Fractional age structured population dynamics with application in epidemiology

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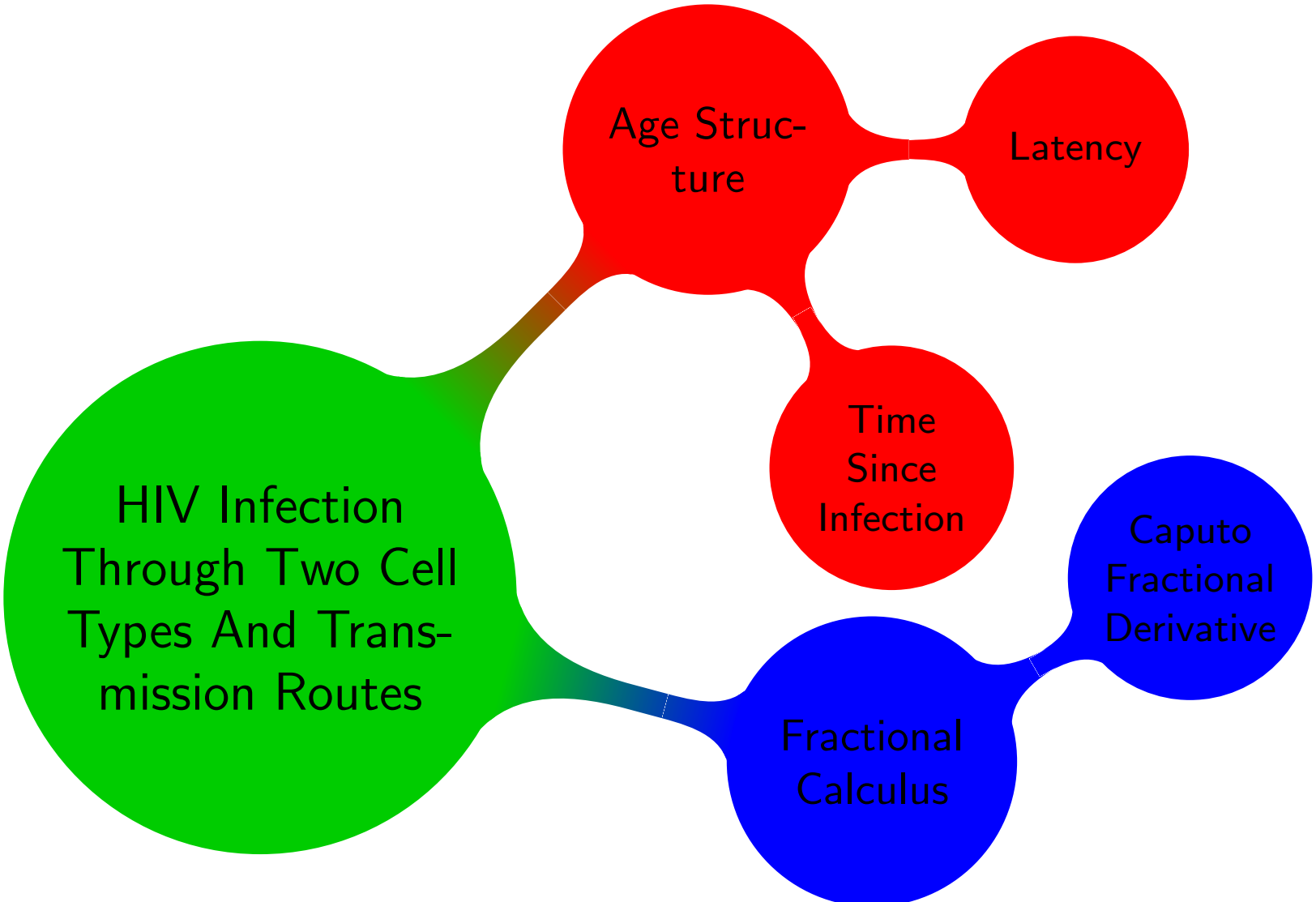
Problem statement



Preliminaries

Definition

The function $\Gamma : (0, \infty) \to \mathbb{R}$ *defined by*

$$\Gamma(\nu) := \int_0^\infty t^{\nu-1} e^{-t} dt,$$

is called Euler's Gamma function.

Definition

The Mittag-Leffler function of order ν *is defined by*

$$E_\nu(t) = \sum_{j=0}^{\infty} \frac{t^j}{\Gamma(j\nu + 1)},$$

for all $\nu \in (0, 1)$.

