International Journal of Current Research and Modern Education (IJCRME)
Impact Factor: 6.925, ISSN (Online): 2455 - 5428
(www.rdmodernresearch.com) Volume 3, Issue 1, 2018

STOCHASTIC MODEL TO FIND THE IDENTIFIABILITY OF ALPHA AMYLASE AND CORTISOL REACTIVITIES IN BREAST CANCER SURVIVORS

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Cite This Article: Dr. P. Senthil Kumar & P. Bharathi Kannammal, "Stochastic Model to Find the Identifiability of Alpha Amylase and Cortisol Reactivities in Breast Cancer Survivors", International Journal of Current Research and Modern Education, Volume 3, Issue 1, Page Number 596-603, 2018.

Abstract:

Overall understanding of the unification of the stress reaction in this population, this paper reveals the diurnal and acute alpha-amylase profiles of breast cancer survivors and women with no history of cancer. Outcome of this study exhibit that breast cancer survivors showed same but raised patterns of alpha amylase concentrations in diurnal and acute profiles corresponding to healthy women, contradict to their Cortisol results which displayed normal diurnal and blunted acute patterns. In this paper, different well known results on parametric identification for stochastic model will be discussed and some new results are presented. Then we present the non-identifiability of the Moolgar-Kar-Venzon-Knudson (MVK) two stage model of carcinogenesis and compared with alpha-amylase and cortisol reactivities in breast cancer survivors.

Key Words: Alpha Amylase, Cortisol, Stress, Breast Cancer Survivor, Identifiability, Non-Identifiability, Hazard Function & Stochastic Models.

Introduction:

Stress is a leading factor in psychological and physical health. Breast cancer survivors in this study as independents with the investigation of breast cancer and at present in relief may do different stressors all through the cancer path. Cortisol is free flow from the adrenal glands via a cascade of happenings initiated by a stressful stimulant which add interplay with a host of biological structures connected to the SNS (Sympathetic Nervous System) [2], [6]. Alpha-amylase is a SNS biomarker and a valid measure of both physical and psychological stress in humans [8], [9].

The focal point of this paper is the enzyme alpha-amylase, a stress biomarker of the SNS which has experienced much less attentiveness than the all-present Cortisol in research on stress physiology [10]. And also we discuss a common approach for solving the identifying problem for finite parametric models. This approach grants for an integrated view point of studying identifiability of variety of stochastic models appearing in biology and medicine oriented models. We consider common methodology for solving the identifiability problem for finite parametric models and non-identifiability of the MVK two stage model of carcinogenesis [3], [4].

Identification Problem for Stochastic Models:

Behavior of a biological or other system described by the identification problem for stochastic model. A system is executed by the equation, $u = g(a,\phi)$; here a is a scalar (or) vector variable, u is an observable scalar, ϕ is a parameter set and g is a known function that relates a to u. ϕ is represented by the elements of real numbers, distributions or functions. We assume ϕ is minimal and $a \in \mathcal{D}$ which is independent of ϕ.

For deterministic models $u = g(a,\phi)$ can be acquired by solving differential, difference or integral equations. For stochastic models $u = g(a,\phi)$ is of the form $U = g(A,\phi)$, here A and U are random variables.

The distribution of random variable U is completely characterized by CDF (Cumulative Distribution Functions). $G_U(u) : \Pr(U \le u)$ or the corresponding survival function

$$\overline{G}_U(u) = 1 - G_U(u) = \Pr(U > u).$$ [3].

In this paper, for stochastic models, for the non-negative observed output random variable U we get $u = g(a,\phi)$ as

$$\overline{G}_U(t) = g(t,\phi), t \ge 0$$

Where $\overline{G}_U$ can be replaced by CDF, PDF(Probability Density Function), Hazard function, characteristic function etc. Also survival and hazard functions of U related as

$$\overline{G}_U(t) = \exp(-\int_0^t Q_U(w)dw),\ t \geq 0$$

The model $u = g(a,\phi)$ is identifiable if $g(a,\phi_1) = g(a,\phi_2)$ for all $a \in \mathcal{D} \Rightarrow \phi_1 = \phi_2$.

