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STOCHASTIC MODEL TO FIND THE PROGNOSIS OF GALLBLADDER ADENOCARCINOMA USING UNIFORM DISTRIBUTION

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ABSTRACT

PSCA and OCT-4 have been thought as markers of cancer stem cells. Although over expression of PSCA and OCT-4 in cancer has been reported, little is known about the clinical and pathological significance with PSCA and OCT-4 expression in gallbladder adenocarcinoma. In this study, over expression of PSCA and OCT-4 was detected in gallbladder adenocarcinoma. Less expression of PSCA and OCT-4 was detected in the pericancerous tissues, gallbladder polyps and gallbladder epithelium with chronic cholecystitis. The over expression of PSCA and OCT-4 was significantly associated with differentiation, tumor mass, lymph node metastasis, invasion of gallbladder adenocarcinoma, and decreased overall survival. A random motion on the Poincare half plane is studied. The mean hyperbolic distance in all versions of the motion and the mean distance from the starting point are evaluated to find the implication for carcinogenesis, progression and prognosis of gallbladder adenocarcinoma due to over expression of PSCA and OCT-4.

INTRODUCTION

Increasing data support that cancer is a stem cell based disease. Cancer stem cells (CSCs) are a subpopulation of tumor cells that selectively possess tumor initiation, self renewal capacity, and ability to give rise to bulk populations of nontumorigenic cancer cell progeny through differentiation. CSCs have been found in different human cancers, including prostate cancer, breast cancer, colon cancer [10], pancreatic cancer, and head and neck squamous cell carcinoma [8]. These observations have dramatic biological and clinical significance due to the increasing evidence suggesting that recurrence of human tumor and treatment failure may reflect the intrinsic quiescence and drug resistance of CSCs. The prostate stem cell antigen (PSCA) gene was originally identified through an analysis of genes up regulated in the human prostate cancer LAPC-4 xenograft model [9]. PSCA protein is highly expressed by a large percentage of human prostate tumors, including metastatic and hormone-refractory cancers, but it has limited expression in normal tissues [11].

Elevated level of PSCA in prostate tumor is correlated with the increased Gleason score, advanced stage, progression and death. PSCA may therefore be a useful predictor of tumor biology and a useful target of immunotherapy against prostate cancer [11]. Moreover,

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PSCA is also strongly expressed in nonprostatic malignancies, including bladder cancer, pancreatic cancer, renal cell carcinoma, and diffuse type gastric cancer. The OCT-4 gene, a POU (Pit-Oct-Unc) domain octamerbinding transcription factor, is a key regulator of self renewal in embryonic stem cells. OCT-4 was expressed in human tumors but not in normal somatic tissues. Some studies have shown that OCT-4 gene was expressed in human breast cancer cells, lung cancer cells, bladder transitional cell carcinoma samples and cell lines, prostate cancer, and oral cancer. A random motion on Poincare half plane at finite velocity on the surface of a three dimensional sphere is used to find the effect of PSCA and OCT-4 in the Bengin and Malignant Lesions of gallbladder. In this case we use

$$E(t)=\frac{e^{\frac{-\lambda t}{2}}}{2}\left[\left(e^{\frac{t}{2}\sqrt{\lambda^2-4c^2}}+e^{\frac{-t}{2}\sqrt{\lambda^2-4c^2}}\right)+\frac{\lambda}{\sqrt{\lambda^2-4c^2}}\left(e^{\frac{t}{2}\sqrt{\lambda^2-4c^2}}-e^{\frac{-t}{2}\sqrt{\lambda^2-4c^2}}\right)\right]$$

to find the implication for Carcinogenesis, Progression and Prognosis of gallbladder adenocarcinoma.

Notations

CSCs	-	Cancer Stem Cells
PSCA	-	Prostate Stem Cell Antigen
POU	-	Pit-Oct-Unc
GBC	-	Gallbladder Carcinoma

Motions with Jumps Backwards to the Starting Point

Motion on hyperbolic spaces have been studied since the end of the Fifties and most of papers devoted to them deal with the so called hyperbolic Brownian motion [1] [6] & [7]. More recently also works concerning two dimensional random motions at finite velocity on planar hyperbolic spaces have been introduced and analyzed. While in the corresponds of motion are supposed to be independent, we present here a planar random motion with interacting components. Its counterpart on the unit sphere is also examined and discussed.