Definition

The Riemann-Liouville fractional integral operator of order ν $I^{\nu} : \mathbb{L}_1[a,b] \to \mathbb{R}$ *is defined as:*

$$I^{\nu} f(t) := \frac{1}{\Gamma(\nu)} \int_a^b (t-x)^{\nu-1} f(x) dx, \quad \text{where} \quad t \in [a,b], \nu \in (0,1),$$

where $\mathbb{L}_1[a,b]$ *is the set of bounded functions.*

Definition

The Caputo fractional differential operator of order ν, ${}_0^C D_t^{\nu}$, *is defined by:*

$$ {}_0^C D_t^{\nu} f(t) := I^{1-\nu} \frac{df(t)}{dt},$$

where $\nu \in (0,1)$ *and* $\frac{df(t)}{dt} \in \mathbb{L}_1[0,b]$.

Definition

Consider a function defined as

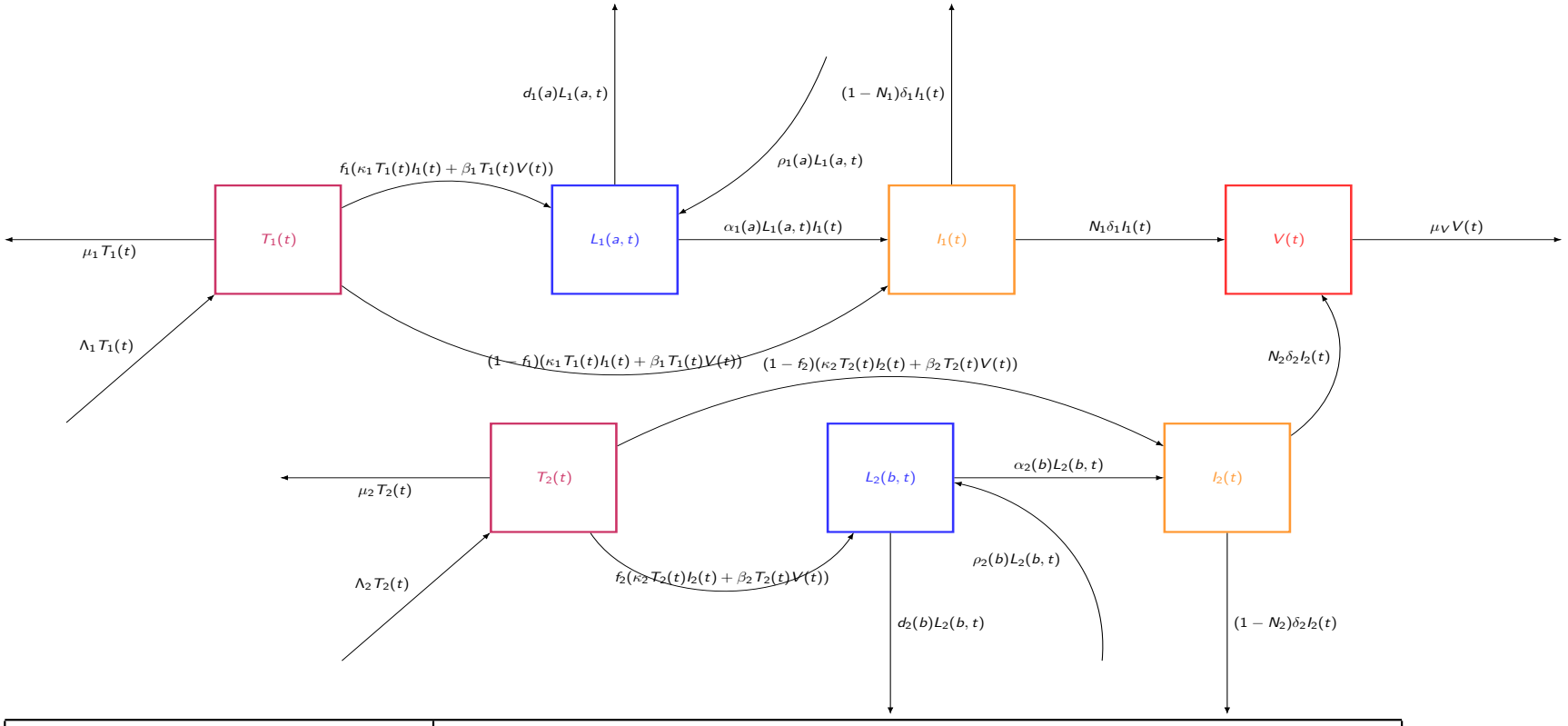
$$\psi(t) = \psi(0)E_\nu(\lambda t^\nu) = \psi_0 \sum_{j=0}^{\infty} \frac{\lambda^j t^{\nu j}}{\Gamma(j\nu + 1)},$$

for all $\nu \in (0, 1)$ *and some constant* λ*, is a solution of the initial value fractional problem* ${}_0^C D_t^\nu \psi(t) = \lambda\psi(t)$ *with* $\psi(0) = \psi_0$.

