Mathematical Modeling and Analysis of Influenza In-host Infection Dynamics

(Supplemental Material)

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1. PRCC Tables

Number of Exposed Cases with 100 Runs

PRCC Values	ECases	β	r_D	$\frac{1}{\tau_E}$	$\frac{1}{\tau_I}$	p	c
0.8187650246	β	0	-6.785742	-3.480713	3.746287	-0.120890	5.128212
0.9736998142	r_D	6.785742	0	3.305029	10.53203	6.664851	11.91395
0.9314292228	$\frac{1}{\tau_E}$	3.480713	-3.305029	0	7.227001	3.359823	8.608925
0.5353914372	$\frac{1}{\tau_I}$	-3.746287	-10.53203	-7.227001	0	-3.867178	1.381925
0.8245864934	p	0.120890	-6.664851	-3.359823	3.867178	0	5.249103
0.373773754	c	-5.128212	-11.91395	-8.608925	-1.381925	-5.249103	0

Table 1: PRCC values and z-values from Sensitivity Analysis for the number of Exposed cases after 100 runs.

Number of Exposed Cases with 500 Runs

PRCC Values	ECases	β	r_D	$\frac{1}{\tau_E}$	$\frac{1}{\tau_I}$	p	c
0.8350660832	β	0	-17.80147	-9.483408	6.876220	-3.052344	9.009770
0.9816410302	r_D	17.80147	0	8.318066	24.67769	14.74913	26.81124
0.947821772	$\frac{1}{\tau_E}$	9.483408	-8.318066	0	16.35963	6.4310637	18.49318
0.6444732506	$\frac{1}{\tau_I}$	-6.876220	-24.67769	-16.35963	0	-9.928564	2.133550
0.8852335403	p	3.052344	-14.74913	-6.431064	9.928564	0	12.062114
0.5577896879	c	-9.009770	-26.81124	-18.49318	-2.133550	-12.06211	0

Table 2: PRCC values and z-values from Sensitivity Analysis for the number of Exposed cases after 500 runs.

Number of Exposed Cases with 1000 Runs

PRCC Values	ECases	β	r_D	$\frac{1}{\tau_E}$	$\frac{1}{\tau_I}$	p	c
0.8151506752	β	0	-24.54984	-12.57757	10.90514	-3.069671	13.27076
0.97781069	r_D	24.54984	0	11.97227	35.45497	21.48017	37.82059
0.9363062818	$\frac{1}{\tau_I}$	12.57757	-11.97227	0	23.48271	9.507898	25.84833
0.5732090415	$\frac{1}{\tau_I}$	-10.905138	-35.45497	-23.48271	0	-13.97481	2.365620
0.8565097409	p	3.069671	-21.48017	-9.507898	13.97481	0	16.34043
0.497528456	c	-13.27076	-37.82060	-25.84833	-2.365620	-16.34043	0

Table 3: PRCC values and z-values from Sensitivity Analysis for the number of Exposed cases after 1000 runs.

Number of Exposed Cases with 2000 Runs

PRCC Values	ECases	β	r_D	$\frac{1}{\tau_E}$	$\frac{1}{\tau_I}$	p	c
0.8068706569	β	0	-25.79477	-14.02252	10.34646	-4.476775	12.64307
0.9791609255	r_D	25.79477	0	11.77224	36.14122	21.31799	38.43784
0.9411410029	$\frac{1}{\tau_E}$	14.02252	-11.77224	0	24.36898	9.545748	26.66560
0.5738147717	$\frac{1}{\tau_I}$	-10.34646	-36.14122	-24.36898	0	-14.82323	2.296618
0.8665625053	p	4.476775	-21.31799	-9.545748	14.82323	0	17.11985
0.5005341624	c	-12.64307	-38.43784	-26.66560	-2.296618	-17.11985	0

Table 4: PRCC values and z-values from Sensitivity Analysis for the number of Exposed cases after 2000 runs.

