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Research article

A mathematical model of cell-mediated immune response to tumor

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Supplementary

S1. Equilibrium properties

According to the above discussion, the endemic equilibrium points of the model (2.3) satisfy the following two conditions:

(1) $T_i^* < p$;

(2) T_i^* $(i = 1, 2)$ are solutions that satisfy the following equation:

$$(3.42\times10^{-3}+\delta-1.7930376\times10^{-5}pq)T^2+(8.26512\times10^{-2}pq-3.42\times10^{-3}p-\delta p+1)T+25.7pq-p=0. \quad \text{(S1)}$$

Therefore, the existence of the equilibrium points of the model are shown in the Table S1.

According to Routh-Hurwitz theroem [32], the local geometric properties of equilibrium points are provided in Table S2 (except from 5 cases showing in Table 2).

S2. Parameters of the cases in the paper

Regarding parameters determination, we take Case 1–5 in Table 2 as an example. Simulation results of the cases 1,3–5 are given in the paper, but those of case 2 are given here.

Figure S1 gives the simulated results for this case with initial condition 1×10^4 NK cells, 1×10^2 CTLs and 1×10^6 tumor cells.

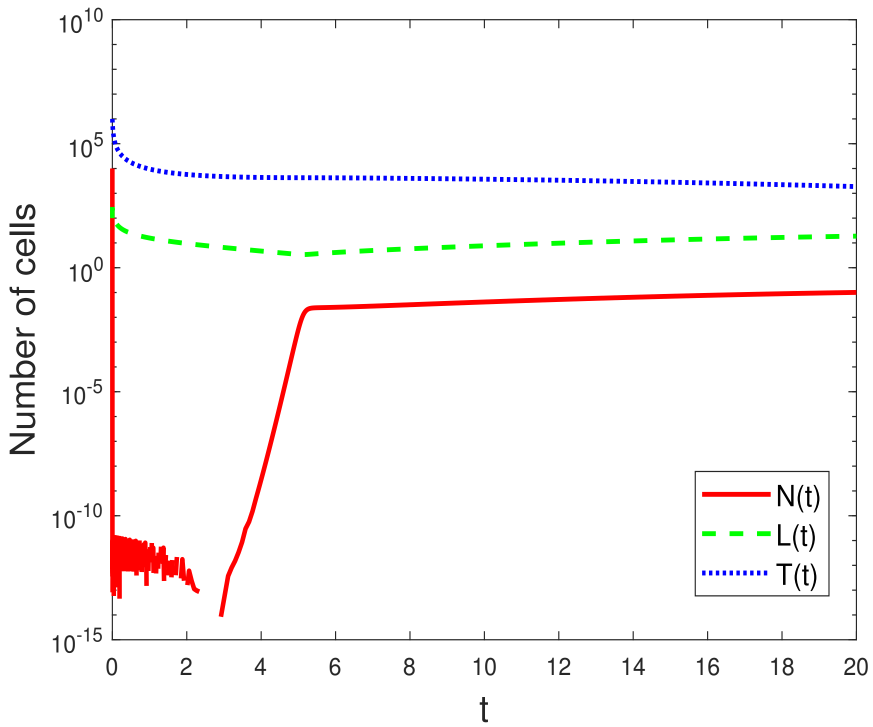

Figure S1. Numerical simulation of Case 2.

S2.1. Case 1

We set $\delta = 7 \times 10^{-5}$, since $\delta \in (6.97222 \times 10^{-5},\ 1.42627 \times 10^{-4})$. Then,

$$p_2^* = \frac{9.35037\times10^{-3}+4.58351\times10\delta}{2.29176\times10\delta^2+9.35037\times10^{-3}\delta+9.53738\times10^{-7}} = 7.2992 \times 10^3,$$
$$p_1^* = \frac{4.78723+2.64196\times10^3\delta}{9.76595\times10^{-4}-4.248276\delta} = 7.320449 \times 10^3$$

let $p = 7.31 \times 10^3$. So,

$$\begin{aligned}
A_1 &= 8.67446 \times 10^{-3} p = 63.323,\\
B_1 &= -(1.86273 \times 10^{-1} + 6.37055 \times 10^{-4} p + 1.65302 \times 10^{-1}\delta p + 1.028 \times 10^2 \delta) = -4.9284,\\
C_1 &= 6.84 \times 10^{-3} + 2\delta + 1.16964 \times 10^{-5} p + \delta^2 p + 6.84 \times 10^{-3}\delta p = 9.589 \times 10^{-2},\\
q_2^* &= \frac{-B_1 + \sqrt{B_1^2 - 4A_1C_1}}{2A_1} = 3.8977 \times 10^{-2}.
\end{aligned}$$

Thus, we obtain $q = 5.1 \times 10^{-1} > q_2^*$. Therefore, the model (2.3) is as follows:

$$\begin{aligned}
N^{'}(t) &= 7.3 \times 10^3 N(t)(1 - 5.1 \times 10^{-1} N(t)) - N(t)T(t),\\
L^{'}(t) &= N(t)T(t) - L(t) - 3.42 \times 10^{-3} L(t)T(t),\\
T^{'}(t) &= 25.7T(t)(1 - 2.04 \times 10^{-4} T(t)) - N(t)T(t) - 7 \times 10^{-5} L(t)T(t).
\end{aligned} \tag{S1}$$

Simulated results for this case, with initial condition 1×10^4 NK cells, 1×10^2 CTLs and 1×10^6 tumor cells, are pictured in Figure 2(a) in the paper.

