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# Find the long term prognostic significance of 6MWT distance in CHF patients using mathematical modelling

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**Abstract**
The aim of the present study was to assess the long term (> 5 years) prognostic significance of the 6 minute walk test distance in a large sample of patients with chronic heart failure, using the exact and approximate solutions of a delay differential equation with various types of nonlocal history conditions.

**Keywords:** Chronic Heart Failure, 6 Minute Walk Test, Cardiopulmonary Exercise, Normal Distribution, Delay Differential equations.

## 1. Introduction

Functional capacity is strongly related to survival in patients with chronic heart failure (CHF**).** Although cardiopulmonary exercise testing (CPET) with metabolic gas exchange measurements is perhaps the "gold standard" method for assessing exercise capacity, it is not widely available, and so more simple tests are commonly used. The 6 minute walk test (6-MWT) is reproducible and sensitive to changes in quality of life [10]. It is a self paced, submaximal test, and exercise intensity mimics activities of daily living in patients with mild-to-moderate heart failure [3, 7]. Thus, the 6-MWT may suit patients with CHF who may experience symptoms such as breathlessness below their peak exercise capacity.

We study the exact and approximate solutions of a delay differential equation with various types of nonlocal history conditions. We establish the existence and uniqueness of mild, strong, and classical solutions for a class of such problems using the method of semidiscretization in time. We also establish a result concerning the global existence of solutions. Finally, we consider some examples and discuss their exact and approximate solutions. Our purpose here is to study the exact and approximate solutions of the suitable delay differential equation $\frac{\partial w}{\partial t}(x,t)-\frac{\partial^2 w}{\partial x^2}(x,t)=f\left(x,t,w(x,t),w(x,t-\tau)\right)$ with a nonlocal condition. In doing so, we first use the method of semi discretization to derive the existence of a unique a strong solution, and then we prove that strong solution is a classical solution if additional conditions are assumed on the operator. The global existence of a solution for $\frac{\partial w}{\partial t}(x,t)-\frac{\partial^2 w}{\partial x^2}(x,t)=f\left(x,t,w(x,t),w(x,t-\tau)\right)$ a non considered problem in [1], is also established with an additional assumption. The result of the paper consists, among other things, in that we obtain a solution of problem of much stronger regularity than in [1, 2].

## 2. Existence and Uniqueness of Solutions

We are concerned here with exact and approximate solutions of the following delay differential equation:

$$\begin{aligned}
&\frac{\partial w}{\partial t}(x,t)-\frac{\partial^2 w}{\partial x^2}(x,t)=f\left(x,t,w(x,t),w(x,t-\tau)\right),0<t\le T<\infty,x\in(a,b)\\
&w(a,t)=w(b,t)=0,t\ge 0\\
&g\left(w_{[-\tau,0]}\right)=\varphi
\end{aligned}\qquad (1)$$

where the sought for real valued function $w$ is defined on $(a,b)\times[-\tau,T],\tau>0,a<b,f$ is a smooth real valued function defined on $(a,b)\times[0,T]\times R^2, g$ is a map from $\ell_0 := C([-\tau,0];L^2(a,b))$ into $L^2(a,b), w_{[-\tau,0]}$ is the restriction of $w$ on $(a,b)\times[-\tau,0]$ and $\varphi\in L^2(a,b)$.

Some of the cases of the nonlocal history function $g$ in which we will be interested are the following.

(i) $g(\psi)(x)=\int_{-\tau}^{0}k(s)\psi(s)(x)ds$ for $x\in(a,b)$ and $\psi\in\ell_0$

(ii) $g(\psi)(x)=\sum_{i=1}^{n}c_i\psi(\theta_i)(x)$ for $x\in(a,b)$ and $\psi\in\ell_0$

(iii) $g(\psi)(x)=\sum_{i=1}^{n}\left(\frac{c_i}{\varepsilon_i}\right)\int_{\theta_i-\varepsilon_i}^{\theta_i}\psi(s)(x)ds$ for $x\in(a,b)$ and $\psi\in\ell_0$

