Existence, positivity and stability for delay differential equations of cellular proliferation

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2. Mathematical analysis of the model
   - Existence and stability

Introduction

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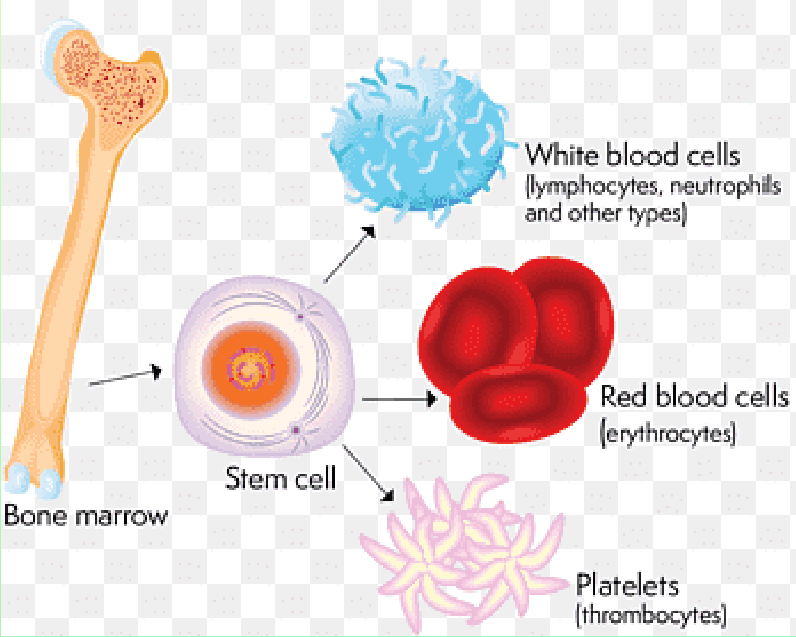
Introduction
A blood cell production model
Mathematical analysis of the model
Existence and stability

The objective of this presentation is the mathematical analysis of a model of production and regulation of blood cells in the bone marrow called hematopoiesis.

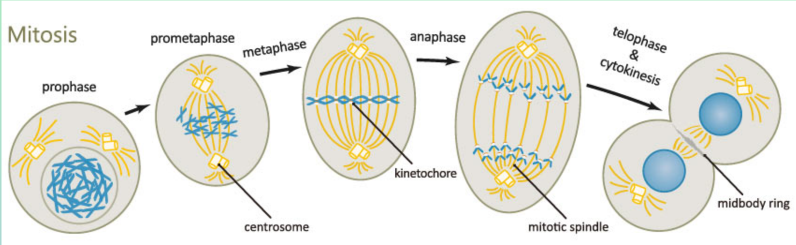
Introduction

The objective of this presentation is the mathematical analysis of a model of production and regulation of blood cells in the bone marrow called hematopoiesis. The modeling of these populations is carried out using a system of delay differential equations.

