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Research Article

Analytical Solutions for the Initial Steps of the Intracellular Dynamics of Influenza A Virus

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Abstract

The present paper resolves two systems of differential equations that describe the initial steps of the intracellular dynamics of the influenza A virus. The first one describes the virus entry process and the next step proposes an approximate solution that is capable of describing the RNA Viral replication process using a deterministic model. Finally, it is necessary to include additional terms in the equations that have been initially proposed in the scientific literature.

Keywords: Influenza; Virus Entry; RNA; Replication, Differential Equations; Deterministic Model

Introduction

The influenza A virus is genetically changing every year which is why it has been difficult to develop an efficient vaccine to prevent it. At this time, we can remember four pandemics of Influenza A where the first occurred in 1918 that was caused by the H1N1 virus with the genes of an avian origin that infected approximately one third of the world's population. In the pandemics of 1957 and 1968, there were more than one thousand deaths worldwide. The 2009 pandemic had more than 60 million registered cases recorded worldwide. For that reason, it is important to develop models that help us to understand the biology of the virus and to be able to develop better strategies that would assist us in order to control the virus.

The first complete mathematical model of the Influenza A virus cycle was proposed by Heldt., *et al.* in 2012 [1]. In the model, they numerically solved a system of 32 differential equations that were capable of modeling the behavior of the intracellular dynamics of the influenza virus. This included the entry virus, the viral replication, the viral transcription and the protein synthesis, and the virus release.

The differential equations originally proposed by Heldt were somewhat incomplete and it was found to be necessary to add additional terms in order to guarantee the equilibrium of the system in the first two steps of the life cycle of the virus. Finally, the equilibrium condition was found for each of the two initial steps of the infection cycle of the influenza A virus.

Methodology

Mathematical model

As indicated in the introduction, we separately resolve the first two steps of the intracellular virus dynamics: 1) the description of virus entry, and 2) the description of the viral replication. Although the complete system proposed by Heldt must be solved in simultaneity, a separate analytical solutions may hopefully increase our intuition.

Figure 1 shows the compartmental model of the first two steps of the intracellular virus dynamics, where the letter (A) describes the viral entry process and (B) describes the viral replication. In this procedure, it is necessary to add additional terms to the system proposed by Heldt., *et al.* and these additional terms are highlighted in blue in the equations for easy identification.

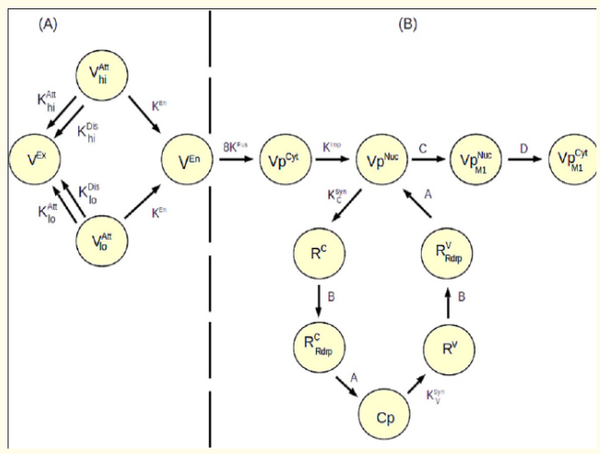


Figure 1: The compartmental model of the entry model (A) and the viral replication employed in the model (B), where we defined $A° K_{NP}^{Bind} P_{NP} - K_{Rrdrp}^{Deg}$, $B° K_{Rdrp}^{Bind} P_{Rdrp} - K_{R}^{Deg}$, $C° K_{M1}^{Bind} P_{M1} + K_{Rnp}^{Deg}$, $D° K^{Exp} P_{Nep} + K_{Rnp}^{Deg}$

Virus entry model

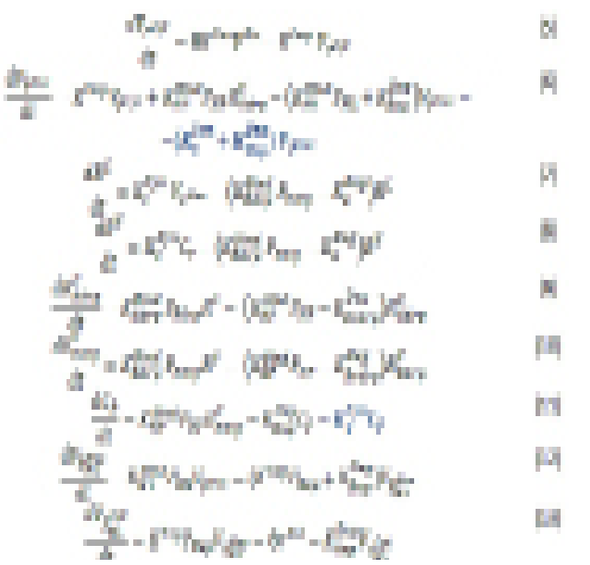
The first mathematical model capable of describing only the virions binding to membrane receptors was proposed by Nunes-Correia., *et al* [2]. It was subsequently modified by Heldt., *et al* [1].

