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On the convergence of series of translated functions and applications

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Abstract

The present work presents some necessary and sufficient conditions for the convergence to a periodic function of a special kind of function series defined by $\sum_{j=0}^{\infty} f(t - jd)$, where $f : \mathbb{R} \mapsto \mathbb{R}^+ \cup \{0\}$ with $f(t) = 0$ for $t < 0$. It also discusses some biological applications that can be derived from these results, by considering each $f(t - jd)$ as describing an isolated effect related to an application at time jd, and the sum of them as an accumulated effect.

Keywords: Function series; Convergence; Periodic function; Effect function; Drug concentration

In the biological sciences, we are commonly interested in effects having decay, which mathematically speaking would correspond to a positive real valued function tending to zero with time. For example, the effect on the blood concentration of a certain drug ($C(t)$) secondary to an intake at time 0 in its simplest form is often modeled by

$$C(t) = A\mathrm{e}^{-bt} I_{\{t \geq 0\}}(t) \tag{1}$$

with $A, b > 0$ (note that $b = \frac{ln2}{t_{1/2}}$, where $t_{1/2}$ is the half-life of the drug, i.e., the time necessary for the blood concentration to be halved), and $I_E(t) = 1$ if $t \in E$, and $I_E(t) = 0$ if $t \notin E$. Moreover, the biological effect ($E(t)$) obtained at time t after a single drug administration at time 0 is usually described as (see the references [1] and [2] for examples)

$$E(t) = \varepsilon_{\max} \frac{C(t)^n}{C(t)^n + IC_{50}^n} \tag{2}$$

where $\varepsilon_{\max}$ is the maximum effect, IC_{50} is the drug concentration necessary to reach half of the maximum effect, and $n \in \mathbb{N}$. Each drug intake would then produce a peak blood concentration followed by exponential decay, leading to an associated biological effect. More generally, let us formalize with the following definition:

Definition 1. We say that $f : \mathbb{R} \mapsto \mathbb{R}^+ \cup \{0\}$ is an *isolated effect function* iff $f(t) = 0$ for $t < 0$, and $f(t) \to 0$ when $t \to \infty$.

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As drug intake is usually administered in a repetitive fashion, we are often interested in functions describing the effect caused by the accumulation of effects obtained from the isolated effect functions administered at different time points, leading us to the following definition:

Definition 2. We say that $\mathcal{F}(t)$ is an *accumulated effect function* iff $\mathcal{F}(t) = \sum_{i=0}^{\infty} f(t-i)$, where $f(t)$ is an isolated effect function, and $i \in I \subset \mathbb{R}$, I ordered, represents the shift to the right of $f(t)$ of time i (note that for each $t \in \mathbb{R}$ the sum is finite).

We will examine the case where each isolated effect function is realized at a constant time interval. Calling this interval d, e.g., the time between drug intakes, we have that the sum of these effects (total blood concentration of the drug after several intakes, for example) will be given by

$$\mathcal{F}(t) \equiv \sum_{j=0}^{\infty} f(t-jd) \tag{3}$$

where j is now an integer. We are usually interested in our accumulated effect function reaching, after some period of time, its values in a limited interval of $\mathbb{R}^+$. In the case of drug blood concentration, we are interested in the blood levels remaining within the therapeutic window (the interval between the minimum effective concentration and the toxic concentration). However, before that, it is necessary to know whether there is convergence of the accumulated effect function to a periodic function of period d, i.e., we want to know whether there exists $\mathcal{G}$, with $\mathcal{G}(t+d) = \mathcal{G}(t)$, such that $\mathcal{F}(t) \to \mathcal{G}(t)$ when $t \to \infty$. We will first find a necessary condition for the existence of such a function. Note that for all $\epsilon > 0$, we would then have that there exists $T > 0$ such that for $t > T$,

$$\|\mathcal{F}(t) - \mathcal{G}(t)\| < \frac{\epsilon}{2}. \tag{4}$$

Then, for $k \in \mathbb{N}$ and for this same T, we have

$$\begin{aligned} \|\mathcal{F}(t+kd) - \mathcal{F}(t)\| &= \|\mathcal{F}(t+kd) - \mathcal{F}(t) + \mathcal{G}(t+kd) - \mathcal{G}(t)\| \\ &\le \|\mathcal{F}(t+kd) - \mathcal{G}(t+kd)\| + \|\mathcal{F}(t) - \mathcal{G}(t)\| = \frac{\epsilon}{2} + \frac{\epsilon}{2} = \epsilon, \end{aligned} \tag{5}$$