Frame Title



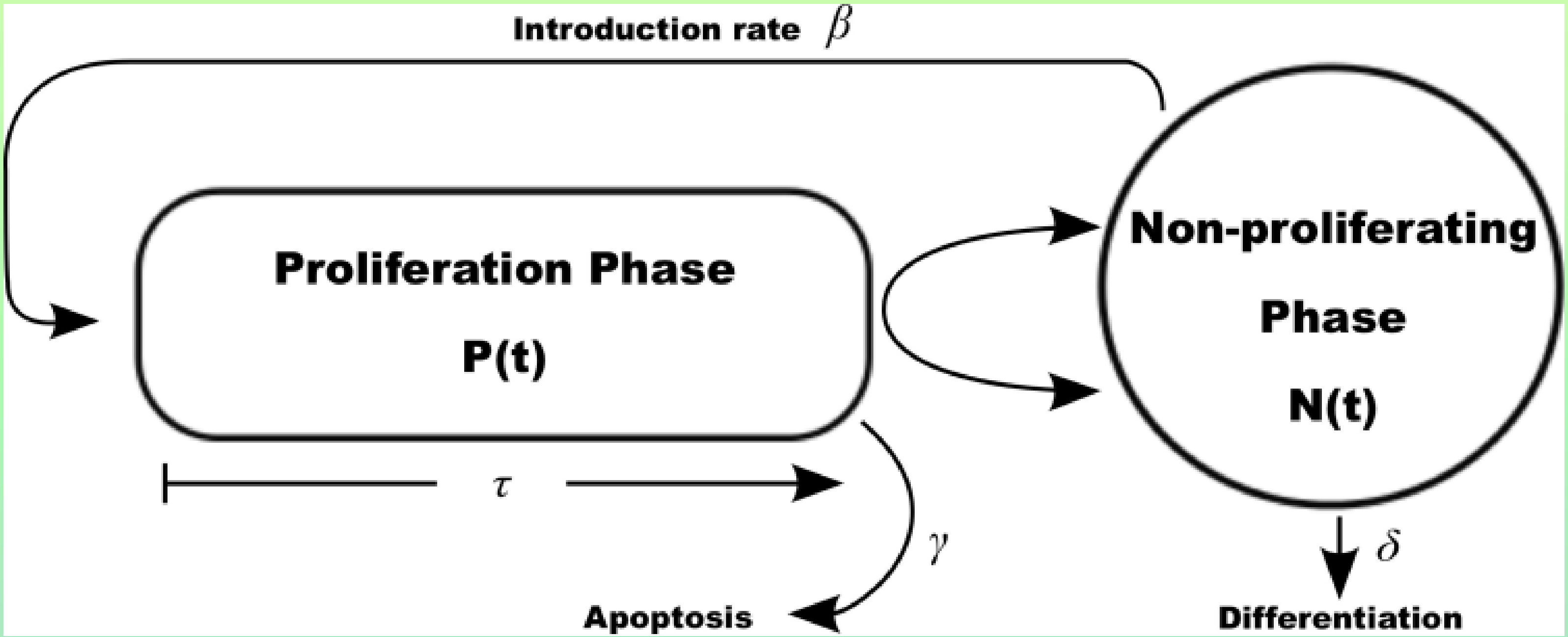
(Source: https://e7.pngegg.com/pngimages/186/568/png-clipart-bone-marrow-hematopoietic-stem-cell-transplantation-organ-transplantation-white-blood-cell-bone-marrow-text-cell-thumbnail.png)



(Source: https://www.genetex.com/upload/media/research/Cell)

A blood cell production model

This model explains the interaction between proliferating cells (P) and non-proliferating cells (N) in a tumor.