Number of Infectious Cases with 100 Runs

PRCC Values	ICases	β	r_D	$\frac{1}{\tau_E}$	$\frac{1}{\tau_I}$	p	c
0.8472567402	β	0	-6.964773	4.965806	-2.916505	-0.378176	4.152177
0.9792463986	r_D	6.964773	0	11.93058	4.048267	6.586596	11.11695
0.4700769672	$\frac{1}{\tau_E}$	-4.965806	-11.93058	0	-7.882312	-5.343983	-0.813629
0.9326953513	$\frac{1}{\tau_I}$	2.916505	-4.048267	7.882312	0	2.538329	7.068682
0.8623432695	p	0.378176	-6.586596	5.343983	-2.538329	0	4.530353
0.5585956599	c	-4.152177	-11.11695	0.813629	-7.068682	-4.530353	0

Table 5: PRCC values and z-values from Sensitivity Analysis for the number of infectious cases after 100 runs.

Number of Infectious Cases with 500 Runs

PRCC Values	ICases	β	r_D	$\frac{1}{\tau_E}$	$\frac{1}{\tau_I}$	p	c
0.8365559793	β	0	-17.75696	12.29364	-8.860972	-1.900536	9.352198
0.9817173522	r_D	17.75696	0	30.05060	8.895991	15.85643	27.10916
0.4011149139	$\frac{1}{\tau_E}$	-12.29364	-30.05060	0	-21.15461	-14.19417	-2.941439
0.9441677021	$\frac{1}{\tau_I}$	8.860972	-8.895991	21.15461	0	6.960436	18.21317
0.8694655814	p	1.900536	-15.85643	14.19417	-6.960436	0	11.25273
0.5460298962	c	-9.352198	-27.10916	2.941439	-18.21317	-11.25273	0

Table 6: PRCC values and z-values from Sensitivity Analysis for the number of infectious cases after 500 runs.

Number of Infectious Cases with 1000 Runs

PRCC Values	ICases	β	r_D	$\frac{1}{\tau_E}$	$\frac{1}{\tau_I}$	p	c
0.8315170275	β	0	-25.046955	16.31431	-12.40345	-2.388506	14.042700
0.9808026026	r_D	25.04695	0	41.36126	12.64350	22.65845	39.08965
0.4301893193	$\frac{1}{\tau_E}$	-16.31431	-41.36126	0	-28.71776	-18.70282	-2.271609
0.9414034042	$\frac{1}{\tau_I}$	12.40345	-12.64350	28.71776	0	10.01494	26.44615
0.861809058	p	2.388506	-22.65845	18.70282	-10.014945	0	16.43121
0.5095921386	c	-14.04270	-39.08965	2.271609	-26.44615	-16.43121	0

Table 7: PRCC values and z-values from Sensitivity Analysis for the number of infectious cases after 1000 runs.

Number of Infectious Cases with 2000 Runs

PRCC Values	ICases	β	r_D	$\frac{1}{\tau_E}$	$\frac{1}{\tau_I}$	p	c
0.8128467366	β	0	-24.86361	15.42654	-12.41065	-2.127387	13.07770
0.9781273761	r_D	24.86361	0	40.29015	12.452960	22.73622	37.94131
0.4155834083	$\frac{1}{\tau_E}$	-15.42654	-40.29015	0	-27.83719	-17.55393	-2.348834
0.934515402	$\frac{1}{\tau_I}$	12.41065	-12.45296	27.83719	0	10.28326	25.48835
0.8428499052	p	2.127387	-22.73622	17.55393	-10.28326	0	15.20509
0.4989149404	c	-13.07770	-37.94131	2.348834	-25.48835	-15.20509	0

Table 8: PRCC values and z-values from Sensitivity Analysis for the number of infectious cases after 2000 runs.

Number of Deaths due to Infection with 100 Runs

PRCC Values	IDeath	β	r_D	$\frac{1}{\tau_E}$	$\frac{1}{\tau_I}$	p	c
0.9407753838	β	0	-7.561800	7.656622	9.969193	3.228404	4.614269
0.993537033	r_D	7.561800	0	15.21842	17.53099	10.79020	12.17607
0.5438874125	$\frac{1}{\tau_E}$	-7.656622	-15.21842	0	2.312571	-4.428218	-3.042353
0.2606645725	$\frac{1}{\tau_I}$	-9.969193	-17.53099	-2.312571	0	-6.740789	-5.354924
0.8527486582	p	-3.228404	-10.79020	4.428218	6.740789	0	1.385865
0.785927044	c	-4.614269	-12.17607	3.042353	5.354924	-1.385865	0

Table 9: PRCC values and z-values from Sensitivity Analysis for the number of deaths due to infection after 100 runs.

