CONTROL OF INFLUENZA A VIRUS INFECTION BY VARYING DEATH RATES OF INFECTED CELLS: ANALYSIS OF A SPATIAL MODEL

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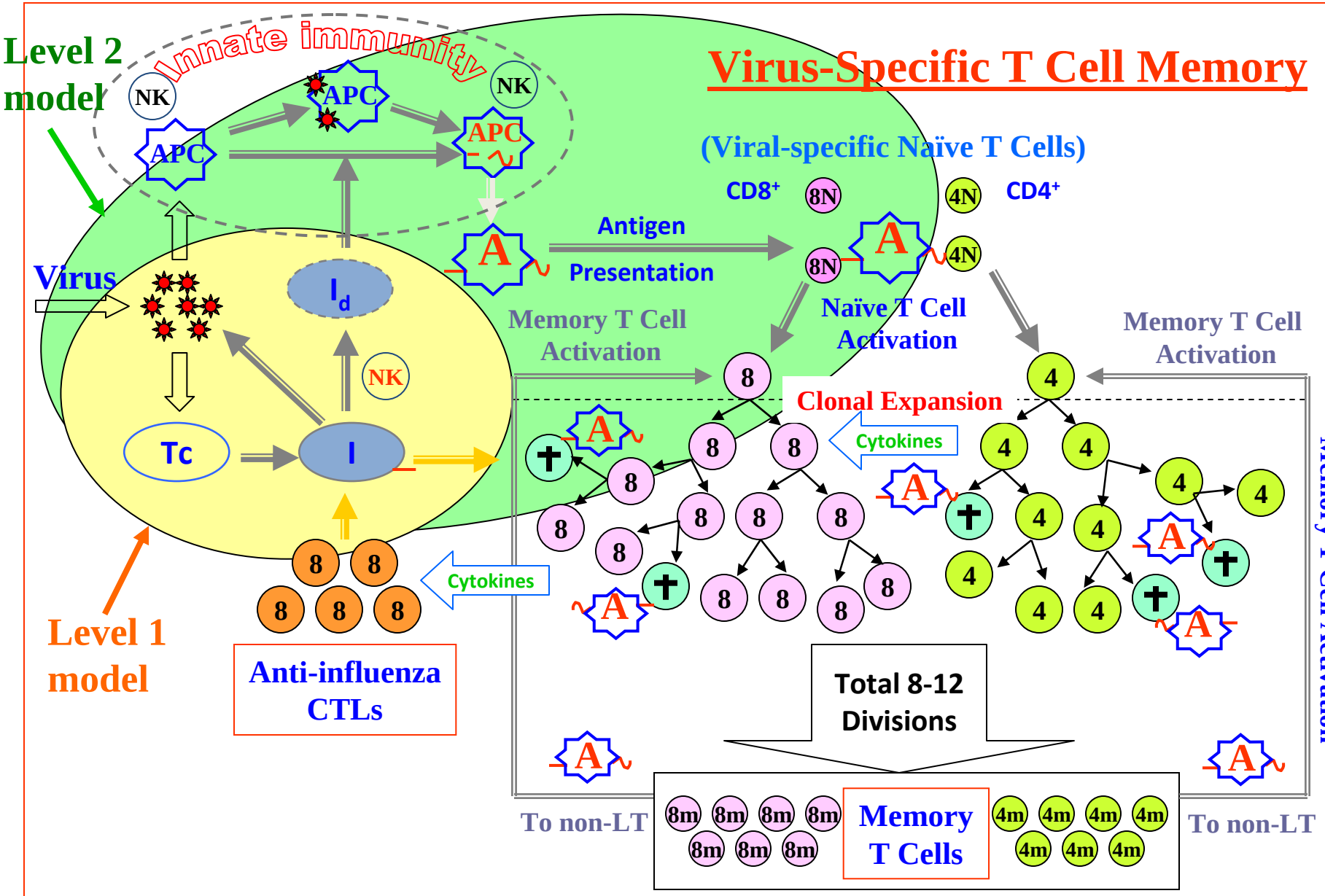
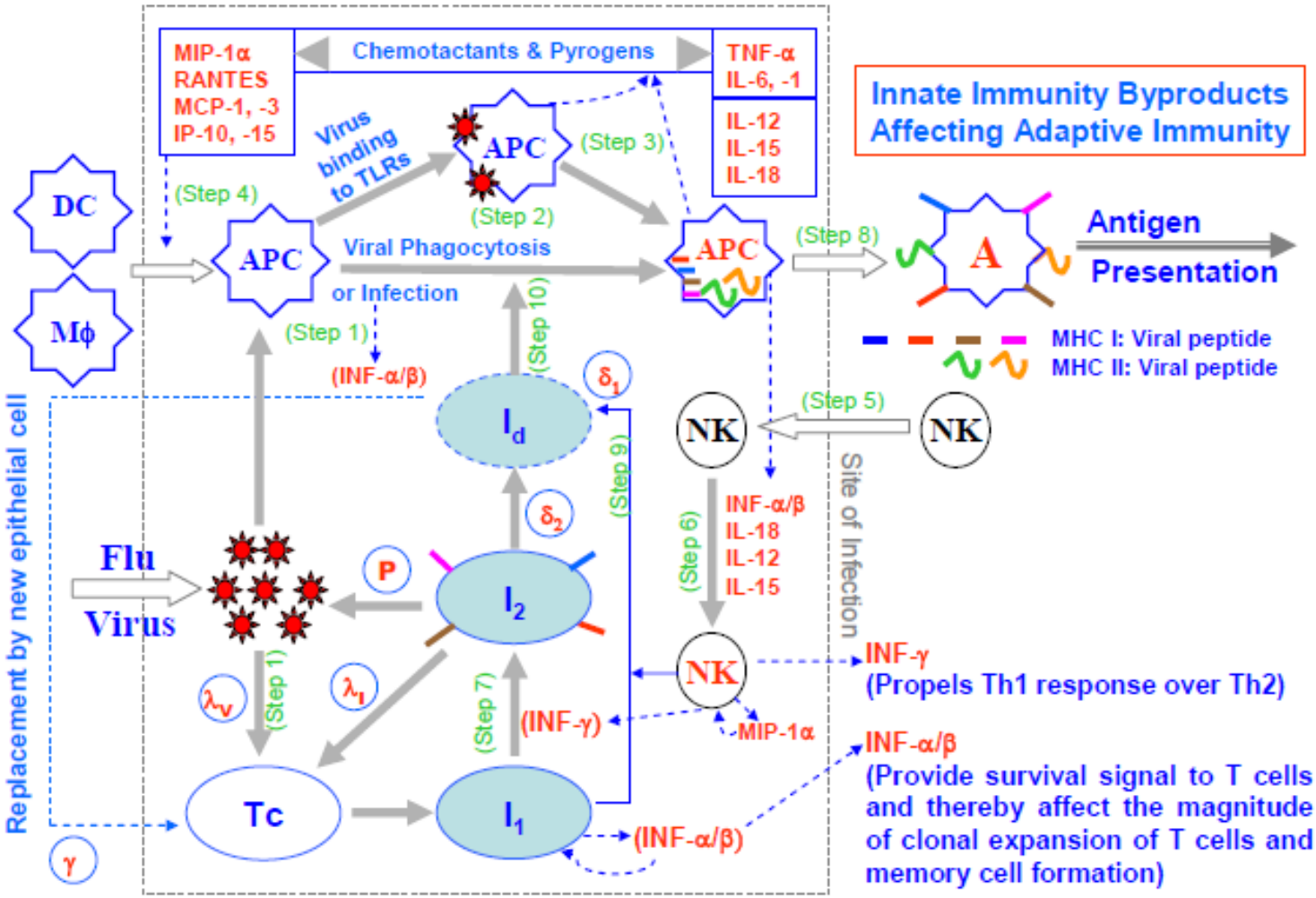
Background