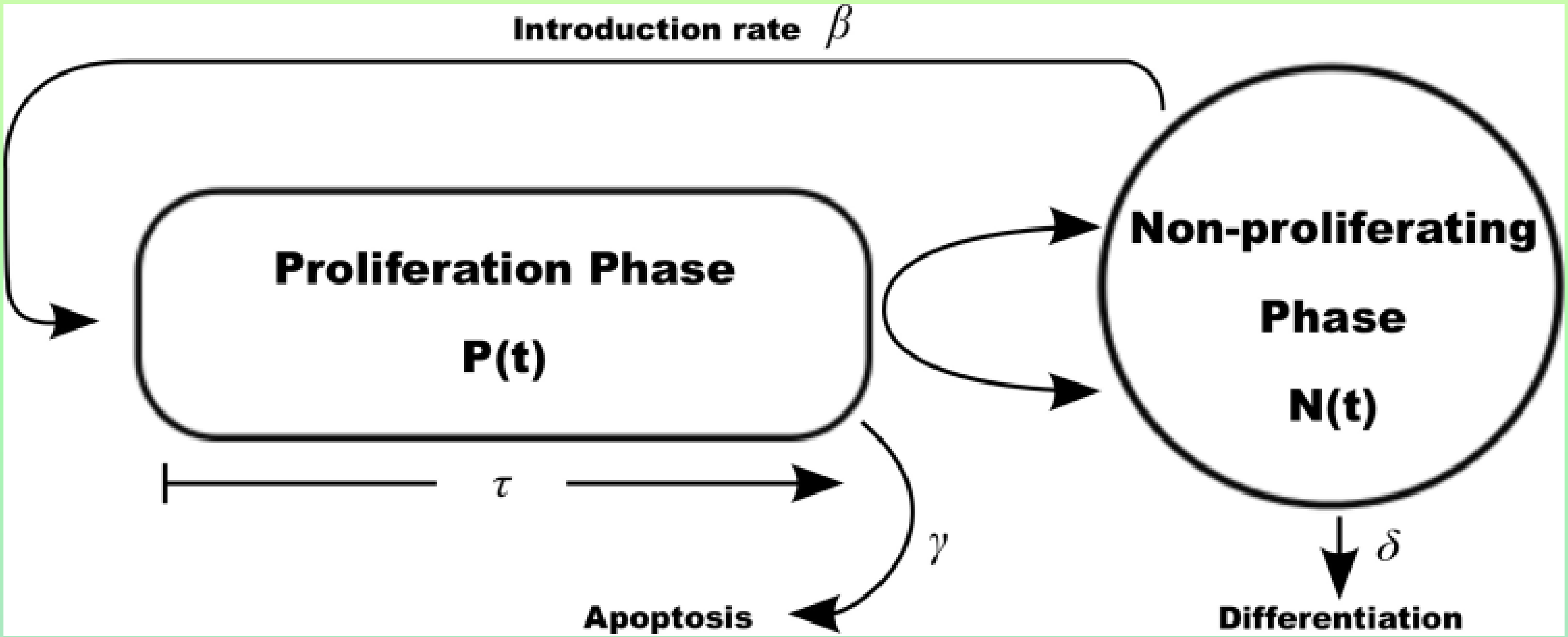


(Source: Alila Medical Images-Fotolia.com)

Cells in the proliferating phase can divide and grow, but cells in the non proliferation grow without dividing.

A blood cell production model

This model explains the interaction between proliferating cells (P) and non-proliferating cells (N) in a tumor.



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Cells in the non-proliferating phase can leave this phase either by mortality with a rate $\delta > 0$ which considers the differentiation, or by entering into proliferation phase with a rate $\beta > 0$.

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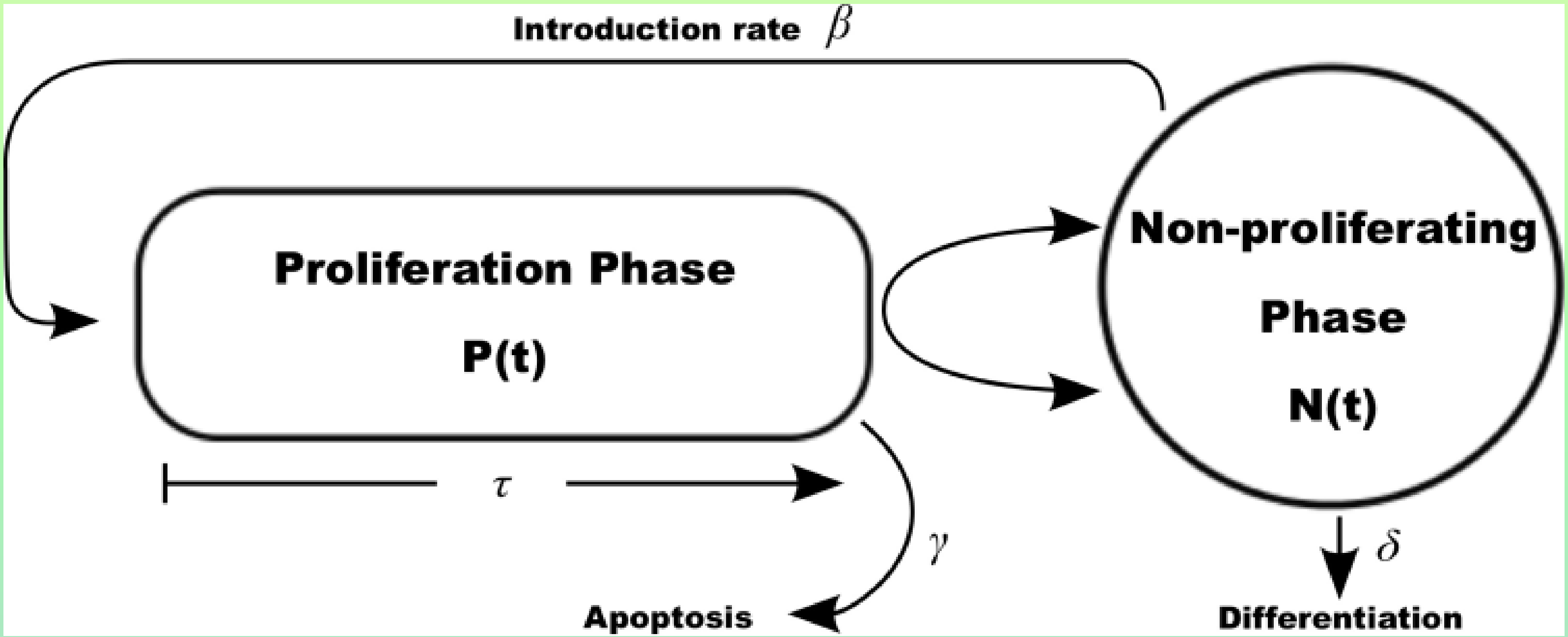