Number of Deaths due to Infection with 500 Runs

PRCC Values	IDeath	β	r_D	$\frac{1}{\tau_E}$	$\frac{1}{\tau_I}$	p	c
0.9197543749	β	0	-18.60324	15.13875	18.63044	5.698412	10.69252
0.9922511265	r_D	18.60324	0	33.74199	37.23368	24.30165	29.29576
0.5519881377	$\frac{1}{\tau_E}$	-15.13875	-33.74199	0	3.491687	-9.440340	-4.446228
0.3785686213	$\frac{1}{\tau_I}$	-18.63044	-37.23368	-3.491687	0	-12.93203	-7.937915
0.8407547826	p	-5.698412	-24.30165	9.440340	12.93203	0	4.994111
0.7187265837	c	-10.69252	-29.29576	4.446228	7.937915	-4.994111	0

Table 10: PRCC values and z-values from Sensitivity Analysis for the number of deaths due to infection after 500 runs.

Number of Deaths due to Infection with 1000 Runs

PRCC Values	IDeath	β	r_D	$\frac{1}{\tau_E}$	$\frac{1}{\tau_I}$	p	c
0.9217810715	β	0	-26.06837	21.11024	27.77618	8.389259	16.04781
0.9922063259	r_D	26.06837	0	47.17861	53.84455	34.45763	42.11618
0.5732780552	$\frac{1}{\tau_E}$	-21.11024	-47.17861	0	6.665937	-12.72098	-5.062429
0.3389729128	$\frac{1}{\tau_I}$	-27.77618	-53.84455	-6.665937	0	-19.38692	-11.72837
0.8407918016	p	-8.389259	-34.45763	12.72098	19.38692	0	7.658554
0.7063273652	c	-16.047813	-42.116183	5.062429	11.72837	-7.658554	0

Table 11: PRCC values and z-values from Sensitivity Analysis for the number of deaths due to infection after 1000 runs.

Number of Deaths due to Infection with 2000 Runs

PRCC Values	IDeath	β	r_D	$\frac{1}{\tau_E}$	$\frac{1}{\tau_I}$	p	c
0.9163586754	β	0	-26.12393	20.29580	26.30186	8.599075	15.34169
0.9916862511	r_D	26.12393	0	46.41973	52.42580	34.72301	41.46563
0.5743929833	$\frac{1}{\tau_E}$	-20.29580	-46.41973	0	6.006065	-11.69672	-4.954103
0.3663822842	$\frac{1}{\tau_I}$	-26.30186	-52.42580	-6.006065	0	-17.70279	-10.96017
0.8272994399	p	-8.599075	-34.72301	11.69672	17.70279	0	6.742620
0.7047181159	c	-15.34169	-41.46563	4.954103	10.96017	-6.742620	0

Table 12: PRCC values and z-values from Sensitivity Analysis for the number of deaths due to infection after 2000 runs.

Number of Virons Cleared with 100 Runs

PRCC Values	Vclear	β	r_D	$\frac{1}{\tau_E}$	$\frac{1}{\tau_I}$	p	c
0.522608818	β	0	-5.354223	3.686859	-1.179973	-7.023793	-12.02889
0.8795292887	r_D	5.354223	0	9.041083	4.174251	-1.669569	-6.674662
0.03333335911	$\frac{1}{\tau_E}$	-3.686859	-9.041083	0	-4.866832	-10.71065	-15.71574
0.6380352065	$\frac{1}{\tau_I}$	1.179973	-4.174251	4.866832	0	-5.843820	-10.84891
0.9247978822	p	7.023793	1.669569	10.71065	5.843820	0	-5.005093
0.9824390488	c	12.02889	6.674662	15.71574	10.84891	5.005093	0

Table 13: PRCC values and z-values from Sensitivity Analysis for the number of virons cleared after 100 runs.