S2.2. Case 2

Since $p \in (p^*,\ 1.53797 \times 10^6)$, and $\delta \in (1.06959,\ +\infty)$, we let $p = 5 \times 10^3$, $\delta = 1.09$. Then, $q = 3.95 \times 10^{-2}$ is fixed, because of $q_5^* = 1.24019 \times 10^{-4} + 3.62629 \times 10^{-2}\delta = 3.96506 \times 10^{-2}$.

Thus, the model (2.3) is as follows:

$$\begin{aligned} N'(t) &= 5 \times 10^3 N(t)(1 - 3.95 \times 10^{-2} N(t)) - N(t)T(t), \\ L'(t) &= N(t)T(t) - L(t) - 3.42 \times 10^{-3} L(t)T(t), \\ T'(t) &= 25.7T(t)(1 - 2.04 \times 10^{-4} T(t)) - N(t)T(t) - 1.09L(t)T(t). \end{aligned} \tag{S2}$$

S2.3. Case 3

Since $\delta \in (1.06959,\ +\infty)$, we let $\delta = 1.08$, fix $q = 6.2 \in (q_5^*,\ q_4^*)$, and thereby obtain

$$\begin{aligned} q_4^* &= 3.89106 \times 10^{-2} + 11.37734\delta = 12.3264378, \\ q_5^* &= 1.24019 \times 10^{-4} + 3.62629 \times 10^{-2}\delta = 3.9287951 \times 10^{-2}, \end{aligned}$$

Then,

$$p_3^* = \frac{3.42 \times 10^{-3} + \delta}{1.79303 \times 10^{-5} q} = 9.7458 \times 10^3,$$

and consequently we have $p = 5 \times 10^3 \in (p^*,\ p_3^*)$. Thus, $p = 5 \times 10^3$, $q = 6.2$, $\delta = 1.08$. Now the model (2.3) is as follows:

$$\begin{aligned} N'(t) &= 5 \times 10^3 N(t)(1 - 6.2N(t)) - N(t)T(t), \\ L'(t) &= N(t)T(t) - L(t) - 3.42 \times 10^{-3} L(t)T(t), \\ T'(t) &= 25.7T(t)(1 - 2.04 \times 10^{-4} T(t)) - N(t)T(t) - 1.08L(t)T(t). \end{aligned} \tag{S3}$$

Simulated results for this case, with initial condition 1×10^4 NK cells, 1×10^2 CTLs and 1×10^6 tumor cells, are pictured in Figure 2(b).

S2.4. Case 4

Since $p \in (0,\ p^*)$, $\delta \in (2.29881 \times 10^{-4},\ +\infty)$, we fix $p = 4.9 \times 10^3$, $\delta = 3 \times 10^{-2}$, and thereby obtain

$$\begin{aligned} A_1 &= 8.67446 \times 10^{-3} p = 42.504854, \\ B_1 &= -(1.86273 \times 10^{-1} + 6.37055 \times 10^{-4} p + 1.65302 \times 10^{-1}\delta p + 1.028 \times 10^2 \delta) = -30.6912365, \\ C_1 &= 6.84 \times 10^{-3} + 2\delta + 1.16964 \times 10^{-5} p + \delta^2 p + 6.84 \times 10^{-3}\delta p = 5.53963236, \\ q_1^* &= \frac{-B_1 - \sqrt{B_1^2 - 4A_1C_1}}{2A_1} = 0.357185. \end{aligned}$$

Then, we set $q = 3 \times 10^{-2} < q_1^*$. Thus, the model (2.3) is as follows:

$$\begin{aligned} N'(t) &= 4.9 \times 10^3 N(t)(1 - 3 \times 10^{-2} N(t)) - N(t)T(t), \\ L'(t) &= N(t)T(t) - L(t) - 3.42 \times 10^{-3} L(t)T(t), \\ T'(t) &= 25.7T(t)(1 - 2.04 \times 10^{-4} T(t)) - N(t)T(t) - 3 \times 10^{-2} L(t)T(t). \end{aligned} \tag{S4}$$

The simulated results for this case with the same initial condition are shown in Figure 2(c).

S2.5. Case 5

At first, we choose $p = 5 \times 10^3$, $q = 3 \times 10^{-2}$, because of $p \in (p^*,\ 5.12687 \times 10^3)$ and $q \in (1.64337 \times 10^{-11},\ q_3^*)$. Then,

$$
\begin{aligned}
A_2 &= -7.37297 \times 10^{-3} p^2 + 3.39861 \times 10 p + 1.05678 \times 10^4 = -3.82595 \times 10^3,\\
B_2 &= -2.61795 \times 10^{-5} p^2 + 1.23166 \times 10^{-1} p + 3.82979 \times 10 = -3.596 \times 10^{-1},\\
\delta^* &= \frac{-B_2 - \sqrt{B_2^2 - 4A_2C_2}}{2A_2} = 2.9648 \times 10^{-3},
\end{aligned}
$$

we set $\delta = 4 \times 10^{-3} > \delta^*$. Hence, the model (2.3) is as follows:

$$
\begin{aligned}
N'(t) &= 5 \times 10^3 N(t)(1 - 3 \times 10^{-2} N(t)) - N(t)T(t),\\
L'(t) &= N(t)T(t) - L(t) - 3.42 \times 10^{-3} L(t)T(t),\\
T'(t) &= 25.7 T(t)(1 - 2.04 \times 10^{-4} T(t)) - N(t)T(t) - 4 \times 10^{-3} L(t)T(t).
\end{aligned}
\tag{S5}
$$

Simulation results of this case are shown in Figure 2(d).

S3. Simulations of additional cases

In this subsection, we give simulations of the 12 cases in Table S2 for the stability of equilibrium points. Here, the parameters p, q, δ of each each case are shown in Table S3. The initial condition of all cases is 1×10^4 NK cells, 1×10^2 CTLs and 1×10^6 tumor cells.