- Influenza A viral infection of respiratory epithelium triggers innate immune response
  - secretion from infected epithelial cells of type-1 interferons, INF-α/β
  - inflammatory & chemotactic cytokines from alveolar macrophages and (mobile) neutrophils
  - dendritic cells (following phagocytosis of newly-synthesized virus particles)
- Leads to
  - activation of **NK (natural killer) cells**
  - viral antigen-bearing **macrophages** and **dendritic cells**
  - Macrophages, DCs lead, via clonal expansion, to **influenza A-specific cytotoxic T lymphocytes (CTLs)**.
- Activated NK cells kill newly-infected epithelial cells
- Anti-influenza CTLs destroy virus-producing epithelial cells


Virus-Specific T Cell Memory
Level 2 model
Innate immunity
NK
APC
APC
NK
APC
(Viral-specific Naïve T Cells)
CD8+
8N
4N
CD4+
Antigen
Presentation
A
Virus
Id
NK
Memory T Cell Activation
Naïve T Cell Activation
Memory T Cell Activation
Clonal Expansion
Cytokines
Tc
I
Level 1 model
Cytokines
Anti-influenza CTLs
Total 8-12 Divisions
To non-LT
Memory T Cells
To non-LT
Memory T Cell Activation

Innate Immunity to Influenza Infection



Level 1 model

$$\frac{dT_{R,\mathbf{x}}}{dt} = -\lambda_V T_{R,\mathbf{x}} V_{\mathbf{x}} - \lambda_I T_{R,\mathbf{x}} \sum_{e\in N_1} I_{2,\mathbf{x}'} + \frac{\gamma}{K} \sum_{e\in N_1} I_{2,\mathbf{x}+e} \quad (1)$$

Regeneration

$$\frac{dI_{1,\mathbf{x}}}{dt} = \lambda_V T_{R,\mathbf{x}} V_{\mathbf{x}} + \lambda_I T_{R,\mathbf{x}} \sum_{e\in N_1} I_{2,\mathbf{x}+e} - kI_{1,\mathbf{x}} - \delta_2 [NK^*]_{\mathbf{x}} I_{1,\mathbf{x}} \quad (2)$$

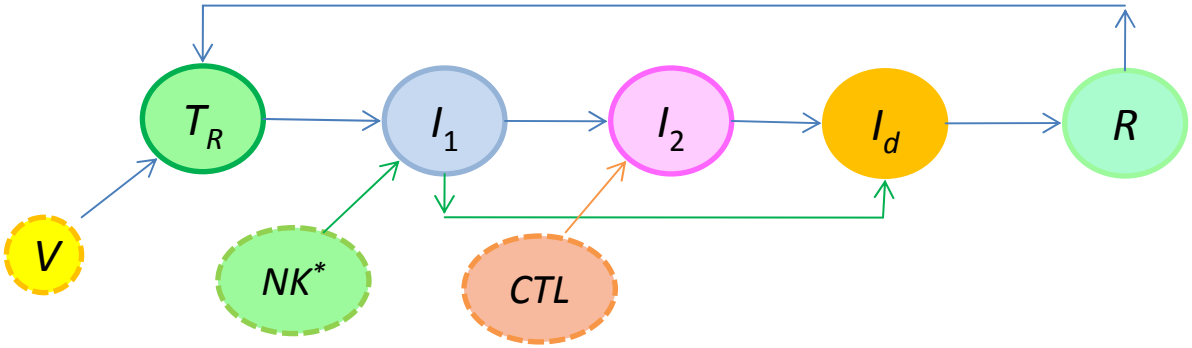
$$\frac{dI_{2,\mathbf{x}}}{dt} = kI_{1,\mathbf{x}} - \delta_1 I_{2,\mathbf{x}} - \delta_3 [CTL] I_{2,\mathbf{x}} \quad (3)$$

$$\frac{dV_{\mathbf{x}}}{dt} = pI_{2,\mathbf{x}} - cV_{\mathbf{x}} - \beta_{APC}[APC]_{\mathbf{x}} V_{\mathbf{x}} - \beta_{NEU}[NEU]_{\mathbf{x}} V_{\mathbf{x}} - \lambda_V (I_{1,\mathbf{x}} + I_{2,\mathbf{x}} + T_{R,\mathbf{x}}) V_{\mathbf{x}} + D_V \nabla^2 V_{\mathbf{x}} \quad (4)$$

$$\frac{dI_{d,\mathbf{x}}}{dt} = \delta_2 [NK^*]_{\mathbf{x}} I_{1,\mathbf{x}} + \delta_1 I_{2,\mathbf{x}} - (\beta_{d,1}[APC]_{\mathbf{x}} + \beta_{d,2}[NEU]_{\mathbf{x}}) I_{d,\mathbf{x}} + \delta_3 [CTL] I_{2,\mathbf{x}} \quad (5)$$

$$\frac{dR_{\mathbf{x}}}{dt} = (\beta_{d,1}[APC]_{\mathbf{x}} + \beta_{d,2}[NEU]_{\mathbf{x}}) I_{d,\mathbf{x}} - \gamma R_{\mathbf{x}} \quad (6)$$

Phagocytosis



Epithelial cell repair & regeneration

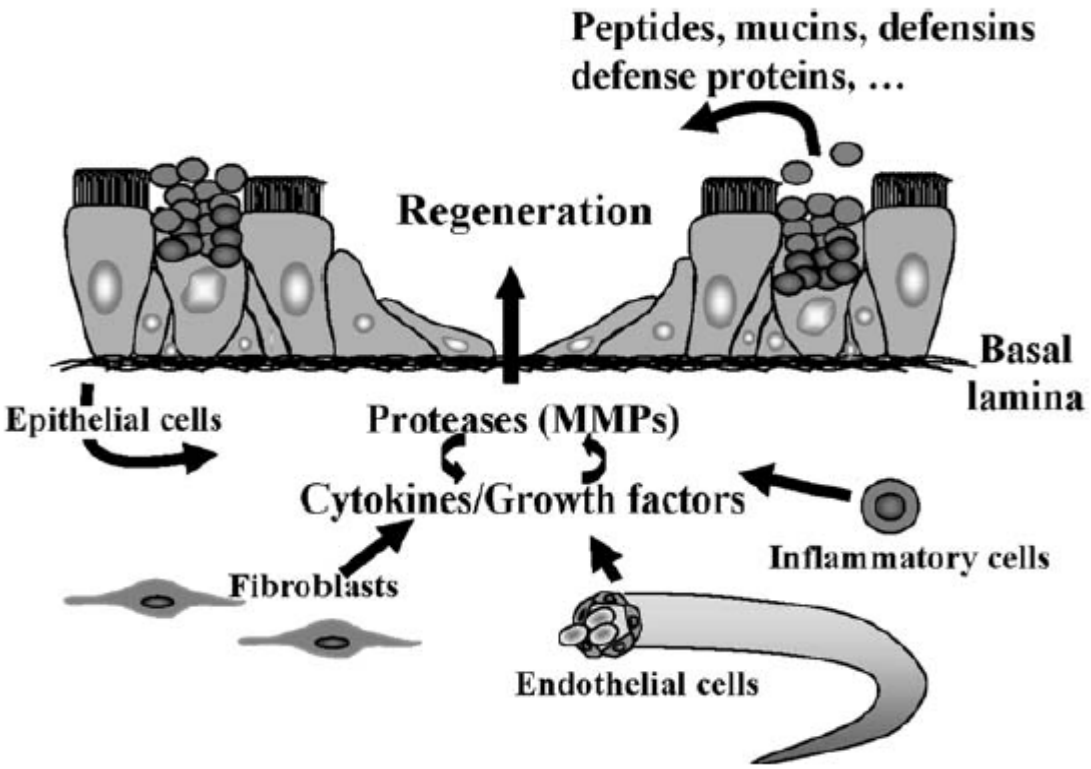


Figure 1. Cellular and molecular factors involved in the **repair and regeneration** of the airway epithelium. These factors, which closely interact during the different steps of airway epithelial regeneration after injury, are modulated by the components of the extracellular matrix; the matrix metalloproteinases (MMPs), cytokines, and growth factors released by the epithelial cells; and by the mesenchymal cells (fibroblasts, inflammatory cells, and chondrocytes).