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In the proliferating phase, the cells are allowed to stay only for a finite time. We note $\tau > 0$ the time duration of the proliferating phase. In this compartment, the cells are eliminated by apoptosis (programmed death) with a rate of $\gamma > 0$.

A blood cell production model

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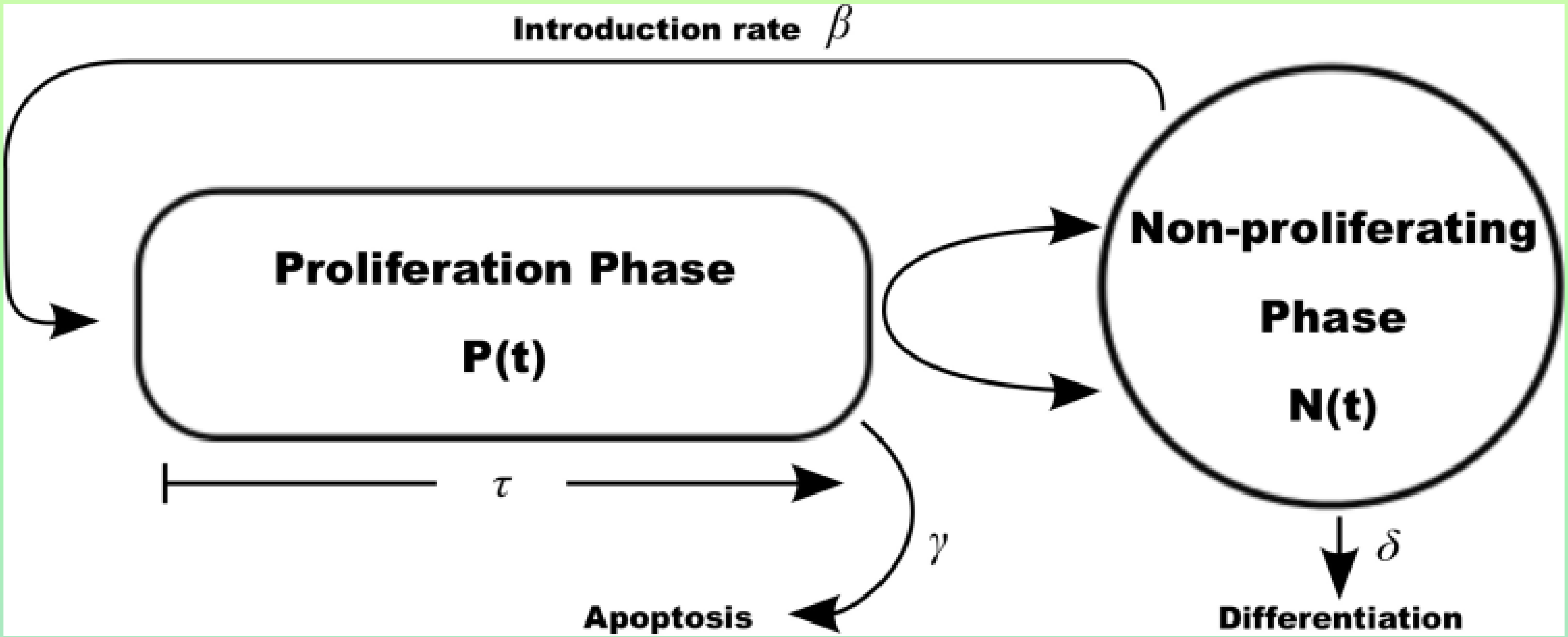

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At the end of the proliferating phase, all the cells divide and each one gives two daughter cells. The latter directly access the non- proliferating phase.