Number of Virons Cleared with 500 Runs

PRCC Values	Vclear	β	r_D	$\frac{1}{\tau_E}$	$\frac{1}{\tau_I}$	p	c
0.4579386643	β	0	-12.28207	4.578262	-5.329070	-17.25895	-28.10644
0.8561042677	r_D	12.28207	0	16.86033	6.953001	-4.976876	-15.82437
0.1997799901	$\frac{1}{\tau_E}$	-4.578262	-16.86033	0	-9.907332	-21.83721	-32.68470
0.6830528232	$\frac{1}{\tau_I}$	5.329069	-6.953001	9.907332	0	-11.92988	-22.77737
0.921096069	p	17.25895	4.976876	21.83721	11.92988	0	-10.84749
0.9796390198	c	28.10644	15.82437	32.68470	22.77737	10.84749	0

Table 14: PRCC values and z-values from Sensitivity Analysis for the number of virons cleared after 500 runs.

Number of Virons Cleared with 1000 Runs

PRCC Values	Vclear	β	r_D	$\frac{1}{\tau_E}$	$\frac{1}{\tau_I}$	p	c
0.471311629	β	0	-17.67633	7.747615	-8.051663	-24.70053	-39.64880
0.8632206436	r_D	17.67633	0	25.42395	9.624670	-7.024193	-21.97247
0.1622547445	$\frac{1}{\tau_E}$	-7.747615	-25.42395	0	-15.79928	-32.44814	-47.39642
0.7031317985	$\frac{1}{\tau_I}$	8.051663	-9.624671	15.79928	0	-16.64886	-31.59714
0.9248272022	p	24.70053	7.024193	32.44814	16.64886	0	-14.94827
0.9798160961	c	39.64880	21.97247	47.39642	31.59714	14.94827	0

Table 15: PRCC values and z-values from Sensitivity Analysis for the number of virons cleared after 1000 runs.

Number of Virons Cleared with 2000 Runs

PRCC Values	Vclear	β	r_D	$\frac{1}{\tau_E}$	$\frac{1}{\tau_I}$	p	c
0.4925516387	β	0	-18.71137	7.684263	-8.508295	-25.19609	-40.97937
0.880954189	r_D	18.71137	0	26.39564	10.20308	-6.484718	-22.26800
0.19181046	$\frac{1}{\tau_E}$	-7.684263	-26.39564	0	-16.19256	-32.88036	-48.66363
0.7266771262	$\frac{1}{\tau_I}$	8.508295	-10.20308	16.19256	0	-16.68780	-32.47108
0.9317276171	p	25.19609	6.484718	32.88036	16.68780	0	-15.78328
0.9830270668	c	40.97937	22.26800	48.66363	32.47108	15.78328	0

Table 16: PRCC values and z-values from Sensitivity Analysis for the number of virons cleared after 2000 runs.

1.1. **Global stability of endermic equilibrium.** Recall the model

$$\frac{\mathrm{d}T}{\mathrm{d}t} = -\beta TV + r_D D \tag{1}$$

$$\frac{\mathrm{d}E}{\mathrm{d}t} = \beta TV - \frac{E}{\tau_E} \tag{2}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \frac{E}{\tau_E} - \frac{I}{\tau_I} \tag{3}$$

$$\frac{\mathrm{d}V}{\mathrm{d}t} = pI - cV \tag{4}$$

Theorem 1.1. *Let $X^* = (T^*, E^*, I^*, V^*)$ be a positive steady state of the system (1-4). Then X^* is globally asymptotically stable with respect to initial conditions in $\overset{\circ}{\Omega}$ if $T^* < T, E^* < E, I^* < I, V^* < V$ and $V* < 4V$, and $pI < cV$.*

Proof. Let us consider the system (1)-(4), we will prove the existence of a Lyapunov function. Let us notice that any steady state holds the following steady state equations:

$$\beta T^* V^* = r_D(N - T^* - E^* - I^*) = \frac{E^*}{\tau_E} = \frac{I^*}{\tau_I} \tag{5}$$

$$pI^* = cV^* \tag{6}$$

We define the function

$$L(\mathbf{X}) = \int_{T^*}^{T} 1 - \frac{T^*}{x}dx + \int_{E^*}^{E} 1 - \frac{E^*}{x}dx + \int_{I^*}^{I} 1 - \frac{I^*}{x}dx + \alpha \int_{V^*}^{V} 1 - \frac{V^*}{x}dx \tag{7}$$

where α is a positive constant, defined later. Notice that for any $X \in \Omega$ is such that $V(X) \geq 0$ where $V(X) = 0$ if and only if $X = X^*$. Furthermore, notice that