Identification of Finite Parametric Models:

The general observation of identification properties of models $u = g(a,\phi)$ (or) $\overline{G}_u(t) = g(t,\phi),\ t \geq 0$ depends on $\phi = (\phi_1,...,\phi_n)$ a finite set of parameters. First solving $g(a,\phi) = h(a), a \in \mathcal{D}$ for ϕ, where h is an output function, all possible independent parameters $\phi_1,\phi_2,...,\phi_n$ are determined by the function h. This commonly results in equations of the form

$$Q_i(\phi_1,...,\phi_n) = L_i(h), \qquad 1 \leq i \leq m \qquad \text{... (1)}$$

With $Q_i : \Theta \to \mathcal{R}$ and functional $L_i, 1 \leq i \leq m$, L_i may involves values or limits of $'h'$ (or) its derivatives at some points (or) at infinity plain (or) weighted integrals of function h and its derivatives. The set of (1) should be not only minimal, but also complete. So that $g(a,\phi) = g(a,\phi')$ for all $x \in \mathcal{D}$ is equivalent to $Q_i(\phi) = Q_i(\phi'),\ 1 \leq i \leq m$.

This means $\xi_i = Q_i(\phi_1,\phi_2,...,\phi_n)\ 1 \leq i \leq m$ ... (2)

are identifiable.

Non-Identifiability of the Moolgavkar-Venzon-Knudson Two-Stage Model of Carcinogenesis:

The most commonly acknowledged mechanistic model of carcinogenesis is referred to as the MVK model. This Markovian model has a deep impact in Carcinogenesis modeling and quantitative analysis of different experimental data. In this and all other mechanistic models of carcinogenesis there are two stages of formation of malignant cells viewed as [1]

- ✓ Initiation of predominant precancerous lesions in the people of vulnerable target normal stem cells.
- ✓ Improvement of initiated cells occurring in the transformation of intermediate cells.

The MVK model is form on the following assumptions:

- ✓ The number of first-generation beginning cells follows a (generally, non-homogeneous) poison process with intensity $\alpha(t)$.
- ✓ An intermediate cell divides into two intermediate daughter cells with rate $\gamma(t)$, dies or differentiates with rate $\mu(t)$, and divides into one intermediate and one malignant cell with rate $\eta(t)$. For the birth-and-death branching Markov process, the usual independence hypotheses are accepted.
- ✓ Tumors begin from a single malignant progenitor cells. Once a malignant cell is produced, its subsequent development is irreversible and guides to appearance of a measurable tumor.

By assumption (ii) and for arbitrary promotion time distribution with CDF G, formation of clonogenic tumor cells is governed by a poison process with the integral rate [5]

$$\mathcal{F}(t) = \int_0^t \alpha(a)G(t-a)da$$

Then the general form of the survival function $F(t)$ of the time to tumor, the probability of no malignant clonogenic cells of time t, is given by

$$F(t) = \exp\left\{-\int_0^t \alpha(a)F(t-a)da\right\} \qquad \text{... (3)}$$

In particular, the constant initiation rate α, we write the formula as

$$F(t) = \exp\left\{-\alpha\int_0^t G(a)da\right\} \qquad \text{... (4)}$$

Compared with $\overline{G} = \exp(-\int_0^t Q_U(w)dw),\ t \geq 0$ which is the survival and hazard function of random variable *U*.

Notice that, in spontaneous carcinogenesis, time to tumor is counted from the moment of birth for induced carcinogenesis, the time is calculated from the basic moment of display to a carcinogen.

Model (3) and (4) was broadly used to describe induced and spontaneous carcinogenesis and hormesis [11]. When the rate of initiation (α) and the death or differentiation (μ), the rates of cell division (γ) and malignant transformation (η) for initiated cells are all constant, and the number of target normal cells is effectively constant, then the formula for the CDF G of the promotion time was obtained by

$$G(t) = \frac{(\gamma - \mu - \eta + z)(\mu + \eta + z - \gamma)(1 - e^{-zt})}{2\gamma[(\gamma - \mu - \eta + z)e^{-zt} + (\mu + \eta + z - \gamma)} \quad \text{... (5)}$$

Where

$$z = \sqrt{(\gamma + \mu + \eta)^2 - 4\gamma\mu} \quad \text{... (6)}$$

Note that

$$\lim_{t\to\infty} G(t) = \frac{\gamma - \mu - \eta + z}{2\gamma} < 1$$

This gives that the probability of the event that no malignant cells are produced is positive. When the parameters α, γ, μ and η are piecewise constant on the same arbitrary time intervals, recursive formula for finding the hazard function of the time of tumor latency were found [7].