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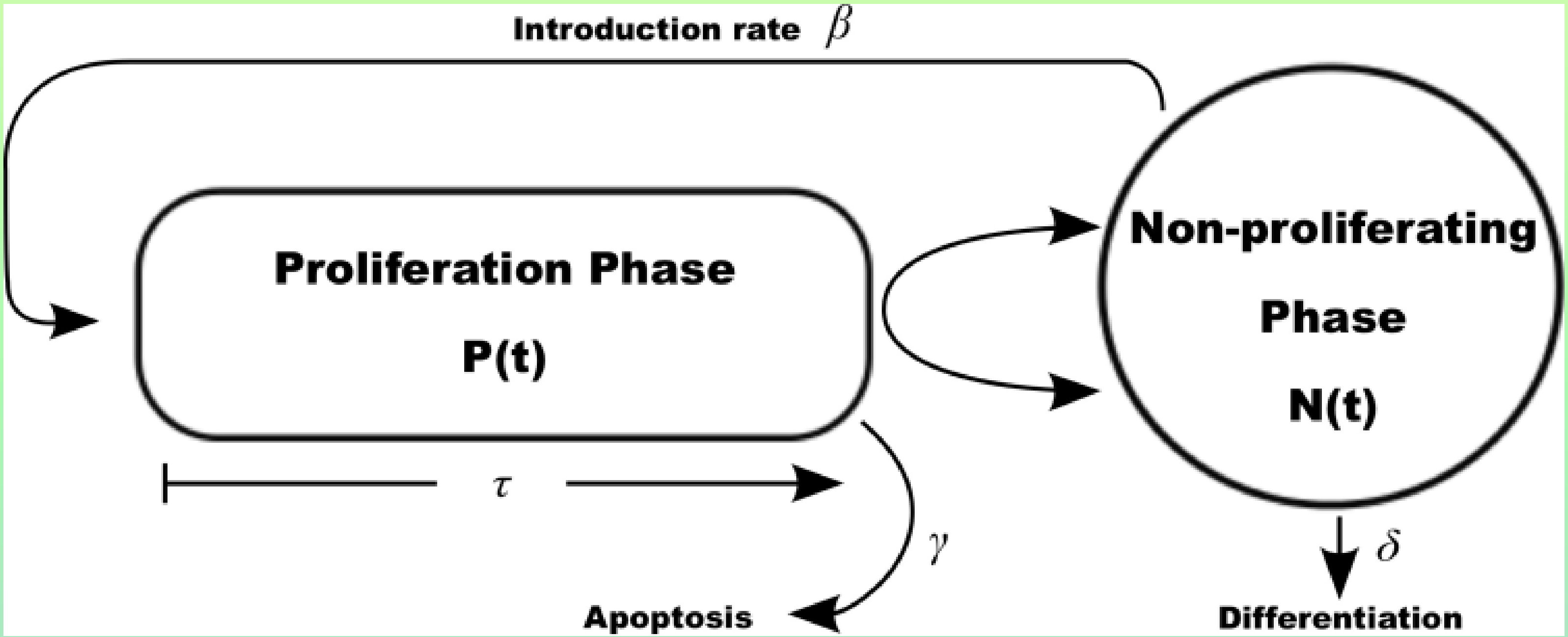

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We assume, for the sake of simplicity, that proliferating and non-proliferating cells die at the same rate, i.e. $\delta = \gamma$.

Mathematical model

Then the populations P and N satisfy the following evolution equations (see M. Adimy [3] or [4]),

$$\begin{cases} \dot{P} &= -\gamma P(t) + \beta N(t) - \mathrm{e}^{-\delta\tau}\beta N(t-\tau), \\ \dot{N} &= -\delta N(t) - \beta N(t) + 2\mathrm{e}^{-\delta\tau}\beta N(t-\tau). \end{cases} \tag{1}$$

we assume that the rate of reintroduction $\beta = \beta(S(t))$ depends on the total population of hematopoietic stem cells denoted by S i.e. $S(t) = N(t) + P(t)$. The function β is naturally assumed to be decreasing and positive with $\lim_{S\to\infty} \beta(S) = 0$.

