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MATHEMATICS

STOCHASTIC MODELING FOR USING AN INFINITE – ALLELE MARKOV BRANCHING PROCESS OF HPA AXIS FUNCTIONING COMBINEDDEX/CRH TEST

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ABSTRACT

We investigated functioning of the Hypothalamic – Pituitary – adrenal (HPA) axis in 12 young people at ultra-high risk for developing psychosis, using the combined dexamethasone corticotrophin releasing hormone (DEX/CRH) test. The focus is the frequency spectrum of the Infinite-Allele Markov branching process, namely the proportion having a given number of copies at a specified time point.

KEYWORDS: Psychologic Stress, Hpa Axis, Cortisol, Frequency Spectrum, Hyper Geometric Function.

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INTRODUCTION

The diathesis – stress model of schizophrenia contents that a combination of factors, including genetic liability, abnormal maturation, early exposures, and stress combine to affect the abnormal substrate thought to underlie schizophrenia [3,10]. In order to further elucidate the relationship between stress response and the pathophysiology of psychosis, it may be of special value to test HPA – axis reactivity during the sub-threshold stage of illness [9].

Consider an Infinite – Allele Markov branching process. Our main focus is the frequency spectrum of this process, that is, the proportion of allele having a given number of copies at a specified time point in [5]. We derive the variance of the frequency spectrum, which is useful for interval estimation and hypothesis testing for process parameters. In addition, we also derive an asymptotic expression for convergence rate to the limit. Simulations are used to illustrate the results for the birth and death process.

NEUTRAL EVOLUTION AND ITS LIMITING MEAN FREQUENCY SPECTRUM

Definition and Basic Properties :

A continuous-time Markov branching process consisting of individuals with exponential life spans with mean Let us assume that upon death, each individual produces a random number of offspring. As usually assumed, the offspring counts are identically distributed according to probability generating function (pgf) , and they are independent conditional on the past process. The mean ' of the offspring distribution is , regardless of the allelic type. We further assume that a newborn individual mutates into a new allelic type with probability independently of the previous history of theprocess. Let us denote by the offspring probability generating function in a clone, started 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 Infinite-Allele Markov Branching process has been developed by[1] in the discrete time case and then by [2] in the continuous-time case.

Let be the number of alleles present in individuals at time and , where subscript indicates that the process begins with individuals carrying the same allele. It has been shown that [2]

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

where $\lambda = a(m-1)$ is the Malthusian parameter of the overall process and $q_{ij}(t)$ is the probability of observing j individuals $(j \geq 1)$ carrying 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

$$E_i[K_t] = \sum_{j=1}^{\infty}\phi_{i,t}(j) = 1 - q_{i0}(t) + iam\mu e^{\lambda t}\int_0^1 e^{-\lambda x}[1 - q_{10}(x)]dx. \quad (2)$$

Let $G_j = \int_0^{\infty} e^{-\lambda t} q_{1j}(t)dt,\ j \geq 0.$ If we define

$\psi_{ij}(t) = \phi_{i,t}(j) / E_i[K_t]$ and

$\psi_j = \lim_{t\to\infty} \psi_{ij}(t)$

$$= \lim_{t\to\infty} \frac{q_{ij}(t) + iam\mu e^{\lambda t}\int_0^t e^{-\lambda x} q_{1j}(x)dx}{1 - q_{i0}(t) + iam\mu e^{\lambda t}\int_0^t e^{-\lambda x}[1 - q_{10}(x)]dx} \quad (3)$$

see the limiting mean frequency spectrum, that is, the expected proportion of alleles present in j individuals as $t \to \infty$, 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 [6], $q_{10}(t) \uparrow q_{10}(\infty)$ <1 and $q_{1j}(t) \to 0$, $j \geq 1$, as $t \to \infty$. Therefore, $e^{\lambda t}\left|\int_0^t e^{-\lambda x} q_{10}(x)dx - q_{10}(\infty)/\lambda\right| \to 0$ and $e^{\lambda t}\int_0^t e^{-\lambda x} q_{1j}(x)dx \to 0$ as $t \to \infty$, for $j \geq 1$. This yields the following asymptotic equivalence:

$$\psi_{ij}(t) - \psi_j \quad t \to \infty \frac{\lambda G_j[1-q_{10}(\infty)-(\lambda(1-q_{i0}(\infty))\backslash iam\mu)]}{(1-\lambda G_0)^2} e^{-\lambda t}. \quad (5)$$

INFINITE – ALLELE MARKOV BRANCHING PROCESS 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 ψ_j, $j \geq 1;$ can be derived. The offspring pgf 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 α, β and μ stand for the death, birth, and mutation probabilities for every individual and $\alpha + \beta = 1.$ Note that under another parameterization where the two newborn individuals die, live, and mutate independently, this pgf may be formulated differently as $h(s) = [\alpha + \beta\mu + \beta(1-\mu)s]^2.$ Under either parameterization, $\lambda = a(2\beta - 1).$ If, as assumed, $M = m(1-\mu) > 1,$ then parameters α and μ are subject to a constraint

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

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

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

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

$j \geq 1,$

where $c = a(B^2 - A^2) = a[2\beta(1-\mu) - 1]$ is the Malthusian parameter of the like-type clone and F is the Gauss hypergeometric function [7], defined as

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

For a detailed derivation, see Appendix A. Note that the supercritical condition also guarantees that the argument of the hypergeometric function remains within its region of definiteness.