Table S1. The existence of endemic equilibria of reduced model (2.3).

Endemic equilibrium	p	q	δ
E_1	$(p_2^*,\ p^*)$	$(q_3^*,\ q_1^*)$	$(2.20443 \times 10^{-4},\ 2.29881 \times 10^{-4})$
	$(5.88973 \times 10^3,\ p_1^*)$	$(q_2^*,\ +\infty)$	$(3.48713 \times 10^{-5},\ 6.97222 \times 10^{-5})$
	$(5.93509 \times 10^3,\ p_2^*)$	$(q_2^*,\ +\infty)$	$(6.97222 \times 10^{-5},\ 1.42627 \times 10^{-4})$
	$(p_3^*,\ p_2^*)$	$(q_3^*,\ q_1^*)$	$(6.97222 \times 10^{-5},\ 1.42627 \times 10^{-4})$
	$(p_2^*,\ p_1^*)$	$(q_2^*,\ +\infty)$	$(6.97222 \times 10^{-5},\ 1.42627 \times 10^{-4})$
	$(6.12015 \times 10^3,\ p_1^*)$	$(q_3^*,\ q_1^*)$	$(1.42627 \times 10^{-4},\ 2.29881 \times 10^{-4})$
	$(5.77715 \times 10^3,\ p_1^*)$	$(q_2^*,\ +\infty)$	$(1.42627 \times 10^{-4},\ 2.29881 \times 10^{-4})$
	$(5.77715 \times 10^3,\ +\infty)$	$(q_2^*,\ 5.40516 \times 10^{-2})$	$(2.29881 \times 10^{-4},\ \delta^*)$
	$(p^*,\ +\infty)$	$(q_4^*,\ +\infty)$	$(\delta^*,\ 3.65258 \times 10^3)$
	$(p^*,\ 1.53797 \times 10^6)$	$(q_3^*,\ q_5^*)$	$(1.06959,\ +\infty)$
E_2	$(0,\ p^*)$	$(0,\ q_1^*)$	$(0,\ 2.20443 \times 10^{-4})$
	$(0,\ p_2^*)$	$(0,\ q_1^*)$	$(2.20443 \times 10^{-4},\ 2.29881 \times 10^{-4})$
	$(p_2^*,\ p^*)$	$(0,\ q_3^*)$	$(2.20443 \times 10^{-4},\ 2.29881 \times 10^{-4})$
	$(0,\ p^*)$	$(0,\ q_1^*)$	$(2.29881 \times 10^{-4},\ +\infty)$
	$(p^*,\ 5.77715 \times 10^3)$	$(0,\ q_1^*)$	$(0,\ \delta^*)$
	$(p^*,\ 5.12687 \times 10^3)$	$(1.64337 \times 10^{-11},\ q_3^*)$	$(\delta^*,\ +\infty)$
E_1, E_2	$(p^*,\ p_3^*)$	$(q_5^*,\ q_4^*)$	$(1.06959,\ +\infty)$

where the values of the parameters are given by

$$
\begin{aligned}
p_1^* &= \tfrac{4.78723+2.64196\times10^3\delta}{9.76595\times10^{-4}-4.24827\delta},\\
p_2^* &= \tfrac{9.35037\times10^{-3}+4.58351\times10\delta}{2.29176\times10\delta^2+9.35037\times10^{-3}\delta+9.53738\times10^{-7}},\\
p_3^* &= \tfrac{3.42\times10^{-3}+\delta}{1.79303\times10^{-5}q},\\
p^* &= 4.90196\times10^3,\\
q_1^* &= \tfrac{-B_1-\sqrt{B_1^2-4A_1C_1}}{2A_1},\\
q_2^* &= \tfrac{-B_1+\sqrt{B_1^2-4A_1C_1}}{2A_1},\\
q_3^* &= \tfrac{1}{25.7},\\
q_4^* &= 3.89106\times10^{-2}+11.37734\delta,\\
q_5^* &= 1.24019\times10^{-4}+3.62629\times10^{-2}\delta,\\
\delta^* &= \tfrac{-B_2-\sqrt{B_2^2-4A_2C_2}}{2A_2},\\
A_1 &= 8.67446\times10^{-3}p,\\
B_1 &= -(1.86273\times10^{-1}+6.37055\times10^{-4}p+1.65302\times10^{-1}\delta p+1.028\times10^2\delta),\\
C_1 &= 6.84\times10^{-3}+2\delta+1.16964\times10^{-5}p+\delta^2p+6.84\times10^{-3}\delta p,\\
A_2 &= -7.37297\times10^{-3}p^2+3.39861\times10p+1.05678\times10^4,\\
B_2 &= -2.61795\times10^{-5}p^2+1.23166\times10^{-1}p+3.82979\times10,\\
C_2 &= 3.46979\times10^{-2}.
\end{aligned}
$$

Table S2. The stability of boundary equilibria and endemic equilibria of model (2.3).

