount of viruses C which has passed through the membrane between 0 to T (per unit surface area):

$$C = \frac{DV_mT}{l} + \frac{2V_ml}{\pi^2}\sum_1^\infty(-1)^n\frac{1-\exp(-TDn^2\pi^2/l^2)}{n^2}. \tag{2.5}$$

Note that, if we use time-varying boundary condition on the mother side, the result will be different from using the average concentration of CMV over the whole pregnancy. Clearly, we can apply the same procedure with the more general setup given in (1.1) with solution given by (1.18), and we will treat the general case in the appendix. Since the total number of viruses that entered the infant throughout pregnancy is not necessarily an integer, we use a Poisson distribution with mean and variance given by (2.1) to turn it into an integer for further uses.

3 Viral Dynamics in Mother

To reflect the viral dynamics in mother, we use a mother proposed by [?] given below:

$$\begin{aligned}
dV_m/dt &= n\delta R_I - cV - fkR_SV,\\
dE/dt &= (1-\epsilon_S)\left(\lambda_E\left(1-\frac{E}{e}\right)E + \rho V\right),\\
dR_I/dt &= kR_SV - \delta R_I - (1-\epsilon_S)mER_I + \alpha_0R_L - \kappa R_I,\\
dR_S/dt &= \lambda_{rep}\left(1-\frac{R_S}{r_S}\right)R_S - kR_SV,\\
dR_L/dt &= \lambda_{rep}\left(1-\frac{R_L}{r_L}\right)R_S + \kappa R_I.
\end{aligned} \tag{3.1}$$

where V denotes viral load (free virus) per μl-blood, E denotes virus-specific immune effector cells per μl-blood, R_I, R_S, and R_L denotes actively-infected, susceptible cells, and latently-infected cells per μl-blood respectively.

With appropriate initial condition, we can obtain the viral load in mother $V(t)$ during pregnancy. We can use a polynomial to approximate $V(t)$

4 Viral Dynamics in Infant

Now let us consider the viral dynamics inside of an infant.

If there are many viruses inside the infant, it is reasonable to use a system of ordinary differential equations to describe the dynamics: Here S denotes susceptible cells, L denotes latent cells, I denotes infected cells, and V denotes virus.

$$
\begin{aligned}
dS/dt &= \lambda - \delta_s S - \beta SV \\
dL/dt &= \beta SV - \alpha L \\
dI/dt &= \alpha L - \delta_I I \\
dV/dt &= pI - \mu V
\end{aligned}
\tag{4.1}
$$

For the parameters, $\delta_s = 1/4.5$ is death rate of susceptible cells, $\lambda = \delta_s * S_0$ is production of new susceptible cells, $\beta = 3 * 10^{-12}$ is infection rate, $\alpha = 1$ is the rate latent cells convert into infected cells, $\delta_I = 0.77$ is the death rate of the infected cell, $p = 1600$ is the production of new virus, and $\mu = 2$ is the death rate of virus. With this model, we can calculate the basic reproduction number R_0, which is given by $\frac{p\beta\lambda}{\mu\delta_S\delta_I}$.

This model is not suitable when V_0 is small, so we can use an analogous stochastic model: we ignore the dynamics of the susceptible cells since the number of susceptible cells that a viruses encounter during its lifetime is relatively a constant. A susceptible cell can go through a latent stage or become an infected cell directly, depending on the type of the susceptible cell. So either of these following two models can happen.