Theorem

Consider an N-dimensional system of Caputo fractional differential equations ${}_0^C D_t^\nu \psi(t) = A\psi(t)$ *of order* ν*, where A is an arbitrary constant* $N \times N$ *matrix. A solution* $\psi(t)$ *of the system is asymptotically stable if and only if all distinct eigenvalues* λ_j *for* $j = 1, 2, \ldots, N$ *of the matrix A satisfy the condition* $|arg(\lambda_j)| > \frac{\nu\pi}{2}$.

Dynamics of HIV infection within-host



$T_1(t), T_2(t)$	Type 1 and 2 target cells
$L_1(a,t), L_2(b,t)$	Type 1 and 2 latently infected cells
$I_1(t), I_2(t)$	Type 1 and 2 productively infected cells
$V(t)$	Viral load at time t

Model Formulation

The dynamics of HIV infection within-host by two cell Types and transmission routes are represented by the Caputo fractional system

$$ {}_0^C D_t^\nu \psi(t) = f(\psi(t)), $$

where $\psi(t) \in \mathbb{X} = \mathbb{R}_+^2 \times (\mathbb{L}_1^+[0,\infty))^2 \times \mathbb{R}_+^3$ is given by

$$ \psi(t) = (T_1(t), T_2(t), I_1(t), I_2(t), I_1(t), I_2(t), V(t))^T $$

and

$$ f(\psi(t)) = \begin{pmatrix} \Lambda_1 - \mu_1 T_1(t) - (\beta_1 V(t) + \kappa_1 I_1(t)) T_1(t) \\ \Lambda_2 - \mu_2 T_2(t) - (\beta_2 V(t) + \kappa_2 I_2(t)) T_2(t) \\ (\rho_1(a) - \alpha_1(a) - d_1(a)) L_1(a,t) - {}_0^C \partial_a^\nu L_1(a,t) \\ (\rho_2(b) - \alpha_2(b) - d_2(b)) L_2(b,t) - {}_0^C \partial_b^\nu L_2(b,t) \\ (1-f_1)(\beta_1 V(t) + \kappa_1 I_1(t)) T_1(t) + A_1(t) - \delta_1 I_1(t) \\ (1-f_2)(\beta_2 V(t) + \kappa_2 I_2(t)) T_2(t) + A_2(t) - \delta_2 I_2(t) \\ N_1 \delta_1 I_1(t) + N_2 \delta_2 I_2(t) - \mu_V V(t) \end{pmatrix} $$

where $A_k(t) = \int_0^\infty \alpha_k(s) L_k(s,t) ds$ and $I_k(t) = \int_0^\infty L_k(s,t) ds$, for $s \in \{a, b\}$ and $k = 1, 2$.

Parameters of the model

- Λ_1, Λ_2 - Recruitment rate for Type 1 and 2 target cells
- μ_1, μ_2 - Death rate of Type 1 and 2 target cells
- β_1, β_2 - Transmission rate per contact with free virons of Type 1 and 2 cells
- κ_1, κ_2 - Transmission rate per contact with productively infected cells for Type 1 and 2 cells
- $\rho_1(a), \rho_2(b)$ - Proliferation rate of latently infected cells
- $\alpha_1(a), \alpha_2(b)$ - Transition rate of latently infected cells to productive infection
- $d_1(a), d_2(b)$ - Death rate of latently infected cells
- f_1, f_2 - Fraction of target cells that become latently infected
- δ_1, δ_2 - Death rate of productively infected Type 1 and 2 cells
- N_1, N_2 - Total number of virons a productively infected cell produces during its entire life cycle
- μ_V - Clearance rate of virons

Well-posedness of the model

- Boundedness - Any solution ψ of the fractional system

$$ {}_0^C D_t^\nu \psi(t) = f(\psi(t)), $$

satisfies the condition

$$ ||\psi||_{\mathbb{X}} \leq \frac{\Lambda_1 + \Lambda_2}{c_3} \text{ for all } t \geq 0, $$

where

$$ c_3 = \min\{\mu_1, \mu_2, c_1, c_2, (1 - N_1)\delta_1, (1 - N_2)\delta_2, \mu_V\}, $$

with

$$ c_1 = \inf_{a \in [0,\infty)} \{d_1(a)\} - \sup_{a \in [0,\infty)} \{\rho_1(a)\} $$

and

$$ c_2 = \inf_{b \in [0,\infty)} \{d_1(b)\} - \sup_{b \in [0,\infty)} \{\rho_2(b)\}. $$

Well-posedness cont.

