

## Stochastic Modeling Neutral Evolution by an Iambp of Cortisol Secretion of Breast Cancer

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### ABSTRACT

Objective Fatigue is one of the most common and distressing symptoms by cancer patients and survivors. To evaluate cortisol responses to an experimental psychologic stressor in fatigued and non fatigued survivors. The focus is the frequency spectrum of the Infinite-Allele Markov branching process (IAMBp), namely the proportion having a given number of copies at a specified time point.

**Keywords:** Breast cancer, fatigue, HPA axis, psychologic stress, IAMBp, frequency spectrum. Hyper geometric function.

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### I. INTRODUCTION

Fatigue is one of the most common and distressing side effects of cancer treatment and is elevated in patients with cancer relative to the general population and may endure for months or years after successful treatment completion. Among breast cancer survivors approximately 30% report persistent fatigue. The etiology of cancer –related fatigue has not been determined neither psychologic (eg. Depression) nor biologic (eg. Hemoglobin, thyroid hormone) factors fully account for fatigue symptomatology in patients with cancer. There are several mechanisms through which chronic inflammation might develop or persist in patients with cancer, including alterations in immune regulatory systems such as the hypothalamic-pituitary-adrenal (HPA) axis defined in [7]. Adrenal cortex-derived steroids have potent effects on proinflammatory cytokine production and activity and disturbances in HPA axis function have been observed in other chronic inflammatory and fatigue-related disorders. The current study was designed to test the dynamic responsiveness of the HPA axis given evidence that blunted HPA axis responses may be associated with susceptibility to inflammatory disease. We used a standardized psychosocial stressor to probe HPA axis activity in fatigued and non fatigued breast cancer survivors.

Consider a Markov branching process with neutral mutations. Suppose that the process starts from a group of individuals carrying the same allele, and individuals can mutate into new allelic variants. We assume that the mutation is independent process, and the offspring distribution is independent of the allelic type that is the selection is neutral for all alleles. We are interested in the frequency spectrum of the IAMBp, which may be defined as the number or proportion of alleles present in a given number of individuals at a specified time point defined in [10]. We rigorously define the IAMBp and the mean frequency spectrum of the IAMBp. Then, we provide explicit expressions for the special case of the birth and death process.

### II. IAMBp and its Limiting Mean Frequency Spectrum

#### 2.1 Definition and Basic Properties in the super critical Case:

Let us consider a continuous-time Markov branching process consisting of individuals with exponential life spans with mean “a”. Let us assume that upon death, each individual produces a random number of off spring. As usually assumed, the offspring counts are identically distributed according to probability generating function  $f(s)$ , and they are independent conditional on the past process. The mean  $f'(1)$  of the offspring distribution is  $m$ , regardless of the allelic type. We further assume that a newborn individual mutates into a new allelic type with probability  $\mu$  independently of the previous history of the process. Let us denote by  $h(s) = f(\mu + (1-\mu)s)$  the offspring probability generating function in a clone, stated by the overall ancestor or any of mutants, containing only the like-type individuals. The entire process is a union over all individual types of such clones. The theory of the IAMBp has been developed by [6] in the discrete time case and then by [9] in the continuous-time case. We will assume  $m > 1$  and  $M = h'(1) > 1$  although some results can be proved without this later assumption.

Let  $\alpha_t(j)$  be the number of alleles present in  $j$  individuals at time  $t$  and  $\phi_{i,t}(j) = E_i[\alpha_t(j)]$ , where subscript  $i$  indicates that the process begins with  $i$  individuals carrying the same allele. It has been shown that [9]

$$\phi_{i,t}(j) = q_{ij}(t) + iam\mu e^{\lambda t} \int_0^t e^{-\lambda x} q_{1j}(x) dx, j \geq 0, \quad (1)$$

Where  $\lambda = a(m-1)$  is the Malthusian parameter of the overall process and  $q_{1j}(t)$  is the probability of observing  $j$  individuals ( $j \geq 1$ ) carrying the parental allele at time  $t$  when starting from  $i$  individuals with the parental allele at time  $t=0$ . Consequently, for the number  $K_t$  of alleles at time  $t$ , we have

$$E_i[K_t] = \sum_{j=1}^{\infty} \phi_{i,t}(j) = 1 - q_{i0}(t) + iam\mu e^{\lambda t} \int_0^t e^{-\lambda x} [1 - q_{i0}(x)] dx \quad (2)$$

