A note on global attractivity of the periodic solution for a model of hematopoiesis

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Abstract

For the generalized periodic model of hematopoiesis

$$x'(t) = -a(t)x(t) + \sum_{i=1}^{m} \frac{b_i(t)}{1 + x(t - \tau_i(t))^n},$$

with $0 < n \leq 1$, sufficient conditions for the global attractivity of its positive periodic solution are given, improving previous results in the literature. The effectiveness of the present criterion is illustrated by a numerical example.

Keywords: Hematopoiesis, Global attractivity, Yorke condition, Periodic solution

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1 Introduction

The delay differential equation (DDE)

$$x'(t) = -\gamma x(t) + \frac{\beta}{1 + x(t - \tau)^n}, \quad t \geq 0, \tag{1.1}$$

where $\gamma, \beta, \tau, n \in (0, \infty)$, was introduced by Mackey and Glass [8] and since then has proven to be a suitable model to describe the hematopoiesis (the process of production, multiplication, and specialization of blood cells in bone marrow). In (1.1), $x(t)$ is the density of the mature cells in the circulation, τ is the time delay between the production of immature cells in the bone marrow and their maturation for release in the bloodstream, γ is a destruction rate, and β is the maximal production rate. More details can be found in [8].

Since Mackey and Glass' publication, model (1.1) has been studied by many researchers (see [1, 4, 5, 6, 7] and references therein) from different points of view. As all coefficients are positive, equation (1.1) has a unique steady state k, which is the positive solution of the equation

$$\gamma k = \frac{\beta}{1 + k^n}.$$

The stability of the equilibrium point k has been studied by several authors. For the case $0 < n \leq 1$, E. Liz et al. [6] proved that k is a global attractor of (1.1) (in the set of positive solutions) without further constraints.

As the environment plays an important role in many biological and ecological dynamical systems, the model is often more realistic if periodic parameters are considered, taking into account the periodicity of the environment. In fact, periodic versions of (1.1) have attracted the attention of several authors (see [1, 5, 10] and references therein).

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For $\omega > 0$, and $a, b : \mathbb{R} \to (0, \infty)$, $\tau : \mathbb{R} \to [0, \infty)$ ω-periodic continuous functions, the model

$$x'(t) = -a(t)x(t) + \frac{b(t)}{1 + x(t - \tau(t))^n}, \ \ t \geq 0, \tag{1.2}$$

has a positive ω-periodic solution $\widetilde{x}(t)$ (see [10]) but, to the best of our knowledge, for $0 < n \leq 1$, to prove or disprove that all positive solutions of (1.2) converge to the positive periodic solution $\widetilde{x}(t)$ remains an open problem [1]. A first contribution to solve this problem was given by G. Liu et al. in [5], where the authors considered the following generalized model of hematopoiesis:

$$x'(t) = -a(t)x(t) + \sum_{i=1}^{m} \frac{b_i(t)}{1 + x(t - \tau_i(t))^n}, \ \ t \geq 0, \tag{1.3}$$

with $m \in \mathbb{N}$, $n \in (0, 1]$, and $a, b_i : \mathbb{R} \to (0, \infty)$, $\tau_i : \mathbb{R} \to [0, \infty)$ ω-periodic continuous functions $i = 1, \ldots, m$. For this equation, G. Liu et al. proved the existence of a unique positive ω-periodic solution $\widetilde{x}(t)$ [5, Theorem 2.1], and established a criterion for its global attractivity in the set of positive solutions [5, Theorem 3.1].

Motivated by the open problem referred to above (see [1, Problem 4]), in this note we give an improvement of the global stability criterion presented in [5, Theorem 3.1]. For this purpose, we insert (1.3) in a more general framework studied in our previous works [2, 3]. An illustrative numerical example in Section 4 shows that the requirements to apply such criterion are easy to check.