The space on which our motion develops is the Poincare upper half plane $H_2^+=\{(x,y):y>0\}$ which is certainly the most popular model of the Lobachevsky hyperbolic space. In the space H_2^+ the distance between points is measured by means of the metric

$$ds^2=\frac{dx^2+dy^2}{y^2} \qquad (1)$$

The propagation of light in a planar non homogeneous medium, according to the Fermat principle, must obey the law

$$\frac{\sin\alpha(y)}{c(x,y)}=\cos t$$

where $\alpha(y)$ is the angle formed by the tangent to the curve of propagation with the vertical at the point with ordinate y. In the case where the velocity $c(x,y)=y$ is independent from the direction, the light propagates on half circles as in H_2^+. It is shown that the light propagates in a non homogeneous half plane H_2^+ with refracting index $n(x,y)=1/y$ with rays having the structure of half circles. Scattered obstacles in the non homogeneous medium cause random deviations in the propagation of light and this lead to the random model analyzed below. The position of points in H_2^+ can be given either in terms of Cartesian coordinates (x,y) or by means of the hyperbolic coordinates (η,α). In particular, η represents the hyperbolic distance of a point of H_2^+ from the origin 0 which has Cartesian coordinates $(0,1)$. We recall than η is evaluated by means of (1) on the arc of a circumference with center located on the x axis and joining (x,y) with the origin 0. The upper half circumference centered on the x axis represents the geodesic lines of the space H_2^+ and play the same role of the straight lines in the Euclidean plane [2] & [3]. The angle α represents the slope of the tangent in 0 to the half circumference passing through (x,y). The formulas which relate the polar hyperbolic coordinates (η,α) to the Cartesian coordinates (x,y) are

$$\begin{cases} x=\dfrac{\sinh\eta\cos\alpha}{\cosh\eta-\sinh\eta\sin\alpha}, \eta>0 \\ y=\dfrac{1}{\cosh\eta-\sinh\eta\sin\alpha}, -\dfrac{\pi}{2}<\alpha<\dfrac{\pi}{2} \end{cases} \qquad (2)$$

for each value of α the relevant geodesic curve is represented by the half circumference with equation

$$(x-\tan\alpha)^2+y^2=\frac{1}{\cos^2\alpha} \qquad (3)$$

for $\alpha=\frac{\pi}{2}$ we get from (3) the positive y axis which also is a geodesic curve of H_2^+. From (2) it is easy to obtain the following expression of the hyperbolic distance η of (x,y) from the origin 0:

$$\cosh\eta=\frac{x^2+y^2+1}{2y} \qquad (4)$$

from (4) it can be seen that all the points having hyperbolic distance η from the origin 0 from a Euclidean circumference with center at $(0, \cosh\eta)$ and radius $\sinh\eta$.

The expression of the hyperbolic distance between two arbitrary points (x_1, y_1) and (x_2, y_2) is instead given by

$$\cosh\eta = \frac{(x_1 - x_2)^2 + y_1^2 + y_2^2}{2y_1y_2} \qquad (5)$$

In fact, by considering the hyperbolic triangle with vertices at $(0,1), (x_1, y_1)$ and (x_2, y_2), by means of the Carnot hyperbolic formula it is simple to show that the distance η between (x_1, y_1) and (x_2, y_2) is given by

$$\cosh\eta = \cosh\eta_1 \cosh\eta_2 - \sinh\eta_1 \sinh\eta_2 \cos(\alpha_1 - \alpha_2) \qquad (6)$$

where (η_1, α_1) and (η_2, α_2) are the hyperbolic coordinates of (x_1, y_1) and (x_2, y_2) respectively. From (3) we obtain that

$$\tan\alpha_i = \frac{x_i^2 + y_i^2 - 1}{2x_i} \text{ for } i = 1, 2, ... \qquad (7)$$

and in view of (4) and (7), after some calculations, formula (5) appears. Instead of the elementary arguments of the proof above we can also invoke the group theory which reduces (x_1, y_1) to $(0,1)$. If $\alpha_1 - \alpha_2 = \frac{\pi}{2}$ the hyperbolic Carnot formula (6) reduces to the hyperbolic Pythagorean Theorem, $\cosh\eta = \cosh\eta_1 \cosh\eta_2$ this plays an important role in the present paper.