for $t > T$. On the other hand,

$$\begin{aligned} \mathcal{F}(t+kd) - \mathcal{F}(t) &= \sum_{j=0}^{\infty} f(t+(k-j)d) - \sum_{j=0}^{\infty} f(t-jd) \\ &= \sum_{j=k}^{\infty} f(t+(k-j)d) + \sum_{j=0}^{k-1} f(t+(k-j)d) - \sum_{j=0}^{\infty} f(t-jd) \\ &= \sum_{j=0}^{k-1} f(t+(k-j)d) = \sum_{j=1}^{k} f(t+jd). \end{aligned} \tag{6}$$

Thus, using (5) and (6),

$$\left\| \sum_{j=1}^{k} f(t+jd) \right\| < \epsilon, \quad \text{for all } k \in \mathbb{N}, \text{ and for } t > T. \tag{7}$$

Letting $k \to \infty$ in (7), we see that the convergence of $\mathcal{F}(t)$ to $\mathcal{G}(t)$ implies the following condition:

$$\forall \epsilon > 0, \quad \text{there exists } T > 0, \text{ such that } \left\| \sum_{j=1}^{\infty} f(t+jd) \right\| < \epsilon, \quad \text{for } t > T. \tag{8}$$

This means that the convergence of the accumulated effect function to a periodic function of period d is dependent on the speed at which the isolated effect function goes to zero.

Example 1. Suppose that a given effect is described by

$$f(t) = \frac{1}{t^p} I_{\{t>0\}}(t), \tag{9}$$

where $0 < p \le 1$. Then, for $k \in \mathbb{N}$ and $t > 0$, we have

$$\begin{aligned} \sum_{j=1}^{\infty} f(t+jd) &= \sum_{j=1}^{\infty} \frac{1}{(t+jd)^p} I_{\{t+jd>0\}}(t+jd) \\ &\ge \sum_{j=1}^{k} \frac{1}{(t+jd)^p} \ge \sum_{j=1}^{k} \frac{1}{(t+kd)^p} = k\frac{1}{(t+kd)^p}, \end{aligned} \tag{10}$$

and we note that this last term can not be bounded by small ϵ for all k. Therefore, condition (8) is not satisfied, which is to say that we have no convergence of the accumulated effect function to a periodic function in this case. •

Example 2. We now take an isolated effect function of the form

$$f(t) = g(t) I_{\{0<t<C\}}(t), \tag{11}$$

$0 < C < \infty$. Then, given $\epsilon > 0$, take $T = C$, and note that

$$\sum_{j=1}^{\infty} f(t+jd) = \sum_{j=1}^{\infty} g(t+jd) I_{\{0<t+jd<C\}}(t+jd) = 0 < \epsilon \tag{12}$$

if $t \ge T$. •

By sketching a graphic with the $f(t-jd)$ of Example 2, one can observe that $\mathcal{F}(t)$ constructed as the sum of them will converge to a periodic function of period d. In fact, this will happen to every accumulated effect function constructed as the sum of isolated effect functions satisfying condition (8), which is also sufficient for the convergence as we shall show below, leading us to enunciate the following theorem:

Theorem 1. *There exists $\mathcal{G}$, with $\mathcal{G}(t+d) = \mathcal{G}(t)$, such that $\mathcal{F}(t) \to \mathcal{G}(t)$ when $t \to \infty$ if, and only if, $\forall \epsilon > 0$, there exists $T > 0$, such that $\left\| \sum_{j=1}^{\infty} f(t+jd) \right\| < \epsilon$, for $t > T$.*

Proof. We have already obtained the necessity; to show sufficiency, let us construct such $\mathcal{G}(t)$. Consider $\mathcal{G}(t) \equiv \sum_{j=-\infty}^{\infty} f(t-jd)$, which is a periodic function of period d if this sum converges for each t. So, we will first show that $\mathcal{G}(t)$ is well defined when condition (8) holds. Take $\epsilon > 0$, consider T satisfying condition (8), and let $J \in \mathbb{N}$ be such that $Jd > T$. Then, for all $t \in \mathbb{R}$, we have