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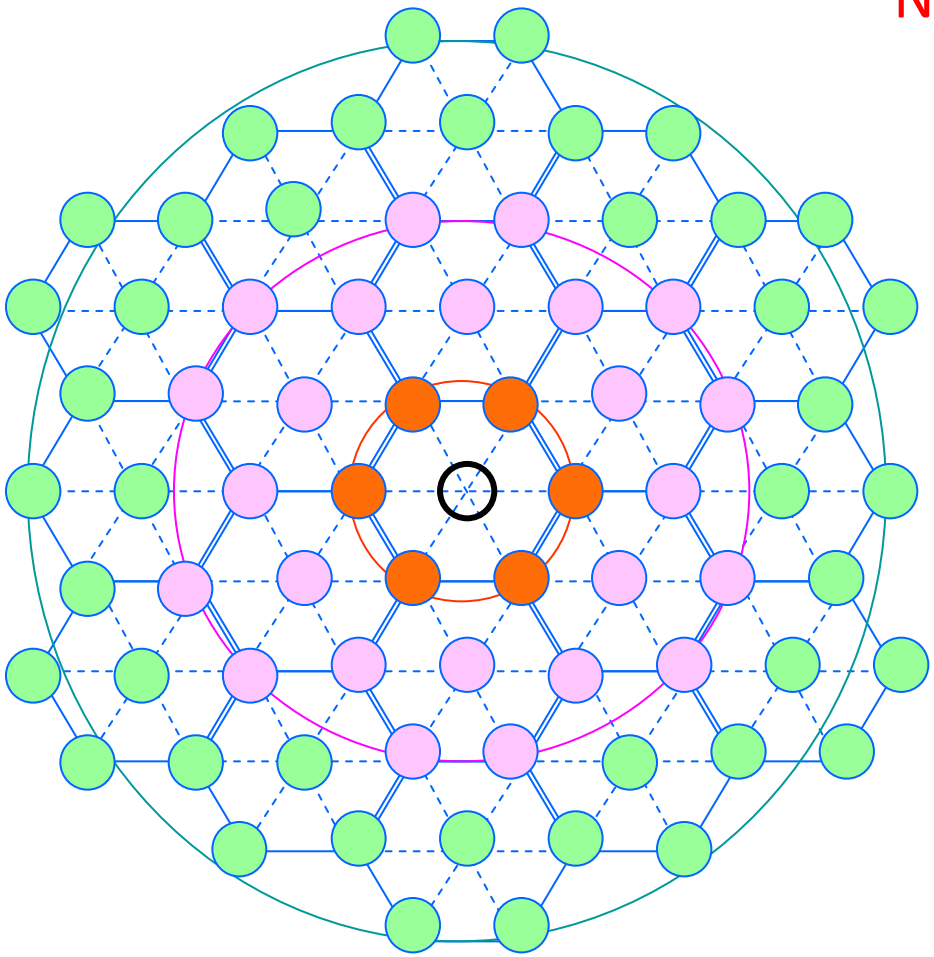
HEXAGONAL LATTICE OF EPITHELIAL CELLS



Neighbourhoods:

N_1 N_2 N_3 …

Linear Stability of Infection-Free Equilibrium (IFE)

- Define $\Delta_2 = \delta_2[NK^*]; \qquad \Delta_3 = \delta_1 + \delta_3[CTL];$

$\rho_1 = \beta_{APC}[APC] + \beta_{NEU}[NEU];$

$\rho_2 = \beta_{d,1}[APC] + \beta_{d,2}[NEU];$

$L_V = \lambda_V \bar{T}_R; \qquad L_I = \lambda_I \bar{T}; \qquad \Lambda = c + \rho_1 + L_V$

(constants)

- In infection-free equilibrium, the $\{T_{R,\mathbf{x}}\}$ constitute a **uniform** hexagonal lattice.
- Introduce a small perturbation

$$\delta\mathbf{X}_{\mathbf{x}} = \left(\delta T_{R,\mathbf{x}}, \delta I_{1,\mathbf{x}}, \delta I_{2,\mathbf{x}}, \delta V_{\mathbf{x}}, \delta I_{d,\mathbf{x}}, \delta R_{\mathbf{x}}\right)$$

about I.F.E. $\mathbf{X}_{\mathbf{0}} = \left(\bar{T}_R, 0, 0, 0, 0, 0\right)$ and linearize

LINEARIZATION ABOUT I.F.E.

$$\delta \dot{T}_{R,\mathbf{x}} = -L_V \delta V_{\mathbf{x}} - L_I \sum_{\mathbf{e}\in N_1} \delta I_{2,\mathbf{x}+\mathbf{e}} + \frac{\gamma}{K} \sum_{\mathbf{e}\in N_1} \delta R_{\mathbf{x}+\mathbf{e}}$$

$$\delta \dot{I}_{1,\mathbf{x}} = L_V \delta V_{\mathbf{x}} + L_I \sum_{\mathbf{e}\in N_1} \delta I_{2,\mathbf{x}+\mathbf{e}} - \left(k + \Delta_2\right) \delta I_{1,\mathbf{x}}$$

$$\delta \dot{I}_{2,\mathbf{x}} = k \delta I_{1,\mathbf{x}} - \Delta_3 \delta I_{2,\mathbf{x}}$$

$$\delta \dot{V}_{\mathbf{x}} = p \delta I_{2,\mathbf{x}} - \left(\Lambda + D_V\right) \delta V_{\mathbf{x}} + \frac{D_V}{K} \sum_{\mathbf{e}\in N_1} \delta V_{\mathbf{x}+\mathbf{e}}$$

$$\delta \dot{I}_{d,\mathbf{x}} = \Delta_2 \delta I_{1,\mathbf{x}} + \Delta_3 \delta I_{2,\mathbf{x}} - \rho_2 \delta I_{d,\mathbf{x}}$$

$$\delta \dot{R}_{\mathbf{x}} = \rho_2 \delta I_{d,\mathbf{x}} - \gamma \delta R_{\mathbf{x}}$$

where $K = \#\{N_1\} = 6$

Let $\delta\mathbf{X} = \delta\mathbf{X}_\mathbf{c} \exp\left(\lambda t + i\mathbf{k}\cdot\mathbf{x}\right)$ ⟹

$$\lambda\delta\mathbf{X}_\mathbf{c} = J_\mathbf{k}\delta\mathbf{X}_\mathbf{c}$$

$$J_\mathbf{k} = \begin{bmatrix} 0 & 0 & -L_I\varphi(\mathbf{k}) & -L_V & 0 & \gamma\dfrac{\varphi(\mathbf{k})}{K} \\ 0 & -(k+\Delta_2) & L_I\varphi(\mathbf{k}) & L_V & 0 & 0 \\ 0 & k & -\Delta_3 & 0 & 0 & 0 \\ 0 & 0 & p & -\Lambda - D_V\left(1-\dfrac{\varphi(\mathbf{k})}{K}\right) & 0 & 0 \\ 0 & \Delta_2 & \Delta_3 & 0 & -\rho_2 & 0 \\ 0 & 0 & 0 & 0 & \rho_2 & -\gamma \end{bmatrix}$$

where $$\varphi(\mathbf{k}) = 2\left(\cos\left(\frac{2\pi}{N_1}k_1\right) + \cos\left(\frac{2\pi}{N_2}k_2\right) + \cos\left(2\pi\left(\frac{k_1}{N_1}+\frac{k_2}{N_2}\right)\right)\right)$$

$$\mathbf{k} = 2\pi\left(\frac{k_1}{N_1}\hat{\mathbf{e}}_\mathbf{1}^* + \frac{k_2}{N_2}\hat{\mathbf{e}}_2^*\right)$$