The populations N and S satisfy the following nonlinear system with delay τ,

$$\begin{cases} \dot{S} &= -\delta S(t) + \mathrm{e}^{-\delta\tau}\beta(S(t-\tau))N(t-\tau), \\ \dot{N} &= -\delta N(t) - \beta(S(t))N(t) + 2\mathrm{e}^{-\delta\tau}\beta(S(t-\tau)N(t-\tau). \end{cases} \tag{2}$$

Existence of solutions

Theorem

For any initial condition $(\varphi, \psi) \in \mathcal{C}([-\tau, 0], \mathbb{R}_+) \times C([-\tau, 0], \mathbb{R}_+)$ *the system* (2) *admits a unique positive solution in* $[0, +\infty[$.

The existence of steady states

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The equilibrium point of (2) is a solution $(S(t), N(t))$ satisfying

$$\dot{S}(t) = \dot{N}(t) = 0.$$

The existence of steady states

If $\beta_0 \leq \delta$

Equilibrium	$\tau \geqslant 0$
X_0	Exists

$\beta_0 > \delta$

Equilibrium	$0 \leqslant \tau < \bar{\tau}$	$\tau \geqslant \bar{\tau}$
X_0	Exists	Exists
X_1	Exists	Do not exists

- $\beta_0 = \beta(0)$

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- $\beta_0 = \beta(0)$
- $\bar{\tau} := \dfrac{1}{\delta} \ln \left(\dfrac{2\beta_0}{\delta + \beta_0} \right),$

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- $S^* = \theta \left(\frac{\beta_0 (2e^{-\delta\tau} - 1)}{\delta} - 1 \right)^{\frac{1}{n}}$ and

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- $S^* = \theta\left(\frac{\beta_0(2e^{-\delta\tau} - 1)}{\delta} - 1\right)^{\frac{1}{n}}$ and
- $N^* = \left(\frac{(2e^{-\delta\tau} - 1)\beta_0}{\delta} - 1\right)^{\frac{1}{n}} \theta\left(\frac{(2e^{-\delta\tau} - 1)}{e^{-\delta\tau}}\right)$

The characteristic equation

Let $f(S,N) = -\delta S(t) + \mathrm{e}^{-\delta\tau}\beta(S(t-\tau))N(t-\tau)$,
and g(S,N) = - $\delta N(t) - \beta(S(t))N(t) + 2\mathrm{e}^{-\delta\tau}\beta(S(t-\tau)N(t-\tau)$.
The characteristic equation of system (2) is defined by

$$\det(\lambda I - A_1 - e^{-\lambda\tau}A_2) = 0$$

Where

$$A_1 = \begin{pmatrix} \frac{\partial f}{\partial \overline{S}}(t) & \frac{\partial f}{\partial \overline{N}}(t) \\ \frac{\partial g}{\partial \overline{S}}(t) & \frac{\partial g}{\partial \overline{N}}(t) \end{pmatrix} \quad and \quad A_2 = \begin{pmatrix} \frac{\partial f}{\partial \overline{S}}(t-\tau) & \frac{\partial f}{\partial \overline{N}}(t-\tau) \\ \frac{\partial g}{\partial \overline{S}}(t-\tau) & \frac{\partial g}{\partial \overline{N}}(t-\tau) \end{pmatrix}$$

Theorem

The characteristic equation

Let $f(S,N) = -\delta S(t) + \mathrm{e}^{-\delta\tau}\beta(S(t-\tau))N(t-\tau)$,
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Theorem

- *If* $\sup\{\mathrm{Re}\lambda : \det(\lambda I - A_1 - e^{-\lambda\tau}A_2) = 0\} < 0$ *then the equilibrium point is locally asymptotically stable.*

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Theorem

- *If* $\sup\{\mathrm{Re}\lambda : \det(\lambda I - A_1 - e^{-\lambda\tau}A_2) = 0\} < 0$ *then the equilibrium point is locally asymptotically stable.*
- *If* $\mathrm{Re}\lambda > 0$ *for some* λ *satisfying* $\det(\lambda I - A_1 - e^{-\lambda\tau}A_2) = 0$ *then the equilibrium point is unstable.*

The stability of X_0

The stability of the X_0 steady state

$\beta_0 \leq \delta$

Equilibrium	$\tau \geqslant 0$
X_0	Stable

$\beta_0 > \delta$

Equilibrium	$0 \leqslant \tau < \bar{\tau}$	$\tau \geqslant \bar{\tau}$
X_0	Unstable	Stable

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