- Positivity - The function $f(\psi(t))$ can be decomposed as

$$f(\psi(t)) = \mathfrak{L}\psi(t) + \mathfrak{M}(\psi(t)).$$

$$\mathfrak{L} = \begin{pmatrix} -\mu_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\mu_2 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -{}^{C}\partial_a^{\nu} + m_1(a) & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -{}^{C}\partial_b^{\nu} + m_2(b) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\delta_1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\delta_2 & 0 \\ 0 & 0 & 0 & 0 & N_1\delta_1 & N_2\delta_2 & -\mu_V \end{pmatrix},$$

$$\mathfrak{M}(\psi(t)) = \begin{pmatrix} \Lambda_1 - \beta_1 T_1(t)V(t) - \kappa_1 T_1(t)I_1(t), \\ \Lambda_2 - \beta_2 T_2(t)V(t) - \kappa_2 T_2(t)I_2(t), \\ 0 \\ 0 \\ (1-f_1)(\beta_1 T_1(t)V(t) + \kappa_1 T_1(t)I_1(t)) + \int_0^{\infty} \alpha_1(a)L_1(a,t)da \\ (1-f_2)(\beta_2 T_2(t)V(t) + \kappa_2 T_2(t)I_2(t)) + \int_0^{\infty} \alpha_2(b)L_2(b,t)db \\ 0 \end{pmatrix}$$

where
$m_k(s) = \alpha_k(s) + d_k(s) - \rho_k(s)$ for all $s \in \{a, b\}$ and $k = 1, 2$.

Well-posedness cont.

- The matrix $\mathcal{M}(\psi(t))$ is positive whenever the condition

$$\frac{\Lambda_k}{(\Lambda_1+\Lambda_2)^2} > \frac{\beta_k+\kappa_k}{c_3^2}$$

is satisfied for all $k = 1, 2$. Therefore the solution space

$$G = \left\{ \psi(t) \in \mathbb{X} : \frac{\Lambda_k}{(\Lambda_1+\Lambda_2)^2} > \frac{\beta_k+\kappa_k}{c_3^2} \text{ for all } k = 1, 2 \right\}$$

is positive invariant.

Equilibrium states

The equilibrium states of the system satisfy the equation $f(\psi^*(t)) = 0$ where $\psi^*(t) = (T_1^*, T_2^*, L_1^*(a), L_2^*(b), I_1^*, I_2^*, V^*)^T$. Let

$$\mathcal{R}_k^{CC} = \frac{\Lambda_k}{\mu_k}(1 + \xi_k f_k - f_k)\frac{\kappa_k}{\delta_k},$$

be the reproduction number of the virus through the cell to cell transmission route. The probability distribution of latent Type k cells is given by

$$\sigma_k(s) = \sum_{j=0}^{\infty} \left(- \frac{a^\nu m_k(s)}{\Gamma(\nu + 1)} \right)^j$$

and the probability of transition by latent Type k cells is defined as

$$\xi_k = \int_0^\infty \alpha_k(s)\sigma_k(s)ds$$

where $s \in \{a, b\}$ and $k = 1, 2$.

Equilibrium states cont.

- Disease-Free-Equilibrium (DFE) - The disease is unable to invade the target populations, hence only the target cells are present.

$$E^0 = \left(\frac{\Lambda_1}{\mu_1}, \frac{\Lambda_2}{\mu_2}, 0, 0, 0, 0, 0\right)^T = \left(T_1^0, T_2^0, 0, 0, 0, 0, 0\right)^T.$$

- Type 1-Dominated-Endemic-Equilibrium - The disease invades only the Type 1 target cells, thus the disease does not spread through Type 2 cells.

$$E_1^* = \left(\left(1 - \frac{\kappa_1 I_1^*}{\mu_1 \mathcal{R}_1^{CC}}\right) T_1^0, \frac{\Lambda_2}{\mu_2}, L_1^*(0)\sigma_1(a), 0, I_1^*, 0, \frac{N_1 \delta_1}{\mu_V} I_1^*\right)^T,$$

where $L_1^*(0) = f_1(\beta_1 T_1^* V^* + \kappa_1 T_1^* I_1^*)$.

Equilibrium states cont.