Let  $G_j = \int_0^{\infty} e^{-\lambda x} q_{1j}(x) dx, j \geq 0$ . If we define  $\psi_{ij}(t) = \phi_{i,t}(j) / E_i[K_t]$  and

$$\psi_j = \lim \psi_{ij}(t)$$

that is

$$\psi_j = \lim \frac{q_{ij}(t) + iam\mu e^{\lambda t} \int_0^t e^{-\lambda x} q_{1j}(x) dx}{1 - q_{i0}(t) + iam\mu e^{\lambda t} \int_0^t e^{-\lambda x} [1 - q_{i0}(x)] dx} \quad (3)$$

as the limiting mean frequency spectrum that is the expected proportion of alleles present in  $j$  individuals as  $t \rightarrow \infty$ , then we see that for the supercritical process such that  $\lambda > 0$ ,

$$\psi_j = \frac{\lambda G_j}{1 - \lambda G_0}, j \geq 1 \quad (4)$$

If  $m > 1$  then the process of the like-type clones is supercritical, and as it is known [2],  $q_{i0}(t) \uparrow q_{i0}(\infty) < 1$  and  $q_{1j}(t) \rightarrow 0, j \geq 1$  as  $t \rightarrow \infty$ .

Therefore,  $e^{\lambda t} \int_0^t e^{-\lambda x} q_{i0}(x) dx - q_{i0}(\infty) / \lambda \rightarrow 0$  and  $e^{\lambda t} \int_0^t e^{-\lambda x} q_{1j}(x) dx \rightarrow 0$  as  $t \rightarrow \infty$ . This yields

the following asymptotic equivalence.

$$\psi_{ij}(t) - \psi_j = \frac{\lambda G_j [1 - q_{i0}(\infty) - (\lambda(1 - q_{i0}(\infty)) / iam\mu)]}{(1 - \lambda G_0)^2} e^{-\lambda t} \quad (5)$$

Details of the proof are omitted, since they appear elementary.

## 2.2 IAMB with Birth and Death Offspring Distribution:

For the Infinite-Allele Markov Branching Process with birth and death offspring distribution  $f(s) = \alpha + \beta s^2, \alpha + \beta = 1$ , we are able to obtain an explicit form for  $G_j, j \geq 0$  therefore; the limiting mean frequency spectrum  $\psi_j, j \geq 1$  can be derived. The offspring Probability generating function of the like-type individuals clone in the birth and death Infinite-Allele Markov Branching Process is written as

$$h(s) = f(\mu + (1 - \mu)s) = \alpha + \beta[\mu + (1 - \mu)s]^2 \quad (6)$$

Where  $\alpha, \beta$  and  $\mu$  stand for the death, birth and mutation probabilities for every individuals and  $\alpha + \beta = 1$ . Note that under another parameterization where the two newborn individuals die, live, and mutate independently, this probability generating function may be formulated differently as

$$h(s) = \alpha + \beta[\mu + (1 - \mu)s]^2 = [\alpha + \beta\mu + \beta(1 - \mu)s]^2$$

Under either parameterization  $M = m(1 - \mu) > 1$ , then parameters  $\alpha$  and  $\mu$  are subject to a constraint

$$(1-\alpha)(1-\mu) > \frac{1}{2} \tag{7}$$

Let us write  $A^2 = \alpha + \beta\mu^2$  and  $B^2 = \beta(1-\mu)^2$  (note, for the other formulation,  $A^2 = (\alpha + \beta\mu)^2$  and  $B^2 = \beta^2(1-\mu)^2$ ). The explicit form of  $G_j$  can be written as

$$G_0 = \frac{1}{c} \frac{A^2}{B^2} \frac{\Gamma(\lambda/c)\Gamma(2)}{\Gamma(2+(\lambda/c))} \times F\left(1, \frac{\lambda}{c}; 2 + \frac{\lambda}{c}; \frac{A^2}{B^2}\right), \tag{8}$$

$$G_j = \frac{1}{c} \left(1 - \frac{A^2}{B^2}\right)^2 \frac{\Gamma(1+(\lambda/c))\Gamma(j)}{\Gamma(j+1+(\lambda/c))} \times F\left(j+1, 1 + \frac{\lambda}{c}; j+1 + \frac{\lambda}{c}; \frac{A^2}{B^2}\right), j \geq 1,$$

