Virus-cytokine arms race in mammalian cell tissue

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After an initial infection occurs in mammalian tissue, a cascade of immune system processes is triggered with the primary objective of safeguarding the host and eliminating the pathogen. However, the molecular mechanisms underlying these processes are still not fully understood. In this study, we develop a mathematical model to propose a novel mechanism of viral response that operates autonomously within single cells. The model is constrained by experimental observations in fibroblast cultures, which reveal a bistable response in individual cells. We focus on the influenza A virus (IAV), whose primary targets include epithelial cells of the upper respiratory tract [1]. One of the most important cellular responses to this virus is the production and secretion of interferon by the infected host cells to the surrounding tissue. Interferon induces the expression of hundreds of interferon-stimulated genes (ISGs), which block virus replication at many levels [2]. In that way, virus and interferon compete to gain control of the tissue - the virus attempts to replicate and spread its genetic material, while interferon aims to suppress viral replication.

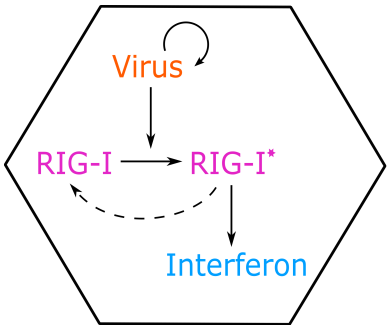

Fig. 1. **Schematic representation of the antiviral response.** Once the virus enters the cell it provokes an instant antiviral response causing the sensor RIG-I to turn to its active state, RIG-I*. When there is a sufficient concentration of active sensor, the cell is able to produce and subsequently secrete interferon.

To understand the mechanisms of interferon expression within the cell, we propose a simple circuit that consists of viral molecules, interferon, and active and inactive RIG-I sensor. RIG-I serves as a sensor for viral infections, playing a crucial role in triggering the activation of type I interferons and other genes that collectively establish a host response with antiviral properties [3]. Following viral entry, the instant antiviral response causes sensor RIG-I to convert to its active state, RIG-I*. Crucially, we assume that active RIG-I stimulates the production of the inactive sensor. Finally, the active sensor triggers the production of interferon within the cell, which will afterwards be secreted to the surrounding tissue. The schematic representation of the proposed antiviral response mechanism is given in Fig. 1. To avoid hyperinflammation, only a small portion of infected cells will indeed induce interferon, therefore it was of great importance to establish a bistable system that would be able to model the stochastic nature of RIG-I activation. To explore the interferon production, we have built a simple stochastic two-variable model that consists of active and inactive RIG-I sensor. As shown by Eq. (1), once the virus v is detected within the cell, the inactive sensor R will turn active R_a. Next, as given in Eq. (2), when there is enough active sensor, the cell will produce more inactive sensor.

$$\frac{dR_a}{dt} = K_r v R - \delta_r R_a \tag{1}$$

$$\frac{dR}{dt} = \frac{\alpha R_a^n}{K_i^n + R_a^n} - \delta_r R - K_r v R \tag{2}$$

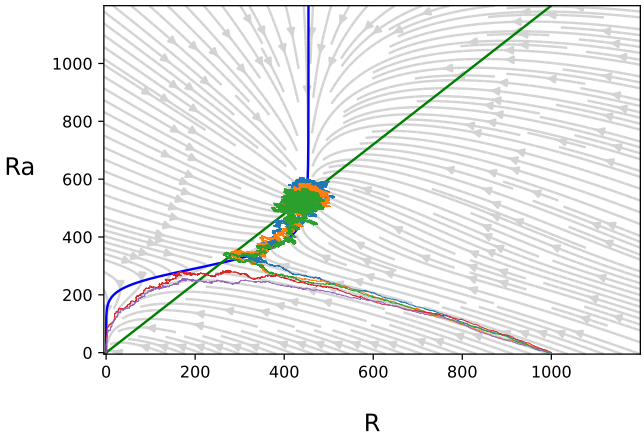

Fig. 2. **Phase portrait.** The system shows the bistable behaviour observed experimentally, where only a portion of cells activates the sensor to produce interferon.

The proposed model produces a bistable response, showing the distribution of active and inactive sensor observed experimentally (Fig. 2). As expected, only a fraction of infected cells activates the sensor leading to the production of interferon. In summary, this study characterizes the relationship between the cellullar sensor machinery and interferon production, contributing to a better understanding of the antiviral response within a single-cell environment.

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