$$\begin{aligned} \dot{L(\mathbf{X})} = \nabla(L(\mathbf{X}) \cdot \dot{\mathbf{X}} &= \left(1 - \frac{T^*}{T}\right)\dot{T} + \left(1 - \frac{E^*}{E}\right)\dot{E} + \left(1 - \frac{I^*}{I}\right)\dot{I} + \alpha\left(1 - \frac{V^*}{V}\right)\dot{V} \\ &= \big(1 - \frac{T^*}{T}\big)\big(-\beta TV + r_D(N - T - E - I)\big) \\ &+ \big(1 - \frac{E^*}{E}\big)\big(\beta TV - \frac{E}{\tau_E}\big) + \big(1 - \frac{I^*}{I}\big)\big(\frac{E}{\tau_E} - \frac{I}{\tau_I}\big)\alpha\big(1 - \frac{V^*}{V}\big)(pI - cV) \end{aligned}$$

Now we strategically add terms that sum to zero and algebraically manipulate the above.

$$
\begin{aligned}
=&\big(1-\frac{T^*}{T}\big)\big(-\beta TV + r_D(N-T-E-I-N+T^*+E^*+I^*) + r_D(N-T^*-E^*-I^*)\big)\\
&+\beta TV - \frac{E}{\tau_E} - \frac{\beta TVE^*}{E} + \frac{E^*}{\tau_E} + \frac{E}{\tau_E} - \frac{I}{\tau_I} - \frac{I^*E}{I\tau_E} + \frac{I^*}{\tau_I} + \alpha\big(1-\frac{V^*}{V}\big)(pI-cV)\\
=&\big(1-\frac{T^*}{T}\big)r_D(T^*-T+E^*-E+I^*-I) + \big(1-\frac{T^*}{T}\big)(-\beta TV)\\
&+\big(1-\frac{T^*}{T}\big)r_D(N-T^*-E^*-I^*) + \beta TV - \beta TV\big(\frac{E^*}{E}\big)\\
&+\frac{E^*}{\tau_E} - \frac{I}{\tau_I} - \frac{I^*E}{I\tau_I} + \frac{I^*}{\tau_I} + \alpha\big(1-\frac{V^*}{V}\big)(pI-cV)
\end{aligned}
$$

$$
\begin{aligned}
=&\big(1-\frac{T^*}{T}\big)r_D(T^*-T+E^*-E+I^*-I) + \beta T^*V + \beta T^*V^* - \frac{T^*}{T}\beta T^*V^* - \frac{E^*}{T^*V^*\tau_E}\\
&\cdot\frac{TVE^*}{E} + \frac{E^*}{\tau_E} - \frac{I^*E}{\tau_E I} - \frac{I}{\tau_I} + \frac{I^*}{\tau_I} + \alpha\big(1-\frac{V^*}{V}\big)(pI-cV)\\
=&\big(1-\frac{T^*}{T}\big)r_D(T^*-T+E^*-E+I^*-I) + \beta T^*V + \frac{I^*}{\tau_I} - \frac{T^*}{T}\frac{I^*}{\tau_I} + \frac{TVE^*}{T^*V^*E}\frac{I^*}{\tau_I} + \frac{I^*}{\tau_I}\\
&-\frac{I^*E}{\tau_E I} - \frac{II^*}{\tau_I I^*}\\
&+\frac{I^*}{\tau_I} + \alpha\big(1-\frac{V^*}{V}\big)(pI-cV)\\
=&\big(1-\frac{T^*}{T}\big)r_D(T^*-T+E^*-E+I^*-I) + \frac{V}{V^*}\frac{I^*}{\tau_I}\\
&+\frac{I^*}{\tau_I} - \frac{T^*}{T}\frac{I^*}{\tau_I} - \big(\frac{TVE^*}{T^*V^*E}\big)\frac{I^*}{\tau_I} + \frac{I^*}{\tau_I}\\
&-\big(\frac{I^*E}{IE^*}\big)\frac{I^*}{\tau_I} - \frac{I}{I^*}\frac{I^*}{\tau_I} + \frac{I^*}{\tau_I} + \alpha\big(1-\frac{V^*}{V}\big)(pI-cV)\\
=&\big(1-\frac{T^*}{T}\big)r_D(T^*-T+E^*-E+I^*-I) + \frac{I^*}{\tau_I}\Big(\frac{V}{V^*} + 1 - \frac{T^*}{T} - \frac{TVE^*}{T^*V^*E}\\
&+1-\frac{I^*E}{IE^*} - \frac{I}{I^*} + 1\Big) + \alpha\big(1-\frac{V^*}{V}\big)(pI-cV)
\end{aligned}
$$