Nonlocal abstract differential and functional differential equations have been extensively studied in the literature. We refer to the works of [2, 4, 6, 11]. Most of them used semigroup theory and fixed point theorem to establish the unique existence and regularity of solution. In [5], the fixed point principle to prove the theorems for existence of mild and classical solutions of nonlocal Cauchy problem of the form

$$u'(t)+Au(t)=f(t,u(t),u(b_1(t)),...,u(b_m(t))),t\in(0,T]$$
$$u(0)+g(u)=u_0 \qquad (2)$$

where $A$ is the infinitesimal generator of a compact $C_0$ semi group in a Banach space. In our recent work [1], we studied the functional differential equation (2) with the nonlocal history condition $h(u_{[-\tau,0]})=\varphi$ where $h$ is a Volterra type operator from $\ell_0$ into itself and $\varphi\in\ell_0$. We made use of method of semidiscretization in time to derive the existence and uniqueness of a strong solution. Many authors have used and developed the method of semidiscretization for nonlinear evolution and nonlinear functional evolution equations, see, for instance, the papers of [1, 8, 9], and the references listed therein.

Our purpose here is to study the exact and approximate solutions of the delay differential equation (1) with a nonlocal condition. In doing so, we first use the method of semidiscretization to derive the existence of a unique strong solution, and then we prove that strong solution is a classical solution if additional conditions are assumed on the operator. The global existence of a solution for (1), a non considered problem in [1], is also established with an additional assumption. The result of the paper consists, among other things, in that we obtain a solution of problem of much stronger regularity than in [1].

The existence and uniqueness results have been established for the more general case of (3). For the sake of completeness, we briefly mention the ideas and the main result of the existence and uniqueness.

If we take $H:=L^2(a,b)$, the real Hilbert space of all real valued square integrable functions on the interval $(a,b)$, and the linear operator $A$ defined by

$$D(A):=\{u\in H:u''\in H,u(a)=u(b)=0\},Au=-u'',$$

then it is well known that $A$ generates an analytic semi group $e^{tA},t\geq 0$ in $H$. If we define $u:[-\tau,T]\to H$ given by $u(t)(x)=w(x,t)$ then (1) may be rewritten as the following evolution equation:

$$u'(t)+Au(t)=F(t,u(t),u(t-\tau)),0<t\leq T \qquad (3)$$
$$h(u_{[-\tau,0]})=\varphi$$

for a suitably defined function $F:[0,T]\times H^2\to H,0<T<\infty,\Phi\in\ell_0:=C([-\tau,0];H)$ the linear operator $A$, defined from the domain $D(A)\subset H$ into $H$, is such that $A$ is the infinitesimal generator of a $C_0$ semi group $S(t),t\geq 0$, of contractions in $H$, the map $h$ is defined from $\ell_0$ into $\ell_0$. Here $\ell_t:=C([-\tau,0];H)$ for $t\in[0,T]$ is the space of all continuous functions from $[-\tau,t]$ into $H$ endowed with supremum norm

$$\|\psi\|_t=\sup_{-\tau\leq\eta\leq t}\|\psi(\eta)\|,\psi\in\ell_t$$

Suppose that there exists a $\chi\in\ell_0$ such that $h(\chi)=\Phi$. Let $\tilde{T}$ be any number such that $0<\tilde{T}\leq T$. A function $u\in\ell_{\tilde{T}}$ such that

$$u(t)=\begin{cases}\chi(t),t\in[-\tau,0]\\ S(t)\chi(0)+\int_0^t S(t-s)F(s,u(s),u(s-\tau))ds,t\in[0,\tilde{T}]\end{cases}$$

is called a mild solution of (3) on $[-\tau,\tilde{T}]$. By a strong solution $u$ of (3) on $[-\tau,\tilde{T}]$, we mean a function $u\in\ell_{\tilde{T}}$ such that $u(t)\in D(A)$ for almost everywhere $t\in[0,\tilde{T}]$, $u$ is differentiable almost everywhere on $[0,\tilde{T}]$ and

$$u'(t)+Au(t)=F(t,u(t),u(t-\tau))$$

almost everywhere $t\in[0,\tilde{T}]$

A mild solution $u$ of (1) on $[-\tau,\tilde{T}]$ is called a classical solution of (1) if $u(t)\in D(A)$ for all $t\in(0,\tilde{T}]$ and $u\in C^1((0,\tilde{T});H)$, and

$$u'(t)+Au(t)=F\left(t,u\left(t\right),u\left(t-\tau\right)\right),t\in(0,\tilde{T}]$$

We have the following existence and uniqueness result for (3).