Where  $c = \alpha(B^2 - A^2) = \alpha[2\beta(1-\mu) - 1]$  is the Malthusian parameter of the like-type clone and the Gauss hypergeometric function [1], defined as

$$F(a, b, c; z) = \frac{\Gamma(c)}{\Gamma(b)\Gamma(c-b)} \int_0^1 t^{b-1} (1-t)^{c-b-1} (1-tz)^{-a} dt, c > b > 0. \tag{9}$$

Note that the supercritical condition also guarantees that the argument of the hyper geometric function remains within its region of definiteness.

It follows that

$$\psi_j = \frac{\lambda G_j}{1 - \lambda G_0}$$

that is

$$\psi_j = \left(\frac{\lambda}{c} \left(1 - \frac{A^2}{B^2}\right)\right)^2 \times \left(\frac{\Gamma(1+\lambda/c)\Gamma(j)}{\Gamma(j+1+\lambda/c)}\right) \times F\left(j+1, 1 + \frac{\lambda}{c}; j+1 + \frac{\lambda}{c}; \frac{A^2}{B^2}\right) \tag{10}$$

$$\times \left(1 - \frac{\lambda}{c} \frac{A^2}{B^2} \frac{\Gamma(\lambda/c)\Gamma(2)}{\Gamma(2+(\lambda/c))} \times F\left(1, \frac{\lambda}{c}; 2 + \frac{\lambda}{c}; \frac{A^2}{B^2}\right)\right)^{-1}, j \geq 1$$

We see that for fixed  $\alpha$ , increasing  $\mu$  causes an increase of  $\psi_1$ . This can be intuitively explained by the offspring probability generating function  $h(s)$  of the like-type clone. From the Probability generating expression  $h(s) = \alpha + \beta[\mu + (1-\mu)s]^2$ , we see that the probability of obtaining on like-type individual in the offspring is  $2(1-\alpha)\mu(1-\mu)$ , which is an increasing function of  $\mu$  for a given  $\alpha$ , under the constraint  $(1-\alpha)(1-\mu) > 1/2$ . Therefore, increasing  $\mu$  will finally lead to an increase of  $\psi_1$ . The effect of  $\alpha$  on  $\psi_1$  when fixing  $\mu$  is not so obvious, but we notice that when fixing  $\mu$  very close to 0, as  $\alpha$  approaches  $1/2$ , the process is approximately critical binary fission; therefore  $\psi_1$  drops down because of almost sure extinction of the process.

Arguably, the frequency spectrum can only be observed in finite time. The finite-time mean frequency spectrum can be obtained by computing  $G_j = \int_0^t e^{-\lambda x} q_{1j}(x) dx, j \geq 0$ , numerically. For the birth and death process, this involves the computation of the incomplete hyper geometric function. The following is a valid question in this context. In order to safely use the limiting mean frequency spectrum, compares the limiting mean frequency spectra, for the birth and death process with parameters.

We see that under this setting, the long-term mean frequency spectrum is almost identical to the limiting mean frequency spectrum when  $t \geq 0$ . In general, this result depends strongly on parameters  $a, \alpha$  and  $\mu$ , for example, small  $\mu$  leads to longer  $t$ . This provides us with some intuitions concerning the sufficiently large  $t$  for approximating the limiting mean frequency spectrum illustrates the difference between the finite-time mean frequency spectrum and the limiting mean frequency spectrum as a function of  $t$ , and for  $j=1,2$ , where lines represent the true difference and markers represent the asymptotic approximation by formula (5).

To emphasize the agreement for  $t$  large, this plotted in semi logarithmic scale. We see that the true difference drops exponentially fast and the asymptotic approximation is good for large  $t$ .