The process begins when the virions bind to neuraminic acids on the cell surface and enter the cell via endocytosis. The term V^{Ex} corresponds to the number of viral particles infected per cell and V_n^{Att} and V^{En} are the virions that correspond to the extracellular medium and the early endosomes. When considering only this first step, it was found to be necessary to include additional terms to the Heldt's model in equations (2), (3) and (4). The system shown in figure 1 can be described with the equations.

where $C_1 = K_{hi}^{Att} B_{hi}^{Tot} + K_{hi}^{Att} B_{hi}^{Tot}$, $C_2 = K_{hi}^{Att} + K^{En}$, $C_3 = K_{lo}^{Att} + K^{En}$ and $C_4 = K^{Fus} + K_{Ven}^{Deg}$

Viral replication

Viral replication is described with the differential equations (5) through (13) based on the original model proposed by Heldt., *et al.* [1] with additional terms in equation (6) and in equation (11). Remember that nuclear vRNPs ($V_{P^{Nuc}}$) synthesize cRNA (R^C). The vRNA (R^V) is directed by cRNPs (C_p) where both terms of synthesis are degraded with a rate K_R^{Deg}. Subsequently, the viral polymerase with cRNA is formed (R_{Rdrp}^C) and vRNA (R_{Rdrp}^V). Later, the M1 protein can bind to vRNP to form M1-v-RNP complexex ($V_{P_{M1}^{Nuc}}$), and finally a complex is formed with the association of NEP to form the NEP-M1-vRNP complexes ($V_{P_{M1}^{Nuc}}$) are transported to the plasma membrane where the virus budding takes place.



In order to analytically solve this system of equations, the following assumption was made: P_{M1}, P_{Rdrp}, P_{NP}, and P_{Nep} were considered to be constant. The equations that define the dynamics of these four terms were not able to be solved analytically.

Results and Discussion

The first model describing the virus entry of influenza A is examined at the critical point:

$$V^{Ex^*} = 0, V_{hi}^{Att*} = 0, V_{lo}^{Att*} = 0, V^{En*} = 0$$

The Jacobian (J) will be denoted in the following way in order to be able to observe each of the terms that are different from zero.

$$J \equiv \begin{pmatrix} J_{11} & J_{12} & J_{13} & J_{14} \\ J_{21} & J_{22} & J_{23} & J_{24} \\ J_{31} & J_{32} & J_{33} & J_{34} \\ J_{41} & J_{42} & J_{43} & J_{44} \end{pmatrix}$$

where

$J_{11} = -C_1, J_{21} = J_{12} = K_{hi}^{Att} B_{hi}^{Tot}, J_{22} = -2(K_{\square}^{En} + K_{hi}^{Att}) - K_{hi}^{Dis}, J_{33} = -2(K_{\square}^{En} + K_{lo}^{Att}) - K_{lo}^{Dis}$

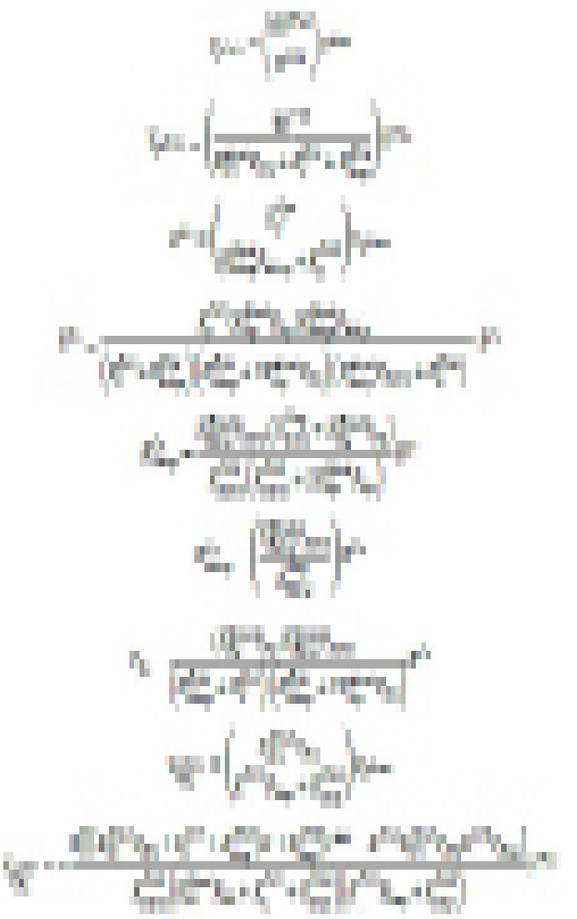
$J_{13} = J_{31} = K_{hi}^{Dis} + K_{hi}^{Att}, J_{42} = J_{43} = K_{\square}^{En}, J_{44} = -C_4 - 8K^{Fus}$

where the expressions C_1 and C_4 were previously defined. In this case, there is a single real eigenvalue given by

$$-\frac{1}{3}\left\{4K^{En} + \left(K_{hi}^{Dis} + K_{lo}^{Dis}\right) + K_{hi}^{Att}(2 + B_{hi}^{Tot}) + K_{lo}^{Att}(2 + B_{lo}^{Tot})\right\}$$