**Theorem 2.1**
Suppose that there exists a Lipschitz continuous $\chi \in \ell_0$ such that $h(\chi)=\Phi$ and $F$ satisfies the condition

$$\left\|F\left(t_1,u_1,v_1\right)-F\left(t_2,u_2,v_2\right)\right\|\le L_F(r)\left[\left|t_1-t_2\right|+\left\|u_1-u_2\right\|+\left\|v_1-v_2\right\|\right] \quad (4)$$

for all $t_i\in[0,T],u_i,v_i\in B_r\left(H,\chi\left(0\right)\right),i=1,2,...$ where $B_r(Z,z_0)$ denotes the closed ball of radius $r>0$ centered at $z_0$ in the Banach space $Z$. Then there exists a strong solution $u$ of (3) either on the whole interval $[-\tau,T]$ or on a maximal interval $[-\tau,t_{\max}),0<t_{\max}\le T$ such that $u$ is a strong solution of (3) on $[-\tau,\tilde{T}]$ for every $0<\tilde{T}<t_{\max}$ and in the latter case,

$$\lim_{t\to t_{\max}}\left\|u(t)\right\|=\infty$$

If, in addition, $S(t)$ is an analytic semi group in $H$, then $u$ is a classical Lipschitz continuous solution on every compact subinterval of the interval of existence. Furthermore, $u$ is unique in $\left\{\psi\in\ell_{\tilde{T}}:\psi=\chi on\left[-\tau,0\right]\right\}$ for every compact subinterval $[-\tau,\tilde{T}]$ of the interval of existence.

### 3. Illustration
Now we illustrate the applicability of our work, we discuss the exact and approximate solutions of some initial boundary value problems.
As a first example, we consider the equation

$$\frac{\partial u}{\partial t}(t,x)-\frac{\partial^2 u}{\partial t^2}(t,x)=u(t-\tau,x)-e^{-2t}(1+e^{2\tau})\sin x,t>0,x\in[0,\pi] \quad (5)$$

with the boundary condition

$$u(t,0)=u(t,\pi)=0,t>0$$

and a nonlocal history condition

$$\frac{1}{\tau}\int_{-\tau}^{0}e^{2s}u(s,x)ds=\sin x,x\in[0,\pi] \quad (6)$$

Where $\tau>1$ is arbitrary. Let $H=L^2\left(\left[0,\pi\right]\right)$. The operator $A$ with domain $D(A)=\left\{v\in H:v''\in H,v(0)=v(\pi)=0\right\}$ is given by

$$Av=-\frac{d^2v}{dx^2},v\in D(A)$$

Then $-A$ is the infinitesimal generator of an analytic semi group $S(t),t\ge 0$, in $H$.
An exact solution of (5) is

$$u(t,x)=e^{-2t}\sin x,t\ge-\tau,x\in[0,\pi]$$

In this case $\chi_1\in\ell_0:=C\left(\left[-\tau,0\right];L^2\left(\left[0,\pi\right]\right)\right)$ is given by

$$\chi_1\left(t\right)\left(x\right)=e^{-2t}\sin x$$

so that the history condition is satisfied.
Divide the interval $I=[0,1]$ into ten subintervals $I_1,I_2,...,I_{10}\left(I_j=\left[t_{j-1},t_j\right],j=1,2,...,10\right)$ of length $h=0.1$. For $t_0=0$, set $u_0(x)=\sin x$ and find, subsequently, for $t_j$, the approximate solutions $u_j,j=1,2,...,10$, so that

$$\frac{u_j\left(x\right)-u_{j-1}\left(x\right)}{h}-u_j''\left(x\right)=\chi_1\left(t_j-\tau\right)\left(x\right)-e^{-2t_j}\left(1+e^{2\tau}\right)\sin x$$
$$u_j\left(0\right)=u_j\left(\pi\right)=0$$

that is,

$$\frac{u_j\left(x\right)-u_{j-1}\left(x\right)}{h}-u_j''\left(x\right)=e^{-2t_j}\sin x \quad (7)$$
$$u_j\left(0\right)=u_j\left(\pi\right)=0$$

is satisfied for $j=1,2,...,10$.
For $j=1$, (7) becomes

$$u_1''\left(x\right)-\frac{1}{h}u_1\left(x\right)=\left(-\frac{1}{h}+e^{-2t_1}\right)\sin x$$
$$u_1\left(0\right)=u_1\left(\pi\right)=0$$