$$\begin{aligned} \|\mathcal{G}(t)\| &= \left\| \sum_{j=-\infty}^{\infty} f(t-jd) \right\| \\ &\le \left\| \sum_{j=-\infty}^{-1} f(t-jd) \right\| + \left\| \sum_{j=0}^{\infty} f(t-jd) \right\| = \left\| \sum_{j=1}^{\infty} f(t+jd) \right\| + \|\mathcal{F}(t)\| \\ &\le \left\| \sum_{j=1}^{J} f(t+jd) \right\| + \left\| \sum_{j=1}^{\infty} f((t+Jd)+jd) \right\| + \|\mathcal{F}(t)\| < \infty, \end{aligned} \tag{13}$$

once the first term in the last line is a finite sum, the middle term is less than ϵ, and $\mathcal{F}(t)$ is finite for each t.

Now, to show the convergence of $\mathcal{F}(t)$ to this $\mathcal{G}(t)$, let $\epsilon > 0$ be given, and let T satisfy condition (8); then, for $t > T$, we have

$$\begin{aligned} \|\mathcal{F}(t) - \mathcal{G}(t)\| &= \left\| \sum_{j=0}^{\infty} f(t-jd) - \sum_{j=-\infty}^{\infty} f(t-jd) \right\| \\ &= \left\| \sum_{j=-\infty}^{-1} f(t-jd) \right\| = \left\| \sum_{j=1}^{\infty} f(t+jd) \right\| < \epsilon. \quad \blacksquare \end{aligned}$$

We present now another example which will be useful for further results.

Example 3. Suppose that a given effect is described by

$$f(t) = \frac{1}{t^p} I_{\{t>0\}}(t), \tag{14}$$

where $p > 1$. We will show that f defined in (14) satisfies condition (8), and, therefore, the accumulated effect function associated with f will converge to a periodic function of period d by Theorem 1. Let $\epsilon > 0$, and consider $K \in \mathbb{N}$, and $T > 0$, such that $\sum_{j=K}^{\infty} \frac{1}{j^p} < \frac{d^p \epsilon}{2}$, and $\frac{K}{T^p} < \frac{\epsilon}{2}$. Then,

$$\sum_{j=1}^{\infty} f(t+jd) = \sum_{j=1}^{\infty} \frac{1}{(t+jd)^p} I_{\{t+jd>0\}}(t+jd)$$
$$= \sum_{j=1}^{K-1} \frac{1}{(t+jd)^p} + \sum_{j=K}^{\infty} \frac{1}{(t+jd)^p} < \sum_{j=1}^{K-1} \frac{1}{t^p} + \frac{1}{d^p} \sum_{j=K}^{\infty} \frac{1}{j^p} < \frac{\epsilon}{2} + \frac{\epsilon}{2} = \epsilon,$$

for $t > T$. •

On the basis of Examples 1 and 3, we can now present the following corollaries of Theorem 1 (using the same notation):

Corollary 1. $\mathcal{F}(t) \to \mathcal{G}(t) \Rightarrow \limsup_{t\to\infty} \frac{\log(f(t))}{\log(t)} \le -1$.

Corollary 2. $\limsup_{t\to\infty} \frac{\log(f(t))}{\log(t)} < -1 \Rightarrow \mathcal{F}(t) \to \mathcal{G}(t)$.

Proof of Corollary 1. If $\limsup_{t\to\infty} \frac{\log(f(t))}{\log(t)} > -1$, then, for all $T > 0$, there exists $\bar{t} > T$, such that $f(\bar{t}) \ge \frac{1}{\bar{t}}$. Therefore, there will always be an arbitrarily big $\bar{t}$ such that $\sum_{j=1}^{\infty} f(\bar{t}+jd) \ge \sum_{j=1}^{\infty} \frac{1}{\bar{t}+jd}$, and we see that condition (8) cannot be satisfied by the argument shown in Example 1. ■

Proof of Corollary 2. If $\limsup_{t\to\infty} \frac{\log(f(t))}{\log(t)} < -1$, then there exists $-p < -1$, and there exists $T_1 > 0$, such that $f(t) < \frac{1}{t^p}$, for $t > T_1$. Therefore, $\sum_{j=1}^{\infty} f(t+jd) < \sum_{j=1}^{\infty} \frac{1}{(t+jd)^p}$, for $t > T_1$. Let $\epsilon > 0$. We already know from Example 3 that there exists $T_2 > 0$, such that $\sum_{j=1}^{\infty} \frac{1}{(t+jd)^p} < \epsilon$, for $t > T_2$. Therefore, take $T = \max\{T_1, T_2\}$, and we see that condition (8) is satisfied. ■