2 Preliminaries and Notations

First, we set some notations. Let $C := C([-\tau, 0]; \mathbb{R})$ be the Banach space of continuous functions from $[-\tau, 0]$ to $\mathbb{R}$ equipped with the sup norm, $\|\varphi\| = \max_{-\tau \leq \theta \leq 0} |\varphi(\theta)|$. For delay functions $\tau_i : [0, \infty) \to [0, \infty)$ continuous and bounded $(1 \leq i \leq m)$, define

$$\tau(t) = \max_{1 \leq i \leq m} \{\tau_i(t)\}, \qquad \tau = \sup_{t \geq 0} \{\tau(t)\},$$

and consider a DDE of the form

$$y'(t) = -a(t)y(t) + \sum_{i=1}^{m} f_i(t, y_t^i), \ \ t \geq 0, \tag{2.1}$$

where $a : [0, \infty) \to [0, \infty)$ is continuous, $f_i(t, y_t^i) = f_i\left(t, y_{|[t-\tau_i(t),t]}\right)$ and $f_i(t, \varphi)$, $i = 1, \ldots, m$, are functions defined for $t \geq 0$ and $\varphi \in C([-\tau_i(t), 0]; \mathbb{R})$ in the following way: for $t \geq 0$ and $\varphi \in C([-\tau_i(t), 0]; \mathbb{R})$, we take the extension $\varphi^* \in C$ of φ which is $\varphi(-\tau_i(t))$ on $[-\tau, -\tau_i(t)]$, and define f_i as the restriction of some continuous function $F_i : [0, \infty) \times C \to \mathbb{R}$, with $F_i(t, \varphi^*) := f_i\left(t, \varphi^*_{|[-\tau_i(t),0]}\right) = f_i(t, \varphi)$. For a DDE (2.1) in C, initial conditions have the form $y_{t_0} = \varphi$ for $\varphi \in C$, where, as usual, y_{t_0} is defined by $y_{t_0}(\theta) = y(t_0 + \theta)$ for $\theta \in [-\tau, 0]$.

Assuming $f(t, 0) = 0$ for $t \geq 0$, in [2, 3] the authors considered the model (2.1) (with and without impulses) and gave sufficient conditions for the stability and global attractivity of the trivial solution. Due to the interpretation of the models under consideration, one frequently restricts the set of *admissible* initial conditions, as well as the set of solutions, so that the concept of attractivity only applies to a subset of initial conditions $S^* \subseteq C$. A set S^* is said to be an *admissible set of initial conditions* for (2.1) if

$$\varphi \in S^* \Rightarrow y_t(\cdot, t_0, \varphi) \in S^*, \qquad \text{for} \qquad t \geq t_0 \geq 0,$$

where $y(t, t_0, \varphi)$ denotes the solution of (2.1) such that $y_{t_0} = \varphi$.

The definition of global attractivity is recalled below.

Definition 2.1. *We say that a solution $y^*(t)$ of a DDE* (2.1) *is* globally attractive *in an admissible set $S^* \subseteq C$ if $y^*_t \in S^*$ and*

$$y^*(t) - y(t) \to 0, \ \text{ as } t \to \infty,$$

for all solutions $y(t)$ with initial condition in S^*.

For the non-impulsive situation, the main assumptions in [2] can be summarized as follows:

(H1) $\displaystyle\int_0^\infty a(u)du = \infty$;

(H2) there are piecewise continuous functions $\lambda_{1,i}, \lambda_{2,i} : [0,\infty) \to [0,\infty)$ such that

$$-\lambda_{1,i}(t)\mathcal{M}^i_t(\varphi) \leq f_i\left(t, \varphi_{|_{[-\tau_i(t),0]}}\right) \leq \lambda_{2,i}(t)\mathcal{M}^i_t(-\varphi), \qquad t \geq 0, \varphi \in S^*, i = 1,\ldots,m,$$

where $\mathcal{M}^i_t(\varphi) = \max\left\{0, \sup_{\theta\in[-\tau_i(t),0]} \varphi(\theta)\right\}$ is the so-called Yorke's functional;

(H3) there is $T > 0$ with $T - \tau(T) > 0$ such that

$$\alpha^*_1\alpha^*_2 < 1, \tag{2.2}$$

where the coefficients $\alpha^*_j := \alpha^*_j(T)$ are given by

$$\alpha^*_j = \sup_{t\geq T} \int_{t-\tau(t)}^t \sum_{i=1}^m \lambda_{j,i}(s)\, \mathrm{e}^{-\int_s^t a(u)du}\, ds, \qquad j = 1,2.$$

Note that the above hypothesis (H2) implies that $f_i(t,0) = 0$ for all $t \geq 0$, thus $y(t) = 0$ is an equilibrium point of (2.1). The following stability result holds:

Theorem 2.1. *[2] Assume (H1)-(H3), with $S^* \subseteq C$ an admissible set of initial conditions for* (2.1)*. If $0 \in S^*$, then the zero equilibrium point is globally attractive (in S^*).*

Recall that, for a function $z(t)$ defined for $t \geq 0$, we say that $z(t)$ is *oscillatory* if it is not eventually zero and it has arbitrarily large zeros; otherwise, it is called *non-oscillatory*.