No.	p	q	δ	O	E_0	E_1	E_2
1	$(p_2^*,\ p^*)$	$(q_3^*,\ q_1^*)$	$(2.20443\times10^{-4},\ 2.29881\times10^{-4})$	us	us	us	nE
2	$(5.88973\times10^3,\ p_1^*)$	$(q_2^*,\ +\infty)$	$(3.48713\times10^{-5},\ 6.97222\times10^{-5})$	us	us	lasn	nE
3	$(5.93509\times10^3,\ p_2^*)$	$(q_2^*,\ +\infty)$	$(6.97222\times10^{-5},\ 1.42627\times10^{-4})$	us	us	us	nE
4	$(p_3^*,\ p_2^*)$	$(q_3^*,\ q_1^*)$	$(6.97222\times10^{-5},\ 1.42627\times10^{-4})$	us	us	lasn	nE
5	$(6.12015\times10^3,\ p_1^*)$	$(q_3^*,\ q_1^*)$	$(1.42627\times10^{-4},\ 2.29881\times10^{-4})$	us	us	lasn	nE
6	$(5.77715\times10^3,\ p_1^*)$	$(q_2^*,\ +\infty)$	$(1.42627\times10^{-4},\ 2.29881\times10^{-4})$	us	us	lasf	*nE*
7	$(5.77715\times10^3,\ +\infty)$	$(q_2^*,\ 5.40516\times10^{-2})$	$(2.29881\times10^{-4},\ \delta^*)$	us	us	lasf	nE
8	$(p^*,\ +\infty)$	$(q_4^*,\ +\infty)$	$(\delta^*,\ 3.65258\times10^3)$	us	us	lasn	nE
9	$(0,\ p^*)$	$(0,\ q_1^*)$	$(0,\ 2.20443\times10^{-4})$	us	lasn	nE	us
10	$(0,\ p_2^*)$	$(0,\ q_1^*)$	$(2.20443\times10^{-4},\ 2.29881\times10^{-4})$	us	lasn	nE	us
11	$(p_2^*,\ p^*)$	$(0,\ q_3^*)$	$(2.20443\times10^{-4},\ 2.29881\times10^{-4})$	us	lasn	nE	us
12	$(p^*,\ p_1^*)$	$(0,\ q_1^*)$	$(0,\ \delta^*)$	us	lasn	nE	us

us: unstable saddle; lasn: locally asymptotically stable node; lasf: locally asymptotically stable focus; nE: nonexistent

Table S3. The values of the fixed parameter p, q, δ for each simulation graph.

No.	p	q	δ	*No.*	p	q	δ
1	4.9×10^3	3.96×10^{-2}	2.27×10^{-4}	2	6×10^3	6.2×10^{-1}	6.8×10^{-5}
3	7.2×10^3	3.9×10^{-2}	6.98×10^{-5}	4	6×10^3	3.9×10^{-2}	6.98×10^{-5}
5	1.5×10^4	3.9×10^{-2}	2.04×10^{-4}	6	1×10^4	1.03×10^{-2}	1.5×10^{-4}
7	7×10^3	5×10^{-2}	3×10^{-4}	8	6×10^3	4.02×10^{-2}	1×10^{-6}
9	1×10^3	9×10^{-5}	3.5×10^{-4}	10	4×10^3	1.98×10^{-2}	2.2×10^{-4}
11	4.7×10^3	1.24×10^{-2}	2.2×10^{-4}	12	5×10^3	1×10^{-3}	2×10^{-3}

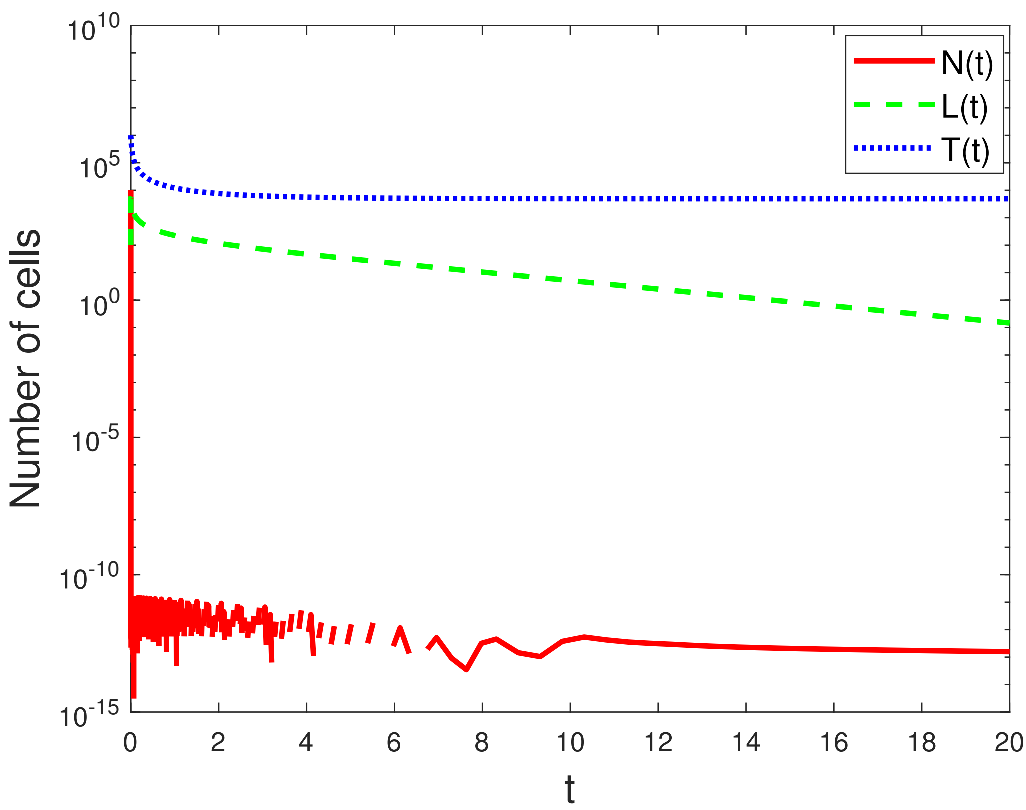

Figure S2. Numerical simulation of Case 1.