Remark 1. Note that for sufficiently well behaved functions f, condition (8) implies Riemann integrability. Therefore, $\lim_{t\to\infty} \frac{\log(f(t))}{\log(t)} < -1$ is a sufficient condition for integrability in these cases. Note further that $\lim_{t\to\infty} \frac{\log(f(t))}{\log(t)} = -1$ does not provide much information about integrability once $\frac{1}{t\log(t)} I_{\{t>2\}}(t)$ is not integrable, whereas $\frac{1}{t\log^2(t)} I_{\{t>2\}}(t)$ is integrable. •

Now, note that $f(t)$, $\mathcal{F}(t)$ and $\mathcal{G}(t)$ can be unbounded. For example, take $f(t) = \frac{1}{t} I_{\{0<t<C\}}(t)$ and $d = C$. However, it is reasonable in applications to suppose that the isolated effect function $f(t)$ is bounded and non-increasing after some point. In these cases, we will have that either $\mathcal{F}(t)$ converges to a periodic function, or $\mathcal{F}(t)$ goes to infinity as $t \to \infty$, as stated in the following theorem:

Theorem 2. *If $f(t)$ is bounded and non-increasing after some point τ, the following claims are equivalent:*
(1) *$\mathcal{F}(t)$ converges to a $\mathcal{G}(t)$ periodic of period d.*
(2) *$\forall \epsilon > 0$, there exists $T > 0$, such that $\|\sum_{j=1}^{\infty} f(t+jd)\| < \epsilon$, for $t > T$.*
(3) *$\mathcal{F}(t)$ is bounded.*

Proof. We already have (1) ⇔ (2) by Theorem 1. Let us show (3) ⇒ (2). Let $M > 0$ be such that $\mathcal{F}(t) < M$ for all t. Then, for $k \in \mathbb{N}$, using (6), we have

$$\left\| \sum_{j=1}^{k} f(t+jd) \right\| = \|\mathcal{F}(t+kd) - \mathcal{F}(t)\| < M. \tag{15}$$

Letting $k \to \infty$ in (15), we get

$$\left\| \sum_{j=1}^{\infty} f(t + jd) \right\| < M. \tag{16}$$

Now, $\forall \epsilon > 0$, there exists $N_{\tau,\epsilon} \in \mathbb{N}$ such that

$$\left\| \sum_{j=1}^{\infty} f((\tau + N_{\tau,\epsilon} d) + jd) \right\| = \left\| \sum_{j=N_{\tau,\epsilon}+1}^{\infty} f(\tau + jd) \right\| < \epsilon. \tag{17}$$

Therefore, take $T = \tau + N_{\tau,\epsilon} d$, and we see that (2) is satisfied.

Now, suppose (2) holds, and let $M > 0$ be such that $f(t) < M$ for all t. Defining $\lceil T \rceil = \min\{j \mid jd \geq T\}$, and $[t] = \max\{j \mid jd \leq t\}$, given $\epsilon > 0$, let T satisfy the condition and consider $\mathcal{G}_\epsilon(t) \equiv \sum_{j=0}^{\lceil T \rceil} f(t + (\lceil T \rceil - [t] - j)d)$, which is a periodic function of period d (once for all $k \in \mathbb{N}$ we have $[t + kd] = [t] + k$). Then, for $t > \lceil T \rceil d$, we have

$$\begin{aligned}
\|\mathcal{F}(t) - \mathcal{G}_\epsilon(t)\| &= \left\| \sum_{j=0}^{\infty} f(t - jd) - \sum_{j=0}^{\lceil T \rceil} f(t + (\lceil T \rceil - [t] - j)d) \right\| \\
&= \left\| \sum_{j=0}^{[t]} f(t - jd) - \sum_{j=[t]-\lceil T \rceil}^{[t]} f(t - jd) \right\| = \left\| \sum_{j=0}^{[t]-\lceil T \rceil - 1} f(t - jd) \right\| \\
&= \left\| \sum_{j=1}^{[t]-\lceil T \rceil} f(t - (j-1)d + ([t] - \lceil T \rceil)d - ([t] - \lceil T \rceil)d) \right\| \\
&= \left\| \sum_{j=1}^{[t]-\lceil T \rceil} f(t + (\lceil T \rceil - [t])d + ([t] - \lceil T \rceil - j + 1)d) \right\| \\
&= \left\| \sum_{k=1}^{[t]-\lceil T \rceil} f((t + (\lceil T \rceil - [t])d) + kd) \right\| \\
&\leq \left\| \sum_{k=1}^{\infty} f((t + (\lceil T \rceil - [t])d) + kd) \right\| = \left\| \sum_{j=1}^{\infty} f(\tau + jd) \right\| < \epsilon,
\end{aligned} \tag{18}$$