The motion considered here is the non Euclidean counterpart of the planar motion with orthogonal deviations studied. The main object of the investigation is the hyperbolic distance of the moving point form the origin. We are able to give explicit expressions for its mean value, also under the condition that the number of changes of direction is known. In the case of motion in H_2^+ with independent components an explicit expression for the distribution of the hyperbolic distance η has been obtained. Here, however, the components of motion are dependent and this excludes any possibility of finding the distribution of the hyperbolic distance $\eta(t)$. We obtain the following explicit formula for the mean value of the hyperbolic distance which reads

$$E\{\cosh\eta(t)\} = e^{\frac{-\lambda t}{2}} \left\{\cosh\frac{t}{2}\sqrt{\lambda^2 + 4c^2} + \frac{\lambda}{\sqrt{\lambda^2 + 4c^2}} \sinh\frac{t}{2}\sqrt{\lambda^2 + 4c^2}\right\} = Ee^{T(t)}$$

where $T(t)$ is a telegraph process with parameters $\frac{\lambda}{2}$ and c. The telegraph process represents the random of a particle moving with constant velocity and changing direction at Poisson paced times.

This section is devoted to motions on the Poincare half plane where the return to the starting point is admitted and occurs at the instants of changes of direction. The mean distance from the origin of these jumping back motions is obtained explicitly by exploiting their relationship with the motion without jumps. In the case where the return to the starting point occurs at the Poisson event T_1, the mean value of the hyperbolic distance $\eta_1(t)$ reads

$$E\{\cosh\eta_1(t) / N(t) \geq 1\} = \frac{\lambda}{\sqrt{\lambda^2 + 4c^2}} \frac{\sinh\frac{t}{2}\sqrt{\lambda^2 + 4c^2}}{\sinh\frac{\lambda t}{2}}$$

The next section considers the motion at finite velocity, with orthogonal deviations at Poisson times, on the unit radius sphere. The main results concern the mean value $E\{\cos d(P_0P_t)\}$, where $d(P_0P_t)$ is the distance of the current point P_t from the starting position P_0. We take profit of the analogy of the spherical motion with its counterpart on the Poincare half plane to discuss the different situations due to the finiteness of the space where the random motion develops.

Motion at Finite Velocity on the Surface of a Three Dimensional Sphere

Let P_0 be a point on the equator of a three dimensional sphere. Let us assume that the particle starts moves from P_0 along the equator in one of the two possible directions (clockwise or counter clockwise) with velocity c. At the first Poisson event (occurring at time T_1) it starts moving on the meridian joining the north pole P_N with the position reached at time T_1 (denoted by P_1) along one of the two possible directions. At the second Poisson event the particle is located at P_2 and its distance from the starting point P_0 is the length of the hypotenuse of a right spherical triangle with cathetus P_0P_1 and P_1P_2; the hypotenuse belongs to the equatorial circumference through P_0 and P_2.

Now the particle continues its motion (in one of the two possible directions) along the equatorial circumference orthogonal to the hypotenuse through P_0 and P_2 until the third Poisson event occurs. In general, the distance $d(P_0P_t)$ of the point P_t from the origin P_0 is the length of the shortest arc of the equatorial circumference through P_0 and P_t and therefore it takes values in the interval $[0,\pi]$. Counter clockwise motions cover the arcs in $[-\pi,0]$ so that the distance is also defined in $[0,\pi]$ or in $[-\pi/2,\pi/2]$ with s shift that avoids negative values for the cosine. By means of the spherical Pythagorean relationship we have that the Euclidean distance $d(P_0P_2)$ satisfies

$$\cos d(P_0P_2)=\cos d(P_0P_1)\cos d(P_1P_2)$$

and, after three displacements,

$$\cos d(P_0P_3)=\cos d(P_0P_2)\cos d(P_2P_3)$$
$$=\cos d(P_0P_1)\cos d(P_1P_2)\cos d(P_2P_3)$$

After n displacement the position P_t on the sphere at time t is given by

$$\cos d(P_0P_t)=\prod_{k=1}^{n}\cos d(P_kP_{k-1})\cos d(P_nP_t)$$

Since $d(P_kP_{k-1})$ is represented by the amplitude of the arc run in the interval (t_k,t_{k-1}), it results

$$d(P_kP_{k-1})=c(t_k-t_{k-1})$$

The mean value $E\{\cos d(P_0P_t)/N(t)=n\}$ is given by

$$E_n(t)=E\{\cos d(P_0P_t)/N(t)=n\}$$
$$=\frac{n!}{t^n}\int_0^t dt_1\int_{t_1}^t dt_2\ldots\int_{t_{n-1}}^t dt_n\prod_{k=1}^{n+1}\cos c(t_k-t_{k-1})$$
$$=\frac{n!}{t^n}H_n(t)$$

where $t_0=0, t_{n+1}=t$ and

$$H_n(t)=\int_0^t dt_1\int_{t_1}^t dt_2\ldots\int_{t_{n-1}}^t dt_n\prod_{k=1}^{n+1}\cos c(t_k-t_{k-1})$$