From this equation, a stable point will always be present for the values of the constants being positive. Figure 2 shows the results that are evaluated at the point (V^{En*},V^{Ex*})=(0,0) where we observe how the red lines show that the different trajectories within the vector field converge. This indicates that it is a point of equilibrium.

The next step describes the replication of the virus. It was possible to derive a critical point according to the simplification described above with the terms P_{M1}, P_{Rdrp}, P_{NP}, and P_{Nep} assumed to be constant:



If we assume that V^{En}=0, then the critical point for the viral replication are also zeros, ie., (V_{pCyt^*} = 0, V_{pNuc^*} = 0, R^{C^*} = 0, R^{V^*} $R_{Rdrp}^{C^*}$ = 0, $R_{Rdrp}^{V^*}$ = 0, $V_{P_{M1}^{Nuc^*}}$ = 0, $V_{P_{M1}^{Cyt^*}}$ = 0).

The determinant of the Jacobian evaluated at this critical point is equal to

$$-K_{Rnp}^{Deg}K_{Rdrp}^{Deg}K_{\square}^{Imp}\left(K_{Rnp}^{Deg}+K_{V}^{Sys}\right)\left(K_{Rdrp}^{Deg}+2K_{Np}^{Bind}P_{Np}\right)\left(K_{Rdrp}^{Bind}P_{Rdrp}+K_{R}^{Deg}\right)^{2}$$
$$\left(K_{M1}^{Bind}P_{M1}+K_{C}^{Sys}+K_{Rnp}^{Deg}\right)\left(K_{\square}^{Exp}P_{Nep}+K_{Rnp}^{Deg}\right)$$

The remaining terms are almost equal to zero.

The eigenvalue is equal to

$$-\frac{\varepsilon\sigma\rho^{2}\varphi^{2}-K_{C}^{Sys}K_{V}^{Sys}(K_{Np}^{Bind}P_{Np}+K_{Rrdrp}^{Deg})^{2}(K_{Rdrp}^{Bind}P_{Rdrp}+K_{R}^{Deg})^{2}}{\rho\varphi[\rho\varphi(\varphi+\rho)+2\varepsilon\sigma(\rho+\varphi)]}$$

where:

$$\varepsilon\equiv\left(K_{M1}^{Bind}P_{M1}+K_{C}^{Sys}+K_{Rnp}^{Deg}\right);\ \sigma\equiv K_{Rnp}^{Deg}+K_{V}^{Sys},$$

$$\rho\equiv\left(K_{Rdrp}^{Bind}P_{Rdrp}+K_{R}^{Deg}\right);\ \varphi\equiv\left(K_{Np}^{Bind}P_{Np}+K_{Rrdrp}^{Deg}\right).$$

From the last expression, it is observed that the system is stable when the eigenvalue is negative which occurs for the condition that $\varepsilon\sigma\rho^{2}\varphi^{2}>K_{C}^{Sys}K_{V}^{Sys}\alpha^{2}\beta^{2}$.

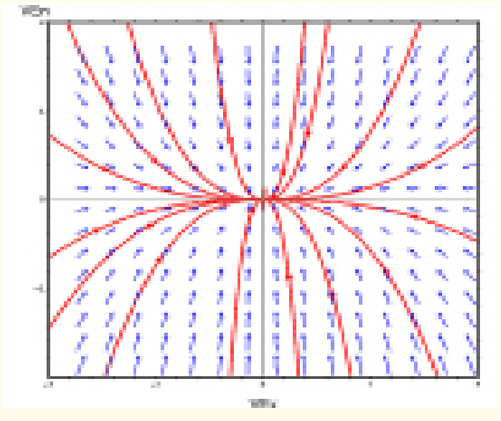


Figure 2: Diagram of the vector field obtained with Python using the matplotlib module

Conclusion

The present paper presents the possibility of analytically solving the first two steps of the intracellular dynamics of the Influenza virus A according to the model originally proposed by Heldt., *et al.* In the first case, an analytical solution is obtained where it is observed that the condition of equilibrium is always reached from the point of view that the number of infected viral particles that reach the cell while the replication process was necessary in order to make an approximation to find an analytical solution. Finally we must simplify the model proposed by Heldt that allows us to describe the last two stages of the virus dynamics, that is, the viral transcription and protein synthesis and finally the virus relay which complicates this solution.

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Conflict of Interest

The author declares no conflicts of interest in this article.

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