$\hat{\mathbf{e}}_\mathbf{1}^*, \hat{\mathbf{e}}_2^*$ ⟹ Basis vectors of reciprocal lattice

Characteristic equation

$$\lambda(\lambda+\gamma)(\lambda+\rho_2)C(\lambda;\mathbf{k})=0$$

$C(\lambda;\boldsymbol{k})$ is a cubic polynomial in λ:

$$C(\lambda;\mathbf{k})=\lambda^3+a_2\lambda^2+a_1\lambda+a_0$$

where

$$a_0=\left(\Delta_3(k+\Delta_2)-kL_I\varphi\right)\left(\Lambda+D_V\left(1-\frac{\varphi(\mathbf{k})}{K}\right)\right)-kpL_V$$

$$a_1=\Delta_3\left(k+\Delta_2+\Lambda+D_V\left(1-\frac{\varphi(\mathbf{k})}{K}\right)\right)+\left(\Lambda+D_V\left(1-\frac{\varphi(\mathbf{k})}{K}\right)\right)(k+\Delta_2)-kL_I\varphi$$

$$a_2=\Delta_3+k+\Delta_2+\Lambda+D_V\left(1-\frac{\varphi(\mathbf{k})}{K}\right)$$

$$\Delta_2=\delta_2[NK^*];\qquad \Delta_3=\delta_1+\delta_3[CTL];\qquad L_V=\lambda_V\bar{T}_R;\qquad L_I=\lambda_I\bar{T};\qquad \Lambda=c+\rho_1+L_V$$

$$\rho_1=\beta_{APC}[APC]+\beta_{NEU}[NEU];\qquad \rho_2=\beta_{d,1}[APC]+\beta_{d,2}[NEU];$$

Routh-Hurwitz criteria

(i) $a_2 > 0;$ (ii) $a_1 a_2 - a_0 > 0;$ (iii) $a_0 (a_1 a_2 - a_0) > 0$

Conclusion

Since $\Lambda + D_V \left(1 - \frac{\varphi}{K}\right) > 0 \quad \forall \mathbf{k}$ it follows that,

for sufficiently large Δ_3 (representing killing of cells by CTLs), the Routh-Hurwitz criteria are satisfied and *the system is stable against spread of infection, independent of the diffusion rate* D_V.

Continuous form of diffusion term

- Replace discrete approximation: $\nabla^2 V_{\mathbf{x}} \approx \frac{1}{K}\sum_{\mathbf{e}\in N_1} V_{\mathbf{x}+\mathbf{e}} - V_{\mathbf{x}}$

  by its continuous form (also an approximation to diffusion!)

  In hexagonal frame:

$$\mathbf{r} = \hat{\mathbf{e}}_1\xi + \hat{\mathbf{e}}_2\eta; \qquad \nabla = \hat{\mathbf{e}}_1^* \frac{\partial}{\partial\xi} + \hat{\mathbf{e}}_2^* \frac{\partial}{\partial\eta}$$

and $\nabla^2 \exp(\lambda t + i\mathbf{k}\cdot\mathbf{x}) = -|\mathbf{k}|^2 \exp(\lambda t + i\mathbf{k}\cdot\mathbf{x})$

where $|\mathbf{k}|^2 = \left|\kappa_1\hat{\mathbf{e}}_1^* + \kappa_2\hat{\mathbf{e}}_2^*\right|^2 = \frac{4}{3}\left(\kappa_1^2 + \kappa_2^2 \pm \kappa_1\kappa_2\right)$

$$\kappa_j \equiv 2\pi\frac{k_j}{N_j}, \quad j = 1,2 \Rightarrow |\mathbf{k}| \le 2\pi$$

- Linearization about IFE gives rise to the alternative characteristic equation with cubic factor

$$C_c(\lambda;\mathbf{k}) = \lambda^3 + b_2\lambda^2 + b_1\lambda + b_0$$

where

$$b_0 = (\Delta_3(k+\Delta_2) - kL_I\varphi)(\Lambda + D_V|\mathbf{k}|^2) - kpL_V$$

$$b_1 = \Delta_3(k+\Delta_2+\Lambda+D_V|\mathbf{k}|^2) + (\Lambda + D_V|\mathbf{k}|^2)(k+\Delta_2) - kL_I\varphi$$

$$b_2 = \Delta_3 + k + \Delta_2 + \Lambda + D_V|\mathbf{k}|^2$$

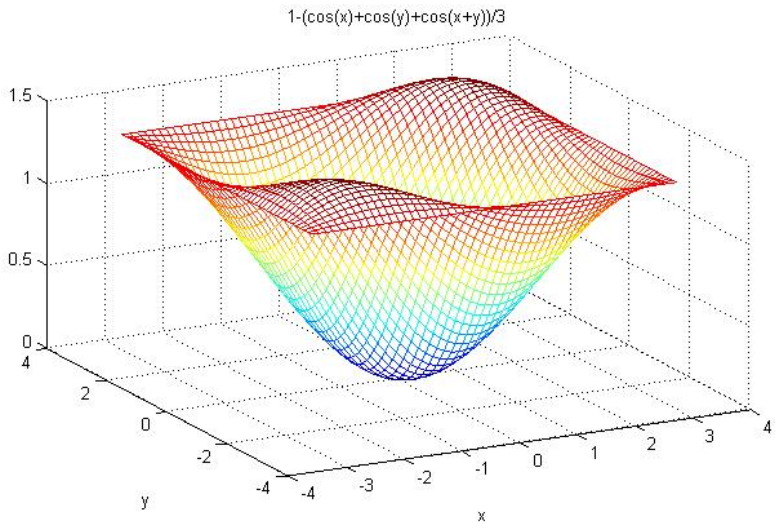
where $|\mathbf{k}| \le 2\pi$

Routh-Hurwitz yields essentially same outcome as before:
For sufficiently large killing rate (Δ_3) of infected cells by CTLs), the system is stable against spread of infection, independent of the diffusion rate D_V.
However: Critical Δ_3 will be different between 'discrete' and 'continuous' diffusion models