The mean value $E\{\cos d(P_0P_t)\}$ is given by

$$E(t)=E\{\cos d(P_0P_t)\}$$
$$=\sum_{n=0}^{\infty}E\{\cos d(P_0P_t)/N(t)=n\}\Pr\{N(t)=n\}$$
$$=e^{-\lambda t}\sum_{n=0}^{\infty}\lambda^n H_n(t)$$

By steps similar to those of the hyperbolic case we have that $H_n(t), t\geq 0$ satisfies the difference differential equation

$$\frac{d^2}{dt^2}H_n=\frac{d}{dt}H_{n-1}-c^2H_n$$

where $H_0(t)=\cos ct$ and therefore we can prove the following:

Theorem: 4.1

The mean value $E(t)=E\{\cos d(P_0P_t)\}$ satisfies

$$\frac{d^2}{dt^2}E=-\lambda\frac{d}{dt}E-c^2E \qquad (8)$$

with initial conditions

$$\begin{cases} E(0)=1 \\ \frac{d}{dt}E(t)/_{t=0}=0 \end{cases} \qquad (9)$$

and has the form

$$E(t)=\begin{cases} e^{-\frac{\lambda t}{2}}\left[\cosh\frac{t}{2}\sqrt{\lambda^2-4c^2}+\frac{\lambda}{\sqrt{\lambda^2-4c^2}}\sinh\frac{t}{2}\sqrt{\lambda^2-4c^2}\right], 0<2c<\lambda \\ e^{-\frac{\lambda t}{2}}\left[1+\frac{\lambda t}{2}\right], \lambda=2c>0 \\ e^{-\frac{\lambda t}{2}}\left[\cosh\frac{t}{2}\sqrt{4c^2-\lambda^2}+\frac{\lambda}{\sqrt{4c^2-\lambda^2}}\sinh\frac{t}{2}\sqrt{4c^2-\lambda^2}\right], 2c>\lambda>0 \end{cases} \qquad (10)$$

Proof:

The solution to the problem (8) and (9) is given by

$$E(t)=\frac{e^{\frac{-\lambda t}{2}}}{2}\left[\left(e^{\frac{t}{2}\sqrt{\lambda^2-4c^2}}+e^{\frac{-t}{2}\sqrt{\lambda^2-4c^2}}\right)+\frac{\lambda}{\sqrt{\lambda^2-4c^2}}\left(e^{\frac{t}{2}\sqrt{\lambda^2-4c^2}}-e^{\frac{-t}{2}\sqrt{\lambda^2-4c^2}}\right)\right]$$

(11)

so that (10) emerges.

For large values of λ, the first expression furnishes $E(t):1$ and therefore the particle hardly leaves the starting point. If $\frac{\lambda}{2}<c$, the mean value exhibits an oscillating behavior; in particular , the oscillations decrease as time goes on, and this means that the particle moves further and further reaching in the limit the poles of the sphere.

Example

108 gallbladder adenocarcinoma patients were studied. Among them 31 cases are males and 77 cases are females with an average age of 52.6 ± 11.2 years. Survival information of 67 cases among 108 adenocarcinoma was obtained. Among them, 20 cases survived over one year and 47 cases survived less than one year with a mean survival time of 9.6 ± 5.2 months. The positive rate of PSCA and OCT-4 in the cases that survival over one year was significantly lower than in those cases that survived less than one year (PSCA: 30.0% versus 61.7%, P < 0.05;

OCT-4: 35.0% versus 63.8%, $P < 0.05$). The univariate Kaplan Meier survival analysis revealed that tumor pathological type ($P = 0.031$), tumor diameter ($P = 0.003$), lymph node metastasis ($P = 0.005$), T stages ($P = 0.003$) and operative procedure ($P < 0.000$) were associated with overall survival in cases with adenocarcinoma. The overall survival was inversely associated with negative or decreased expression of PSCA ($P = 0.013$) and OCT-4 ($P = 0.029$). The average survival time in patients having PSCA (-) OCT-4 (-) expression was significantly higher than in ones having PSCA (+) OCT-4 (+) ($P = 0.013$) are shown in figure [8-14].