Model 1: Susceptible cell with latent stage:

$$
\begin{array}{rll}
S \to L & \text{with} & c_1 = \beta SV, \\
L \to \phi & \text{with} & V_m = \delta_I, \\
L \to I & \text{with} & c_3 = \alpha, \\
I \to \phi & \text{with} & c_4 = \delta_I, \\
\phi \to V & \text{with} & c_5 = p, \\
V \to \phi & \text{with} & c_6 = \mu.
\end{array}
\tag{4.2}
$$

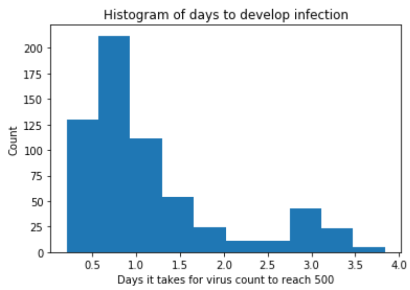
Model 2: Susceptible cell without latent stage:

$$
\begin{array}{rll}
S \to I & \text{with} & c_1 = \beta SV, \\
I \to \phi & \text{with} & V_m = \delta_I, \\
\phi \to V & \text{with} & c_3 = p, \\
V \to \phi & \text{with} & c_4 = \mu.
\end{array}
\tag{4.3}
$$

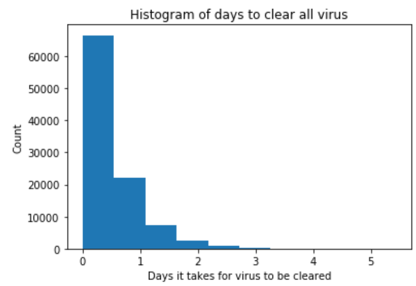
Therefore, if the ratio between the susceptible cells that go through latent stage and the susceptible cells that become infected cells is $r : (1-r)$, we draw a uniform random variable s between 0 and 1, and if $s < r$, we run model 1 given by (4.2), else if $s > r$, we run model 2 given by (4.3) (In our sample runs, we use $r = 0.5$). Note that in (4.2), we include the dynamics where latent cell can die as well. With initial values $S_0 = 400$, $L_0 = 0$, $I_0 = 0$, $V_0 = 1$, we run Gillespie algorithm 10^6 times with two stopping criteria: 1. no more viruses is left; 2. viruses count has reached 500.

Now that we have an rate of infection when there is only one virus, we can calculate the infection if there are $n = 330.85$ viruses (calculated using (2.1)) that try to infect the infant independently:

$$\text{Probability of Infection} = 1 - (1 - 0.0533\%)^{330.85} = 0.1617 = 16.17\%. \quad (4.4)$$



(a) On average, it takes 1.23 days to develop an infection.



(b) On average, it takes 0.49 days to clear all viruses.

Figure 1: Sample result from running Gillespie algorithm 10^6 times. Out of these runs, infection is developed 533 times. The probability of developing an infection 0.0533%.

5 Probability of CMV Transmission through Placenta

In Section 2, we obtain the total number of viruses that enter the infant throughout the pregnancy. Since these viruses enter at different time, we consider the dynamics separately. If any of the viruses that entered the placenta reproduce to reach 500 copies as described in Section 4, we consider the infant is infected with CMV. One sample result of 10^6 runs, CMV infection developed 162,800 times;

Algorithm 1 Probability of CMV Transmission through Placenta

```
MaxIter ← 5,000
NumOfViruses ← Poisson(C, C, MaxIter)
Count ← 0
for j=1:MaxIter do
  for i=1:NumOfViruses[j] do
    Gillespie Algorithm for viral dynamics in infant
  end for
  if Infected then
    count ← count + 1
  end if
end for
```

thus, giving an infection rate of 16.28%. CMV is transmitted from mother to fetus in approximately 35% of pregnancies in which a maternal primary infection occurs. Higher value of concentration on the mother side will bring this probability higher.

6 Parameters used

Parameter	Description	Value	Unit	Source
D	Diffusion inside of placenta	0.0069	$mm^2 \cdot day^{-1}$	
S_0	Number of target cell a virus can encounter	400	day^{-1}	
μ	Clearance rate of CMV	2	day^{-1}	
β	Infection rate of CMV	$0.0012/S_0$	day^{-1}	
δ_I	Death rate of latent cells and infected cells	0.77	day^{-1}	
α	Conversion rate from latent cells to infected cells	1	day^{-1}	
p	Production rate of viruses	1600	day^{-1}	
r	Percentage of different type of target cells	0.5	-	

7 Appendix

Here we explain how to solve the diffusion equation in 1D with time-varying boundary condition.