The survival function of the time of tumor latency in the MVK model with constant parameters $\alpha, \gamma, \mu, \eta$ is

$$F(t) = \left[\frac{2ze^{-(\gamma-\mu-\eta+z)t/2}}{(\gamma - \mu - \eta + z)e^{-zt} + (\mu + \eta + z - \gamma)}\right]^{\alpha/\gamma} \quad \text{… (7)}$$

Where *z* is specified in equation (6) to exhibit dependence of the function F on the four biologically motivated parameters notationally

We write $F(t) = F(t; \alpha, \gamma, \mu, \eta)$

Theorem 1:

The equality $F(t; \alpha_1, \gamma_1, \mu_1, \eta_1) = F(t; \alpha_2, \gamma_2, \mu_2, \eta_2),\ t \geq 0$ holds if and only if $\frac{\alpha_1}{\gamma_1} = \frac{\alpha_2}{\gamma_2}$ $\gamma_1 - \mu_1 - \eta_1 = \gamma_2 - \mu_2 - \eta_2$ and $(\gamma_1 + \mu_1 + \eta_1)^2 - 4\gamma_1\mu_1 = (\gamma_2 + \mu_2 + \eta_2)^2 - 4\gamma_2\mu_2$

It comes after that parameters

$$\delta = \frac{\alpha}{\gamma}, \rho = \gamma - \mu - \eta \text{ and } z = \sqrt{(\gamma + \mu + \eta)^2 - 4\gamma\mu} \quad \text{... (8)}$$

are identifiable. Here ρ can be interpreted as the effective birth rate clearly they are independent and the parametric dimension of the MVK model is three. The range of the parametric vector $\xi = (\delta, \rho, z)$ is given by

$$\mathcal{M} = \{(\delta, \rho, z) : \delta > 0,\ \rho \in \mathcal{R},\ z > |\rho|\}$$

Conversely, given any $\xi \in \mathcal{M}$, we take an arbitrary $\gamma > (z - \rho)/2$ and set

$$\alpha = \gamma\delta, \mu = \frac{(2\gamma - \rho)^2 - z^2}{4\gamma}, \eta = \frac{z^2 - \rho^2}{4\gamma}$$

To find that $\alpha, \gamma, \mu, \eta > 0$ and relations (8) are satisfied. Thus, there is infinitely many parameter sets $\phi = (\alpha, \gamma, \mu, \eta)$ corresponding to each parameter vector ξ and hence to each survival function (7).

One more way to show that set of all model parameters ϕ determined by the function $F(t)$ given one of them, $\phi_0 = (\alpha_0, \gamma_0, \mu_0, \eta_0)$ as follows.

We set,

$$\alpha = k\alpha_0, \quad k > 0$$

Solving two parameter sets equation in theorem 1 and to get

$$\alpha = k\alpha_0, \quad \gamma = k\gamma_0$$

$$\mu = (k-1)\gamma_0 + \mu_0 + \frac{k-1}{k}\eta_0, \eta = \frac{\eta_0}{k} \qquad \text{... (9)}$$

The claim $\mu > 0$ leads to the restriction $k > k_0$, where

$$k_0 = \frac{[(\gamma_0 - \mu_0 - \eta_0)^2 + 4\gamma_0\eta_0]^{1/2} + [\gamma_0 - \mu_0 - \eta_0]}{2\gamma_0}, 0 < k_0 < 1$$

Together with ϕ_0, the whole curve [equation (9)] of parameter vectors ϕ with $k > k_0$ pertains to the same function $F(t)$.

In terms of parameters δ, ρ, z the function $F(t)$ takes on a form

$$F(t) = \left[\frac{2ze^{-(z+\rho)t/2}}{(z+\rho)e^{-zt} + z - \rho}\right], \text{ Compare with (7)}$$

Further simplification we introduce a new set of identifiable parameters (x, y, δ), where $x = \frac{(z-\rho)}{2}$ and $y = \frac{(z+\rho)}{2}$ clearly $x, y > 0$ and

$$F(t) = \left[\frac{(x+y)e^{xt}}{y + xe^{(x+y)t}}\right]^{\delta} \qquad \text{... (10)}$$

for the corresponding hazard function we have

$$h(t) = \delta xy \frac{e^{(x+y)t} - 1}{y + xe^{(x+y)t}} \qquad \text{... (11)}$$

Comparison of equation (11) with (9), the following relation between parameters Y_m, ν, q introduced and parameters $x, y, \delta : Y_m = \delta xy, \nu = y - x, q = x.$

It was shown that the four rates in the MVK model are not jointly identifiable; it is not proved rigorously there that parameters Y_m, ν, q are identifiable from the time-to-tumor distribution.

