Analysis of a Cell-Cell Fusion Model Incorporating Cell Growth and Death Growth

Gabriel McCarthy and Hana M. Dobrovolny

Department of Physics and Astronomy, Texas Christian University, Fort Worth, TX, USA

Background

- Syncytia are multi-nucleated cells that can occur due to virus infections.
- To better understand viral dynamics it is important to understand how syncytia populations evolve during an infection.
- Ordinary Differential Equation (ODE) models can be used to model the growth of syncytia both in vivo and in vitro.
- We can account for more complicated behaviors of cells like cell growth using ODE models that may lead to unexpected behaviors.
- We could potentially account for long lasting syncytia populations using ODE models.

Cell-Cell Fusion Assay

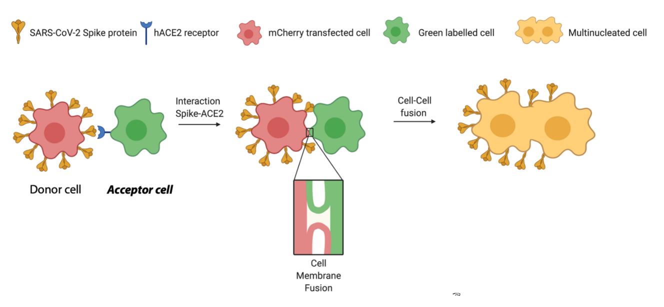

Image from Papa et. al (2020)

- One group of cells (donor cells) expresses the virus surface protein and is stained with one dye.
- A second group of cells (acceptor cells) expresses the cell surface receptor and is stained with a second dye.
- When the cells fuse, the syncytia will fluoresce with both dyes.
- Experiments typically measure the area covered by syncytia as a function of time.

Simple Asymmetric Model

These processes, can most simply be represented as the set of ODE's below. Where S represents the population of syncytia, D represents the population of donor cells, and A represents the number of acceptors. The structure of this model gives rise to a conservation law for the total populations N as seen below.

$$\begin{aligned}\frac{dD}{dt} &= -\gamma DA\\ \frac{dA}{dt} &= -\gamma DA - \gamma SA\\ \frac{dS}{dt} &= 2\gamma DA + \gamma SA\\ N &= D + A + S\end{aligned}$$

Proposed Extension

The asymmetric model neglects both cell regeneration and death which both certainly occur in actual cell cultures and within the body. To account for death and regeneration we will include the following modifications.

- A logistic like growth term for the donor and acceptor cells.
- A constant death term for the syncytia

The modified model can be seen below.

$$\begin{aligned}\frac{dD}{dt} &= -\gamma DA + r_D D\left(1 - \frac{D+A+S}{K}\right)\\ \frac{dA}{dt} &= -\gamma DA - \gamma SA + r_A A\left(1 - \frac{D+A+S}{K}\right)\\ \frac{dS}{dt} &= 2\gamma DA + \gamma SA - \delta S\end{aligned}$$

- In this model, all parameters are assumed to be positive.
- There is no longer a simple conservation law for the total population of the cells.
- The models include the following parameters that determine the behavior of the model over time.

Parameter	Name
γ	Syncytia Formation Rate
r_D	Natural Growth Rate of Donor Cells
r_A	Natural Growth Rate of Acceptor Cells
K	Carrying Capacity of the Environment
δ	Syncytia Death Rate

Fixed Points

To analyze the overall behavior of the system we will use the fixed points and their stability. To do this, we solve $\dot{\mathbf{X}} = \mathbf{0}$ where $\mathbf{X}$ is our ODE system and then evaluate the Jacobian. The relevant fixed points for this model can be seen below.

$$\begin{aligned}\mathbf{x}_1 &= (0,0,0)\\ \mathbf{x}_2 &= (K,0,0)\\ \mathbf{x}_3 &= (0,K,0)\\ \mathbf{x}_4 &= \left(0, \frac{\delta}{\gamma}, \frac{r_A(\gamma K - \delta)}{\gamma(\gamma K + r_A)}\right)\\ \mathbf{x}_5 &= \left(\frac{A_{eq} r_A}{r_D}\left(\frac{\delta - A_{eq}\gamma}{\delta + A_{eq}\gamma}\right), \frac{r_D K}{K\gamma + r_D + r_A}, \frac{2A_{eq}^2 r_A}{r_D(\delta + A_{eq}\gamma)}\right)\\ A_{eq} &= \frac{r_D K}{K\gamma + r_D + r_A}\end{aligned}$$

Jacobian

The stability of each fixed point depends on the eigenvalues of the Jacobian matrix of the system evaluated at each fixed point. The Jacobian of the system can be seen below.

$$\mathbf{J} = \begin{bmatrix} -\gamma A + r_D(1 - \frac{2D+A+S}{K}) & -D(\gamma + \frac{r_D}{K}) & -\frac{Dr_D}{K}\\ -A(\gamma + \frac{r_A}{K}) & -\gamma D - \gamma S + r_A(1 - \frac{D+2A+S}{K}) & -A(\gamma + \frac{r_A}{K})\\ 2\gamma A & 2\gamma D + \gamma S & \gamma A - \delta \end{bmatrix}$$

Determining the stability at each fixed point is a non-trivial task which involves computing the eigenvalues of a rank 3 matrix. To do this we made use of Maple to aid in the computation, however, computing exact stability criteria of these matrices may not always be possible.