$$\frac{\partial q}{\partial t} = D\frac{\partial q^2}{\partial x^2}. \tag{7.1}$$

with boundary conditions:

$$q = c_1(t)e^{\mu t} = b_1(t), \quad x = 0, \quad t \geq 0, \tag{7.2}$$

$$q = V_m(t)e^{\mu t} = b_2(t), \quad x = l, \quad t \geq 0, \tag{7.3}$$

and initial condition:

$$q = f(x), \quad 0 < x < l, \quad t = 0. \tag{7.4}$$

We assume the solution to be of the partitioned form:

$$q(x,t) = s(x,t) + v(x,t)$$

So that:

$$s_t + v_t = Ds_{xx} + Dv_{xx} \tag{7.5}$$

Translating the boundary/initial conditions:

$$s(x,0) + v(x,0) = f(x)$$
$$s(0,t) + v(0,t) = b_1(t)$$
$$s(l,t) + v(l,t) = b_2(t)$$

We assume $s(x,t)$ to be linear in x but time-dependent, so the general form of $s(x,t)$ is:

$$s(x,t) = a(t)x + b(t) \tag{7.6}$$

So:

$$s_{xx} = 0$$

So with $s(0,t)$ and $s(l,t)$ we get:

$$b(t) = b_1(t)$$
$$a(t)L + b(t) = b_2(t)$$
$$a(t) = \frac{b_2(t) - b_1(t)}{l}$$

Plugging in to (7.6) gives

$$s(x,t) = \frac{b_2(t) - b_1(t)}{l}x + b_1(t)$$

From (7.5) and $s_{xx} = 0$, we get:

$$v_t = Dv_{xx} - s_t$$

We solve the homogeneous equation first:

$$v_t = Dv_{xx}$$

With boundary conditions:

$$v(0,t) = 0, \quad v(l,t) = 0$$

Using the Ansatz:

$$v(x,t) = X(x)T(t)$$

Obtaining separation of variables:

$$\frac{1}{D}\frac{T'}{T} = \frac{X''}{X} = -m^2$$

ODE for $X(x)$:

$$X'' + m^2X = 0, \quad X = c_1 \cos mx + c_2 \sin mx$$

With boundary conditions:

$$c_1 = 0$$
$$m = \frac{n\pi}{l}, n = 1, 2, 3....$$
$$X_n(x) = \sin\left(\frac{n\pi x}{l}\right)$$

Now for the non-homogeneous PDE:

$$v_t = Dv_{xx} - s_t$$

With boundary/initial conditions:

$$v(0,t) = 0, \quad v(l,t) = 0$$
$$v(x,0) = f(x) - s(x,0)$$

Assume the solution to be of the form:

$$v(x,t) = \sum_{n=1}^{+\infty} T_n(t)X_n(x)$$
$$s_t = \frac{b_2'(t) - b_1'(t)}{l}x + b_1'(t) = -\sum_{n=1}^{+\infty} Q_n(t)X_n(x)$$
$$Q_n(t) = -\frac{\int_0^l s_t X_n(x)dx}{\int_0^l X_n(x)X_n(x)dx}$$

Our solution must of course obey the original equation, so:

$$\frac{\partial}{\partial t}\sum_{n=1}^{+\infty} T_n(t)X_n(x) = D\frac{\partial^2}{\partial t^2}\left[\sum_{n=1}^{+\infty} T_n(t)X_n(x)\right] + \sum_{n=1}^{+\infty} Q_n(t)X_n(x)$$

We know that:

$$X_n''(x) = -m^2 X_n(x)$$

So:

$$\sum_{n=1}^{+\infty} T_n'(t)X_n(x) = \sum_{n=1}^{+\infty} -Dm^2 T_n(t)X_n(x) + \sum_{n=1}^{+\infty} Q_n(t)X_n(x)$$
$$\sum_{n=1}^{+\infty} [T_n'(t) + Dm^2 T_n(t)]X_n(x)] = \sum_{n=1}^{+\infty} Q_n(t)X_n(x)$$