Example:

The breast cancer survivors and women without a pervious diagnosis of breast cancer were taken for this study. Participants were instructed the correct method of collecting saliva samples at home. For two consecutive days the saliva samples were collected at time points t_1, t_2, t_3, t_4, t_5.

Then a lab visit was occurred within seven days following the home-based saliva collection. On that day participants were asked to collect saliva samples at home then in the lab totally seven saliva samples collected at time points $T_1, T_2, T_3, T_4, T_5, T_6, T_7$. At each time points of collection of saliva samples, participants were asked to indicate their subjective stress level on the VAS (Visual Analog Scale).

Diurnal Alpha Amylase:

A 2^5 mixed-design ANOVA was used in this study to asses' difference in mean alpha-amylase concentration over two consecutive days. The connecting subject factor was control (or) breast cancer survivor group and time $(t_1, t_2, t_3, t_4, t_5)$

First we analyze the diurnal alpha-amylase data which shows in fig (1).

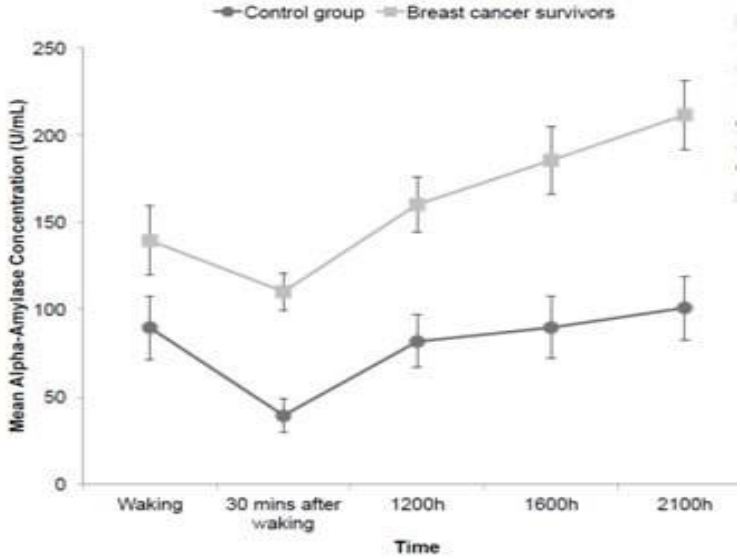

Figure 1: Mean diurnal alpha-amylase concentrations

The statistical results showed no significant interaction between these two factors. Fig.(1) shows that the group basal levels of alpha-amylase clearly different, the slopes of both patterns are similar.

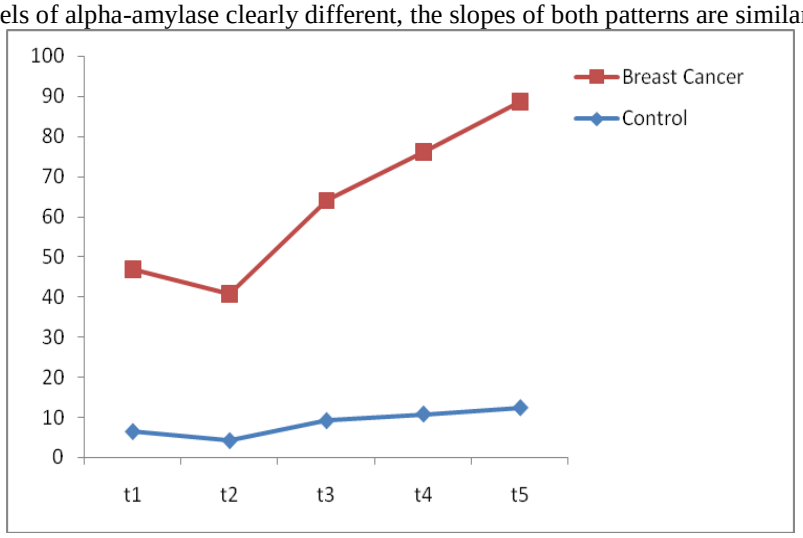

Figure 1a

Figure 2 Shows the plot of cortisol data. There is a contrast in the diurnal cortisol profiles for the two groups which are virtually superimposable.