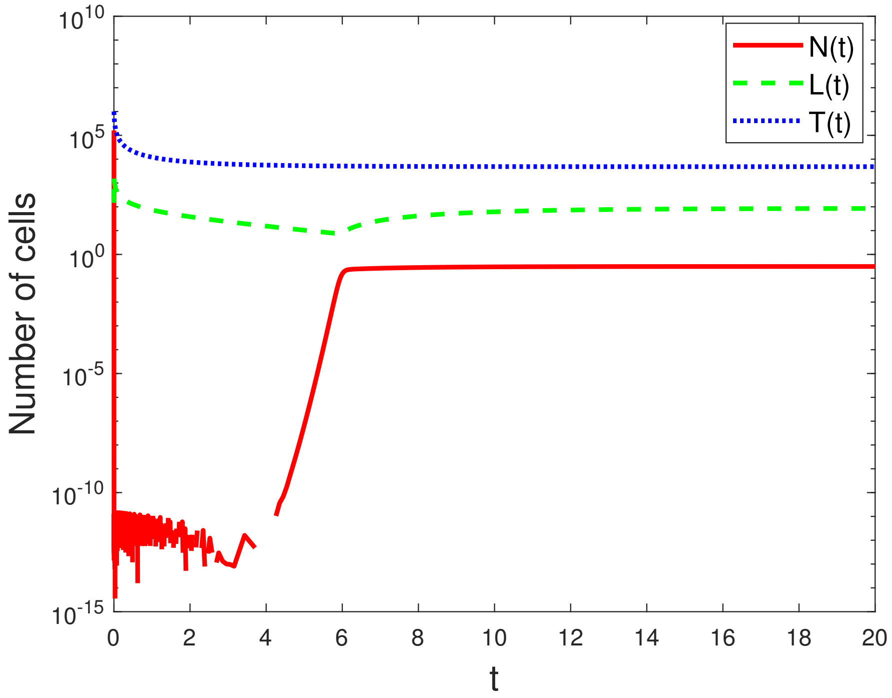

Figure S3. Numerical simulation of Case 2.

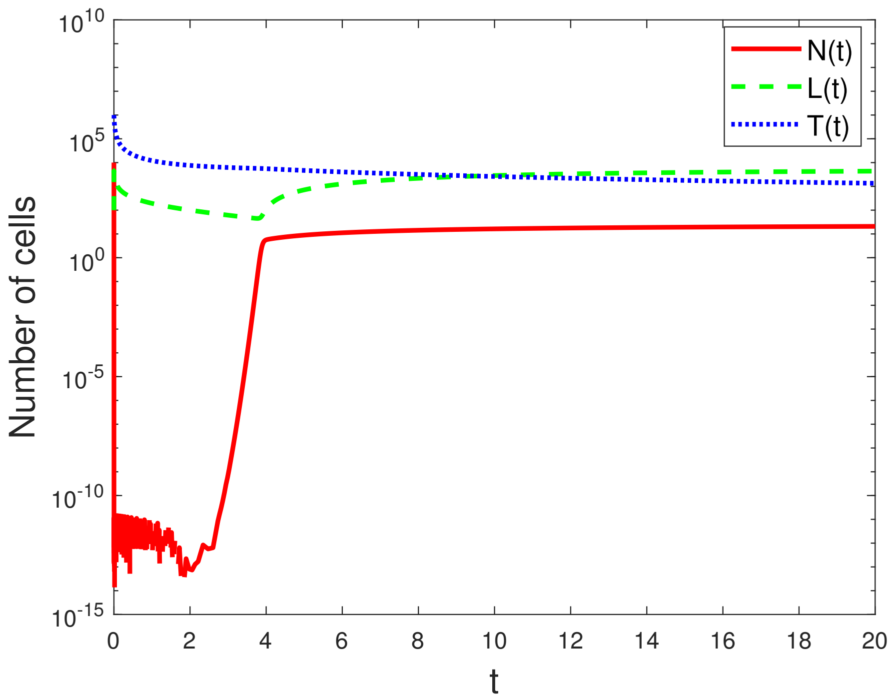

Figure S4. Numerical simulation of Case 3.

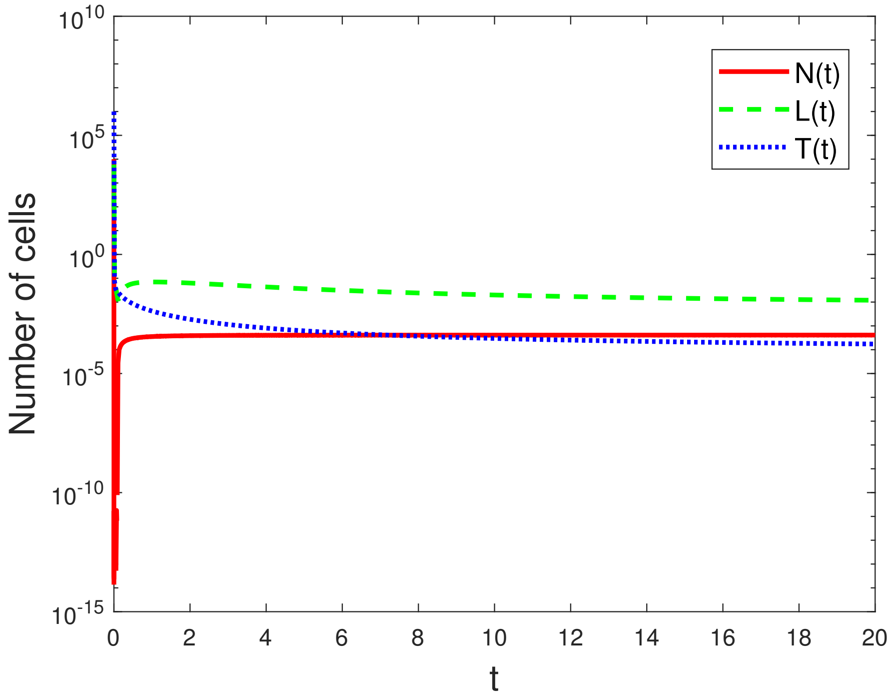

Figure S5. Numerical simulation of Case 4.