It follows that

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

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

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

We see that for fixed $\alpha,$ increasing μ causes an increase of $\psi_1.$ This can be intuitively explained by the offspring pgf $h(s)$ of the like-type clone. From the pgf expression $h(s) = \alpha + \beta[\mu + (1-\mu)s]^2,$ we see that the probability of obtaining one like-type individual in the offspring is $2(1-\alpha)\mu(1-\mu),$ which is an increasing function of μ for a given α, under the constraint $(1-\alpha)(1-\mu) > \frac{1}{2}.$ Therefore, increasing μ will finally lead to an increase of $\psi_1.$ The effect of α on ψ_1 when fixing μ is not so obvious, but we notice that when fixing μ very close to 0, as α approaches $\frac{1}{2}$, the process is approximately critical binary fission; therefore, ψ_1 drops down because of almost sure extinction of the process, as seen from the tail behavior of the solid .

The frequency spectrum can only be observed in finite time. The finite-time mean frequency spectrum can be obtained by computing $G_j(t) = \int_0^t e^{-\lambda x} q_{1j}(x)dx,\ j \geq 0$ numerically. For the birth and death process, this involves the computation of the incomplete hypergeometric function. The following is a valid question in this context. In order to safely use the limiting mean frequency spectrum, how long should the process history be? For the birth and death process with parameters $a = 1$, $\alpha = 0.25$, and $\mu = 10^{-4}$. We see that under this setting, the long-term mean frequency spectrum is almost identical to the limiting mean frequency spectrum when $t \geq 28$.

In general, this result depends strongly on parameters $a, \alpha,$ and μ, for example, small μ leads to longer t. This provides us with some intuitions concerning the sufficientlylarge t for approximating the

limiting mean frequencyspectrum. The difference between the finite-time mean frequency spectrum and the limiting mean frequency spectrum as a function of t, for large t, $t \in [15,35]$ and for $j = 1,2.$

Given the observed long-term mean frequency spectrum, the parameters θ of the Infinite – Allele Markov Branching Process, such as α, μ in the birth and death process, can be estimated by equating the observed long-term mean frequency spectrum ψ_{obs} 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 α and μ for example by solving

$$(\Gamma(j_1)\Gamma(k_1+1+\frac{\lambda}{c})\times F(j_1+1,1+\frac{\lambda}{c};j_1+1+\frac{\lambda}{c};\frac{A^2}{B^2}))\times(\Gamma(k_1)\Gamma(j_1+1+\frac{\lambda}{c})\times$$
$$F(k_1+1,1+\frac{\lambda}{c};k_1+1+\frac{\lambda}{c};\frac{A^2}{B^2}))^{-1}=\frac{\psi_{obs}(j_1)}{\psi_{oba}(k_1)} \quad (11)$$
$$(\Gamma(j_2)\Gamma(k_2+1+\frac{\lambda}{c})\times F(j_2+1,1+\frac{\lambda}{c};j_2+1+\frac{\lambda}{c};\frac{A^2}{B^2}))\times(\Gamma(k_2)\Gamma(j_2+1+\frac{\lambda}{c})$$
$$\times F(k_2+1,1+\frac{\lambda}{c};k_2+1+\frac{\lambda}{c};\frac{A^2}{B^2}))^{-1}=\frac{\psi_{obs}(j_2)}{\psi_{obs}(k_2)}$$

for positive integers $j_1 \neq k_1,\ j_2 \neq k_2,$ where λ/c and A^2/B^2 are both functions of α and $\mu.$

VARIANCE OF THE FREQUENCY SPECTRUM:

Moment estimators based on the mean frequency spectrum only give point estimates of the process parameters. In order to quantify the uncertainty of point estimates, an interval estimator is needed, which requires more information about the distribution of the statistic $\alpha_t(j)$. First, it can be seen that [2]

$$\alpha_t(j) = I_{0,j}(t) + \sum_{n=1}^{N_t}\sum_{k=1}^{U_n} I_{n,k,j}(t-T_n), \quad (12)$$

where $T_1, T_2, \ldots\ldots$ are the successive split times of the process, $I_{0,j}(t),\ I_{n,k,j}(t)$ are two indicators, and $I_{0,j}(t)=1$ if there are j individuals alive at time t carrying the parental allele, and $I_{n,k,j}(t)=1,$ for $n,k \geq 1$ if the k th individual born at time $T_n\ (T_n < t)$ mutates to a novel allelic type and further produces j individuals carrying this allele t time units later. N_t is the number of split times in $(0,t],$ and U_n is the number of offspring produced at time T_n. Obtaining the distribution of $\alpha_t(j)$ is not elementary. However, it may still be possible to define a confidenceinterval (CI) based on the first and second moments of $\alpha_t(j)$.