Given the observed long-term mean frequency spectrum, the parameters of the Infinite-Allele Markov Branching Process, such as  $\alpha, \mu$  in the birth and death process, can be estimated by equating the observed long-term mean frequency spectrum  $\psi_{abs}$  from the sample to the expected limiting mean frequency spectrum  $\psi_{exp}$  from formula (3) and solving for the process parameters. In the case of the birth and death process, we may estimate  $\alpha$  and  $\mu$  for example by solving

$$\begin{aligned} & \left( \Gamma(j_1) \Gamma\left(k_1 + 1 + \frac{\lambda}{c}\right) \times F\left(j_1 + 1, 1 + \frac{\lambda}{c}; j_1 + 1 + \frac{\lambda}{c}; \frac{A^2}{B^2}\right) \right) \\ & \times \left( \Gamma(k_1) \Gamma\left(j_1 + 1 + \frac{\lambda}{c}\right) \times F\left(k_1 + 1, 1 + \frac{\lambda}{c}; k_1 + 1 + \frac{\lambda}{c}; \frac{A^2}{B^2}\right) \right)^{-1} = \frac{\psi_{abs}(j_1)}{\psi_{abs}(k_1)} \\ & \left( \Gamma(j_2) \Gamma\left(k_2 + 1 + \frac{\lambda}{c}\right) \times F\left(j_2 + 1, 1 + \frac{\lambda}{c}; j_2 + 1 + \frac{\lambda}{c}; \frac{A^2}{B^2}\right) \right) \\ & \times \left( \Gamma(k_2) \Gamma\left(j_2 + 1 + \frac{\lambda}{c}\right) \times F\left(k_2 + 1, 1 + \frac{\lambda}{c}; k_2 + 1 + \frac{\lambda}{c}; \frac{A^2}{B^2}\right) \right)^{-1} = \frac{\psi_{abs}(j_2)}{\psi_{abs}(k_2)} \end{aligned} \quad (11)$$

For positive integers  $j_1 \neq k_1, j_2 \neq k_2$ , where  $\lambda/c$  and  $\frac{A^2}{B^2}$  are both functions of  $\alpha$  and  $\mu$ .

There is no explicit solution for such estimator, but numerical search according to some criteria is feasible. Another possibility is to minimize the distance between the observed long-term mean frequency spectrum and the expected limiting mean frequency spectrum that is

$$\hat{\theta} = \arg \min_{\theta} \left[ \psi_{abs} - \psi_{exp}(\theta) \right]_2.$$

The estimated parameters can be used to check the goodness of fit of the Infinite-Allele Markov Branching Process model. Another interesting problem is to test whether two sets of parameters are identical, given two observed mean frequency spectra. A simple approach is to use Pearson's  $\chi^2$  test, such as in [1] and [8]. However, there may be restrictions to applying the  $\chi^2$  test such as small cell counts and inappropriateness due to the finite length of the observed spectrum. This motivates us to develop an interval estimator for the Infinite-Allele Markov Branching Process parameters.

### III. Example

Salivary cortisol levels for non fatigued women by more than 4-fold after the TSST. Whereas fatigued women showed a negligible change over this period main effects for group time, and the group-by-time interaction remained significant in analyses with 3 assessment points. Analyses were conducted to control for factors that different between fatigued and non fatigued subjects and may influence HPA axis responsiveness. The fatigue group-by-time interaction remained significant in analysis controlling for potential demographic and medical confounds fatigue income material status cancer treatment and depressive symptoms two of the fatigued women respond cigarette use in the past week; removal of these subject shown the data set yielded the same pattern of results in [3],[4],[5]. Mean salivary free cortisol levels before, during and after experimental psychologic stress in fatigued and nonfatigued breast cancer survivors. The stressor occurred during the first 30 minutes indicated on the graph (fig.1).