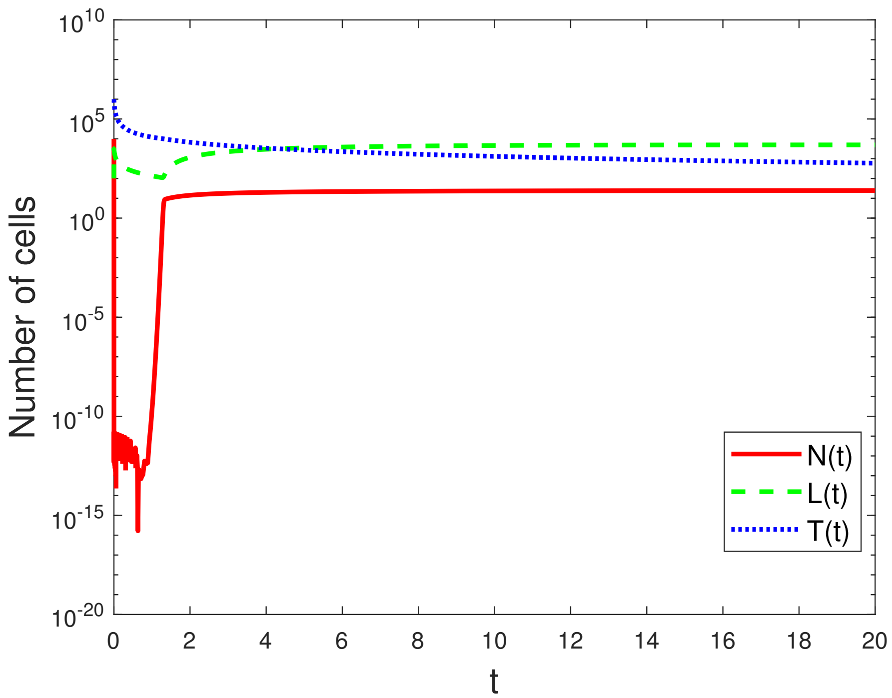

Figure S6. Numerical simulation of Case 5.

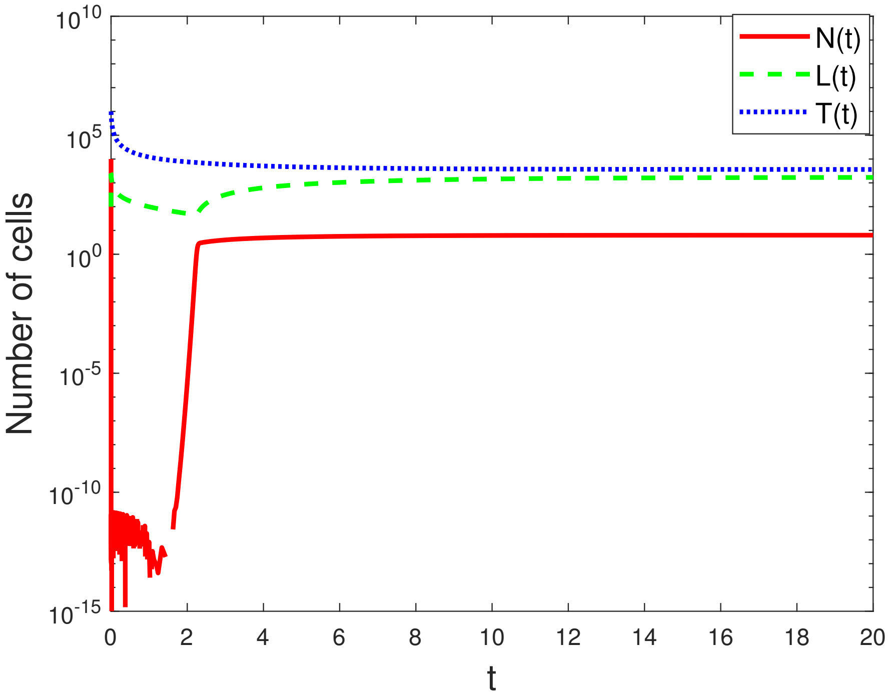

Figure S7. Numerical simulation of Case 6.