where $\tau \equiv t - ([t] - \lceil T \rceil)d \geq T$, since $t - [t]d \geq 0$, and $\lceil T \rceil d \geq T$.

Then, for $t \leq Td$, we have that

$$\mathcal{F}(t) = \sum_{j=0}^{\infty} f(t - jd) = \sum_{j=0}^{[t]} f(t - jd) \leq [t]M, \tag{19}$$

whereas for $t > Td$, using (18), and the definition of $\mathcal{G}_\epsilon(t)$, we have that

$$\mathcal{F}(t) \leq \mathcal{G}_\epsilon(t) + \epsilon = \sum_{j=0}^{\lceil T \rceil} f(t + (\lceil T \rceil - [t] - j)d) + \epsilon \leq \lceil T \rceil M + \epsilon, \tag{20}$$

which completes the proof of Theorem 2. ■

Remark 2. Note that the requirement for f to be non-increasing after some point cannot be discarded. For example, take as an isolated effect function $f(t) = \frac{1}{t} I_{\{t>1\}}(t) I_{\{t \in \mathbb{Q}\}}(t)$, which leads to an associated accumulated effect function $\mathcal{F}(t)$ bounded by one when $d \in \mathbb{R} \setminus \mathbb{Q}$, and which does not satisfy condition (8) by an argument similar to that used in Example 1. •

Lastly, we note that the results presented here are easily extensible for n-dimensional isolated effect functions defined by $f(t) = (f_1(t), \ldots, f_n(t))$, where each $f_i(t)$ is an isolated effect function, with associated n-dimensional accumulated effect functions given by $\mathcal{F}(t) = (\mathcal{F}_1(t), \ldots, \mathcal{F}_n(t))$, where $\mathcal{F}_i(t) = \sum_{j=0}^{\infty} f_i(t - jd)$.

As an application of these results, let us consider the blood level of a drug after a periodic dose intake of interval d given by $\mathcal{F}(t) = \sum_{j=0}^{\infty} C(t - jd)$, where $C(t)$ is given in (1). We would like to know whether the drug concentration will tend to a periodic function, or whether it will accumulate in the body. We note that

$$\lim_{t\to\infty} \frac{\log(C(t))}{\log(t)} = \lim_{t\to\infty} \frac{\log(A\mathrm{e}^{-bt})}{\log(t)} = \lim_{t\to\infty} \frac{-bt}{\log(t)} = -\infty < -1. \tag{21}$$

Therefore, *independently* of the drug half-life ($t_{1/2}$), and of the dose interval being considered (d), the accumulated drug concentration in blood will always converge to a periodic function, which is not completely intuitive, as we could imagine that $d \ll t_{1/2}$ would imply an infinite drug accumulation in the body. However, an important point is that we should always differentiate mathematical idealization from the actual process. For example, the presence of saturation effects after a certain threshold is very common in biology (for instance, the speed of drug metabolization by the liver may saturate with increasing dosage). In these cases, the pattern of decay of the next isolated effect function would change after the saturation threshold, which is to say that the isolated effect would no longer be properly modeled by the same f.

As another example, consider the biological effect of drug intake modeled by the function $E(t)$ described in (2). As the biological effect is dependent on the accumulated blood concentration of the drug (based on a clear biological interpretation), the accumulated biological drug effect should not be regarded as $\sum_{j=0}^{\infty} E(t - jd)$, but as $\varepsilon_{\max} \frac{\mathcal{F}(t)^n}{\mathcal{F}(t)^n + IC_{50}^n}$, with $\mathcal{F}(t) = \sum_{j=0}^{\infty} C(t - jd)$. As we have already seen in this case, $\mathcal{F}(t)$ converges to a periodic function, and the same should happen to the accumulated biological drug effect, once it is constructed as a composition $h(\mathcal{F}(t))$, for a continuous $h(t)$.

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