Stability of Fixed Points

The first fixed point $\mathbf{x}_1$ corresponds to the trivial fixed point of the system. The Jacobian evaluated at $\mathbf{x}_1$ is a diagonal matrix, and as such the fixed points are the entries along the diagonal. The evaluated Jacobian and eigenvalues can be see below.

$$\mathbf{J}_1 = \begin{bmatrix} r_D & 0 & 0\\ 0 & r_A & 0\\ 0 & 0 & -\delta\end{bmatrix} \implies \text{Eigenvalues} = \begin{bmatrix} r_D\\ r_A\\ -\delta\end{bmatrix}$$

The second fixed point $\mathbf{x}_2$ corresponds to a saturated system only containing donor cells. The Jacobian evaluated at $\mathbf{x}_2$ is no longer diagonal, and as such the eigenvalues must be computed. The evaluated Jacobian and eigenvalues can be see below.

$$\mathbf{J}_2 = \begin{bmatrix} -r_D & -\gamma K - r_D & -r_D\\ 0 & -\gamma K & 0\\ 0 & 2\gamma K & -\delta\end{bmatrix} \implies \text{Eigenvalues} = \begin{bmatrix} -r_D\\ -\delta\\ -K\gamma\end{bmatrix}$$

The third fixed point $\mathbf{x}_3$ corresponds to a saturated system only containing acceptor cells. The Jacobian evaluated at $\mathbf{x}_3$ is not diagonal, so the eigenvalues must be computed. The evaluated Jacobian and eigenvalues can be see below.

$$\mathbf{J}_3 = \begin{bmatrix} -\gamma K & 0 & 0\\ -\gamma K - r_A & -r_A & -\gamma K - r_A\\ 2\gamma K & 0 & \gamma K - \delta\end{bmatrix} \implies \text{Eigenvalues} = \begin{bmatrix} -r_A\\ -K\gamma\\ K\gamma - \delta\end{bmatrix}$$

These first 3 fixed points represent relatively uninteresting scenarios, as there is only type of cell present. The fixed points $\mathbf{x_4}$ and $\mathbf{x_5}$ represent more interesting scenarios with the coexistence of several types of cells. This could potentially allow for long lasting populations of synctyia. As such, their stability is of particular interest.

Stability Continued

The fourth fixed point $\mathbf{x}_4$ corresponds to a system containing only acceptor and donor cells. This is possible due to the asymmetric nature of the model. The Jacobian evaluated at $\mathbf{x}_4$ is not diagonal, so the eigenvalues must be computed. The evaluated Jacobian and eigenvalues are seen below..

$$\mathbf{J}_4 = \begin{bmatrix} -\delta + r_D(\frac{\gamma K - \delta}{\gamma K + r_A}) & 0 & 0\\ -\delta(1 + \frac{r_A}{\gamma K}) & -\frac{r_A\delta}{\gamma K} & -\delta(1 + \frac{r_A}{\gamma K})\\ 2\delta & \frac{r_A(\gamma K - \delta)}{(\gamma K + r_A)} & 0\end{bmatrix}$$

$$\text{Eigenvalues} = \begin{bmatrix} \frac{-r_A\delta + \sqrt{-4K^2\delta\gamma^2 r_A + 4K\delta^2\gamma r_A + \delta^2 {r_A}^2}}{2K\gamma}\\ -\frac{r_A\delta + \sqrt{-4K^2\delta\gamma^2 r_A + 4K\delta^2\gamma r_A + \delta^2 {r_A}^2}}{2K\gamma}\\ -\frac{K\delta\gamma - K\gamma r_D + r_A\delta + \delta r_D}{K\gamma + r_A}\end{bmatrix}$$

Finally for $\mathbf{x}_5$, this corresponds to a system containing populations of all 3 types of cells in equilibrium. The resulting matrix is unwieldy, and as such will be omitted from this poster.

Stability Conditions

Using our determined eigenvalues we can determine the stability of these fixed points, the results are summarized below.

- $\mathbf{x}_1$ is an unstable fixed point and $\mathbf{x}_2$ is a stable fixed point.
- $\mathbf{x}_3$ is a stable fixed point given $K\gamma < \delta$.
- $\mathbf{x}_4$ is stable if $K\gamma > \delta$ and $K\gamma(r_D - \delta) < \delta(r_A + r_D)$. Additionally, this fixed point can have imaginary eigenvalues and thus oscillatory behavior if $\delta(4K\gamma + r_A) < 4K^2\gamma^2$.
- $\mathbf{x}_5$ The exact conditions for stability are couldn't be determined by computation of the eigenvalues, so alternative methods like the Routh-Hurwitz Stability Criterion will be considered in the future.

Conclusions

- Modification of a simple model for Cell-Cell Fusion incorporating cell growth and death leads to more complex behaviors.
- The modified model has 5 fixed points as compared to 1 in the unmodified model.
- These 5 fixed points account for a variety of scenarios, and 1 is always unstable, 1 always stable, 2 have determinable stability criteria, and 1 fixed point must be assessed using other criteria.
- This model can account for long lasting syncytia populations as indicated by the fourth and fifth fixed points.