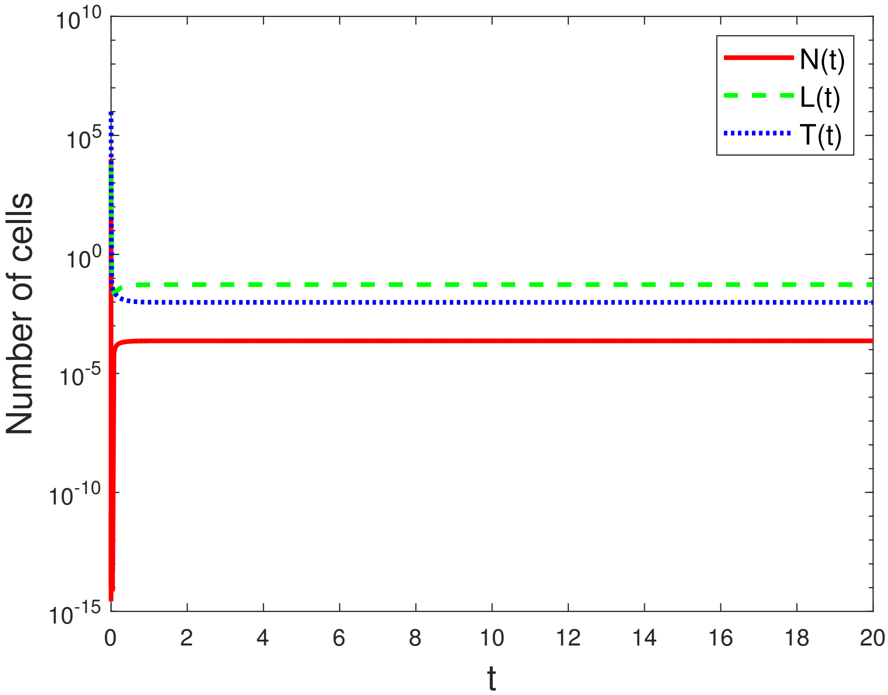

Figure S8. Numerical simulation of Case 7.

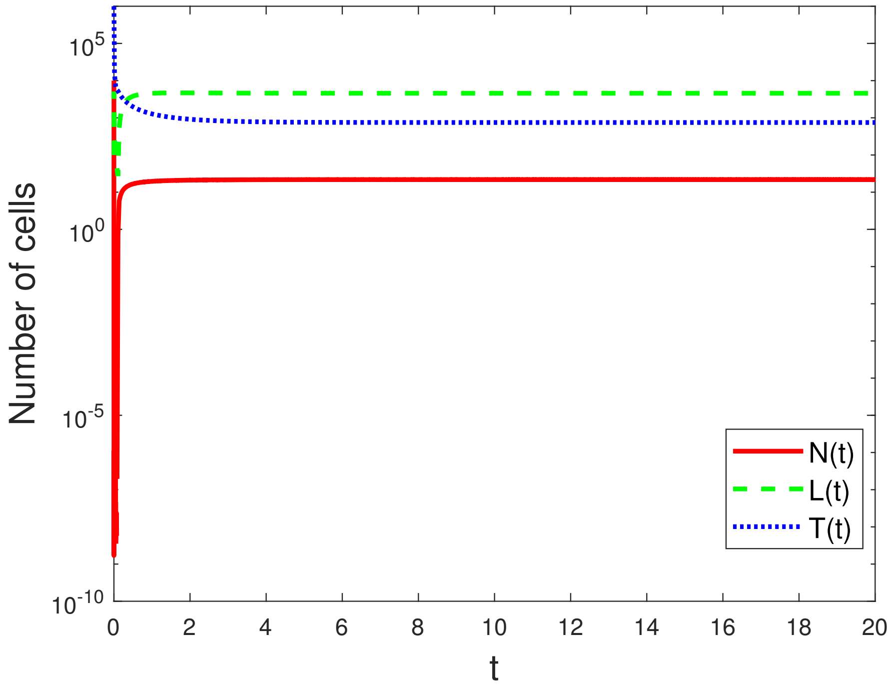

Figure S9. Numerical simulation of Case 8.

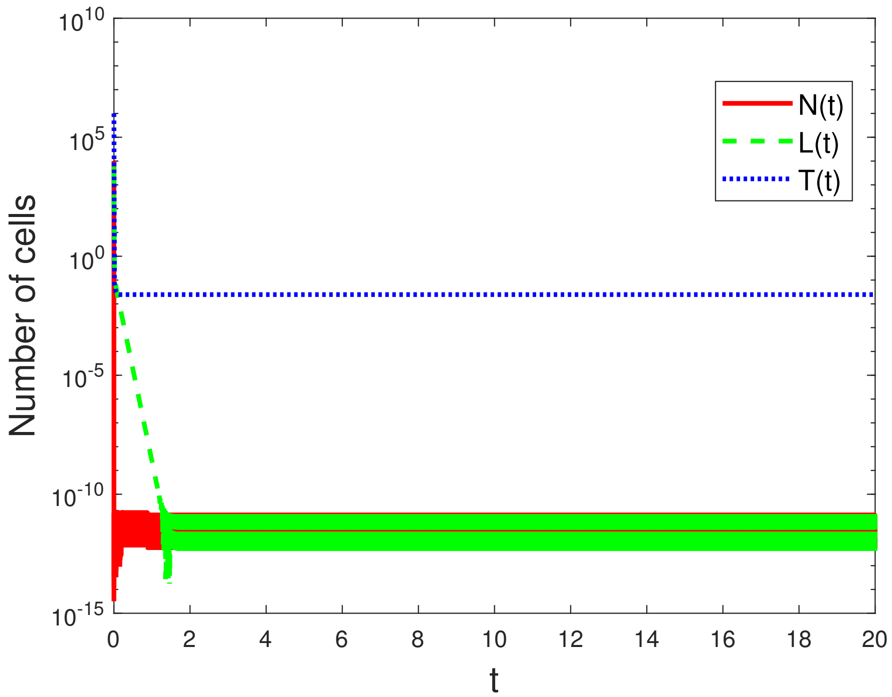

Figure S10. Numerical simulation of Case 9.