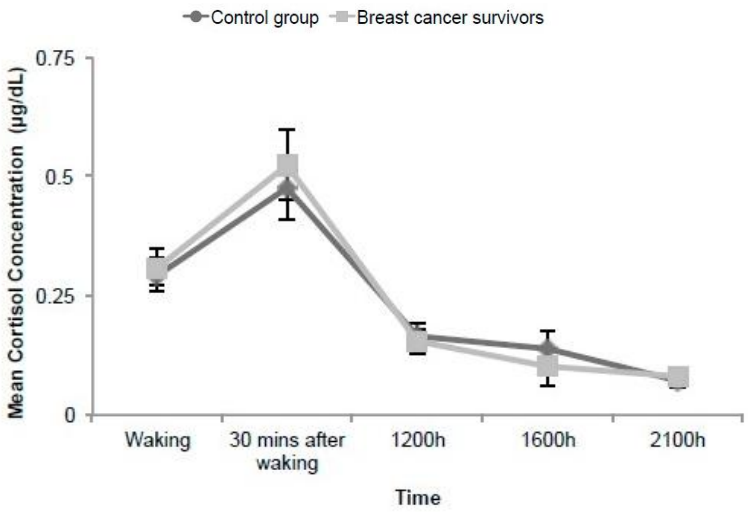

Figure 2: Mean diurnal cortisol concentrations

In addition that, the relationship between time since diagnosis and diurnal alpha amylase concentrations no significant correlations were found.

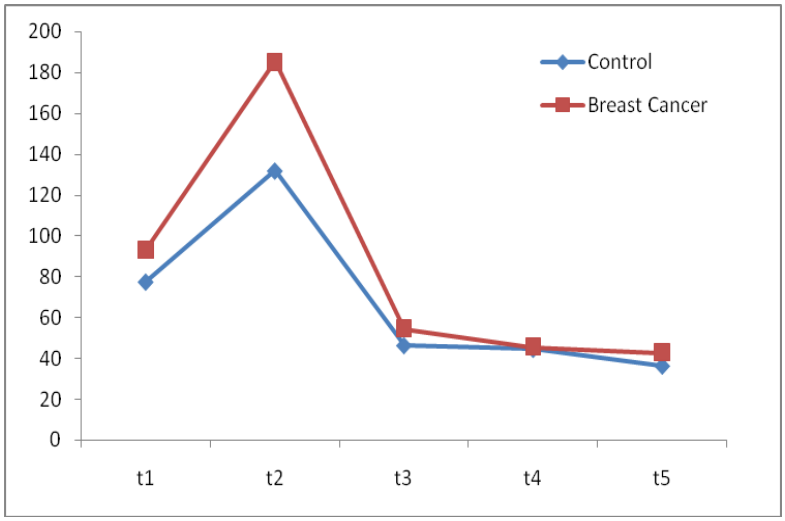

Figure 2a

Acute Alpha-Amylase:

A 2^7 mixed design ANOVA was used in this study to analyse salivary acute alpha-amylase levels. The connecting group factor was breast cancer survivor or control participants and time $(T_1, T_2, T_3, T_4, T_5, T_6, T_7)$. The analysis showed that no interaction between this two factors and revealed that salivary alpha-amylase levels at T_3 significantly differed from all other time points. Moreover, there is no significant difference between T_1 and T_7, suggesting that all participants came back to baseline within one hour by following the Trier social stress test.