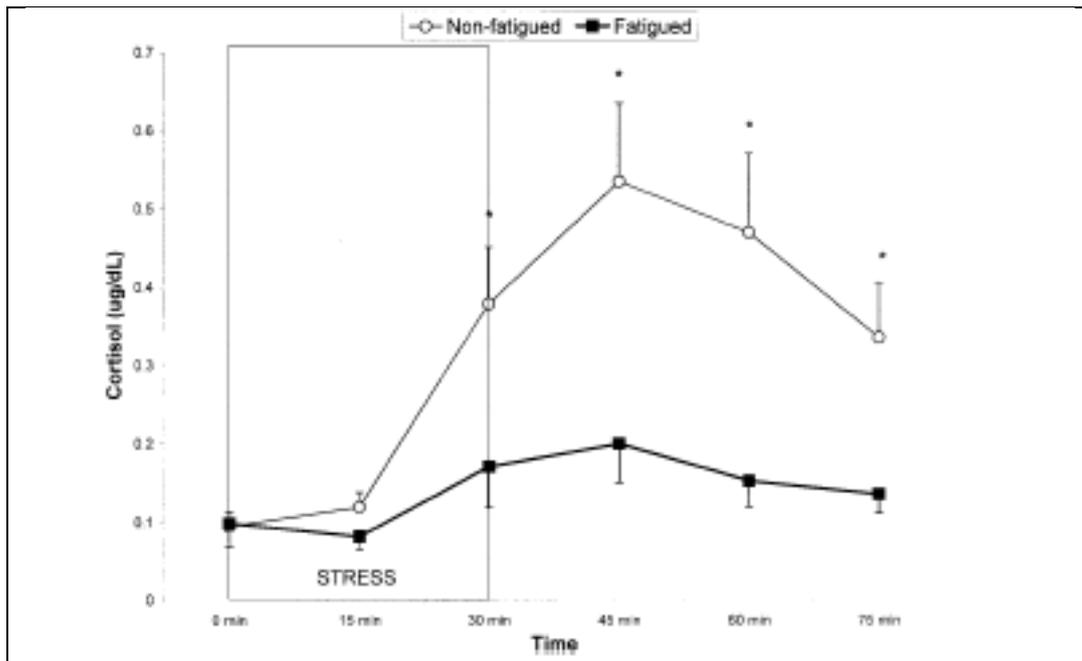


Fig. 1.

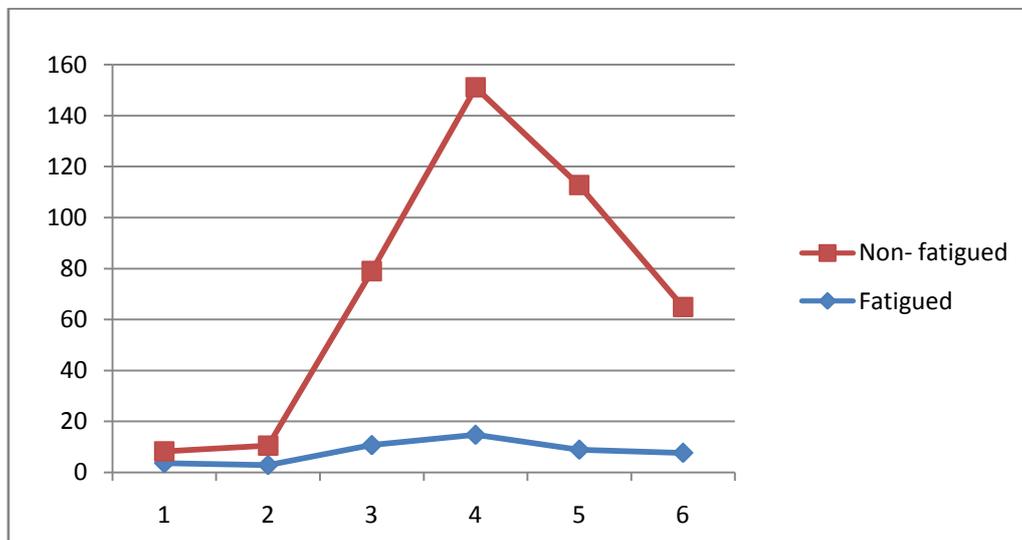


Fig.2.

#### IV. Conclusion

This paper is rigorously defined the IAMBP and the mean frequency spectrum of the IAMBP. Then, we provide explicit expressions for the special case of the birth and death process, which is used for cortisol responses to an experimental psychologic stressor in fatigued and non fatigued survivors. Participants included 27 breast cancer survivors (11 fatigued, 16 non fatigued). Analyses were conducted to control for factors that differed between fatigued and nonfatigued subjects and may influence HPA axis responsiveness as in fig.1. At the completion of the process, it concludes that from fig (2), the results coincide with the medical findings.

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