Consequently, we solve a second order ordinary differential equation. In this case, the solution is

$$u_1\left(x\right)=\frac{1}{1+h}\left(1-he^{-2h}\right)\sin x$$

Similarly, for $j=2$, (7) yields

$$u''(x)-\frac{1}{h}u_2(x)=\left(-\frac{1}{h(1+h)}\left(1-he^{-2t_1}\right)+e^{-2t_2}\right)\sin x$$
$$u_2(0)=u_2(\pi)=0$$

On solving this equation in the same way as before, we get

$$u_2(x)=\frac{1}{\left(1+h\right)^2}\left[1-he^{-2h}\left(1+\left(1+h\right)e^{-2h}\right)\right]\sin x$$

Similar results are easily obtained for $j=3,4,...,10$. Thus we have

$$u_j(x)=\frac{1}{(1+h)^j}\left[1-he^{-2h}\left(1+(1+h)e^{-2h}+(1+h)^2e^{-4h}+...+(1+h)^{j-1}e^{2(j-1)h}\right)\right]\sin x$$

or

$$u_j(x)=\frac{1}{(1+h)^j}\left[1-he^{-2h}\left(\frac{1-(1+h)^je^{2jh}}{1-(1+h)e^{2h}}\right)\right]\sin x,\ j=1,2,...,10$$

Putting here $h=0.1$ and rounding off to six decimals, we finally obtain the approximate solutions $u_j(x)$ at

$$t_j,\ j=1,2,...,10.$$

We also calculate the exact solution of (5) for $t=t_1=0.1,...,t=t_{10}=1$

In the next step we choose another function

$$\chi_2(t)(x)=\frac{2\tau}{1-e^{-2\tau}}\sin x$$

in $\ell_0$ which differs from $\chi_1$ and satisfies the history condition (6).

Divide the interval $I=[0,1]$ into the same number of subintervals with step length $h=0.1$. For $t_0=0$, set $u_0(x)=\left(2\tau/1-e^{-2\tau}\right)\sin x$ and find the approximations $u_j$ so that

$$\frac{u_j(x)-u_{j-1}(x)}{h}-u_j''(x)=\chi_2(t_j-\tau)(x)-e^{-2t_j}\left(1+e^{2\tau}\right)\sin x$$
$$u_j(0)=u_j(\pi)=0$$

that is,

$$\frac{u_j(x)-u_{j-1}(x)}{h}-u_j''(x)=\left[\frac{-2\tau}{1-e^{-2\tau}}+e^{-2t_j}\left(1+e^{2\tau}\right)\right]\sin x$$
$$u_j(0)=u_j(\pi)=0$$

is fulfilled for $j=1,2,...,10$.

Following the calculations similar to the previous case, we obtain the approximate solutions $u_j,\ j=1,2,...,10$ as follows:

$$u_1(x)=\left[\frac{\tau}{\sinh 2\tau}-\frac{h}{(1+h)}e^{-2h}\right]\left(1+e^{2\tau}\right)\sin x$$

$$u_2(x)=\left[\frac{\tau}{\sinh 2\tau}-\frac{he^{-2h}}{(1+h)^2}\left(1+(1+h)e^{2h}\right)\right]\left(1+e^{2\tau}\right)\sin x$$

and

$$u_j(x)=\left[\frac{\tau}{\sinh 2\tau}-\frac{he^{-2h}}{(1+h)^j}\left(\frac{1-(1+h)^je^{-2jh}}{1-(1+h)e^{-2h}}\right)\right]\left(1+e^{2\tau}\right)\sin x,\ j=1,2,...,10$$