Approximations to $-\nabla^2$

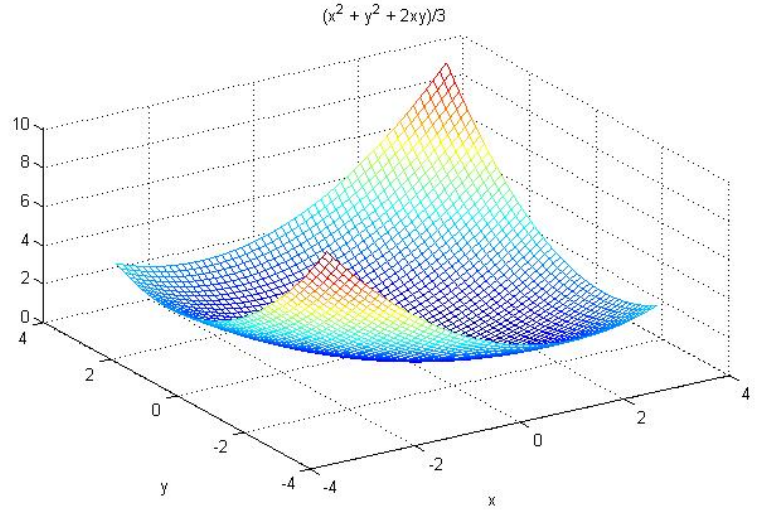
Numerical simulations

$$1-\tfrac{1}{6}\varphi(\mathbf{k})$$



Continuous

$$|\mathbf{k}|^2$$

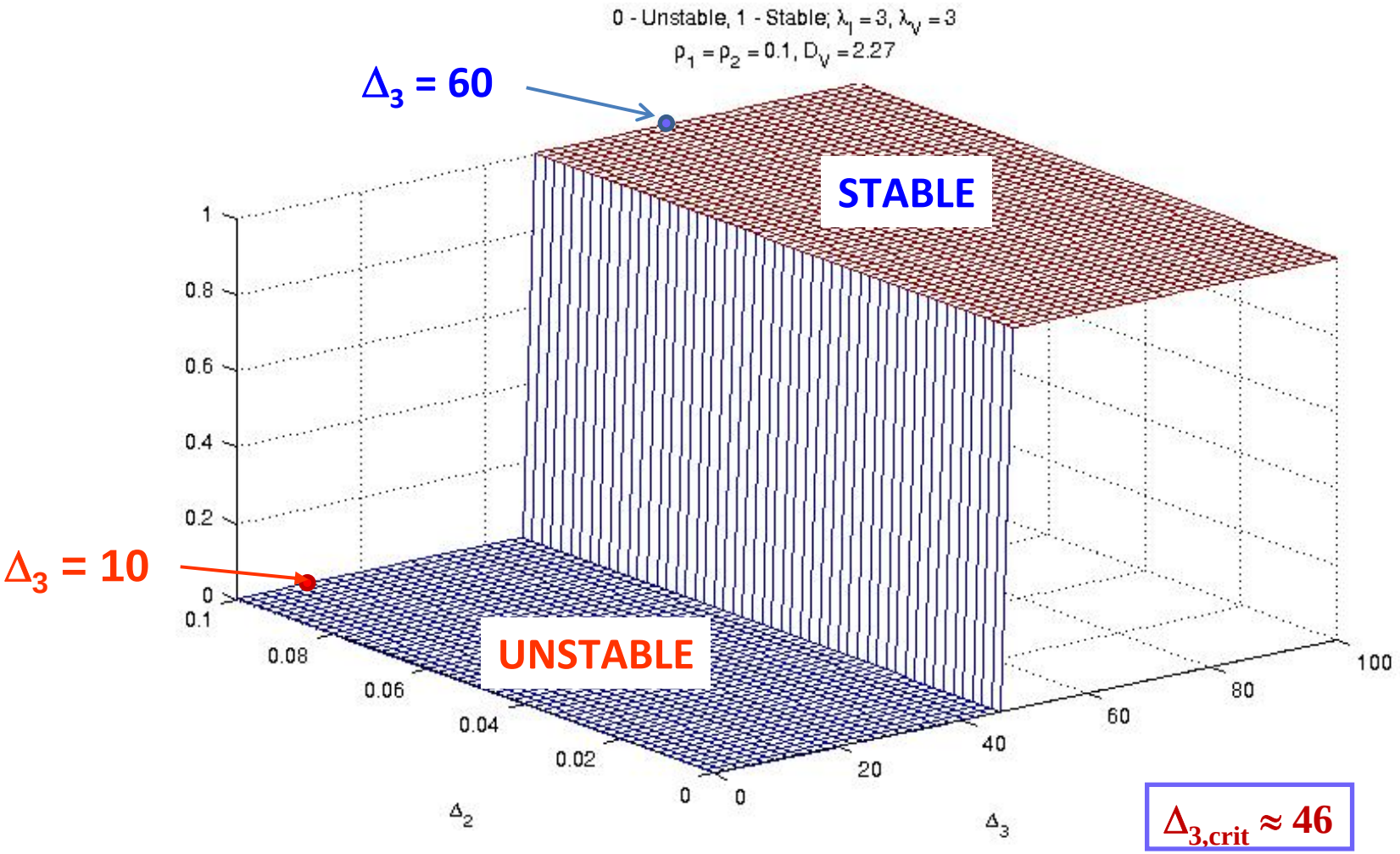


Parameter values

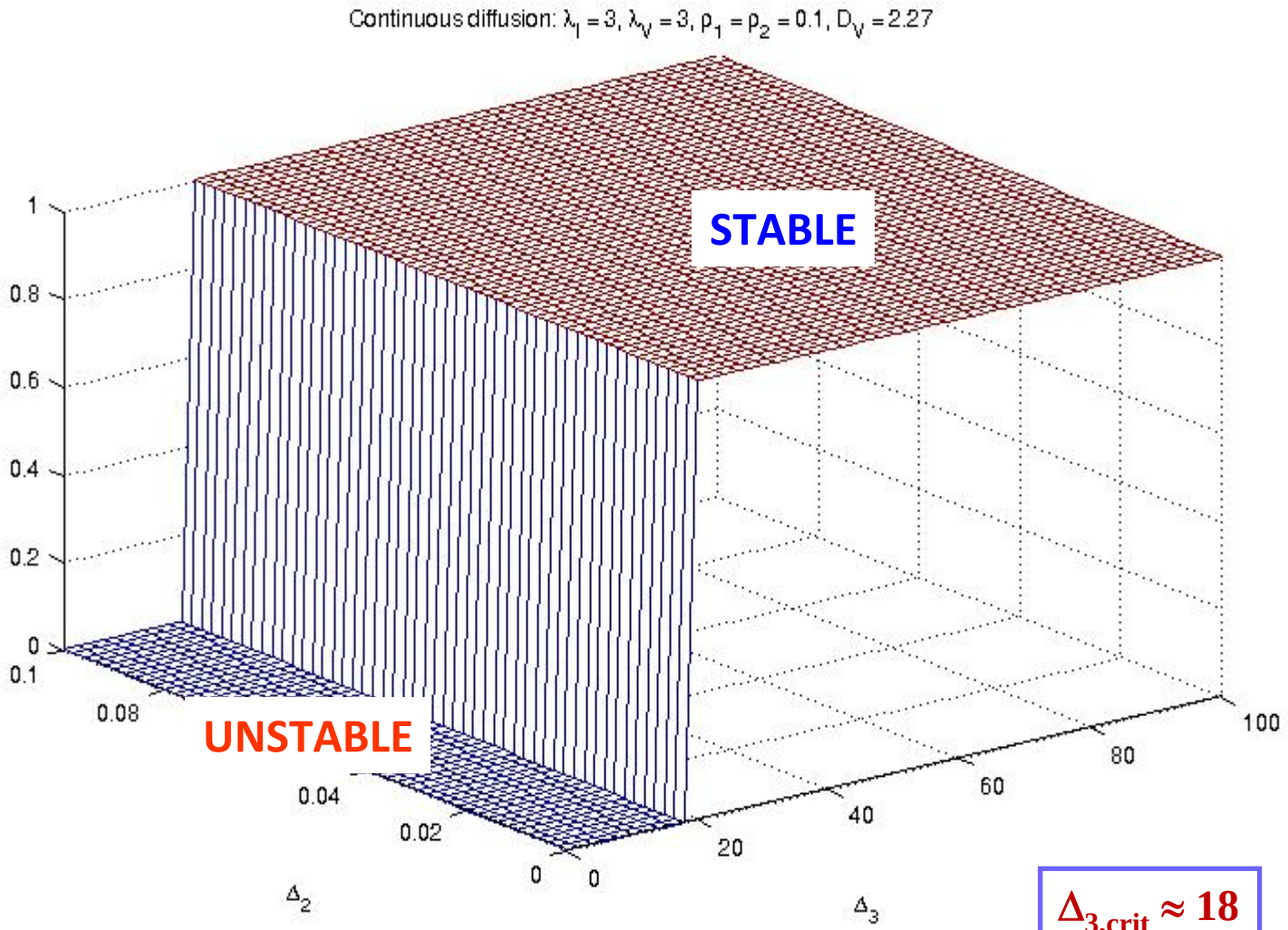
Parameter		Value
λ_I	Infection rate due to contact with I_2 cells	3 d^{-1}
λ_V	Infection rate due to free virus	3 d^{-1}
γ	Replacement rate, vacant epithelial cell sites (R)	3 d^{-1}
k	Rate of $I_1 \rightarrow I_2$ (infected → infectious) transition	4 d^{-1}
δ_1	Death rate of I_2 by viral infection alone	0.1 d^{-1}
δ_2	Death rate of I_1 by NK*	0.1 d^{-1}
δ_3	Death rate of I_2 due to CTLs	(variable)
$\beta_{APC,1}$	Rate of viral phagocytosis (by APC)	*
β_{NEU}	Rate of viral phagocytosis (by neutrophils)	*
$\beta_{d,1}$	Rate of uptake of dead cells by APC	*
$\beta_{d,2}$	Rate of uptake of dead cells by neutrophils	*
p	Rate of production of free virus by infected cell	50
c	Viral clearance rate	2 d^{-1}
D_V	Diffusion constant (scaled to cell spacing)	2.27 d^{-1}