So that:

$$T_n'(t) + Dm^2 T_n(t) = Q_n(t)$$

Solve with an integration factor to:

$$T_n(t) = e^{-Dm^2 t}\int_0^t e^{Dm^2\tau}Q_n(\tau)d\tau + C_n e^{-Dm^2 t}$$

Using the initial condition:

$$v(x,0) = f(x) - s(x,0) = \sum_{n=1}^{+\infty} T_n(0)X_n(x) = \sum_{n=1}^{+\infty} C_n X_n(x)$$

So:

$$C_n = \frac{\int_0^l [f(x) - s(x,0)]X_n(x)dx}{\int_0^l X_n(x)X_n(x)dx}$$

Now we consider the more general case when $V_m(t)$ is solved from the ODE system (3.1) and approximated by a cubic polynomial $V_m(t) = at^3 + bt^2 + ct + d$, $c_1(t) = 0$, $f(x) = 0$, and there is also clearance rate mu. From the solution given in (1.18), we obtain that:

$$c(x,t) = q(x,t)e^{-\mu t} = s(x,t)e^{-\mu t} + v(x,t)e^{-\mu t} =: \tilde{s}(x,t) + \tilde{v}(x,t)$$

$$\tilde{s}(x,t) = \left(\frac{b_2(t) - b_1(t)}{l}x + b_1(t)\right)e^{-\mu t} = \left(\frac{(V_m(t)e^{\mu t} - 0)x}{l} + 0\right)e^{-\mu t} = \frac{V_m(t)x}{l}$$

$$\tilde{v}(x,t) = e^{-\mu t}\sum_{n=1}^{+\infty} T_n(t)\sin\left(\frac{n\pi x}{l}\right) = \sum_{n=1}^{+\infty} T_n(t)e^{-\mu t}\sin\left(\frac{n\pi x}{l}\right) := \sum_{n=1}^{+\infty} \tilde{T}_n(t)\sin\left(\frac{n\pi x}{l}\right)$$

$$\begin{aligned}
Q_n(t) &= -\frac{\int_0^l s_t X_n(x)dx}{\int_0^l X_n(x)X_n(x)dx} = -\frac{2}{l}\int_0^l s_t \sin\left(\frac{n\pi x}{l}\right)dx \\
&= -\frac{2}{l}(V_m(t)\mu + V_m'(t))e^{\mu t}\int_0^l \frac{x}{l}\sin\left(\frac{n\pi x}{l}\right)dx = \frac{2(-1)^n}{n\pi}(V_m(t)\mu + V_m'(t))e^{\mu t}
\end{aligned}$$

$$\begin{aligned}
C_n &= \frac{\int_0^l [f(x) - s(x,0)]X_n(x)dx}{\int_0^l X_n(x)X_n(x)dx} = \frac{2}{l}\int_0^l [f(x) - s(x,0)]\sin\left(\frac{n\pi x}{l}\right)dx \\
&= -\frac{2}{l}V_m(0)\int_0^l \frac{x}{l}\sin\left(\frac{n\pi x}{l}\right)dx = \frac{2(-1)^n}{n\pi}V_m(0)
\end{aligned}$$

For simplicity of notation, let $\alpha = Dm^2 + \mu$.

$$\begin{aligned}
\tilde{T}_n(t) &= e^{-Dm^2 t}e^{-\mu t}\int_0^t e^{Dm^2\tau}Q_n(\tau)d\tau + C_n e^{-Dm^2 t}e^{-\mu t} \\
&= e^{-\alpha t}\int_0^t e^{\alpha\tau}\frac{2(-1)^n}{n\pi}(V_m(\tau)\mu + V_m'(\tau))d\tau + C_n e^{-\alpha t} \\
&= \frac{2(-1)^n}{n\pi}\left(\underbrace{e^{-\alpha t}\int_0^t e^{\alpha\tau}(V_m(\tau)\mu + V_m'(\tau))d\tau}_{R(t)} + V_m(0)e^{-\alpha t}\right) \\
&= \frac{2(-1)^n}{n\pi}\left(R(t) + V_m(0)e^{-\alpha t}\right)
\end{aligned}$$