Remark 2.1. In [2], (H3) was used only to treat the case of oscillatory solutions. Moreover, from the proofs of Lemmas 2.2, 2.4 and Theorems 2.1, 2.2 in [2], the conclusion of Theorem 2.1 is obtained under (H1), (H3) and a weaker version of (H2), as follows: for solutions $y(t)$ of (2.1) with initial condition in S^*,

(i) if $y(t)$ is non-oscillatory, the solution-segment y_t satisfies

(H2*) for $i = 1,\ldots,m$ and large $t \geq 0$,

$$f_i\left(t, y_{|_{[t-\tau_i(t),t]}}\right) \leq 0 \text{ if } y_{|_{[t-\tau_i(t),t]}} \geq 0 \text{ and } f_i\left(t, y_{|_{[t-\tau_i(t),t]}}\right) \geq 0 \text{ if } y_{|_{[t-\tau_i(t),t]}} \leq 0;$$

(ii) if $y(t)$ is oscillatory, (H2) is satisfied for large t with $\varphi_{|_{[-\tau_i(t),0]}}$ replaced by $y_{|_{[t-\tau_i(t),t]}}$.

We now go back to the generalized model of hematopoiesis (1.3). For the functions a, b_i and τ_i in (1.3), we shall denote

$$\tau(t) = \max_{1\leq i\leq m}\{\tau_i(t)\}, \qquad \tau = \max_{t\in[0,\omega]}\{\tau(t)\}, \qquad \bar{a} = \max_{t\in[0,\omega]}\{a(t)\}, \qquad \text{and} \qquad \underline{b}_i = \min_{t\in[0,\omega]}\{b_i(t)\},$$

and consider it in the phase space $C = C([-\tau,0];\mathbb{R})$.

By biological reasons, only positive solutions of (1.3) are meaningful and therefore hereafter we consider the set of initial conditions as

$$S = \{\varphi \in C : \varphi(\theta) \geq 0 \text{ for } -\tau \leq \theta < 0,\ \varphi(0) > 0\}.$$

It is easy to show that S is an admissible set for (1.3), i.e., $x_t(\cdot, t_0, \varphi) \in S$ for $t \geq t_0 \geq 0$ and $\varphi \in S$, where $x(t, t_0, \varphi)$ denotes the solution of (1.3) with initial condition $x_{t_0} = \varphi$.

In this note, we study the global attractivity of an ω-periodic solution $\widetilde{x}(t)$ of (1.3) in the set S, whose existence was established in [5]. We shall use some uniform lower bound estimates proven in [5, Lemmas 3.1, 3.2, and 3.3].

Lemma 2.2. *[5] The positive ω-periodic solution of* (1.3)*, $\widetilde{x}(t)$, satisfies*

$$\widetilde{x}(t) \geq x_1 \exp\left(-\sup_{t\in[0,\omega]} \int_{t-\tau}^{t} a(u)du\right) =: X_1, \qquad \text{for all } t \in \mathbb{R}, \tag{2.3}$$

where x_1 is the unique positive solution of the equation

$$\bar{a}x = \sum_{i=1}^{m} \frac{b_i}{1+x^n}.$$

Lemma 2.3. *[5] If $x(t)$ is a positive solution of* (1.3) *such that $x(t) - \widetilde{x}(t)$ is oscillatory, then there is $T_x > T$ such that*

$$x(t) \geq X_1, \qquad \text{for } t \geq T_x. \tag{2.4}$$

Remark 2.2. In fact, in the proof of [5, Lemma 3.1], there is an oversight in the definition of X_1, and the correct definition should be as above in (2.3).