$$=\big(1-\frac{T^*}{T}\big)r_D(T^*-T+E^*-E+I^*-I)+\frac{I^*}{\tau_I}\big(1-\frac{T^*}{T}-\frac{TVE^*}{T^*V^*E}-\frac{I^*E}{IE^*}-\frac{I}{I^*}\big)$$
$$+\frac{I^*}{\tau_I}\big(\frac{V}{V^*}+2\big)+\alpha\big(1-\frac{V^*}{V}\big)(pI-cV)$$

We know that the first term, $\big(1-\frac{T^*}{T}\big)r_D(T^*-T+E^*-E+I^*-I)$ is negative from our conditions. Looking at the second term, we want the magnitude of the negative terms to be greater than the positive terms. As in the local stability, we will utilize the Arithmetic Geometric Mean. Since there are 4 negative terms we know the following:

$$\sum_{i=1}^{4}\mathcal{N}_i \geq 4\left(\prod_{i=1}^{4}\mathcal{N}_1\right)^{\frac{1}{4}} \tag{8}$$

So, it is enough to show that four times the fourth root of the product of the negative terms is greater than 1.

$$4\left(\prod_{i=1}^{4}\mathcal{N}_1\right)^{\frac{1}{4}} = 4\Big(\frac{T^*}{T}\cdot\frac{TVE^*}{T^*V^*E}\cdot\frac{I^*E}{IE^*}\cdot\frac{I}{I^*}\Big)^{\frac{1}{4}} = 4\Big(\frac{V}{V^*}\Big)^{\frac{1}{4}} \tag{9}$$

Setting this result greater than 1 and rearranging our terms, we obtain the inequality $V > \frac{1}{4}V^*$, which follows from our hypotheses. So, this term is negative.

We are now left with two terms, $\frac{I^*}{\tau_I}\left(\frac{V}{V^*}+2\right)$ and $\alpha\left(1-\frac{V^*}{V}\right)(pI-cV)$. Due to our conditions, we know that the term attached to α is negative. So, we define α so that we ensure the negative term overpowers the only remaining positive one. We define α as:

$$\alpha = k\cdot\frac{I^*}{\tau_I}\left(\frac{V}{V^*}+2\right) \tag{10}$$

where k is some constant that is larger than one when multiplied with $\left(1-\frac{V^*}{V}\right)(pI-cV)$. □

Lemma 2 The expected number of infectious cells at time t when transitioning from y exposed/infectious cells to y exposed/infectious cells is denoted $\mathbb{E}(i)$, and is

given by

$$\mathbb{E}(i) = \frac{y^2}{2y+1}.$$

Implications of Lemma 2: Any time we know the combined number of exposed/infectious cells, y, we can calculate the expected number of infectious cells. We may also use this to replace the random variable $\mathcal{V}$ with the virus production rate per infectious cell times the expected number of infectious cells, $V(y) = p \cdot \frac{y^2}{2y+1}$. Thus, we are able to eliminate all random variables from our matrix. Lemma 2 also provides us with the ability to approximate the number of infectious cells at any time point in our stochastic simulations.

Proof/reasoning of Lemma 2: From Table **??**, we see that there are $y+1$ different states at time t, corresponding to $i = 0, 1, ..., y$. The first y of these states have 2 possible outcomes, no change or an exposed cell becoming infectious. The only exception is for the case when $i = y$ at time t, which only has one outcome because there are no exposed cells to become infectious. Thus, there are $2y + 1$ possible events.

$$\begin{aligned}
\mathbb{E}(i) &= \frac{2}{2y+1}(0) + \frac{2}{2y+1}(1) + \cdots + \frac{2}{2y+1}(y-1) + \frac{1}{2y+1}y \\
&= \frac{2}{2y+1}(0+1+\cdots+y-1) + \frac{y}{2y+1} \qquad (11) \\
&= \frac{\cancel{2}}{2y+1} \cdot \frac{(y-1)y}{\cancel{2}} + \frac{y}{2y+1} = \frac{y^2}{2y+1}.
\end{aligned}$$