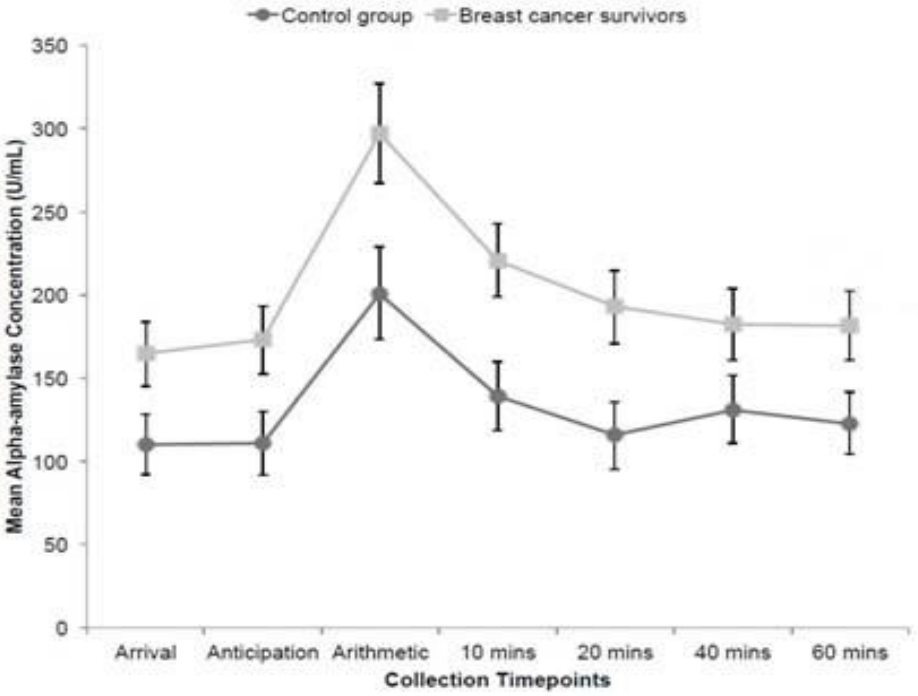

Figure 3: Mean acute alpha-amylase concentrations

Acute alpha-amylase profile is same to their salivary alpha amylase diurnal profile, comparatively breast cancer survivors had a higher basal level of alpha-amylase to the control group and a parallel time course, in spite of the difference in concentrations.

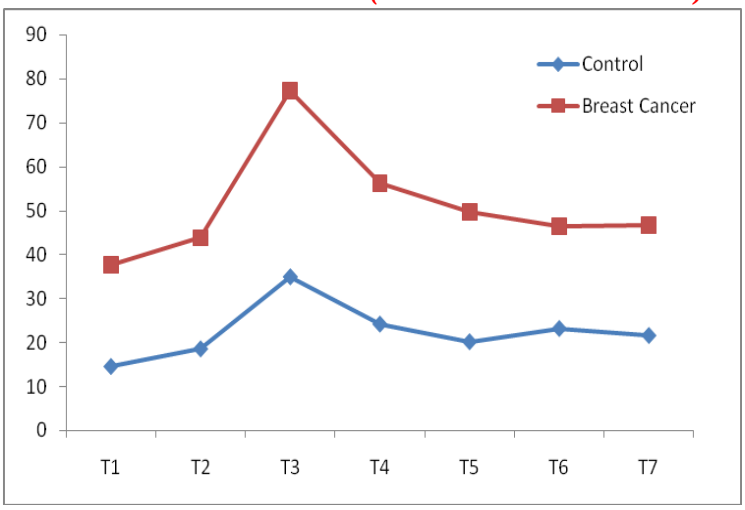

Figure 3a

Figure 3 patterns contrasts with their acute cortisol patterns which shown in Fig (4). These were noticeably different between the two groups with breast cancer survivors showing a blunted cortisol response relative to that of the control group [10].

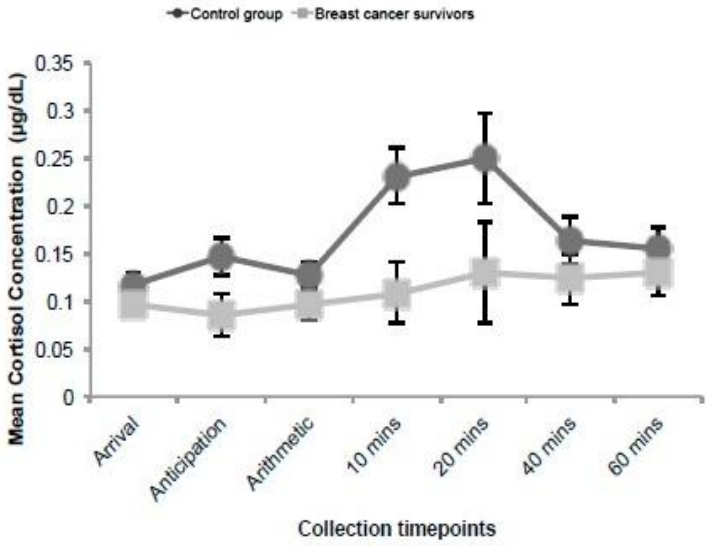

Figure 4: Mean acute cortisol concentrations

In addition we also examined the relationship between at all seven time points since diagnosis and acute alpha-amylase concentration no significant correlations were found.