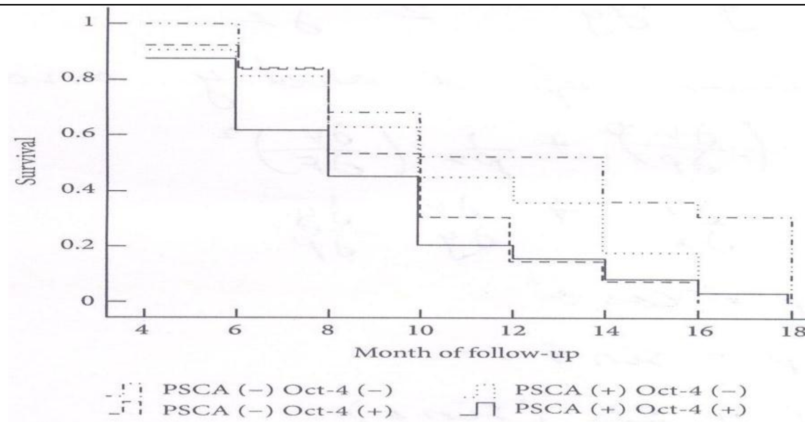
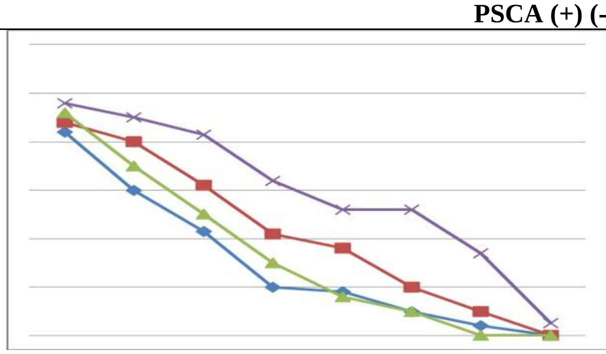
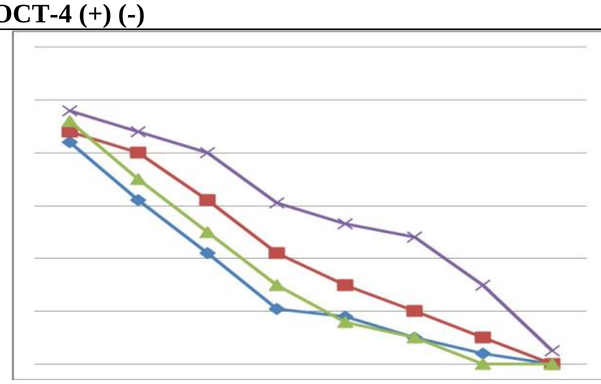


Figure 1 (a) & (b). The Kaplan Meier plots of overall survival in patients with gallbladder adenocarcinoma and with PSCA (+) (-) and OCT-4 (+) (-)



Violet Line: PSCA (-) OCT-4 (-)
Red Line: PSCA (+) OCT-4 (-)
Green Line: PSCA (-) OCT-4 (+)
Blue Line: PSCA (+) OCT-4 (+)
Figure 1 (b): The Kaplan Meier plots of overall survival in patients with Gallbladder Adenocarcinoma and with PSCA (+) (-) and OCT-4 (+) (-)
(Taking fewer values for every Two months)



Violet Line: PSCA (-) OCT-4 (-)
Red Line: PSCA (+) OCT-4 (-)
Green Line: PSCA (-) OCT-4 (+)
Blue Line: PSCA (+) OCT-4 (+)
Figure 2: The Kaplan Meier plots of overall survival in patients with Gallbladder Adenocarcinoma and with PSCA (+) (-) and OCT-4 (+) (-)
(Using Uniform Distribution)

CONCLUSION

Our study revealed that the expression of PSCA and OCT-4 was increased in gallbladder adenocarcinoma. The over expression of PSCA and OCT-4 was correlated with decreased survival and might serve as important biological marker for reflecting the carcinogenesis, progression, metastasis, or invasive potential and prognosis of gallbladder carcinoma. Measurement of PSCA and OCT-4 expression could be a tool for early detection of GBC in benign lesions as well as population screening. The development of gene therapy to target PSCA and OCT-4 can be applied to GBC and may hold promise to improve patient survival. The mean hyperbolic distance in all versions of the motion on the Poincare half plane with a Pythagorean compass gives the same result given above. This results while using motion on Poincare half plane also gives the same result by using uniform distribution. The medical reports Figure 1(a) are beautifully fitted with the mathematical model Figure 1(b), (i.e) the results coincide with the mathematical and medical report.

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