- Type 2-Dominated-Endemic-Equilibrium - The disease invades only the Type 2 target cells, thus the disease does not spread through Type 1 cells.

$$E_2^* = \left(\frac{\Lambda_1}{\mu_1}, \left(1 - \frac{\kappa_2 I_2^*}{\mu_2 \mathcal{R}_2^{CC}} \right) T_2^0, 0, L_2^*(0)\sigma_2(b), 0, I_2^*, \frac{N_2 \delta_2}{\mu_V} I_2^* \right)^T,$$

  where $L_2^*(0) = f_2(\beta_2 T_2^* V^* + \kappa_2 T_2^* I_2^*)$.

- Disease Endemic Equilibrium - The disease invades the target populations by spreading through both Type 1 and Type 2 cells.

$$E_3^* = E_1^* + E_2^* - E_0.$$

Basic reproduction number

The basic reproduction number through Type k cells is given by

$$\mathcal{R}_k = \frac{\Lambda_k}{\mu_k}(1+\xi_k f_k - f_k)\left(\frac{\beta_k N_k}{\mu_V} + \frac{\kappa_k}{\delta_k}\right) = \mathcal{R}_k^{CV} + \mathcal{R}_k^{CC} \text{ for all } k = 1, 2.$$

Reproduction number of the disease through cell-to-cell transmission route

$$\mathcal{R}_k^{CC} = \frac{\Lambda_k}{\mu_k}(1 + \xi_k f_k - f_k)\frac{\kappa_k}{\delta_k}$$

Reproduction number of the disease through cell-to-virus transmission route

$$\mathcal{R}_k^{CV} = \frac{\Lambda_k}{\mu_k}(1 + \xi_k f_k - f_k)\frac{\beta_k N_k}{\mu_V}.$$

The reproduction of HIV within-host through each cell type occurs due to reproduction of the disease by cell-to-cell and cell-to-virus transmission.

Stability of the DFE

Let

$$\phi(t) = \phi_0 E_\nu(\lambda t^\nu) \text{ where } \phi(0) = \phi_0$$

be a solution of the system

$$_0^C D_t^\nu \psi(t) = f(\psi(t)), \psi(0) = \psi_0.$$

Then the eigenvalues λ of the linearized fractional system

$$_0^C D_t^\nu \phi(t) = \lambda \phi(t)$$

satisfy the characteristic equation

$$C^0(\lambda) = \frac{A_0(\lambda)}{1 - A_2(\lambda)} + A_2(\lambda) = 1$$

Local Asymptotic Stability

where

$$A_0(\lambda) = \frac{[T_1^0\beta_1 N_2\delta_2][T_2^0\beta_2 N_1\delta_1]\bar{\xi}_{1,\lambda}\bar{\xi}_{2,\lambda}}{(\lambda+\mu_V)^2(\lambda+\delta_1)(\lambda+\delta_2)},$$

$$A_1(\lambda) = \bar{\xi}_{1,\lambda}\left(\frac{\beta_1 N_1\delta_1}{(\lambda+\mu_V)(\lambda+\delta_1)} + \frac{\kappa_1}{\lambda+\delta_1}\right)T_1^0$$

and

$$A_2(\lambda) = \bar{\xi}_{2,\lambda}\left(\frac{\beta_2 N_2\delta_2}{(\lambda+\mu_V)(\lambda+\delta_2)} + \frac{\kappa_2}{\lambda+\delta_2}\right)T_2^0,$$

with

$$\sigma_{k,\lambda}(s) = \sum_{j=0}^{\infty}\left(-\frac{s^\nu(m_k(s)+\lambda)}{\Gamma(\nu+1)}\right)^j, \xi_{k,\lambda} = \int_0^\infty \alpha_k(s)\sigma_{k,\lambda}(s)ds \text{ and}$$

$$\bar{\xi}_{k,\lambda} = 1 + \xi_{k,\lambda}f_k + f_k$$

where $s \in \{a, b\}$ and $k = 1, 2$.

Local Asymptotic Stability cont.

Theorem

The DFE is locally asymptotically stable provided $|arg(\lambda)| > \frac{\pi\nu}{2}$ *for all* $\nu \in (0,1)$, *otherwise the DFE is unstable.*

Proof.

- **Case 1 ($\lambda \in \mathbb{R}$):** If $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 < 1$ then $\lambda < 0$.
- **Case 2 ($\lambda \in \mathbb{C}$):** The real part of the eigenvalue λ is strictly negative, that is $\Re(\lambda) < 0$.

Therefore it follows that $|arg(\lambda)| \in (\frac{\pi}{2}, \pi]$, that is $|arg(\lambda)| > \frac{\pi\nu}{2}$ for all $\nu \in (0,1)$.

□

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