3 Global Attractivity

In this section, we prove the following criterion for the global attractivity of the positive ω-periodic solution of (1.3), which improves the stability criterion in [5, Theorem 3.1].

Theorem 3.1. *If there is $T > 0$ such that*

$$\frac{nX_1^{n-1}}{(1+X_1^n)^2} \sup_{t\geq T} \int_{t-\tau(t)}^{t} \sum_{i=1}^{m} b_i(s)\, \mathrm{e}^{-\int_s^t a(u)du}\, ds < 1, \tag{3.1}$$

then the positive ω-periodic solution $\widetilde{x}(t)$ of (1.3) *is globally attractive (in the set of all positive solutions).*

Proof. By the change of variables $y(t) = x(t) - \widetilde{x}(t)$, model (1.3) is reduced to

$$y'(t) = -a(t)y(t) + \sum_{i=1}^{m} b_i(t) \left[\frac{1}{1+(y(t-\tau_i(t)) + \widetilde{x}(t-\tau_i(t)))^n} - \frac{1}{1+\widetilde{x}(t-\tau_i(t))^n}\right], \quad t \geq 0. \tag{3.2}$$

Clearly, zero is an equilibrium point and the equation (3.2) has the form of the DDE (2.1) with

$$f_i(t,\varphi) = b_i(t) \left[\frac{1}{1+(\varphi(-\tau_i(t)) + \widetilde{x}(t-\tau_i(t)))^n} - \frac{1}{1+\widetilde{x}(t-\tau_i(t))^n}\right], \tag{3.3}$$

for all $t \geq 0$, $\varphi \in C$, and $i = 1, \ldots, m$. As only positive solutions of (1.3) are admissible, naturally

$$\widetilde{S} = \{\varphi \in C : \varphi(\theta) \geq -\widetilde{x}(\theta) \text{ for } -\tau \leq \theta < 0, \varphi(0) > -\widetilde{x}(0)\} \tag{3.4}$$

is the set of admissible initial conditions for (3.2). We need to show that the zero equilibrium of (3.2) is globally attractive in $\widetilde{S}$ and, in order to do so, the cases of oscillatory and non-oscillatory solutions are considered separately.

On the one hand, as the positive continuous function $a(t)$ is ω-periodic, then (H1) holds, and, on the other hand, it is clear that hypothesis (H2*) holds for all $\varphi \in \widetilde{S}$. Consequently, from [2, Lemma 2.2] we conclude that all non-oscillatory solutions of (3.2) converge to zero as $t \to \infty$.

Now we consider $y(t)$ an oscillatory solution of (3.2) with an initial condition in $\widetilde{S}$. Naturally, $y(t) = x(t) - \widetilde{x}(t)$ for some $x(t)$ positive solution of (1.3) and by Lemma 2.3 there is $T_x > T$ such that (2.4) holds. From Lemma 2.4 and Theorem 2.2 in [2] (see Remark 2.1), it is enough to show that hypothesis (H2) holds for $\varphi \in \widetilde{S}$ replaced by y_t, for all $t > T_x$.

For $t > T_x$ and $i \in \{1, \dots, m\}$, the Lagrange's Theorem allows us to conclude that there is $\xi = \xi(t, y)$ between $y(t - \tau_i(t)) + \widetilde{x}(t - \tau_i(t)) = x(t - \tau_i(t))$ and $\widetilde{x}(t - \tau_i(t))$ such that

$$\begin{aligned} f_i(t, y_t) &= b_i(t) \left[\frac{1}{1 + (y(t - \tau_i(t)) + \widetilde{x}(t - \tau_i(t)))^n} - \frac{1}{1 + \widetilde{x}(t - \tau_i(t))^n} \right] \\ &= -\frac{n\xi^{n-1} b_i(t)}{(1 + \xi^n)^2} y(t - \tau_i(t)). \end{aligned}$$

From Lemmas 2.2 and 2.3, we know that $\widetilde{x}(t) \geq X_1$ and $x(t) \geq X_1$ for all $t > T_x$. Consequently, $\xi = \xi(t, y) \geq X_1$ for all $t \geq T_x$ and, as $\sigma \mapsto \frac{n\sigma^{n-1}}{(1+\sigma^n)^2}$ is a non-increasing function on $(0, \infty)$, we have

$$f_i(t, y_t) = \frac{n\xi^{n-1}}{(1 + \xi^n)^2} b_i(t) \big(- y(t - \tau_i(t)) \big) \leq \frac{n\xi^{n-1}}{(1 + \xi^n)^2} b_i(t) \mathcal{M}_t^i(-y_t) \leq \frac{nX_1^{n-1}}{(1 + X_1^n)^2} b_i(t) \mathcal{M}_t^i(-y_t).$$