In this case the exact solution is obtained by solving the partial differential equation

$$\frac{\partial u}{\partial t}(t,x)-\frac{\partial^2u}{\partial x^2}(t,x)=\frac{2\tau}{1-e^{-2\tau}}\sin x-e^{-2t}\left(1+e^{2\tau}\right)\sin x,t>0,x\in[0,\pi]$$
$$u(t,0)=u(t,\pi)=0,t>0 \qquad (8)$$

$$u(x,0)=\frac{2\tau}{1-e^{-2\tau}}\sin x,x\in[0,\pi]$$

We take the solution of the form

$$u(t,x)=T(t)\sin x$$

Putting this into (8), we get a first order linear differential equation in $T(t)$ which can be solved by calculating the integrating factor. Thus we have

$$T(t)=\frac{2\tau}{1-e^{-2\tau}}-\left(1+e^{2\tau}\right)\left(e^{-t}-e^{-2t}\right)$$

Therefore, the exact solution is

$$u(t,x)=\left[\frac{\tau}{\sinh 2\tau}-\left(e^{-t}-e^{-2t}\right)\right]\left(1+e^{2\tau}\right)\sin x$$

On comparison of approximate solutions with exact solution of problem (5) at discrete values of variable $t$ in both cases, it is observed that they are very much similar to each other. It is also seen that for $\chi_1\neq\chi_2$ in $\ell_0$, the corresponding solutions are different, which implies the existence of unique solution of (5).

As a second example, we consider the same partial differential equation with a different nonlocal history condition:

$$\frac{\partial u}{\partial t}(t,x)-\frac{\partial^2u}{\partial x^2}(t,x)=u(t-\tau,x)-e^{-2t}\left(1+e^{2\tau}\right)\sin x,t>0,x\in[0,\pi]$$
$$u(t,0)=u(t,\pi)=0,t>0 \qquad (9)$$
$$\frac{1}{2e^{2\tau}}u(-\tau,x)+\frac{1}{2}u(0,x)=\sin x,x\in[0,\pi]$$

An exact solution of (9) is

$$u(t,x)=e^{-2t}\sin x,t\geq-\tau,x\in[0,\pi]$$

In a similar manner as before, for $\chi_1\in\ell_0$ given by $\chi_1(t)(x)=e^{-2t}\sin x$, approximations $u_j$ at discrete values $t_j,\ j=1,2,...,10$ of $t$ are

$$u_j(x)=\frac{1}{(1+h)^j}\left[1-he^{-2h}\left(\frac{1-(1+h)^je^{2jh}}{1-(1+h)e^{2h}}\right)\right]\sin x,\ j=1,2,...,10$$

Next, we choose $\chi_2 \in \ell_0$, such that $\chi_1 \neq \chi_2$ satisfying the nonlocal history condition of (9), and given by

$$\chi_2(t)(x) = \frac{2e^{2\tau}}{1+e^{2\tau}} \sin x$$

Following the similar steps of the previous example, here we get the approximate solutions

$$u_j(x) = \left[ \frac{2e^{2\tau}}{\left(1+e^{2\tau}\right)^2} - \frac{he^{-2h}}{(1+h)^j} \left( \frac{1-(1+h)^j e^{-2jh}}{1-(1+h)e^{-2h}} \right) \right] \left(1+e^{2\tau}\right) \sin x, \; j = 1, 2, ..., 10$$

and the exact solution

$$u(t,x) = \left[ \frac{2e^{2\tau}}{\left(1+e^{2\tau}\right)^2} - \left(e^{-t} - e^{-2t}\right) \right] \left(1+e^{2\tau}\right) \sin x, \; j = 1, 2, ..., 10 \quad (10)$$

Putting $h = 0.1$ in both cases, approximate as well as exact solutions are obtained.