Then flux through the placenta can be easily calculated:

$$c(x,t) = \frac{V_m(t)}{l}x + \sum_1^\infty \sin\left(\frac{n\pi x}{l}\right)\frac{2(-1)^n}{n\pi}(R(t) + V_m(0)e^{-\alpha t}) \tag{7.7}$$

$$\partial_x c|_{x=0} = \frac{V_m(t)}{l} + \sum_1^\infty \frac{2(-1)^n l}{n^2\pi^2}(R(t) + V_m(0)e^{-\alpha t}) \tag{7.8}$$

$$\begin{aligned}\int_0^T D\partial_x c|_{x=0}dt &= \frac{D}{l}\underbrace{\int_0^T V_m(t)dt}_{\bar{V}_m(T)} + \sum_1^\infty \frac{2D(-1)^n}{l}\left(\underbrace{\int_0^T R(t)dt}_{\bar{R}(T)} + V_m(0)\frac{1-e^{-\alpha T}}{\alpha}\right) \\ &= \frac{D}{l}\int_0^T V_m(t)dt + \sum_1^\infty \frac{2D(-1)^n}{l} \\ &\quad * \left(\int_0^T e^{-\alpha t}\int_0^t e^{\alpha\tau}(V_m(\tau)\mu + V_m'(\tau))d\tau dt + V_m(0)\frac{1-e^{-\alpha T}}{\alpha}\right)\end{aligned} \tag{7.9}$$

Note that $\alpha = Dm^2 + \mu = D\frac{n^2\pi^2}{l^2} + \mu$ depends on n, this means that it will be much better if we have a closed form for $V_m(t)$. Otherwise, (7.9) will be rather difficult to calculate. We can approximate $V_m(t)$ using piece-wise functions, but we should keep in mind that the if we have n pieces, the number of integrals in $\bar{R}(t)$ we need to calculate is $\frac{n(n+1)}{2}$.

Now we explicitly use the assumption that $V_m(t) = at^3 + bt^2 + ct + d$, then $V_m(t)\mu + V_m'(t) = \mu at^3 + (\mu b + 3a)t^2 + (\mu c + 2b)t + (\mu d + c) =: a_1t^3 + b_1t^2 + c_1t + d_1$. then $R(t)$ can be calculated explicitly:

$$\begin{aligned}R(t) =& \frac{1}{\alpha^4}(-6a_1 + 6a_1e^{-\alpha t}) + \frac{1}{\alpha^3}(2b_1 - 2b_1e^{-\alpha t} + 6a_1t) \\ &+ \frac{1}{\alpha^2}(-c_1 + c_1e^{-\alpha t} - 2b_1t - 3a_1t^2) \\ &+ \frac{1}{\alpha}(d_1 - d_1e^{-\alpha t} + c_1t + b_1t^2 + a_1t^3)\end{aligned} \tag{7.10}$$

$$\bar{V}_m(T) = \frac{a}{4}T^4 + \frac{b}{3}T^3 + \frac{c}{2}T^2 + dT \tag{7.11}$$

$$\begin{aligned}\bar{R}(t) =& \frac{1}{\alpha^5}(6a_1 - 6a_1e^{-\alpha T}) + \frac{1}{\alpha^4}(-2b_1 + 2b_1e^{-\alpha T} - 6a_1T) \\ &+ \frac{1}{\alpha^4}(c_1 - c_1e^{-\alpha T} + 2b_1t + 3a_1T^2) \\ &+ \frac{1}{\alpha^2}(-d_1 + d_1e^{-\alpha T} - c_1t - b_1T^2 - a_1T^3) \\ &+ \frac{1}{\alpha}\left(\frac{a_1}{4}T^4 + \frac{b_1}{3}T^3 + \frac{c_1}{2}T^2 + d_1T\right)\end{aligned} \tag{7.12}$$