* Level-1 model incorporates these, and [APC], [NEU], into constants ρ_1, ρ_2

Stability (of IFE) conferred by CTLs: Discrete diffusion approximation



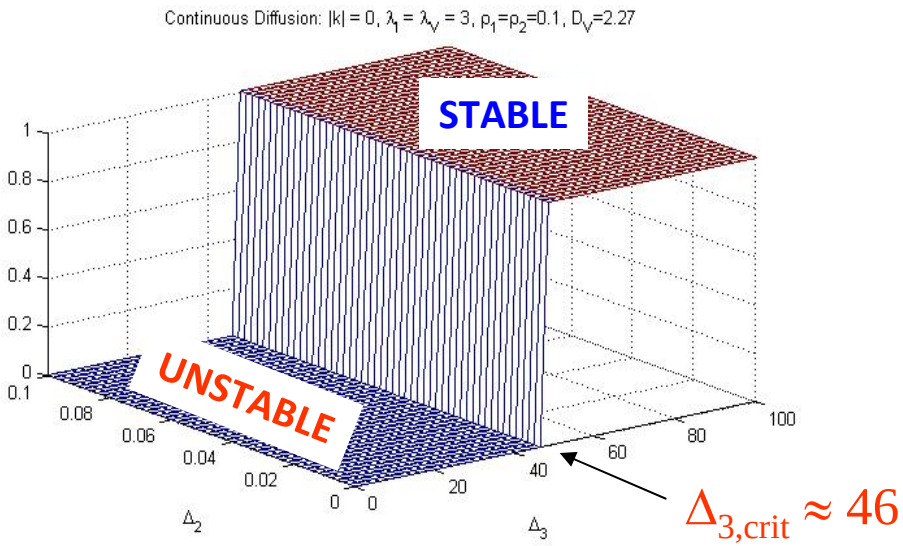
Stability (of IFE) conferred by CTLs: Continuous diffusion approximation



$\Delta_{3,crit} \approx 18$

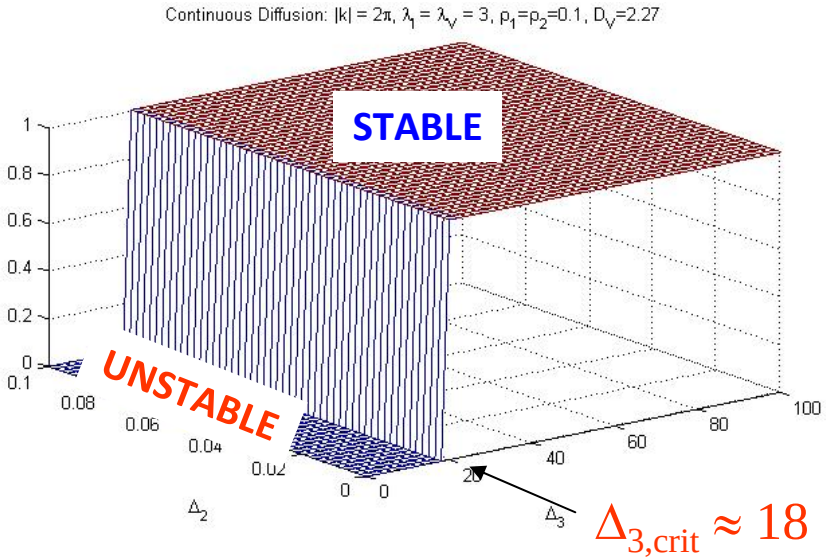
Continuous diffusion approximation: Dependence on |k|

$|\mathbf{k}| = 0$



$\Delta_{3,\text{crit}} \approx 46$

$|\mathbf{k}| = 2\pi$

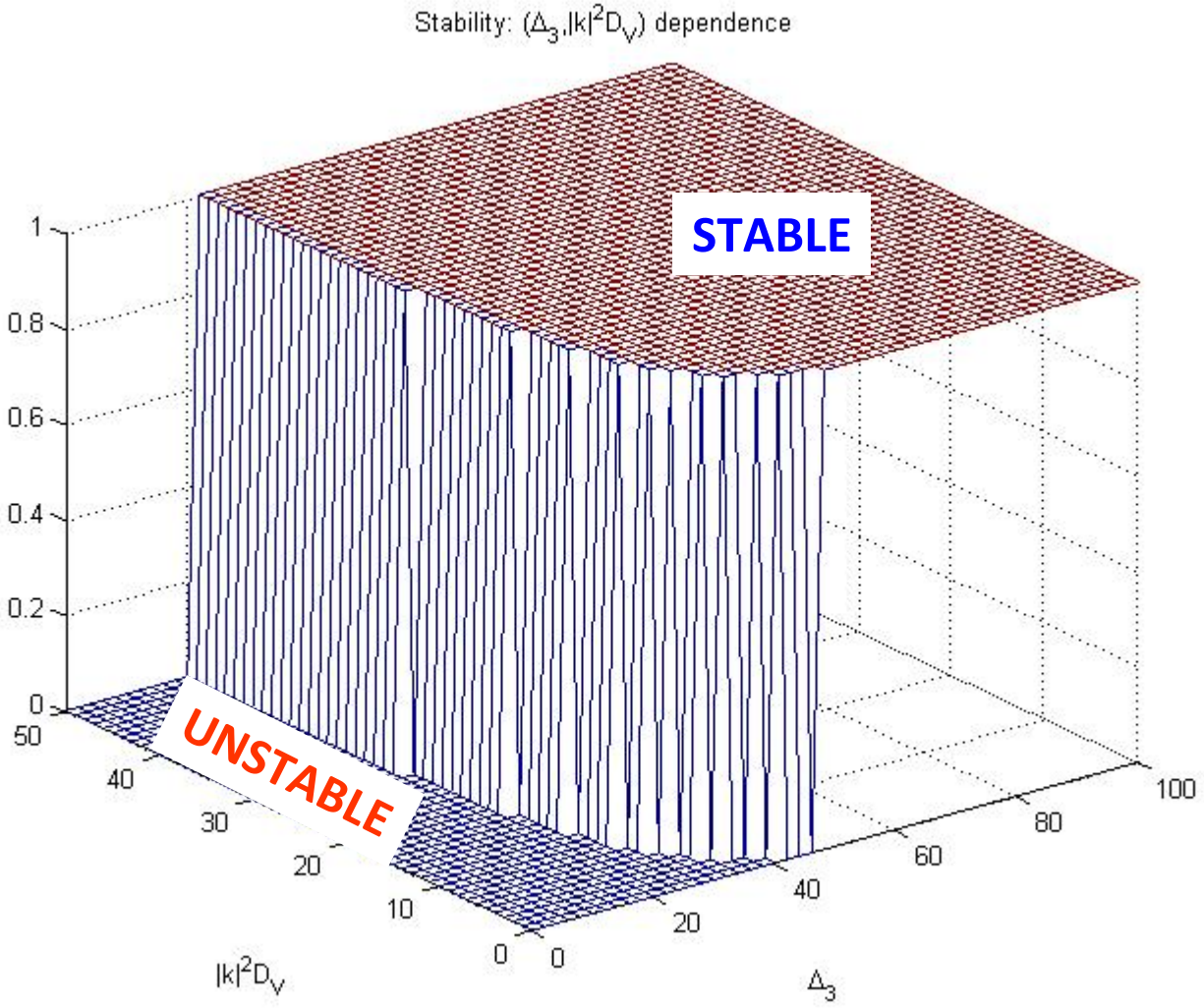


$\Delta_{3,\text{crit}} \approx 18$

Thus,

- As [CTL] increases, fine-scale ($|\mathbf{k}|$ large) infection regions disappear before coarse-scale ($|\mathbf{k}|$ small)
- As D_V increases, $\Delta_{3,\text{crit}}$ (and hence $[\text{CTL}]_{\text{crit}}$ required to prevent infection) increases