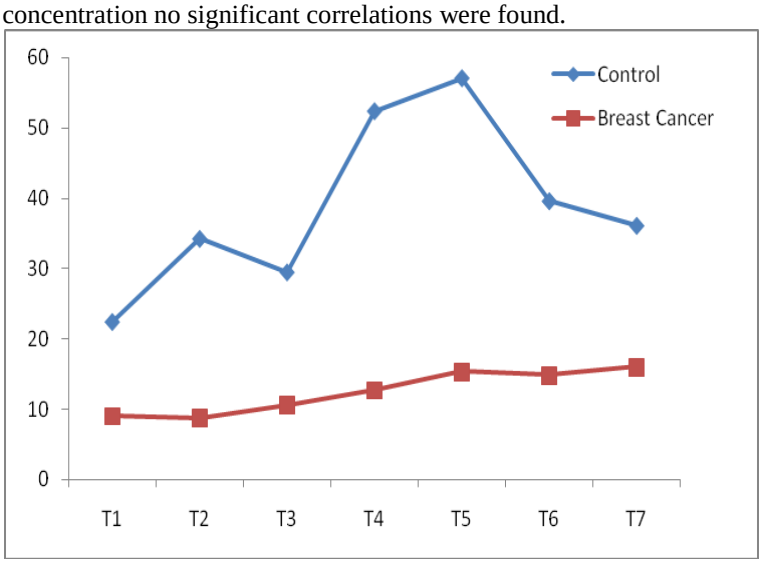

Figure 4a

Conclusion:

The mathematical model to evaluate the reactivity of alpha-amylase and Cortisol in the breast cancer survivors and without breast cancer women which are fitted with non-identifiablity of the MVK Two stage stochastic model and the corresponding is obtained (see fig 1(a), 2(a), 3(a), 4(a)). The results of these analyses shows that breast cancer survivors displayed raised basal salivary alpha-amylase levels, but the patterns paralleled the alpha-amylase reactivity of healthy women. The patterns were not related to the occurrence of stressful events in either group. The results synchronizes with the mathematical and medical report.

References:

1. Armitage, P., and Doll, R., "The two-stage theory of carcinogenesis in relation to the age distribution of human cancers." Br. J. Cancer., 11 (1957): 161-169.
2. Couture-Lalande, M., Lebel, S., and Bielajew, C., "Analysis of the cortisol diurnal rhythmicity and cortisol reactivity in long-term breast cancer survivors." Breast Cancer Manag, 3 (2014): 465-476.
3. Hanin, L.G., "Identification Problem for Stochastic Models with Application to Carcinogenesis, Cancer Detection and Radiation Biology." Discrete Dynamics in Nature and Society, 7(3) (2002): 177-189.
4. Hanin, L.G., and Boucher, K.M., "Identifiability of parameters in the Yakovlev-Polig model of carcinogenesis." Math. Biosci., 160 (1999): 1-24.
5. Hanin, L.G., and Yakovlev, A.Yu., "A nonidentifiability aspect of the two-stage model of carcinogenesis." Risk. Anal., 16(5) (1996): 711-715.
6. Hellhammer, D.H., Wust, S., Kudielka, B.M., "Salivary cortisol as a biomarker in stress research." Psychoneuroendocrinology, 34 (2009): 163-171.
7. Moolgavkar, S.H., and Luebeck, G., "Two-event model for carcinogenesis: biological, mathematical, and statistical considerations." Risk Anal., 10 (1990): 323-341.
8. Nater, U., and Rohleder, N., "Salivary alpha-amylase as a non-invasive biomarker for the sympathetic nervous system: Current state of research." Psychoneuroendocrinology, 34 (2009): 486-496.
9. Strahler, J., Mueller, A., Rosenloecher, F., Kirschbaum, C., and Rohleder, N., "Salivary α-amylase stress reactivity across different age groups." Psychophysiology, 47 (2010): 587-595.
10. Wan, C., Couture-Lalande, M.-E., Narain, T.A., Lebel, S., and Bielajew, C., "Salivary Alpha-Amylase Reactivity in Breast Cancer Survivors." International Journal of Environmental Research and Public Health, 13(353) (2016): 1-15.
11. Yakovlev, A.Yu., and Polig, E., "A diversity of responses displayed by a stochastic model of radiation carcinogenesis allowing for cell death". Math. Biosci.,132(1996):1-33