## 4. Example

The 6 minute walk test (6-MWT) is used to assess patients with chronic heart failure (CHF). The prognostic significance of the 6-MWT distance during long term follow up (>5 years) is unclear. 1,667 patients (median [inter quartile range, IQR] age 72 [65–77]; 75% males) with heart failure due to left ventricular systolic impairment undertook a 6-MWT as part of their baseline assessment and were followed up for 5 years. At 5 years follow up, those patients who died (n = 959) were older at baseline and had a higher log NT-proBNP than those who survived to 5 years (n = 708). 6-MWT distance was lower in those who died [163 (153) m versus 269 (160) m; P < 0.0001]. Median 6-MWT distance was 300 (150–376) m, and quartile ranges were < 46 m, 46 – 240 m, 241 – 360 m, and > 360m. 6-MWT distance was a predictor of all cause mortality (HR0.97; 95% CI 0.96-0.97; Chi-square = 184.1; P < 0.0001). Independent predictors of all cause mortality were decreasing 6-MWT distance, increasing age, increasing NYHA classification, increasing log NT-proBNP, decreasing diastolic blood pressure, decreasing sodium, and increasing urea [3, 7, 10]. The figure shows a Kaplan Meier survival curve for the patients divided by quartiles of 6-MWT distance (< 46 m: event free survival 24%; 46 – 240 m: event free survival 29%; 241 – 360 m: event free survival 45%; > 360 m: event frees survival 70%).

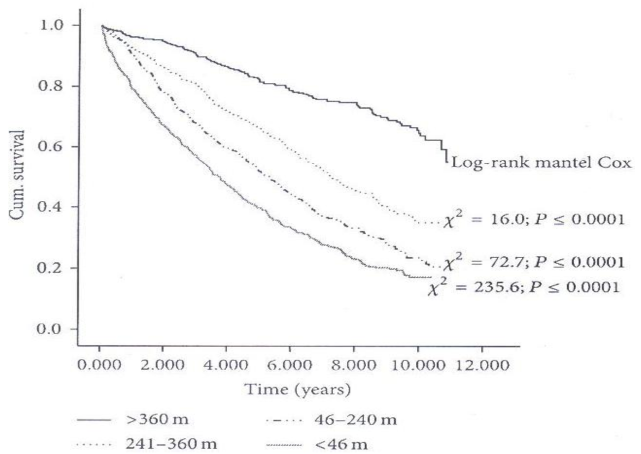
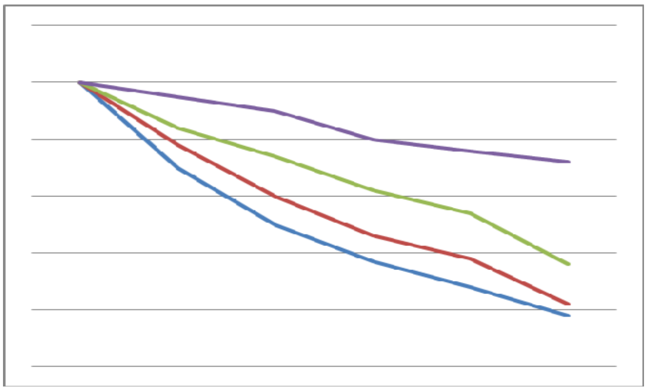



**Fig 1:** Kaplan Meier survival curve showing quartiles of 6-MWT distance (m) (<46 m, vent free survival 24%; 46 – 240 m, event free survival 29%; 241 – 360 m, event free survival 45%; > 360 m, event free survival 70%).



Blue Line: < 46 m
Red Line: 46 – 240 m
Green Line: 241 – 360 m
Violet Line: > 360 m

**Fig 2:** Kaplan Meier survival curve showing quartiles of 6-MWT distance (m) (<46 m, vent free survival 24%; 46 – 240 m, event free survival 29%; 241 – 360 m, event free survival 45%; > 360 m, event free survival 70%) using the normal distribution.

## 5. Conclusion

The 6-MWT is an independent predictor of all cause mortality following long term (5-year) follows up in patients with CHF. It provides similar or better discriminatory power than other routinely collected physical and biochemical variables and, as such, might make a reasonable target for treatment. The exact solution of the partial differential equation with a different nonlocal history conditions using normal distribution gives the same results as mentioned above. By using normal distribution the mathematical model gives the result as same as the medical report. The medical reports {Figure (1)} are beautifully fitted with the mathematical model {Figure (2)}; the results coincide with the mathematical and medical report.

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