Stability: Dependence on [CTL], diffusion

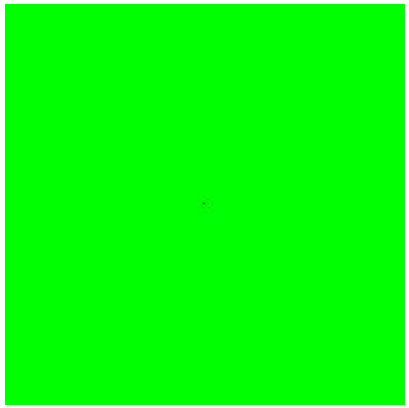


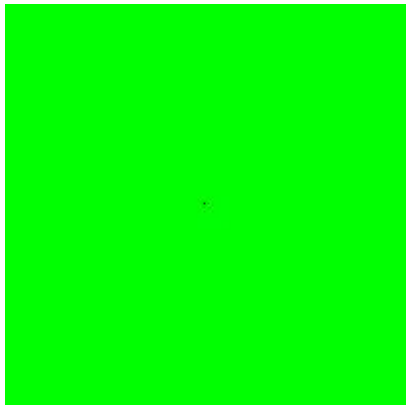
SPATIAL PROGRESSION OF INFECTION

(Seed infection: $V = 1$ at centre)

Stable configuration: $\Delta_3 = 60$

$\Delta_{3,crit} \approx 46$

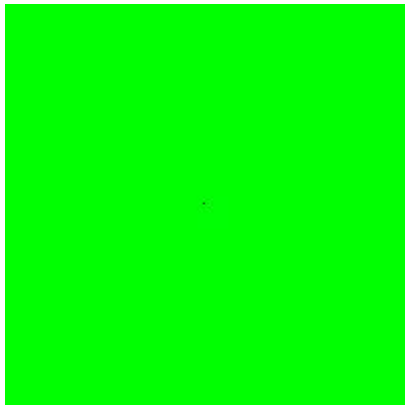


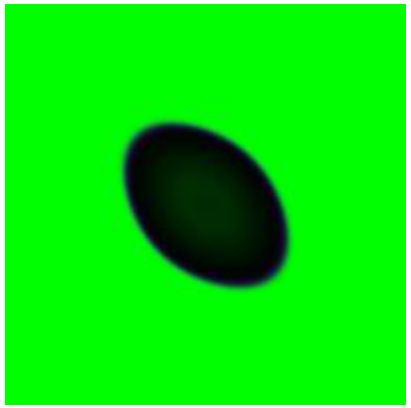


$t = 0$

$t = 10$ days

Unstable configuration: $\Delta_3 = 10$





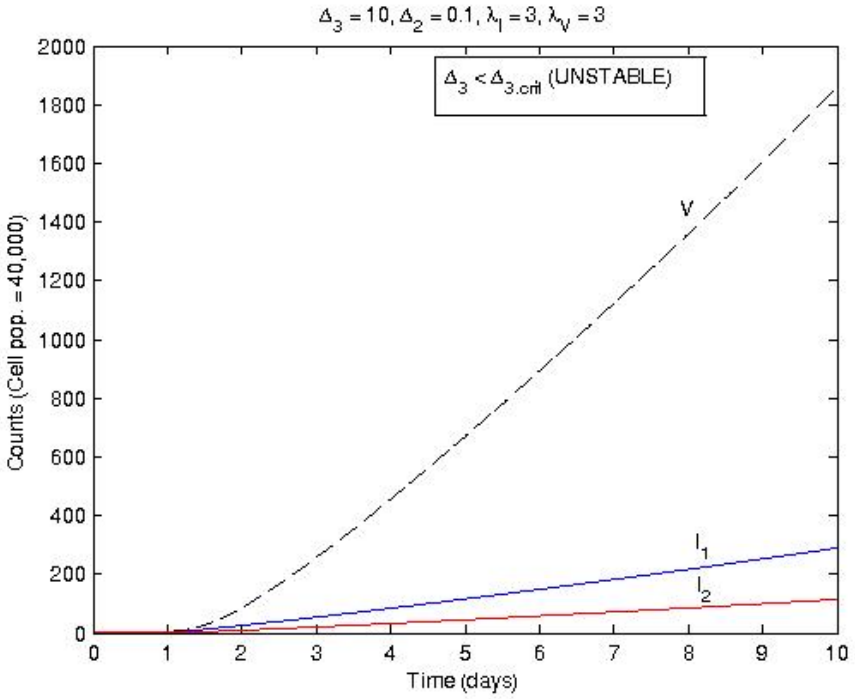
Population counts for virus & infected cells

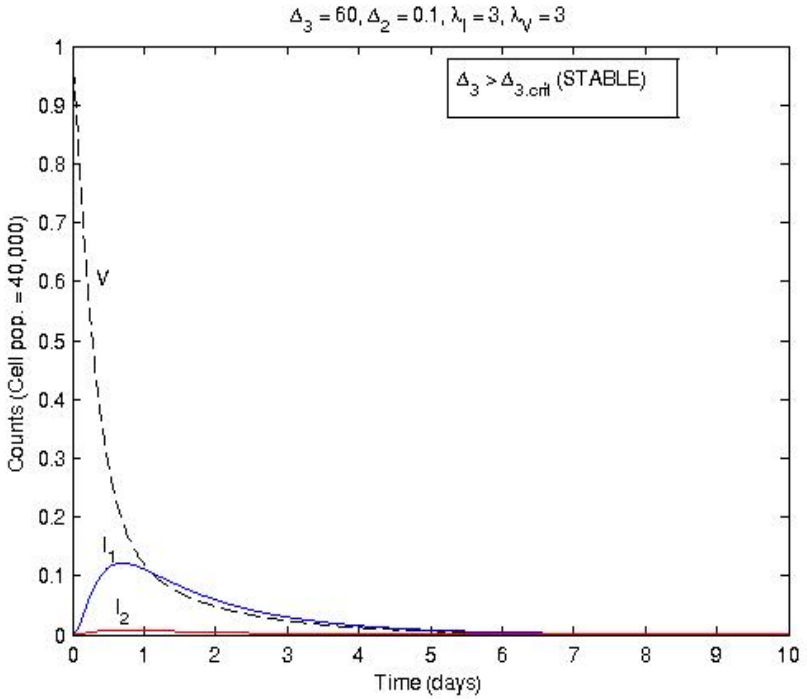
$$\Delta_3 \equiv \delta_1 + \delta_3[\text{CTL}];\quad \Delta_2 \equiv \delta_2[\text{NK}^*]$$

Unstable ($\Delta_3 = 10 < \Delta_{3,\text{crit}}$)

Stable ($\Delta_3 = 60 > \Delta_{3,\text{crit}}$)