Analogously, we have

$$f_i(t, y_t) = -\frac{n\xi^{n-1}}{(1 + \xi^n)^2} b_i(t) y(t - \tau_i(t)) \geq -\frac{n\xi^{n-1}}{(1 + \xi^n)^2} b_i(t) \mathcal{M}_t^i(y_t) \geq -\frac{nX_1^{n-1}}{(1 + X_1^n)^2} b_i(t) \mathcal{M}_t^i(y_t).$$

Thus, (H2) holds, with $\varphi = y_t$, for $t > 0$ large and

$$\lambda_{1,i}(t) = \lambda_{2,i}(t) = \frac{nX_1^{n-1}}{(1 + X_1^n)^2} b_i(t).$$

Finally, condition (3.1) is equivalent to (2.2) with $\alpha_1^* = \alpha_2^*$, and we conclude that $y(t) \to 0$ as $t \to \infty$. The proof is complete. $\square$

Remark 3.1. In [5, Theorem 3.1], G. Liu et al. prove that the positive ω-periodic solution $\widetilde{x}(t)$ of (1.3) is a global attractor of all positive solutions if

$$\frac{nX_1^{n-1}}{1 + X_1^n} \frac{\mathrm{e}^{A(\omega)}}{\mathrm{e}^{A(\omega)} - 1} \int_0^\omega \sum_{i=1}^m b_i(s) ds \leq 1, \tag{3.5}$$

where $A(\omega) = \displaystyle\int_0^\omega a(u) du$. We claim that (3.1) is a weaker condition than (3.5). In fact, for $t > 0$

and considering $N(t) \in \mathbb{N}$ such that $\tau(t) \in \big((N(t)-1)\omega, N(t)\omega\big]$, we have

$$\begin{aligned}
\int_{t-\tau(t)}^{t} \sum_{i=1}^{m} b_i(s)\, \mathrm{e}^{-\int_s^t a(u)du}\, ds &\le \sum_{j=1}^{N(t)} \int_{t-j\omega}^{t-(j-1)\omega} \sum_{i=1}^{m} b_i(s)\, \mathrm{e}^{-\int_s^t a(u)du}\, ds \\
&= \sum_{j=1}^{N(t)} \mathrm{e}^{-(j-1)A(\omega)} \int_{t-j\omega}^{t-(j-1)\omega} \sum_{i=1}^{m} b_i(s)\, \mathrm{e}^{-\int_s^{t-(j-1)\omega} a(u)du}\, ds \\
&= \left(\sum_{j=1}^{N(t)} \left(\mathrm{e}^{-A(\omega)}\right)^{j-1}\right) \int_{t-\omega}^{t} \sum_{i=1}^{m} b_i(s)\, \mathrm{e}^{-\int_s^t a(u)du}\, ds \\
&= \frac{\mathrm{e}^{-N(t)A(\omega)}-1}{\mathrm{e}^{-A(\omega)}-1} \int_{t-\omega}^{t} \sum_{i=1}^{m} b_i(s)\, \mathrm{e}^{-\int_s^t a(u)du}\, ds \\
&< \frac{\mathrm{e}^{A(\omega)}}{\mathrm{e}^{A(\omega)}-1} \int_{t-\omega}^{t} \sum_{i=1}^{m} b_i(s)\, \mathrm{e}^{-\int_s^t a(u)du}\, ds \\
&\le \frac{\mathrm{e}^{A(\omega)}}{\mathrm{e}^{A(\omega)}-1} \int_{0}^{\omega} \sum_{i=1}^{m} b_i(s) ds,
\end{aligned}$$

which shows that condition (3.5) implies condition (3.1). Therefore, Theorem 3.1 improves the stability criterion in [5]. Moreover, the example given below shows that condition (3.1) is strictly less restrictive than condition (3.5).

