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The Role of Cellular Heterogeneity in the Type I Interferon Response

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Type I Interferons (IFN) play an essential role in control of viral infection. The presence of viral molecules within a cell can, through a wide array of pathways, induce the transcription and secretion of IFN, and extracellular IFN can bind to the IFN receptor, leading to the transcription of so-called interferon stimulated genes (ISGs), which are directly associated with viral control. Hence, induction of IFN serves as an initial alarm of the immune system, and extracellular IFN serves to put cells into an antiviral state, mediated through ISGs, thereby controlling or limiting infection.

Almost all cell types can produce IFN in response to viral infection, but work across several groups has shown that the IFN response is heterogeneous, with only a small fraction of cells within a given cell type actually expressing IFN in response to infection. Mechanistically, this heterogeneity has been associated with varying protein, expression levels in IFN associated pathways, but a functional role for the heterogeneous response has yet to be suggested.

Here, we present several ODE models of the IFN response to viral infection. Through these models, we make the case that the IFN response must balance protection against excessive inflammation by moderating extracellular IFN levels, and that heterogeneity plays a key role in achieving this balance.