Let $\eta_{i,t}(j) = Var_i(\alpha_t(j))$ be the variance frequency spectrum; by the law of total variance and independence between the indicators in the expression of $\alpha_t(j)$. we have,

$$\eta_{i,t}(t) = q_{ij}(t)[1-q_{ij}(t)] + im^2\mu^2[C(t) + (\lambda+a)e^{\lambda t}\int_0^t e^{-\lambda x}C(x)dx] + \quad (13)$$
$$iam\mu e^{\lambda t}\int_0^t e^{-\lambda x}q_{1j}(x)dx + ia(\sigma^2-m)\mu^2 e^{\lambda t}\times\int_0^t e^{-\lambda x}q_{1j}^2(x)dx,$$

Where

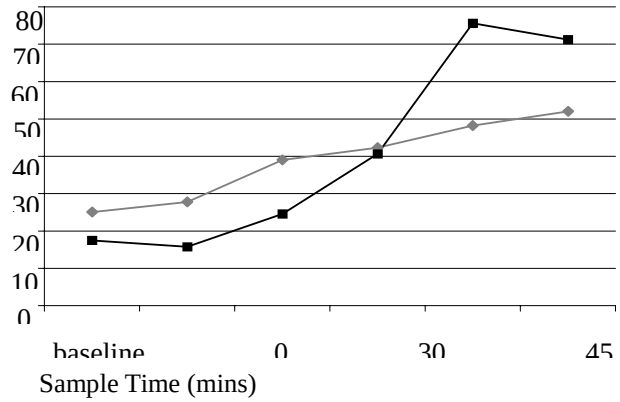
$$C(t) = a\int_0^t [q_{1j}(x) + (\sigma^2+m^2)\beta_1^2(x)]e^{-a(t-x)}dx - \quad (14)$$
$$[a\int_0^t q_{1j}(x)e^{-a(t-x)}dx]^2 - [am\int_0^t \beta_1(x)e^{-a(t-x)}dx]^2$$

In expression (14), $\beta_1(x) = ae^{\lambda x}\int_0^x e^{-\lambda u}q_{1j}(u)du,$ and σ^2 is the variance of the offspring distribution, regardless of allelic types[4]. This is useful for checking model validity and for testing whether two observed mean frequency spectra are from the same Infinite – Allele Markov Branching Process Model.

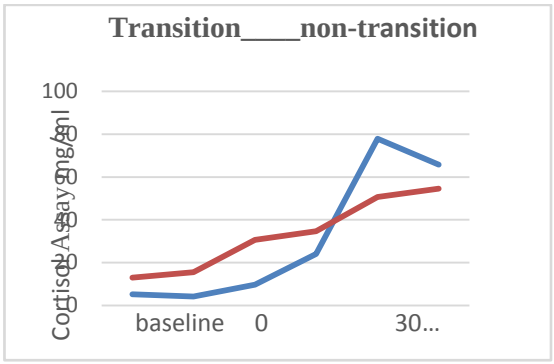
EXAMPLE

Cortisol was assayed using a previously reported procedure [6] and ACTH sent to a commercial laboratory for testing. The small sample size precluded any statistical analyses; therefore only qualitative data is presented. Over a two year period from baseline assessment, three of the 12 participants developed an acute psychotic illness, in each case meeting the DSM-IV diagnostic criteria for schizophrenia [1]. For the DEX/CRH test, mean cortisol levels were equivalent between the groups at baseline and during the early stages of the test, although higher mean cortisol levels were apparent among participants that did not subsequently make the transition to psychosis, peaking at 60 min (see Fig. 1).

Transition____non-transition



Fig(1)



Fig(2)

CONCLUSION

The paper is rigorously defined the Infinite – Allele Markov Branching Process and the mean frequency spectrum of the Infinite – Allele Markov Branching Process. Thus, we provide explicit expressions for the special case of the birth and death process, which is used for cortisol response to an experimental psychologic stressor in transition and non transition survivors. 12 participants developed an acute psychotic illness. Analyses were conducted to cortisol for factors that differed between transition and non transition 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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