4 Numerical example

In this section, a numerical example is given to illustrate the effectiveness of the new result presented in Theorem 3.1. Here, we have used the Matlab software [9], to plot the numerical simulation of the solutions.

Letting $n = 1$, $m = 2$, $a(t) = 1+\frac{1}{2}\cos(2\pi t)$, $b_1(t) = \frac{3}{8}\left(1+\frac{1}{2}\cos(2\pi t)\right)$, $b_2(t) = \frac{3}{8}\left(1+\frac{1}{2}\sin(2\pi t)\right)$, and $\tau_1(t) = \tau_2(t) = \frac{1}{2}(1+\sin(2\pi t))$ in the hematopoiesis model (1.3), we have de DDE

$$x'(t) = -\left(1+\frac{1}{2}\cos(2\pi t)\right)x(t) + \frac{6+\frac{3}{2}\left(\cos(2\pi t)+\sin(2\pi t)\right)}{8(1+x(t-\frac{1}{2}(1+\sin(2\pi t))))}, \qquad t \ge 0. \tag{4.1}$$

Eq. (4.1) is 1-periodic and, by easy computations, we can see that $X_1 = \frac{\sqrt{2}-1}{2}\mathrm{e}^{-1}$ and

$$\int_{t-\tau(t)}^{t} (b_1(s)+b_2(s))\, \mathrm{e}^{-\int_s^t a(u)du}\, ds \le \int_0^1 (b_1(s)+b_2(s))ds = \frac{3}{4},$$

thus $\frac{3}{4}\frac{1}{(1+X_1)^2} \approx 0.64757 < 1$. Consequently, from Theorem 3.1, the positive 1-periodic solution $\widetilde{x}(t)$ of (4.1) attracts all positive solutions. See the numerical simulations for three solutions shown in Figure 1.

However, since

$$\frac{nX_1^{n-1}}{1+X_1^n}\frac{\mathrm{e}^{A(\omega)}}{\mathrm{e}^{A(\omega)}-1}\int_0^{\omega}\sum_{i=1}^{m} b_i(s)ds = \frac{2\,\mathrm{e}}{2\,\mathrm{e}+\sqrt{2}-1}\frac{\mathrm{e}}{\mathrm{e}-1}\frac{3}{4} \approx 1.10248 > 1,$$

condition (3.5) is not satisfied, thus the result of G. Liu et al. [5] cannot be applied to this example.

Figure 1 illustrates our example by plotting the graph of three solutions of (4.1) with the following initial conditions in S:

$$\begin{aligned}
&x_0 = \varphi_1, \text{ where } \varphi_1(\theta) = \cos(\theta), \text{ for } \theta \in [-1, 0];\\
&x_0 = \varphi_2, \text{ where } \varphi_2(\theta) = 0.5\,\mathrm{e}^{\theta}, \text{ for } \theta \in [-1, 0];\\
&x_0 = \varphi_3, \text{ where } \varphi_3(\theta) = 0.1 - \sin(\pi\theta), \text{ for } \theta \in [-1, 0].
\end{aligned}$$

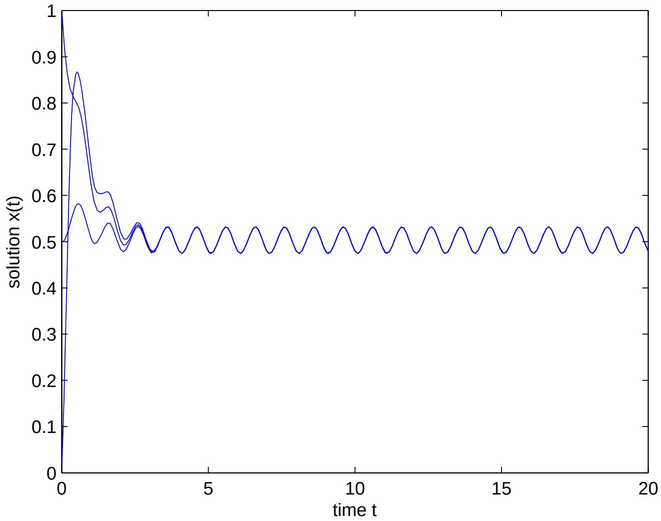

Figure 1: Behavior of three positive solutions of (4.1).

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