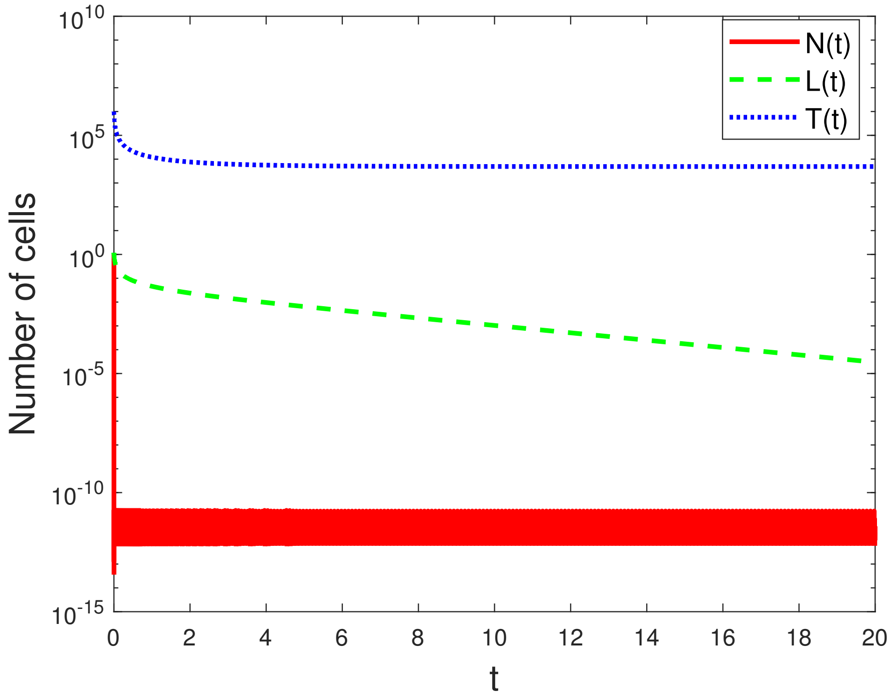

Figure S11. Numerical simulation of Case 10.

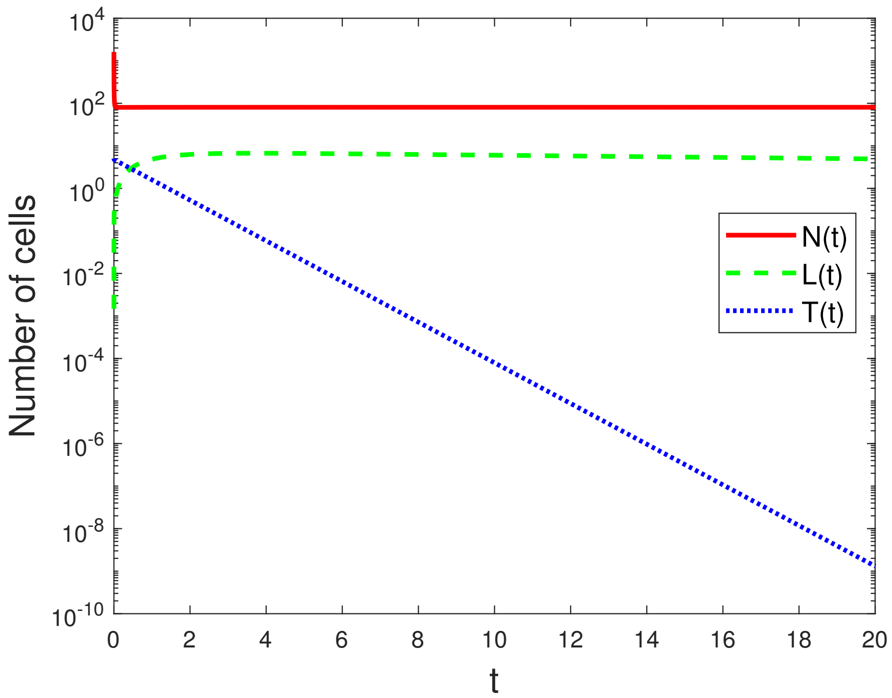

Figure S12. Numerical simulation of Case 11.

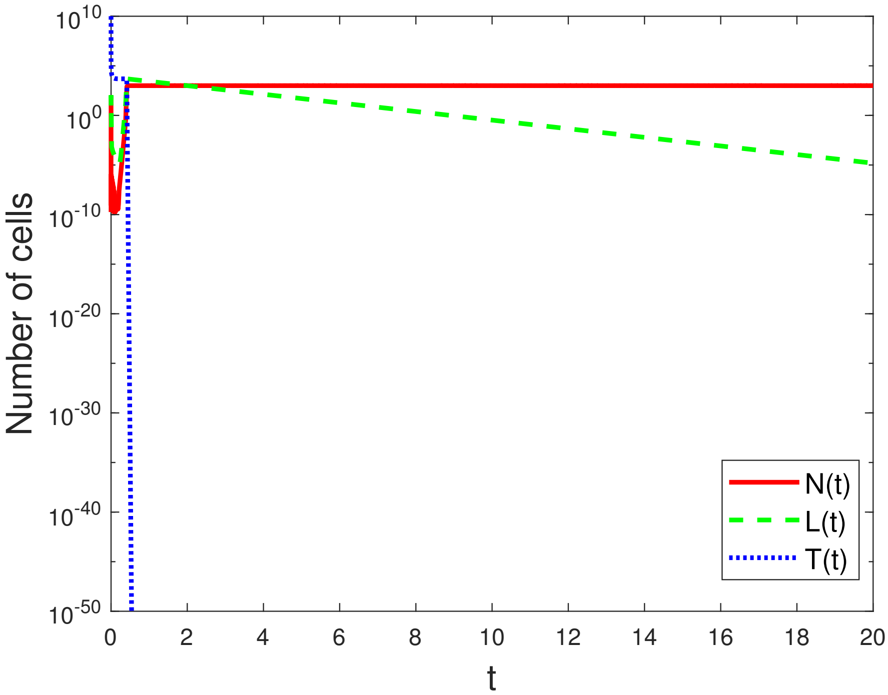

Figure S13. Numerical simulation of Case 12.