$\Delta_{3,\text{crit}} \approx 46$



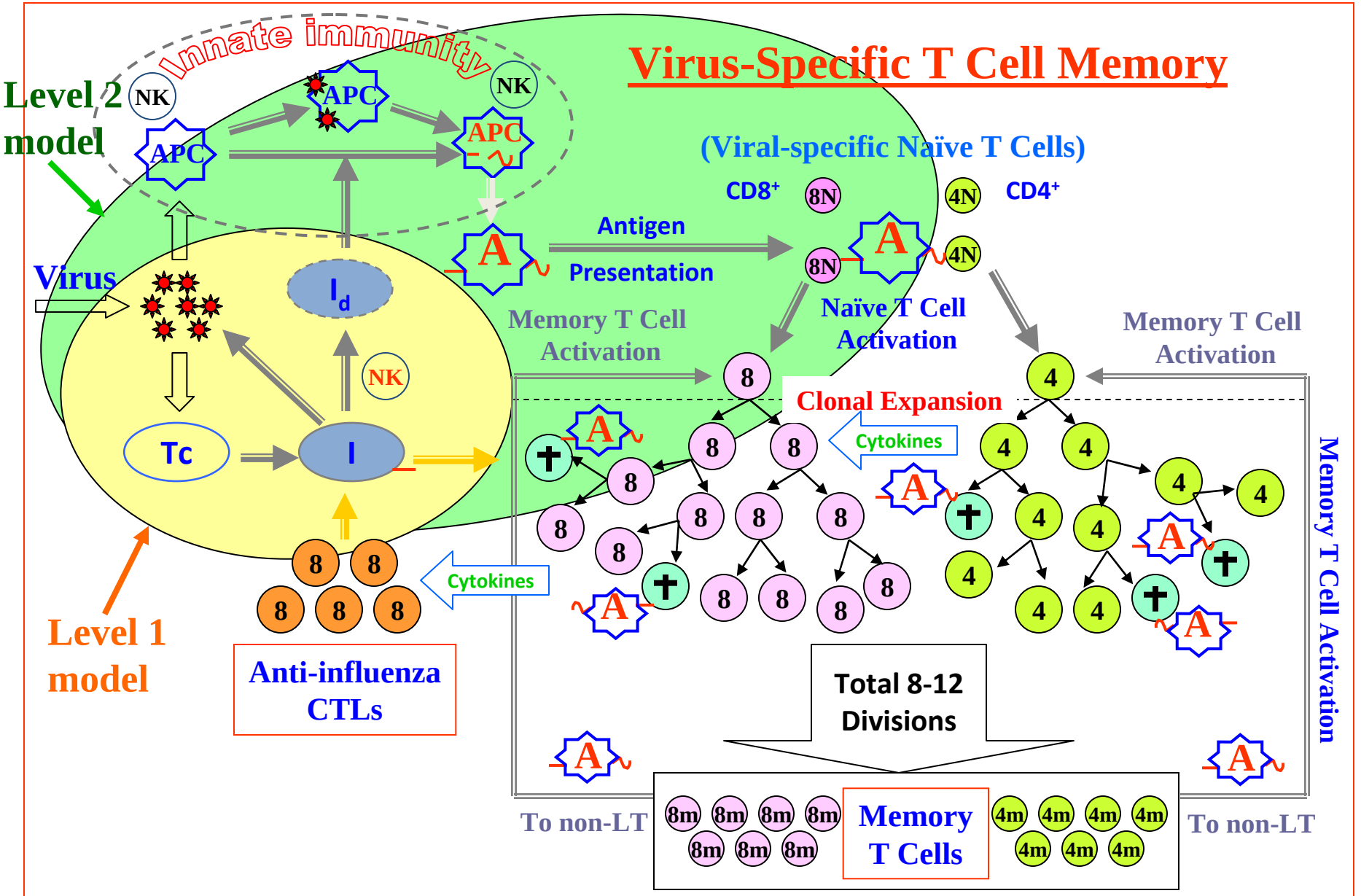


Linear stability analysis correctly predicts:

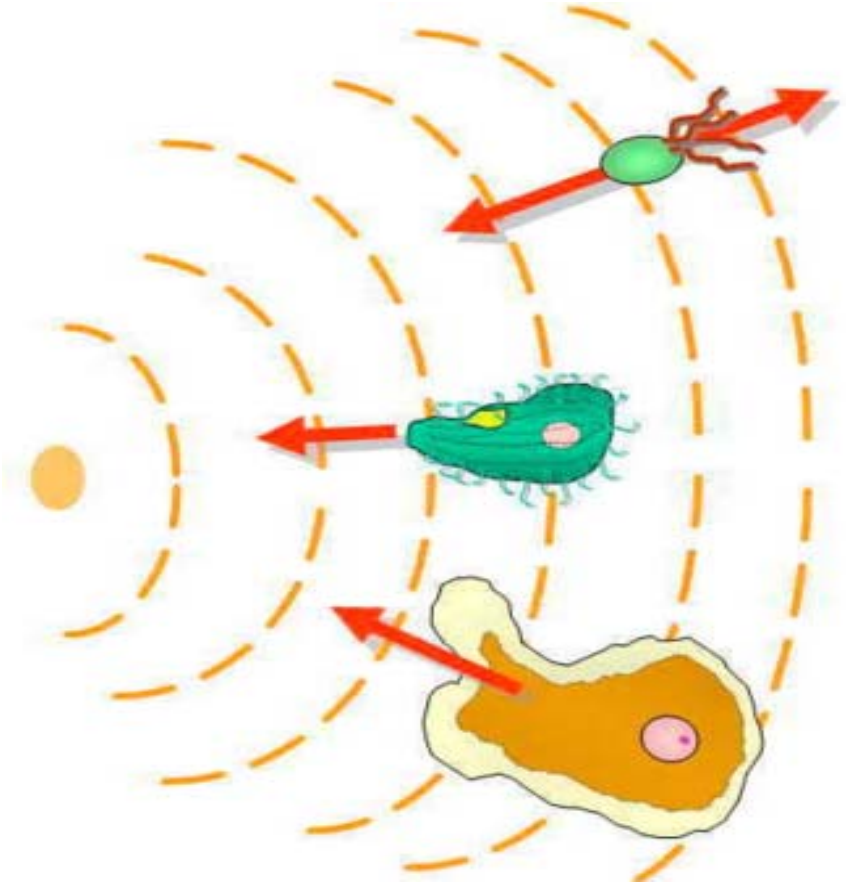
1. Transition between outbreak and suppression, when [CTL] is sufficiently raised;
2. Insensitivity to [NK^*];
3. Critical [CTL] depends on value of diffusion constant D_V, with fine-scale features disappearing before coarse-scale

Under construction:
'Level 2' model of innate immune system

- Level-1 includes immune system only in a parametric sense, via death rates of infected epithelial cells
- **NEXT STEP**: Include strategic components of innate immune system, and couple its dynamics to Level 1 system. Current Level-2 model comprises
  - $INF\alpha/\beta$, $APC \rightarrow APC^*$, chemotactic and inflammatory cytokines, INFα,β, INFγ, NK $\rightarrow$ NK*, neutrophils, Dendritic Cells
  - Diffusion and **chemotaxis**


Virus-Specific T Cell Memory
Innate immunity
Level 2 model
NK
APC
APC
NK
APC
(Viral-specific Naïve T Cells)
CD8+
8N
4N
CD4+
Antigen
Presentation
A
Virus
Id
Memory T Cell Activation
Naïve T Cell Activation
Memory T Cell Activation
NK
Tc
I
8
4
Clonal Expansion
Cytokines
Cytokines
Level 1 model
Anti-influenza CTLs
Total 8-12 Divisions
To non-LT
8m
Memory T Cells
4m
To non-LT
Memory T Cell Activation

Example of chemotaxis



Directional cell migration in case of leukocytes (bottom two cells) but not bacteria (cell on top)

From: Francis Lin, Physics Dept., U of Manitoba